

## Supporting Information

### Intramolecular Friedel–Crafts Acylation Reaction Promoted by 1,1,1,3,3,3-Hexafluoroisopropanol

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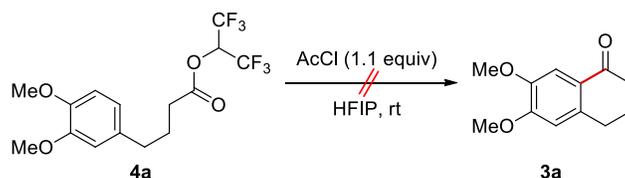
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## General Information

Reactions were performed under an inert atmosphere (argon, Ar or nitrogen, N<sub>2</sub>) either in flame-dried or oven-dried glassware, or glass sample vial with rubber-lined cap. The stainless steel needles used for handling anhydrous solvents and reagents were oven dried and flushed with N<sub>2</sub> prior to use. Plastic syringes were flushed with N<sub>2</sub> before use. All chemicals were used as received from commercial source, without further purification. Dichloromethane (DCM) and tetrahydrofuran (THF) were dried by passage through neutral alumina columns using a commercial solvent purification system prior to use. Thin-layer chromatography (TLC) was performed using commercial glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished with UV light. Flash chromatography was carried out on a normal or reverse phase CombiFlash<sup>®</sup> purification system (4, 12, or 24 g normal phase silica flash columns or 50 g HP C18 Gold column were used). Infrared (IR) spectra were acquired as thin films or solids. All nuclear magnetic resonance (NMR) spectra (<sup>1</sup>H, <sup>13</sup>C, APT, COSY, HSQC, HMBC, and NOESY) were recorded on either a 400 MHz or a 500 MHz with a dual carbon/proton cryoprobe instrument. NMRs were recorded in deuterated solvents (chloroform, dimethyl sulfoxide, or methylene chloride). Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent ( $\delta$  7.26, 2.50, and 5.32 ppm with respect to CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub>, and CD<sub>2</sub>Cl<sub>2</sub> for <sup>1</sup>H NMR and  $\delta$  77.23, 39.52, and 53.84 ppm with respect to CDCl<sub>3</sub>, DMSO-*d*<sub>6</sub>, and CD<sub>2</sub>Cl<sub>2</sub> for <sup>13</sup>C NMR, respectively). Coupling constants are given in Hertz (Hz). HRMS data were collected with a LCT Premier time-of-flight mass spectrometer and an electrospray ion source (ESI). Melting points were determined on an automated melting point apparatus and are uncorrected. Sample concentrator using N<sub>2</sub> gas was utilized for the concentration of reaction mixtures.

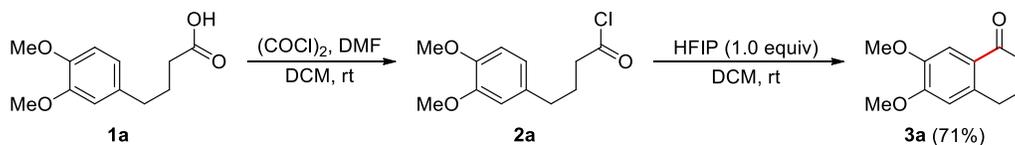
4-(3,4-Dimethoxyphenyl)butanoic acid **1a**, 4-(2-thienyl)butyric acid **1e**, 3-(2-naphthylthio)propionic acid **1l**,  $\alpha$ -phenyl-*o*-toluic acid **1o**, 2-phenoxybenzoic acid **1r**, 3-(3-thienyl)propanoic acid **1ac**, 3-(1-methyl-1*H*-indol-3-yl)propanoic acid **1ad**, and 1,1'-biphenyl]-2-carboxylic acid **1al** were commercially purchased.

## Experimental Procedures for Scheme 2 (Control Experiments to Probe Mechanism)



### (a) Reaction of 4a with acetyl chloride in HFIP:

To a solution of 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(3,4-dimethoxyphenyl)butanoate **4a** (37.3 mg, 0.100 mmol, 1.0 equiv) in HFIP (0.25 mL) in a flame-dried N<sub>2</sub>-flushed 1 dram vial at rt was added acetyl chloride (7.79  $\mu$ L, 0.110 mmol, 1.1 equiv) and the resulting reaction mixture was stirred at rt for 1.5 h. No reaction was observed and crude <sup>1</sup>H NMR only showed peaks corresponding to **4a**.

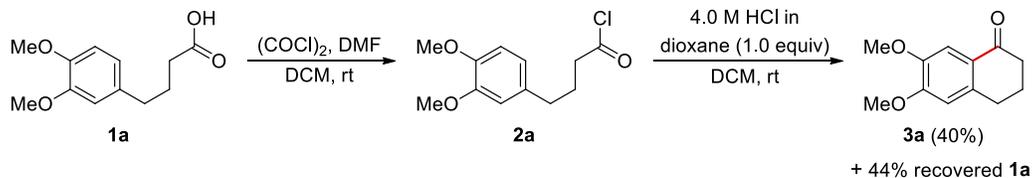


### (b) Reaction of 2a with 1 equiv of HFIP in DCM:

**Procedure (Step-1):** Following the general procedure A for Step-1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min.

#### **Procedure (Step-2):**

To a solution of the crude acid chloride **2a** in anhydrous DCM (1.5 mL) in a capped vial at rt was added HFIP (31.6  $\mu$ L, 0.300 mmol, 1.0 equiv) using a microsyringe and the resultant reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N<sub>2</sub> and the resulting residue was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (43.8 mg, 71%) as a colorless solid.

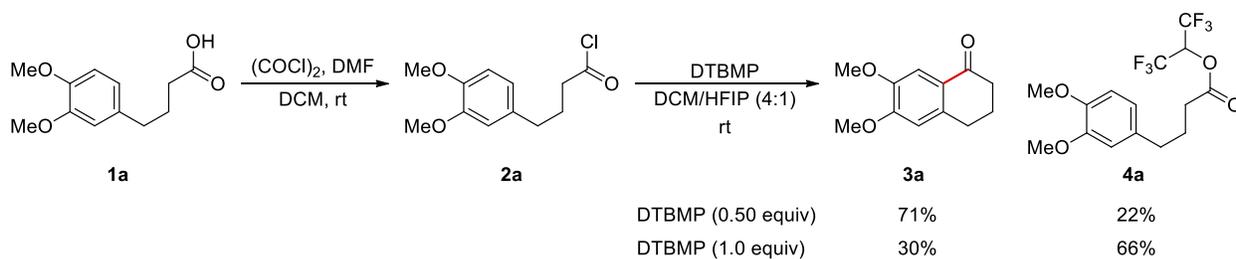


**(c) Reaction of 2a with 1 equiv of HCl in DCM:**

**Procedure (Step-1):** Following the general procedure A for Step-1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min.

**Procedure (Step-2):**

To a solution of the crude acid chloride **2a** in anhydrous DCM (1.5 mL) at rt was added hydrogen chloride (4.0 M solution in dioxane) (75.0  $\mu\text{L}$ , 0.300 mmol, 1.0 equiv) and the resultant reaction mixture was stirred at rt for 1.5 h. Reaction mixture was partially concentrated under  $\text{N}_2$  and the resulting solution including the rinsings in DCM was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–60% EtOAc/hexanes over 30 min) afforded **3a** (26.0 mg, 42%) as a colorless solid. Acid **1a** was recovered in 44% yield (29.9 mg) as a colorless solid.



**(d) Reaction of 2a in the presence of a proton scavenger, DTBMP:**

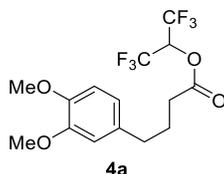
**Procedure (Step-1):** Following the general procedure A for Step-1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min.

**Procedure (Step-2):**

To the same 2-dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.2 mL) followed by the addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP; 61.6 mg, 0.300 mmol, 1.0 equiv). To the resulting suspension was added HFIP (0.30 mL) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under  $\text{N}_2$  and the residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash

purification system using a 12 g normal phase silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **3a** as an off-white solid (18.5 mg, 30%) and **4a** as a colorless oil (74.5 mg, 66%).

In a similar way as described above for Step-2, when 0.50 equiv DTBMP (30.8 mg, 0.150 mmol) was used, **3a** (44.2 mg, 71%) was isolated as an off-white solid and **4a** (25.0 mg, 22%) was obtained as a colorless oil.

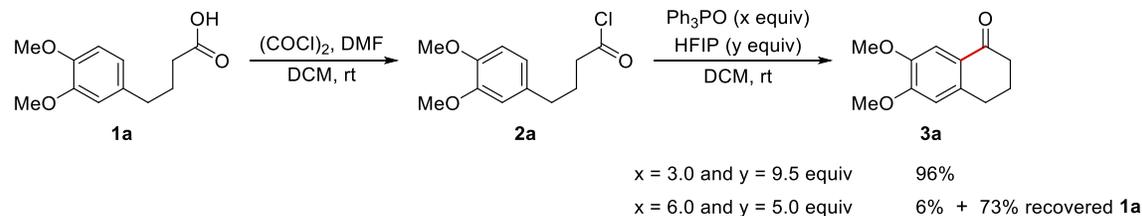


**(e) Reaction of 2a in the presence of pyridine:**

**Procedure (Step-1):** Following the general procedure **B** for Step-1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (22.4 mg, 0.100 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (16.9  $\mu$ L, 0.200 mmol, 2.0 equiv) in 15 min.

**Procedure (Step-2):**

To the same 1 dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (0.25 mL) followed by the addition of pyridine (16.2  $\mu$ L, 0.200 mmol, 2.0 equiv). To the resulting solution was added HFIP (0.25 mL) and the reaction mixture was stirred at rt for 4 h. Reaction mixture was concentrated under  $N_2$  and the resulting residue was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 4 g normal phase silica flash column (0–15% EtOAc/hexanes over 15 min) afforded 1,1,1,3,3,3-hexafluoropropan-2-yl 4-(3,4-dimethoxyphenyl)butanoate **4a** (35.4 mg, 95%) as a colorless oil. TLC (30% EtOAc/hexanes):  $R_f$  = 0.76;  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  6.80 (d,  $J$  = 7.9 Hz, 1H), 6.68–6.72 (m, 2H), 5.79 (hept,  $J$  = 6.2 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.62 (t,  $J$  = 7.5 Hz, 2H), 2.52 (t,  $J$  = 7.4 Hz, 2H), 2.00 (p,  $J$  = 7.4 Hz, 2H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ ):  $\delta$  170.4, 149.3, 147.8, 133.4, 120.5, 116.4–124.9 (m, 2C), 112.0, 111.6, 66.6 (p,  $J$  = 34.7 Hz, 1C), 56.1, 56.0, 34.5, 32.6, 26.5; IR (neat) 1779, 1516, 1196, 1106  $cm^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $C_{15}H_{16}F_6O_4$   $[M + H]^+$ : 375.1031, found: 375.1022.



**(f) Reaction of 2a in the presence of a strong hydrogen bond acceptor, Ph<sub>3</sub>PO:**

**Procedure (Step-1):** Following the general procedure A for Step-1, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min.

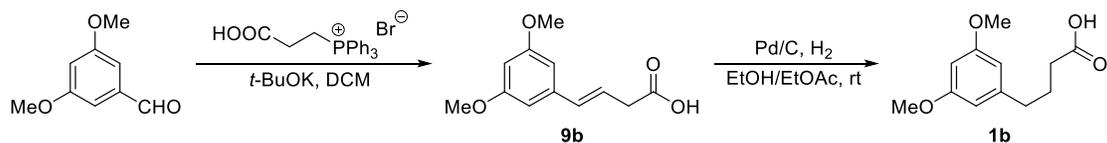
**Procedure (Step-2 with 9.5 Equiv of HFIP and 3.0 Equiv of Ph<sub>3</sub>PO)**

To the same 2 dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.2 mL) followed by the addition of triphenylphosphine oxide (Ph<sub>3</sub>PO; 251 mg, 0.900 mmol, 3.0 equiv). To the resulting solution was added HFIP (0.300 mL, 2.85 mmol, 9.5 equiv) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N<sub>2</sub> and the residue obtained was dissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (59.3 mg, 96%) as a very pale yellow solid.

**Procedure (Step-2 with 5.0 Equiv of HFIP and 6.0 Equiv of Ph<sub>3</sub>PO)**

To the same 2 dram vial containing the crude acid chloride intermediate **2a** at rt was added anhydrous DCM (1.34 mL) followed by the addition of Ph<sub>3</sub>PO (501 mg, 1.80 mmol, 6.0 equiv). To the resulting solution was added HFIP (0.158 mL, 1.50 mmol, 5.0 equiv) and the reaction mixture was stirred at rt for 1.5 h. Reaction mixture was concentrated under N<sub>2</sub> and the residue obtained was dissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g normal phase silica flash column (0–60% EtOAc/hexanes over 30 min) afforded **3a** (4.00 mg, 6%) as a colorless solid. Acid **1a** was recovered in 73% yield (49.3 mg; corrected yield based on ca. 93% purity) as a colorless solid.

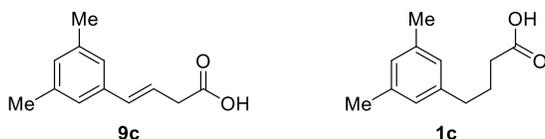
## Syntheses of new compounds



### 4-(3,5-Dimethoxyphenyl)butanoic acid (**1b**):<sup>1</sup>

To a cooled solution of (2-carboxyethyl)triphenylphosphonium bromide (1.50 g, 3.60 mmol, 1.2 equiv) in DCM (5.0 mL) at 0 °C under N<sub>2</sub> atmosphere was added 3,5-dimethoxybenzaldehyde (0.500 g, 3.00 mmol, 1.0 equiv). To the resulting mixture, potassium *tert*-butoxide (0.840 g, 7.50 mmol, 2.5 equiv) was added portion wise and the reaction mixture was allowed to stir at rt for 12 h. The reaction was quenched with water and DCM layer was separated and discarded. The aqueous layer was acidified with 1 M HCl to pH 1 and extracted with EtOAc (10 mL × 3). The combined organic layers were washed with water (10 mL × 1), brine once, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification on a Combiflash purification system using a silica flash column (70:30 hexanes/EtOAc) afforded (*E*)-4-(3,5-dimethoxyphenyl)but-3-enoic acid **9b**<sup>2</sup> (0.153 g, 23%) as a colorless solid.

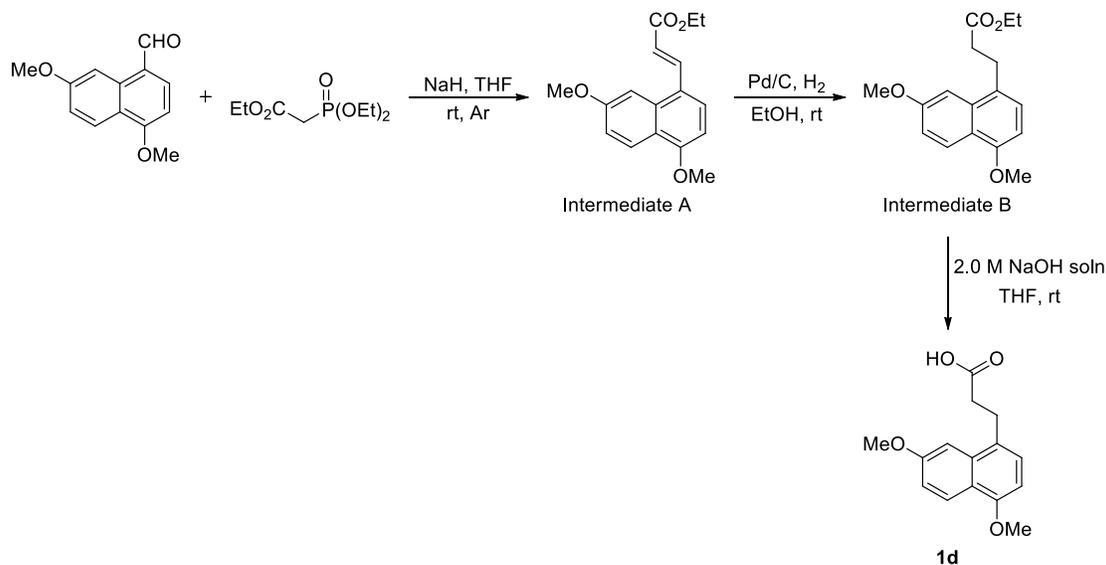
To a solution of compound **9b** (0.152 g, 0.680 mmol) in EtOAc (2.0 mL) under Ar atmosphere was added 10% of palladium(II) carbon (15.0 mg, 10 wt%) followed by EtOH (6.0 mL). The reaction mixture was evacuated under vacuum and flushed with hydrogen (H<sub>2</sub>; 3 cycles) and was continued to stir under H<sub>2</sub> atmosphere at rt for 1 h. The reaction mixture was filtered through a pad of celite followed by EtOH rinsings. Solvent evaporation afforded **1b** (0.142 g, 93%) as a colorless solid.



### 4-(3,5-Dimethylphenyl)butanoic acid (**1c**):

Following the procedure described for compound **1b**, 3,5-dimethylbenzaldehyde (1.00 g, 7.45 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.71 g, 8.94 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.09 g, 18.6 mmol, 2.5 equiv) to afford (*E*)-4-(3,5-dimethylphenyl)but-3-enoic acid **9c** (0.475 g, 33%) as a colorless oil. TLC (50% EtOAc/Hexanes): R<sub>f</sub> = 0.30; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.00 (dd, *J* = 1.7, 0.9 Hz, 2H), 6.93–6.84 (m, 1H), 6.46 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.25 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.28 (dd, *J* = 7.1, 1.4 Hz, 2H), 2.30 (d, *J* = 0.8 Hz, 6H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 177.2, 138.2 (2C), 136.8, 134.4, 129.6, 124.4 (2C), 120.6, 38.1, 21.4 (2C); IR (neat) 3700–2300, 1755 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>12</sub>H<sub>15</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 191.1072, found: 191.1043.

Compound **9c** (0.420 g, 2.21 mmol) was then reduced with palladium(II) carbon (0.0420 g, 10 wt%) under H<sub>2</sub> atmosphere to afford **1c** (0.400 g, 94%) as a colorless solid. Mp: 61–62 °C; TLC (50% EtOAc/Hexanes): R<sub>f</sub> = 0.50; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.84 (d, *J* = 1.8 Hz, 1H), 6.82–6.77 (m, 2H), 2.65–2.55 (m, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.29 (d, *J* = 0.8 Hz, 6H), 1.95 (p, *J* = 7.5 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 180.0, 141.3, 138.1 (2C), 127.9, 126.5 (2C), 35.1, 33.6, 26.4, 21.5 (2C); IR (neat) 3400–2300, 1687 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>12</sub>H<sub>17</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 193.1229, found: 193.1213.



### 3-(4,7-Dimethoxynaphthalen-1-yl)propanoic acid (**1d**):

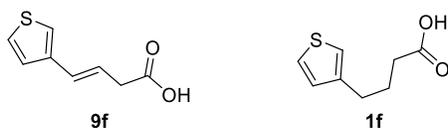
Following a modification of the literature procedure,<sup>3</sup> 3-(4,7-dimethoxynaphthalen-1-yl)propanoic acid **1d** was prepared from 4,7-dimethoxy-1-naphthaldehyde in the following manner:

To a suspension of sodium hydride (60% dispersion in mineral oil) (72.0 mg, 1.80 mmol, 1.2 equiv; washed with hexanes once) in anhydrous THF (4.0 mL) in a flame-dried RBF at rt under Ar was added a solution of triethyl phosphonoacetate (403 mg, 1.80 mmol, 1.2 equiv) in anhydrous THF (1.5 mL, including the washings) slowly over 5 min (effervescence was observed). The resulting solution was stirred at rt for 30 min. A solution of 4,7-dimethoxy-1-naphthaldehyde (324 mg, 1.50 mmol, 1.0 equiv) in anhydrous THF (2.5 mL, including the washings) was added slowly to the reaction mixture over 15 min and the stirring was continued at rt for 2 h. Some unreacted 4,7-dimethoxy-1-naphthaldehyde was observed by TLC, so additional sodium hydride (24.0 mg, 0.600 mmol, 0.40 equiv) and triethyl phosphonoacetate (101 mg, 0.450 mmol, 0.30 equiv) was directly added into the reaction mixture and the reaction mixture was continued to stir at rt for another 1 h. Reaction mixture was concentrated, diluted with water (30 mL), and extracted with ether (25 mL × 2). The combined organic layers were washed with brine (30 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to afford 429 mg of crude **Intermediate A**

[(*E*)-ethyl 3-(4,7-dimethoxynaphthalen-1-yl)acrylate] as a semisolid residue, which was used as such for the next hydrogenation step.

To a solution of the crude **Intermediate A** (429 mg) in ethanol (8.0 mL) under N<sub>2</sub> was added 10% of palladium(II) carbon (43.1 mg, 0.405 mmol, 10 wt%). The resulting suspension was evacuated under vacuum and flushed with H<sub>2</sub> twice and was continued to stir under H<sub>2</sub> atmosphere at rt for 3.5 h. The reaction mixture was filtered through a Celite bed followed by ether rinsings. Solvent evaporation afforded crude **Intermediate B** [(ethyl 3-(4,7-dimethoxynaphthalen-1-yl)propanoate] as an oily residue, which was used as such for the next saponification step.

To a solution of **Intermediate B** in THF (4.0 mL) at rt in an open-flask was added sodium hydroxide (2.0 M solution in deionized water; 6.00 mL, 12.00 mmol, 8.0 equiv) and the resulting biphasic solution was stirred at rt for 12 h. Reaction mixture was acidified with 1.0 M aqueous HCl with stirring until acidic (pH = 1) and the resulting aqueous suspension was extracted with DCM (25 mL × 2). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give a creamish-orange solid. The solid was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% MeOH/DCM over 25 min) afforded **1d** (347 mg, 89% over 3 steps) as a creamish solid. Mp: 148.5–150 °C; TLC (30% EtOAc/hexanes): R<sub>f</sub> = 0.21; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.16 (brs, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 1H), 7.15 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.17 (t, *J* = 7.5 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 174.0, 157.8, 153.8, 133.4, 127.4, 126.4, 123.8, 120.1, 116.6, 102.7, 101.9, 55.3, 55.1, 34.4, 27.1; IR (neat) 3350–2350, 1710, 1692 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>17</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 261.1127, found: 261.1118.

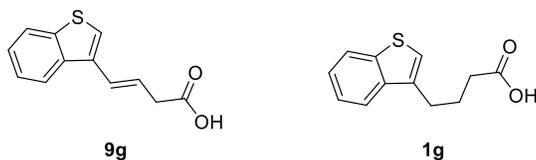


#### 4-(Thiophen-3-yl)butanoic acid (**1f**):

Following the procedure described for compound **1b**, 3-thiophenecarboxaldehyde (1.00 g, 8.92 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (4.44 g, 10.7 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.50 g, 22.3 mmol, 2.5 equiv) to afford (*E*)-4-(thiophen-3-yl)but-3-enoic acid **9f**<sup>†</sup> (0.375 g, 26%) as a golden brown solid. Mp: 90–92 °C; TLC (50% EtOAc/Hexanes): R<sub>f</sub> = 0.40; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.29–7.25 (m, 1H), 7.21 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.14 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.53 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.13 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.26 (dd, *J* = 7.1, 1.5 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 177.5, 139.5, 128.4, 126.3, 125.2, 122.3, 120.9,

38.0; IR (neat) 3400–2100, 1705  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_9\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$ : 169.0323, found: 169.0309.

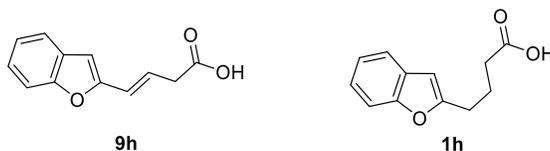
Compound **9f** (0.357 g, 2.12 mmol) was then reduced with palladium(II) carbon (0.0357 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1f** (0.360 g, 99%) as a colorless oil. TLC (50% EtOAc/Hexanes):  $R_f = 0.60$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.28–7.24 (m, 1H), 6.95 (ddt,  $J = 8.0, 4.3, 2.2$  Hz, 2H), 2.71 (t,  $J = 7.5$  Hz, 2H), 2.49–2.26 (m, 2H), 1.97 (p,  $J = 7.4$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  179.2, 141.7, 128.3, 125.7, 120.8, 33.5, 29.6, 25.7; IR (neat) 3500–2300, 1700  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_{11}\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$ : 171.0480, found: 171.0463.



#### 4-(Benzo[*b*]thiophen-3-yl)butanoic acid (**1g**):<sup>5</sup>

Following the procedure described for compound **1b**, thianaphthene-3-carboxaldehyde (1.00 g, 6.16 mmol, 1.0 equiv) was reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.07 g, 7.39 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.73 g, 15.4 mmol, 2.5 equiv) to afford (*E*)-4-(benzo[*b*]thiophen-3-yl)but-3-enoic acid **9g** (0.550 g, 41%) as an orange solid. Mp: 93–95  $^\circ\text{C}$ ; TLC (50% EtOAc/hexanes):  $R_f = 0.30$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94–7.81 (m, 2H), 7.44 (s, 1H), 7.43–7.33 (m, 2H), 6.80 (dq,  $J = 15.9, 1.3$  Hz, 1H), 6.37 (dt,  $J = 15.9, 7.1$  Hz, 1H), 3.38 (dd,  $J = 7.2, 1.5$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  176.1, 140.7, 137.8, 133.6, 126.6, 124.7, 124.5, 123.1, 122.9, 122.5, 122.1, 38.3; IR (neat) 3300–2200, 1681  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{11}\text{O}_2\text{S}$   $[\text{M} + \text{H}]^+$ : 219.0480, found: 219.0465.

Compound **9g** (0.424 g, 1.94 mmol) was then reduced with palladium(II) carbon (0.0424 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1g** (0.354 g, 83%) as a colorless solid.

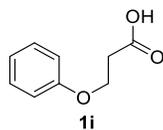


#### 4-(Benzofuran-2-yl)butanoic acid (**1h**):<sup>6</sup>

Following the procedure described for compound **1b**, 2-benzofurancarboxaldehyde (1.00 g, 6.84 mmol, 1.0 equiv) were reacted with (2-carboxyethyl)triphenylphosphonium bromide (3.41 g, 8.21 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.92 g, 17.1 mmol, 2.5 equiv) to afford impure (*E*)-4-(benzofuran-2-yl)but-3-enoic acid **9h** (0.450 g, 33%; >85% pure as determined by  $^1\text{H}$  NMR) as a yellow

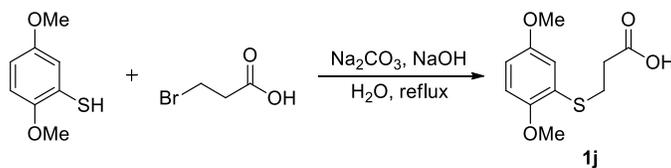
solid. Mp: 110–112 °C; TLC (50% EtOAc/hexanes):  $R_f$  = 0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (ddd,  $J$  = 7.6, 1.4, 0.7 Hz, 1H), 7.46–7.41 (m, 1H), 7.28–7.41 (m, 1H), 7.19 (td,  $J$  = 7.5, 1.0 Hz, 1H), 6.60–6.44 (m, 3H), 3.35 (d,  $J$  = 6.3 Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  176.5, 155.0, 154.1, 129.0, 124.8, 123.2, 123.0, 122.7, 121.1, 111.2, 104.8, 37.9; IR (neat) 3400–2100, 1687  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_9\text{O}_3$  [ $\text{M} - \text{H}$ ] $^-$ : 201.0552, found: 201.0556.

Compound **9h** (0.300 g, 1.48 mmol; impure) was then reduced with palladium(II) carbon (0.0300 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1h** (0.235 g, 78%) as a colorless solid. Mp: 76–78 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.50;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.53–7.46 (m, 1H), 7.44–7.39 (m, 1H), 7.25–7.12 (m, 2H), 6.43 (d,  $J$  = 0.9 Hz, 1H), 2.86 (t,  $J$  = 7.1 Hz, 2H), 2.47 (t,  $J$  = 7.4 Hz, 2H), 2.10 (p,  $J$  = 7.4 Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  179.1, 158.1, 155.0, 129.0, 123.6, 122.7, 120.5, 111.0, 102.9, 33.2, 27.8, 22.9; IR (neat) 3400–2300, 1692  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{11}\text{O}_3$  [ $\text{M} - \text{H}$ ] $^-$ : 203.0708, found: 203.0709.



### 3-Phenoxypropanoic acid (**1i**):<sup>7</sup>

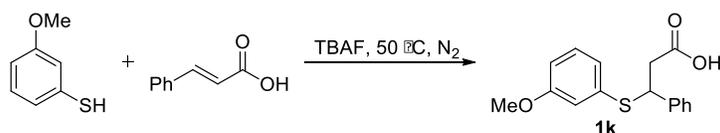
To a solution of phenol (0.500 g, 5.30 mmol, 1.0 equiv) and 3-bromopropionic acid (0.810 mg, 5.30 mmol, 1.0 equiv) in DMF (5.0 mL) at rt under Ar atmosphere was added  $\text{Cs}_2\text{CO}_3$  (3.46 g, 10.6 mmol, 2.0 equiv) and the resulting suspension was continued to stir at rt for 15 h. The reaction mixture was quenched with 1 M HCl to pH 1 and the aqueous layer was extracted with EtOAc (10 mL  $\times$  3). The combined organic layers were washed with water (10 mL  $\times$  1), brine once, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **1i** (0.148 g, 17%) as a colorless solid.



### 3-((2,5-Dimethoxyphenyl)thio)propanoic acid (**1j**):

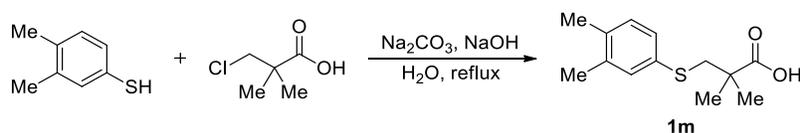
Following a reported procedure,<sup>8</sup> to a suspension of 3-bromopropionic acid (225 mg, 1.47 mmol, 1.05 equiv) in deionized water (5.0 mL) at rt was added anhydrous sodium carbonate (163 mg, 1.54 mmol, 1.1 equiv) slowly. After the effervescence ceased, the clear solution was cooled to ca. 5–10 °C and this cold solution was added to a turbid solution of 2,5-dimethoxybenzenethiol (238 mg, 1.40 mmol, 1.0 equiv) in

sodium hydroxide (84.0 mg, 2.10 mmol, 1.5 equiv) and deionized water (3.0 mL) at rt in a big microwave vial (10–20 mL capacity). The vial was sealed and the resulting turbid solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. Reaction mixture was cooled to rt and extracted with EtOAc (30 mL × 1) and the EtOAc layer was discarded. The aqueous layer was acidified with 2 M aqueous HCl solution (10 mL) and the resulting turbid solution was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The oil obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 25 min) afforded **1j** (257 mg, 76%) as a colorless crystalline solid. Mp: 100–102 °C; TLC (50% EtOAc/hexanes): R<sub>f</sub> = 0.37; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.84 (brs, 1H), 6.91 (d, *J* = 2.9 Hz, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 6.74 (dd, *J* = 8.9, 2.9 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 7.4 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.2, 153.8, 152.4, 124.1, 117.1, 112.4, 111.8, 56.4, 55.9, 34.2, 27.1; IR (neat) 3670–2380, 1707 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>15</sub>O<sub>4</sub>S [M + H]<sup>+</sup>: 243.0691, found: 243.0666.



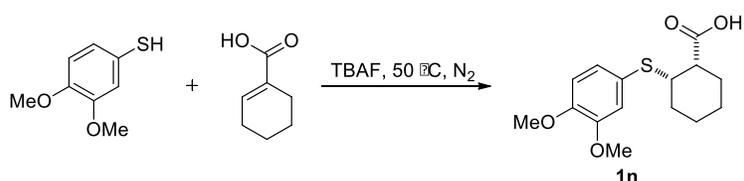
### 3-((3-Methoxyphenyl)thio)-3-phenylpropanoic acid (**1k**):

Following a modification of the reported procedure,<sup>9</sup> to a mixture of 3-methoxybenzenethiol (421 mg, 3.00 mmol, 2.0 equiv) and *trans*-cinnamic acid (223 mg, 1.50 mmol, 1.0 equiv) in a dried N<sub>2</sub>-flushed 2 dram vial at rt was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.751 mL, 0.751 mmol, 0.50 equiv). The vial was capped and the resulting suspension was stirred at 50 °C under N<sub>2</sub> for 6 h (most of the THF was evaporated within 2 h). Reaction mixture was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **1k** (272 mg, 63%) as a colorless solid. Mp: 81–83 °C; TLC (25% EtOAc/hexanes, run twice): R<sub>f</sub> = 0.32; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.64 (brs, 1H), 7.26–7.17 (complex, 5H), 7.11 (m, 1H), 6.88 (m, 1H), 6.76–6.72 (m, 2H), 4.59 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.65 (s, 3H), 2.94 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 177.0, 159.8, 140.4, 134.7, 129.8, 128.7 (2C), 127.9 (3C), 125.6, 118.3, 114.4, 55.4, 48.7, 40.8; IR (neat) 3500–2400, 1707 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>17</sub>O<sub>3</sub>S [M + H]<sup>+</sup>: 289.0898, found: 289.0881.



### 3-((3,4-Dimethylphenyl)thio)-2,2-dimethylpropanoic acid (**1m**):

Following a reported procedure,<sup>8</sup> to a suspension of 3-chloro-2,2-dimethylpropanoic acid (215 mg, 1.58 mmol, 1.05 equiv) in deionized water (5.0 mL) at rt was added anhydrous sodium carbonate (175 mg, 1.65 mmol, 1.1 equiv) slowly. After the effervescence ceased, the clear solution was cooled to ca. 5–10 °C and this cold solution was added to a turbid solution of 3,4-dimethylbenzenethiol (207 mg, 1.50 mmol, 1.0 equiv) in sodium hydroxide (90.0 mg, 2.25 mmol, 1.5 equiv) and deionized water (3.0 mL) at rt in a big microwave vial. The vial was sealed and the resulting turbid solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. Reaction mixture was cooled to rt and acidified with 2 M aqueous HCl solution (10 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The oil obtained was dissolved in hexanes containing a small amount of DCM and the solution was loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **1m** (330 mg, 92%) as an almost colorless crystalline solid. Mp: 70–71.5 °C; TLC (30% EtOAc/hexanes): *R<sub>f</sub>* = 0.51; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.66 (brs, 1H), 7.20 (s, 1H), 7.15 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 3.16 (s, 2H), 2.23 (d, *J* = 4.0 Hz, 6H), 1.31 (s, 6H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 183.5, 137.4, 135.3, 133.7, 132.1, 130.3, 128.4, 45.4, 44.2, 24.8 (2C), 19.9, 19.5; IR (neat) 3400–2300, 1693 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>13</sub>H<sub>19</sub>O<sub>2</sub>S [M + H]: 239.1106, found: 239.1080.



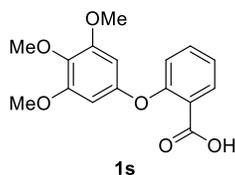
### Rel-(1*S*,2*S*)-2-((3,4-Dimethoxyphenyl)thio)cyclohexanecarboxylic acid (**1n**):

Following a modification of the reported procedure,<sup>9</sup> to a mixture of 3,4-dimethoxybenzenethiol (511 mg, 3.00 mmol, 2.0 equiv) and 1-cyclohexene-1-carboxylic acid (189.2 mg, 1.500 mmol, 1.0 equiv) in a dried N<sub>2</sub>-flushed 2 dram vial at rt was added 1.0 M solution of tetrabutylammonium fluoride in THF (0.750 mL, 0.750 mmol, 0.50 equiv). The vial was capped and the resulting solution was stirred at 50 °C under N<sub>2</sub> for 1 h. Reaction mixture was dissolved in a minimum quantity of DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded impure **1n** as a colorless solid. Recrystallization of the solid from



mL  $\times$  1), brine once, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded ethyl 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoate **10q** (0.340 g, 76%) as a colorless oil. TLC (10% EtOAc/hexanes):  $R_f$  = 0.50; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.09–7.98 (m, 1H), 7.66–7.56 (m, 1H), 7.33–7.27 (m, 2H), 7.22–7.05 (m, 3H), 6.90 (d,  $J$  = 1.1 Hz, 1H), 6.56–6.46 (m, 1H), 5.72 (d,  $J$  = 0.8 Hz, 2H), 4.42 (q,  $J$  = 7.1 Hz, 2H), 2.37 (d,  $J$  = 1.1 Hz, 3H), 1.43 (t,  $J$  = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.3, 140.6, 137.0, 132.9, 131.0, 129.1, 128.3, 127.3, 127.2, 126.4, 121.9, 119.2, 119.0, 111.2, 109.8, 61.4, 48.5, 14.6, 9.9; IR (neat) 1712 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>19</sub>H<sub>20</sub>NO<sub>2</sub> [M + H]<sup>+</sup>: 294.1494, found: 294.1463.

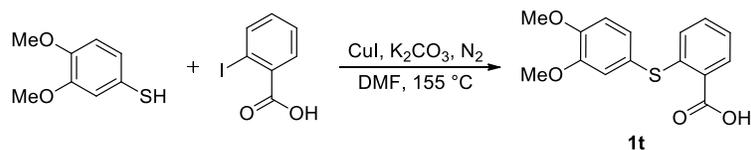
To a solution of **10q** (0.330 g, 1.12 mmol, 1.0 equiv) in THF (6.0 mL) was added a suspension of LiOH (0.108 g, 4.50 mmol, 4.0 equiv) in water (2.0 mL) and the resulting mixture was stirred at 50 °C for 24 h. The reaction mixture was acidified with 1 M HCl to pH 1 and the mixture was extracted with EtOAc (10 mL  $\times$  3). The combined organic layers were washed with water (10 mL  $\times$  1), brine once, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification on a Combiflash purification system using a silica flash column (95:5 DCM/MeOH) afforded **1q** (0.225 g, 76%) as a colorless solid. Mp: 166–168 °C; TLC (10% EtOAc/hexanes):  $R_f$  = 0.10; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.20 (dt,  $J$  = 6.9, 1.4 Hz, 1H), 7.69–7.57 (m, 1H), 7.44–7.30 (m, 2H), 7.22–7.07 (m, 3H), 6.96–6.87 (m, 1H), 6.51 (dd,  $J$  = 7.2, 2.0 Hz, 1H), 5.78 (s, 2H), 2.38 (t,  $J$  = 1.0 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  173.0, 141.9, 137.0, 134.2, 132.2, 129.1, 127.44, 127.42, 126.6, 126.4, 122.0, 119.3, 119.1, 111.4, 109.7, 48.6, 9.9; IR (neat) 3200–2000, 1679 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>17</sub>H<sub>16</sub>NO<sub>2</sub> [M + H]<sup>+</sup>: 266.1181, found: 266.1185.



### 2-(3,4,5-Trimethoxyphenoxy)benzoic acid (**1s**):

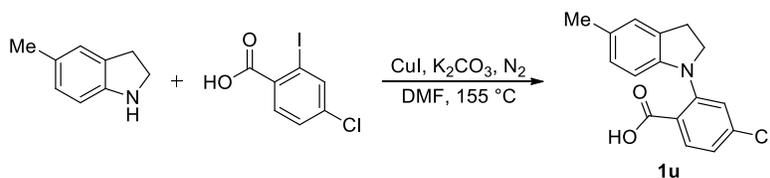
Following a modification of the reported procedure,<sup>11</sup> to a solution of 2-bromobenzoic acid (0.500 g, 2.48 mmol, 1.0 equiv) in DMF (15 mL) were added 3,4,5-trimethoxyphenol (0.916 g, 4.97 mmol, 2.0 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (1.14 g, 7.46 mmol, 3.0 equiv), pyridine (40.0  $\mu$ L), copper (0) (20.0 mg), and copper iodide (20.0 mg) in succession and the resulting mixture was refluxed for 2 h. The reaction mixture was acidified with 1 M HCl to pH 1 and the mixture was extracted with EtOAc (10 mL  $\times$  3). The combined organic layers were washed with water (10 mL  $\times$  1), brine once, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **1s** (0.350 g, 46%) as a colorless solid. Mp: 144–145 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.10; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.16 (dd,  $J$  = 7.9, 1.8 Hz, 1H), 7.49 (ddd,  $J$  =

8.3, 7.3, 1.8 Hz, 1H), 7.23–7.16 (m, 1H), 6.90 (dd,  $J = 8.4, 0.9$  Hz, 1H), 6.35 (s, 2H), 3.84 (s, 3H), 3.81 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.0, 157.8, 154.3, 151.32, 151.30, 135.5, 134.9, 133.3, 123.4, 119.9, 118.0, 97.9 (2C), 61.2, 56.4 (2C); IR (neat) 3400–2200, 1692, 1670, 1596  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_6$   $[\text{M} + \text{H}]^+$ : 305.1025, found: 305.0996.



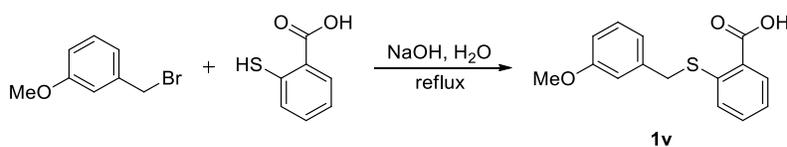
### 2-((3,4-Dimethoxyphenyl)thio)benzoic acid (**1t**):<sup>12</sup>

Following a slight modification of the reported procedure,<sup>13</sup> to a solution of 3,4-dimethoxybenzenethiol (255 mg, 1.50 mmol, 1.0 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried  $\text{N}_2$ -flushed microwave vial at rt was added potassium carbonate (207 mg, 1.50 mmol, 1.0 equiv) and copper(I) iodide (57.1 mg, 0.300 mmol, 0.20 equiv). The vial was sealed with a  $\text{N}_2$  balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 18 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL  $\times$  3). The combined organic layers were washed with water (60 mL  $\times$  3), brine (60 mL  $\times$  1), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue obtained was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% MeOH/DCM over 50 min) afforded impure **1t** as a brownish-grey solid. Trituration of the solid with ether twice and with ether containing few drops of DCM once afforded pure **1t** (238 mg, 55%) as an off-white solid after filtration and drying under vacuum. Mp: 216–220 °C (shrink above 200 °C; lit.<sup>12</sup> mp: 215–217 °C); TLC (5% MeOH/DCM):  $R_f = 0.37$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.16 (brs, 1H), 7.91 (dd,  $J = 7.8, 1.5$  Hz, 1H), 7.35 (td,  $J = 8.1, 7.4, 1.6$  Hz, 1H), 7.08–7.18 (m, 4H), 6.69 (d,  $J = 8.1$  Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ )  $\delta$  167.4, 150.1, 149.6, 143.5, 132.4, 130.9, 128.9, 126.6, 126.0, 124.1, 122.0, 118.5, 112.8, 55.7, 55.6; IR (neat) 3350–2200, 1668  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$ : 291.0691, found: 291.0675.



### 4-Chloro-2-(5-methylindolin-1-yl)benzoic acid (**1u**):

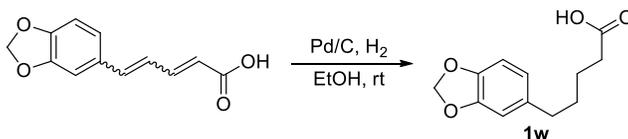
Following a slight modification of the reported procedure,<sup>13</sup> to a solution of 5-methylindoline (266 mg, 2.00 mmol, 1.0 equiv) and 4-chloro-2-iodobenzoic acid (565 mg, 2.00 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried N<sub>2</sub>-flushed microwave vial at rt was added potassium carbonate (276 mg, 2.00 mmol, 1.0 equiv) and copper(I) iodide (76.0 mg, 0.400 mmol, 0.20 equiv). The vial was sealed with a N<sub>2</sub> balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 16 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL × 3). The combined organic layers were washed with water (50 mL × 3), brine (50 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 24 g silica flash column (0–2% MeOH/DCM over 40 min) afforded **1u** as an orange oily solid, which showed some decomposition to a corresponding oxidized indole byproduct in CDCl<sub>3</sub> overtime at rt. Repurification of an impure sample of **1u** on a Combiflash purification system using a 12 g silica flash column (100% DCM over 40 min) afforded a slightly impure (ca. 94% pure) **1u** (195 mg, 34%; contaminated with ca. 6% of the corresponding indole byproduct) as a yellowish-orange solid. Mp: 131–139 °C (shrink above 125 °C); TLC (4% MeOH/DCM): R<sub>f</sub> = 0.53; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 14.21 (brs, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.12 (s, 1H), 6.93 (m, 1H), 6.38 (d, *J* = 8.0 Hz, 1H), 3.74 (apparent t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.9 Hz, 2H), 2.31 (s, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.6, 149.3, 146.6, 140.6, 133.6, 133.4, 132.2, 128.5, 128.4, 126.1, 126.0, 125.5, 113.2, 59.4, 29.4, 21.0; IR (neat) 3400–2200, 1721, 1688 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>15</sub>ClNO<sub>2</sub> [M + H]<sup>+</sup>: 288.0791, found: 288.0784.



### 2-((3-Methoxybenzyl)thio)benzoic acid (**1v**):

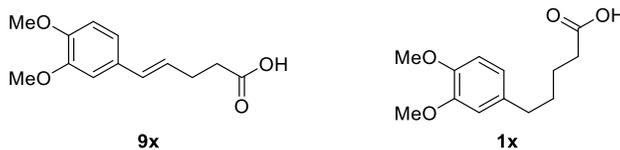
Following a modification of the reported procedure,<sup>8</sup> to a turbid solution of 2-mercaptobenzoic acid (200 mg, 1.30 mmol, 1.0 equiv) and sodium hydroxide (114 mg, 2.85 mmol, 2.2 equiv) in deionized water (5.0 mL) in a big microwave vial at rt was added 3-methoxybenzyl bromide (274 mg, 1.36 mmol, 1.05 equiv). The vial was sealed and the turbid biphasic solution was stirred at refluxing temperature (100–105 °C) for 1.5 h. Reaction mixture was cooled to rt and extracted with EtOAc (15 mL × 1) and the EtOAc layer was discarded. The aqueous layer was acidified with 2 M aqueous HCl solution (10 mL) and the resulting turbid solution was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (30 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The solid obtained was suspended in DCM with

few drops of MeOH and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% MeOH/DCM over 50 min) afforded **1v** (313 mg, 88%) as a colorless fluffy solid. Mp: 196–199 °C (lit.<sup>14</sup> mp: 199–201 °C); TLC (3% MeOH/DCM):  $R_f = 0.45$ ; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 13.04 (s, 1H), 7.88 (dd,  $J = 7.8, 1.2$  Hz, 1H), 7.52–7.47 (m, 2H), 7.26–7.19 (m, 2H), 7.01–6.99 (m, 2H), 6.84 (m, 1H), 4.17 (s, 2H), 3.74 (s, 3H); <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 167.4, 159.3, 141.3, 138.2, 132.4, 130.9, 129.5, 127.6, 125.7, 124.0, 121.4, 114.8, 112.6, 55.0, 35.7; IR (neat) 3400–2350, 1685 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>15</sub>H<sub>15</sub>O<sub>3</sub>S [M + H]<sup>+</sup>: 275.0742, found: 275.0742.



#### 5-(1,3-Benzodioxol-5-yl)pentanoic acid (**1w**):<sup>15</sup>

To a suspension of 5-(1,3-benzodioxol-5-yl)-2,4-pentadienoic acid (218 mg, 1.00 mmol, 1.0 equiv) in ethanol (5.0 mL) in an oven-dried 25 mL under N<sub>2</sub> was added palladium(II) carbon (10 wt%) (21.3 mg, 0.200 mmol, 0.20 equiv). The resulting suspension was evacuated under vacuum and flushed with H<sub>2</sub> twice and was continued to stir under H<sub>2</sub> atmosphere at rt for 5 h. Reaction mixture was concentrated and the residue obtained was diluted with DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded **1w** (203 mg, 91%) as a colorless crystalline solid. Mp: 95–97 °C; TLC (30% EtOAc/hexanes, run twice):  $R_f = 0.50$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.71 (brs, 1H), 6.72 (d,  $J = 7.9$  Hz, 1H), 6.67 (d,  $J = 1.5$  Hz, 1H), 6.62 (dd,  $J = 7.9, 1.7$  Hz, 1H), 5.92 (s, 2H), 2.56 (t,  $J = 7.1$  Hz, 2H), 2.37 (t,  $J = 7.0$  Hz, 2H), 1.65 (m, 4H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 180.2, 147.8, 145.8, 136.0, 121.3, 109.0, 108.3, 100.9, 35.4, 34.1, 31.2, 24.3; IR (neat) 3300–2400, 1702 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>12</sub>H<sub>13</sub>O<sub>4</sub> [M – H]<sup>-</sup>: 221.0814, found: 221.0828.

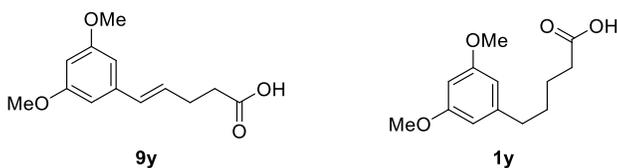


#### 5-(3,4-Dimethoxyphenyl)pentanoic acid (**1x**):<sup>16</sup>

Following the procedure described for compound **1b**, 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.10 g, 7.22 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.69 g, 15.0 mmol, 2.5 equiv) to afford (*E*)-5-(3,4-

dimethoxyphenyl)pent-4-enoic acid **9x** (0.615 g, 43%) as a colorless solid. Mp: 114–116 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.30;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.95–6.85 (m, 2H), 6.80 (d,  $J$  = 8.2 Hz, 1H), 6.39 (d,  $J$  = 15.5 Hz, 1H), 6.16–6.01 (m, 1H), 3.88 (d,  $J$  = 9.6 Hz, 6H), 2.54 (d,  $J$  = 0.7 Hz, 4H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.6, 149.3, 148.8, 131.1, 130.7, 126.3, 119.3, 111.5, 109.0, 56.2, 56.1, 34.0, 28.1; IR (neat) 2934, 1719, 1695, 1512  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 237.1127, found: 237.1106.

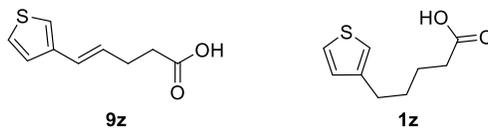
Compound **9x** (0.600 g, 2.54 mmol) was then reduced with palladium(II) carbon (0.0600 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1x** (0.530 g, 88%) as a colorless solid.



### 5-(3,5-Dimethoxyphenyl)pentanoic acid (**1y**):<sup>17</sup>

Following the procedure described for compound **1b**, 3,5-dimethoxybenzaldehyde (0.500 g, 3.01 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (1.55 g, 3.61 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (0.844 g, 7.52 mmol, 2.5 equiv) to afford (*E*)-5-(3,5-dimethoxyphenyl)pent-4-enoic acid **9y** (0.370 g, 52%) as a colorless solid. Mp: 104–106 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.30;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.50 (d,  $J$  = 2.3 Hz, 2H), 6.42–6.33 (m, 2H), 6.25–6.15 (m, 1H), 3.79 (s, 6H), 2.61–2.47 (m, 4H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.8, 161.1 (2C), 139.5, 131.4, 128.8, 104.5 (2C), 99.8, 55.5 (2C), 33.8, 28.0; IR (neat) 3300–2100, 1701, 1579  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_4$   $[\text{M} + \text{H}]^+$ : 237.1127, found: 237.1098.

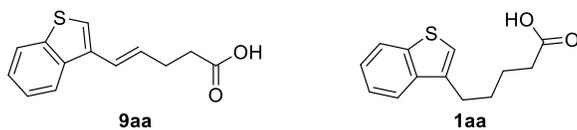
Compound **9y** (0.300 g, 1.27 mmol) was then reduced with palladium(II) carbon (0.0300 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1y** (0.295 g, 98%) as a colorless solid.



### 5-(Thiophen-3-yl)pentanoic acid (**1z**):<sup>18</sup>

Following the procedure described for compound **1b**, 3-thiophenecarboxaldehyde (1.00 g, 8.92 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (4.59 g, 10.7 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (2.50 g, 22.3 mmol, 2.5 equiv) to afford (*E*)-5-(thiophen-3-yl)pent-4-enoic acid **9z**<sup>19</sup> (1.01 g, 62%) as a brown solid.

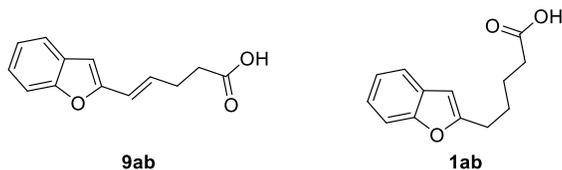
Compound **9z** (0.657 g, 3.95 mmol) was then reduced with palladium(II) carbon (0.0657 g, 10 wt%) under H<sub>2</sub> atmosphere to afford **1z** (0.320 g, 44%) as a colorless solid.



#### 5-(Benzo[*b*]thiophen-3-yl)pentanoic acid (**1aa**):

Following the procedure described for compound **1b**, thianaphthene-3-carboxaldehyde (1.00 g, 6.16 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.17 g, 7.39 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.73 g, 15.4 mmol, 2.5 equiv) to afford (*E*)-5-(benzo[*b*]thiophen-3-yl)pent-4-enoic acid **9aa** (0.750 g, 52%) as a colorless solid. Mp: 97–98 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.30; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.91–7.81 (m, 2H), 7.45–7.30 (m, 3H), 6.72 (dd,  $J$  = 15.9, 1.2 Hz, 1H), 6.34–6.21 (m, 1H), 2.67–2.55 (m, 4H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 178.4, 140.6, 137.9, 134.2, 130.2, 124.6, 124.4, 123.8, 123.1, 122.1, 121.5, 33.9, 28.5; IR (neat) 3300–2100, 1701 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>13</sub>H<sub>11</sub>O<sub>2</sub>S [M – H]<sup>-</sup>: 231.0480, found: 231.0489.

Compound **9aa** (0.300 g, 1.29 mmol) was then reduced with palladium(II) carbon (0.0300 g, 10 wt%) under H<sub>2</sub> atmosphere to afford **1aa** (0.300 g, 99%) as a colorless solid. Mp: 99–100 °C; TLC (20% EtOAc/Hexanes):  $R_f$  = 0.40; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.92–7.80 (m, 1H), 7.79–7.69 (m, 1H), 7.45–7.30 (m, 2H), 7.10 (d,  $J$  = 1.1 Hz, 1H), 2.95–2.78 (m, 2H), 2.43 (t,  $J$  = 6.9 Hz, 2H), 1.80 (m, 4H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 179.8, 140.7, 139.2, 136.5, 124.4, 124.0, 123.1, 121.8, 121.4, 34.1, 28.7, 28.4, 24.7; IR (neat) 3200–2200, 1699, 1687 cm<sup>-1</sup>; HRMS (ESI)  $m/z$  calcd for C<sub>13</sub>H<sub>13</sub>O<sub>2</sub>S [M – H]<sup>-</sup>: 233.0636, found: 233.0644.

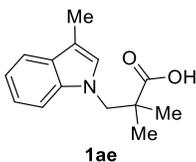


#### 5-(Benzofuran-2-yl)pentanoic acid (**1ab**):

Following the procedure described for compound **1b**, 2-benzofurancarboxaldehyde (1.00 g, 6.84 mmol, 1.0 equiv) was reacted with (2-carboxypropyl)triphenylphosphonium bromide (3.53 g, 8.21 mmol, 1.2 equiv) in the presence of potassium *tert*-butoxide (1.92 g, 17.1 mmol, 2.5 equiv) to afford impure (*E*)-5-(benzofuran-2-yl)pent-4-enoic acid **9ab** (0.950 g, 64%; >85% pure as determined by <sup>1</sup>H NMR) as a colorless solid. Mp: 106–108 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.30; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52–7.48 (m, 1H), 7.42 (dq,  $J$  = 8.2, 0.9 Hz, 1H), 7.26–7.16 (m, 2H), 6.54–6.32 (m, 3H), 2.60 (m, 4H);

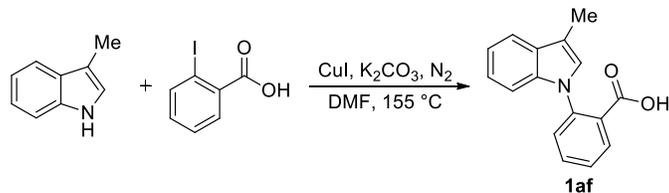
$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  179.0, 154.9, 154.7, 130.7, 129.2, 124.5, 123.0, 121.0, 120.2, 111.0, 103.8, 33.6, 28.0; IR (neat) 3300–2100, 1697  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 217.0865, found: 217.0835.

Compound **9ab** (0.300 g, 1.39 mmol; impure) was then reduced with palladium(II) carbon (0.0300 g, 10 wt%) under  $\text{H}_2$  atmosphere to afford **1ab** (0.150 g, 50%) as a colorless solid. Mp: 124–126  $^\circ\text{C}$ ; TLC (20% EtOAc/Hexanes):  $R_f$  = 0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.15 (brs, 1H), 7.52–7.45 (m, 1H), 7.43–7.38 (m, 1H), 7.24–7.15 (m, 2H), 6.40 (d,  $J$  = 1.0 Hz, 1H), 2.88–2.73 (m, 2H), 2.42 (t,  $J$  = 7.1 Hz, 2H), 1.89–1.67 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  179.7, 158.9, 154.9, 129.1, 123.4, 122.7, 120.4, 110.9, 102.4, 33.9, 28.3, 27.3, 24.3; IR (neat) 3300–2100, 1705  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{15}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 219.1021, found: 219.0990.



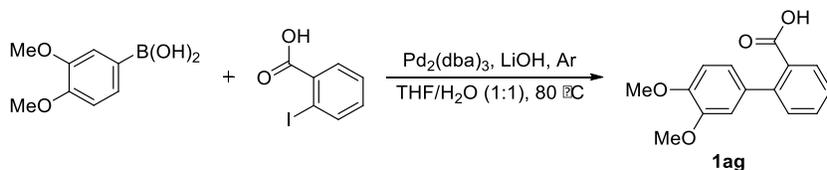
### 2,2-Dimethyl-3-(3-methyl-1H-indol-1-yl)propanoic acid (**1ae**):

Following a modification of the reported procedure,<sup>20</sup> to a cooled solution of 3-methylindole (0.300 g, 2.29 mmol, 1.0 equiv) in DMF (5 mL) at 0  $^\circ\text{C}$  under Ar atmosphere was added sodium hydride (60% dispersion in mineral oil) (0.320 g, 8.00 mmol, 3.5 equiv). After stirring for 10 min at 0  $^\circ\text{C}$ , 3-chloro-2,2-dimethylpropanoic acid (0.344 g, 2.51 mmol, 1.1 equiv) and potassium iodide (0.0380 g, 0.228 mmol, 0.10 equiv) were added and the reaction mixture was continued to stir at 0  $^\circ\text{C}$  for 15 min. The reaction mixture was then heated to 50  $^\circ\text{C}$  and continued to stir at 50  $^\circ\text{C}$  for 24 h. The reaction was quenched with water and acidified with 1 M HCl to pH 1. The aqueous layer was extracted with EtOAc (10 mL  $\times$  3) and the combined organic layers were washed with (10 mL  $\times$  1), brine once, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **1ae** (0.0850 g, 16%) as a colorless solid. Mp: 72–74  $^\circ\text{C}$ ; TLC (10% EtOAc/Hexanes):  $R_f$  = 0.20;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (dt,  $J$  = 7.8, 1.0 Hz, 1H), 7.33 (dt,  $J$  = 8.2, 0.9 Hz, 1H), 7.19 (ddd,  $J$  = 8.2, 7.0, 1.2 Hz, 1H), 7.09 (ddd,  $J$  = 7.9, 7.0, 1.0 Hz, 1H), 6.88 (d,  $J$  = 1.1 Hz, 1H), 4.27 (s, 2H), 2.31 (d,  $J$  = 1.1 Hz, 3H), 1.29 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  181.9, 137.8, 128.7, 126.7, 121.8, 119.1, 118.9, 111.3, 109.8, 53.7, 45.4, 23.9 (2C), 9.8; IR (neat) 3300–2100, 1700  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$   $[\text{M} + \text{H}]^+$ : 232.1338, found: 232.1315.



### 2-(3-Methyl-1H-indol-1-yl)benzoic acid (**1af**):

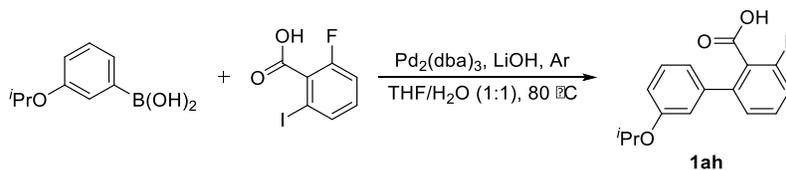
Following a slight modification of the reported procedure,<sup>13</sup> to a solution of 3-methyl-1H-indole (197 mg, 1.50 mmol, 1.0 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) in a flame-dried N<sub>2</sub>-flushed microwave vial at rt was added potassium carbonate (207 mg, 1.50 mmol, 1.0 equiv) and copper(I) iodide (57.1 mg, 0.300 mmol, 0.20 equiv). The vial was sealed with a N<sub>2</sub> balloon inserted into a septum and the resulting suspension was stirred at 155 °C for 18 h (effervescence was observed and hood lights were kept off). Reaction mixture was quenched with 1.0 M aqueous HCl (10 mL), diluted with water (20 mL), and extracted with DCM (25 mL × 3). The combined organic layers were washed with water (60 mL × 3), brine (60 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The oily residue obtained was dissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2.5% MeOH/DCM over 50 min) afforded impure **1af** as an orange-brown oil. Repurification of impure **1af** on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded a partial separation of pure **1af** (112 mg, 30%) as a creamish-orange solid. Mp: 102–108 °C (shrink above 95 °C); TLC (5% MeOH/DCM): R<sub>f</sub> = 0.41; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.66 (brs, 1H), 8.05–8.08 (m, 1H), 7.64–7.68 (m, 2H), 7.45–7.49 (m, 2H), 7.16–7.23 (m, 3H), 7.00 (d, *J* = 1.1 Hz, 1H), 2.42 (d, *J* = 1.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.4, 139.7, 137.5, 133.8, 132.2, 129.6, 128.8, 127.3 (2C), 126.7, 122.5, 119.8, 119.3, 113.0, 109.9, 9.8; IR (neat) 3500–2200, 1690, 1600 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub> [M + H]<sup>+</sup>: 252.1025, found: 252.1013.



### 3',4'-Dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (**1ag**):<sup>21</sup>

Following a modification of the reported procedure,<sup>22</sup> to a solution of (3,4-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min

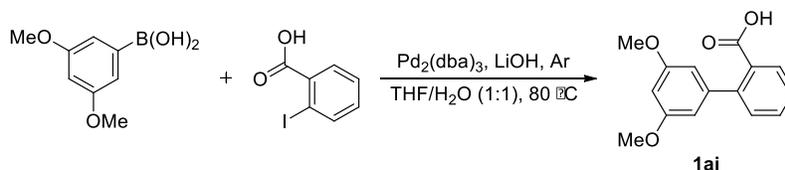
(till effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N<sub>2</sub> and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The solid residue obtained was suspended in DCM containing few drops of MeOH and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded **1ag** (235 mg, 61%) as a colorless solid with light orange tinge. Mp: 164–166 °C (lit.<sup>21</sup> mp: 162–165 °C); TLC (4% MeOH/DCM, run twice): R<sub>f</sub> = 0.52; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>) δ 12.77 (brs, 1H), 7.65 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H), 7.42–7.39 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H); <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>) δ 170.2, 148.3, 148.2, 140.4, 133.2, 132.7, 130.6, 130.3, 128.7, 126.8, 120.5, 112.2, 111.6, 55.5, 55.4; IR (neat) 3315, 1719 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>15</sub>H<sub>15</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 259.0970, found: 259.0957.



### 3-Fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carboxylic acid (**1ah**):

Following a modification of the reported procedure,<sup>22</sup> to a solution of (3-isopropoxyphenyl)boronic acid (283 mg, 1.58 mmol, 1.05 equiv) and 2-fluoro-6-iodobenzoic acid (399 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting solution was stirred at rt for 5 min (till effervescence ceased). The solution was degassed with Ar for 1 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 13 h. Reaction mixture was partially concentrated under N<sub>2</sub> and acidified with 2 M aqueous HCl solution (15 mL) followed by the addition of water (20 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The oily residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 24 g silica flash column (0–3% MeOH/DCM over 60 min)

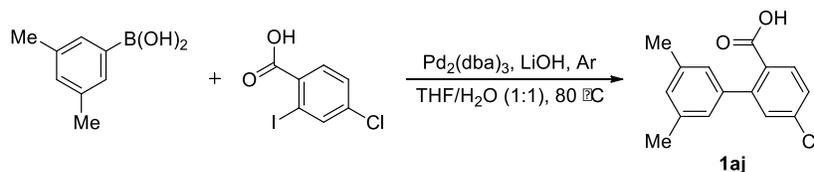
afforded impure **1ah** as a pale orange oil. Impure **1ah** was dissolved in 1.5 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification was carried out on a reverse-phase Combiflash system (0% ACN/H<sub>2</sub>O both containing 0.1% CF<sub>3</sub>CO<sub>2</sub>H over 2 min followed by 0–70% ACN/H<sub>2</sub>O both containing 0.1% CF<sub>3</sub>CO<sub>2</sub>H from 2–32 min). Elutions containing product were concentrated under vacuum in Genevac. The resulting colorless solid was dissolved in DCM and filtered through a short bed containing a mixture of Na<sub>2</sub>SO<sub>4</sub> and silica gel using a phase separator tabless. Concentration and drying under vacuum afforded pure **1ah** (262 mg, 64%) as a colorless partially oily crystalline solid. Mp: 103–105 °C; TLC (3% MeOH/DCM): R<sub>f</sub> = 0.19; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.91 (brs, 1H), 7.47 (m, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.14 (m, 1H), 6.99–6.92 (m, 3H), 4.57 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 6H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.5, 160.0 (d, *J* = 252.5 Hz, 1C), 158.1, 143.0 (d, *J* = 2.3 Hz, 1C), 140.5 (d, *J* = 2.2 Hz, 1C), 131.9 (d, *J* = 9.1 Hz, 1C), 129.8, 125.9 (d, *J* = 3.1 Hz, 1C), 120.7, 120.5 (d, *J* = 15.8 Hz, 1C), 116.3, 115.8, 114.9 (d, *J* = 21.6 Hz, 1C), 70.4, 22.2 (2C); IR (neat) 3400–2400, 1738, 1704, 1573 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>14</sub>FO<sub>2</sub> [M – OH]<sup>+</sup>: 257.0972, found: 257.0952.



