Highly Efficient Synthesis of Benzodioxins with a 2-Site Quaternary Carbon Structure by Secondary Amine-Catalyzed Dual Michael Cascade Reactions

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1. General Information

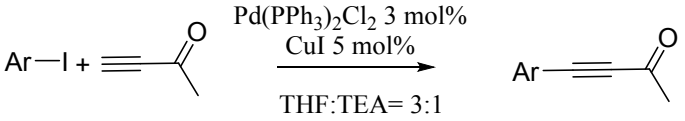
Unless otherwise noted, all reactions were carried out open to air, in the oven-dried glass tubes with magnetic stirring. All substituted salicylic acids and solvents were purchased from commercial suppliers. Analytical thin layer chromatography (TLC) was performed using Silica Gel60 F254 aluminum plate (Merck), and visualized with UV light (254 nm). The pure products were obtained by means of column chromatography which was performed on silica gel (200~300 mesh, Qingdao Haiyang Chemical Co., Ltd).

2. Instrumentation

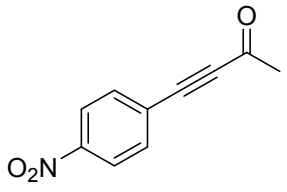
The NMR spectra were recorded on a Bruker Avance Ⅲ 400 spectrometer and tetramethylsilane (TMS) was selected as the internal standard. Chemical shifts were reported in ppm from internal TMS (δ), all coupling constants (*J* values) were reported in Hertz (Hz). LC-MS data were collected on a SHIMADZU LC MS machine (ESI). High resolution mass spectra (HR-MS) were obtained on a SHIMADZU LCMS-IT-TOF Mass Spectrometer.

3. Synthetic Procedures

3.1 General procedure for the synthesis of substituted 3-butyn-2-ones (Method A):[1]



Prior to use, tetrahydrofuran (THF), and triethylamine (TEA) were degassed by bubbling argon for at least 30 minutes. An oven-dried flask (100 mL) charged with a magnetic stirring bar was added aryl iodides (ArI, 2 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%) and CuI (5 mol%), then dissolved with THF (20 mL), followed with 10 mL TEA. The mixture was recharged with argon for three times, add 3-butyn-2-one (1.2 equiv) in dropwise. The resulting black mixture was stirred overnight at RT. While reaction was finished, it was diluted with 30 mL of ethyl acetate and washed with brine (30 mL × 3). The organic layers were combined and then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Petroleum Ether / EtOAc).



:

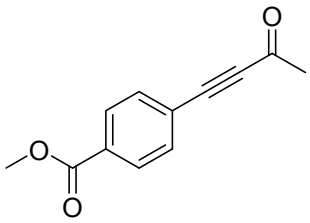
4-(4-nitrophenyl)but-3-yn-2-one :

Pale yellow solid, 64% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 – 8.22 (m, 2H), 7.77 – 7.70 (m, 2H), 2.49 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.3, 148.5, 133.8, 126.7. 123.8, 91.2, 86.4, 32.6.

Spectral data matched those reported in the literature.[2]



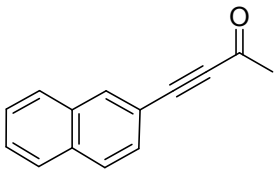
methyl 4-(3-oxobut-1-yn-1-yl) benzoate:

Colorless oil, 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 3.95 (s, 1H), 2.48 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.3, 166.1, 132.8, 131.8, 129.7, 124.4, 89.8, 88.5, 52.5, 32.8.

LC-MS(ESI+) Calcd for [$C_{12}H_{10}O_3$]: m/z 202.2, found $[M+H]^+$: 203.1



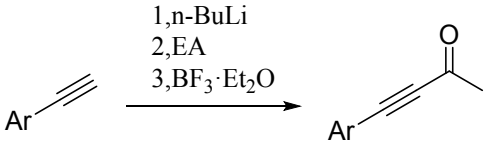
4-(naphthalen-2-yl)but-3-yn-2-one:

Colorless oil, 72% yield.

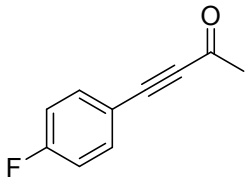
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (m, 1H), 7.91 – 7.82 (m, 3H), 7.62 – 7.49 (m, 3H), 2.48 (s, 3H).

Spectral data matched those reported in the literature.[3]

3.2 General procedure for the synthesis of substituted 3-butyn-2-ones (Method B):[4]



Ethynylbenzene (3 mmol) was dissolved in freshly degassed THF (2 mL), and the solution was cooled to -78 °C. To the solution, n-BuLi (2.5 M, 1.2 mL, 3 mmol) was added. After being stirred for 1 h at -78 °C, ethyl acetate (EA, 1 mL, 10 mmol) dissolved in THF (2 mL) was added in dropwise. After half an hour stirring, 0.5 mL $BF_3{\cdot}Et_2O$ was added subsequently, and the reaction was kept under -78 °C for 1 hour. The reaction was quenched by sat. NH_4Cl aq., and the solvent was removed under a reduced pressure. The residue was purified by column chromatography (Petroleum ether : EA = 1: 3) to afford the desired ynone.

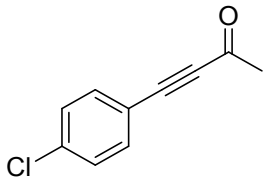


4-(4-fluorophenyl)but-3-yn-2-one:

Colorless oil, 62% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 – 7.53 (m, 2 H), 7.12 – 7.03 (m, 2H), 2.44 (s, 3H,).

Spectral data matched those reported in the literature.[5]

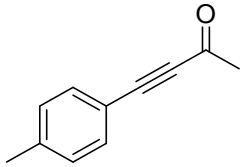


4-(4-chlorophenyl)but-3-yn-2-one:

Light yellow oil, 46% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.36 (m, 2H), 2.45 (s, 3H).

Spectral data matched those reported in the literature.[5]

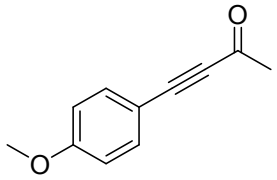


4-(p-tolyl)but-3-yn-2-one:

Colorless oil, 33% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.19 (m, 2 H), 2.44 (s, 3H), 2.38 (s, 3H).

Spectral data matched those reported in the literature.[5]

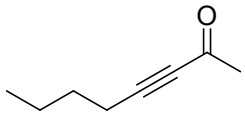


4-(4-methoxyphenyl)but-3-yn-2-one:

Yellow solid, 24% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (m, 2H), 6.88 (m, 2H), 3.82 (s, 3H), 2.41 (s, 3H).

Spectral data matched those reported in the literature.[5]



oct-3-yn-2-one:

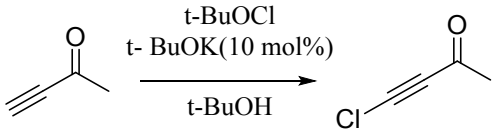
Colorless oil, 32% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 – 2.33 (m, 2H), 2.31 (s, 3H), 1.60 – 1.52 (m, 2H), 1.43 (ddd, J = 9.3, 7.0, 3.7 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.9, 94.1, 81.4, 32.8, 29.7, 21.9, 18.6, 13.5.

LC-MS (ESI+) Calcd for [$C_8H_{12}O$]: m/z 124.1, found $[M+H]^+$: 125.1.

3.3 Procedure for the synthesis of 4-chloro-3-butyn-2-one:[6]



To a stirred solution of 3-butyn-2-one (136.06 mg, 2 mmol) and t-BuOCl (1 equiv.) in 20 mL t-BuOH, t-BuOK(10 mol%) was added in two equal portions giving each time a slightly exothermic reaction. The mixture was stirred for 2 hours, and then was purified by column chromatograph to afford the desired 4-chloro-3-butyn-2-one.

4-chlorobut-3-yn-2-one:

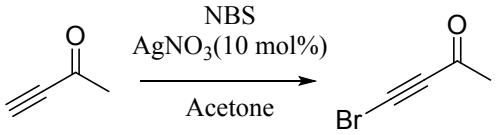
colorless solid, 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H).

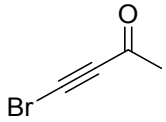
^{13}C NMR (101 MHz, $CDCl_3$): δ 182.9, 80.9, 67.8, 31.8.

LC-MS (ESI+) Calcd for [C_4H_3ClO]: m/z 102.5, found $[M+H]^+$: 103.5.

3.4 Procedure for the synthesis of 4-bromobut-3-yn-2-one:[6]



In a 100 mL bottom flask is placed 5 mmol of 3-butyn-2-one in 10 mL of acetone, stirred under room temperature and added 0.5 mmol of $AgNO_3$ in portion. After 5 minutes, 5.5 mmol of NBS (1.1 equiv.) was added and the mixture was stirred for 3h, filtered by Celite and washed with acetone in 3 times, and the solvent was removed *in vacuo*, the residue was purified by column chromatography.



4-bromobut-3-yn-2-one:

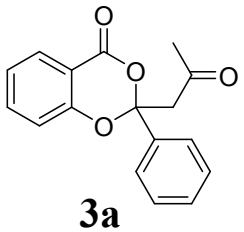
Yellow liquid, 52% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H).

Spectral data matched those reported in the literature.[6]

3.5 General procedure for the synthesis of substituted 4*H*-benzo[*d*][1,3]dioxin-4-ones:

To a solution of substituted salicylic acid (0.3 mmol), substituted 3-butyn-2-one (0.3 mmol), and DCM (2 mL), after stirred for 5 minutes, 5 μL (0.06 mmol) of morpholine was added. The reaction was kept for overnight. After the reaction finished, the solution was concentrated *in vacuo*, and the crude product was purified by column chromatography (EA: Hexane = 1 / 3) to afford the terminal product.



3a

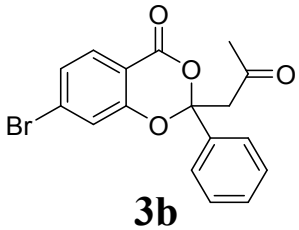
2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3a) :

Yellow oil, 91 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.52 (ddd, *J* = 7.6, 7.1, 1.5 Hz, 3H), 7.32 (ddd, *J* = 9.7, 5.5, 2.4 Hz, 3H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.07 – 6.99 (m, 1H), 3.38 – 3.20 (m, 2H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.4, 160.5, 155.9, 138.6, 136.7, 129.8, 129.5, 128.8, 126.3, 123.2, 117.4, 114.6, 105.6, 55.3, 31.9.

HR-MS (ESI): $C_{17}H_{14}O_4$, $[M+Na]^+$, Calcd.: 305.0787, Found: 305.0784.



3b

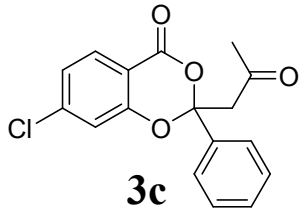
7-bromo-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3b) :

Yellow oil, 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.39 – 7.32 (m, 4H), 7.19 (dd, *J* = 8.4, 1.7 Hz, 1H), 3.32 – 3.23(m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 159.8, 156.2, 138.1, 131.1, 130.9, 129.7, 129.0, 126.9, 126.2, 120.7, 113.5, 106.1, 55.0, 31.9.

HR-MS (ESI): $C_{17}H_{13}O_4Br$, $[M+Na]^+$, Calcd.: 382.9889, Found: 382.9884.



3c

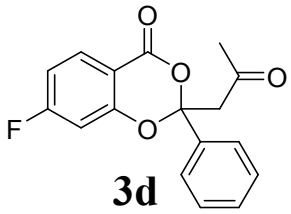
7-chloro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3c) :

Yellow oil, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.39 – 7.31 (m, 3H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.03 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.33 – 3.22 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 159.7, 156.4, 142.7, 138.1, 131.0, 129.7, 129.0, 126.2, 124.0, 117.8, 113.1, 106.1, 55.0, 31.8.

HR-MS (ESI): $C_{17}H_{13}O_4Cl$, $[M+Na]^+$, Calcd.: 339.0395, Found: 339.0389.



3d

7-fluoro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3d) :

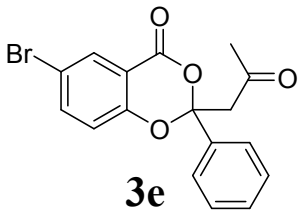
Colorless oil, 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.39 – 7.30 (m, 3H), 6.83 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.76 (td, *J* = 8.5, 2.3 Hz, 1H), 3.33 – 3.23 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.0, 167.7 (d, *J* = 258.3 Hz), 159.6, 157.6 (d, *J* = 13.5 Hz), 138.2, 132.3 (d, *J* = 11.3 Hz), 129.7, 129.0, 126.2, 111.5 (d, *J* = 22.7 Hz), 111.1 (d, *J* = 2.8 Hz), 106.1, 104.9 (d, *J* = 25.4 Hz), 55.0, 31.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –97.98.

HR-MS (ESI): $C_{17}H_{13}O_4F$, $[M+Na]^+$, Calcd. : 323.0690, Found: 323.0688.



3e

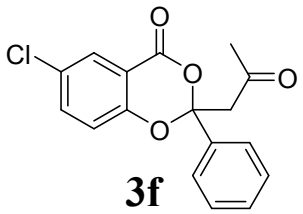
6-bromo-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3e) :

Yellow oil, 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 2.4 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.34 (dd, *J* = 5.2, 2.0 Hz, 3H), 7.03 (d, *J* = 8.8 Hz, 1H), 3.46 – 3.13 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.0, 159.2, 154.9, 139.5, 138.1, 132.3, 129.8, 129.0, 126.3, 119.3, 116.1, 115.7, 106.0, 55.0, 31.9.

HR-MS (ESI): $C_{17}H_{13}O_4Br$, $[M+Na]^+$, Calcd.: 382.9889, Found: 382.9892.



3f

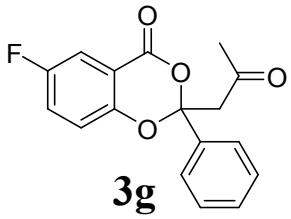
6-chloro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3f) :

Light yellow oil, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2.5 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.34 (dd, *J* = 8.4, 2.9 Hz, 3H), 7.09 (d, *J* = 8.8 Hz, 1H), 3.36 – 3.21 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.0, 159.4, 154.4, 138.1, 136.6, 129.7, 129.3, 129.0, 128.6, 126.3, 119.0, 115.7, 106.0, 55.0, 31.9.

HR-MS (ESI): $C_{17}H_{13}O_4Cl$, $[M+Na]^+$, Calcd: 339.0395, Found: 339.0397.



3g

6-fluoro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3g) :

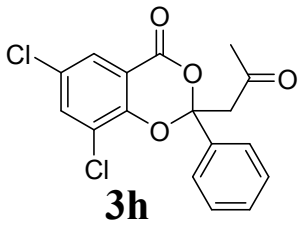
Colorless oil, 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.7, 2.9 Hz, 3H), 7.33 (td, *J* = 4.8, 2.5 Hz, 3H), 7.25 (s, 1H), 7.11 (dd, *J* = 9.0, 4.1 Hz, 1H), 3.35 – 3.22 (m, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.1, 159.6 (d, *J* = 2.5 Hz), 157.7 (d, *J* = 244.4 Hz), 152.1 (d, *J* = 2.2 Hz), 138.2, 129.7, 128.9, 126.3, 124.1 (d, *J* = 24.3 Hz), 119.1 (d, *J* = 7.5 Hz), 115.5 (d, *J* = 24.6 Hz), 115.4 (d, *J* = 8.3 Hz), 106.0, 55.1, 31.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ –117.92.

HR-MS (ESI): $C_{17}H_{13}O_4F$, $[M+Na]^+$, Calcd: 323.0690, Found: 323.0680.



3h

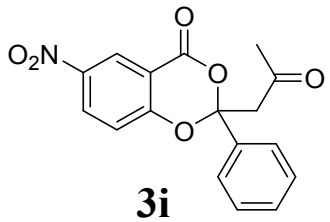
6,8-dichloro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3h) :

Brightly yellow solid, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.91 (m, 2H), 7.88 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 7.6, 5.0 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 2H), 3.82 – 3.77 (d, *J* =16 Hz, 1H), 3.68 – 3.62 (d, *J* = 16 Hz, 1H),1.96 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.50, 158.24, 150.23, 136.82, 136.28, 133.78, 128.75, 128.50, 128.17, 127.57, 123.79, 115.46, 107.07, 45.84, 24.25.

HR-MS (ESI): $C_{17}H_{12}O_4Cl_2$, $[M+Na]^+$, Calcd.: 373.0005, Found: 373.0007.



3i

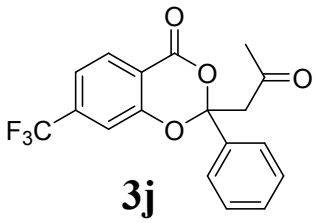
6-nitro-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3i) :

Yellow oil, 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, *J* = 2.7 Hz, 1H), 8.43 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.12 (d, *J* = 9.1 Hz, 1H), 3.83 – 3.79 (d, *J* = 16 Hz, 1H), 3.71 – 3.65 (d, *J* = 16 Hz, 1H), 1.99 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.3, 159.7, 158.1, 143.0, 136.7, 133.9, 131.4, 128.9, 128.4, 126.0, 118.8, 113.3, 107.2, 45.8, 24.5.

HR-MS (ESI): $C_{17}H_{13}NO_6$, $[M+Na]^+$, Calcd.: 350.0635, Found: 350.0627.



3j

2-(2-oxopropyl)-2-phenyl-7-(trifluoromethyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3j) :

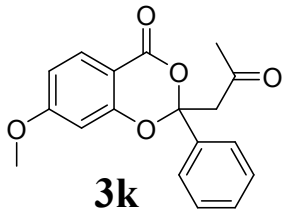
Colorless oil, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.1 Hz, 1H), 7.50 (ddd, *J* = 6.0, 4.2, 2.5 Hz, 2H), 7.40 (d, *J* = 0.4 Hz, 1H), 7.36 (dt, *J* = 3.3, 1.0 Hz, 3H), 7.32 – 7.29 (m, 1H), 3.32 (d, *J* = 1.8 Hz, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.66, 159.27, 155.93, 137.94 (q, *J* = 33.2 Hz), 137.87, 130.82, 129.85, 129.07, 128.79 (q, *J* = 37.8 Hz), 126.30, 122.71 (q, *J* = 273.3 Hz), 119.79 (q, *J* = 3.4 Hz), 114.89 (q, *J* = 3.8 Hz), 106.29, 54.90, 31.88.

^{19}F NMR (376 MHz, $CDCl_3$): δ –63.69.

HR-MS (ESI): $C_{18}H_{13}O_4F_3$, $[M+ Na]^+$, Calcd.: 373.0658, Found: 373.0652.



3k

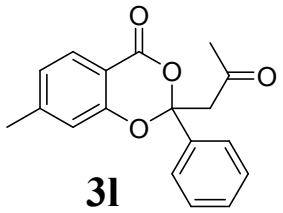
7-methoxy-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3k) :

Colorless oil, 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 – 7.63 (m, 1H), 7.51 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.42 – 7.31 (m, 3H), 6.57 (dd, *J* = 10.8, 2.3 Hz, 2H), 3.85 (s, 3H), 3.31 – 3.26 (d, *J* = 12 Hz, 1H), 3.24 – 3.19 (d, *J* = 16 Hz, 1H) 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 166.5, 160.3, 157.8, 138.8, 131.4, 129.4, 128.8, 126.1, 110.8, 107.2, 105.5, 101.3, 55.8, 55.4, 31.8.

HR-MS (ESI): $C_{18}H_{16}O_5$, $[M+ Na]^+$, Calcd.: 335.0890, Found: 335.0884.



3l

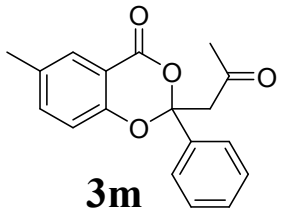
7-methyl-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3l) :

Colorless oil, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.37 – 7.29 (m, 3H), 6.62 – 6.52 (m, 2H), 3.86 (s, 3H), 3.29-3.25 (d, *J* = 16 Hz, 1H), 3.23 – 3.19 (d, *J* = 16 Hz, 1H) 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 166.5, 160.3, 157.8, 138.8, 131.4, 129.4, 128.8, 126.1, 110.9, 107.2, 105.5, 101.3, 55.8, 55.4, 31.9.

HR-MS (ESI): $C_{18}H_{16}O_4$, $[M+Na]^+$, Calcd.: 319.0941, Found: 319.0939.



3m

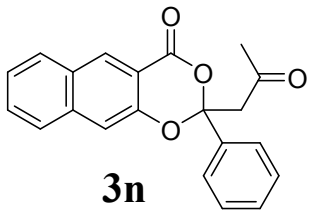
6-methyl-2-(2-oxopropyl)-2-phenyl-4*H*-benzo[*d*][1,3]dioxin-4-one (3m) :

Colorless oil, 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 1.6 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.36 – 7.29 (m, 4H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.29 – 3.26 (d, *J* = 16 Hz, 1H), 3.24 - 3.21(d, *J* = 16 Hz, 1H) 2.33 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 160.7, 153.9, 138.8, 137.6, 132.9, 129.6, 129.4, 128.8, 126.3, 117.1, 114.2, 105.5, 55.4, 31.8, 20.5.

HR-MS (ESI): $C_{18}H_{16}O_4$, $[M+Na]^+$, Calcd.: 319.0941, Found: 319.0938.



3n

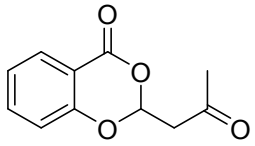
2-(2-oxopropyl)-2-phenyl-4*H*-naphtho[2,3-*d*][1,3]dioxin-4-one (3n) :

Yellow oil, 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (s, 1H), 7.78 (dd, *J* = 18.5, 8.3 Hz, 2H), 7.59 – 7.52 (m, 3H), 7.49 (s, 1H), 7.40 (dd, *J* = 11.2, 3.9 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.29 – 7.22 (m, 2H), 3.44 – 3.22 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5, 161.0, 151.0, 138.8, 137.6, 132.6, 129.8, 129.7, 129.5, 129.2, 128.9, 127.0, 126.5, 125.7, 114.7, 113.3, 105.7, 55.5, 31.9.

HR-MS (ESI): $C_{21}H_{16}O_4$, $[M+Na]^+$, Calcd.: 355.0941, Found: 355.0935.



3o

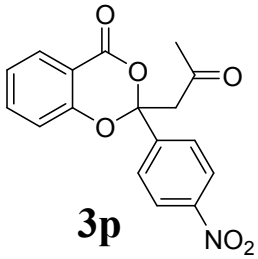
2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3o) :

Colorless oil, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.70 – 7.54 (m, 1H), 7.25 – 7.16 (m, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.09 (t, *J* = 5.2 Hz, 1H), 3.26-3.24 (d, *J* = 8 Hz, 1H), 3.24 – 3.22 (d, *J* = 8 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 161.6, 158.1, 136.4, 130.3, 123.7, 116.7, 114.4, 97.9, 47.2, 31.1.

HR-MS (ESI): $C_{11}H_{10}O_4$, $[M+Na]^+$, Calcd.: 229.0471, Found: 229.0454.



3p

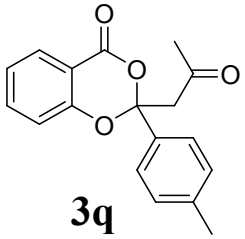
2-(4-nitrophenyl)-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3p) :

Dark brown oil, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 – 8.16 (m, 2H), 7.84 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.63 – 7.53 (m, 1H), 7.19 – 7.08 (m, 2H), 3.41 – 3.27 (m, 2H), 2.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.2, 159.6, 155.5, 148.5, 145.2, 137.2, 130.1, 127.8, 124.0, 123.9, 117.3, 114.2, 104.7, 54.3, 31.9.

HR-MS (ESI): $C_{17}H_{13}NO_6$, $[M+ Na]^+$, Calcd.: 350.0635, Found: 350.0627.



3q

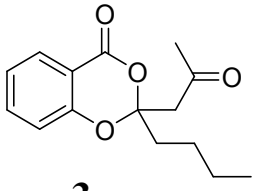
2-(2-oxopropyl)-2-(*p*-tolyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3q) :

Colorless oil, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.11 (dd, *J* = 8.1, 1.4 Hz, 3H), 7.07 – 7.01 (m, 1H), 3.34 – 3.20 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 160.6, 156.0, 139.5, 136.6, 135.6, 129.8, 129.5, 126.2, 123.1, 117.4, 114.7, 105.8, 55.5, 31.8, 21.1.

HR-MS (ESI): $C_{18}H_{16}O_4$, $[M+ Na]^+$, Calcd.: 319.0941, Found: 319.0926.



3r

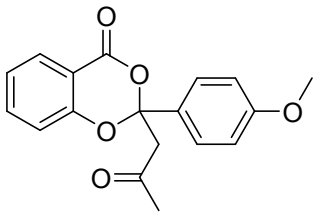
2-butyl-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3r) :

Colorless oil, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.20 – 7.15 (m, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 3.16 – 3.05 (m, 2H), 2.26 (s, 3H), 2.11 – 2.05 (m, 2H), 1.51 (dd, *J* = 10.5, 4.2 Hz, 2H), 1.33 (dd, *J* = 14.5, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.4, 160.2, 155.4, 136.8, 129.7, 123.1, 117.3, 113.5, 107.1, 49.3, 36.4, 31.9, 25.2, 22.4, 13.8.

HR-MS (ESI): $C_{15}H_{18}O_4$, $[M+ Na]^+$, Calcd.: 285.1097, Found: 285.1085.



3s

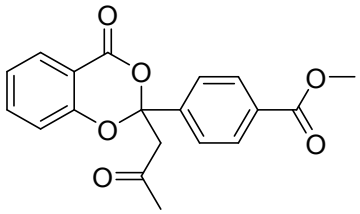
2-(4-methoxyphenyl)-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3s) :

Pale yellow oil, 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.53 (ddd, *J* = 9.0, 7.5, 1.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.14 – 7.02 (m, 2H), 6.87 – 6.77 (m, 2H), 3.76 (s, 3H), 3.42 – 3.16 (m, 2H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 160.6, 160.2, 155.9, 136.6, 130.5, 129.8, 127.8, 123.1, 117.4, 114.7, 114.1, 105.7, 55.5, 55.2, 31.8.

HR-MS (ESI): $C_{18}H_{16}O_5$, $[M+Na]^+$, Calcd.: 335.0890, Found: 335.0880.



3t

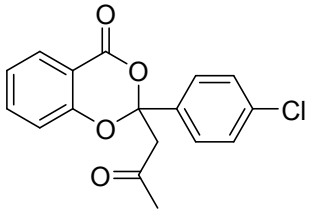
methyl 4-(4-oxo-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-2-yl)benzoate (3t) :

Colorless oil, 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.80 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.56 – 7.51 (m, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.06 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.88 (s, 3H), 3.35 – 3.22 (m, 2H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8, 166.1, 160.1, 155.7, 143.2, 136.9, 131.2, 130.0, 129.9, 126.9, 126.5, 123.5, 117.4, 105.2, 54.8, 52.3, 31.9.

HR-MS (ESI): $C_{19}H_{16}O_6$, $[M+Na]^+$, Calcd.: 363.0839, Found: 363.0834.



3u

2-(4-chlorophenyl)-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3u) :

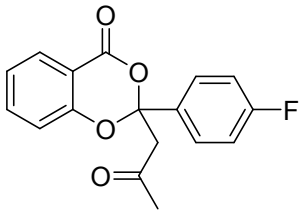
Pale yellow oil, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.55 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.30 (d, *J* = 2.1 Hz, 2H), 7.13 – 7.03 (m, 2H), 3.37 – 3.21 (m, 2H), 2.33 (s,

3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.2, 160.2, 155.7, 137.1, 136.9, 136.4, 135.7, 130.0, 129.1, 127.9, 123.5, 119.4, 117.3, 55.0, 31.9.

HR-MS (ESI): $C_{17}H_{13}O_4Cl$, $[M+Na]^+$, Calcd.: 339.0395, Found: 339.0385.



3v

2-(4-fluorophenyl)-2-(2-oxopropyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (3v) :

Yellow oil, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.58 – 7.47 (m, 3H), 7.13 – 7.04 (m, 2H), 7.03 – 6.97 (m, 2H), 3.28 (d, *J* = 7.0 Hz, 2H), 2.32 (s, 3H).

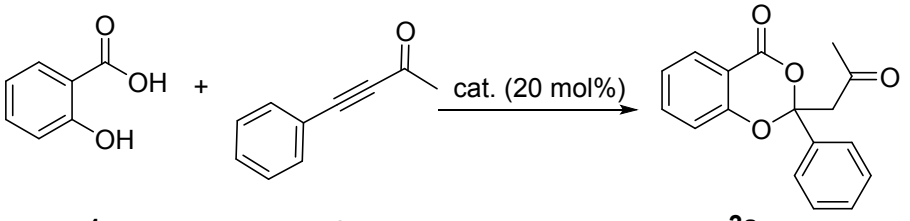
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.1, 163.1 (d, *J* = 249.8 Hz), 160.2, 155.7, 136.8, 134.5 (d, *J* = 3.1 Hz), 129.9, 128.4 (d, *J* = 8.6 Hz), 123.4, 117.3, 115.9 (d, *J* = 22.0 Hz), 114.5, 105.3, 55.2, 31.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ –111.29.

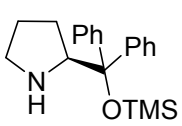
HR-MS (ESI): $C_{17}H_{13}O_4F$, $[M+Na]^+$, Calcd: 323.0690, Found: 323.0687.

4. Enantioselective investigation:

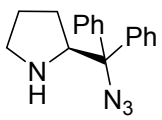
Table S1. Exploration of enantioselective dual Michael cascade reactions.[a]



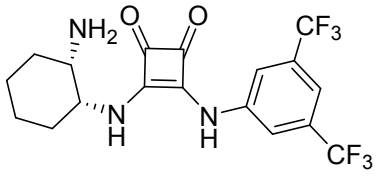
1a **2a** **3a**



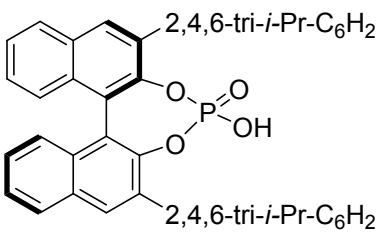
I



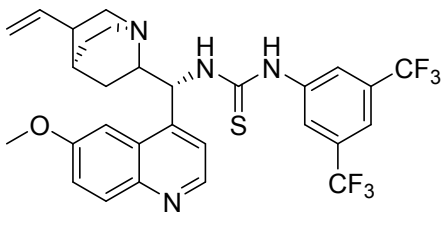
II



III



IV



V

entry	cat.	Yield(%)[b]	ee (%)[c]
1	I	87	0
2	II	83	0
3	III+ morpholine[d]	84	2
4	IV+ morpholine[d]	89	0
5	V+ morpholine[d]	91	4

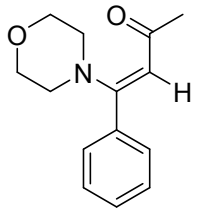
[a] Reaction conditions: unless specified, reactions were carried out with **1a** (0.3 mmol) and 1equiv. **2a** for 24 h under RT in 2 mL of DCM, the catalyst loading is 20 mol%.

[b] Isolated yields.

[c] Determined by Agilent HPLC with chiral column.

[d] 20 mol% morpholine was added into the reaction with chiral catalysts III, IV and V respectively.

5. NMR characterization of the intermediate species:



intermediate **3**

Intermediate 3:

Light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.40 (m, 3H), 7.29 (t, *J* = 4.3 Hz, 2H), 5.43 (s, 1H), 3.77 – 3.61 (m, 4H), 3.18 – 2.94 (m, 4H), 1.72 (s, 3H).

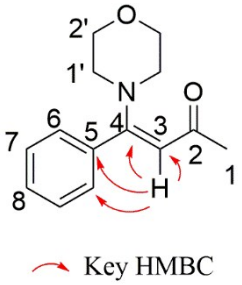
^{13}C NMR (101 MHz, $CDCl_3$): δ 197.1, 162.5, 136.0, 129.5, 129.0, 128.8, 103.5, 66.5, 48.2, 29.9.

Table S2. Key HMBC correlations of intermediate **3**:

^{1}H and ^{13}C NMR data of intermediate **3** (in $CDCl_3$):

Position	δ_H	δ_C
1	1.72 (s)	29.9
2		197.1
3	5.43 (s)	103.5
4		162.5
5		136.0
6	7.29 (t)	129.5
7	7.49 – 7.40 (m)	129.0
8	7.49 – 7.40 (m)	128.8
1'	3.18 – 2.94 (m)	48.2
2'	3.77 – 3.61 (m)	66.5

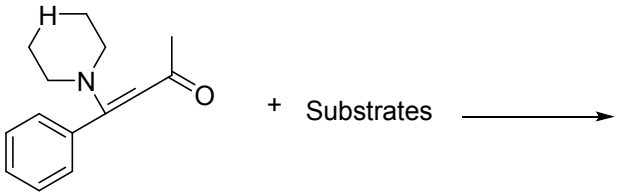
Figure S1. The key HMBC correlations of intermediate **3**:



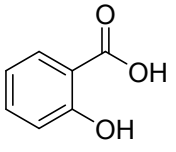
6. Control experiments

Table S3. Control experiments on the salicylic acid substrates:[a]

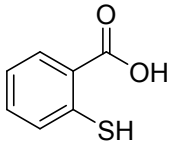
Entry	Substrates	Yield (%)[b]
1	Salicylic acid	94%
2	Thiosalicylic acid	-
3	CH_3COOH	-
4	Phthalic acid	-
4	Malonic acid	-
5	Birch-Me	-
6	Pyrocatechol	72% (**4a**)



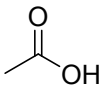
Intermediate **3**



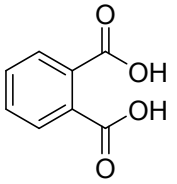
Salicylic acid



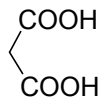
ThioSalicylic acid



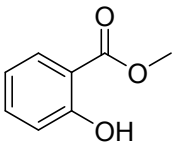
HOAc



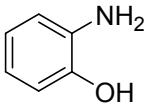
Phthalic acid



Malonic acid



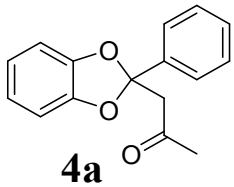
Birch-Me



Pyrocatechol

[a] Reaction conditions: unless specified, reactions were carried out with intermediate **3** (0.3 mmol) and 1 equiv. **substrates** listed above, reacted for 24 h at RT in 2 mL of DCM.

[b] Isolated yields.



4a

1-(2-phenylbenzo[*d*][1,3]dioxol-2-yl)propan-2-one (4a)

Colorless oil, 72.3% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.44 – 7.36 (m, 3H), 6.93 – 6.78 (m, 4H), 3.40 (s, 2H), 2.19 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.2, 146.7, 139.6, 129.3, 128.5, 125.2, 121.9, 115.0, 109.0, 53.3, 31.4.

HR-MS (ESI): $C_{16}H_{14}O_3$, $[M+ Na]^+$, Calcd.: 277.0835, Found: 277.0828.

7. References

1 P. A. Deyris, T. Cañeque, Y. Wang, P. Retailleau, F. Bigi, R. Maggi, G. Maestri and M. Malacria, *ChemCatChem*, 2015, **7**, 3266–3269.

2 F. Scho, Y. Zi, I. Vilotijevic, F. Schomberg, Y. Zi and I. Vilotijevic, *Chem. Commun.*, 2018, **54**, 3266–3269.

3 T. Letters, G. Y. Press, G. Bartoli, C. Cimarelli, S. Chimiche, C. Organica, G. Palmieri, M. Bosco and R. Dalpozzo, *Tetrahedron Lett.*, 1991, **32**, 7091–7092.

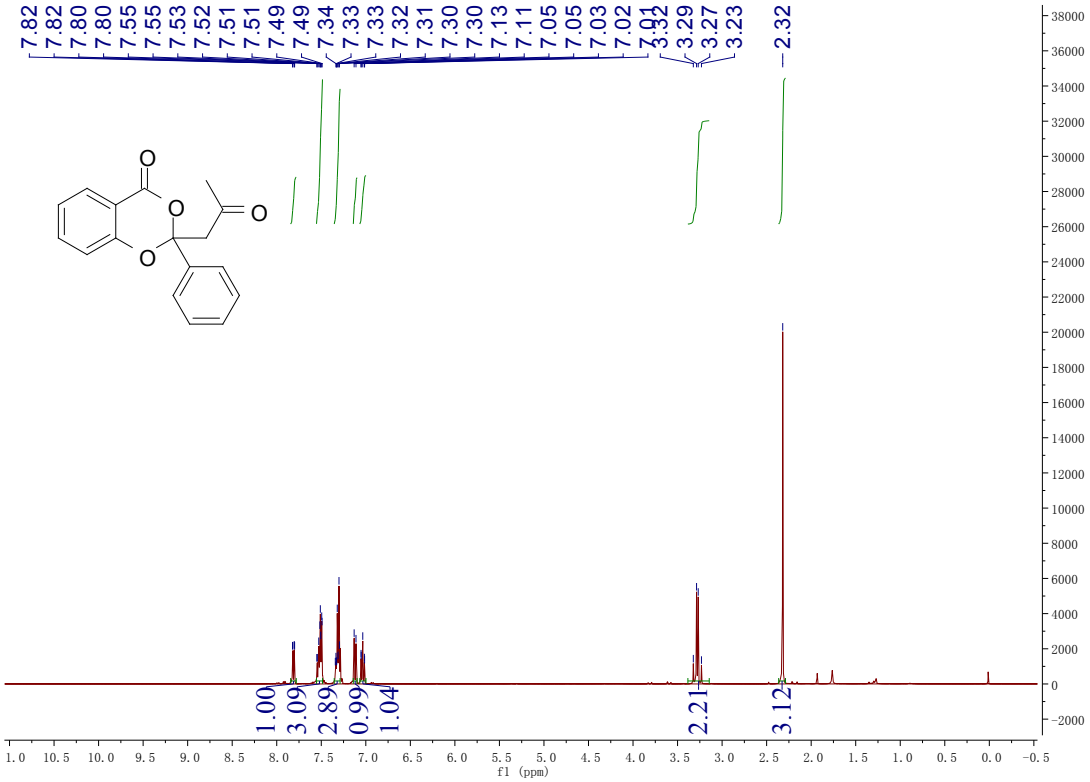
4 Y. Sadamitsu, K. Komatsuki, K. Saito and T. Yamada, *Org. Lett.*, 2017, **19**, 3191–3194.

5 J. Liu, X. Xie and S. Ma, *Synthesis*, 2012, **44**, 1569–1576.

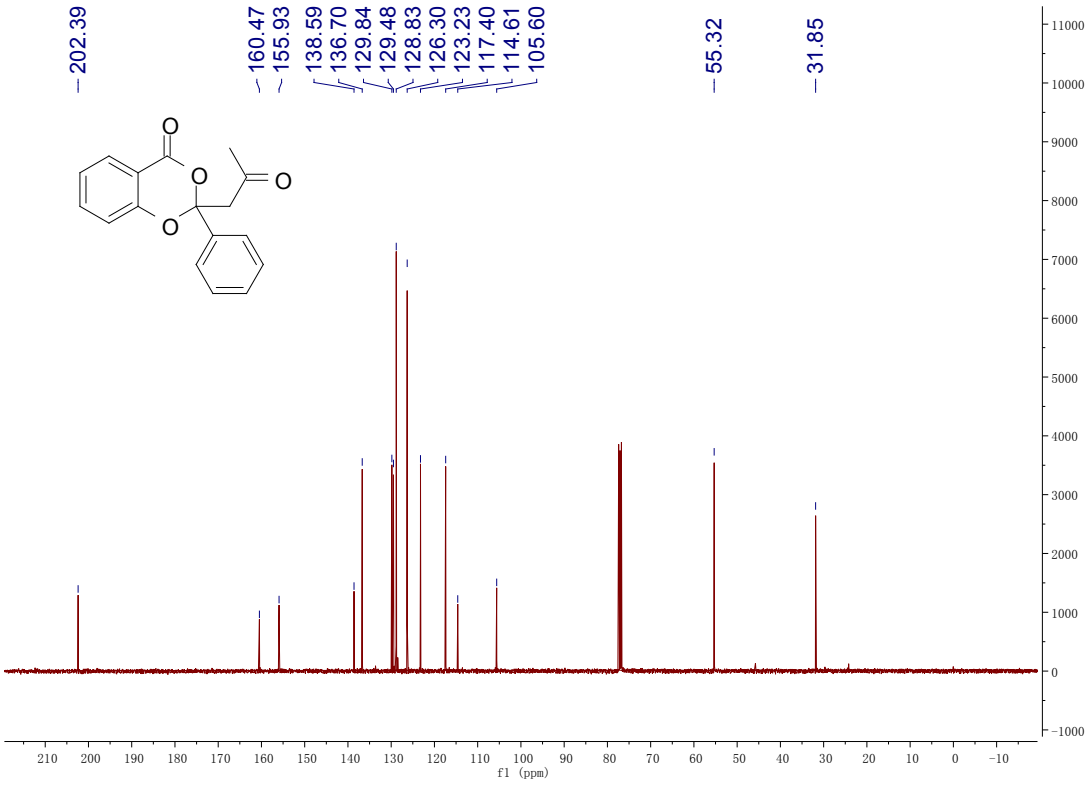
6 T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441–449.

8. NMR spectra.

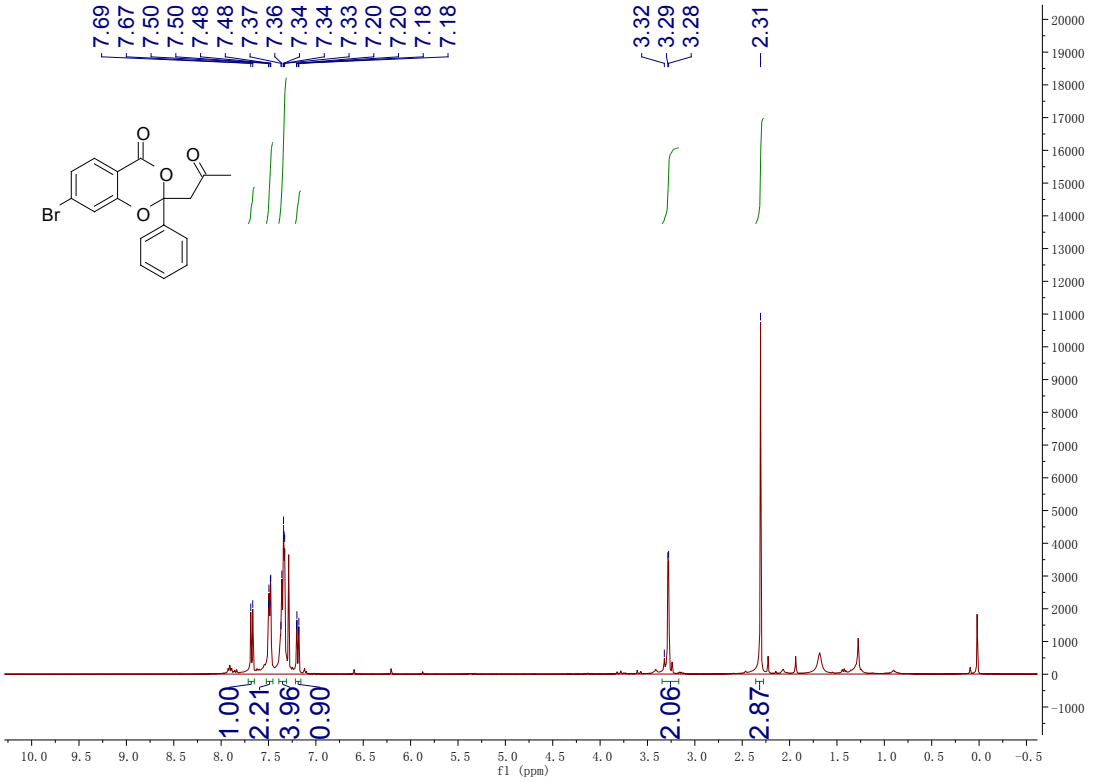
^{1}H NMR for **3a**



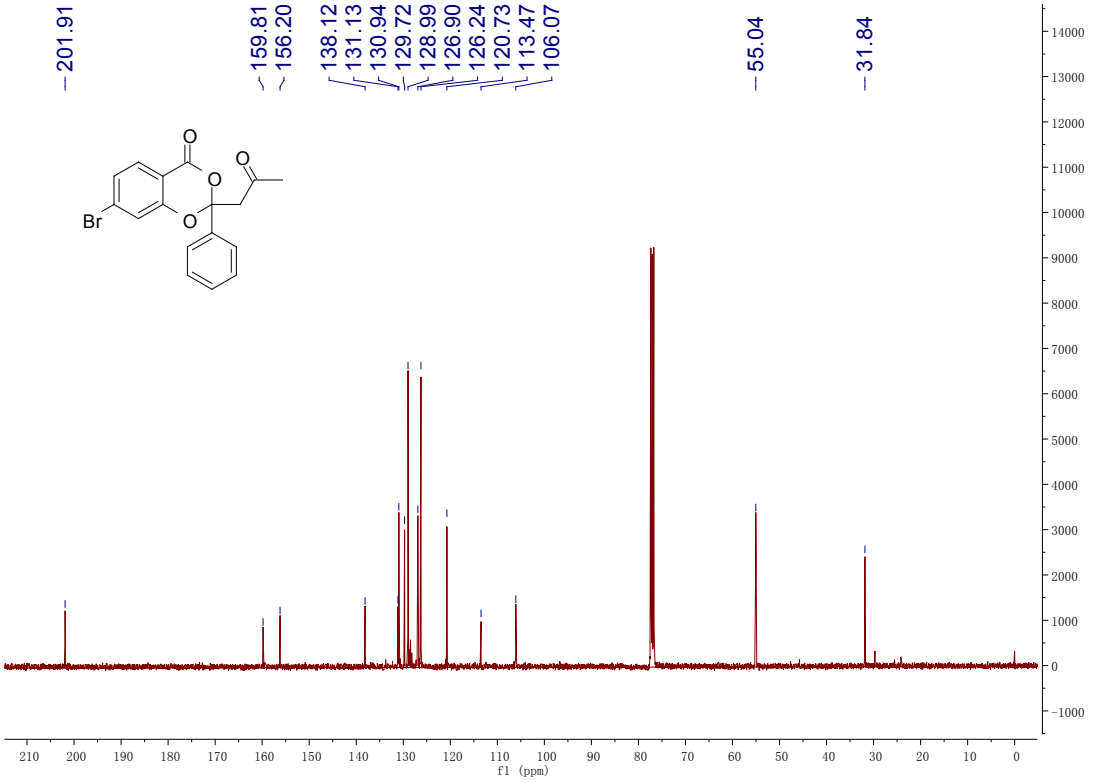
^{13}C NMR for **3a**



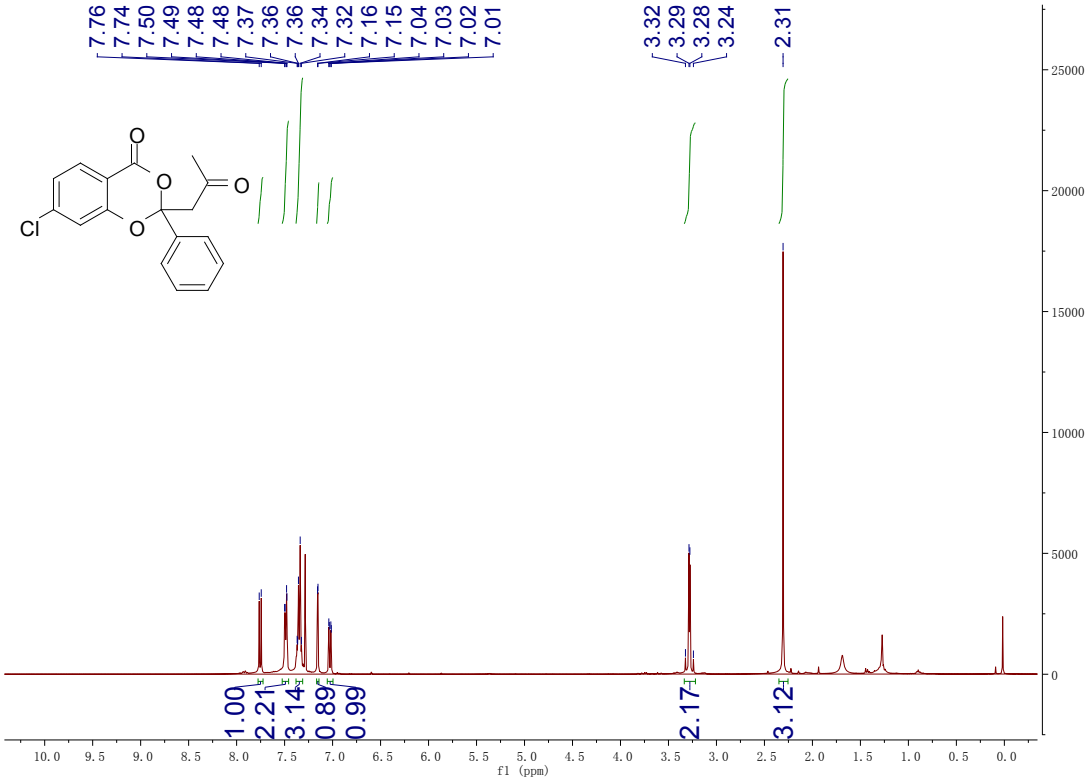
^{1}H NMR for **3b**:



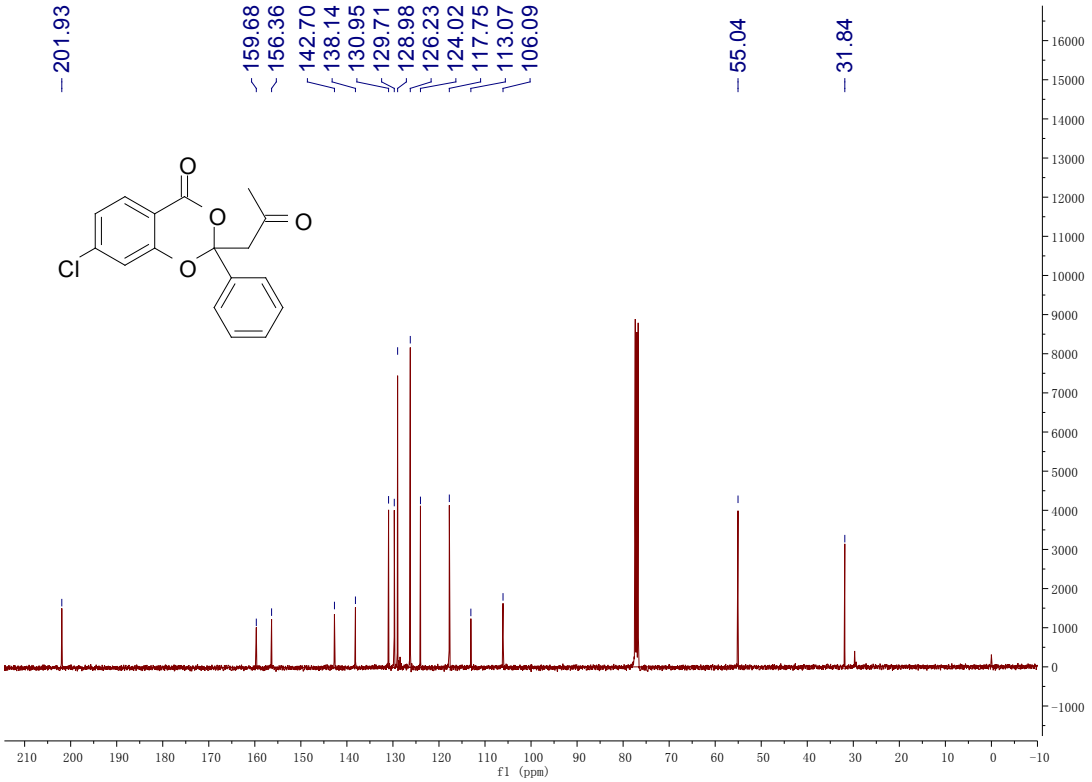
^{13}C NMR for **3b**:



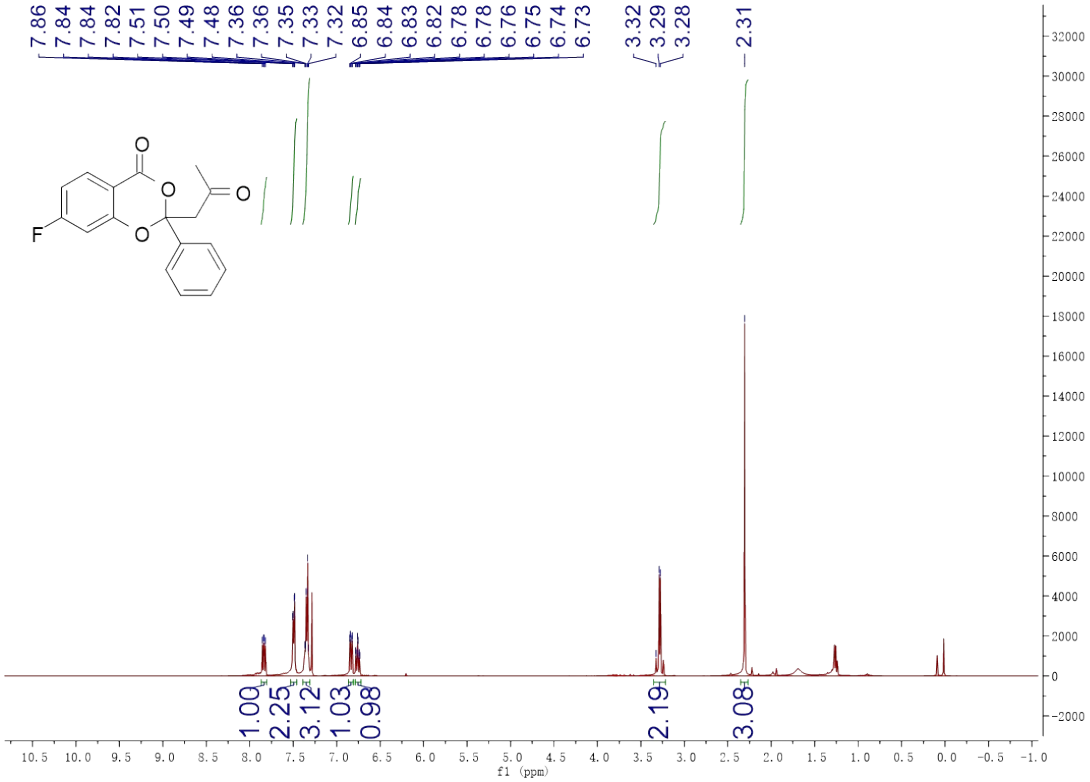
^{1}H NMR for **3c**:



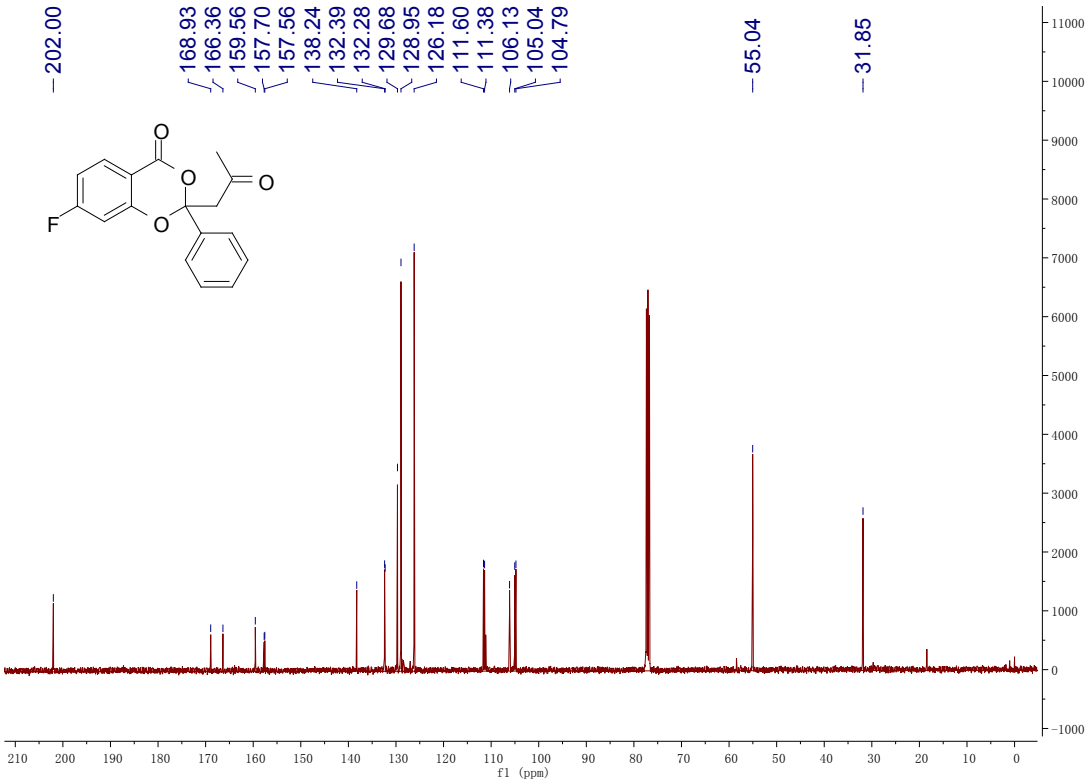
^{13}C NMR for **3c**:



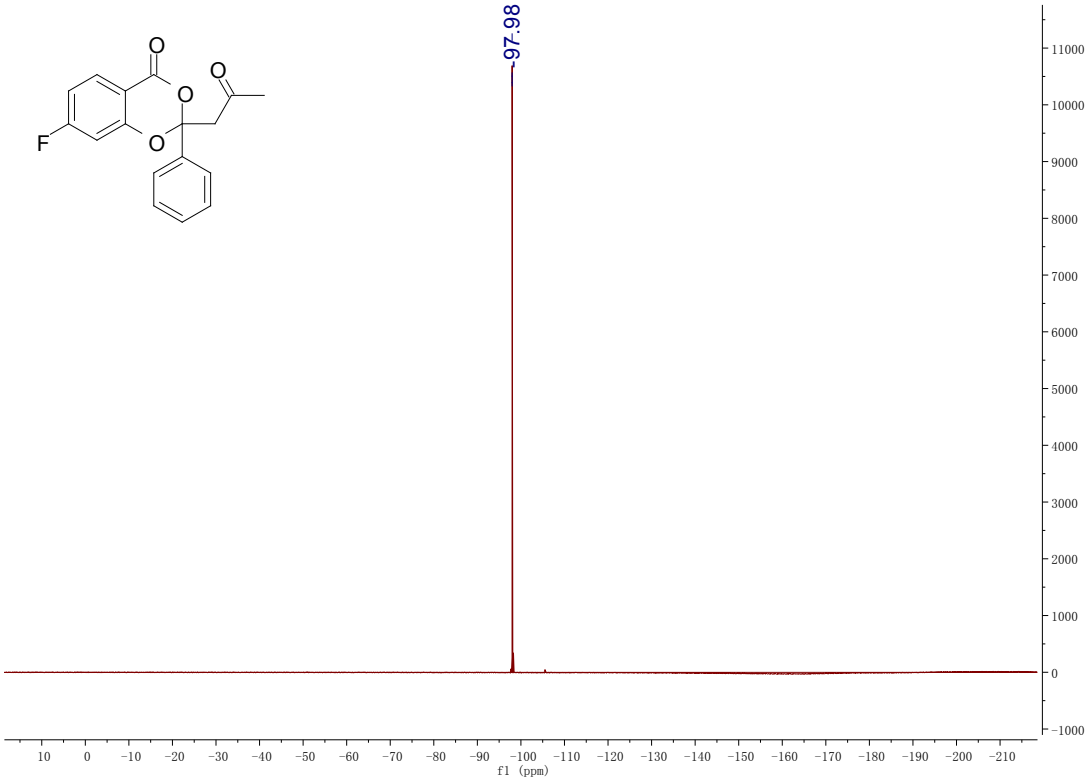
^{1}H NMR for **3d**:



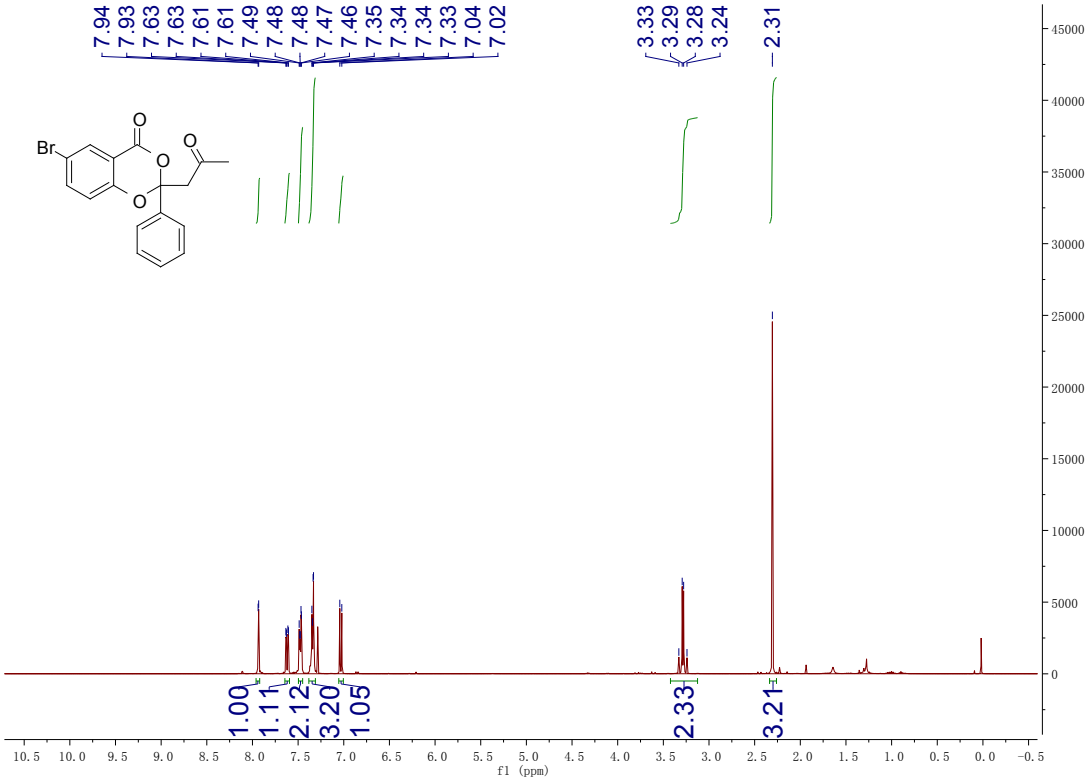
^{13}C NMR for **3d**:



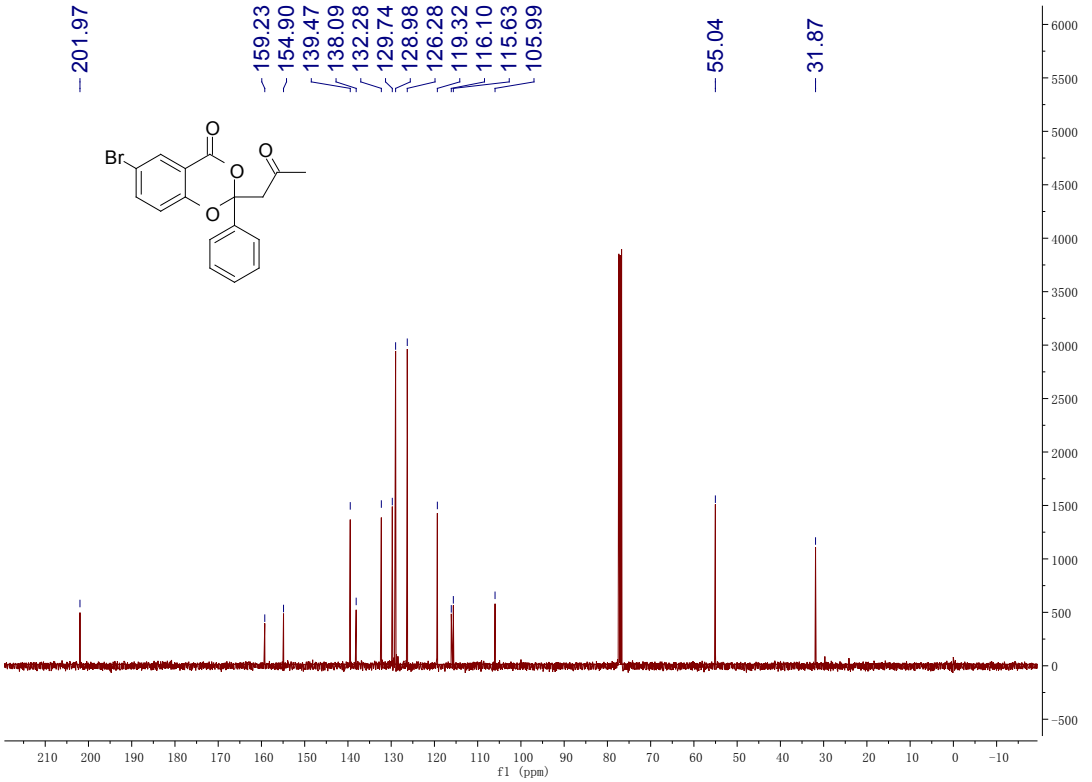
^{19}F NMR for **3d**:



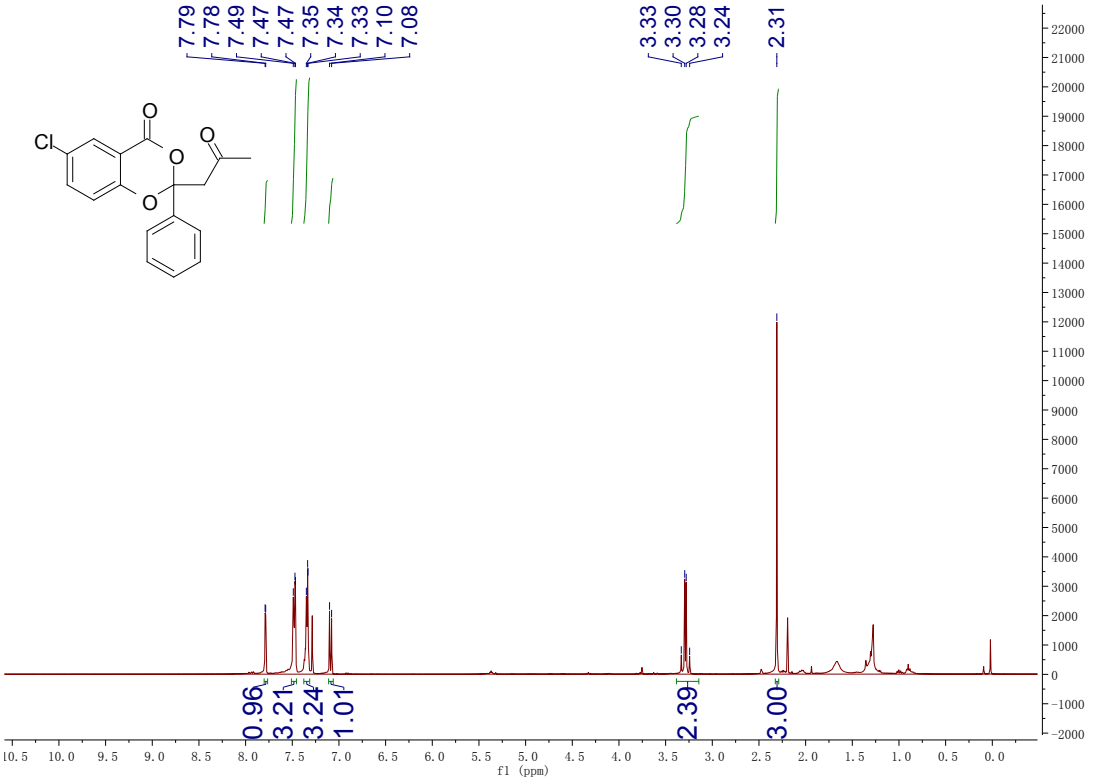
^{1}H NMR for **3e**:



