Supporting Information

Facile synthesis of 1,4-oxazines by ruthenium-catalyzed tandem N-H insertion/cyclization of α-amino ketones and diazo pyruvates

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1. General Information

All the reactions were carried in a flame-dried or oven-dried flask containing a magnetic stir. All ^{1}H-NMR (400 MHz), and ^{13}C-NMR (101 MHz) spectra were recorded on a Bruker spectrometer in DMSO-d_6. Tetramethylsilane (TMS) served as an internal standard ($\delta = 0$) for ^{1}H-NMR, DMSO ($\delta = 39.5$) were used as internal standards for ^{13}C-NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet). HRMS spectra were recorded on IonSpec FT-ICR. α-amino ketones and diazopyruvates were synthesized from reported procedures.[1-3]

2. Experimental Procedures

2.1. General procedure for the preparation of 1,4-oxazine (GP-1):

An oven-dried 10 mL test tube was charged with $RuCl_3.xH_2O$ (10 mol%), α-amino ketone **1** (0.15 mmol, 24.5–43.6 mg), 4 Å MS (100 mg) and 1,4-dioxane (3 mL). To this well-stirred suspension was added diazo pyruvate **2a** (0.35 mmol) in 1,4-dioxane (1.5 mL) over 5 minutes via syringe at room temperature. Then, the mixture was allowed to stir for 1.2–1.8 hours at 45 ^{o}C before the reaction mixture was filtered through Celite and concentrated in vacuo to obtain the crude mixture. The crude mixture was purified by flash column chromatography on silica gel (eluent: petroleum ether / EtOAc= 18:1 to 10:1) to get the pure product **3** (51–88%).

2.2. Procedure for the gram-scale synthesis of 3b:

An oven-dried 100 mL flask was charged with $RuCl_3.xH_2O$ (10 mol%, 85 mg), α-amino ketone **1** (3.8 mmol, 0.8 g), 4 Å MS (500 mg) and 1,4-dioxane (7 mL). To this well-stirred suspension was added diazo pyruvate **2a** (8.7 mmol, 1.4 g) in 1,4-dioxane (15 mL) over 15 minutes via syringe at room temperature. Then, the mixture was allowed to stir for 1.5 hours at 45 ^{o}C before the reaction mixture was filtered through celite and concentrated in vacuo to get the crude mixture. The crude mixture was purified by flash column chromatography on silica gel (eluent: petroleum ether / EtOAc= 16:1 to 12:1) to get the pure product **3b** (0.95g, 74%).

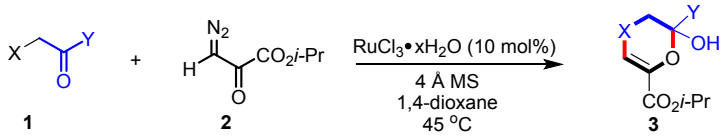
2.3. CCK-8 Assay

HCT116 cells (human colon cancer) was purchased from Cell bank of China Science Academy (Shanghai, China), and cultured aseptically in 5% CO_2 at 37℃ with the corresponding medium supplemented with 10% (V/V) fetal bovine serum and each of penicillin G and streptomycin (100 units per ML). *In vitro* cytotoxicity of the compounds was evaluated by CCK-8 assay. HCT116 cells were seeded in 96-well plates at a concentration 3000-3500 cells/well and incubated for 24 h before compound administration. Each tested compound was dissolved in DMSO (30 mM) and diluted in media. Then the compound was added to the cells at 20 μM. The control cells were treated with the vehicle DMSO. After 72 h incubation, the old medium was removed and 100 μL new medium containing 10 μL CCK-8 solution (5 gL-1) was added to each well, incubated for additional 4 h. Finally, the optical density (OD) was measured at 450 nm and 620 nm (reference wavelength) using a microplate reader (spectraMax M5/M5e, Sunnyvale, CA, USA). IC_{50} value was determined by testing the inhibitory effects of the compound with 10 gradient-dilution concentrations with at least three replicates per concentration.

3. References

1) G. E. B.-Medina, S. O.-Soto, A. Cabrera and M. A.-Valencia, *Eur. J. Org. Chem.* 2019, **23**, 3763–3770.
2) V. L. Pietra, L. Marinelli, S. Cosconati, F. S. D. Leva, E. Nuti, S. Santamaria, I. Pugliesi, M. Morelli, F. Casalini, A. Rossello, C. L. Motta, S. Taliani, R. Visse, H. Nagase, F. D. Settimo and E. Novellino, *Eur. J. Med. Chem.* 2012, **47**, 1433–152.
3) P.Muller and S. Chappellet, *Helv. Chim. Acta,* 2005, **88**, 1010.
4) V. Ručilova, M. Malo, and M. Soural, *Eur. J. Org. Chem.* 2018, 564-570.

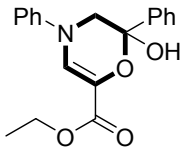
4. Table S1: Limitation of the Reaction:



entry	X	Y	3
1	$-NH_2$	Ph	N.D
2	$-NHCH_2CH_3$	Ph	N.D
3	-SH	Ph	N.D
4	-OH	Ph	N.D
5	$-CH_2$-NH-Ph	Ph	N.D
6	-NH-Ph	2-thiophene	<10% (NMR is not clean, unstable)

5. Characterization Data of the Products:

Ethyl 2-hydroxy-2,4-diphenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3a):



3a

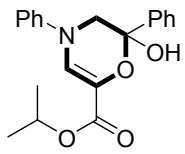
Synthesized from α-amino ketone **1a** (31 mg) and ethyl diazopyruvate **2a** (49.1 mg) by following **GP-1** on a 0.15 mmol scale of **1a**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3a** (33.1 mg, 69%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (m, 2H), 7.48 (s, 1H), 7.45 – 7.27 (m, 5H), 7.23 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 6.8 Hz, 1H), 4.18 (q, *J* = 7.1, 2H), 3.75 (d, *J* = 12.1 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.99, 144.04, 141.43, 129.37, 128.48, 128.08, 126.12, 124.16, 121.75, 119.92, 115.97, 93.39, 59.49, 53.37, 14.41.

HRMS (ESI): calcd. for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$ = 348.1212 found 348.1227.

Isopropyl 2-hydroxy-2,4-diphenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3b):



3b

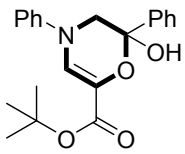
Synthesized from α-amino ketone **1a** (31.2 mg) and isopropyl diazopyruvate **2b** (50 mg) by following **GP-1** on a 0.15 mmol scale of **1a**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3b** (43.4 mg, 86%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.37 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.23 (br s, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.00 (t, *J* = 7.2 Hz, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.74 (d, *J* = 12.1 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.52, 144.07, 141.45, 129.37, 128.47, 128.08, 126.12, 124.43, 121.71, 119.75, 115.95, 93.42, 66.74, 53.35, 21.84, 21.81.

HRMS (ESI): calcd. for $C_{20}H_{22}NO_4$ $[M+H]^+$ = 340.1549 found 340.1572.

Tert-butyl 2-hydroxy-2,4-diphenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3c):



3c

Synthesized from α-amino ketone **1a** (41.9 mg) and *tert*-butyl diazopyruvate **2c** (66 mg) by following **GP-1** on a 0.2 mmol scale of

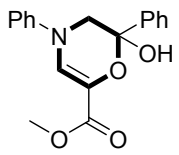
1a. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 14:1) to afford 1,4-oxazine **3c** (54.2 mg, 77%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, *J* = 6.7 Hz, 2H), 7.47 – 7.26 (m, 6H), 7.18 (d, *J* = 1.5 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 7.01 (t, *J* = 7.2 Hz, 1H), 3.73 (d, *J* = 12.1 Hz, 1H), 3.41 (d, *J* = 12.1 Hz, 1H), 1.49 (s, 9H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.27, 144.16, 141.53, 129.37, 128.43, 128.05, 126.10, 125.06, 121.54, 119.29, 115.84, 93.42, 79.43, 53.25, 28.03.

HRMS (ESI): calcd. for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ = 376.1525 found 376.1512.

Methyl 2-hydroxy-2,4-diphenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3d):



3d

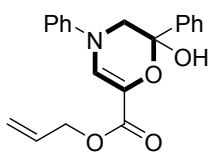
Synthesized from α-amino ketone **1a** (31.6 mg) and methyl diazopyruvate **2d** (44.2 mg) by following **GP-1** on a 0.15 mmol scale of **1a**. Isolated by flash chromatography on silica gel (PE/EtOAc = 15:1 to 10:1) to afford 1,4-oxazine **3d** (33.6 mg, 72%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, *J* = 6.0 Hz, 2H), 7.50 (s, 1H), 7.47 – 7.27 (m, 5H), 7.23 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.00 (t, *J* = 6.1 Hz, 1H), 3.75 (d, *J* = 12.1 Hz, 1H), 3.70 (s, 3H), 3.46 (d, *J* = 12.1 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.44, 144.01, 141.41, 129.36, 128.49, 128.08, 126.11, 123.93, 121.79, 120.08, 115.99, 93.33, 53.38, 50.99.

HRMS (ESI): calcd. for $C_{18}H_{17}NO_4Na$ $[M+Na]^+$ = 334.1055 found 334.1053.

Allyl 2-hydroxy-2,4-diphenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3e):



3e

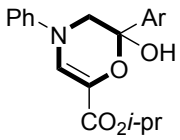
Synthesized from α-amino ketone **1a** (31.2 mg) and allyl diazopyruvate **2e** (51 mg) by following **GP-1** on a 0.15 mmol scale of **1a**. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 14:1) to afford 1,4-oxazine **3e** (36 mg, 72%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 – 7.49 (m, 3H), 7.46 – 7.28 (m, 5H), 7.25 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.01 (t, *J* = 7.0 Hz, 1H), 6.10-5.94 (m, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.1 Hz, 1H), 4.67 (s, 2H), 3.76 (d, *J* = 12.1 Hz, 1H), 3.47 (d, *J* = 12.1 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.62, 144.01, 141.41, 133.16, 129.38, 128.50, 128.09, 126.11, 123.83, 121.87, 120.32, 117.60, 116.06, 93.37, 63.98, 53.44.

HRMS (ESI): calcd. for $C_{20}H_{20}NO_4$ $[M+H]^+$ = 338.1392 found 338.1369.

Isopropyl 2-(3-chlorophenyl)-2-hydroxy-4-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3f):



3f
(Ar=3-Cl-C_6H_4)

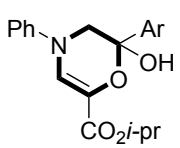
Synthesized from α-amino ketone **1b** (36.7 mg) and isopropyl diazopyruvate **2b** (54.1 mg) by following **GP-1** on a 0.15 mmol scale of **1b**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3f** (34 mg, 61%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 – 7.56 (m, 1H), 7.54 – 7.43 (m, 4H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.01 (t, *J* = 7.3 Hz, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.79 (d, *J* = 12.1 Hz, 1H), 3.50 (d, *J* = 12.1 Hz, 1H), 1.27 (d, *J* = 6.2, 3H), 1.25 (d, *J* = 6.3, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.40, 143.97, 143.80, 132.86, 130.14, 129.37, 128.47, 126.18, 124.94, 124.19, 121.83, 119.94, 116.05, 93.02, 66.82, 52.92, 21.83, 21.79.

HRMS (ESI): calcd. for $C_{20}H_{21}NO_4Cl$ $[M+H]^+$ = 374.1159 found 374.1141.

Isopropyl 2-hydroxy-4-phenyl-2-(*p*-tolyl)-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3g):



3g
(Ar=4-Me-C_6H_4)

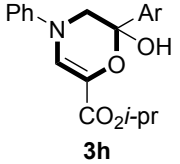
Synthesized from α-amino ketone **1c** (33.6 mg) and isopropyl diazopyruvate **2b** (54 mg) by following **GP-1** on a 0.15 mmol scale of **1c**. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 14:1) to afford 1,4-oxazine **3g** (34.7 mg, 66%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 – 7.40 (m, 3H), 7.36 – 7.29 (t, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 1.5 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 5.01 (hept, *J* = 6.2 Hz, 1H), 3.70 (d, *J* = 12.1 Hz, 1H), 3.44 (d, *J* = 12.1 Hz, 1H), 2.32 (s, 3H), 1.26 (d, *J* = 6.2, 3H), 1.24 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.53, 144.05, 138.59, 137.71, 129.38, 128.60, 126.02, 124.44, 121.67, 119.68, 115.89, 93.47, 66.71, 53.33, 21.84, 21.80, 20.69.

HRMS (ESI): calcd. for $C_{21}H_{23}NO_4Na$ $[M+Na]^+$ = 376.1525 found 376.1512.

Isopropyl 2-(4-bromophenyl)-2-hydroxy-4-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate carboxylate (3h):



3h
(Ar=4-Br-C_6H_4)

Synthesized from α-amino ketone **1d** (43.2 mg) and isopropyl diazopyruvate **2b** (54.9 mg) by following **GP-1** on a 0.15 mmol scale

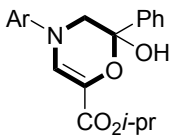
of **1d**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3h** (39.2 mg, 63%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.63 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.44 (s, 1H), 7.33 (t, *J* = 8.0 Hz, 3H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.75 (d, *J* = 12.1 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 1.26 (d, *J* = 6.2, 3H), 1.24 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.41, 143.98, 140.83, 131.06, 129.38, 128.47, 124.27, 121.90, 121.81, 119.86, 116.00, 93.22, 66.80, 53.00, 21.83, 21.79.

HRMS (ESI): calcd. for $C_{20}H_{21}NO_4Br$ $[M+H]^+$ = 418.0654 found 418.0676.

Isopropyl 4-(3-bromophenyl)-2-hydroxy-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3i):



3i
(Ar=3-Br-C_6H_4)

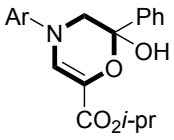
Synthesized from α-amino ketone **1e** (43.6 mg) and isopropyl diazopyruvate **2b** (55.6 mg) by following **GP-1** on a 0.15 mmol scale of **1e**. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 14:1) to afford 1,4-oxazine **3i** (41.5 mg, 67%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 – 7.51 (m, 2H), 7.46– 7.36 (m, 4H), 7.30 – 7.23 (m, 3H), 7.18 – 7.09 (m, 2H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.78 (d, *J* = 12.1 Hz, 1H), 3.42 (d, *J* = 12.1 Hz, 1H), 1.27 (d, *J* = 6.2, 3H), 1.25 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.42, 145.50, 141.22, 131.12, 128.52, 128.07, 126.15, 125.36, 124.09, 122.51, 118.79, 118.41, 114.85, 93.61, 67.00, 53.21, 21.80, 21.77.

HRMS (ESI): calcd. for $C_{20}H_{21}NO_4Br$ $[M+H]^+$ = 418.0654 found 418.0625.

Isopropyl 4-(3-bromophenyl)-2-hydroxy-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3j):



3j
(Ar=3-SCH_3-C_6H_4)

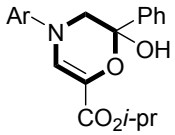
Synthesized from α-amino ketone **1f** (39.1 mg) and isopropyl diazopyruvate **2b** (57.6 mg) by following **GP-1** on a 0.15 mmol scale of **1f**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3j** (29.9 mg, 51%) as Semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, *J* = 7.2 Hz, 2H), 7.41 – 7.38 (m, 4H), 7.26 (t, *J* = 8.1 Hz, 1H), 7.22 (s, 1H), 6.89 (s, 2H), 6.88 (s, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.76 (d, *J* = 12.1 Hz, 1H), 3.45 (d, *J* = 12.1 Hz, 1H), 2.48 (s, 3H), 1.27 (d, *J* = 6.2, 3H), 1.25 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.50, 144.62, 141.38, 139.62, 129.75, 128.48, 128.07, 126.16, 124.75, 119.50, 119.09, 113.16, 112.71, 93.50, 66.84, 53.34, 21.83, 21.80, 14.51.

HRMS (ESI): calcd. for $C_{21}H_{23}NO_4NaS$ $[M+Na]^+$ = 408.1245 found 408.1271.

Isopropyl 4-(4-chlorophenyl)-2-hydroxy-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3k):



3k
(Ar=4-Cl-C_6H_4)

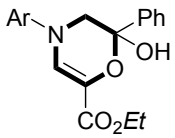
Synthesized from α-amino ketone **1g** (36 mg) and isopropyl diazopyruvate **2b** (56.1 mg) by following **GP-1** on a 0.15 mmol scale of **1g**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3k** (42.3 mg, 77%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, *J* = 6.7 Hz, 2H), 7.46 – 7.31 (m, 6H), 7.26 (d, *J* = 1.2 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.73 (d, *J* = 12.1 Hz, 1H), 3.44 (d, *J* = 12.1 Hz, 1H), 1.26 (d, *J* = 6.2, 3H), 1.24 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.44, 142.93, 141.26, 129.07, 128.52, 128.09, 126.12, 125.37, 124.95, 119.14, 117.52, 93.51, 66.90, 53.29, 21.81, 21.78.

HRMS (ESI): calcd. for $C_{20}H_{21}NO_4Cl$ $[M+H]^+$ = 374.1159 found 374.1141.

Ethyl 2-hydroxy-4-(4-methoxyphenyl)-2-phenyl-3,4-dihydro-2H-1,4-oxazine-6-carboxylate (3l):



3l
(Ar=4-OMe-C_6H_4)

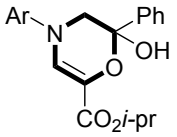
Synthesized from α-amino ketone **1h** (35.9 mg) and ethyl diazopyruvate **2a** (50.4 mg) by following **GP-1** on a 0.15 mmol scale of **1h**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3l** (33.7 mg, 64%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (s, 2H), 7.45 – 7.32 (m, 4H), 7.16 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 4.15 (br, 2H), 3.72 (s, 3H), 3.66 (d, *J* = 12.1 Hz, 1H), 3.46 (d, *J* = 12.1 Hz, 1H), 1.24 (br, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.02, 154.75, 141.54, 138.20, 128.41, 128.05, 126.10, 123.26, 121.17, 117.92, 114.58, 93.08, 59.30, 55.29, 54.17, 14.43.

HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ $[M+H]^+$ = 356.1498 found 356.1480.

Isopropyl 2-hydroxy-4-(naphthalen-2-yl)-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3m):



3m
(Ar=4-Ph-C_6H_4)

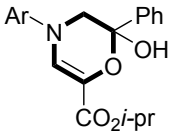
Synthesized from α-amino ketone **1i** (42.8 mg) and isopropyl diazopyruvate **2b** (57 mg) by following **GP-1** on a 0.15 mmol scale of **1i**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 10:1) to afford 1,4-oxazine **3m** (37.1 mg, 60%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 – 7.61 (m, 4H), 7.58 (d, *J* = 6.8 Hz, 2H), 7.50 (s, 1H), 7.46 – 7.38 (m, 5H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.26 (m, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 5.03 (hept, *J* = 6.2 Hz, 1H), 3.80 (d, *J* =12.1, 1H), 3.50 (d, *J* = 12.1, 1H), 1.28 (d, *J* = 6.2 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 1H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.50, 143.39, 141.40, 139.47, 133.32, 128.89, 128.50, 128.10, 127.52, 126.86, 126.13, 126.07, 124.73, 119.38, 116.28, 93.53, 66.83, 53.31, 21.81, 21.85.

HRMS (ESI): calcd. for $C_{26}H_{26}NO_4$ $[M+H]^+$ = 416.1862 found 416.1838.

Isopropyl 4-(3,5-dimethylphenyl)-2-hydroxy-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3n):



3n
(Ar=3,5-Me_2-C_6H_3)

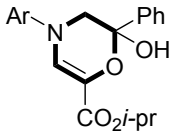
Synthesized from α-amino ketone **1j** (35.9 mg) and isopropyl diazopyruvate **2b** (54.1 mg) by following **GP-1** on a 0.15 mmol scale of **1j**. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 14:1) to afford 1,4-oxazine **3n** (42.1 mg, 76%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.54 (d, *J* = 6.7 Hz, 2H), 7.48 – 7.33 (m, 4H), 7.18 (d, *J* = 1.5 Hz, 1H), 6.72 (s, 2H), 6.64 (s, 1H), 5.01 (hept, *J* = 6.2 Hz, 1H), 3.71 (d, *J* = 12.1 Hz, 1H), 3.42 (m, 1H), 2.25 (s, 6H), 1.26 (d, *J* = 6.2, 3H), 1.24 (d, *J* = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.62, 144.07, 141.49, 138.56, 128.44, 128.07, 126.11, 124.15, 123.45, 119.91, 113.74, 93.35, 66.72, 53.48, 21.86, 21.82, 21.01.

HRMS (ESI): calcd. for $C_{22}H_{25}NO_4Na$ $[M+Na]^+$ = 390.1681 found 390.1654.

Isopropyl 2-hydroxy-4-(naphthalen-2-yl)-2-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3o):



3o
(Ar=2-napthyl)

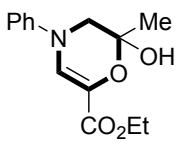
Synthesized from α-amino ketone **1k** (39 mg) and isopropyl diazopyruvate **2b** (55.7 mg) by following **GP-1** on a 0.15 mmol scale of **1k**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3o** (44.5 mg, 76%) as brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.67 – 7.56 (m, 3H), 7.51 – 7.32 (m, 7H), 7.29 (d, J = 1.5 Hz, 1H), 5.04 (hept, J = 6.2 Hz, 1H), 3.90 (d, J = 12.1 Hz, 1H), 3.57 (d, J = 12.1 Hz, 1H), 1.29 (d, J = 6.2, 3H), 1.27 (d, J = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.57, 141.60, 141.42, 133.84, 129.20, 128.81, 128.51, 128.11, 127.41, 126.95, 126.63, 126.17, 124.80, 124.04, 119.63, 117.06, 111.25, 93.59, 66.87, 53.48, 21.87, 21.83.

HRMS (ESI): calcd. for $C_{24}H_{24}NO_4$ $[M+H]^+$ = 390.1705 found 390.1675.

Ethyl 2-hydroxy-2-methyl-4-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3p):



3p

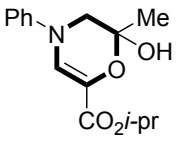
Synthesized from α-amino ketone **1l** (24.5 mg) and ethyl diazopyruvate **2a** (49.9 mg) by following **GP-1** on a 0.15 mmol scale of **1l**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 10:1) to afford 1,4-oxazine **3p** (31.2 mg, 73%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 – 7.25 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 6.99 (br, 1H), 6.72 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.60 (d, J = 12.1 Hz, 1H), 3.34 – 3.37 (m, 1H), 1.46 (s, 3H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.98, 144.07, 129.38, 123.53, 121.50, 119.28, 115.59, 92.71, 59.38, 52.09, 24.87, 14.38.

HRMS (ESI): calcd. for $C_{14}H_{17}NO_4Na$ $[M+Na]^+$ = 286.1055 found 286.1045.

Isopropyl 2-hydroxy-2-methyl-4-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3q):



3q

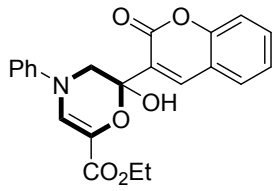
Synthesized from α-amino ketone **1l** (29.8 mg) and isopropyl diazopyruvate **2b** (72 mg) by following **GP-1** on a 0.2 mmol scale of **1l**. Isolated by flash chromatography on silica gel (PE/EtOAc = 18:1 to 12:1) to afford 1,4-oxazine **3q** (48.5 mg, 88%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (t, J = 7.3 Hz, 3H), 7.08 (d, J = 7.8 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 6.72 (d, J = 1.0 Hz, 1H), 4.98 (hept, J = 6.2 Hz, 1H), 3.58 (d, J = 12.1 Hz, 1H), 3.35 (m, 1H), 1.46 (s, 3H), 1.23 (d, J = 6.2, 3H), 1.22 (d, J = 6.2, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.54, 144.11, 129.39, 123.83, 121.46, 119.11, 115.57, 92.76, 66.63, 52.06, 24.88, 21.80, 21.78.

HRMS (ESI): calcd. for $C_{15}H_{20}NO_4$ $[M+H]^+$ = 278.1392 found 278.1369.

Ethyl 2-hydroxy-2-(2-oxo-2H-chromen-3-yl)-4-phenyl-3,4-dihydro-*2H*-1,4-oxazine-6-carboxylate (3r):



3r

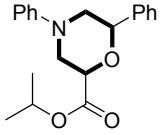
Synthesized from α-amino ketone **1m** (41.9 mg) and ethyl diazopyruvate **2a** (49 mg) by following **GP-1** on a 0.15 mmol scale of **1m**. Isolated by flash chromatography on silica gel (PE/EtOAc = 16:1 to 12:1) to afford 1,4-oxazine **3r** (41.8 mg, 71%) as semi-solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.85 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.67 (m, 1H), 7.53 (s, 1H), 7.44 (t, *J* = 4.1 Hz, 2H), 7.42 – 7.31 (m, 3H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.02 (t, *J* = 7.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.92 (d, *J* = 12.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.64, 158.19, 153.28, 143.97, 141.18, 132.65, 129.45, 129.26, 125.76, 124.81, 123.28, 121.98, 120.24, 118.11, 116.05, 115.87, 92.04, 59.65, 49.88, 14.39.

HRMS (ESI): calcd. for $C_{22}H_{19}NO_6Na$ $[M+Na]^+$ = 416.1110 found 416.1075.

Isopropyl -4,6-diphenylmorpholine-2-carboxylate (4b):



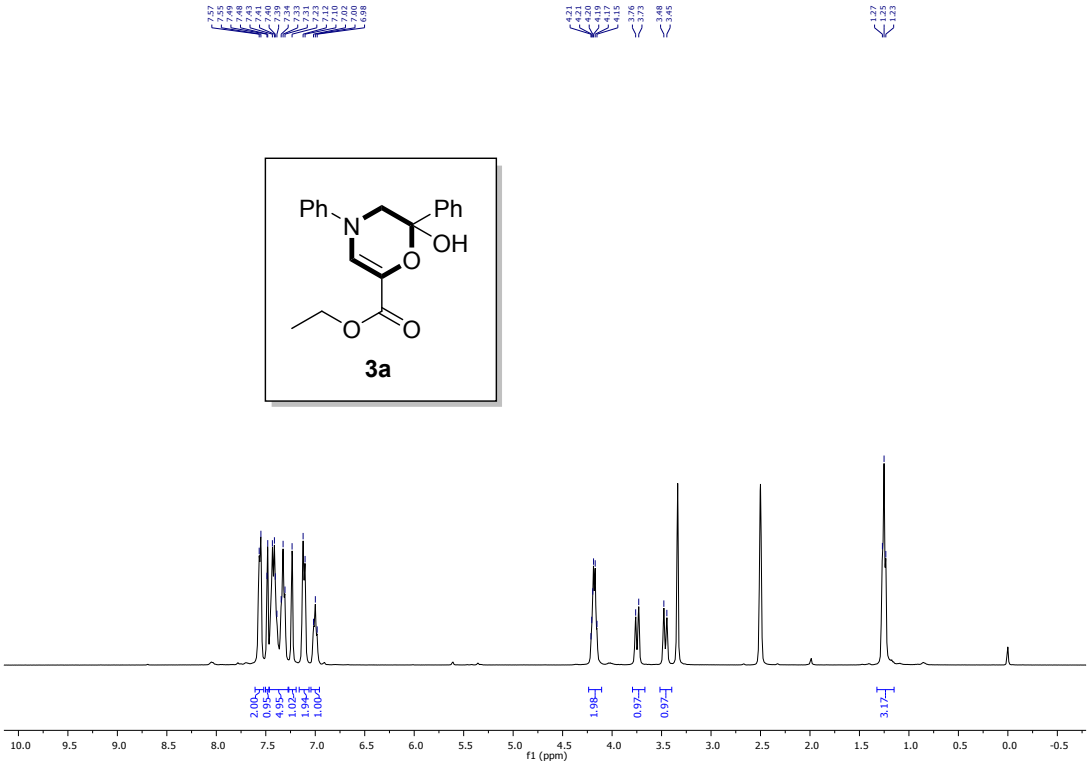
4b

The desired product **4b** (61%) was synthesized by using reported method.[4] **^{1}H NMR (400 MHz, DMSO-d$_6$)** δ 7.49 (d, J = 7.1 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.32 (m, 1H), 7.25 (m, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.85 (t, J = 7.3 Hz, 1H), 5.02 (hept, J = 6.2 Hz, 1H), 4.77 (dd, J = 10.6, 2.4 Hz, 1H), 4.48 (dd, J = 10.9, 2.8 Hz, 1H), 3.85 (d, J = 11.7 Hz, 1H), 3.75 (d, J = 11.9 Hz, 1H), 2.77 (t, J = 11.5 Hz, 1H), 2.63 (dd, J = 12.2, 10.6 Hz, 1H), 1.26 (d, J = 6.2 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H).

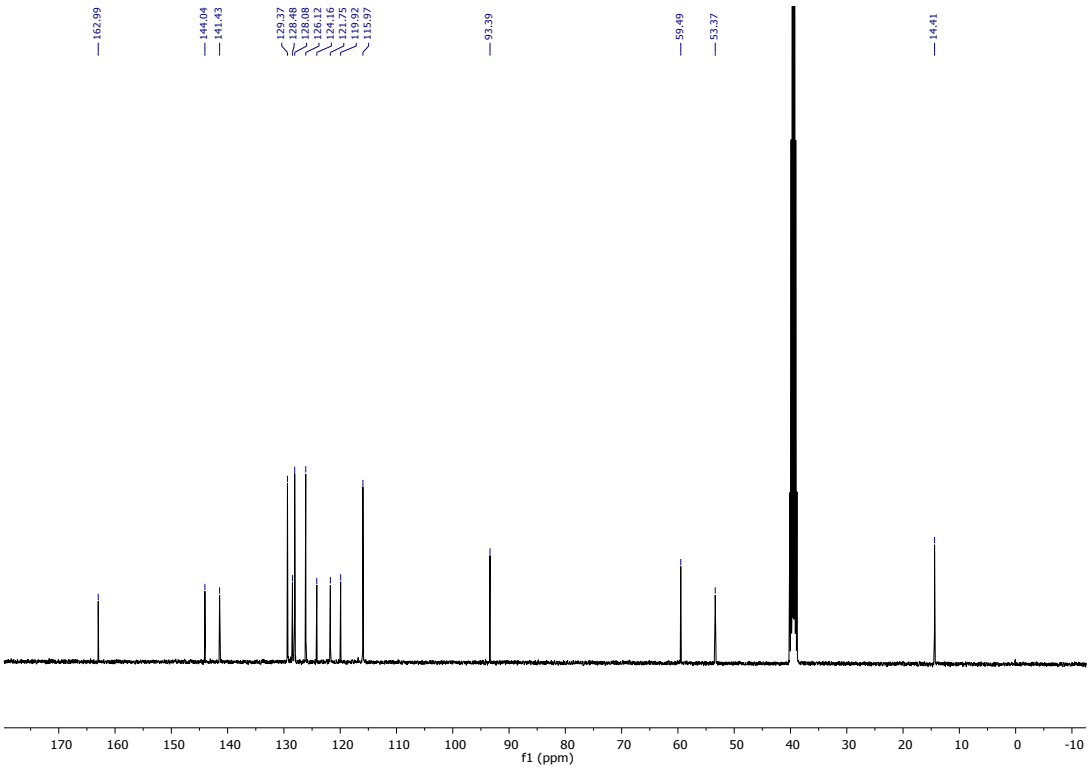
^{13}C NMR (126 MHz, DMSO) δ 168.72, 150.66, 139.73, 129.56, 128.71, 128.41, 126.90, 120.29, 116.41, 77.24, 74.76, 68.89, 54.63, 50.04, 21.96.

HRMS (ESI): calcd. for $C_{20}H_{24}NO_3$ $[M+H]+$ = 326.1756 found 326.1741.

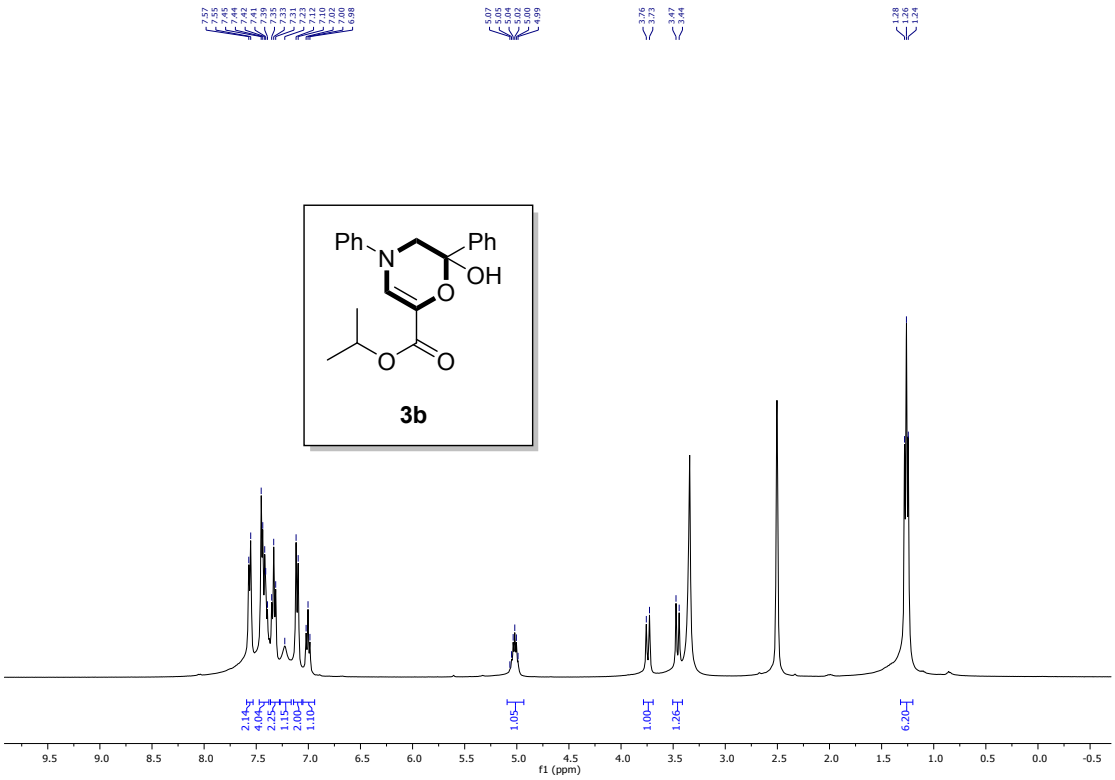
6. NMR Spectra of the Products



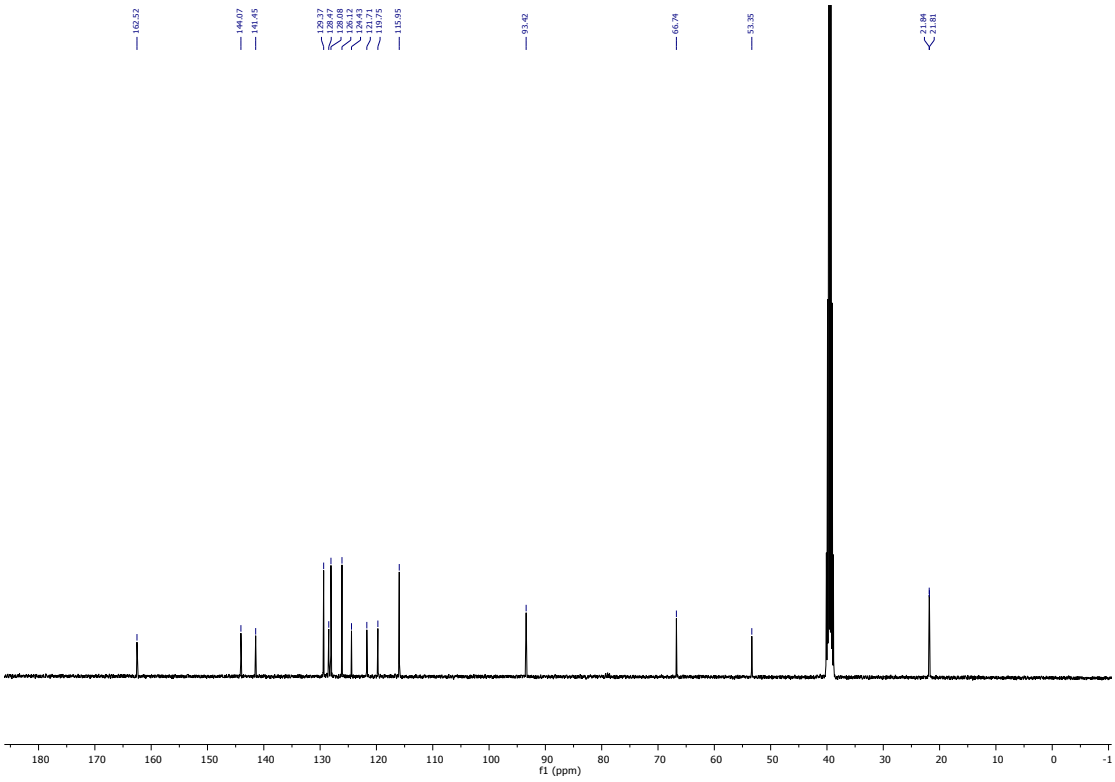
^{1}H NMR (400 MHz) spectrum of compound **3a** in DMSO-d_6



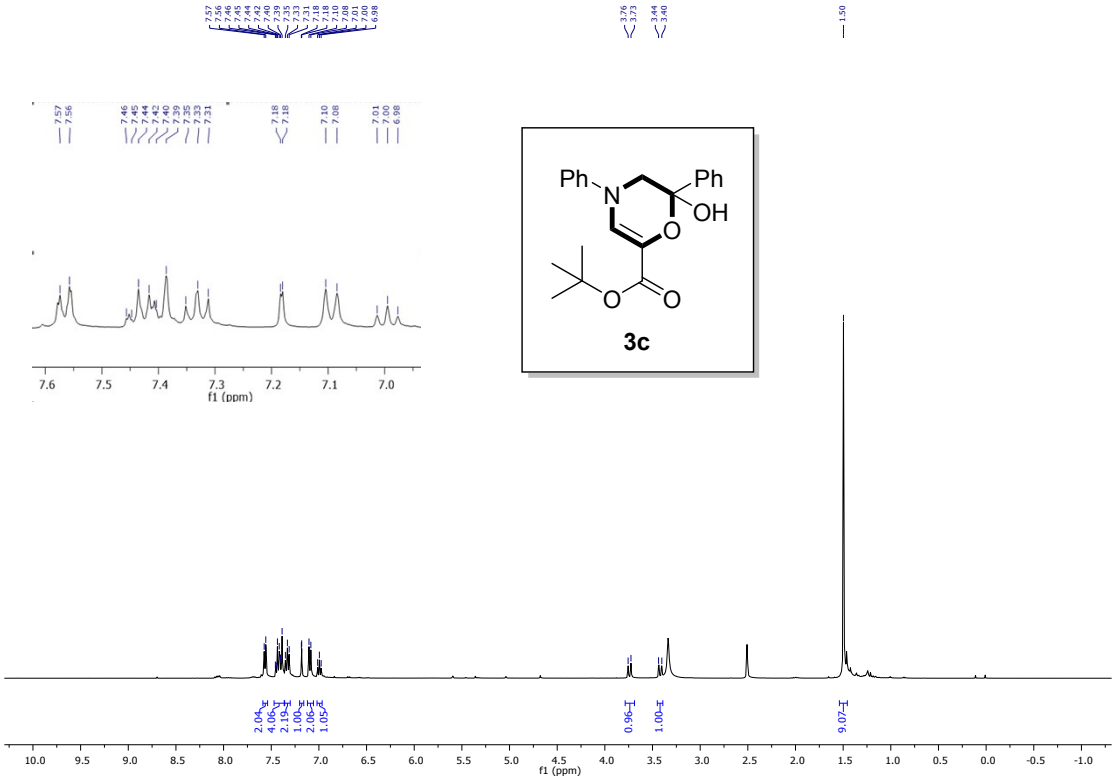
^{13}C NMR (101 MHz) spectrum of compound **3a** in DMSO-d_6



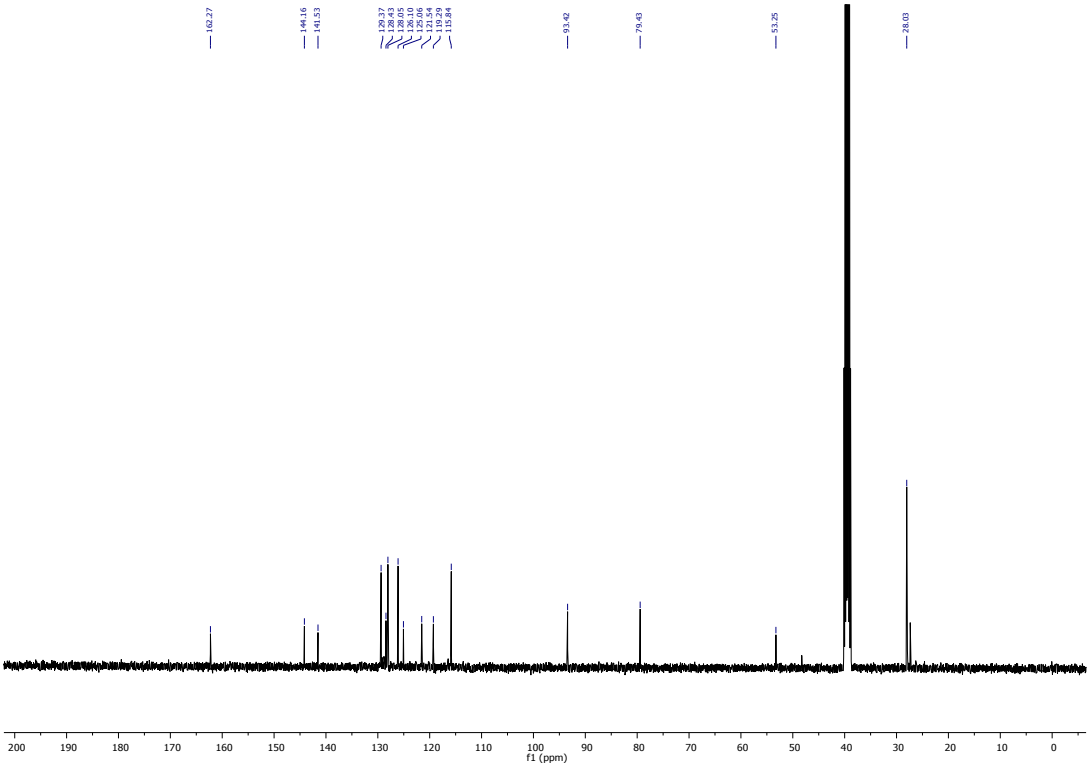
^{1}H NMR (400 MHz) spectrum of compound **3b** in DMSO-d_6



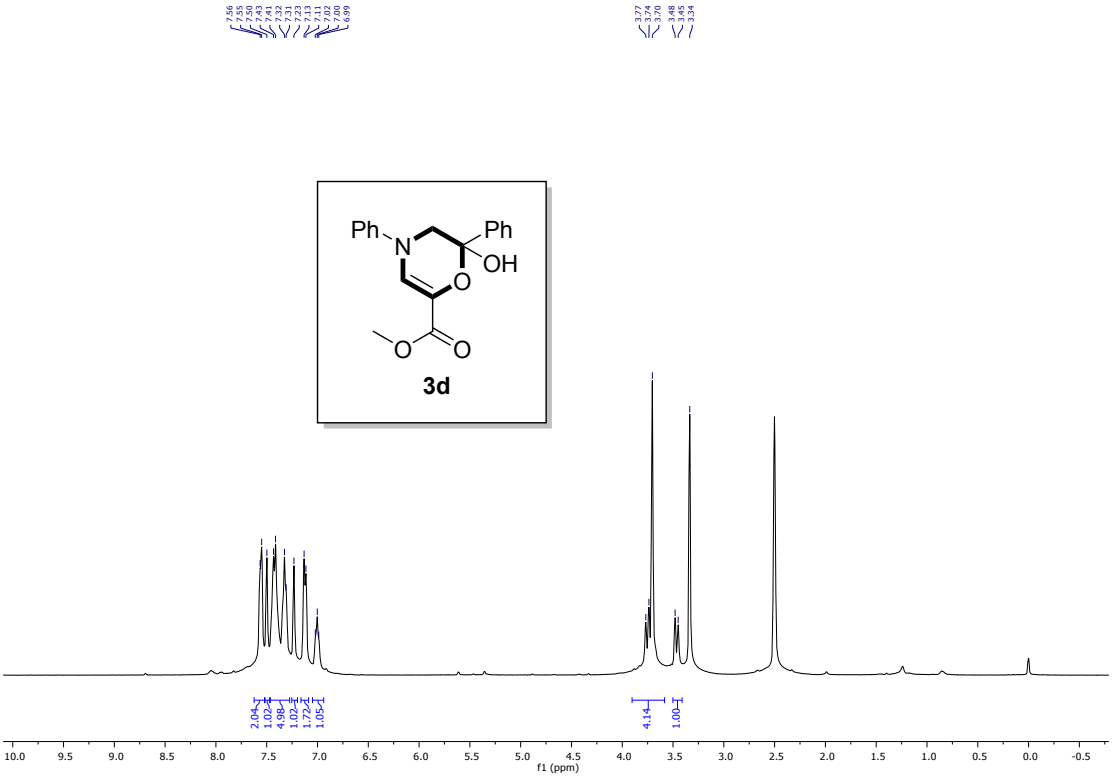
^{13}C NMR (101 MHz) spectrum of compound **3b** in DMSO-d_6