### 3',5'-Dimethoxy-[1,1'-biphenyl]-2-carboxylic acid (**1ai**):<sup>23</sup>

Following a modification of the reported procedure,<sup>22</sup> to a suspension of (3,5-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 2-iodobenzoic acid (372 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (till effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N<sub>2</sub> and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (15 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue obtained was redissolved in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 24 g silica flash column (0–1% MeOH/DCM over 40 min) afforded impure **1ai** as a creamish solid. Recrystallization of the solid from DCM/ether mixture (suspended solid in ether was dissolved by the dropwise addition of DCM. Hexanes was then added till

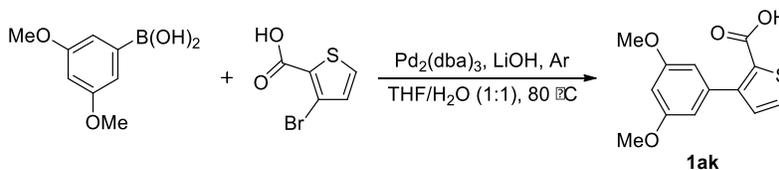
the solution became slightly turbid) afforded pure **1ai** (232 mg, 60%) as a colorless small plate-like crystals after filtration and drying under vacuum. Mp: 145.5–147 °C; TLC (3% MeOH/DCM):  $R_f$  = 0.32;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.81 (brs, 1H), 7.93 (dd,  $J$  = 7.8, 1.1 Hz, 1H), 7.55 (td,  $J$  = 7.5, 1.4 Hz, 1H), 7.45–7.38 (m, 2H), 6.51 (d,  $J$  = 2.2 Hz, 2H), 6.47 (t,  $J$  = 2.2 Hz, 1H), 3.80 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  173.8, 160.6 (2C), 143.23, 143.18, 132.1, 131.1, 130.6, 129.7, 127.5, 107.0 (2C), 99.9, 55.6 (2C); IR (neat) 3300–2300, 1682, 1592  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_4$  [ $\text{M} + \text{H}$ ] $^+$ : 259.0970, found: 259.0960.



### 5-Chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid (**1aj**):

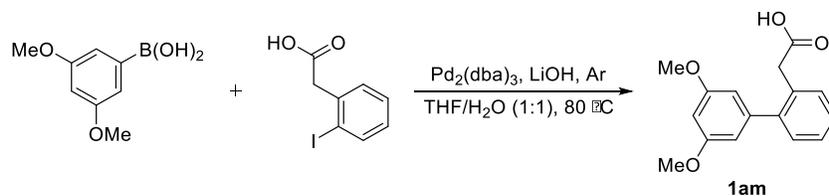
Following a modification of the reported procedure,<sup>22</sup> to a solution of (3,5-dimethylphenyl)boronic acid (236 mg, 1.58 mmol, 1.05 equiv) and 4-chloro-2-iodobenzoic acid (424 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting solution was stirred at rt for 5 min (till effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under  $\text{N}_2$  and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL  $\times$  3). The combined organic layers were washed with brine (50 mL  $\times$  1), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The solid residue obtained was suspended in DCM and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded impure **1aj** as a creamish-orange solid. Impure **1aj** was dissolved in 1.5 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification was carried out on a reverse-phase Combiflash system (0% ACN/ $\text{H}_2\text{O}$  both containing 0.1%  $\text{CF}_3\text{CO}_2\text{H}$  over 2 min followed by 0–70% ACN/ $\text{H}_2\text{O}$  both containing 0.1%  $\text{CF}_3\text{CO}_2\text{H}$  from 2–32 min). Elutions containing product were concentrated under vacuum in Genevac. The resulting creamish solid was dissolved in ether and filtered through a short bed containing a mixture of  $\text{Na}_2\text{SO}_4$  and silica gel using a phase separator tabless. Concentration and drying under vacuum afforded pure **1aj** (320 mg, 82%) as a pale creamish-orange crystalline solid. Mp: 154–156 °C; TLC (30% EtOAc/hexanes):  $R_f$  = 0.22;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.20 (brs, 1H), 7.88 (m, 1H),

7.39–7.36 (m, 2H), 7.01 (s, 1H), 6.93 (s, 2H), 2.34 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  173.3, 145.7, 139.8, 138.4, 137.8 (2C), 132.3, 131.5, 129.7, 127.7, 127.3, 126.3 (2C), 21.5 (2C); IR (neat) 3350–2150, 1687  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{ClO}$   $[\text{M} - \text{OH}]^+$ : 243.0571, found: 243.0566.



### 3-(3,5-Dimethoxyphenyl)thiophene-2-carboxylic acid (**1ak**):

Following a modification of the reported procedure,<sup>22</sup> to a suspension of (3,5-dimethoxyphenyl)boronic acid (287 mg, 1.58 mmol, 1.05 equiv) and 3-bromothiophene-2-carboxylic acid (311 mg, 1.50 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (90.0 mg, 3.75 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (till effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (20.6 mg, 0.0220 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under  $\text{N}_2$  and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (15 mL). The resulting suspension was extracted with DCM (25 mL  $\times$  3). The combined organic layers were washed with brine (50 mL  $\times$  1), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The solid residue obtained was suspended in DCM containing few drops of MeOH and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a 12 g silica flash column (0–2% MeOH/DCM over 40 min) afforded impure **1ak** as a creamish-orange solid. Impure **1ak** was dissolved in 2.0 mL DMSO and loaded on a 50 g HP C18 Gold column. Repurification was carried out on a reverse-phase Combiflash system (0% ACN/ $\text{H}_2\text{O}$  both containing 0.1%  $\text{CF}_3\text{CO}_2\text{H}$  over 2 min followed by 0–70% ACN/ $\text{H}_2\text{O}$  both containing 0.1%  $\text{CF}_3\text{CO}_2\text{H}$  from 2–32 min). Elutions containing product were concentrated under vacuum in Genevac. The resulting colorless solid was dissolved in DCM and filtered through a short bed containing a mixture of  $\text{Na}_2\text{SO}_4$  and silica gel using a phase separator tabless. Concentration and drying under vacuum afforded pure **1ak** (120 mg, 30%) as a colorless solid. Mp: 147.5–149 °C; TLC (3% MeOH/DCM):  $R_f$  = 0.29;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  12.18 (brs, 1H), 7.57 (d,  $J$  = 5.1 Hz, 1H), 7.10 (d,  $J$  = 5.1 Hz, 1H), 6.61 (d,  $J$  = 2.3 Hz, 2H), 6.50 (t,  $J$  = 2.3 Hz, 1H), 3.81 (s, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.7, 160.4 (2C), 149.8, 137.4, 132.1, 131.9, 126.9, 107.7 (2C), 100.6, 55.6 (2C); IR (neat) 3300–2300, 1686, 1597  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{O}_4\text{S}$   $[\text{M} + \text{H}]^+$ : 265.0535, found: 265.0524.



**2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetic acid (**1am**):**

Following a modification of the reported procedure,<sup>22</sup> to a solution of (3,5-dimethoxyphenyl)boronic acid (147 mg, 0.807 mmol, 1.05 equiv) and 2-iodophenylacetic acid (200 mg, 0.763 mmol, 1.0 equiv) in degassed THF (2.0 mL) in a flame-dried microwave vial at rt under Ar was added a sonicated solution of lithium hydroxide (46.0 mg, 1.91 mmol, 2.5 equiv) in degassed deionized water (2.0 mL) (solvents were degassed with Ar under sonication for 5 min) and the resulting slightly turbid solution was stirred at rt for 5 min (till effervescence ceased). The solution was degassed with Ar for 2 min followed by the addition of tris(dibenzylideneacetone)dipalladium (0) (10.5 mg, 0.0114 mmol, 0.015 equiv). The vial was sealed with a septum and the resulting suspension was stirred at 80 °C for 14 h. Reaction mixture was partially concentrated under N<sub>2</sub> and acidified with 2 M aqueous HCl solution (10 mL) followed by the addition of water (25 mL). The resulting suspension was extracted with DCM (25 mL × 3). The combined organic layers were washed with brine (50 mL × 1), dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **1am** (150 mg, 72%) as a colorless solid. Mp: 128–130 °C; TLC (50% EtOAc/Hexanes): R<sub>f</sub> = 0.70; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41–7.27 (m, 4H), 6.47 (s, 3H), 3.78 (s, 6H), 3.65 (s, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 177.9, 160.8 (2C), 143.1, 142.8, 131.2, 130.6, 130.1, 127.9, 127.6, 107.5 (2C), 99.9, 55.6 (2C), 38.6; IR (neat) 3400–2200, 1687, 1592 cm<sup>-1</sup>; HRMS (ESI) m/z calcd for C<sub>16</sub>H<sub>17</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 273.1127, found: 273.1098.

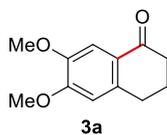
### General procedure C for the Friedel–Crafts reaction in HFIP (Figure 1)

#### Procedure (Step-1 → Synthesis of Acid Chloride):

To a solution of acid **1** (0.300 mmol, 1.0 equiv) in anhydrous DCM (1.5 mL) in a flame-dried N<sub>2</sub>-flushed 2 dram vial at rt under N<sub>2</sub> blanket was added a small drop (catalytic; using a 21G needle) of DMF. Then oxalyl chloride (0.390 or 0.600 mmol, 1.3 or 2.0 equiv) was added dropwise (gas evolution was observed; the cap was opened for a while under N<sub>2</sub> blanket to release the pressure) and the reaction mixture was stirred at rt for a specified period (25–90 min). Reaction mixture was concentrated under N<sub>2</sub> using sample concentrator and the residue obtained was dried under vacuum for ~15–20 min. The crude acid chloride **2** was used as such for the Step-2.

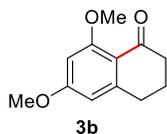
#### Procedure (Step-2 → Friedel-Crafts Acylation):

To the same 2 dram vial containing the crude acid chloride intermediate **2** at rt was added HFIP (0.75 mL, substrate concentration is 0.40 M) quickly and the vial was capped immediately. The resultant reaction mixture was stirred at rt for 2–6 h, unless otherwise noted. Reaction mixture was concentrated under N<sub>2</sub> and the resulting residue was dissolved in a minimum quantity of DCM or ether and loaded on a silica gel in a sample cartridge. Purification on a Combiflash purification system using a normal phase silica flash column (4, 12, or 24 g) afforded the cyclized product **3** after concentration and drying under vacuum.



#### 6,7-Dimethoxy-3,4-dihydronaphthalen-1(2H)-one (**3a**):<sup>24,25</sup>

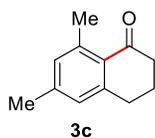
Following the general procedure C, 4-(3,4-dimethoxyphenyl)butanoic acid **1a** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,4-dimethoxyphenyl)butanoyl chloride **2a** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2a** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2 h. Purification on a Combiflash purification system using a 4 g silica flash column (0–40% EtOAc/hexanes over 20 min) afforded **3a** (59.9 mg, 97%) as a colorless solid.



#### 6,8-Dimethoxy-3,4-dihydronaphthalen-1(2H)-one (**3b**):<sup>26</sup>

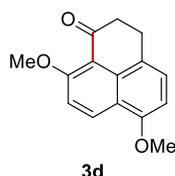
Following the general procedure C, 4-(3,5-dimethoxyphenyl)butanoic acid **1b** (67.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,5-dimethoxyphenyl)butanoyl chloride **2b** using oxalyl chloride (50.8  $\mu$ L,

0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2b** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3b** (53.0 mg, 86%) as a brown solid. Mp: 64–66 °C; TLC (50% EtOAc/Hexanes):  $R_f = 0.30$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.36–6.28 (m, 2H), 3.88 (s, 3H), 3.84 (s, 3H), 2.92–2.83 (m, 2H), 2.63–2.52 (m, 2H), 2.06–1.96 (m, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.3, 164.0, 162.8, 149.5, 116.7, 104.9, 97.4, 56.2, 55.6, 41.0, 31.8, 23.1; IR (neat) 1665, 1596  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{15}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 207.2490, found: 207.0998.



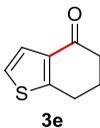
### 6,8-Dimethyl-3,4-dihydronaphthalen-1(2H)-one (**3c**):<sup>27</sup>

Following the general procedure C, 4-(3,5-dimethylphenyl)butanoic acid **1c** (57.6 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3,5-dimethylphenyl)butanoyl chloride **2c** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2c** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3c** (38.0 mg, 73%) as a yellow oil.



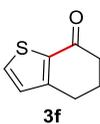
### 6,9-Dimethoxy-2,3-dihydro-1H-phenalen-1-one (**3d**):

Following the general procedure C, 3-(4,7-dimethoxynaphthalen-1-yl)propanoic acid **1d** (78.1 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(4,7-dimethoxynaphthalen-1-yl)propanoyl chloride **2d** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2d** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 50 min) afforded **3d** (37.0 mg, 51%) as a olive green solid. Mp: 124–127 °C (melted with decomposition); TLC (30% EtOAc/hexanes):  $R_f = 0.22$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.44 (d,  $J = 9.4$  Hz, 1H), 7.27–7.24 (m, 2H), 6.64 (d,  $J = 7.8$  Hz, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 3.24 (apparent t,  $J = 7.2$  Hz, 2H), 2.85 (apparent t,  $J = 7.2$  Hz, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  198.1, 158.3, 154.6, 134.6, 130.2, 126.4, 124.5, 120.1, 115.8, 112.6, 102.1, 56.7, 55.7, 40.8, 28.8; IR (neat) 1676, 1588, 1248, 1042  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{15}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 243.1021, found: 243.1006.



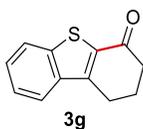
### 6,7-Dihydrobenzo[*b*]thiophen-4(5*H*)-one (**3e**):<sup>28</sup>

Following the general procedure C, 4-(2-thienyl)butyric acid **1e** (51.1 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(2-thienyl)butanoyl chloride **2e** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2e** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–15% EtOAc/hexanes over 30 min) afforded **3e** (37.0 mg, 81%) as a pale yellow oil.



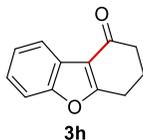
### 5,6-Dihydrobenzo[*b*]thiophen-7(4*H*)-one (**3f**):<sup>29</sup>

Following the general procedure C, 4-(thiophen-3-yl)butanoic acid **1f** (51.0 mg, 0.300 mmol, 1 equiv) was converted to 4-(thiophen-3-yl)butanoyl chloride **2f** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2f** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3f** (33.0 mg, 72%) as a colorless oil. TLC (20% EtOAc/Hexanes):  $R_f = 0.40$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (d,  $J = 4.9$  Hz, 1H), 6.97 (d,  $J = 4.9$  Hz, 1H), 2.88 (t,  $J = 6.1$  Hz, 2H), 2.69–2.50 (m, 2H), 2.18 (tt,  $J = 6.5, 5.7$  Hz, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  192.5, 152.8, 136.8, 133.9, 128.4, 38.5, 26.2, 24.6; IR (neat)  $1653\text{ cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_8\text{H}_9\text{OS}$   $[\text{M} + \text{H}]^+$ : 153.0374, found: 153.0350.



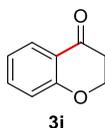
### 2,3-Dihydrodibenzo[*b,d*]thiophen-4(1*H*)-one (**3g**):<sup>5</sup>

Following the general procedure C, 4-(benzo[*b*]thiophen-3-yl)butanoic acid **1g** (66.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(benzo[*b*]thiophen-3-yl)butanoyl chloride **2g** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2g** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3g** (60.0 mg, 99%) as a colorless solid.



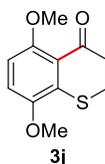
**3,4-Dihydrodibenzo[*b,d*]furan-1(2*H*)-one (3h):**<sup>30</sup>

Following the general procedure C, 4-(benzofuran-2-yl)butanoic acid **1h** (61.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(benzofuran-2-yl)butanoyl chloride **2h** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2h** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3h** (50.0 mg, 90%) as a colorless oil.



**Chroman-4-one (3i):**<sup>31</sup>

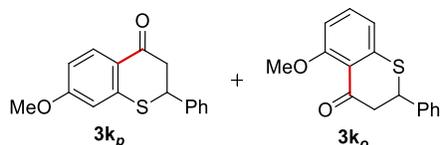
Following the general procedure C, 3-phenoxypropanoic acid **1i** (49.8 mg, 0.300 mmol, 1.0 equiv) was converted to 3-phenoxypropanoyl chloride **2i** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2i** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3i** (31.0 mg, 70%) as a colorless oil.



**5,8-Dimethoxythiochroman-4-one (3j):**<sup>32</sup>

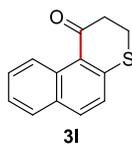
Following the general procedure C, 3-((2,5-dimethoxyphenyl)thio)propanoic acid **1j** (72.7 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((2,5-dimethoxyphenyl)thio)propanoyl chloride **2j** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2j** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 50 min) afforded **3j** (35.5 mg, 53%) as a creamish yellow solid. Mp: 133–136 °C; TLC (40% EtOAc/hexanes):  $R_f$  = 0.31; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.89 (d,  $J$  = 9.0 Hz, 1H), 6.64 (d,  $J$  = 9.0 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.16–3.13 (m, 2H), 2.93–2.90 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  194.2, 155.4, 149.0, 133.7, 122.2,

115.1, 108.4, 56.8, 56.7, 41.0, 25.5; IR (neat) 1677, 1575  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{11}\text{H}_{13}\text{O}_3\text{S}$  [ $\text{M} + \text{H}$ ] $^+$ : 225.0585, found: 225.0578.



### 7-Methoxy-2-phenylthiochroman-4-one (**3k<sub>p</sub>**) and 5-Methoxy-2-phenylthiochroman-4-one (**3k<sub>o</sub>**):

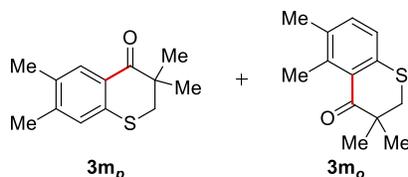
Following the general procedure C, 3-((3-methoxyphenyl)thio)-3-phenylpropanoic acid **1k** (86.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((3-methoxyphenyl)thio)-3-phenylpropanoyl chloride **2k** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2k** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **3k<sub>p</sub>** (50.0 mg, 62%) and **3k<sub>o</sub>** (10.8 mg, 13%) as light yellow solids (combined yield = 60.8 mg, 75%; **3k<sub>p</sub>**:**3k<sub>o</sub>** = 82:18). For **3k<sub>p</sub>**: mp: 82.5–84.5  $^{\circ}\text{C}$ ; TLC (20% EtOAc/hexanes):  $R_f$  = 0.52;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.10–8.13 (m, 1H), 7.31–7.43 (m, 5H), 6.73–6.75 (m, 2H), 4.71 (dd,  $J$  = 12.9, 3.1 Hz, 1H), 3.83 (s, 3H), 3.27 (dd,  $J$  = 16.5, 12.9 Hz, 1H), 3.15 (dd,  $J$  = 16.5, 3.1 Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.2, 163.7, 144.4, 138.7, 131.5, 129.1, 128.6, 127.6, 124.3, 112.9, 110.6, 55.7, 46.6, 45.9; IR (neat) 1665, 1587  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_2\text{S}$  [ $\text{M} + \text{H}$ ] $^+$ : 271.0793, found: 271.0787. For **3k<sub>o</sub>**: mp: 110.5–113.5  $^{\circ}\text{C}$  (shranked  $>100$   $^{\circ}\text{C}$ ); TLC (20% EtOAc/hexanes):  $R_f$  = 0.22;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29–7.43 (m, 6H), 6.87 (dd,  $J$  = 7.9, 1.0 Hz, 1H), 6.74 (m, 1H), 4.69 (dd,  $J$  = 13.0, 3.2 Hz, 1H), 3.91 (s, 3H), 3.34 (dd,  $J$  = 15.7, 13.0 Hz, 1H), 3.18 (dd,  $J$  = 15.7, 3.2 Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.4, 161.6, 144.3, 138.7, 133.9, 129.2, 128.6, 127.6, 121.0, 119.5, 109.0, 56.4, 48.9, 45.4; IR (neat) 1672, 1579  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_2\text{S}$  [ $\text{M} + \text{H}$ ] $^+$ : 271.0793, found: 271.0789.



### 2,3-Dihydro-1H-benzo[f]thiochromen-1-one (**3l**):<sup>8</sup>

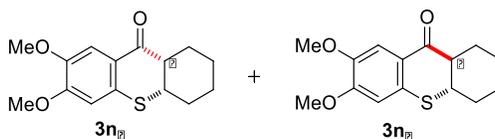
Following the general procedure C, 3-(2-naphthylthio)propionic acid **1l** (69.7 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(2-naphthylthio)propionyl chloride **2l** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2l** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 4 g silica flash

column (0–5% EtOAc/hexanes over 50 min) afforded **3i** (59.4 mg, 92%) as a pale yellow turbid oil. TLC (10% ether/hexanes, run twice):  $R_f = 0.38$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.17 (m, 1H), 7.73 (m, 2H), 7.60 (ddd,  $J = 8.6, 6.9, 1.5$  Hz, 1H), 7.44 (ddd,  $J = 8.0, 6.9, 1.1$  Hz, 1H), 7.26 (d,  $J = 8.7$  Hz, 1H), 3.27 (m, 2H), 3.09 (m, 2H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  196.2, 145.3, 133.7, 132.6, 131.9, 129.3, 128.6, 126.3, 125.79, 125.77, 125.5, 41.4, 26.5; IR (neat) 1657, 1588  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}\text{OS}$   $[\text{M} + \text{H}]^+$ : 215.0531, found: 215.0528.



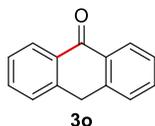
### 3,3,6,7-Tetramethylthiochroman-4-one (**3m<sub>p</sub>**) and 3,3,5,6-Tetramethylthiochroman-4-one (**3m<sub>o</sub>**):

Following the general procedure **C**, 3-((3,4-dimethylphenyl)thio)-2,2-dimethylpropanoic acid **1m** (71.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3-((3,4-dimethylphenyl)thio)-2,2-dimethylpropanoyl chloride **2m** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2m** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 24 g silica flash column (0–10% EtOAc/hexanes over 20 min) afforded a partial separation of **3m<sub>p</sub>** (39.5 mg) as a colorless solid and **3m<sub>o</sub>** (19.0 mg) as a colorless oily solid and a small amount (5.00 mg) was obtained as a mixture of **3m<sub>p</sub>** and **3m<sub>o</sub>** (combined yield = 63.5 mg, 96%; **3m<sub>p</sub>**:**3m<sub>o</sub>** = 64:36). For **3m<sub>p</sub>**: mp: 89–90.5  $^{\circ}\text{C}$ ; TLC (4% EtOAc/hexanes):  $R_f = 0.35$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (s, 1H), 6.98 (s, 1H), 3.04 (s, 2H), 2.23 (d,  $J = 3.5$  Hz, 6H), 1.30 (s, 6H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  198.6, 143.1, 138.5, 133.9, 130.9, 128.0, 127.7, 41.1, 39.6, 23.8 (2C), 20.0, 19.3; IR (neat) 1671, 1597, 1368, 1064  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{OS}$   $[\text{M} + \text{H}]^+$ : 221.1000, found: 221.0970. For **3m<sub>o</sub>**: TLC (4% EtOAc/hexanes):  $R_f = 0.43$ ;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08 (d,  $J = 8.0$  Hz, 1H), 6.98 (d,  $J = 8.0$  Hz, 1H), 3.00 (s, 2H), 2.35 (s, 3H), 2.25 (s, 3H), 1.32 (s, 6H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  203.3, 140.4, 138.7, 135.4, 133.2, 132.1, 124.8, 44.7, 40.5, 24.3 (2C), 20.6, 18.0; IR (neat) 1676  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{OS}$   $[\text{M} + \text{H}]^+$ : 221.1000, found: 221.0992.



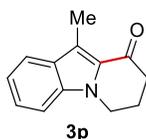
### Rel-(4a*S*,9a*S*)-6,7-Dimethoxy-2,3,4,4a-tetrahydro-1*H*-thioxanthen-9(9a*H*)-one (**3n<sub>o</sub>**) and Rel-(4a*S*,9a*R*)-6,7-Dimethoxy-2,3,4,4a-tetrahydro-1*H*-thioxanthen-9(9a*H*)-one (**3n<sub>r</sub>**):

Following the general procedure C, Rel-(1*S*,2*S*)-2-((3,4-dimethoxyphenyl)thio)cyclohexanecarboxylic acid] **1n** (88.9 mg, 0.300 mmol, 1.0 equiv) was converted to Rel-(1*S*,2*S*)-2-((3,4-dimethoxyphenyl)thio)cyclohexanecarbonyl chloride] **2n** with oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2n** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded a partial separation of **3n<sub>a</sub>** (17.5 mg) and remaining as a mixture of **3n<sub>a</sub>** and **3n<sub>b</sub>** (65.4 mg) as very pale orange viscous oils (combined yield = 82.9 mg, 99%; **3n<sub>a</sub>**:**3n<sub>b</sub>** = 93:7). For **3n<sub>a</sub>**: TLC (20% EtOAc/hexanes, run twice):  $R_f$  = 0.59;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (s, 1H), 6.63 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.73 (brs, 1H), 2.82 (m, 1H), 2.24 (m, 1H), 1.90–1.74 (complex, 3H), 1.65 (m, 1H), 1.57–1.48 (complex, 2H), 1.47–1.40 (m, 1H);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta$  195.9, 153.9, 147.2, 135.2, 123.0, 110.8, 109.0, 56.4, 56.2, 48.9, 43.2, 29.9, 24.9, 23.9, 23.2; IR (neat) 1656, 1592  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{19}\text{O}_3\text{S}$  [ $\text{M} + \text{H}$ ] $^+$ : 279.1055, found: 279.1046. For **3n<sub>b</sub>**: TLC (20% EtOAc/hexanes, run twice):  $R_f$  = 0.64; Characteristic peaks only for **3n<sub>b</sub>** in a mixture (**3n<sub>a</sub>**:**3n<sub>b</sub>** = ca. 91:9):  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 (s, 1H), 6.59 (s, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.31 (td,  $J$  = 12.2, 4.0 Hz, 1H);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  195.0, 153.6, 135.3, 123.8, 110.9, 108.6, 51.7, 45.3, 32.2, 26.4, 25.5, 25.4.



### Anthracen-9(10*H*)-one (**3o**):<sup>33</sup>

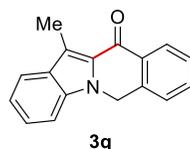
Following the general procedure C,  $\alpha$ -phenyl-*o*-toluic acid **1o** (63.6 mg, 0.300 mmol, 1.0 equiv) was converted to 2-benzylbenzoyl chloride **2o** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2o** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3o** (45.0 mg, 77%) as a colorless solid.



### 10-Methyl-7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one (**3p**):<sup>34</sup>

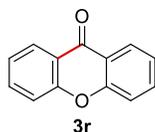
Following the general procedure C, 4-(3-methyl-1*H*-indol-1-yl)butanoic acid **1p** (65.0 mg, 0.300 mmol, 1.0 equiv) was converted to 4-(3-methyl-1*H*-indol-1-yl)butanoyl chloride **2p** using oxalyl chloride (50.8

$\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2p** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3p** (43.0 mg, 72%) as a brown solid.



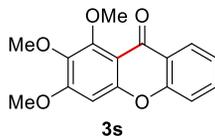
### 12-Methylindolo[1,2-*b*]isoquinolin-11(6*H*)-one (**3q**):

Following the general procedure C, 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoic acid **1q** (79.6 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3-methyl-1*H*-indol-1-yl)methyl)benzoyl chloride **2q** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 90 min. The crude acid chloride **2q** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3q** (54.0 mg, 73%) as a yellow solid. Mp: 203–205 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.70;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.36 (dd,  $J$  = 7.9, 1.4 Hz, 1H), 7.79 (dd,  $J$  = 8.1, 1.0 Hz, 1H), 7.63 (td,  $J$  = 7.5, 1.4 Hz, 1H), 7.56–7.50 (m, 1H), 7.49–7.41 (m, 3H), 7.25–7.20 (m, 1H), 5.46 (s, 2H), 2.90–2.77 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.8, 136.8, 136.1 (2C), 133.0, 131.7, 128.2, 128.1, 127.3, 126.3, 126.2, 121.7, 120.8, 120.3, 110.1, 44.6, 10.5; IR (neat) 1644  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{17}\text{H}_{14}\text{NO}$   $[\text{M} + \text{H}]^+$ : 248.1075, found: 248.1053.



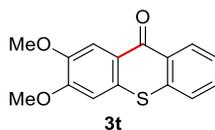
### 9*H*-Xanthen-9-one (**3r**):<sup>35</sup>

Following the general procedure C, 2-phenoxybenzoic acid **1r** (64.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-phenoxybenzoyl chloride **2r** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2r** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 4 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3r** (45.4 mg, 77%) as a colorless solid.



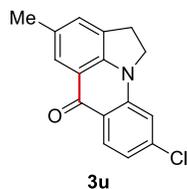
### 1,2,3-Trimethoxy-9H-xanthen-9-one (**3s**):<sup>36</sup>

Following the general procedure C, 2-(3,4,5-trimethoxyphenoxy)benzoic acid **1s** (91.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3,4,5-trimethoxyphenoxy)benzoyl chloride **2s** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2s** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3s** (80.0 mg, 93%) as a colorless solid. Mp: 125–127 °C; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.60;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (dd,  $J$  = 8.0, 1.7 Hz, 1H), 7.65 (ddd,  $J$  = 8.6, 7.1, 1.7 Hz, 1H), 7.41–7.37 (m, 1H), 7.34 (ddd,  $J$  = 8.1, 7.1, 1.1 Hz, 1H), 6.74 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.91 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  175.5, 158.9, 155.4, 154.8, 153.8, 139.8, 134.1, 126.9, 124.0, 122.7, 117.3, 111.1, 96.3, 62.2, 61.7, 56.5; IR (neat) 2946, 1650, 1598  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_5$   $[\text{M} + \text{H}]^+$ : 287.0919, found: 287.0916.



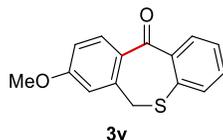
### 2,3-Dimethoxy-9H-thioxanthen-9-one (**3t**):<sup>37</sup>

Following the general procedure C, 2-((3,4-dimethoxyphenyl)thio)benzoic acid **1t** (87.1 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3,4-dimethoxyphenyl)thio)benzoyl chloride **2t** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2t** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded **3t** (76.3 mg, 93%) as a creamish-yellow solid. Mp: 174.5–177.5 °C (lit.<sup>37</sup> mp: 172–173 °C); TLC (2% MeOH/DCM):  $R_f$  = 0.25;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.58 (m, 1H), 7.99 (s, 1H), 7.56–7.48 (m, 2H), 7.43 (m, 1H), 6.84 (s, 1H), 3.98 (s, 3H), 3.95 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.7, 153.5, 148.8, 137.1, 131.7, 131.4, 129.8, 128.8, 126.2, 125.9, 123.3, 110.2, 106.7, 56.4, 56.3; IR (neat) 1625, 1588  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{13}\text{O}_3\text{S}$   $[\text{M} + \text{H}]^+$ : 273.0585, found: 273.0552.



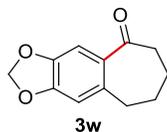
**9-Chloro-4-methyl-1H-pyrrolo[3,2,1-de]acridin-6(2H)-one (3u):**

Following the general procedure C, 4-chloro-2-(5-methylindolin-1-yl)benzoic acid (ca. 94% pure) **1u** (86.3 mg, 0.300 mmol, 1.0 equiv) was converted to 4-chloro-2-(5-methylindolin-1-yl)benzoyl chloride **2u** using oxalyl chloride (33.0  $\mu$ L, 0.390 mmol, 1.3 equiv) in 25 min (oxalyl chloride was added over 5 min). The crude acid chloride **2u** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% MeOH/DCM over 50 min) provided impure **3u** as an insoluble yellow fluorescent solid. Trituration of impure **3u** with  $\text{CD}_2\text{Cl}_2$  and filtration under suction (including additional washings by  $\text{CD}_2\text{Cl}_2$ ) afforded pure **3u** (66.2 mg, 82%) as a bright yellow fluorescent solid (almost insoluble in all solvents). Mp: >240  $^\circ\text{C}$ ; TLC (2% MeOH/DCM):  $R_f$  = 0.27;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  8.41 (d,  $J$  = 8.7 Hz, 1H), 7.83 (m, 1H), 7.39 (m, 1H), 7.30 (d,  $J$  = 1.9 Hz, 1H), 7.21 (dd,  $J$  = 8.7, 1.9 Hz, 1H), 4.49 (dd,  $J$  = 8.4, 7.7 Hz, 2H), 3.57 (t,  $J$  = 8.0 Hz, 2H), 2.47 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  176.7, 144.1, 140.8, 139.6, 133.1, 132.5, 130.2, 130.0, 122.3, 121.7, 121.5, 119.1, 114.1, 49.0, 28.1, 21.6; IR (neat) 1627, 1610  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{13}\text{ClNO}$   $[\text{M} + \text{H}]^+$ : 270.0686, found: 270.0678.



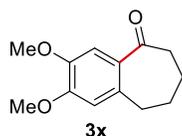
**8-Methoxydibenzo[b,e]thiepin-11(6H)-one (3v):<sup>14,24</sup>**

Following the general procedure C, 2-((3-methoxybenzyl)thio)benzoic acid **1v** (82.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-((3-methoxybenzyl)thio)benzoyl chloride **2v** with oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2v** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% EtOAc/hexanes over 50 min) afforded **3v** (62.3 mg, 81%) as a colorless solid.



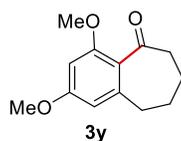
**6,7,8,9-Tetrahydro-5H-cyclohepta[4,5]benzo[1,2-*d*][1,3]dioxol-5-one (3w):**

Following the general procedure C, 5-(benzo[*d*][1,3]dioxol-5-yl)pentanoic acid **1w** (66.7 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzo[*d*][1,3]dioxol-5-yl)pentanoyl chloride **2w** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2w** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 6 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–20% EtOAc/hexanes over 40 min) afforded **3w** (36.3 mg, 59%) as a pale yellow viscous oil. TLC (30% EtOAc/hexanes):  $R_f$  = 0.66;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (s, 1H), 6.63 (s, 1H), 5.97 (s, 2H), 2.84 (m, 2H), 2.68 (m, 2H), 1.86–1.73 (complex, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  203.9, 151.1, 146.8, 138.4, 132.8, 109.8, 108.8, 101.8, 40.8, 32.7, 25.2, 20.6; IR (neat) 1660, 1615  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{12}\text{H}_{13}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 205.0865, found: 205.0844.



**2,3-Dimethoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (3x):<sup>38</sup>**

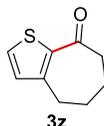
Following the general procedure C, 5-(3,4-dimethoxyphenyl)pentanoic acid **1x** (71.4 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(3,4-dimethoxyphenyl)pentanoyl chloride **2x** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid **2x** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (80:20 hexanes/EtOAc) afforded **3x** (37.0 mg, 56%) as a colorless solid.



**2,4-Dimethoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-one (3y):**

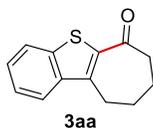
Following the general procedure C, 5-(3,5-dimethoxyphenyl)pentanoic acid **1y** (65.0 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(3,5-dimethoxyphenyl)pentanoyl chloride **2y** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2y** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system

using a silica flash column (50:50 hexanes/EtOAc) afforded **3y** (40.0 mg, 61%) as a colorless oil. TLC (50% EtOAc/Hexanes):  $R_f$  = 0.40;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.36 (d,  $J$  = 2.2 Hz, 1H), 6.26 (d,  $J$  = 2.2 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 2.72 (dd,  $J$  = 7.1, 5.4 Hz, 2H), 2.67–2.54 (m, 2H), 1.77 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.8, 162.4, 158.7, 142.0, 122.6, 105.9, 97.2, 56.2, 55.6, 42.4, 33.1, 25.6, 22.3; IR (neat) 2935, 1683, 1597  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{17}\text{O}_3$   $[\text{M} + \text{H}]^+$ : 221.1178, found: 221.1151.



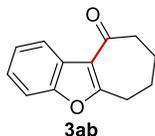
#### 4,5,6,7-Tetrahydro-8H-cyclohepta[b]thiophen-8-one (**3z**):<sup>18</sup>

Following the general procedure C, 5-(thiophen-3-yl)pentanoic acid **1z** (55.3 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(thiophen-3-yl)pentanoyl chloride **2z** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2z** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3z** (36.0 mg, 72%) as a colorless oil.



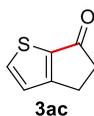
#### 7,8,9,10-Tetrahydro-6H-benzo[b]cyclohepta[d]thiophen-6-one (**3aa**):

Following the general procedure C, 5-(benzo[b]thiophen-3-yl)pentanoic acid **1aa** (70.0 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzo[b]thiophen-3-yl)pentanoyl chloride **2aa** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2aa** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3aa** (44.0 mg, 68%) as an off-white solid. Mp: 82–83  $^{\circ}\text{C}$ ; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.60;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89–7.81 (m, 2H), 7.51–7.37 (m, 2H), 3.26–3.13 (m, 2H), 2.96–2.83 (m, 2H), 2.17–1.94 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  197.5, 143.4, 141.7, 141.3, 140.1, 127.6, 124.7, 124.0, 123.2, 42.4, 27.1, 25.7, 21.8; IR (neat) 1689, 1616  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{OS}$   $[\text{M} + \text{H}]^+$ : 217.0687, found: 217.0693.



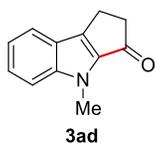
**6,7,8,9-Tetrahydro-10H-cyclohepta[b]benzofuran-10-one (3ab):**

Following the general procedure C, 5-(benzofuran-2-yl)pentanoic acid **1ab** (65.5 mg, 0.300 mmol, 1.0 equiv) was converted to 5-(benzofuran-2-yl)pentanoyl chloride **2ab** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ab** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3ab** (43.0 mg, 72%) as a colorless solid. Mp: 73–75  $^{\circ}\text{C}$ ; TLC (50% EtOAc/Hexanes):  $R_f$  = 0.30;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29–8.21 (m, 1H), 7.43–7.36 (m, 1H), 7.33–7.26 (m, 2H), 3.25–3.15 (m, 2H), 2.91–2.81 (m, 2H), 2.17–2.05 (m, 2H), 2.05–1.95 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  197.8, 166.3, 154.0, 127.1, 125.0, 124.4, 123.0, 118.3, 110.6, 45.2, 30.2, 24.9, 22.9; IR (neat) 1638, 1580  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 201.0916, found: 201.0912.



**4,5-Dihydro-6H-cyclopenta[b]thiophen-6-one (3ac):**<sup>39</sup>

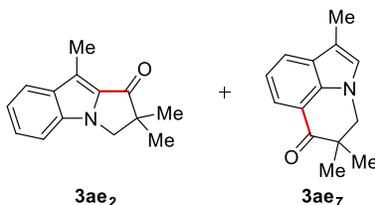
Following the general procedure C, 3-(3-thienyl)propanoic acid **1ac** (47.0 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(thiophen-3-yl)propanoyl chloride **2ac** using oxalyl chloride (38.1  $\mu\text{L}$ , 0.450 mmol, 1.5 equiv) in 15 min. The crude acid chloride **2ac** was dissolved in HFIP (1.5 mL) and the resultant reaction mixture was stirred at rt for 16 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded **3ac** (6.00 mg, 14%) as a colorless solid.



**4-Methyl-1,2-dihydrocyclopenta[b]indol-3(4H)-one (3ad):**<sup>40,41</sup>

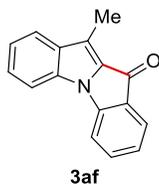
Following the general procedure C, 3-(1-methyl-1H-indol-3-yl)propanoic acid **1ad** (61.0 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(1-methyl-1H-indol-3-yl)propanoyl chloride **2ad** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ad** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash

purification system using a 4 g silica flash column (0–30% EtOAc/hexanes over 45 min) afforded **3ad** (39.3 mg, 71%) as a creamish yellow solid.



**2,2,9-Trimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-one and 1,5,5-Trimethyl-4,5-dihydro-6H-pyrrolo[3,2,1-ij]quinolin-6-one (3ae<sub>2</sub> and 3ae<sub>7</sub>):**

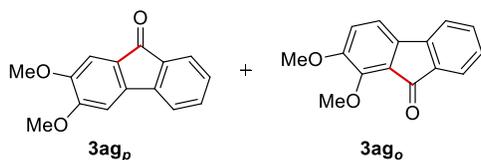
Following the general procedure C, 2,2-dimethyl-3-(3-methyl-1H-indol-1-yl)propanoic acid **1ae** (69.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2,2-dimethyl-3-(3-methyl-1H-indol-1-yl)propanoyl chloride **2ae** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2ae** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (90:10 hexanes/EtOAc) afforded an inseparable mixture of **3ae<sub>2</sub>** and **3ae<sub>7</sub>** (50.0 mg, 78%, **3ae<sub>2</sub>**:**3ae<sub>7</sub>** = 85:15) as a pale yellow oil. TLC (10% EtOAc/Hexanes):  $R_f$  = 0.80 (overlapping spots of **3ae<sub>2</sub>** and **3ae<sub>7</sub>**); **3ae<sub>2</sub>**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.74–7.70 (m, 1H), 7.37–7.33 (m, 2H), 7.17 (ddd,  $J$  = 8.1, 5.7, 2.2 Hz, 1H), 4.15 (s, 2H), 2.58 (s, 3H), 1.39 (s, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  199.4, 135.3, 132.7, 131.4, 125.4 (2C), 122.3, 120.6, 110.6, 54.7, 50.3, 24.9 (2C), 9.0. **3ae<sub>7</sub>**: Characteristic peaks only: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 7.77 (dd,  $J$  = 7.8, 0.9 Hz, 1H), 6.94 (d,  $J$  = 1.2 Hz, 1H), 4.07 (s, 2H), 2.36 (d,  $J$  = 1.1 Hz, 3H), 1.30 (s, 6H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  128.8, 125.7, 119.9, 119.6, 116.4, 113.2, 55.9, 43.6, 23.8, 9.9. For a mixture of **3ae<sub>2</sub>** and **3ae<sub>7</sub>**: IR (neat) 1698, 1568  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for C<sub>14</sub>H<sub>16</sub>NO [M + H]<sup>+</sup>: 214.1232, found: 214.1204.



**11-Methyl-10H-indolo[1,2-a]indol-10-one (3af):**

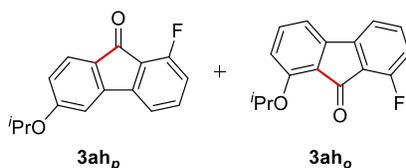
Following the general procedure C, 2-(3-methyl-1H-indol-1-yl)benzoic acid **1af** (75.3 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3-methyl-1H-indol-1-yl)benzoyl chloride **2af** using oxalyl chloride (33.0  $\mu$ L, 0.390 mmol, 1.3 equiv) in 50 min (oxalyl chloride was added over 10 min). The crude acid chloride **2af** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h.

Purification on a Combiflash purification system using a 12 g silica flash column (0–15% EtOAc/hexanes over 30 min) afforded **3af** (60.6 mg, 87%) as an orange-brown solid. Mp: 153–156 °C; TLC (2% MeOH/DCM):  $R_f$  = 0.62;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (ddd,  $J$  = 7.5, 1.2, 0.58 Hz, 1H), 7.56 (dt,  $J$  = 8.0, 0.90 Hz, 1H), 7.46 (td,  $J$  = 7.8, 1.3 Hz, 1H), 7.43–7.36 (m, 2H), 7.27 (m, 1H), 7.10 (ddd,  $J$  = 8.1, 6.6, 1.5 Hz, 1H), 7.03 (td,  $J$  = 7.5, 0.78 Hz, 1H), 2.54 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  182.1, 145.2, 135.2, 134.4, 133.8, 133.0, 130.1, 128.4, 125.0, 123.4, 123.0, 122.5, 121.5, 111.4, 111.2, 9.5; IR (neat) 1678, 1619, 1605, 1473, 1323  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{12}\text{NO}$   $[\text{M} + \text{H}]^+$ : 234.0919, found: 234.0901.



### 2,3-Dimethoxy-9H-fluoren-9-one (3ag<sub>p</sub>) and 1,2-Dimethoxy-9H-fluoren-9-one (3ag<sub>o</sub>):<sup>42</sup>

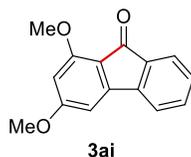
Following the general procedure C, 3',4'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid **1ag** (77.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3',4'-dimethoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ag** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ag** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–30% EtOAc/hexanes over 30 min) afforded a complete separation of **3ag<sub>p</sub>** (65.5 mg, 91%) as an orange solid and **3ag<sub>o</sub>** (1.50 mg, 2%) as a yellowish-orange solid (combined yield = 67.0 mg, 93%; **3ag<sub>p</sub>**:**3ag<sub>o</sub>** = 98:2).



### 1-Fluoro-6-isopropoxy-9H-fluoren-9-one (3ah<sub>p</sub>) and 1-Fluoro-8-isopropoxy-9H-fluoren-9-one (3ah<sub>o</sub>):

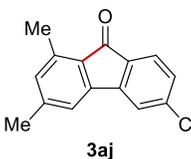
Following the general procedure C, 3-fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carboxylic acid **1ah** (82.3 mg, 0.300 mmol, 1.0 equiv) was converted to 3-fluoro-3'-isopropoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ah** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ah** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–10% EtOAc/hexanes over 40 min) afforded a mixture of **3ah<sub>p</sub>** and **3ah<sub>o</sub>** (combined yield = 76.3 mg, 99%; **3ah<sub>p</sub>**:**3ah<sub>o</sub>** = 76:24) as a yellow

oily solid. For a mixture of products (**3ah<sub>p</sub>**: **3ah<sub>o</sub>** = 76:24 by <sup>1</sup>H NMR): TLC (15% EtOAc/hexanes): R<sub>f</sub> = 0.39; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.54 (**3ah<sub>p</sub>**; d, *J* = 8.3 Hz, 1H), 7.41–7.34 (**3ah<sub>p</sub>** and **3ah<sub>o</sub>**; m, 3H), 7.22 (**3ah<sub>o</sub>**; d, *J* = 7.4 Hz, 1H), 7.20 (**3ah<sub>p</sub>**; d, *J* = 7.3 Hz, 1H), 7.05 (**3ah<sub>o</sub>**; dd, *J* = 7.3, 0.60 Hz, 1H), 6.94 (**3ah<sub>p</sub>**; d, *J* = 2.1 Hz, 1H), 6.89–6.84 (**3ah<sub>p</sub>** and **3ah<sub>o</sub>**; m, 2H), 6.80 (**3ah<sub>o</sub>**; d, *J* = 8.4 Hz, 1H), 6.69 (**3ah<sub>p</sub>**; dd, *J* = 8.3, 2.2 Hz, 1H), 4.72–4.59 (**3ah<sub>p</sub>** and **3ah<sub>o</sub>**; m, 2H), 1.40 (**3ah<sub>o</sub>**; d, *J* = 6.1 Hz, 6H), 1.36 (**3ah<sub>p</sub>**; d, *J* = 6.1 Hz, 6H); <sup>13</sup>C NMR (For **3ah<sub>p</sub>**; 101 MHz, CDCl<sub>3</sub>) δ 188.9 (d, *J* = 0.97 Hz, 1C), 164.0, 159.1 (d, *J* = 262.4 Hz, 1C), 146.1 (d, *J* = 3.4 Hz, 1C), 145.6 (d, *J* = 3.9 Hz, 1C), 136.4 (d, *J* = 8.4 Hz, 1C), 136.3, 126.46, 121.1 (d, *J* = 12.8 Hz, 1C), 117.8 (d, *J* = 20.9 Hz, 1C), 116.3 (d, *J* = 3.1 Hz, 1C, completely overlapped with **3ah<sub>o</sub>** peak), 115.2, 108.7, 70.8, 22.1 (2C); (For **3ah<sub>o</sub>**; 101 MHz, CDCl<sub>3</sub>) δ 188.0 (d, *J* = 1.2 Hz, 1C), 159.2 (d, *J* = 262.8 Hz, 1C), 157.5, 145.6 (1C, overlapped with **3ah<sub>p</sub>** peak), 145.5 (d, *J* = 3.7 Hz, 1C), 136.1 (d, *J* = 8.3 Hz, 1C), 126.54, 121.2, 120.4 (d, *J* = 12.4 Hz, 1C), 117.5 (d, *J* = 20.7 Hz, 1C), 117.3, 116.3 (d, *J* = 3.1 Hz, 1C, completely overlapped with **3ah<sub>p</sub>** peak), 113.3, 72.2, 22.2 (2C); IR (neat; for a mixture of **3ah<sub>p</sub>** and **3ah<sub>o</sub>**) 1703, 1619, 1587, 1455, 1211, 1107 cm<sup>-1</sup>; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>14</sub>FO<sub>2</sub> [M + H]<sup>+</sup>: 257.0978, found for **3ah<sub>p</sub>**: 257.0940 and found for **3ah<sub>o</sub>**: 257.0939.



### 1,3-Dimethoxy-9H-fluoren-9-one (**3ai**):<sup>43</sup>

Following the general procedure C, 3',5'-dimethoxy-[1,1'-biphenyl]-2-carboxylic acid **1ai** (77.5 mg, 0.300 mmol, 1.0 equiv) was converted to 3',5'-dimethoxy-[1,1'-biphenyl]-2-carbonyl chloride **2ai** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2ai** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 2.5 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–50% EtOAc/hexanes over 25 min) afforded **3ai** (71.5 mg, 99%) as a light yellow solid.



### 6-Chloro-1,3-dimethyl-9H-fluoren-9-one (**3aj**):

Following the general procedure C, 5-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carboxylic acid **1aj** (78.2 mg, 0.300 mmol, 1.0 equiv) was converted to 5-chloro-3',5'-dimethyl-[1,1'-biphenyl]-2-carbonyl chloride **2aj** using oxalyl chloride (50.8 μL, 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2aj** was

dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 3 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3aj** (70.5 mg, 97%) as a light yellow solid. Mp: 159.5–161 °C; TLC (15% EtOAc/hexanes):  $R_f$  = 0.67;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J$  = 7.8 Hz, 1H), 7.31 (d,  $J$  = 1.7 Hz, 1H), 7.17 (dd,  $J$  = 7.8, 1.8 Hz, 1H), 7.00 (s, 1H), 6.80 (s, 1H), 2.51 (s, 3H), 2.31 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.1, 145.5, 145.2, 143.9, 140.3, 139.7, 133.3, 133.1, 129.0, 128.8, 124.8, 120.5, 119.2, 22.1, 17.8; IR (neat) 1701, 1599, 1137, 1062  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{15}\text{H}_{12}\text{ClO}$  [ $\text{M} + \text{H}$ ] $^+$ : 243.0577, found: 243.0556.



#### 5,7-Dimethoxy-8H-indeno[2,1-b]thiophen-8-one (**3ak**):

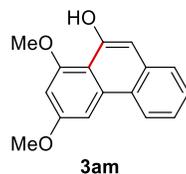
Following the general procedure C, 3-(3,5-dimethoxyphenyl)thiophene-2-carboxylic acid **1ak** (79.3 mg, 0.300 mmol, 1.0 equiv) was converted to 3-(3,5-dimethoxyphenyl)thiophene-2-carbonyl chloride **2ak** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 60 min. The crude acid chloride **2ak** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using a 12 g silica flash column (0–40% EtOAc/hexanes over 40 min) afforded **3ak** (53.0 mg, 72%) as a yellowish-orange solid. Mp: 169.5–172 °C (shrink above 150 °C); TLC (30% EtOAc/hexanes):  $R_f$  = 0.28;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (d,  $J$  = 4.7 Hz, 1H), 7.00 (d,  $J$  = 4.7 Hz, 1H), 6.35 (d,  $J$  = 1.9 Hz, 1H), 6.10 (d,  $J$  = 1.9 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  183.3, 166.8, 159.5, 155.0, 143.6, 139.3, 136.8, 119.9, 115.5, 101.5, 96.5, 56.0, 55.9; IR (neat) 1711, 1688, 1616, 1591, 1215, 1130, 1048  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{13}\text{H}_{11}\text{O}_3\text{S}$  [ $\text{M} + \text{H}$ ] $^+$ : 247.0429, found: 247.0399.



#### 9H-Fluoren-9-one (**3al**):<sup>44,45</sup>

Following the general procedure C, 1,1'-biphenyl]-2-carboxylic acid **1al** (59.5 mg, 0.300 mmol, 1.0 equiv) was converted to 1,1'-biphenyl]-2-carbonyl chloride **2al** using oxalyl chloride (50.8  $\mu\text{L}$ , 0.600 mmol, 2.0 equiv) in 45 min. The crude acid chloride **2al** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 4 h. Purification on a Combiflash purification system using

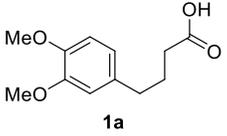
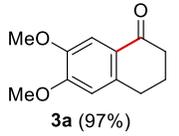
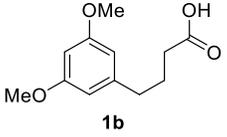
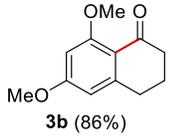
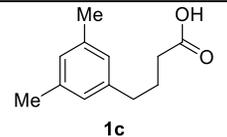
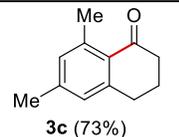
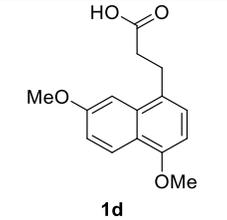
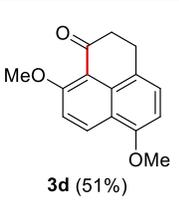
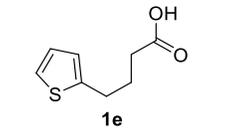
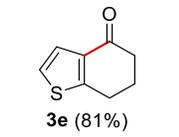
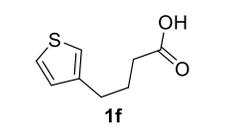
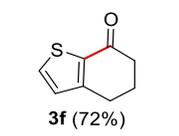
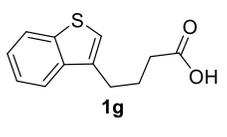
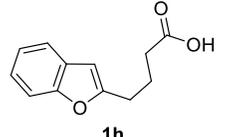
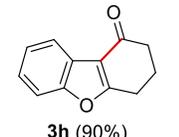
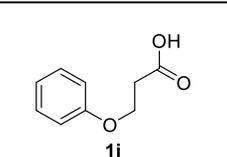
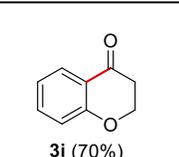
a 12 g silica flash column (0–5% EtOAc/hexanes over 50 min) afforded **3al** (6.50 mg, 12%) as a yellow oily solid.

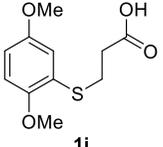
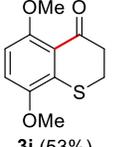
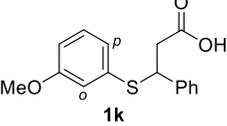
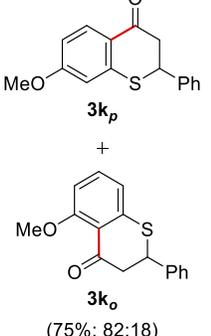
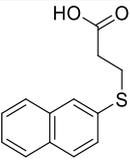
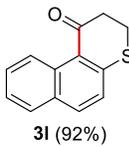
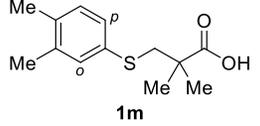
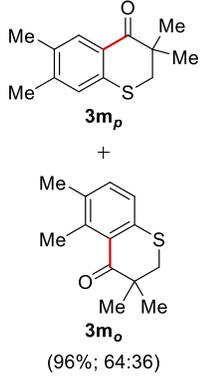
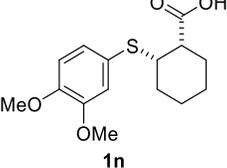
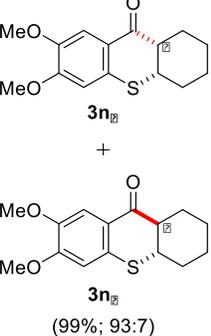
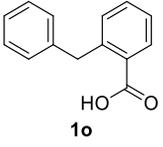
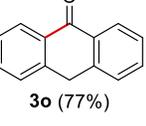


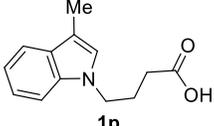
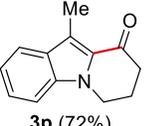
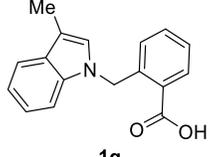
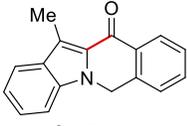
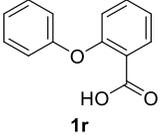
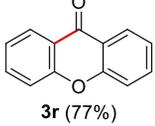
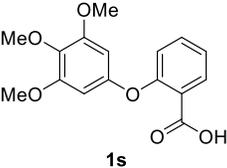
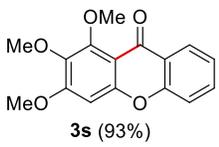
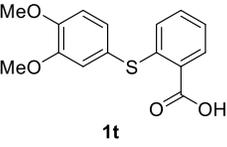
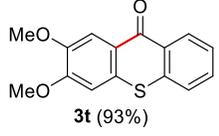
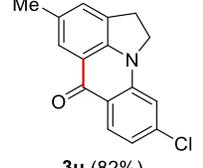
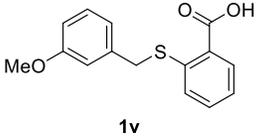
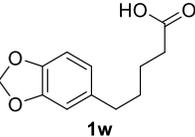
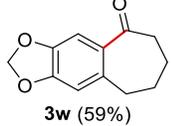
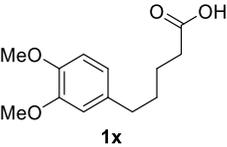
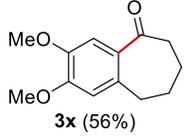
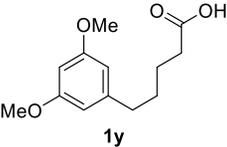
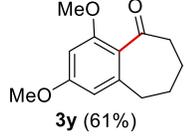
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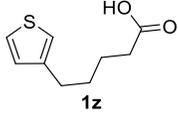
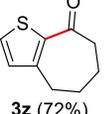
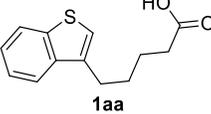
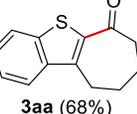
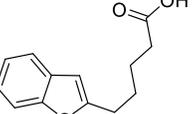
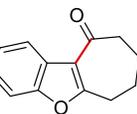
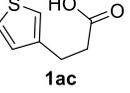
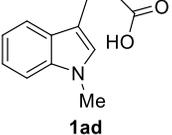
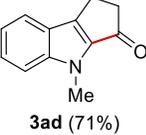
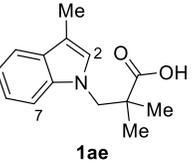
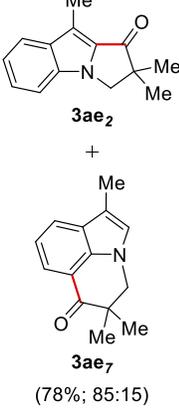
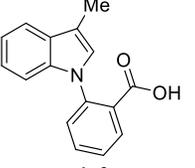
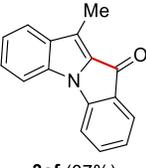
Following the general procedure C, 2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetic acid **1am** (82.0 mg, 0.300 mmol, 1.0 equiv) was converted to 2-(3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetyl chloride **2am** using oxalyl chloride (50.8  $\mu$ L, 0.600 mmol, 2.0 equiv) in 30 min. The crude acid chloride **2am** was dissolved in HFIP (0.75 mL) and the resultant reaction mixture was stirred at rt for 5 h. Purification on a Combiflash purification system using a silica flash column (50:50 hexanes/EtOAc) afforded **3am** (50.0 mg, 66%) as a yellow solid. Mp: 143–144 °C; TLC (50% EtOAc/Hexanes):  $R_f = 0.70$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.33 (s, 1H), 8.47–8.39 (m, 1H), 7.73–7.65 (m, 2H), 7.50 (ddd,  $J = 8.0, 6.9, 1.2$  Hz, 1H), 7.41 (ddd,  $J = 8.3, 6.9, 1.4$  Hz, 1H), 6.97 (s, 1H), 6.71 (d,  $J = 2.2$  Hz, 1H), 4.09 (s, 3H), 4.02 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 157.8, 152.3, 135.0, 134.5, 127.6, 127.0, 125.0, 123.5, 123.2, 110.9, 105.7, 98.9, 97.6, 56.7, 55.7; IR (neat) 3327, 1638, 1615  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 255.1021, found: 255.0994.