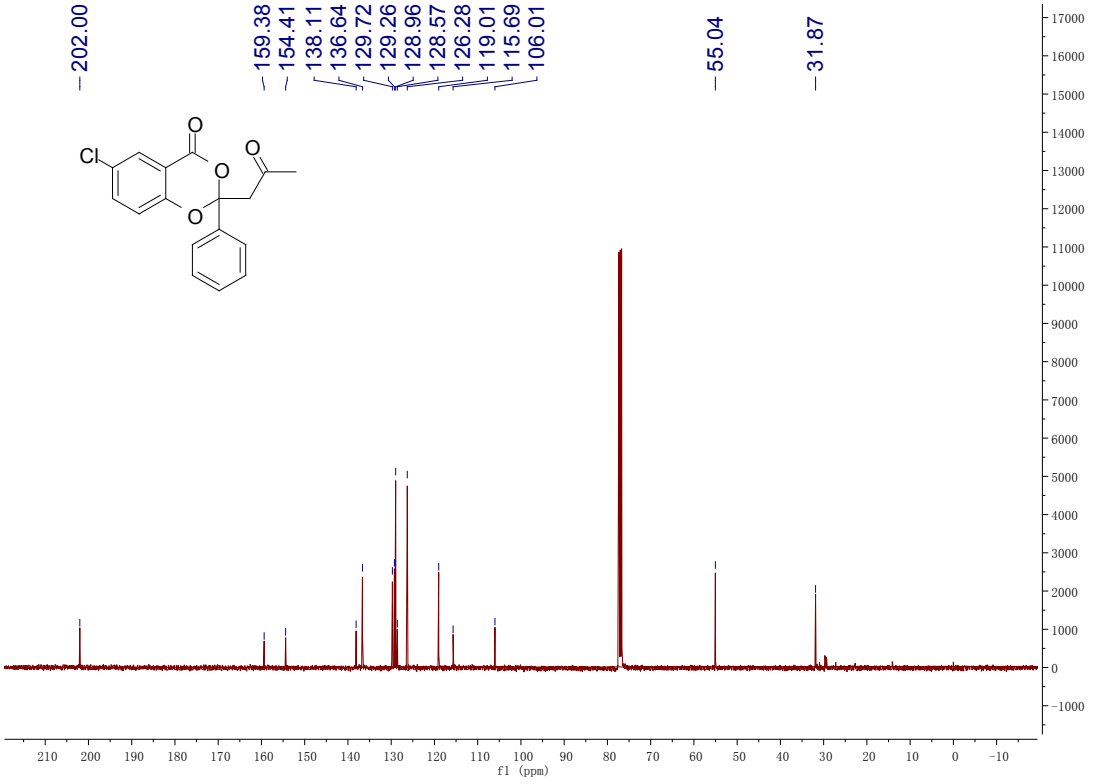
^{13}C NMR for **3e**:



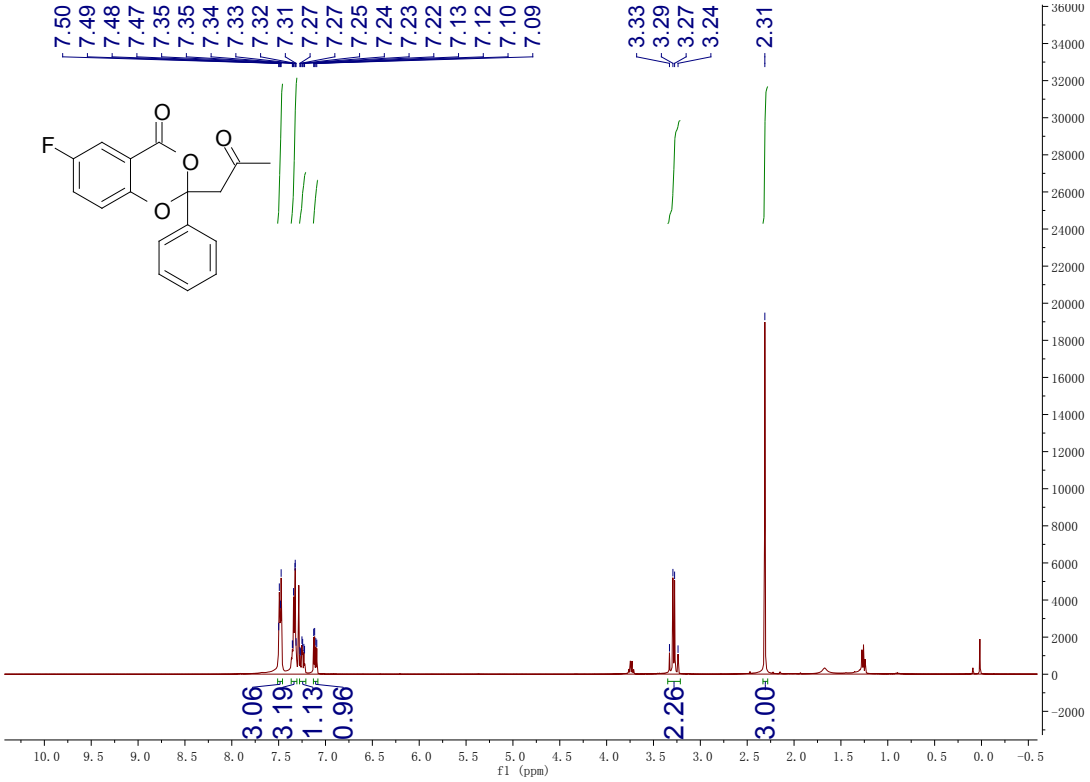
^{1}H NMR for **3f**:



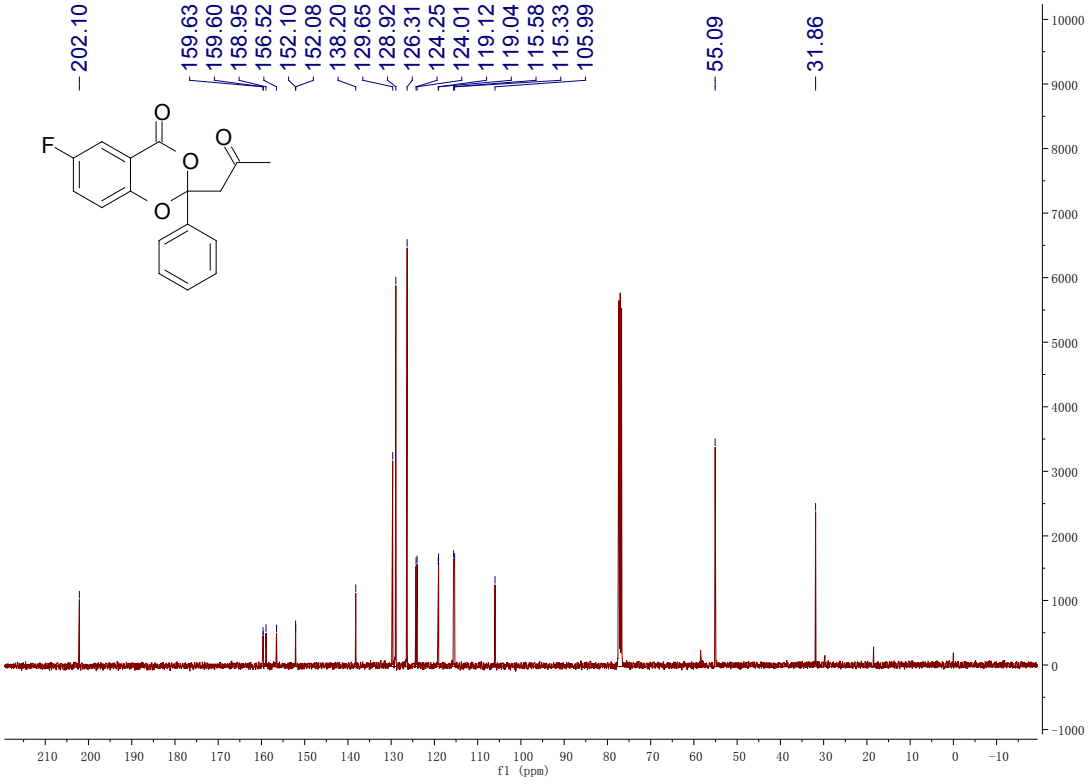
^{13}C NMR for **3f**:



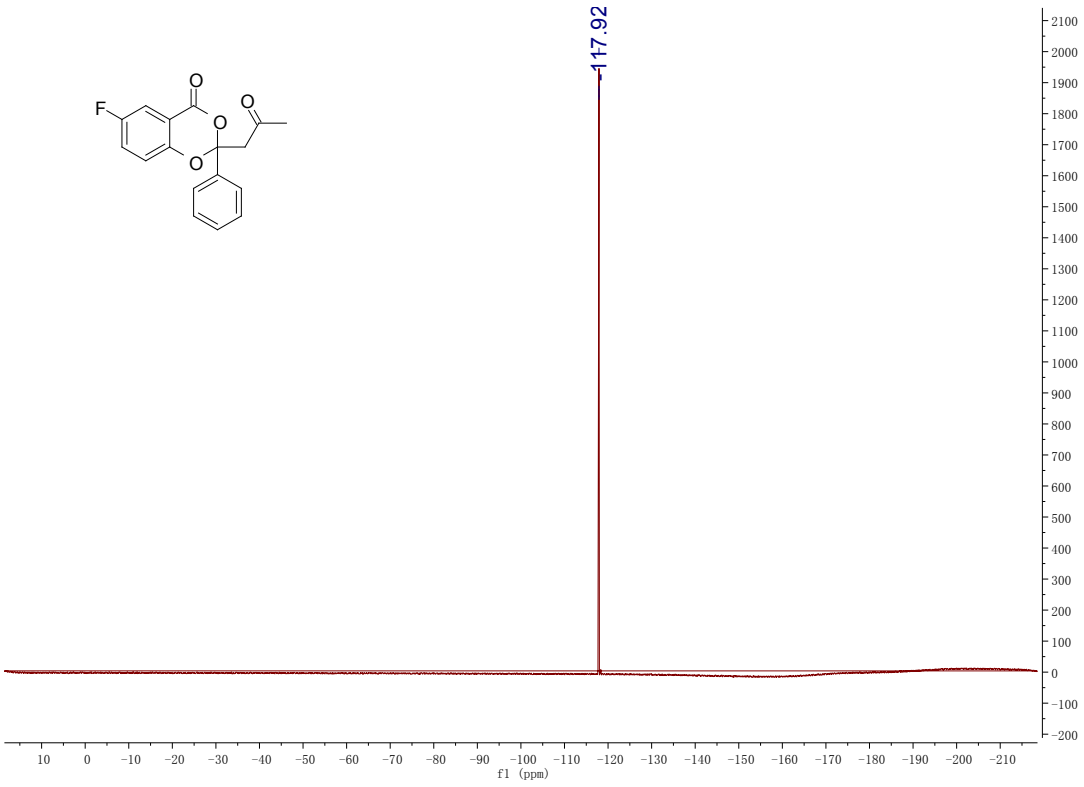
^{1}H NMR for **3g**:



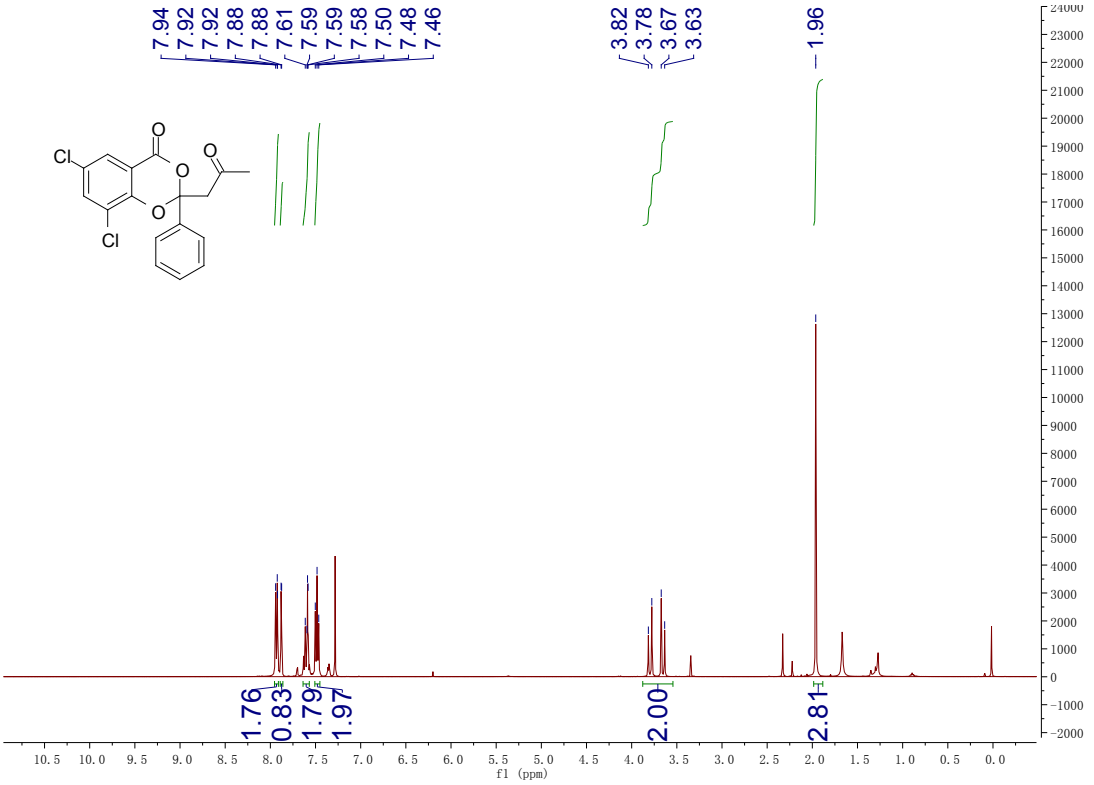
^{13}C NMR for **3g**:



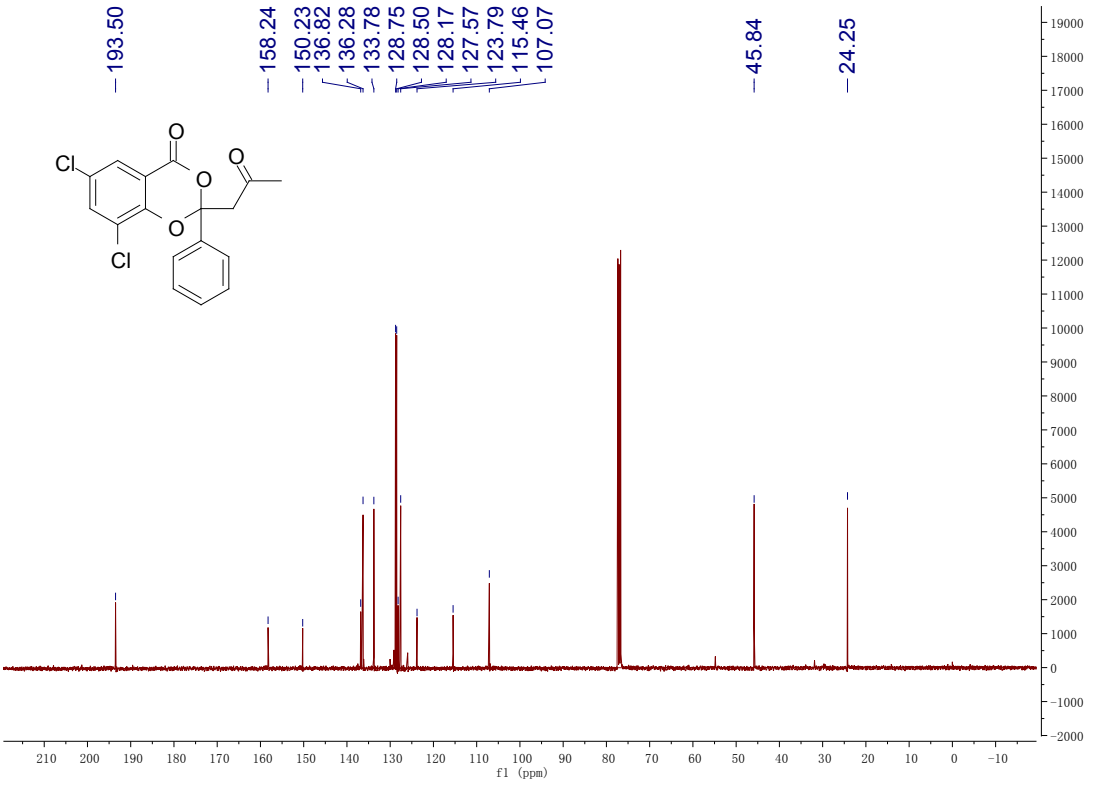
^{19}F NMR for **3g**:



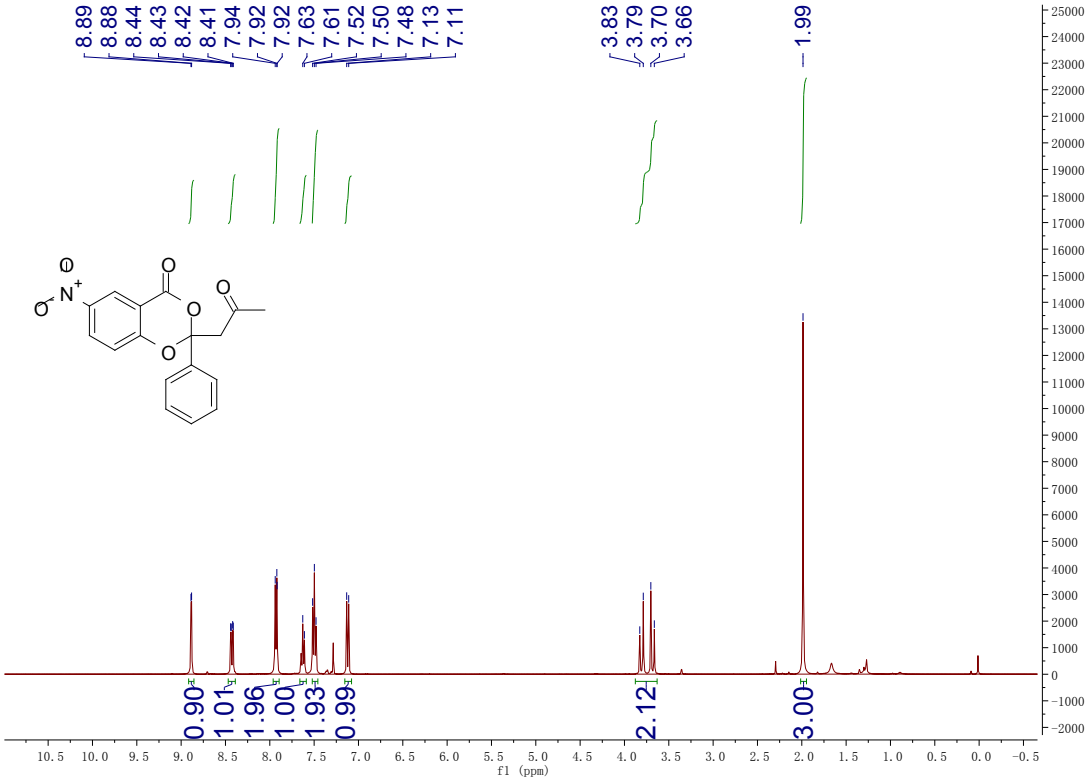
^{1}H NMR for **3h**:



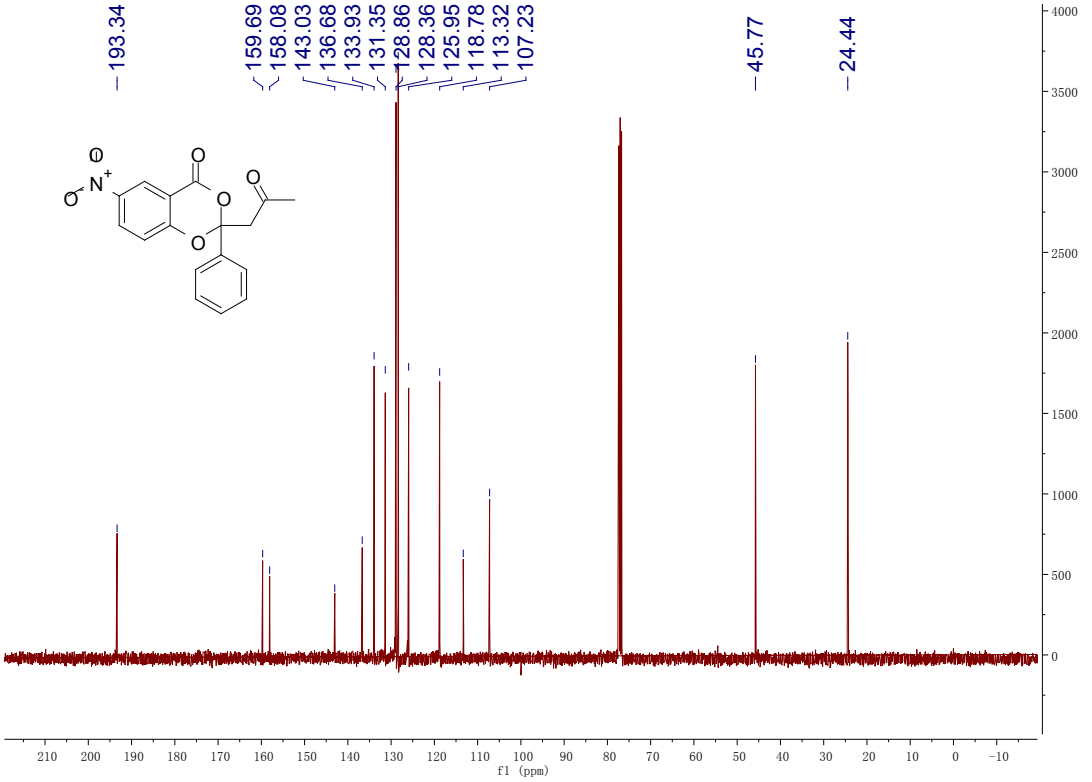
^{13}C NMR for **3h:**



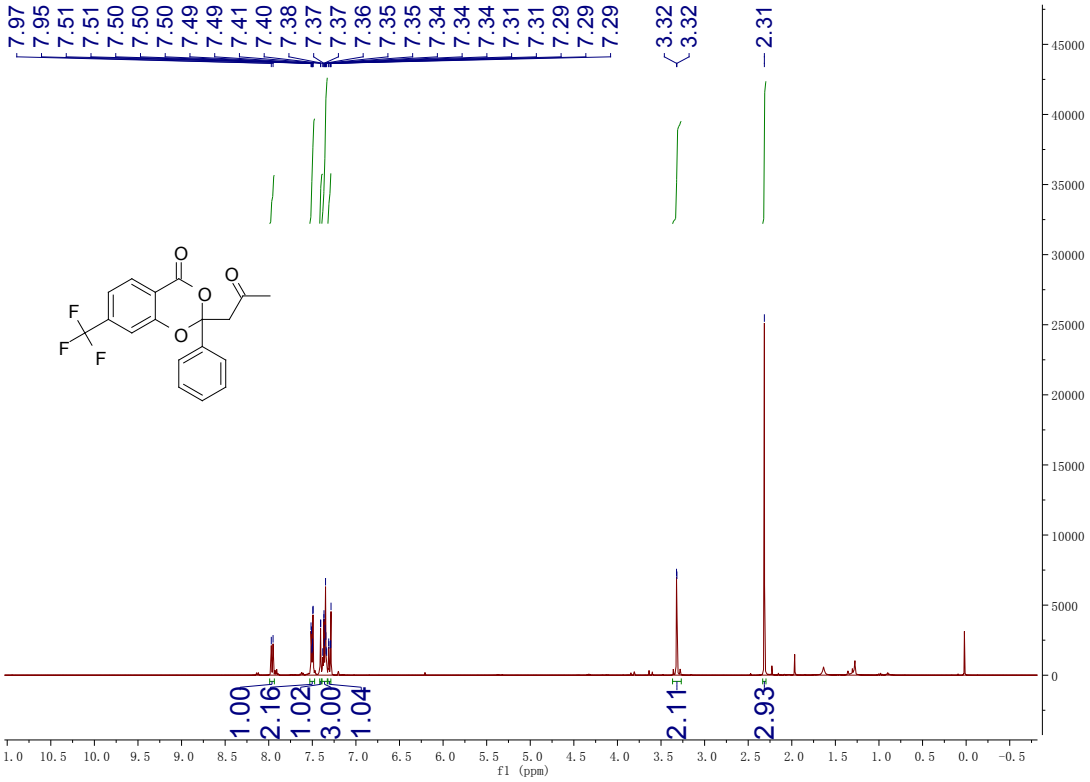
^{1}H NMR for **3i**:



^{13}C NMR for **3i:**



^{1}H NMR for **3j**:



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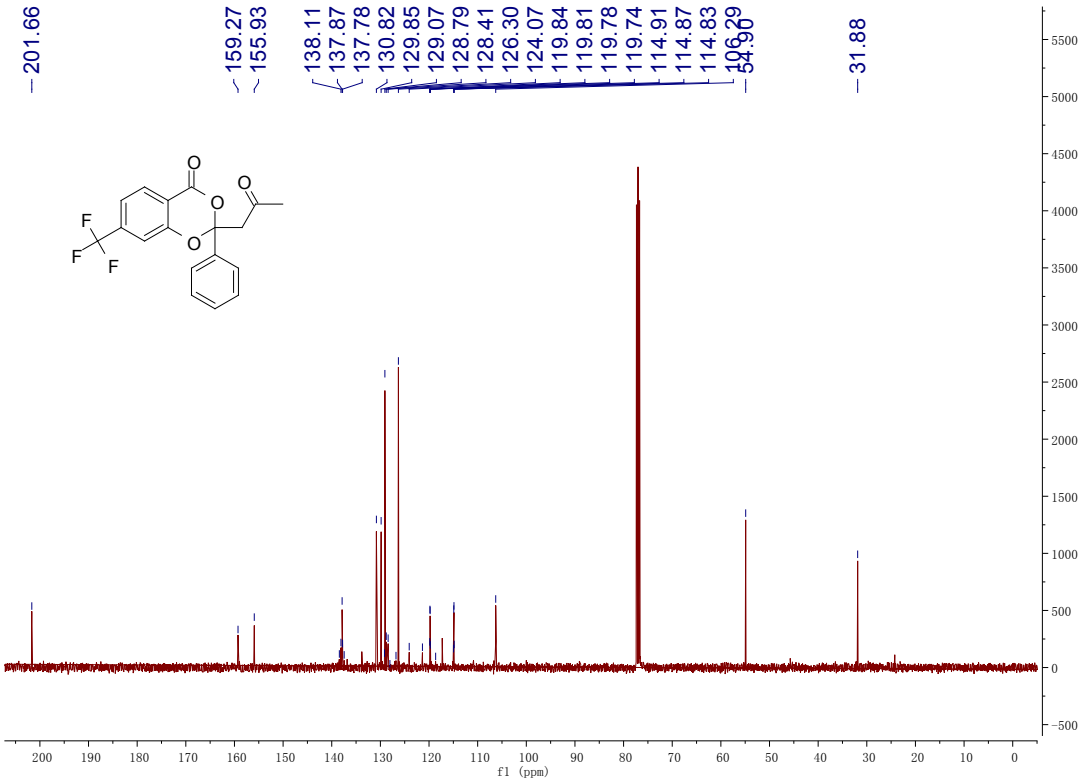
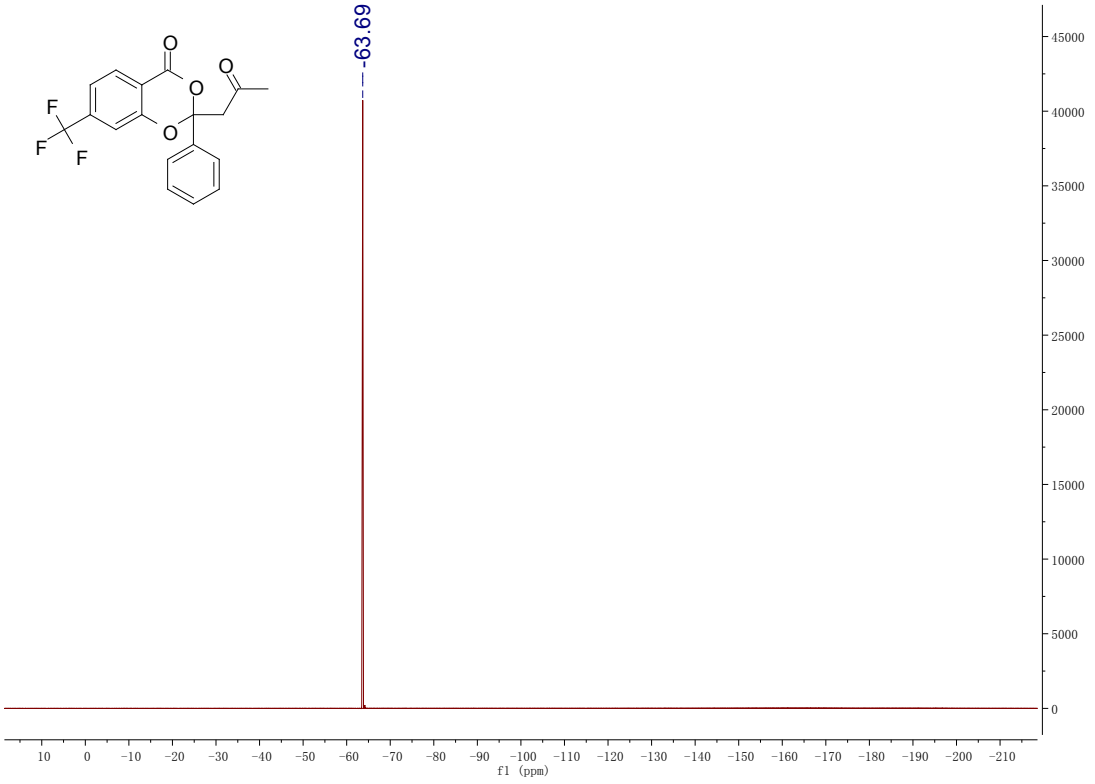


^{19}F NMR for **3j:**



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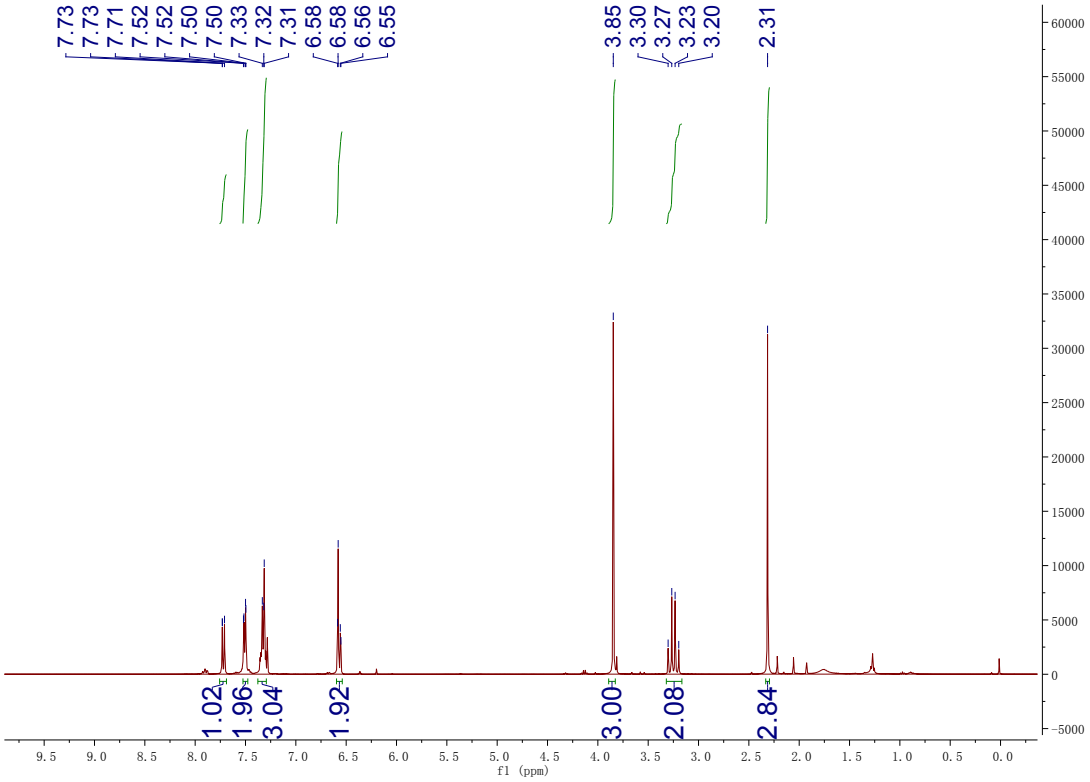

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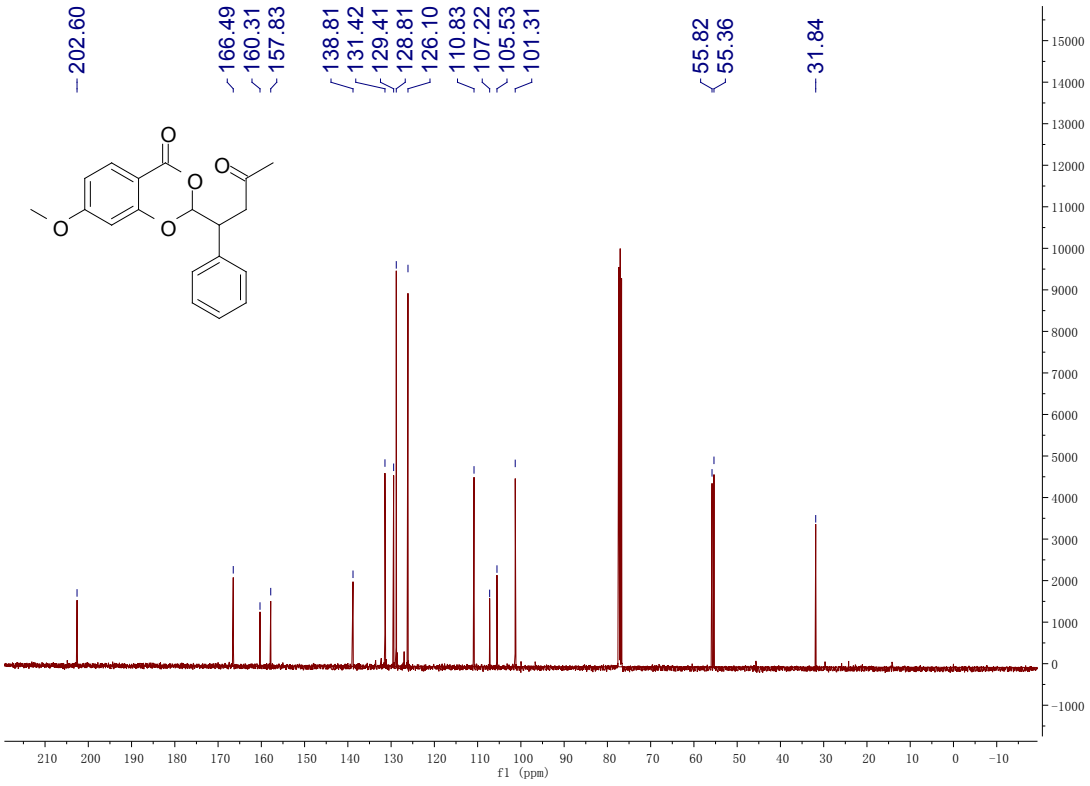
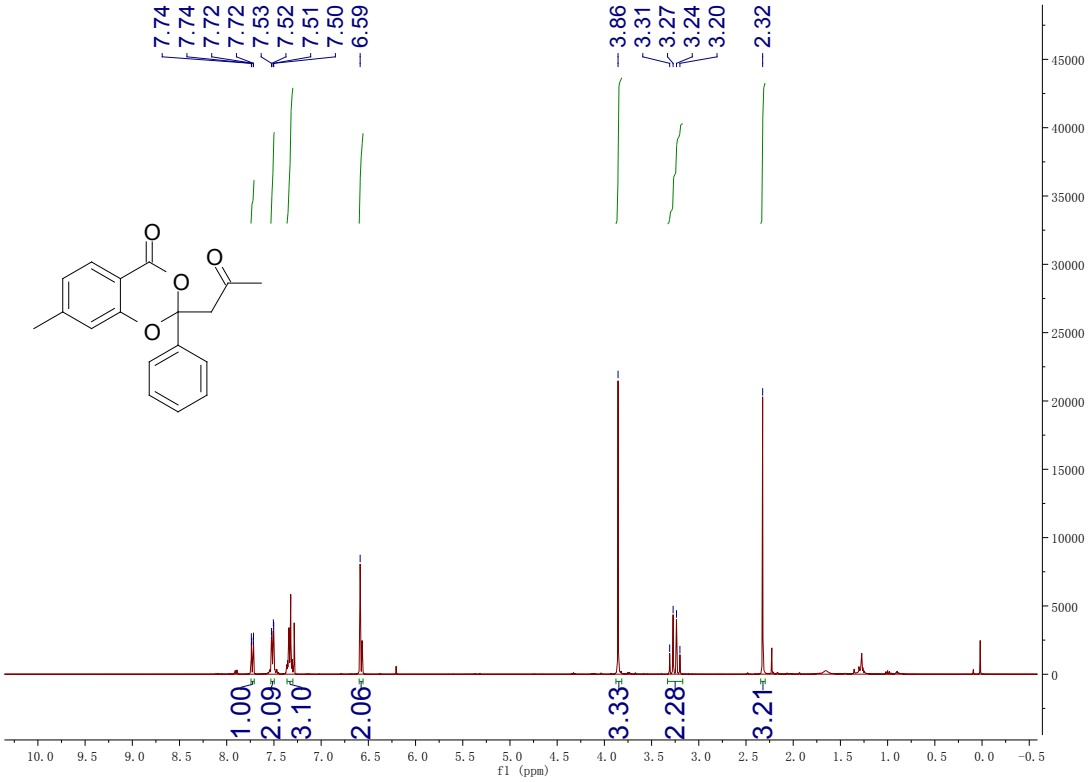


^{1}H NMR for **3l**:



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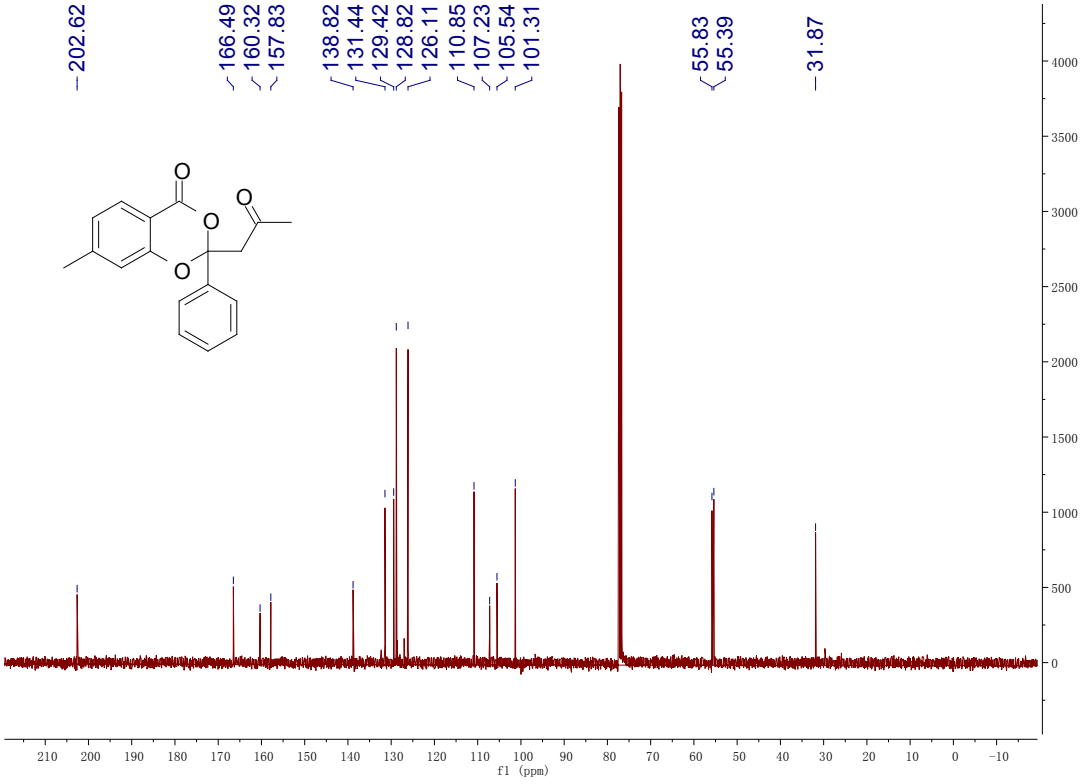
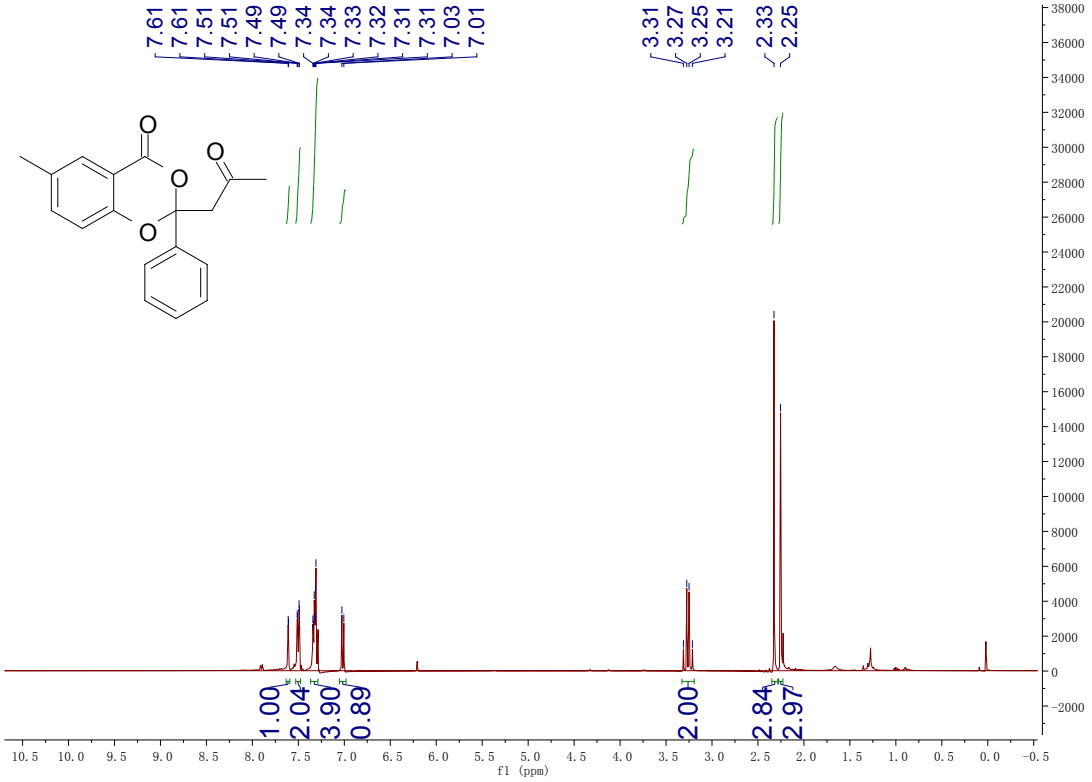
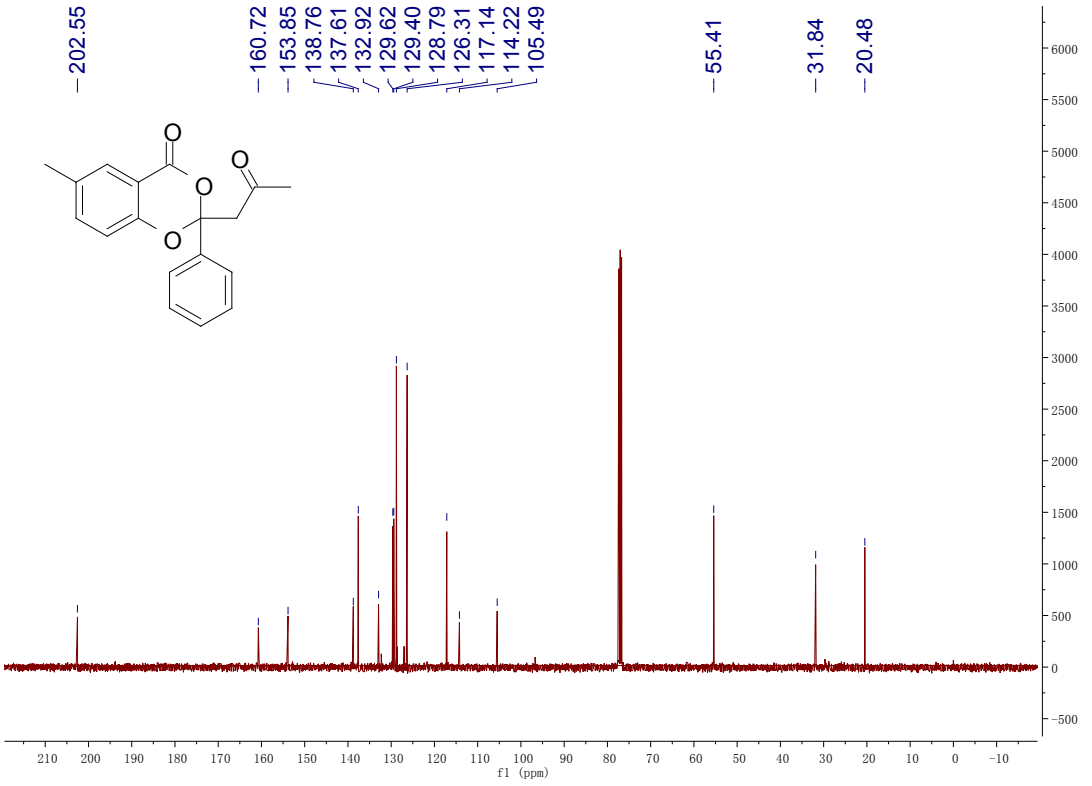


