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Supplementary Information

Regioselective Synthesis of Isoquinolinonediones through Remote Unactivated C(sp^3)-H Bonds

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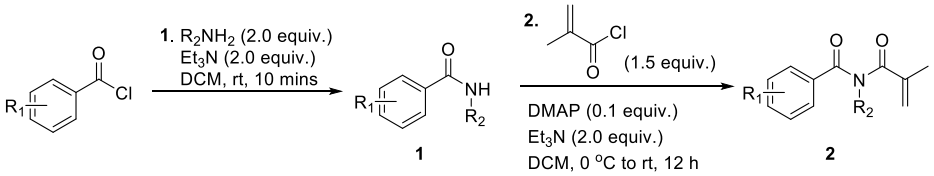
1. General information

The reagents and solvents were purchased from commercial suppliers and used without further purification unless noted. All reactions were monitored by TLC with silica gel-coated plates. Product purification was accomplished by flash chromatography using 200-300 mesh silica gel. ^{1}H (400 MHz) NMR, ^{13}C (101 MHz) NMR, and ^{19}F (376 MHz) NMR spectra were recorded on a Varian spectrometer in $CDCl_3$. Measurements were done at ambient temperature. ^{1}H NMR chemical shifts are referenced to the residual hydrogen signals of the deuterated solvent (7.26 ppm for $CDCl_3$). The ^{13}C NMR chemical shifts are referenced to the ^{13}C signals of the deuterated solvent (77.16 ppm for $CDCl_3$). Abbreviations used in the description of NMR data are listed as follows: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet. Mass spectra were measured with a HRMS-APCI instrument using ESI ionization.

2. Preparation of substrates

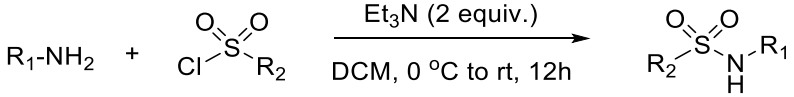
2.1 General Procedure for the synthesis of *N*-methacryloyl-*N*-methylbenzamide substrates[1-4]



STEP 1: A dried round-bottom flask was charged with a magnetic stirring bar, aniline (10 mmol), triethylamine (10 mmol), and DCM (30 mL). Benzoyl chloride (5 mmol) dissolved in DCM (10 mL) was added slowly for 5 mins at room temperature, and the mixture was stirred for 30 mins. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated NaCl solution (100 mL) and extracted with DCM (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified via column chromatography to give **1** (98% yield).

STEP 2: A dried round-bottom flask was charged with a magnetic stirring bar, benzamide **1** (5 mmol), triethylamine (10 mmol), DMAP (0.5 mmol), and DCM (30 mL). Methacryloyl chloride (10 mmol) dissolved in DCM (10 mL) was added slowly for 5 mins at 0 °C, and the mixture was stirred for 12 h at room temperature. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated NaCl solution (100 mL) and extracted with DCM (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified via column chromatography to give **2** (91% yield).

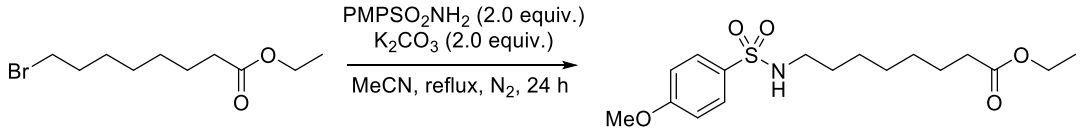
2.2 General Procedure for the synthesis of *N*-protected amine from free amines and sulfonyl chloride[5-8]



A dried round-bottom flask was charged with a magnetic stirring bar, free amine (5 mmol), triethylamine (10 mmol), and DCM (30 mL). Sulfuryl chloride (10 mmol) dissolved in DCM (10

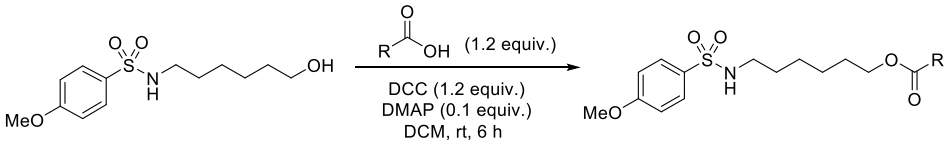
mL) was added slowly for 5 mins at 0 °C, and the mixture was stirred for 2-12 h at room temperature. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated NaCl solution (100 mL) and extracted with DCM (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified via column chromatography to give corresponding sulfonamide products (85-96% yields).

2.3 Procedure for the synthesis of ethyl 8-((4-methoxyphenyl)sulfonamido)octanoate[9]



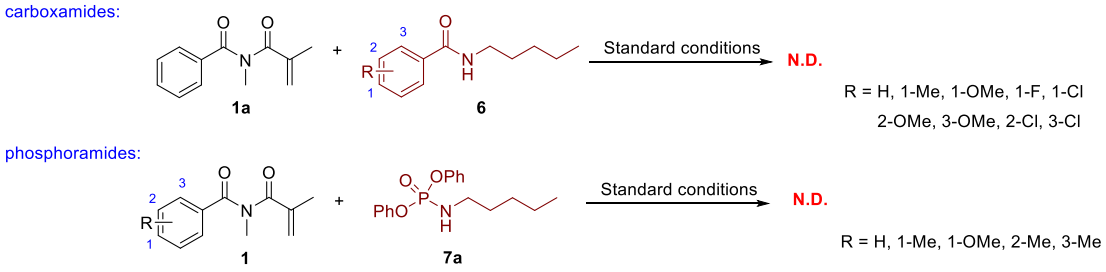
A dried round-bottom flask was charged with a magnetic stirring bar, free amine alkyl bromide (2.0 mmol), *p*-methoxyphenylsulfonamide (4.0 mmol), K_2CO_3 (4.0 mmol), and MeCN (10 mL). Then the reaction mixture was heated to reflux for 12 hours. After being cooled to room temperature, the reaction was quenched with saturated NaCl solution (50 mL) and extracted with EtOAc (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified via column chromatography to give the desired product (63% yield).

2.4 General Procedure for the synthesis of *N*-protected amine substrates from free alcohol intermediates and acid [9]



A dried round-bottom flask was charged with a magnetic stirring bar, *N*-(6-hydroxyhexyl)-4-methoxybenzenesulfonamide (1.0 mmol), acid (1.2 mmol), DCC (1.2 mmol), DMAP (0.1 mmol) and DCM (10 mL). The mixture was stirred for 6 h at room temperature. The reaction was monitored by TLC. After completion, the reaction was quenched with saturated NaCl solution (50 mL) and extracted with DCM (15 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified via column chromatography to give the desired products (64% yield).

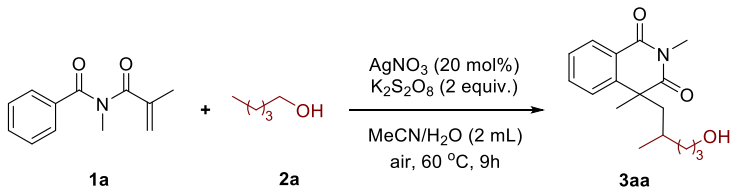
2.5 Unsuccessful substrates



Standard conditions: $AgNO_3$ (10 mol%) and $K_2S_2O_8$ (2.0 equiv.) in MeCN/H_2O (1 mL/1 mL) under air atmosphere and stirred at 60 °C for 9 h.

3. Optimization studies

3.1 Optimization of the conditions for the cascade addition/cyclization of aliphatic alcohols



1a 2a 3aa

Entry	Changes from standard conditions [a]	Yield [b] (%)
1	None	76
2	NMP / H_2O as solvent	N.D.
3	DMA / H_2O as solvent	35
4	DMF / H_2O as solvent	47
5	DMSO / H_2O as solvent	N.D.
6	DMPU / H_2O as solvent	17
7	Acetone / H_2O as solvent	42
8	AgCl, Ag_2CO_3, CF_3COOAg, $CuCl_2$, $FeCl_3$ as catalyst	55, 59, 46, N.D., N.D.
9	$Na_2S_2O_8$, $(NH_4)_2S_2O_8$ as oxidant	66, 48
10	1 equiv. of $K_2S_2O_8$	64
11	10 mol% of $AgNO_3$	58
12	Without $K_2S_2O_8$	N.D.
13	Without $AgNO_3$	N.D.
14	100 °C, 80 °C, 40 °C	34, 51, 39

[a] Reaction condition: **1a** (0.3 mmol), **2a** (0.9 mmol), $AgNO_3$ (20 mol%), and $K_2S_2O_8$ (2.0 equiv.) in MeCN/H_2O (1 mL/1 mL) under air atmosphere and stirred at 60 °C for 9 h. [b] Isolated yields based on **1a**.

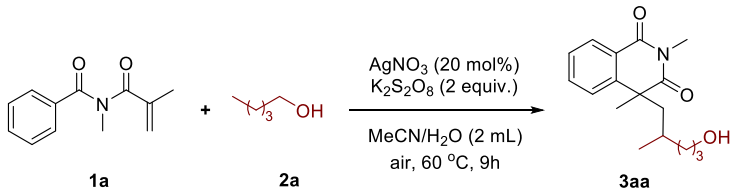
3.2 Optimization of the conditions for the cascade addition/cyclization of sulfonamides

1a 4c 5ac

Entry	Changes from standard conditions [a]	Yield [b] (%)
1	None	72
2	NMP / H_2O as solvent	N.D.
3	DMA / H_2O as solvent	28
4	DMF / H_2O as solvent	54
5	DMSO / H_2O as solvent	36
6	DMPU / H_2O as solvent	24
7	Acetone / H_2O as solvent	61
8	AgCl, Ag_2CO_3, CF_3COOAg $CuCl_2$, $FeCl_3$ as catalyst	44, 67, 51, N.D., N.D.
9	$Na_2S_2O_8$, $(NH_4)_2S_2O_8$ as oxidant	58, 55
10	1 equiv. of $K_2S_2O_8$	59
11	10 mol% of $AgNO_3$	64
12	Without $K_2S_2O_8$	N.D.
13	Without $AgNO_3$	N.D.
14	100 °C, 80 °C, 40 °C	29, 48, 55

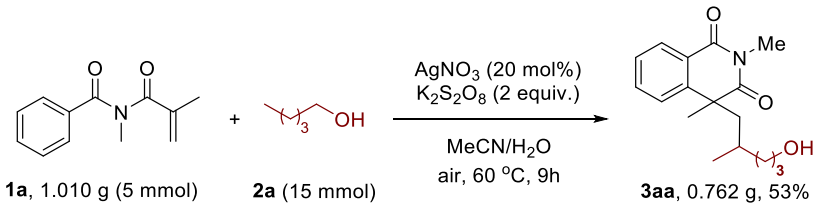
[a] Reaction condition: **1a** (0.3 mmol), **4c** (0.33 mmol), $AgNO_3$ (20 mol%), and $K_2S_2O_8$ (2.0 equiv.) in MeCN/H_2O (1 mL/1 mL) under air atmosphere and stirred at 60 °C for 9 h. [b] Isolated yields based on **1a**.

4. General procedure for the synthesis of products (3aa as an example)



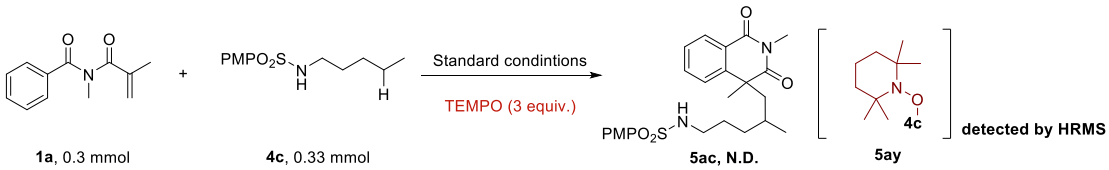
To a Schlenk-tube was charged with **1a** (0.3 mmol), **2a** (0.9 mmol), $AgNO_3$ (0.06 mmol), $K_2S_2O_8$ (0.6 mmol), MeCN (1.0 mL) and H_2O (1.0 mL). The mixture was stirred at 60 °C for 9 hours. After completion, the reaction was quenched with saturated NaCl solution (10 mL) and extracted with EtOAc (4 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (PE/EtOAc = 6/1-4/1) to afford **3aa** (76%) as a yellow oil.

5. Gram-scale experiments (3aa and 5ac, 3aa as an example)

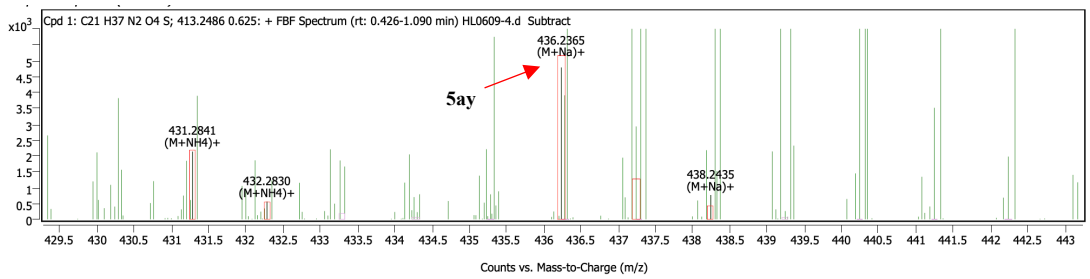


A 250 mL dried round-bottom flask was charged with a magnetic stirring bar, *N*-methacryloyl-*N*-methylbenzamide (5 mmol), 1-pentanol (15 mmol), silver nitrate (1 mmol), $K_2S_2O_8$ (10 mmol), MeCN (10 mL) and H_2O (10 mL). The resulting mixture was stirred at 60 °C using an oil bath for 9 hours. After completion, the reaction was quenched with saturated NaCl solution (30 mL) and extracted with EtOAc (10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography. Compound **3aa** was isolated in 53% yield (0.762 g) as a yellow oil.

6. Mechanistic studies

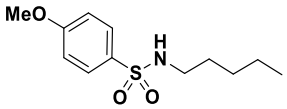


Standard conditions: $AgNO_3$ (10 mol%) and $K_2S_2O_8$ (2.0 equiv.) in MeCN/H_2O (1 mL/1 mL) under air atmosphere and stirred at 60 °C for 9 h.



The reaction was completely inhibited by radical inhibitors 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), and the radical adducts **5ay** was detected by HRMS ($[M+Na]^+$ =436.2365).

7. Characterization date



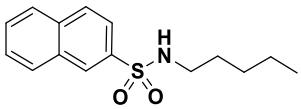
4-methoxy-*N*-pentylbenzenesulfonamide (4c)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 95%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.75 (m, 2H), 6.94 – 6.89 (m, 2H), 5.19 (s, 1H), 3.80 (dd, *J* = 8.2, 4.1 Hz, 3H), 2.86 – 2.79 (m, 2H), 1.44 – 1.33 (m, 2H), 1.19 – 1.14 (m, 4H), 0.79 – 0.73 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.75, 162.73, 131.53, 129.18, 129.17, 114.19, 55.60, 43.15, 29.10, 29.08, 28.64, 22.11, 13.86, 13.85.

Data are consistent with reported in the literature[9].



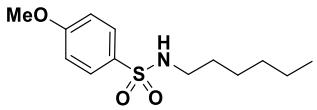
***N*-pentylnaphthalene-2-sulfonamide (4m)**

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 94%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.45 (m, 1H), 7.99 – 7.93 (m, 2H), 7.93 – 7.82 (m, 2H), 7.66 – 7.57 (m, 2H), 5.03 (s, 1H), 2.99 – 2.95 (m, 2H), 1.49 – 1.42 (m, 2H), 1.25 – 1.17 (m, 4H), 0.81 – 0.76 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.79, 136.77, 134.80, 132.18, 129.51, 129.24, 128.75, 128.45, 127.92, 127.54, 122.39, 122.37, 43.31, 29.29, 29.26, 28.64, 22.12, 13.85.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{15}H_{19}NO_2S$: 278.1209. Found: 278.1210.

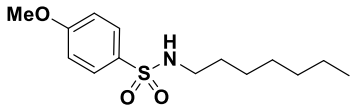


***N*-hexyl-4-methoxybenzenesulfonamide (4n)**

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 96%.

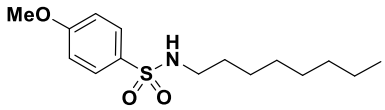
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.43 (s, 1H), 3.86

(s, 3H), 2.90 (t, *J* = 7.1 Hz, 2H), 1.49 – 1.38 (m, 2H), 1.31 – 1.13 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.81, 131.66, 129.20, 114.20, 55.59, 43.19, 31.23, 29.49, 26.19, 22.44, 13.91.
Data are consistent with reported in the literature[9].



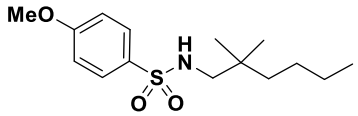
<u>*N*-heptyl-4-methoxybenzenesulfonamide (4o)</u>

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 93%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 4.52 (s, 1H), 3.86 (s, 3H), 2.93 – 2.88 (m, 2H), 1.50 – 1.36 (m, 2H), 1.32 – 1.12 (m, 8H), 0.85 (t, *J* = 6.6 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.82, 131.58, 129.23, 114.21, 55.61, 43.19, 31.63, 29.51, 28.74, 26.49, 22.52, 14.04.
Data are consistent with reported in the literature[9].



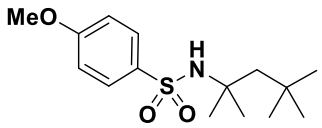
<u>4-methoxy-*N*-octylbenzenesulfonamide (4p)</u>

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 95%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.9 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 4.67 (s, 1H), 3.86 (s, 3H), 2.90 (t, *J* = 7.2 Hz, 2H), 1.49 – 1.35 (m, 2H), 1.30 – 1.13 (m, 10H), 0.85 (t, *J* = 6.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.81, 131.67, 129.20, 114.20, 55.58, 43.18, 31.70, 29.51, 29.07, 29.01, 26.52, 22.58, 14.03.
Data are consistent with reported in the literature[9].



<u>*N*-(2,2-dimethylheptyl)-4-methoxybenzenesulfonamide (4q)</u>

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 87%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.56 (t, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 2.66 (d, *J* = 6.8 Hz, 2H), 1.26 – 1.05 (m, 6H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.79, 131.74, 129.20, 114.19, 55.57, 52.99, 39.28, 33.64, 25.87, 24.92, 23.39, 14.01.
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{25}NO_3S$: 300.1628. Found: 300.1629.



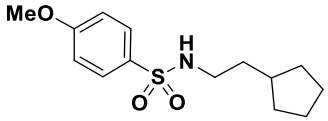
4-methoxy-*N*-(2,4,4-trimethylpentan-2-yl)benzenesulfonamide (4r)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 84%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 2H), 7.00 – 6.88 (m, 2H), 4.58 (s, 1H), 3.86 (d, *J* = 0.9 Hz, 3H), 1.52 (s, 2H), 1.24 (d, *J* = 1.2 Hz, 6H), 0.98 (d, *J* = 0.9 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.41, 135.45, 129.12, 113.94, 58.44, 55.65, 55.58, 31.63, 29.38.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{15}H_{25}NO_3S$: 300.1628. Found: 300.1630.



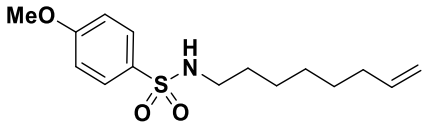
***N*-(2-cyclopentylethyl)-4-methoxybenzenesulfonamide (4s)**

Prepared by **General Procedure C** on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 89%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.72 (m, 2H), 7.01 – 6.92 (m, 2H), 4.56 (t, *J* = 6.2 Hz, 1H), 3.86 (s, 3H), 2.93 – 2.90 (m, 2H), 1.76 – 1.63 (m, 3H), 1.59 – 1.52 (m, 2H), 1.49 – 1.41 (m, 4H), 1.04 – 0.94 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.80, 131.58, 129.21, 114.20, 55.61, 42.60, 37.30, 35.78, 32.41, 24.99.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{14}H_{21}NO_3S$: 284.1315. Found: 284.1316.



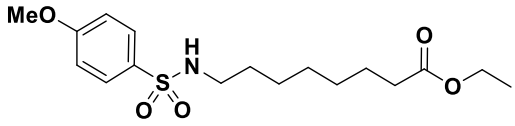
4-methoxy-*N*-(oct-7-en-1-yl)benzenesulfonamide (4t)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 88%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 7.4 Hz, 2H), 5.81 – 5.71 (m, 1H), 4.98 – 4.90 (m, 2H), 4.52 (s, 1H), 3.86 (s, 3H), 2.90 (d, *J* = 7.2 Hz, 2H), 2.01 – 1.96 (m, 2H), 1.46 – 1.40 (m, 2H), 1.36 – 1.18 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.83, 138.87, 131.60, 129.22, 114.35, 114.22, 55.61, 43.15, 33.59, 29.47, 28.65, 28.51, 26.36.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{15}H_{23}NO_3S$: 298.1471. Found: 298.1473.



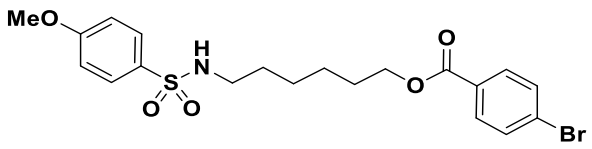
ethyl 8-((4-methoxyphenyl)sulfonamido)octanoate (4u)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 63%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 4.58 (s, 1H), 4.13 – 4.08 (m, 2H), 3.89 (s, 3H), 2.92 (t, *J* = 6.1 Hz, 2H), 2.27 (t, *J* = 7.1 Hz, 2H), 1.66 – 1.52 (m, 2H), 1.52 – 1.37 (m, 2H), 1.35 – 1.16 (m, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.82, 162.82, 131.55, 129.21, 114.22, 60.23, 55.62, 43.12, 34.25, 29.44, 28.88, 28.68, 26.31, 24.77, 14.26.

Data are consistent with reported in the literature[9].



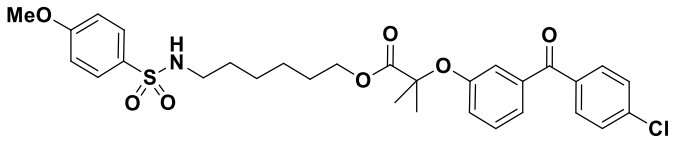
6-((4-methoxyphenyl)sulfonamido)hexyl 4-bromobenzoate (4v)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 87%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 3H), 2.92 (t, *J* = 6.8 Hz, 2H), 1.73 – 1.67 (m, 2H), 1.52 – 1.45 (m, 2H), 1.43 – 1.28 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.91, 162.86, 131.70, 131.66, 131.08, 129.32, 129.19, 127.96, 114.24, 65.06, 55.60, 43.00, 29.43, 28.50, 26.14, 25.48.

Data are consistent with reported in the literature[9].



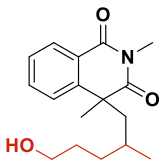
6-((4-methoxyphenyl)sulfonamido)hexyl 2-(3-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (4w)

Prepared on a 10 mmol scale. The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (5:1-4:1). White oil, yield 82%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.0 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 4H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.71 (t, *J* = 5.0 Hz, 1H), 4.11 (t, *J* = 6.4 Hz, 2H), 3.86 (s, 3H), 2.86 – 2.81 (m, 2H), 1.67 (s, 6H), 1.57 – 1.44 (m, 2H), 1.34 – 1.27 (m, 2H), 1.19 – 1.13 (m, 2H), 1.11 – 1.02 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.53, 173.74, 162.79, 159.80, 138.60, 136.19, 132.02, 131.69, 131.29, 130.27, 129.21, 128.61, 116.96, 114.20, 79.43, 65.52, 55.61, 43.07, 29.48, 28.22, 26.05, 25.46, 25.34.

Data are consistent with reported in the literature[9].



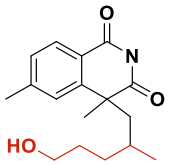
4-(5-hydroxy-2-methylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3aa)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 76% (dr = 1:1.2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 1H), 7.65 – 7.60 (m, 1H), 7.45 – 7.36 (m, 2H), 3.50 – 3.40 (m, 2H), 3.37 (s, 3H), 2.39 (dd, *J* = 14.0, 5.5 Hz, 0.52H), 2.26 (dd, *J* = 14.0, 8.5 Hz, 0.46H), 2.02 (dd, *J* = 13.9, 3.0 Hz, 0.46H), 1.81 (dd, *J* = 14.0, 5.9 Hz, 0.55H), 1.59 (d, *J* = 4.0 Hz, 3H), 1.44 (s, 1H), 1.38 – 1.28 (m, 2H), 1.15 – 0.97 (m, 3H), 0.59 (d, *J* = 6.1 Hz, 1.36H), 0.44 (d, *J* = 6.5 Hz, 1.58H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.94, 176.85, 164.50, 164.43, 143.93, 143.57, 133.85, 133.78, 128.88, 127.29, 127.27, 125.85, 125.72, 124.75, 124.61, 62.89, 49.84, 49.06, 47.11, 46.70, 33.92, 32.92, 31.33, 30.78, 30.08, 29.84, 29.73, 29.41, 27.24, 27.18, 20.79, 19.46.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{17}H_{23}NO_3$: 290.1751. Found: 290.1753.



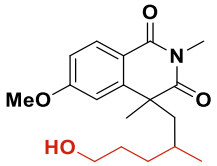
4-(5-hydroxy-2-methylpentyl)-2,4,6-trimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ba)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 79% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 1H), 7.26 – 7.13 (m, 2H), 3.50 – 3.39 (m, 2H), 3.35 (s, 3H), 2.43 (s, 3H), 2.36 (dd, *J* = 14.0, 5.4 Hz, 0.52H), 2.24 (dd, *J* = 14.0, 8.4 Hz, 0.50H), 1.99 (dd, *J* = 14.0, 3.1 Hz, 0.50H), 1.78 (dd, *J* = 14.0, 5.9 Hz, 0.54H), 1.57 (d, *J* = 4.2 Hz, 3H), 1.52 (s, 1H), 1.45 – 1.27 (m, 2H), 1.15 – 0.95 (m, 3H), 0.58 (d, *J* = 6.1 Hz, 1.49H), 0.44 (d, *J* = 6.4 Hz, 1.50H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12, 177.02, 164.52, 164.45, 144.70, 144.60, 143.96, 143.59, 128.90, 128.88, 128.40, 128.37, 126.16, 126.06, 122.27, 122.14, 62.90, 62.87, 49.86, 48.95, 47.04, 46.62, 33.90, 32.95, 31.32, 30.71, 30.07, 29.75, 29.67, 29.43, 27.14, 27.08, 21.98, 20.82, 19.47.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1909.

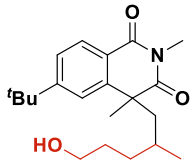


4-(5-hydroxy-2-methylpentyl)-6-methoxy-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ca)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 77% (dr = 1:1.5).

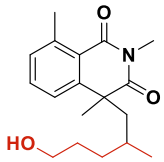
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.18 (m, 1H), 6.96 – 6.93 (m, 1H), 6.85 – 6.81 (m, 1H), 3.88 (d, *J* = 1.5 Hz, 3H), 3.48 – 3.42 (m, 2H), 3.34 (s, 3H), 2.37 (dd, *J* = 14.0, 5.5 Hz, 0.60H), 2.25 (dd, *J* = 13.9, 8.5 Hz, 0.42H), 1.97 (dd, *J* = 14.0, 3.1 Hz, 0.40H), 1.76 (dd, *J* = 14.0, 5.9 Hz, 0.64H), 1.57 (d, *J* = 3.7 Hz, 3H), 1.52 (s, 1H), 1.46 – 1.30 (m, 2H), 1.16 – 0.94 (m, 3H), 0.59 (d, *J* = 6.2 Hz, 1.21H), 0.48 (d, *J* = 6.5 Hz, 1.83H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.03, 176.92, 164.12, 164.08, 164.06, 164.00, 146.21, 145.83, 131.22, 117.83, 117.72, 113.17, 113.12, 110.96, 110.76, 62.90, 62.88, 55.60, 55.59, 49.93, 49.01, 47.30, 46.89, 33.94, 32.92, 31.49, 30.90, 30.07, 29.76, 29.74, 29.43, 27.08, 27.02, 20.85, 19.47.
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}NO_4$: 320.1856. Found: 320.1858.



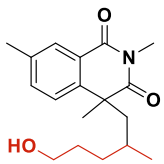
6-(*tert*-butyl)-4-(5-hydroxy-2-methylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3da)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 83% (dr = 1:1.2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.12 (m, 1H), 7.47 – 7.31 (m, 2H), 3.48 – 3.37 (m, 2H), 3.34 (s, 3H), 2.38 (dd, *J* = 14.0, 4.8 Hz, 0.55H), 2.23 (dd, *J* = 14.0, 8.4 Hz, 0.44H), 2.02 (dd, *J* = 14.1, 3.2 Hz, 0.46H), 1.79 (dd, *J* = 13.9, 5.8 Hz, 0.57H), 1.68 (s, 1H), 1.57 (d, *J* = 2.9 Hz, 3H), 1.47 – 1.36 (m, 1H), 1.33 (s, 9H), 1.31 – 1.24 (m, 1H), 1.13 – 0.94 (m, 3H), 0.57 (d, *J* = 6.2 Hz, 1.34H), 0.38 (d, *J* = 6.2 Hz, 1.63H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 177.23, 177.13, 164.45, 164.38, 157.55, 157.47, 143.48, 143.14, 128.66, 124.62, 124.58, 122.61, 122.39, 122.21, 122.04, 62.84, 62.78, 49.87, 48.94, 47.36, 46.89, 35.30, 33.99, 33.21, 31.35, 31.08, 31.05, 30.80, 30.14, 29.87, 29.84, 29.43, 27.11, 27.05, 20.82, 19.80.
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{31}NO_3$: 346.2377. Found: 346.2380.



4-(5-hydroxy-2-methylpentyl)-2,4,8-trimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ea)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 81% (dr = 1:1.3).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 1H), 7.31 – 7.20 (m, 2H), 3.52 – 3.41 (m, 2H), 3.34 (s, 3H), 2.78 (d, *J* = 2.1 Hz, 3H), 2.35 (dd, *J* = 14.0, 5.5 Hz, 0.58H), 2.24 (dd, *J* = 14.0, 8.4 Hz, 0.48H), 1.98 (dd, *J* = 14.0, 3.1 Hz, 0.45H), 1.77 (dd, *J* = 14.0, 5.9 Hz, 0.62H), 1.58 (d, *J* = 4.1 Hz, 3H), 1.48 (s, 1H), 1.46 – 1.29 (m, 2H), 1.18 – 0.96 (m, 3H), 0.60 (d, *J* = 6.2 Hz, 1.28H), 0.47 (d, *J* = 6.5 Hz, 1.68H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.65, 176.57, 165.02, 164.95, 145.26, 144.95, 142.48, 142.45, 132.64, 132.56, 131.24, 131.22, 124.13, 124.01, 123.15, 123.05, 62.92, 62.90, 50.36, 49.53, 47.06, 46.65, 33.95, 32.92, 31.53, 30.84, 29.97, 29.75, 29.43, 27.21, 27.16, 24.12, 24.08, 20.85, 19.52.
HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1908.



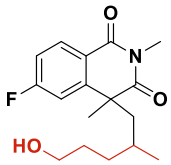
4-(5-hydroxy-2-methylpentyl)-2,4,7-trimethylisoquinoline-1,3(2*H*,4*H*)-dione (3fa)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 74% (dr = 1:1.9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.00 (m, 1H), 7.45 – 7.38 (m, 1H), 7.33 – 7.26 (m, 1H), 3.48 – 3.42 (m, 2H), 3.36 (s, 3H), 2.41 (s, 3H), 2.36 (dd, *J* = 13.9, 5.5 Hz, 0.66H), 2.24 (dd, *J* = 13.9, 8.6 Hz, 0.39H), 1.99 (dd, *J* = 13.9, 3.0 Hz, 0.38H), 1.78 (dd, *J* = 13.9, 5.8 Hz, 0.66H), 1.55 (d, *J* = 4.3 Hz, 3H), 1.49 (s, 1H), 1.45 – 1.27 (m, 2H), 1.16 – 0.93 (m, 3H), 0.57 (d, *J* = 6.1 Hz, 1.02H), 0.45 (d, *J* = 6.4 Hz, 1.97H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.27, 177.17, 164.78, 164.71, 141.13, 140.75, 137.25, 137.23, 135.02, 134.96, 128.97, 125.89, 125.76, 124.61, 124.47, 63.02, 49.89, 49.05, 46.93, 46.49, 34.07, 33.00, 31.55, 30.94, 30.18, 29.94, 29.86, 29.53, 27.33, 27.27, 21.08, 20.95, 19.48.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1909.



6-fluoro-4-(5-hydroxy-2-methylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ga)

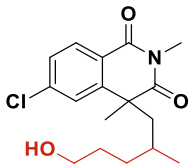
The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 67% (dr = 1:1.4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.25 (m, 1H), 7.17 – 7.01 (m, 2H), 3.54 – 3.41 (m, 2H), 3.36 (s, 3H), 2.40 (dd, *J* = 14.1, 5.4 Hz, 0.59H), 2.28 (dd, *J* = 14.1, 8.6 Hz, 0.44H), 1.95 (dd, *J* = 14.0, 3.0 Hz, 0.42H), 1.74 (dd, *J* = 14.0, 5.9 Hz, 0.61H), 1.58 (d, *J* = 4.0 Hz, 3H), 1.47 (s, 1H), 1.40 – 1.28 (m, 2H), 1.17 – 0.96 (m, 3H), 0.59 (d, *J* = 6.2 Hz, 1.27H), 0.48 (d, *J* = 6.4 Hz, 1.77H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.42, 176.31, 167.62, 167.55, 165.07, 165.01, 163.52, 163.46, 147.15, 147.06, 146.74, 146.65, 132.02, 132.00, 131.92, 131.91, 121.25, 121.22, 121.13, 121.10, 115.47, 115.45, 115.25, 115.23, 112.72, 112.58, 112.50, 112.36, 62.85, 49.90, 49.07, 47.37, 47.35, 46.96, 46.94, 33.97, 32.91, 31.33, 30.77, 30.09, 29.86, 29.71, 29.39, 27.25, 27.19, 20.79, 19.33.

^{19}F NMR (376 MHz, $CDCl_3$) δ -103.54, -103.63.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}FNO_3$: 308.1656. Found: 308.1657.

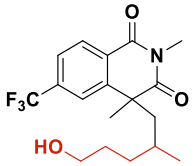


6-chloro-4-(5-hydroxy-2-methylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ha)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 60% (dr = 1:1.3).

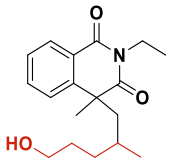
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 1H), 7.43 – 7.33 (m, 2H), 3.51 – 3.42 (m, 2H), 3.35 (s, 3H), 2.38 (dd, *J* = 14.1, 5.4 Hz, 0.58H), 2.27 (dd, *J* = 14.1, 8.6 Hz, 0.43H), 1.97 (dd, *J* = 14.0, 3.1 Hz, 0.43H), 1.76 (dd, *J* = 14.1, 6.0 Hz, 0.61H), 1.58 (d, *J* = 4.3 Hz, 3H), 1.55 (s, 1H), 1.47 – 1.29 (m, 2H), 1.14 – 1.00 (m, 3H), 0.58 (d, *J* = 6.2 Hz, 1.29H), 0.47 (d, *J* = 6.4 Hz, 1.73H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.27, 176.15, 163.63, 163.57, 145.71, 145.31, 140.50, 140.44, 130.54, 130.52, 127.98, 127.95, 126.00, 125.91, 123.25, 123.13, 62.82, 49.85, 48.86, 47.20, 46.79, 33.92, 32.93, 31.27, 30.65, 30.09, 29.81, 29.64, 29.39, 27.30, 27.24, 20.84, 19.38.
HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{17}H_{22}ClNO_3$: 324.1361. Found: 324.1364.



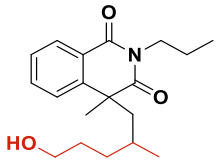
4-(5-hydroxy-2-methylpentyl)-2,4-dimethyl-6-(trifluoromethyl)isoquinoline-1,3(2*H*,4*H*)-dione (3ia)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 71% (dr = 1:2).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 – 8.34 (m, 1H), 7.71 – 7.61 (m, 2H), 3.51 – 3.41 (m, 2H), 3.39 (s, 3H), 2.44 (dd, *J* = 14.1, 5.1 Hz, 0.63H), 2.31 (dd, *J* = 14.2, 8.8 Hz, 0.37H), 2.04 (dd, *J* = 14.2, 3.5 Hz, 0.36H), 1.82 (dd, *J* = 14.1, 6.0 Hz, 0.64H), 1.62 (d, *J* = 4.3 Hz, 3H), 1.49 (s, 1H), 1.45 – 1.28 (m, 2H), 1.16 – 0.94 (m, 3H), 0.59 (d, *J* = 6.4 Hz, 1H), 0.43 (d, *J* = 6.2 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.05, 175.93, 163.31, 163.24, 144.76, 144.37, 135.68, 135.62, 135.46, 135.41, 135.25, 135.19, 135.03, 134.98, 129.77, 129.75, 127.62, 127.49, 124.30, 124.02, 124.00, 123.97, 123.03, 123.00, 122.97, 122.94, 122.91, 122.49, 62.71, 62.63, 49.94, 48.82, 47.32, 46.90, 33.90, 33.07, 31.12, 30.50, 30.12, 29.84, 29.55, 29.38, 27.39, 27.32, 20.75, 19.53.
^{19}F NMR (376 MHz, $CDCl_3$) δ -63.16, -63.17.
HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{22}F_3NO_3$: 358.1625. Found: 358.1627.



2-ethyl-4-(5-hydroxy-2-methylpentyl)-4-methylisoquinoline-1,3(2*H*,4*H*)-dione (3ja)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 52% (dr = 1:1.8).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.65 – 7.53 (m, 1H), 7.45 – 7.35 (m, 2H), 4.11 – 3.99 (m, 2H), 3.51 – 3.39 (m, 2H), 2.39 (dd, *J* = 14.0, 5.4 Hz, 0.65H), 2.29 (dd, *J* = 14.0, 8.7 Hz, 0.37H), 2.02 (dd, *J* = 14.0, 3.3 Hz, 0.37H), 1.81 (dd, *J* = 14.0, 6.1 Hz, 0.67H), 1.57 (d, *J* = 5.5 Hz, 3H), 1.45 – 1.31 (m, 2H), 1.22 – 1.18 (m, 3H), 1.15 – 0.96 (m, 3H), 0.59 (d, *J* = 6.3 Hz, 1.08H), 0.44 (d, *J* = 6.5 Hz, 1.91H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.43, 176.30, 163.96, 163.91, 143.95, 143.58, 133.75, 133.68, 128.88, 128.86, 127.24, 127.20, 125.89, 125.76, 124.85, 124.72, 62.90, 49.71, 48.53, 46.95, 46.59, 35.67, 35.62, 33.88, 33.12, 31.73, 31.01, 30.20, 29.95, 29.79, 29.65, 20.68, 19.55, 13.10, 12.92.
HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1908.



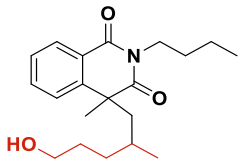
4-(5-hydroxy-2-methylpentyl)-4-methyl-2-propylisoquinoline-1,3(2*H*,4*H*)-dione (3ka)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 43% (dr = 1:1.6).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.24 (m, 1H), 7.67 – 7.59 (m, 1H), 7.50 – 7.37 (m, 2H), 4.05 – 3.90 (m, 2H), 3.50 – 3.43 (m, 2H), 2.42 (dd, *J* = 14.0, 5.3 Hz, 0.65H), 2.31 (dd, *J* = 14.0, 8.4 Hz, 0.41H), 2.04 (dd, *J* = 14.1, 3.3 Hz, 0.41H), 1.84 (dd, *J* = 14.0, 6.3 Hz, 0.67H), 1.68 – 1.62 (m, 2H), 1.59 (d, *J* = 5.4 Hz, 3H), 1.56 (s, 1H), 1.46 – 1.29 (m, 2H), 1.18 – 1.01 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.61 (d, *J* = 6.1 Hz, 1.19H), 0.45 (d, *J* = 6.4 Hz, 1.90H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.61, 176.49, 164.18, 164.12, 143.98, 143.57, 133.73, 133.66, 128.95, 128.93, 127.24, 127.21, 125.89, 125.75, 124.82, 124.67, 62.92, 49.57, 48.43, 47.02, 46.65, 42.14, 42.05, 33.85, 33.18, 31.88, 31.21, 30.24, 29.97, 29.78, 29.63, 21.17, 21.03, 20.64, 19.56, 11.48.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{19}H_{27}NO_3$: 318.2064. Found: 318.2066.



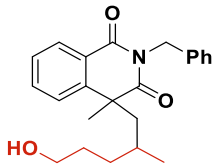
2-butyl-4-(5-hydroxy-2-methylpentyl)-4-methylisoquinoline-1,3(2*H*,4*H*)-dione (3la)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 40% (dr = 1:1.6).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.21 (m, 1H), 7.67 – 7.56 (m, 1H), 7.46 – 7.33 (m, 2H), 4.03 – 3.92 (m, 2H), 3.41 – 3.47 (m, 2H), 2.39 (dd, *J* = 14.0, 5.4 Hz, 0.63H), 2.28 (dd, *J* = 14.0, 8.5 Hz, 0.39H), 2.01 (dd, *J* = 14.1, 3.3 Hz, 0.39H), 1.81 (dd, *J* = 14.0, 6.2 Hz, 0.65H), 1.63 – 1.58 (m, 2H), 1.56 (d, *J* = 5.5 Hz, 3H), 1.43 – 1.26 (m, 4H), 1.15 – 0.97 (m, 3H), 0.95 – 0.91 (m, 3H), 0.58 (d, *J* = 6.2 Hz, 1.15H), 0.42 (d, *J* = 6.4 Hz, 1.85H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.60, 176.46, 164.16, 164.11, 143.97, 143.57, 133.72, 133.65, 128.92, 128.90, 127.24, 127.21, 125.88, 125.75, 124.83, 124.69, 62.90, 49.61, 48.44, 47.00, 46.64, 40.42, 40.34, 33.86, 33.17, 31.85, 31.17, 30.23, 29.97, 29.78, 29.64, 20.63, 20.34, 20.31, 19.54, 13.82, 13.80.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{20}H_{29}NO_3$: 332.2220. Found: 332.2221.



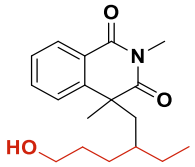
2-benzyl-4-(5-hydroxy-2-methylpentyl)-4-methylisoquinoline-1,3(2*H*,4*H*)-dione (3ma)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 64% (dr = 1:1.4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 7.64 – 7.60 (m, 1H), 7.48 – 7.43 (m, 2H), 7.42 – 7.35 (m, 2H), 7.31 – 7.25 (m, 2H), 7.25 – 7.20 (m, 1 H), 5.27 – 5.11 (m, 2H), 3.41 – 3.25 (m, 2H), 2.38 (dd, *J* = 14.0, 5.6 Hz, 0.61H), 2.27 (dd, *J* = 14.0, 8.3 Hz, 0.42H), 2.00 (dd, *J* = 14.0, 3.7 Hz, 0.42H), 1.81 (dd, *J* = 14.0, 6.4 Hz, 0.61H), 1.57 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 1H), 1.34 – 1.13 (m, 2H), 1.05 – 0.84 (m, 3H), 0.43 (d, *J* = 6.3 Hz, 1.24H), 0.38 (d, *J* = 6.5 Hz, 1.75H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.55, 176.49, 164.24, 164.17, 143.95, 143.62, 137.23, 136.99, 133.91, 133.85, 129.14, 129.11, 128.38, 128.34, 127.46, 127.32, 127.29, 125.95, 125.79, 124.75, 124.62, 62.86, 62.77, 49.76, 48.73, 47.19, 46.89, 43.71, 43.68, 33.71, 33.01, 31.69, 31.17, 30.11, 29.85, 29.73, 29.53, 20.54, 19.48.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{23}H_{27}NO_3$: 366.2064. Found: 366.2066.



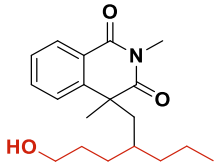
4-(2-ethyl-5-hydroxypentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ab)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 67% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.65 – 7.60 (m, 1H), 7.45 – 7.37 (m, 2H), 3.47 – 3.41 (m, 1H), 3.37 (s, 3H), 3.35 – 3.31 (m, 1H), 2.31 – 2.22 (m, 1H), 1.91 – 1.81 (m, 1H), 1.62 (d, *J* = 3.3 Hz, 3H), 1.53 (s, 1H), 1.33 – 1.15 (m, 2H), 1.07 – 0.98 (m, 2H), 0.96 – 0.80 (m, 3H), 0.67 (t, *J* = 7.3 Hz, 1.49H), 0.58 (t, *J* = 7.1 Hz, 1.52H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.02, 176.77, 164.51, 143.77, 143.69, 133.79, 128.80, 128.78, 127.30, 125.80, 125.78, 124.84, 124.76, 62.94, 62.85, 47.33, 46.98, 46.95, 35.72, 35.65, 30.30, 29.79, 29.45, 29.20, 28.76, 28.71, 27.21, 27.16, 26.42, 25.81, 10.42, 10.21.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1910.



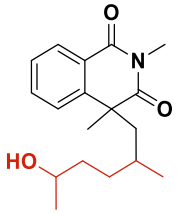
4-(5-hydroxy-2-propylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ac)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 59% (dr = 1:1.1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.25 (m, 1H), 7.67 – 7.63 (m, 1H), 7.48 – 7.39 (m, 2H), 3.52 – 3.43 (m, 1H), 3.39 (s, 3H), 3.27 – 3.33 (m, 1H), 2.33 – 2.26 (m, 1H), 1.92 – 1.86 (m, 1H), 1.64 (d, *J* = 3.7 Hz, 3H), 1.59 (s, 1H), 1.50 – 1.20 (m, 3H), 1.09 – 1.01 (m, 2H), 1.00 – 0.82 (m, 4H), 0.73 (t, *J* = 7.1 Hz, 1.39H), 0.62 (t, *J* = 7.2 Hz, 1.57H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.01, 176.80, 164.49, 143.77, 143.71, 133.77, 128.79, 128.78, 127.28, 125.80, 125.79, 124.86, 124.81, 62.95, 62.86, 47.84, 47.17, 46.97, 36.32, 35.79, 34.11, 34.02, 30.23, 29.97, 29.76, 29.26, 29.20, 28.79, 27.19, 27.14, 19.15, 18.99, 14.20, 14.03.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{19}H_{27}NO_3$: 318.2064. Found: 318.2065.



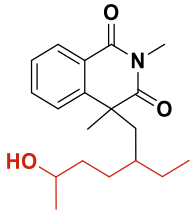
4-(5-hydroxy-2-methylhexyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ad)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 56%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 1H), 7.65 – 7.60 (m, 1H), 7.47 – 7.36 (m, 2H), 3.64 – 3.51 (m, 1H), 3.37 (d, *J* = 1.1 Hz, 3H), 2.42 – 2.36 (m, 0.60H), 2.26 (dd, *J* = 14.0, 8.5 Hz, 0.46H), 2.04 – 1.97 (m, 0.52H), 1.84 – 1.78 (m, 0.63H), 1.59 (d, *J* = 3.6 Hz, 3H), 1.50 (s, 1H), 1.37 – 1.27 (m, 1H), 1.25 – 1.15 (m, 2H), 1.12 – 0.97 (m, 5H), 0.58 (d, *J* = 6.1 Hz, 1.21H), 0.44 (dd, *J* = 6.4, 3.8 Hz, 1.67H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.94, 176.81, 164.49, 164.43, 143.94, 143.61, 133.84, 133.78, 133.76, 128.88, 127.28, 127.26, 125.85, 125.84, 125.75, 124.75, 124.61, 68.17, 68.15, 68.02, 67.96, 49.88, 49.76, 49.10, 47.10, 46.72, 46.69, 36.20, 36.16, 35.87, 35.82, 33.96, 33.84, 32.82, 32.76, 31.38, 31.31, 30.87, 30.78, 30.35, 30.17, 30.09, 30.01, 27.23, 27.19, 27.16, 23.57, 23.45, 23.32, 20.81, 20.76, 19.48.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1909.



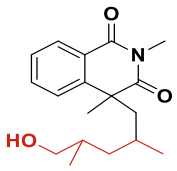
4-(2-ethyl-5-hydroxyhexyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ae)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 59%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.25 (m, 1H), 7.67 – 7.62 (m, 1H), 7.48 – 7.37 (m, 2H), 3.66 – 3.43 (m, 1H), 3.39 (d, *J* = 1.2 Hz, 3H), 2.36 – 2.24 (m, 1H), 1.93 – 1.83 (m, 1H), 1.64 (d, *J* = 4.2 Hz, 3H), 1.54 (s, 1H), 1.22 – 1.09 (m, 4H), 1.07 – 0.99 (m, 3H), 0.97 – 0.84 (m, 3H), 0.72 – 0.68 (m, 1.40H), 0.63 – 0.58 (m, 1.46H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.09, 176.94, 176.76, 176.73, 164.50, 143.82, 143.78, 143.71, 143.70, 133.78, 133.76, 133.73, 128.81, 128.79, 127.28, 125.84, 125.78, 124.88, 124.84, 124.78, 68.22, 68.10, 68.03, 67.98, 47.48, 47.35, 47.02, 46.99, 46.96, 46.94, 46.71, 46.44, 35.96, 35.91, 35.81, 35.76, 35.68, 35.64, 35.20, 35.12, 30.45, 30.28, 29.86, 29.70, 29.42, 28.52, 28.50, 27.23, 27.20, 27.15, 26.43, 26.40, 25.85, 25.80, 23.62, 23.39, 23.34, 23.29, 10.46, 10.40, 10.23, 10.20.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{19}H_{27}NO_3$: 318.2064. Found: 318.2067.



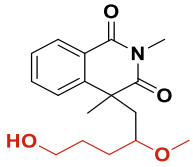
4-(5-hydroxy-2,4-dimethylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3af)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 52%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.25 (m, 1H), 7.68 – 7.61 (m, 1H), 7.48 – 7.40 (m, 2H), 3.39 (d, *J* = 2.9 Hz, 3H), 3.34 – 3.15 (m, 2H), 2.40 – 2.35 (m, 0.60H), 2.31 (dd, *J* = 14.0, 8.2 Hz, 0.24H), 2.19 (dd, *J* = 14.0, 8.6 Hz, 0.16H), 2.04 – 1.96 (m, 0.42H), 1.87 (dd, *J* = 13.9, 5.7 Hz, 0.33H), 1.79 (dd, *J* = 13.9, 6.7 Hz, 0.30H), 1.62 (t, *J* = 2.4 Hz, 3H), 1.57 (s, 1H), 1.53 – 1.44 (m, 1H), 1.19 – 1.03 (m, 2H), 0.81 (d, *J* = 6.6 Hz, 1H), 0.77 – 0.66 (m, 1H), 0.65 – 0.56 (m, 3H), 0.47 – 0.40 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.80, 176.76, 164.39, 144.17, 144.14, 133.31, 133.30, 128.95, 128.94, 127.28, 126.71, 126.66, 124.30, 68.64, 68.62, 53.46, 53.32, 45.80, 45.79, 39.98, 39.91, 34.09, 34.07, 33.69, 33.46, 33.38, 28.14, 28.05, 27.32, 27.25, 27.23, 23.57, 23.41.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1910.



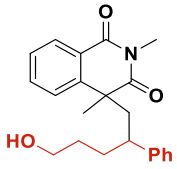
4-(5-hydroxy-2-methoxypentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ag)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 58%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.66 – 7.59 (m, 1H), 7.49 – 7.39 (m, 2H), 3.59 – 3.50 (m, 2H), 3.40 (d, *J* = 1.0 Hz, 3H), 3.00 – 2.91 (m, 1H), 2.81 (d, *J* = 1.1 Hz, 3H), 2.43 – 2.33 (m, 1H), 2.19 (dd, *J* = 14.5, 7.5 Hz, 1H), 2.02 (s, 1H), 1.65 (d, *J* = 0.9 Hz, 3H), 1.57 – 1.46 (m, 2H), 1.41 – 1.36 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.58, 164.60, 144.23, 133.54, 128.56, 127.07, 125.81, 124.28, 78.30, 62.70, 56.22, 47.57, 46.18, 29.98, 29.26, 27.72, 27.18.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{17}H_{23}NO_4$: 306.1700. Found: 306.1702.



4-(5-hydroxy-2-phenylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (5ah)

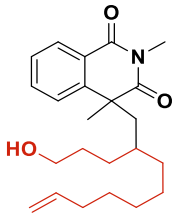
The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 55%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.94 (m, 1H), 7.35 – 7.31 (m, 1H), 7.23 – 7.10 (m, 2H), 6.94 – 6.89 (m, 3H), 6.66 – 6.58 (m, 2H), 3.43 – 3.39 (m, 2H), 3.37 (s, 3H), 2.67 (dd, *J* = 13.7, 4.6 Hz,

1H), 2.33 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.27 – 2.20 (m, 1H), 1.57 (s, 3H), 1.55 – 1.43 (m, 2H), 1.26 – 1.11 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.64, 164.32, 143.47, 143.35, 133.26, 128.49, 128.08, 127.28, 126.81, 125.93, 125.78, 124.32, 62.54, 49.49, 47.13, 43.31, 33.64, 30.77, 30.33, 27.05.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{22}H_{25}NO_3$: 352.1907. Found: 352.1909.



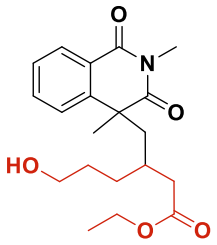
4-(2-(3-hydroxypropyl)non-8-en-1-yl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ai)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 51%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.64 – 7.59 (m, 1H), 7.44 – 7.39 (m, 2H), 5.85 – 5.68 (m, 1H), 4.99 – 4.84 (m, 2H), 3.47 – 3.40 (m, 1H), 3.36 (d, *J* = 1.5 Hz, 3H), 3.34 – 3.30 (m, 1H), 2.33 – 2.18 (m, 1H), 2.01 – 1.96 (m, 1H), 1.93 – 1.83 (m, 2H), 1.61 (d, *J* = 1.4 Hz, 3H), 1.36 – 1.18 (m, 6H), 1.07 – 0.83 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.96, 176.77, 164.46, 143.74, 143.70, 139.00, 133.75, 128.79, 127.29, 125.80, 124.84, 124.81, 114.23, 114.20, 62.92, 62.84, 47.69, 47.23, 46.98, 46.94, 34.33, 34.25, 33.94, 33.71, 33.67, 33.38, 30.19, 29.96, 29.88, 29.41, 29.33, 29.29, 29.21, 29.07, 28.83, 28.72, 27.19, 27.16, 25.85, 25.66.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}NO_3$: 372.2533. Found: 372.2535.



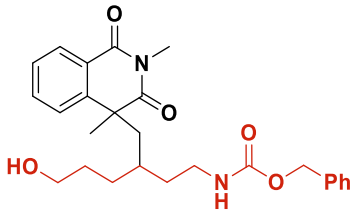
ethyl 3-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-6-hydroxyhexanoate (3aj)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 53%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.23 (m, 1H), 7.67 – 7.61 (m, 1H), 7.47 – 7.38 (m, 2H), 4.09 – 3.94 (m, 2H), 3.46 – 3.39 (m, 1H), 3.37 (d, *J* = 2.7 Hz, 3H), 3.33 – 3.30 (m, 1H), 2.42 (dd, *J* = 14.2, 7.6 Hz, 0.41H), 2.30 (dd, *J* = 14.2, 7.3 Hz, 0.68H), 2.11 – 2.00 (m, 2H), 1.93 (dd, *J* = 8.4, 5.0 Hz, 0.58H), 1.84 (dd, *J* = 15.6, 7.4 Hz, 0.62H), 1.75 (s, 1H), 1.60 (d, *J* = 13.9 Hz, 3H), 1.51 – 1.27 (m, 3H), 1.20 – 1.16 (m, 3H), 1.12 – 0.97 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.79, 176.53, 172.52, 172.44, 164.28, 164.26, 143.23, 143.01, 133.91, 128.99, 128.94, 127.52, 127.48, 126.07, 125.64, 124.92, 124.63, 62.41, 62.19, 60.38, 60.30, 47.17, 46.91, 46.79, 45.47, 39.00, 38.91, 31.75, 31.45, 31.38, 30.97, 29.81, 29.53, 28.97, 28.62, 27.25, 27.23, 14.16, 14.15.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}NO_5$: 362.1962. Found: 362.1964.



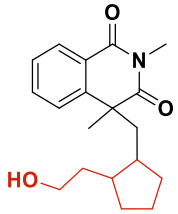
benzyl (3-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-6-hydroxyhexyl)carbamate (3ak)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 53%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 1H), 7.64 – 7.55 (m, 1H), 7.42 – 7.37 (m, 2H), 7.36 – 7.28 (m, 5H), 5.08 – 4.99 (m, 2H), 4.79 (s, 0.53H), 4.45 (s, 0.42H), 3.41 (t, *J* = 6.3 Hz, 1H), 3.35 (d, *J* = 3.0 Hz, 3H), 3.29 – 3.17 (m, 1H), 3.12 – 2.77 (m, 2H), 2.35 – 2.24 (m, 1H), 1.91 (s, 1H), 1.90 – 1.83 (m, 1H), 1.60 (s, 3H), 1.33 – 1.10 (m, 4H), 1.07 – 0.79 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.01, 176.75, 164.29, 164.28, 156.42, 156.32, 143.47, 143.40, 136.64, 136.57, 133.97, 133.88, 128.90, 128.54, 128.50, 128.14, 128.12, 128.08, 128.06, 128.02, 127.46, 125.81, 125.77, 124.79, 124.67, 66.60, 62.33, 62.04, 47.02, 46.85, 46.80, 46.64, 38.17, 37.98, 34.39, 33.85, 31.52, 30.22, 30.13, 29.61, 29.16, 28.73, 28.44, 27.22.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{26}H_{32}N_2O_5$: 453.2384. Found: 453.2386.



