Electronic Supplementary Material (ESI) for Green Chemistry.
This journal is © The Royal Society of Chemistry 2019

# Electronic Supplementary Information

## g-$C_3N_4$-Based heterogeneous photocatalyst for visible light mediated aerobic benzylic C-H oxygenations

Pengxin Geng,[a,b] Yurong Tang,[b] Guanglong Pan,[b] Wentao Wang,[c] Jinchuan Hu,*[a] and Yunfei Cai *[b]

[a]College of Chemisty, Chongqing Normal University, Chongqing 401331, P. R. China. E-mail: hujc20@139.com
[b]School of Chemistry and Chemical Engineering & Chongqing Key Laboratory of Theoretical and Computational Chemistry, Chongqing University, 174 Shazheng Street, Chongqing 400030, P. R. China. E-mail: yf.cai@cqu.edu.cn
[c]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China

## Table of contents

## 1. General information

All chemical were obtained from commercial supplier and were used without further purification unless otherwise stated. All solvents were dried and distilled under argon prior to use. Solvents for chromatography were of technical grade and distilled prior to use. Glassware was pre-dried in an oven at 110 °C for several hours and cooled prior to use. Analytical thin layer chromatography was carried out using silica gel GF254, visualized under UV light (at 254 nm). Proton NMR ($^1H$) were recorded at 500 MHz, and Carbon NMR ($^{13}C$) at 126 MHz NMR spectrometer. All the NMR spectra were processed in either MestReNova software. Chemical shifts (δ) are given in ppm. The XRD spectra was obtained with an X'Pert Pro MPD (Philips, Netherlands) X-ray diffraction spectrometer using Cu-Ka radiation ($\lambda$ = 1.79 Å). FT-IR spectra were collected using a Nicolet IS10 FTIR spectrometer (Thermo Inc., America). Atomic force microscopy (AFM, NanoScope quadrex, Vecco Corporation American, Tapping Mode, pinpoint: TESP7 Vecco) was used to performed the characterization of g-$C_3N_4$.

## 2. Synthesis of various carbon nitride catalysts

The g-$C_3N_4$ photocatalyst was synthesized by the classic and facile method,[1] which consisted of directly heating melamine at different programmed temperatures in air. In detail, 4 g melamine was placed in a crucible with a cover, and heated to the desired temperature for 3 h at a heating rate of 3 °C $min^{-1}$. The resultant g-$C_3N_4$ samples were designated g-$C_3N_4$ (450 °C, g-$C_3N_4$ (500 °C), g-$C_3N_4$ (550 °C), g-$C_3N_4$ (600 °C) and g-$C_3N_4$ (650 °C), respectively, according to different polymerization temperatures of 450, 500, 550, 600 and 650 °C. For comparison, g-$C_3N_4$ was also prepared from other precursor by a similar procedure. 4 g urea (or dicyandiamide or guanidine hydrochloride) was placed in a crucible with a cover, and heated to 550 °C for 3 h at a heating rate of 3 °C $min^{-1}$ to obtain g-$C_3N_4$ (urea 550 °C) or (dicyandiamide 550 °C) or (guanidine hydrochloride 550 °C).

**Synthesis of mpg-$C_3N_4$:** mpg-$C_3N_4$ was prepared according to previously reported method.[2] In brief, cyanamide (3 g) was dissolved in 12.25 g 40% dispersion of 12-nm $SiO_2$ particles (Ludox HS40) in water with stirring at 333 K overnight. The resulting transparent mixtures were then heated at a rate of 2.3 K/min over 4 h to reach a temperature of 823 K and then tempered at this temperature for another 4 h. The resulting brown-yellow powder was treated with a 4.0 M $NH_4HF_2$ for 24 h to remove the silica template. The powders were then centrifuged and washed three times with distilled water and twice with ethanol. Finally the powders were dried at 343 K under vacuum for overnight. To prepare bulk g-$C_3N_4$, cyanamide was directly heated to 823 K and then tempered at this temperature for another 4 h.

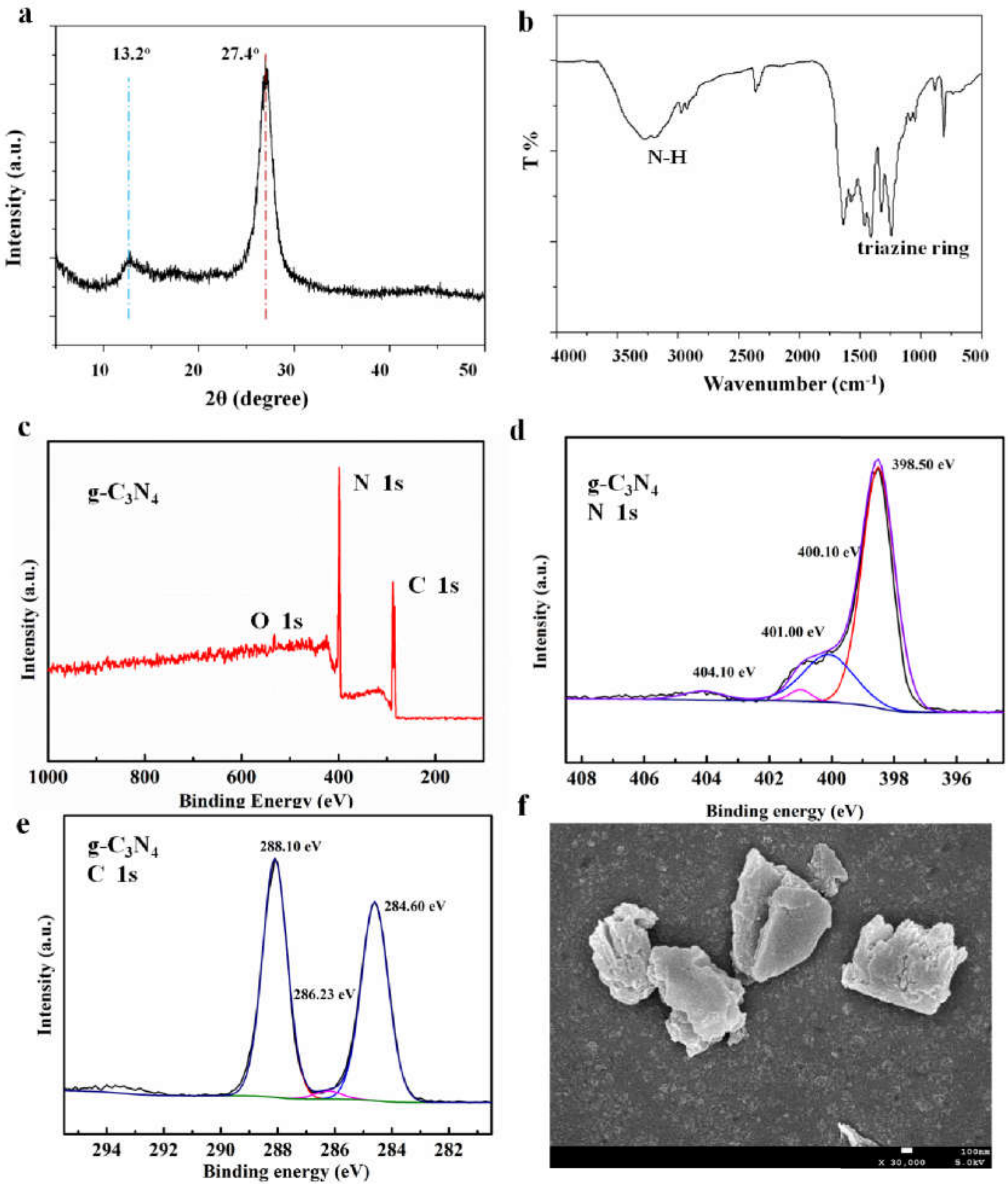
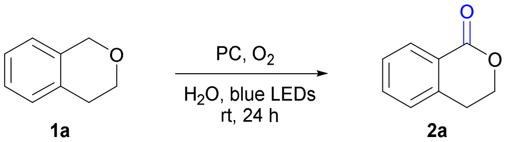


**Fig. S1** (a) XRD patterns, (b) FT-IR spectra, (c) XPS survey, (d) N1s spectra, (e) C1s spectra, (f) SEM image of the g-$C_3N_4$ prepared by pyrolysis of melamine at 600 °C

The optimal g- $C_3N_4$ catalyst used in this work was charaterized by XRD, XPS and SEM (Fig. S1).

## 3. Extra optimization of the reaction conditions

**Table S1** Screening of carbon nitrides in the photo-oxidation of isochroman **1a** to isochromanone **2a** [a]



| entry | PC (precursor, temperature) | yield (%)[b] |
|---|---|---|
| 1 | mpg-$C_3N_4$ | 59 |
| 2 | g-$C_3N_4$ (urea, 550 °C) | 66 |
| 3 | g-$C_3N_4$ (dicyandiamide, 550 °C) | 67 |
| 4 | g-$C_3N_4$ (guanidine hydrochloride, 550 °C) | 67 |
| 5 | g-$C_3N_4$ (melamine, 450 °C) | 59 |
| 6 | g-$C_3N_4$ (melamine, 500 °C) | 68 |
| 7 | g-$C_3N_4$ (melamine, 550 °C) | 68 |
| 8 | g-$C_3N_4$ (melamine, 600 °C) | 77 |
| 9 | g-$C_3N_4$ (melamine, 650 °C) | 77 |

[a]Reaction conditions: **1a** (0.2 mmol), PC (10 mg), $H_2O$ (2 mL), $O_2$ balloon, 6W blue LEDs, 24 h, rt. [b]Yields determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

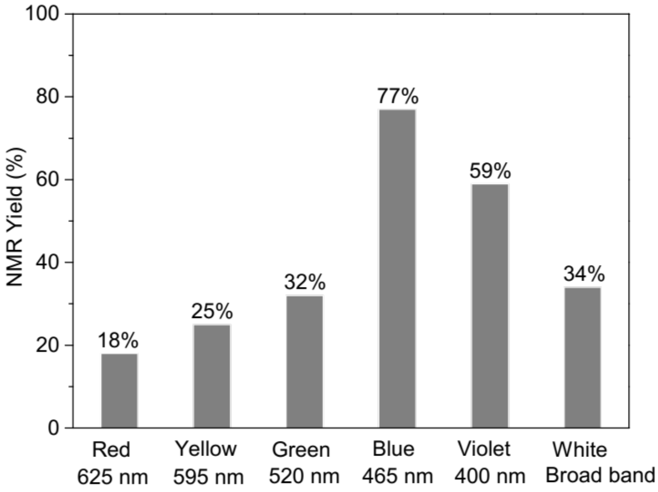


**Fig. S2** Effect of the light source on the g-$C_3N_4$ photocatalyzed aerobic oxidation of isochroman **1a**

## 4. General procedures (GPs) for the g-$C_3N_4$ photocatalyzed reactions

### 4.1 GP1

A dry reaction tube was charged with g-$C_3N_4$ (10 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, $H_2O$ (2.0 mL) and substrate (0.2 mmol) were added via syringe. The solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (465 nm) at room temperature for 24 h, with adequate fans to keep the reaction below 35 °C (Fig. S3). After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 5:1~10:1). For comparison, two 34W Kessil PR160-456 lamp (40W, 25%) were used as alternative light sources (Fig. S4), similar yield of **2a** was obtained from substrate **1a**.

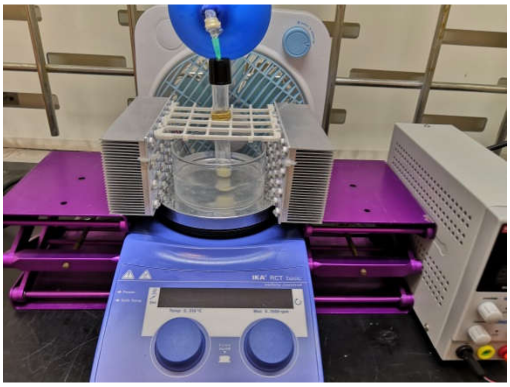


**Fig. S3**

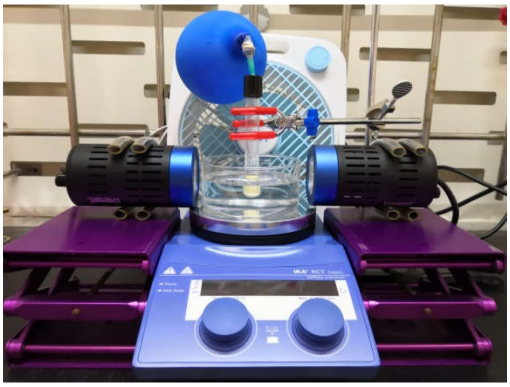


**Fig. S4**

### 4.2. GP2

A dry reaction tube was charged with solid substrate (0.2 mmol) and g-$C_3N_4$ (10 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, dry DMSO (2.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (465 nm) at room temperature for 24 h, with adequate fans to keep the reaction below 35 °C. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 60-mL separatory funnel, and washed with water (3 × 5 ml), then dried over anhydrous $Na_2SO_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 5:1~10:1).

### 4.3. GP3

A dry reaction tube was charged with **5b** (0.2 mmol) and g-$C_3N_4$ (20 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, dry 1,2-Dichloroethane (2.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (465 nm) at room temperature for 24 h with adequate fans to keep the reaction below 35 °C. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$.

After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 10:1).

### 4.4. **GP4**

A dry reaction tube was charged with **5d** (0.2 mmol) and g-$C_3N_4$ (20 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, dry DMSO (2.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 24 W violet LEDs (400 nm) at 50°C for 24 h. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 60-mL separatory funnel, and washed with water (3 × 5 ml), then dried over anhydrous $Na_2SO_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 30:1).

### 4.5. GP5

A dry reaction tube was charged with substrate (0.2 mmol) and g-$C_3N_4$ (20 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, dry DMSO (4.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 24 W blue LEDs (465 nm) at room temperature for 8 h with adequate fans to keep the reaction below 35 °C. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 60-mL separatory funnel, and washed with water (3 × 5 ml), then dried over anhydrous $Na_2SO_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 5:1).

### 4.6. GP6

A dry reaction tube was charged with substrate (0.2 mmol, 1 equiv.), $K_2CO_3$ (0.1 mmol, 0.5 equiv) and g-$C_3N_4$ (20 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, dry DMSO (4.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (465 nm) at room temperature for 24 h with adequate fans to keep the reaction below 35 °C. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. The reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 60-mL separatory funnel, and washed with water (3 × 5 ml), then dried over anhydrous $Na_2SO_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 5:1).

### 4.7. GP7

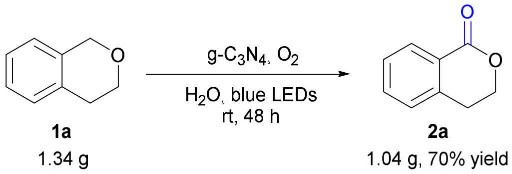
A dry reaction tube was charged with ethylbenzene **5e** (0.2 mmol) and g-$C_3N_4$ (20 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, $d_6$-DMSO (2.0 mL) were added via syringe. The solution was stirred at a distance of ~5 cm from a 24 W violet LEDs (400 nm) at 50°C for 48 h. Yield of desired product

**6e** determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

### 4.8. Recycling test

A dry reaction tube was charged with g-$C_3N_4$ (10 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, $H_2O$ (2.0 mL) and **1a** (0.2 mmol, 1.0 equiv.) were added via syringe. The solution was stirred at a distance of ~5 cm from a 6 W blue LEDs (465 nm) at room temperature for 24 h with adequate fans to keep the reaction below 35 °C. After completion, the reaction mixture was centrifuged to separate g-$C_3N_4$ and the liquid mixture. The catalyst g-$C_3N_4$ was washed thoroughly with methyl alcohol (3 × 3 mL) and $H_2O$ (5 × 3 mL) and reused in the subsequent recycling reaction. The combined liquid mixture was evapored and analyzed by crude $^1$H NMR using 1,3,5-trimethoxybenzene (0.05 mmol) as an internal standard to determined the yield of **2a**.

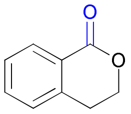
### 4.9. Gram-scale synthesis of 2a



A dry reaction tube was charged with g-$C_3N_4$ (500 mg). It was capped with a rubber septum, evacuated and backfilled with oxygen. Then, $H_2O$ (50 mL) and **1a** (10 mmol, 1.34 g) were added via syringe. The solution was stirred at a distance of ~5 cm from 4*6 W blue LEDs (465 nm) at room temperature for 48 h, with adequate fans to keep the reaction below 35 °C. After complete consumption of the starting material (followed by TLC), the mixture was filtered to remove the g-$C_3N_4$. The resulting mixture was extracted with ethyl acetate (3× 50 mL). The organic layer was dried over $MgSO_4$. After removal of solvents, the crude product was purified via silica gel flash column chromatography (petroleum ether /ethyl acetate 5:1~10:1). The product **2a** was isolated as colorless oil (1.04 g, 70% yield).

## 5. Characterization of the products 2a-s, 4a-l, 6a-6d, 8 and 9.

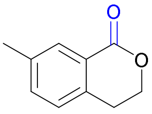
### Isochroman-1-one (2a):



**2a**

According to **GP1** starting from **1a** (0.2 mmol), the product **2a** was isolated after flash chromatography (petroleum ether/ethyl acetate 8:1), colorless liquid; 77% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, $J$ = 7.8 Hz, 1H), 7.54 (t, $J$ = 7.5 Hz, 1H), 7.39 (t, $J$ = 7.6 Hz, 1H), 7.27 (d, $J$ = 7.6 Hz, 1H), 4.54 (t, $J$ = 5.9 Hz, 2H), 3.07 (t, $J$ = 5.9 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.20, 139.62, 133.73, 130.37, 127.70, 127.31, 125.31, 67.36, 27.83. Data are consistent with those reported in the literature.[3]

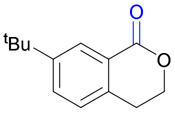
### 7-Methylisochroman-1-one (2b):



**2b**

According to **GP1** starting from **1b** (0.2 mmol), the product **2b** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid; 72% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.35 (d, $J$ = 7.6 Hz, 1H), 7.16 (d, $J$ = 7.7 Hz, 1H), 4.52 (t, $J$ = 6.0 Hz, 2H), 3.02 (t, $J$ = 5.9 Hz, 2H), 2.39 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.45, 137.60, 136.61, 134.58, 130.65, 127.15, 125.08, 67.47, 27.49, 21.03. Data are consistent with those reported in the literature.[3]

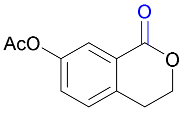
### 7-(Tert-butyl)isochroman-1-one (2c):



**2c**

According to **GP1** starting from **1c** (0.2 mmol), the product **2c** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 74% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.21 (d, $J$ = 8.0 Hz, 1H), 4.52 (t, $J$ = 6.0 Hz, 2H), 3.03 (t, $J$ = 5.9 Hz, 2H), 1.34 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.64, 151.00, 136.68, 131.04, 127.08, 127.06, 124.85, 67.42, 34.77, 31.21, 27.43. Data are consistent with those reported in the literature.[4]

### 1-Oxoisochroman-7-yl acetate (2d):

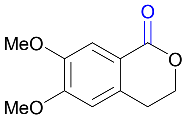


**2d**

According to **GP2** starting from **1d** (0.2 mmol), the product **2d** was isolated after flash chromatography (petroleum ether/ethyl acetate 4:1), white solid, 69% yield; $^1$H

NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 1.2 Hz, 1H), 7.32 – 7.27 (m, 2H), 4.55 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 6.0 Hz, 2H), 2.32 (s, 3H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 169.31, 164.28, 149.95, 137.05, 128.53, 127.35, 126.53, 123.32, 67.40, 27.33, 21.02. Data are consistent with those reported in the literature.[3]

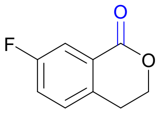
**6,7-Dimethoxyisochroman-1-one (2e):**



**2e**

According to **GP2** starting from **1e** (0.2 mmol), the product **2e** was isolated after flash chromatography (petroleum ether/ethyl acetate 3:1), white solid, 58% yield; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.69 (s, 1H), 4.52 (t, *J* = 6.0 Hz, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 2.99 (t, *J* = 5.9 Hz, 2H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 165.24, 153.67, 148.53, 134.00, 117.45, 111.87, 109.16, 67.40, 56.21, 27.52. Data are consistent with those reported in the literature.[5]

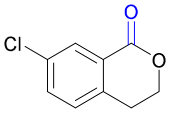
**7-Fluoroisochroman-1-one (2f):**



**2f**

According to **GP1** starting from **1f** (0.2 mmol), the product **2f** was isolated after flash chromatography (petroleum ether/ethyl acetate 8:1), white solid, 74% yield; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 5.5 Hz, 2H), 4.55 (t, J = 5.9 Hz, 2H), 3.05 (t, J = 5.9 Hz, 2H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 164.09, 161.88 (d, $J_{C\text{-}F}$ = 247.1 Hz), 135.31 (d, $J_{C\text{-}F}$ = 3.2 Hz), 129.11 (d, $J_{C\text{-}F}$ = 7.4 Hz), 127.01 (d, $J_{C\text{-}F}$ = 7.7 Hz), 121.11 (d, $J_{C\text{-}F}$ = 22.0 Hz), 116.82 (d, $J_{C\text{-}F}$ = 23.1 Hz), 67.50, 27.17. Data are consistent with those reported in the literature.[3]

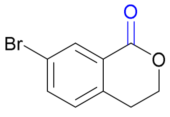
**7-Chloroisochroman-1-one (2g):**



**2g**

According to **GP1** starting from **1g** (0.2 mmol), the product **2g** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 71% yield; $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 8.1, 2.0 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 4.54 (t, J = 6.0 Hz, 2H), 3.05 (t, J = 5.9 Hz, 2H); $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 163.93, 137.79, 133.75, 130.23, 128.78, 126.79, 67.30, 27.31. Data are consistent with those reported in the literature.[3]

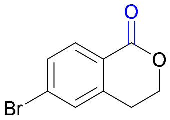
**7-Bromoisochroman-1-one (2h):**



**2h**

According to **GP1** starting from **1h** (0.2 mmol), the product **2h** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 77% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.23 (s, 1H), 7.66 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 4.54 (t, *J* = 6.0 Hz, 2H), 3.03 (t, *J* = 5.9 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 163.79, 138.28, 136.62, 133.18, 129.01, 127.02, 121.40, 67.25, 27.38. Data are consistent with those reported in the literature.[6]

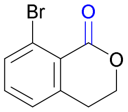
### 6-Bromoisochroman-1-one (2i):



**2i**

According to **GP1** starting from **1i** (0.2 mmol), the product **2i** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 74% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.46 (s, 1H), 4.54 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 5.9 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.42, 141.27, 132.05, 131.23, 130.38, 128.80, 124.22, 67.14, 27.64. Data are consistent with those reported in the literature.[7]

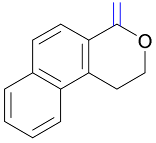
### 8-Bromoisochroman-1-one (2j):



**2j**

According to **GP1** starting from **1j** (0.2 mmol), the product **2j** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 75% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 4.47 (t, *J* = 5.8 Hz, 2H), 3.08 (t, *J* = 5.8 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 161.96, 142.62, 134.64, 133.43, 126.60, 124.80, 100.00, 66.55, 29.31. Data are consistent with those reported in the literature.

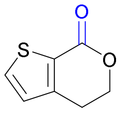
### 1,2-Dihydro-4H-benzo[f]isochromen-4-one (2k):



**2k**

According to **GP2** starting from **1k** (0.2 mmol), the product **2k** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 80% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 7.0 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.67 – 7.61 (m, 2H), 4.68 (t, *J* = 6.1 Hz, 2H), 3.45 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.54, 138.57, 135.66, 129.88, 128.93, 128.72, 127.81, 127.26, 125.23, 124.42, 122.50, 66.72, 24.23. Data are consistent with those reported in the literature.[8]

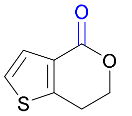
**4,5-Dihydro-7H-thieno[2,3-c]pyran-7-one (2l):**



**2l**

According to **GP1** starting from **1l** (0.2 mmol), the product **2l** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 30% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 5.0 Hz, 1H), 7.01 (d, *J* = 4.9 Hz, 1H), 4.59 (t, *J* = 6.2 Hz, 2H), 3.02 (t, *J* = 6.2 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 161.21, 147.47, 134.45, 126.78, 126.57, 68.40, 25.14. Data are consistent with those reported in the literature.[3]

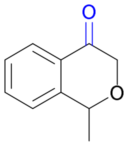
**6,7-Dihydro-4H-thieno[3,2-c]pyran-4-one (2m):**



**2m**

According to **GP1** starting from **1m** (0.2 mmol), the product **2m** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 47% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.2 Hz, 1H), 7.17 (d, *J* = 5.2 Hz, 1H), 4.60 (t, *J* = 6.1 Hz, 2H), 3.16 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 161.27, 148.96, 128.17, 126.96, 124.02, 67.73, 24.65. HRMS ($ESI^+$): *m/z* calcd for $C_7H_6O_2S$ $[M + Na]^+$ 176.9981, found 176.9980.

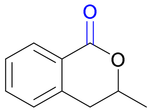
**4-Methylisochroman-1-one (2n):**



**2n**

According to **GP1** starting from **1n** (0.2 mmol), the product **2n** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), colorless liquid, 75% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 4.52 (dd, *J* = 10.9, 4.0 Hz, 1H), 4.25 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.22 – 3.13 (m, 1H), 1.38 (d, *J* = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.17, 144.59, 133.93, 130.52, 127.57, 125.71, 124.43, 72.49, 31.78, 16.71. Data are consistent with those reported in the literature.[3]

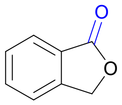
### 3-Methylisochroman-1-one (2o):



**2o**

According to **GP1** starting from **1o** (0.2 mmol), the product **2o** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), colorless liquid, 70% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 4.74 – 4.63 (m, 1H), 3.02 – 2.89 (m, 2H), 1.53 (d, *J* = 6.3 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.64, 139.13, 133.70, 130.31, 127.67, 127.33, 125.04, 75.10, 34.92, 20.95. Data are consistent with those reported in the literature.[3]

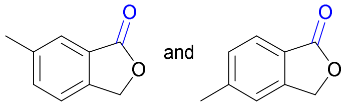
### Isobenzofuran-1(3H)-one (2p):



**2p**

According to **GP1** starting from **1p** (0.2 mmol), the product **2p** was isolated after flash chromatography (petroleum ether/ethyl acetate 8:1), colorless liquid, 71% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.7 Hz, 1H), 5.34 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.14, 146.56, 134.05, 129.08, 125.81, 125.78, 122.14, 69.69. Data are consistent with those reported in the literature.[3]

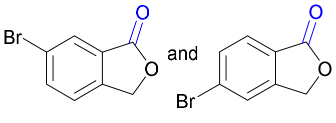
### 6-Methylisobenzofuran-1(3H)-one/5-Methylisobenzofuran-1(3H)-one (2q):



**2q**

According to **GP1** starting from **1q** (0.2 mmol), the product **2q** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), **6-Methylisobenzofuran-1(3H)-one**: colorless liquid, 43% yield (**1**:1.15); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 5.28 (s, 2H), 2.47 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.32, 143.92, 139.30, 135.23, 125.91, 125.72, 121.81, 69.63, 21.27. Data are consistent with those reported in the literature.[7] **5-Methylisobenzofuran-1(3H)-one:** colorless liquid, 52% yield (1:**1.15**); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 5.27 (s, 2H), 2.50 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 171.22, 147.16, 145.30, 130.23, 125.50, 123.20, 122.41, 69.45, 22.07. Data are consistent with those reported in the literature.[9]

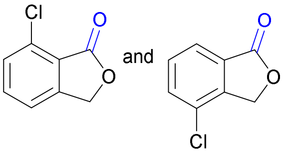
**6-Bromoisobenzofuran-1(3H)-one/5-Bromoisobenzofuran-1(3H)-one (2r):**



**2r**

According to **GP1** starting from **1r** (0.2 mmol), the product **2r** was isolated after flash chromatography (petroleum ether/ethyl acetate 10:1), **6-Bromoisobenzofuran-1(3H)-one**: white solid, 39% yield, (**1**:1.34) $^1$H NMR (500 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.80 (d, *J* = 9.4 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 5.29 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.51, 145.16, 137.14, 128.80, 127.88, 123.75, 123.06, 69.55. Data are consistent with those Reported in the literature.[1] **5-Bromoisobenzofuran-1(3H)-one** white solid, 52% yield (1:**1.34**);$^1$H NMR (500 MHz, CDCl$_3$) δ 7.79 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 3.9 Hz, 2H), 5.31 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.05, 148.27, 132.77, 129.34, 127.10, 125.64, 124.80, 68.94. Data are consistent with those reported in the literature.[3]

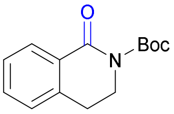
**7-Chloroisobenzofuran-1(3H)-one/4-Chloroisobenzofuran-1(3H)-one (2s):**



**2s**

According to **GP1** starting from **1s** (0.2 mmol), the product **2s** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), **7-Chloroisobenzofuran-1(3H)-one**: white solid, 40% yield (**1**:1.35); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.61 (t, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 5.28 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.96, 148.90, 135.03, 133.58, 130.52, 122.55, 120.54, 68.32. Data are consistent with those reported in the literature.[8] **4-Chloroisobenzofuran-1(3H)-one:** white solid, 54% yield (1:**1.35**); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 5.31 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 169.97, 144.55, 133.93, 130.85, 128.80, 128.00, 124.16, 68.64. Data are consistent with those reported in the literature.[10]

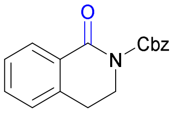
**Tert-butyl 1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (4a):**



**4a**

According to **GP5** starting from **3a** (0.2 mmol), the product **4a** was isolated after flash chromatography (dichloromethane/ethyl acetate 40:1), white solid, 64% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.16 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.01 (t, *J* = 6.1 Hz, 2H), 1.59 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.00, 153.21, 139.58, 132.88, 129.68, 129.41, 127.26, 127.19, 83.27, 44.47, 28.38, 28.15. Data are consistent with those reported in the literature.[15]

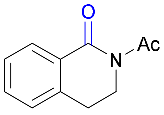
### Benzyl 1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (4b):



**4b**

According to **GP5** starting from **3b** (0.2 mmol), the product **4b** was isolated after flash chromatography (dichloromethane/ethyl acetate 80:1), white solid, 70% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 3H), 7.40 – 7.32 (m, 4H), 7.22 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 2H), 4.12 – 4.05 (m, 2H), 3.01 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.79, 154.55, 139.60, 135.48, 133.19, 129.82, 129.07, 128.65, 128.35, 128.13, 127.40, 127.31, 68.80, 44.83, 28.30. Data are consistent with those Reported in the literature.[15]

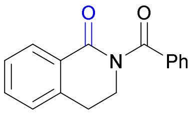
### 2-Acetyl-3,4-dihydroisoquinolin-1(2H)-one (4c):



**4c**

According to **GP5** starting from **3c** (0.2 mmol), the product **4c** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 41% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 4.12 (t, *J* = 6.3 Hz, 2H), 3.00 (t, *J* = 6.2 Hz, 2H), 2.67 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.82, 165.81, 140.30, 133.44, 129.57, 129.06, 127.40, 41.77, 28.18, 27.68. Data are consistent with those reported in the literature.[15]

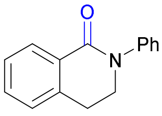
### 2-Benzoyl-3,4-dihydroisoquinolin-1(2H)-one (4d):



**4d**

According to **GP5** starting from **3d** (0.2 mmol), the product **4d** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 60% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 2H), 7.50 (d, *J* = 7.4 Hz, 0H), 7.44 – 7.34 (m, 3H), 7.32 (d, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 6.2 Hz, 2H), 3.19 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 140.20, 136.28, 133.69, 131.72, 129.77, 128.25, 128.18, 127.72, 127.47, 44.35, 28.54. Data are consistent with those Reported in the literature.[15]

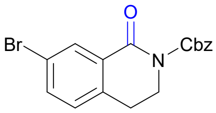
## 2-Phenyl-3,4-dihydroisoquinolin-1(2H)-one (4e):



**4e**

According to **GP6** starting from **3e** (0.2 mmol), the product **4e** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), white solid, 73% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 8.0 Hz, 6H), 7.43 – 7.34 (m, 3H), 7.24 (t, *J* = 7.7 Hz, 2H), 3.98 (t, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 6.4 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 164.25, 143.16, 138.37, 132.09, 129.77, 128.96, 128.78, 127.24, 127.01, 126.29, 125.37, 49.46, 28.67. Data are consistent with those reported in the literature.[15]

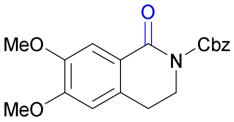
## Benzyl 7-bromo-1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (4f):



**4f**

According to **GP5** starting from **3f** (0.2 mmol), the product **4f** was isolated after flash chromatography (dichloromethane/ethyl acetate 80:1), white solid, 60% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 5.36 (s, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 2.96 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.45, 154.28, 138.31, 136.03, 135.29, 132.55, 130.77, 129.05, 128.67, 128.42, 128.13, 121.24, 99.99, 68.97, 44.60, 27.81. HR-MS (ESI$^+$): *m/z* calcd for $C_{17}H_{14}BrNO_3$ $[M + Na]^+$ 382.0049, found 382.0048.

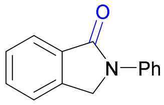
## Benzyl 6,7-dimethoxy-1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (4g):



**4g**

According to **GP5** starting from **3g** (0.2 mmol), the product **4g** was isolated after flash chromatography (dichloromethane/ethyl acetate 80:1), white solid, 68% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 6.64 (s, 1H), 5.36 (s, 2H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.93 (s, 3H), 3.92 (s, 6H), 2.95 (t, *J* = 6.1 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.92, 163.65, 154.73, 153.24, 148.35, 135.56, 134.04, 128.63, 128.29, 128.08, 121.40, 111.37, 109.20, 85.32, 68.71, 56.16, 56.15, 45.06, 28.02. HRMS (ESI$^+$): *m/z* calcd for $C_{19}H_{19}NO_5$ $[M + Na]^+$ 364.1155, found 364.1155.

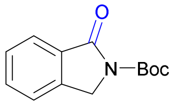
### 2-Phenylisoindolin-1-one (4h):



**4h**

According to **GP6** starting from **3h** (0.2 mmol), the product **4h** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 59% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 4.82 (s, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.55, 140.16, 139.53, 133.26, 132.11, 129.18, 128.40, 124.50, 124.16, 122.66, 119.49, 50.75. Data are consistent with those reported in the literature.[16]

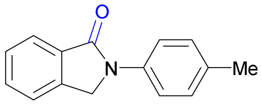
### Tert-butyl 1-oxoisoindoline-2-carboxylate (4i):



**4i**

According to **GP6** starting from **3i** (0.2 mmol), the product **4i** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 54% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.1 Hz, 1H), 7.49 (t, *J* = 9.0 Hz, 2H), 4.76 (s, 2H), 1.61 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.69, 150.46, 140.70, 133.54, 131.50, 128.52, 125.03, 123.06, 83.18, 49.17, 28.17. Data are consistent with those reported in the literature.[16]

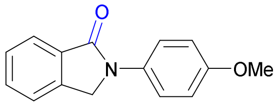
### 2-(p-Tolyl)isoindolin-1-one (4j):



**4j**

According to **GP6** starting from **3j** (0.2 mmol), the product **4j** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 68% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.78 (s, 2H), 2.33 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 167.42, 140.20, 136.98, 134.20, 133.35, 131.94, 129.69, 128.33, 124.06, 122.62, 119.61, 50.88, 20.89. Data are consistent with those reported in the literature.[16]

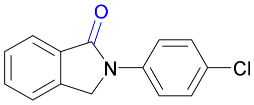
### 2-(4-Methoxyphenyl)isoindolin-1-one (4k):



**4k**

According to **GP6** starting from **3k** (0.2 mmol), the product **4k** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 72% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 2H), 7.57 (t, *J* = 7.0 Hz, 1H), 7.53 – 7.45 (m, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.79 (s, 2H), 3.82 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.29, 156.65, 140.18, 133.31, 132.67, 131.84, 128.34, 124.04, 122.60, 121.52, 114.36, 55.53, 51.20. Data are consistent with those reported in the literature.[16]

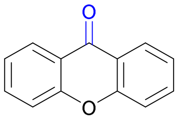
**2-(4-Chlorophenyl)isoindolin-1-one (4l):**



**4l**

According to **GP6** starting from **3l** (0.2 mmol), the product **4l** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 63% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 6.9 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 4.79 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.54, 139.91, 138.12, 132.91, 132.34, 129.52, 129.16, 128.53, 124.20, 122.68, 120.39, 50.65. Data are consistent with those reported in the literature.[16]

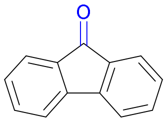
**9H-xanthen-9-one (6a):**



**6a**

According to **GP1** starting from **5a** (0.2 mmol), the product **6a** was isolated after flash chromatography (petroleum ether/ethyl acetate 8:1), white solid, 80% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.34 (d, *J* = 7.9 Hz, 2H), 7.72 (t, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 177.27, 156.21, 134.85, 126.77, 123.94, 121.88, 118.01. Data are consistent with those reported in the literature.[11]

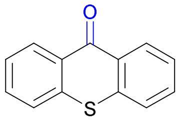
**9H-fluoren-9-one (6b):**



**6b**

According to **GP1** starting from **5b** (0.2 mmol), the product **6b** was isolated after flash chromatography (petroleum ether/ethyl acetate 20:1), white solid, 62% yield; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.48 (dt, *J* = 14.6, 7.2 Hz, 4H), 7.28 (t, *J* = 7.3 Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 193.96, 144.46, 134.72, 134.17, 129.10, 124.34, 120.34. Data are consistent with those reported in the literature.[11]

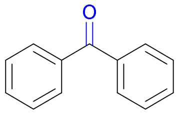
### 9H-thioxanthen-9-one (6c):



**6c**

According to **GP3** starting from **5c** (0.2 mmol), the product **6c** was isolated after flash chromatography (petroleum ether/ethyl acetate 8:1), white solid, 56% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.1 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 179.97, 137.30, 132.28, 129.88, 129.25, 126.32, 126.00. Data are consistent with those reported in the literature.[12]

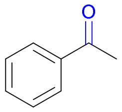
### Benzophenone (6d):



**6d**

According to **GP4** starting from **5d** (0.2 mmol), the product **6d** was isolated after flash chromatography (petroleum ether/ethyl acetate 30:1), white solid, 54% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 4H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 4H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 196.79, 137.64, 132.46, 130.10, 128.32. Data are consistent with those reported in the literature.[13]

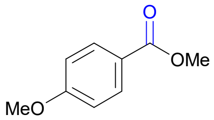
### Acetophenone (6e):



**6e**

According to **GP7** starting from **5e** (0.2 mmol), the product **6e** determined by $^{1}$H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, 28% yield; $^{1}$H NMR (500 MHz, DMSO) δ 7.95 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 2.51 (s, 3H).

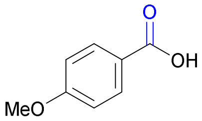
### Methyl 4-methoxybenzoate (8):



**8**

According to **GP1** starting from **7** (0.2 mmol), the product **8** was isolated after flash chromatography (petroleum ether/ethyl acetate 20:1), white solid, 68% yield; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.89, 163.36, 131.61, 122.66, 113.63, 55.43, 51.85. Data are consistent with those reported in the literature.[14]

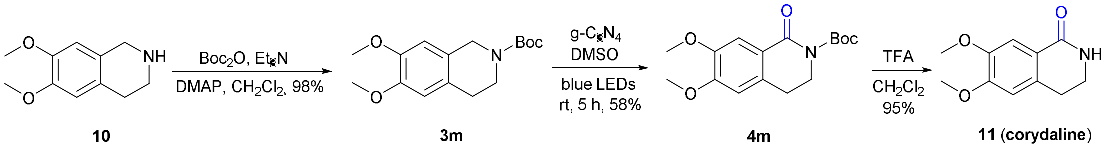
**4-Methoxybenzoic acid (9):**



**9**

According to **GP1** starting from **7** (0.2 mmol), the product **9** was isolated after flash chromatography (petroleum ether/ethyl acetate 1:1), yellow solid, 23% yield; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 170.29, 163.04, 131.34, 120.67, 112.75, 54.47. Data are consistent with those reported in the literature.[14]

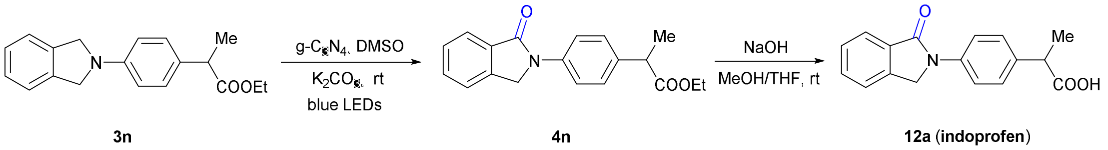
## 6. General procedure for the synthesis of corydaline 11.



**Tert-butyl 6,7-dimethoxy-1-oxo-3,4-dihydroisoquinoline-2(1H)-carboxylate (4m):** According to **GP5** starting from **3m** (0.2 mmol), the product **4m** was isolated after flash chromatography (dichloromethane/ethyl acetate 40:1), yellow solid, 58% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 1H), 6.64 (s, 1H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 2.94 (t, *J* = 5.8 Hz, 2H), 1.59 (s, 9H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 163.91, 153.50, 152.98, 148.24, 133.93, 121.73, 111.30, 109.14, 83.07, 56.12, 56.09, 44.71, 28.16, 28.06. Data are consistent with those reported in the literature.[16]

**6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2H)-one (11):** The **4m** (22.2 mg, 0.07 mmol) was dissolved in anhydrous $CH_2Cl_2$ (5 mL) in a 25-mL, round-bottomed flask. TFA (10.4 µL, 0.14 mmol, 2.0 equiv) was then added slowly and cautiously to the reaction solution at room temperature. After complete addition, the reaction was stirred at room temperature. After 1 h, the reaction mixture was diluted with $CH_2Cl_2$ (3 mL), transferred to a 60-mL separatory funnel, and washed with water (3 mL), 10% aq. $Na_2CO_3$ solution (3 mL), and brine (3 mL), then dried over anhydrous $Na_2SO_4$, decanted. After removal of solvents, the crude product was purified via silica gel flash column chromatography (ethyl acetate 100%), yellow solid, 95% yield; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 1H), 6.68 (s, 1H), 6.44 (s, 1H), 3.93 (s, 6H), 3.56 (s, 2H), 2.93 (t, *J* = 6.5 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 166.55, 152.22, 148.08, 132.67, 121.39, 110.20, 109.61, 56.14, 56.07, 40.50, 28.03. Data are consistent with those reported in the literature.

## 7. General procedure for the synthesis of Indoprofen 12a.



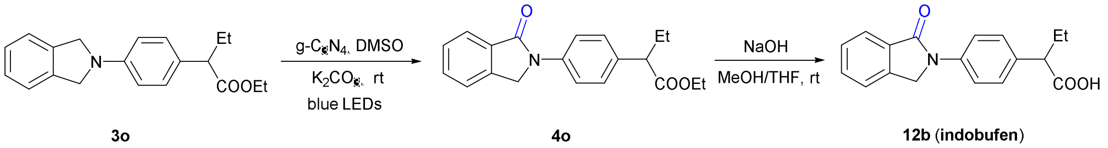
### Synthesis of ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate (4n):

According to **GP6** starting from **3n** (0.2 mmol), the product **4n** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 65% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 7.5 Hz, 1H), 7.82 (d, $J$ = 8.5 Hz, 2H), 7.60 (t, $J$ = 7.4 Hz, 1H), 7.51 (t, $J$ = 7.9 Hz, 2H), 7.37 (d, $J$ = 8.6 Hz, 2H), 4.85 (s, 2H), 4.21 – 4.06 (m, 2H), 3.72 (q, $J$ = 7.1 Hz, 1H), 1.51 (d, $J$ = 7.2 Hz, 4H), 1.22 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.53, 167.52, 140.13, 138.44, 136.82, 133.20, 132.12, 128.44, 128.27, 124.19, 122.66, 119.69, 60.84, 50.77, 45.04, 18.58, 14.17. Data are consistent with those reported in the literature.[17]

### Synthesis of 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoic acid (12a):

Ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate **4n** (10 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and 2 M NaOH(aq) (1 mL) was added. THF was added until reaction mixture was clear. Reaction mixture was stirred at room temperature and followed by TLC. After reaction was completed, the mixture was acidified using 3 M HCl. Product was extracted with ethyl acetate and the combined EtOAc fractions were washed with brine and dried over $MgSO_4$. Solvent was removed and 9.3 mg of yellow solid of indoprofen **12a** was obtained, 98% yield; $^1$H NMR (500 MHz, DMSO) δ 12.37 (s, 1H), 7.91 (d, $J$ = 8.4 Hz, 2H), 7.84 (d, $J$ = 7.5 Hz, 1H), 7.73 (d, $J$ = 5.7 Hz, 2H), 7.60 (t, $J$ = 6.7 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 2H), 5.07 (s, 2H), 3.74 (q, $J$ = 7.0 Hz, 1H), 1.43 (d, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (126 MHz, DMSO) δ 175.33, 166.52, 141.00, 138.12, 137.00, 132.41, 132.19, 128.16, 127.91, 123.31, 123.18, 119.44, 50.42, 44.08, 18.45. Data are consistent with those reported in the literature.[17]

## 8. General procedure for the synthesis of Indobufen 12b.



### Ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)butanoate (4o):

According to **GP6** starting from **3o** (0.2 mmol), the product **4o** was isolated after flash chromatography (petroleum ether/ethyl acetate 5:1), yellow solid, 63% yield; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 7.5 Hz, 0H), 7.82 (d, $J$ = 8.5 Hz, 1H), 7.60 (t, $J$ = 7.4 Hz, 0H), 7.51 (t, $J$ = 7.9 Hz, 1H), 7.38 (d, $J$ = 8.5 Hz, 1H), 4.85 (s, 2H), 4.19 – 4.07 (m, 2H), 3.45 (t, $J$ = 7.7 Hz, 1H), 2.10 (td, $J$ = 14.7, 7.5 Hz, 1H), 1.86 – 1.75 (m, 1H), 1.23 (t, $J$ = 7.1 Hz, 2H), 0.91 (t, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.06, 167.51, 140.12, 138.50, 135.37, 133.22, 132.11, 128.74, 128.43, 124.19, 122.65, 119.59, 60.72, 53.00, 50.76, 26.78, 14.21, 12.18. Data are consistent with those reported in the literature.[17]

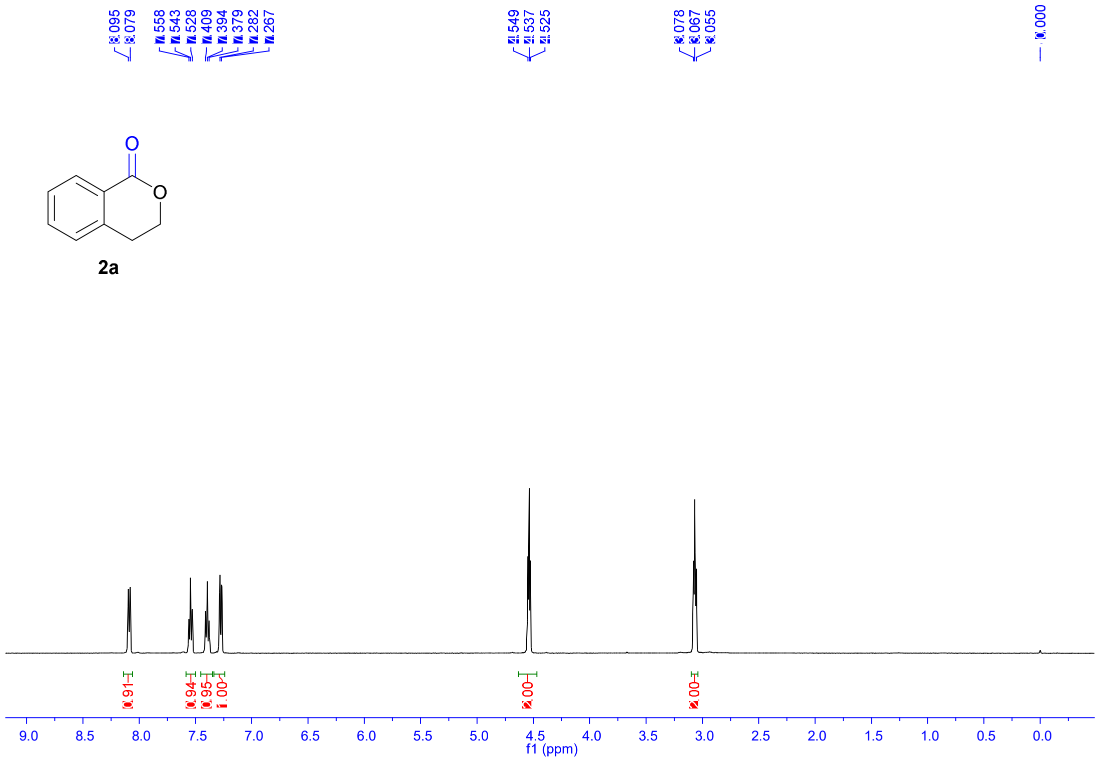
**2-(4-(1-Oxoisoindolin-2-yl)phenyl)butanoic acid (12b):**

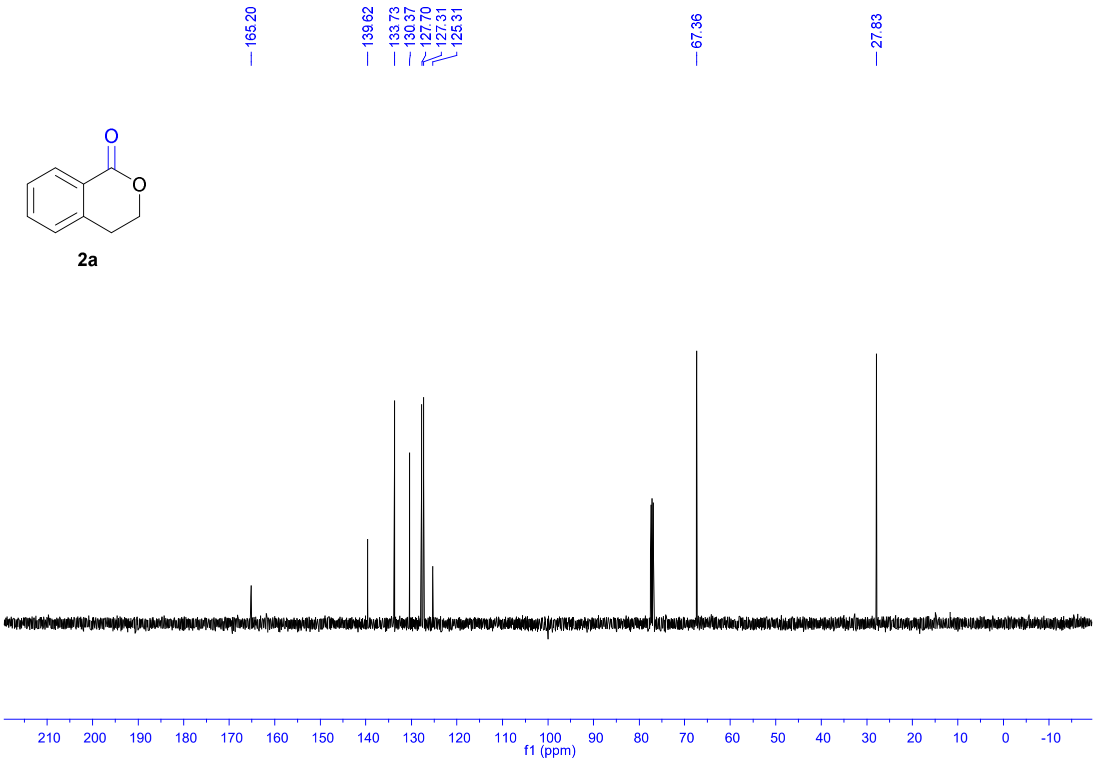
Ethyl 2-(4-(1-oxoisoindolin-2-yl)phenyl)propanoate **4o** (12 mg, 0.03 mmol) was dissolved in MeOH (1 mL) and 2 M NaOH(aq) (1 mL) was added. THF was added until reaction mixture was clear. Reaction mixture was stirred at RT and followed by TLC. After reaction was completed, the mixture was acidified using 3 M HCl. Product was extracted with ethyl acetate and the combined EtOAc fractions were washed with brine and dried over $MgSO_4$. Solvent was removed and 11.2 mg of yellow solid of **12b** was obtained, 98% yield; $^1$H NMR (500 MHz, DMSO) δ 12.30 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.60 (t, *J* = 5.8 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 5.07 (s, 2H), 3.48 (t, *J* = 7.6 Hz, 1H), 2.04 (dd, *J* = 13.6, 7.2 Hz, 1H), 1.78 – 1.69 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); $^{13}$C NMR (126 MHz, DMSO) δ 174.79, 166.54, 141.00, 138.23, 135.40, 132.41, 132.19, 128.30, 128.16, 123.31, 123.19, 119.36, 52.00, 50.40, 26.08, 12.01. Data are consistent with those reported in the literature.[17]

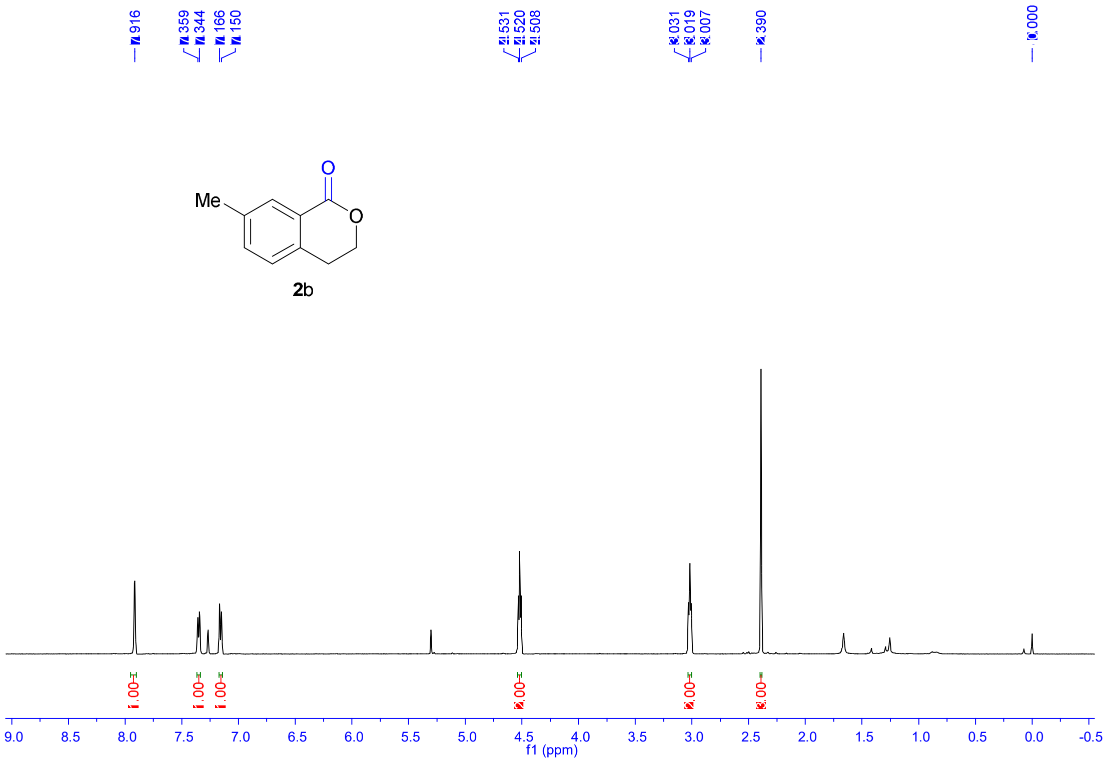
## 9. References

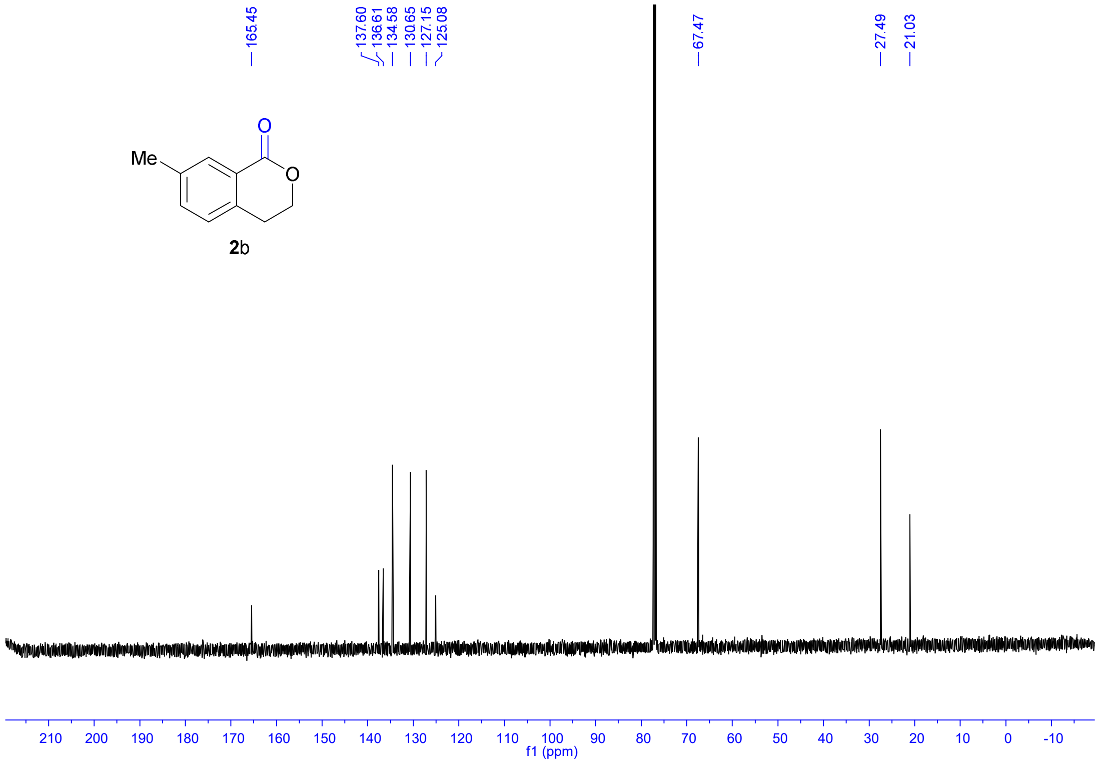
1. S. C. Yan, Z. S. Li and Z. G. Zou, *Langmuir,* 2009, **25**, 10397–10401.
2. X. Wang, K. Maeda, X. Chen, K. Takanabe, K. Domen, Y. Hou, X. Fu and M. Antonietti, *J. Am. Chem. Soc.*, 2009, **131**, 1680–1681.
3. A. Gonzalez-de-Castro, C. M. Robertson and J. Xiao, *J. Am. Chem. Soc.*, 2014, **136**, 8350–8360.
4. Z. Zhang, Y. Gao, Y. Liu, J. Li, H. Xie, H. Li and W. Wang, *Org. Lett.*, 2015, **17**, 5492–5495.
5. A.-R. Song, J. Yu and C. Zhang, *Synthesis*, 2012, **44**, 2903–2909.
6. H. Yanai and T. Taguchi, *Chem. Commun.*, 2012, **48**, 8967–8969.
7. A. Rioz‐Martínez, G. de Gonzalo, D. E. T. Pazmiño, M. W. Fraaije, and V. Gotor, *Eur. J. Org. Chem.*, 2009, **15**, 2526–2532.
8. R. Audebert, J. Neel. Bulletin de la Societe Chimique de France[M]. 1985.
9. T. Fukuyama, T. Bando and I. Ryu, *Synthesis*, 2018, **50**, 3015–3021.
10. C. Soucy, D. Favreau and M. Kayser, *J. Org. Chem.*, 1987, **52**, 129–134.
11. D. Riemer, B. Mandaviya, W. Schilling, A. C. Götz, T. Kühl, M. Finger and S. Das, *ACS Catal.*, 2018, **8**, 3030−3034.
12. X. Tian, F. Ren, B. Zhao, Y.-L. Ren, S. Zhao and J. Wang, *Catal. Commun.*, 2018, **106**, 44–49.
13. C, Liu, G. Li, S. Shi, G. Meng, R. Lalancette, R. Szostak and M. Szostak, *ACS Catal.*, 2018, **8**, 9131–9139.
14. L. C. Finney, L. J. Mitchell and C. J. Moody, *Green Chem.*, 2018, **20**, 2242–2249.
15. K. C. C. Aganda, B. Hong and A. Lee, Adv. *Synth. Catal.*, 2018, **361**, 1124–1129.
16. J. W. Park and Y. K. Chung, *ACS Catal.*, 2015, **5**, 4846–4850.
17. T. Thatikonda, S. K. Deepake and U. Das, *Org. Lett.*, 2019, **21**, 2532–2535.

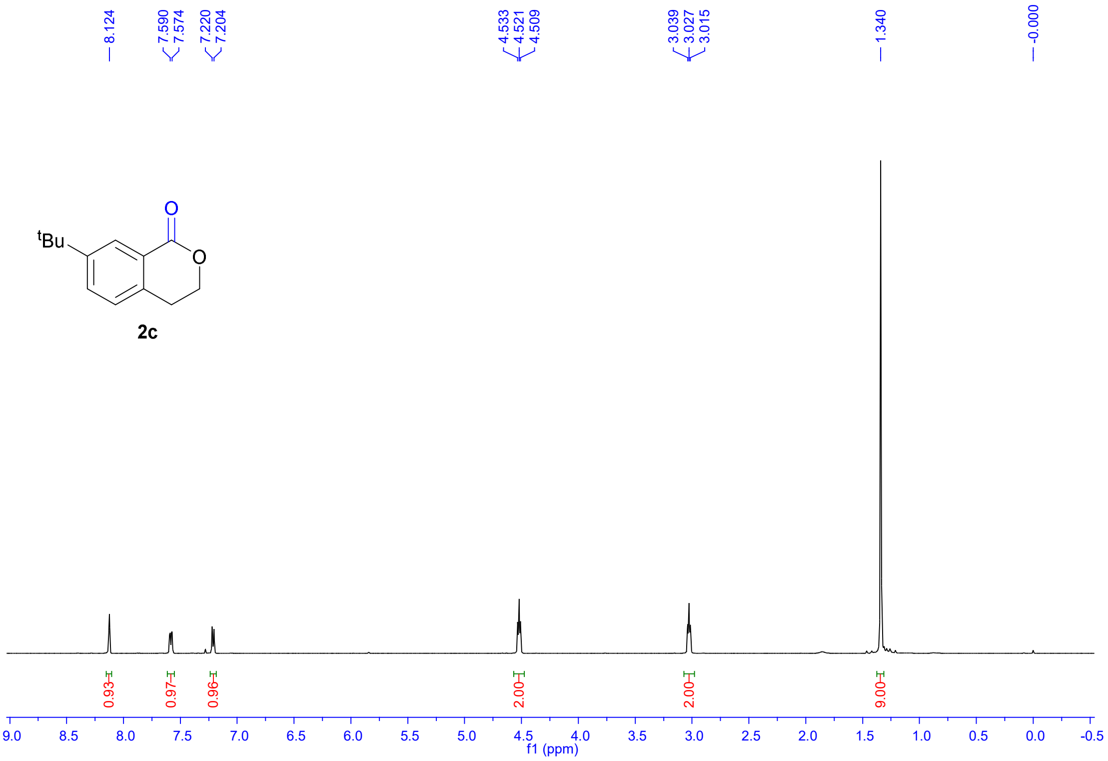
## 10. $^{1}$H NMR and $^{13}$C NMR spectra of products

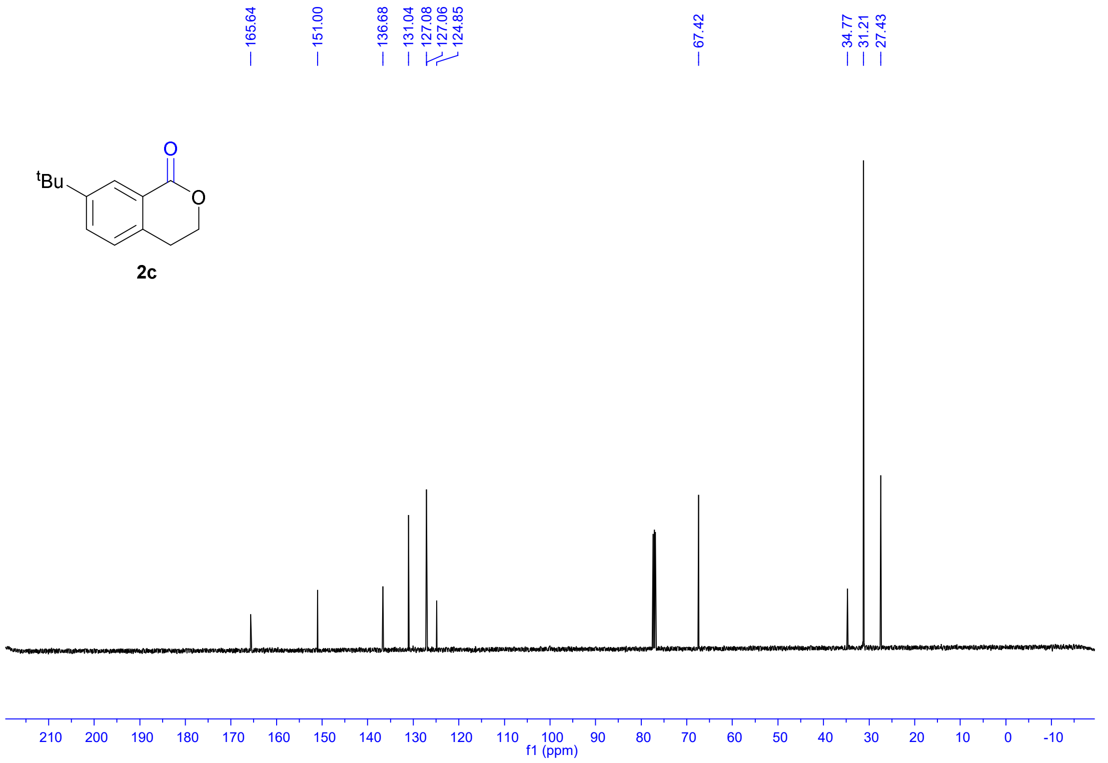




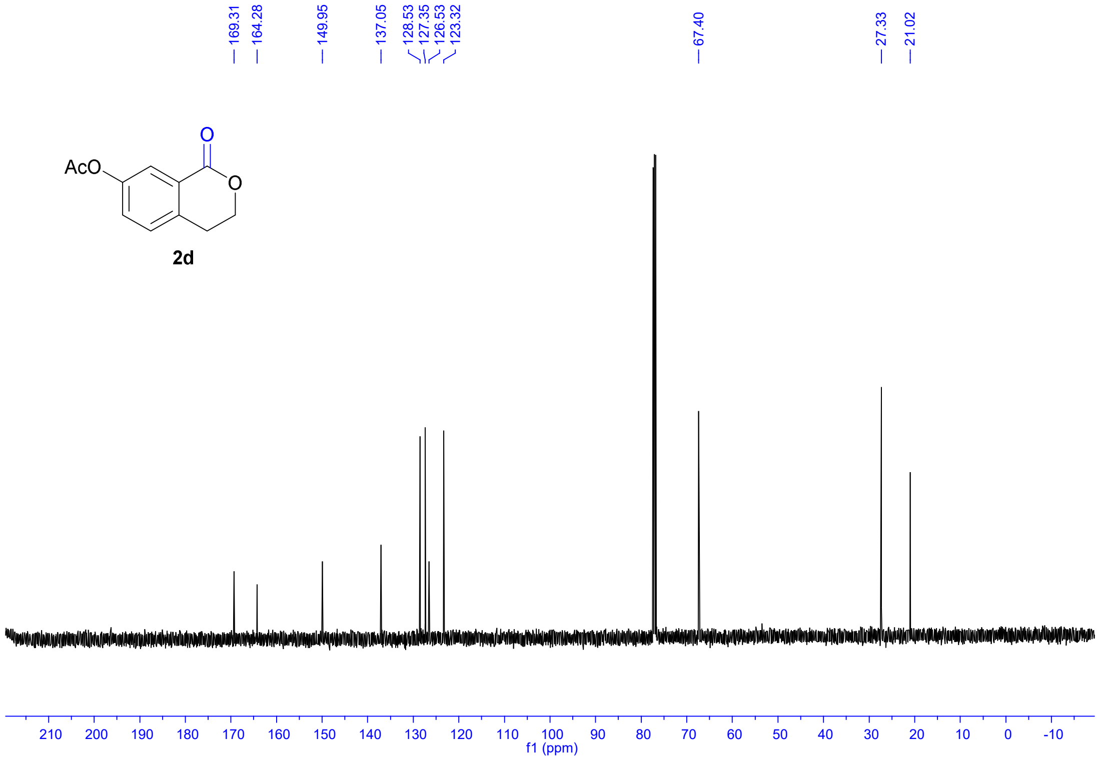

7.916
7.359
7.344
7.166
7.150
4.531
4.520
4.508
3.031
3.019
3.007
2.390
0.000
Me
O
O
2b
1.00
1.00
1.00
2.00
2.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

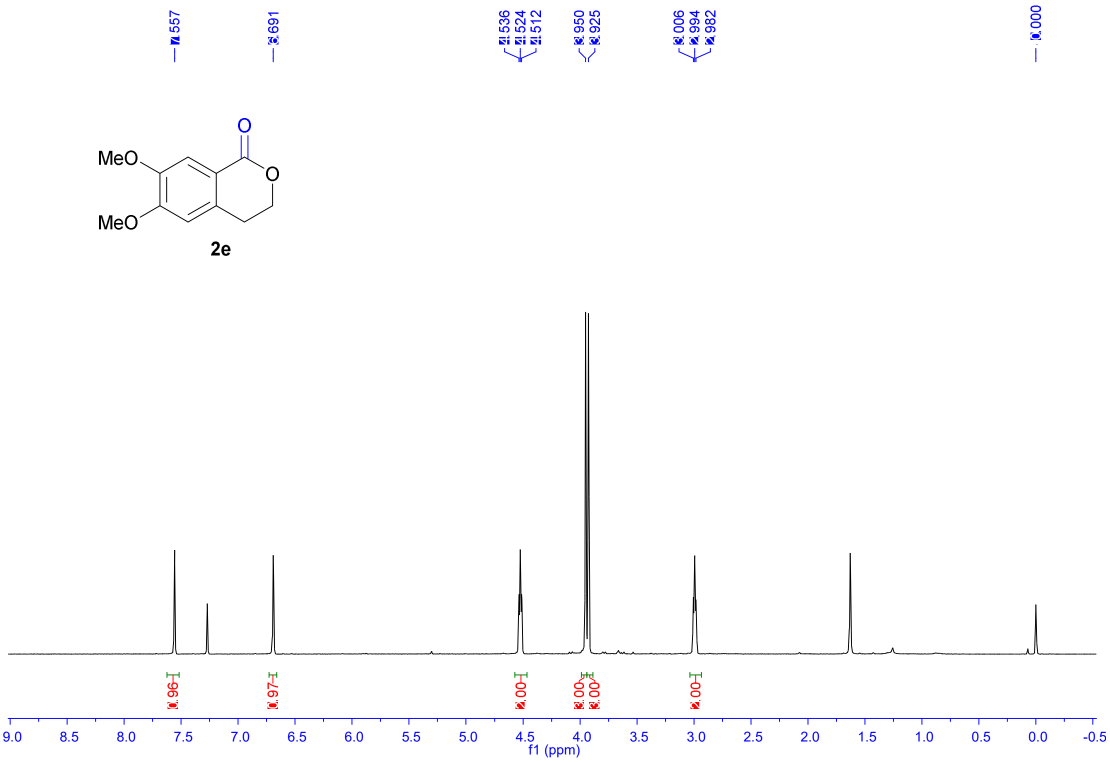

165.45
137.60
136.61
134.58
130.65
127.15
125.08
67.47
27.49
21.03
Me
O
O
2b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

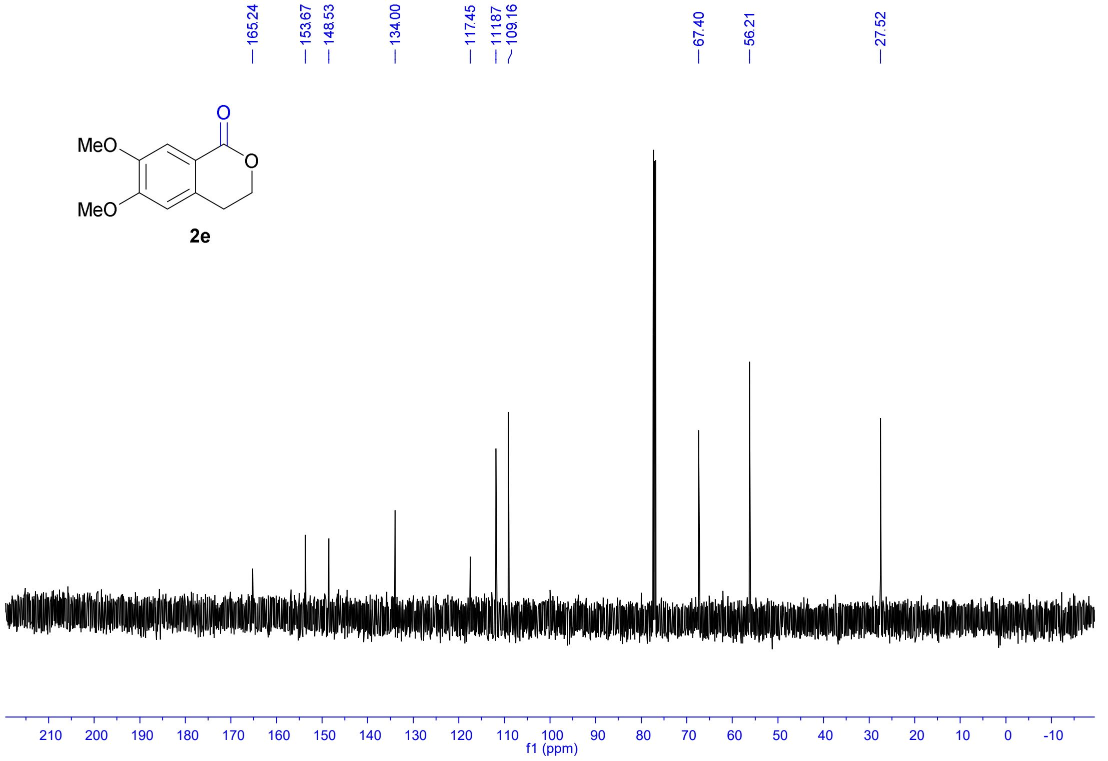

8.124
7.590
7.574
7.220
7.204
4.533
4.521
4.509
3.039
3.027
3.015
1.340
-0.000
tBu
O
O
2c
0.93
0.97
0.96
2.00
2.00
9.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

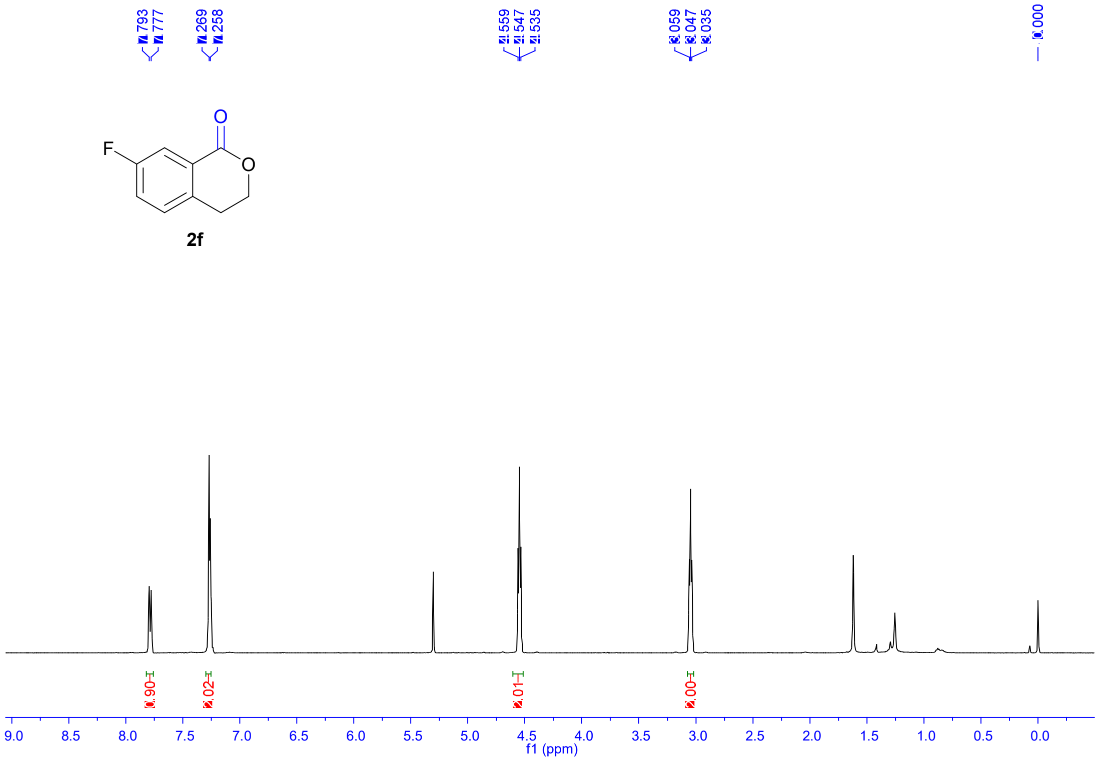

165.64
151.00
136.68
131.04
127.08
127.06
124.85
67.42
34.77
31.21
27.43
tBu
O
O
2c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

