

*Supporting Information for*

## **A formal vinylic substitution reaction for the synthesis of $\alpha$ , $\beta$ -unsaturated enol esters and their anticancer potential**

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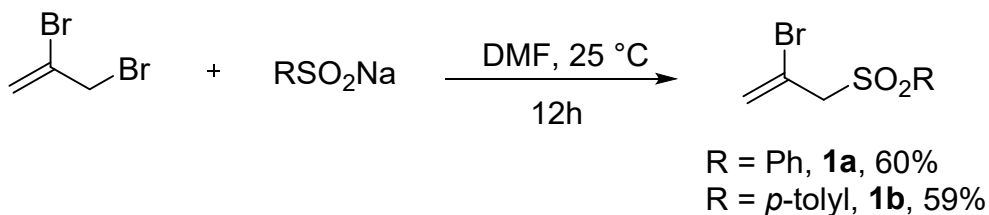
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### **1. General Information**

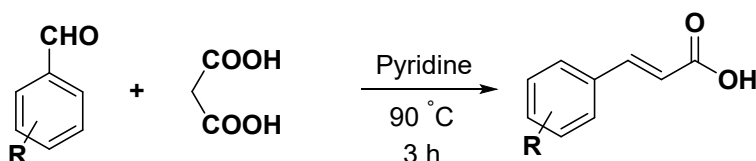
All  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded in  $\text{CDCl}_3$  at ambient temperature, chemical shift  $\delta$  are given in ppm on a scale downfield from TMS, and the coupling constant  $J$  are in Hz. The signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublet; m, multiplet. FTIR spectra were recorded as neat. Melting points were recorded on an electrothermal apparatus and are uncorrected. All the reagents and solvents were used without further purification unless specified otherwise. Technical grade ethyl acetate, petroleum ether, used for column chromatography were distilled prior to use. Column chromatography was carried out using silica gel (100- 200 mesh) packed in glass columns. All reactions were performed in oven dried glassware with magnetic stirring. TLC analysis was performed on commercially prepared 60 F254 silica gel plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining by  $\text{KMnO}_4$ . High-resolution mass spectra were recorded with q-TOF electrospray mass spectrometer. All purchased chemicals were used as received.

## 2. Preparation of 1-(2-bromoallyl)sulfonylbenzene **1a** and 1-(2-bromoallyl)sulfonyl-4-methylbenzene **1b**<sup>1</sup>



Sodium benzene sulfinate or sodium-*p*-toluene sulfinate (10 mmol) was added to DMF (10 mL) in a round bottom flask and left to stir for 20 minutes. To this suspension, 2,3-dibromopropene (10 mmol) was added and stirred at room temperature under nitrogen for 12 hrs. After the completion of the reaction, ice and ethylacetate (20 mL) were added and stirred for 15 minutes. Water (20 mL) was added and the organic layer was separated in a separatory funnel. The aqueous layer was extracted with ethyl acetate (2 X 10 mL), the organic layers were combined and the solvent was removed on a rotavapor. The residue obtained was purified by column chromatography on silica gel using ethyl acetate and hexane mixtures as eluent to obtain pure samples of **1a** or **1b**.

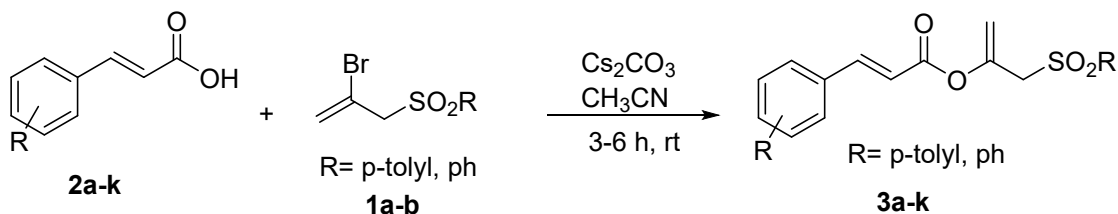
## 3. Preparation of substituted cinnamic acids



Pyridine (3 ml) was added to a mixture of malonic acid (3 mmol) and aryl aldehyde (1.5 mmol) in a 50 mL RB flask. The solution was heated at 90 °C for three hours. The mixture was allowed to cool and 2N HCl (10 mL) was added. The solution was then extracted with ethyl acetate (3 X 10 mL), the combined organic extracts was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel column using petroleum ether-ethyl acetate as eluent to afford the substituted cinnamic acids.

<sup>1</sup>S. Ma, Q. Wei, *J. Org. Chem.*, 1999, **64**, 1026.

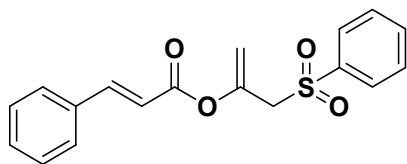
#### 4. The 'formal vinylic substitution reaction'



Cesium carbonate (1.50 mmol) was added to a magnetically stirred solution of the unsaturated carboxylic acid (0.68 mmol) and the bromoallyl sulfone (0.88 mmol) in acetonitrile (8 mL) at ambient temperature. When TLC analysis indicated that the reaction is complete (3-6 h), the solvent was removed on a rotavapor, deionized water (20 mL) was added and the aqueous solution was extracted with ethyl acetate (3X 15 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated on a rotavapor. The residue on column chromatography on silica gel using petroleum ether-ethyl acetate as eluent afforded analytically pure samples of the products.

#### 5. Spectroscopic data for unsaturated enol esters

##### 3-(phenylsulfonyl)prop-1-en-2-yl cinnamate, **3a**



Yellow solid, 151 mg, 68%

**Melting Point:** 72-74 °C

$R_f$  = 0.5 (30 % ethyl acetate in hexane).

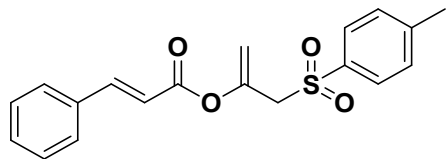
**IR (KBr)  $\nu_{\text{max}}$ :** 1719, 1628, 1448, 1307, 1244, 1195, 1139, 1082, 976, 919, 862, 759, 689  $\text{cm}^{-1}$ .

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$**  4.11 (s, 2H), 4.98 (d,  $J=1.2$  Hz, 1H), 5.19 (d,  $J=1.2$  Hz, 1H), 6.22 (d,  $J=16.0$  Hz, 1H), 7.95 (d,  $J=7.2$  Hz, 2H), 7.26-7.62 (m, 9H).

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$**  60.7, 110.3, 116.2, 128.3, 128.6, 129.0, 129.1, 130.9, 133.8, 133.9, 138.4, 144.1, 146.9, 164.4.

**HRMS:** calcd for  $\text{C}_{18}\text{H}_{16}\text{O}_4\text{SNa}$  [ $\text{M}+\text{Na}$ ] 351.0667; found 351.0665.

3-tosylprop-1-en-2-yl cinnamate, **3b**



Yellow solid, 165 mg, 71%

**Melting Point:** 112-114 °C

**R<sub>f</sub>** = 0.5 (30 % ethyl acetate in hexane).

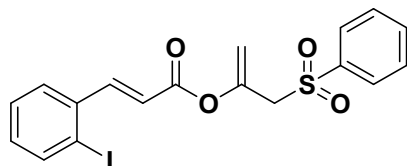
**IR (KBr) v<sub>max</sub>:** 1719, 1628, 1448, 1307, 1244, 1195, 1139, 1082, 976, 919, 862, 759, 689 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.30 (s, 3H), 4.12 (s, 2H), 4.99 (d, J = 1.6 Hz, 1H), 5.20 (d, J = 2.0 Hz, 1H), 6.22 (d, J = 16.0 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.42 (m, 3H), 7.50 (m, 2H), 7.56 (d, J = 16.0 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.5, 60.6, 110.0, 1116.3, 128.2, 128.6, 129.0, 129.7, 130.8, 133.8, 135.6, 144.3, 145.0, 146.7, 164.3.

**HRMS:** calcd for C<sub>19</sub>H<sub>18</sub>O<sub>4</sub>SNa [M+H] 365.0823; found 343.1000.

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(2-iodophenyl)acrylate, **3c**



Green-yellow solid, 148 mg, 48%

**Melting Point:** 99-100 °C

**R<sub>f</sub>** = 0.5 (30 % ethyl acetate in hexane).

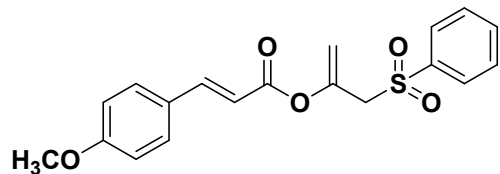
**IR (KBr) v<sub>max</sub>:** 2917, 1713, 1623, 1303, 1151, 1008, 900, 757, 678 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 4.13 (s, 2H), 4.98 (d, J=1.6Hz, 1H), 5.21 (d, J=1.6Hz, 1H), 6.12 (d, J=15.6Hz, 1H), 7.07-7.11 (t, J=8.0 Hz, 1H), 7.36-7.40 (t, J=7.6Hz, 1H), 7.49-7.59 (m, 4H), 7.84 (d, J=15.6Hz, 1H), 7.91-7.96 (m, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 60.5, 101.4, 110.3, 119.1, 127.4, 128.6, 129.2, 131.7, 133.9, 137.1, 138.3, 140.2, 144.1, 149.9, 163.6.

**HRMS:** calcd for C<sub>18</sub>H<sub>15</sub>IO<sub>4</sub>SNa [M+Na] 476.9633; found 476.9630.

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(4-methoxyphenyl)acrylate, **3d**



Cream solid, 207 mg, 85%

**Melting Point:** 97-100 °C

**R<sub>f</sub>** = 0.4 (30 % ethyl acetate in hexane).

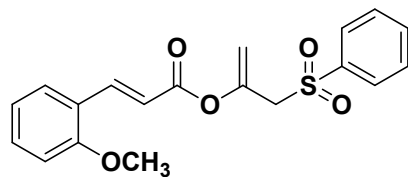
**IR (KBr) v<sub>max</sub>:** 1724, 1594, 1510, 1247, 1122, 987, 822, 686 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ** 3.85 (s, 3H), 4.11 (s, 2H), 4.96 (s, 1H), 5.17 (d, *J*=1.2Hz, 1H), 6.08 (d, *J*=16.0 Hz, 1H), 7.95 (d, *J*=7.2 Hz, 2H), 7.42-7.56 (m, 6H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ** 55.4, 60.7, 110.1, 113.5, 114.4, 126.6, 128.6, 129.1, 130.0, 133.8, 138.52, 144.23, 146.65, 161.87, 164.75.

**HRMS:** calcd for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>SNa [M+Na] 381.0773; found 381.0773.

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(2-methoxyphenyl)acrylate, **3e**



White solid, 200 mg, 82%

**Melting Point:** 76-78 °C

**R<sub>f</sub>** = 0.4 (30 % ethyl acetate in hexane).

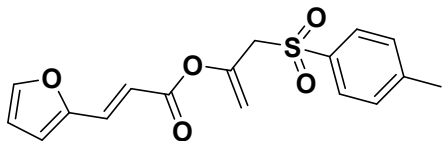
**IR (KBr) v<sub>max</sub>:** 1715, 1617, 1452, 1310, 1238, 1145, 893, 753, 693 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ** 3.90 (s, 3H), 4.12 (s, 2H), 4.97 (d, *J*=1.6 Hz, 1H), 5.18 (d, *J*=1.6 Hz, 1H), 6.31 (d, *J*=16.0 Hz, 1H), 6.92-6.99 (m, 2H), 7.36-7.44 (m, 2H), 7.51-7.60 (m, 3H), 7.88 (d, *J*=16.0 Hz, 1H), 7.95 (d, *J*=7.2Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ** 55.4, 60.7, 110.1, 111.2, 116.6, 120.7, 122.8, 128.6, 129.1, 132.0, 133.9, 138.5, 142.5, 144.2, 158.5, 165.0.

**HRMS:** calcd for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>SNa [M+Na] 381.0773; found 381.0770.

3-tosylprop-1-en-2-yl (E)-3-(furan-2-yl)acrylate, **3f**



Yellow solid, 151 mg, 67%

**Melting Point:** 87-88 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

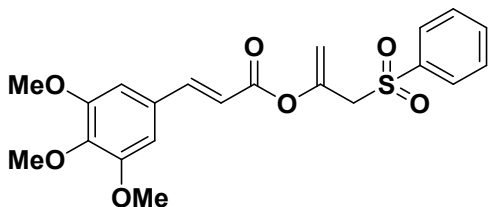
**IR (KBr) v<sub>max</sub>:** 1715, 1629, 1246, 1142, 1078, 996, 928, 747, 680 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.08 (s, 3H), 3.83 (s, 2H), 4.71 (d, *J*=1.2 Hz, 1H), 4.91(d, *J*=1.2Hz, 1H), 5.78 (d, *J*=15.6 Hz, 1H), 6.25 (t, *J*=1.6 Hz, 1H), 6.39 (d, *J*=3.2 Hz, 1H), 6.98-7.07(m, 4H), 7.55 (d, *J*=8.4 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.50, 60.66, 110.01, 112.60, 113.82, 115.98, 128.62, 129.81, 132.65, 135.58, 144.35, 145.01, 145.36, 150.49, 164.36.

