

Supporting Information

Rh-Thiavinyl Carbenes from 1,2,3-Thiadiazoles Enable Modular Synthesis of Multisubstituted Thiophenes

Daria Kurandina and Vladimir Gevorgyan*

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois
60607-7061, United States

*e-mail: vlad@uic.edu

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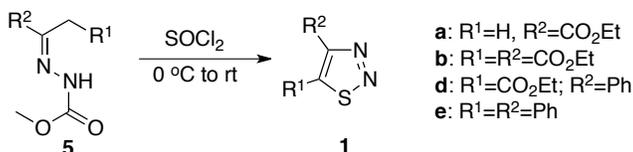
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1. General Information

GC-MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) or DPX-400 (400 MHz) instrument. HRMS analyses were performed on Micromass 70 VSE mass spectrometer. Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. All manipulations with transition metal catalysts were conducted in oven-dried glassware under inert atmosphere using a combination of glovebox and standard Schlenk techniques unless otherwise noted. Anhydrous DCM and THF (BHT-free) was purchased from Aldrich, degassed with argon, and dried by passage through activated alumina on an Innovative Technology PureSolv system. Chlorobenzene anhydrous (99.8%) was purchased from Aldrich. Other dry solvent were prepared using P_2O_5 . All commercially available compounds were purchased from Acros Organics, Strem Chemicals, Aldrich, Gelest Inc., Alfa Aesar, Oakwood Products, Inc., Ark Pharm, Inc., AK Scientific Inc., Matrix Scientific, or ChemImpex International and used without further purification. $[\text{Rh}(\text{COD})\text{Cl}]_2$ catalyst and DPPF ligand were purchased from Pressure Chemical Company and Strem Chemicals, respectively and stored under inert atmosphere.

2. Synthesis of 1,2,3-Thiadiazoles

1,2,3- Thiadiazoles **1a**, **b**, **d**, **e** were synthesized according to the slightly modified known procedure¹ from the corresponding hydrazones **5**:



To a solution of hydrazone **5** (10 mmol) in CH₂Cl₂ (10 mL) SOCl₂ (3.6 mL, 50 mmol, 5.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (10 mL) and washed with 5% NaHCO₃ solution (3×10 mL). The combined organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography to afford 1,2,3-thiadiazole **1**.

Synthesis of hydrazone **5a**:

To a solution of methyl hydrazinecarboxylate (0.9 g, 10 mmol, 1.0 equiv) in ethanol (20 mL) ethyl pyruvate (1.1 mL, 10 mmol, 1.0 equiv) was added. The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The crude hydrazone **5a** was washed with ethanol, dried in the air and used for the next step without further purification.

Synthesis of hydrazone **5b**²:

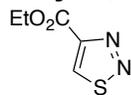
To a solution of methyl hydrazinecarboxylate (0.9 g, 10 mmol, 1.0 equiv) in methanol (20 mL) diethyl acetylenedicarboxylate (1.6 mL, 10 mmol, 1.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The crude hydrazone **5b** was washed with ethanol, dried in the air and used for the next step without further purification.

Synthesis of hydrazone **5d**:

To a solution of methyl hydrazinecarboxylate (0.9 g, 10 mmol, 1.0 equiv) in toluene (10 mL) ethyl benzoylacetate (1.7 mL, 10 mmol, 1.0 equiv) and a catalytic amount of PTSA were added. The reaction mixture was stirred at 60 °C overnight and then concentrated *in vacuo*. The crude hydrazone **5d** was with ethanol, dried in the air and used for the next step without further purification.

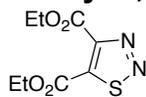
Synthesis of hydrazone **5e**³:

To a solution of methyl hydrazinecarboxylate (0.9 g, 10 mmol, 1.0 equiv) in methanol (10 mL) deoxybenzoin (2.0 g, 10 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 60 °C overnight and then concentrated *in vacuo*. The crude hydrazone **5e** was with ethanol, dried in the air and used for the next step without further purification.

Ethyl 1,2,3-thiadiazole-4-carboxylate, 1a¹:

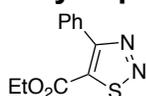
synthesized from **5a** (yield 45%)

¹H NMR (400 MHz, CDCl₃) δ 9.26 (s, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 159.60, 154.92, 142.33, 62.34, 14.26.

Diethyl 1,2,3-thiadiazole-4,5-dicarboxylate, 1b⁴:

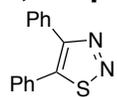
synthesized from **5b** (yield 91%)

¹H NMR (400 MHz, CDCl₃) δ 4.53 (q, *J* = 7.2 Hz, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 159.58, 158.61, 153.16, 148.38, 63.70, 62.89, 14.02, 13.93.

Ethyl 4-phenyl-1,2,3-thiadiazole-5-carboxylate, 1d⁵:

synthesized from **5d** (yield 64%)

¹H NMR (400 MHz, CDCl₃) δ 7.91–7.89 (m, 2H), 7.52–7.50 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 162.80, 159.50, 139.82, 130.12, 130.06, 129.75, 128.29, 62.86, 14.00.

4,5-Diphenyl-1,2,3-thiadiazole, 1e⁶:

synthesized from **5e** (yield 68%)

¹H NMR (500 MHz, CDCl₃) δ 7.64–7.62 (m, 1H), 7.42–7.35 (m, 4H).

¹³C NMR (126 MHz, CDCl₃) δ 157.54, 150.89, 130.92, 129.77, 129.33, 129.17, 129.15, 128.92, 128.71, 127.89.

Ethyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate, 1c⁷:

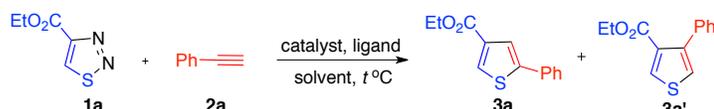
synthesized according to the known procedure⁷ from the corresponding diazo compound⁸ and Lawesson's reagent:



To a solution of ethyl benzoylacetate (1.7 mL, 10 mmol, 1.0 equiv) and 4-acetamidobenzenesulfonyl azide (2.6 g, 11 mmol, 1.1 equiv) in CH₃CN (60 mL) Et₃N (2.8 mL, 30 mmol, 3.0 equiv) was added slowly at 0 °C. The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (EtOAc:hexanes: 1:4) to yield compound **6**. Then **6** was dissolved in toluene (50 mL) and treated with Lawesson's reagent (4.9 g, 12 mmol, 1.2 equiv). The reaction was heated at reflux for 4 hours, then cooled to room temperature and concentrated *in vacuo*. The resulting oil was purified by column chromatography (Et₂O:hexanes (30:70)) to give **1c** (yield 61%). ¹H NMR (400 MHz, CDCl₃) δ 7.55–7.46 (m, 5H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.90, 160.43, 148.46, 130.62, 129.74, 128.63, 126.10, 62.09, 14.03.

3. Optimization Table for Transannulation Reaction of 1,2,3-Thiadiazoles with Alkynes

Model reaction:^a

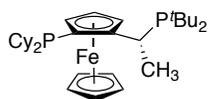


| no. | catalyst (2 mol %) | ligand (5 mol %) | solvent (1 M) | t (°C) | time (h) | yield ^b (%) | Ratio (3a:3a') ^b |
|-----|--|---------------------|------------------|--------|-------------|---------------------------|--------------------------------|
| 1 | Rh ₂ (Oct) ₄ | - | PhCl | 130 | 15 | 1 | 1:1 |
| 2 | Rh ₂ (DOSP) ₄ | - | PhCl | 130 | 15 | 3 | 1:1 |
| 3 | [Rh(COD)Cl] ₂ | - | PhCl | 130 | 12 | 5 | 1:0 |
| 4 | [Rh(COD)Cl] ₂ | DiPPF | PhCl | 130 | 1 | 24 | 6.9:1 |
| 5 | [Rh(COD)Cl] ₂ | Josiphos (1) | PhCl | 130 | 1 | 34 | 4.1:1 |
| 6 | [Rh(COD)Cl] ₂ | Josiphos (2) | PhCl | 130 | 12 | 70 ^c | 10:1 |
| 7 | [Rh(COD)Cl] ₂ | Josiphos (3) | PhCl | 130 | 1 | 34 | 8.3:1 |
| 8 | [Rh(COD)Cl] ₂ | DPPE | PhCl | 130 | 1 | 93 | 5.4:1 |
| 9 | [Rh(COD)Cl] ₂ | (S,S)-DIOP | PhCl | 130 | 1 | 95 | 7.1:1 |
| 10 | [Rh(COD)Cl] ₂ | (S,S)-DpePhoS | PhCl | 130 | 1 | 100 | 2.0:1 |
| 11 | [Rh(COD)Cl] ₂ | (S,S)-XantPhoS | PhCl | 130 | 1 | 100 | 2.0:1 |
| 12 | [Rh(COD)Cl] ₂ | (S,S)-ChiraPhos | PhCl | 130 | 1 | 85 | 2.0:1 |
| 13 | [Rh(COD)Cl] ₂ | (S,S)-SpanPhoS | PhCl | 130 | 1 | 67 | 5.5:1 |
| 14 | [Rh(COD)Cl] ₂ | (S,S)-NorPhoS | PhCl | 130 | 1 | 100 | 5.2:1 |
| 15 | [Rh(COD)Cl] ₂ | (S,S)-DPPBz | PhCl | 130 | 1 | 53 | 3.4:1 |
| 16 | [Rh(COD)Cl] ₂ | (S,S)-BDPP | PhCl | 130 | 1 | 100 | 1.9:1 |
| 17 | Rh ₂ (Oct) ₄ | DPPF | PhCl | 130 | 12 | 1 | 0.4:1 |
| 18 | Rh ₂ (DOSP) ₄ | DPPF | PhCl | 130 | 12 | 6 | 1.5:1 |
| 19 | [Rh(Me ₅ C ₅) ₂ Cl ₂] ₂ | DPPF | PhCl | 130 | 1.5 | 97 | 18.6:1 |
| 20 | RhCl ₃ ·H ₂ O ^d | DPPF | PhCl | 130 | 1.5 | 100 | 16.7:1 |
| 21 | [Rh(COD)Cl] ₂ | DPPF | PhCl | 130 | 0.1 | 98 | 19.0:1 |
| 22 | [Rh(COD)OH] ₂ | DPPF | PhCl | 130 | 1.5 | 47 | 7.3:1 |
| 23 | Rh(COD)(CN) ₂ BF ₄ ^d | DPPF | PhCl | 130 | 1.5 | 29 | 1.7:1 |
| 24 | [Rh(nonborene)Cl] ₂ | DPPF | PhCl | 130 | 1.5 | 79 | 24.3:1 |
| 25 | Rh(CO) ₂ (acac) ^d | DPPF | PhCl | 130 | 12 | 21 | 5.7:1 |
| 26 | Rh(PPh ₃) ₃ Cl ^d | DPPF | PhCl | 130 | 12 | 81 | 7.4:1 |
| 27 | [Rh(cyclooctene) ₂ Cl] ₂ | DPPF | PhCl | 130 | 12 | 84 | 21.3:1 |
| 28 | Rh(COD)(acac) ^d | DPPF | PhCl | 130 | 12 | 18 | 5.6:1 |
| 29 | [Ir(cod)Cl] ₂ | DPPF | PhCl | 130 | 12 | <1 | - |
| 30 | [Ir(Me ₅ C ₅) ₂ Cl ₂] ₂ | DPPF | PhCl | 130 | 12 | <1 | - |
| 31 | Ru(cod)(Me ₅ C ₅)Cl ^d | DPPF | PhCl | 130 | 12 | NR | - |
| 32 | Ni(DPPF)Cl ₂ ^d | DPPF | PhCl | 130 | 12 | <1 | - |

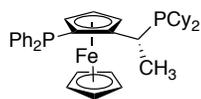
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|-----------|--|-------------|-----------------|-----------|----------|------------|---------------|
| 33 | $\text{Pd}(\text{DPPF})\text{Cl}_2^d$ | DPPF | PhCl | 130 | 12 | NR | - |
| 34 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | mesitylene | 130 | 1.5 | 92 | 13.1:1 |
| 35 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | 1,2-DCE | 130 | 1.5 | 100 | 17.5:1 |
| 36 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | DMF | 130 | 1.5 | 87 | 8.6:1 |
| 37 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | CHCl_3 | 130 | 1.5 | 53 | 13.4:1 |
| 38 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | PhCl | 90 | 1.5 | 100 | 27.2:1 |
| 39 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | PhCl | 80 | 1.5 | 100 | 30.6:1 |
| 40 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | PhCl | 70 | 5 | 100 | 40.2:1 |
| 41 | $[\text{Rh}(\text{COD})\text{Cl}]_2$ | DPPF | PhCl | 60 | 7 | 100 | 43.6:1 |
| 43 | $\text{Fe}_2(\text{CO})_9^e$ | - | PhCl | 150 | 12 | dec. | - |
| 42 | - | - | PhCl | 130 | 12 | NR | - |

^aThe reactions were run on 0.1 mmol in 0.1 mL of dry solvent (1 M solution) under inert atmosphere. ^bThe yield and ratio were determined by GC-MS with pentadecane as internal standart. ^cIsolated yield (ratio was determined by ¹H NMR). ^d4 mol % of the catalyst was used. ^e100 mol % of the catalyst was used.

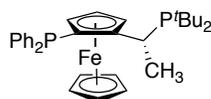
Josiphos (1):



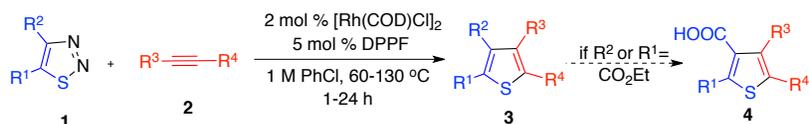
Josiphos (2):



Josiphos (3):



4. Procedures for Transannulation Reaction of 1,2,3-Thiadiazoles with Alkynes

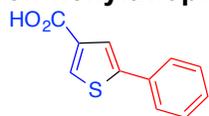


General procedure A: In a glovebox 1 mL Weaton microreactor was charged with 1,2,3-thiadiazole **1** (0.25 mmol), [Rh(COD)Cl]₂ (2.5 mg, 0.005 mmol, 2 mol %), DPPF (6.9 mg, 0.0125 mmol, 5 mol %) (alkyne **2**, if solid, was added at this point too). Dry chlorobenzene (250 μ L, 1 M) was added to the mixture, followed by alkyne **2** (0.5 mmol, 2 equiv). The microreactor was capped with Teflon pressure cap and placed into a preheated aluminum-heating block. The reaction mixture was heated until full consumption of 1,2,3-thiadiazole (as judged by GC-MS analysis). Upon completion the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the crude product was purified by column chromatography to afford the corresponding thiophene **3**.

General procedure B:^a In a glovebox 1 mL Weaton microreactor was charged with 1,2,3-thiadiazole **1** (0.5 mmol), [Rh(COD)Cl]₂ (4.9 mg, 0.01 mmol, 2 mol %), DPPF (13.9 mg, 0.025 mmol, 5 mol %). Dry chlorobenzene (500 μ L, 1 M) was added to the mixture, followed by alkyne **2** (1 mmol, 2 equiv). The microreactor was capped with Teflon pressure cap and placed into a preheated aluminum heating block. The reaction mixture was refluxed until full consumption of 1,2,3-thiadiazole (as judged by GC-MS analysis). Upon completion, the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and the crude product was purified by flash chromatography (EtOAc). The crude thiophene **3** was dried under vacuum at room temperature, dissolved in of THF/MeOH (30% MeOH) mixture (650 μ L) and transferred to a 5 mL round bottom flask equipped with a reflux condenser. To the mixture was added LiOH·H₂O (50 mg, 1.2 mmol, 1.2 equiv) in water (500 μ L), followed by catalytic amount of tetra-*n*-butylammonium fluoride. The reaction mixture was refluxed for 12 hours and then allowed to cool to room temperature before acidifying with 1 M HCl. The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layer was washed with saturated NH₄Cl solution (5 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The corresponding carboxylic acid **4** was isolated by column chromatography (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)).

^aGeneral procedure B was applied for the thiophenes which were difficult to purify by column chromatography.

5-Phenylthiophene-3-carboxylic acid, 4aa⁹:



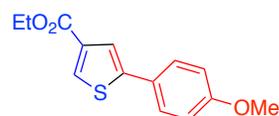
synthesized according to *General procedure B*: first step was run at 60 °C, 7 h; 100.0 mg (yield 98 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid.

¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, *J* = 1.2 Hz, 1H), 7.75 (d, *J* = 1.3 Hz, 1H), 7.64–7.62 (m, 2H), 7.44–7.40 (m, 2H), 7.36–7.32 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 167.59, 145.46, 133.61, 133.38, 133.30, 129.06, 128.26, 125.97, 123.42.

HRMS (ESI) calcd. for C₁₁H₉O₂S [M]⁻H: 203.0167, found: 203.0166.

Ethyl 5-(4-methoxyphenyl)thiophene-3-carboxylate, 3ab¹⁰:



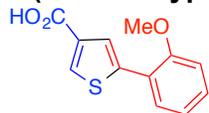
synthesized according to *General procedure A* at 60 °C, 7 h; 53.6 mg (yield 82 %) was isolated (eluent EtOAc:hexanes (gradient from 1:100 to 1:25 to 1:10)). White solid, *R*_f=0.25 (EtOAc:hexanes (1:10)).

¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 0.7 Hz, 1H), 7.59 (d, *J* = 0.7 Hz, 1H), 7.53 (ap. d, *J* = 8.6 Hz, 2H), 6.92 (ap. d, *J* = 8.6 Hz, 2H), 4.34 (d, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ 162.83, 159.61, 144.88, 134.49, 130.69, 127.21, 126.35, 122.27, 114.37, 60.69, 55.35, 14.37.

HRMS (ESI) calcd. for C₁₄H₁₅O₃S [M]⁺H: 263.0742, found: 263.0741.

5-(2-Methoxyphenyl)thiophene-3-carboxylic acid, 4ac:



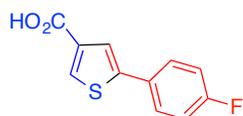
synthesized to *General procedure B*: first step was run at 60 °C, 12 h; 73.2 mg (yield 62 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid.

¹H NMR (500 MHz, acetone-*d*₆) δ 8.21 (d, *J* = 1.3 Hz, 1H), 7.91 (d, *J* = 1.3 Hz, 1H), 7.77 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 7.04 (td, *J* = 7.7, 1.0 Hz, 1H), 3.97 (s, 3H).

¹³C NMR (101 MHz, acetone-*d*₆) δ 163.14, 155.66, 140.16, 133.39, 132.70, 129.21, 127.89, 125.29, 122.04, 121.01, 111.96, 55.10.

HRMS (ESI) calcd. for C₁₂H₉O₃S [M]⁻H: 233.0272, found: 233.0271.

5-(4-Fluorophenyl)thiophene-3-carboxylic acid, 4ad:



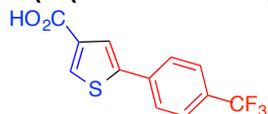
synthesized according to *General procedure B*: first step was run at 80 °C, 5 h; 102.0 mg (yield 92 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid.

¹H NMR (400 MHz, acetone-*d*₆) δ 8.21 (d, *J* = 1.3 Hz, 1H), 7.79–7.73 (m, 3H), 7.25–7.19 (m, 2H).

¹³C NMR (101 MHz, acetone-*d*₆) δ 162.62 (s), 162.60 (d, *J* = 247.5 Hz), 143.65 (s), 135.00 (s), 132.15 (s), 130.01 (d, *J* = 3.2 Hz), 127.78 (d, *J* = 8.2 Hz), 123.69 (s), 115.93 (d, *J* = 22.1 Hz).

HRMS (ESI) calcd. for C₁₁H₆FO₂S [M]⁻H: 221.0073, found: 221.0073.

5-(4-(Trifluoromethyl)phenyl)thiophene-3-carboxylic acid, 4ae:

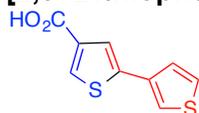


synthesized according to *General procedure B*: first step was run at 80 °C, 12 h; 77.2 mg (yield 57 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid.

¹H NMR (400 MHz, acetone-*d*₆) δ 8.30 (d, *J* = 1.3 Hz, 1H), 7.95–7.93 (m, 3H), 7.77 (ap. d, *J* = 8.2 Hz, 2H).

¹³C NMR (101 MHz, acetone-*d*₆) δ 162.61 (s), 142.85 (s), 137.18 (s), 135.26 (s), 133.48 (s), 129.16 (q, *J* = 32.3 Hz), 126.16 (s), 126.05 (q, *J* = 5.5 Hz), 125.31 (s), 124.32 (q, *J* = 271.7 Hz).

HRMS (ESI) calcd. for C₁₂H₆F₃O₂S [M]⁻H: 271.0041, found: 271.0037.

