Synthesis of 4-alkylated isocoumarins via Pd-catalyzed α-arylation reaction

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Table of Contents

1. General Considerations 2

2. Optimization Studies 3

2.1 General Optimization Procedure 3

2.2 Investigation of Ligand.....4

2.3 Investigation of Palladium Source 5

2.4 Investigation of Base.....6

2.5 Investigation of Solvent 6

2.6 Investigation of Desiccant.....7

2.7 Investigation of Catalyst Loading.....7

2.8 Investigation of Aldehyde Equivalents 8

2.9 Investigation of Reaction Time and Temperature 8

3. Product Characterization.....9

Functionalization Reactions:.....22

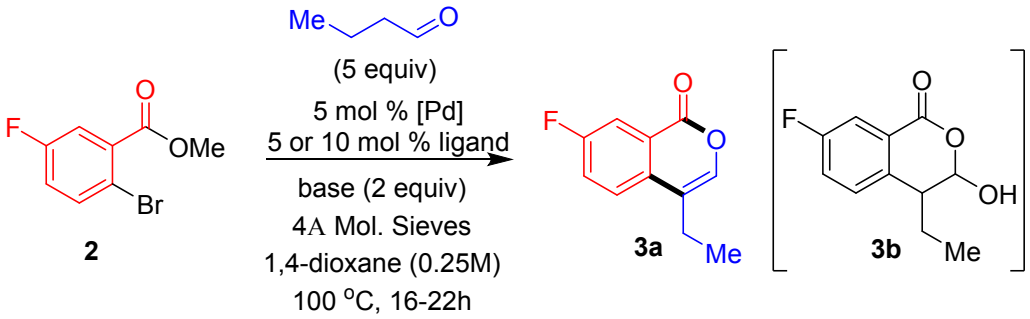
4. NMR Spectra.....25

1. General Considerations

DriSolv solvents were purchased from EMD Millipore corporation. Analytical thin layer chromatography (TLC) was performed using 250 µm Silica Gel 60 F254 pre-coated plates. Flash column chromatography was performed using an Isco with RediSep silica columns. Proton nuclear magnetic resonance (1H NMR) spectra were recorded using a Bruker AVANCE III HD NanoBay 400 NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm), CDCl3 (7.26 ppm), MeOD (3.31 ppm), or $(CD_3)_2SO$ (2.50 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; b, broad; Carbon-13 nuclear magnetic resonance (13C NMR) spectra were recorded using a Bruker AVANCE III HD NanoBay 400 NMR spectrometer at 101 MHz. Chemical shifts are reported in ppm relative to the carbon resonance of CDCl3 (77.23 ppm), MeOD (49.01 ppm), or $(CD_3)_2SO$ (39.58 ppm). High resolution mass spectra (HRMS) are reported as m/z (relative ratio). An Agilent 1260 Infinity Series was used for ESI-TOF analysis (Agilent model 6230). Accurate m/z are reported for the molecular ion [M+H]+ unless stated otherwise. When heating is indicated in procedure, the reaction was performed using an IKA hot plate with an aluminum block and a thermocouple. Hydrogenation was performed using a Thales-Nano H-Cube® Mini continuous flow hydrogenation reactor using 30 mm length catalyst cartridges purchased from the supplier.

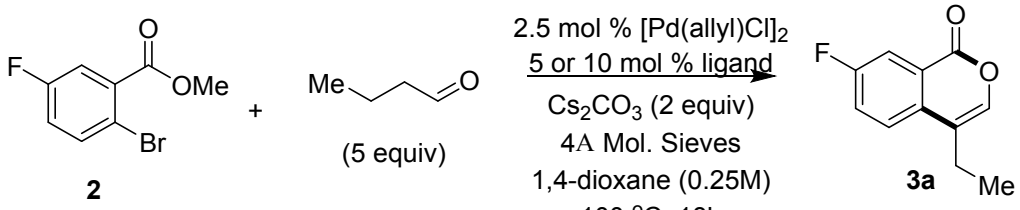
2. Optimization Studies

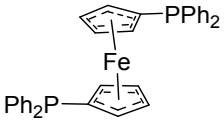
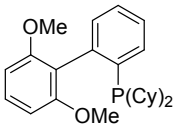
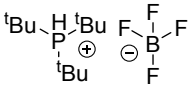
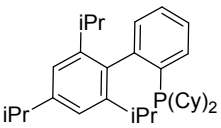
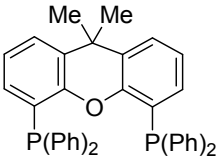
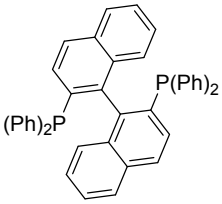
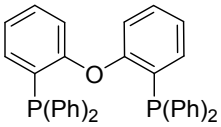
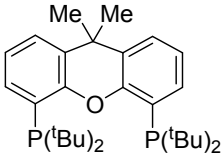
2.1 General Optimization Procedure



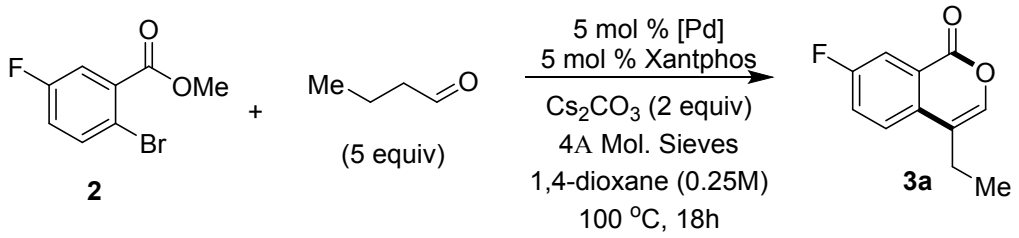
To a 2-dram vial was added [Pd] source (0.010 mmol, 5 mol %), ligand (0.010 mmol, 5 mol % for bidentate ligands, 0.020 mmol; 10 mol % for monodentate ligands), base (0.40 mmol, 2 equiv), 4Å molecular sieves (100 mg) and a magnetic stir bar. The vial was sealed with a Teflon-lined PTFE cap and cycled three times under vacuum and released to argon. The vial was briefly uncapped as methyl 2-bromo-5-fluorobenzoate **2** (29.6 µL, 0.20 mmol, 1.0 equiv) was added by micropipette. The vial was resealed and solvent (0.8 mL) was added followed by butyraldehyde (90 µL, 1.0 mmol, 5.0 equiv). The resulting mixture was stirred in a heated aluminum block at 100 °C for 16–22 h and then allowed to cool to room temperature. The mixture was diluted with EtOAc (approx. 1.5 mL) and filtered through a short plug of celite. The filter cake was washed with EtOAc (5 x 1.5 mL), and the filtrate was concentrated. 4,4'-Difluorobenzophenone (internal standard) and $CDCl_3$ were added. The yield of product **3a** (and **3b**, where appropriate) was determined by ^{19}F NMR spectroscopic analysis.

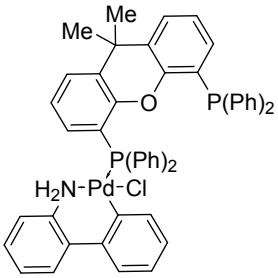
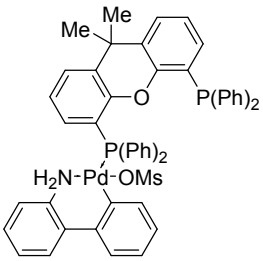
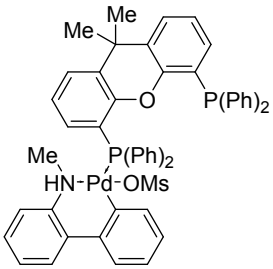
2.2 Investigation of Ligand



entry	*ligand (mol %)*		*yield (%)*
1		dppf (10 mol %)	3
2		SPhos (10 mol %)	11
3		$PtBu_3 \cdot HBF_4$ (10 mol %)	16
4		XPhos (10 mol %)	6
5		Xantphos (5 mol %)	29
6		(rac)-BINAP (5 mol %)	0
7		DPEPhos (5 mol %)	0
8		t-BuXantphos (5 mol %)	0

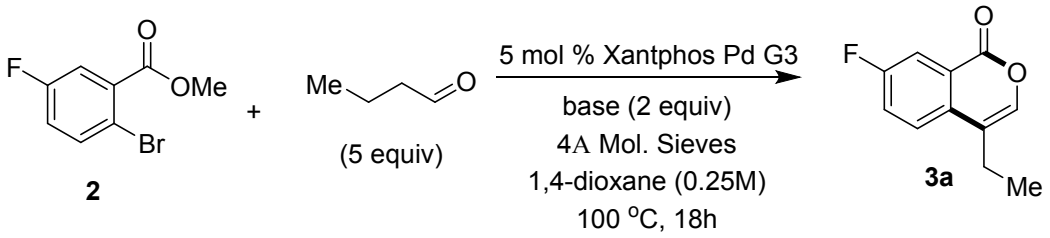
2.3 Investigation of Palladium Source



entry	*Pd Source (mol %)*		*yield (%)*
1	$[Pd(allyl)Cl]_2$ (2.5 mol %)		25
2	$Pd(OAc)_2$ (5 mol %)		46
3	$Pd_2(dba)_3$ (2.5 mol %)		66
4		Xantphos Pd G2[a]	65
5		Xantphos Pd G3[a]	70
6		XantPhos Pd G4[a]	64
7	None		0

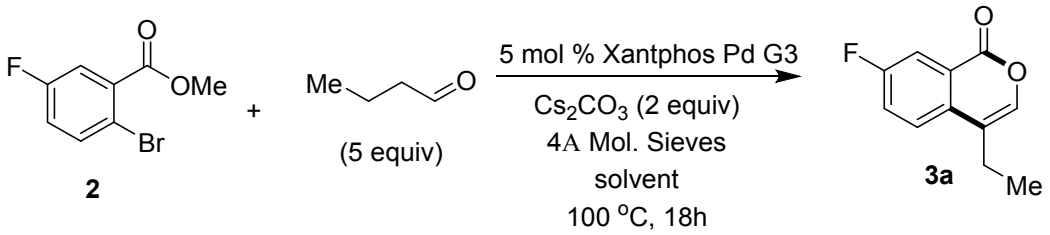
[a] No exogenous Xantphos ligand was added to the vial.

2.4 Investigation of Base



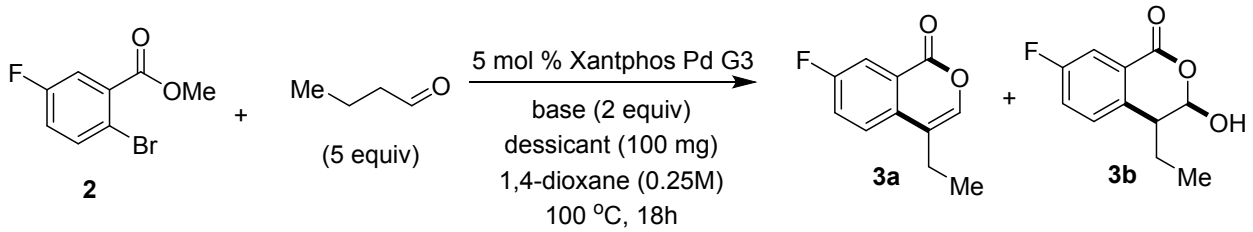
entry	base	yield (%)
1	Cs_2CO_3	73
2	KO^tBu	0
3	K_2CO_3	7
4	K_3PO_4	55
5	Na_2CO_3	0
6	LDA (1 M in hexanes/THF)	0
7	NaH (60% dispersion in mineral oil)	0
8	$LiOH{\cdot}H_2O$	0

2.5 Investigation of Solvent



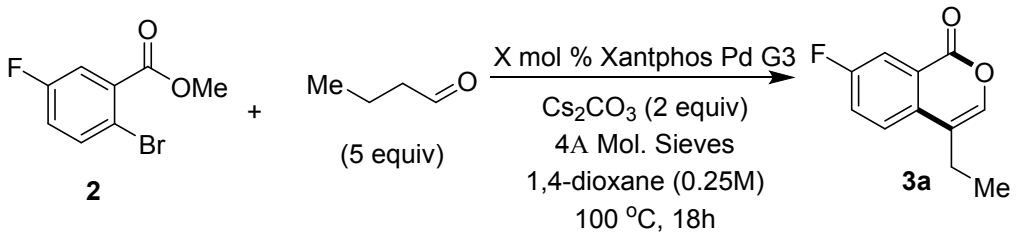
entry	solvent (M)	yield (%)
1	1,4-dioxane (0.25M)	73
2	DMA (0.25M)	53
3	toluene (0.25M)	67
4	MeCN (0.25M)	11
5	cyrene (0.25M)	0
6	1,4-dioxane (0.2M)	61
7	1,4-dioxane (0.33M)	77
8	1,4-dioxane (0.5M)	61

2.6 Investigation of Desiccant



entry	desiccant	yield **3a** (%)	yield **3b** (%)
1	4Å molecular sieves	73	0
2	$MgSO_4$	40	12
3	Na_2SO_4	45	8
4	None	19	25

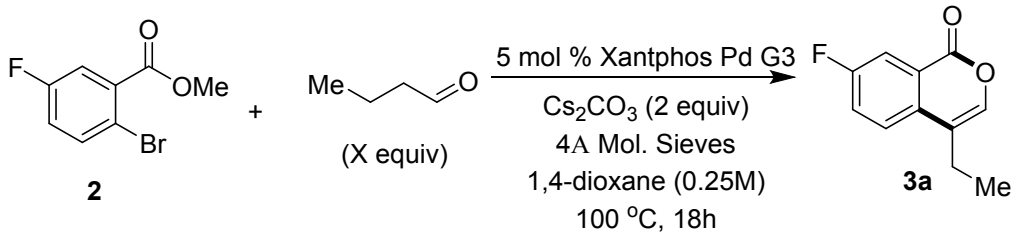
2.7 Investigation of Catalyst Loading



entry	*mol % Xantphos Pd G3*	*yield (%)*[a] *run 1, run 2 (avg.)*
1	5	72, 75 (74)
2	2.5	37, 31 (34)
3	1	19, 24 (22)
4	0.5	7, 15 (11)

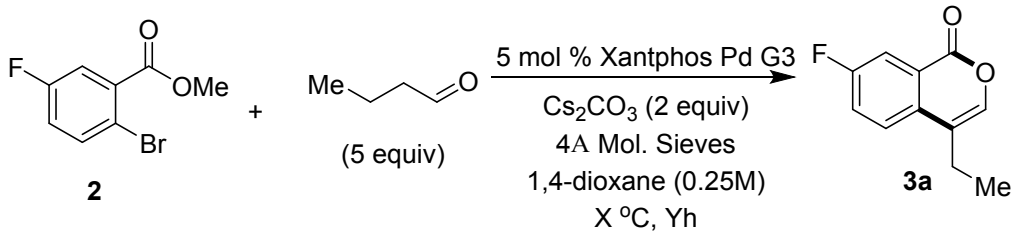
[a] Duplicate reactions at each catalyst loading were performed.

2.8 Investigation of Aldehyde Equivalents



entry	*equiv butyraldehyde*	*yield (%)*
1	10	48
2	7.5	57
3	5	70
4	2.5	39
5	1.25	25

2.9 Investigation of Reaction Time and Temperature

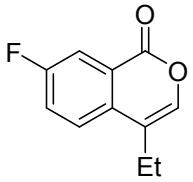


entry	*time (h)*	*temp (°C)*	*yield (%)*
1	1	100	20
2	2	100	34
3	3	100	37
4	4	100	44
5	6	100	48
6	18	100	65
7	18	80	41
8	18	60	26
9	18	rt	0

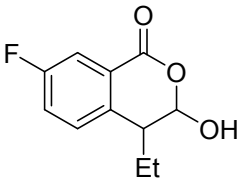
3. Product Characterization

3.1 General Procedure 1:

To a microwave vial was added the solid aryl halide (1.0 mmol, 1.0 equiv), Xantphos Pd G3 (49 mg, 0.05 mmol, 5 mol %), Cs_2CO_3 (652 mg, 2.0 mmol, 2.0 equiv), and 4Å powdered molecular sieves (500 mg). The vial was sealed and evacuated and backfilled with Argon three times. Liquid aryl halides (1.0 mmol, 1.0 equiv) were added at this stage. The corresponding aldehyde or ketone (5 mmol, 5.0 equiv) and 1,4-dioxane (3.0 mL) were added by syringe and the flask placed in a hot plate at 100 °C and stirred for 16 h. The mixture was cooled to room temperature and diluted with EtOAc then filtered to remove solids. The mixture was concentrated and purified by column chromatography (SiO_2, EtOAc/heptane) to afford the final products.



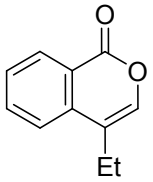
4-Ethyl-7-fluoro-1*H*-isochromen-1-one (3a). Synthesized according to General Procedure 1 from methyl 2-bromo-5-fluorobenzoate (233 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 153 mg, 80% yield; Run 2: 160 mg, 83% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 1H), 7.58 (dd, *J* = 8.9, 4.9 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.10 (d, *J* = 1.3 Hz, 1H), 2.68 – 2.57 (m, 2H), 1.28 (td, *J* = 7.4, 0.9 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -110.79. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.0 (d, *J* = 249.8 Hz), 161.9 (d, *J* = 3.4 Hz), 140.2 (d, *J* = 2.6 Hz), 133.6 (d, *J* = 2.8 Hz), 125.2 (d, *J* = 7.7 Hz), 123.5 (d, *J* = 8.0 Hz), 123.0 (d, *J* = 22.8 Hz), 117.9, 115.8 (d, *J* = 23.1 Hz), 20.7, 13.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_9O_2FH^+$ 193.0665; found 193.0664.



4-Ethyl-7-fluoro-3-hydroxyisochroman-1-one (3b). Synthesized according to General Procedure 1 from methyl 2-bromo-5-fluorobenzoate (233 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol) in the absence of 4Å powdered molecular sieves. Purification by column chromatography

(0-10%-50% EtOAc/heptane) afforded **3a** as the first fraction (36 mg, 19% yield) and **3b** as the second fraction as a colorless oil (54 mg, 25%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.40 (m, 1H), 6.98 (dt, *J* = 8.7, 2.6 Hz, 2H), 5.55 (d, *J* = 1.6 Hz, 1H), 2.78 – 2.52 (m, 1H), 1.50 (s, 1H), 1.28 (s, 1H), 0.68 (t, *J* = 7.4 Hz, 4H). ^{19}F NMR (377 MHz, Chloroform-*d*) δ -113.50. ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.81 (d, *J* = 247.2 Hz), 161.78 (d, *J* = 568.4 Hz), 137.22 (d, *J* = 3.3 Hz), 133.61, 121.48 (d, *J* = 21.9 Hz), 117.48 (d, *J* = 906.7 Hz), 116.57 (d, *J* = 23.2 Hz), 99.14, 44.01, 27.08, 11.45. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{11}O_3FH^+$ 211.0782; found 211.0785.



4-Ethyl-1*H*-isochromen-1-one (4). Synthesized according to General Procedure 1 from methyl 2-bromobenzoate (215 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 149 mg, 80% yield; Run 2: 137 mg, 79% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (dd, J = 7.9, 1.4 Hz, 1H), 7.78 (m, 1H), 7.61 – 7.49 (m, 2H), 7.13 (s, 1H), 2.63 (q, J = 7.4 Hz, 2H), 1.28 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ 162.6, 140.8, 136.9, 134.6, 130.1, 128.2, 122.6, 121.5, 118.3, 20.5, 13.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{10}O_2H^+$ 175.0759; found 175.0766.

From Ar-Cl: Synthesized according to General Procedure 1 from methyl-2-chlorobenzoate (171 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 103 mg, 59% yield; Run 2: 116 mg, 62% yield). Analytical data identical to that above.

From Ar-I: Synthesized according to General Procedure 1 from methyl 2-iodobenzoate (262 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 101 mg, 58% yield; Run 2: 107 mg, 61% yield). Analytical data identical to that above.

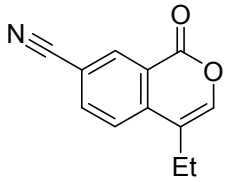
From Ar-OTf: Synthesized according to General Procedure 1 from ethyl 2-(trifluoromethyl sulfonyloxy)benzoate (Run 1: 335 mg, 1.12 mmol, Run 2: 298 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as an off-white solid (Run 1: 128 mg, 65% yield; Run 2: 118 mg, 68% yield). Analytical data identical to that above.

From ethyl ester: Synthesized according to General Procedure 1 from ethyl 2-bromobenzoate (229 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column

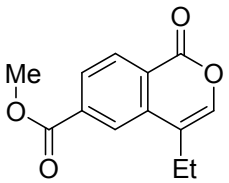
chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 127 mg, 73% yield; Run 2: 135 mg, 78% yield). Analytical data identical to that above.

From isopropyl ester: Synthesized according to General Procedure 1 from isopropyl 2-bromobenzoate (243 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 146 mg, 84% yield; Run 2: 174 mg, 77% yield). Analytical data identical to that above.

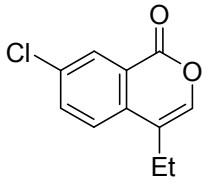
From tert-butyl ester: Synthesized according to General Procedure 1 from *tert*-butyl 2-bromobenzoate (257 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 140 mg, 80% yield; Run 2: 134 mg, 77% yield). Analytical data identical to that above.



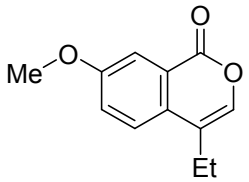
4-Ethyl-1-oxo-1*H*-isochromene-7-carbonitrile (5). Synthesized according to General Procedure 1 from methyl 2-bromo-5-cyanobenzoate (240 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-30% EtOAc/heptane) afforded the product as a yellow solid (Run 1: 103 mg, 52% yield; Run 2: 101 mg, 51% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.63 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.99 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.67 (dd, *J* = 8.3, 0.6 Hz, 1H), 7.24 (s, 1H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.30 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.5, 143.6, 140.3, 136.8, 134.6, 123.8, 122.1, 117.7, 117.5, 111.9, 20.4, 13.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_9NO_2H^+$ 200.0712; found 200.0710.



Methyl 4-ethyl-1-oxo-1*H*-isochromene-6-carboxylate (6). Synthesized according to General Procedure 1 from dimethyl 2-bromoterephthalate (273 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-30% EtOAc/heptane) afforded the product as a-white solid (Run 1: 190 mg, 82% yield; Run 2: 178 mg, 77% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (dd, *J* = 8.2, 0.6 Hz, 1H), 8.23 (dd, *J* = 1.6, 0.6 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.17 (t, *J* = 1.3 Hz, 1H), 4.00 (s, 3H), 2.68 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.31 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.9, 161.8, 141.4, 137.0, 135.4, 130.4, 128.4, 124.5, 124.2, 118.2, 52.8, 20.4, 13.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{12}O_4H^+$ 233.0814; found 233.0818.

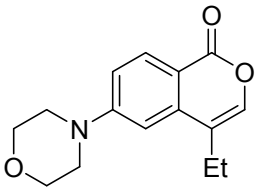


7-Chloro-4-ethyl-1*H*-isochromen-1-one (7). Synthesized according to General Procedure 1 from methyl 2-bromo-5-chlorobenzoate (249 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). The reaction was run at 70 °C for 16 hours. Purification by column chromatography (0-20% EtOAc/heptane) afforded the product as a-white solid (Run 1: 164 mg, 79% yield; Run 2: 154 mg, 74% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (d, J = 2.3 Hz, 1H), 7.72 (dd, J = 8.6, 2.3 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.12 (t, J = 1.3 Hz, 1H), 2.61 (qd, J = 7.5, 1.3 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.4, 141.0, 135.3, 134.9, 134.1, 129.5, 124.3, 122.8, 117.8, 20.4, 13.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_9O_2ClH^+$ 209.0369; found 209.0368.

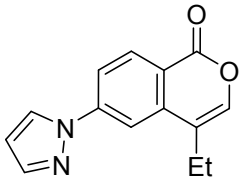


4-Ethyl-7-methoxy-1*H*-isochromen-1-one (8). Synthesized according to General Procedure 1 from methyl 2-bromo-5-methoxybenzoate (Run 1: 245 mg, 1.0 mmol; Run 2: 267 mg, 1.09 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as a-white solid (Run 1: 151 mg, 74% yield; Run 2: 165 mg, 81% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 2.8 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.06 (t, *J* = 1.3 Hz, 1H), 3.92 (s, 3H), 2.61 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.27 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.8, 159.3, 138.8, 130.6, 124.3, 124.1, 122.7, 118.2, 110.6, 55.7, 20.5, 13.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}O_3H^+$ 205.0865; found 205.0863.

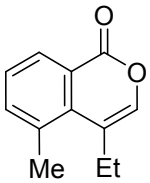
Synthesized according to General Procedure 1 in a 100 mL RBF from methyl 2-bromo-5-methoxybenzoate (3.2g, 13.1 mmol), Xantphos Pd G3 (568 mg, 0.6 mmol), Cs_2CO_3 (7.8 g, 24 mmol), 4Å powdered molecular sieves (5 g) and butyraldehyde (5.4 mL, 60 mmol) in1,4-dioxane (40 mL).Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as a-white solid (1.89g, 71% yield).



4-Ethyl-6-morpholino-1*H*-isochromen-1-one (9). Synthesized according to General Procedure 1 from methyl 2-chloro-4-morpholinobenzenecarboxylate (255 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as a pale yellow solid (Run 1: 151 mg, 58% yield; Run 2: 140 mg, 54% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.07 (t, *J* = 1.3 Hz, 1H), 7.03 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 3.97 – 3.83 (m, 4H), 3.46 – 3.32 (m, 4H), 2.56 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.27 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.6, 155.2, 141.3, 138.6, 131.8, 118.0, 114.8, 112.2, 105.0, 66.5, 47.4, 20.5, 13.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{15}H_{17}NO_3H^+$ 260.1287; found 260.1290.

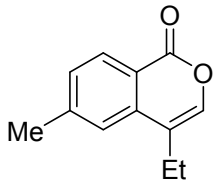


4-Ethyl-6-(1*H*-pyrazol-1-yl)-1*H*-isochromen-1-one (10). Synthesized according to General Procedure 1 from methyl 2-chloro-4-(1*H*-pyrazol-1-yl)benzoate (236 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-50% EtOAc/heptane) afforded the product as a-white solid (Run 1: 173 mg, 72% yield; Run 2: 172 mg, 72% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 2.6 Hz, 1H), 7.96 (d, *J* = 2.1 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.17 (t, *J* = 1.3 Hz, 1H), 6.57 (dd, *J* = 2.6, 1.8 Hz, 1H), 2.69 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.32 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.9, 144.5, 142.5, 141.8, 138.7, 132.1, 127.1, 119.0, 118.1, 118.0, 111.9, 109.0, 20.5, 13.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{12}N_2O_2H^+$ 241.0977; found 241.0978.

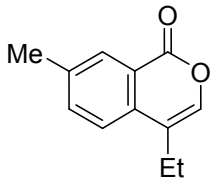


4-Ethyl-5-methyl-1*H*-isochromen-1-one (11). Synthesized according to General Procedure 1 from methyl 2-bromo-3-methylbenzoate (229 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 93 mg, 49% yield; Run 2: 94 mg, 50% yield). ^{1}H NMR (400 MHz, Chloroform-*d*)

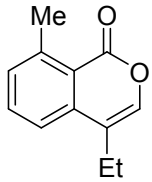
δ 8.33 – 8.26 (m, 1H), 7.57 – 7.49 (m, 1H), 7.46 – 7.37 (m, 1H), 7.05 (s, 1H), 2.79 (qd, *J* = 7.4, 1.3 Hz, 2H), 2.72 (s, 3H), 1.22 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.1, 141.0, 138.8, 135.6, 133.9, 128.9, 127.9, 122.9, 119.4, 24.2, 23.2, 15.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}O_2H^+$ 189.0916; found 189.0912.



4-Ethyl-6-methyl-1*H*-isochromen-1-one (12). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 234 mg, 1.02 mmol; Run 2: 231 mg, 1.0 mmol) and butyraldehyde (Run 1: 0.46 mL, 5.1 mmol; Run 2: 0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 172 mg, 89% yield; Run 2: 166 mg, 88% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.11 (s, 1H), 2.61 (qd, *J* = 7.4, 1.2 Hz, 2H), 2.52 (s, 3H), 1.28 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.7, 145.7, 140.9, 137.0, 130.1, 129.5, 122.7, 119.1, 118.2, 22.3, 20.5, 13.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}O_2H^+$ 189.0916; found 189.0919.

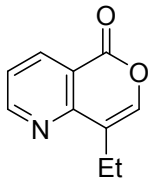


4-ethyl-7-methyl-1*H*-isochromen-1-one (13). Synthesized according to General Procedure 1 from methyl 2-bromo-5-methylbenzoate (Run 1: 247 mg, 1.08 mmol; Run 2: 229 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a-white solid (Run 1: 167 mg, 82% yield; Run 2: 143 mg, 76% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.03 (m, 1H), 7.60 – 7.53 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.06 (s, 1H), 2.59 (qd, *J* = 7.5, 1.3 Hz, 2H), 2.46 (s, 3H), 1.25 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.8, 140.0, 138.4, 135.8, 134.4, 129.8, 122.5, 121.4, 118.3, 21.3, 20.5, 13.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}O_2H^+$ 189.0916; found 189.09012.

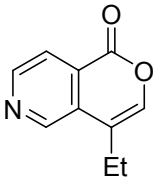


4-Ethyl-8-methyl-1*H*-isochromen-1-one (14). Synthesized according to General Procedure 1 from methyl 2-bromo-6-methylbenzoate (229 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0

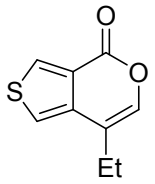
mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a-white solid (Run 1: 117 mg, 62% yield; Run 2: 130 mg, 69% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (t, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32 (dt, *J* = 7.4, 1.0 Hz, 1H), 7.08 (s, 1H), 2.84 (s, 3H), 2.58 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.26 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.9, 144.0, 140.7, 138.4, 133.8, 131.2, 120.5, 120.0, 118.1, 23.7, 20.8, 13.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{12}O_2H^+$ 189.0916; found 189.0915.



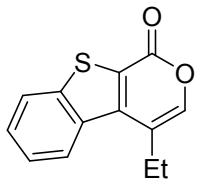
8-Ethyl-5*H*-pyrano[4,3-*b*]pyridin-5-one (15). Synthesized according to General Procedure 1 from methyl 2-chloronicotinate (172 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). The reaction was run at 70 °C for 16 hours. Purification by column chromatography (0-50% EtOAc/heptane) afforded the product as a-white solid (Run 1: 96 mg, 55% yield; Run 2: 106 mg, 61% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.98 (dd, *J* = 4.7, 1.9 Hz, 1H), 8.56 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.46 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.33 (t, *J* = 1.3 Hz, 1H), 2.77 (qd, *J* = 7.5, 1.3 Hz, 2H), 1.28 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.6, 155.5, 154.0, 144.3, 137.8, 123.1, 121.3, 118.0, 19.6, 13.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_9NO_2H^+$ 176.0712; found 176.0710.



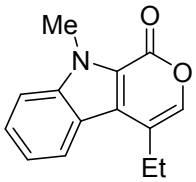
4-Ethyl-1*H*-pyrano[4,3-*c*]pyridin-1-one (16). Synthesized according to General Procedure 1 from methyl 3-bromoisonicotinate (216 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-50% EtOAc/heptane) afforded the product as a-white solid (Run 1: 101 mg, 58% yield; Run 2: 89 mg, 51% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 0.9 Hz, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 8.10 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.19 (t, *J* = 1.3 Hz, 1H), 2.72 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.33 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.9, 148.8, 146.1, 142.2, 130.5, 127.1, 121.6, 116.7, 19.9, 13.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_9NO_2H^+$ 176.0712; found 176.0711.



7-Ethyl-4*H*-thieno[3,4-*c*]pyran-4-one (17). Synthesized according to General Procedure 1 from methyl 4-bromothiophene-3-carboxylate (221 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as an orange solid (Run 1: 100 mg, 56% yield; Run 2: 101 mg, 56% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (d, *J* = 3.1 Hz, 1H), 7.33 (d, *J* = 3.1 Hz, 1H), 6.88 (s, 1H), 2.55 (qd, *J* = 7.5, 1.4 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.6, 138.8, 137.7, 133.8, 125.8, 117.5, 116.7, 21.3, 12.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_9H_8O_2SH^+$ 181.0323; found 181.0323.

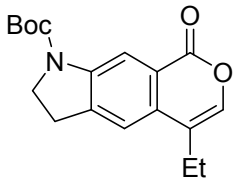


4-Ethyl-1*H*-benzo[4,5]thieno[2,3-*c*]pyran-1-one (18). Synthesized according to General Procedure 1 from methyl 3-chlorobenzo[*b*]thiophene-2-carboxylate (227 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as a pale yellow-white solid (Run 1: 183 mg, 79% yield; Run 2: 183 mg, 79% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 – 8.22 (m, 1H), 8.02 – 7.94 (m, 1H), 7.59 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.53 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 7.31 (t, *J* = 1.2 Hz, 1H), 2.98 (qd, *J* = 7.4, 1.3 Hz, 2H), 1.38 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.4, 143.5, 143.3, 142.1, 134.7, 128.3, 125.7, 125.5, 125.2, 123.7, 119.3, 22.2, 13.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{10}O_2SH^+$ 231.0480; found 231.0481.

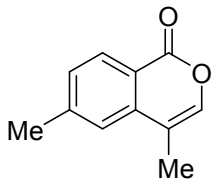


4-Ethyl-9-methylpyrano[3,4-*b*]indol-1(9*H*)-one (19). Synthesized according to General Procedure 1 from ethyl 3-bromo-1-methyl-1*H*-indole-2-carboxylate (282 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) afforded the product as an off-white solid (Run 1: 173 mg, 76% yield; Run 2: 193 mg, 85% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.96 (m, 1H), 7.59 – 7.48 (m, 2H), 7.30 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1H), 7.14 (t, *J* = 1.2 Hz, 1H), 4.25 (s, 3H), 2.92 (qd, *J* = 7.4, 1.2 Hz, 2H),

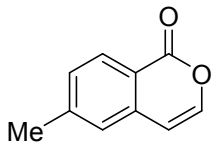
1.38 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.7, 141.1, 138.6, 127.4, 124.5, 123.0, 121.7, 121.1, 120.9, 119.3, 110.7, 31.3, 21.9, 13.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{13}NO_2H^+$ 228.1025; found 228.1024.



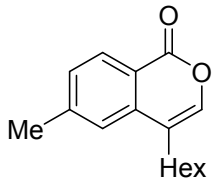
***tert*-Butyl 5-ethyl-8-oxo-3,8-dihydropyrano[4,3-*f*]indole-1(2*H*)-carboxylate (20).** Synthesized according to General Procedure 1 from 1-(*tert*-butyl) 6-methyl 5-bromoindoline-1,6-dicarboxylate (356 mg, 1.0 mmol) and butyraldehyde (0.45 mL, 5.0 mmol). Purification by column chromatography (0-50% EtOAc/heptane) afforded the product as a yellow solid (Run 1: 272 mg, 86% yield; Run 2: 253 mg, 80% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (br m, 1H; mixture of rotamers), 7.28 (s, 1H, overlaps with $CHCl_3$), 7.01 (s, 1H), 4.06 (t, *J* = 8.7 Hz, 2H), 3.23 (td, *J* = 8.7, 1.3 Hz, 2H), 2.66 – 2.43 (m, 2H), 1.62 (br s, 9H), 1.25 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6/Pyridine-d_5) δ 162.2, 152.0, 143.3, 141.1, 140.1, 132.1, 120.5, 119.8, 118.3, 112.7, 81.1, 47.9, 28.4, 27.6, 20.2, 13.7. HRMS (ESI-) m/z: $[M-H]^-$ calculated for $C_{18}H_{20}NO_4^-$ 314.1392; found 314.1387; (ESI+) m/z: [M-tBu+2H] calculated for $C_{14}H_{12}NO_4H_2^+$ 260.0923; found 260.0894.



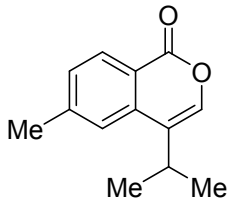
4,6-Dimethyl-1H-isochromen-1-one (21). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 261 mg, 1.1 mmol; Run 2: 230 mg, 1.0 mmol) and propionaldehyde (Run 1: 0.41 mL, 5.7 mmol; Run 2: 0.36 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 89 mg, 45% yield; Run 2: 78 mg, 45% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.28 (s, 1H), 7.14 – 7.09 (m, 1H), 2.52 (s, 3H), 2.15 (d, *J* = 1.2 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 162.7, 145.7, 141.2, 137.6, 129.9, 129.6, 123.1, 119.0, 112.7, 22.2, 12.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{11}H_{10}O_2H^+$ 175.0759; found 175.0757.



6-Methyl-1H-isochromen-1-one (22). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 248 mg, 1.08 mmol; Run 2: 238 mg, 1.04 mmol) and acetaldehyde (Run 1: 0.3 mL, 5.4 mmol; Run 2: 0.3 mL, 5.2 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as an off-white solid (Run 1: 47 mg, 27% yield; Run 2: 39 mg, 24% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.19 (m, 2H), 6.44 (d, *J* = 5.6 Hz, 1H), 2.48 (s, 3H). 13C NMR (101 MHz, Chloroform-d) δ 162.3, 145.9, 144.8, 136.6, 129.9, 129.6, 125.6, 119.5, 106.9, 22.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{10}H_8O_2H^+$ 161.0603; found 161.0607.

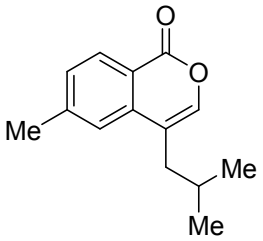


4-Hexyl-6-methyl-1H-isochromen-1-one (23). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 233 mg; Run 2: 233 mg, 1.02 mmol) and octanal (0.80 mL, 5.1 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 198 mg, 80% yield; Run 2: 203 mg, 82% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.09 (s, 1H), 2.57 – 2.49 (m, 5H), 1.62 (p, *J* = 7.5 Hz, 2H), 1.46 – 1.22 (m, 6H), 0.95 – 0.87 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.6, 145.6, 141.2, 137.0, 130.1, 129.4, 122.8, 119.2, 116.8, 31.6, 29.1, 28.6, 27.3, 22.6, 22.3, 14.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{20}O_2H^+$ 245.1542; found 245.1550.