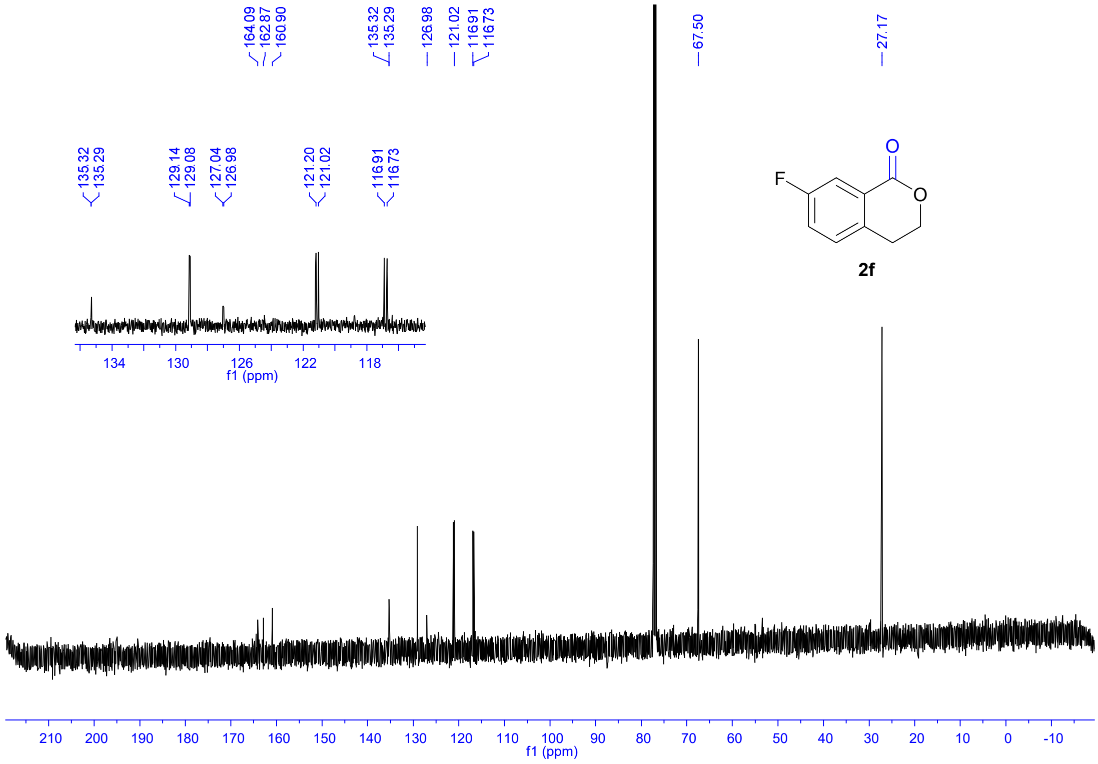

7.810
7.808
7.310
7.293
7.289
7.285
7.273
4.558
4.546
4.534
3.071
3.059
3.047
2.322
0.000
AcO
O
O
2d
0.90
2.00
2.00
2.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

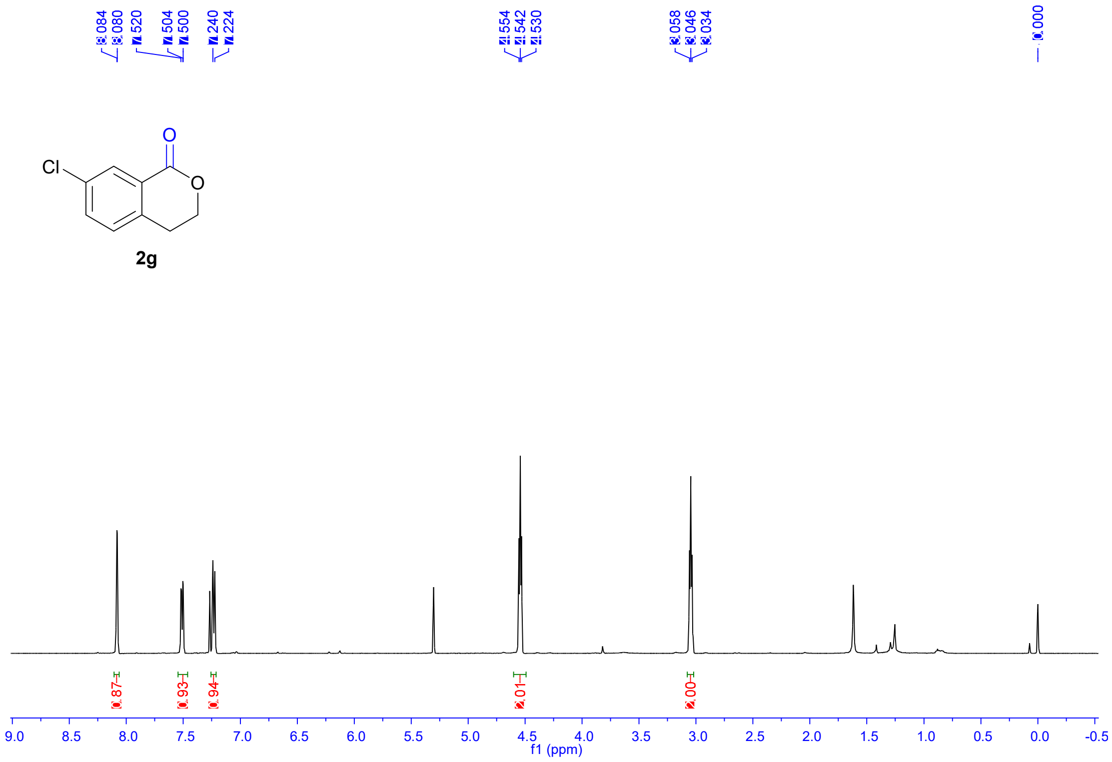

169.31
164.28
149.95
137.05
128.53
127.35
126.53
123.32
67.40
27.33
21.02
AcO
O
O
2d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

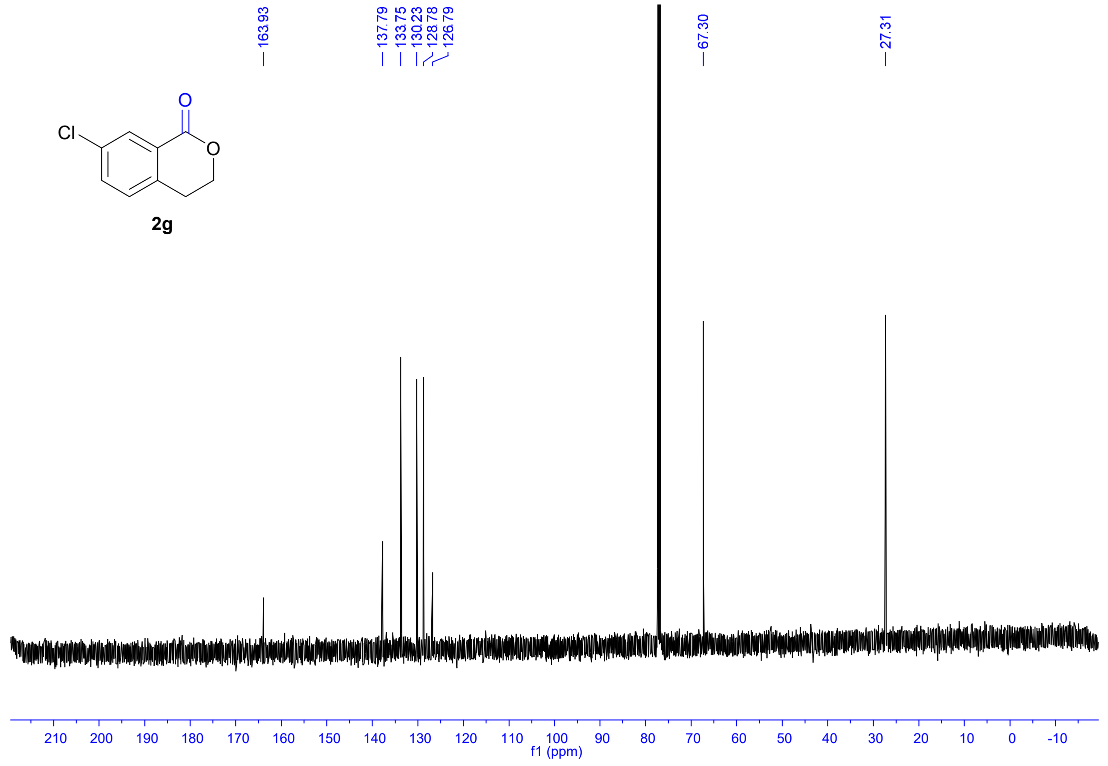

7.557
6.691
4.536
4.524
4.512
3.950
3.925
3.006
2.994
2.982
0.000
MeO
MeO
O
O
2e
0.96
0.97
2.00
3.00
3.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

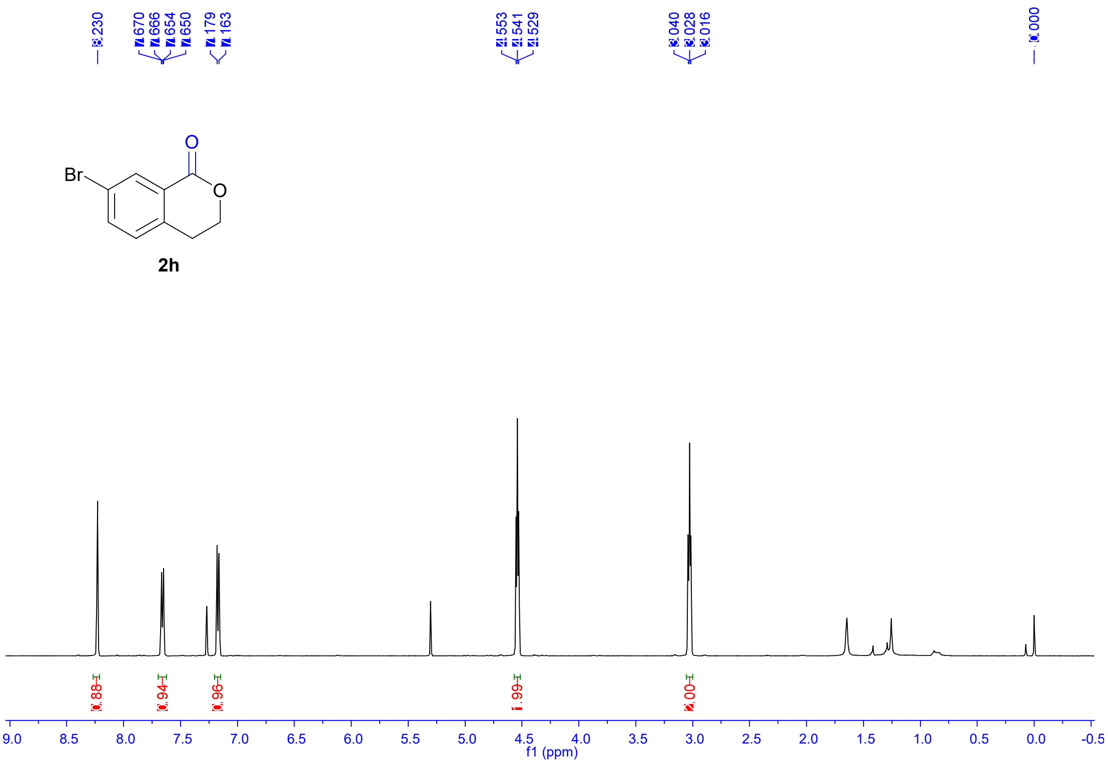

165.24
153.67
148.53
134.00
117.45
111.87
109.16
67.40
56.21
27.52
MeO
MeO
O
O
2e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

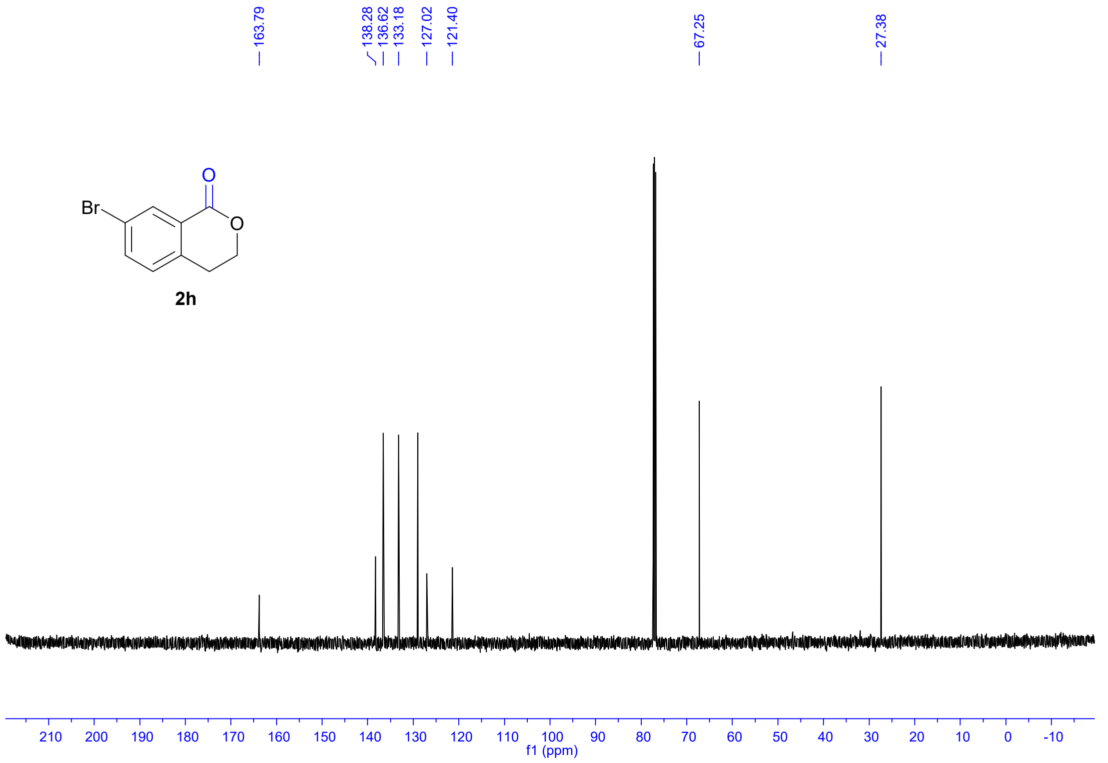

7.793
7.777
7.269
7.258
4.559
4.547
4.535
3.059
3.047
3.035
0.000
F
O
O
2f
0.90
2.02
2.01
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

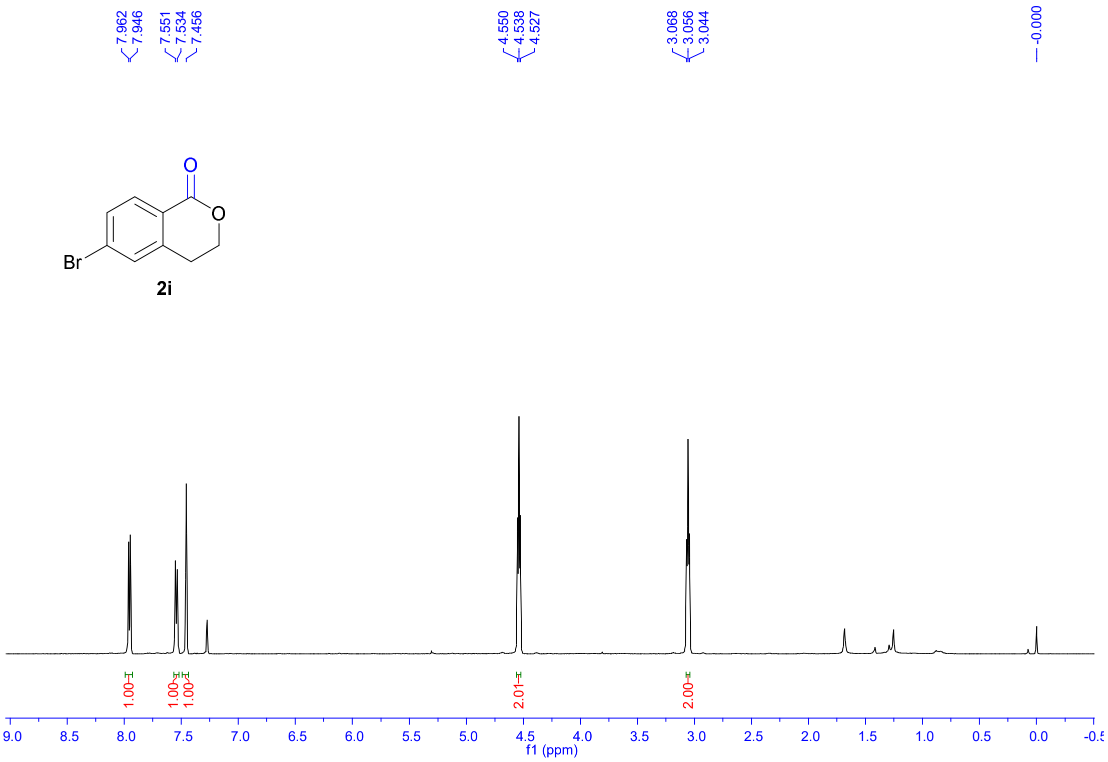

164.09
162.87
160.90
135.32
135.29
126.98
121.02
116.91
116.73
67.50
27.17
135.32
135.29
129.14
129.08
127.04
126.98
121.20
121.02
116.91
116.73
134 130 126 122 118
f1 (ppm)
F
O
O
2f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

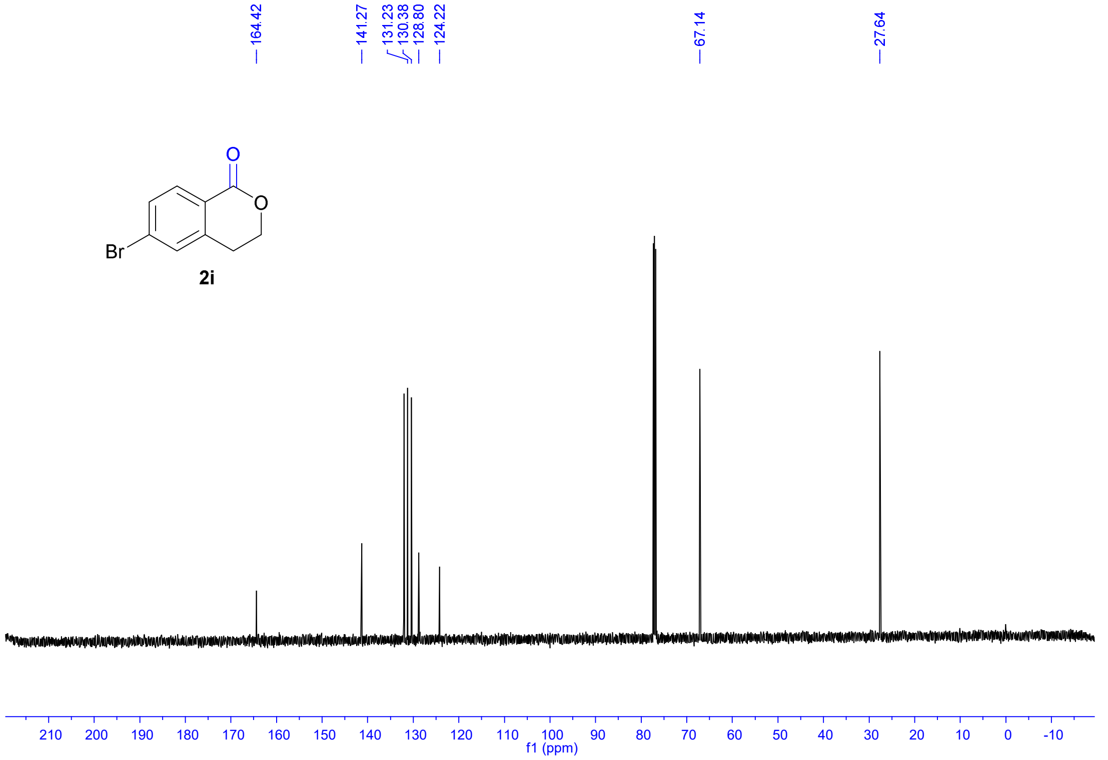

8.084
8.080
7.520
7.504
7.500
7.240
7.224
4.554
4.542
4.530
3.058
3.046
3.034
0.000
Cl
O
O
2g
0.87
0.93
0.94
2.01
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

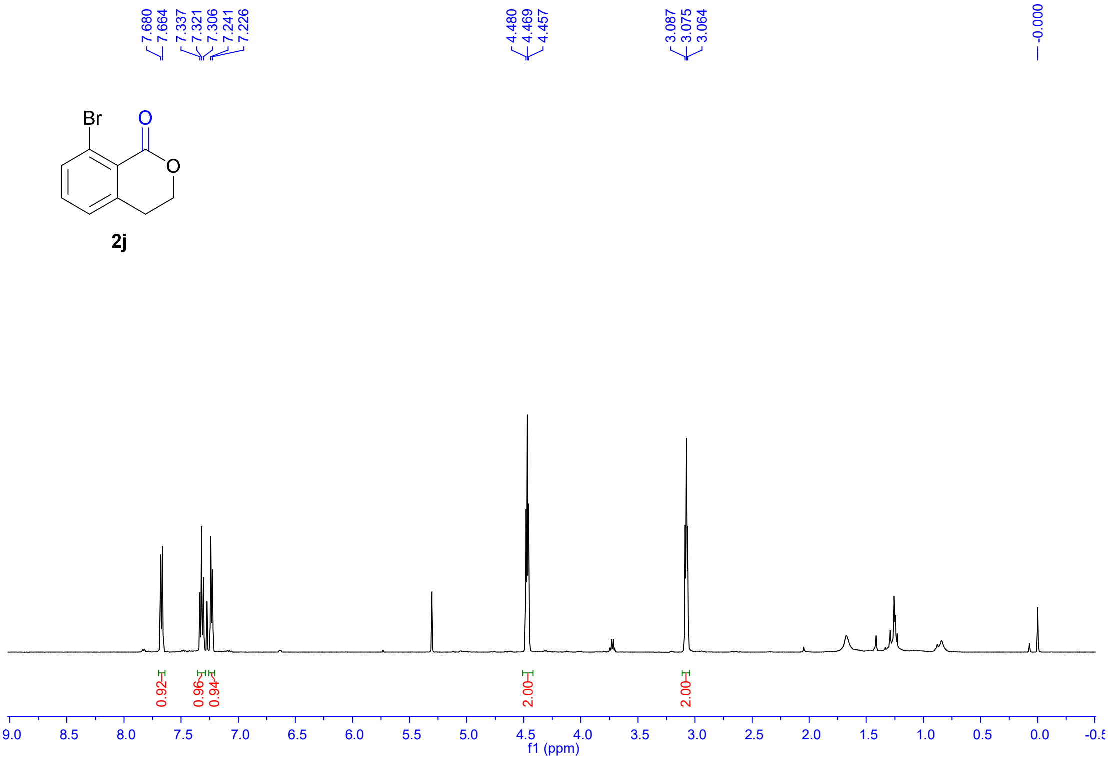

163.93
137.79
133.75
130.23
128.78
126.79
67.30
27.31
Cl
O
O
2g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

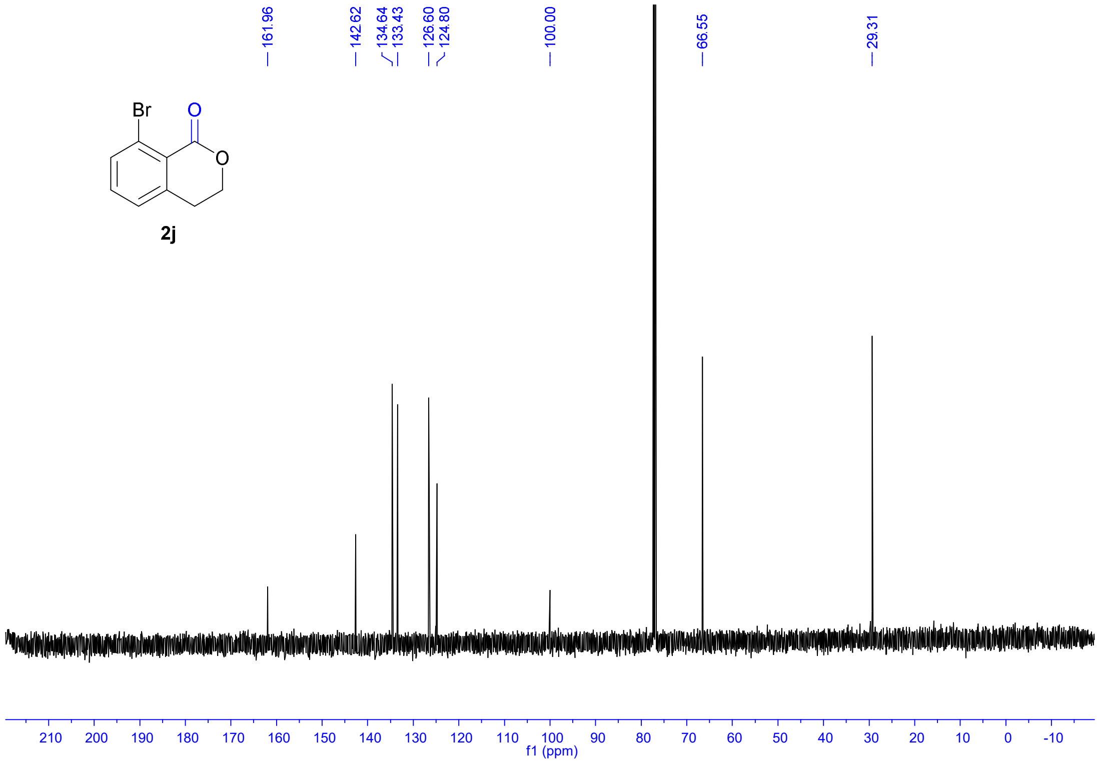

8.230
7.670
7.666
7.654
7.650
7.179
7.163
4.553
4.541
4.529
3.040
3.028
3.016
0.000
Br
O
O
2h
0.88
0.94
0.96
1.99
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

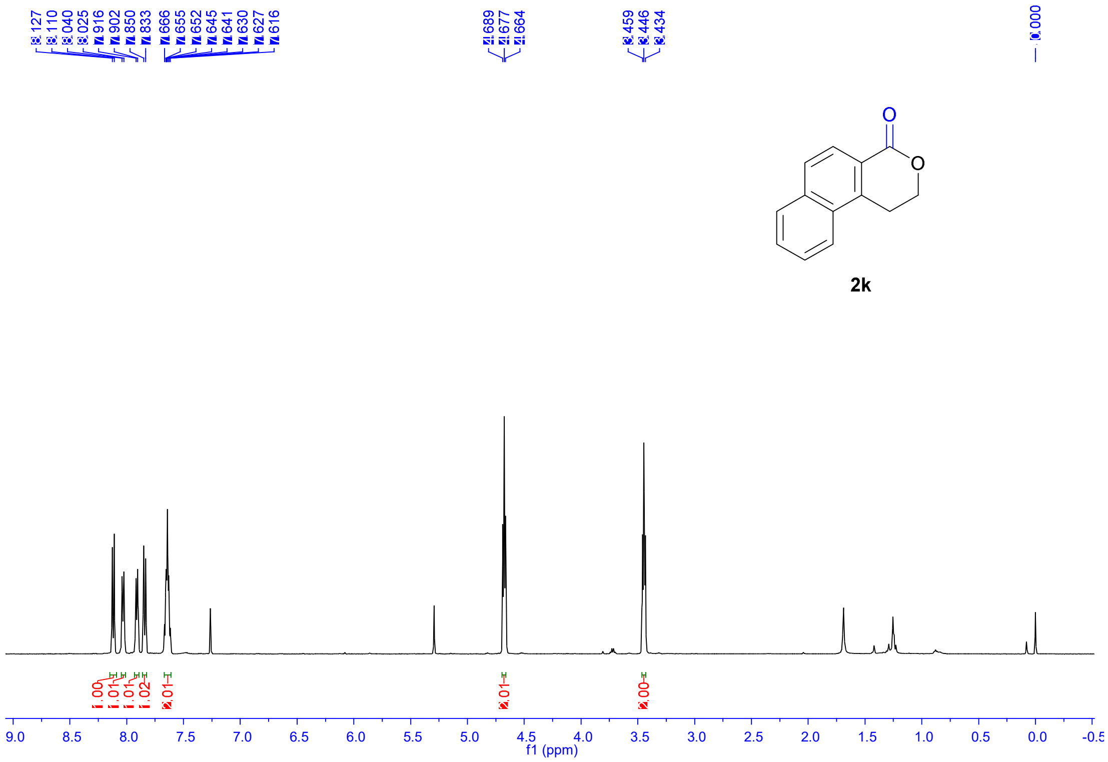

163.79
138.28
136.62
133.18
127.02
121.40
67.25
27.38
Br
O
O
2h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

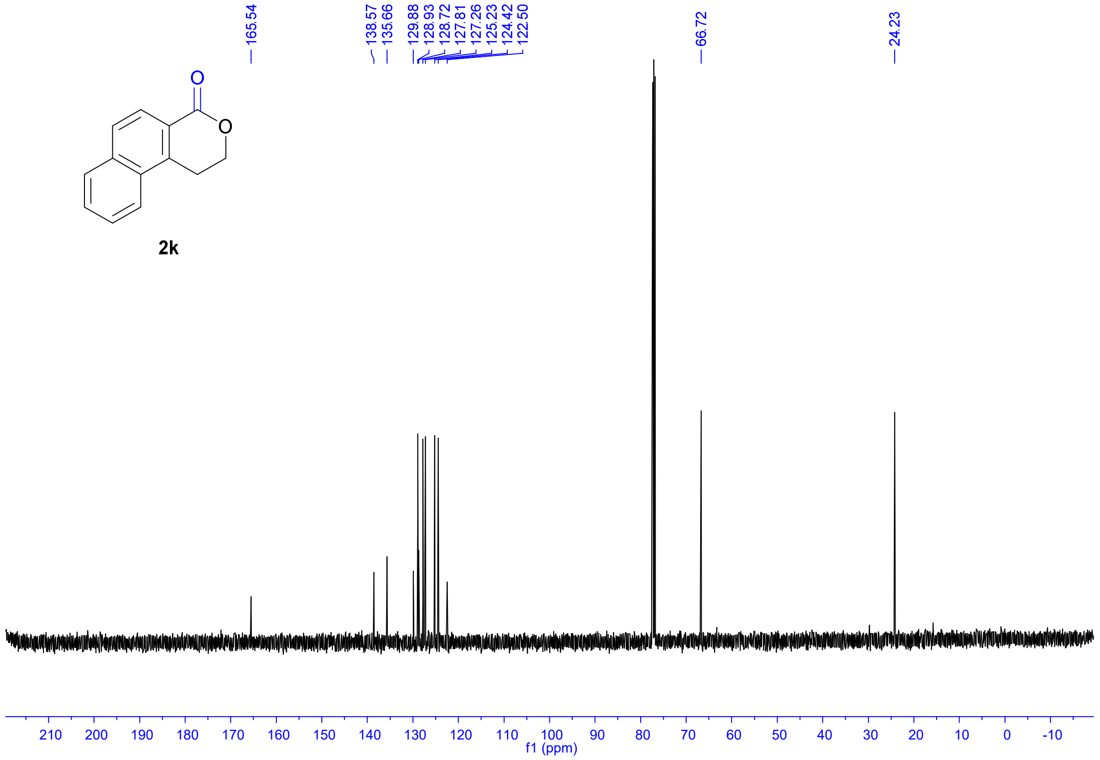

7.962
7.946
7.551
7.534
7.456
4.550
4.538
4.527
3.068
3.056
3.044
-0.000
O
O
Br
2i
1.00
1.00
1.00
2.01
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

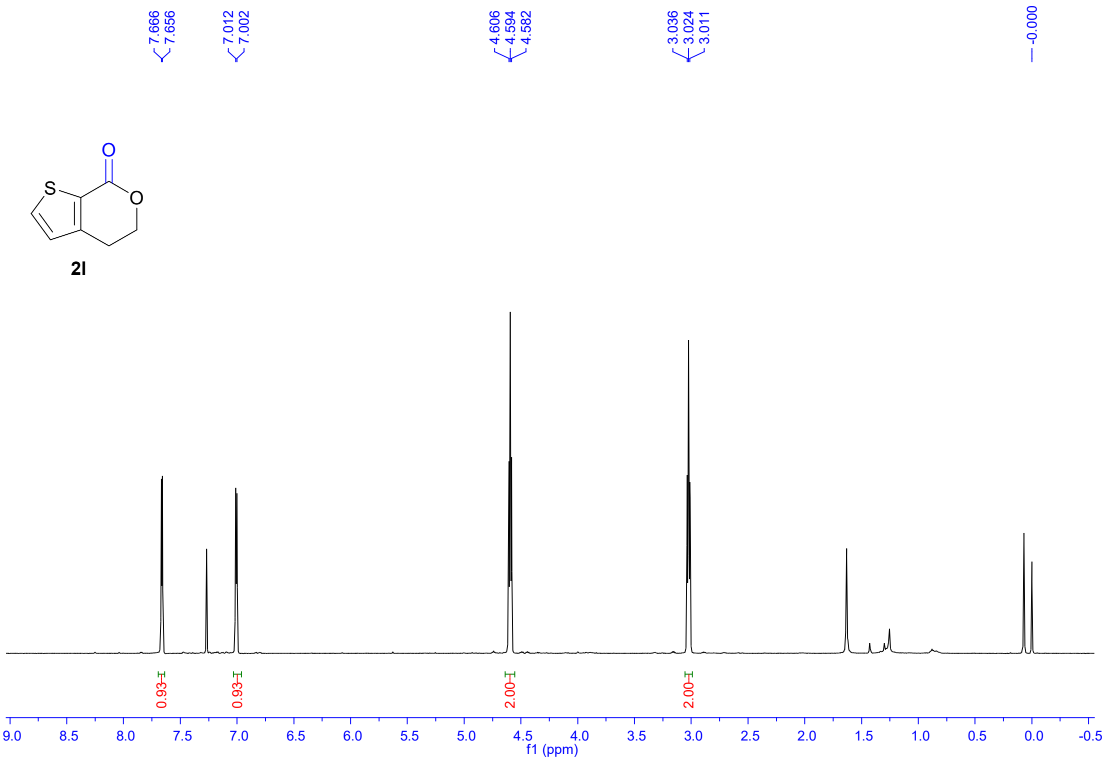

164.42
141.27
131.23
130.38
128.80
124.22
67.14
27.64
O
O
Br
2i
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.680
7.664
7.337
7.321
7.306
7.241
7.226
4.480
4.469
4.457
3.087
3.075
3.064
-0.000
Br
O
O
2j
0.92
0.96
0.94
2.00
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

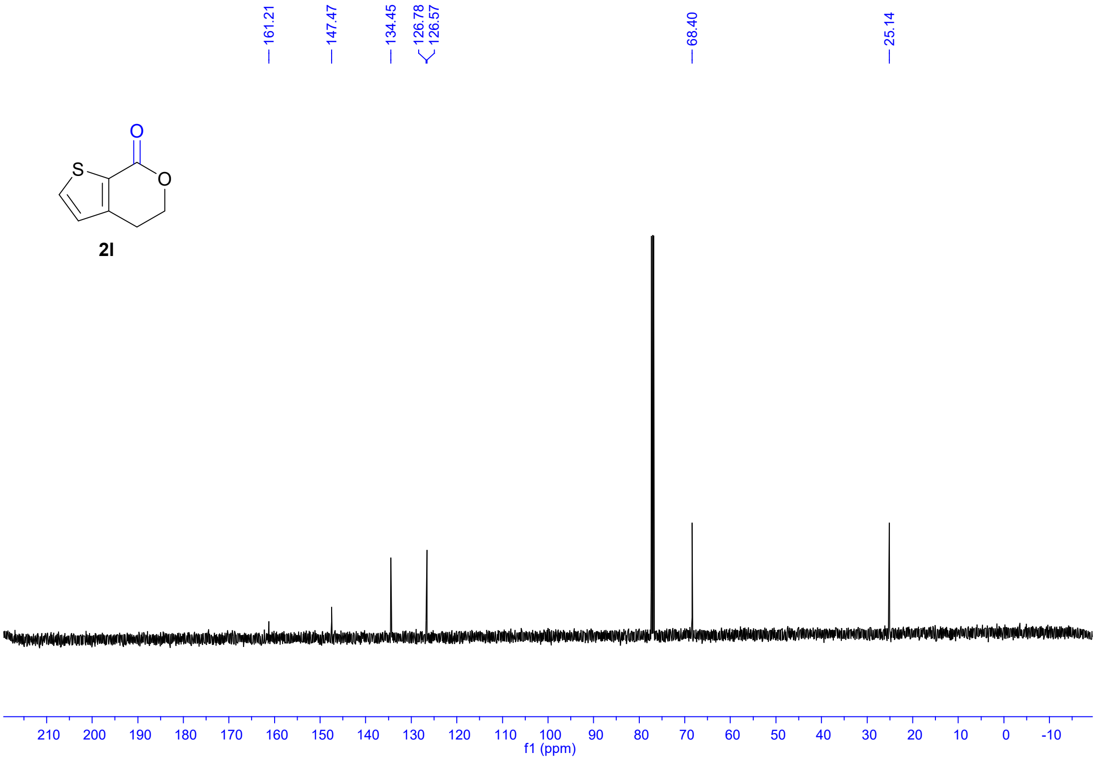

161.96
142.62
134.64
133.43
126.60
124.80
100.00
66.55
29.31
Br
O
O
2j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.127
8.110
8.040
8.025
7.916
7.902
7.850
7.833
7.666
7.655
7.652
7.645
7.641
7.630
7.627
7.616
4.689
4.677
4.664
3.459
3.446
3.434
0.000
O
O
2k
1.00
1.01
1.01
1.02
2.01
2.01
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