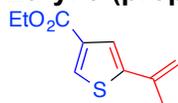
[2,3'-Bithiophene]-4-carboxylic acid, 4af:

synthesized according to *General procedure B*: first step was run at 80 °C, 12 h; 70.5 mg (yield 67 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid. The ratio of inseparable isomers determined by NMR is 33:1.

^1H NMR (500 MHz, acetone- d_6) δ 8.14 (d, J = 1.3 Hz, 1H), 7.73 (ap. dd, J = 2.9, 1.3 Hz, 1H), 7.67 (d, J = 1.3 Hz, 1H), 7.58 (ap. dd, J = 5.0, 2.9 Hz, 1H), 7.47 (ap. dd, J = 5.0, 1.3 Hz, 1H).

^{13}C NMR (126 MHz, acetone- d_6) δ 162.78, 139.82, 134.68, 134.62, 131.33, 127.19, 125.85, 123.55, 120.68.

HRMS (ESI) calcd. for $\text{C}_9\text{H}_5\text{O}_2\text{S}_2$ [M]–H: 208.9731, found: 208.9729.

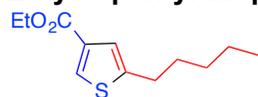
Ethyl 5-(prop-1-en-2-yl)thiophene-3-carboxylate, 3ag:

synthesized according to *General procedure A* at 80 °C, 12 h; 46.6 mg (yield 95 %) was isolated (eluent EtOAc:hexanes (gradient from 1:100 to 1:50 to 1:20)). Yellow oil, R_f =0.50 (EtOAc:hexanes (1:10)).

^1H NMR (400 MHz, CDCl_3) δ 7.91 (s, 1H), 7.40 (s, 1H), 5.38 (s, 1H), 5.00 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 162.71, 146.25, 136.74, 133.92, 131.20, 123.83, 112.31, 60.64, 21.54, 14.33.

HRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{13}\text{O}_2\text{S}$ [M]+H: 197.0636, found: 197.0636.

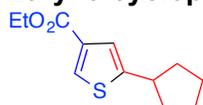
Ethyl 5-pentylthiophene-3-carboxylate, 3ah¹⁰:

synthesized according to *General procedure A* at 80 °C, 7 h; 53.0 mg (yield 94 %) was isolated (eluent EtOAc:hexanes (1:10)). Yellow oil, R_f =0.63 (EtOAc:hexanes (1:10)). The ratio of inseparable isomers determined by NMR is 20:1.

^1H NMR (500 MHz, CDCl_3) δ 7.88 (d, J = 1.3 Hz, 1H), 7.19 (d, J =1.3 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 1.68 (m, 2H), 1.37–1.34 (m, 7H), 0.90 (m, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 162.97, 146.52, 133.34, 130.32, 124.42, 60.47, 31.14, 31.10, 29.86, 22.33, 14.35, 13.94.

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{19}\text{O}_2\text{S}$ [M]+H: 227.1106, found: 227.1105.

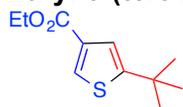
Ethyl 5-cyclopentylthiophene-3-carboxylate, 3ai:

synthesized according to *General procedure A* at 80 °C, 4 h; 51.4 mg (yield 92 %) was isolated (eluent EtOAc:hexanes (gradient from 1:50 to 1:10)). Yellow oil, R_f =0.48 (EtOAc:hexanes (1:10)). The ratio of inseparable isomers determined by NMR is 42:1.

^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 1.3 Hz, 1H), 7.21 (m, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.25–3.17 (m, 1H), 2.17–2.06 (m, 2H), 1.82–1.72 (m, 2H), 1.71–1.61 (m, 4H), 1.35 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ 163.00, 151.45, 133.18, 129.99, 122.99, 60.45, 41.00, 35.21, 25.05, 14.35.

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{17}\text{O}_2\text{S}$ [M]+H: 225.0949, found: 225.0951.

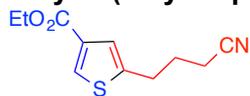
Ethyl 5-(tert-butyl)thiophene-3-carboxylate, 3aj:

synthesized according to *General procedure A* at 80 °C, 5 h; 48.4 mg (yield 88 %) was isolated (eluent EtOAc:hexanes (gradient from 1:10 to 1:5)). Colorless oil, $R_f=0.52$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.88 (d, $J = 1.3$ Hz, 1H), 7.23 (d, $J = 1.3$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 1.38 (s, 9H), 1.35 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 163.03, 158.17, 133.01, 129.89, 121.81, 60.44, 34.54, 32.30, 14.36.

HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{17}\text{O}_2\text{S}$ [M]+H: 213.0949, found: 213.0947.

Ethyl 5-(3-cyanopropyl)thiophene-3-carboxylate, 3ak:

synthesized according to *General procedure A* at 80 °C, 7 h; 42.0 mg (yield 75 %) was isolated (eluent EtOAc:hexanes (gradient from 1:10 to 1:2)). Colorless oil, $R_f=0.07$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.92 (d, $J = 1.3$ Hz, 1H), 7.24 (d, $J = 1.2$ Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 2.97 (t, $J = 7.3$ Hz, 2H), 2.38 (t, $J = 7.1$ Hz, 2H), 2.02 (ap. p, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 162.63, 142.86, 133.78, 131.19, 125.63, 118.95, 60.66, 28.46, 26.92, 16.24, 14.32.

HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{13}\text{NNaO}_2\text{S}$ [M]+Na: 246.0565, found: 246.0566.

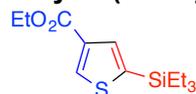
Ethyl 5-(3-chloropropyl)thiophene-3-carboxylate, 3al:

synthesized according to *General procedure A* at 80 °C, 7 h; 56.7 mg (yield 98 %) was isolated (eluent EtOAc:hexanes (gradient from 1:100 to 1:10)). Orange oil, $R_f=0.40$ (EtOAc:hexanes (1:10)). The ratio of inseparable isomers determined by NMR is 21:1.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.91 (d, $J = 1.3$ Hz, 1H), 7.24 (ap. s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.57 (t, $J = 6.3$ Hz, 2H), 2.99 (t, $J = 7.3$ Hz, 2H), 2.17–2.10 (m, 2H), 1.36 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 162.78, 143.92, 133.63, 130.87, 125.30, 60.59, 43.59, 33.81, 26.82, 14.34.

HRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{14}\text{ClO}_2\text{S}$ [M]+H: 233.0403, found: 233.0405.

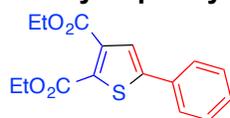
Ethyl 5-(triethylsilyl)thiophene-3-carboxylate, 3am:

synthesized according to *General procedure A* at 60 °C, 7 h; 49.1 mg (yield 73 %) was isolated (eluent EtOAc:hexanes (gradient from 1:100 to 1:10)). Colorless oil, $R_f=0.57$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.31 (d, $J = 0.8$ Hz, 1H), 7.64 (d, $J = 0.7$ Hz, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H), 0.99 (t, $J = 7.8$ Hz, 9H), 0.81 (q, $J = 7.7$ Hz, 6H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 163.06, 138.25, 137.57, 135.37, 135.21, 60.55, 14.37, 7.23, 4.22.

HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_2\text{SSi}$ [M]+H: 271.1188, found: 271.1190.

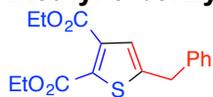
Diethyl 5-phenylthiophene-2,3-dicarboxylate, 3ba:

synthesized according to *General procedure A* at 60 °C, 30 min; 73.2 mg (yield 96 %) was isolated (eluent Et_2O :hexanes (30:70)). Yellow solid, $R_f=0.27$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.63–7.60 (m, 2H), 7.44–7.37 (m, 4H), 4.43–4.34 (m, 4H), 1.42–1.36 (m, 6H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 164.24, 161.04, 148.87, 138.25, 132.59, 131.96, 129.17, 129.12, 126.19, 124.17, 61.75, 14.17, 14.10.

HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{16}\text{NaO}_4\text{S}$ [M]+Na: 327.0667, found: 327.0665.

Diethyl 5-benzylthiophene-2,3-dicarboxylate, 3bn:

synthesized according to *General procedure A* at 80 °C, 1 h; 65.3 mg (yield 82 %) was isolated (eluent EtOAc:hexanes (gradient from 1:25 to 1:9 to 1:5)). Yellow oil, $R_f=0.27$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35–7.22 (m, 5H), 6.97 (s, 1H), 4.37–4.27 (m, 4H), 4.11 (s, 2H), 1.37–1.31 (m, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 161.03, 149.87, 138.61, 137.48, 128.82, 128.66, 127.06, 126.52, 61.60, 61.53, 36.20, 14.14, 14.06.

HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{19}\text{O}_4\text{S}$ $[\text{M}]^+\text{H}$: 319.1004, found: 319.1004.

Diethyl 5-((pivaloyloxy)methyl)thiophene-2,3-dicarboxylate, 3bo:

synthesized according to *General procedure A* at 80 °C, 1 h; 82.2 mg (yield 96 %) was isolated (eluent EtOAc:hexanes (gradient from 1:50 to 1:25 to 1:5)). Yellow oil, $R_f=0.18$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.20 (s, 1H), 5.20 (d, $J = 0.7$ Hz, 2H), 4.38–4.31 (m, 4H), 1.38–1.33 (m, 6H), 1.21 (s, 9H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 177.88, 163.81, 160.93, 143.33, 136.83, 134.36, 128.09, 61.83, 61.68, 60.09, 29.66, 27.04, 14.11, 14.05.

HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{23}\text{NaO}_6\text{S}$ $[\text{M}]^+\text{Na}$: 365.1035, found: 365.1033

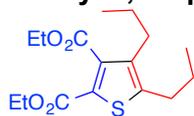
Diethyl 5-octylthiophene-2,3-dicarboxylate, 3bp:

synthesized according to *General procedure A* at 60 °C, 7 h; 77.0 mg (yield 90 %) was isolated (eluent EtOAc:hexanes (1:10)). Orange oil, $R_f=0.30$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.93 (s, 1H), 4.38–4.29 (m, 4H), 2.78 (t, $J = 7.6$ Hz, 2H), 1.70–1.63 (m, 2H), 1.38–1.27 (m, 16H), 0.87 (t, $J = 6.9$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 164.57, 161.14, 151.59, 137.44, 125.70, 61.53, 61.44, 31.78, 31.21, 30.07, 29.18, 29.10, 28.92, 22.61, 14.15, 14.07.

HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{23}\text{O}_6\text{S}$ $[\text{M}]^+\text{H}$: 341.1787, found: 341.1787.

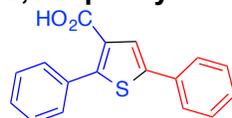
Diethyl 4,5-dipropylthiophene-2,3-dicarboxylate, 3bq:

synthesized according to *General procedure A* at 130 °C, 24 h; 45.0 mg (yield 58 %) was isolated (eluent EtOAc:hexanes (gradient from 1:100 to 1:25 to 1:5)). Colorless oil, $R_f=0.5$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 4.39 (q, $J = 7.1$ Hz, 2H), 4.29 (q, $J = 7.1$ Hz, 2H), 2.73–2.69 (m, 2H), 2.49–2.45 (m, 2H), 1.73–1.64 (m, 2H), 1.55–1.45 (m, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.00 (t, $J = 7.3$ Hz, 3H), 0.91 (t, $J = 7.3$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.42, 161.14, 147.58, 139.95, 137.34, 61.58, 61.18, 30.24, 29.01, 24.59, 23.75, 14.19, 14.07, 13.98, 13.79.

HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{24}\text{NaO}_4\text{S}$ $[\text{M}]^+\text{Na}$: 335.1293, found: 335.1290.

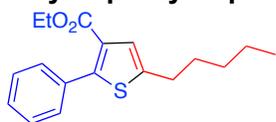
2,5-Diphenylthiophene-3-carboxylic acid, 4ca¹¹:

synthesized according to *General procedure B*: first step was run at 60 °C, 30 min; 113.4 mg (yield 81 %) was isolated over two steps (eluent EtOAc:hexanes (gradient from 1:50 to 1:1 to 1:0)). Brown solid.

$^1\text{H NMR}$ (400 MHz, acetone- d_6) δ 7.81 (s, 1H), 7.74–7.71 (m, 2H), 7.61–7.58 (m, 2H), 7.48–7.41 (m, 5H), 7.39–7.35 (m, 1H).

$^{13}\text{C NMR}$ (101 MHz, acetone- d_6) δ 163.26, 149.29, 142.23, 133.30, 133.18, 129.66, 129.17, 128.56, 128.16, 128.00, 125.92, 125.46.

HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{13}\text{O}_2\text{S}$ $[\text{M}]^+\text{H}$: 281.0636, found: 281.0634

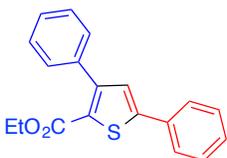
Ethyl 5-pentyl-2-phenylthiophene-3-carboxylate, 3ch:

synthesized according to *General procedure A* at 60 °C, 7 h; 74.5 mg (yield 99 %) was isolated (eluent EtOAc:hexanes 1:20). Brown oil, $R_f=0.53$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.49–7.47 (m, 2H), 7.39–7.36 (m, 3H), 7.19 (s, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.79 (t, $J = 7.4$ Hz, 1H), 1.74–1.67 (m, 2H), 1.40 – 1.37 (m, 4H), 1.18 (t, $J = 7.1$ Hz, 3H), 0.93 (t, $J = 7.0$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 163.49, 148.36, 144.36, 133.82, 129.75, 128.18, 127.78, 127.66, 126.49, 60.32, 31.21, 31.05, 29.80, 22.38, 14.00, 13.97.

HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{23}\text{O}_2\text{S}$ $[\text{M}]+\text{H}$: 303.1419, found: 303.1419.

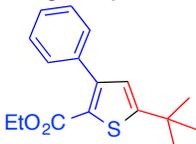
Ethyl 3,5-diphenylthiophene-2-carboxylate, 3da¹²:

synthesized according to *General procedure A* at 60 °C, 7 h; 64.6 mg (yield 84 %) was isolated (eluent EtOAc:hexanes gradient from 1:300 to 1:50 to 1:10), then crystallization from hexanes. Yellow solid, $R_f=0.40$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68–7.65 (m, 2H), 7.52–7.48 (m, 2H), 7.45–7.37 (m, 6H), 7.29 (s, 1H), 4.25 (q, $J = 7.1$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 162.06, 149.27, 148.28, 135.90, 133.23, 129.17, 129.09, 128.82, 127.95, 127.78, 127.39, 126.12, 60.94, 14.11.

HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{17}\text{O}_2\text{S}$ $[\text{M}]+\text{H}$: 309.0949, found: 309.0948.

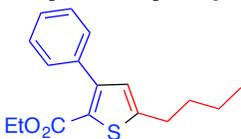
Ethyl 5-(tert-butyl)-3-phenylthiophene-2-carboxylate, 3dj:

synthesized according to *General procedure A* at 80 °C, 5 h; 54.0 mg (yield 75 %) was isolated (eluent EtOAc:hexanes (1:10)). Yellow oil, $R_f=0.47$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.49–7.46 (m, 2H), 7.42–7.34 (m, 3H), 6.86 (s, 1H), 4.23 (q, $J = 7.1$ Hz, 1H), 1.44 (s, 9H), 1.25 (t, $J = 7.1$ Hz, 2H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 162.40, 162.24, 148.32, 136.32, 129.20, 127.67, 126.59, 124.02, 60.66, 34.94, 32.14, 14.14.

HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{21}\text{O}_2\text{S}$ $[\text{M}]+\text{H}$: 289.1262, found: 289.1266.

Ethyl 5-butyl-3-phenylthiophene-2-carboxylate, 3dr:

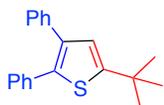
synthesized according to *General procedure A* at 60 °C, 7 h; 69.6 mg (yield 97 %) was isolated (eluent EtOAc:hexanes (1:100)). Ratio of inseparable regioisomers determined by NMR is 11:1. Colorless oil, $R_f=0.48$ (EtOAc:hexanes (1:10)).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.46–7.34 (m, 5H), 6.79 (t, $J = 0.8$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 2.83 (t, $J = 7.6$ Hz, 2H), 1.74–1.67 (m, 2H), 1.42 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.95 (t, $J = 7.3$ Hz, 3H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 162.13, 151.14, 148.52, 136.16, 129.18, 129.08, 127.69, 127.66, 60.65, 33.33, 29.95, 22.13, 14.10, 13.74.

HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{20}\text{NaO}_2\text{S}$ $[\text{M}]+\text{Na}$: 311.1082, found: 311.1083.

5-(*tert*-Butyl)-2,3-diphenylthiophene, 3ej:



synthesized according to *General procedure A* at 80 °C, 2 h; 58.5 mg (yield 80 %) was isolated (eluent hexanes). Colorless oil, $R_f=0.57$ (EtOAc:hexanes (1:10)).

^1H NMR (400 MHz, CDCl_3) δ 7.49–7.13 (m, 10H), 6.92 (s, 1H), 1.48 (s, 9H).

^{13}C NMR (101 MHz, CDCl_3) δ 155.99, 137.26, 137.08, 135.41, 134.74, 129.17, 129.11, 128.35, 128.30, 126.99, 126.68, 125.07, 34.61, 32.41.

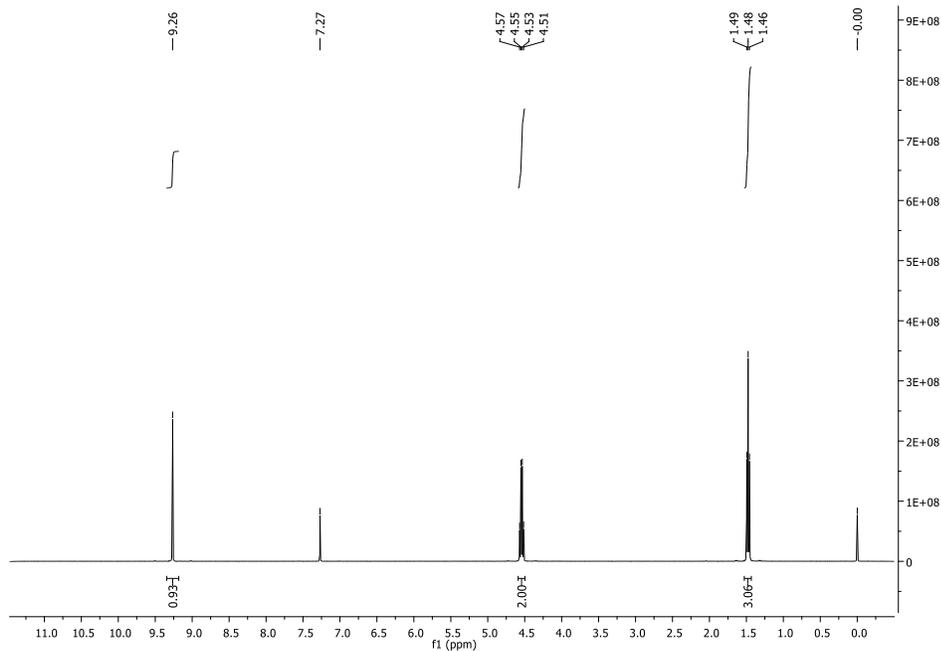
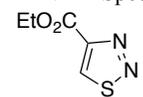
HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{21}\text{S}$ $[\text{M}]^+\text{H}$: 293.1364, found: 293.1351.