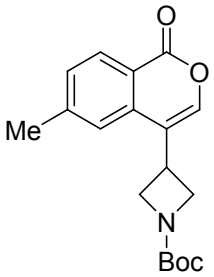


4-Isopropyl-6-methyl-1H-isochromen-1-one (24). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 240 mg, 1.05 mmol; Run 2: 230 mg, 1.0 mmol) and isovaleraldehyde (Run 1: 0.56 mL, 5.2 mmol; Run 2: 0.54 mL, 5.0 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 137 mg, 65% yield; Run 2: 130 mg, 64% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.39 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.11 (d, *J* = 0.8 Hz, 1H), 3.12 (hept, *J* = 7.1 Hz, 1H),

2.52 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.6, 145.5, 140.5, 136.7, 130.2, 129.3, 122.5, 122.5, 119.2, 25.7, 22.4, 22.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{13}H_{14}O_2H^+$ 203.1072; found 203.1074.

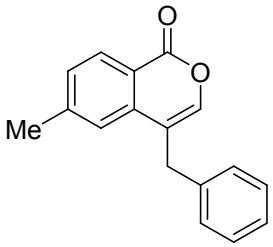


4-Isobutyl-6-methyl-1H-isochromen-1-one (25). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 230 mg, 1.0 mmol; Run 2: 280 mg, 1.2 mmol) and 4-methylpentanal (Run 1: 0.62 mL, 5.0 mmol; Run 2: 0.76 mL, 6.1 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as an off-white solid (Run 1: 162 mg, 74% yield; Run 2: 203 mg, 77% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.26 (m, 2H), 7.07 (s, 1H), 2.51 (s, 3H), 2.39 (d, *J* = 7.1 Hz, 2H), 1.93 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 6H), ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.7, 145.6, 141.9, 137.1, 130.2, 129.4, 123.1, 119.2, 115.7, 36.6, 27.2, 22.5, 22.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}O_2H^+$ 217.1229; found 217.1231.

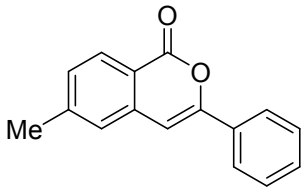


***tert*-Butyl 3-(6-methyl-1-oxo-1H-isochromen-4-yl)azetidine-1-carboxylate (26)**. Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 232 mg, 1.0 mmol) and *tert*-butyl 3-(2-oxoethyl)azetidine-1-carboxylate (1.0 g, 5.0 mmol). Purification by column chromatography (0-40% EtOAc/heptane) provided the product with impurities. The mixture was adsorbed on silica and purified by column chromatography (30% EtOAc/heptane) to afford the product as a colorless oil (Run 1: 243 mg, 76% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.22 (s, 1H), 7.06 (s, 1H), 4.37 (t, *J* = 8.5 Hz, 2H), 4.08 – 3.99 (m, 2H), 3.94 – 3.82 (m, 1H), 2.51 (s, 3H), 1.46 (s, 9H).^{13}C NMR (101 MHz,

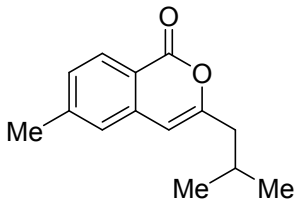
Chloroform-*d*) δ 161.9, 156.1, 146.1, 141.6, 135.7, 130.5, 130.1, 122.3, 119.0, 116.2, 80.0, 28.4, 27.1, 22.4. (ESI+) m/z: [M-tBu+2H] calculated for $C_{14}H_{12}NO_4H_2^+$ 260.0923; found 260.0905.



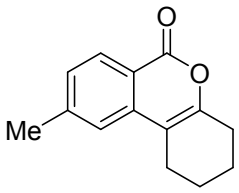
4-Benzyl-6-methyl-1H-isochromen-1-one (27). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 236 mg, 1.03 mmol; Run 2: 234 mg, 1.02 mmol) and 3-phenylpropionaldehyde (Run 1: 0.68 mL, 5.2 mmol; Run 2: 0.67 mL, 5.1 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 203 mg, 79% yield; Run 2: 204 mg, 80% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.41 – 7.28 (m, 3H), 7.26 – 7.20 (m, 4H), 7.05 (s, 1H), 3.90 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.4, 145.7, 143.0, 137.8, 136.8, 130.1, 129.6, 128.7, 128.5, 126.8, 123.4, 119.1, 115.7, 33.5, 22.2. (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{14}O_2H^+$ 251.1072; found 251.1080.



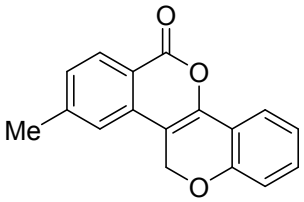
6-Methyl-3-phenyl-1H-isochromen-1-one (28). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 231 mg, 1.0 mmol; Run 2: 243 mg, 1.06 mmol) and acetophenone (Run 1: 0.59 mL, 5.0 mmol; Run 2: 0.62 mL, 5.3 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 175 mg, 73% yield; Run 2: 199 mg, 79% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 8.0 Hz, 1H), 7.94 – 7.85 (m, 2H), 7.51 – 7.40 (m, 3H), 7.35 – 7.29 (m, 2H), 6.91 (s, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.4, 153.6, 146.0, 137.6, 132.1, 129.9, 129.6, 129.6, 128.8, 126.0, 125.2, 118.1, 101.8, 22.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{16}H_{12}O_2H^+$ 237.0916; found 237.0920.



3-Isobutyl-6-methyl-1H-isochromen-1-one (29). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 254 mg, 1.1 mmol; Run 2: 250 mg, 1.1 mmol) and 4-methyl-2-pentanone (Run 1: 0.69 mL, 5.5 mmol; Run 2: 0.68 mL, 5.5 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a colorless oil (Run 1: 117 mg, 49% yield; Run 2: 138 mg, 59% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.15 (s, 1H), 6.18 (s, 1H), 2.46 (s, 3H), 2.37 (d, *J* = 7.2 Hz, 2H), 2.21 – 2.08 (m, 1H), 0.97 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.2, 157.3, 145.8, 137.7, 129.4, 129.0, 125.0, 117.7, 103.9, 42.8, 26.6, 22.2, 22.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{16}O_2H^+$ 217.1229; found 217.1234.

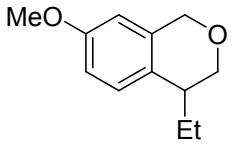


9-Methyl-1,2,3,4-tetrahydro-6H-benzo[c]chromen-6-one (30). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 230 mg, 1.0 mmol; Run 2: 243 mg, 1.06 mmol) and cyclohexanone (Run 1: 0.52 mL, 5.0 mmol; Run 2: 0.55 mL, 5.3 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 137 mg, 64% yield; Run 2: 144 mg, 63% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.21 (s, 1H), 2.63 – 2.52 (m, 4H), 2.48 (s, 3H), 1.95 – 1.78 (m, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 162.8, 152.4, 145.5, 138.1, 129.7, 128.4, 121.5, 118.1, 109.2, 27.4, 22.7, 22.2, 22.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{14}H_{14}O_2H^+$ 215.1072; found 215.1080.

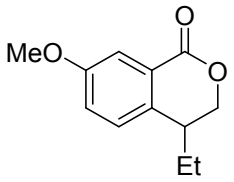


9-Methyl-6H,11H-isochromeno[4,3-c]chromen-6-one (31). Synthesized according to General Procedure 1 from methyl 2-bromo-4-methylbenzoate (Run 1: 231 mg, 1.0 mmol: Run 2: 241 mg, 1.05 mmol) and 4-chromanone (Run 1: 747 mg, 5.0 mmol; Run 2: 780 mg, 5.3 mmol). Purification by column chromatography (0-10% EtOAc/heptane) afforded the product as a white solid (Run 1: 230 mg, 86% yield; Run 2: 212 mg, 76% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 8.1 Hz, 1H), 7.75 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.38 – 7.26 (m, 2H), 7.10 (s, 1H), 7.04 (td, *J* = 7.6, 1.0 Hz, 1H), 6.93 (dd, *J* = 8.2, 0.8 Hz, 1H), 5.41 (s, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.4, 155.0, 146.3, 144.9, 134.3, 131.3, 130.6, 129.3, 122.7, 121.9, 121.1, 118.4, 116.9, 116.2, 103.5, 64.1, 22.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{17}H_{12}O_3H^+$ 265.0865; found 265.0871.

Functionalization Reactions:

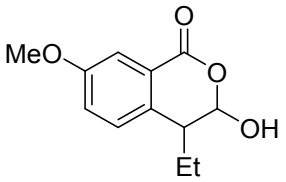


4-Ethyl-7-methoxyisochromane (32). Isocoumarin **8** (204 mg, 1.0 mmol) was placed in a 5 mL reaction vial and evacuated and backfilled with N_2 three times. THF (2 mL) was added by syringe followed by $NaBH_4$ (57 mg, 1.5 mmol). The vial was resealed and heated to 65 °C for 18 hours. The reaction was allowed to cool and poured into aqueous NH_4Cl (20 mL). Product was extracted with EtOAc (15 ml x 3) and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Purification by column chromatography (0-60% EtOAc/heptane) afforded the product as a white solid (126 mg, 65% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.15 (m, 1H), 6.94 – 6.85 (m, 2H), 4.91 – 4.79 (m, 1H), 4.41 (t, *J* = 10.8 Hz, 1H), 3.94 – 3.83 (m, 1H), 3.81 (s, 3H), 3.55 (q, *J* = 10.2 Hz, 1H), 3.14 – 2.99 (m, 1H), 1.75 – 1.65 (m, 2H), 0.81 (d, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.7, 141.2, 133.5, 127.0, 114.6, 114.5, 68.0, 63.5, 55.2, 43.6, 25.1, 12.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{16}O_2H^+$ 193.1229; found 193.1238.

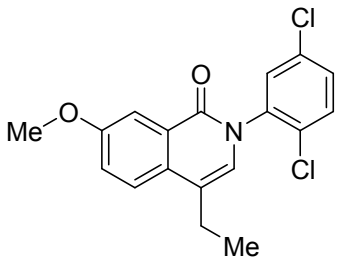


4-Ethyl-7-methoxyisochroman-1-one (33). Isocoumarin **8** (204 mg, 1.0 mmol) was placed in a 20 mL scintillation vial. EtOAc (10 mL) was added and the solution was hydrogenated in a Thales-Nano H-Cube® Mini continuous flow hydrogenation reactor using a 20% $Pd(OH)_2$/C cartridge at a H_2 pressure of 20 bar at 70 °C for 2 hours in a continuous loop-flow manner. Purification by column chromatography (0-60% EtOAc/heptane) afforded the product as a white solid (180 mg, 87% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 2.7 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.52 (dd, *J* = 11.1, 3.5 Hz, 1H), 4.44 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.84 (s, 3H), 2.72 (tt, *J* = 7.2, 3.3 Hz, 1H), 1.77 – 1.68 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz,

Chloroform-*d*) δ 165.2, 158.9, 136.0, 128.2, 125.2, 121.5, 112.9, 70.7, 55.6, 38.2, 25.8, 11.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{14}O_3H^+$ 207.1021; found 207.1024.

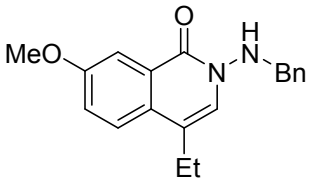


4-Ethyl-3-hydroxy-7-methoxyisochroman-1-one (34). Isocoumarin **8** (540 mg, 2.6 mmol) was placed in a 5 mL reaction vial and dissolved in EtOH (5.4 mL). A solution of LiOH (100 mg, 4.2 mmol) in water (1.0 mL) was added and the reaction stirred at rt for 3 hours. The reaction was then poured into aqueous NH_4Cl (30 mL). Product was extracted with EtOAc (20 ml x 3) and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Purification by column chromatography (0-60% EtOAc/heptane) afforded the product as a colorless oil which solidified on standing (490 mg, 83% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (s, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 7.16 – 7.10 (m, 1H), 5.83 (s, 1H), 3.84 (s, 3H), 2.90 (t, *J* = 7.4 Hz, 1H), 1.90 – 1.70 (m, 1H), 1.70 – 1.49 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.2, 159.0, 133.5, 130.0, 124.7, 122.0, 113.0, 98.9, 55.7, 43.9, 27.2, 11.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{12}H_{14}O_4H^+$ 223.0970; found 223.0978.



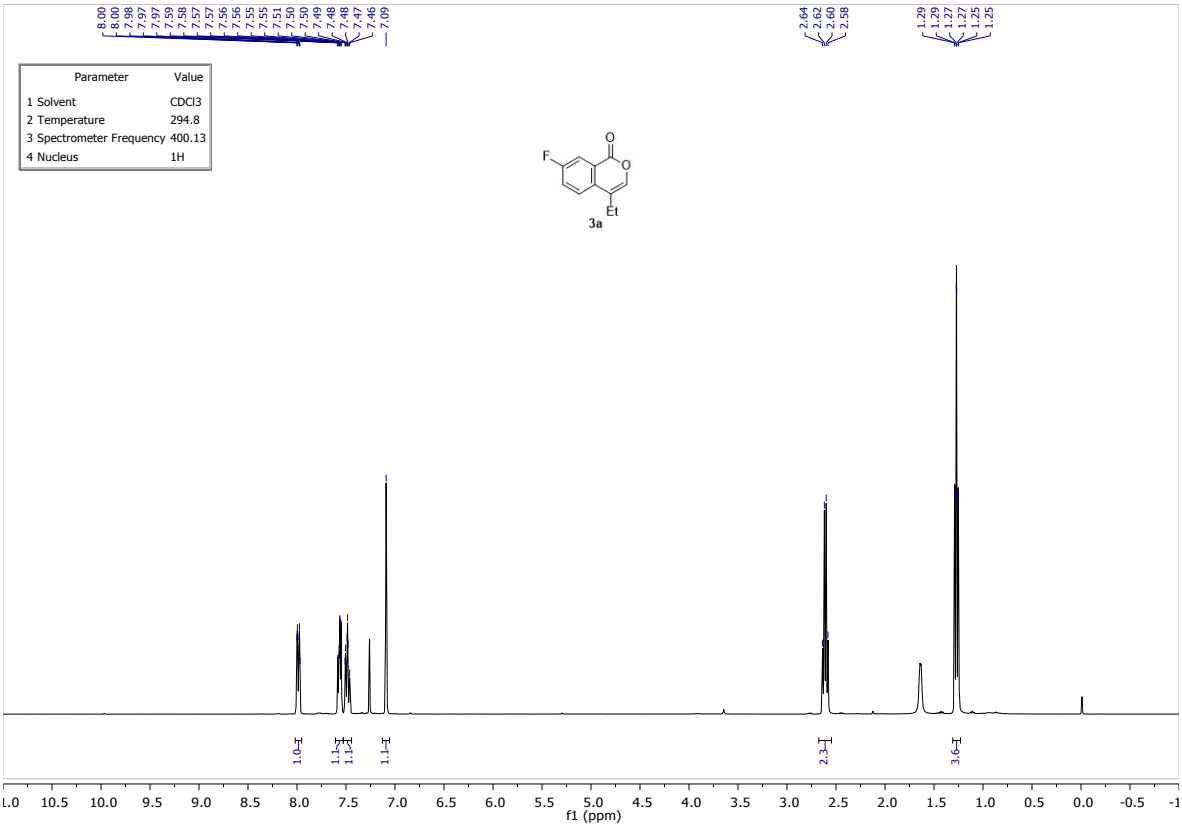
2-(2,5-Dichlorophenyl)-4-ethyl-7-methoxyisoquinolin-1(2H)-one (35). Hydroxy-isochromanone **34** (111 mg, 0.5 mmol) was placed in a 5 mL reaction vial and dissolved in AcOH (1 mL). 2,5-Dichloroaniline (121 mg, 0.75 mmol) was added and the reaction was heated to 90 °C for 3 hours. The reaction was allowed to cool and then poured into aqueous $NaHCO_3$ (10 mL). Product was extracted with CH_2Cl_2 (10 ml x 3) and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Purification by column chromatography (0-60% EtOAc/heptane) afforded the product as a white solid (108 mg, 62% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 2.8 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.42 – 7.33 (m, 2H), 6.68 (s, 1H), 3.94 (s, 3H), 2.74 (qd, *J* = 7.5, 1.2 Hz, 2H), 1.30 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.9, 158.8, 139.9, 133.2, 131.3, 130.9, 130.8, 130.0, 129.9,

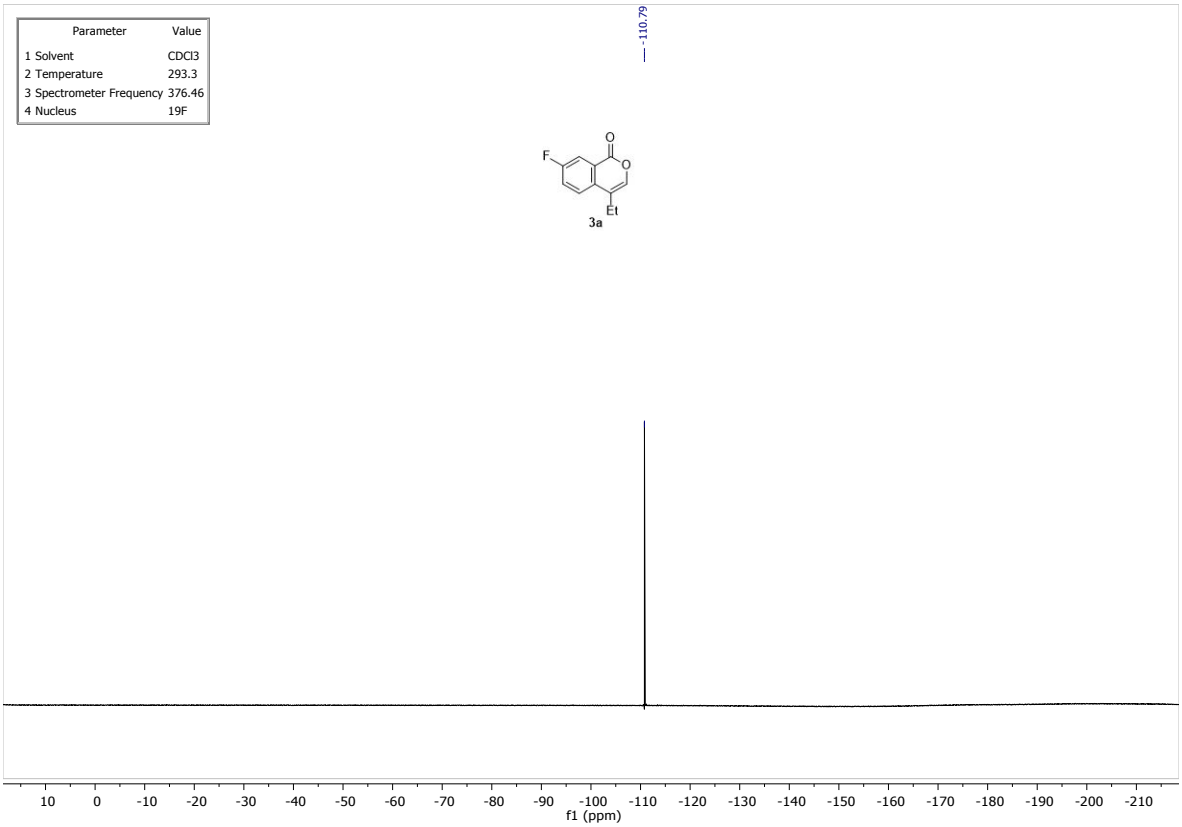
127.4, 125.5, 124.7, 123.0, 118.5, 108.8, 55.6, 22.4, 13.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{18}H_{15}Cl_2NO_2H^+$ 348.0558; found 348.0568.

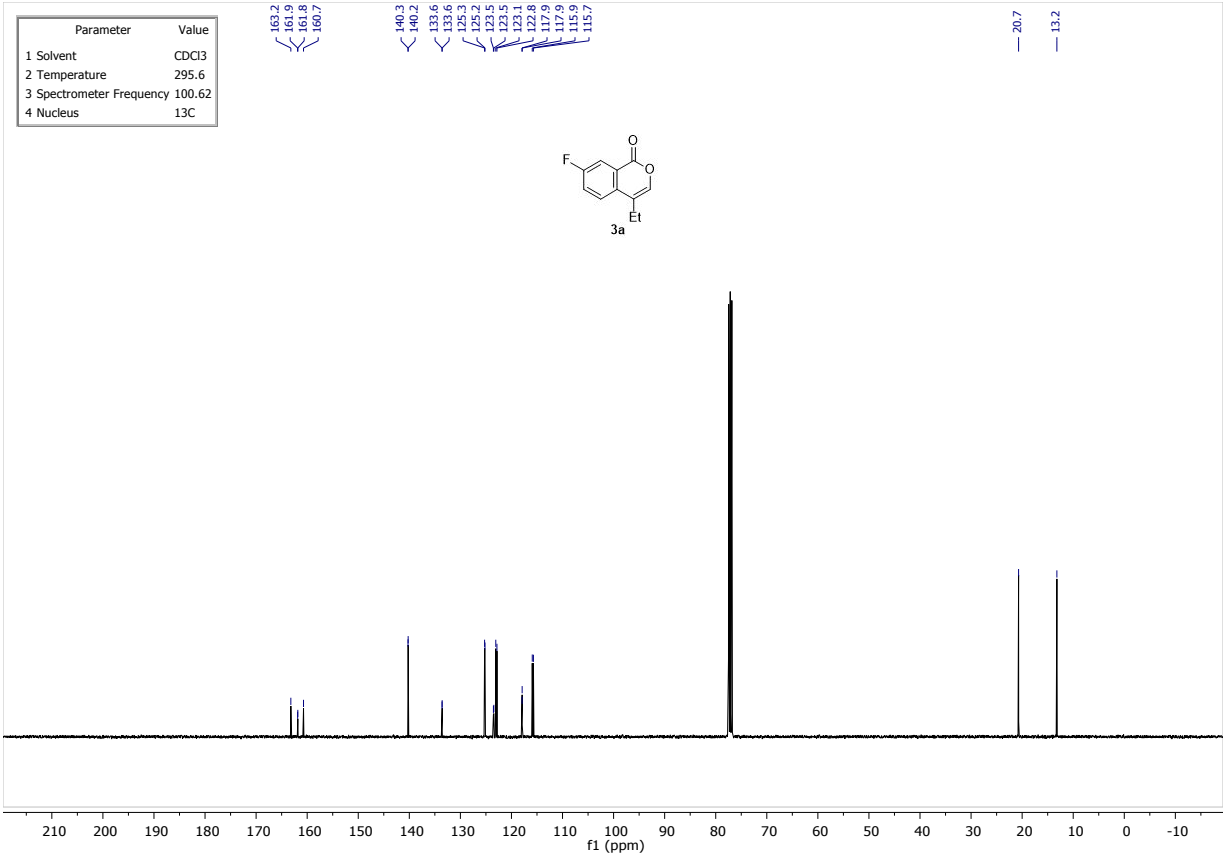


2-(Benzylamino)-4-ethyl-7-methoxyisoquinolin-1(2H)-one (36). Hydroxy-isochromanone **34** (166 mg, 0.75 mmol) was placed in a 5 mL reaction vial and dissolved in AcOH (1 mL). Benzylhydrazine dihydrochloride (219 mg, 1.125 mmol) was added and the reaction was heated to 90 °C for 3 hours. The reaction was allowed to cool and then poured into aqueous $NaHCO_3$ (10 mL). Product was extracted with EtOAc (10 ml x 3) and the combined organic phases were washed with brine (20 mL) and dried over $MgSO_4$. Purification by column chromatography (0-60% EtOAc/heptane) afforded the product as a white solid (183 mg, 79% yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 2.8 Hz, 1H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.38 – 7.28 (m, 4H), 6.87 (s, 1H), 6.31 (t, *J* = 5.7 Hz, 1H), 4.19 (d, *J* = 5.6 Hz, 2H), 3.95 (s, 3H), 2.63 (qd, *J* = 7.4, 1.1 Hz, 2H), 1.17 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.3, 158.4, 136.5, 130.5, 129.4, 128.6, 127.9, 127.0, 126.9, 124.5, 122.6, 117.3, 107.7, 56.1, 55.6, 22.2, 13.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $C_{19}H_{12}N_2O_2H^+$ 309.1603; found 309.1615.

4. NMR Spectra



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125.2
123.5
123.5
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20.7
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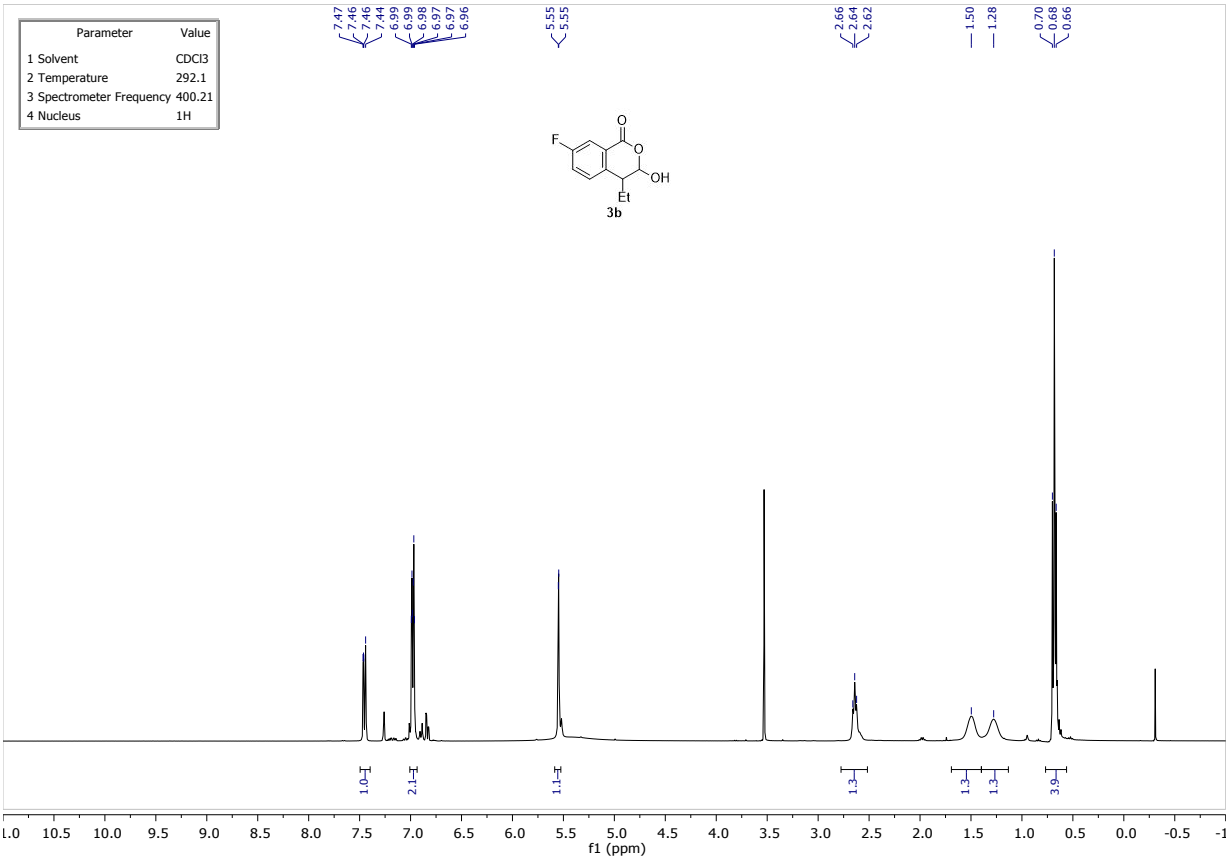
O
O
Et
3a
f1 (ppm)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5.55
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2.64
2.62
1.50
1.28
0.70
0.68
0.66
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Et
3b
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1.1
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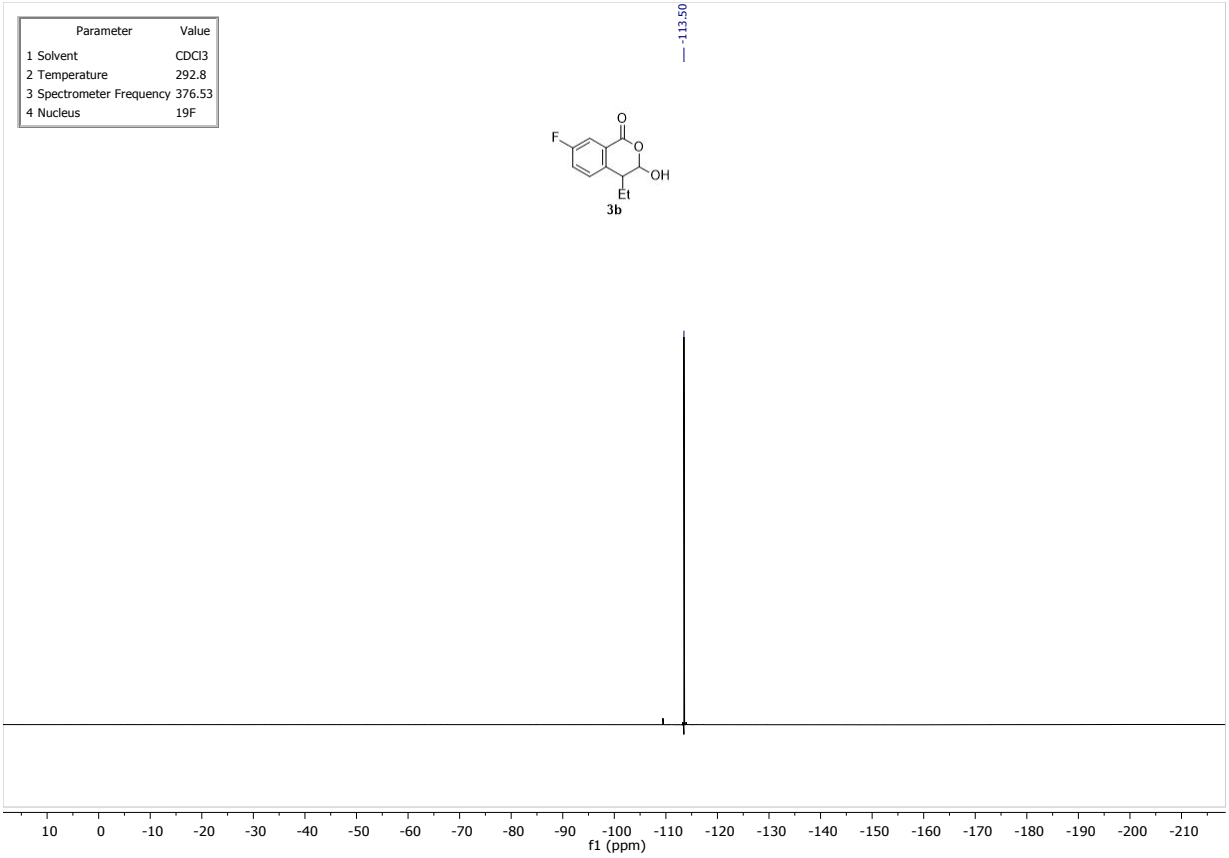
1.3
1.3
3.9
f1 (ppm)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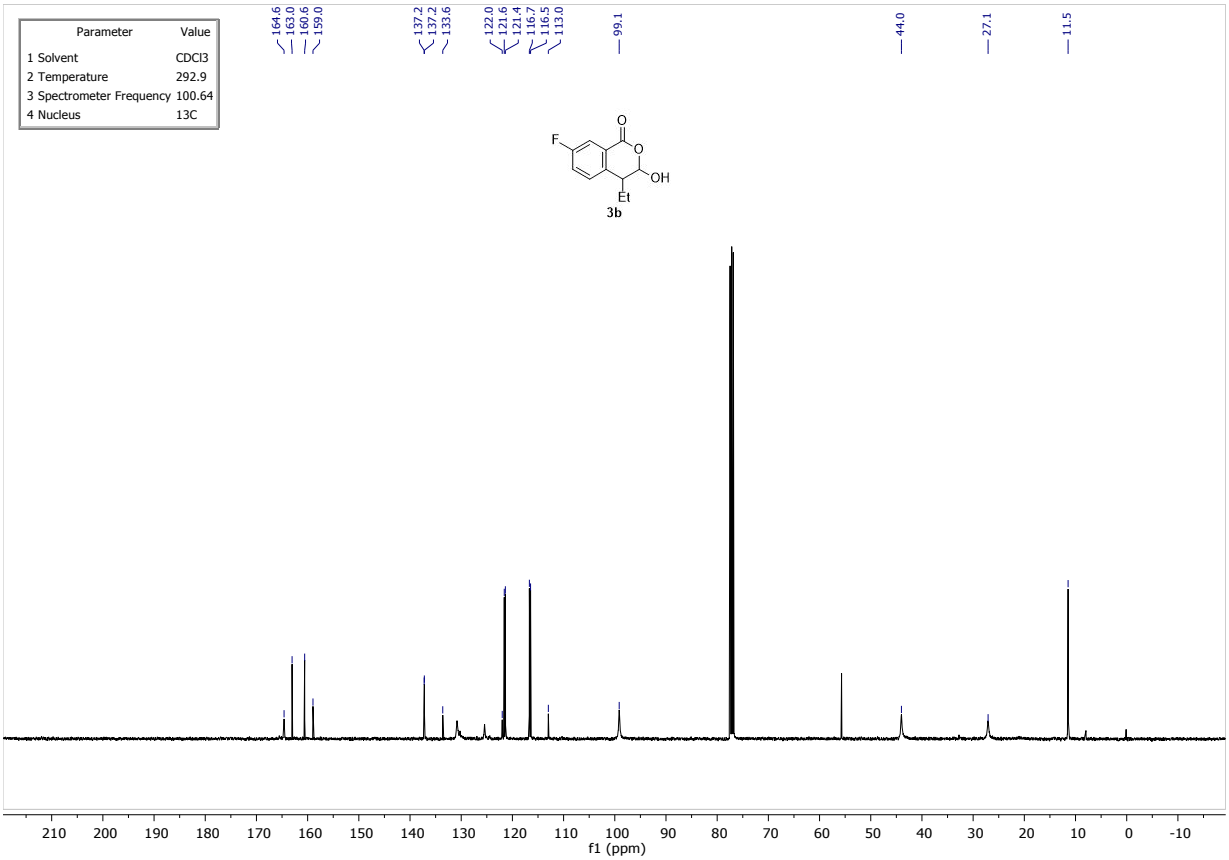
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137.2
133.6
122.0
121.6
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116.7
116.5
113.0
99.1
44.0
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OH
Et
3b
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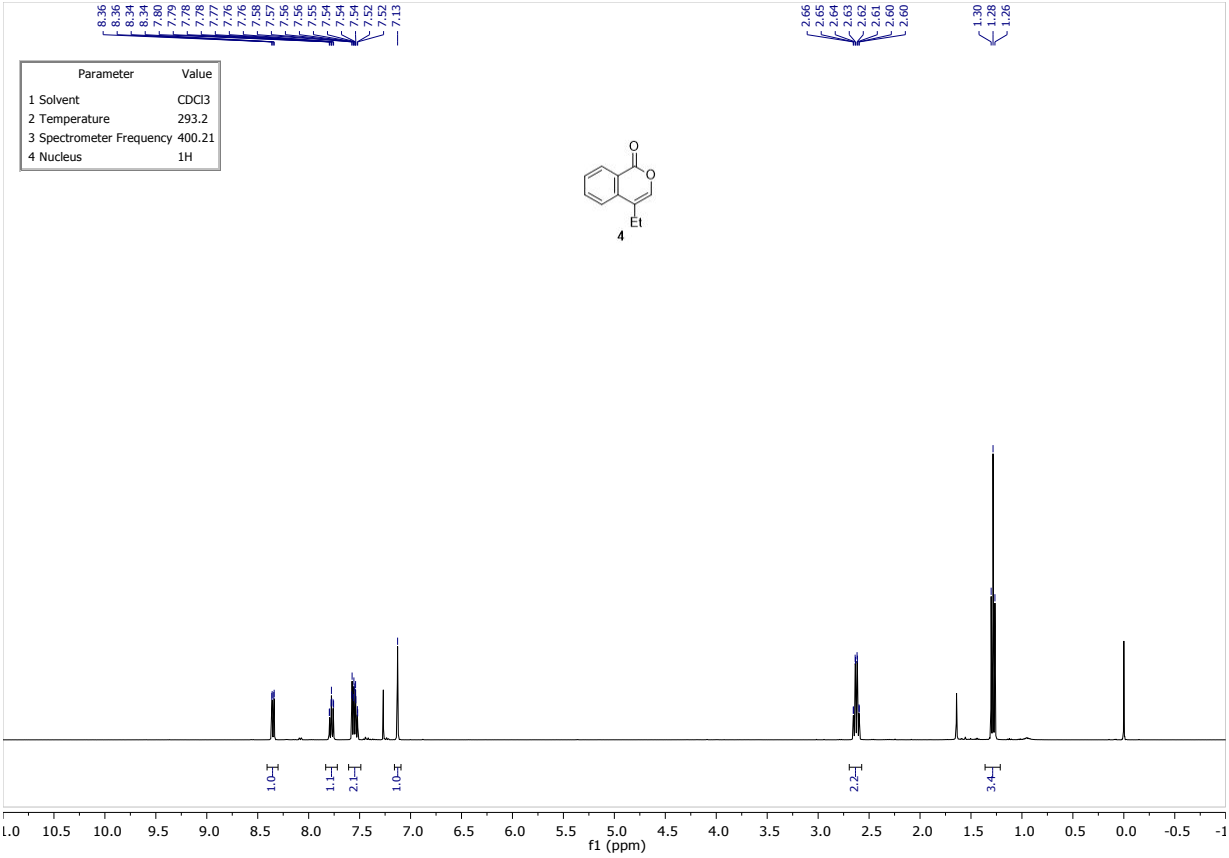
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1.30 1.28 1.26
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O
Et
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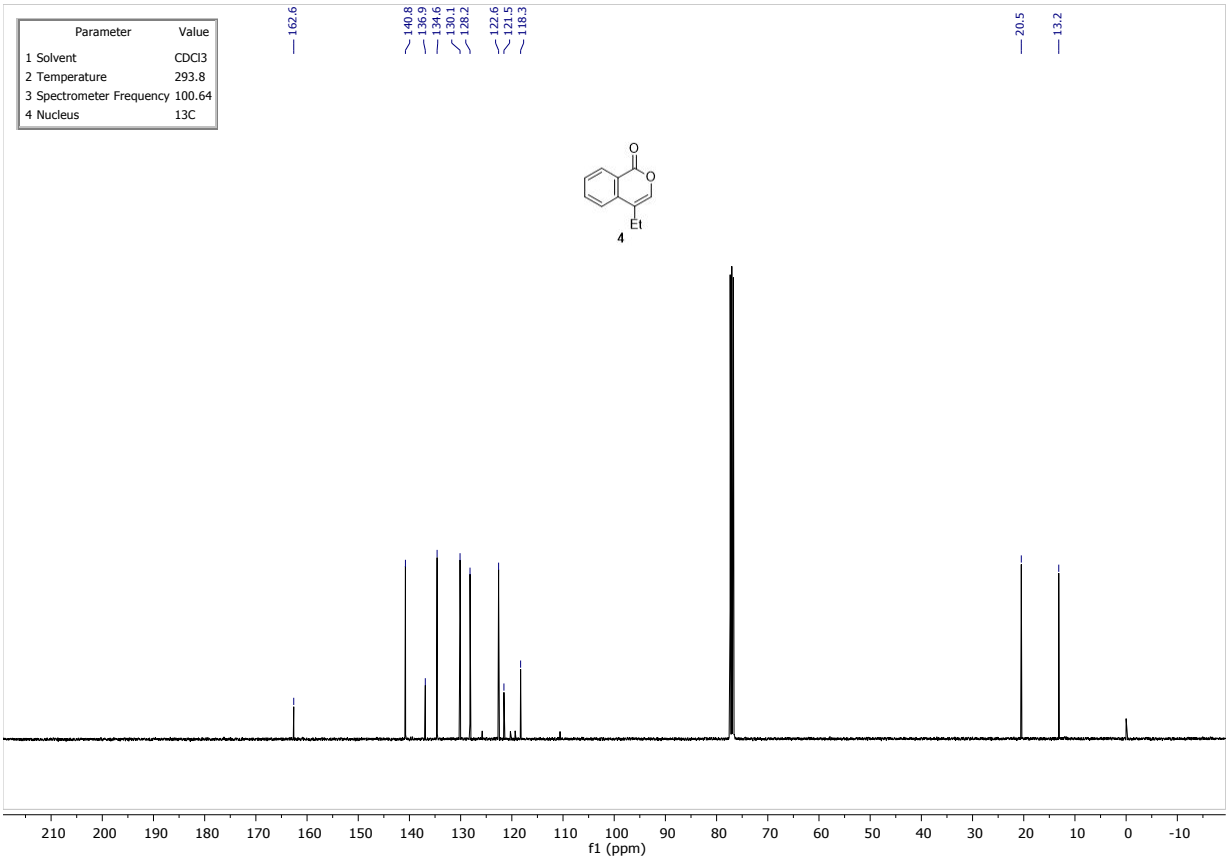
162.6
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20.5 13.2
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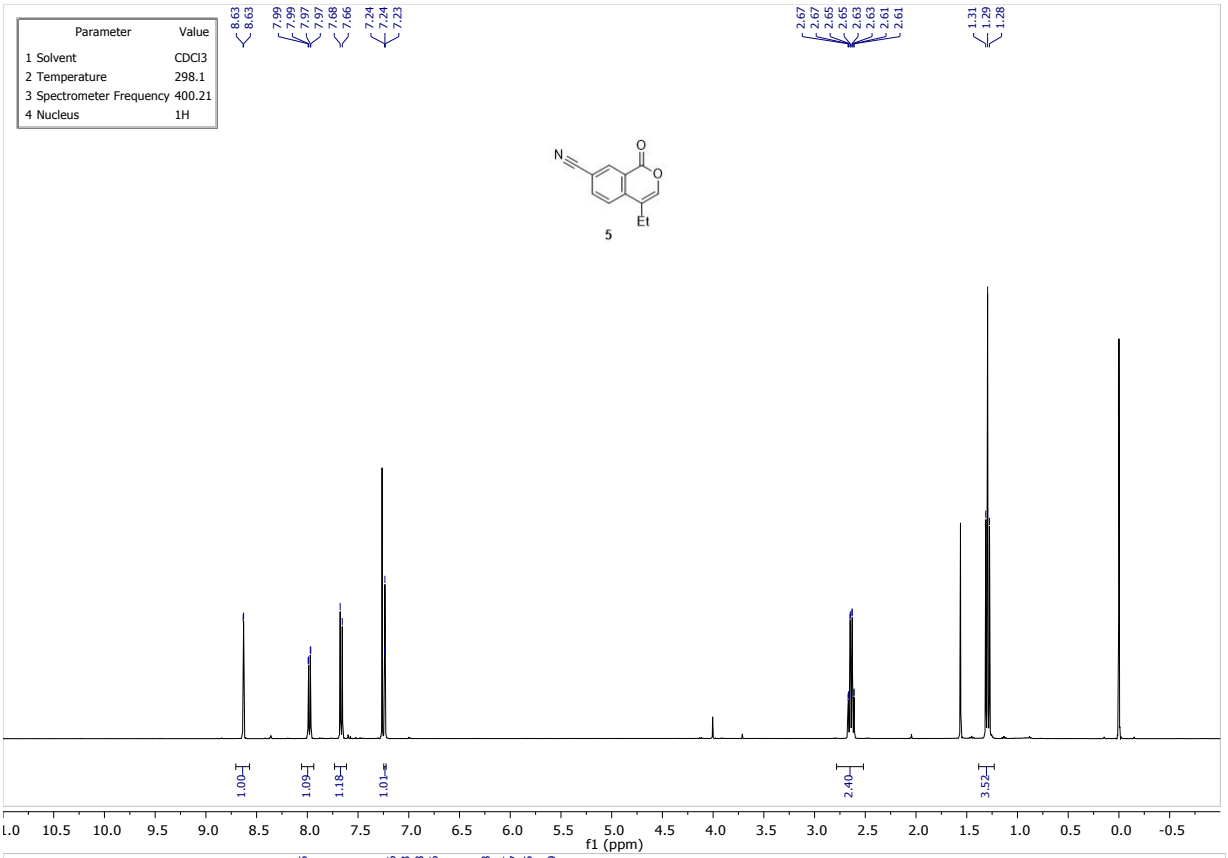
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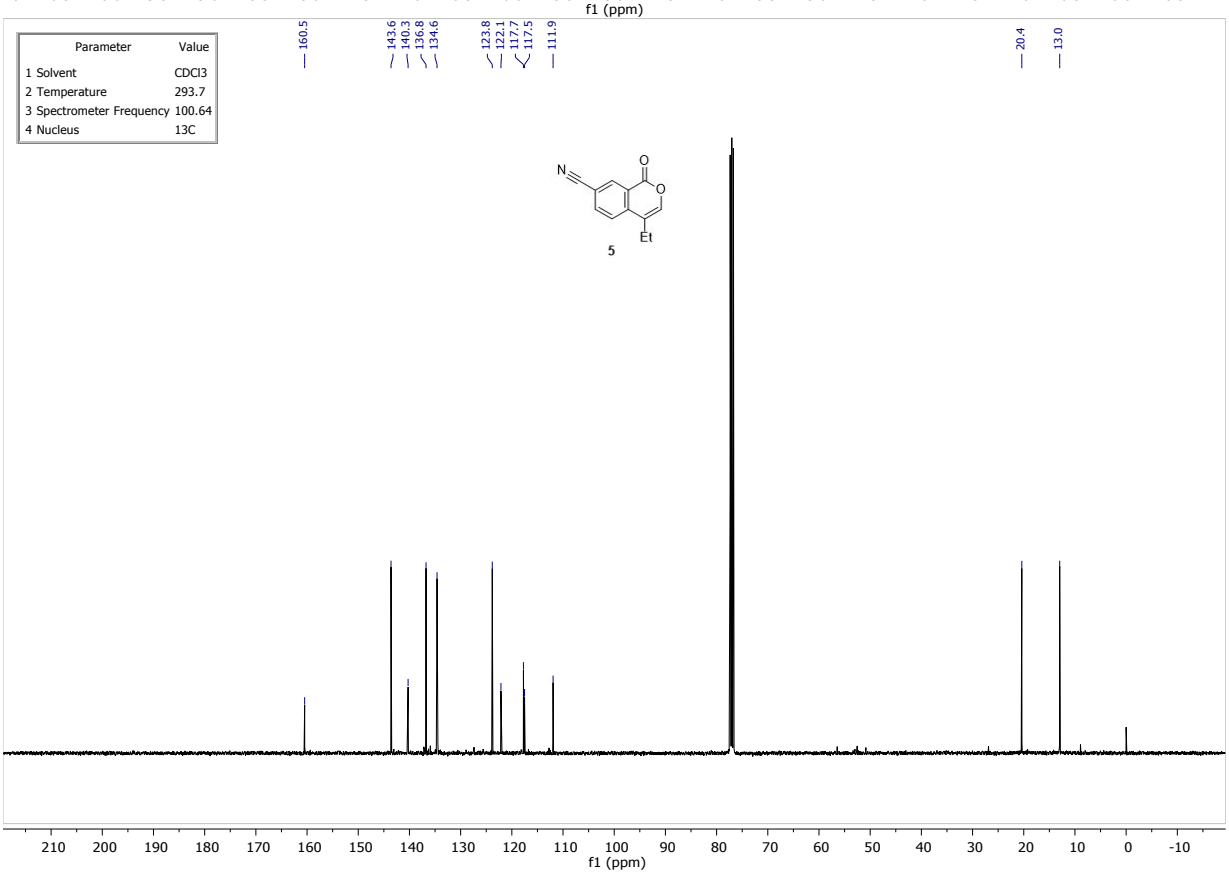
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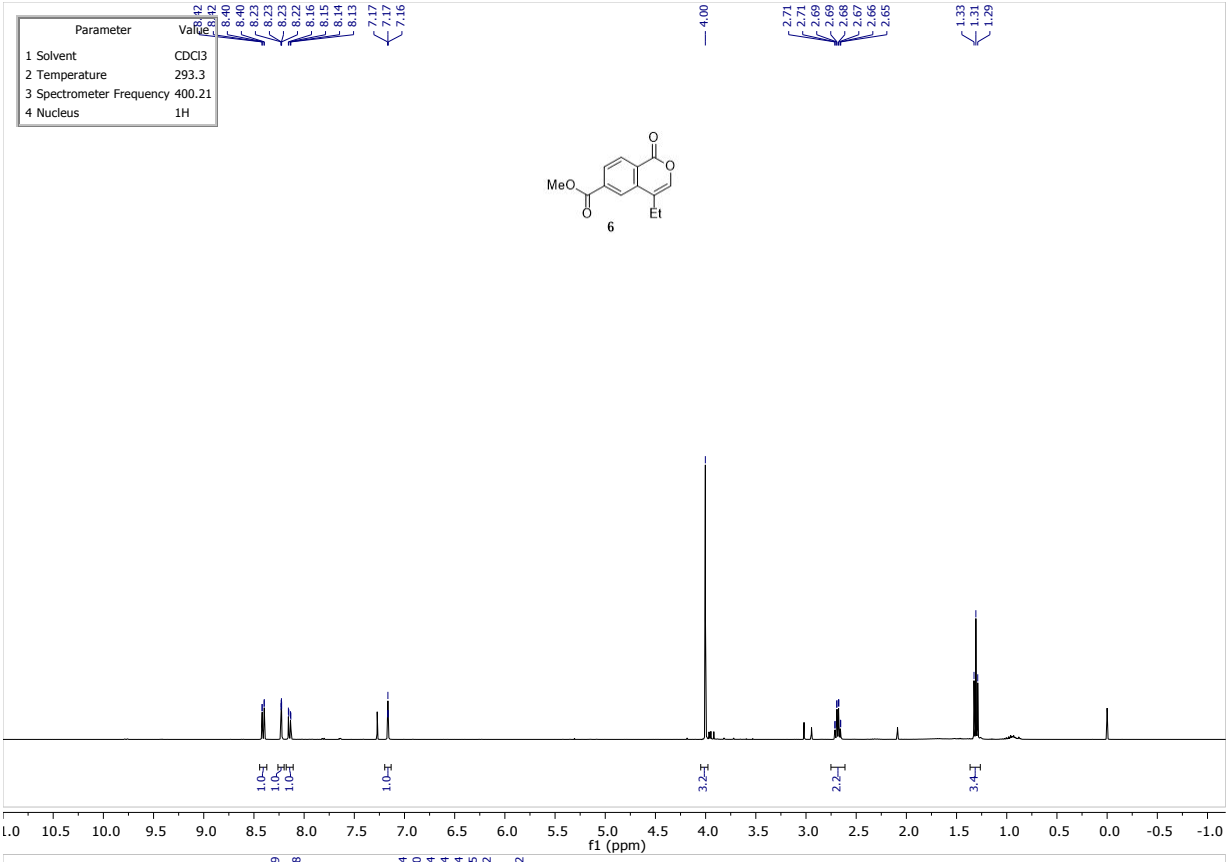
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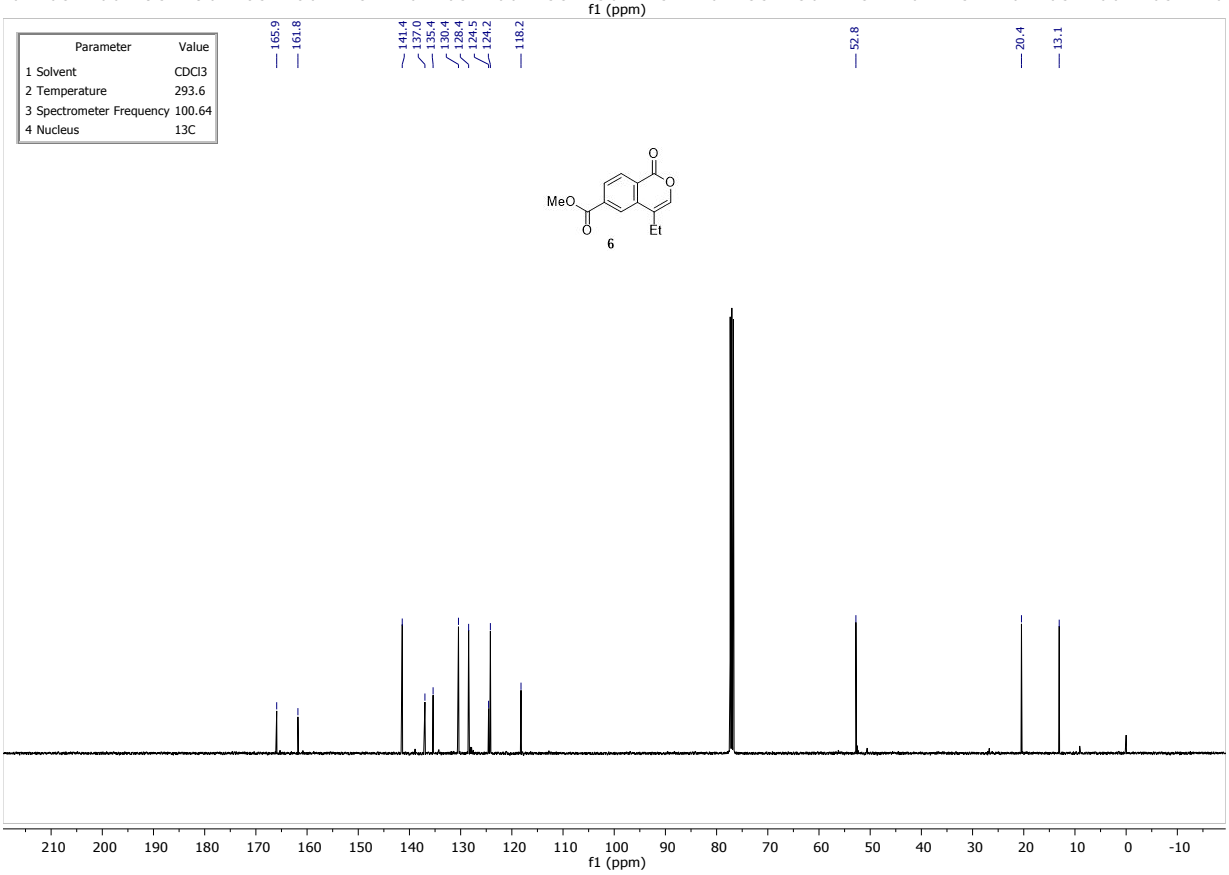