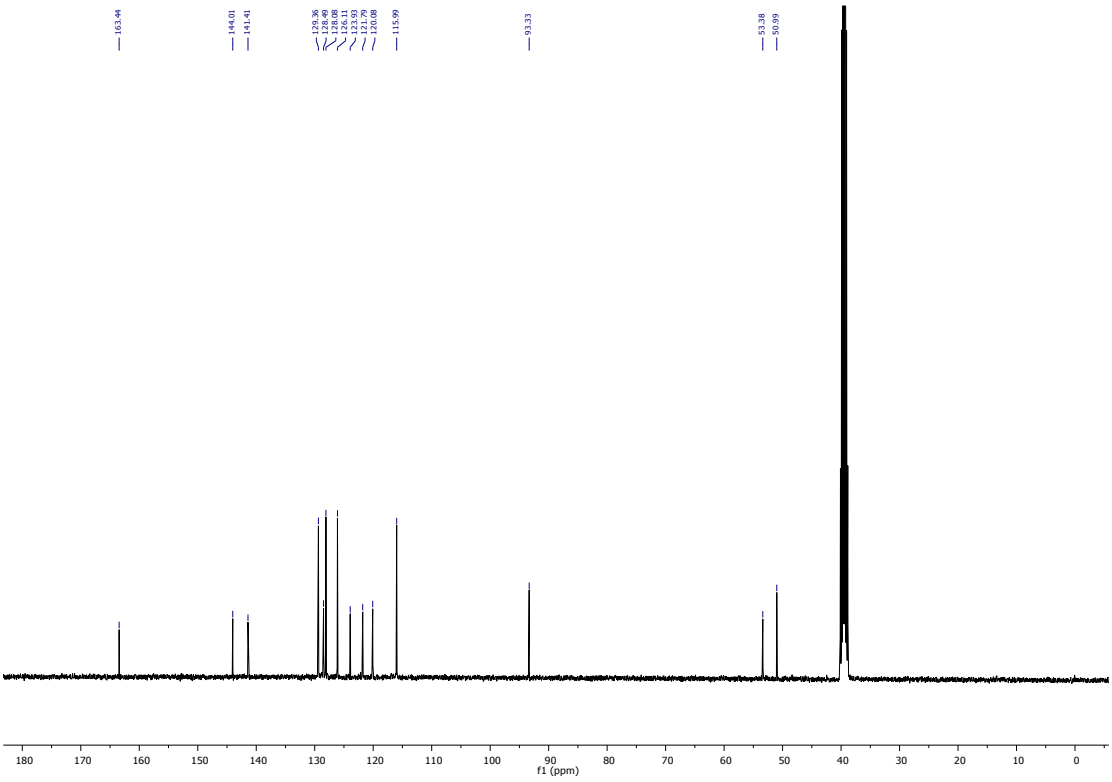
^{1}H NMR (400 MHz) spectrum of compound **3c** in DMSO-d_6



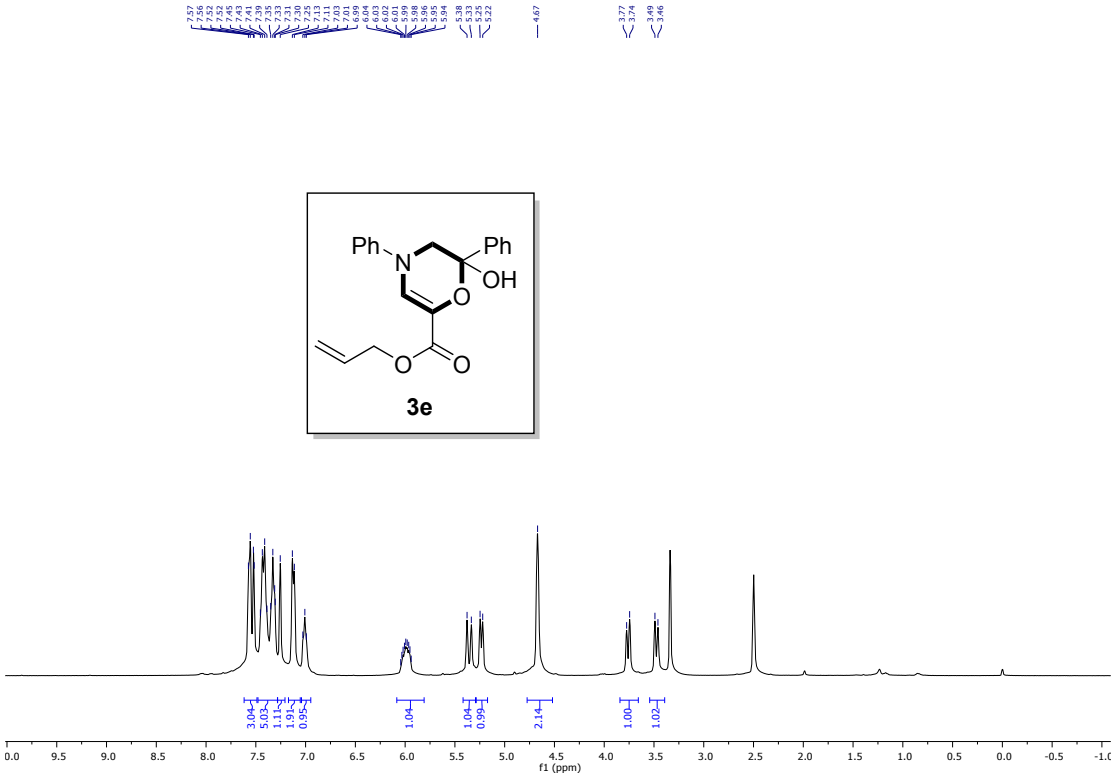
^{13}C NMR (101 MHz) spectrum of compound **3c** in DMSO-d_6



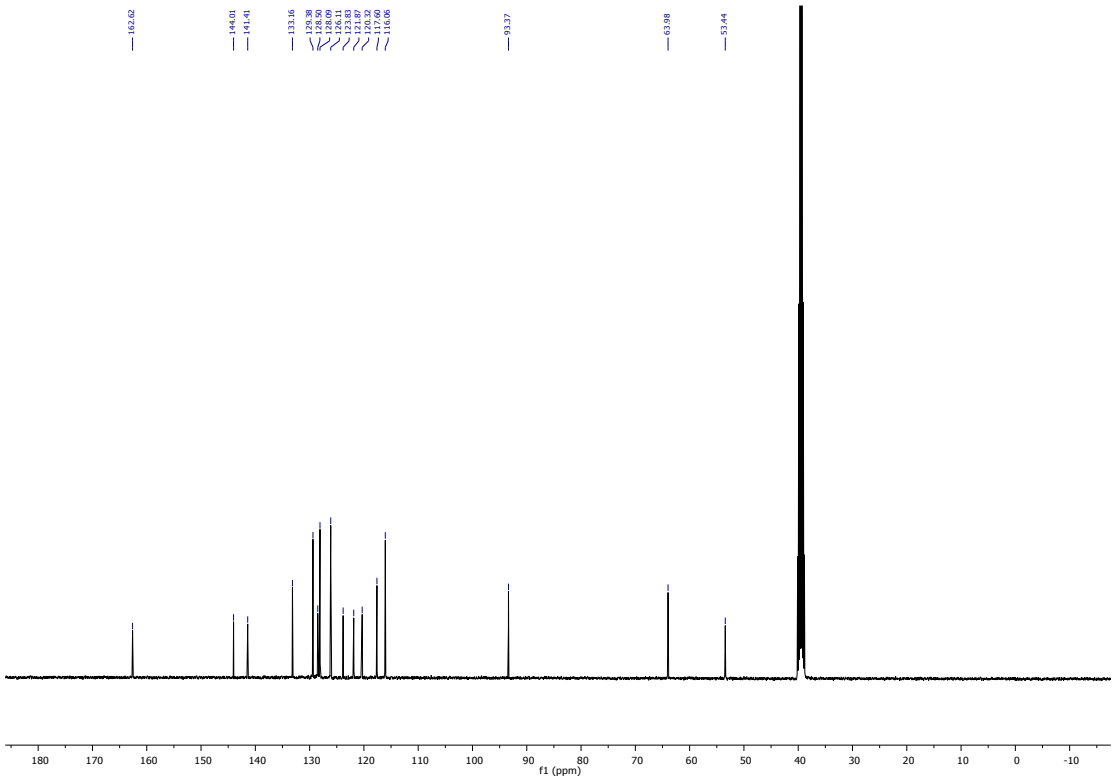
^{1}H NMR (400 MHz) spectrum of compound **3d** in DMSO-d_6



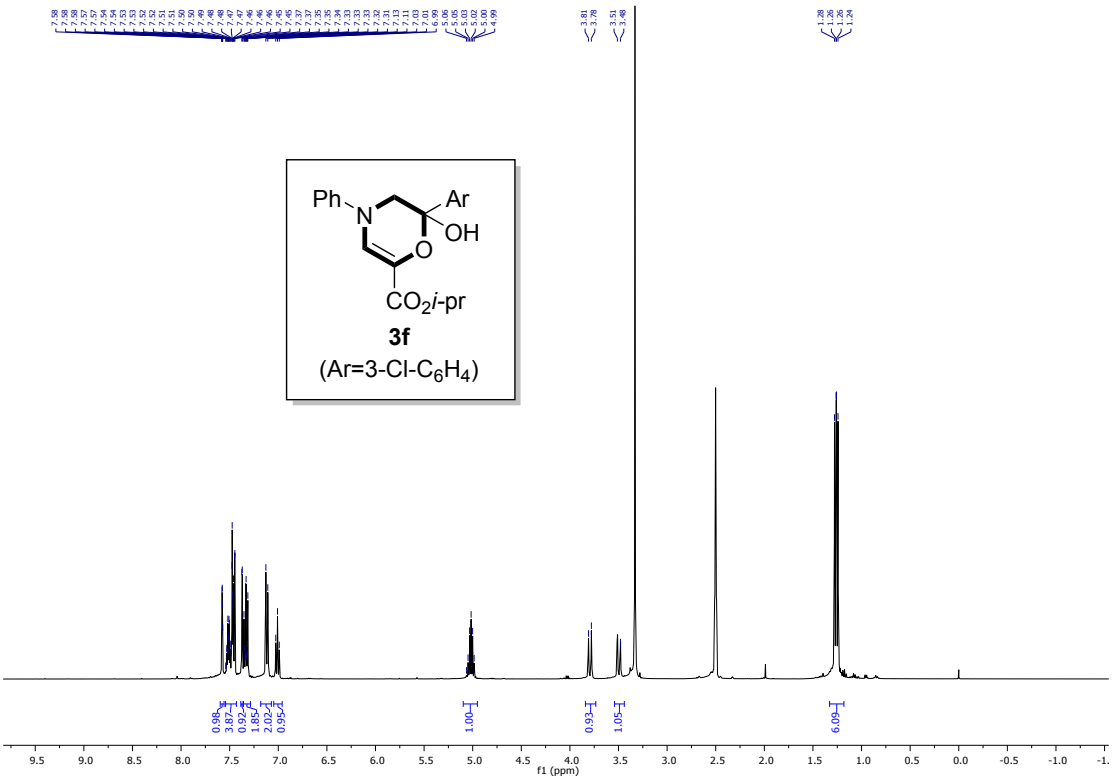
^{13}C NMR (101 MHz) spectrum of compound **3d** in DMSO-d_6



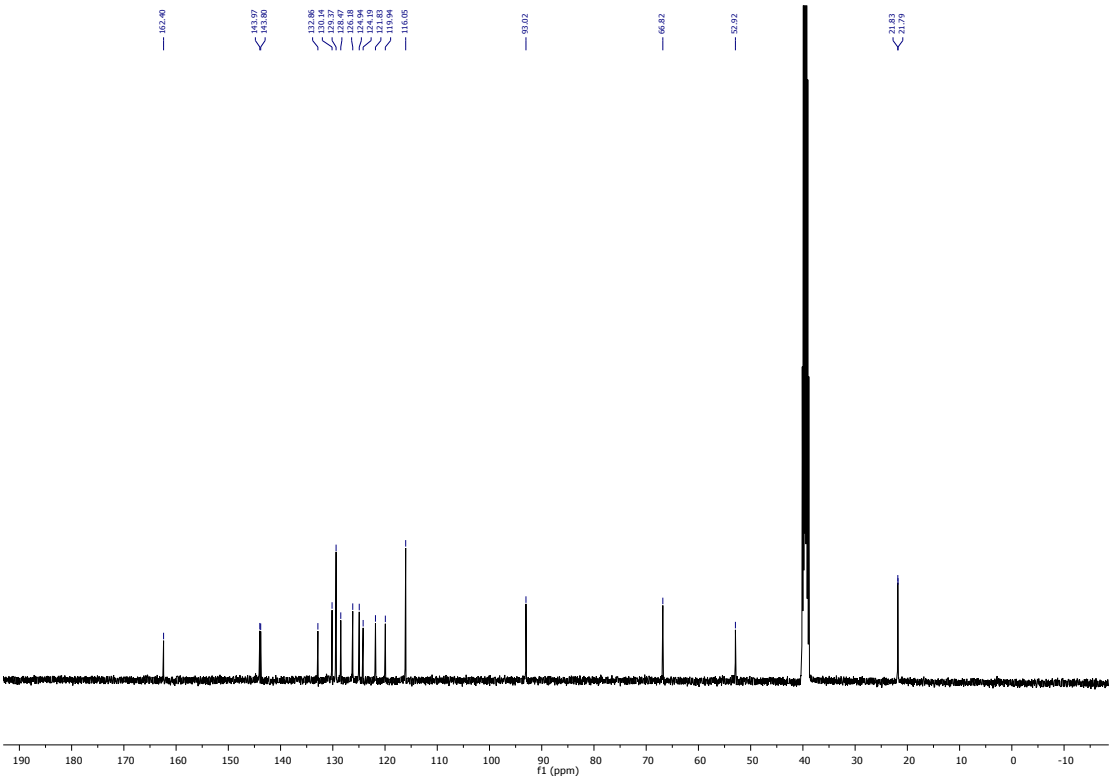
^{1}H NMR (400 MHz) spectrum of compound **3e** in DMSO-d_6



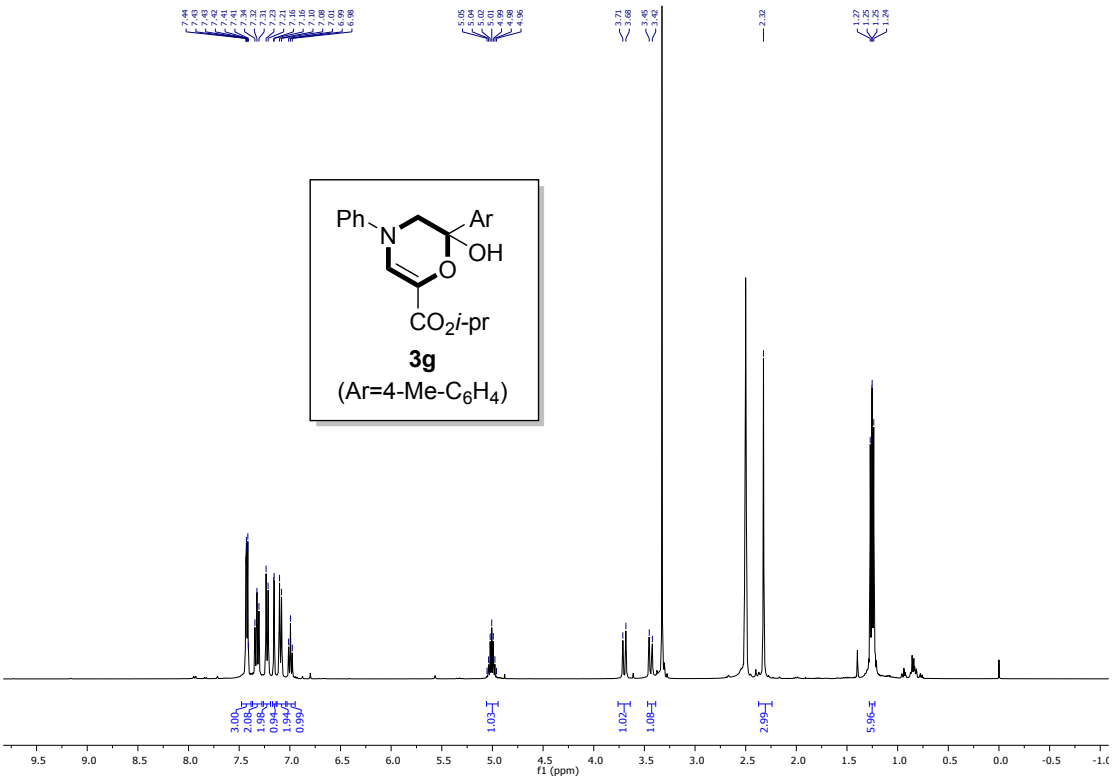
^{13}C NMR (101 MHz) spectrum of compound **3e** in DMSO-d_6



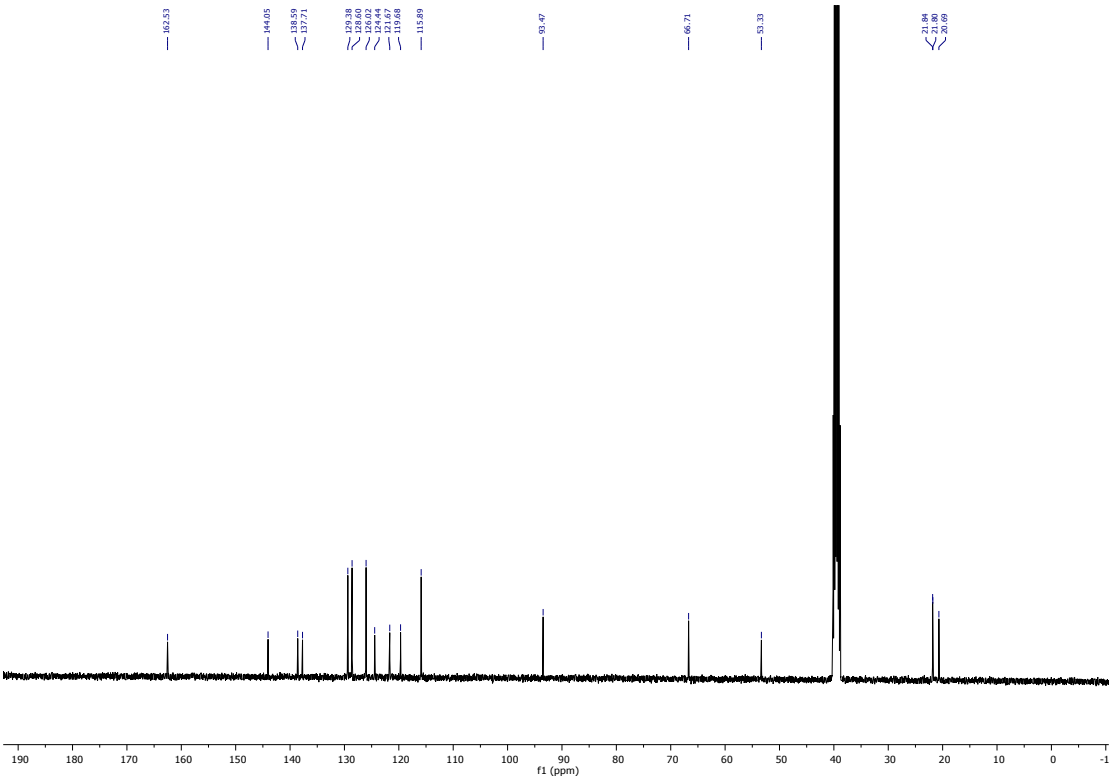
^{1}H NMR (400 MHz) spectrum of compound **3f** in DMSO-d_6



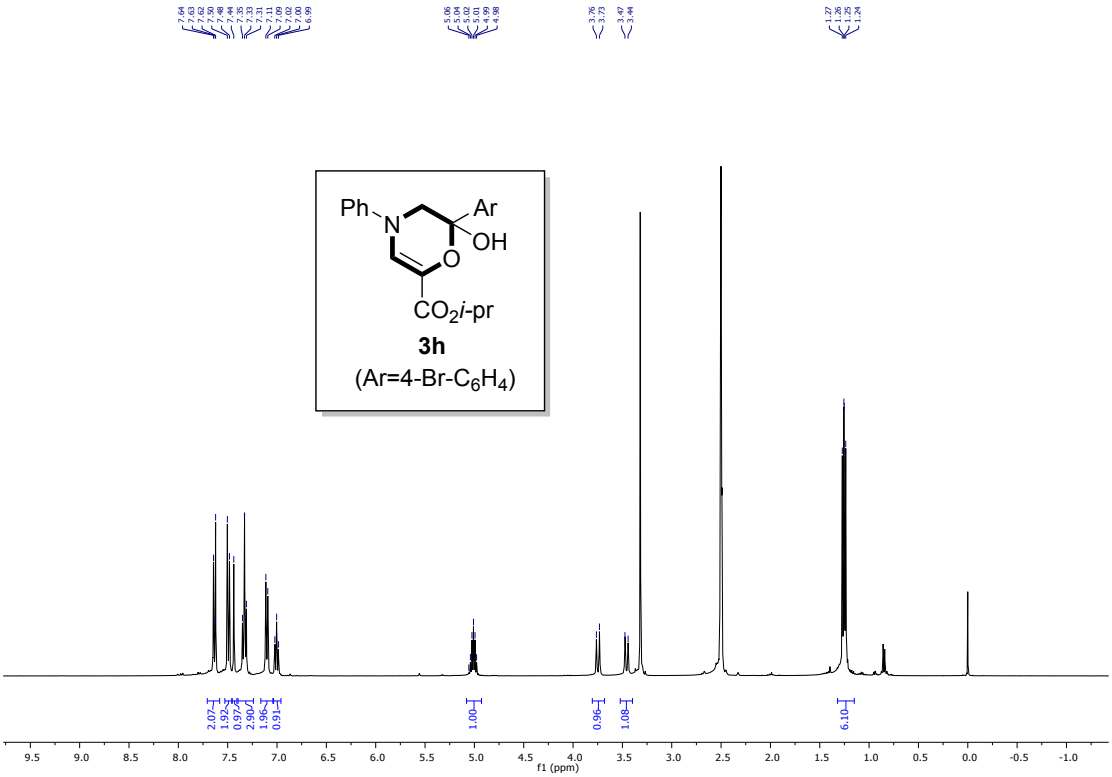
^{13}C NMR (101 MHz) spectrum of compound **3f** in DMSO-d_6



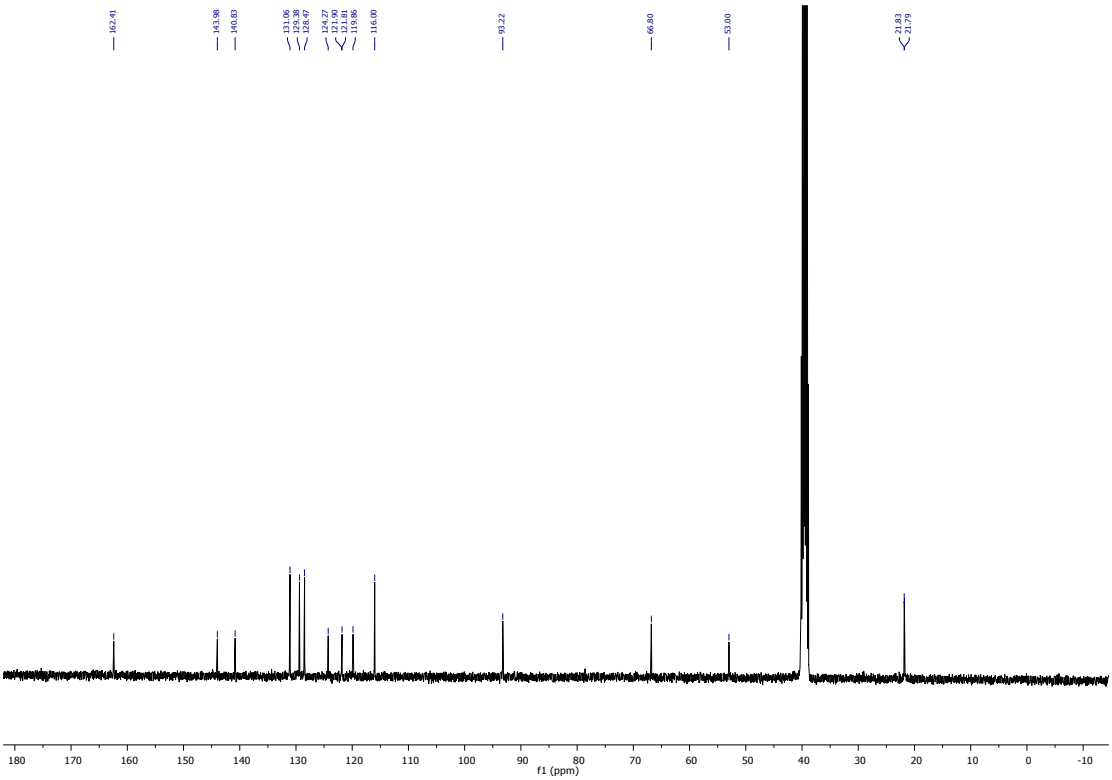
^{1}H NMR (400 MHz) spectrum of compound **3g** in DMSO-d_6



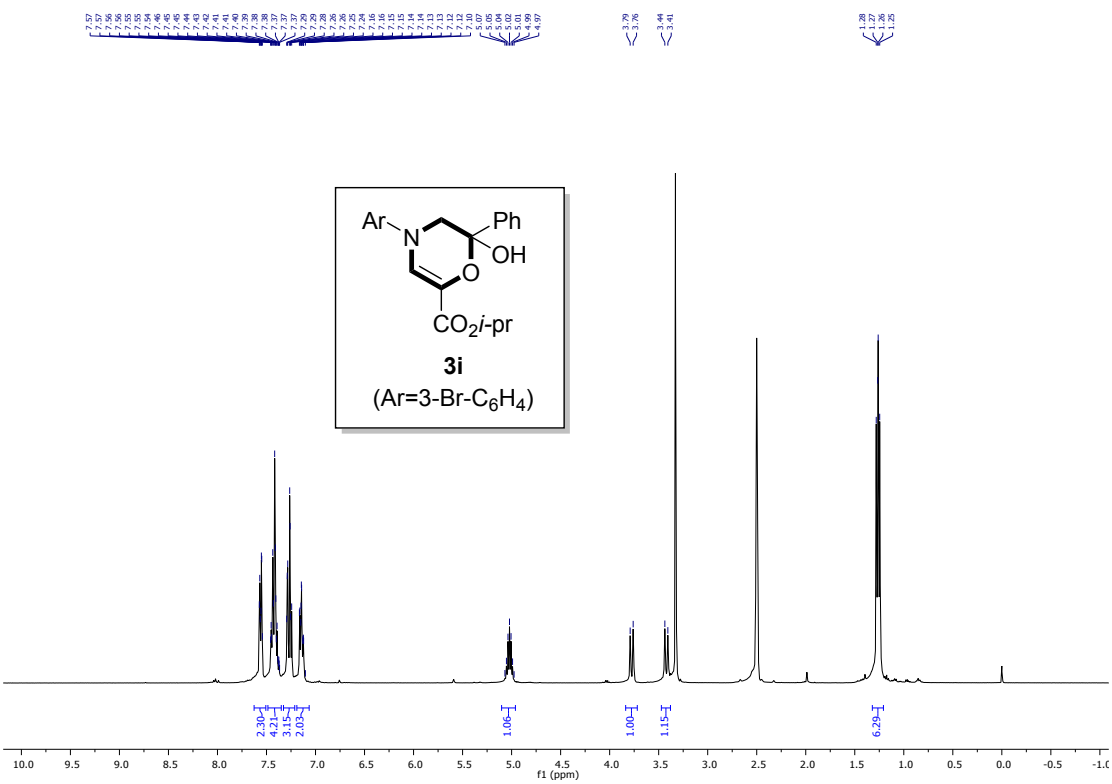
^{13}C NMR (101 MHz) spectrum of compound **3g** in DMSO-d_6



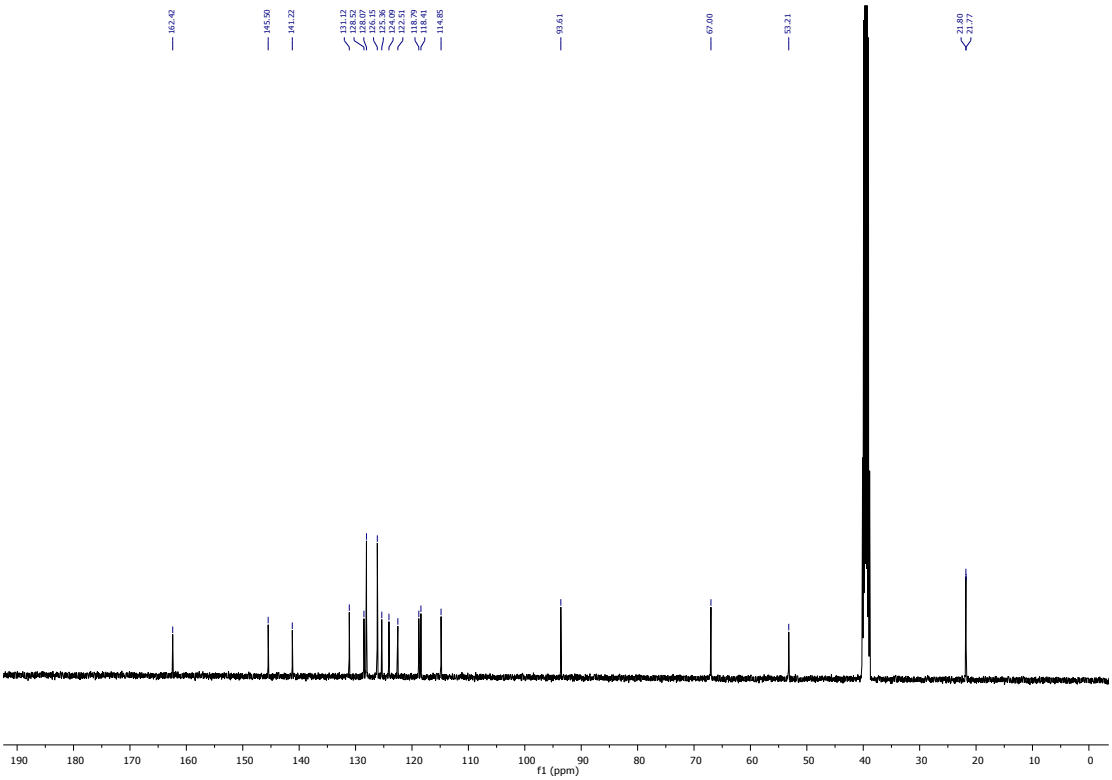
^{1}H NMR (400 MHz) spectrum of compound **3h** in DMSO-d_6