5. References

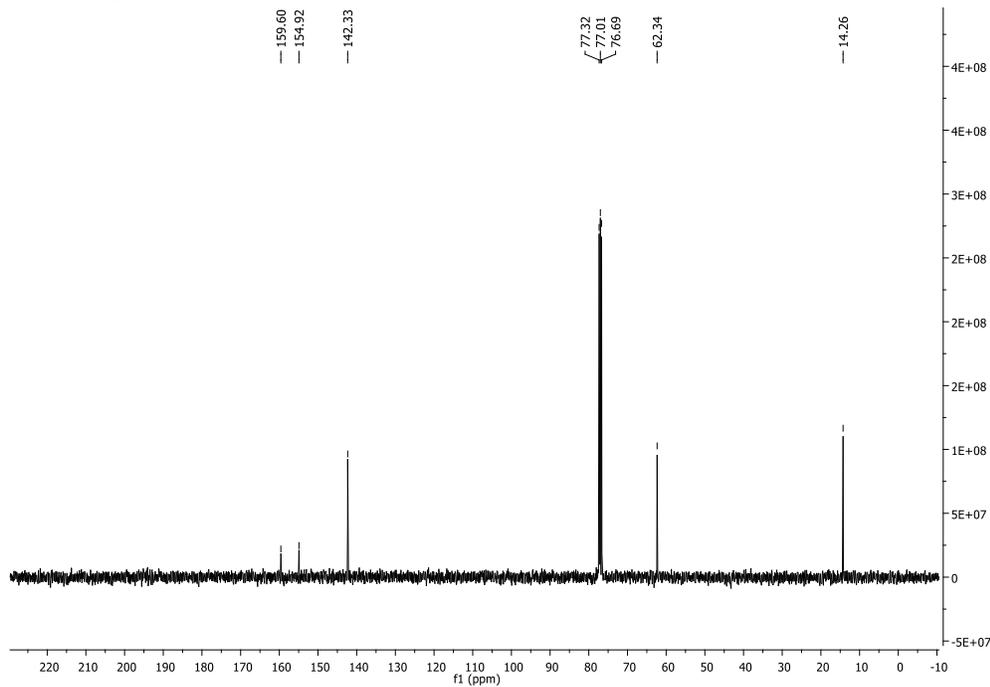
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6. Spectral data

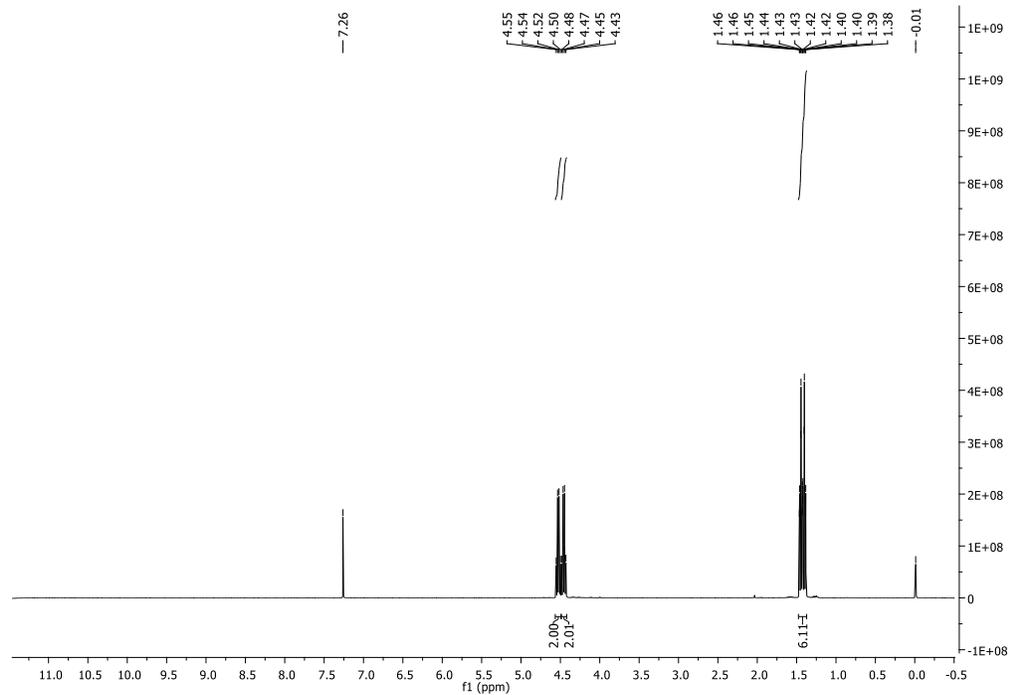
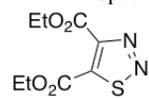
¹H NMR Spectrum of **1a**