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Et
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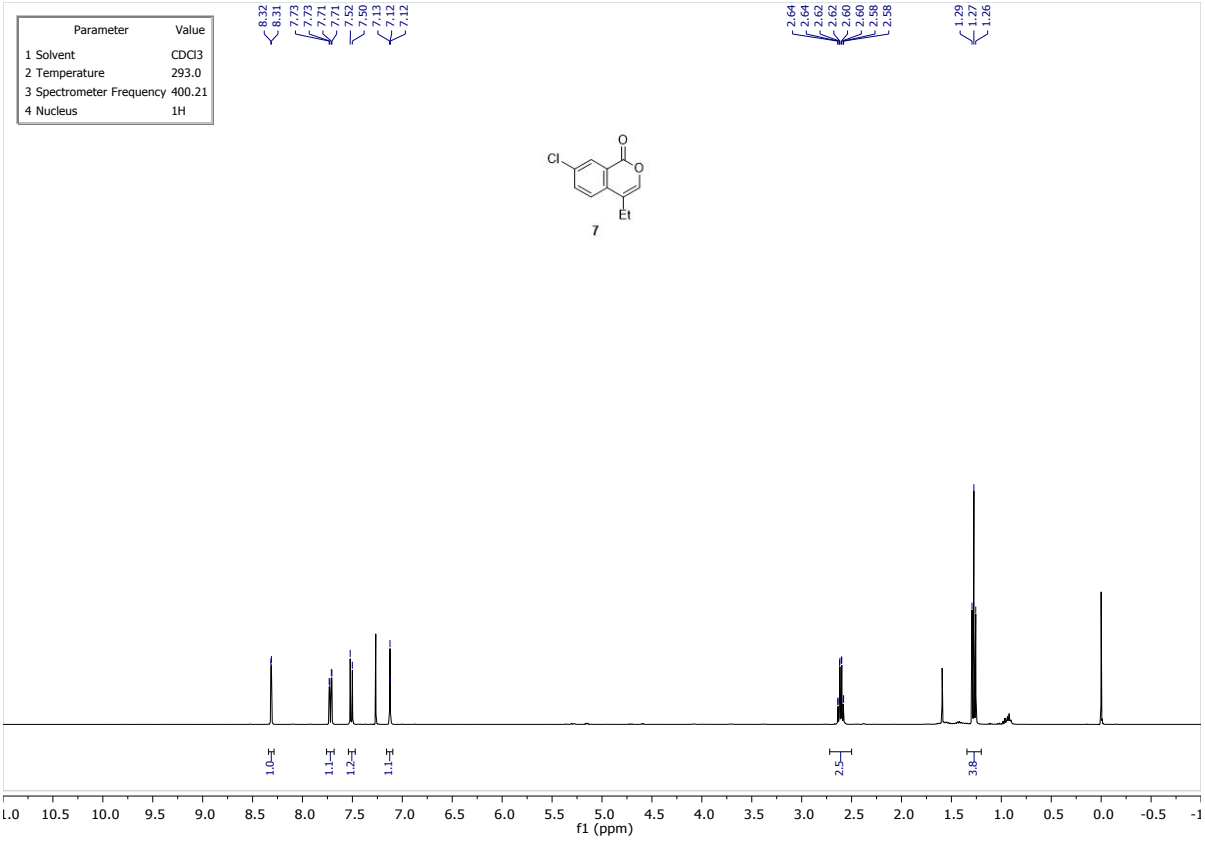
f1 (ppm)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O
Et
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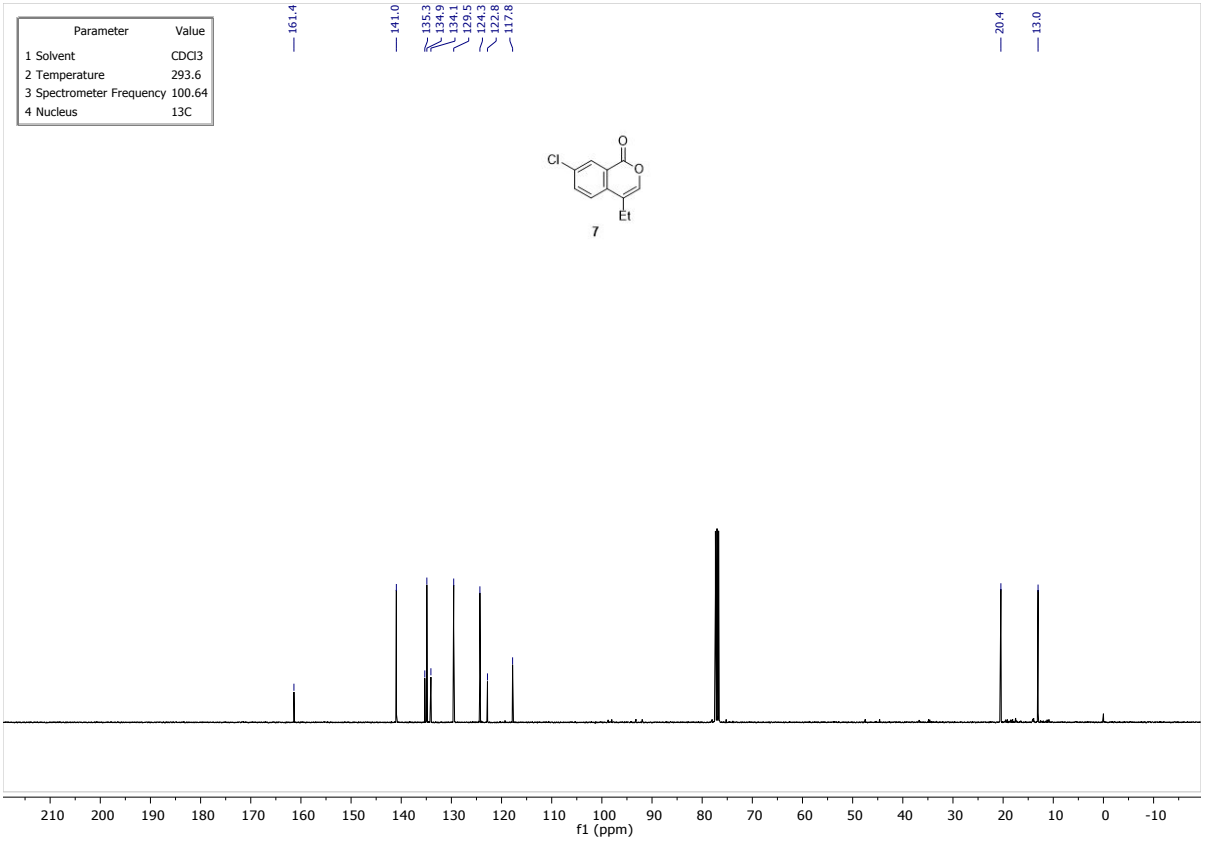
f1 (ppm)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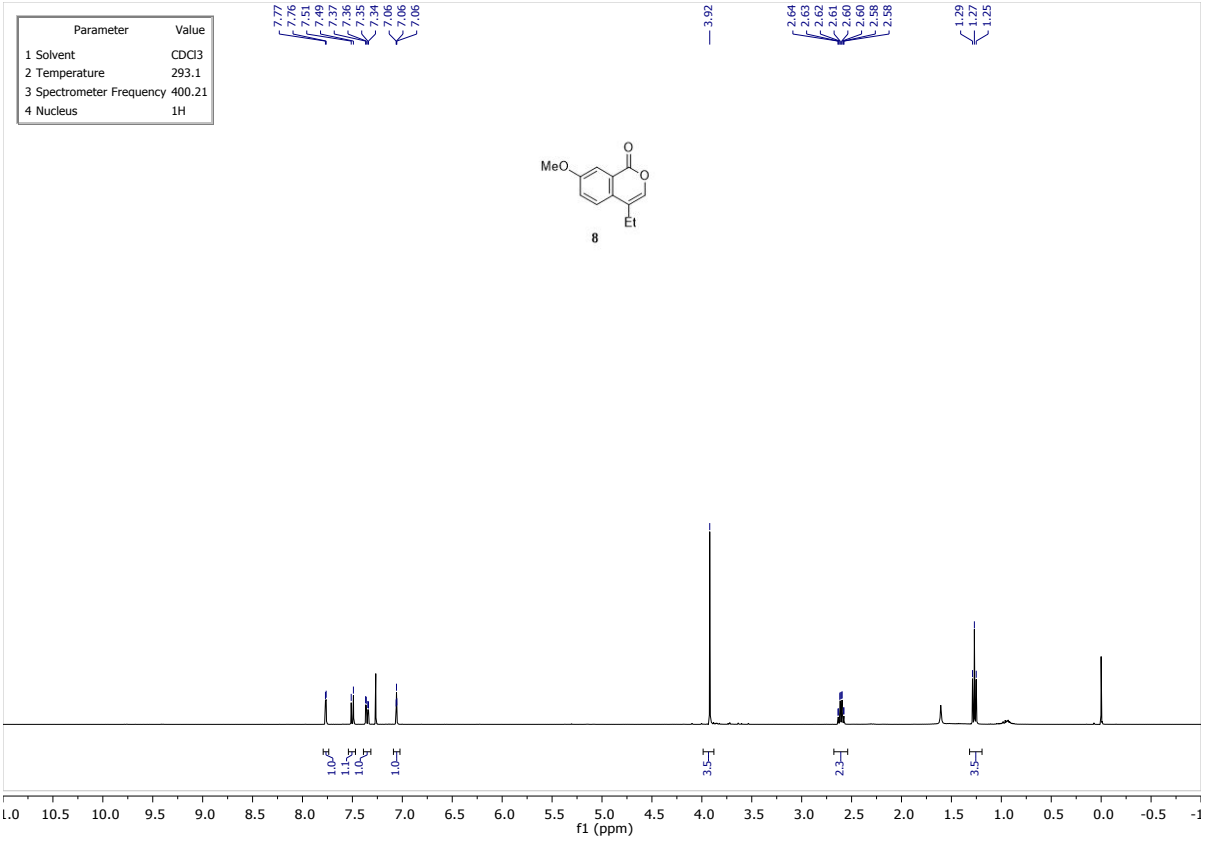
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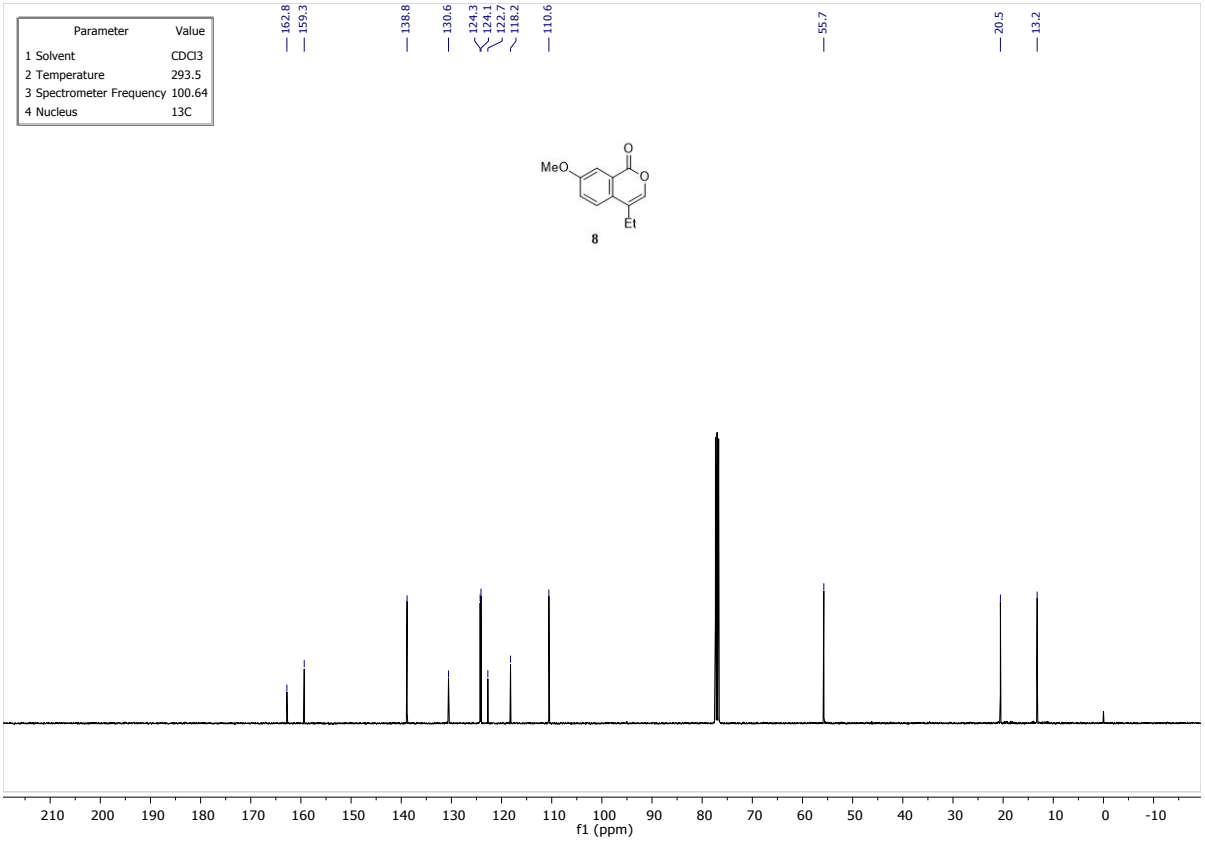
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O
Et
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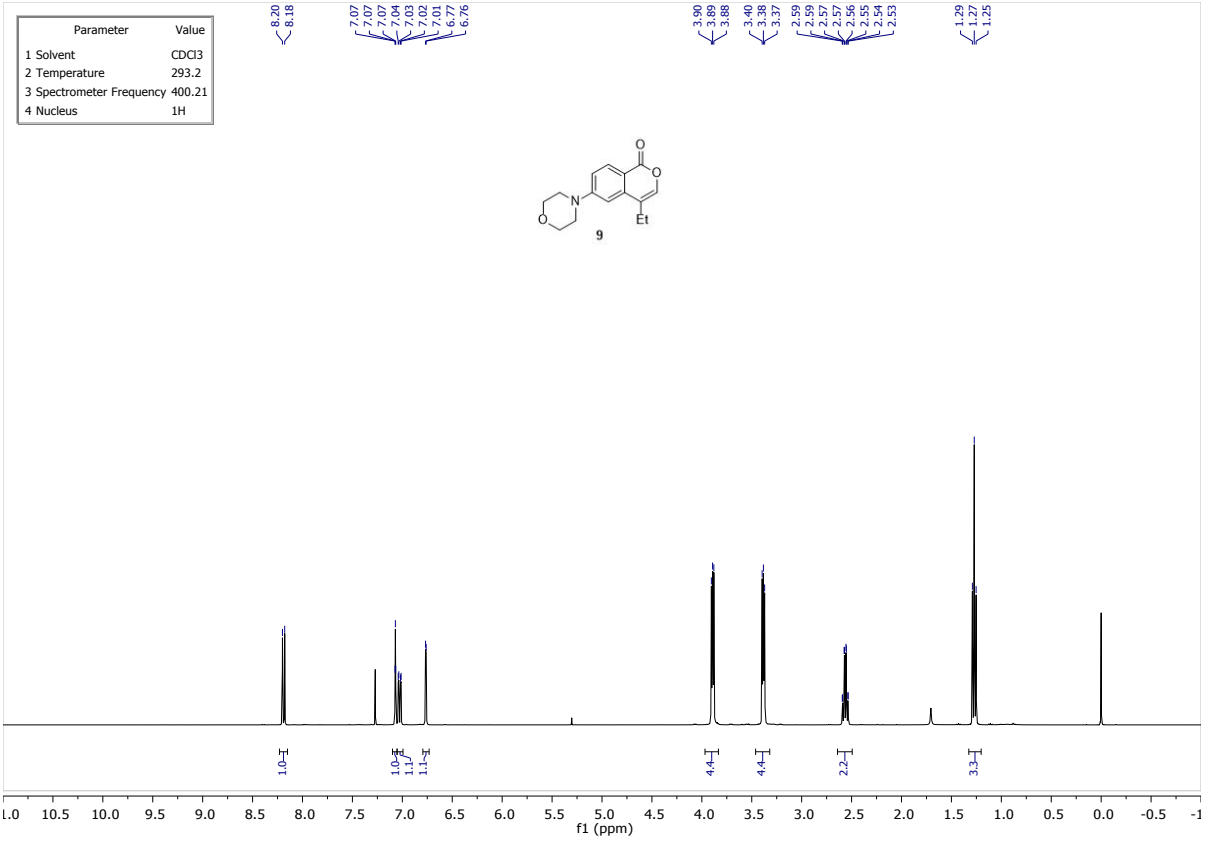
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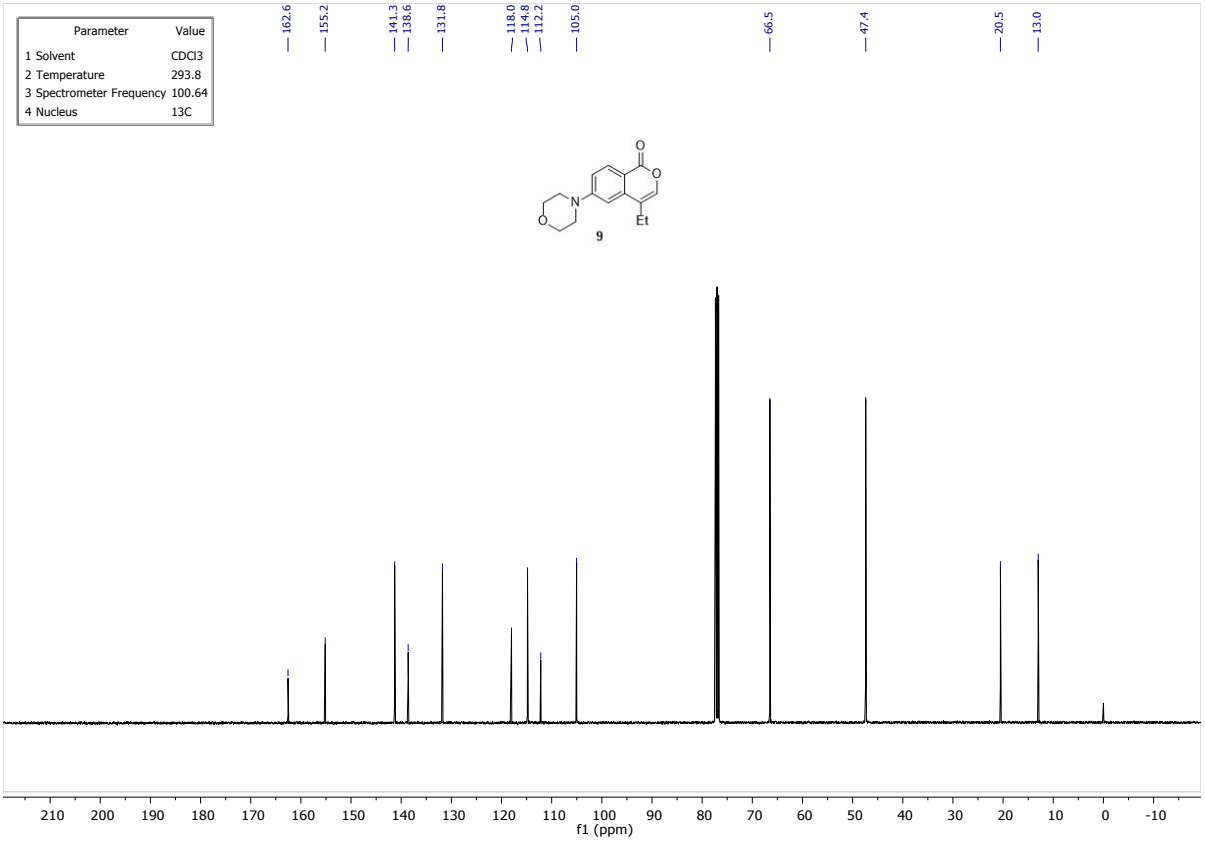
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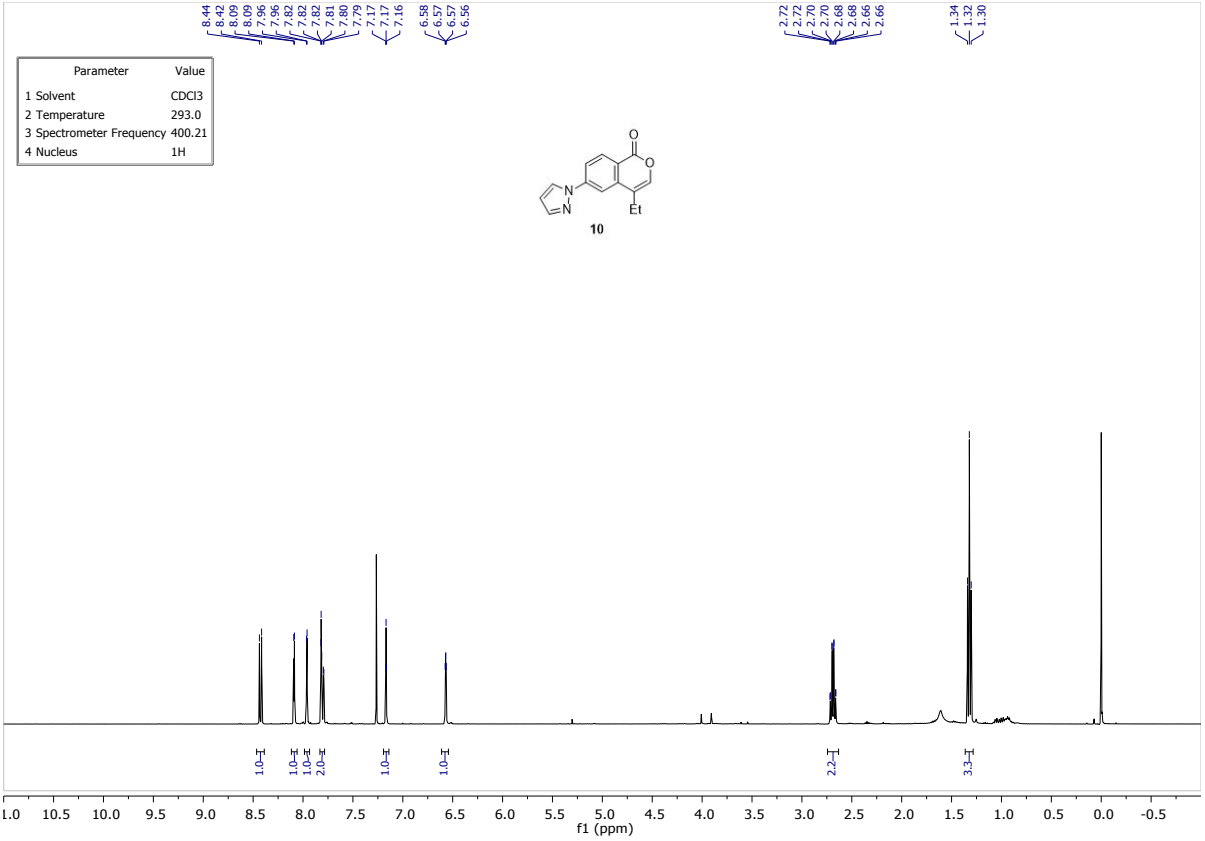
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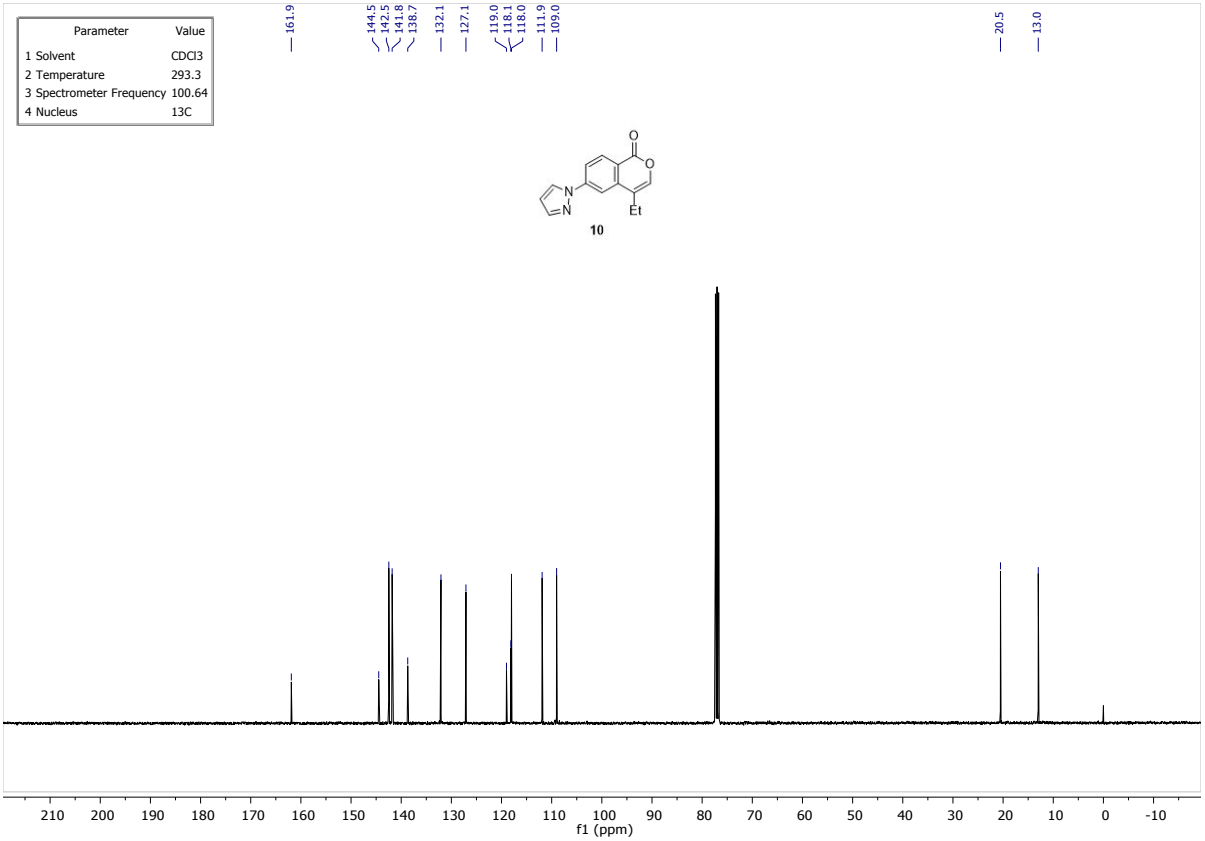
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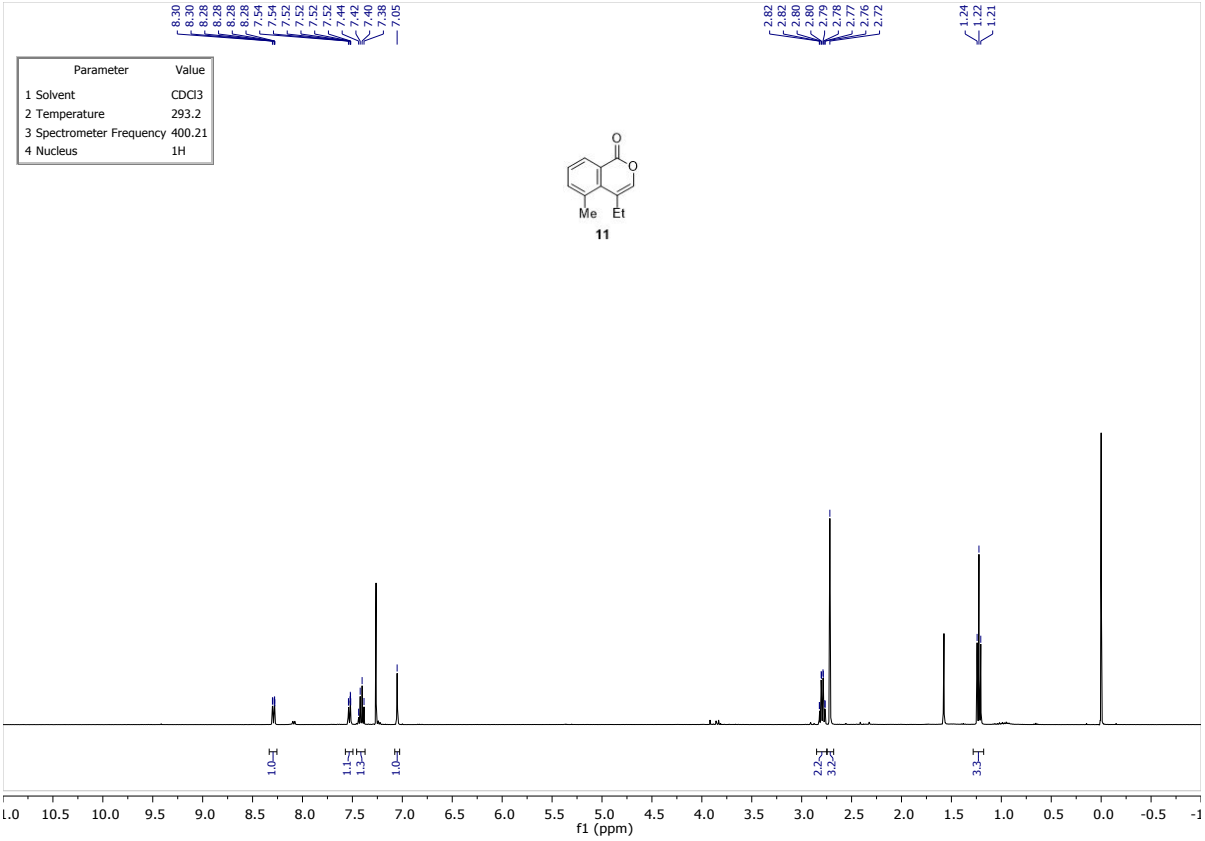
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Me Et
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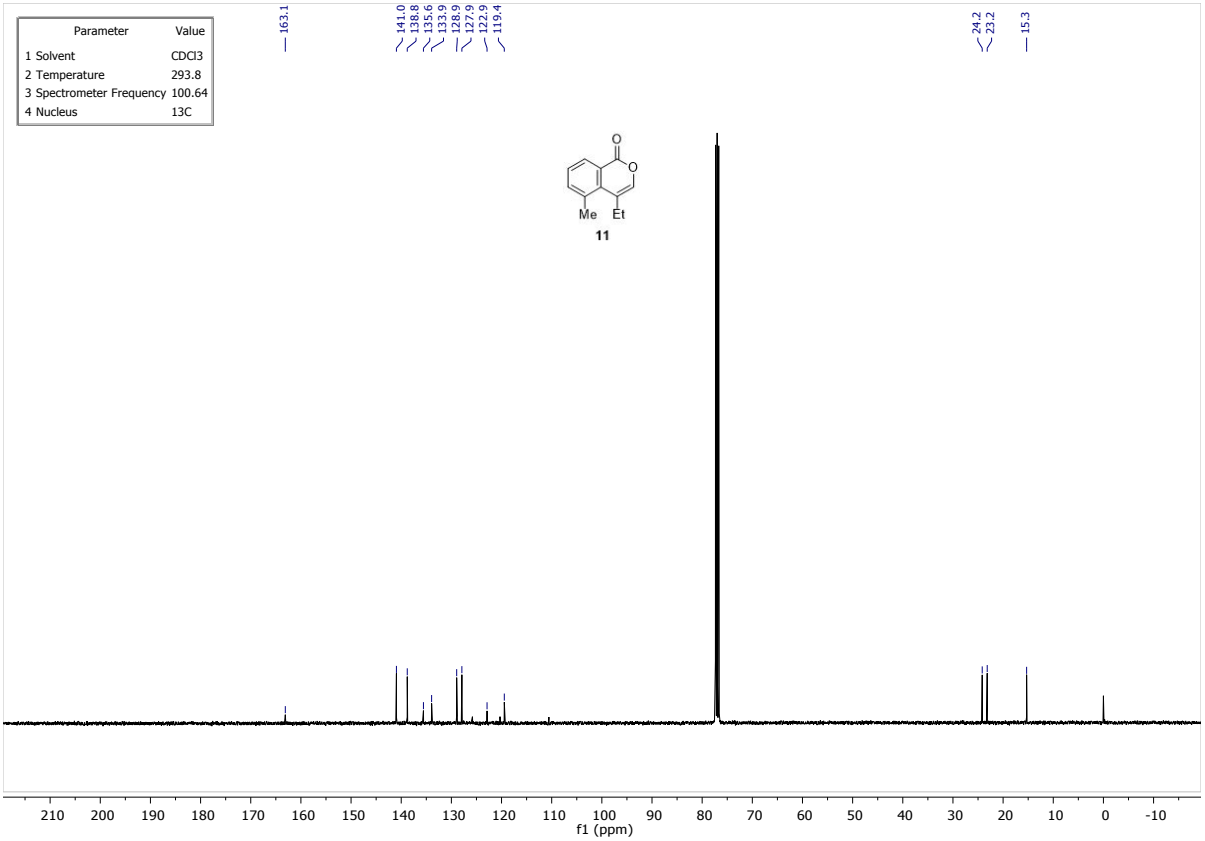
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Me Et
11
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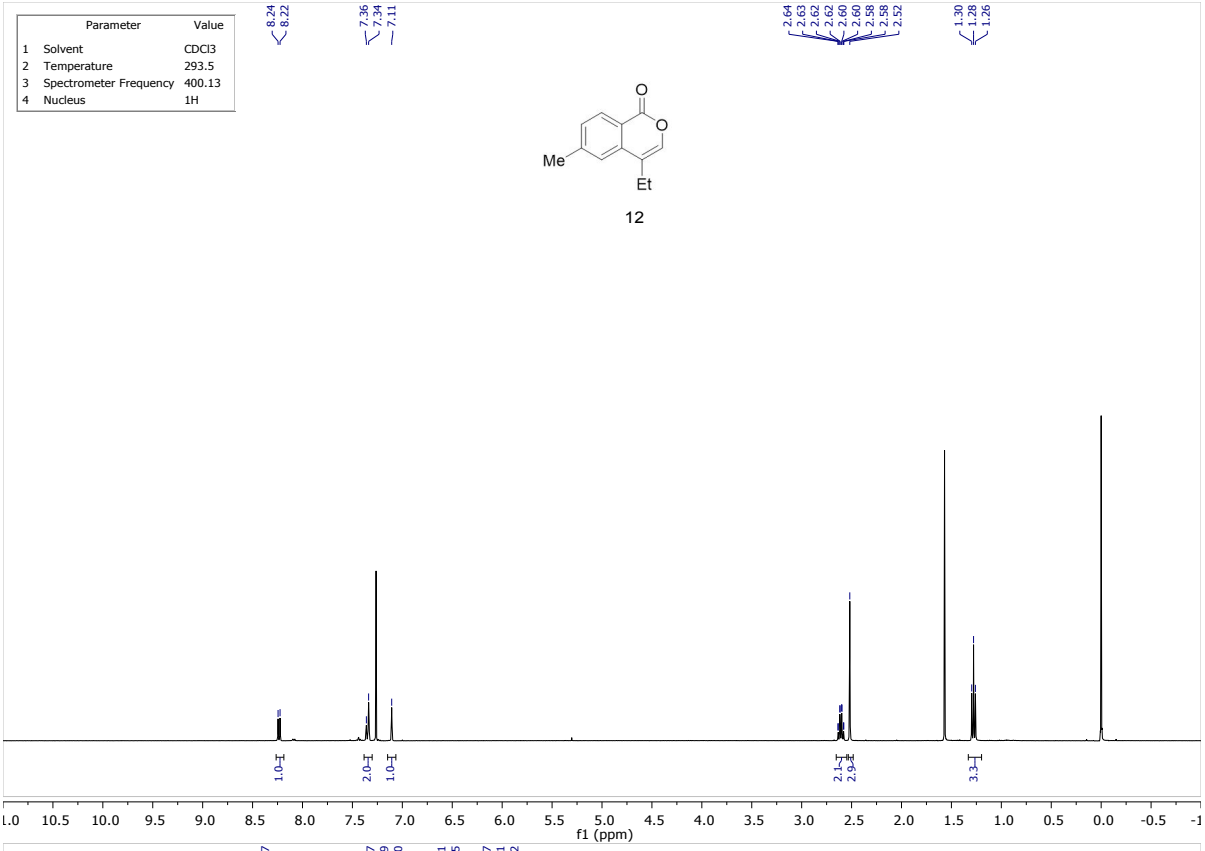
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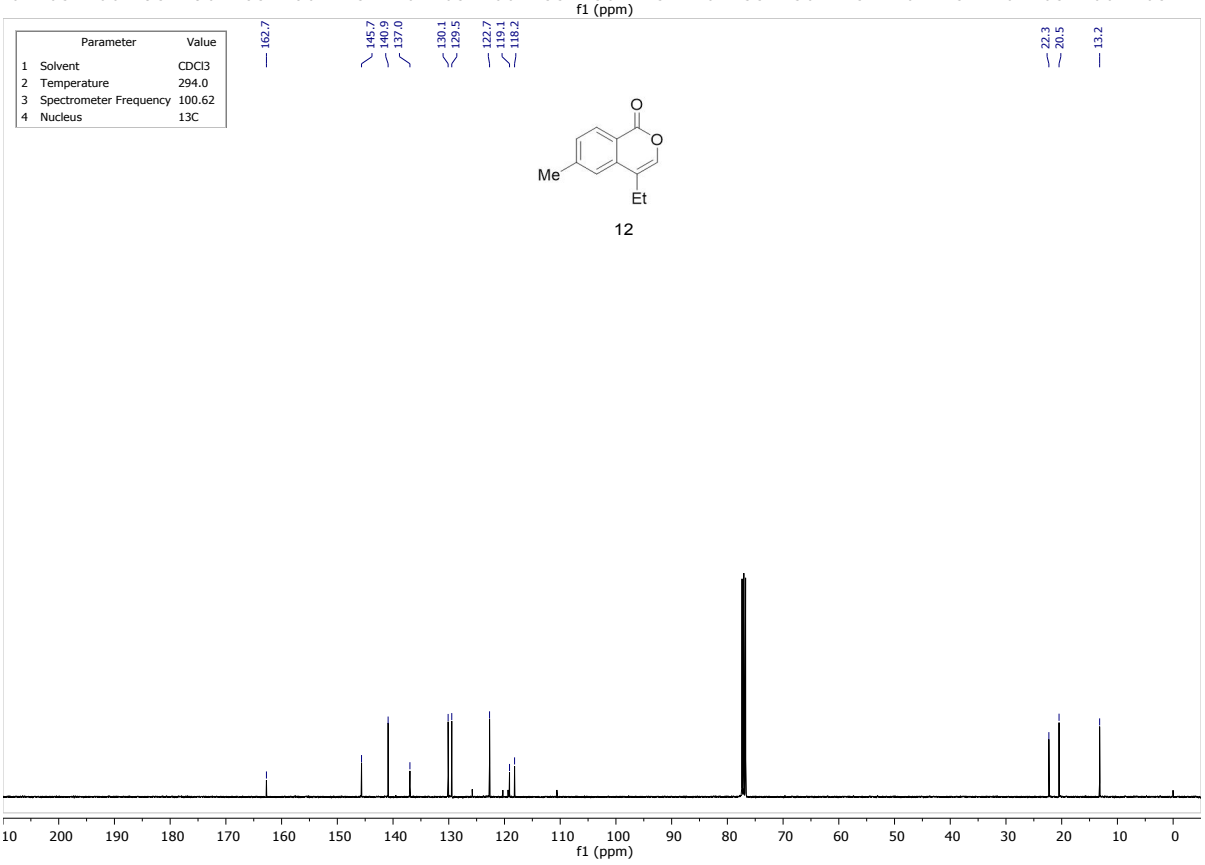
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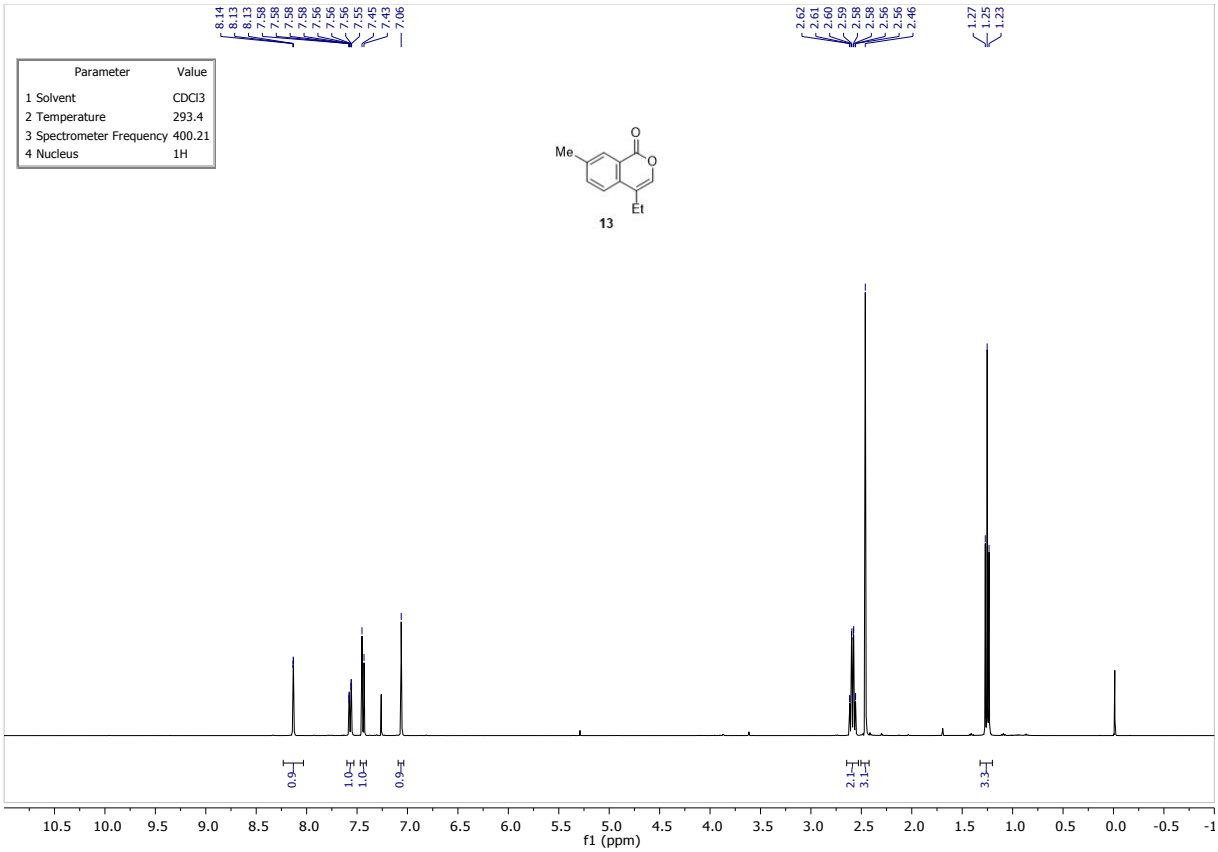
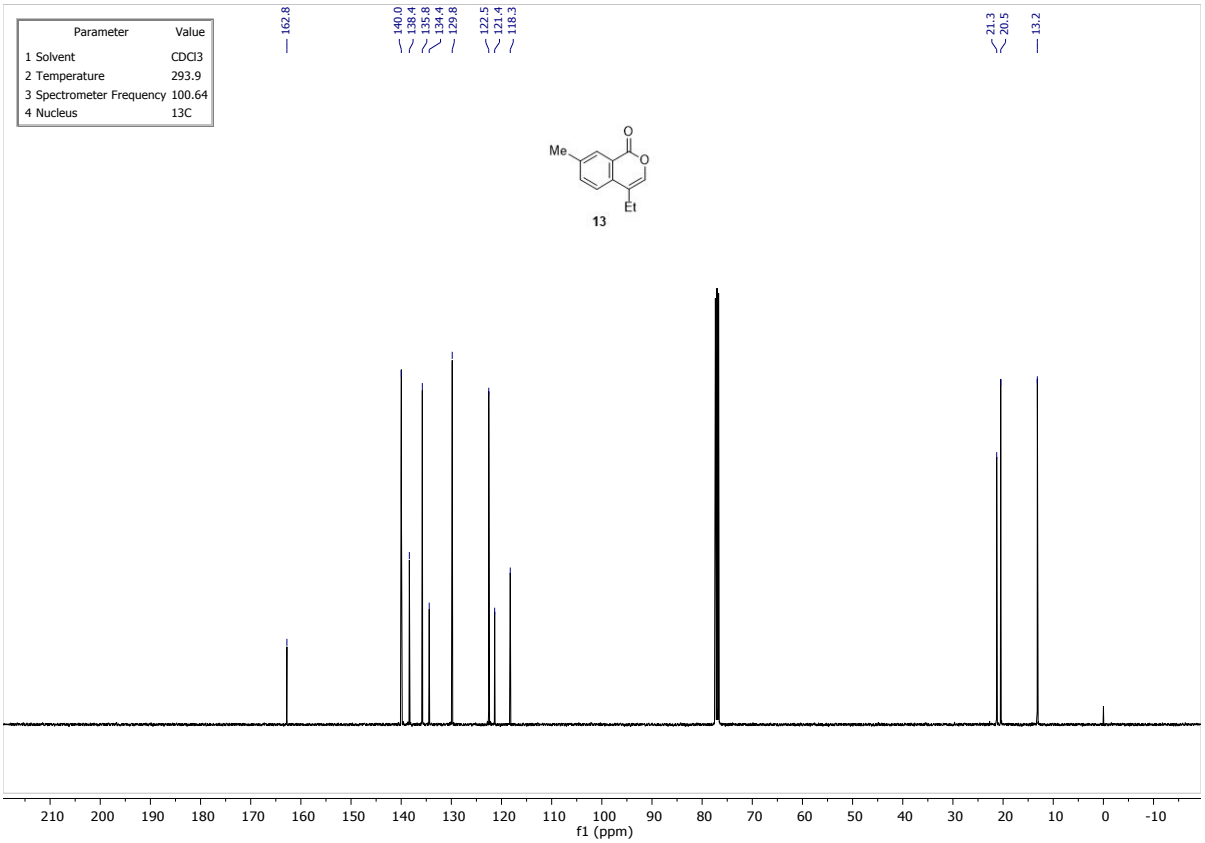
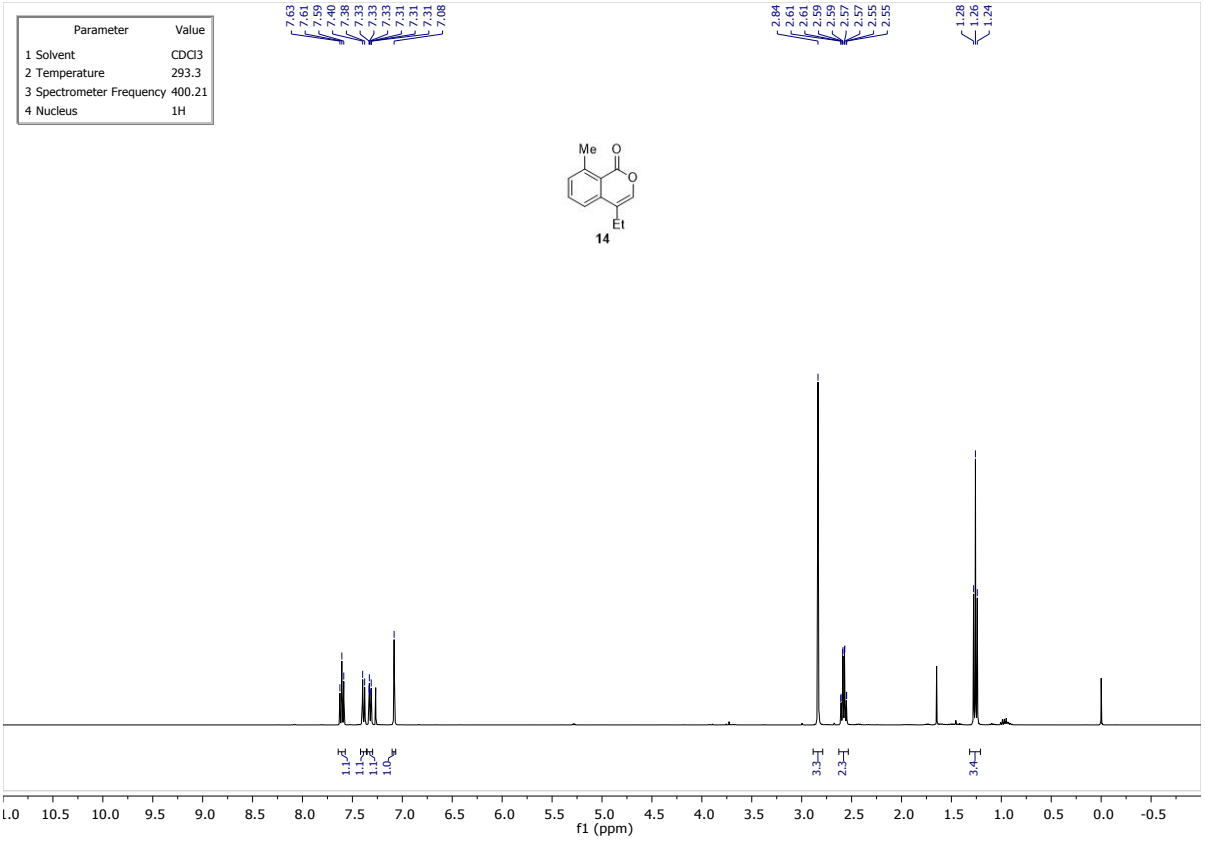
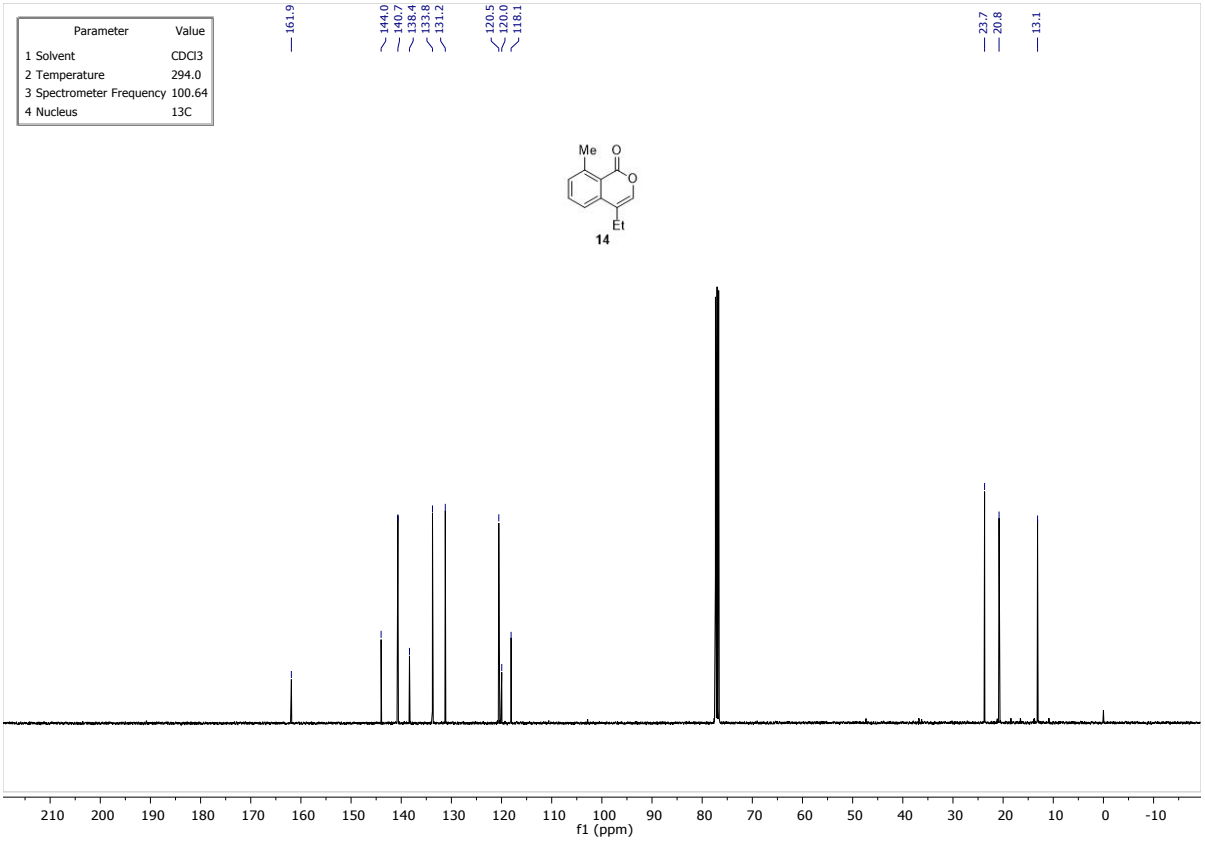
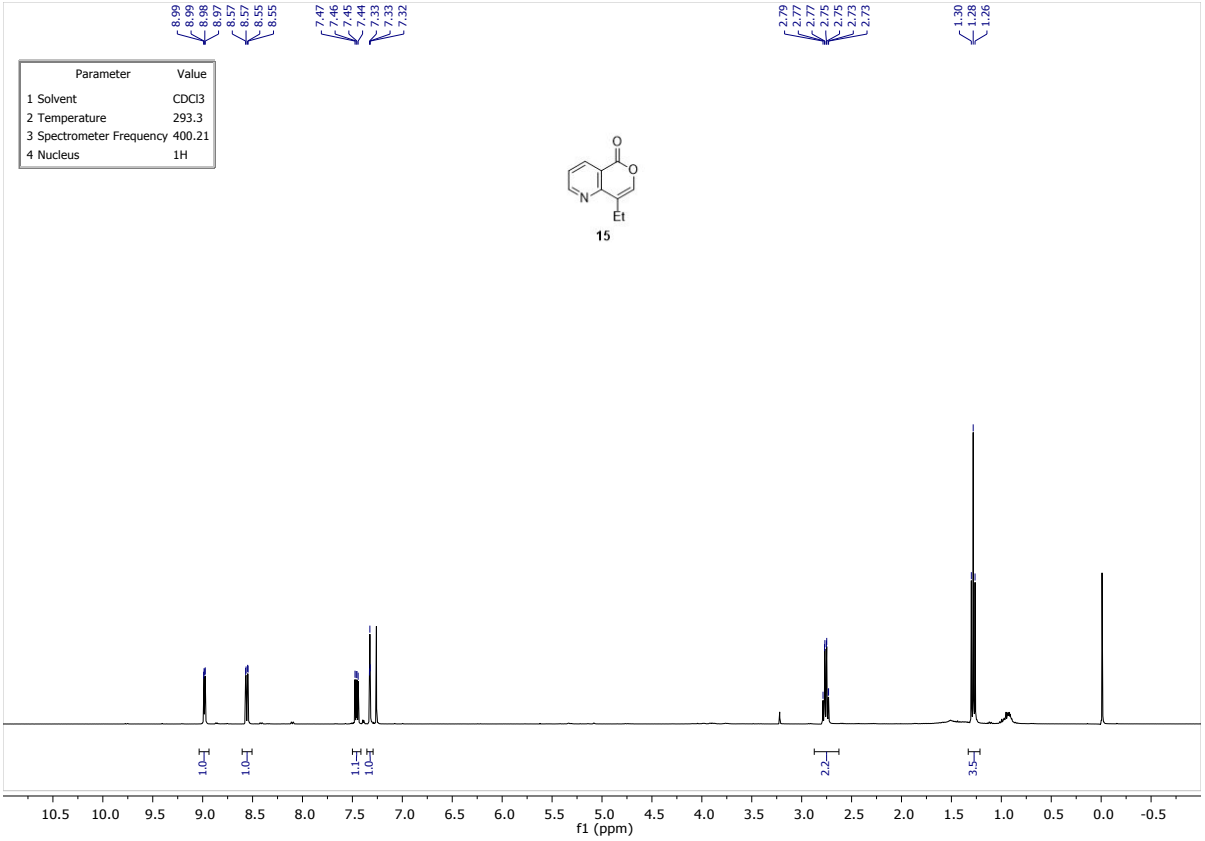
119.1
118.2
22.3
20.5
13.2
O
O
Me
Et
12
f1 (ppm)


