

Hydroxyl-Directed C–H Carbonylation Enabled by Mono-*N*-Protected Amino Acid Ligands: An Expedient Route to 1-Isochromanones

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SUPPORTING INFORMATION

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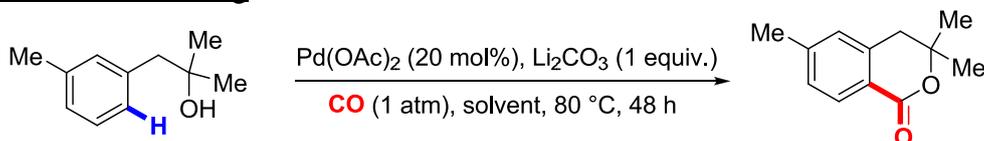
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General Information

All solvents were used as received from commercial sources without further purification. Anhydrous solvents were prepared according to standard methods.¹ The preparation of starting materials **1a–1t** has previously been described by our group^{2,3} based on earlier literature precedent.⁴ **1u** was prepared according to a literature procedure.⁵ Reagents used to prepare these alcohol substrates were purchased from Acros, Sigma-Aldrich, TCI and Alfa-Aesar and were used as received without further purification. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. (+)-Menthyl(O₂C)-Leu-OH was prepared according to our group's previous report.⁶ Palladium acetate was purchased from Sigma-Aldrich and used without further purification. Dichloromethane was purchased from Acros and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on Bruker-AV (400 MHz and 100 MHz, respectively) and Bruker-DRX (500 MHz and 125 MHz, respectively) instruments internally referenced to TMS or residual chloroform signals. High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

Experimental Section for Hydroxyl-Directed C–H Carbonylation

Table S1: Solvent screening

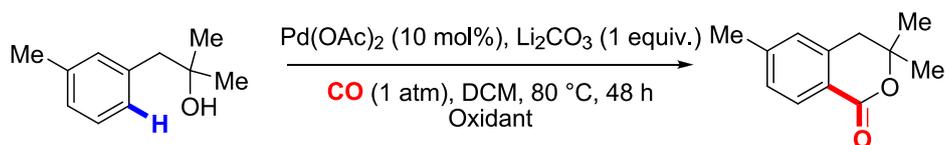


Entry	Solvent	% Conv. ^a	Entry	Solvent	% Conv. ^a
1	EtOAc	<1	6	MeCN	0
2	<i>t</i> -BuOH	0	7	1,4-dioxane	4
3	DMF	0	8	DCM	12
4	THF	<1	9	C ₆ F ₆	<1
5	<i>n</i> -hexanes	5			

^a The conversion was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard.

Solvent screening for hydroxyl-directed C–H carbonylation: To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)₂ (4.5 mg, 0.02 mmol), 2-methyl-1-(*m*-tolyl)propan-2-ol (**2c**) (32.8 mg, 0.20 mmol), Li₂CO₃ (14.8 mg, 0.20 mmol), solvent (2 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the conversion was determined by ¹H NMR analysis of the crude material using CH₂Br₂ as an internal standard.

Table S2: Oxidant screening

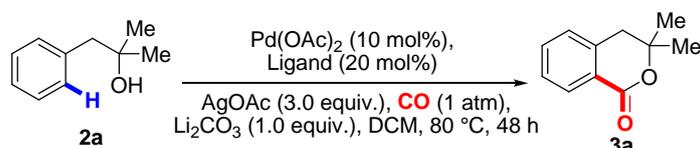


Entry	Oxidant (equiv.)	% Conv. ^a	Entry	Oxidant (equiv.)	% Conv. ^a
1	AgOAc (2)	38	5 ^b	AgOAc (4)	5
2	AgOAc (3)	35	6	Ag ₂ CO ₃ (2) / Cu(OAc) (2)	0
3	Ag ₂ CO ₃ (2)	4	7	Ag ₂ CO ₃ (2) / Cu(OAc) (1)	<1
4	Ag ₂ O (2)	9	8	Ag ₂ CO ₃ (1) / Cu(OAc) (1)	0

^a The conversion was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard. ^b CO/N₂ = 1:1.

Oxidant screening for hydroxyl-directed C–H carbonylation: To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)₂ (4.5 mg, 0.02 mmol), 2-methyl-1-(m-tolyl)propan-2-ol (**2c**) (30.0 mg, 0.20 mmol), oxidant, Li₂CO₃ (14.8 mg, 0.20 mmol), dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the conversion was determined by ¹H NMR analysis of the crude material using CH₂Br₂ as an internal standard.

Table S3: Ligand screening

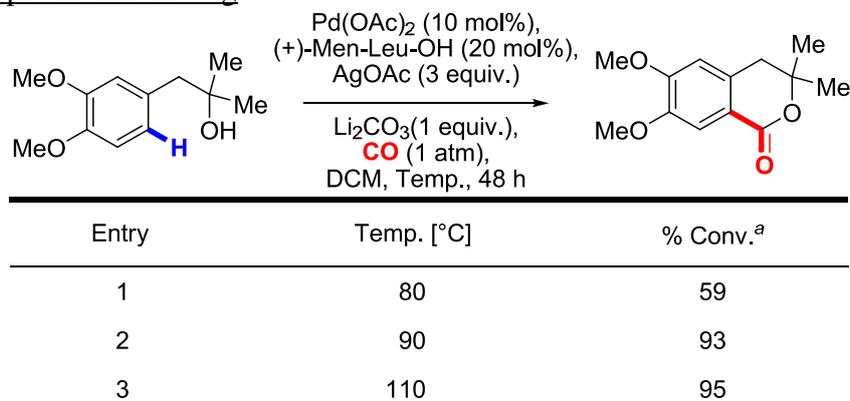


Entry	Ligand	% Conv. ^a	Entry	Ligand	% Conv. ^a
1	—	35	9	Boc-Acpc-OH	53
2	Boc-Ile-OH·0.5 H ₂ O	46	10	Boc- <i>tert</i> -Leu-OH	7
3	Boc-Ala-OH	27	11	Boc-Leu-OH·H ₂ O	66
4	Boc-Phe-OH	26	12	Ac-Leu-OH	35
5	Boc-Ser-OH	5	13	Fmoc-Leu-OH	20
6	Boc-Nva-OH	54	14	Bz-Leu-OH	12
7	Boc-Nle-OH	34	15	(+)-Men-Leu-OH	67
8	Boc- α -Me-Ala-OH	5			

^a The conversion was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard. (+)-Men-Leu-OH = (+)-Menthyl(O₂C)-Leu-OH.

Ligand screening for hydroxyl-directed C–H carbonylation: To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)₂ (4.5 mg, 0.02mmol, 10 mol%), 2-methyl-1-phenylpropan-2-ol (**2a**) (30.0 mg, 0.20 mmol), ligand (0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), Li₂CO₃ (14.8 mg, 0.20 mmol), dichloromethane (5.0mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 80 °C for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the conversion was determined by ¹H NMR analysis of the crude material using CH₂Br₂ as an internal standard.

Table S4: Temperature screening



^a The conversion was determined by ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as an internal standard. (+)-Men-Leu-OH = (+)-Menthyl(O₂C)-Leu-OH.

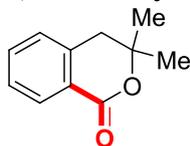
Temperature screening for hydroxyl-directed C–H carbonylation: To a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stirring bar, were added Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol%), 1-(3,4-dimethoxyphenyl)-2-methylpropan-2-ol (**2h**) (30.0 mg, 0.20 mmol), (+)-Men-Leu-OH (12.5 mg, 0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), Li₂CO₃ (14.8 mg, 0.20 mmol), dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to different temperatures for 48 hours. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the conversion was determined by ¹H NMR analysis of the crude material using CH₂Br₂ as an internal standard.

General procedures

General procedure for hydroxyl-directed C–H carbonylation: A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with the phenethyl alcohol **2** (0.20 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), Li₂CO₃ (73.8 mg, 0.20 mmol), (+)-Menthyl(O₂C)-Leu-OH (12.5 mg, 0.04 mmol), AgOAc (100.1 mg, 0.60 mmol), and dichloromethane (5.0 mL). The tube was evacuated then back-filled with CO (×3, balloon), capped, and heated to 110 °C for 48 hours. *A note of caution: these reactions were performed at a temperature that is well above the boiling point of DCM (approximately 40 °C), leading to substantial pressure build-up in the sealed reaction vessel. As such, proper precautions (including the use of a blast shield) should be taken when performing these experiments.* After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel flash column chromatography using hexanes/EtOAc as the eluent.

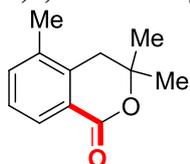
Characterization of new compounds

3,3-Dimethylisochroman-1-one (3a):



^1H NMR (500 MHz, CDCl_3): δ = 8.10 (d, J = 7.5 Hz, 1 H), 7.54 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.22 (d, J = 7.5 Hz, 1 H), 3.03 (s, 2 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.08, 138.05, 133.74, 130.06, 127.91, 127.51, 124.81, 80.66, 39.47, 27.55 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 177.0910, found 177.0907.