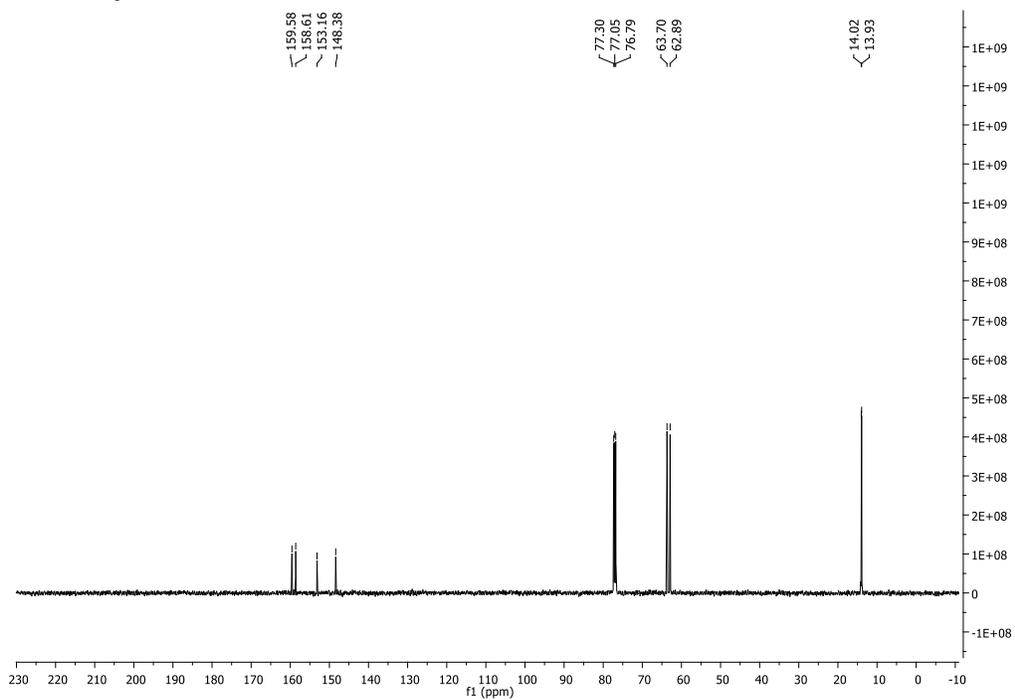
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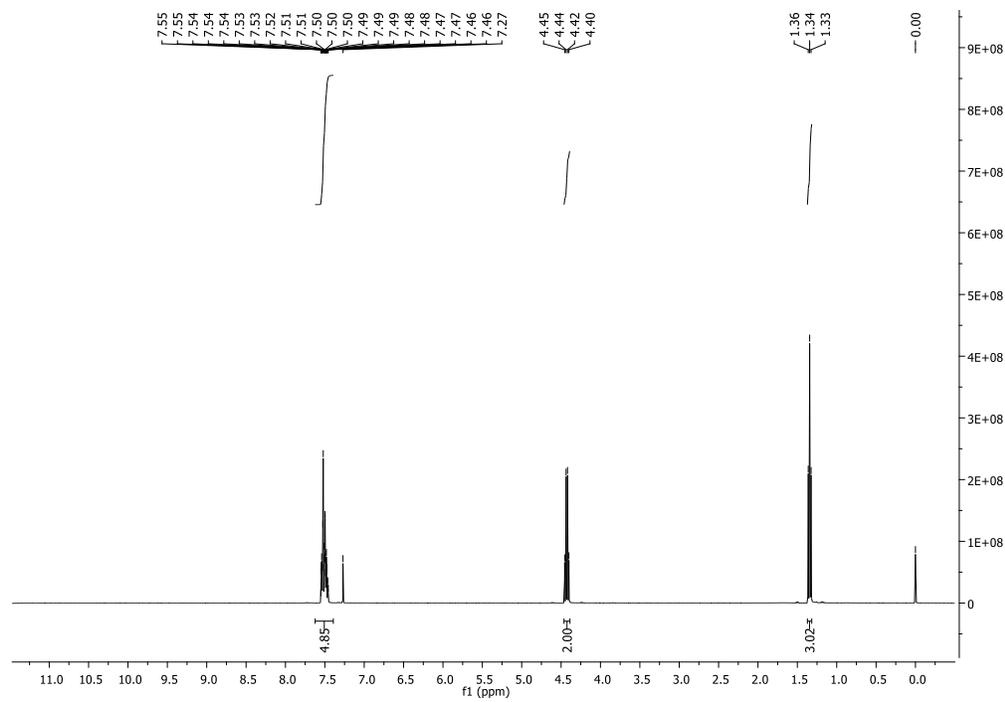
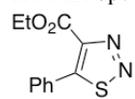
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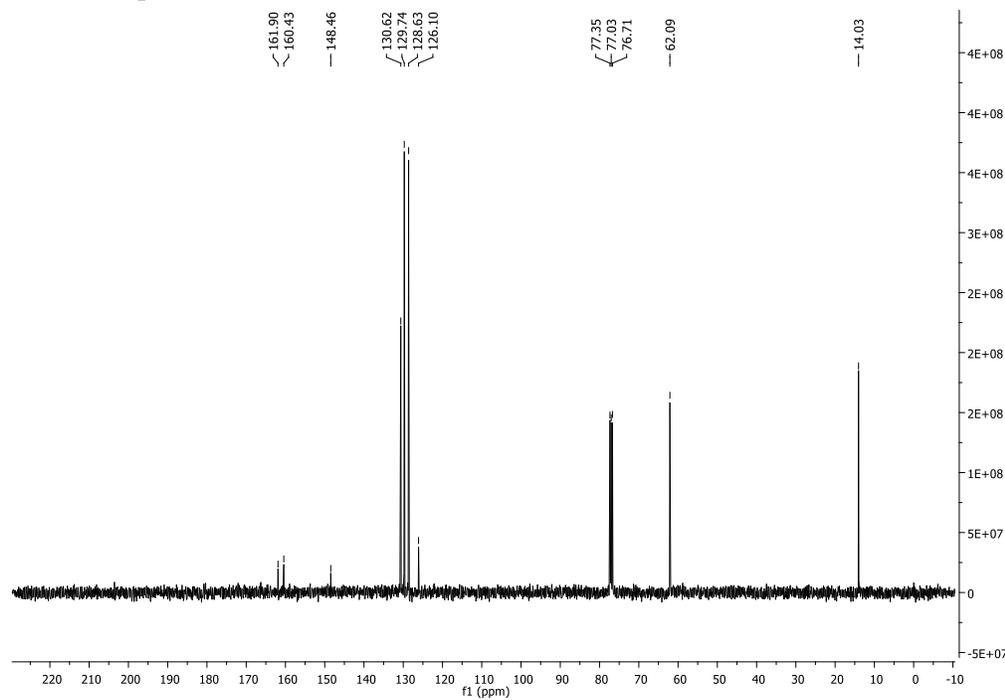
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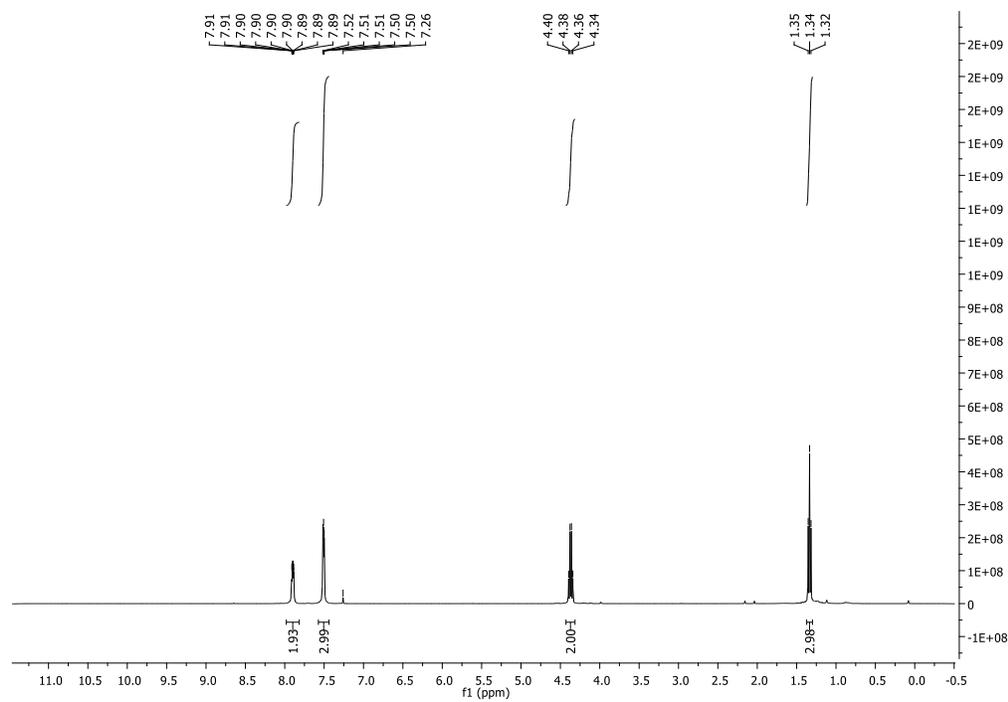
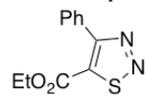
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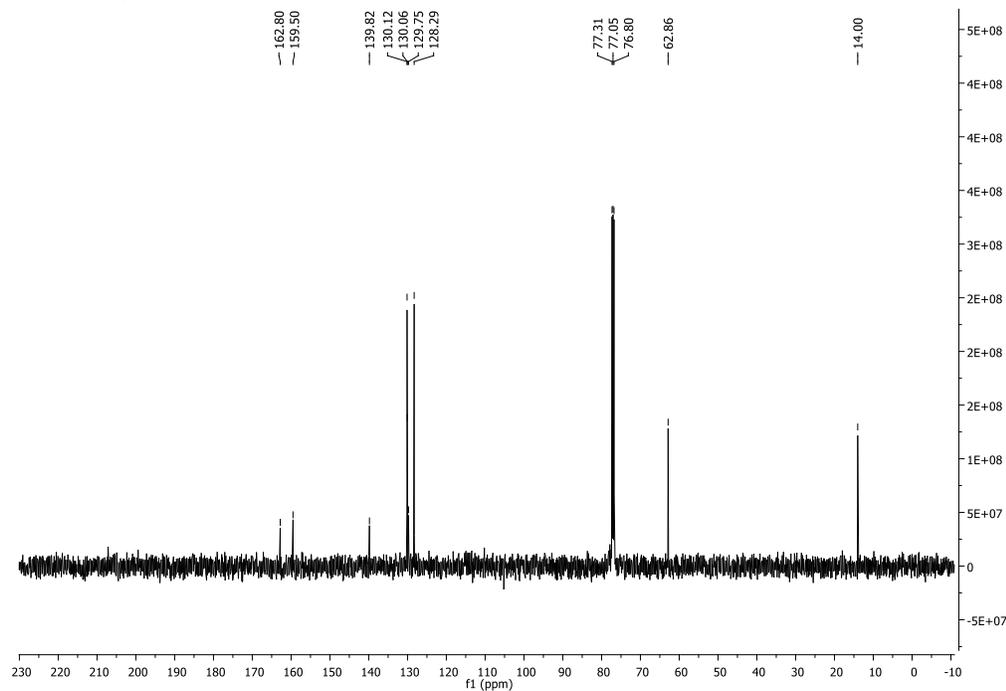
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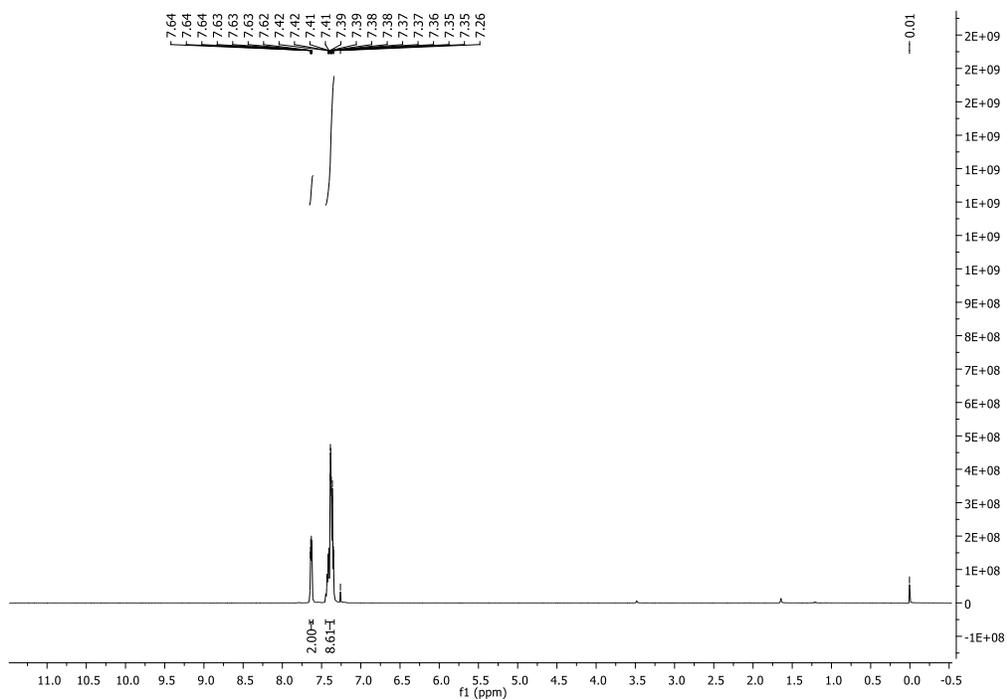
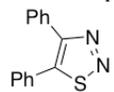
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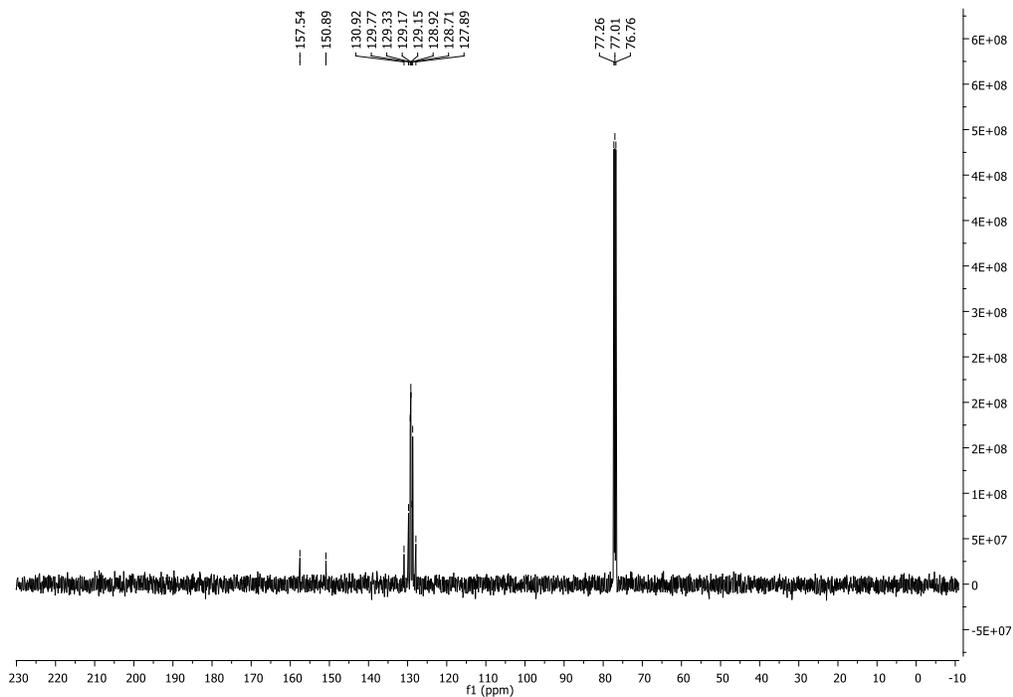
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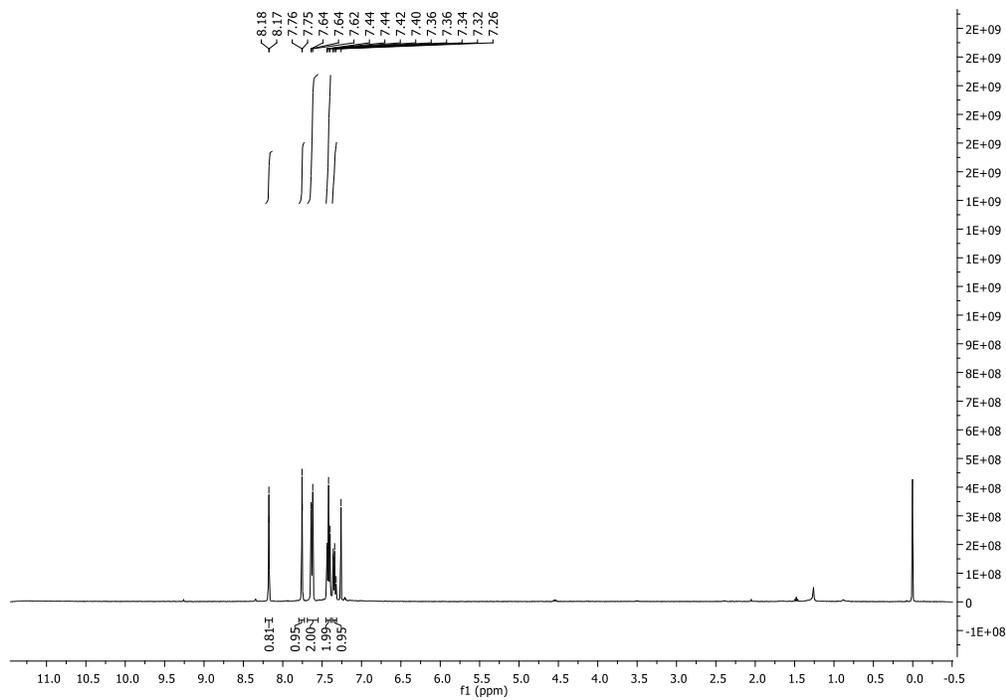
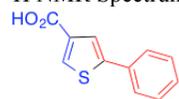
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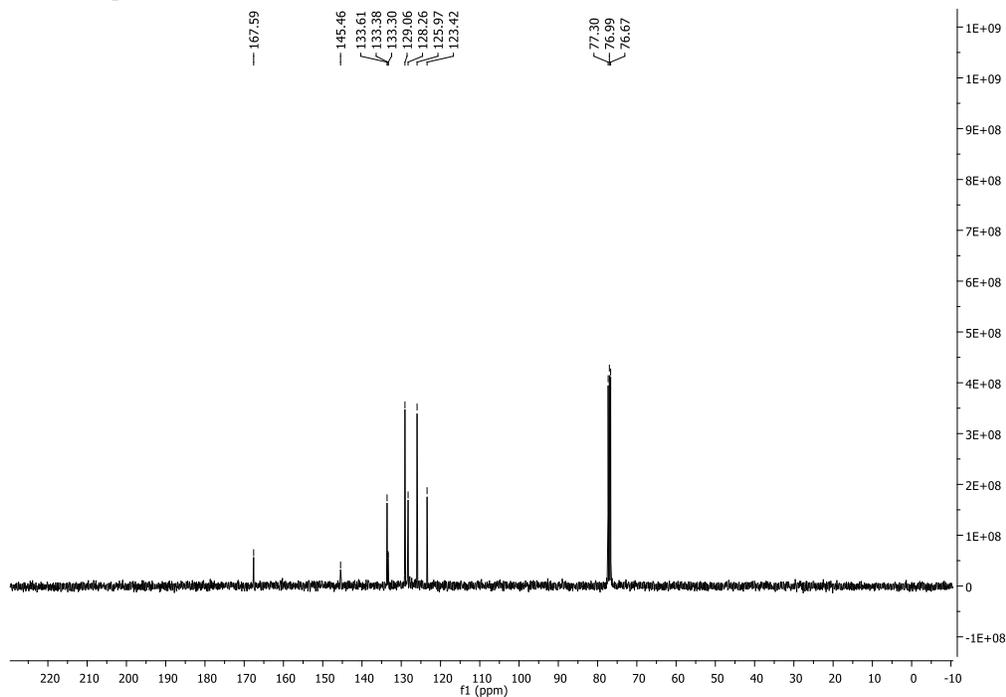
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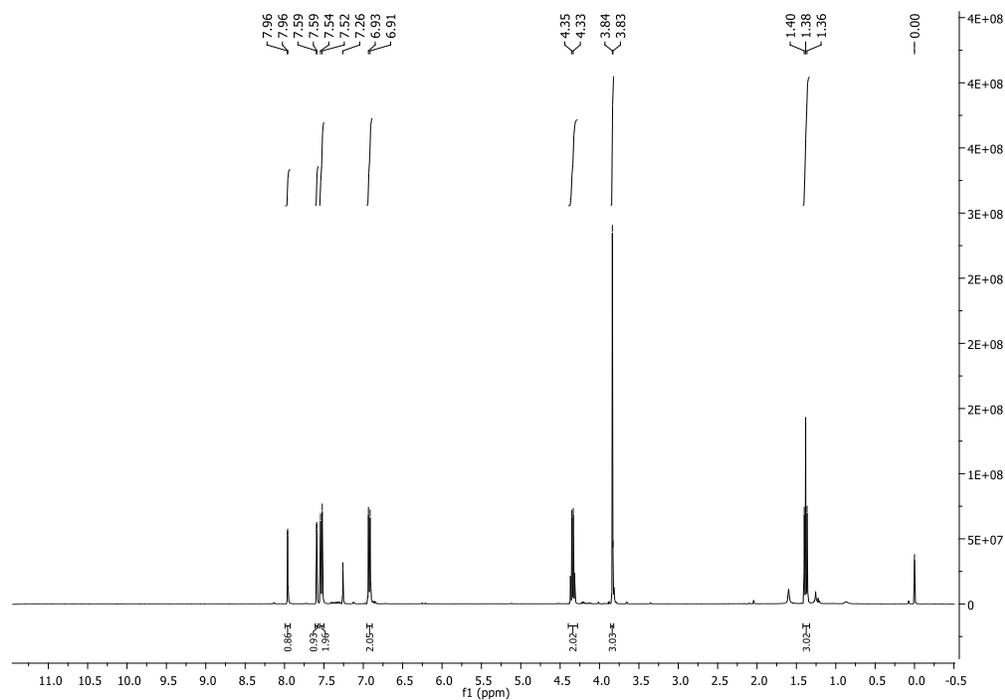
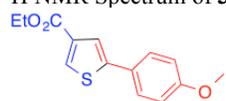
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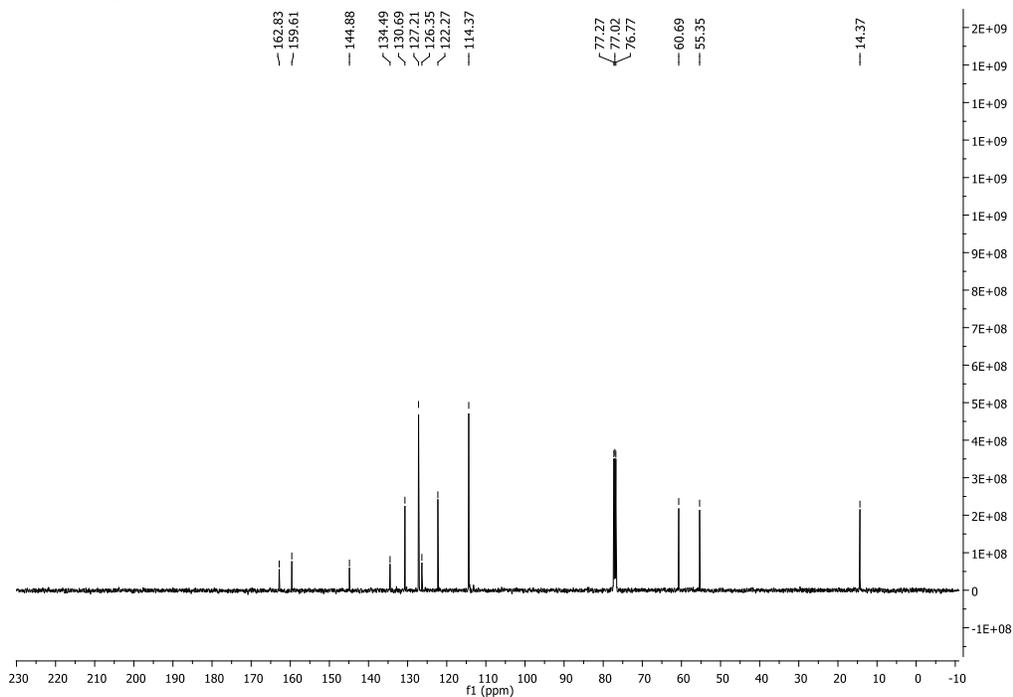
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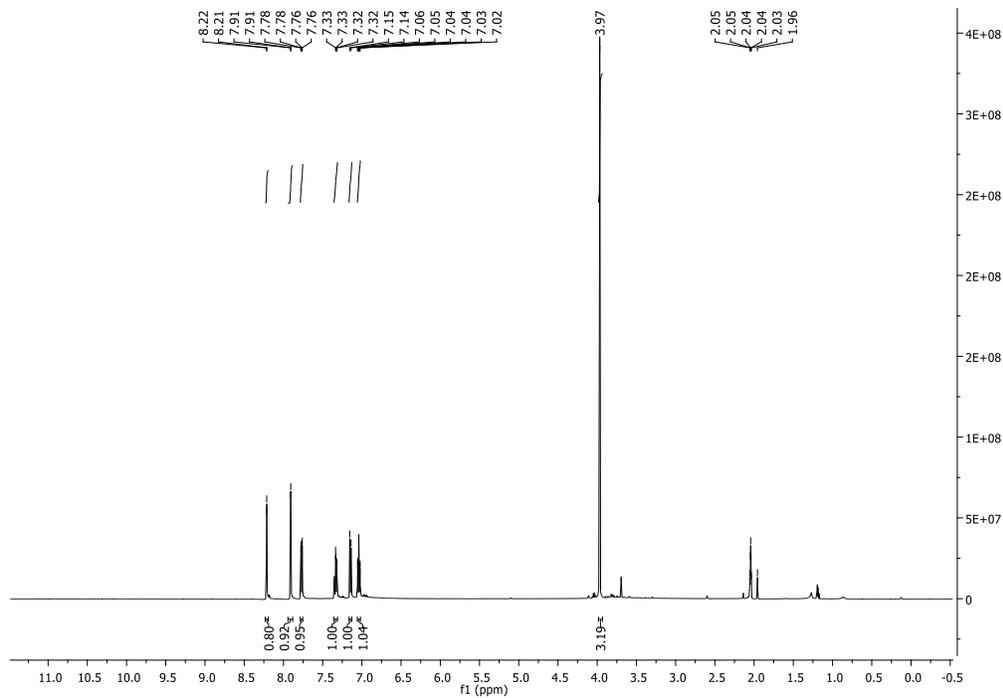
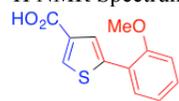
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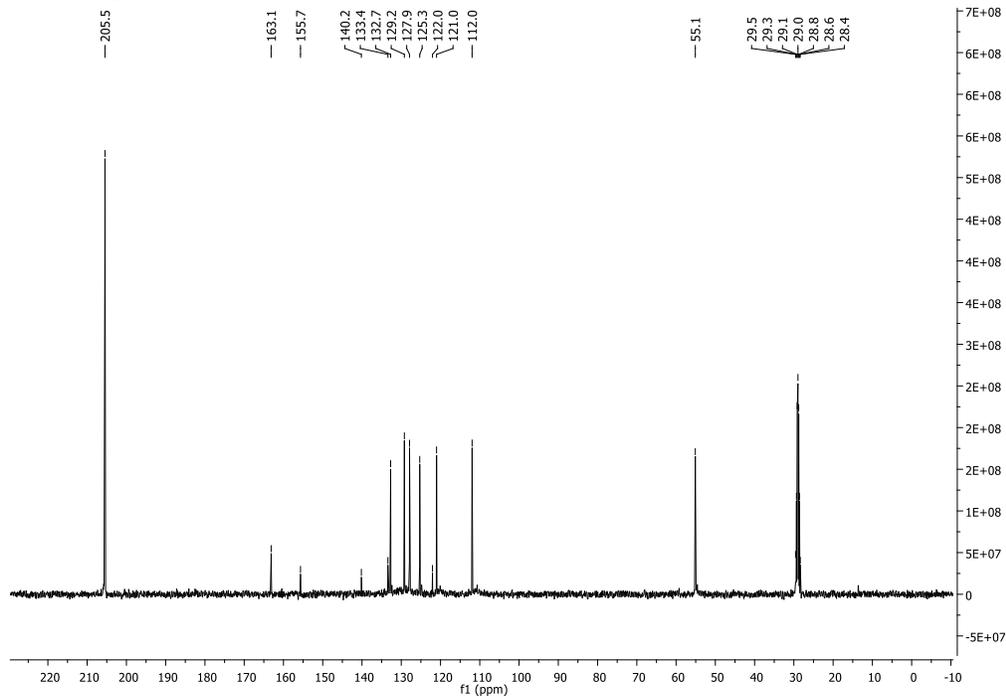
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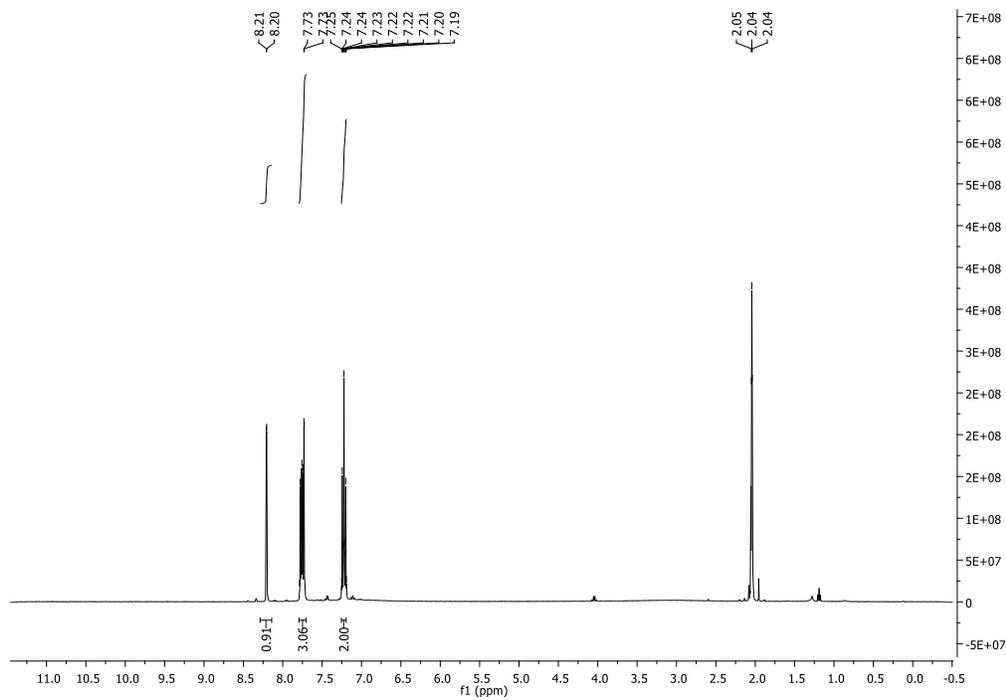
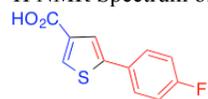
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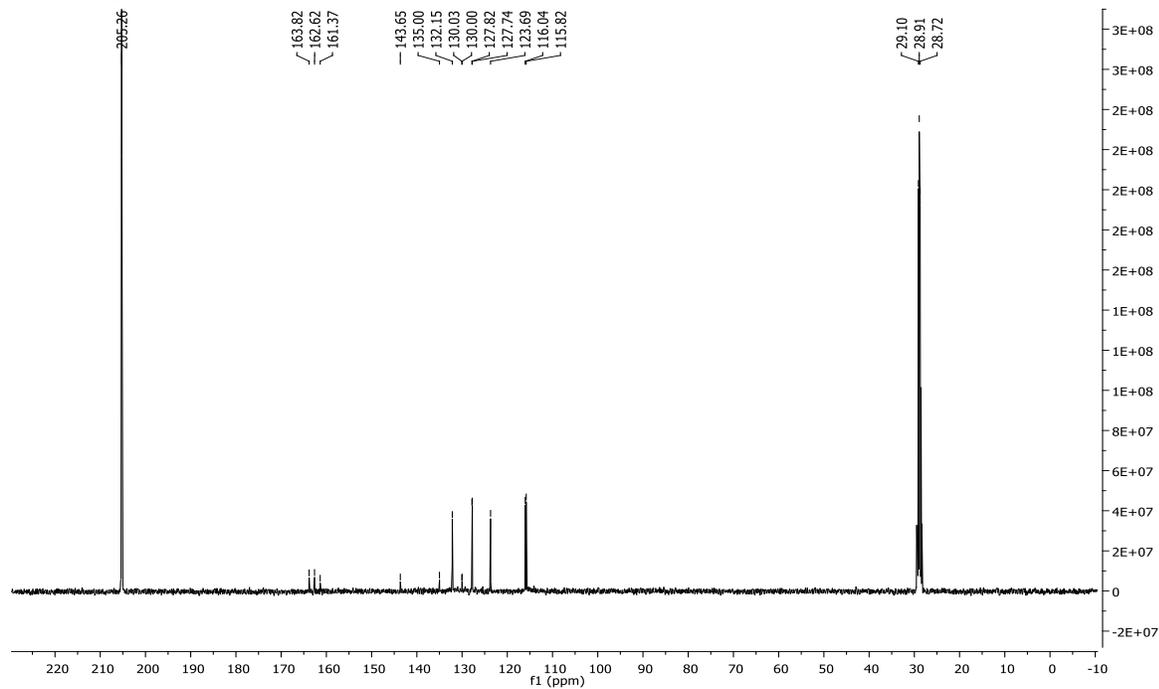
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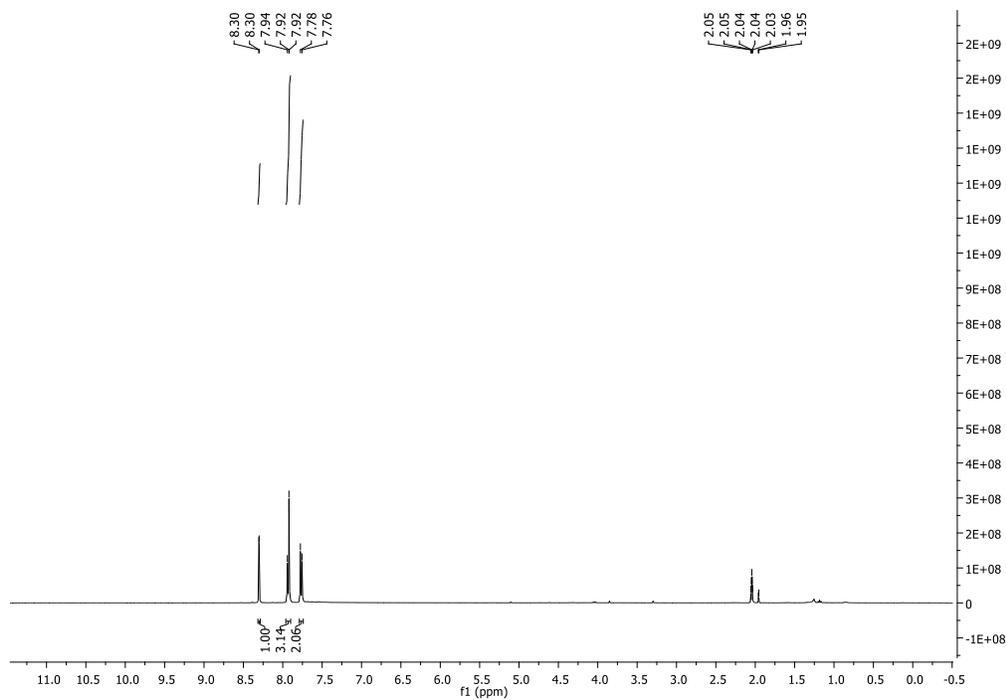
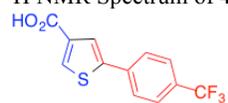
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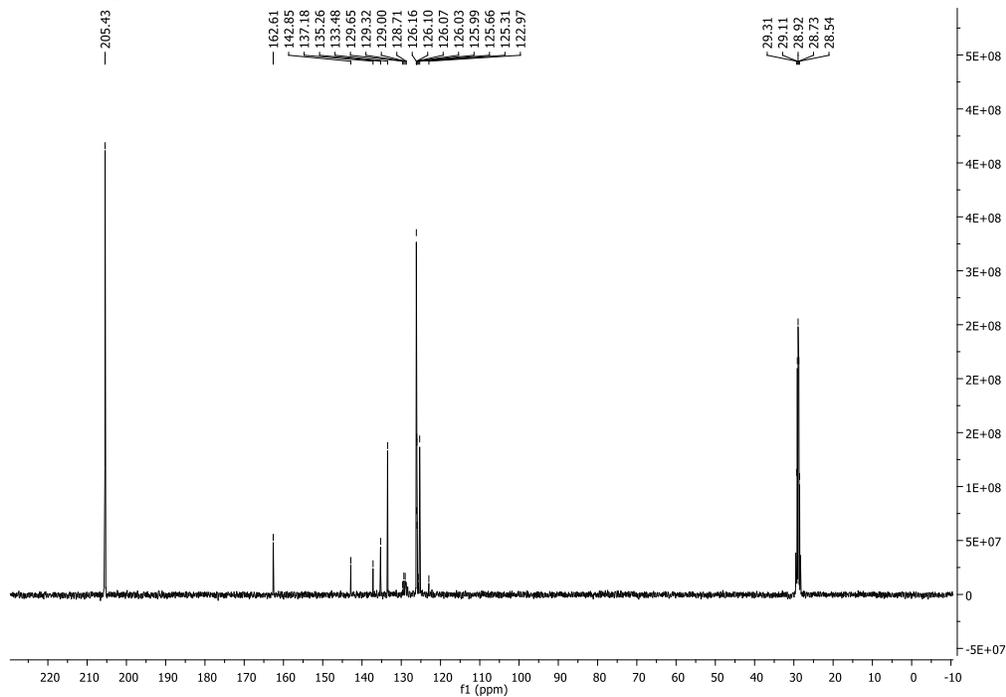
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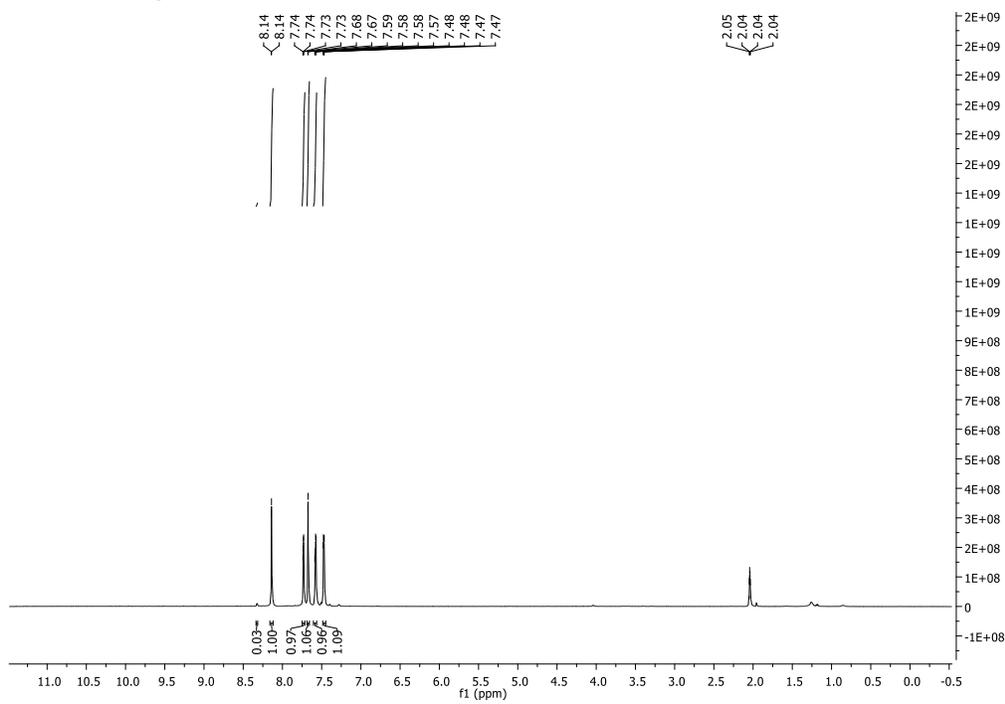
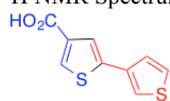
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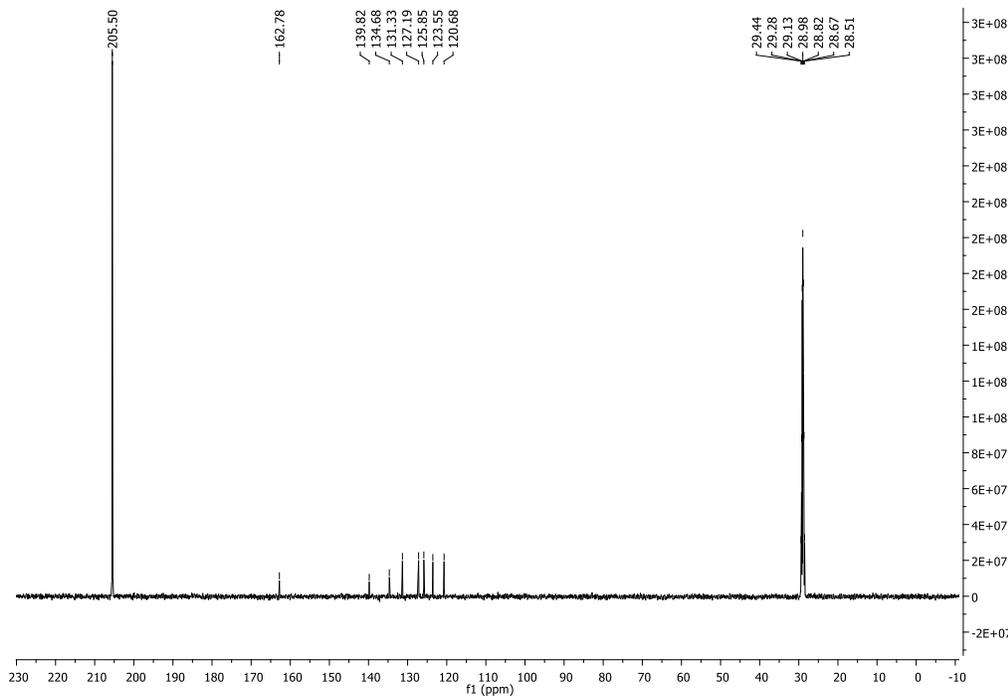
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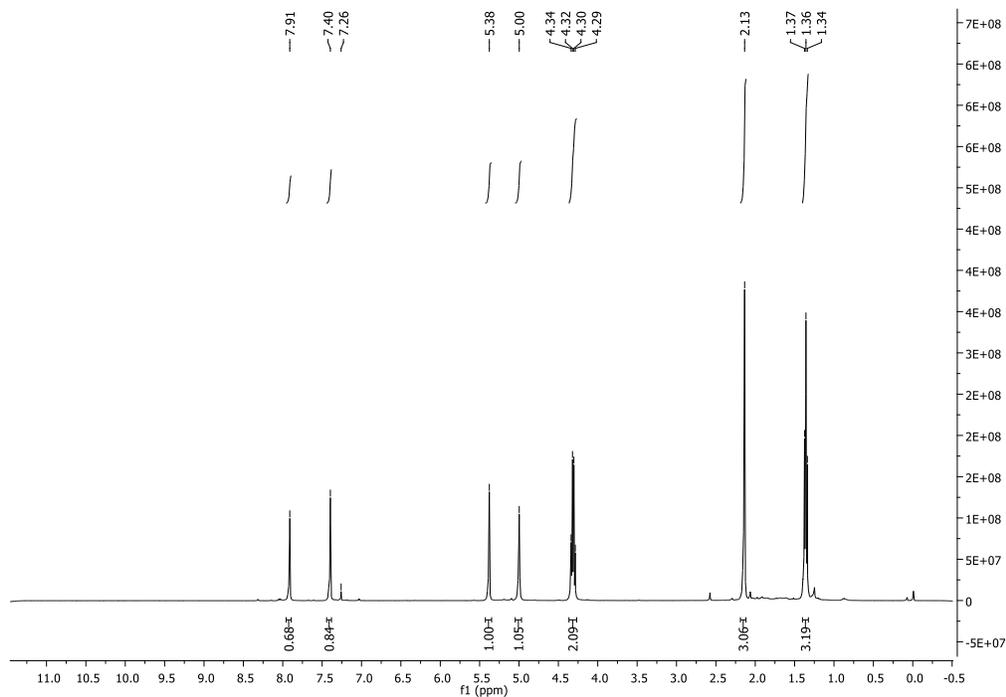
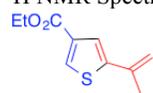
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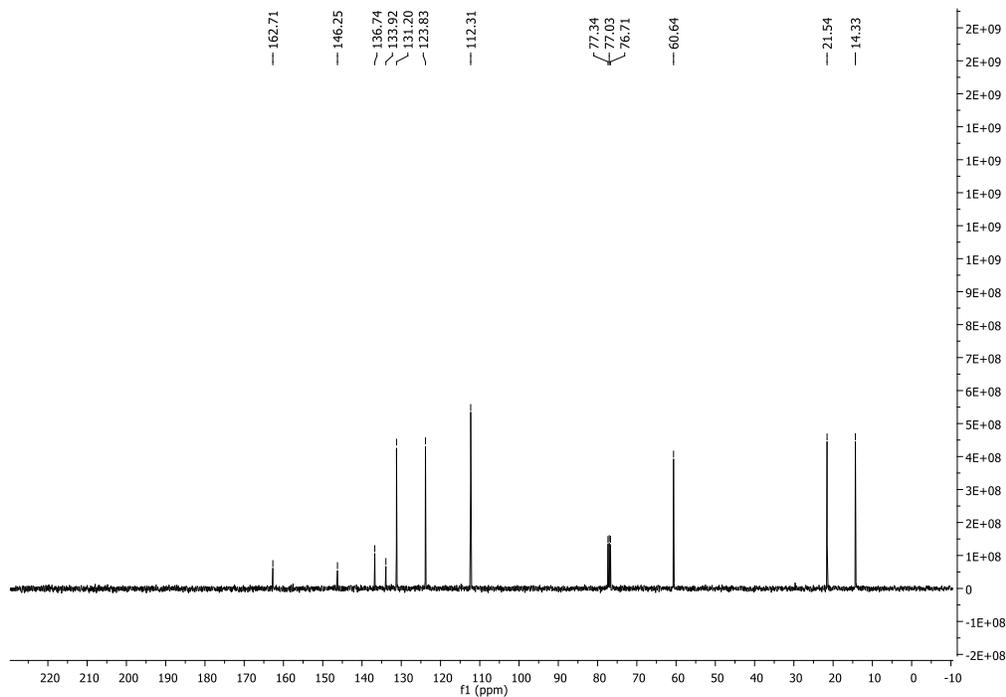
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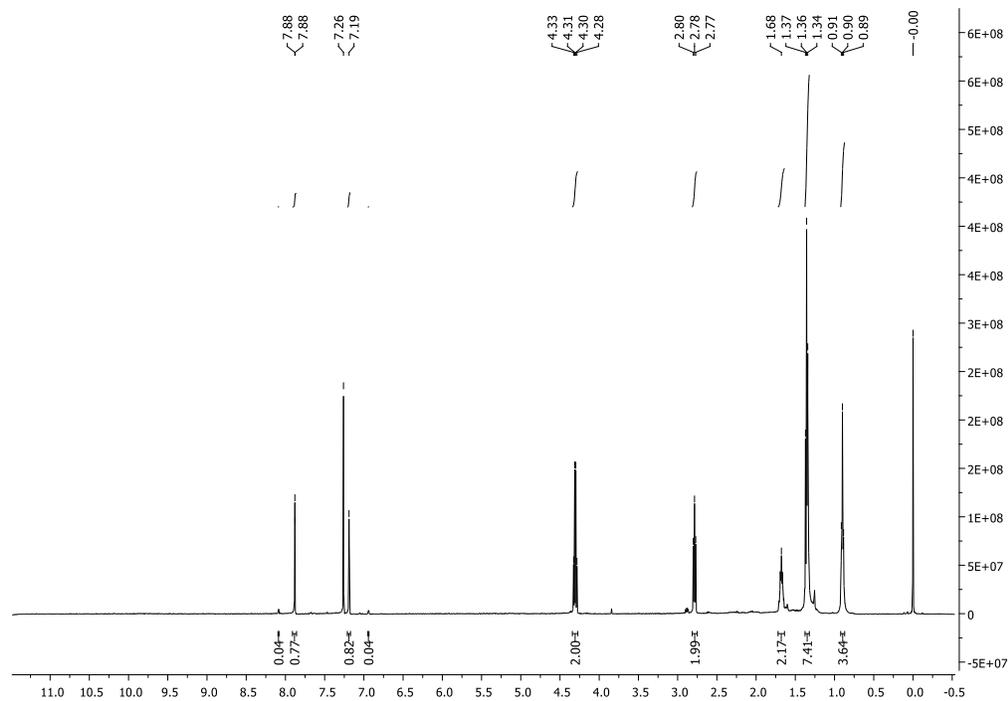
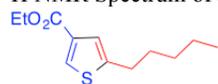
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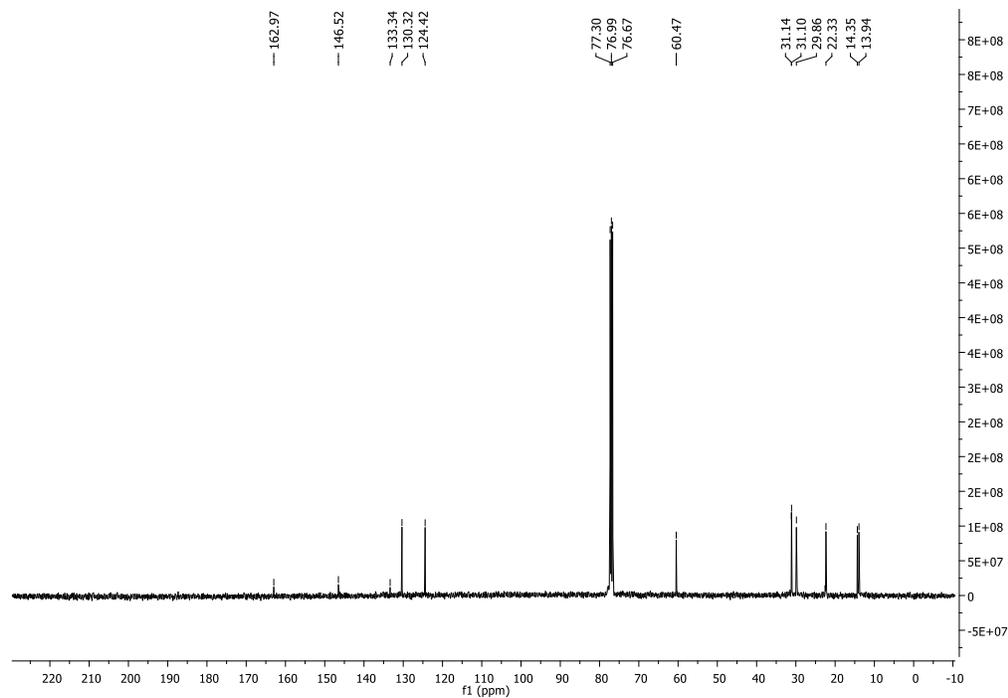
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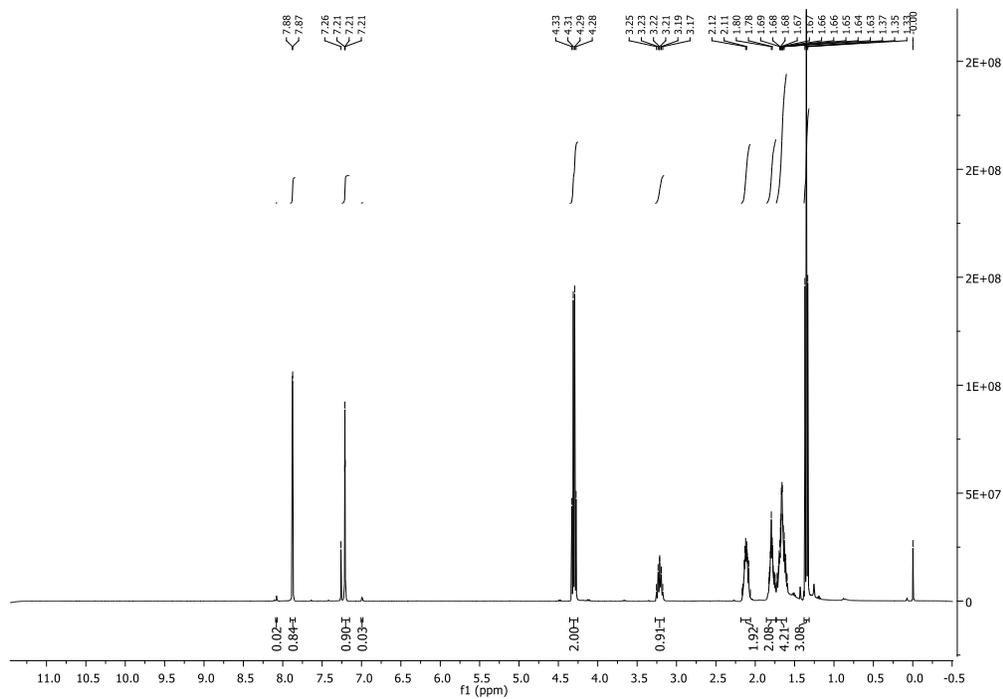
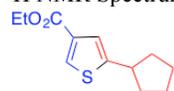
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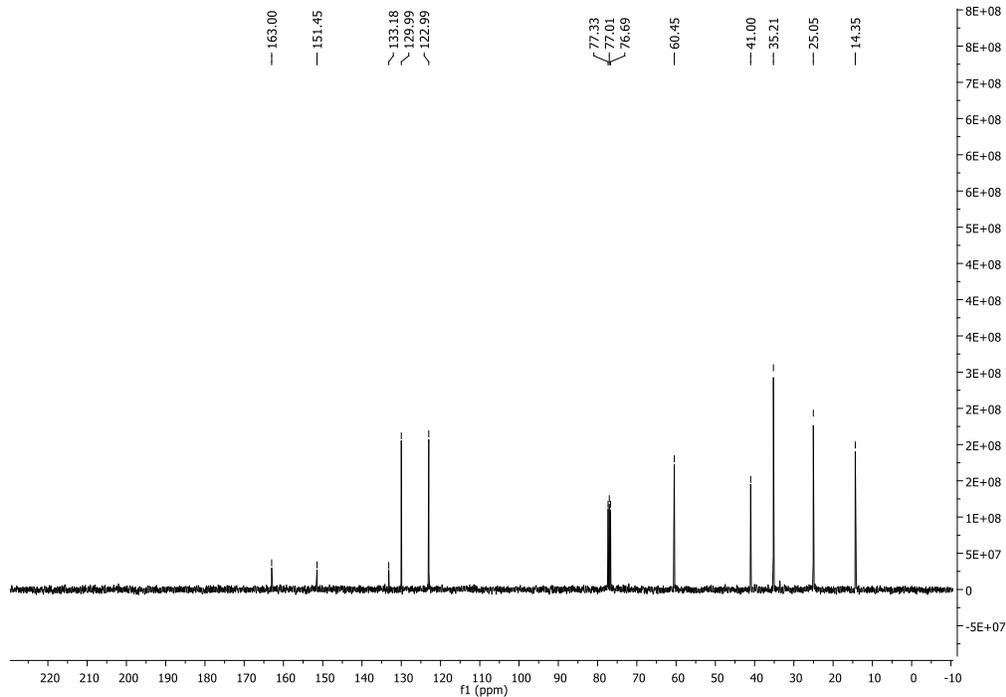
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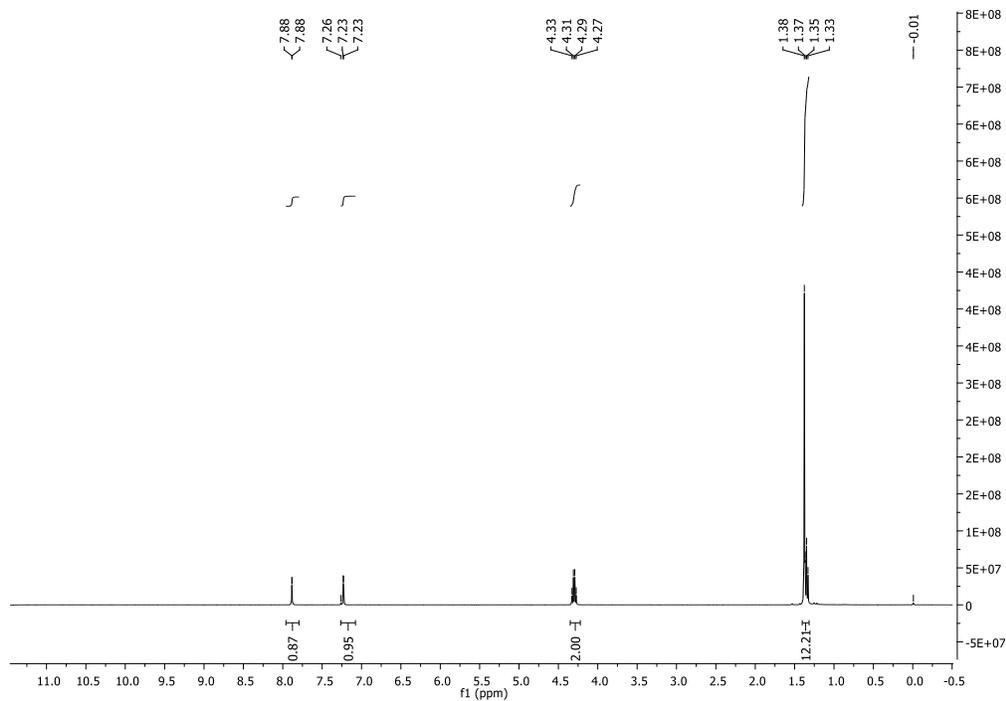
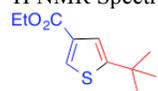
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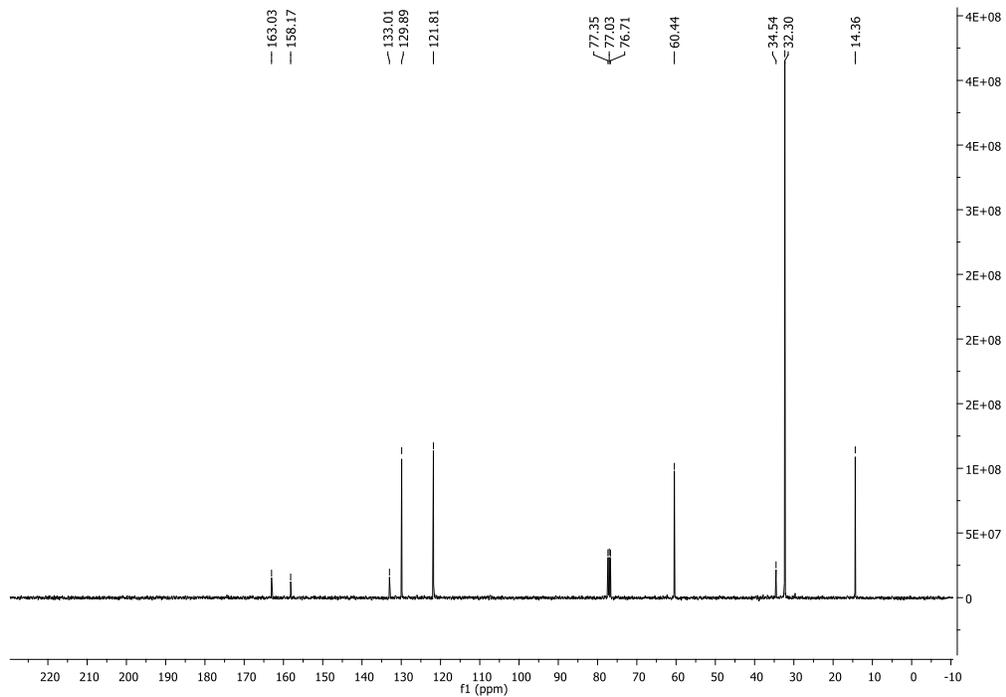
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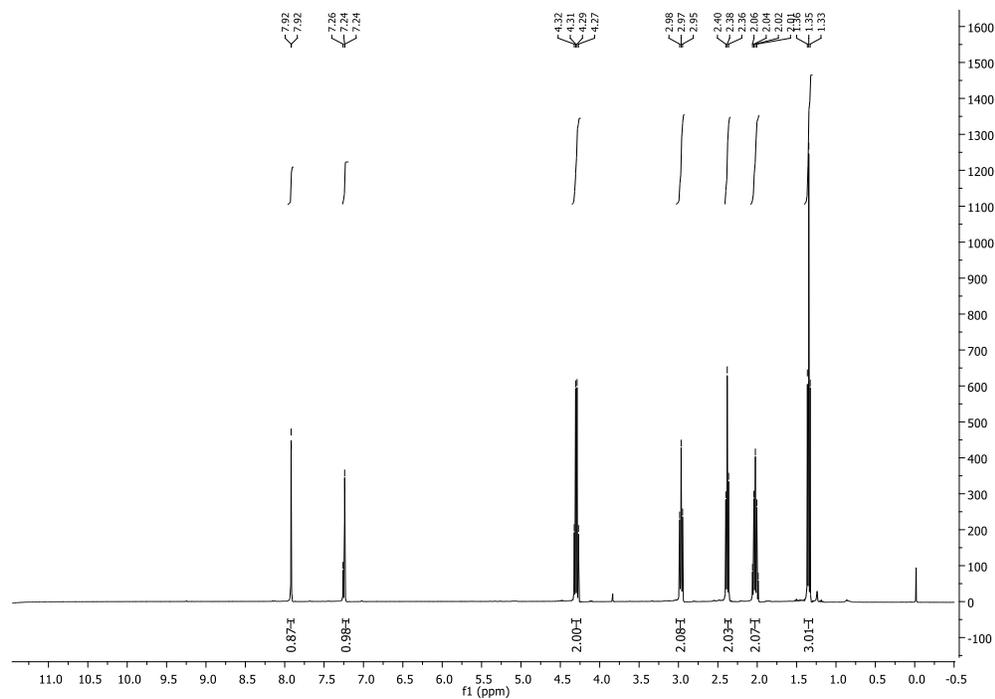
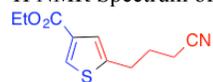
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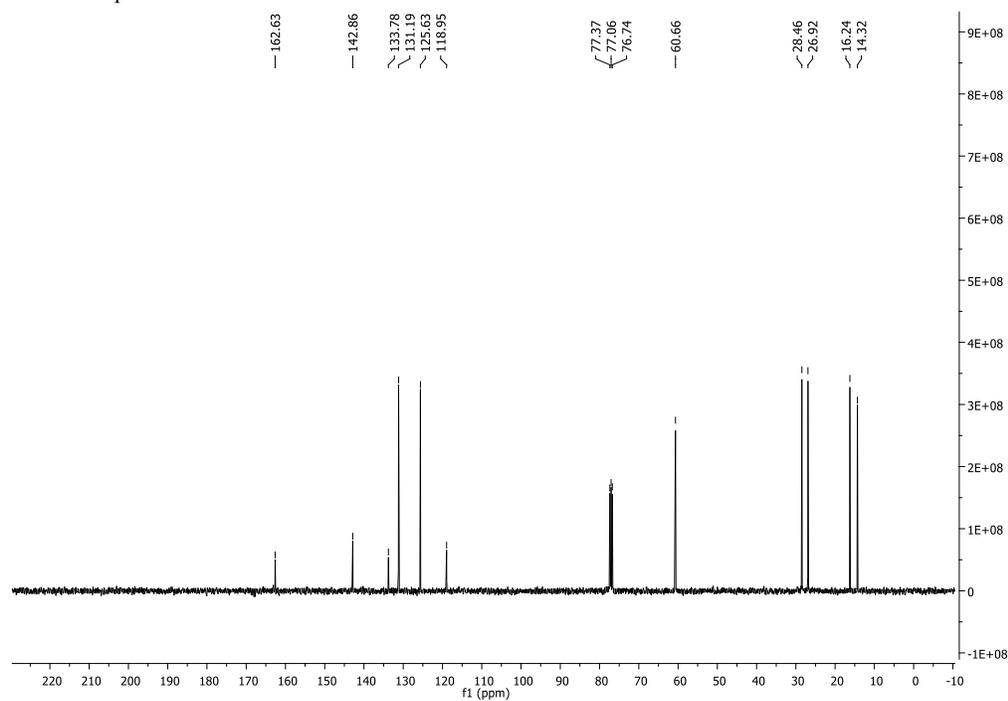
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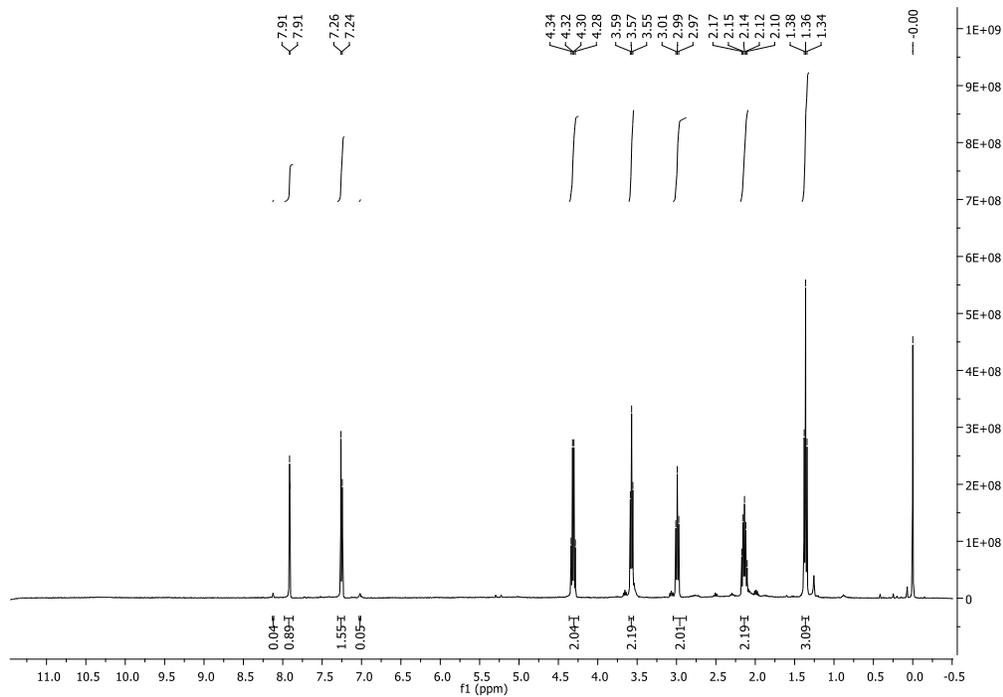
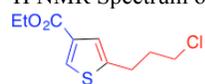
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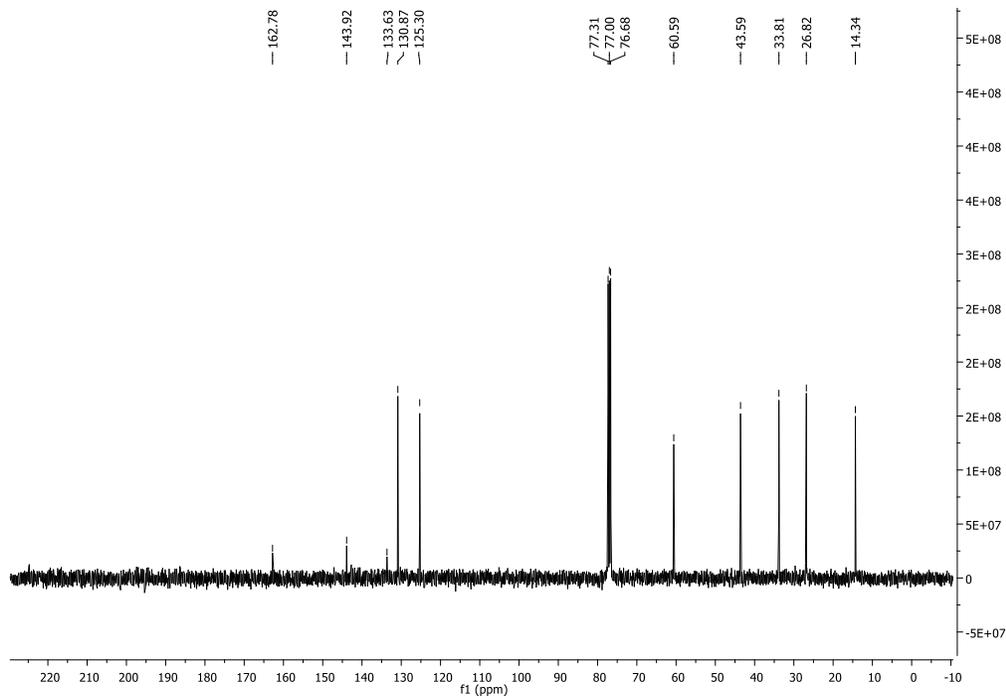
¹³C NMR Spectrum of 3ak