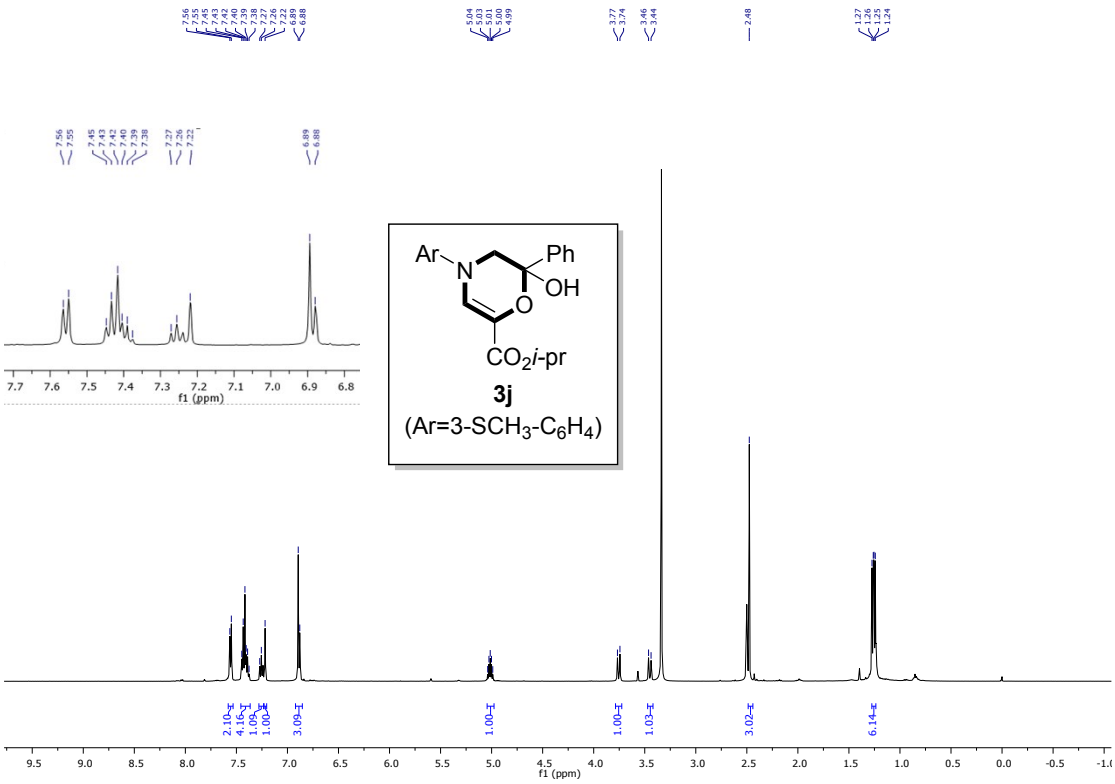
^{13}C NMR (101 MHz) spectrum of compound **3h** in DMSO-d_6



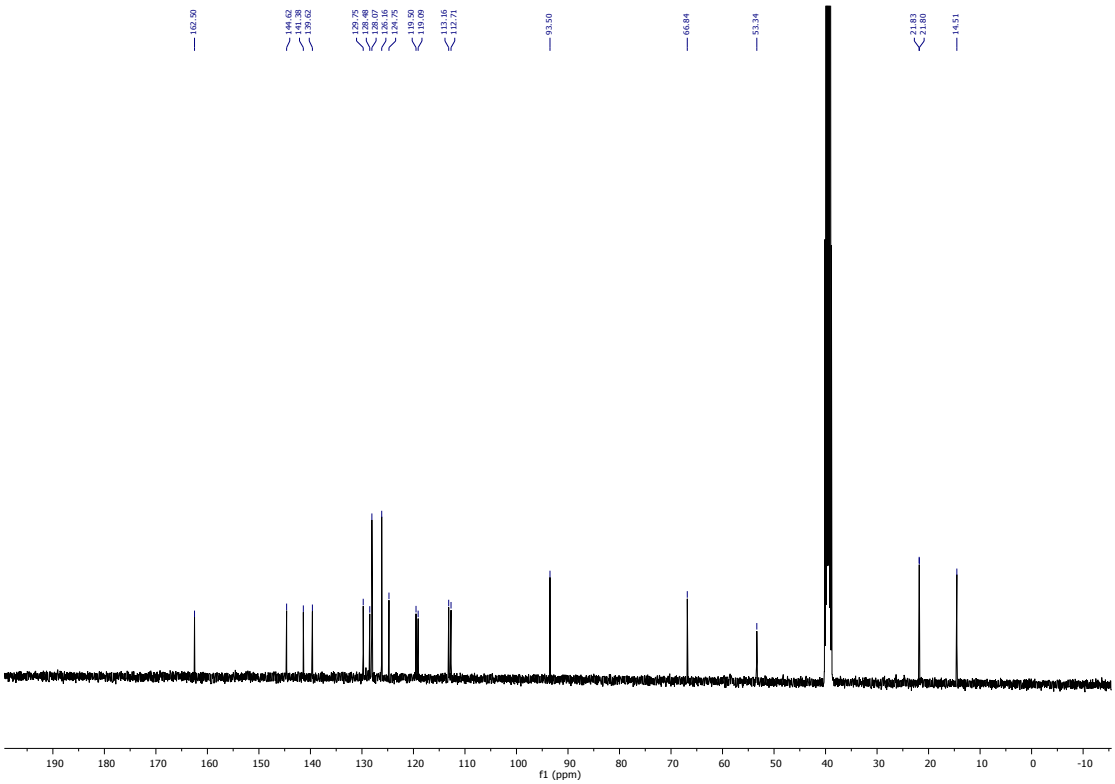
^{1}H NMR (400 MHz) spectrum of compound **3i** in DMSO-d_6



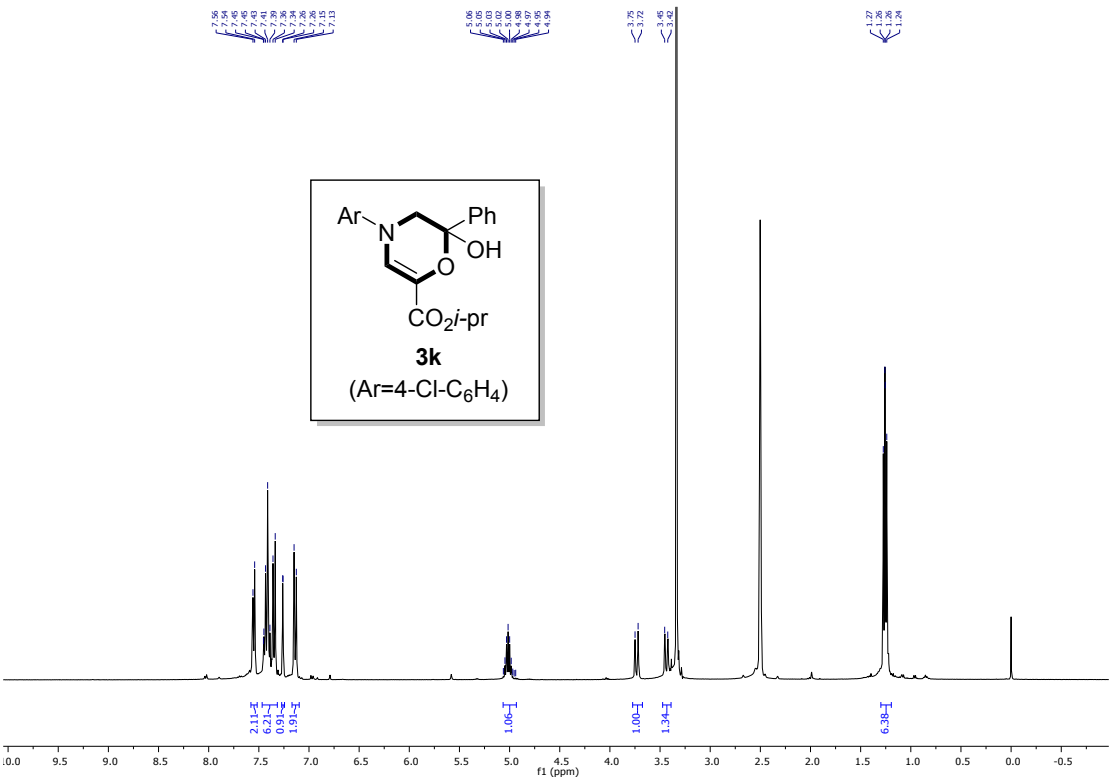
^{13}C NMR (101 MHz) spectrum of compound **3i** in DMSO-d_6



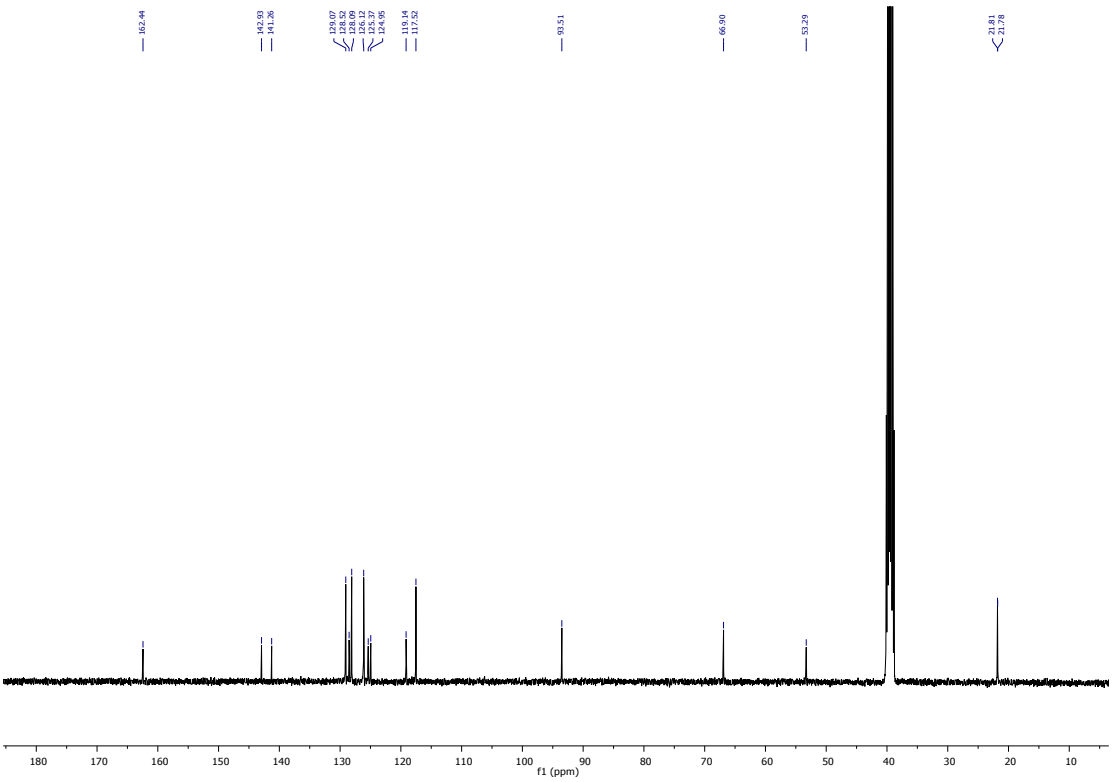
^{1}H NMR (400 MHz) spectrum of compound **3j** in DMSO-d_6



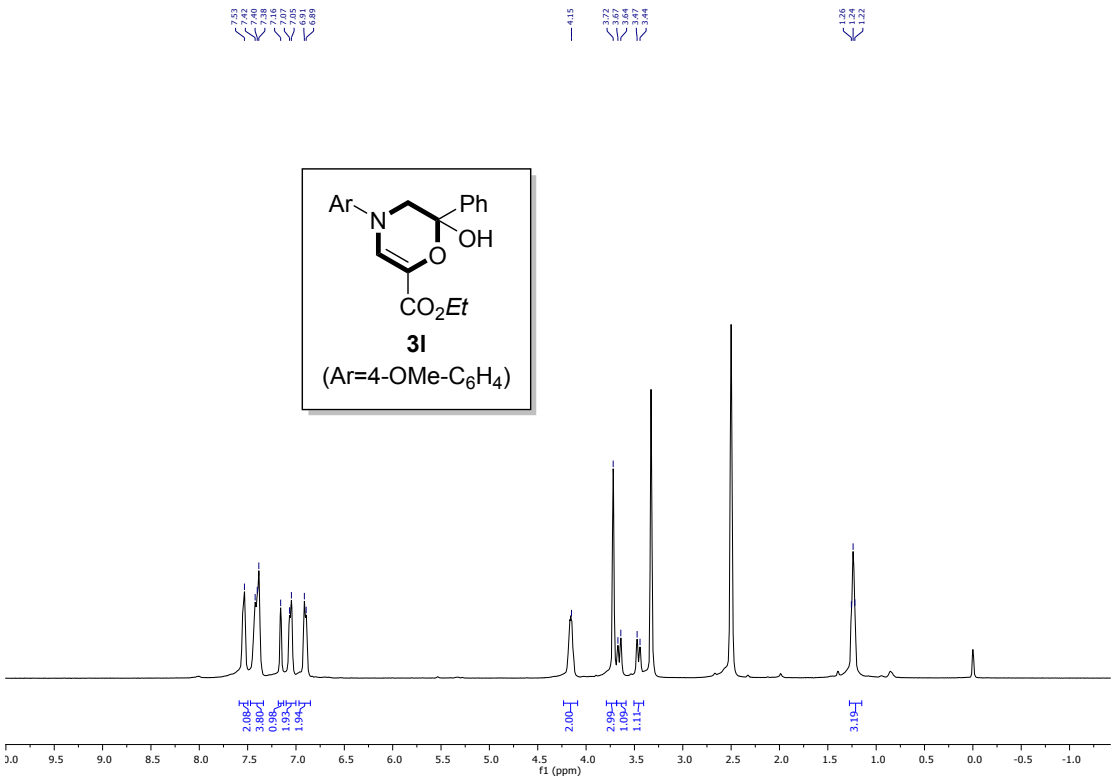
^{13}C NMR (101 MHz) spectrum of compound **3j** in DMSO-d_6



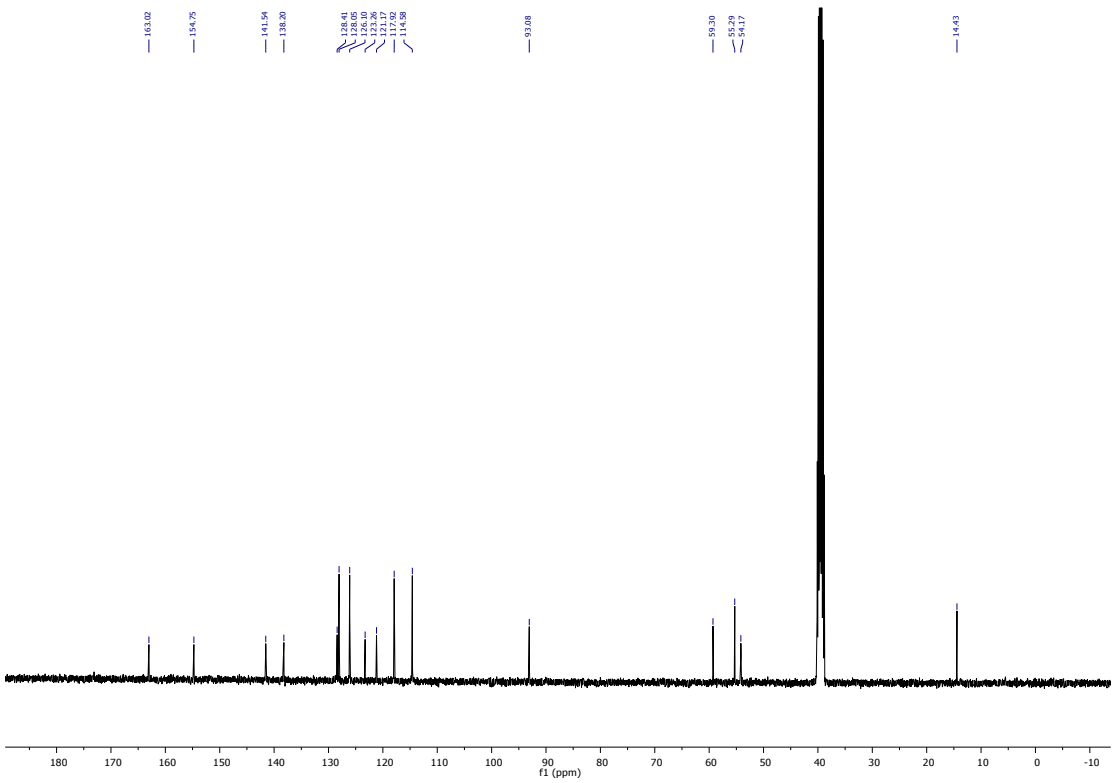
^{1}H NMR (400 MHz) spectrum of compound **3k** in DMSO-d_6