3,3,5-Trimethylisochroman-1-one (3b):



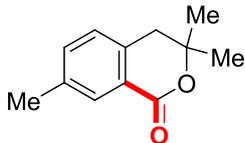
^1H NMR (500 MHz, CDCl_3): δ = 7.98 (d, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.27 (t, J = 7.5 Hz, 1 H), 2.94 (s, 2 H), 2.31 (s, 3 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.47, 136.50, 135.53, 135.11, 127.89, 126.83, 124.75, 79.84, 36.39, 27.79, 18.88 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{21}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 191.1067, found 191.1069.

3,3,6-Trimethylisochroman-1-one (3c):



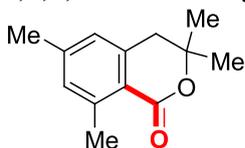
^1H NMR (400 MHz, CDCl_3): δ = 7.98 (d, J = 8.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 7.02 (s, 1 H), 2.97 (s, 2 H), 2.40 (s, 3 H), 1.45 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.20, 144.65, 138.06, 128.46, 128.33, 122.09, 80.49, 39.42, 27.52, 21.69 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 191.1067, found 191.1069.

3,3,7-Trimethylisochroman-1-one (3d):



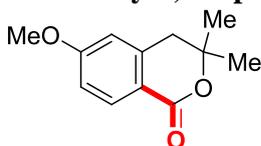
^1H NMR (500 MHz, CDCl_3): δ = 7.91 (s, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 2.98 (s, 2 H), 2.39 (s, 3 H), 1.45 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.35, 137.30, 135.04, 134.56, 130.30, 127.79, 124.48, 80.70, 39.07, 27.50, 20.95 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 191.1067, found 191.1069.

3,3,6,8-Tetramethylisochroman-1-one (3e):



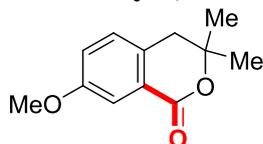
^1H NMR (500 MHz, CDCl_3): δ = 6.99 (s, 1 H), 6.84 (s, 1 H), 2.93 (s, 2 H), 2.64 (s, 3 H), 2.34 (s, 3 H), 1.41 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 164.51, 143.30, 142.63, 139.11, 131.77, 126.50, 120.57, 79.30, 40.50, 27.23, 21.36 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 205.1223, found 205.1219.

6-Methoxy-3,3-dipropylisochroman-1-one (3f):



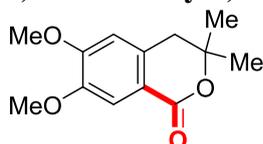
^1H NMR (500 MHz, CDCl_3): δ = 8.04 (d, J = 8.5 Hz, 1 H), 6.87 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1 H), 6.69 (d, J = 2.5 Hz, 1 H), 3.87 (s, 3 H), 2.98 (s, 2 H), 1.45 (s, 6 H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 164.97, 163.85, 140.35, 132.28, 117.27, 113.03, 112.80, 80.24, 55.44, 39.72, 27.46 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 207.1016, found 207.1021.

7-Methoxy-3,3-dimethylisochroman-1-one (3g):



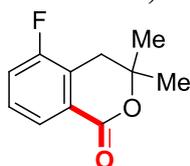
^1H NMR (500 MHz, CDCl_3): δ = 7.60 (d, J = 2.5 Hz, 1 H), 7.14–7.08 (m, 2 H), 3.85 (s, 3 H), 2.96 (s, 2 H), 1.46 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.15, 158.85, 130.24, 129.03, 125.51, 121.51, 112.81, 81.02, 55.55, 38.63, 27.46 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 207.1016, found 207.1017.

6,7-Dimethoxy-3,3-dimethylisochroman-1-one (3h):



^1H NMR (500 MHz, CDCl_3): δ = 7.56 (s, 1 H), 6.66 (s, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 2.95 (s, 2 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 165.06, 153.64, 148.21, 132.30, 116.79, 111.62, 109.79, 80.56, 56.07, 39.02, 27.46 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 237.1121, found 237.1123.

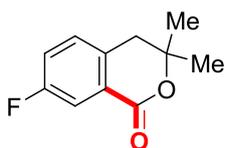
5-Fluoro-3,3-dimethylisochroman-1-one (3i):



^1H NMR (500 MHz, CDCl_3): δ = 7.92 (d, J = 8.5 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.30 (td, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1 H), 3.04 (s, 2 H), 1.49 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 163.91 (d, $J_{\text{C-F}}$ = 3.8 Hz), 159.43 (d, $J_{\text{C-F}}$ = 245.5 Hz), 128.24 (d, $J_{\text{C-F}}$ = 7.8 Hz), 126.61 (d, $J_{\text{C-F}}$ = 4.4 Hz), 125.71 (d, $J_{\text{C-F}}$ = 3.5 Hz), 125.11 (d, $J_{\text{C-F}}$ = 18.9 Hz), 120.30 (d, $J_{\text{C-F}}$ = 21.3 Hz), 80.66,

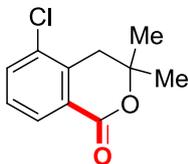
32.16 (d, $J_{C-F} = 2.2$ Hz), 27.68 ppm; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}FO_2$ (M+H)⁺ 195.0816, found 195.0818.

7-Fluoro-3,3-dimethylisochroman-1-one (3j):



¹H NMR (500 MHz, CDCl₃): $\delta = 7.78$ (dd, $J_1 = 8.5$ Hz, $J_2 = 3.0$ Hz, 1 H), 7.27–7.20 (m, 2 H), 3.00 (s, 2 H), 1.46 (s, 6 H) ppm; ¹³C NMR (125 MHz, CDCl₃): $\delta = 164.01$ (d, $J_{C-F} = 2.5$ Hz), 161.76 (d, $J_{C-F} = 245.4$ Hz), 133.72 (d, $J_{C-F} = 3.1$ Hz), 129.66 (d, $J_{C-F} = 7.4$ Hz), 126.48 (d, $J_{C-F} = 7.5$ Hz), 121.03 (d, $J_{C-F} = 21.8$ Hz), 116.52 (d, $J_{C-F} = 23.0$ Hz), 81.11, 38.73, 27.47 ppm; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{12}FO_2$ (M+H)⁺ 195.0816, found 195.0821.

5-Chloro-3,3-dimethylisochroman-1-one (3k):



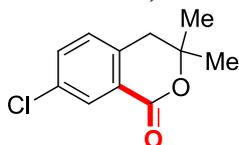
¹H NMR (500 MHz, CDCl₃): $\delta = 7.05$ (dd, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 7.61 (dd, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 7.34 (t, $J_1 = 7.5$ Hz, $J_2 = 0.5$ Hz, 1 H), 3.12 (s, 2 H), 1.49 (s, 6 H) ppm; ¹³C NMR (125 MHz, CDCl₃): $\delta = 164.13$, 136.00, 134.17, 133.28, 128.62, 128.10, 126.66, 80.27, 36.62, 27.71 ppm; HRMS(ESI) m/z Calcd for $C_{11}H_{12}ClO_2$ (M+H)⁺ 211.0526, [(M+H)+2]⁺ 213.0496, found 211.0522, 213.0495, (M+H)⁺: [(M+2)+H]⁺ = 3:1.

6-Chloro-3,3-dimethylisochroman-1-one (3l):



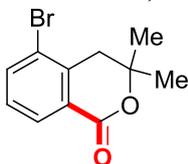
^1H NMR (500 MHz, CDCl_3): δ = 8.04 (d, J = 8.0 Hz, 1 H), 7.36 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 3.00 (s, 2 H), 1.47 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 164.18, 140.09, 139.75, 131.60, 128.00, 123.27, 80.74, 39.23, 27.51 ppm; HRMS(ESI) m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{ClO}_2$ ($\text{M}+\text{H}$) $^+$ 211.0526, found 211.0528.

7-Chloro-3,3-dimethylisochroman-1-one (3m):



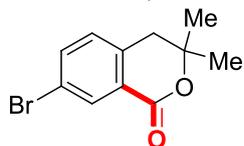
^1H NMR (500 MHz, CDCl_3): δ = 8.08 (d, J = 2.0 Hz, 1 H), 7.51 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 1 H), 3.00 (s, 2 H), 1.46 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 163.86, 136.29, 133.54, 129.38, 126.30, 80.97, 38.90, 27.51; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{ClO}_2$ ($\text{M}+\text{H}$) $^+$ 211.0526, found 211.0522.

5-Bromo-3,3-dimethylisochroman-1-one (3n):



^1H NMR (500 MHz, CDCl_3): δ = 8.09 (dd, J_1 = 8.0 Hz, J_2 = 0.5 Hz, 1 H), 7.78 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 7.28 (td, J_1 = 8.0 Hz, J_2 = 0.5 Hz, 1 H), 3.11 (s, 2 H), 1.49 (s, 6 H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ = 164.16, 137.79, 137.43, 129.29, 128.53, 126.83, 123.52, 80.23, 39.40, 27.68 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{BrO}_2$ ($\text{M}+\text{H}$) $^+$ 255.0015, $[(\text{M}+\text{H})+2]^+$ 257.0000, found 255.0022, 2557.0002, ($\text{M}+\text{H}$) $^+$: $[(\text{M}+2)+\text{H}]^+$ = 1:1.

7-Bromo-3,3-dimethylisochroman-1-one (3o):



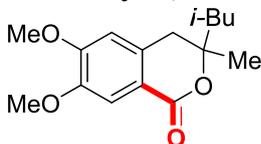
^1H NMR (500 MHz, CDCl_3): δ = 7.24 (d, J = 2.0 Hz, 1 H), 7.66 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 2.98 (s, 2 H), 1.46 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ = 163.72, 136.78, 136.66, 132.87, 129.62, 126.52, 121.17, 80.93, 38.95, 27.51; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{11}\text{H}_{12}\text{BrO}_2$ ($\text{M}+\text{H}$) $^+$ 255.0015, $[(\text{M}+\text{H})+2]^+$ 257.0000, found 255.0017, 256.9995, ($\text{M}+\text{H}$) $^+$: $[(\text{M}+2)+\text{H}]^+$ = 1:1.

3-Benzyl-3-methylisochroman-1-one (3p):



^1H NMR (500 MHz, CDCl_3): δ = 8.11 (d, J = 7.5 Hz, 1 H), 7.54 (td, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1 H), 7.38 (t, J = 7.5 Hz, 1 H), 7.32–7.29 (m, 2 H), 7.27–7.23 (m, 1 H), 7.21–7.18 (m, 3 H), 3.09–2.85 (m, 4 H), 1.41 (s, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 164.84, 137.89, 135.86, 133.88, 130.54, 130.06, 128.30, 127.99, 127.52, 126.94, 125.03, 82.76, 46.26, 36.84, 25.46 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 253.1223, found 253.1224.

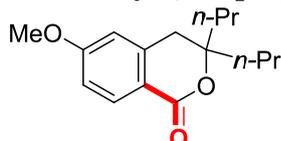
3-*iso*-butyl-6,7-dimethoxy-3-methylisochroman-1-one (3q):



^1H NMR (500 MHz, CDCl_3): δ = 7.56 (s, 1 H), 6.64 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.03 (d, J = 16.0 Hz, 1 H), 2.87 (d, J = 16.0 Hz, 1 H), 1.95–1.87 (m, 1 H), 1.70 (dd, J_1 = 14.5 Hz, J_2 = 6.5 Hz, 2 H), 1.59 (dd, J_1 = 14.5 Hz, J_2 = 5.5 Hz, 2 H), 1.44 (s, 3 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.96

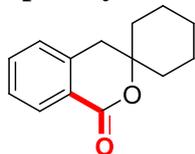
(d, $J = 6.5$ Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 164.99, 153.62, 148.17, 132.28, 117.06, 111.60, 109.83, 83.13, 56.08, 48.62, 38.17, 25.42, 24.51, 24.32, 24.08$ ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{23}\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 279.1591, found 279.1588.

6-Methoxy-3,3-dipropylisochroman-1-one (3r):



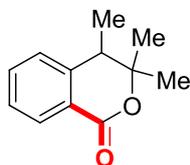
^1H NMR (500 MHz, CDCl_3): $\delta = 7.03$ (d, $J = 8.5$ Hz, 1 H), 6.86 (dd, $J_1 = 8.5$ Hz, $J_2 = 2.5$ Hz, 1 H), 6.68 (d, $J = 2.5$ Hz, 1 H), 3.87 (s, 3 H), 2.95 (s, 2 H), 1.73–1.59 (m, 2 H), 1.48–1.32 (m, 2 H), 0.89 (t, $J = 7.5$ Hz, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 164.97, 163.82, 140.31, 132.16, 117.72, 112.88, 112.81, 84.56, 55.43, 39.67, 36.04, 16.88, 14.32$ ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3$ ($\text{M}+\text{H}$) $^+$ 263.1642, found 263.164.

Spiro[cyclohexane-1,3'-isochroman]-1'-one (3s):



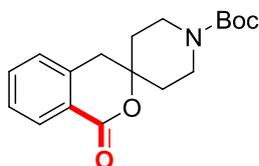
^1H NMR (500 MHz, CDCl_3): $\delta = 8.08$ (d, $J = 7.5$ Hz, 1 H), 7.52 (td, $J_1 = 7.5$ Hz, $J_2 = 1.5$ Hz, 1 H), 7.36 (t, $J = 7.5$ Hz, 1 H), 7.21 (d, $J = 7.5$ Hz, 1 H), 3.01 (s, 2 H), 1.92–1.88 (m, 2 H), 1.82–1.74 (m, 2 H), 1.63–1.46 (m, 5 H), 1.41–1.33 (m, 1 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta = 165.00, 137.69, 133.68, 129.92, 128.00, 127.36, 125.19, 81.77, 38.15, 36.07, 25.28, 21.62$ ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{14}\text{H}_{17}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 217.1223, found 217.1219.

3,3,4-Trimethylisochroman-1-one (3t):



^1H NMR (500 MHz, CDCl_3): δ = 8.08 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 7.55 (t, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 7.39 (td, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 2.98 (q, J = 7.0 Hz, 2 H), 1.43 (s, 3 H), 1.39 (s, 3 H), 1.32 (d, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 164.96, 144.12, 133.93, 129.91, 127.20, 126.63, 124.13, 83.06, 41.23, 27.64, 23.89, 16.38 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 190.0994, found 190.0995.

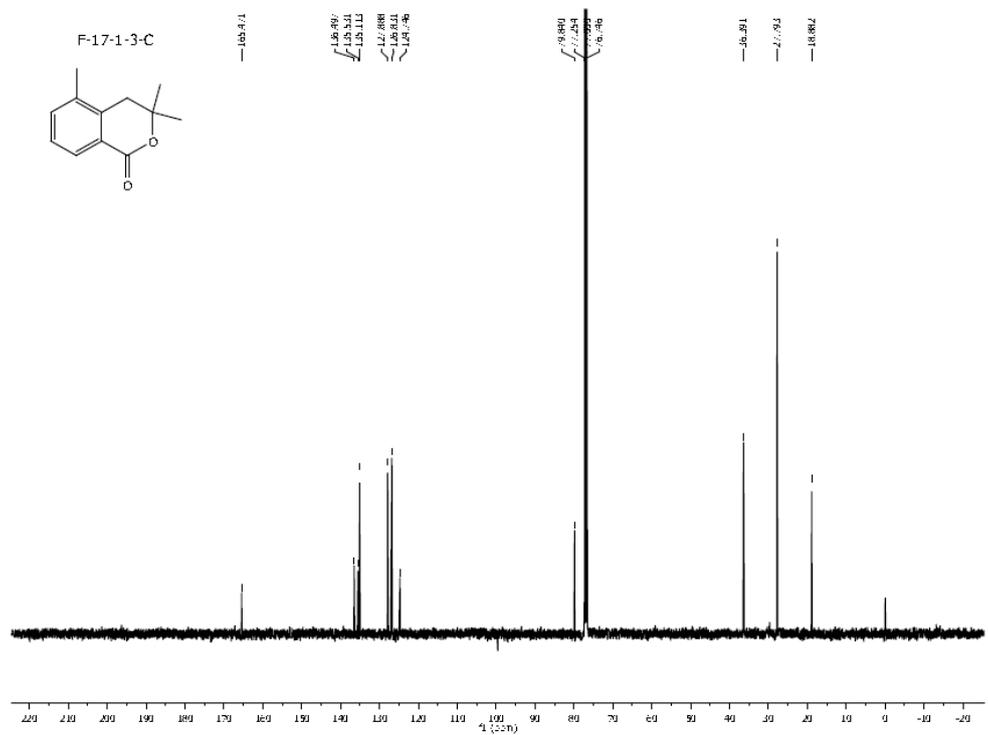
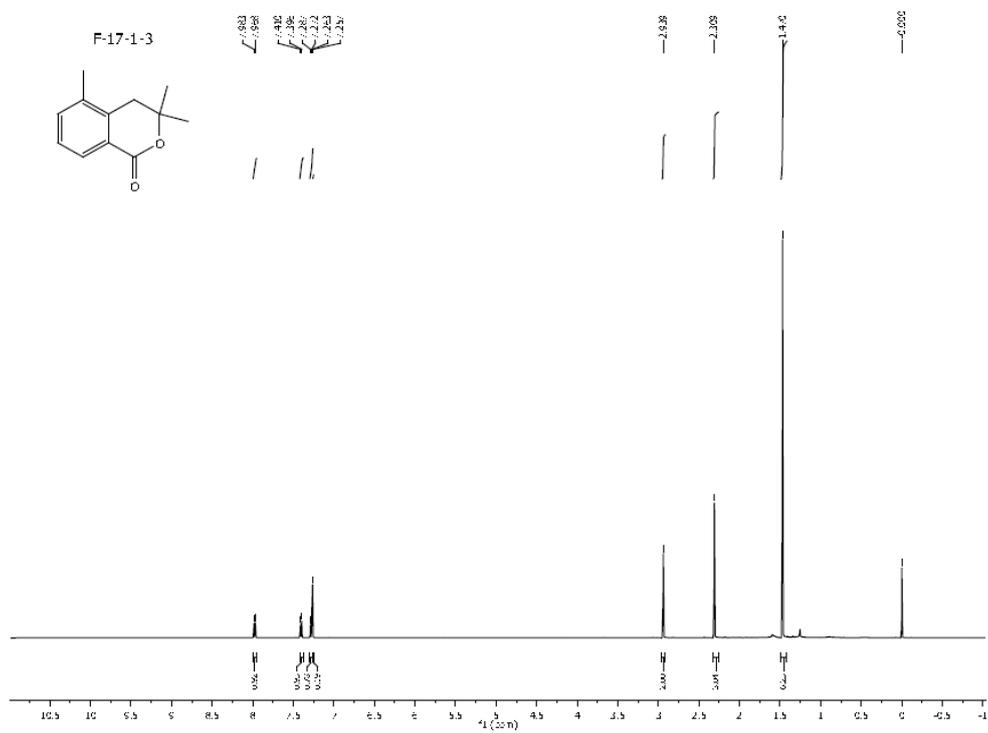
***tert*-Butyl 1-oxospiro[isochroman-3,4'-piperidine]-1'-carboxylate (3u):**

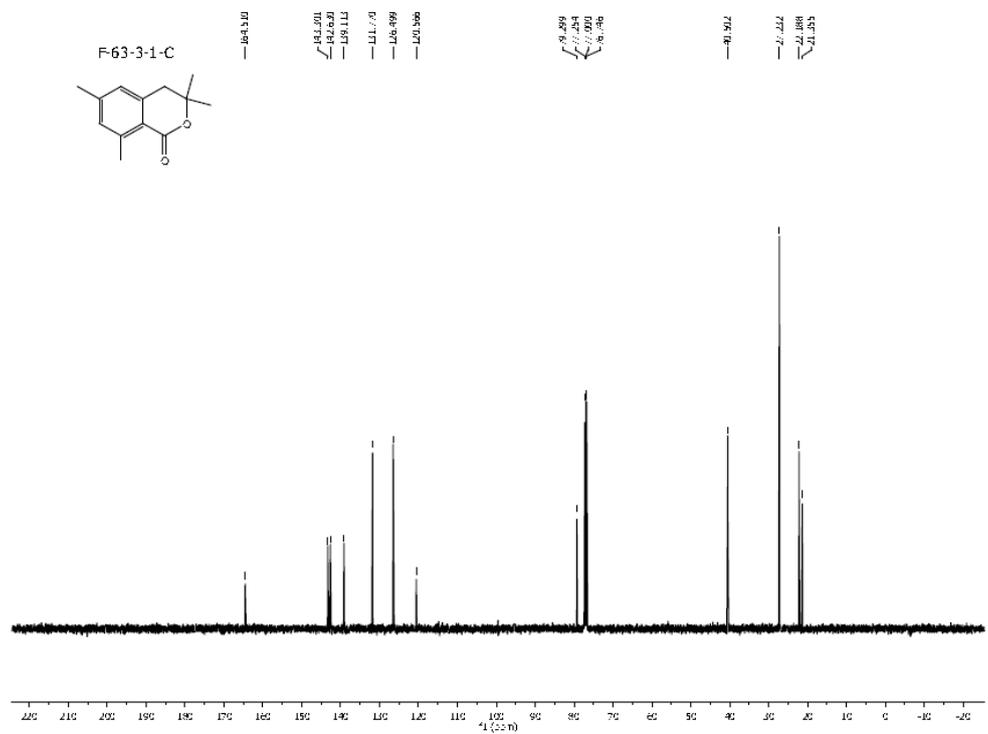
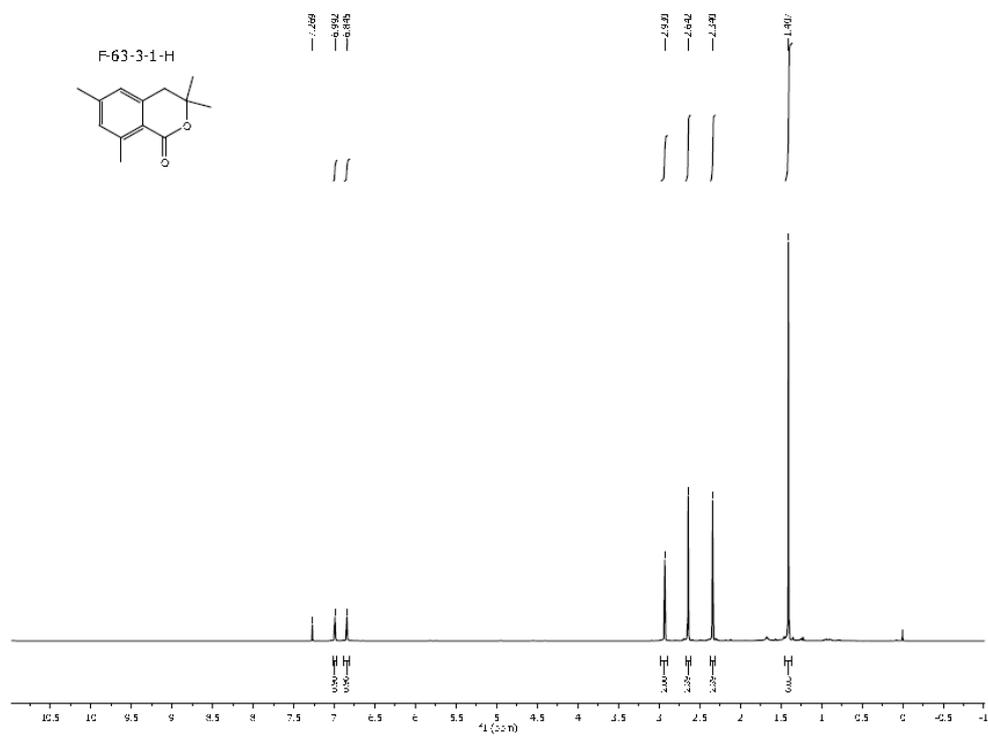