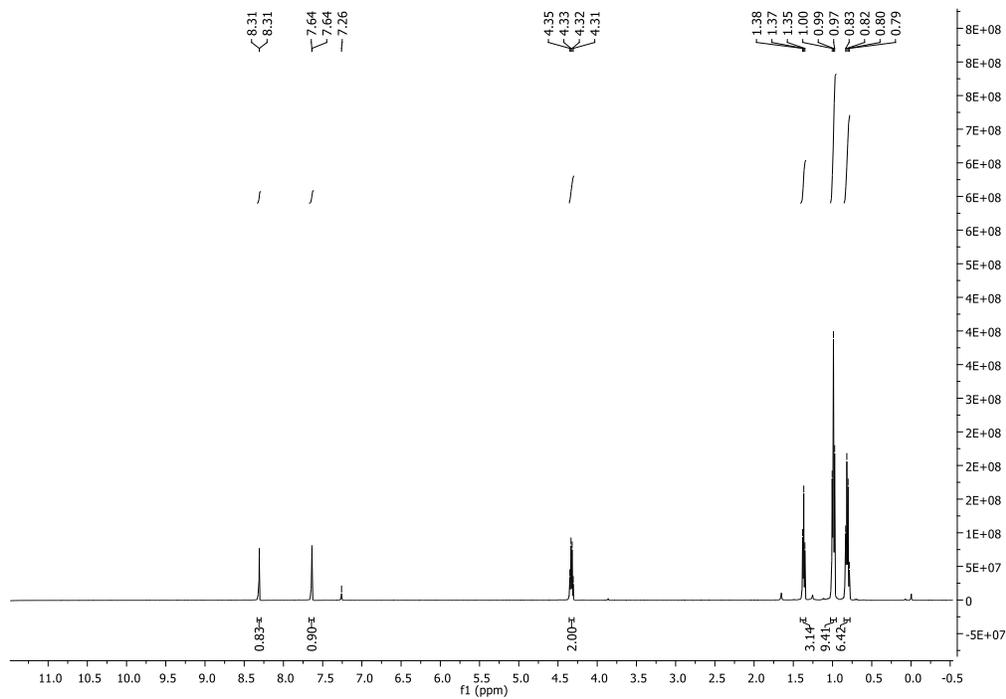
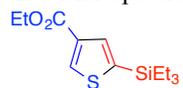
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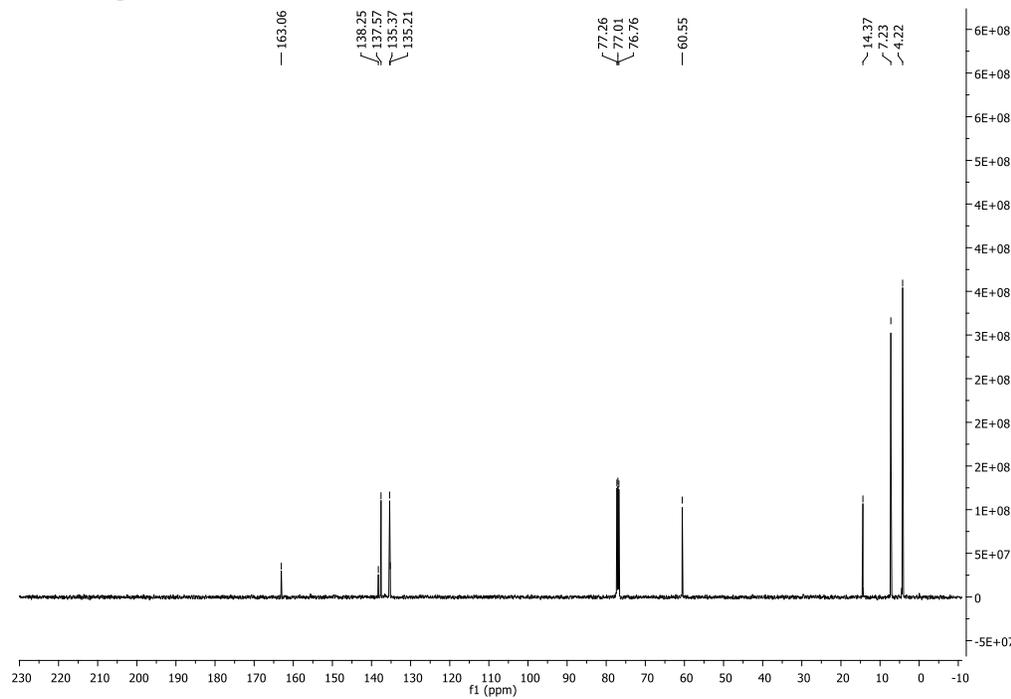
¹³C NMR Spectrum of 3al