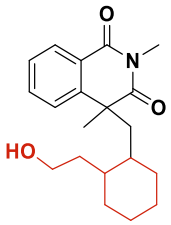
4-((2-(2-hydroxyethyl)cyclopentyl)methyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3al)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 63%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.67 – 7.57 (m, 1H), 7.46 – 7.37 (m, 2H), 3.66 – 3.45 (m, 2H), 3.37 (d, *J* = 5.0 Hz, 3H), 2.25 – 2.51 (m, 0.54H), 2.24 – 2.16 (m, 0.46H), 1.82 – 1.74 (m, 1H), 1.71 – 1.64 (m, 2H), 1.62 (d, *J* = 3.4 Hz, 3H), 1.40 – 1.18 (m, 4H), 1.07 – 0.87 (m, 2.39H), 1.06 – 0.71 (m, 3.11H), 0.51 – 0.41 (m, 0.63H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.89, 176.84, 164.61, 164.48, 144.13, 143.67, 133.94, 133.57, 128.81, 128.76, 127.34, 127.27, 126.15, 125.49, 124.86, 124.57, 61.95, 61.91, 49.26, 48.28, 47.78, 47.06, 43.49, 43.18, 43.02, 42.58, 37.22, 37.02, 32.81, 31.14, 31.11, 30.91, 30.32, 29.56, 27.28, 27.13, 23.96, 23.94.

HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}NO_3$: 316.1907. Found: 316.1910.



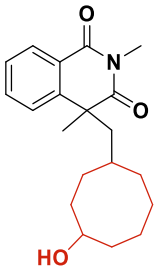
4-((2-(2-hydroxyethyl)cyclohexyl)methyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3am)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 58%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 1H), 7.63 – 7.57 (m, 1H), 7.46 – 7.38 (m, 2H), 3.60 – 3.47 (m, 2H), 3.37 (s, 3H), 2.54 (dd, *J* = 14.0, 3.0 Hz, 0.69H), 2.31 (dd, *J* = 14.1, 4.2 Hz, 0.33H), 1.85 (dd, *J* = 14.1, 7.1 Hz, 0.60H), 1.76 (dd, *J* = 14.0, 7.2 Hz, 0.49H), 1.74 – 1.73 (m, 1H), 1.72 – 1.65 (m, 2H), 1.61 (d, *J* = 3.0 Hz, 3H), 1.48 – 1.34 (m, 3H), 1.21 – 1.01 (m, 3H), 0.96 – 0.62 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.95, 176.72, 164.60, 144.22, 144.00, 133.74, 133.66, 128.84, 128.82, 127.32, 127.28, 125.96, 125.77, 124.50, 61.28, 60.79, 47.60, 47.38, 37.98, 37.54, 36.08, 32.45, 30.65, 30.39, 29.91, 29.22, 28.45, 27.18, 27.15, 24.77, 24.49.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{20}H_{27}NO_3$: 330.2064. Found: 330.2065.



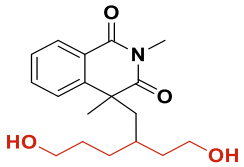
4-((4-hydroxycyclooctyl)methyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3an)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 69%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.64 – 7.60 (m, 1H), 7.47 – 7.33 (m, 2H), 3.75 – 3.50 (m, 1H), 3.40 – 3.28 (m, 3H), 2.45 – 2.23 (m, 1H), 1.91 – 1.82 (m, 1H), 1.78 – 1.68 (m, 1H), 1.58 – 1.57 (m, 3H), 1.54 – 1.48 (m, 4H), 1.44 – 1.20 (m, 4H), 1.17 – 0.93 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.79, 176.77, 164.45, 143.72, 143.67, 133.86, 133.82, 133.80, 133.78, 128.88, 128.86, 128.83, 127.31, 127.30, 127.28, 127.26, 125.76, 125.68, 125.66, 124.66, 72.21, 72.15, 71.40, 71.37, 50.09, 50.01, 49.10, 48.95, 46.99, 46.96, 46.92, 34.80, 34.76, 34.58, 34.55, 34.49, 34.36, 34.30, 33.01, 32.94, 32.14, 32.11, 31.39, 31.16, 31.13, 31.02, 30.94, 30.02, 29.70, 29.10, 28.88, 27.69, 27.26, 27.19, 27.16, 25.45, 25.34, 24.75, 24.65, 23.48, 23.22, 21.95, 21.91.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{20}H_{27}NO_3$: 330.2064. Found: 330.2067.



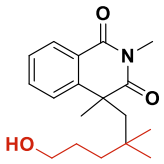
4-(5-hydroxy-2-(2-hydroxyethyl)pentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ao)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 43%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 1H), 7.66 – 7.61 (m, 1H), 7.47 – 7.39 (m, 2H), 3.56 – 3.42 (m, 2H), 3.37 (d, *J* = 3.6 Hz, 3H), 3.34 – 3.22 (m, 2H), 2.37 – 2.30 (m, 1H), 1.94 – 1.85 (m, 1H), 1.74 (s, 2H), 1.62 (d, *J* = 2.8 Hz, 3H), 1.46 – 1.03 (m, 6H), 0.95 – 0.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.20, 176.92, 164.41, 143.62, 143.53, 133.93, 133.85, 128.89, 127.45, 125.84, 125.72, 124.83, 124.76, 62.67, 62.51, 60.23, 59.98, 47.22, 47.15, 46.92, 37.04, 36.43, 31.30, 31.10, 30.28, 30.17, 30.06, 29.42, 28.85, 28.50, 27.25.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_4$: 320.1856. Found: 320.1858.



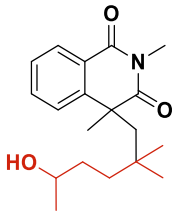
4-(5-hydroxy-2,2-dimethylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ap)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 71%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 1H), 7.64 – 7.60 (m, 1H), 7.50 – 7.40 (m, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.39 (s, 3H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.05 (d, *J* = 14.4 Hz, 1H), 1.60 (s, 3H), 1.52 (s, 1H), 1.52 – 1.41 (m, 2H), 1.03 – 0.85 (m, 2H), 0.54 (s, 3H), 0.43 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.77, 164.40, 144.12, 133.32, 128.94, 127.29, 126.64, 124.29, 63.47, 53.20, 45.80, 39.87, 34.08, 33.67, 28.17, 27.29, 27.23, 27.17.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{18}H_{25}NO_3$: 304.1907. Found: 304.1910.



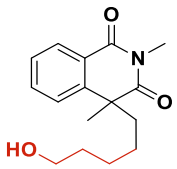
4-(5-hydroxy-2,2-dimethylhexyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3aq)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 70%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.26 (m, 1H), 7.65 – 7.58 (m, 1H), 7.51 – 7.39 (m, 2H), 3.60 – 3.54 (m, 1H), 3.40 (d, *J* = 1.1 Hz, 3H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.04 (dd, *J* = 14.4, 2.7 Hz, 1H), 1.61 (s, 3H), 1.50 (s, 1H), 1.36 – 1.26 (m, 2H), 1.12 (dd, *J* = 6.2, 1.2 Hz, 3H), 1.03 – 0.84 (m, 2H), 0.54 (d, *J* = 8.0 Hz, 3H), 0.42 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.80, 176.76, 164.39, 144.17, 144.14, 133.31, 133.30, 128.95, 128.94, 127.28, 126.71, 126.66, 124.30, 68.64, 68.62, 53.46, 53.32, 45.80, 45.79, 39.98, 39.91, 34.09, 34.07, 33.69, 33.46, 33.38, 28.14, 28.05, 27.32, 27.25, 27.23, 23.57, 23.41.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{19}H_{27}NO_3$: 318.2064. Found: 318.2065.



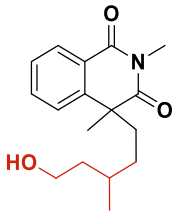
4-(5-hydroxypentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3ar)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 41%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 1H), 7.66 – 7.62 (m, 1H), 7.45 – 7.37 (m, 2H), 3.50 (t, *J* = 6.5 Hz, 2H), 3.38 (s, 3H), 2.32 – 2.25 (m, 1H), 1.90 – 1.80 (m, 1H), 1.61 (s, 3H), 1.42 (s, 1H), 1.42 – 1.26 (m, 2H), 1.28 – 1.15 (m, 2H), 0.98 – 0.70 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.74, 164.54, 143.66, 134.06, 128.78, 127.29, 125.17, 124.91, 62.64, 47.73, 43.22, 32.25, 29.27, 27.12, 25.65, 24.92.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{16}H_{21}NO_3$: 276.1594. Found: 276.1595.



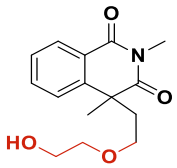
4-(5-hydroxy-3-methylpentyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3as)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 45%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.69 – 7.57 (m, 1H), 7.48 – 7.36 (m, 2H), 3.59 – 3.46 (m, 2H), 3.37 (s, 3H), 2.39 – 2.20 (m, 1H), 1.95 – 1.77 (m, 1H), 1.60 (s, 3H), 1.54 (s, 1H), 1.49 – 1.34 (m, 2H), 1.28 – 1.13 (m, 1H), 0.94 – 0.85 (m, 1H), 0.79 – 0.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.76, 176.74, 164.54, 143.66, 134.07, 134.06, 128.78, 127.29, 125.13, 125.11, 124.93, 60.73, 47.69, 40.42, 40.40, 39.28, 39.13, 32.09, 32.08, 29.51, 29.49, 29.38, 29.33, 27.12, 19.37, 19.31.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{17}H_{23}NO_3$: 290.1751. Found: 290.1753.



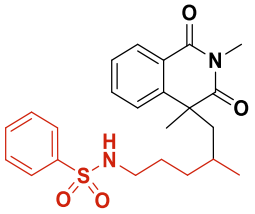
4-(2-(2-hydroxyethoxy)ethyl)-2,4-dimethylisoquinoline-1,3(2*H*,4*H*)-dione (3at)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 44%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.25 (m, 1H), 7.66 – 7.62 (m, 1H), 7.49 – 7.38 (m, 2H), 3.47 (t, *J* = 4.5 Hz, 2H), 3.37 (s, 3H), 3.28 – 3.17 (m, 1H), 3.15 – 3.11 (m, 1H), 3.00 – 2.93 (m, 1H), 2.83 – 2.76 (m, 1H), 2.09 – 2.03 (m, 1H), 1.89 (s, 1H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.89, 164.58, 142.82, 128.88, 127.43, 125.40, 125.07, 72.24, 67.49, 61.65, 45.50, 42.47, 29.68, 27.21.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{15}H_{19}NO_4$: 278.1387. Found: 278.1390.



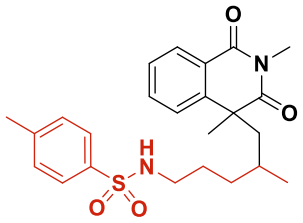
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)benzenesulfonamide (5aa)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 64% (dr = 1:1.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.85 – 7.80 (m, 2H), 7.64 – 7.59 (m, 1H), 7.58 – 7.54 (m, 1H), 7.51 – 7.48 (m, 2H), 7.43 – 7.31 (m, 2H), 4.67 – 4.62 (m, 1H), 3.34 (d, *J* = 12.0 Hz, 3H), 2.84 – 2.69 (m, 2H), 2.31 (dd, *J* = 14.1, 5.4 Hz, 0.62H), 2.19 (dd, *J* = 14.0, 8.6 Hz, 0.41H), 1.92 (dd, *J* = 14.1, 3.3 Hz, 0.40H), 1.74 (dd, *J* = 14.0, 6.3 Hz, 0.60H), 1.55 (d, *J* = 4.3 Hz, 3H), 1.38 – 1.18 (m, 2H), 1.09 – 0.84 (m, 3H), 0.49 (d, *J* = 6.2 Hz, 1.21H), 0.35 (d, *J* = 6.5 Hz, 1.83H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.86, 176.78, 164.40, 164.37, 143.78, 143.38, 139.99, 139.94, 134.00, 133.84, 132.61, 132.57, 129.11, 128.92, 128.87, 127.36, 127.34, 127.03, 126.98, 125.83, 125.72, 124.65, 124.49, 49.16, 48.66, 47.12, 46.61, 43.31, 43.18, 34.59, 33.81, 31.36, 30.91, 29.90, 29.55, 27.24, 27.20, 26.65, 26.12, 20.67, 19.29.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{23}H_{28}N_2O_4S$: 429.1843. Found: 429.1847.



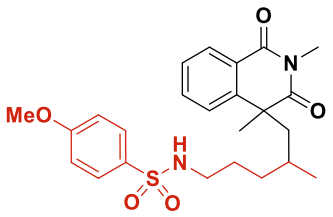
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-4-methylbenzenesulfonamide (5ab)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 69% (dr = 1:1.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.73 – 7.67 (m, 2H), 7.63 – 7.60 (m, 1H), 7.45 – 7.32 (m, 2H), 7.30 – 7.28 (m, 2H), 4.53 – 4.48 (m, 1H), 3.35 (d, *J* = 12.0 Hz, 3H), 2.83 – 2.67 (m, 2H), 2.41 (s, 3H), 2.31 (dd, *J* = 14.0, 5.4 Hz, 0.62H), 2.20 (dd, *J* = 14.1, 8.6 Hz, 0.40H), 1.92 (dd, *J* = 14.1, 3.3 Hz, 0.41H), 1.74 (dd, *J* = 14.1, 6.4 Hz, 0.62H), 1.56 (d, *J* = 4.2 Hz, 3H), 1.38 – 1.19 (m, 2H), 1.08 – 0.88 (m, 3H), 0.50 (d, *J* = 6.2 Hz, 1.18H), 0.35 (d, *J* = 6.6 Hz, 1.82H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.86, 176.77, 164.40, 164.37, 143.79, 143.39, 143.32, 136.99, 136.93, 133.99, 133.83, 129.70, 128.92, 128.88, 127.35, 127.10, 127.05, 125.83, 125.71, 124.50, 49.18, 48.66, 47.12, 46.61, 43.27, 43.15, 34.62, 33.83, 31.38, 30.90, 29.92, 29.56, 27.23, 27.19, 26.64, 26.12, 21.53, 20.67, 19.28.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{24}H_{30}N_2O_4S$: 443.1999. Found: 443.2001.



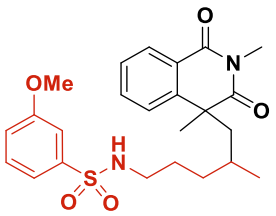
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-4-methoxybenzenesulfonamide (5ac)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 72% (dr = 1:1.4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 1H), 7.79 – 7.72 (m, 2H), 7.65 – 7.58 (m, 1H), 7.47 – 7.32 (m, 2H), 6.99 – 6.95 (m, 2H), 4.38 – 4.28 (m, 1H),3.87 (s, 3H), 3.35 (d, *J* = 6.8 Hz, 3H), 2.79 – 2.68 (m, 2H), 2.32 (dd, *J* = 14.0, 5.3 Hz, 0.57H), 2.21 (dd, *J* = 14.0, 8.4 Hz, 0.43H), 1.93 (dd, *J* = 13.8, 3.1 Hz, 0.42H), 1.75 (dd, *J* = 14.0, 6.2 Hz, 0.63H), 1.57 (d, *J* = 1.8 Hz, 3H), 1.38 – 1.19 (m, 2H), 1.08 – 0.87 (m, 3H), 0.51 (d, *J* = 6.0 Hz, 1.22H), 0.36 (d, *J* = 6.4 Hz, 1.72H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87, 176.76, 164.40, 164.37, 162.83, 162.81, 143.80, 143.39, 134.00, 133.83, 131.55, 131.52, 129.20, 129.16, 128.91, 128.87, 127.35, 125.84, 125.72, 124.66, 124.50, 114.23, 55.65, 55.63, 49.21, 48.65, 47.12, 46.61, 43.24, 43.11, 34.64, 33.87, 31.38, 30.88, 29.92, 29.57, 27.23, 27.20, 26.60, 26.11, 20.68, 19.29.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{24}H_{30}N_2O_5S$: 459.1948. Found: 459.1950.



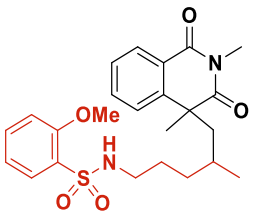
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-3-methoxybenzenesulfonamide (5ad)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 74% (dr = 1:1.4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.21 (m, 1H), 7.63 – 7.59 (m, 1H), 7.46 – 7.37 (m, 4H), 7.35 – 7.32 (m, 1H), 7.09 – 7.06 (m, 1H), 4.73 – 4.69 (m, 1H), 3.83 (d, *J* = 2.3 Hz, 3H), 3.34 (d, *J* = 7.1 Hz, 3H), 2.84 – 2.65 (m, 2H), 2.30 (dd, *J* = 14.0, 5.1 Hz, 0.60H), 2.19 (dd, *J* = 14.0, 8.5 Hz, 0.40H), 1.92 (dd, *J* = 13.9, 2.9 Hz, 0.45H), 1.74 (dd, *J* = 14.0, 6.2 Hz, 0.63H), 1.55 (d, *J* = 3.2 Hz, 3H), 1.39 – 1.18 (m, 2H), 1.11 – 0.85 (m, 3H), 0.49 (d, *J* = 6.0 Hz, 1.26H), 0.34 (d, *J* = 6.4 Hz, 1.74H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87, 176.78, 164.40, 164.37, 159.94, 143.78, 143.37, 141.10, 141.05, 134.00, 133.84, 130.18, 130.16, 128.92, 128.87, 127.36, 127.34, 125.83, 125.71, 124.65, 124.49, 119.18, 119.11, 118.96, 118.86, 111.82, 111.72, 55.67, 49.17, 48.65, 47.12, 46.61, 43.36, 43.24, 34.62, 33.85, 31.36, 30.89, 29.92, 29.56, 27.23, 27.19, 26.65, 26.13, 20.67, 19.28.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{24}H_{30}N_2O_5S$: 459.1948. Found: 459.1951.



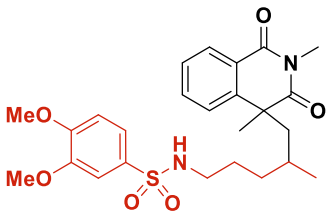
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-2-methoxybenzenesulfonamide (5ae)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 71% (dr = 1:2.6).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.21 (m, 1H), 7.88 – 7.85 (m, 1H), 7.66 – 7.58 (m, 1H), 7.56 – 7.51 (m, 1H), 7.44 – 7.31 (m, 2H), 7.10 – 7.00 (m, 2H), 4.85 – 4.78 (m, 1H), 3.97 (d, *J* = 14.3 Hz, 3H), 3.33 (d, *J* = 16.3 Hz, 3H), 2.73 – 2.64 (m, 2H), 2.30 (dd, *J* = 14.0, 5.1 Hz, 0.70H), 2.19 (dd, *J* = 14.0, 8.6 Hz, 0.28H), 1.92 (dd, *J* = 14.0, 2.9 Hz, 0.30H), 1.74 (dd, *J* = 14.0, 6.4 Hz, 0.78H), 1.56 (d, *J* = 3.4 Hz, 3H), 1.38 – 1.17 (m, 2H), 1.08 – 0.83 (m, 3H), 0.49 (d, *J* = 6.1 Hz, 0.84H), 0.34 (d, *J* = 6.4 Hz, 2.15H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87, 176.68, 164.39, 164.36, 156.09, 156.06, 143.78, 143.34, 134.48, 134.44, 134.00, 133.81, 130.46, 130.37, 128.90, 128.87, 127.38, 127.35, 127.33, 127.24, 125.84, 125.70, 124.65, 124.51, 120.77, 120.73, 112.11, 112.08, 56.39, 56.37, 49.34, 48.55, 47.10, 46.59, 43.63, 43.44, 34.71, 33.99, 31.48, 30.86, 30.01, 29.58, 27.23, 27.15, 26.62, 26.15, 20.67, 19.27.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{24}H_{30}N_2O_5S$: 459.1948. Found: 459.1951.



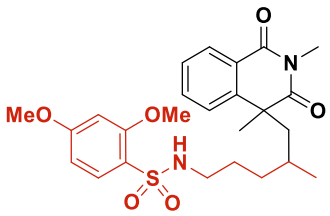
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-3,4-dimethoxybenzenesulfonamide (5af)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 76% (dr = 1:1.3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.64 – 7.59 (m, 1H), 7.45 – 7.29 (m, 4H), 6.94 – 6.91 (m, 1H), 4.52 – 4.46 (m, 1H), 3.93 – 3.90 (m, 6H), 3.35 (d, *J* = 5.6 Hz, 3H), 2.80 – 2.69 (m, 2H), 2.31 (dd, *J* = 14.0, 5.2 Hz, 0.45H), 2.21 (dd, *J* = 14.0, 8.3 Hz, 0.58H), 1.92 (dd, *J* = 13.9, 2.9 Hz, 0.58H), 1.75 (dd, *J* = 14.0, 6.2 Hz, 0.54H), 1.56 (d, *J* = 2.1 Hz, 3H), 1.40 – 1.18 (m, 2H), 1.07 – 0.81 (m, 3H), 0.51 (d, *J* = 5.9 Hz, 1.69H), 0.36 (d, *J* = 6.4 Hz, 1.35H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.84, 176.76, 164.39, 164.35, 152.50, 152.45, 149.15, 143.77, 143.38, 133.97, 133.83, 131.54, 128.91, 128.88, 127.36, 127.33, 125.82, 125.69, 124.67, 124.50, 121.00, 120.96, 110.52, 109.56, 109.54, 56.26, 56.20, 56.19, 49.19, 48.69, 47.11, 46.60, 43.30, 43.19, 34.68, 33.88, 31.36, 30.91, 29.94, 29.58, 27.23, 27.19, 26.62, 26.11, 20.70, 19.27.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{25}H_{32}N_2O_6S$: 489.2054. Found: 489.2057.



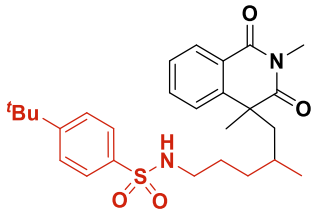
<u>*N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-2,4-dimethoxybenzenesulfonamide (5ag)</u>

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 77% (dr = 1:1.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.21 (m, 1H), 7.81 – 7.74 (m, 1H), 7.63 – 7.59 (m, 1H), 7.45 – 7.30 (m, 2H), 6.57 – 6.49 (m, 2H), 4.76 – 4.71 (m, 1H), 3.92 (d, *J* = 14.5 Hz, 3H), 3.85 (d, *J* = 1.1 Hz, 3H), 3.33 (d, *J* = 14.6 Hz, 3H), 2.69 – 2.59 (m, 2H), 2.30 (dd, *J* = 13.9, 5.0 Hz, 0.63H), 2.19 (dd, *J* = 13.9, 8.7 Hz, 0.42H), 1.93 (dd, *J* = 14.0, 2.9 Hz, 0.49H), 1.74 (dd, *J* = 14.0, 6.4 Hz, 0.76H), 1.55 (d, *J* = 3.7 Hz, 3H), 1.37 – 1.17 (m, 2H), 1.07 – 0.86 (m, 3H), 0.49 (d, *J* = 6.0 Hz, 1.25H), 0.34 (d, *J* = 6.4 Hz, 1.88H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.89, 176.67, 164.72, 164.69, 164.40, 164.37, 157.56, 157.52, 143.80, 143.34, 134.01, 133.81, 132.16, 132.09, 128.89, 128.86, 127.34, 127.32, 125.85, 125.71, 124.64, 124.50, 119.55, 119.44, 104.41, 104.37, 99.50, 56.32, 55.76, 55.74, 49.39, 48.53, 47.10, 46.58, 43.59, 43.40, 34.75, 34.06, 31.49, 30.83, 30.03, 29.59, 27.22, 27.14, 26.55, 26.12, 20.68, 19.27.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{25}H_{32}N_2O_6S$: 489.2054. Found: 489.2056.



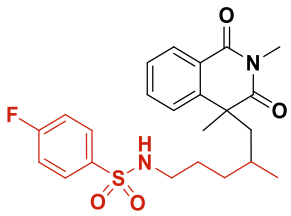
<u>4-(*tert*-butyl)-*N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)benzenesulfonamide (5ah)</u>

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 70% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 1H), 7.76 – 7.71 (m, 2H), 7.63 – 7.59 (m, 1H), 7.51 – 7.48 (m, 2H), 7.44 – 7.32 (m, 2H), 4.69 – 4.56 (m, 1H), 3.35 – 3.32 (m, 3H), 2.82 – 2.68 (m, 2H), 2.32 (dd, *J* = 14.4, 4.7 Hz, 0.52H), 2.20 (dd, *J* = 14.1, 7.9 Hz, 0.53H), 1.98 – 1.91 (m, 0.58H), 1.77 – 1.71 (m, 0.64H), 1.55 (t, *J* = 2.5 Hz, 3H), 1.36 – 1.28 (m, 9H), 1.27 – 1.19 (m, 2H), 1.08 – 0.84 (m, 3H), 0.48 (d, *J* = 5.5 Hz, 1.59H), 0.33 (dt, *J* = 6.6, 1.8 Hz, 1.42H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.86, 176.77, 164.39, 164.36, 156.36, 156.28, 143.79, 143.39, 136.90, 136.85, 134.01, 133.83, 128.92, 128.87, 127.34, 126.91, 126.86, 126.07, 125.83, 125.74, 124.65, 124.50, 49.21, 48.65, 47.12, 46.62, 43.30, 43.16, 35.14, 34.60, 33.83, 31.40, 31.11, 30.89, 29.92, 29.57, 27.23, 27.20, 26.66, 26.14, 20.67, 19.28.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{36}N_2O_4S$: 485.2469. Found: 485.2471.



<u>*N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-4-fluorobenzenesulfonamide (5ai)</u>

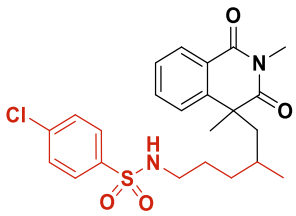
The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 46% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 1H), 7.88 – 7.79 (m, 2H), 7.64 – 7.61 (m, 1H), 7.45 – 7.32 (m, 2H), 7.19 – 7.16 (m, 2H), 4.59 (t, *J* = 6.1 Hz, 0.48H), 4.51 (t, *J* = 6.2 Hz, 0.48H), 3.36 (d, *J* = 7.4 Hz, 3H), 2.85 – 2.68 (m, 2H), 2.32 (dd, *J* = 14.1, 5.4 Hz, 0.49H), 2.21 (dd, *J* = 14.0, 8.5 Hz, 0.50H), 1.93 (dd, *J* = 14.1, 3.4 Hz, 0.51H), 1.75 (dd, *J* = 14.0, 6.2 Hz, 0.50H), 1.57 (d, *J* = 1.5 Hz, 3H), 1.40 – 1.17 (m, 2H), 1.10 – 0.87 (m, 3H), 0.52 (d, *J* = 6.3 Hz, 1.50H), 0.37 (d, *J* = 6.5 Hz, 1.48H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.82, 166.29, 164.39, 164.36, 163.76, 143.73, 143.39, 136.09, 136.06, 133.97, 133.87, 129.82, 129.77, 129.73, 129.68, 128.94, 128.92, 127.39, 127.36, 125.82, 125.68, 124.69, 124.50, 116.45, 116.43, 116.23, 116.21, 49.04, 48.76, 47.12, 46.62, 43.27, 43.16, 34.58, 33.73, 31.31, 31.00, 29.89, 29.56, 27.25, 27.22, 26.67, 26.08, 20.70, 19.29.

^{19}F NMR (565 MHz, $CDCl_3$) δ -105.37, -105.57.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{23}H_{27}FN_2O_4S$: 447.1748. Found: 447.1750.



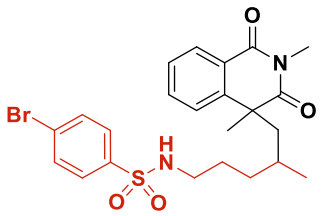
<u>4-chloro-*N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)benzenesulfonamide (5aj)</u>

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 54% (dr = 1:2).

^{1}H NMR (400 MHz, CDCl3) δ 8.24 – 8.22 (m, 1H), 7.79 – 7.73 (m, 2H), 7.64 – 7.60 (m, 1H), 7.52 – 7.31 (m, 4H), 7.47 – 7.63 (m, 1H), 3.36 – 3.34 (m, 3H), 2.83 – 2.70 (m, 2H), 2.31 (dd, *J* = 14.2, 5.0 Hz, 0.66H), 2.21 (dd, *J* = 14.3, 7.7 Hz, 0.35H), 1.95 – 1.88 (m, 0.41H), 1.77 – 1.72 (m, 0.67H), 1.56 (s, 3H), 1.42 – 1.18 (m, 2H), 1.09 – 0.86 (m, 3H), 0.51 (d, *J* = 5.4 Hz, 1.00H), 0.36 (d, *J* = 6.3 Hz, 1.97H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.83, 164.40, 164.36, 143.74, 143.39, 139.09, 139.02, 138.54, 133.98, 133.87, 129.40, 128.94, 128.91, 128.54, 128.49, 127.39, 127.36, 125.82, 125.68, 124.67, 124.48, 49.04, 48.72, 47.12, 46.61, 43.28, 43.17, 34.56, 33.73, 31.32, 31.00, 29.88, 29.54, 27.25, 27.23, 26.65, 26.08, 20.70, 19.29.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{23}H_{27}ClN_2O_4S$: 463.1453. Found: 463.1455.



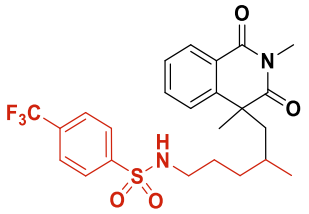
4-bromo-*N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)benzenesulfonamide (5ak)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 52% (dr = 1:1.7).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.22 (m, 1H), 7.74 – 7.59 (m, 5H), 7.46 – 7.32 (m, 2H), 4.70 (t, *J* = 6.1 Hz, 0.62H), 4.72 – 4.59 (m, 0.37H), 3.36 (d, *J* = 5.3 Hz, 3H), 2.82 – 2.67 (m, 2H), 2.32 (dd, *J* = 14.0, 5.3 Hz, 0.63H), 2.21 (dd, *J* = 14.1, 8.4 Hz, 0.40H), 1.92 (dd, *J* = 13.9, 3.1 Hz, 0.42H), 1.75 (dd, *J* = 14.0, 6.1 Hz, 0.61H), 1.57 (d, *J* = 1.2 Hz, 3H), 1.39 – 1.19 (m, 2H), 1.09 – 0.86 (m, 3H), 0.51 (d, *J* = 6.0 Hz, 1.06H), 0.36 (d, *J* = 6.4 Hz, 1.77H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.84, 164.40, 164.36, 143.73, 143.39, 139.07, 133.98, 133.87, 132.40, 132.39, 128.95, 128.93, 128.64, 128.58, 127.56, 127.50, 127.40, 127.38, 125.82, 125.67, 124.69, 124.49, 49.00, 48.75, 47.13, 46.62, 43.28, 43.16, 34.55, 33.70, 31.31, 31.02, 29.87, 29.54, 27.26, 27.24, 26.67, 26.07, 20.71, 19.30.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{23}H_{27}BrN_2O_4S$: 507.0948. Found: 507.0951.



***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)-4-(trifluoromethyl)benzenesulfonamide (5al)**

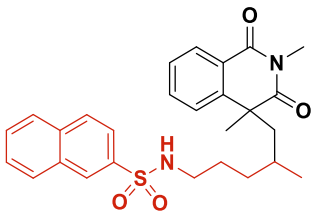
The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 41% (dr = 1:1.9).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.22 (m, 1H), 7.98 – 7.93 (m, 2H), 7.79 – 7.76 (m, 2H), 7.65 – 7.60 (m, 1H), 7.46 – 7.32 (m, 2H), 4.74 (t, *J* = 6.0 Hz, 0.59H), 4.61 (t, *J* = 6.1 Hz, 0.33H), 3.36 (d, *J* = 5.5 Hz, 3H), 2.87 – 2.74 (m, 2H), 2.33 (dd, *J* = 14.0, 5.4 Hz, 0.66H), 2.22 (dd, *J* = 13.9, 8.2 Hz, 0.38H), 1.92 (dd, *J* = 14.0, 3.2 Hz, 0.37H), 1.76 (dd, *J* = 14.1, 6.1 Hz, 0.70H), 1.57 (s, 3H), 1.45 – 1.19 (m, 2H), 1.08 – 0.83 (m, 3H), 0.52 (d, *J* = 6.0 Hz, 1.01H), 0.37 (d, *J* = 6.4 Hz, 1.94H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.87, 176.81, 164.39, 164.35, 143.69, 143.40, 133.96, 133.89, 128.95, 127.58, 127.52, 127.41, 127.38, 126.35, 126.32, 126.28, 126.24, 125.80, 125.66, 124.70, 124.49, 48.89, 48.81, 47.13, 46.63, 43.33, 43.22, 34.49, 33.60, 31.22, 31.07, 29.84, 29.52, 27.25, 27.23, 26.74, 26.07, 20.71, 19.28.

^{19}F NMR (376 MHz, $CDCl_3$) δ -63.08, -63.09.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{24}H_{27}F_3N_2O_4S$: 497.1716. Found: 497.1718.



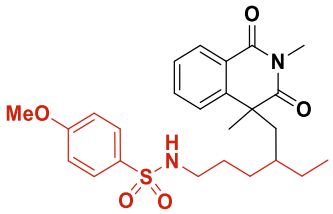
***N*-(5-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-4-methylpentyl)naphthalene-2-sulfonamide (5am)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 44% (dr = 1:1.5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.37 (m, 1H), 8.23 – 8.20 (m, 1H), 8.00 – 7.93 (m, 3H), 7.83 – 7.78 (m, 1H), 7.68 – 7.55 (m,3H), 7.42 – 7.27 (m, 2H), 4.65 – 4.56 (m, 1H), 3.32 (d, *J* = 16.3 Hz, 3H), 2.87 – 2.74 (m, 2H), 2.29 (dd, *J* = 14.0, 5.2 Hz, 0.60H), 2.16 (dd, *J* = 13.9, 8.5 Hz, 0.40H), 1.86 (dd, *J* = 14.0, 3.0 Hz, 0.36H), 1.71 (dd, *J* = 14.0, 6.3 Hz, 0.75H), 1.53 (d, *J* = 9.8 Hz, 3H), 1.40 – 1.18 (m, 2H), 1.10 – 0.82 (m, 3H), 0.47 (d, *J* = 6.0 Hz, 1.17H), 0.32 (d, *J* = 6.4 Hz, 1.78H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.83, 176.77, 164.38, 164.35, 143.77, 143.35, 136.78, 136.73, 134.79, 133.94, 133.81, 132.18, 132.16, 129.52, 129.51, 129.26, 129.22, 128.93, 128.87, 128.85, 128.76, 128.43, 128.38, 127.94, 127.92, 127.64, 127.56, 127.34, 127.31, 125.79, 125.64, 124.65, 124.49, 122.36, 122.30, 77.37, 77.05, 76.74, 49.05, 48.65, 47.10, 46.57, 43.35, 43.24, 34.61, 33.79, 31.30, 30.92, 29.88, 29.53, 27.23, 27.18, 26.69, 26.14, 20.66, 19.28.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{30}N_2O_4S$: 479.1999. Found: 479.2001.



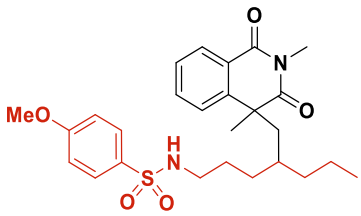
***N*-(4-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)hexyl)-4-methoxybenzenesulfonamide (5an)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 69% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 1H), 7.80 – 7.70 (m, 2H), 7.65 – 7.57 (m, 1H), 7.45 – 7.34 (m, 2H), 7.00 – 6.90 (m, 2H), 4.50 (t, *J* = 6.1 Hz, 0.50H), 4.37 (t, *J* = 6.2 Hz, 0.42H), 3.86 (d, *J* = 1.9 Hz, 3H), 3.39 – 3.30 (m, 3H), 2.86 – 2.53 (m, 2H), 2.24 – 2.17 (m, 1H), 1.85 – 1.73 (m, 1H), 1.59 (d, *J* = 5.5 Hz, 3H), 1.36 – 1.08 (m, 2H), 0.99 – 0.75 (m, 5H), 0.61 (t, *J* = 7.3 Hz, 1.24H), 0.53 (t, *J* = 7.0 Hz, 1.44H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.94, 176.64, 164.41, 164.37, 162.85, 162.82, 143.60, 143.53, 133.92, 133.84, 131.57, 131.52, 129.23, 129.21, 129.16, 128.85, 128.79, 127.40, 127.36, 125.78, 125.73, 124.77, 124.67, 114.23, 55.64, 55.62, 47.02, 46.97, 46.91, 45.89, 43.37, 43.14, 35.59, 35.51, 30.46, 30.29, 29.80, 29.60, 27.24, 27.15, 26.35, 26.13, 25.71, 25.30, 10.42, 10.16.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{25}H_{32}N_2O_5S$: 473.2105. Found: 473.2107.



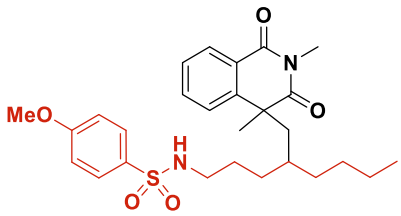
***N*-(4-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)heptyl)-4-methoxybenzenesulfonamide (5ao)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 64% (dr = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 1H), 7.79 – 7.71 (m, 2H), 7.63 – 7.60 (m, 1H), 7.44 – 7.35 (m, 2H), 6.97 – 6.96 (m, 2H), 4.50 (s, 0.45H), 4.36 (s, 0.51H), 3.86 (d, *J* = 1.3 Hz, 3H), 3.34 (d, *J* = 13.1 Hz, 3H), 2.78 – 2.57 (m, 2H), 2.23 – 2.18 (m, 1H), 1.83 – 1.71 (m, 1H), 1.59 (d, *J* = 8.7 Hz, 3H), 1.35 – 1.03 (m, 3H), 0.98 – 0.72 (m, 6H), 0.67 (t, *J* = 7.2 Hz, 1.50H), 0.56 (t, *J* = 7.3 Hz, 1.41H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.96, 176.69, 164.41, 164.37, 162.84, 162.80, 143.58, 143.54, 133.93, 133.85, 131.54, 131.50, 129.22, 129.20, 129.16, 128.84, 128.78, 127.40, 127.36, 125.79, 125.75, 124.75, 124.68, 114.22, 55.64, 55.62, 47.47, 46.97, 46.88, 46.38, 43.37, 43.15, 36.19, 35.63, 33.96, 33.89, 30.79, 30.41, 30.12, 29.81, 27.24, 27.15, 26.09, 25.29, 19.12, 18.92, 14.15, 13.98.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{26}H_{34}N_2O_5S$: 487.2261. Found: 487.2264.



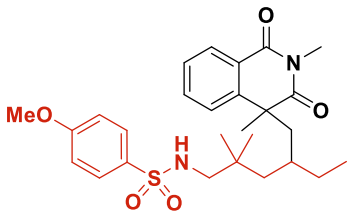
***N*-(4-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)octyl)-4-methoxybenzenesulfonamide (5ap)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 57% (dr = 1:1.4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.21 (m, 1H), 7.80 – 7.70 (m, 2H), 7.64 – 7.59 (m, 1H), 7.45 – 7.34 (m, 2H), 7.00 – 6.92 (m, 2H), 4.50 (d, *J* = 6.6 Hz, 0.50H), 4.36 (t, *J* = 6.3 Hz, 0.45H), 3.86 (d, *J* = 0.9 Hz, 3H), 3.34 (d, *J* = 7.5 Hz, 3H), 2.78 – 2.59 (m, 2H), 2.27 – 2.13 (m, 1H), 1.88 – 1.74 (m, 1H), 1.58 (d, *J* = 4.5 Hz, 3H), 1.32 – 1.00 (m, 4H), 0.96 – 0.80 (m, 7H), 0.80 – 0.73 (m, 1.82H), 0.69 – 0.67 (m, 1.28H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.92, 176.66, 164.39, 164.36, 162.85, 162.82, 143.61, 143.57, 133.90, 133.80, 131.60, 131.57, 129.22, 129.16, 128.84, 128.79, 127.39, 127.34, 125.78, 125.76, 124.78, 124.70, 114.22, 55.63, 55.60, 47.50, 47.01, 46.89, 46.50, 43.38, 43.17, 34.20, 34.13, 33.61, 33.05, 30.82, 30.37, 30.20, 29.84, 28.20, 28.01, 27.22, 27.14, 26.14, 25.38, 22.79, 22.58, 13.92, 13.88.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{36}N_2O_5S$: 501.2418. Found: 501.2421.



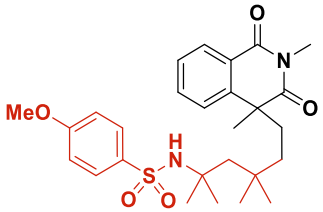
***N*-(4-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-2,2-dimethylhexyl)-4-methoxybenzenesulfonamide (5aq)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 49%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H), 7.84 – 7.72 (m, 2H), 7.68 – 7.60 (m, 1H), 7.48 – 7.40 (m, 2H), 7.00 – 6.98 (m, 2H), 4.51 (t, *J* = 7.0 Hz, 0.69H), 4.37 (t, *J* = 6.8 Hz, 0.30H), 3.89 (s, 3H), 3.37 (d, *J* = 6.6 Hz, 3H), 2.55 – 2.43 (m, 2H), 2.36 (dd, *J* = 14.0, 7.4 Hz, 0.38H), 2.23 (dd, *J* = 14.3, 4.8 Hz, 0.64H), 1.97 (dd, *J* = 14.2, 6.4 Hz, 0.74H), 1.85 (dd, *J* = 14.3, 3.5 Hz, 0.30H), 1.61 (d, *J* = 3.3 Hz, 3H), 1.08 – 0.87 (m, 4H), 0.80 – 0.74 (m, 1H), 0.73 – 0.61 (m, 6H), 0.58 – 0.50 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.86, 176.70, 164.38, 164.36, 162.83, 162.77, 143.97, 143.33, 133.81, 133.77, 131.71, 131.57, 129.20, 129.17, 129.14, 128.86, 128.83, 127.43, 127.36, 126.16, 125.86, 124.86, 124.49, 114.24, 114.20, 55.63, 55.61, 54.02, 53.87, 49.00, 48.18, 47.12, 46.93, 43.38, 43.30, 34.40, 34.23, 32.32, 31.82, 31.05, 30.46, 27.61, 27.16, 27.14, 27.03, 25.30, 25.22, 24.92, 24.73, 9.72, 9.67.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{36}N_2O_5S$: 501.2418. Found: 501.2420.



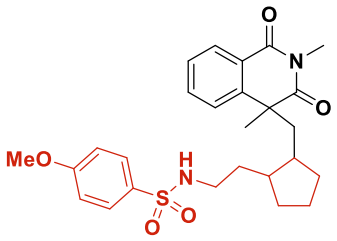
***N*-(6-(2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,4,4-trimethylhexan-2-yl)-4-methoxybenzenesulfonamide (5ar)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 43%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.23 (m, 1H), 7.80 – 7.71 (m, 2H), 7.66 – 7.61 (m, 1H), 7.46 – 7.36 (m, 2H), 6.96 – 6.88 (m, 2H), 4.45 (s, 1H), 3.86 (s, 3H), 3.37 (s, 3H), 2.29 – 2.22 (m, 1H), 1.87 – 1.79 (m, 1H), 1.60 (s, 3H), 1.46 – 1.32 (m, 2H), 1.25 (s, 1H), 1.14 – 1.12 (m, 6H), 0.98 (s, 1H), 0.86 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.67, 164.48, 162.44, 143.54, 135.39, 134.06, 129.06, 128.81, 127.32, 125.15, 124.99, 113.97, 58.21, 55.57, 52.51, 47.62, 39.83, 37.20, 33.65, 31.63, 29.83, 29.44, 29.42, 28.40, 28.22, 27.13.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{36}N_2O_5S$: 501.2418. Found: 501.2419.



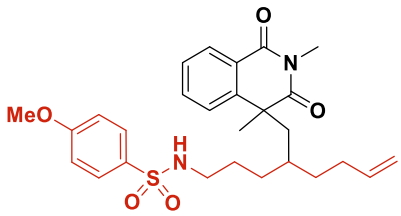
***N*-(2-(2-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)cyclopentyl)ethyl)-4-methoxybenzenesulfonamide (5as)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 63%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.20 (m, 1H), 7.85 – 7.74 (m, 2H), 7.62 – 7.58 (m, 1H), 7.45 – 7.27 (m, 2H), 7.04 – 6.90 (m, 2H), 4.66 – 4.53 (m, 1H), 3.87 (s, 3H), 3.34 (d, *J* = 5.6 Hz, 3H), 2.99 – 2.72 (m, 2H), 2.40 (dd, *J* = 13.7, 2.2 Hz, 0.60H), 2.15 (dd, *J* = 13.8, 10.6 Hz, 0.43H), 2.03 (dd, *J* = 13.8, 2.6 Hz, 0.48H), 1.71 (dd, *J* = 13.7, 9.8 Hz, 0.56H), 1.59 (d, *J* = 3.2 Hz, 3H), 1.41 – 0.98 (m, 6H), 0.91 – 0.37 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.73, 164.53, 162.82, 143.99, 134.06, 133.62, 131.56, 129.27, 129.25, 129.21, 128.82, 128.73, 127.38, 127.30, 126.16, 125.49, 124.48, 114.27, 114.25, 55.66, 55.63, 48.80, 47.99, 47.73, 46.97, 43.86, 43.55, 43.47, 42.44, 42.22, 42.13, 33.94, 33.75, 32.78, 31.13, 30.83, 30.56, 30.38, 29.69, 27.26, 27.10, 23.86, 23.79.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{26}H_{32}N_2O_5S$: 485.2105. Found: 485.2108.



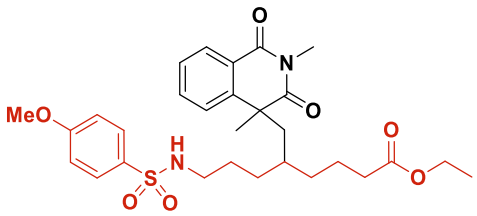
***N*-(4-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)oct-7-en-1-yl)-4-methoxybenzenesulfonamide (5at)**

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 54%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.20 (m, 1H), 7.80 – 7.70 (m, 2H), 7.64 – 7.60 (m, 1H), 7.45 – 7.34 (m, 2H), 6.98 – 6.95 (m, 2H), 5.57 – 5.34 (m, 1H), 4.92 – 4.67 (m, 2H), 4.57 (t, *J* = 5.2 Hz, 0.49H), 4.44 (q, *J* = 5.8 Hz, 0.50H), 3.86 (s, 3H), 3.33 (d, *J* = 6.3 Hz, 3H), 2.77 – 2.57 (m, 2H), 2.26 – 2.19 (m, 1H), 1.85 – 1.79 (m, 1H), 1.74 – 1.62 (m, 2H), 1.58 (d, *J* = 4.8 Hz, 3H), 1.29 – 1.08 (m, 2H), 1.02 – 0.78 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.89, 176.64, 164.35, 164.31, 162.85, 162.82, 143.48, 143.43, 138.16, 138.12, 133.96, 133.91, 131.51, 131.48, 129.23, 129.16, 128.90, 128.82, 127.45, 127.42, 125.78, 124.75, 124.67, 114.65, 114.64, 114.24, 55.65, 55.63, 47.17, 46.96, 46.83, 46.28, 43.32, 43.11, 33.59, 33.58, 33.15, 32.47, 30.62, 30.51, 30.32, 29.97, 29.93, 27.25, 27.20, 26.04, 25.22.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{27}H_{34}N_2O_5S$: 499.2261. Found: 499.2262.



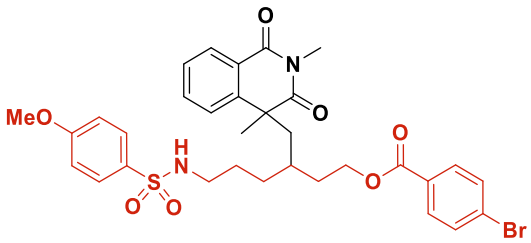
ethyl 5-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-8-((4-methoxyphenyl)sulfonamido)octanoate (5au)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 65%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.21 (m, 1H), 7.79 – 7.72 (m, 2H), 7.65 – 7.60 (m, 1H), 7.47 – 7.34 (m, 2H), 6.98 – 6.95 (m, 2H), 4.50 (s, 0.51H), 4.35 (s, 0.44H), 4.10 – 4.04 (m, 2H), 3.87 (d, *J* = 1.1 Hz, 3H), 3.36 – 3.33 (m, 3H), 2.77 – 2.59 (m, 2H), 2.27 – 2.05 (m, 2H), 1.97 – 1.91 (m, 1H), 1.86 – 1.77 (m, 1H), 1.60 – 1.58 (m, 3H), 1.41 – 1.25 (m, 3H), 1.24 – 1.20 (m, 3H), 1.18 – 1.09 (m, 1H), 1.00 – 0.76 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.82, 176.60, 173.37, 173.34, 164.29, 164.26, 162.85, 162.82, 143.46, 143.39, 133.97, 133.92, 131.55, 131.51, 129.23, 129.16, 128.92, 128.87, 127.48, 127.43, 125.76, 125.69, 124.71, 124.69, 114.23, 60.28, 55.63, 55.61, 47.01, 46.93, 46.89, 45.98, 43.27, 43.08, 34.15, 34.06, 34.03, 33.97, 33.29, 32.69, 30.56, 30.02, 29.87, 27.27, 27.17, 25.97, 25.19, 21.31, 21.08, 14.24.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{29}H_{38}N_2O_7S$: 559.2472. Found: 559.2474.



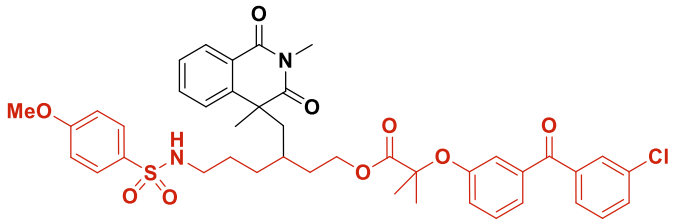
3-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-6-((4-methoxyphenyl)sulfonamido)hexyl 4-bromobenzoate (5av)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 42%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 1H), 7.79 – 7.65 (m, 4H), 7.62 – 7.50 (m, 3H), 7.41 – 7.28 (m, 2H), 7.00 – 6.93 (m, 2H), 4.53 (t, *J* = 6.1 Hz, 0.46H), 4.42 (t, *J* = 6.3 Hz, 0.54H), 4.16 – 3.96 (m, 2H), 3.86 (s, 3H), 3.33 (d, *J* = 3.7 Hz, 3H), 2.80 – 2.73 (m, 1H), 2.67 – 2.62 (m, 1H), 2.39 – 2.28 (m, 1H), 1.96 – 1.85 (m, 1H), 1.59 (d, *J* = 2.2 Hz, 3H), 1.43 – 1.32 (m, 2H), 1.29 – 1.20 (m, 2H), 1.16 – 0.90 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.73, 176.61, 165.66, 165.63, 164.14, 162.87, 162.84, 143.14, 143.04, 134.03, 131.76, 131.72, 131.50, 131.44, 131.04, 131.00, 129.23, 129.15, 128.96, 128.94, 128.88, 128.85, 128.18, 128.12, 127.49, 127.47, 125.73, 125.48, 124.65, 124.63, 114.26, 62.28, 55.65, 55.63, 46.83, 46.81, 46.49, 45.57, 43.15, 42.95, 32.87, 32.19, 31.20, 30.97, 30.78, 30.54, 30.46, 29.77, 27.31, 27.24, 26.01, 25.07.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{32}H_{35}BrN_2O_7S$: 671.1421. Found: 671.1424.



3-((2,4-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-6-((4-methoxyphenyl)sulfonamido)hexyl 2-(4-benzoylphenoxy)-2-methylpropanoate (5aw)

The crude was purified by silica gel column chromatography with petroleum ether/ethyl acetate (6:1-4:1). Yellow oil, yield 41%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.16 (m, 1H), 7.78 – 7.73 (m, 2H), 7.71 – 7.56 (m, 5H), 7.47 – 7.30 (m, 4H), 6.99 – 6.92 (m, 2H), 6.76 – 6.69 (m, 2H), 4.89 – 4.83 (m, 1H), 4.13 – 3.91 (m, 1H), 3.85 (s, 3H), 3.31 (d, J = 6.3 Hz, 3H), 2.70 – 2.50 (m, 2H), 2.28 – 2.14 (m, 1H) 1.83 – 1.77 (m, 1H), 1.60 – 1.50 (m, 9H), 1.28 – 1.15 (m, 2H), 1.14 – 1.01 (m, 2H), 0.99 – 0.78 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.60, 194.55, 176.55, 176.51, 173.54, 173.48, 164.13, 164.07, 162.77, 159.66, 159.56, 143.10, 138.65, 136.10, 134.08, 134.04, 132.05, 132.02, 131.69, 131.56, 131.36, 131.31, 130.38, 130.20, 129.85, 129.22, 129.15, 129.04, 128.90, 128.62, 127.55, 127.51, 125.78, 125.60, 124.62, 124.54, 117.06, 116.88, 114.26, 114.21, 79.28, 63.02, 62.95, 60.42, 55.64, 55.62, 46.87, 46.75, 46.20, 45.53, 43.17, 43.00, 32.48, 31.99, 31.31, 31.28, 30.88, 30.37, 30.17, 29.45, 27.28, 27.18, 25.92, 25.73, 25.61, 25.06, 24.99, 24.76, 21.08, 14.21.

HRMS (ESI) m/z: $[M + H]^+$ Calced for $C_{42}H_{45}ClN_2O_9S$: 789.2607. Found: 789.2611.

8. References

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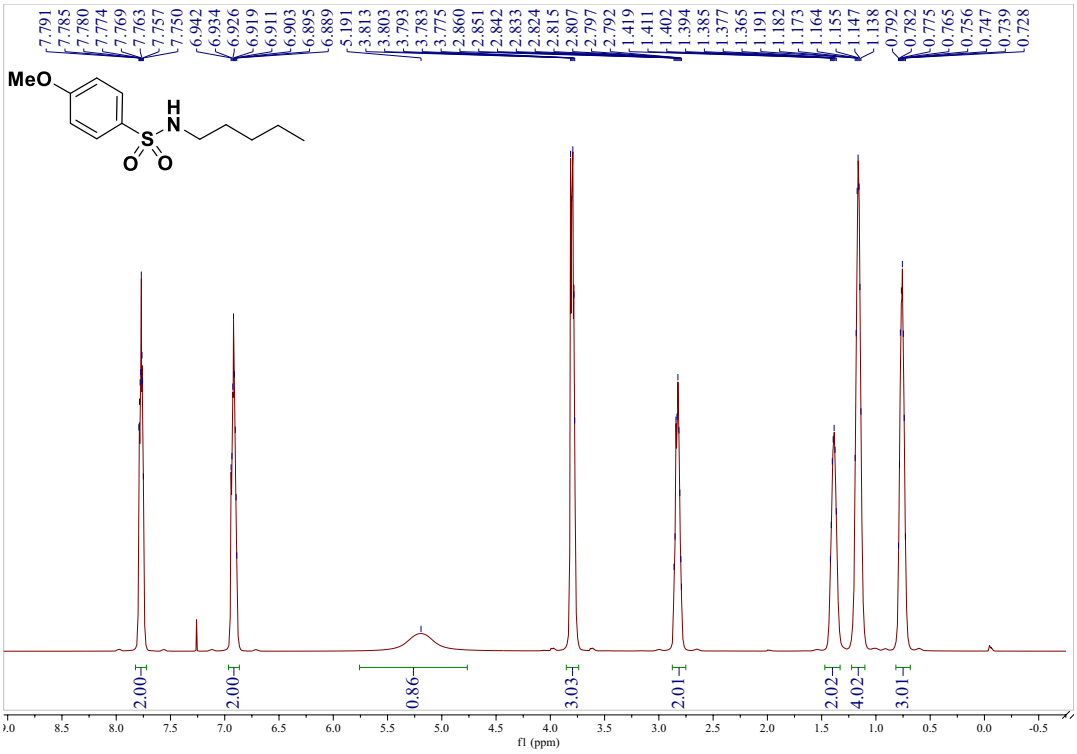
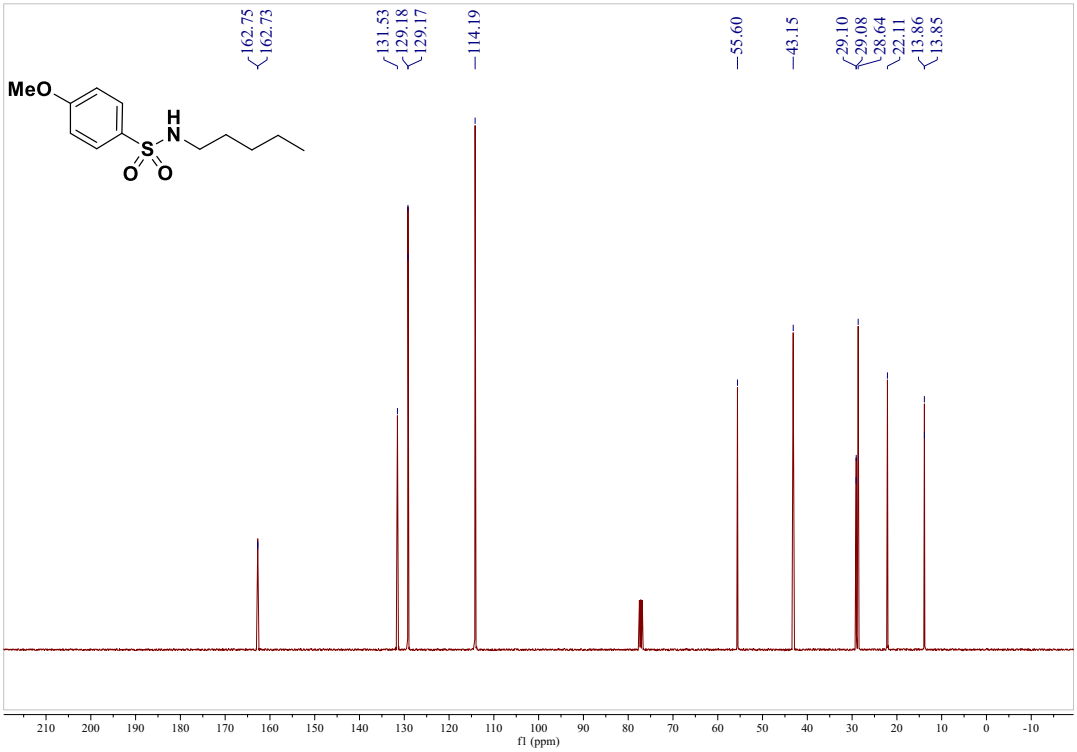
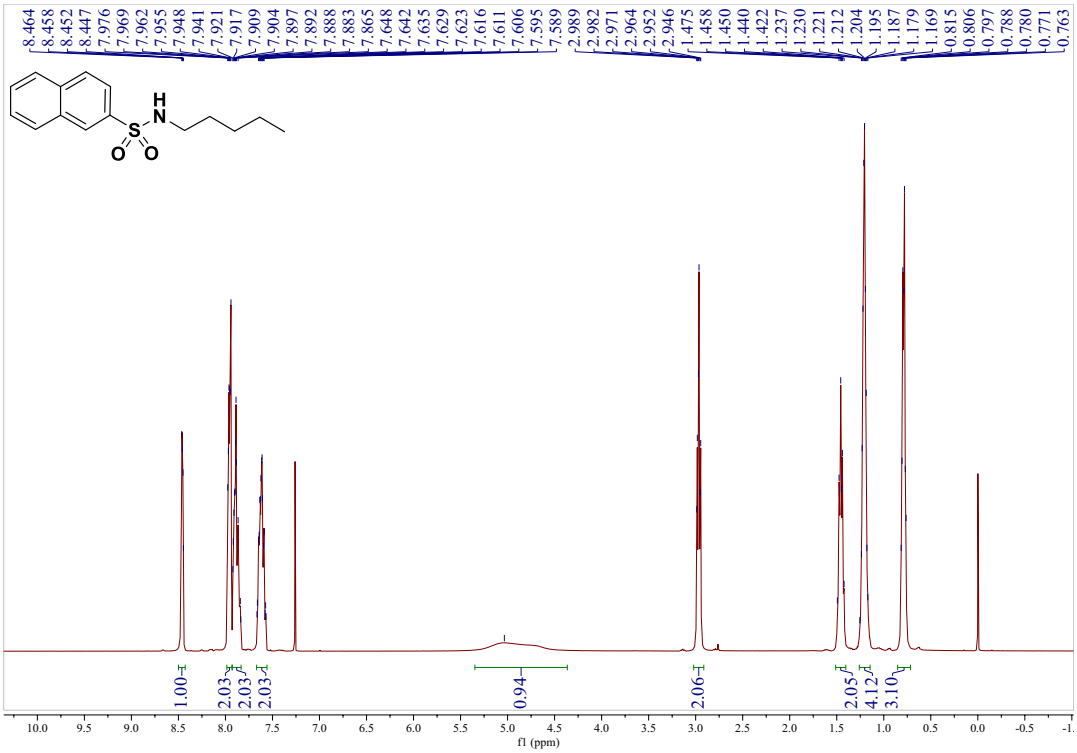
9. Copies of NMR Spectra

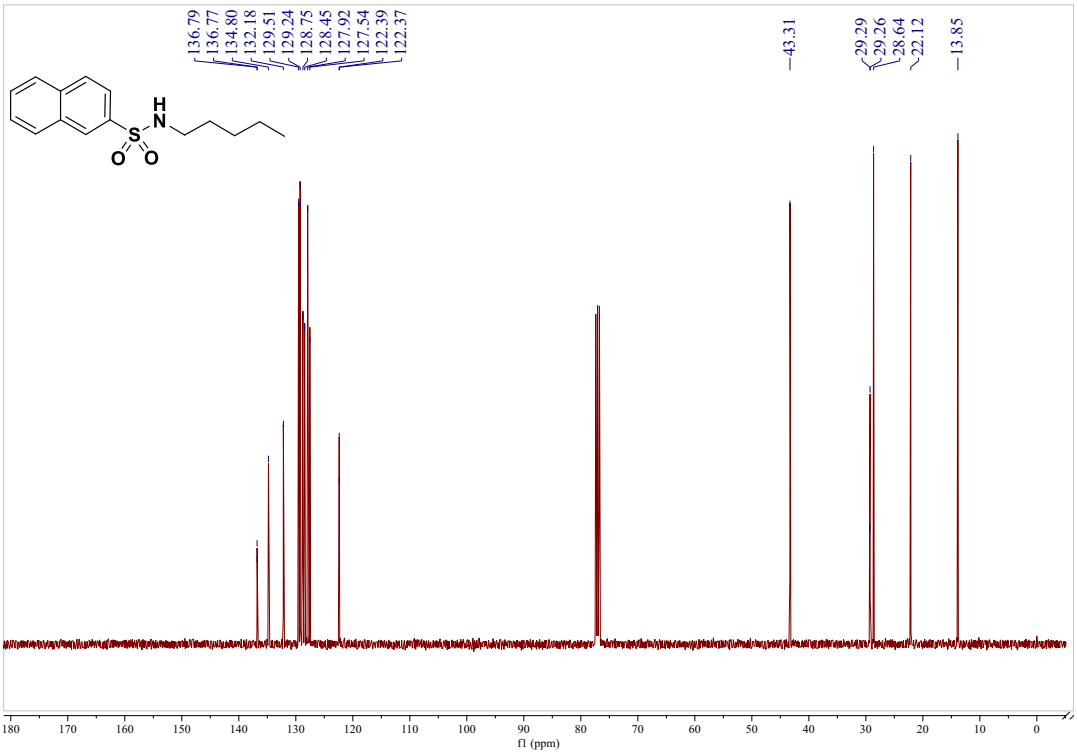
^{1}H and **^{13}C NMR** spectra of **4c**:



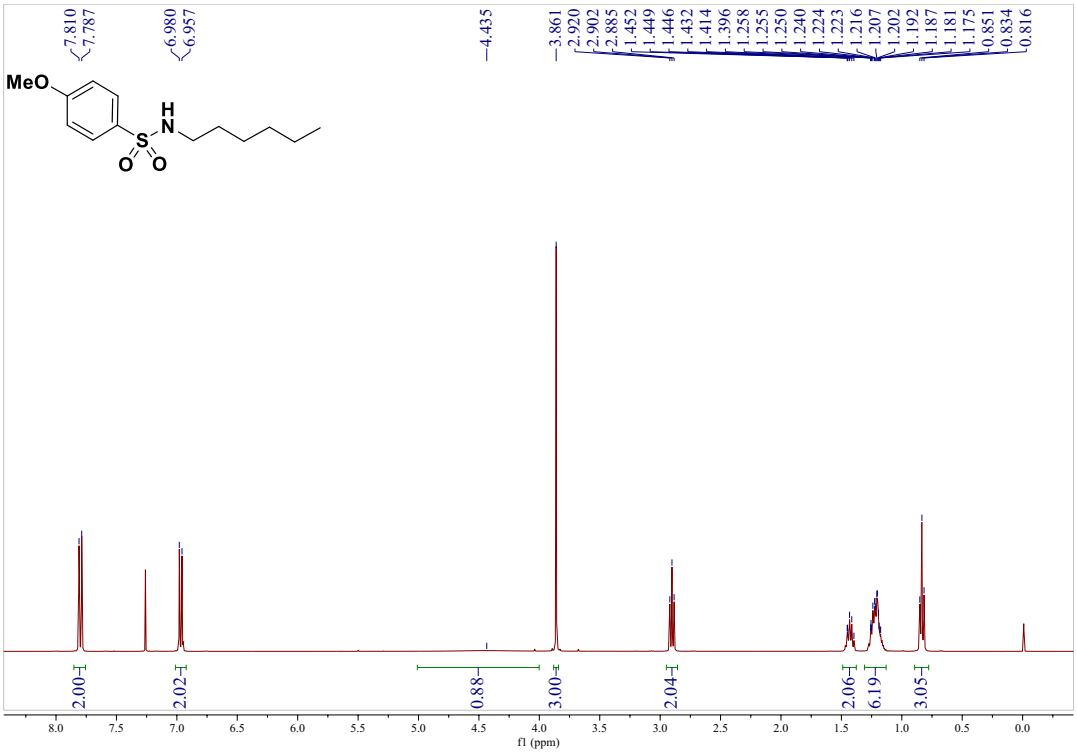


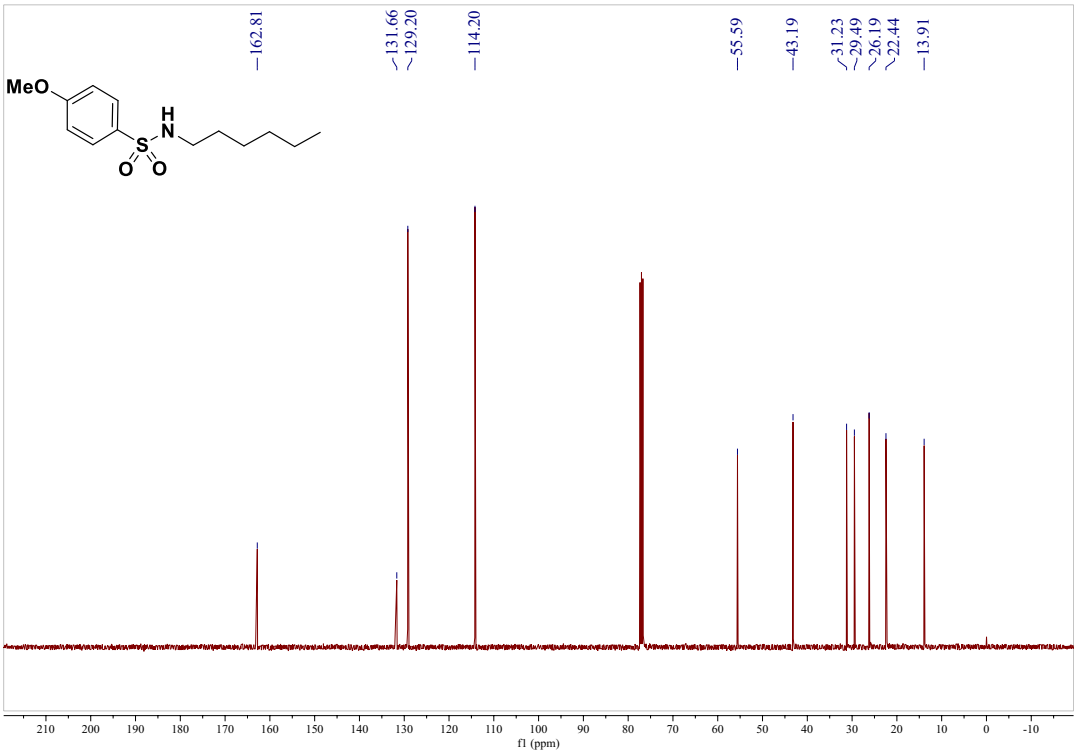
^{1}H and **^{13}C NMR** spectra of **4m**:



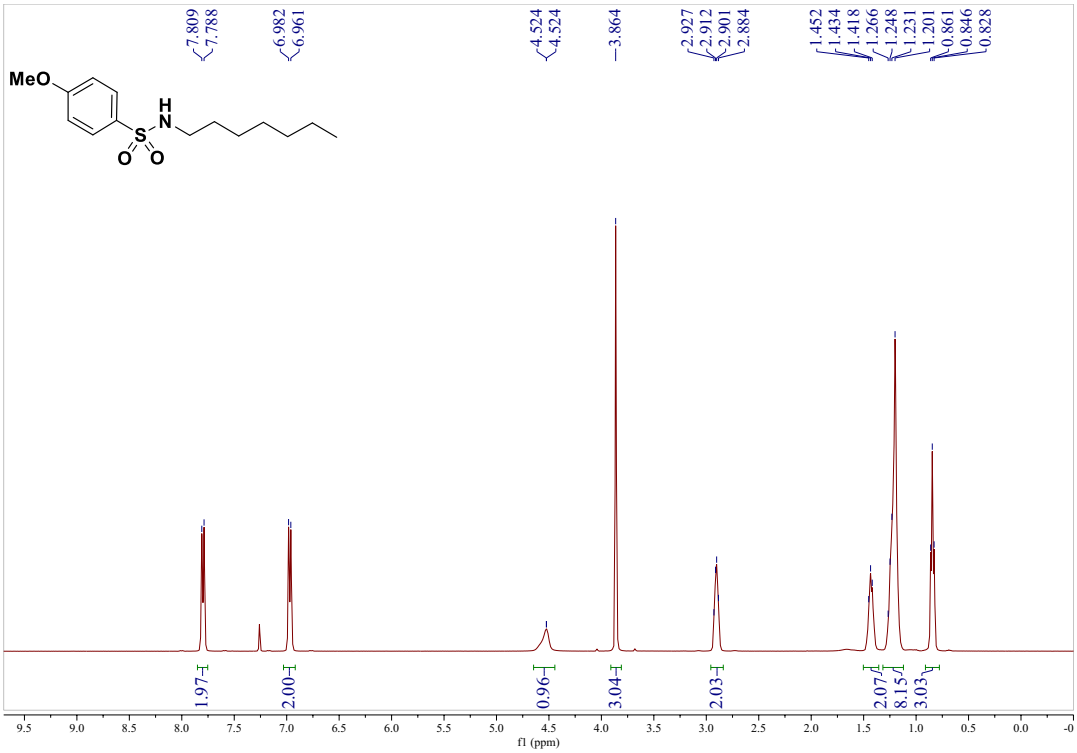


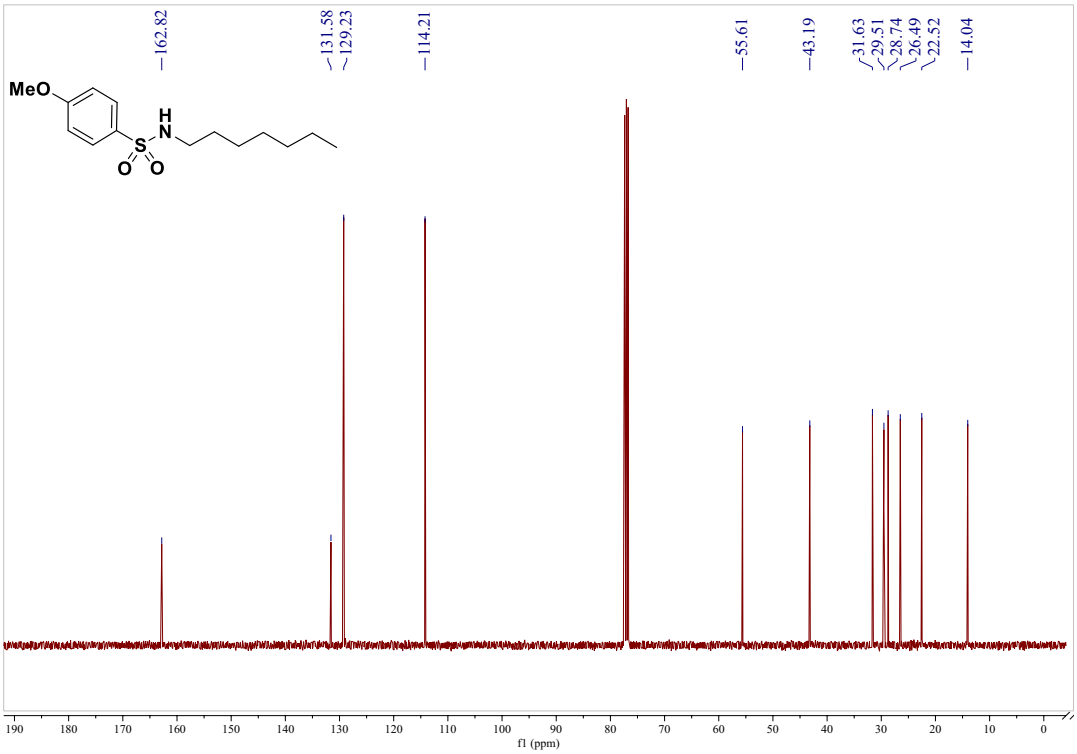
^{1}H and ^{13}C NMR spectra of **4n**:



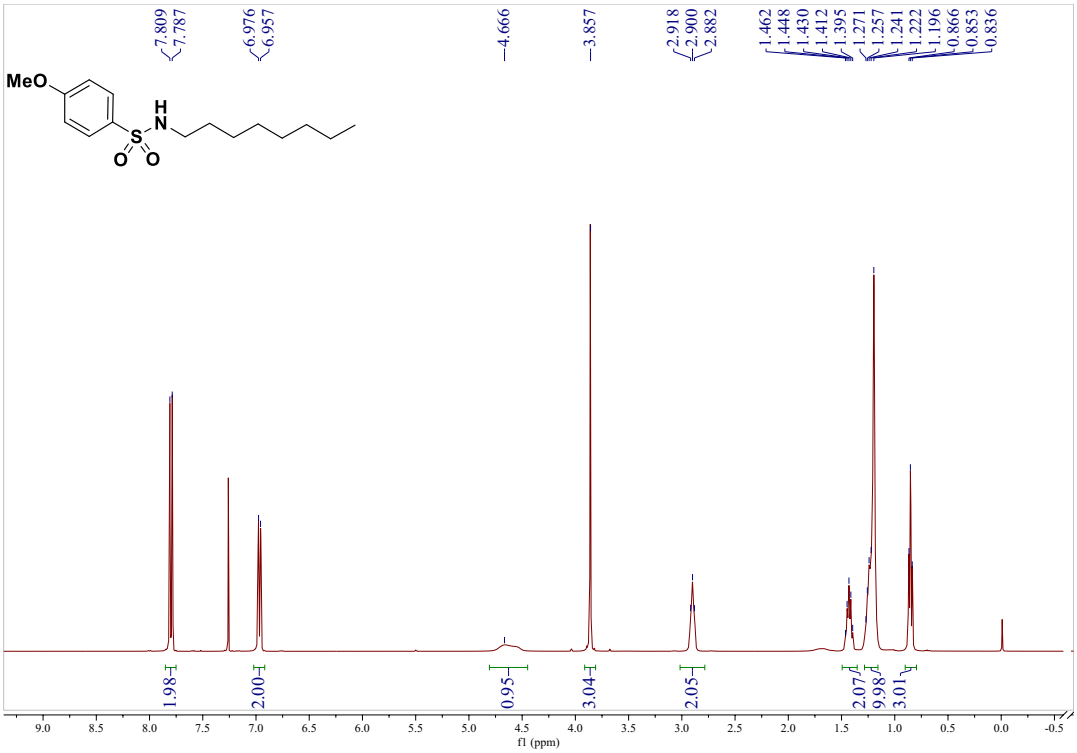


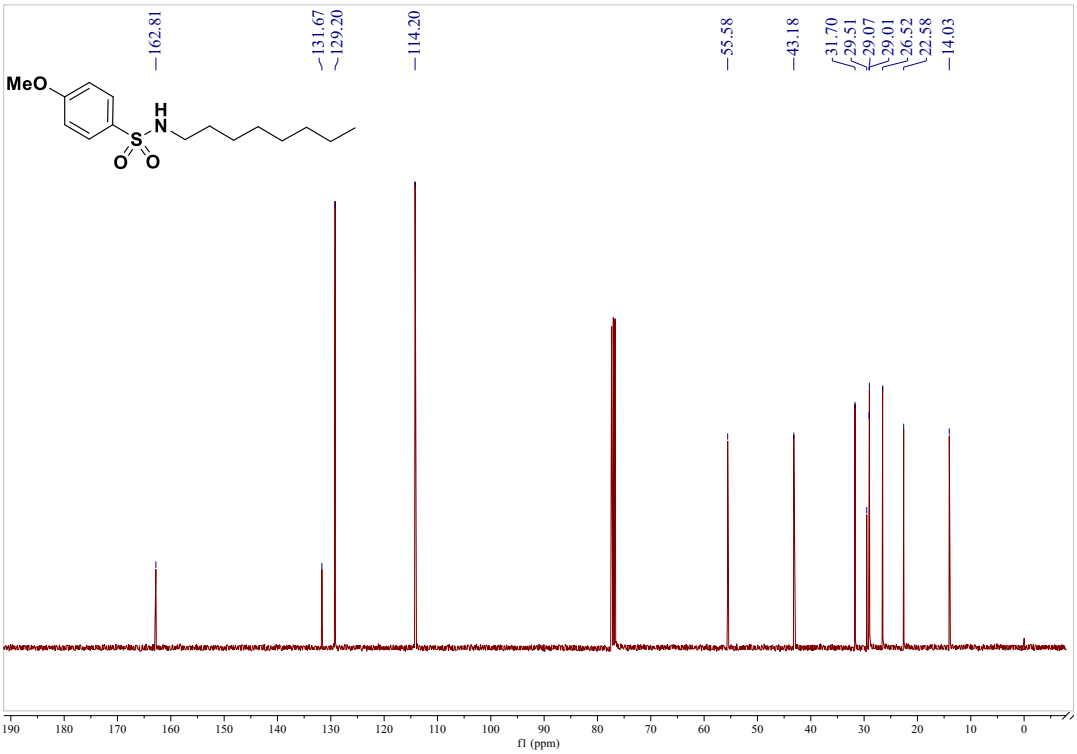
^{1}H and ^{13}C NMR spectra of **4o**:



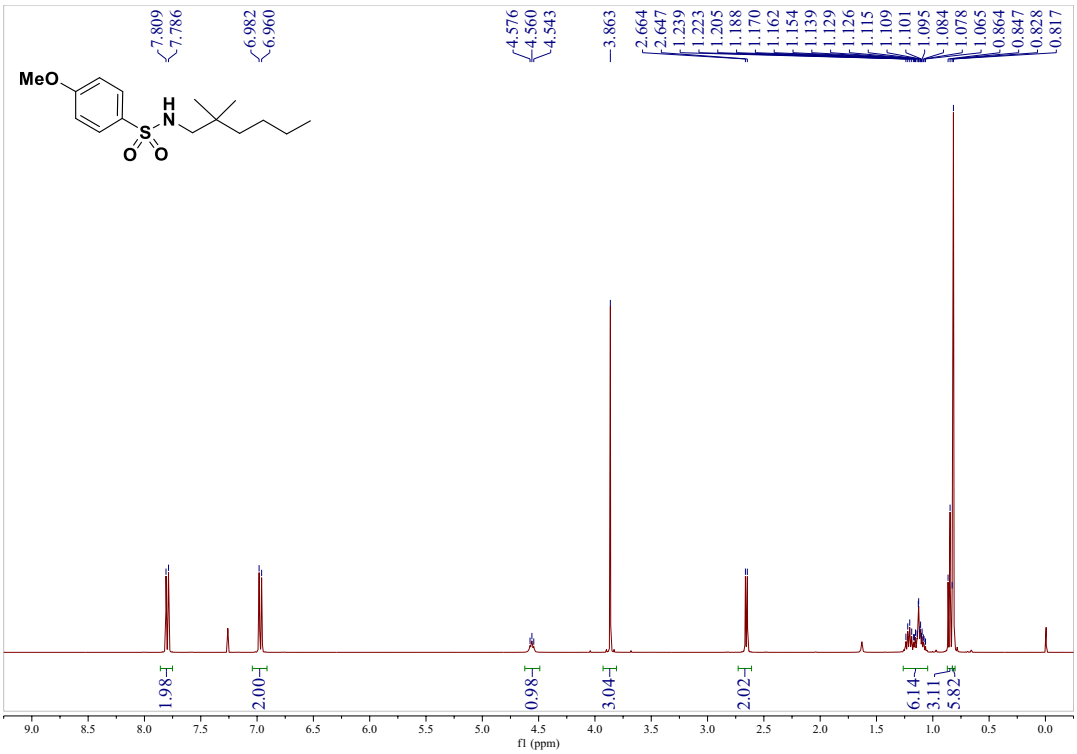


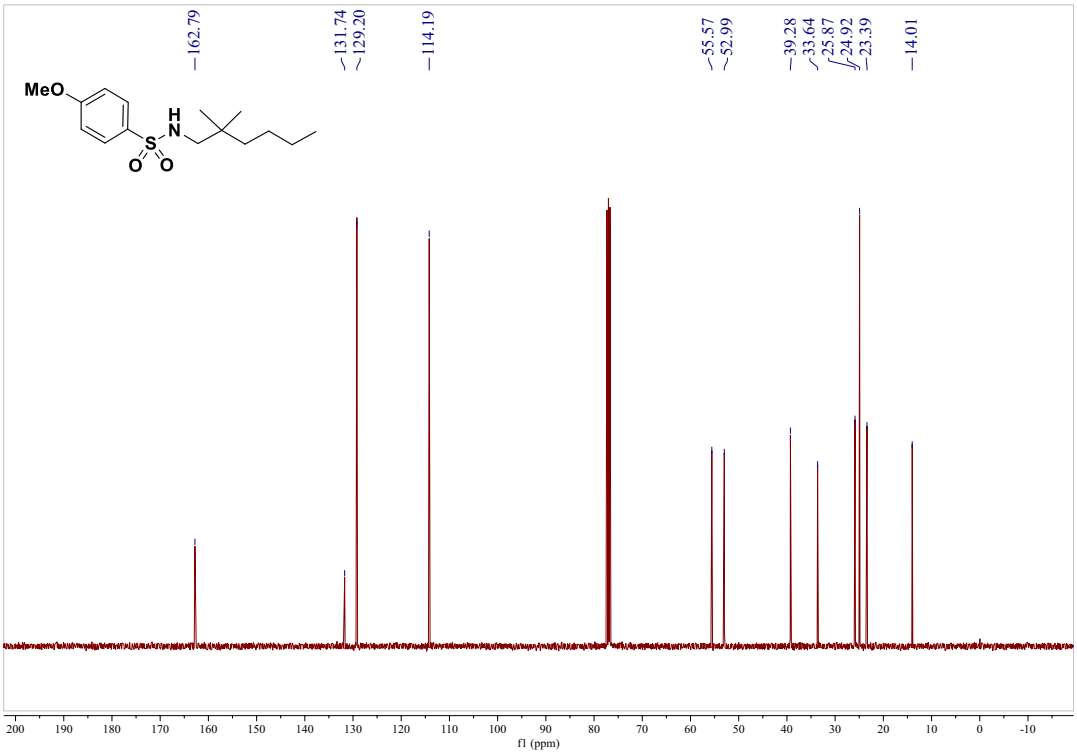
^{1}H and ^{13}C NMR spectra of **4p**:



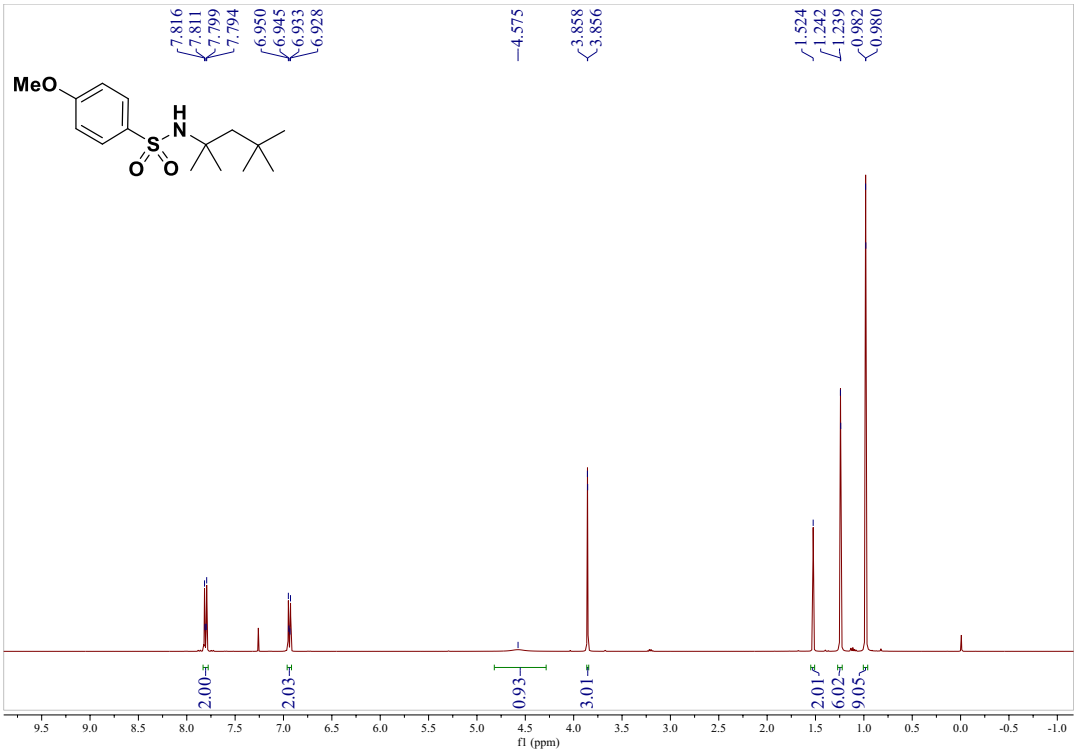


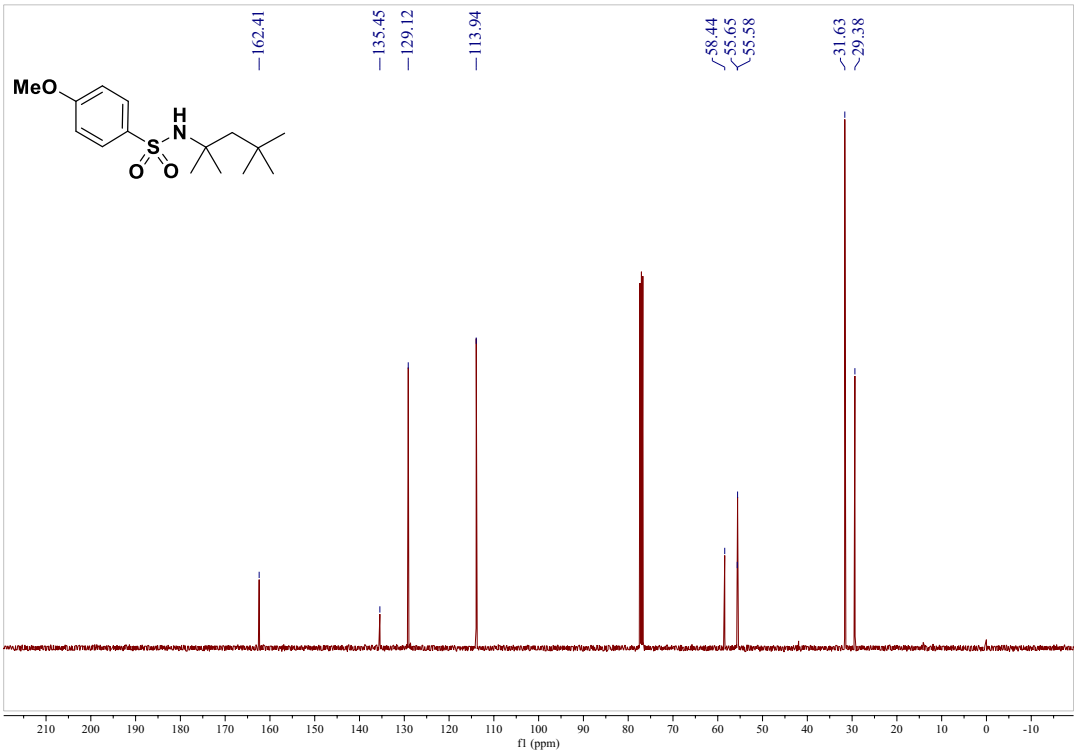
^{1}H and ^{13}C NMR spectra of **4q**:



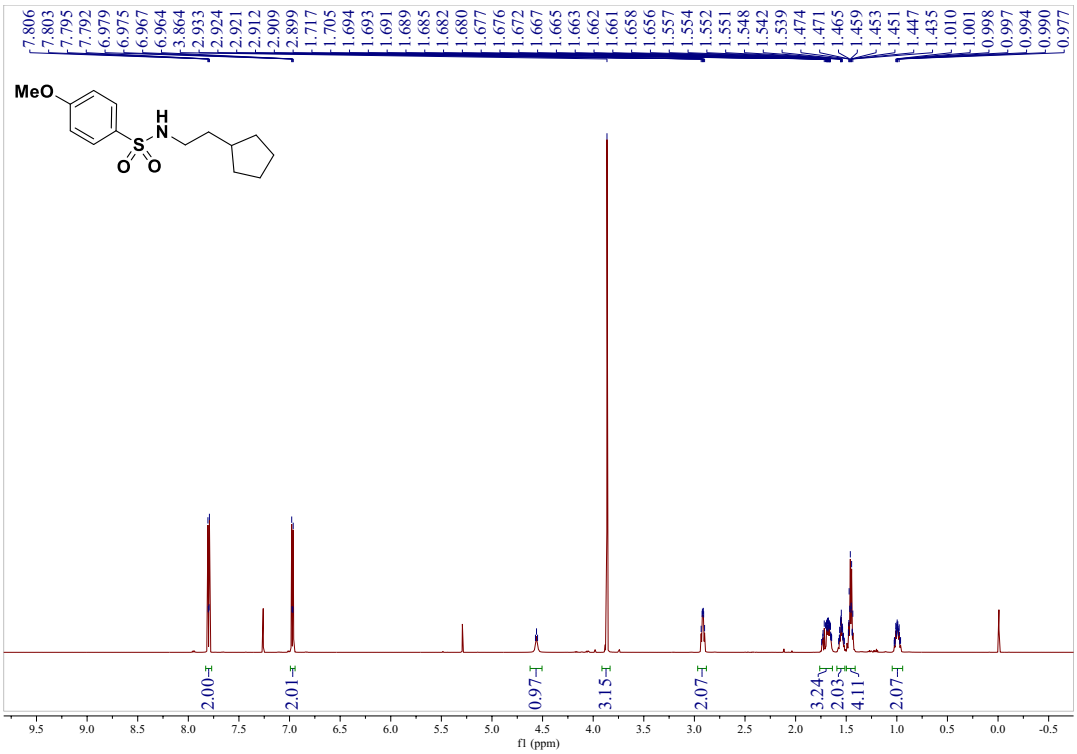


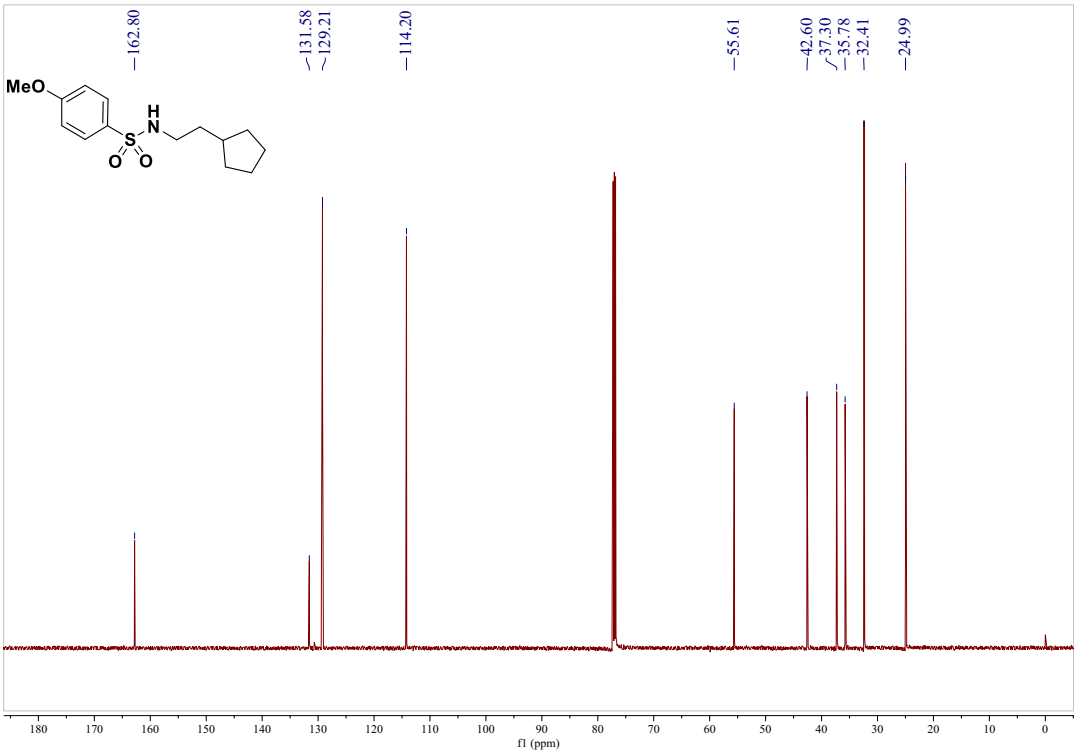
^{1}H and ^{13}C NMR spectra of **4r**:



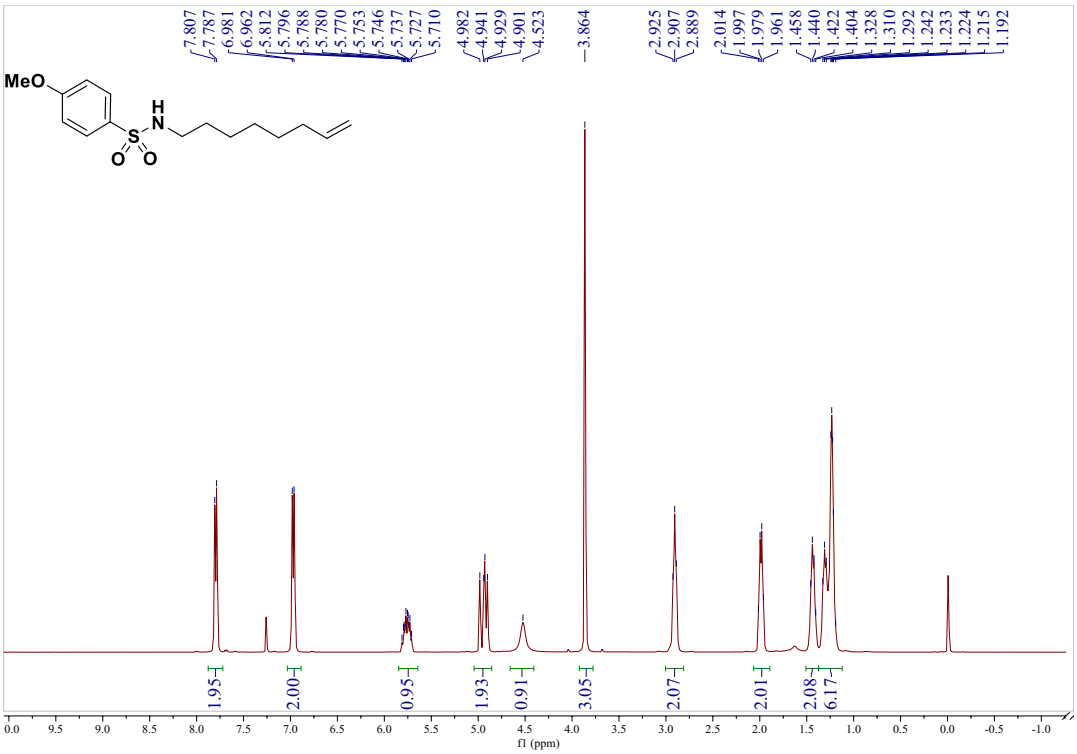


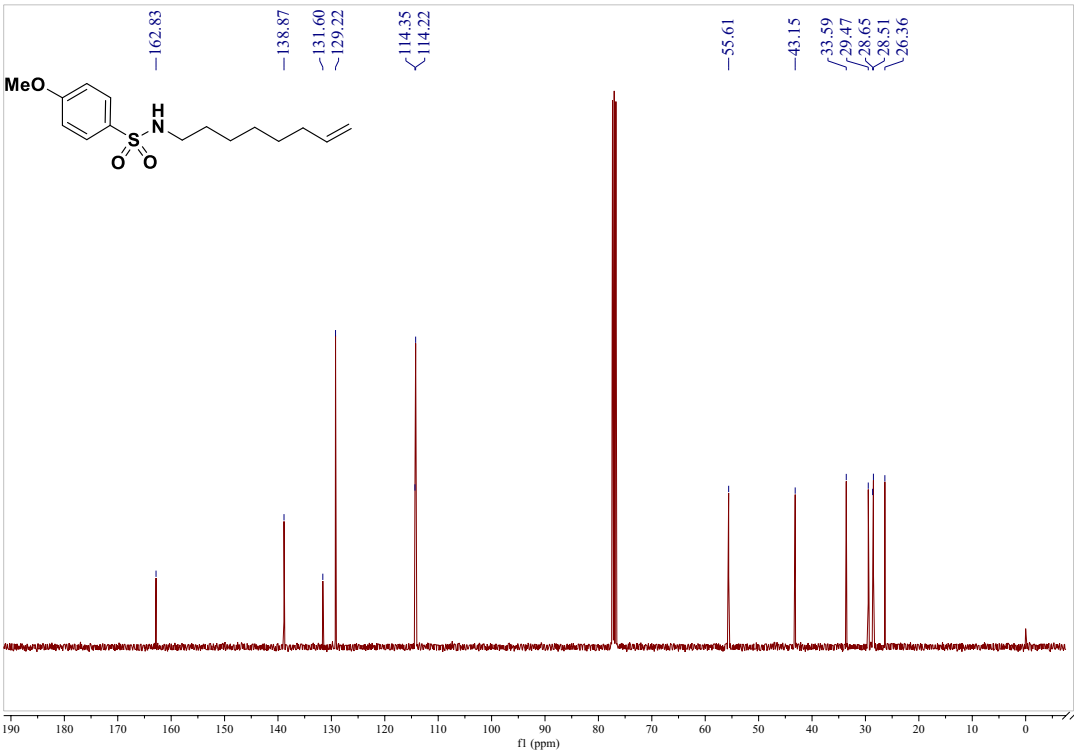
^{1}H and ^{13}C NMR spectra of **4s**:



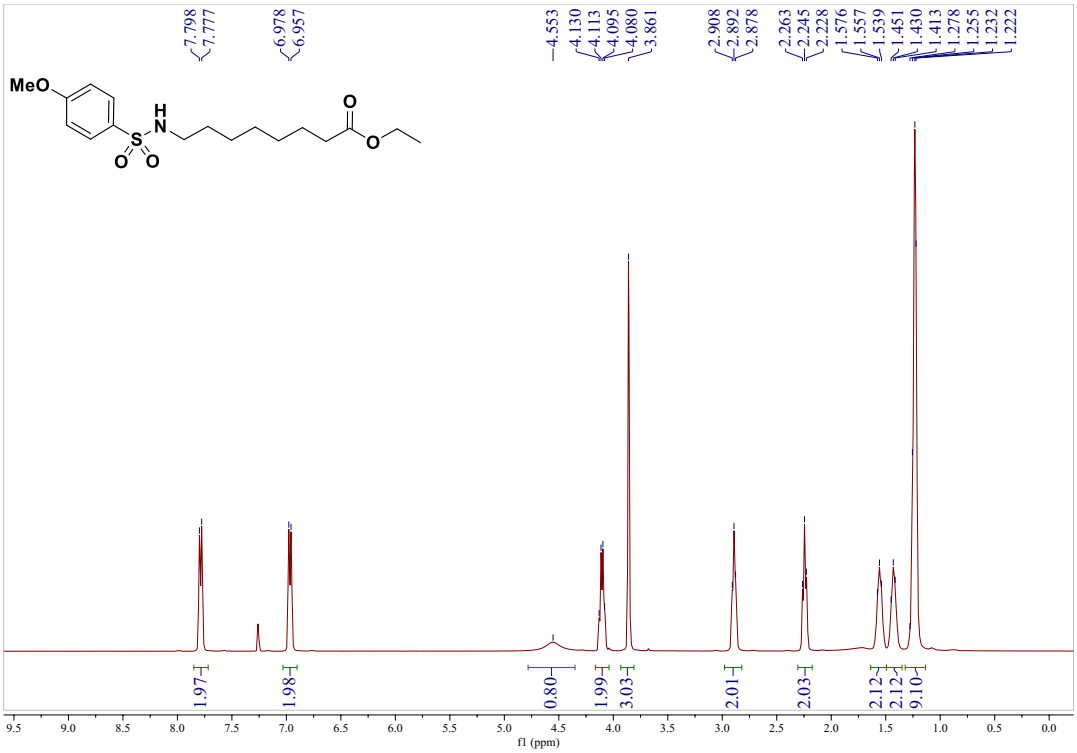


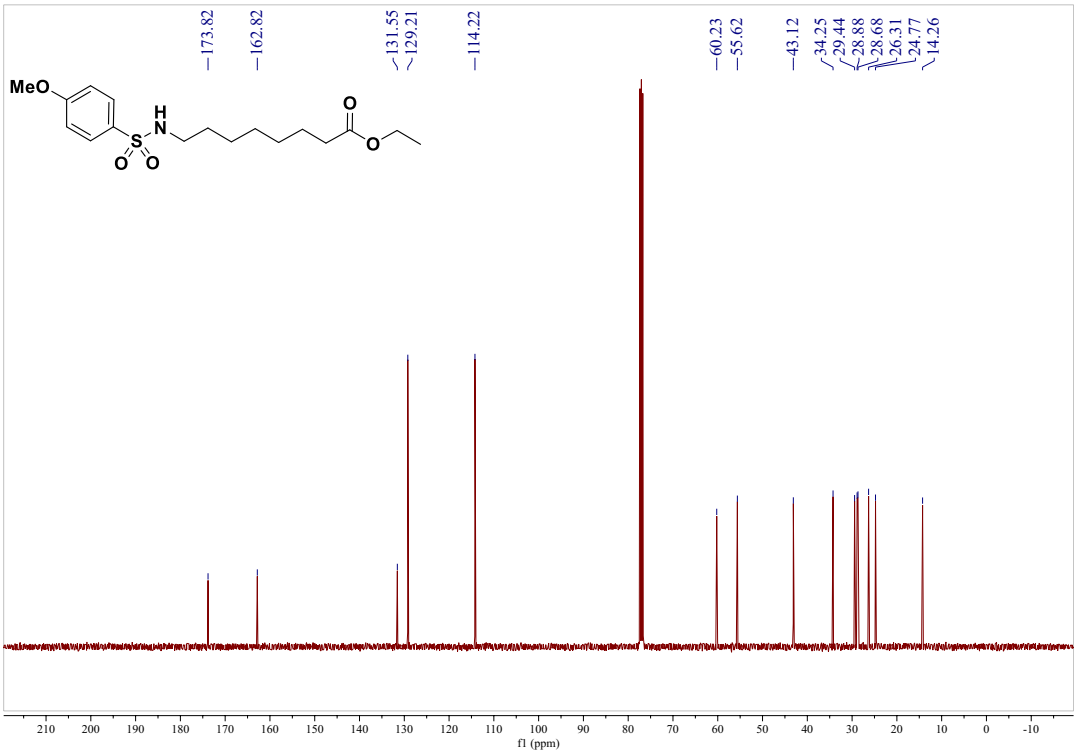
^{1}H and ^{13}C NMR spectra of **4t**:



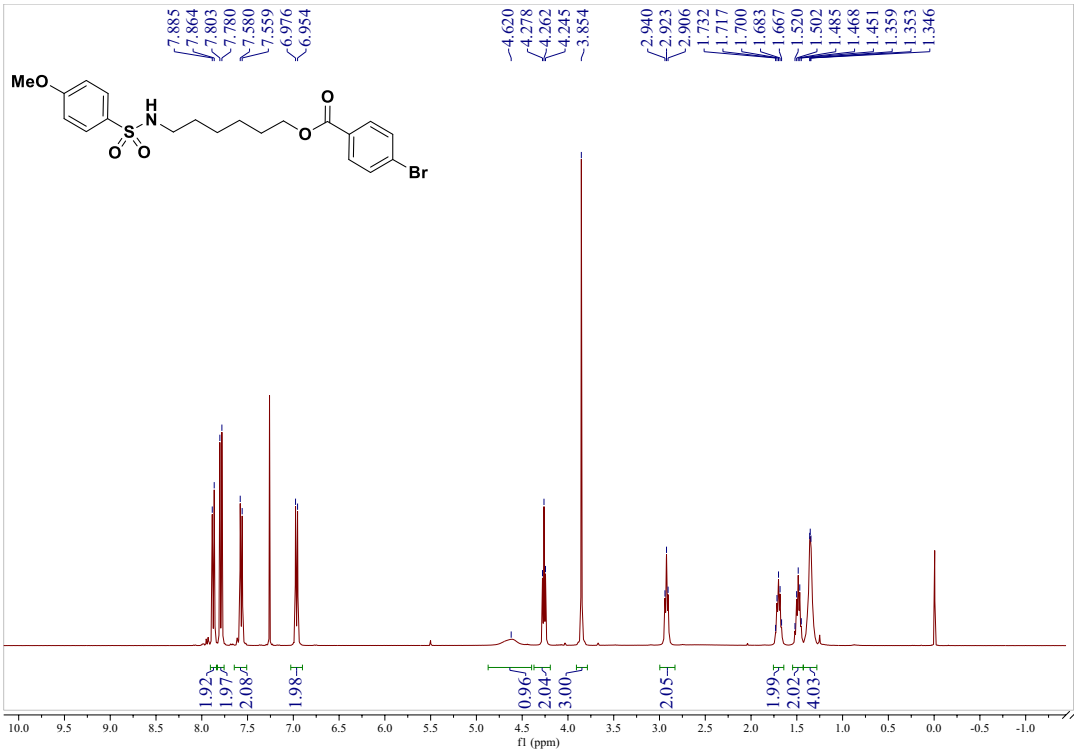


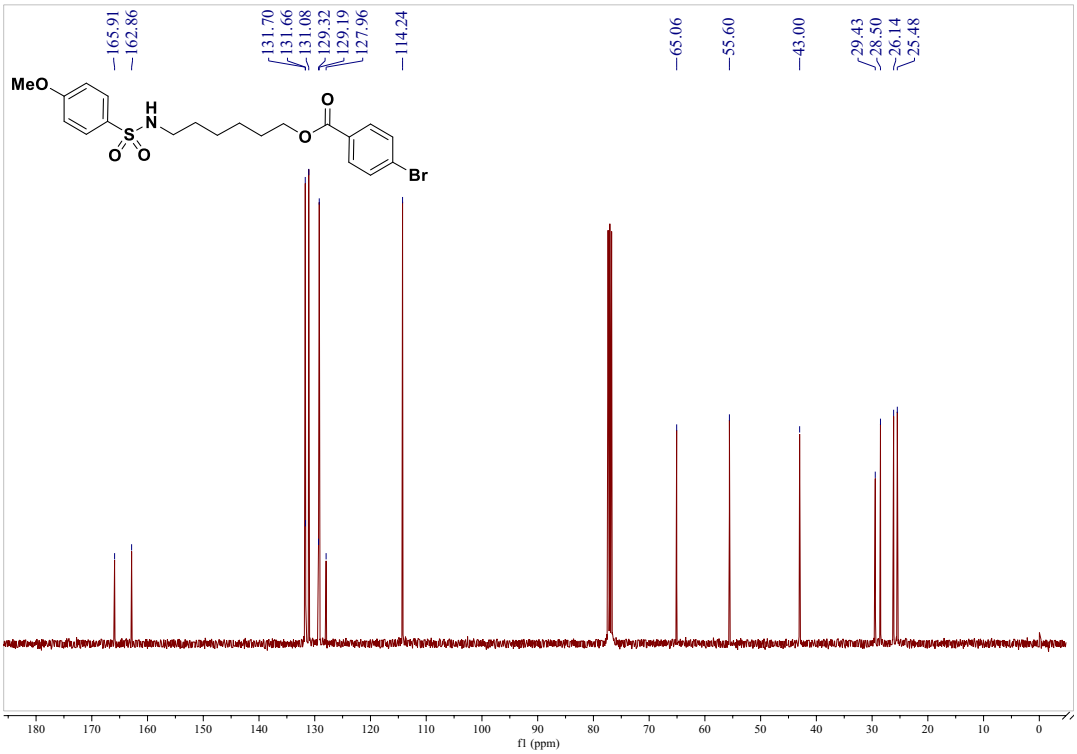
^{1}H and ^{13}C NMR spectra of **4u**:



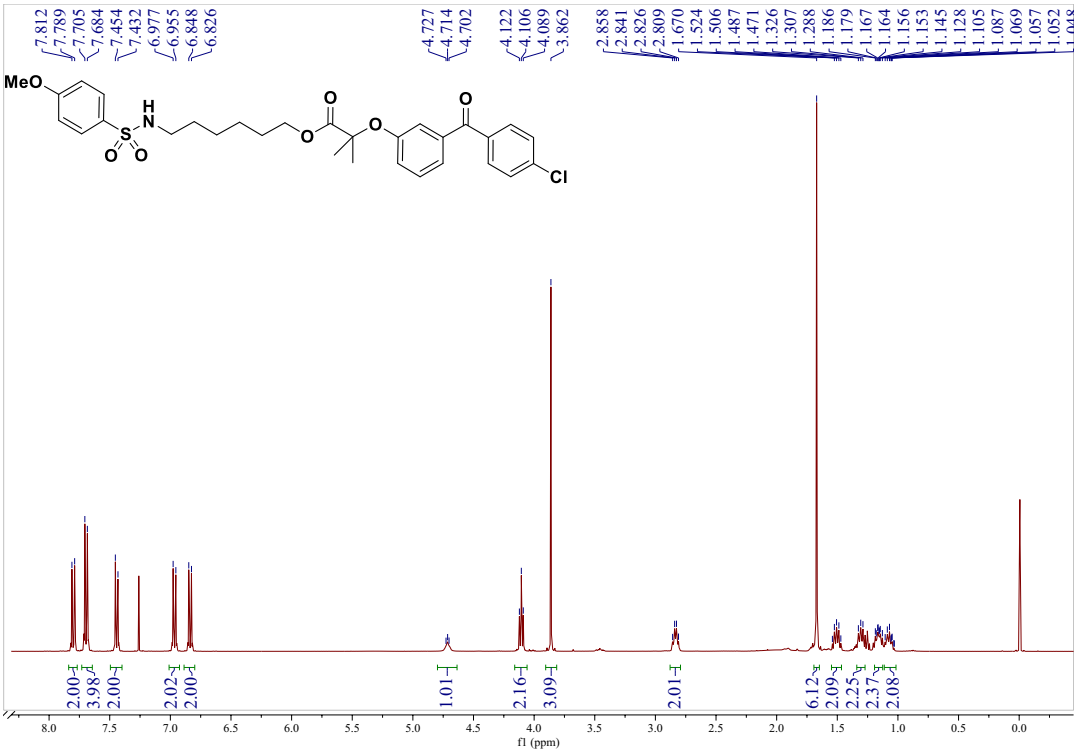


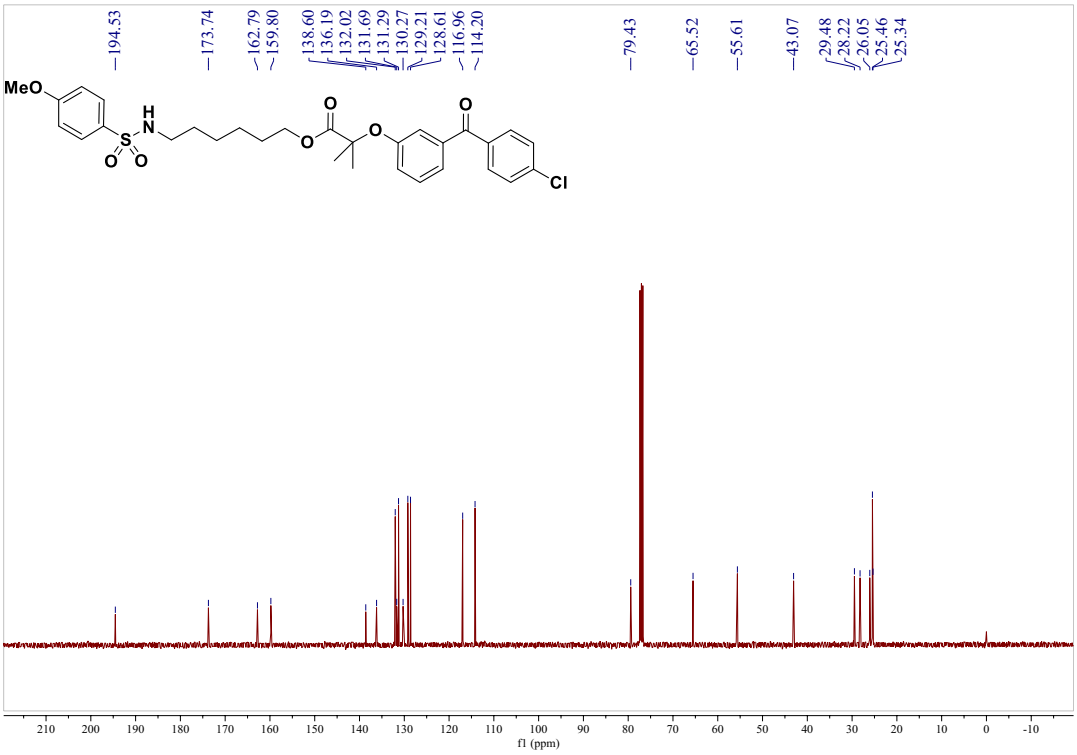
^{1}H and ^{13}C NMR spectra of **4v**:



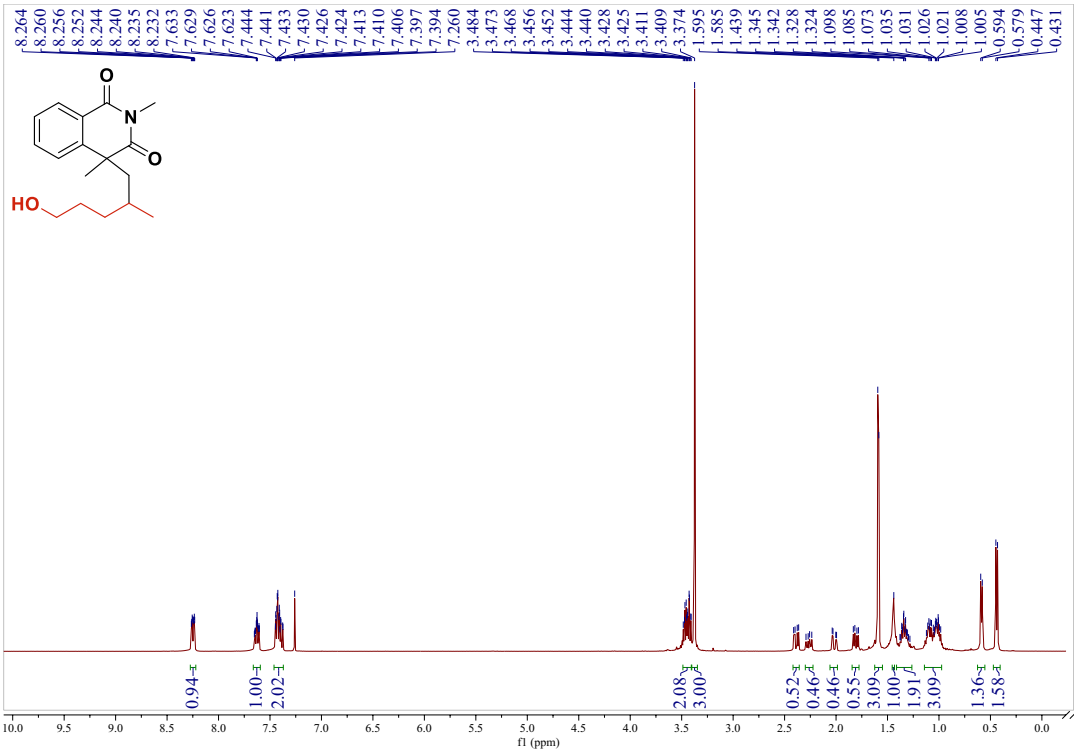


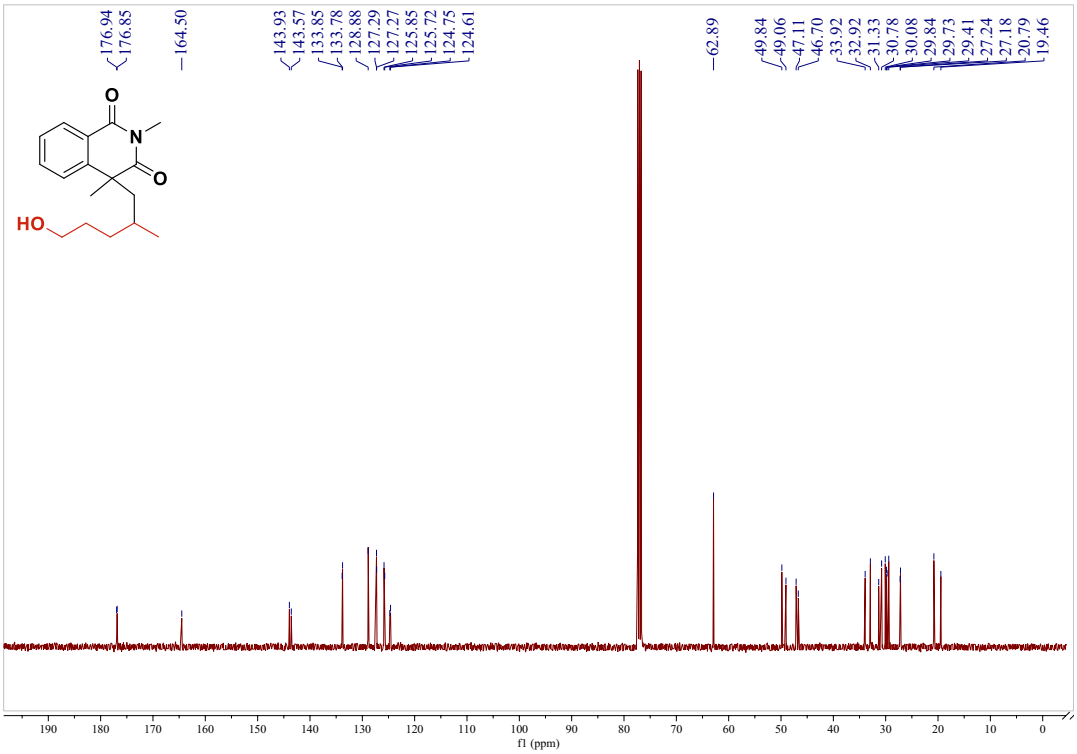
^{1}H and ^{13}C NMR spectra of **4w**:



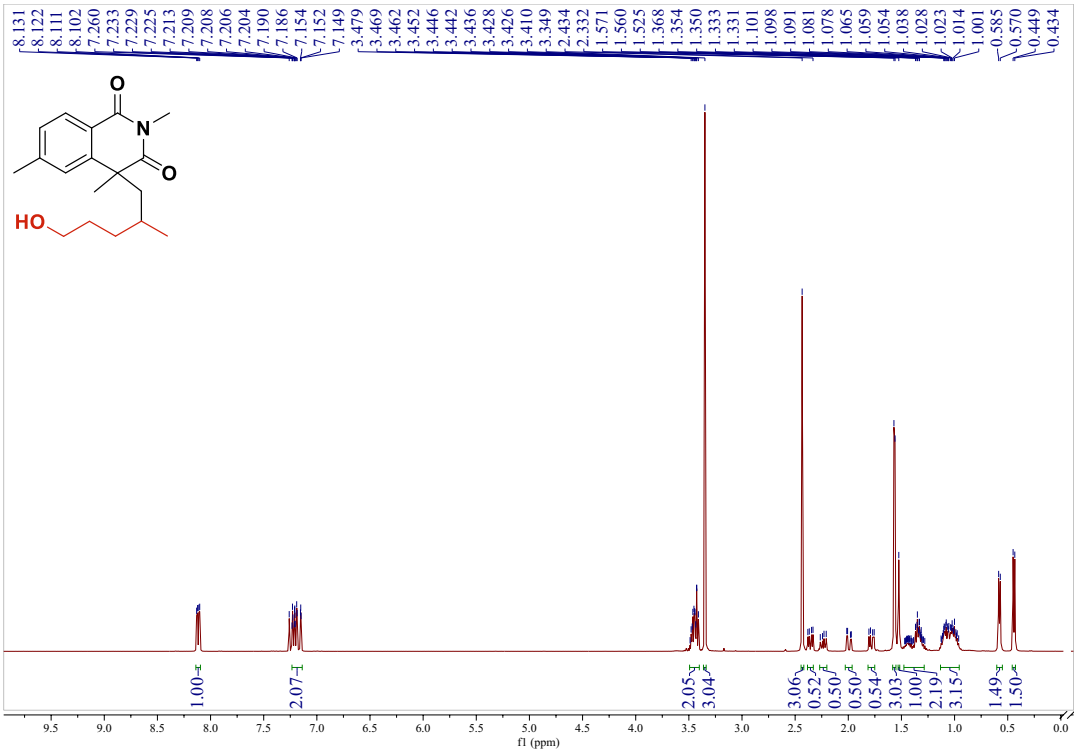


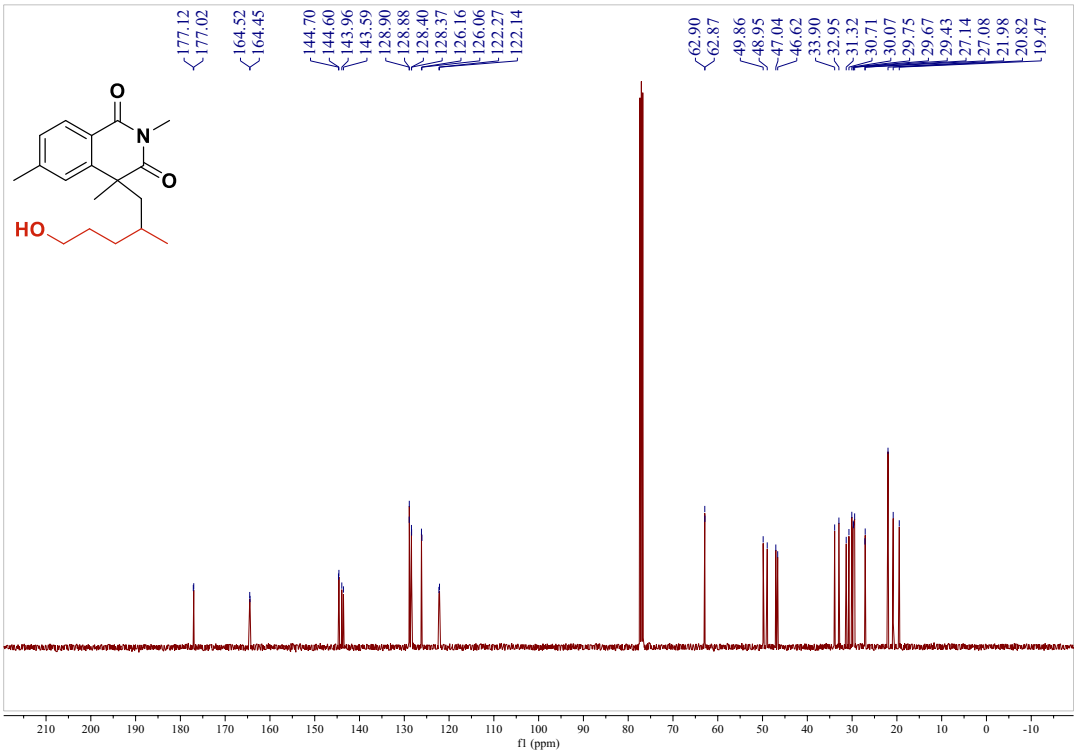
^{1}H and ^{13}C NMR spectra of **3aa**:



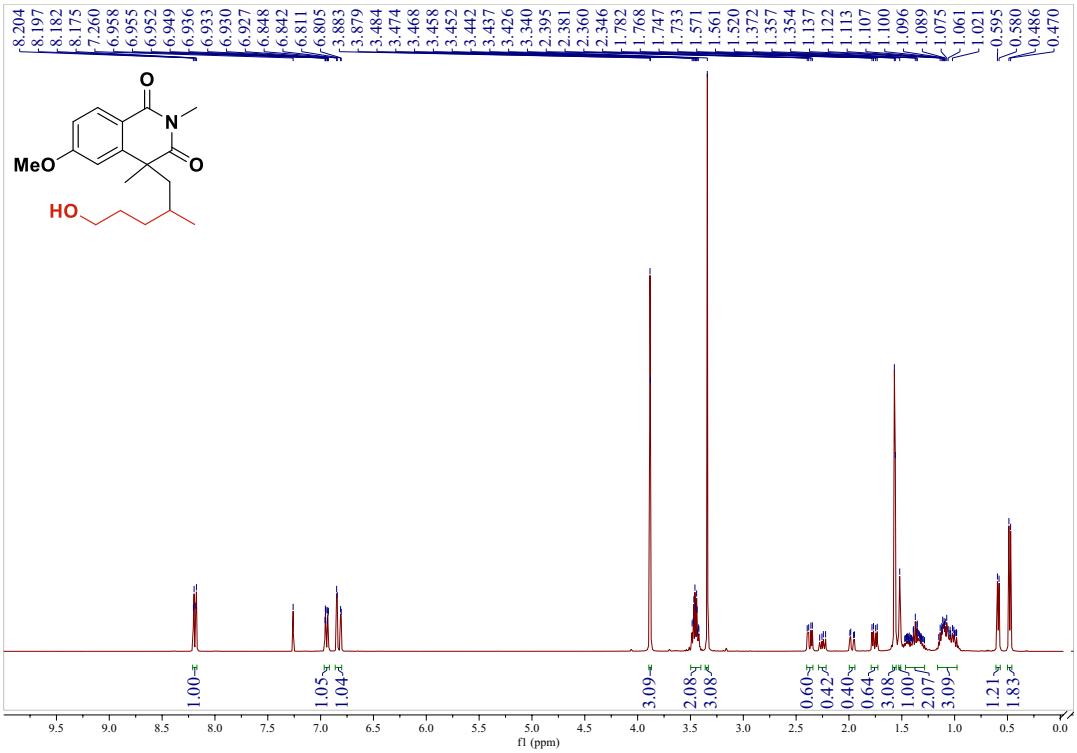


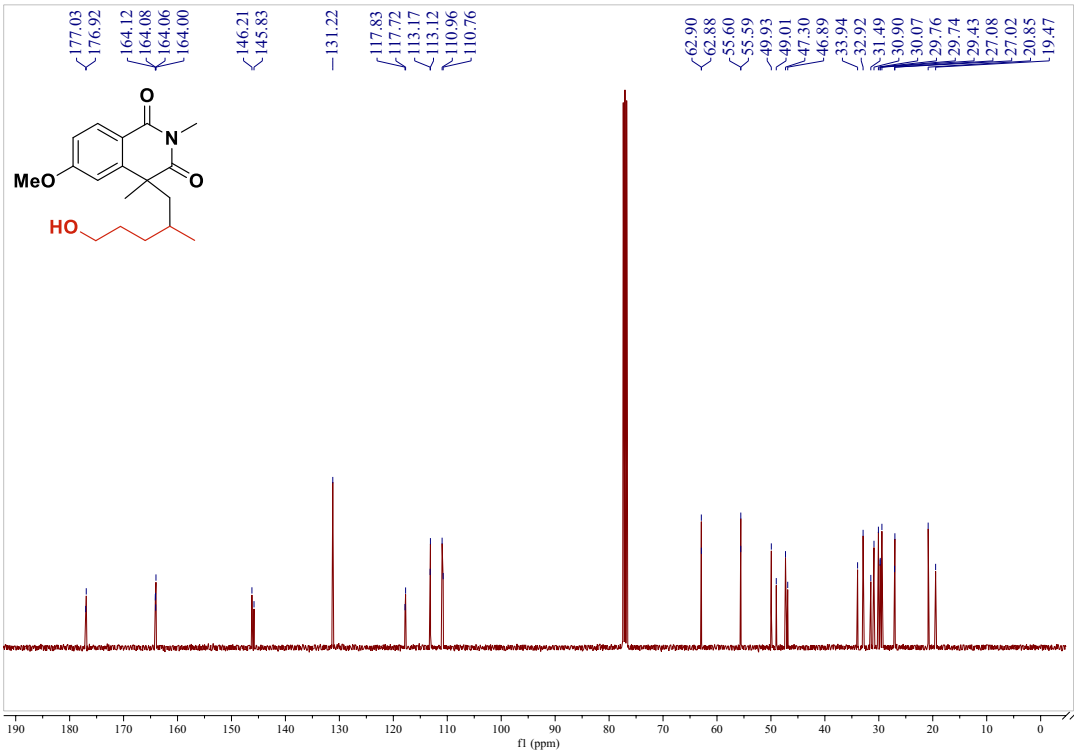
^{1}H and ^{13}C NMR spectra of **3ba**:



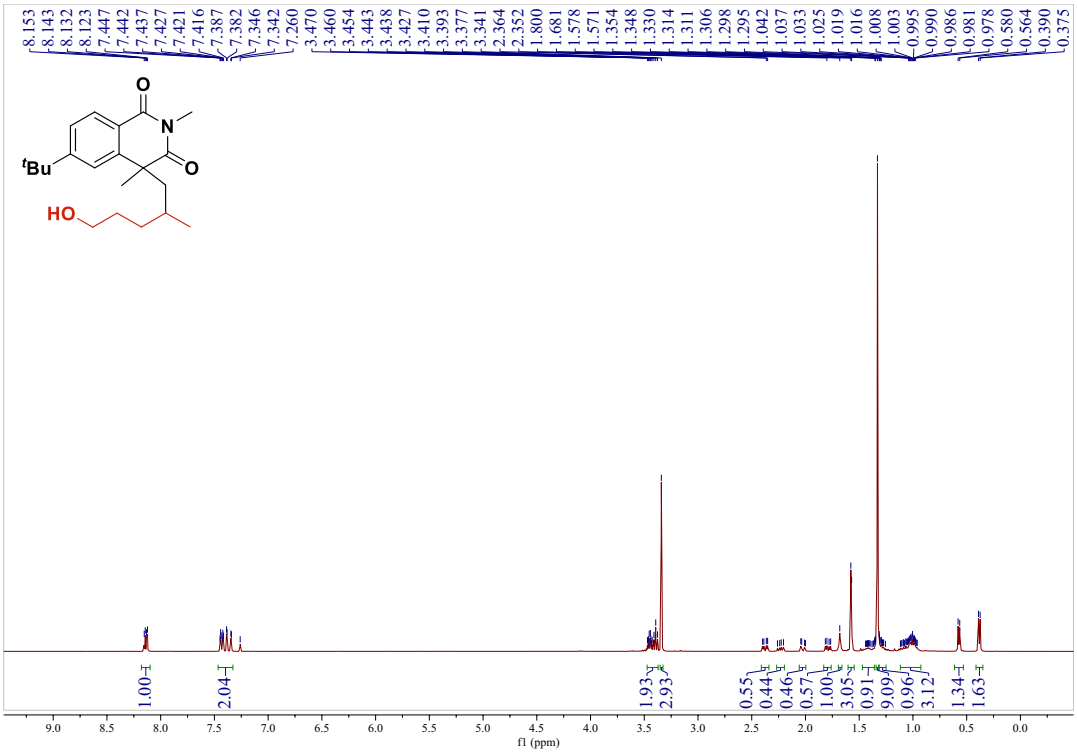


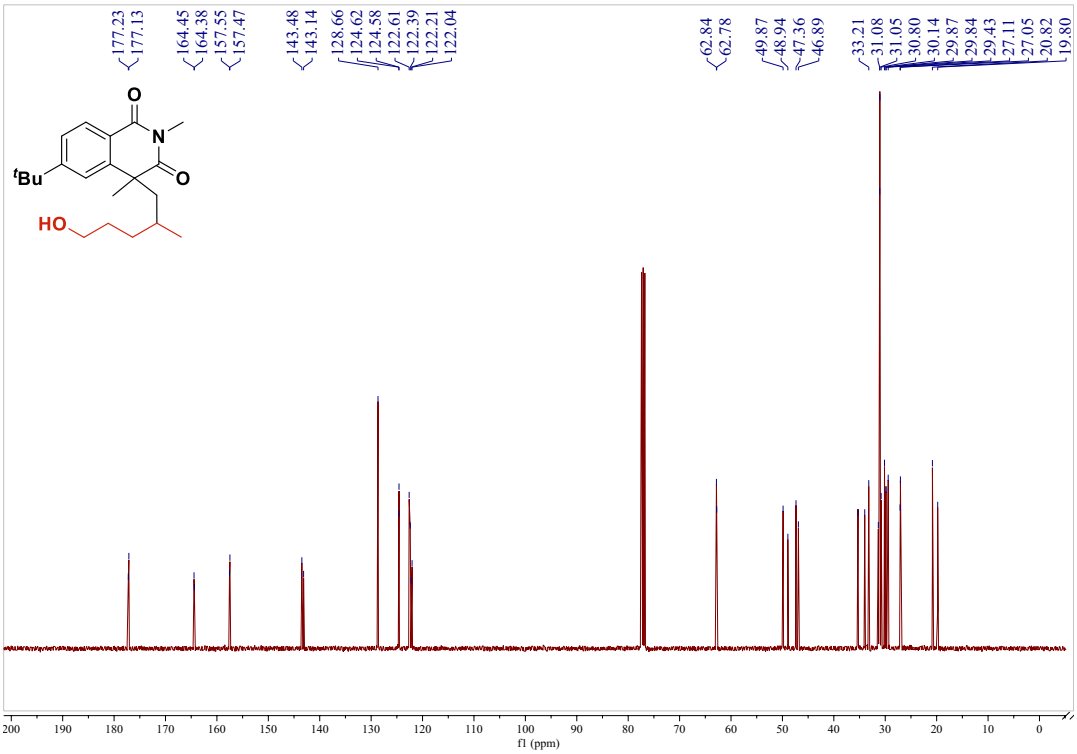
^{1}H and ^{13}C NMR spectra of **3ca**:



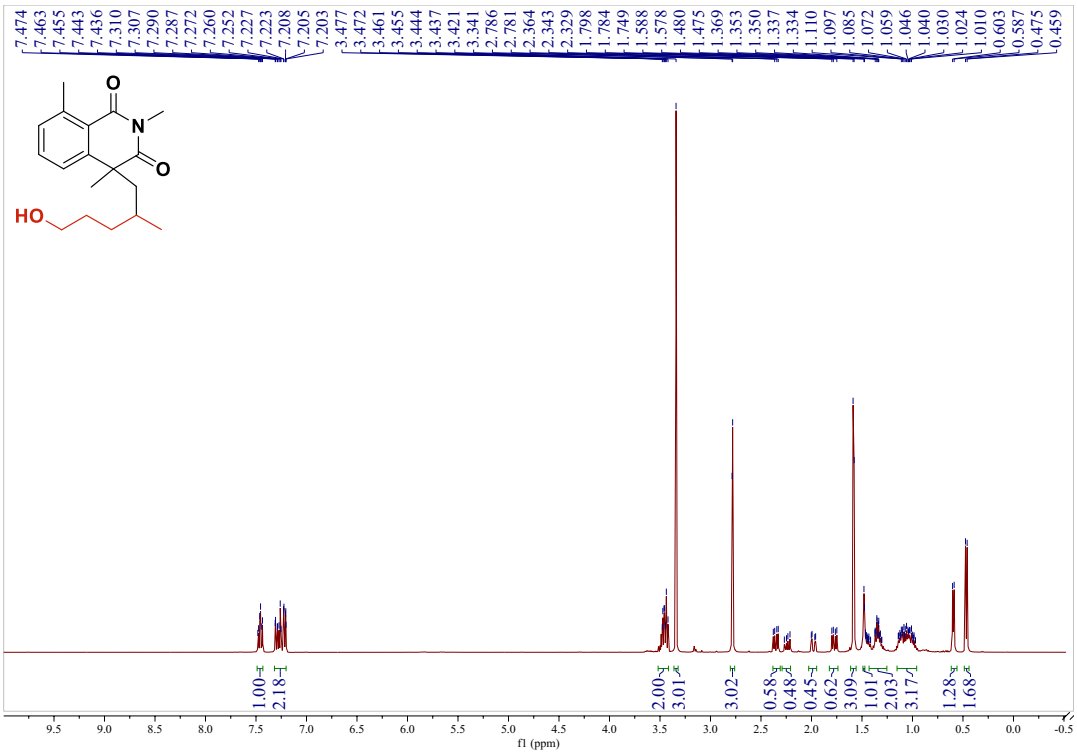


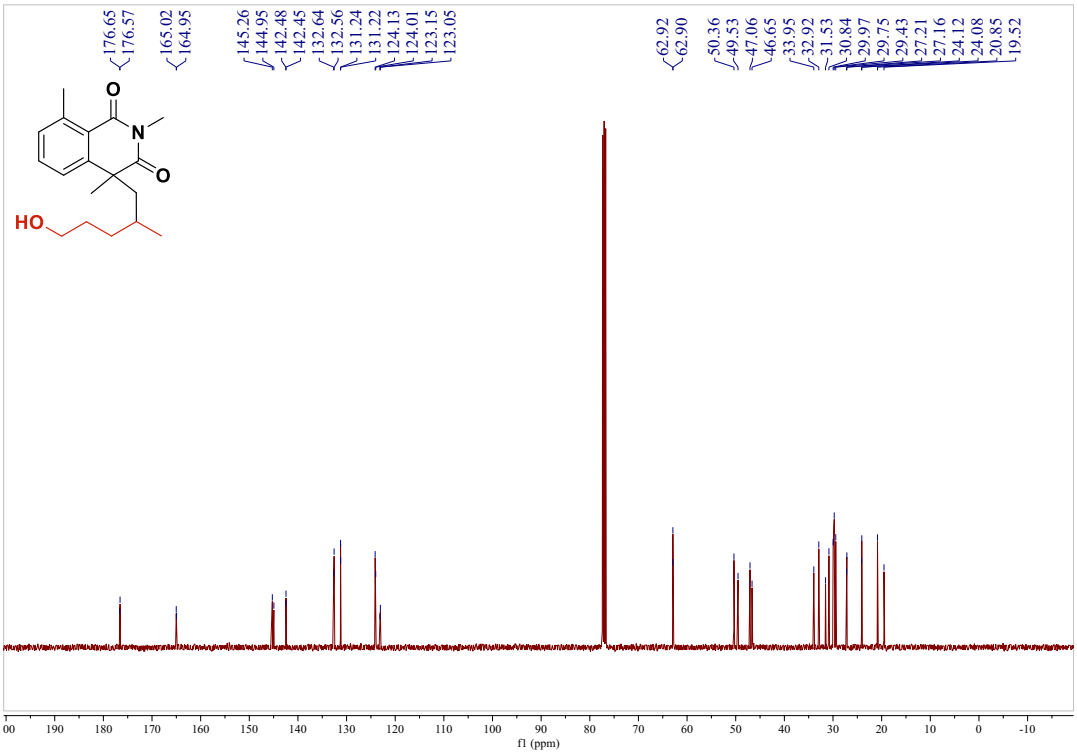
^{1}H and ^{13}C NMR spectra of **3da**:



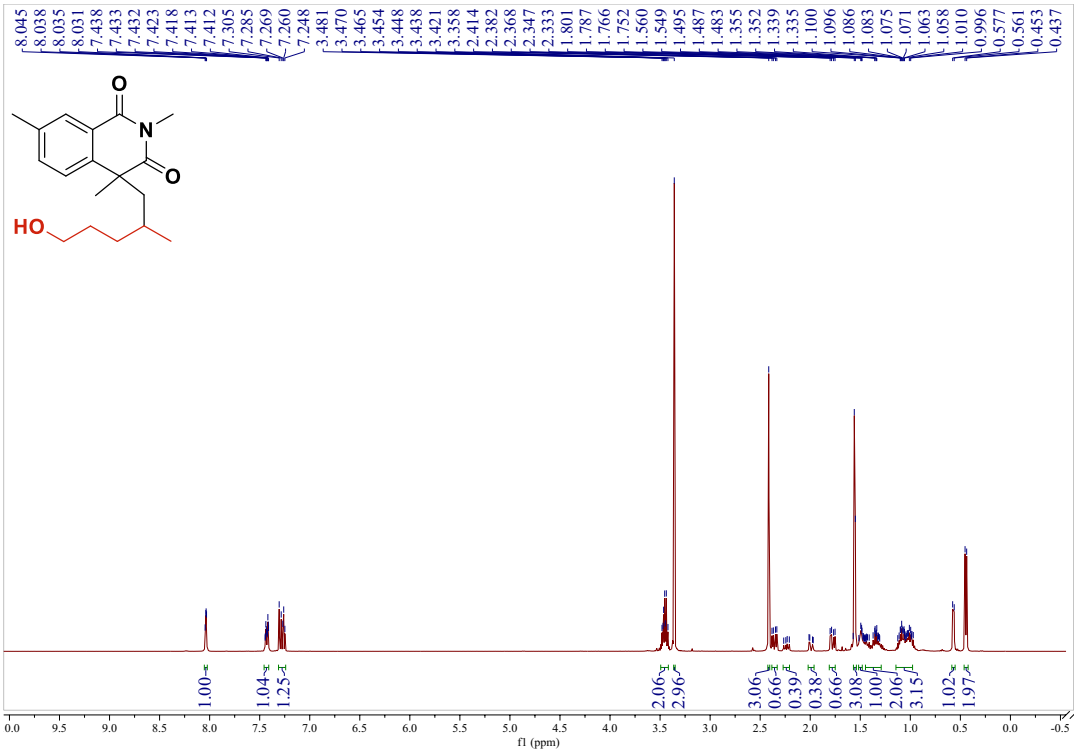


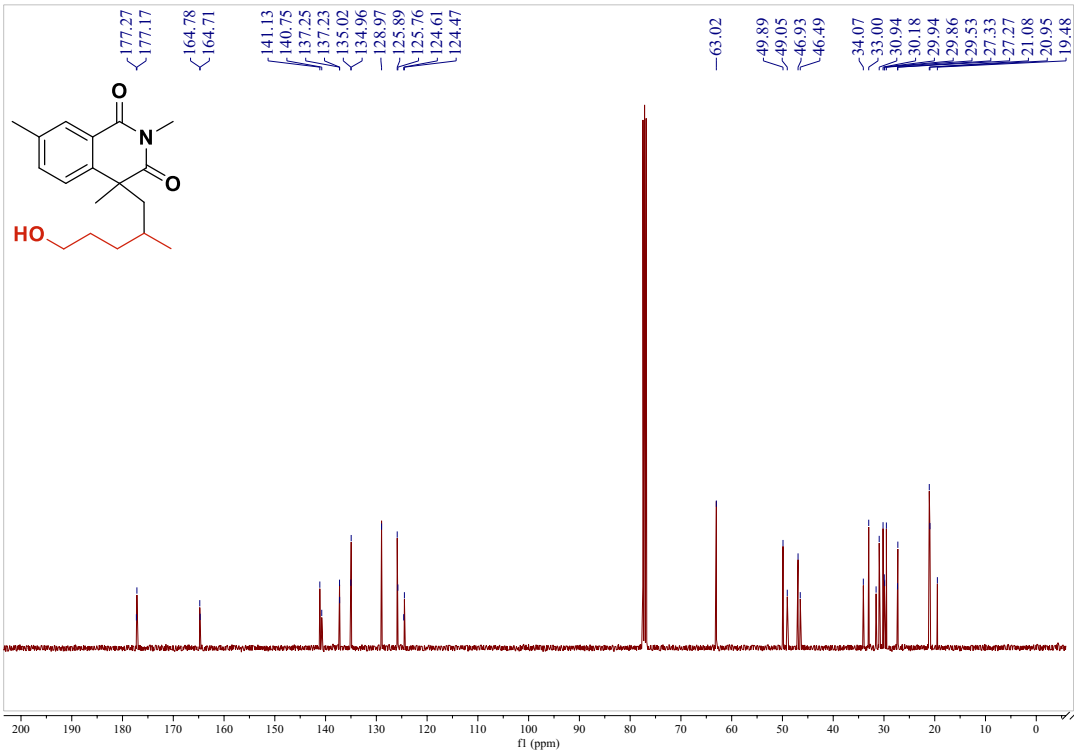
^{1}H and **^{13}C NMR** spectra of **3ea**:



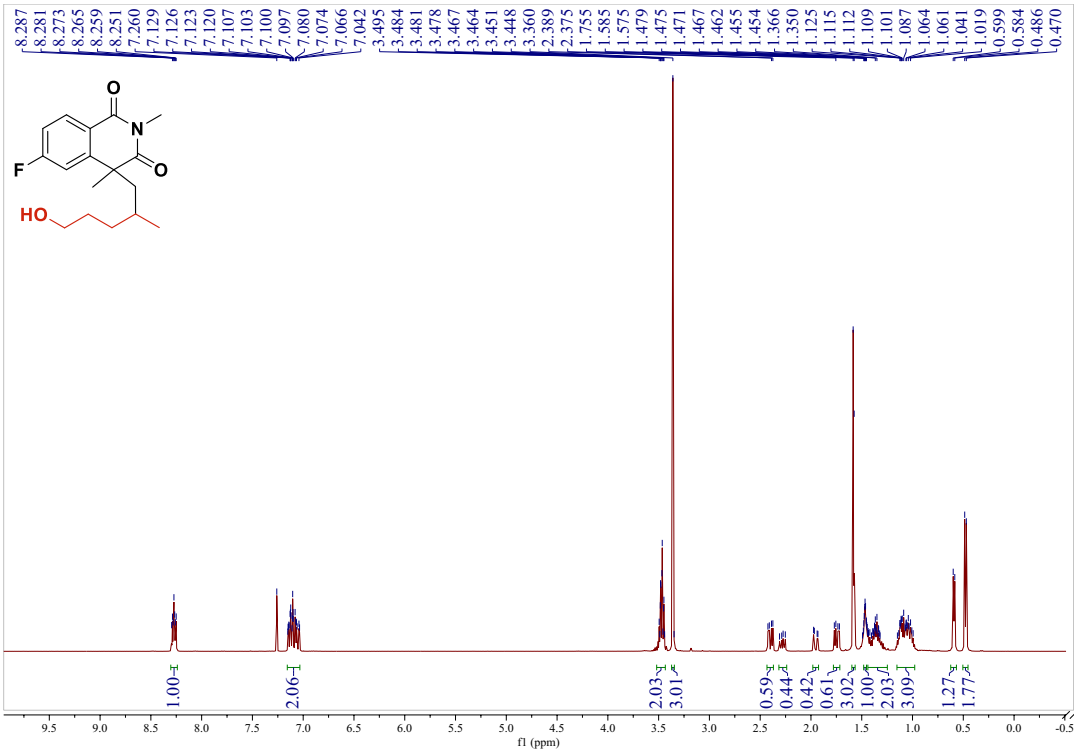


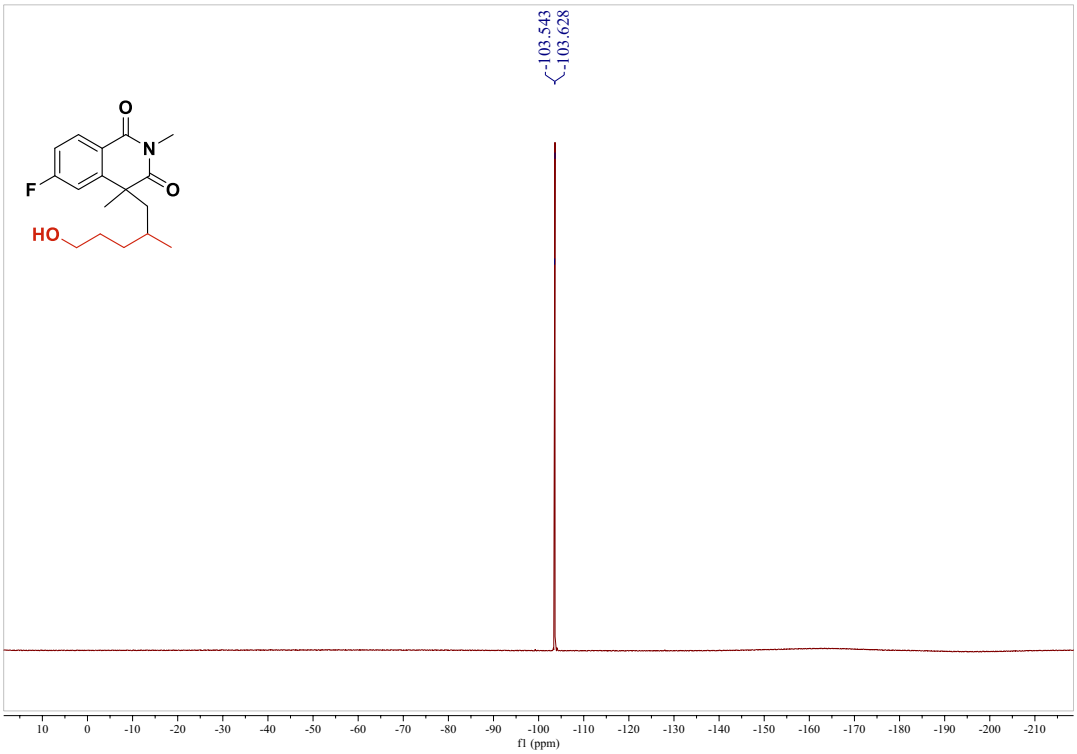
^{1}H and ^{13}C NMR spectra of **3fa**:

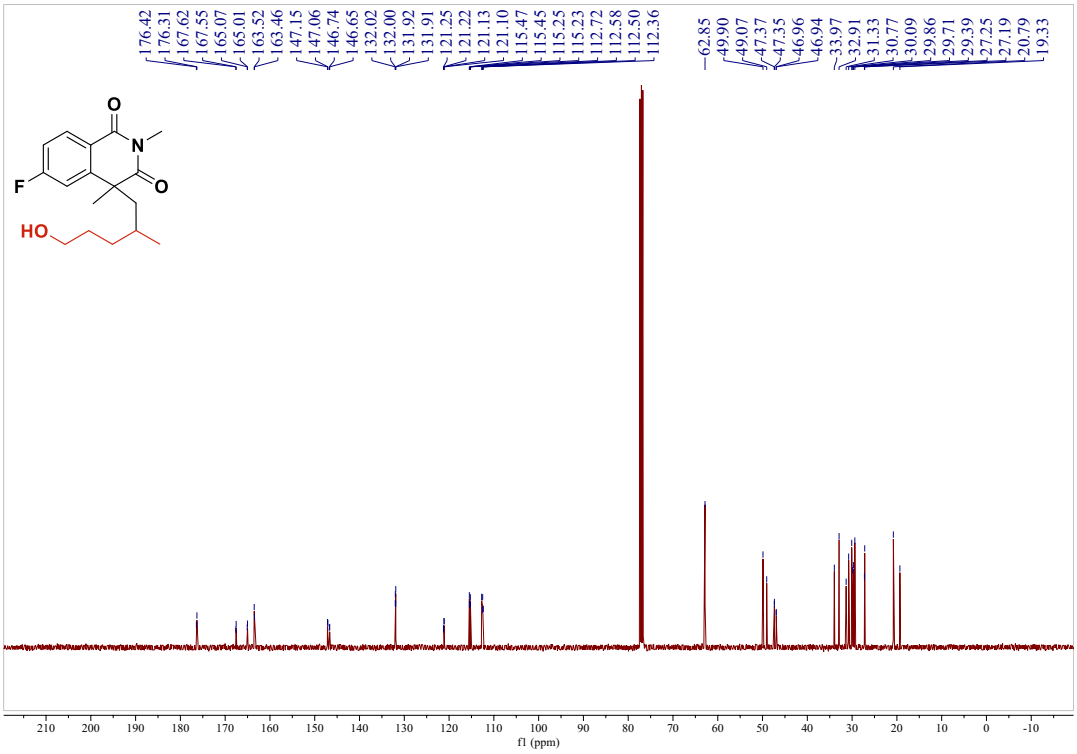




^{1}H ^{19}F and ^{13}C NMR spectra of **3ga**:






176.42
176.31
167.62
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163.46
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147.06
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146.65
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132.00
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121.22
121.13
121.10
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115.25
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112.50
112.36
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47.35
46.96
46.94
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29.39
27.25
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O
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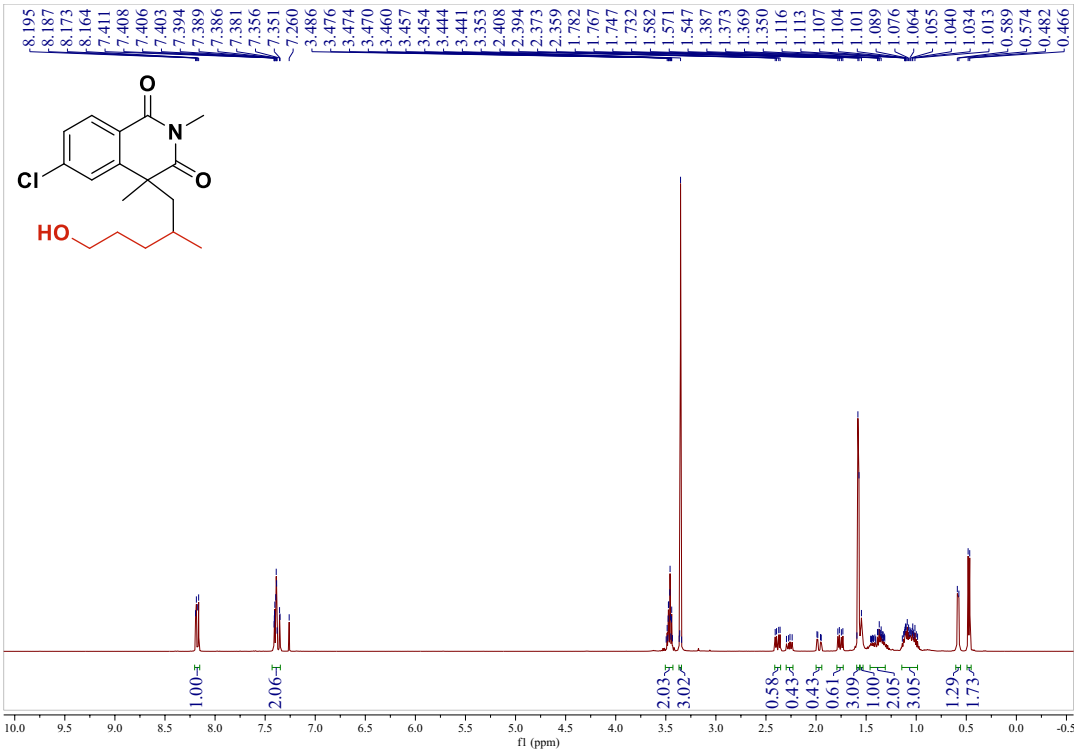
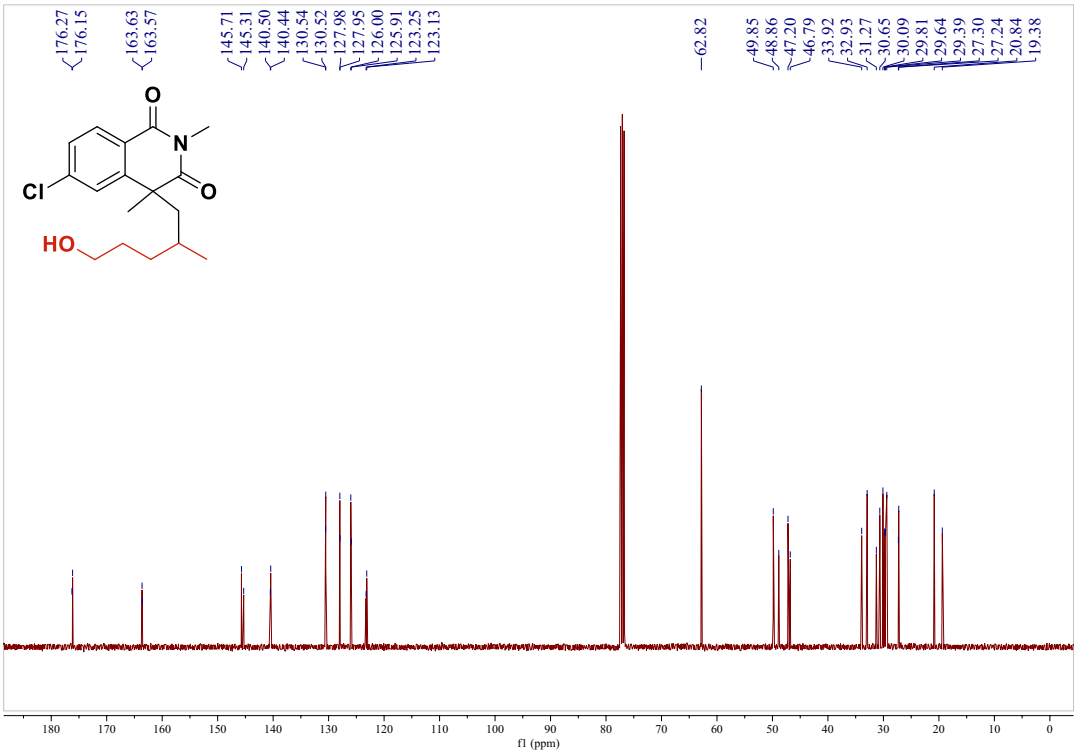
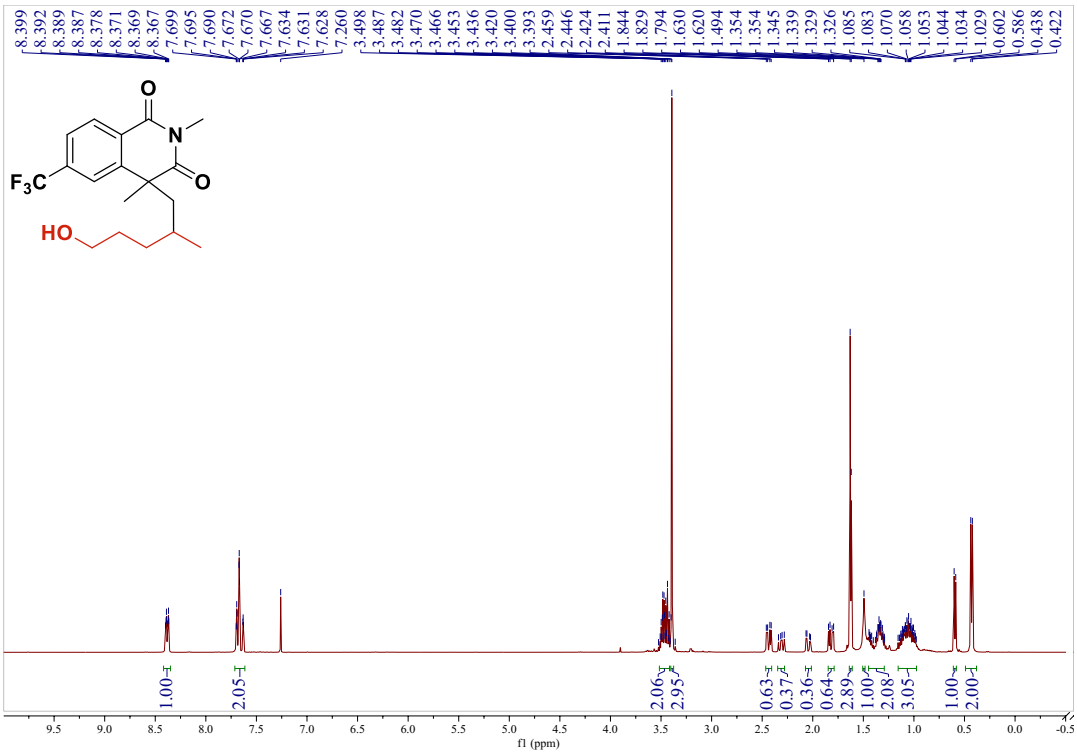
HO
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

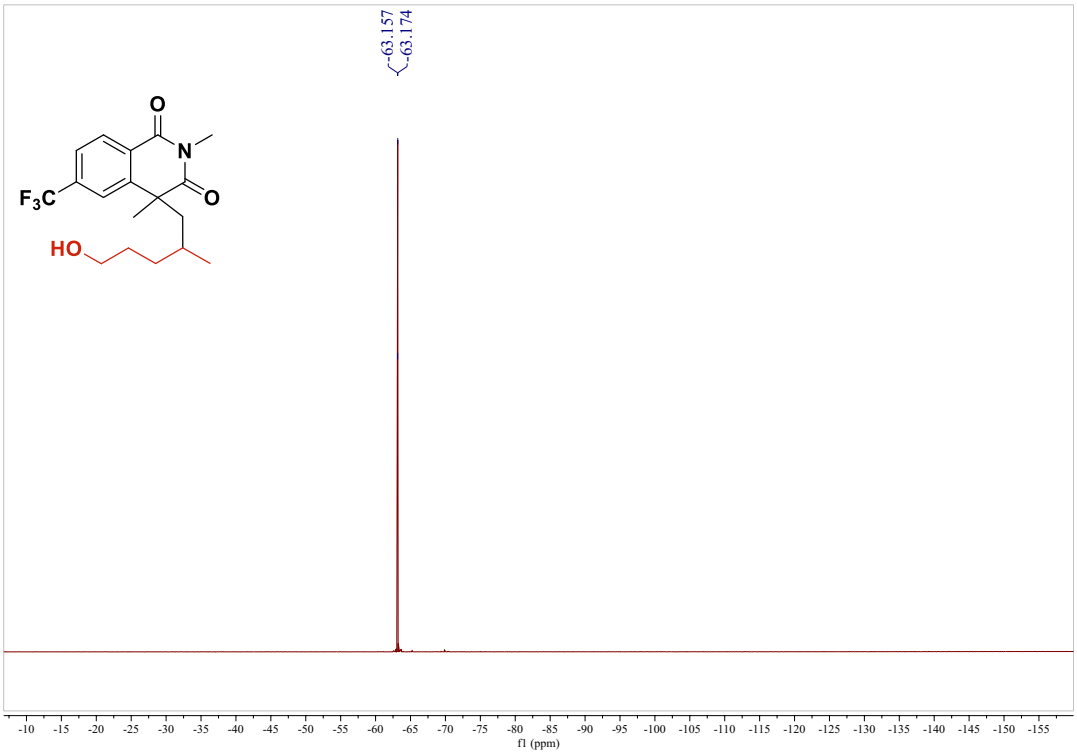
^{1}H and ^{13}C NMR spectra of **3ha**:

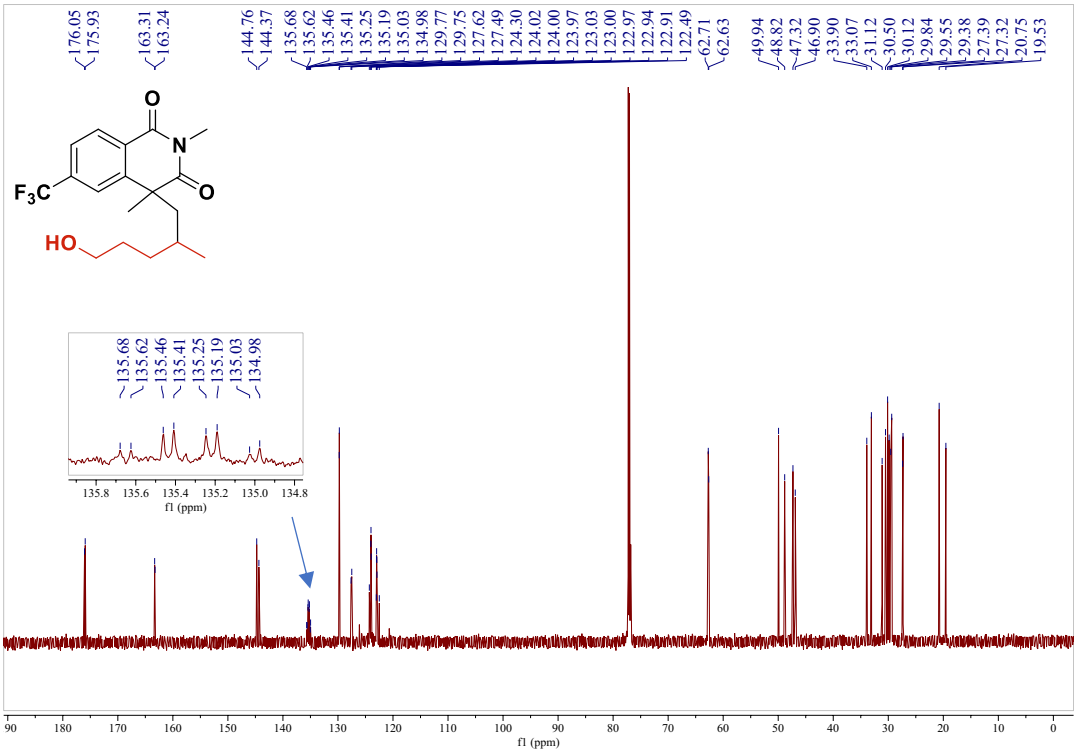




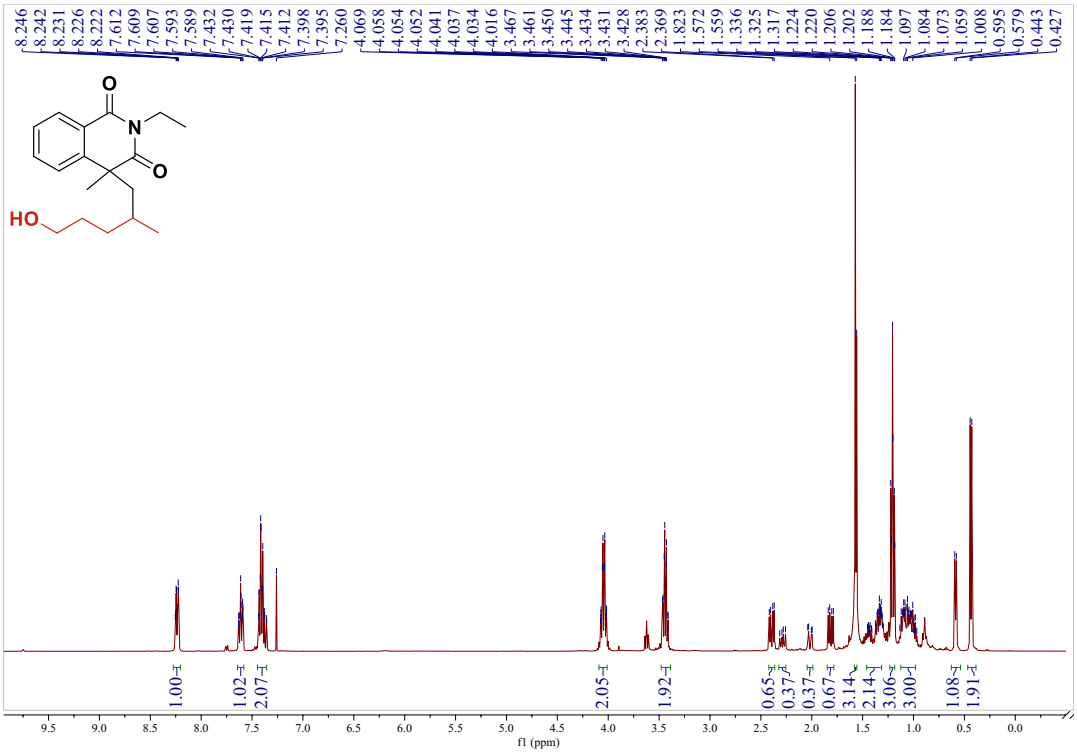
^{1}H ^{19}F and ^{13}C NMR spectra of **3ia**:

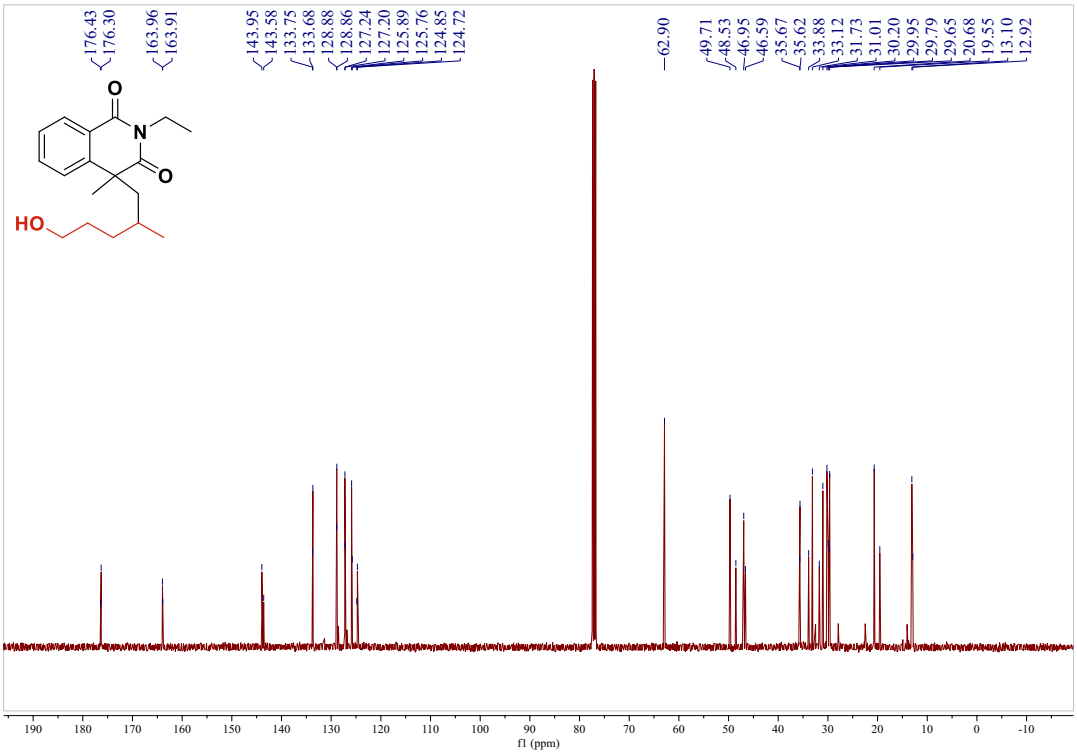




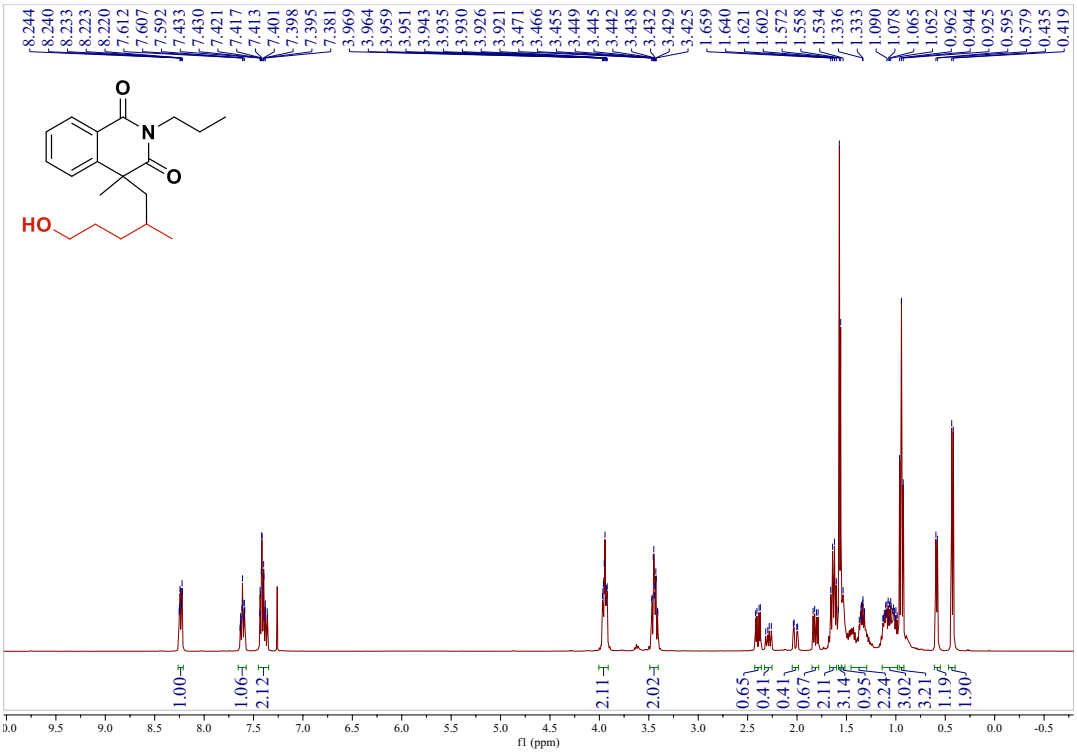

176.05
175.93
163.31
163.24
144.76
144.37
135.68
135.62
135.46
135.41
135.25
135.19
135.03
134.98
129.77
129.75
127.62
127.49
124.30
124.02
124.00
123.97
123.03
123.00
122.97
122.94
122.91
122.49
62.71
62.63
49.94
48.82
47.32
46.90
33.90
33.07
31.12
30.50
30.12
29.84
29.55
29.38
27.39
27.32
20.75
19.53
O
N
O
F3C
HO
135.8
135.6
135.4
135.2
135.0
134.8
f1 (ppm)
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

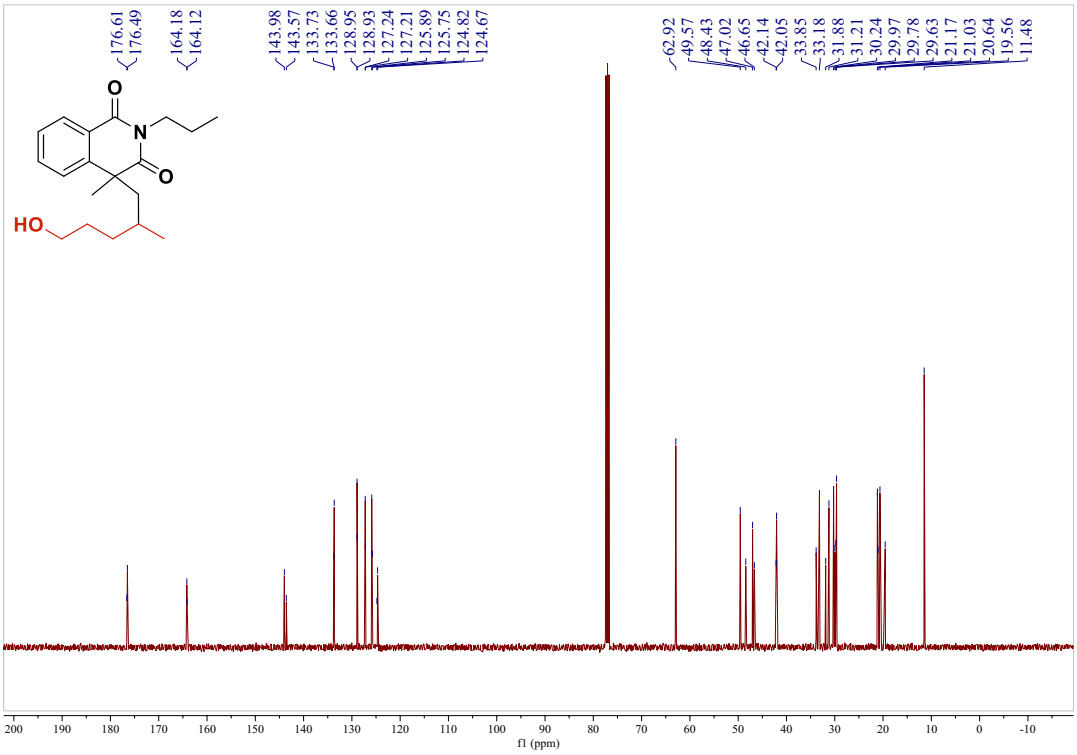
^{1}H and ^{13}C NMR spectra of **3ja**:



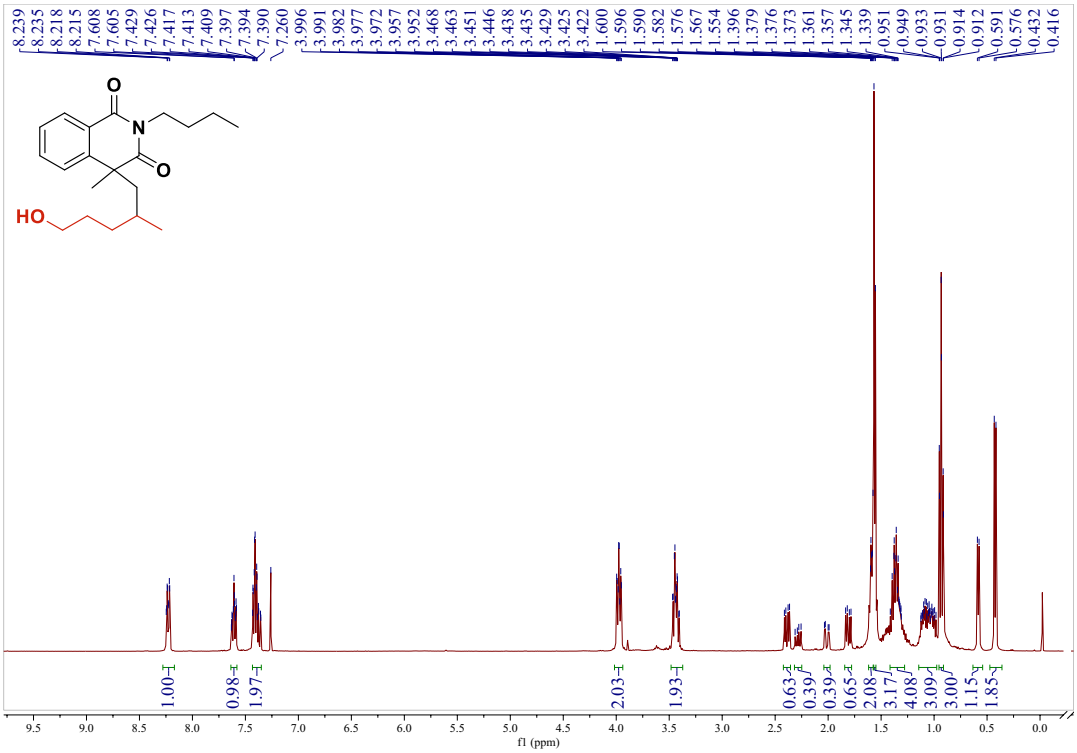


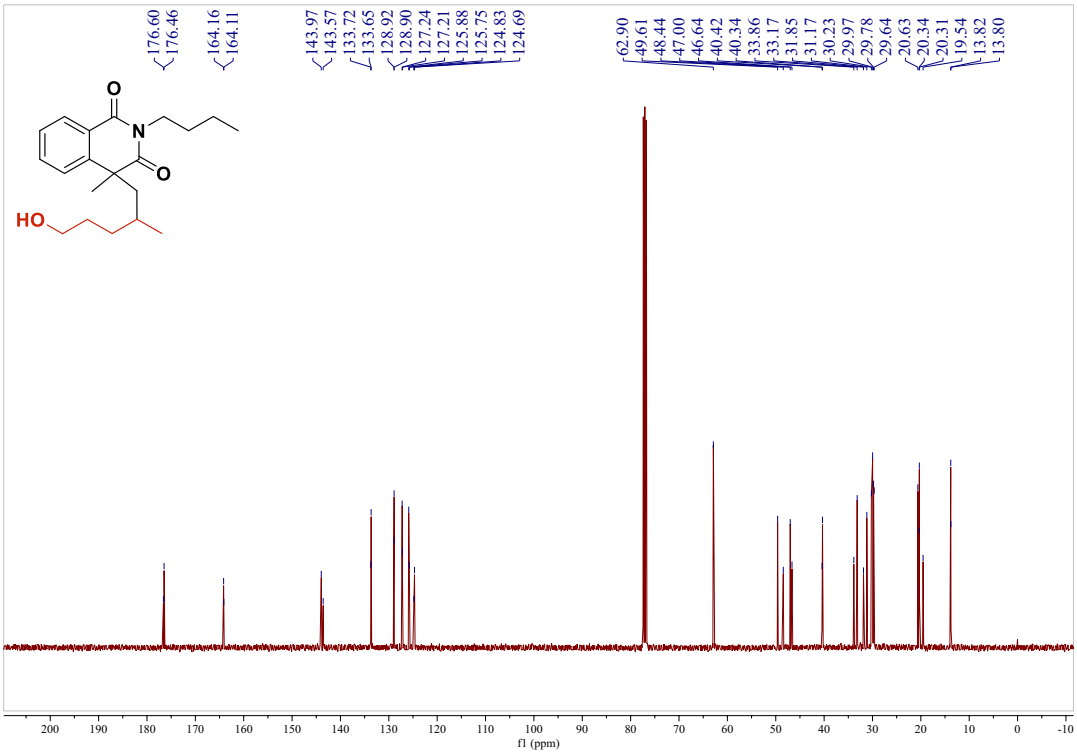
^{1}H and ^{13}C NMR spectra of **3ka**:



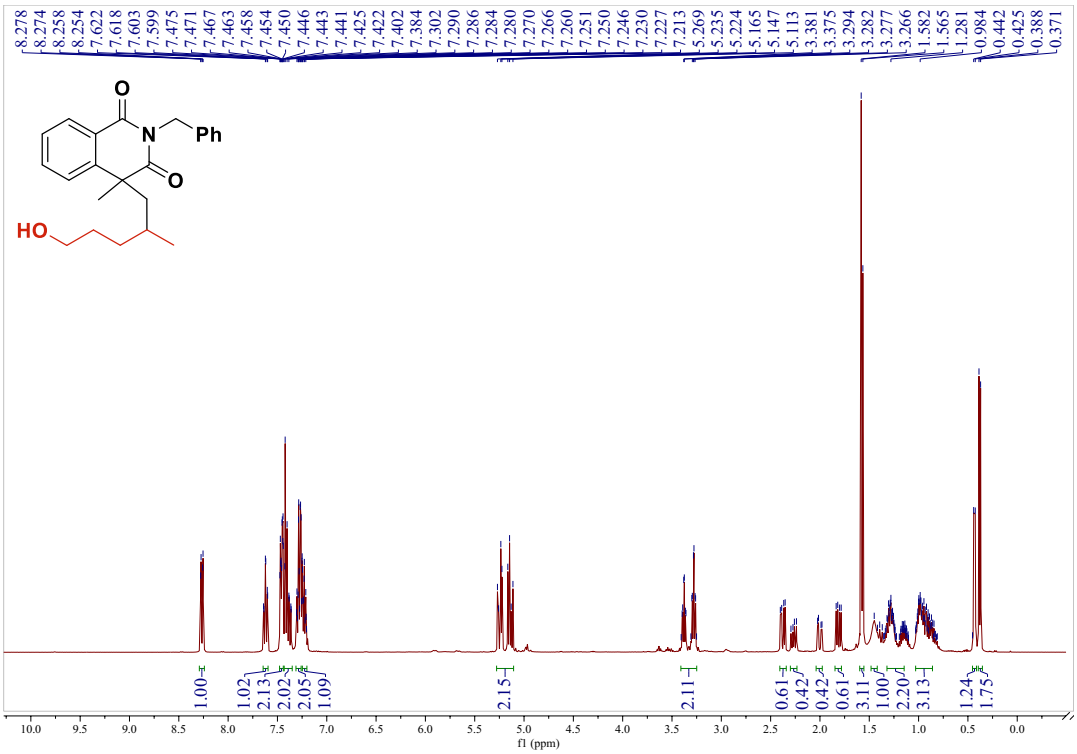


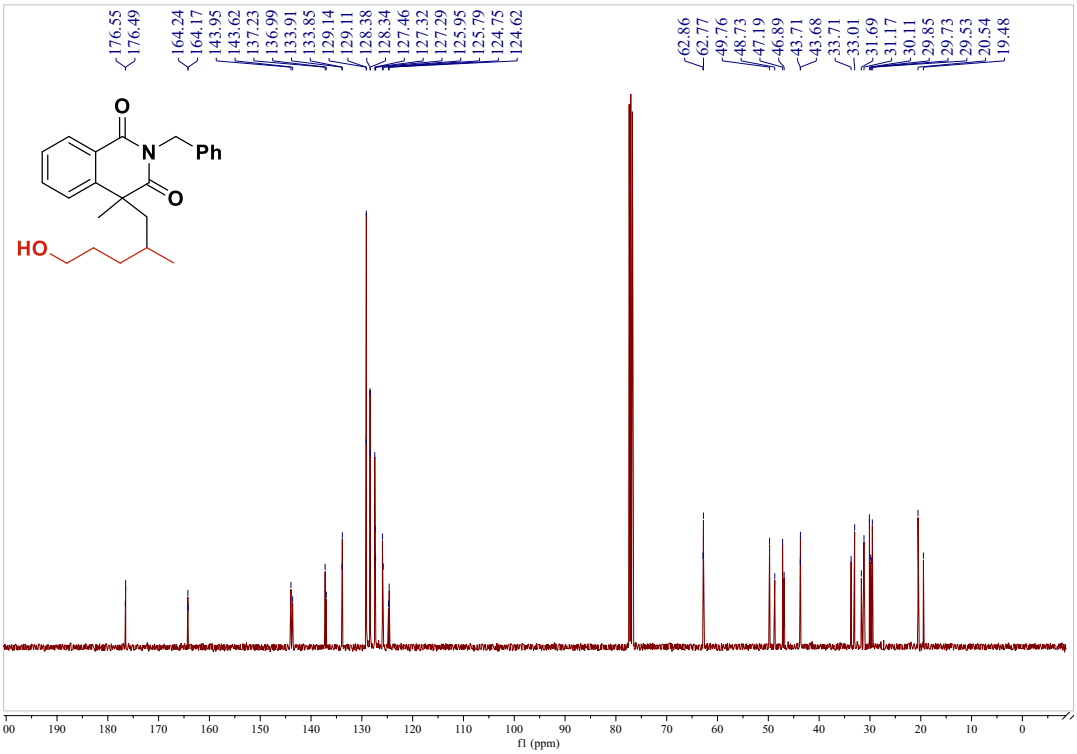
^{1}H and ^{13}C NMR spectra of **3la**:



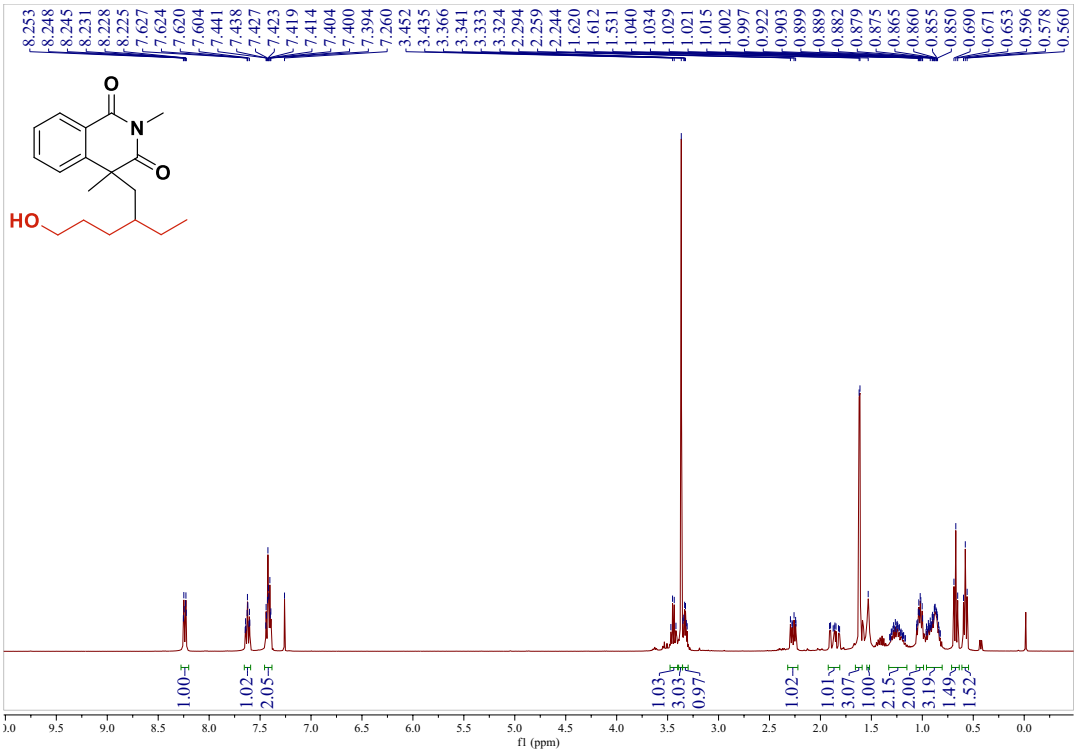


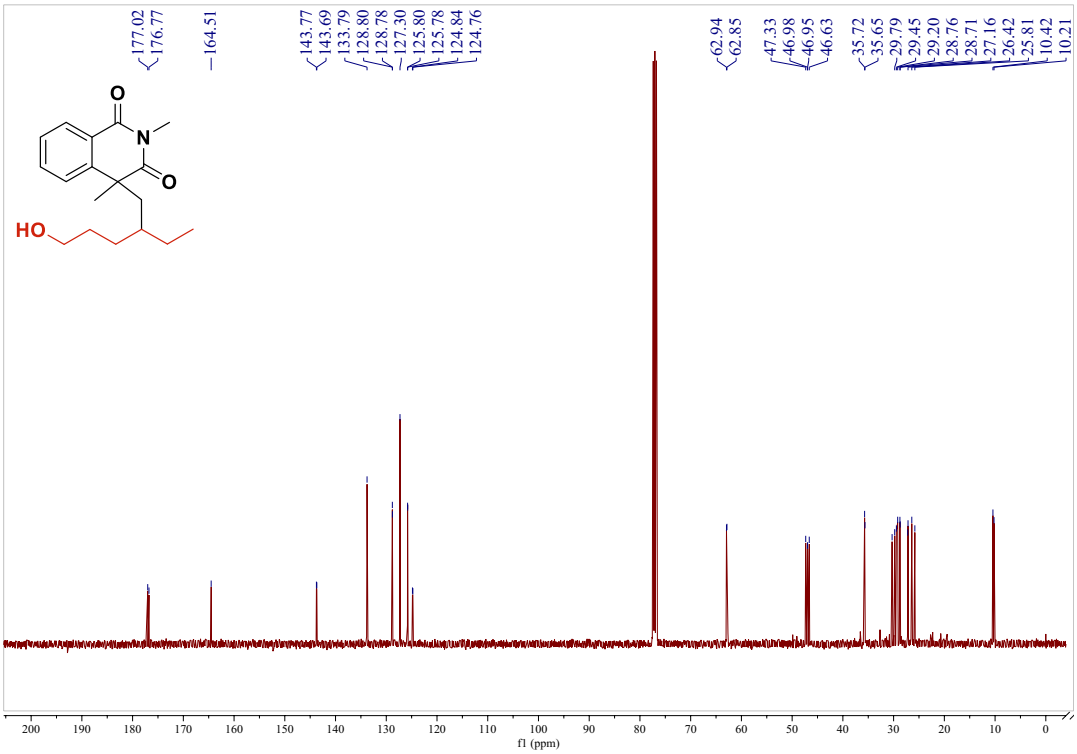
^{1}H and ^{13}C NMR spectra of **3ma**:



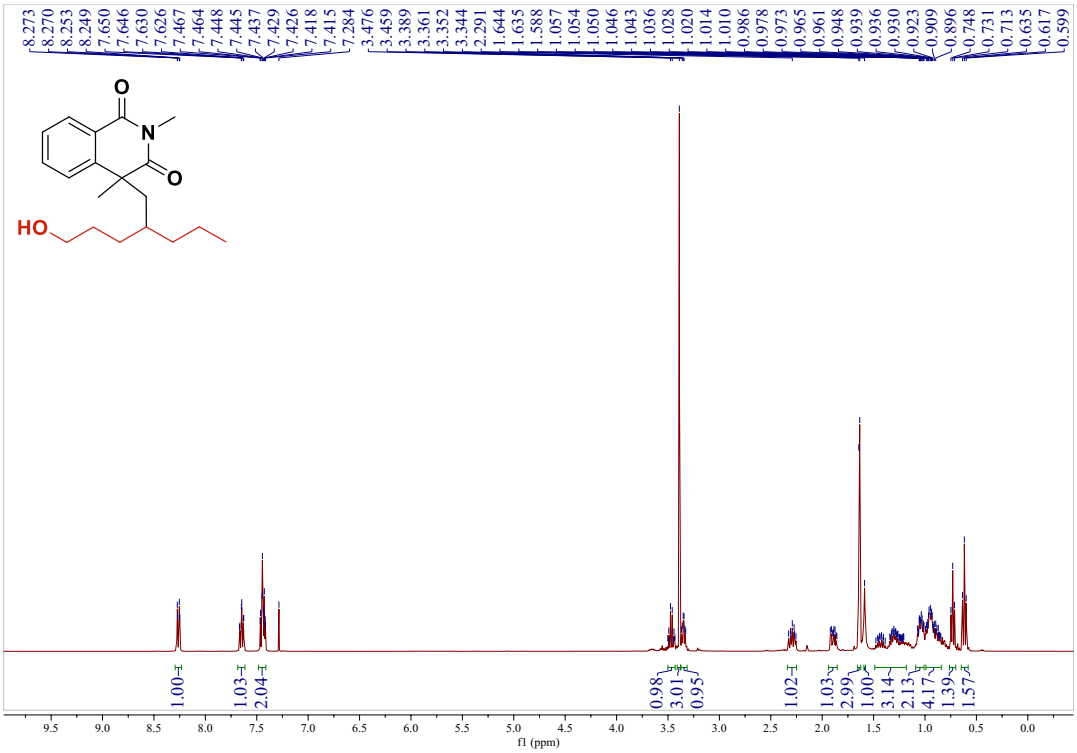


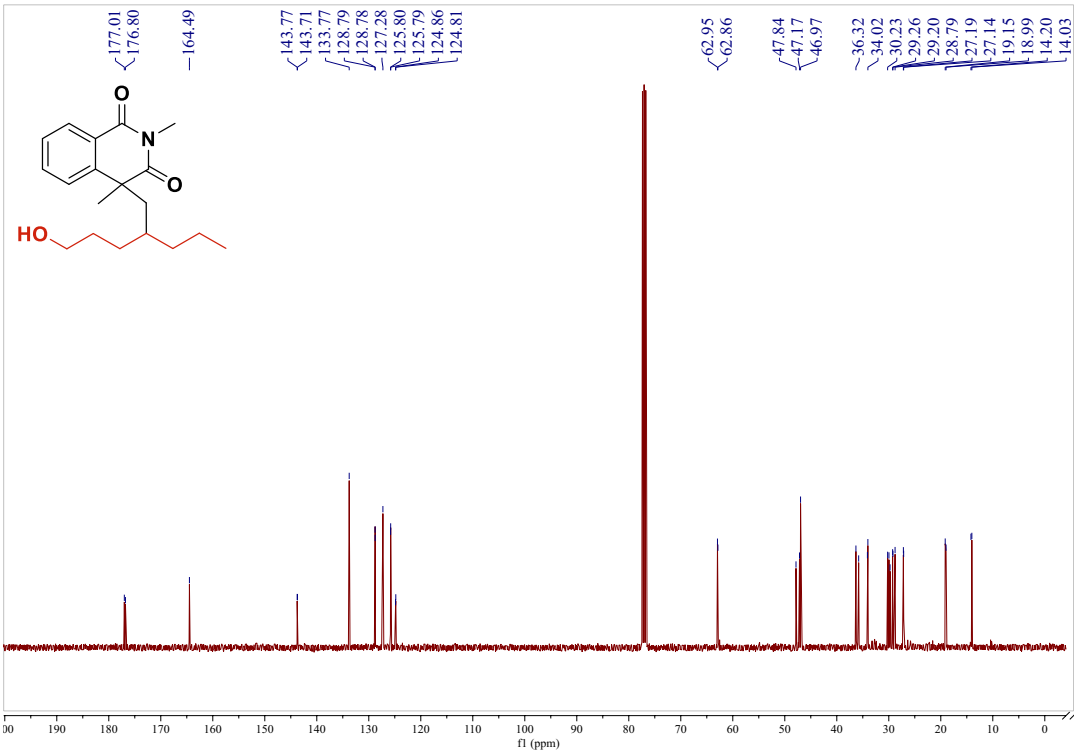
^{1}H and ^{13}C NMR spectra of **3ab**:



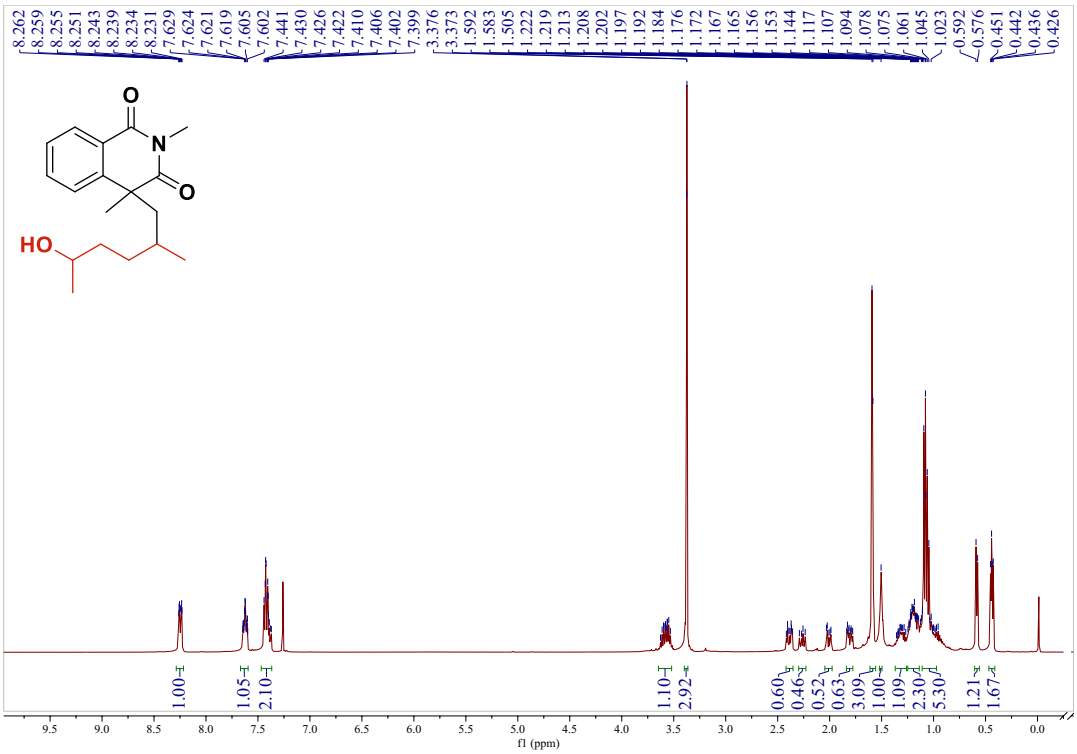


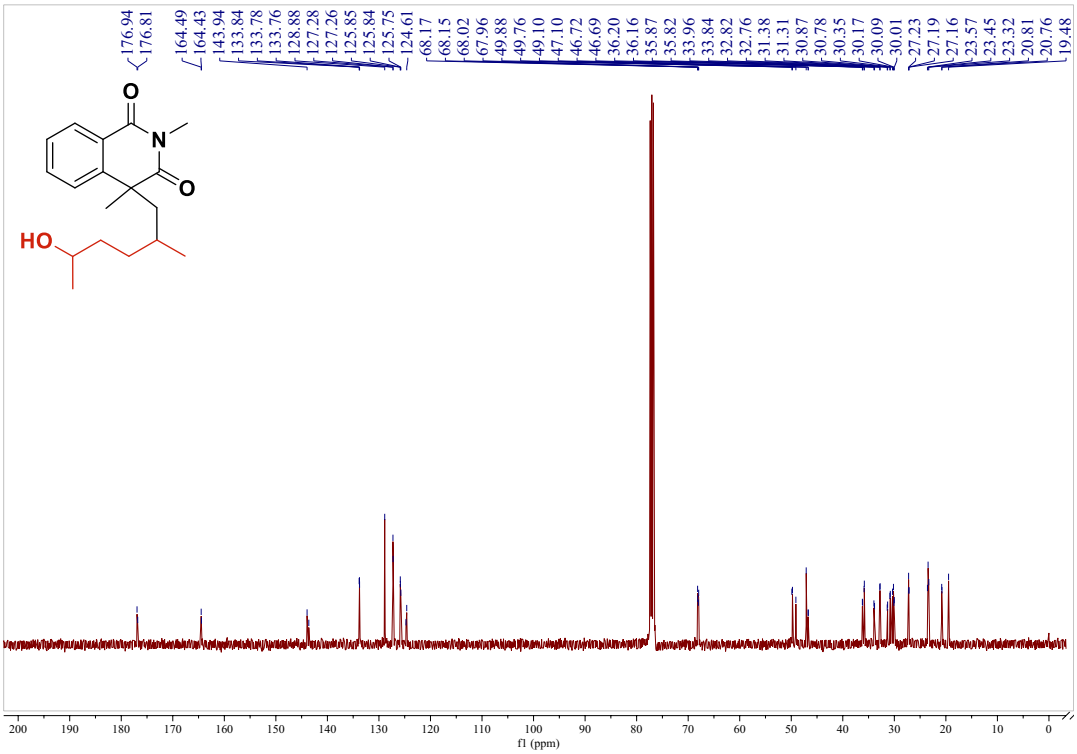
^{1}H and ^{13}C NMR spectra of **3ac**:



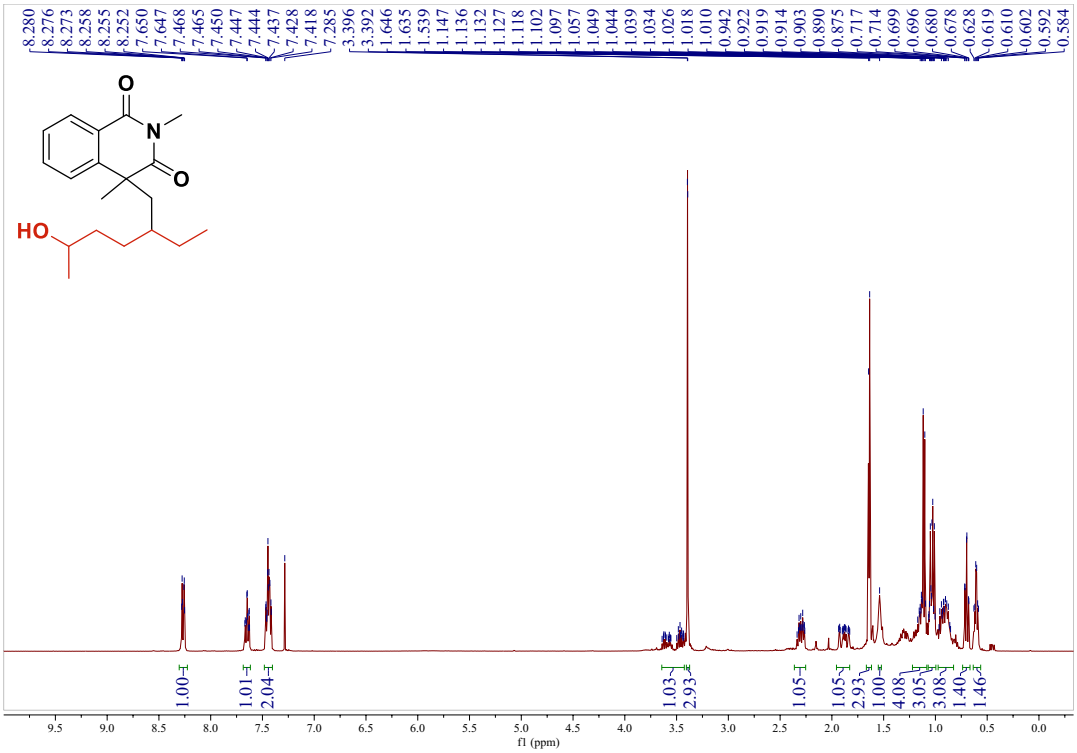


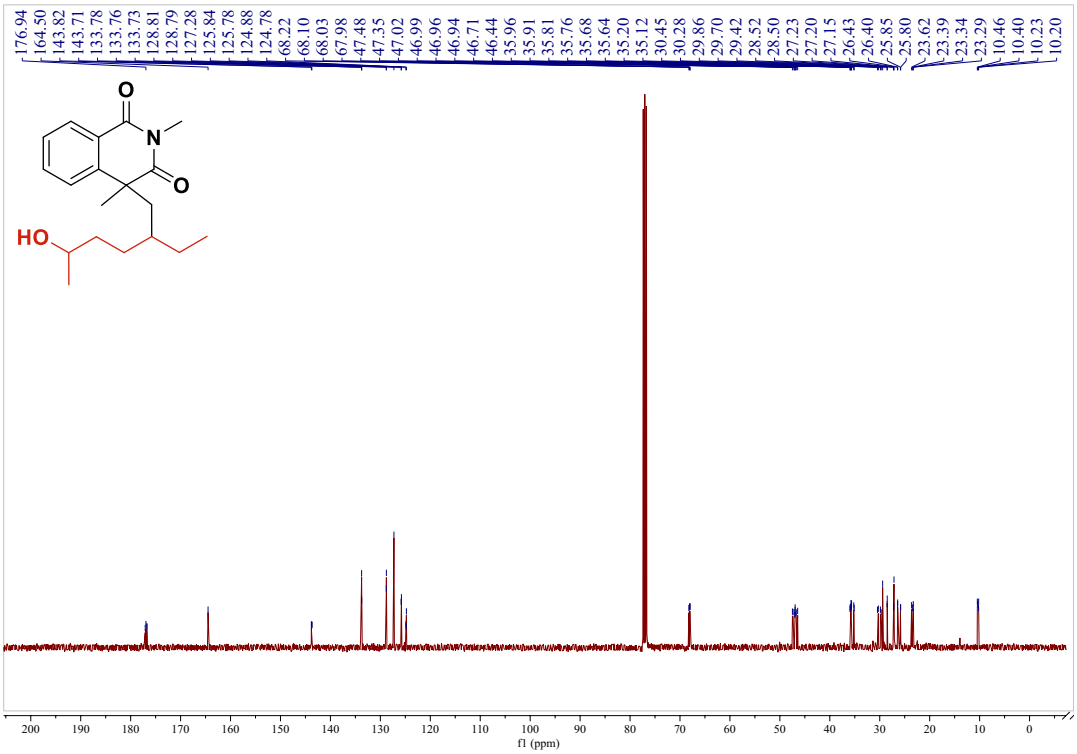
^{1}H and ^{13}C NMR spectra of **3ad**:



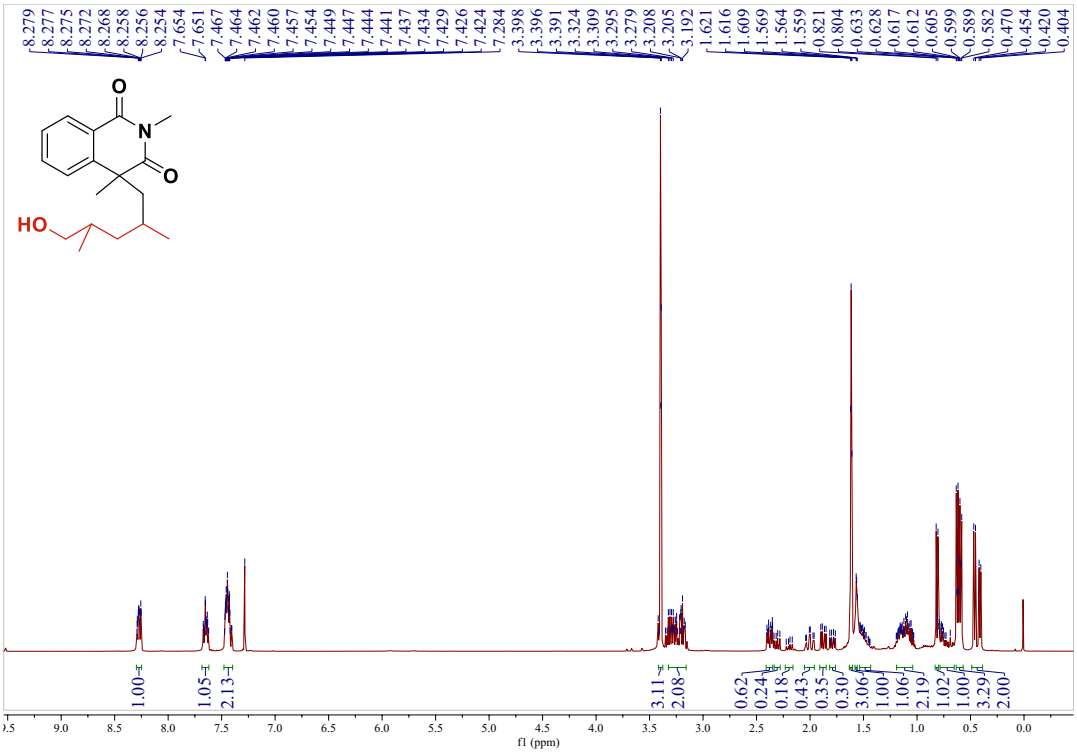


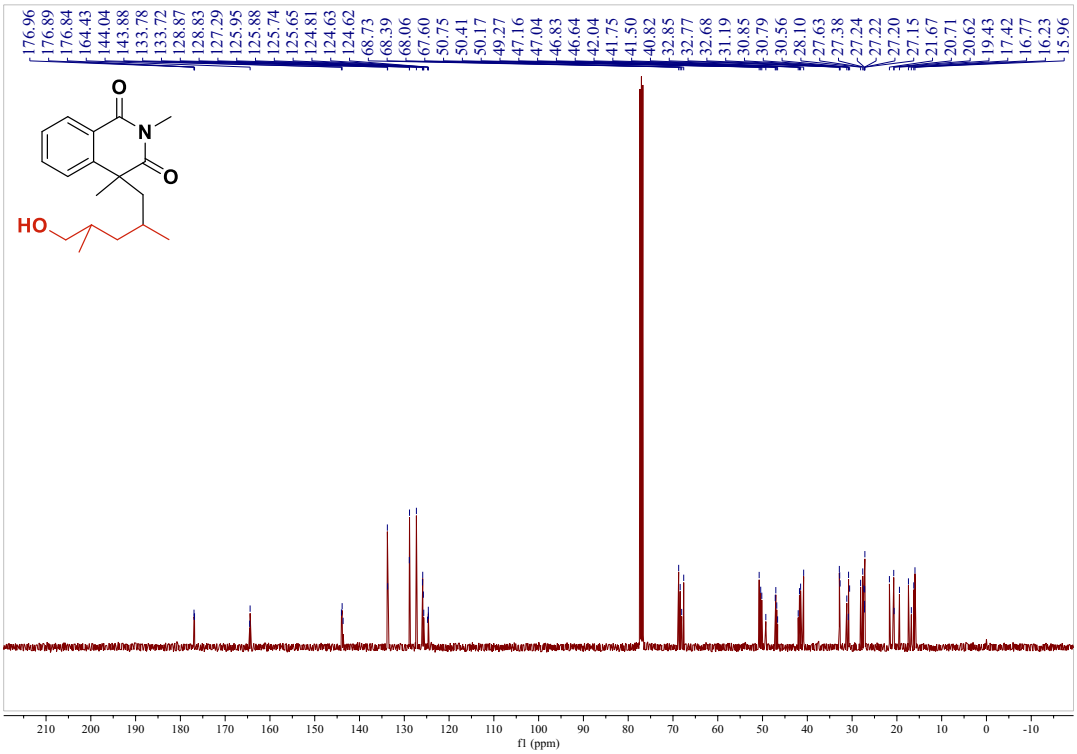
^{1}H and ^{13}C NMR spectra of **3ae**:



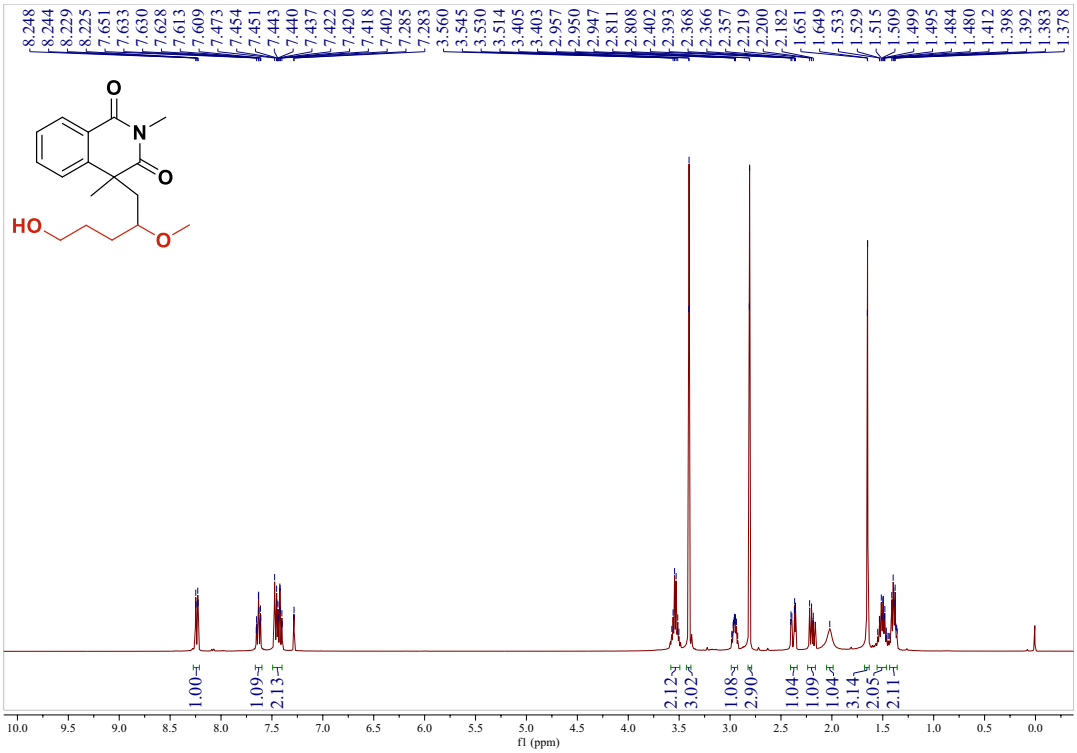


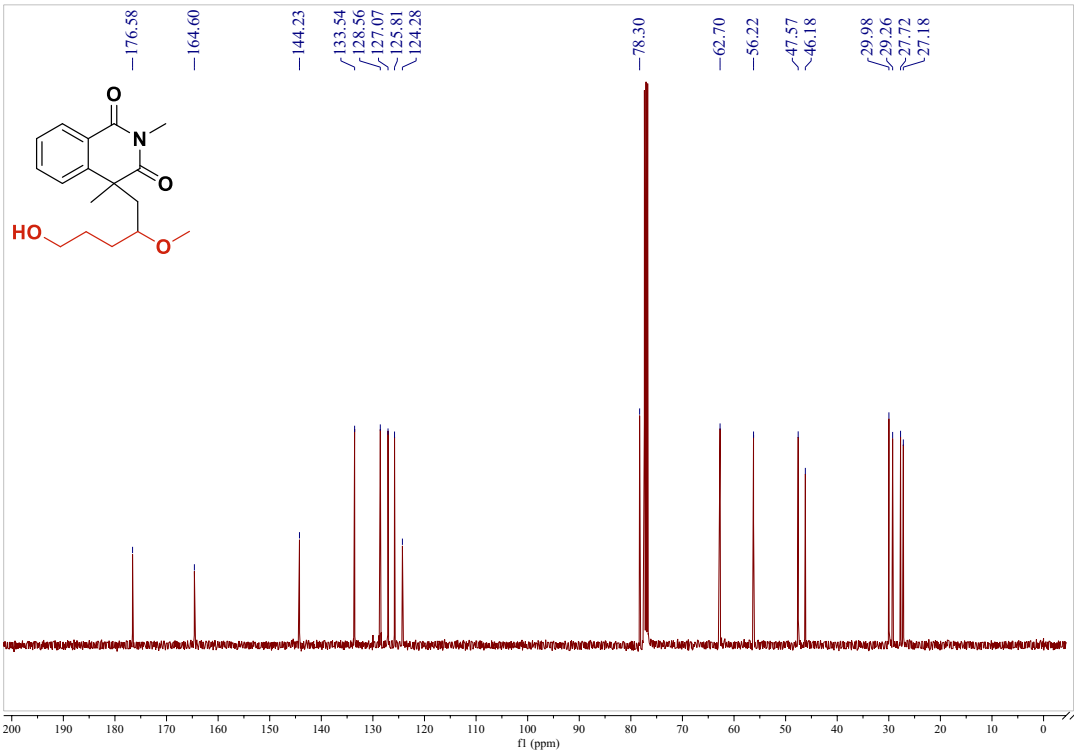
^{1}H and ^{13}C NMR spectra of **3af**:



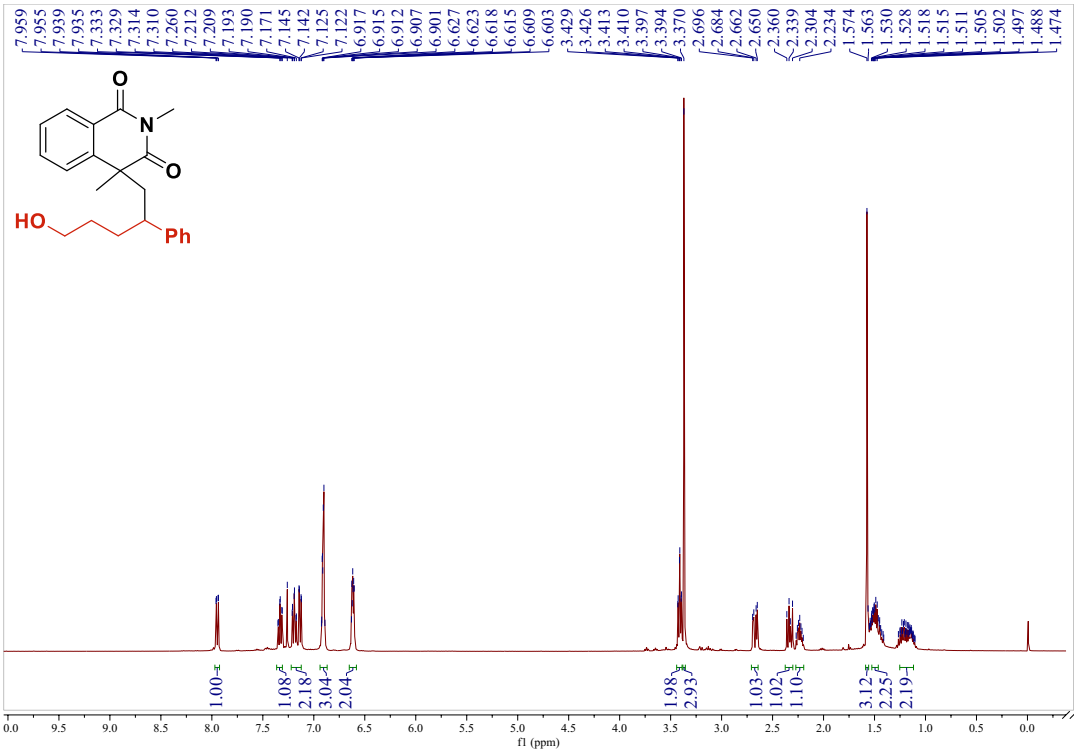


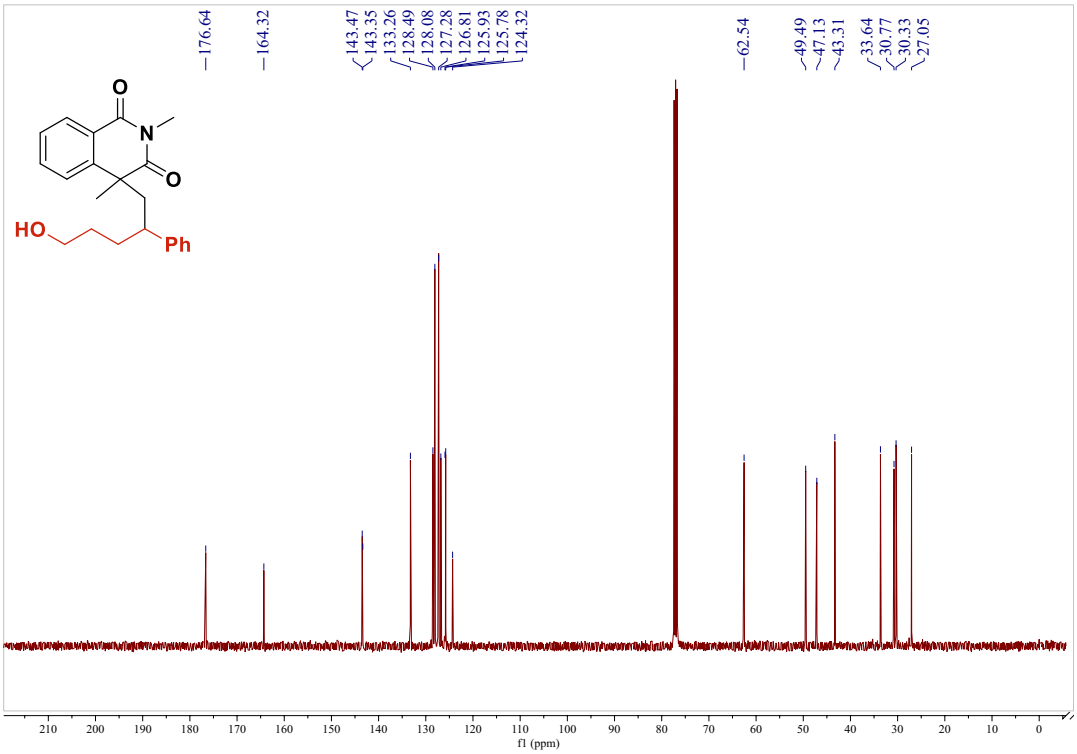
^{1}H and ^{13}C NMR spectra of **3ag**:



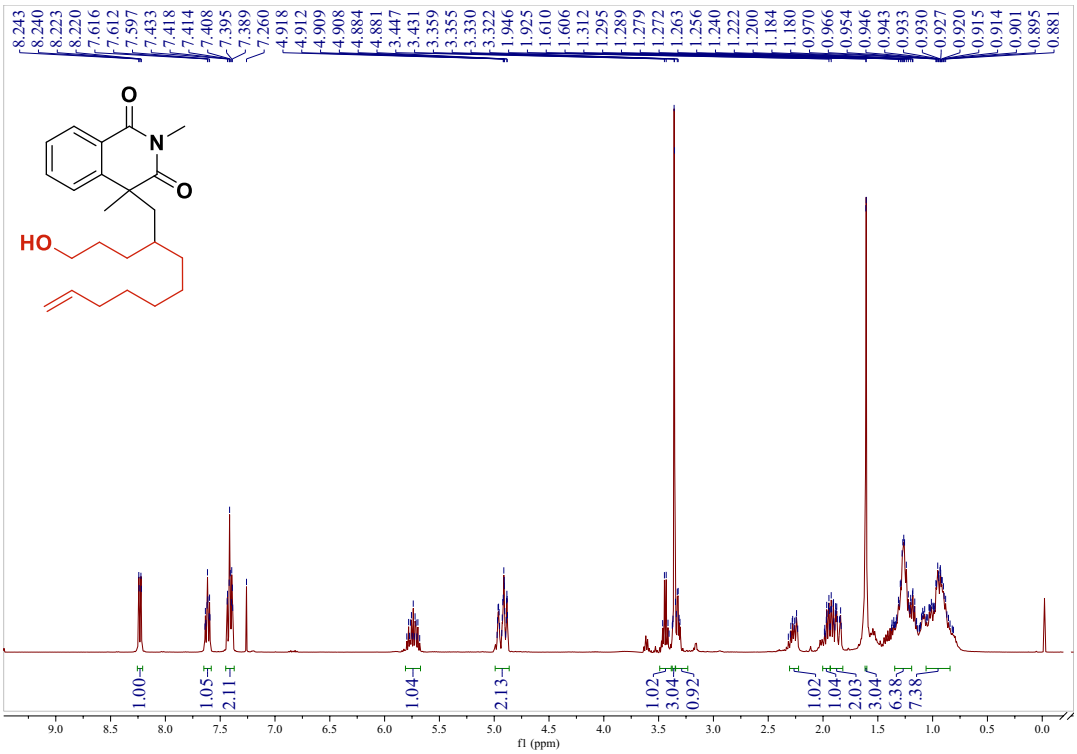


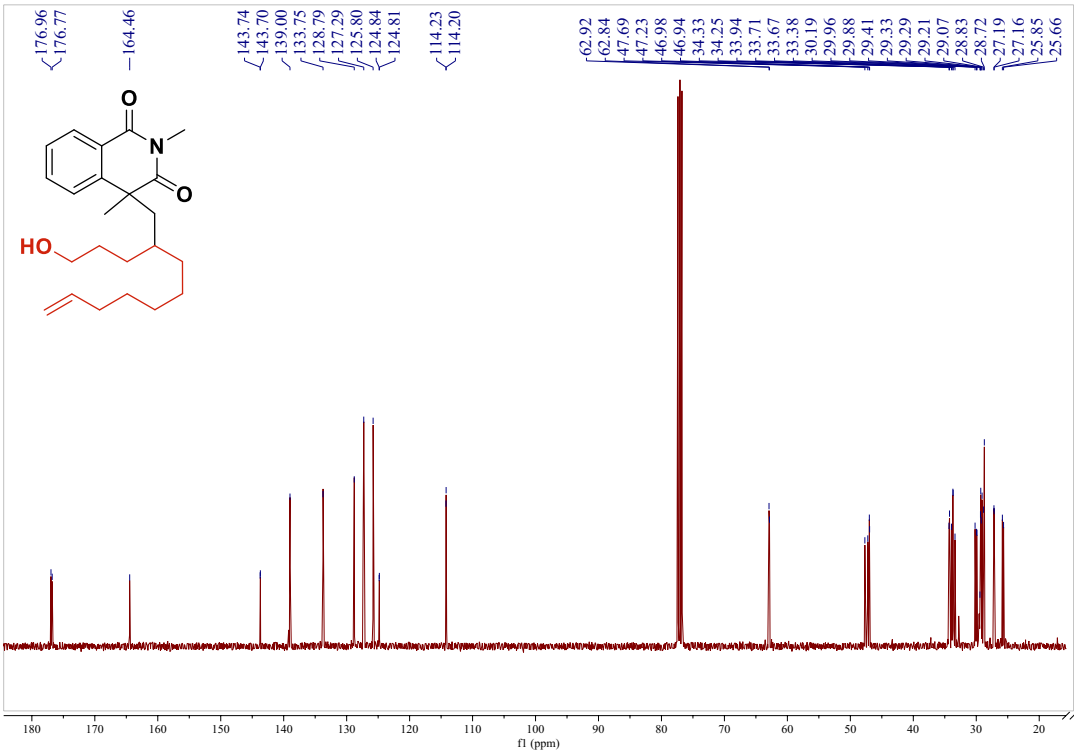
^{1}H and ^{13}C NMR spectra of **3ah**:



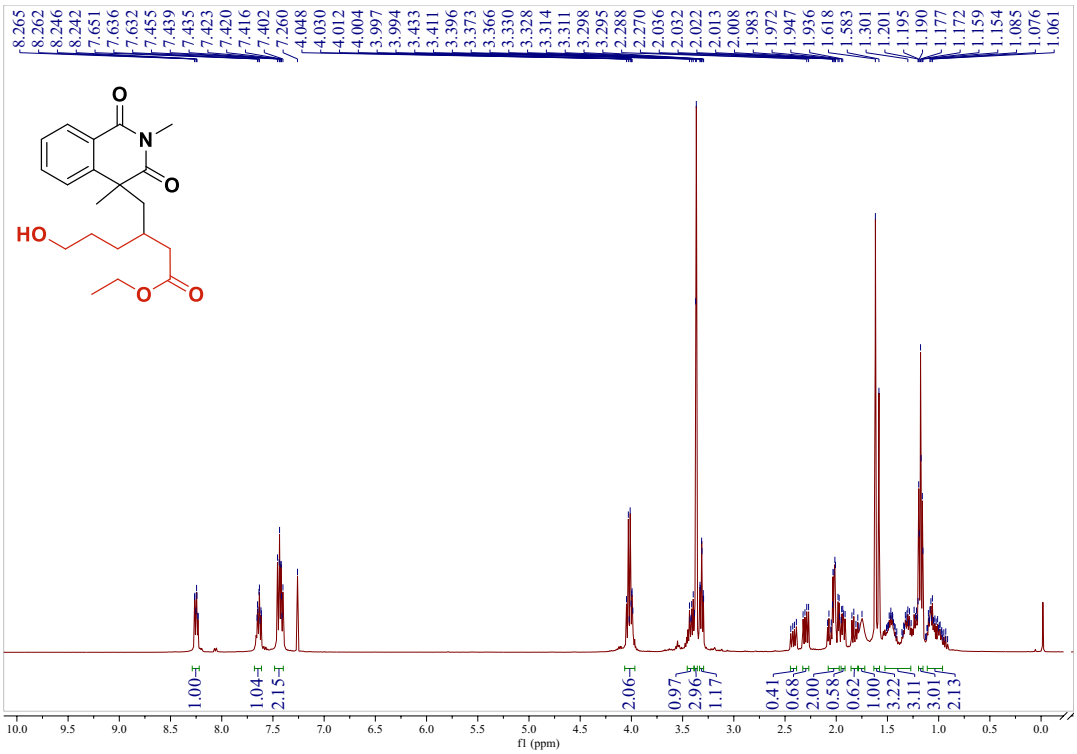


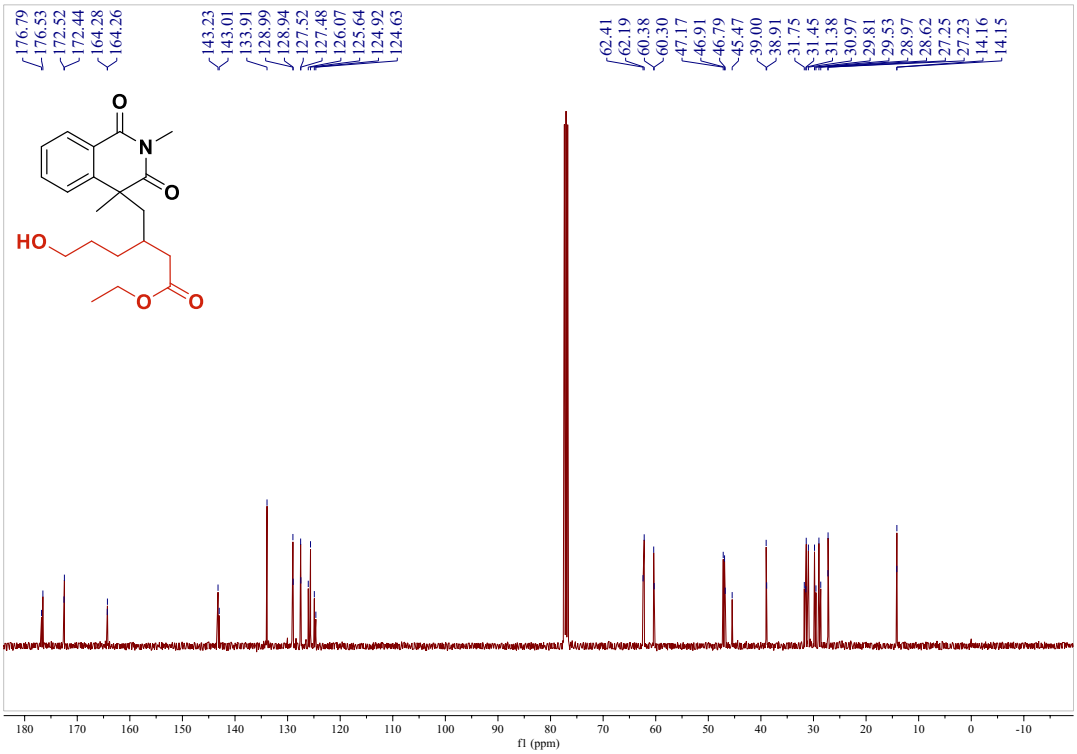
^{1}H and ^{13}C NMR spectra of **3ai**:



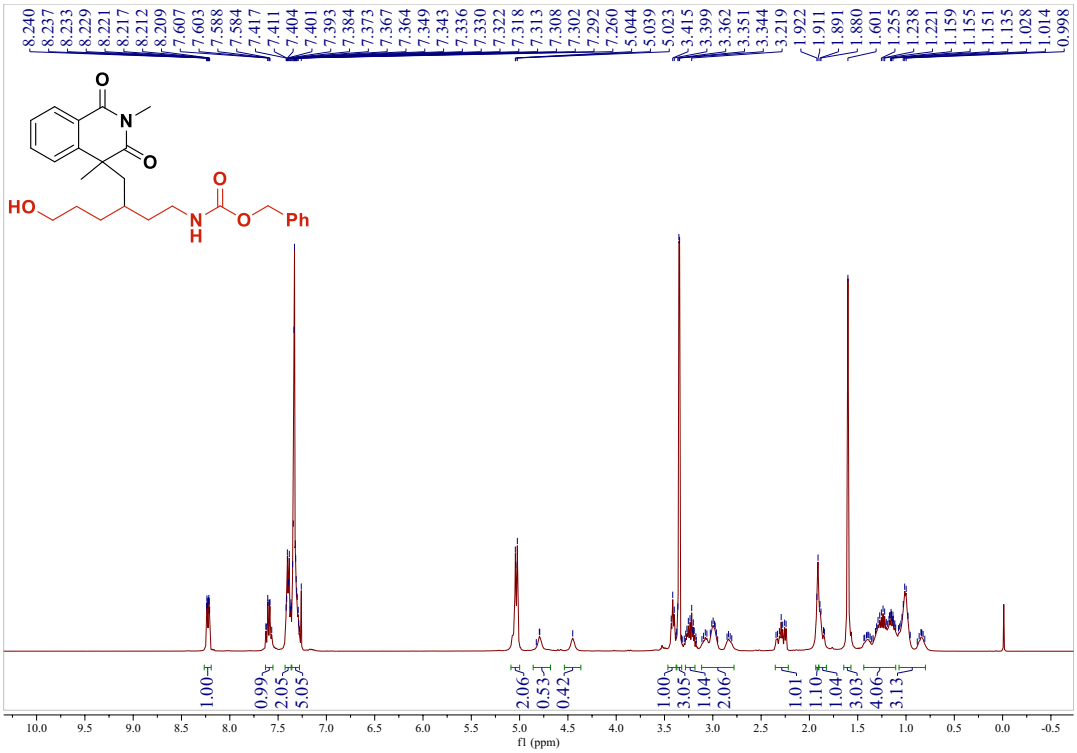


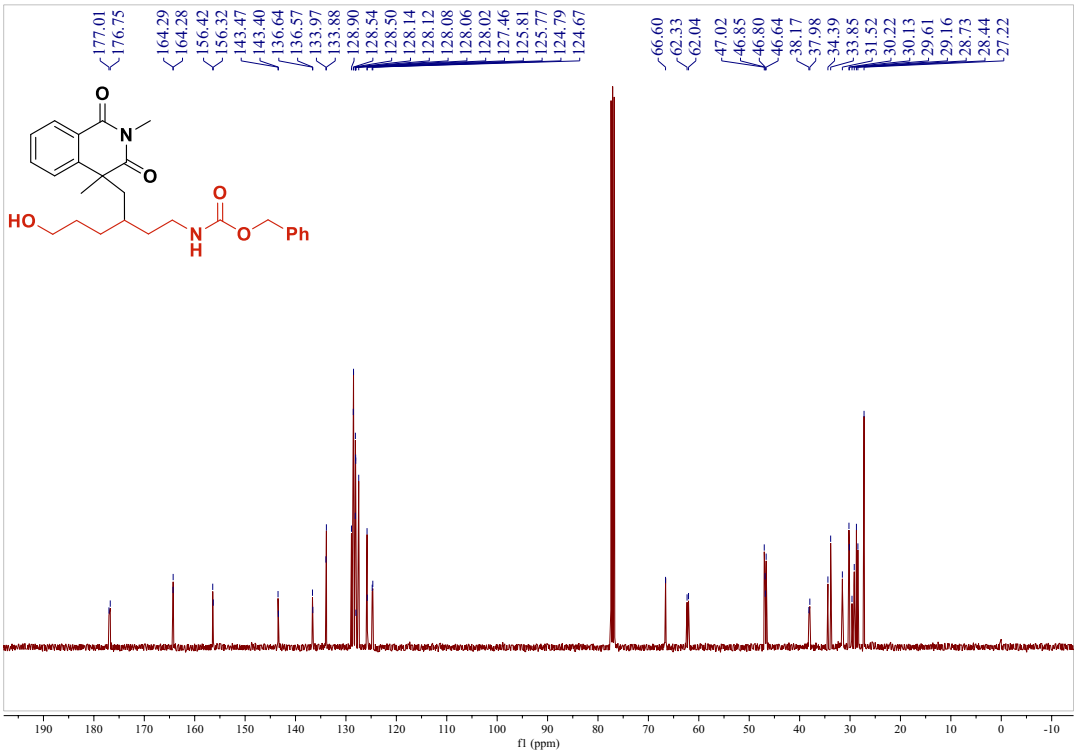
^{1}H and ^{13}C NMR spectra of **3aj**:



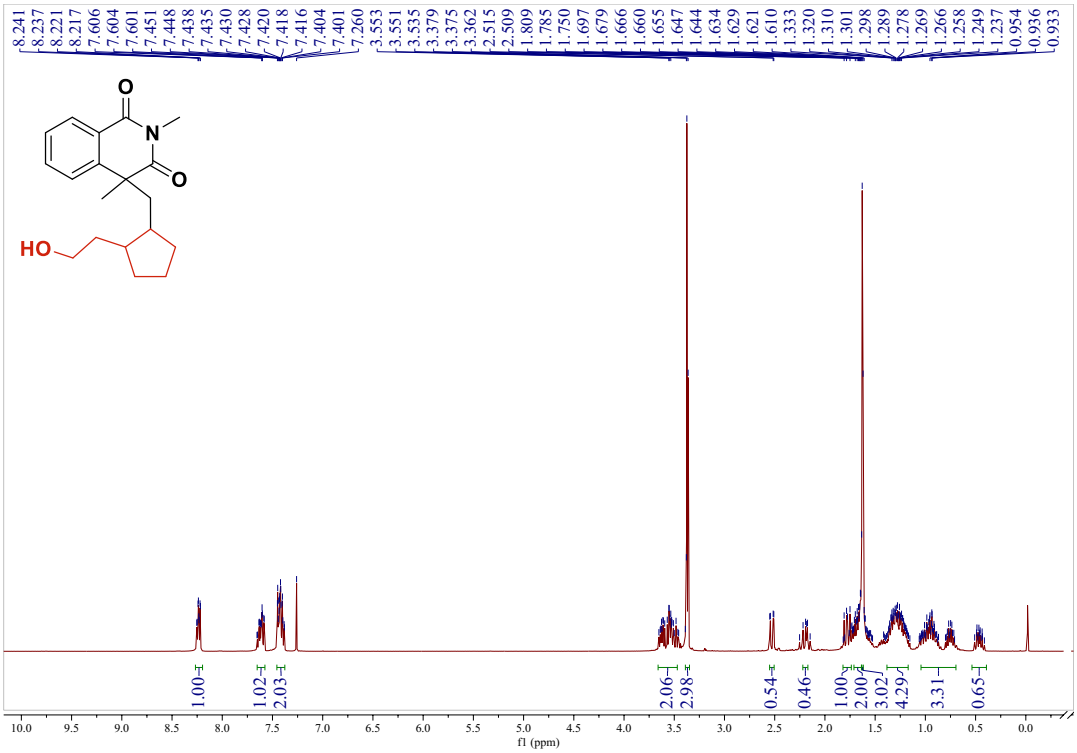


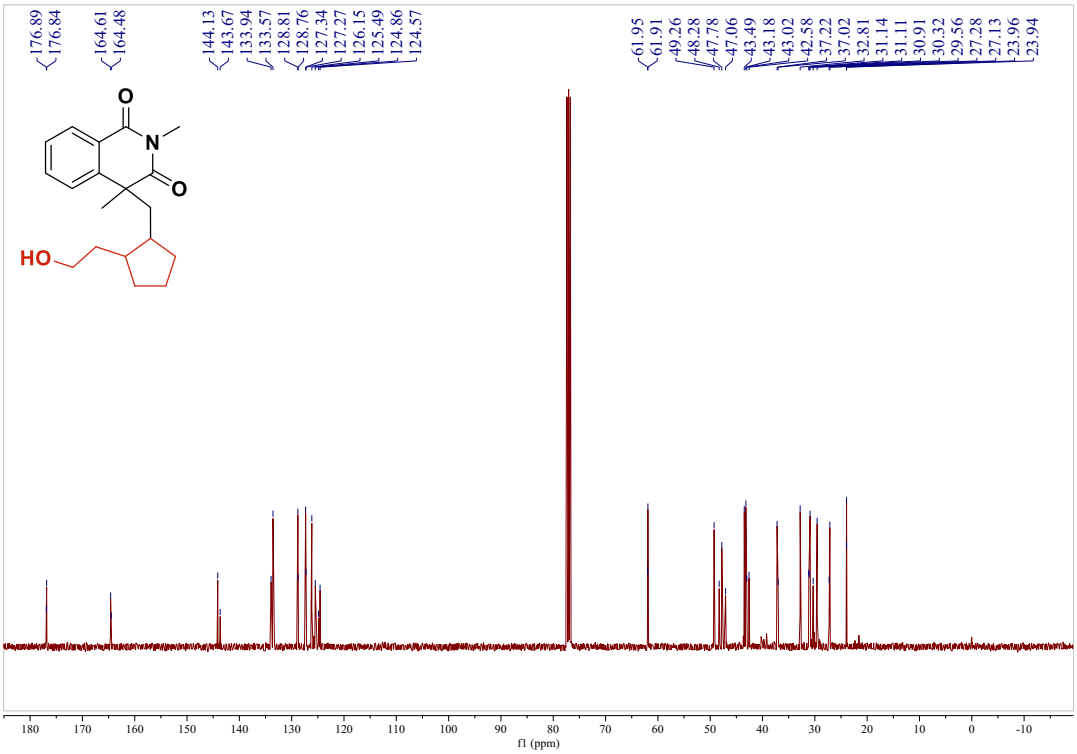
^{1}H and ^{13}C NMR spectra of **3ak**:



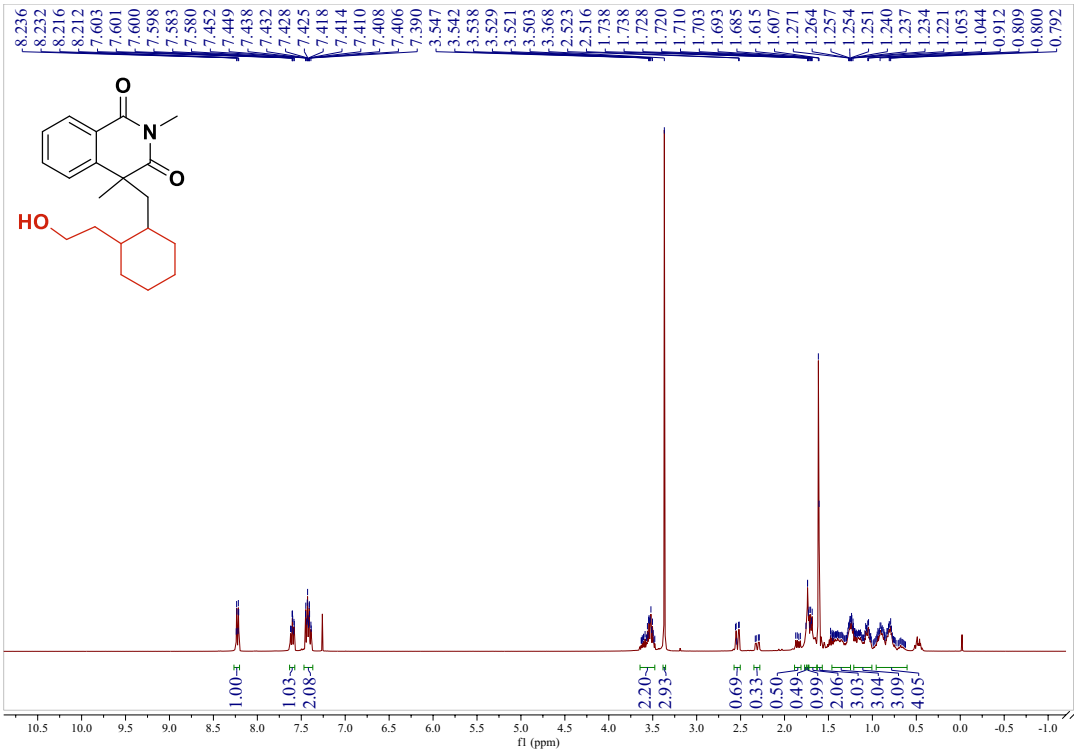


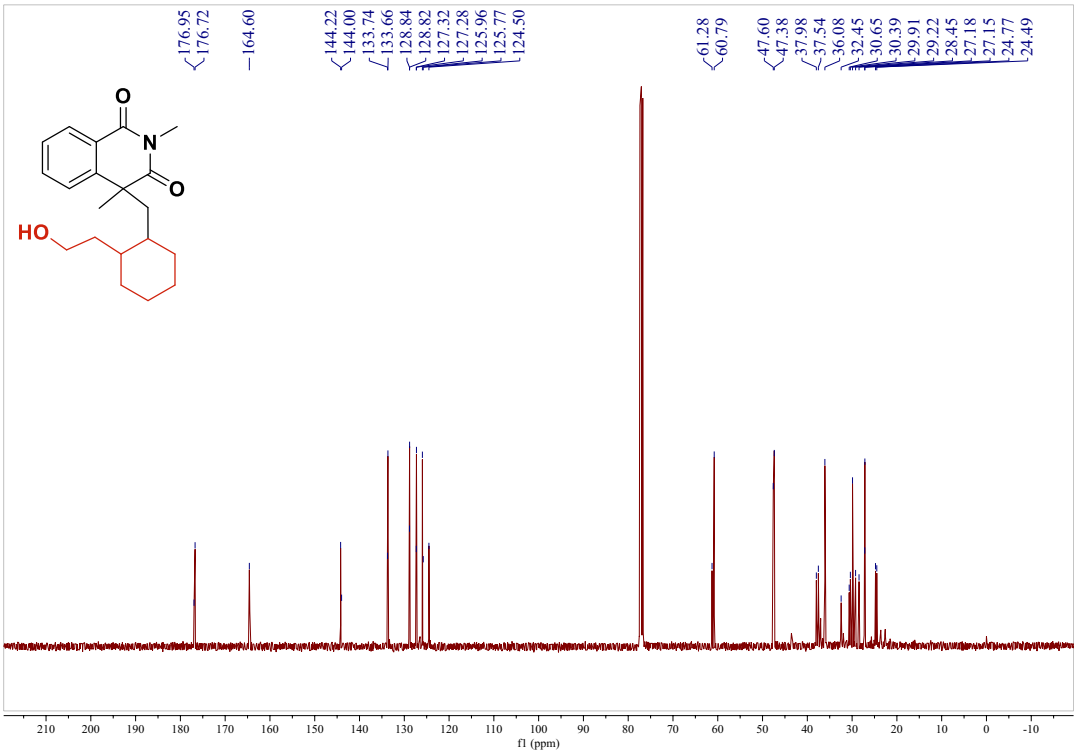
^{1}H and ^{13}C NMR spectra of **3al**:



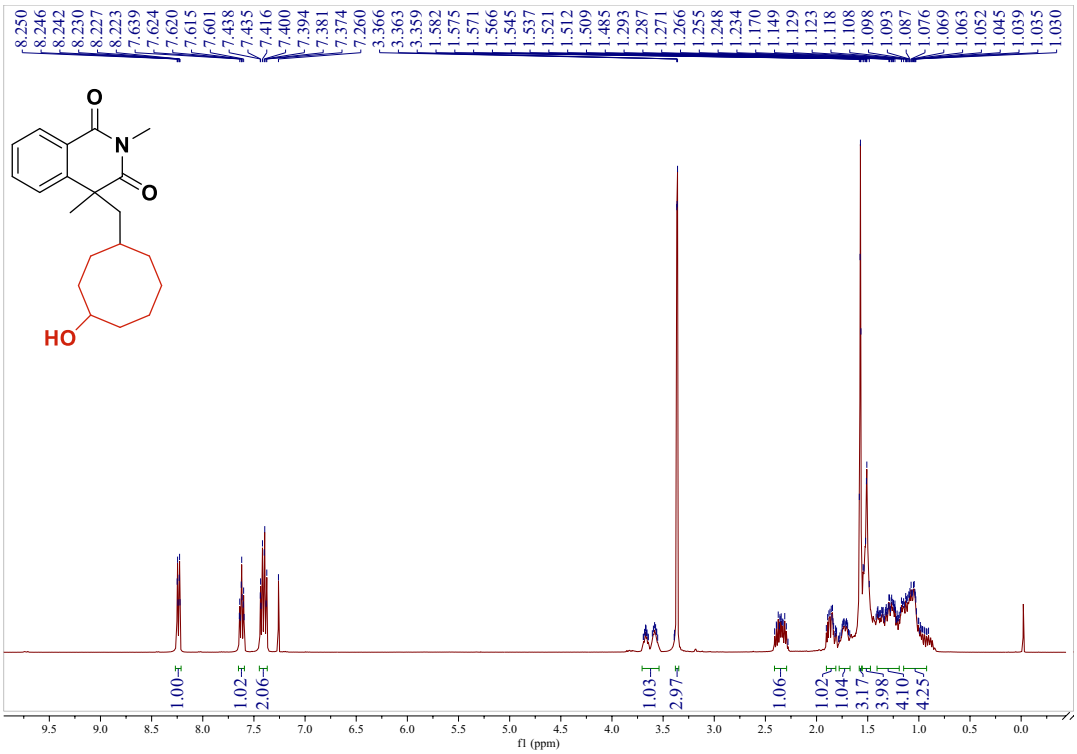


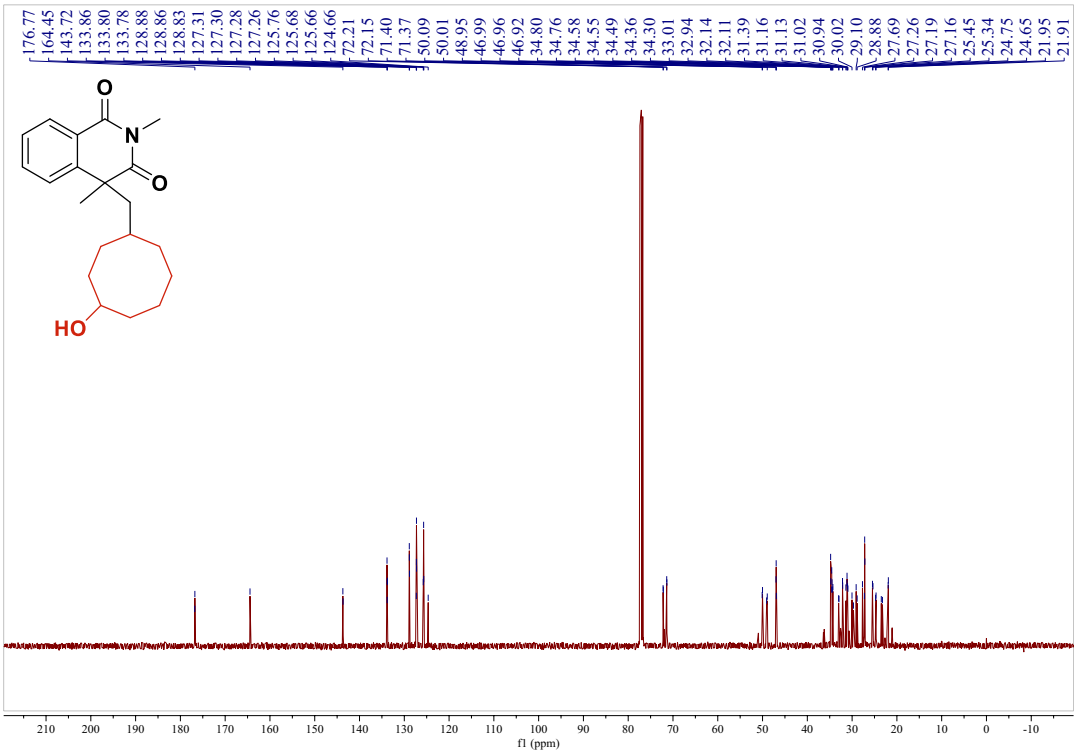
^{1}H and ^{13}C NMR spectra of **3am**:



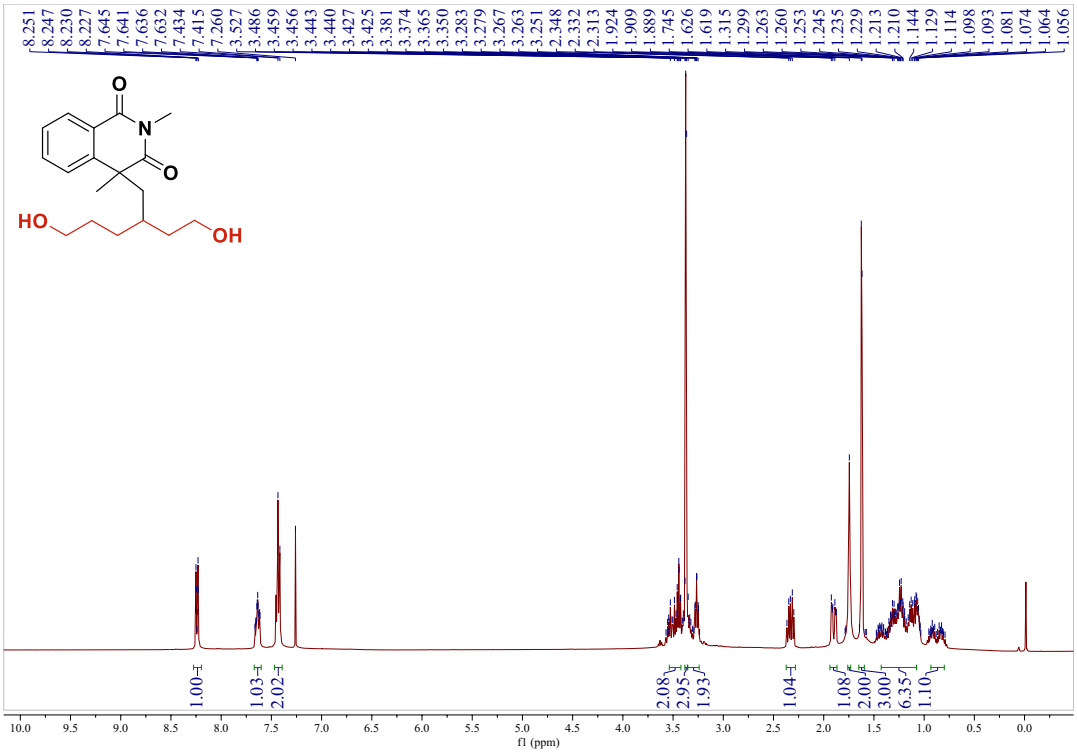


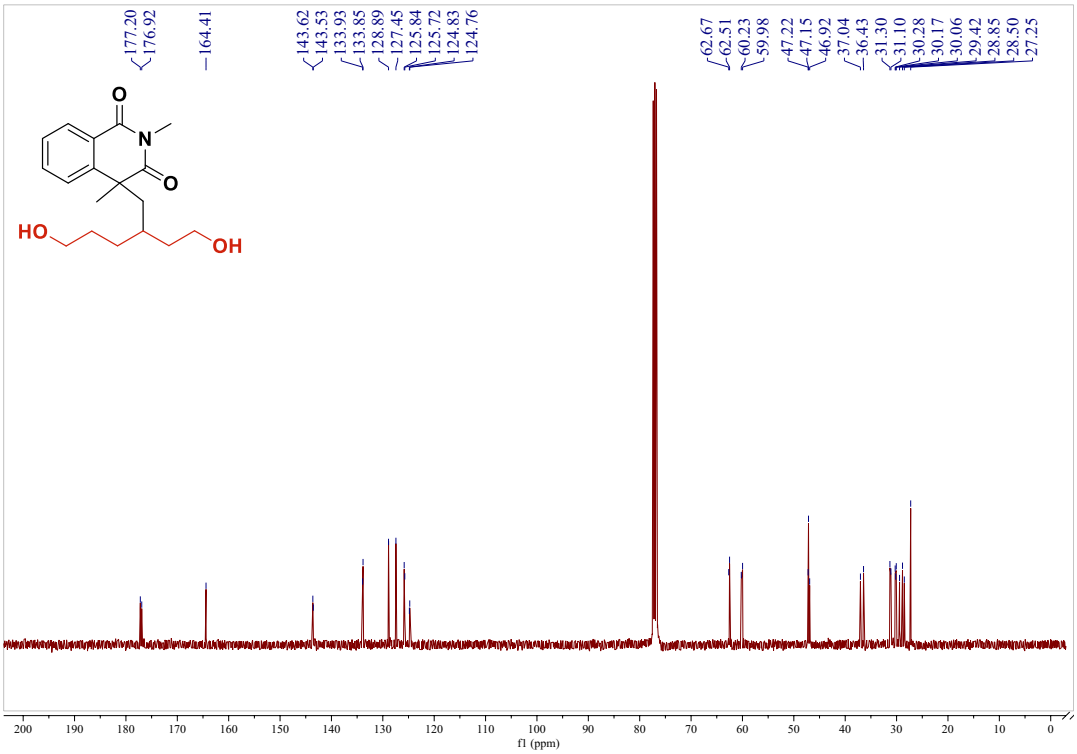
^{1}H and ^{13}C NMR spectra of **3an**:



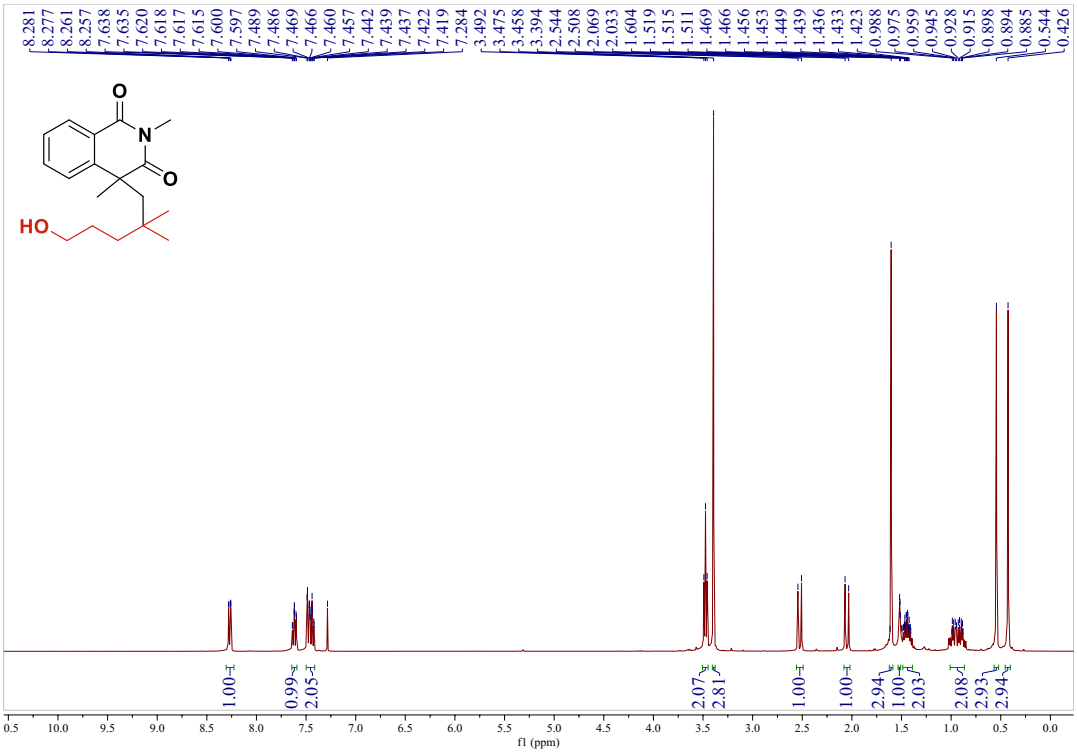


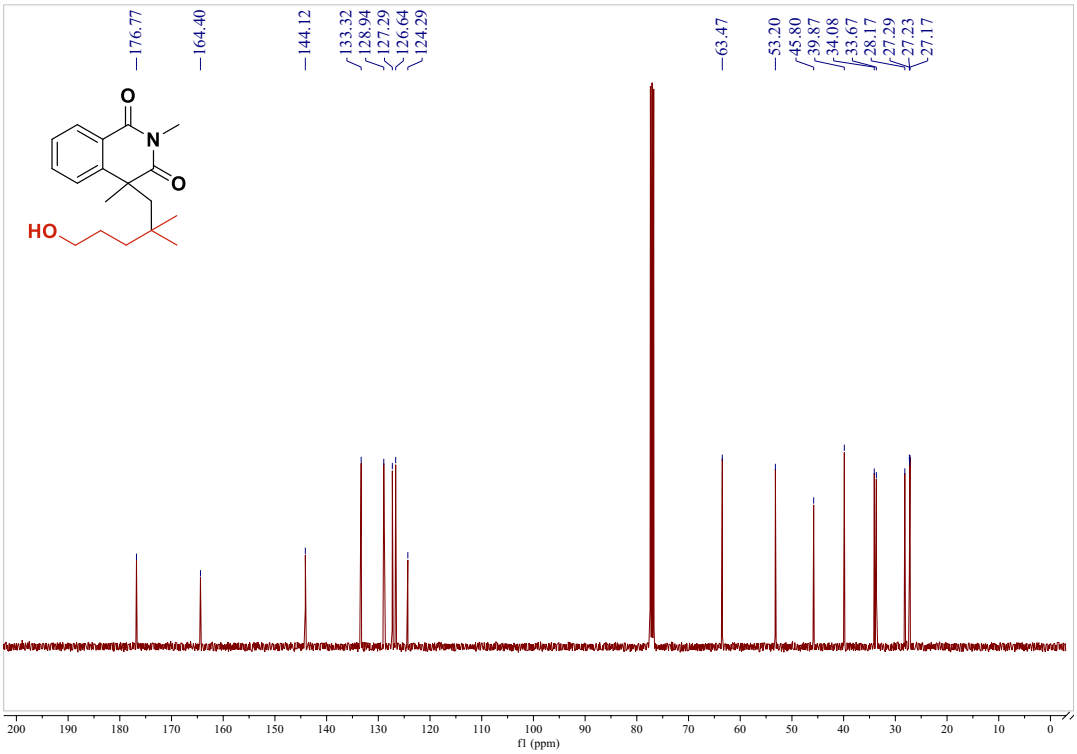
^{1}H and **^{13}C NMR** spectra of **3ao**:



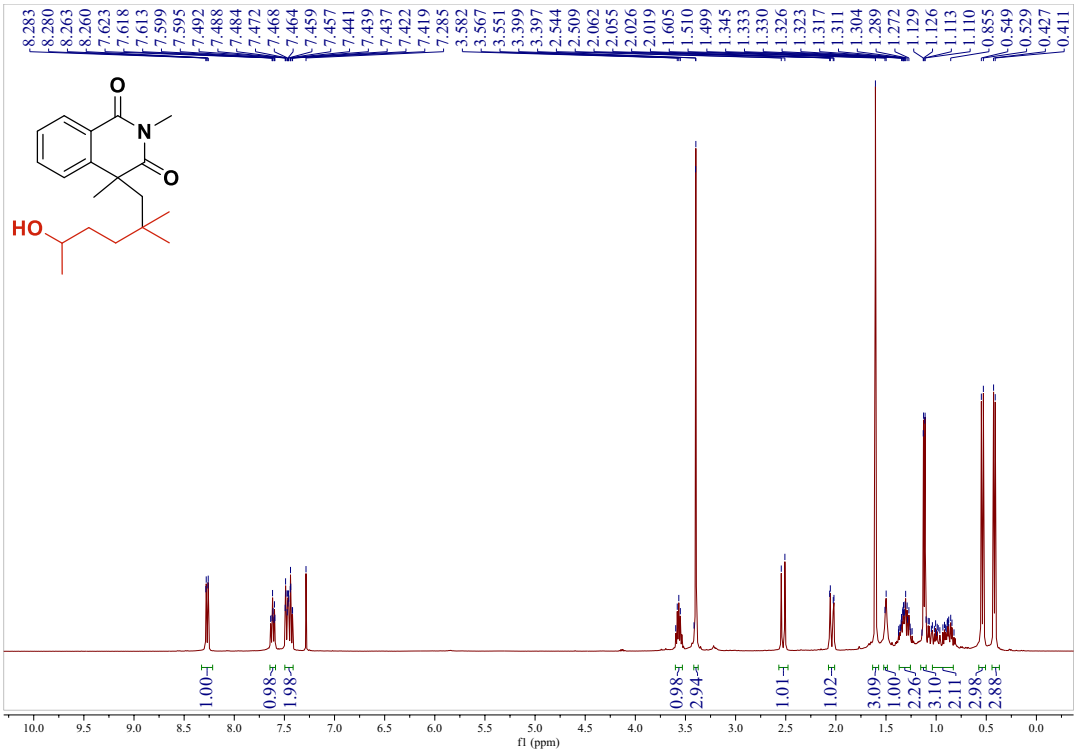


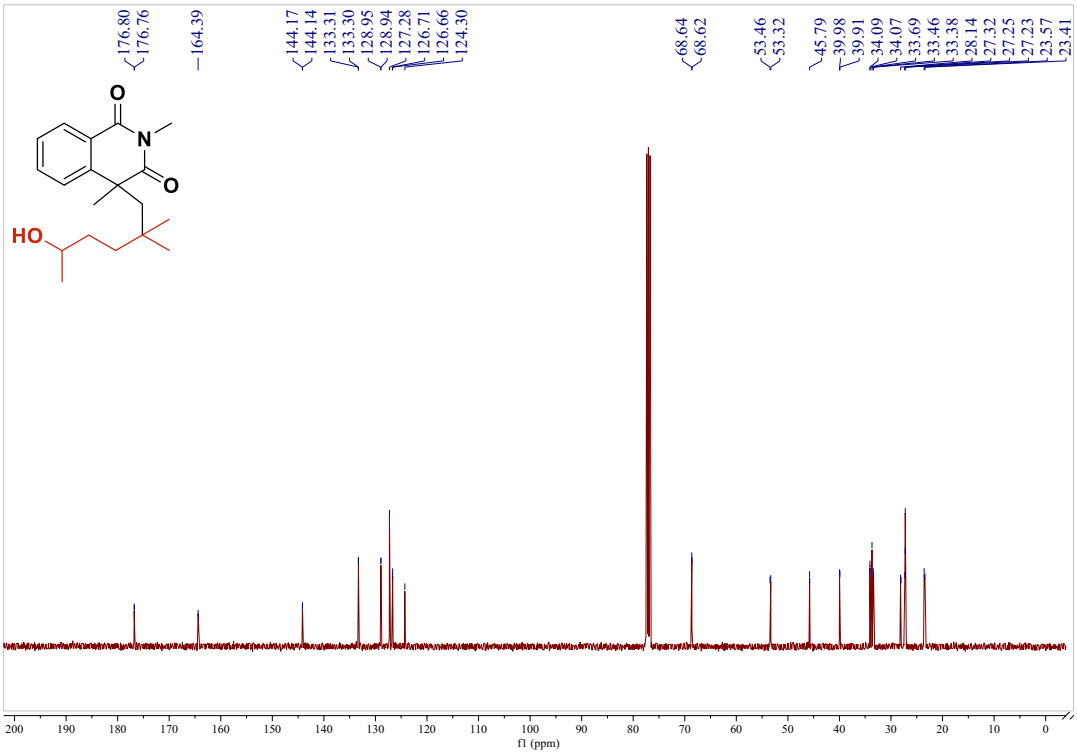
^{1}H and ^{13}C NMR spectra of **3ap**:



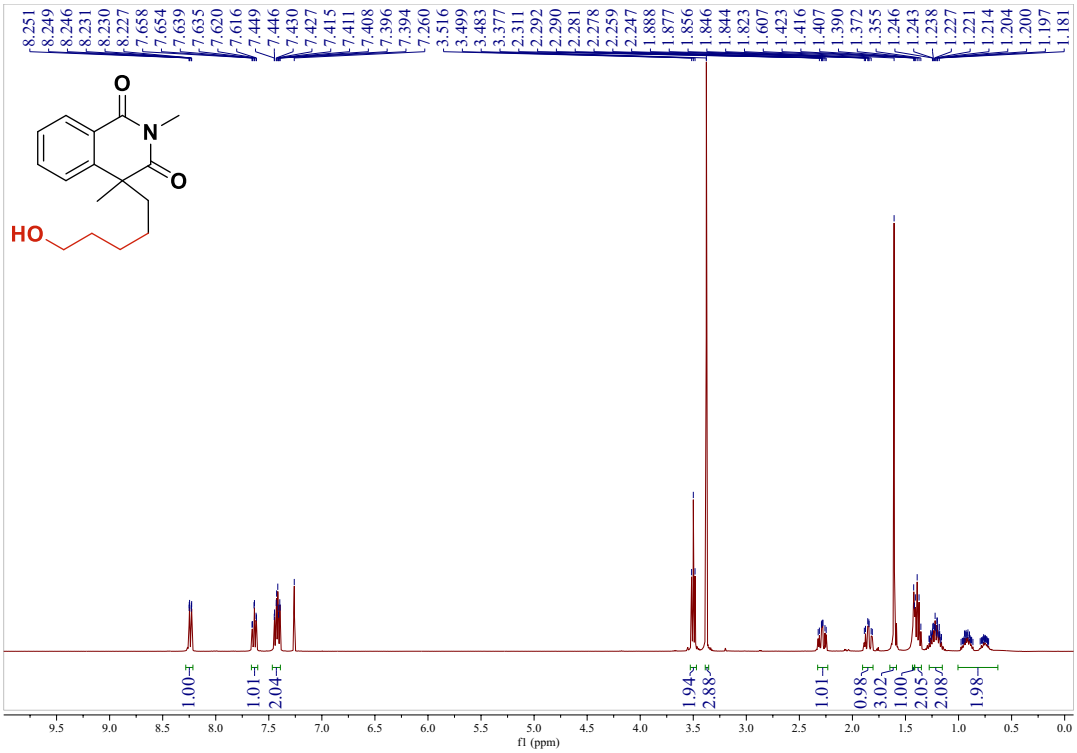


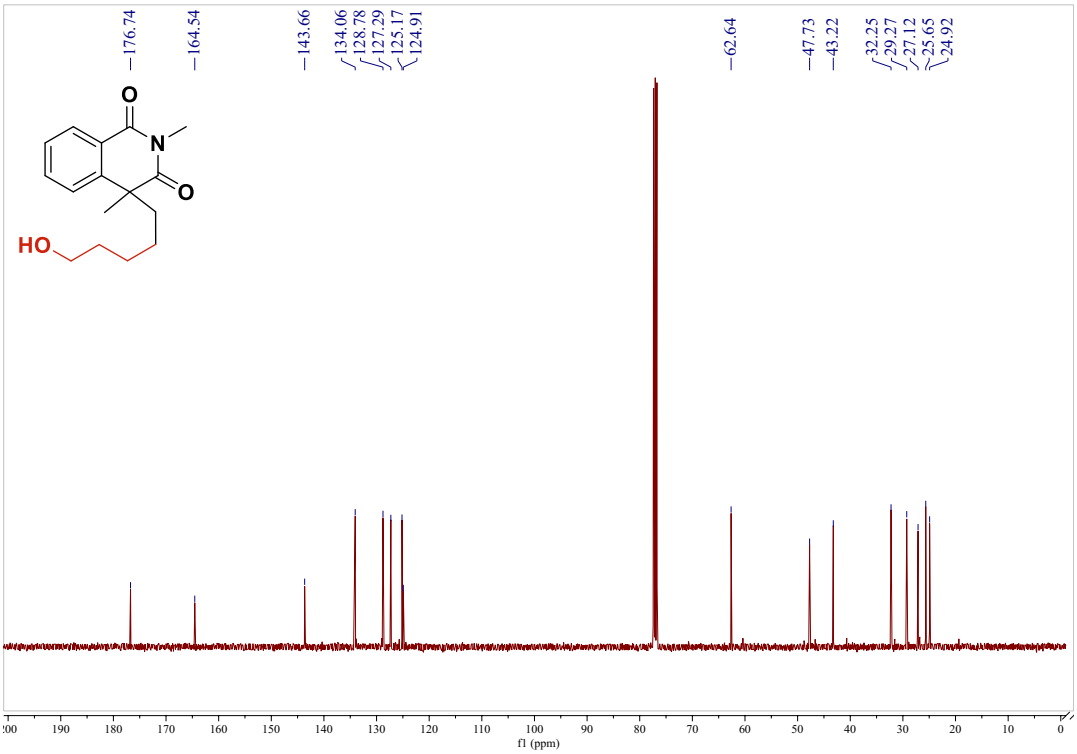
^{1}H and ^{13}C NMR spectra of **3aq**:



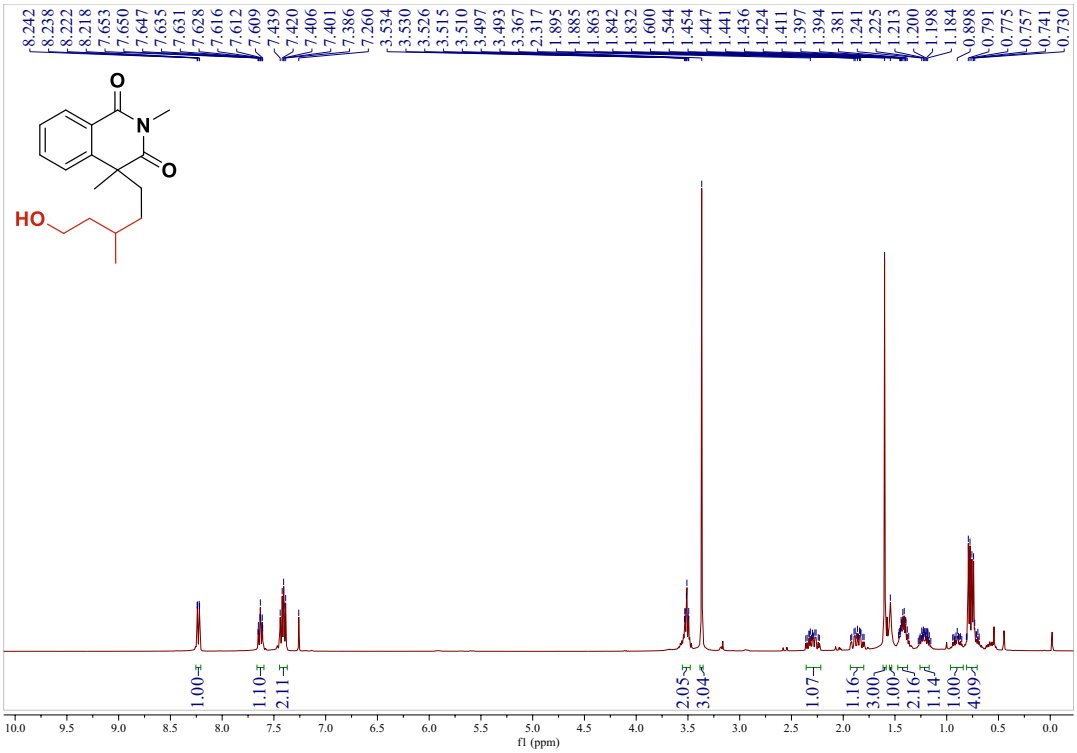


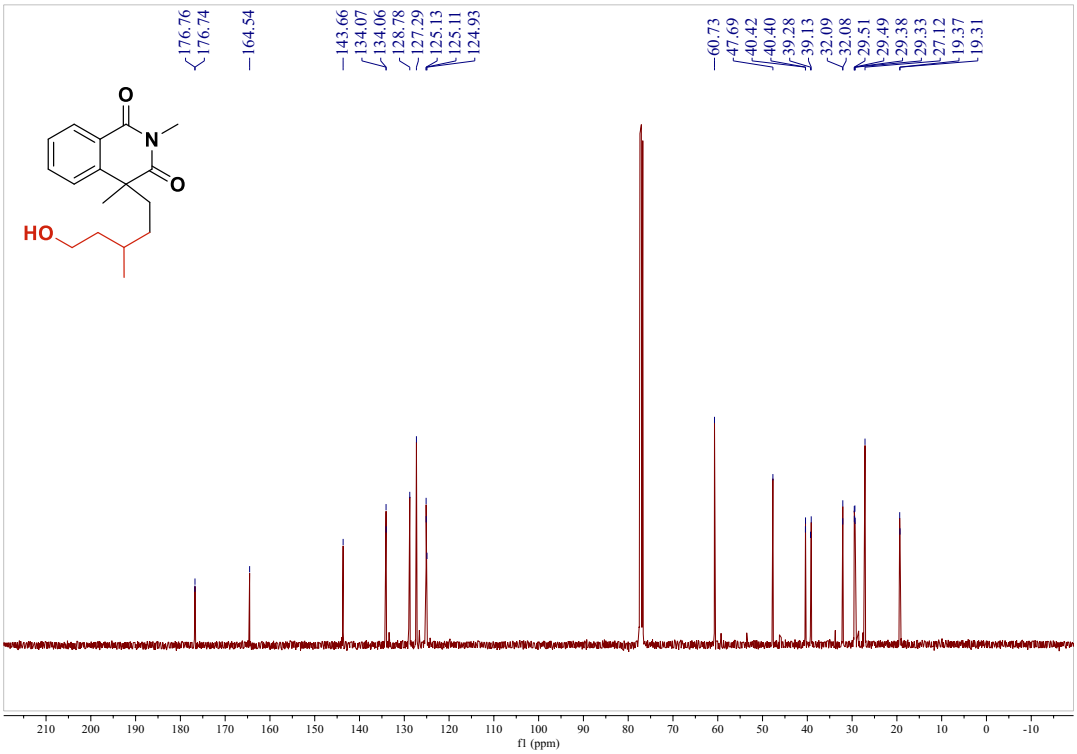
^{1}H and ^{13}C NMR spectra of **3ar**:



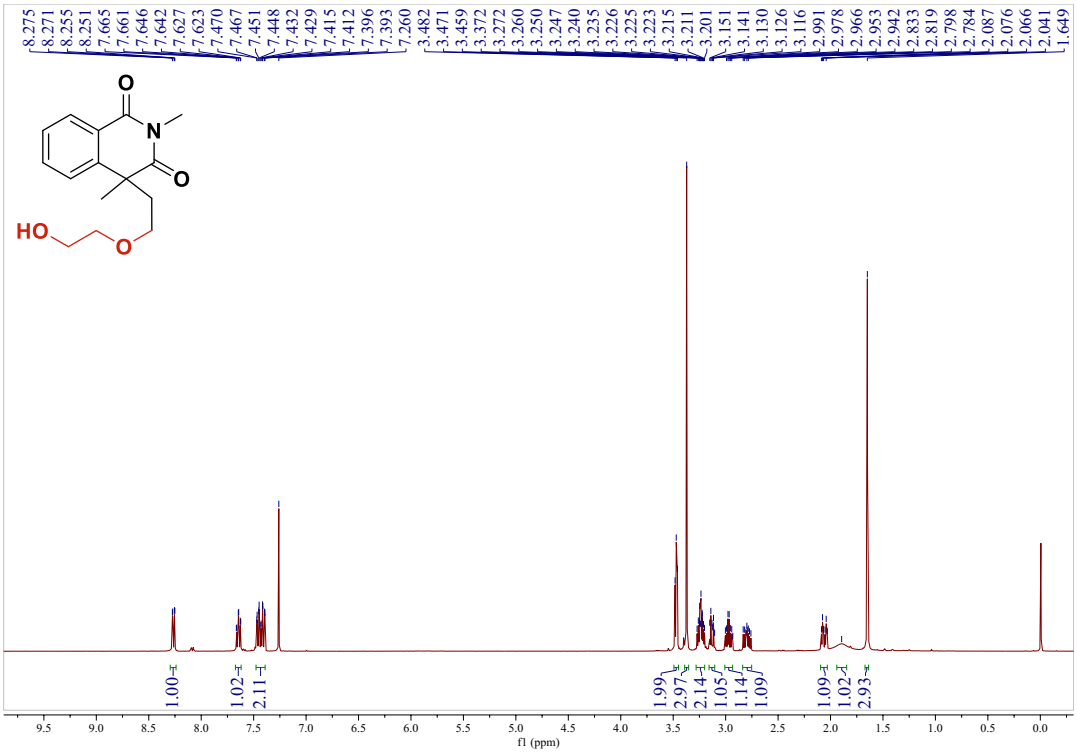


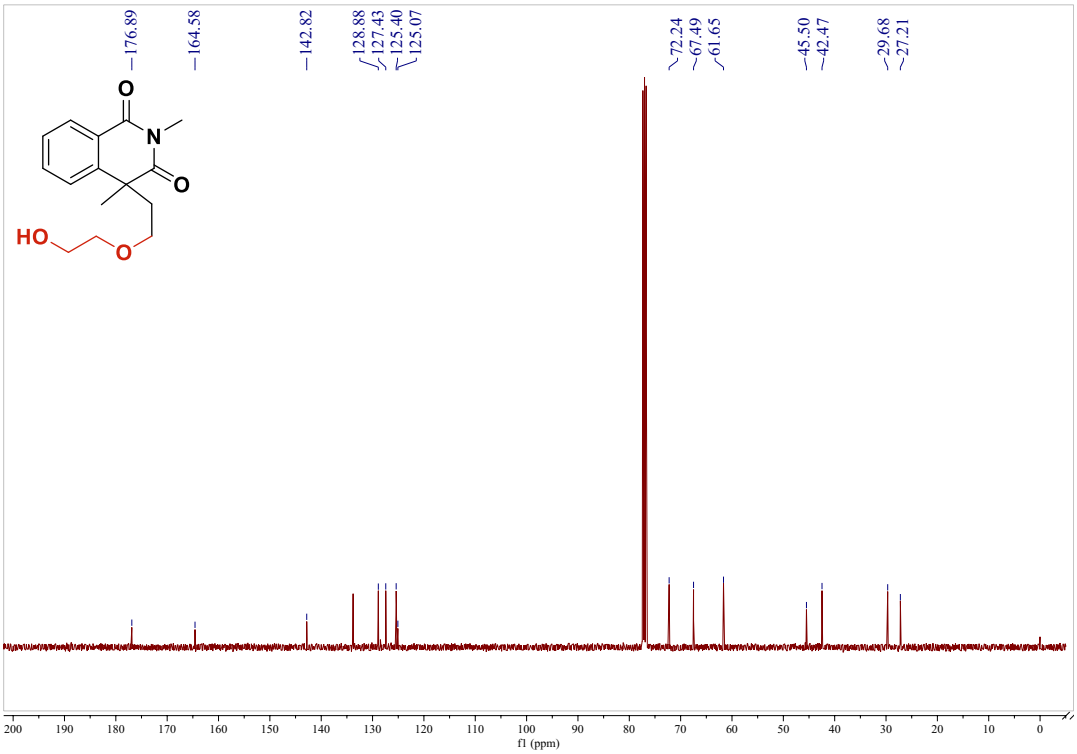
^{1}H and **^{13}C NMR** spectra of **3as**:



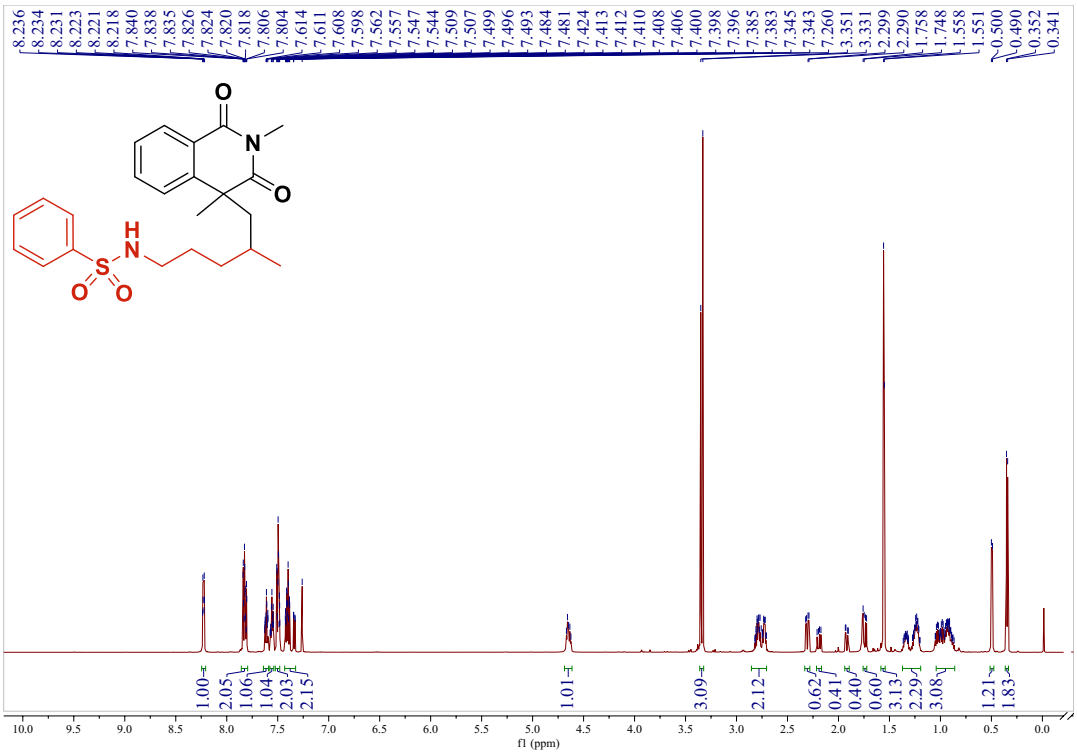


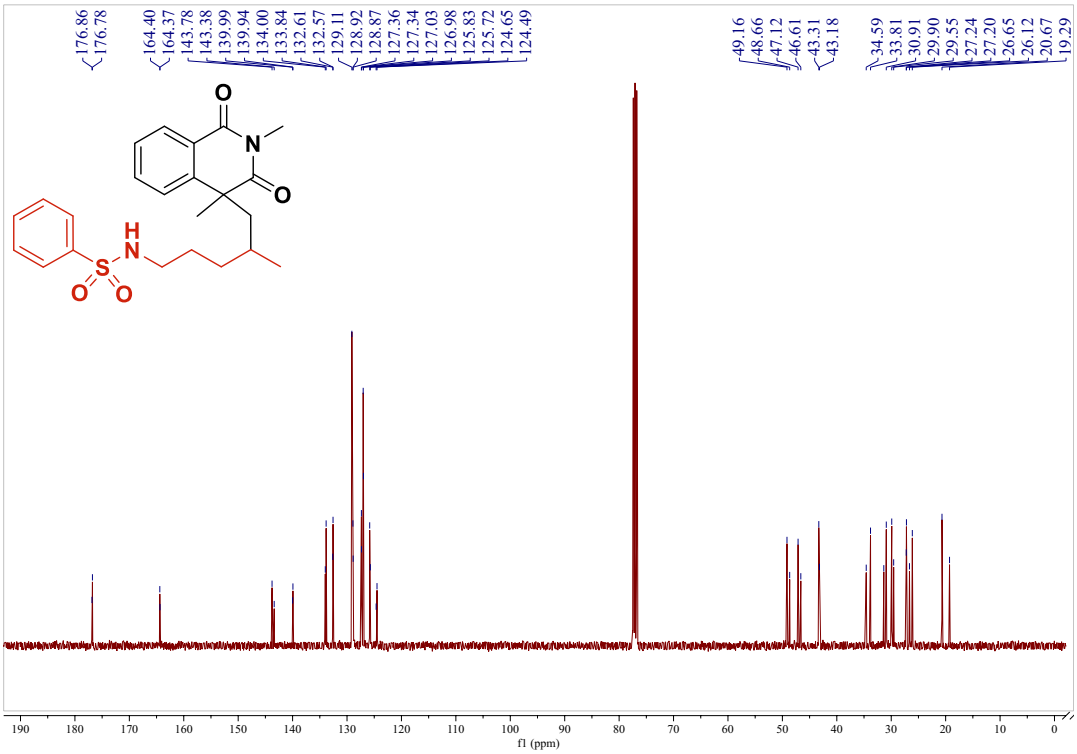
^{1}H and ^{13}C NMR spectra of **3at**:



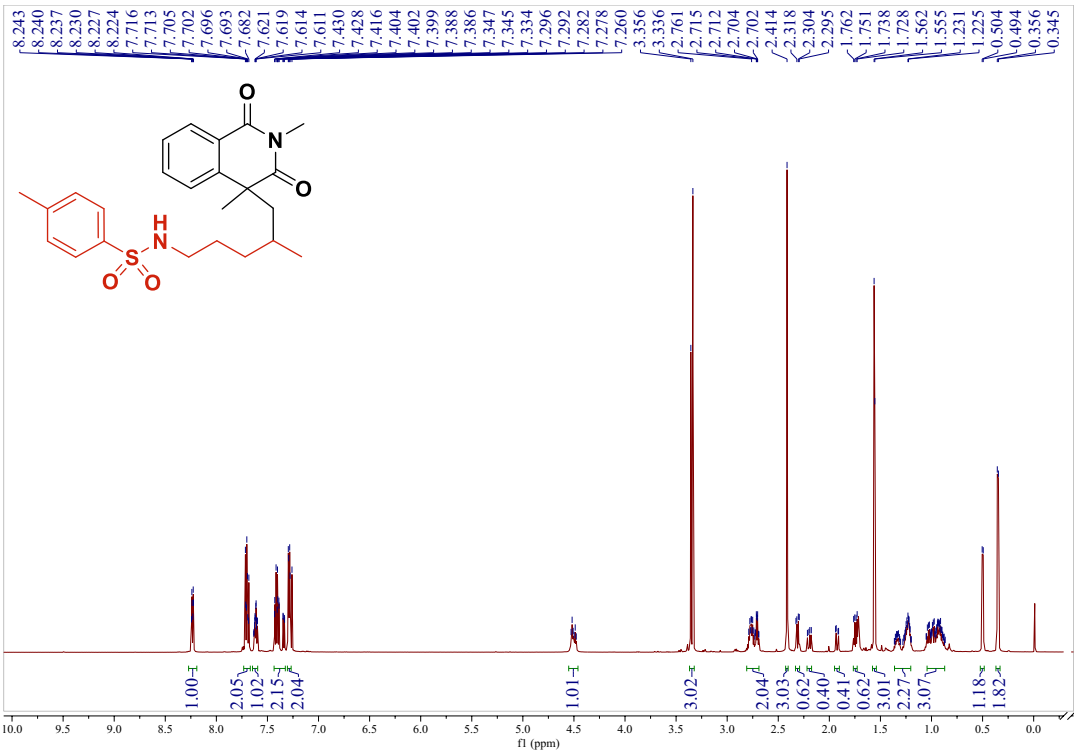


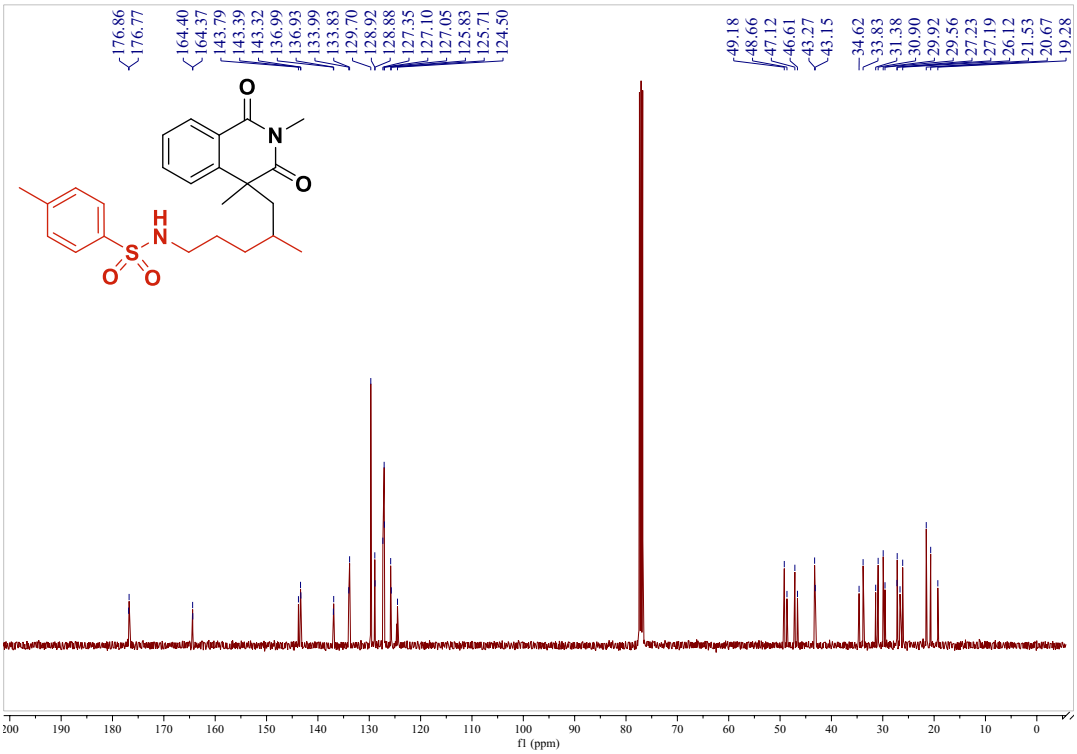
^{1}H and ^{13}C NMR spectra of **5aa**:



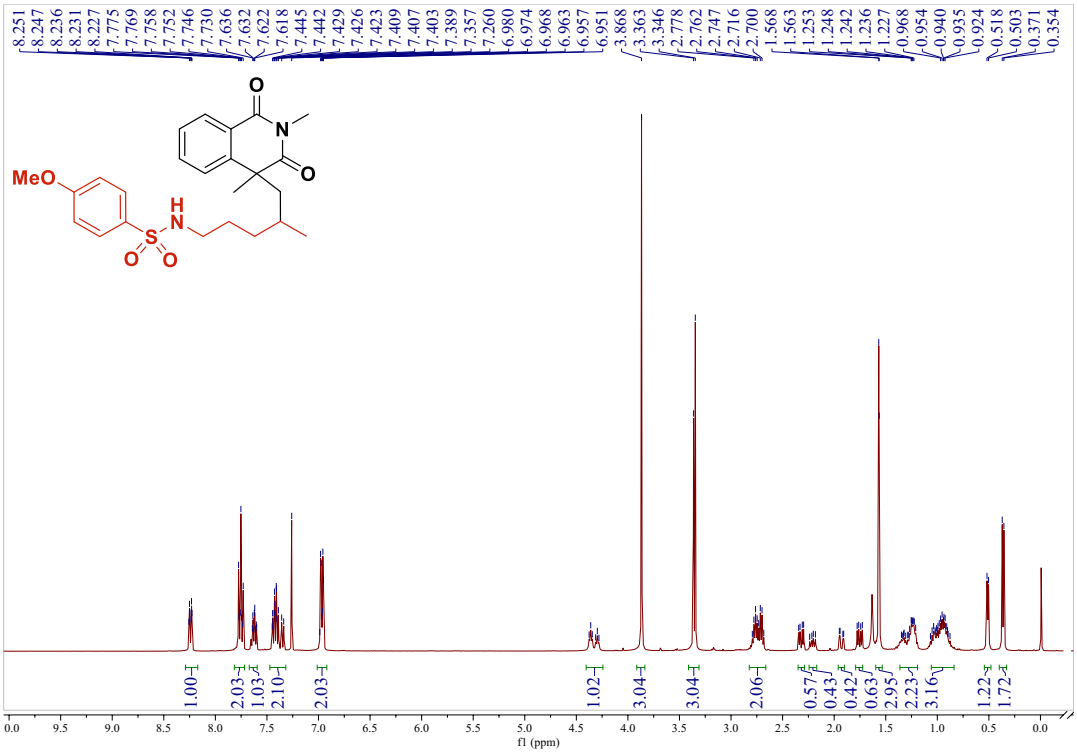


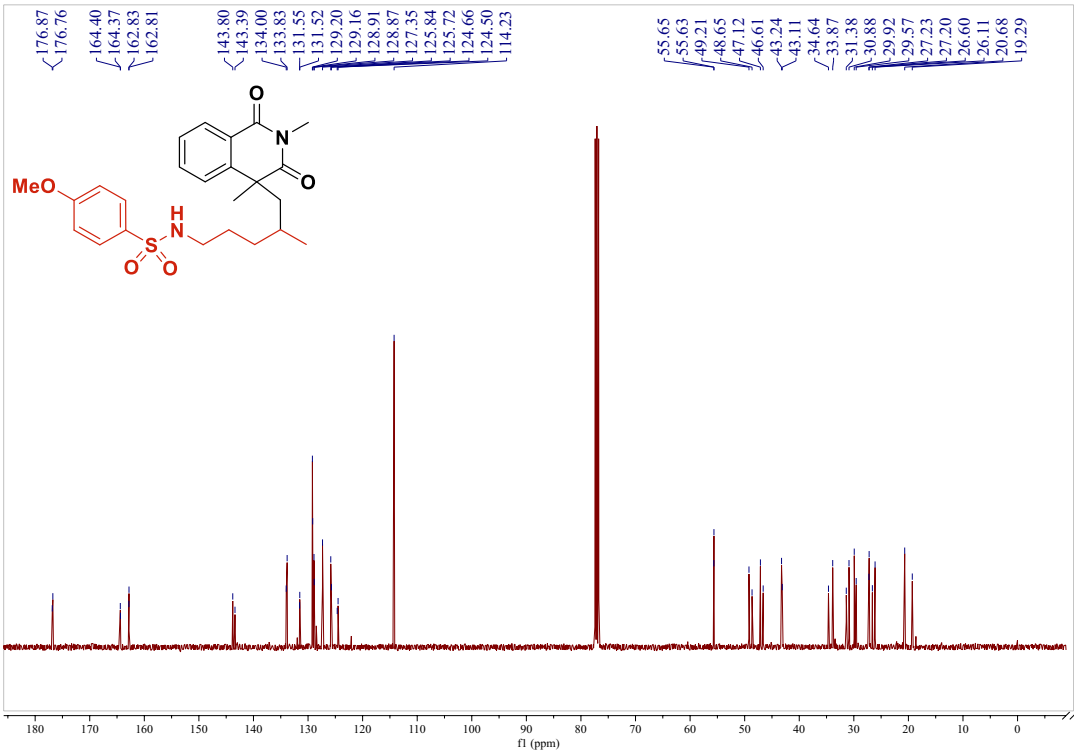
^{1}H and ^{13}C NMR spectra of **5ab**:



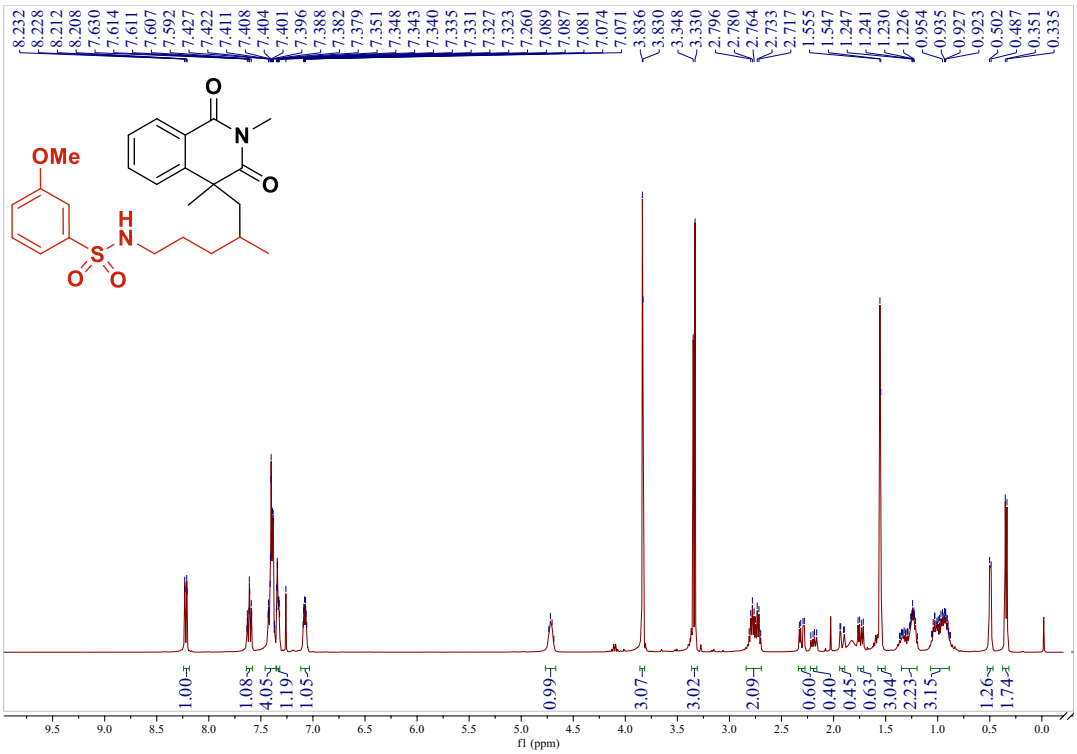


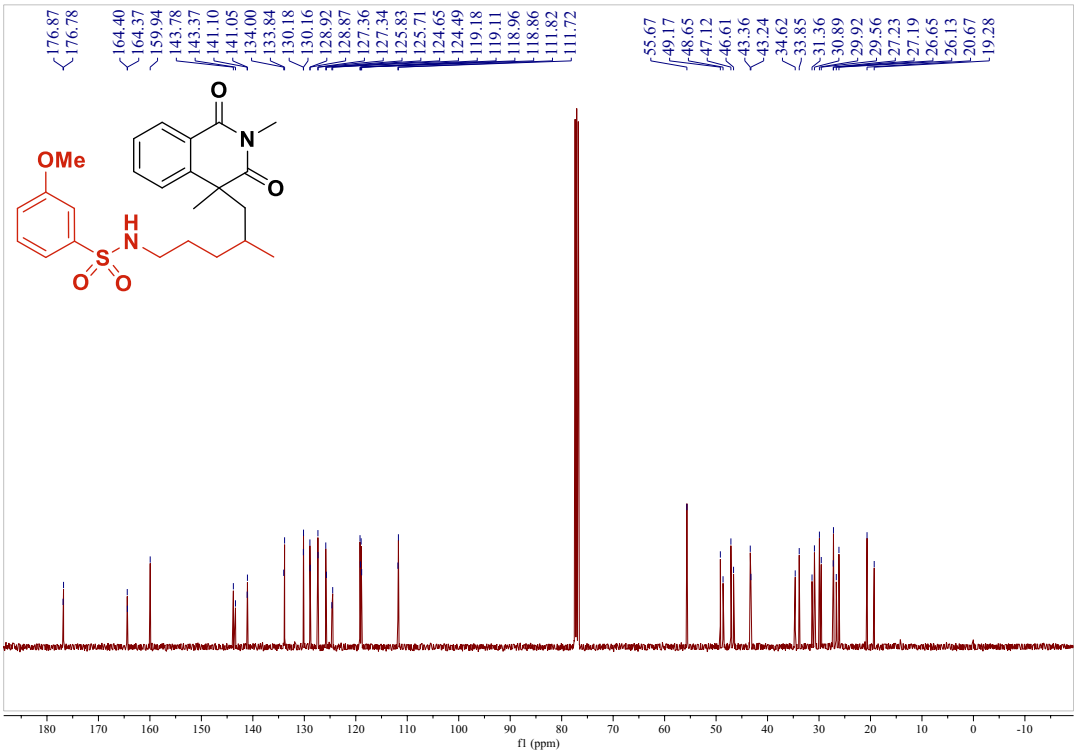
^{1}H and ^{13}C NMR spectra of **5ac**:



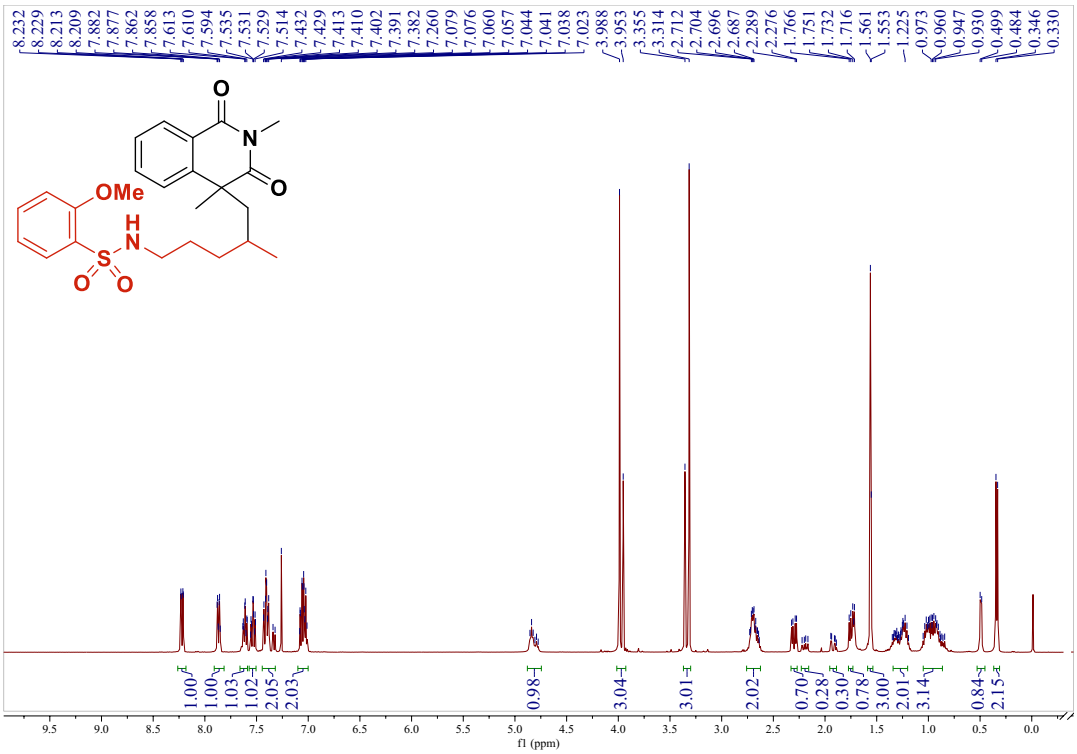


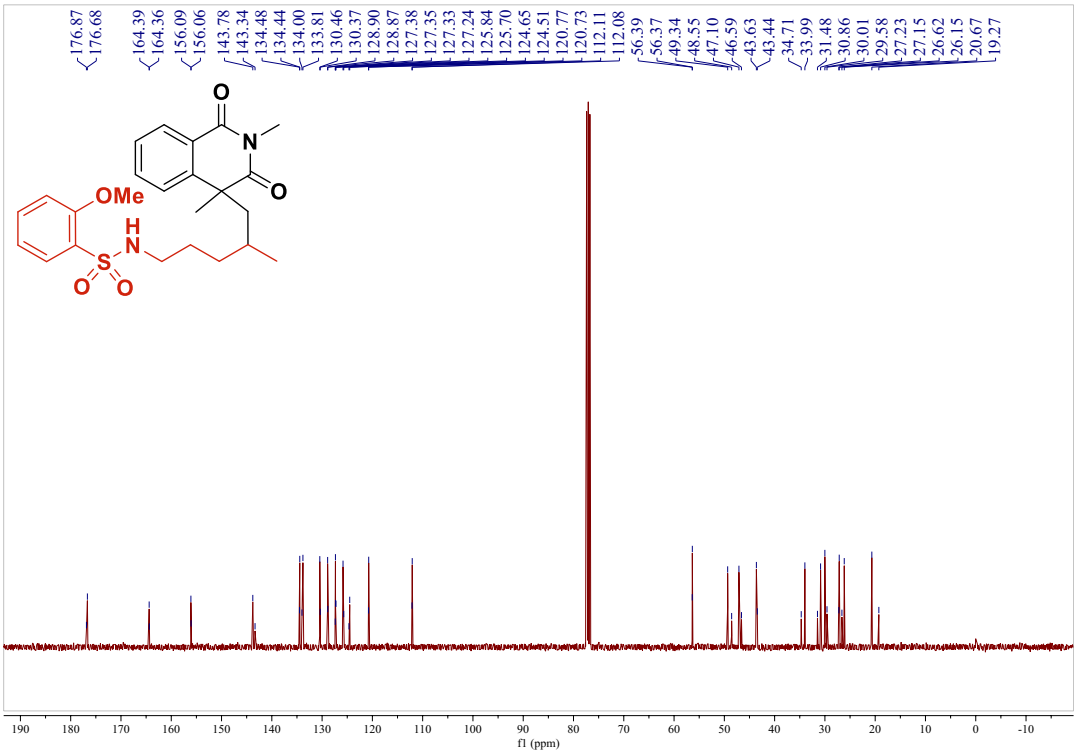
^{1}H and ^{13}C NMR spectra of **5ad**:



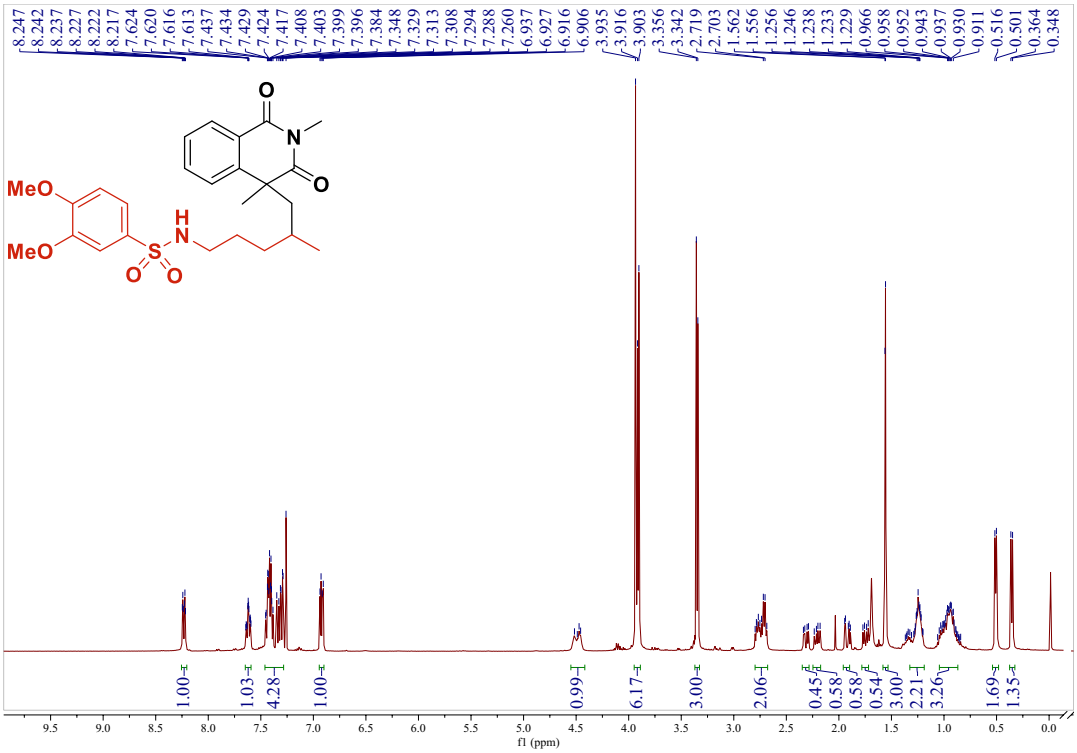


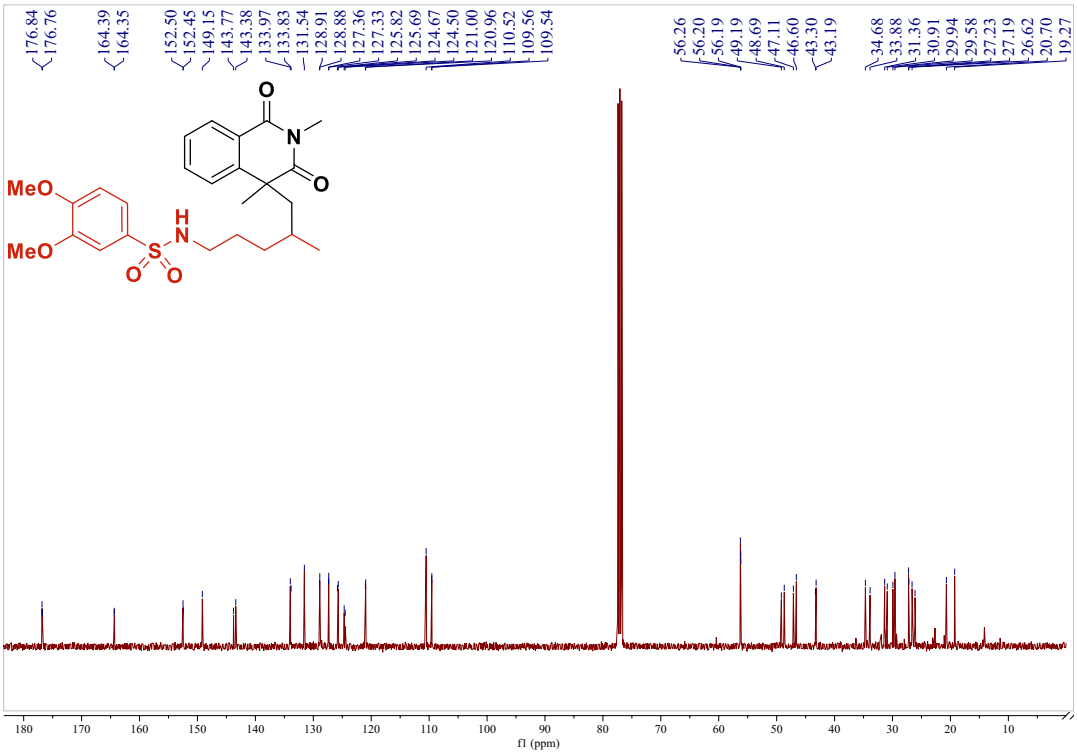
^{1}H and ^{13}C NMR spectra of **5ae**:



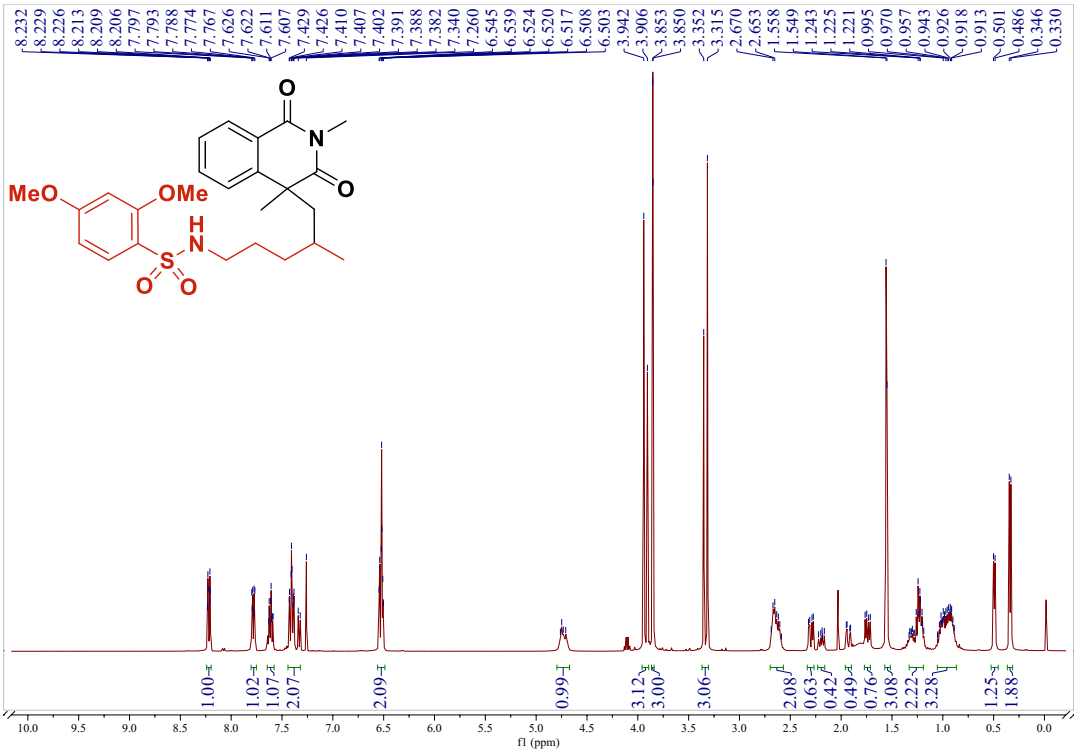


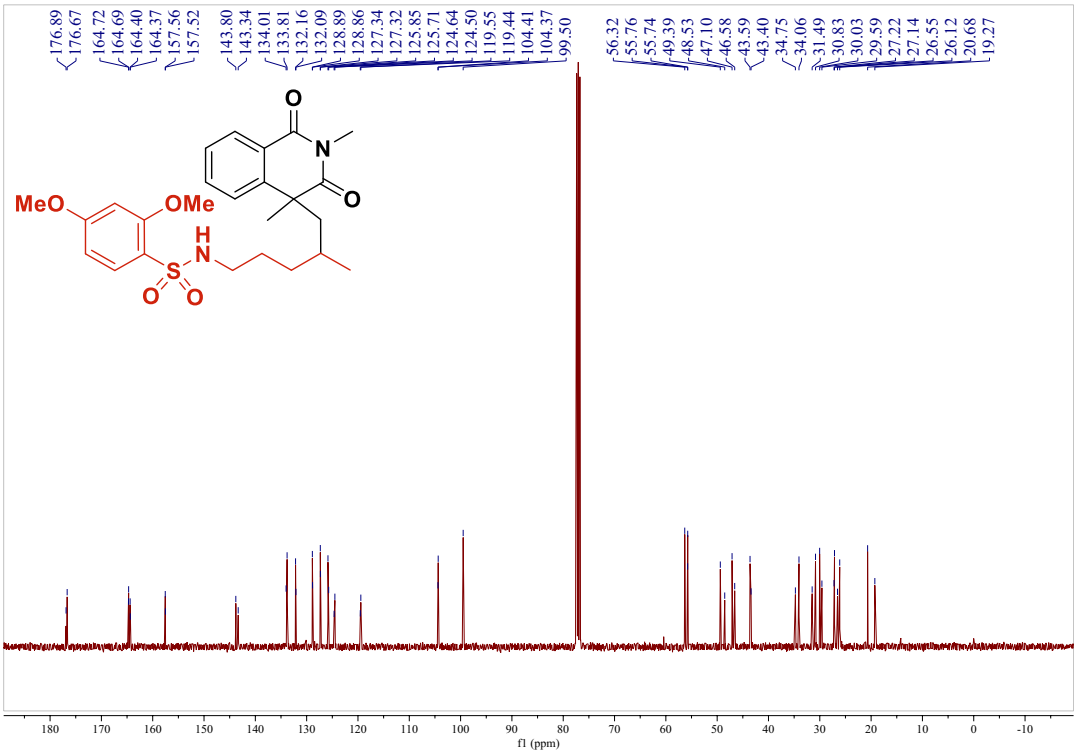
^{1}H and ^{13}C NMR spectra of **5af**:



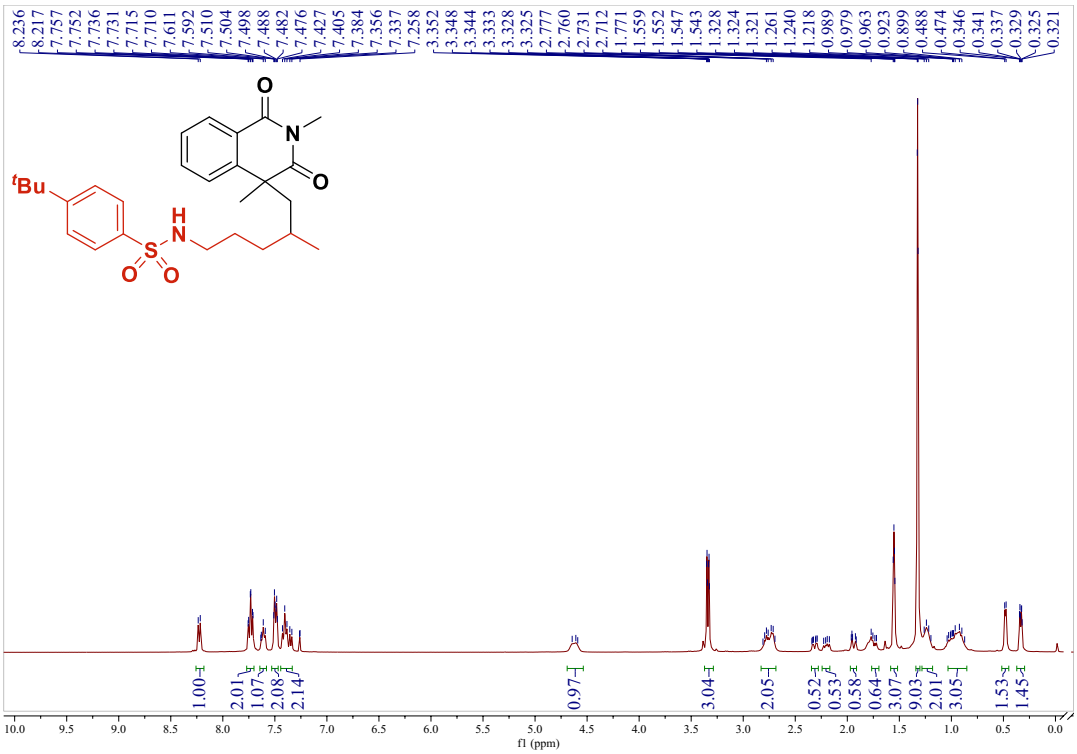


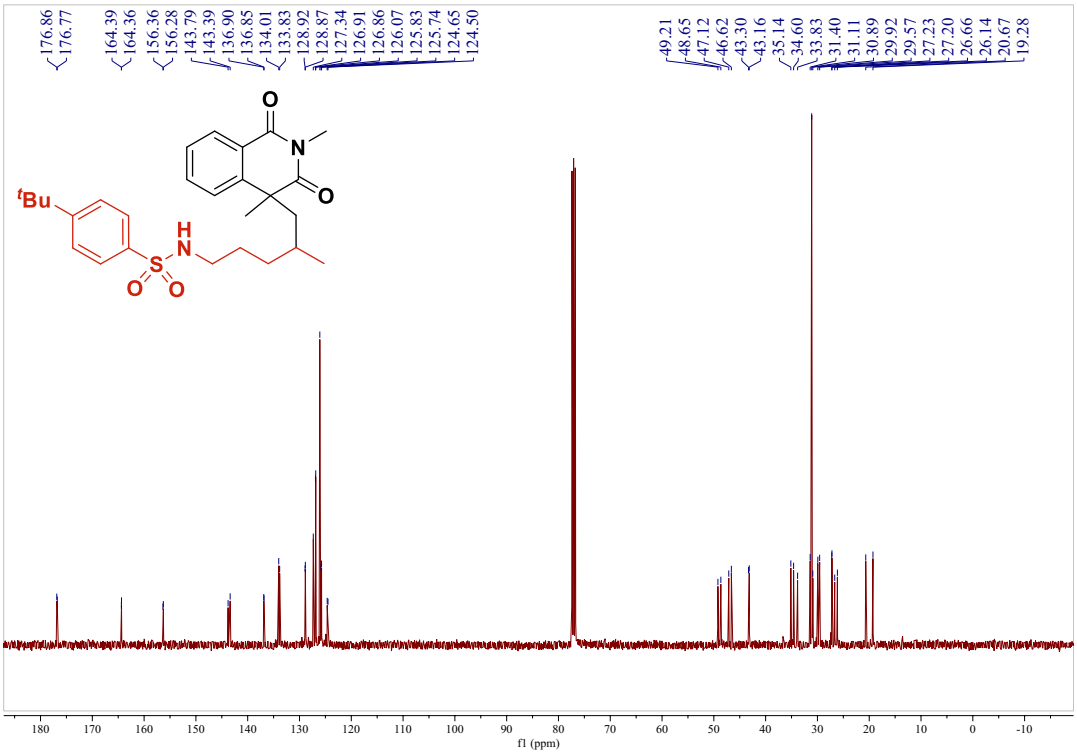
^{1}H and ^{13}C NMR spectra of **5ag**:



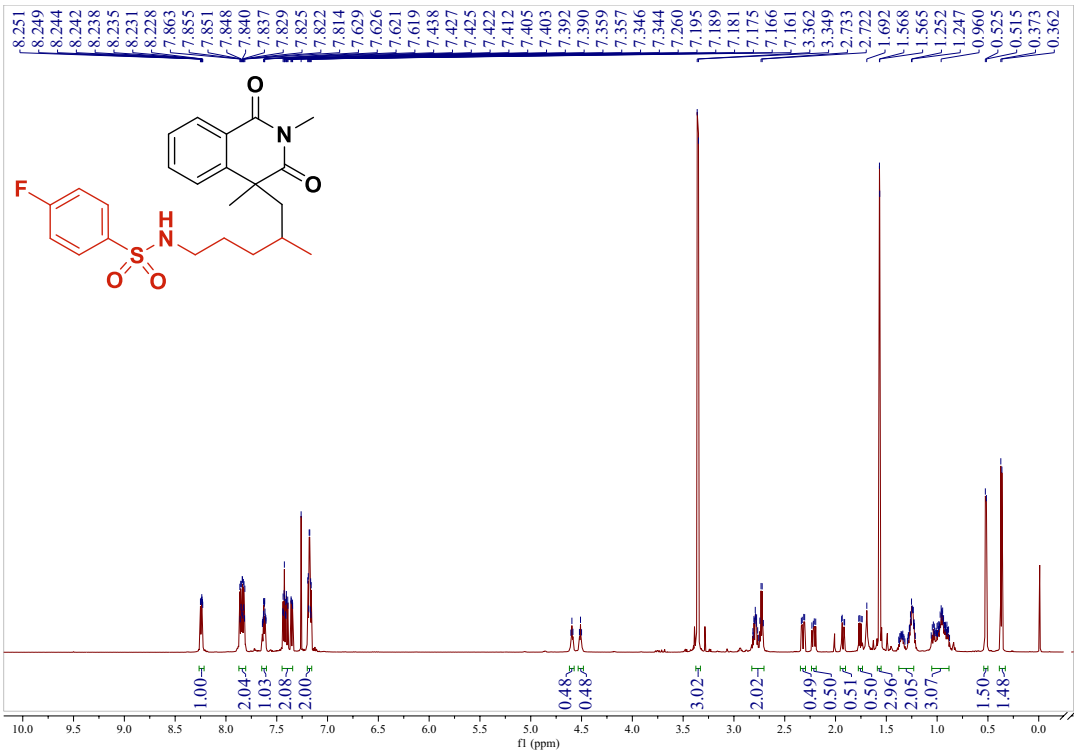


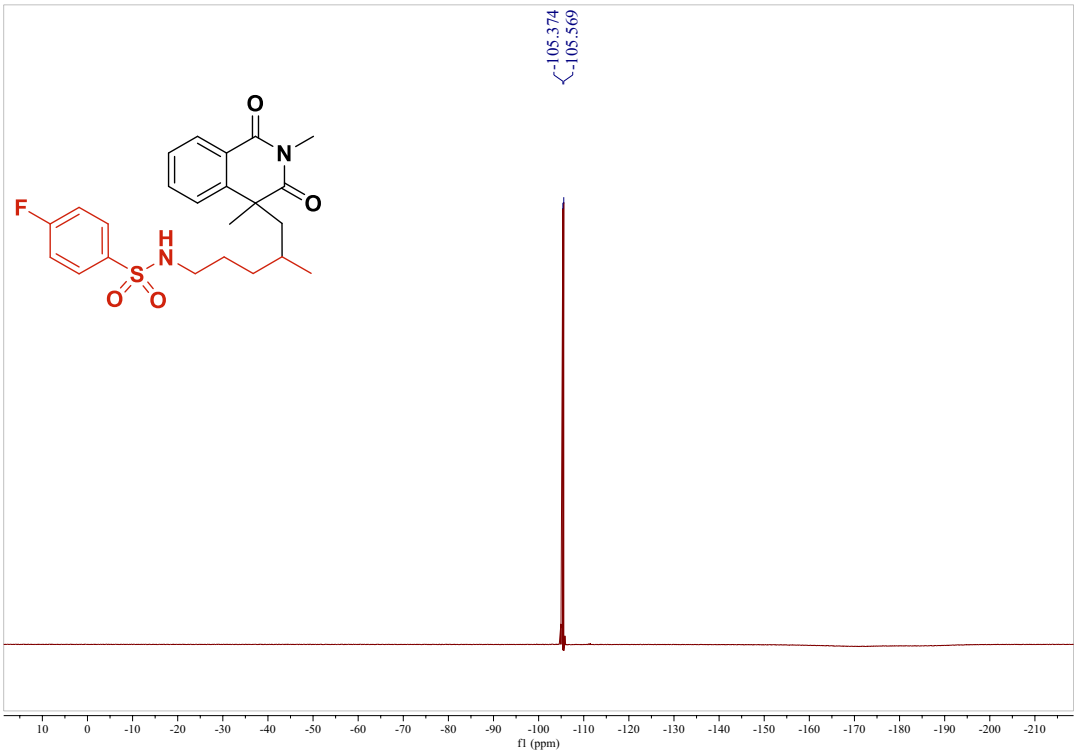
^{1}H and ^{13}C NMR spectra of **5ah**:

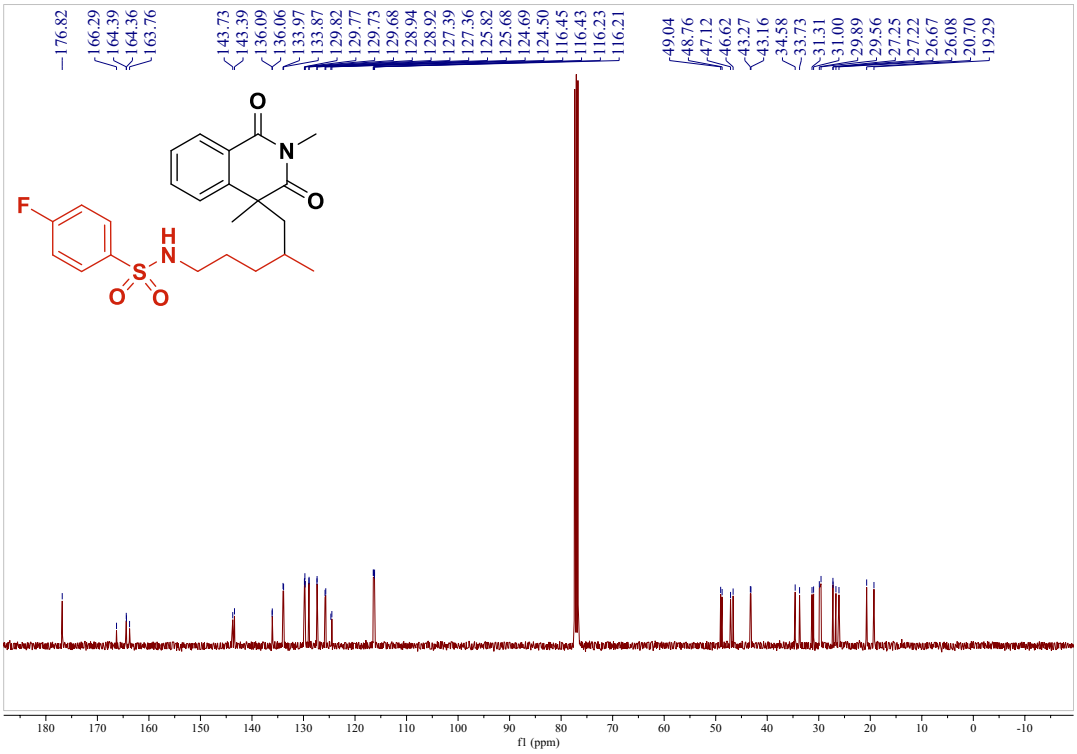




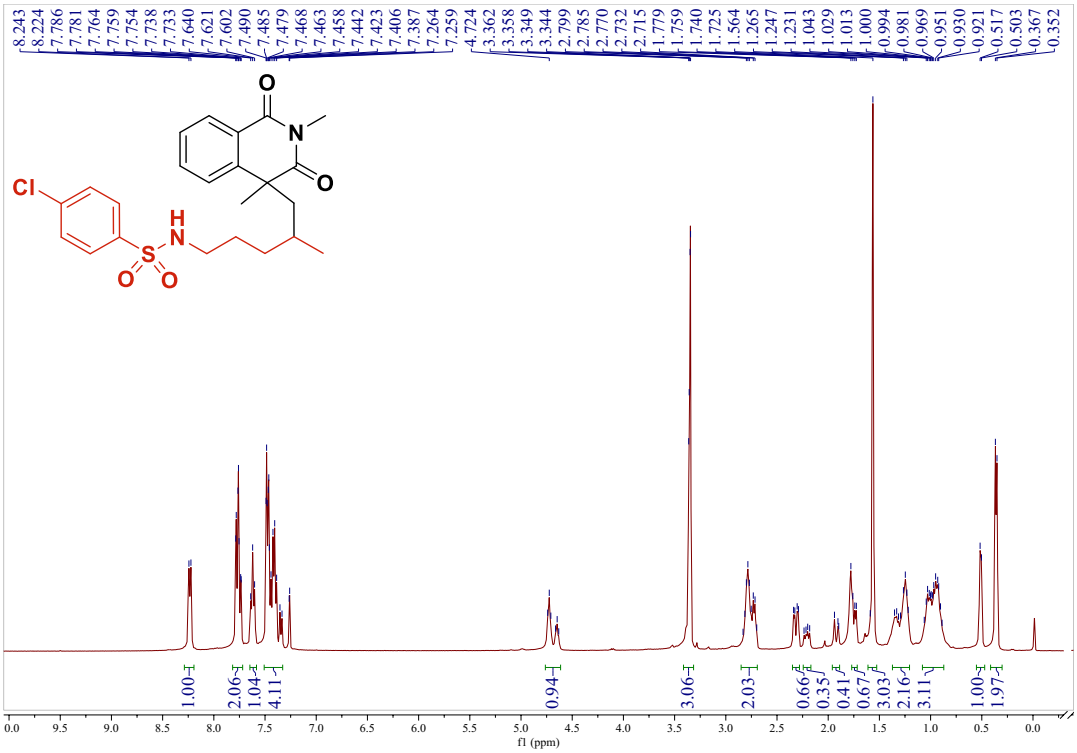
^{1}H ^{19}F and ^{13}C NMR spectra of **5ai**:

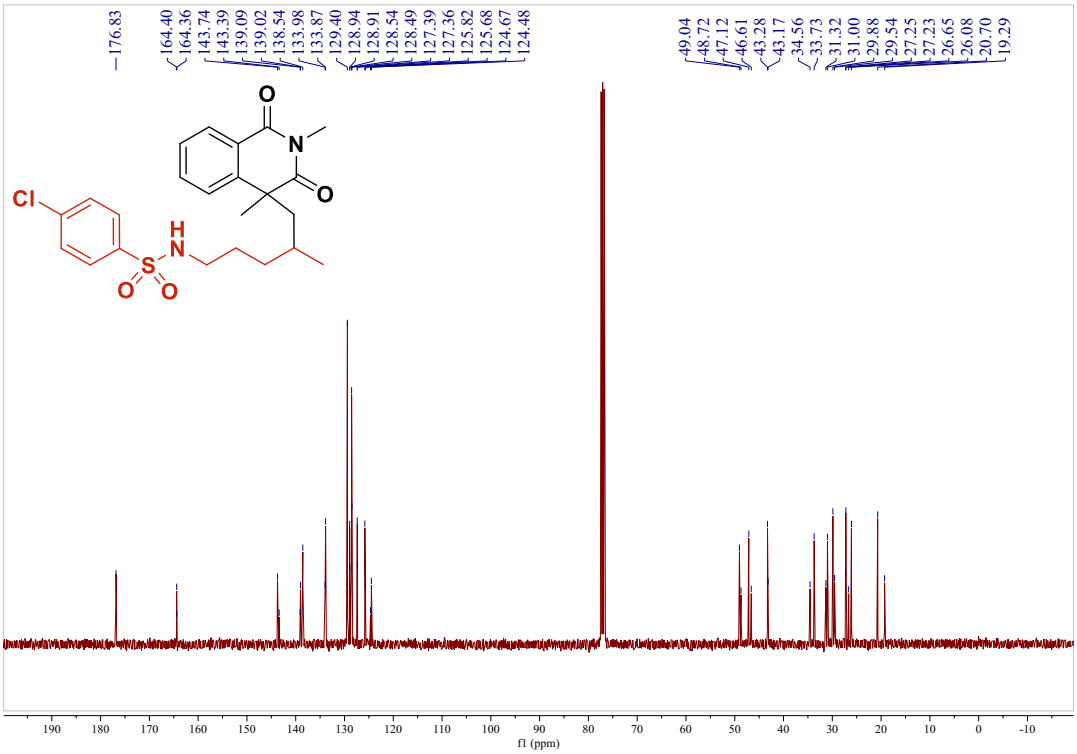




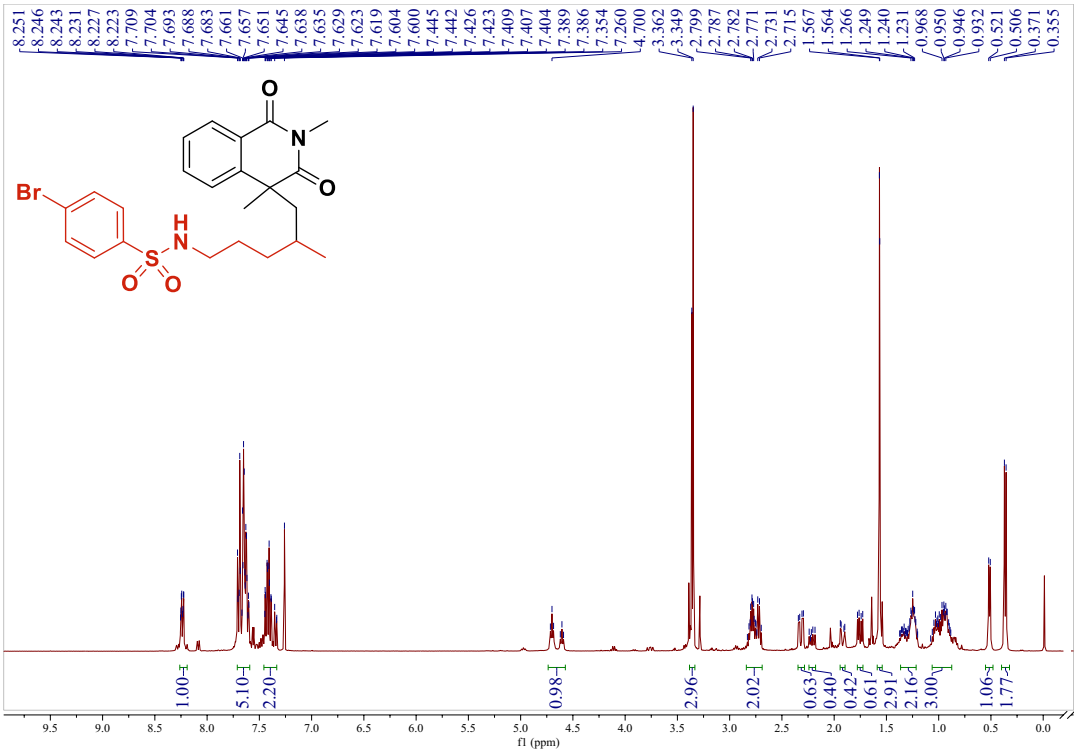

176.82
166.29
164.39
164.36
163.76
143.73
143.39
136.09
136.06
133.97
133.87
129.82
129.77
129.73
129.68
128.94
128.92
127.39
127.36
125.82
125.68
124.69
124.50
116.45
116.43
116.23
116.21
49.04
48.76
47.12
46.62
43.27
43.16
34.58
33.73
31.31
31.00
29.89
29.56
27.25
27.22
26.67
26.08
20.70
19.29
O
N
O
F
H
N
S
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

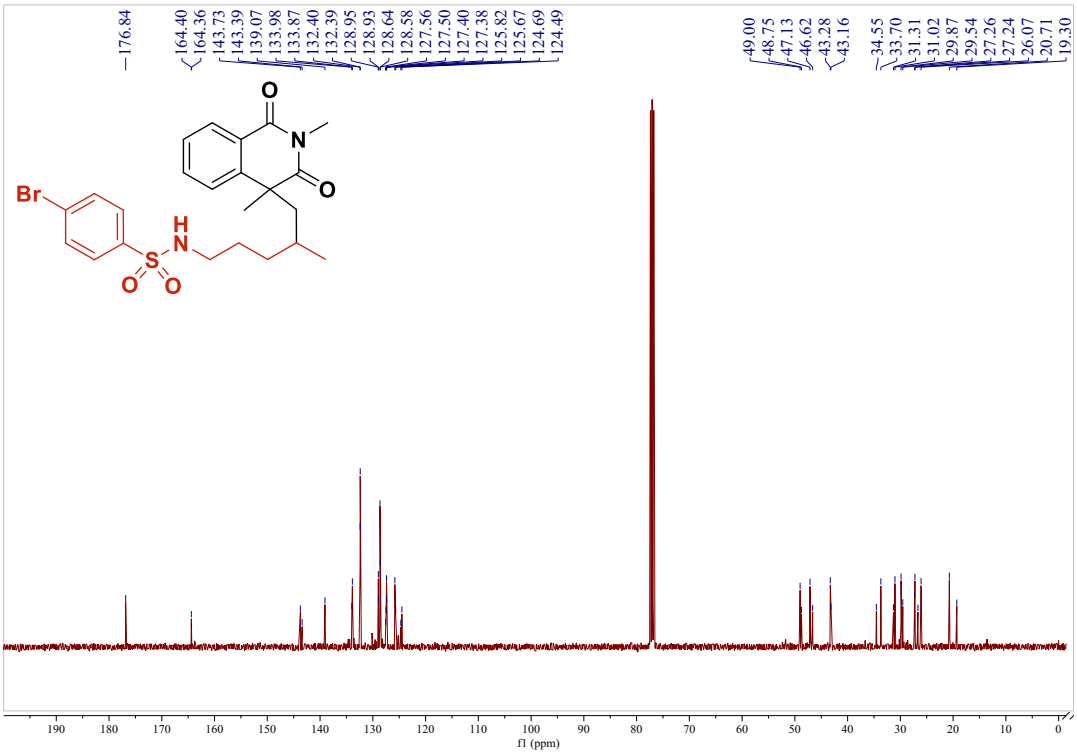
^{1}H and **^{13}C NMR** spectra of **5aj**:



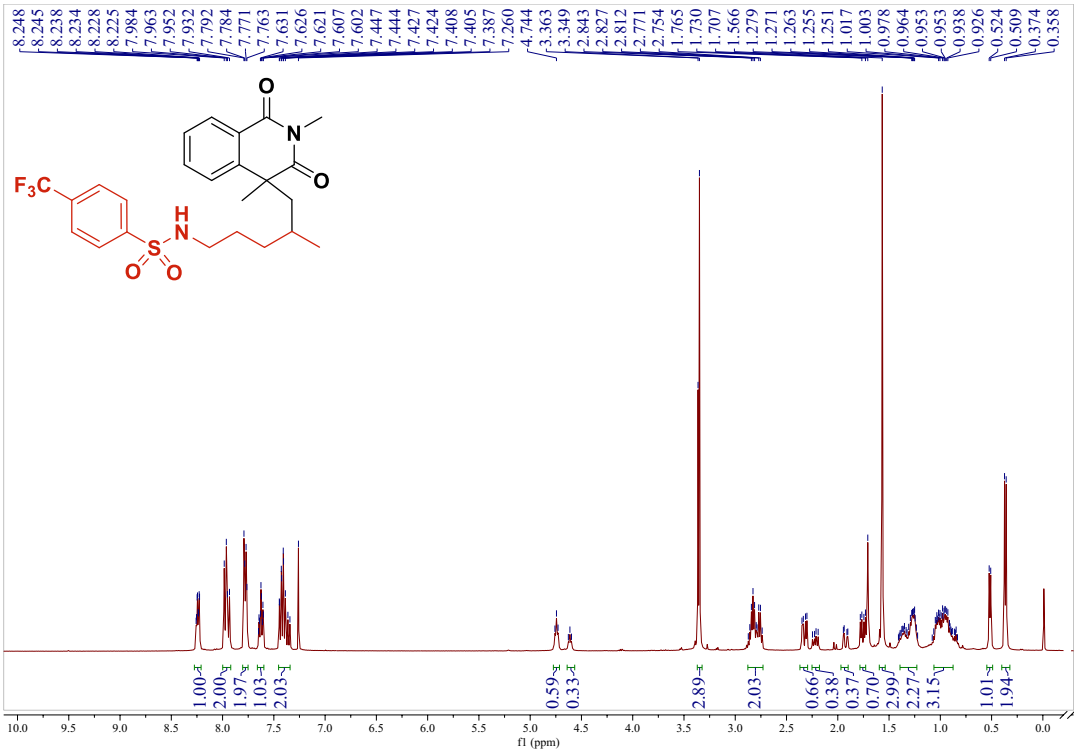


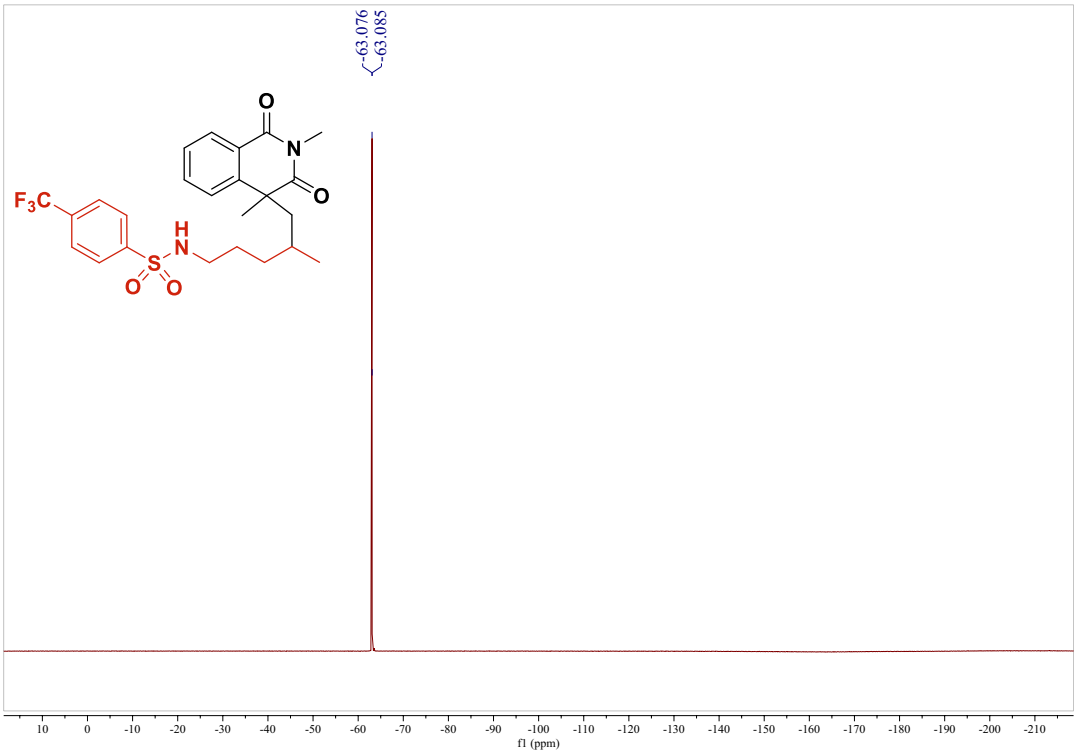
^{1}H and ^{13}C NMR spectra of **5ak**:

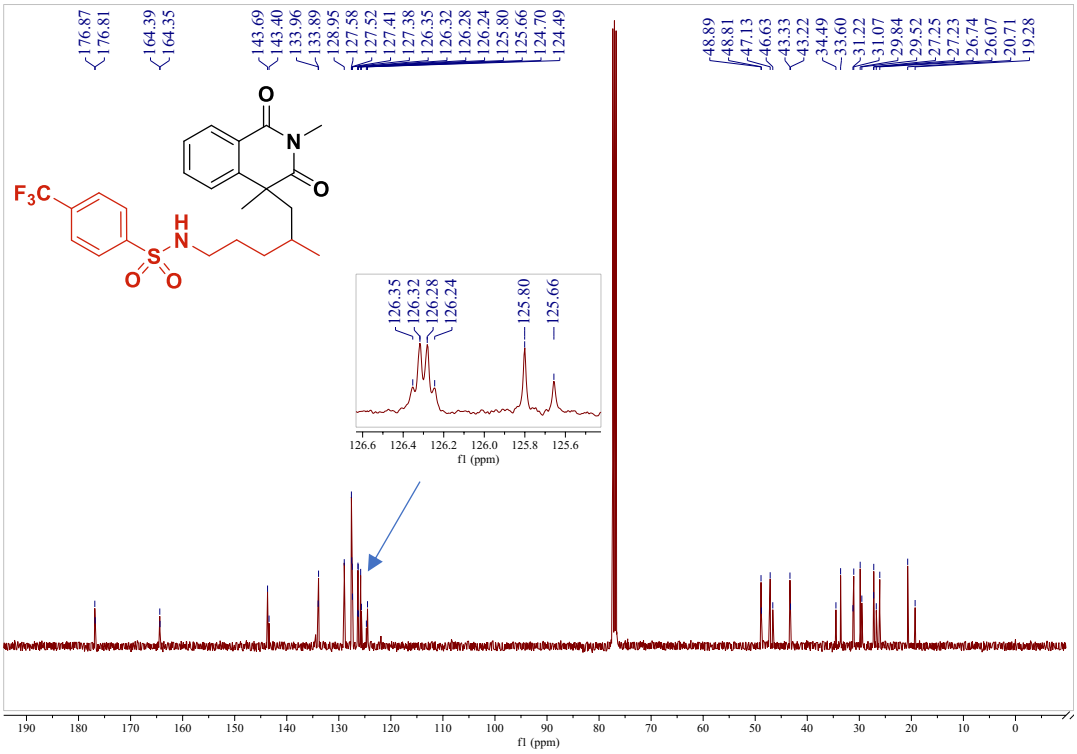




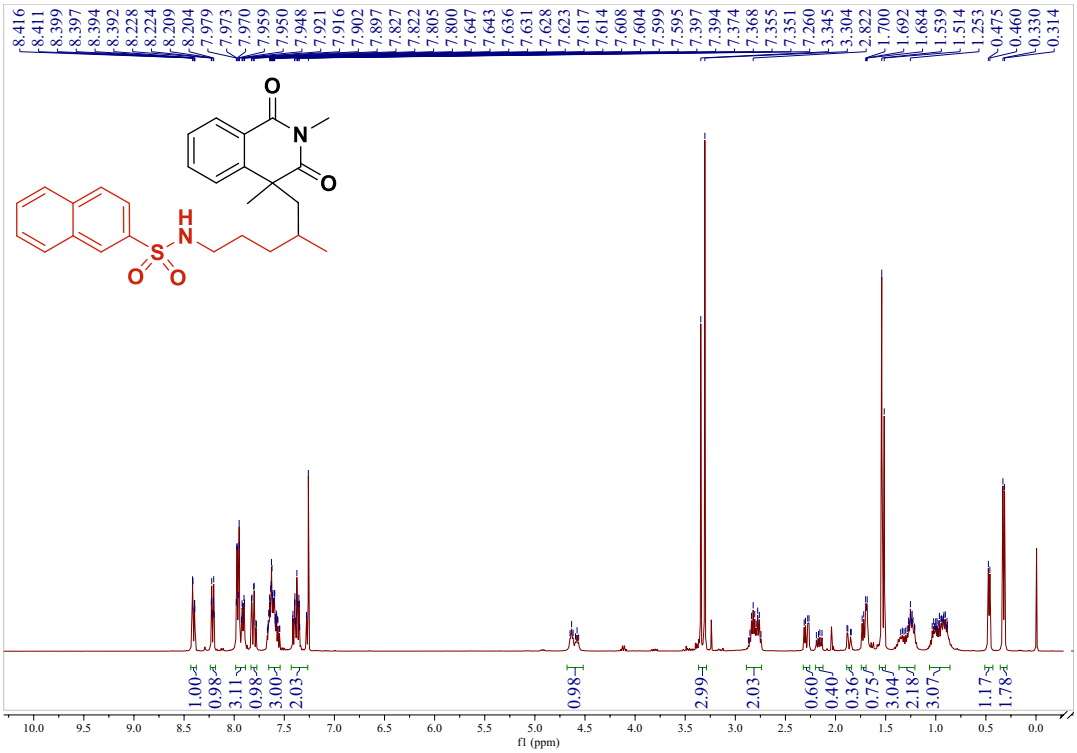
^{1}H ^{19}F and ^{13}C NMR spectra of **5al**:

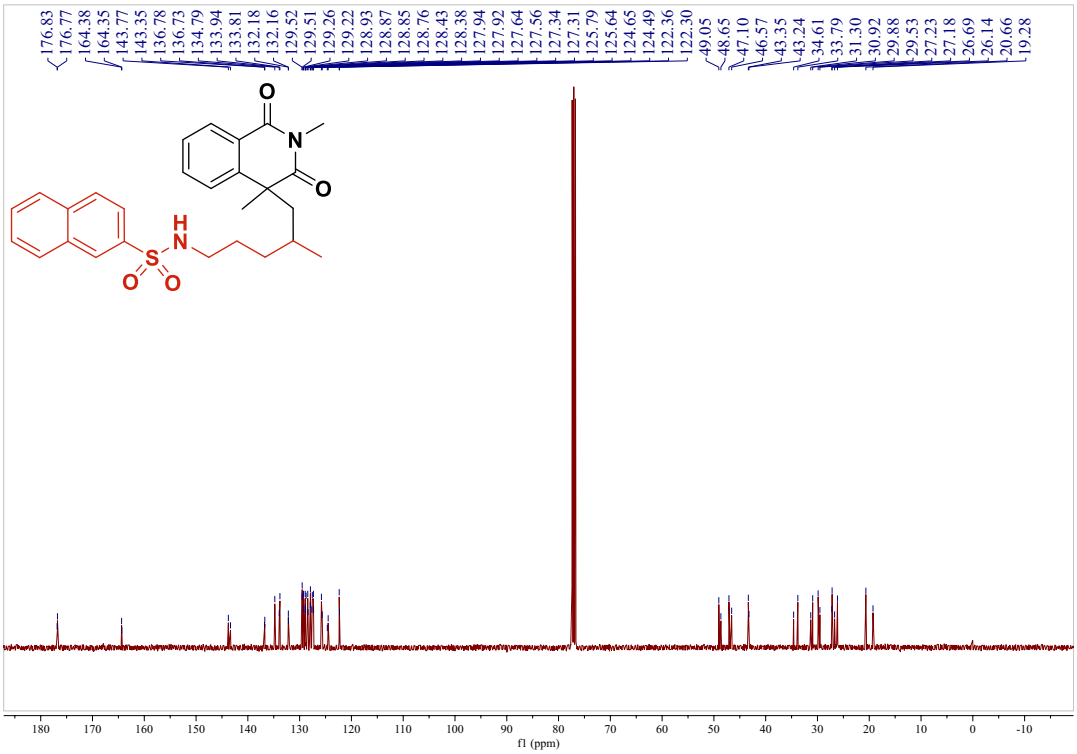




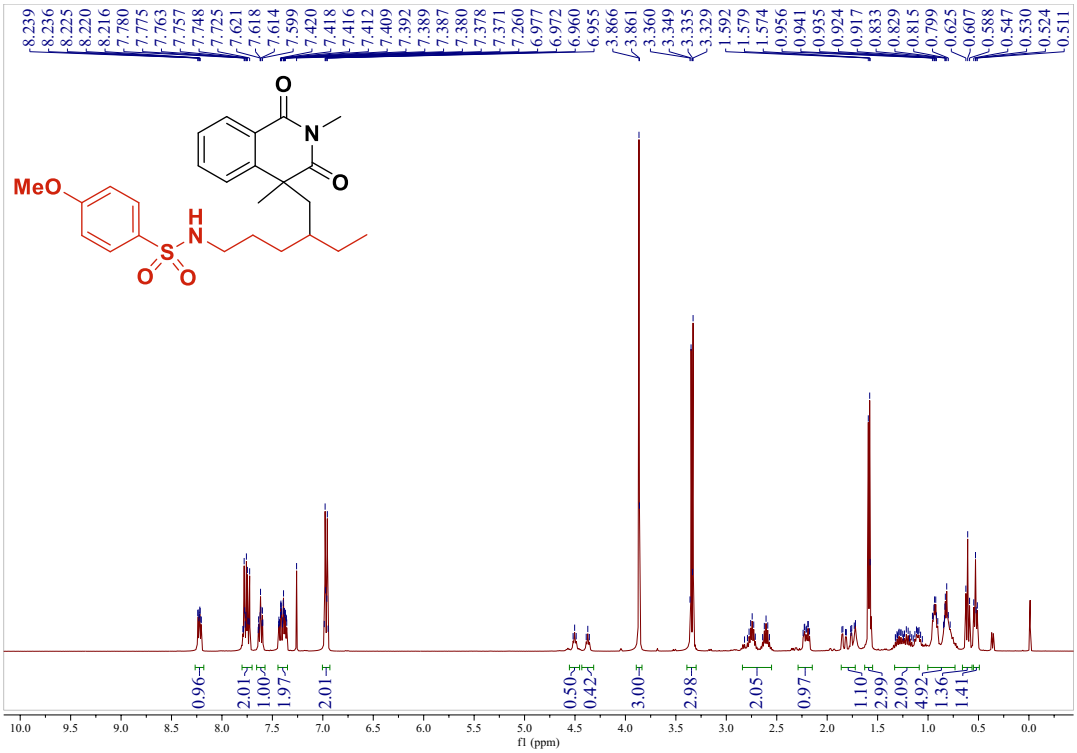

176.87
176.81
164.39
164.35
143.69
143.40
133.96
133.89
128.95
127.58
127.52
127.41
127.38
126.35
126.32
126.28
126.24
125.80
125.66
124.70
124.49
48.89
48.81
47.13
46.63
43.33
43.22
34.49
33.60
31.22
31.07
29.84
29.52
27.25
27.23
26.74
26.07
20.71
19.28
O
N
O
F3C
H
N
S
O
O
126.35
126.32
126.28
126.24
125.80
125.66
126.6 126.4 126.2 126.0 125.8 125.6
f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

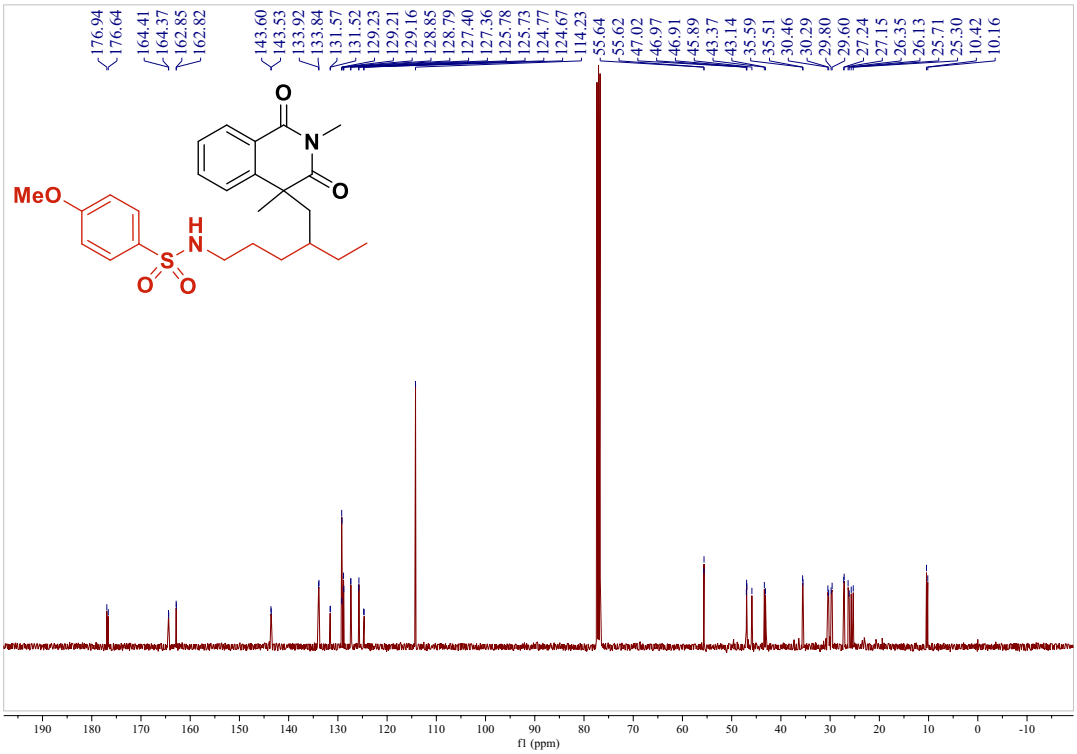
^{1}H and ^{13}C NMR spectra of **5am**:



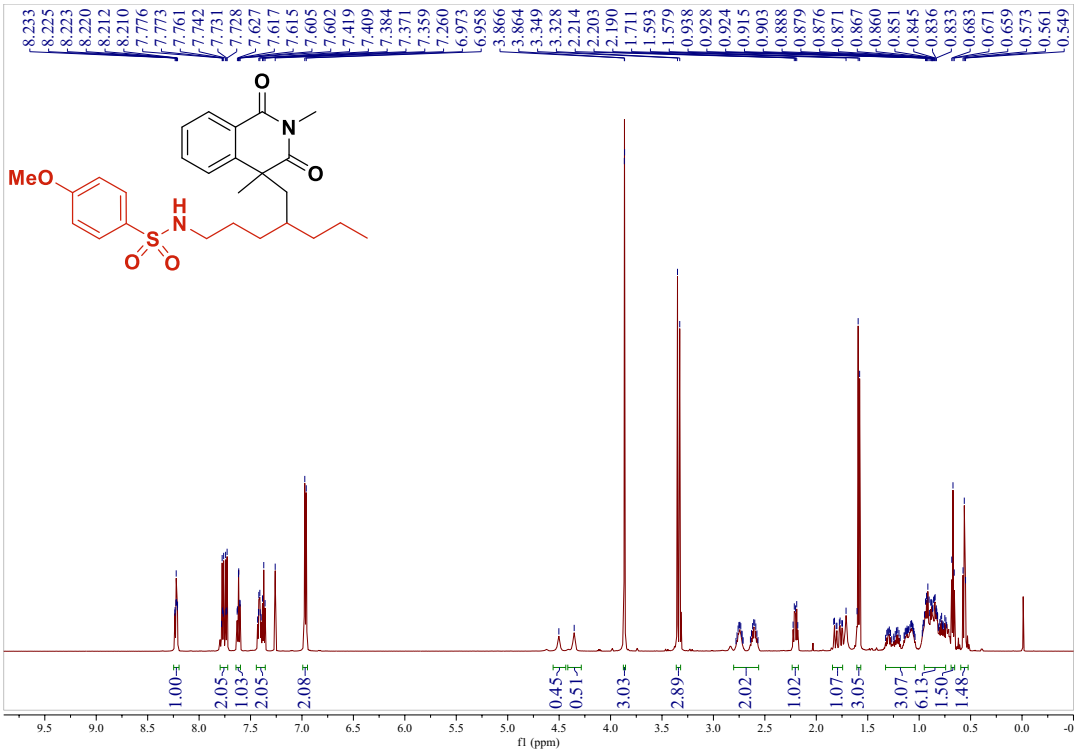


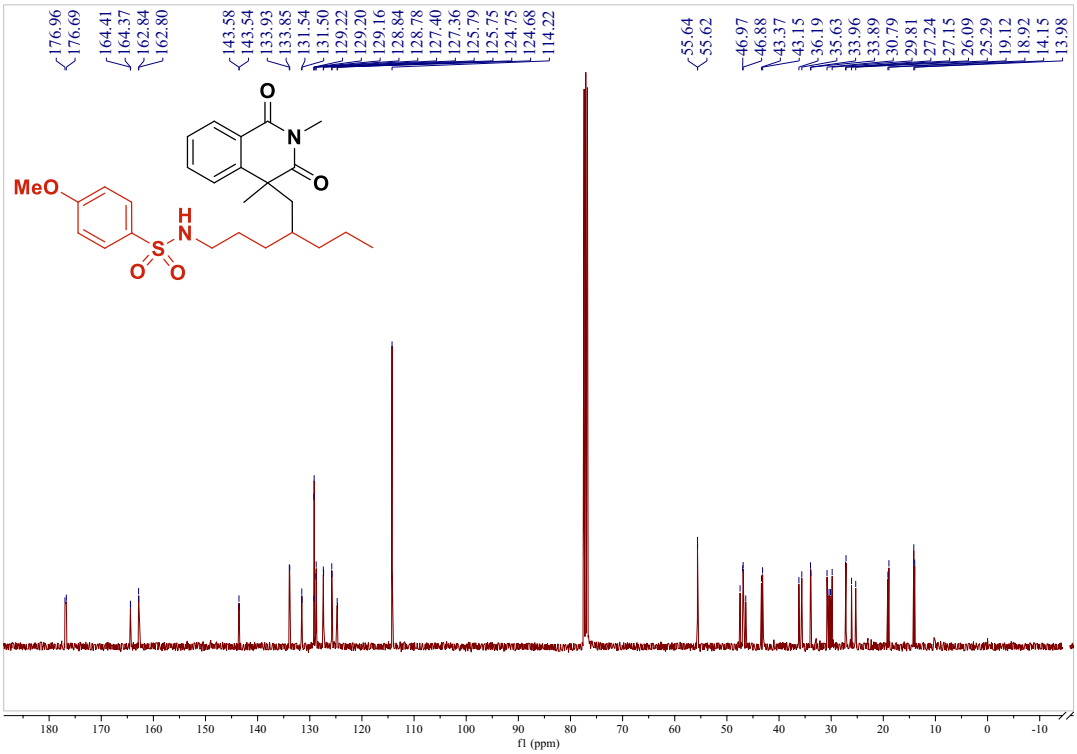
^{1}H and ^{13}C NMR spectra of **5an**:



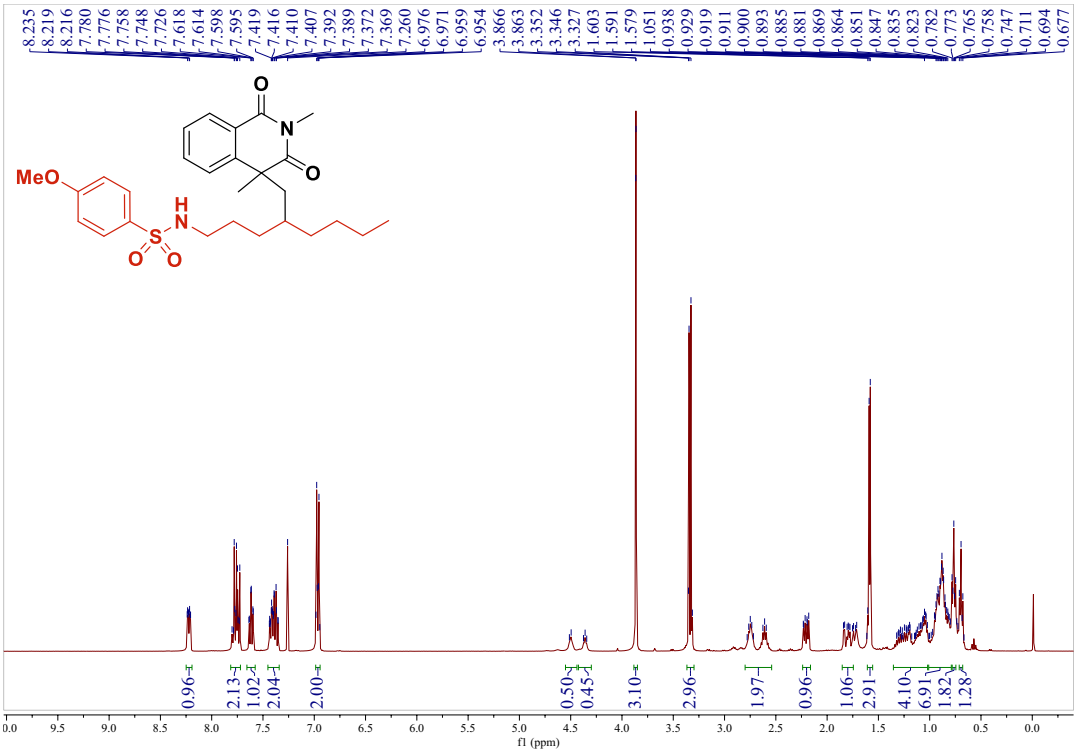


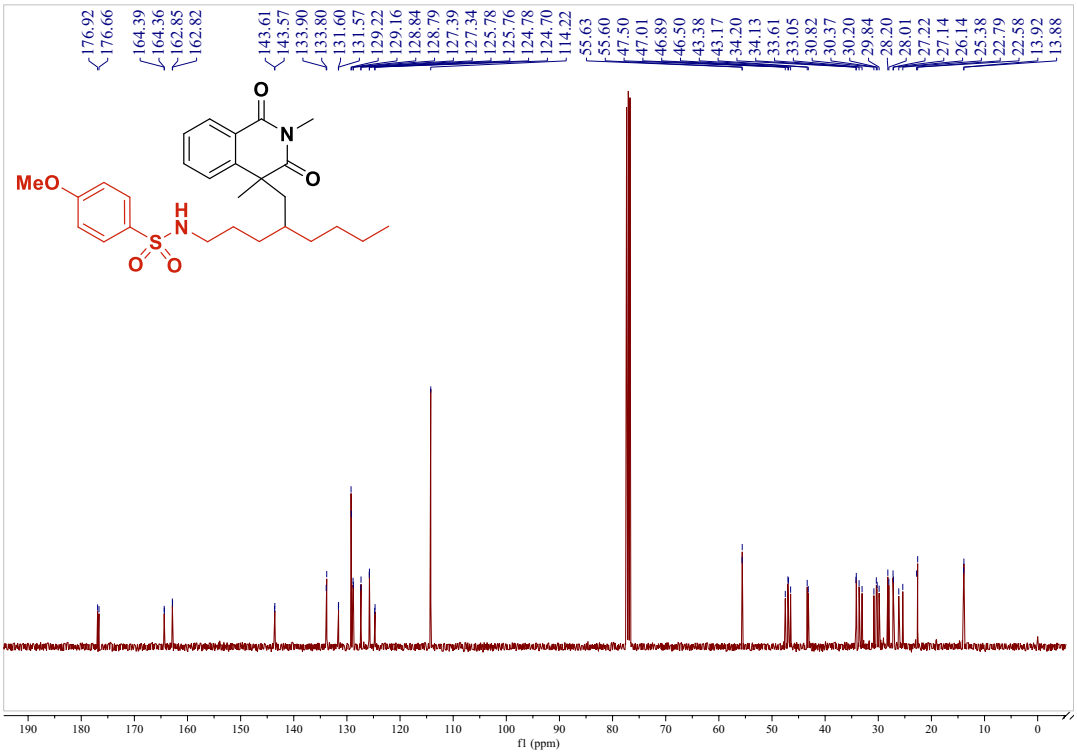
^{1}H and ^{13}C NMR spectra of **5ao**:



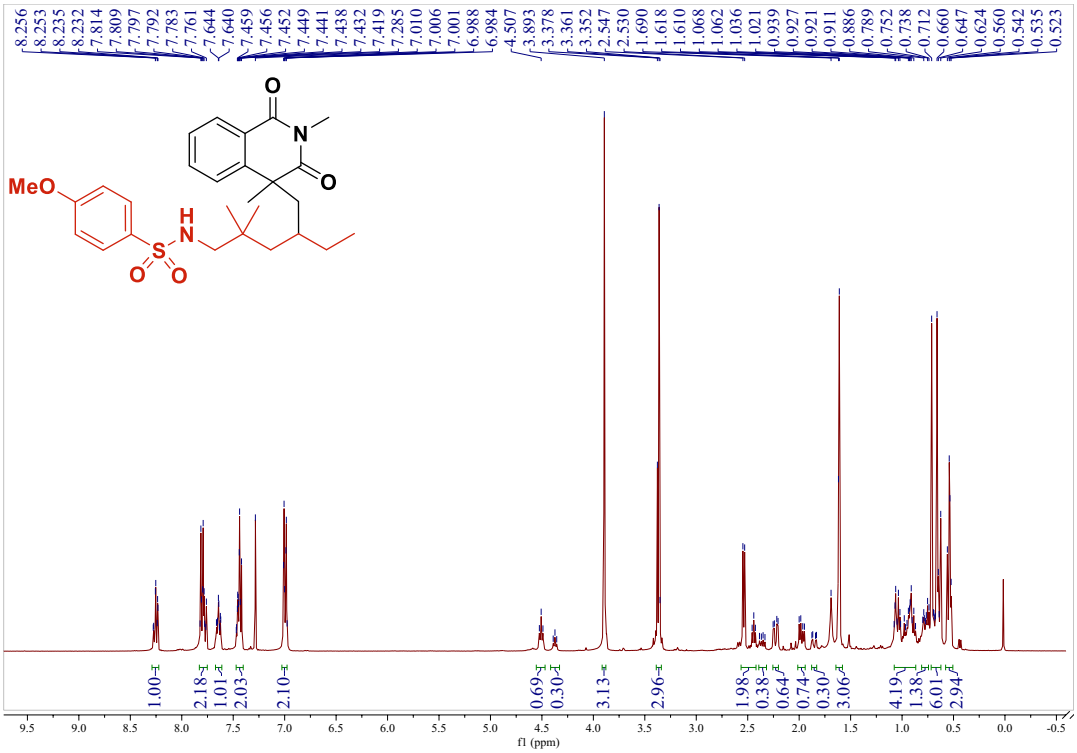


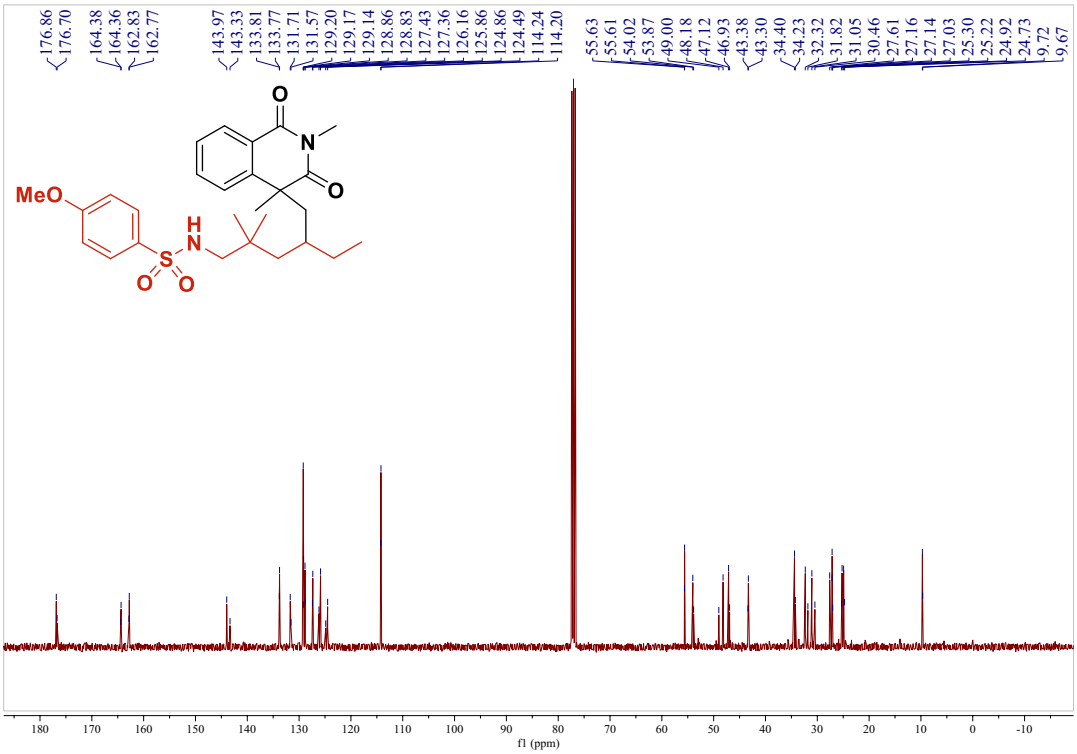
^{1}H and ^{13}C NMR spectra of **5ap**:



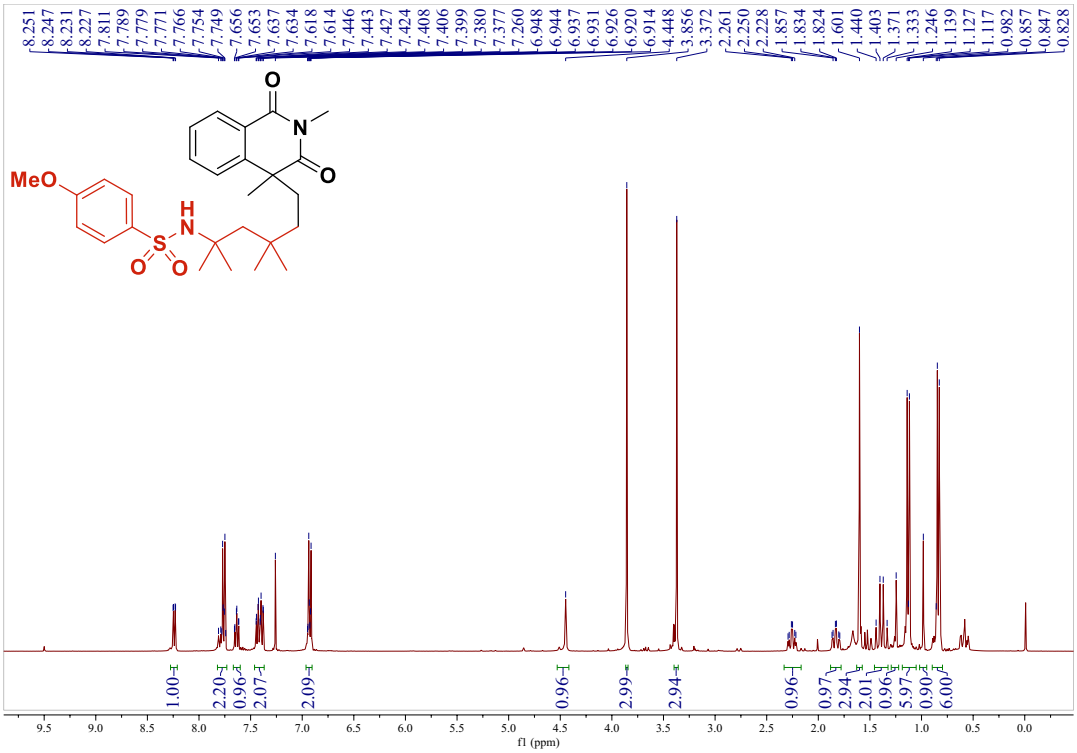


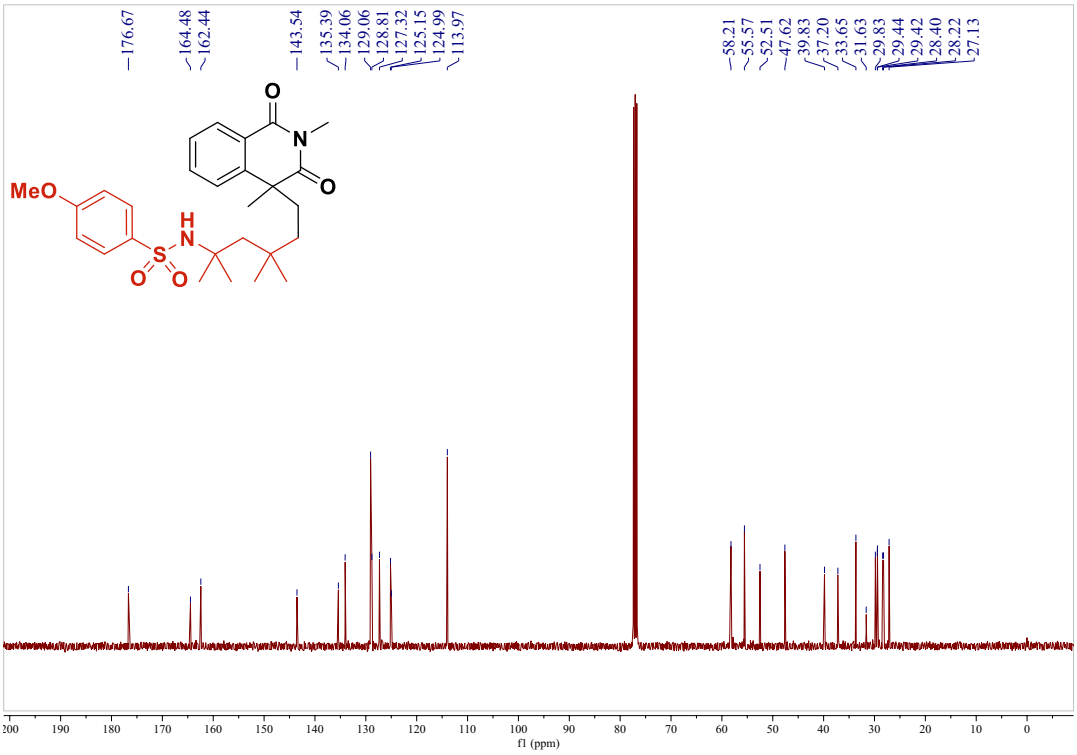
^{1}H and ^{13}C NMR spectra of **5aq**:



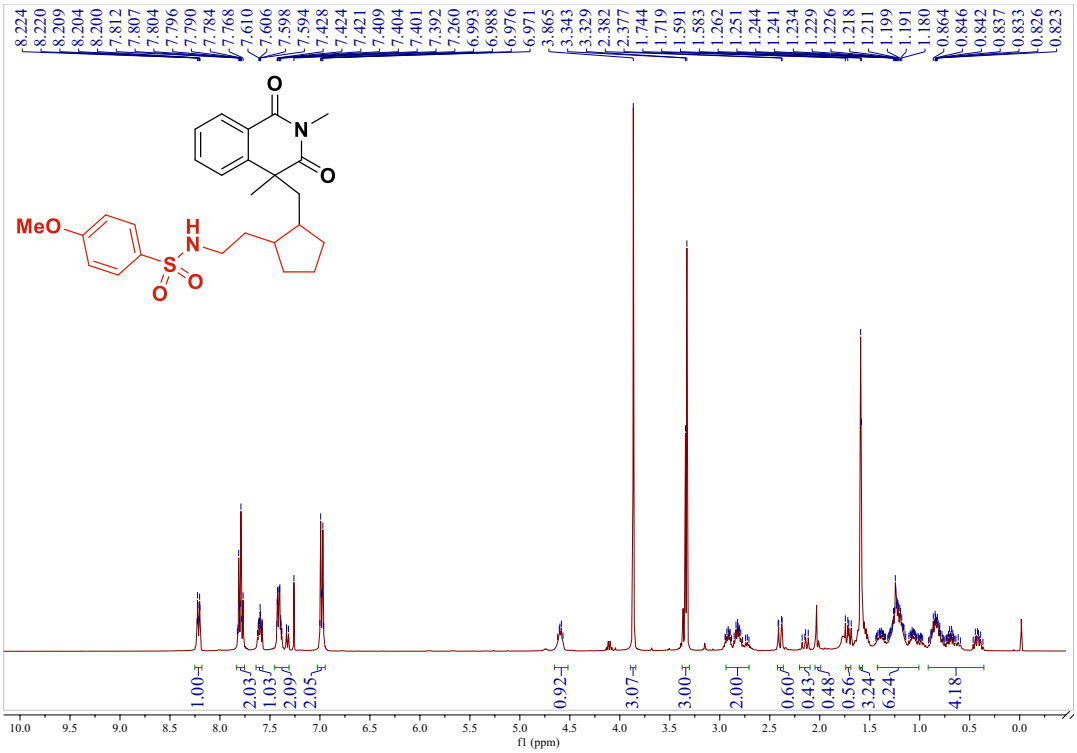


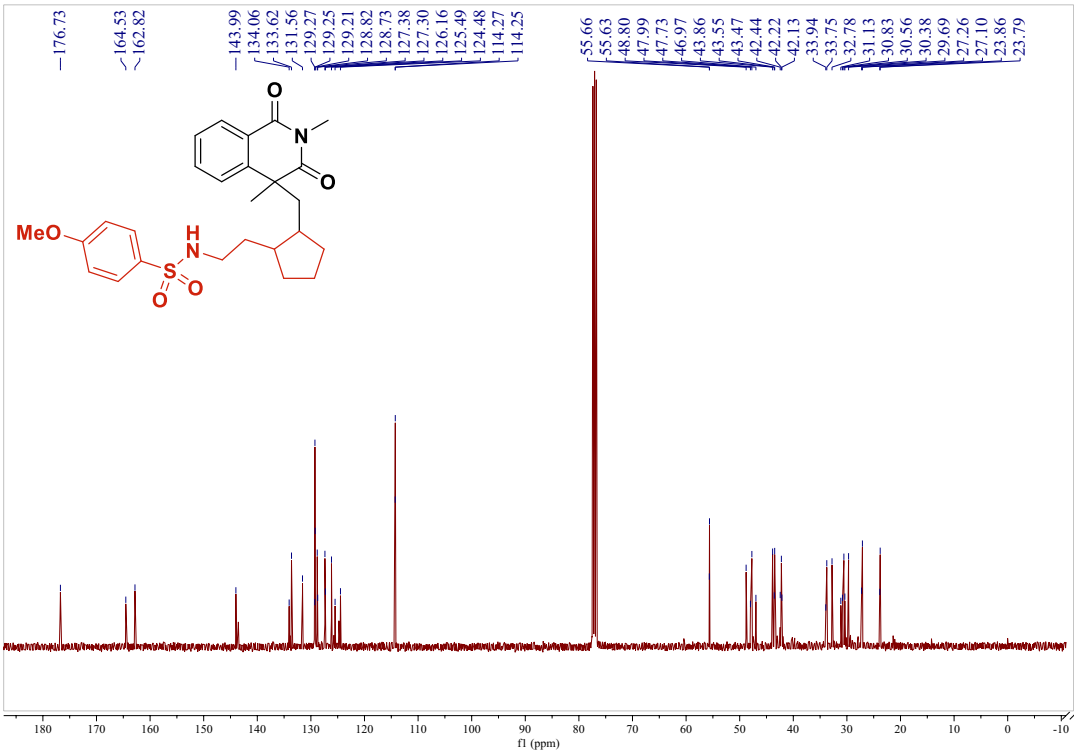
^{1}H and ^{13}C NMR spectra of **5ar**:



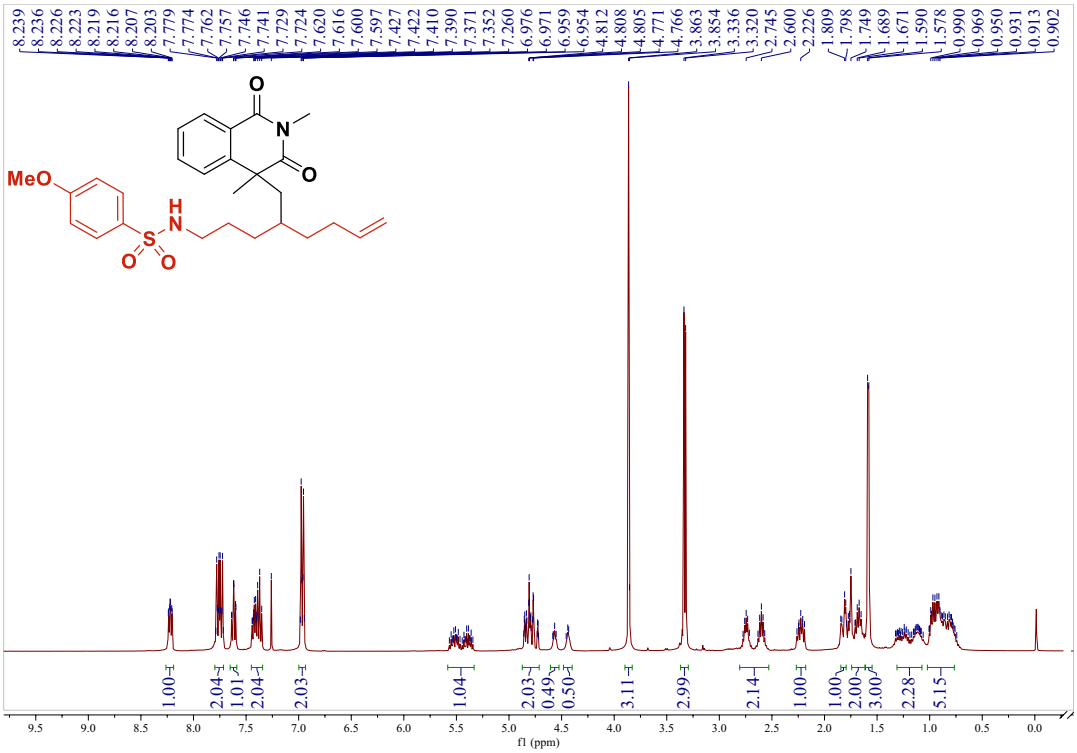


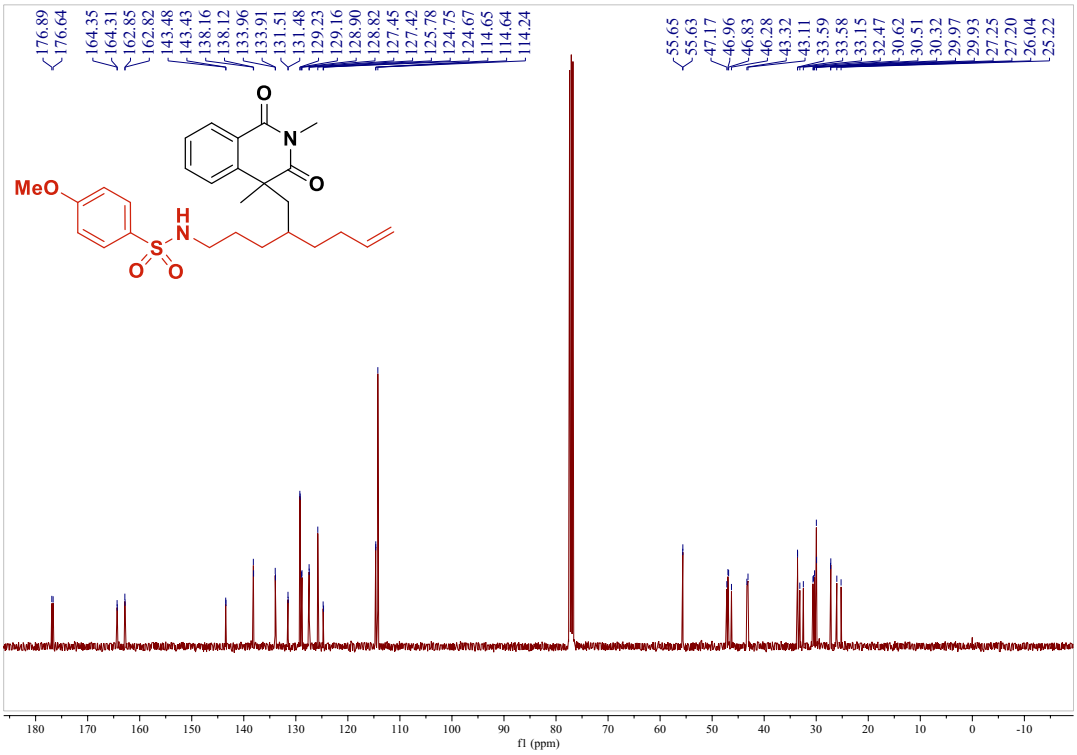
^{1}H and ^{13}C NMR spectra of **5as**:



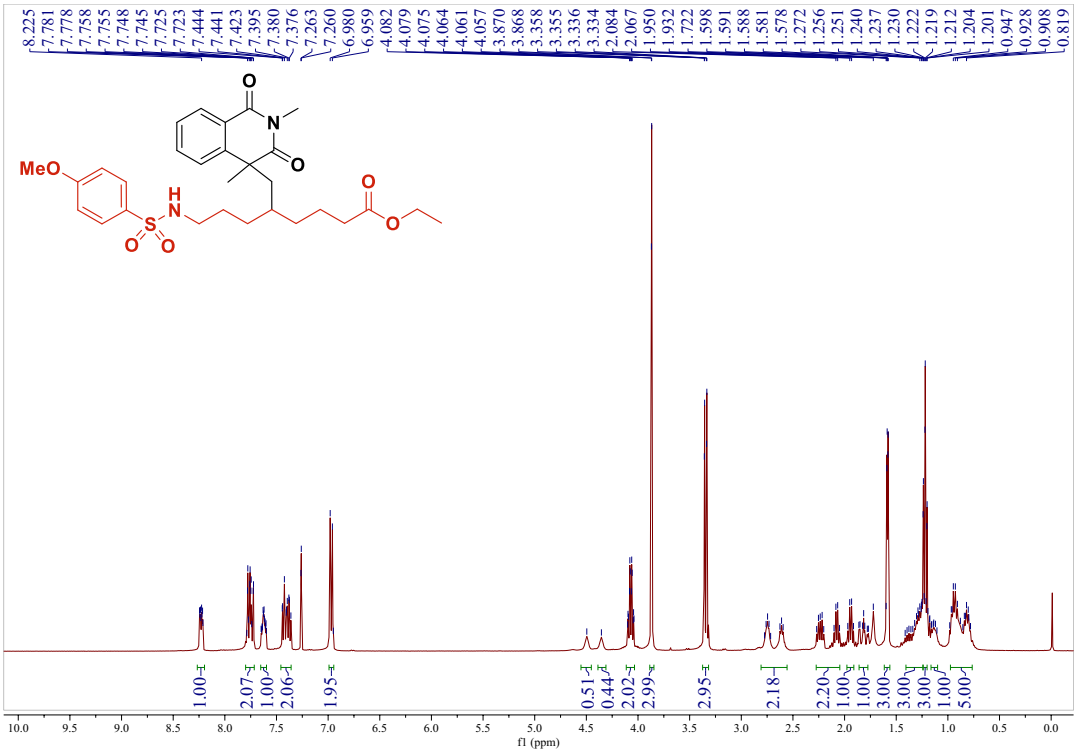


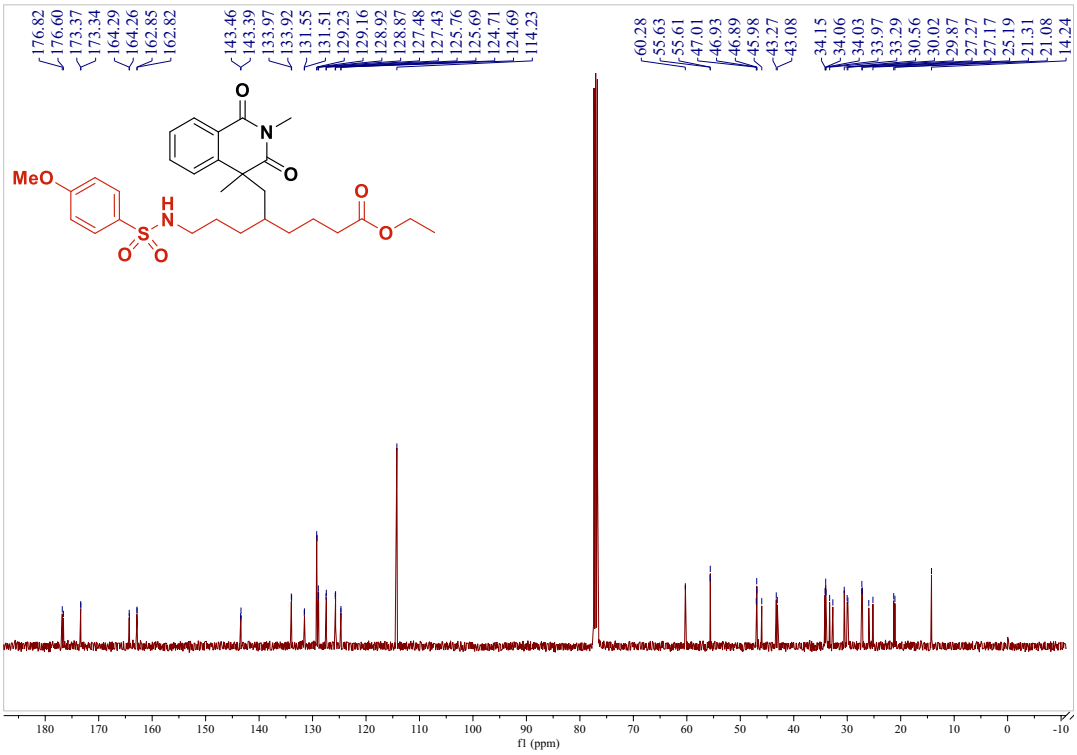
^{1}H and ^{13}C NMR spectra of **5at**:



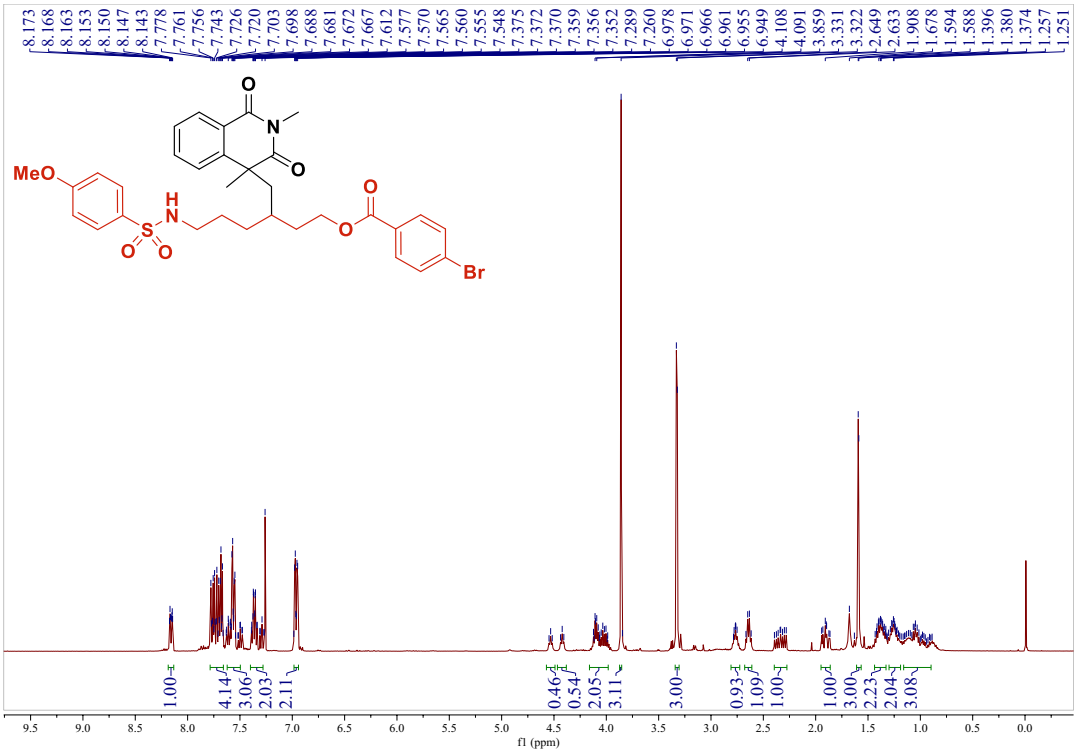


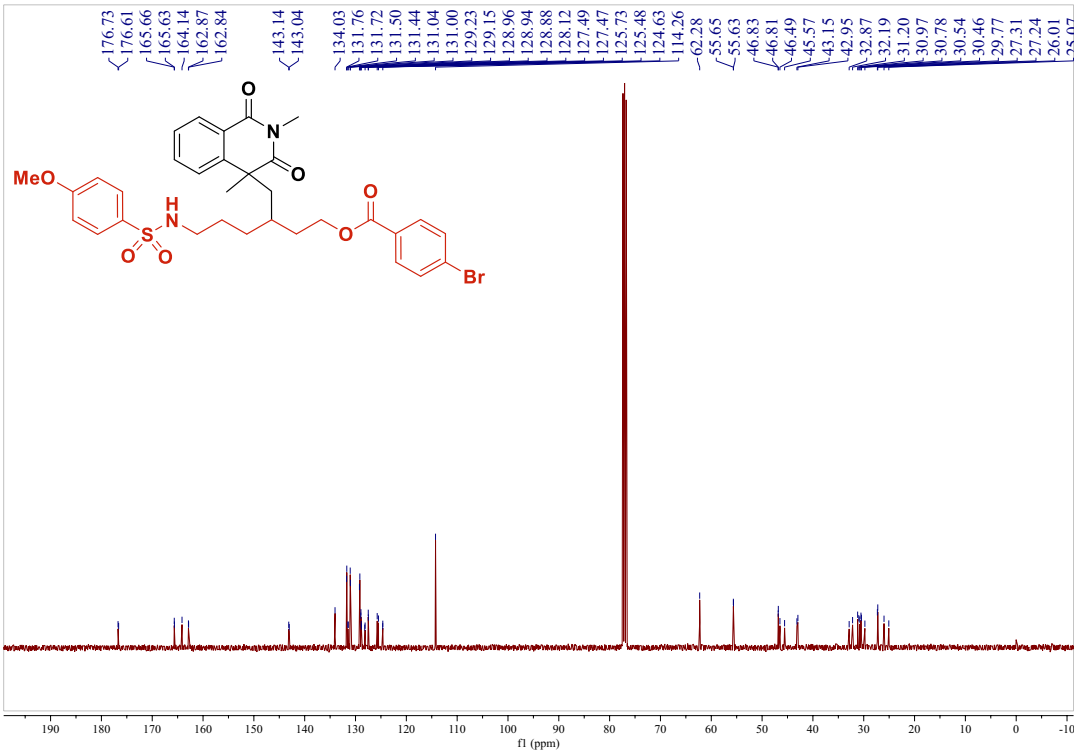
^{1}H and ^{13}C NMR spectra of **5au**:





^{1}H and ^{13}C NMR spectra of **5av**:





^{1}H and ^{13}C NMR spectra of **5aw**: