Supporting Information

Continuous-flow electrosynthesis of 4-(sulfonylmethyl)isoquinoline-1,3(2H,4H)-diones from N-Alkyl-N-methacryloyl benzamides under metal-free and oxidant-free

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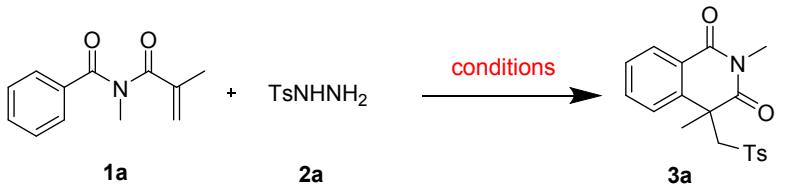
1.General information

Unless otherwise indicated, all the regents and solvents were purchased from commercial suppliers and used without any further purification. ^{1}H spectra were recorded in $CDCl_3$ or (Methyl sulfoxide)-d6 on 400MHz NMR spectrometers and resonances (•) are given in parts per million relatives to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q =quartet, p = penta, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, m = multiplet, br = broad), coupling constant (J) in Hertz (Hz), and integration. ^{13}C NMR were recorded at 100 MHz and chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent. Column chromatography was generally performed on Silicycle silica gel (200-300 mesh). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated silica gel plates (HSGF 254) and visualized the course of the reactions using a UV light (254 nm or 365 nm). High-resolution mass spectra (HRMS) were obtained on an Agilent mass spectrometer using ESI-TOF (electrosprayionization-time of flight).

2. Optimization of reaction conditions in electrolytic batch reactor

Table S1. Optimization of reaction conditions in electrolytic batch[a]



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

Entry	Anode/cathode	Solvent	Electrolyte(equiv.)	I (mA)	Yield[b] (%)
1	C (+)/Pt (-)	DCE	nBu_4NPF_6 (2)	15	12
2	C (+)/Pt (-)	DMF	nBu_4NPF_6 (2)	15	14
3	C (+)/Pt (-)	MeCN	nBu_4NPF_6 (2)	15	22
4	C (+)/Pt (-)	1,4-Dioxane/H_2O (4/1)	nBu_4NPF_6 (2)	15	44
5	C (+)/Pt (-)	MeCN/H_2O (2/1)	nBu_4NPF_6 (2)	15	62
6	C (+)/Pt (-)	**MeCN/H_2O (3/1)**	**nBu_4NPF_6 (2)**	**15**	**76**
7	C (+)/Pt (-)	MeCN/H_2O (4/1)	nBu_4NPF_6 (2)	15	72
8	C (+)/Pt (-)	MeCN/H_2O (5/1)	nBu_4NPF_6 (2)	15	69
9	C (+)/Pt (-)	MeCN/H_2O (3/1)	$LiClO_4$ (2)	15	71
10	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NBF_4 (2)	15	67
11	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NI (2)	15	15
12	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	0	0
13	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	5	31
14	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	10	52
15	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	20	41
16	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (1)	15	65
17	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (3)	15	74
18	Pt (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	15	12
19	C (+)/C (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	15	42
20	C/PVDF (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	15	71
21	C (+)/Cu (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	15	64
22	C (+)/Pt (-)	MeCN/H_2O (3/1)	nBu_4NPF_6 (2)	15	75[c]

[a] Reaction conditions: undivided cell, graphite anode, Pt plate cathode, constant current =15 mA, **1a** (0.5mmol), **2a** (1.5 mmol), electrolyte (1.0 mmol), solvent (10 mL), under air, room temperature, 3h. [b] Isolated yield. [c] N_2 instead of air.

A series of conditions including electrode, electrolyte, current, solvent and reactant equivalent radio were also screened in a batch reactor. The N-Alkyl-N-methacryloyl benzamides **1a** and 4-methylbenzenesulfonyl hydrazide **2a** were chosen as the model reaction to search for optimal reaction conditions. With $^{n}Bu_4NPF_6$ as the electrolyte and the current of the 15 mA, a series of solvents were explored. The results disclosed that the cosolvent of CH_3CN/H_2O (v/v=3:1) might be the best choice (Table S1 entries 1-8). Moreover, the effect of

various electrolytes was also investigated. However, the other electrolytes such as $LiClO_4$, nBu_4NBF_4 and nBu_4NI could not improve the yield of **3a** (Table S1 entries 9-11). Compared with the reaction condition of 15 mA, the reaction conditions of 5, 10, and 20 mA all resulted in a lower conversion (Table S1, entries 13–15). Further exploration focused on electrochemical parameters, and the reaction was shown to fail to proceed without the applied constant current (Table S1, entry 12). Either decreasing or increasing the equivalents of nBu_4NPF_6 led to lower yield (Table S1, entries 16–17). In addition, the reaction with different electrodes could resulted in a drop of the yields of product **3a** (Table S1 entries 18-21). Finally, N_2 atmosphere instead of air was tested, and the results show that the yield of product **3a** was no obvious change (Table S1 entries 22).

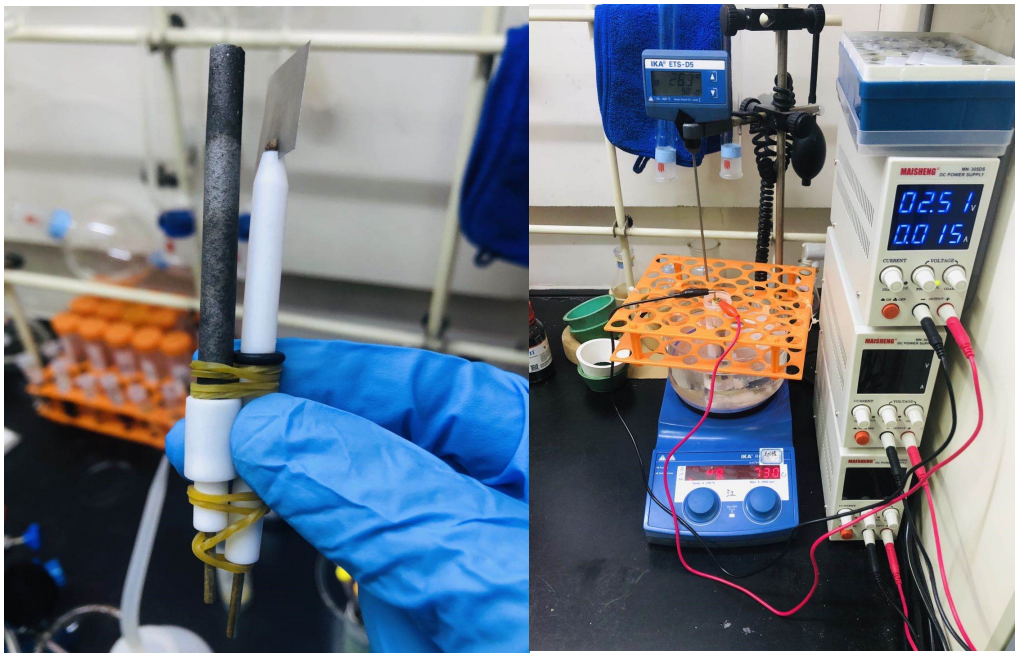


Figure S1 electrodes and batch reactor

graphite rod anode：Φ 6 mm; Pt plate cathode: 20 mm×20 mm×0.1 mm.

3. Electrochemistry continuous flow system

Reactions are performed in a novel flow electrochemistry system (the Asia Flux module). This system includes pumps, flow cell, working prototype cell holder and control module. The flow cell consists of pairs of electrodes separated by a gasket. Electrode materials include stainless steel, carbon, magnesium and stainless steel with a platinum coating (also discussing copper, tin, and titanium) and the cell can be divided by a membrane to isolate the chemistry at the anode from the chemistry at the cathode. The working prototype cell holder holds the electrodes in place, enables quick fluidic and electrical connections and locates in the syrris range of temperature controllers (e.g. The Asia Chip Climate Controller). The control modulecontrols the current/voltage applied to the electrodes, displays the temperature and locates the holder on the front of the module for room temperature applications.

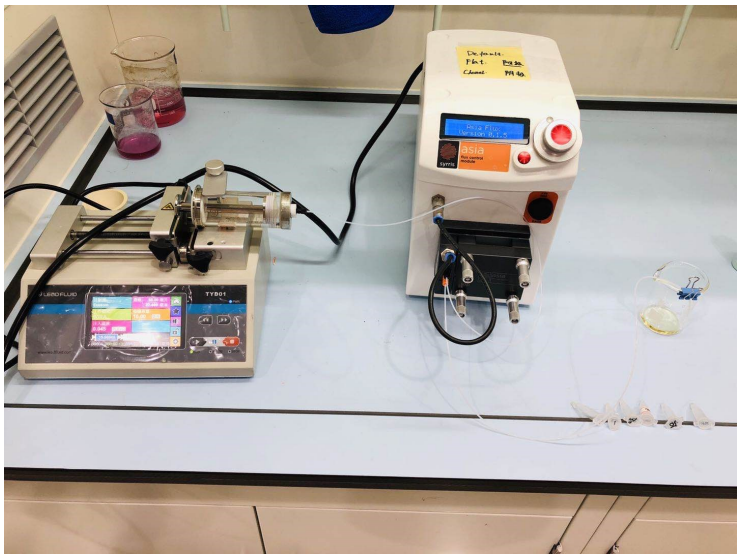


Figure S2 Electrochemistry continuous flow system

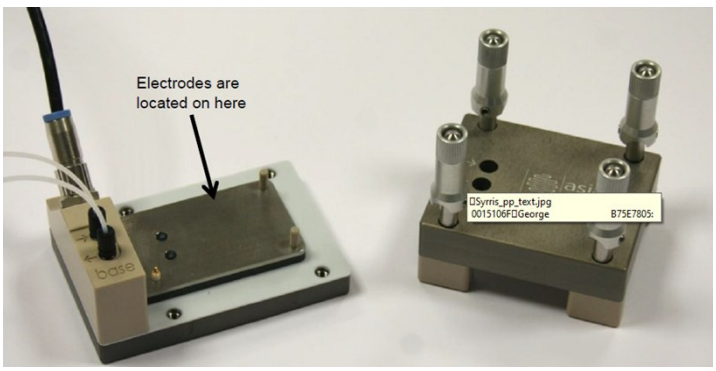


Figure S3 Flow cell holder

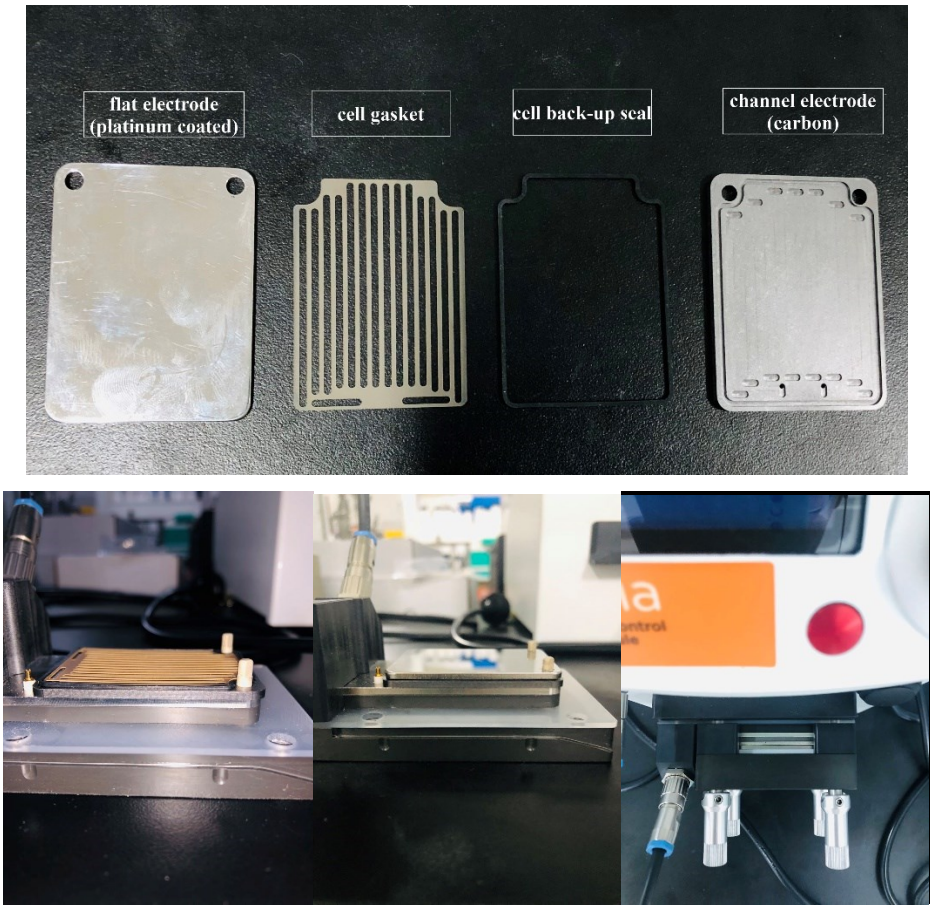
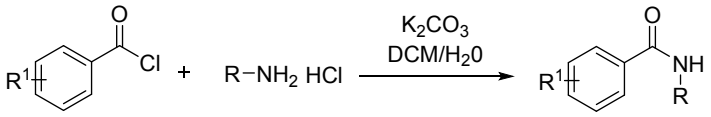


Figure S4 Flow cell materials and gasket

Carbon plate: 50 mm x 40 mm x 2.5 mm; Pt plate: 50 mm x 40 mm x 2.5 mm; flow cell volume =225 µL

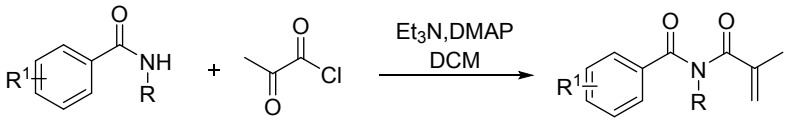
4. General procedure for the synthesis of product 3a in electrochemistry continuous flow system

General procedure for synthesis of N-methyl benzamide[1]



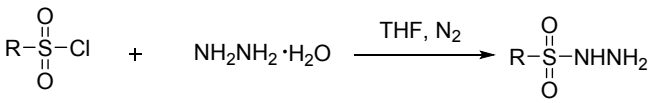
A 100-mL round bottom flask was charged with methylamine hydrochloride (15 mmol), K_2CO_3 (20 mmol) in Ethyl acetate (20 mL) and H_2O (10 mL) and benzoyl chloride (10 mmol) was added slowly to the reaction mixture at 0℃. After that, the residue was stirred at room temperature for 4-6 h. The reaction was completed by TLC monitoring, the organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The resulting residue was purified by flash silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 1: 1) to afford the desired products with 93% yield.

General procedure for synthesis of N-methacryloyl-N-methylbenzamide 1a[1]



A 100-mL round bottom flask was charged with N-methyl benzamide (10 mmol), DMAP (1 mmol), triethylamine (20 mmol) in dichloromethane (20 mL) and methacryloyl chloride (15 mmol) was added slowly to the reaction mixture at 0℃. After that, the residue was stirred at room temperature for 4-6 h. The reaction was completed by TLC monitoring, the organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The resulting residue was purified by flash silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 3: 1) to afford the desired products **1a** with 77% yield.

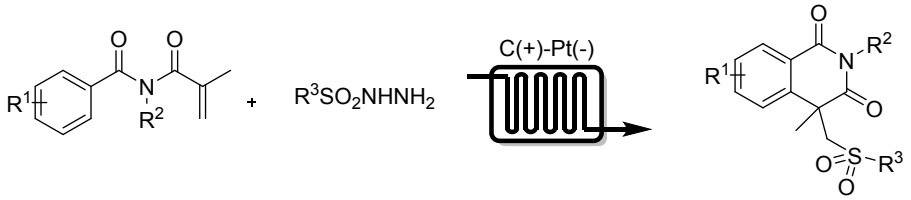
General procedure for the preparation of sulfonyl hydrazides 2a[2]



Sulfonyl hydrazides were prepared according to a literature procedure. The

hydrazinemonohydrate (30 mmol) was added dropwise into the solution of sulfonyl chloride (10 mmol) in THF (50 mL) under nitrogen at 0 °C. Subsequently, the mixture was further stirred at 0 °C for 30minutes. After the completion of the reaction, the solvent was removed by evaporation, and the residue was extracted with dichloromethane (3 x 20 mL), and the combined organic layer was washed with water, and brine, and dried over Na_2SO_4.Concentration in vacuum followed by silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 1: 1) to give the desired product **2a** in yields range from 70-95%.

General procedure for the synthesis of product 3a in electrochemistry continuous flow system



First, assembled and installed the flow electrochemistry device, the anode as graphite plate, cathode as platinum plate and the cell volume was 225 μL. Second, **1a** (0.5 mmol), **2a** (1 mmol, 2 equiv.) and nBu_4NPF_6 (1.0 mmol, 2 equiv.) were dissolved in CH_3CN/H_2O (10 mL, v/v = 3/1). The reaction mixture was pumped into the flow cell via a syringe and electrolyzed at a constant current of 15 mA at room temperature. The flow rate was 225 μL/min and residence time 1 minute. The out flow of the reaction mixture was collected. The solvent was removed with a rotary evaporator. The pure product **3a** was obtained by flash chromatography on silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 3: 2).

5. Procedure for cyclic voltammetry (CV)

Cyclic voltammetry was performed in a three-electrode cell connected to a schlenk line under nitrogen at room temperature. The working electrode was a steady glassy carbon disk electrode, the counter electrode a platinum wire. The reference was an Ag/AgCl electrode submerged in saturated aqueous KCl solution. (1) A mixed solvent ($MeCN/H_2O$= 3/1, 10 mL) containing nBu_4NPF_6 (1 mmol) were poured into the electrochemical cell in cyclic voltammetry

experiments. The scan rate was 0.10 V/s, ranging from 0 V to 2.5 V. (2) **1a** (0.5 mmol) and a mixed solvent (MeCN/H_2O= 3/1, 10 mL) containing nBu_4NPF_6 (1 mmol) were poured into the electrochemical cell in cyclic voltammetry experiments. The scan rate was 0.10 V/s, ranging from 0V to 2.5 V. (3) **2a** (1 mmol) and a mixed solvent (MeCN/H_2O= 3/1, 10 mL) containing nBu_4NPF_6 (1 mmol) were poured into the electrochemical cell in cyclic voltammetry experiments. The scan rate was 0.10 V/s, ranging from 0V to 2.5 V.

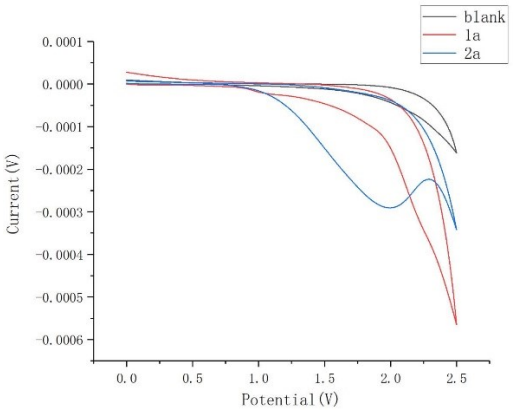
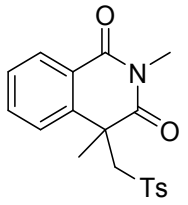


Figure S5 Cyclic voltammogram: (1) black; (2) **1a** 0.5 mmol; (3) **2a** 1 mmol.

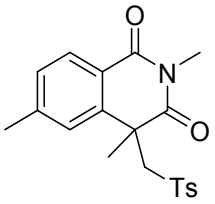
6. Faradaic efficiency of 3a[3]

$$\eta = \frac{moles\ of\ product\ (measurd\ by\ isolated)}{j\left(\frac{mA}{cm^2}\right) \times \frac{t(s)}{nF}} \times 100\% = 31.79\%$$

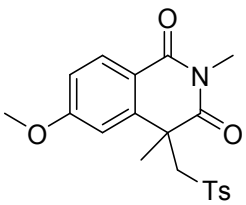
7. Analytical data of products 3[4-7]



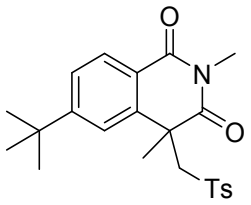
2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3a**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 79% isolated yield, m. p. = 140.2-142.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (d, J = 7.5 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 7.3 Hz, 1H), 7.14 (d, J = 8.1 Hz, 2H), 4.43 (d, J = 14.6 Hz, 1H), 3.91 (d, J = 14.6 Hz, 1H), 3.39 (s, 3H), 2.38 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.38, 163.83, 144.52, 139.12, 137.10, 133.45, 129.68, 129.16, 128.02, 127.59, 125.97, 124.70, 64.78, 45.35, 31.58, 27.54, 21.59. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{19}H_{20}NSO_4^{+}$ 358.1108 found 358.1172.



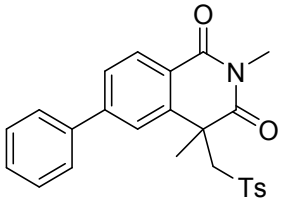
2,4,6-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3b**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 77% isolated yield, m. p. = 196.7-199.3℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.10 (d, J = 8.0 Hz, 2H), 6.78 (s, 1H), 4.44 (d, J = 14.7 Hz, 1H), 3.89 (d, J = 14.7 Hz, 1H), 3.40 (s, 3H), 2.37 (s, 3H), 2.15 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.43, 163.79, 144.31, 144.22, 138.77, 137.20, 129.47, 129.18, 129.03, 127.48, 126.38, 122.32, 64.76, 45.21, 31.51, 27.43, 21.51, 21.49. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{20}H_{22}NSO_4^{+}$ 372.1624 found 372.1653.



6-methoxy-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3c**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 75% isolated yield, m. p. = 178.0-180.4℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 3.84 (d, J = 14.7 Hz, 1H), 3.70 (s, 3H), 3.38 (s, 3H), 2.38 (s, 3H), 1.56 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.38, 163.60, 163.45, 144.39, 141.09, 137.27, 131.47, 129.55, 127.61, 117.74, 114.14, 110.85, 64.79, 55.35, 45.58, 31.71, 27.41, 21.55. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{20}H_{22}NSO_5^{+}$ 388.1213 found 388.1282.

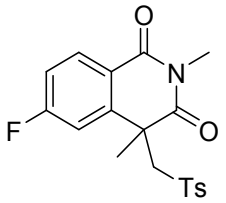


6-(tert-butyl)-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3d**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 74% isolated yield, m. p. = 167.1-168.4℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, J = 8.3 Hz, 1H), 7.43 (dd, J = 8.4, 1.7 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 1.6 Hz, 1H), 7.11 (d, J = 8.1 Hz, 2H), 4.46 (d, J = 14.7 Hz, 1H), 3.96 (d, J = 14.7 Hz, 1H), 3.39 (s, 3H), 2.35 (s, 3H), 1.59 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 13C NMR (101 MHz, Chloroform-d) δ 174.64, 163.81, 157.36, 144.44, 138.85, 137.34, 129.63, 129.06, 127.71, 125.57, 122.49, 122.32, 65.18, 45.65, 35.17, 31.79, 30.88, 27.45, 21.60. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{23}H_{28}NSO_4^{+}$ 414.1734 found 414.1763.

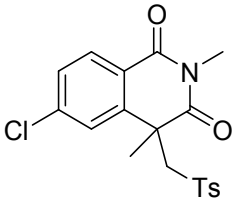


2,4-dimethyl-6-phenyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3e**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 70% isolated yield, m. p. = 192.9-194.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (d, J = 8.2 Hz, 1H), 7.60 (dd, J = 8.2, 1.6 Hz, 1H), 7.45 – 7.38 (m, 3H), 7.35 (dd, J = 7.8, 1.7 Hz, 2H),

7.27 (s, 1H), 7.26 (d, J = 1.9 Hz, 1H), 7.23 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 8.0 Hz, 2H), 4.52 (d, J = 14.8 Hz, 1H), 4.02 (d, J = 14.8 Hz, 1H), 3.43 (s, 3H), 2.16 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.50, 163.72, 146.20, 144.62, 139.41, 138.82, 137.22, 129.83, 129.62, 128.89, 128.62, 127.45, 127.20, 126.76, 124.56, 123.65, 65.00, 45.64, 31.57, 27.60, 21.44. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{25}H_{24}NSO_4^+$ 434.1421 found 434.1397.

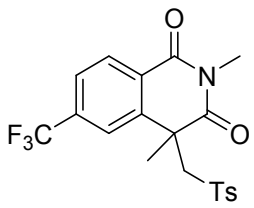


6-fluoro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3f**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 75% isolated yield, m. p. = 186.3-189.2℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 – 8.25 (m, 1H), 7.37 (d, J = 6.8 Hz, 2H), 7.17 (d, J = 7.7 Hz, 2H), 7.13 – 7.06 (m, 1H), 6.81 (dd, J = 9.2, 2.4 Hz, 1H), 4.46 – 4.39 (m, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.40 (s, 3H), 2.39 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.88, 165.77 (d, J=254 Hz), 162.88, 144.84, 142.07 (d, J=9 Hz), 136.99, 132.22 (d, J=10 Hz), 129.76, 127.51, 121.26 (d, J=3 Hz), 116.00 (d, J=22 Hz), 112.99 (d, J=23 Hz), 64.63, 45.51, 31.44, 27.57, 21.55. ^{19}F NMR (400 MHz, Chloroform-*d*) δ -103.64 (s, 1F). HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{19}H_{19}NFSO_4^+$ 376.1013 found 376.1094.

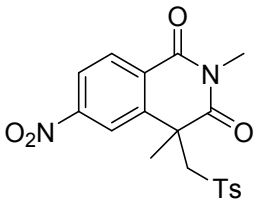


6-chloro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3g**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 77% isolated yield, m. p. = 208.1-210.9℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, J = 8.5 Hz, 1H), 7.34 (dd, J = 8.5, 1.9 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 6.97 (d, J = 1.9 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 3.83 (d, J = 14.8 Hz, 1H), 3.42 (s, 3H), 2.40 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 13C NMR (101 MHz, Chloroform-d) δ 173.72, 162.97, 144.88, 140.53, 140.08, 136.88, 130.79, 129.79, 128.63, 127.33, 126.22, 123.38,

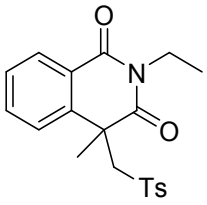
64.65, 45.29, 31.33, 27.66, 21.60. HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{19}NClSO_4^+$ 392.0718 found 392.0727.



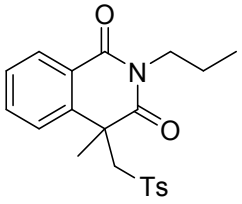
2,4-dimethyl-4-(tosylmethyl)-6-(trifluoromethyl)isoquinoline-1,3(2H,4H)-dione (**3h**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 63% isolated yield, m. p. = 192.6-194.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.33 – 7.20 (m, 3H), 7.09 (d, J = 8.1 Hz, 2H), 4.47 (d, J = 14.9 Hz, 1H), 4.01 (d, J = 14.9 Hz, 1H), 3.45 (s, 3H), 2.35 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.71, 162.72, 144.95, 139.86, 136.75, 134.74 (q, J = 33 Hz), 129.99, 129.75, 127.80, 127.16, 124.82 (q, J = 3 Hz), 123.14 (q, J = 4 Hz), 122.95 (d, J = 272 Hz), 64.79, 45.37, 31.04, 27.73, 21.42. ^{19}F NMR (400 MHz, Chloroform-*d*) δ -63.13 (s, 3F). HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{20}H_{19}NF_3SO_4^+$ 426.0981 found 426.0964.



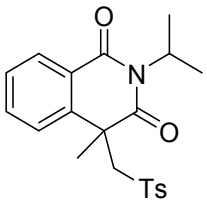
2,4-dimethyl-6-nitro-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3i**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 47% isolated yield, m. p. = 208.5-209.0℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, J = 8.7 Hz, 1H), 8.20 (dd, J = 8.7, 2.1 Hz, 1H), 7.90 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.50 (d, J = 14.8 Hz, 1H), 3.95 (d, J = 14.8 Hz, 1H), 3.47 (s, 3H), 2.35 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.27, 162.09, 150.32, 145.03, 140.56, 136.80, 130.96, 129.94, 129.52, 127.25, 122.70, 121.56, 64.52, 45.52, 31.05, 27.95, 21.43. HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{19}H_{19}N_2SO_6^+$ 403.0958 found 403.0931.



2-ethyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3j**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 72% isolated yield, m. p. = 112.7-114.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (dd, J = 7.7, 1.5 Hz, 1H), 7.42 – 7.32 (m, 4H), 7.20 – 7.10 (m, 3H), 4.44 (d, J = 14.6 Hz, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.91 (d, J = 14.6 Hz, 1H), 2.38 (s, 3H), 1.56 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.97, 163.37, 144.44, 139.21, 137.37, 133.34, 129.69, 129.20, 127.96, 127.52, 125.88, 124.87, 64.71, 45.36, 36.06, 31.59, 21.59, 12.74. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{20}H_{22}NSO_4^{+}$ 372.1264 found 372.1255.