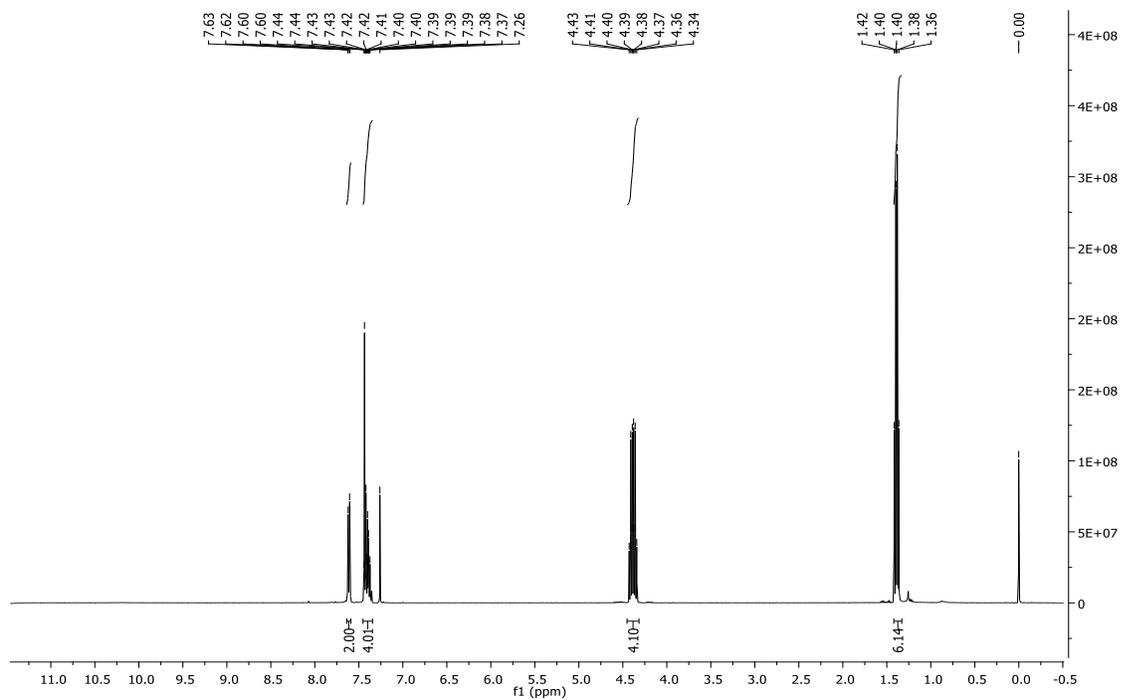
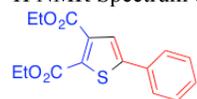
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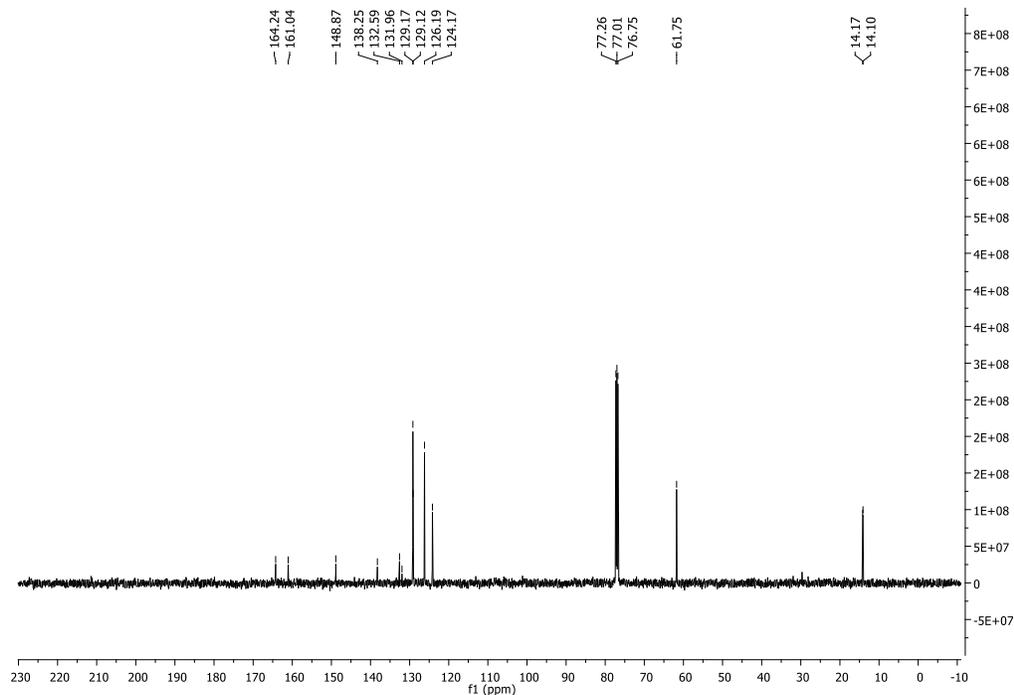
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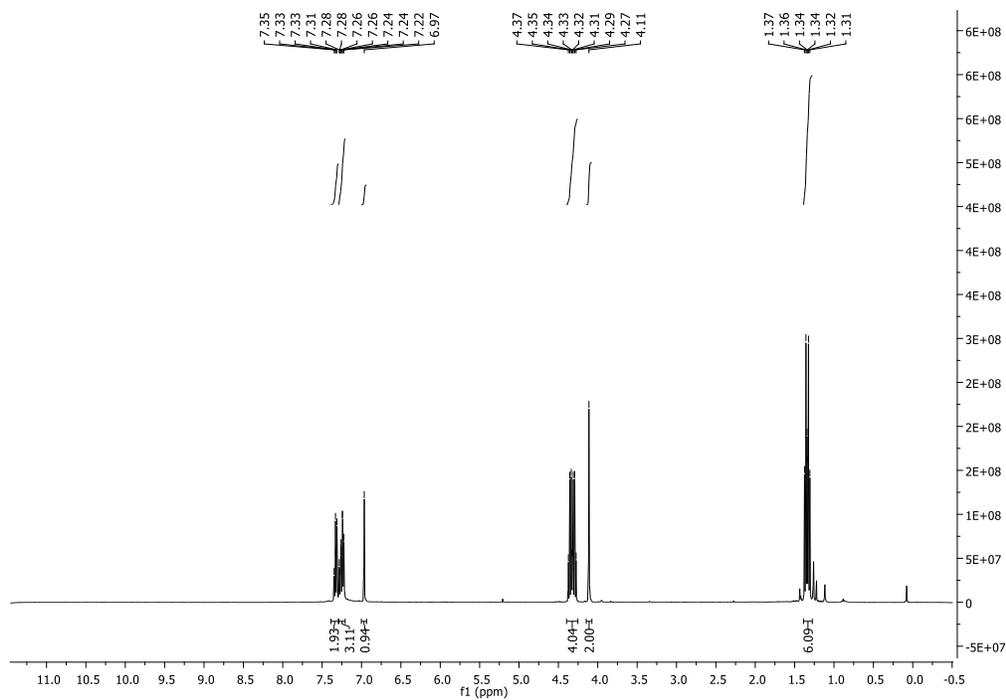
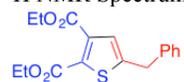
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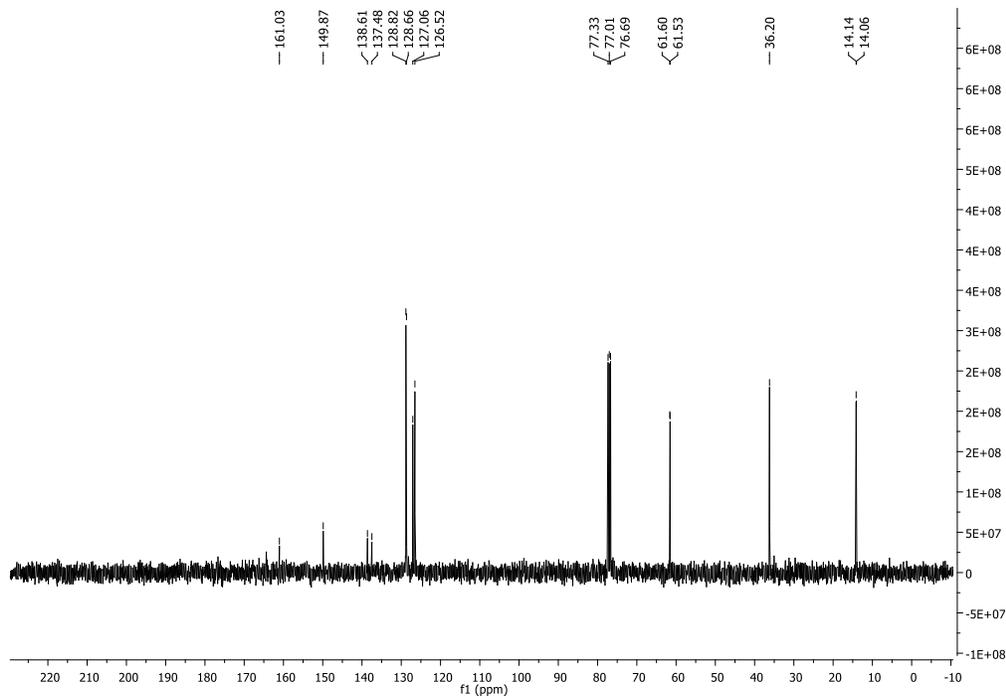
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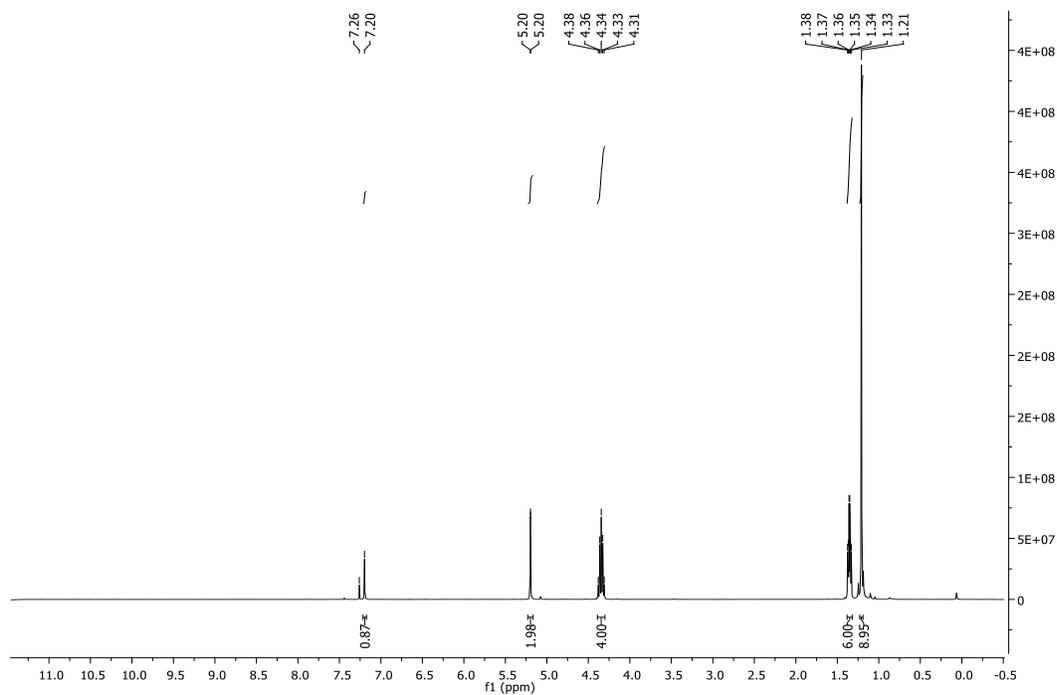
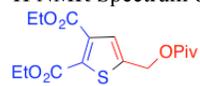
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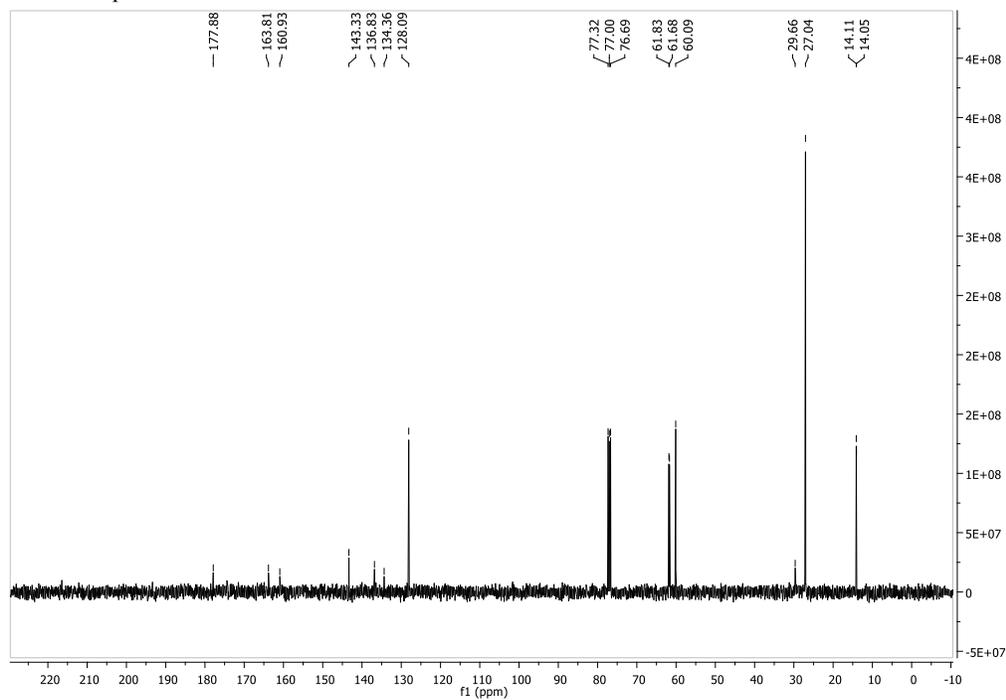
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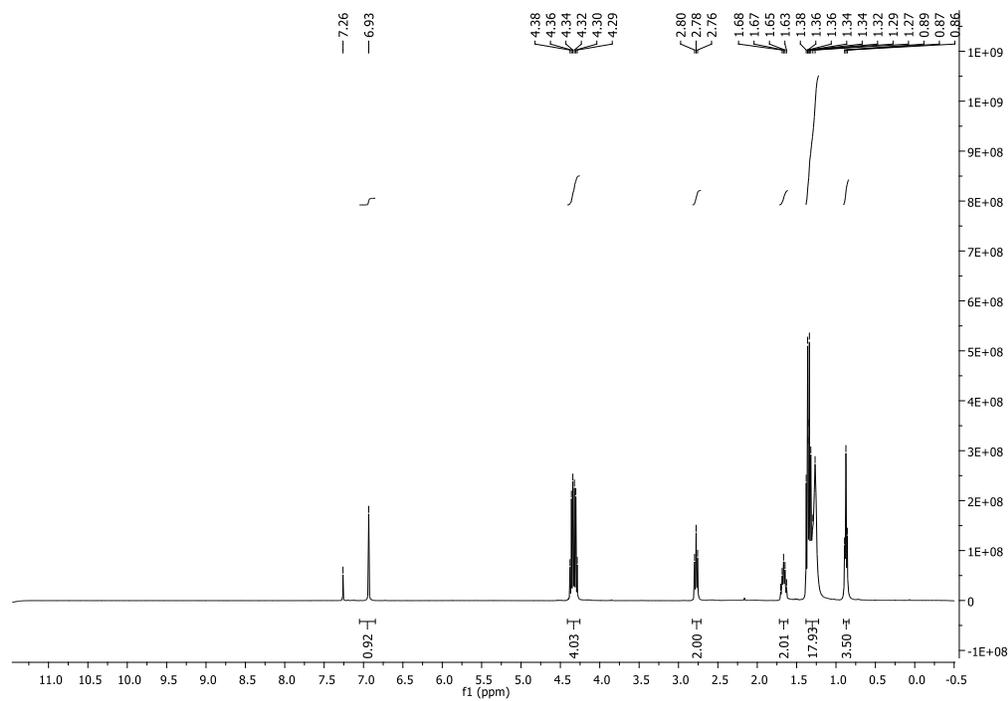
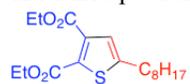
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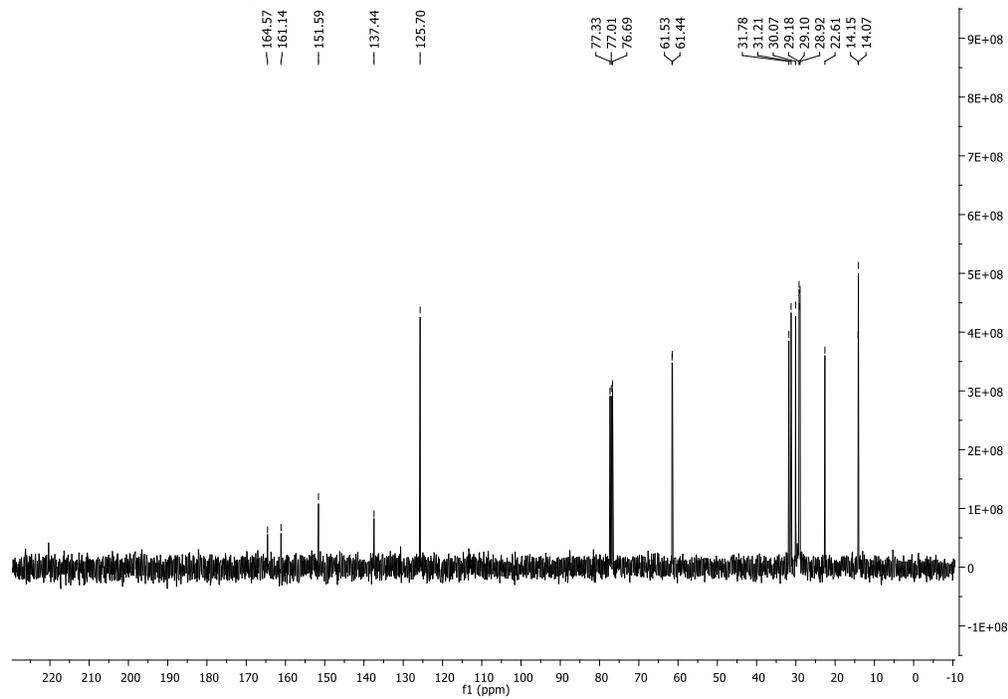
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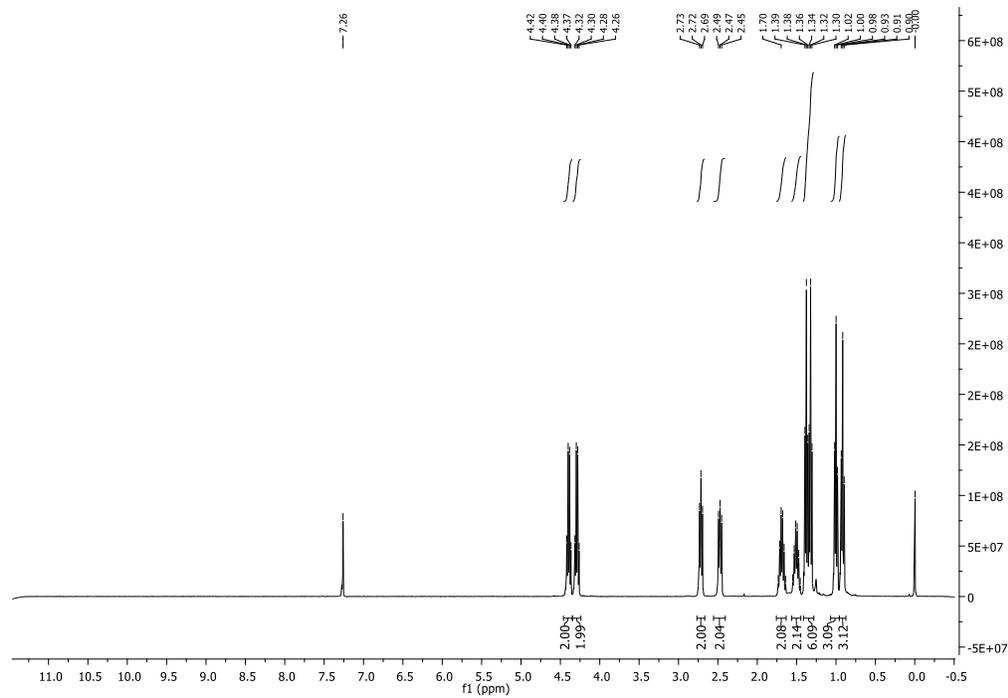
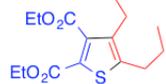
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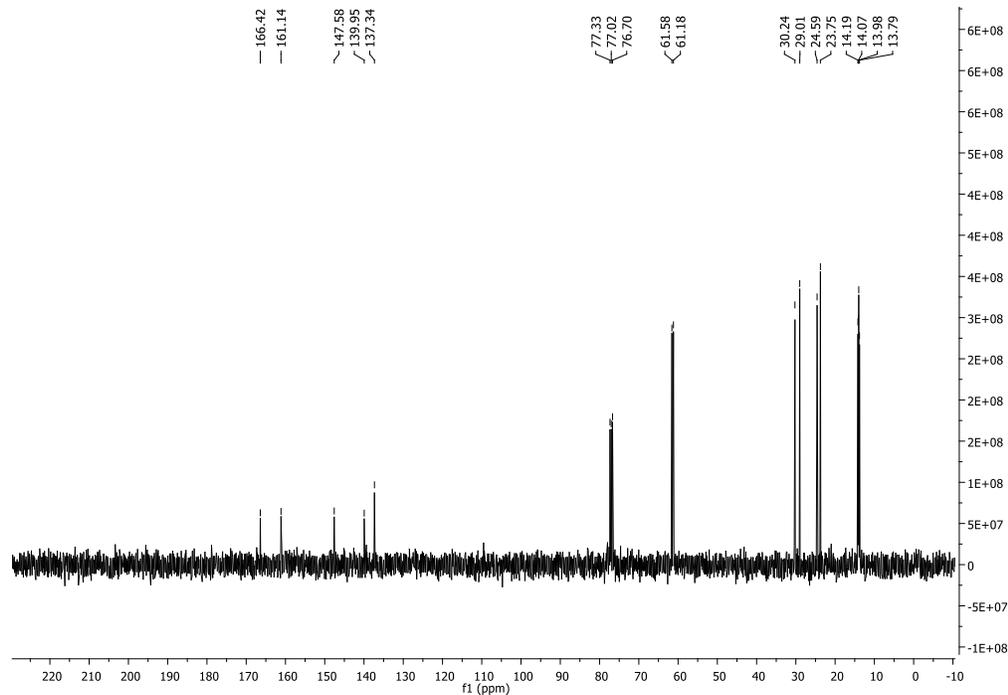
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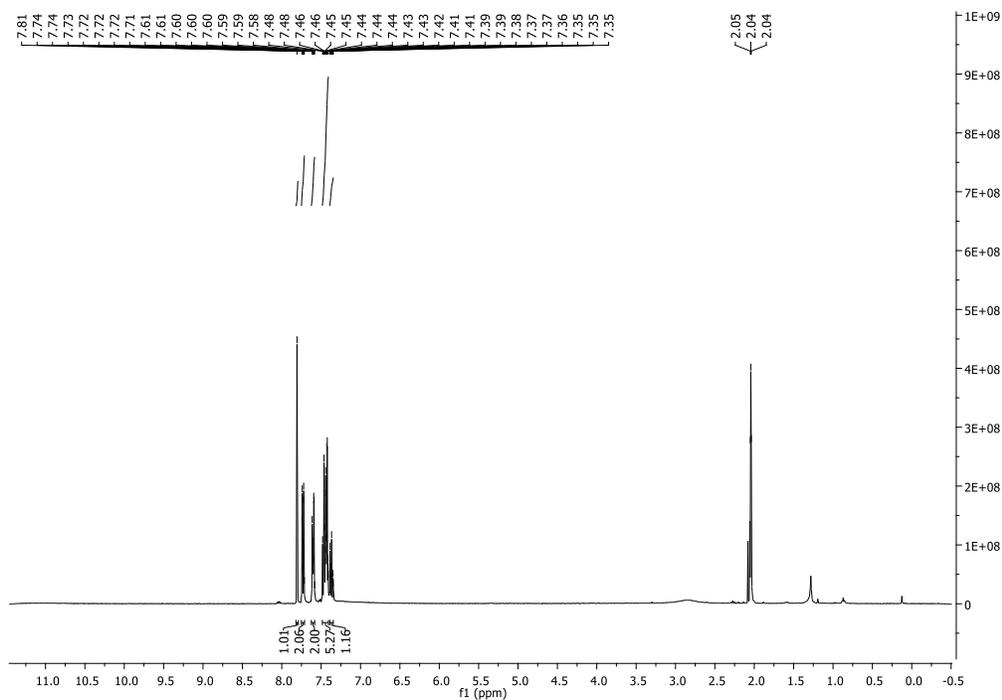
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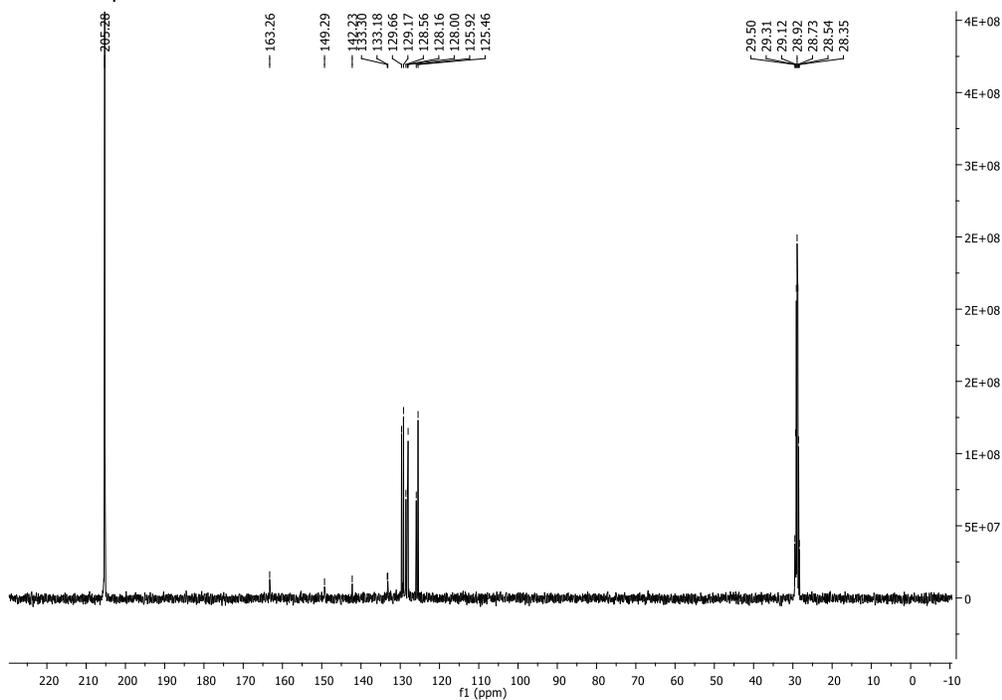
¹³C NMR Spectrum of **3bq**