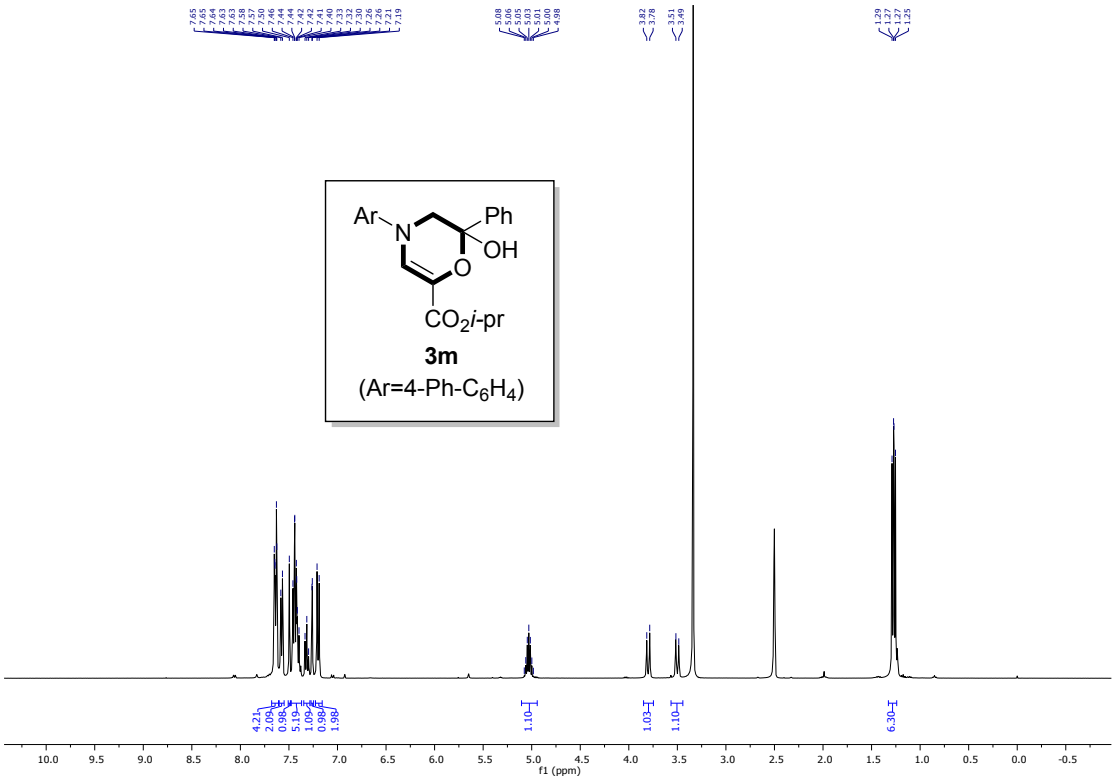
^{13}C NMR (101 MHz) spectrum of compound **3k** in DMSO-d_6



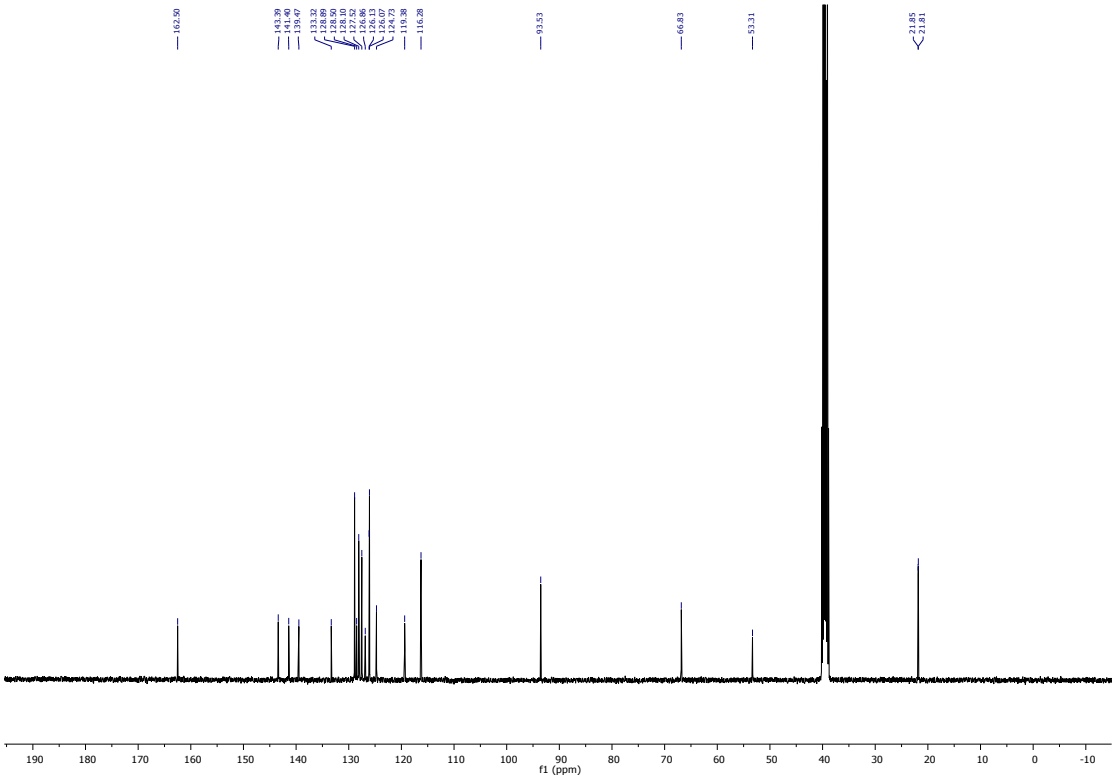
^{1}H NMR (400 MHz) spectrum of compound **3l** in DMSO-d_6



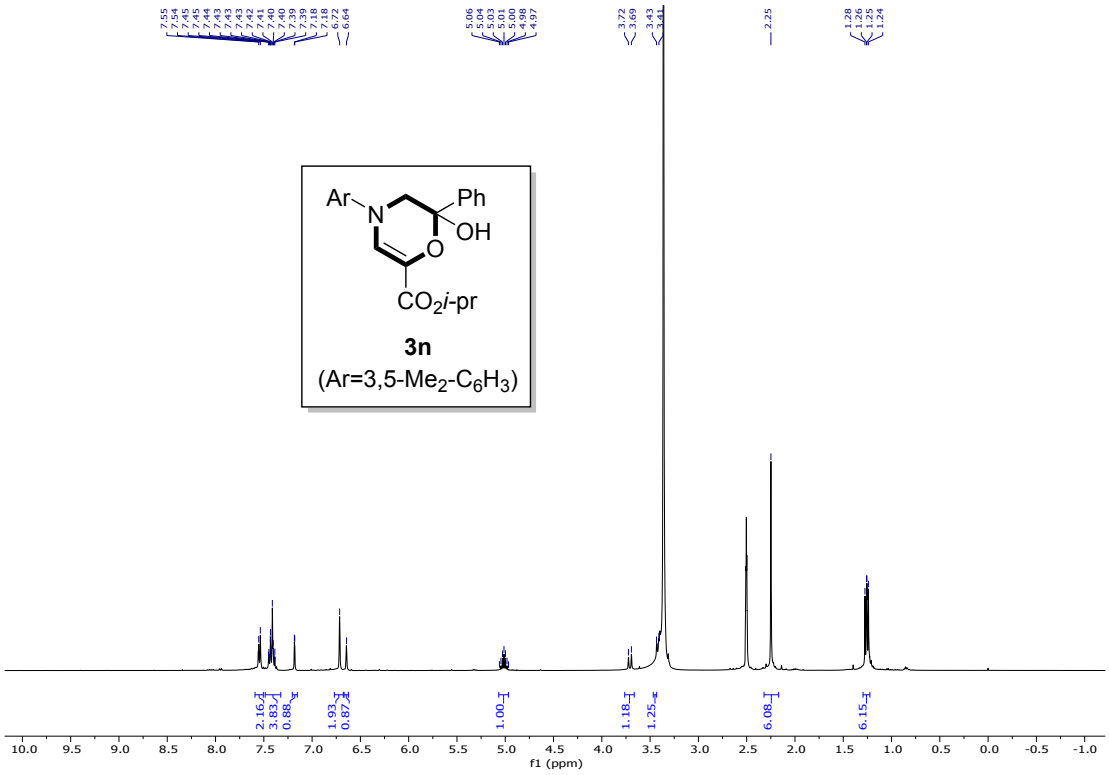
^{13}C NMR (101 MHz) spectrum of compound **3l** in DMSO-d_6



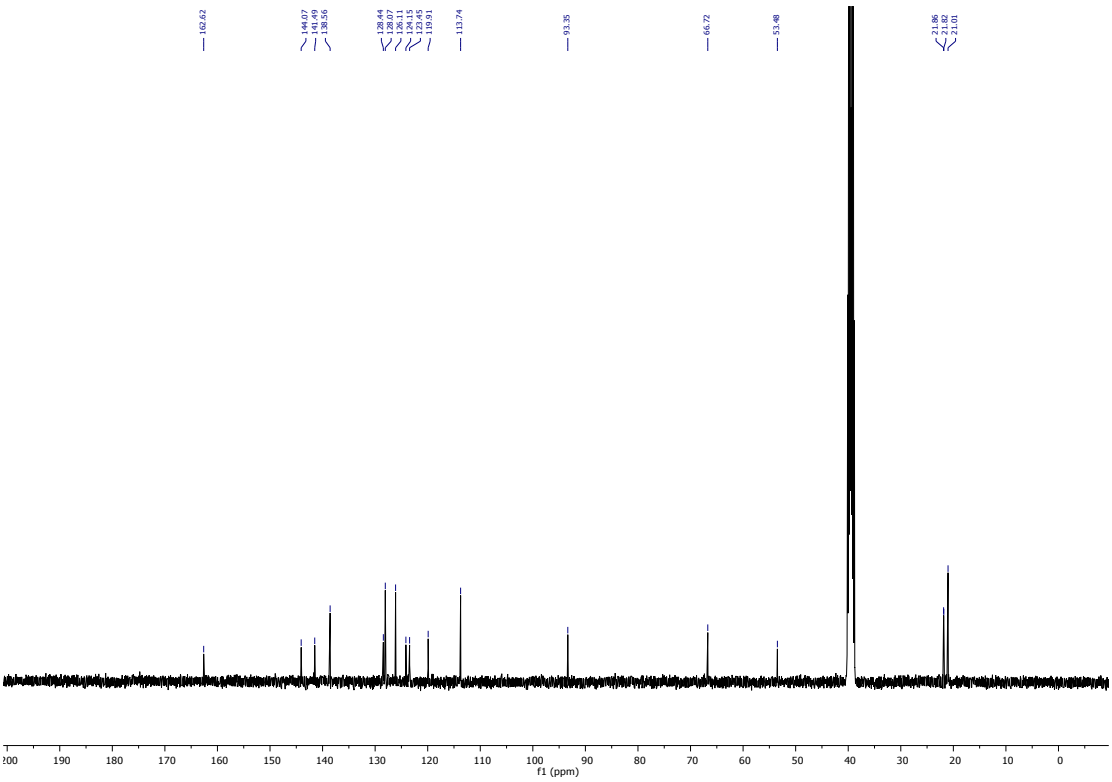
^{1}H NMR (400 MHz) spectrum of compound **3m** in DMSO-d_6



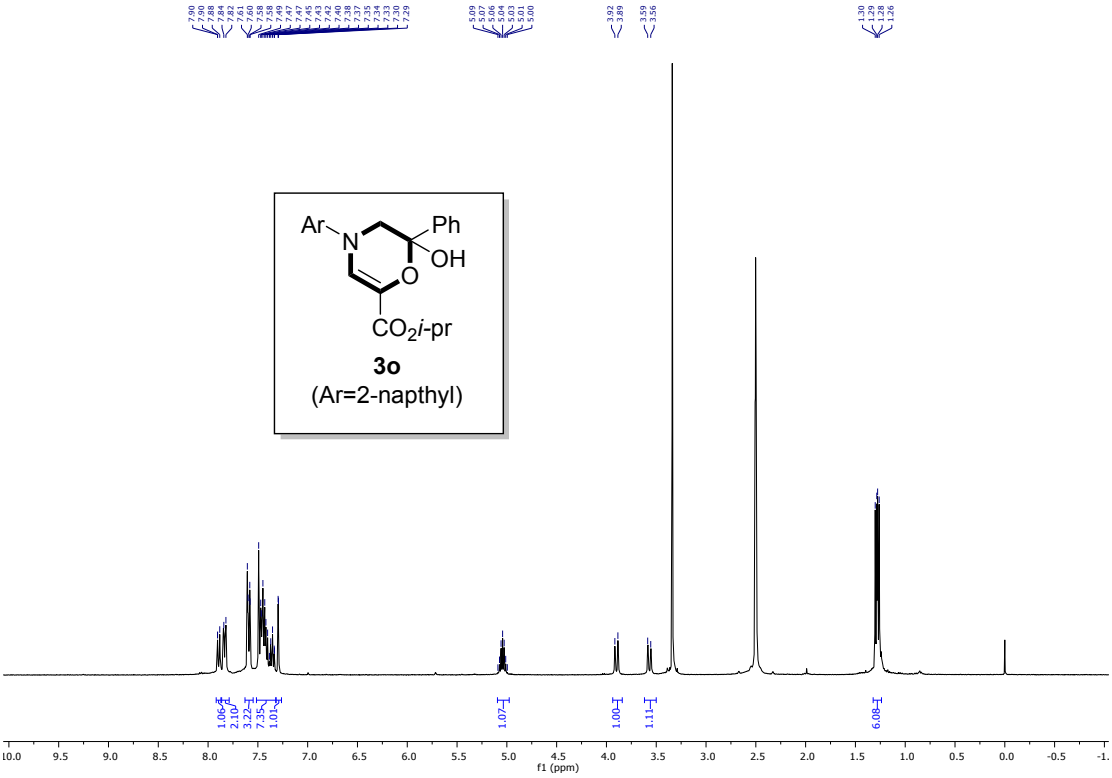
^{13}C NMR (101 MHz) spectrum of compound **3m** in DMSO-d_6