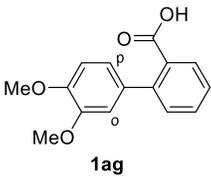
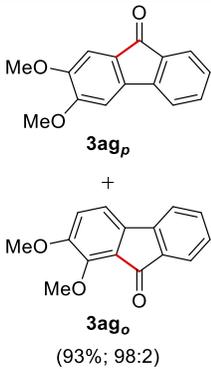
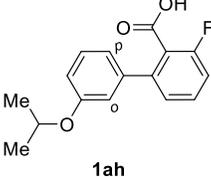
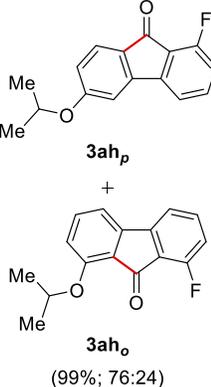
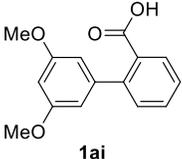
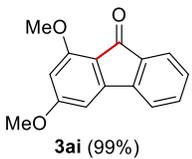
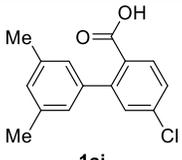
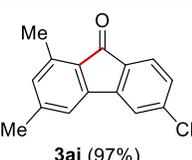
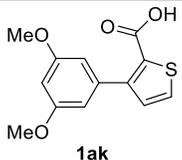
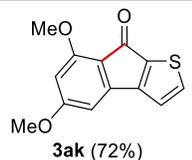
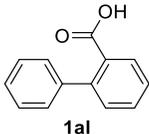
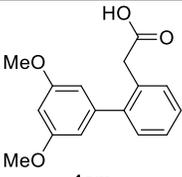
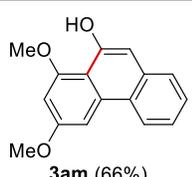
**Table S1 | Comparison of Product Yields Obtained from the Present Work (Figure 3) with those Previously Reported in the Literature Along with their Corresponding Reaction Conditions.**

entry	carboxylic acid	product (% yield)	time (h)	reported yield (conditions) <sup>ref</sup>
1	 <b>1a</b>	 <b>3a (97%)</b>	2	I. 93% (Polyphosphoric acid (PPA), DCM, reflux, 2h) <sup>25</sup> II. 97% (1.1 equiv trichloroacetic anhydride, 70 °C, 6 min) <sup>24</sup>
2	 <b>1b</b>	 <b>3b (86%)</b>	5	96% (1.1 equiv SnCl <sub>4</sub> , DCM, 0 °C, 2 h) <sup>26</sup>
3	 <b>1c</b>	 <b>3c (73%)</b>	5	–
4	 <b>1d</b>	 <b>3d (51%)</b>	4	–
5	 <b>1e</b>	 <b>3e (81%)</b>	3	I. 85% (H <sub>3</sub> PO <sub>4</sub> , Ac <sub>2</sub> O, 120–140 °C, 3 h) <sup>46</sup> II. 76% (Eaton's reagent, 100 °C, 5 min) <sup>47</sup> III. 62% (1.2 equiv SnCl <sub>2</sub> , EtOAc, 0 °C to rt, 3.5 h) <sup>28</sup>
6	 <b>1f</b>	 <b>3f (72%)</b>	5	I. 72% (SOCl <sub>2</sub> , 1 drop pyridine, 70 °C, 24 h) <sup>48</sup> II. 71% (P <sub>2</sub> O <sub>5</sub> , MeSO <sub>3</sub> H, rt, 90 min) <sup>29</sup> III. 78% (SOCl <sub>2</sub> , 4 drops pyridine, reflux, 8 h) <sup>49</sup>
7	 <b>1g</b>	 <b>3g (99%)</b>	5	54% (AlCl <sub>3</sub> , rt, 12 h) <sup>50</sup>
8	 <b>1h</b>	 <b>3h (90%)</b>	5	–
9	 <b>1i</b>	 <b>3i (70%)</b>	5	I. 81% (H <sub>3</sub> PO <sub>4</sub> , P <sub>2</sub> O <sub>5</sub> , rt, 24 h) <sup>51</sup> II. 53% (1 mol % Bi[N(SO <sub>2</sub> CF <sub>3</sub> ) <sub>2</sub> ], <i>p</i> -xylene, 180 °C, 20 h) <sup>52</sup> III. 98% (10 mol % Eu(OTf) <sub>3</sub> , 180 °C, 14 h) <sup>53</sup> IV. 87% (H <sub>3</sub> PO <sub>4</sub> , P <sub>2</sub> O <sub>5</sub> , 100 °C, 2 h) <sup>54</sup>

10	 <p><b>1j</b></p>	 <p><b>3j (53%)</b></p>	5	53% (PPA, 80 °C, 3 h) <sup>32</sup>
11	 <p><b>1k</b></p>	 <p><b>3k<sub>p</sub></b> + <b>3k<sub>o</sub></b> (75%; 82:18)</p>	4	–
12	 <p><b>1l</b></p>	 <p><b>3l (92%)</b></p>	3	48% (PPA, 60 °C, 2 h) <sup>8</sup>
13	 <p><b>1m</b></p>	 <p><b>3m<sub>p</sub></b> + <b>3m<sub>o</sub></b> (96%; 64:36)</p>	3	–
14	 <p><b>1n</b></p>	 <p><b>3n<sub>R</sub></b> + <b>3n<sub>S</sub></b> (99%; 93:7)</p>	3	–
15	 <p><b>1o</b></p>	 <p><b>3o (77%)</b></p>	5	I. >99% (BF <sub>3</sub> ·2CF <sub>3</sub> CH <sub>2</sub> OH, DCM, rt) <sup>55</sup> II. 90% (1.5 equiv POCl <sub>3</sub> , reflux, 30 min) <sup>56</sup> III. 92% (Nafion-H, <i>m</i> -dichlorobenzene, reflux, 3 h) <sup>57</sup>

16	 <b>1p</b>	 <b>3p (72%)</b>	5	I. 60% (PPA, 90°C, 1 h) <sup>58</sup> II. 96% (PPA, 90°C, 1 h) <sup>10</sup>
17	 <b>1q</b>	 <b>3q (73%)</b>	5	–
18	 <b>1r</b>	 <b>3r (77%)</b>	4	I. 99% (7.5 equiv AlCl <sub>3</sub> , 8.5 equiv NaCl, 200 °C, 25 min) <sup>59</sup> II. 67% (H <sub>2</sub> SO <sub>4</sub> , 100 °C, 3 h) <sup>35</sup>
19	 <b>1s</b>	 <b>3s (93%)</b>	5	92% (MeSO <sub>3</sub> H, 4.0 equiv P <sub>2</sub> O <sub>5</sub> , rt, 18 h) <sup>36</sup>
20	 <b>1t</b>	 <b>3t (93%)</b>	2.5	Reaction of ethyl ester of <b>1t</b> in PPA at 100 °C for 1 h gave the same yield. <sup>37</sup>
21 <sup>d</sup>	 <b>1u</b>	 <b>3u (82%)</b>	3	–
22	 <b>1v</b>	 <b>3v (81%)</b>	4	I. 70% (1.1 equiv trichloroacetic anhydride, 70 °C, 6 h) <sup>24</sup> II. 72% (SnCl <sub>4</sub> , benzene, 0 °C, 25 min) <sup>14</sup>
23	 <b>1w</b>	 <b>3w (59%)</b>	6	–
24	 <b>1x</b>	 <b>3x (56%)</b>	5	80% (PCl <sub>5</sub> , SnCl <sub>4</sub> , CS <sub>2</sub> , reflux, 35 h) <sup>60</sup>
25	 <b>1y</b>	 <b>3y (61%)</b>	5	–

26	 <b>1z</b>	 <b>3z (72%)</b>	5	–
27	 <b>1aa</b>	 <b>3aa (68%)</b>	5	–
28	 <b>1ab</b>	 <b>3ab (72%)</b>	5	–
29	 <b>1ac</b>	 <b>3ac (14%)</b>	16	I. 30% (MeSO <sub>3</sub> H, P <sub>2</sub> O <sub>5</sub> , rt, 1 h) <sup>61</sup> II. 54% (MeSO <sub>3</sub> H, P <sub>2</sub> O <sub>5</sub> , rt, 40 min) <sup>62</sup> III. 44% (HF, 30 °C, 12 h) <sup>63</sup>
30	 <b>1ad</b>	 <b>3ad (71%)</b>	4	I. 76% (PPA, toluene, reflux, 4 h) <sup>41</sup> II. 95% (PPA, toluene, reflux, 4 h) <sup>40</sup>
31	 <b>1ae</b>	 <b>3ae<sub>2</sub></b> + <b>3ae<sub>7</sub></b> (78%; 85:15)	5	–
32	 <b>1af</b>	 <b>3af (87%)</b>	2.5	–

33	 <p><b>1ag</b></p>	 <p><b>3ag<sub>p</sub></b> + <b>3ag<sub>o</sub></b> (93%; 98:2)</p>	2.5	For <b>3ag<sub>p</sub></b> : 94% (7.0 equiv trifluoroacetic anhydride, CHCl <sub>3</sub> , rt, 30 min) <sup>42</sup>
34	 <p><b>1ah</b></p>	 <p><b>3ah<sub>p</sub></b> + <b>3ah<sub>o</sub></b> (99%; 76:24)</p>	3.5	–
35	 <p><b>1ai</b></p>	 <p><b>3ai</b> (99%)</p>	2.5	86% (trifluoroacetic anhydride/CHCl <sub>3</sub> (1:3), rt, 30 min) <sup>43</sup>
36	 <p><b>1aj</b></p>	 <p><b>3aj</b> (97%)</p>	3	–
37	 <p><b>1ak</b></p>	 <p><b>3ak</b> (72%)</p>	4	–
38	 <p><b>1al</b></p>	 <p><b>3al</b> (12%)</p>	4	I. 100% (7.5 equiv AlCl <sub>3</sub> , 8.5 equiv NaCl, 180–190 °C, 20 min) <sup>59</sup> II. 99% (PPA, 120 °C, 2 h) <sup>64</sup>
39	 <p><b>1am</b></p>	 <p><b>3am</b> (66%)</p>	5	–

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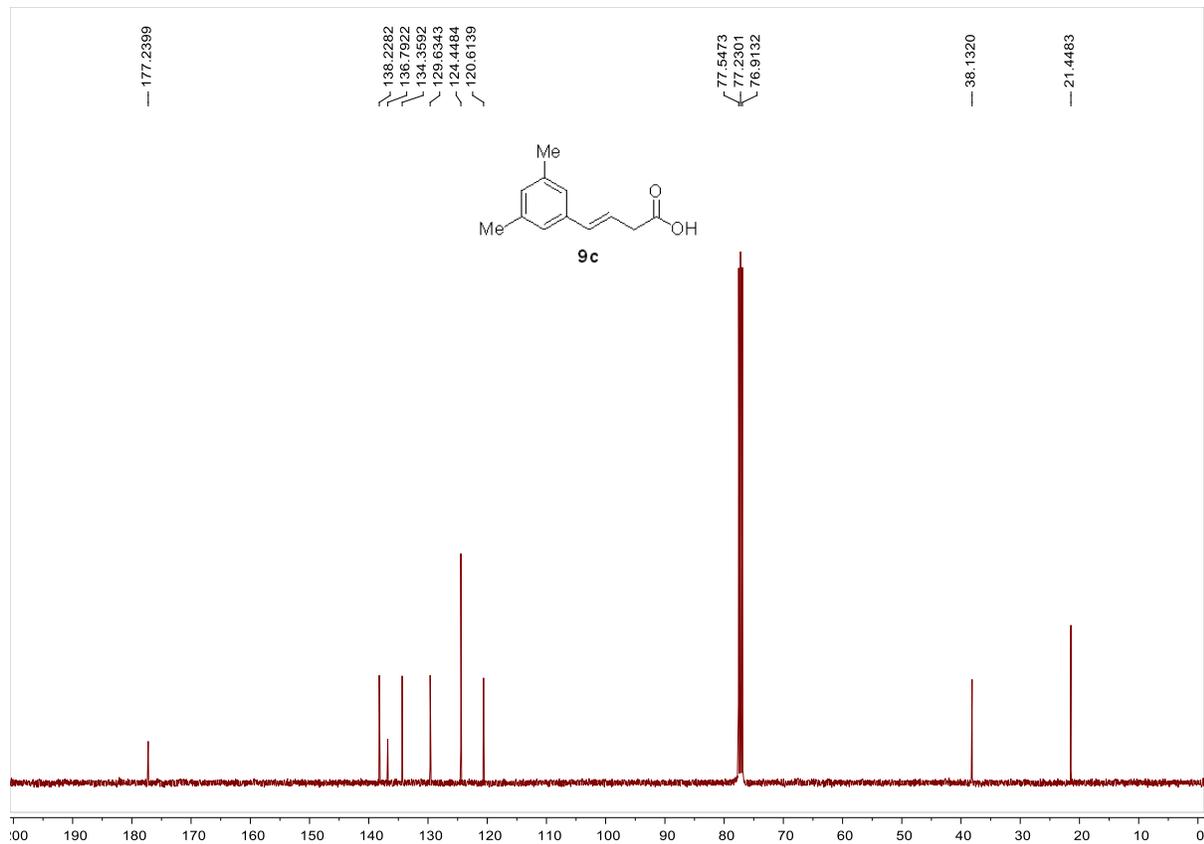
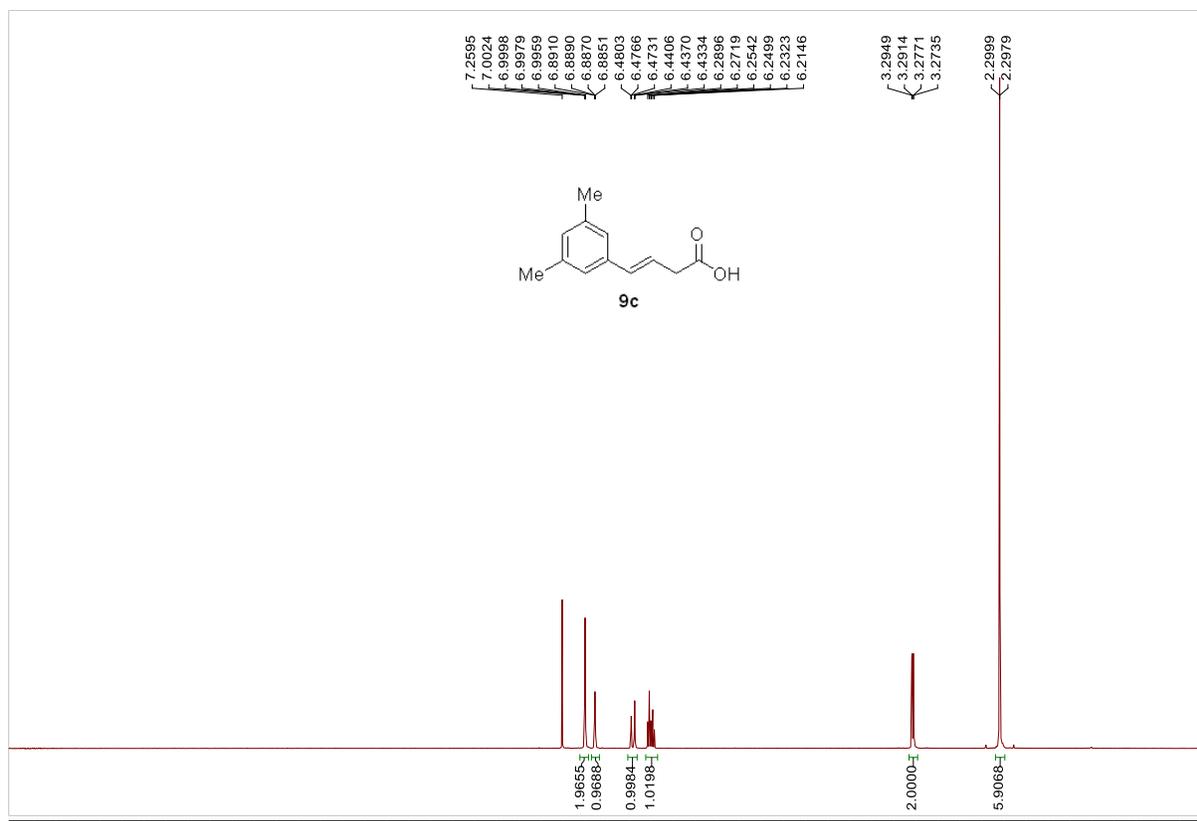
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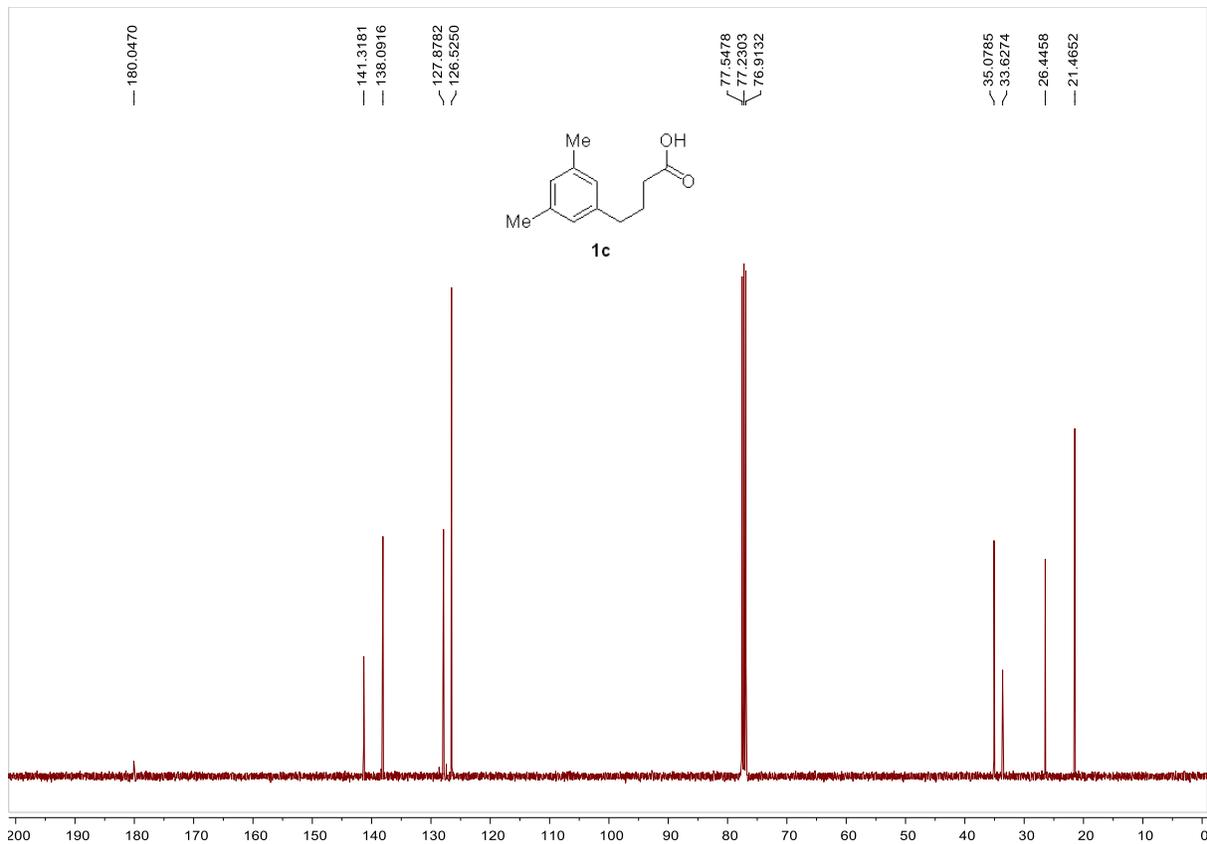
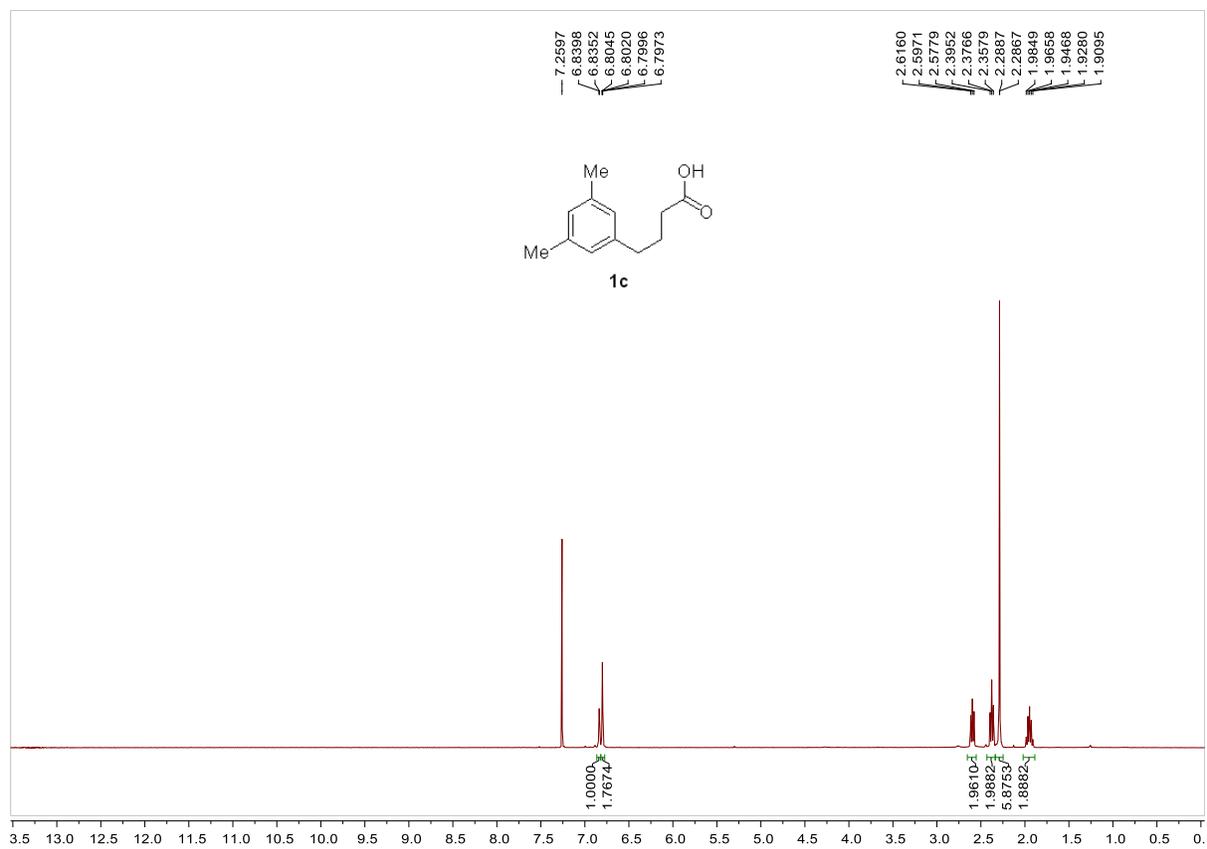
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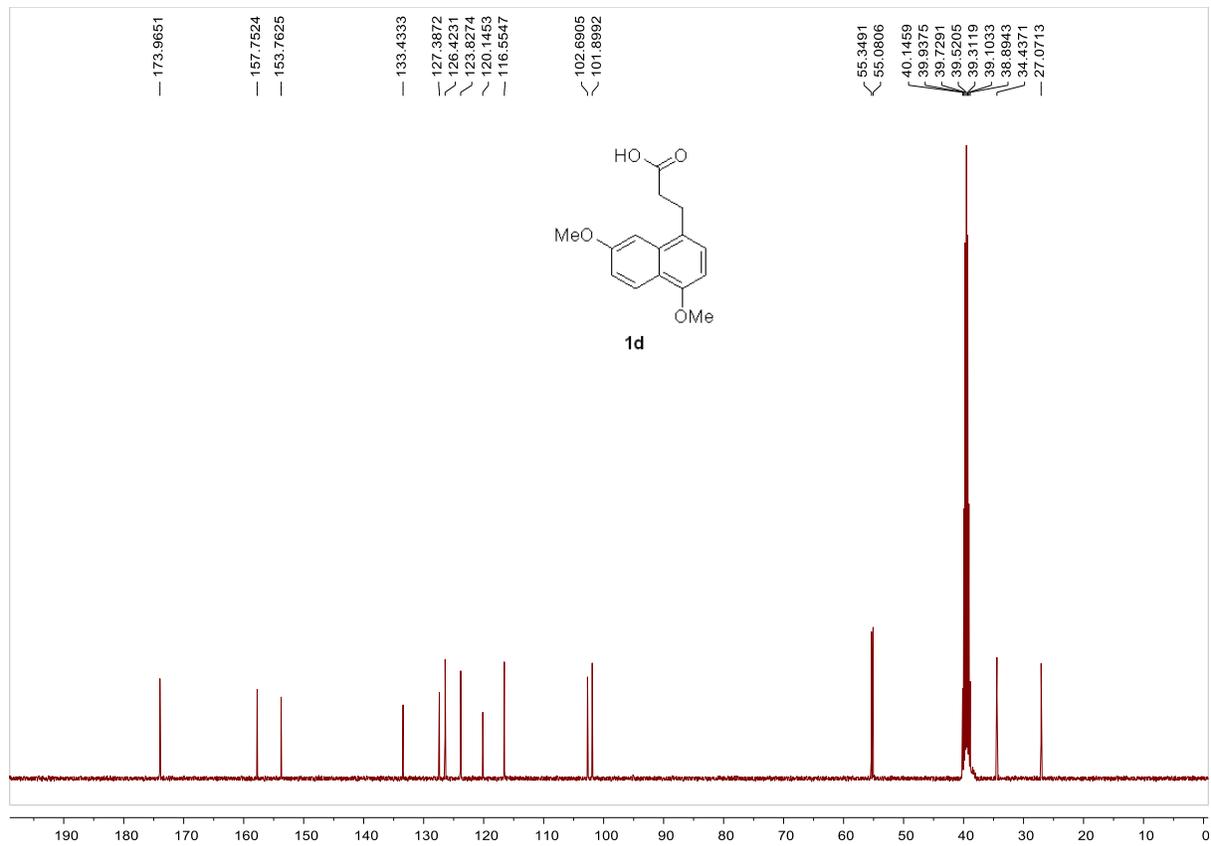
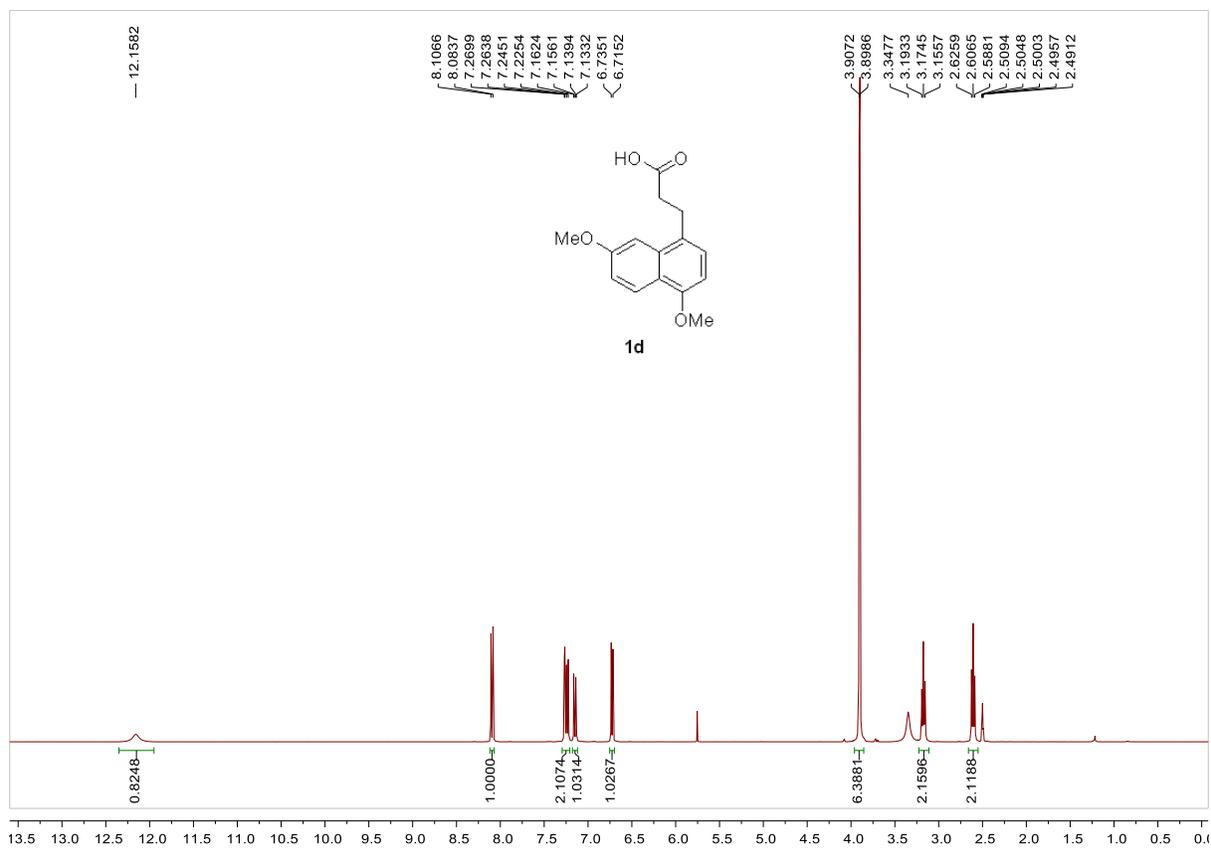
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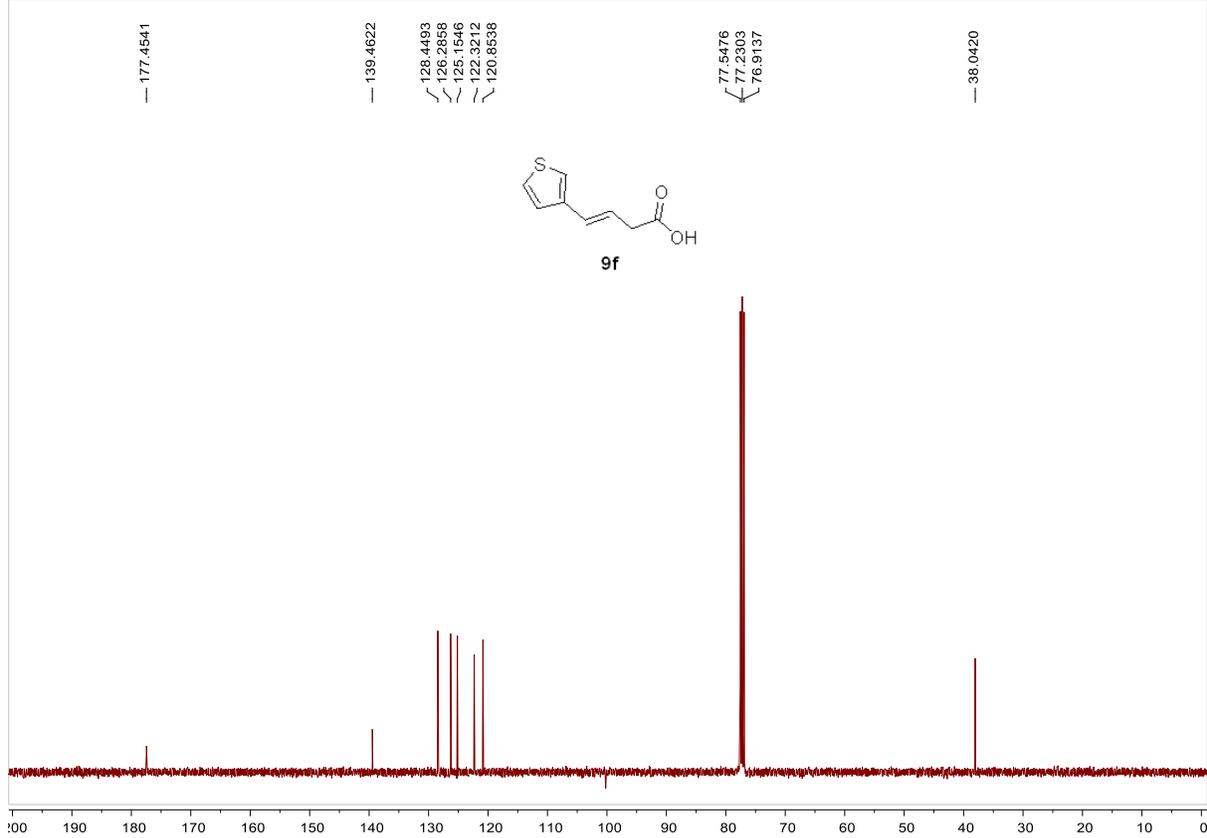
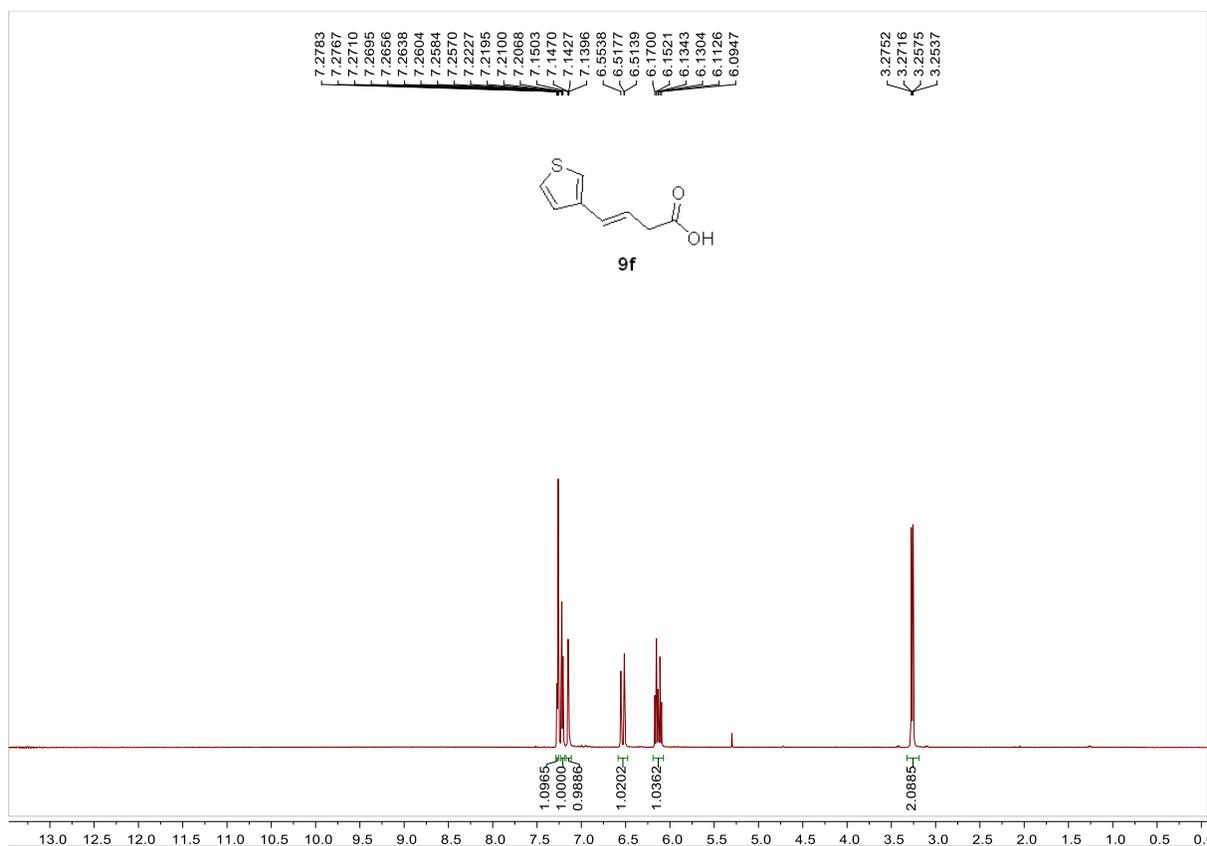
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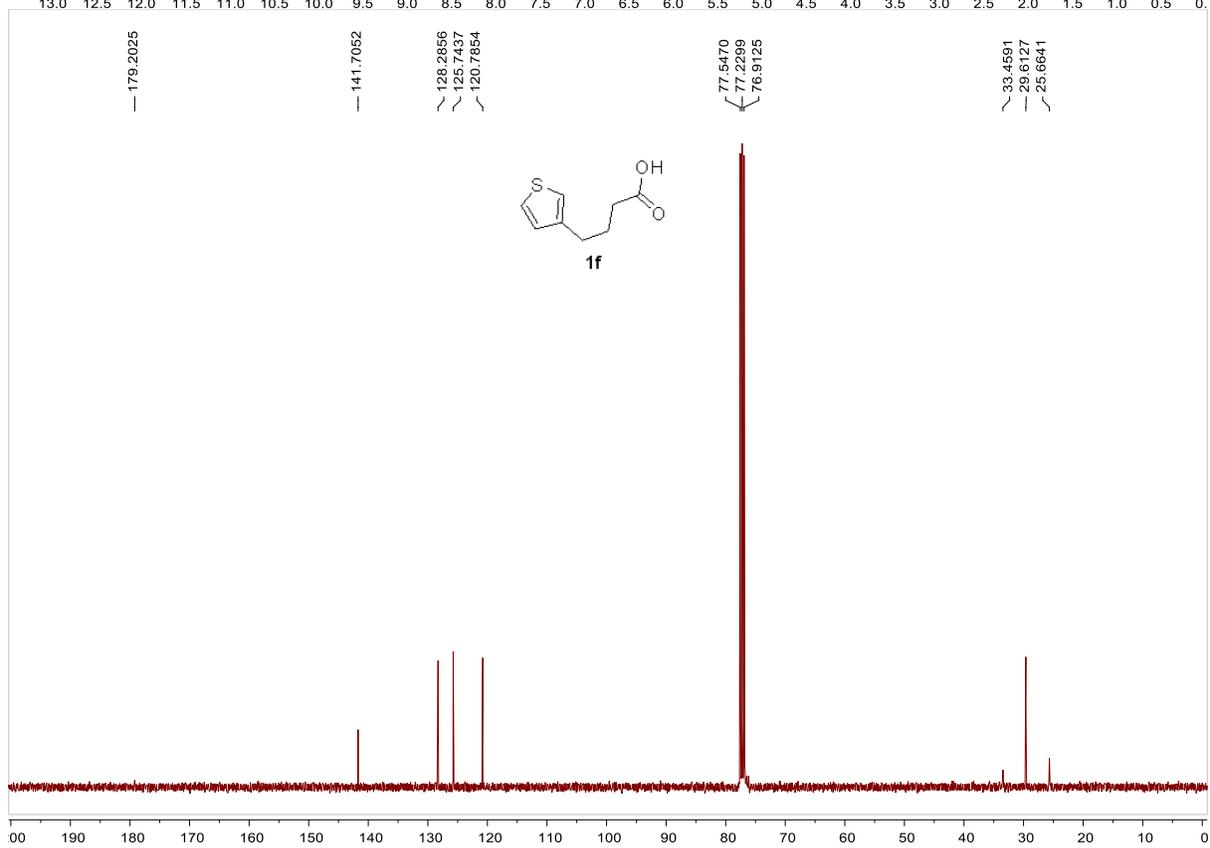
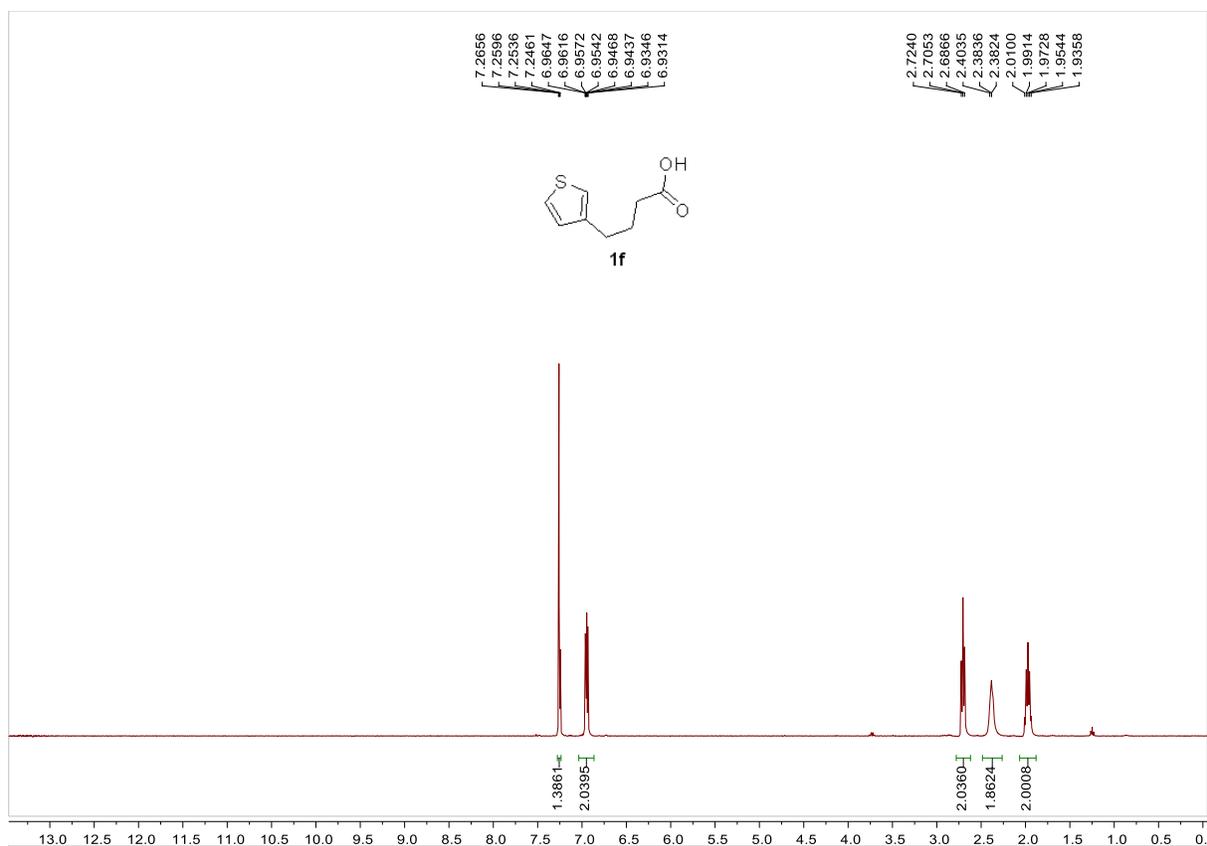
## **$^1\text{H}$ and $^{13}\text{C}$ Spectra of Acid Precursors**

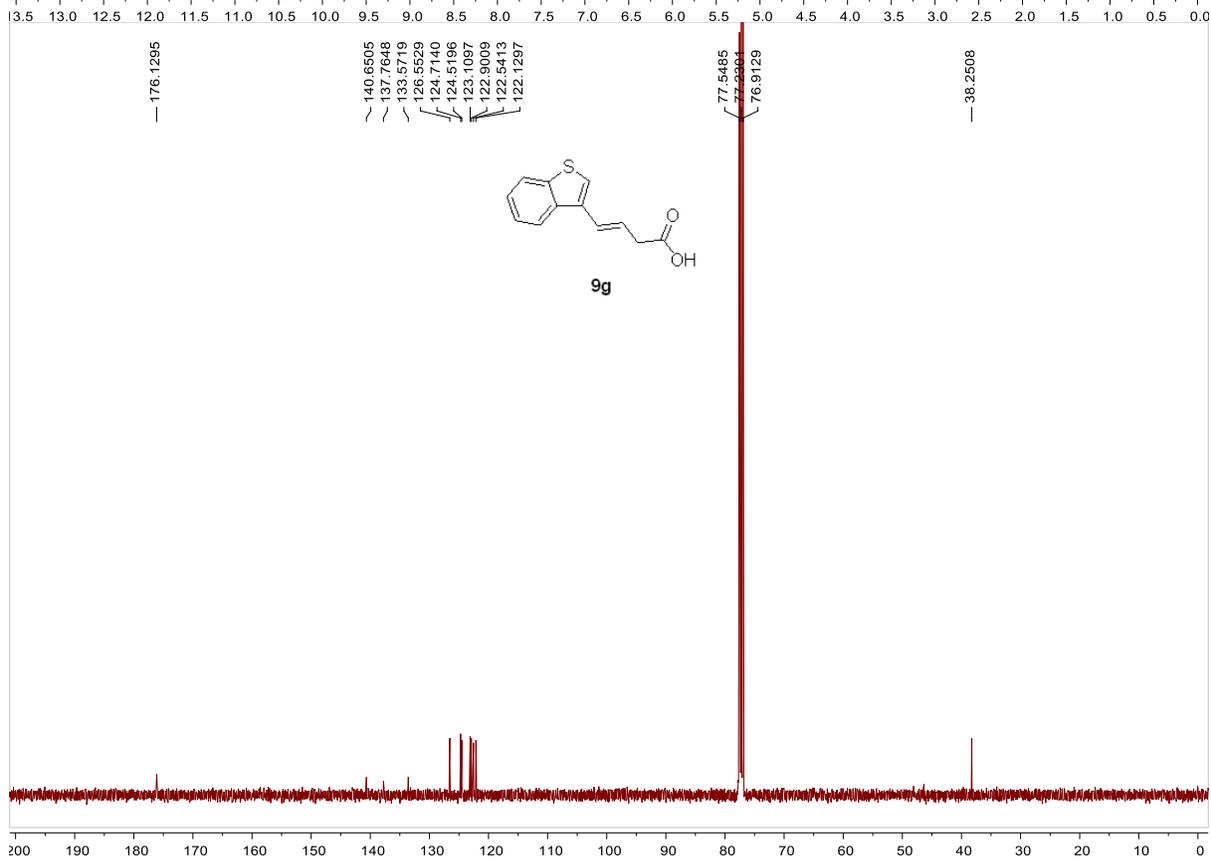
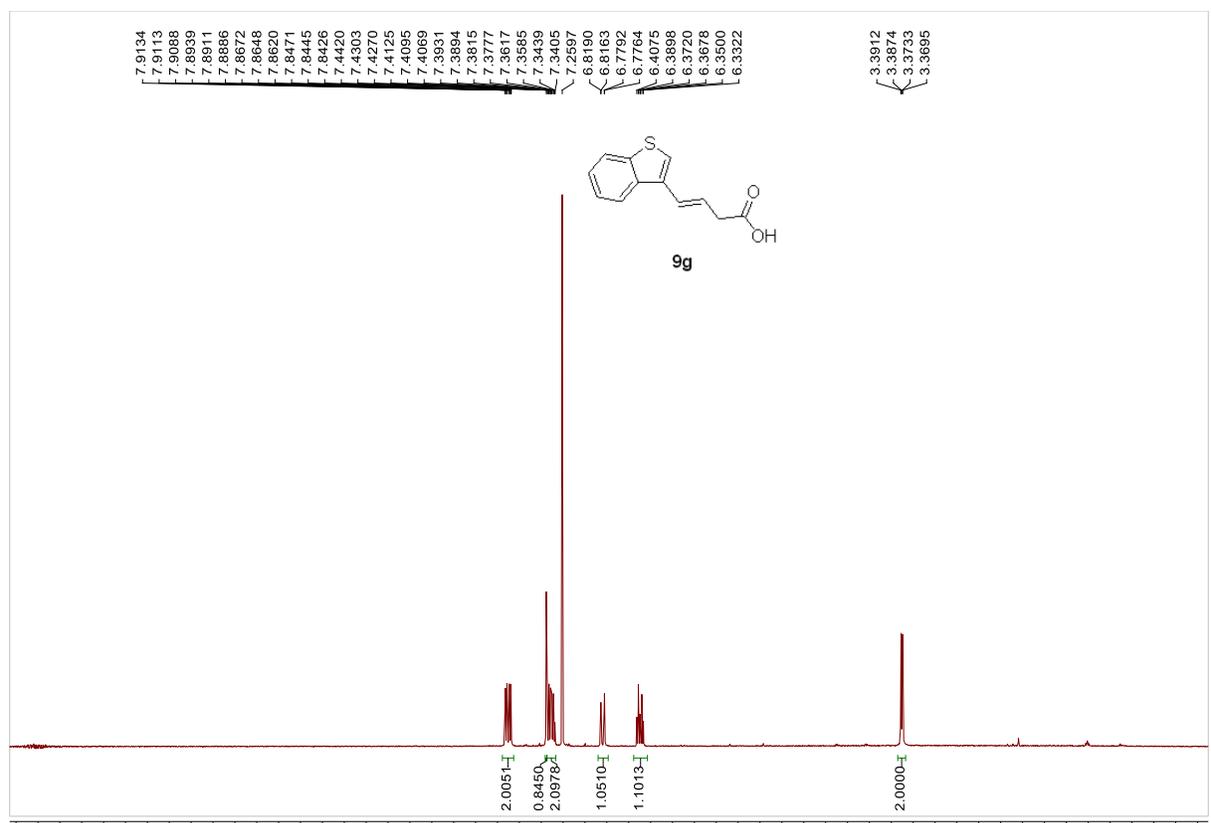


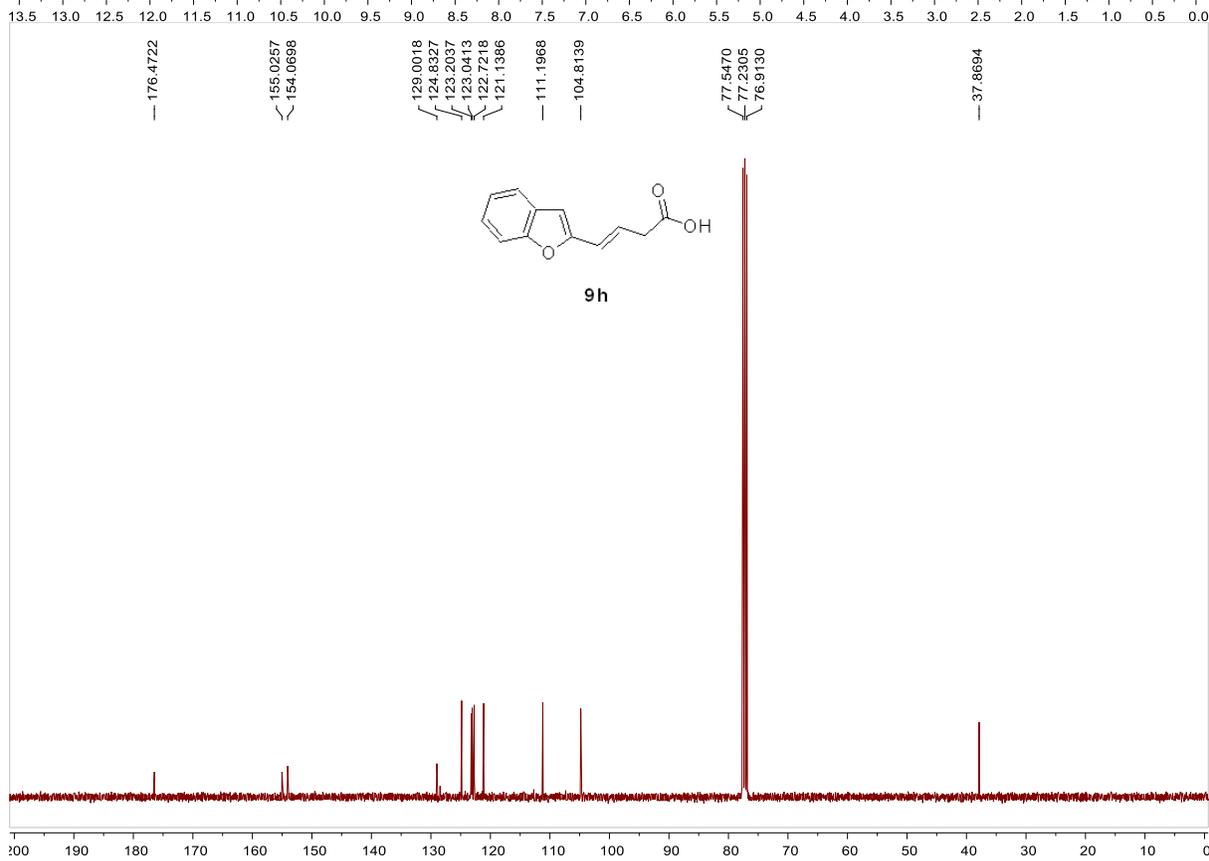
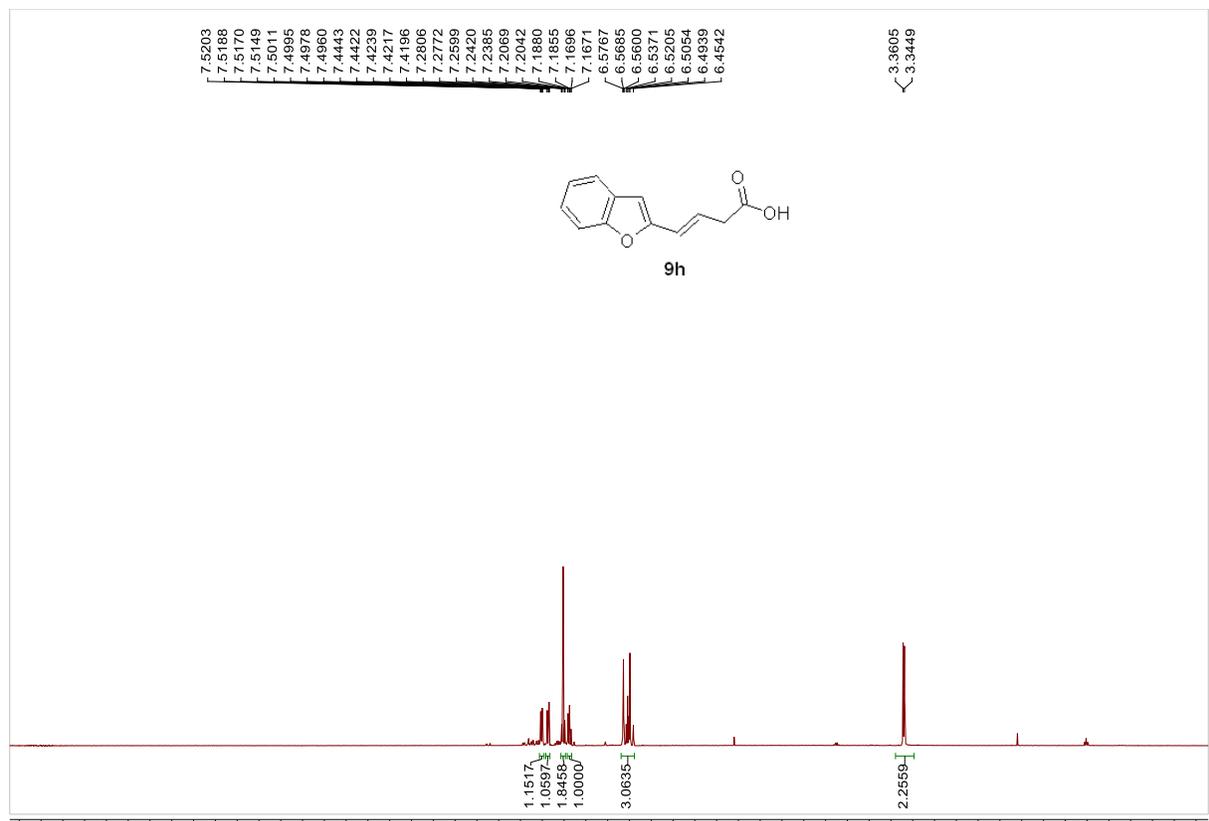


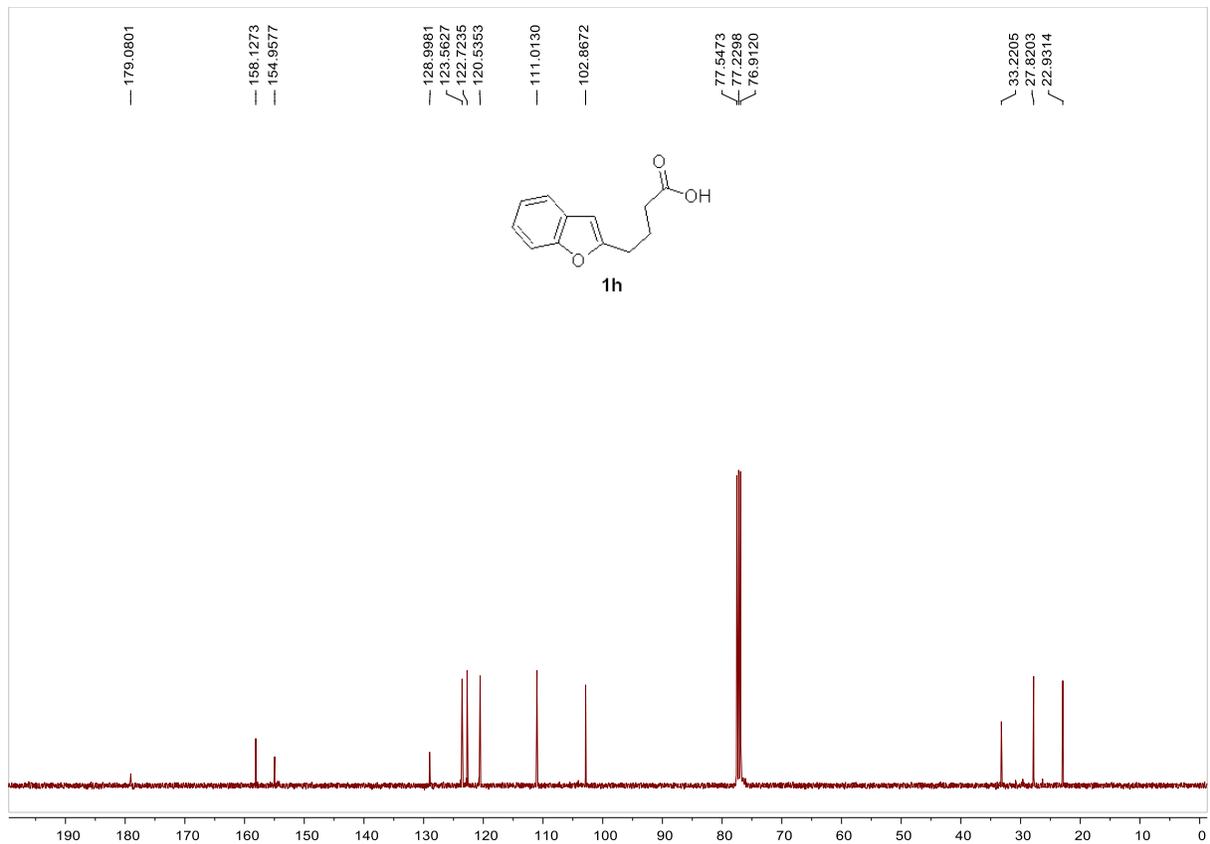
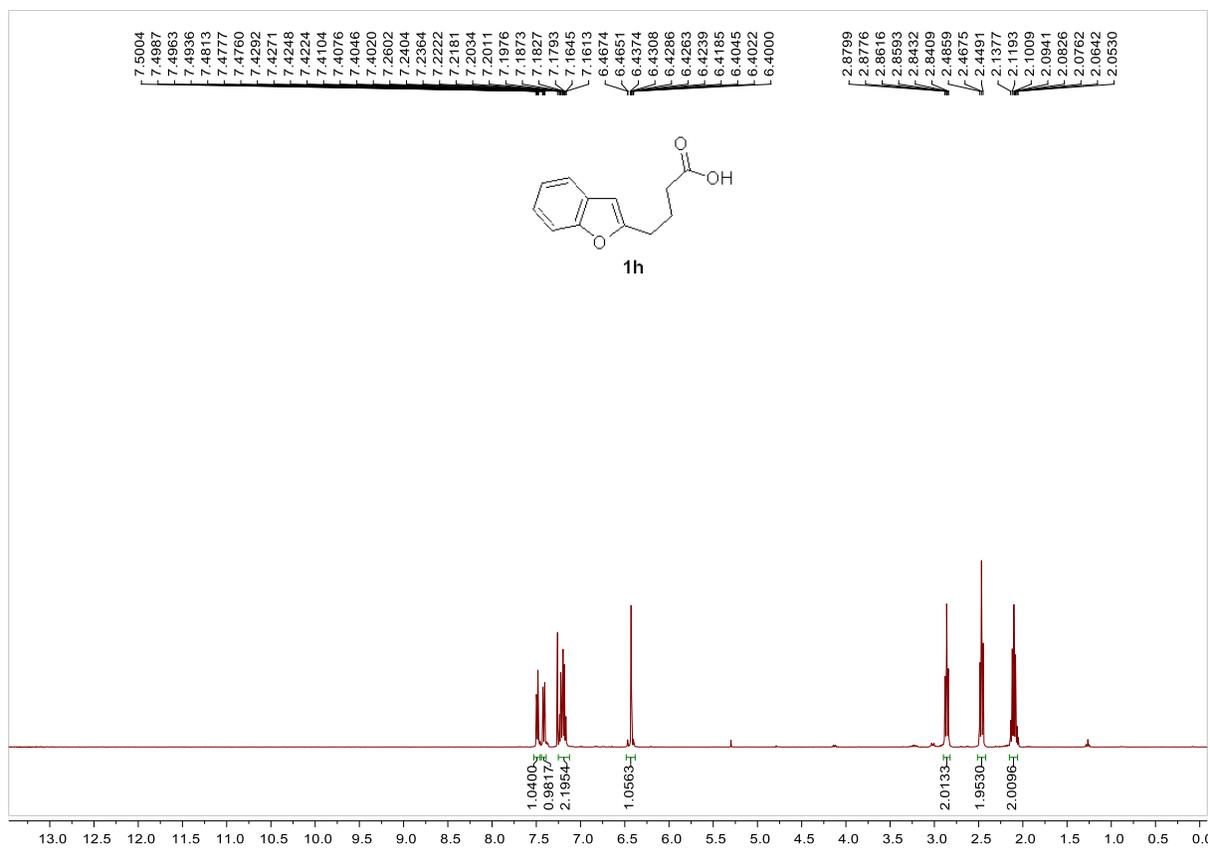


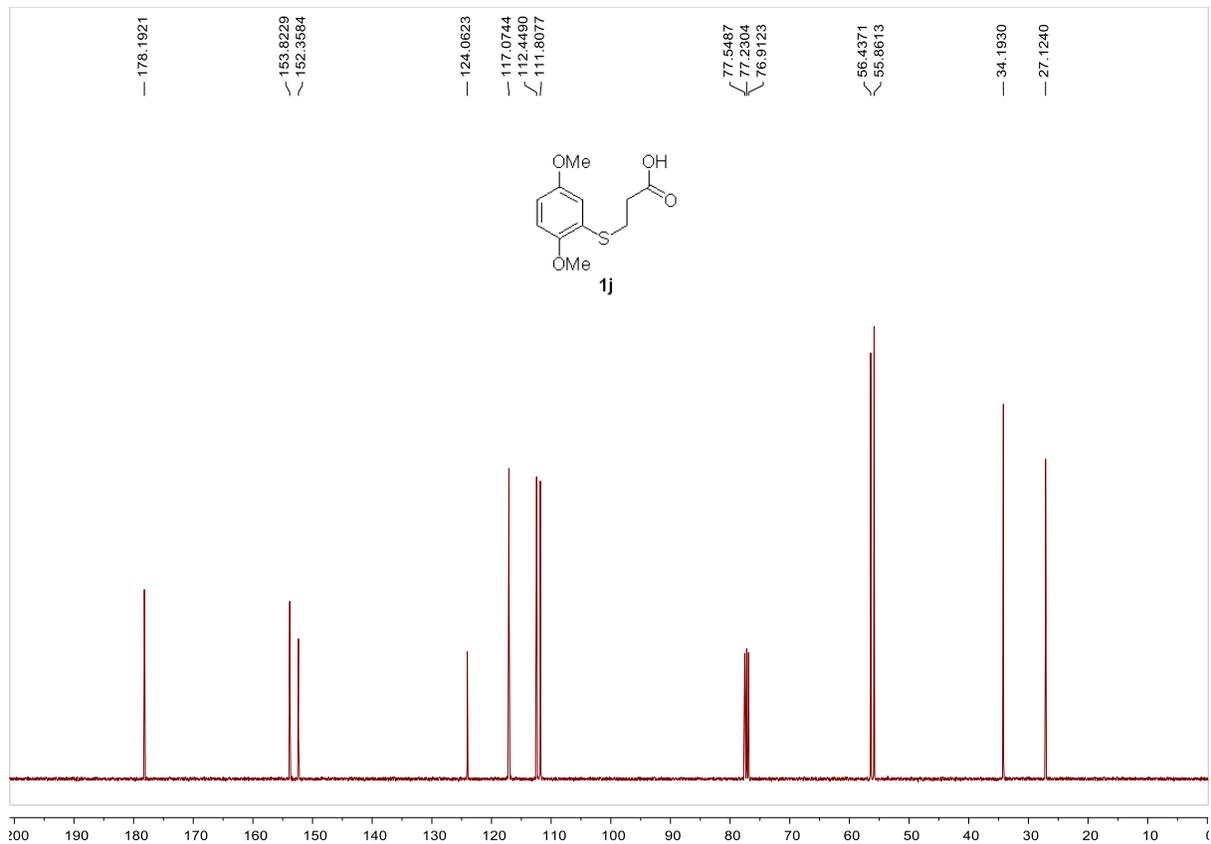
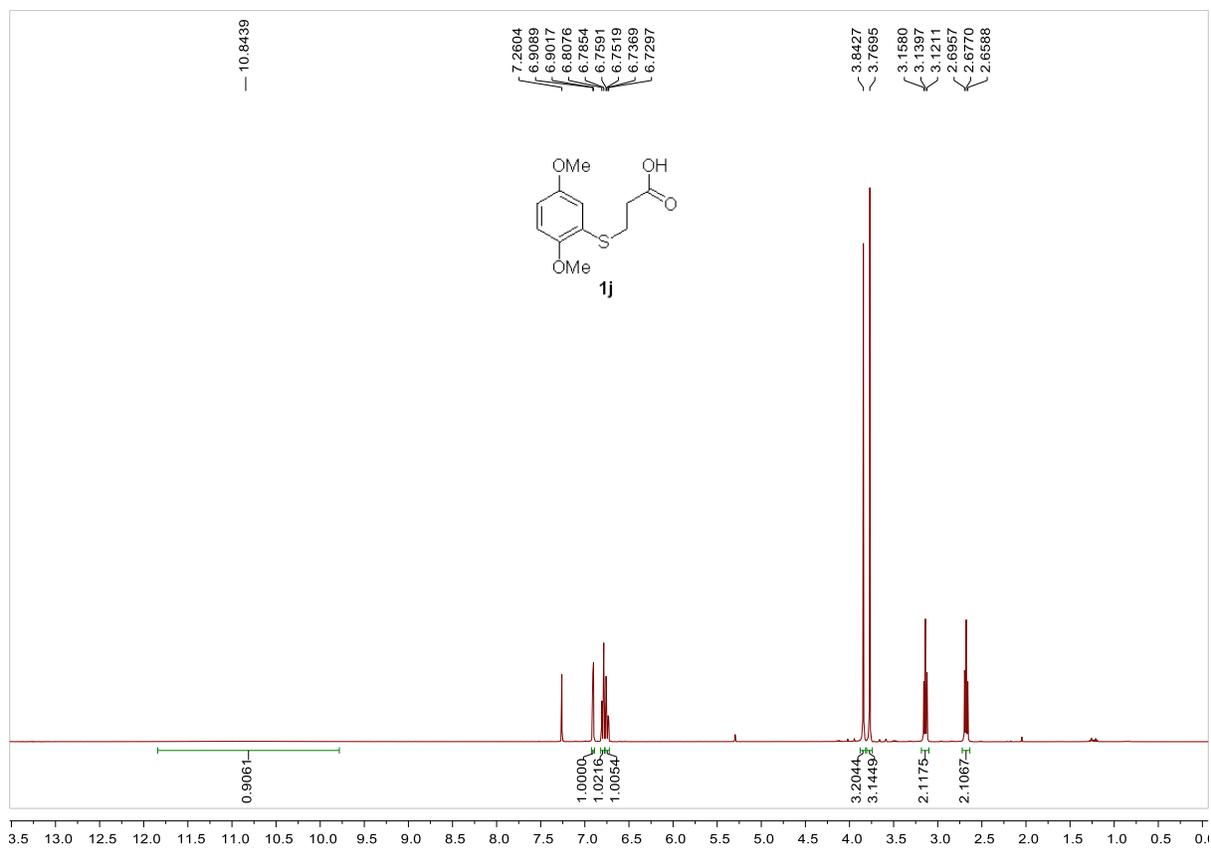


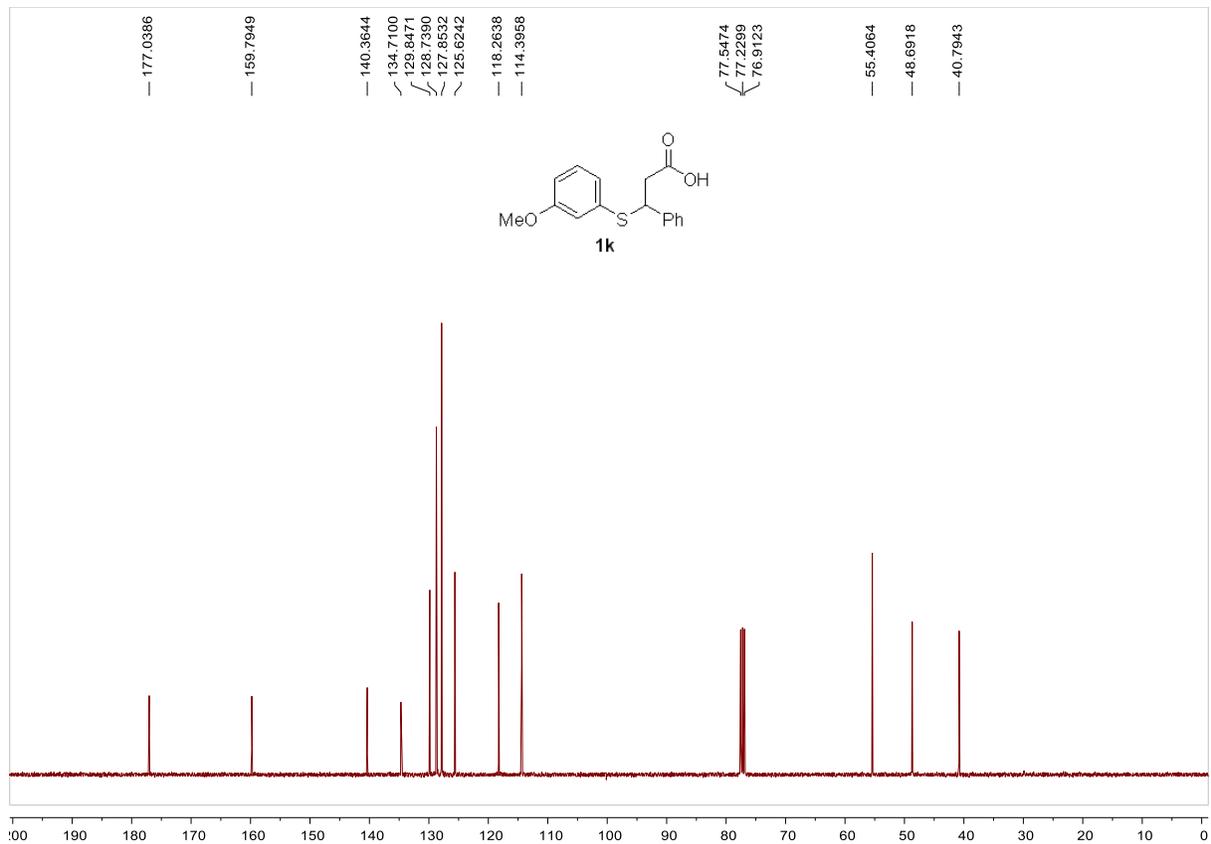
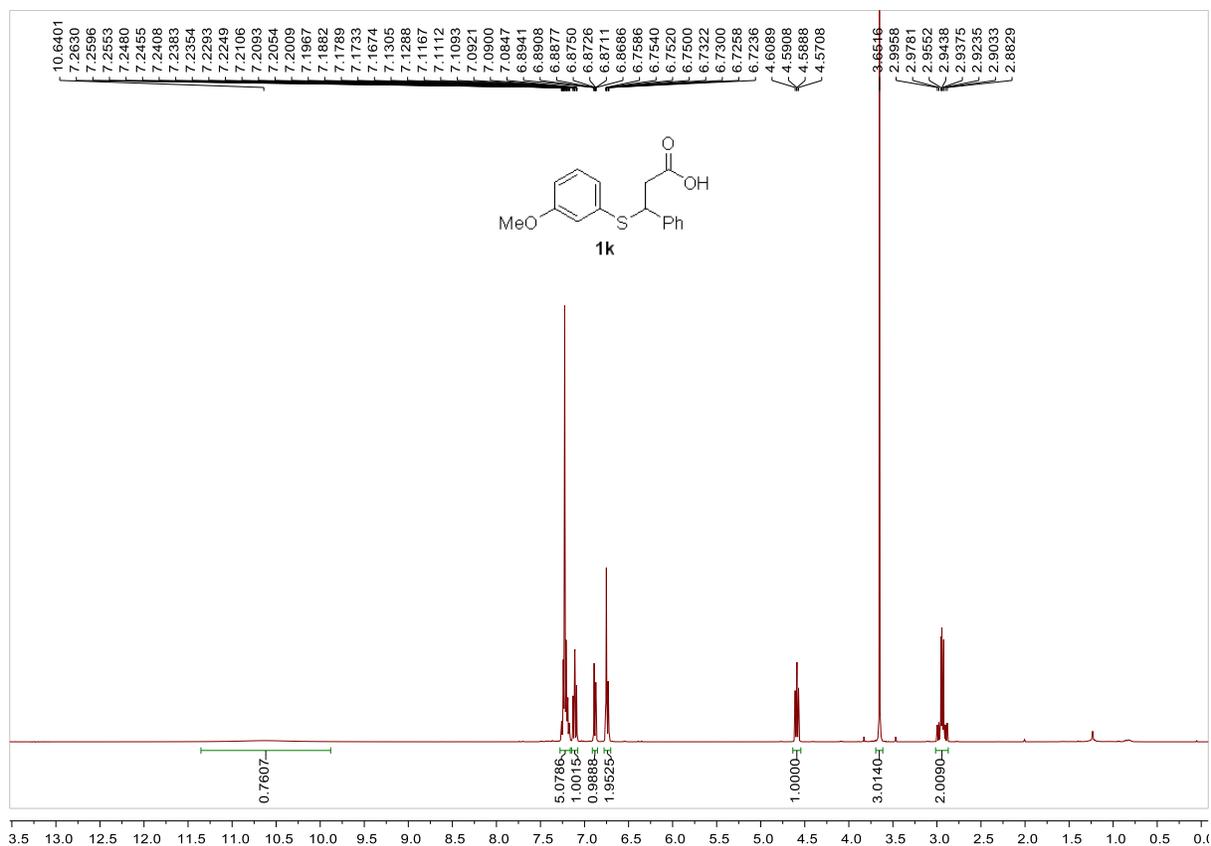


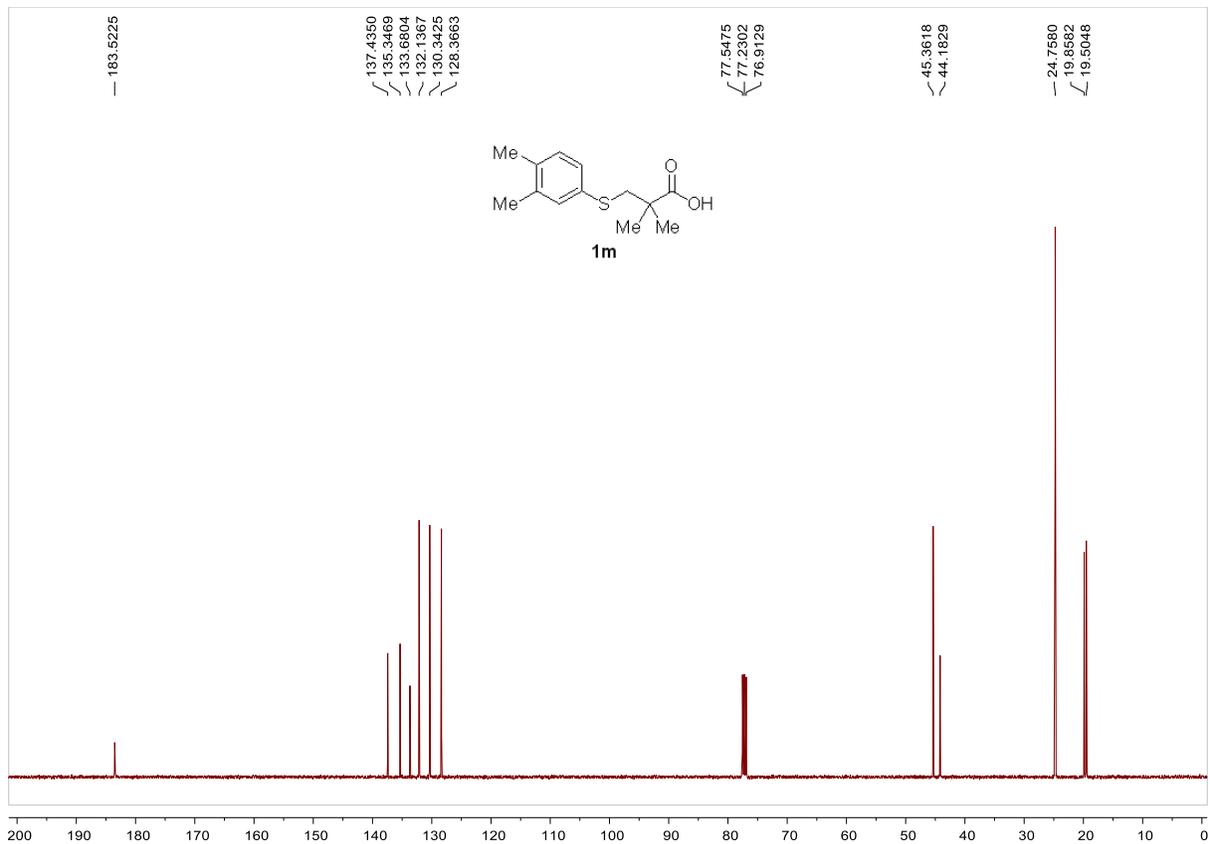
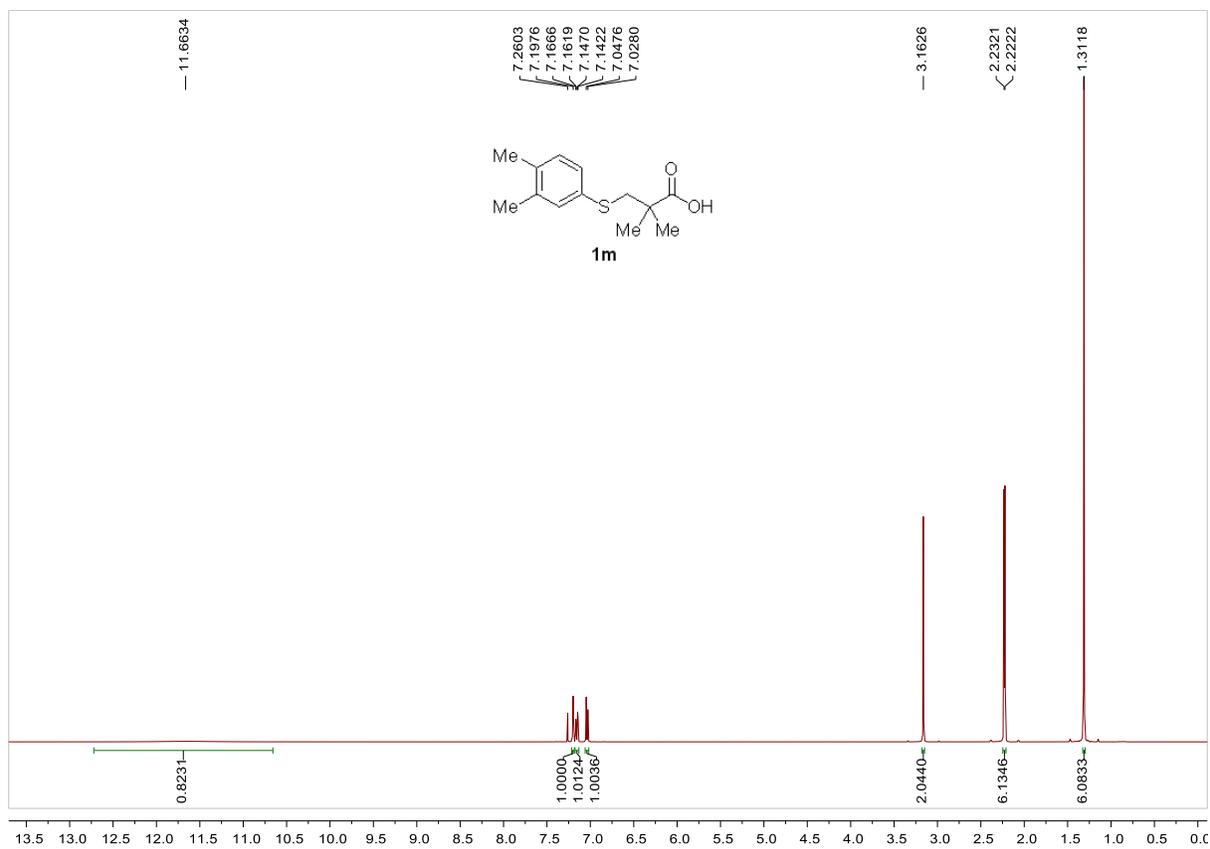


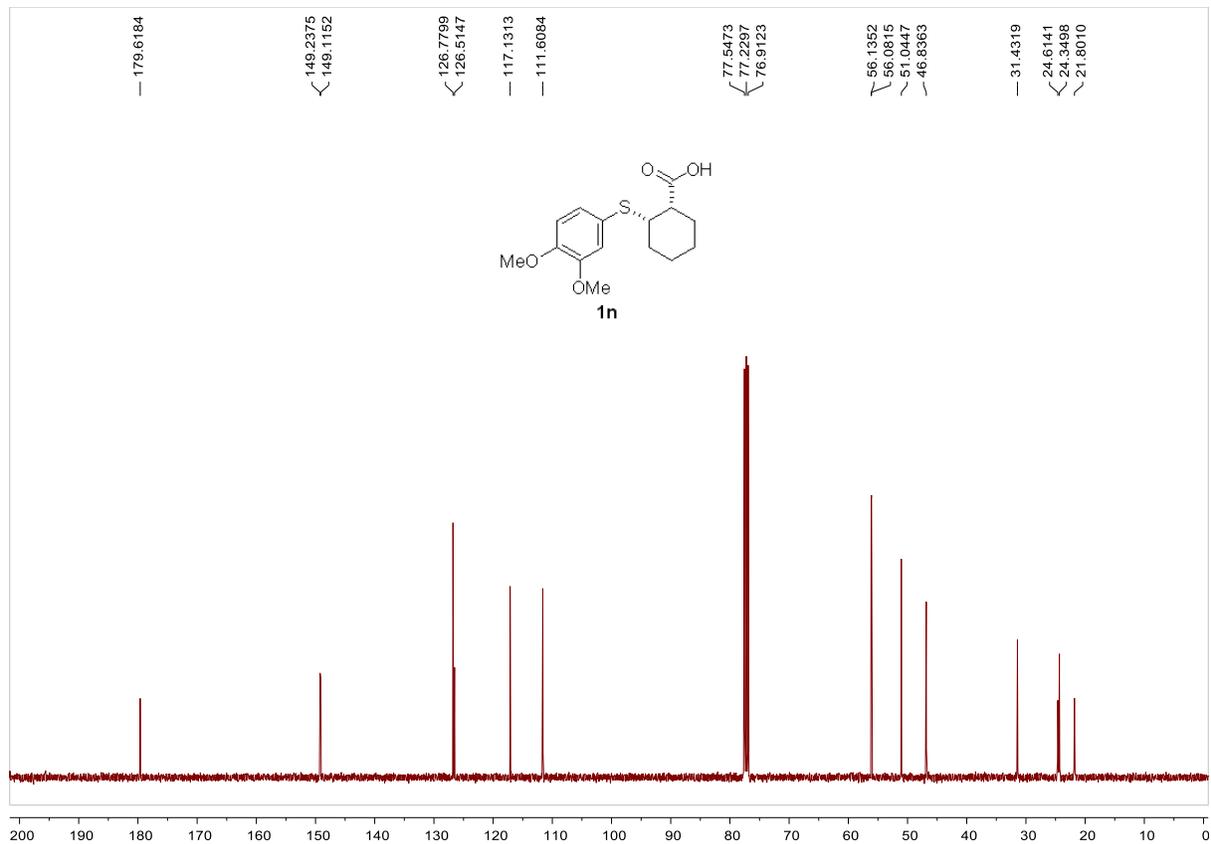
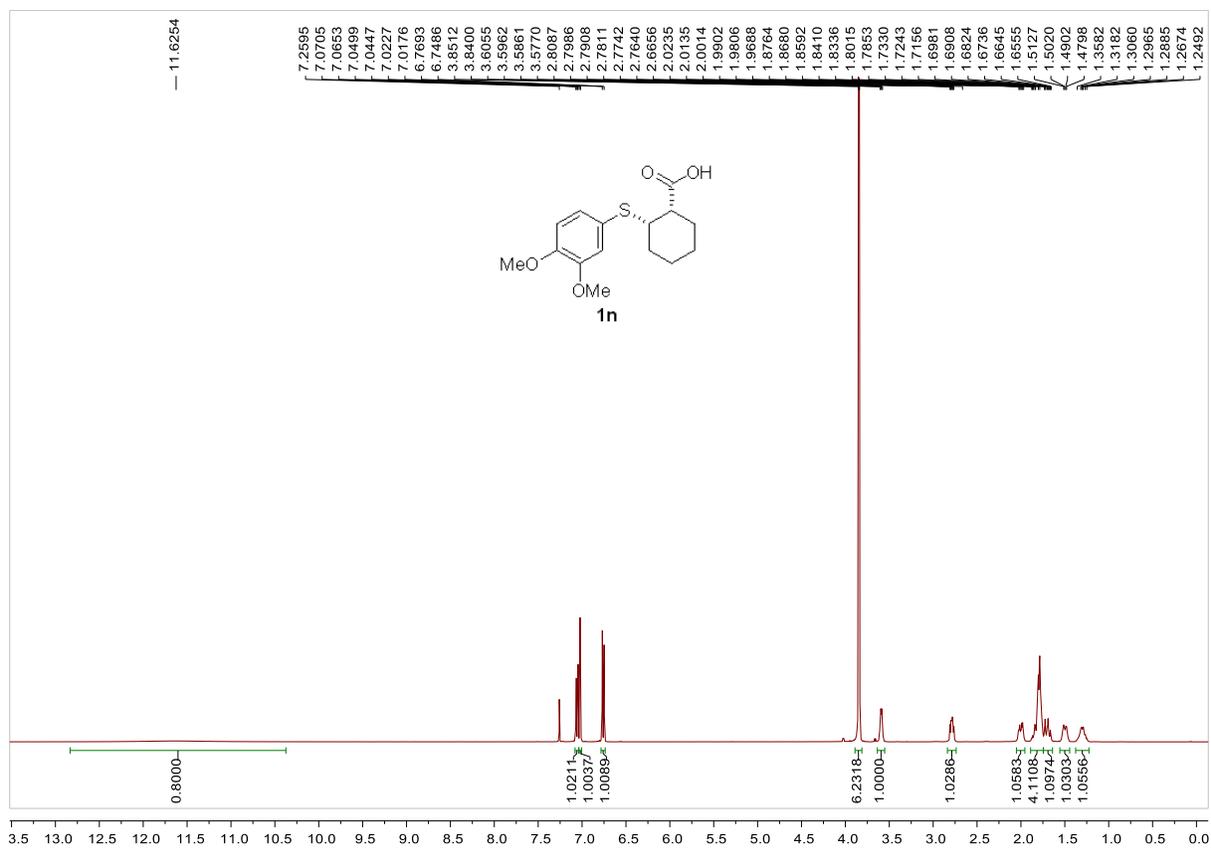


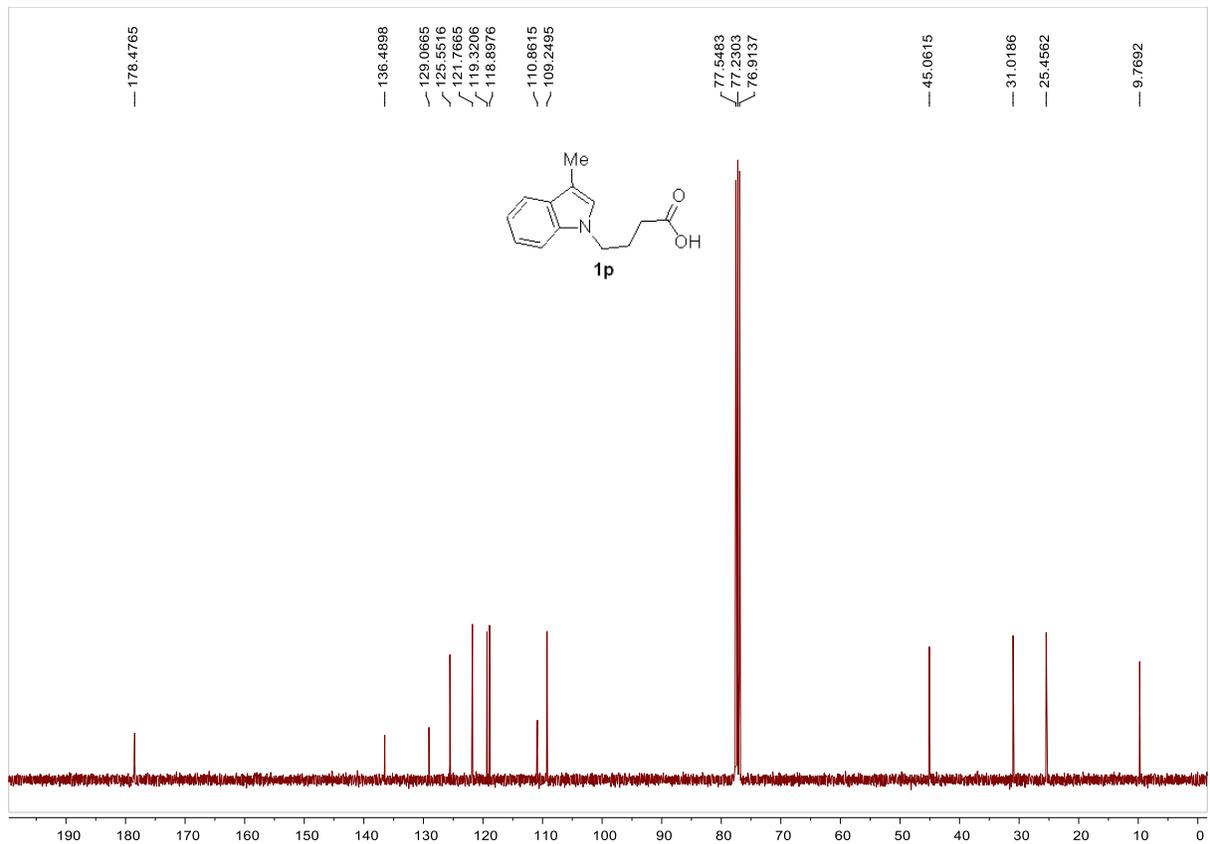
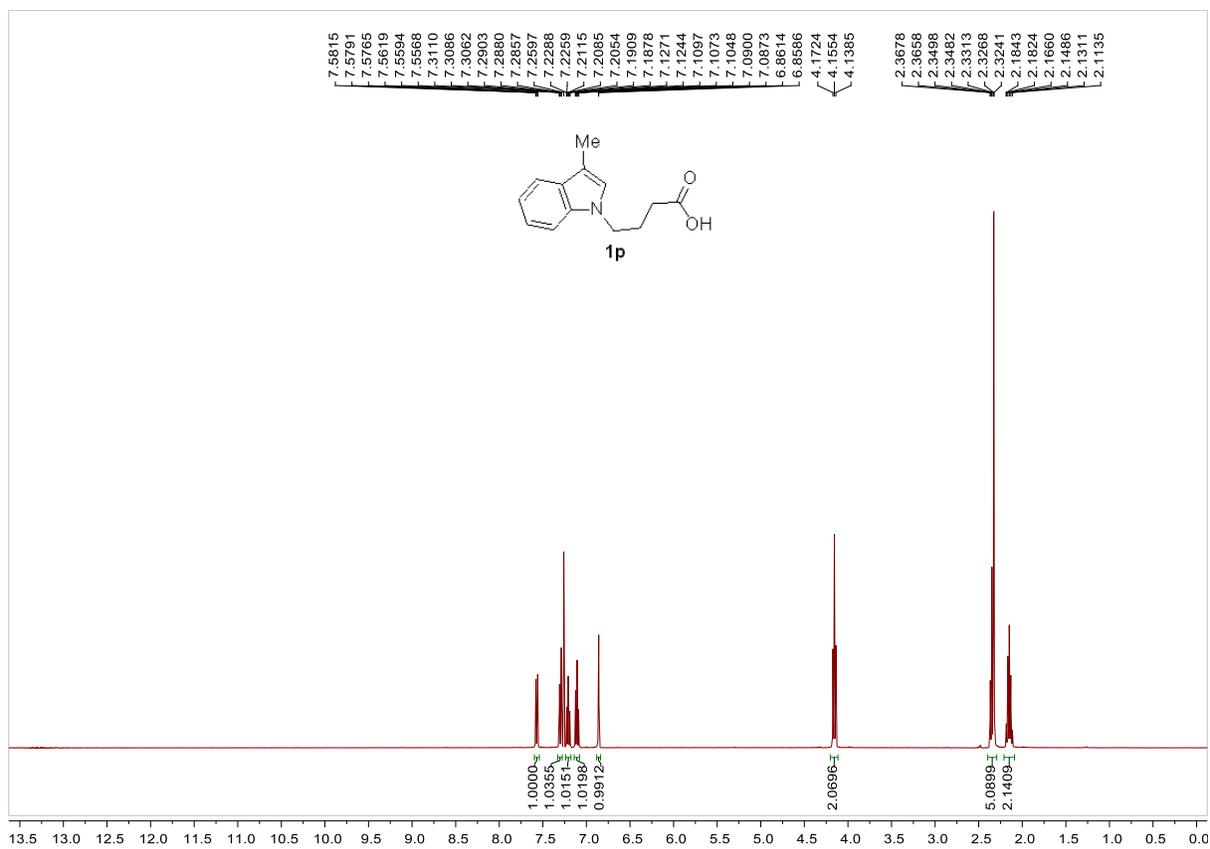


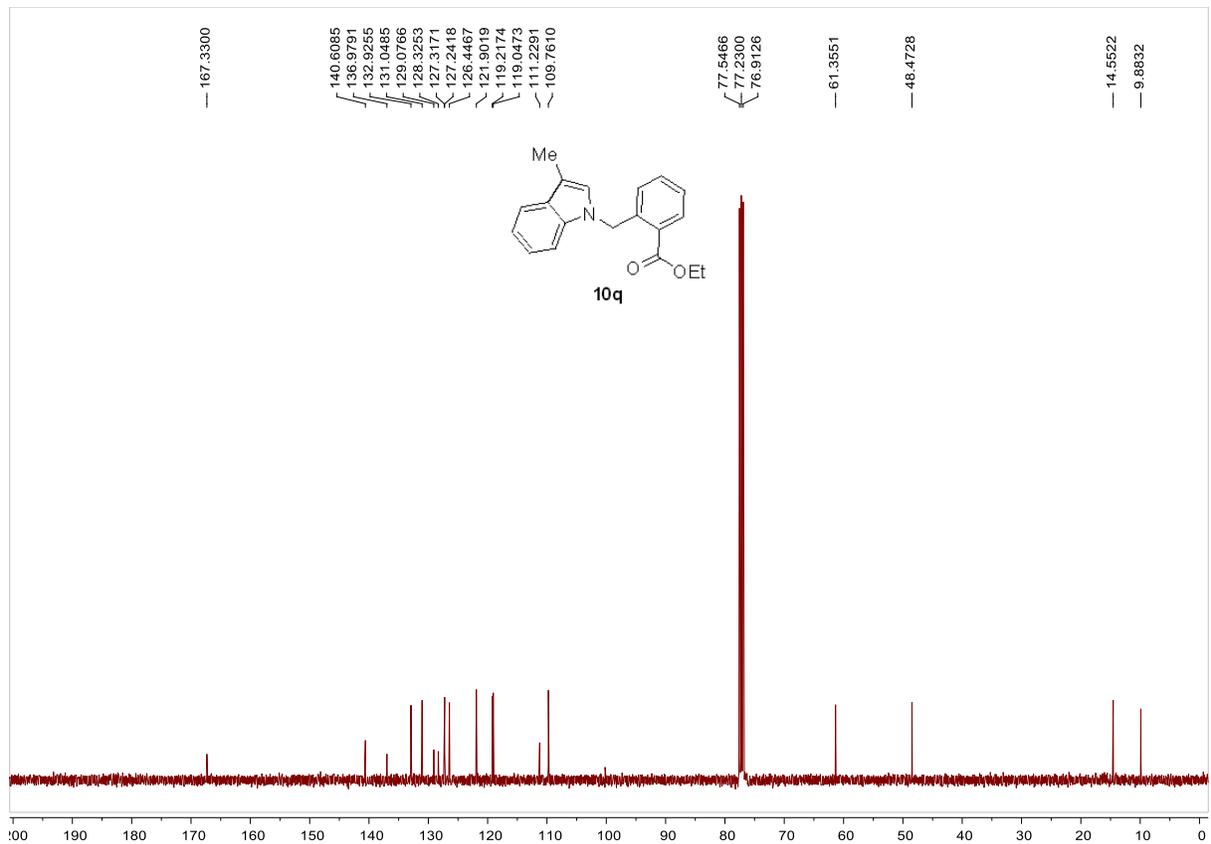
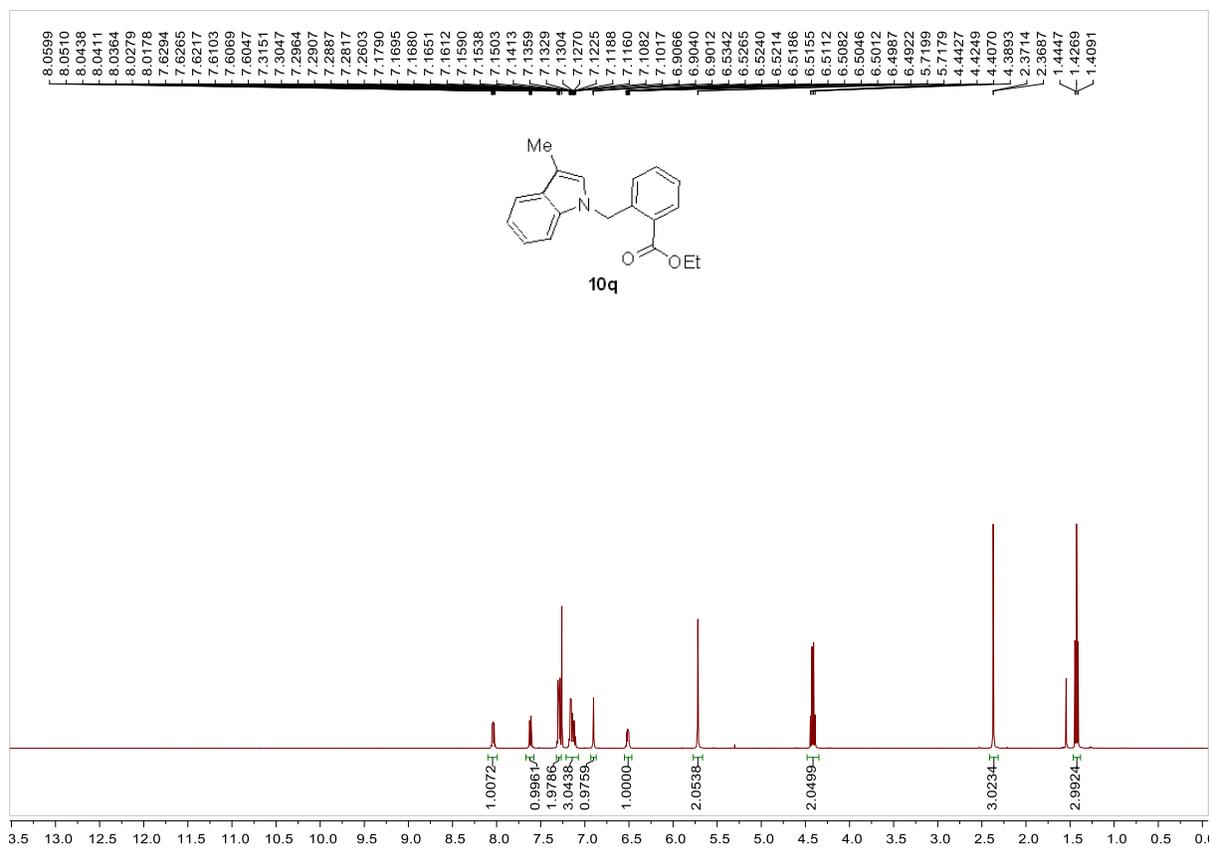


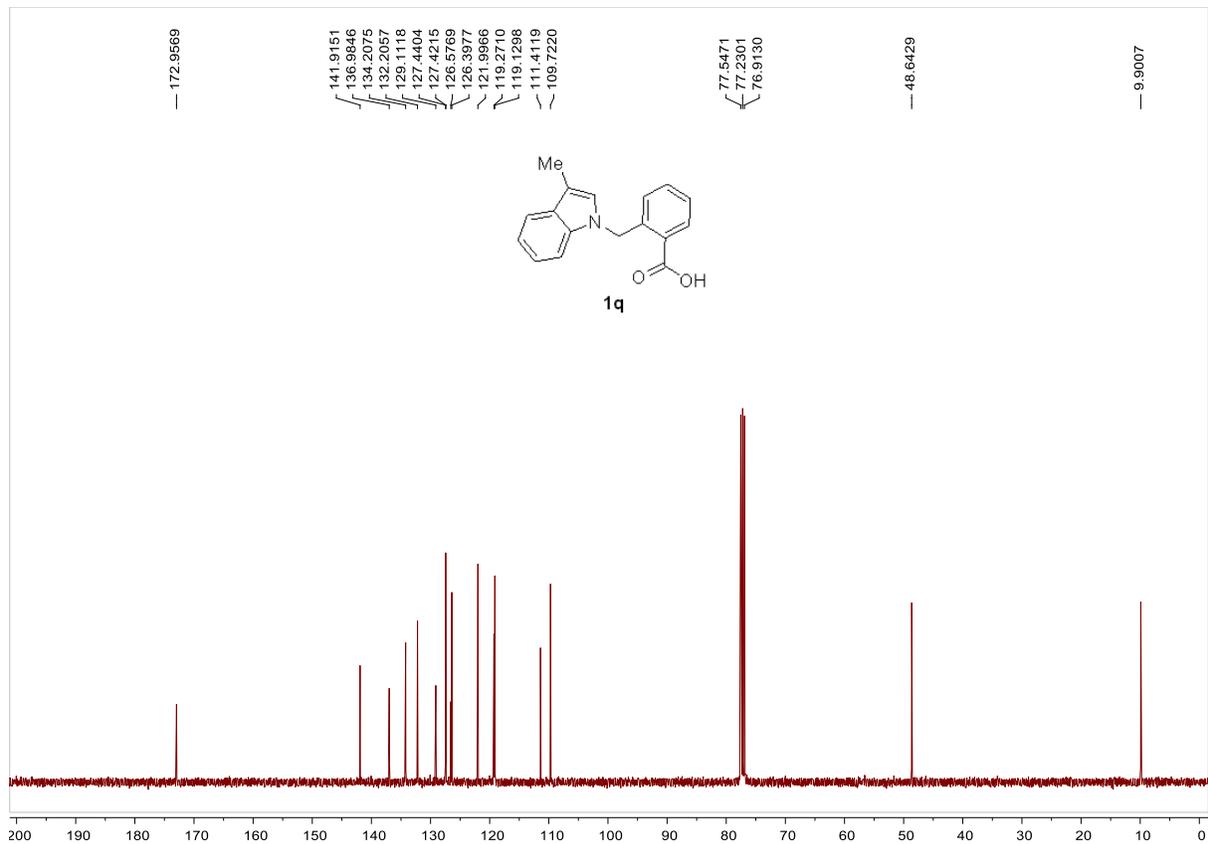
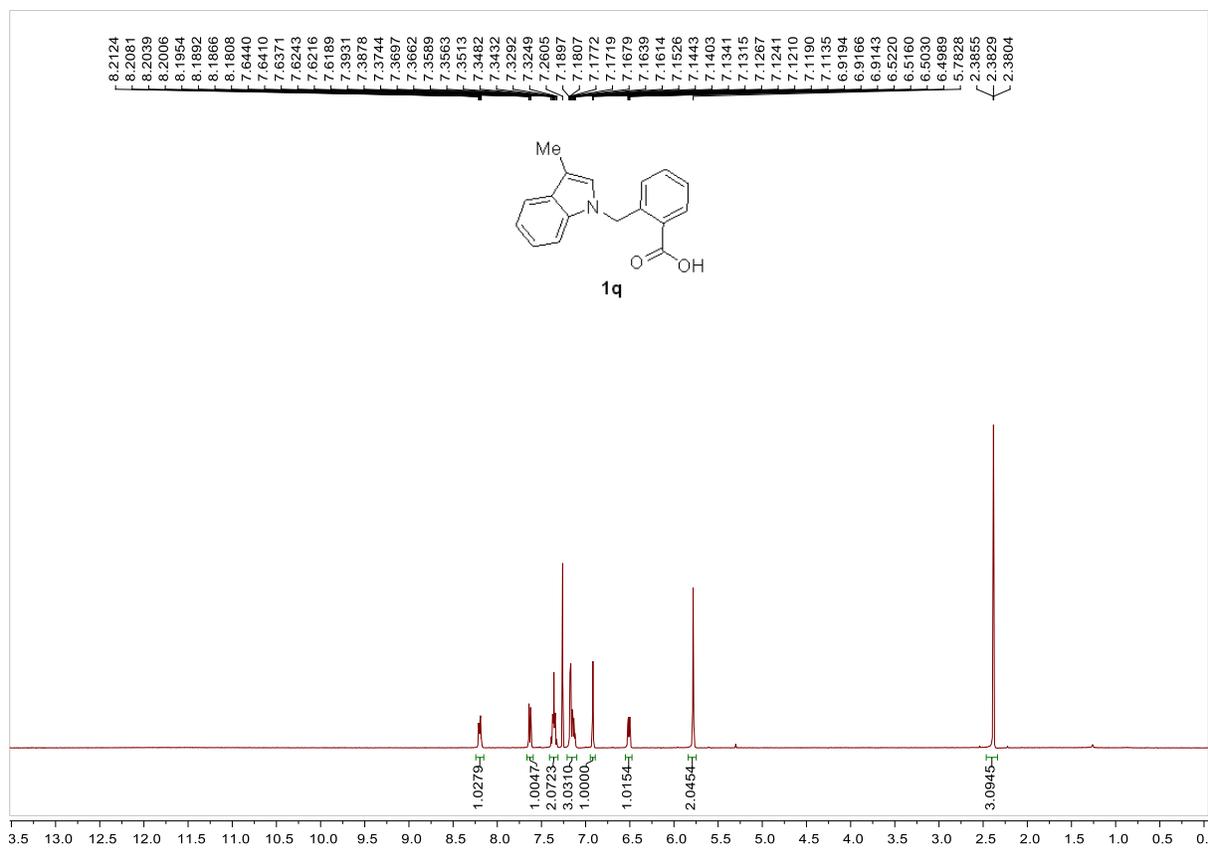


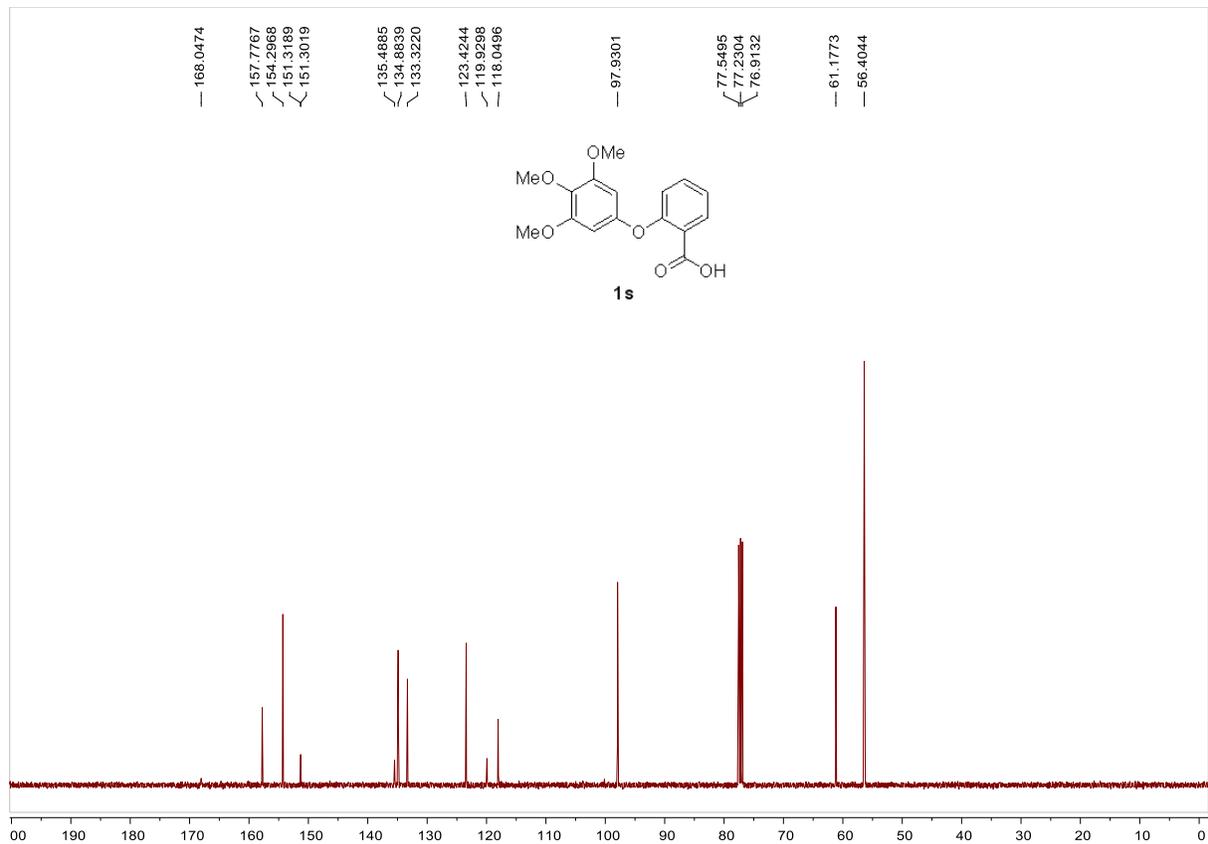
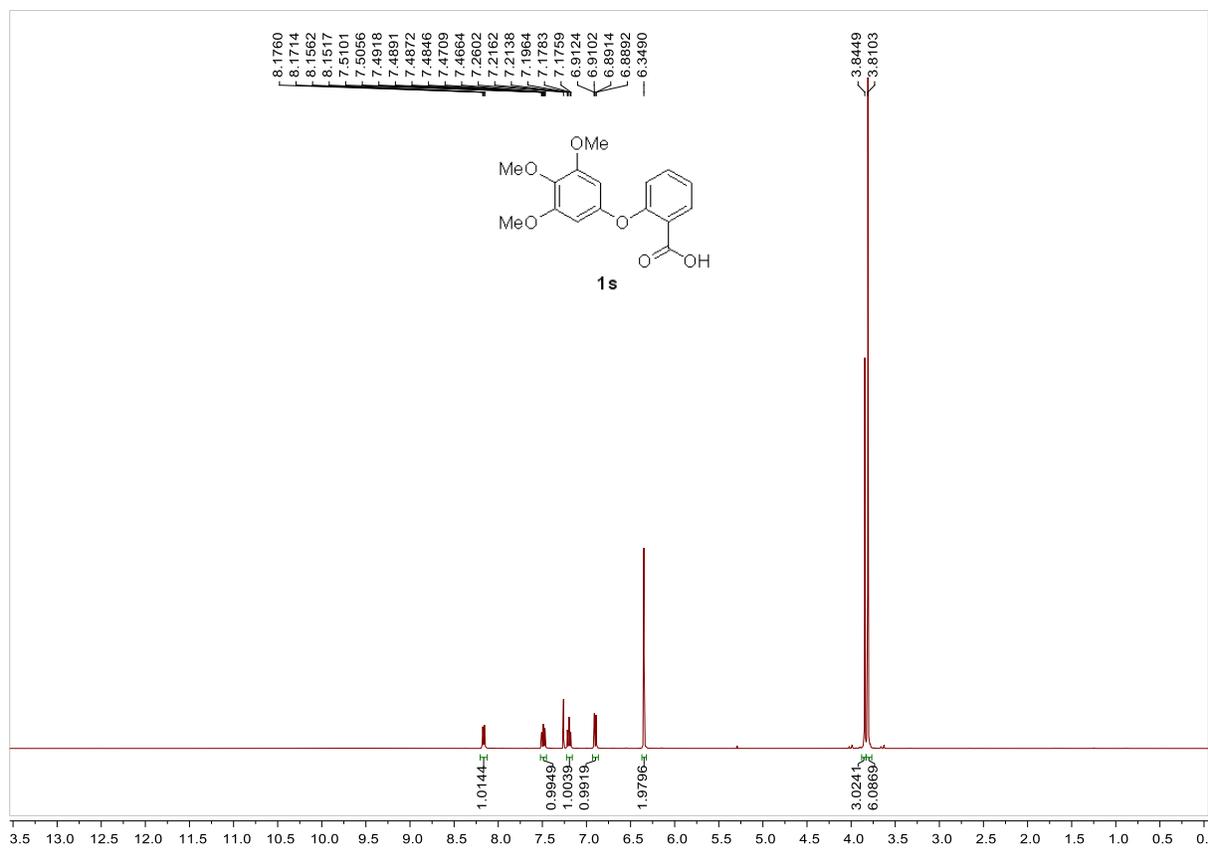


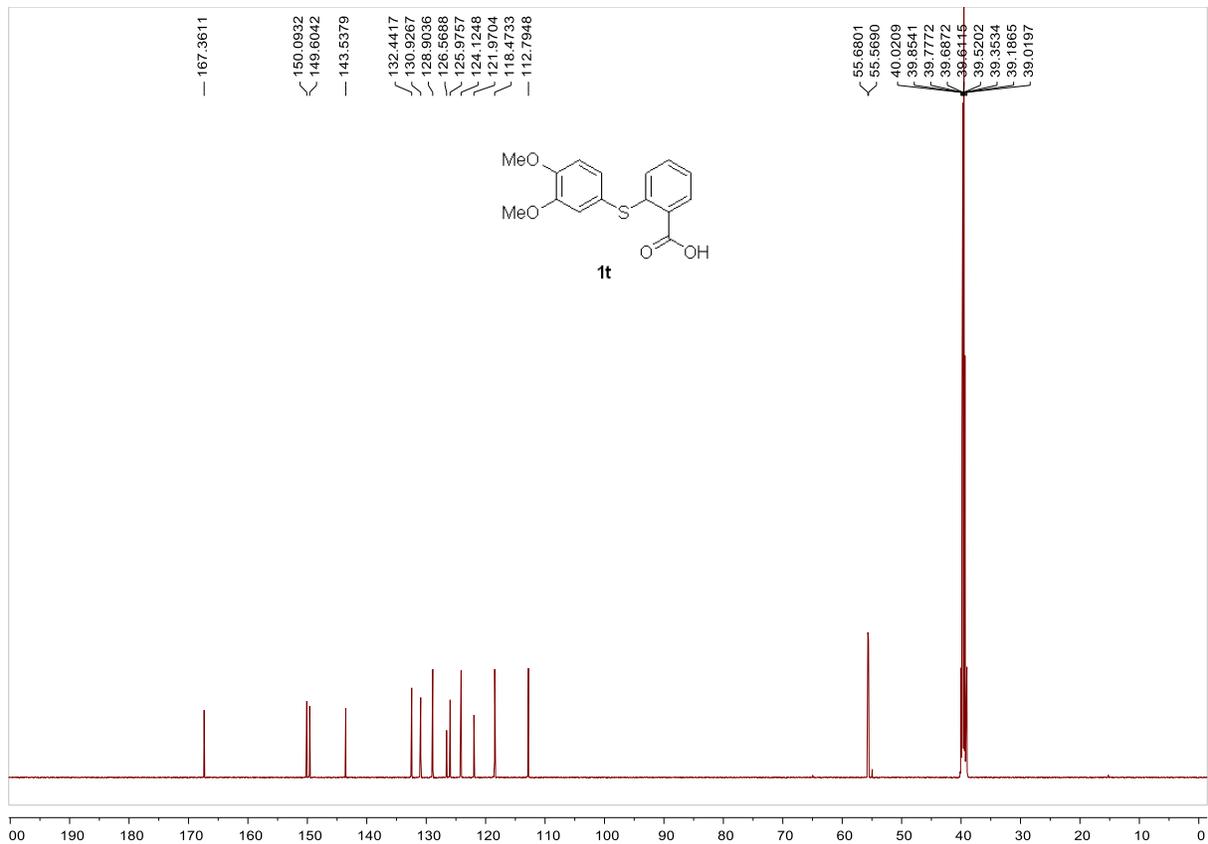
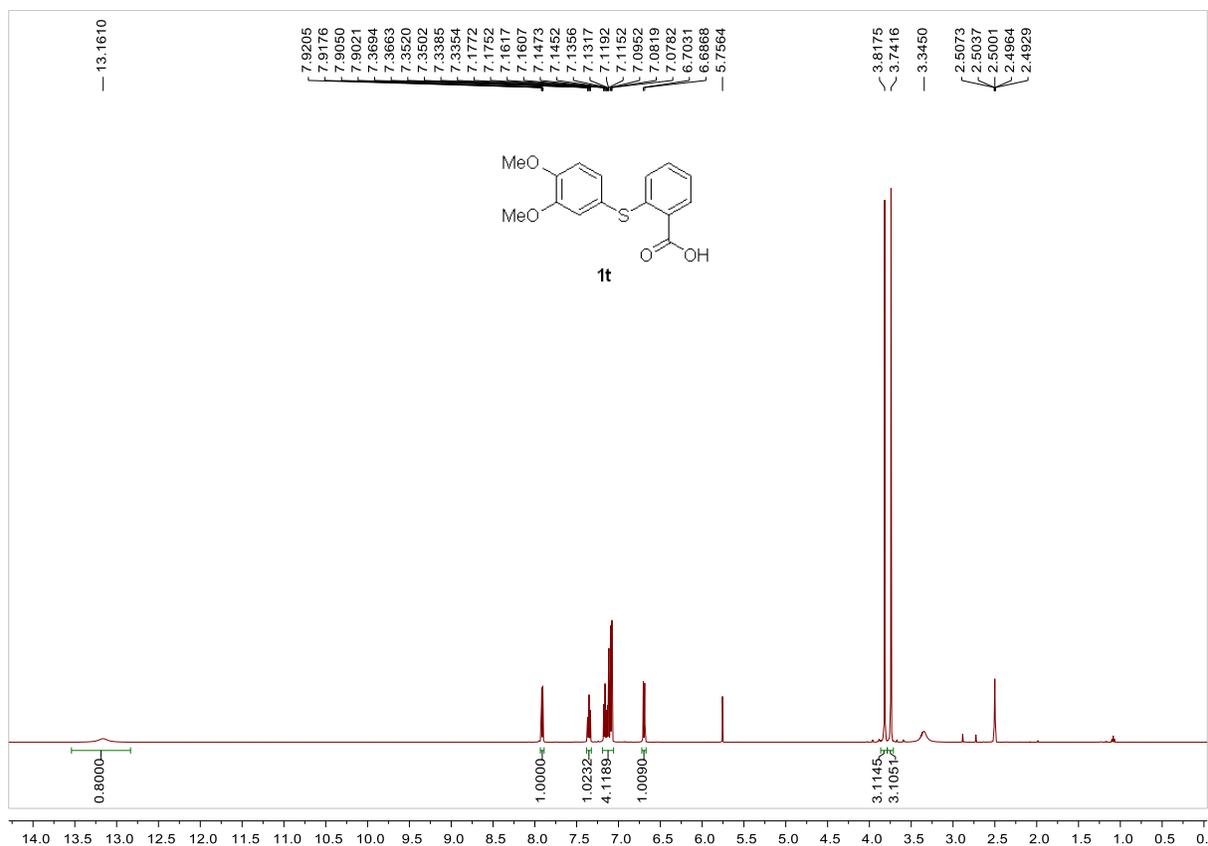


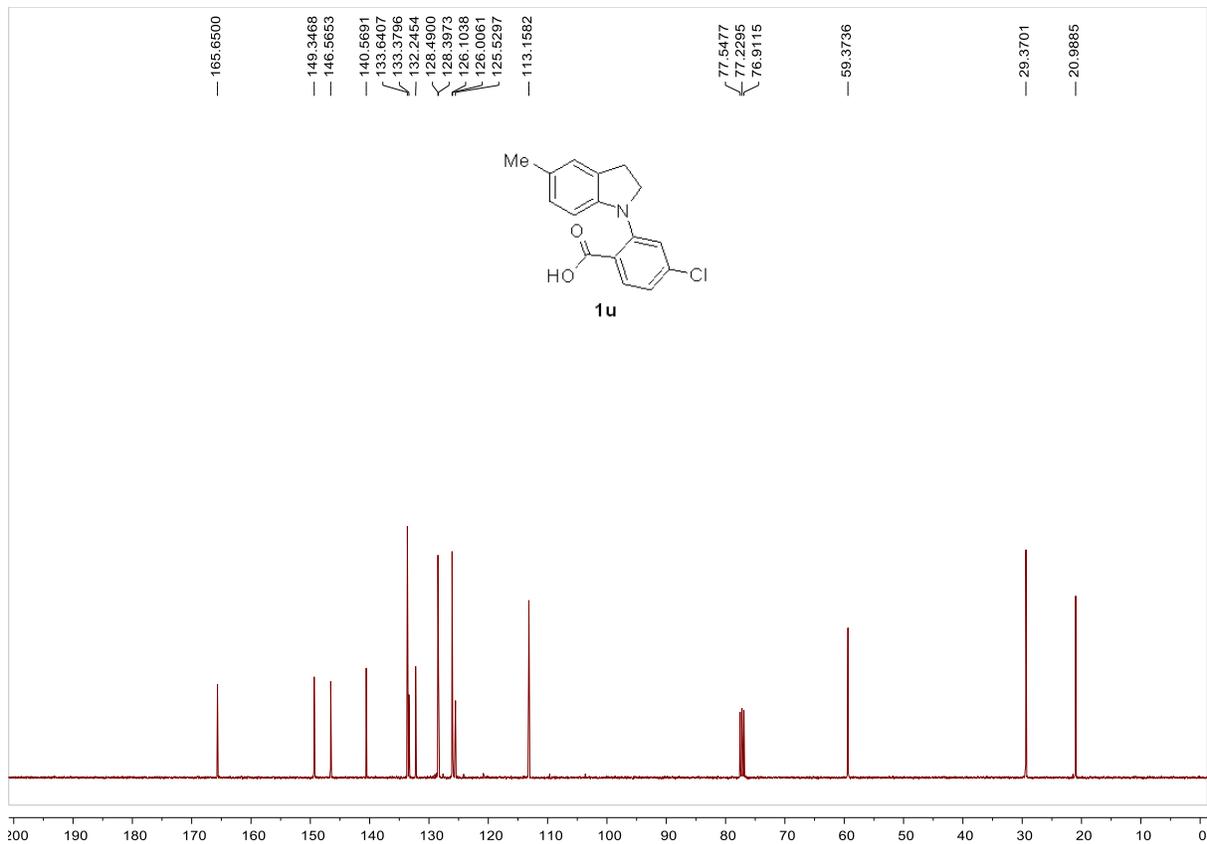
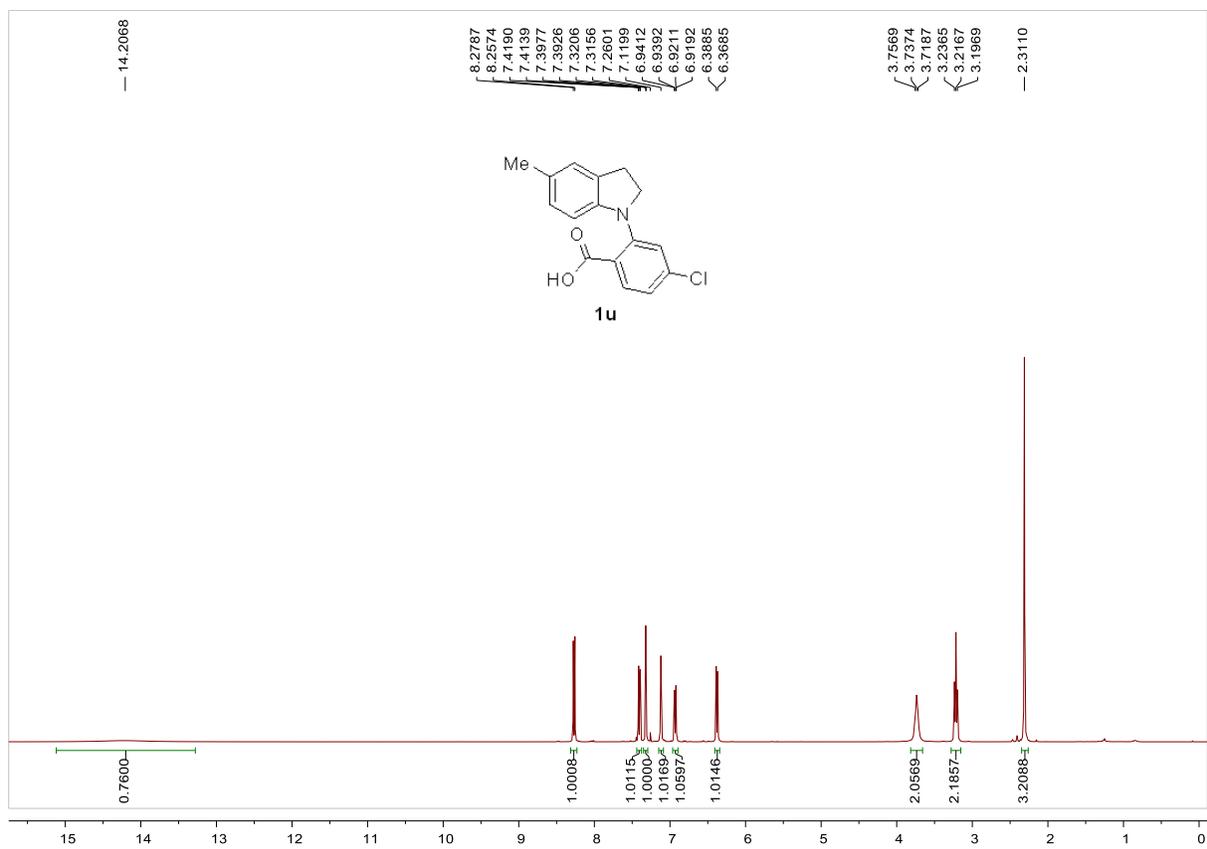


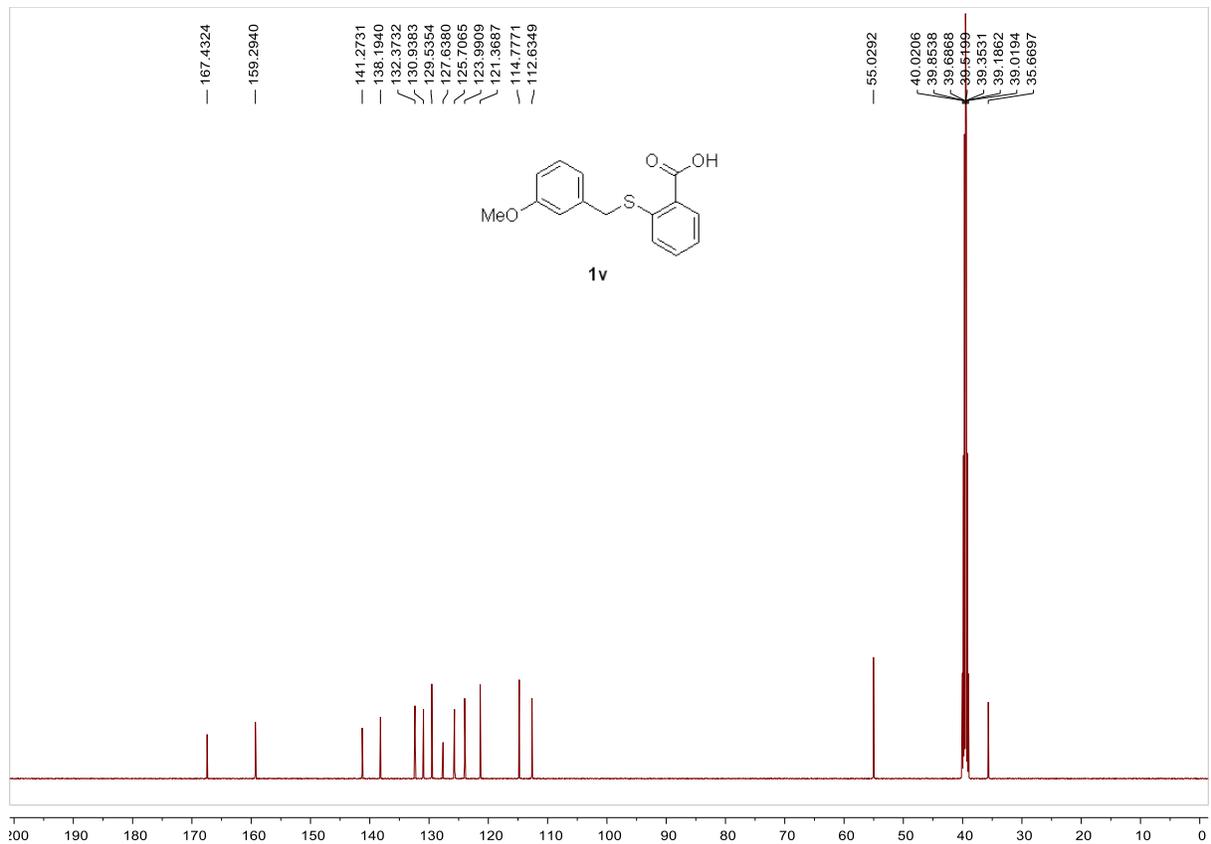
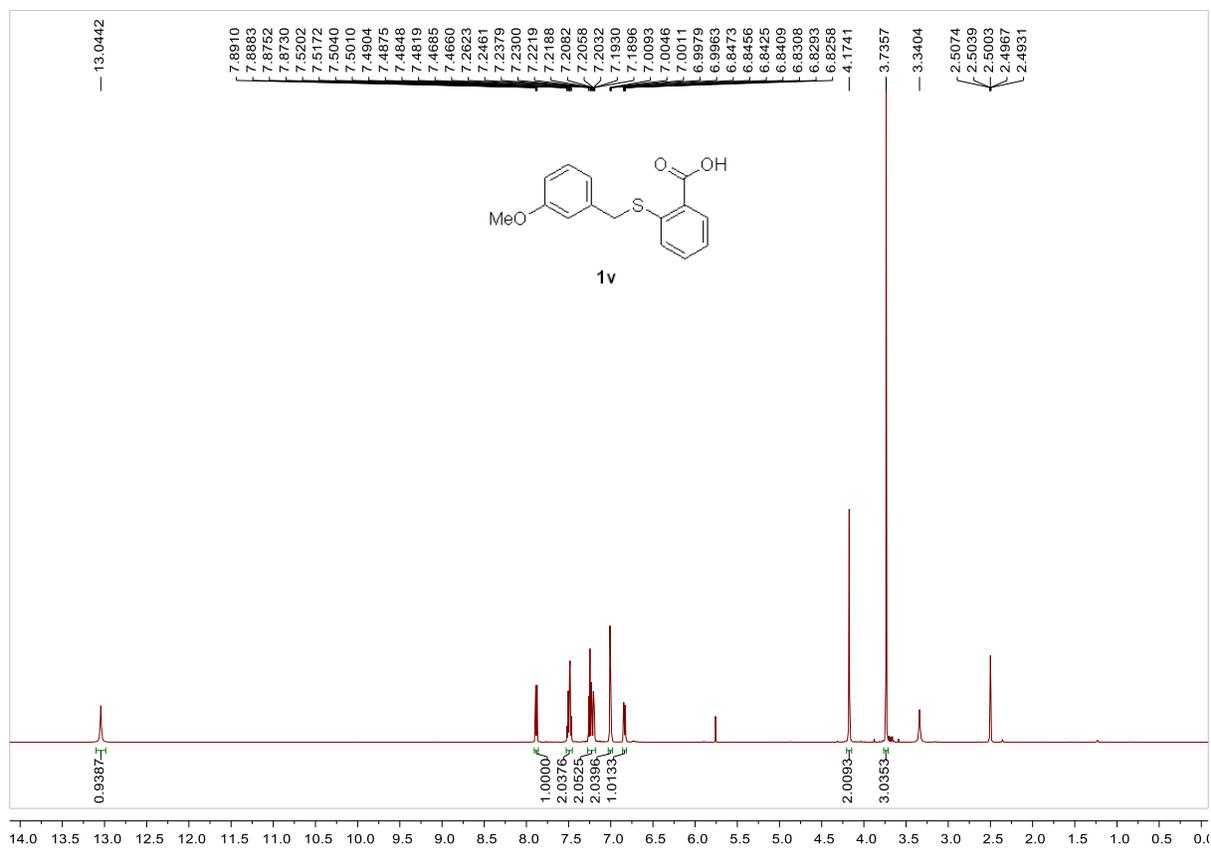


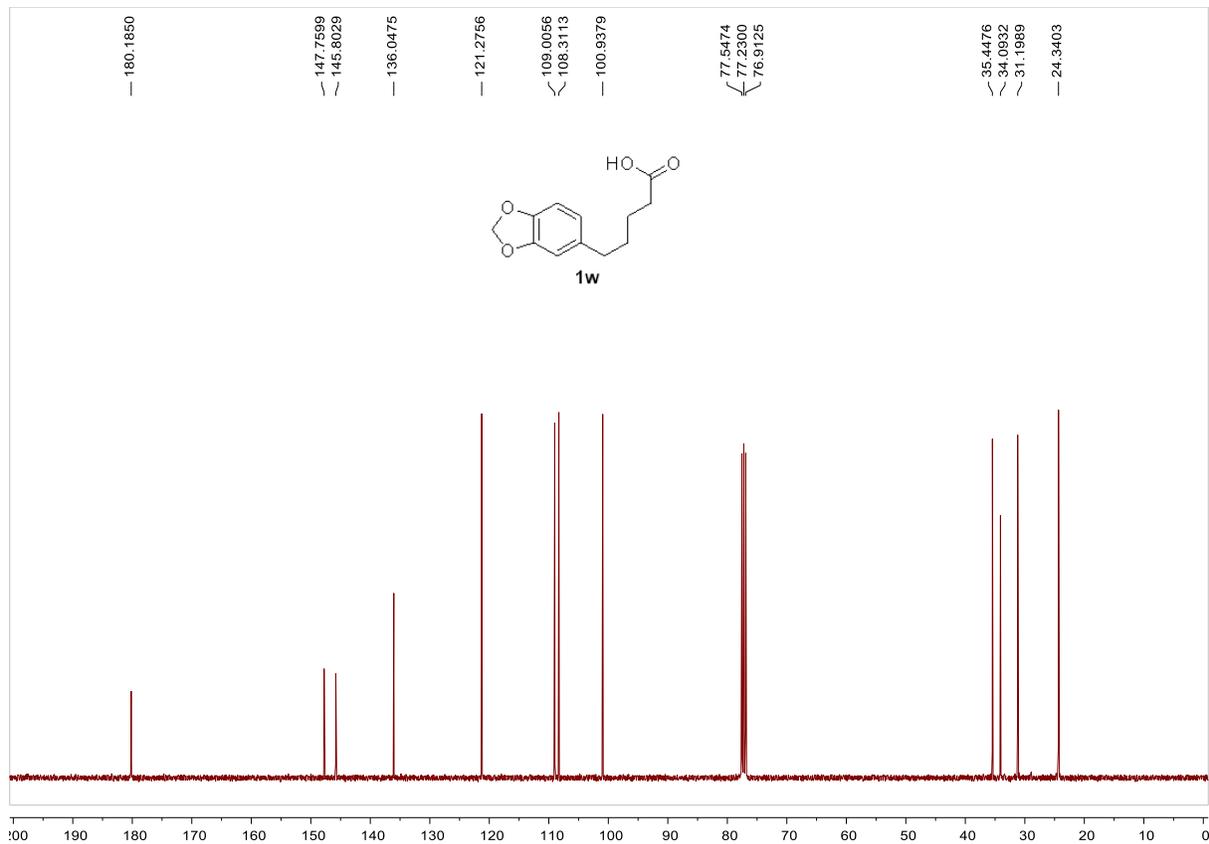
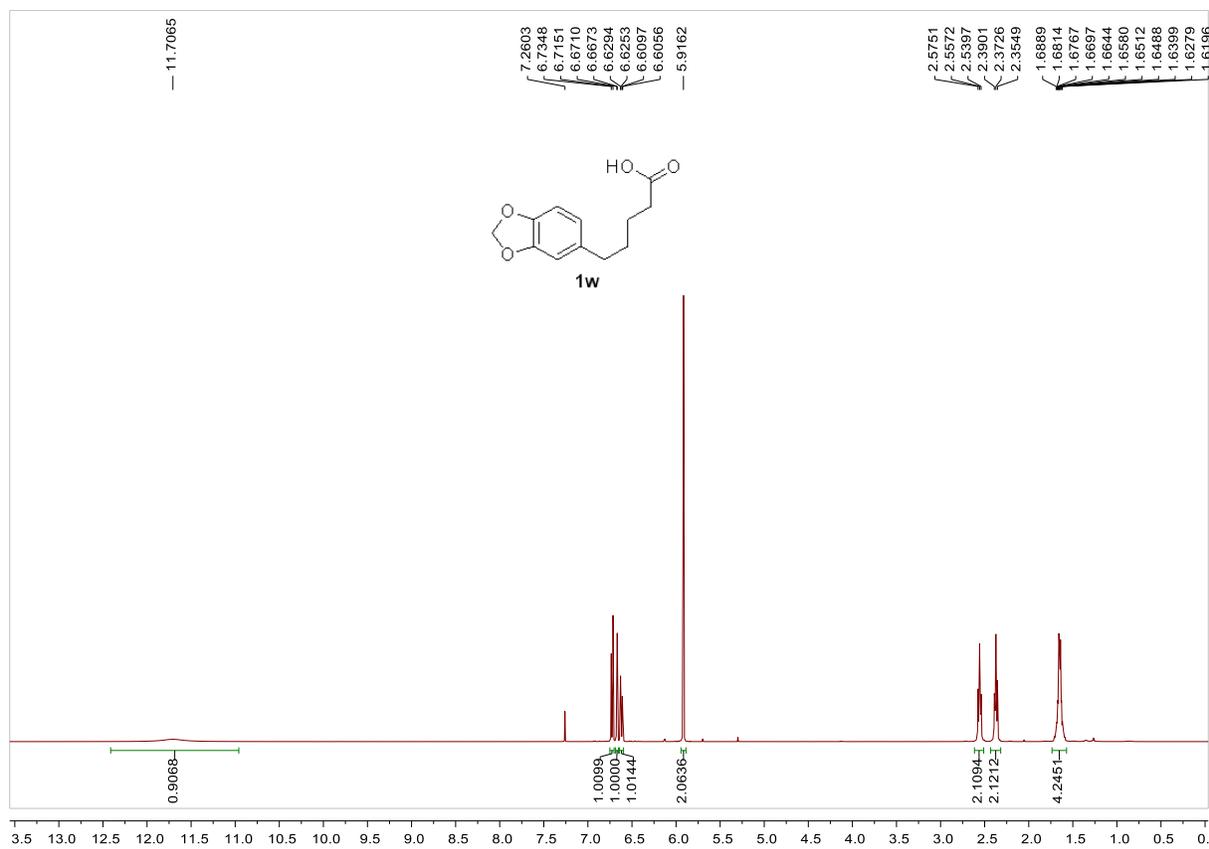


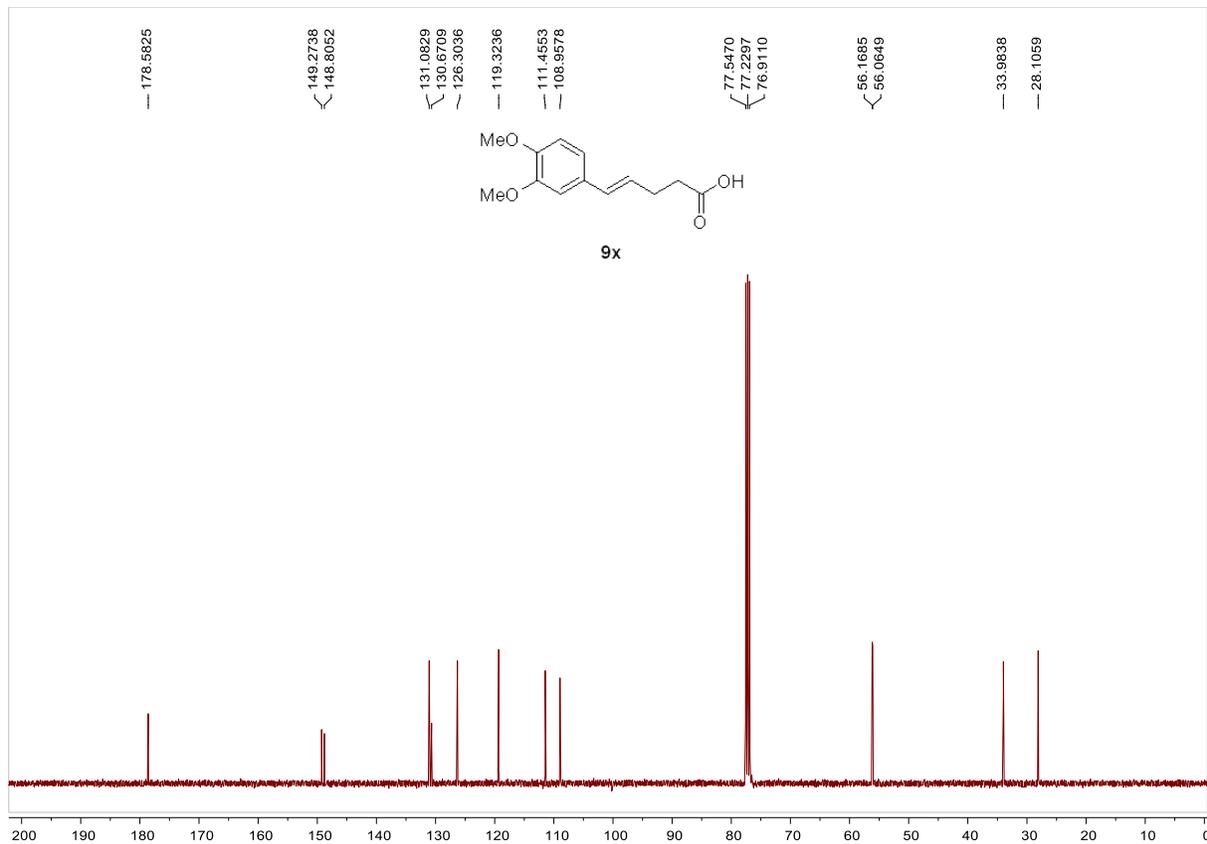
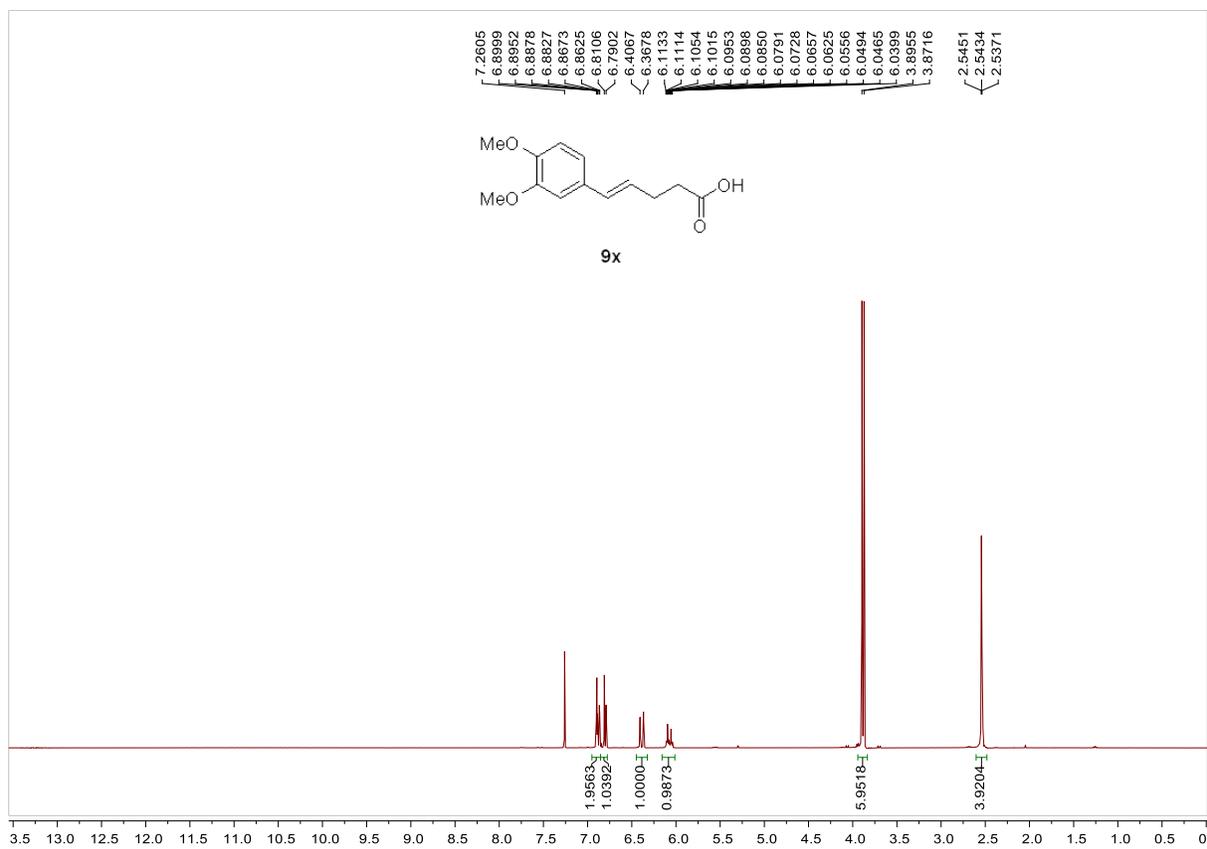


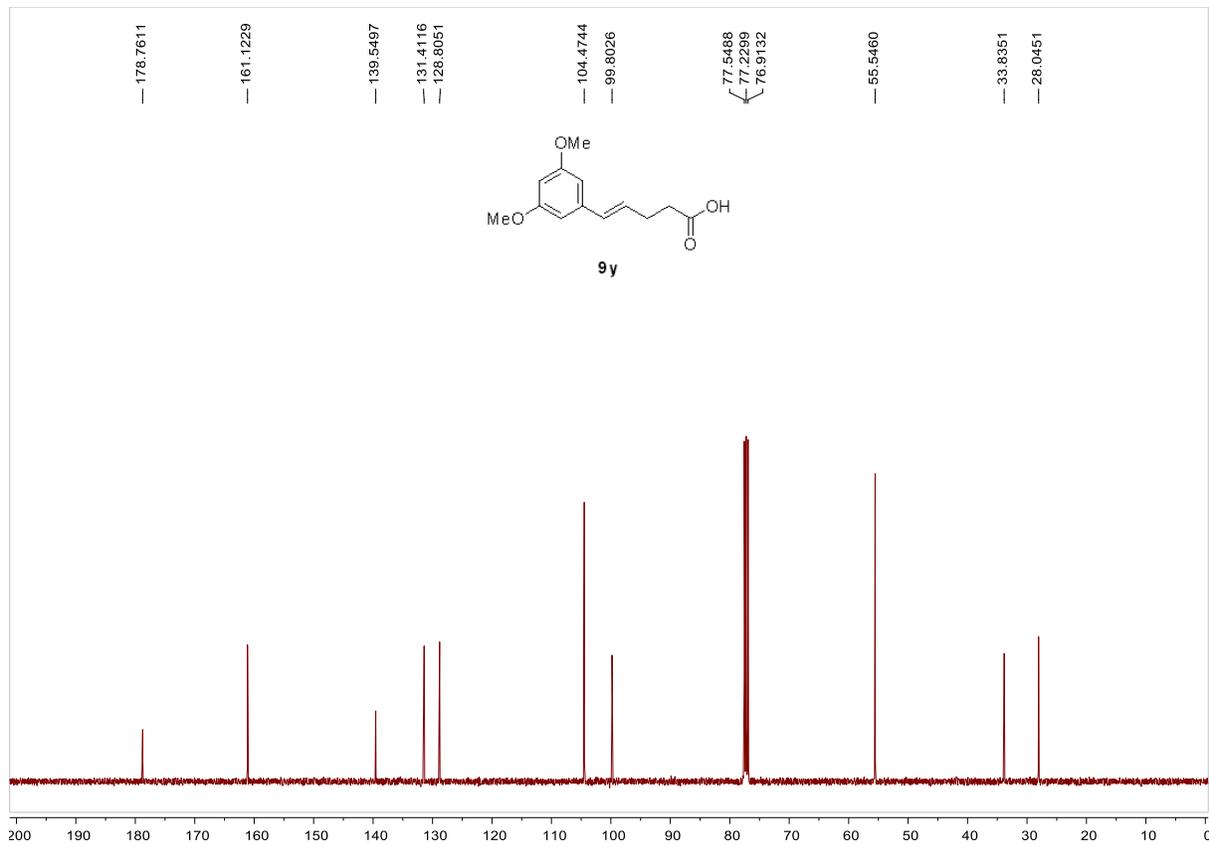
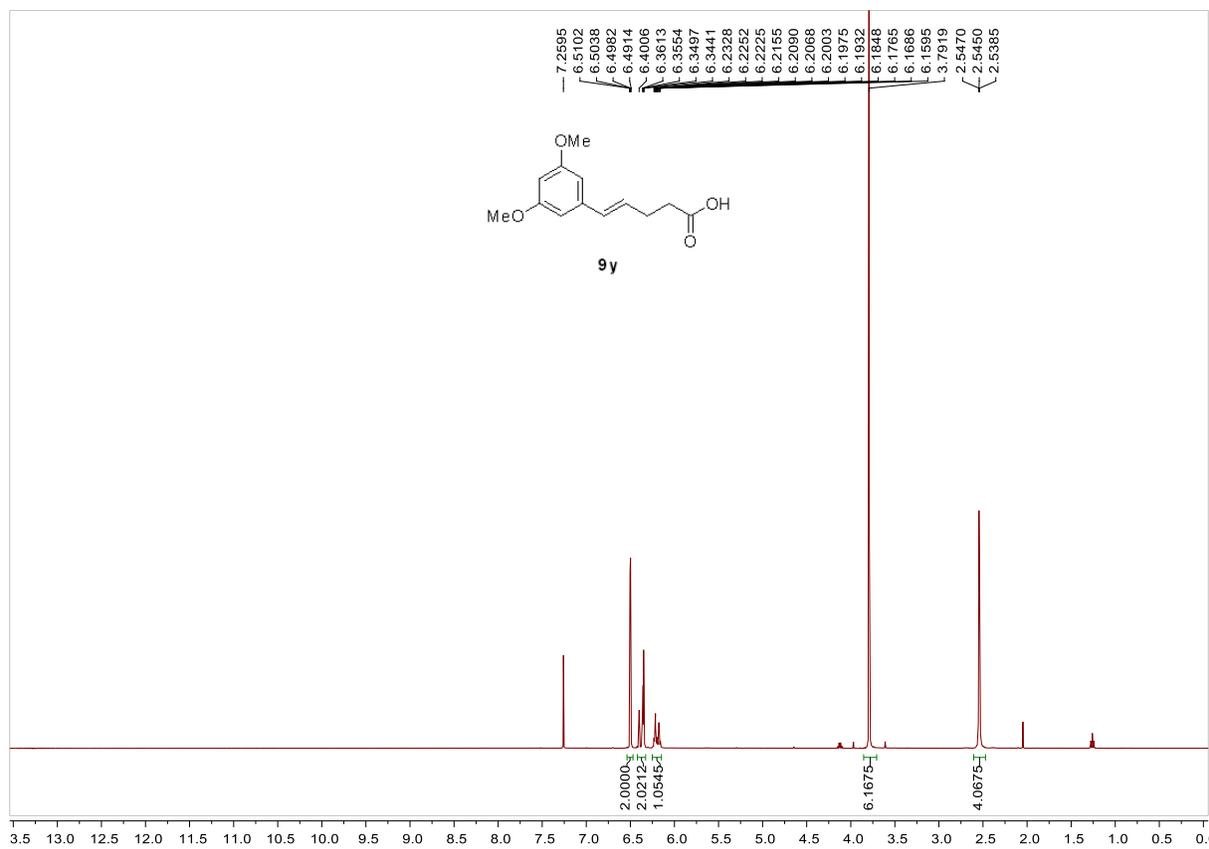


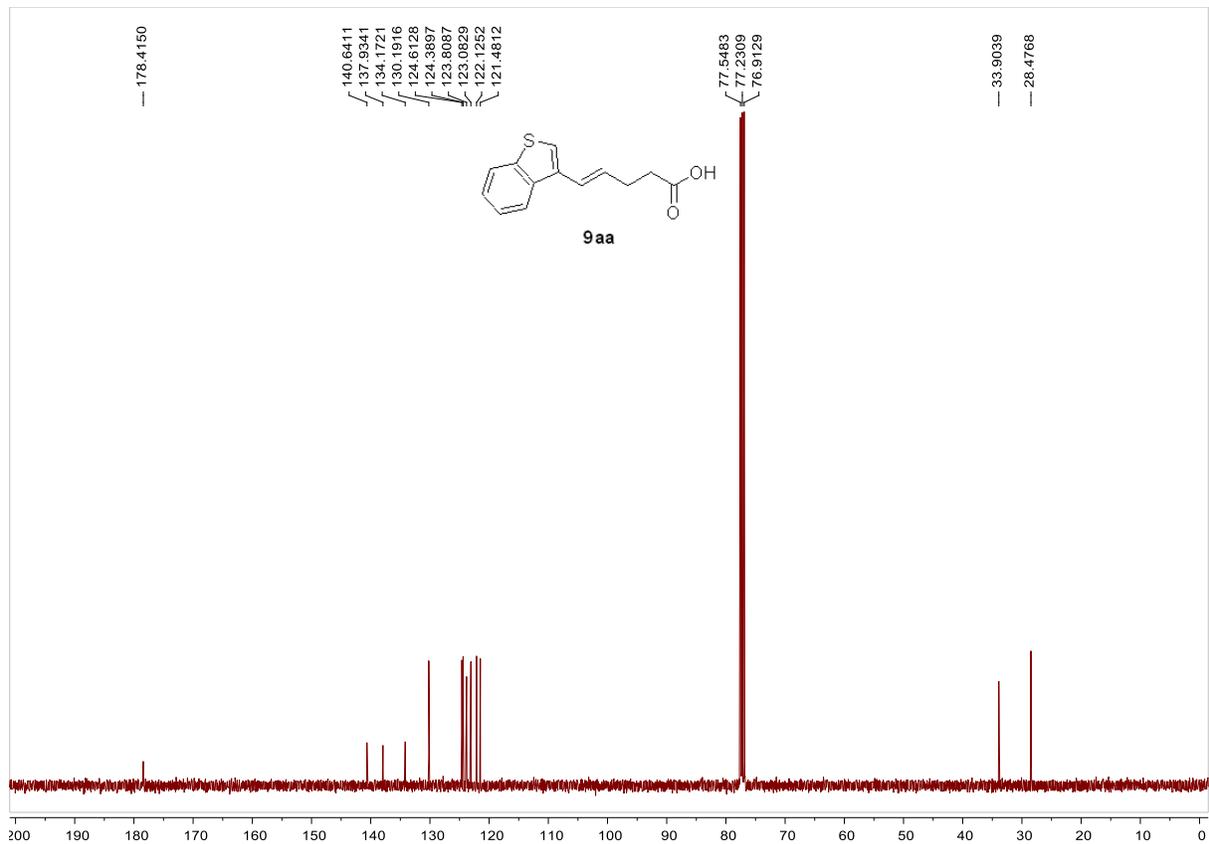
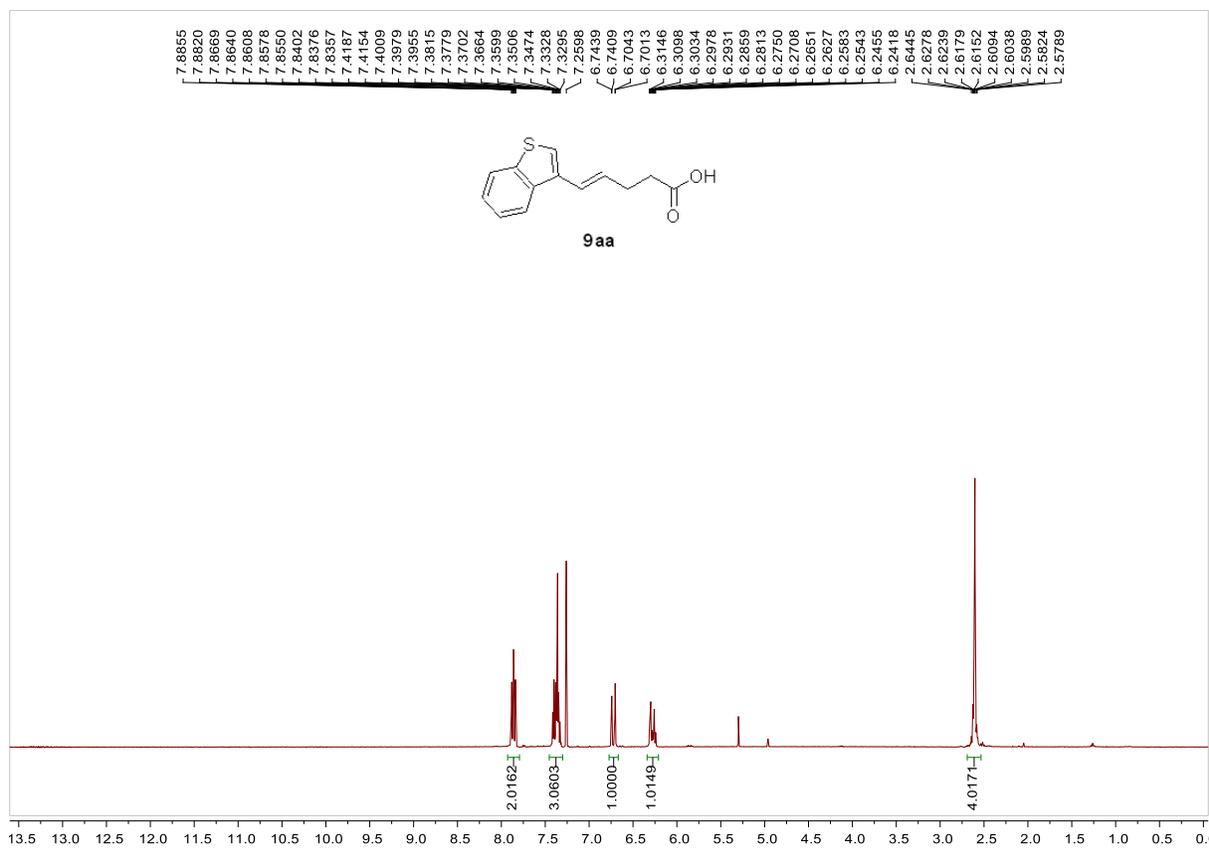


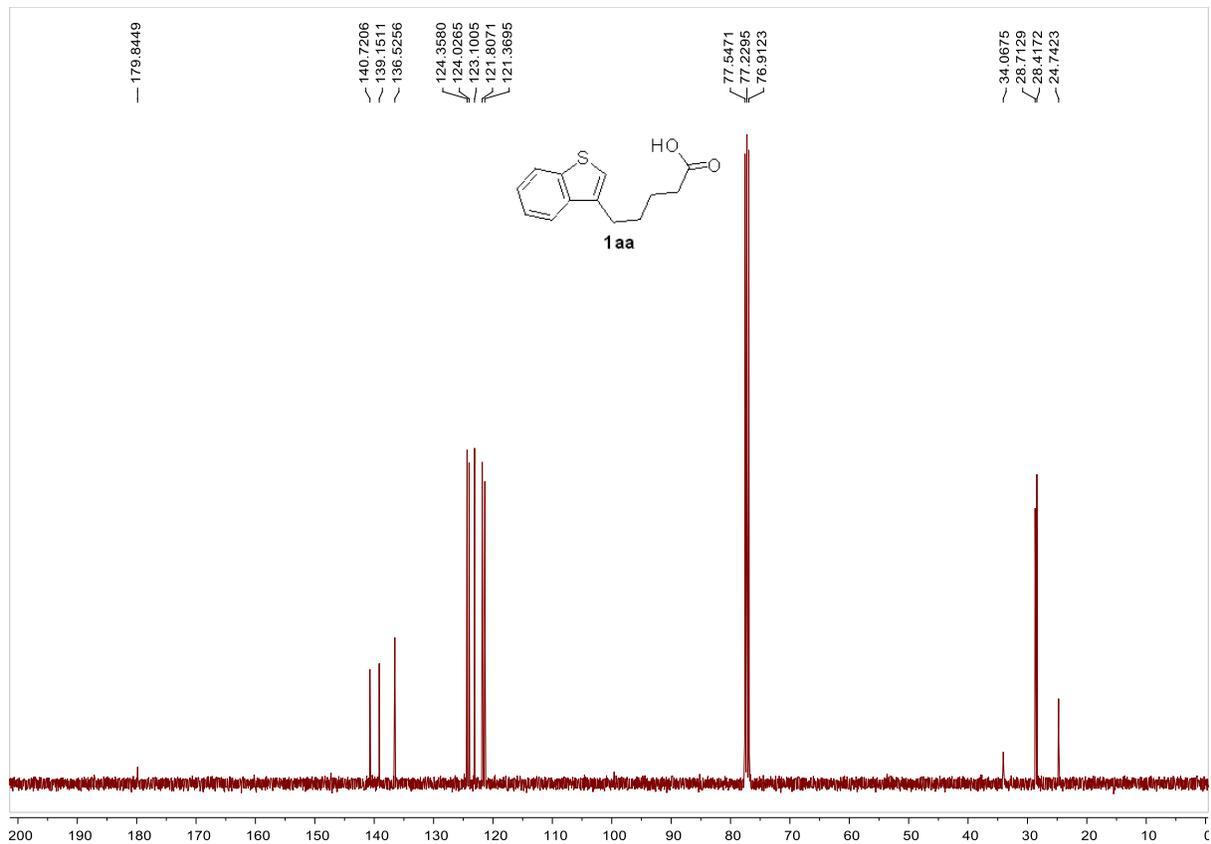
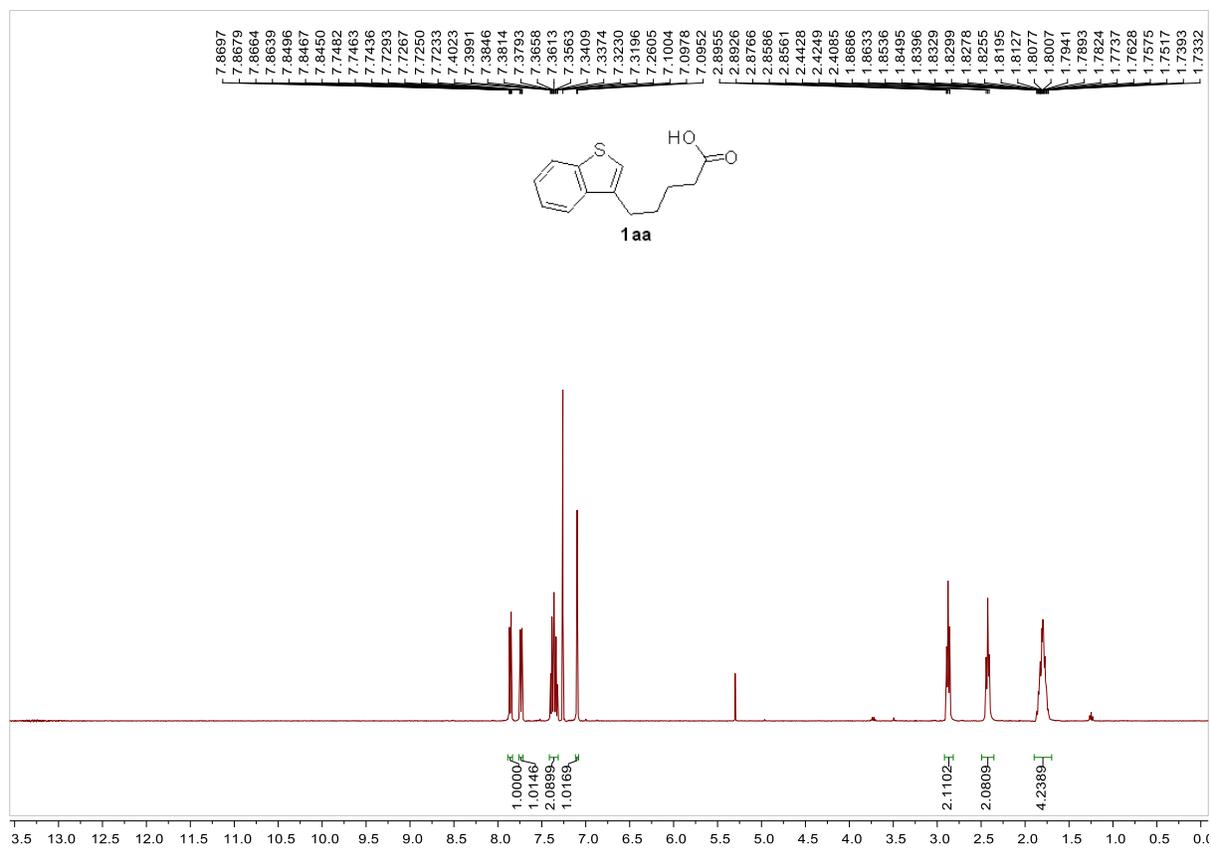


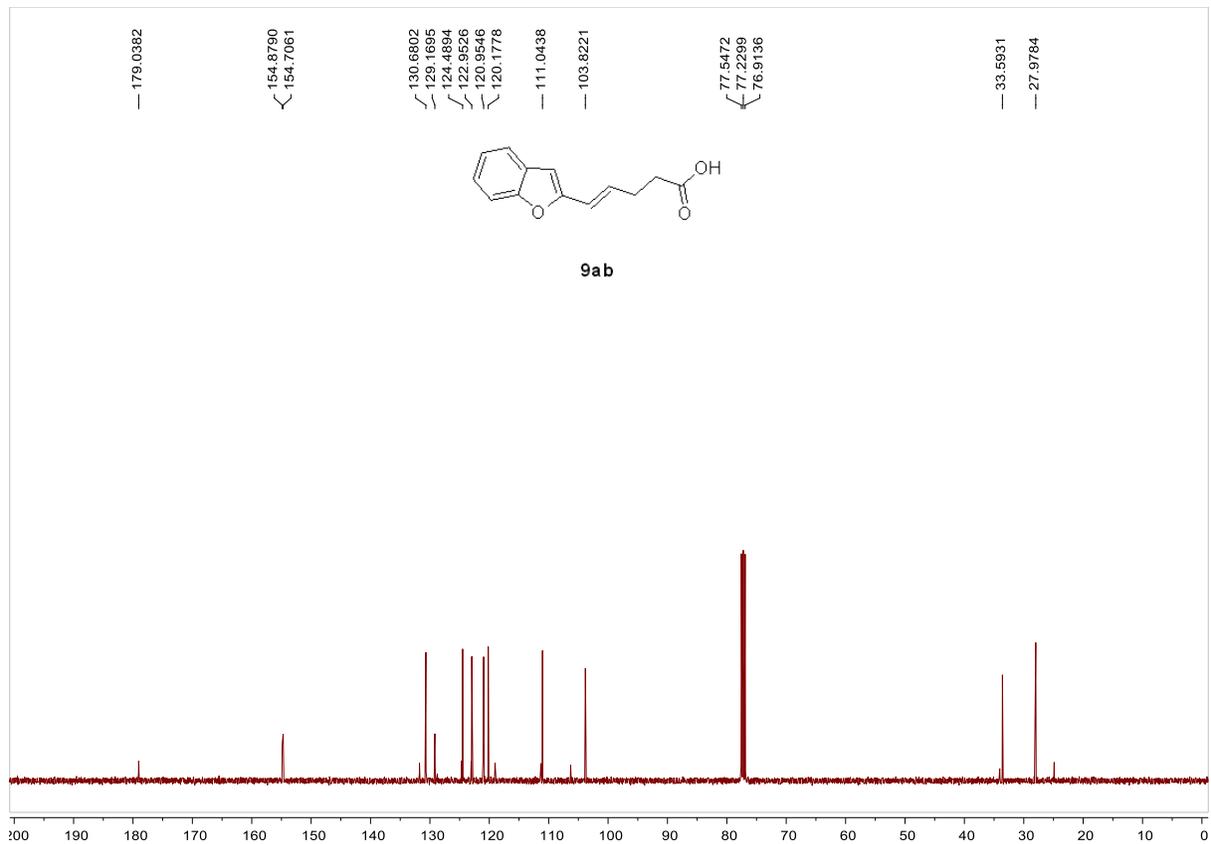
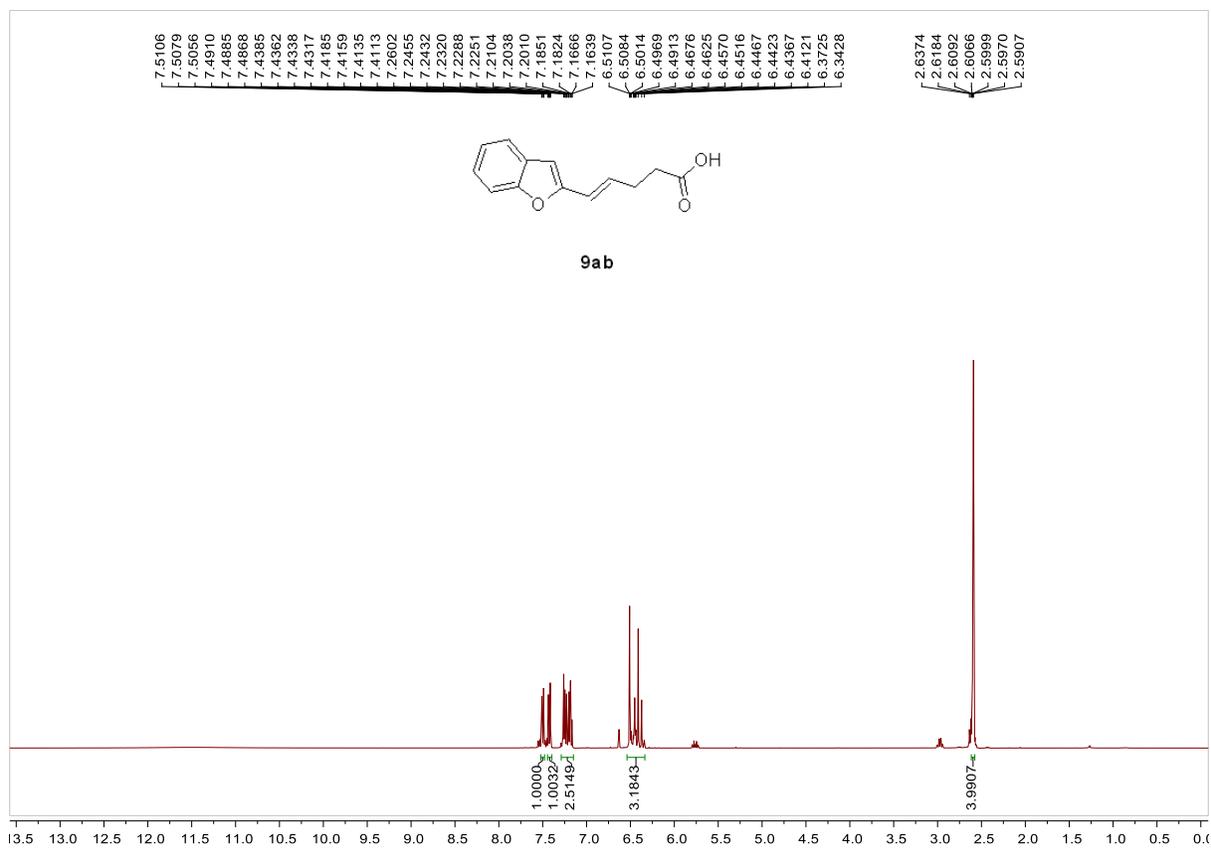


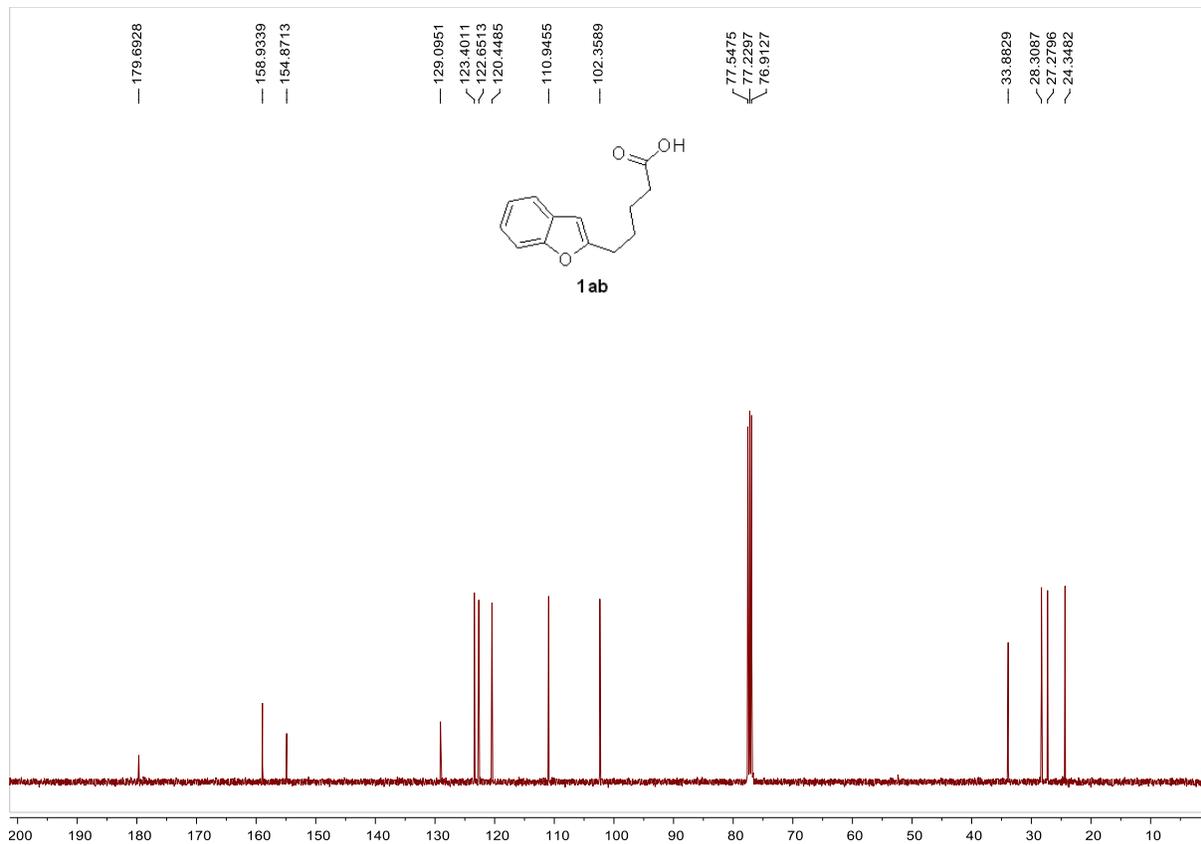
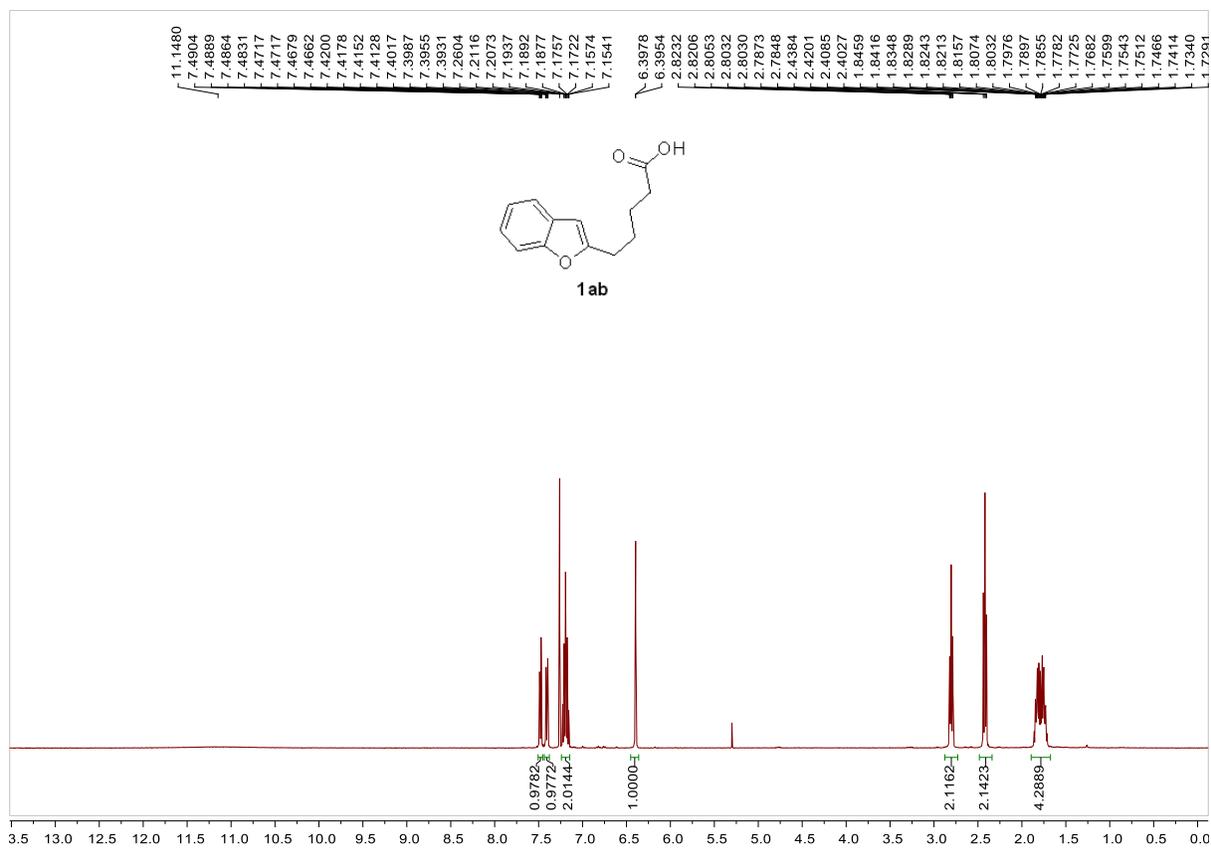


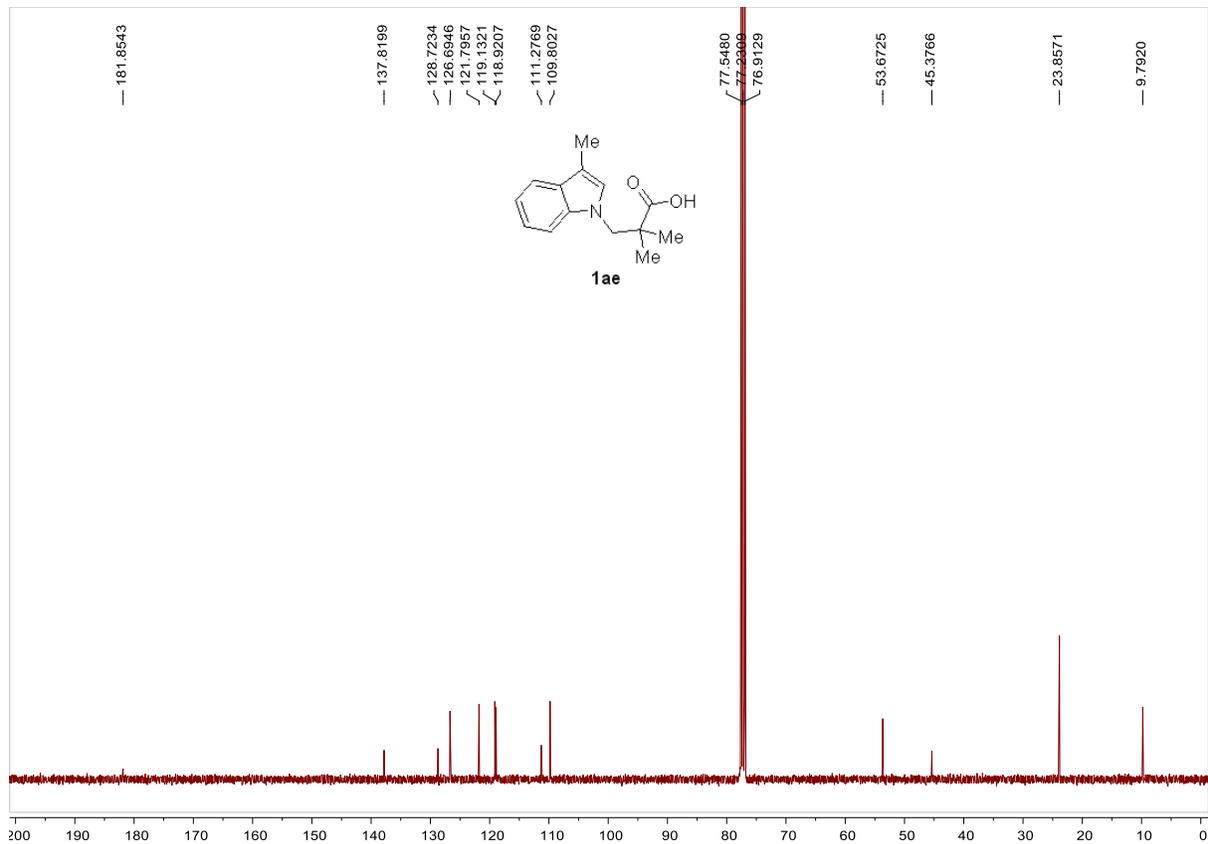
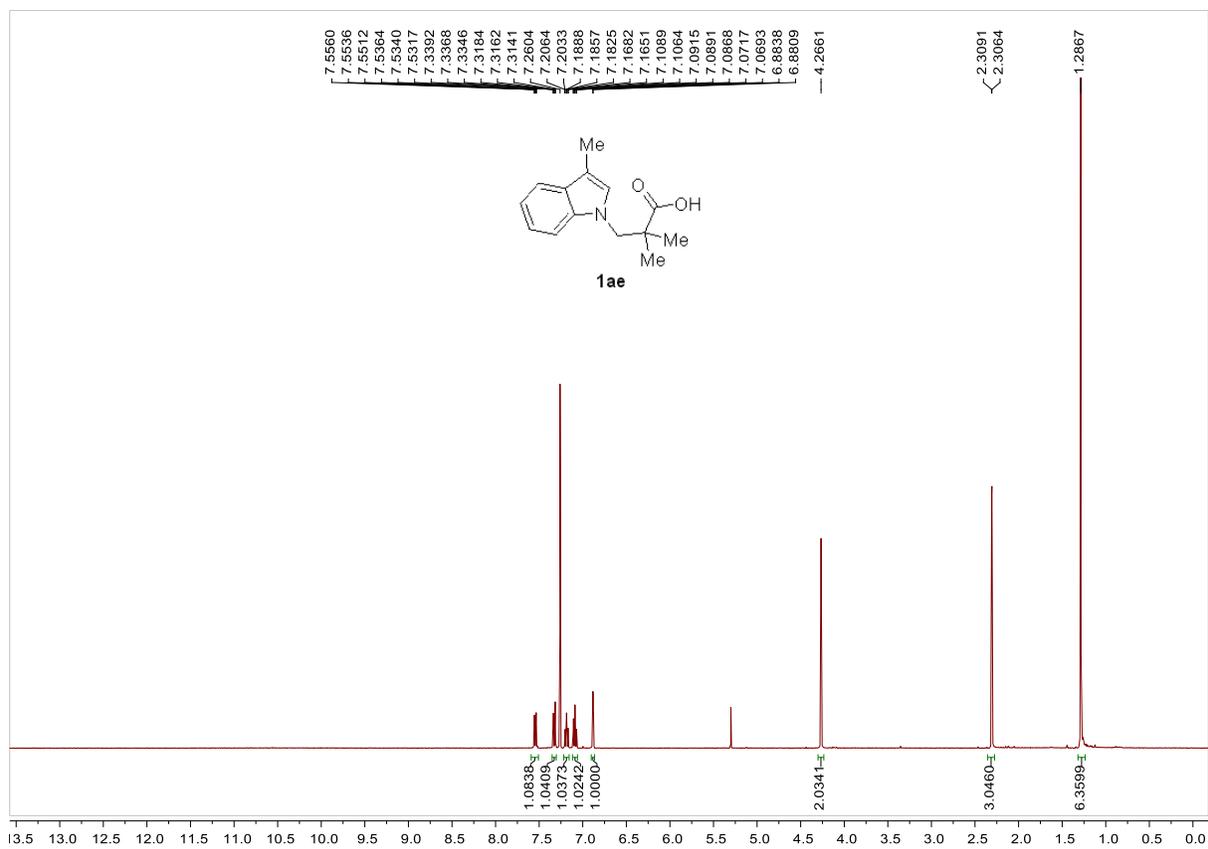


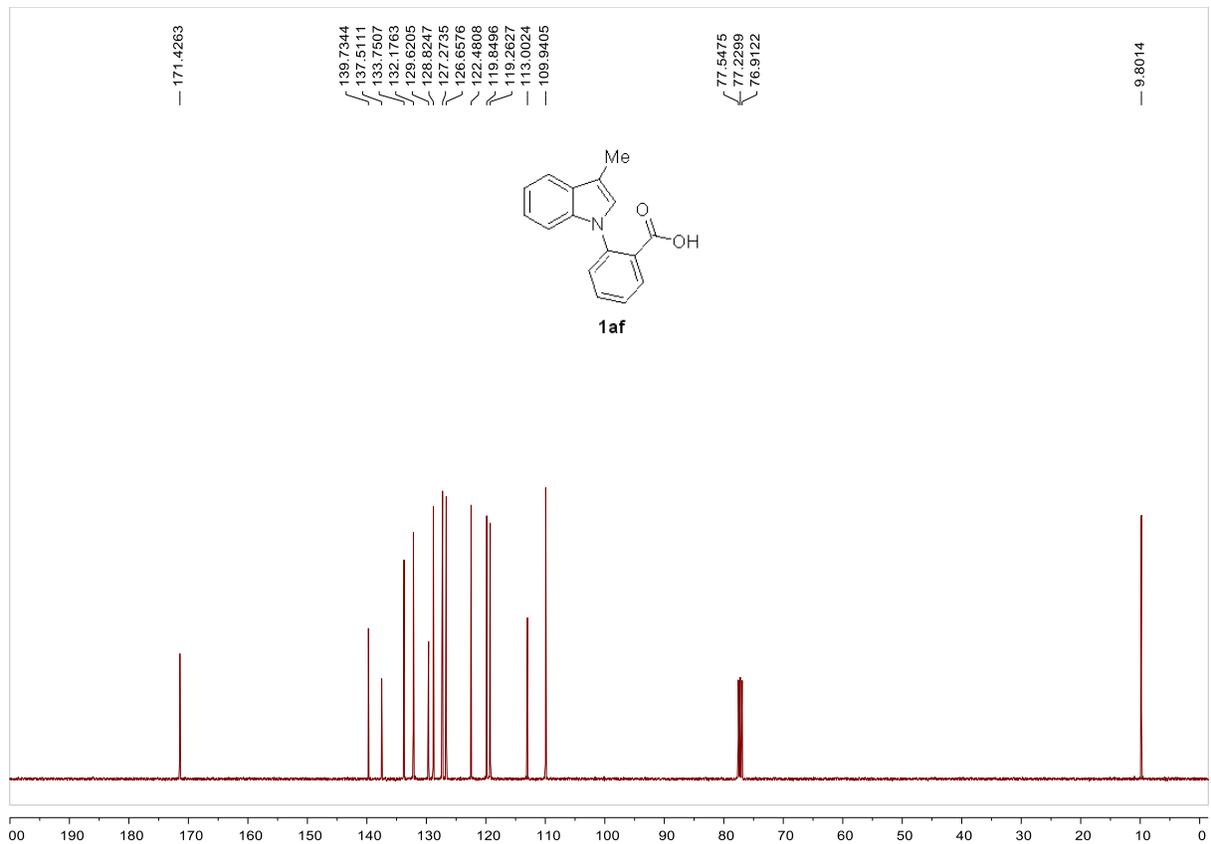
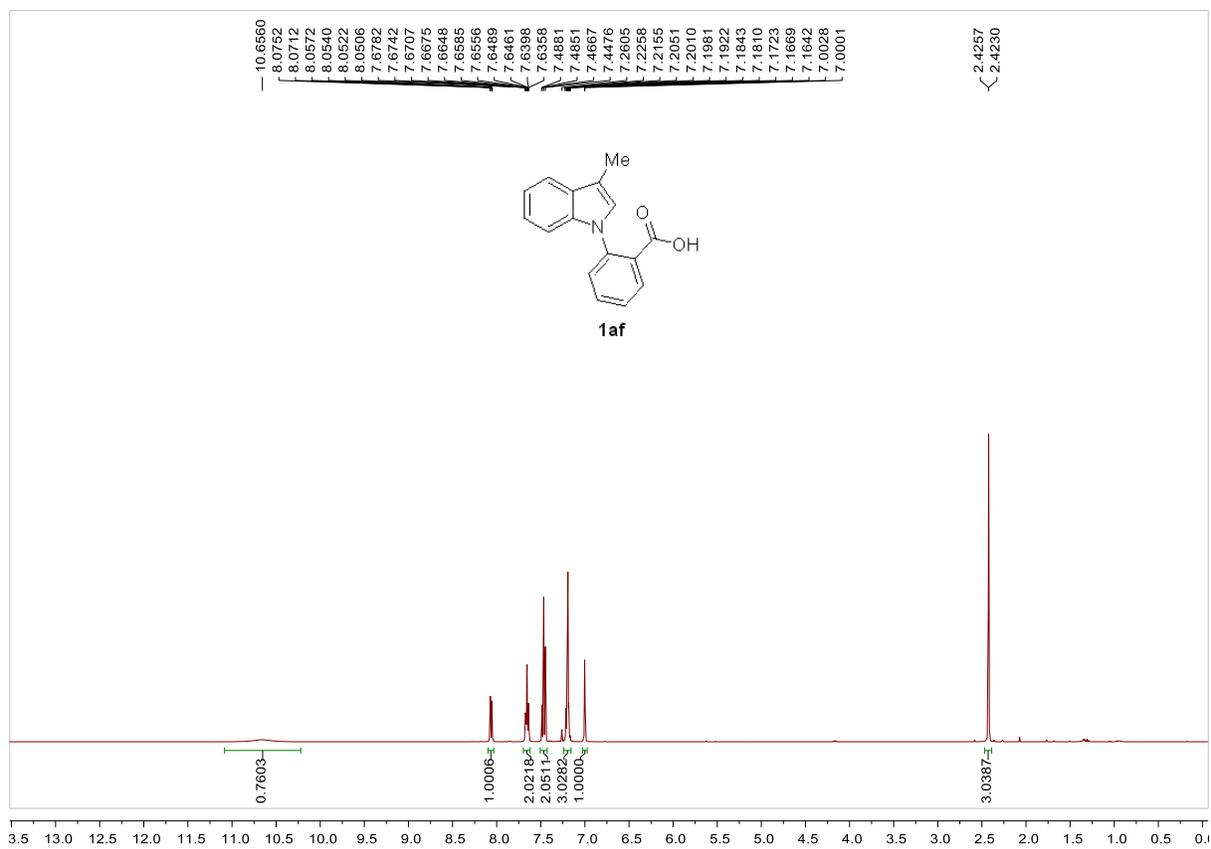


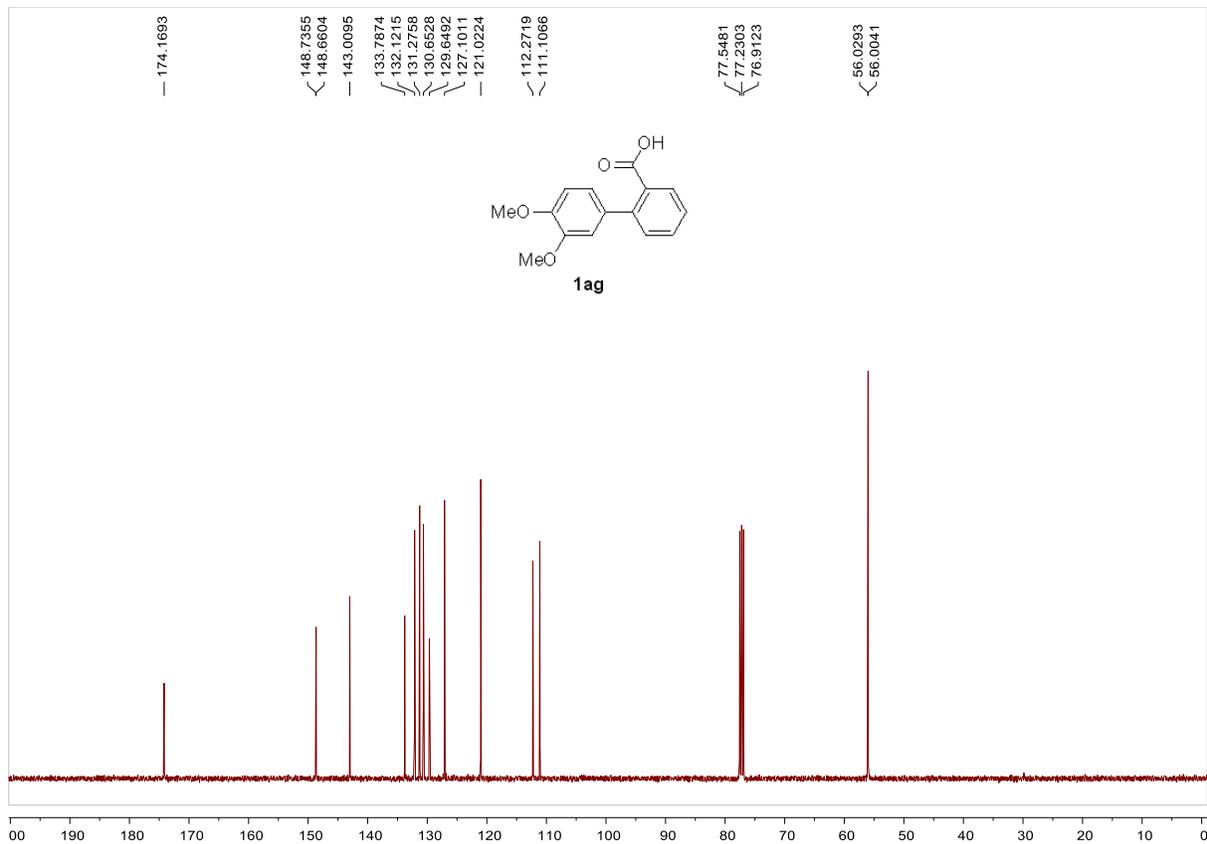
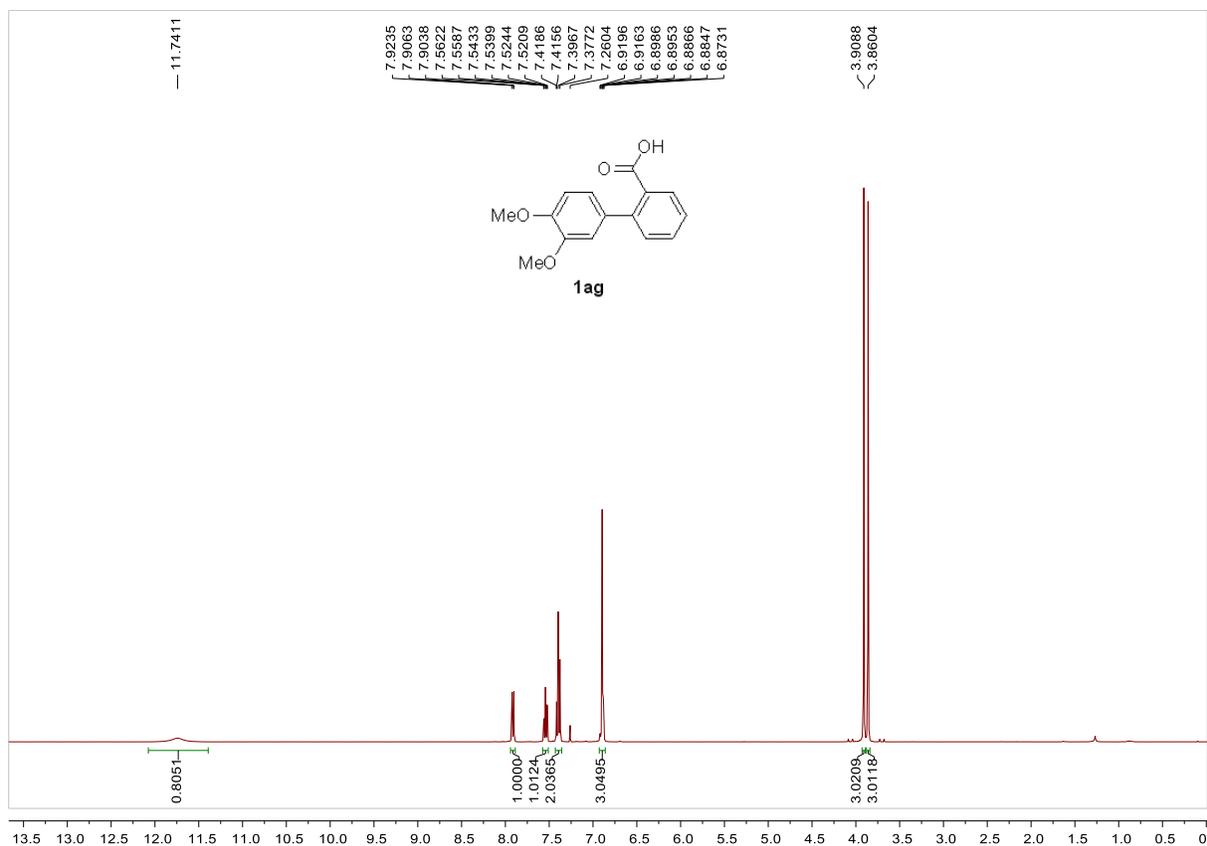


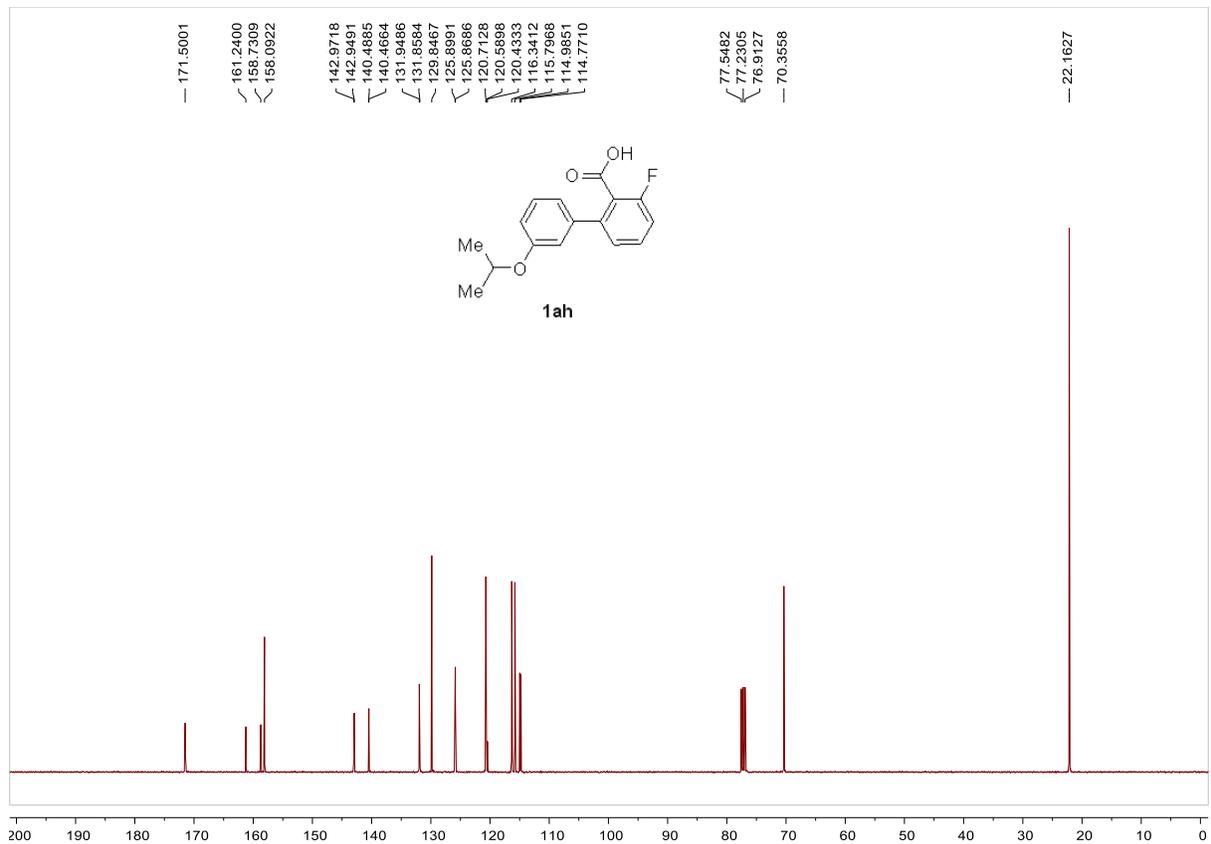
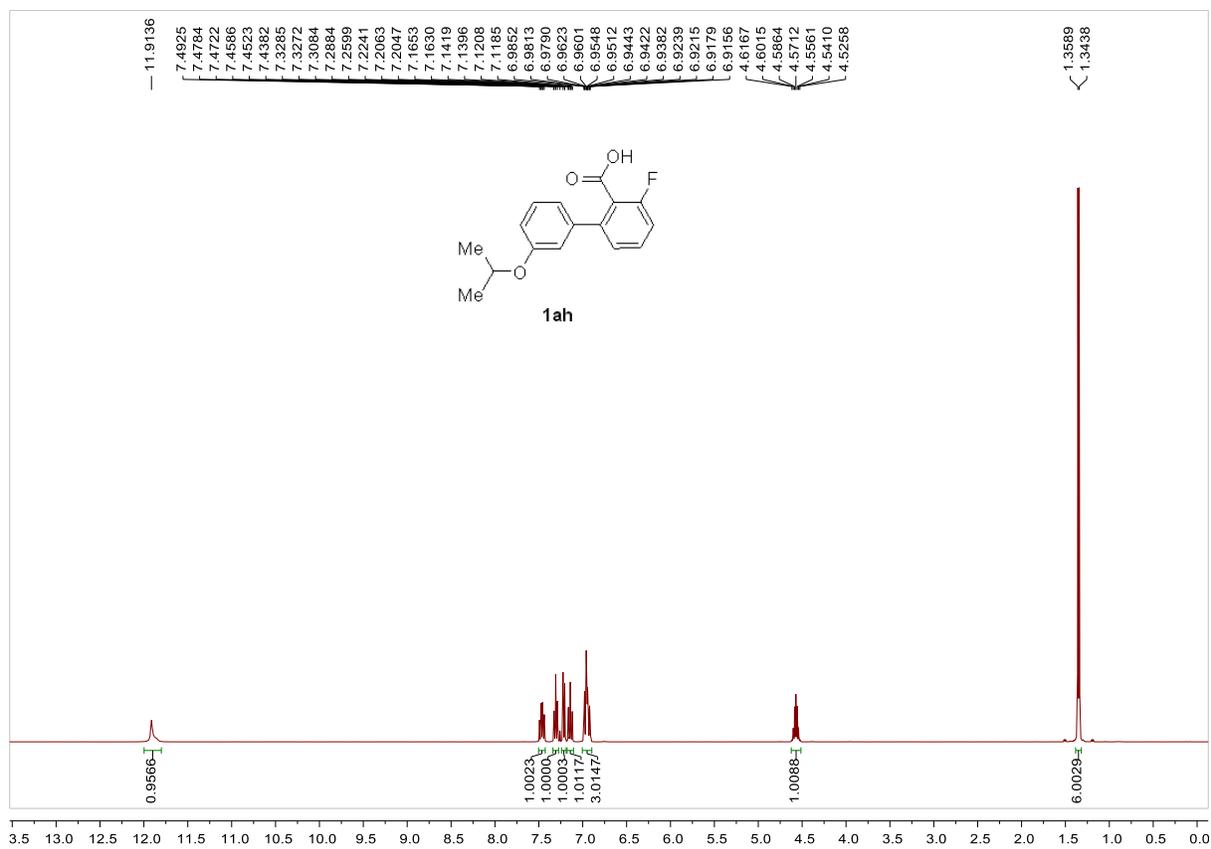


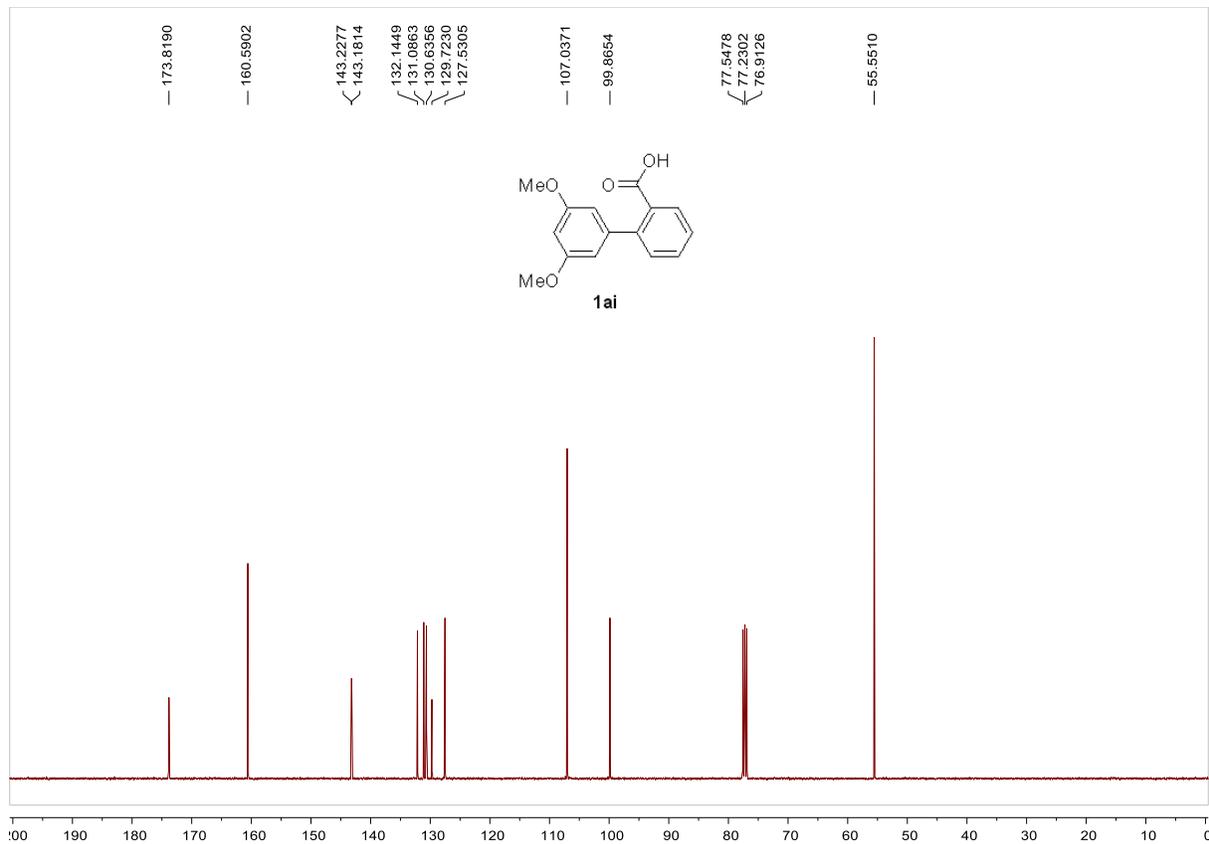
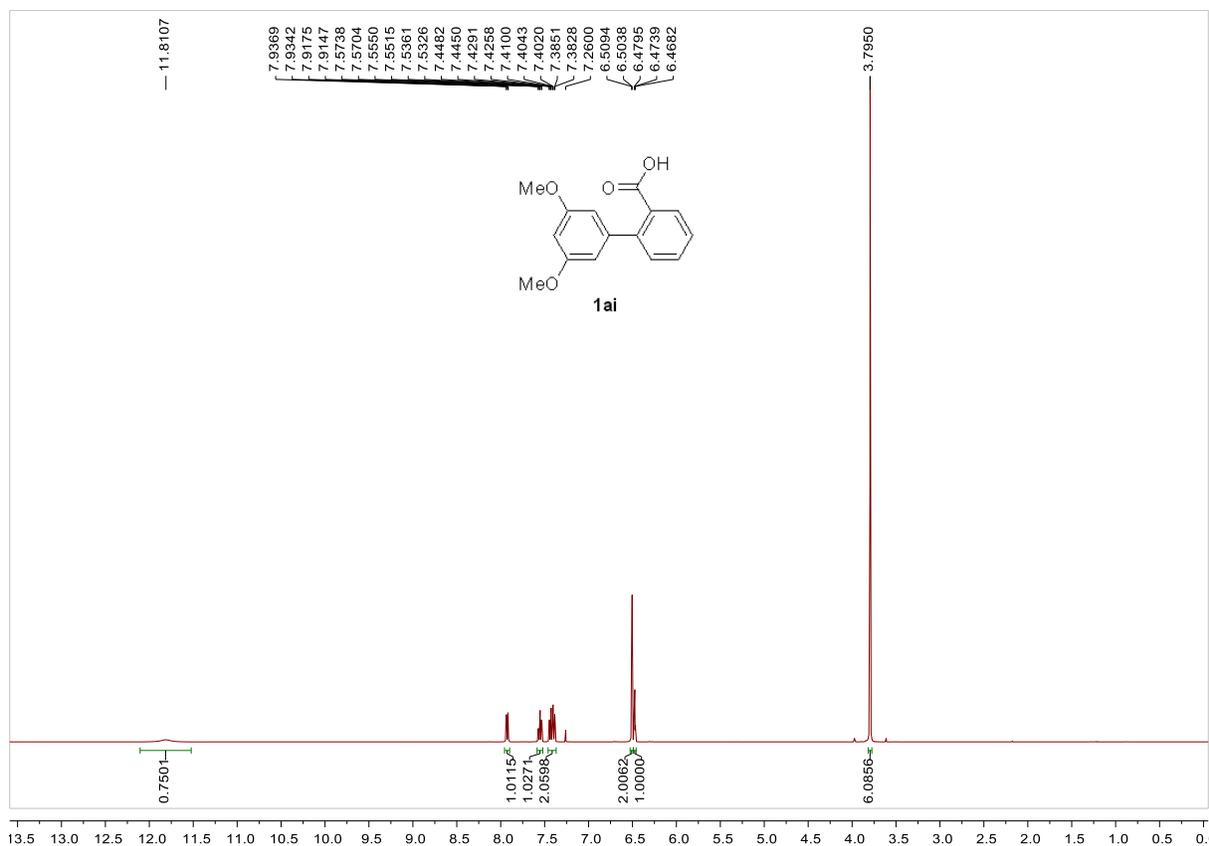


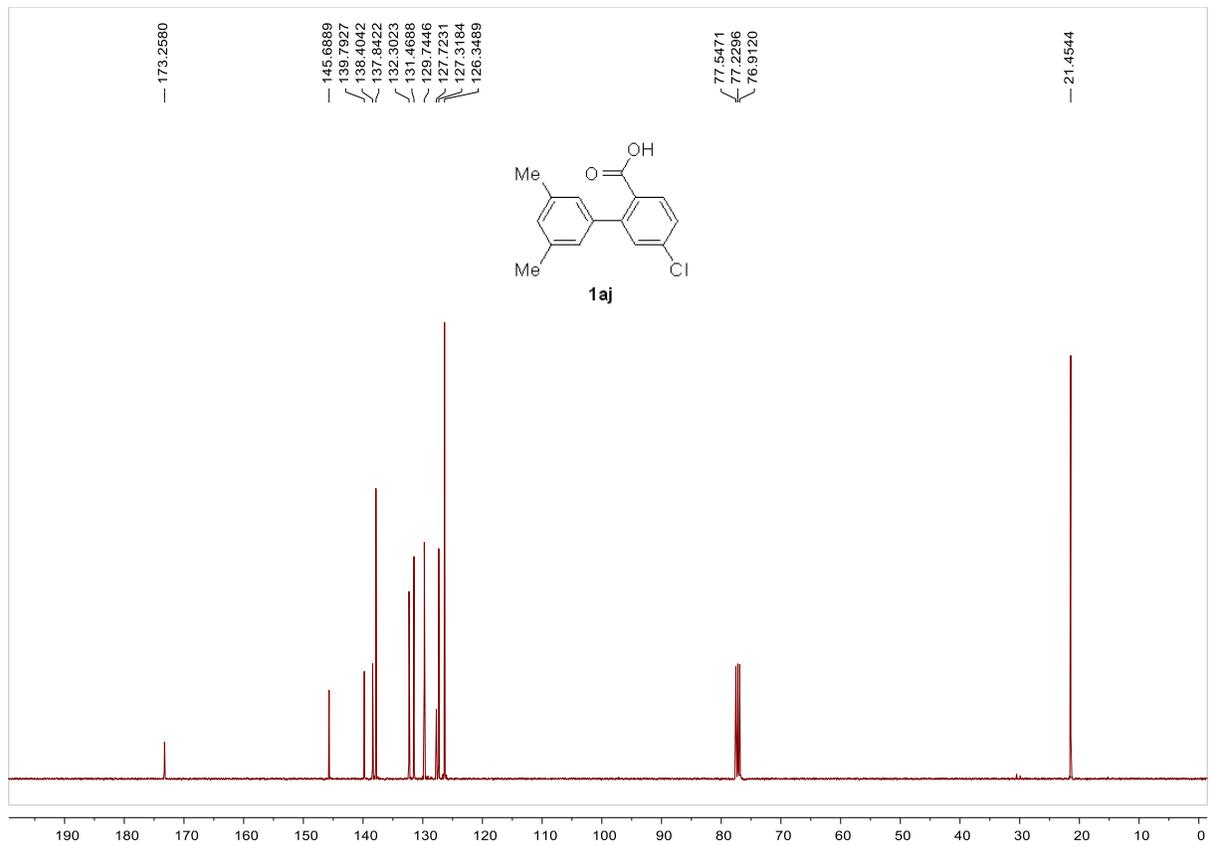
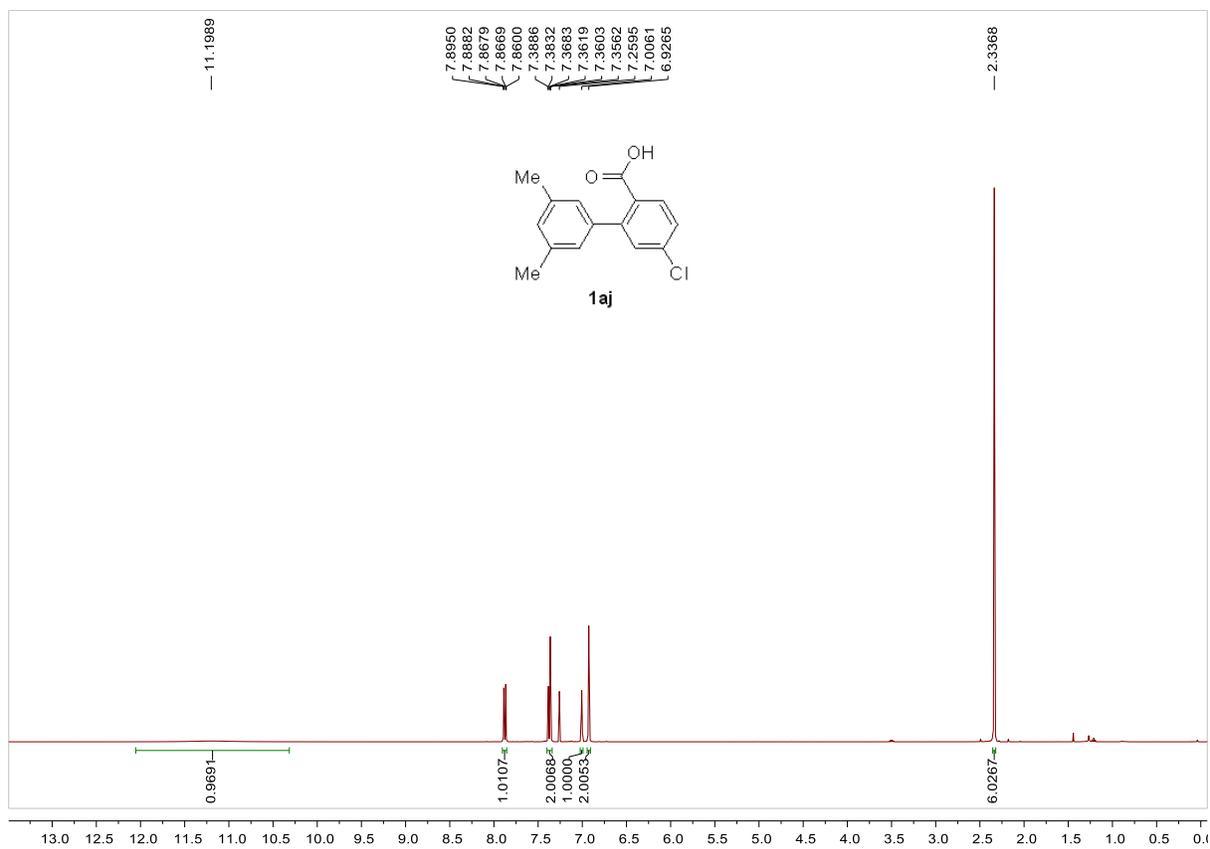


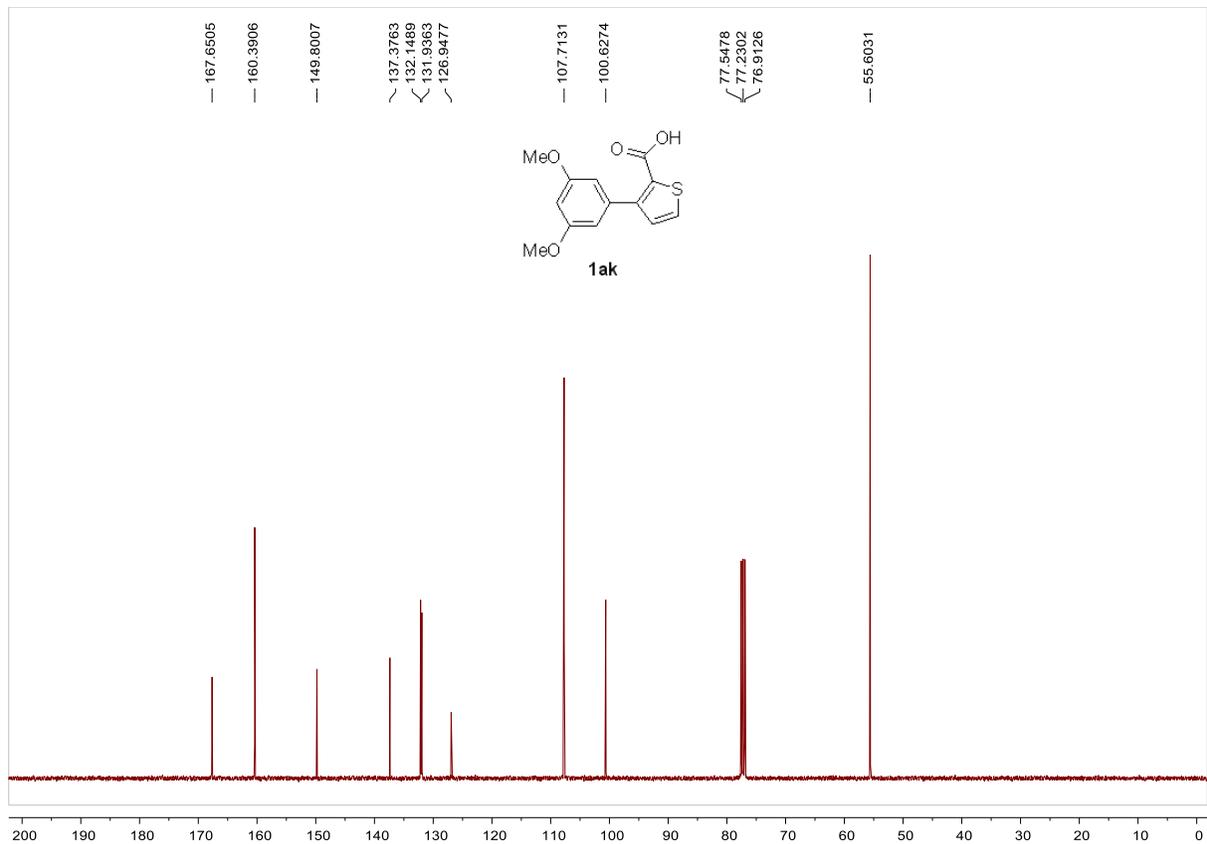
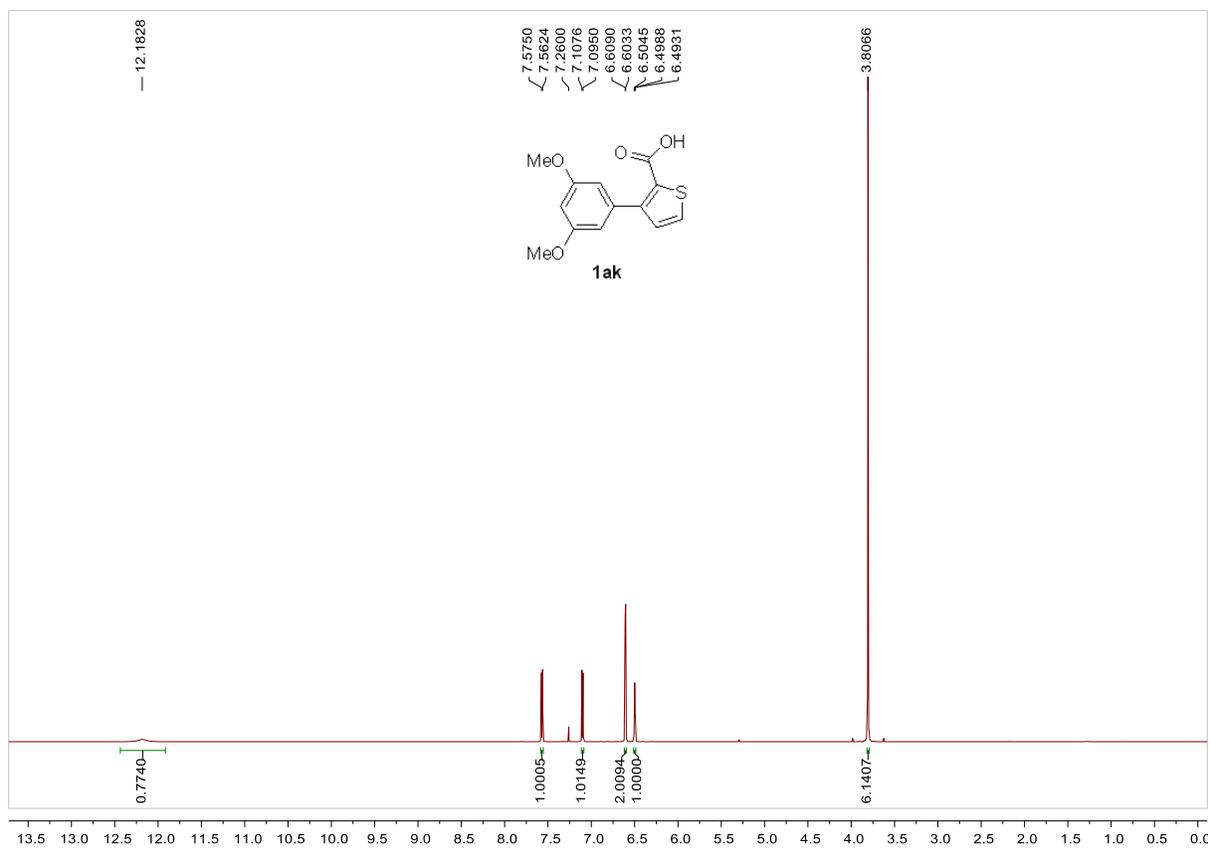


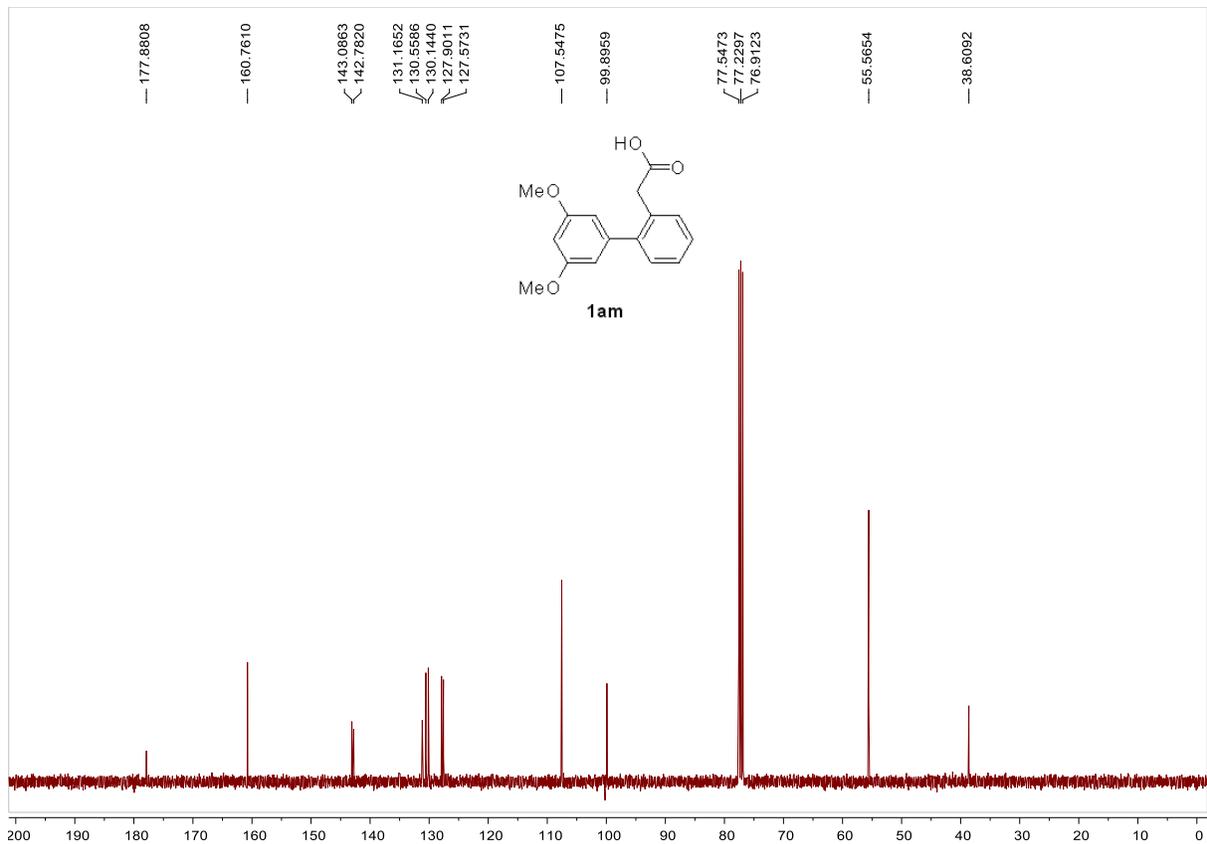
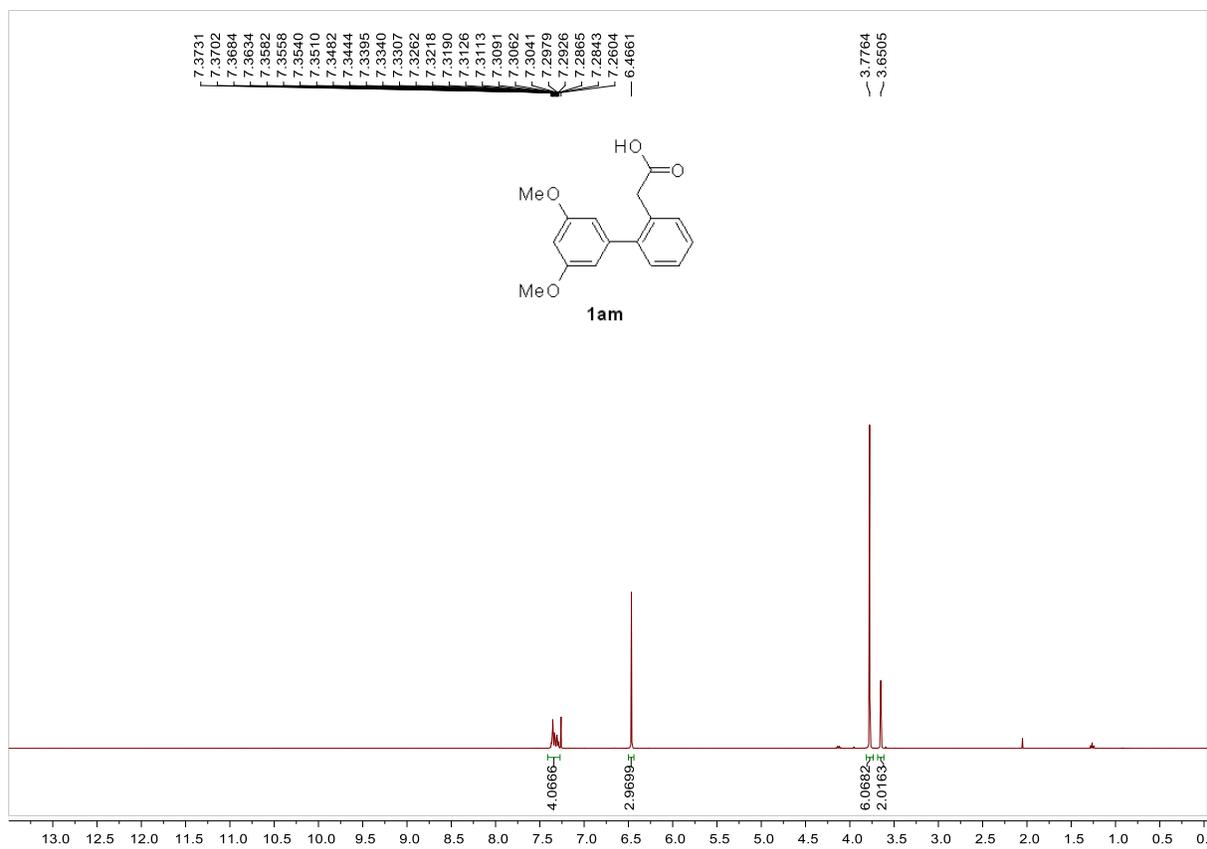






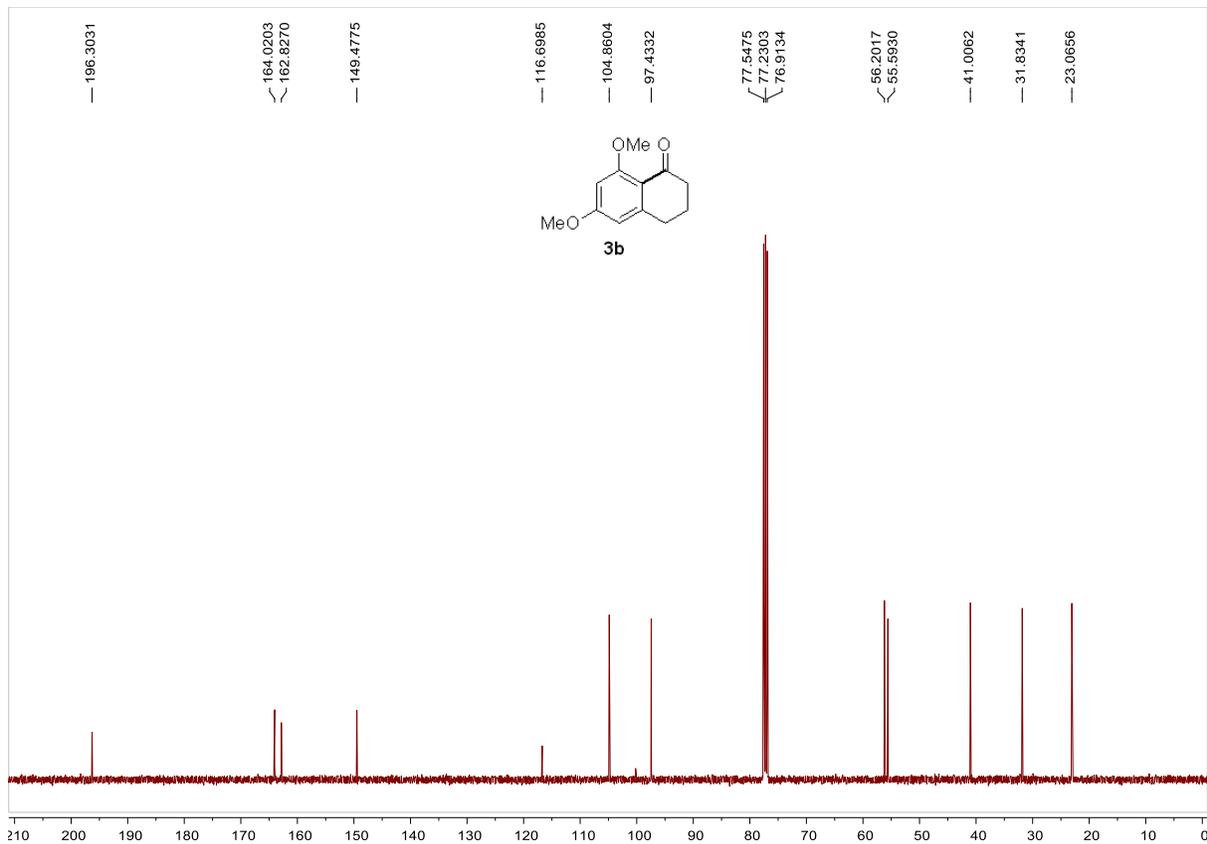
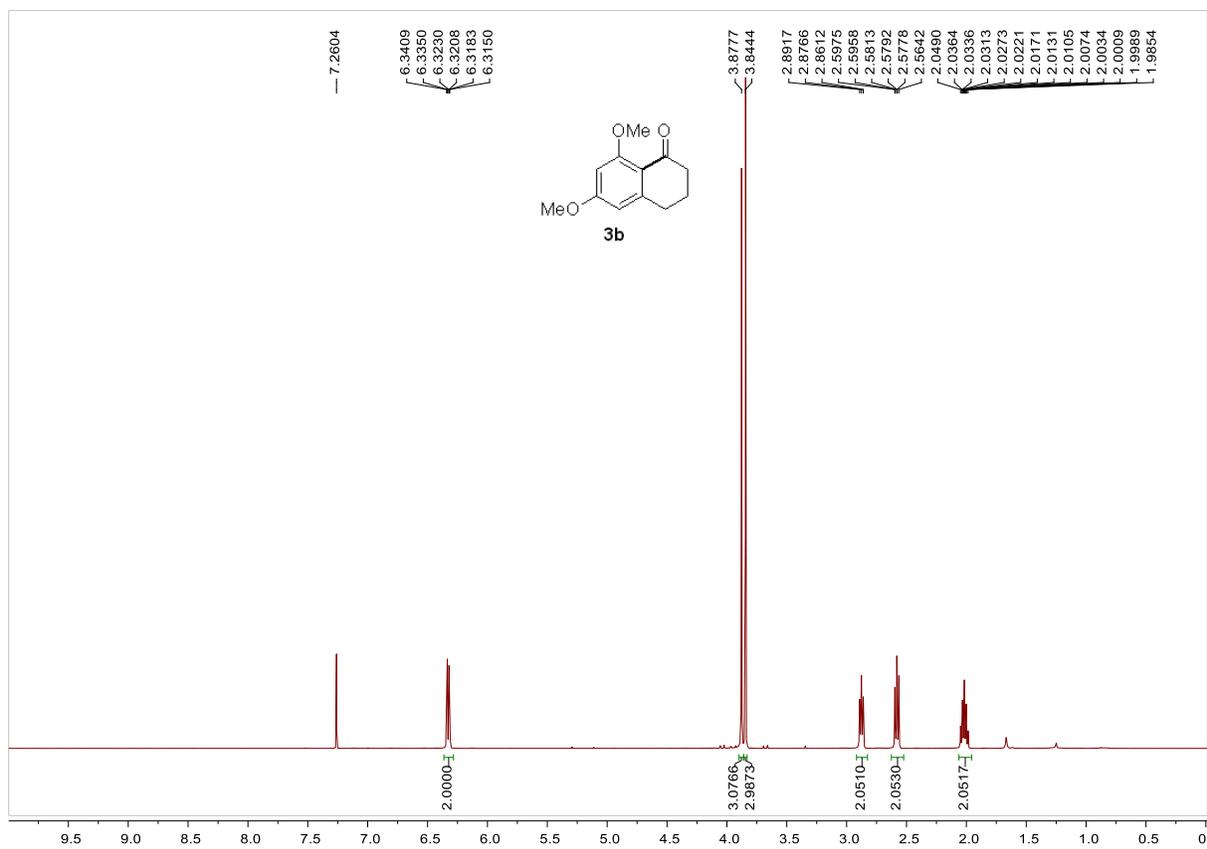


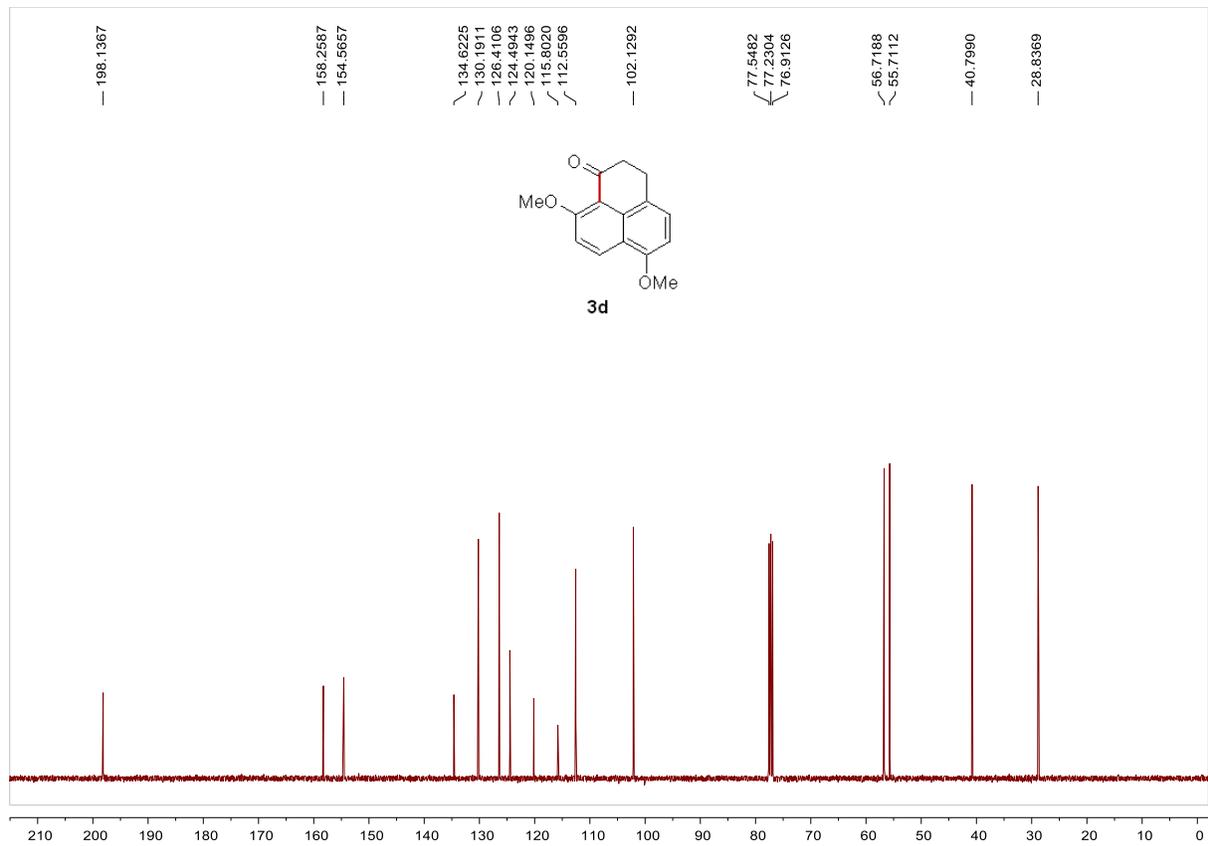
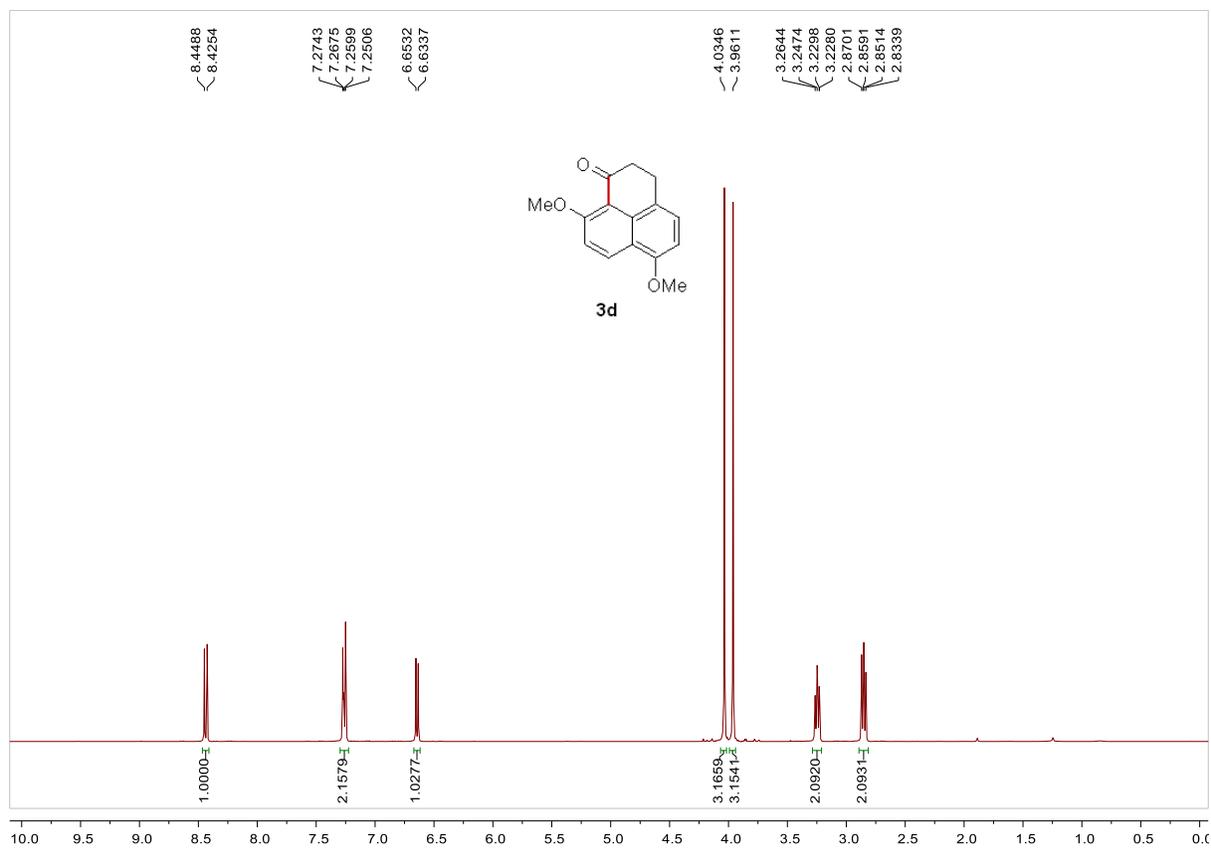


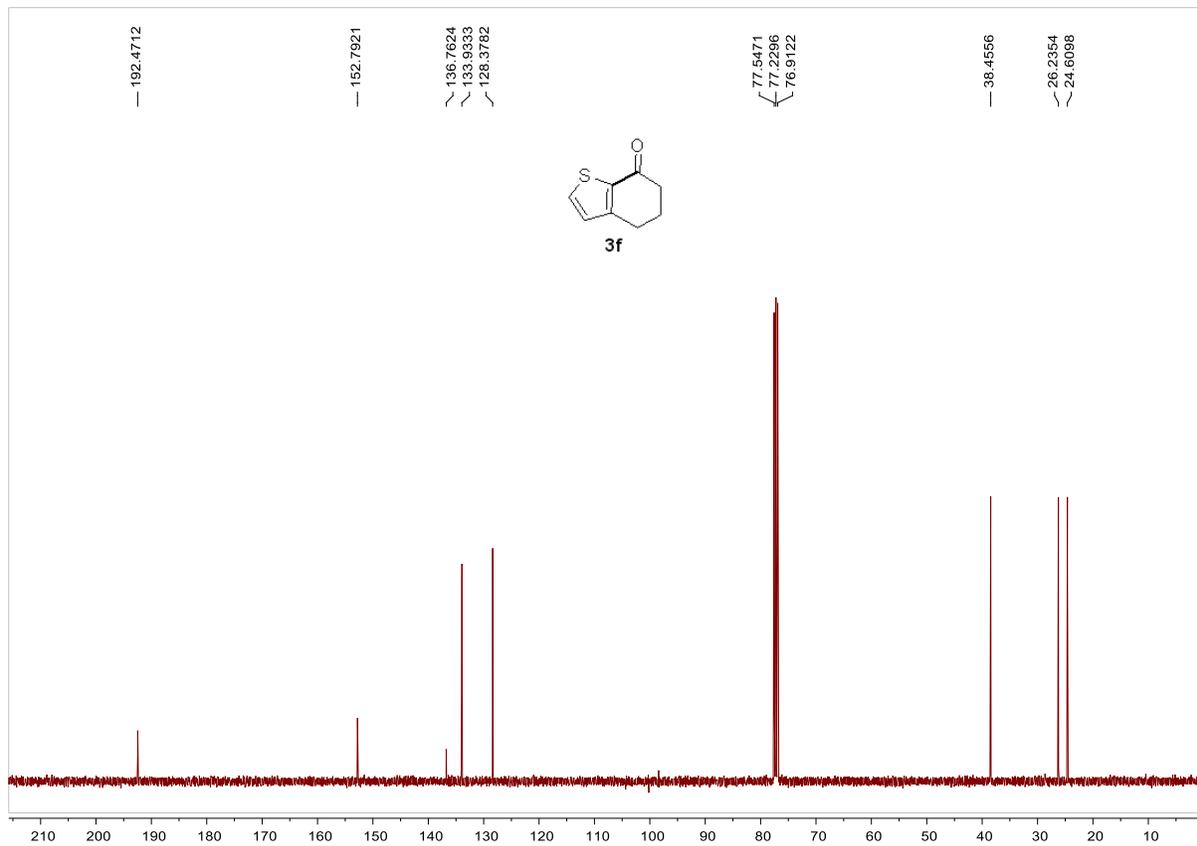
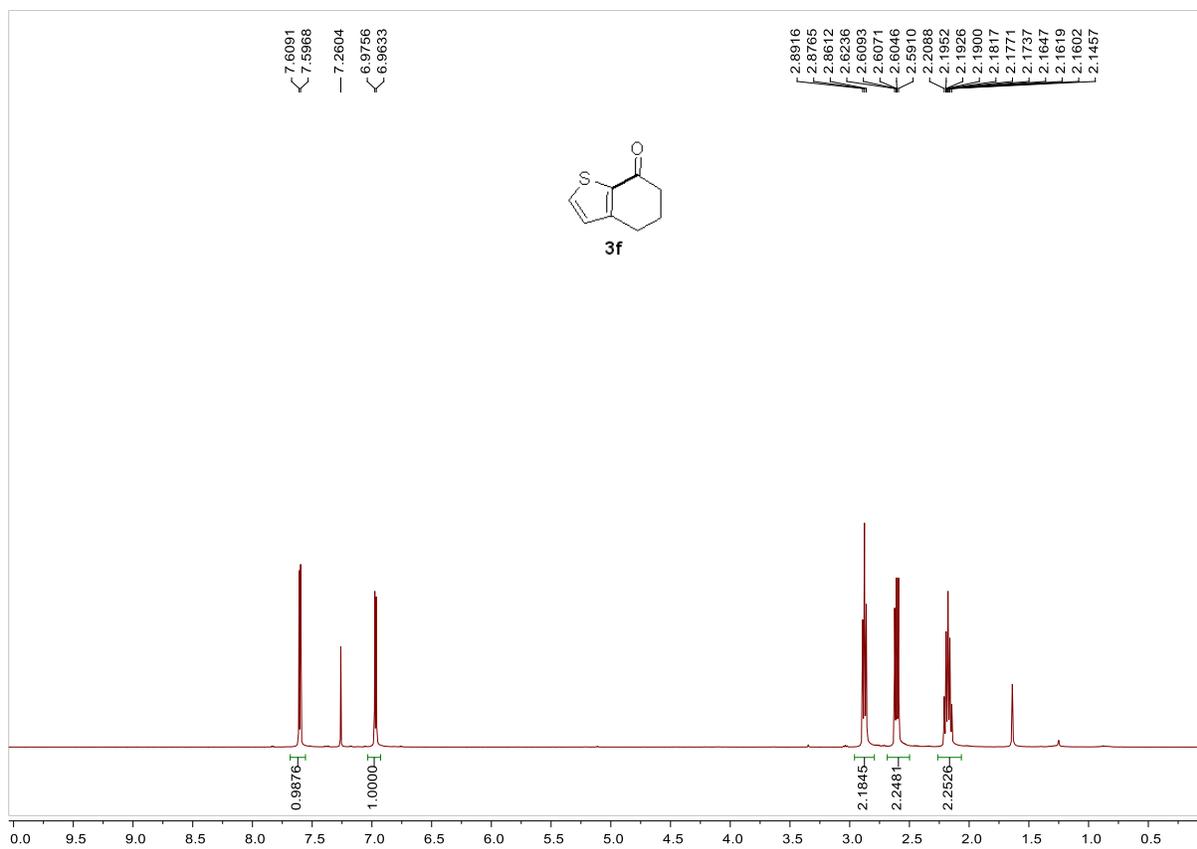


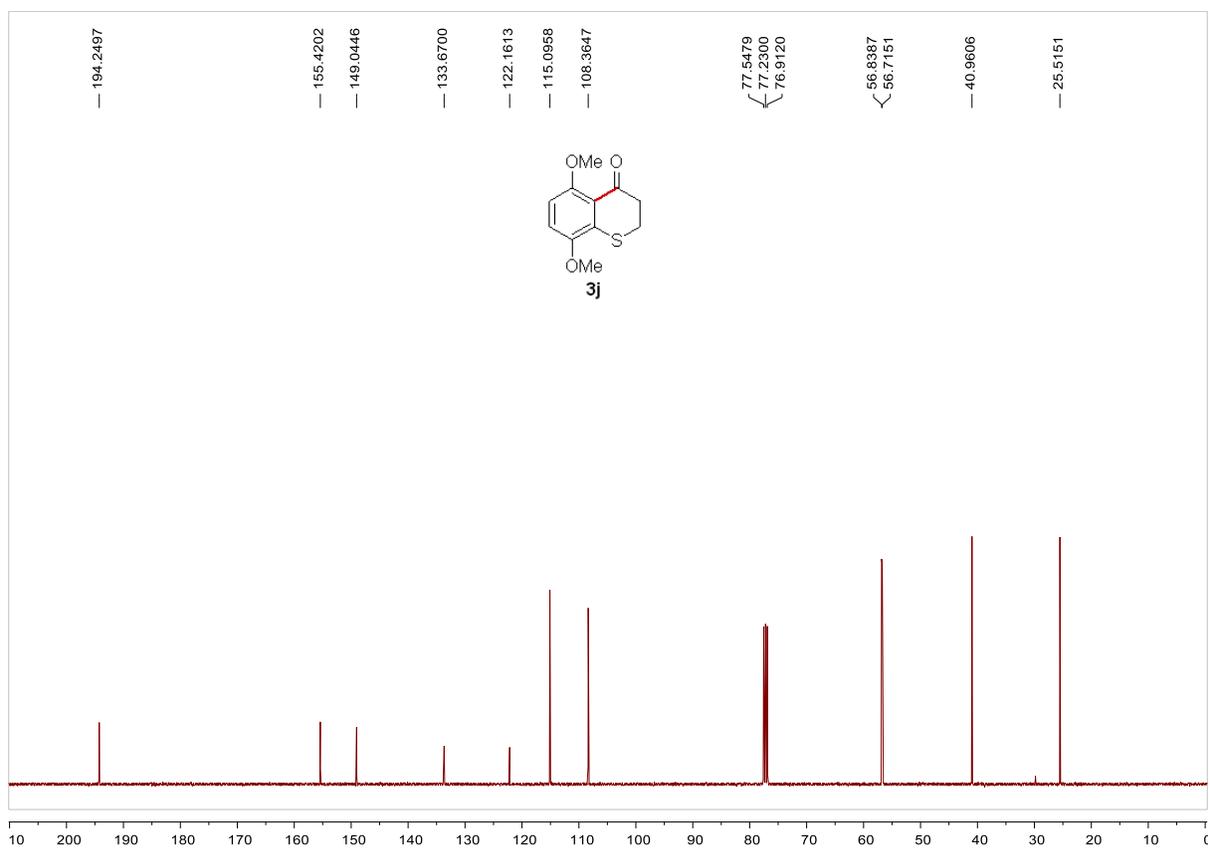
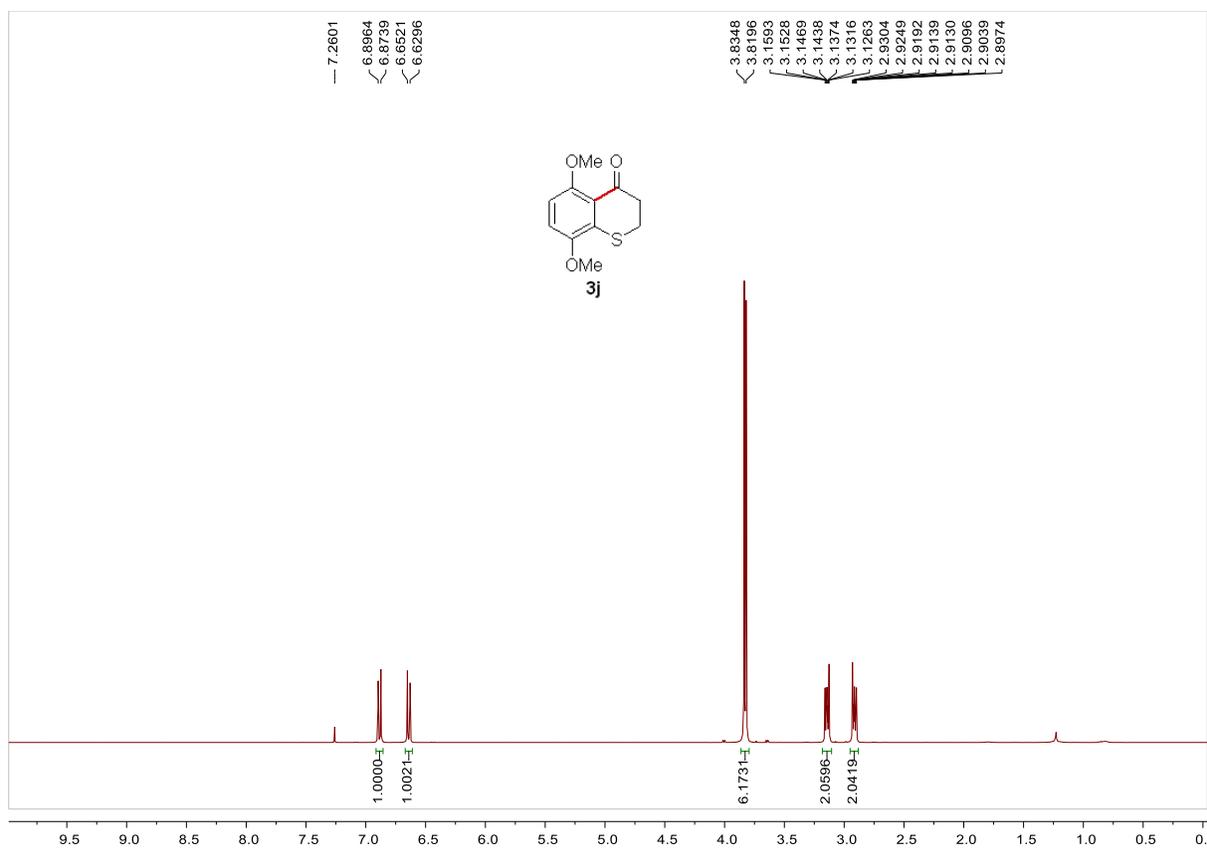


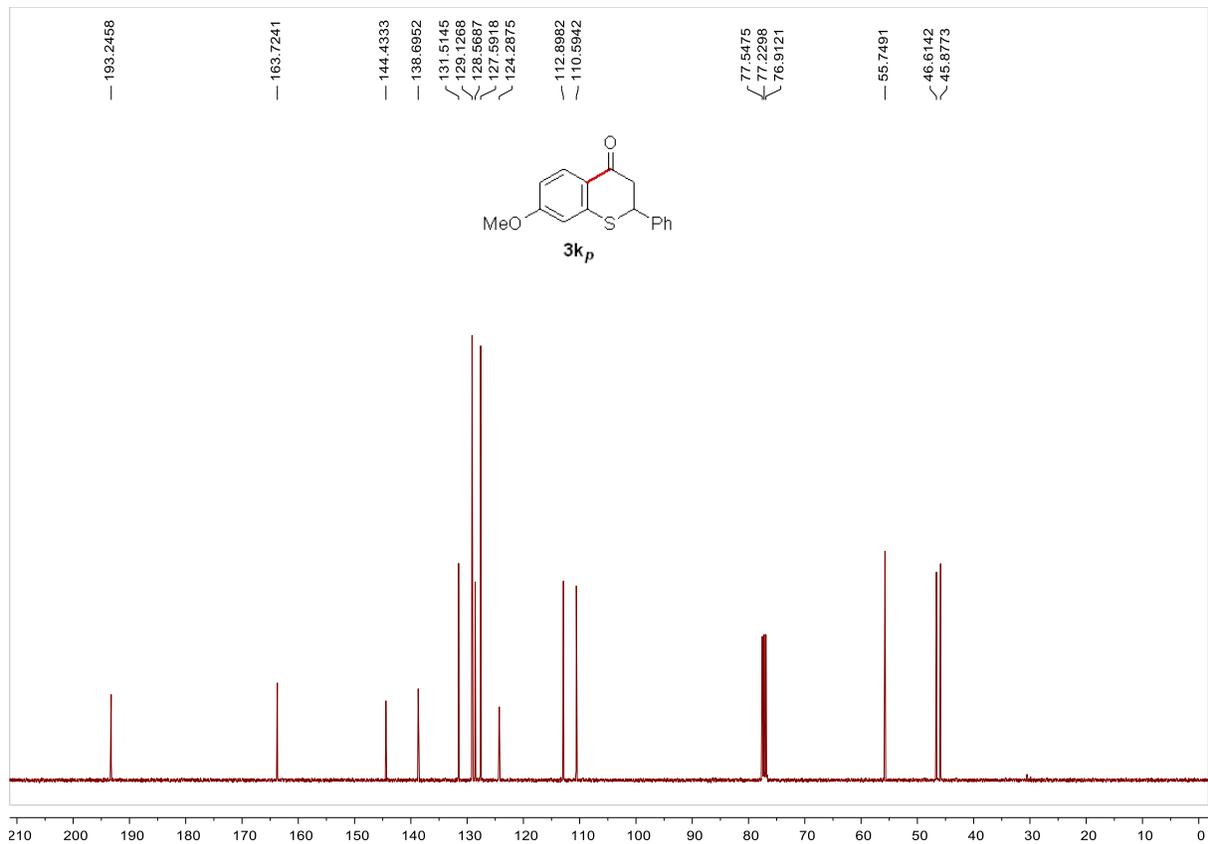
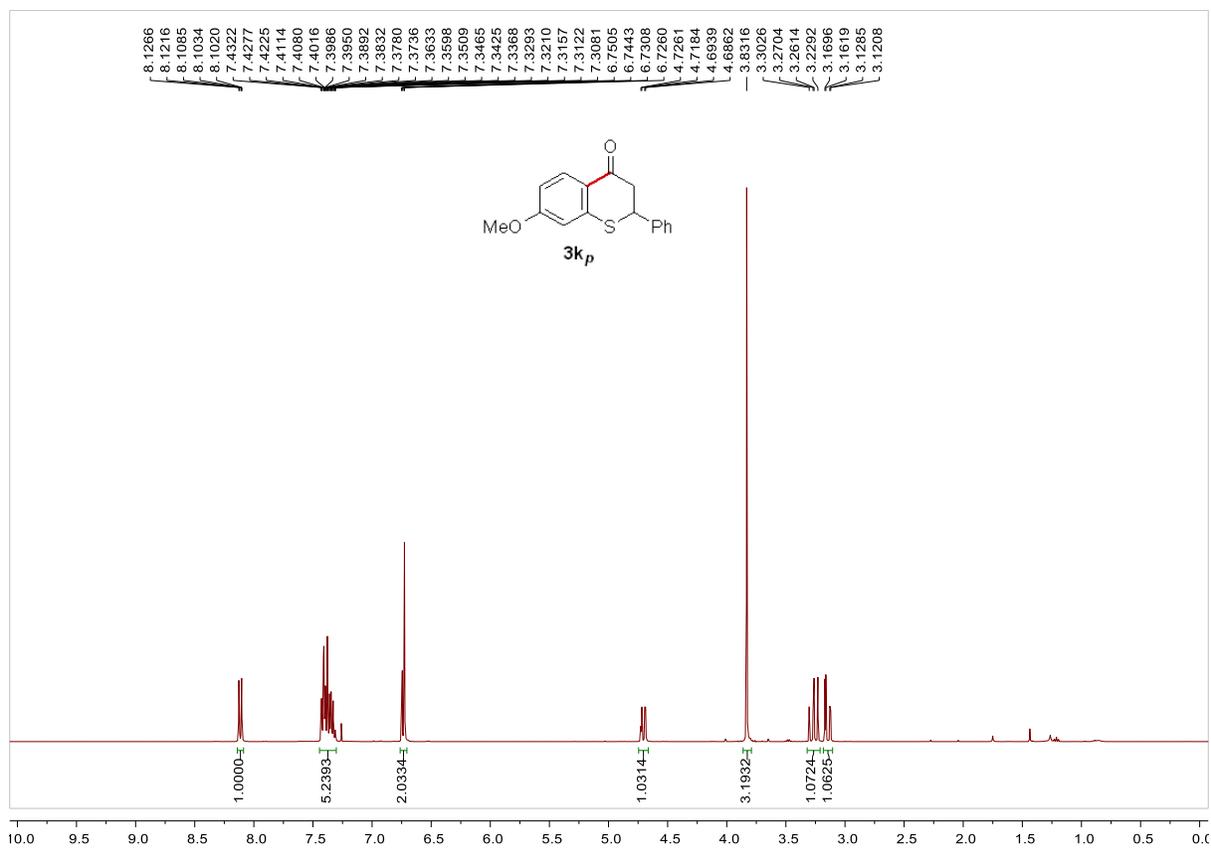
**$^1\text{H}$  and  $^{13}\text{C}$  Spectra of Newly Reported Ketones**

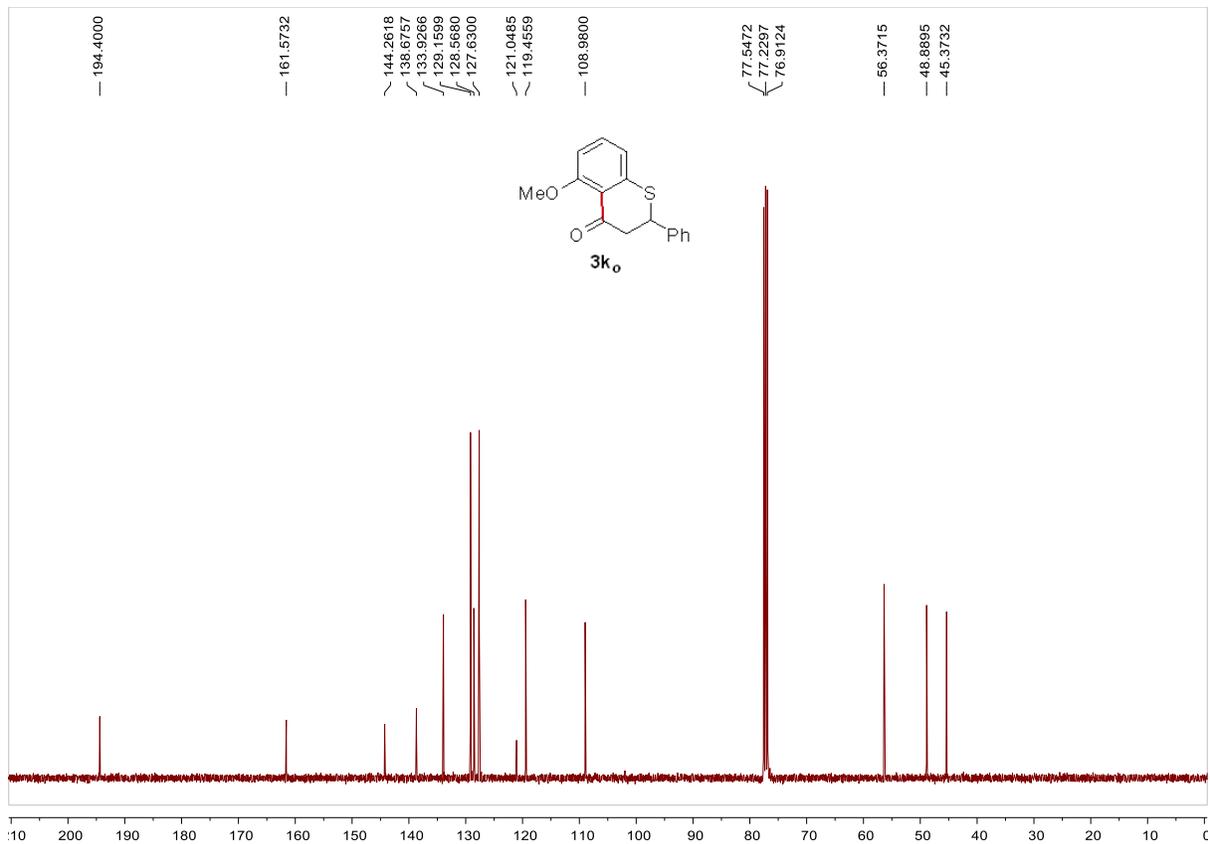
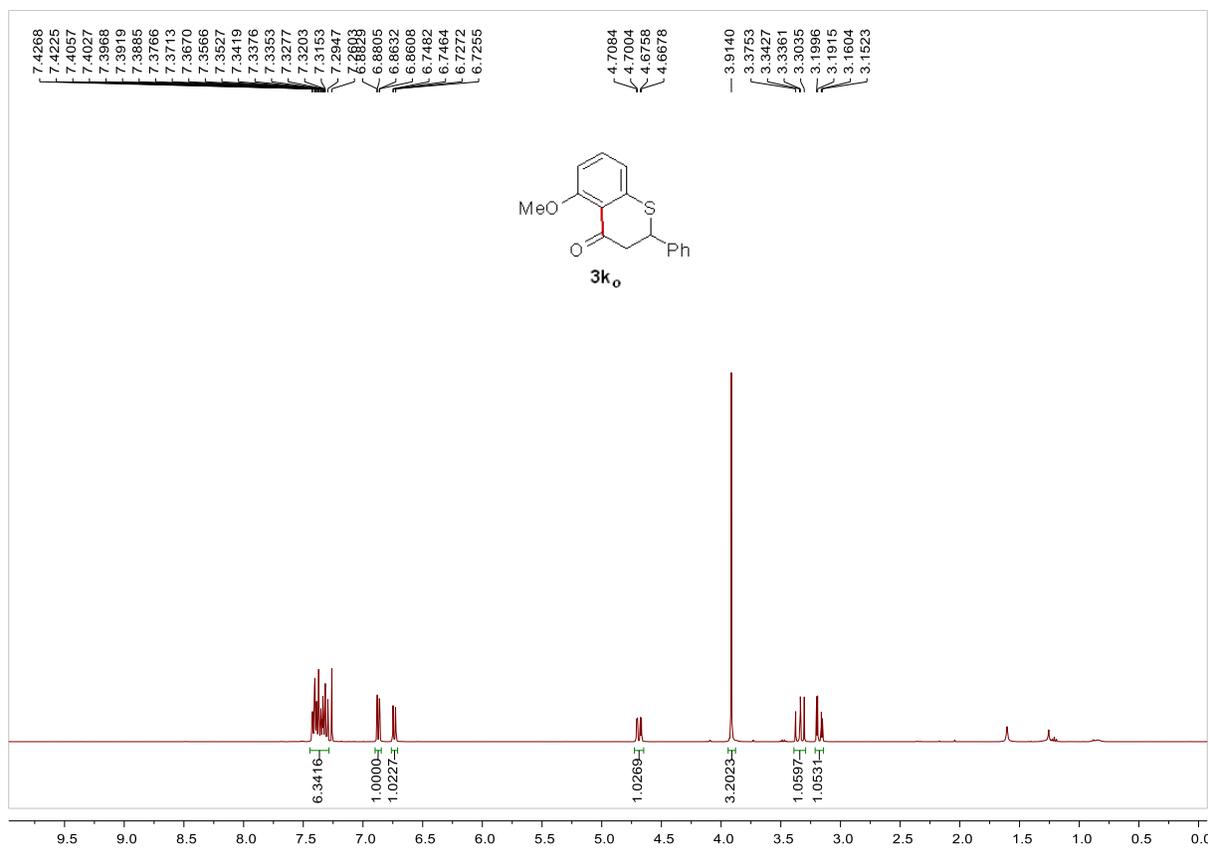


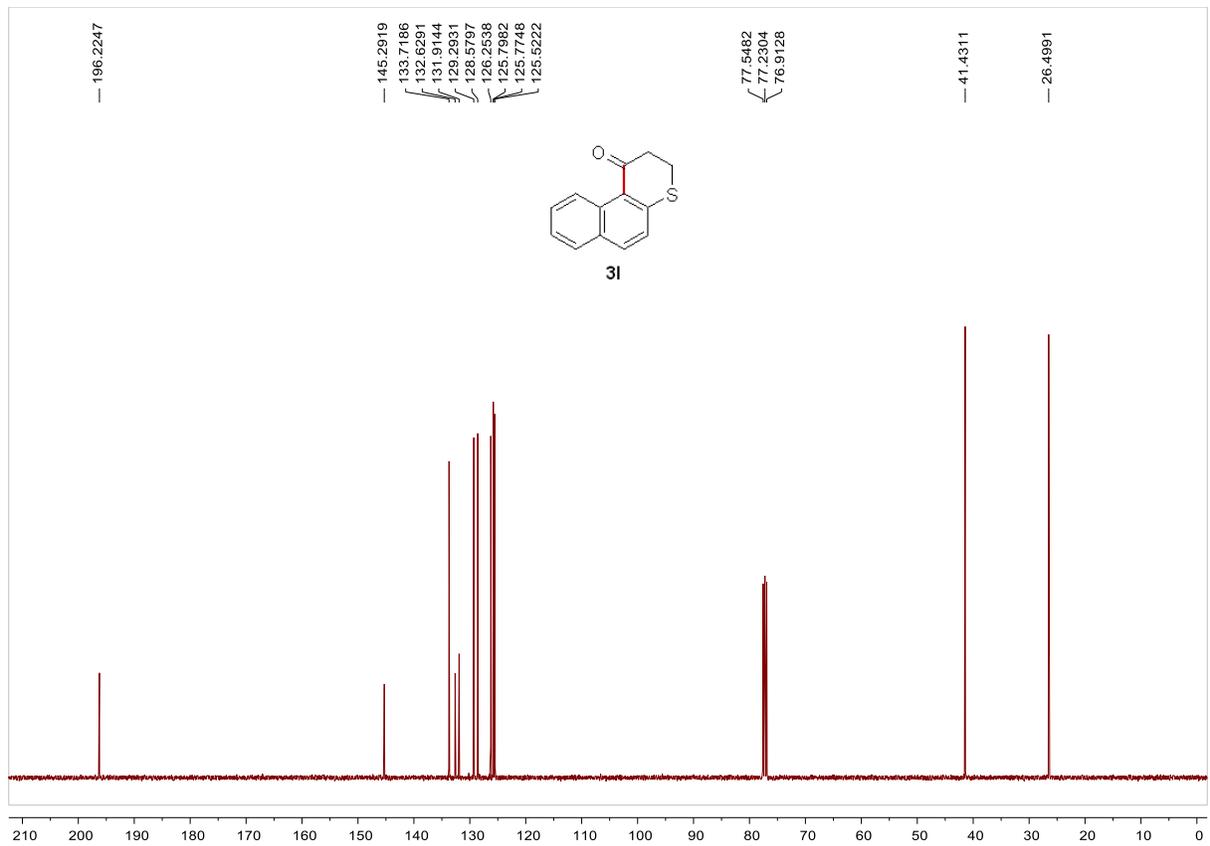
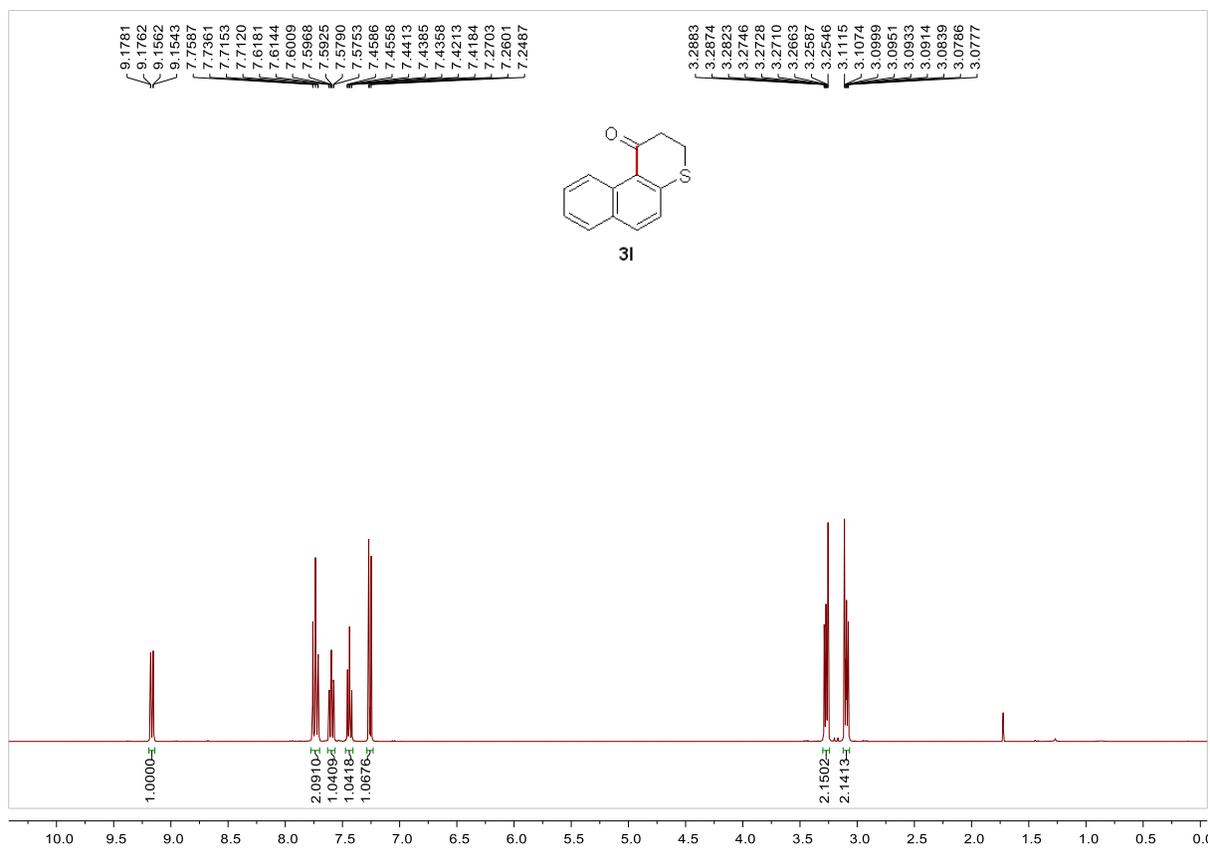


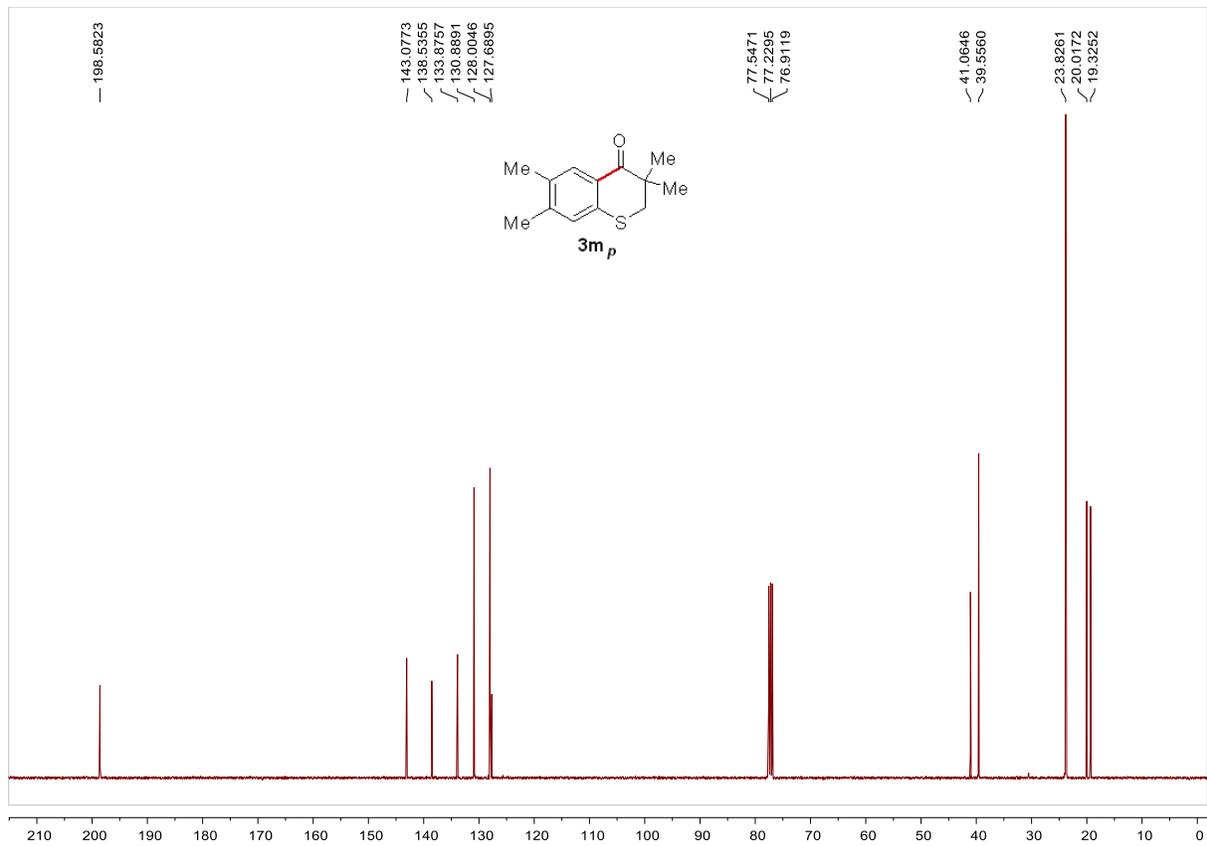
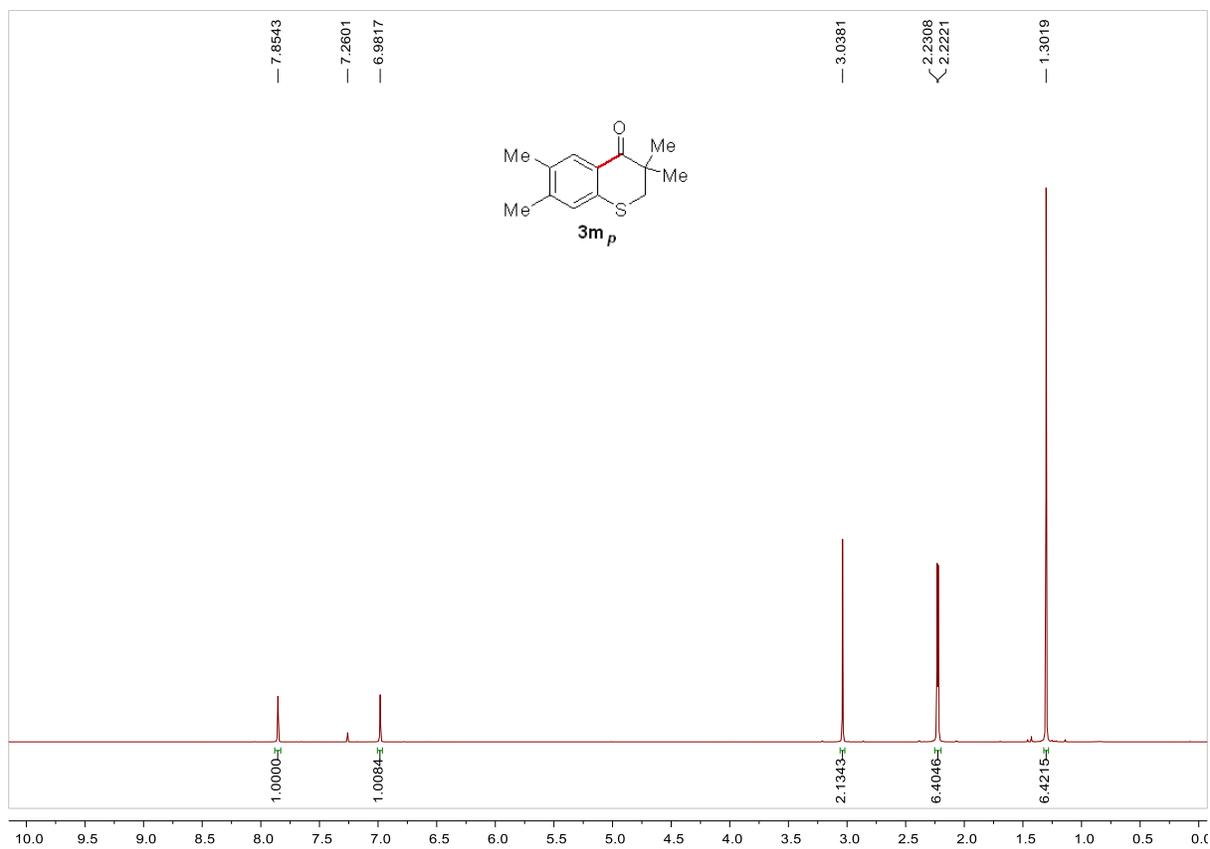


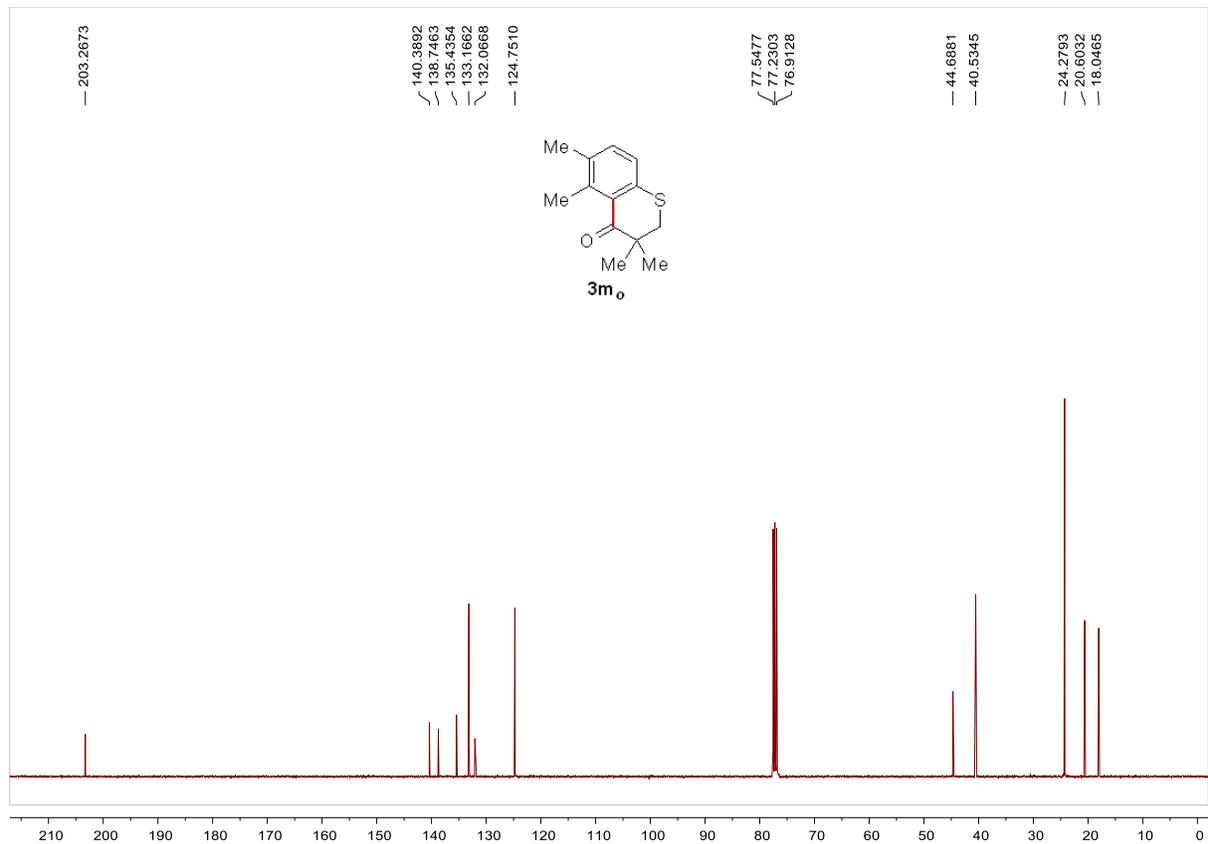
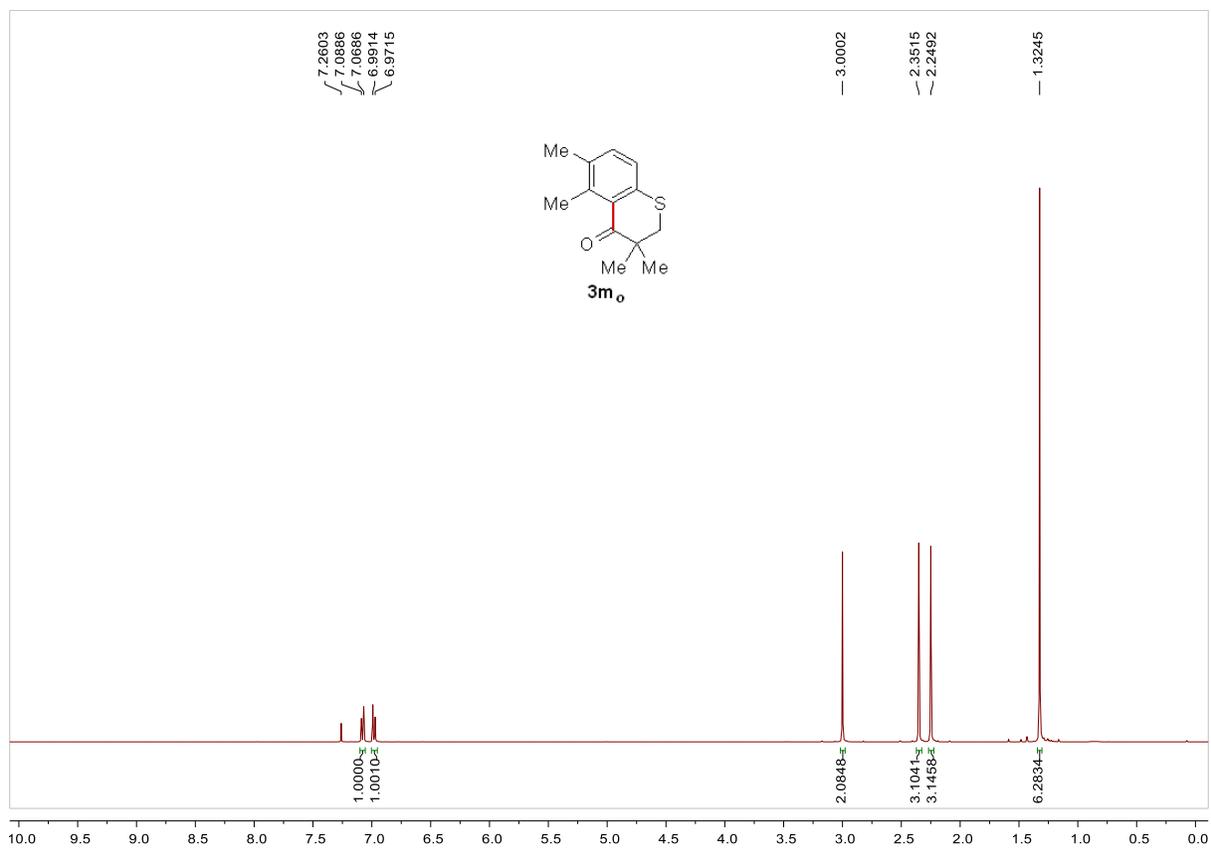


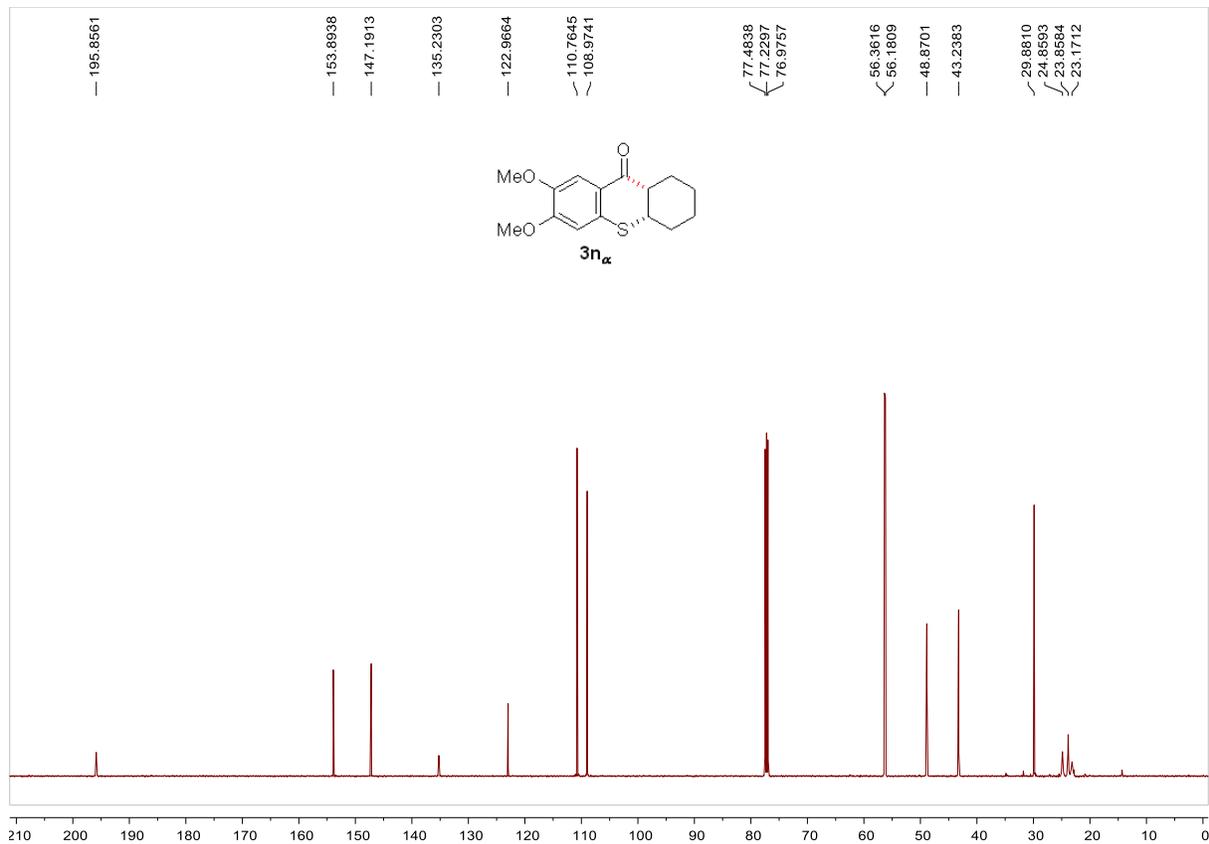
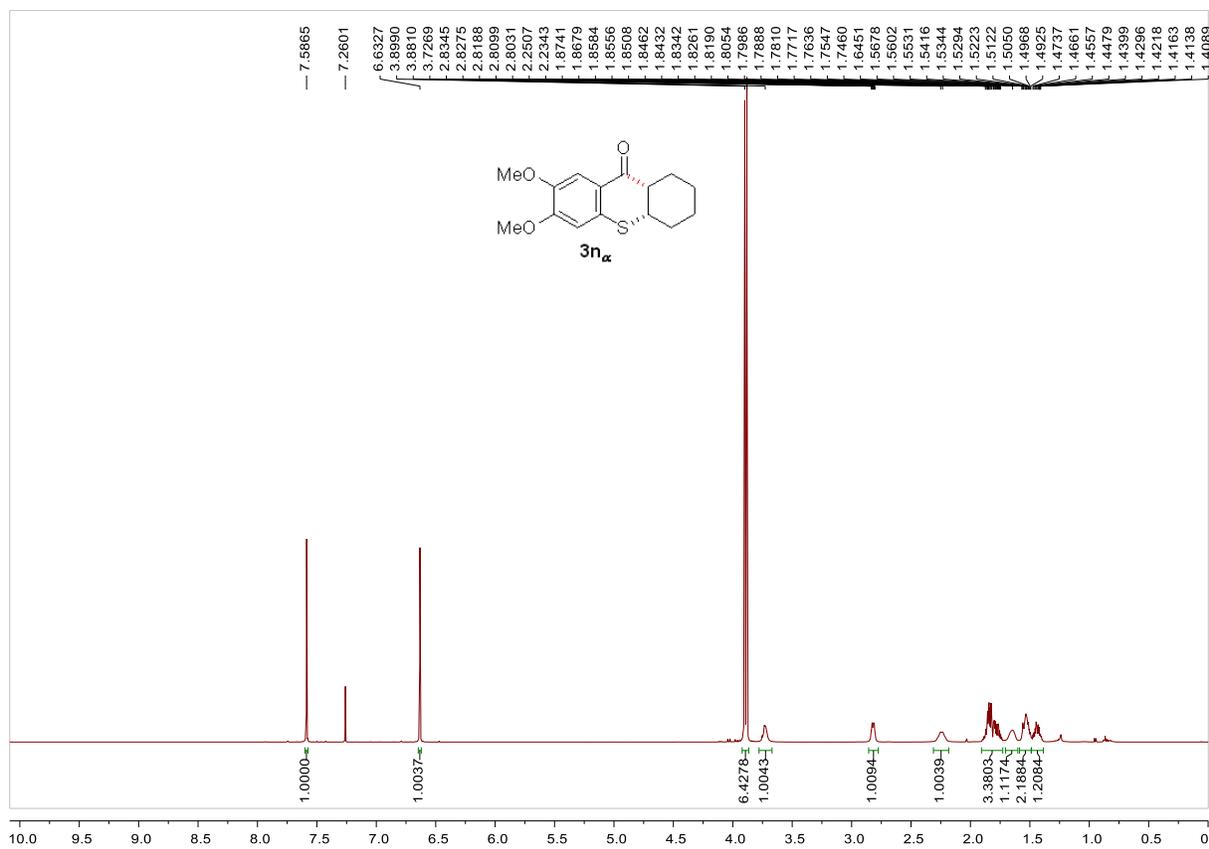


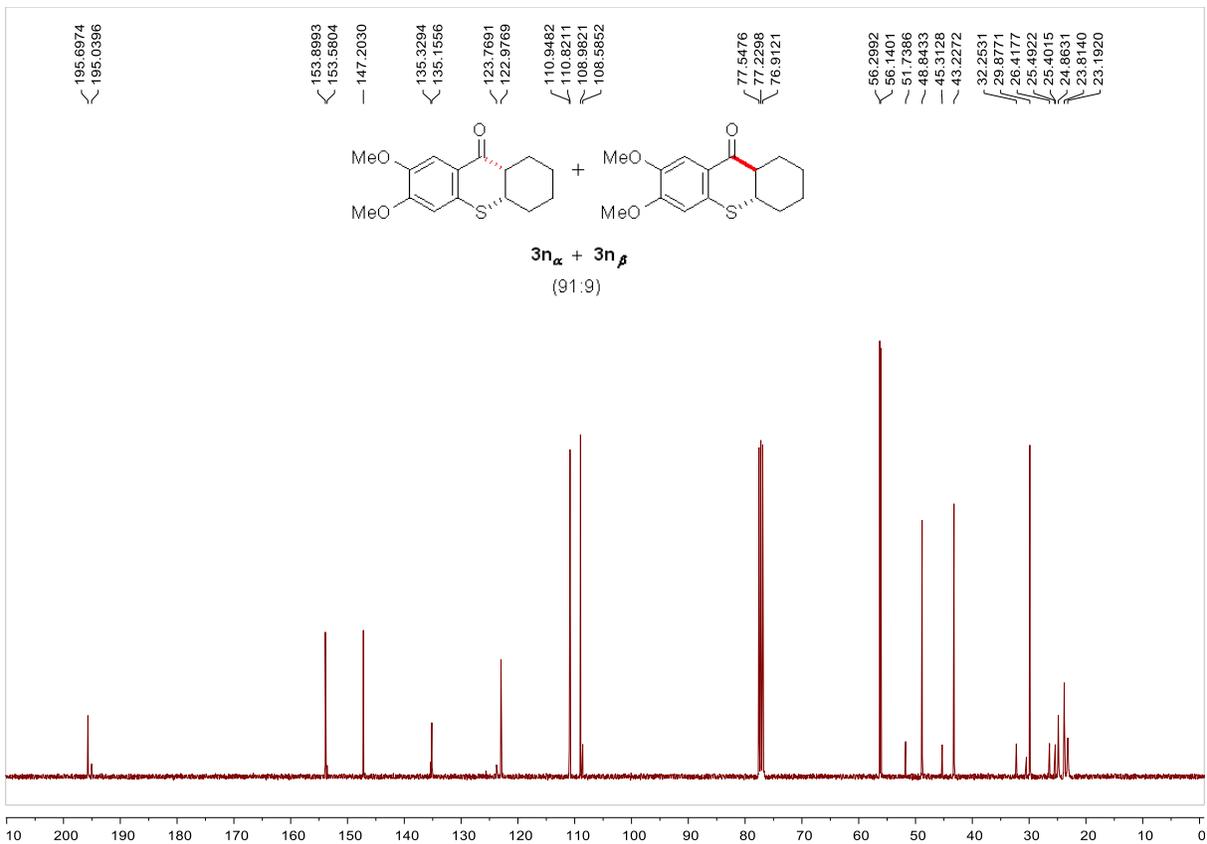
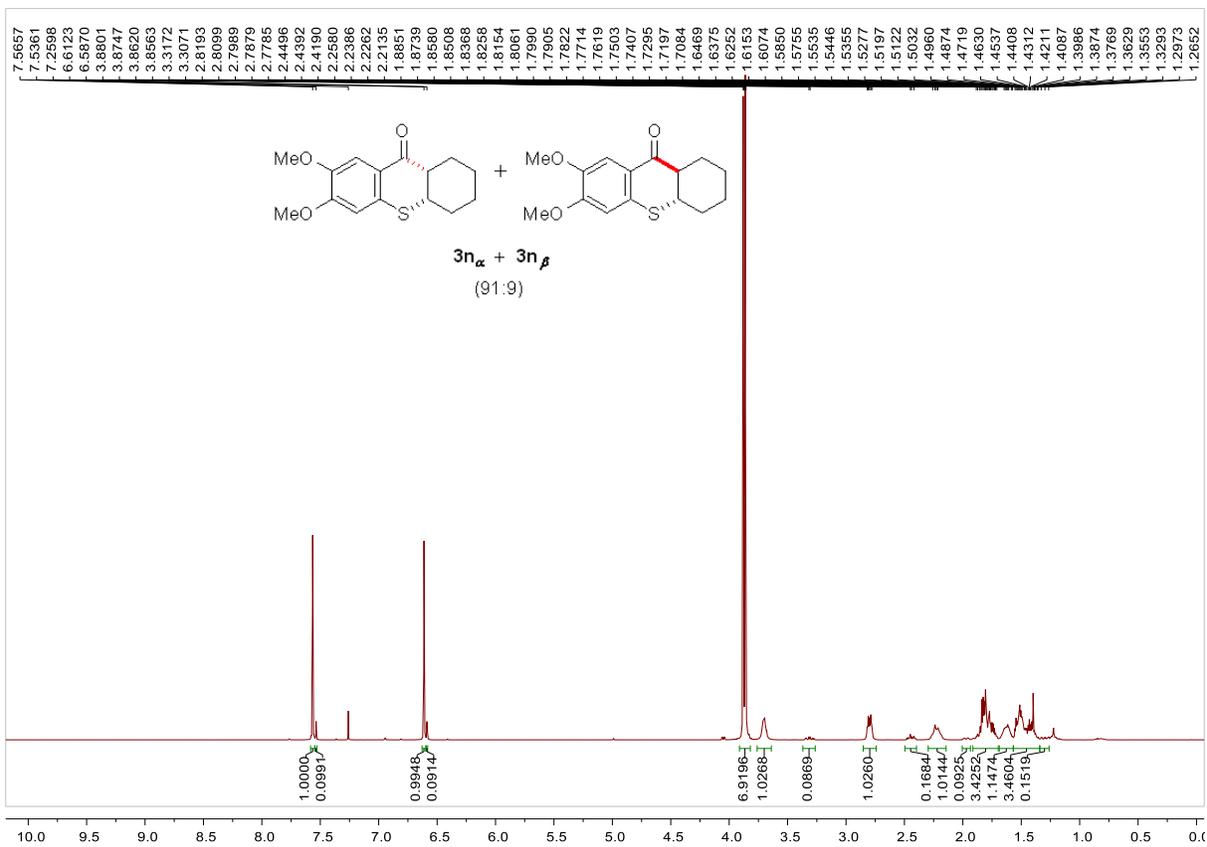


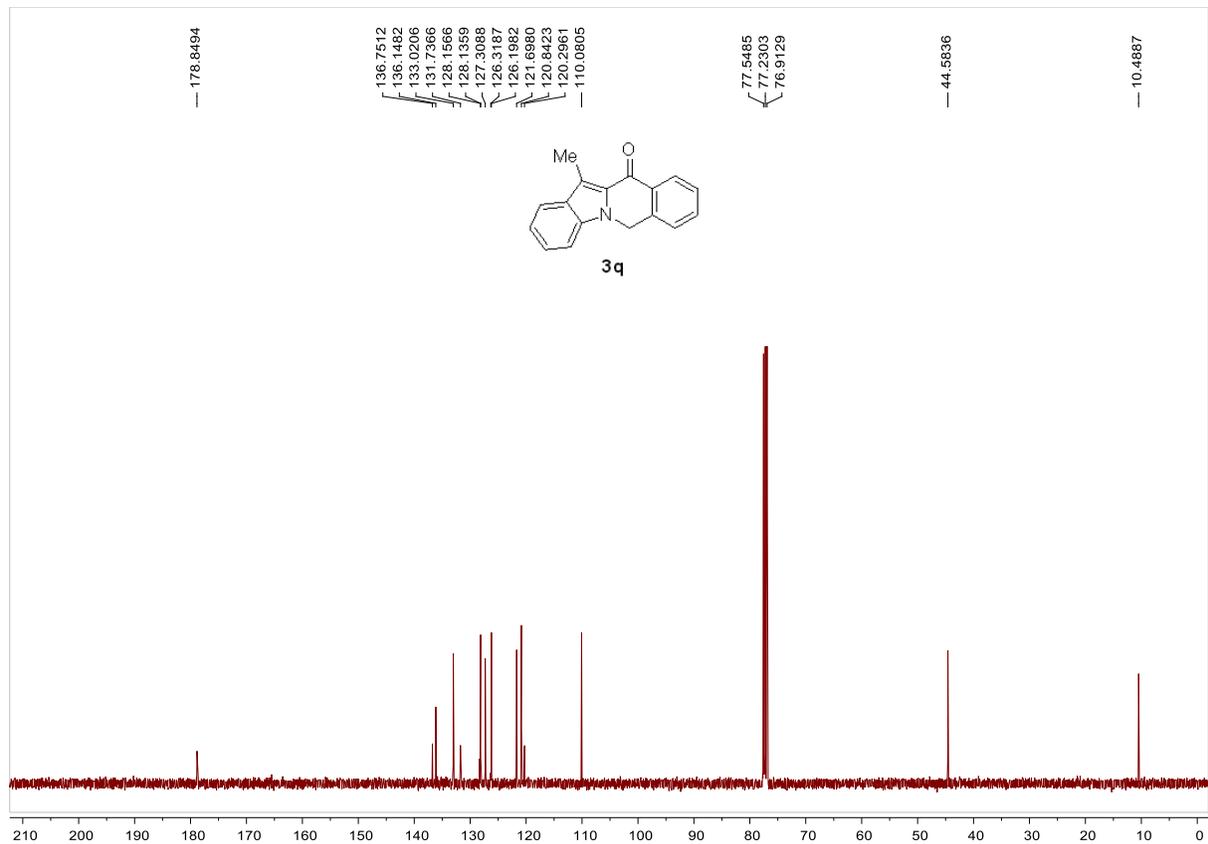
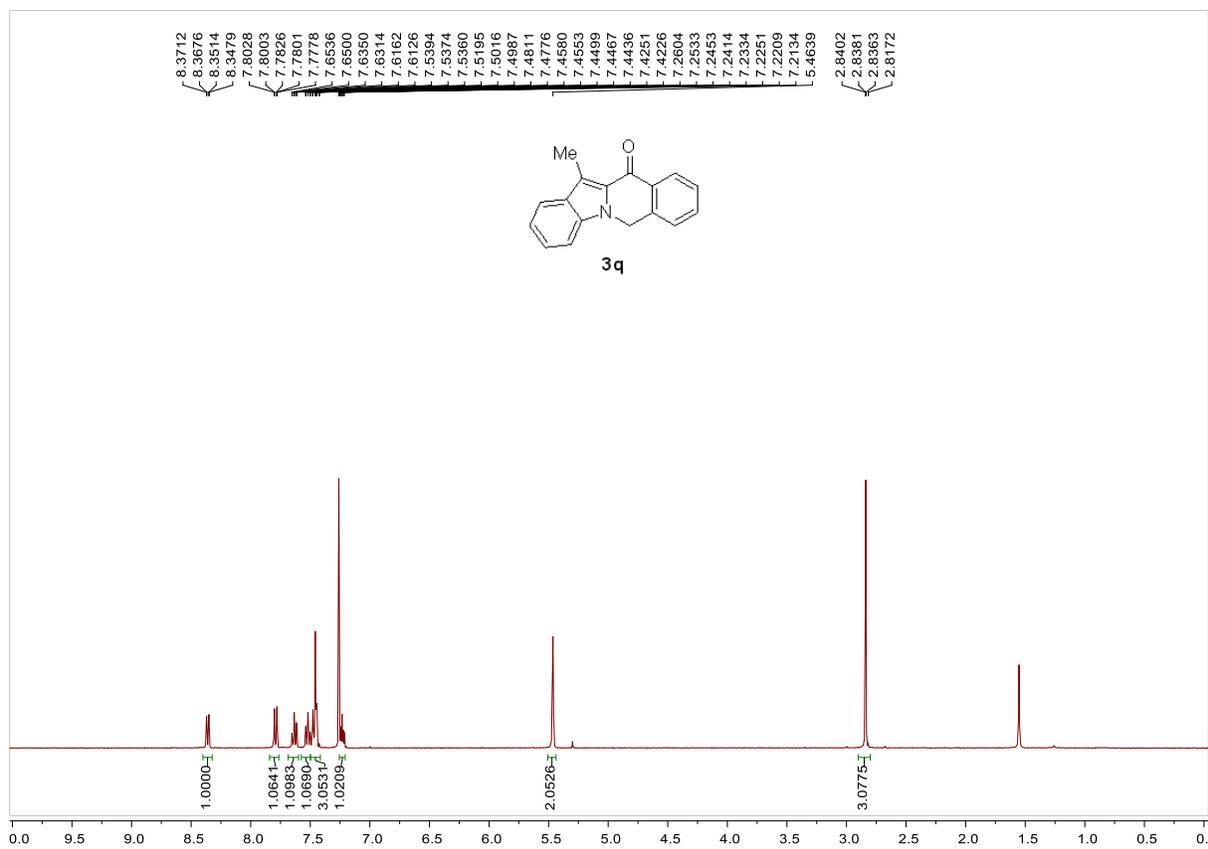


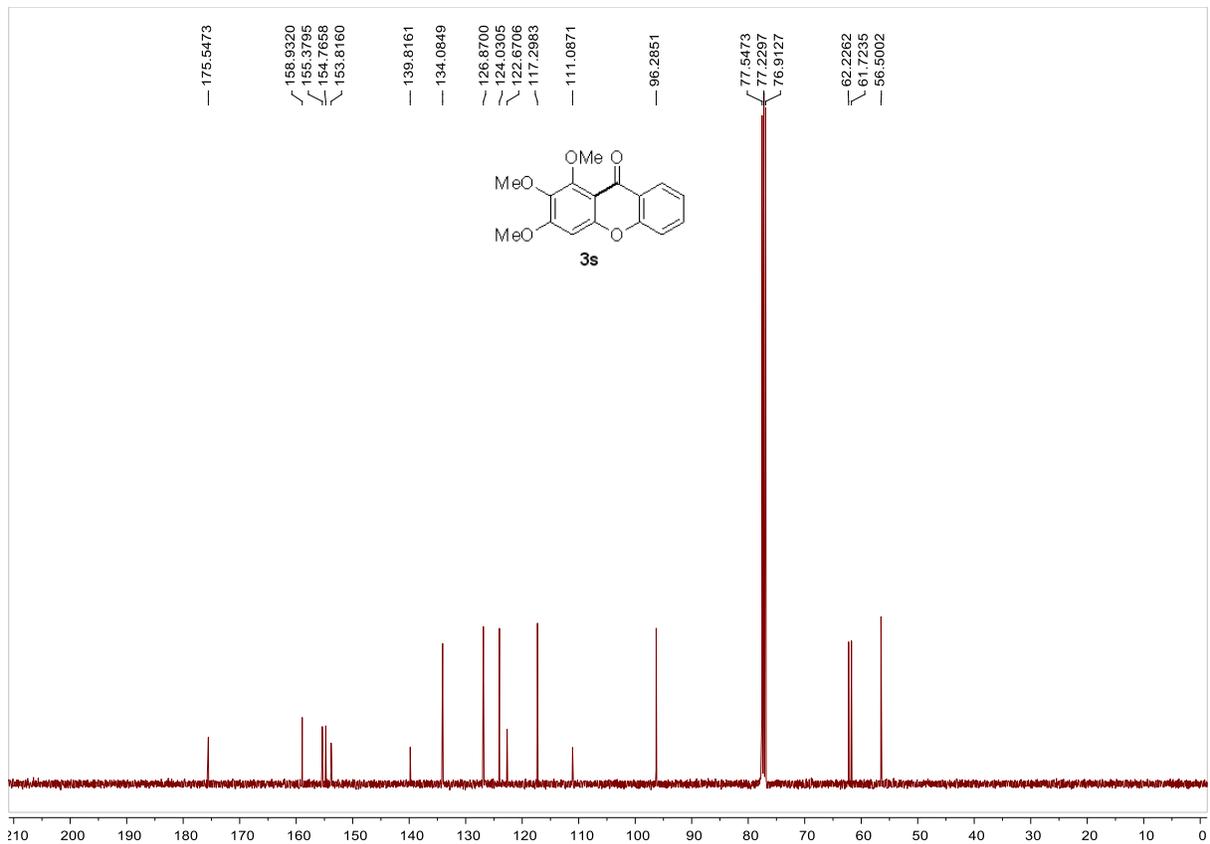
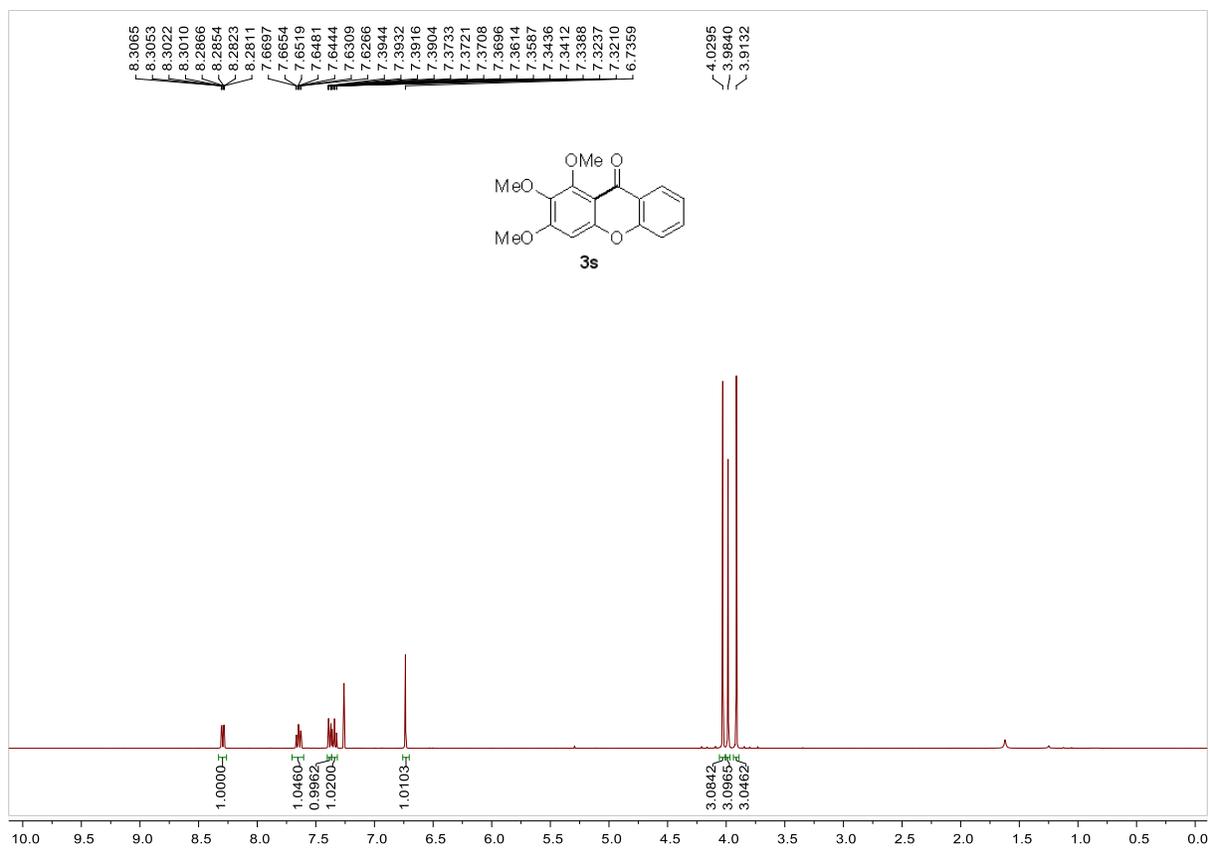


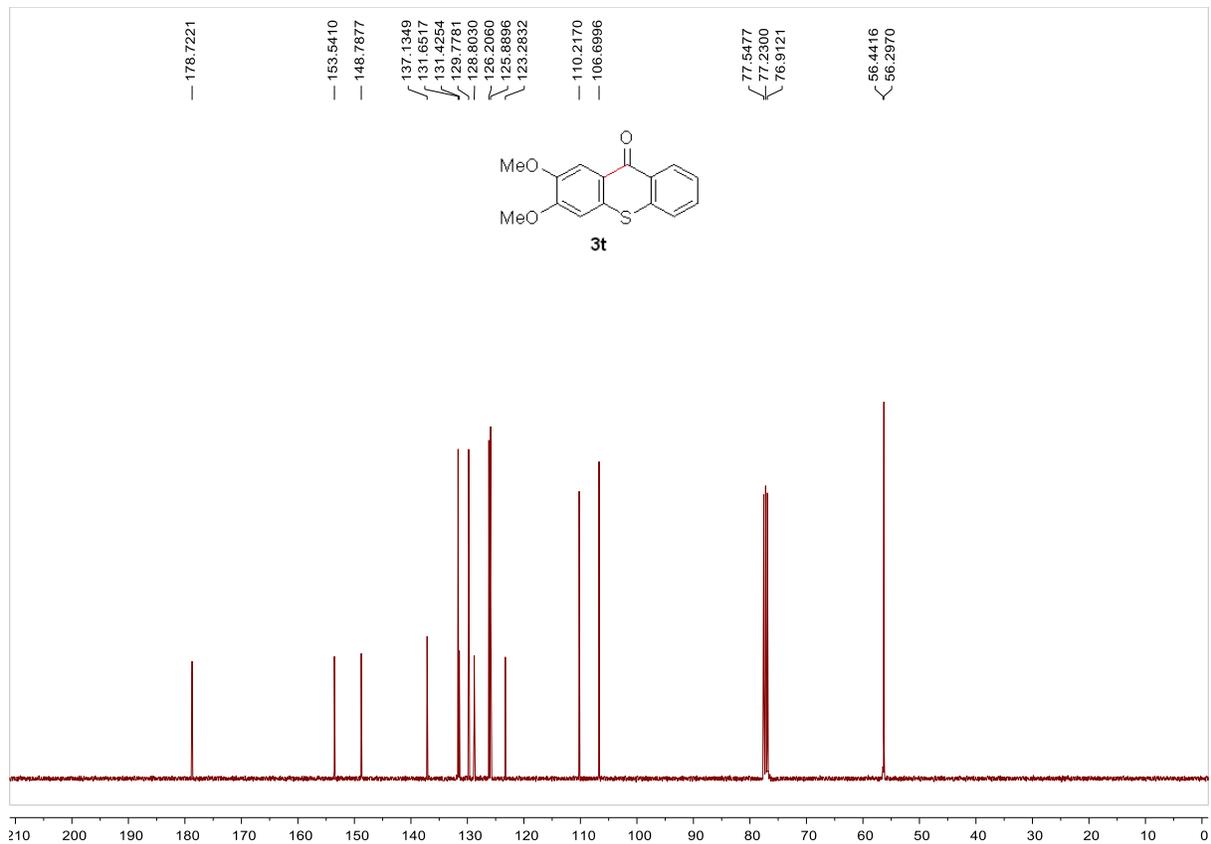
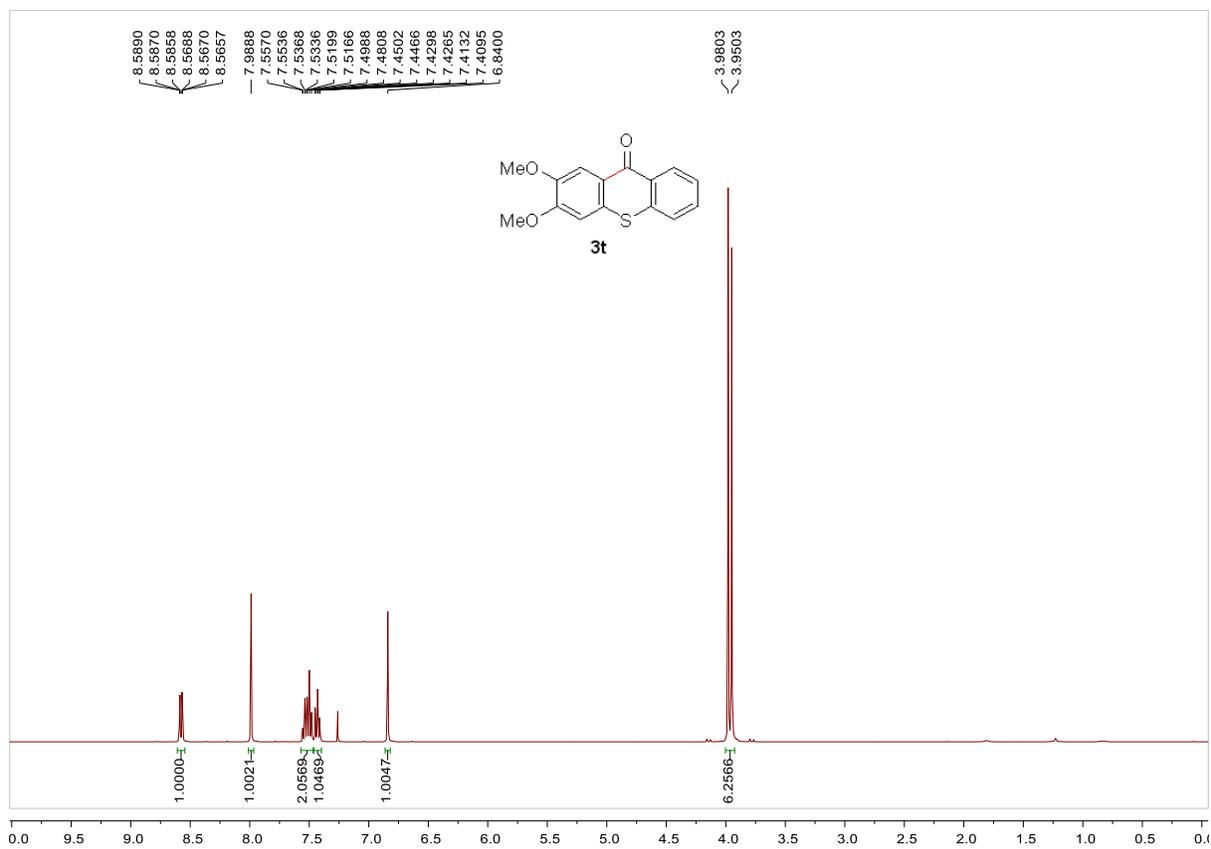


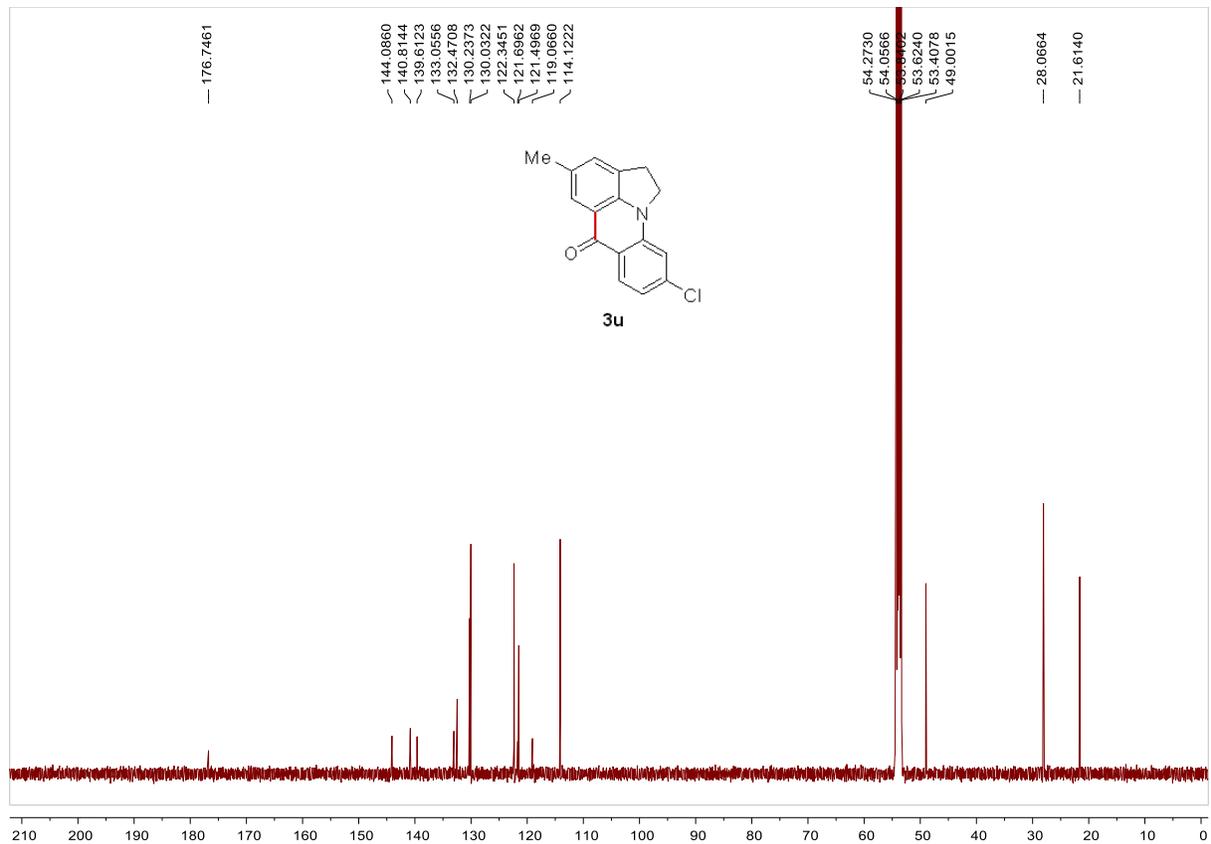
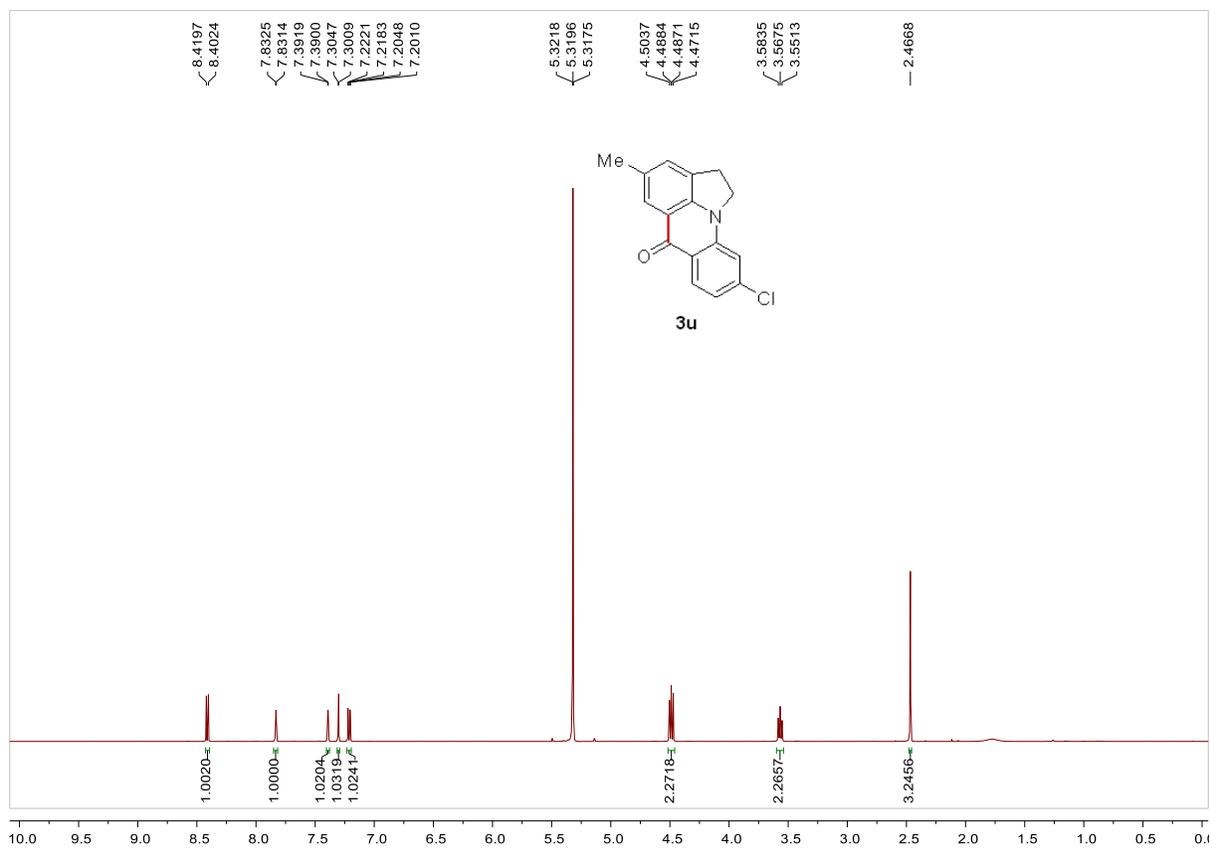