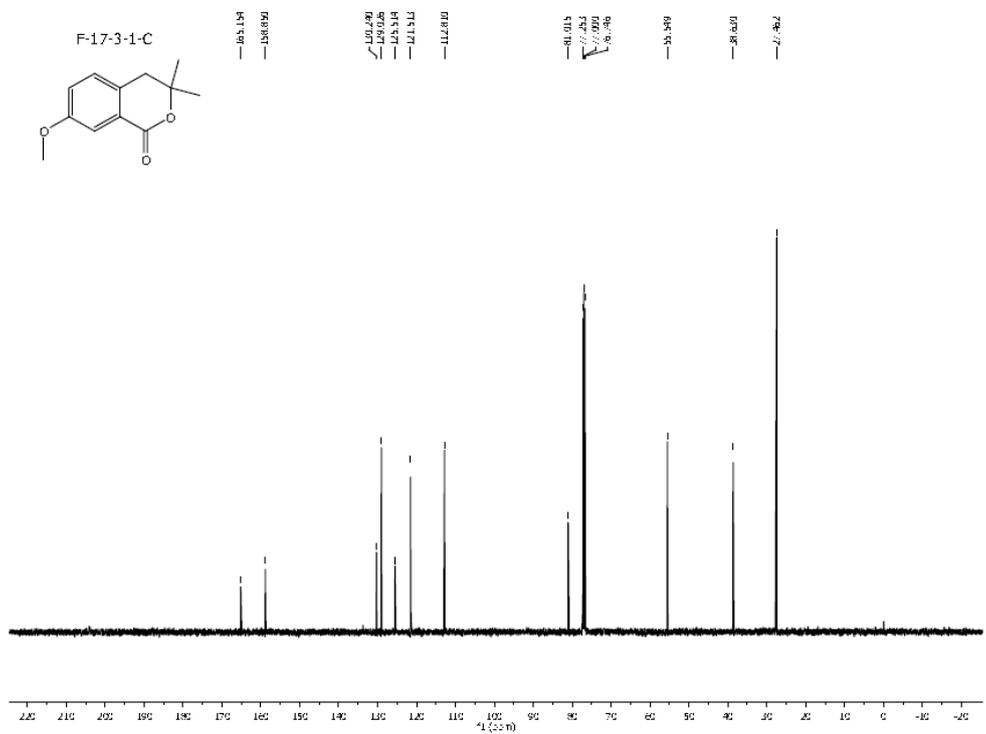
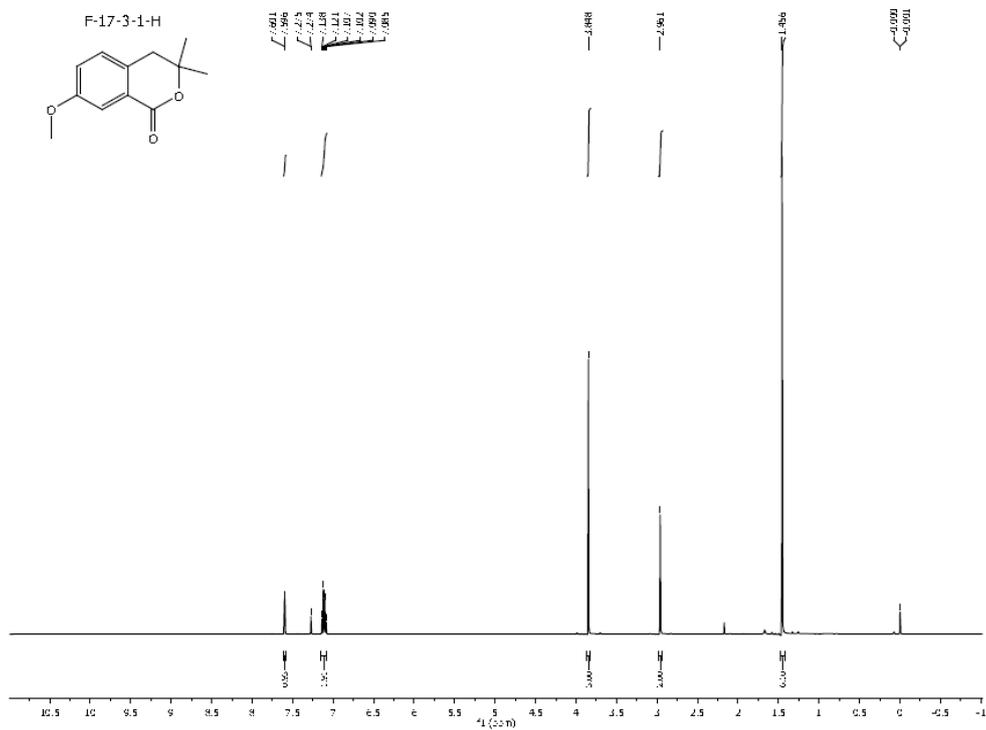
^1H NMR (500 MHz, CDCl_3): δ = 8.08 (d, J = 8.0 Hz, 1 H), 7.57–7.54 (m, 1 H), 7.39 (t, J = 7.5 Hz, 1 H), 7.24 (d, J = 8.0 Hz, 1 H), 3.85 (br, 2 H), 3.32 (br, 2 H), 3.03 (s, 2 H), 1.92 (d, J = 13.0 Hz, 2 H), 1.68–1.62 (m, 2 H), 1.46 (s, 9 H) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ = 164.22, 154.53, 136.81, 133.98, 129.96, 128.01, 127.59, 124.68, 79.59, 79.22, 40.0–38.5 (br, 1 C), 38.40, 35.31, 28.27 ppm; HRMS (ESI-TOF) m/z Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4\text{Na}$ ($\text{M}+\text{Na}$) $^+$ 340.1519, found 340.1520.