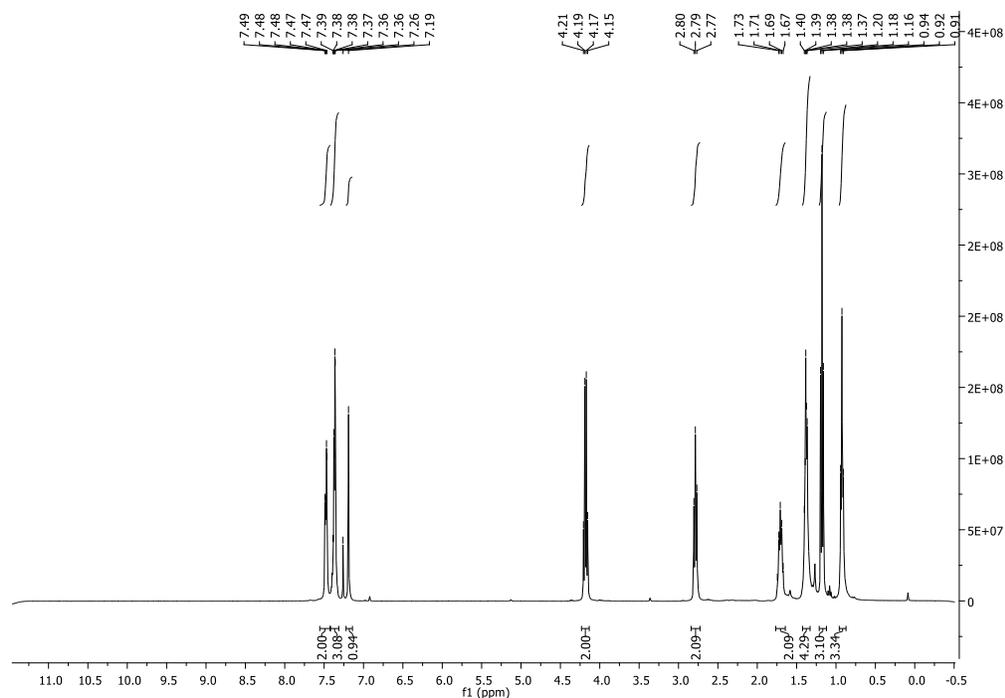
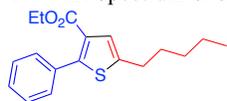
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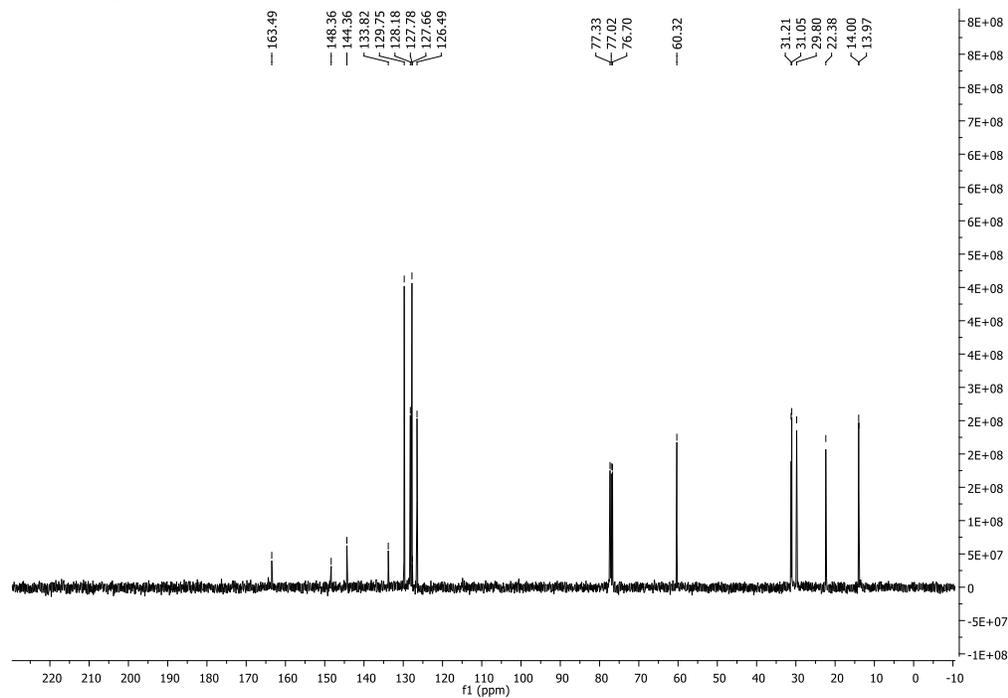
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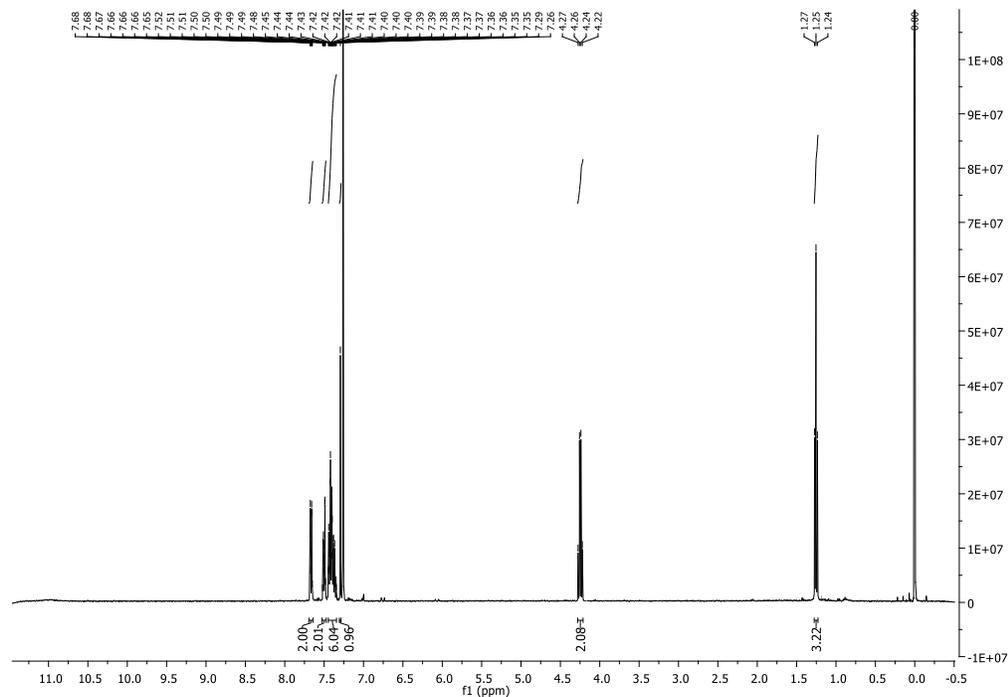
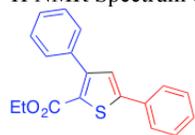
¹H NMR Spectrum of 3ch



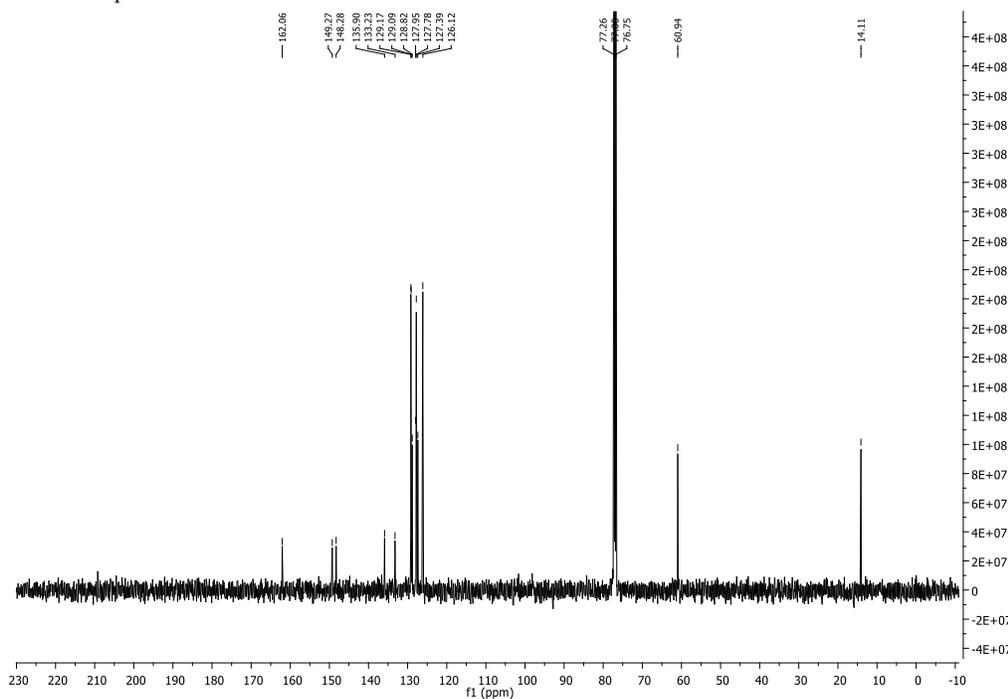
¹³C NMR Spectrum of 3ch



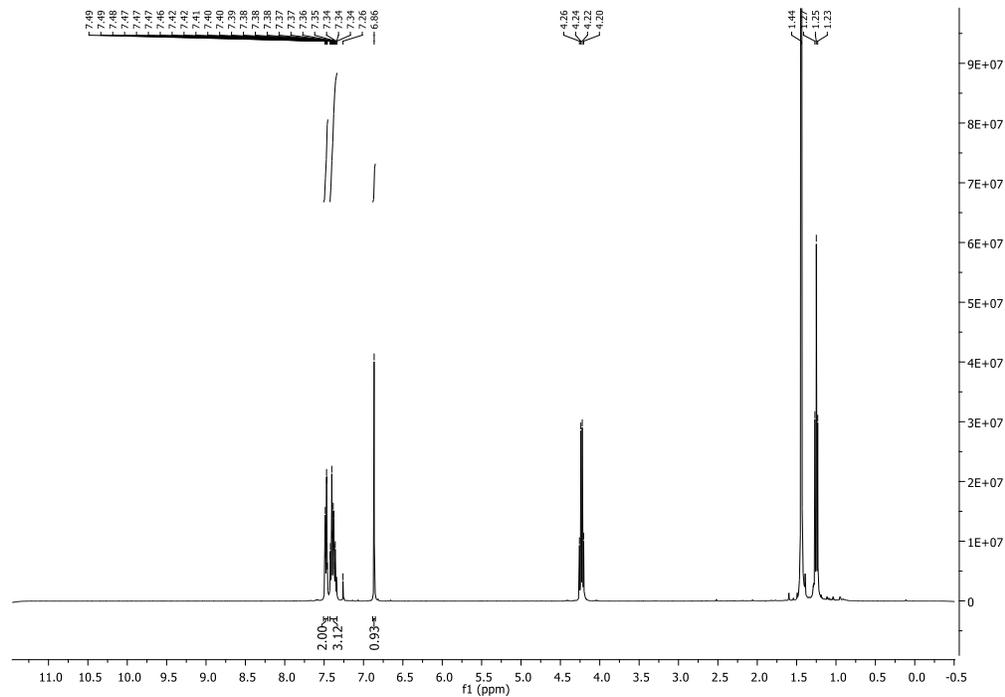
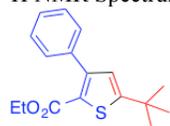
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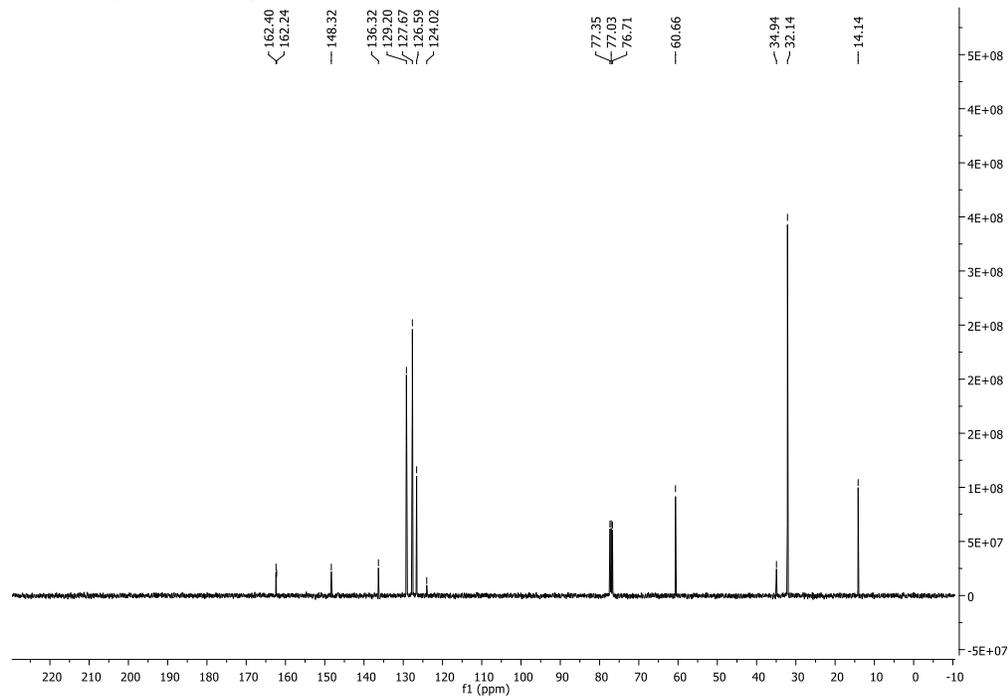
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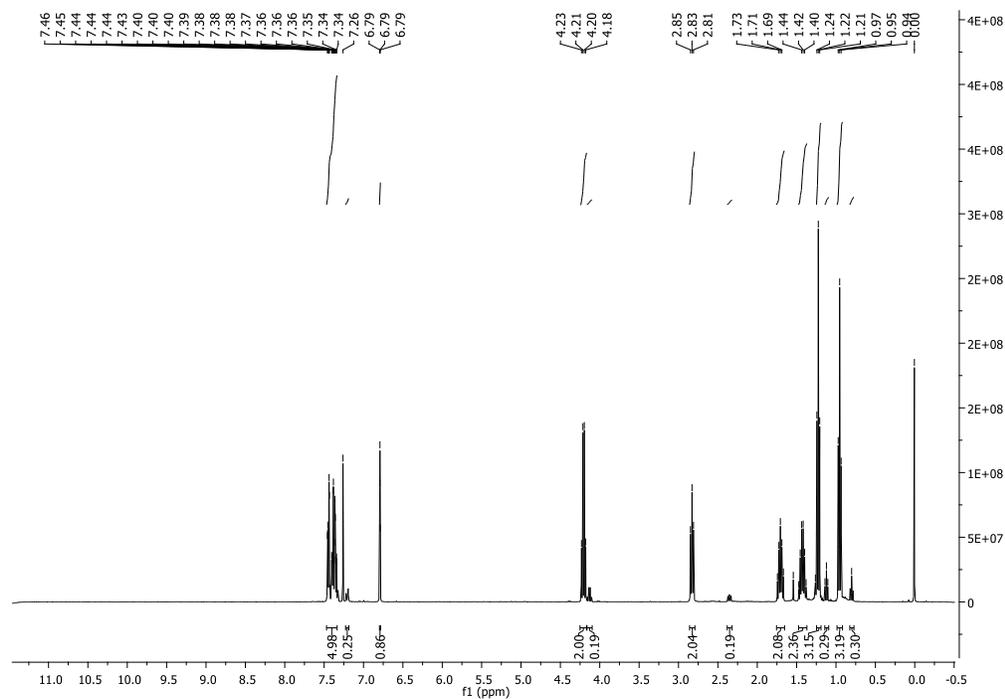
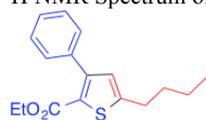
¹H NMR Spectrum of 3dj



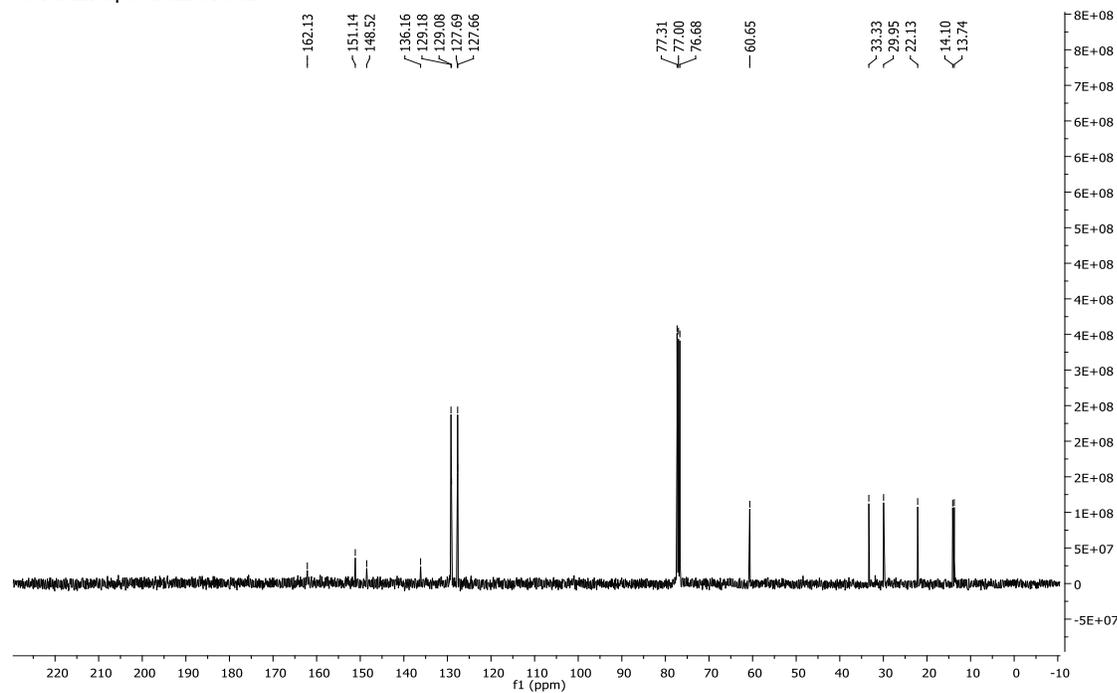
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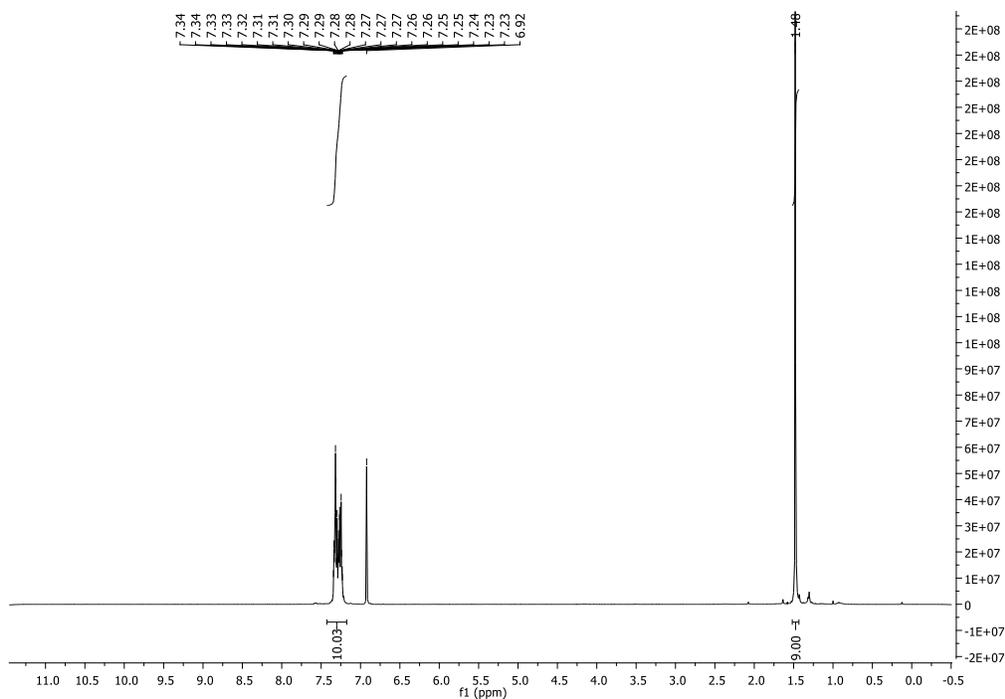
¹H NMR Spectrum of 3dr



¹³C NMR Spectrum of 3dr



¹H NMR Spectrum of 3ej



¹³C NMR Spectrum of 3ej