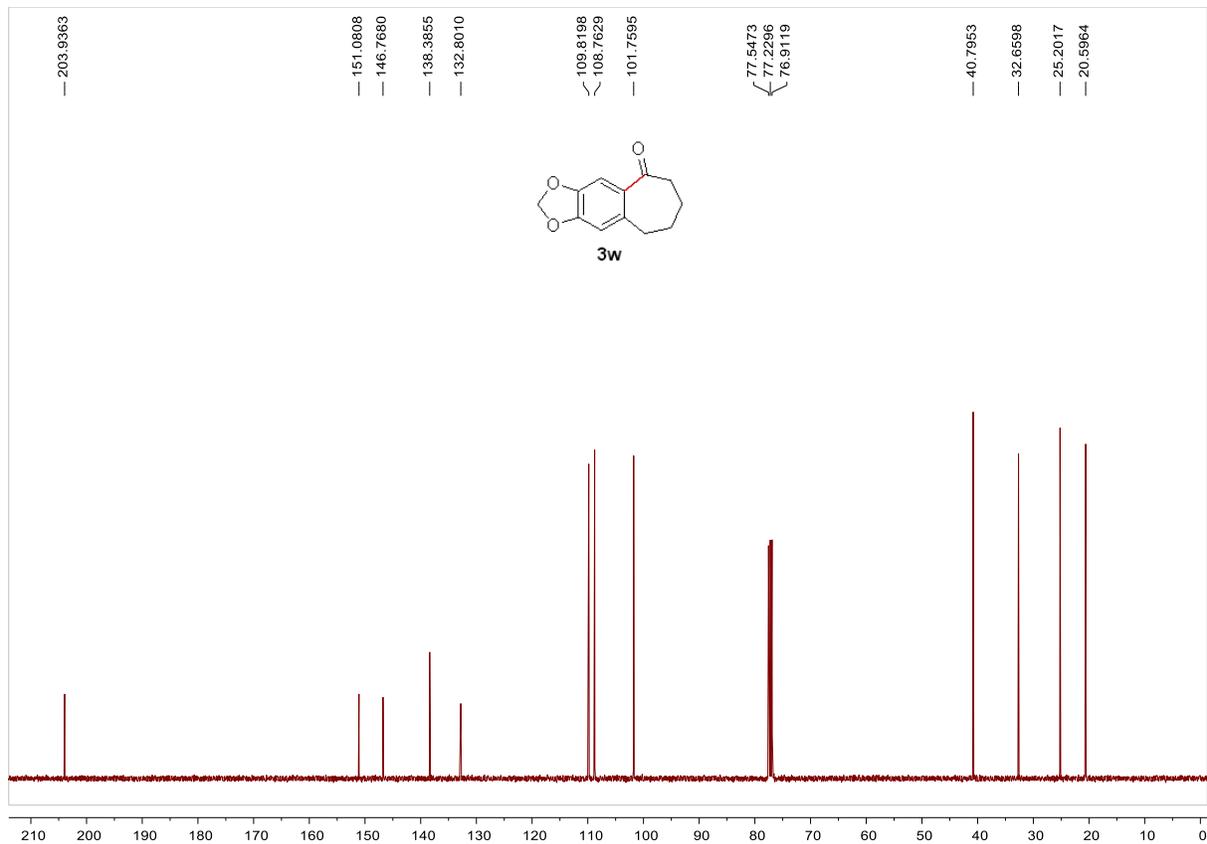
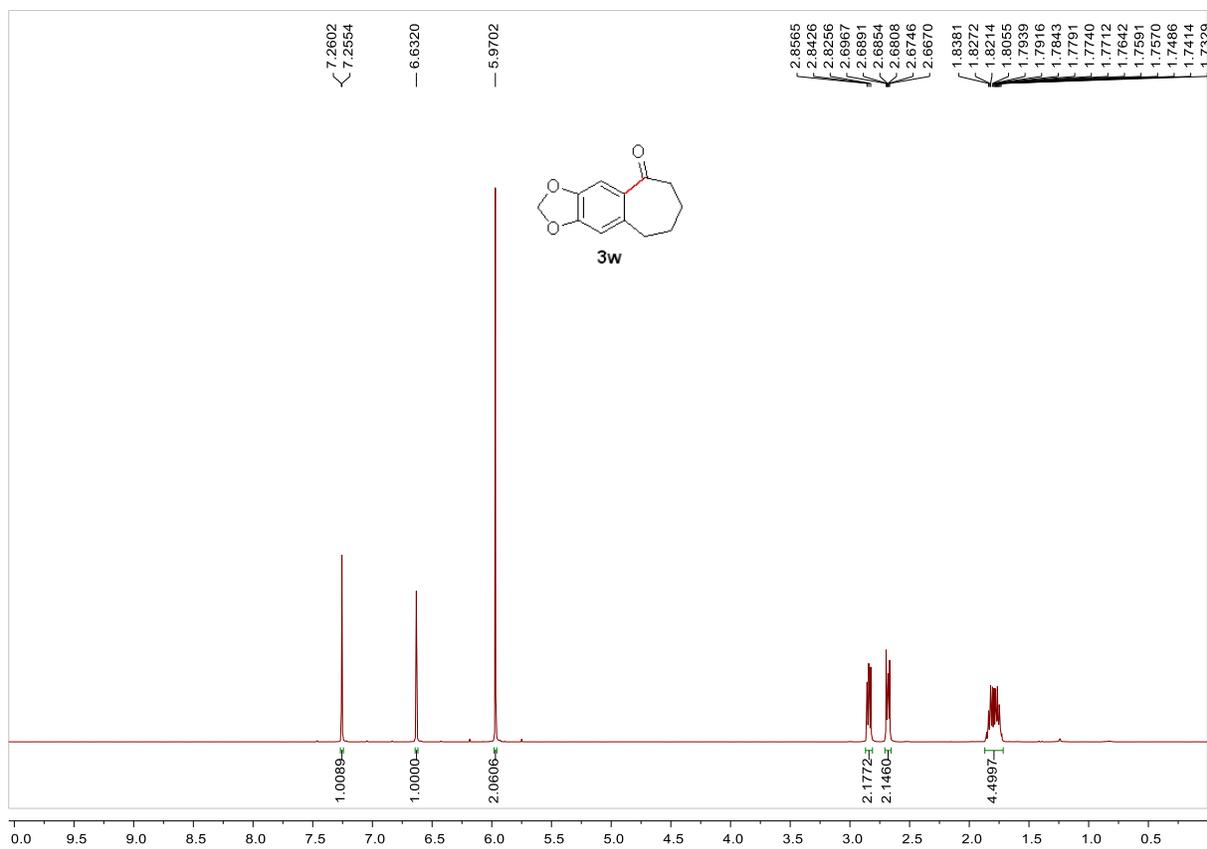


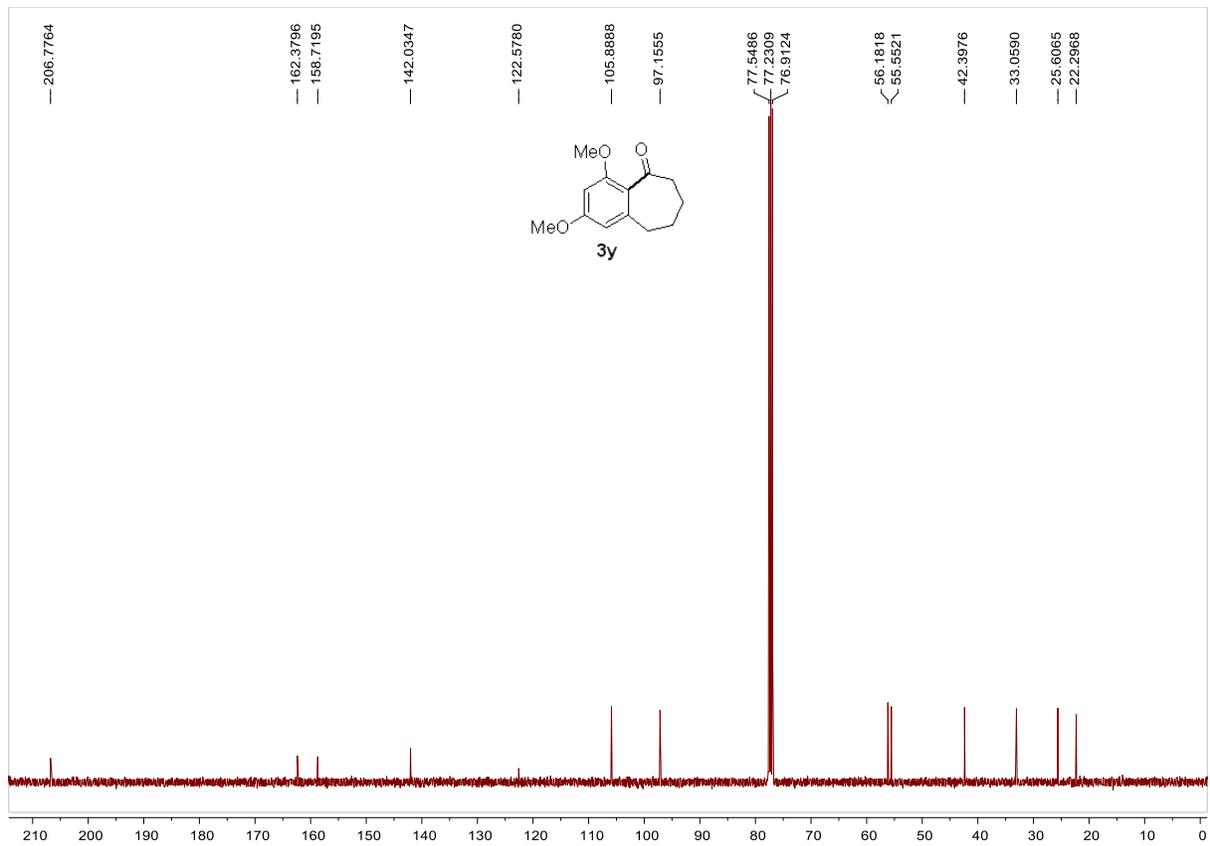
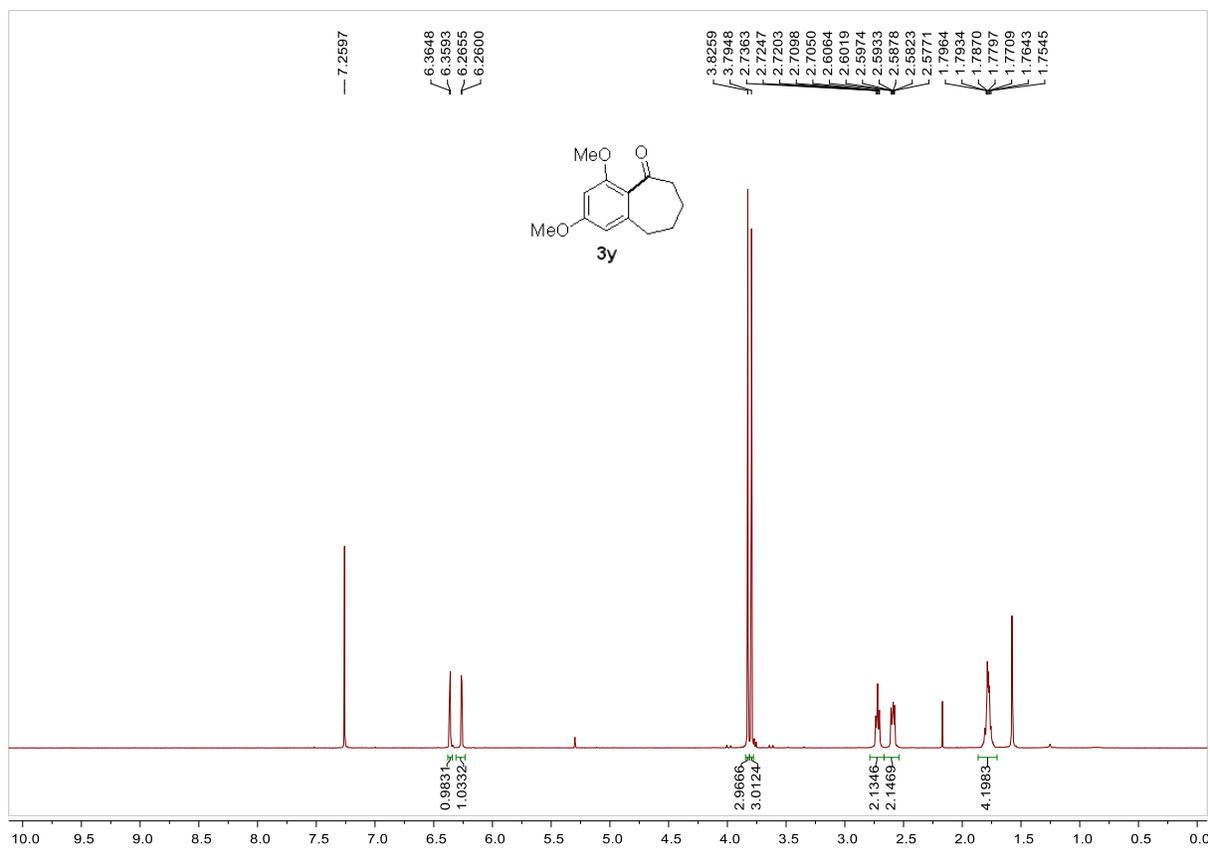


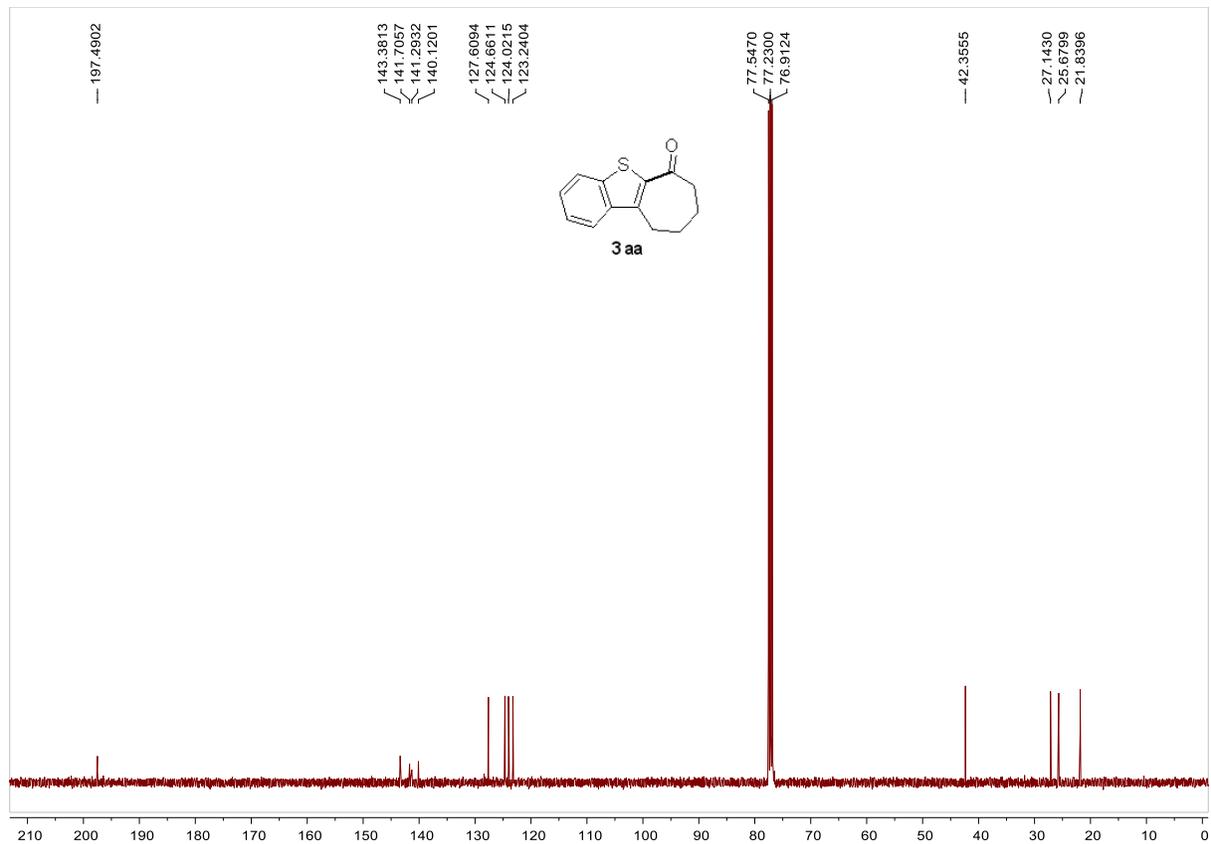
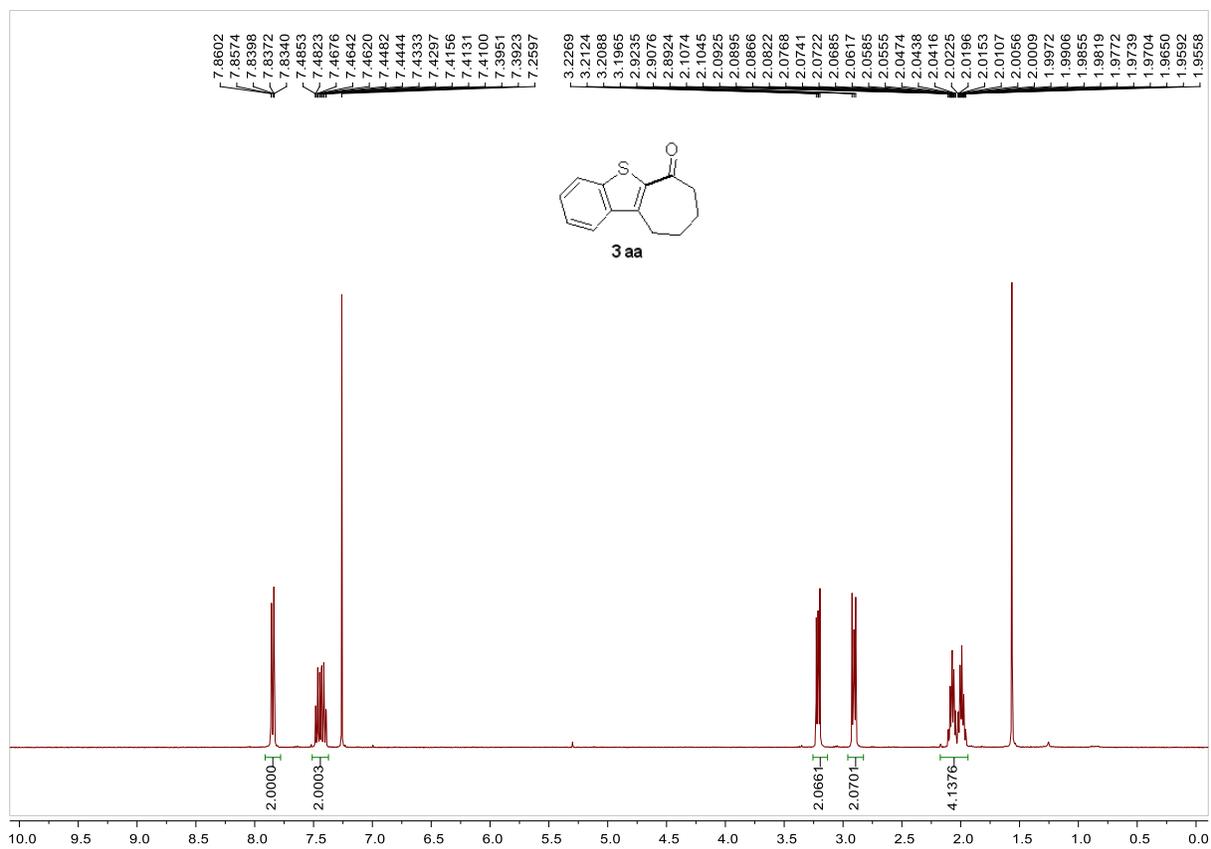


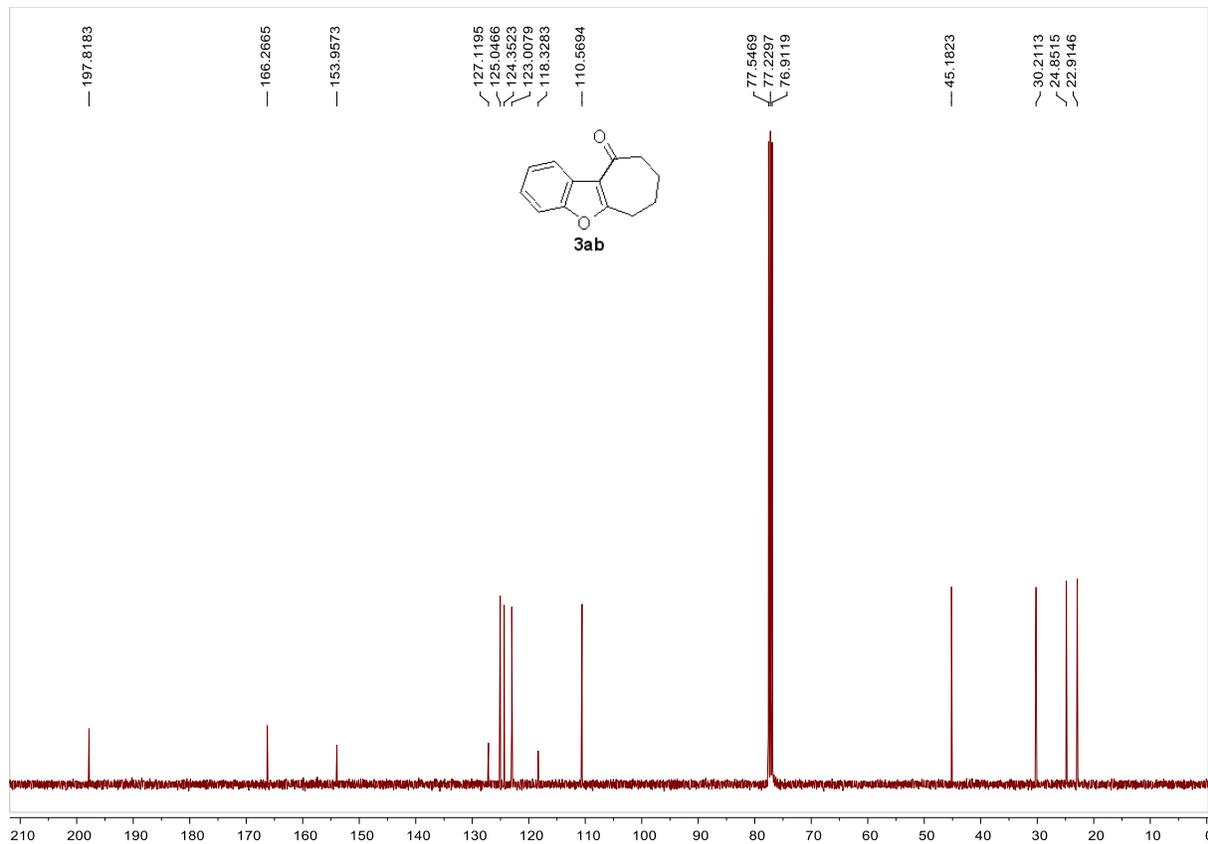
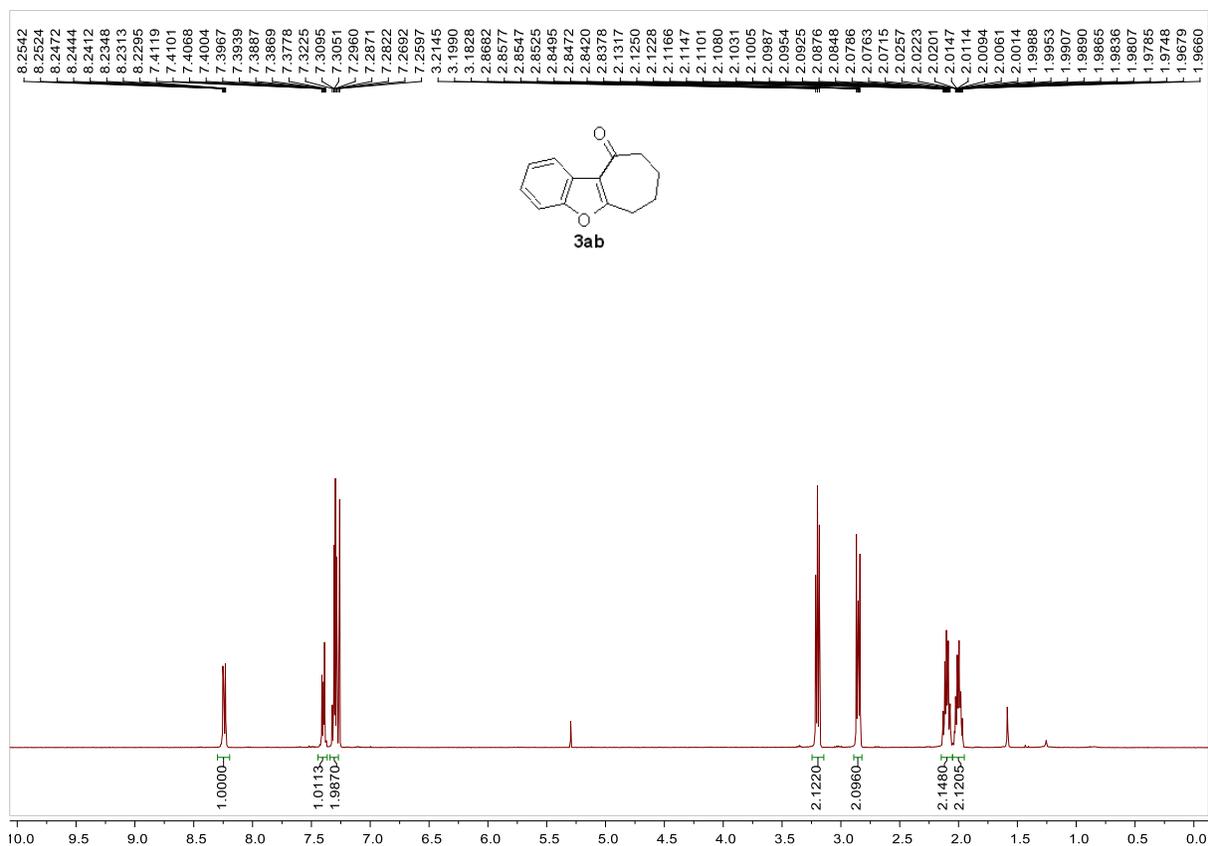


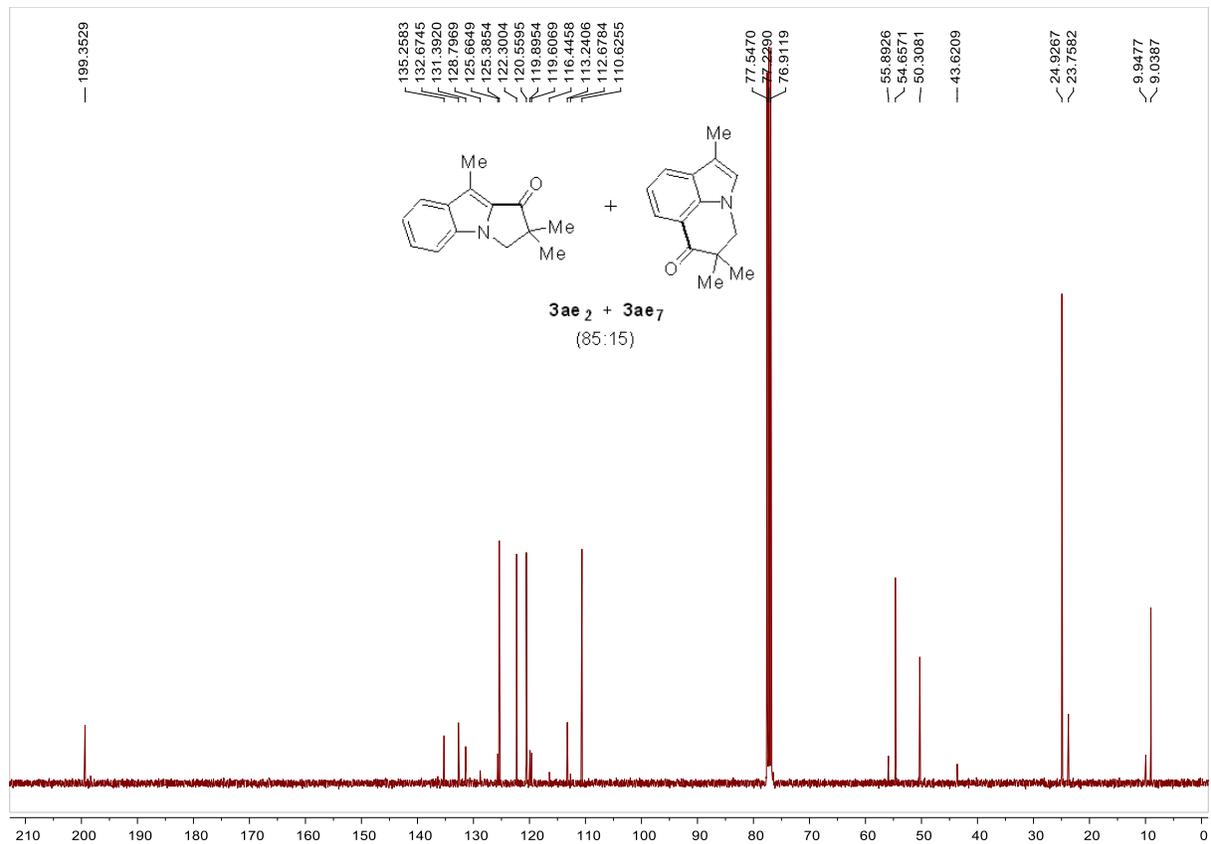
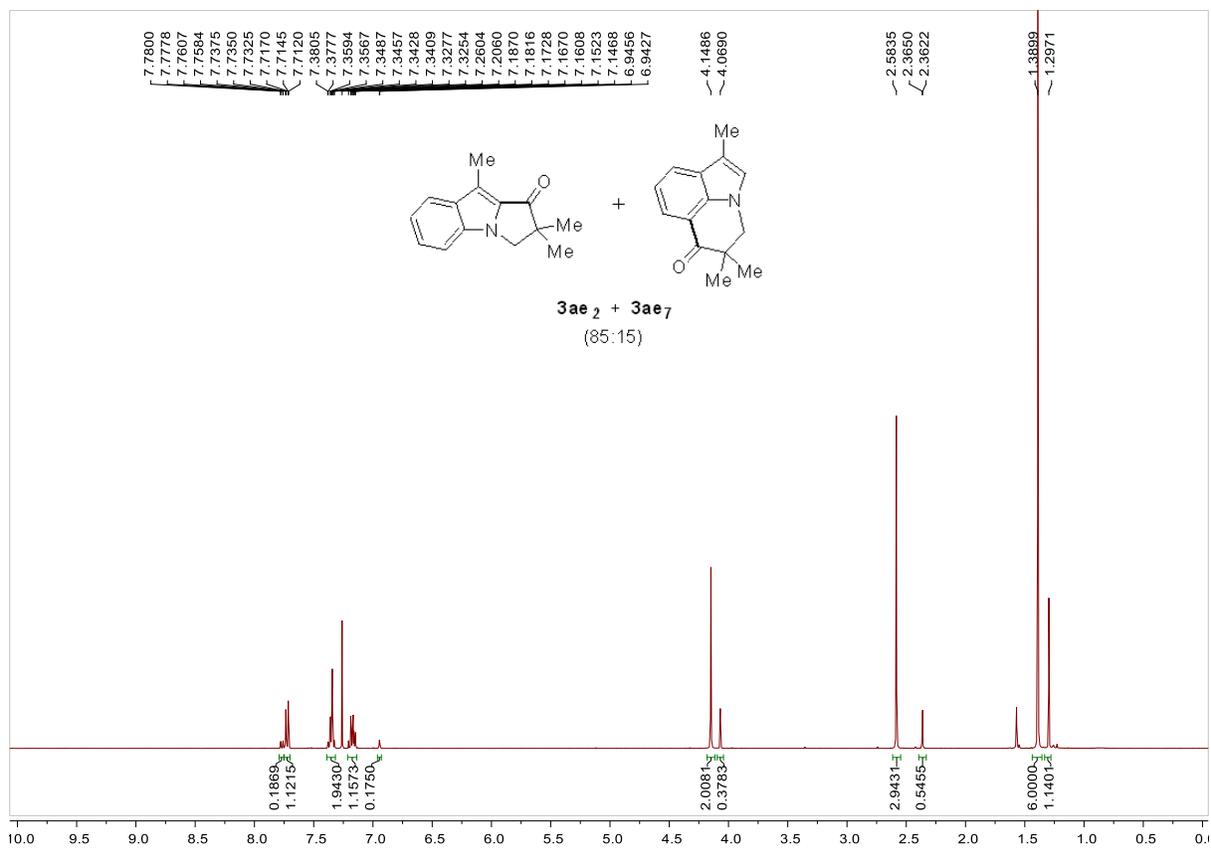


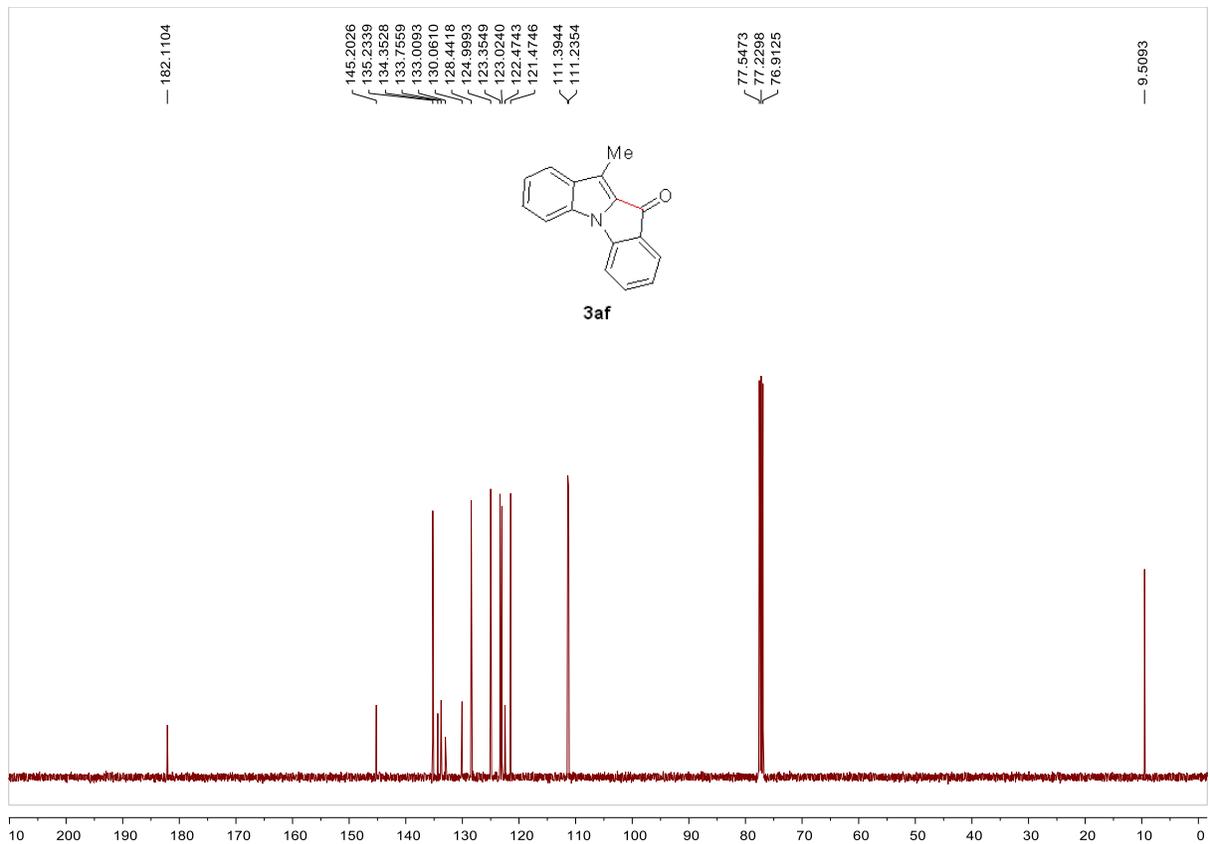
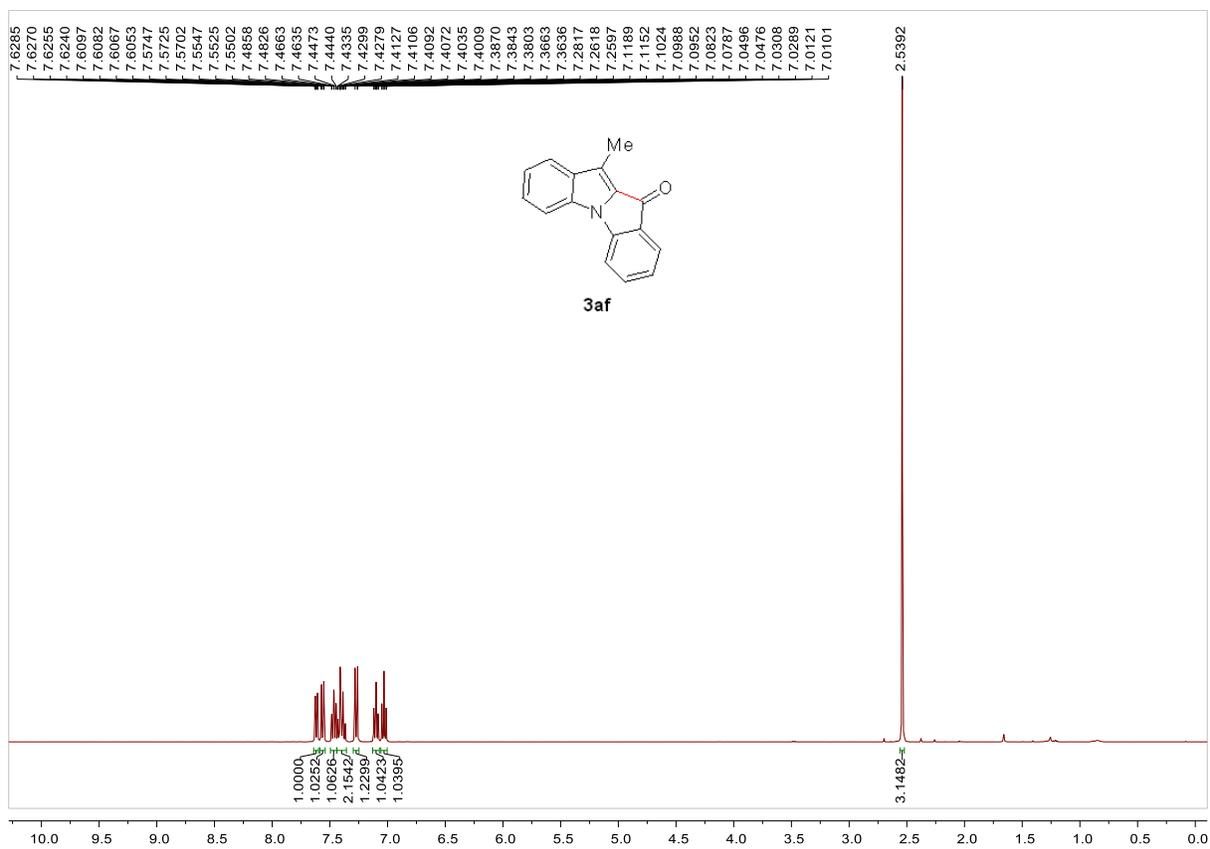


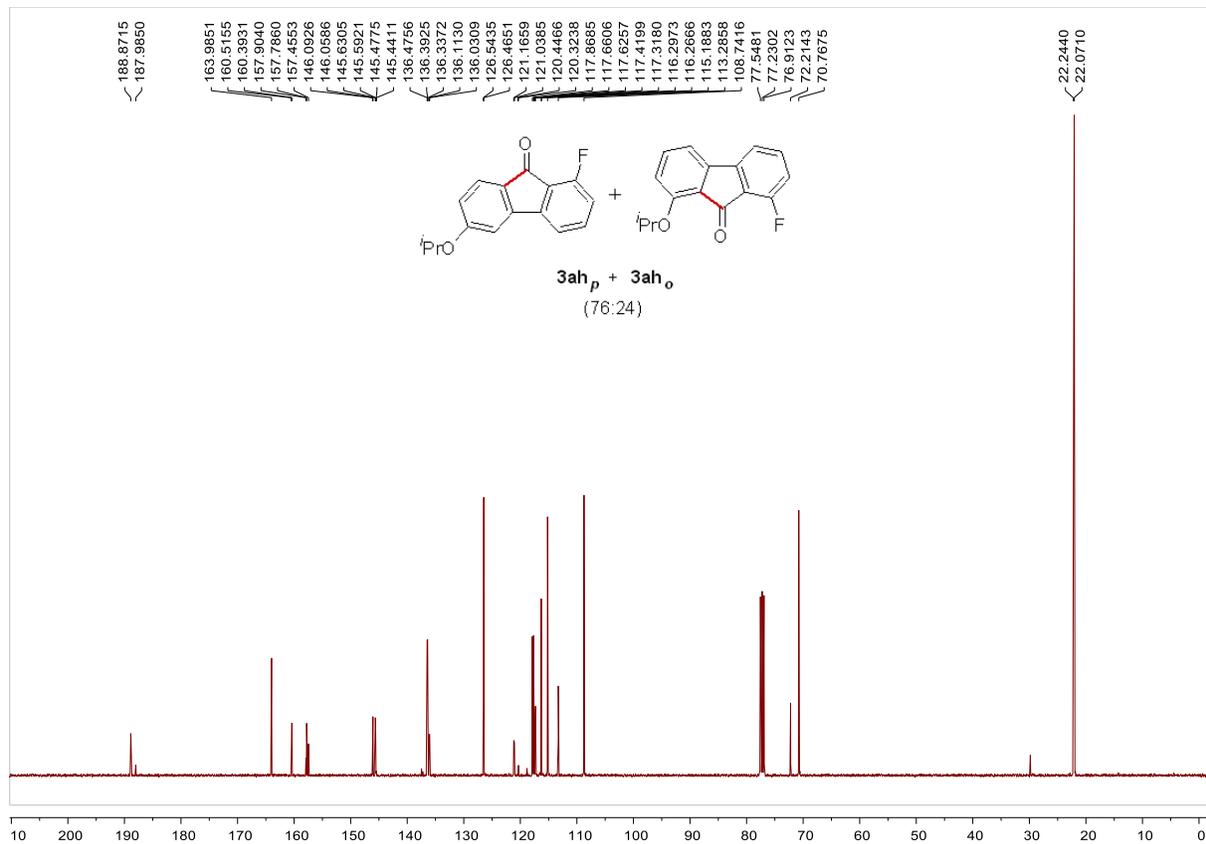
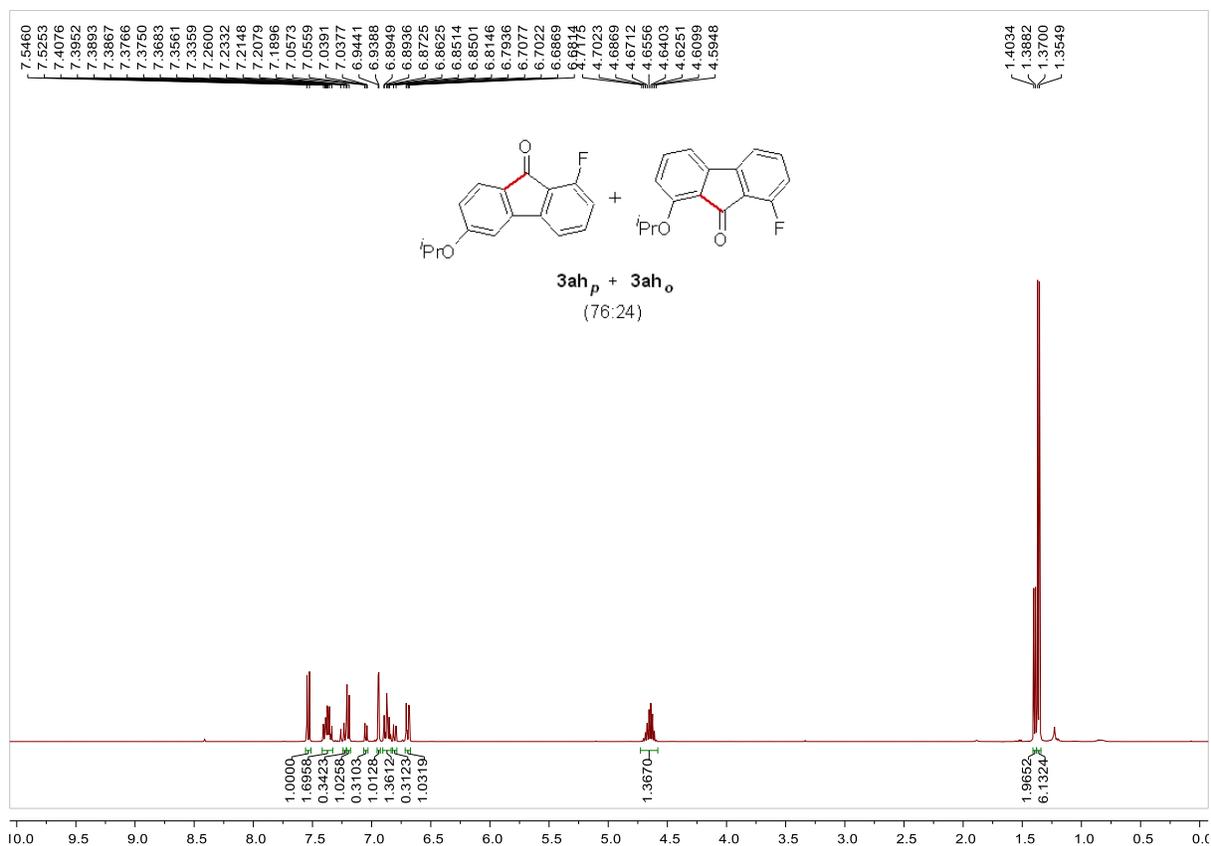


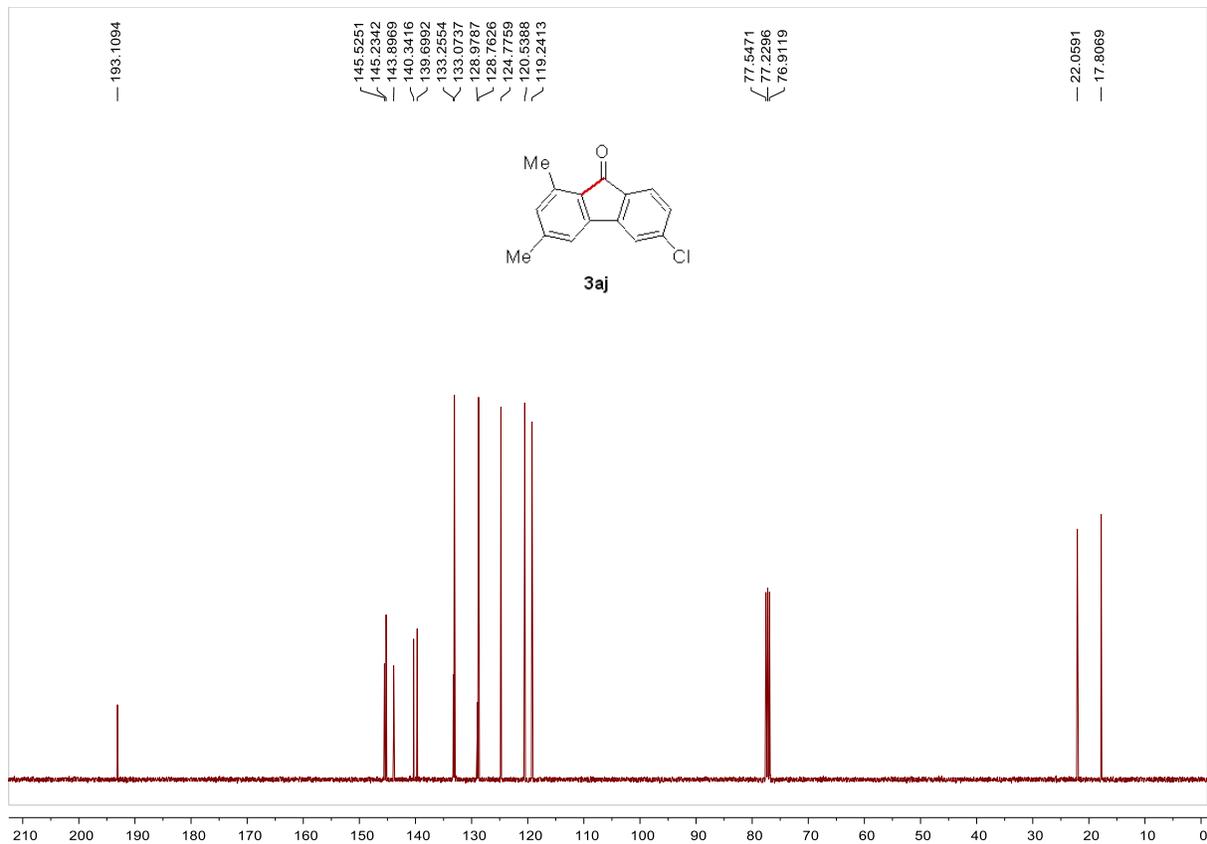
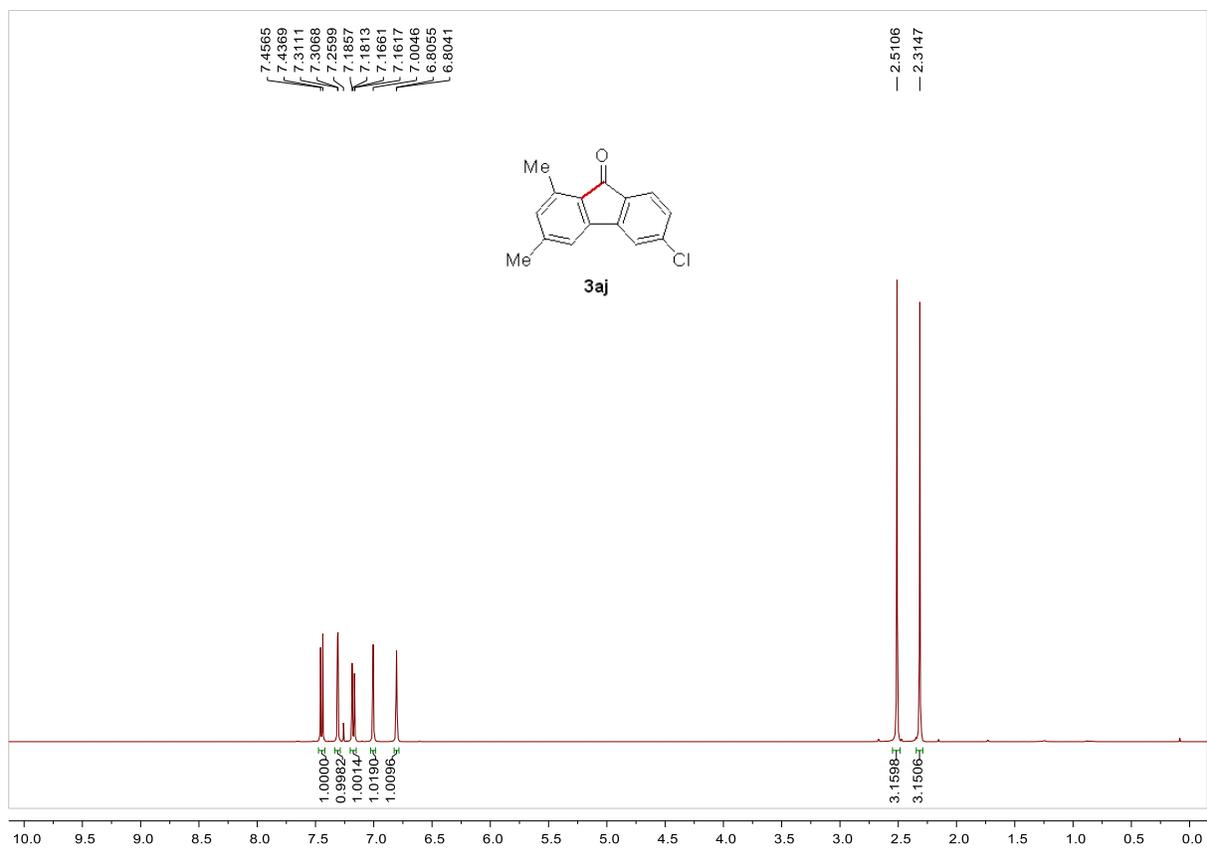


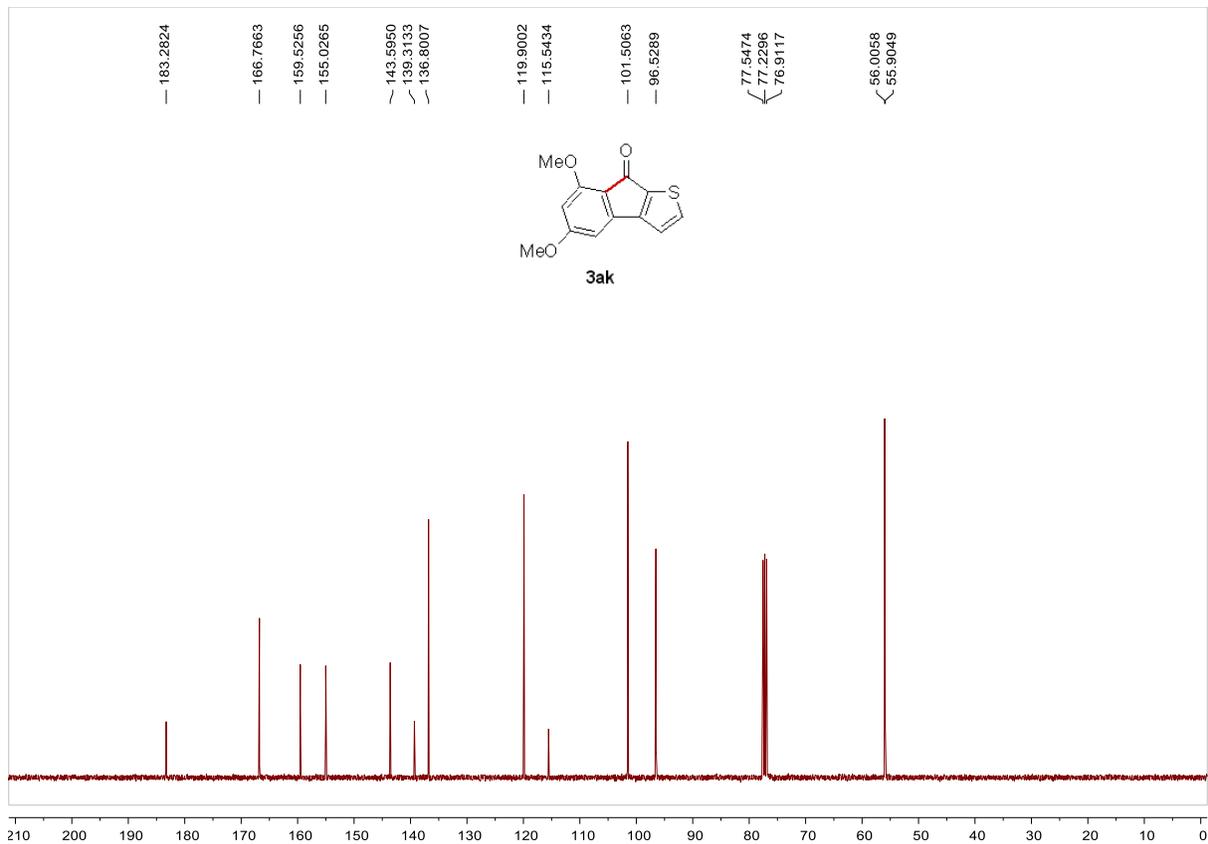
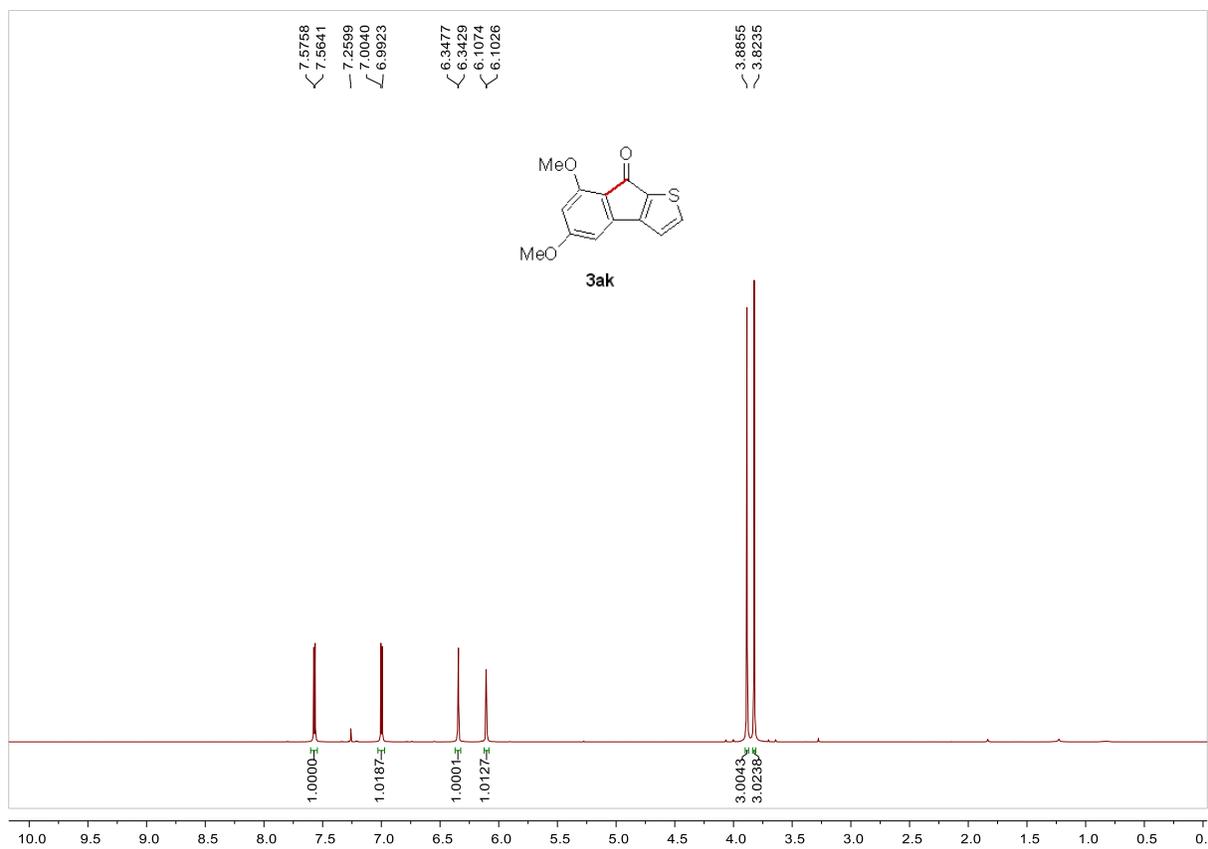


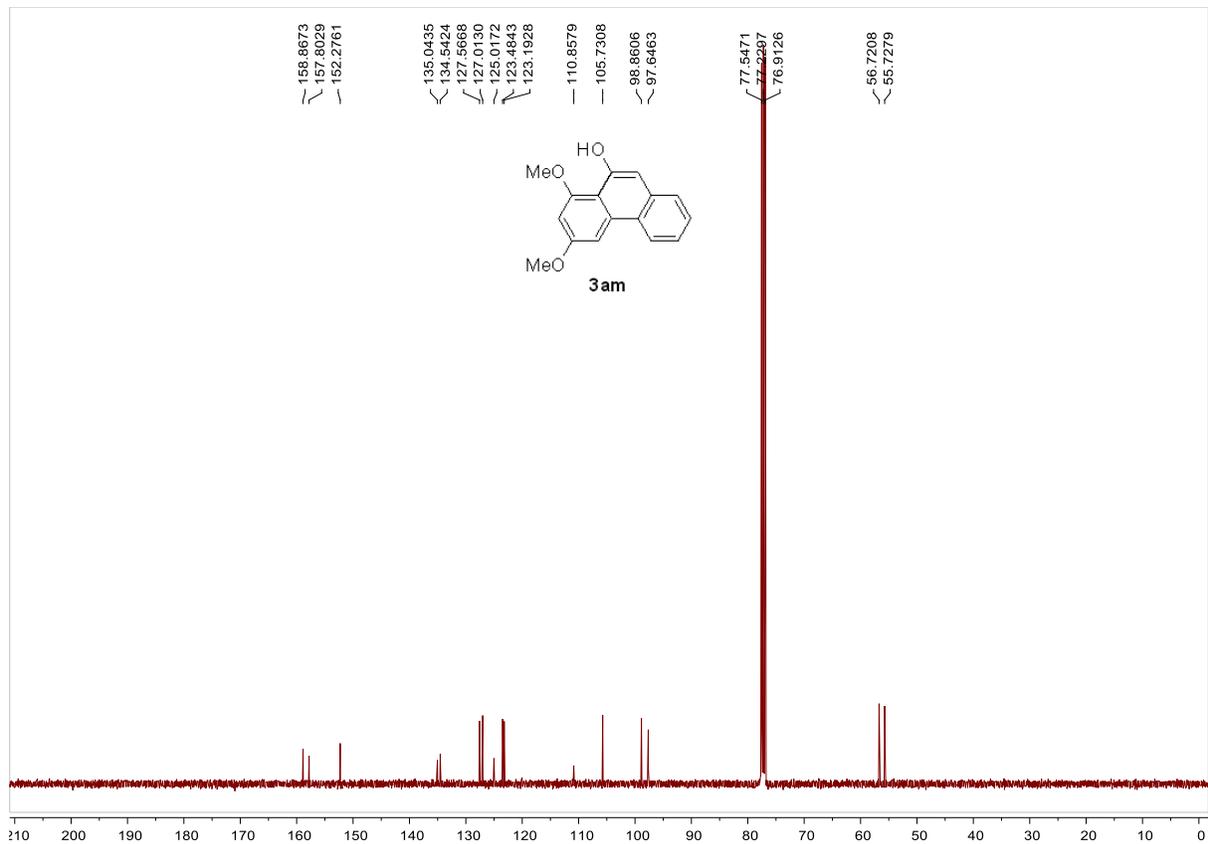
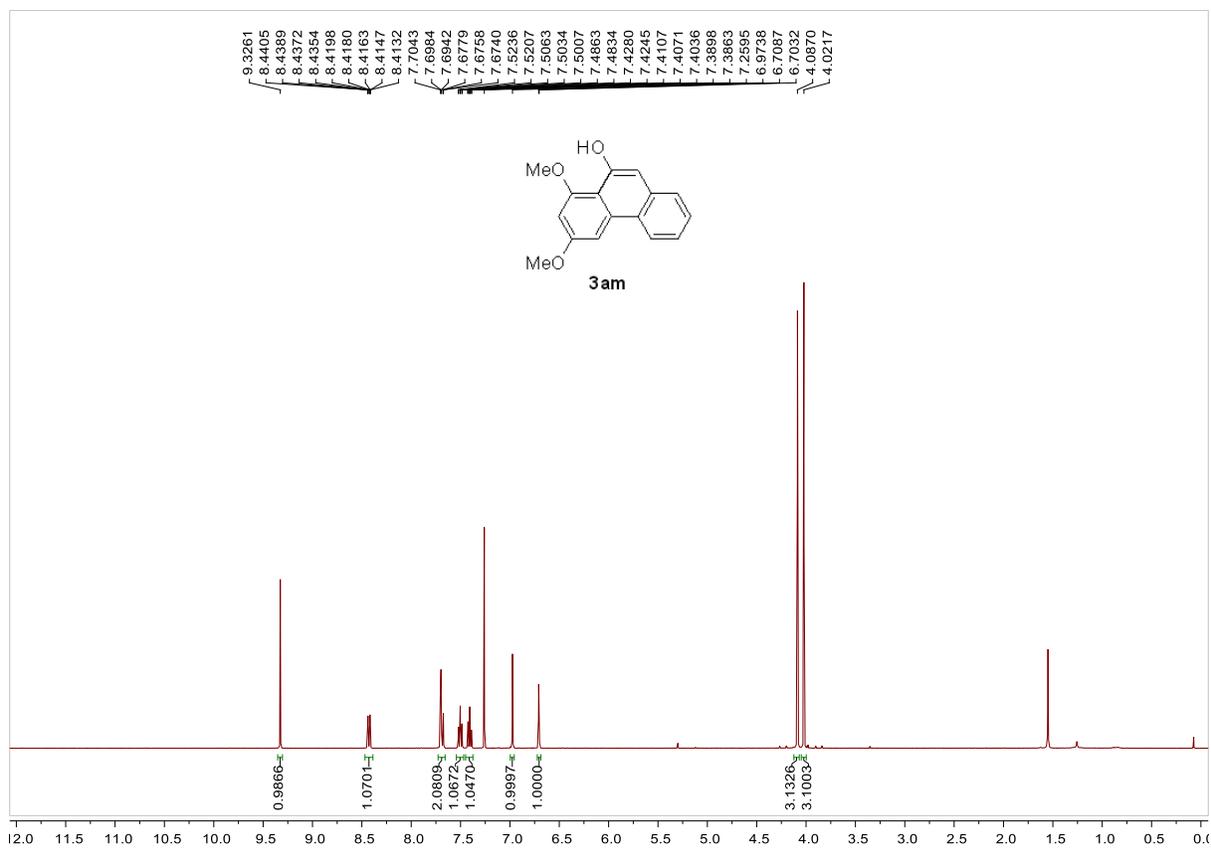












**$^1\text{H}$  and  $^{13}\text{C}$  Spectra of Previously Reported Ketones**