**HRMS:** calcd for C<sub>17</sub>H<sub>16</sub>O<sub>5</sub>SNa [M+Na] 355.0615; found 355.0614.

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(3,4,5-trimethoxyphenyl)acrylate, **3g**



White solid, 190 mg, 67%

**Melting Point:** 110-112 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

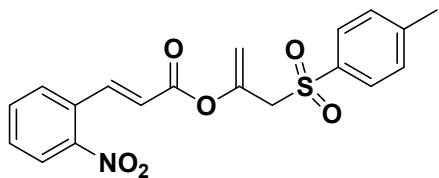
**IR (KBr) v<sub>max</sub>:** 1709, 1630, 1451, 1262, 1126, 993, 902, 828 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 3.90 (s, 9H), 4.11(s, 2H), 4.93 (d, *J*=2.0 Hz,1H), 5.18 (d, *J*=2.0 Hz, 1H), 6.21 (d, *J*=16.0 Hz, 1H), 6.73 (s, 2H), 7.96 (d, *J*=7.6 Hz, 2H), 7.50-7.64 (m, 4H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 56.20, 61.01, 105.51, 110.27, 115.74, 128.64, 129.17, 133.91, 138.39, 140.58, 144.10, 146.97, 153.45, 164.44.

**HRMS:** calcd for C<sub>21</sub>H<sub>22</sub>O<sub>7</sub>SNa [M+Na] 441.0984; found 441.0983

3-tosylprop-1-en-2-yl (E)-3-(2-nitrophenyl)acrylate, **3h**



Yellow solid, 150 mg, 57%

**Melting Point:** 92-94 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

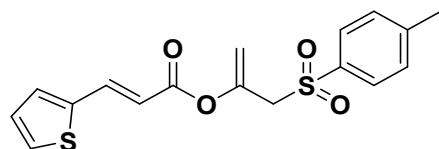
**IR (KBr) v<sub>max</sub>:** 2930, 1731, 1524, 1319, 1145, 1085, 899, 754 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.32 (s, 3H), 4.08 (s, 2H), 4.96 (d, *J*=2.0 Hz, 1H), 5.21 (d, *J*=2.0 Hz, 1H), 6.29 (d, *J*=15.0 Hz, 2H), 7.37-7.26 (m, 3H), 7.63-7.56 (m, 3H), 7.91-7.57 (m, 2H), 8.0-8.00 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.5, 60.58, 110.3, 121.5, 125.0, 128.7, 129.1, 129.8, 130.8, 142.0, 144.2, 163.2.

**HRMS:** calcd for C<sub>19</sub>H<sub>17</sub>NO<sub>6</sub>SNa [M+Na] 410.0674; found 410.0672.

3-tosylprop-1-en-2-yl (E)-3-(thiophen-2-yl)acrylate, **3i**



White solid, 163 mg, 69%

**Melting Point:** 98-100 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

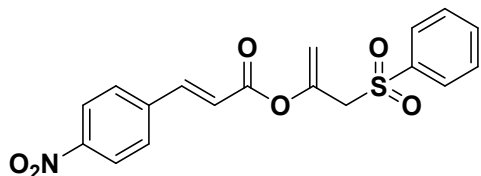
**IR (KBr) v<sub>max</sub>:** 2986, 2926, 1718, 1619, 1420, 1364, 1124, 1082, 894, 855, 706 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.33 (s, 3H), 4.10 (s, 2H), 4.98 (d, *J* = 1.6 Hz, 1H), 5.18 (d, *J* = 1.6 Hz, 1H), 7.09 (t, *J* = 3.6 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 5.2 Hz, 1H), 7.64 (d, *J* = 15.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.5, 60.6, 110.0, 114.8, 128.3, 128.6, 129.4, 129.7, 131.8, 135.6, 139.0, 144.3, 145.0, 164.1.

**HRMS:** calcd for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>S<sub>2</sub>Na [M+Na] 371.0388; found 371.0387.

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(4-nitrophenyl)acrylate, **3j**



White solid, 150 mg, 59%

**Melting Point:** 90-92 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

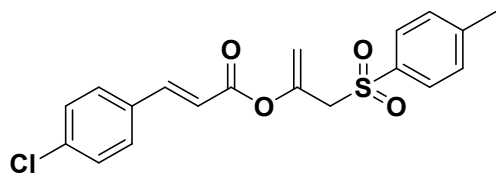
**IR (KBr) v<sub>max</sub>:** 2930, 1731, 1584, 1319, 1145, 1085, 899, 754 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 4.03 (s, 2H), 4.87 (d, *J*=2.0 Hz, 1H), 5.14 (d, *J*=2.0 Hz, 1H), 6.37 (d, *J*=16.0 Hz, 1H), 7.50 (t, *J*=7.6 Hz, 2H), 7.56-7.61 (m, 4H), 7.89 (d, *J*=7.2 Hz, 2H), 8.21 (d, *J*=8.8 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 60.4, 110.5, 120.7, 124.2, 128.6, 128.9, 129.2, 133.9, 138.3, 139.8, 143.8, 143.9, 148.8, 163.4.

**HRMS:** calcd for C<sub>18</sub>H<sub>15</sub>NO<sub>6</sub>SNa [M+Na] 396.0518; found 396.0518

3-(phenylsulfonyl)prop-1-en-2-yl (E)-3-(4-chlorophenyl)acrylate, **3k**



Yellow solid, 148 mg, 60%

**Melting Point:** 92-94 °C

**R<sub>f</sub>** = 0.5 (30 % ethyl acetate in hexane).

**IR (KBr) v<sub>max</sub>:** 2918, 1725, 1629, 1305, 1135, 897, 812 cm<sup>-1</sup>.

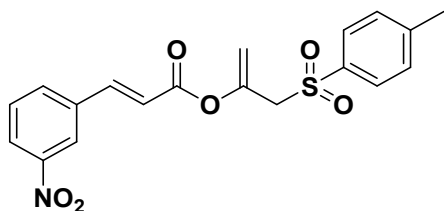
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.32 (s, 3H), 4.08 (s, 2H), 4.94 (d, *J*=1.6 Hz, 1H), 5.17 (d, *J*=1.6 Hz, 1H), 6.21 (d, *J*=16.0 Hz, 1H), 7.32 (d, *J*=8.4 Hz, 2H), 7.36-7.42 (m, 4H), 7.52 (d, *J*=16.0 Hz, 1H), 7.81 (d, *J*=8.4 Hz, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.6, 60.5, 110.1, 116.9, 128.6, 129.3, 129.4, 129.7, 132.3, 135.5, 136.8, 144.2, 145.2, 164.1.

**HRMS:** calcd for C<sub>19</sub>H<sub>17</sub>O<sub>4</sub>SNa [M+Na] 399.0433; found 399.0432.



3-tosylprop-1-en-2-yl (E)-3-(3-nitrophenyl)acrylate, **3l**



White solid, 160 mg, 61 %

**Melting Point:** 97-98 °C

**R<sub>f</sub>** = 0.3 (30 % ethyl acetate in hexane).

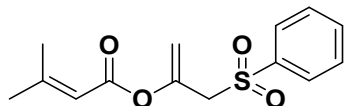
**IR (KBr) v<sub>max</sub>:** 3070, 2999, 2926, 1728, 1640, 1530, 1351, 1316, 1202, 1140, 1083, 984, 709 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 2.37 (s, 3H), 4.10 (s, 2H), 4.96 (s, 1H), 5.21 (s, 1H), 6.42 (d, J = 16.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.66-7.61(m, 2H), 7.83 (d, J = 7.6 Hz, 2H), 8.28 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 21.5, 60.4, 110.3, 119.7, 122.5, 125.0, 128.6, 129.8, 29.8, 130.1, 133.7, 135.4, 135.6, 143.7, 144.1, 145.1, 148.7, 163.5.

**HRMS:** calcd for C<sub>19</sub>H<sub>17</sub>O<sub>6</sub>NSNa [M+Na] 410.0674; found 410.0670.

3-(phenylsulfonyl)prop-1-en-2-yl 3-methylbut-2-enoate, **3m**



Greenish yellow solid, 101 mg, 53%

**Melting Point:** 72-74 °C

**R<sub>f</sub>** = 0.5 (30 % ethyl acetate in hexane).

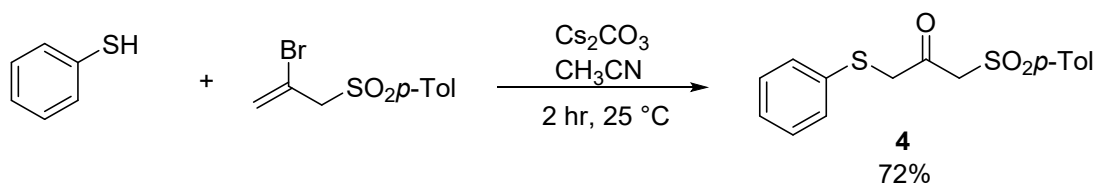
**IR (KBr) v<sub>max</sub>:** 2924, 1728, 1646, 1443, 1314, 1217, 1123, 1073, 896 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ 1.88 (s, 3H), 2.12 (s, 3H), 4.06 (s, 2H), 4.87 (d, J=1.2 Hz, 1H), 5.06 (d, J=1.2 Hz, 1H), 5.47 (s, 1H), 7.57 (t, J=8.0 Hz, 2H), 7.67 (t, J=7.2 Hz, 1H), 7.93 (d, J=7.6 Hz, 2H).

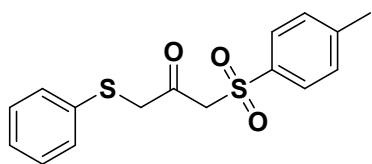
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)** δ 20.4, 27.5, 60.6, 109.9, 114.4, 128.6, 129.0, 133.8, 138.4, 144.0, 160.7, 163.7.

**HRMS:** calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>SNa [M+Na] 303.0667; found 303.0667.

## 6. Reaction of Thiophenol and 2-bromoallyl sulfone 1b



Cesium carbonate (1.50 mmol) was added to a solution of the thiophenol (0.68 mmol) and the bromoallylsulfone (0.88mmol) in acetonitrile (8 mL) at ambient temperature and stirred for 2 hours. The solvent was removed on a rotavapor, deionized water (20 mL) was added and the aqueous solution was extracted with ethyl acetate (3X 15 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate and concentrated on a rotavapor. The residue on column chromatography on silica gel using petroleum ether-ethyl acetate as eluent afforded analytically pure samples of the products.



Yellow semi- solid, 156 mg, 72%

$R_f$  = 0.5 (30 % ethyl acetate in hexane).

**IR (KBr)  $\nu_{max}$ :** 3059, 2990, 2924, 1718, 1596, 1481, 1321, 1150, 1086, 814, 739, 691  $cm^{-1}$ .

**$^1H$  NMR (400 MHz,  $CDCl_3$ )**  $\delta$  2.32 (s, 3H), 3.79 (s, 2H), 4.27 (s, 2H), 7.13-7.22 (m, 7H), 7.59 (d,  $J=8.4Hz$ , 2H).

**$^{13}C$  NMR (100 MHz,  $CDCl_3$ )**  $\delta$  20.5, 43.6, 63.1, 126.3, 127.1, 128.1, 128.8, 129.0, 132.1, 134.2, 144.4, 191.5.

**HRMS:** calcd for  $C_{16}H_{16}O_3S_2$  320.0541; found 320.0549.

## 7. Evaluation of anti-proliferative activity

### Materials and methodology

**Culture of animal cell line:** A549 cells (Human lung adenocarcinoma cells) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS: Gibco), and Penicillin-Streptomycin with a continuous supply of 5%  $CO_2$  at 37°C i.e., in a  $CO_2$  incubator

### Cell viability assay or anti-proliferative activity

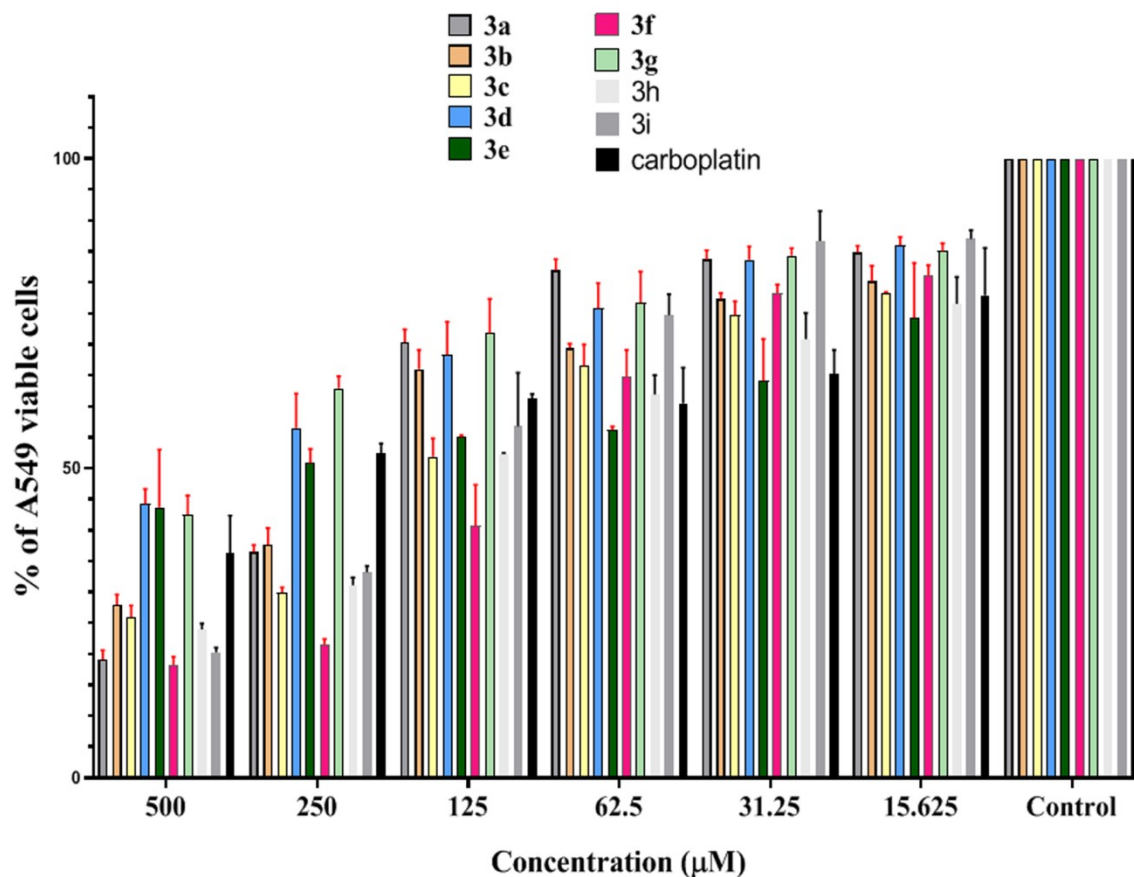
Cell viability was investigated with an MTT assay using yellow (3-(4,5-dimethylthiazole-2-yl)-2,5-biphenyl tetrazolium bromide (MTT) salt. After the culture reached sufficient confluency, cells were harvested with 0.25% trypsin-EDTA. Cell counting was done with a hemocytometer. In 96 well plates,  $1 \times 10^4$  cells/well were seeded and incubated for 24 hours in a CO<sub>2</sub> incubator for cell attachment and growth. After 24 hours, test compounds with varying concentrations (starting from 500  $\mu$ M as the highest concentration) were added to the culture plate and incubated for 48 hours.