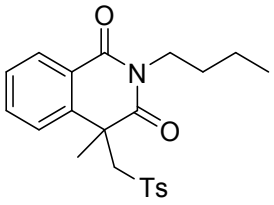


4-methyl-2-propyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3k**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 70% isolated yield, m. p. = 125.3-127.8℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dd, J = 7.5, 1.7 Hz, 1H), 7.47 – 7.34 (m, 4H), 7.17 (t, J = 7.3 Hz, 3H), 4.46 (d, J = 14.6 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.89 (d, J = 14.5 Hz, 1H), 2.39 (s, 3H), 1.73 (dt, J = 15.4, 7.5 Hz, 2H), 1.57 (s, 3H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.15, 163.53, 144.43, 139.20, 137.38, 133.29, 129.67, 129.30, 127.96, 125.78, 124.82, 64.57, 45.44, 42.45, 31.78, 21.57, 20.86, 11.47. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{21}H_{24}NSO_4^{+}$ 386.1421 found 386.1479.

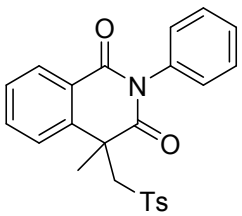


2-isopropyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3l**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 :

1) in 71% isolated yield, m. p. = 141.1-142.4℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.26 (dd, J = 7.8, 1.4 Hz, 1H), 7.41 – 7.30 (m, 4H), 7.14 (d, J = 8.0 Hz, 2H), 7.13 – 7.10 (m, 1H), 5.25 (p, J = 6.9 Hz, 1H), 4.44 (d, J = 14.5 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 2.38 (s, 3H), 1.59 – 1.51 (m, 9H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.35, 163.90, 144.30, 139.12, 137.61, 133.08, 129.65, 129.26, 127.88, 127.44, 125.59, 125.41, 64.74, 45.85, 45.67, 31.46, 21.56, 19.54, 19.22. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{21}H_{24}NSO_4^+$ 386.1421 found 386.1471.

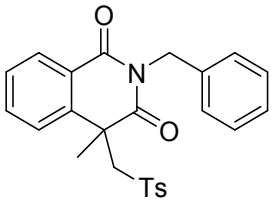


2-butyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3m**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 66% isolated yield, m. p. = 133.2-135.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dd, J = 7.6, 1.7 Hz, 1H), 7.44 – 7.34 (m, 4H), 7.16 (td, J = 5.4, 4.9, 2.4 Hz, 3H), 4.46 (d, J = 14.6 Hz, 1H), 4.01 (td, J = 7.7, 3.0 Hz, 2H), 3.89 (d, J = 14.6 Hz, 1H), 2.39 (s, 3H), 1.73 – 1.62 (m, 2H), 1.56 (s, 3H), 1.43 (dt, J = 15.1, 7.5 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.10, 163.51, 144.41, 139.19, 137.36, 133.28, 129.66, 129.27, 127.95, 127.55, 125.78, 124.84, 64.58, 45.43, 40.75, 31.75, 29.54, 21.57, 20.30, 13.85. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{22}H_{26}NSO_4^+$ 400.1577 found 400.1542.

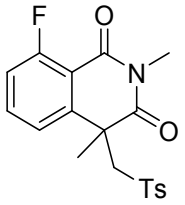


4-methyl-2-phenyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3n**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 62% isolated yield, m. p. = 213.1-214.5℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.36 – 8.27 (m, 1H), 7.54 (t, J = 7.6 Hz, 2H), 7.49 – 7.41 (m, 5H), 7.40 – 7.31 (m, 2H), 7.24 (d, J = 4.3 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 4.45 (d, J = 14.5 Hz, 1H), 3.94 (d, J = 14.5 Hz, 1H), 2.39 (s, 3H), 1.70

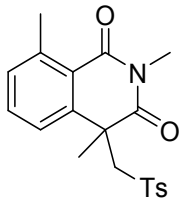
(s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.51, 163.87, 144.49, 139.39, 137.49, 135.55, 133.70, 129.78, 129.69, 129.37, 128.74, 128.46, 128.20, 127.55, 126.01, 124.99, 65.23, 45.91, 31.46, 21.61. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{24}H_{22}NSO_4^+$ 420.1264 found 420.1231.



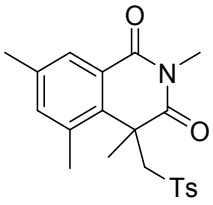
2-benzyl-4-methyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3o**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 68% isolated yield, m. p. = 174.1-177.9℃. ^{1}H NMR (400 MHz, Chloroform-d) 8.28 (dd, J = 5.8, 3.5 Hz, 1H), 7.46 (d, J = 7.3 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.35 (dd, J = 8.4, 2.3 Hz, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.25 – 7.19 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 5.29 – 5.16 (m, 2H), 4.46 (d, J = 14.6 Hz, 1H), 3.92 (d, J = 14.6 Hz, 1H), 2.38 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 174.31, 163.59, 144.53, 139.43, 137.51, 137.03, 133.60, 129.72, 129.50, 128.46, 128.44, 128.06, 127.64, 127.38, 125.85, 124.75, 64.45, 45.87, 44.06, 31.78, 21.62. HRMS (TOF) m/z [M + H]+ Calcd for $C_{25}H_{24}NSO_4^+$ 434.1421 found 434.1472.



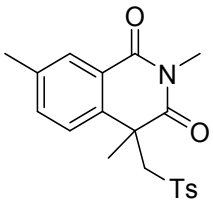
8-fluoro-2,4-dimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3p**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 61% isolated yield, m. p. = 177.1-178.0℃. ^{1}H NMR (400 MHz, Chloroform-*d*) 7.52 – 7.40 (m, 3H), 7.22 (d, J = 7.6 Hz, 2H), 7.12 (t, J = 9.3 Hz, 2H), 4.45 (d, J = 14.5 Hz, 1H), 3.89 (d, J = 14.6 Hz, 1H), 3.37 (s, 3H), 2.41 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.55, 162.63 (d, J = 266 Hz), 160.71 (d, J = 5Hz), 144.81, 141.74, 137.18, 134.55 (d, J = 11 Hz), 129.78, 127.66, 122.01, 116.61 (d, J = 22Hz), 113.74, 64.76, 45.38, 31.87, 27.41, 21.62. ^{19}F NMR (400 MHz, Chloroform-*d*) δ -108.65 (s, 1F). HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{19}H_{19}NFSO_4^+$ 376.1013 found 376.1044.



2,4,8-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3q**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 67% isolated yield, m. p. = 182.3-184.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 7.7 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.7 Hz, 1H), 4.45 (d, J = 14.5 Hz, 1H), 3.87 (d, J = 14.5 Hz, 1H), 3.37 (s, 3H), 2.81 (s, 3H), 2.40 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.04, 164.34, 144.51, 143.01, 140.54, 137.35, 132.32, 132.09, 129.62, 127.73, 124.20, 123.00, 65.01, 45.57, 32.18, 27.54, 24.16, 21.61. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{20}H_{22}NSO_4^{+}$ 372.1624 found 372.1673.

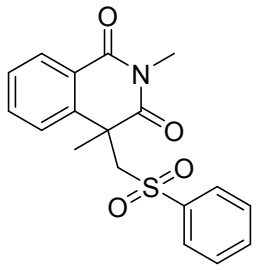


2,4,5,7-tetramethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3r**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 71% isolated yield, m. p. = 202.2-204.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.2 Hz, 2H), 7.02 (s, 1H), 4.48 (d, J = 14.8 Hz, 1H), 4.24 (d, J = 14.8 Hz, 1H), 3.36 (s, 3H), 2.40 (s, 6H), 2.36 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.59, 164.25, 144.53, 139.21, 138.00, 136.66, 135.72, 133.63, 129.48, 128.35, 127.79, 125.72, 62.00, 46.05, 27.82, 27.74, 22.36, 21.63, 20.72. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{21}H_{24}NSO_4^{+}$ 386.1421 found 386.1472.

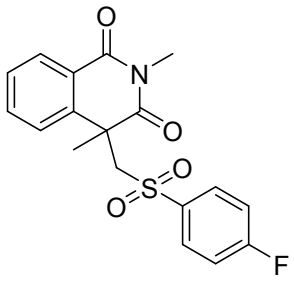


2,4,7-trimethyl-4-(tosylmethyl)isoquinoline-1,3(2H,4H)-dione (**3s**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 62%

isolated yield, m. p. = 134.4-136.8℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (s, 1H), 7.32 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.0 Hz, 3H), 7.03 (d, J = 8.0 Hz, 1H), 4.39 (d, J = 14.6 Hz, 1H), 3.89 (d, J = 14.6 Hz, 1H), 3.38 (s, 3H), 2.38 (s, 6H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.49, 163.98, 144.34, 138.06, 137.18, 136.20, 134.38, 129.54, 129.08, 127.59, 125.93, 124.46, 64.98, 45.02, 31.41, 27.48, 21.53, 20.98. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{20}H_{22}NSO_4^+$ 372.1624 found 372.1633.

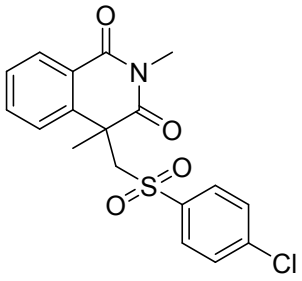


2,4-dimethyl-4-((phenylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**3t**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 77% isolated yield, m. p. = 175.1-177.1℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dd, J = 7.7, 1.4 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.2 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.35 – 7.32 (m, 1H), 7.15 (d, J = 7.6 Hz, 1H), 4.46 (d, J = 14.6 Hz, 1H), 3.94 (d, J = 14.6 Hz, 1H), 3.41 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.39, 163.82, 140.08, 138.98, 133.49, 133.48, 129.23, 129.12, 128.16, 127.52, 125.87, 124.72, 64.74, 45.37, 31.53, 27.60. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{18}NSO_4^+$ 344.0951 found 344.0955.

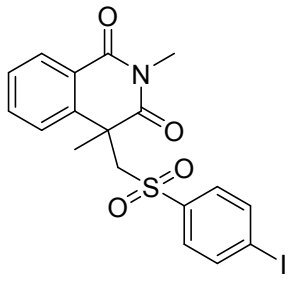


4-(((4-fluorophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3u**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 75% isolated yield, m. p. = 165.2-167.6℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (dd, J = 6.9, 2.3 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.46 – 7.37 (m, 2H), 7.17 (dd, J = 7.5, 1.4

Hz, 1H), 7.03 (t, J = 8.6 Hz, 2H), 4.47 (d, J = 14.7 Hz, 1H), 3.93 (d, J = 14.7 Hz, 1H), 3.43 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.34, 165.54 (d, J = 255 Hz) 163.73, 139.00, 136.26 (d, J = 3 Hz), 133.51, 130.47 (d, J = 10 Hz), 129.34, 128.24, 125.80, 124.78, 116.39 (d, J = 23 Hz), 64.90, 45.43, 31.50, 27.61. ^{19}F NMR (400 MHz, Chloroform-*d*) δ -103.35 (s, 1F). HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}NFSO_4^+$ 362.0857 found 362.0881.

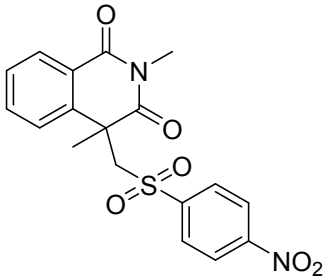


4-(((4-chlorophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3v**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 68% isolated yield, m. p. = 153.9-155.6℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (dd, J = 7.7, 1.6 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.33 (d, J = 8.7 Hz, 2H), 7.18 – 7.13 (m, 1H), 4.46 (d, J = 14.7 Hz, 1H), 3.92 (d, J = 14.7 Hz, 1H), 3.42 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.28, 163.70, 140.26, 138.94, 138.58, 133.54, 129.38, 129.35, 129.06, 128.24, 125.80, 124.78, 64.84, 45.42, 31.51, 27.61. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}NClSO_4^+$ 378.0561 found 378.0521.

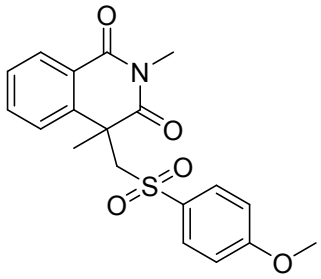


4-(((4-iodophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3w**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 69% isolated yield, m. p. = 183.1-186.8℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 8.5 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.28 (td, J = 7.6, 1.3 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 3H), 4.35 (d, J = 14.7 Hz, 1H), 3.85 (d, J = 14.7 Hz, 1H), 3.33 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.25, 163.69, 139.66, 138.88, 138.34,

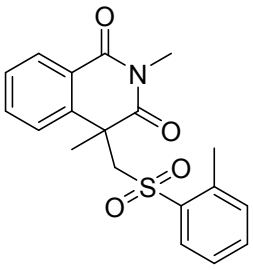
133.59, 129.27, 128.86, 128.18, 125.86, 124.74, 101.52, 64.78, 45.36, 31.46, 27.63. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}NISO_4^+$ 369.9917 found 369.9984.



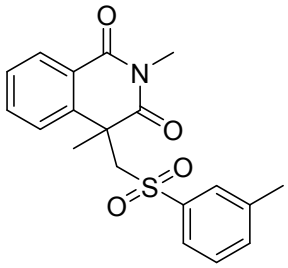
2,4-dimethyl-4-(((4-nitrophenyl)sulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**3x**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 58% isolated yield, m. p. = 189.2-190.5℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.24 (dd, J = 7.8, 1.4 Hz, 1H), 8.14 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 8.9 Hz, 2H), 7.37 (td, J = 7.7, 1.1 Hz, 1H), 7.33 – 7.27 (m, 1H), 7.09 (d, J = 7.9 Hz, 1H), 4.45 (d, J = 14.7 Hz, 1H), 3.91 (d, J = 14.7 Hz, 1H), 3.38 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.20, 162.55, 149.48, 144.75, 137.86, 132.53, 128.56, 128.03, 127.44, 124.56, 123.88, 123.19, 63.85, 44.55, 30.38, 26.66. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}N2SO_6^+$ 389.0802 found 389.0871.



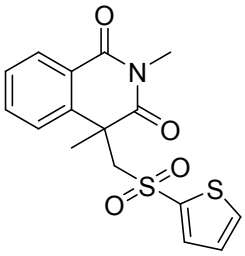
4-(((4-methoxyphenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3y**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 68% isolated yield, m. p. = 166.2-169.4℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (dd, J = 6.2, 3.1 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.37 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 7.21 – 7.16 (m, 1H), 6.79 (d, J = 9.0 Hz, 2H), 4.43 (d, J = 14.6 Hz, 1H), 3.90 (d, J = 14.6 Hz, 1H), 3.82 (s, 3H), 3.39 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.39, 163.83, 163.51, 139.17, 133.46, 131.54, 129.78, 129.16, 128.05, 126.00, 124.71, 114.26, 64.91, 55.74, 45.39, 31.59, 27.54. HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{19}H_{20}NSO_5^+$ 374.1057 found 374.1061.



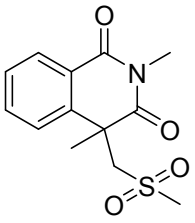
2,4-dimethyl-4-((o-tolylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**3z**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 62% isolated yield, m. p. = 182.7-184.9℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 (dd, J = 7.6, 1.5 Hz, 1H), 7.32 – 7.22 (m, 3H), 7.14 (t, J = 7.4 Hz, 2H), 7.06 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 4.35 (d, J = 14.6 Hz, 1H), 3.84 (d, J = 14.6 Hz, 1H), 3.27 (s, 3H), 2.56 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.16, 162.74, 137.97, 136.85, 136.52, 132.50, 132.30, 131.44, 128.42, 128.07, 127.10, 125.44, 124.65, 123.63, 62.70, 44.10, 30.49, 26.46, 19.27. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{19}H_{20}NSO_4^{+}$ 358.1108 found 358.1121.



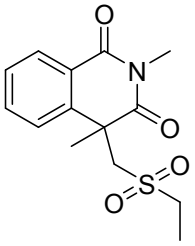
4-(((3-chlorophenyl)sulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3aa**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 66% isolated yield, m. p. = 173.4-174.6℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 (dd, J = 7.8, 1.2 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.23 – 7.18 (m, 3H), 7.17 – 7.12 (m, 1H), 7.06 – 6.98 (m, 2H), 4.35 (d, J = 14.7 Hz, 1H), 3.87 (d, J = 14.7 Hz, 1H), 3.32 (s, 3H), 2.18 (s, 3H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 173.32, 162.77, 138.76, 138.22, 137.92, 133.26, 132.28, 127.97, 127.89, 127.02, 126.83, 124.92, 123.74, 123.56, 63.87, 44.23, 30.38, 26.50, 20.16. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{18}H_{17}NClSO_4^{+}$ 378.0561 found 378.0552.



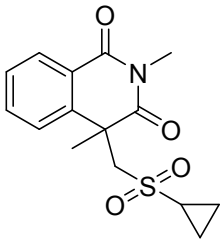
2,4-dimethyl-4-((thiophen-2-ylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**3ab**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 : 1) in 61% isolated yield, m. p. = 173.1-174.3℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 – 8.18 (m, 1H), 7.61 – 7.52 (m, 1H), 7.44 – 7.36 (m, 2H), 7.23 – 7.16 (m, 1H), 7.07 (d, J = 2.8 Hz, 1H), 6.93 – 6.83 (m, 1H), 4.54 (d, J = 14.7 Hz, 1H), 4.07 (d, J = 14.7 Hz, 1H), 3.41 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.23, 163.79, 141.17, 138.98, 134.34, 134.06, 133.55, 129.19, 128.14, 127.77, 125.75, 124.72, 66.17, 45.42, 31.44, 27.57. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{16}H_{16}NS_2O_4^{+}$ 350.0515 found 350.0531.



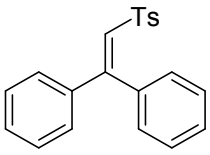
2,4-dimethyl-4-((methylsulfonyl)methyl)isoquinoline-1,3(2H,4H)-dione (**3ac**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2 1) in 69% isolated yield, m. p. = 108.6-110.5℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (dd, J = 7.9, 1.1 Hz, 1H), 7.69 (td, J = 7.7, 1.4 Hz, 1H), 7.54 – 7.47 (m, 2H), 4.31 (d, J = 14.7 Hz, 1H), 3.83 (d, J = 14.7 Hz, 1H), 3.42 (s, 3H), 2.60 (s, 3H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.62, 163.73, 139.89, 134.00, 129.72, 128.39, 125.25, 124.83, 63.40, 45.60, 43.88, 31.29, 27.56. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{13}H_{16}NSO_4^{+}$ 282.0795 found 282.0774.

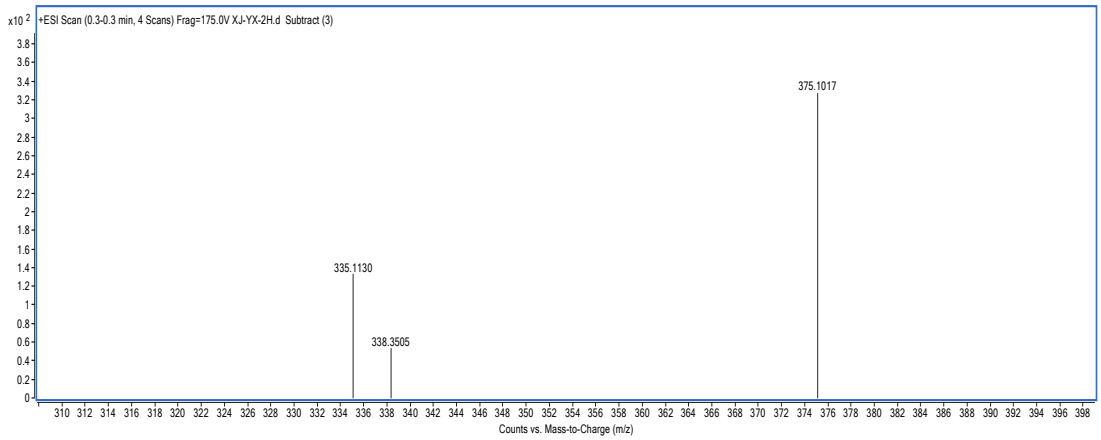


4-((ethylsulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3ad**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2: 1) in 70% isolated yield, m. p. = 141.1-142.5℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (dd, J = 8.1, 1.4 Hz, 1H), 7.72 – 7.63 (m, 1H), 7.54 – 7.44 (m, 2H), 4.26 (d, J = 14.5 Hz, 1H), 3.76 (d, J = 14.5 Hz, 1H), 3.42 (s, 3H), 2.70 (hept, J = 6.8 Hz, 2H), 1.63 (s, 3H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.75, 163.81, 140.04, 133.86, 129.59, 128.30, 125.30, 124.70, 60.46, 50.17, 45.42, 31.43, 27.55, 6.31. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{14}H_{18}NSO_4^{+}$ 296.0951 found 296.0918.



4-((cyclopropylsulfonyl)methyl)-2,4-dimethylisoquinoline-1,3(2H,4H)-dione (**3ae**) white solid was obtained by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 2: 1) in 68% isolated yield, m. p. = 126.5-128.4℃. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dd, J = 7.8, 1.1 Hz, 1H), 7.71 – 7.65 (m, 1H), 7.50 (td, J = 8.3, 1.7 Hz, 2H), 4.39 (d, J = 14.5 Hz, 1H), 3.84 (d, J = 14.5 Hz, 1H), 3.43 (s, 3H), 1.97 (tt, J = 8.0, 4.8 Hz, 1H), 1.65 (s, 3H), 1.04 (dt, J = 7.3, 3.5 Hz, 2H), 0.85 (dd, J = 8.0, 2.2 Hz, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 174.65, 163.80, 140.02, 133.72, 129.57, 128.32, 125.68, 124.75, 62.87, 45.41, 32.11, 31.38, 27.56, 5.34, 4.97. HRMS (TOF) m/z [M + H]$^{+}$ Calcd for $C_{15}H_{18}NSO_4^{+}$ 308.0951 found 308.0921.





(2-tosylethene-1,1-diyl)dibenzene (**5a**) was detected by HRMS. HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{21}H_{19}SO_2^+$ 335.1100 found 335.1130.

8. References

[1] Y. Q. Yuan, P. S. Kumar, C. N. Zhang, M. H. Yang, S. R. Guo, Org. Biomol. Chem., 2017, 15, 7330-7338.

[2] Y. Yuan, Y. Yu, J. Qiao, P. Liu, B. Yu, W. Zhang, H. Liu, M. He, Z. Huang, A. Lei, Chem. Commun., 2018, 54, 11471-11474.

[3] M. W. Zheng, X. Yuan, Y. S. Cui, J. K. Qiu, G. Li, K. Guo, Org. Lett., 2018, 20, 7784-7789.

[4] W. Yu, P. Hu, Y. Fan, C. Yu, X. Yan, X. Li, X. Xu, Org. Biomol. Chem., 2015, 13, 3308-3313.

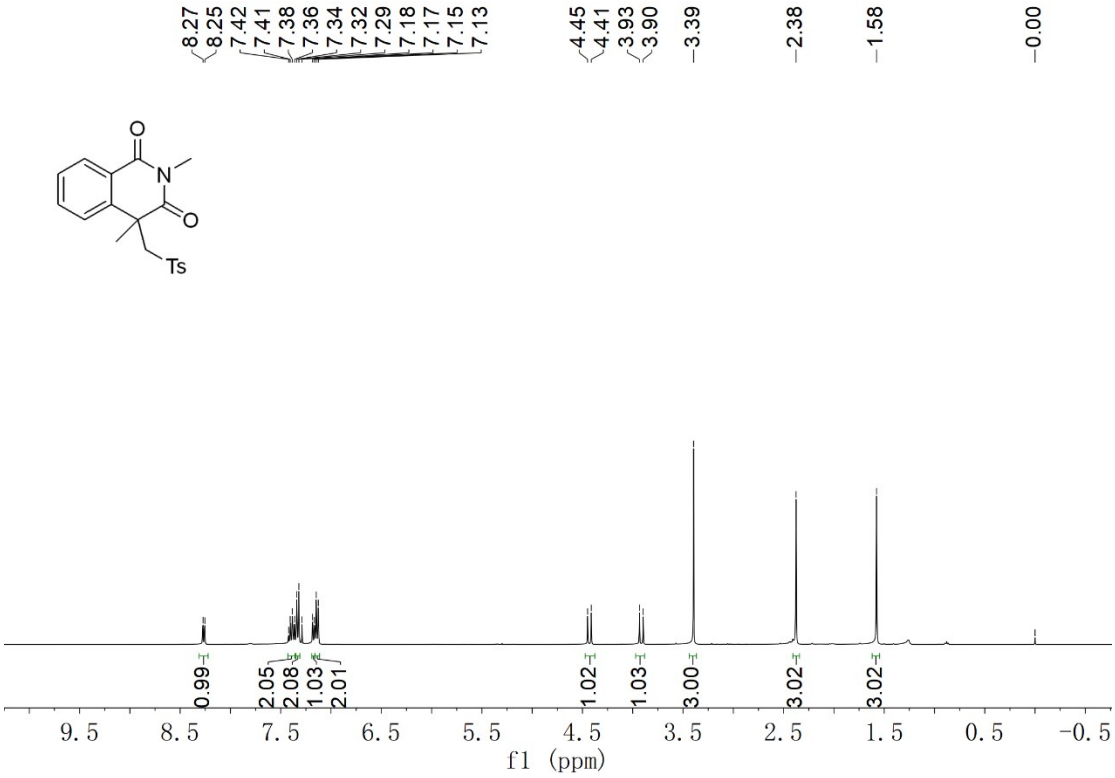
[5] K.-L. Zuo, Y.-H. He, Z. Guan, Eur. J. Org. Chem., 2019, 2019, 939-948.

[6] X. Liu, T. Cong, P. Liu, P. Sun, Org. Biomol. Chem., 2016, 14, 9416-9422.

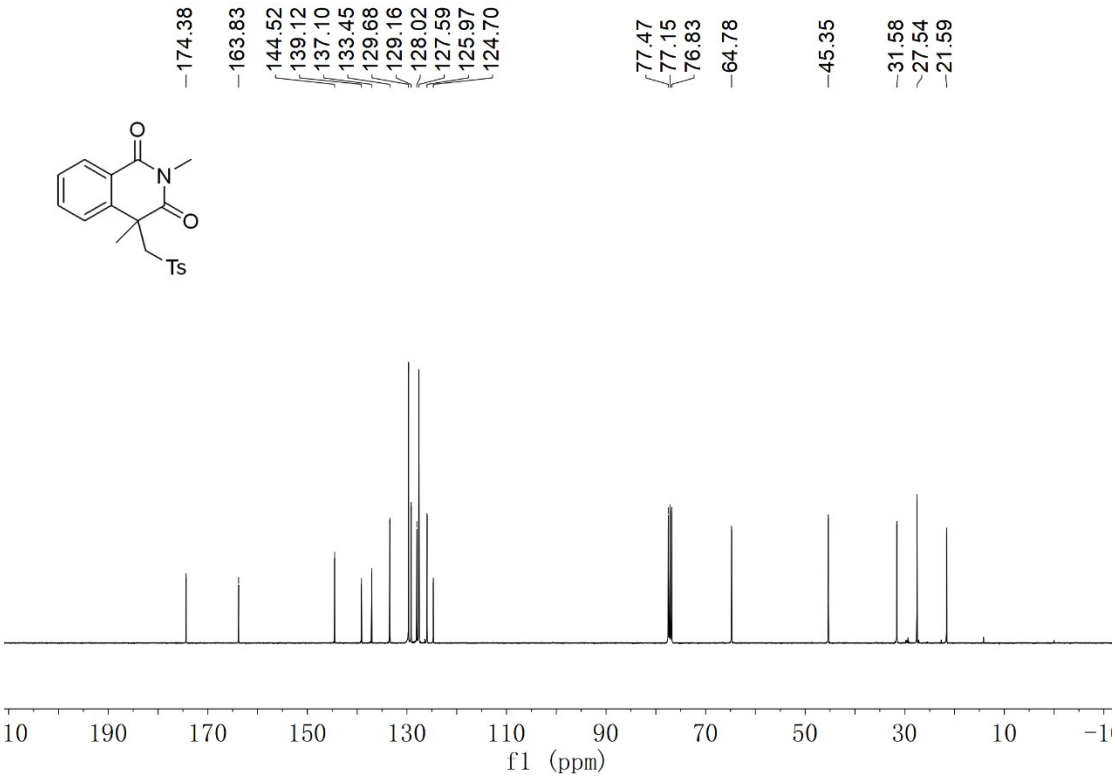
[7] X.-F. Xia, S.-L. Zhu, D. Wang, Y.-M. Liang, Adv. Syn. Catal., 2017, 359, 859-865.

9. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra

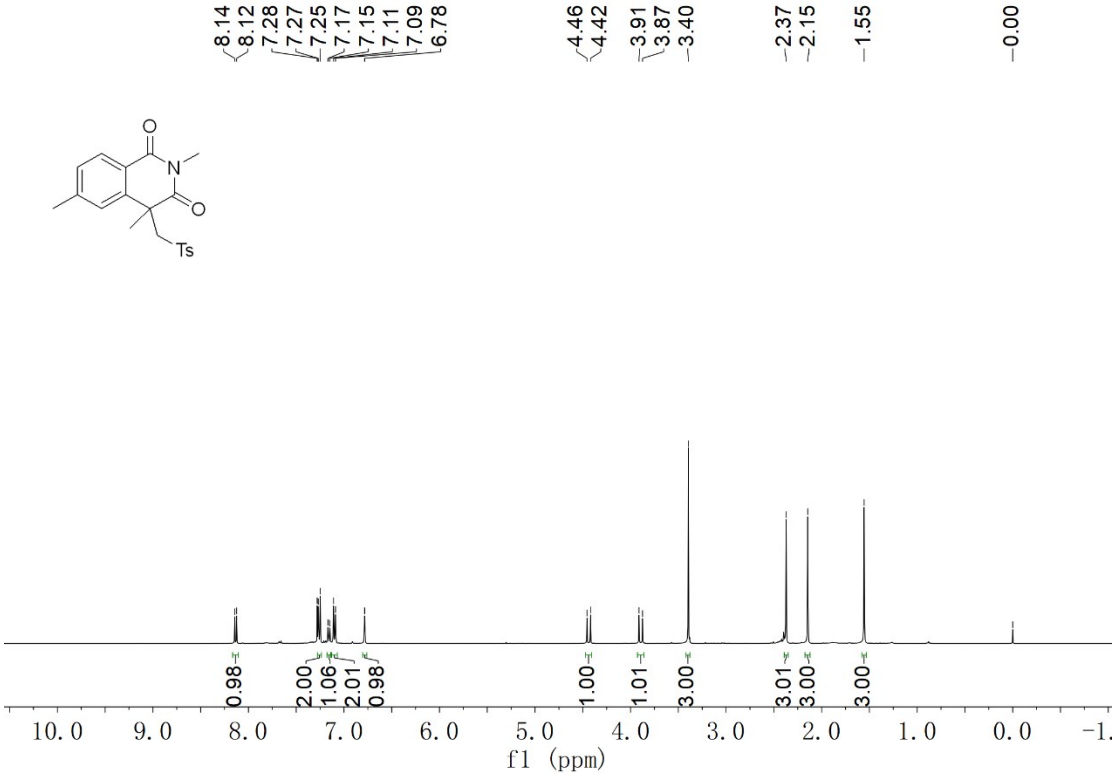
^{1}H NMR of compound **3a**



^{13}C NMR of compound **3a**

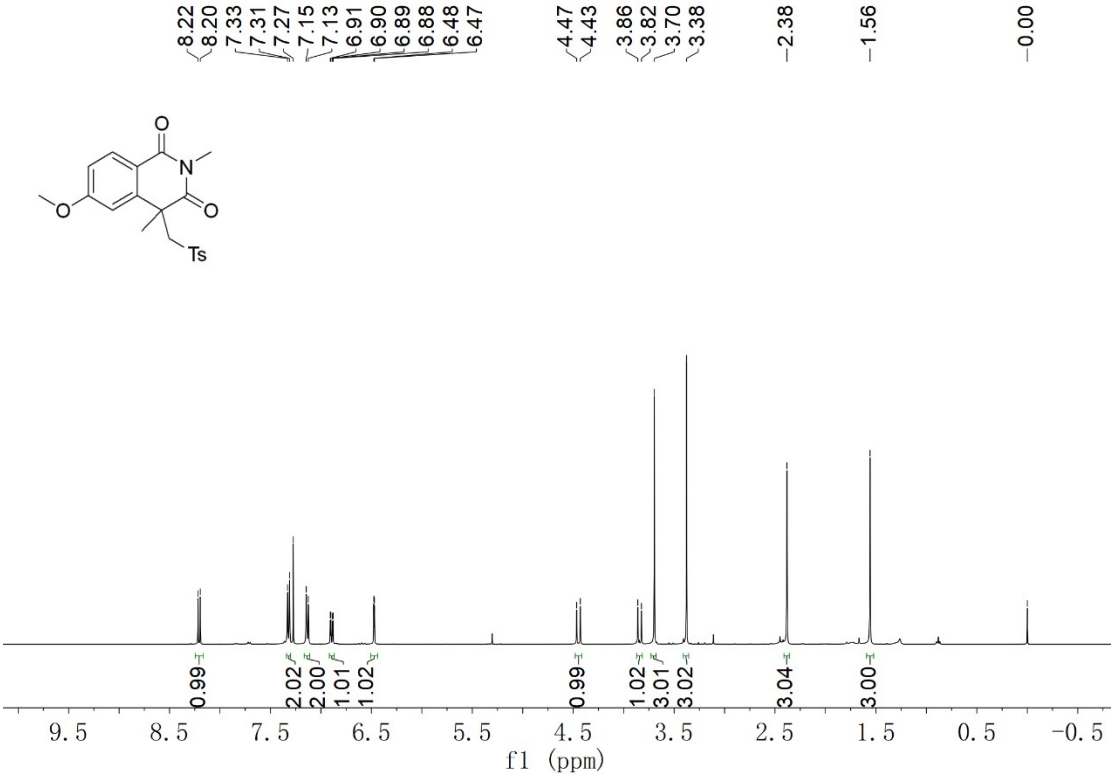


^{1}H NMR of compound **3b**

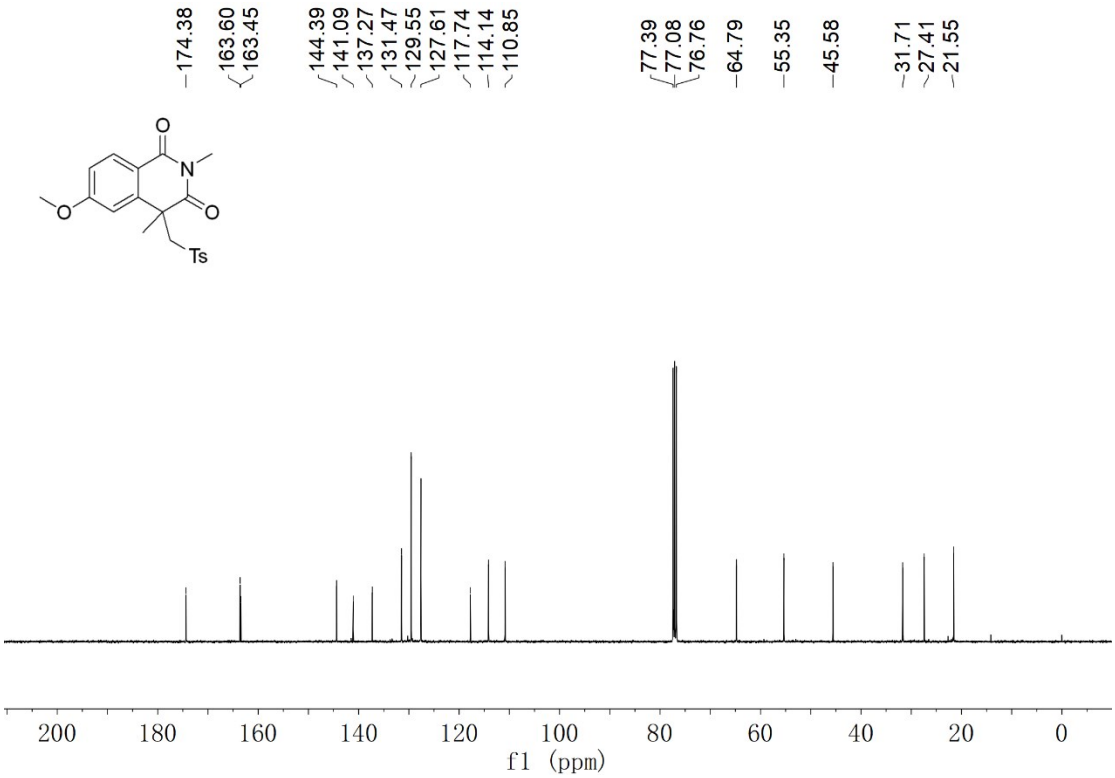


^{13}C NMR of compound **3b**

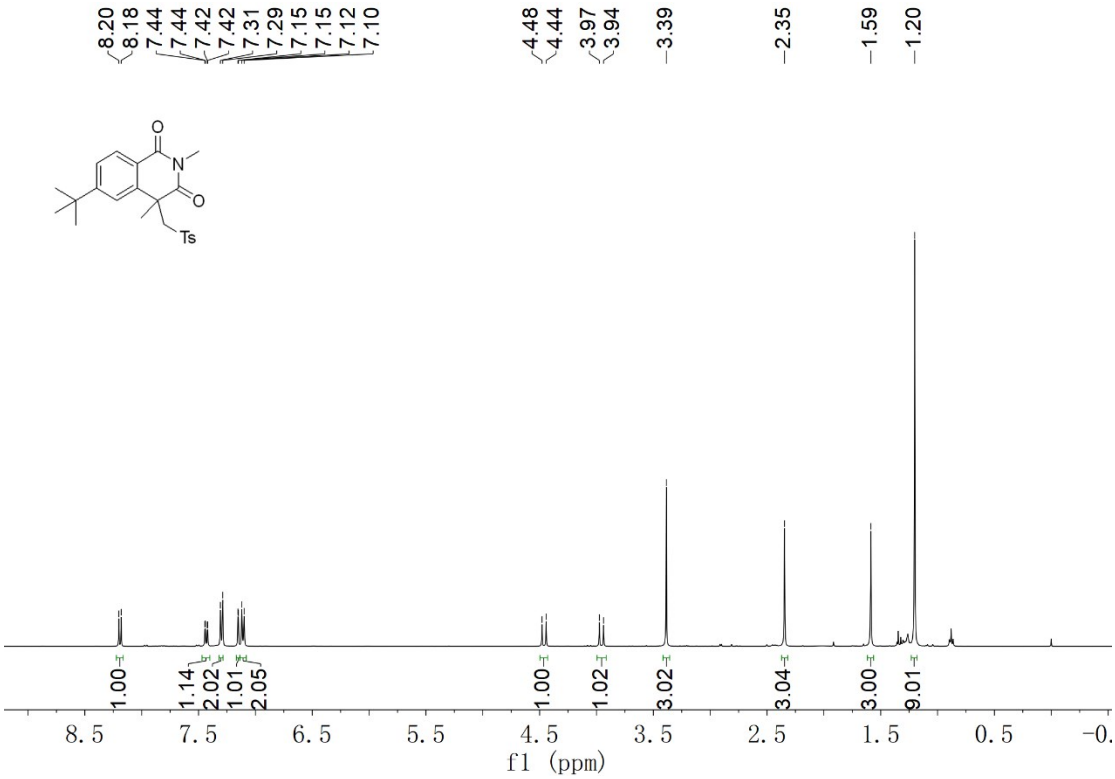
^{1}H NMR of compound **3c**



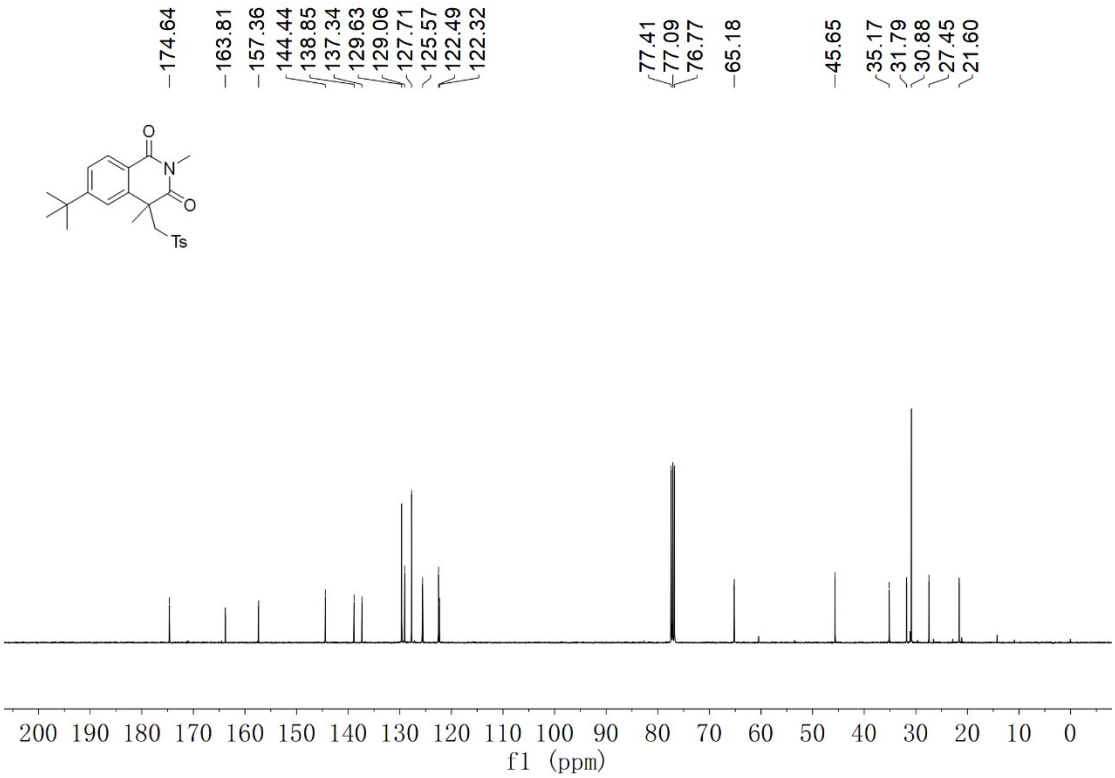
^{13}C NMR of compound **3c**



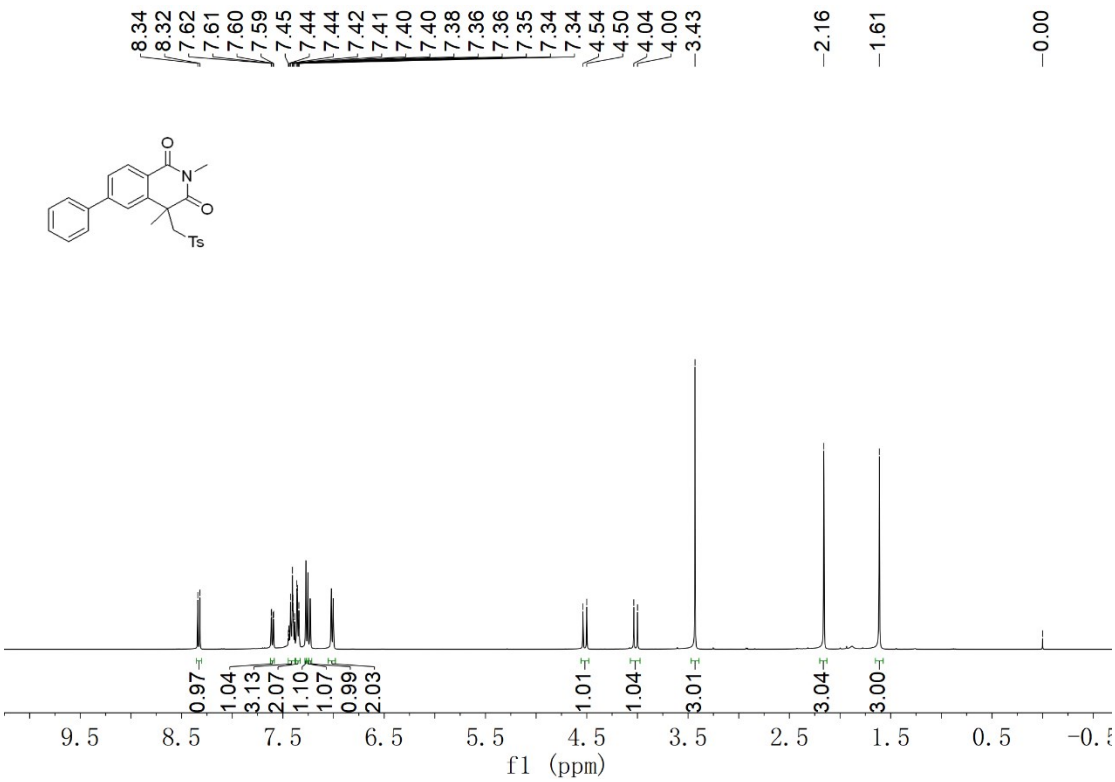
^{1}H NMR of compound **3d**



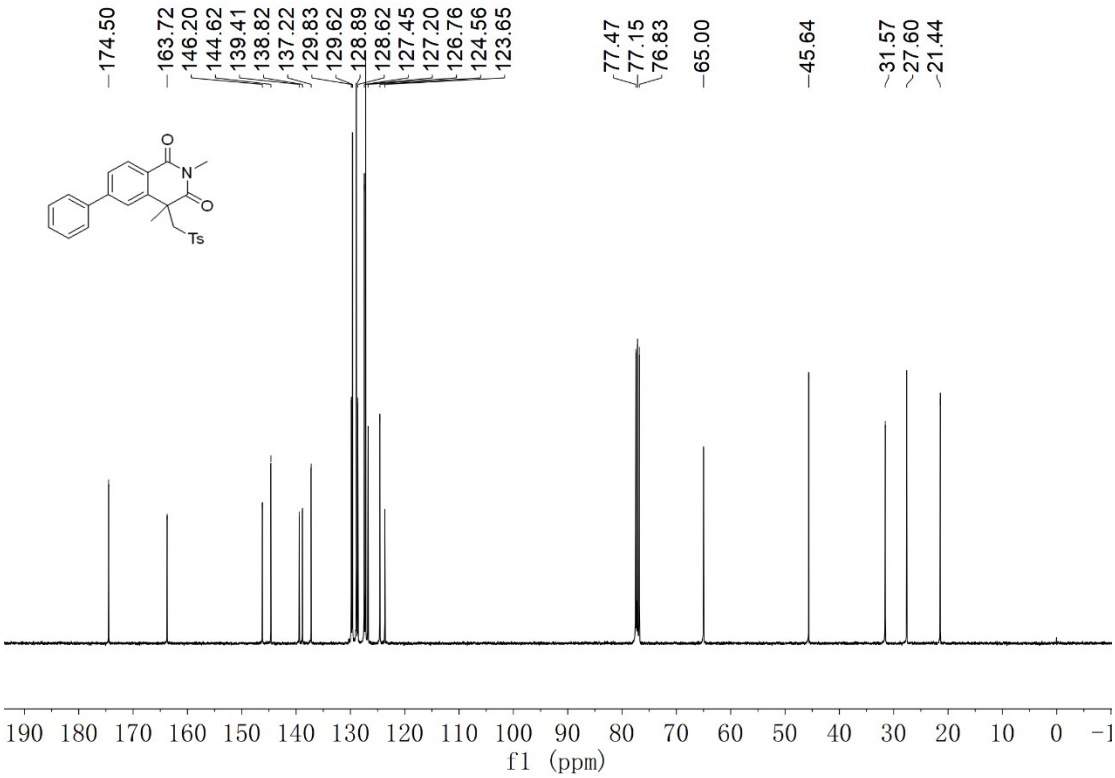
^{13}C NMR of compound **3d**



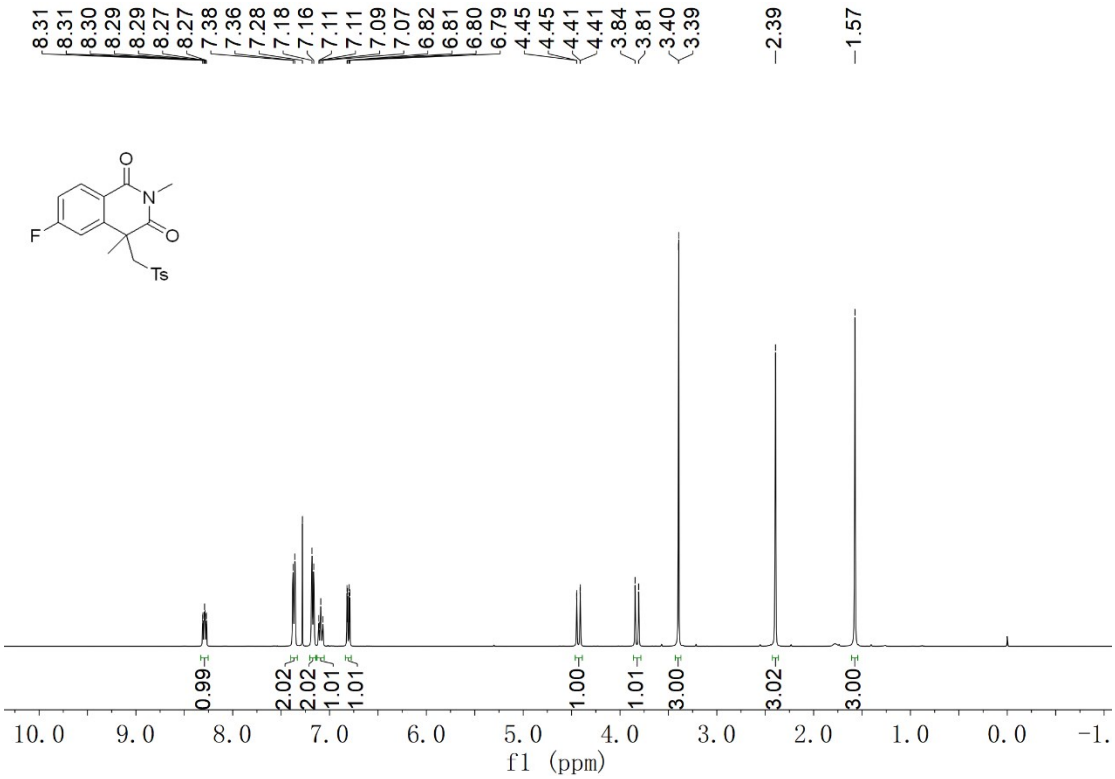
^{1}H NMR of compound **3e**



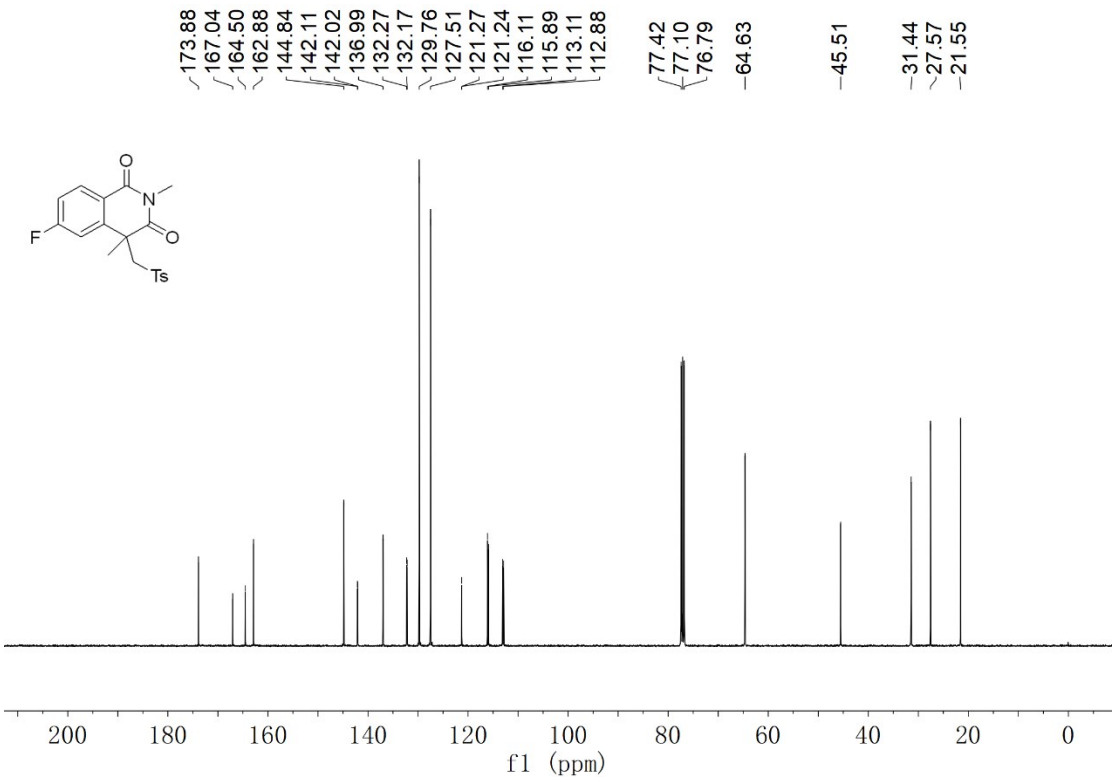
^{13}C NMR of compound **3e**



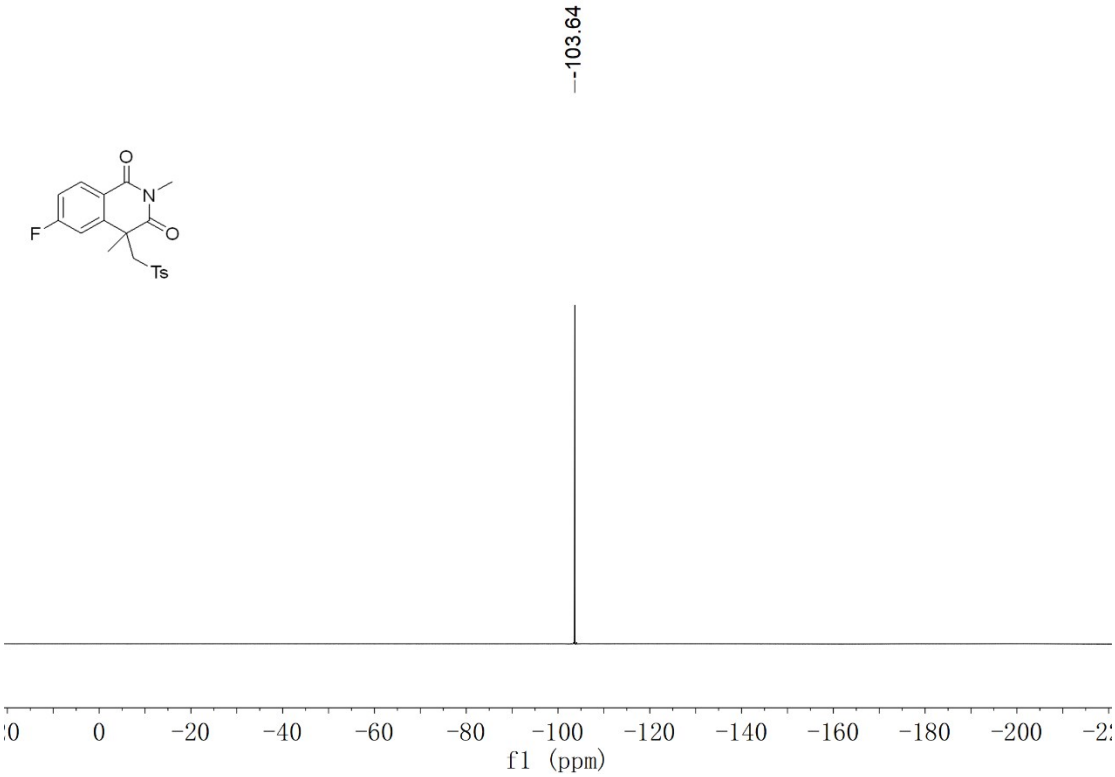
^{1}H NMR of compound **3f**



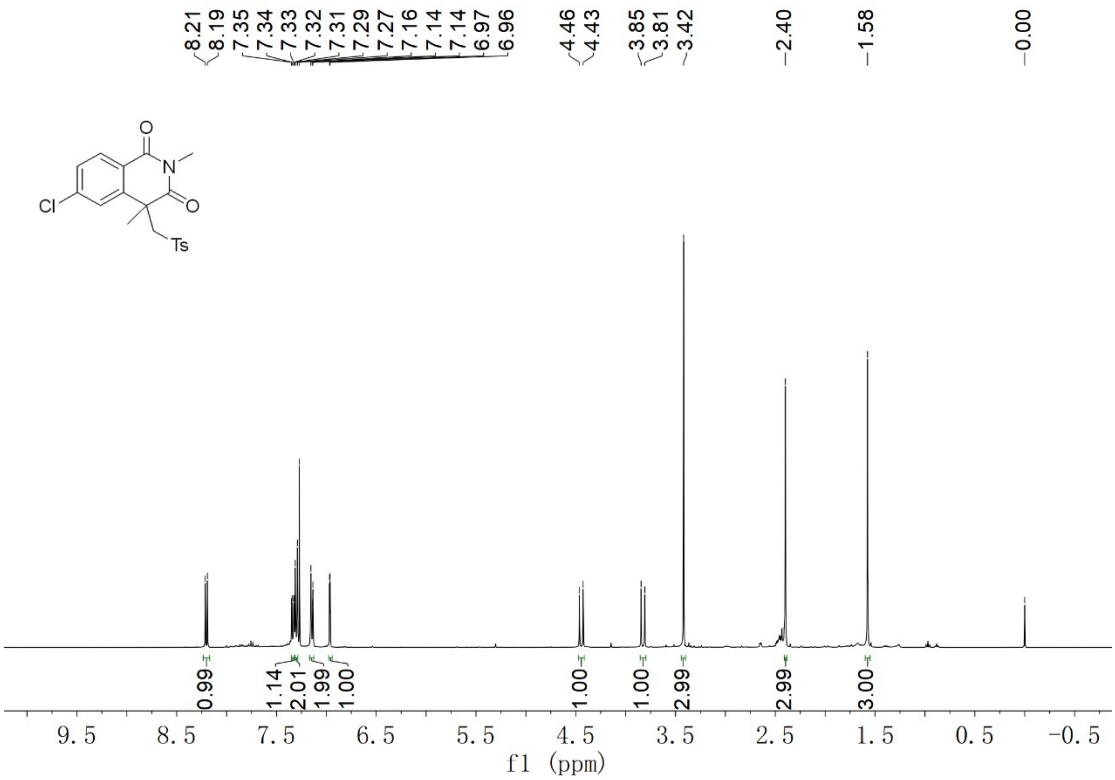
^{13}C NMR of compound **3f**



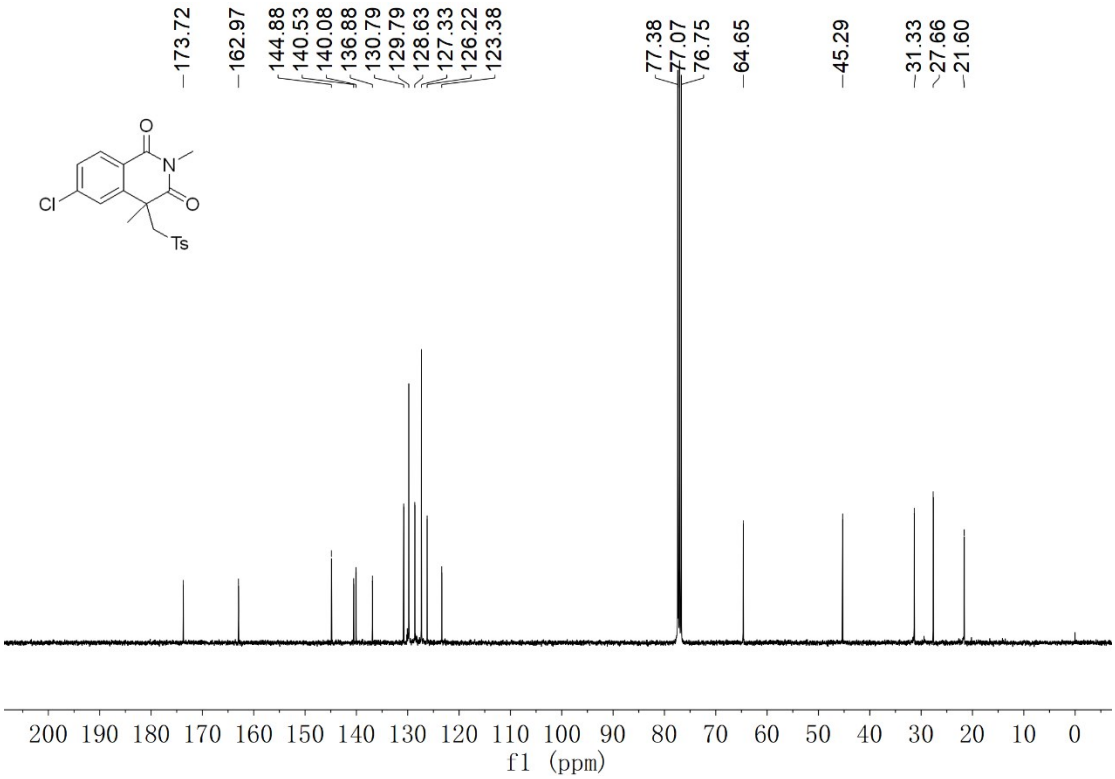
^{19}F NMR of compound **3f**



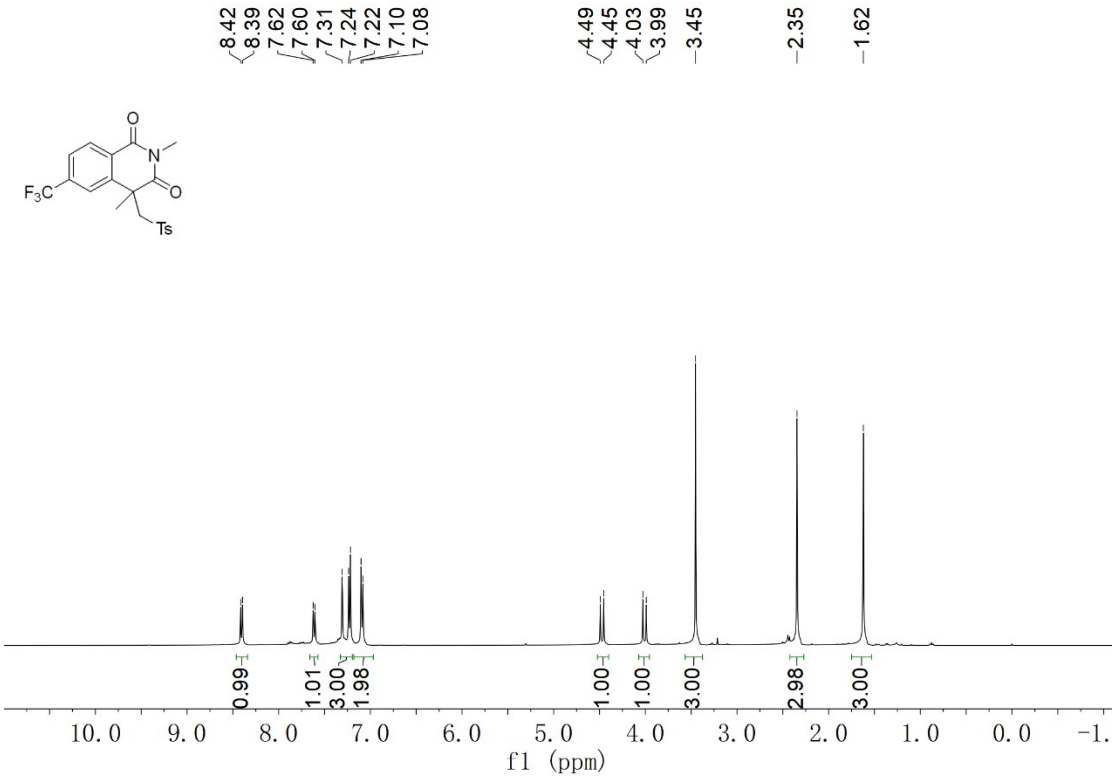
^{1}H NMR of compound **3g**



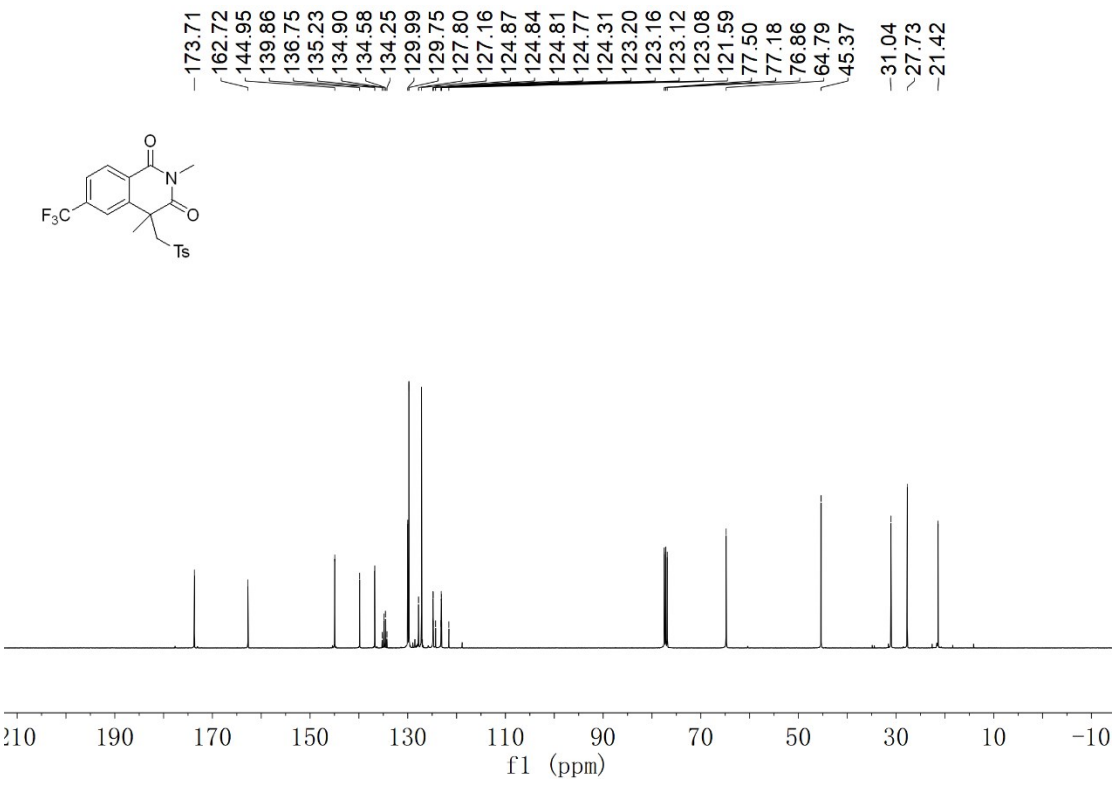
^{13}C NMR of compound **3g**



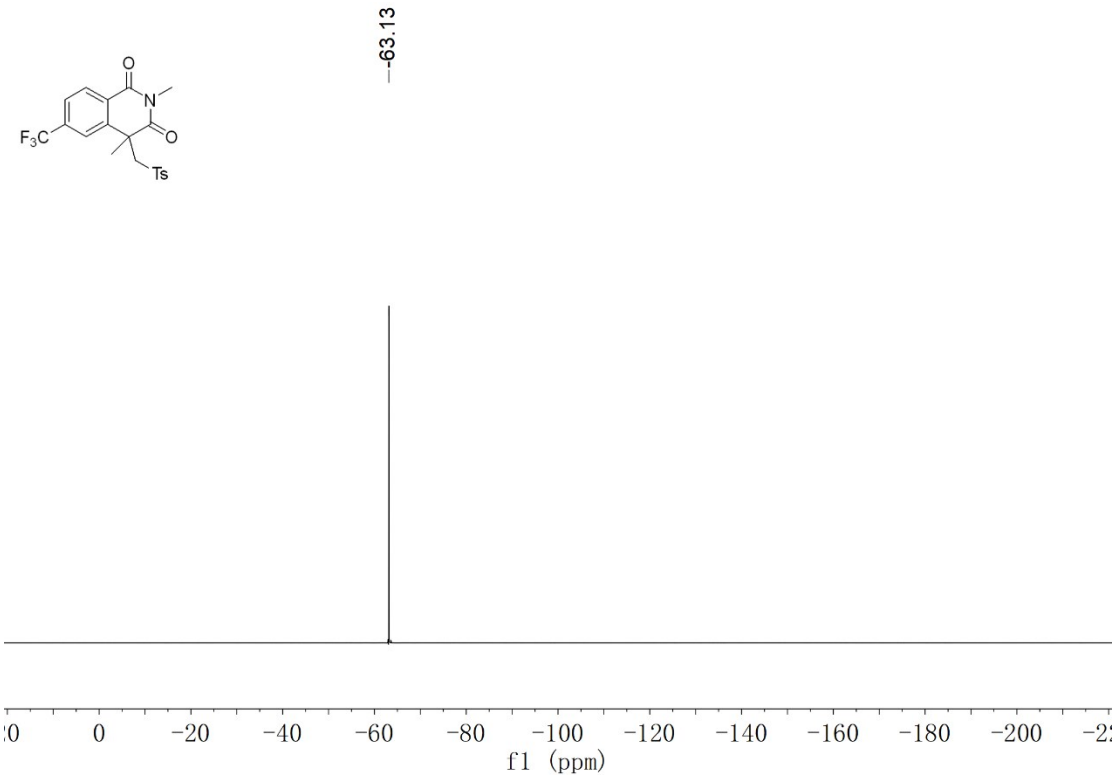
^{1}H NMR of compound **3h**



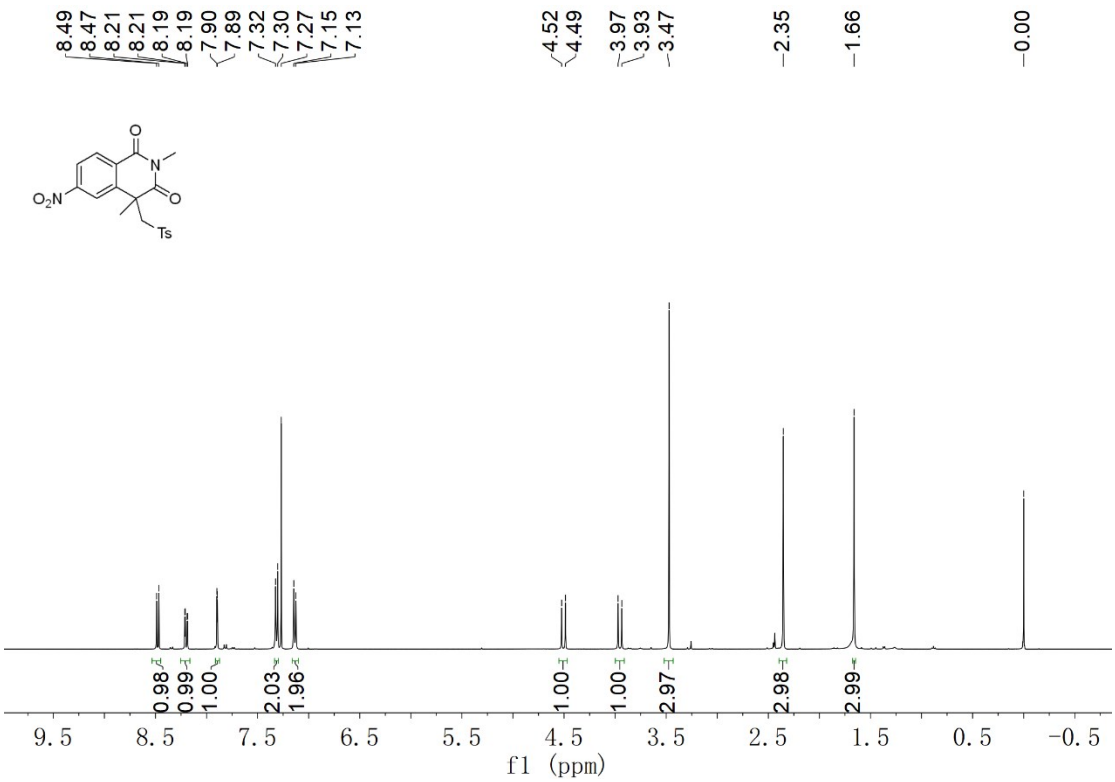
^{13}C NMR of compound **3h**



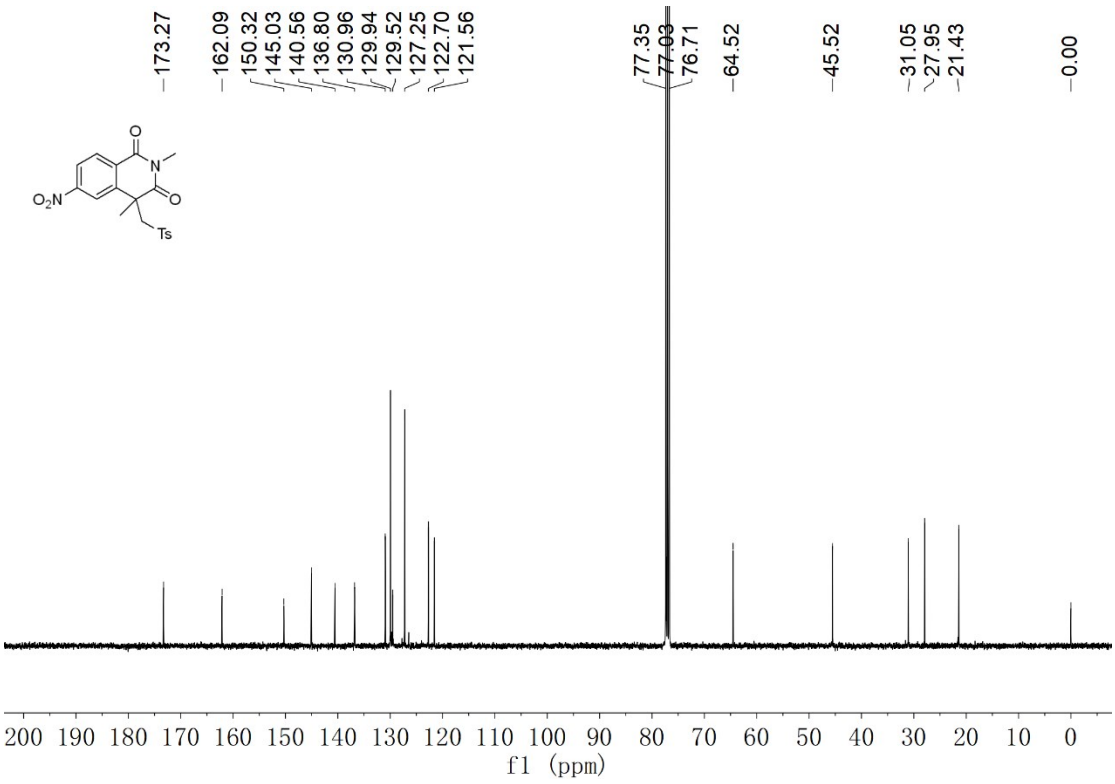
^{19}F NMR of compound **3h**



^{1}H NMR of compound **3i**



^{13}C NMR of compound **3i**



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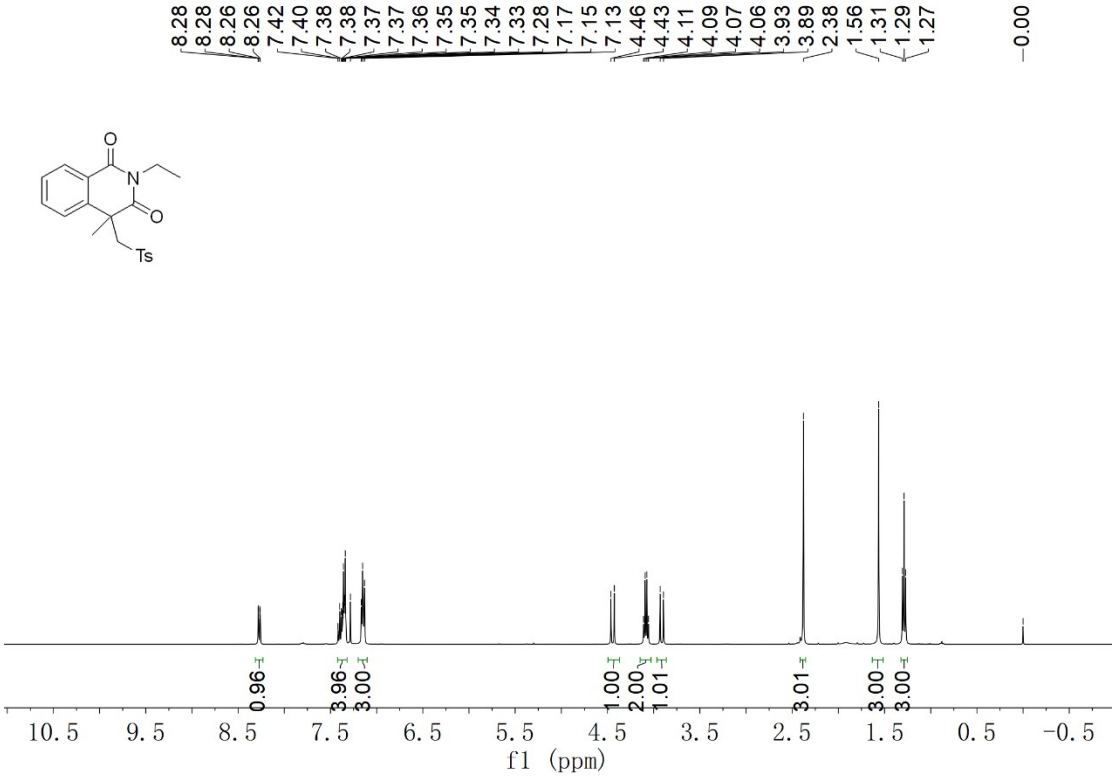

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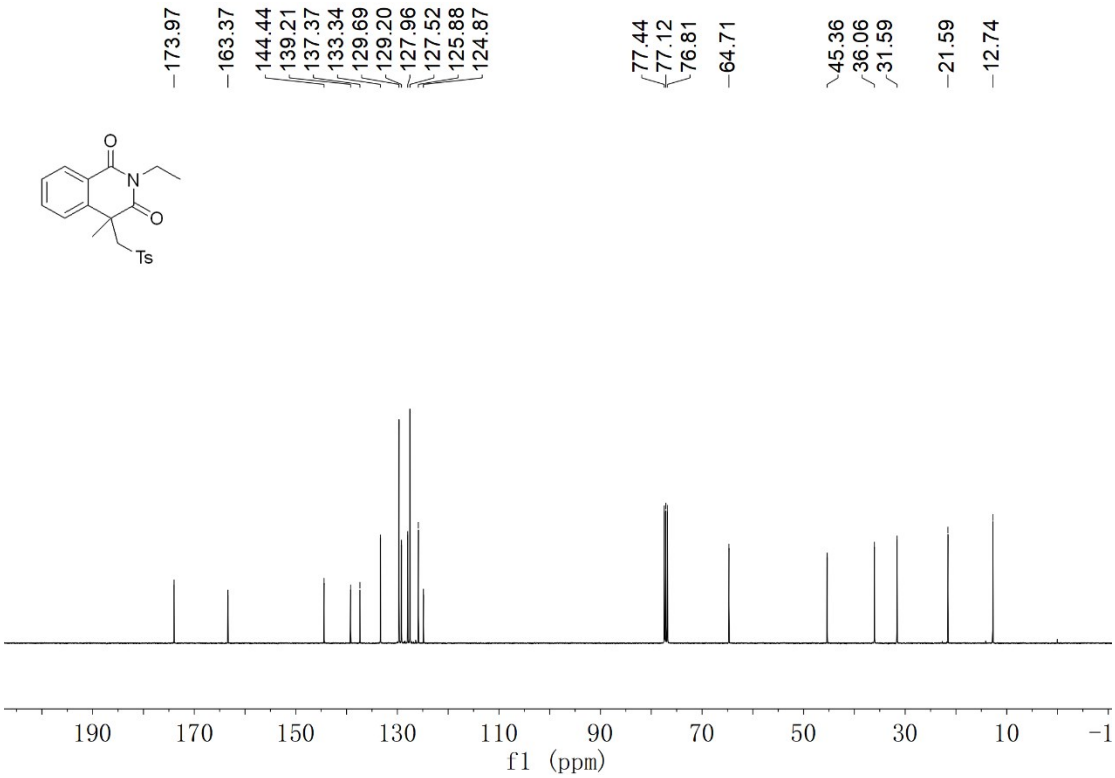

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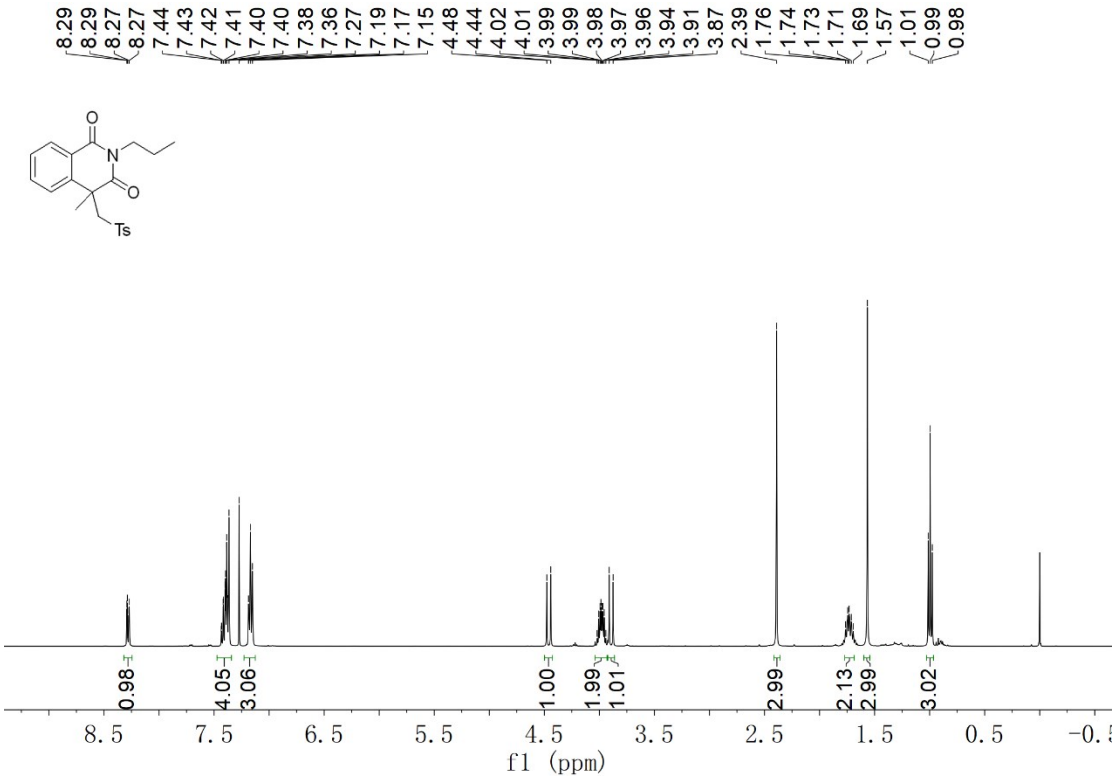

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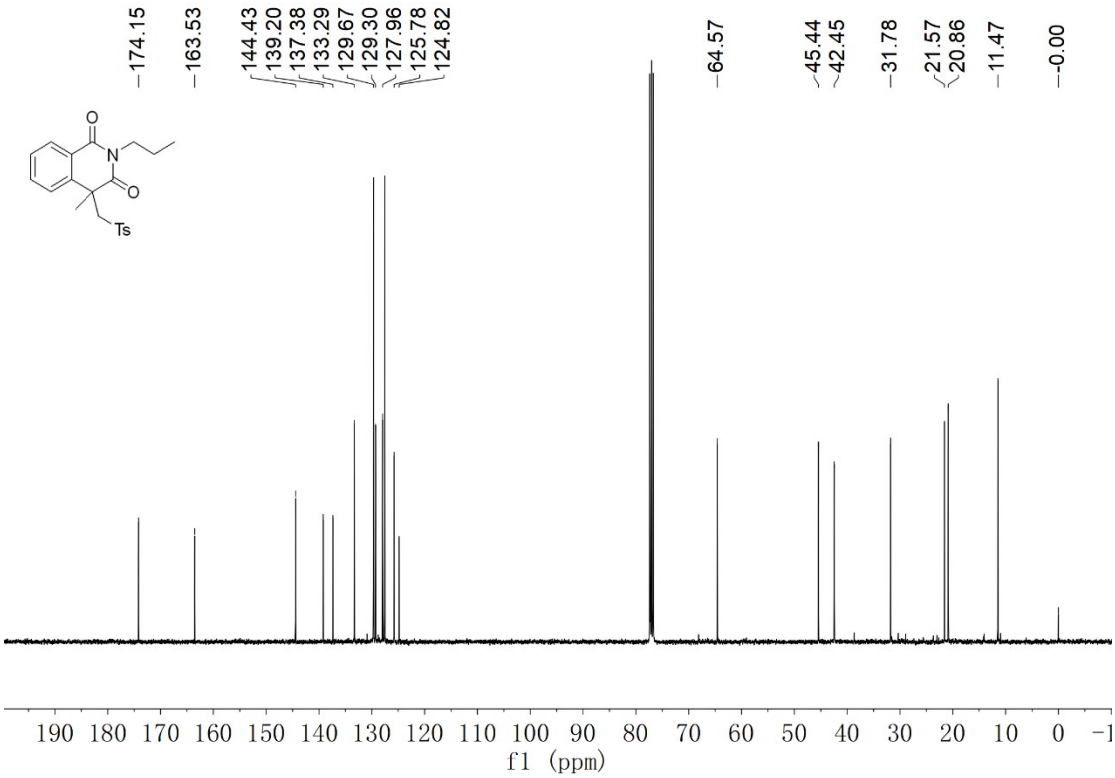
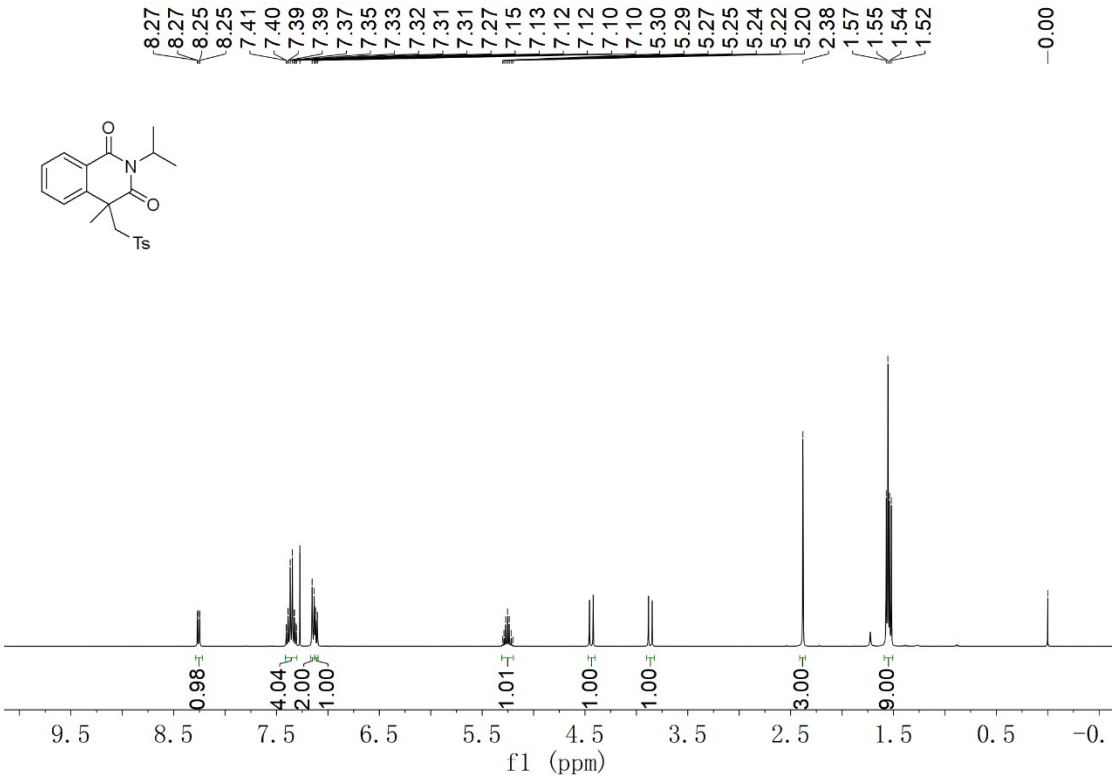
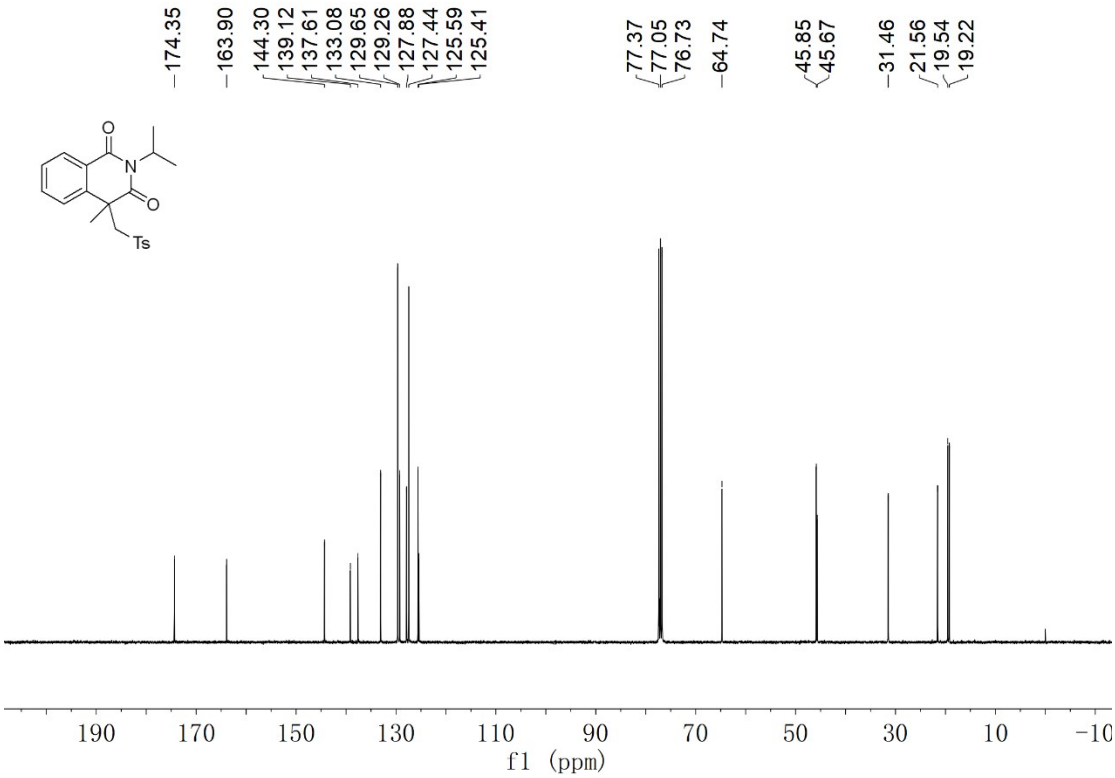


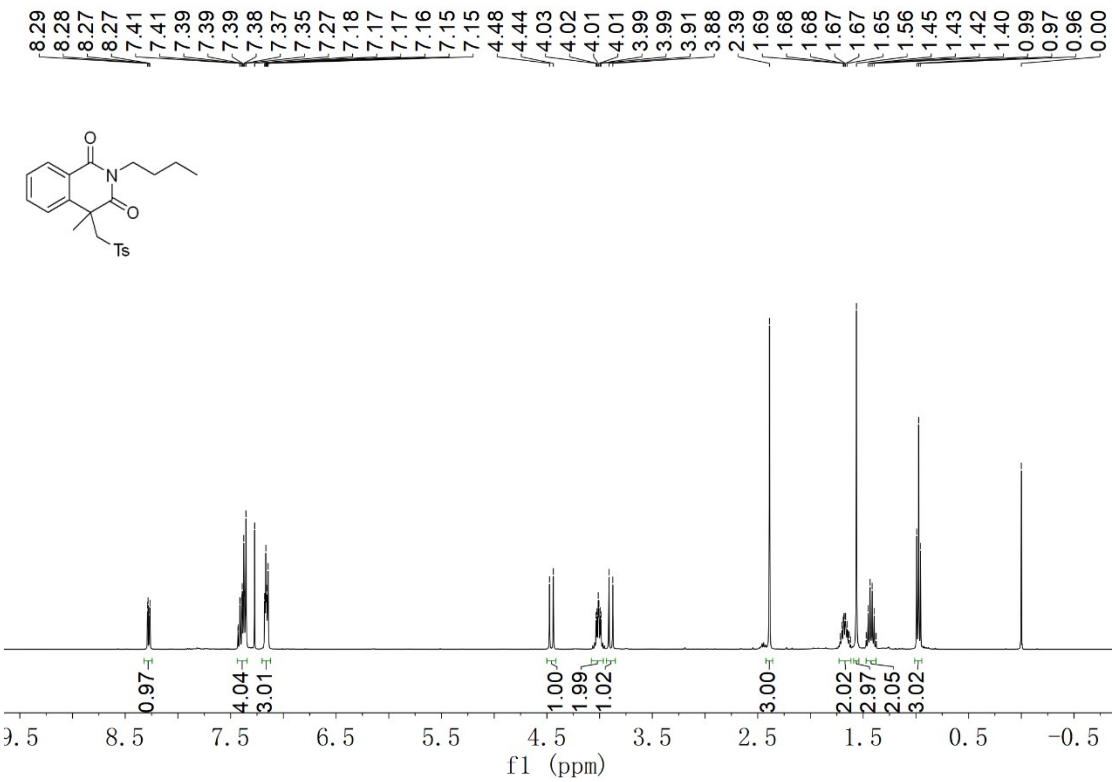
^{1}H NMR of compound **3l**



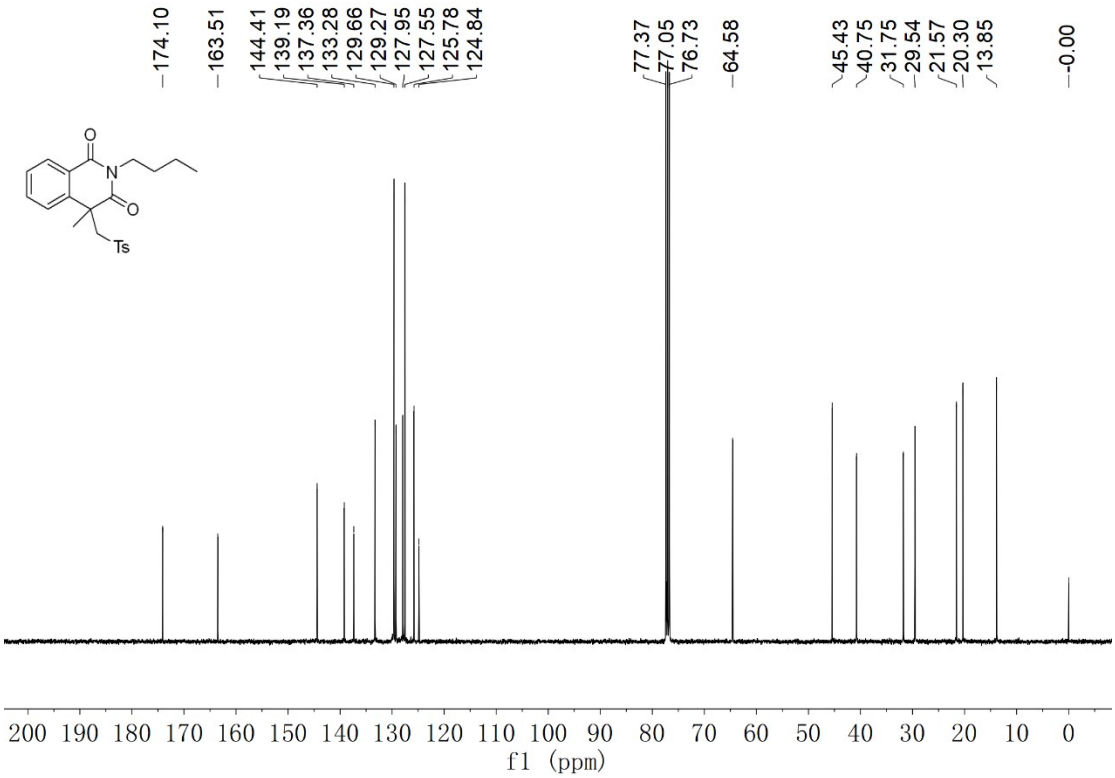
^{13}C NMR of compound **3l**



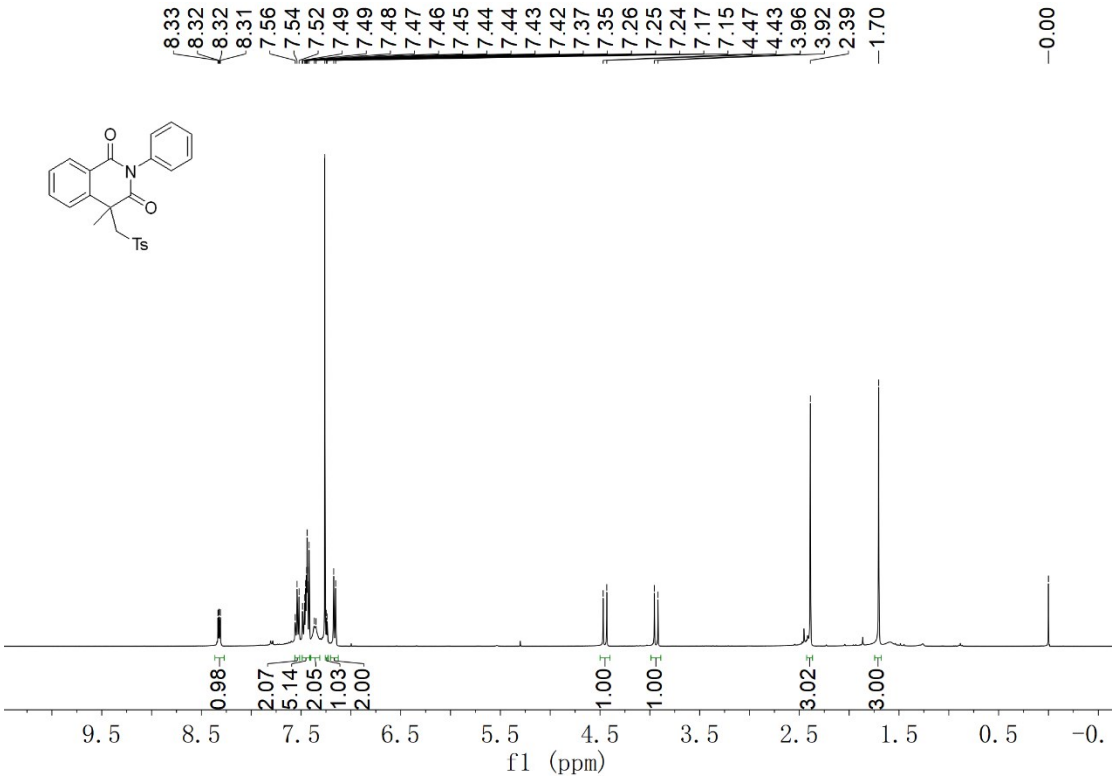
^{1}H NMR of compound **3m**



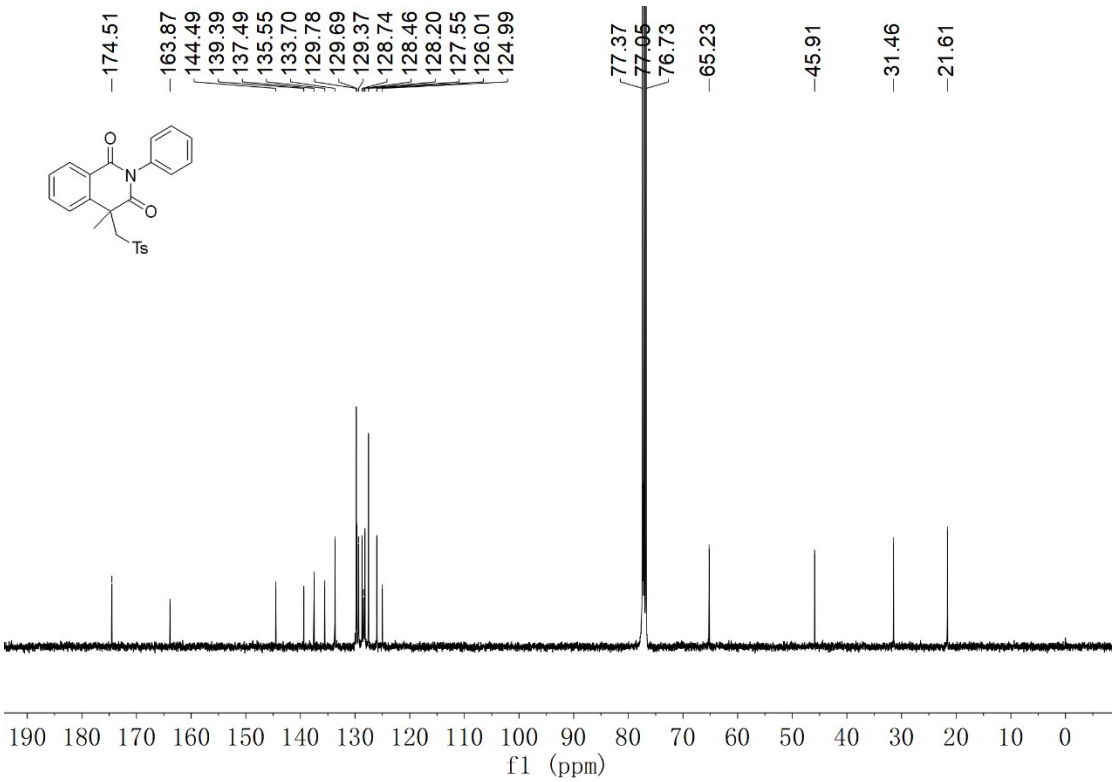
^{13}C NMR of compound **3m**



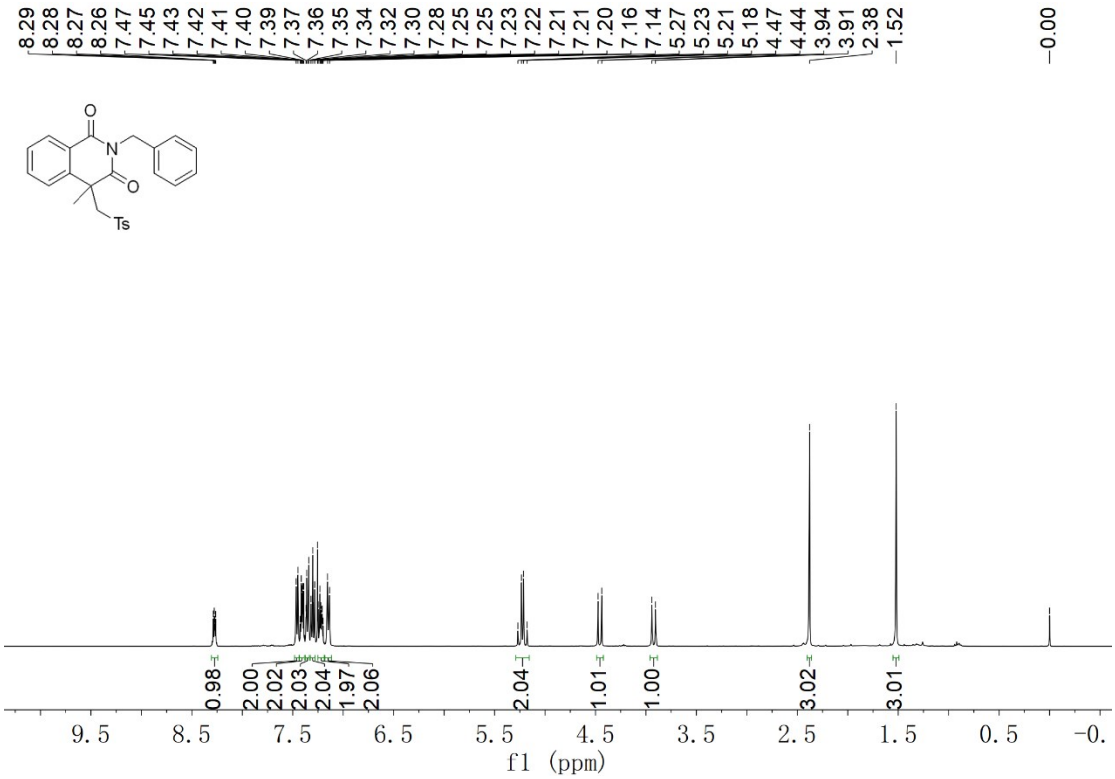
^{1}H NMR of compound **3n**



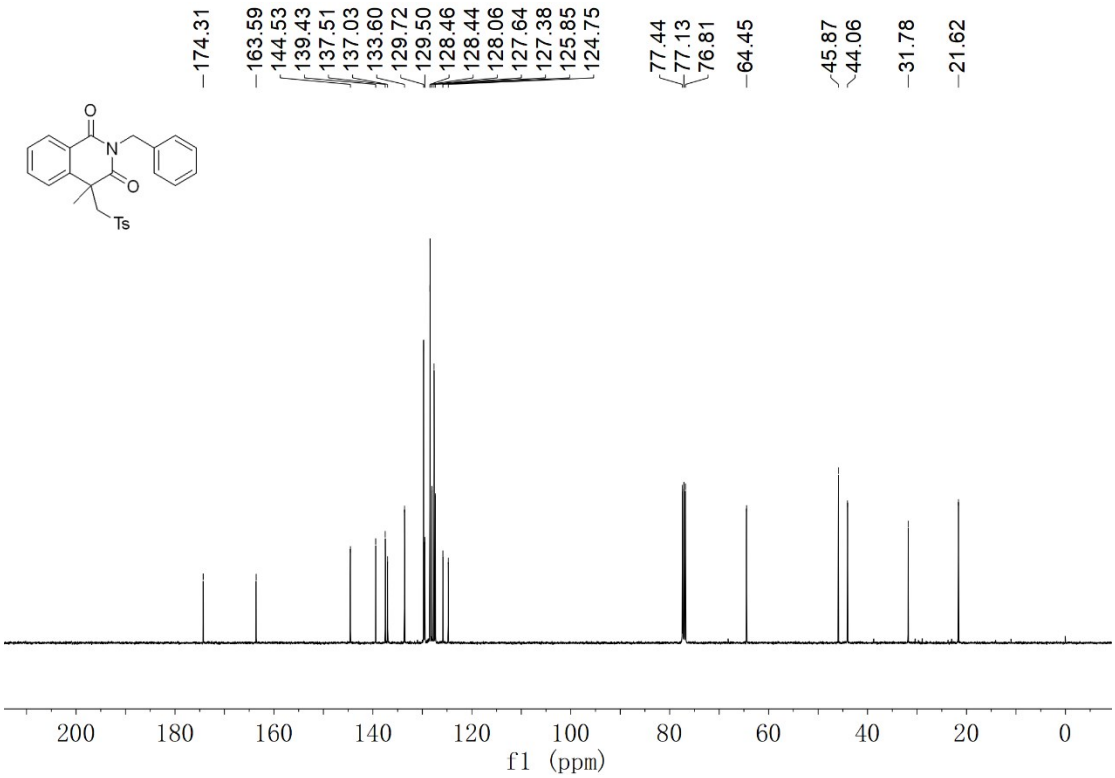
^{13}C NMR of compound **3n**



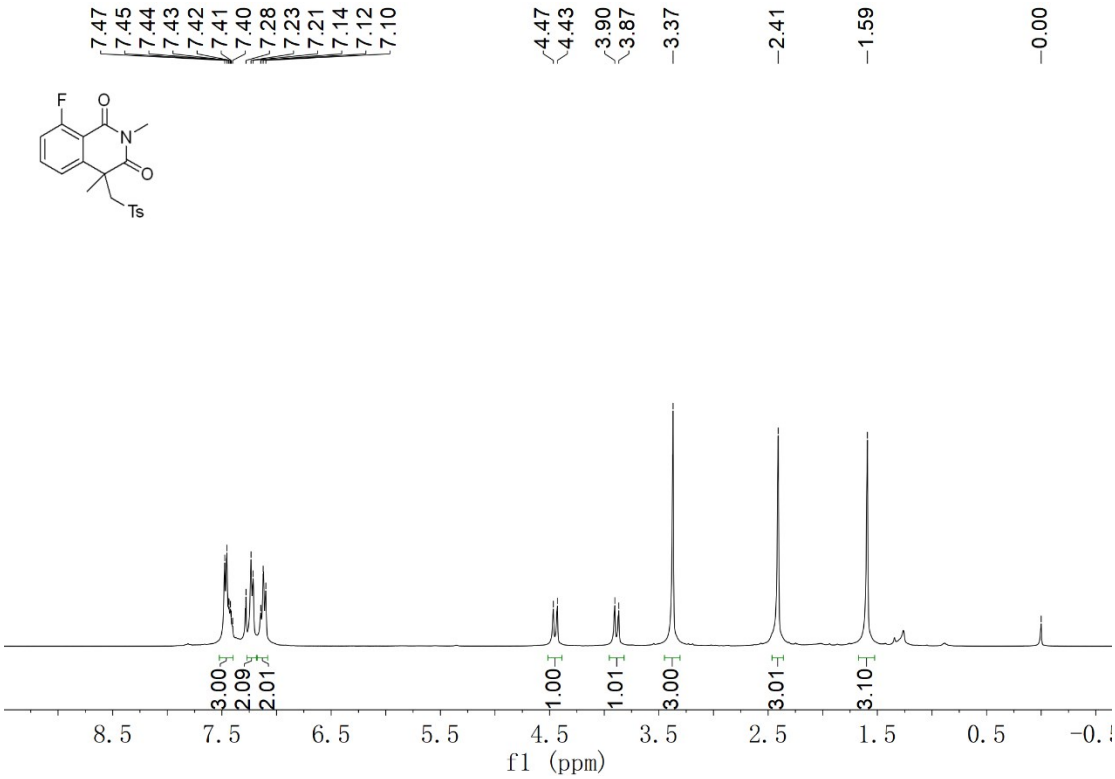
^{1}H NMR of compound **3o**



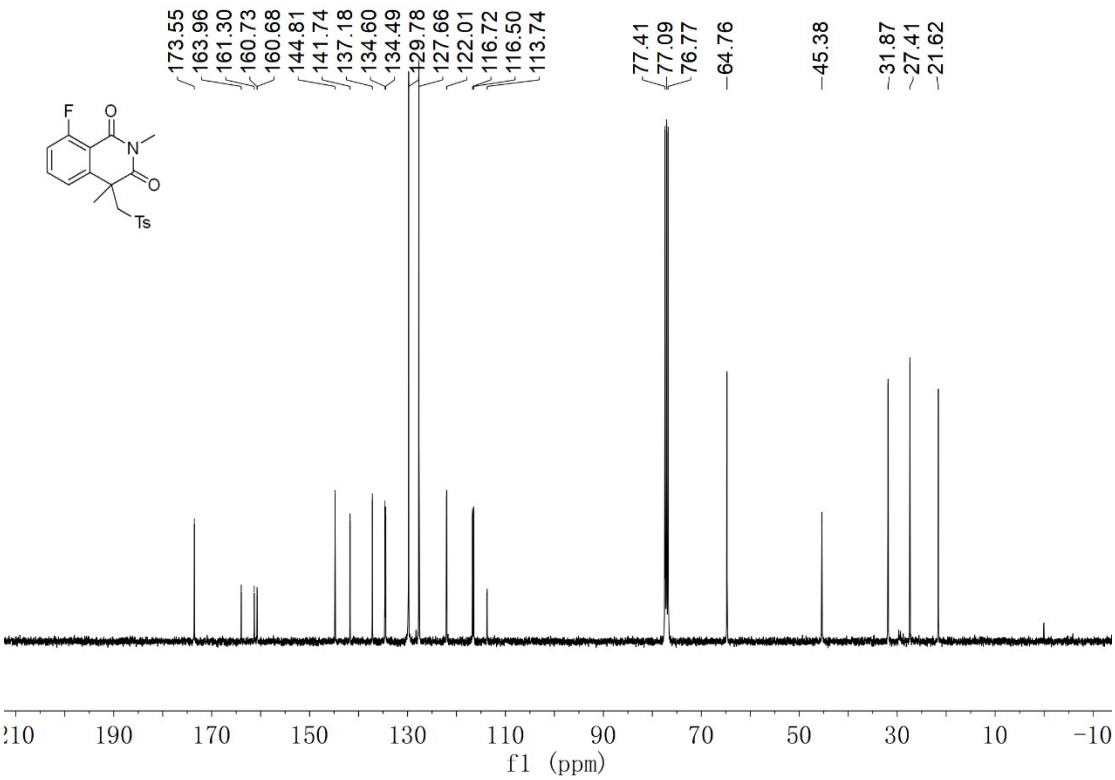
^{13}C NMR of compound **3o**



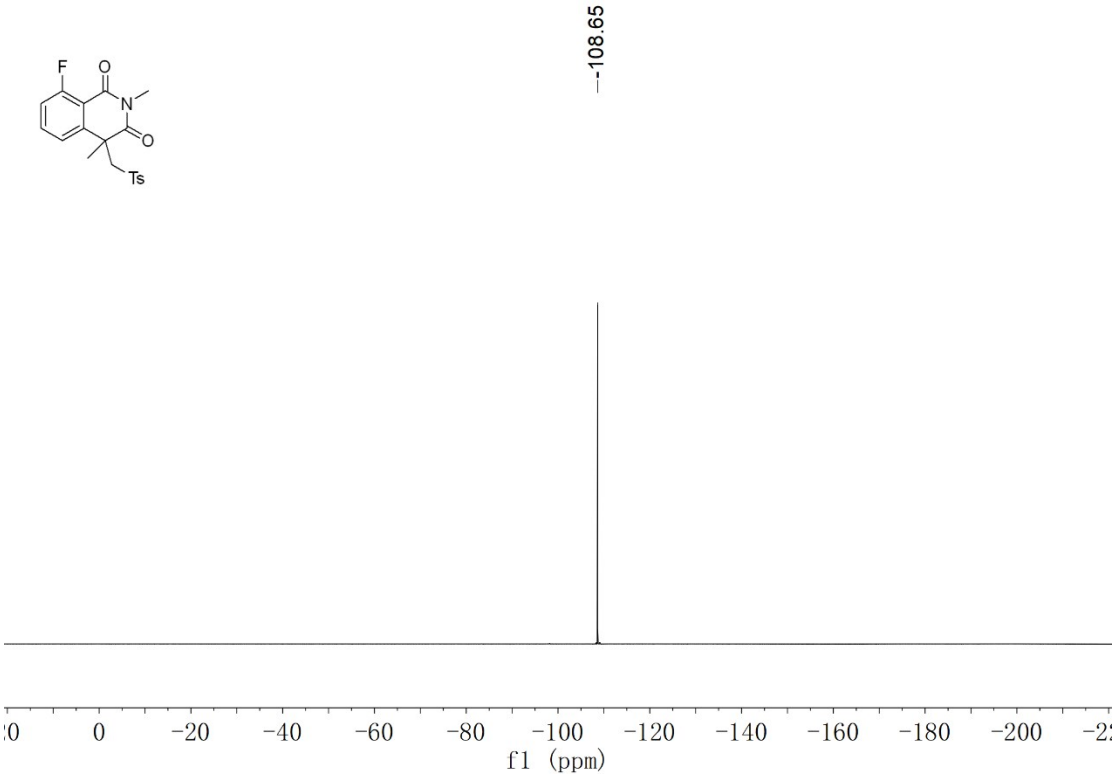
^{1}H NMR of compound **3p**



^{13}C NMR of compound **3p**



^{19}F NMR of compound **3p**



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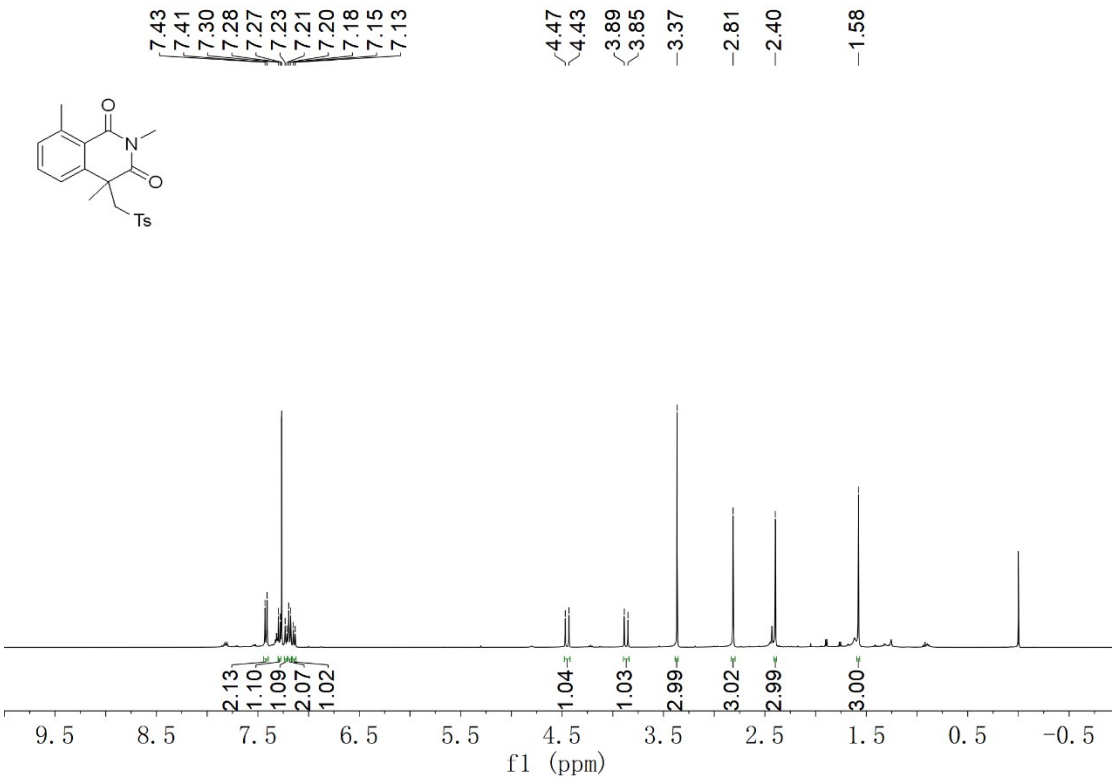

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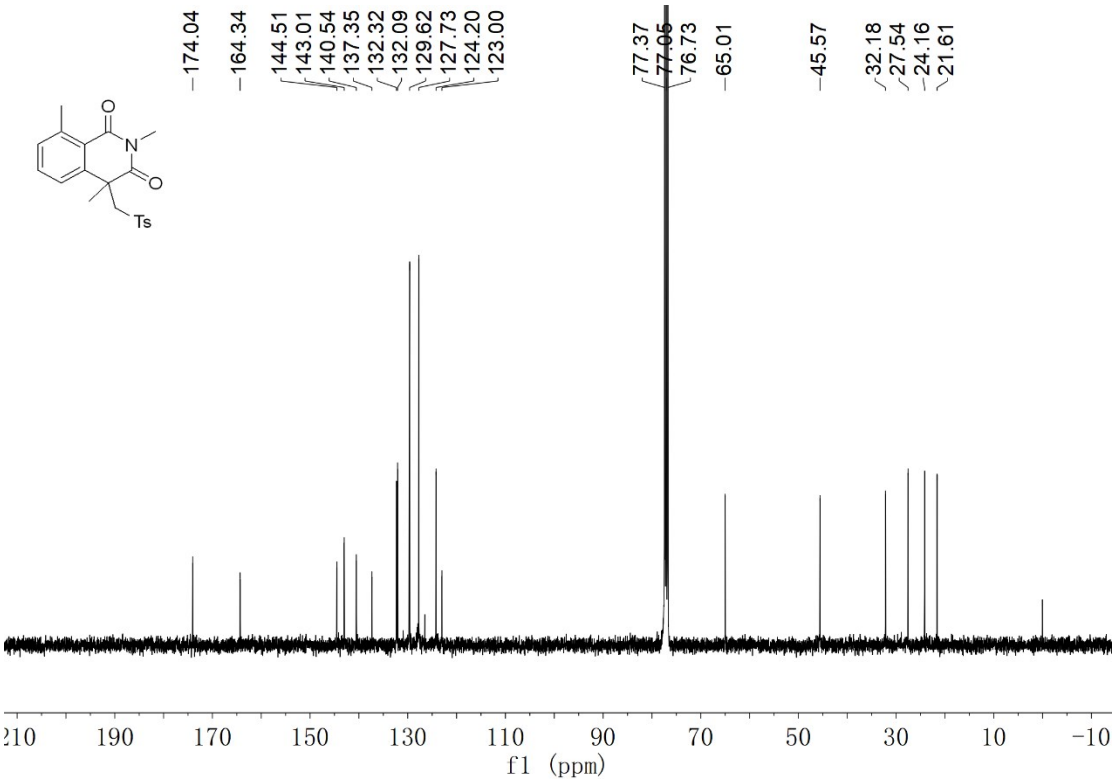
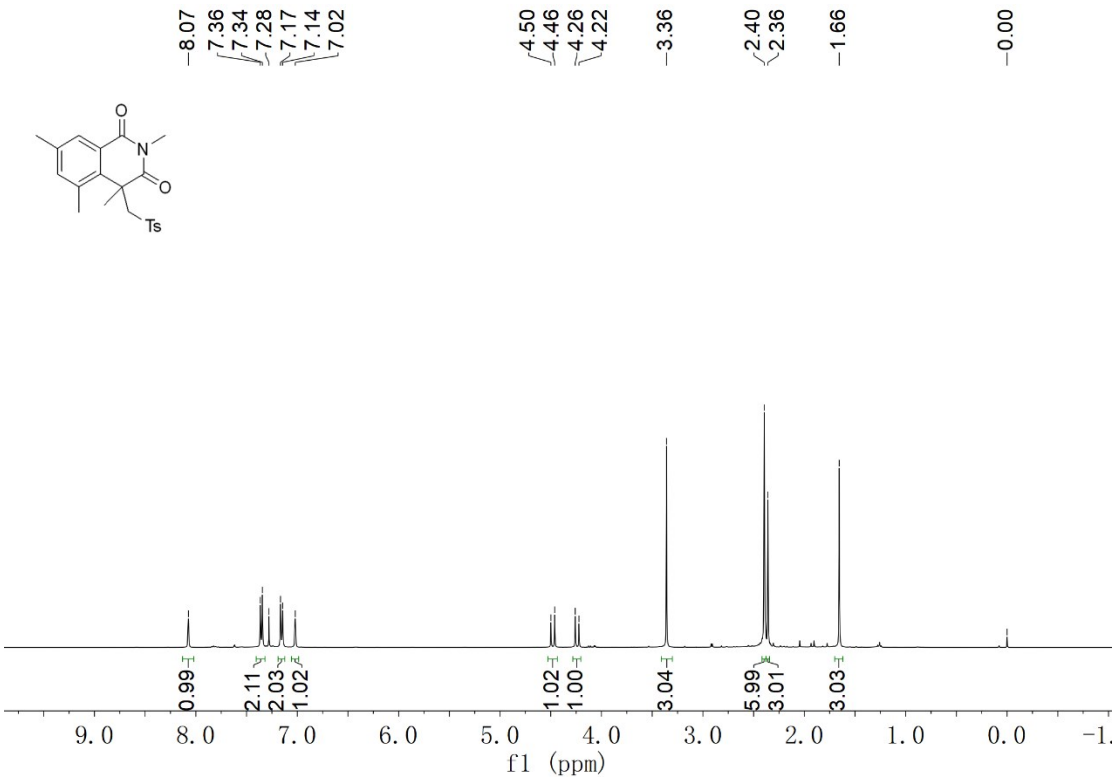


^{1}H NMR of compound **3r**



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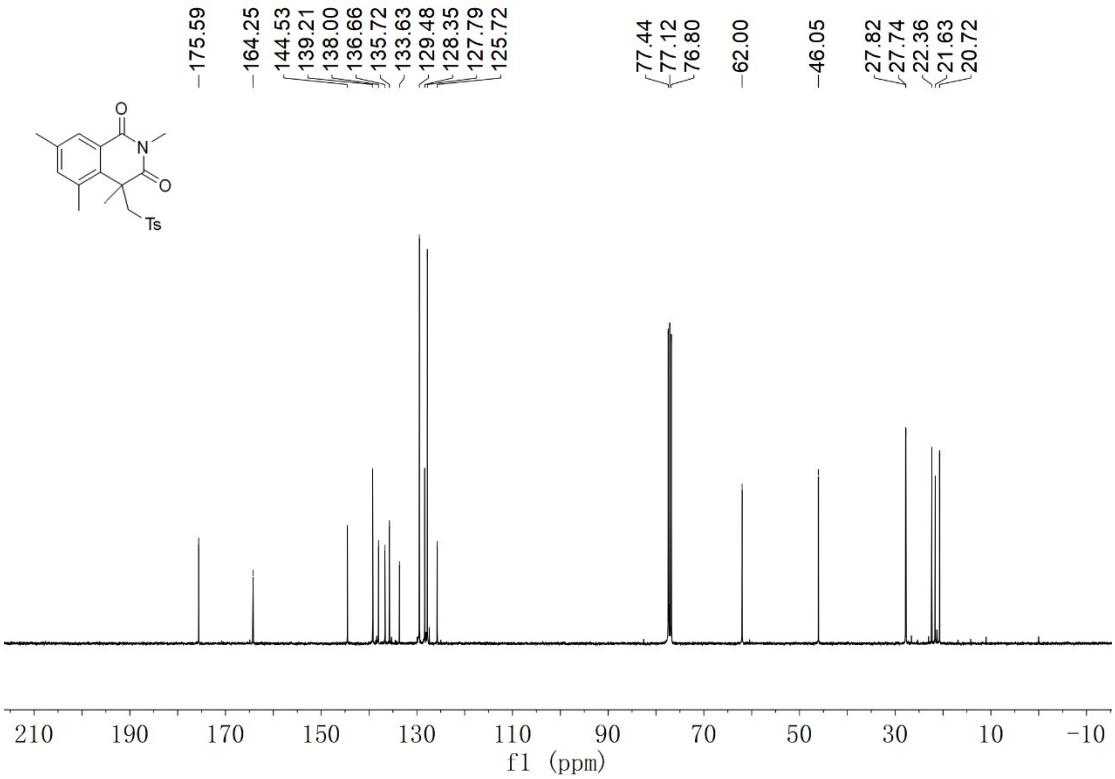

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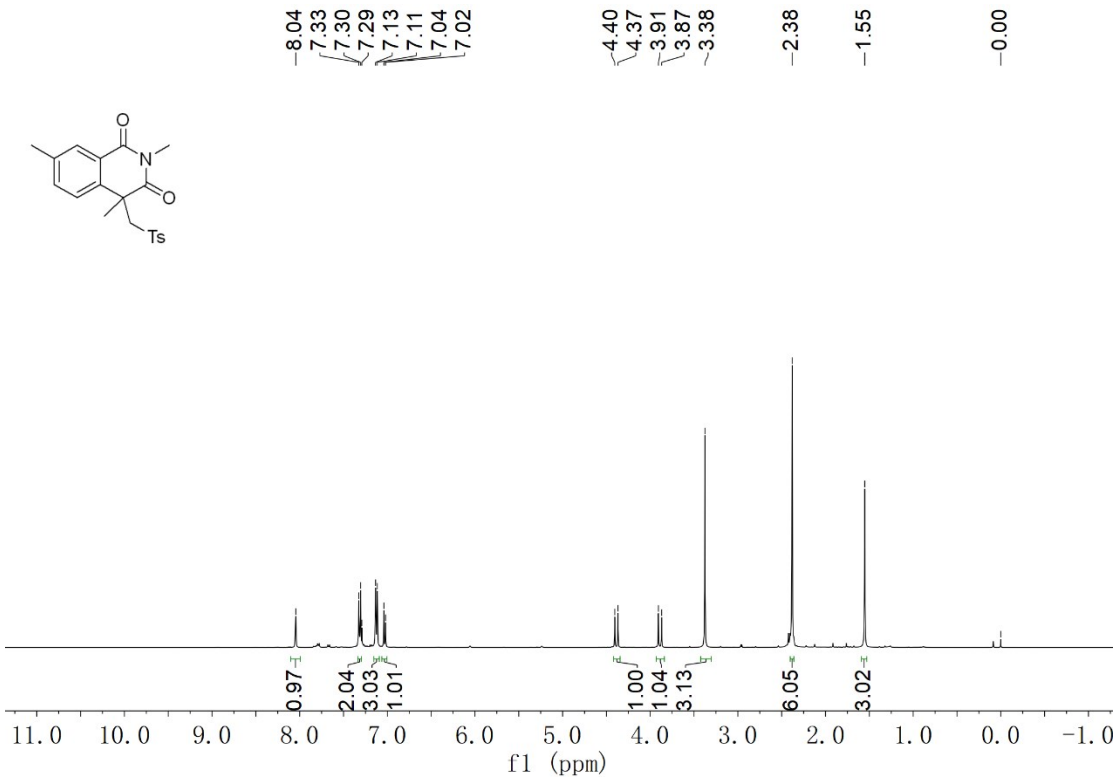

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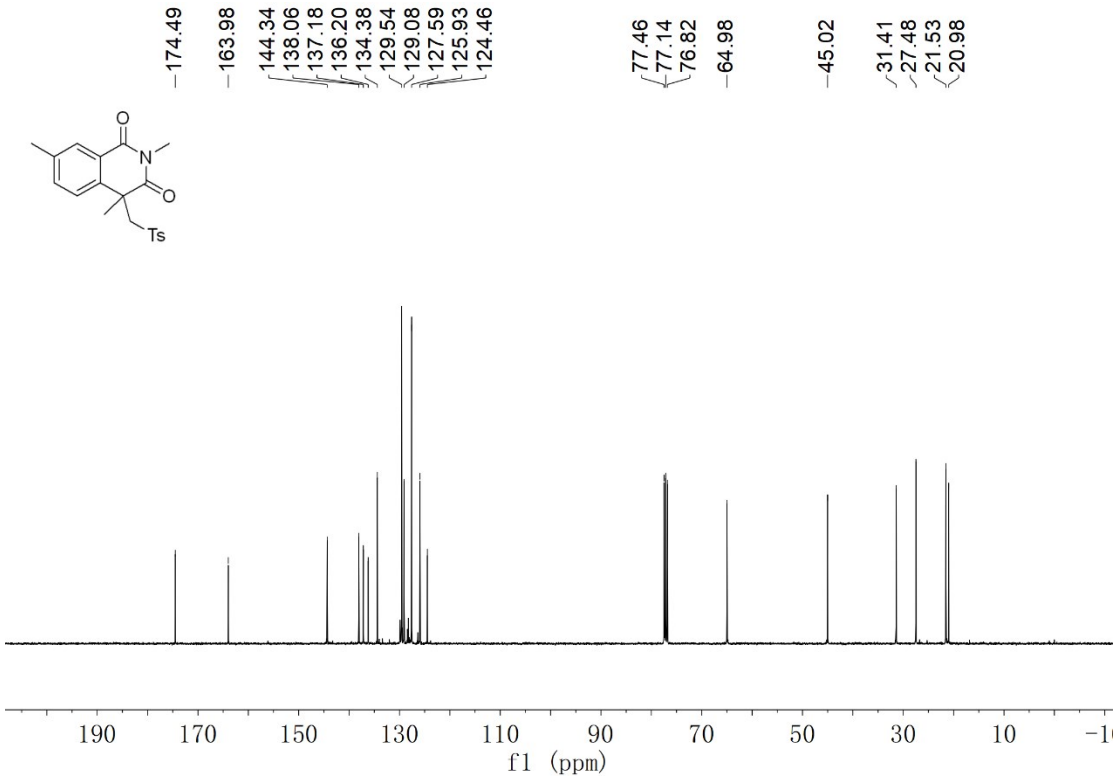
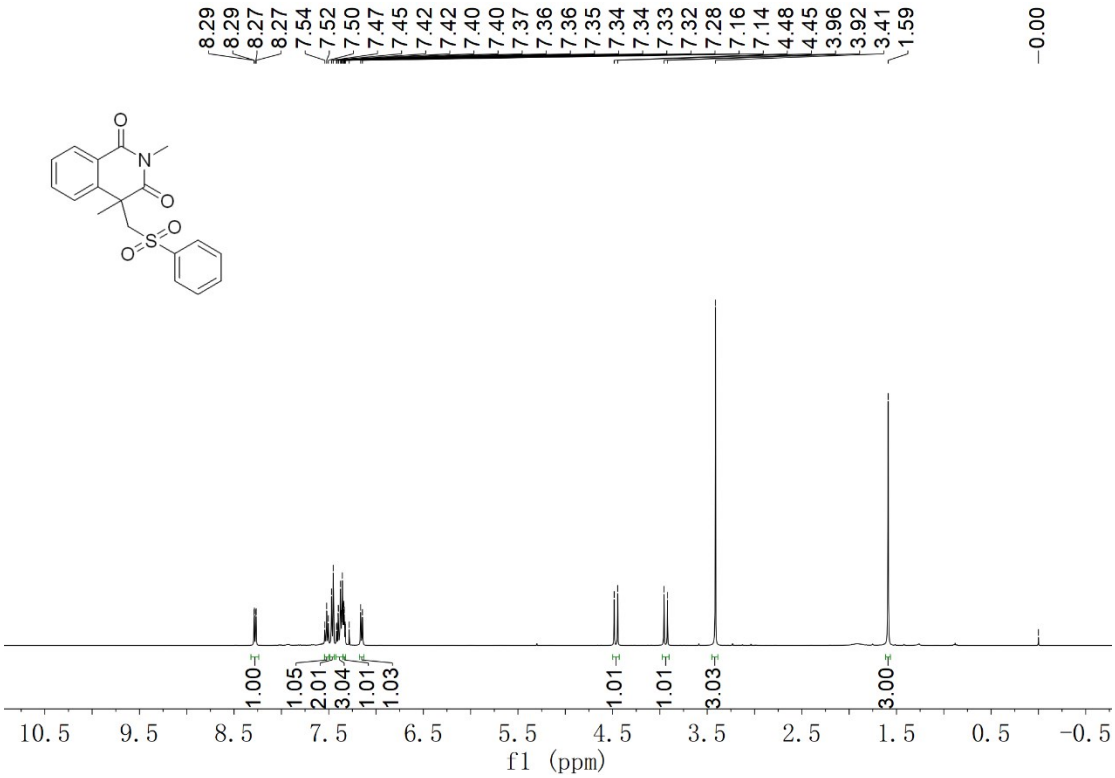


^{1}H NMR of compound **3t**



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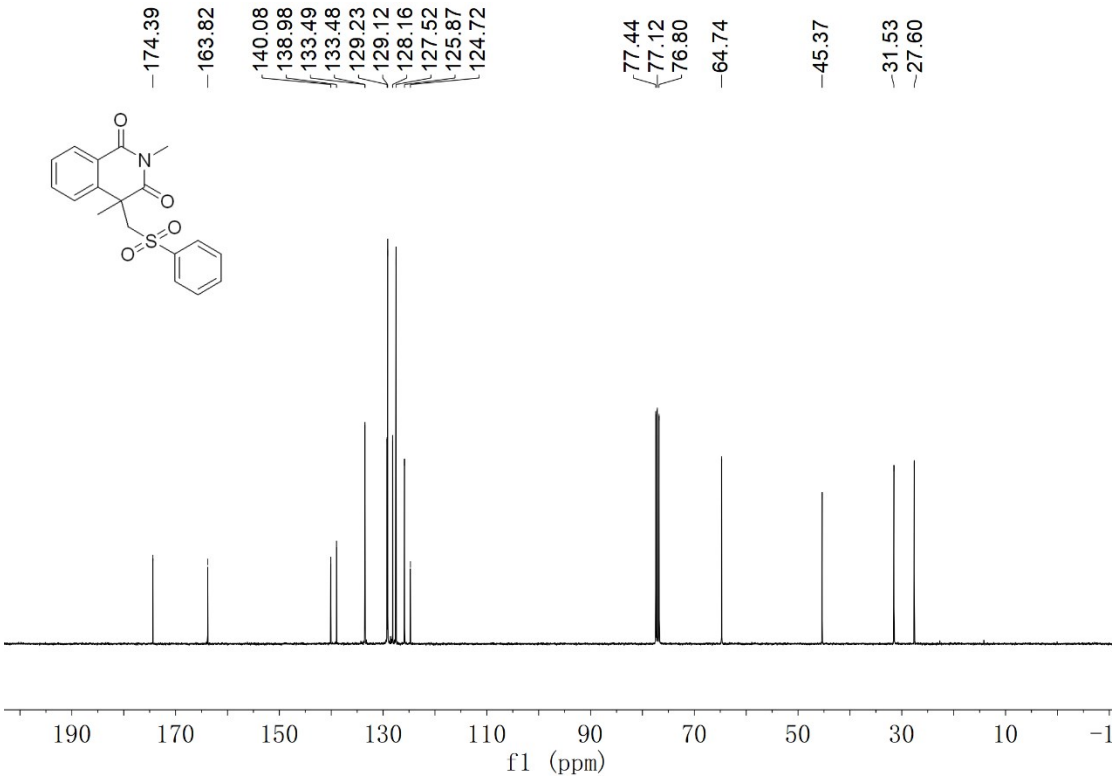

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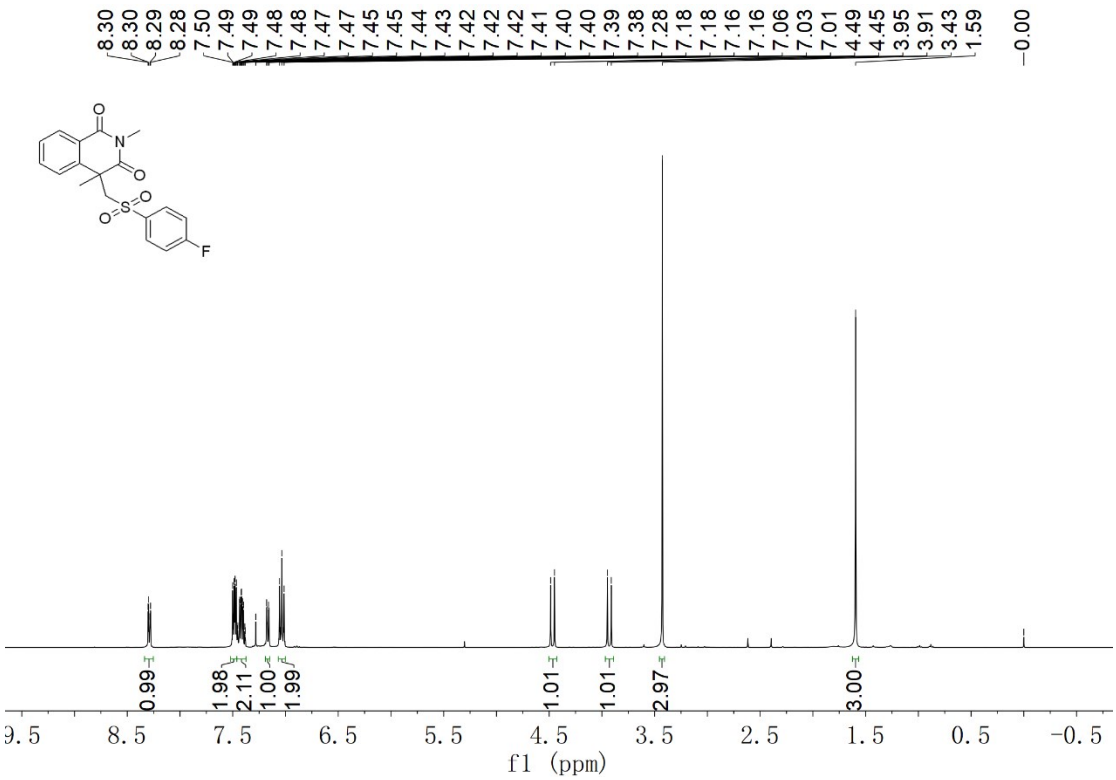

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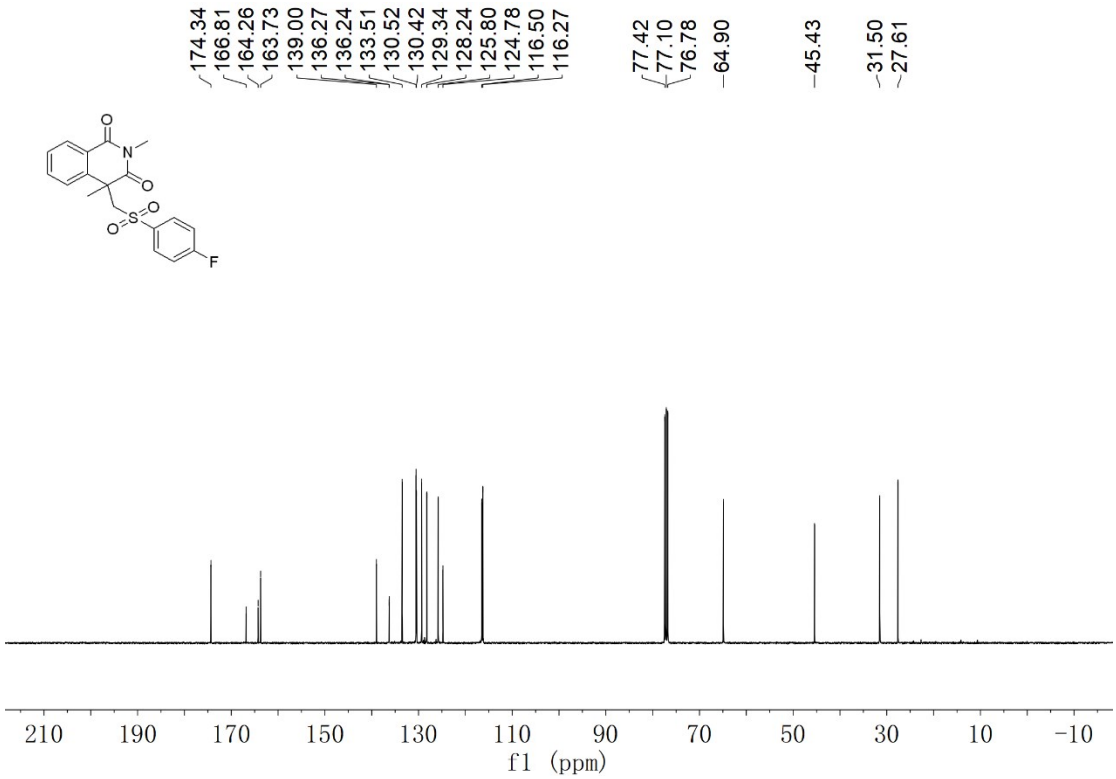
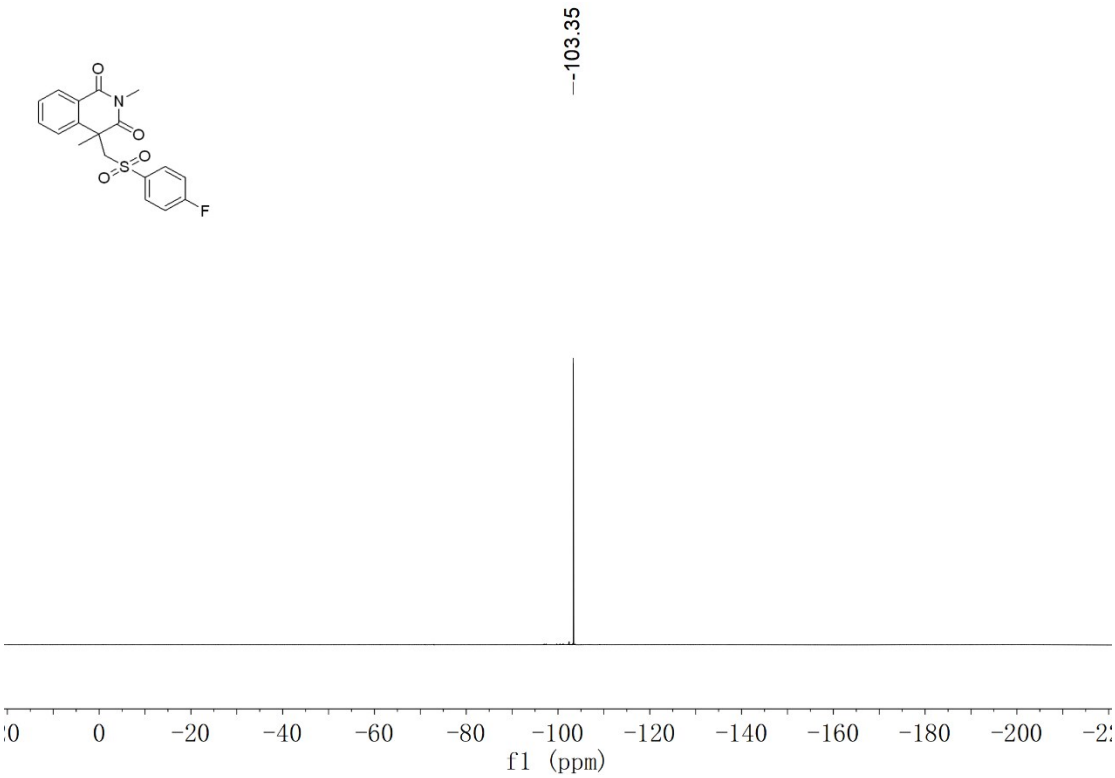


^{19}F NMR of compound **3u**



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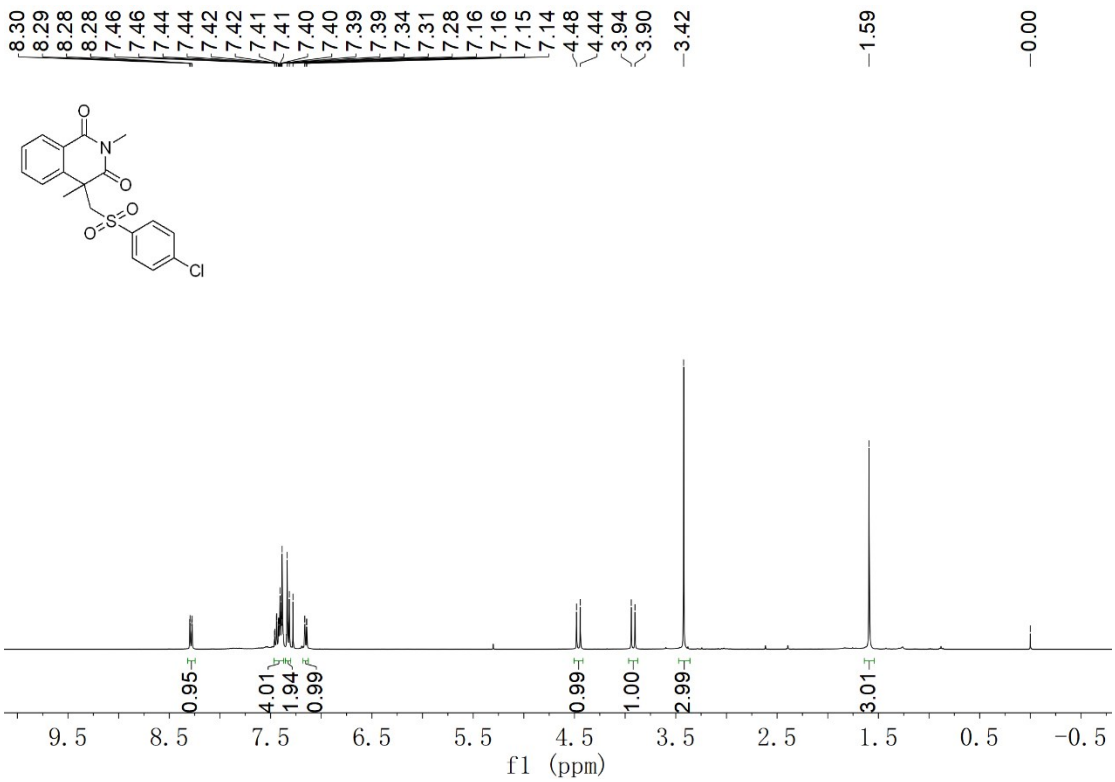

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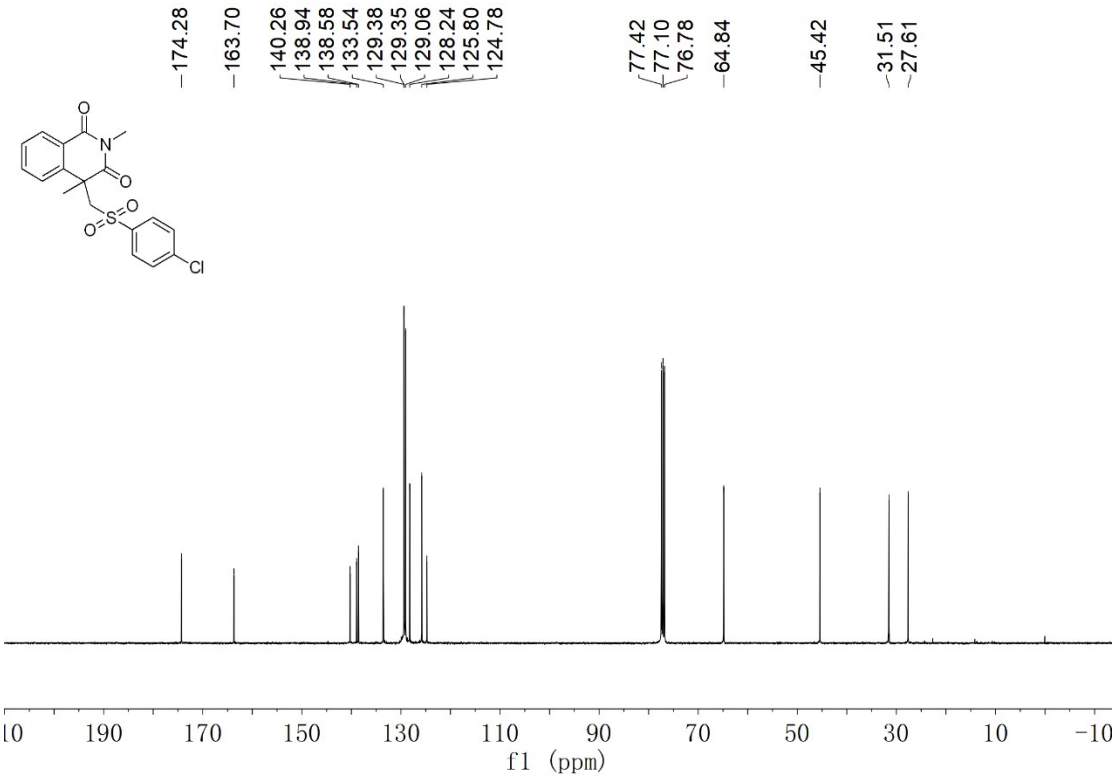

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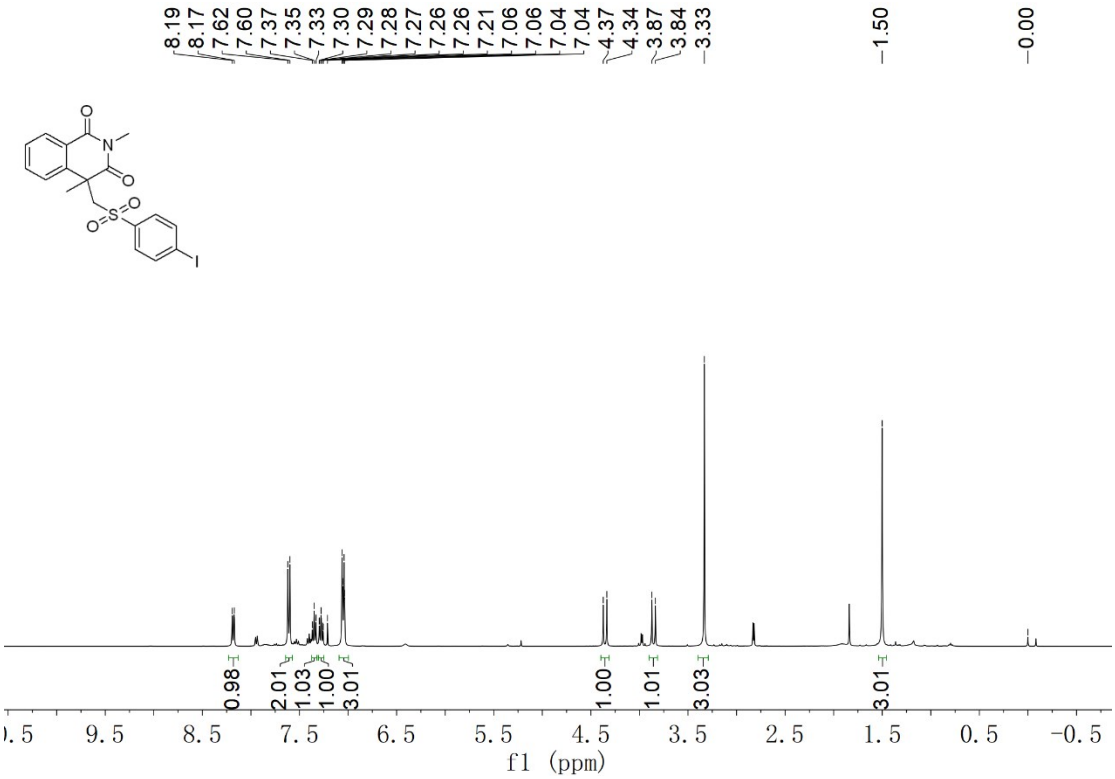
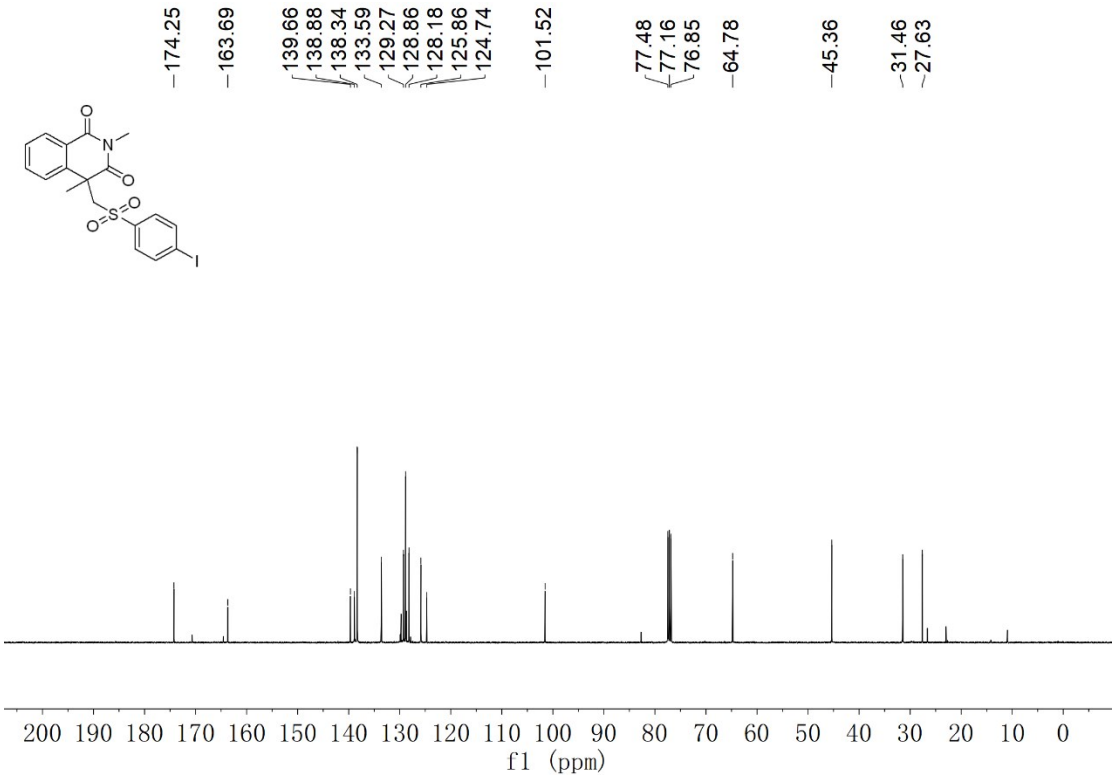


^{13}C NMR of compound **3w**



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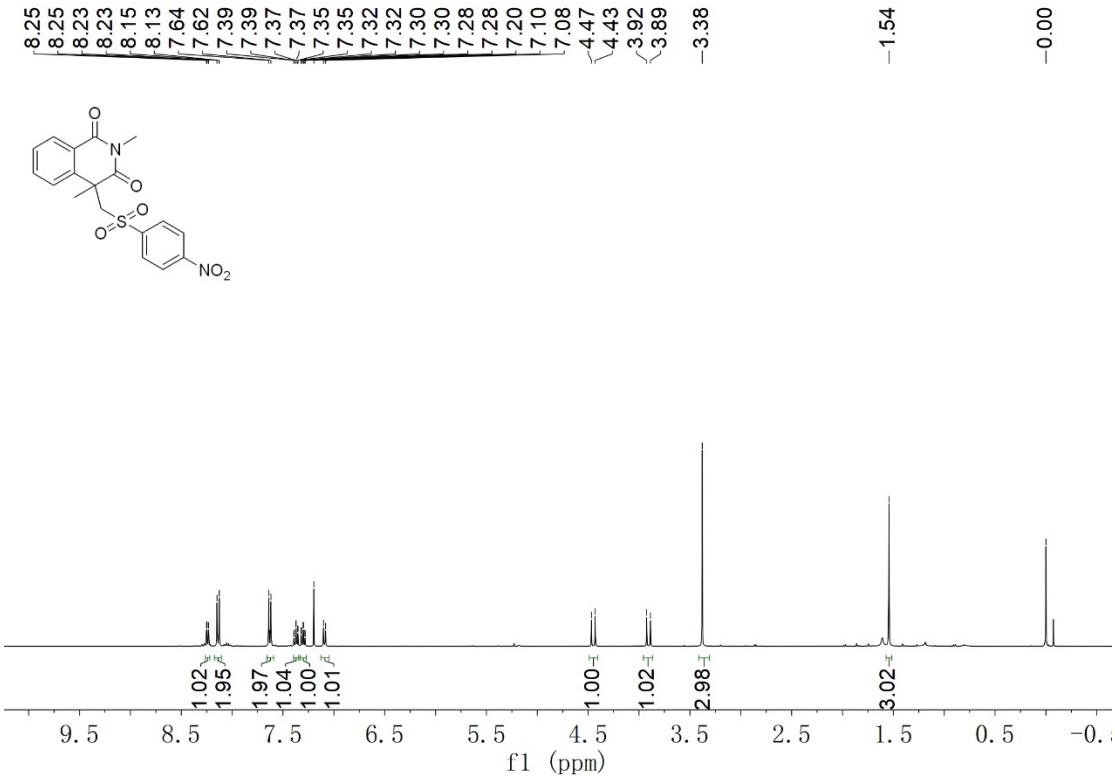

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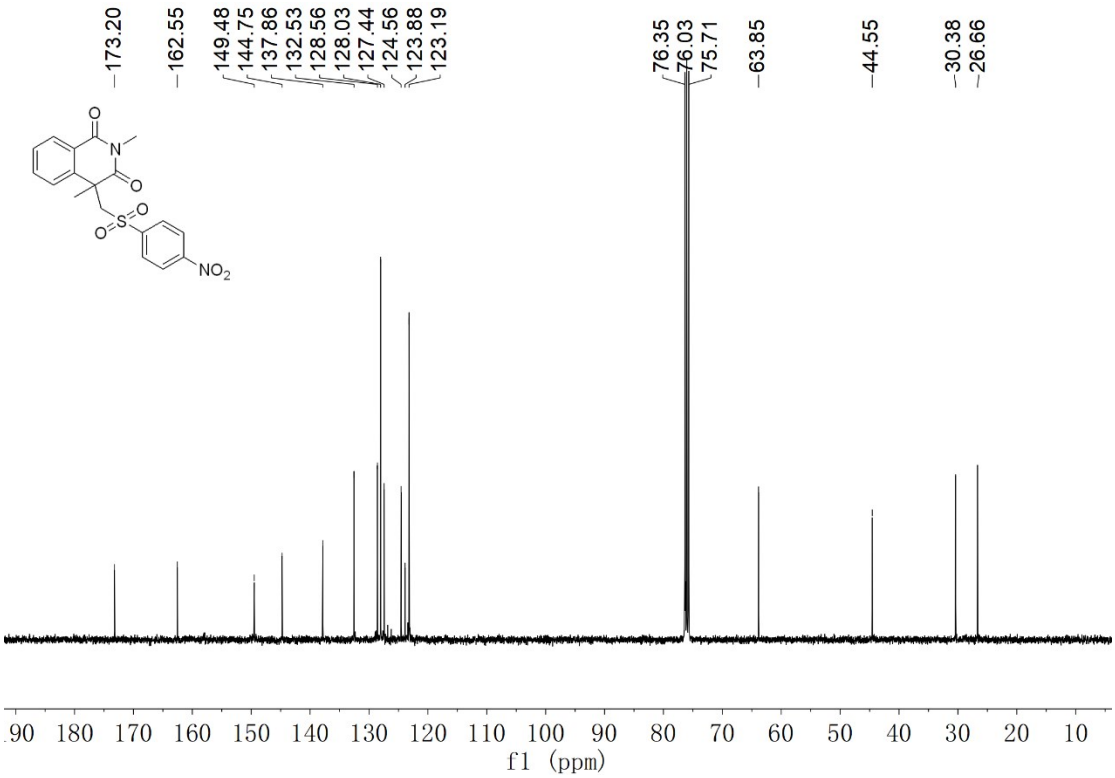

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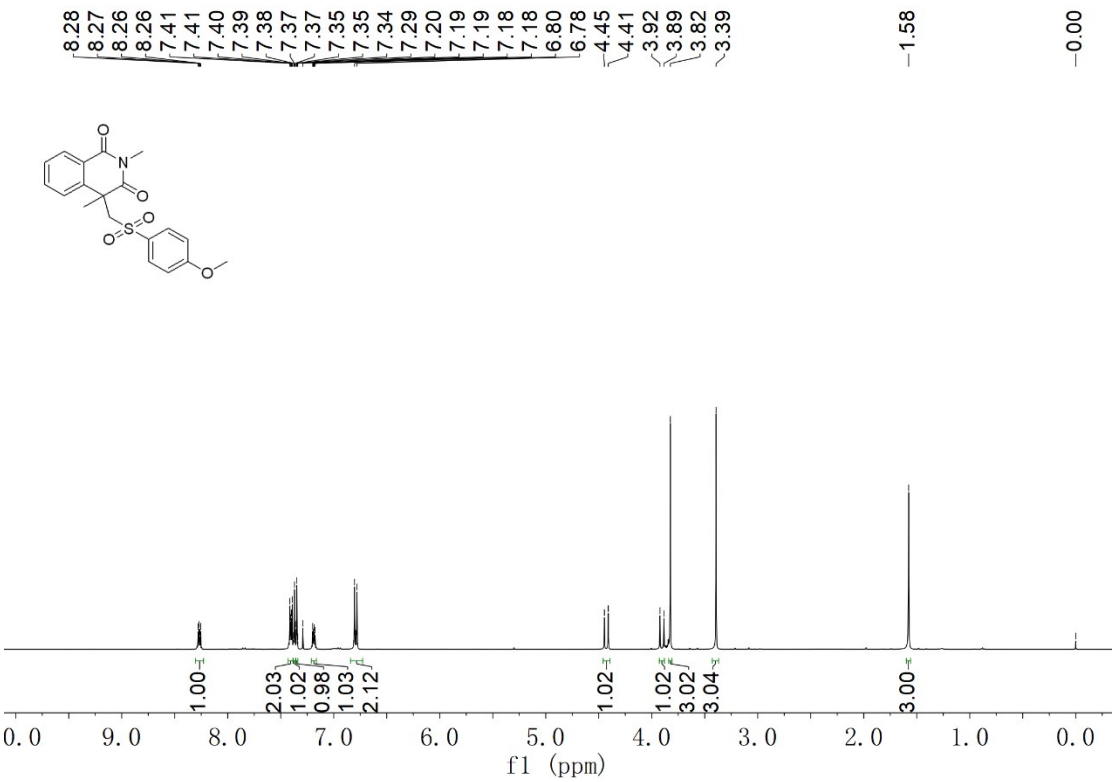
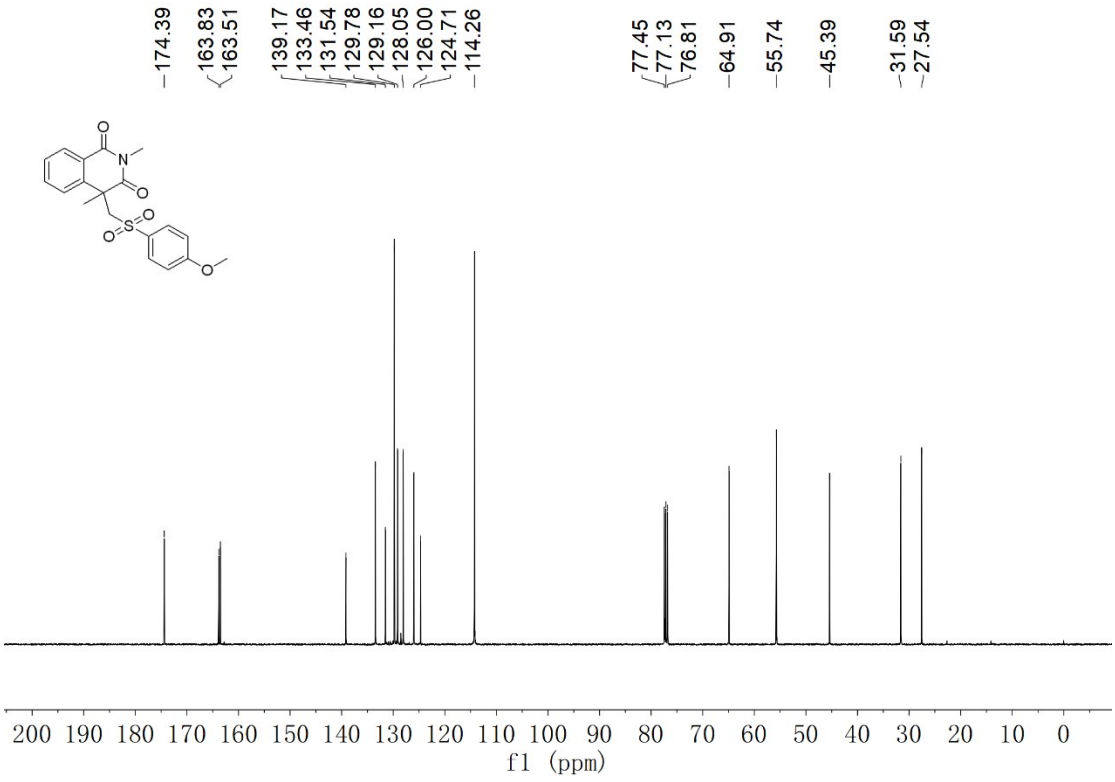


^{13}C NMR of compound **3y**



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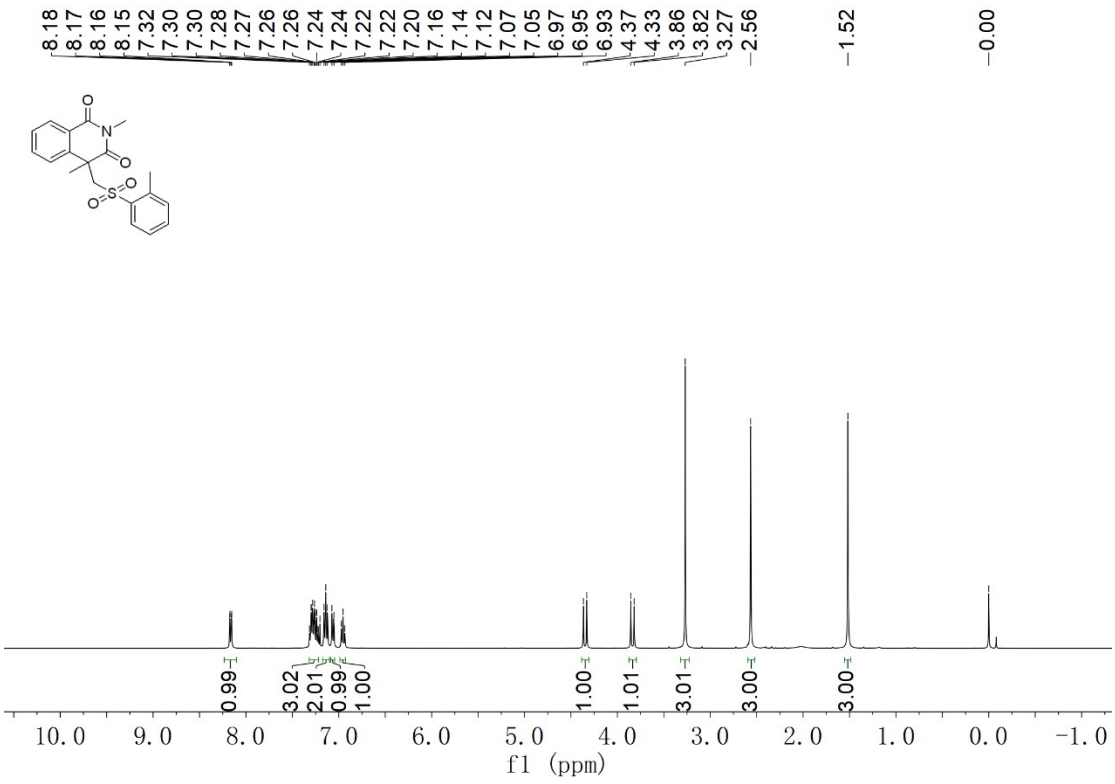

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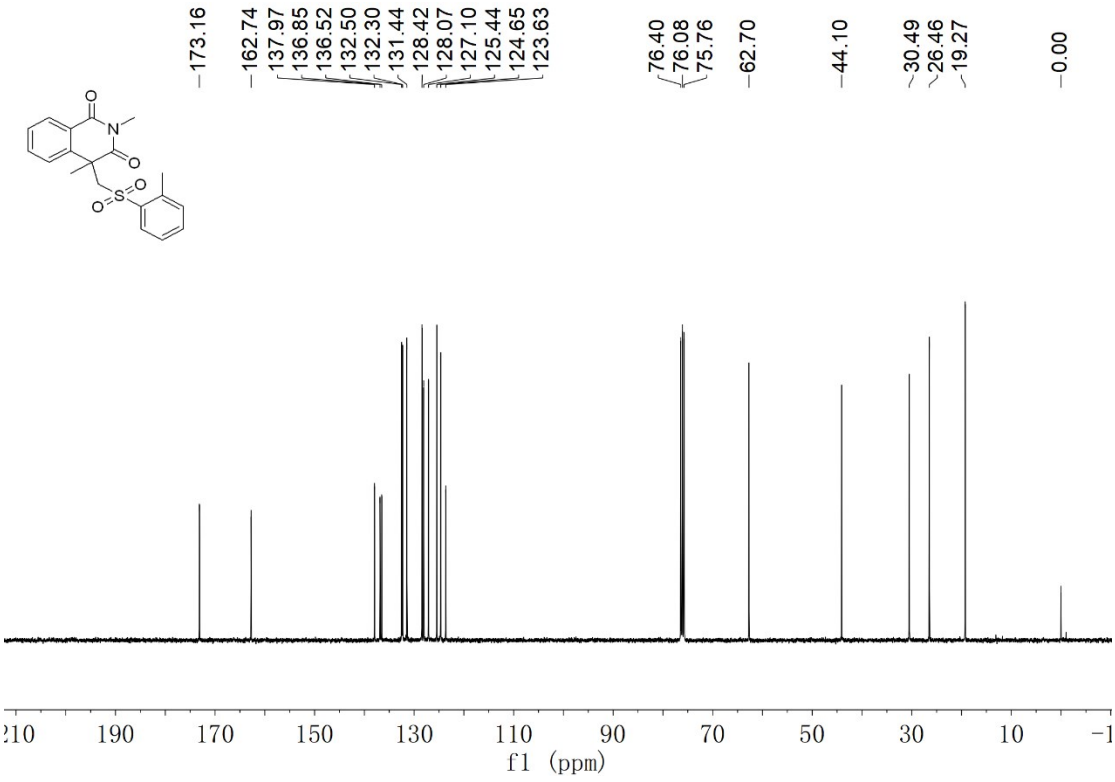

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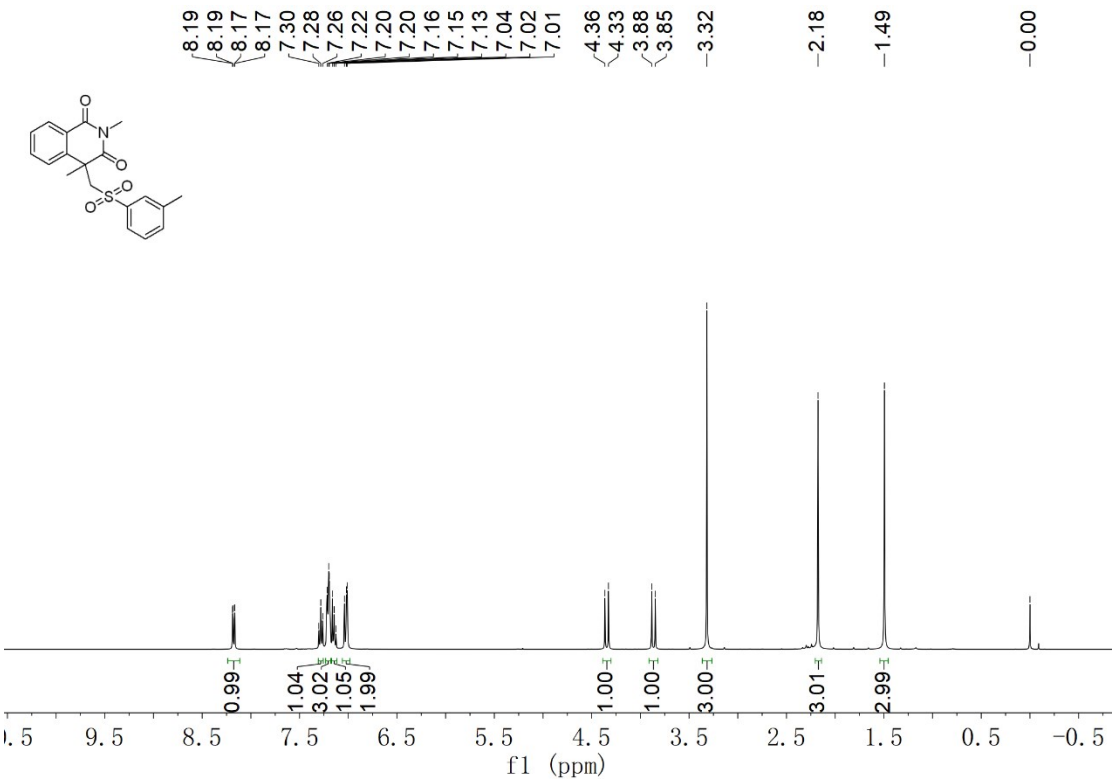
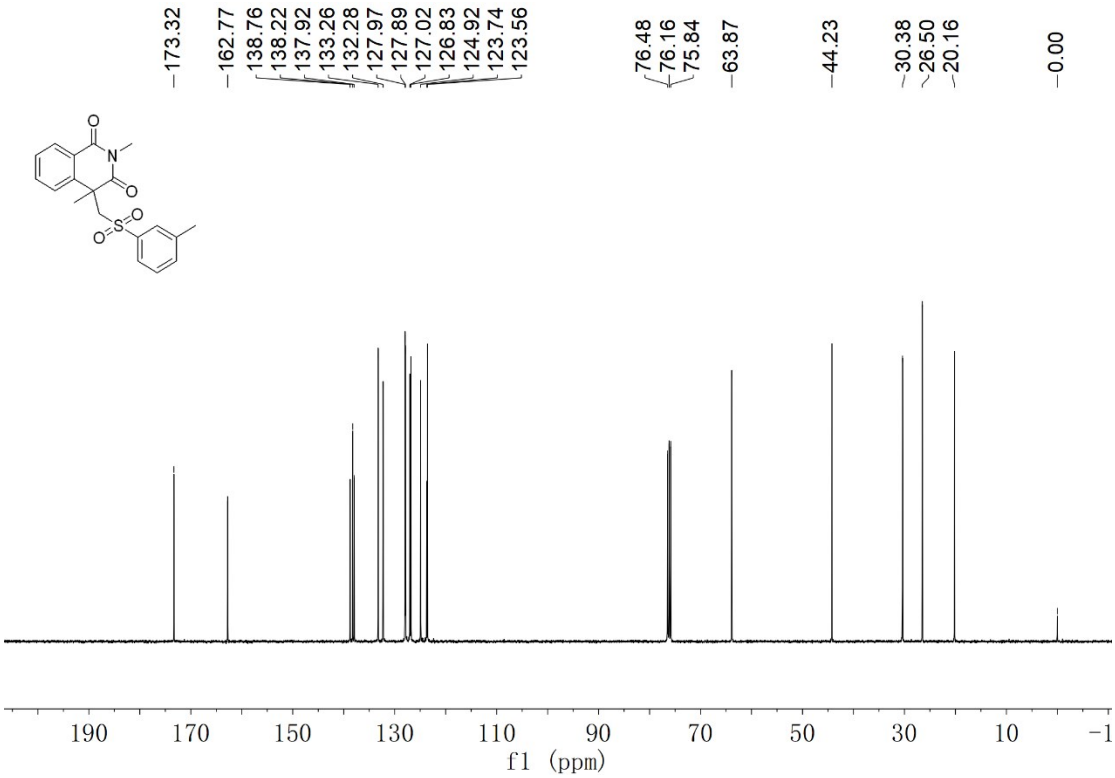
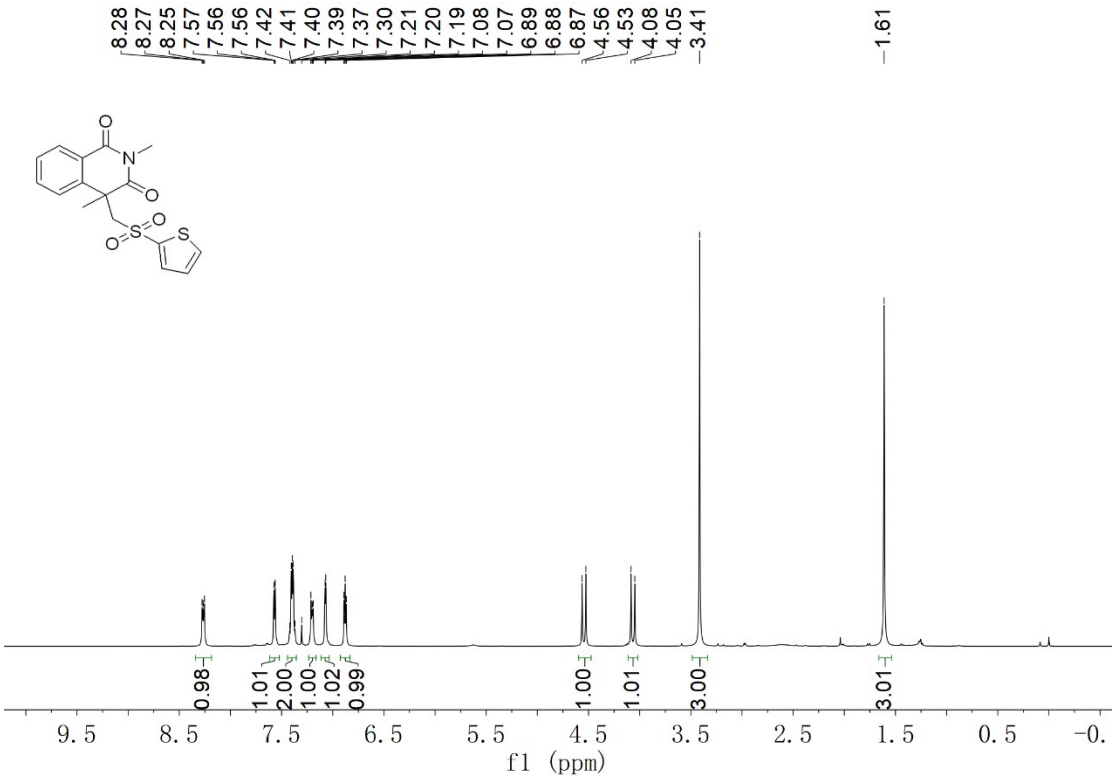


^{13}C NMR of compound **3aa**



^{1}H NMR of compound **3ab**



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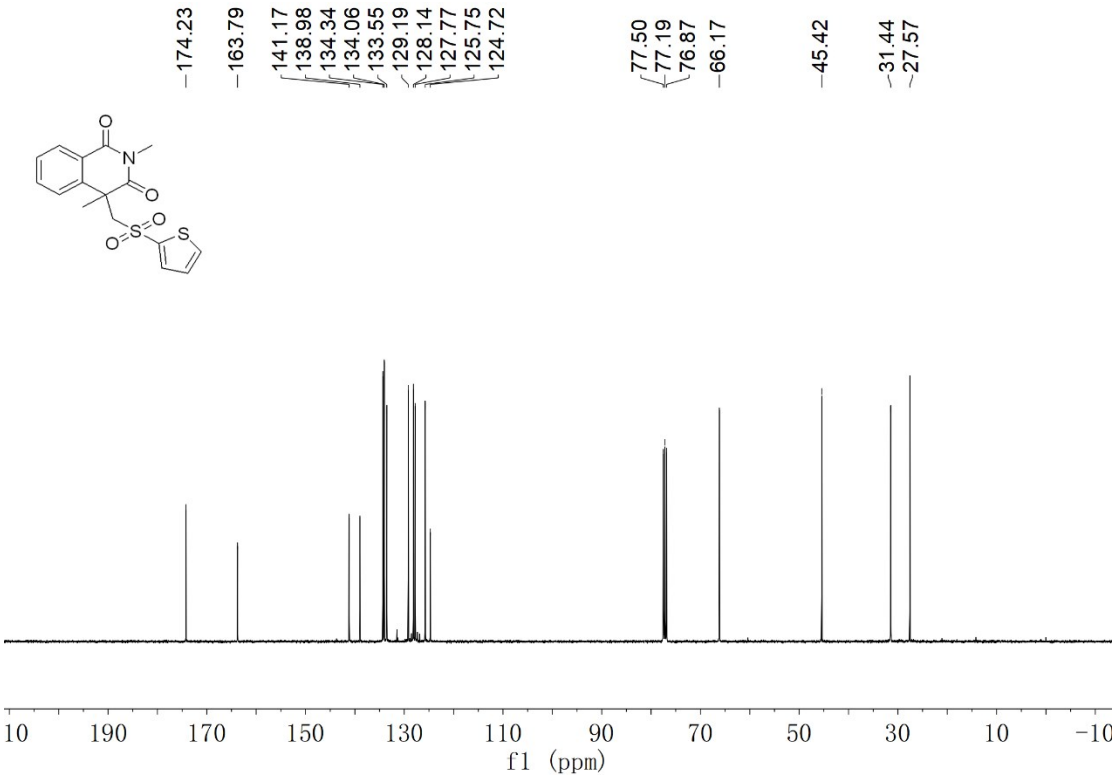

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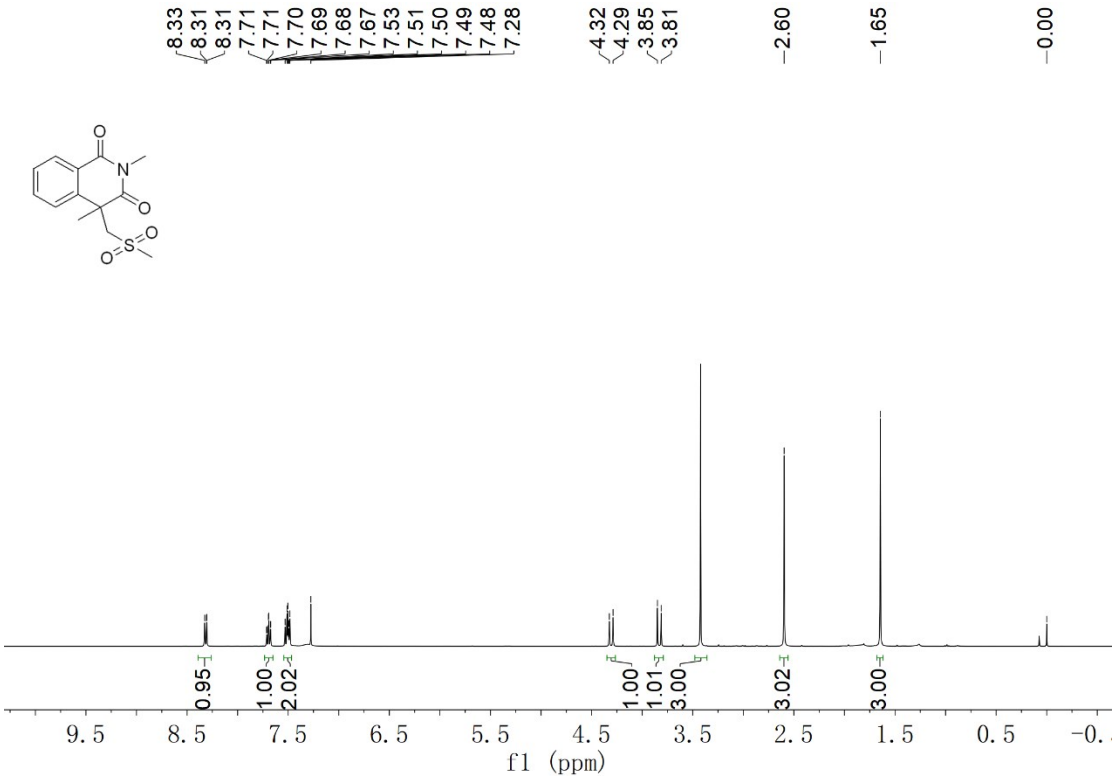

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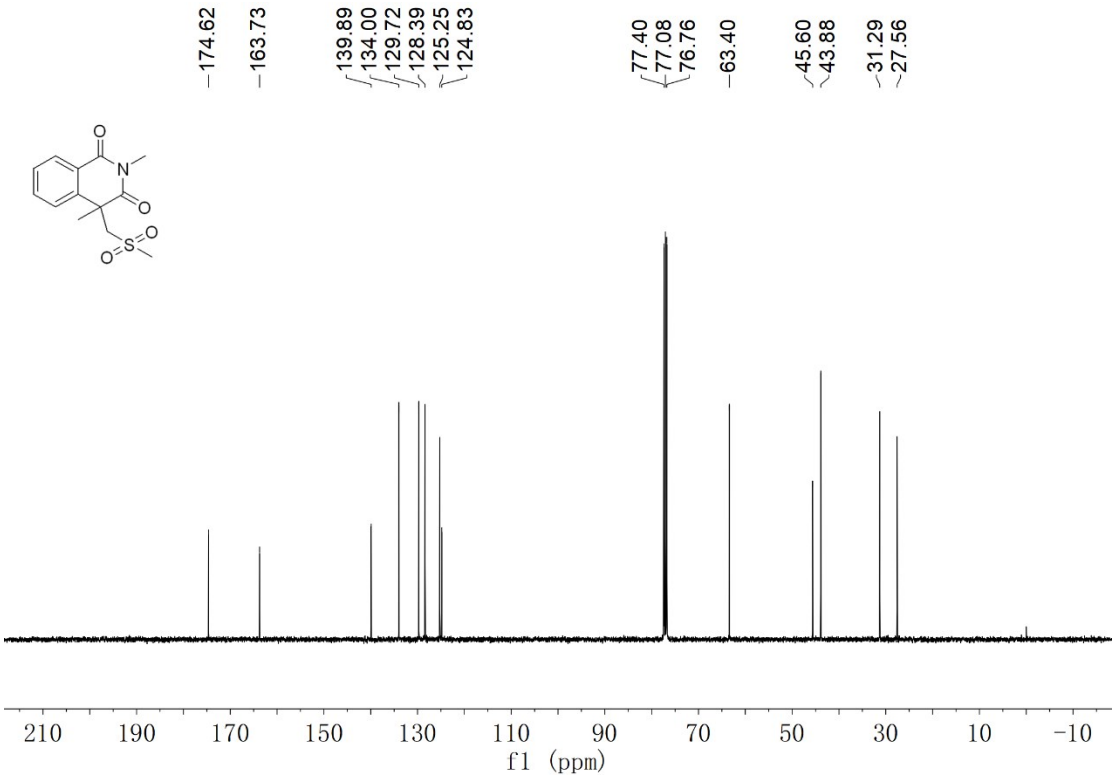

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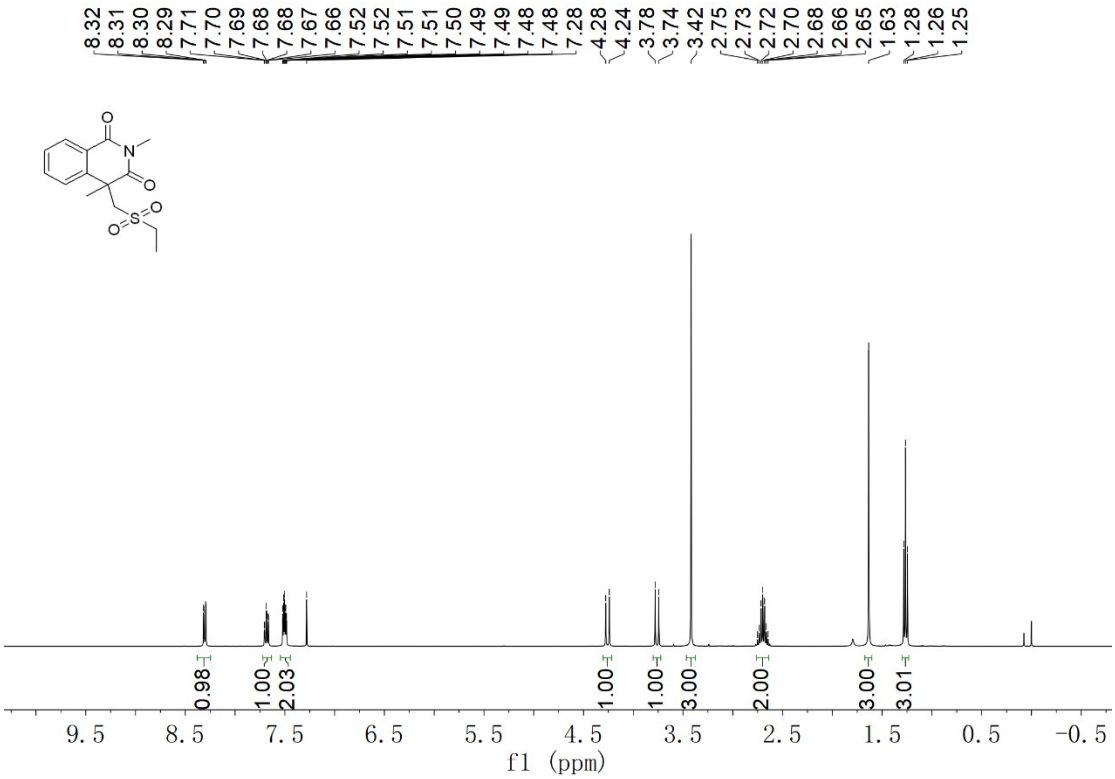

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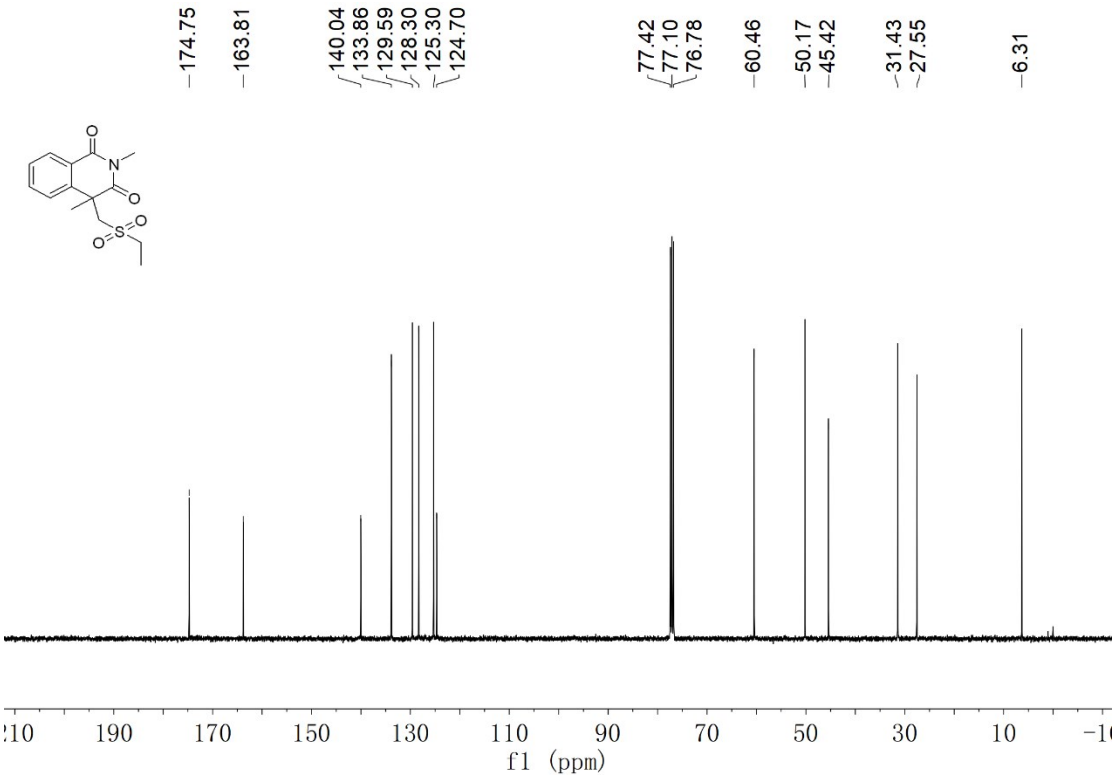

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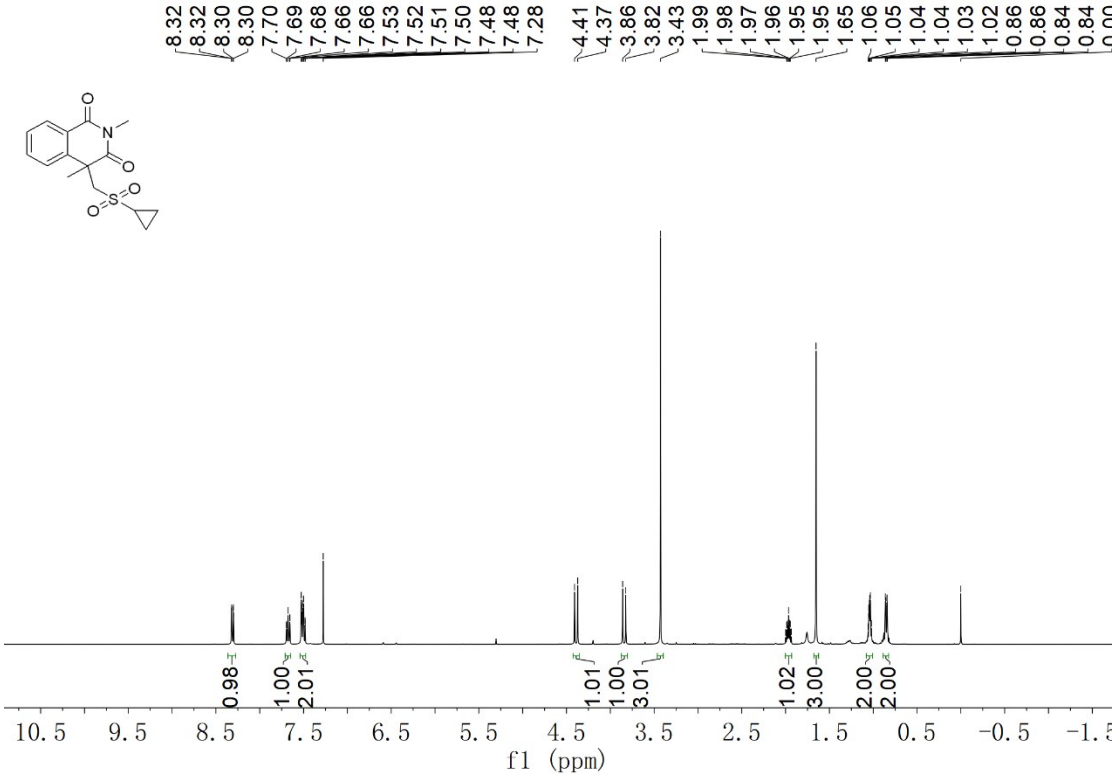
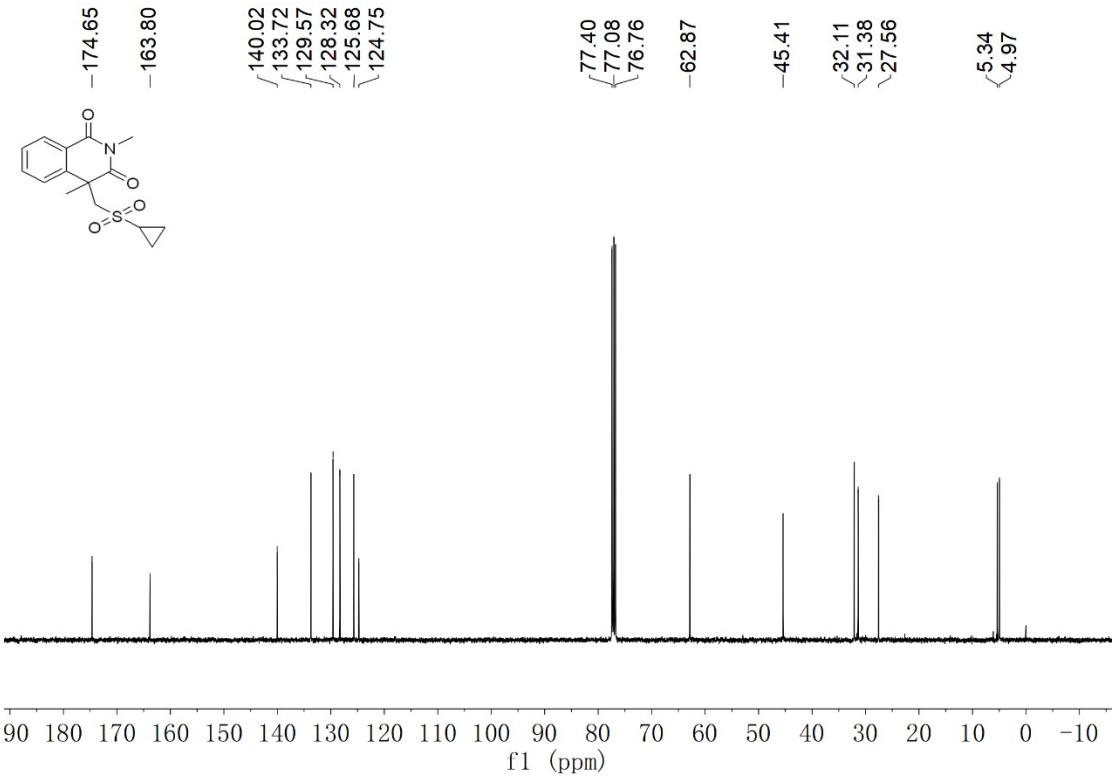


^{13}C NMR of compound **3ae**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77.08
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32.11
31.38
27.56
5.34
4.97
90 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)