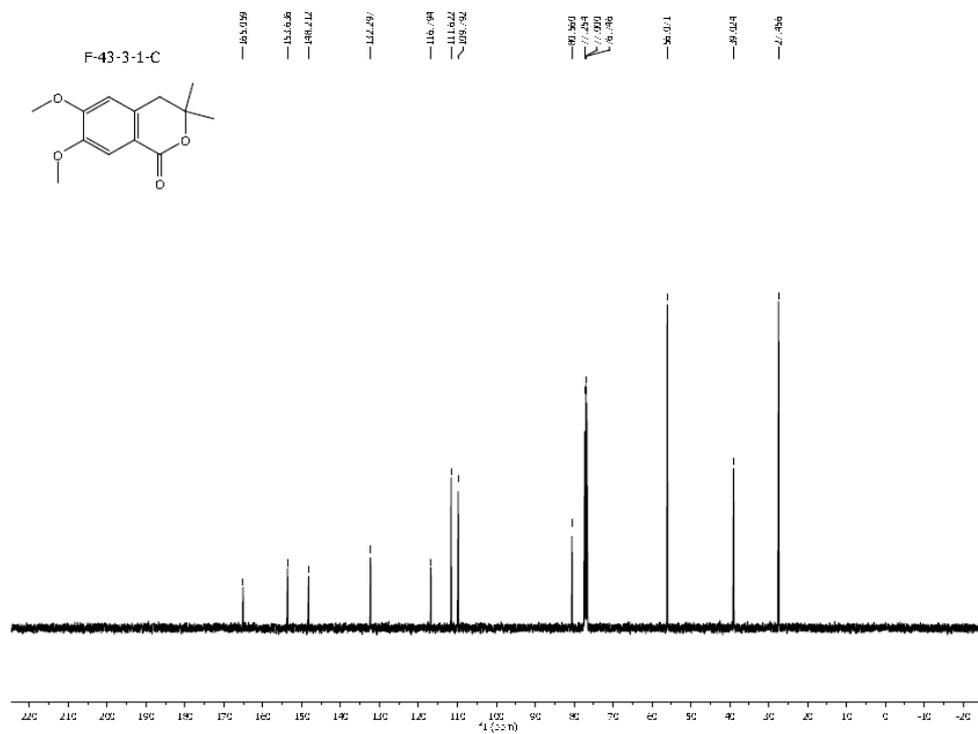
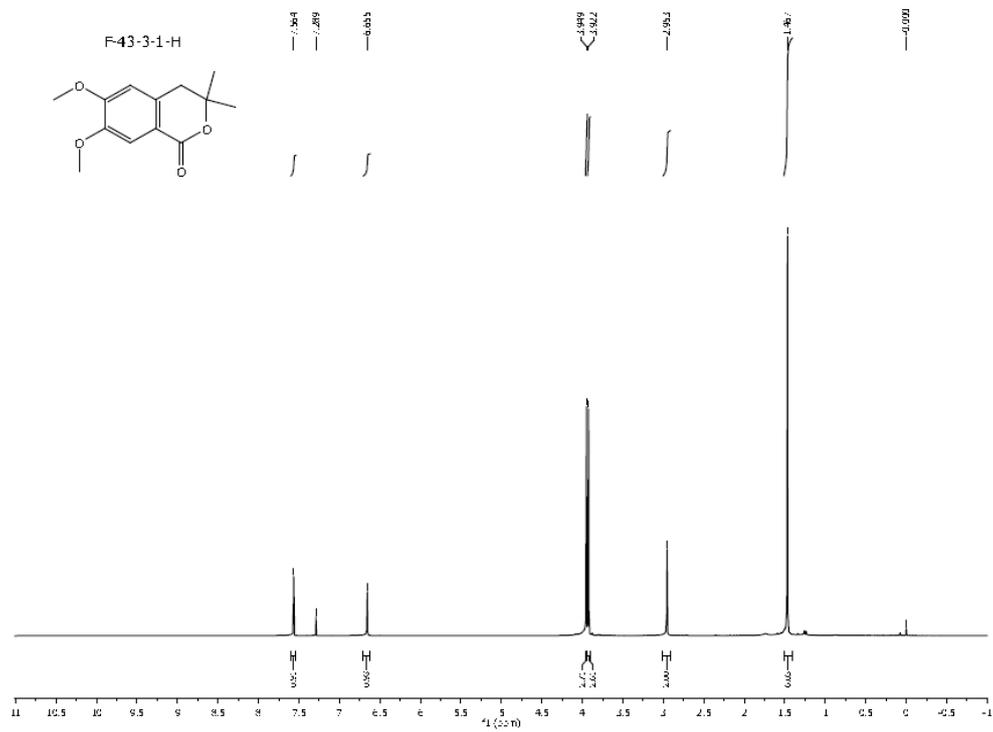
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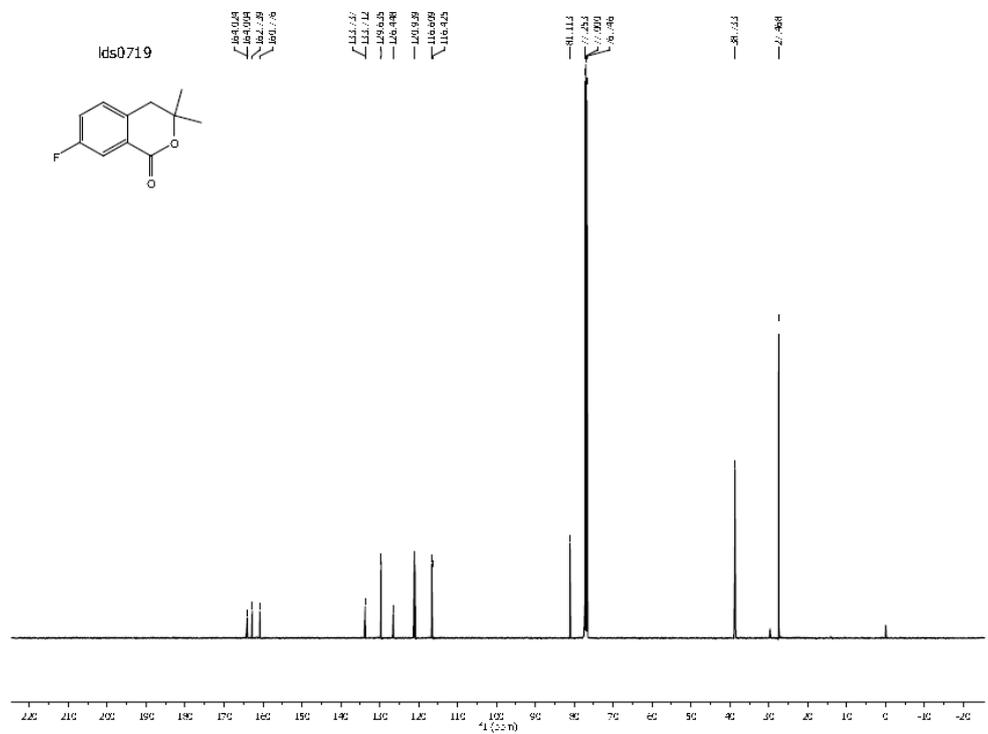
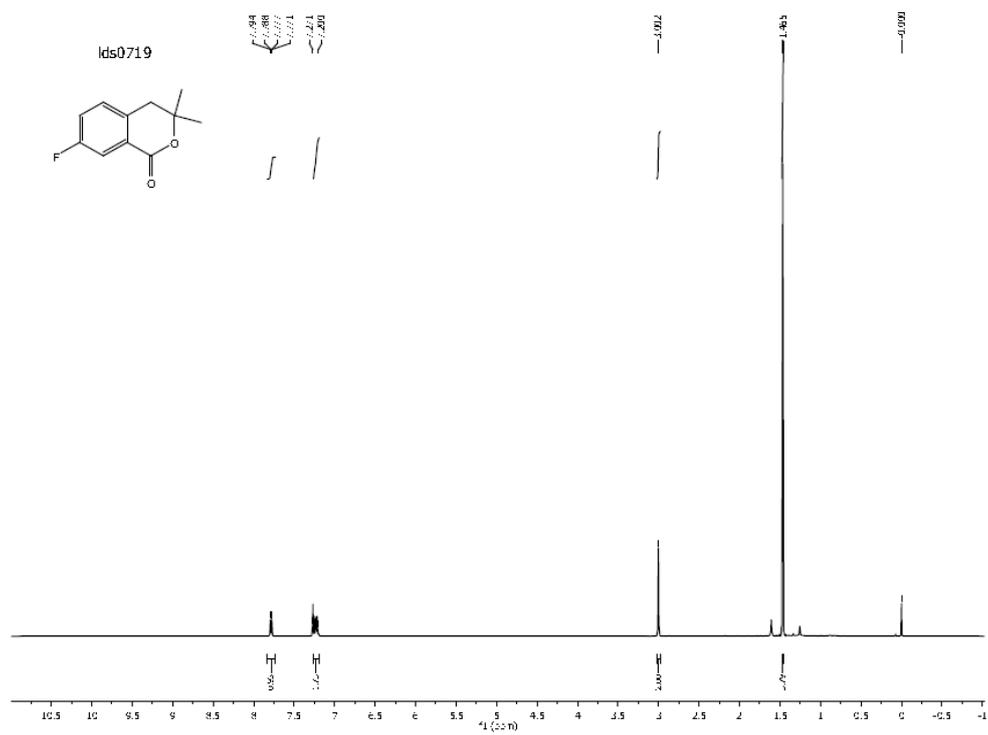
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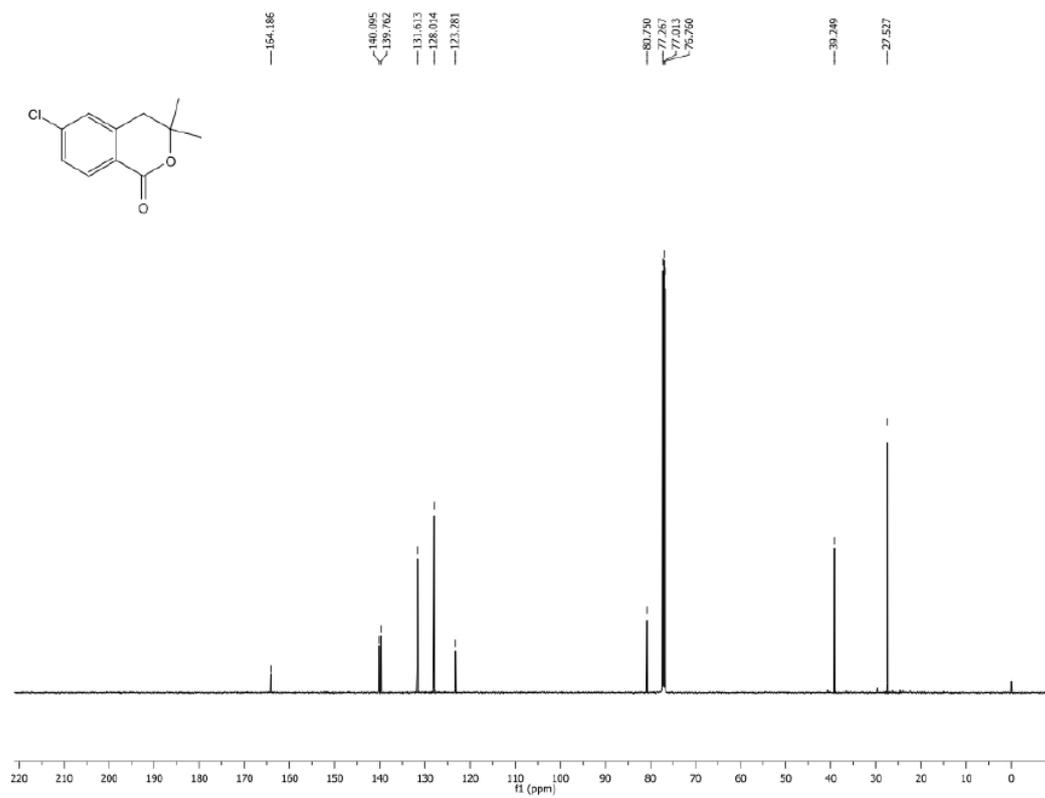
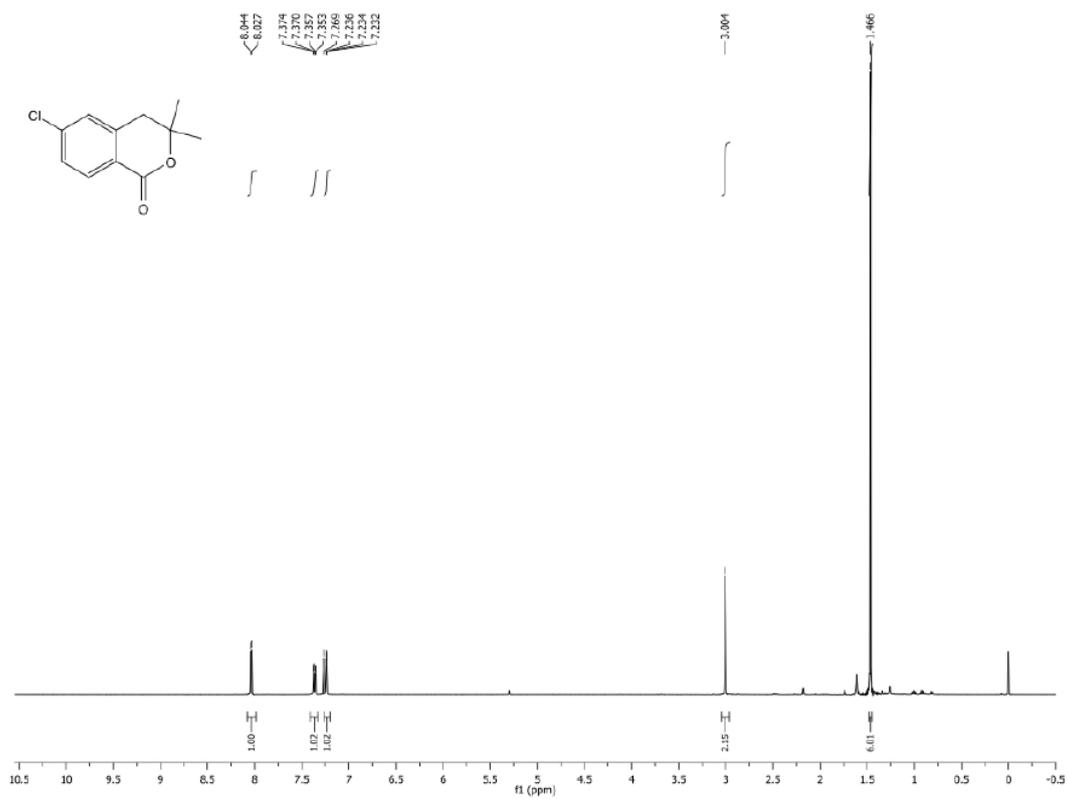


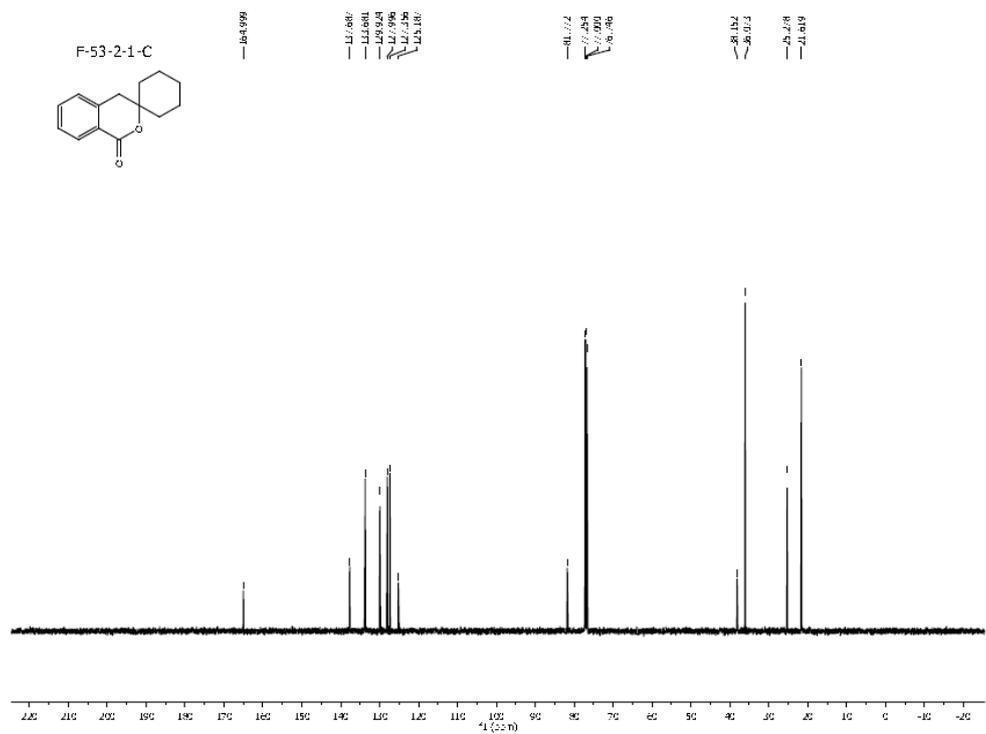
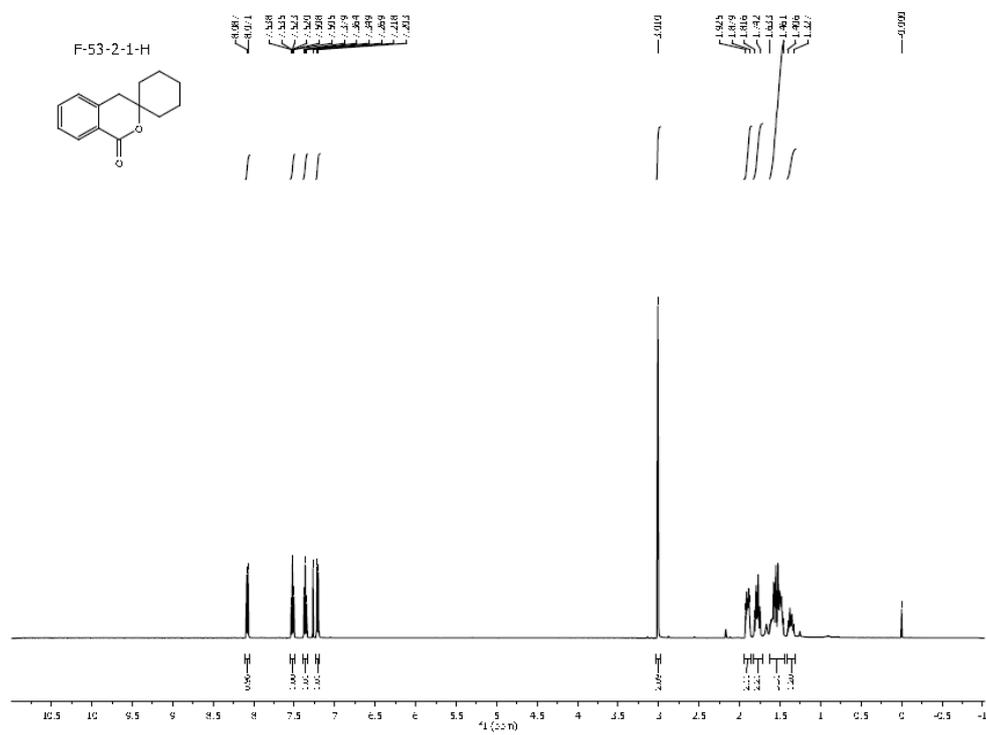


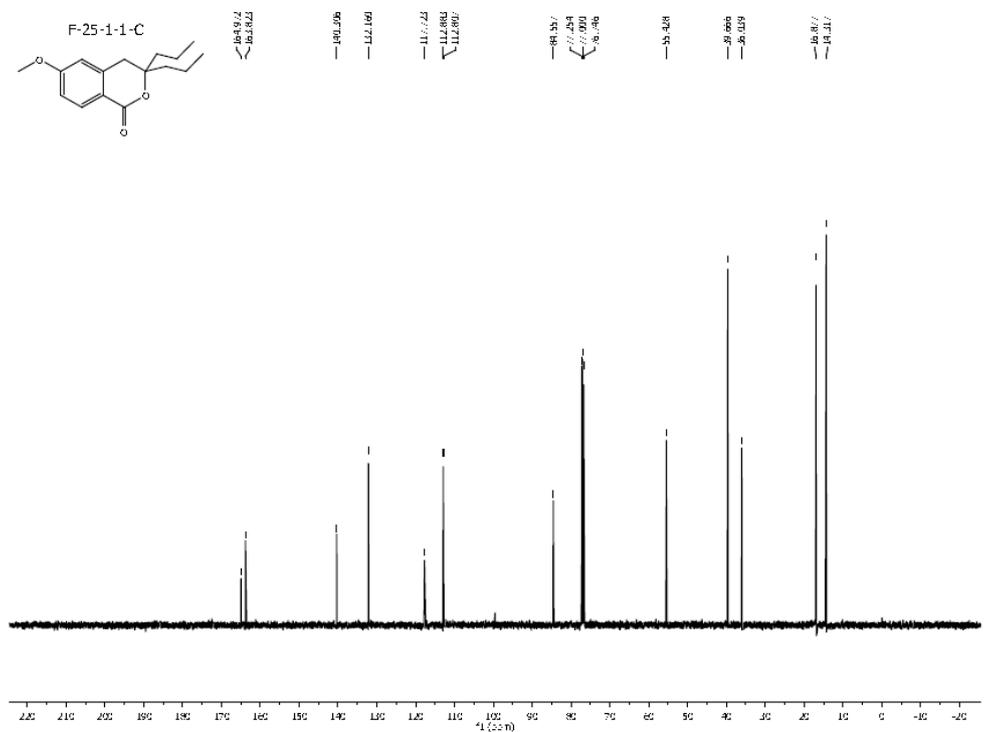
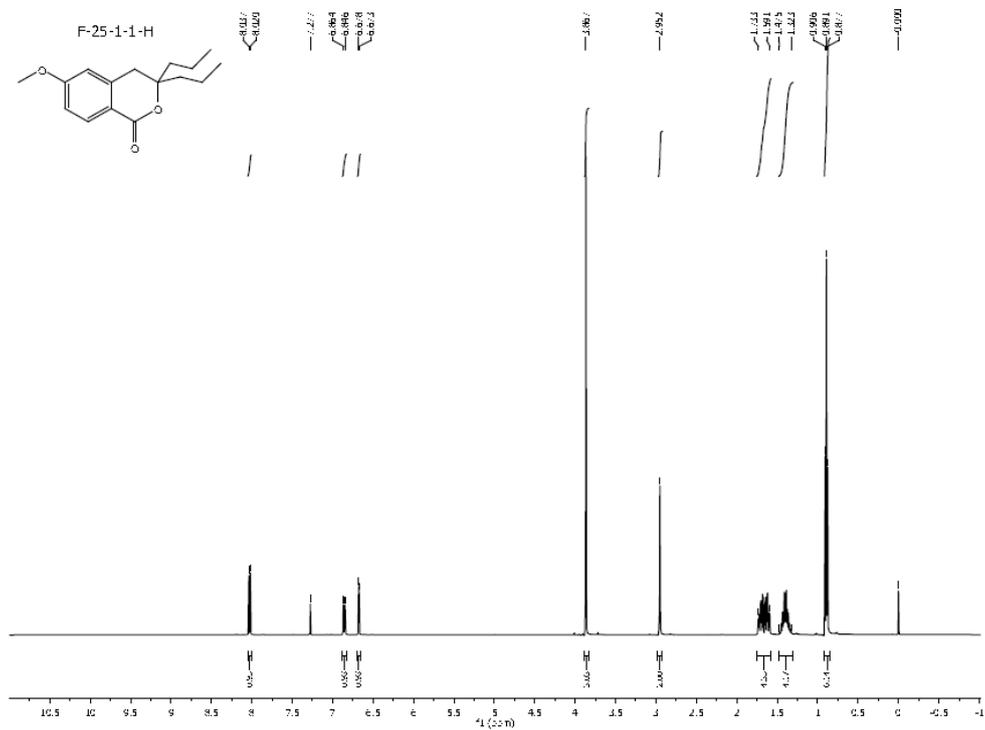