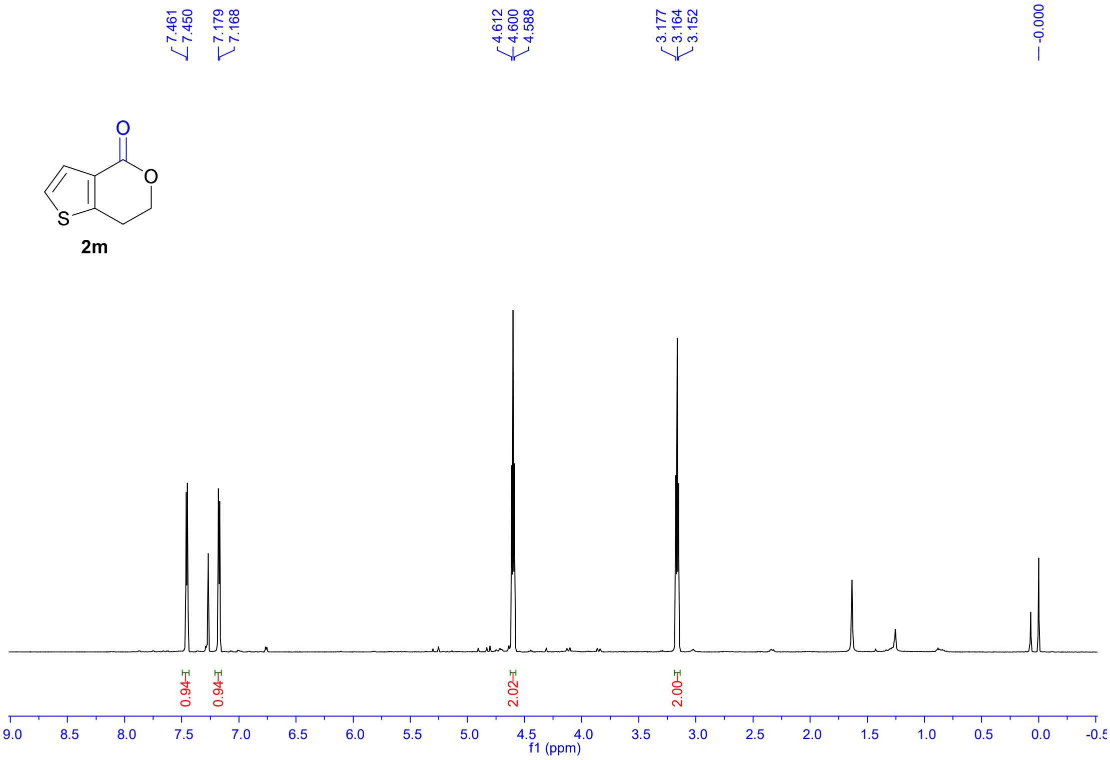

165.54
138.57
135.66
129.88
128.93
128.72
127.81
127.26
125.23
124.42
122.50
66.72
24.23
O
O
2k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

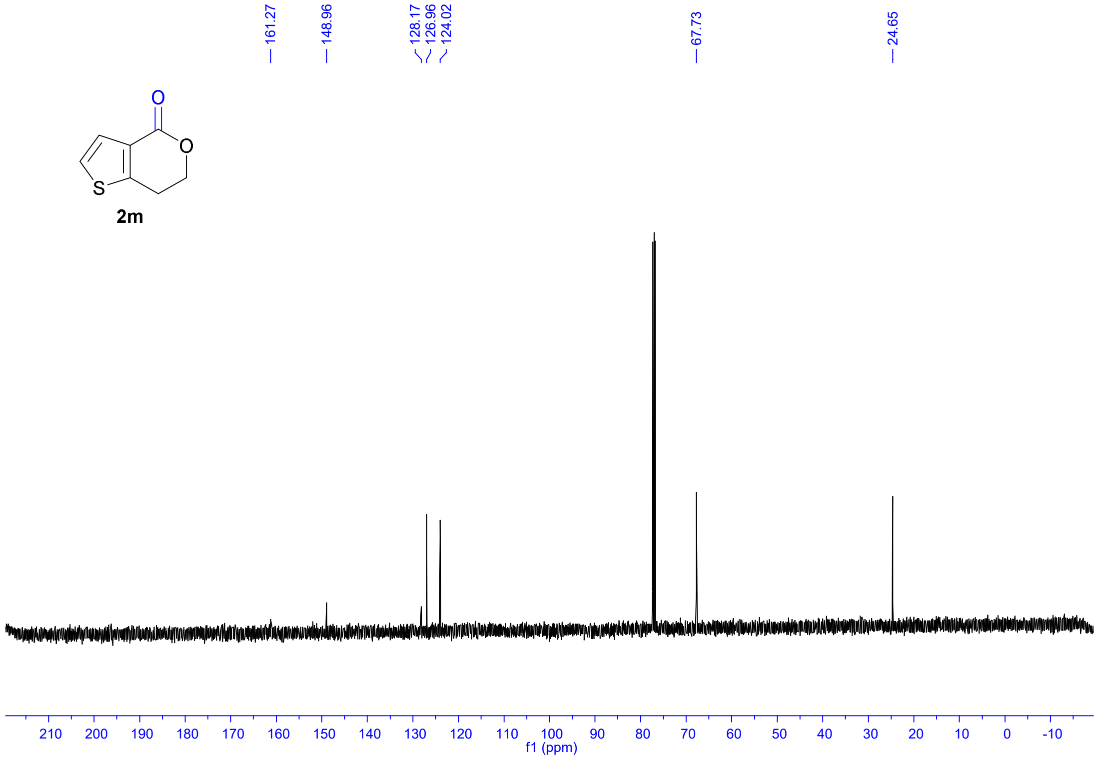

7.666
7.656
7.012
7.002
4.606
4.594
4.582
3.036
3.024
3.011
-0.000
S
O
O
0.93
0.93
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

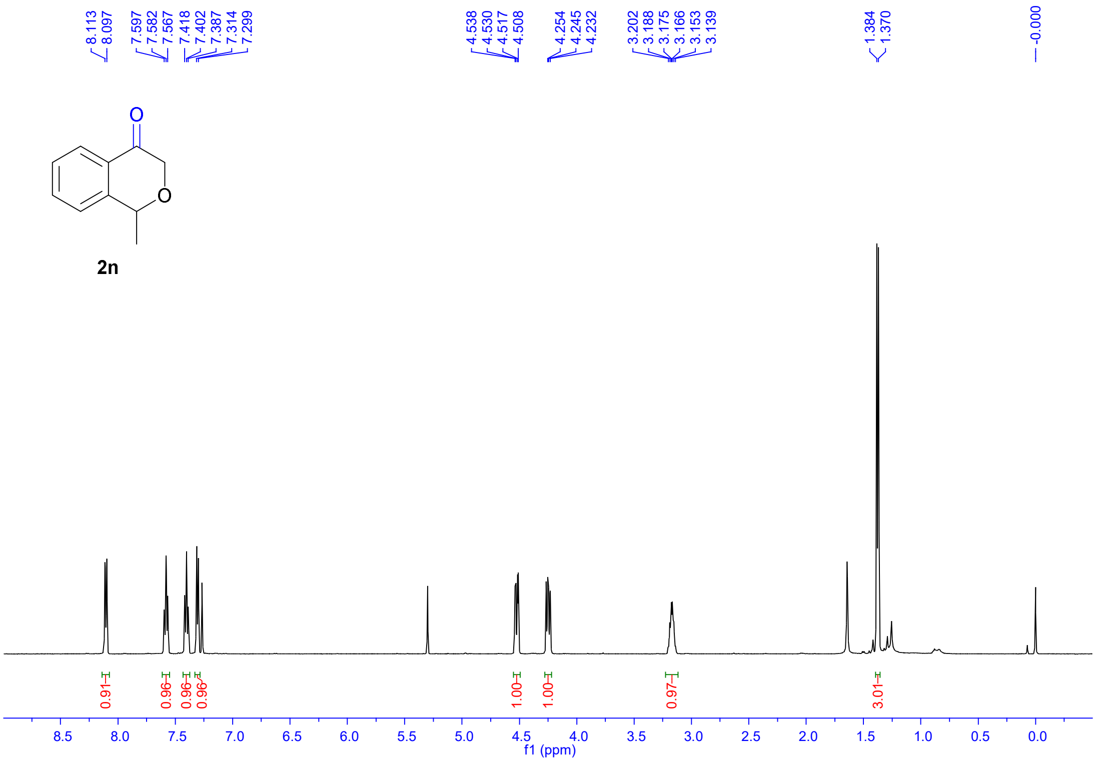
**2l**

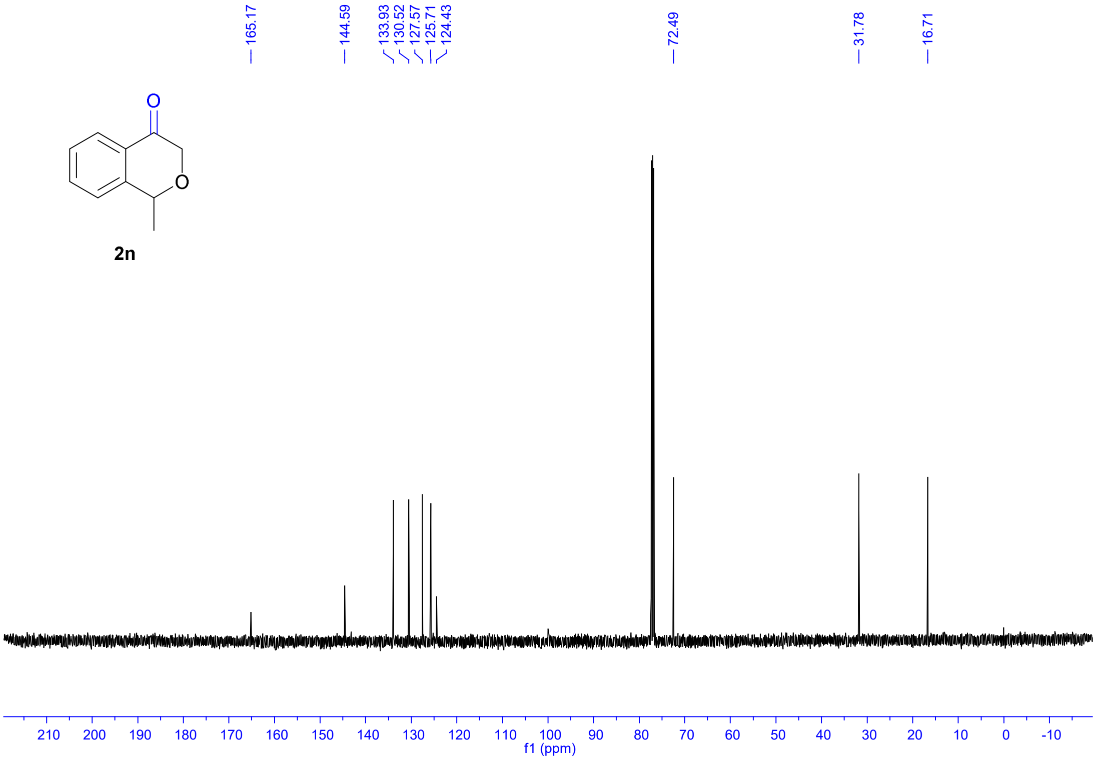

161.21
147.47
134.45
126.78
126.57
68.40
25.14
S
O
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

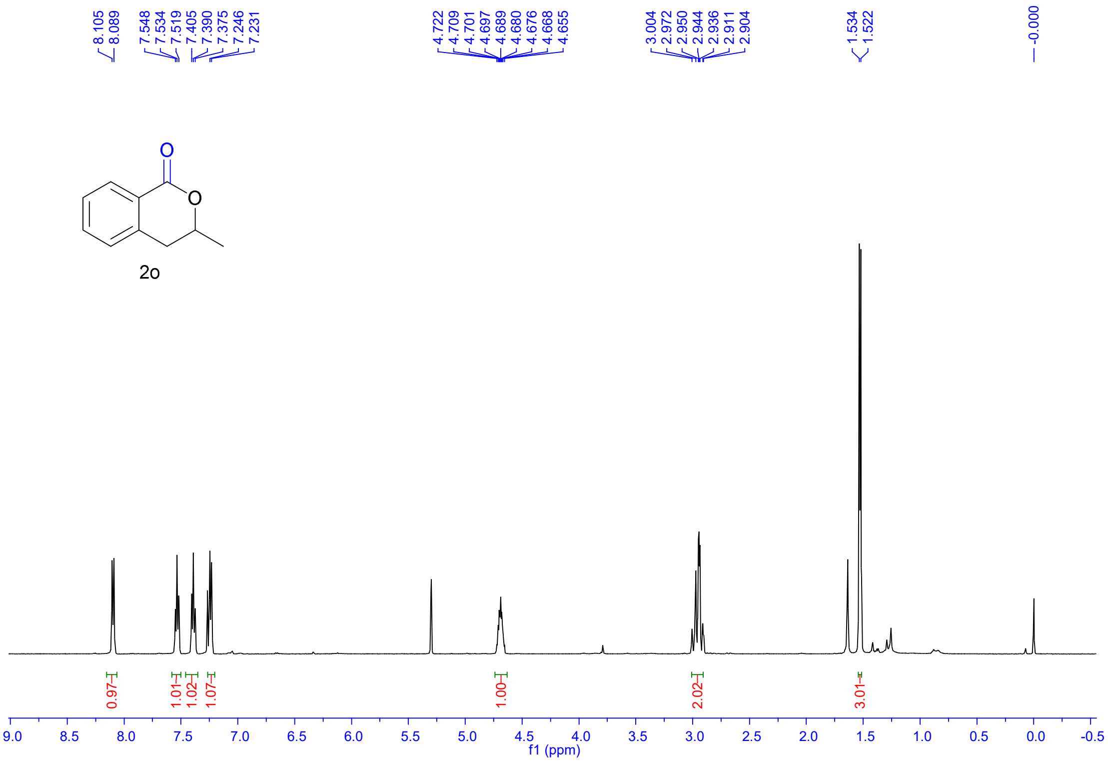
**2l**

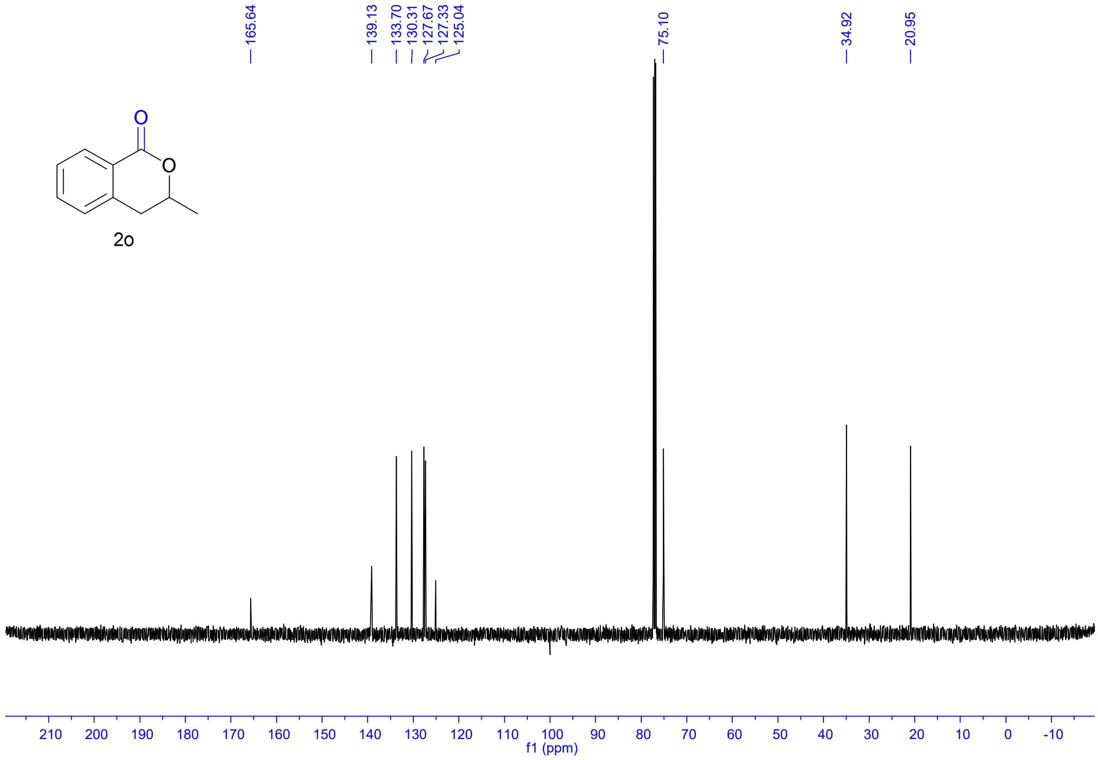

7.461
7.450
7.179
7.168
4.612
4.600
4.588
3.177
3.164
3.152
-0.000
O
O
S
2m
0.94
0.94
2.02
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

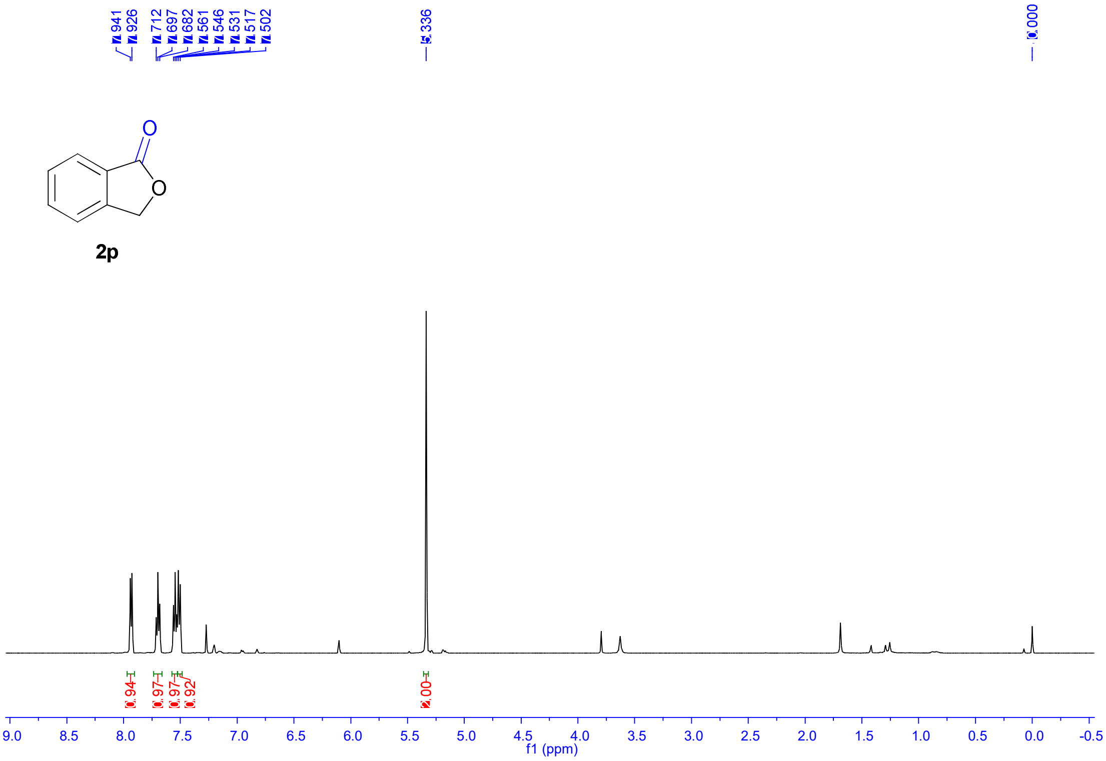

161.27
148.96
128.17
126.96
124.02
67.73
24.65
O
O
S
2m
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

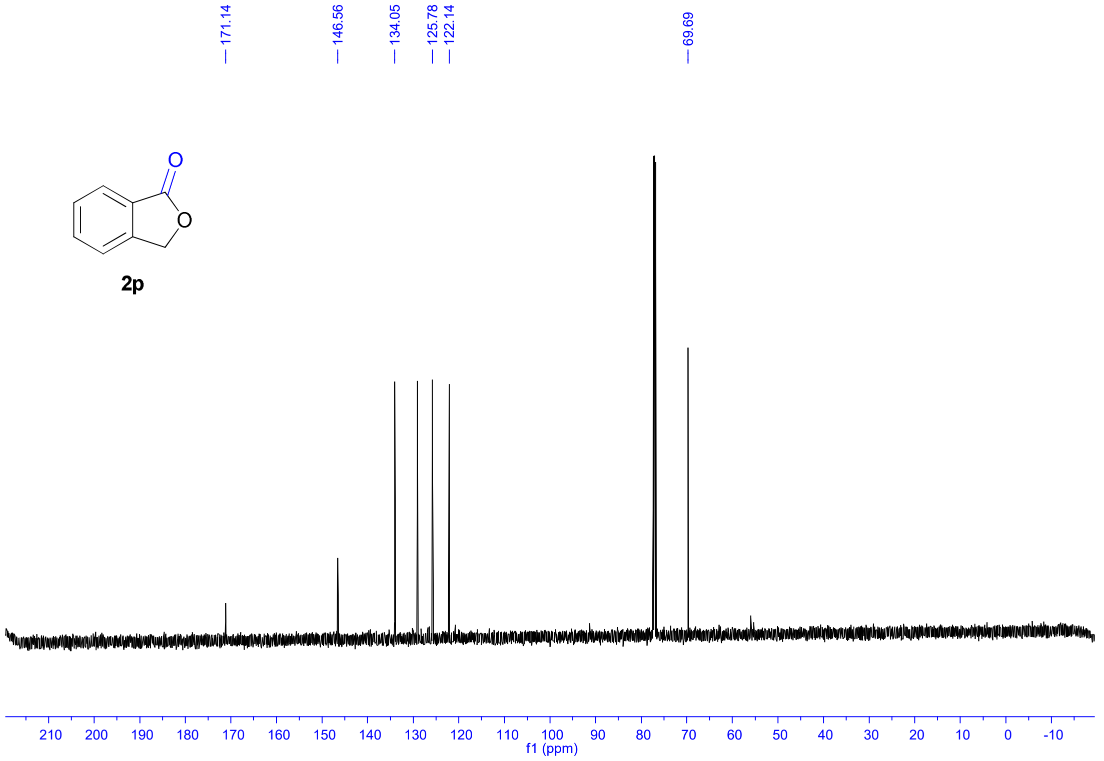

8.113
8.097
7.597
7.582
7.567
7.418
7.402
7.387
7.314
7.299
4.538
4.530
4.517
4.508
4.254
4.245
4.232
3.202
3.188
3.175
3.166
3.153
3.139
1.384
1.370
-0.000
O
O
2n
0.91
0.96
0.96
0.96
1.00
1.00
0.97
3.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

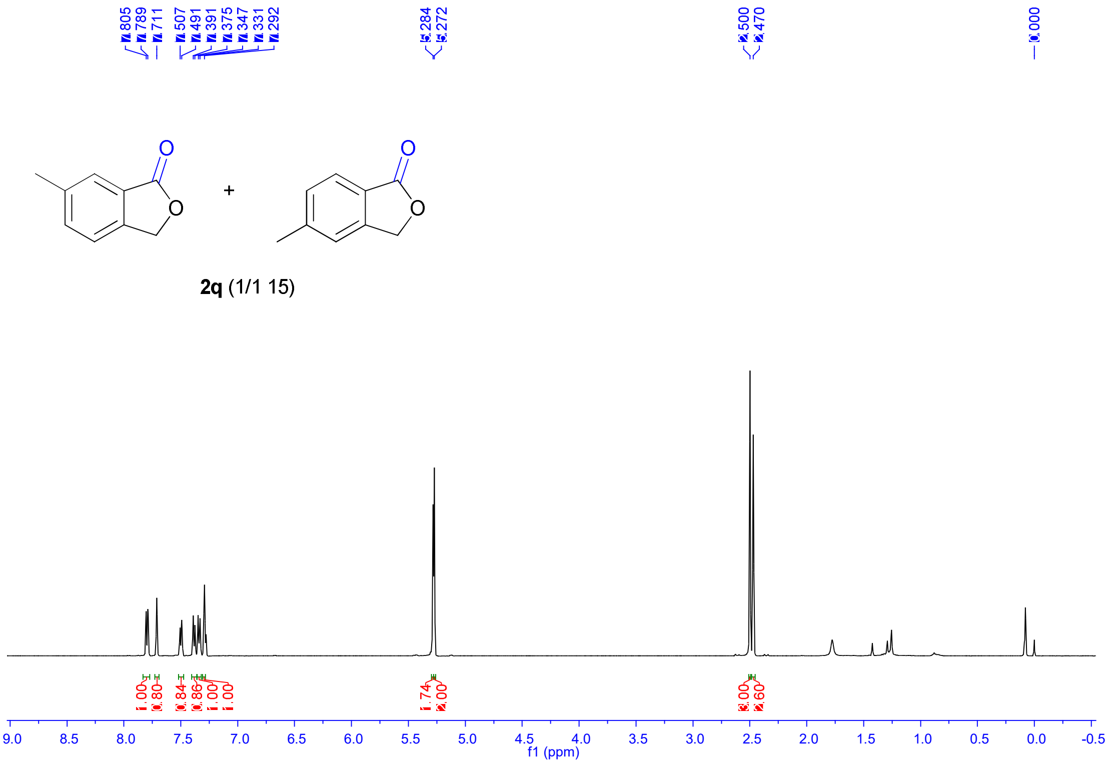

165.17
144.59
133.93
130.52
127.57
125.71
124.43
72.49
31.78
16.71
O
O
2n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

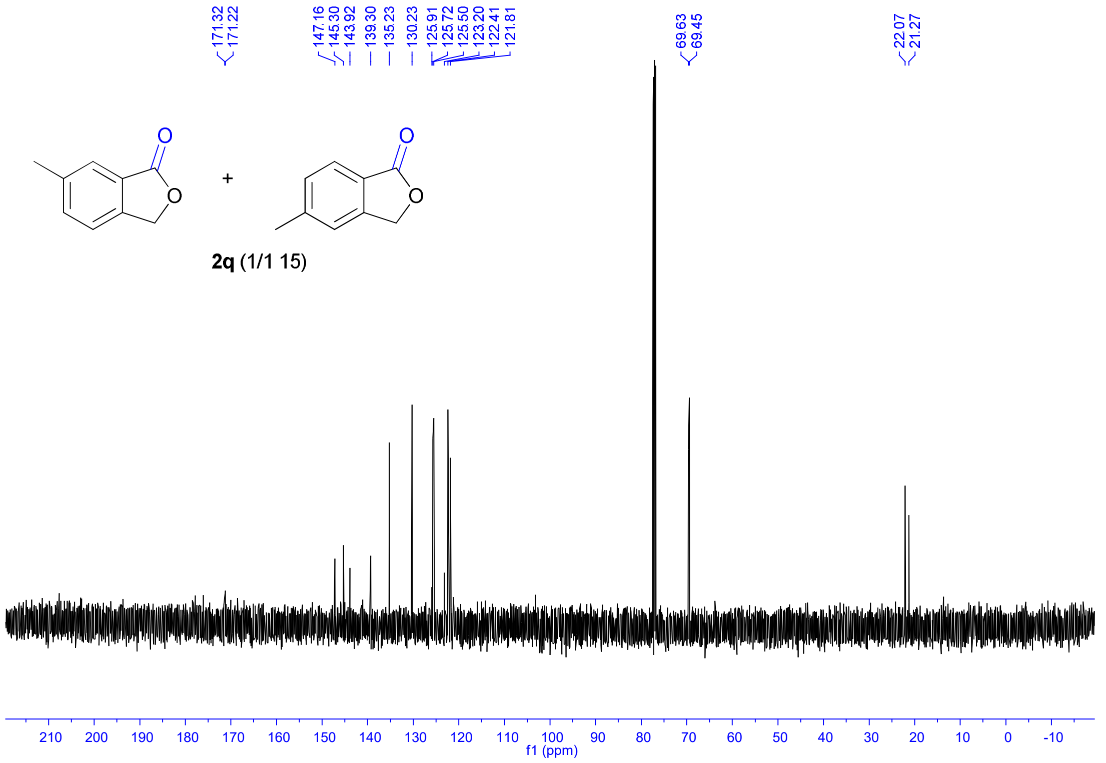

8.105
8.089
7.548
7.534
7.519
7.405
7.390
7.375
7.246
7.231
4.722
4.709
4.701
4.697
4.689
4.680
4.676
4.668
4.655
3.004
2.972
2.950
2.944
2.936
2.911
2.904
1.534
1.522
-0.000
O
O
2o
0.97
1.01
1.02
1.07
1.00
2.02
3.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

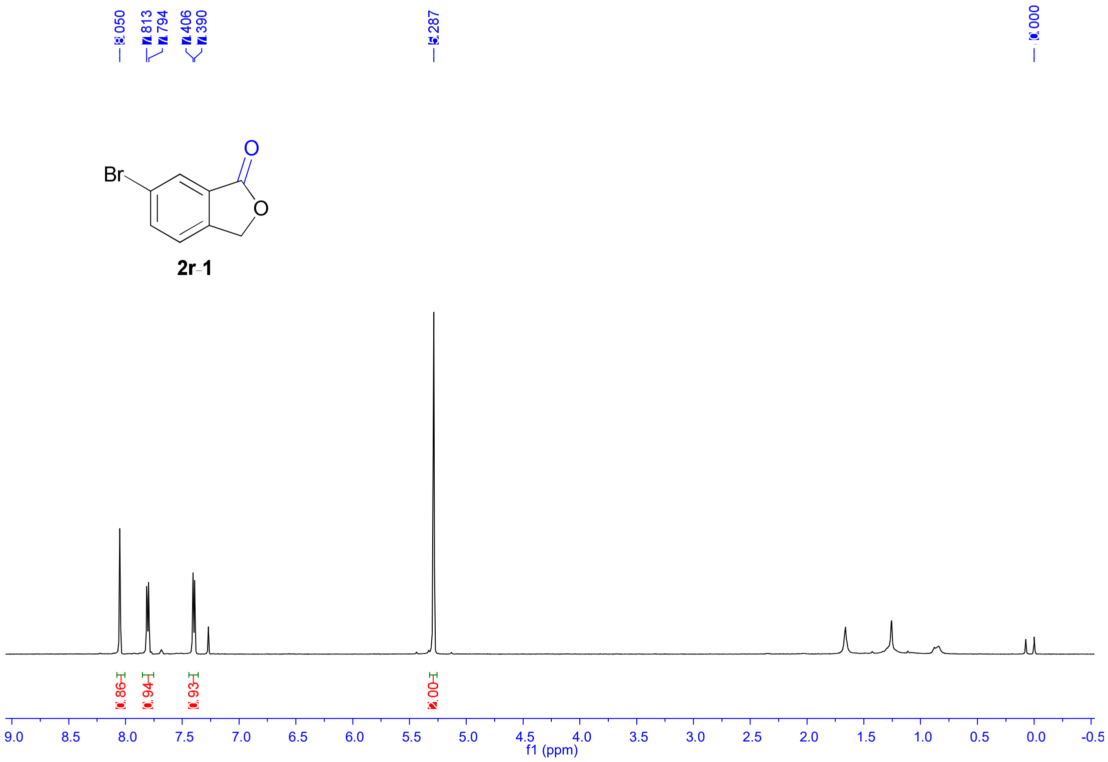

165.64
139.13
133.70
130.31
127.67
127.33
125.04
75.10
34.92
20.95
O
O
2o
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

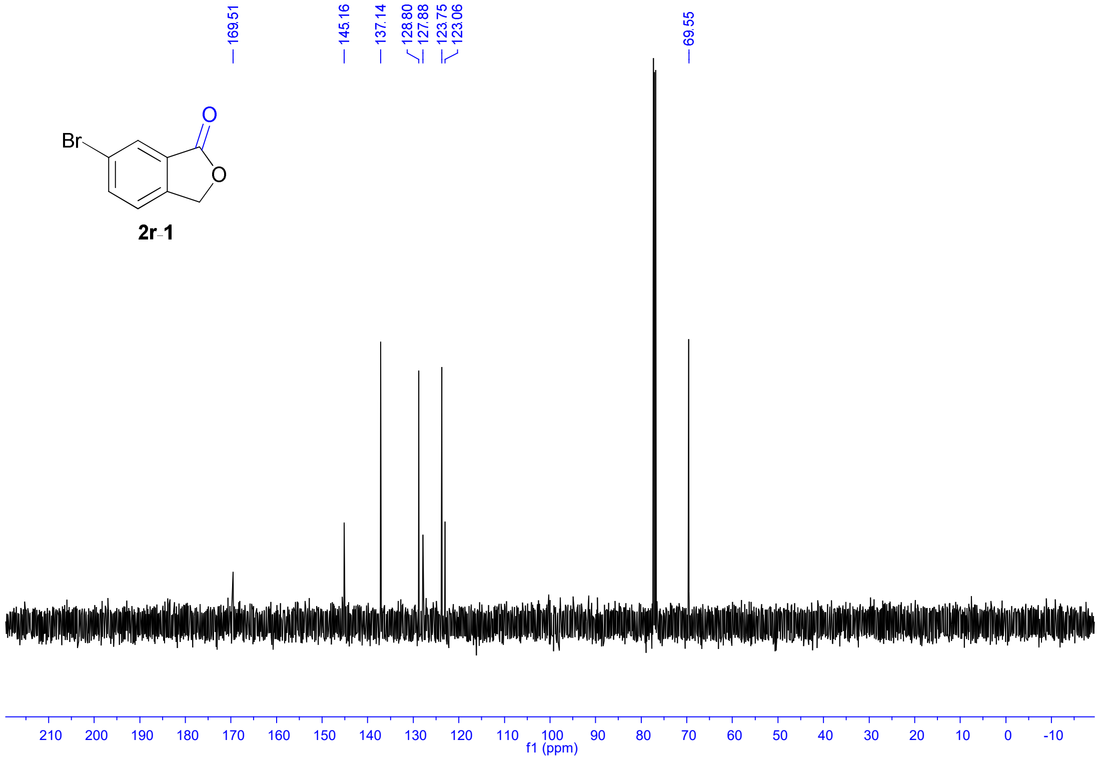

7.941
7.926
7.712
7.697
7.682
7.561
7.546
7.531
7.517
7.502
5.336
0.000
2p
0.94
0.97
0.97
0.92
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

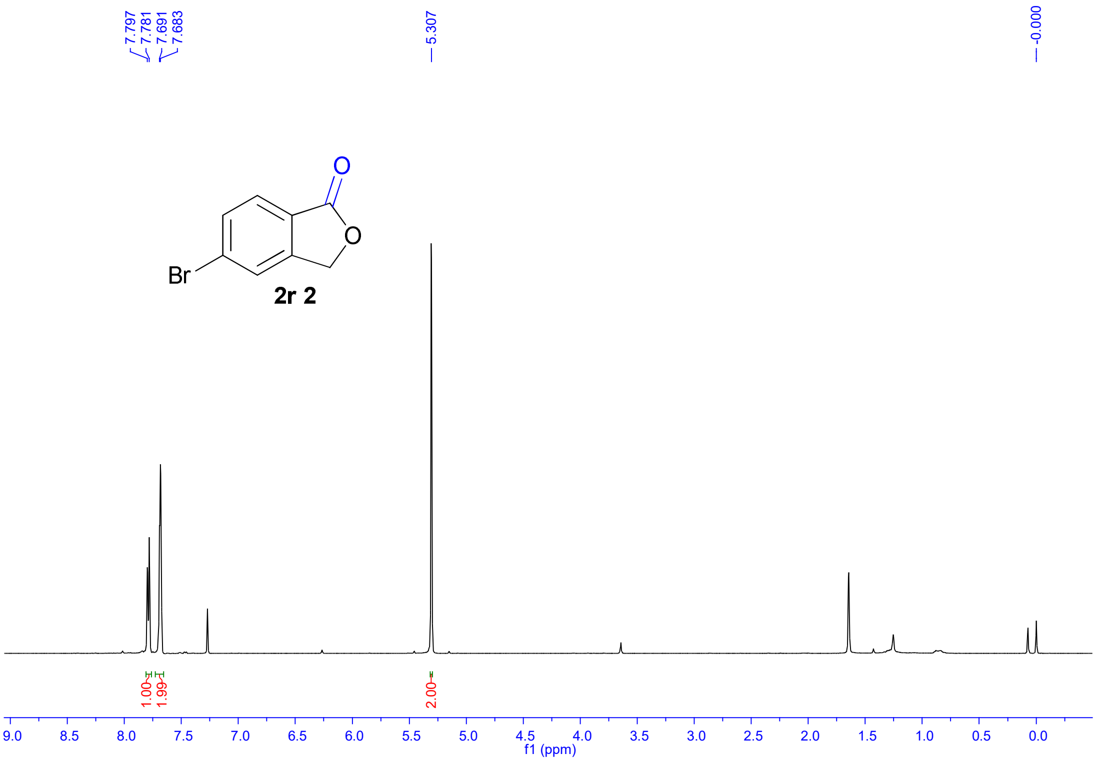

171.14
146.56
134.05
125.78
122.14
69.69
2p
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.805
7.789
7.711
7.507
7.491
7.391
7.375
7.347
7.331
7.292
5.284
5.272
2.500
2.470
0.000
O
O
+
O
O
**2q** (1/1 15)
1.00
0.80
0.84
0.86
1.00
1.00
1.74
2.00
3.00
2.60
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

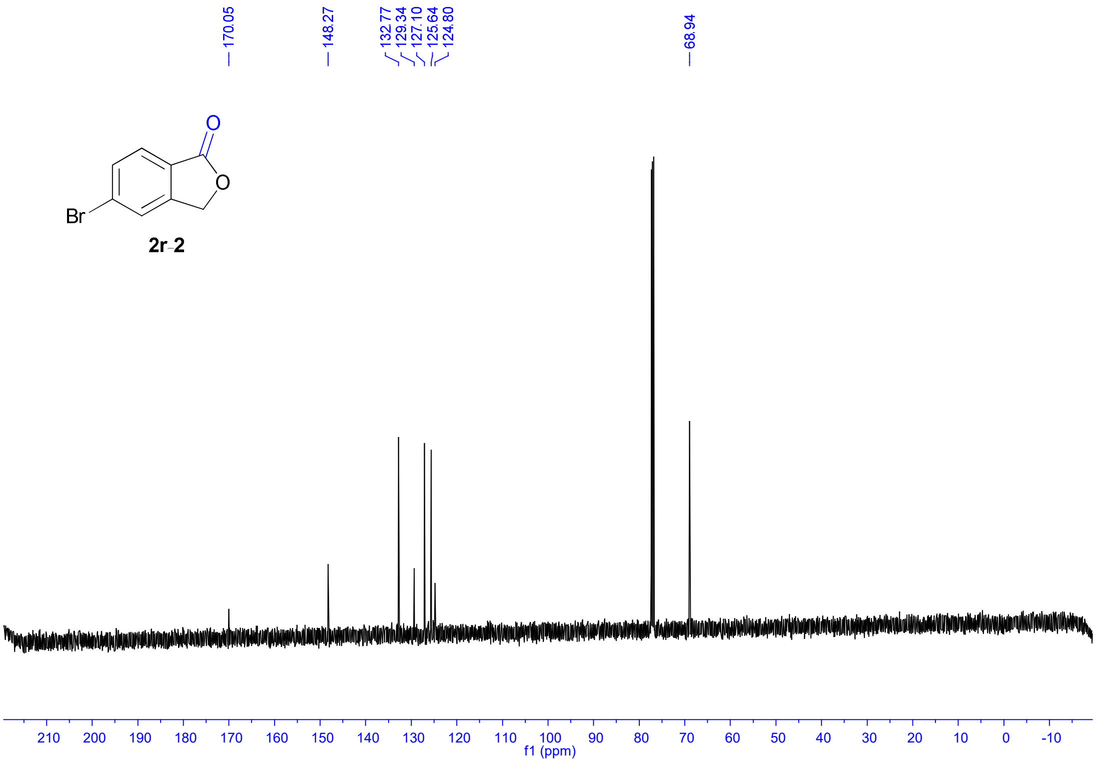

171.32
171.22
147.16
145.30
143.92
139.30
135.23
130.23
125.91
125.72
125.50
123.20
122.41
121.81
69.63
69.45
22.07
21.27
O
O
+
O
O
**2q** (1/1 15)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.050
7.813
7.794
7.406
7.390
5.287
0.000
Br
O
O
2r-1
0.86
0.94
0.93
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

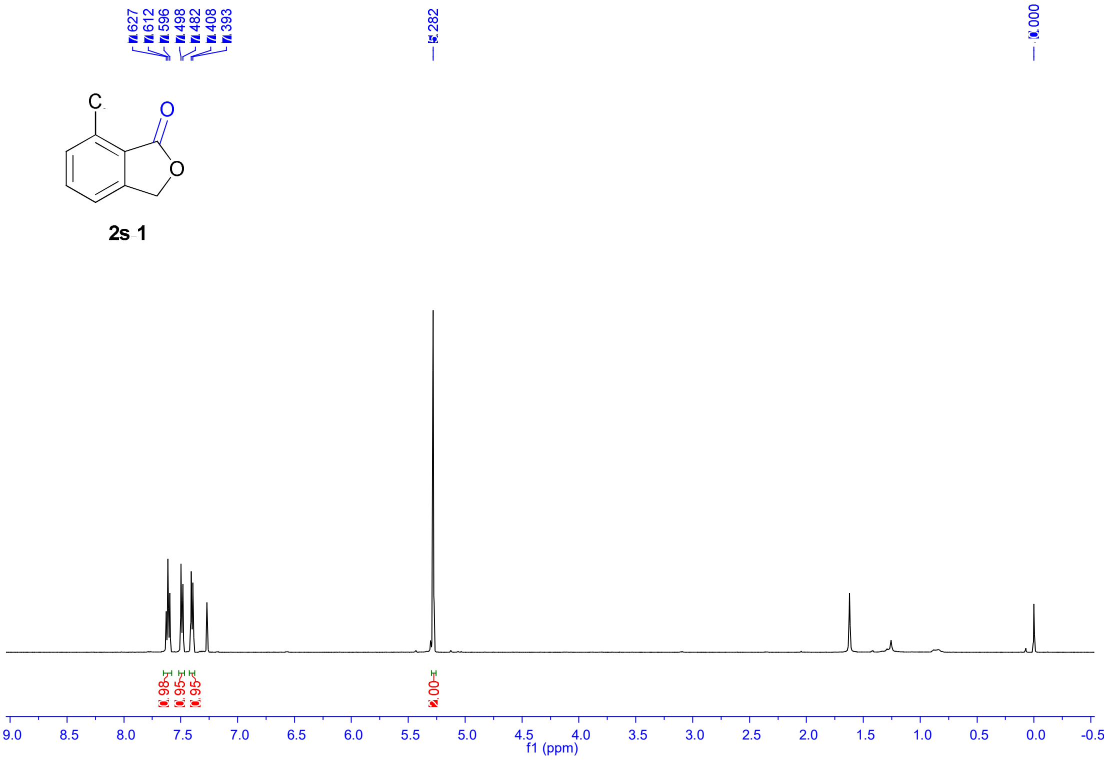

169.51
145.16
137.14
128.80
127.88
123.75
123.06
69.55
Br
O
O
2r-1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

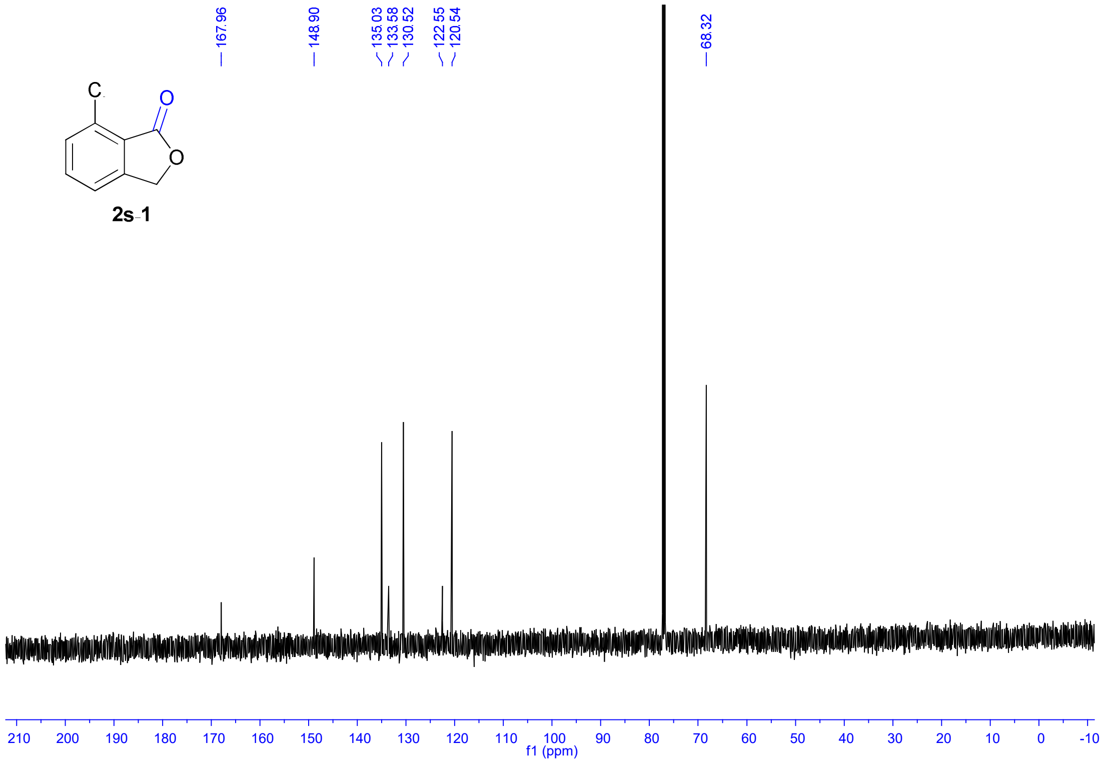

7.797
7.781
7.691
7.683
5.307
-0.000
O
O
Br
1.00
1.99
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

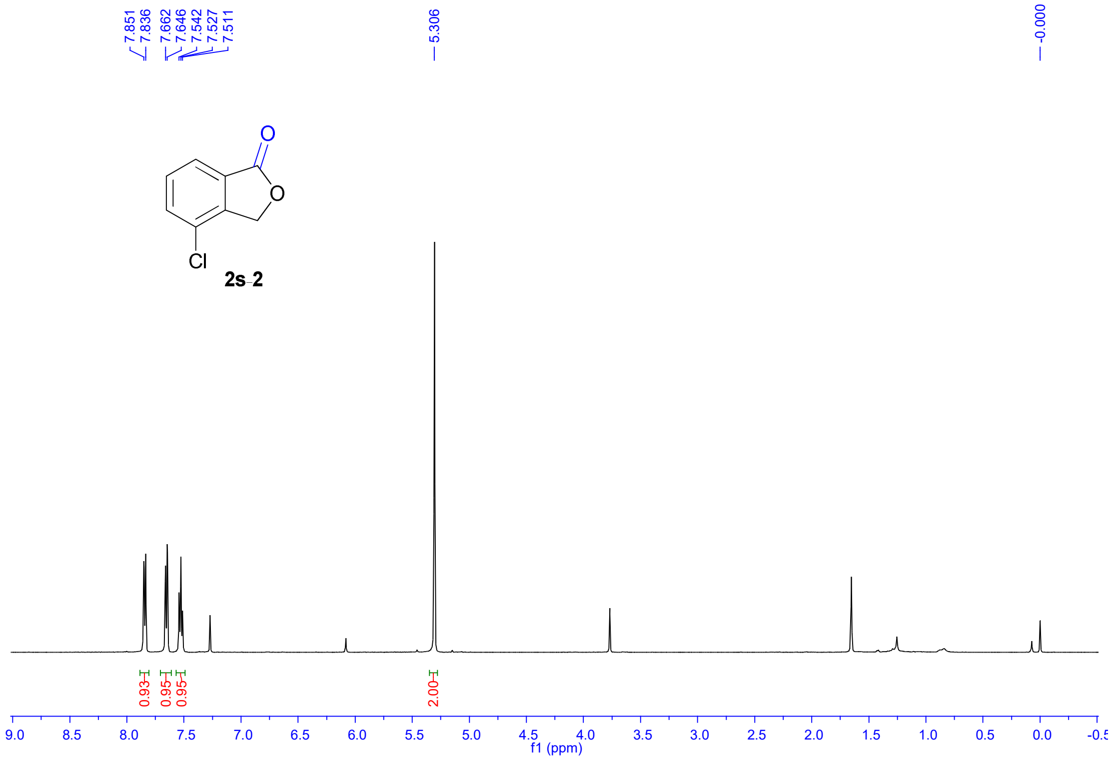
**2r 2**

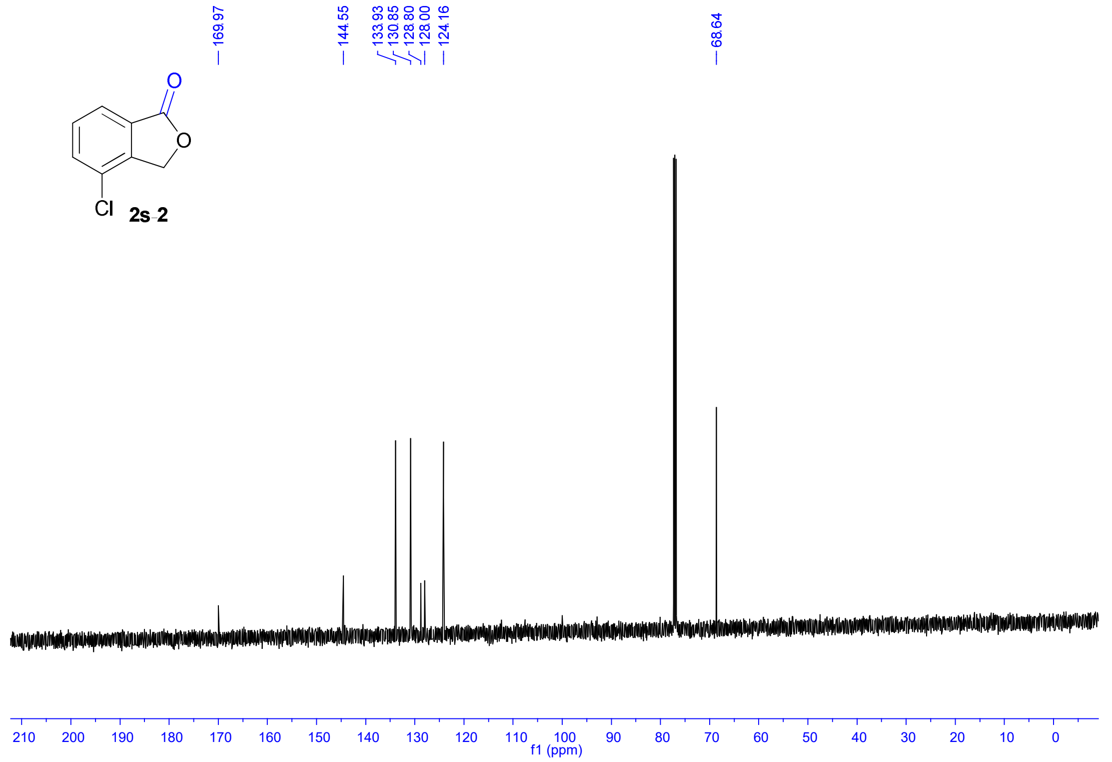

170.05
148.27
132.77
129.34
127.10
125.64
124.80
68.94
O
O
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

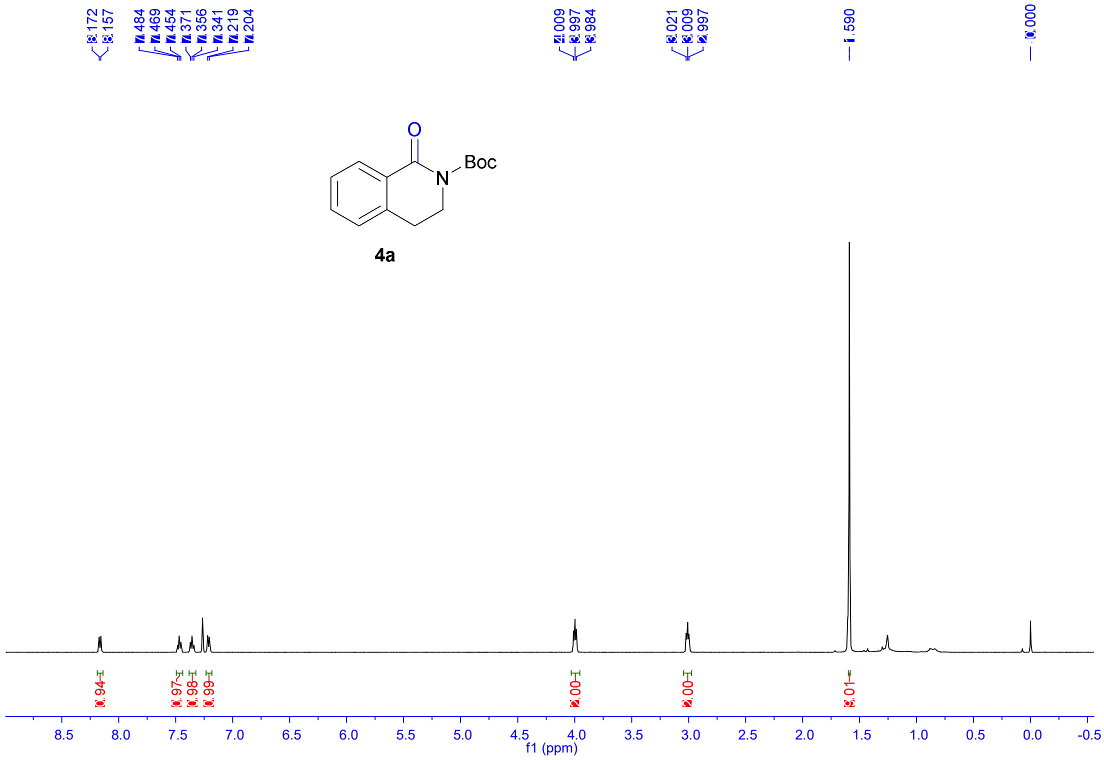
**2r 2**

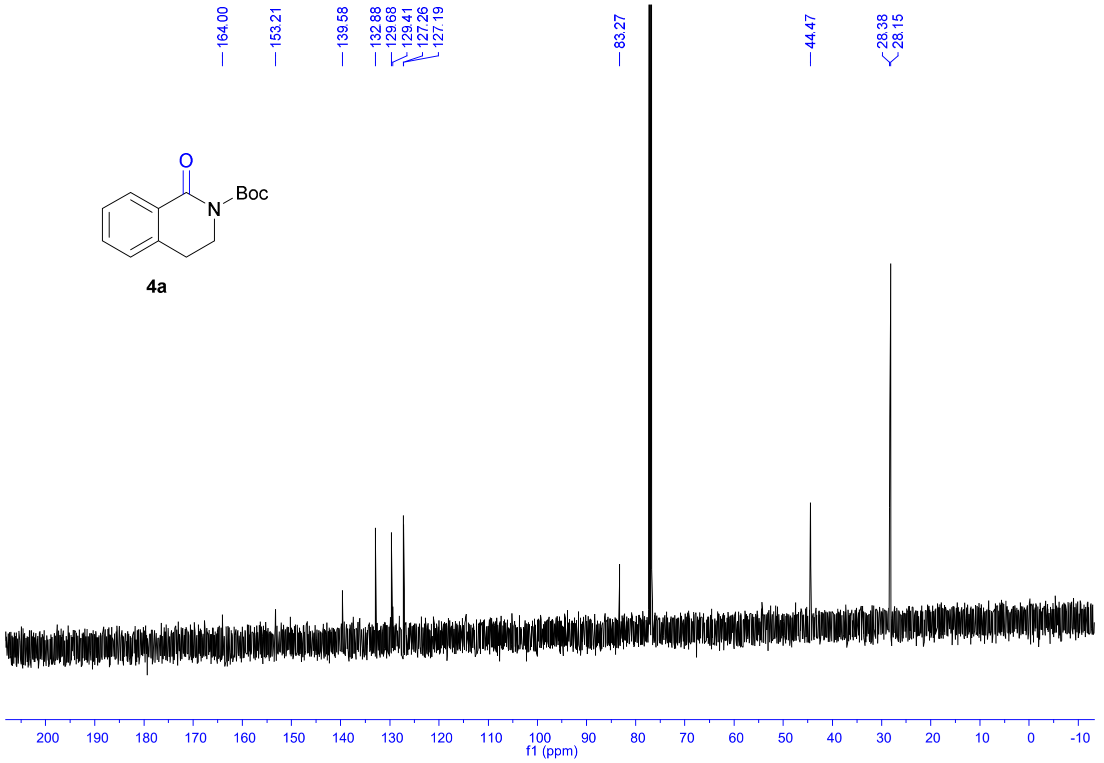

7.627
7.612
7.596
7.498
7.482
7.408
7.393
5.282
0.000
C
O
O
2s-1
0.98
0.95
0.95
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

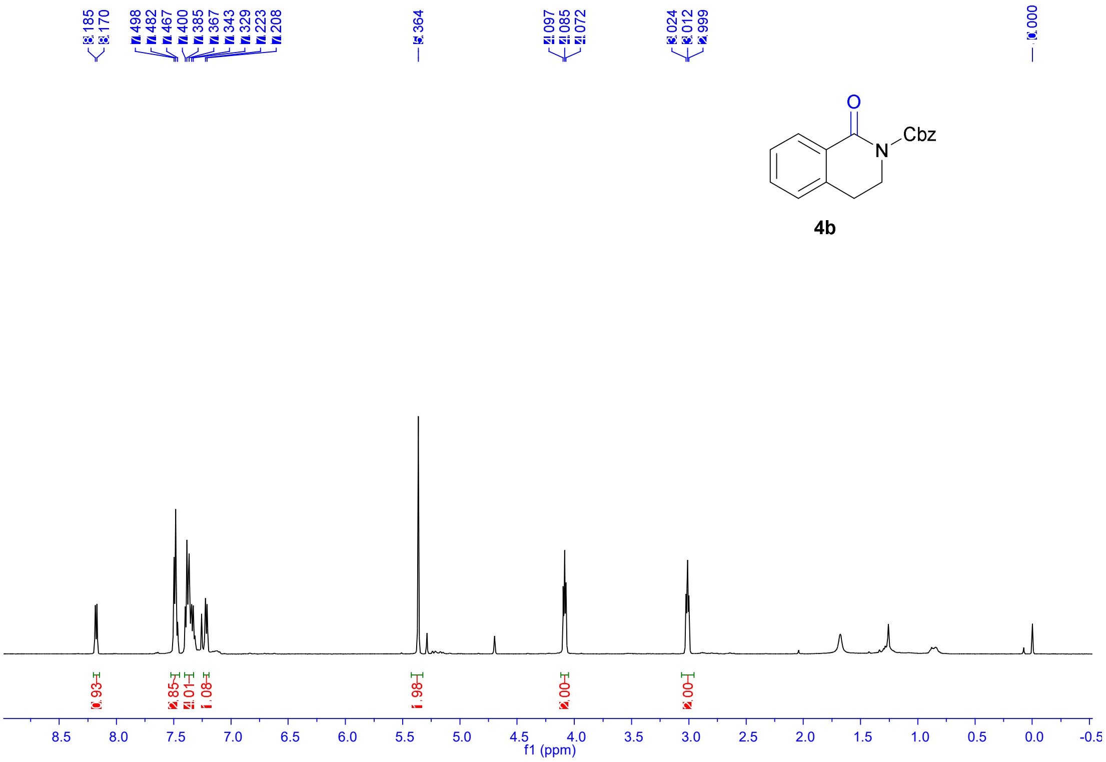

167.96
148.90
135.03
133.58
130.52
122.55
120.54
68.32
C
O
O
2s-1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

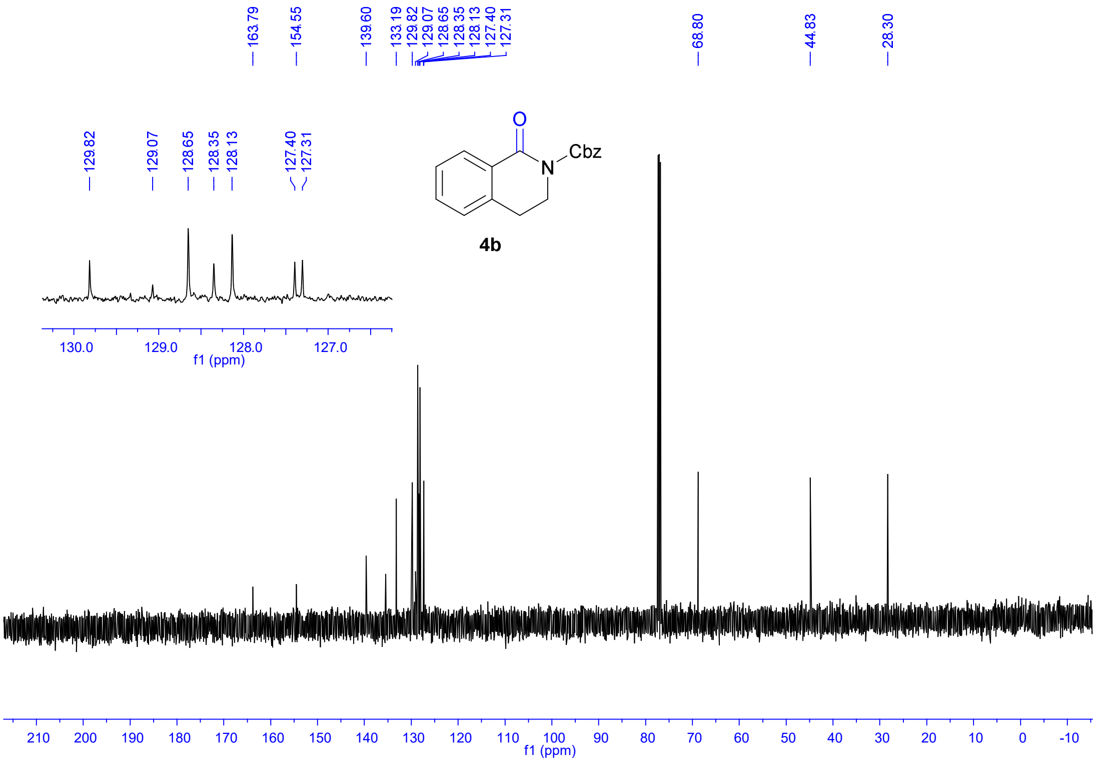

7.851
7.836
7.662
7.646
7.542
7.527
7.511
5.306
-0.000
O
O
Cl
2s-2
0.93
0.95
0.95
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

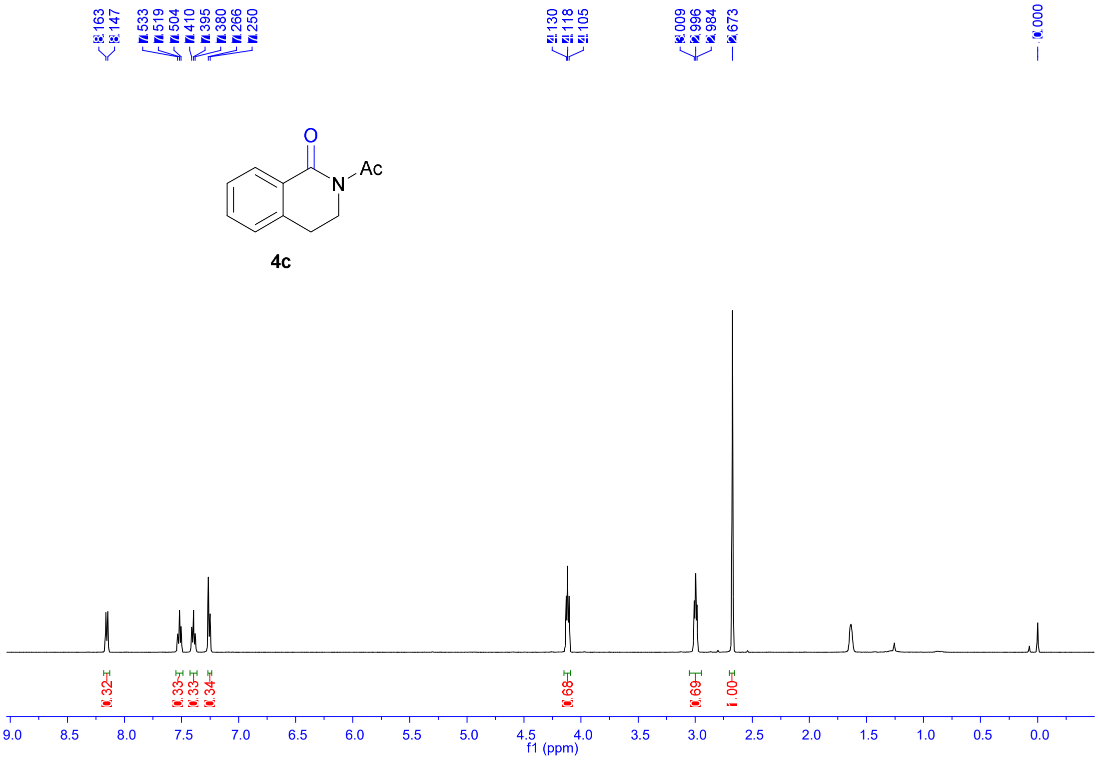

169.97
144.55
133.93
130.85
128.80
128.00
124.16
68.64
O
O
Cl
2s-2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

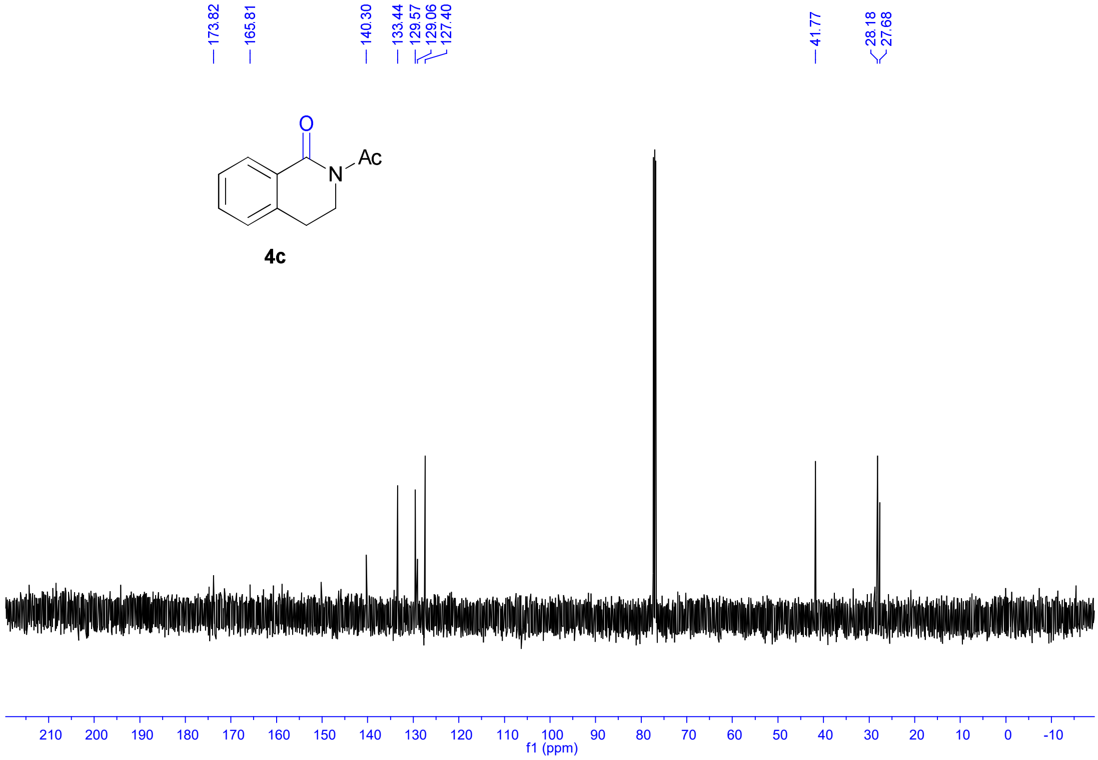

8.172
8.157
7.484
7.469
7.454
7.371
7.356
7.341
7.219
7.204
4.009
3.997
3.984
3.021
3.009
2.997
1.590
0.000
O
N
Boc
4a
0.94
0.97
0.98
0.99
2.00
2.00
9.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

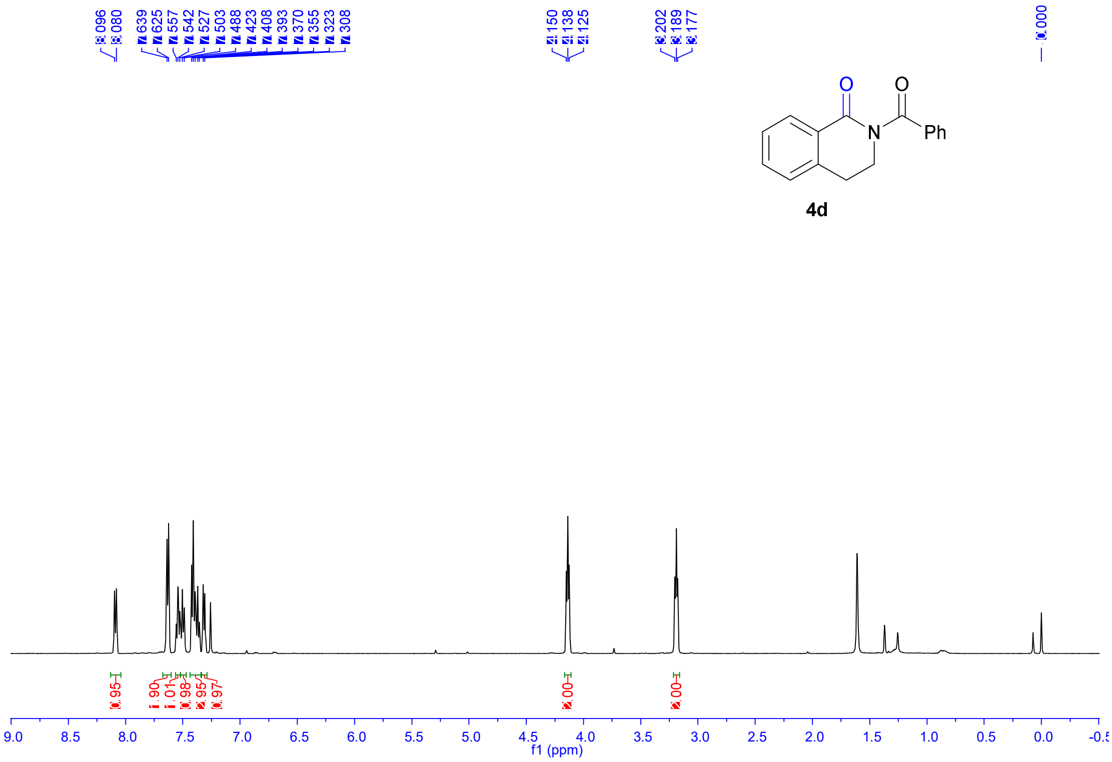

164.00
153.21
139.58
132.88
129.68
129.41
127.26
127.19
83.27
44.47
28.38
28.15
O
N
Boc
4a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.185
8.170
7.498
7.482
7.467
7.400
7.385
7.367
7.343
7.329
7.223
7.208
5.364
4.097
4.085
4.072
3.024
3.012
2.999
0.000
O
N
Cbz
4b
0.93
2.85
2.01
1.08
1.98
2.00
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

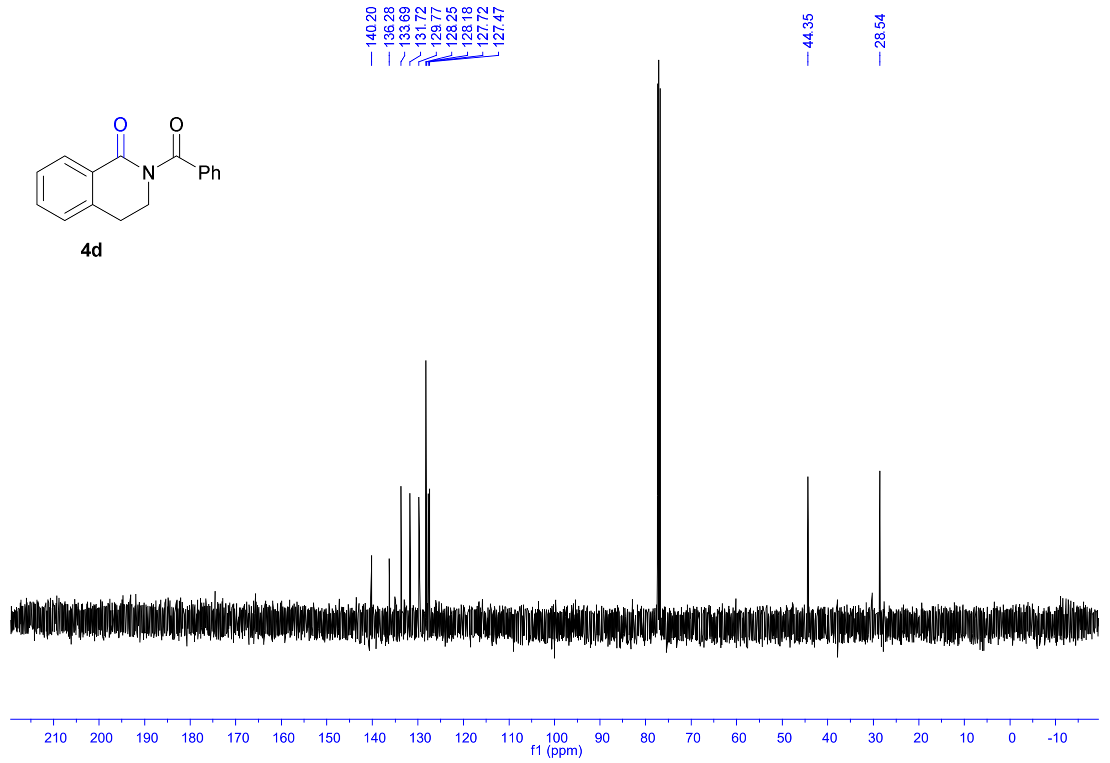

163.79
154.55
139.60
133.19
129.82
129.07
128.65
128.35
128.13
127.40
127.31
68.80
44.83
28.30
129.82
129.07
128.65
128.35
128.13
127.40
127.31
130.0
129.0
128.0
127.0
f1 (ppm)
O
N
Cbz
4b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


8.163
8.147
7.533
7.519
7.504
7.410
7.395
7.380
7.266
7.250
4.130
4.118
4.105
3.009
2.996
2.984
2.673
0.000
O
N
Ac
4c
0.32
0.33
0.33
0.34
0.68
0.69
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

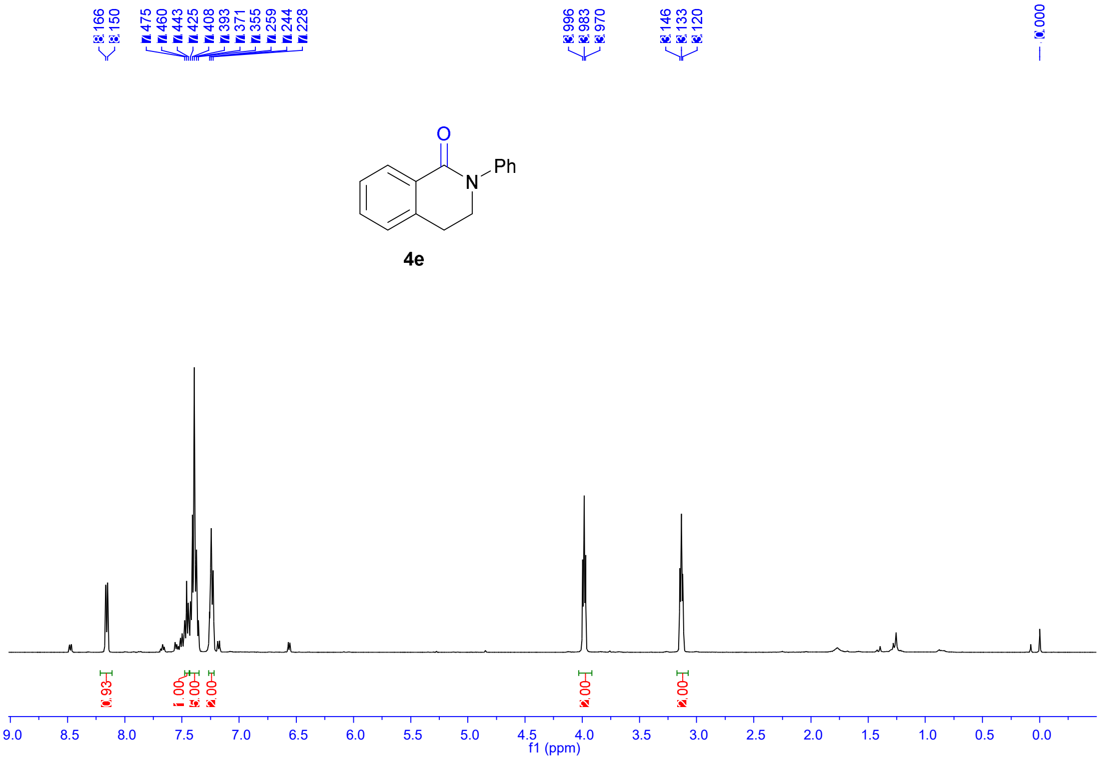

173.82
165.81
140.30
133.44
129.57
129.06
127.40
41.77
28.18
27.68
O
N
Ac
4c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

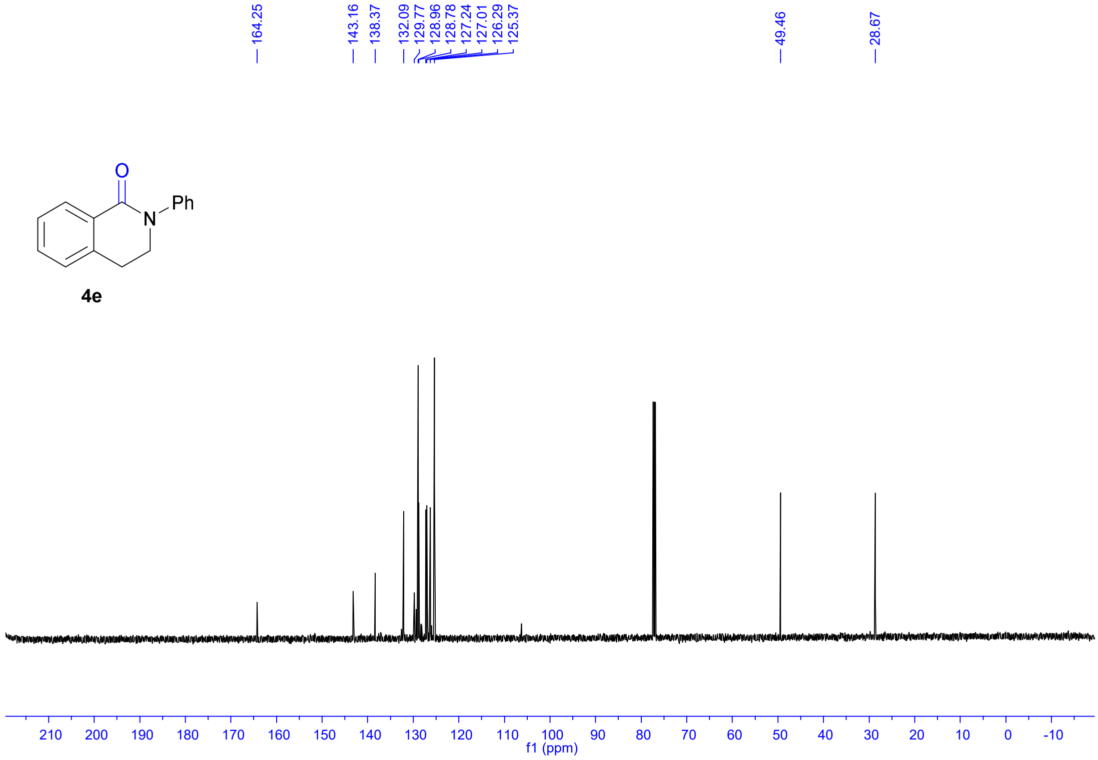

8.096
8.080
7.639
7.625
7.557
7.542
7.527
7.503
7.488
7.423
7.408
7.393
7.370
7.355
7.323
7.308
4.150
4.138
4.125
3.202
3.189
3.177
0.000
O
O
N
Ph
0.95
1.90
1.01
0.98
2.95
0.97
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

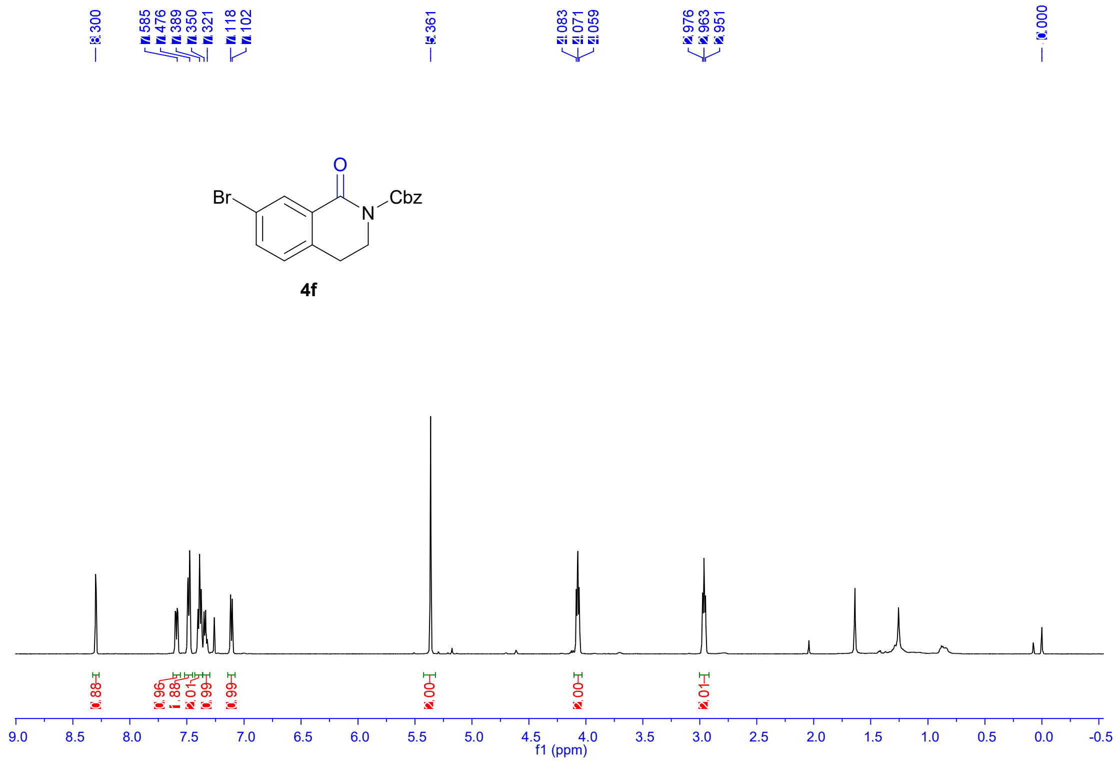
**4d**

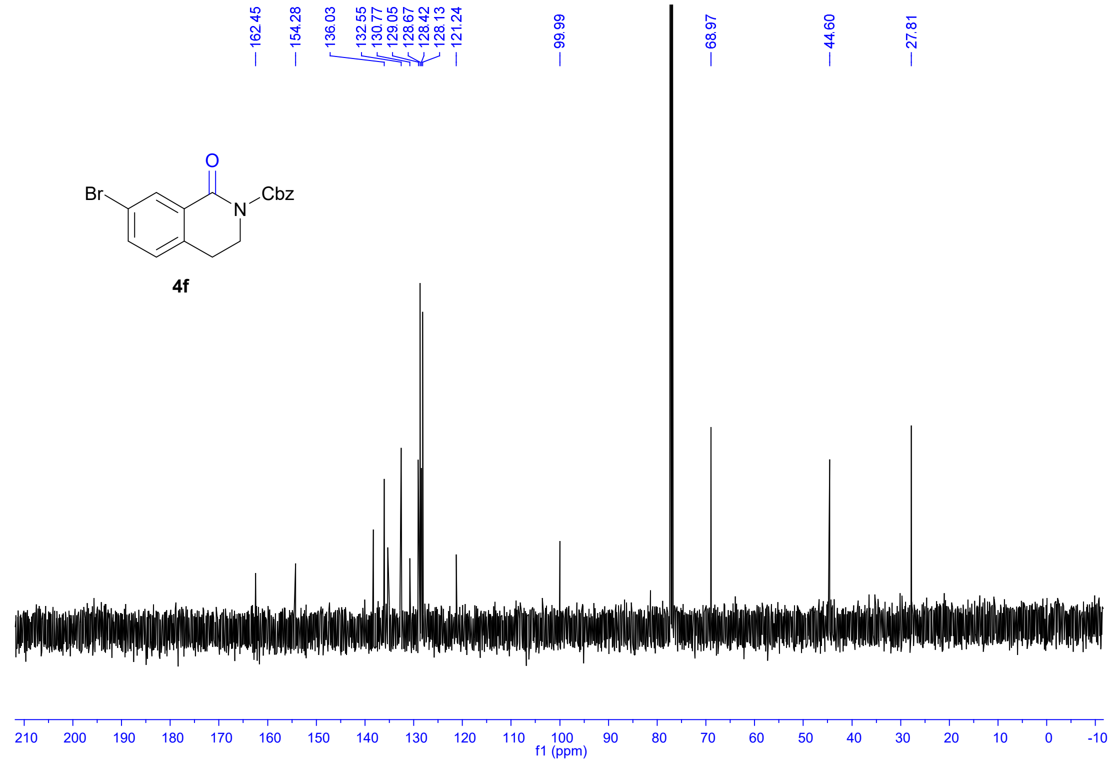

140.20
136.28
133.69
131.72
129.77
128.25
128.18
127.72
127.47
44.35
28.54
O
O
N
Ph
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

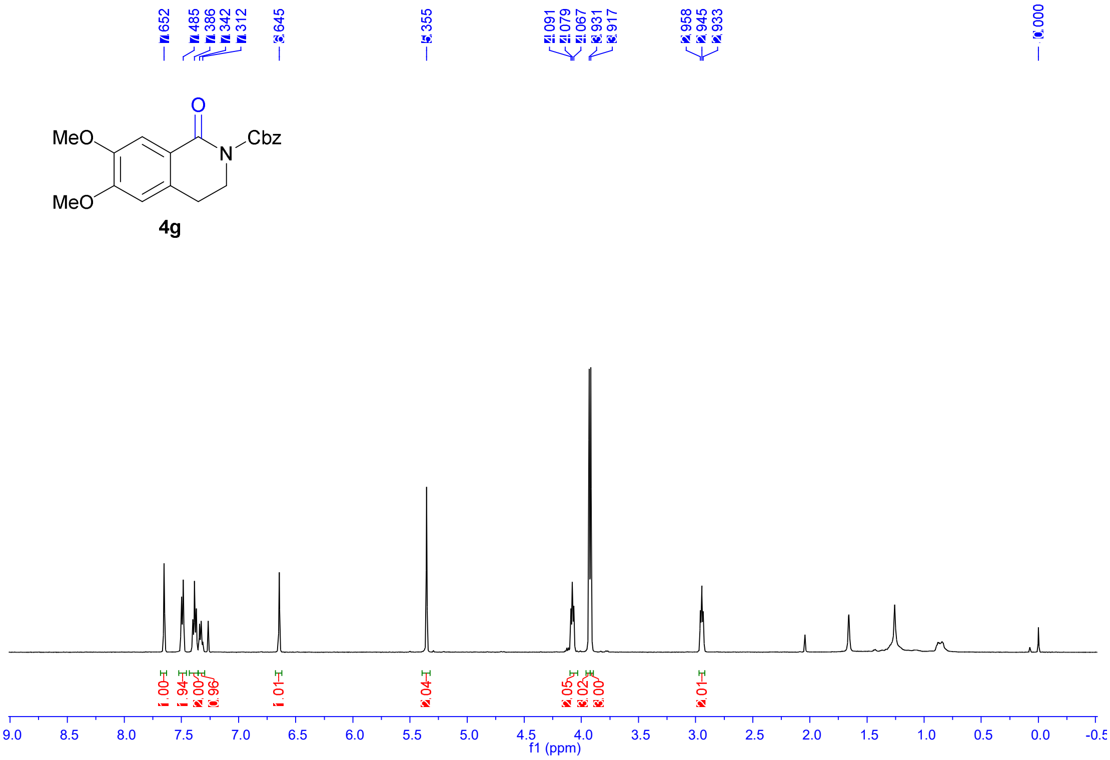
**4d**


8.166
8.150
7.475
7.460
7.443
7.425
7.408
7.393
7.371
7.355
7.259
7.244
7.228
3.996
3.983
3.970
3.146
3.133
3.120
0.000
O
N
Ph
4e
0.93
1.00
5.00
2.00
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

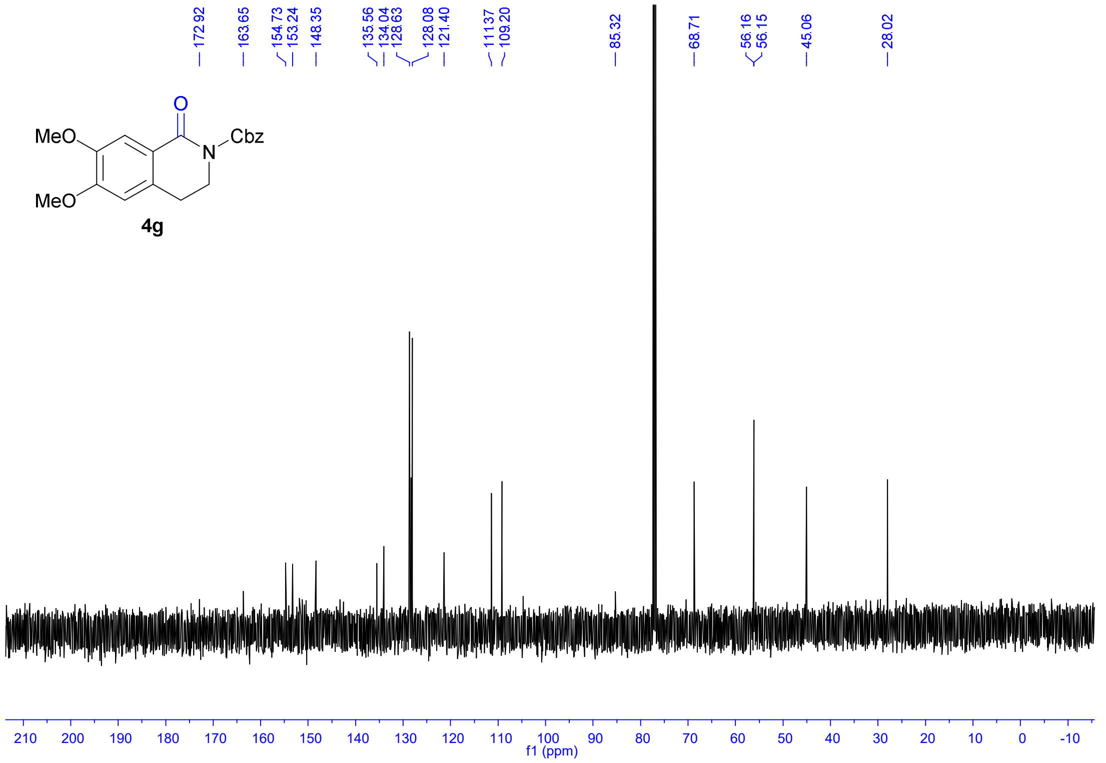

164.25
143.16
138.37
132.09
129.77
128.96
128.78
127.24
127.01
126.29
125.37
49.46
28.67
O
N
Ph
4e
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


4f
8.300
7.585
7.476
7.389
7.350
7.321
7.118
7.102
5.361
4.083
4.071
4.059
2.976
2.963
2.951
0.000
Br
O
N
Cbz
0.88
0.96
1.88
2.01
0.99
0.99
2.00
2.00
2.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

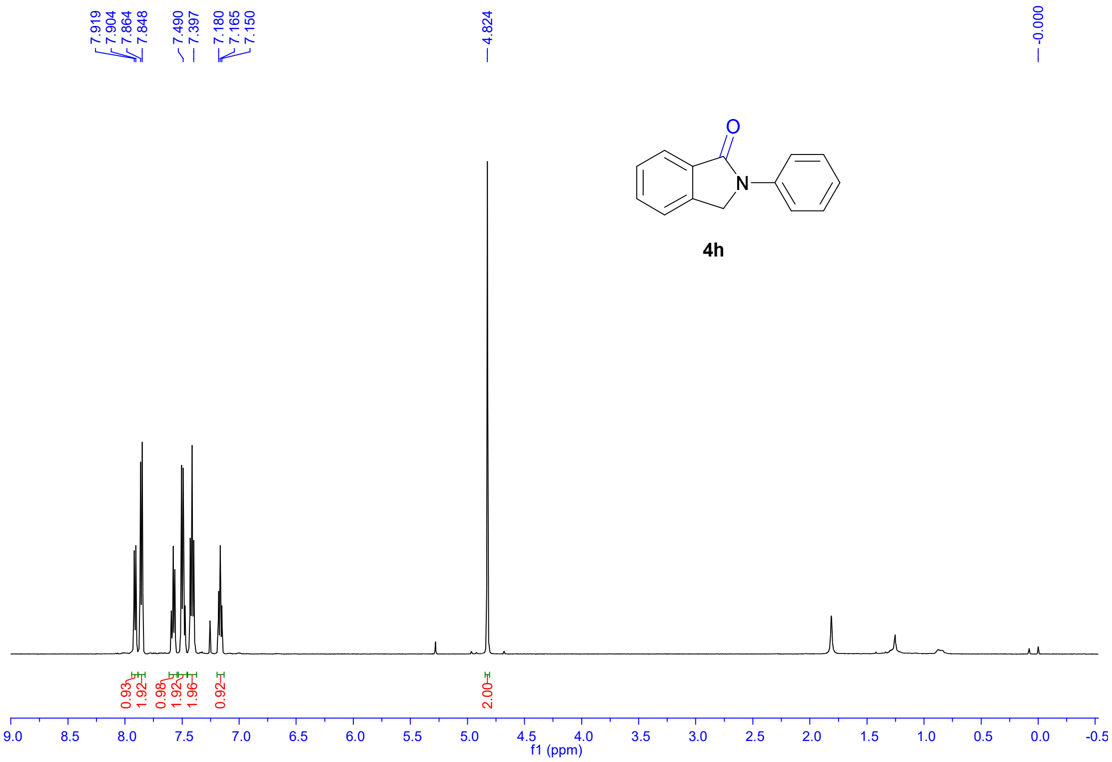

4f
162.45
154.28
136.03
132.55
130.77
129.05
128.67
128.42
128.13
121.24
99.99
68.97
44.60
27.81
Br
O
N
Cbz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


7.652
7.485
7.386
7.342
7.312
6.645
5.355
4.091
4.079
4.067
3.931
3.917
2.958
2.945
2.933
0.000
MeO
MeO
O
N
Cbz
1.00
1.94
2.00
0.96
1.01
2.04
2.05
3.02
3.00
2.01
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

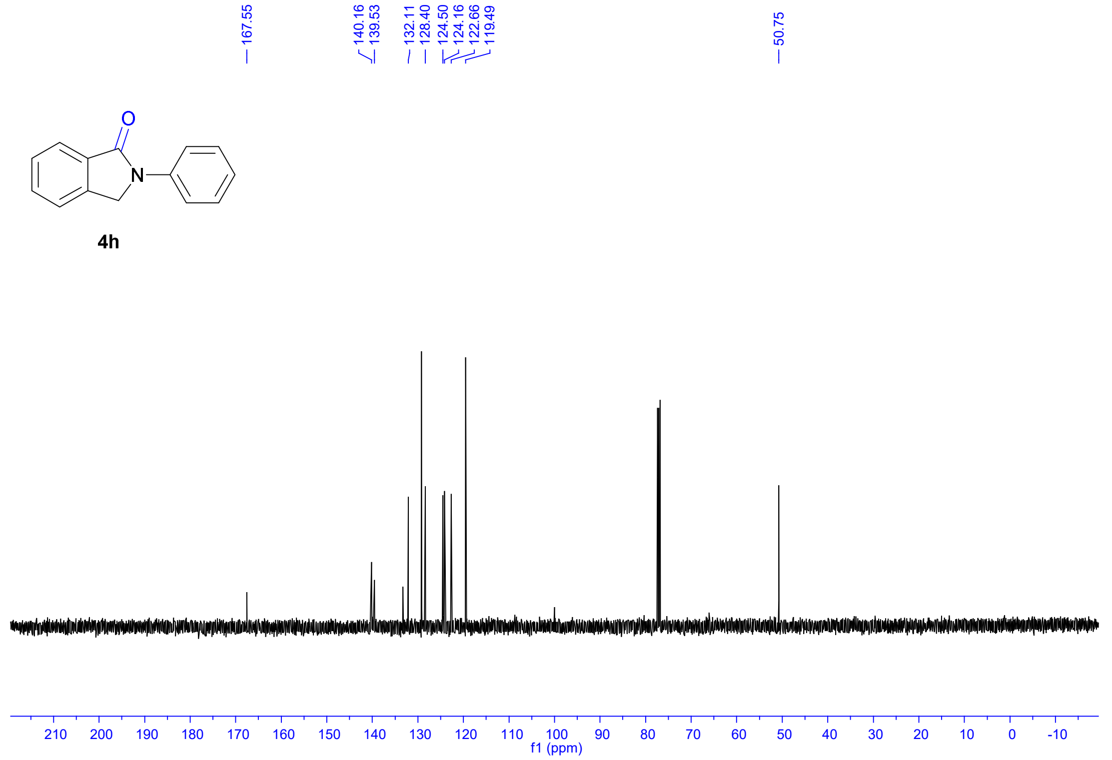
4g


172.92
163.65
154.73
153.24
148.35
135.56
134.04
128.63
128.08
121.40
111.37
109.20
85.32
68.71
56.16
56.15
45.06
28.02
MeO
MeO
O
N
Cbz
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

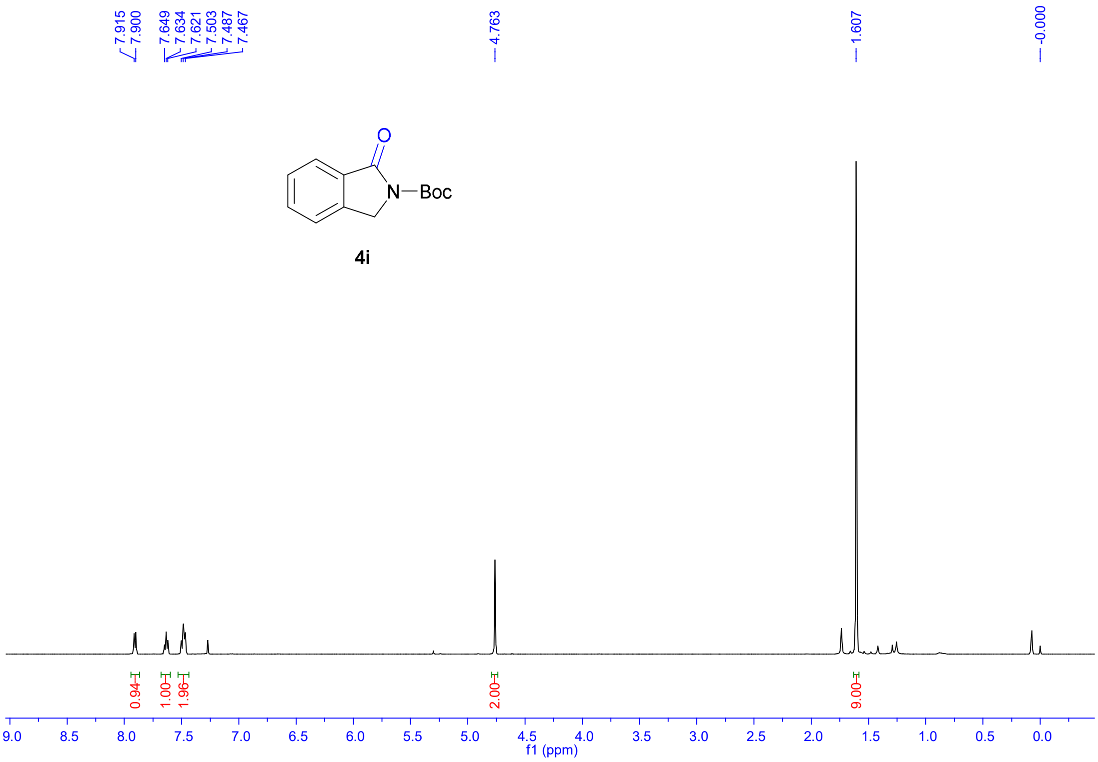
4g

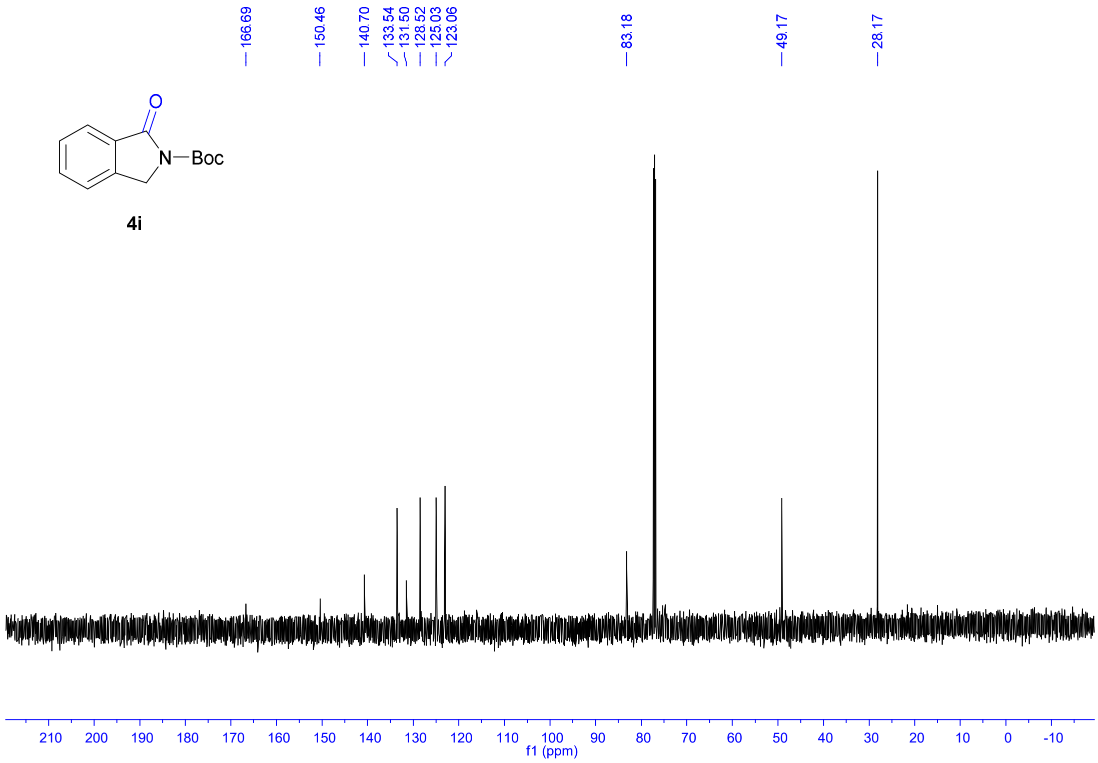

**4h**

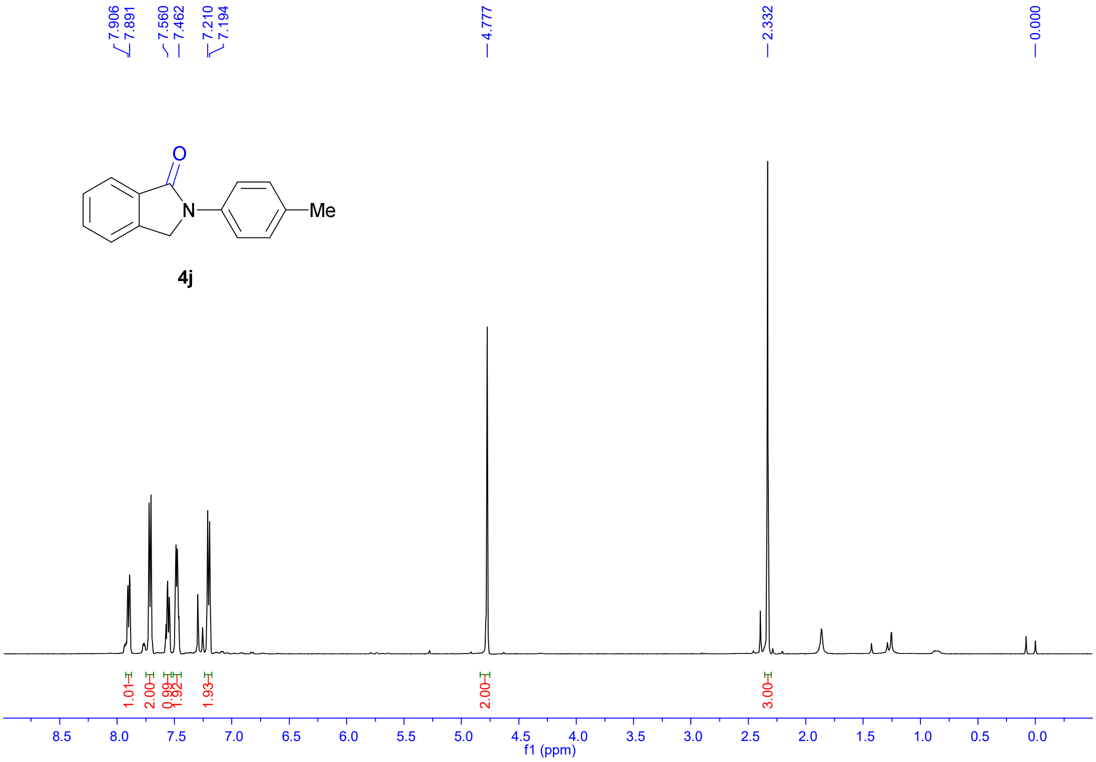
7.919
7.904
7.864
7.848
7.490
7.397
7.180
7.165
7.150
4.824
-0.000
O
N
0.93
1.92
0.98
1.92
1.96
0.92
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

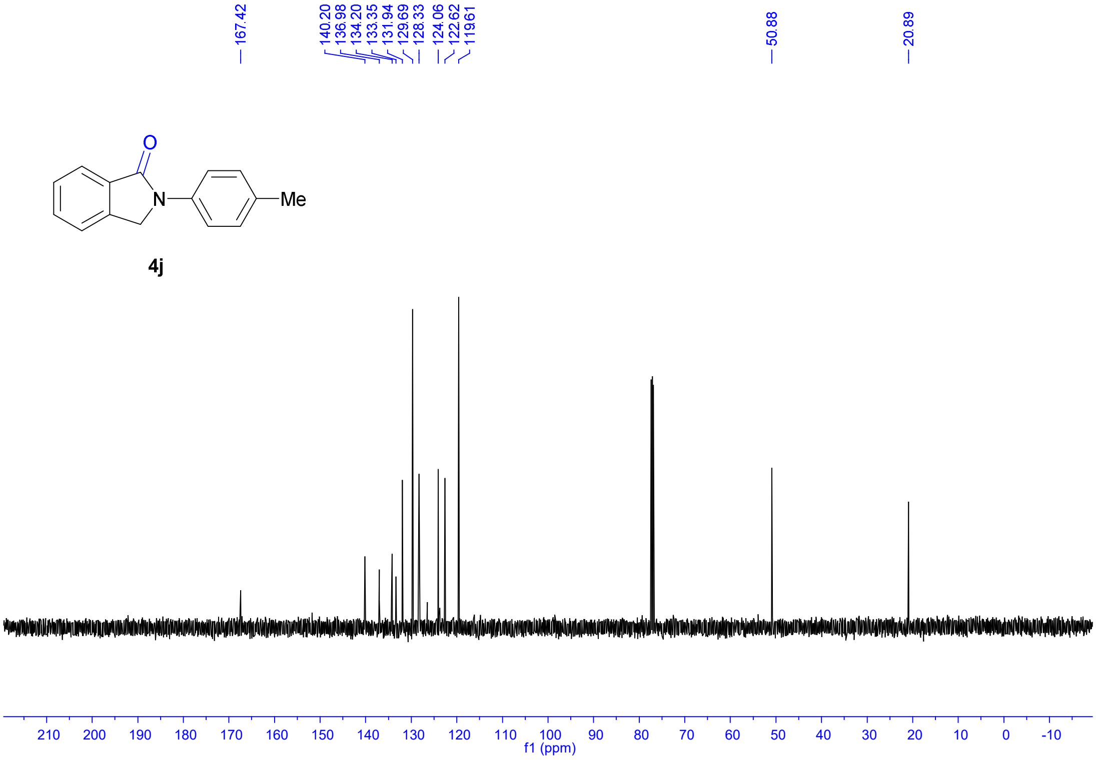

**4h**

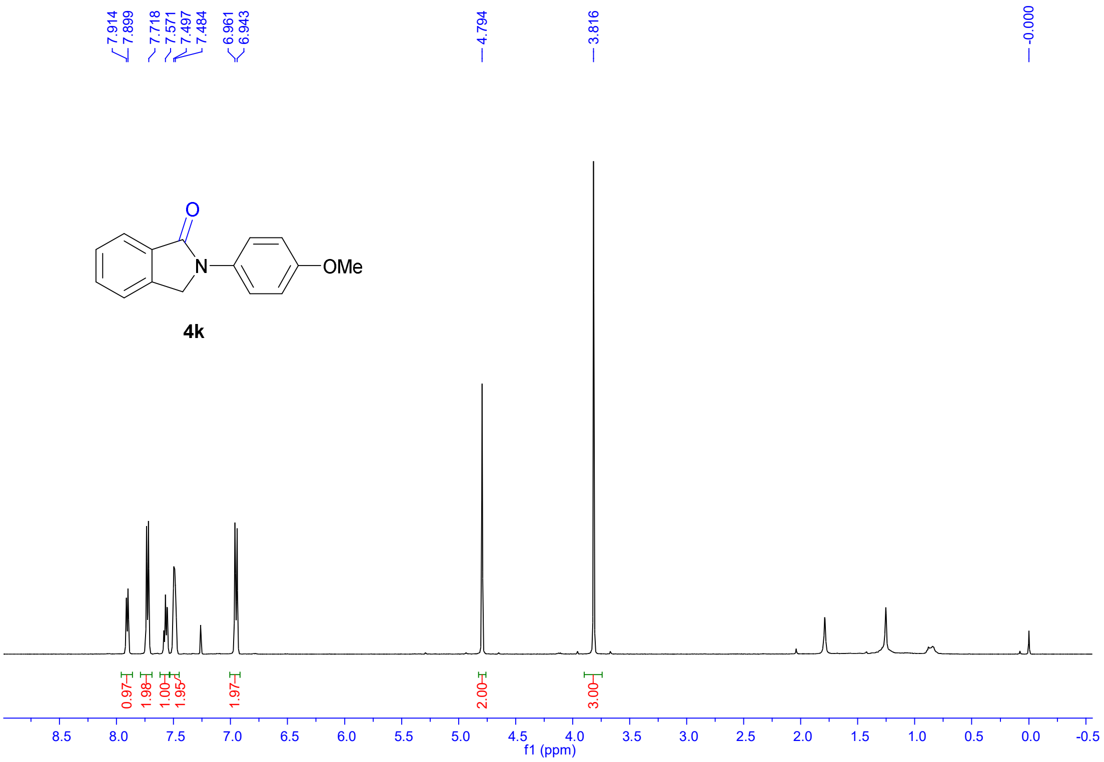
167.55
140.16
139.53
132.11
128.40
124.50
124.16
122.66
119.49
50.75
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

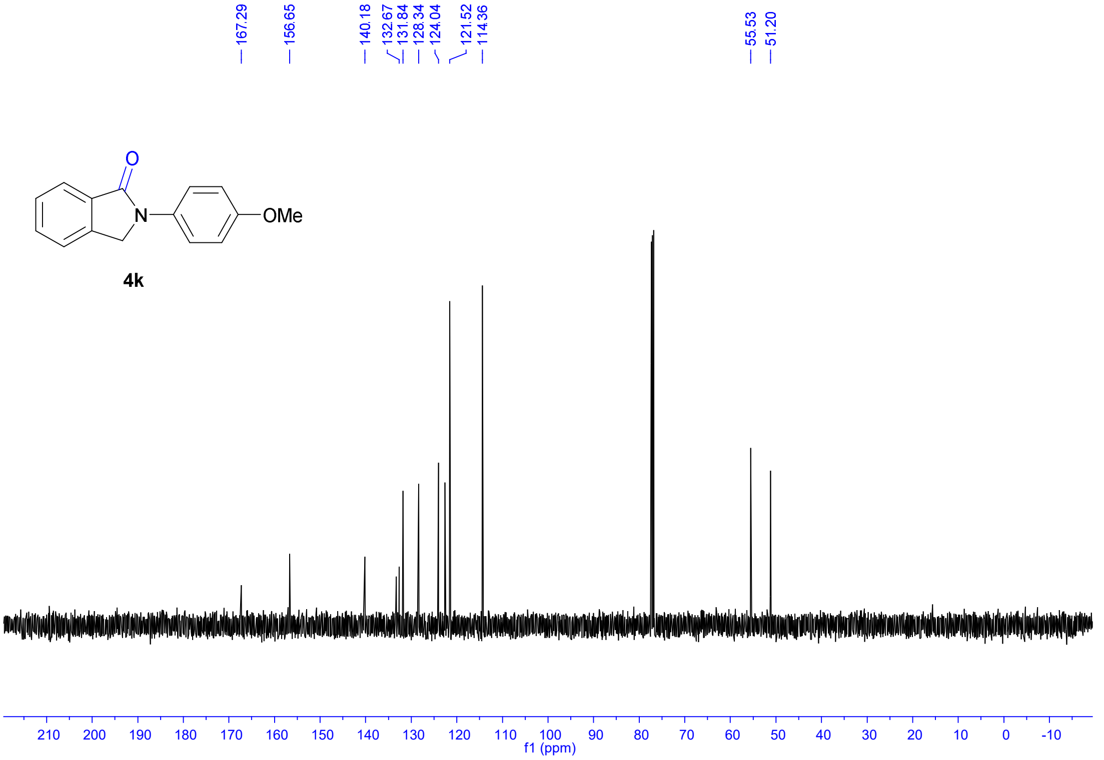

7.915
7.900
7.649
7.634
7.621
7.503
7.487
7.467
4.763
1.607
-0.000
O
N—Boc
4i
0.94
1.00
1.96
2.00
9.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

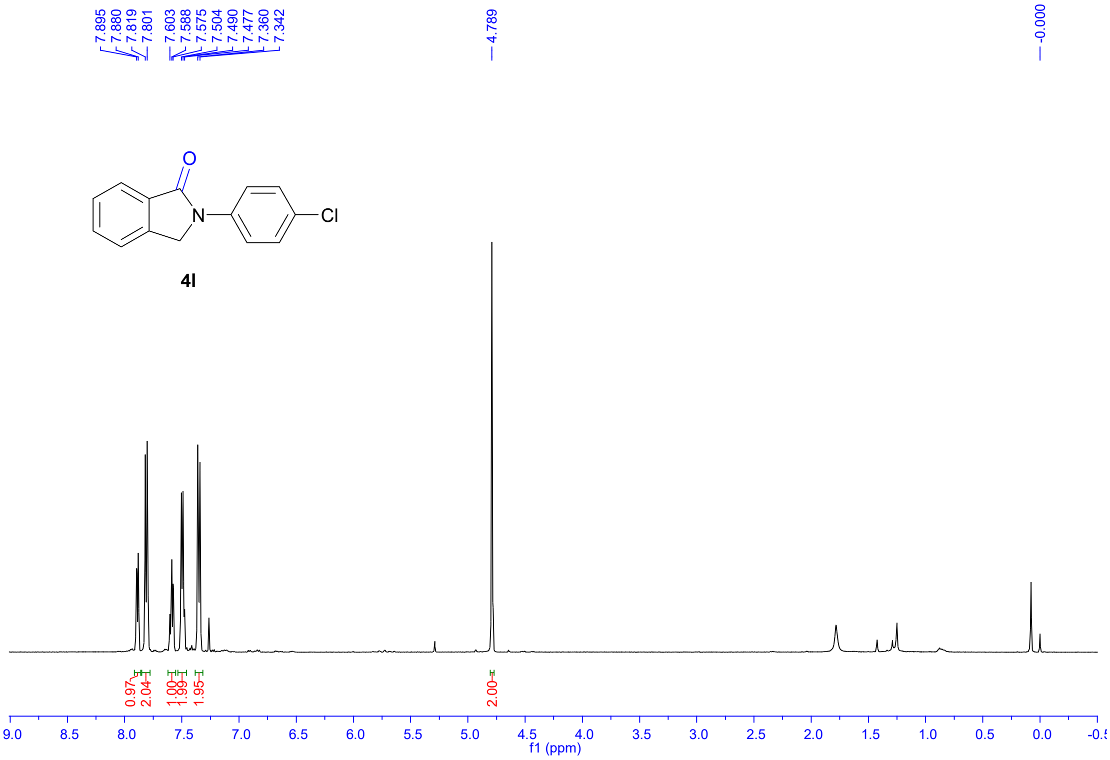

166.69
150.46
140.70
133.54
131.50
128.52
125.03
123.06
83.18
49.17
28.17
O
N—Boc
4i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

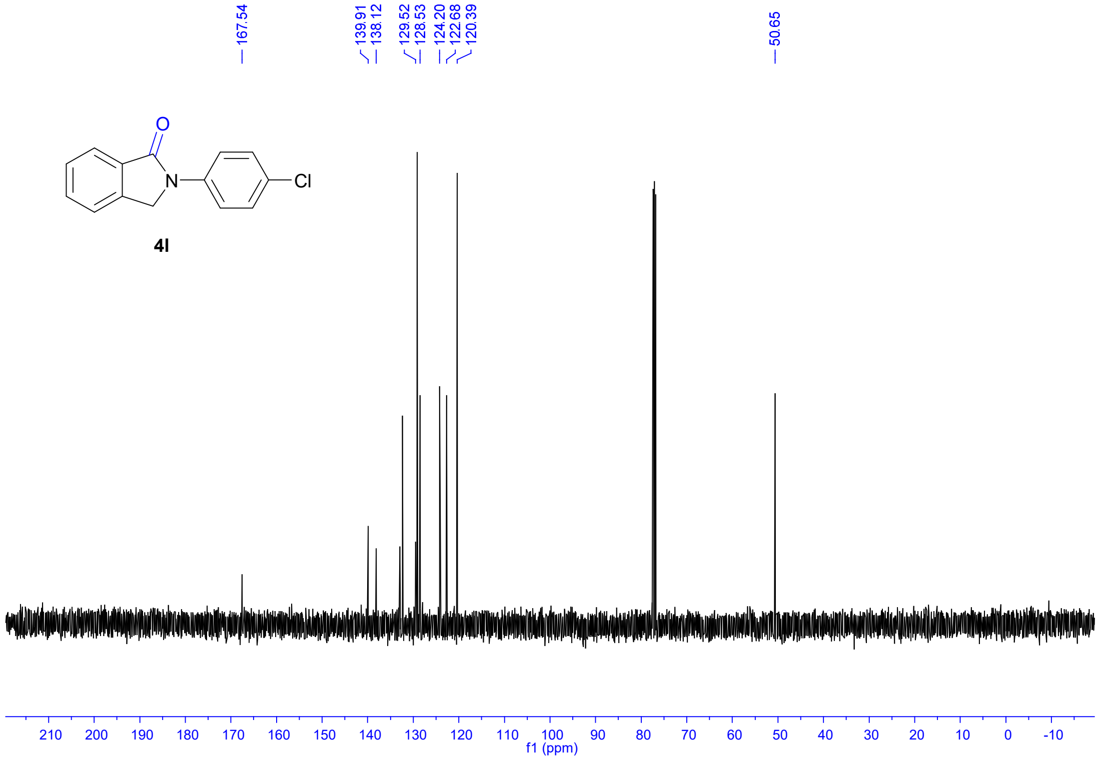

7.906
7.891
7.560
7.462
7.210
7.194
4.777
2.332
0.000
O
N
Me
4j
1.01
2.00
0.99
1.92
1.93
2.00
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

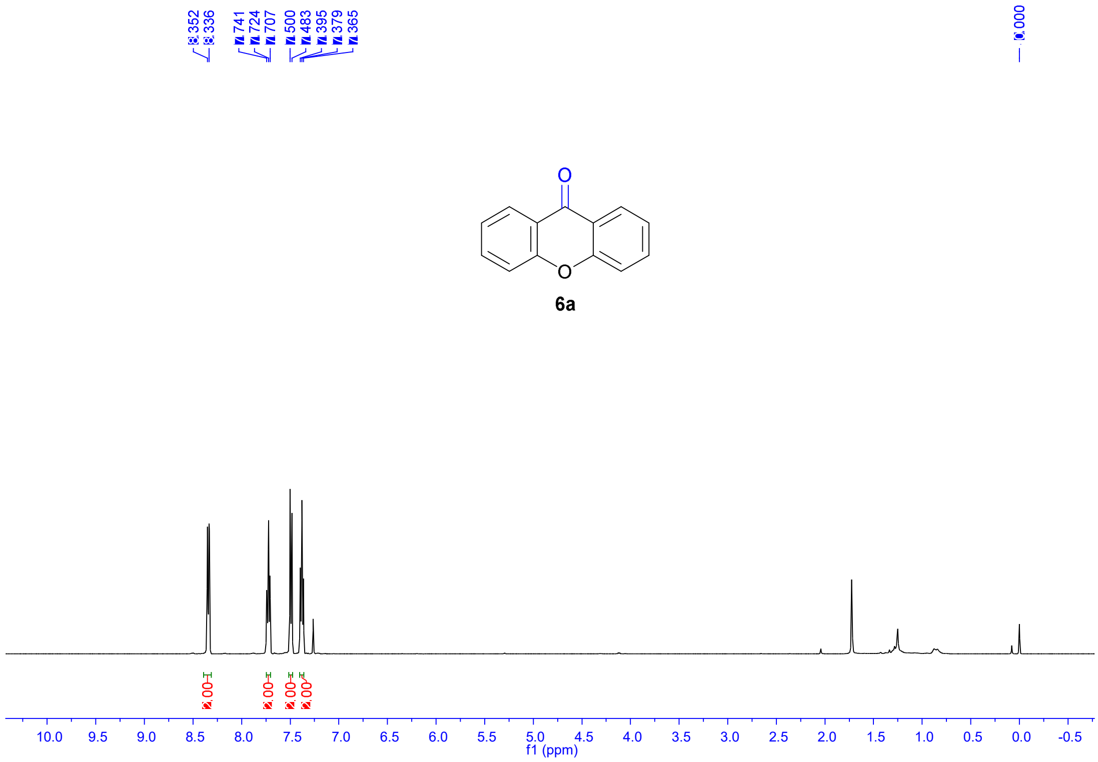

167.42
140.20
136.98
134.20
133.35
131.94
129.69
128.33
124.06
122.62
119.61
50.88
20.89
O
N
Me
4j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

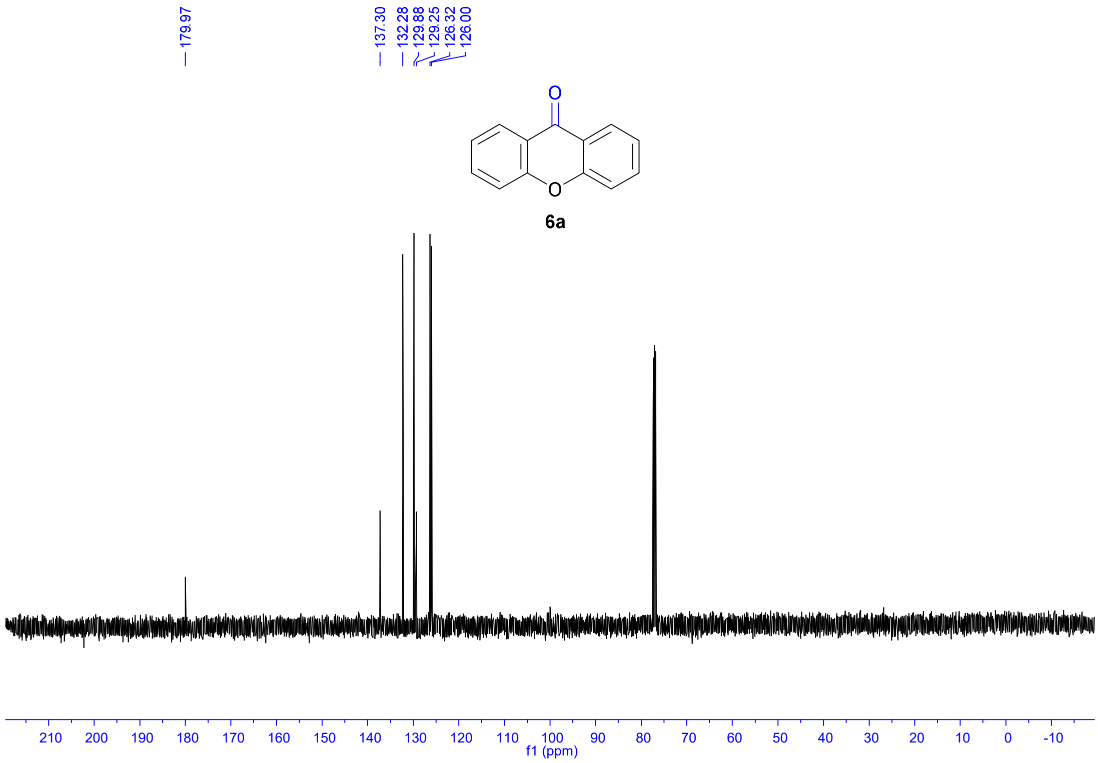

7.914
7.899
7.718
7.571
7.497
7.484
6.961
6.943
4.794
3.816
-0.000
O
N
OMe
4k
0.97
1.98
1.00
1.95
1.97
2.00
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

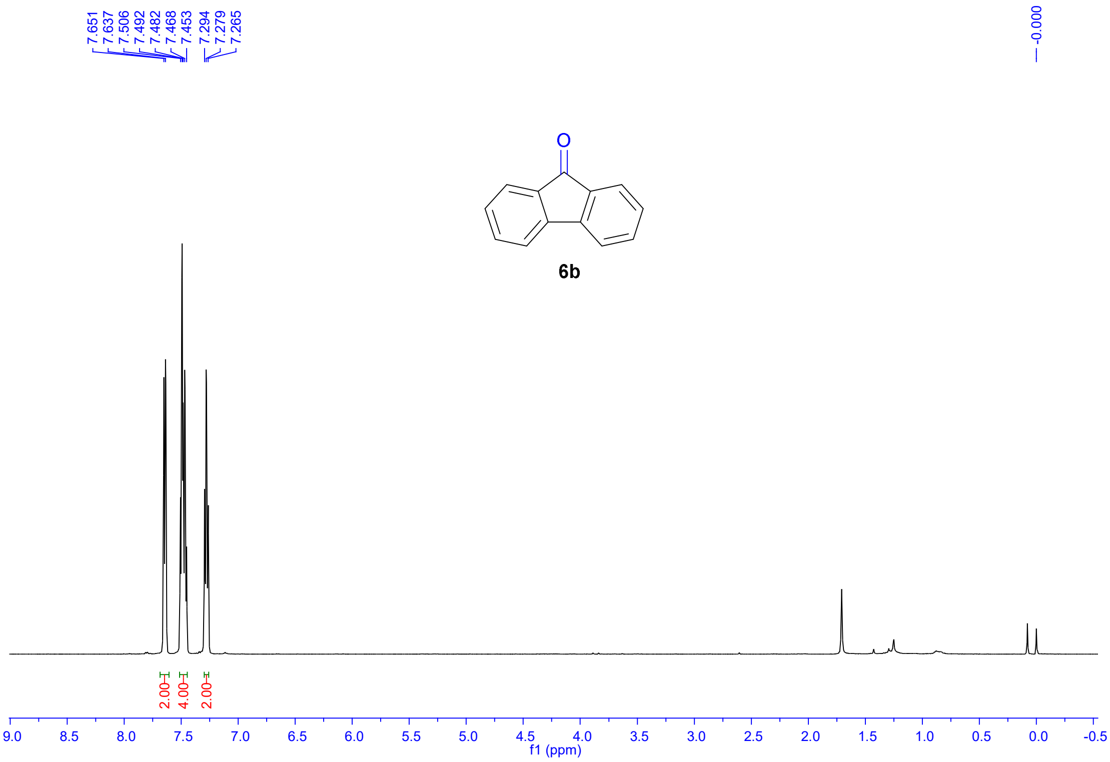

167.29
156.65
140.18
132.67
131.84
128.34
124.04
121.52
114.36
55.53
51.20
O
N
OMe
4k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

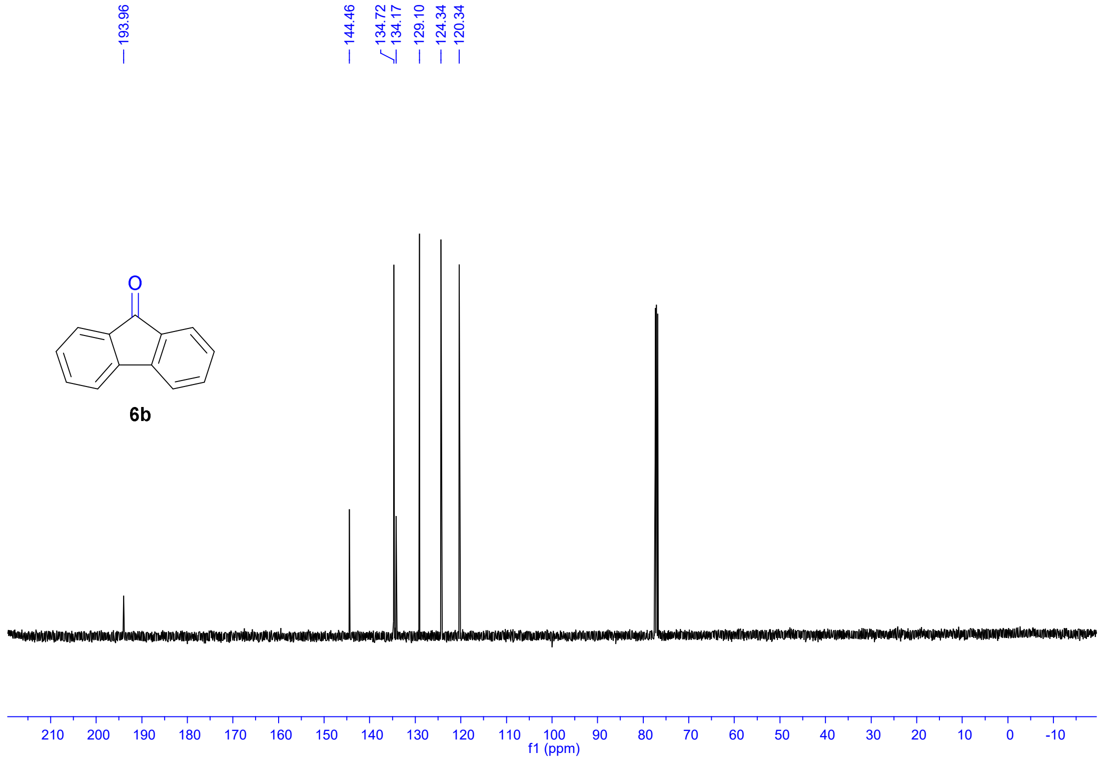

7.895
7.880
7.819
7.801
7.603
7.588
7.575
7.504
7.490
7.477
7.360
7.342
4.789
-0.000
O
N
Cl
4l
0.97
2.04
1.00
1.99
1.95
2.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

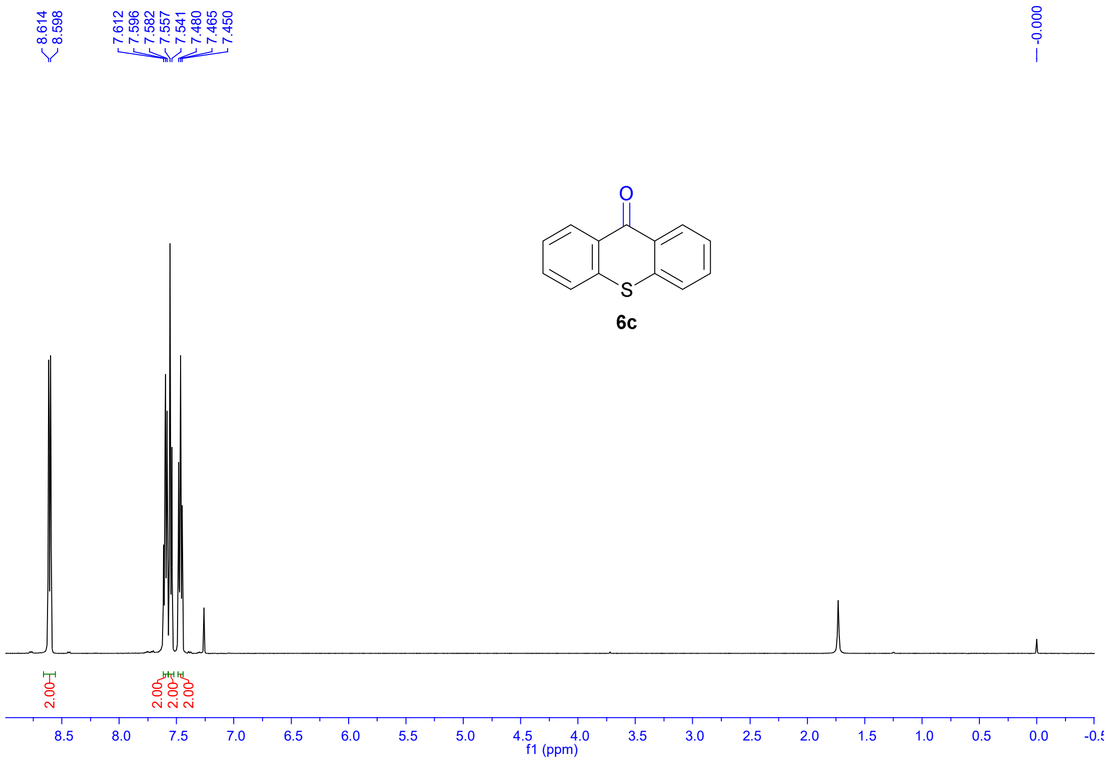

167.54
139.91
138.12
129.52
128.53
124.20
122.68
120.39
50.65
O
N
Cl
4l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

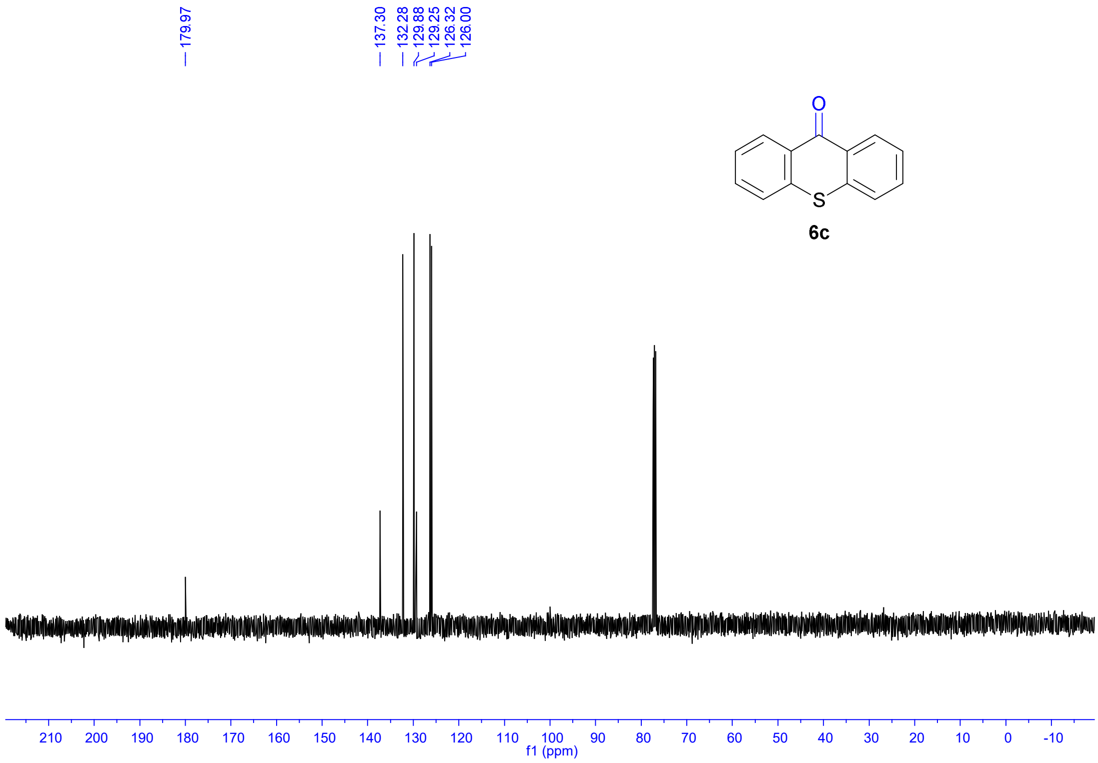

8.352
8.336
7.741
7.724
7.707
7.500
7.483
7.395
7.379
7.365
0.000
O
O
6a
2.00
2.00
2.00
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

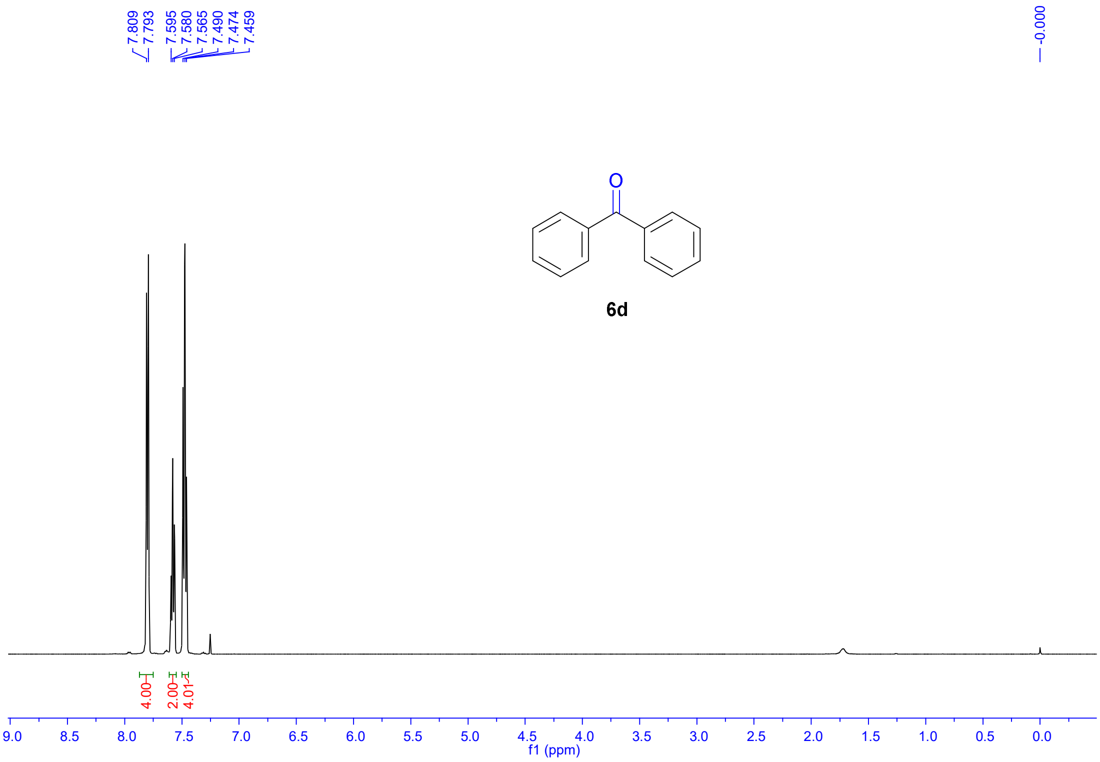

179.97
137.30
132.28
129.88
129.25
126.32
126.00
O
O
6a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

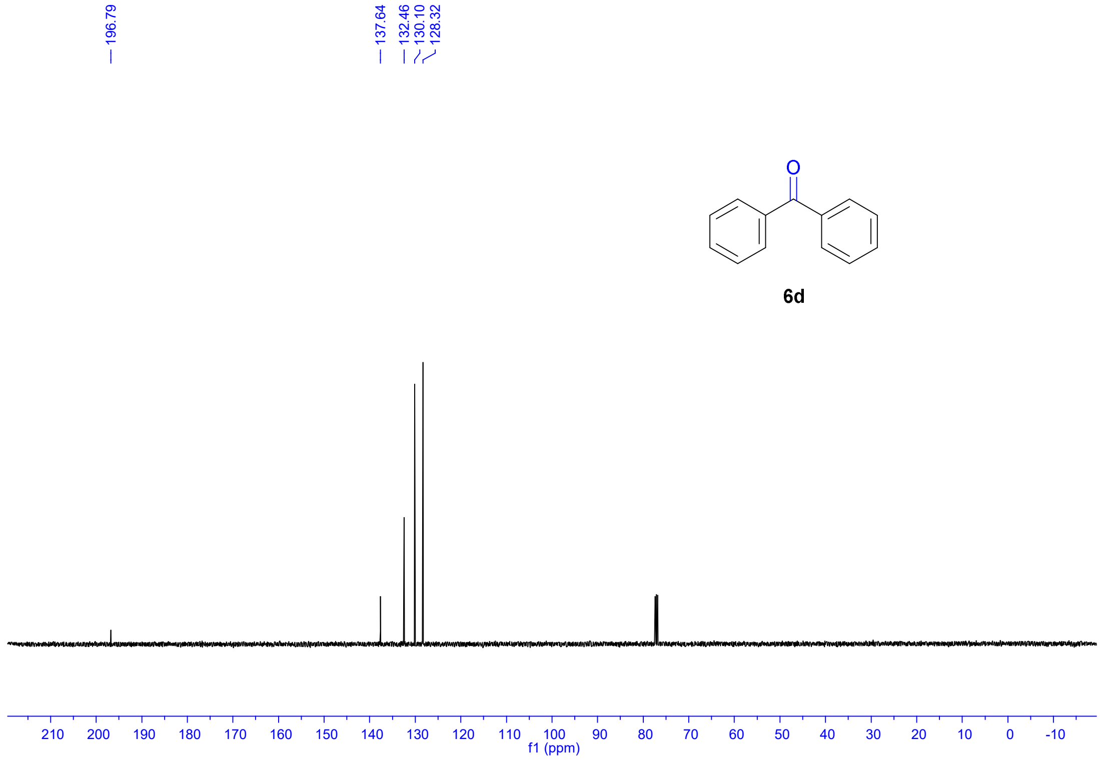

7.651
7.637
7.506
7.492
7.482
7.468
7.453
7.294
7.279
7.265
-0.000
O
6b
2.00
4.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

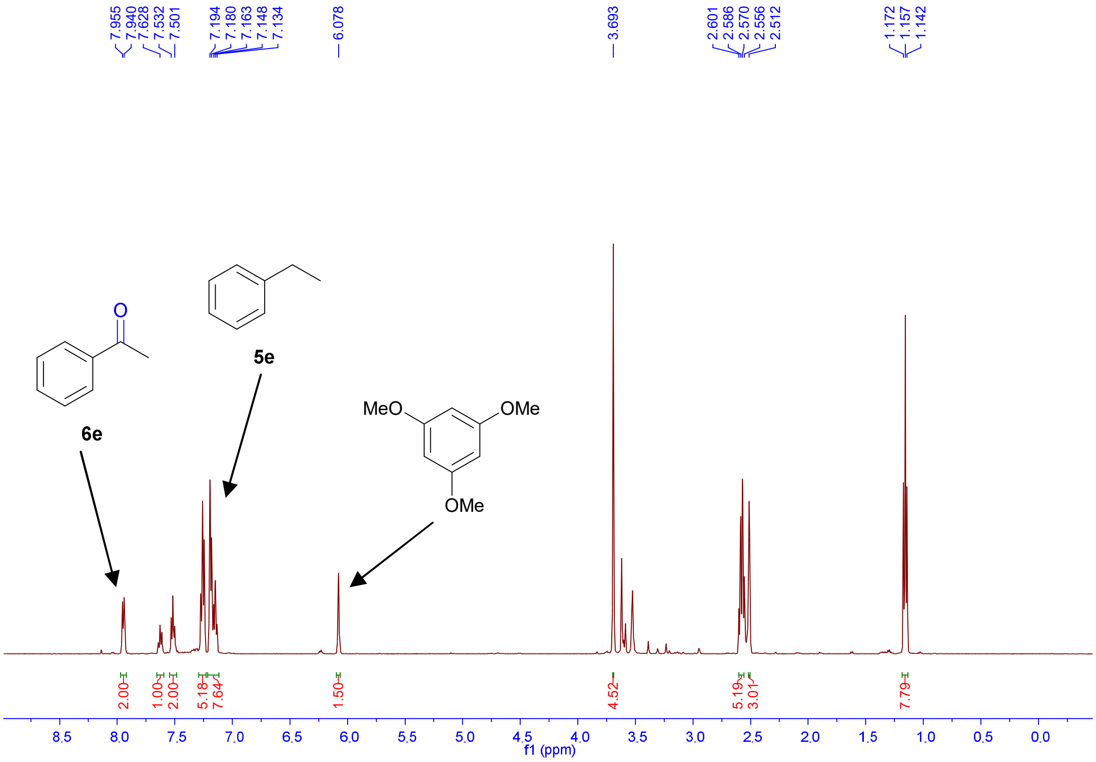

193.96
144.46
134.72
134.17
129.10
124.34
120.34
O
6b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

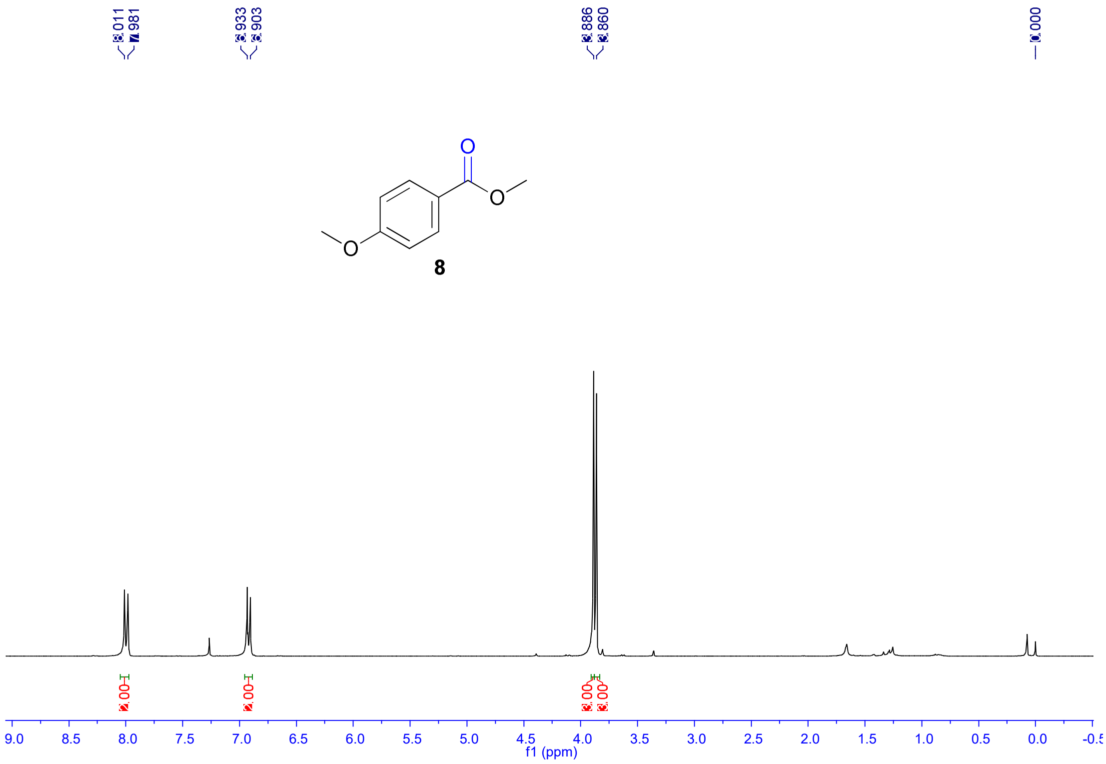

8.614
8.598
7.612
7.596
7.582
7.557
7.541
7.480
7.465
7.450
-0.000
O
S
6c
2.00
2.00
2.00
2.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

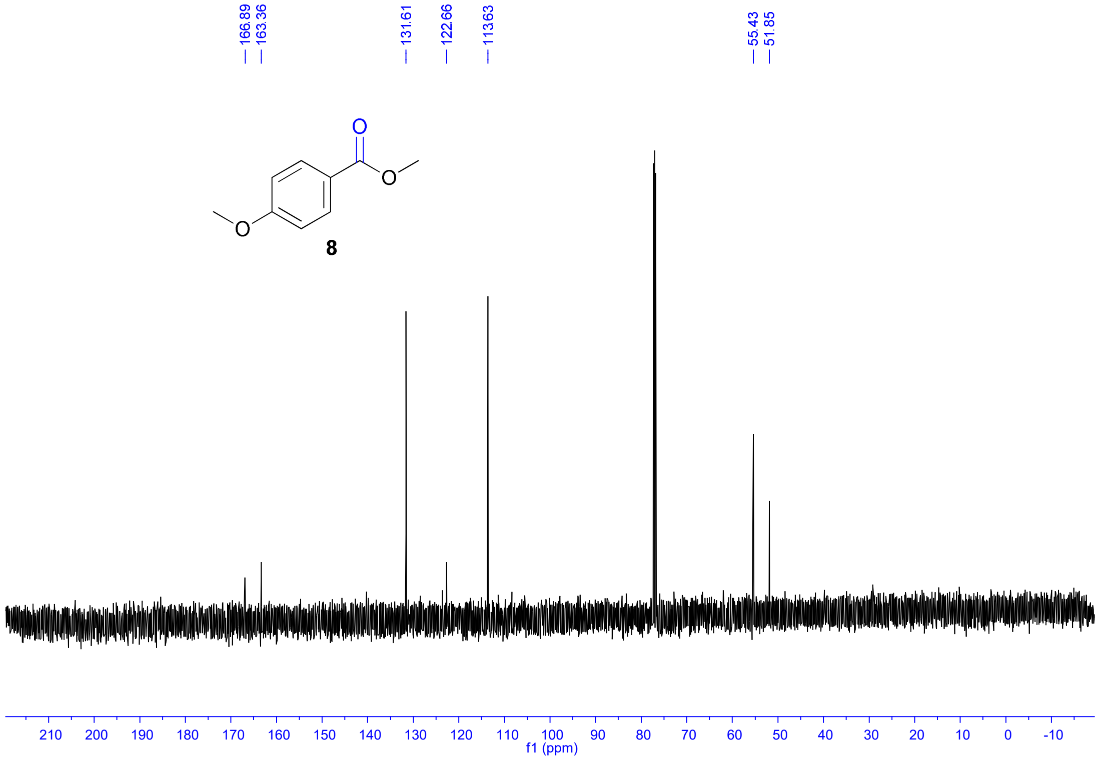

179.97
137.30
132.28
129.88
129.25
126.32
126.00
O
S
6c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

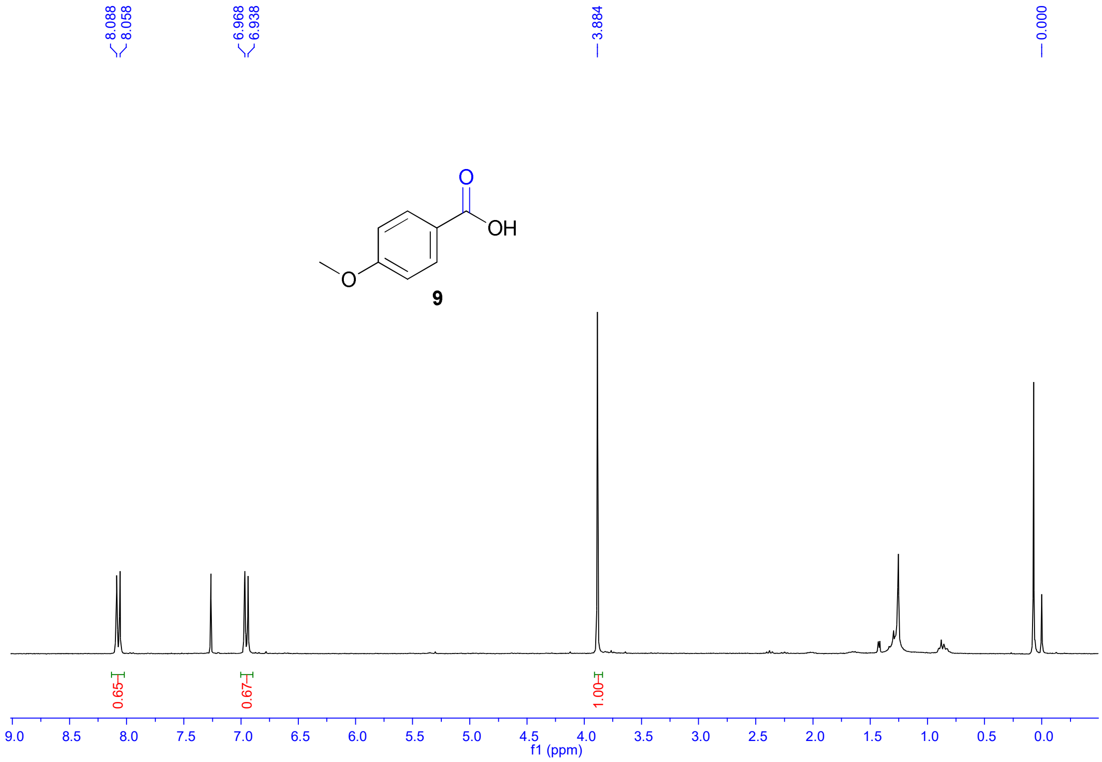

7.809
7.793
7.595
7.580
7.565
7.490
7.474
7.459
-0.000
O
6d
4.00
2.00
4.01
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

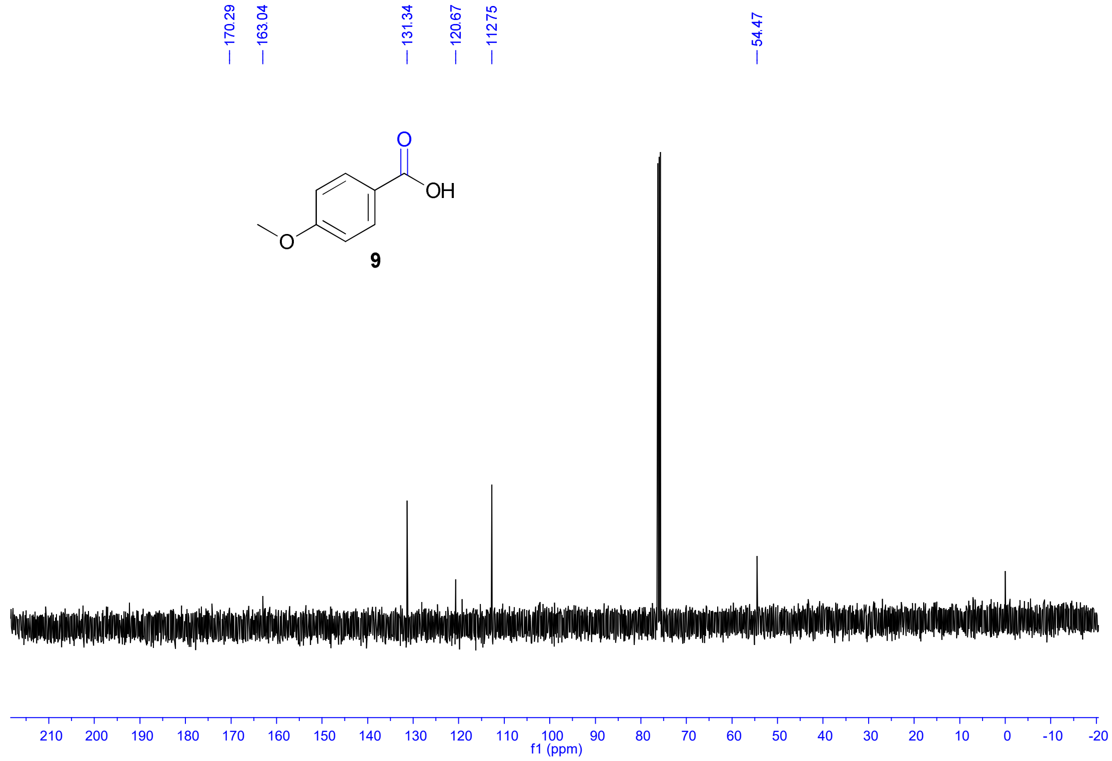

196.79
137.64
132.46
130.10
128.32
O
6d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

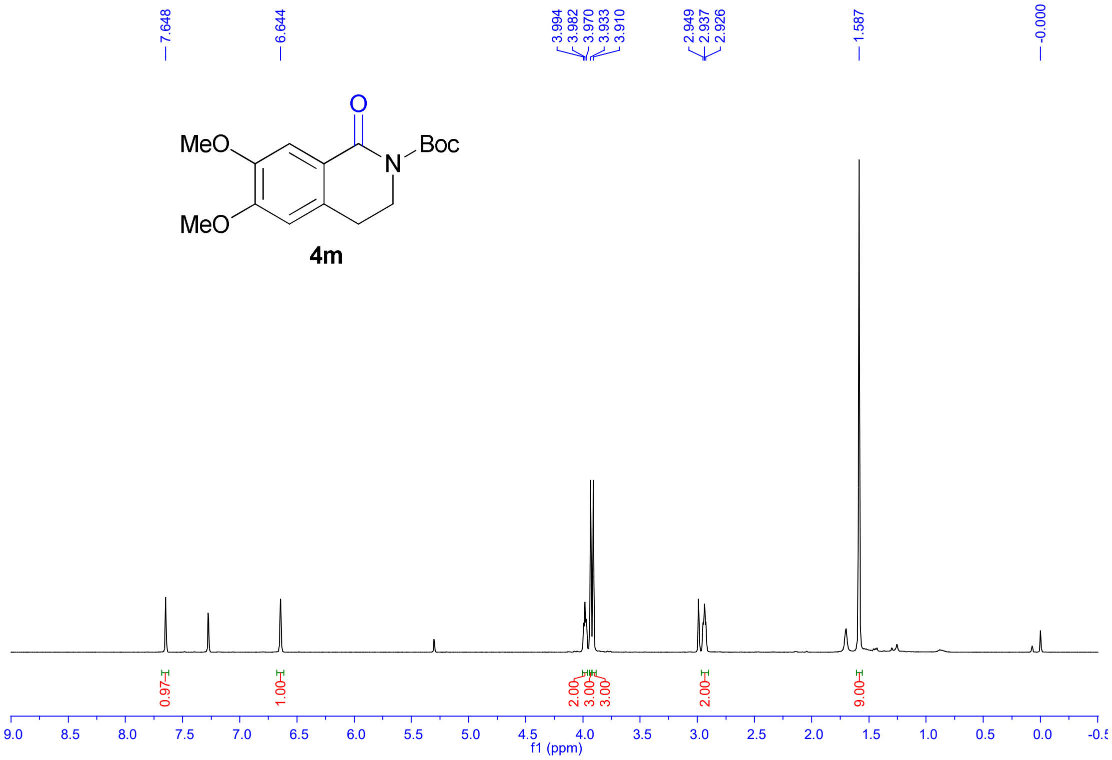

7.955
7.940
7.628
7.532
7.501
7.194
7.180
7.163
7.148
7.134
6.078
3.693
2.601
2.586
2.570
2.556
2.512
1.172
1.157
1.142
O
5e
6e
MeO
OMe
OMe
2.00
1.00
2.00
5.18
7.64
1.50
4.52
5.19
3.01
7.79
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

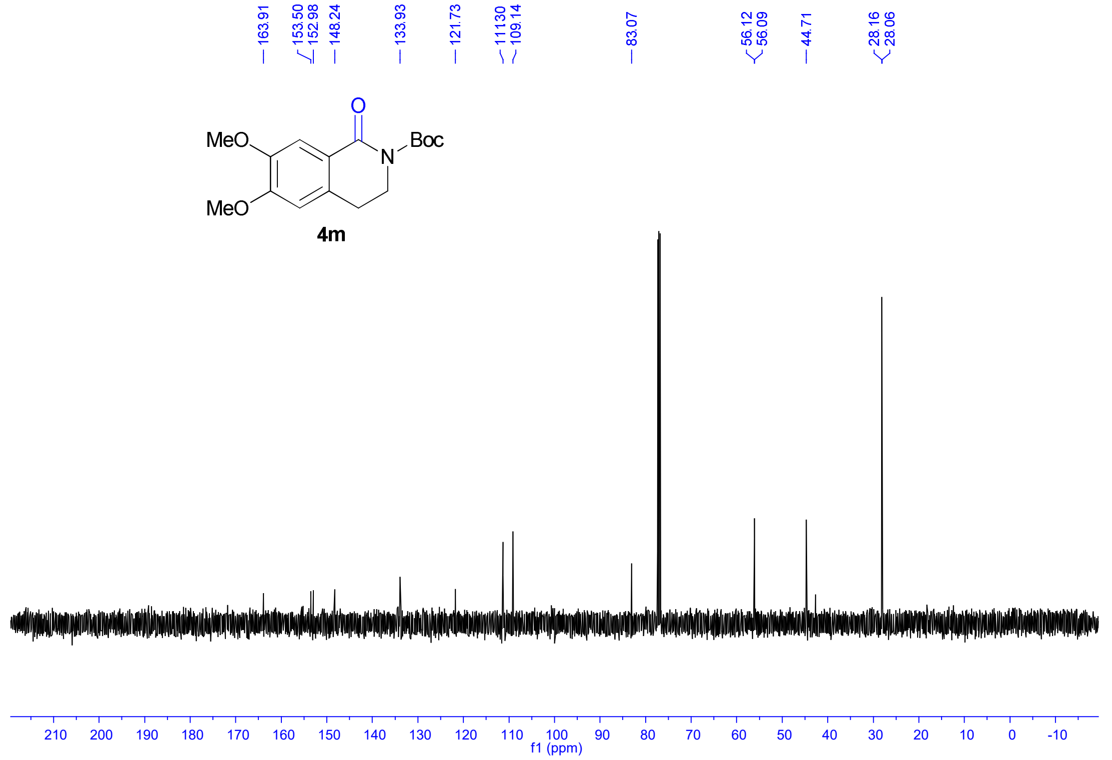

8.011
7.981
6.933
6.903
3.886
3.860
0.000
O
O
O
8
2.00
2.00
3.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

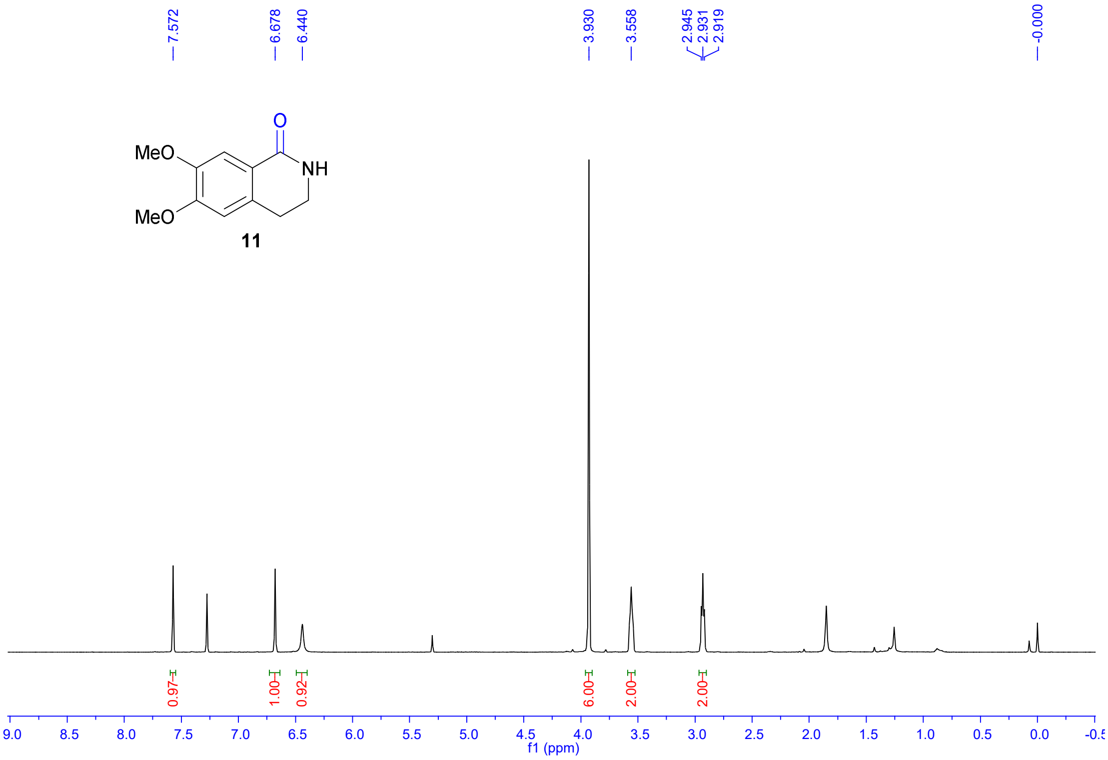

166.89
163.36
131.61
122.66
113.63
55.43
51.85
O
O
O
8
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

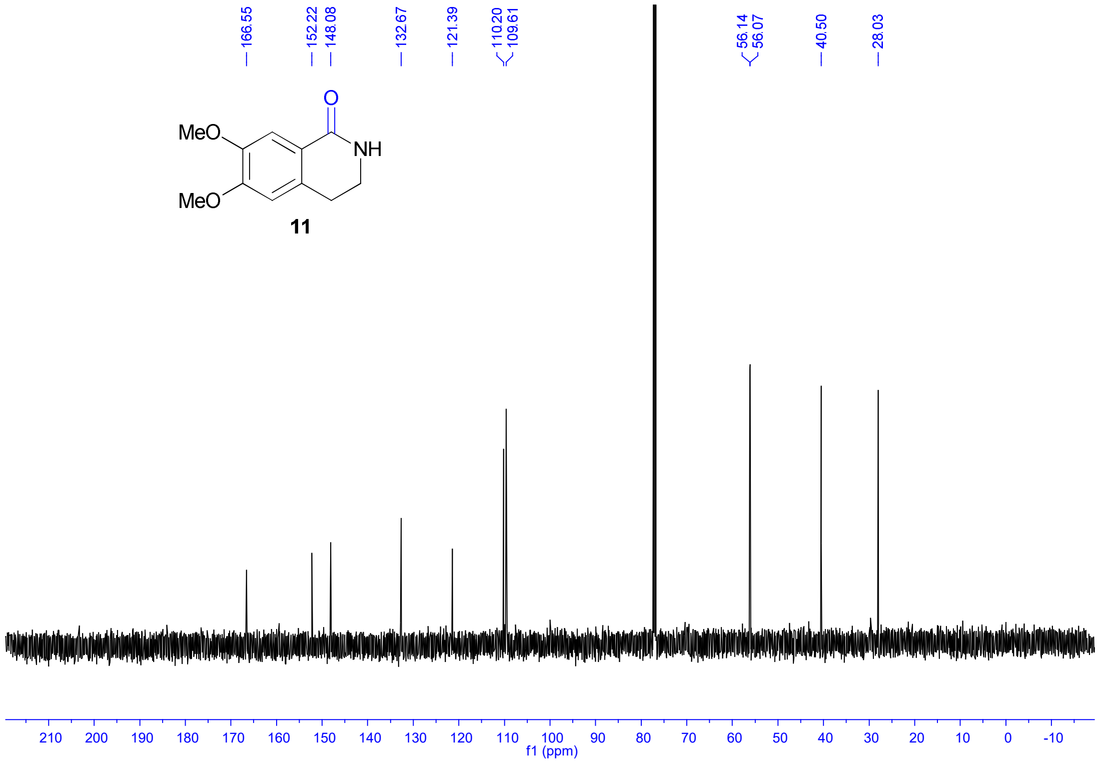

8.088
8.058
6.968
6.938
3.884
0.000
O
OH
O
9
0.65
0.67
1.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

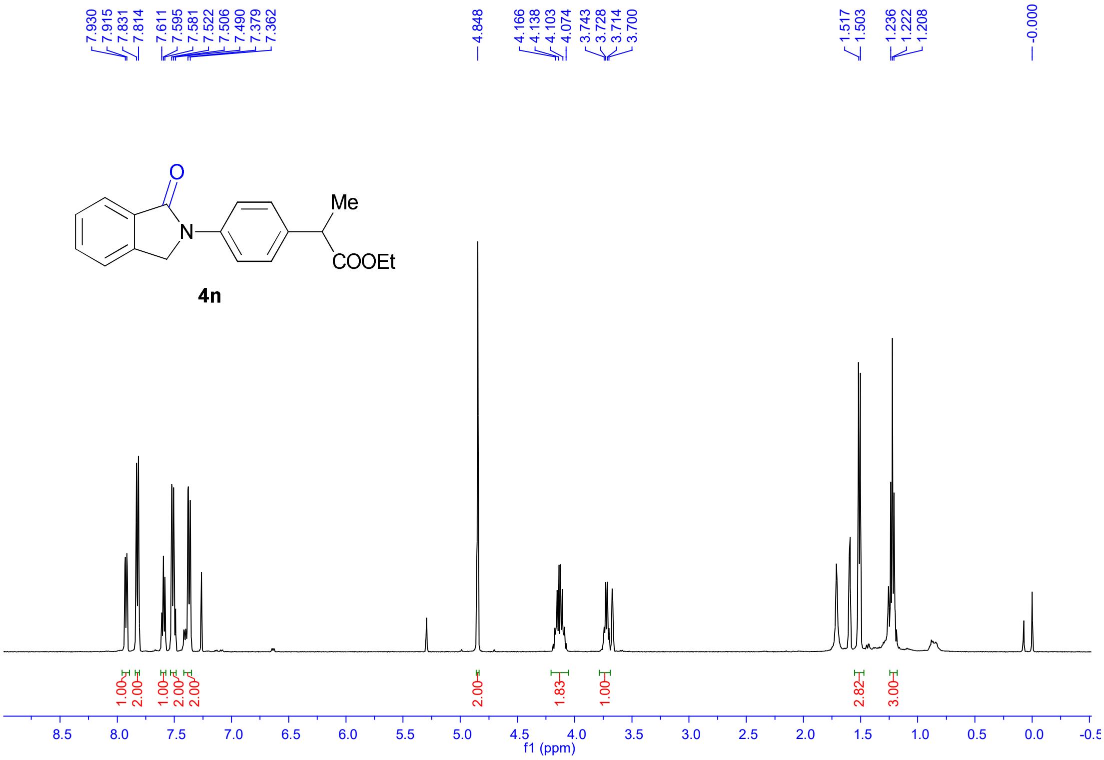

170.29
163.04
131.34
120.67
112.75
54.47
O
OH
O
9
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

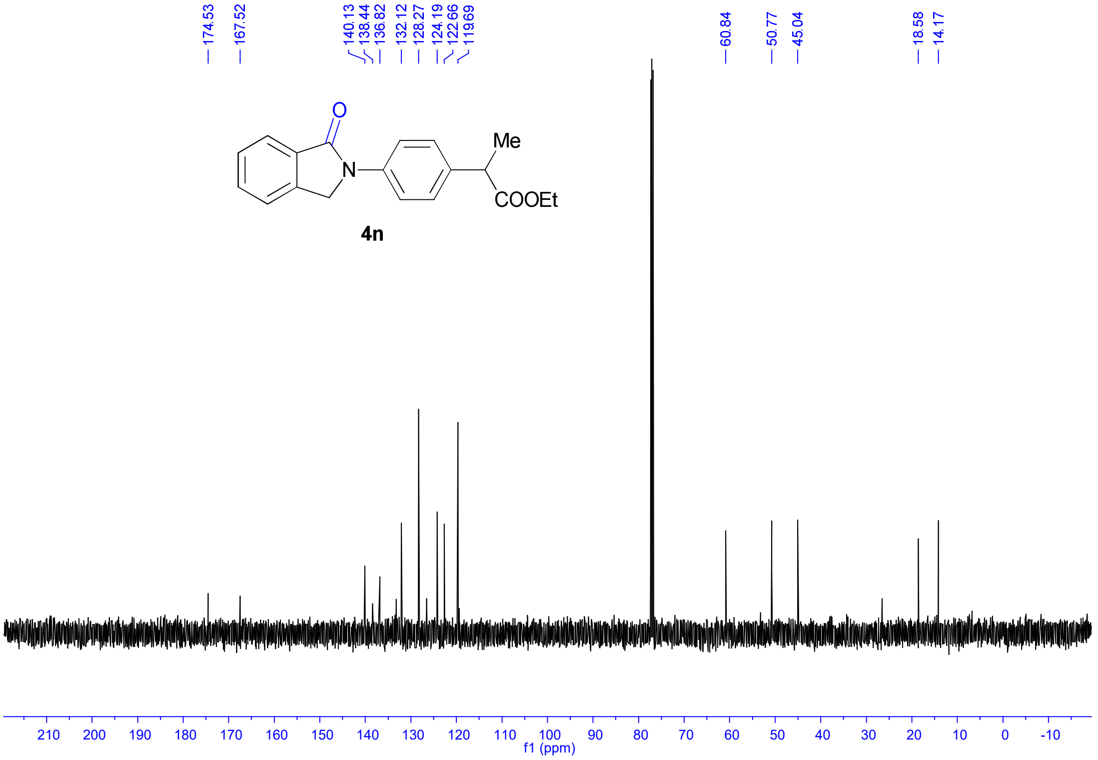

7.648
6.644
3.994
3.982
3.970
3.933
3.910
2.949
2.937
2.926
1.587
-0.000
MeO
MeO
O
N
Boc
4m
0.97
1.00
2.00
3.00
3.00
2.00
9.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

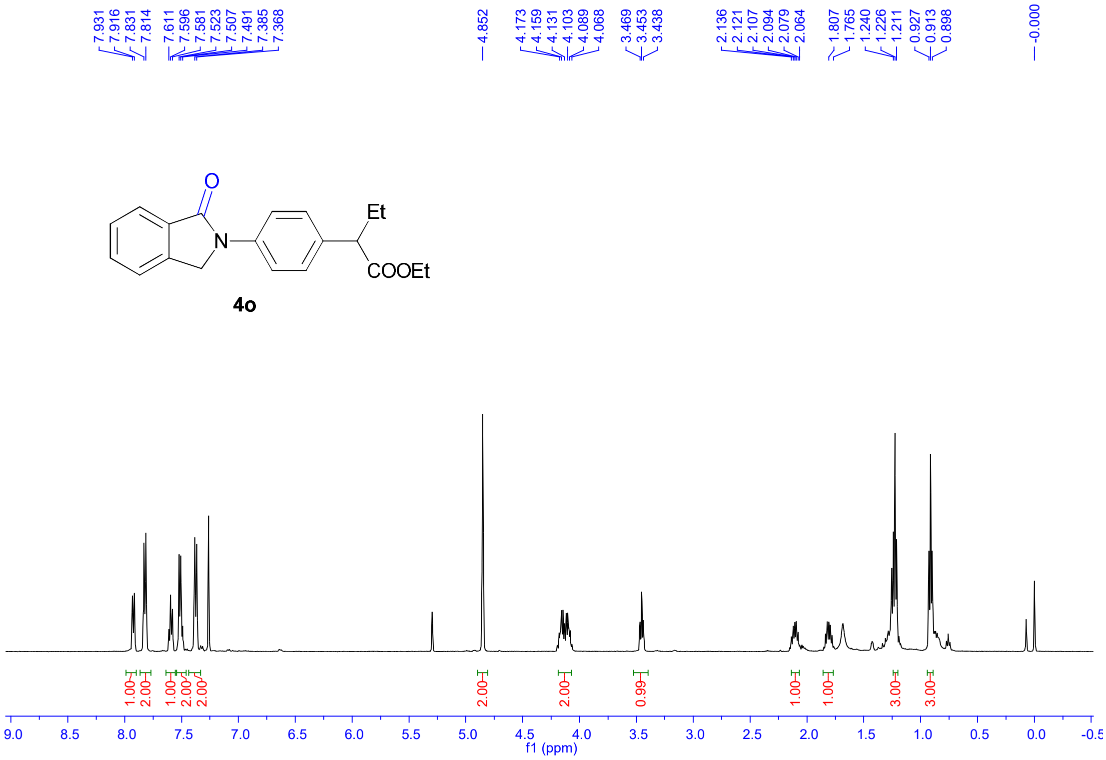

163.91
153.50
152.98
148.24
133.93
121.73
11130
109.14
83.07
56.12
56.09
44.71
28.16
28.06
MeO
MeO
O
N
Boc
4m
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

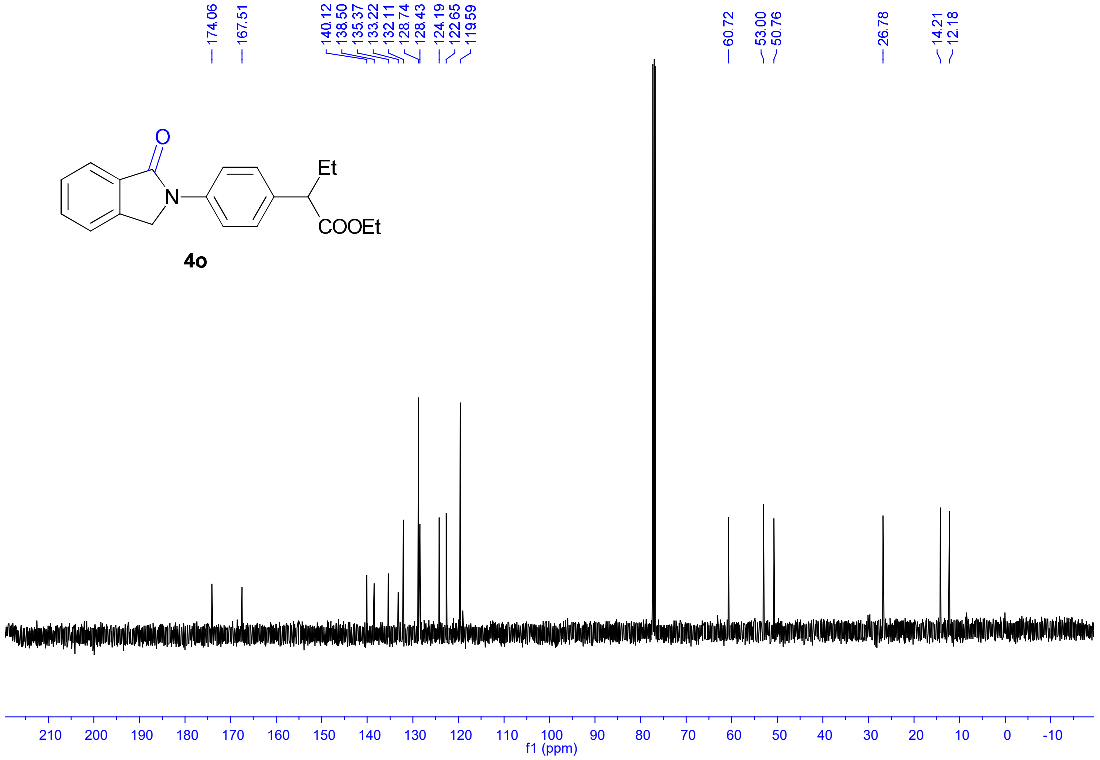

7.572
6.678
6.440
3.930
3.558
2.945
2.931
2.919
-0.000
MeO
MeO
O
NH
11
0.97
1.00
0.92
6.00
2.00
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

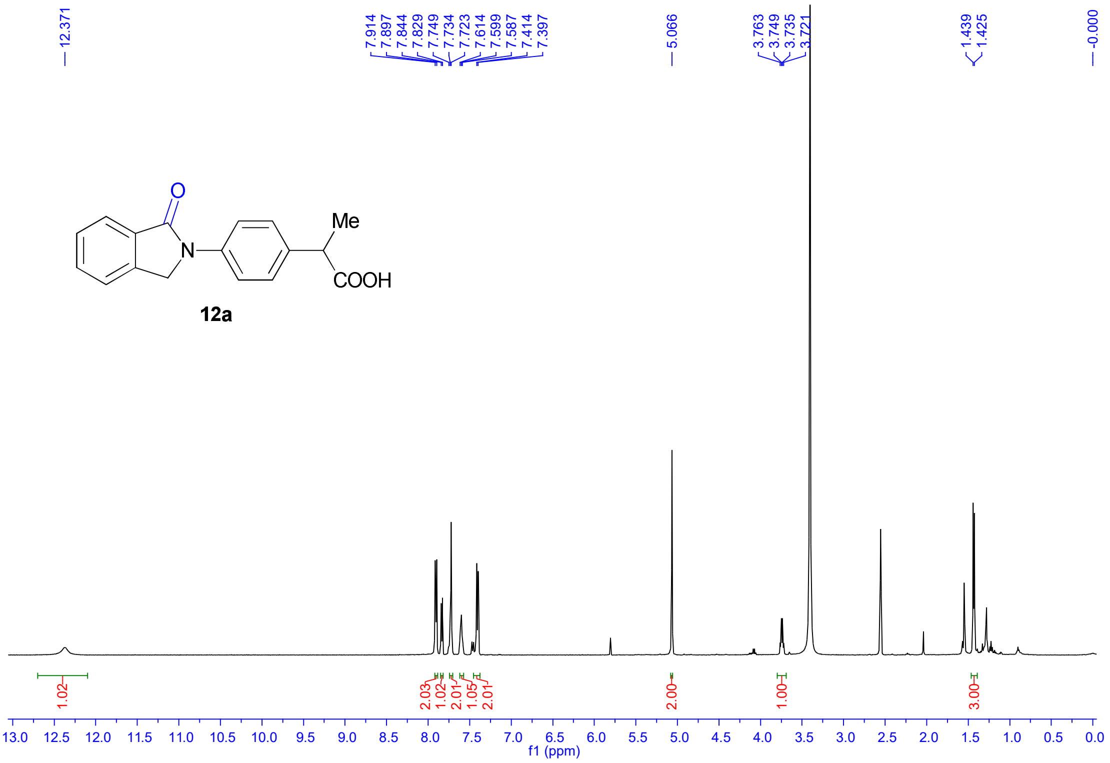

166.55
152.22
148.08
132.67
121.39
110.20
109.61
56.14
56.07
40.50
28.03
MeO
MeO
O
NH
11
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

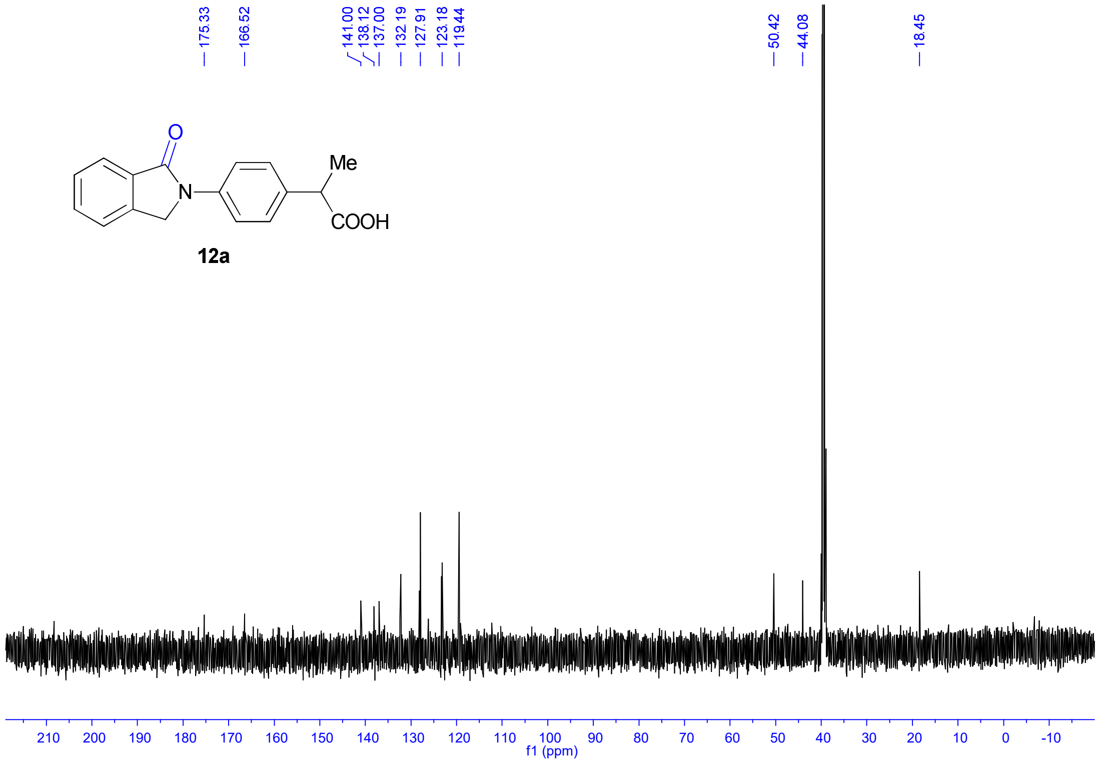

7.930
7.915
7.831
7.814
7.611
7.595
7.581
7.522
7.506
7.490
7.379
7.362
4.848
4.166
4.138
4.103
4.074
3.743
3.728
3.714
3.700
1.517
1.503
1.236
1.222
1.208
-0.000
O
N
Me
COOEt
4n
1.00
2.00
1.00
2.00
2.00
2.00
1.83
1.00
2.82
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

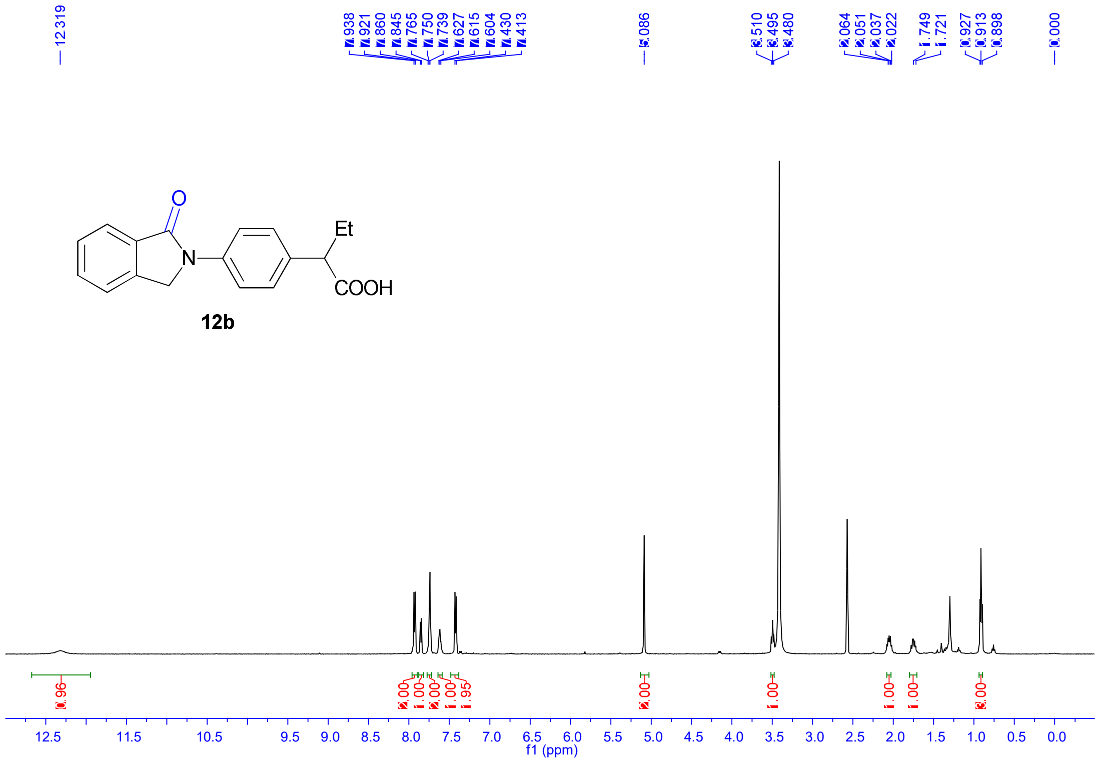

174.53
167.52
140.13
138.44
136.82
132.12
128.27
124.19
122.66
119.69
60.84
50.77
45.04
18.58
14.17
O
N
Me
COOEt
4n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

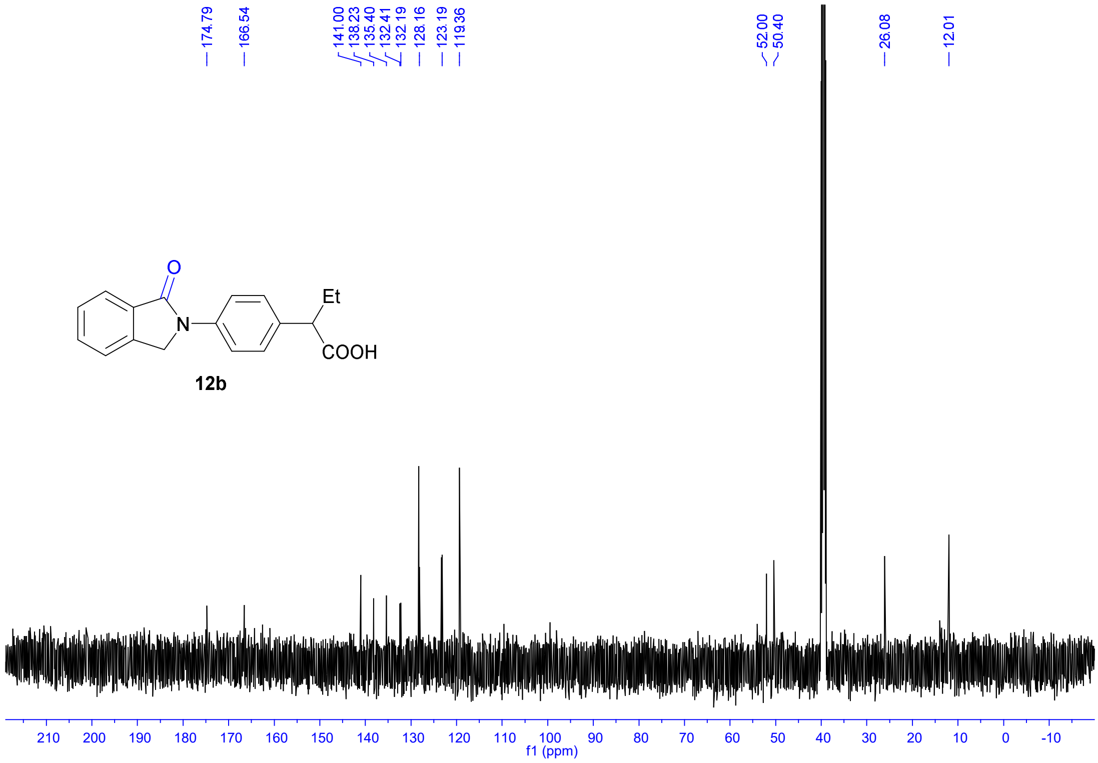

7.931
7.916
7.831
7.814
7.611
7.596
7.581
7.523
7.507
7.491
7.385
7.368
4.852
4.173
4.159
4.131
4.103
4.089
4.068
3.469
3.453
3.438
2.136
2.121
2.107
2.094
2.079
2.064
1.807
1.765
1.240
1.226
1.211
0.927
0.913
0.898
-0.000
O
N
Et
COOEt
4o
1.00
2.00
1.00
2.00
2.00
2.00
2.00
0.99
1.00
1.00
3.00
3.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


174.06
167.51
140.12
138.50
135.37
133.22
132.11
128.74
128.43
124.19
122.65
119.59
60.72
53.00
50.76
26.78
14.21
12.18
O
N
Et
COOEt
4o
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


12.371
7.914
7.897
7.844
7.829
7.749
7.734
7.723
7.614
7.599
7.587
7.414
7.397
5.066
3.763
3.749
3.735
3.721
1.439
1.425
-0.000
O
N
Me
COOH
12a
1.02
2.03
1.02
2.01
1.05
2.01
2.00
1.00
3.00
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


175.33
166.52
141.00
138.12
137.00
132.19
127.91
123.18
119.44
50.42
44.08
18.45
O
N
Me
COOH
12a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


12.319
7.938
7.921
7.860
7.845
7.765
7.750
7.739
7.627
7.615
7.604
7.430
7.413
5.086
3.510
3.495
3.480
2.064
2.051
2.037
2.022
1.749
1.721
0.927
0.913
0.898
0.000
O
N
Et
COOH
12b
0.96
2.00
1.00
2.00
1.00
1.95
2.00
1.00
1.00
1.00
3.00
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


174.79
166.54
141.00
138.23
135.40
132.41
132.19
128.16
123.19
11936
52.00
50.40
26.08
12.01
O
N
Et
COOH
12b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)