^{1}H NMR for **3m**:



^{13}C NMR for **3m**:



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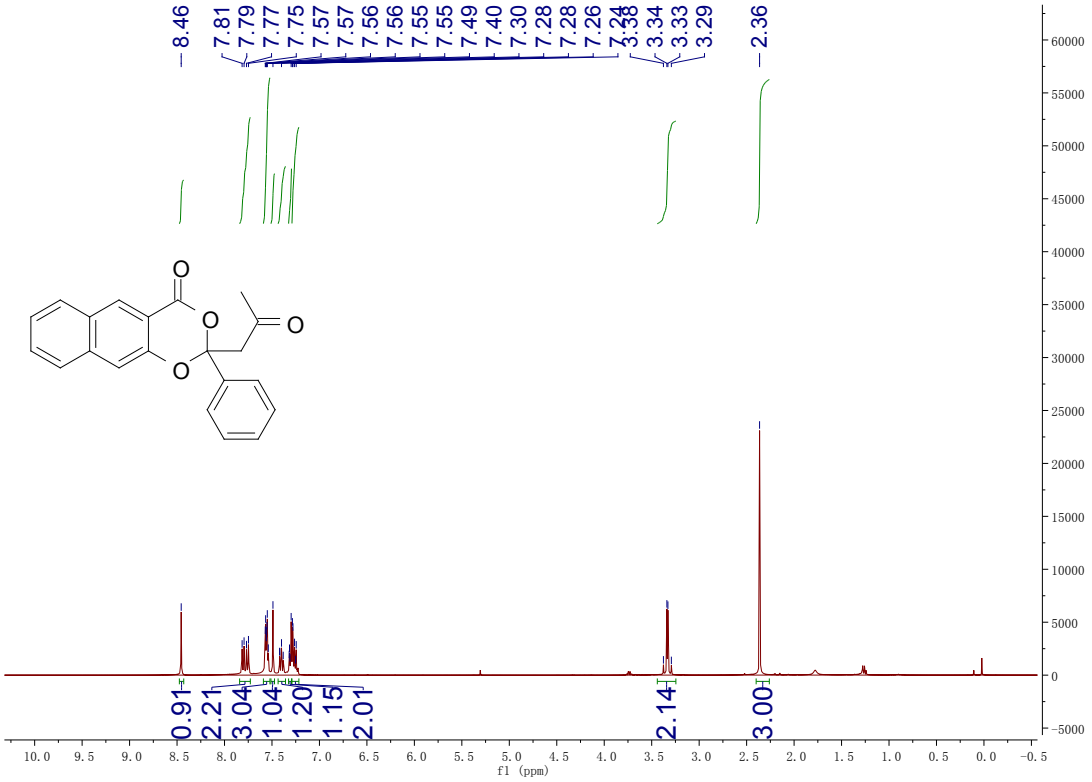
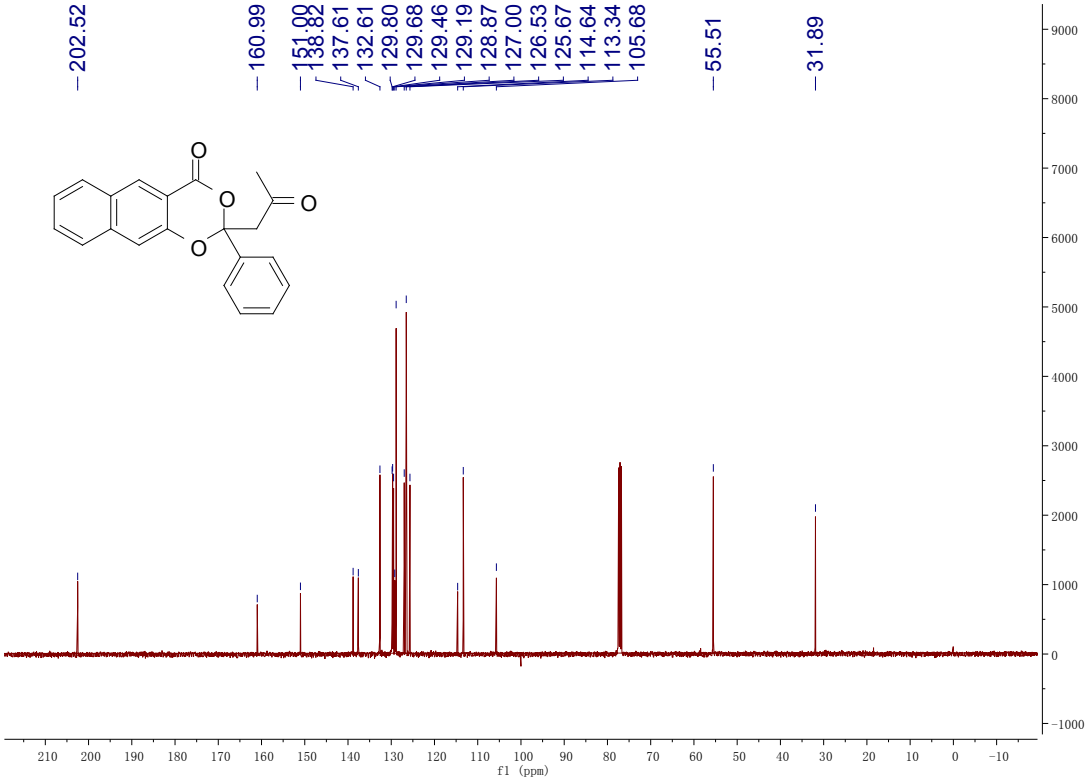
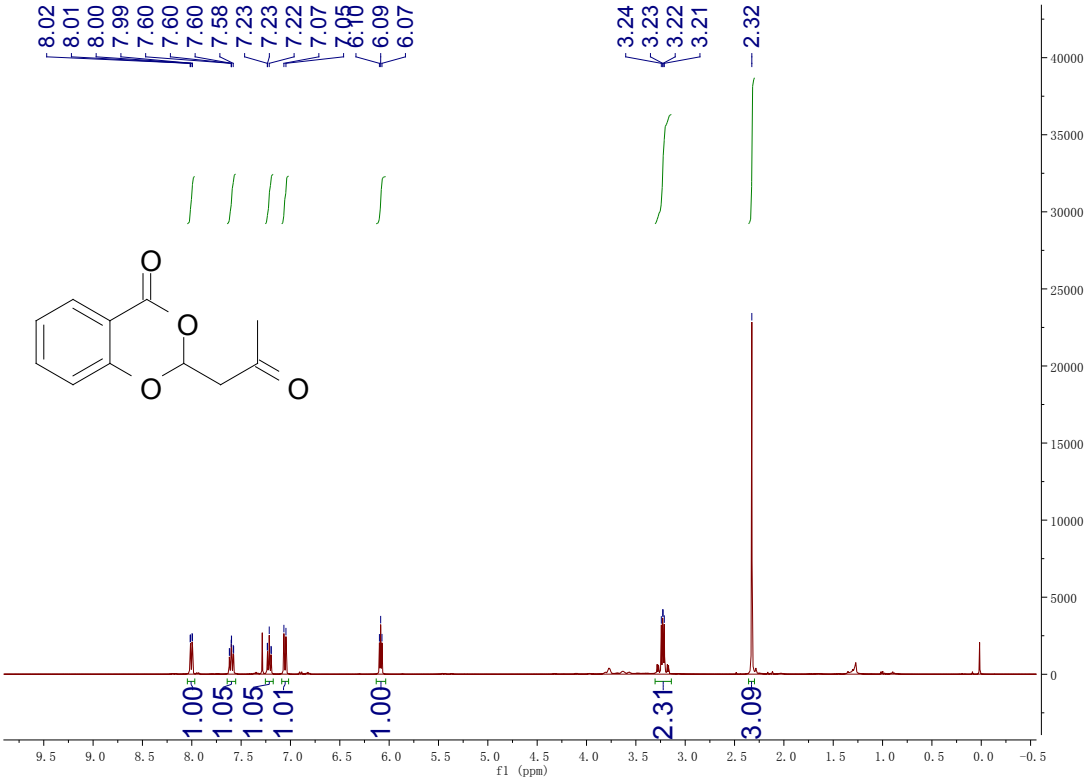


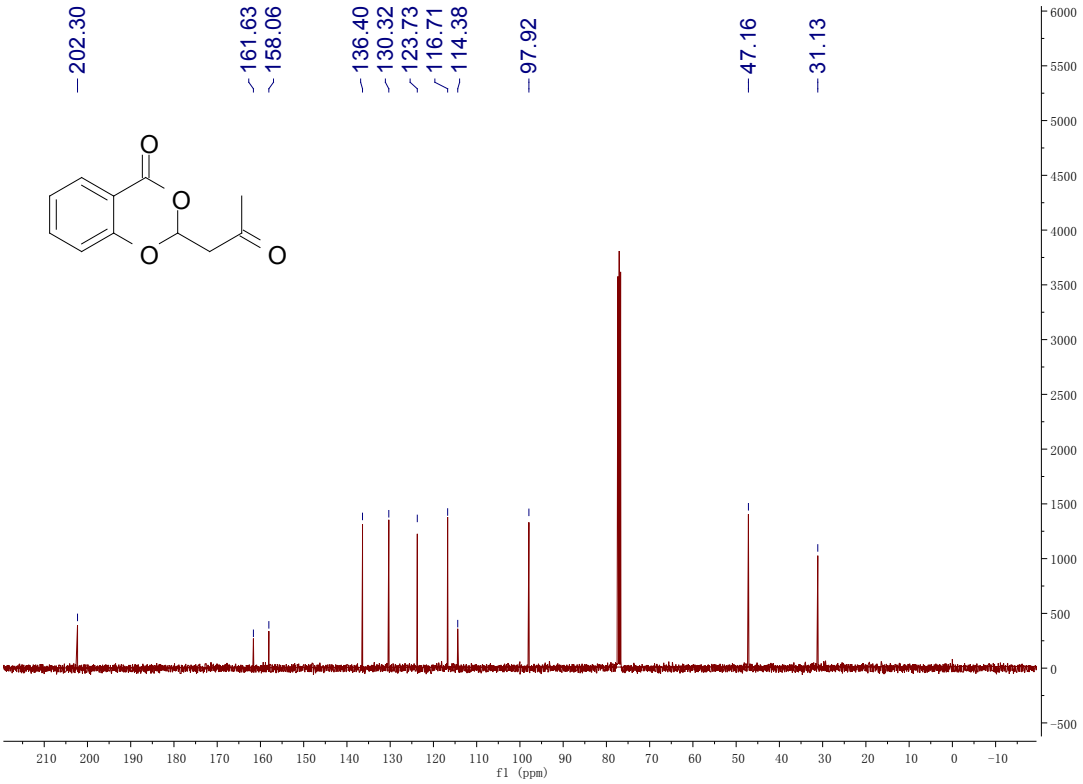
^{13}C NMR for **3n**:



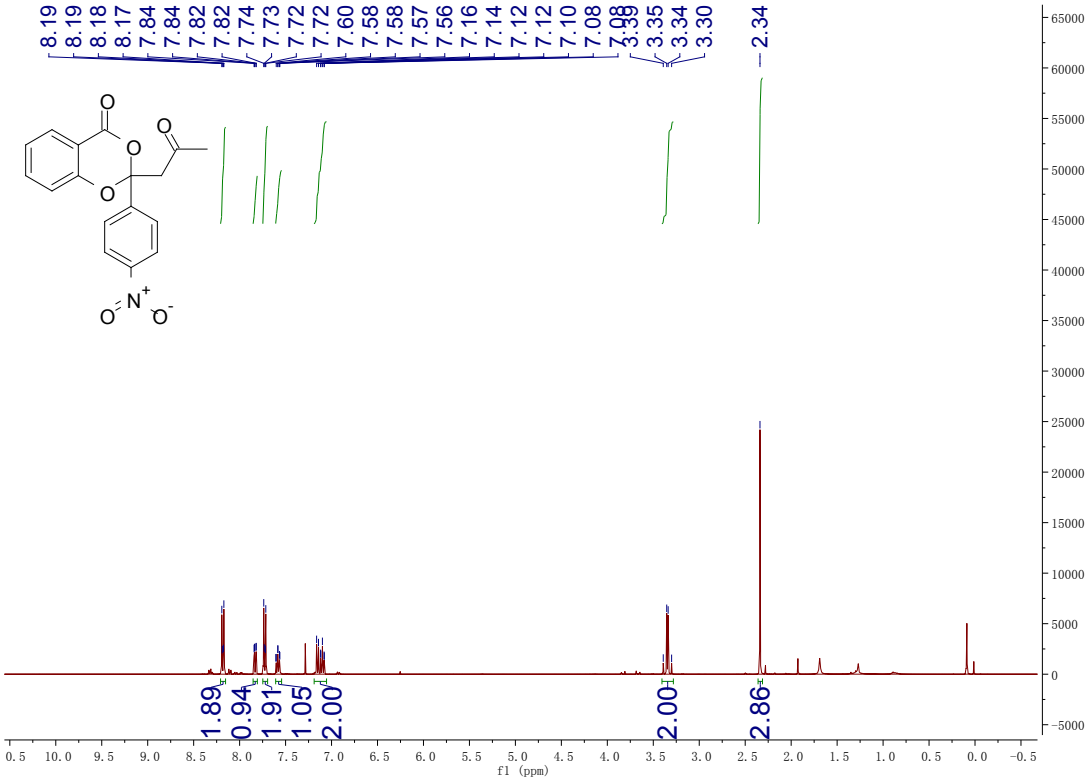
^{1}H NMR for **3o**:



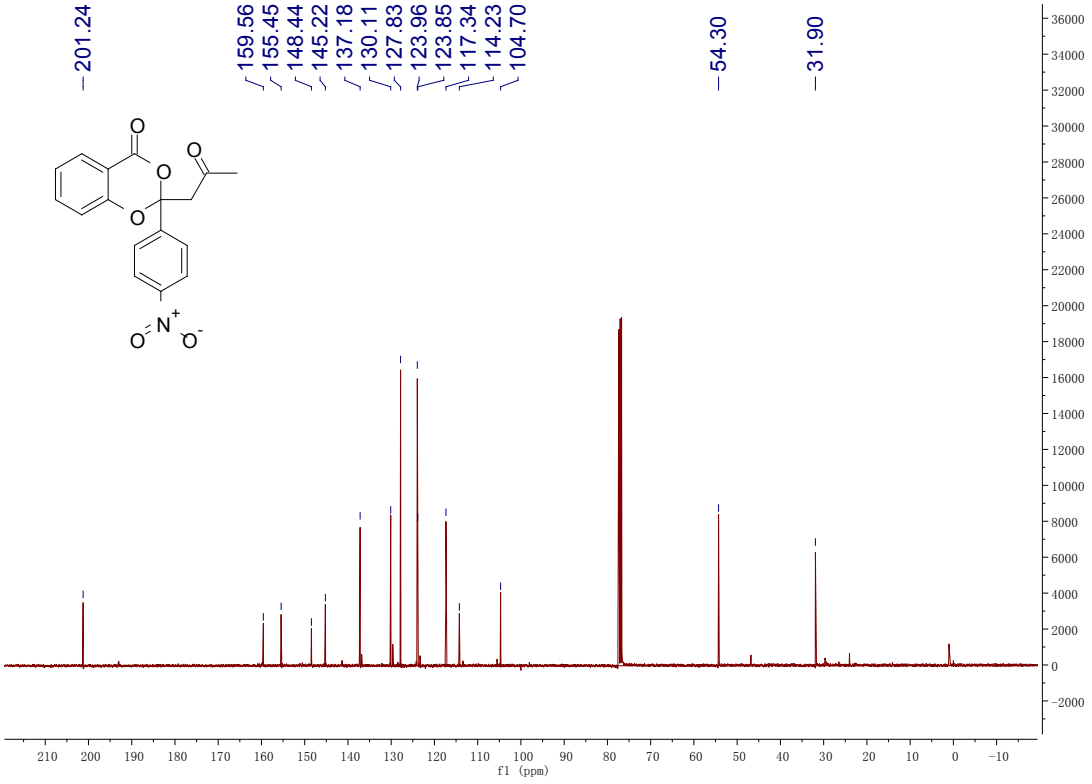
^{13}C NMR for **3o**:



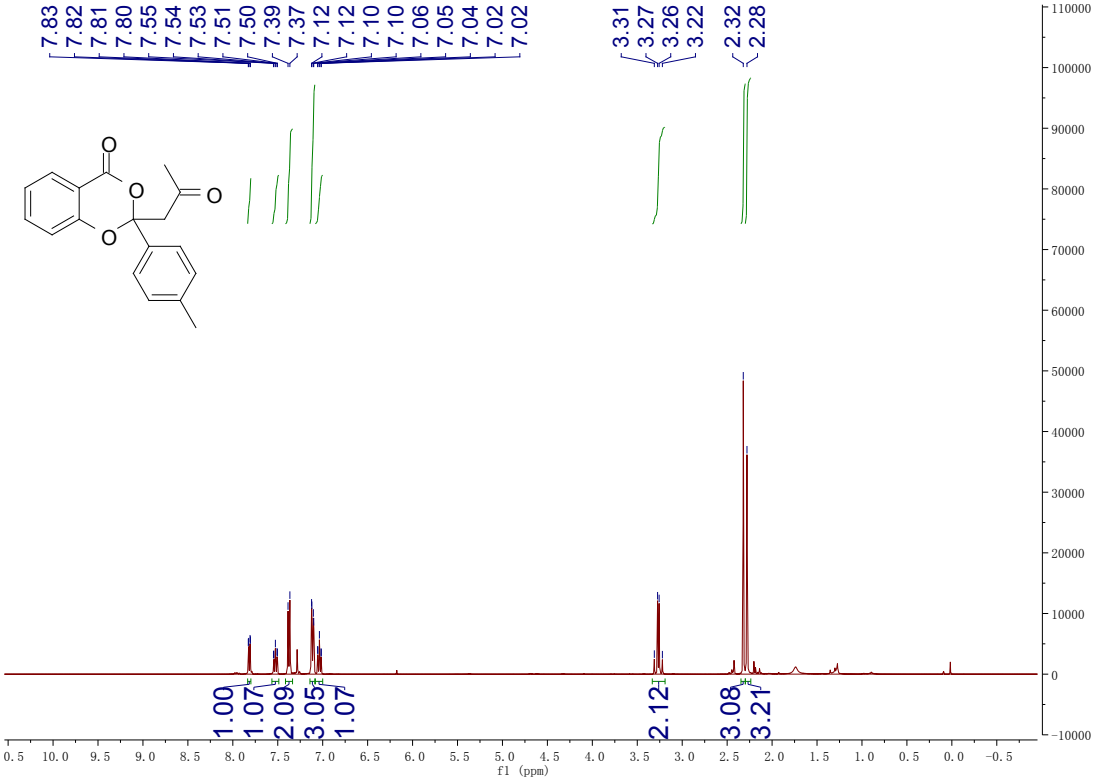
^{1}H NMR for **3p**:



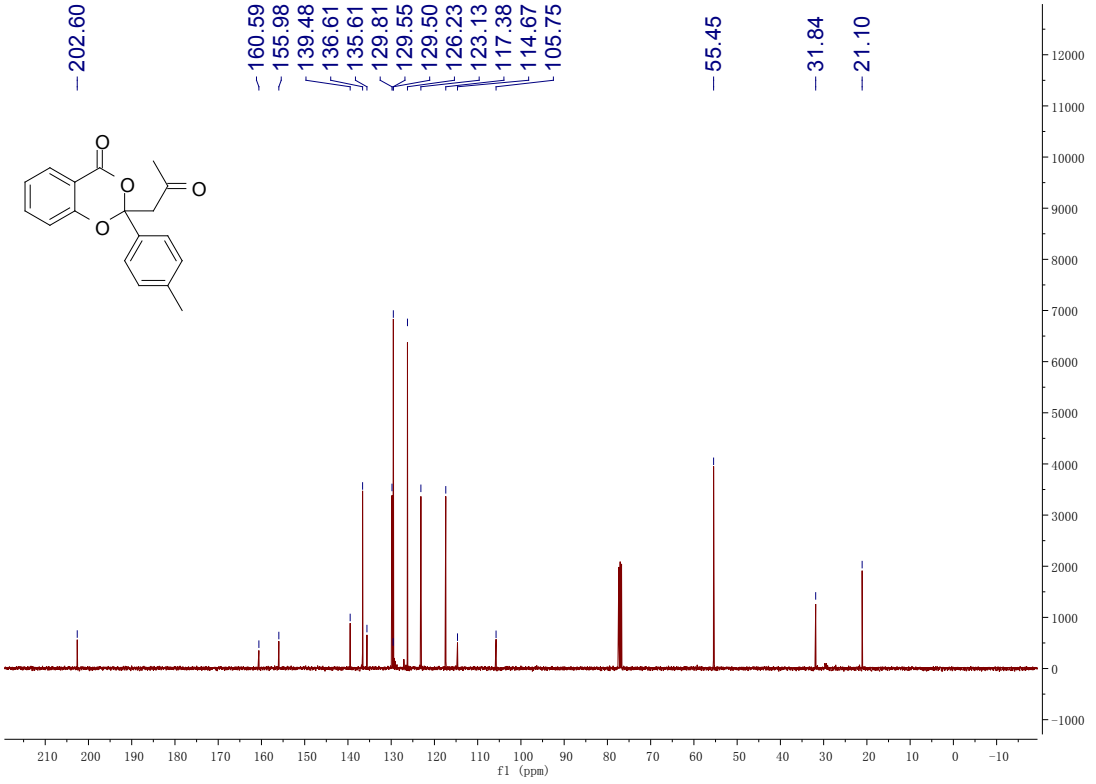
^{13}C NMR for **3p**:



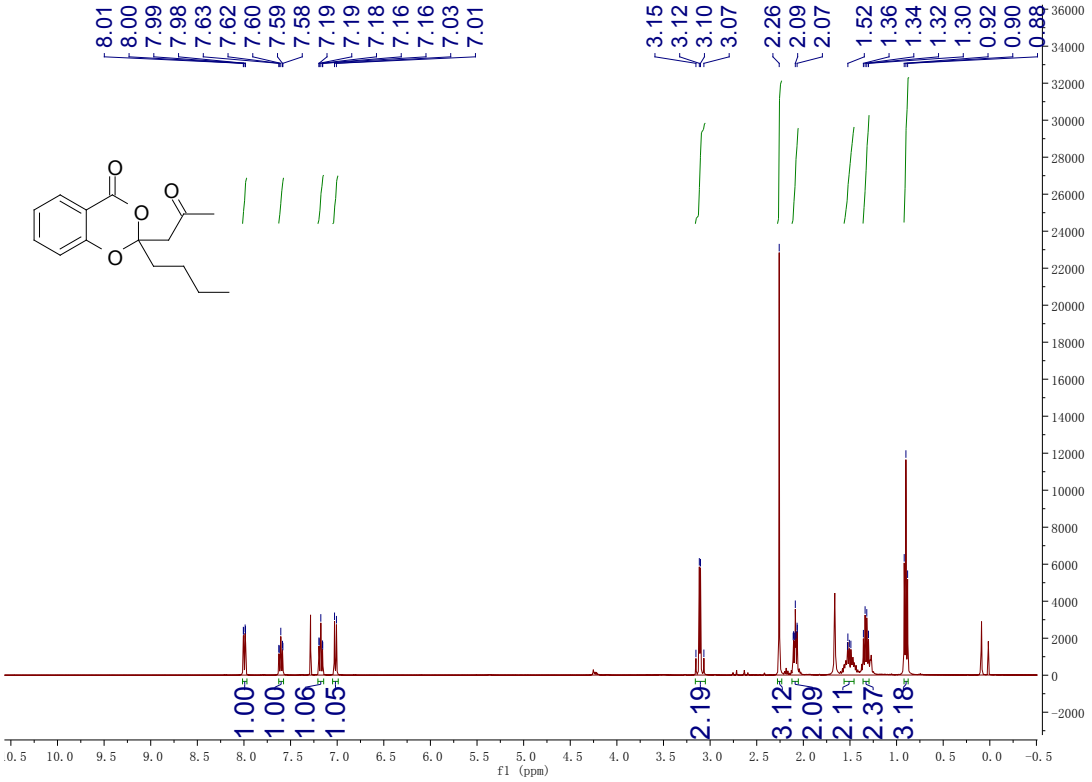
^{1}H NMR for **3q**:



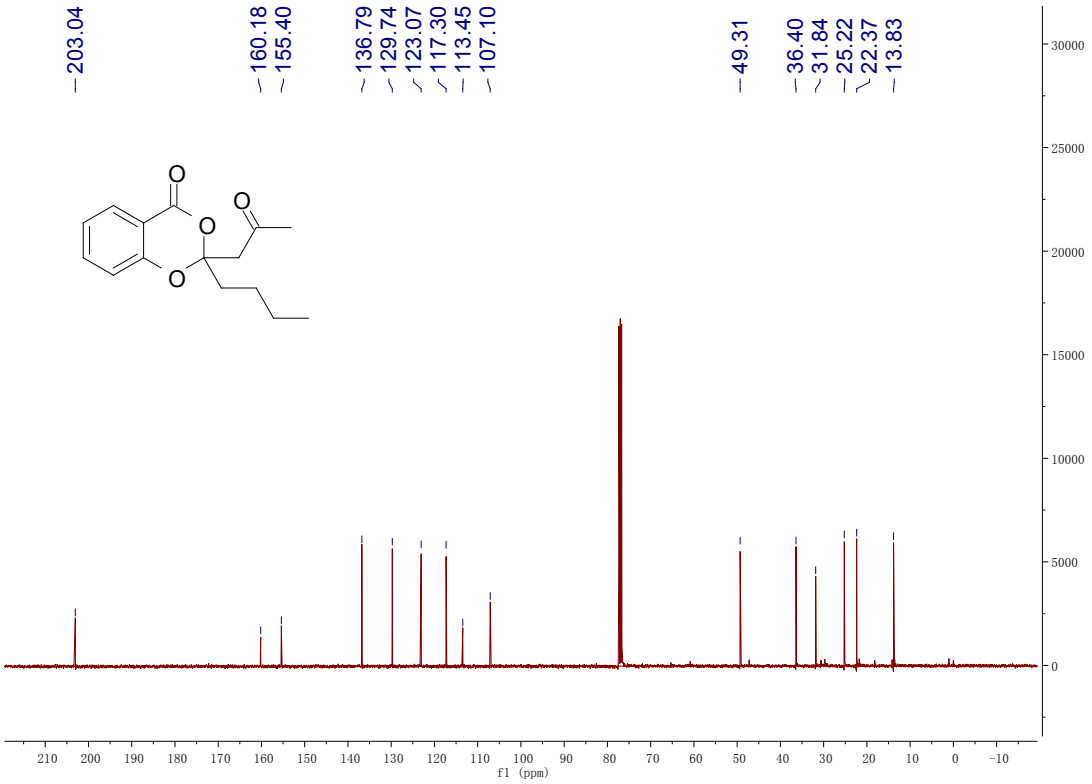
^{13}C NMR for **3q**:



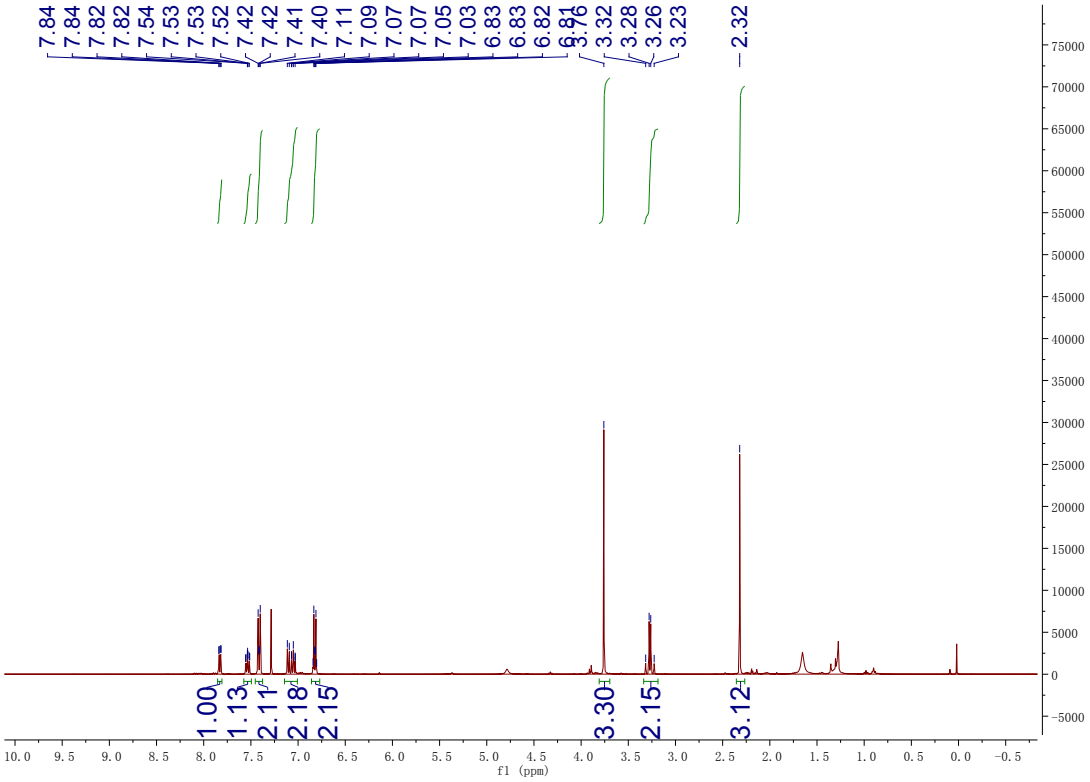
^{1}H NMR for **3r**:



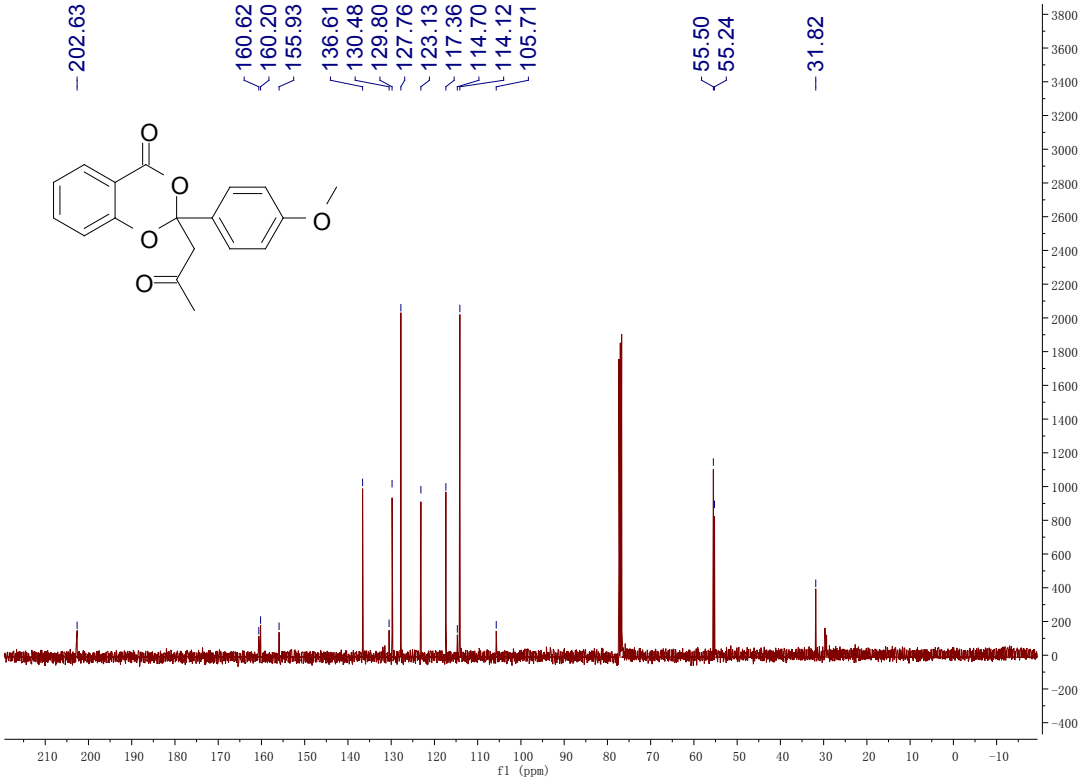
^{13}C NMR for **3r**:



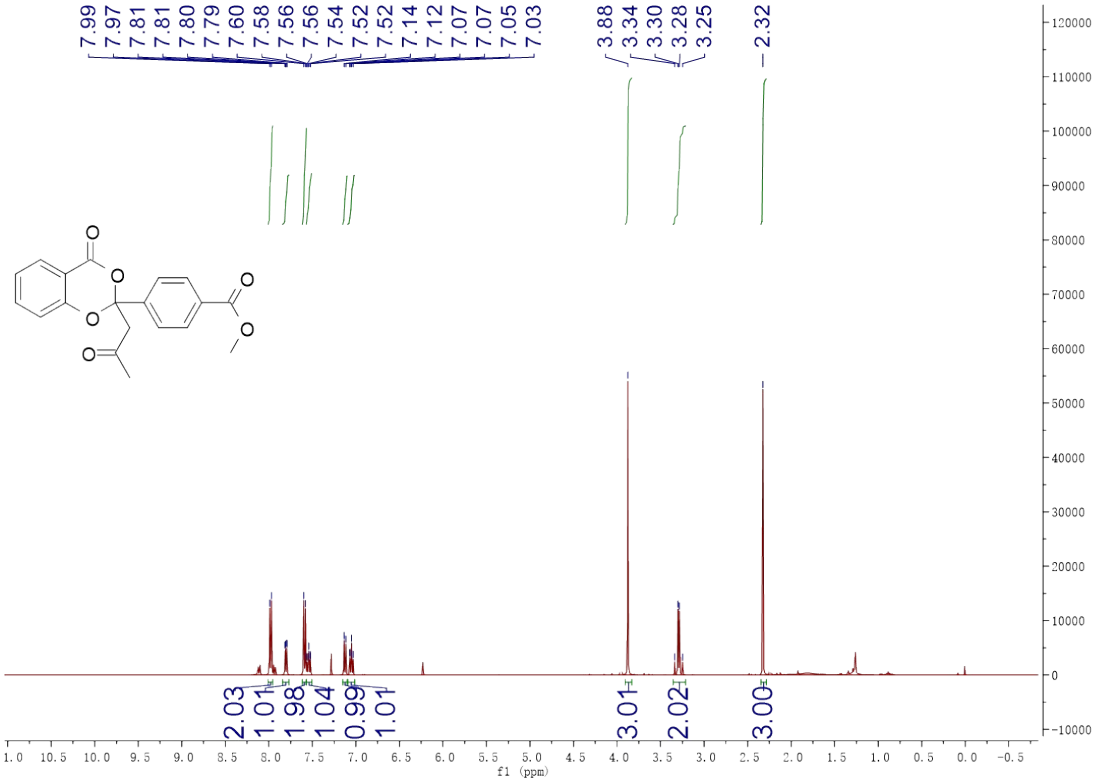
^{1}H NMR for **3s**:



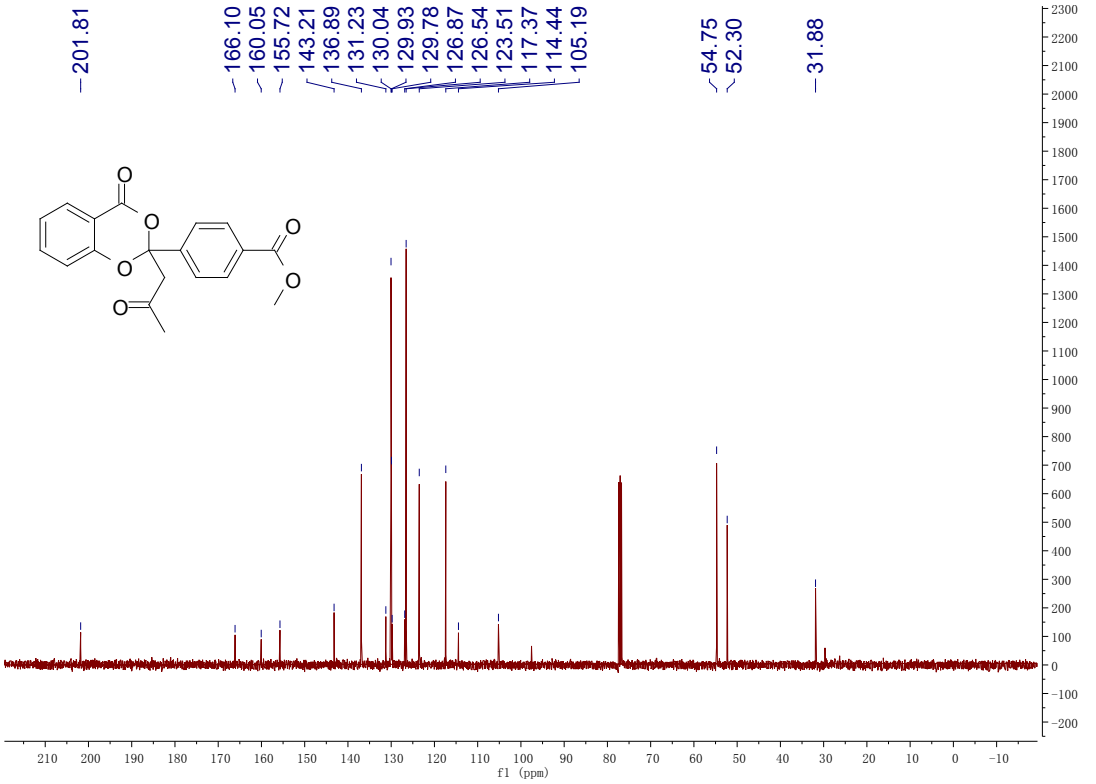
^{13}C NMR for **3s**:



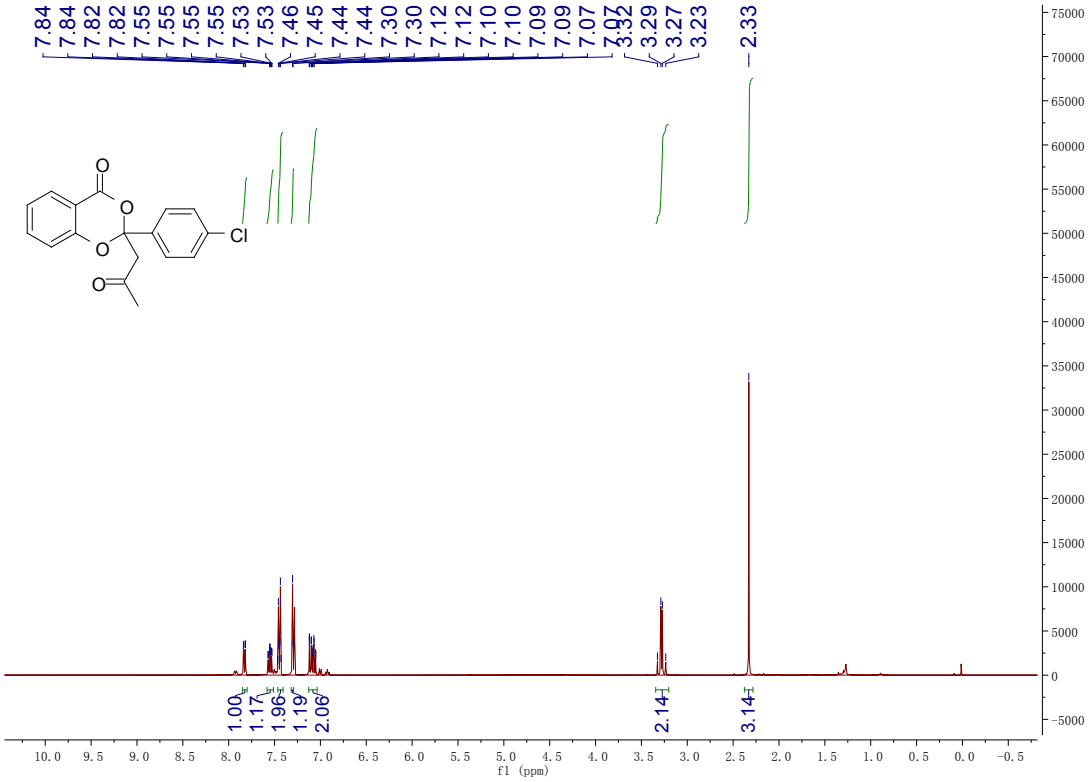
^{1}H NMR for **3t**:



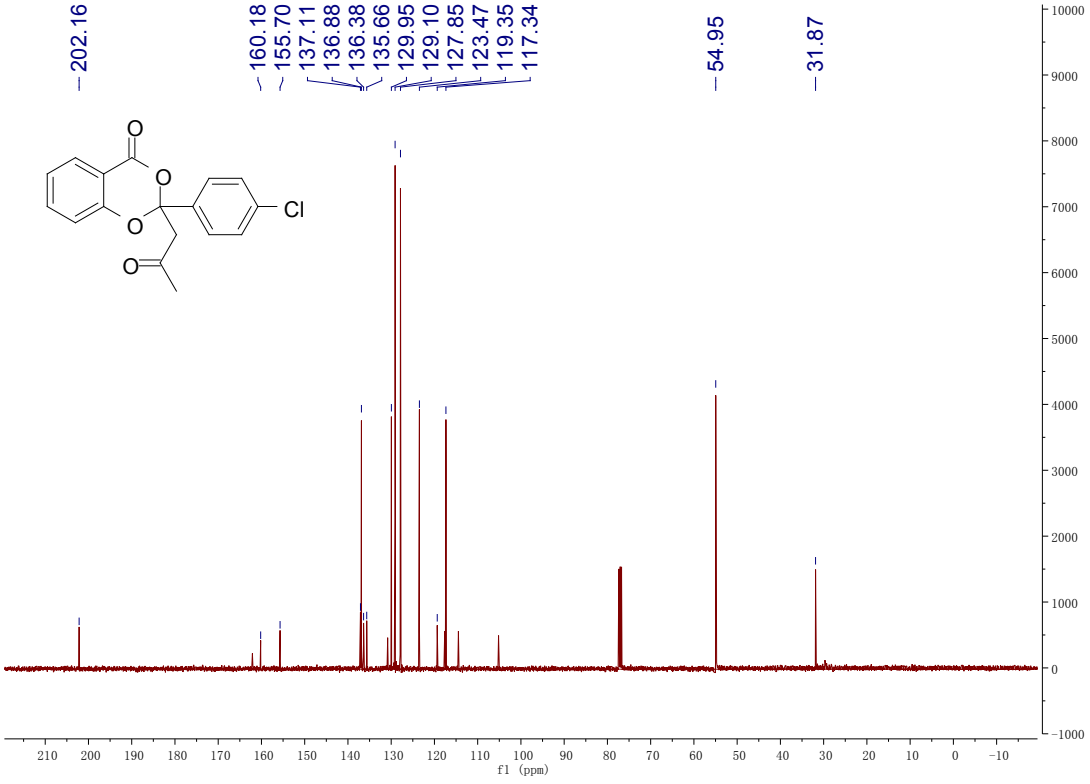
^{13}C NMR for **3t**:



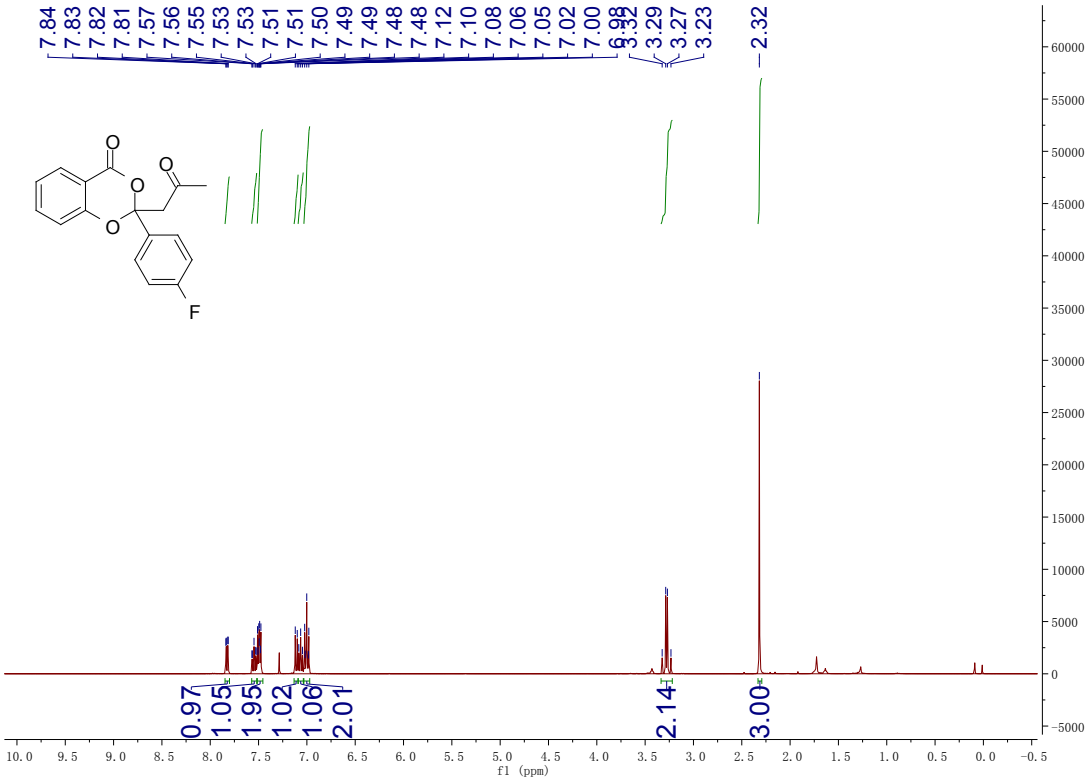
^{1}H NMR for **3u**:



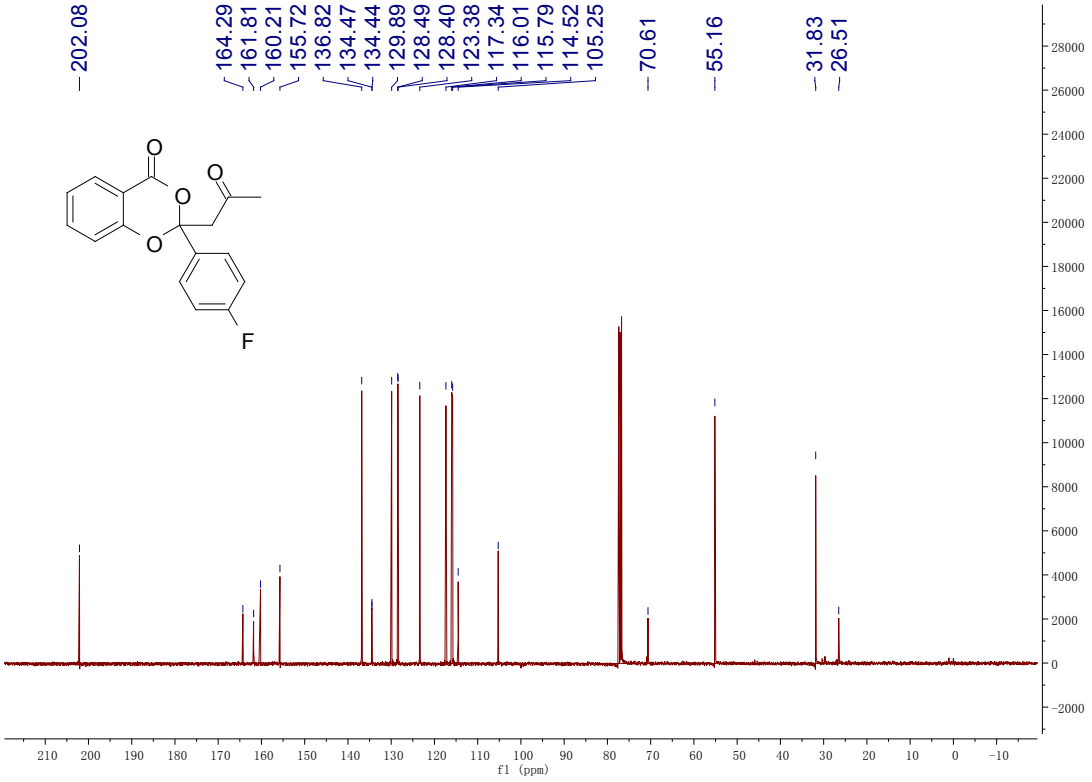
^{13}C NMR for **3u**:



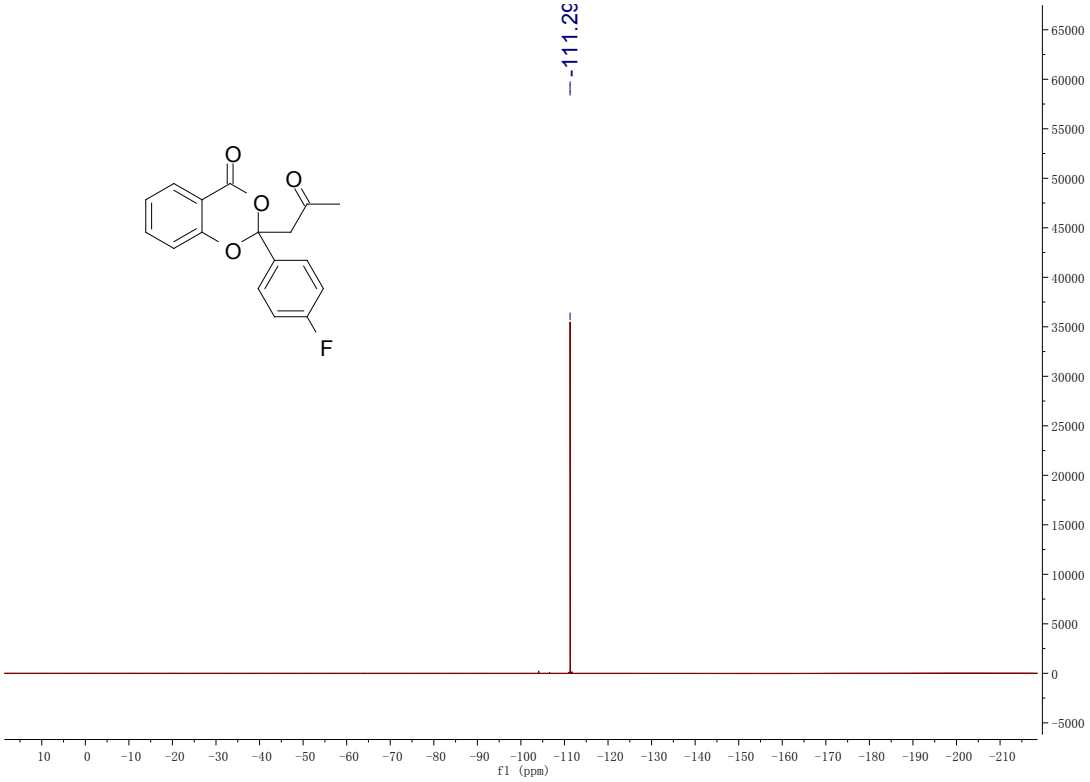
^{1}H NMR for **3v**:



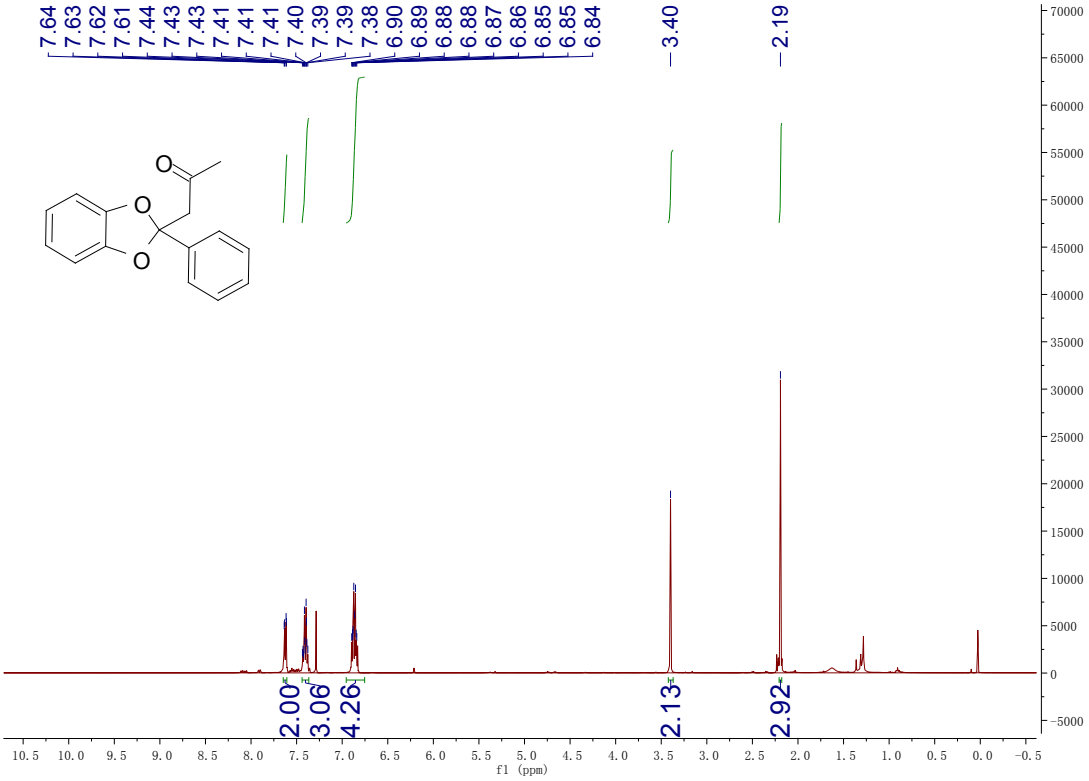
^{13}C NMR for **3v**:



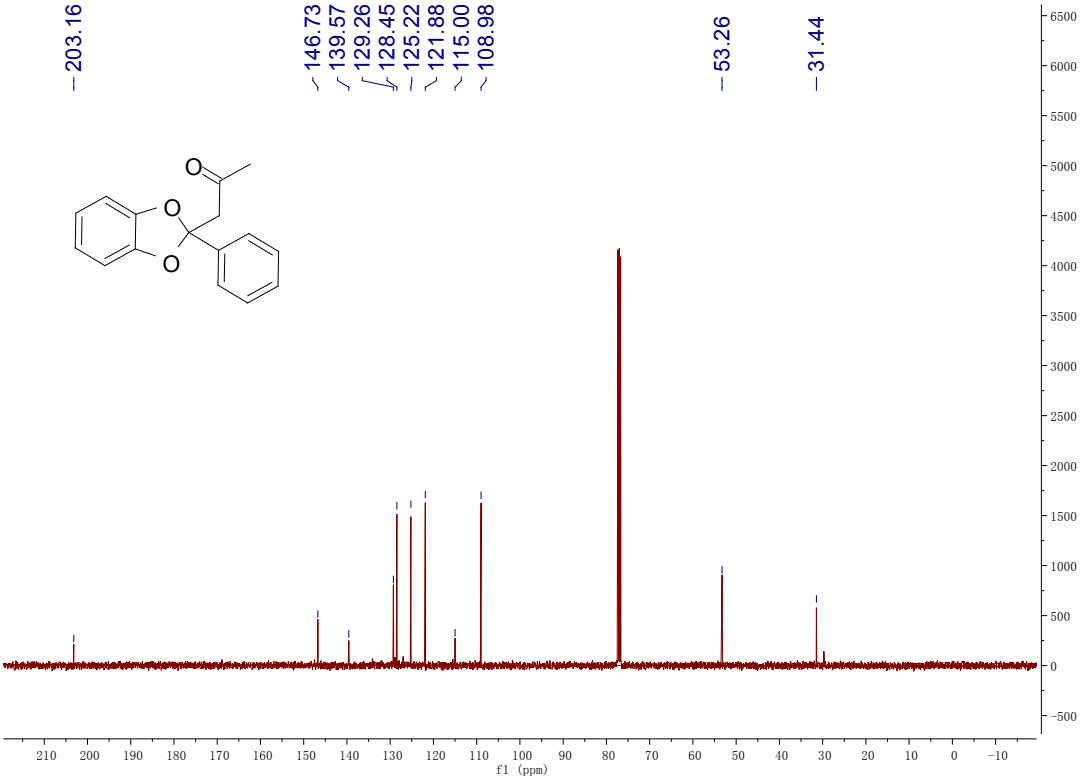
^{19}F NMR for **3v**:



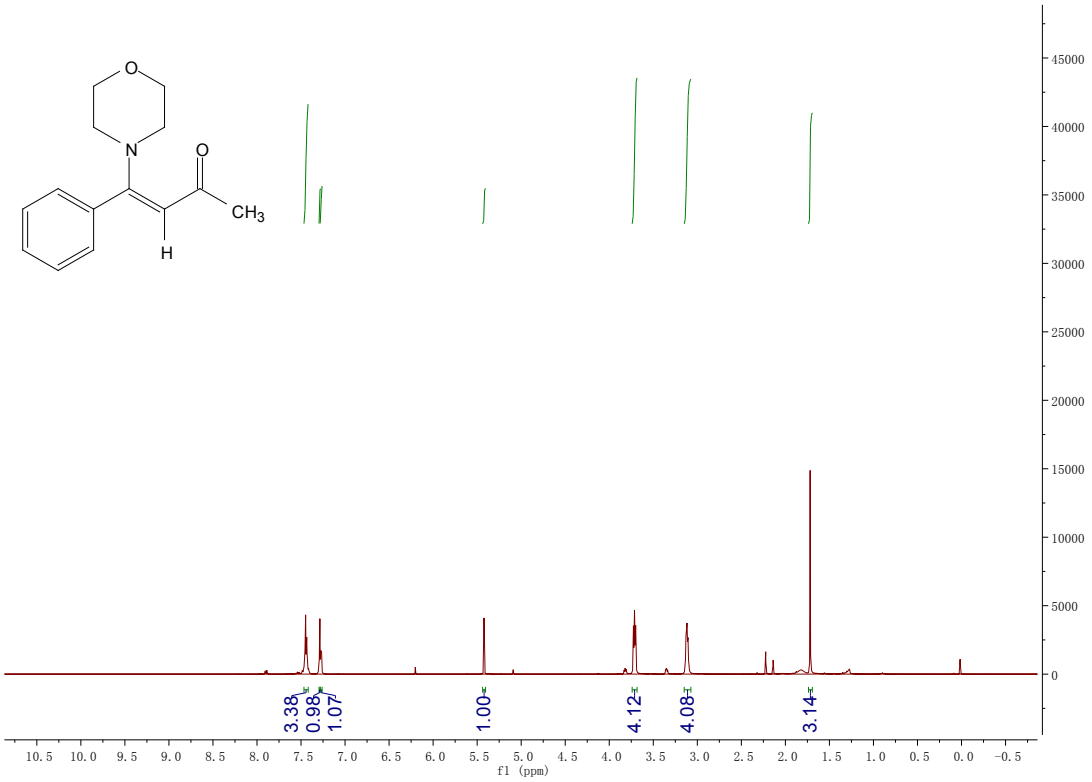
^{1}H NMR for **4a**:



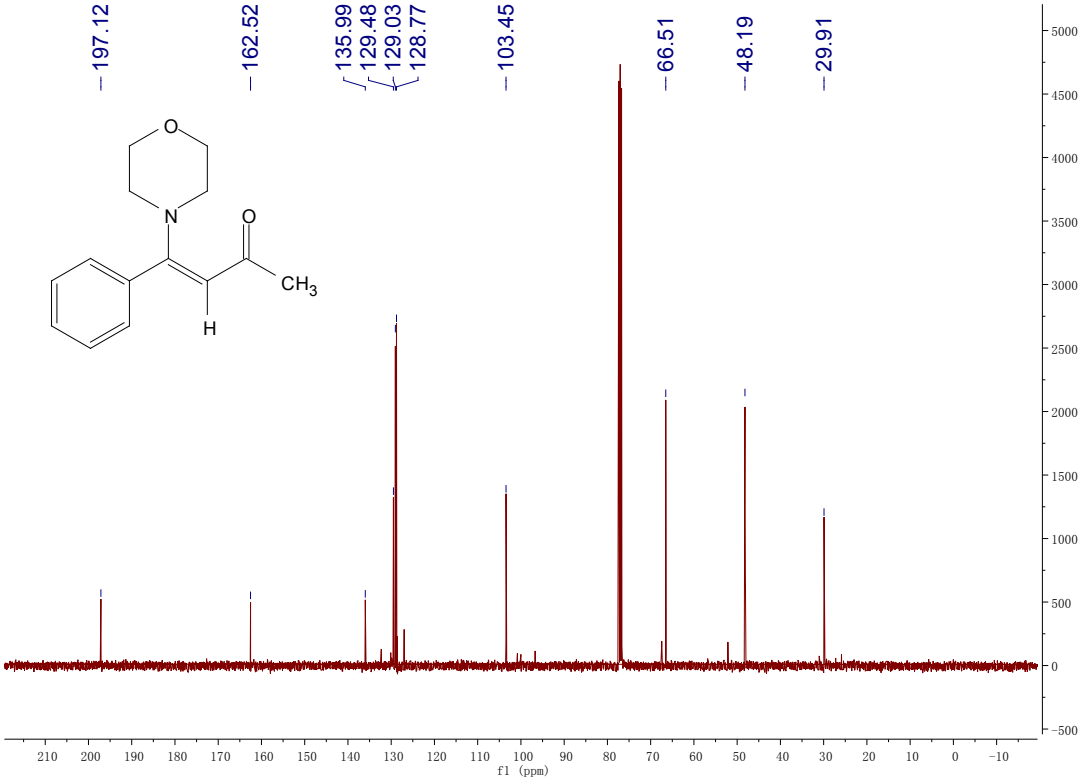
^{13}C NMR for **4a**:



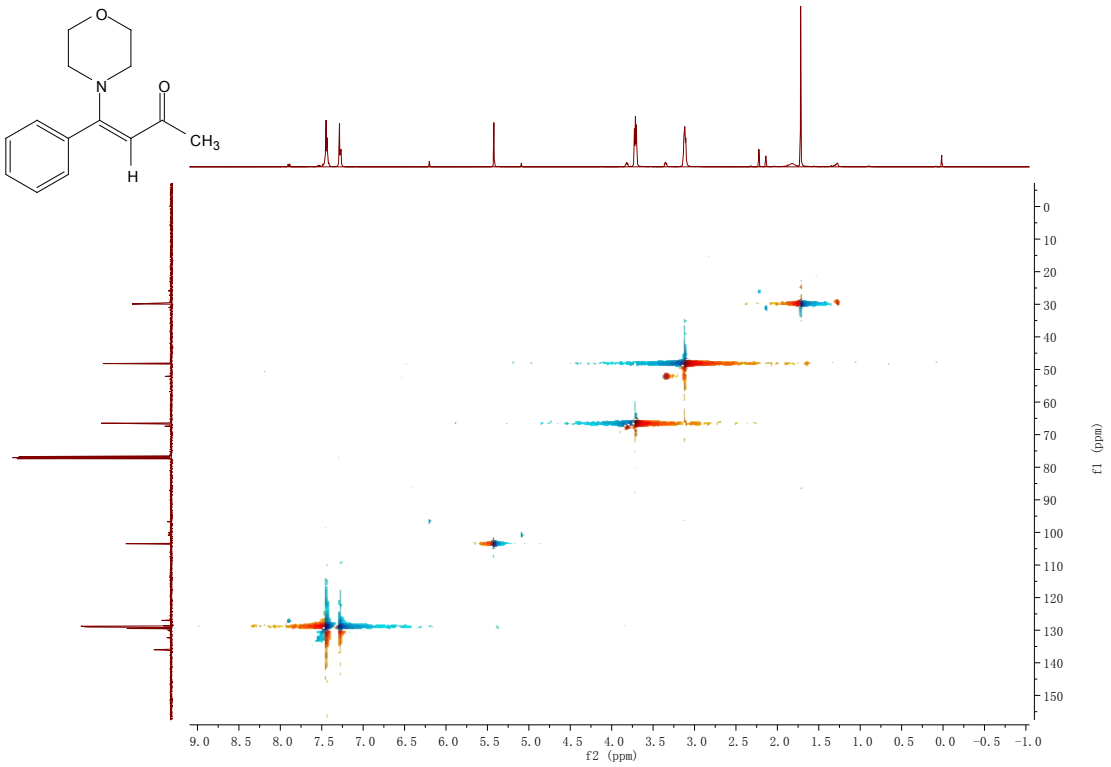
^{1}H NMR for intermediate **5**:



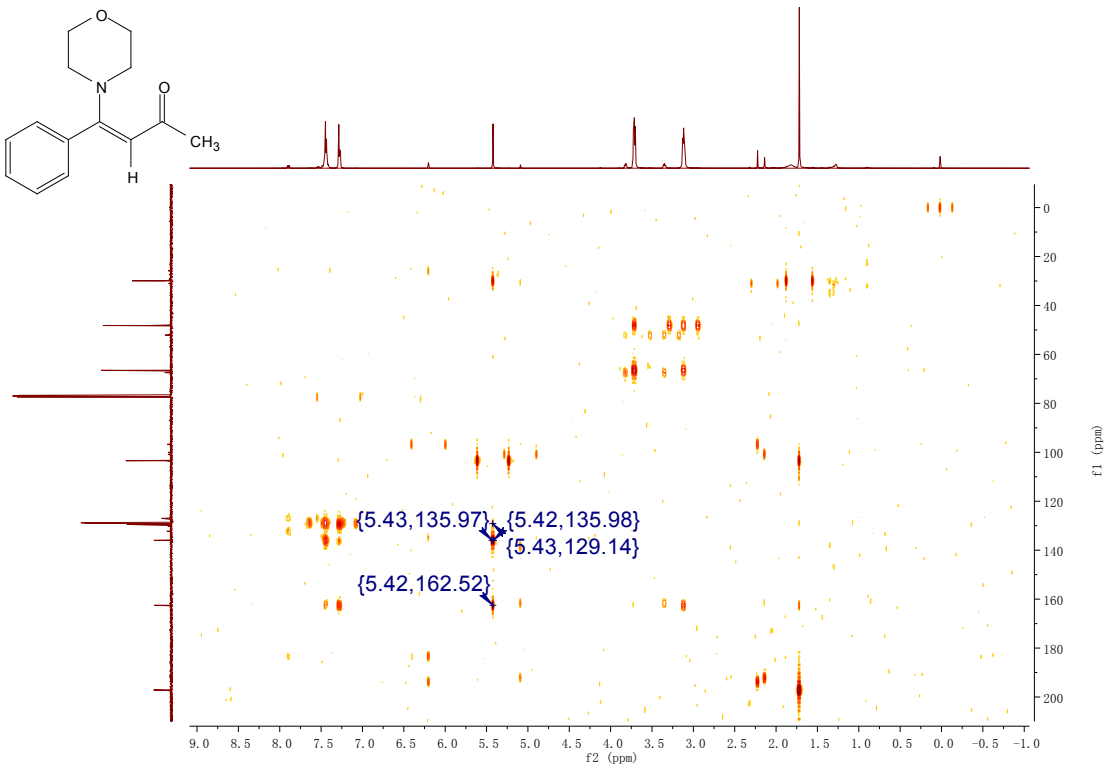
^{13}C NMR for intermediate **5**:



HSQC for intermediate **5**:



HMBC for intermediate **5**:



Expansion of the HMBC spectrum correlation for δ 5.43 (^{1}H NMR) proton signal: