Supporting Information

Multiple Remote C(sp^3)-H Functionalizations of Aliphatic Ketones via Bimetal Cu-Pd Synergistically Catalyzed Successive Dehydrogenation Desaturation

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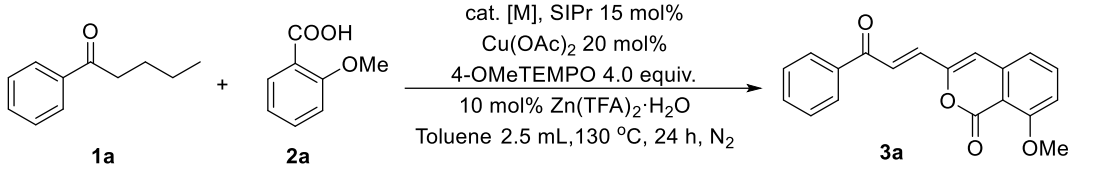
Contents

1. General Information

All reactions were conducted in oven-dried vials with a magnetic stir bar under nitrogen atmosphere. Unless otherwise noted, materials were purchased from Alfa Aesar, Admas, TCI, Bide, and other commercial suppliers and were used as received. Benzene, Toluene, PhF, $PhCF_3$, 1,4-Dioxane were distilled from Na and stored under nitrogen. 1,2-Dichlorobenzene was distilled over CaH_2 and stored under nitrogen. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (377 MHz) spectra were recorded in $CDCl_3$ solutions using a Bruker AVANCE 400 spectrometer. Calibration was done using tetramethylsilane (0 ppm) or residual undeuterated solvent $CHCl_3$ (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). The data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet), coupling constant *J* (Hz) and integration. HRMS were performed by the Shanghai Mass Spectrometry Center in Shanghai Institute of Organic Chemistry, Chinese Academic of Sciences (Instrument: Thermo Scientific Q Exactive HF Orbitrap-FTMS, Operation Mode: ESI Positive Ion Mode).

2. Reaction Condition Optimization

Table S1. Catalyst evaluation

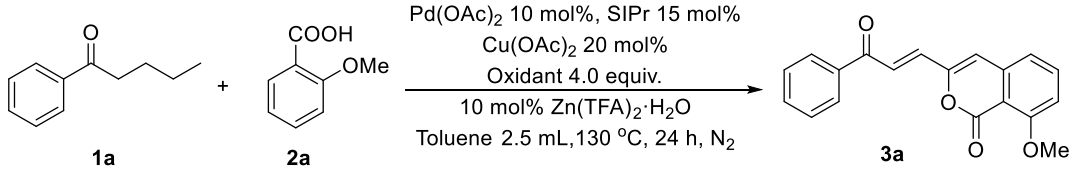


1a 2a 3a

Entry[a]	[M] (mol%)	Yield (%)[b]
1	$[RhCp^*Cl_2]_2$ (5 mol%)	n.d.
2	$Rh(PPh_3)_3Cl$ (10 mol%)	n.d.
3	$[Rh(COD)Cl_2]_2$ (5 mol%)	n.d.
4	$[Ru(p\text{-cym})Cl_2]_2$ (5 mol%)	n.d.
5	$[IrCp^*Cl_2]_2$ (5 mol%)	n.d.
6	$[Ir(COD)Cl_2]_2$ (5 mol%)	n,d,
7	$Pd(OAc)_2$ (10 mol%)	81 %
8	$Pd(TFA)_2$ (10 mol%)	72 %
9	$Pd(PPh_3)_4$ (10 mol%)	58 %

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), [M]-catalyst (10 mol%), $Cu(OAc)_2$ (20 mol%), $Zn(TFA)_2{\cdot}H_2O$ (10 mol%), 4-OMe-TEMPO (4.0 equiv.) and Toluene (2.5 mL), 130 °C, 24 h. [b] Yields of isolated products.

Table S2. Oxidant evaluation



1a 2a 3a

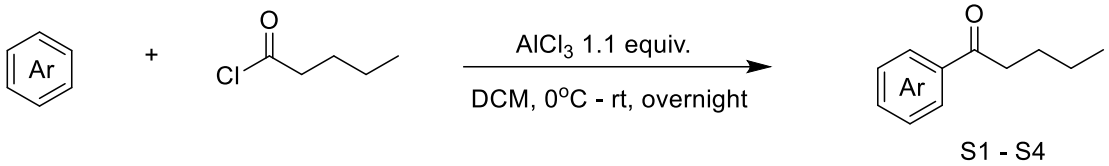
Entry[a]	Oxidant (equiv.)	Yield (%)[b]
1	TEMPO	70 %
2	4-OMe-TEMPO	81 %

Entry[a]	Oxidant (equiv.)	Yield (%)[b]
3	4-NHAc-TEMPO	76 %
4	O_2 ball	n.d.
5	NHPI	n.d.
6	tBuOOtBu	n.d.
7	tBuOOH	n.d.
8	Ag_2CO_3	trace
9	AgOAc	trace

[a] Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (20 mol%), $Zn(TFA)_2 \cdot H_2O$ (10 mol%), Oxidant (4.0 equiv.) and Toluene (2.5 mL), 130 °C, 24 h. [b] Yields of isolated products.

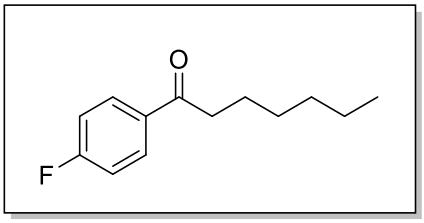
3. Synthesis and Characterization of Substrates

General Procedure 1 for Synthesis of Aryl butyl, hexyl ketones (S1-S4)



To a solution of anhydrous aluminium trichloride (1.1 equiv) in DCE (10 mL) at 0°C was added acid chloride (1.1 equiv), slowly, the reaction mixture was stirred at 0 °C for 10 min, followed by addition of a solution of arene in DCE (10 mL DCE,10 mmol 1equiv) during 10 min, the reaction mixture was slowly warmed to room temperature and allowed to stir at room temperature for completion of the reaction (monitored by TLC). the reaction mixture was cooled to 0 °C and quenched with ice cold water (20 mL). The reaction mixture was extracted with ethyl acetate (3 x 20 mL), and combined organic layer was washed with dilute HCl (25 mL, 2N), sodium carbonate solution (25 mL, saturated solution) and finally with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (0–5% EtOAc in petroleum ether) to afford the product **S1 – S4**. (All characterization data are in accordance with the literature [1],[2],[3],[4]).

1-(4-fluorophenyl)heptan-1-one (S1)



Following the general procedure **1** with fluorobenzene (0.96 g, 10 mmol), heptanoyl chloride (1.63 g, 11 mmol). The reaction mixture was stirred at room temperature for overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a white solid.

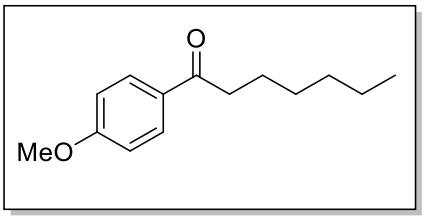
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.13 (t, *J* = 8.6 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 1.73 (dt, *J* = 14.9, 7.4 Hz, 2H), 1.46 – 1.16 (m, 6H), 0.89 (t, *J*

= 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.96, 165.60 (d, *J* = 254.2 Hz), 133.48 (d, *J* = 2.9 Hz), 130.63 (d, *J* = 9.2 Hz), 115.58 (d, *J* = 21.8 Hz), 38.53, 31.63, 29.00, 24.29, 22.51, 14.02.

^{19}F NMR (376 MHz, $CDCl_3$) δ -105.75.

1-(4-methoxyphenyl)heptan-1-one (S2)

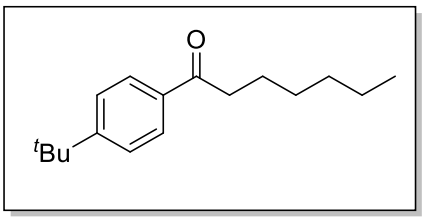


Following the general procedure **1** with anisole (1.1g, 10 mmol), heptanoyl chloride (1.63 g, 11 mmol). The reaction mixture was stirred at room temperature for overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.00 – 2.75 (m, 2H), 1.72 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.44 – 1.24 (m, 6H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.29, 163.26, 130.30, 130.18, 113.63, 55.43, 38.31, 31.68, 29.10, 24.59, 22.53, 14.05.

1-(4-(tert-butyl)phenyl)heptan-1-one (S3)



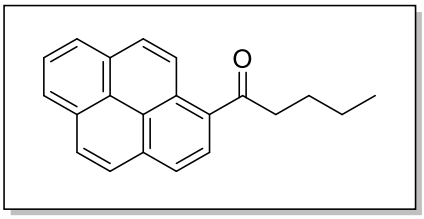
Following the general procedure **1** with tert-butylbenzene (1.34 g, 10 mmol), heptanoyl chloride (1.63 g, 11 mmol). The reaction mixture was stirred at room temperature for

overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 1.73 (dt, *J* = 14.9, 7.5 Hz, 2H), 1.48 – 1.19 (m, 15H), 0.89 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.23, 156.45, 134.47, 127.98, 125.41, 38.49, 35.01, 31.64, 31.04, 29.05, 24.41, 22.50, 14.02.

1-(pyren-1-yl)pentan-1-one (S4)



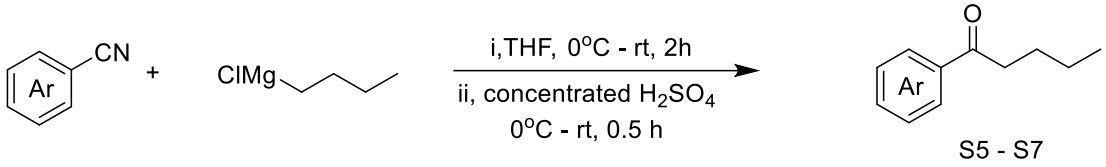
Following the general procedure **1** with pyrene (2.02 g, 10 mmol), pentanoyl chloride (1.32g, 11 mmol). The reaction mixture was stirred at room temperature for overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 9.4 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.25 – 8.17 (m, 3H), 8.14 (dd, *J* = 8.5, 3.4 Hz, 2H), 8.04 (dd, *J* = 8.3, 6.1 Hz, 2H), 3.26 – 3.12 (m, 2H), 1.86 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.49 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.41, 133.49, 132.90, 131.03, 130.50, 129.40, 129.30, 129.17, 127.03, 126.30, 126.11, 125.92, 125.88, 124.95, 124.76, 124.30, 123.95, 42.37, 27.07, 22.54, 13.98.

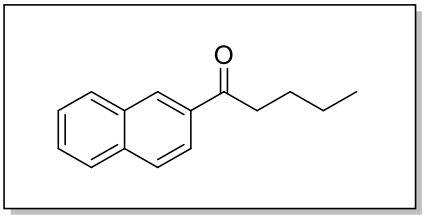
HRMS-ESI (positive) M = $C_{21}H_{18}O$: calculated $(M+Na)^+$ m/z 309.1250; found $(M+Na)^+$ m/z 309.1249.

General Procedure 2 for Synthesis of Aryl butyl ketones (S5-S7)



Under nitrogen atmosphere, to a solution of the n-BuMgCl (12 mmol) in dry toluene (20 mL) at 0 °C was added dropwise nitrile (10 mmol) over a period of 0.5 h, then the reaction mixture was moved to room temperature. After 2 h of stirring at room temperature, the reaction mixture was poured onto ice, and concentrated H_2SO_4 (2 mL) was added. The resulting reaction mixture was stirred at room temperature for additional 0.5 h. The reaction mixture was extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated reduced pressure. The residue was purified by flash chromatography (0–5% EtOAc in petroleum ether) to afford the product **S5 – S7**. (All characterization data are in accordance with the literature[1],[5],[6]).

1-(naphthalen-2-yl)pentan-1-one (S5)

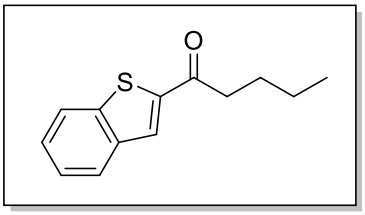


Following the general procedure **2** with 2-naphthonitrile (1.53 g, 10 mmol), n-BuMgCl (12 mmol). Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.04 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.96 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.57 (dt, *J* = 14.8, 6.9 Hz, 2H), 3.10 (t, *J* = 7.4 Hz, 2H), 1.84 – 1.71 (m, 2H), 1.51 – 1.39 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.53, 135.47, 134.38, 132.52, 129.57, 129.50, 128.35, 128.29, 127.73, 126.67, 123.94, 38.38, 26.62, 22.51, 13.97.

1-(benzo[b]thiophen-2-yl)pentan-1-one (S6)

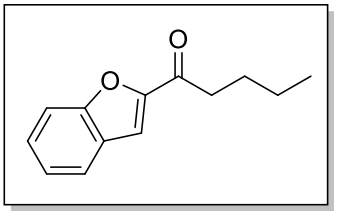


Following the general procedure **2** with benzo[b]thiophene-2-carbonitrile (1.6 g, 10 mmol), n-BuMgCl (12 mmol). Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.86 (t, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 14.3, 7.7 Hz, 2H), 2.99 (t, *J* = 7.5 Hz, 2H), 1.77 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.54 – 1.26 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 195.00, 143.85, 142.35, 139.11, 128.73, 127.23, 125.80, 124.88, 122.91, 38.95, 26.80, 22.41, 13.85.

1-(benzofuran-2-yl)pentan-1-one (S7)

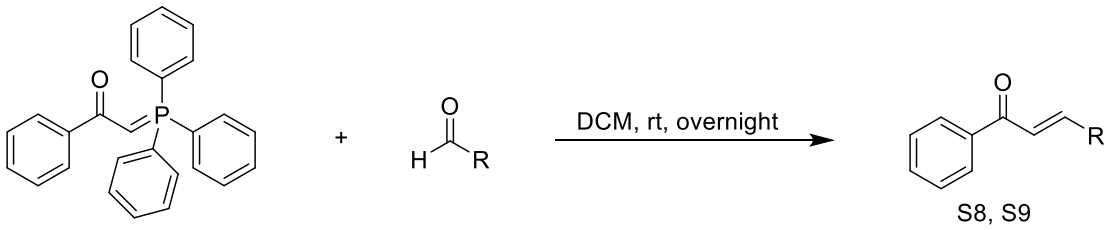


Following the general procedure **2** with benzofuran-2-carbonitrile (1.43 g, 10 mmol), n-BuMgCl (12 mmol). Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.48 (dd, *J* = 14.1, 6.0 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 1.77 (dt, *J* = 15.1, 7.5 Hz, 2H), 1.44 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H).

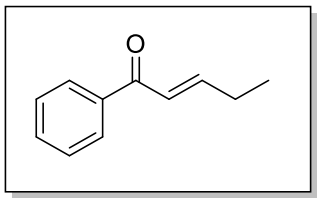
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.73, 155.55, 152.66, 128.09, 127.05, 123.82, 123.21, 112.55, 112.44, 38.68, 26.39, 22.42, 13.86.

General Procedure 3 for Synthesis of Aryl Alkenyl ketones (S8, S9)



Under nitrogen atmosphere, to a solution of (Benzoylmethylene)triphenylphosphorane (2.0 g, 5.3 mmol) in dry DCM (25 mL) at rt was added dropwise aldehyde (6.0 mmol) over a period of 5 min. The reaction was monitored by TLC. The resulting suspension was filtered through a silica gel pad with EtOAc and concentrated under vacuo. The residue was purified by flash chromatography (0–5% EtOAc in petroleum ether) to afford the product S8, S9 as a colorless oil. (All characterization data are in accordance with the literature[7]).

1-phenylpent-2-en-1-one (S8)

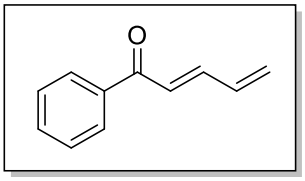


Following the general procedure 3 with (Benzoylmethylene)triphenylphosphorane (2.0 g, 5.3 mmol), propionaldehyde (0.35 g, 6 mmol). The reaction mixture was stirred at room temperature for overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (dd, *J* = 8.0, 7.0 Hz, 2H), 7.11 (dt, *J* = 15.2, 6.3 Hz, 1H), 6.87 (dd, *J* = 15.4, 0.9 Hz, 1H), 2.35 (p, *J* = 7.4 Hz, 2H), 1.14 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.93, 151.18, 137.90, 132.47, 128.40, 128.38, 124.87, 25.81, 12.24.

1-phenylpenta-2,4-dien-1-one (S9)

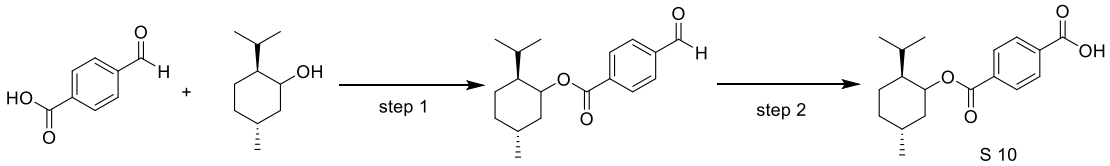


Following the general procedure 3 with (Benzoylmethylene)triphenylphosphorane (2.0 g, 5.3 mmol), acrylaldehyde (0.34 g, 6 mmol). The reaction mixture was stirred at room temperature for overnight. Purification by silica gel flash chromatography (0–5% EtOAc in petroleum ether) gave the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 15.1, 11.0 Hz, 1H), 7.00 (d, *J* = 15.2 Hz, 1H), 6.59 (dt, *J* = 16.9, 10.5 Hz, 1H), 5.72 (d, *J* = 16.9 Hz, 1H), 5.59 (d, *J* = 9.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.66, 144.67, 137.87, 135.33, 132.73, 128.53, 128.37, 126.81, 126.13.

Synthesis of menthol derivative (S10)



The compound was prepared by literature procedure.[8]

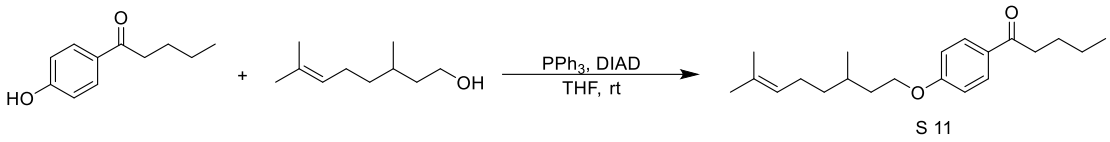
Step 1. To a solution of anhydrous 4-formylbenzoic acid (1.0 g, 6.66 mmol) in DCE (20 mL) were added *N*,*N*-dimethyl-4-aminopyridine (0.163 g, 1.34 mmol), menthol (1.36 g, 8.7 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (1.52 g, 7.3 mmol). The reaction mixture was stirred at room temperature for completion of the reaction (monitored by TLC). The reaction mixture was extracted with ethyl acetate (3 x 20 mL), and combined organic layer was washed with dilute HCl (25 mL, 2N), sodium carbonate solution (25 mL, saturated solution) and finally with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the curde product.

Step 2. The crude was dissolved in DMF (30mL) and oxone (4.3 g, 7 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 6 h, and then diluted with aqueous HCl (25 mL, 2N). The resulting mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer was washed with dilute HCl (25 mL, 2N), and brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (10–25% EtOAc in petroleum ether) to afford **S10** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (q, *J* = 8.6 Hz, 4H), 4.98 (td, *J* = 10.9, 4.4 Hz, 1H), 2.15 (d, *J* = 11.6 Hz, 1H), 2.06 – 1.91 (m, 1H), 1.75 (d, *J* = 12.3 Hz, 2H), 1.66 – 1.54 (m, 2H), 1.14 (ddd, *J* = 17.8, 9.1, 4.5 Hz, 2H), 1.02 – 0.89 (m, 7H), 0.81 (dd, *J* = 6.9, 4.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.83, 165.31, 134.78, 133.85, 129.90, 129.45, 75.41, 47.14, 40.81, 34.19, 31.38, 26.44, 23.52, 21.96, 20.69, 16.42.

Synthesis of citronellol derivative (S11)



S 11

The compound was prepared by literature procedure.[1] Under nitrogen atmosphere, to a solution of citronellol (1.0 g, 6.0 mmol), 1-(4-hydroxyphenyl)pentan-1-one (1.07 g, 6.0 mmol) and PPh_3 (1.88 g, 7.2 mmol) in dry THF (35 mL) at 0 °C was added dropwise DIAD (1.46 g, 7.2 mmol) over a period of 5 min. The reaction mixture was stirred at room temperature for completion of the reaction (monitored by TLC). After complete disappearance of starting material, the solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography(5–15% EtOAc in petroleum ether) to give the product S11 as a colorless oil.

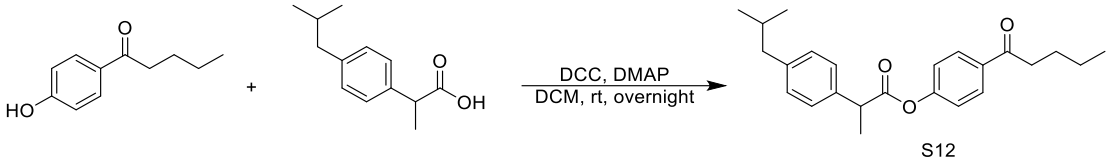
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 5.10 (t, *J* = 7.7 Hz, 1H), 4.10 – 3.97 (m, 2H), 2.98 – 2.72 (m, 2H), 2.10 – 1.94 (m, 2H), 1.85

(dt, *J* = 12.4, 6.9 Hz, 1H), 1.76 – 1.55 (m, 10H), 1.40 (dq, *J* = 14.1, 7.0 Hz, 3H), 1.29 – 1.15 (m, 1H), 0.95 (dd, *J* = 9.0, 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 198.90, 162.76, 131.15, 130.13, 129.80, 124.43, 113.96, 66.32, 37.80, 36.95, 35.81, 29.31, 26.61, 25.58, 25.29, 22.41, 19.37, 17.51, 13.84.

HRMS-ESI (positive) M = $C_{21}H_{32}O_2$: calculated $(M+H)^+$ m/z 317.2475; found $(M+H)^+$ m/z 317.2473.

Synthesis of Ibuprofen derivative (S12)



S12

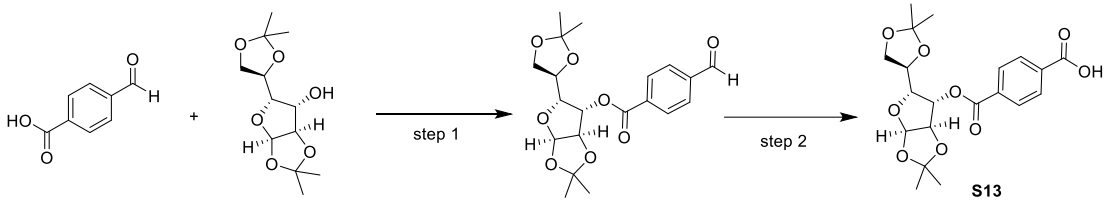
The compound was prepared by literature procedure.[1] Under nitrogen atmosphere, to a solution of Ibuprofen (1.24 g, 6.0 mmol), DMAP (0.073 g, 0.6 mmol) and DCC (1.86 g, 9 mmol) in dry DCM (35 mL) at rt was added dropwise a solution of 1-(4-hydroxyphenyl)pentan-1-one (2.14 g, 12 mmol) in DCM (15 mL) over a period of 5 min. The reaction mixture was stirred at room temperature for completion of the reaction (monitored by TLC). After complete disappearance of starting material, the solvent was evaporated under reduced pressure and the resulting oil was purified by flash chromatography(5–20% EtOAc in petroleum ether) to give the product S12 as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 3.99 (q, *J* = 7.1 Hz, 1H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.51 (d, *J* = 7.2 Hz, 2H), 1.90 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.74 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.65 (d, *J* = 7.1 Hz, 3H), 1.43 (dq, *J* = 14.6, 7.4 Hz, 2H), 0.97 (dd, *J* = 15.1, 7.0 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.14, 172.61, 154.32, 140.89, 136.80, 134.47, 129.50, 129.48, 127.10, 121.48, 45.19, 44.95, 38.17, 30.10, 26.34, 22.35, 22.30, 18.37, 13.85.

HRMS-ESI (positive) M = $C_{24}H_{30}O_3$: calculated $(M+H)^+$ m/z 367.2268; found $(M+H)^+$ m/z 367.2266.

Synthesis of Diacetone-D-glucose derivative (S13)



Step 1. To a solution of anhydrous 4-formylbenzoic acid (1.0 g, 6.66 mmol) in DCE (20 mL) were added *N*,*N*-dimethyl-4-aminopyridine (0.163 g, 1.34 mmol), Diacetone-D-glucose (2.26 g, 8.7 mmol) and *N*,*N*'-dicyclohexylcarbodiimide (1.52 g, 7.3 mmol). The reaction mixture was stirred at room temperature for completion of the reaction (monitored by TLC). The reaction mixture was extracted with ethyl acetate (3 x 20 mL), and combined organic layer was washed with dilute HCl (25 mL, 2N), sodium carbonate solution (25 mL, saturated solution) and finally with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the curde product.

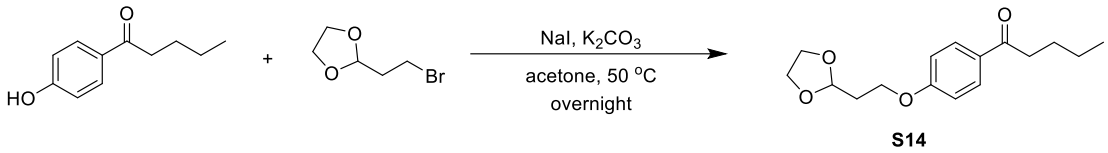
Step 2. The crude was dissolved in DMF (30mL) and oxone (4.3 g, 7 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 6 h, and then diluted with aqueous HCl (25 mL, 2N). The resulting mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic layer was washed with dilute HCl (25 mL, 2N), and brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (10–25% EtOAc in petroleum ether) to afford **S13** as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (q, *J* = 8.6 Hz, 4H), 5.98 (d, *J* = 3.6 Hz, 1H), 5.53 (d, *J* = 2.9 Hz, 1H), 4.65 (d, *J* = 3.6 Hz, 1H), 4.54 – 4.43 (m, 1H), 4.34 (dd, *J* = 8.6, 2.9 Hz, 1H), 4.26 – 4.07 (m, 2H), 1.58 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.43, 164.31, 133.65, 133.40, 130.16, 129.59, 112.49, 109.94, 105.13, 83.32, 79.64, 72.38, 67.41, 27.01, 26.69, 26.17, 25.05.

HRMS-ESI (positive) M = $C_{24}H_{30}O_3$: calculated $(M+Na)^+$ m/z 431.1313; found $(M+Na)^+$ m/z 431.1310.

1-(4-(2-(1,3-dioxolan-2-yl)ethoxy)phenyl)pentan-1-one (S14)



S14

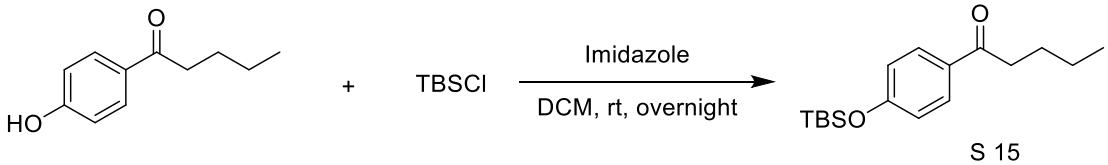
To a solution of K_2CO_3 (2.07 g, 15 mmol), NaI (0.224 g, 1.5 mmol) and 1-(4-hydroxyphenyl)pentan-1-one (1.78 g, 10 mmol) in acetone (15 mL) at rt was added dropwise 2-(2-bromoethyl)-1,3-dioxolane (2.14 g, 12 mmol). The reaction mixture was stirred at 50 °C for overnight. Upon cooling to room temperature, the reaction mixture was diluted with 30 mL of ethyl acetate and washed with water. The organic phase was dried with Na_2SO_4, filtered, concentrated and purified by flash chromatography (0–10% EtOAc in petroleum ether) to give S14 as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.09 (t, *J* = 4.7 Hz, 1H), 4.18 (t, *J* = 6.5 Hz, 2H), 4.05 – 3.95 (m, 2H), 3.93 – 3.84 (m, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.25 – 2.09 (m, 2H), 1.79 – 1.58 (m, 2H), 1.49 – 1.27 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.16, 162.49, 130.22, 130.10, 114.06, 101.76, 64.90, 63.74, 37.93, 33.55, 26.67, 22.47, 13.90.

HRMS-ESI (positive) M = $C_{16}H_{22}O_4$: calculated $(M+H)^+$ m/z 279.1591; found $(M+Na)^+$ m/z 279.1591.

1-(4-((tert-butyldimethylsilyl)oxy)phenyl)pentan-1-one (S15)



S 15

The compound was prepared by literature procedure.[1] To a solution of 1-(4-hydroxyphenyl)pentan-1-one (1.78 g, 10 mmol) and imidazole (0.82 g, 12 mmol) in dry CH_2Cl_2 (25 mL) was added TBSCl (1.65 g, 11 mmol) at ambient temperature. The reaction mixture was stirred for overnight. The reaction was quenched with H_2O,

extracted with CH_2Cl_2. dried with Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (0–10% EtOAc in petroleum ether) to give S15 as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 1.75 – 1.59 (m, 2H), 1.46 – 1.29 (m, 2H), 1.05 – 0.79 (m, 12H), 0.21 (d, *J* = 1.4 Hz, 6H).

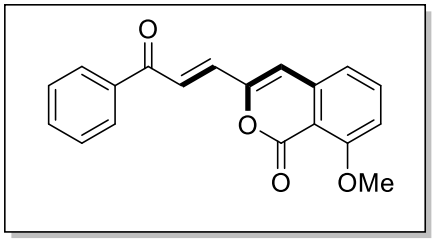
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.05, 159.92, 130.63, 130.09, 119.73, 37.86, 26.56, 25.47, 22.42, 18.11, 13.86, -4.51.

4. Synthesis and Characterization of Products

I: General Procedure for remote γ, δ-Csp^3-H functionalization of aliphatic acyclic ketones: In a nitrogen-filled glovebox, a 35 mL Schlenk tube equipped with a stir bar was charged with carboxylic acid (0.2 mmol), $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol). The tube was fitted with a rubber septum and moved out of the glove box. Then Toluene (2.5 mL) and ketone (0.24 mmol) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced with a Teflon screwcap under nitrogen flow (if the the substituted ketone was solid, it was added to the tube in the glove box). The reaction mixture was stirred at 130 ^oC for 24 h. Upon cooling to room temperature, the reaction mixture was diluted with 10 mL of DCM. followed by filtration through a pad of silica gel. The filtrate was concentrated under reduced pressure, and then purified by flash chromatography on silica gel to provide the corresponding product.

II: General Procedure for remote ε, ζ-Csp^3-H functionalization of aliphatic acyclic ketones: In a nitrogen-filled glovebox, a 35 mL Schlenk tube equipped with a stir bar was charged with carboxylic acid (0.2 mmol), $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol). The tube was fitted with a rubber septum and moved out of the glove box. Then Toluene (2.5 mL) and ketone (0.24 mmol) were added in turn to the Schlenk tube through the rubber septum using syringes, and then the septum was replaced with a Teflon screwcap under nitrogen flow (if the the substituted ketone was solid, it was added to the tube in the glove box). The reaction mixture was stirred at 130 ^oC for 24 h. Upon cooling to room temperature, the reaction mixture was diluted with 10 mL of DCM. followed by filtration through a pad of silica gel. The filtrate was concentrated under reduced pressure, and then purified by flash chromatography on silica gel to provide the corresponding product.

(E)-8-methoxy-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3a)



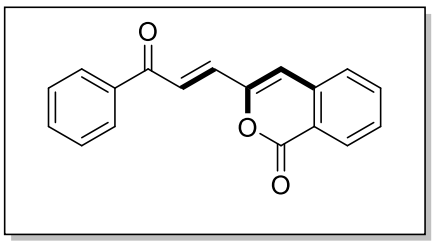
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0496 g, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 15.1 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 15.1 Hz, 1H), 7.12 – 6.96 (m, 2H), 6.67 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.10, 161.66, 157.93, 150.86, 138.98, 137.32, 136.01, 133.95, 133.27, 128.64, 128.62, 124.30, 118.83, 112.15, 111.62, 110.10, 56.32.

HRMS-ESI (positive) M = $C_{19}H_{14}O_4$: calculated $(M+H)^+$ m/z 307.0965; found $(M+H)^+$ m/z 307.0964.

(E)-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3b)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), benzoic acid (0.0245 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography

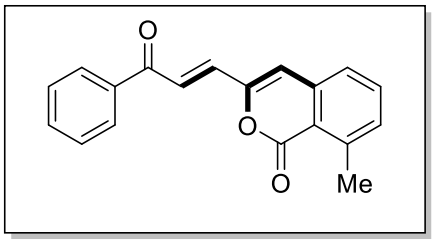
(10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0456 g, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 15.1 Hz, 1H), 7.75 (t, *J* = 7.2 Hz, 1H), 7.65 – 7.48 (m, 5H), 7.40 (d, *J* = 15.1 Hz, 1H), 6.77 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.14, 161.30, 150.71, 137.40, 136.32, 135.10, 134.16, 133.40, 130.02, 129.70, 128.75, 128.68, 126.76, 124.27, 121.94, 112.12.

HRMS-ESI (positive) M = $C_{18}H_{12}O_3$: calculated $(M+H)^+$ m/z 277.0859; found $(M+H)^+$ m/z 277.0859.

(E)-8-methyl-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3c)



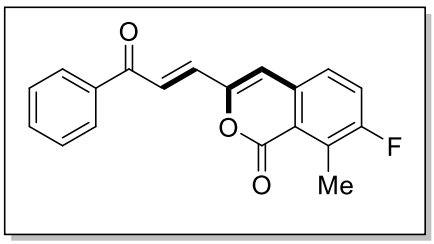
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2-methylbenzoic acid (0.0273 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ^oC for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0445 g, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.01 (m, 2H), 7.79 (d, *J* = 15.1 Hz, 1H), 7.64 – 7.49 (m, 4H), 7.35 (dd, *J* = 16.4, 7.7 Hz, 3H), 6.70 (s, 1H), 2.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.24, 160.65, 150.31, 144.07, 137.80, 137.48, 134.23, 134.09, 133.33, 132.72, 128.73, 128.67, 125.09, 124.03, 120.26, 112.79, 23.20.

HRMS-ESI (positive) M = $C_{19}H_{14}O_3$: calculated $(M+H)^+$ m/z 291.1016; found $(M+H)^+$ m/z 291.1014.

(E)-7-fluoro-8-methyl-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3d)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 3-fluoro-2-methylbenzoic acid (0.0308 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0376 g, 61% yield).

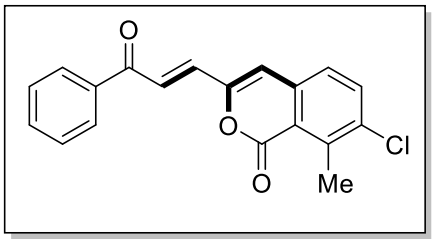
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.05 (m, 2H), 7.79 (d, *J* = 15.1 Hz,1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.43 (t, *J* = 8.8 Hz, 1H), 7.38 – 7.31 (m, 2H), 6.69 (s, 1H), 2.77 (d, *J* = 2.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.16, 161.13 (d, *J* = 248.0 Hz), 160.17 (d, *J* = 3.5 Hz), 149.84 (d, *J* = 2.9 Hz), 137.43, 134.12 (d, *J* = 3.1 Hz), 133.82, 133.37, 130.22 (d, *J* = 17.8 Hz), 128.75, 128.67, 126.02 (d, *J* = 8.9 Hz), 123.98, 122.31 (d, *J* = 25.9 Hz), 121.87 (d, *J* = 5.1 Hz), 112.02 (d, *J* = 2.3 Hz), 12.75 (d, *J* = 6.3 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -110.58.

HRMS-ESI (positive) M = $C_{19}H_{13}FO_3$: calculated $(M+H)^+$ m/z 309.0921; found $(M+H)^+$ m/z 309.0920.

(E)-7-chloro-8-methyl-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3e)



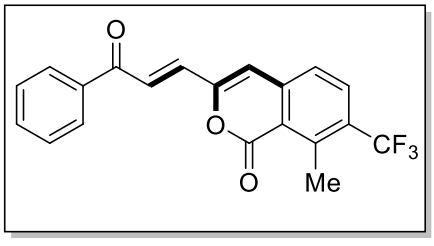
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 3-chloro-2-methylbenzoic acid (0.0341 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0371 g, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 15.1 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 15.1 Hz, 1H), 7.28 (d, *J* = 11.2 Hz, 1H), 6.67 (s, 1H), 2.95 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.10, 159.88, 150.68, 141.49, 137.46, 136.83, 136.64, 135.47, 133.59, 133.38, 128.76, 128.68, 125.46, 124.57, 121.62, 111.86, 18.48.

HRMS-ESI (positive) M = $C_{19}H_{13}ClO_3$: calculated $(M+H)^+$ m/z 325.0626; found $(M+H)^+$ m/z 325.0626.

(E)-8-methyl-3-(3-oxo-3-phenylprop-1-en-1-yl)-7-(trifluoromethyl)-1H-isochromen-1-one (3f)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g,

0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2-methyl-3-(trifluoromethyl)benzoic acid (0.0410 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0456 g, 64% yield).

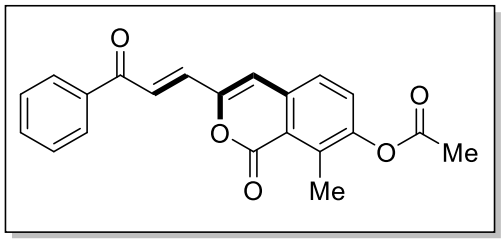
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.3 Hz, 2H), 7.93 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 15.1 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 15.1 Hz, 1H), 6.70 (s, 1H), 2.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.93, 159.58, 151.88, 144.33, 140.56, 137.24, 133.52, 133.31, 131.31 (q, *J* = 5.9 Hz), 130.70 (q, *J* = 29.7 Hz), 128.79, 128.69, 125.43, 124.67, 123.76 (q, *J* = 274.3 Hz), 121.46, 111.31, 18.02 (q, *J* = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -59.87.

HRMS-ESI (positive) M = $C_{20}H_{14}O_3F_3$: calculated $(M+H)^+$ m/z 359.0890; found $(M+H)^+$ m/z 359.0888.

(E)-8-methyl-1-oxo-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-7-yl acetate (3g)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 3-acetoxy-2-methylbenzoic acid (0.0391 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0375 g, 54% yield).

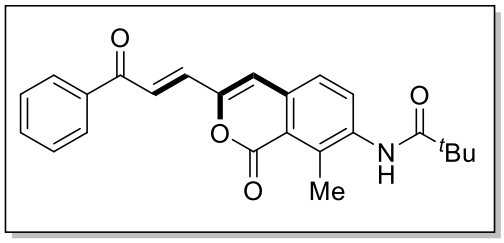
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.4 Hz, 2H), 7.79 (d, *J* = 15.1 Hz, 1H), 7.61

(t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 7.42 – 7.31 (m, 3H), 6.69 (s, 1H), 2.68 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.09, 168.92, 160.17, 150.23, 149.89, 137.36, 135.85, 135.76, 133.75, 133.30, 129.07, 128.67, 128.60, 125.46, 124.13, 121.41, 112.07, 20.68, 14.40.

HRMS-ESI (positive) M = $C_{21}H_{16}O_5$: calculated $(M+H)^+$ m/z 349.1071; found $(M+H)^+$ m/z 349.1071.

(E)-N-(8-methyl-1-oxo-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-7-yl)pivalamide (3h)



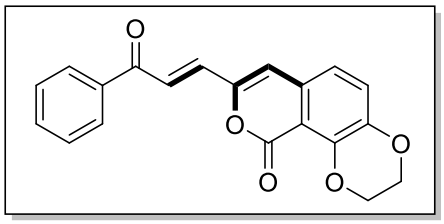
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2-methyl-3-pivalamidobenzoic acid (0.0471 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0487 g, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.3 Hz, 2H), 7.74 (d, J = 15.1 Hz, 1H), 7.65 – 7.49 (m, 4H), 7.32 (dd, J = 18.4, 8.4 Hz,2H), 6.67 (s, 1H), 2.77 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.03, 176.99, 160.39, 149.68, 137.64, 137.31, 135.22, 134.83, 133.74, 133.18, 130.85, 128.60, 128.51, 125.03, 123.58, 120.47, 112.46, 39.62, 27.46, 15.24.

HRMS-ESI (positive) M = $C_{24}H_{23}NO_4$: calculated $(M+H)^+$ m/z 390.1700; found $(M+H)^+$ m/z 390.1701.

(E)-8-(3-oxo-3-phenylprop-1-en-1-yl)-2,3-dihydro-10H-[1,4]dioxino[2,3-h]isochromen-10-one (3i)



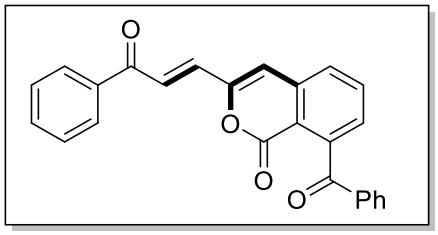
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2,3-dihydrobenzo[b][1,4]dioxine-5-carboxylic acid (0.0362 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (20–40% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0481 g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.4 Hz, 2H), 7.77 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 15.1 Hz, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.64 (s, 1H), 4.51 (dd, *J* = 5.1, 3.0 Hz, 2H), 4.38 (dd, *J* = 5.0, 3.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.24, 158.15, 149.21, 145.67, 144.33, 137.54, 134.11, 134.09, 133.24, 131.66, 128.68, 124.73, 123.31, 119.60, 112.52, 110.93, 64.86, 63.81.

HRMS-ESI (positive) M = $C_{20}H_{15}O_5$: calculated $(M+H)^+$ m/z 335.0914; found $(M+H)^+$ m/z 335.0912.

(E)-8-benzoyl-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3j)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g,

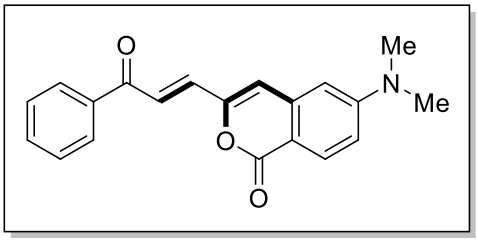
0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 2-benzoylbenzoic acid (0.0452 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0438 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.79 – 7.72 (m, 3H), 7.65 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.46 (dt, *J* = 20.0, 7.9 Hz, 5H), 7.38 (d, *J* = 15.1 Hz, 1H), 6.84 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.14, 188.95, 159.35, 151.32, 143.40, 137.22, 137.17, 136.65, 134.83, 133.52, 133.44, 133.37, 129.18, 128.73, 128.59, 128.50, 128.23, 127.70, 124.98, 119.35, 111.52.

HRMS-ESI (positive) M = $C_{25}H_{17}O_4$: calculated $(M+H)^+$ m/z 381.1121; found $(M+H)^+$ m/z 381.1121.

(E)-6-(dimethylamino)-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3k)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-(dimethylamino)benzoic acid (0.0337 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0408 g, 64% yield).

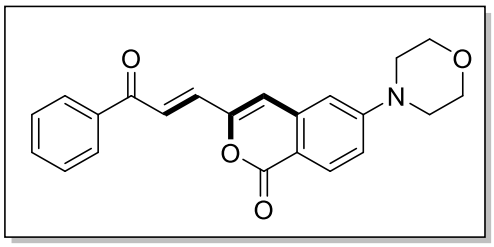
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 15.1

Hz, 1H), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.64 (s. 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 3.12 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.35, 161.74, 154.25, 150.78, 137.99, 137.56, 134.86, 133.27, 131.59, 128.69, 128.68, 123.64, 113.86, 113.15, 109.58, 106.16, 40.09.

HRMS-ESI (positive) M = $C_{20}H_{18}O_3N$: calculated $(M+H)^+$ m/z 320.1281; found $(M+H)^+$ m/z 320.1282.

(E)-3-(3-oxo-3-phenylprop-1-en-1-yl)-6-(piperidin-1-yl)-1H-isochromen-1-one (3l)



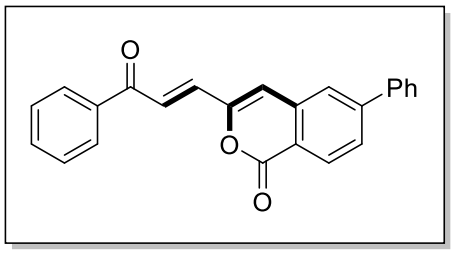
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-(piperidin-1-yl)benzoic acid (0.0412 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0492 g, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.9 Hz, 1H), 8.08 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 15.1 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.75 (s, 1H), 6.64 (s, 1H), 3.87 (t, *J* = 4.5 Hz, 4H), 3.38 (t, *J* = 4.5 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.18, 161.26, 155.17, 150.94, 138.07, 137.42, 134.52, 133.30, 131.57, 128.68, 128.63, 123.90, 115.93, 112.72, 112.13, 108.75, 66.32, 47.05.

HRMS-ESI (positive) M = $C_{22}H_{19}NO_4$: calculated $(M+H)^+$ m/z 362.1387; found $(M+H)^+$ m/z 362.1388.

(E)-3-(3-oxo-3-phenylprop-1-en-1-yl)-6-phenyl-1H-isochromen-1-one (3m)



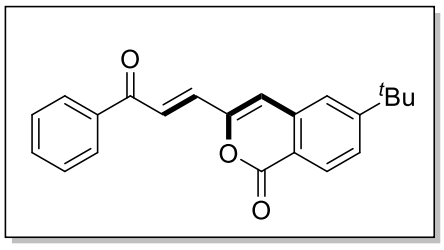
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), [1,1'-biphenyl]-4-carboxylic acid (0.0396 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0331 g, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 15.1 Hz, 1H), 7.81 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.67 (ddd, *J* = 21.5, 13.4, 4.3 Hz, 4H), 7.58 – 7.46 (m, 5H), 7.43 (d, *J* = 15.1 Hz, 1H), 6.84 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.18, 161.28, 151.08, 148.06, 138.98, 137.45, 136.85, 134.21, 133.43, 130.64, 129.17, 128.95, 128.78, 128.72, 128.69, 127.41, 124.93, 124.41, 120.58, 112.29.

HRMS-ESI (positive) M = $C_{24}H_{16}O_3$: calculated $(M+Na)^+$ m/z 375.0992; found $(M+Na)^+$ m/z 375.0993.

(E)-6-(tert-butyl)-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (3n)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr

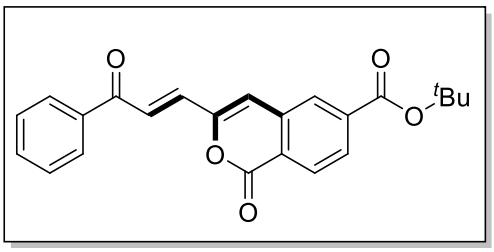
(0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-(tert-butyl)benzoic acid (0.0356 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0531 g, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.83 (d, *J* = 15.1 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.55 – 7.48 (m, 3H), 7.41 (d, *J* = 15.1 Hz, 1H), 6.78 (s, 1H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.13, 161.28, 159.22, 150.61, 137.43, 136.28, 134.32, 133.31, 129.79, 128.69, 128.63, 127.64, 123.92, 123.19, 119.46, 112.76, 35.42, 30.89.

HRMS-ESI (positive) M = $C_{22}H_{20}O_3$: calculated $(M+H)^+$ m/z 333.1485; found $(M+H)^+$ m/z 333.1485.

tert-butyl(E)-1-oxo-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromene-6-carboxylate (3o)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-(tert-butoxycarbonyl)benzoic acid (0.0445 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0546 g, 73% yield).

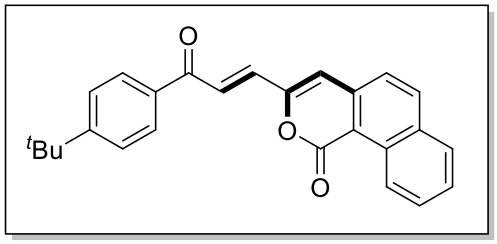
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 8.6 Hz, 1H), 8.16 – 7.98 (m, 4H), 7.84 (d, *J* = 15.1 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 15.1 Hz,

1H), 6.84 (s, 1H), 1.64 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.03, 163.94, 160.70, 151.22, 137.92, 137.34, 136.24, 133.86, 133.46, 130.12, 129.79, 128.78, 128.69, 127.92, 124.78, 124.36, 111.74, 82.63, 28.07.

HRMS-ESI (positive) M = $C_{23}H_{20}O_5$: calculated $(M+H)^+$ m/z 377.1384; found $(M+H)^+$ m/z 377.1385.

(E)-3-(3-(4-(tert-butyl)phenyl)-3-oxoprop-1-en-1-yl)-1H-benzo[h]isochromen-1-one (3p)



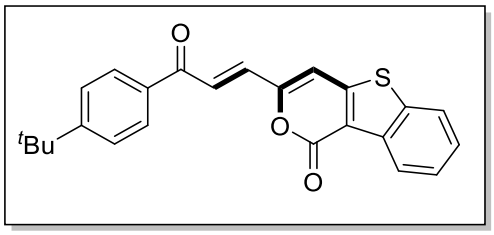
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(tert-butyl)phenyl)pentan-1-one (0.0523 g, 0.24 mmol), 1-naphthoic acid (0.0345 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0512 g, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (d, *J* = 8.7 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 1H), 7.88 (d, *J* = 5.4 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 15.1 Hz, 1H), 6.83 (s, 1H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.56, 160.56, 157.31, 151.85, 138.82, 136.55, 134.77, 133.51, 133.30, 131.51, 129.69, 128.76, 128.70, 127.51, 126.70, 125.71, 124.94, 123.93, 115.80, 112.50, 35.16, 31.03.

HRMS-ESI (positive) M = $C_{26}H_{22}O_3$: calculated $(M+H)^+$ m/z 383.1642; found $(M+H)^+$ m/z 383.1641.

(E)-3-(3-(4-(tert-butyl)phenyl)-3-oxoprop-1-en-1-yl)-1H-benzo[4,5]thieno[3,2-c]pyran-1-one (3q)



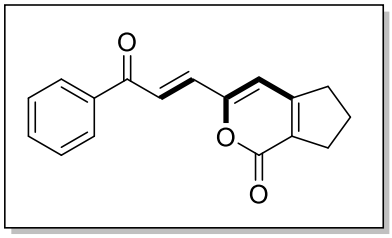
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(tert-butyl)phenyl)pentan-1-one (0.0523 g, 0.24 mmol), benzo[b]thiophene-3-carboxylic acid (0.0356 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0505 g, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 15.1 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.63 – 7.48 (m, 4H), 7.40 (d, *J* = 15.1 Hz, 1H), 7.03 (s, 1H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.44, 157.53, 156.75, 153.55, 151.15, 138.66, 135.38, 134.70, 132.91, 128.77, 126.98, 126.55, 126.06, 125.80, 124.95, 122.30, 119.39, 107.61, 35.24, 31.06.

HRMS-ESI (positive) M = $C_{24}H_{20}O_3S$: calculated $(M+H)^+$ m/z 389.1206; found $(M+H)^+$ m/z 389.1205.

(E)-3-(3-oxo-3-phenylprop-1-en-1-yl)-6,7-dihydrocyclopenta[c]pyran-1(5H)-one (3r)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g,

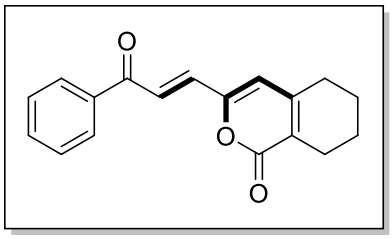
0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), cyclopent-1-ene-1-carboxylic acid (0.0225 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0218 g, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 15.1 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 13.7 Hz, 1H), 6.49 (s, 1H), 2.88 (t, *J* = 7.6 Hz, 4H), 2.16 (q, *J* = 15.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.06, 160.10, 158.64, 155.88, 137.29, 133.46, 130.24, 128.75, 128.67, 125.24, 110.10, 34.04, 30.02, 22.66.

HRMS-ESI (positive) M = $C_{17}H_{14}O_3$: calculated $(M+H)^+$ m/z 267.1016; found $(M+H)^+$ m/z 267.1016.

(E)-3-(3-oxo-3-phenylprop-1-en-1-yl)-5,6,7,8-tetrahydro-1H-isochromen-1-one (3s)



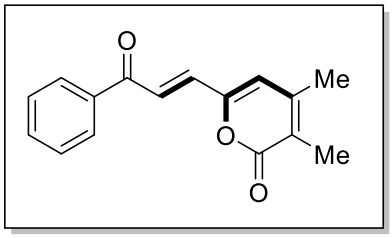
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), cyclohex-1-ene-1-carboxylic acid (0.0254 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0307 g, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.3 Hz, 2H), 7.79 (d, *J* = 15.2 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 15.2 Hz, 1H), 6.22 (s, 1H), 2.58 – 2.40 (m, 4H), 1.78 (dd, *J* = 3.0, 2.2 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.97, 161.92, 152.55, 150.35, 137.26, 133.52, 133.35, 128.68, 128.59, 125.62, 124.48, 113.70, 28.82, 23.63, 21.52, 21.18.

HRMS-ESI (positive) M = $C_{18}H_{16}O_3$: calculated $(M+H)^+$ m/z 281.1172; found $(M+H)^+$ m/z 281.1173.

(E)-3,4-dimethyl-6-(3-oxo-3-phenylprop-1-en-1-yl)-2H-pyran-2-one (3t)



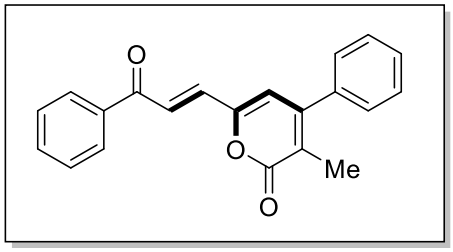
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), (E)-2-methylbut-2-enoic acid (0.0204 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0261 g, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 15.6 Hz, 1H), 6.29 (s, 1H), 2.18 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.02, 162.39, 152.61, 148.84, 137.32, 133.42, 133.34, 128.74, 128.66, 124.69, 124.40, 114.90, 19.33, 12.98.

HRMS-ESI (positive) M = $C_{16}H_{14}O_3$: calculated $(M+H)^+$ m/z 255.1016; found $(M+H)^+$ m/z 255.1016.

(E)-3-methyl-6-(3-oxo-3-phenylprop-1-en-1-yl)-4-phenyl-2H-pyran-2-one (3u)



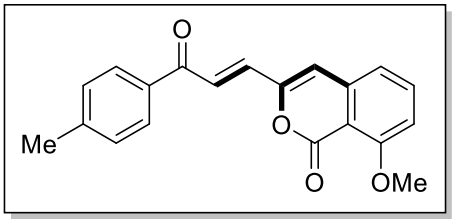
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), (E)-2-methyl-3-phenylacrylic acid (0.0324 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0291g, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.3 Hz, 2H), 7.84 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.56 – 7.43 (m, 5H), 7.33 (dd, *J* = 14.4, 8.3 Hz, 3H), 6.46 (s, 1H), 2.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.86, 162.78, 152.94, 151.14, 137.24, 136.71, 133.39, 133.35, 129.12, 128.72, 128.71, 128.62, 127.85, 124.84, 124.14, 113.94, 14.57.

HRMS-ESI (positive) M = $C_{21}H_{16}O_3$: calculated $(M+H)^+$ m/z 317.1172; found $(M+H)^+$ m/z 317.1176.

(E)-8-methoxy-3-(3-oxo-3-(p-tolyl)prop-1-en-1-yl)-1H-isochromen-1-one (4a)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(p-tolyl)pentan-1-one (0.0425 g,

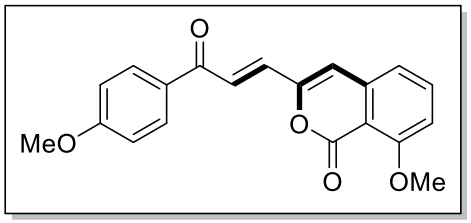
0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0490 g, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 15.1 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* = 17.3, 10.2 Hz,3H), 7.04 (t, *J* = 7.4 Hz, 2H), 6.65 (s, 1H), 4.03 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.61, 161.68, 158.00, 151.00, 144.27, 139.07, 135.99, 134.85, 133.60, 129.36, 128.80, 124.47, 118.81, 111.94, 111.55, 110.11, 56.34, 21.65.

HRMS-ESI (positive) M = $C_{20}H_{16}O_4$: calculated $(M+H)^+$ m/z 321.1121; found $(M+H)^+$ m/z 321.1121.

(E)-8-methoxy-3-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-1H-isochromen-1-one (4b)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(4-methoxyphenyl)pentan-1-one (0.0461 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0481 g, 72% yield).

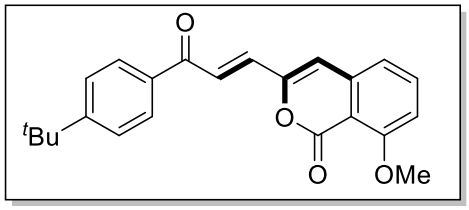
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 15.0 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 15.0 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 2H), 6.99 (d, *J* = 8.8

Hz, 2H), 6.65 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.45, 163.82, 161.73, 158.13, 151.13, 139.18, 136.02, 133.31, 131.11, 130.44, 124.51, 118.82, 113.91, 111.80, 111.52, 110.15, 56.38, 55.50.

HRMS-ESI (positive) M = $C_{20}H_{16}O_5$: calculated $(M+H)^+$ m/z 337.1071; found $(M+H)^+$ m/z 337.1070.

(E)-3-(3-(4-(tert-butyl)phenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4c)



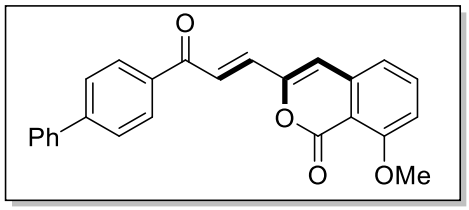
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(tert-butyl)phenyl)pentan-1-one (0.0523 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0599 g, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 15.1 Hz, 2H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 15.1 Hz, 1H), 7.04 (t, J = 6.7 Hz, 2H), 6.66 (s, 1H), 4.03 (s, 3H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.67, 161.72, 158.04, 157.20, 151.06, 139.12, 136.01, 134.80, 133.64, 128.69, 125.65, 124.55, 118.83, 111.96, 111.58, 110.17, 56.37, 35.14, 31.02.

HRMS-ESI (positive) M = $C_{23}H_{22}O_4$: calculated $(M+Na)^+$ m/z 385.1410; found $(M+Na)^+$ m/z 385.1413.

(E)-3-(3-([1,1'-biphenyl]-4-yl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4d)



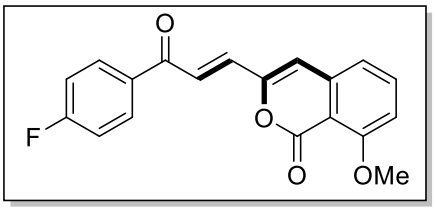
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-([1,1'-biphenyl]-4-yl)pentan-1-one (0.0571 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0471 g, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 15.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 6.6 Hz, 3H), 7.48 (t, *J* = 6.5 Hz, 2H), 7.39 (dd, *J* = 18.9, 11.1 Hz, 2H), 7.04 (t, *J* = 7.0 Hz, 2H), 6.67 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.48, 161.66, 157.96, 150.91, 145.87, 139.62, 139.01, 136.03, 135.99, 133.86, 129.26, 128.86, 128.21, 127.22, 127.18, 124.27, 118.84, 112.15, 111.61, 110.10, 56.31.

HRMS-ESI (positive) M = $C_{25}H_{18}O_4$: calculated $(M+H)^+$ m/z 383.1278; found $(M+H)^+$ m/z 383.1277.

(E)-3-(3-(4-fluorophenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4e)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g,

0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-fluorophenyl)pentan-1-one (0.0432 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0502 g, 78% yield).

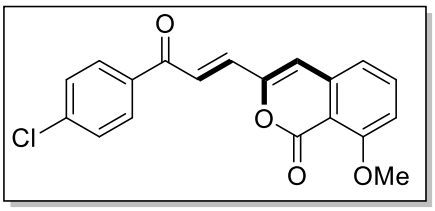
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.75 (d, *J* = 15.0 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 15.1 Hz, 1H), 7.19 (t, *J* = 8.6 Hz, 2H), 7.05 (dd, *J* = 8.0, 4.0 Hz, 2H), 6.67 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.44 (s), 165.82 (d, *J* = 255.4 Hz), 161.68 (s), 157.88 (s), 150.77 (s), 138.95 (s), 136.03 (s), 134.17 (s), 133.75 (d, *J* = 2.9 Hz), 131.32 (d, *J* = 9.4 Hz), 123.86 (s), 118.87 (s), 115.80 (d, *J* = 21.8 Hz), 112.32 (s), 111.69 (s), 110.13 (s), 56.35 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ -104.33.

HRMS-ESI (positive) M = $C_{19}H_{13}FO_4$: calculated $(M+H)^+$ m/z 325.0871; found $(M+H)^+$ m/z 325.0870.

(E)-3-(3-(4-chlorophenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4f)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-chlorophenyl)pentan-1-one (0.0472 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a

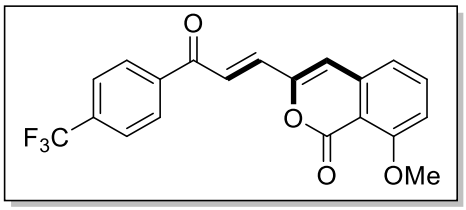
yellow solid (0.0461 g, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 15.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 15.1 Hz, 1H), 7.05 (dd, *J* = 8.0, 3.6 Hz, 2H), 6.68 (s, 1H), 4.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.87, 161.75, 157.94, 150.79, 139.82, 138.98, 136.10, 135.71, 134.44, 130.10, 129.02, 123.80, 118.94, 112.52, 111.78, 110.21, 56.41.

HRMS-ESI (positive) M = $C_{19}H_{13}ClO_4$: calculated $(M+H)^+$ m/z 341.0575; found $(M+H)^+$ m/z 341.0574.

(E)-8-methoxy-3-(3-oxo-3-(4-(trifluoromethyl)phenyl)prop-1-en-1-yl)-1H-isochromen-1-one (4g)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(trifluoromethyl)phenyl)pentan-1-one (0.0552 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0558 g, 75 % yield).

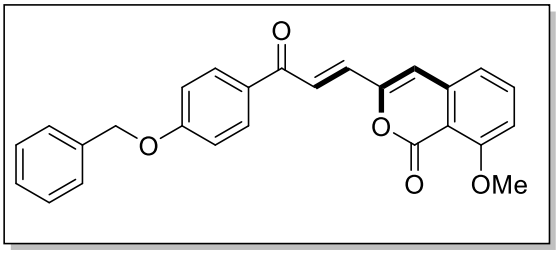
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.1 Hz, 2H), 7.85 – 7.73 (m, 3H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 15.0 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 2H), 6.70 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.16 (s), 161.71 (s), 157.84 (s), 150.56 (s), 140.05 (q, *J* = 1.2 Hz), 138.82 (s), 136.11 (s), 134.98 (s), 134.37 (q, *J* = 32.7 Hz), 128.92 (s), 125.67 (q, *J* = 3.7 Hz), 123.56 (s), 123.50 (q, *J* = 272.7 Hz), 118.97 (s), 112.88 (s), 111.89 (s), 110.15 (s), 56.35 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.94.

HRMS-ESI (positive) M = $C_{20}H_{13}F_3O_4$: calculated $(M+H)^+$ m/z 375.0839; found $(M+H)^+$ m/z 375.0836.

(E)-3-(3-(4-(benzyloxy)phenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4h)



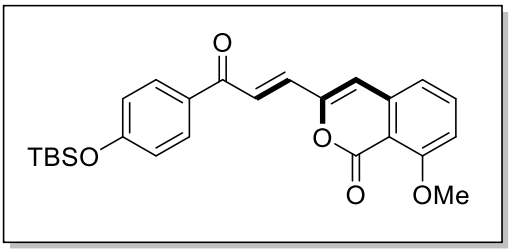
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(benzyloxy)phenyl)pentan-1-one (0.0644 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0586 g, 71 % yield).

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 15.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.49 – 7.24 (m, 6H), 7.03 (dd, *J* = 19.0, 8.5 Hz, 4H), 6.62 (s, 1H), 5.14 (s, 2H), 4.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.28, 162.83, 161.60, 157.98, 150.97, 139.04, 135.94, 133.24, 131.00, 130.51, 128.54, 128.11, 127.38, 124.31, 118.74, 114.64, 111.74, 111.45, 110.01, 70.03, 56.27.

HRMS-ESI (positive) M = $C_{26}H_{20}O_5$: calculated $(M+H)^+$ m/z 413.1834; found $(M+H)^+$ m/z 413.1834.

(E)-3-(3-(4-((tert-butyldimethylsilyl)oxy)phenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4i)



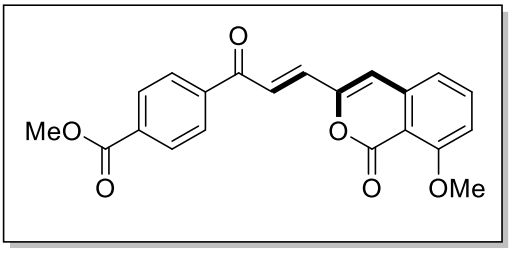
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-((tert-butyldimethylsilyl)oxy)phenyl)pentan-1-one (0.0702 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0645 g, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 15.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.49 – 7.24 (m, 6H), 7.03 (dd, J = 19.0, 8.5 Hz, 4H), 6.62 (s, 1H), 5.14 (s, 2H), 4.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.28, 162.83, 161.60, 157.98, 150.97, 139.04, 135.94, 133.24, 131.00, 130.51, 128.54, 128.11, 127.38, 124.31, 118.74, 114.64, 111.74, 111.45, 110.01, 70.03, 56.27.

HRMS-ESI (positive) M = $C_{26}H_{20}O_5$: calculated $(M+H)^+$ m/z 413.1834; found $(M+H)^+$ m/z 413.1834.

methyl (E)-4-(3-(8-methoxy-1-oxo-1H-isochromen-3-yl)acryloyl)benzoate (4j)



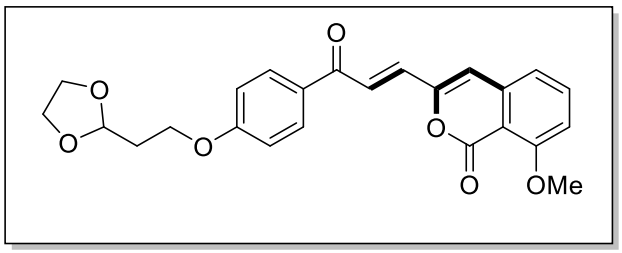
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), methyl 4-pentanoylbenzoate (0.0528 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0291 g, 40% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 18.4, 8.2 Hz, 4H), 7.80 (d, *J* = 15.1 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 15.1 Hz, 1H), 7.07 (dd, *J* = 7.8, 3.9 Hz, 2H), 6.70 (s, 1H), 4.05 (s, 3H), 3.97 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.74, 166.21, 161.80, 157.95, 150.76, 140.71, 138.97, 136.14, 134.77, 133.96, 129.91, 128.60, 124.02, 112.76, 111.87, 110.27, 56.44, 52.48.

HRMS-ESI (positive) M = $C_{21}H_{16}O_6$: calculated $(M+H)^+$ m/z 365.1020; found $(M+H)^+$ m/z 365.1021.

(E)-3-(3-(4-(2-(1,3-dioxolan-2-yl)ethoxy)phenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4k)



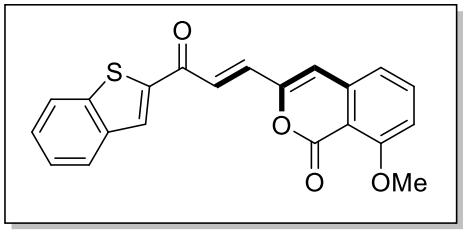
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-(2-(1,3-dioxolan-2-yl)ethoxy)phenyl)pentan-1-one (0.0668 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0515 g, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 15.0 Hz, 1H), 7.65 (t, *J* = 8.1 Hz, 1H), 7.32 (d, *J* = 15.1 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 5.11 (t, *J* = 4.7 Hz, 1H), 4.22 (t, *J* = 6.5 Hz, 2H), 4.03 (s, 3H), 4.03 – 3.99 (m, 2H), 3.90 (dd, *J* = 8.7, 5.1 Hz, 2H), 2.21 (dd, *J* = 11.3, 6.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.37, 163.06, 161.68, 158.07, 151.10, 139.15, 135.99, 133.26, 131.07, 130.39, 124.45, 118.80, 114.34, 111.76, 111.48, 110.10, 101.72, 64.89, 63.84, 56.36, 33.51.

HRMS-ESI (positive) M = $C_{24}H_{22}O_7$: calculated $(M+H)^+$ m/z 423.1438; found $(M+H)^+$ m/z 423.1438.

(E)-3-(3-(benzo[b]thiophen-2-yl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4l)



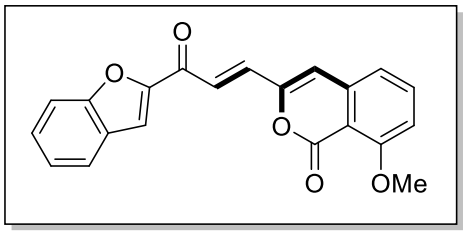
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(benzo[b]thiophen-2-yl)pentan-1-one (0.0523 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0478 g, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 7.9 Hz,1H), 7.78 (d, *J* = 15.0 Hz,1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.47 (dt, *J* = 14.9, 7.1 Hz, 2H), 7.38 (d, *J* = 15.0 Hz, 1H), 7.06 (t, *J* = 7.0 Hz, 1H), 6.70 (s, 1H), 4.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.80, 161.81, 158.08, 150.81, 144.92, 143.00, 139.29, 139.07, 136.15, 133.55, 130.33, 127.77, 126.36, 125.13, 123.82, 122.97, 119.01, 112.64, 111.80, 110.26, 56.47.

HRMS-ESI (positive) M = $C_{21}H_{14}O_4S$: calculated $(M+H)^+$ m/z 363.0686; found $(M+H)^+$ m/z 363.0686.

(E)-3-(3-(benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4m)



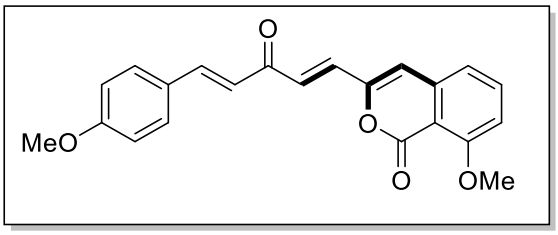
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(benzofuran-2-yl)pentan-1-one (0.0485 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0366 g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 3.5 Hz, 2H), 7.67 (t, *J* = 8.8 Hz, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 15.2 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 2H), 6.70 (s, 1H), 4.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.81, 161.77, 158.00, 156.03, 153.26, 150.74, 138.99, 136.11, 133.80, 128.70, 127.16, 124.09, 124.04, 123.48, 119.02, 114.55, 112.78, 112.59, 111.84, 110.25, 56.44.

HRMS-ESI (positive) M = $C_{21}H_{14}O_5$: calculated $(M+H)^+$ m/z 347.0914; found $(M+H)^+$ m/z 347.0914.

8-methoxy-3-((1E,4E)-5-(4-methoxyphenyl)-3-oxopenta-1,4-dien-1-yl)-1H-isochromen-1-one (4n)



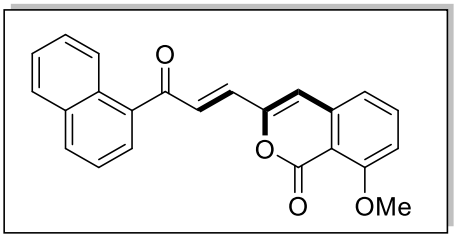
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), (E)-1-(4-methoxyphenyl)hept-1-en-3-one (0.0523 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0418 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.1 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 15.2 Hz, 1H), 7.22 (d, *J* = 15.2 Hz, 1H), 7.03 (dd, *J* = 7.9, 5.2 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 16.1 Hz, 1H), 6.61 (s, 1H), 4.02 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.11, 161.86, 161.72, 158.18, 151.05, 144.22, 139.19, 136.04, 132.25, 130.32, 127.17, 127.03, 124.54, 118.83, 114.47, 111.76, 111.51, 110.11, 56.38, 55.39.

HRMS-ESI (positive) M = $C_{22}H_{18}O_5$: calculated $(M+H)^+$ m/z 363.1227; found $(M+H)^+$ m/z 363.1226.

(E)-8-methoxy-3-(3-(naphthalen-1-yl)-3-oxoprop-1-en-1-yl)-1H-isochromen-1-one (4o)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr

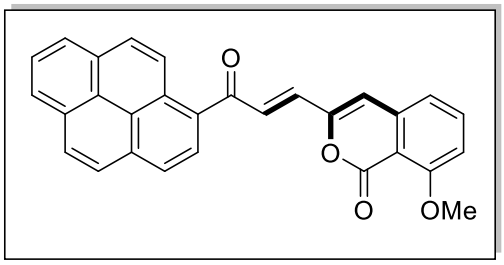
(0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(naphthalen-1-yl)pentan-1-one (0.0509 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0446 g, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.14 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 8.01 – 7.85 (m, 3H), 7.62 (dt, *J* = 9.0, 7.9 Hz, 3H), 7.40 (d, *J* = 15.0 Hz, 1H), 7.03 (t, *J* = 7.7 Hz, 2H), 6.67 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.83, 161.73, 158.13, 151.03, 139.09, 136.05, 135.66, 134.73, 133.92, 132.50, 130.64, 129.73, 128.67, 128.66, 127.73, 126.84, 124.33, 124.19, 118.89, 112.23, 111.64, 110.17, 56.39.

HRMS-ESI (positive) M = $C_{23}H_{16}O_4$: calculated $(M+Na)^+$ m/z 379.0941; found $(M+Na)^+$ m/z 379.0947.

(E)-8-methoxy-3-(3-oxo-3-(pyren-1-yl)prop-1-en-1-yl)-1H-isochromen-1-one (4p)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(pyren-1-yl)pentan-1-one (0.0687 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0445 g, 52% yield).

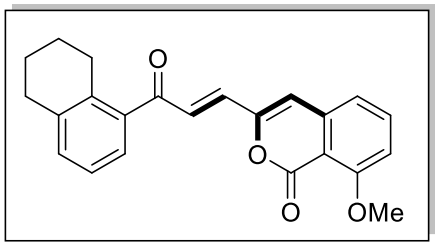
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, *J* = 9.2 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.29

– 8.15 (m, 5H), 8.15 – 8.02 (m, 2H), 7.83 (d, *J* = 15.2 Hz, 1H), 7.64 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 15.2 Hz, 1H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.64 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.46, 161.79, 157.96, 151.02, 139.09, 136.01, 134.20, 133.95, 132.59, 131.08, 130.59, 129.81, 129.63, 129.58, 129.14, 127.22, 126.99, 126.42, 126.35, 126.15, 124.92, 124.75, 124.30, 124.12, 118.87, 112.15, 111.68, 110.26, 56.42.

HRMS-ESI (positive) M = $C_{29}H_{18}O_4$: calculated $(M+H)^+$ m/z 431.1278; found $(M+H)^+$ m/z 431.1276.

(E)-8-methoxy-3-(3-oxo-3-(5,6,7,8-tetrahydronaphthalen-1-yl)prop-1-en-1-yl)-1H-isochromen-1-one (4q)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(5,6,7,8-tetrahydronaphthalen-1-yl)pentan-1-one (0.0518 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0506 g, 70% yield).

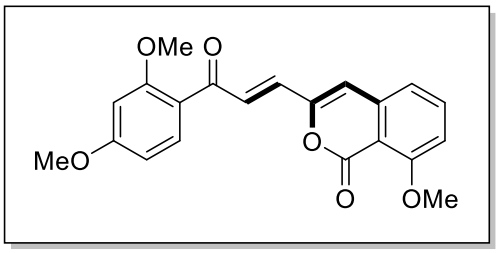
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.71 (m, 3H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 15.1 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.10 – 6.97 (t, J = 6.7 Hz, 2H), 6.65 (s, 1H), 4.04 (s, 3H), 3.02 – 2.74 (m, 4H), 1.87 – 1.80 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.85, 161.68, 158.13, 151.08, 143.65, 139.12, 137.62, 136.00, 134.82, 133.45, 129.58, 129.47, 125.75, 124.61, 118.81, 111.90, 111.53, 110.09, 56.36, 29.65, 29.27, 22.87, 22.71.

HRMS-ESI (positive) M = $C_{23}H_{20}O_4$: calculated $(M+H)^+$ m/z 361.1434; found $(M+H)^+$

m/z 361.1436.

(E)-3-(3-(2,4-dimethoxyphenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4r)



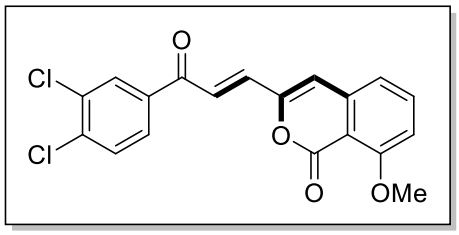
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(2,4-dimethoxyphenyl)pentan-1-one (0.0532 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0561 g, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 15.3 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 15.1 Hz, 1H), 6.97 (t, *J* = 7.1 Hz, 2H), 6.55 (s, 1H), 6.51 (d, *J* = 8.7 Hz, 1H), 6.44 (s, 1H), 3.97 (s, 3H), 3.88 (s, 3H), 3.82 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.97, 164.56, 161.52, 160.73, 157.98, 151.38, 139.20, 135.78, 132.88, 131.07, 129.87, 121.42, 118.54, 111.14, 110.90, 109.96, 105.26, 98.20, 56.20, 55.60, 55.41.

HRMS-ESI (positive) M = $C_{21}H_{18}O_6$: calculated $(M+H)^+$ m/z 367.1176; found $(M+H)^+$ m/z 367.1175.

(E)-3-(3-(3,4-dichlorophenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (4s)



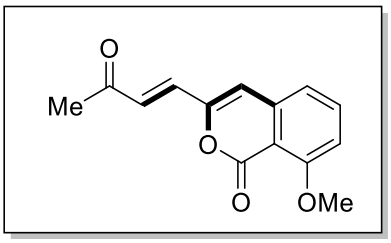
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(3,4-dichlorophenyl)pentan-1-one (0.0552 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0423 g, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.0 Hz, 1H), 7.92 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 15.0 Hz, 1H), 7.06 (dd, *J* = 8.1, 2.0 Hz, 2H), 6.70 (s, 1H), 4.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 186.92, 161.85, 157.90, 150.68, 138.93, 137.96, 137.01, 136.17, 135.11, 133.55, 130.85, 130.60, 127.72, 123.30, 119.04, 112.96, 111.97, 110.31, 56.47.

HRMS-ESI (positive) M = $C_{19}H_{12}Cl_2O_4$: calculated $(M+H)^+$ m/z 375.0185; found $(M+H)^+$ m/z 375.0184.

(E)-8-methoxy-3-(3-oxobut-1-en-1-yl)-1H-isochromen-1-one (4t)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), hexan-2-one (0.0601 g, 0.6 mmol),

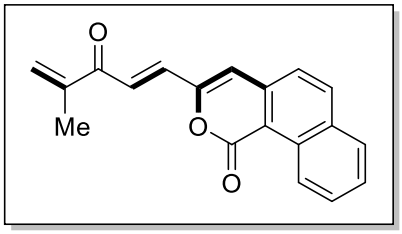
2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0258 g, 53% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, *J* = 8.1 Hz, 1H), 7.09 – 6.89 (m, 4H), 6.59 (s, 1H), 4.01 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.26, 161.72, 157.88, 150.50, 138.96, 136.05, 132.17, 128.57, 118.77, 111.86, 111.63, 110.14, 56.38, 29.46.

HRMS-ESI (positive) M = $C_{14}H_{12}O_4$: calculated $(M+H)^+$ m/z 245.0808; found $(M+H)^+$ m/z 245.0808.

(E)-3-(4-methyl-3-oxopenta-1,4-dien-1-yl)-1H-benzo[h]isochromen-1-one (4u)



Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1862 g, 1.0 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 2-methylheptan-3-one (0.0768 g, 0.6 mmol), 1-naphthoic acid (0.0345 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0242 g, 42% yield).

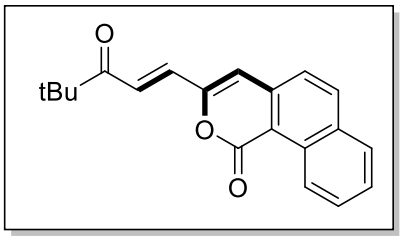
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.79 (t, *J* = 7.3 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 10.5 Hz, 1H), 6.83 (s, 1H), 6.23 (s, 1H), 5.97 (d, *J* = 1.0 Hz, 1H), 2.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 190.59, 160.65, 151.87, 145.29, 138.91, 136.61, 133.54, 132.64, 131.58, 129.75, 128.80, 127.54, 126.74, 126.31, 124.23, 123.94, 115.80,

112.27, 17.86.

HRMS-ESI (positive) M = $C_{19}H_{14}O_3$: calculated $(M+Na)^+$ m/z 313.0835; found $(M+Na)^+$ m/z 313.0840.

(E)-3-(4,4-dimethyl-3-oxopent-1-en-1-yl)-1H-benzo[h]isochromen-1-one (4v)



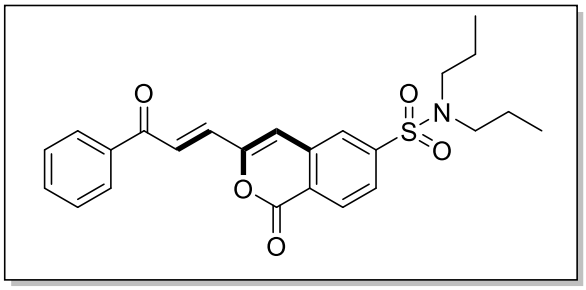
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 2,2-dimethylheptan-3-one (0.0852 g, 0.6 mmol), 1-naphthoic acid (0.0345 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0233g, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 8.7 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.80 (t, *J* = 7.4 Hz, 1H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.43 (d, *J* = 15.1 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 6.82 (s, 1H), 1.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.97, 160.67, 151.83, 138.91, 136.59, 133.53, 132.43, 131.58, 129.74, 128.79, 127.52, 126.74, 124.38, 123.92, 115.79, 112.22, 43.51, 26.01.

HRMS-ESI (positive) M = $C_{20}H_{18}O_3$: calculated $(M+Na)^+$ m/z 329.1148; found $(M+Na)^+$ m/z 329.1151.

(E)-1-oxo-3-(3-oxo-3-phenylprop-1-en-1-yl)-N,N-dipropyl-1H-isochromene-6-sulfonamide (5a)



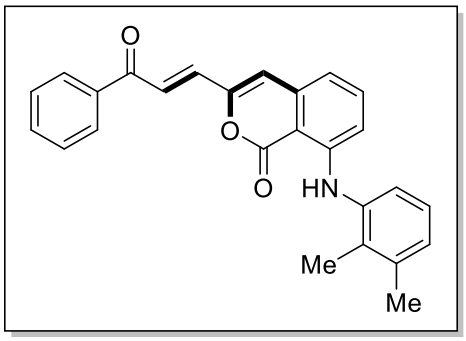
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), probenecid(0.0570 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0649g, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 2H), 7.98 (d, *J* = 1.5 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.87 (d, *J* = 15.1 Hz, 1H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 15.1 Hz, 1H), 6.84 (s, 1H), 3.33 – 2.99 (m, 4H), 1.98 – 1.34 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.88, 160.05, 152.06, 146.74, 137.21, 136.98, 133.58, 133.48, 131.19, 128.82, 128.70, 126.87, 125.49, 125.22, 124.06, 110.94, 21.95, 11.12.

HRMS-ESI (positive) M = $C_{24}H_{25}NO_5S$: calculated $(M+H)^+$ m/z 440.1526; found $(M+H)^+$ m/z 440.1529.

(E)-8-((2,3-dimethylphenyl)amino)-3-(3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromen-1-one (5b)



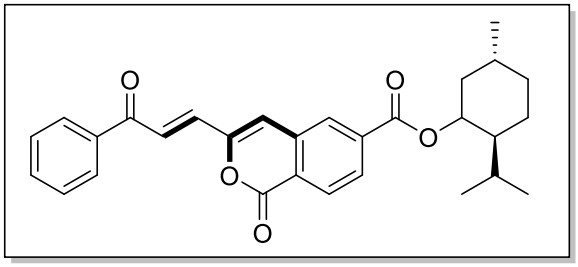
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), mefenamic acid (0.0482 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0568g, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H), 8.09 (d, *J* = 7.1 Hz, 2H), 7.78 (d, *J* = 15.1 Hz, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.36 (dd, *J* = 15.6, 8.7 Hz, 2H), 7.21 – 7.06 (m, 3H), 6.74 – 6.61 (m, 3H), 2.34 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.14, 163.64, 150.66, 149.73, 138.47, 137.66, 137.53, 137.49, 135.92, 134.15, 133.23, 133.20, 128.67, 128.62, 127.85, 126.14, 123.97, 123.66, 114.31, 113.82, 112.74, 103.77, 20.54, 14.03.

HRMS-ESI (positive) M = $C_{26}H_{21}NO_3$: calculated $(M+H)^+$ m/z 396.1594; found $(M+H)^+$ m/z 396.1596.

(2S,5R)-2-isopropyl-5-methylcyclohexyl1-oxo-3-((E)-3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromene-6-carboxylate (5c)



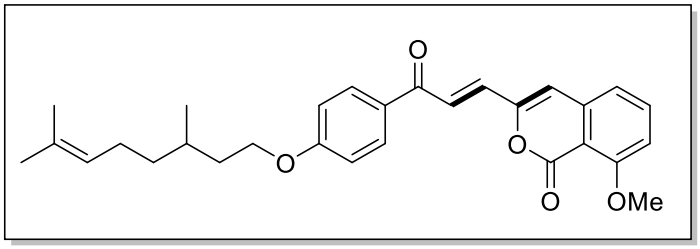
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-((((2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)carbonyl)benzoic acid (0.0608 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0632g, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.6 Hz, 1H), 8.17 (d, *J* = 6.7 Hz, 2H), 8.08 (d, *J* = 7.5 Hz, 2H), 7.84 (d, *J* = 15.1 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 15.1 Hz, 1H), 6.85 (s, 1H), 5.00 (td, *J* = 10.8, 4.3 Hz, 1H), 2.13 (d, *J* = 11.8 Hz, 1H), 1.93 (ddd, *J* = 12.9, 6.3, 4.3 Hz, 1H), 1.75 (d, *J* = 10.8 Hz, 2H), 1.59 (t, *J* = 11.4 Hz, 2H), 1.15 (dd, *J* = 23.6, 11.8 Hz, 2H), 0.94 (dd, *J* = 6.6, 3.3 Hz, 7H), 0.80 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.00, 164.43, 160.62, 151.30, 137.32, 136.71, 136.34, 133.81, 133.47, 130.26, 129.83, 128.78, 128.69, 128.06, 124.86, 124.57, 111.65, 76.11, 47.15, 40.82, 34.16, 31.43, 26.51, 23.44, 21.98, 20.74, 16.41.

HRMS-ESI (positive) M = $C_{29}H_{30}O_5$: calculated $(M+H)^+$ m/z 459.2166; found $(M+H)^+$ m/z 459.2166

(E)-3-(3-(4-((3,7-dimethyloct-6-en-1-yl)oxy)phenyl)-3-oxoprop-1-en-1-yl)-8-methoxy-1H-isochromen-1-one (5d)



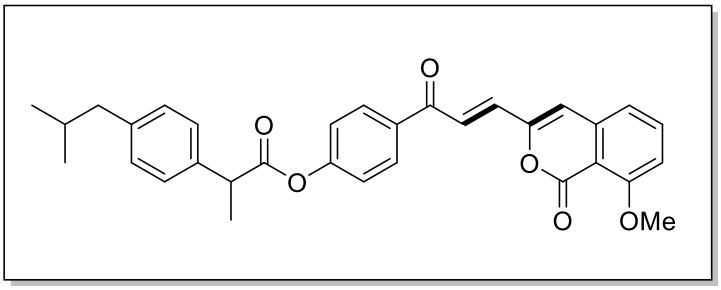
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-(4-((3,7-dimethyloct-6-en-1-yl)oxy)phenyl)pentan-1-one (0.0759 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a pale yellow solid (0.0442g, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 15.0 Hz, 1H), 7.64 (t, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 15.0 Hz, 1H), 7.08 – 6.93 (m, 4H), 6.64 (s, 1H), 5.11 (t, *J* = 7.0 Hz, 1H), 4.08 (dt, *J* = 8.8, 4.3 Hz, 2H), 4.02 (s, 3H), 2.01 (dt, *J* = 15.2, 7.5 Hz, 2H), 1.86 (td, *J* = 13.4, 6.3 Hz, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.41 (ddd, *J* = 12.1, 9.7, 6.1 Hz, 2H), 1.25 (td, *J* = 12.9, 8.2 Hz, 2H), 0.98 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.34, 163.41, 161.66, 158.10, 151.09, 139.14, 135.99, 133.17, 131.29, 131.07, 130.15, 124.47, 118.78, 114.32, 111.72, 111.47, 110.07, 66.53, 56.32, 36.98, 35.83, 29.35, 25.64, 25.33, 19.44, 17.59.

HRMS-ESI (positive) M = $C_{29}H_{32}O_9$: calculated $(M+H)^+$ m/z 461.2323; found $(M+H)^+$ m/z 461.2323.

(E)-4-(3-(8-methoxy-1-oxo-1H-isochromen-3-yl)acryloyl)phenyl 2-(4-isobutylphenyl)propanoate (5e)



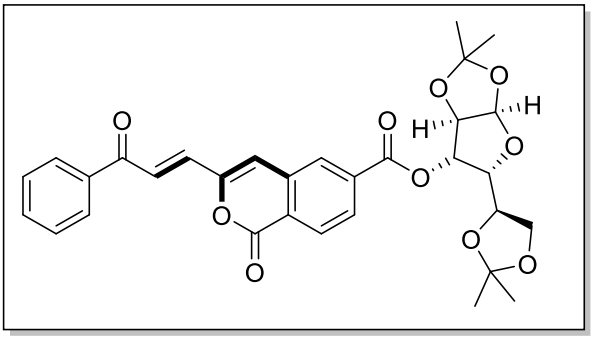
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 4-pentanoylphenyl 2-(4-isobutylphenyl)propanoate (0.0878 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ^oC for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0579g, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 15.1 Hz, 1H), 7.66 (t, *J* = 8.1 Hz, 1H), 7.37 – 7.28 (m, 4H), 7.16 (d, *J* = 8.5 Hz, 4H), 7.05 (dd, *J* = 7.9, 5.2 Hz, 2H), 4.03 (s, 3H), 3.97 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.87 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.63 (d, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 187.93, 172.63, 161.70, 158.31, 154.80, 150.76, 140.96, 139.00, 136.73, 136.19, 134.76, 134.16, 130.27, 129.54, 127.13, 121.77, 118.93, 112.42, 111.72, 110.04, 56.33, 45.23, 44.95, 30.11, 22.32, 18.38.

HRMS-ESI (positive) M = $C_{32}H_{30}O_6$: calculated $(M+H)^+$ m/z 511.2115; found $(M+H)^+$ m/z 511.2117.

(3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl 1-oxo-3-((E)-3-oxo-3-phenylprop-1-en-1-yl)-1H-isochromene-6-carboxylate (5f)



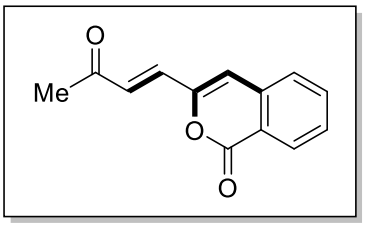
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one (0.0389 g, 0.24 mmol), 4-((((3aR,5R,6S,6aR)-5-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro [2,3-d] [1,3] dioxol-6-yl) oxy)carbonyl)benzoic acid (0.0816 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0582g, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 8.1 Hz, 1H), 8.16 (d, *J* = 9.0 Hz, 2H), 8.09 (d, *J* = 7.4 Hz, 2H), 7.86 (d, *J* = 15.1 Hz, 1H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 15.1 Hz, 1H), 6.85 (s, 1H), 6.00 (d, *J* = 3.6 Hz, 1H), 5.57 (d, *J* = 2.5 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.35 (qd, *J* = 8.5, 3.8 Hz, 2H), 4.13 (ddd, *J* = 12.9, 8.7, 4.9 Hz, 2H), 1.58 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.81, 163.58, 160.27, 151.50, 137.18, 136.43, 135.29, 133.57, 133.45, 130.40, 129.58, 128.73, 128.61, 128.13, 125.03, 124.97, 112.45, 111.21, 109.51, 105.05, 83.20, 79.81, 77.44, 72.40, 67.37, 26.81, 26.60, 26.12, 25.12.

HRMS-ESI (positive) M = $C_{31}H_{30}O_{10}$: calculated $(M+H)^+$ m/z 563.1912; found $(M+H)^+$ m/z 563.1912.

(E)-3-(3-oxobut-1-en-1-yl)-1H-isochromen-1-one (5g) [Large Scale]



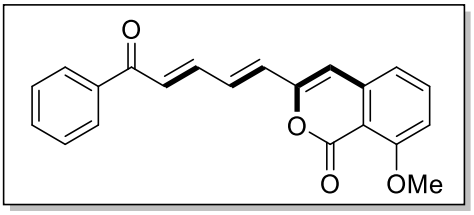
Following the general procedure **(I)** with $Pd(OAc)_2$ (0.1 g, 0.5 mmol), SIPr (0.27 g, 0.75 mmol), $Cu(OAc)_2$ (0.185 g, 1.0 mmol), TEMPO (3.12 g, 20 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.15 g, 0.5 mmol), hexan-2-one (1.5 g, 15 mmol), benzoic acid (0.61 g, 5 mmol), and toluene (60 mL). The reaction mixture was stirred at 130 ºC for 24 h. Purification by silica gel flash chromatography (10–30% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.438 g, 41% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 7.9 Hz, 1H), 7.76 (td, *J* = 7.7, 1.3 Hz, 1H), 7.58 (td, *J* = 7.9, 1.1 Hz, 1H), 7.10 (d, *J* = 15.5 Hz, 1H), 7.00 (d, *J* = 15.5 Hz, 1H), 6.72 (s, 1H), 2.38 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.12, 161.06, 150.21, 136.16, 135.04, 132.39, 129.94, 129.66, 128.43, 126.64, 121.84, 111.79, 29.31.

HRMS-ESI (positive) M = $C_{13}H_{10}O_3$: calculated $(M+H)^+$ m/z 215.0703; found $(M+H)^+$ m/z 215.0703.

8-methoxy-3-((1E,3E)-5-oxo-5-phenylpenta-1,3-dien-1-yl)-1H-isochromen-1-one (7a)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol),

1-phenylheptan-1-one (0.0456 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 ºC for 24 h.

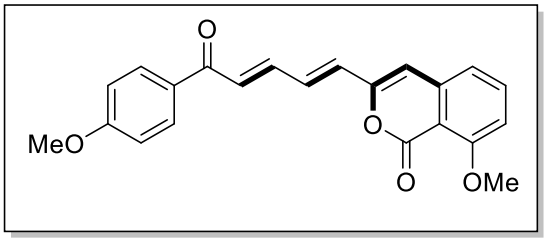
Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0276 g, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.3 Hz, 2H), 7.65 – 7.46 (m, 5H), 7.32 (dd, *J* = 15.0, 11.6 Hz, 1H), 7.22 (d, *J* = 14.8 Hz, 1H), 6.99 (dd, *J* = 8.0, 5.0 Hz, 2H), 6.54 (d, *J* = 15.0 Hz, 1H), 6.46 (s, 1H), 4.02 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.97, 161.72, 158.30, 151.68, 142.40, 139.65, 137.80, 135.94, 132.97, 131.00, 130.80, 128.67, 128.39, 128.02, 118.47, 110.88, 109.68, 108.70, 56.36.

HRMS-ESI (positive) M = $C_{13}H_{10}O_3$: calculated $(M+H)^+$ m/z 333.1121; found $(M+H)^+$ m/z 333.1121.

8-methoxy-3-((1E,3E)-5-(4-methoxyphenyl)-5-oxopenta-1,3-dien-1-yl)-1H-isochromen-1-one (7b)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-(4-methoxyphenyl)heptan-1-one (0.0528 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0232 g, 32% yield).

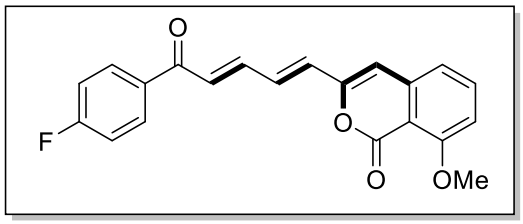
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.8 Hz, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.52 (dd, *J* = 14.6, 11.7 Hz, 1H), 7.31 (dd, *J* = 14.9, 11.8 Hz, 1H), 7.23 (d, *J* = 14.8 Hz, 1H), 7.02 – 6.92 (m, 4H), 6.52 (d, *J* = 15.0 Hz, 1H), 6.44 (s, 1H), 4.02 (s, 3H), 3.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$):δ 188.18, 163.54, 161.73, 158.33, 151.80, 141.59, 139.74, 135.91, 131.19, 130.79, 130.73, 130.30, 128.05, 118.44, 113.90, 110.80, 109.68, 108.44,

56.35, 55.49.

HRMS-ESI (positive) M = $C_{22}H_{18}O_5$: calculated $(M+Na)^+$ m/z 385.1046; found $(M+Na)^+$ m/z 385.1044.

3-((1E,3E)-5-(4-fluorophenyl)-5-oxopenta-1,3-dien-1-yl)-8-methoxy-1H-isochromen-1-one (7c)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol),
1-(4-fluorophenyl)heptan-1-one (0.0499 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (20–50% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0315 g, 45% yield).

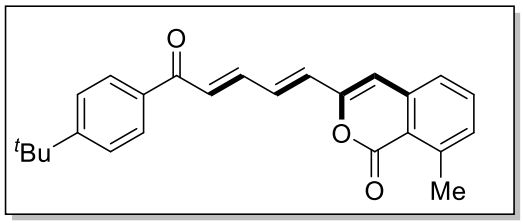
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, *J* = 8.3, 5.5 Hz, 2H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 14.5, 11.8 Hz, 1H), 7.32 (dd, *J* = 14.8, 11.9 Hz, 1H), 7.19 (dd, *J* = 15.0, 6.2 Hz, 3H), 6.99 (dd, *J* = 7.9, 3.6 Hz, 2H), 6.55 (d, *J* = 15.0 Hz, 1H), 6.46 (s, 1H), 4.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.30, 165.69 (d, *J* = 254.7 Hz), 161.77, 158.26, 151.66, 142.62, 139.65, 135.95, 134.21 (d, *J* = 2.8 Hz), 131.02 (d, *J* = 9.3 Hz), 131.01,130.88, 127.55, 118.50, 115.82 (d, *J* = 21.8 Hz), 110.96, 109.75, 108.81, 56.38.

^{19}F NMR (376 MHz, $CDCl_3$): δ -105.14.

HRMS-ESI (positive) M = $C_{21}H_{15}FO_4$: calculated $(M+H)^+$ m/z 351.1027; found $(M+H)^+$ m/z 351.1028.

3-((1E,3E)-5-(4-(tert-butyl)phenyl)-5-oxopenta-1,3-dien-1-yl)-8-methyl-1H-isochromen-1-one (7d)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol),

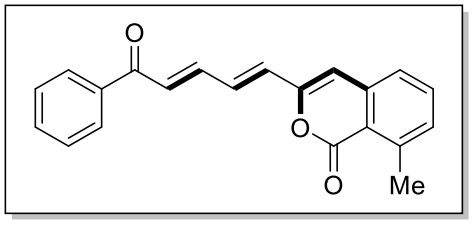
1-(4-(tert-butyl)phenyl)heptan-1-one (0.0591 g, 0.24 mmol), 2-methylbenzoic acid (0.0274 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0283 g, 38% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.6 Hz, 2H), 7.58 – 7.49 (m, 4H), 7.28 (ddd, *J* = 26.1, 14.7, 10.3 Hz, 4H), 6.55 (d, *J* = 15.0 Hz, 1H), 6.48 (s, 1H), 2.83 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.51, 160.90, 156.79, 151.05, 143.89, 142.10, 138.36, 135.21, 134.12, 131.93, 130.68, 130.62, 128.39, 128.00, 125.65, 124.60, 119.62, 109.15, 35.13, 31.07, 23.20.

HRMS-ESI (positive) M = $C_{25}H_{24}O_3$: calculated $(M+H)^+$ m/z 373.1798; found $(M+H)^+$ m/z 373.1797.

8-methyl-3-((1E,3E)-5-oxo-5-phenylpenta-1,3-dien-1-yl)-1H-isochromen-1-one (7e)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0

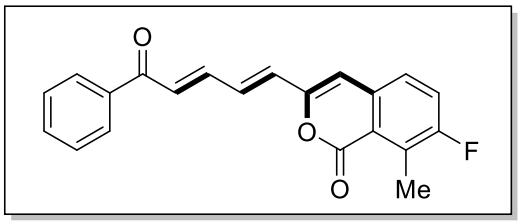
mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol),
1-phenylheptan-1-one (0.0456 g, 0.24 mmol), 2-methylbenzoic acid (0.0274 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0233 g, 37% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 7.6 Hz, 2H), 7.63 – 7.43 (m, 5H), 7.32 – 7.15 (m, 4H), 6.55 (d, *J* = 15.0 Hz, 1H), 6.48 (s, 1H), 2.83 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 189.95, 160.82, 150.95, 143.87, 142.51, 138.28, 137.80, 134.10, 132.93, 131.96, 130.95, 130.43, 128.65, 128.38, 127.80, 124.61, 119.61, 109.29, 23.18.

HRMS-ESI (positive) M = $C_{21}H_{16}O_3$: calculated $(M+H)^+$ m/z 317.1172; found $(M+H)^+$ m/z 317.1173.

7-fluoro-8-methyl-3-((1E,3E)-5-oxo-5-phenylpenta-1,3-dien-1-yl)-1H-isochromen-1-one (7f)



Following the general procedure **(II)** with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0148 g, 0.08 mmol), TEMPO (0.1560 g, 1.0 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol),
1-(4-(tert-butyl)phenyl)heptan-1-one (0.0591 g, 0.24 mmol), 3-fluoro-2-methylbenzoic acid (0.0308 g, 0.2 mmol), and toluene (2.5 mL). The reaction mixture was stirred at 130 °C for 24 h. Purification by silica gel flash chromatography (10–20% EtOAc in petroleum ether) gave the title compound as a yellow solid (0.0187 g, 28% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.55 (dq, *J* = 21.6, 7.2 Hz, 4H), 7.39 (t, *J* = 8.8 Hz, 1H), 7.33 – 7.18 (m, 3H), 6.55 (d, *J* = 15.0 Hz, 1H), 6.47 (s, 1H), 2.76 (s, 3H).

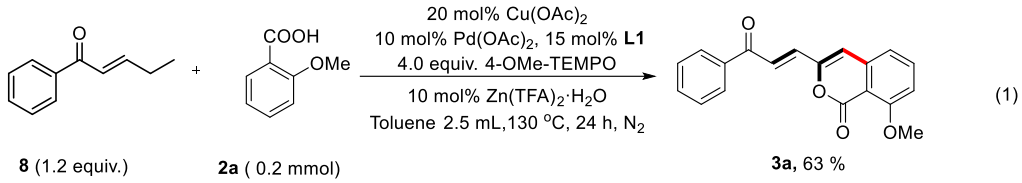
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.98, 160.69 (d, *J* = 247.0 Hz), 160.40 (d, *J* = 3.6 Hz), 150.53 (d, *J* = 3.0 Hz), 142.43, 137.82, 134.65 (d, *J* = 3.0 Hz), 132.98, 130.56 (d, *J* = 18.1 Hz), 129.95 (d, *J* = 17.8 Hz), 128.69, 128.41, 127.94, 125.49 (d, *J* = 8.7 Hz), 122.37, 122.12, 121.16 (d, *J* = 4.8 Hz), 108.51 (d, *J* = 2.1 Hz), 12.72 (d, *J* = 6.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -111.89.

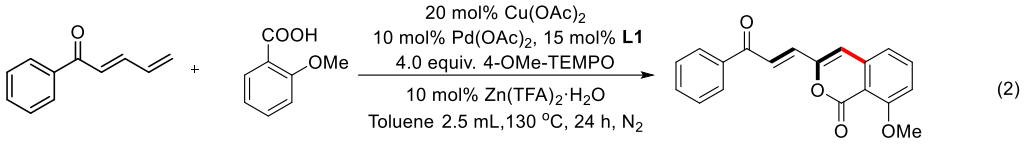
HRMS-ESI (positive) M = $C_{22}H_{18}O_5$: calculated $(M+H)^+$ m/z 335.1078; found $(M+H)^+$ m/z 335.1080.

5. Experimental Procedures for Mechanistic Studies

Experiments for identification of enone and dienone as reaction intermediates.



8 (1.2 equiv.) **2a** (0.2 mmol) **3a,** 63 % (1)

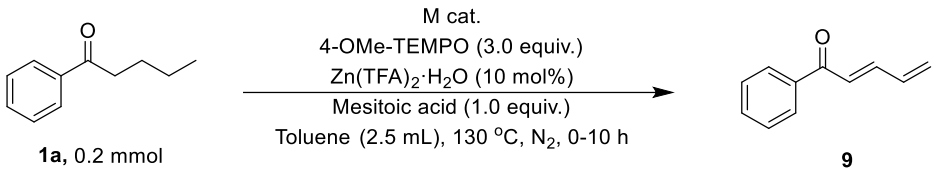


9 (1.2 equiv.) **2a** (0.2 mmol) **3a**, 47 % (2)

Experiment in eq. 1, the reaction was conducted with $Pd(OAc)_2$ (0.0043 g, 0.02 mmol), SIPr (0.0108 g, 0.03 mmol), $Cu(OAc)_2$ (0.0074 g, 0.04 mmol), 4-OMe-TEMPO (0.1490 g, 0.8 mmol), $Zn(TFA)_2{\cdot}H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpent-2-en-1-one **8** (0.0384 g, 0.24 mmol), 2-methoxybenzoic acid (0.0305 g, 0.2 mmol) in Toluene (2.5 mL) at 130 ^oC under N_2 for 24 h. After cooling to room temperature, the product **3a** was isolated by column chromatography in 63 % yield.

Following the procedure of experiment in eq. 1, the experiment in eq. 2 was conducted in using 1-phenylpenta-2,4-dien-1-one **9** (0.0379 g, 0.24 mmol) instead of **8** as substrate. After cooling to room temperature, the reaction was observed to provide **3a** in 47 % yield.

Kinetic Time Course Experiments for Successive dehydrogenation of aliphatic ketone to dienone with varying catalysts.



(3)

Experiments in eq. 3 were conducted with 4-OMe-TEMPO (0.1118 g, 0.6 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one **1a** (0.0326 g, 0.2 mmol), mesitoic acid (0.0328 g, 0.2 mmol), Toluene (2.5 mL) at 130 °C under N_2 in the condition of varying catalysts [$Pd(OAc)_2$ (10 mol%), SIPr (15 mol%)], [$Cu(OAc)_2$ (20 mol%)], [$Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (20 mol%), SIPr (15 mol%)] for specific time (0 – 10 h). Then the reaction's yield (**9**) was analyzed by HPLC using nitrobenzene as an internal standard.

Table S3. Time course data for successive dehydrogenation of aliphatic ketone to dienone with varying catalysts.

M cat. / Time (h)	$Pd(OAc)_2$(10 mol%) SIPr (15 mol%)	$Cu(OAc)_2$ (20 mol %)	$Pd(OAc)_2$(10 mol%) Cu(OAc)2 (20 mol%) SIPr (15 mol%)
0	0	0	0
2	0	0	1.4
4	0	1.9	8.1
6	0	9.7	15.6
8	0	13.2	26.8
10	0	13.6	41.4

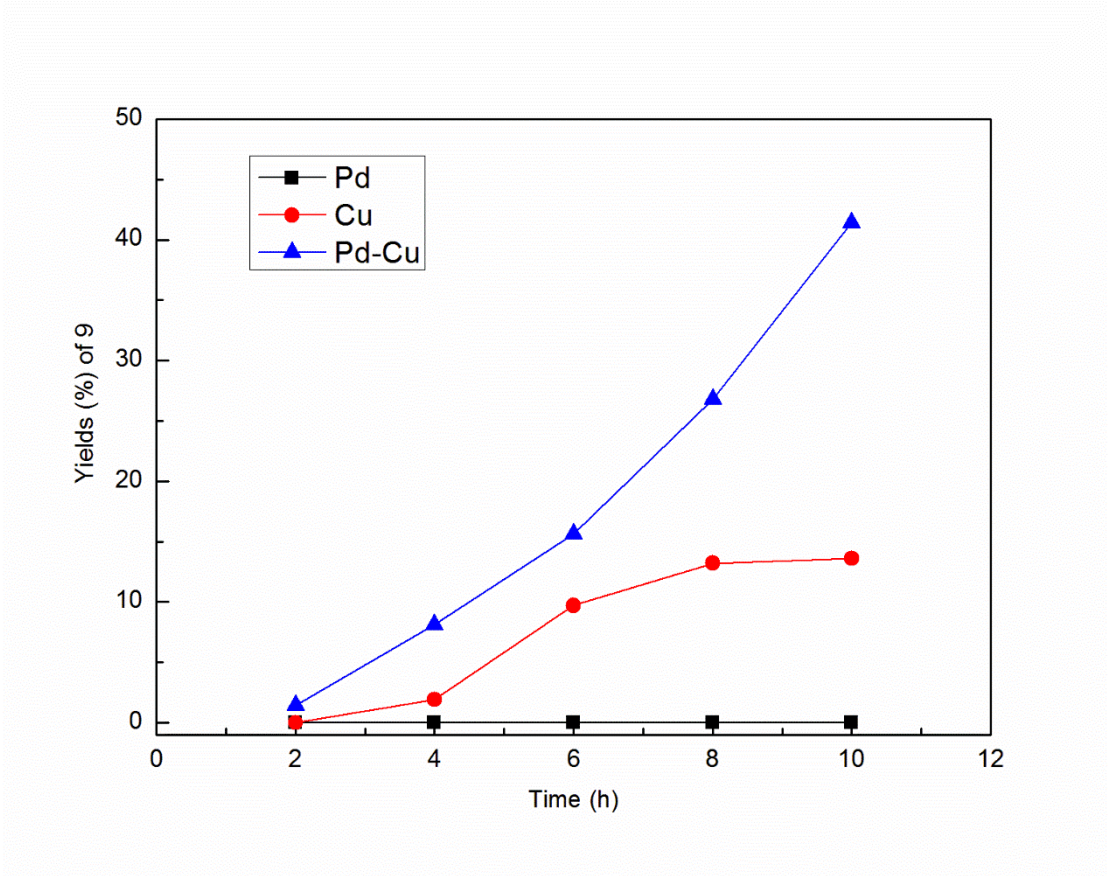
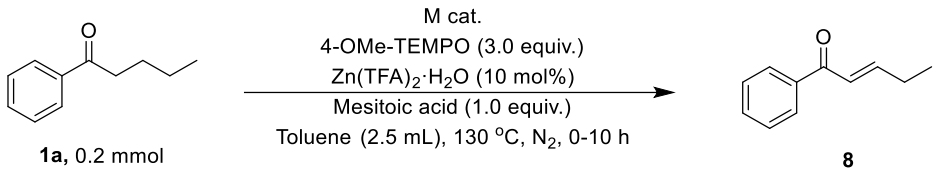


Figure S1. Kinetic time course of the successive dehydrogenation of aliphatic ketone to dienone with Pd (black), Cu (red), and bimetallic Cu-Pd (blue).

Kinetic Time Course Experiments for dehydrogenation of aliphatic ketone to enone with varying catalysts.



(4)

Experiments in eq. 4 were conducted with 4-OMe-TEMPO (0.1118 g, 0.6 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpentan-1-one **1a** (0.0326 g, 0.2 mmol), mesitoic acid (0.0328 g, 0.2 mmol), Toluene (2.5 mL) at 130 °C under N_2 in the condition of varying catalysts [$Pd(OAc)_2$ (0.0043g, 10 mol%), SIPr (0.0108 g, 15 mol%)], [$Cu(OAc)_2$ (0.0074 g, 20 mol%)], [$Pd(OAc)_2$ (0.0043 g, 10 mol%), $Cu(OAc)_2$ (0.0074 g, 20 mol%), SIPr (0.0108 g, 15 mol%)] for specific time (0 – 10 h). Then the reaction's yield (**8**) was analyzed by HPLC using nitrobenzene as an internal standard.

Table S4. Time course data for dehydrogenation of aliphatic ketone to enone with varying catalysts.

M cat. / Time (h)	$Pd(OAc)_2$(10 mol%) SIPr (15 mol%)	$Cu(OAc)_2$ (20 mol %)	$Pd(OAc)_2$(10 mol%) Cu(OAc)2 (20 mol%) SIPr (15 mol%)
0	0	0	0
2	1.4	14.2	16.7
4	1.7	33.9	30.6
6	2.1	26.7	8.3
8	2.2	15.3	10.1
10	2.6	6.8	24.5

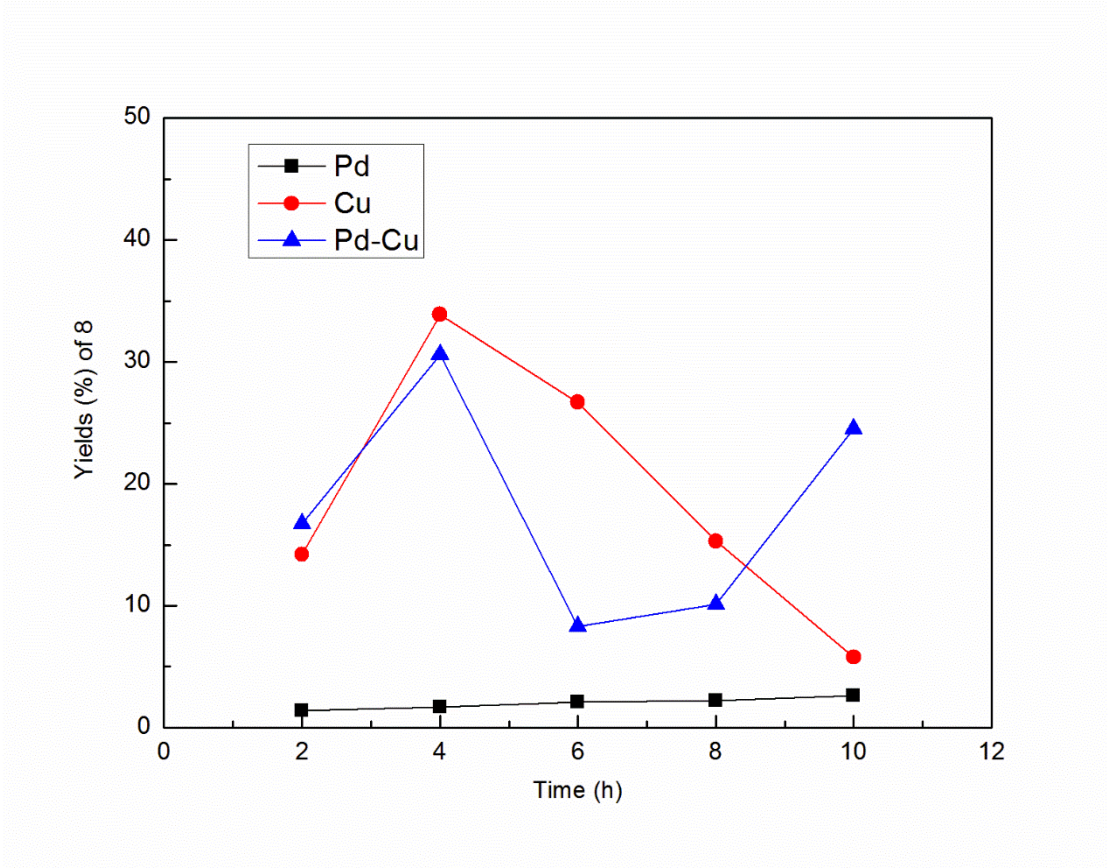
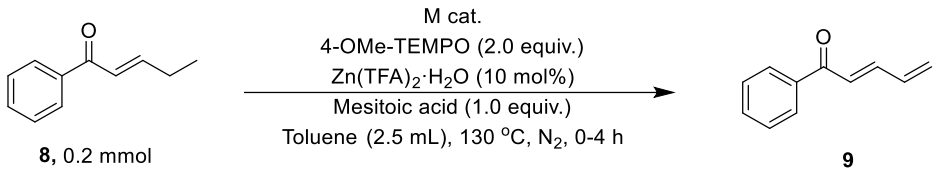


Figure S2. Kinetic time course of the dehydrogenation of aliphatic ketone to enone with Pd (black), Cu (red), and bimetallic Cu-Pd (blue).

Kinetic Time Course Experiments for dehydrogenation of enone to dienone with Pd and bimetallic Cu-Pd catalysis system.



(5)

Experiments in eq. 5 were conducted with 4-OMe-TEMPO (0.1118 g, 0.6 mmol), $Zn(TFA)_2 \cdot H_2O$ (0.0060 g, 0.02 mmol), 1-phenylpent-2-en-1-one **8** (0.0323 g, 0.2 mmol), mesitoic acid (0.0328 g, 0.2 mmol), Toluene (2.5 mL) at 130 °C under N_2 in the condition of varying catalysts [$Pd(OAc)_2$ (0.0043g, 10 mol%), SIPr (0.0108 g, 15 mol%)] or [$Pd(OAc)_2$ (0.0043 g, 10 mol%), $Cu(OAc)_2$ (0.0074 g, 20 mol%), SIPr (0.0108 g, 15 mol%)] for specific time (0 – 10 h). Then the reaction's yield (**9**) was analyzed by HPLC using nitrobenzene as an internal standard.

Table S5. Time course data for dehydrogenation of enone to dienone with Pd and bimetallic Cu-Pd catalysis system.

M cat. / Time (h)	$Pd(OAc)_2$(10 mol%) SIPr (15 mol%)	$Pd(OAc)_2$(10 mol%) Cu(OAc)2 (20 mol%) SIPr (15 mol%)
0	0	0
1	12.9	8.7
1.5	18.7	13.7
2	21.2	16.9
3	27.0	22.0
4	30.4	25.0

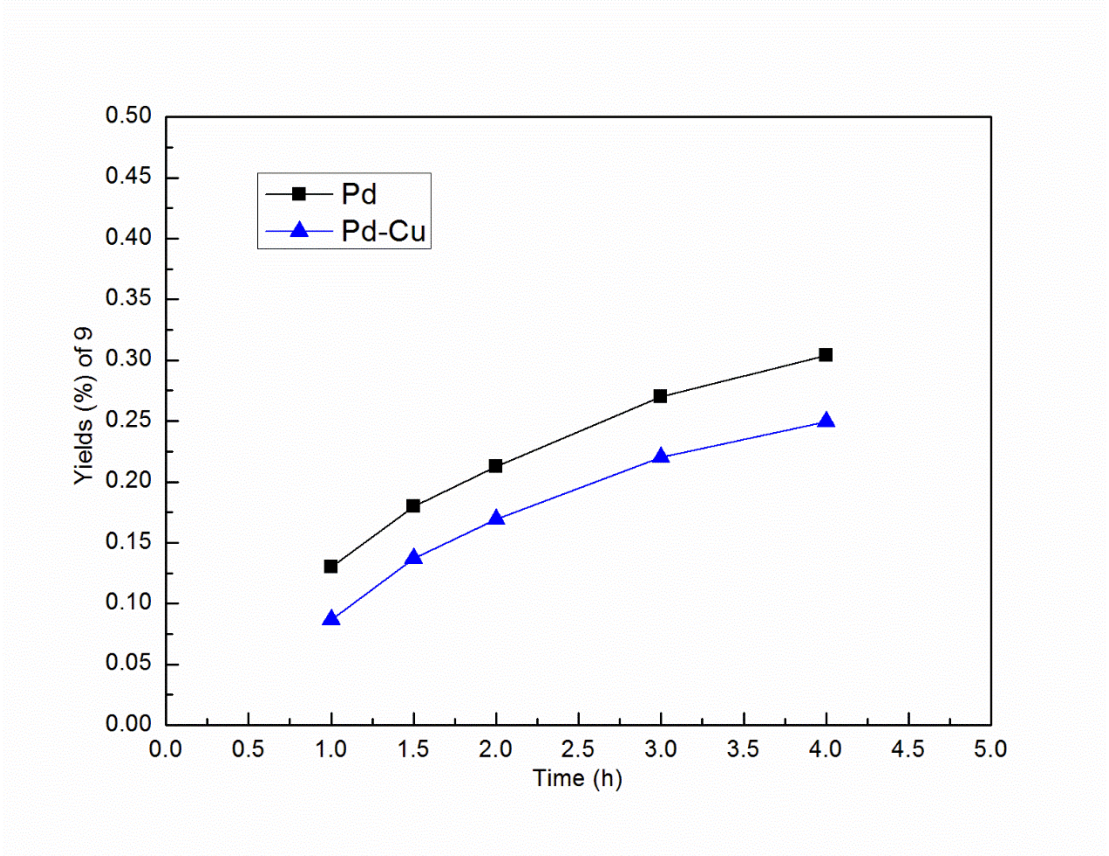


Figure S3. Kinetic time course of the dehydrogenation of enone to dienone with Pd (black),and bimetallic Cu-Pd (blue).

6. Crystal Data and Structure Refinement for 7c

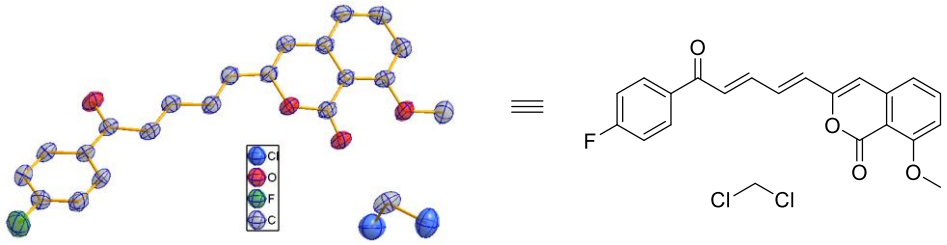


Figure S4. Crystal structure of 7c (C6pF, CCDC 2151796). Ellipsoids drawn at 50% probability level. Hydrogen atoms have been omitted for clarity.

Method: 0.15 mmol 7c was dissolved in 2 mL CH_2Cl_2 and crystallized by volatilization method in a 5 mL vial at room temperature, pale yellow crystal was collected.

CCDC	**2151796**
Empirical formula	**$C_{22}H_{17}Cl_2FO_4$**
Formula weight	**435.25**
Temperature/K	**260(2)**
Crystal system	**monoclinic**
Space group	**P 2_1/c**
a/Å	**16.218(2)**
b/Å	**10.9800(15)**
c/Å	**11.7185(16)**
α/°	**90°**
β/°	**107.344(7)°**
γ/°	**90°**
Volume/Å^3	**1991.9(5)**
Z	**4**
Density (calculated)	**1.451 g/cm^3**
Absorption coefficient	**0.362 mm^{-1}**
F(000)	**896**
Crystal size/mm^3	**0.12 x 0.1 x 0.18**

2Θ range for data collection/°	**2.274 to 25.050°**
Index ranges	**-19<=h<=19, -13<=k<=13, -13<=l<=13**
Reflections collected	**36123**
Refinement method	**Full-matrix least-squares on F2**
Independent reflections	**3511[R(int) = 0.1615]**
Data/restraints/parameters	**3511/ 0 / 263**
Goodness-of-fit on F^2	**1.052**
Final R indexes [I>=2σ (I)]	**R 1 = 0.0602 wR2 = 0.1394**
Final R indexes [all data]	**R 1 = 0.1472 wR2 = 0.1999**
Largest diff. peak/hole / e $Å^{-3}$	**0.243and -0.340 e $Å^{-3}$**

7. References

(1) ***J. Am. Chem. Soc.*** **2020,** ***142*****, 18118–18127.**

(2) ***J. Med. Chem.*** **1992,** ***35*****, 1818–1828.**

(3) ***Chem. Eur. J.*** **2021,** ***27*****, 2868–2874.**

(4) ***Org. Lett.*** **2018,** ***20*****, 1546–1549.**

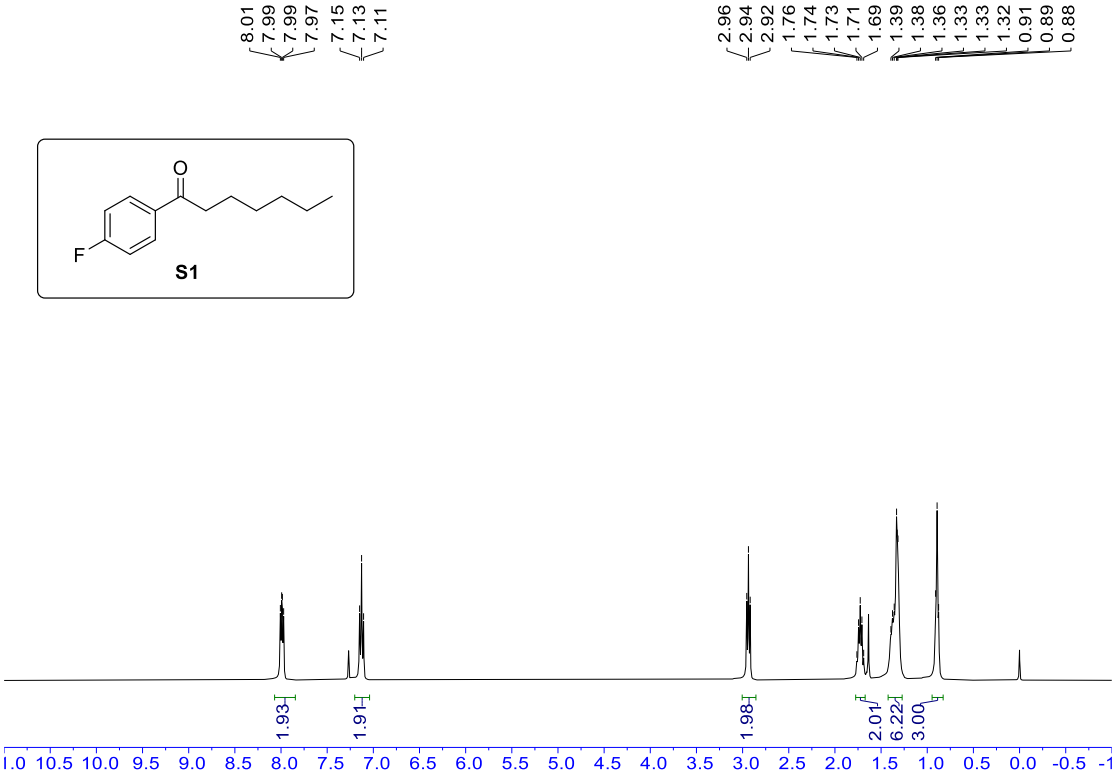
(5) ***J. Med. Chem.*** **2006,** ***49*****, 1420–1432.**

(6) ***Angew. Chem. Int. Ed.*** **2014,** ***53*****, 8416–8420.**

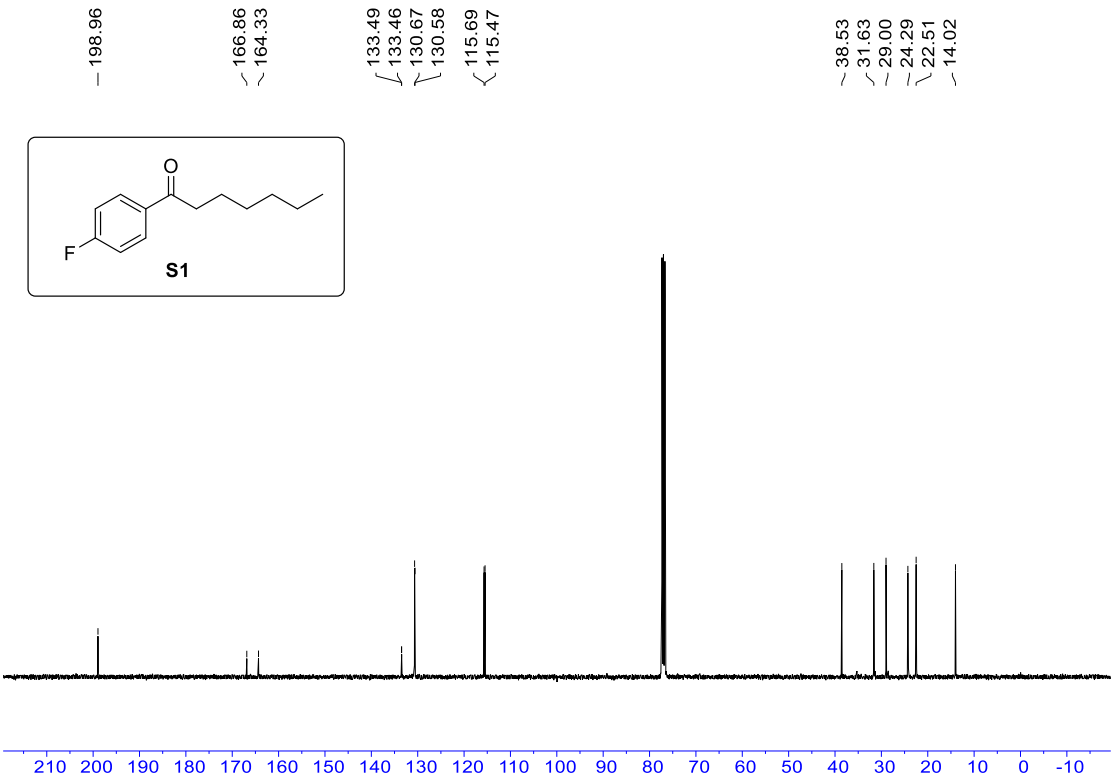
(7) ***Tetrahedral Lett.*** **2016,** ***57,*** **2315–2319.**

(8) ***Angew. Chem. Int. Ed.*** **2020,** ***59*****, 3465–3469**

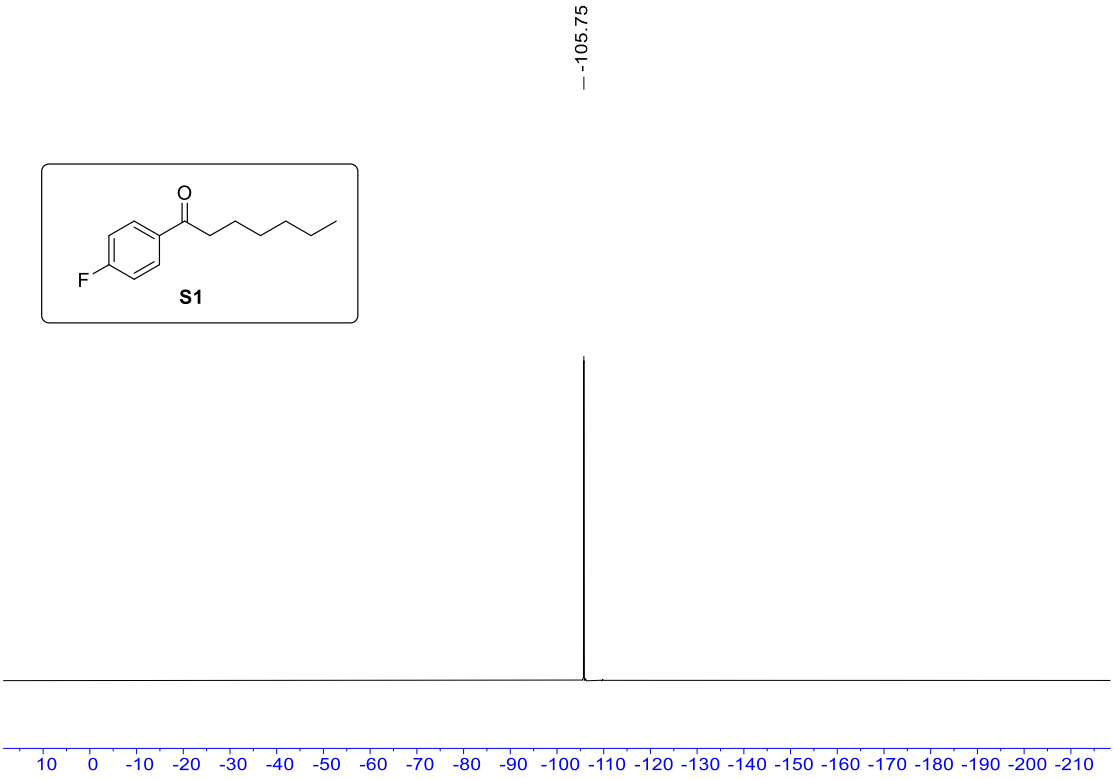
8. 1H, 13C and 19F NMR Spectra of Compounds



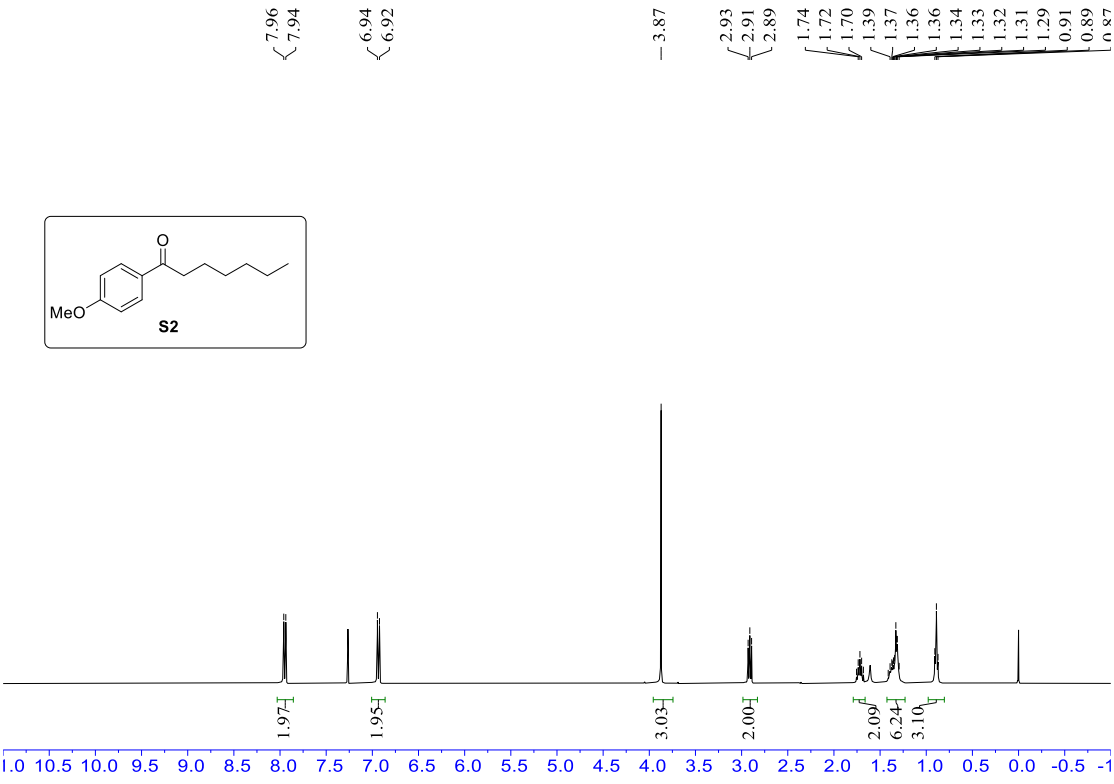
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S1



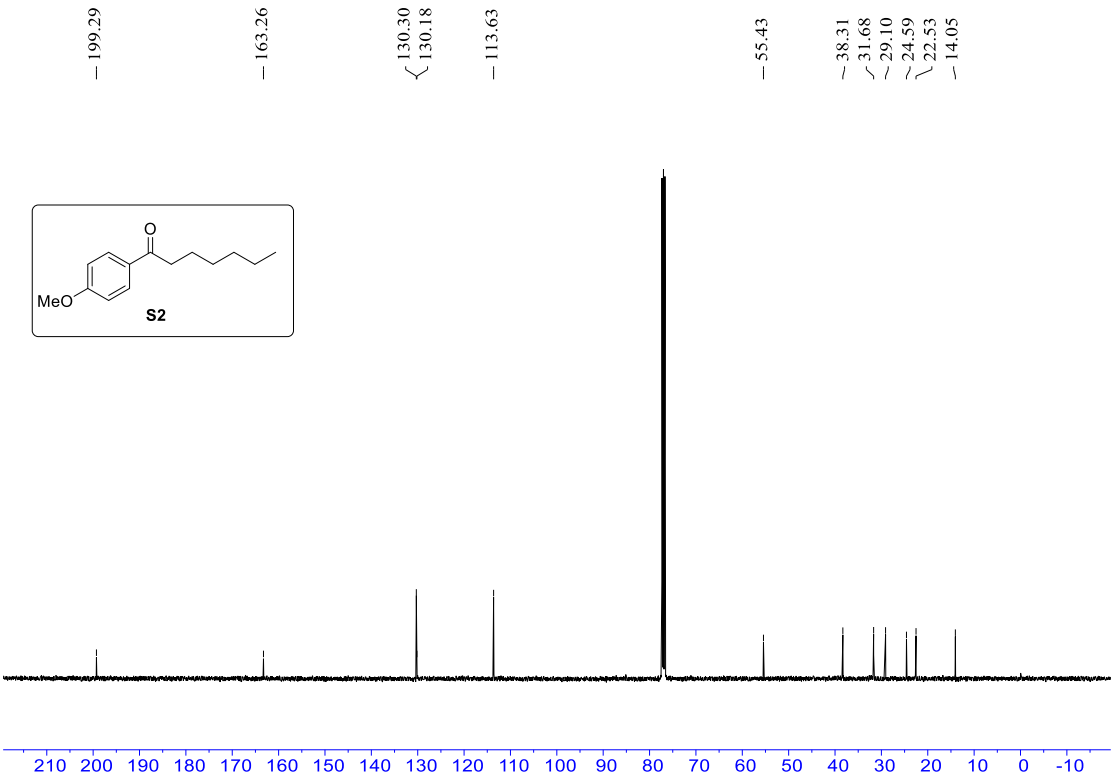
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S1



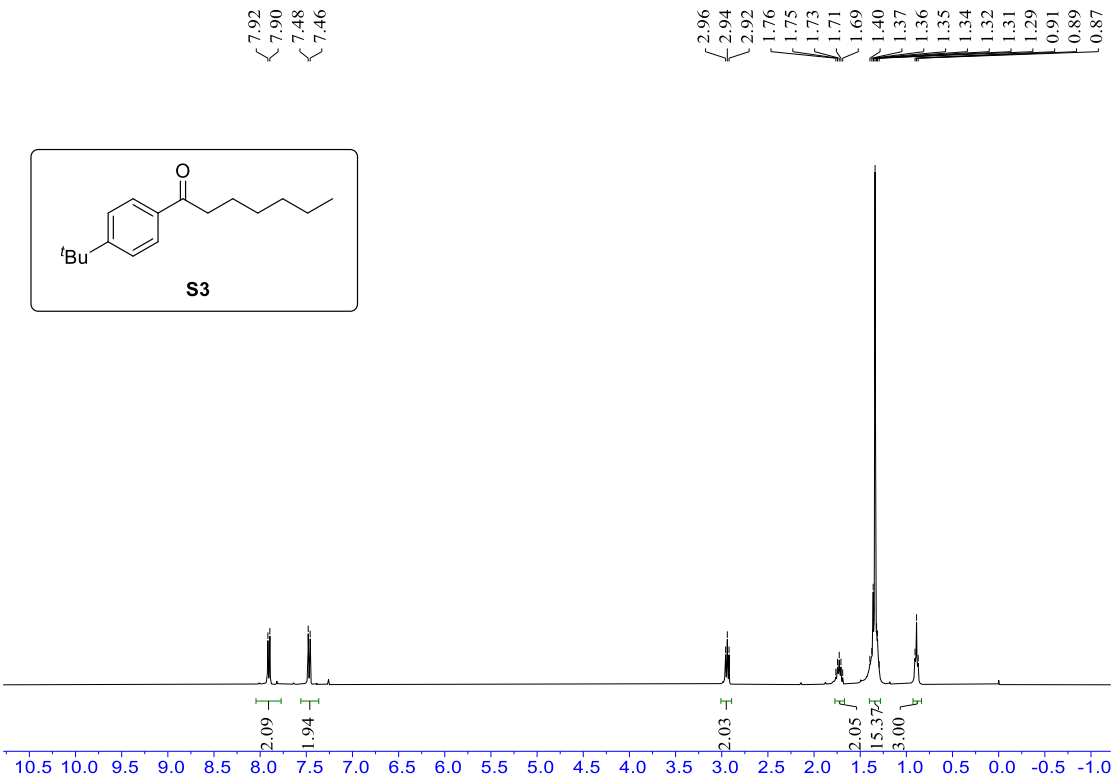
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for S1



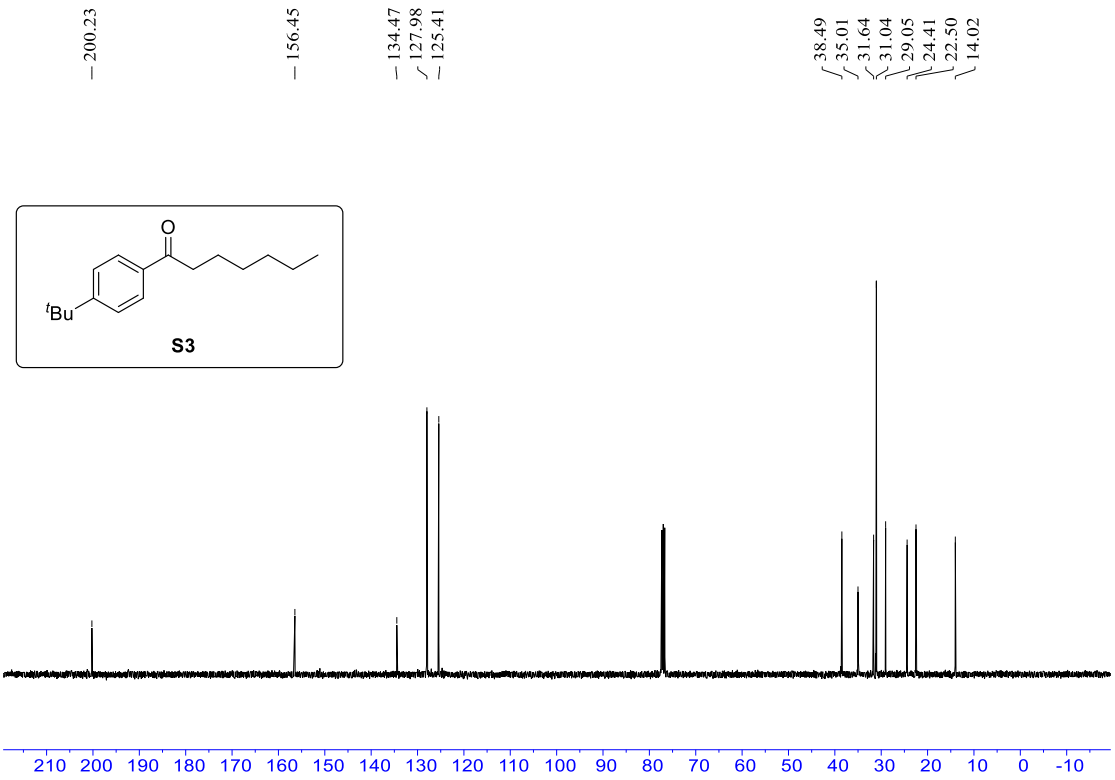
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S2



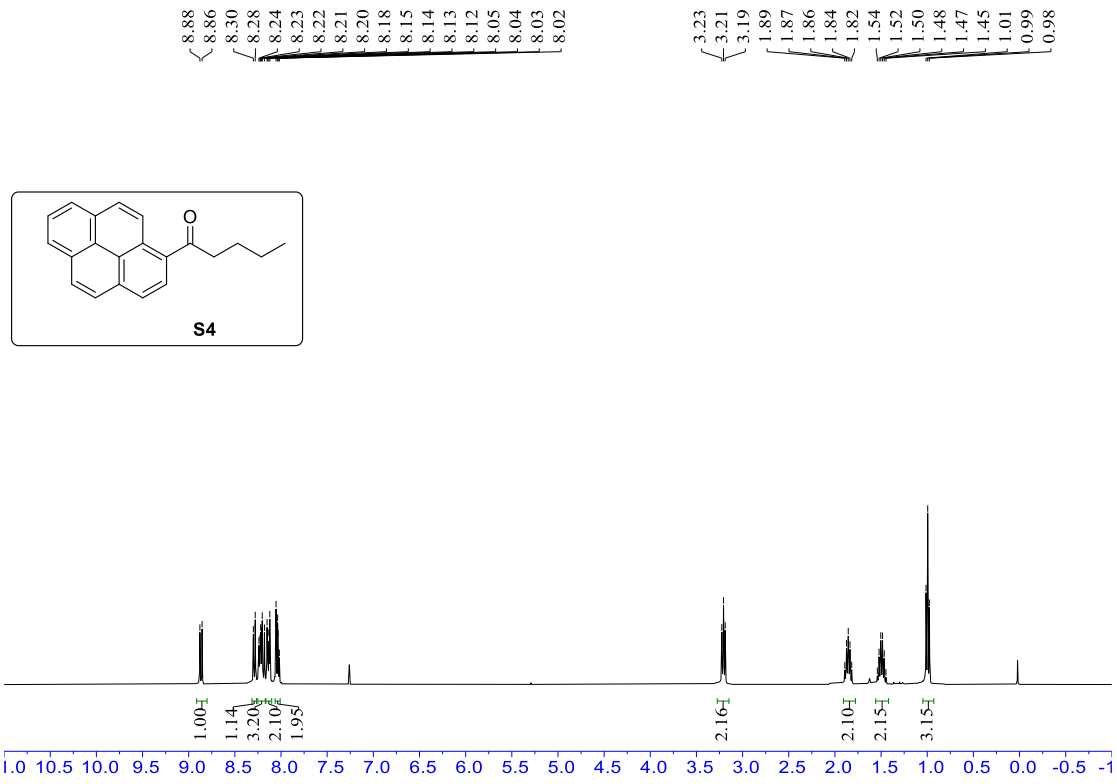
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S2



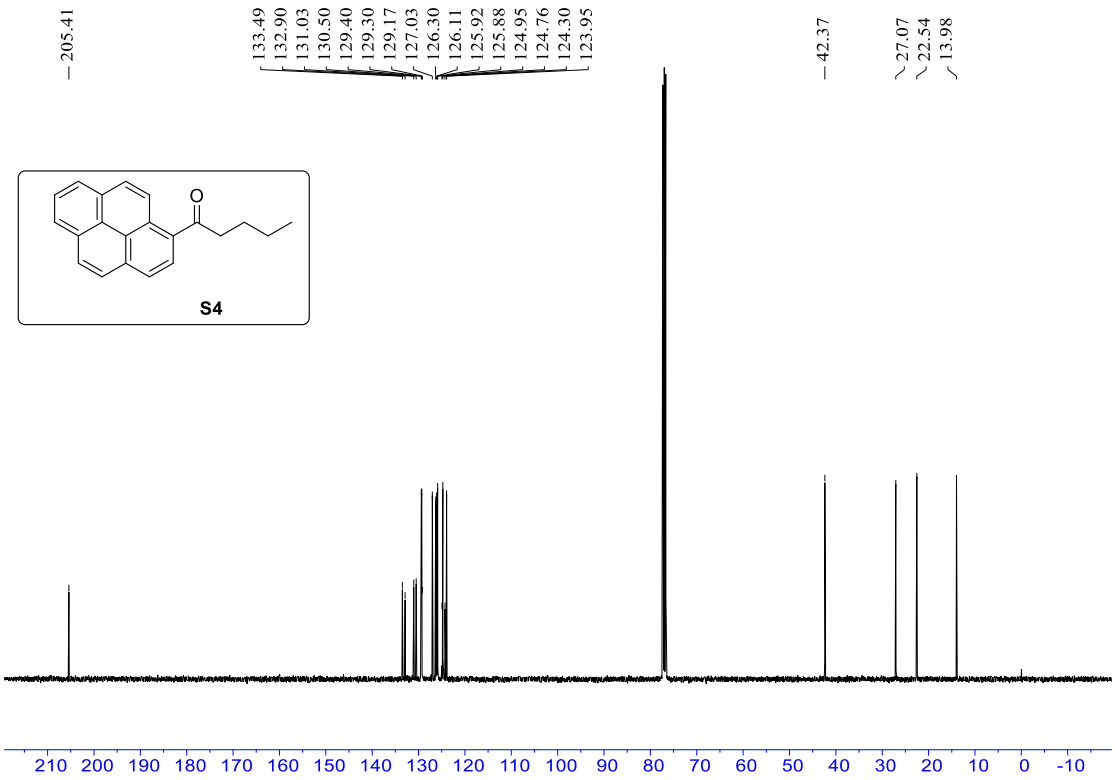
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S3



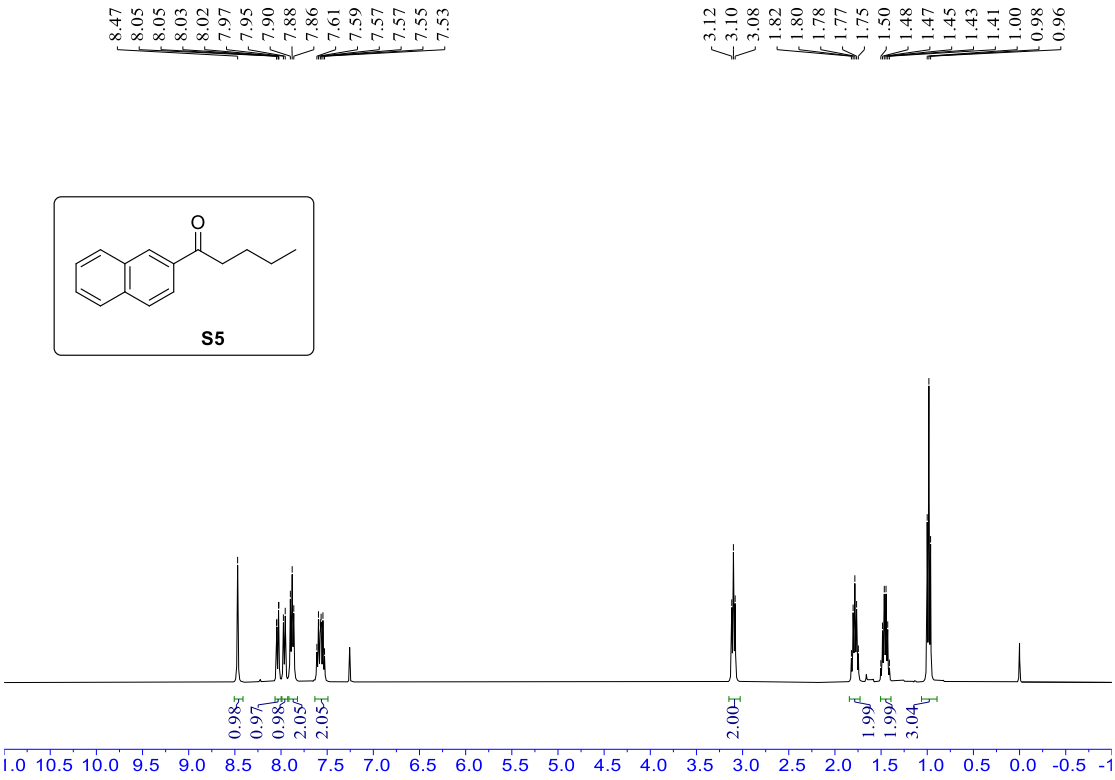
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S3



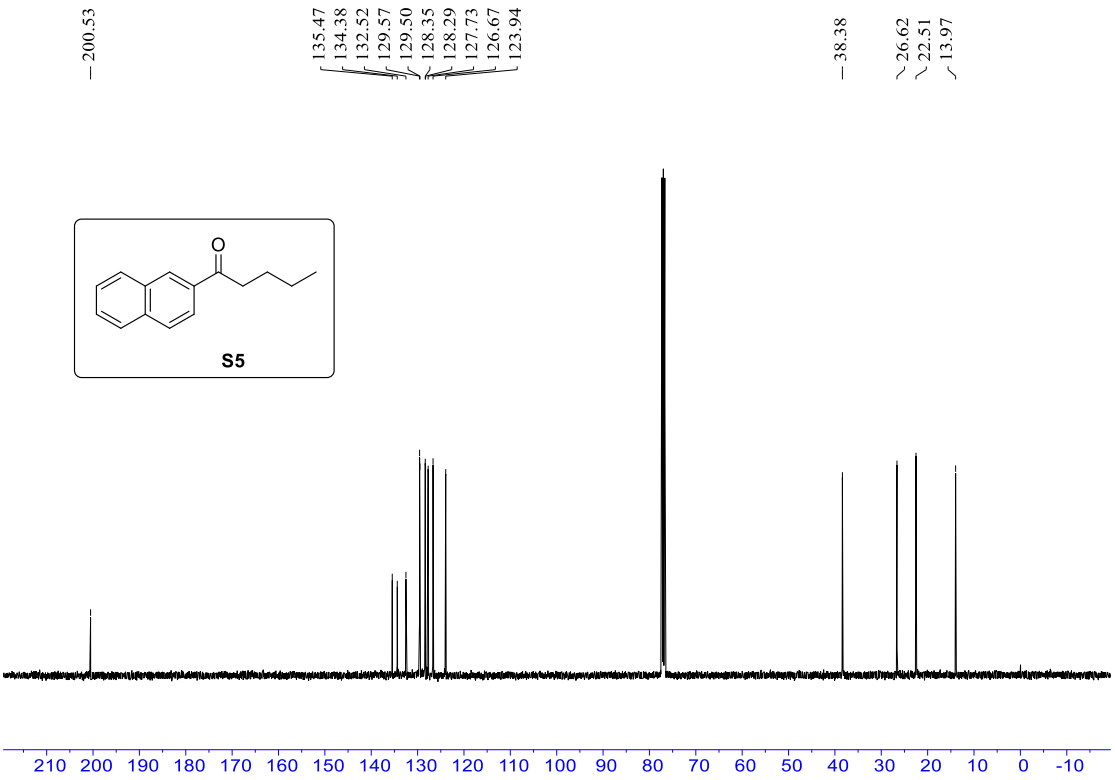
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S4



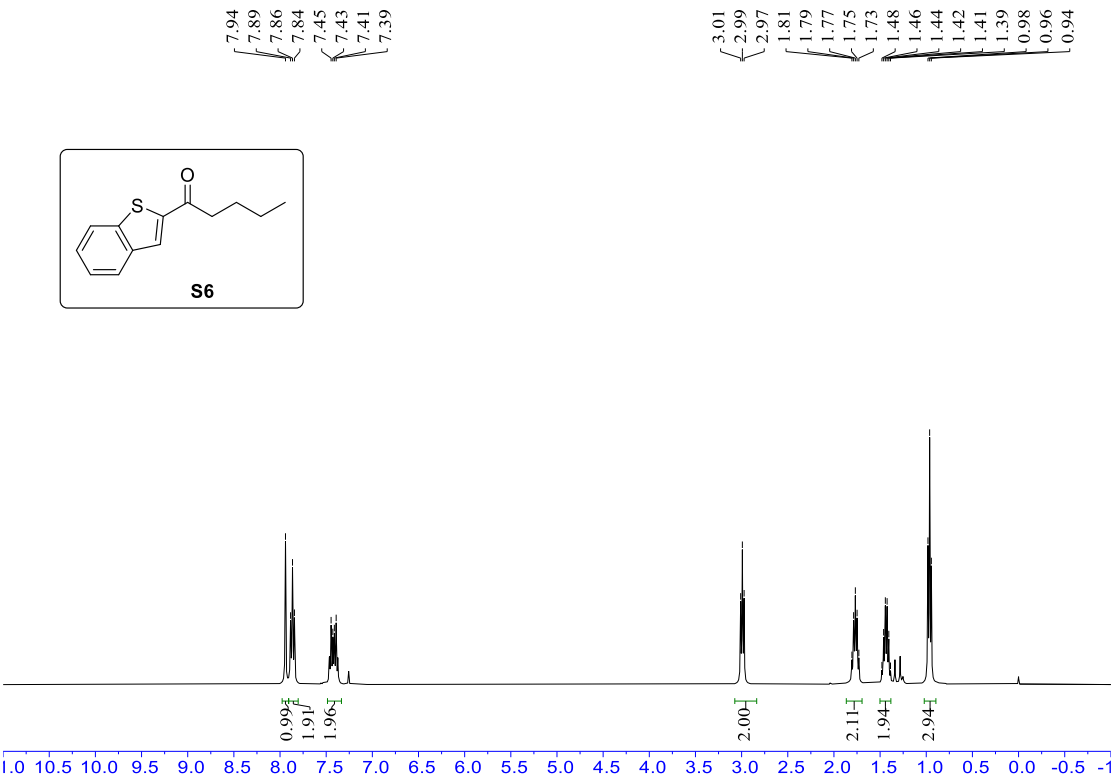
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S4



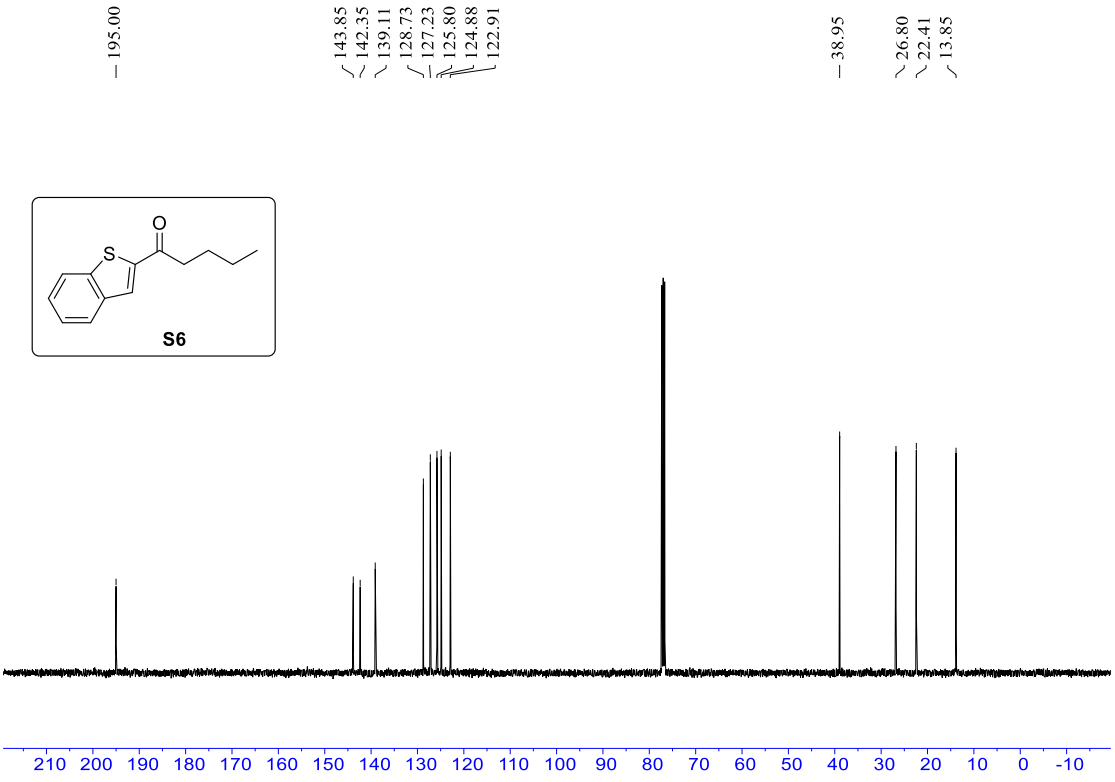
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S5



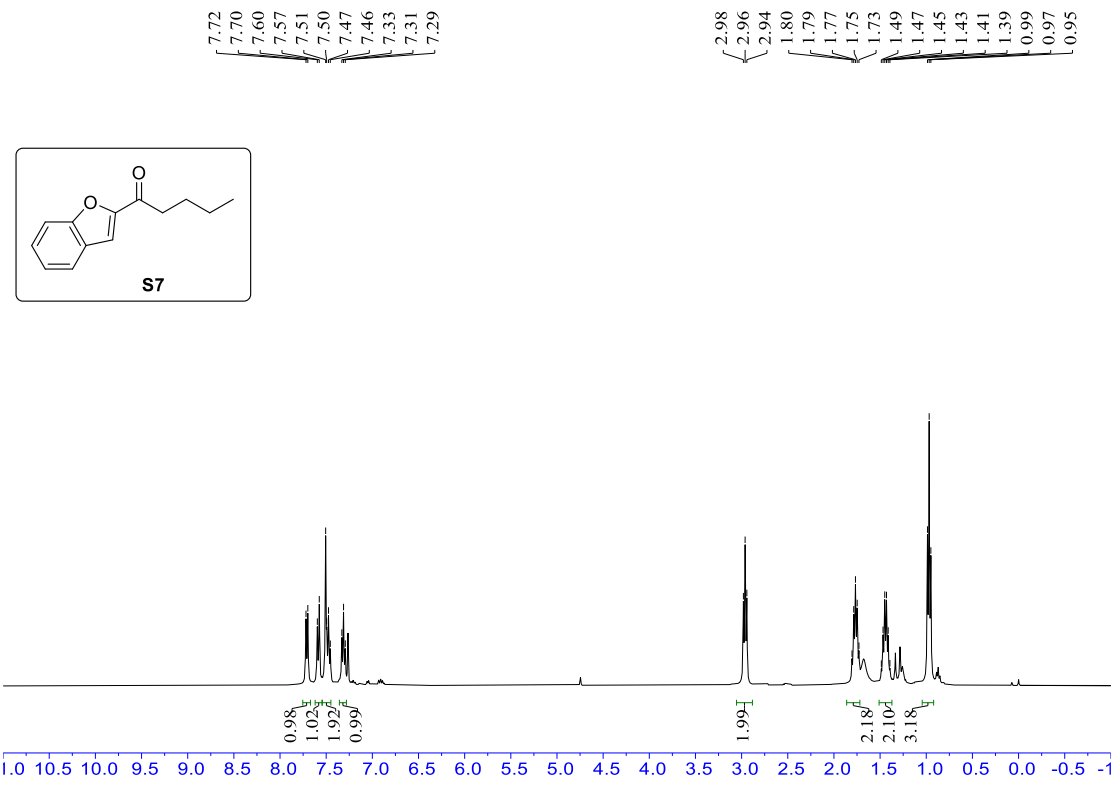
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S5



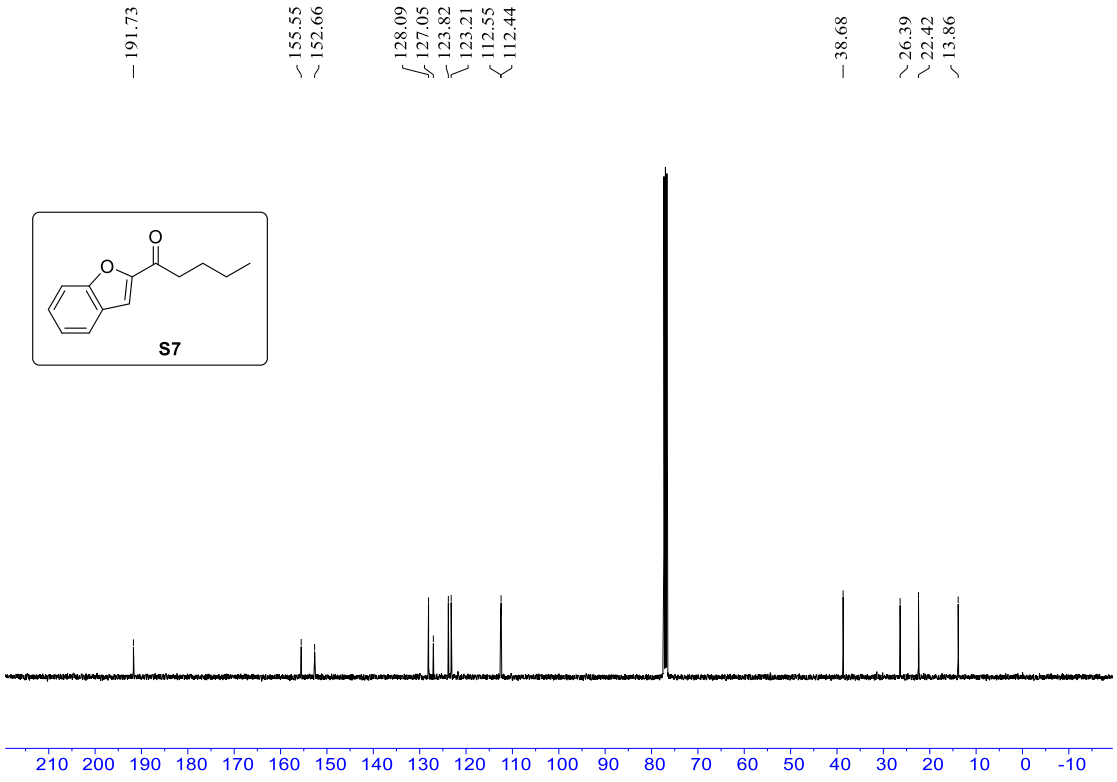
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S6



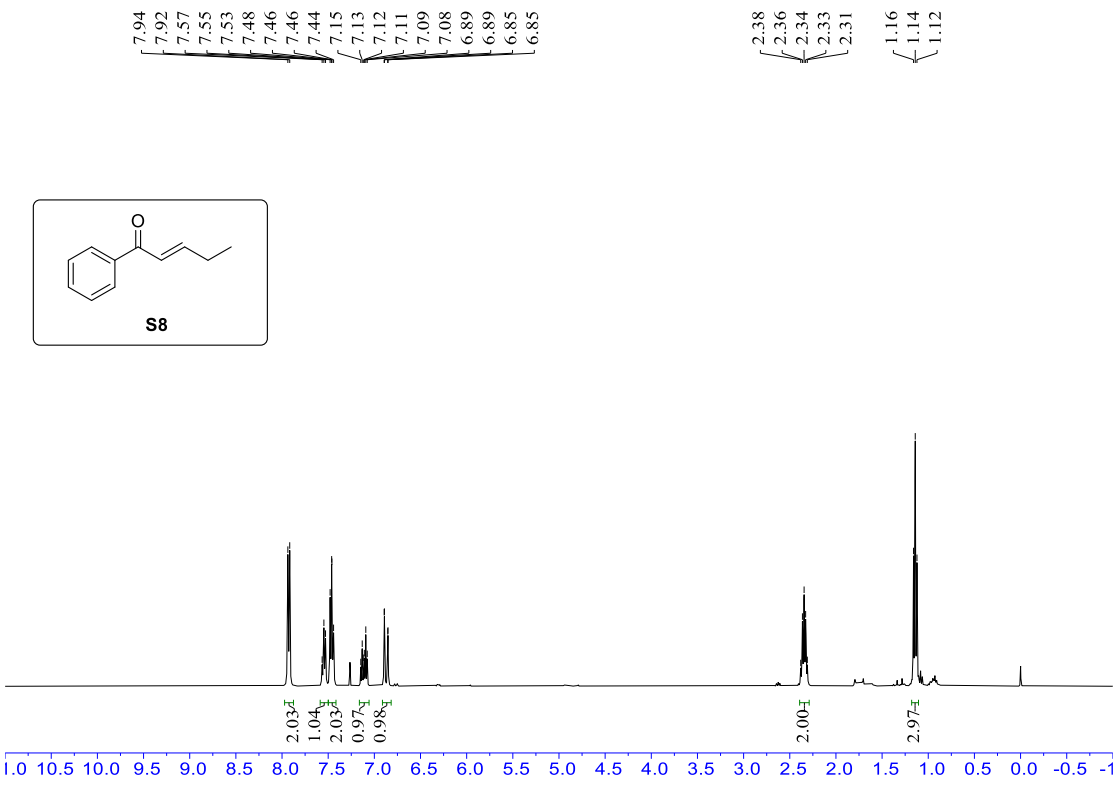
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S6



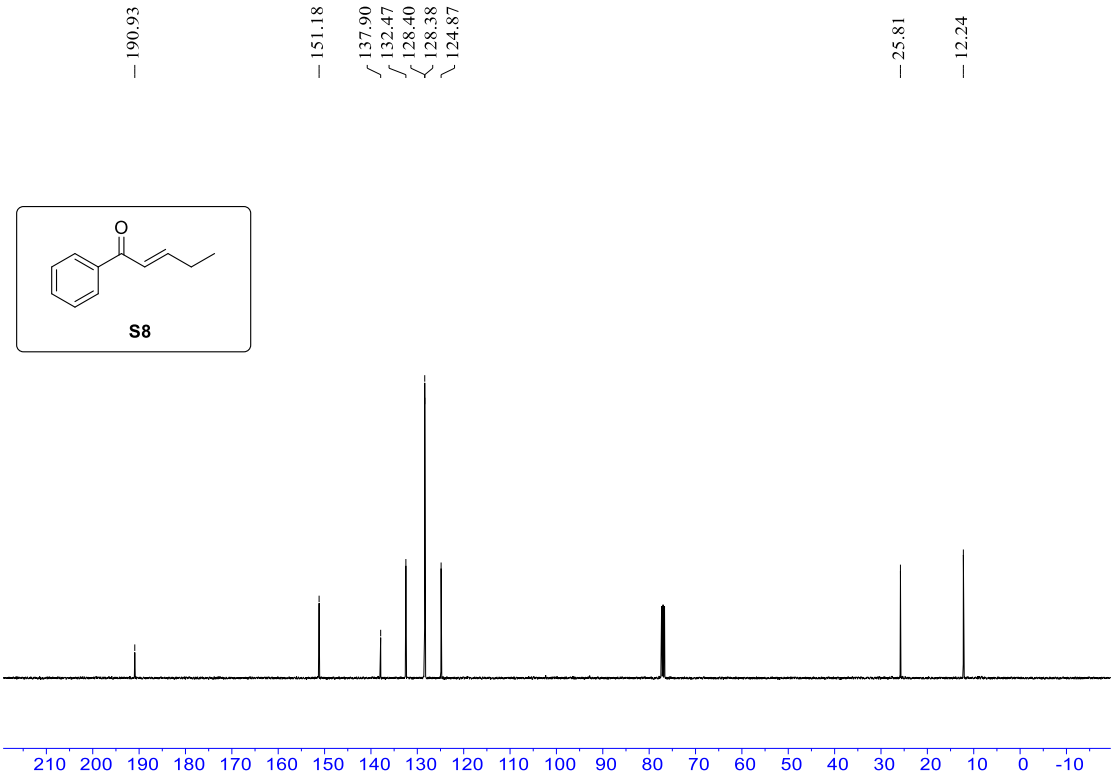
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S7



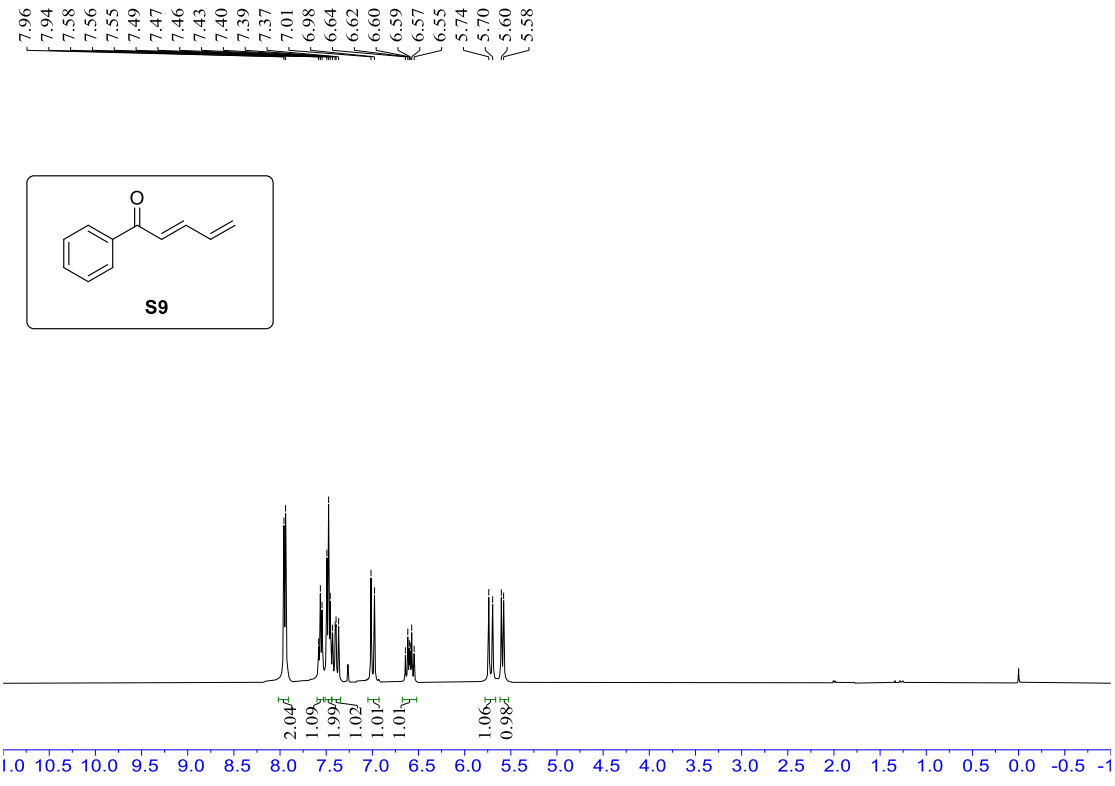
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S7



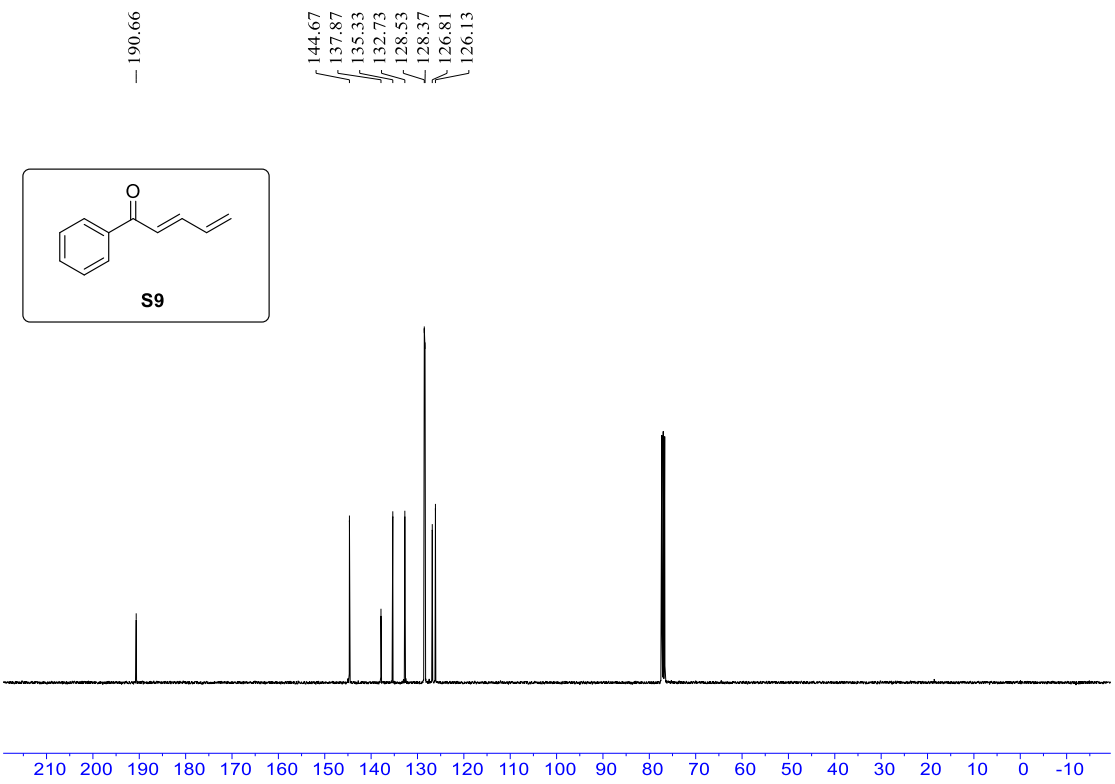
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S8



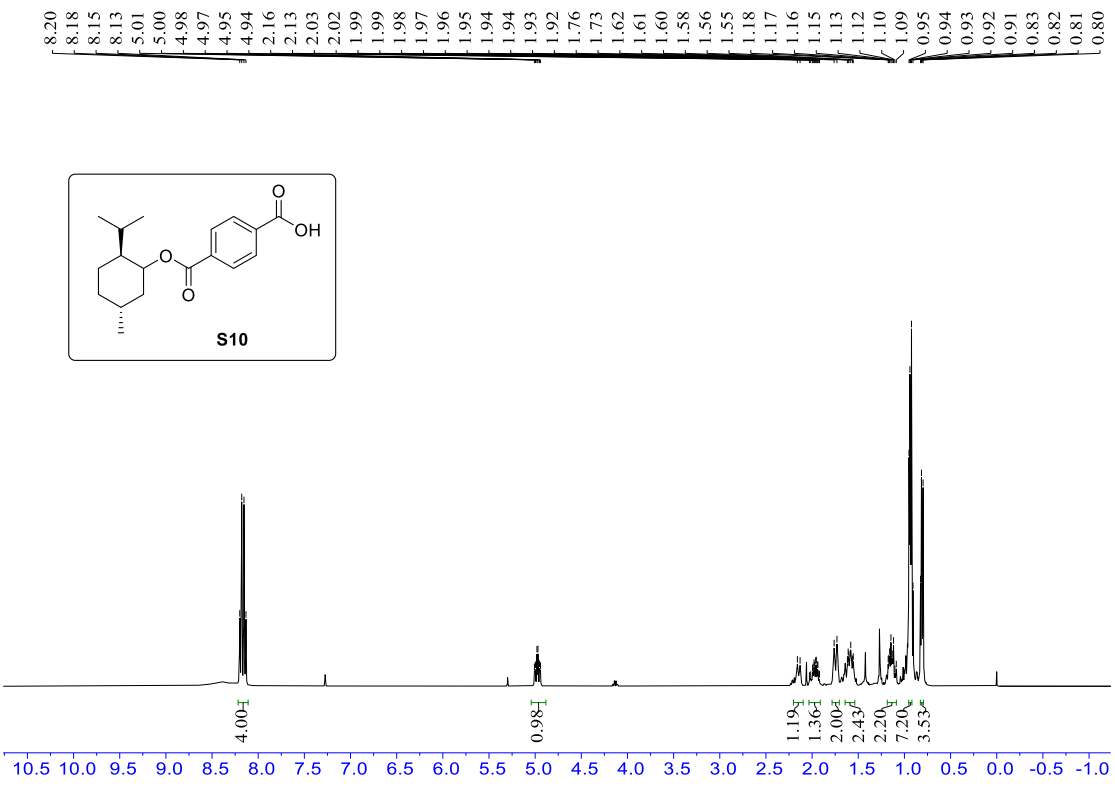
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S8



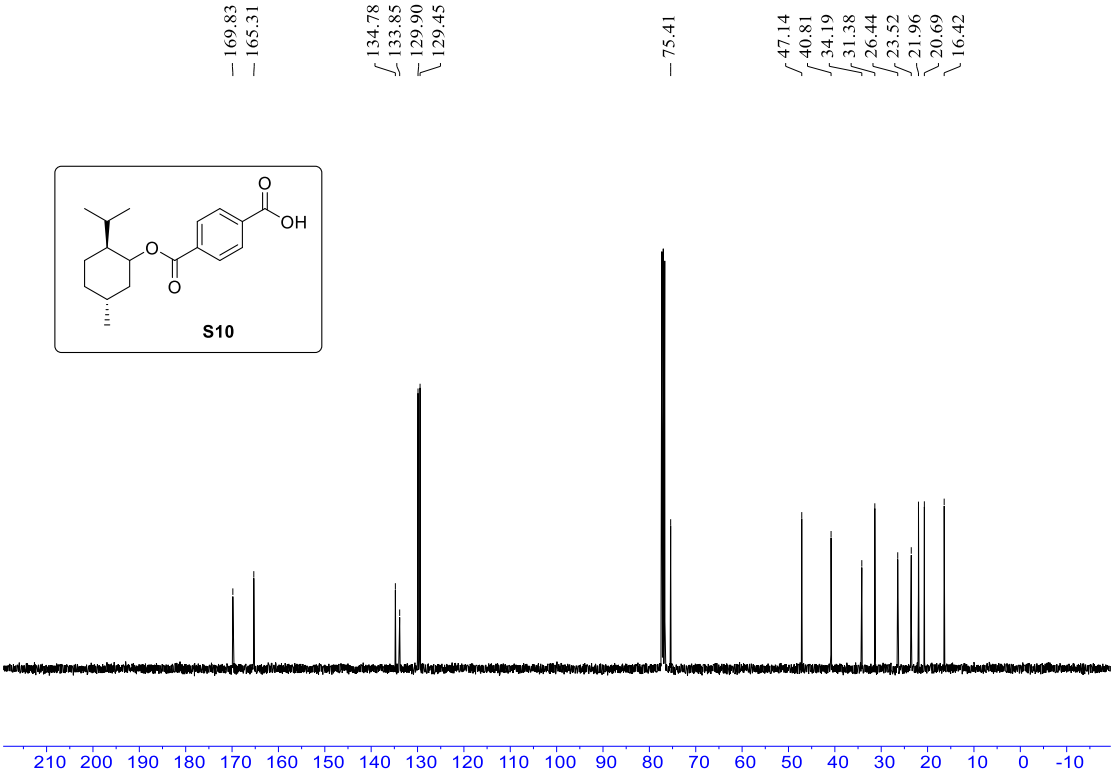
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S9



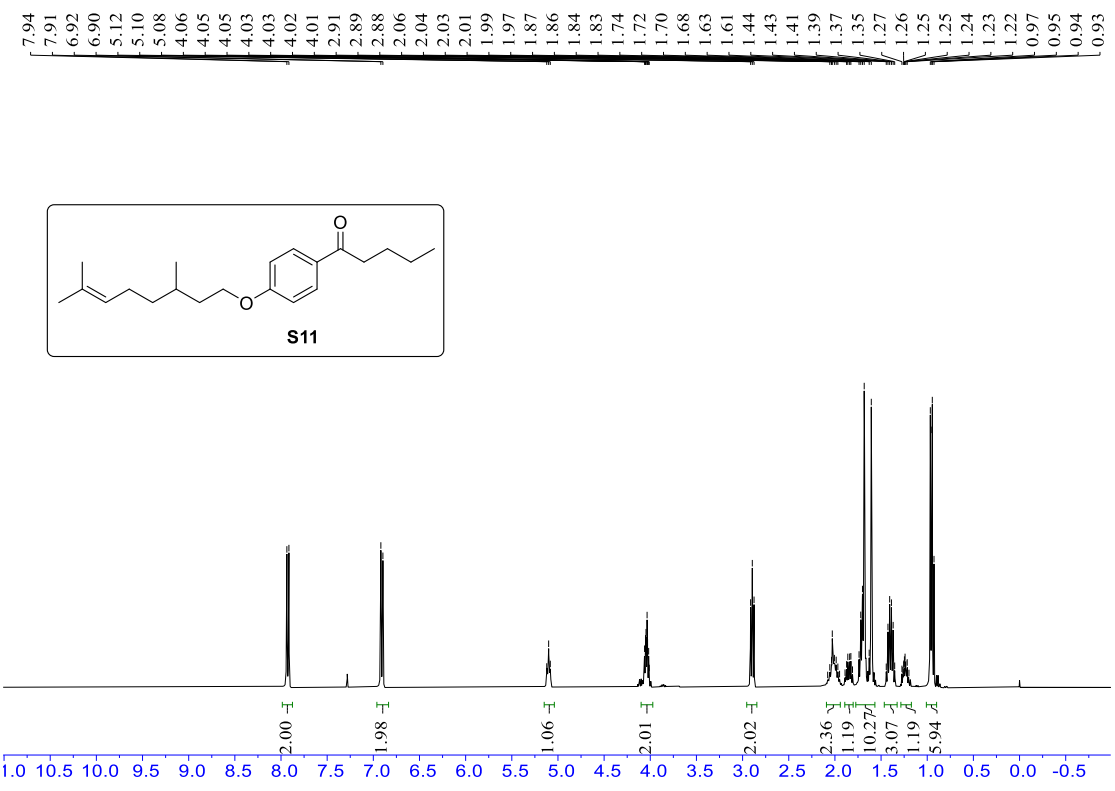
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S9



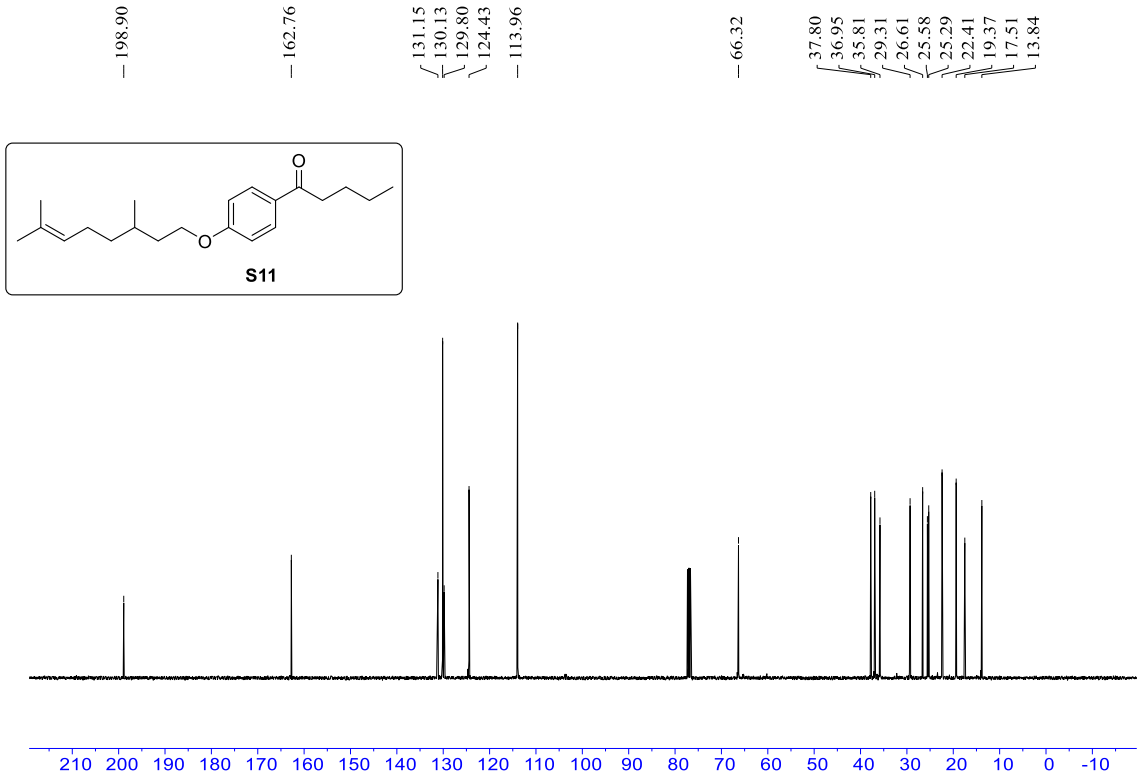
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S10



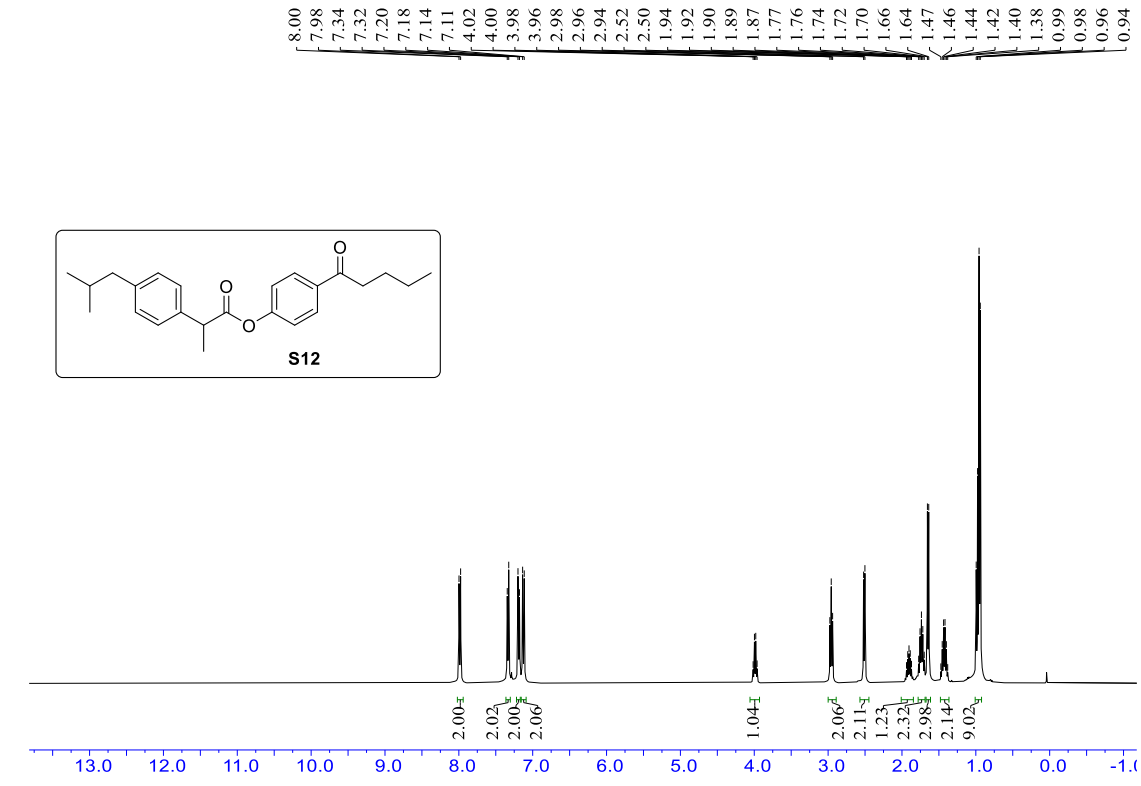
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S10



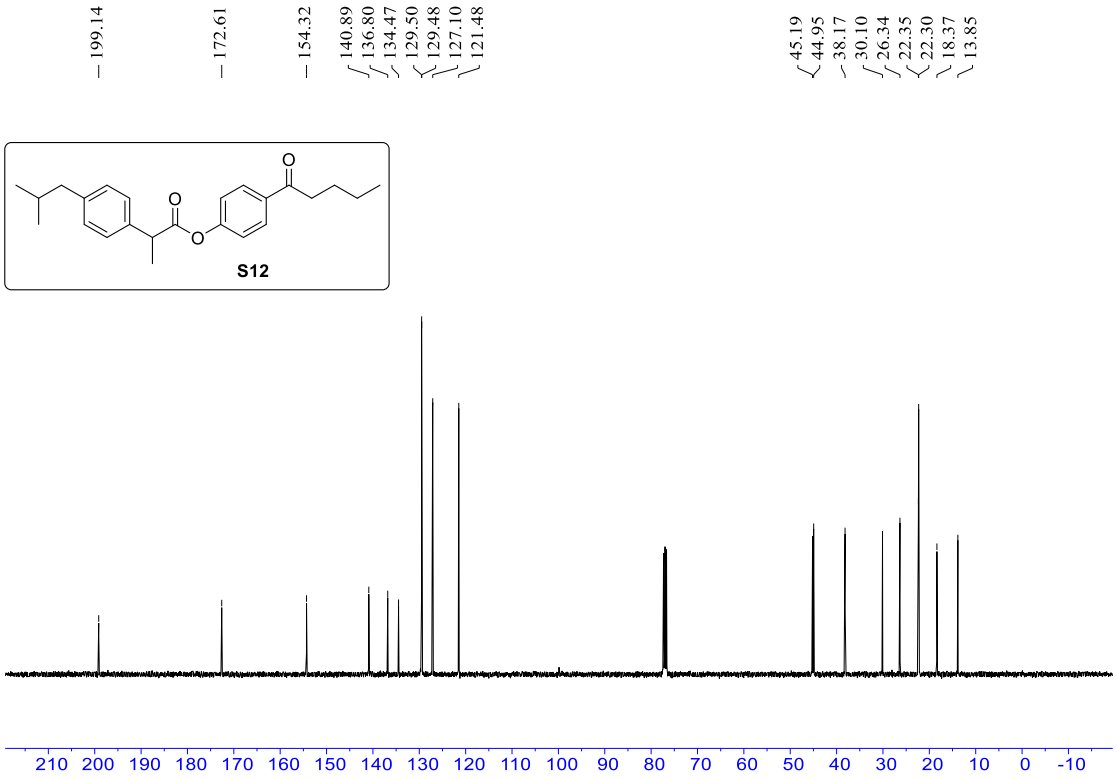
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S11



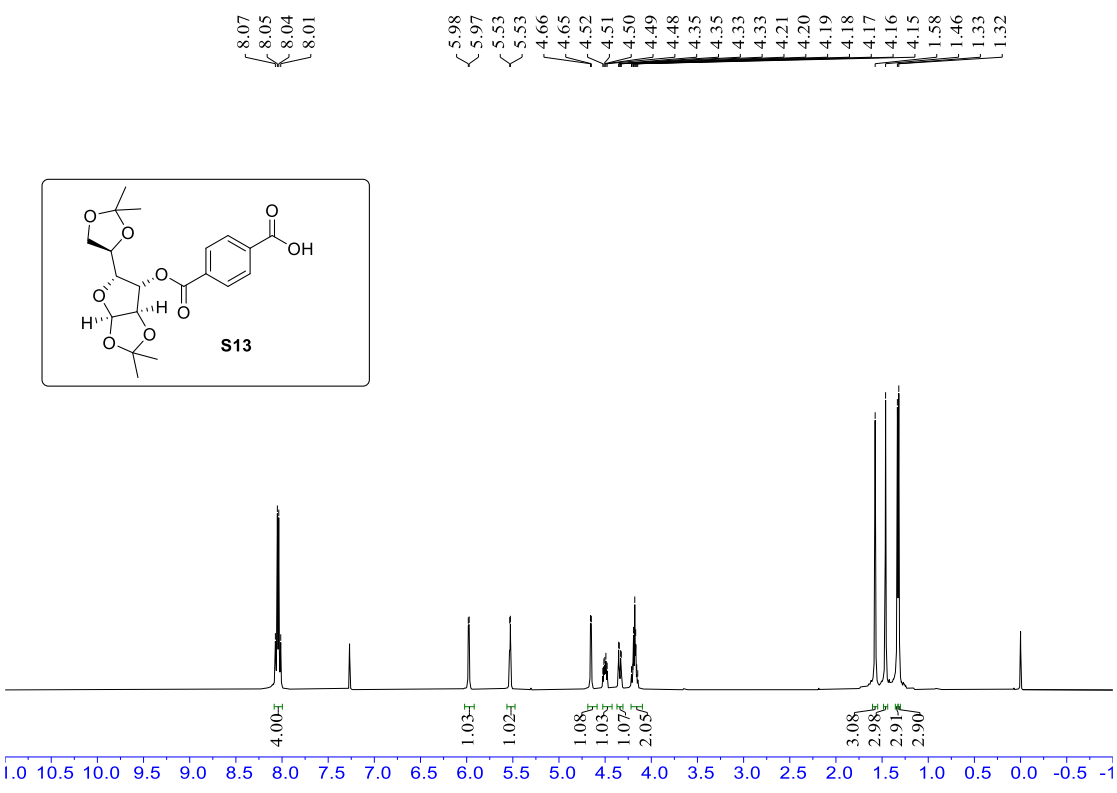
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S11



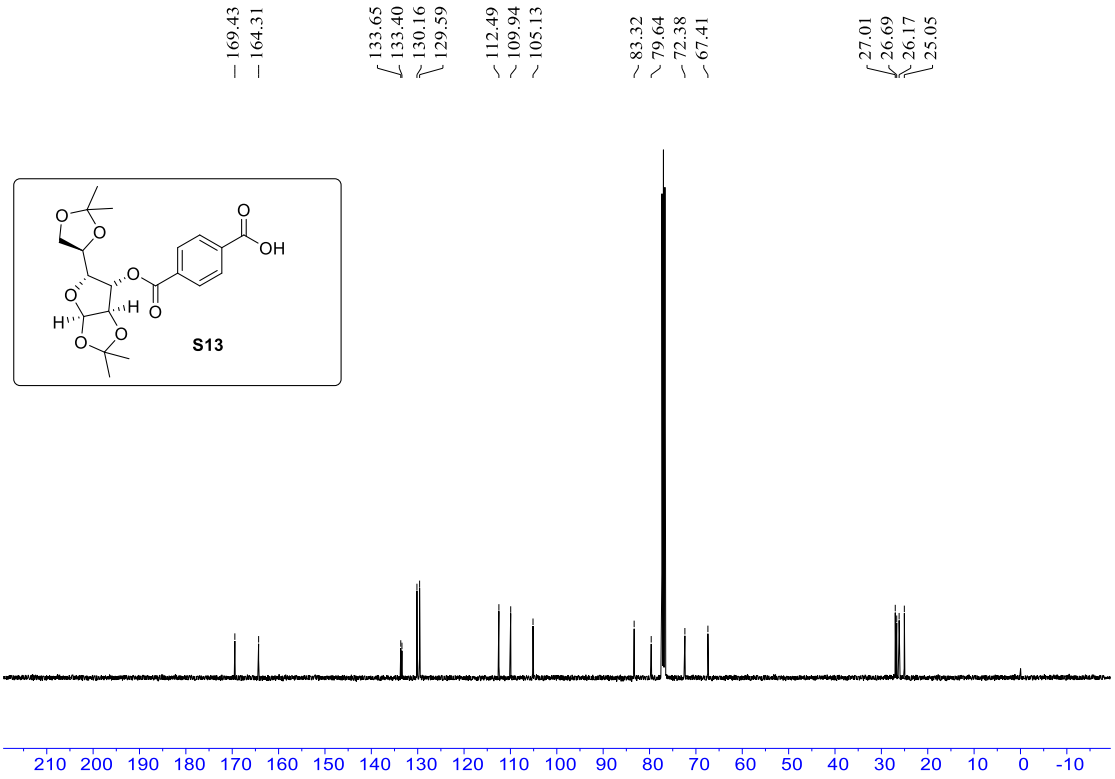
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S12