The viability of the treated cell culture with test compounds was assessed after 48 hours of incubation. The wells were gently washed with 1X phosphate buffer saline (PBS) to remove the test compounds and added MTT salt solution (5mg/mL in 1X PBS) then incubated at 37°C. After 3 hours of incubation, DMSO was used to solubilize the formazan crystal and incubated for 30 minutes. The 96 well plates were then read for absorbance in Synergy H1 microplate reader at 492 nm. IC<sub>50</sub> values were calculated for each test compound in GraphPad Prism 8.0.1 by fitting the experimental results to the sigmoidal equation.

## Results

Anti-proliferative activity of compounds **3a** to **3i** against the human lung adenocarcinoma cells are described below. The starting experimental concentrations of all the test compounds and standard anti-cancer drug carboplatin were 500  $\mu$ M. All the tested compounds possess anti-proliferative activity against lung cancer cells. Compounds **3f**, **3h**, **3c**, **3i**, **3b**, and **3e** showed higher anticancer efficacy with IC<sub>50</sub> values  $93.8 \pm 11$ ,  $107.425 \pm 9.7$ ,  $118.05 \pm 11.3$ ,  $152.3 \pm 16$ ,  $164.45 \pm 7.3$ ,  $173.2 \pm 6.3$  respectively (Figure 1).

The experimental IC<sub>50</sub> values of these compounds were lower when compared to the standard drug carboplatin ( $187.5 \pm 6.5$ ) against human lung cancer cells. Further, compounds **3a**, **3d**, and **3g** exhibit lower anti-proliferative activity than carboplatin with more IC<sub>50</sub> values  $191.95 \pm 6$ ,  $300 \pm 67.5$ , and  $332.15 \pm 43.05$  respectively. Among all the compounds **3f**, **3h**, **3c**, **3i**, **3b**, and **3e** suggests having higher efficiency as carboplatin anticancer drug (Table 1).



Fi

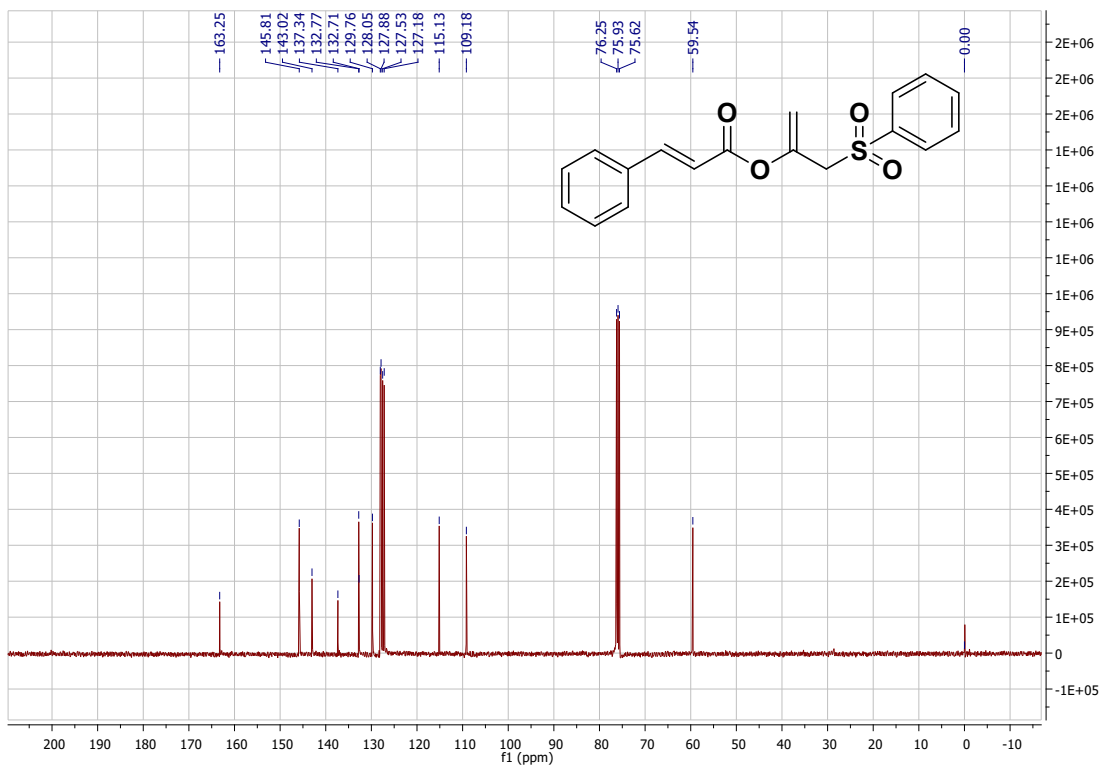
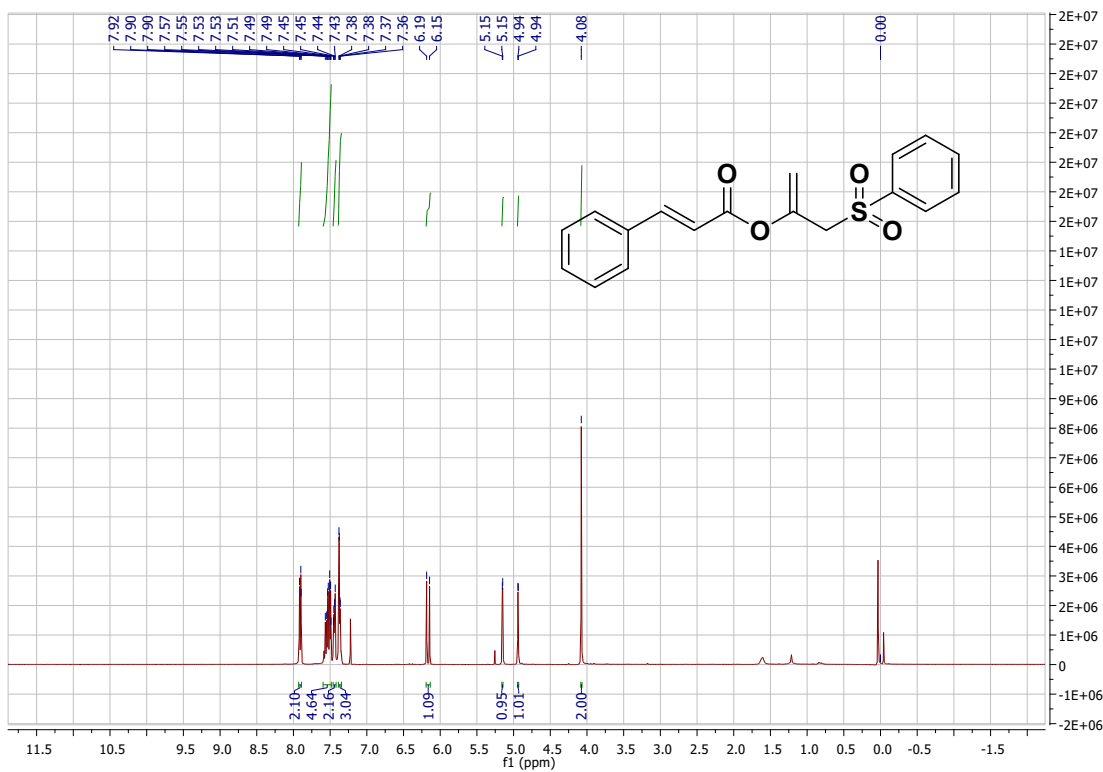
**Figure 1.** Percentage of A549 viable cells on treatment with varying concentration of compounds **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**. The standard carboplatin was taken as a positive control against A549 lung cancer cells, n=3 (Number of experiments performed).

**Table 1.** Efficacy of compounds 3a to 3i along with standard drug carboplatin inhibitory concentrations (IC<sub>50</sub>) on A549 human lung adenocarcinoma cells.

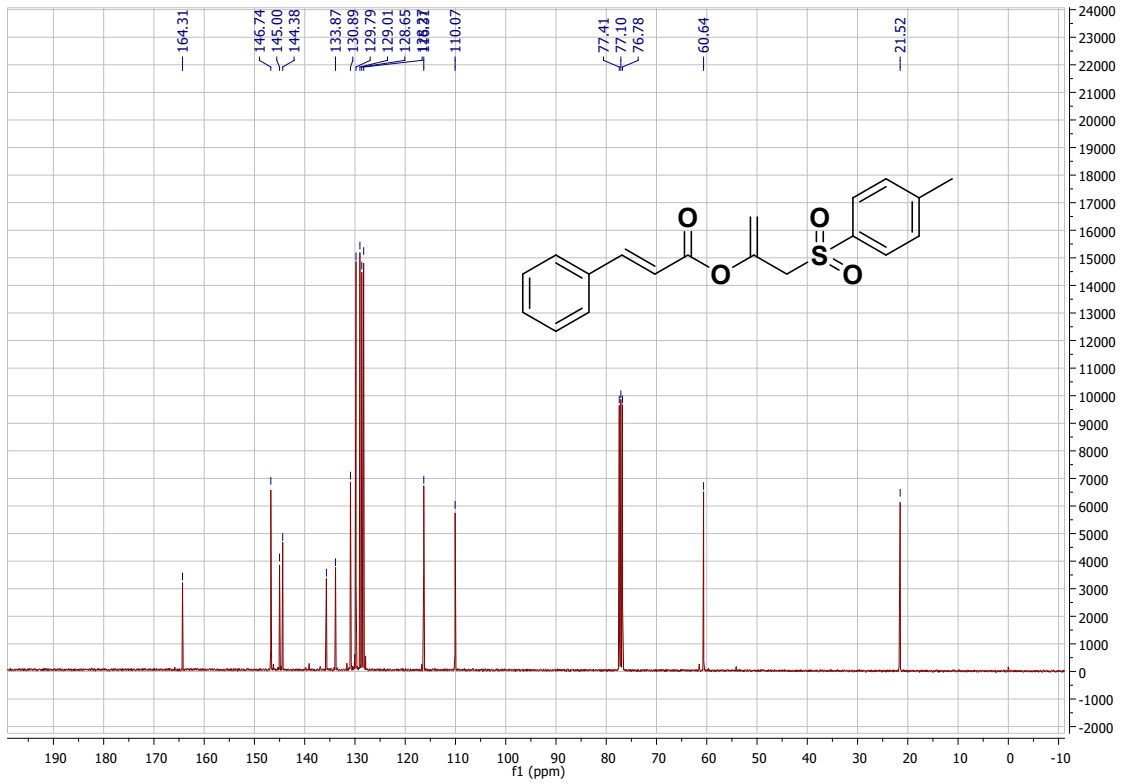
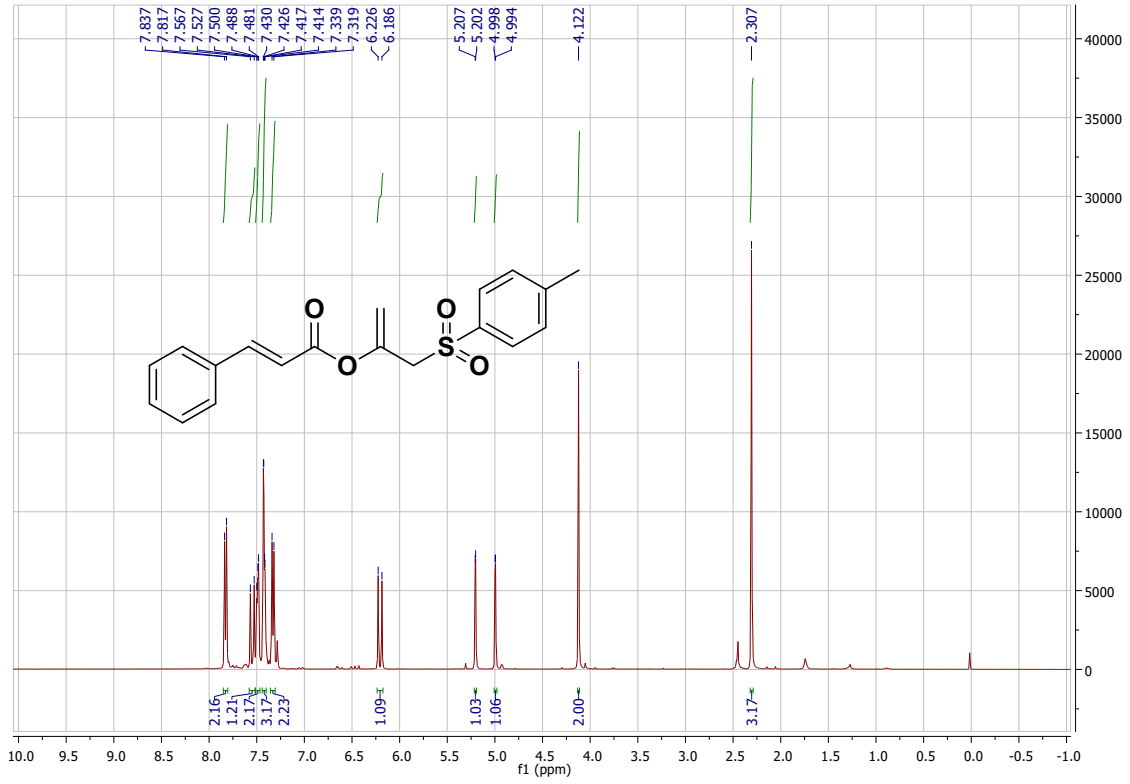
Compound	Molecular Weight	IC <sub>50</sub> (µM) ± S.E.M.
3a	328.28	191.95 ± 6
3b	342.40	164.45 ± 7.3
3c	377.17	118.05 ± 11.3
3d	281.30	300 ± 67.5
3e	281.30	173.2 ± 6.3
3f	318.34	93.8 ± 11
3g	418.46	332.15 ± 43.05
3h	387.08	107.425 ± 9.7
3i	348.43	152.3 ± 16
<b>Carboplatin</b>		<b>187.5 ± 6.5</b>

## 7. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of new compounds

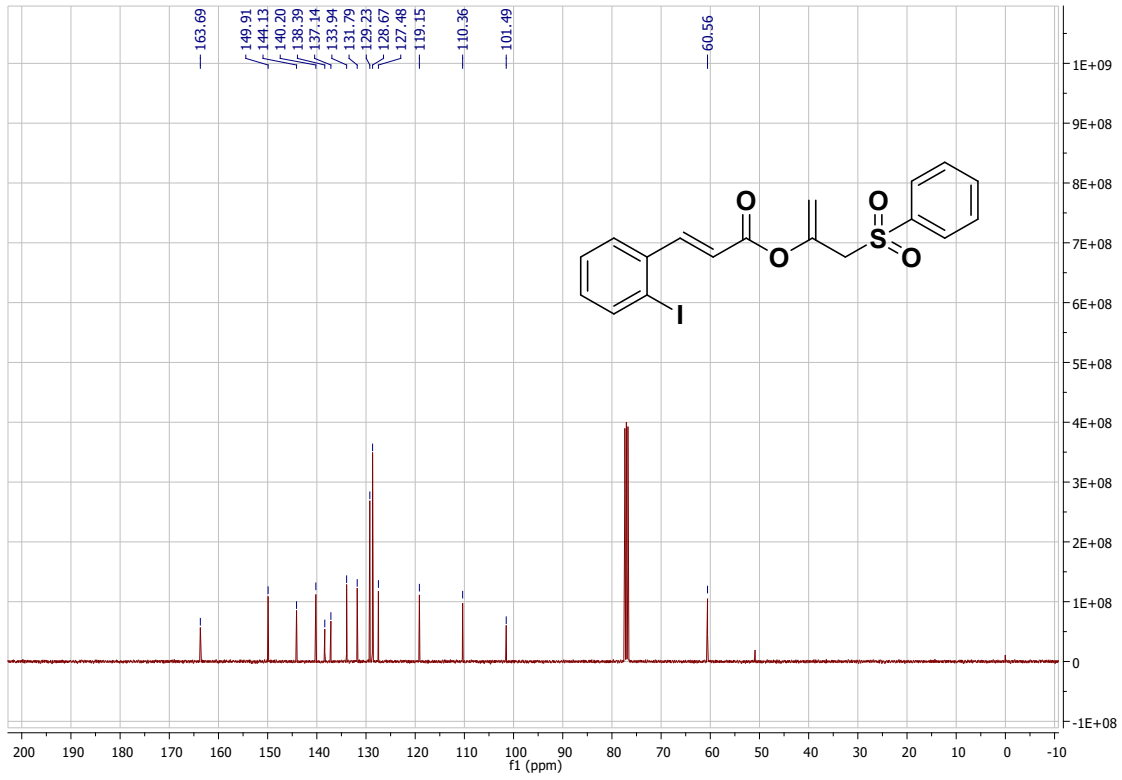
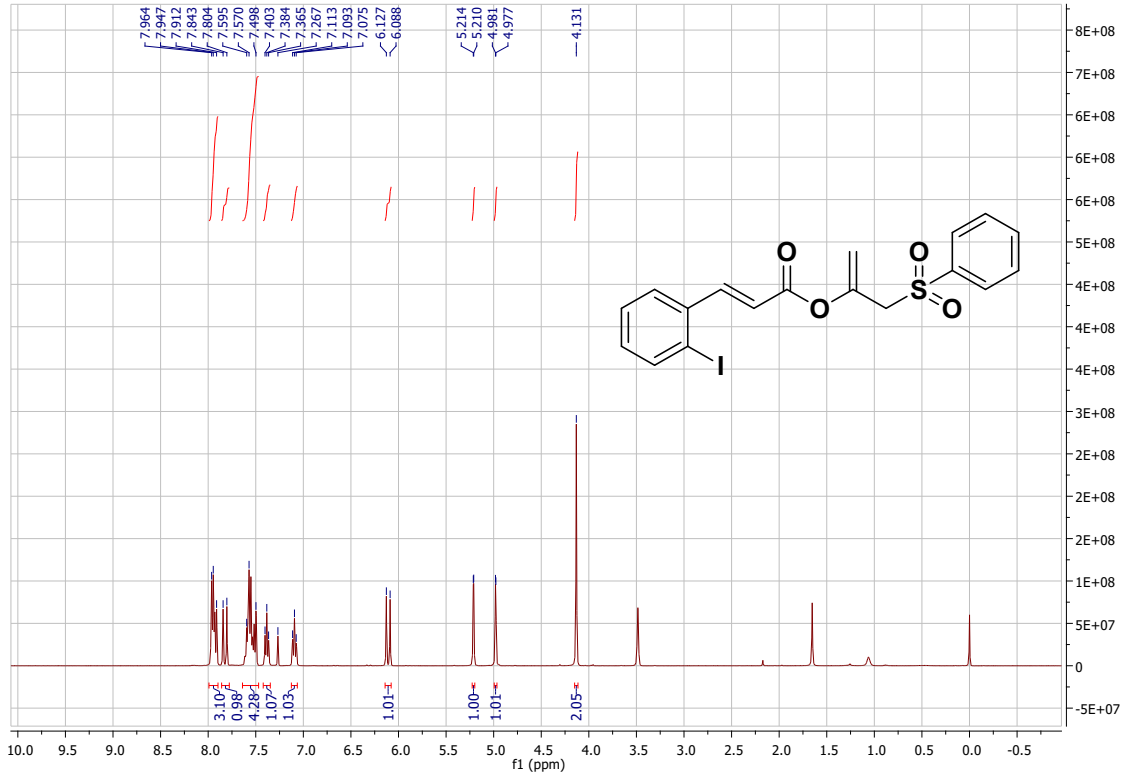
3a



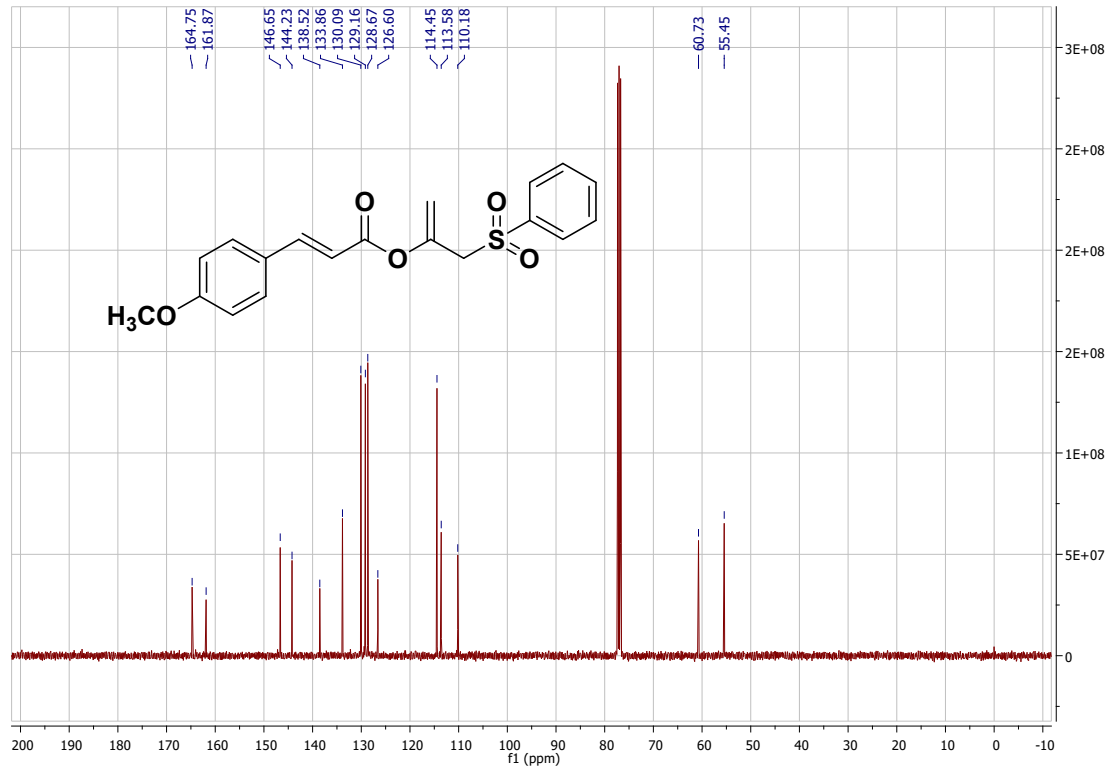
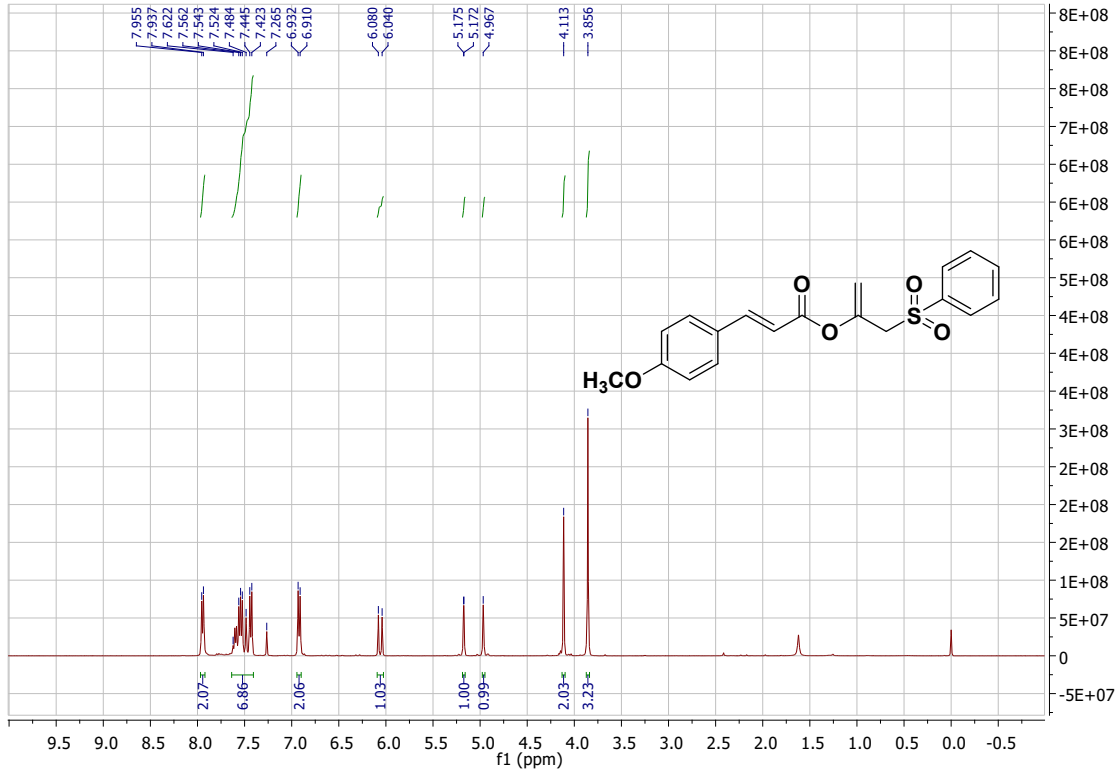
3b



3c

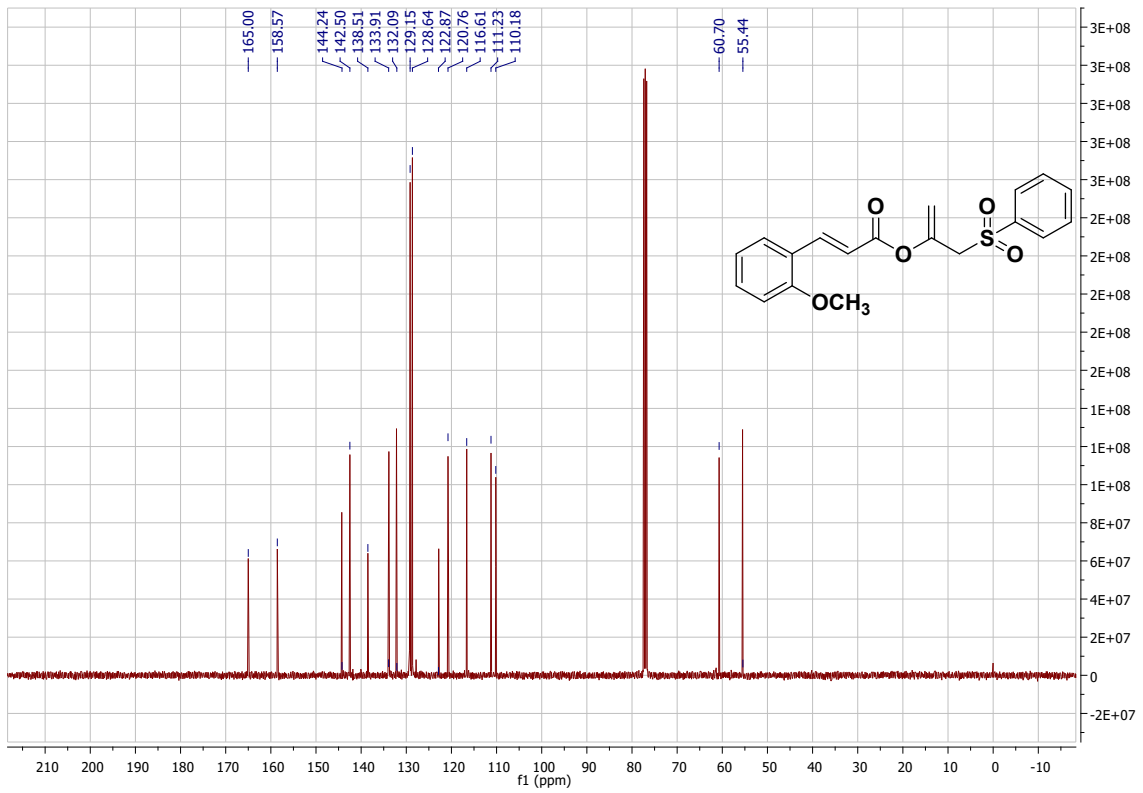
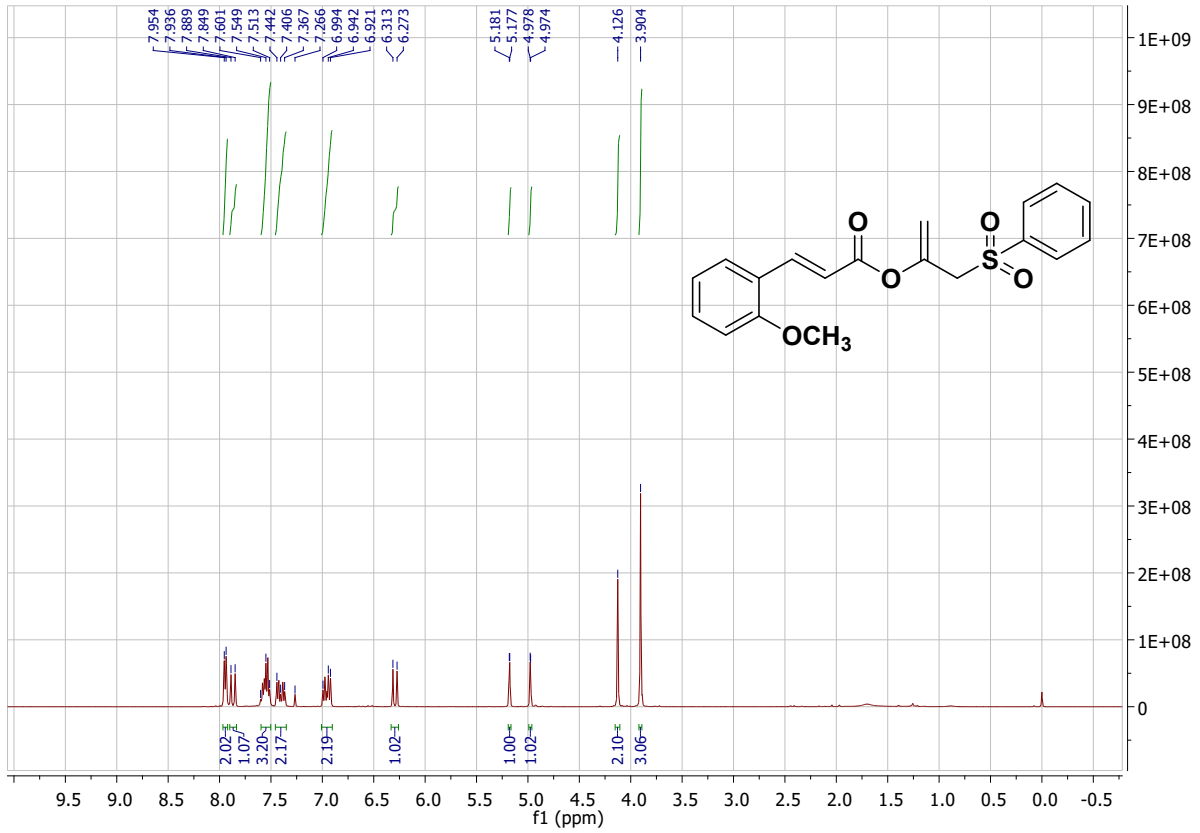


### 3d

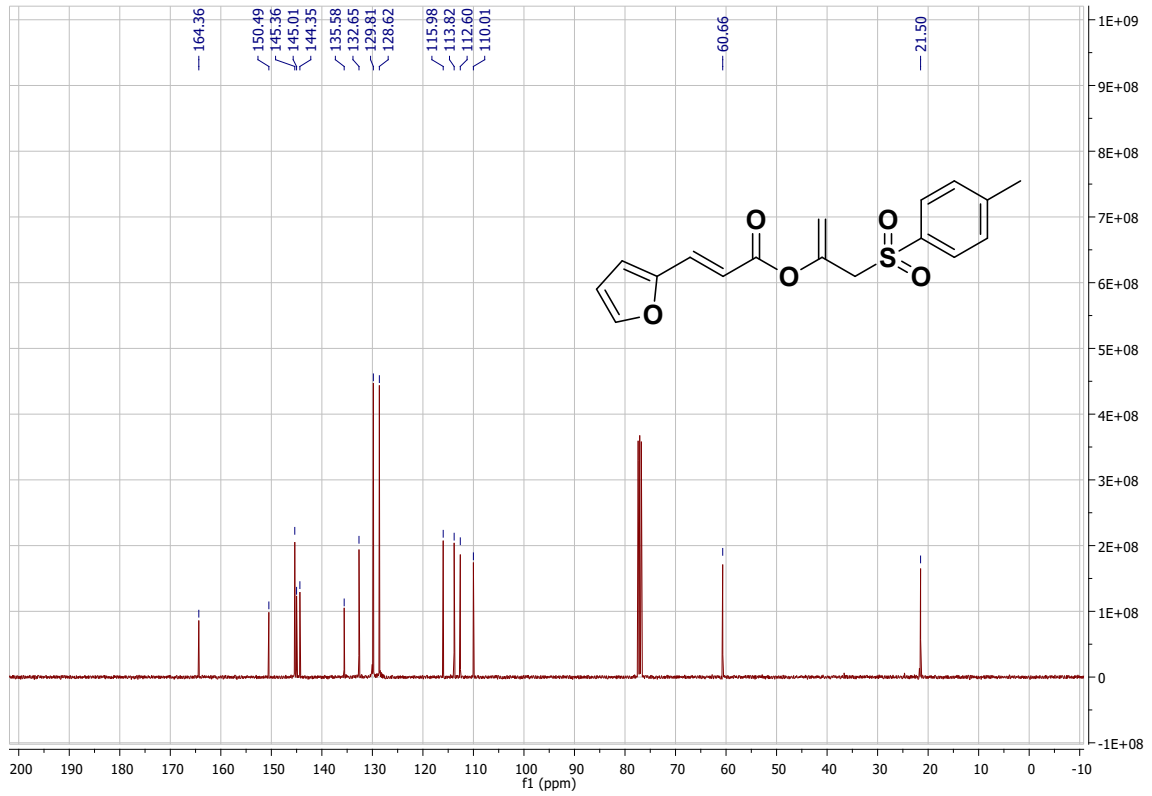
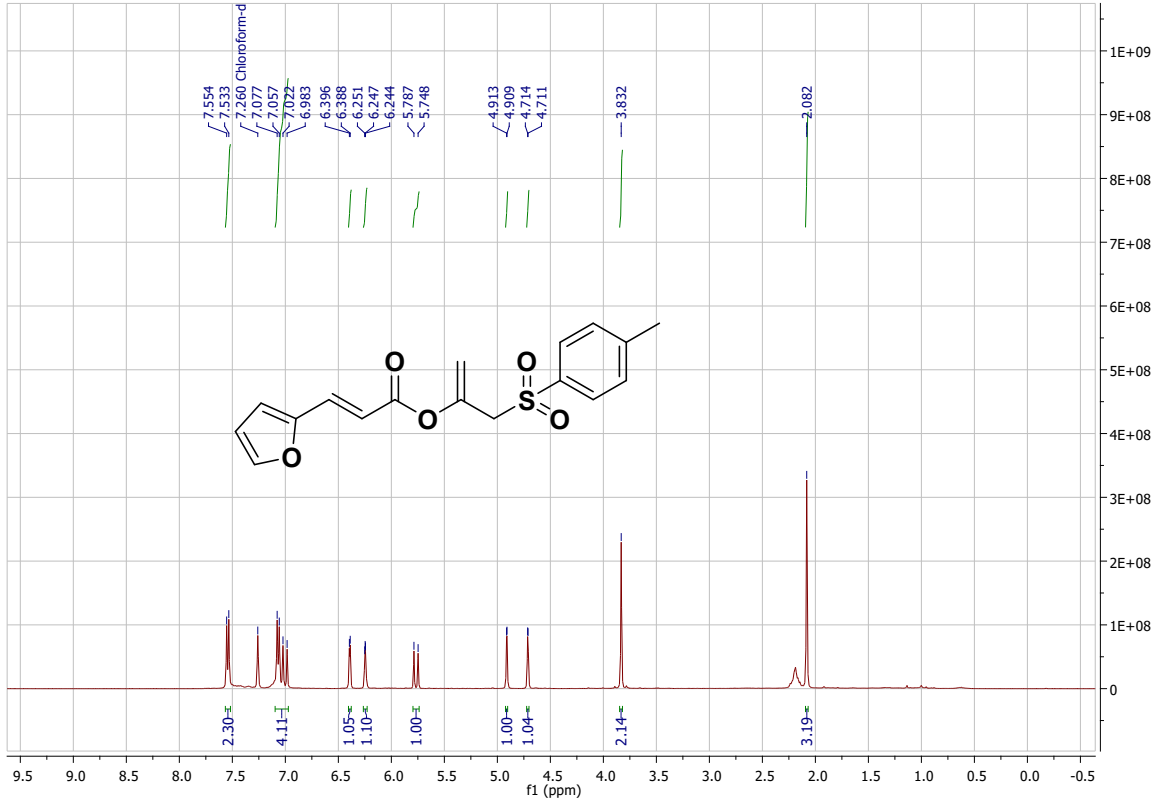




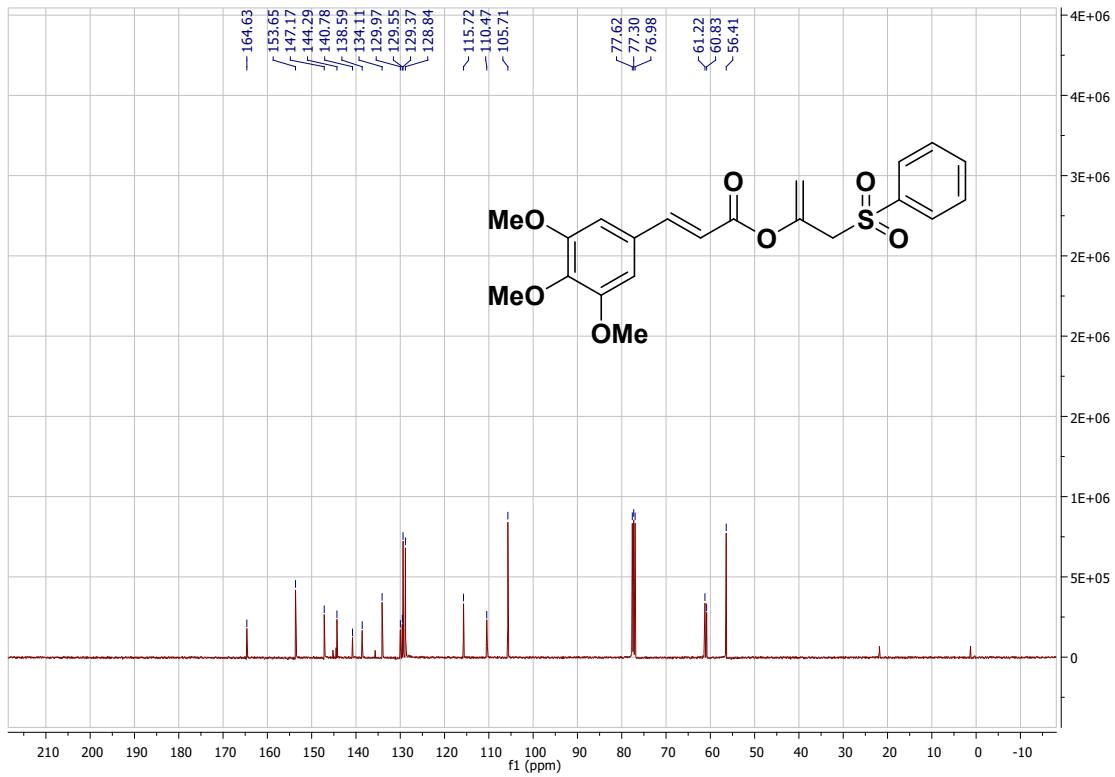
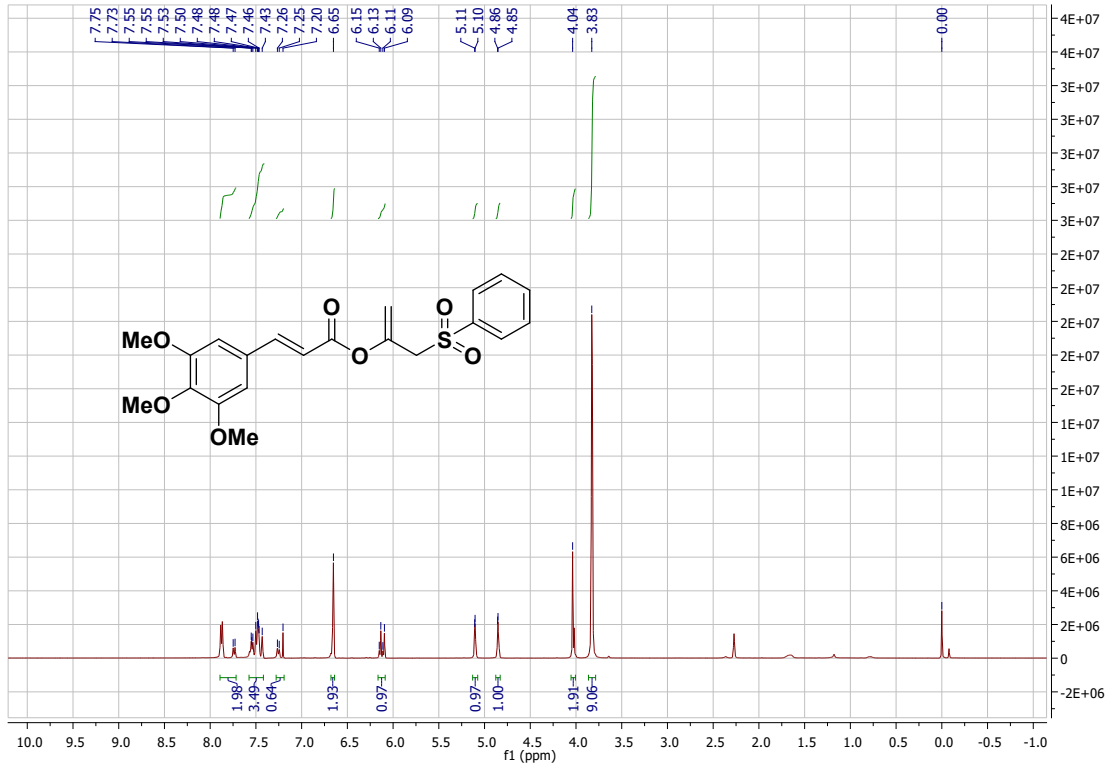
3e



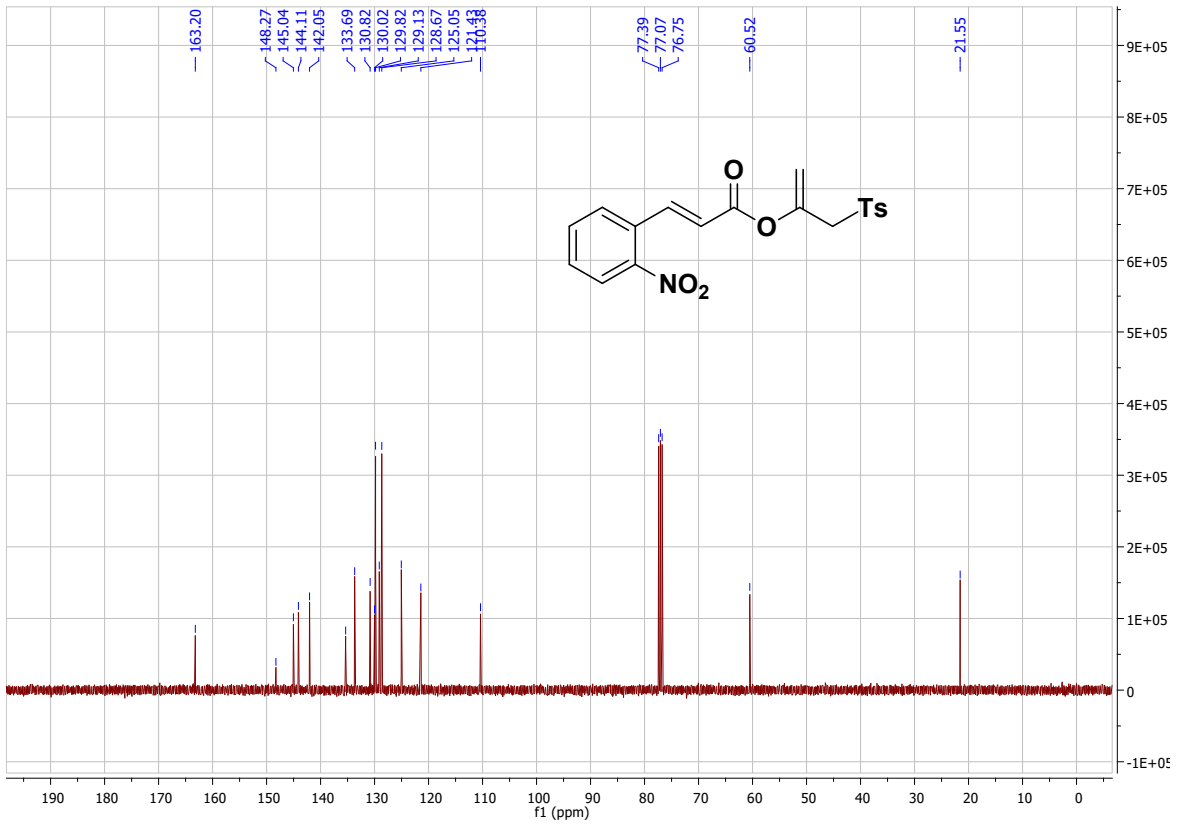
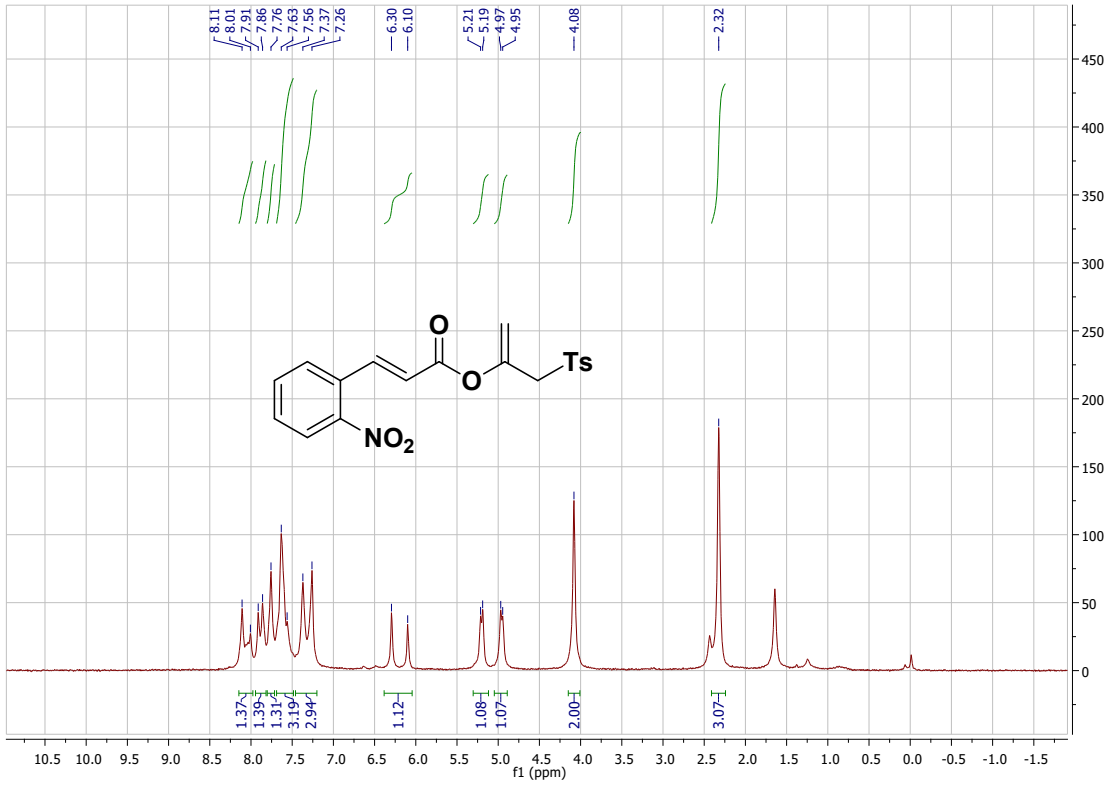
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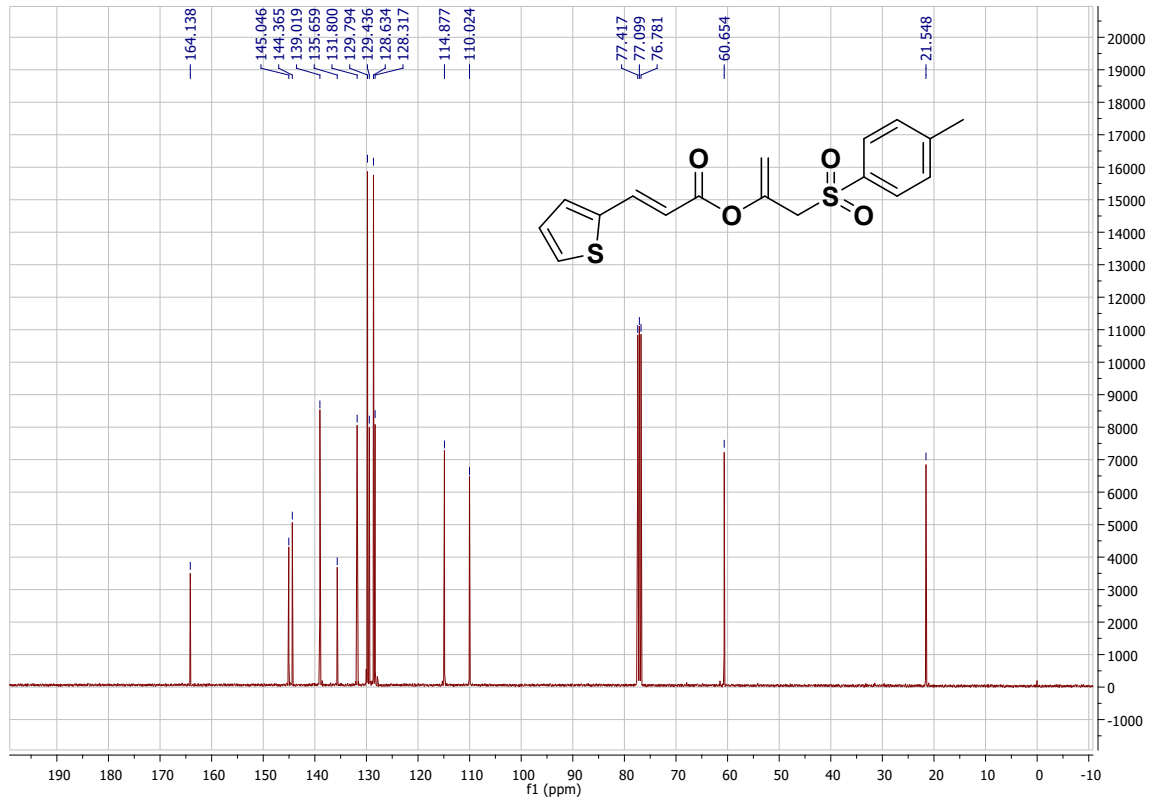
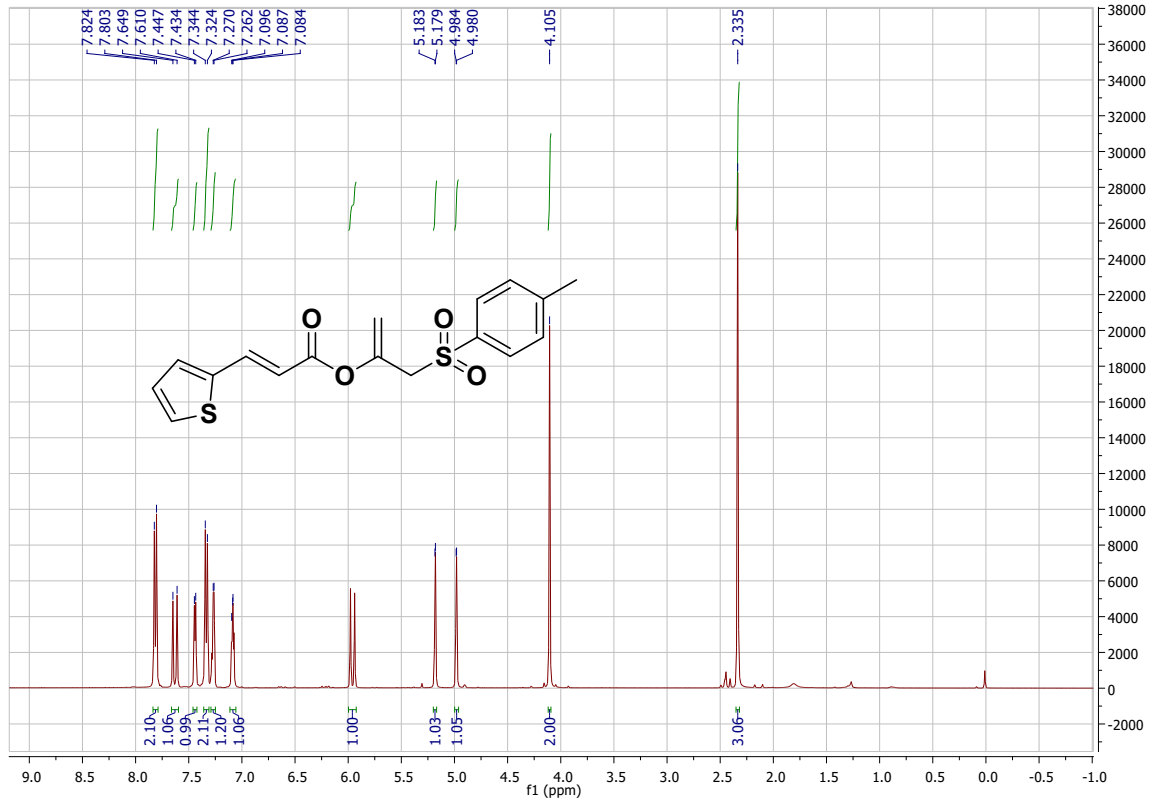
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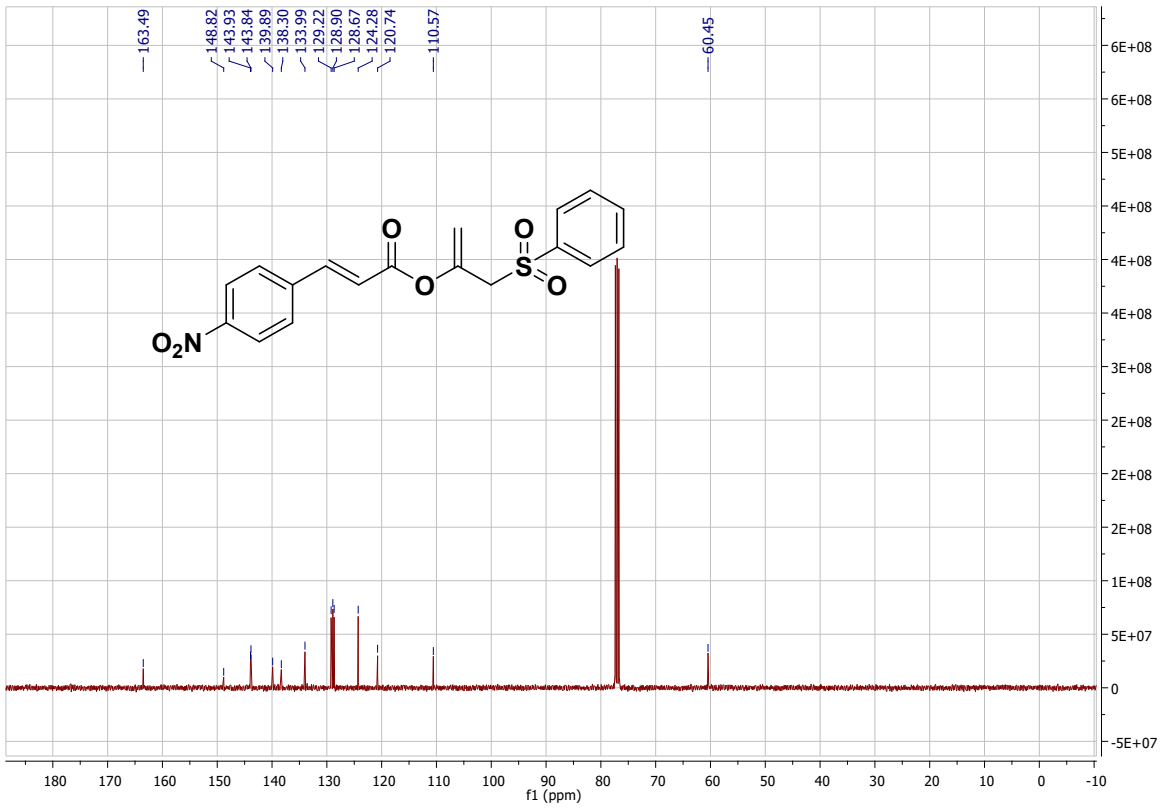
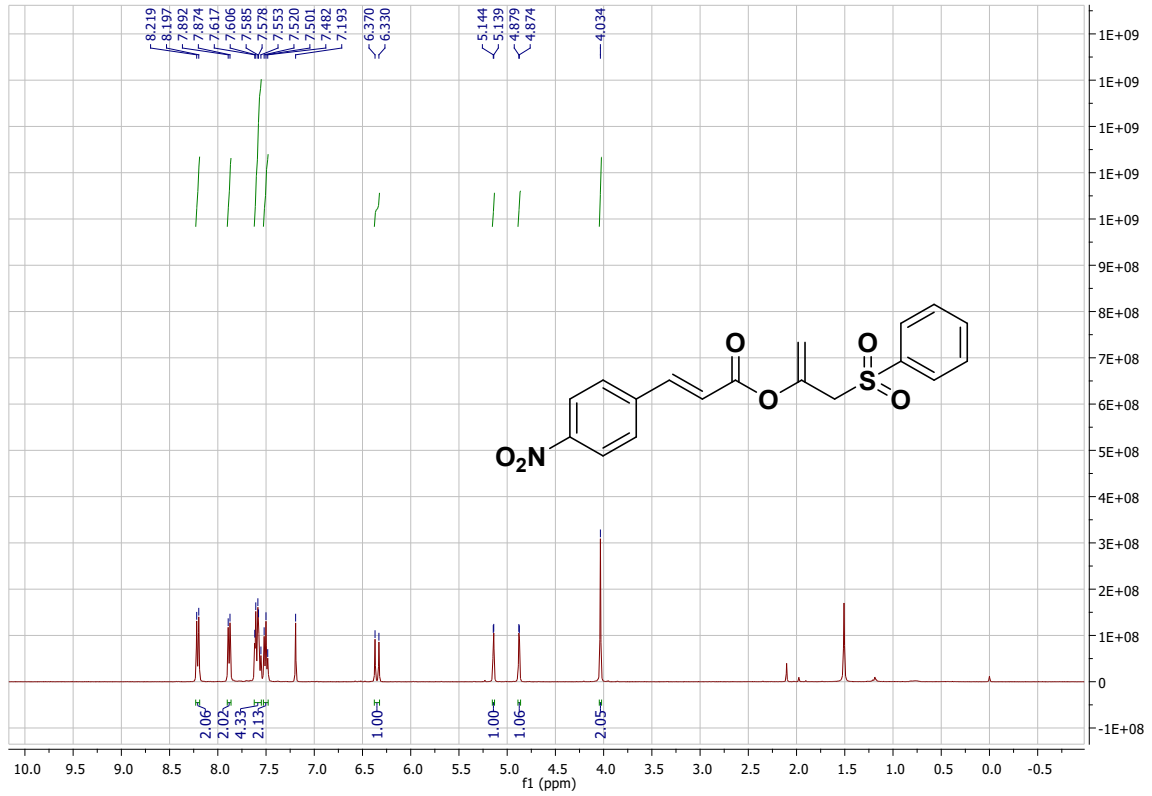
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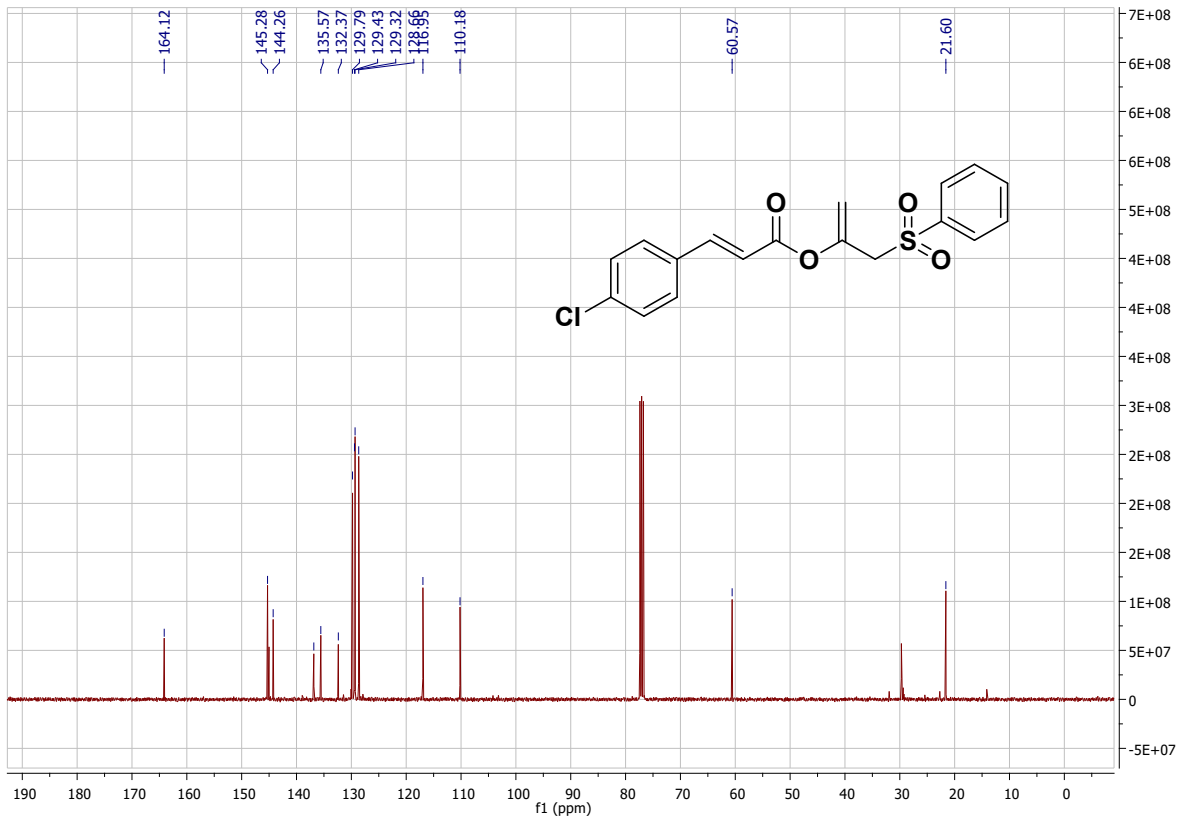
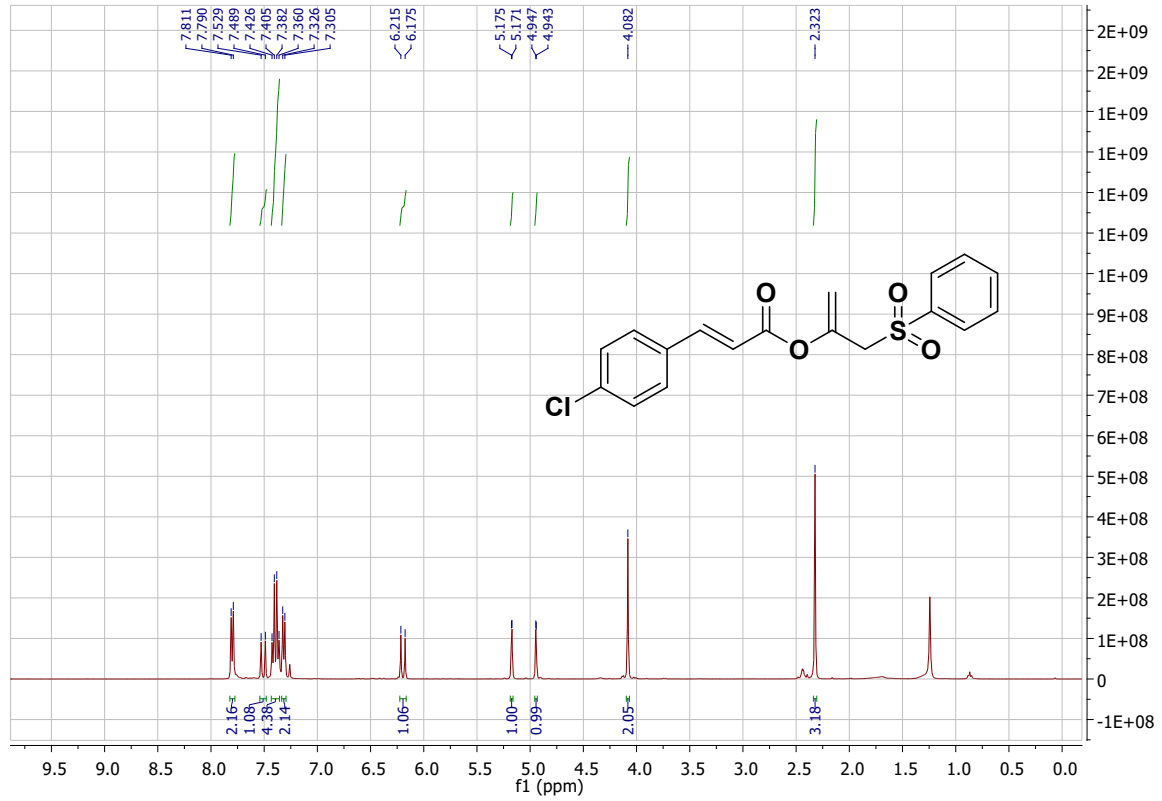
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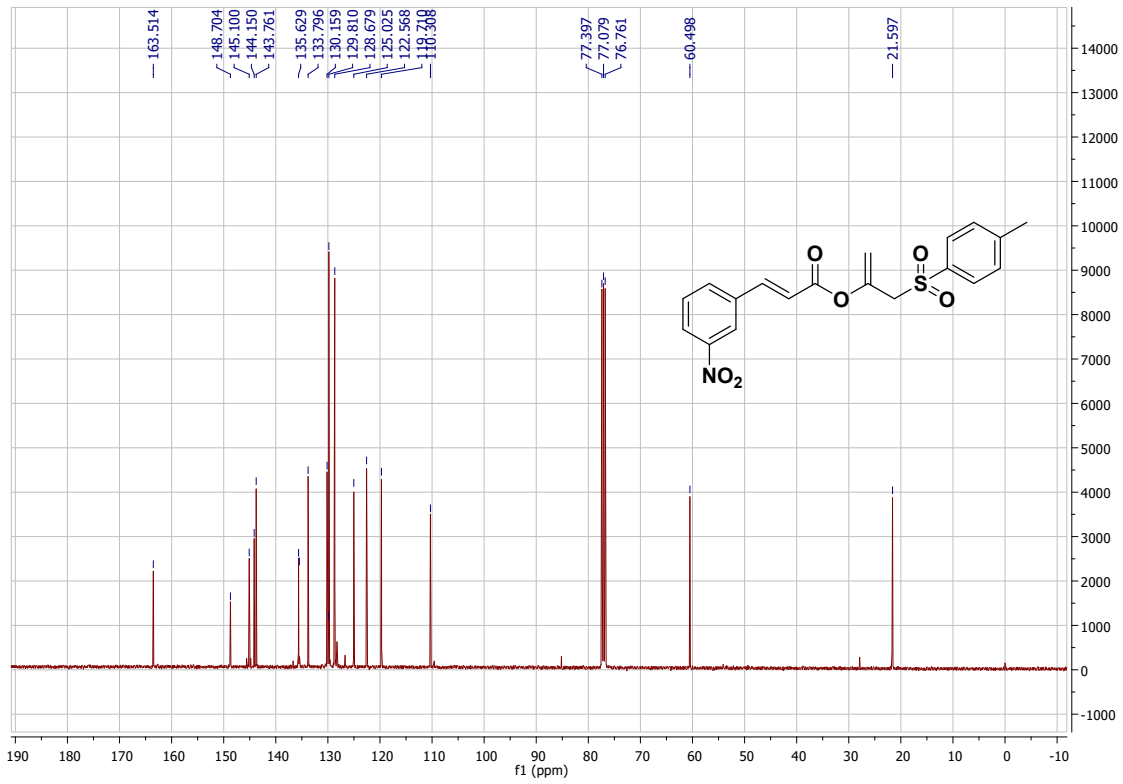
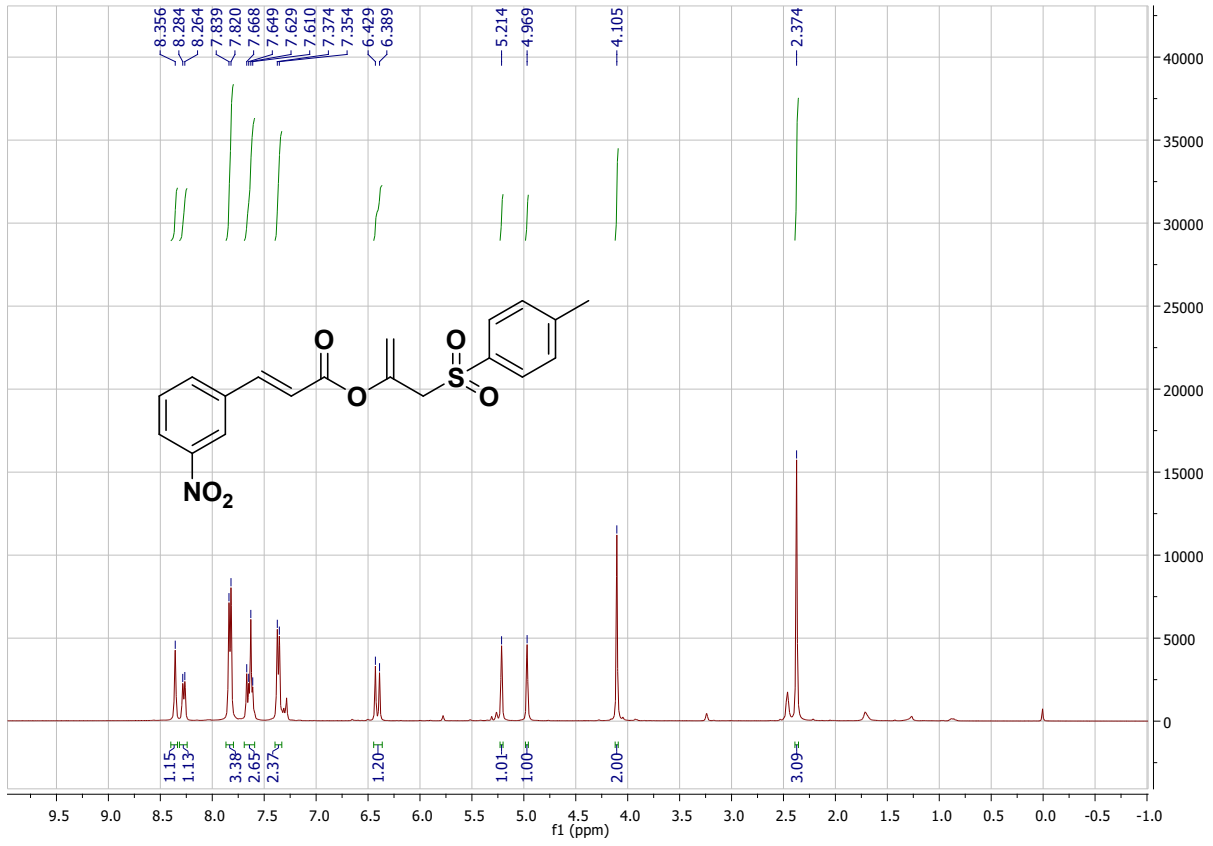
3j



3k

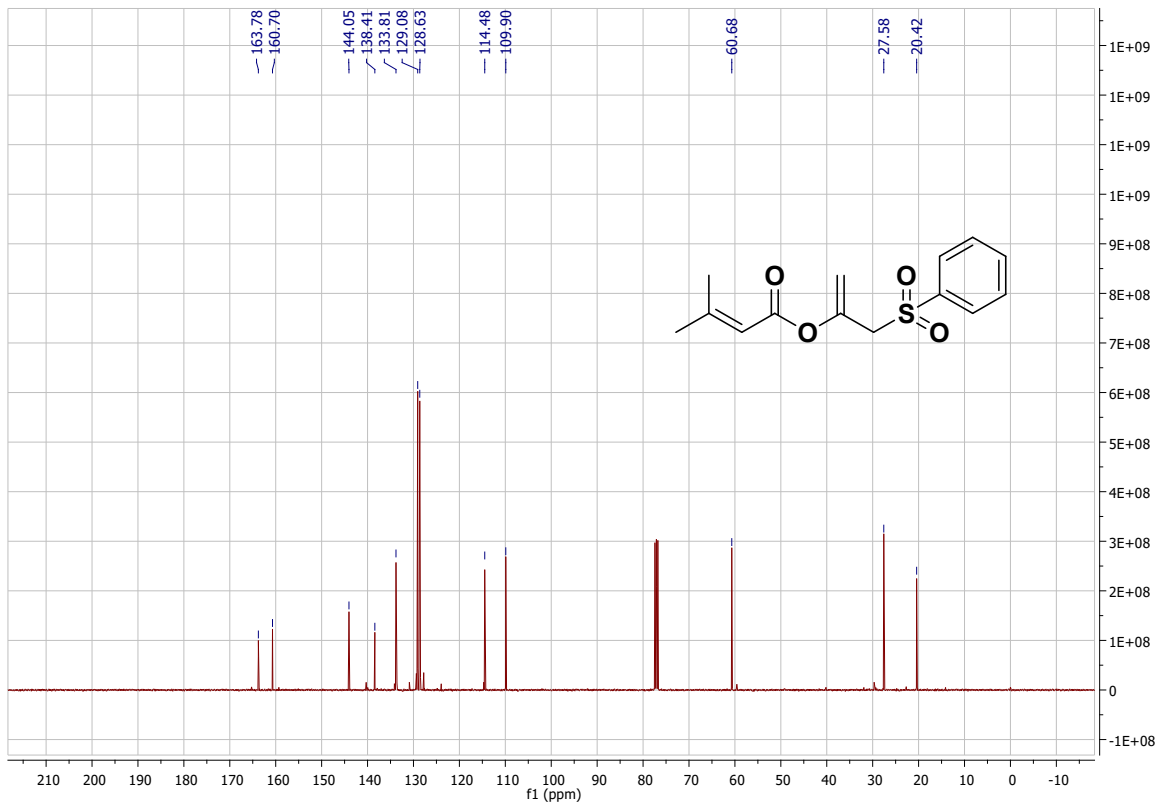
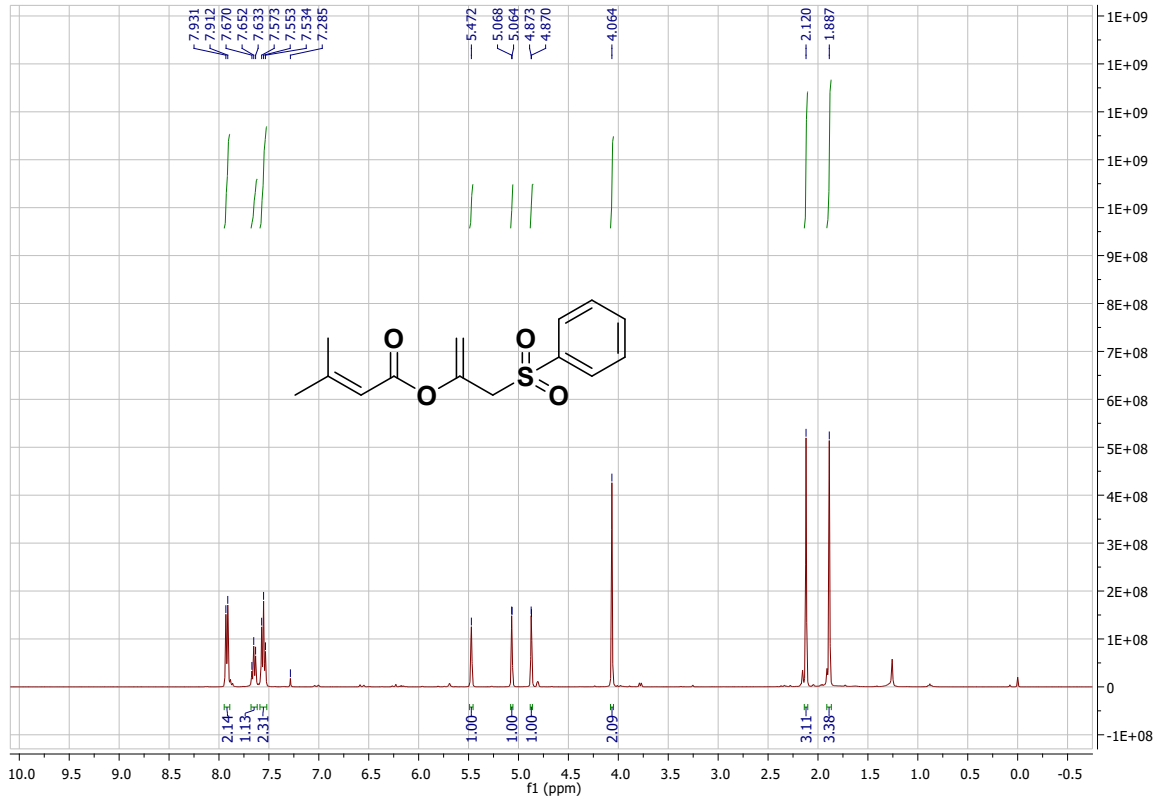


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### 3m



4