8.14
8.13
8.13
7.58
7.58
7.58
7.56
7.56
7.56
7.55
7.45
7.43
7.06
2.62
2.61
2.60
2.59
2.58
2.58
2.56
2.56
2.46
1.27
1.25
1.23
Parameter Value
1 Solvent CDCl3
2 Temperature 293.4
3 Spectrometer Frequency 400.21
4 Nucleus 1H
Me
O
O
Et
13
0.9
1.0
1.0
0.9
2.1
3.1
3.3
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 -0.5 -1
f1 (ppm)


162.8
140.0
138.4
135.8
134.4
129.8
122.5
121.4
118.3
21.3
20.5
13.2
Parameter Value
1 Solvent CDCl3
2 Temperature 293.9
3 Spectrometer Frequency 100.64
4 Nucleus 13C
Me
O
O
Et
13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.3
3 Spectrometer Frequency 400.21
4 Nucleus 1H
7.63 7.61 7.59 7.40 7.38 7.33 7.33 7.33 7.31 7.31 7.31 7.31 7.08
2.84 2.61 2.61 2.59 2.59 2.57 2.57 2.55 2.55
1.28 1.26 1.24
Me
O
O
Et
14
1.1 1.1 1.1 1.0
3.3
2.3
3.4
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 294.0
3 Spectrometer Frequency 100.64
4 Nucleus 13C
161.9
144.0 140.7 138.4 133.8 131.2
120.5 120.0 118.1
23.7 20.8
13.1
Me
O
O
Et
14
f1 (ppm)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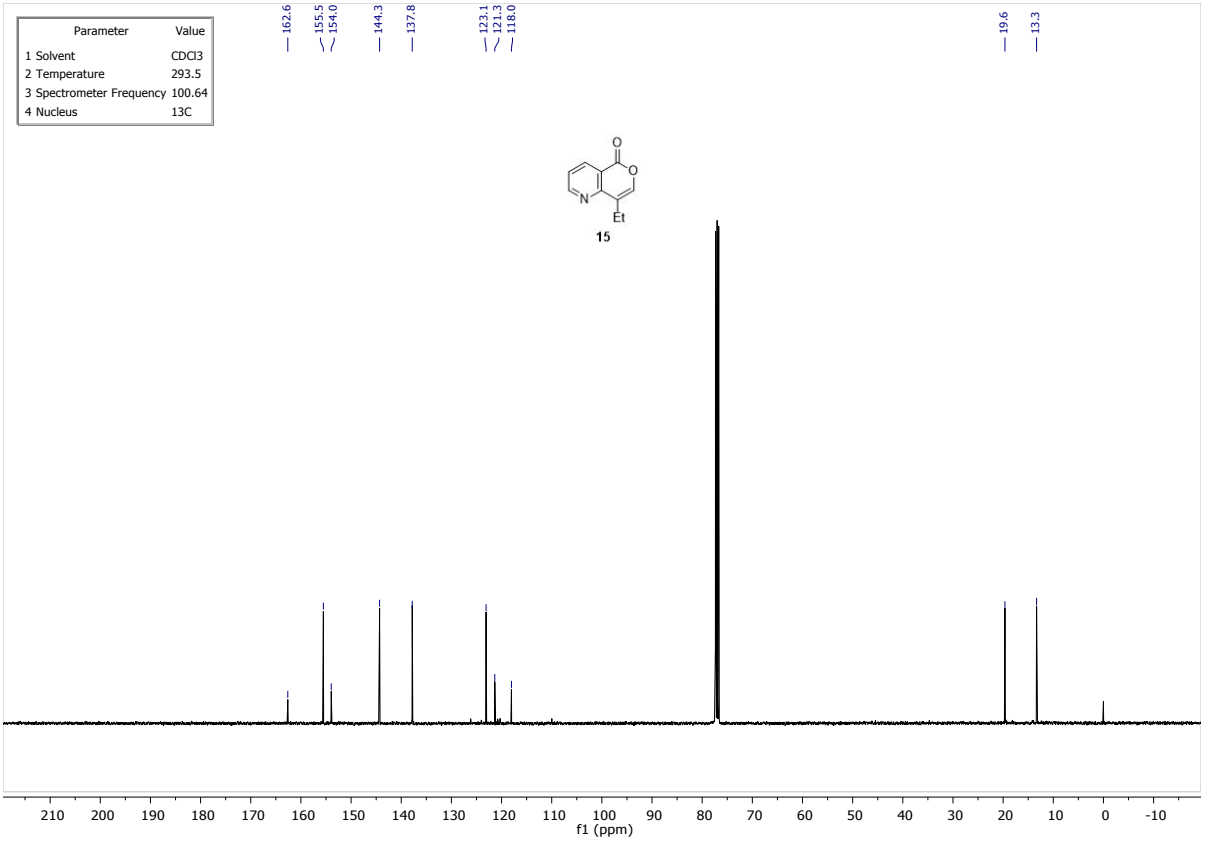
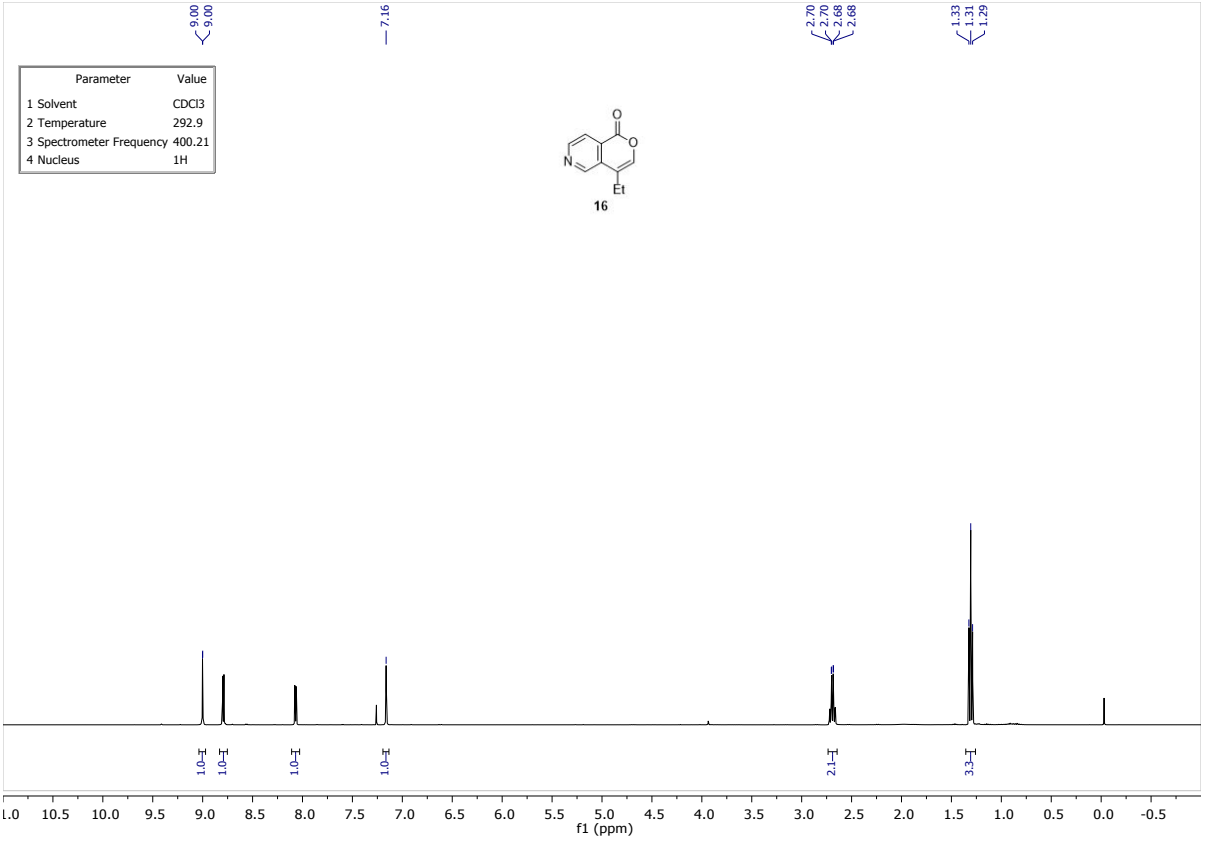
8.99
8.98
8.97
8.57
8.57
8.55
8.55
7.47
7.46
7.45
7.44
7.33
7.33
7.32
2.79
2.77
2.77
2.75
2.75
2.73
2.73
1.30
1.28
1.26
Parameter Value
1 Solvent CDCl3
2 Temperature 293.3
3 Spectrometer Frequency 400.21
4 Nucleus 1H
O
O
N
Et
15
1.0
1.0
1.1
1.0
2.2
3.5
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


162.6
155.5
154.0
144.3
137.8
123.1
121.3
118.0
19.6
13.3
Parameter Value
1 Solvent CDCl3
2 Temperature 293.5
3 Spectrometer Frequency 100.64
4 Nucleus 13C
O
O
N
Et
15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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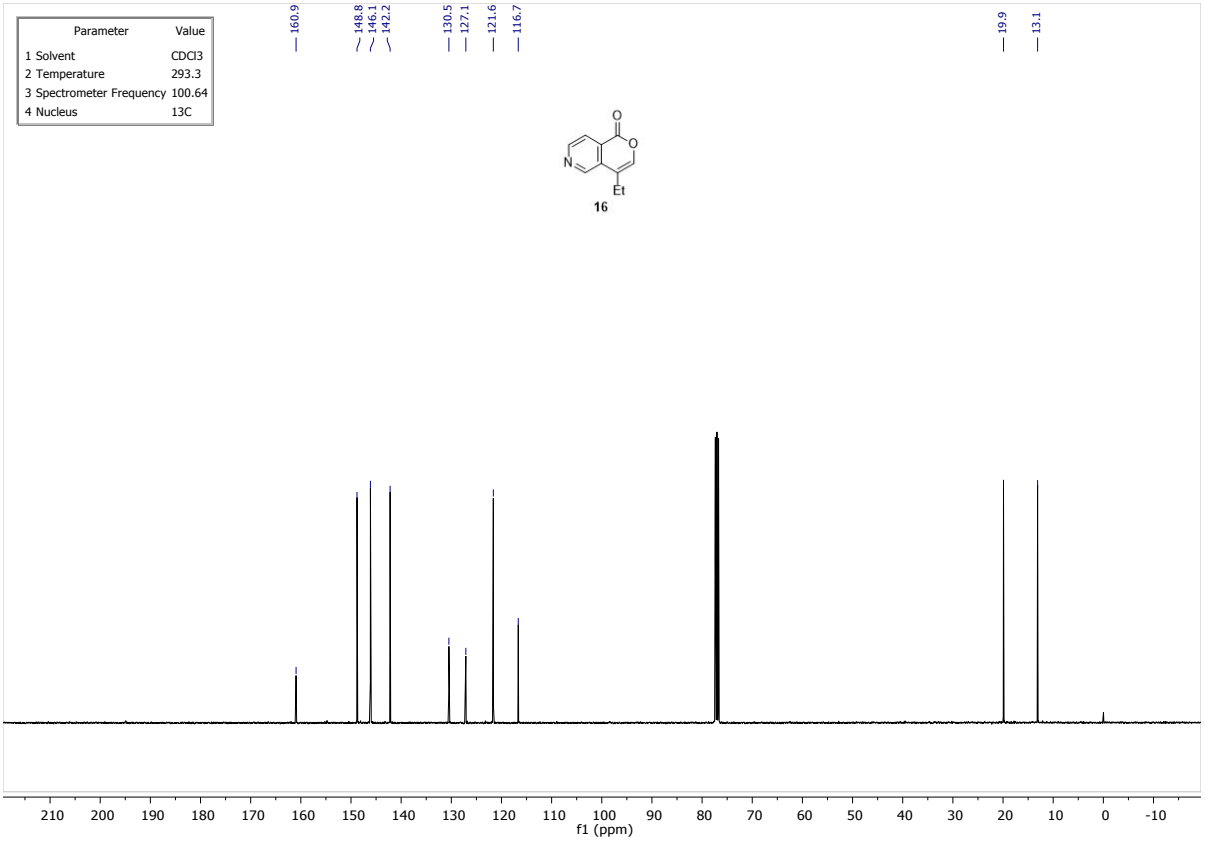
9.00
7.16
2.70
2.70
2.68
2.68
1.33
1.31
1.29
Parameter Value
1 Solvent CDCl3
2 Temperature 292.9
3 Spectrometer Frequency 400.21
4 Nucleus 1H
O
O
N
Et
16
1.0
1.0
1.0
1.0
2.1
3.3
f1 (ppm)


160.9
148.8
146.1
142.2
130.5
127.1
121.6
116.7
19.9
13.1
Parameter Value
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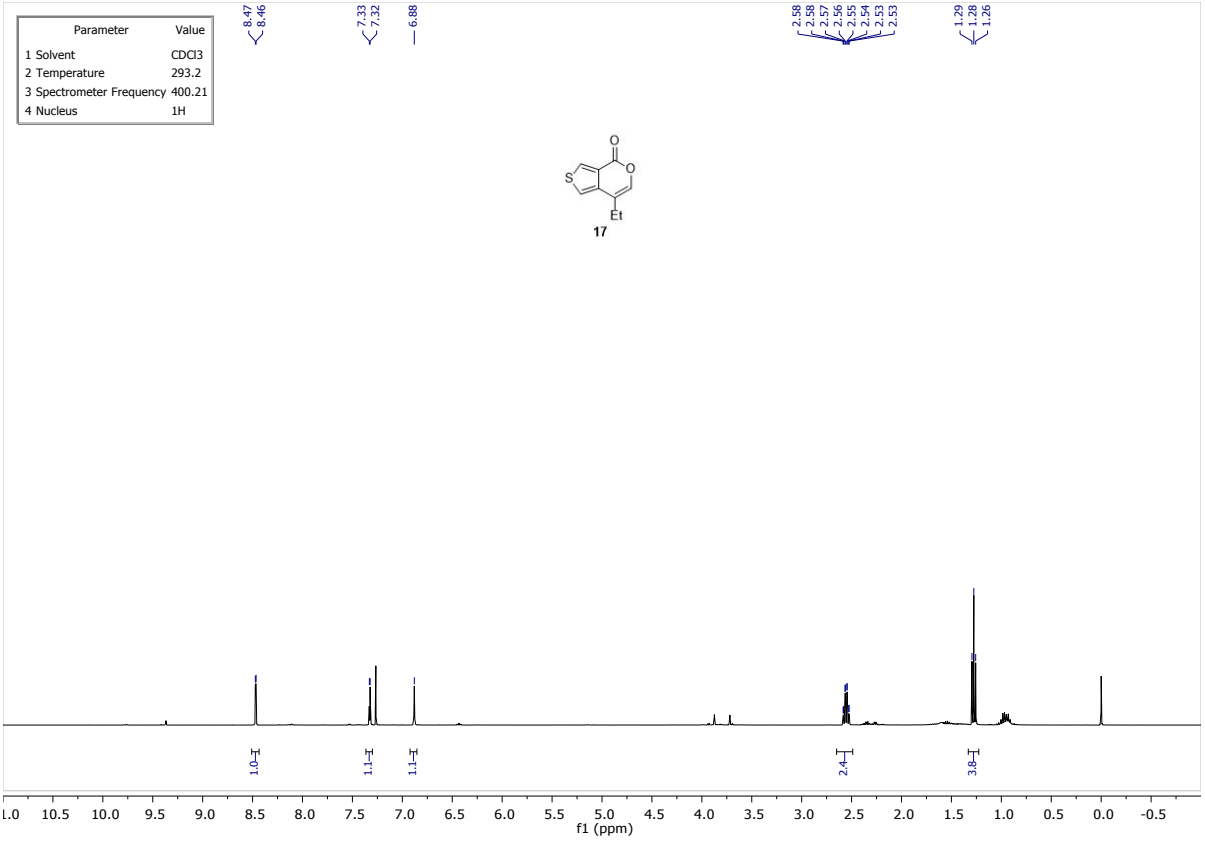
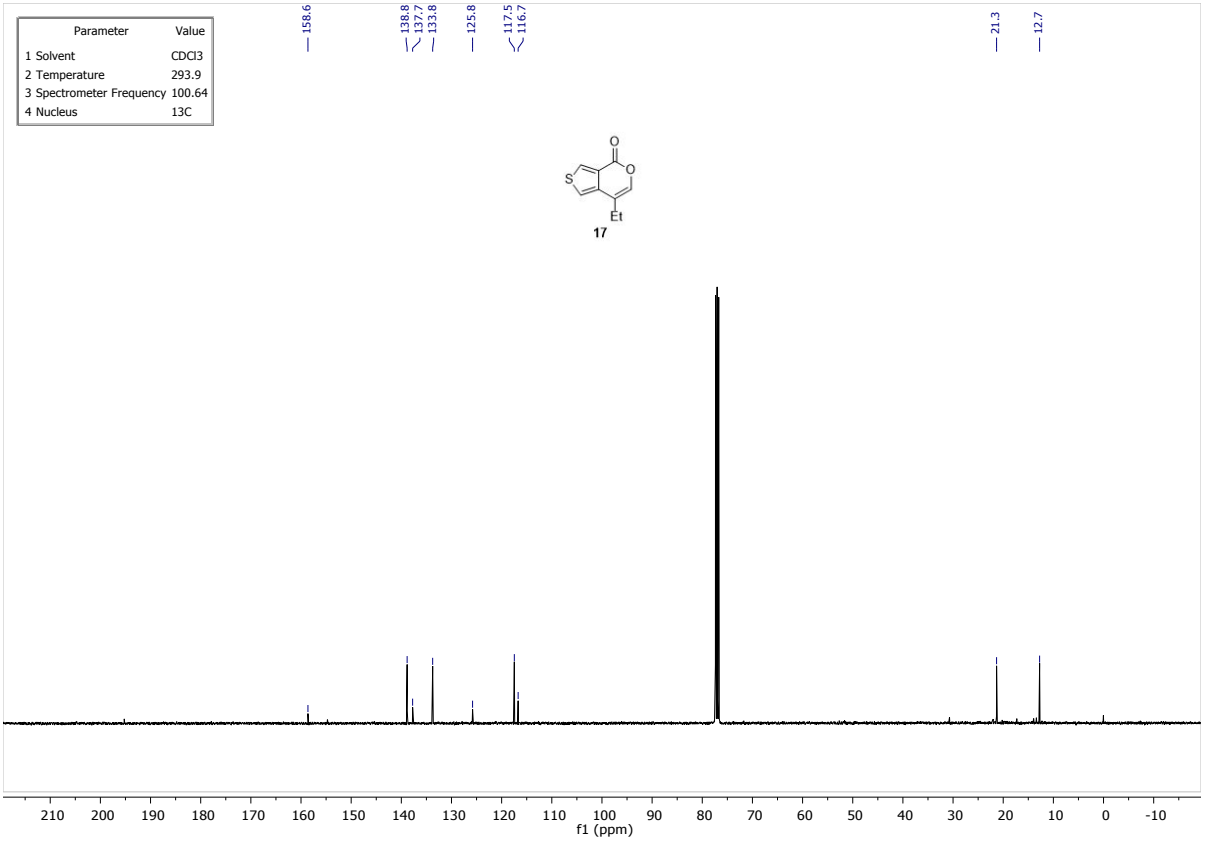
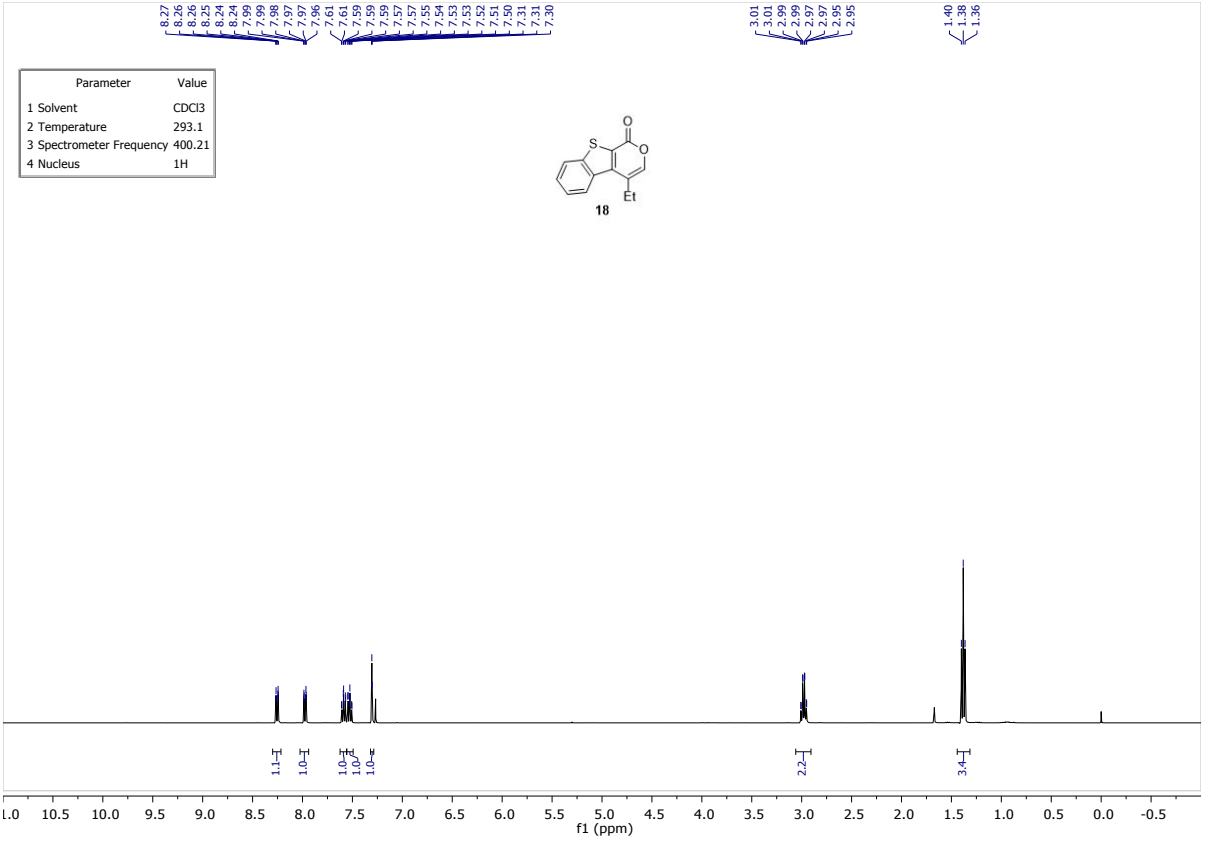
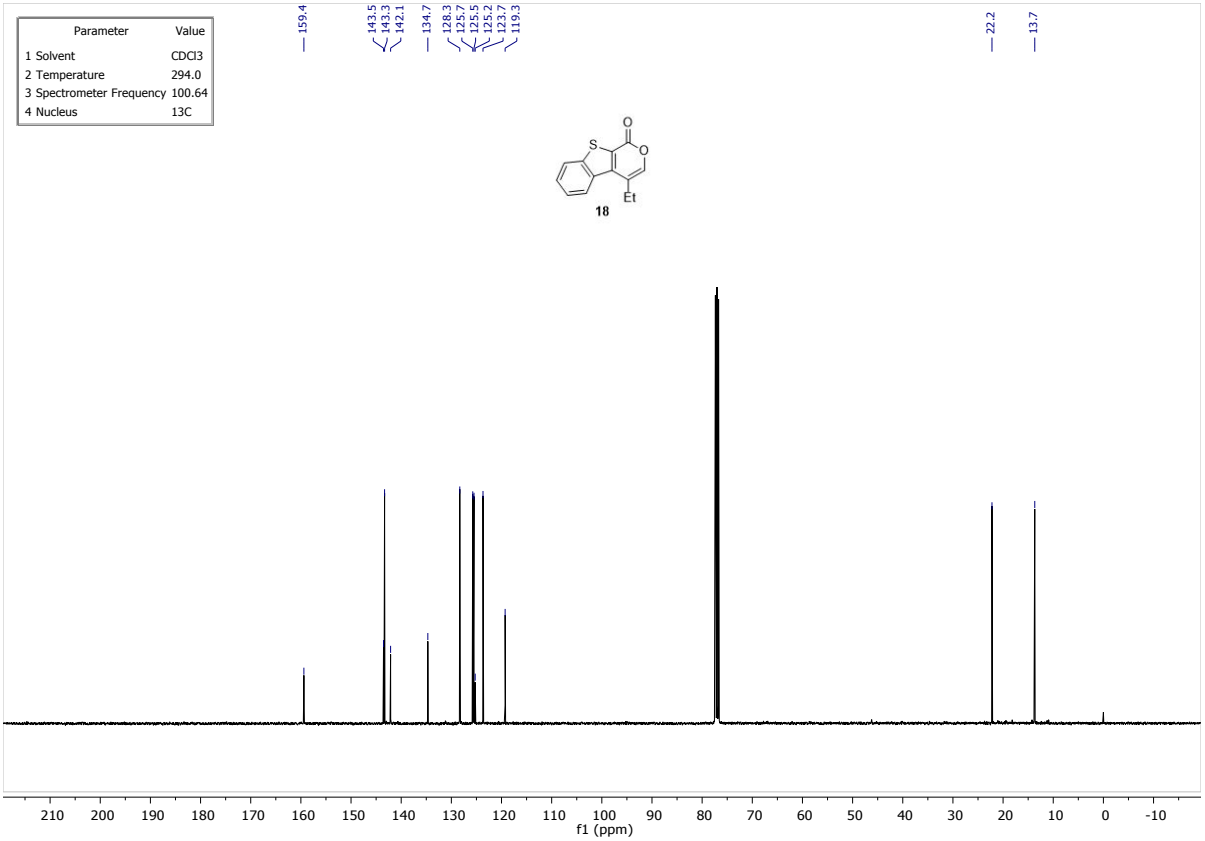
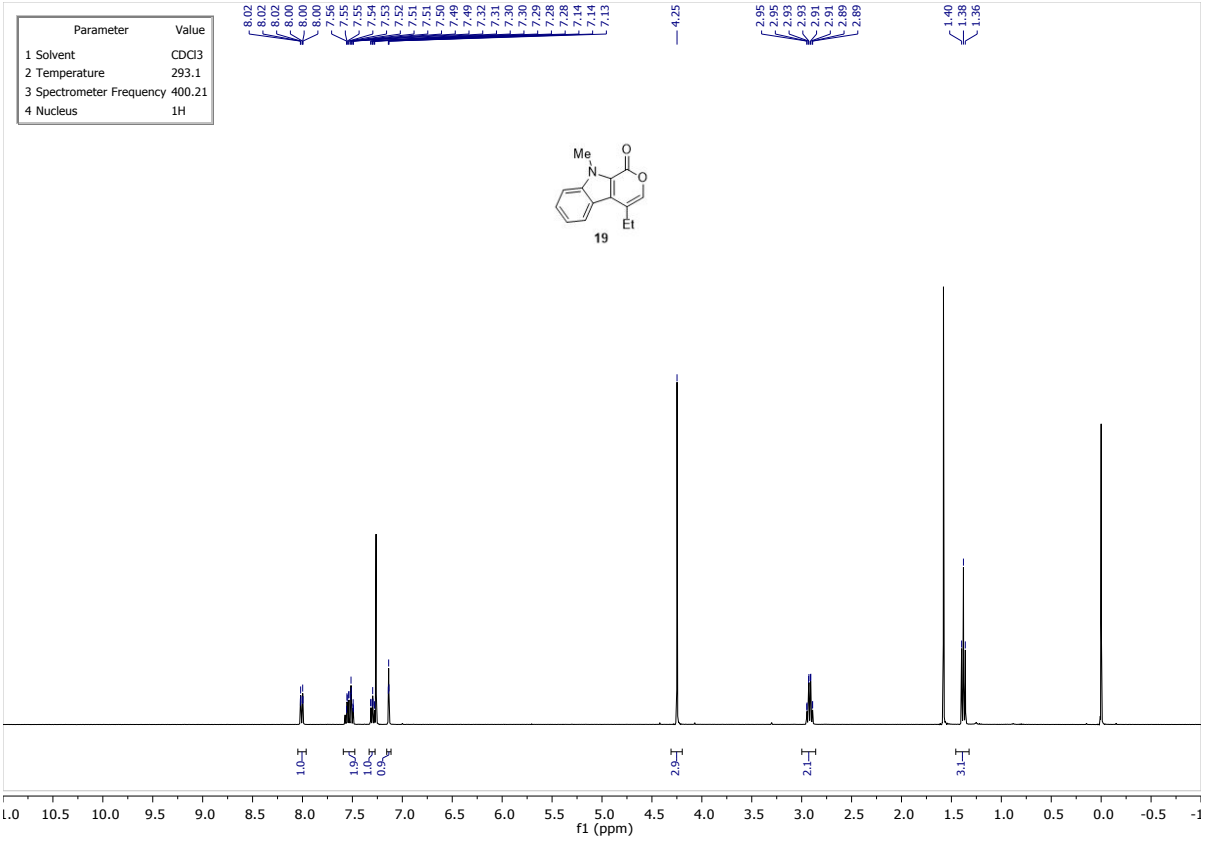
2 Temperature 293.3
3 Spectrometer Frequency 100.64
4 Nucleus 13C
O
O
N
Et
16
f1 (ppm)

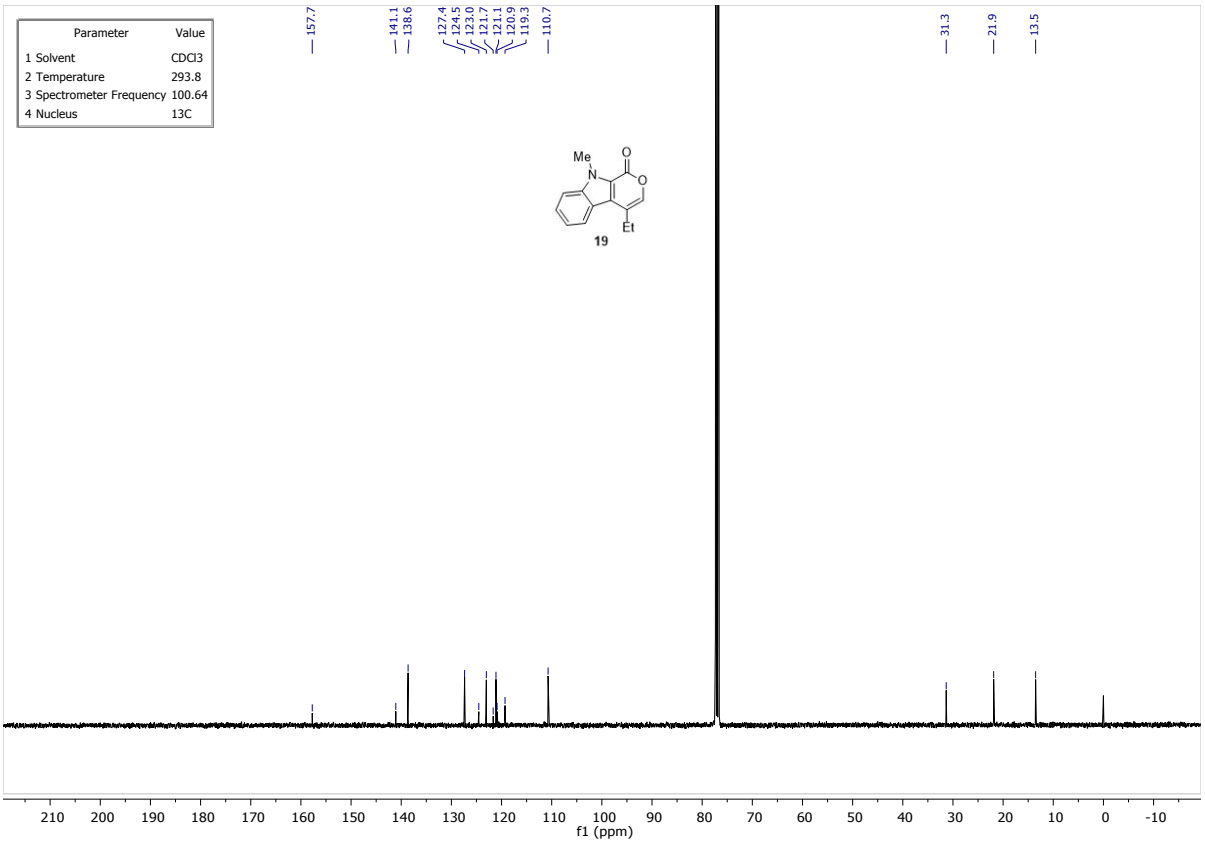

Parameter Value
1 Solvent CDCl3
2 Temperature 293.2
3 Spectrometer Frequency 400.21
4 Nucleus 1H
8.47
8.46
7.33
7.32
6.88
2.58
2.58
2.57
2.56
2.55
2.54
2.53
2.53
1.29
1.28
1.26
O
S
O
Et
17
1.0
1.1
1.1
2.4
3.8
f1 (ppm)

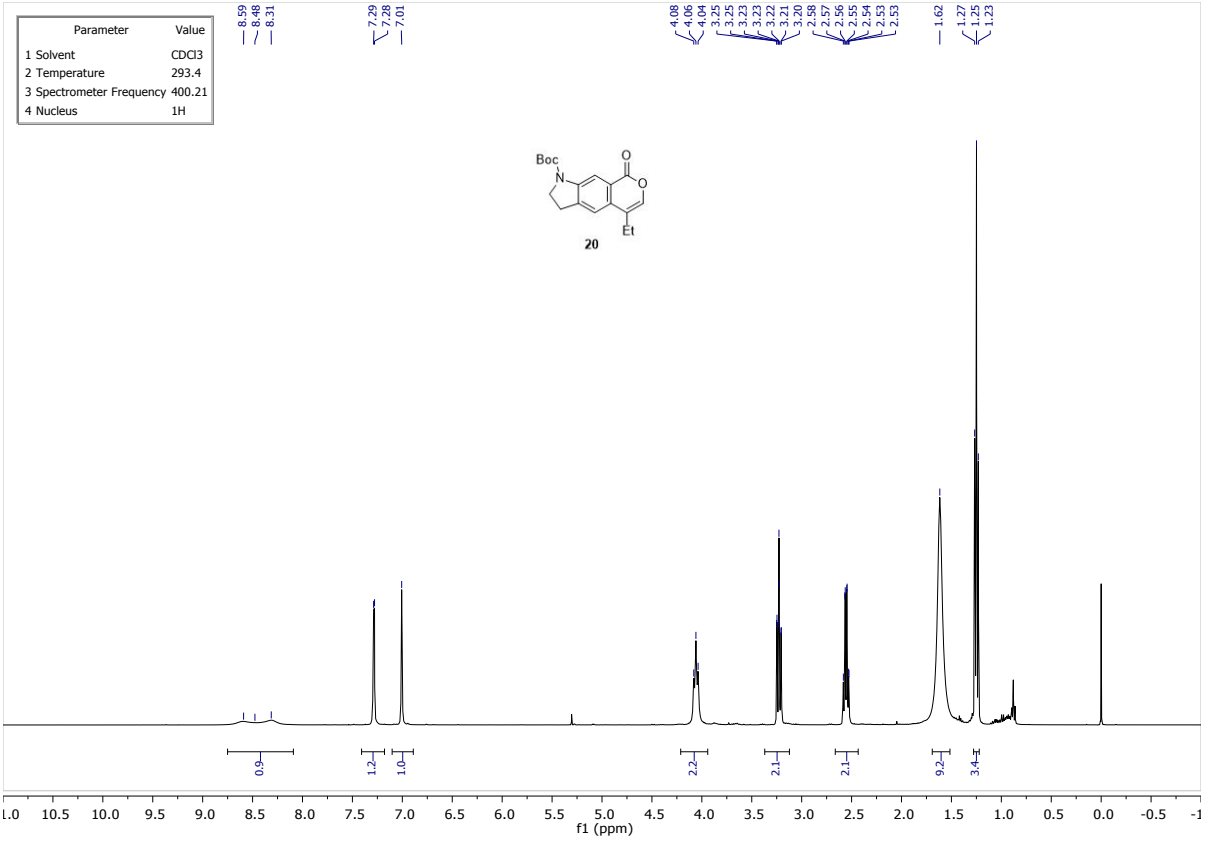

Parameter Value
1 Solvent CDCl3
2 Temperature 293.9
3 Spectrometer Frequency 100.64
4 Nucleus 13C
158.6
138.8
137.7
133.8
125.8
117.5
116.7
21.3
12.7
O
S
O
Et
17
f1 (ppm)

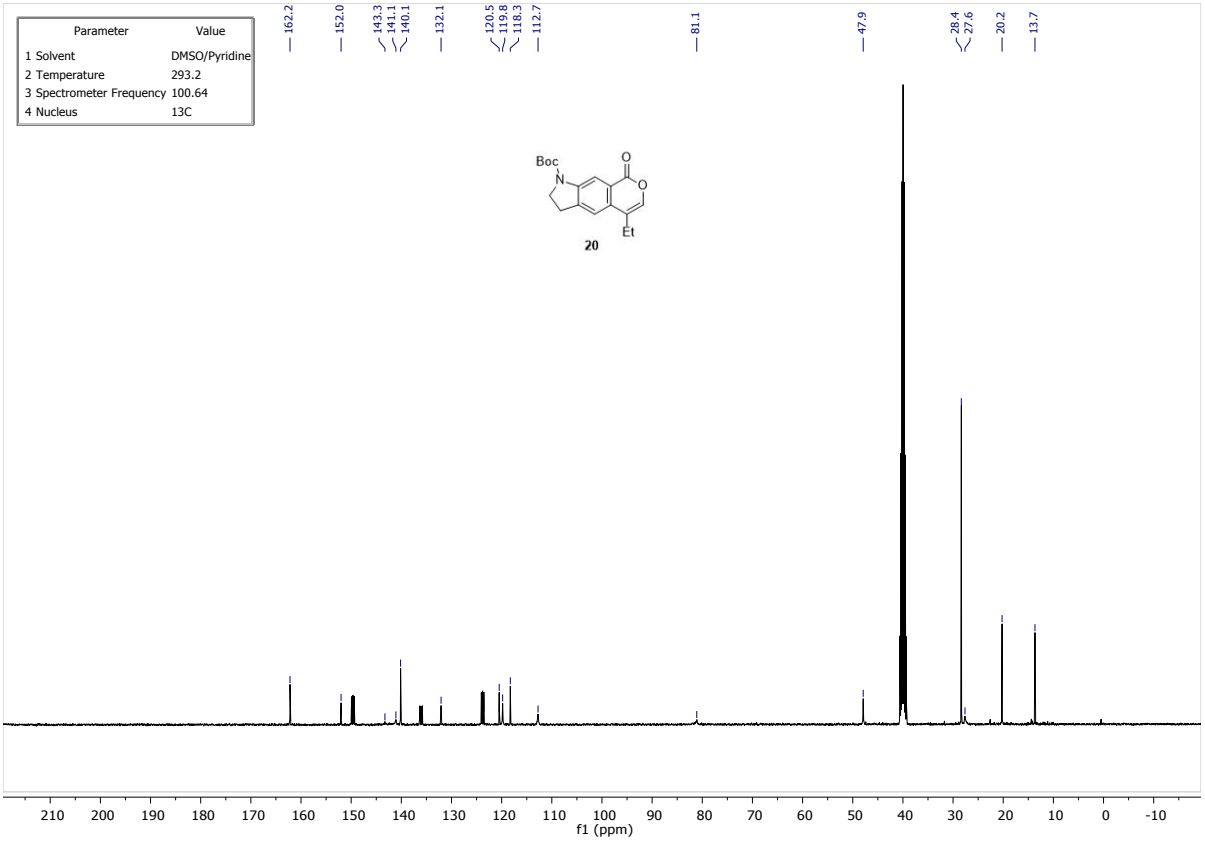

8.27 8.26 8.26 8.26 8.25 8.24 8.24 7.99 7.99 7.98 7.97 7.97 7.96 7.61 7.61 7.59 7.59 7.59 7.57 7.57 7.55 7.54 7.53 7.53 7.52 7.51 7.50 7.31 7.30
3.01 3.01 2.99 2.99 2.97 2.97 2.95 2.95
1.40 1.38 1.36
Parameter Value
1 Solvent CDCl3
2 Temperature 293.1
3 Spectrometer Frequency 400.21
4 Nucleus 1H
S
O
O
Et
18
1.1 1.0 1.0 1.0 1.0 1.0
2.2
3.4
f1 (ppm)