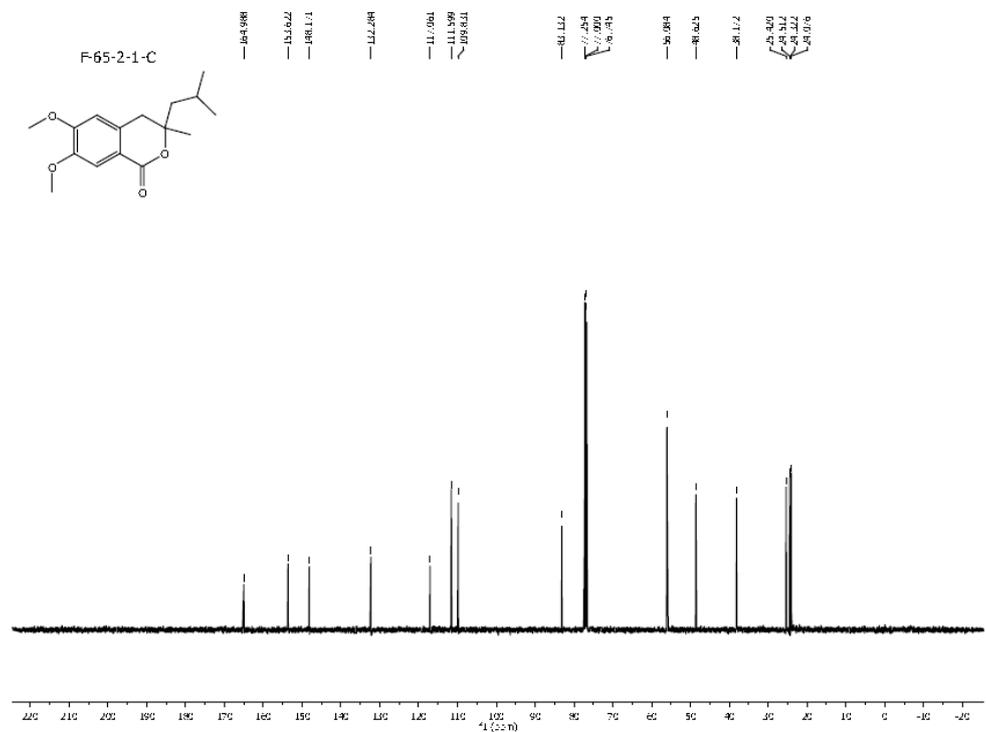
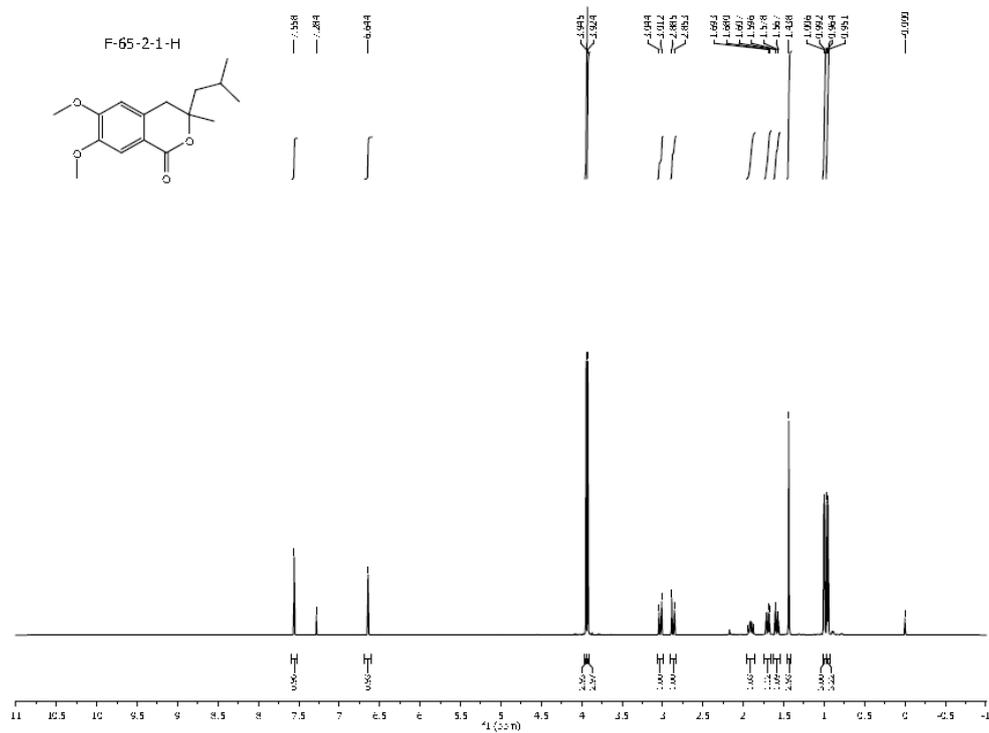




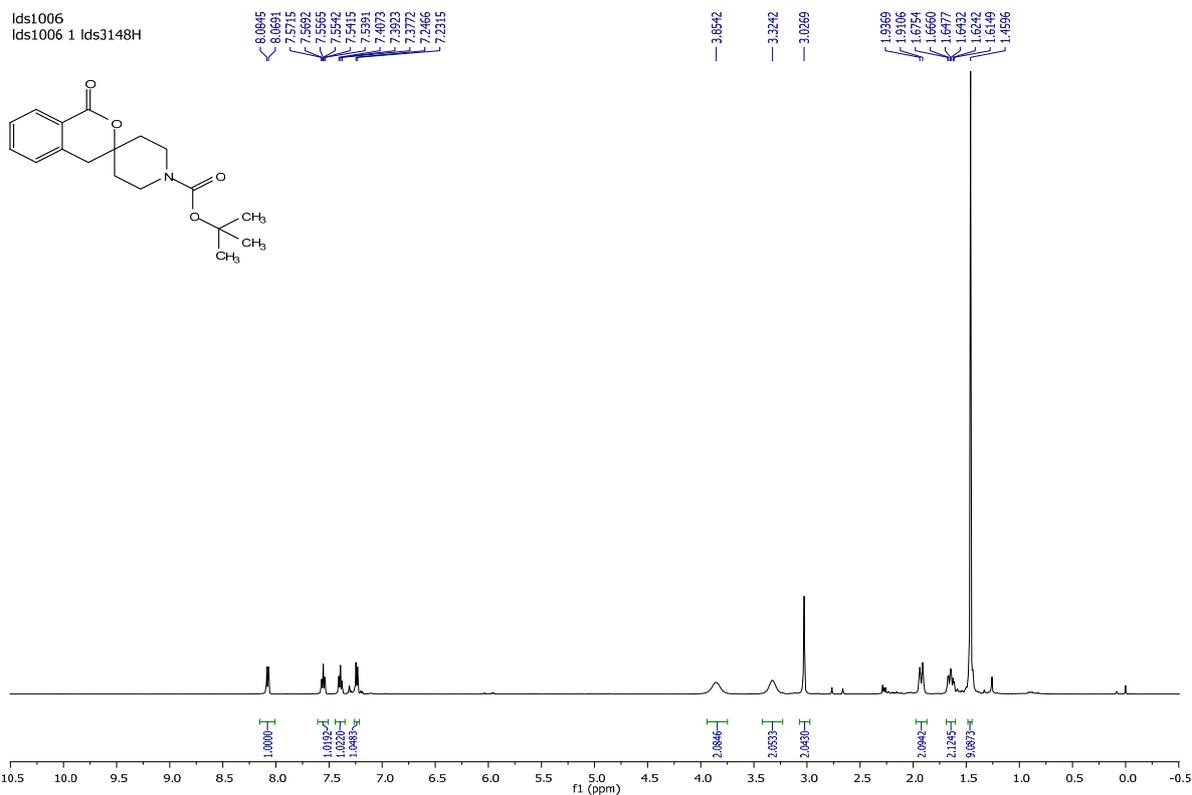








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