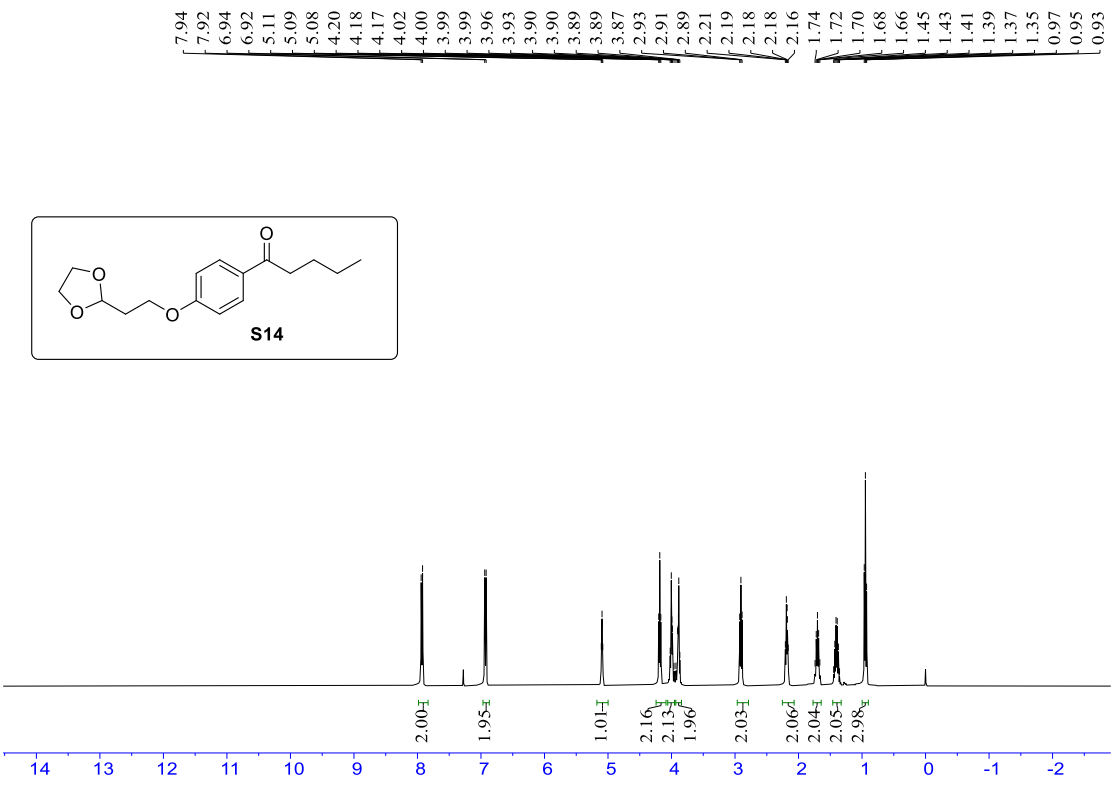
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S12



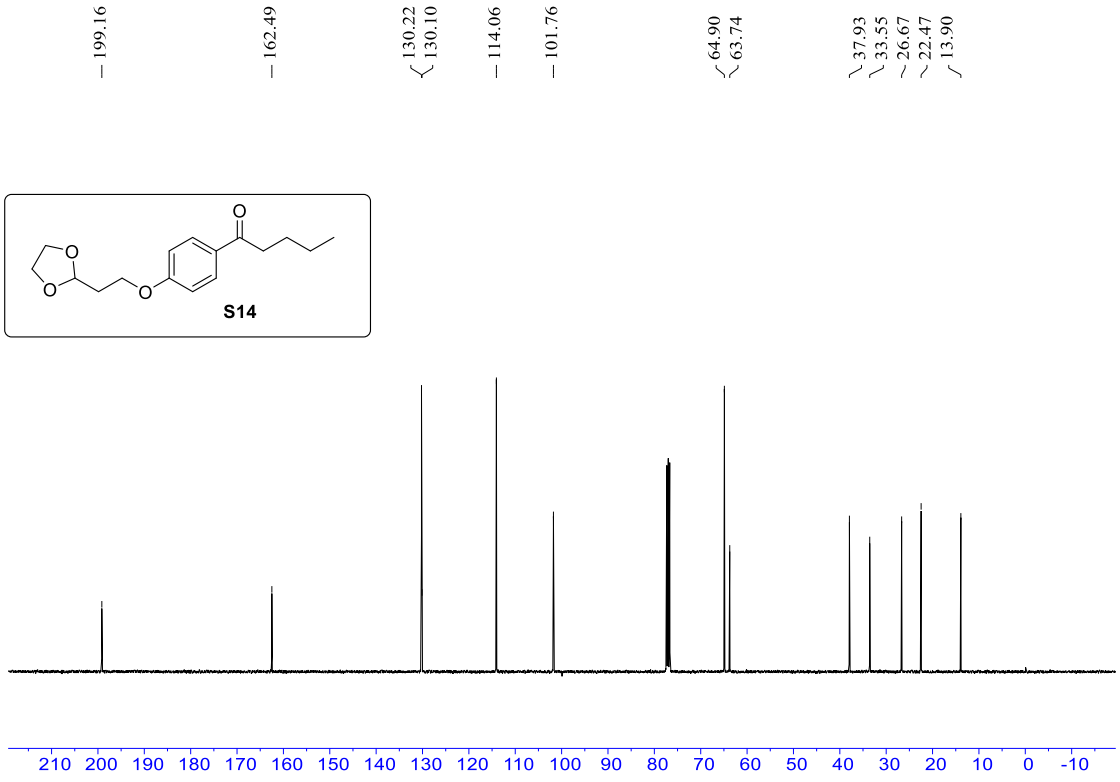
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S13



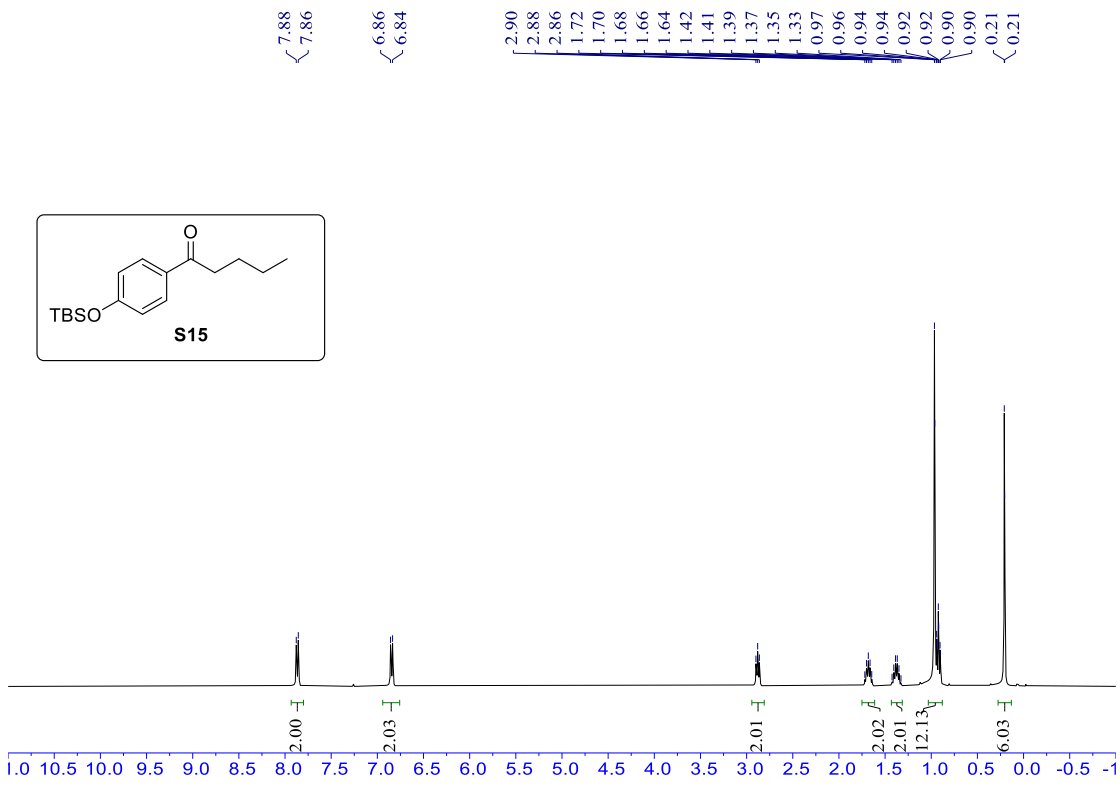
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S13



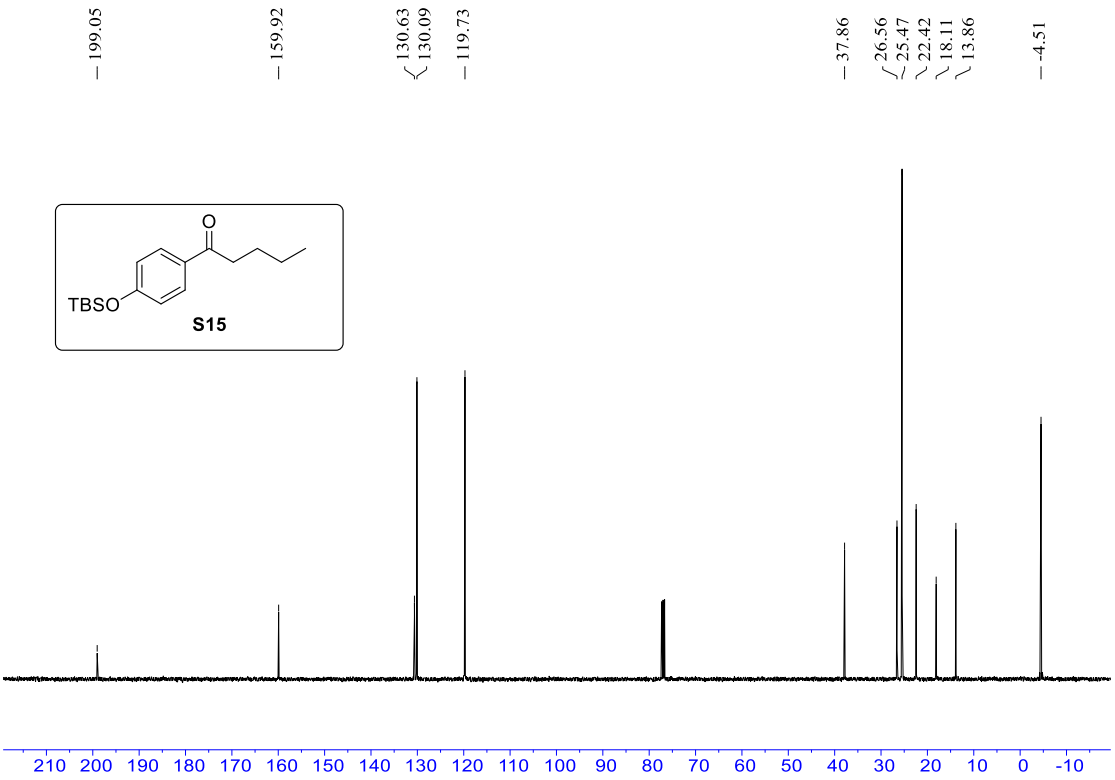
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S14



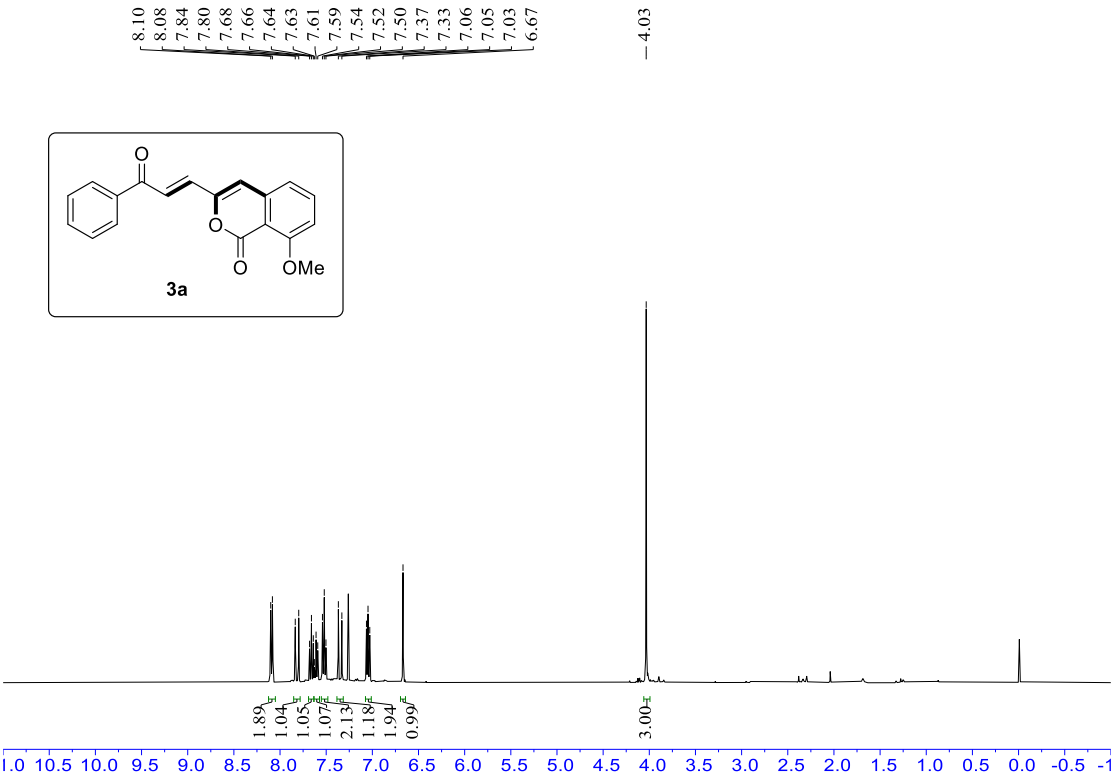
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S14



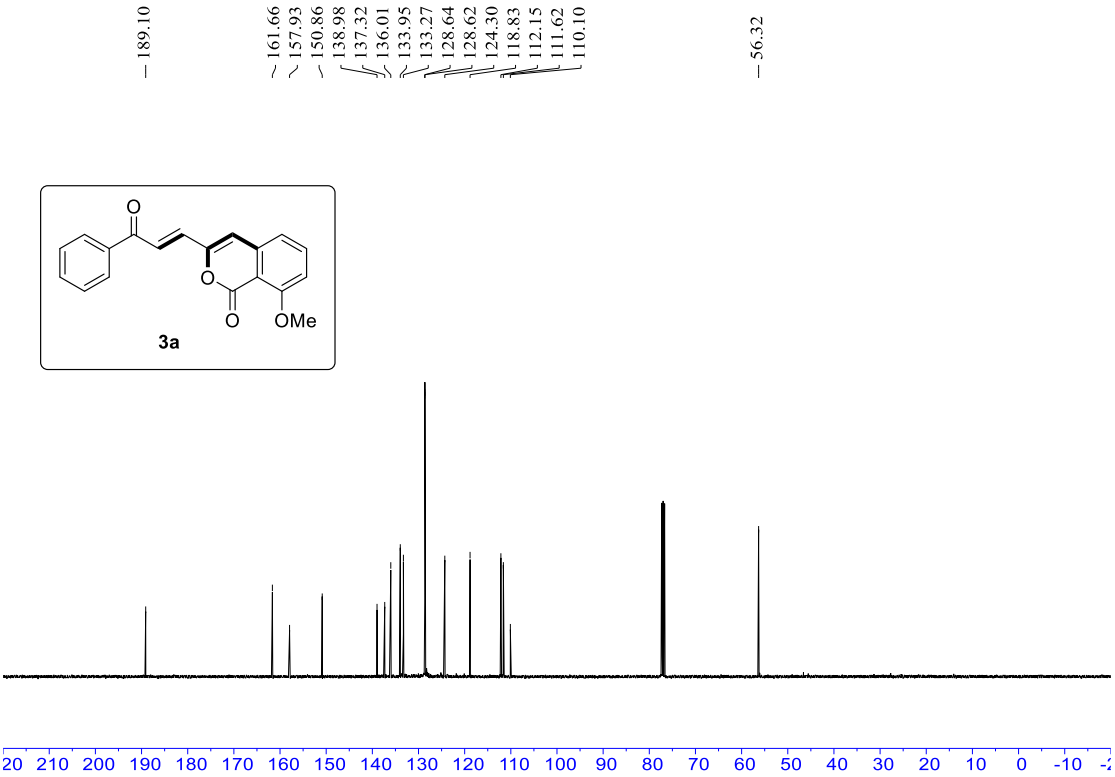
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for S15



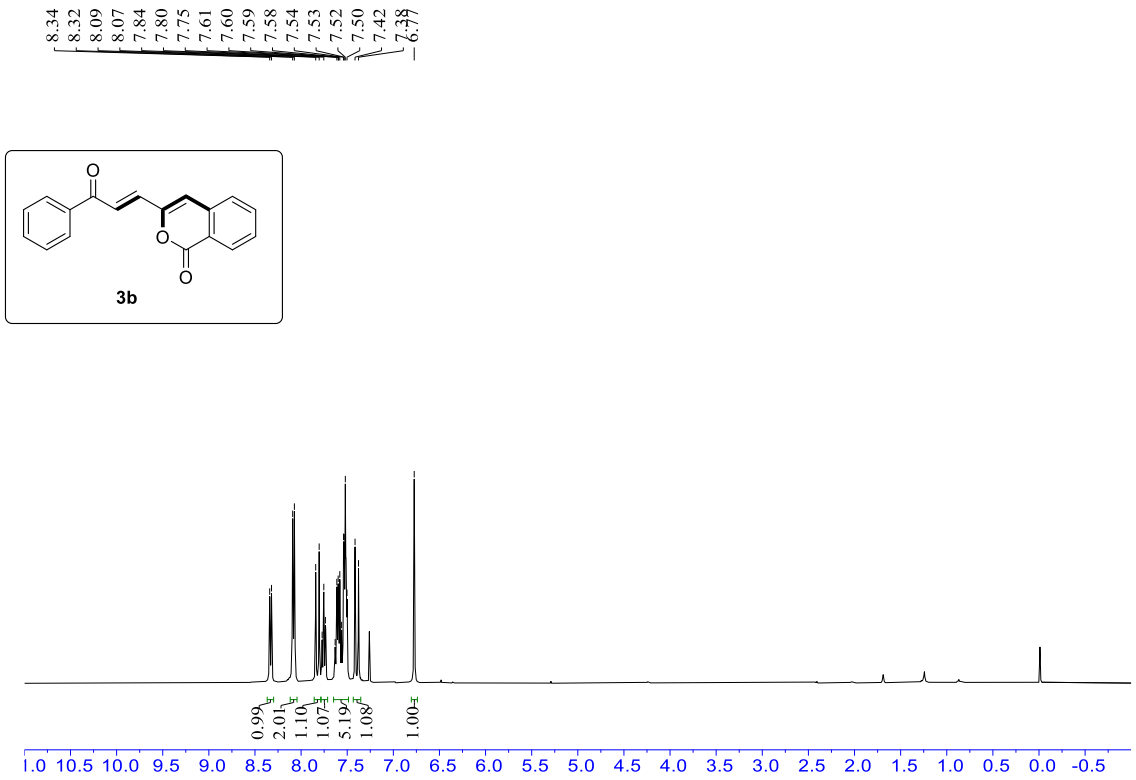
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for S15



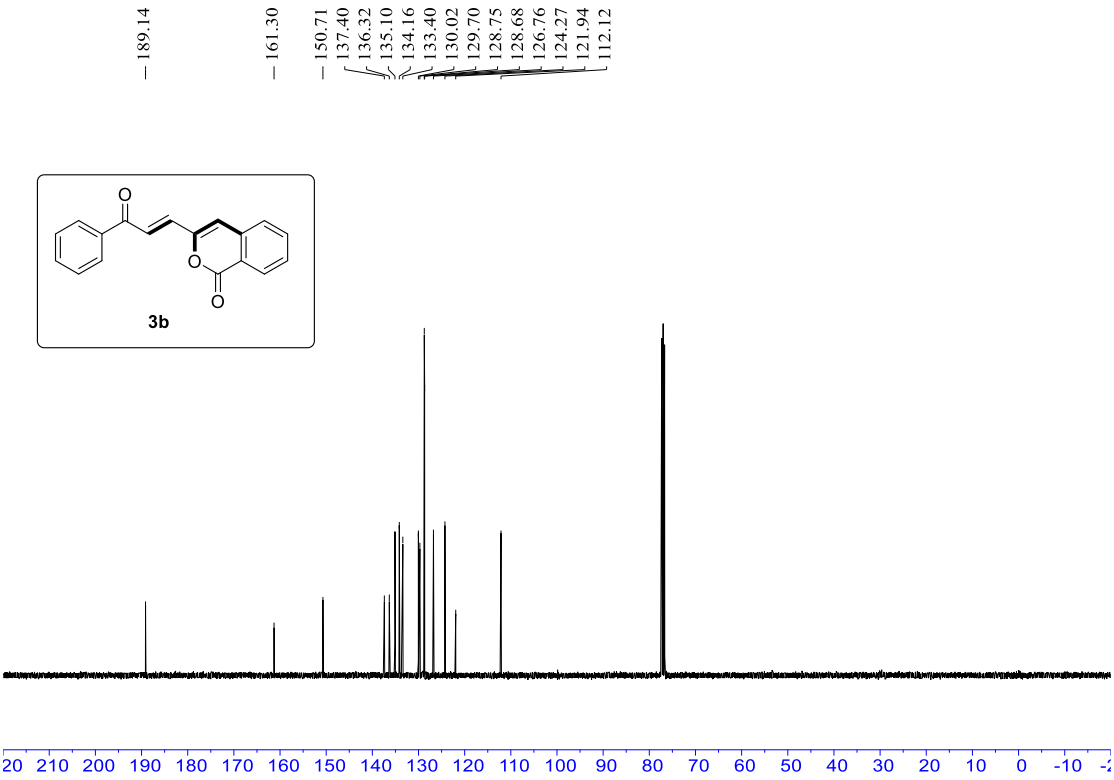
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3a**



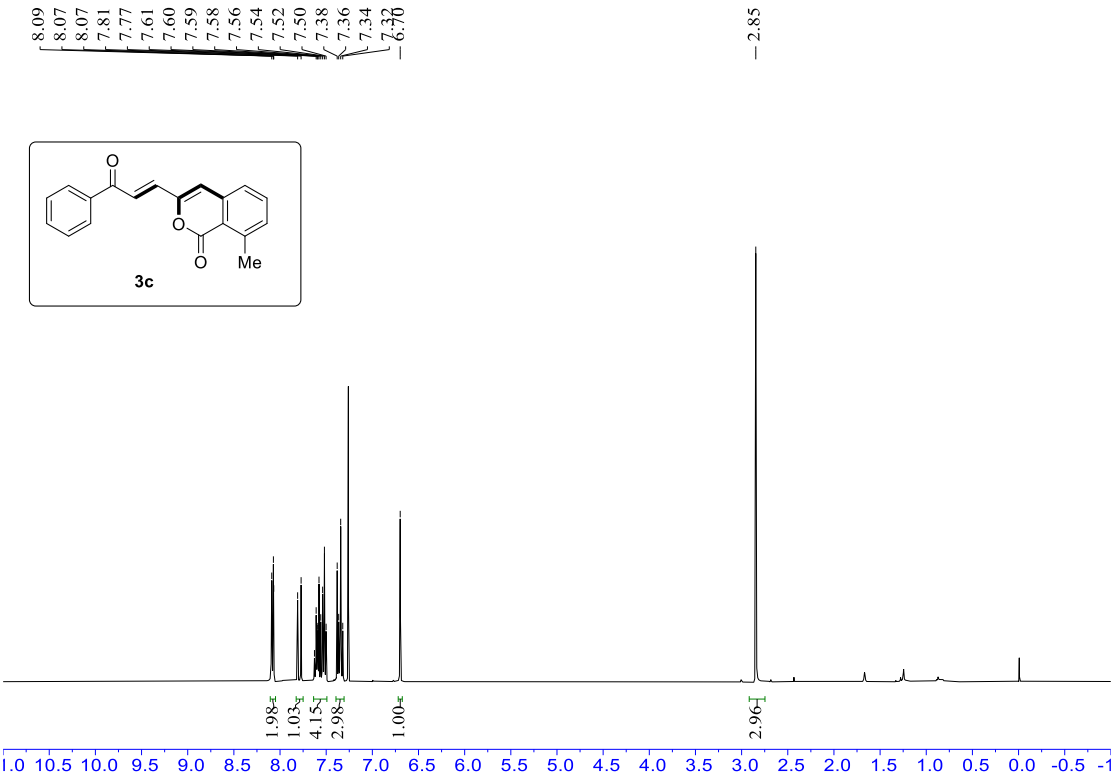
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3a**



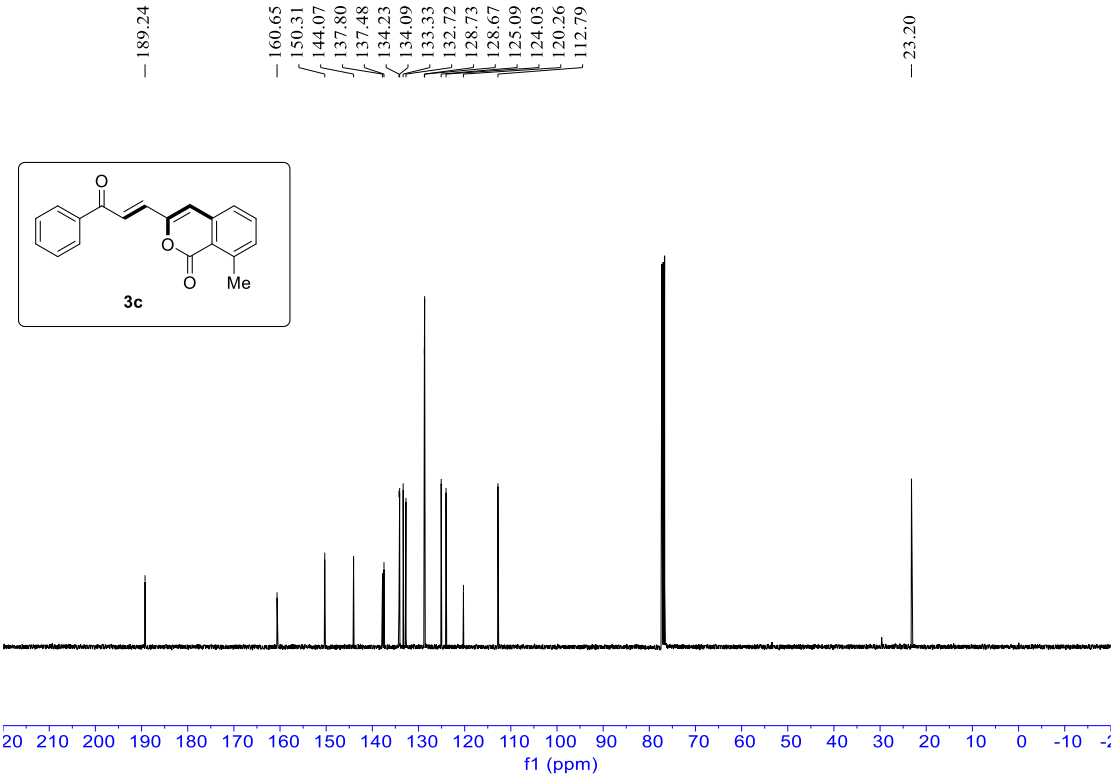
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3b**



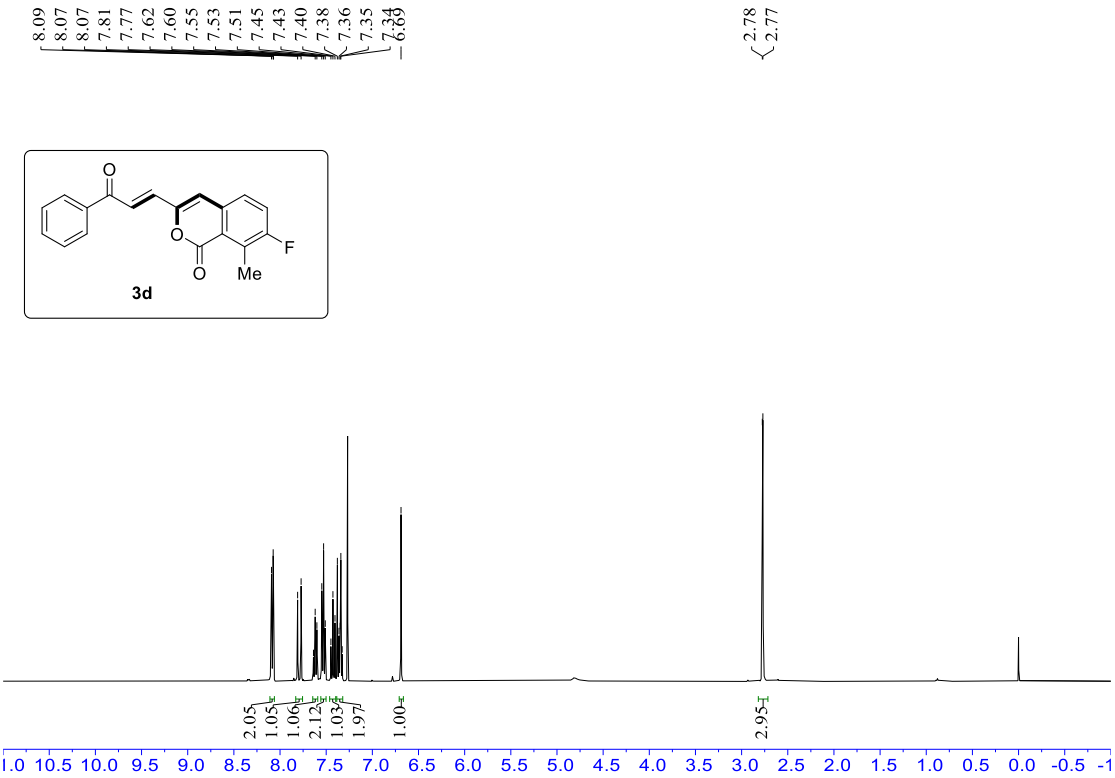
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3b**



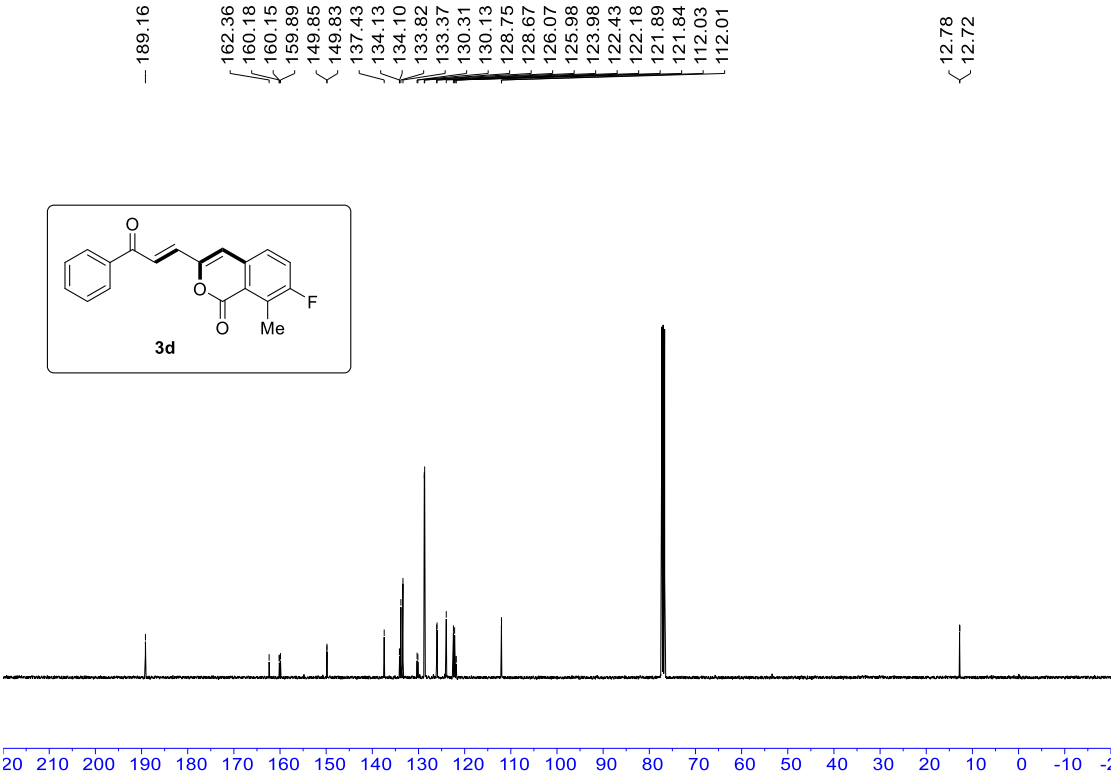
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3c**



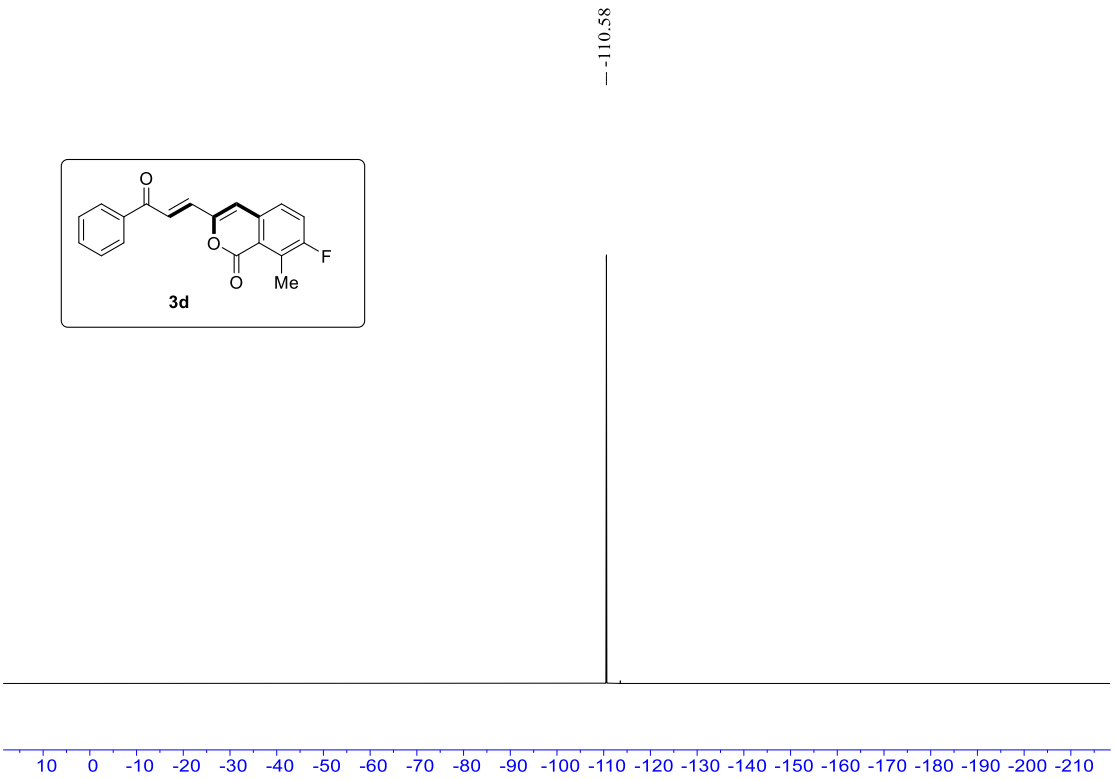
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3c**



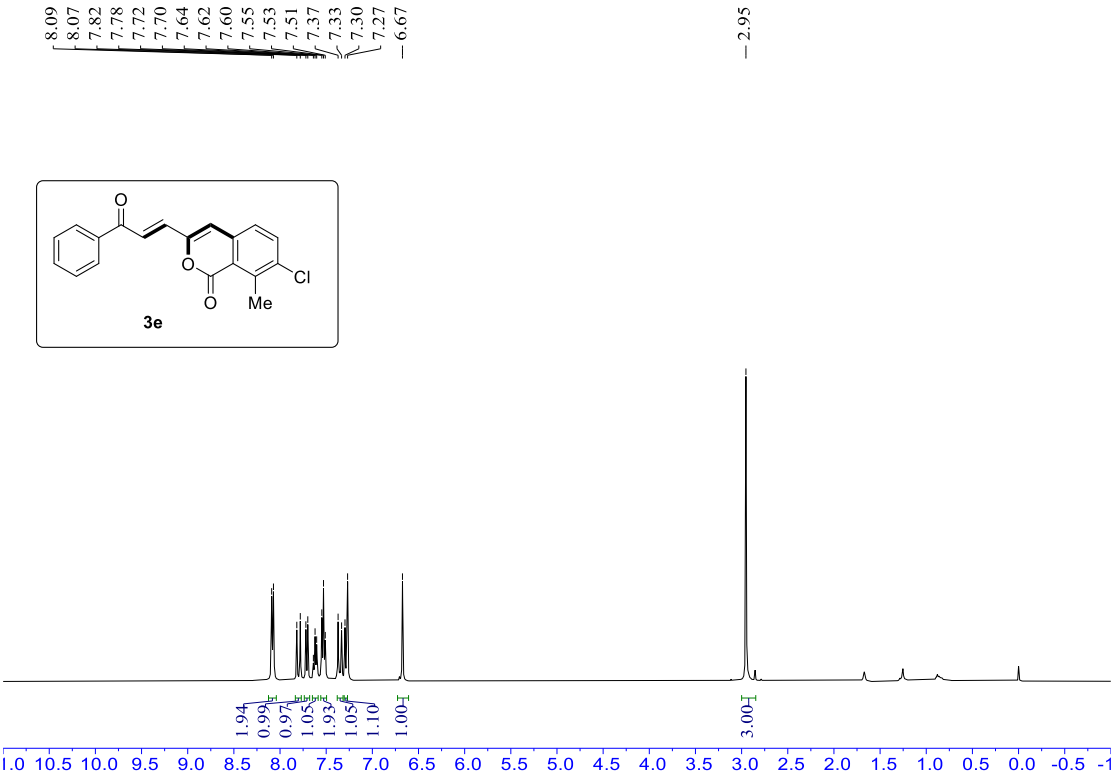
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3d**



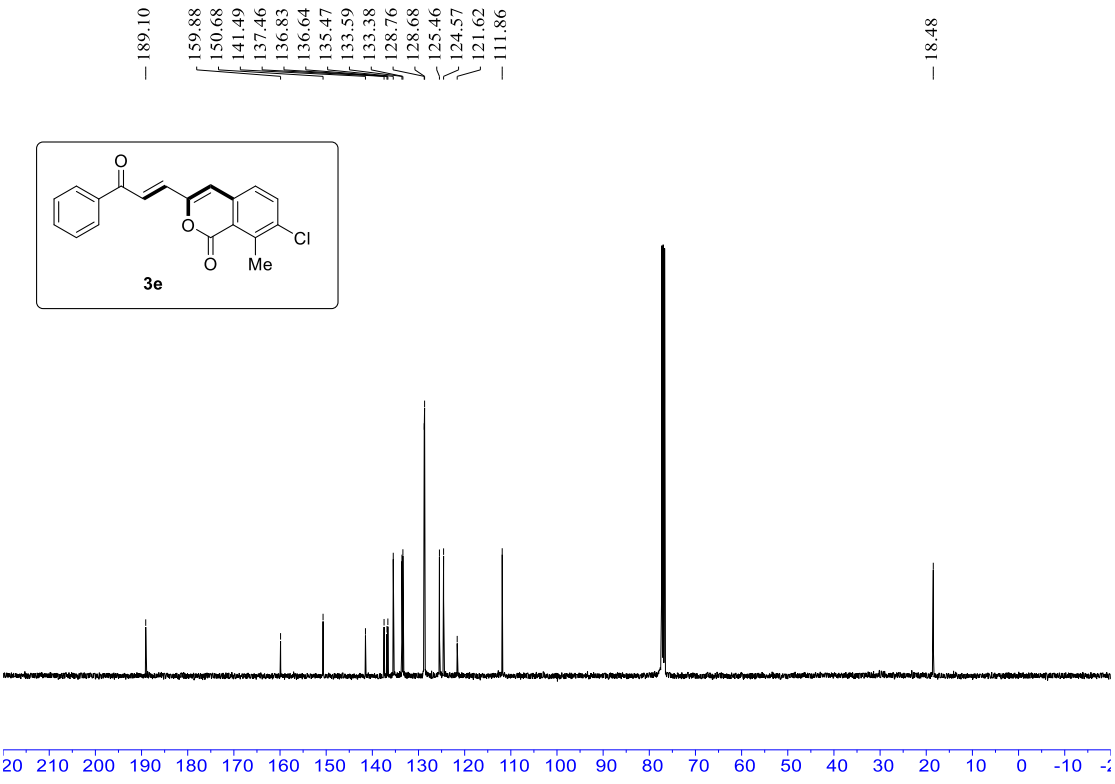
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3d**



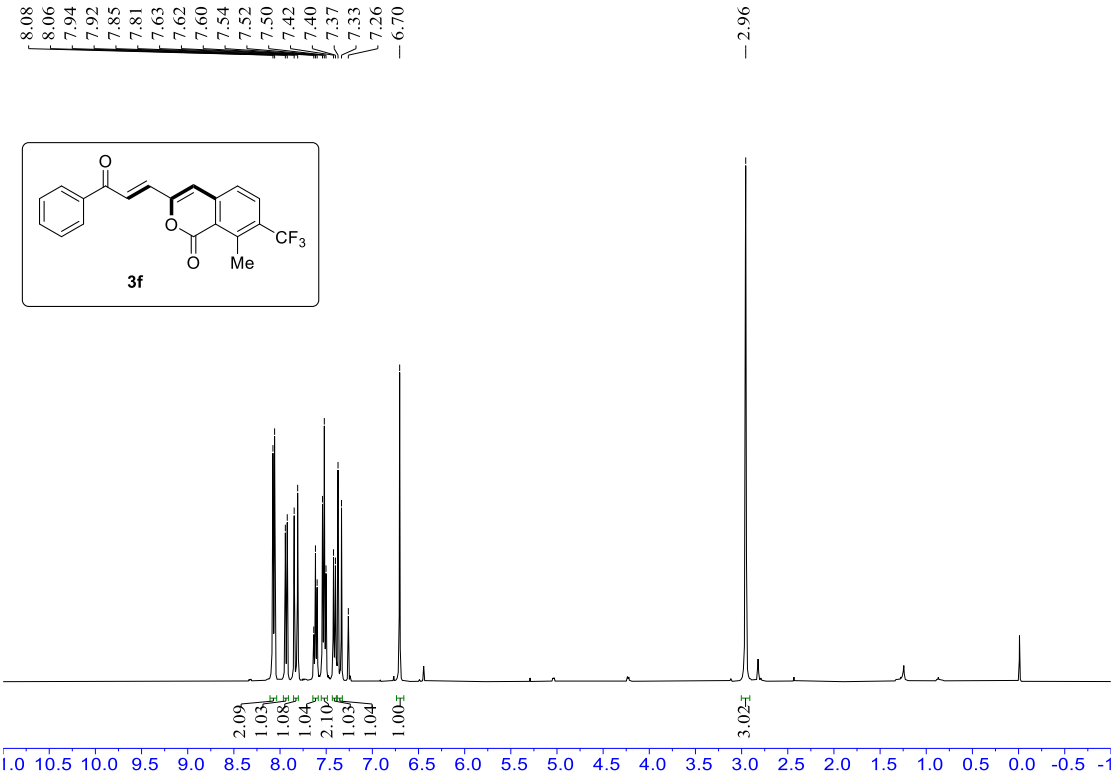
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **3d**



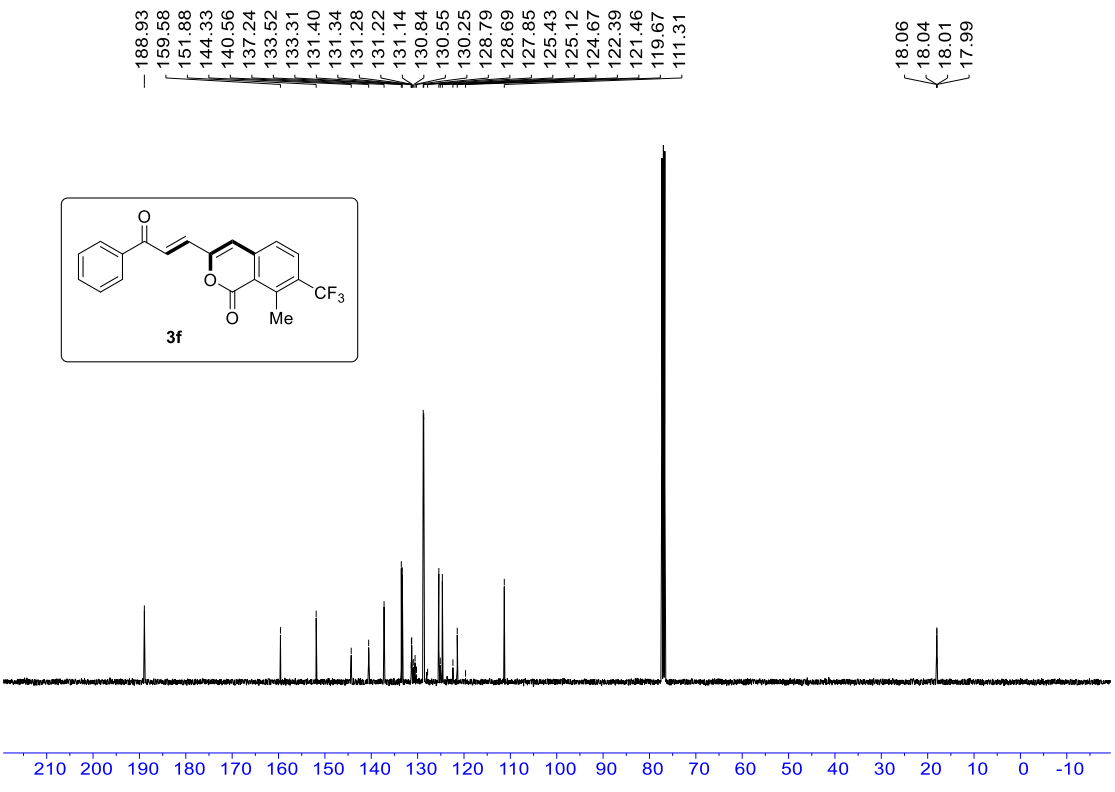
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3e**



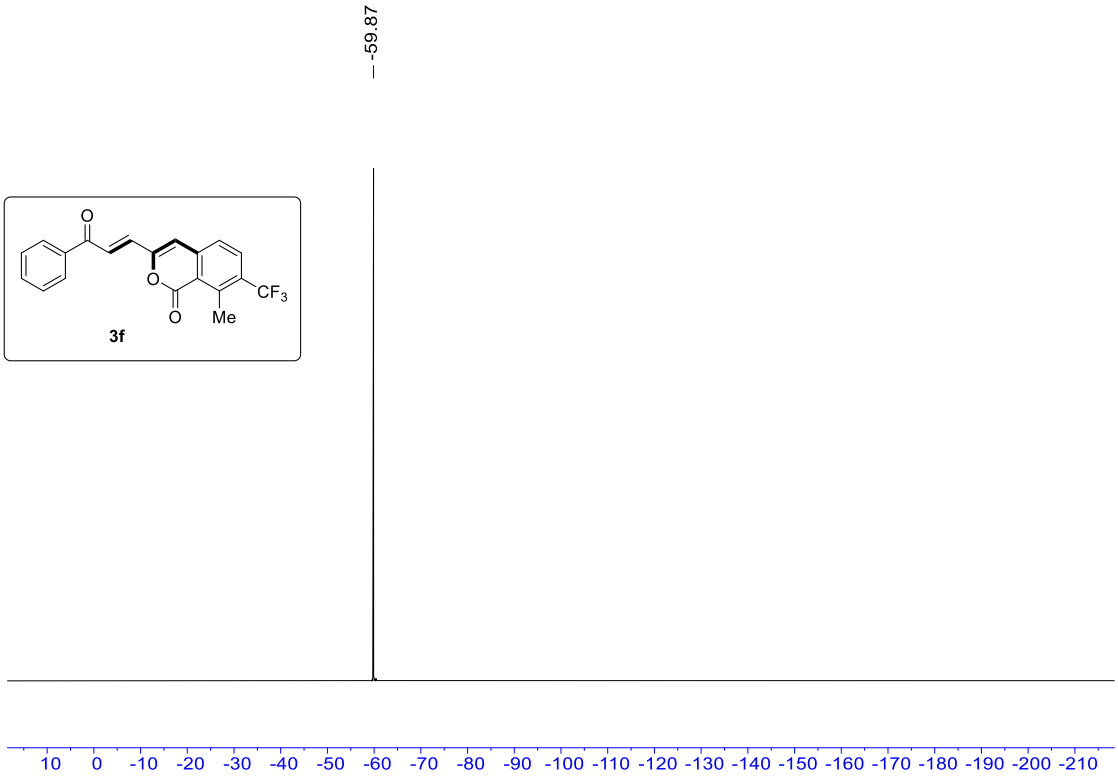
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3e**



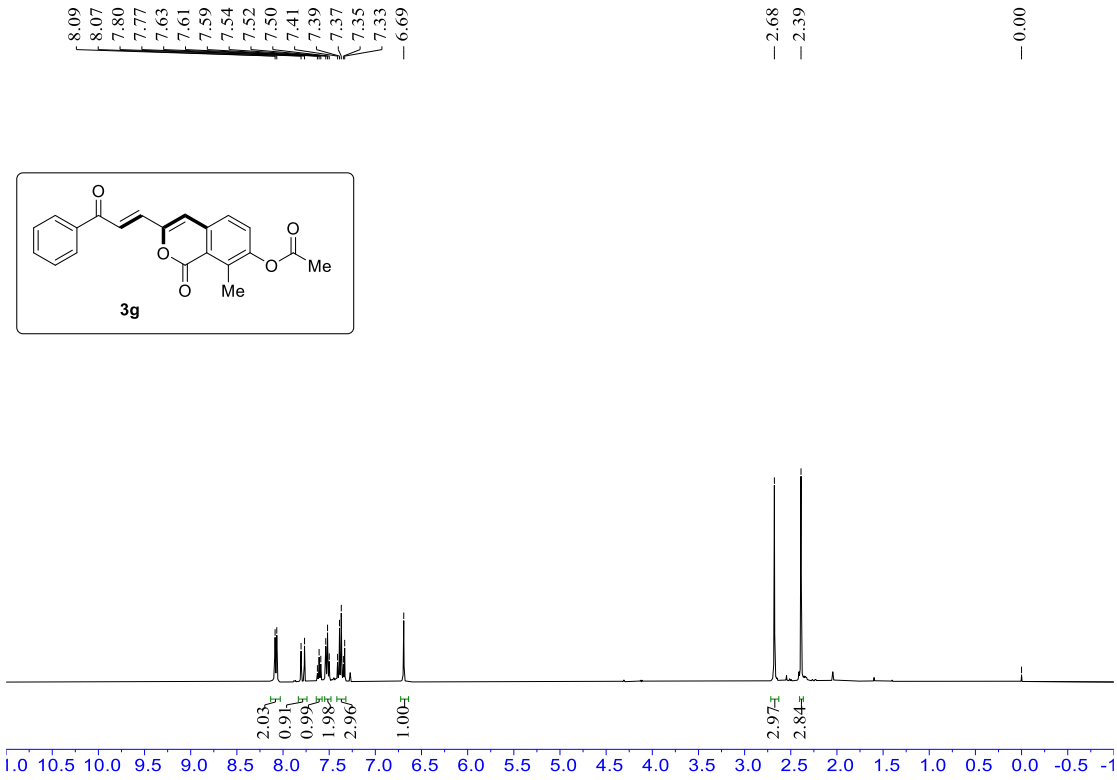
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3f**



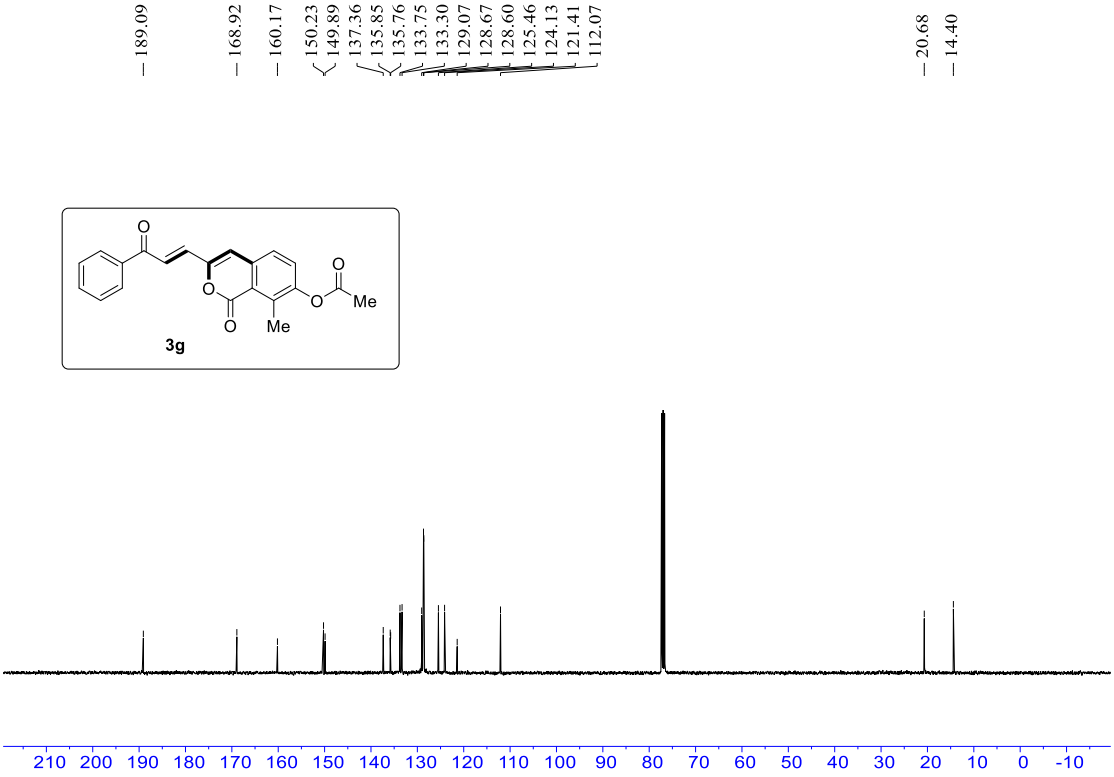
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3f**



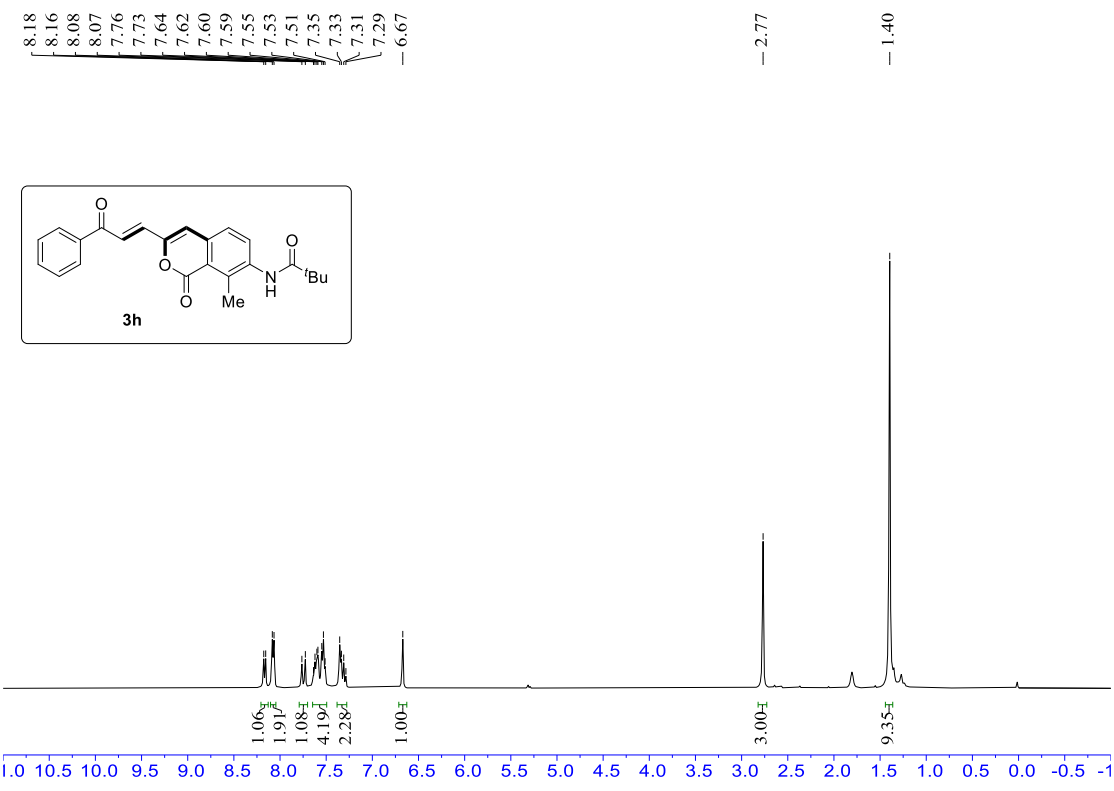
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **3f**



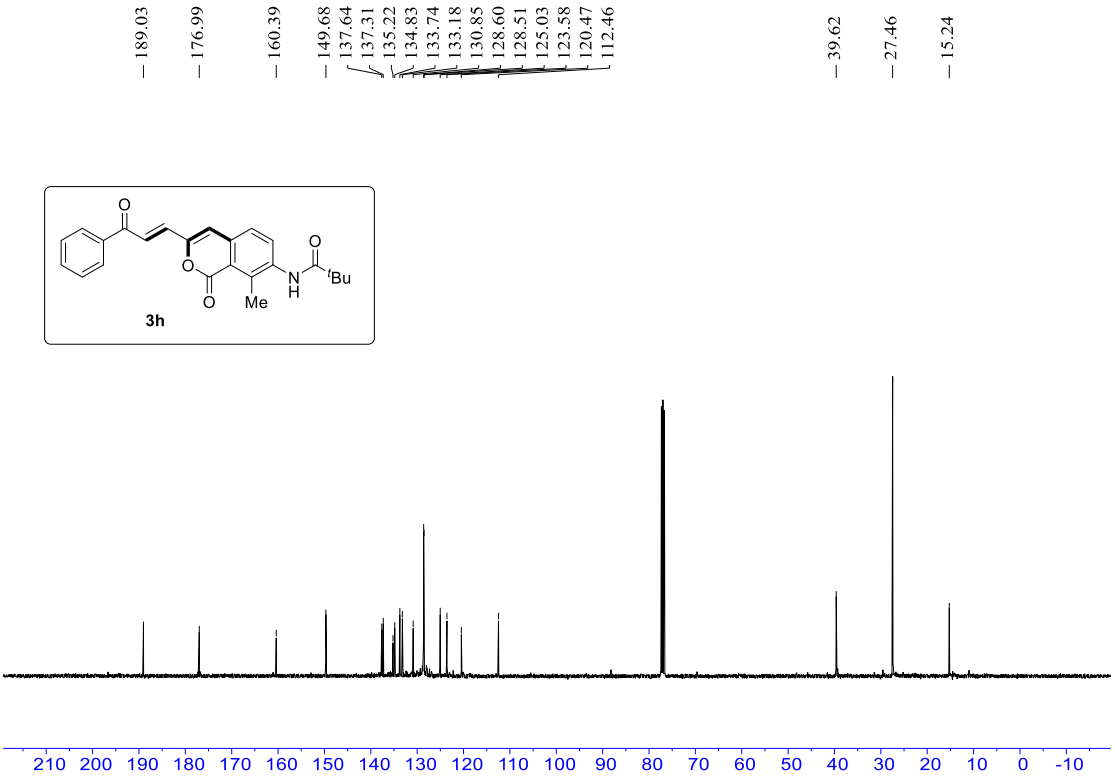
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3g**



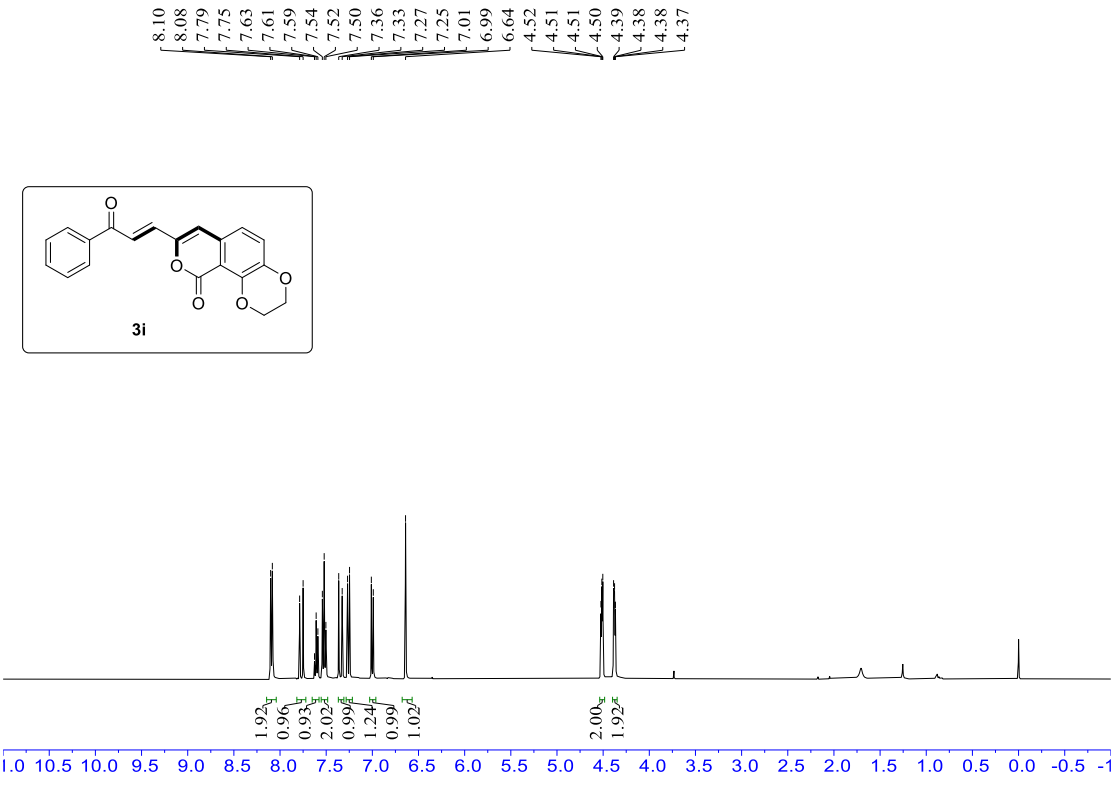
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3g**



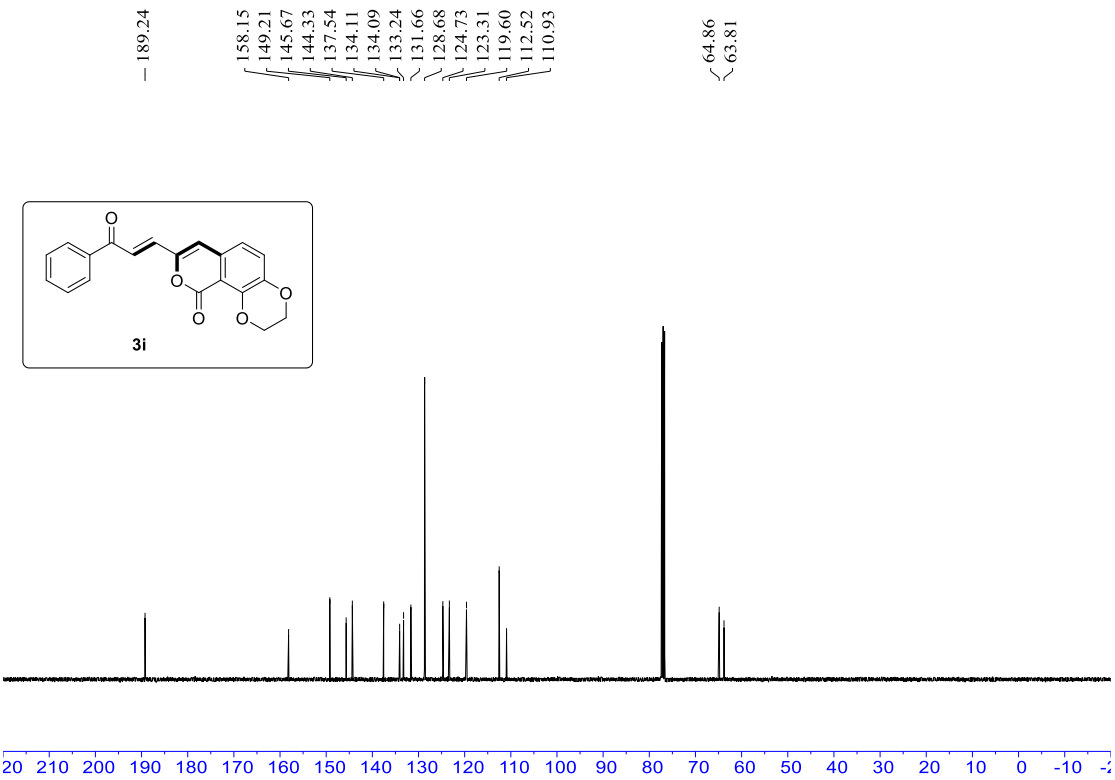
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3h**



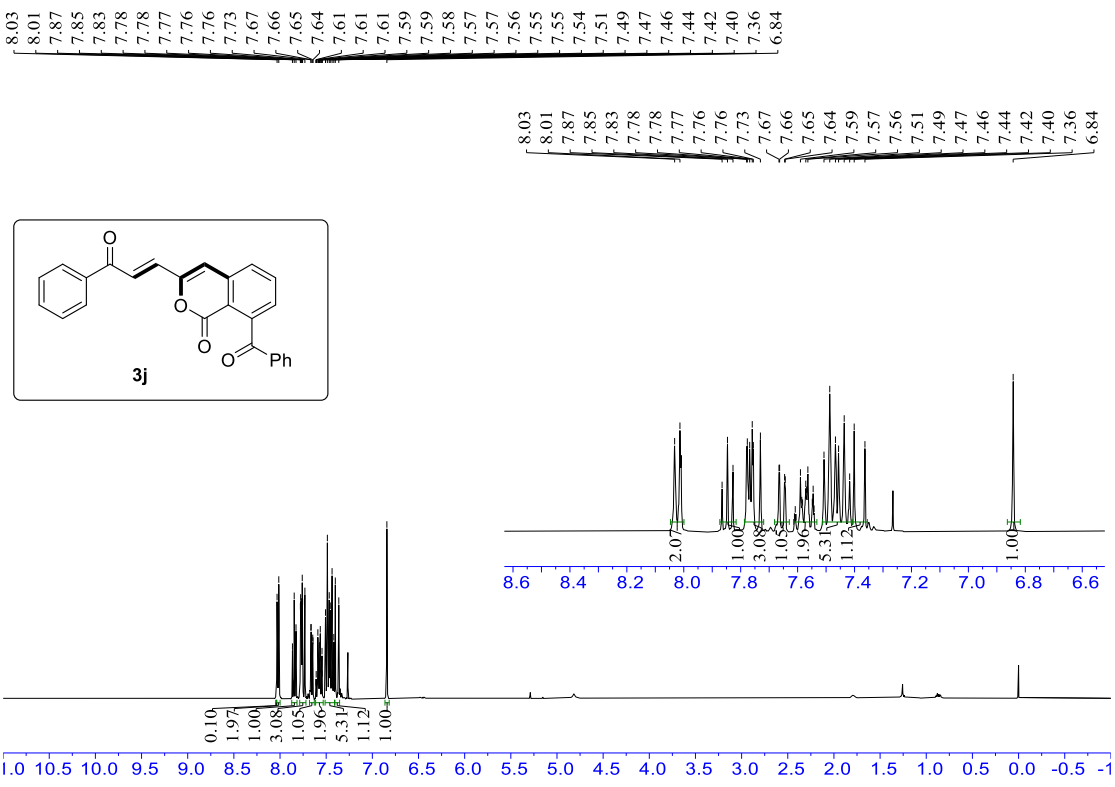
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3h**



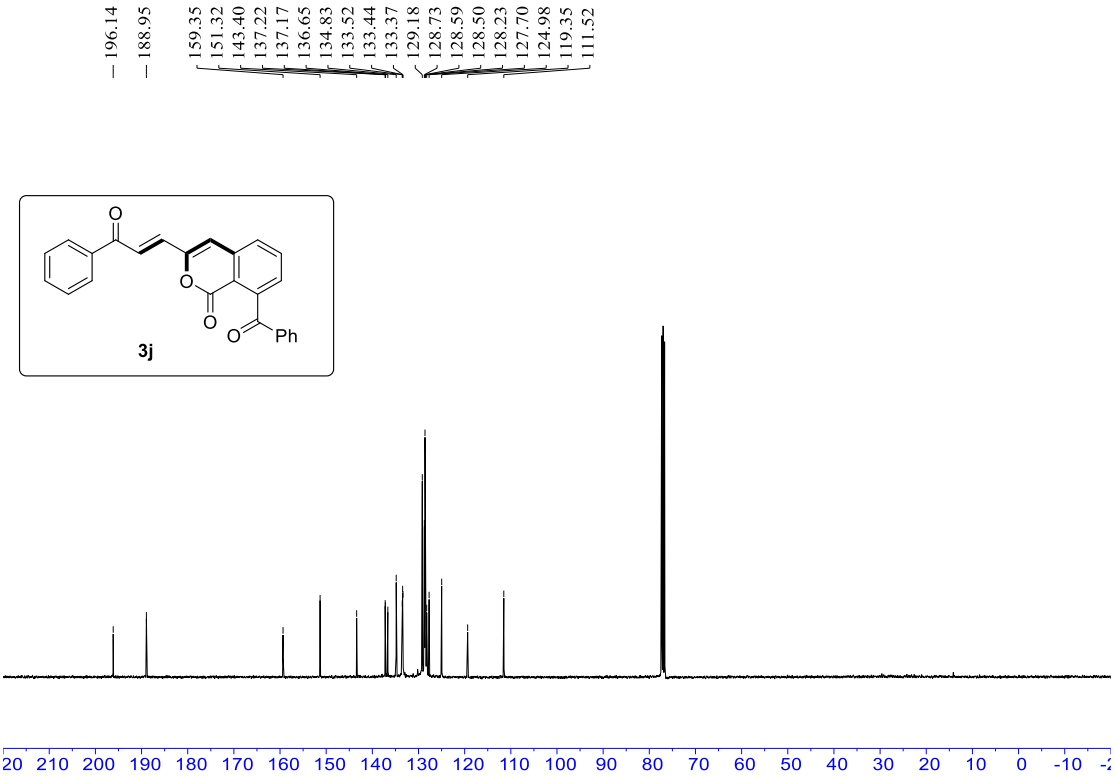
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3i**



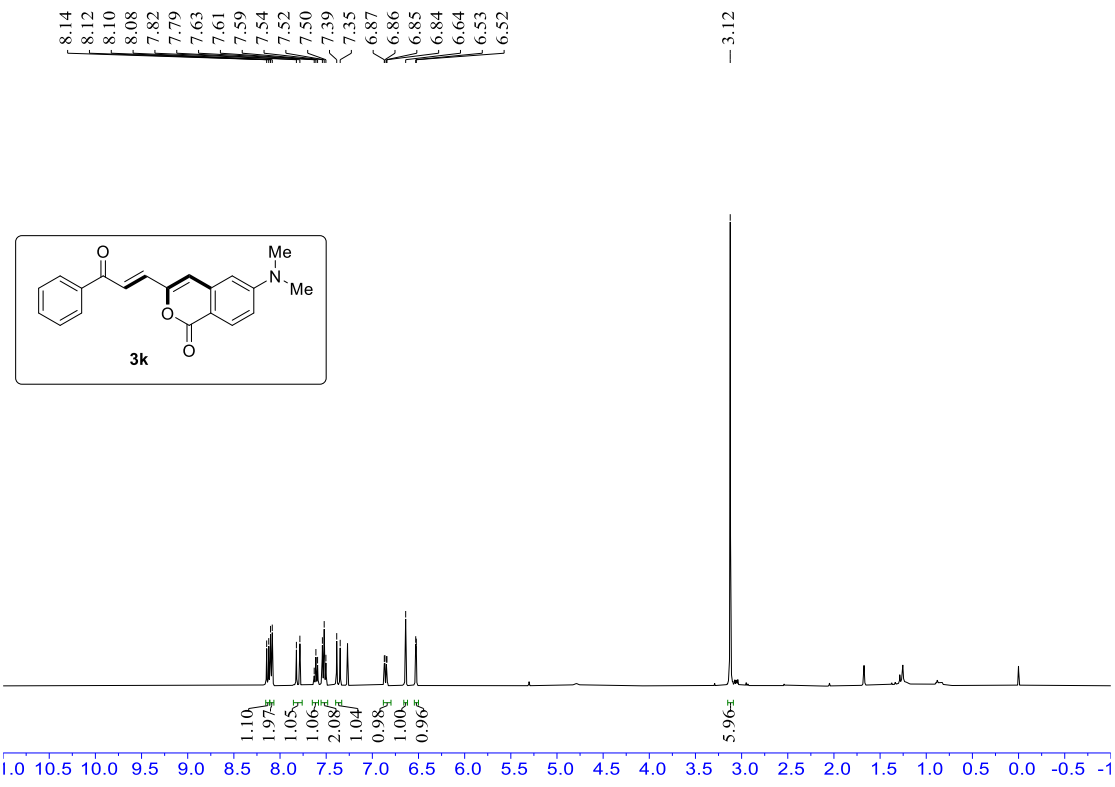
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3i**



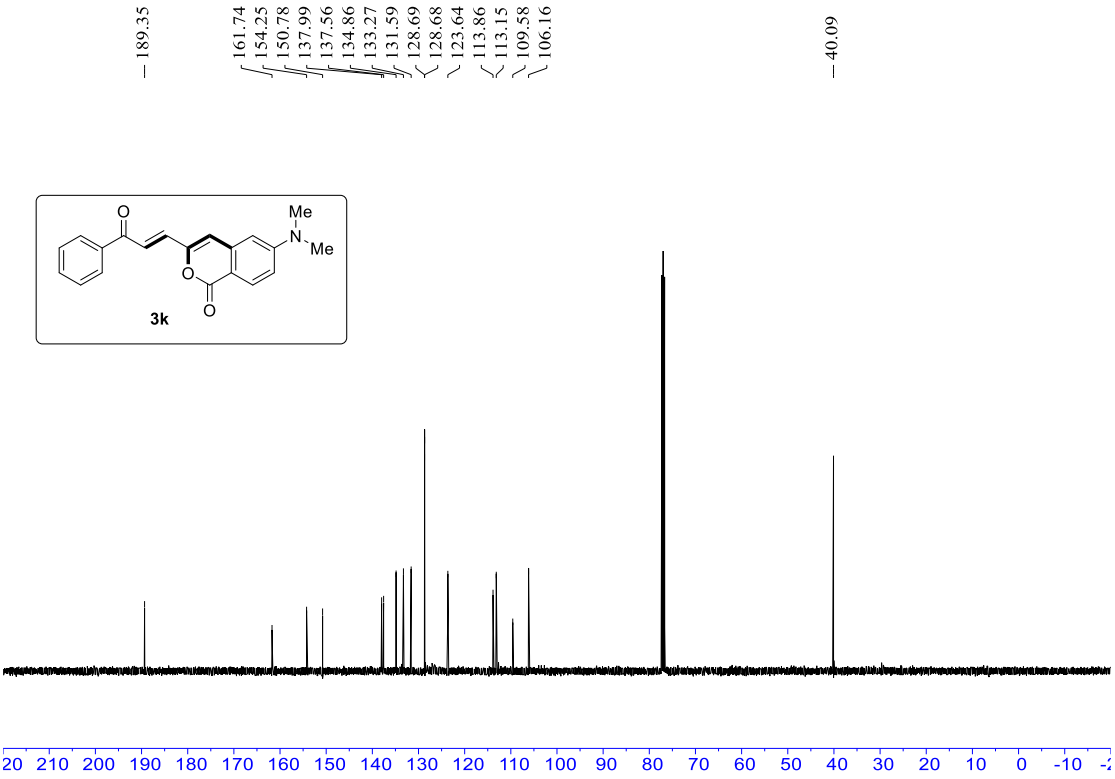
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3j**



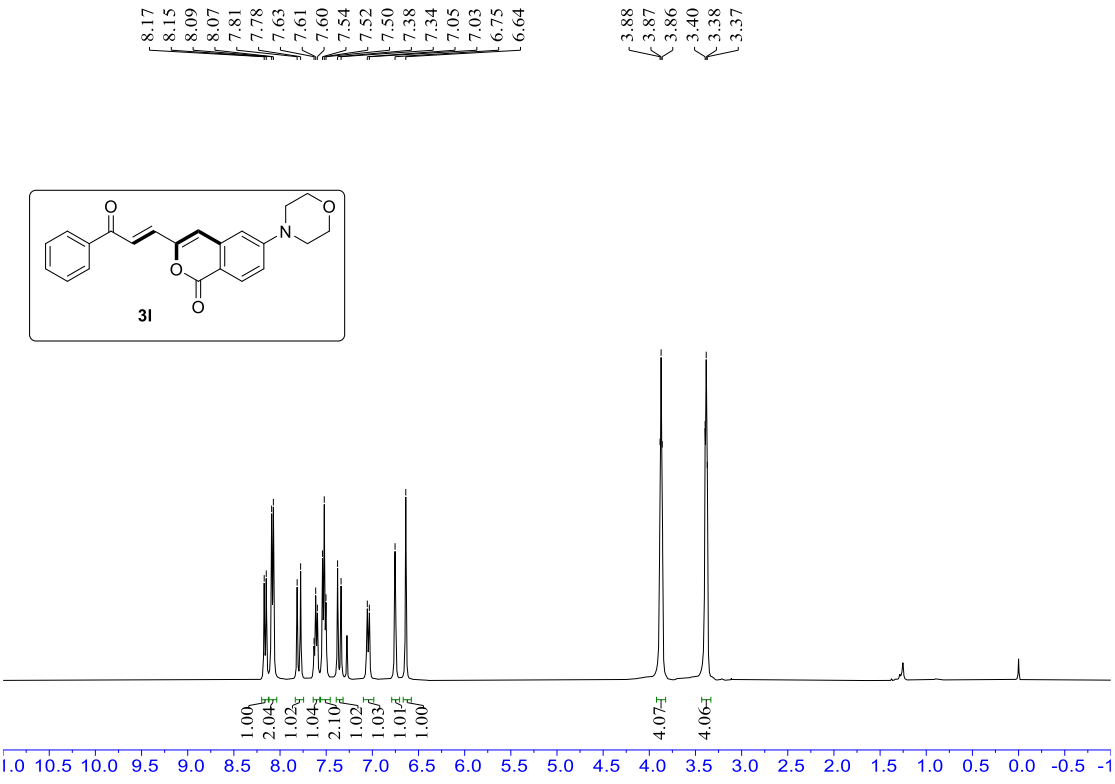
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3j**



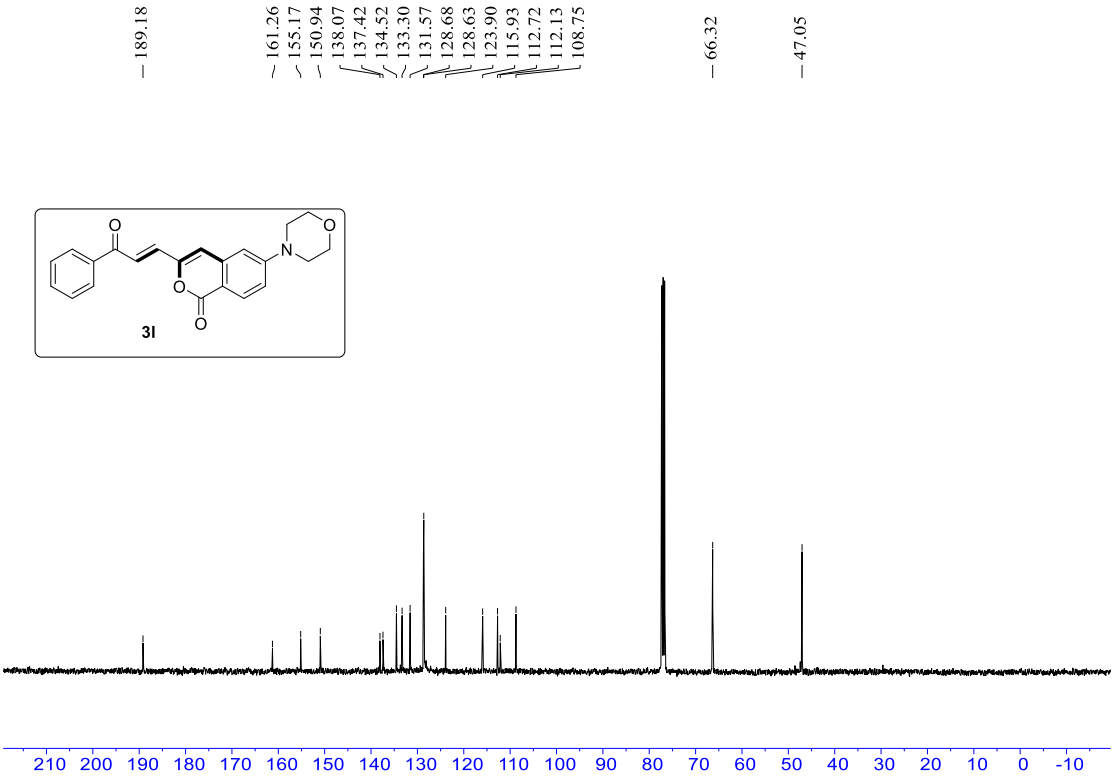
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3k**



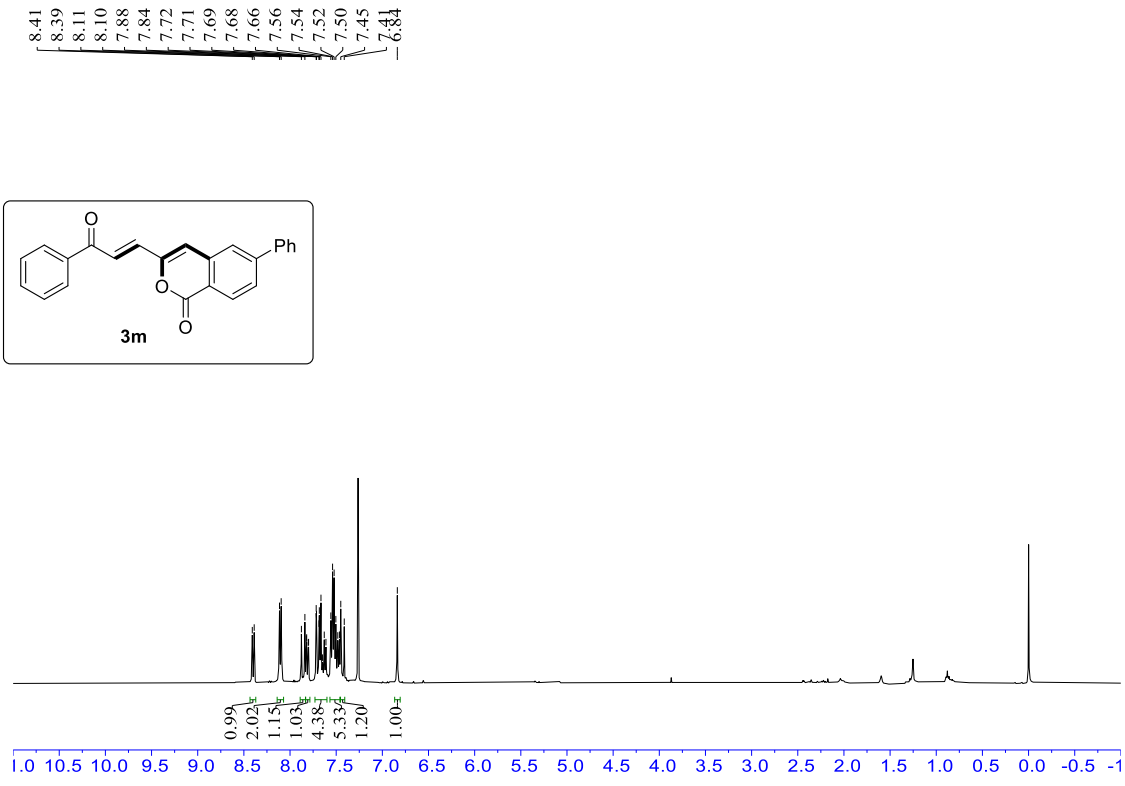
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3k**



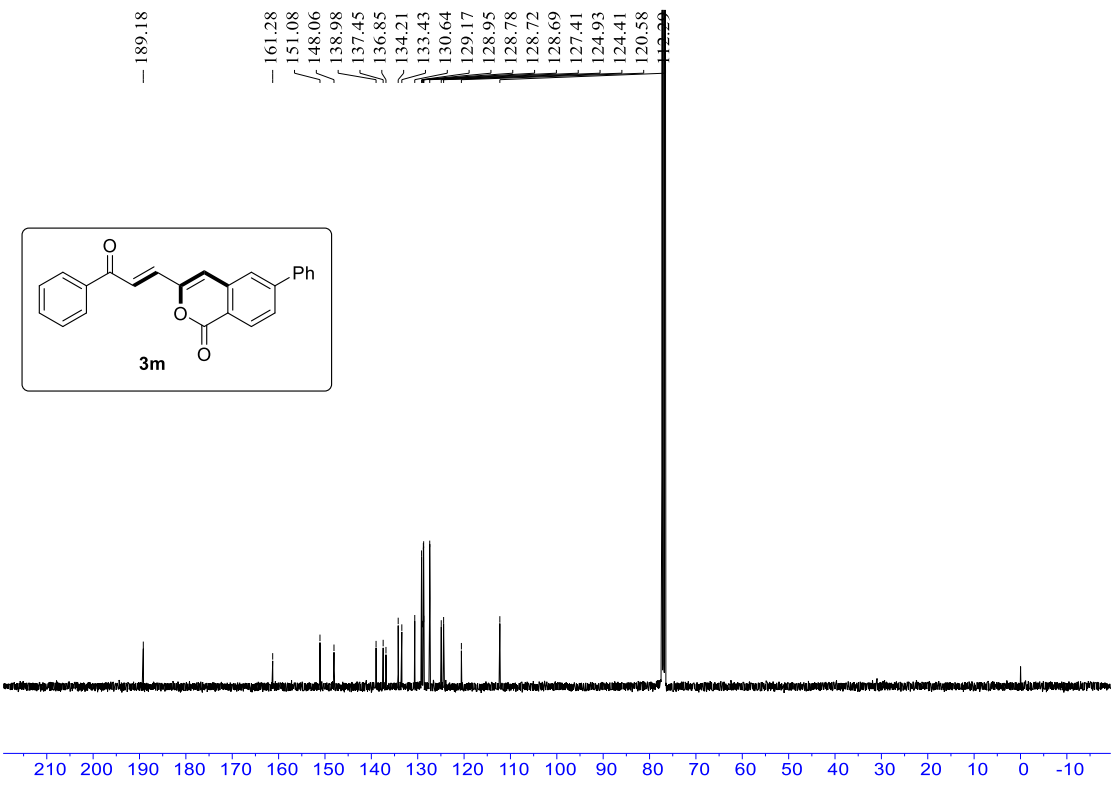
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3l**



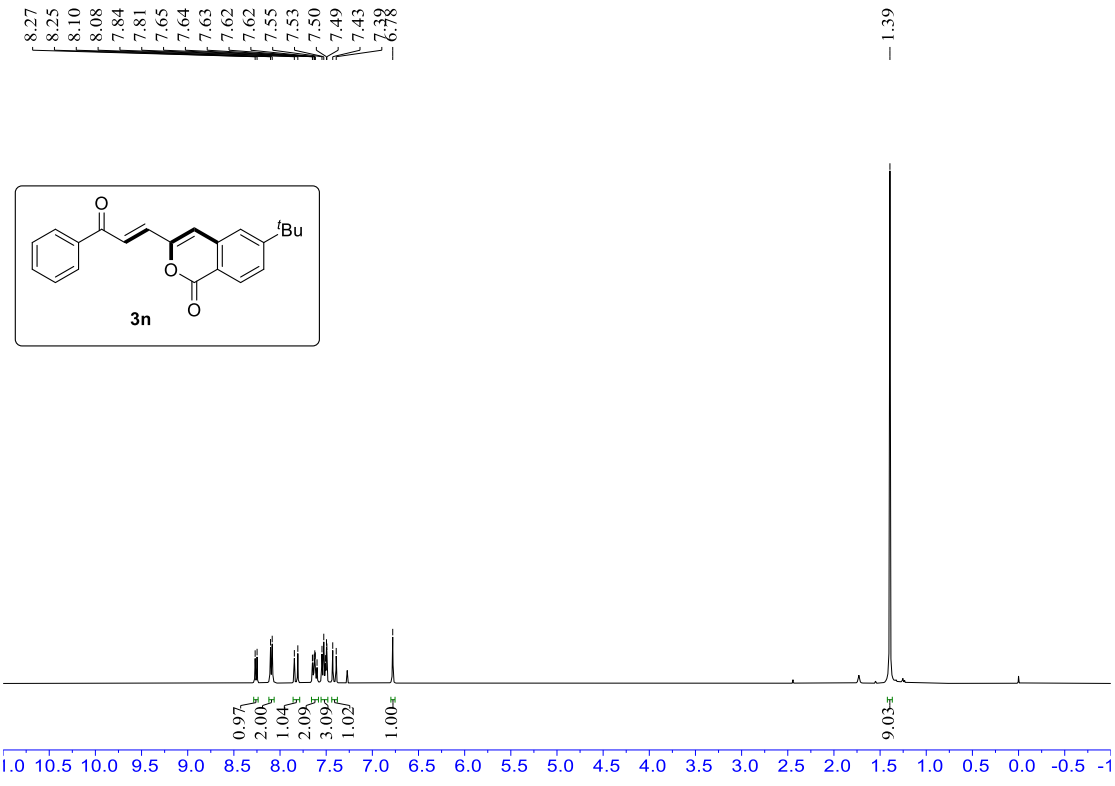
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3l**



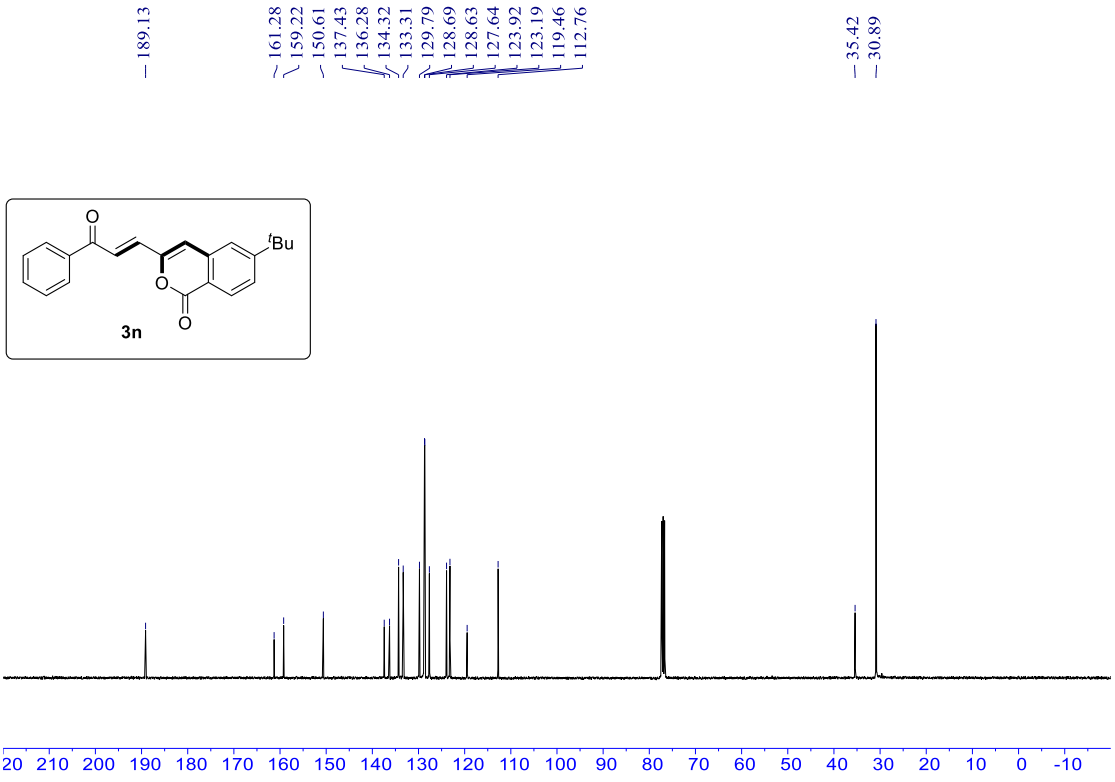
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3m**



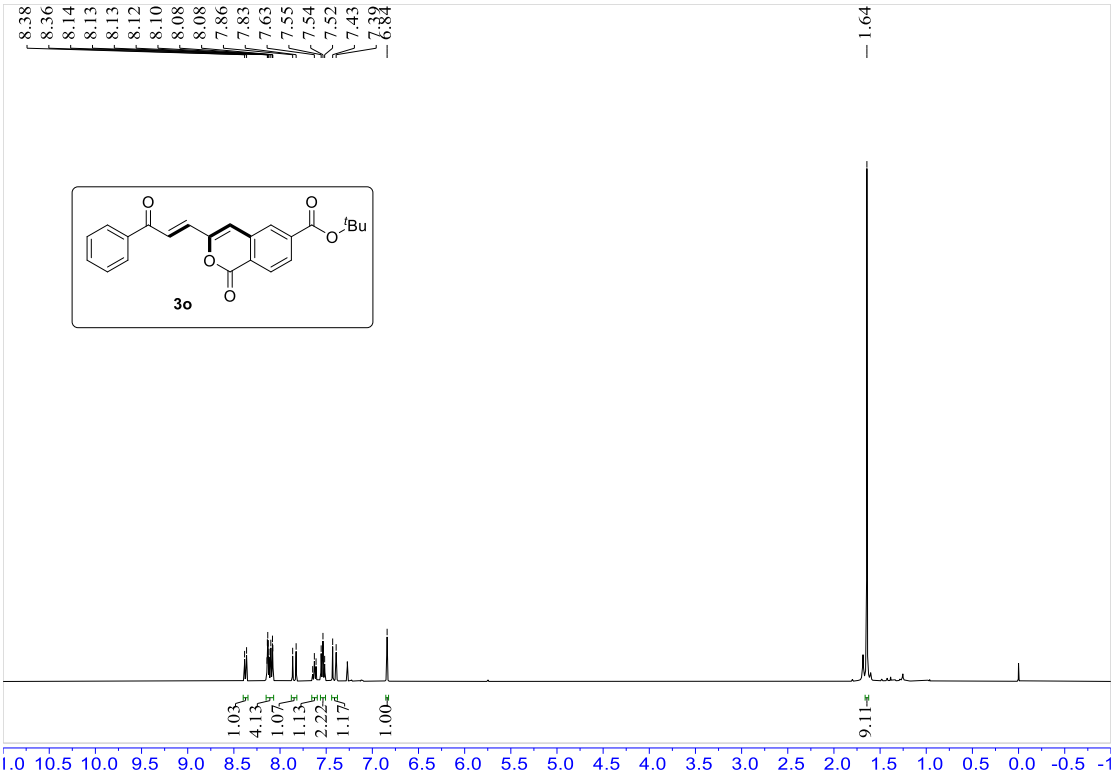
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3m**



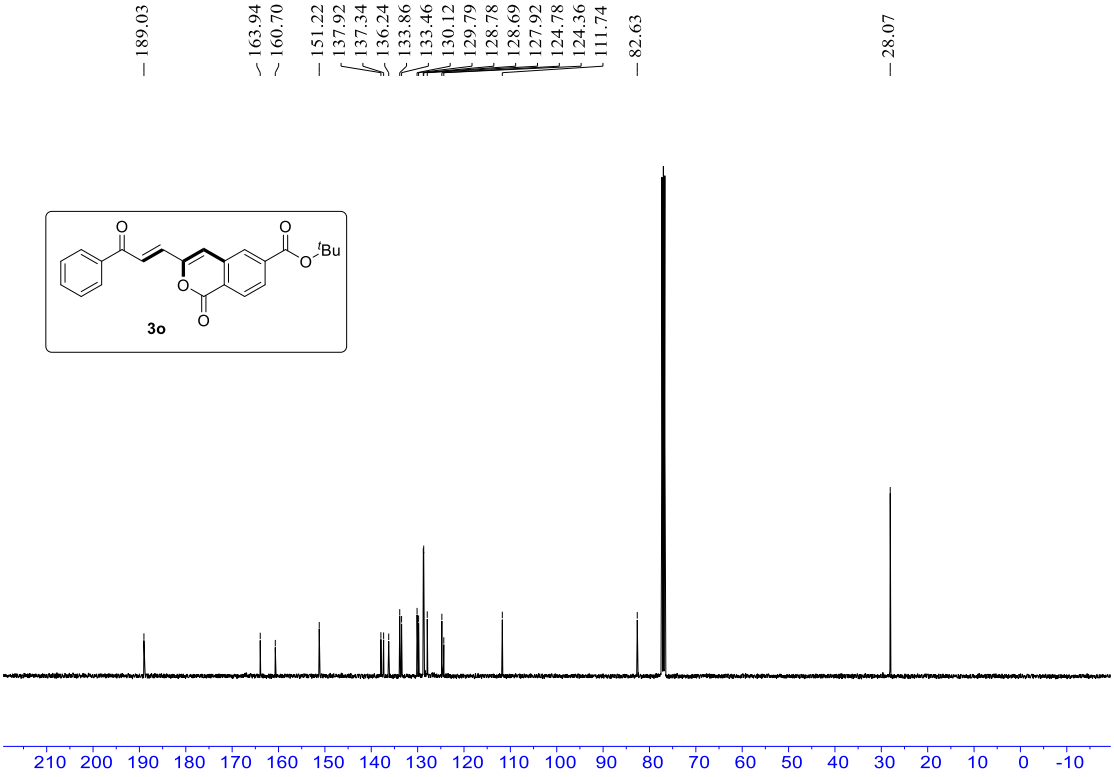
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3n**



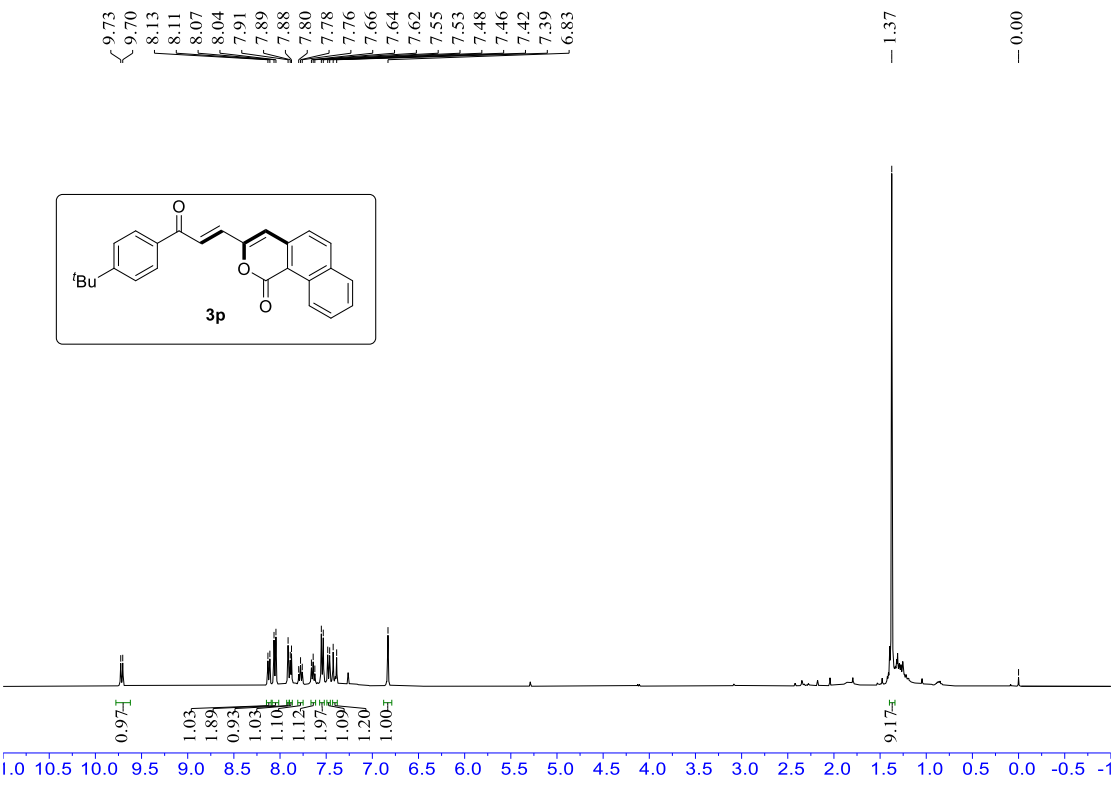
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3n**



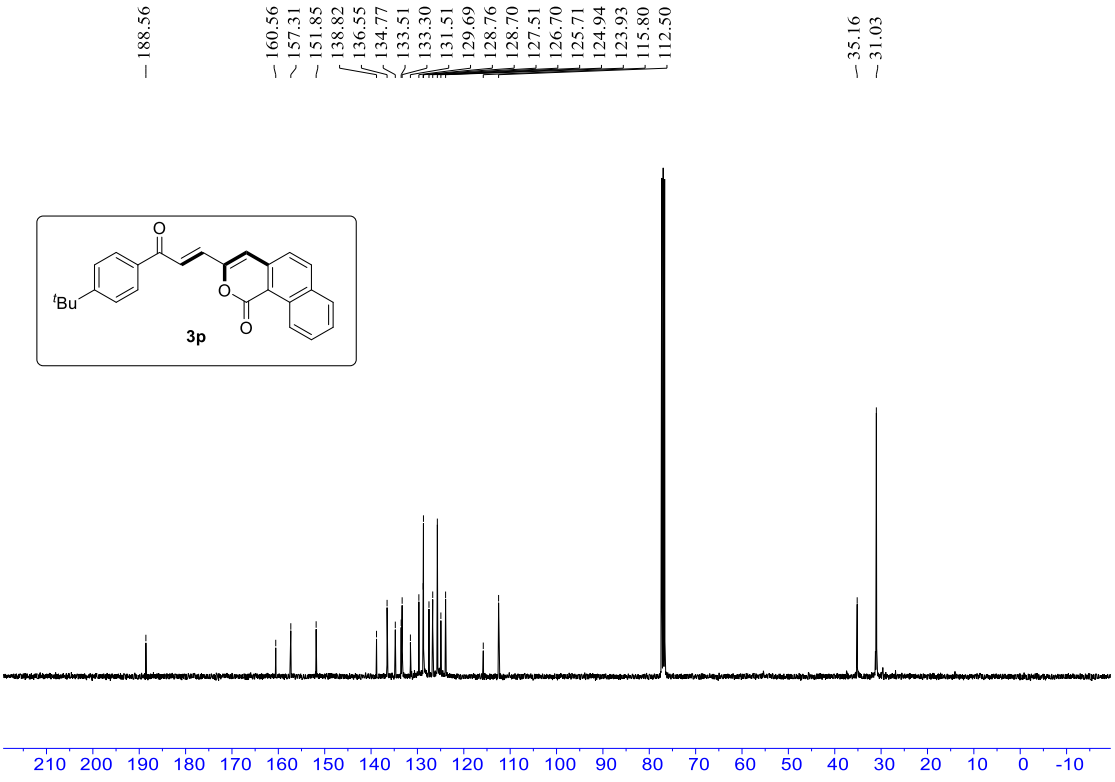
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3o**



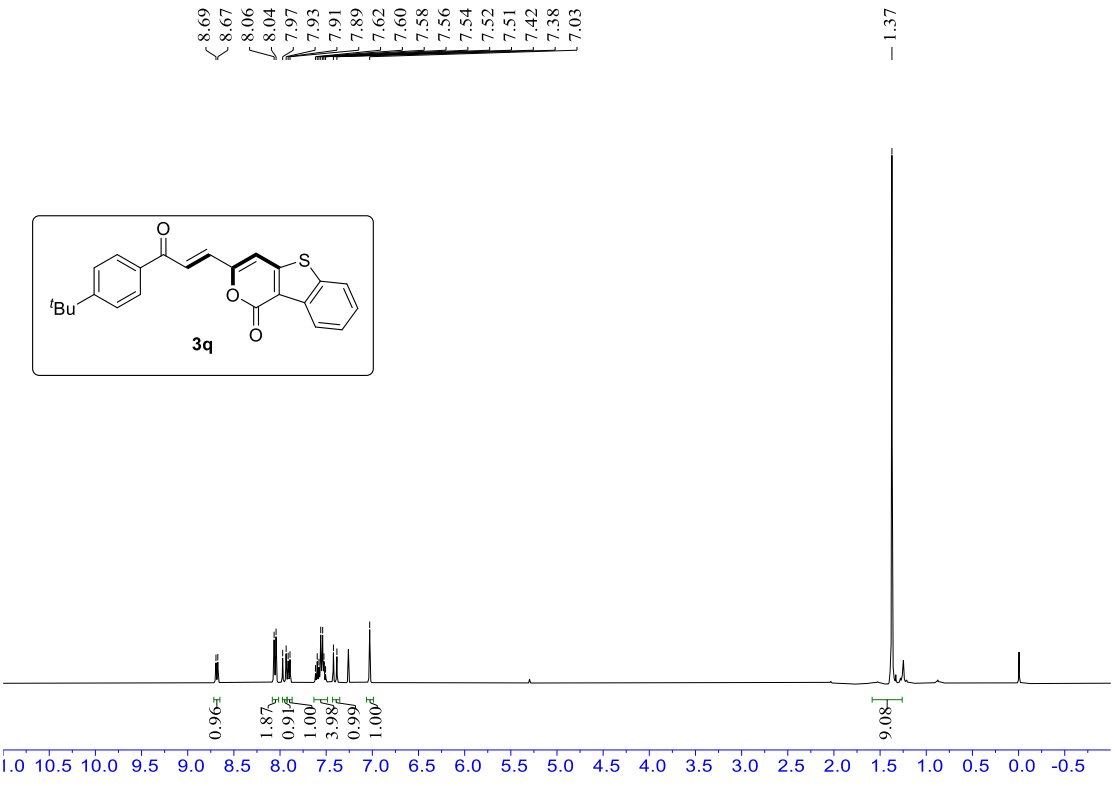
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3o**



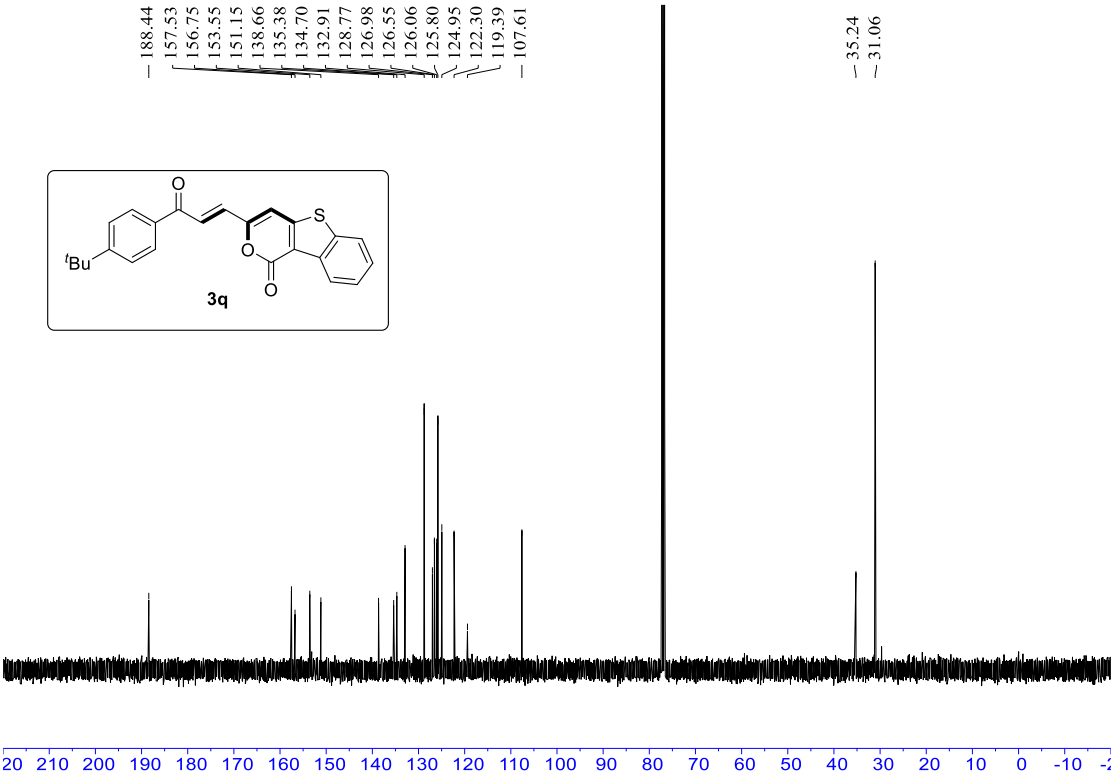
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3p**



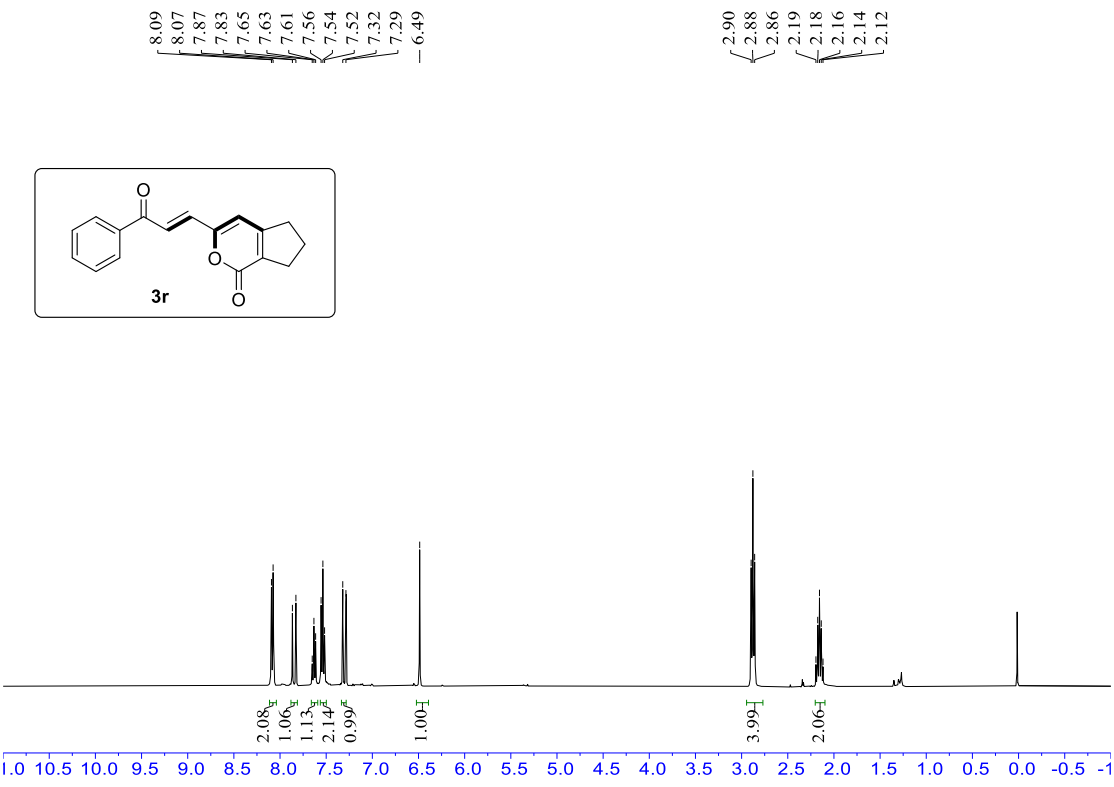
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3p**



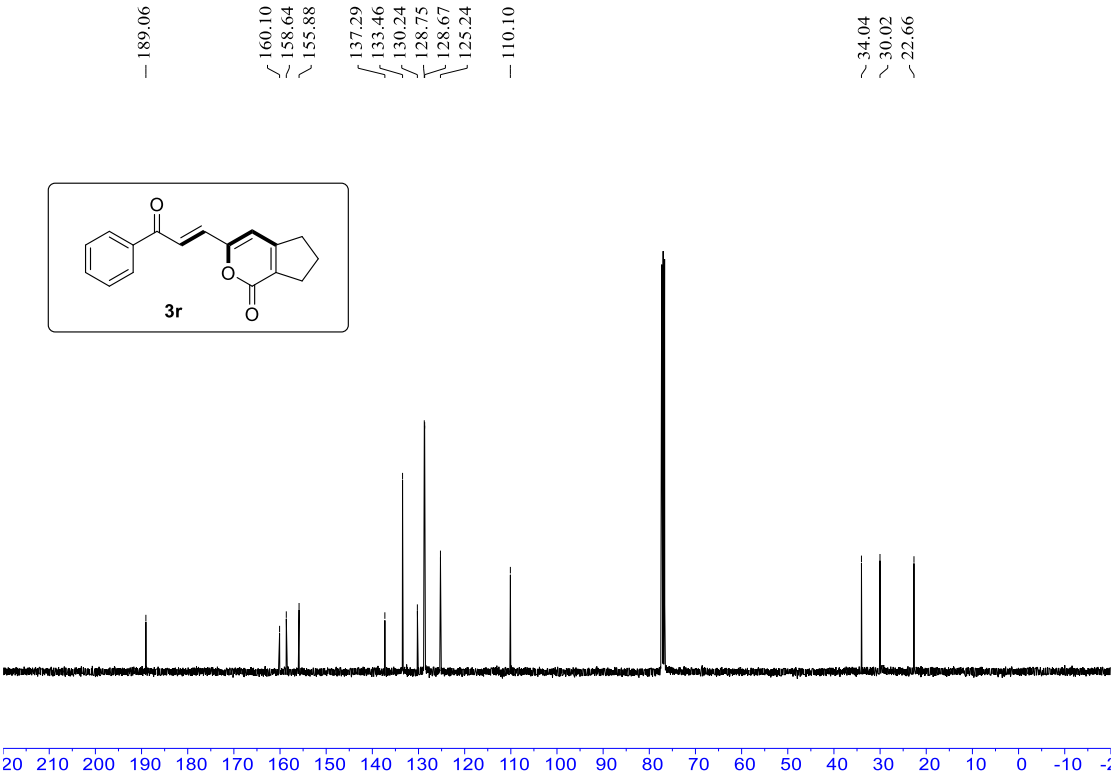
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3q**



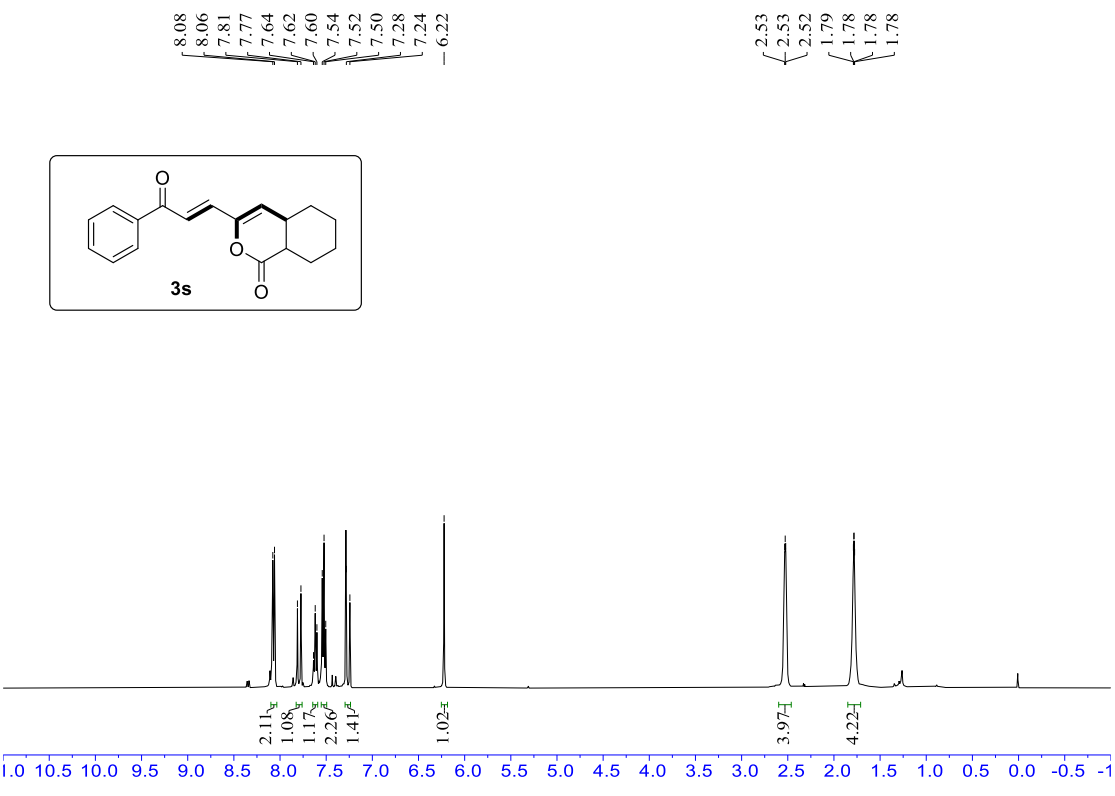
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3q**



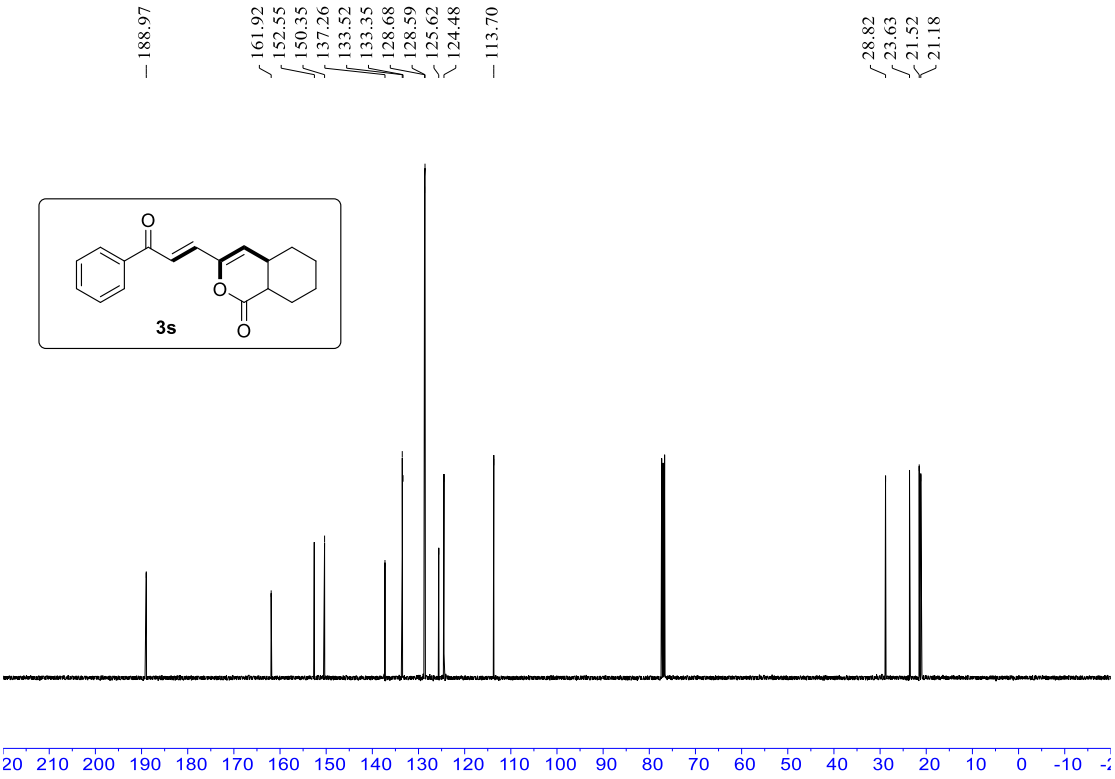
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3r**



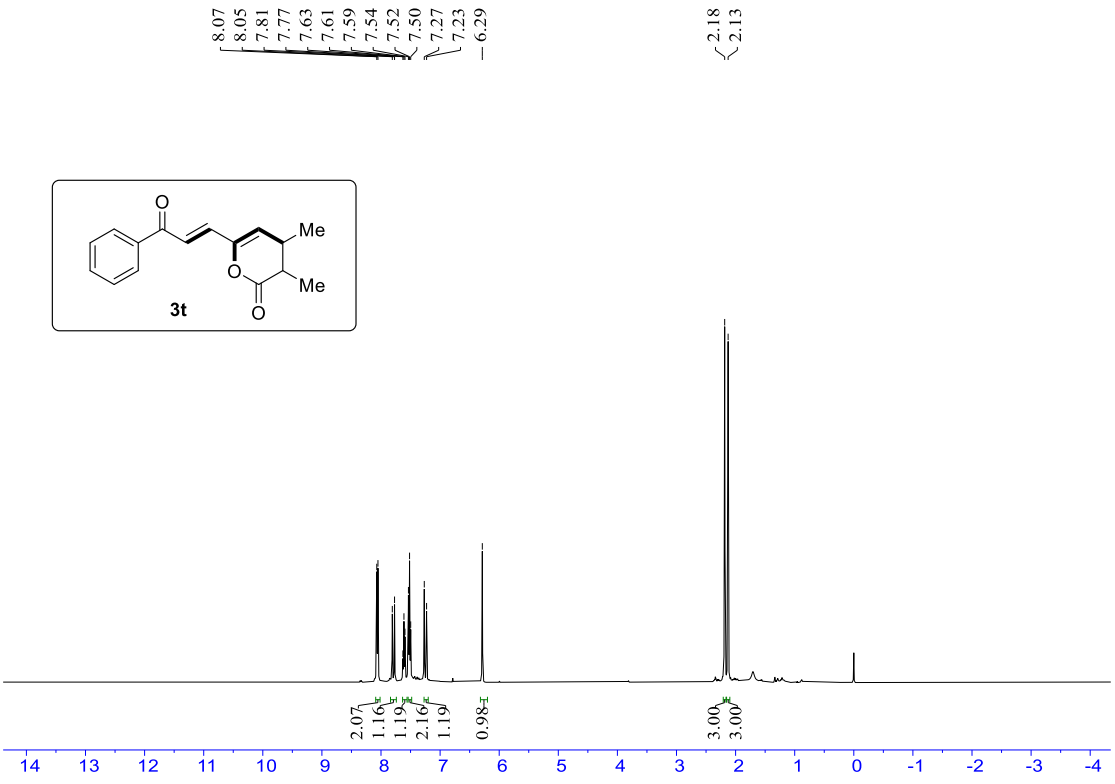
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3r**



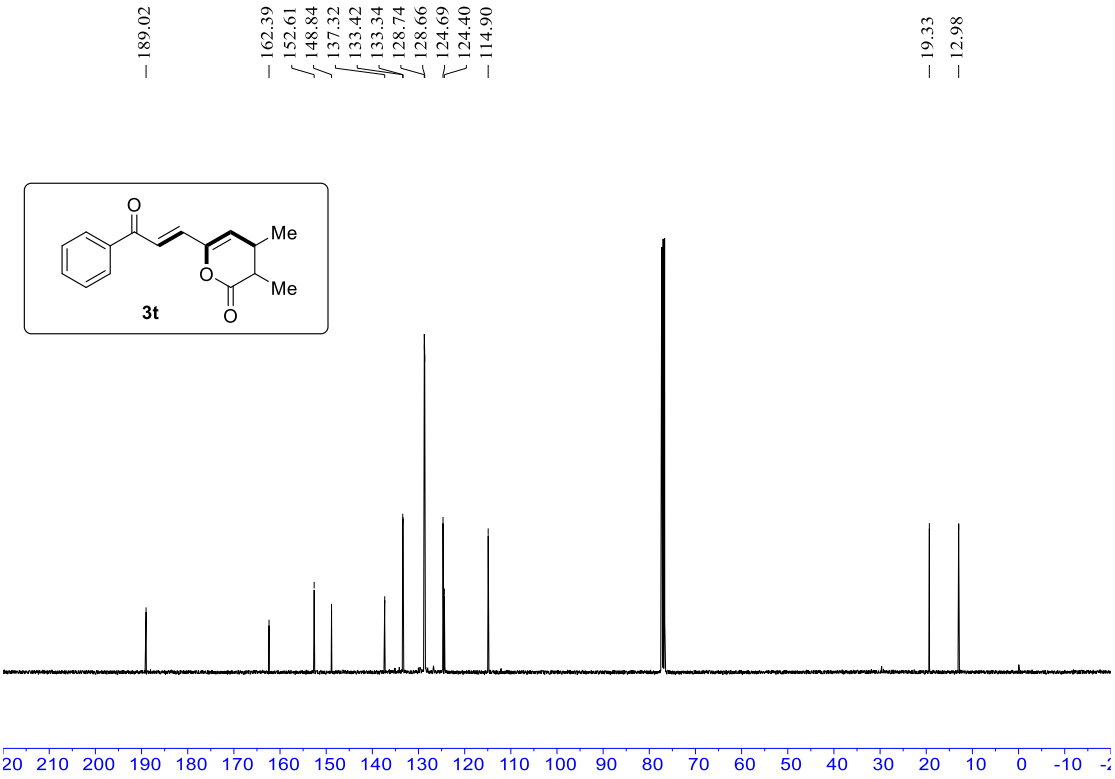
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3s**



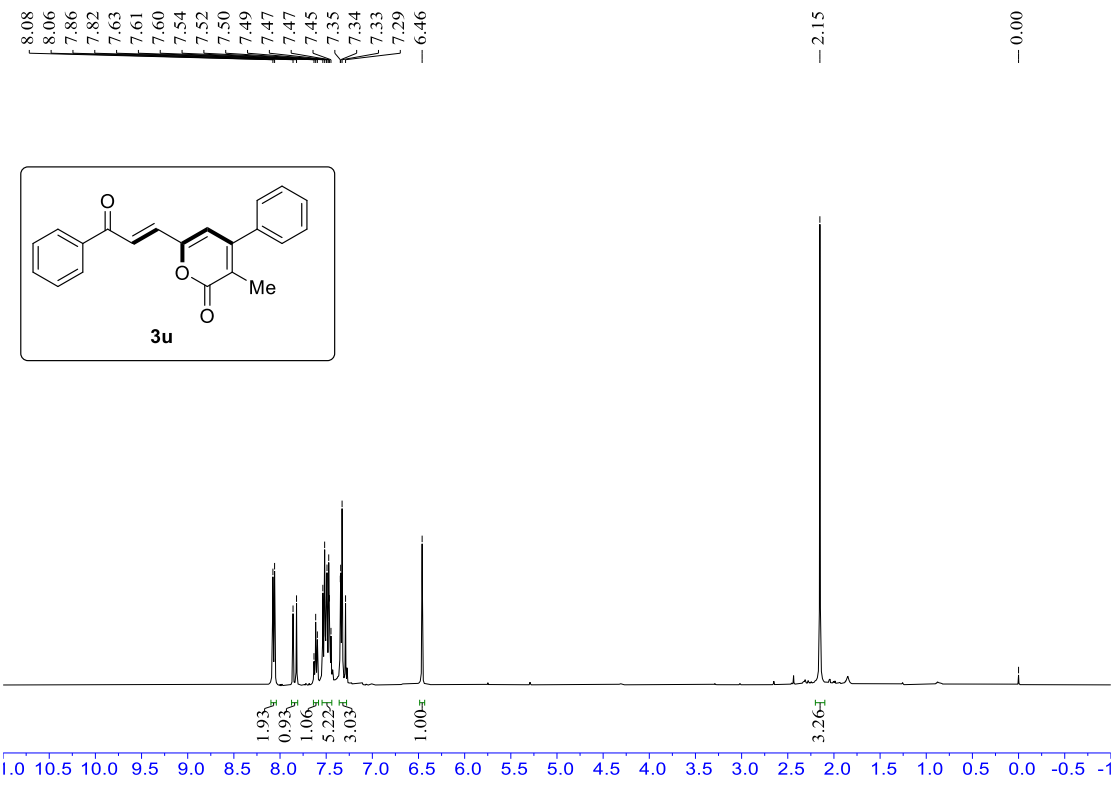
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3s**



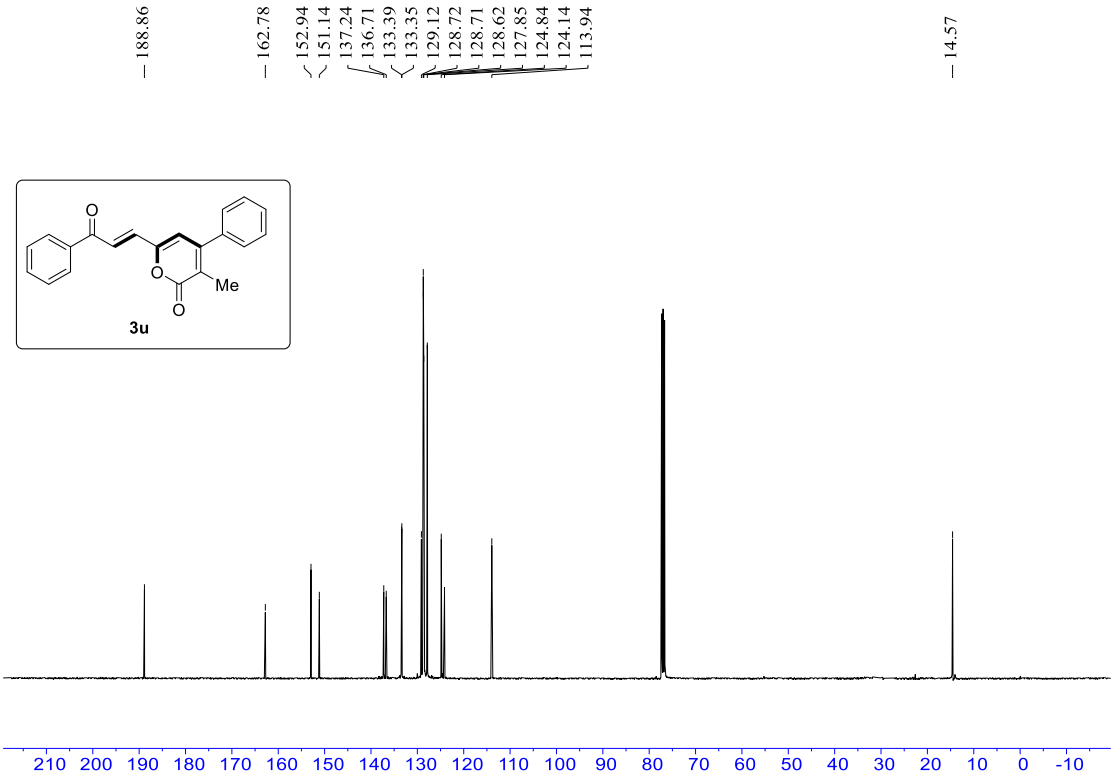
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3t**



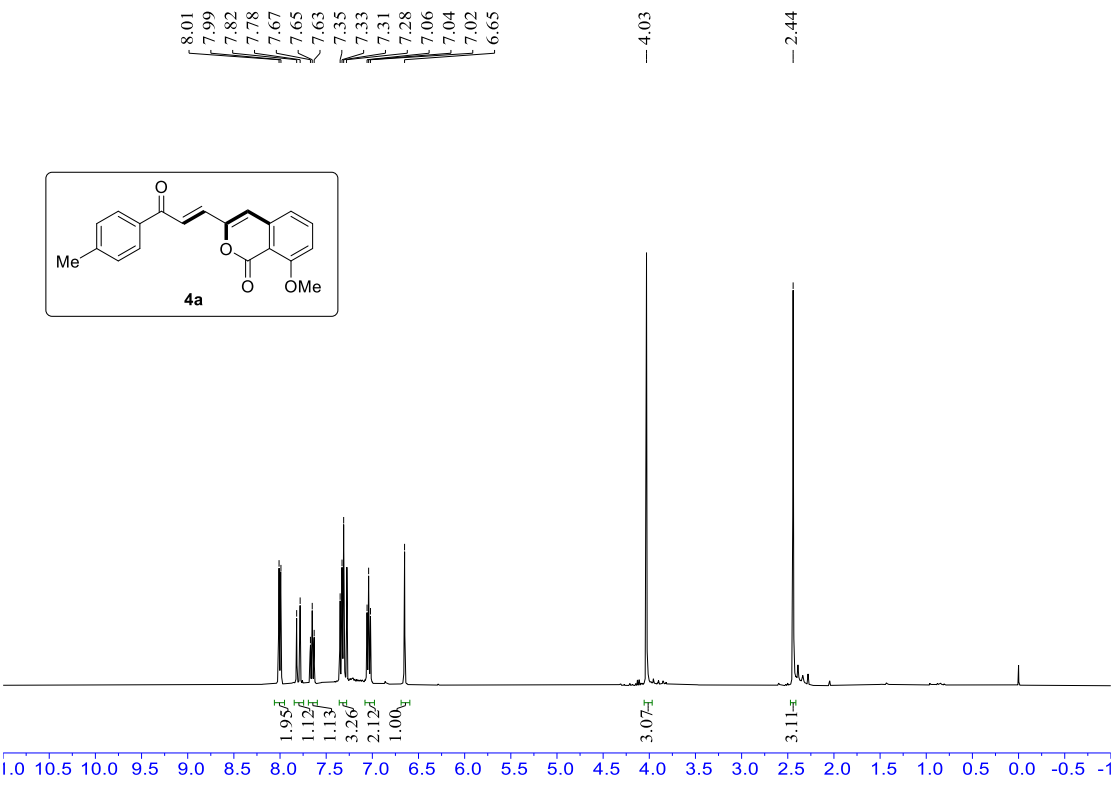
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3t**



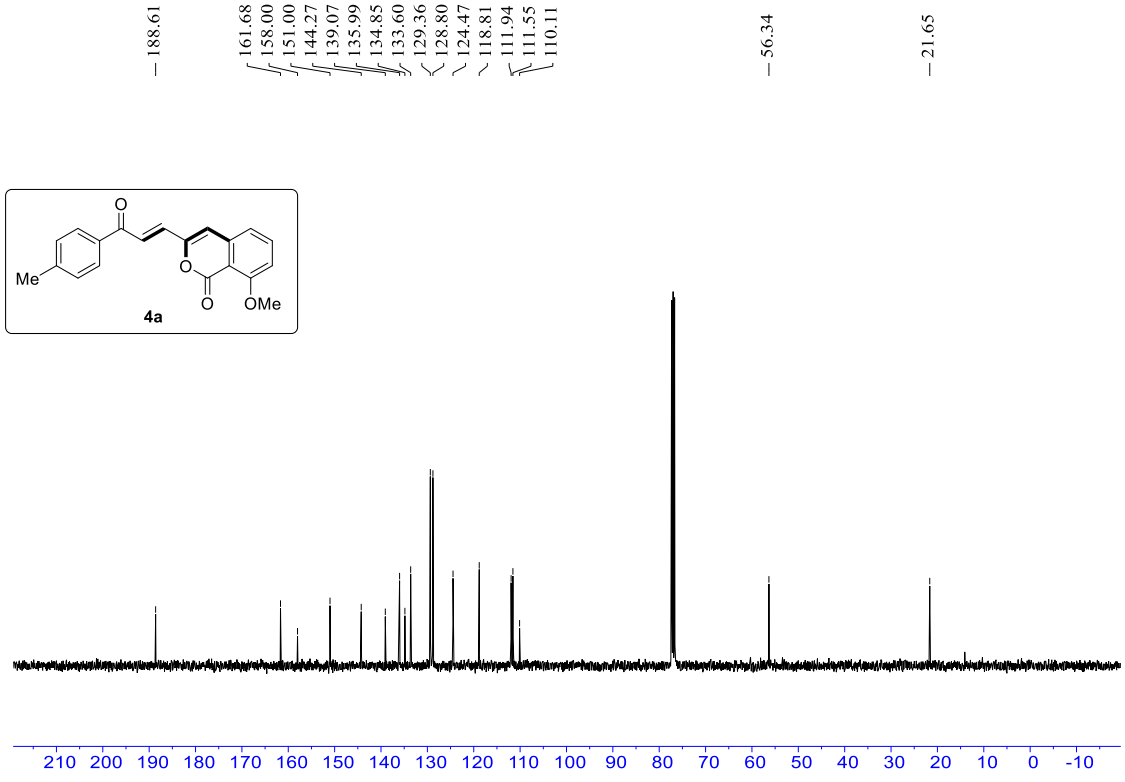
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3u**



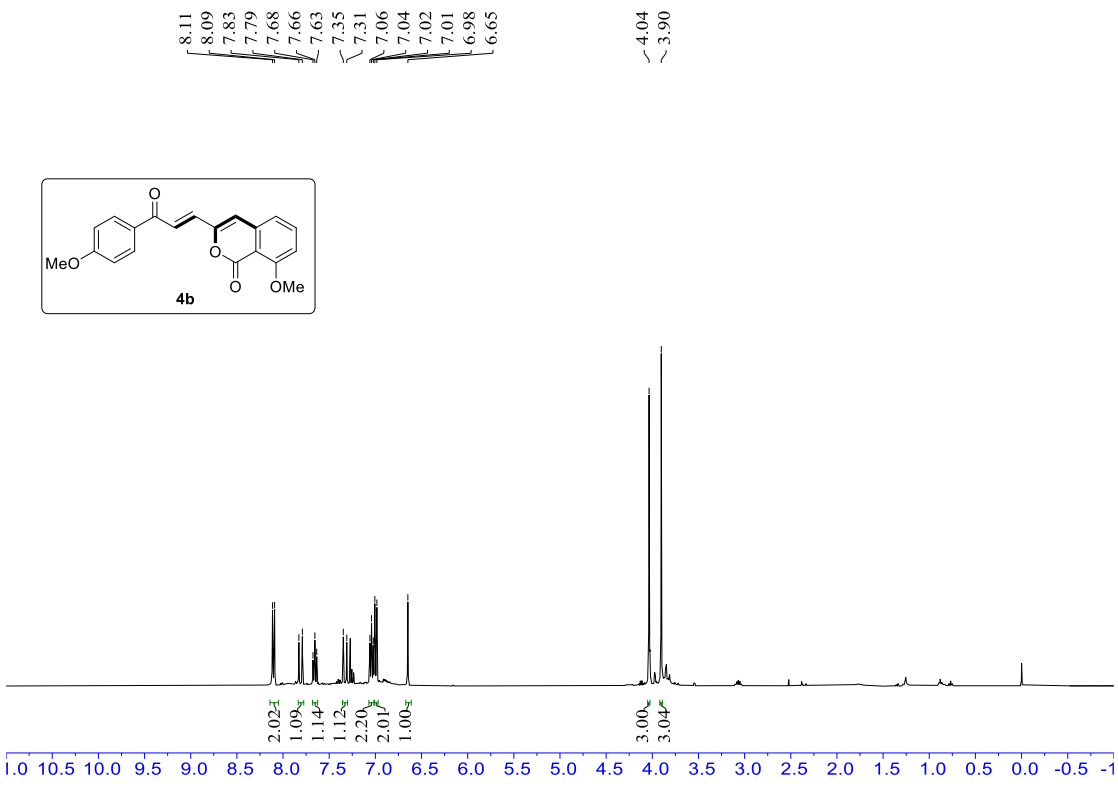
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3u**



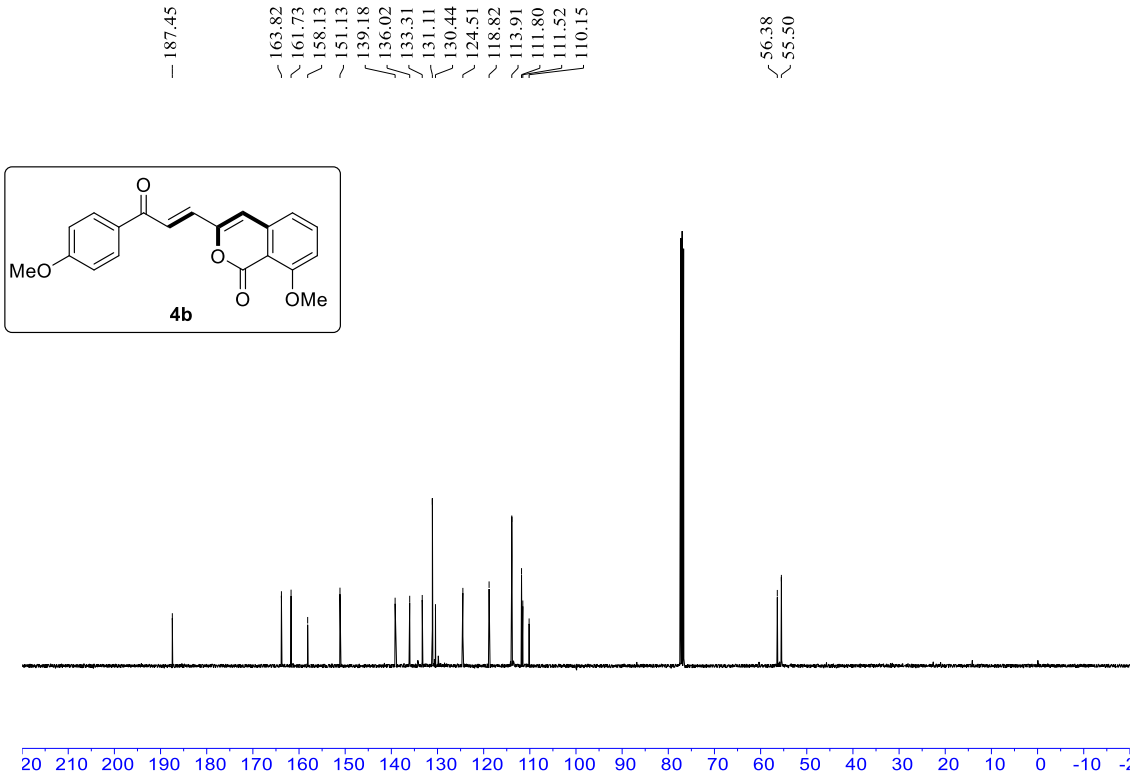
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4a**



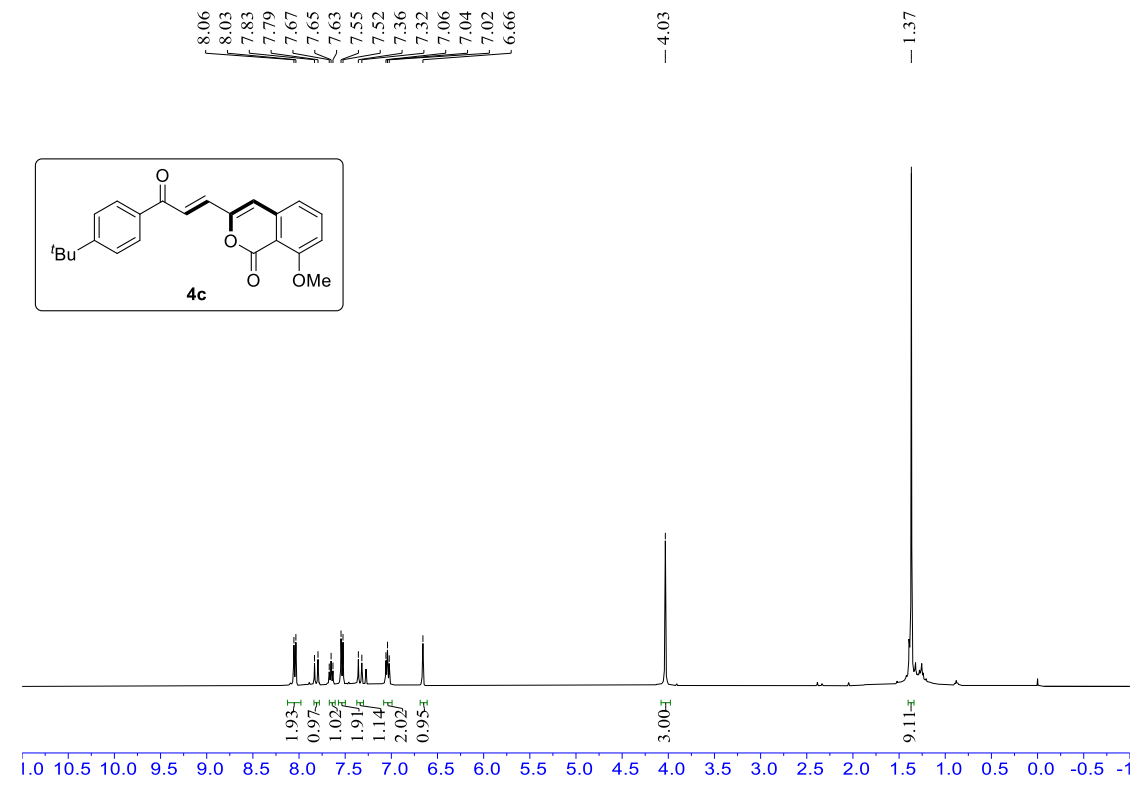
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4a**



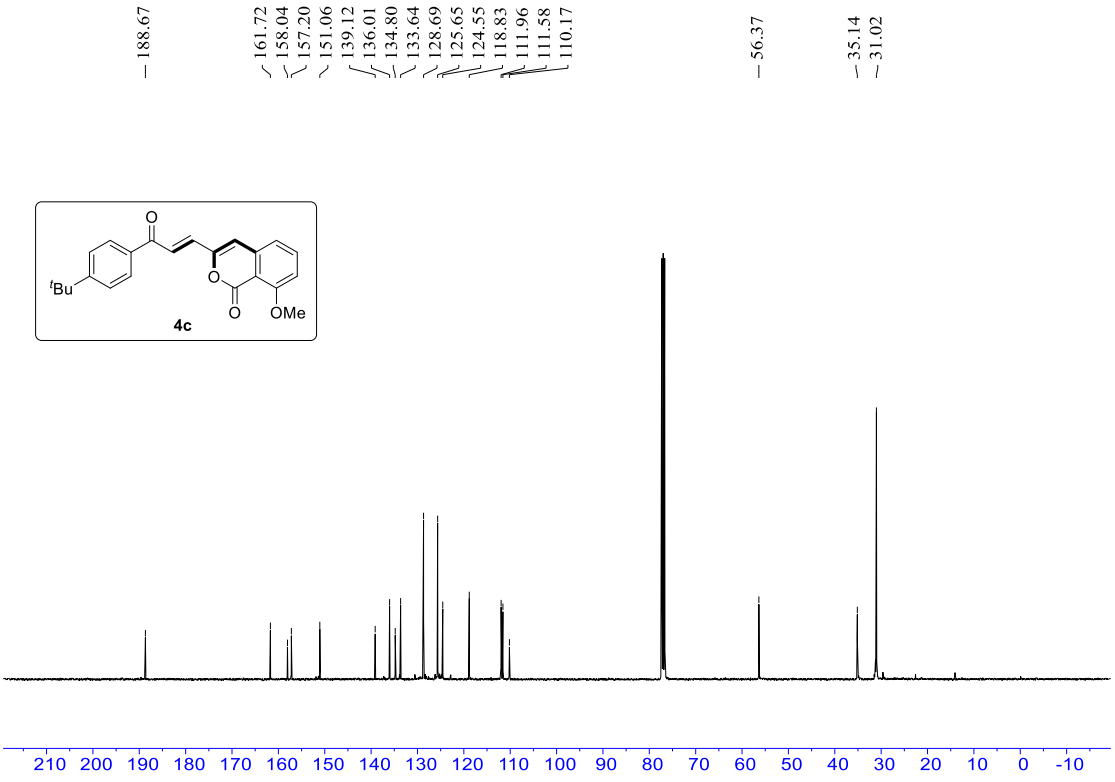
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4b**



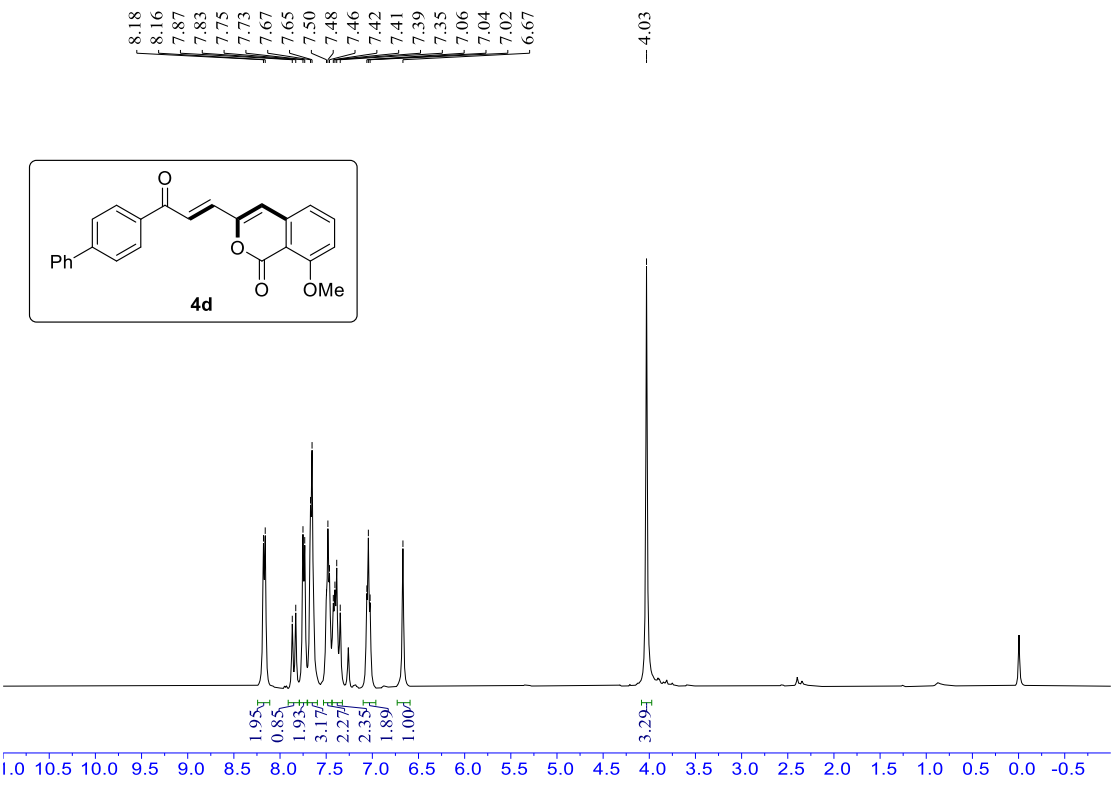
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4b**



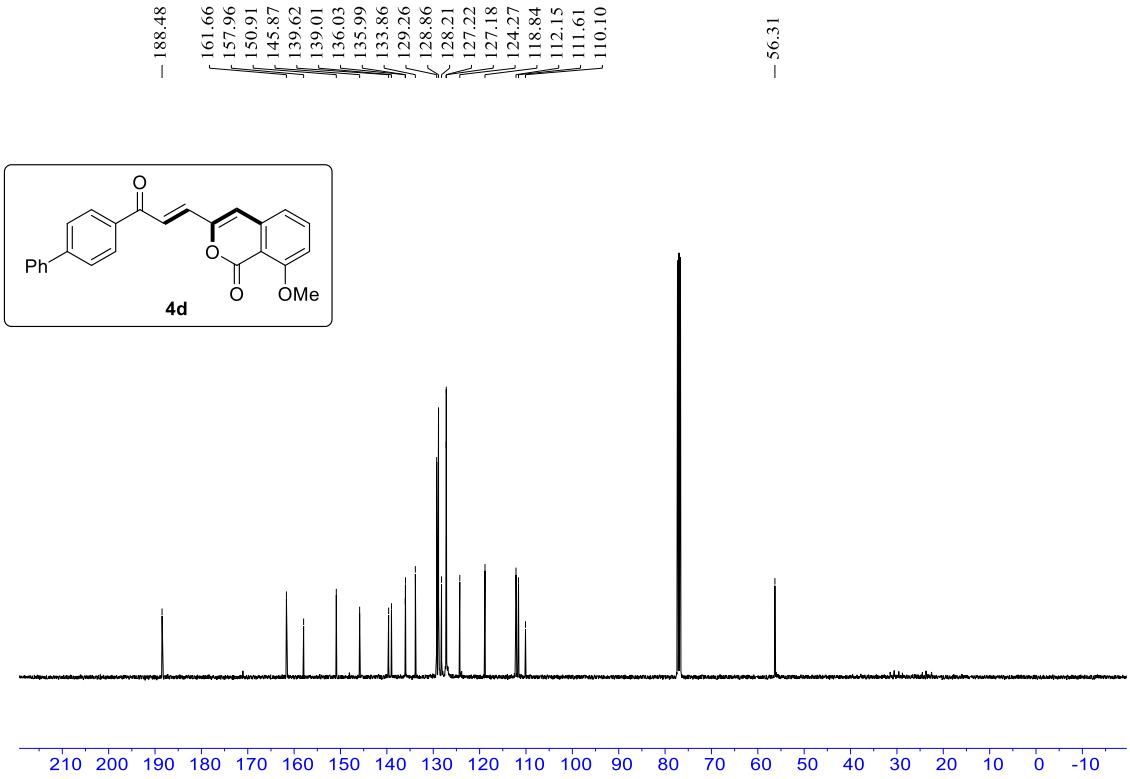
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4c**



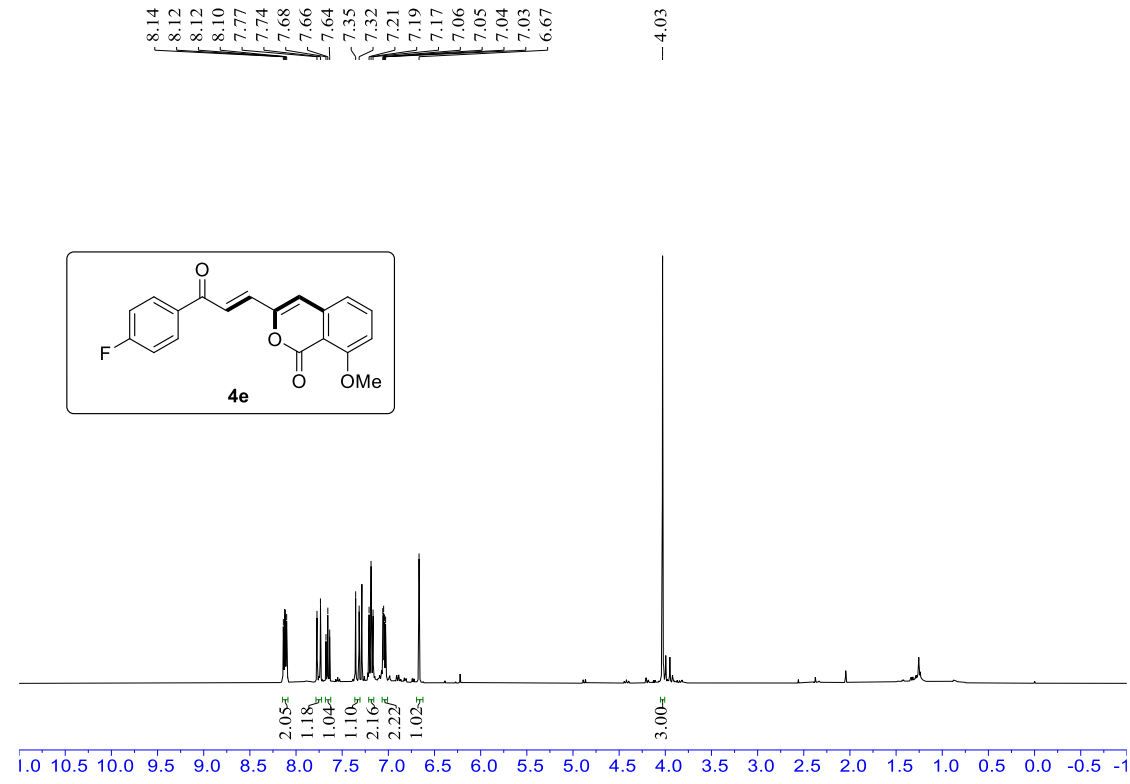
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4c**



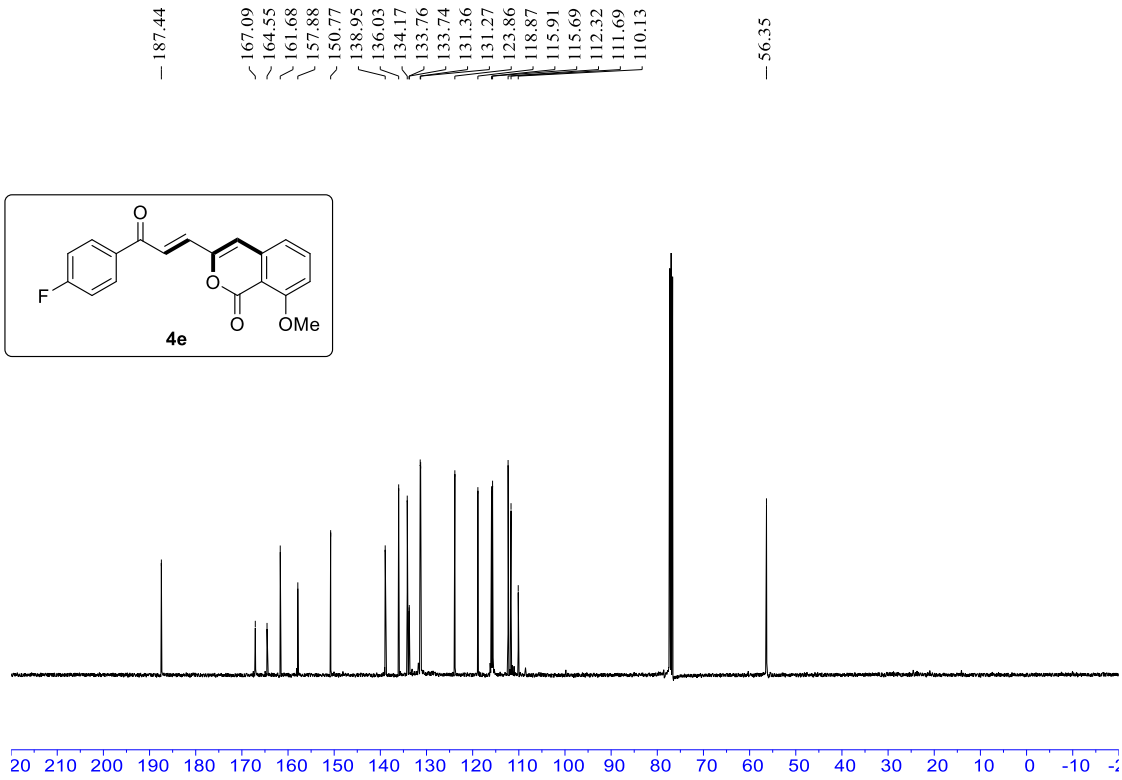
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4d**



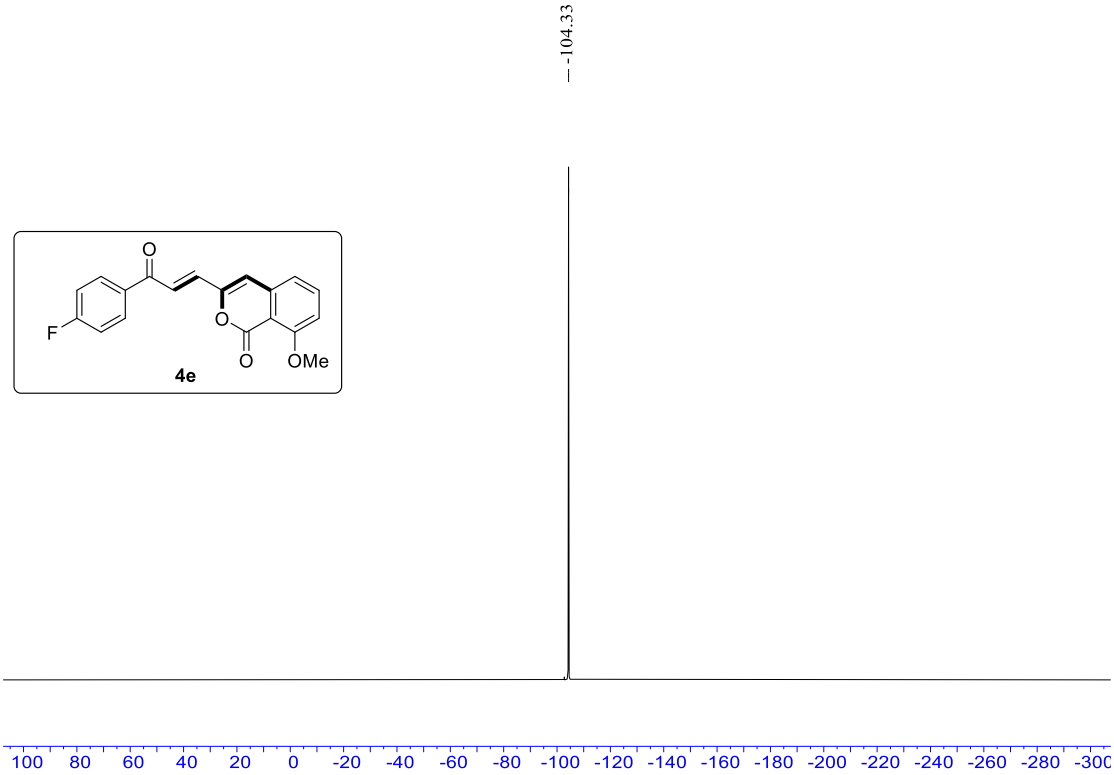
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4d**



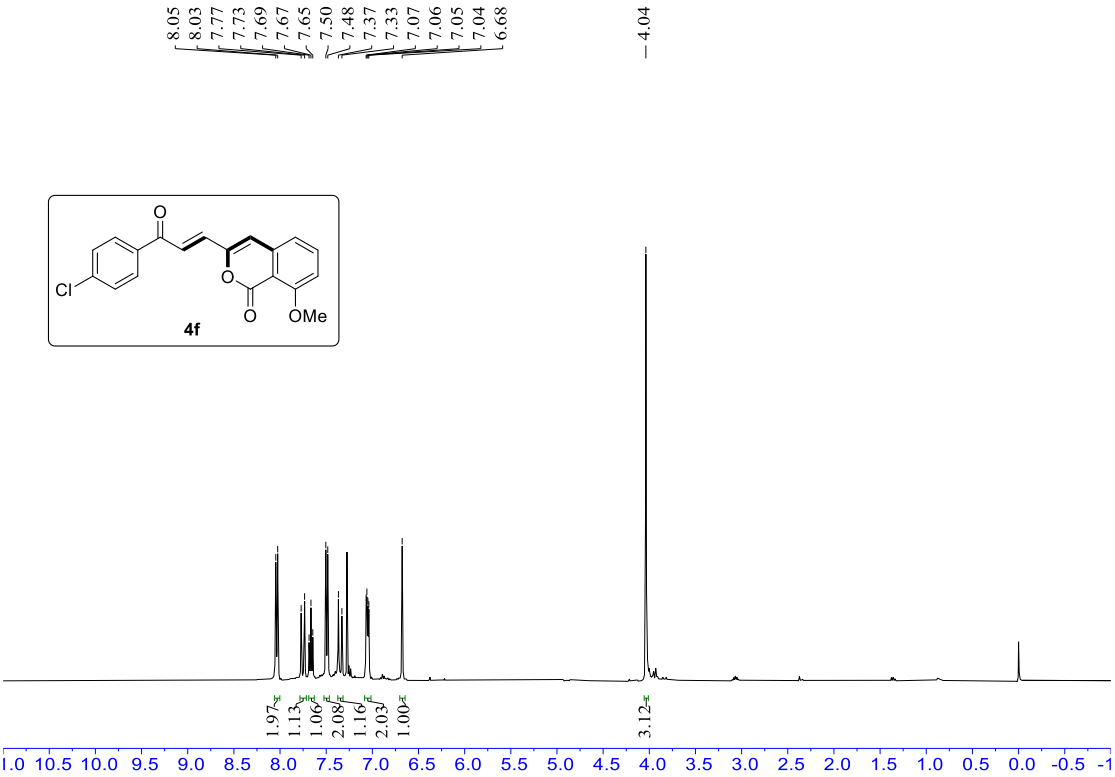
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4e**



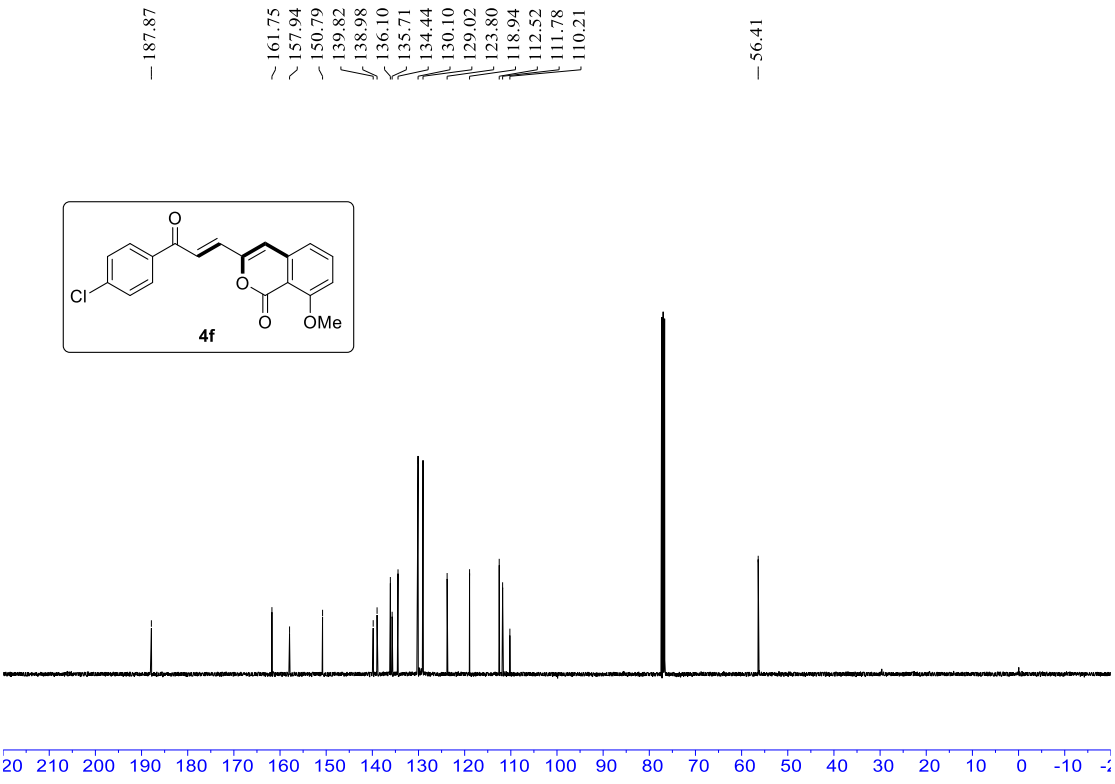
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4e**



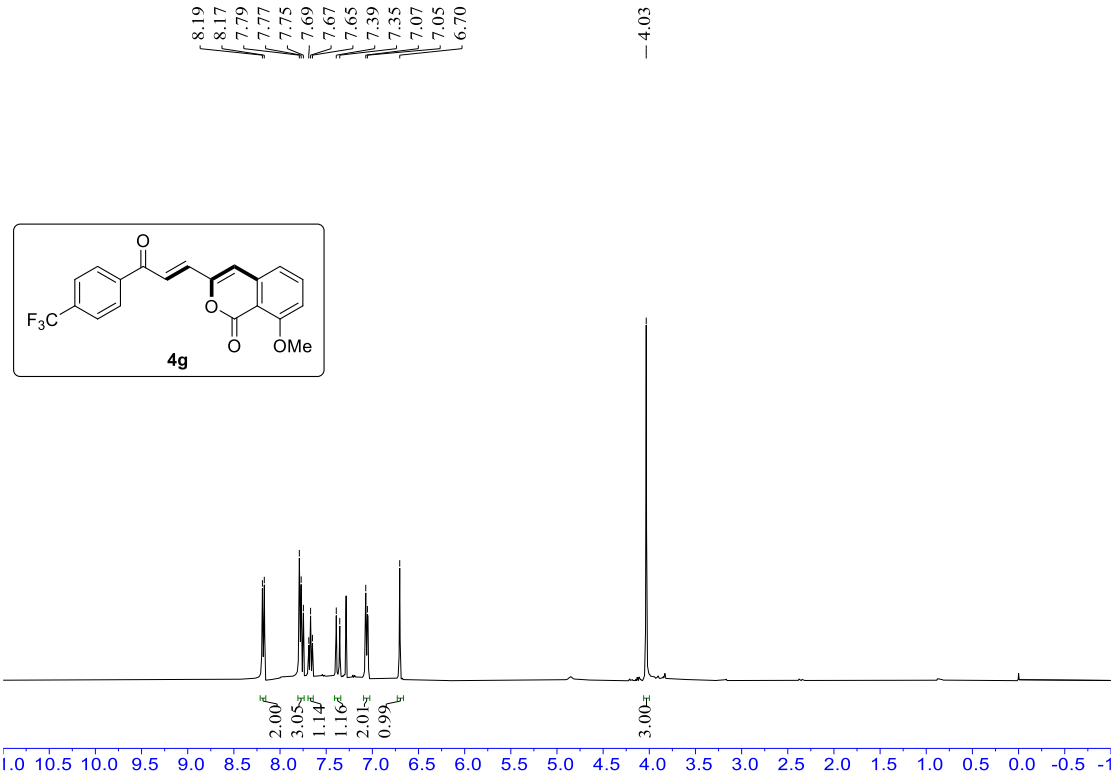
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **4e**



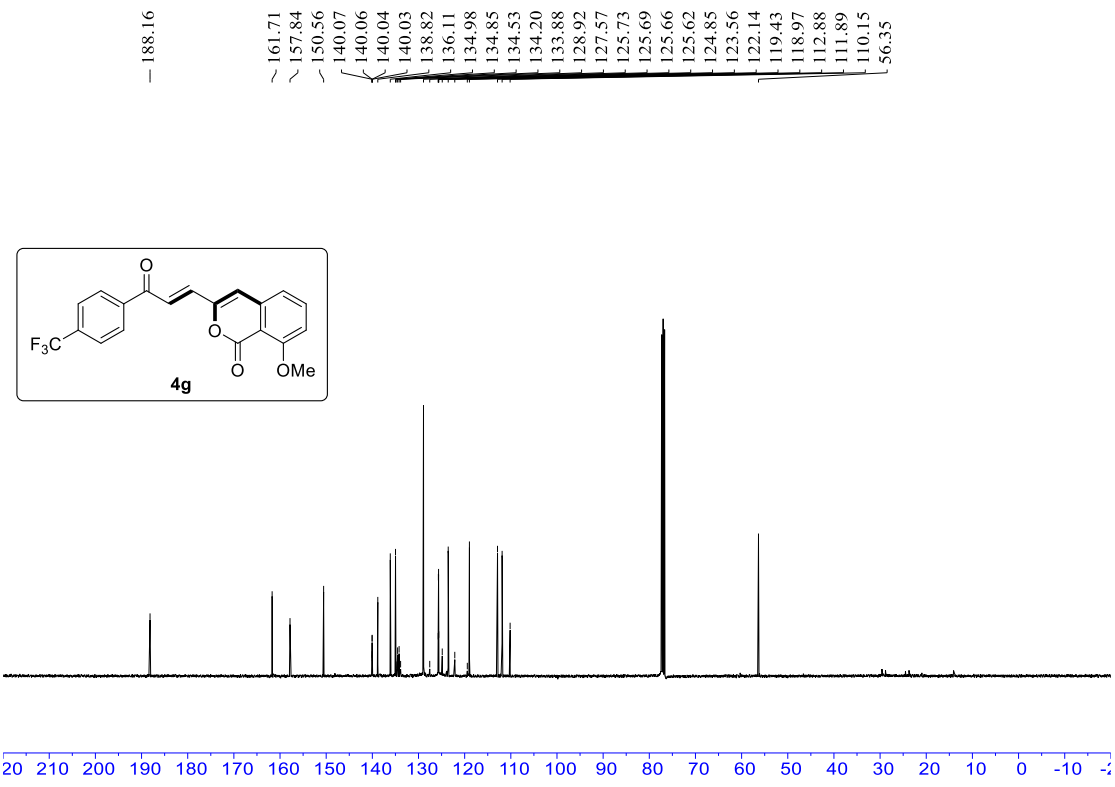
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4f**



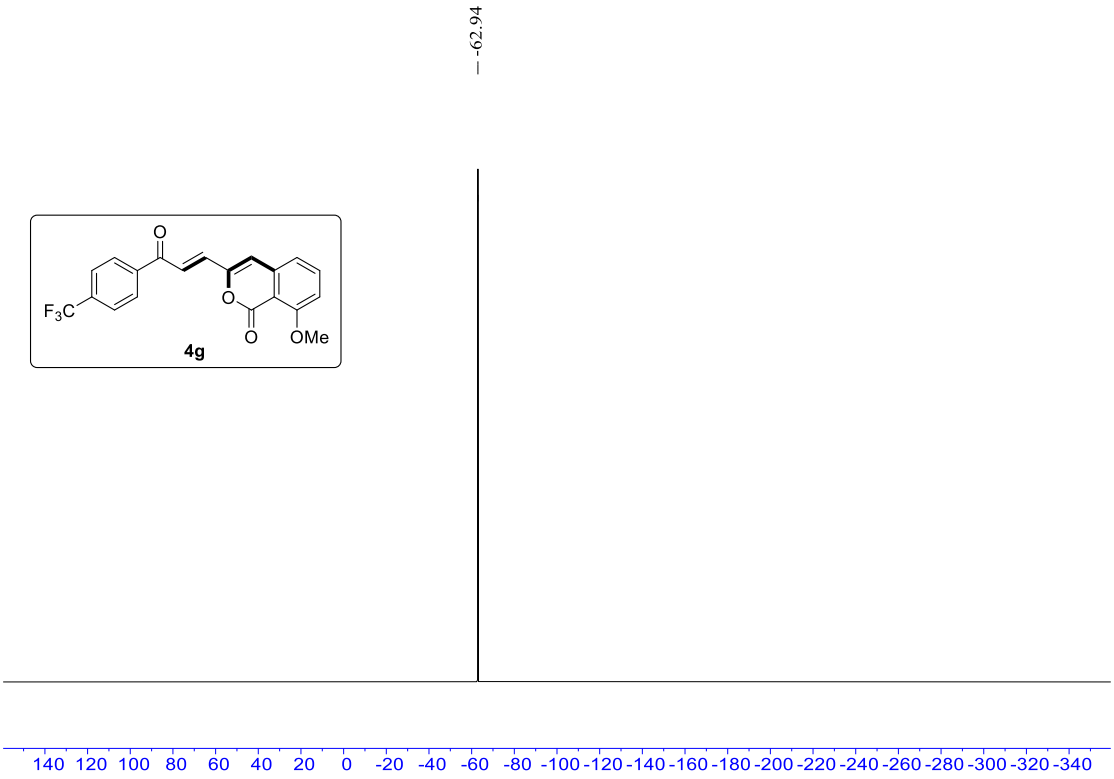
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4f**



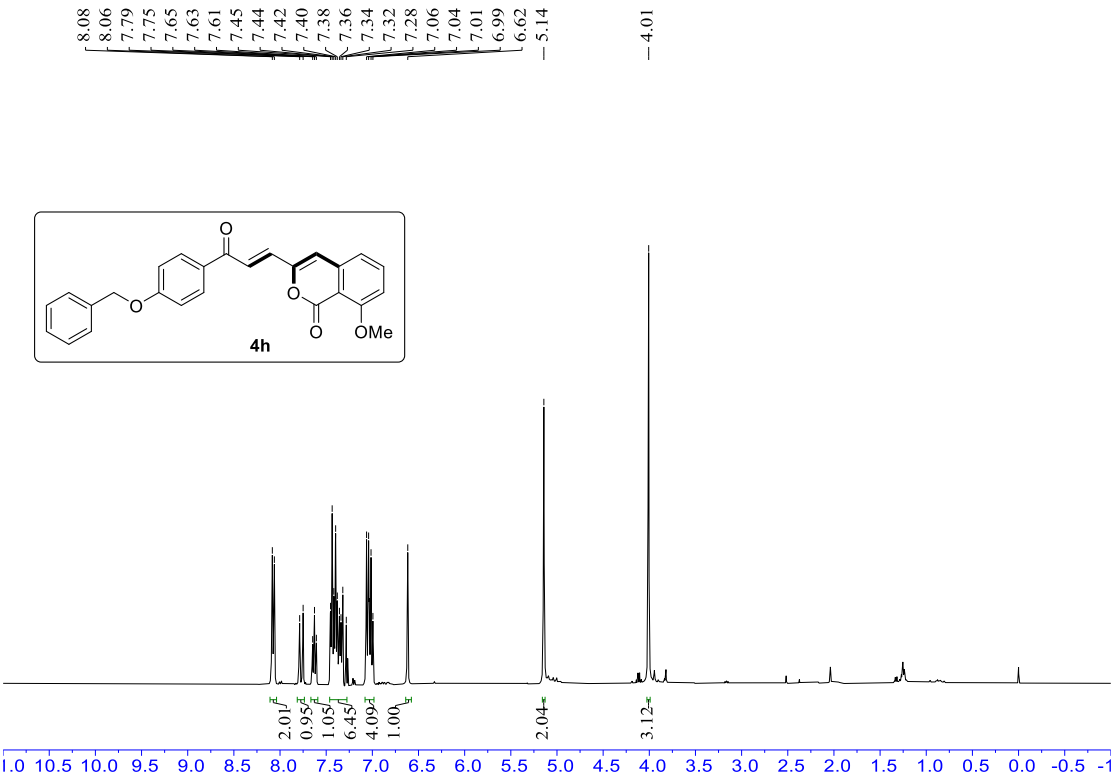
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4g**



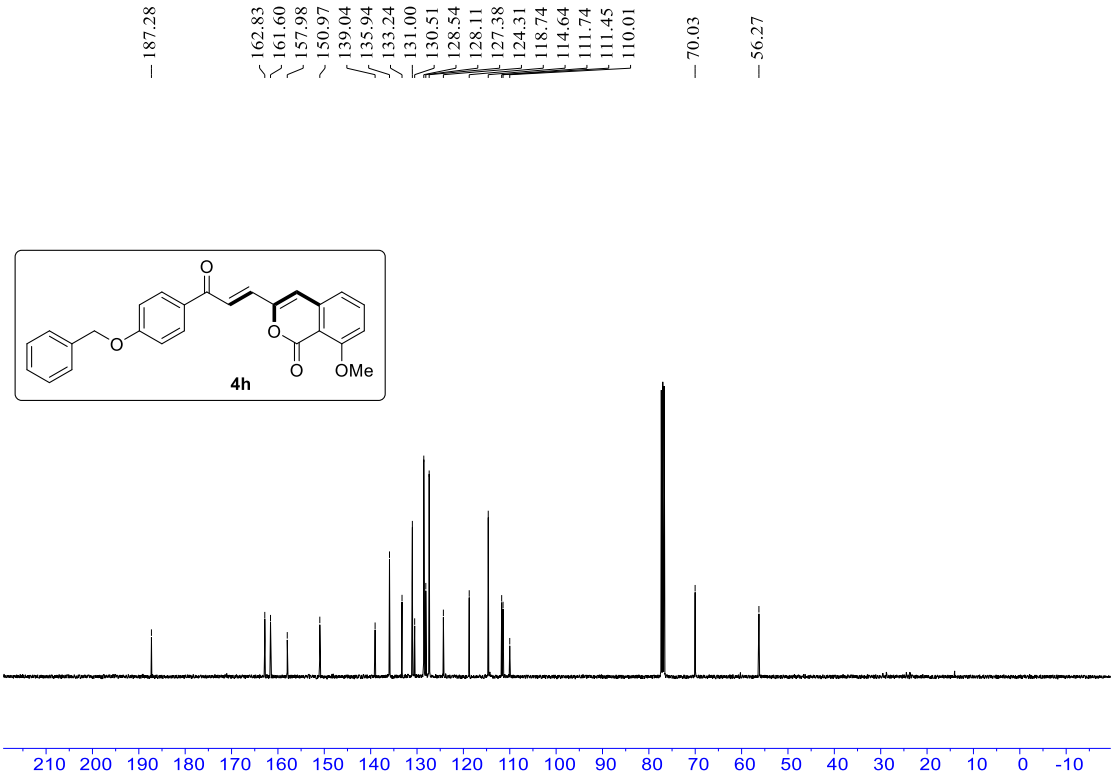
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4g**



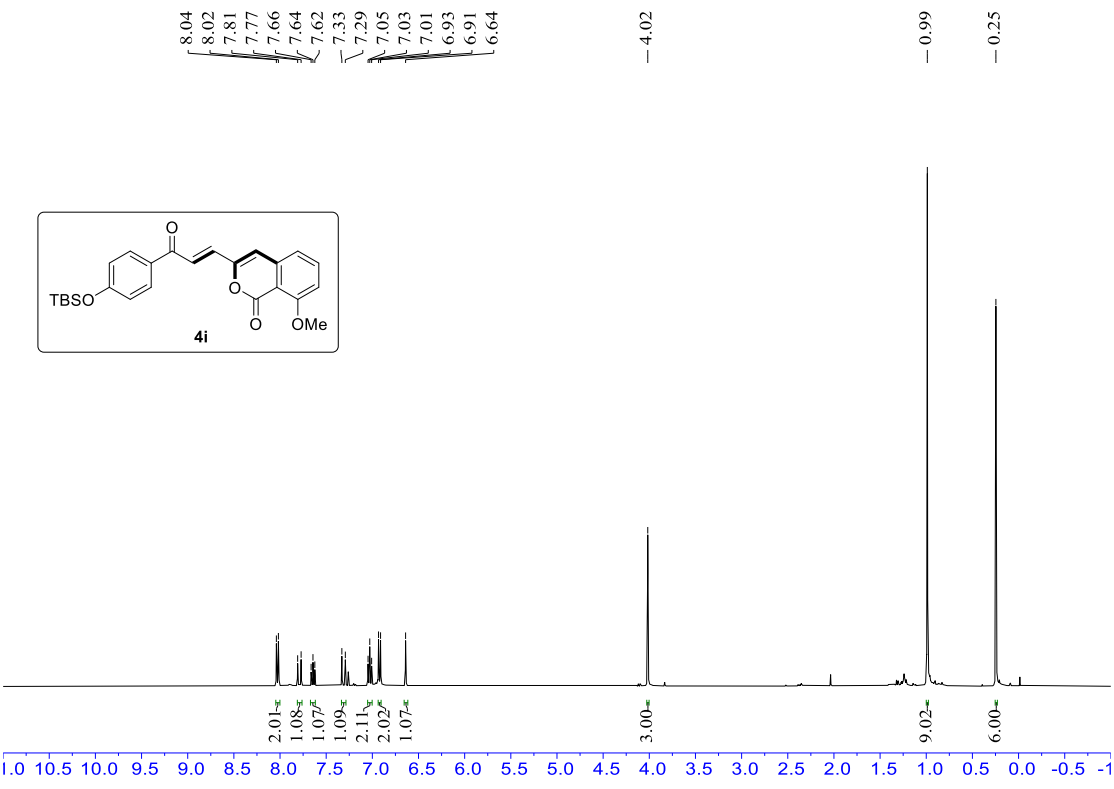
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **4g**



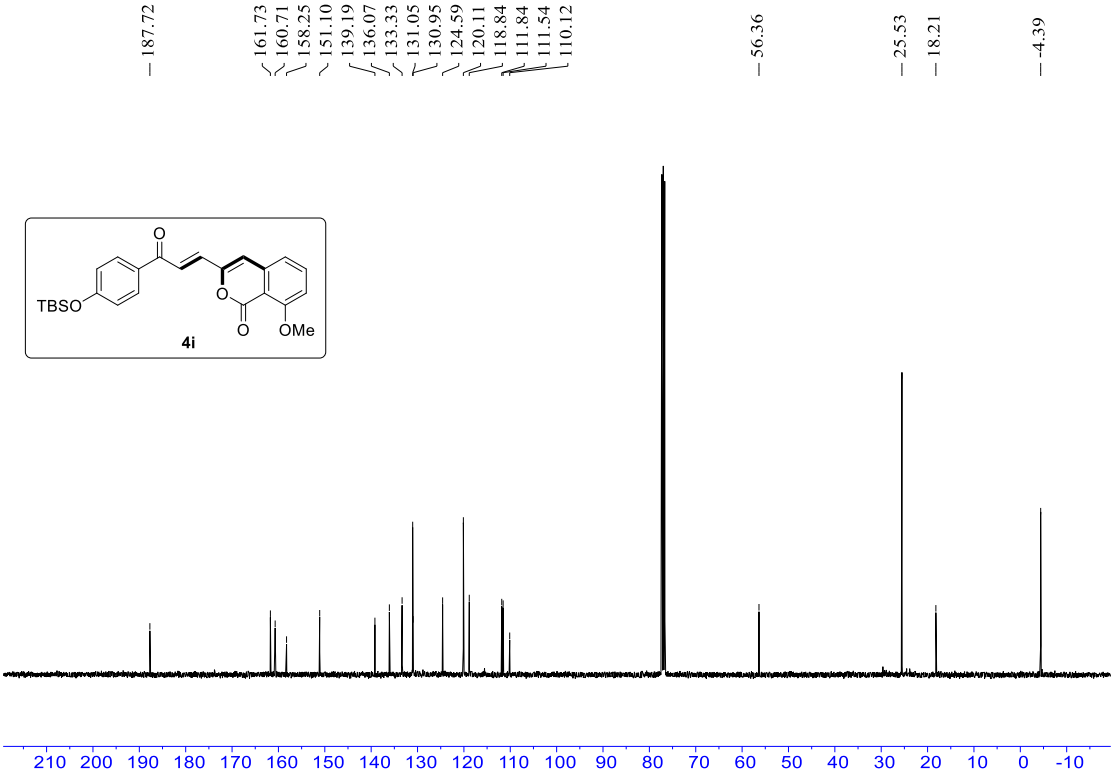
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4h**



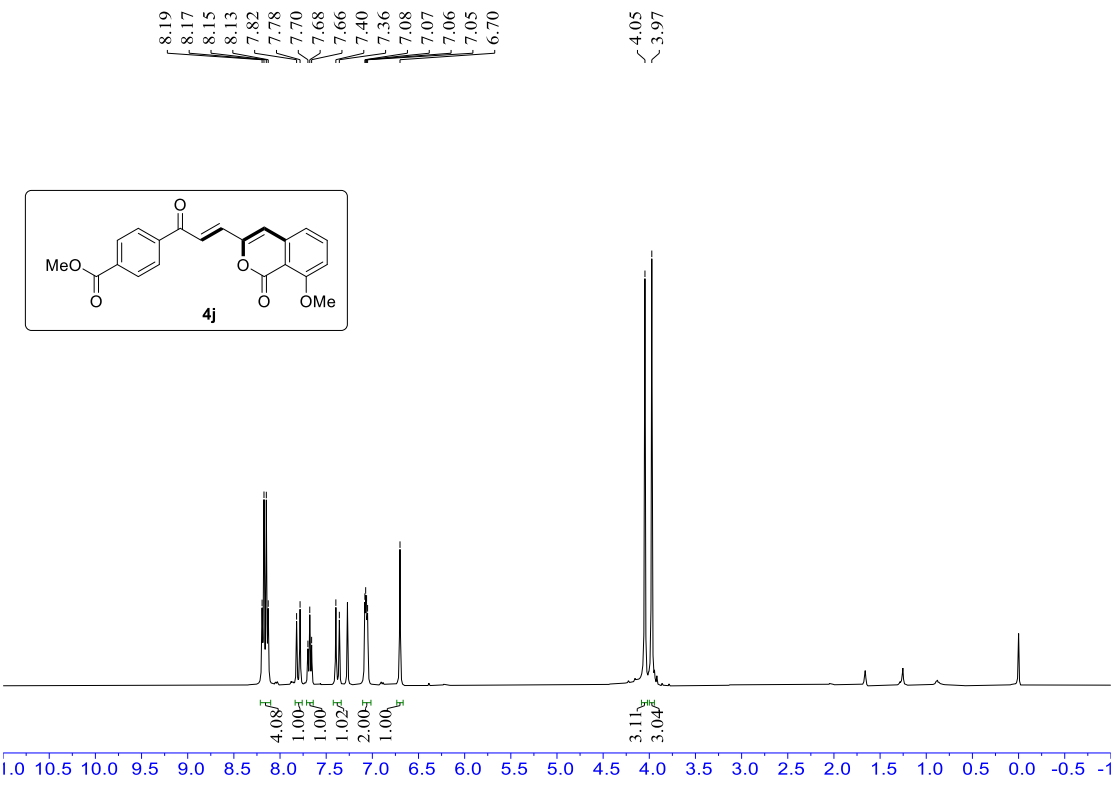
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4h**



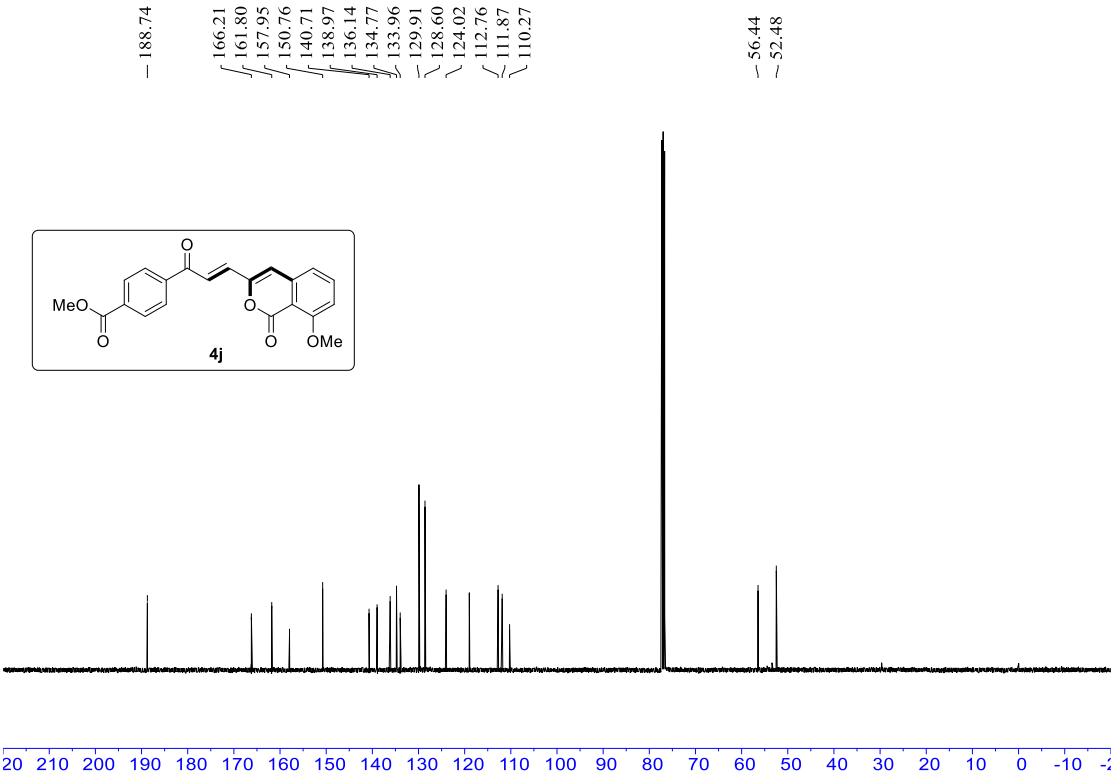
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4i**



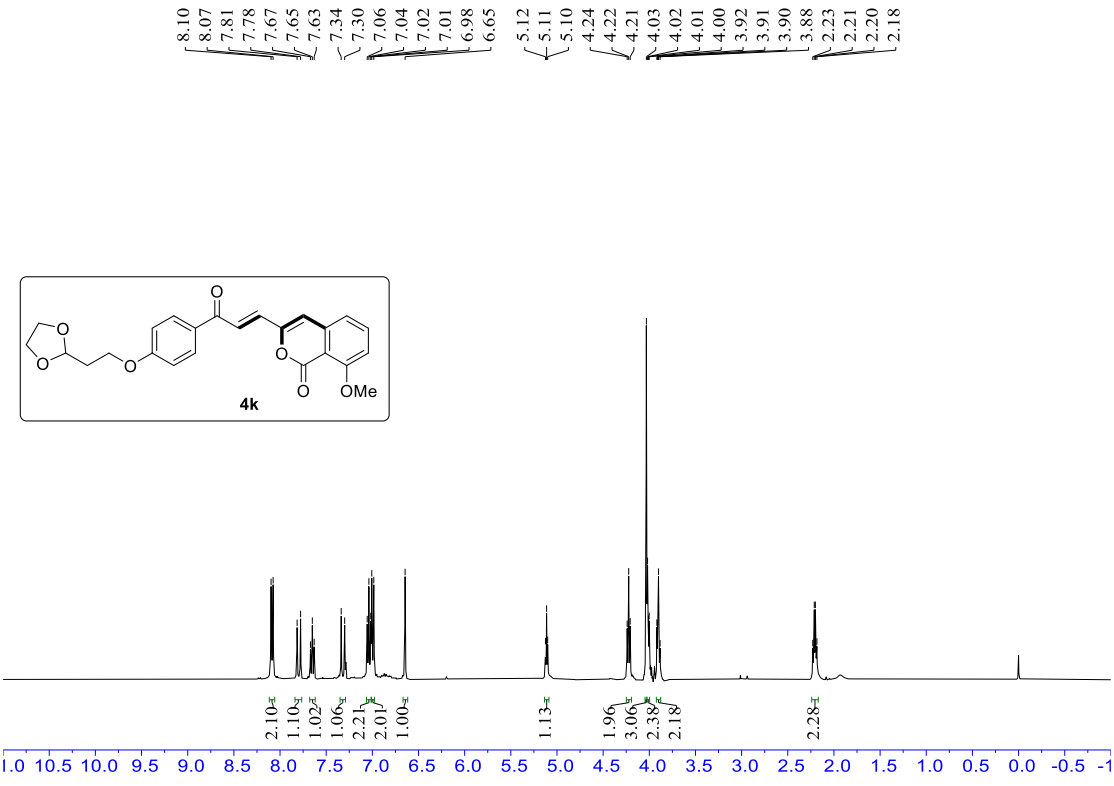
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4i**



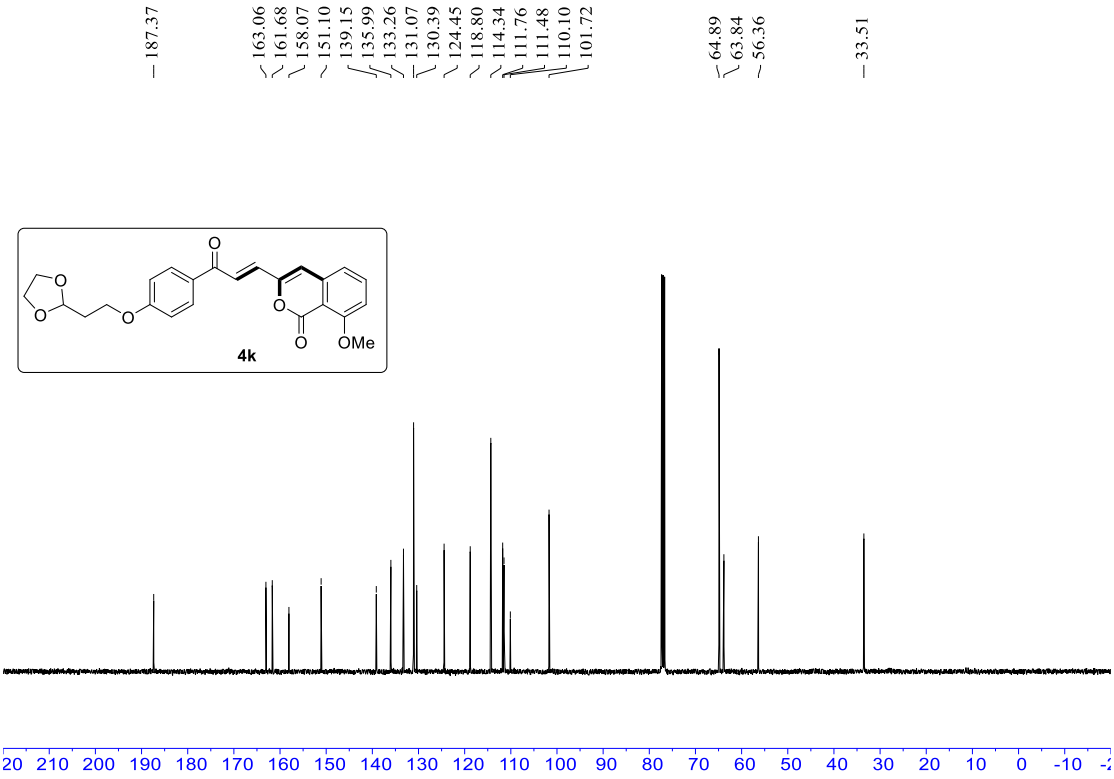
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4j**



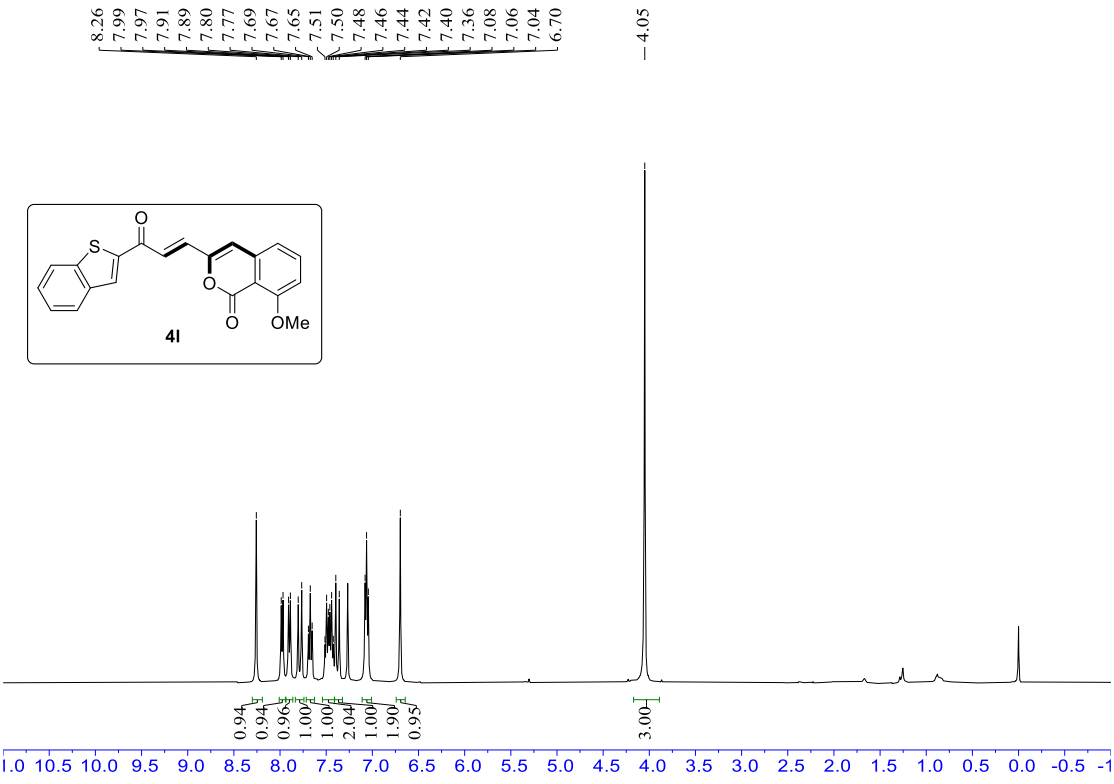
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4j**



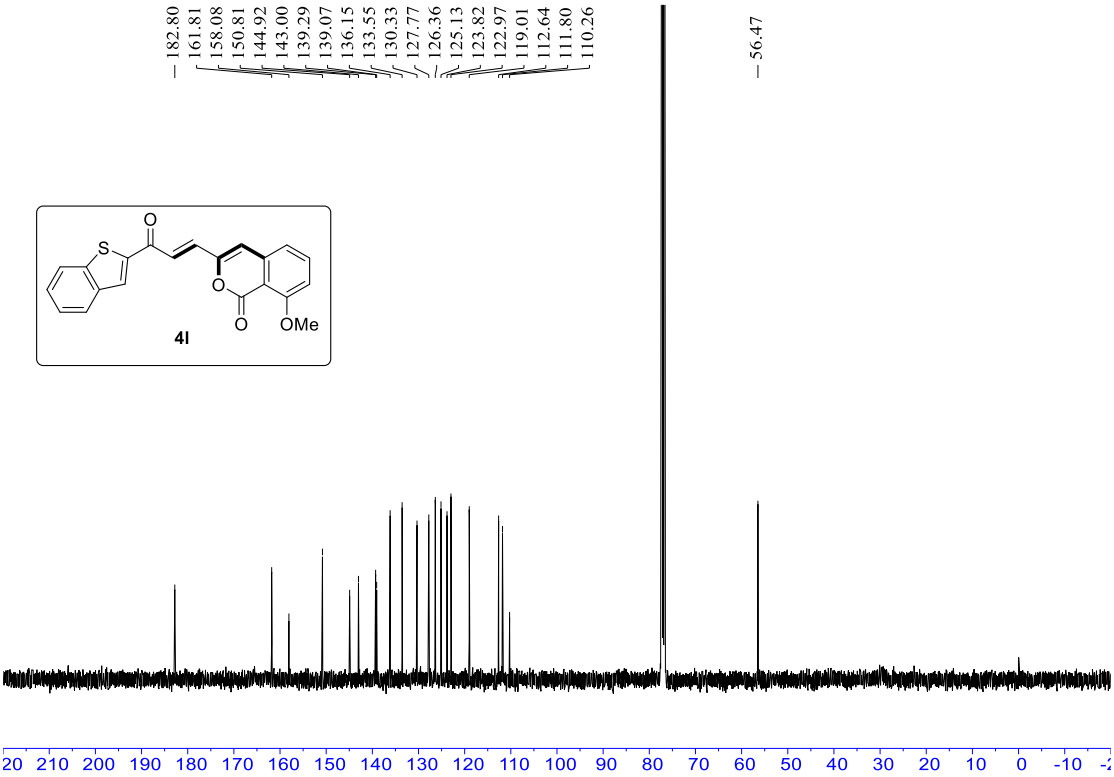
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4k**



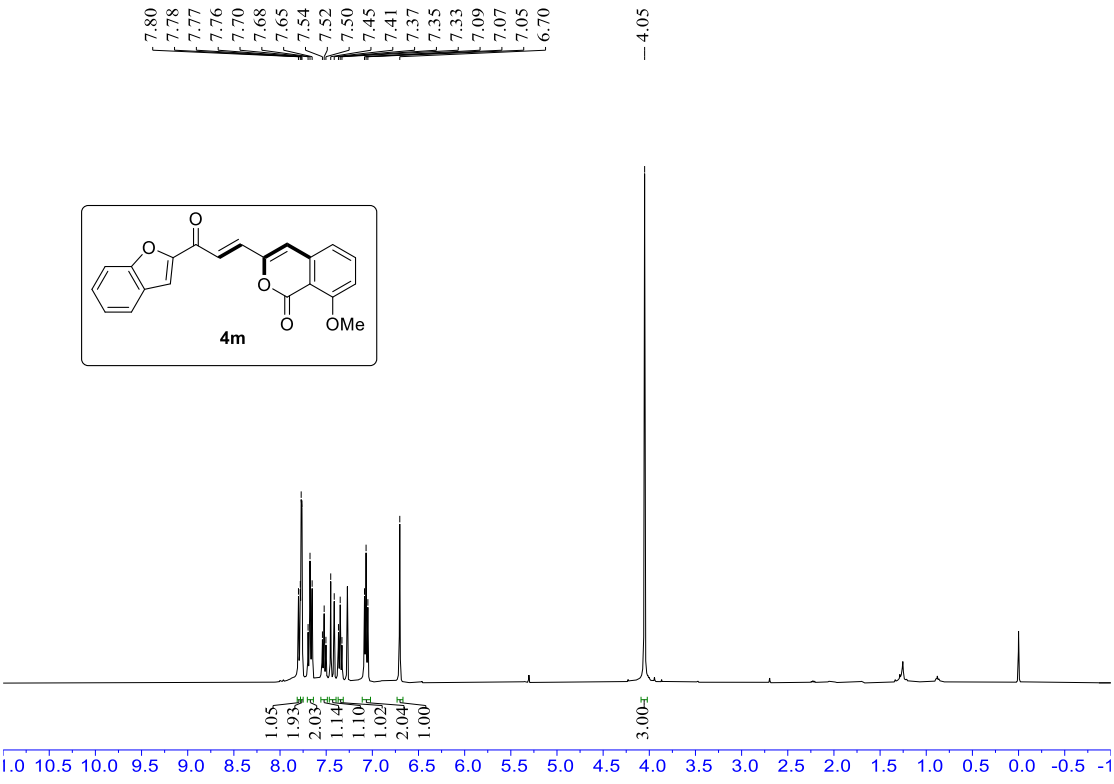
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4k**



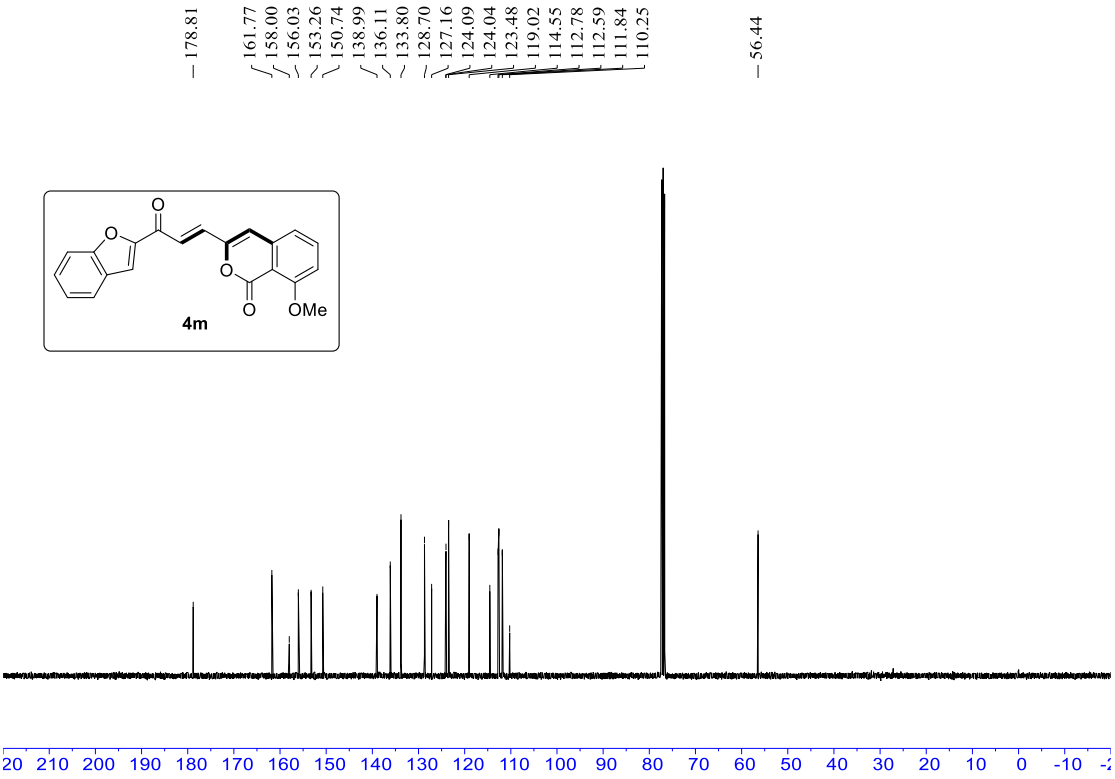
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4l**



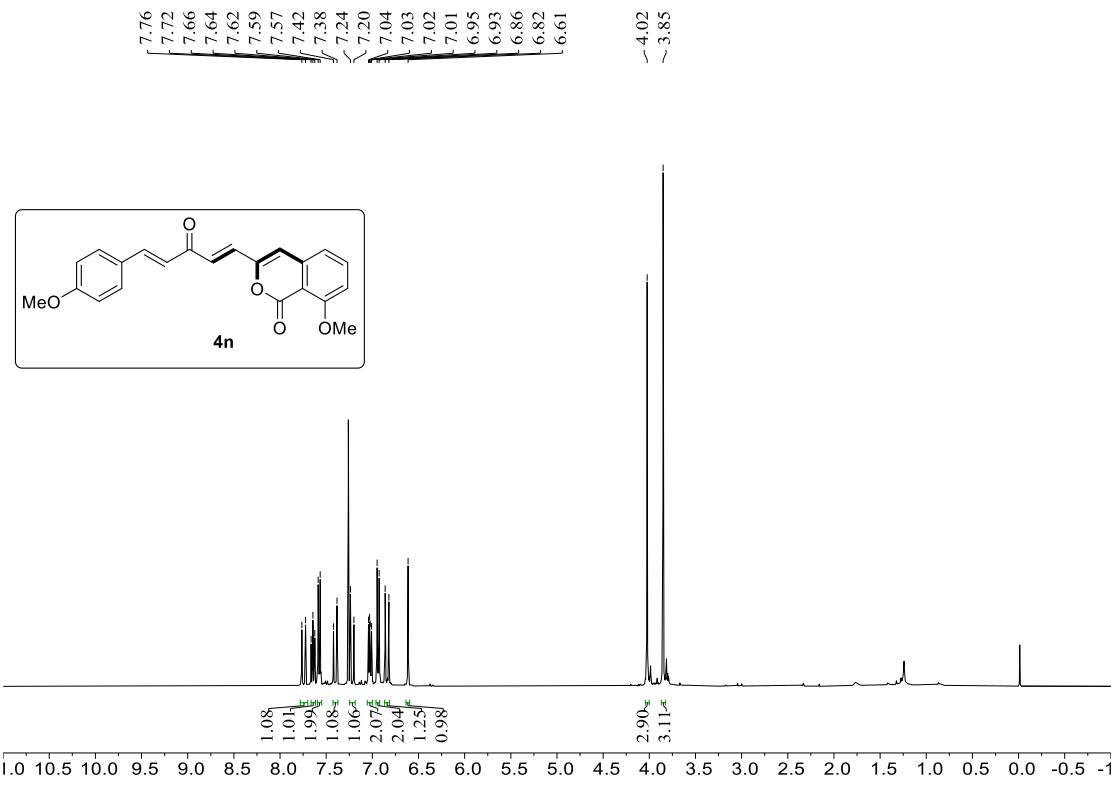
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4l**



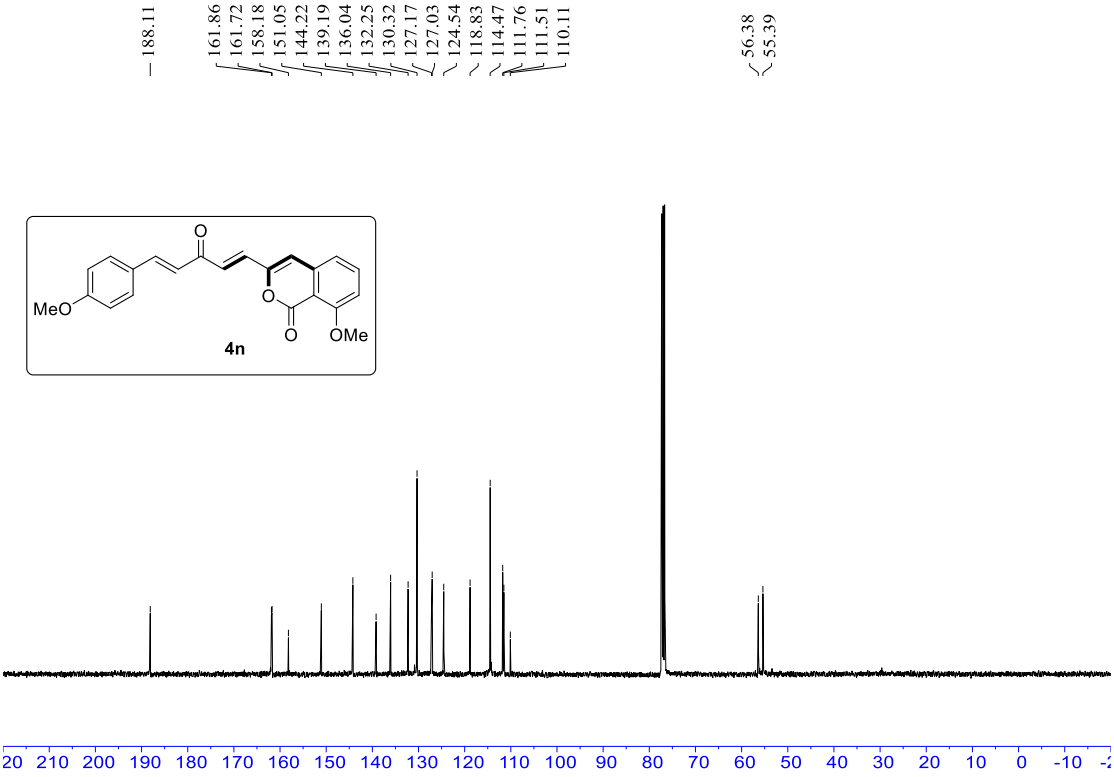
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4m**



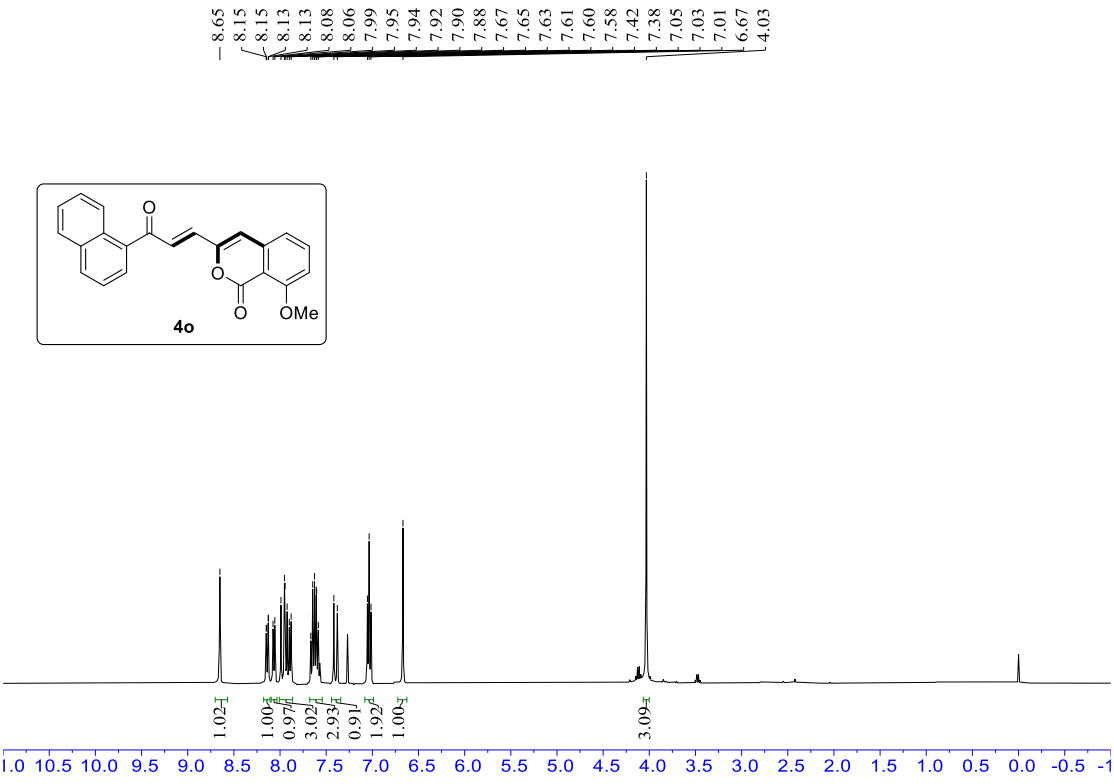
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4m**



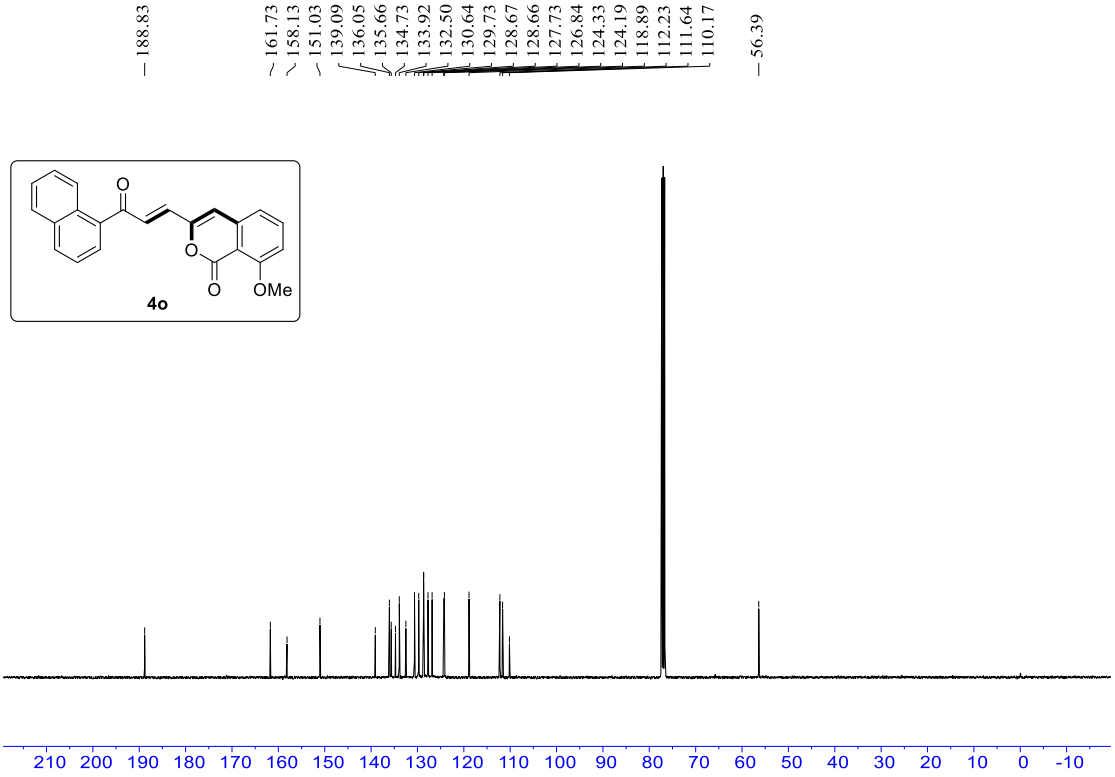
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4n**



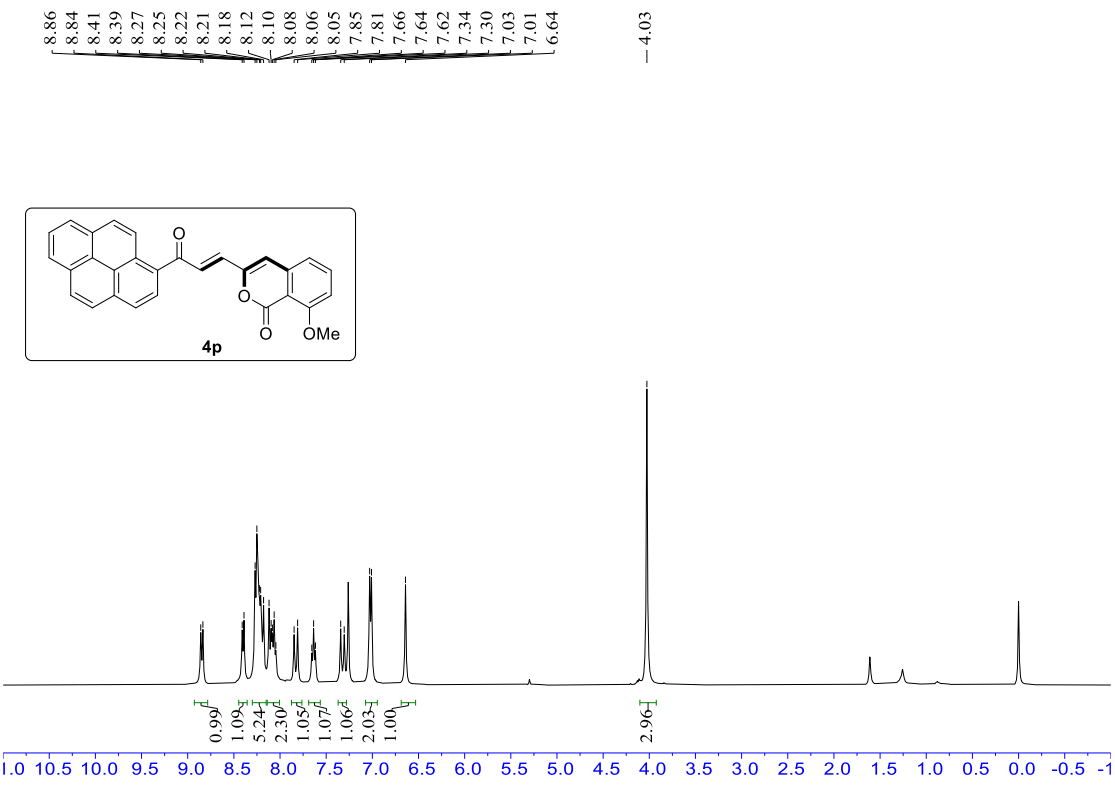
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4n**



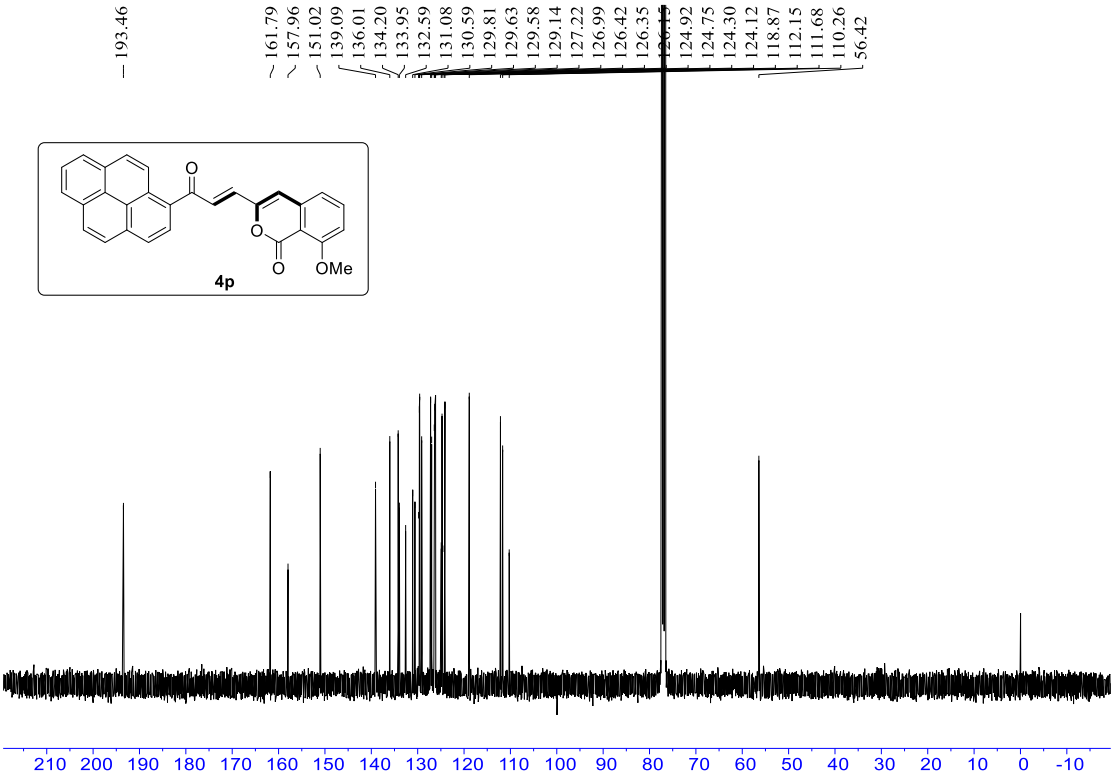
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4o**



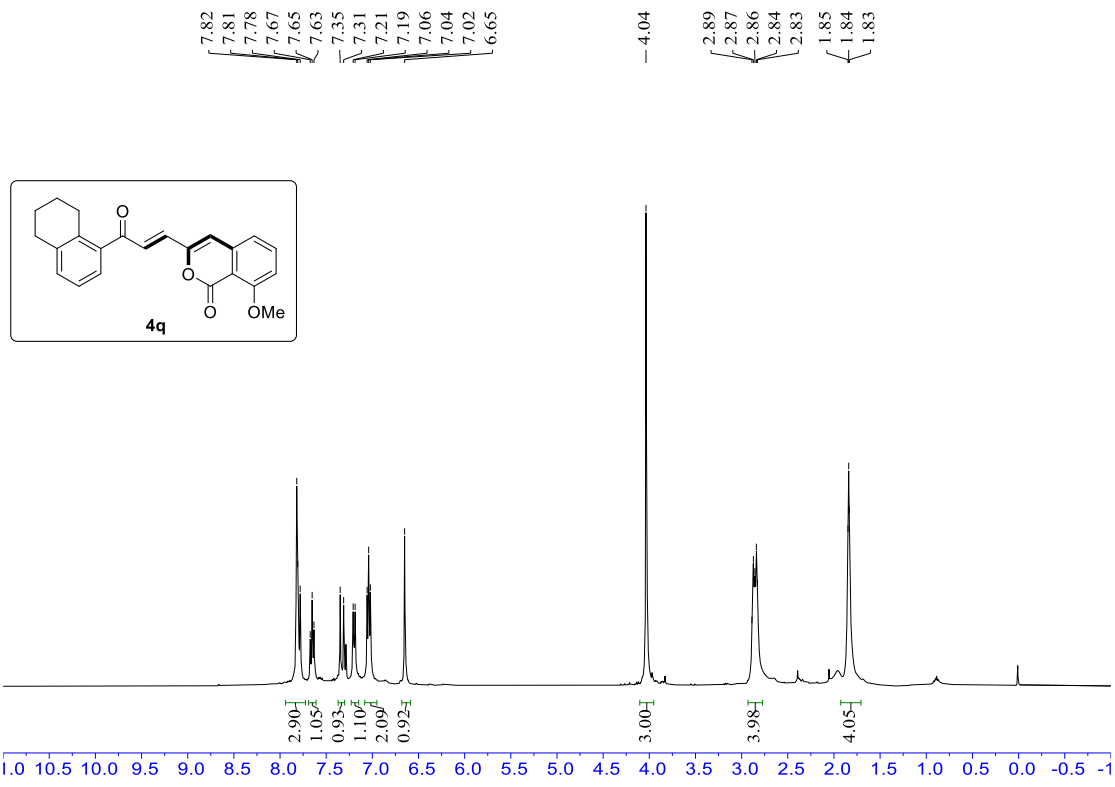
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4o**



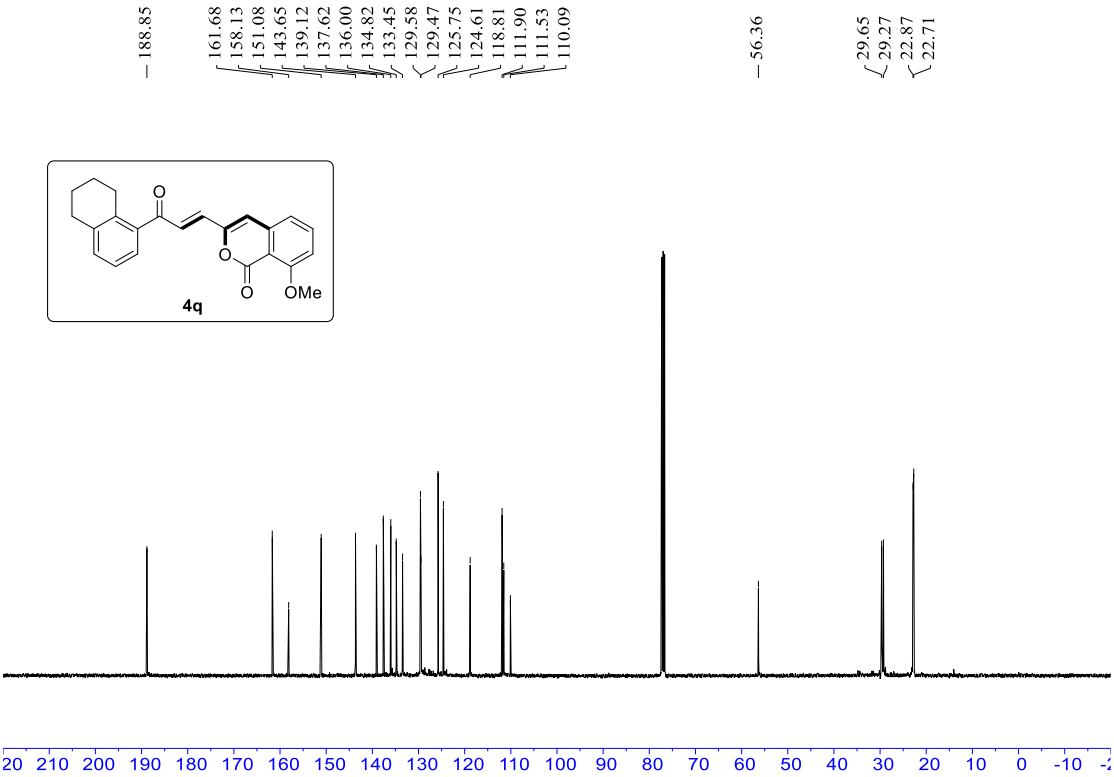
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4p**



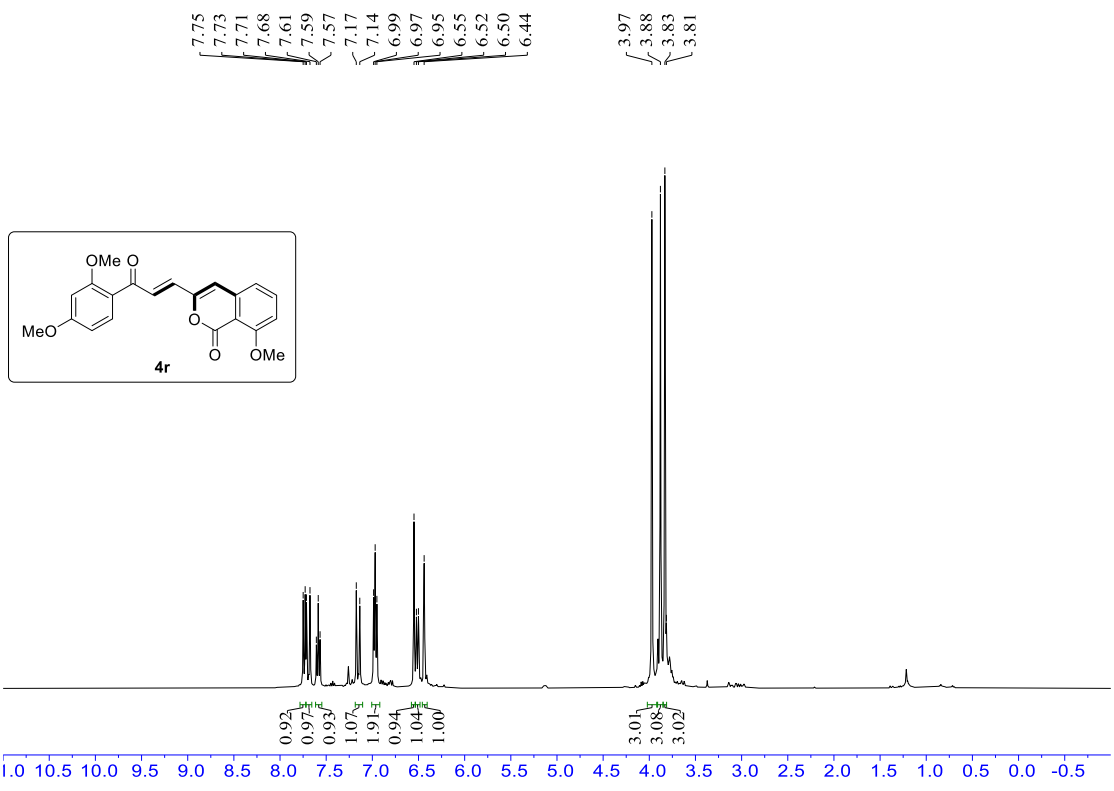
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4p**



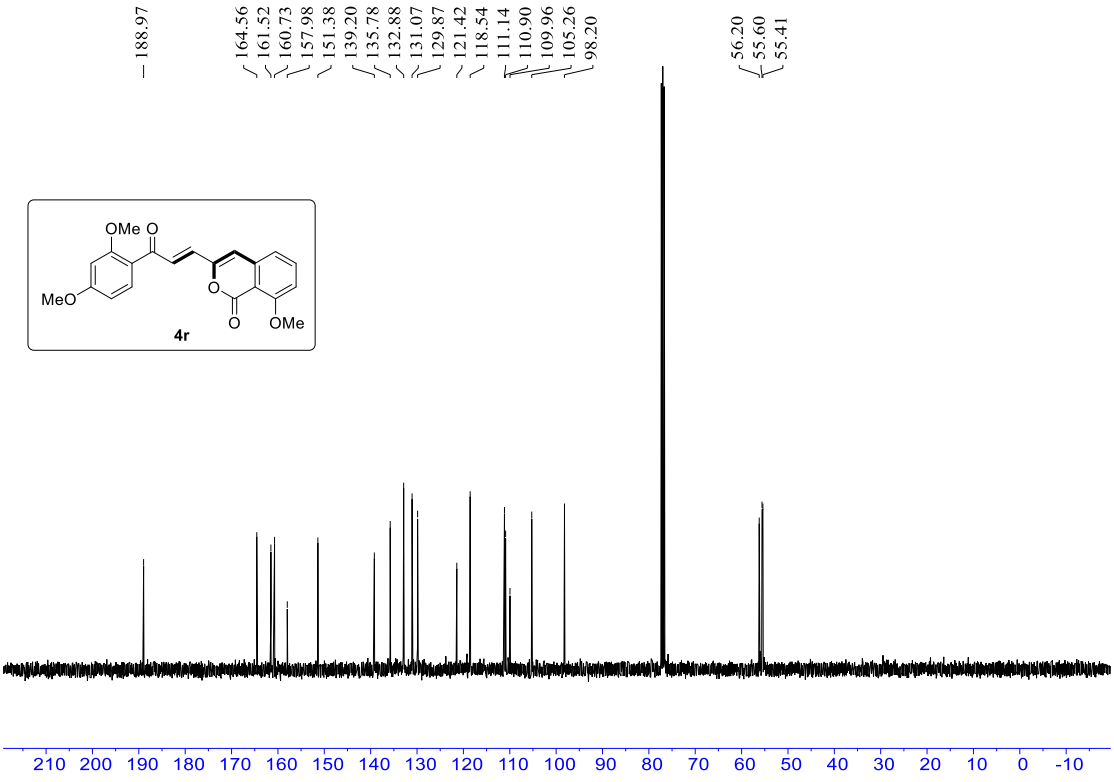
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4q**



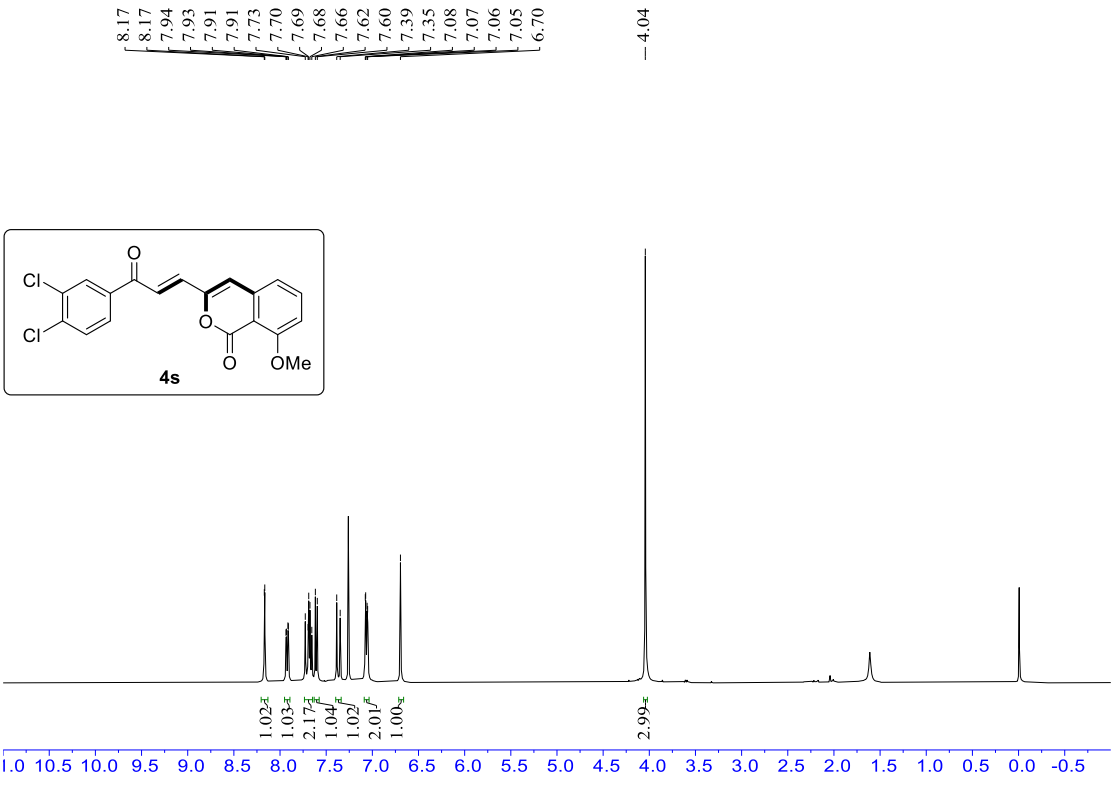
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4q**



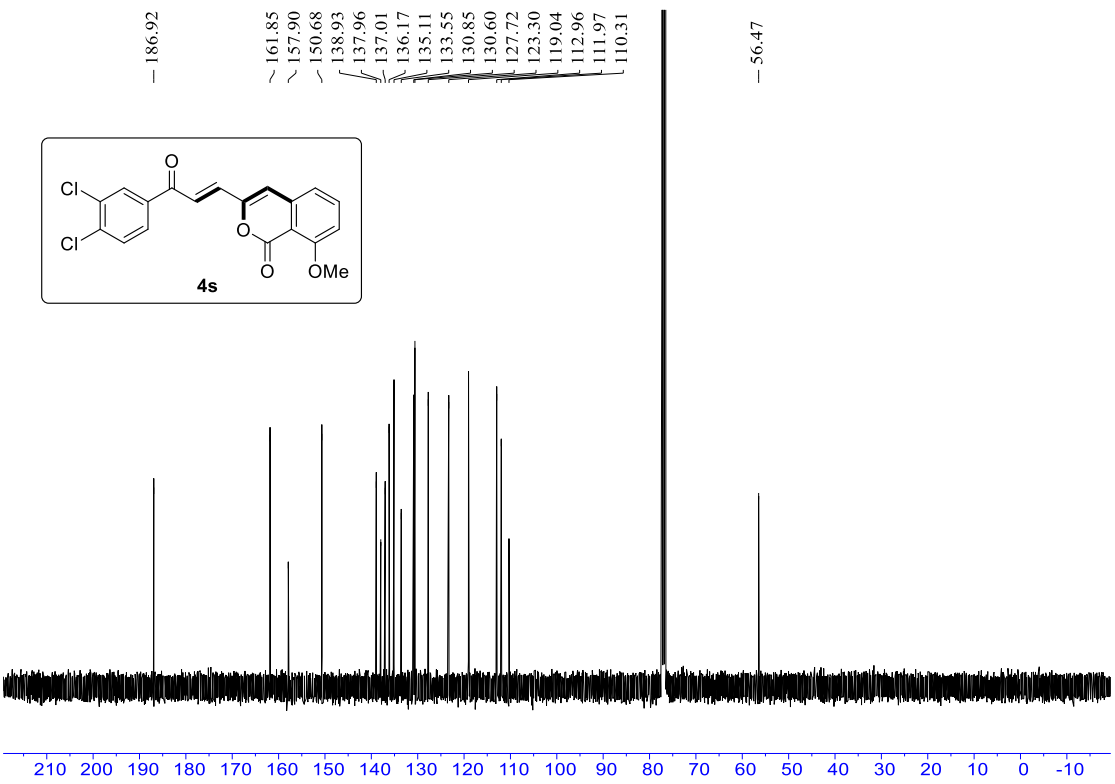
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4r**



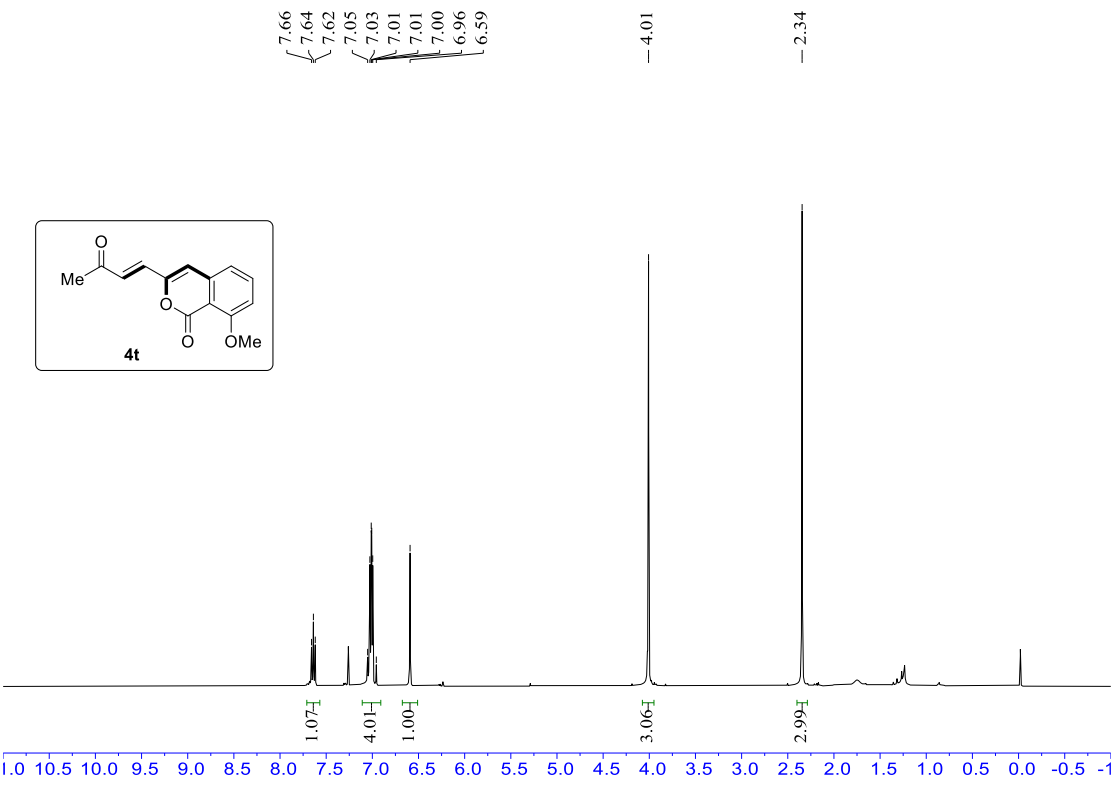
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4r**



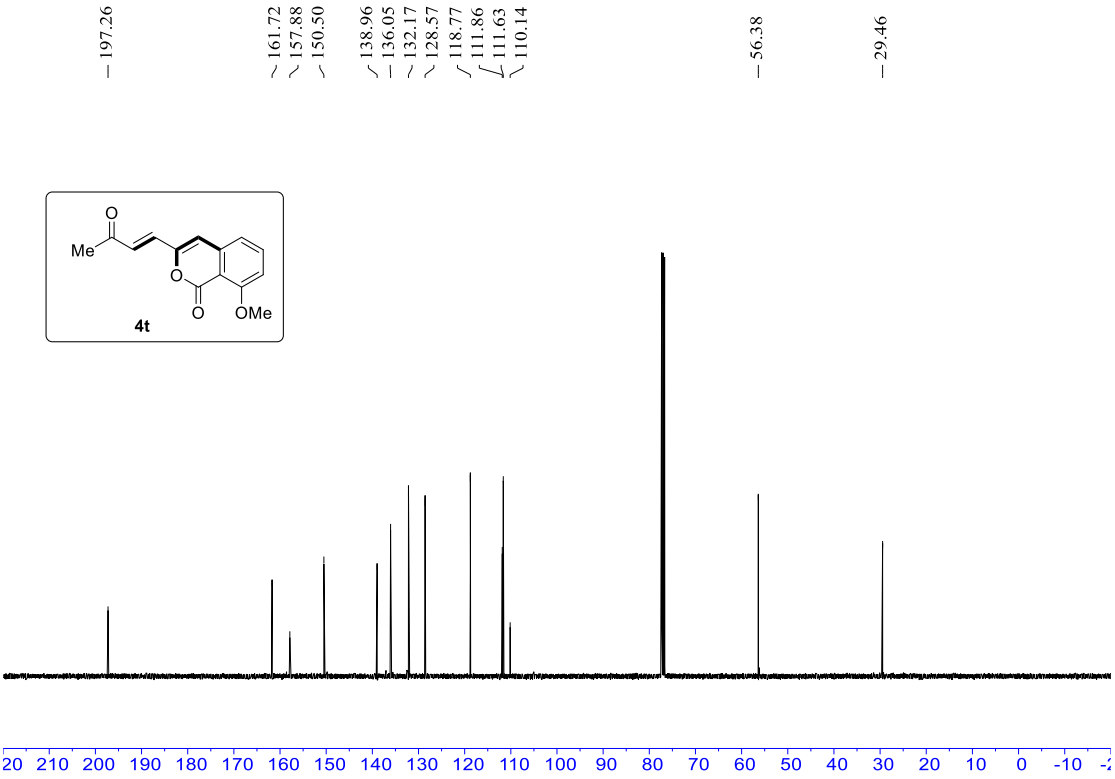
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4s**



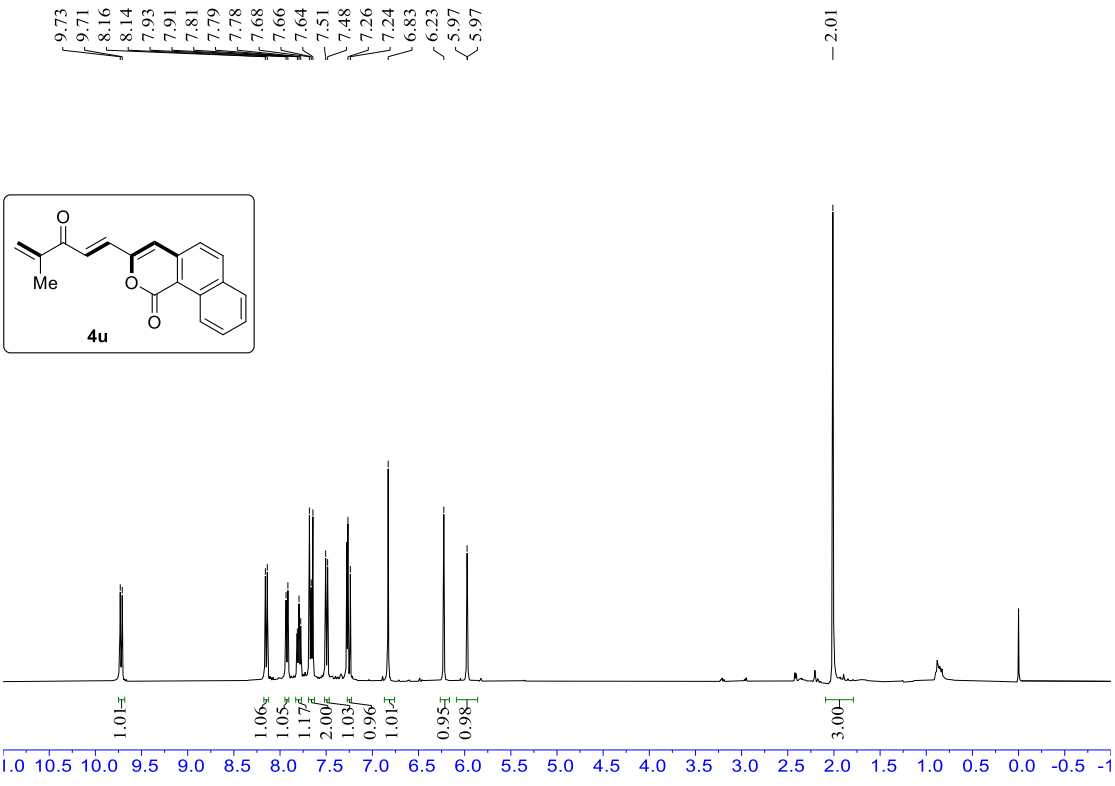
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4s**



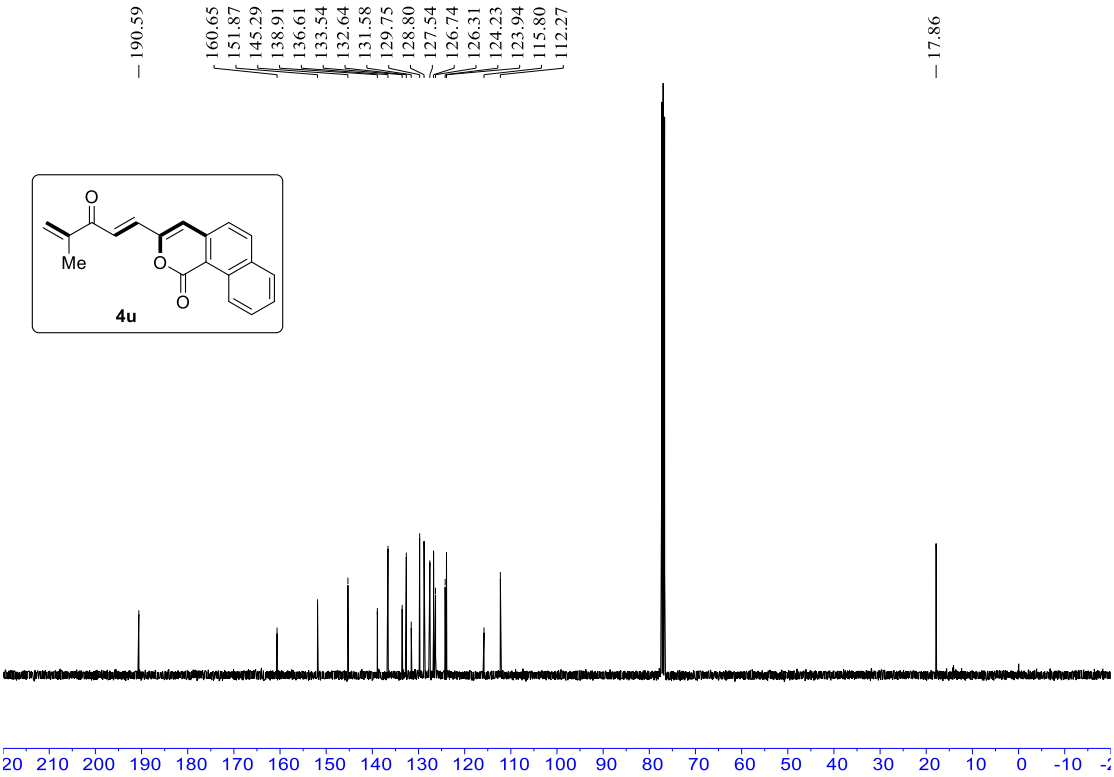
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4t**



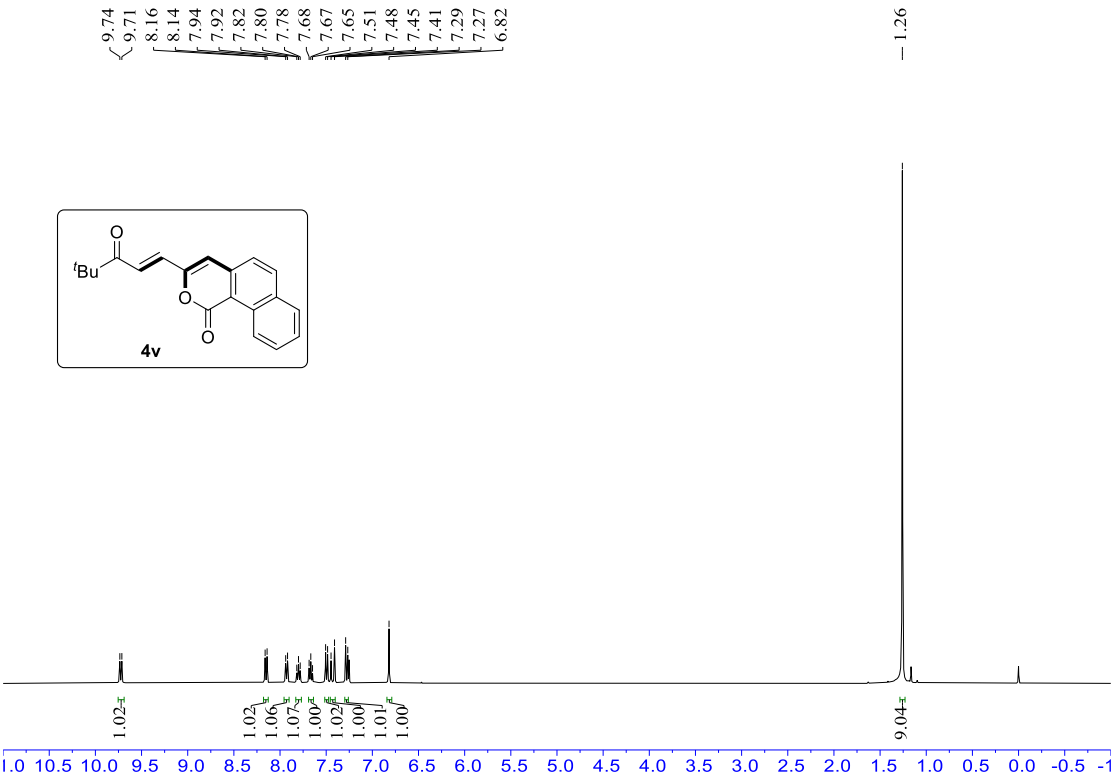
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4t**



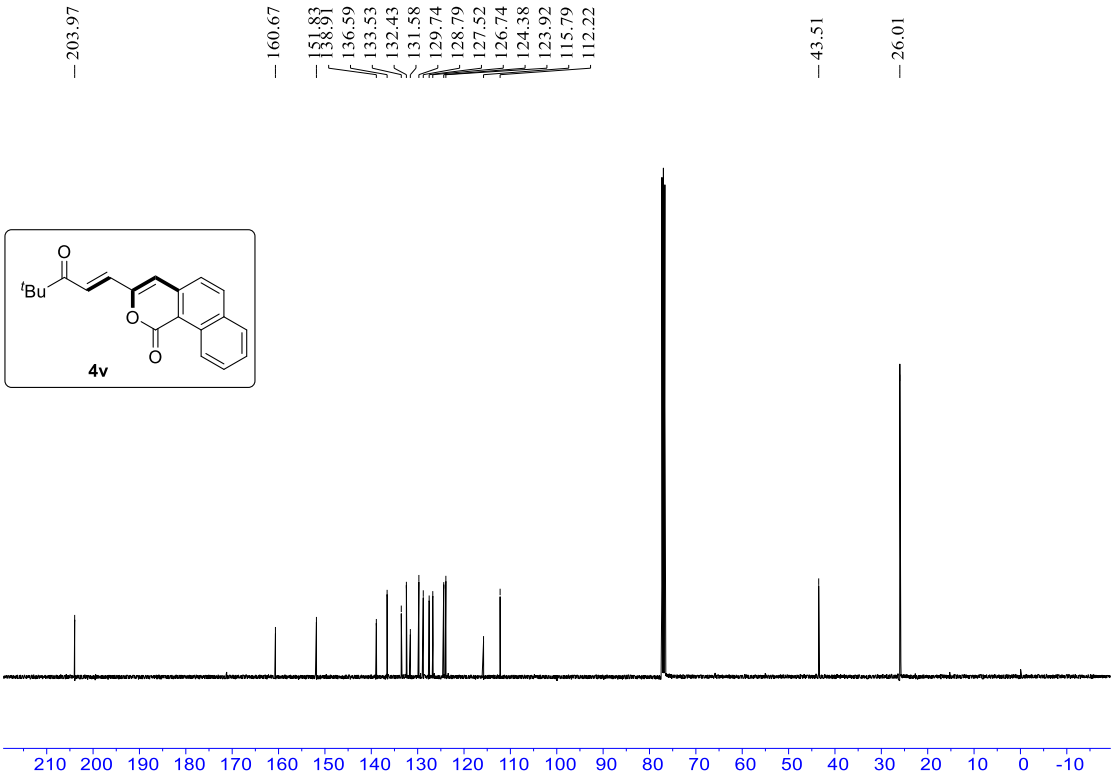
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4u**



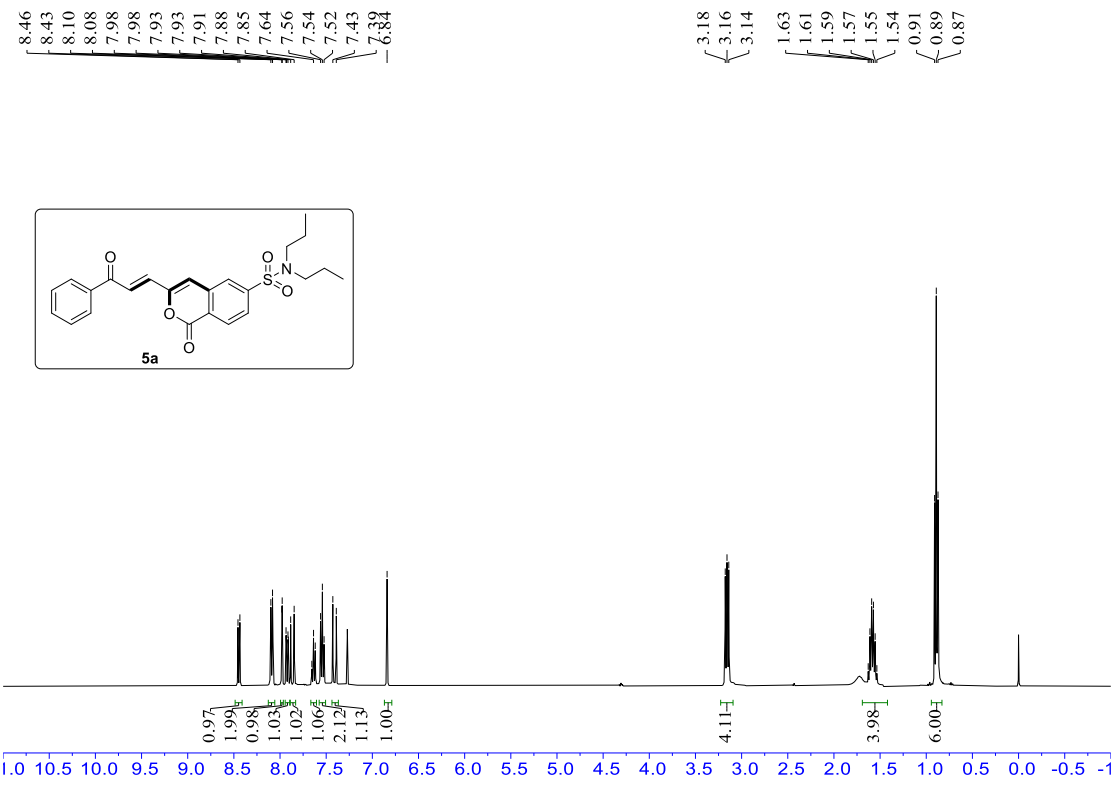
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4u**



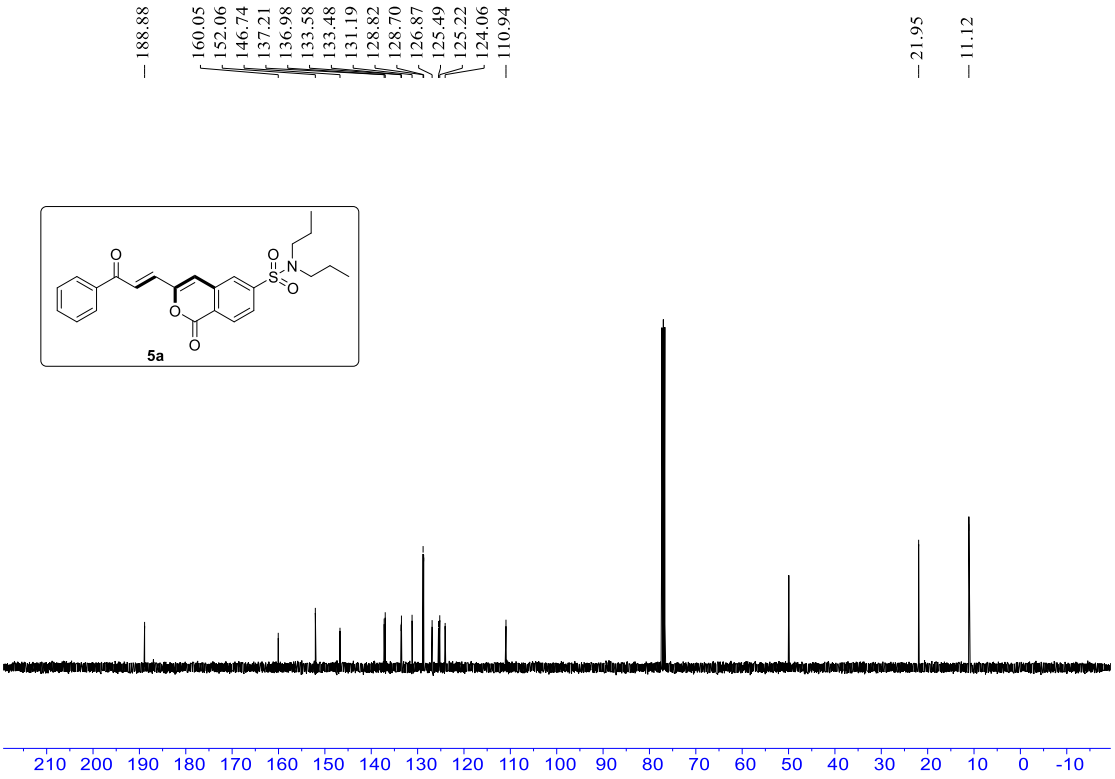
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4v**



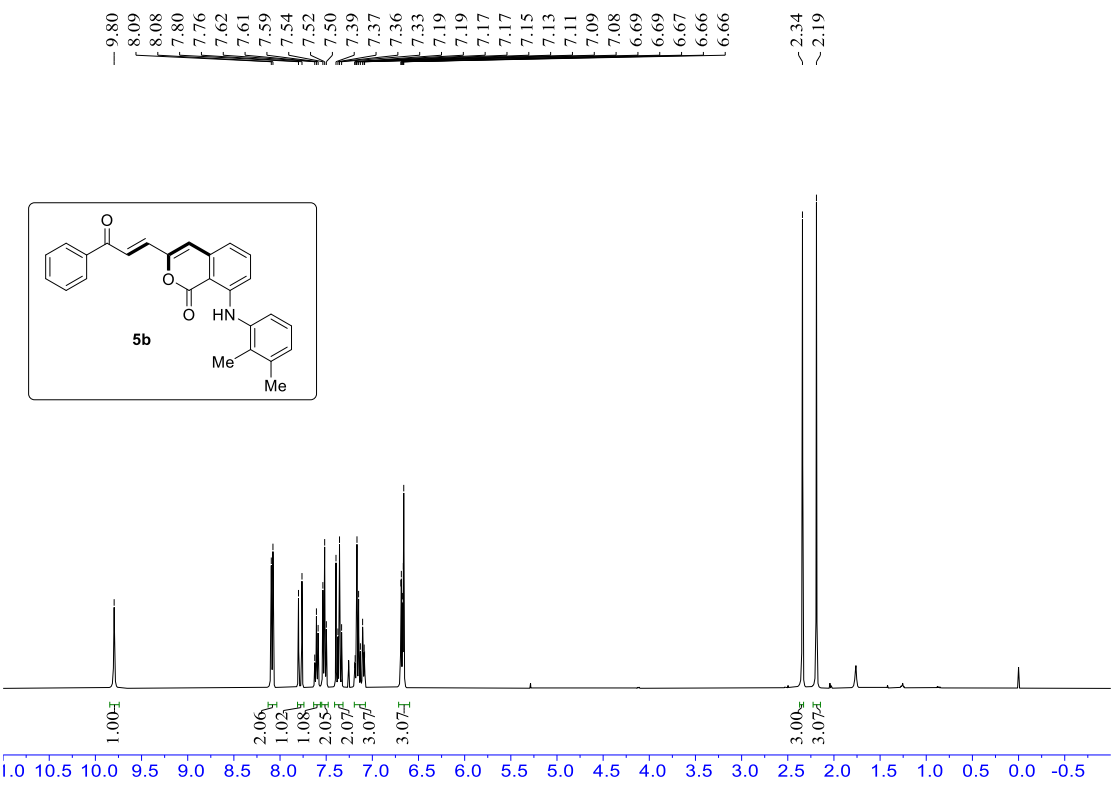
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4v**



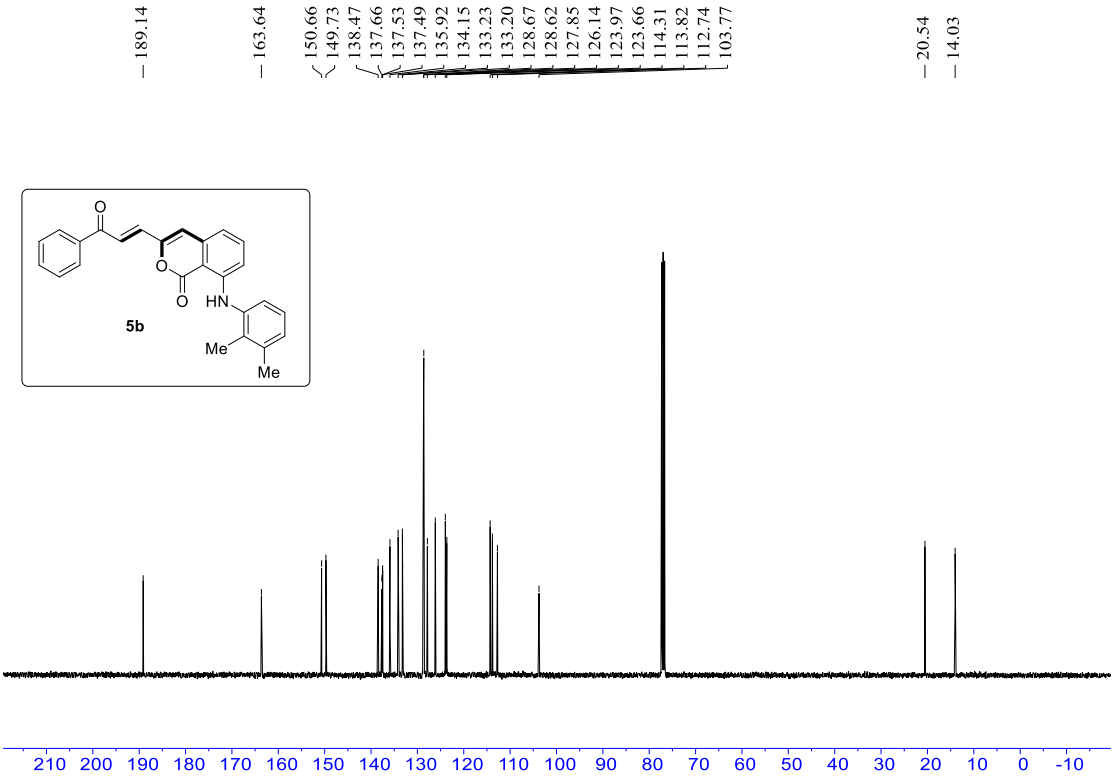
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5a**



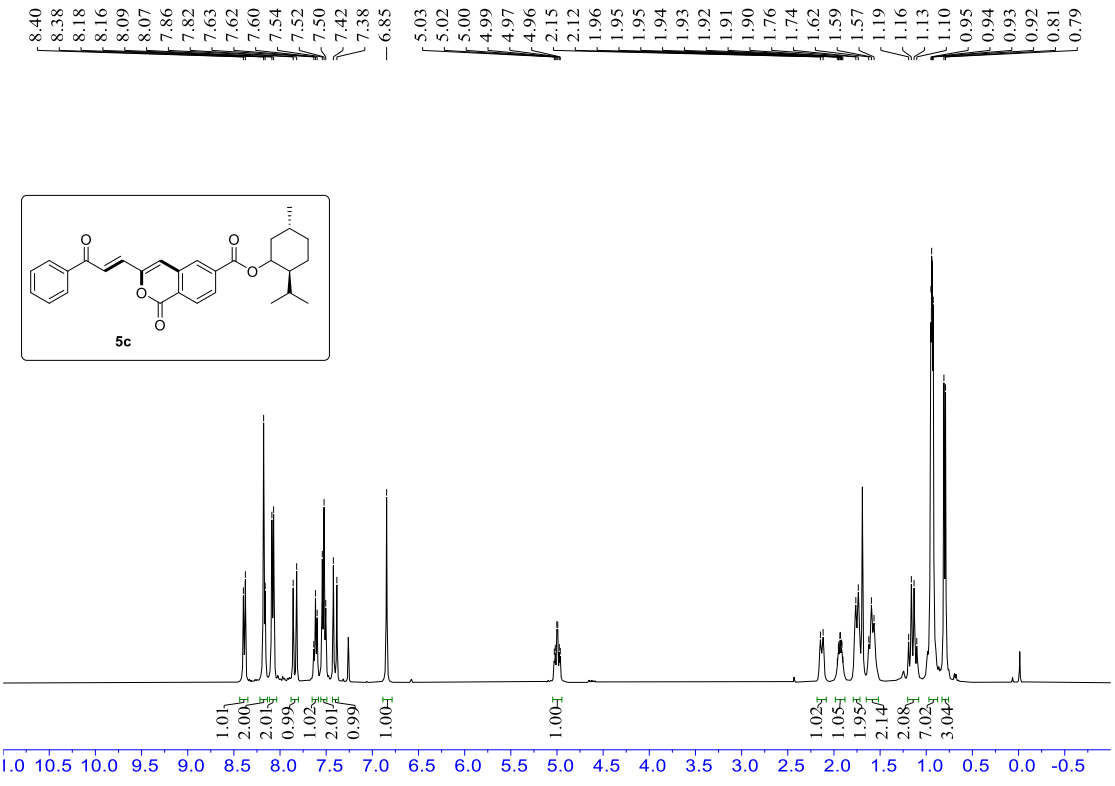
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5a**



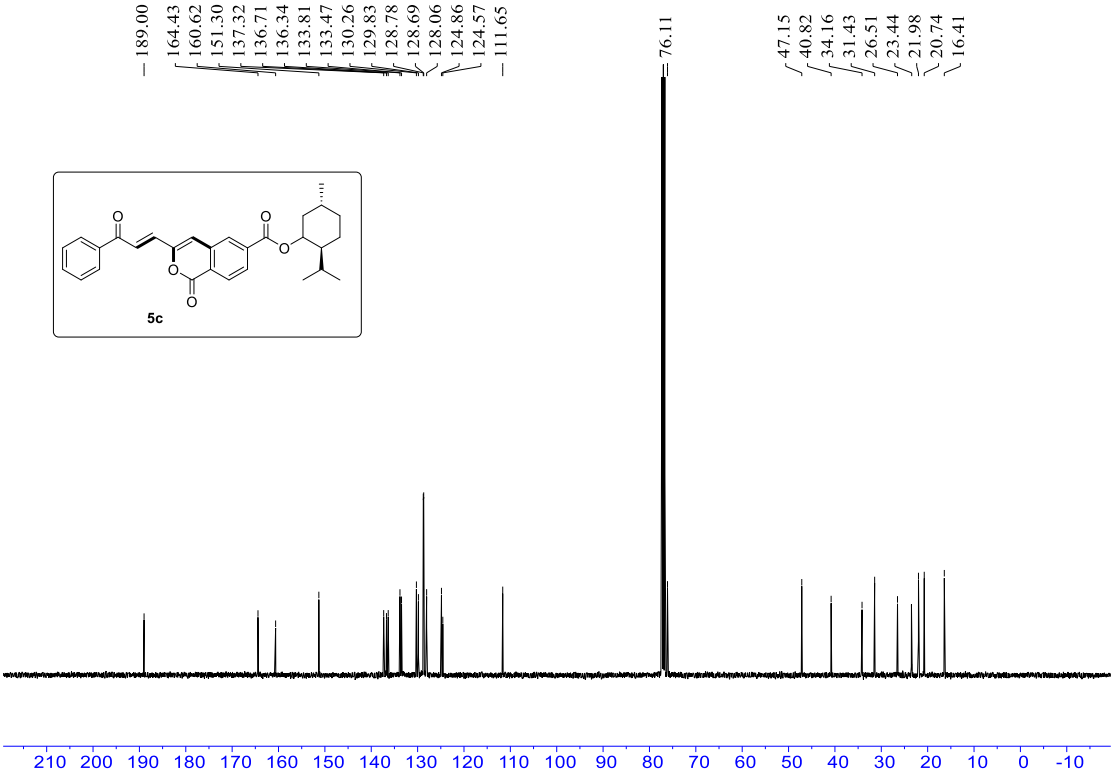
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5b**



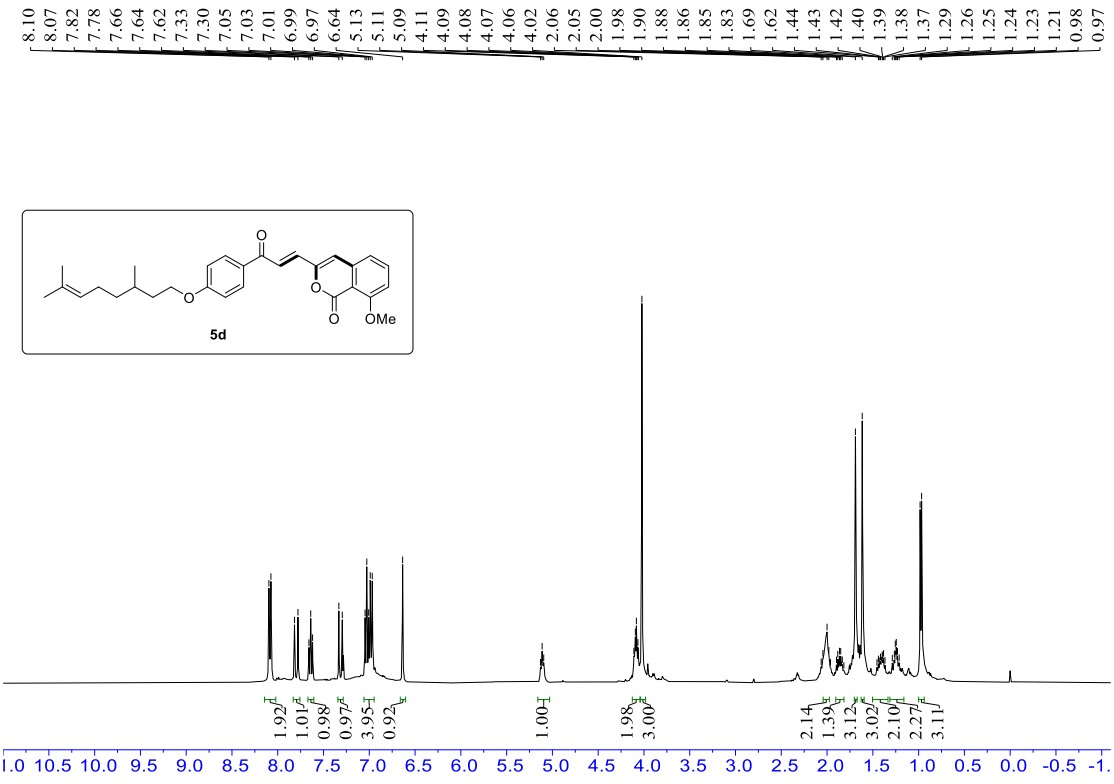
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5b**



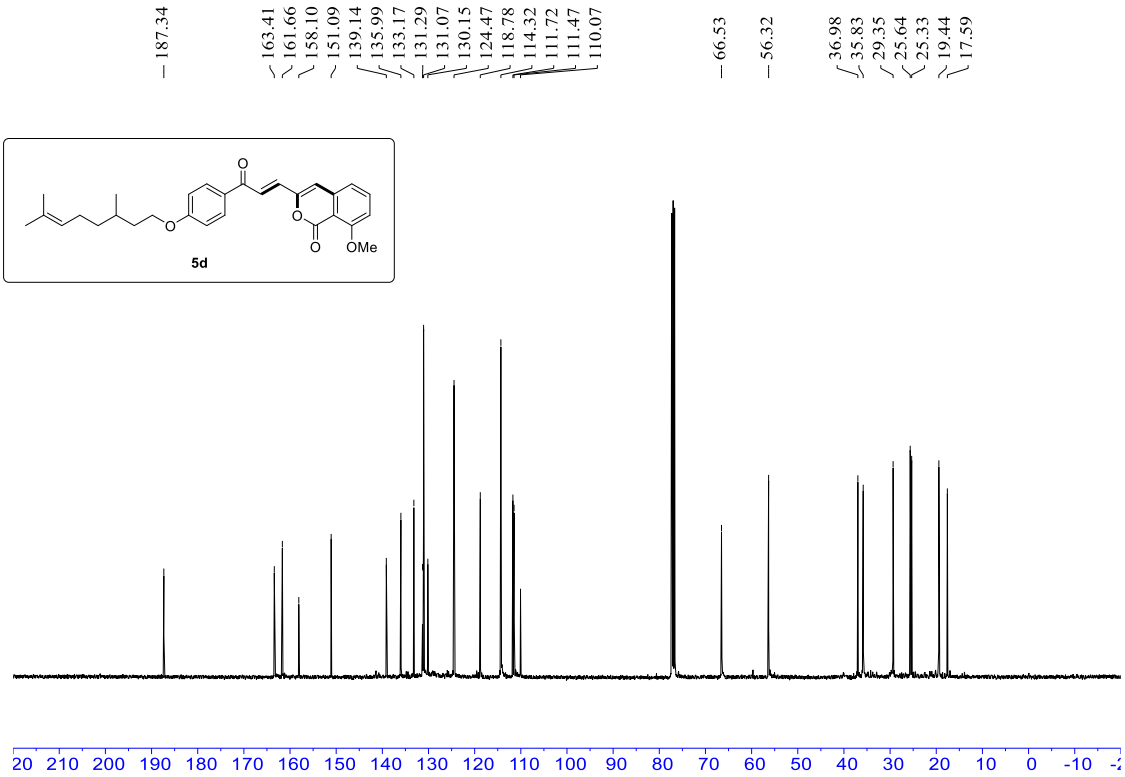
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5c**



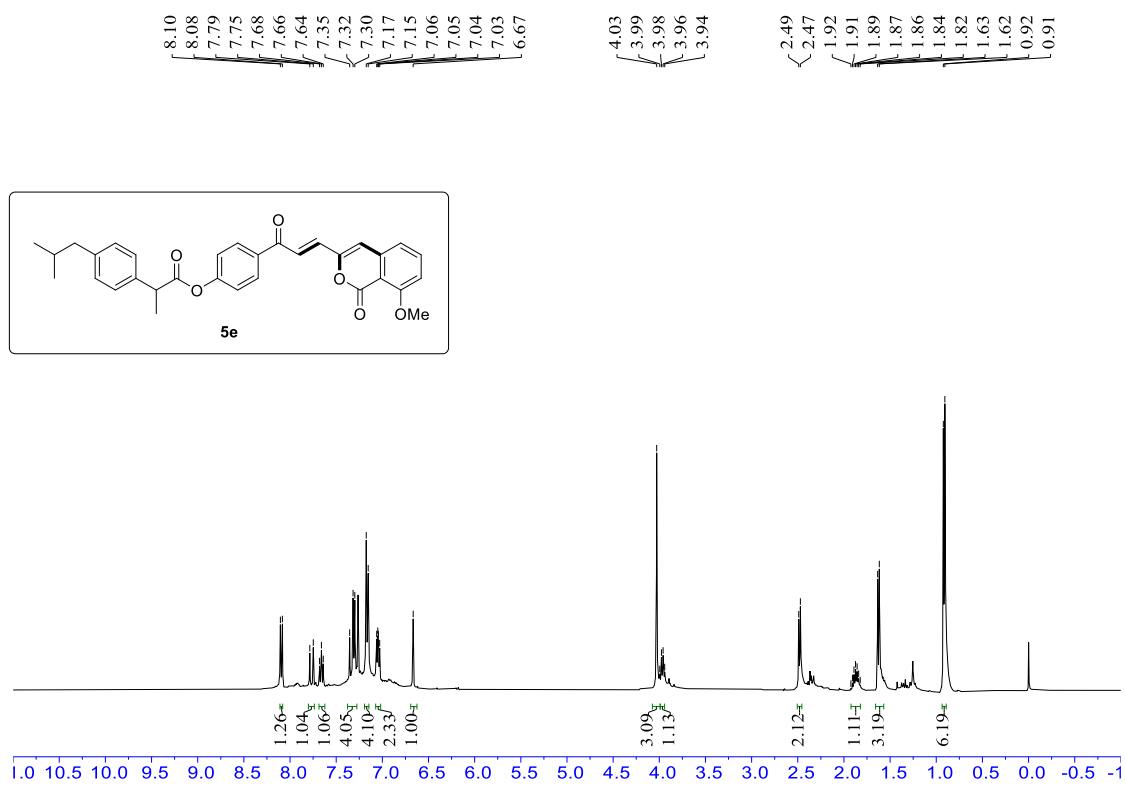
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5c**



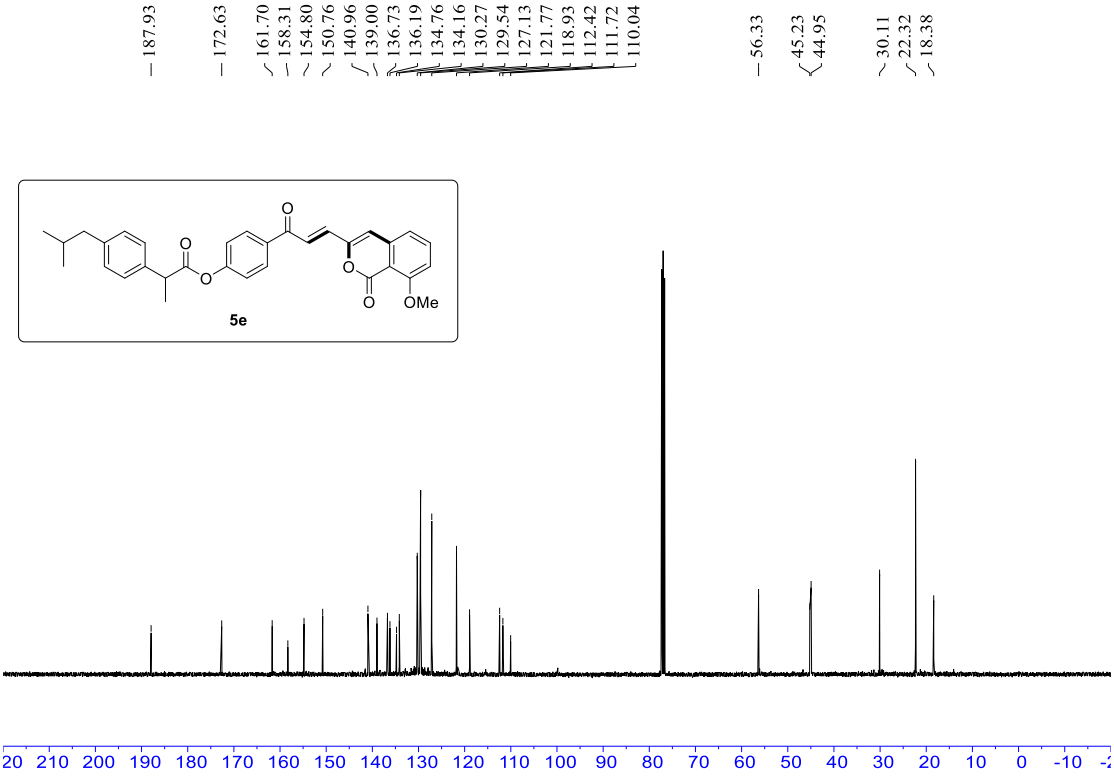
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5d**



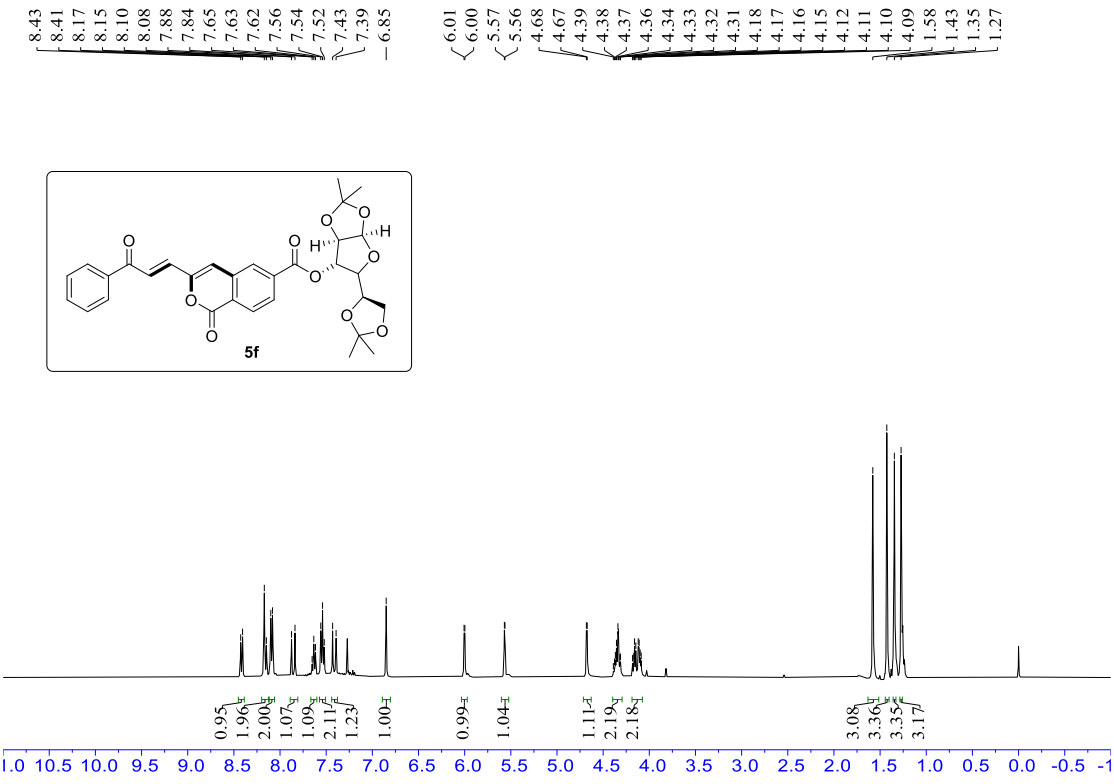
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5d**



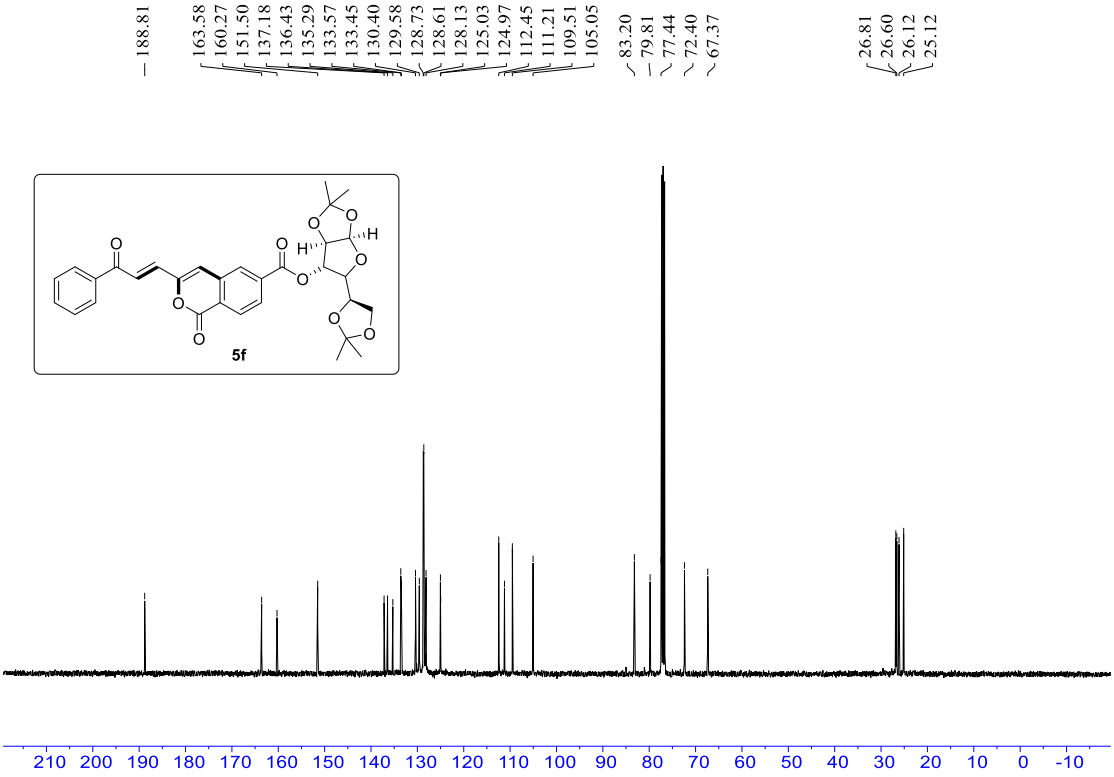
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5e**



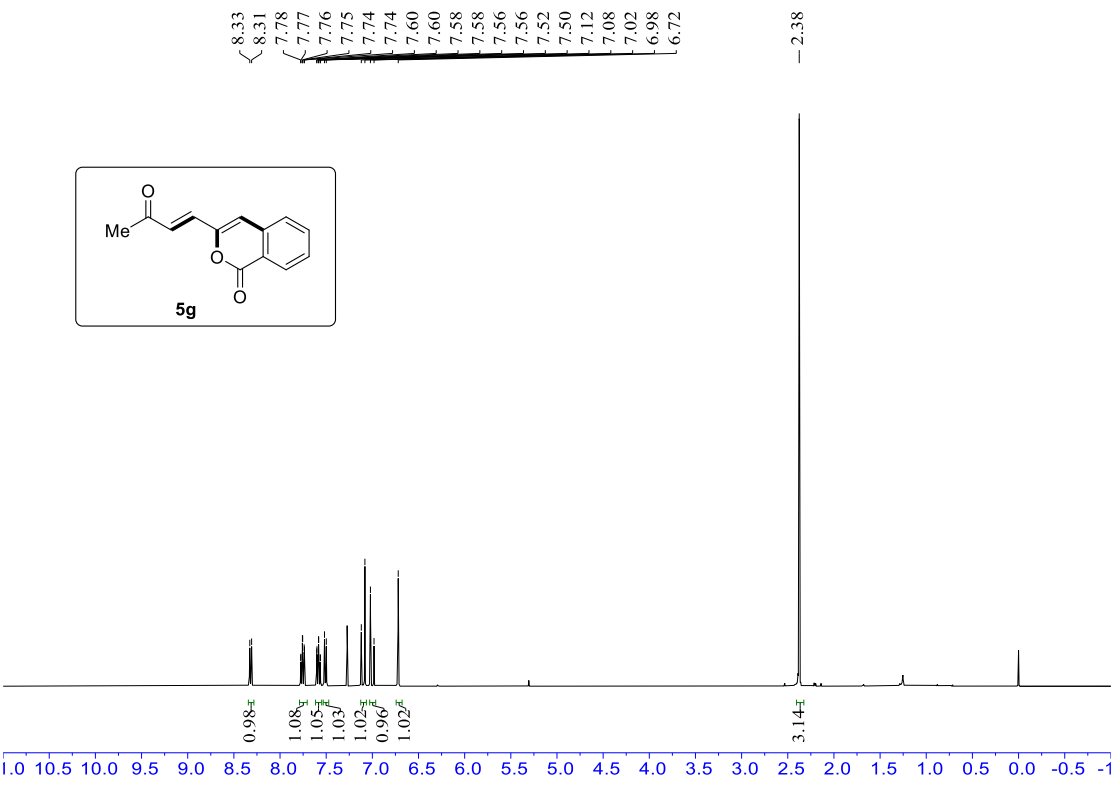
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5e**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5f**

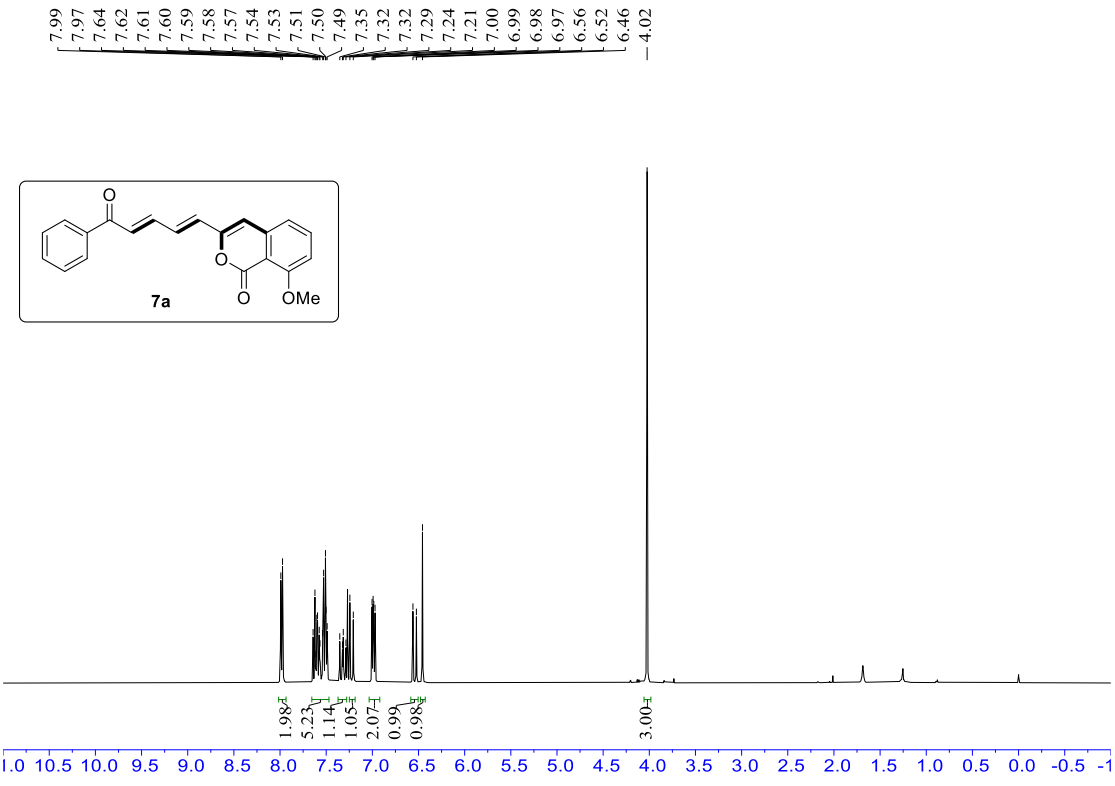


^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5f**

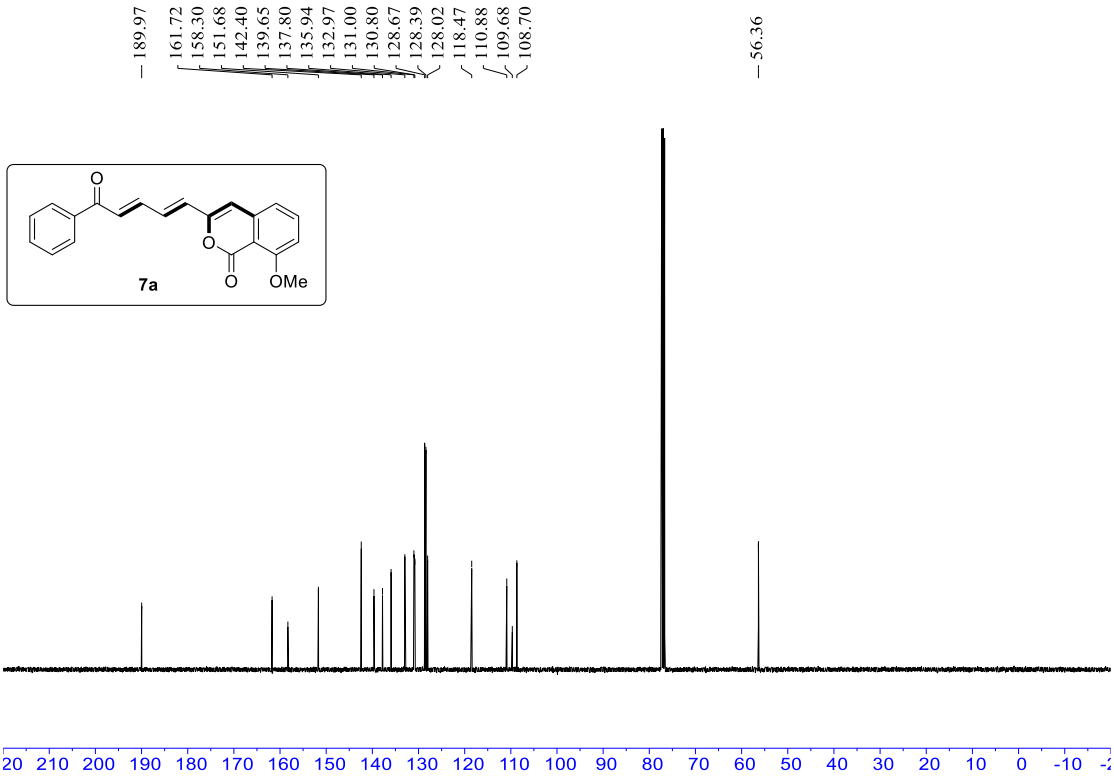


^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **5g**

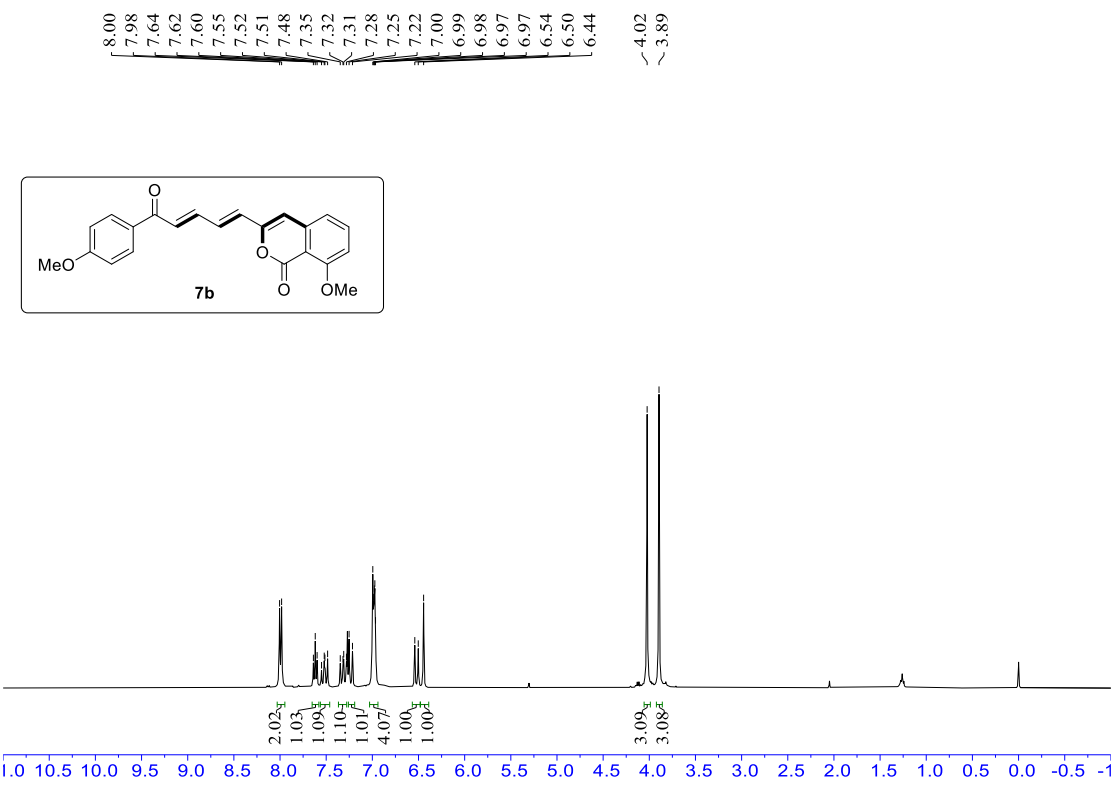
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **5g**



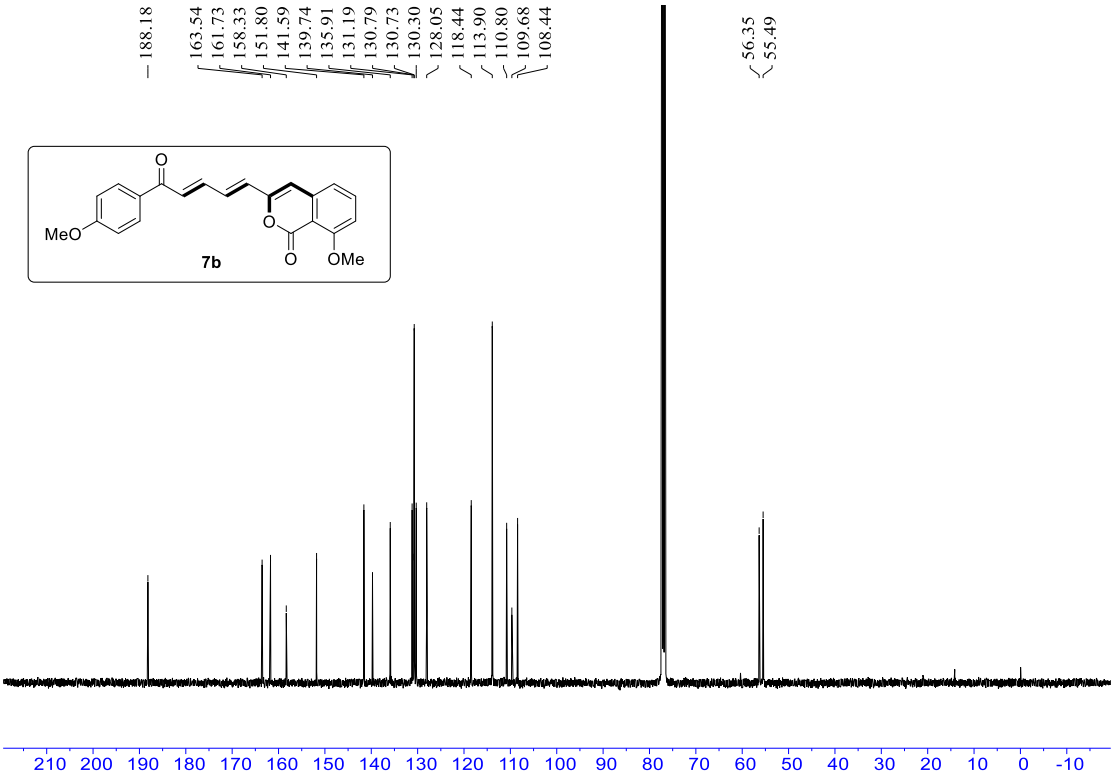
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7a**



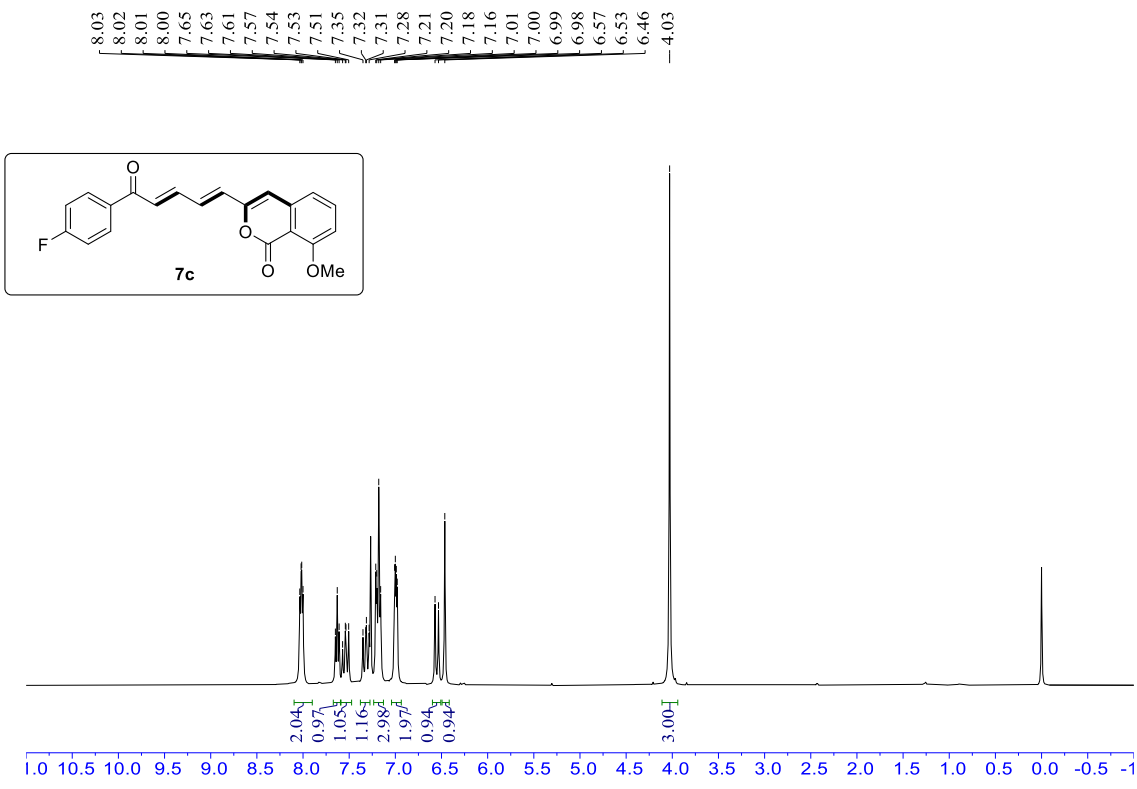
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7a**



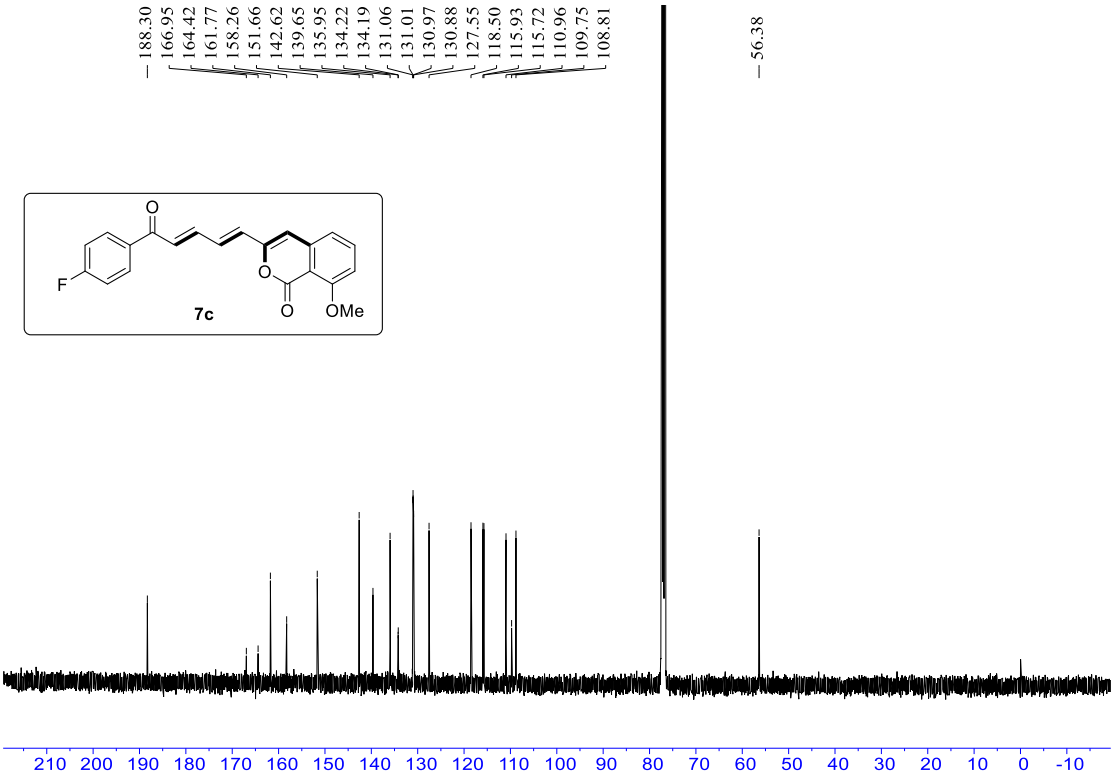
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7b**



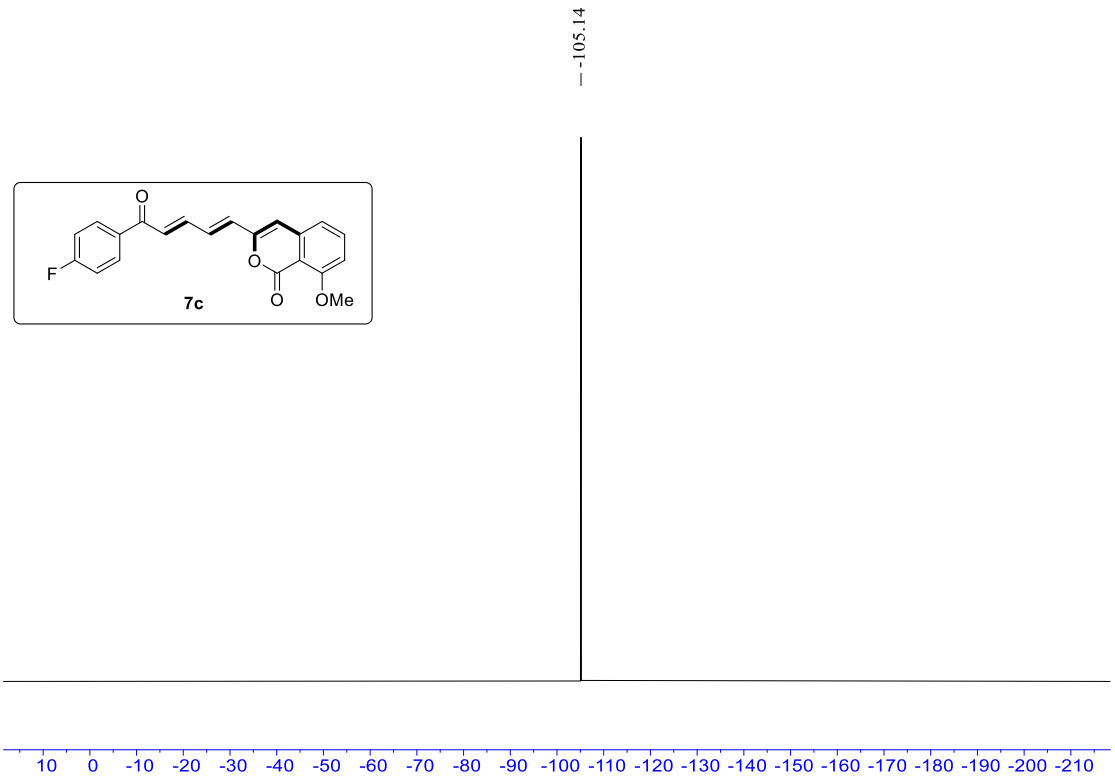
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7b**



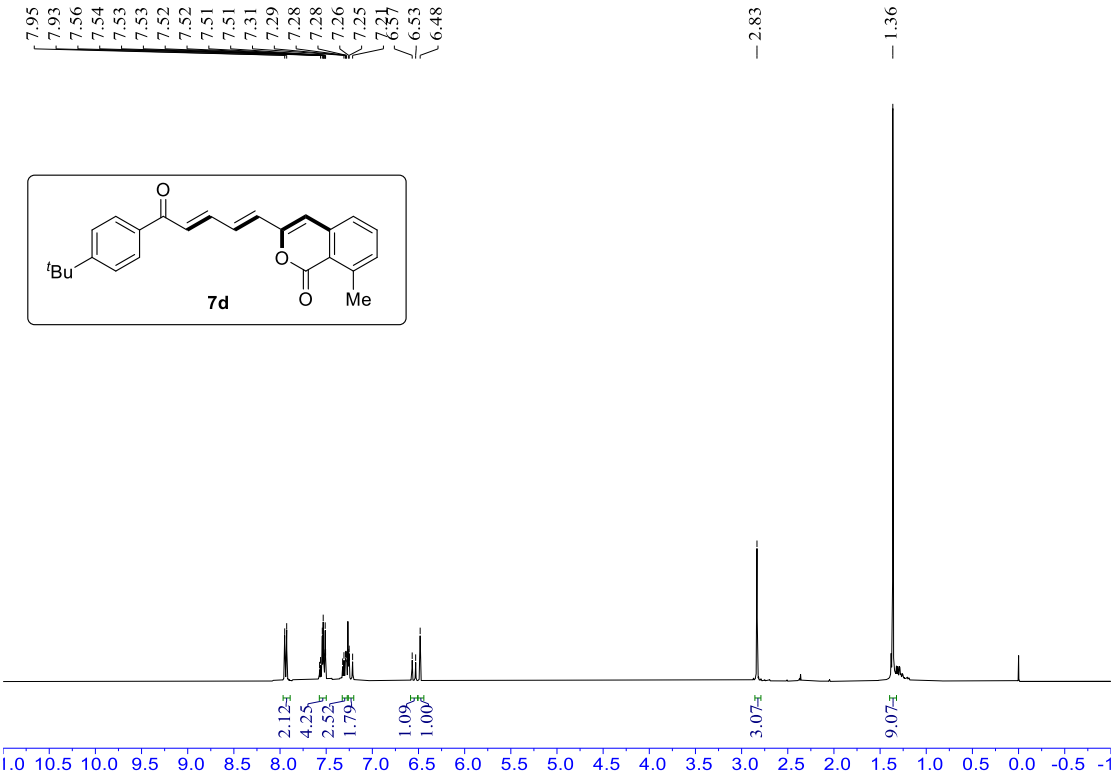
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7c**



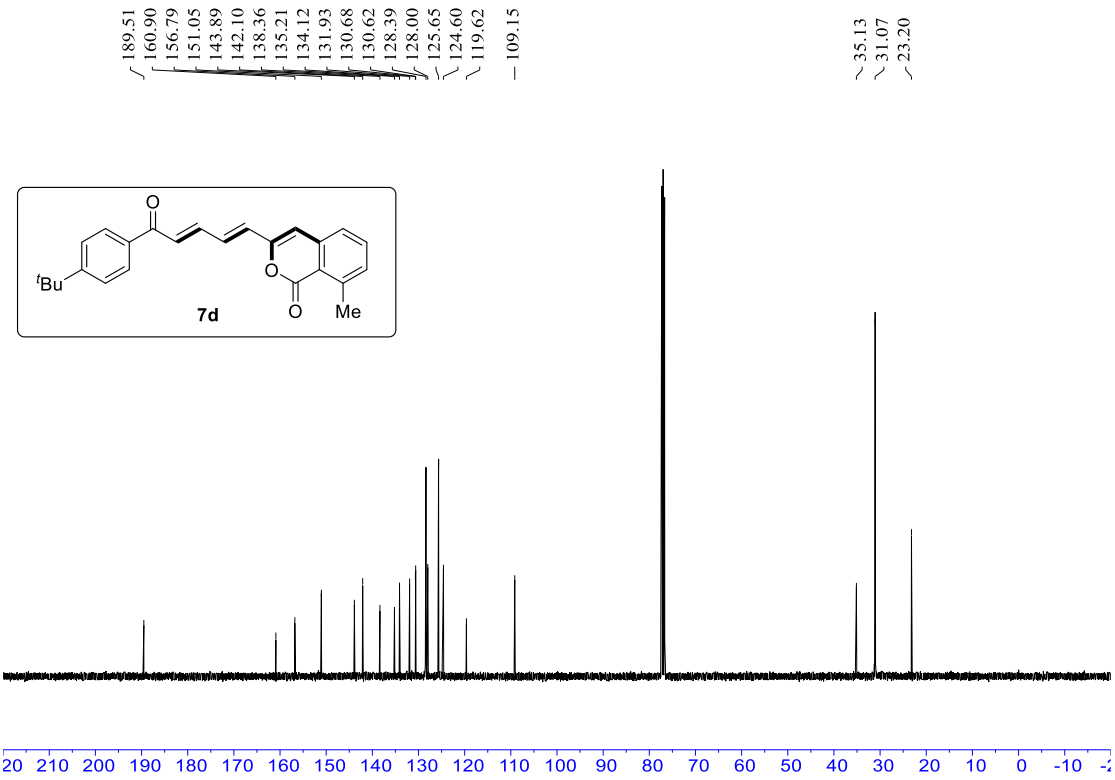
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7c**



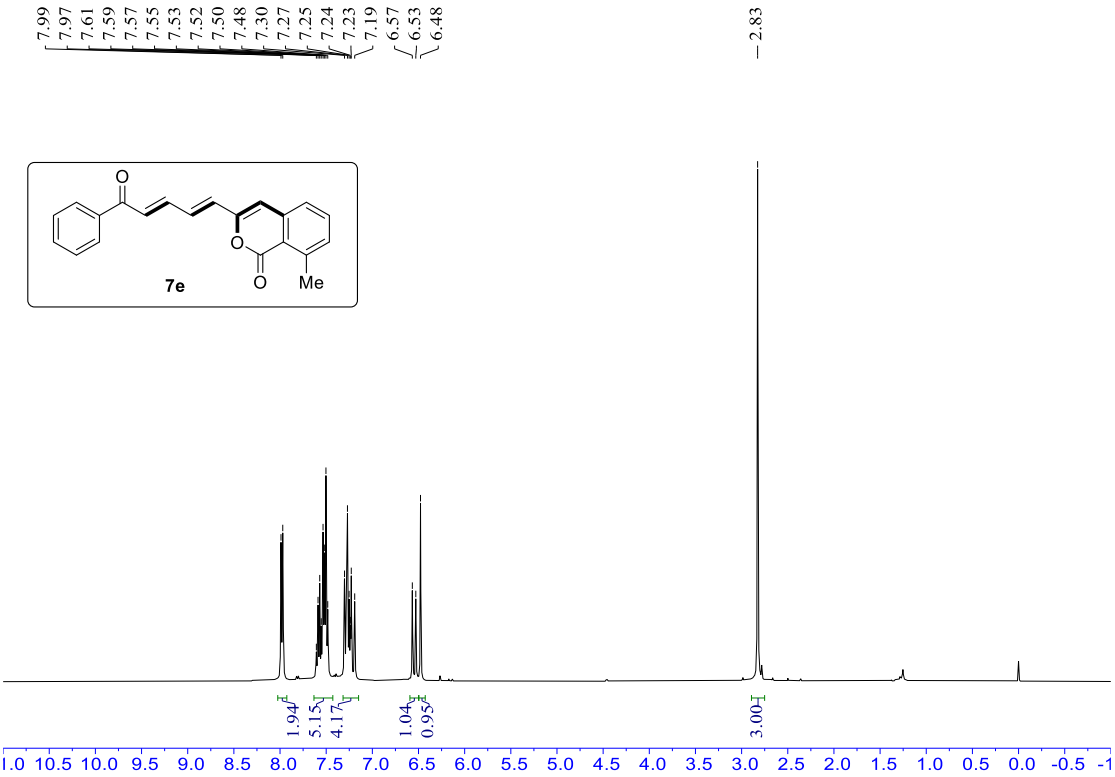
^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **7c**



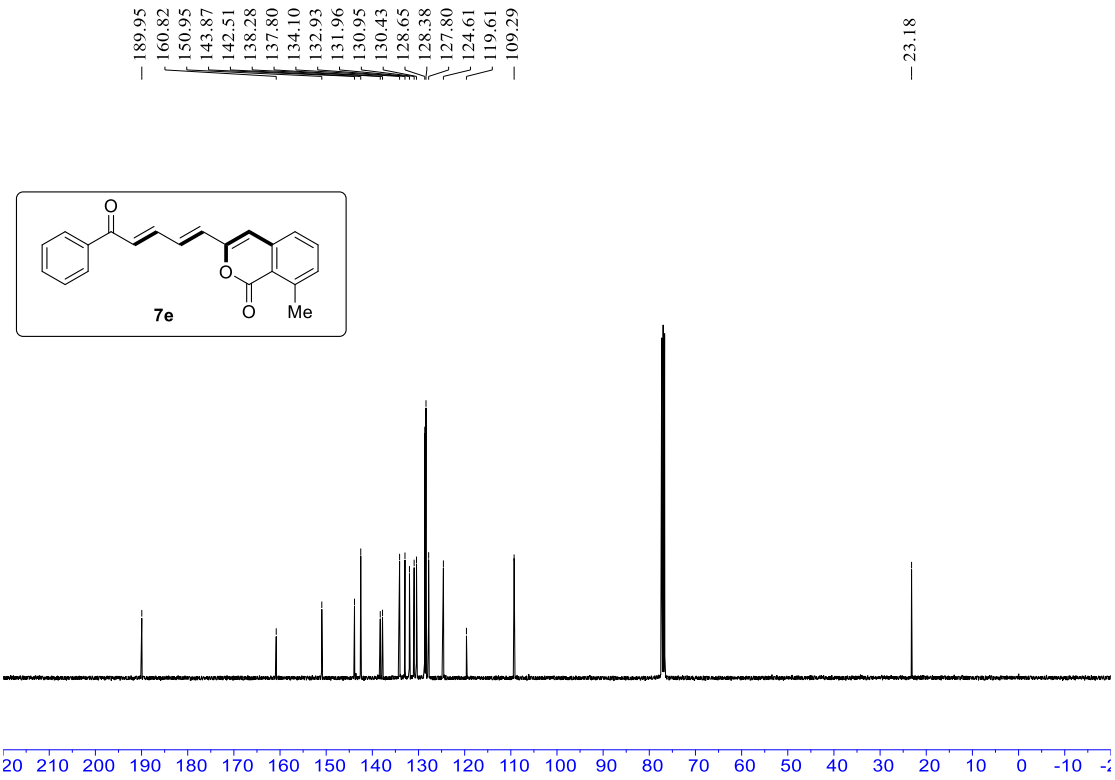
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7d**



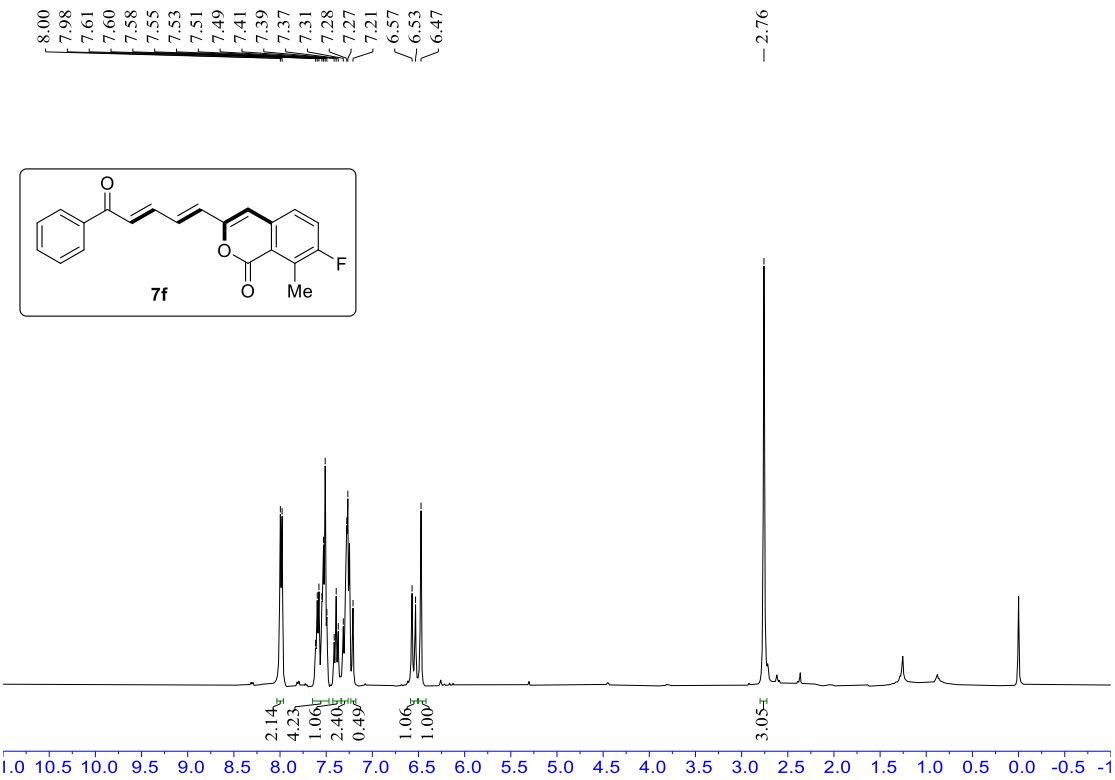
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7d**



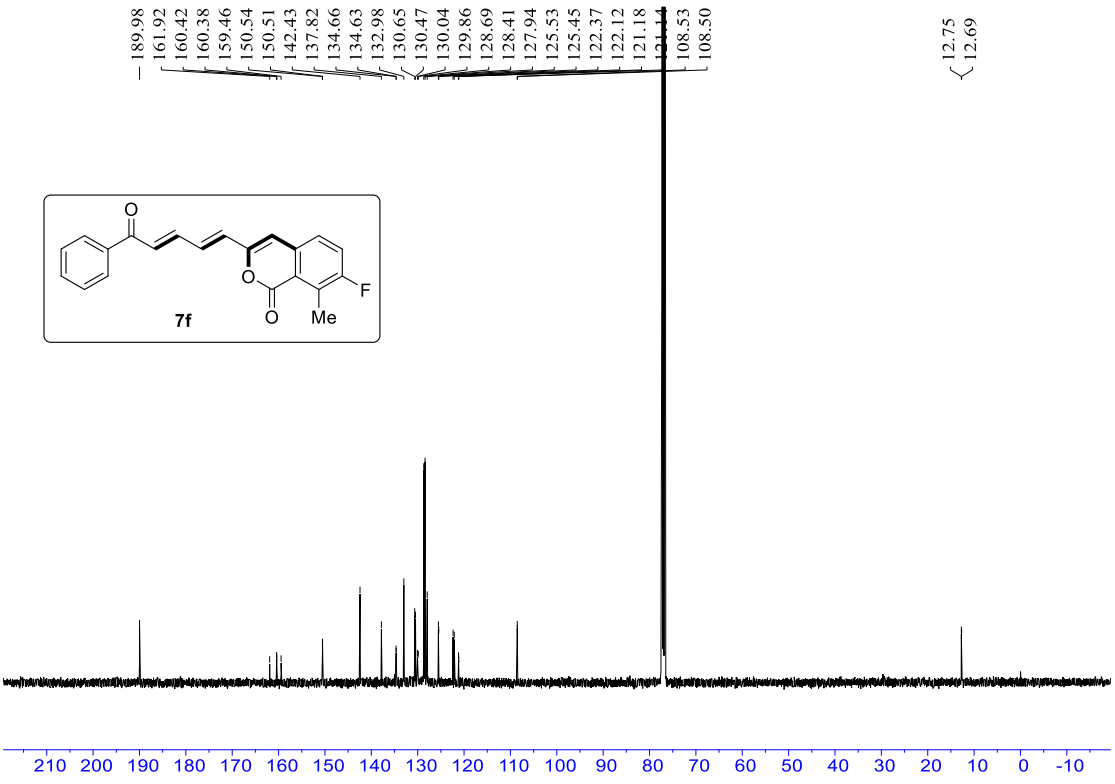
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7e**



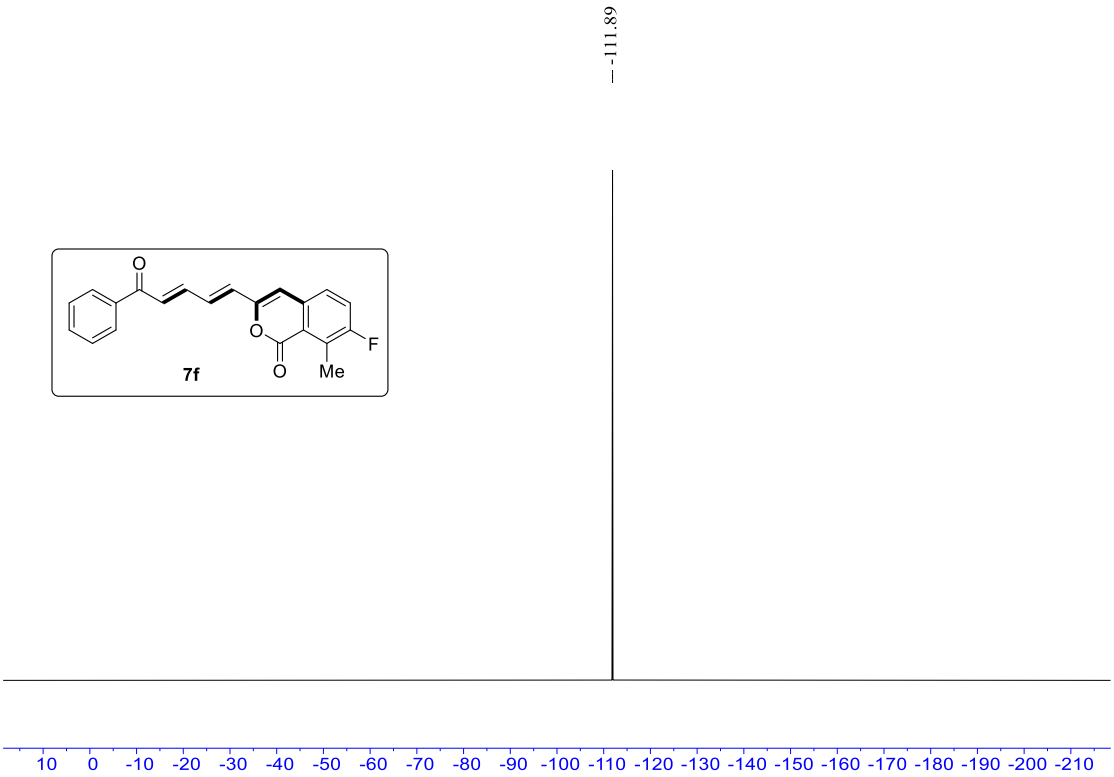
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7e**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **7f**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **7f**



^{19}F NMR (376 MHz, $CDCl_3$) spectrum for **7f**