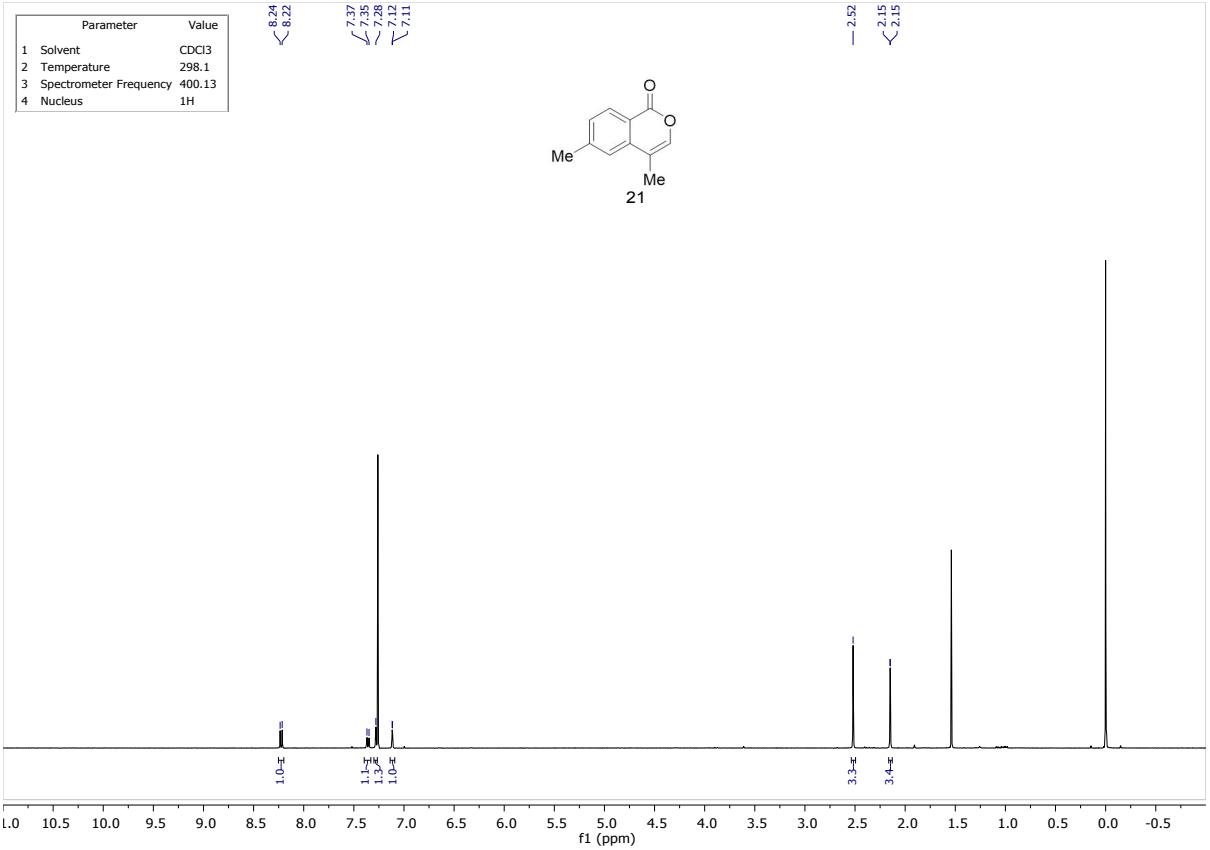

Parameter Value
1 Solvent CDCl3
2 Temperature 294.0
3 Spectrometer Frequency 100.64
4 Nucleus 13C
159.4
143.5 143.3 142.1
134.7
128.3 125.7 125.5 125.2 123.7 119.3
22.2
13.7
S
O
O
Et
18
f1 (ppm)

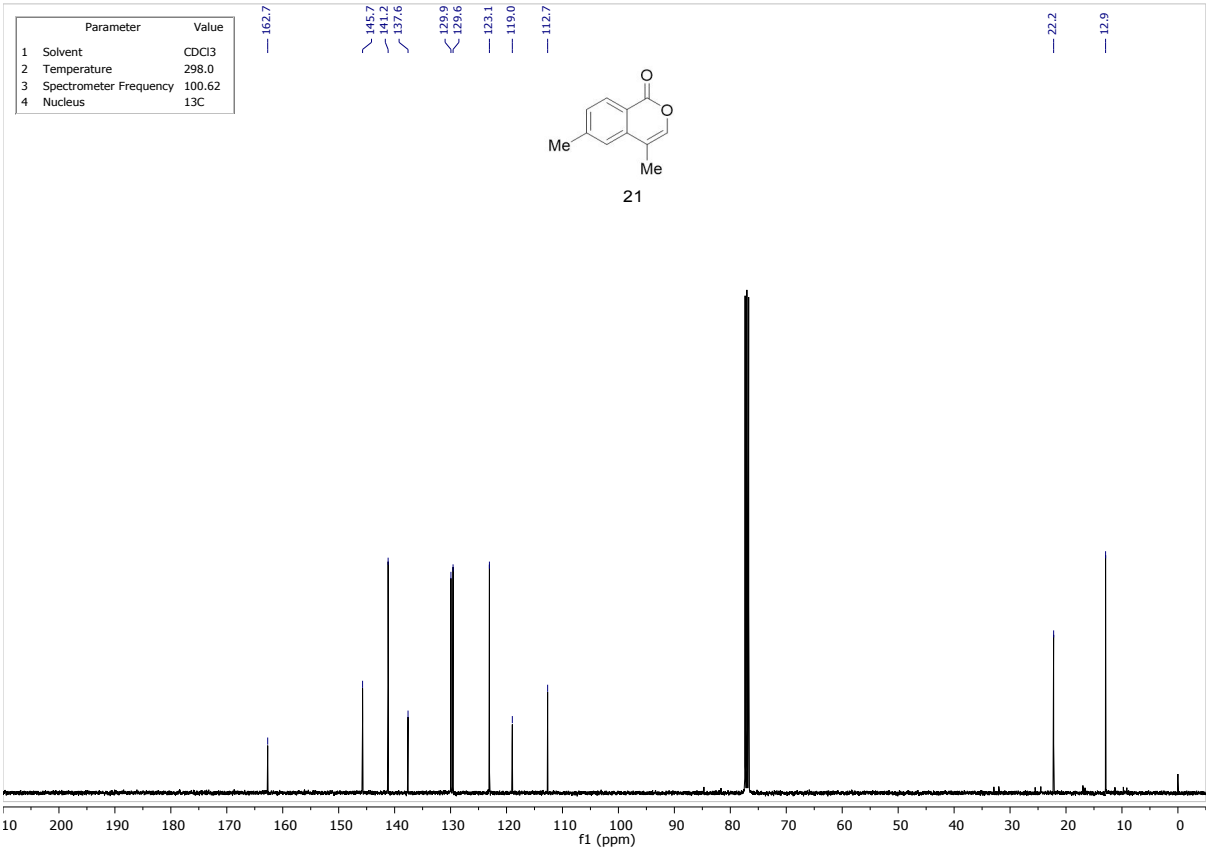

Parameter Value
1 Solvent CDCl3
2 Temperature 293.1
3 Spectrometer Frequency 400.21
4 Nucleus 1H
8.02 8.02 8.02 8.00 8.00 8.00 7.56 7.55 7.55 7.54 7.53 7.52 7.51 7.51 7.50 7.49 7.49 7.32 7.31 7.30 7.30 7.29 7.28 7.28 7.14 7.14 7.13
4.25
2.95 2.95 2.93 2.93 2.91 2.91 2.89 2.89
1.40 1.38 1.36
Me
N
O
O
Et
19
1.0 1.9 1.0 0.9 2.9 2.1 3.1
f1 (ppm)

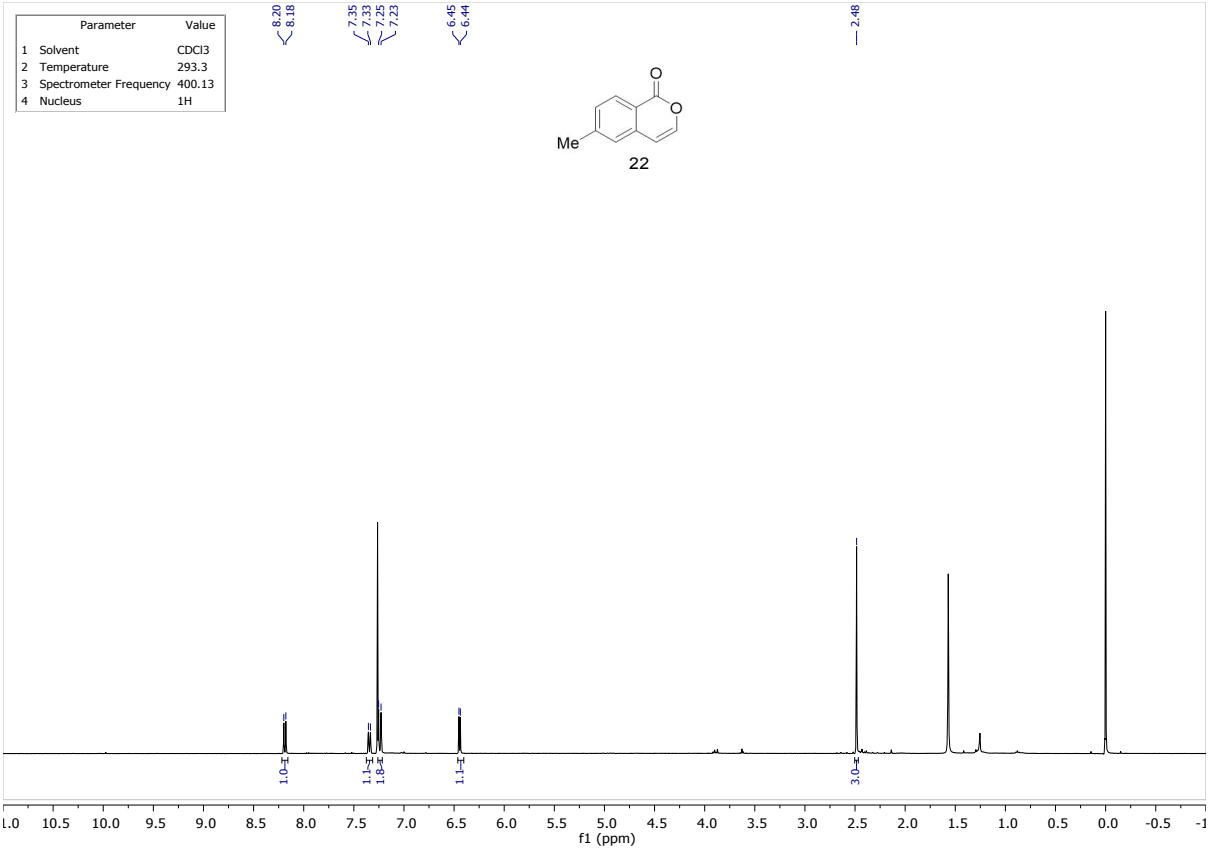

Parameter Value
1 Solvent CDCl3
2 Temperature 293.8
3 Spectrometer Frequency 100.64
4 Nucleus 13C
157.7
141.1 138.6
127.4 124.5 123.0 121.7 121.1 120.9 119.3
110.7
31.3
21.9
13.5
Me
N
O
O
Et
19
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.4
3 Spectrometer Frequency 400.21
4 Nucleus 1H
8.59 8.48 8.31 7.29 7.28 7.01 4.08 4.06 4.04 3.25 3.25 3.23 3.23 3.22 3.21 3.20 2.58 2.57 2.56 2.55 2.54 2.53 2.53 1.62 1.27 1.25 1.23
Boc
N
O
O
Et
20
0.9 1.2 1.0 2.2 2.1 2.1 9.2 3.4
f1 (ppm)


Parameter Value
1 Solvent DMSO/Pyridine
2 Temperature 293.2
3 Spectrometer Frequency 100.64
4 Nucleus 13C
162.2 152.0 143.3 141.1 140.1 132.1 120.5 119.8 118.3 112.7 81.1 47.9 28.4 27.6 20.2 13.7
Boc
N
O
O
Et
20
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 298.1
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.24
8.22
7.37
7.35
7.28
7.12
7.11
2.52
2.15
2.15
O
O
Me
Me
21
1.0
1.1
1.3
1.0
3.3
3.4
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.7
145.7
141.2
137.6
129.9
129.6
123.1
119.0
112.7
22.2
12.9
O
O
Me
Me
21
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.3
3 Spectrometer Frequency 400.13
4 Nucleus 1H
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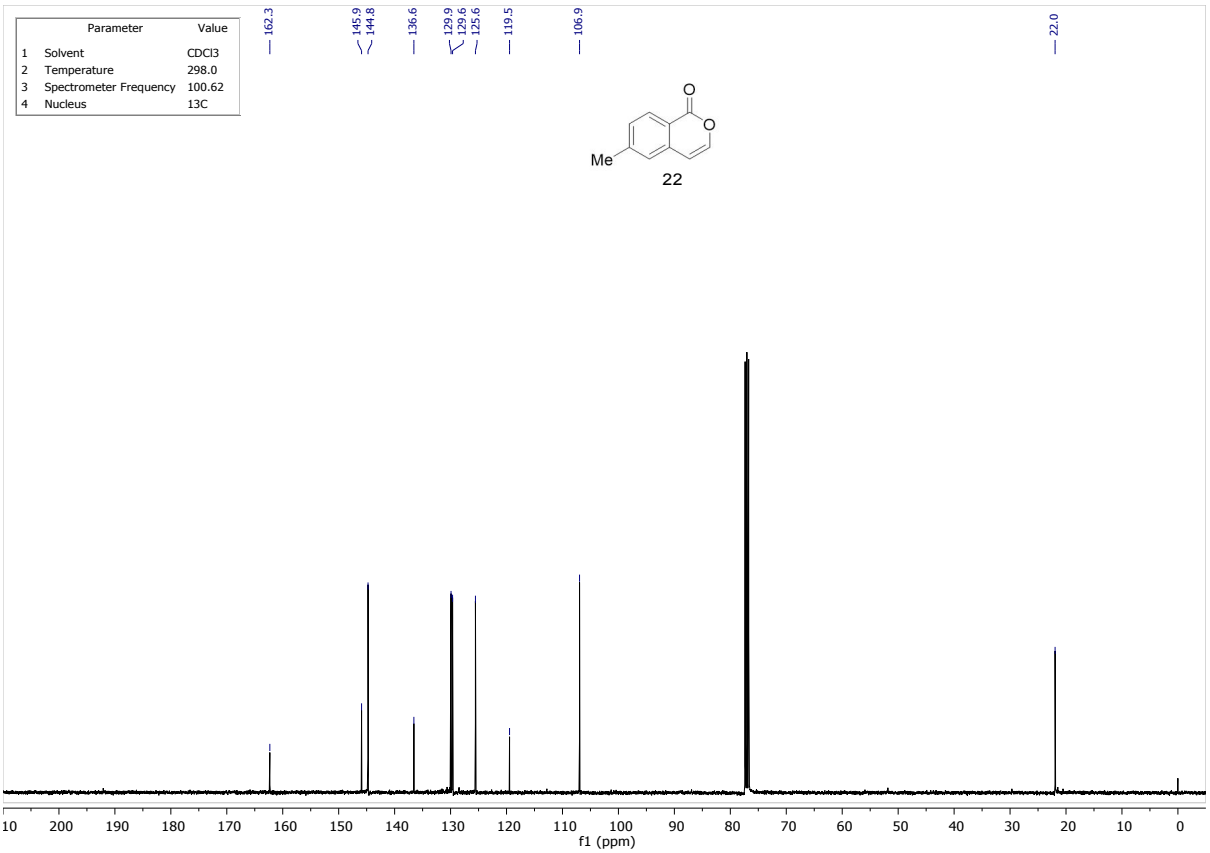
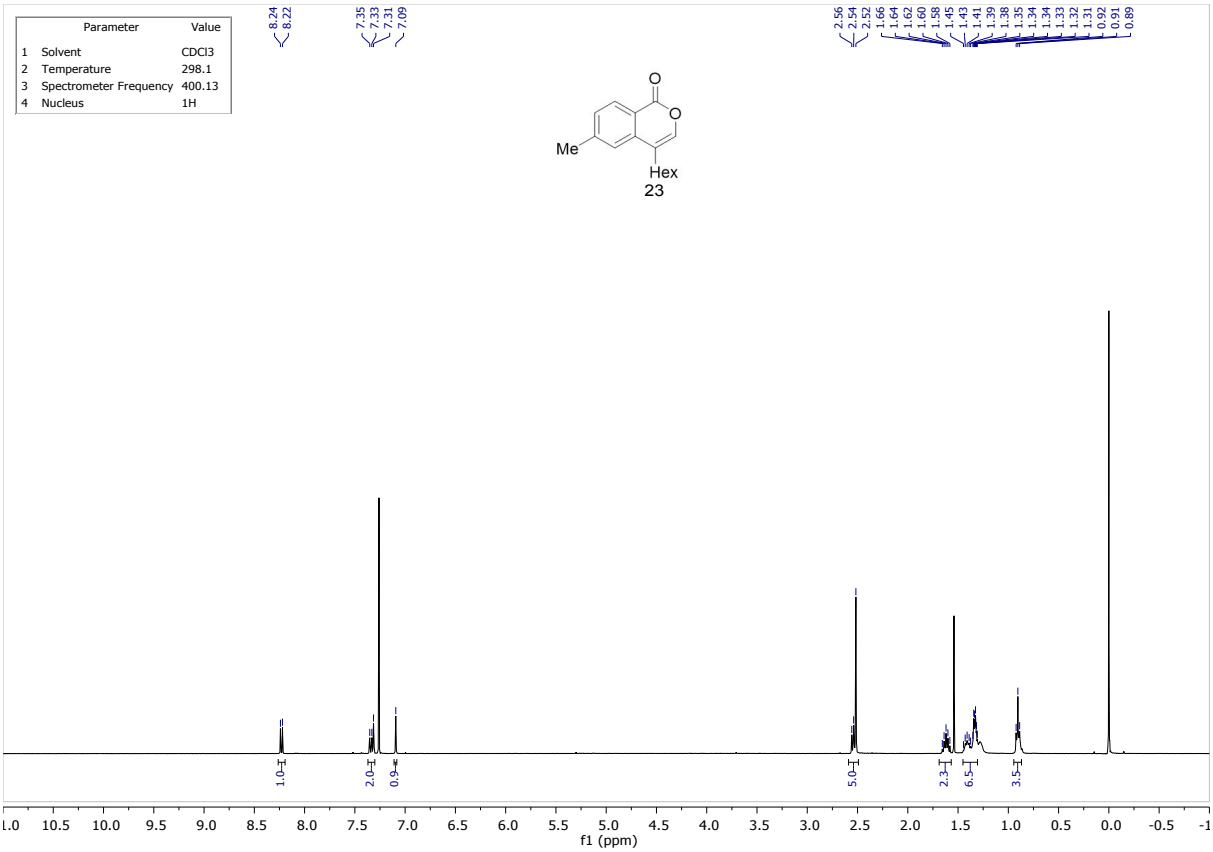
8.18
7.35
7.33
7.25
7.23
6.45
6.44
2.48
Me
22
1.0
1.1
1.8
1.1
3.0
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.3
145.9
144.8
136.6
129.9
129.6
125.6
119.5
106.9
22.0
Me
22
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 298.1
3 Spectrometer Frequency 400.13
4 Nucleus 1H
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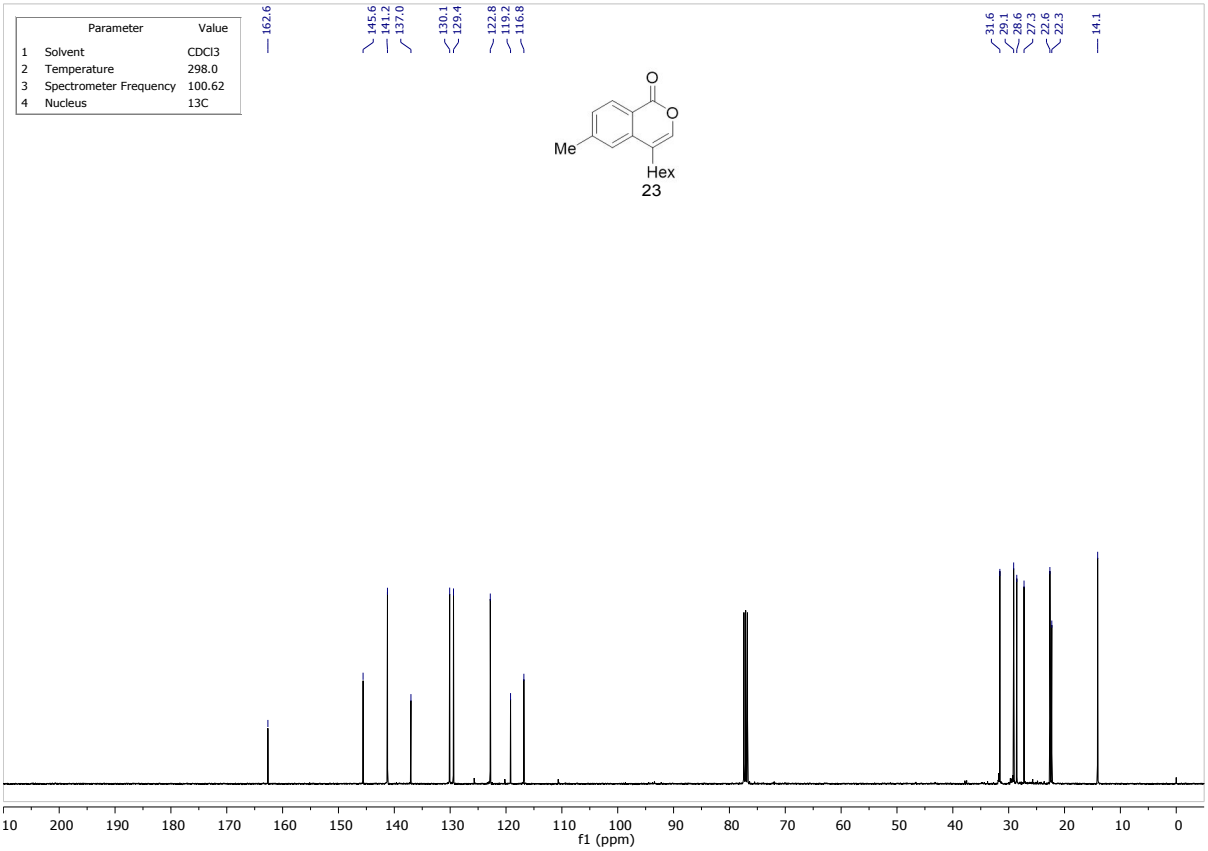
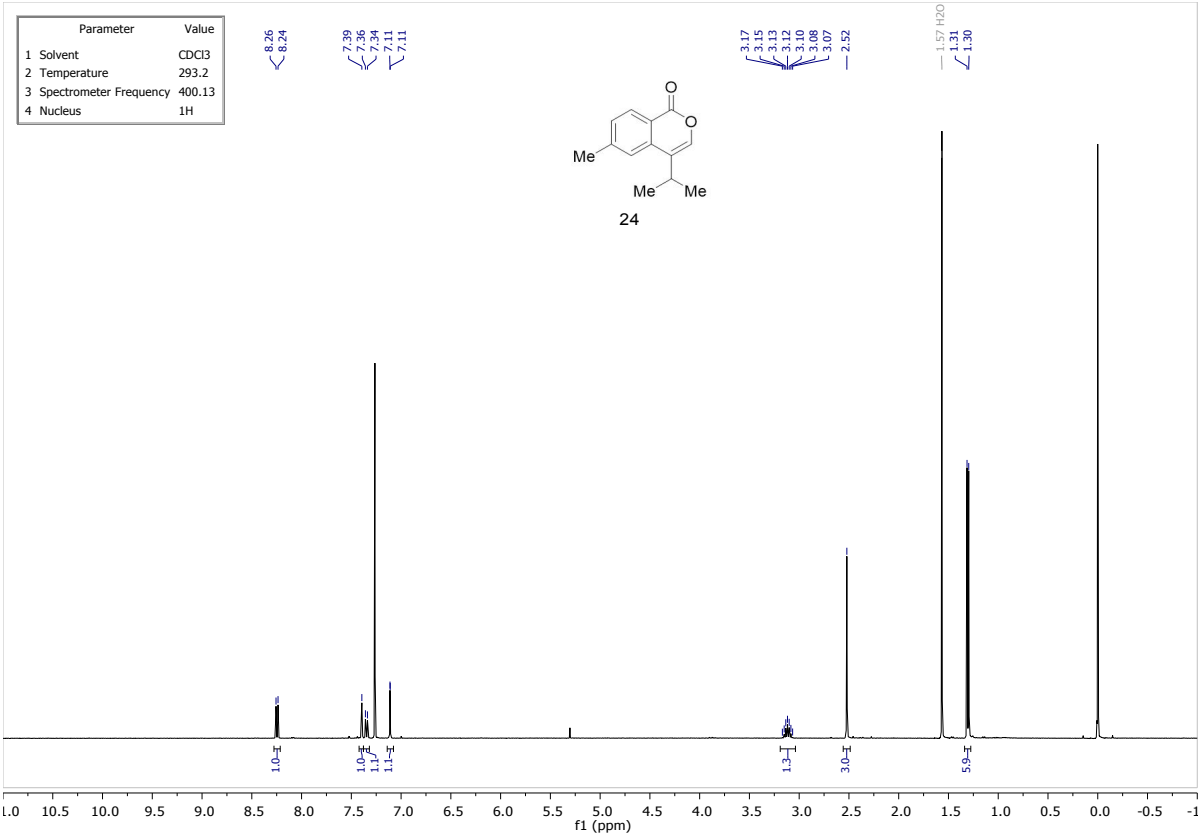
8.22
7.35
7.33
7.31
7.09
2.56
2.54
2.52
1.66
1.64
1.62
1.60
1.58
1.45
1.43
1.41
1.39
1.38
1.35
1.34
1.34
1.33
1.32
1.31
0.92
0.91
0.89
O
O
Me
Hex
23
1.0
2.0
0.9
5.0
2.3
6.5
3.5
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.6
145.6
141.2
137.0
130.1
129.4
122.8
119.2
116.8
31.6
29.1
28.6
27.3
22.6
22.3
14.1
O
O
Me
Hex
23
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.2
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.26
8.24
7.39
7.36
7.34
7.11
7.11
3.17
3.15
3.13
3.12
3.10
3.08
3.07
2.52
1.57 H2O
1.31
1.30
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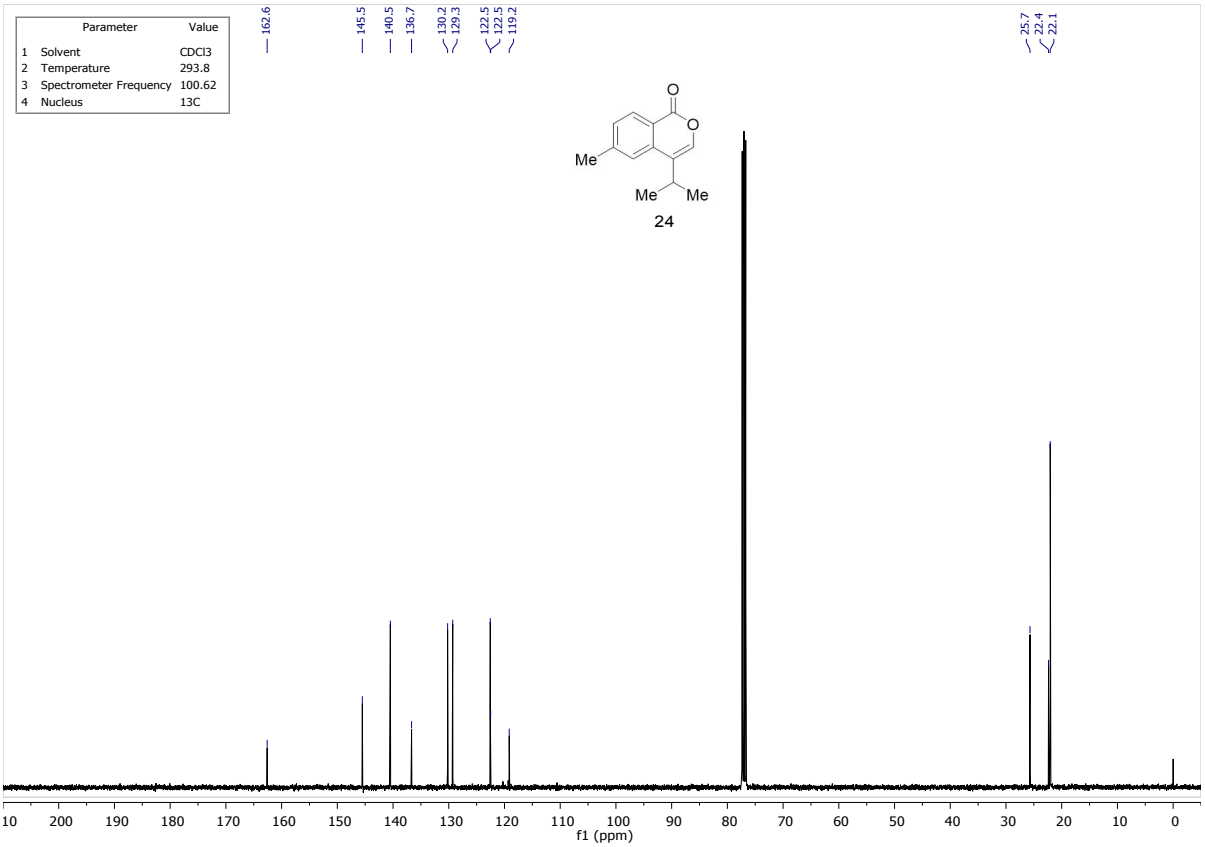
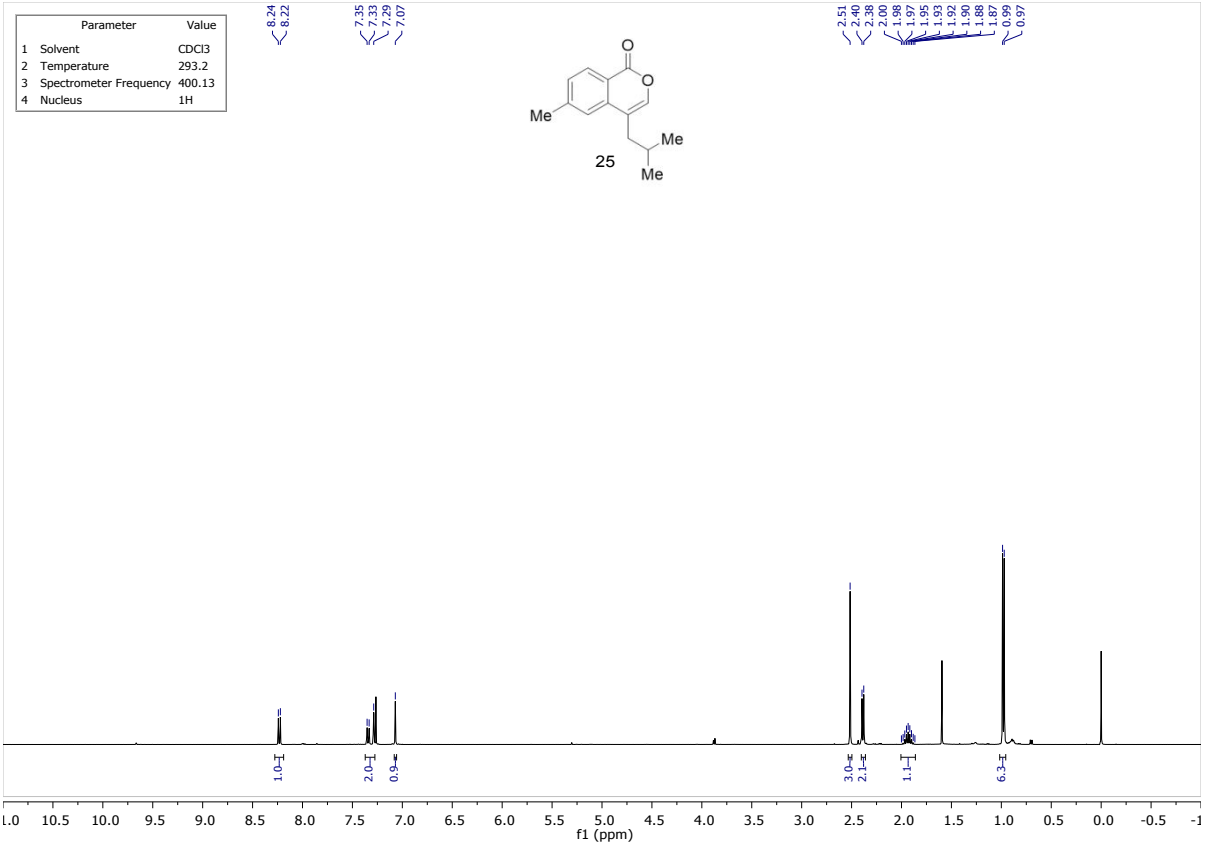
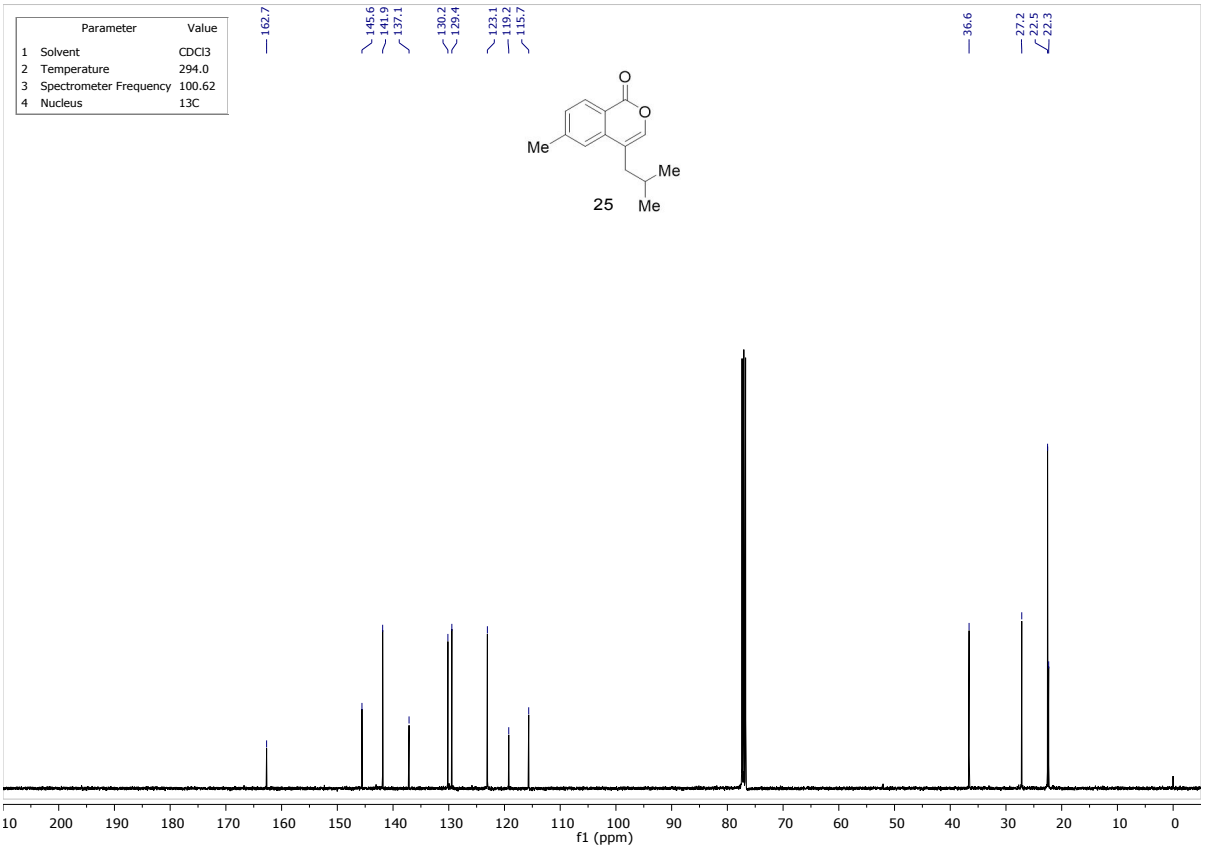
Me
24
1.0
1.0
1.1
1.1
1.3
3.0
5.9
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.8
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.6
145.5
140.5
136.7
130.2
129.3
122.5
122.5
119.2
25.7
22.4
22.1
Me
Me
Me
24
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.2
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.24
8.22
7.35
7.33
7.29
7.07
2.51
2.40
2.38
2.00
1.98
1.97
1.95
1.93
1.92
1.90
1.88
1.87
0.99
0.97
O
O
Me
Me
Me
25
1.0
2.0
0.9
3.0
2.1
1.1
6.3
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 294.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.7
145.6
141.9
137.1
130.2
129.4
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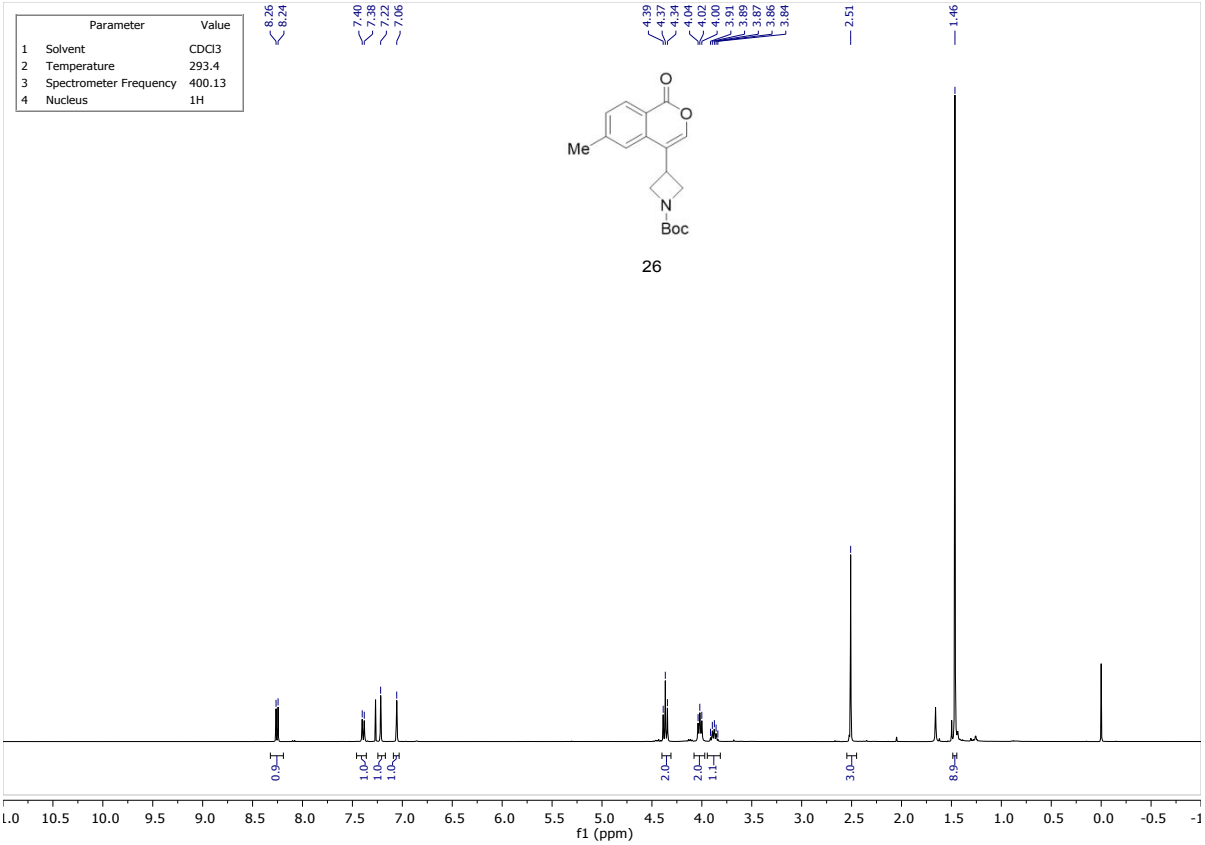
22.3
O
O
Me
Me
Me
25
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.4
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.26
8.24
7.40
7.38
7.22
7.06
4.39
4.37
4.34
4.04
4.02
4.00
3.91
3.89
3.87
3.86
3.84
2.51
1.46
Me
N
Boc
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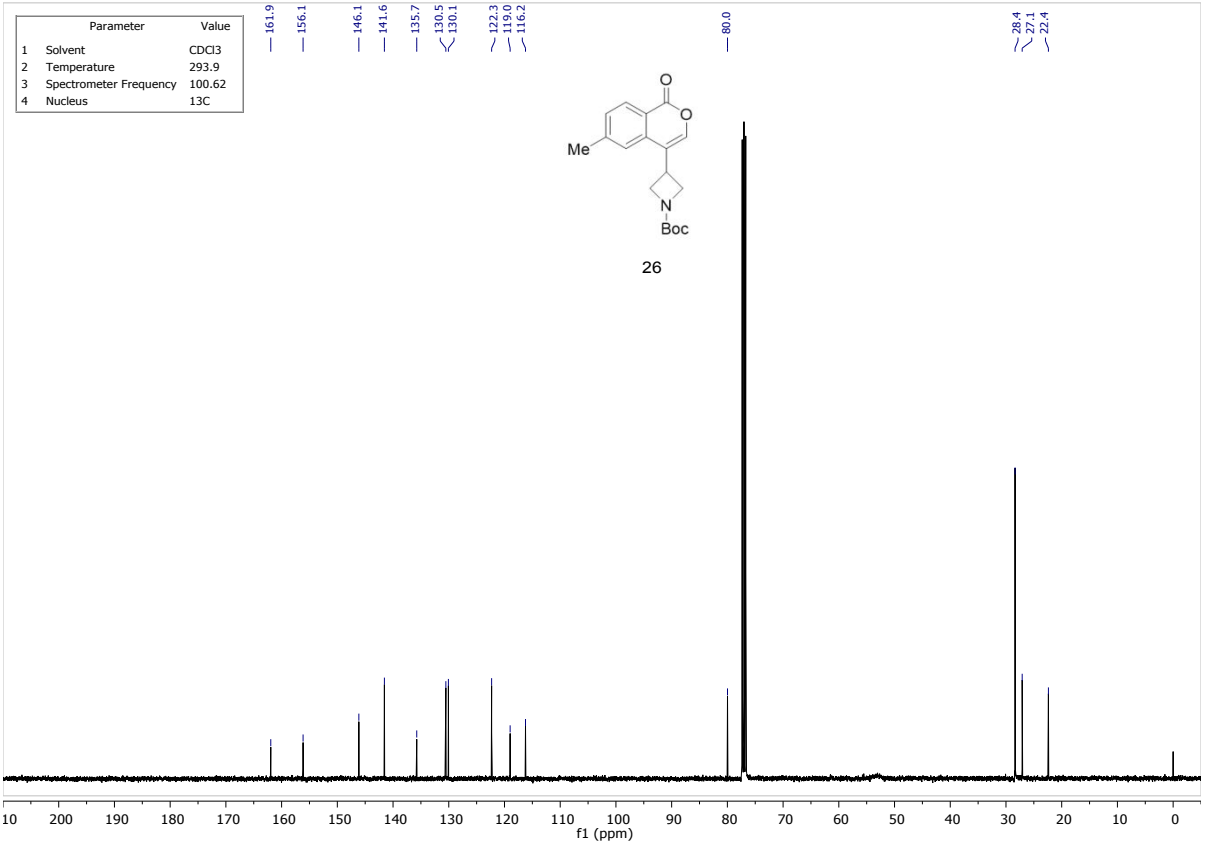
1.0
1.0
1.0
2.0
2.0
1.1
3.0
8.9
f1 (ppm)


Parameter Value
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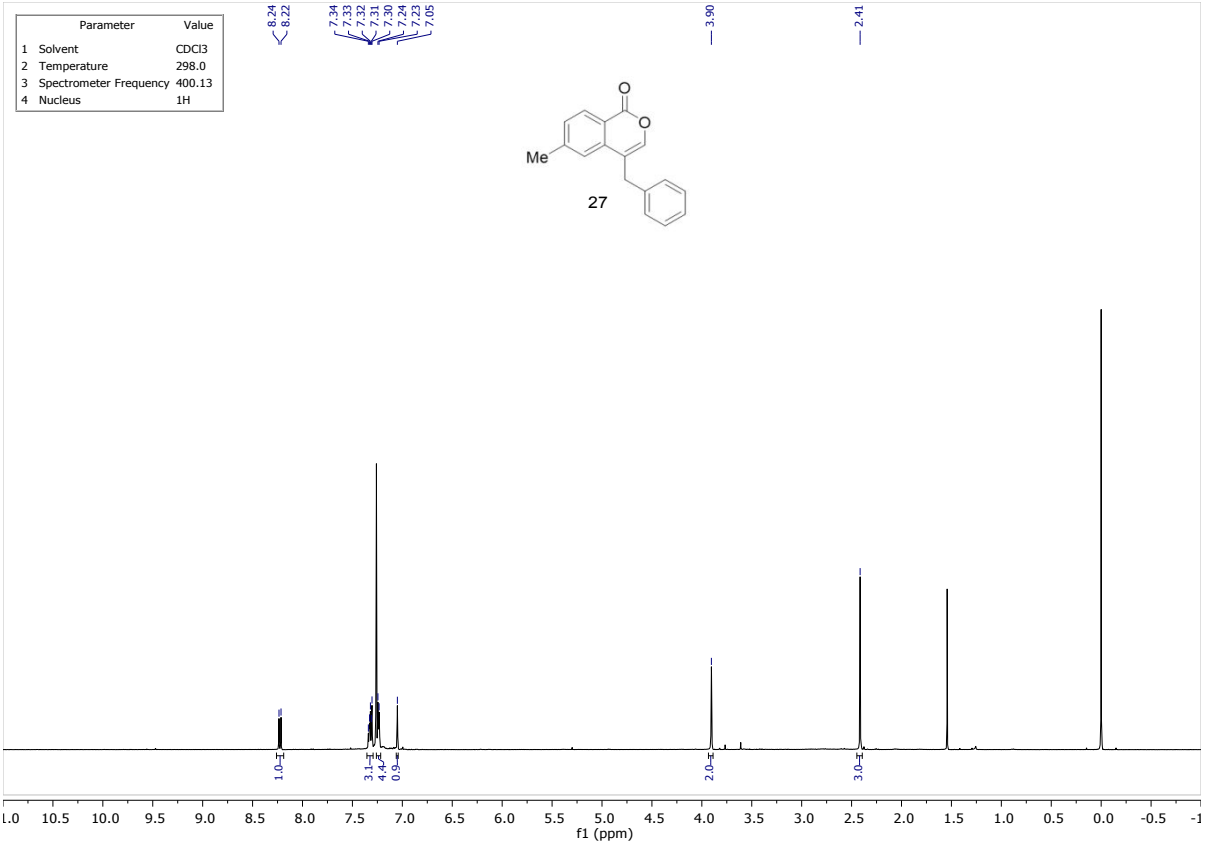
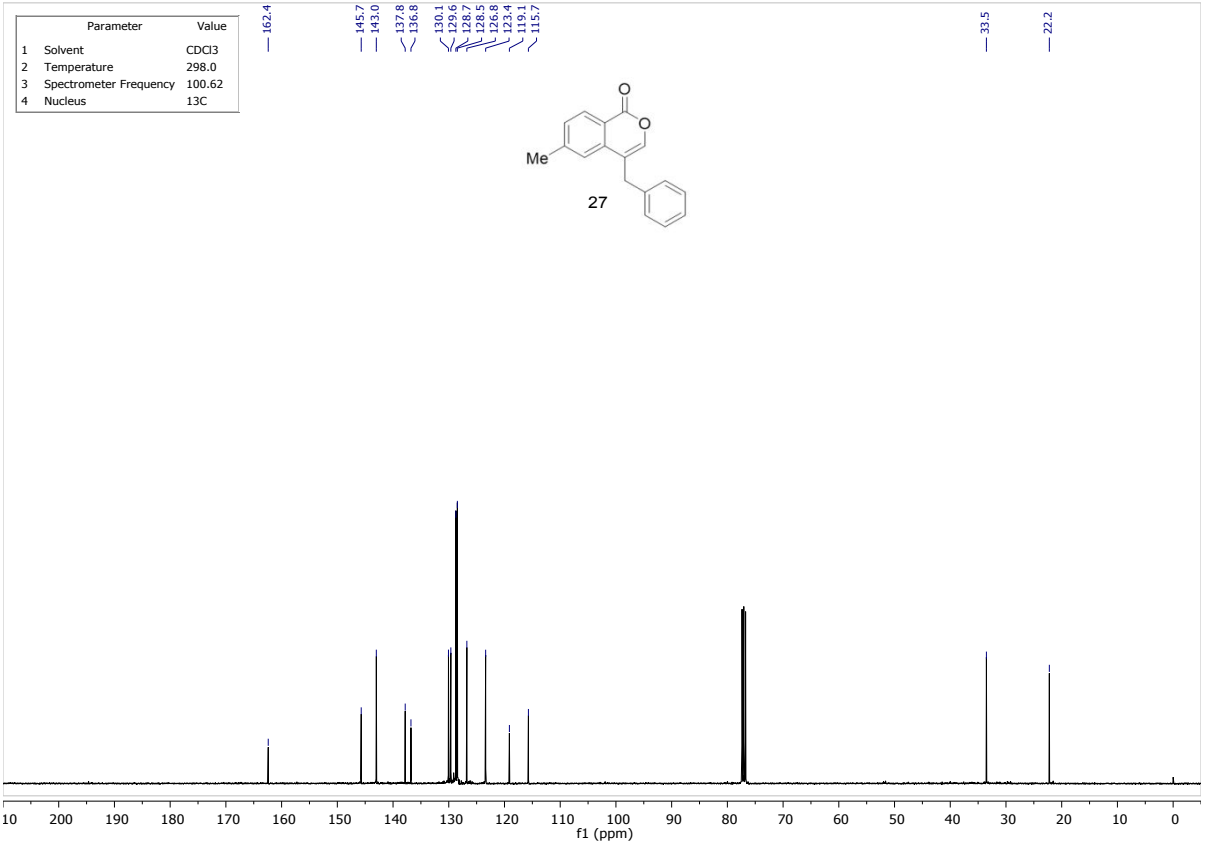
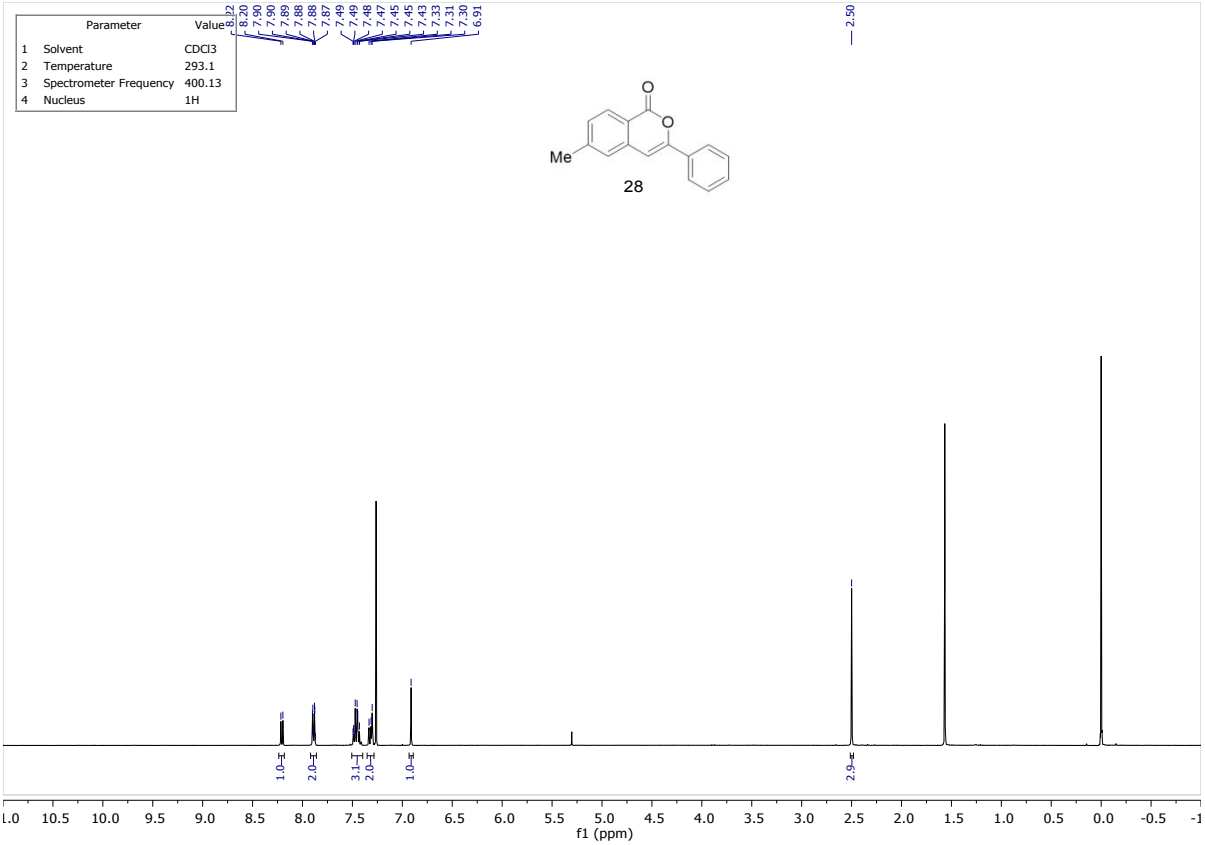
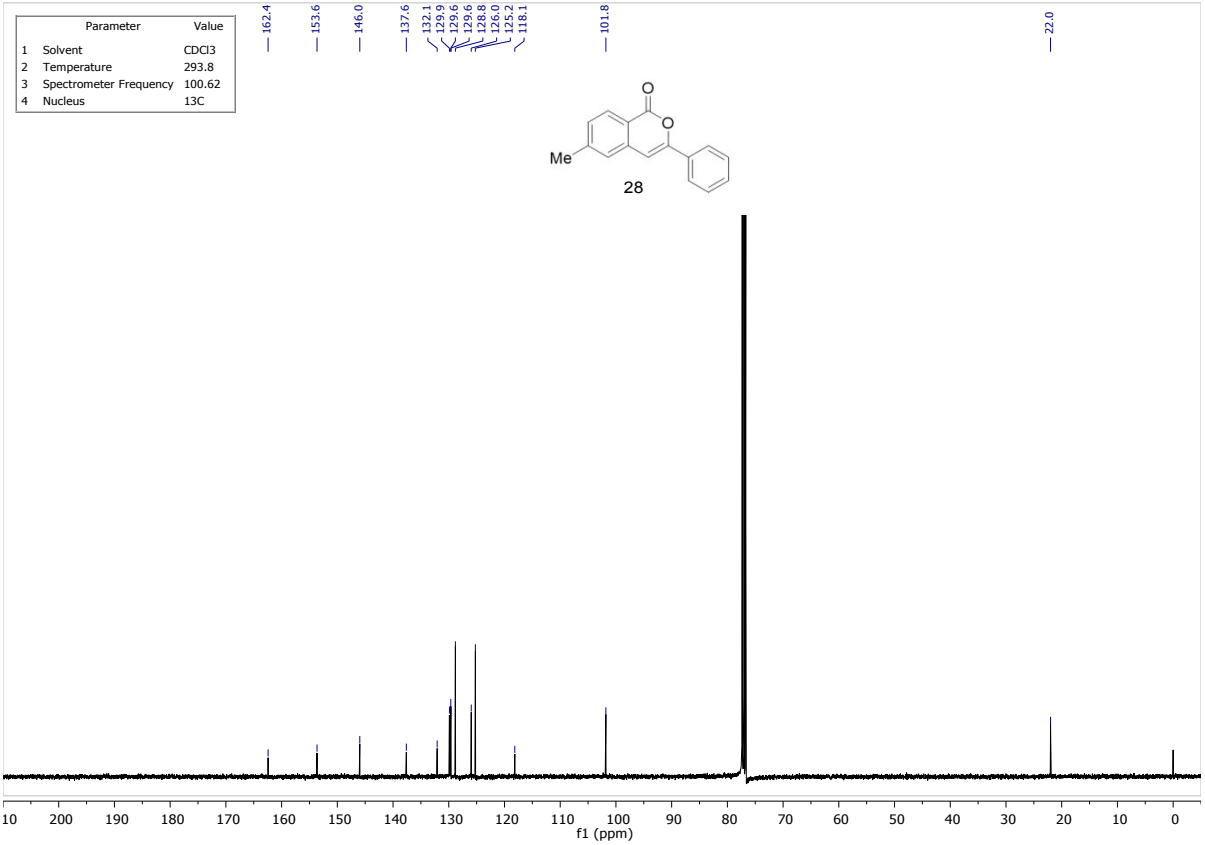
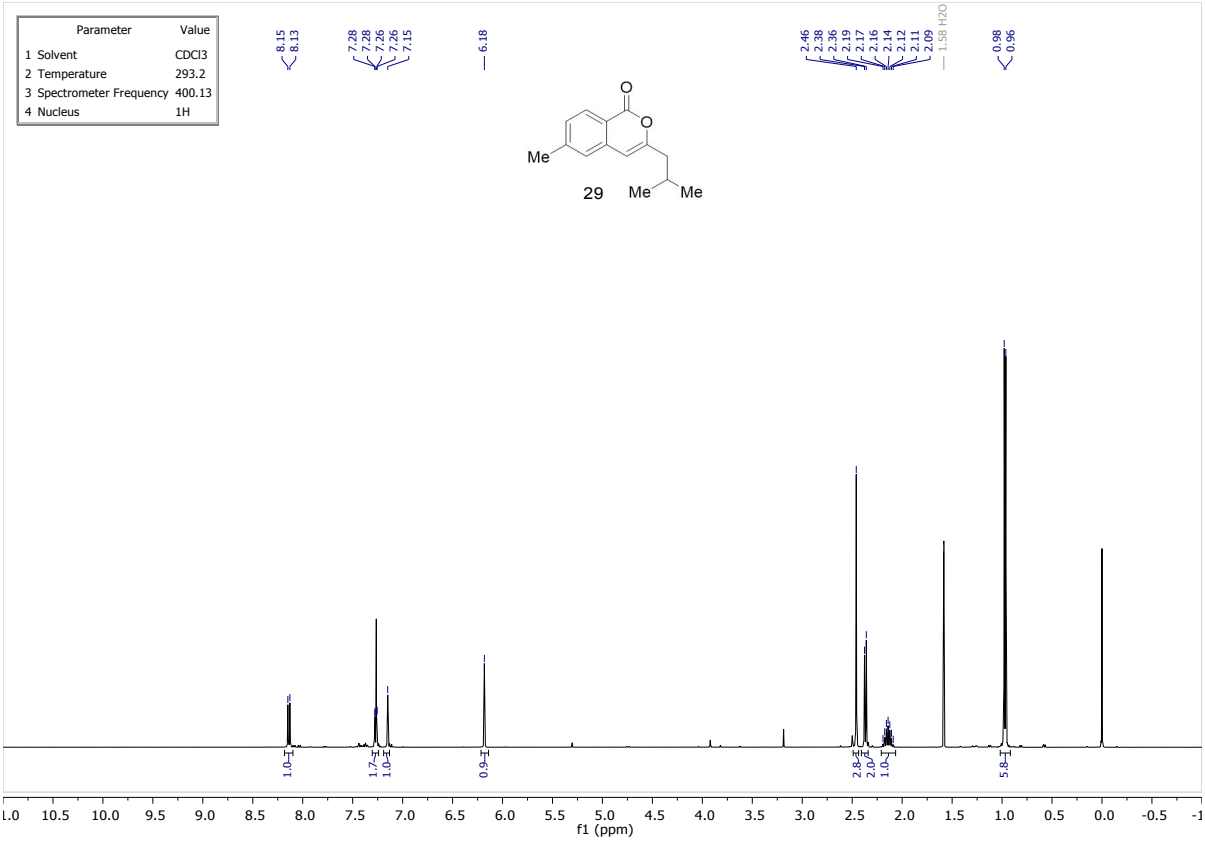
2 Temperature 293.9
3 Spectrometer Frequency 100.62
4 Nucleus 13C
161.9
156.1
146.1
141.6
135.7
130.5
130.1
122.3
119.0
116.2
80.0
28.4
27.1
22.4
Me
N
Boc
26
f1 (ppm)

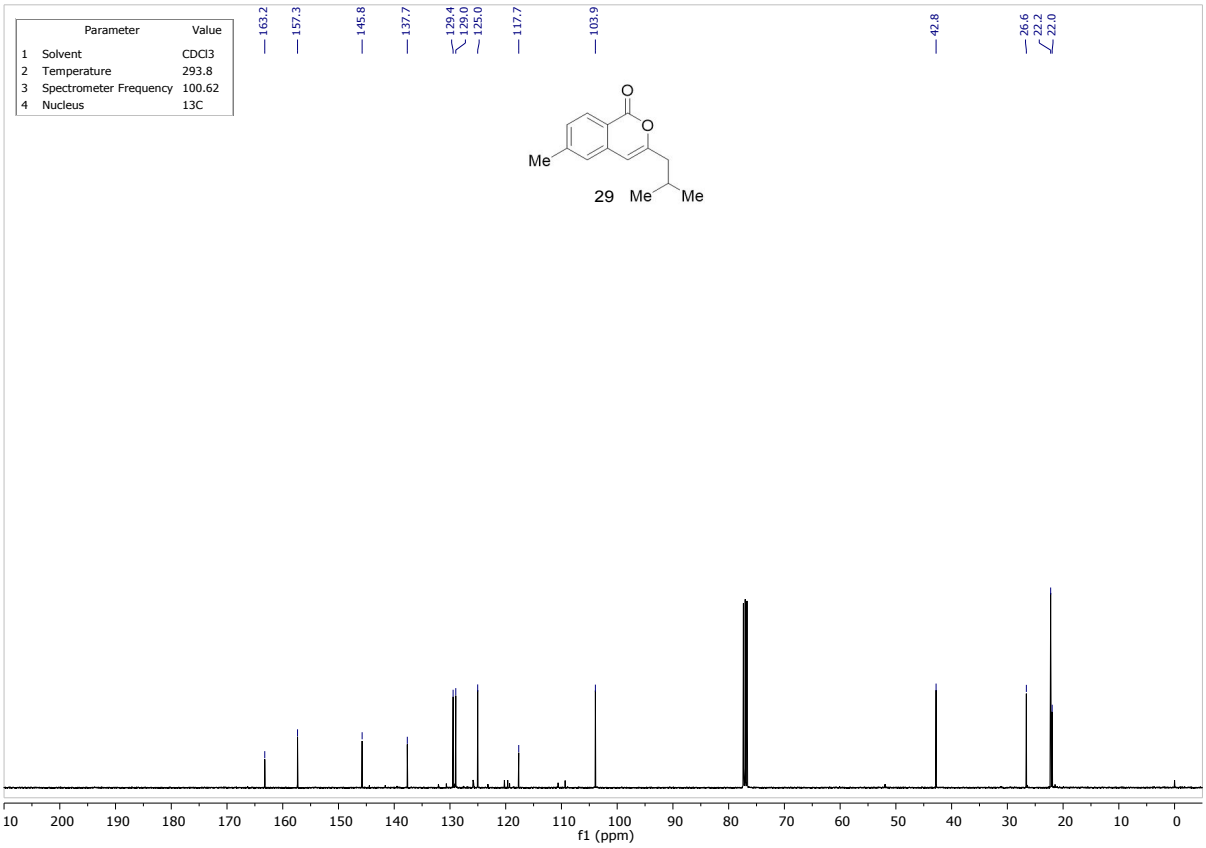

Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.24
8.22
7.34
7.33
7.32
7.31
7.30
7.24
7.23
7.05
3.90
2.41
Me
27
1.0
3.1
4.4
0.9
2.0
3.0
f1 (ppm)

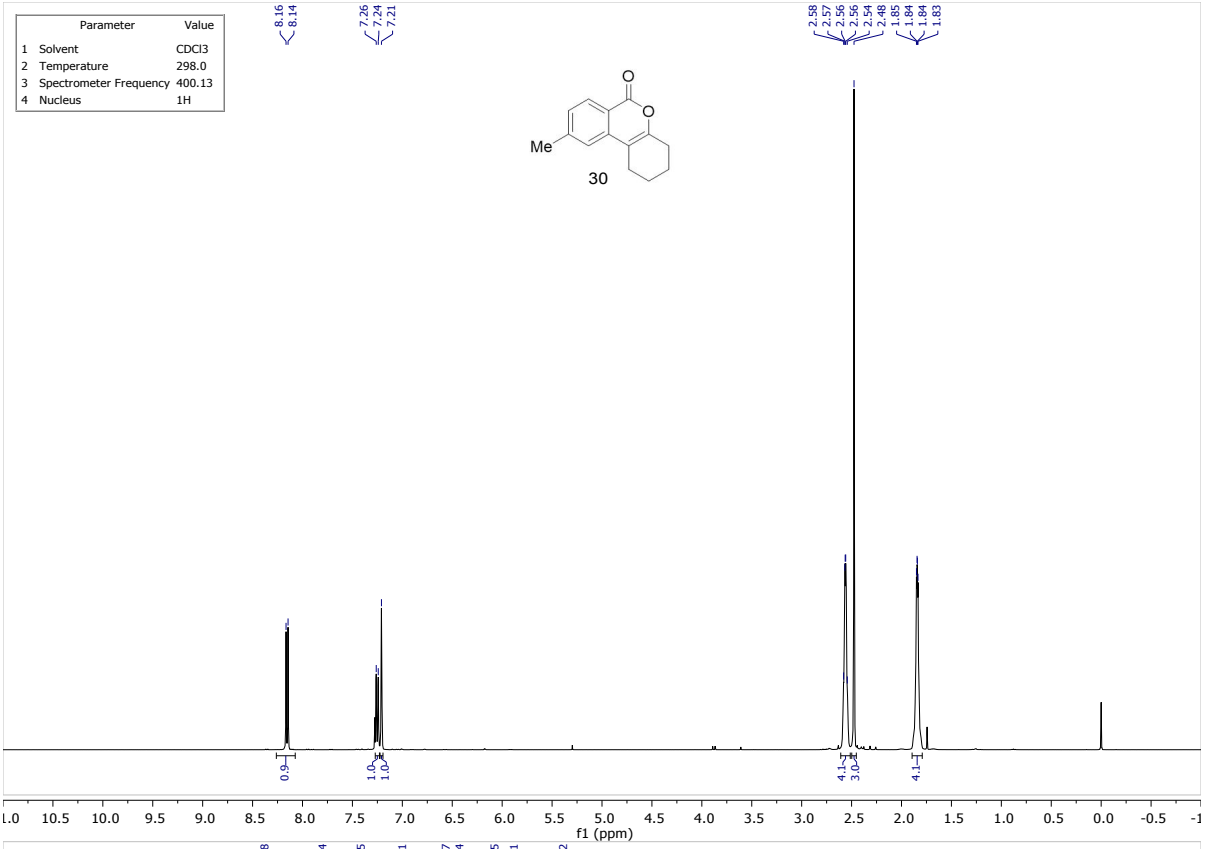

Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.4
145.7
143.0
137.8
136.8
130.1
129.6
128.7
128.5
126.8
123.4
119.1
115.7
33.5
22.2
Me
27
f1 (ppm)

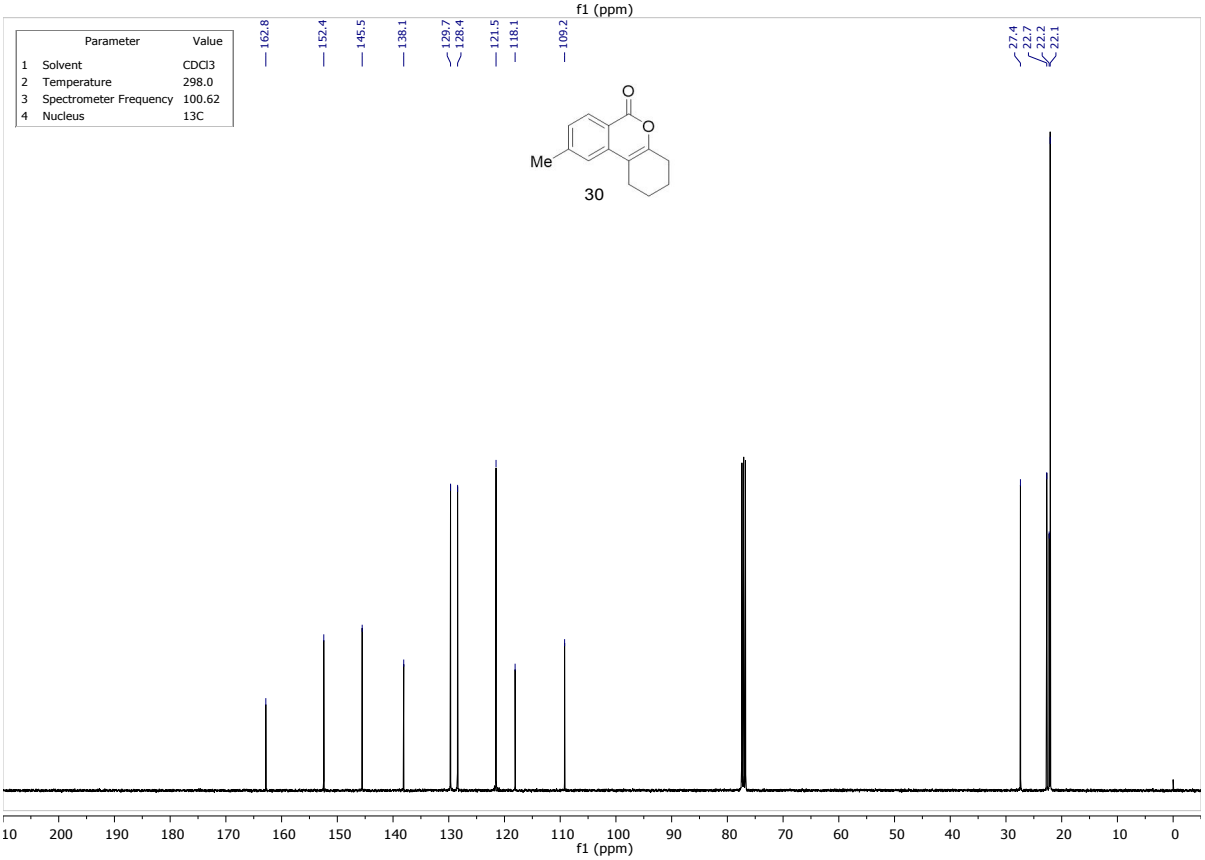

Parameter Value
1 Solvent CDCl3
2 Temperature 293.1
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.22
8.20
7.90
7.90
7.89
7.88
7.88
7.87
7.49
7.49
7.48
7.47
7.45
7.45
7.43
7.33
7.31
7.30
6.91
2.50
Me
28
1.0
2.0
3.1
2.0
1.0
2.9
f1 (ppm)

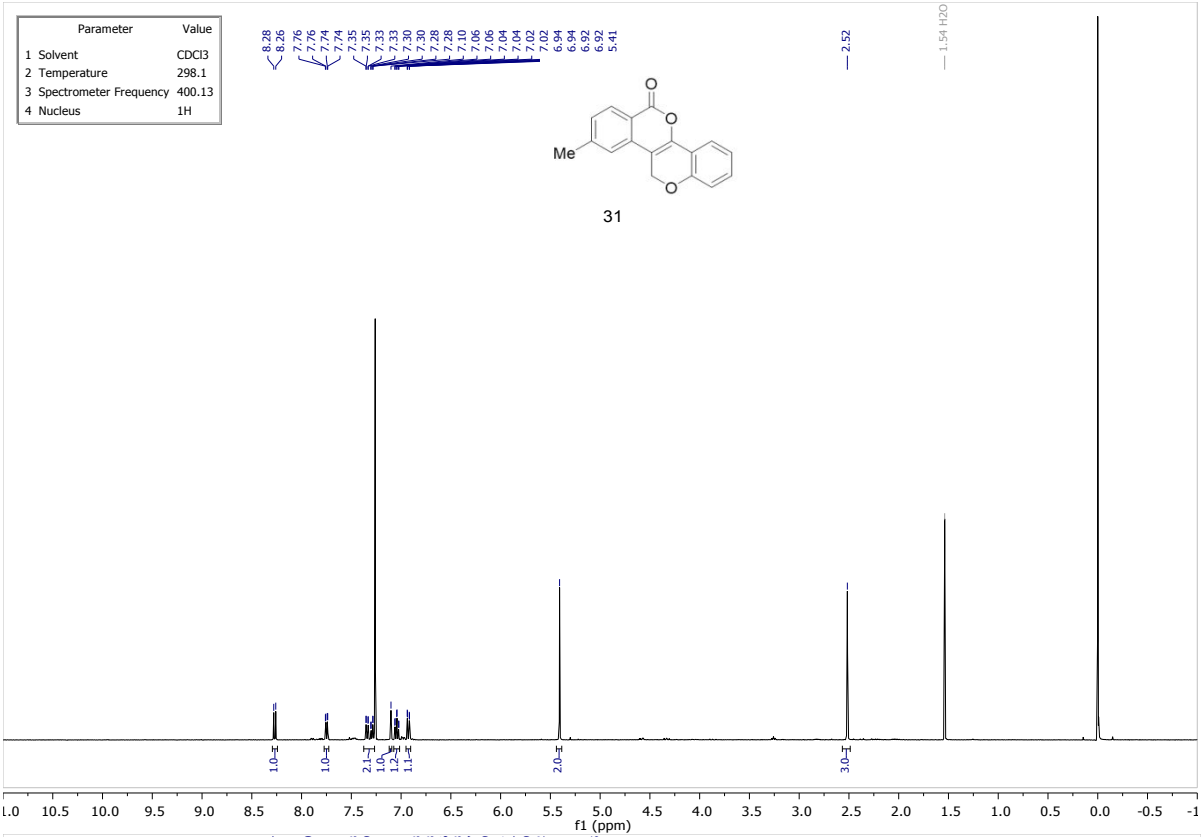

Parameter Value
1 Solvent CDCl3
2 Temperature 293.8
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.4
153.6
146.0
137.6
132.1
129.9
129.6
129.6
128.8
126.0
125.2
118.1
101.8
22.0
Me
28
f1 (ppm)

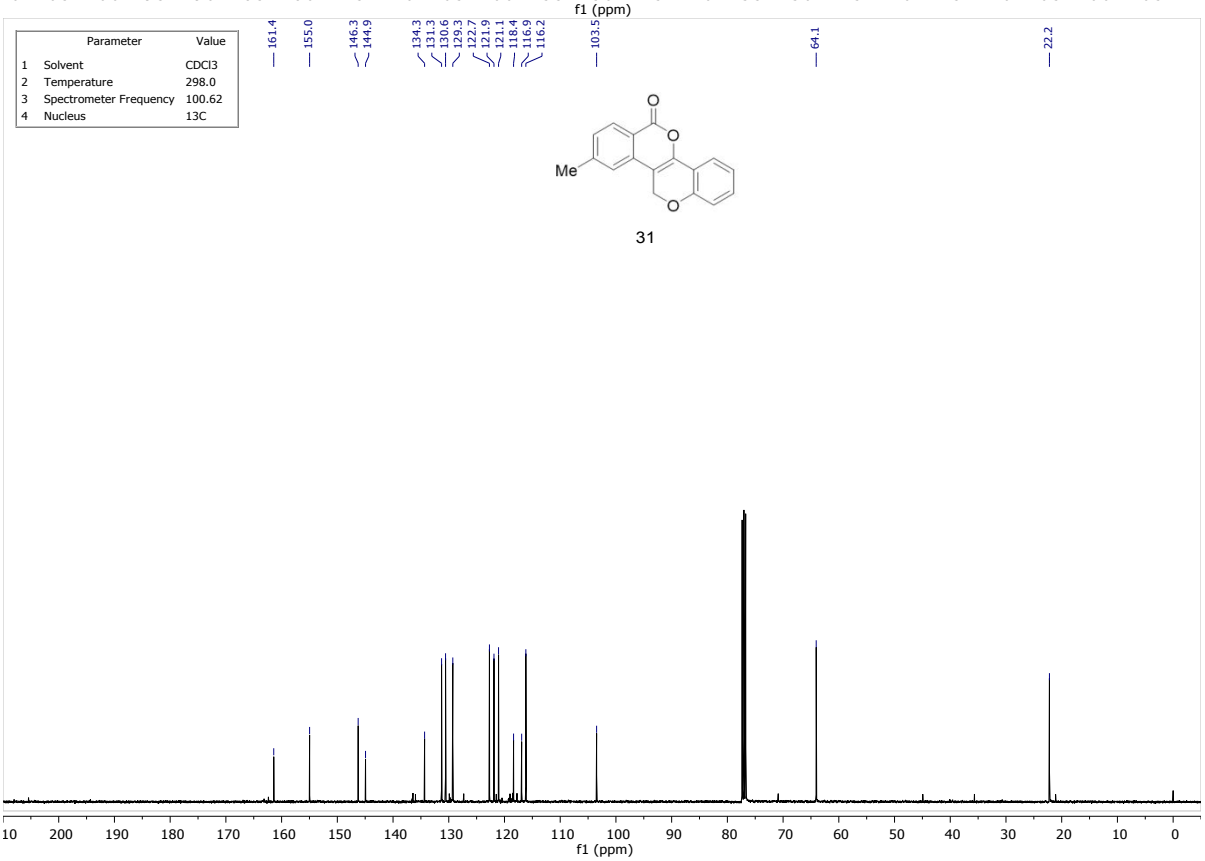

Parameter Value
1 Solvent CDCl3
2 Temperature 293.2
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.15
8.13
7.28
7.28
7.26
7.26
7.15
6.18
2.46
2.38
2.36
2.19
2.17
2.16
2.14
2.12
2.11
2.09
1.58 H2O
0.98
0.96
O
O
Me
29
Me
Me
1.0
1.7
1.0
0.9
2.8
2.0
1.0
5.8
f1 (ppm)

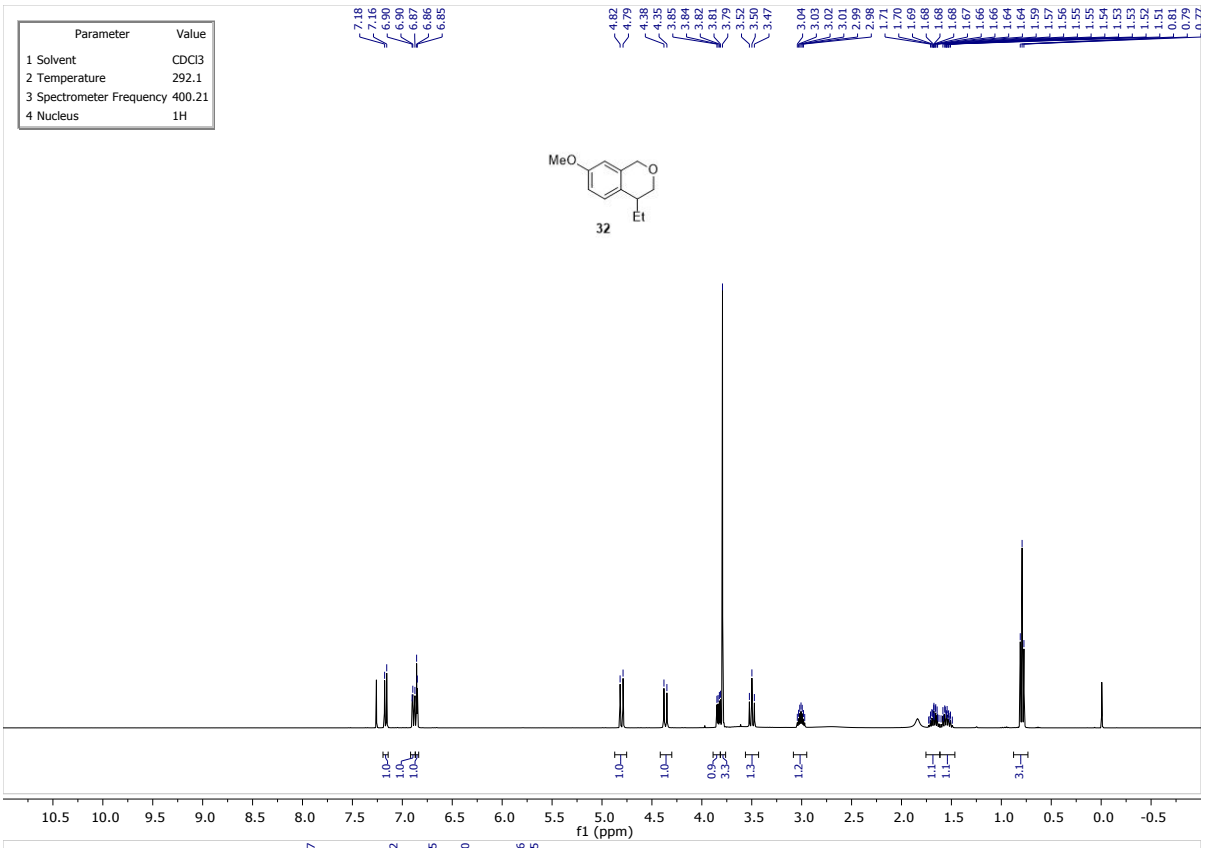

Parameter Value
1 Solvent CDCl3
2 Temperature 293.8
3 Spectrometer Frequency 100.62
4 Nucleus 13C
163.2
157.3
145.8
137.7
129.4
129.0
125.0
117.7
103.9
42.8
26.6
22.2
22.0
O
O
Me
29
Me
Me
f1 (ppm)

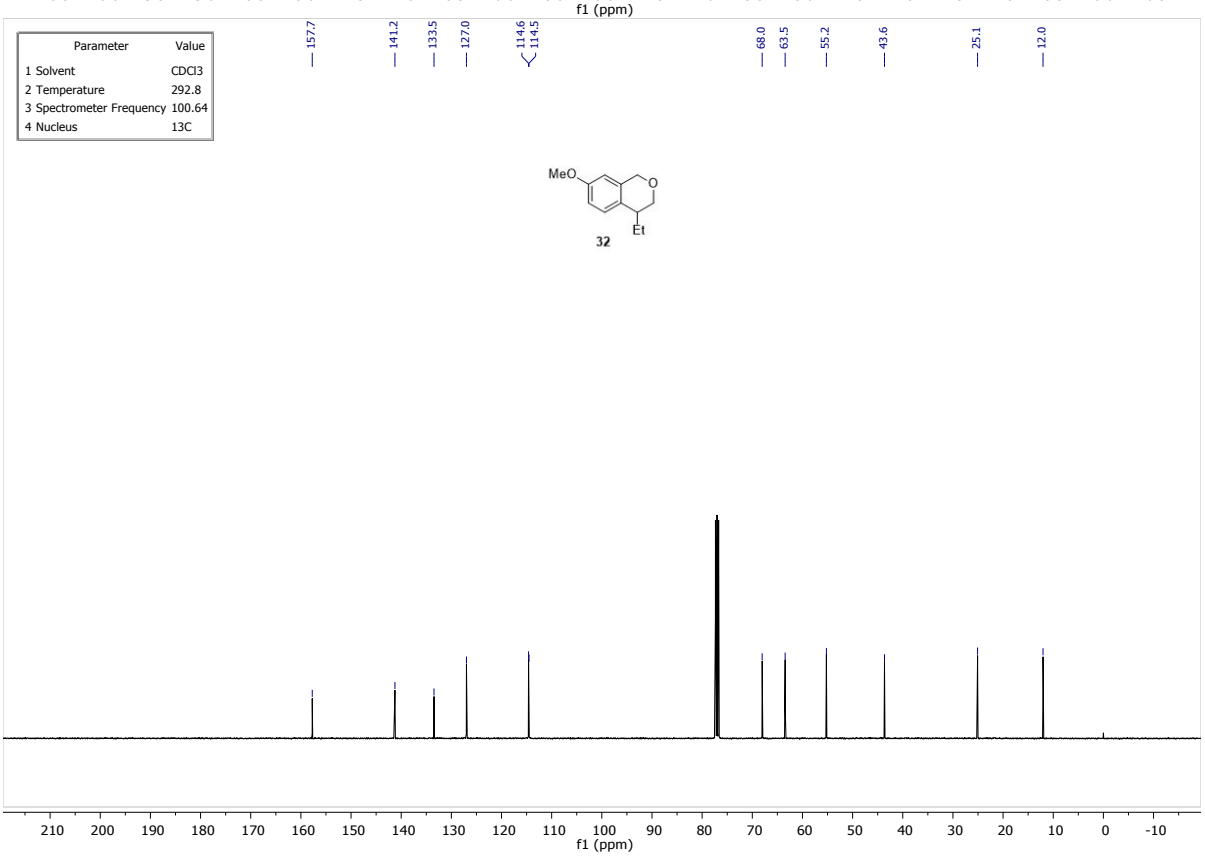

Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.16
8.14
7.26
7.24
7.21
2.58
2.57
2.56
2.56
2.54
2.48
1.85
1.84
1.84
1.83
Me
30
0.9
1.0
1.0
4.1
3.0
4.1
f1 (ppm)

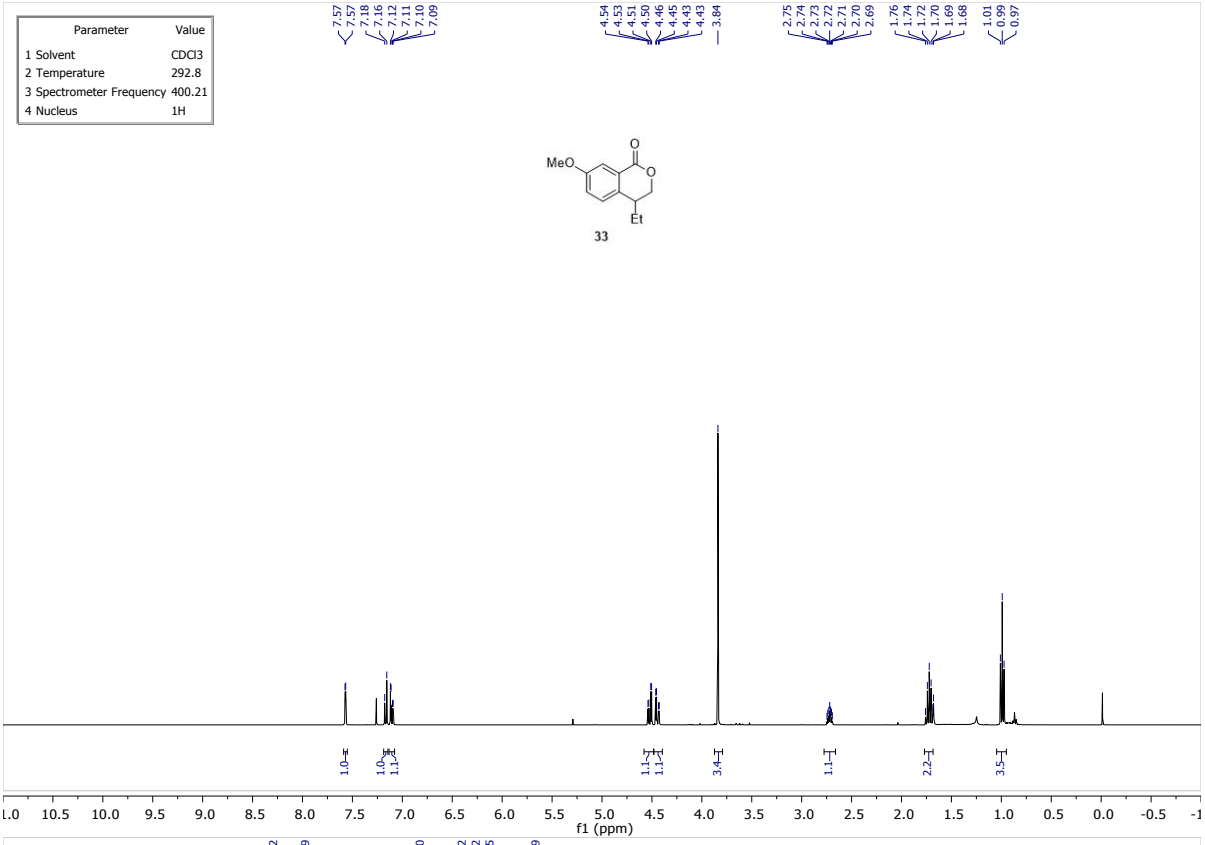

Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
162.8
152.4
145.5
138.1
129.7
128.4
121.5
118.1
109.2
27.4
22.7
22.2
22.1
Me
30
f1 (ppm)

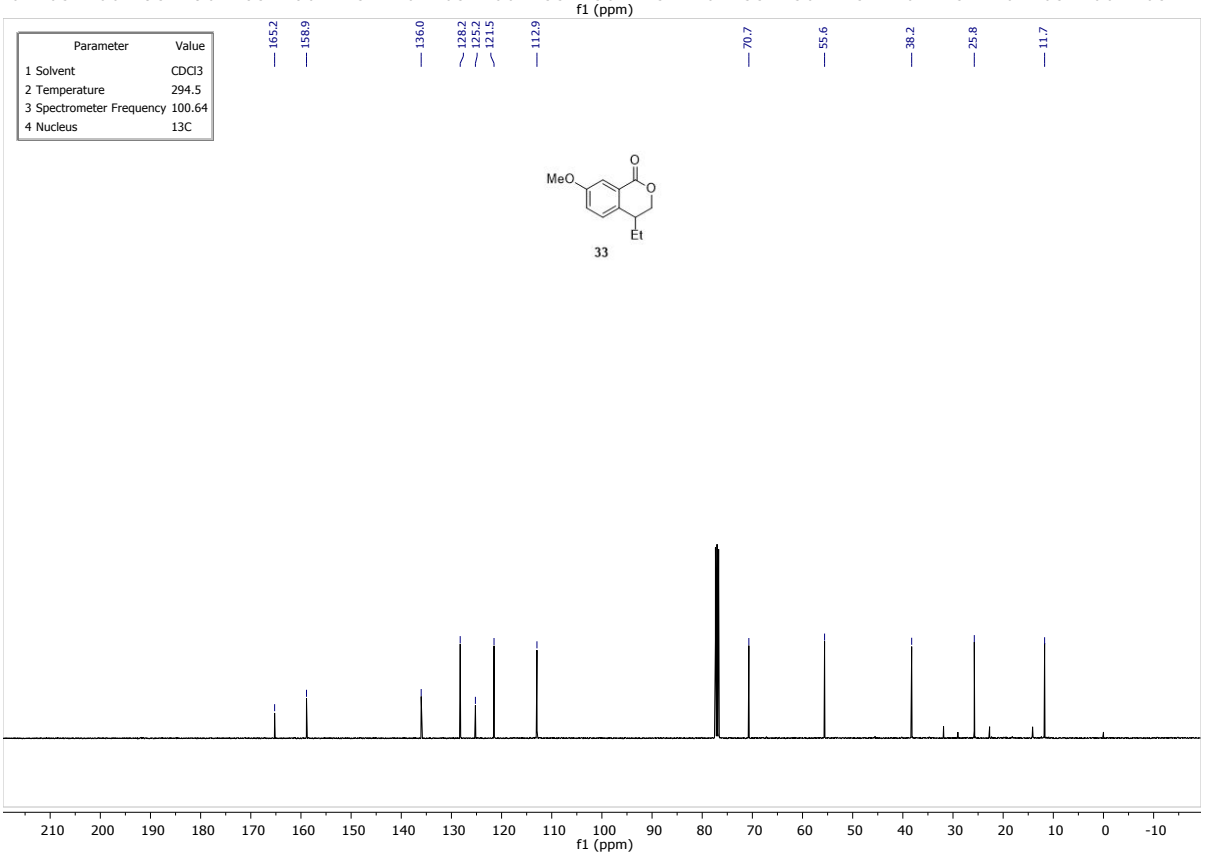

Parameter Value
1 Solvent CDCl3
2 Temperature 298.1
3 Spectrometer Frequency 400.13
4 Nucleus 1H
8.28 8.26 7.76 7.76 7.74 7.74 7.35 7.35 7.33 7.33 7.30 7.30 7.28 7.28 7.10 7.06 7.06 7.04 7.04 7.02 7.02 6.94 6.94 6.92 6.92 5.41
2.52
1.54 H2O
Me
31
1.0 1.0 2.1 1.0 1.2 1.1 2.0 3.0
f1 (ppm)

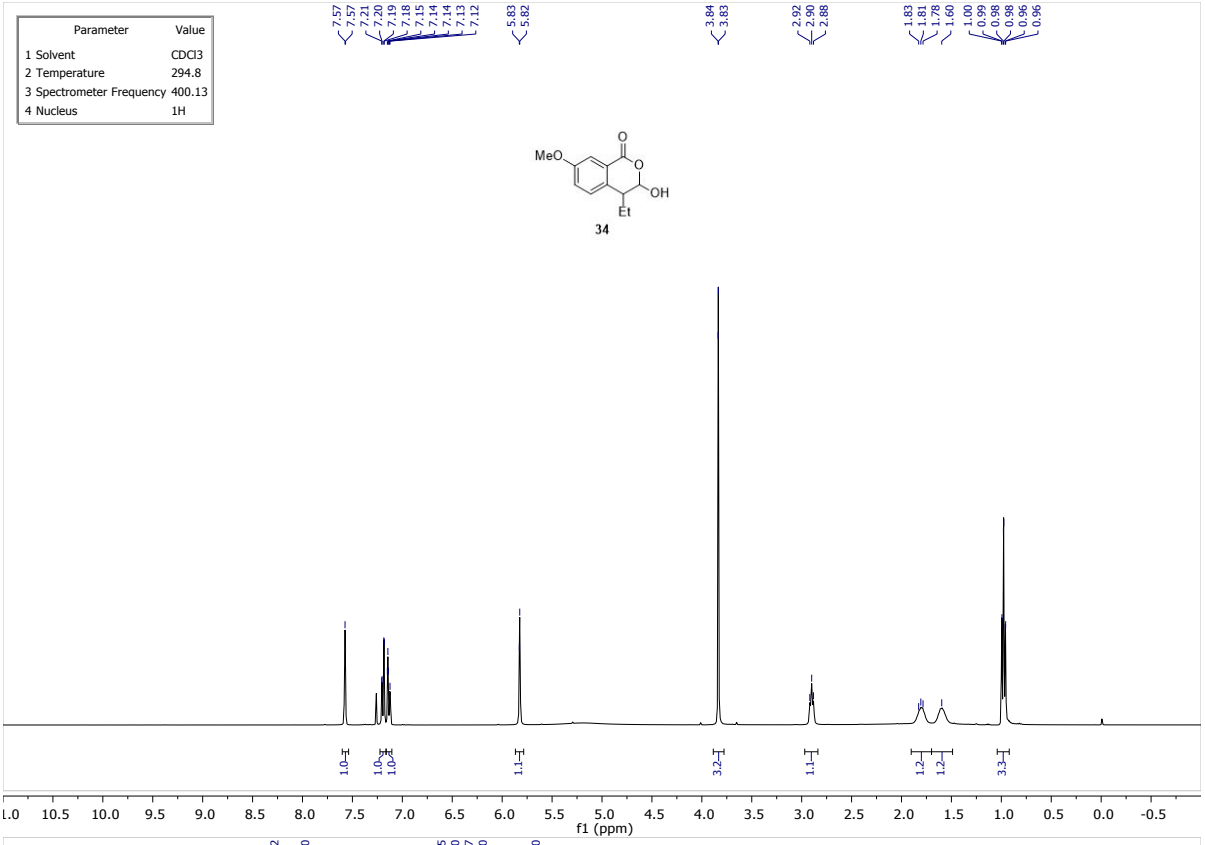

Parameter Value
1 Solvent CDCl3
2 Temperature 298.0
3 Spectrometer Frequency 100.62
4 Nucleus 13C
161.4 155.0 146.3 144.9 134.3 131.3 130.6 129.3 122.7 121.9 121.1 118.4 116.9 116.2 103.5 64.1 22.2
Me
31
f1 (ppm)

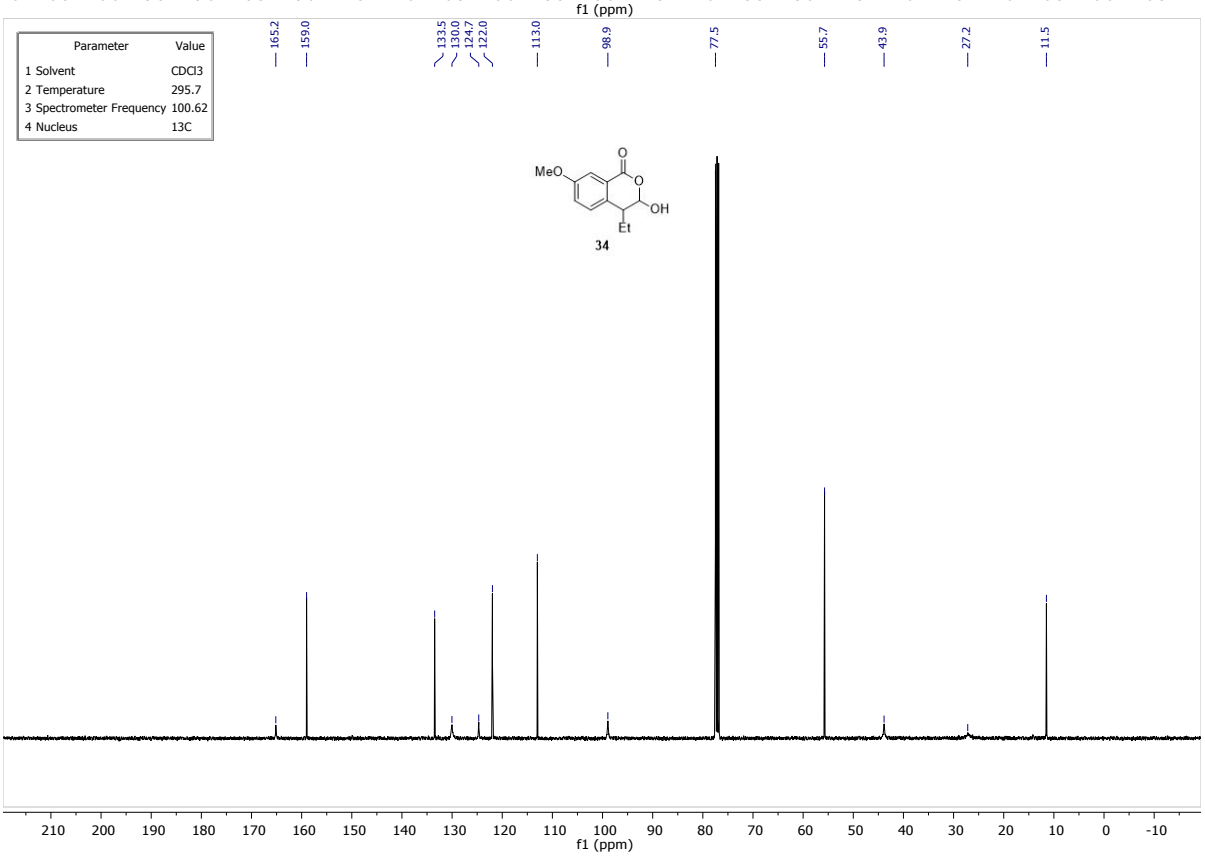

Parameter Value
1 Solvent CDCl3
2 Temperature 292.1
3 Spectrometer Frequency 400.21
4 Nucleus 1H
MeO
O
Et
32
f1 (ppm)

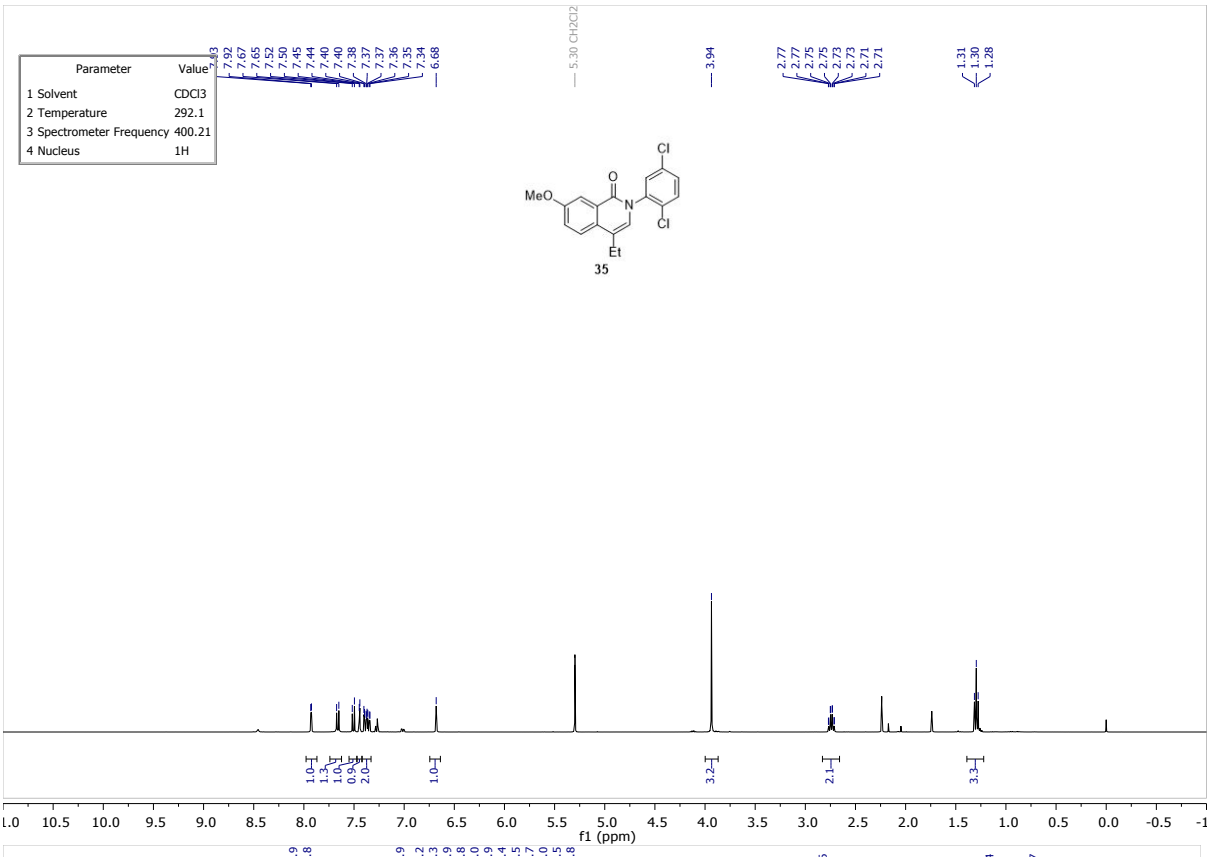

Parameter Value
1 Solvent CDCl3
2 Temperature 292.8
3 Spectrometer Frequency 100.64
4 Nucleus 13C
MeO
O
Et
32
f1 (ppm)

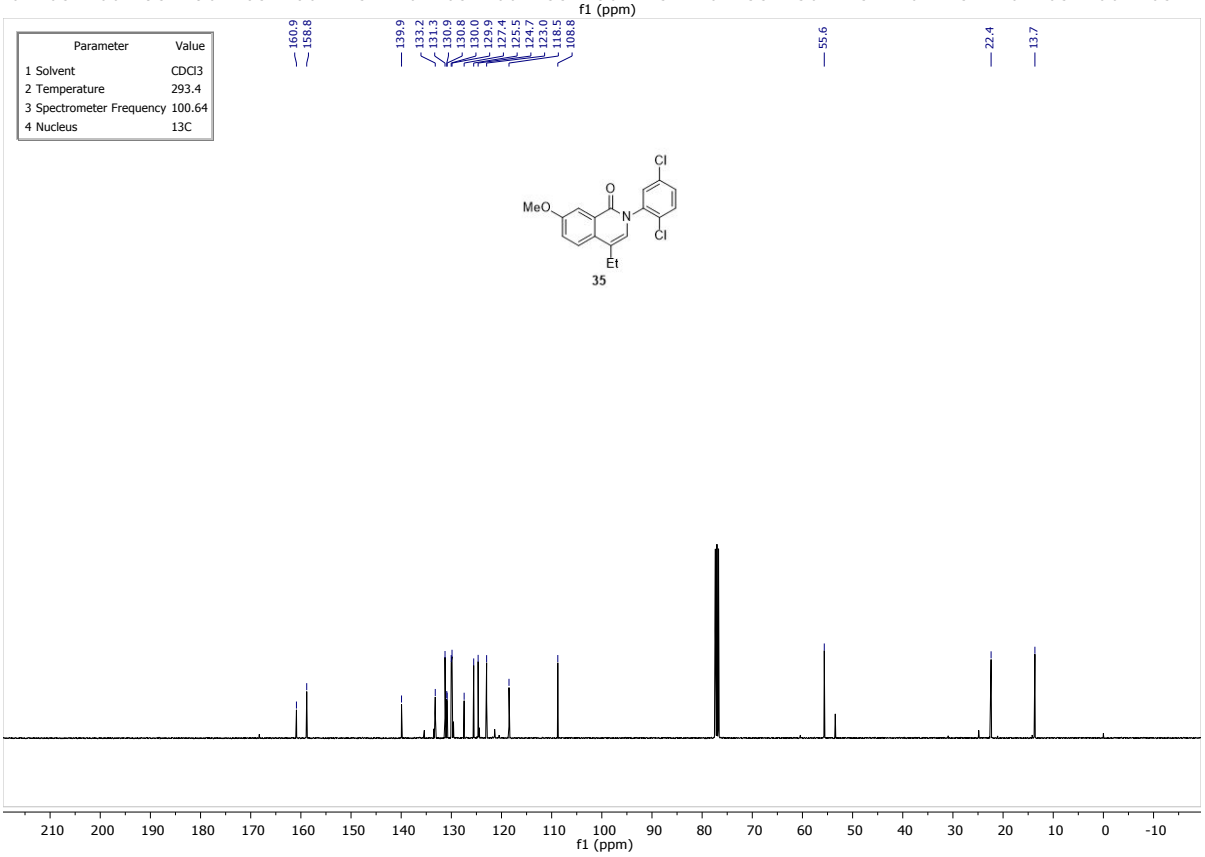

Parameter Value
1 Solvent CDCl3
2 Temperature 292.8
3 Spectrometer Frequency 400.21
4 Nucleus 1H
MeO
O
O
Et
33
f1 (ppm)

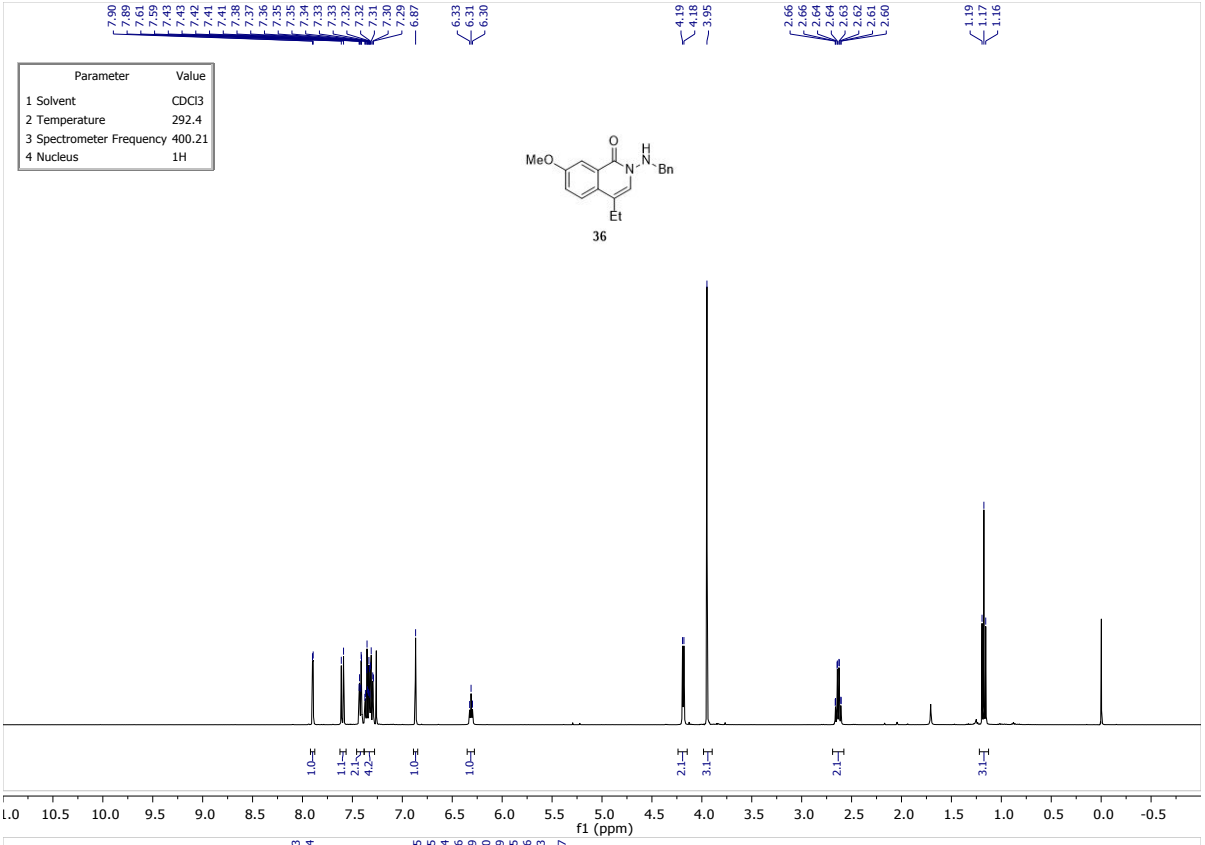

Parameter Value
1 Solvent CDCl3
2 Temperature 294.5
3 Spectrometer Frequency 100.64
4 Nucleus 13C
MeO
O
O
Et
33
f1 (ppm)

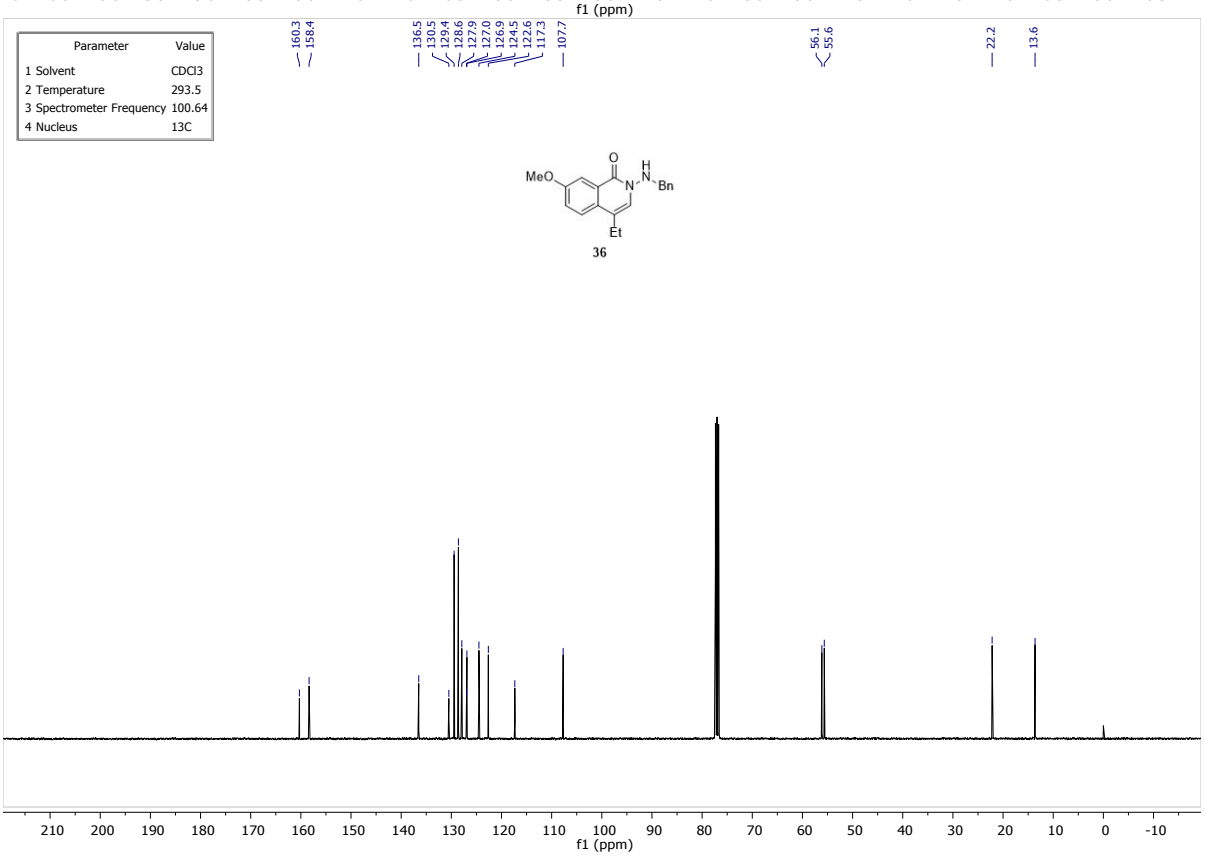

Parameter Value
1 Solvent CDCl3
2 Temperature 294.8
3 Spectrometer Frequency 400.13
4 Nucleus 1H
7.57 7.57 7.21 7.20 7.19 7.18 7.15 7.14 7.14 7.13 7.12
5.83 5.82
3.84 3.83
2.92 2.90 2.88
1.83 1.81 1.78 1.60
1.00 0.99 0.98 0.98 0.96 0.96
MeO
O
OH
Et
34
1.0 1.0 1.0 1.1 3.2 1.1 1.2 1.2 3.3
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 295.7
3 Spectrometer Frequency 100.62
4 Nucleus 13C
165.2 159.0 133.5 130.0 124.7 122.0 113.0 98.9 77.5 55.7 43.9 27.2 11.5
MeO
O
OH
Et
34
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 292.1
3 Spectrometer Frequency 400.21
4 Nucleus 1H
5.30 CH2Cl2
3.94
2.77 2.77 2.75 2.75 2.73 2.73 2.71 2.71
1.31 1.30 1.28
7.92 7.67 7.65 7.52 7.50 7.45 7.44 7.40 7.40 7.38 7.37 7.37 7.36 7.35 7.34
6.68
MeO
O
N
Cl
Cl
Et
35
1.0 1.3 1.0 0.9 2.0
1.0
3.2
2.1
3.3
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.4
3 Spectrometer Frequency 100.64
4 Nucleus 13C
160.9 158.8
139.9
133.2 131.3 130.9 130.8 130.0 129.9 127.4 125.5 124.7 123.0 118.5 108.8
55.6
22.4
13.7
MeO
O
N
Cl
Cl
Et
35
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 292.4
3 Spectrometer Frequency 400.21
4 Nucleus 1H
MeO
O
H
N
N
Bn
Et
36
f1 (ppm)


Parameter Value
1 Solvent CDCl3
2 Temperature 293.5
3 Spectrometer Frequency 100.64
4 Nucleus 13C
MeO
O
H
N
N
Bn
Et
36
f1 (ppm)