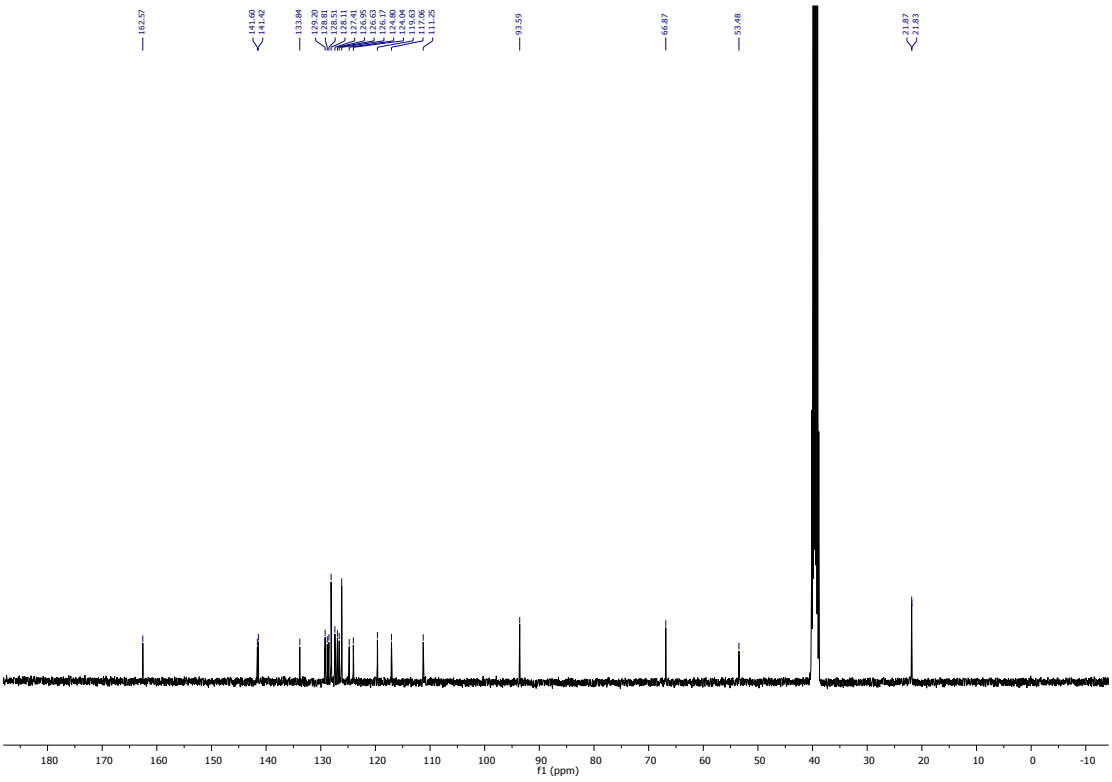
^{1}H NMR (400 MHz) spectrum of compound **3n** in DMSO-d_6



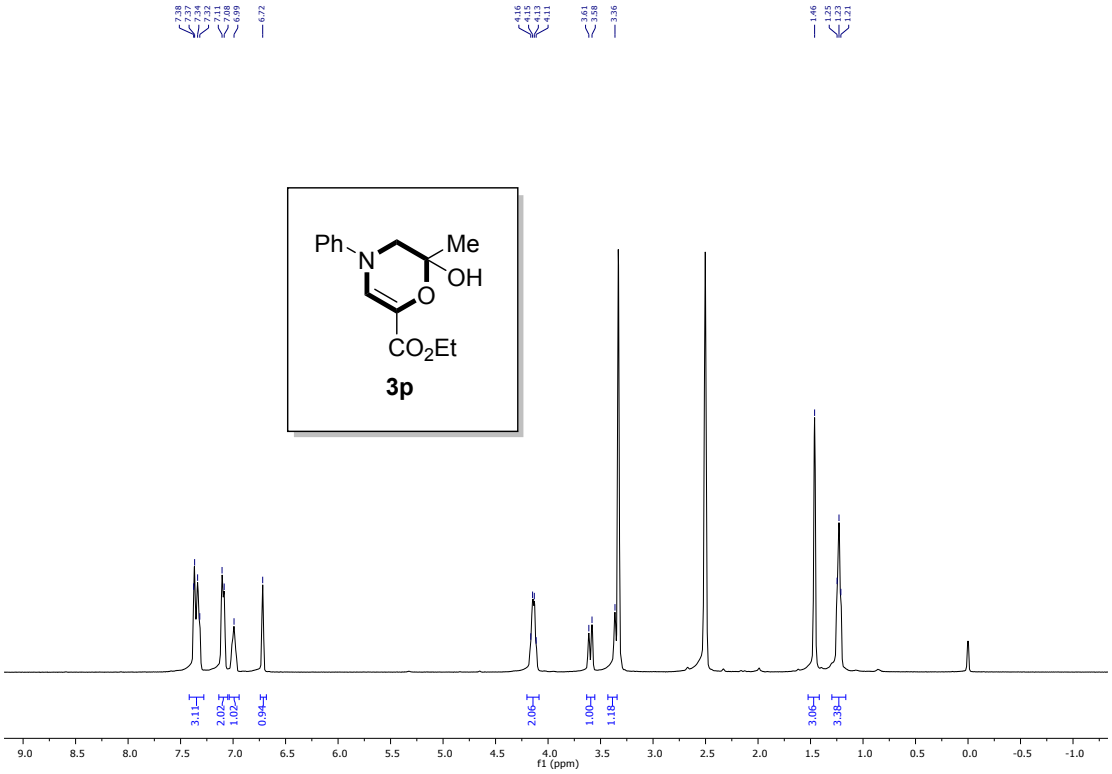
^{13}C NMR (101 MHz) spectrum of compound **3n** in DMSO-d_6



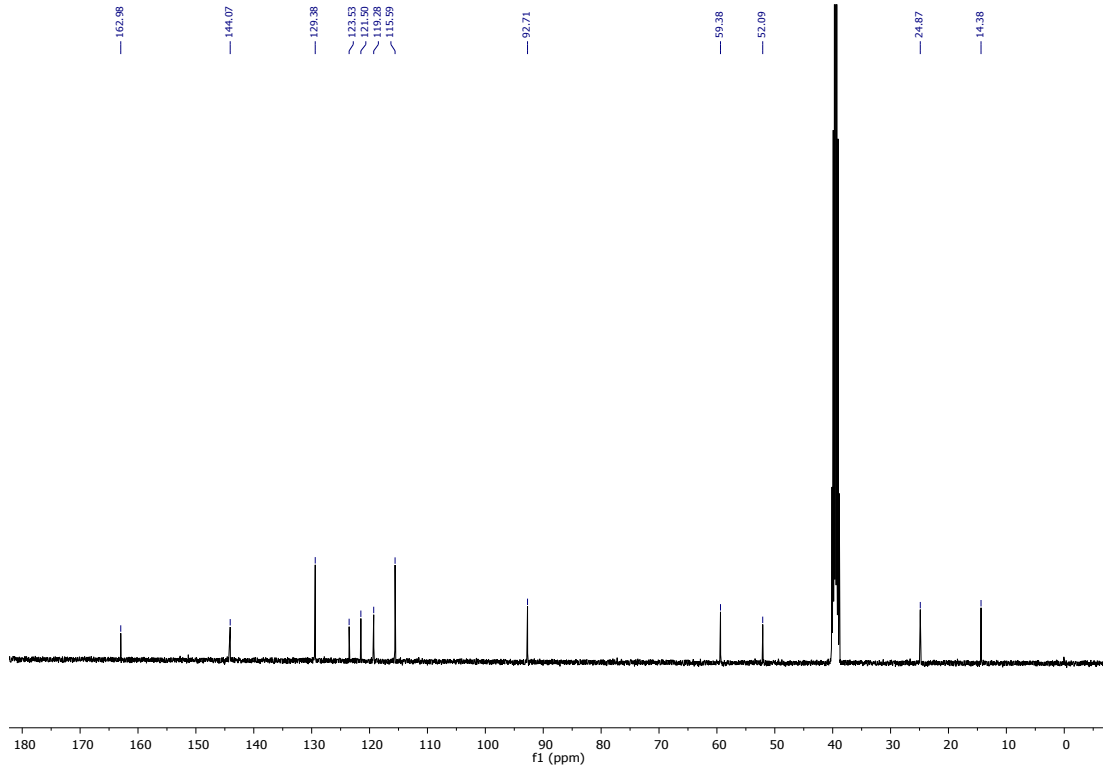
^{1}H NMR (400 MHz) spectrum of compound **3o** in DMSO-d_6



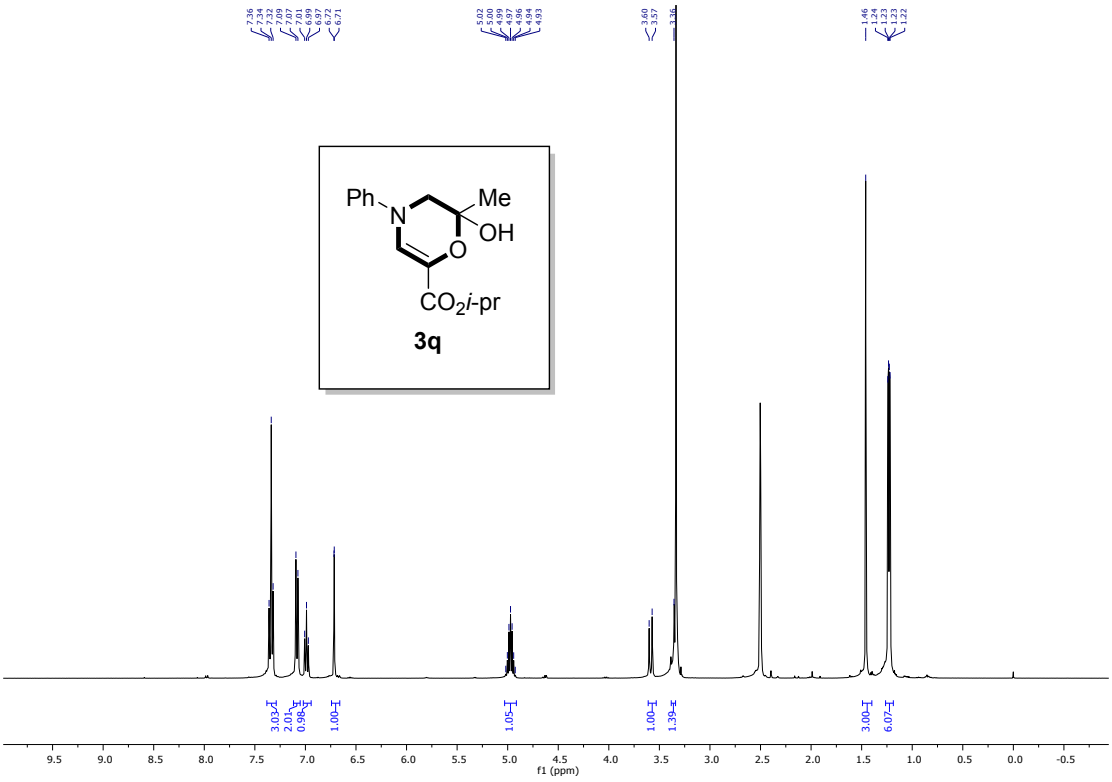
^{13}C NMR (101 MHz) spectrum of compound **3o** in DMSO-d_6



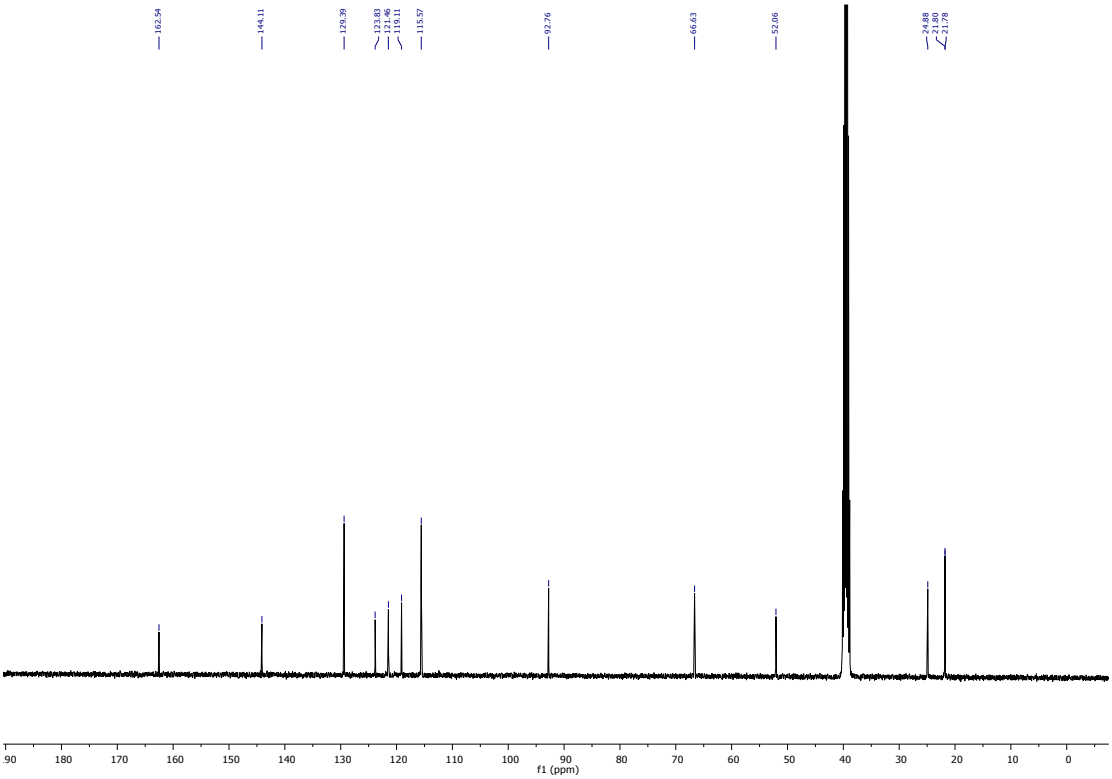
^{1}H NMR (400 MHz) spectrum of compound **3p** in DMSO-d_6



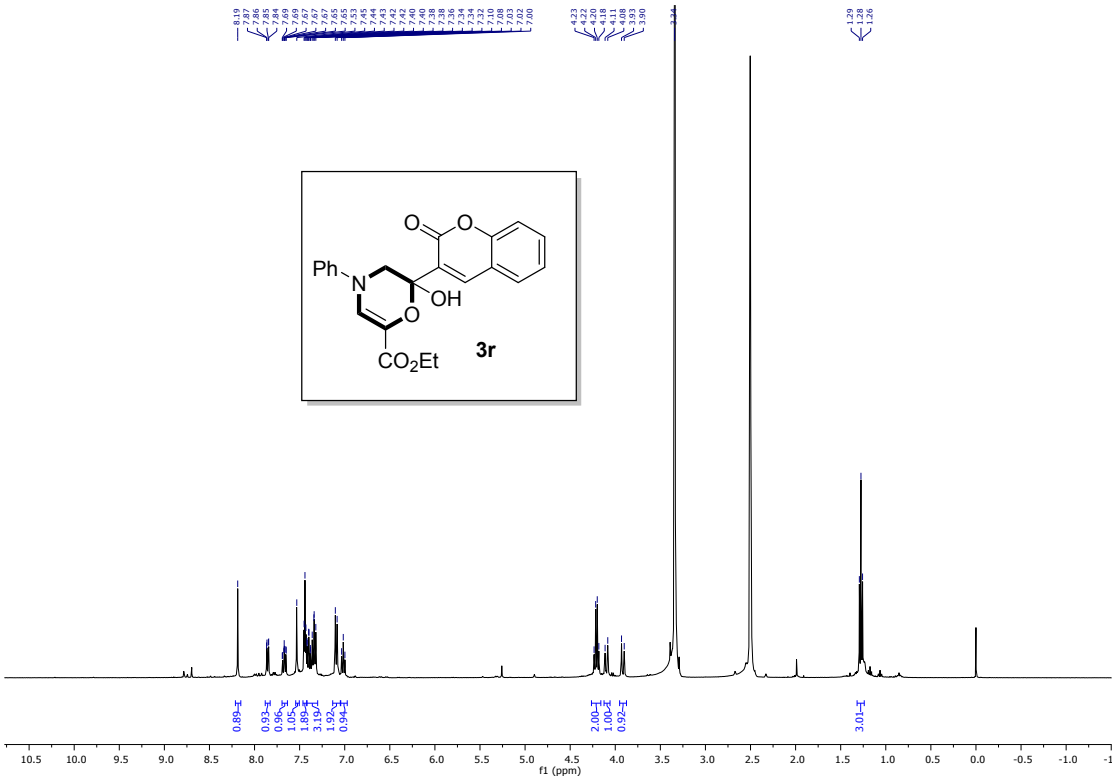
^{13}C NMR (101 MHz) spectrum of compound **3p** in DMSO-d_6



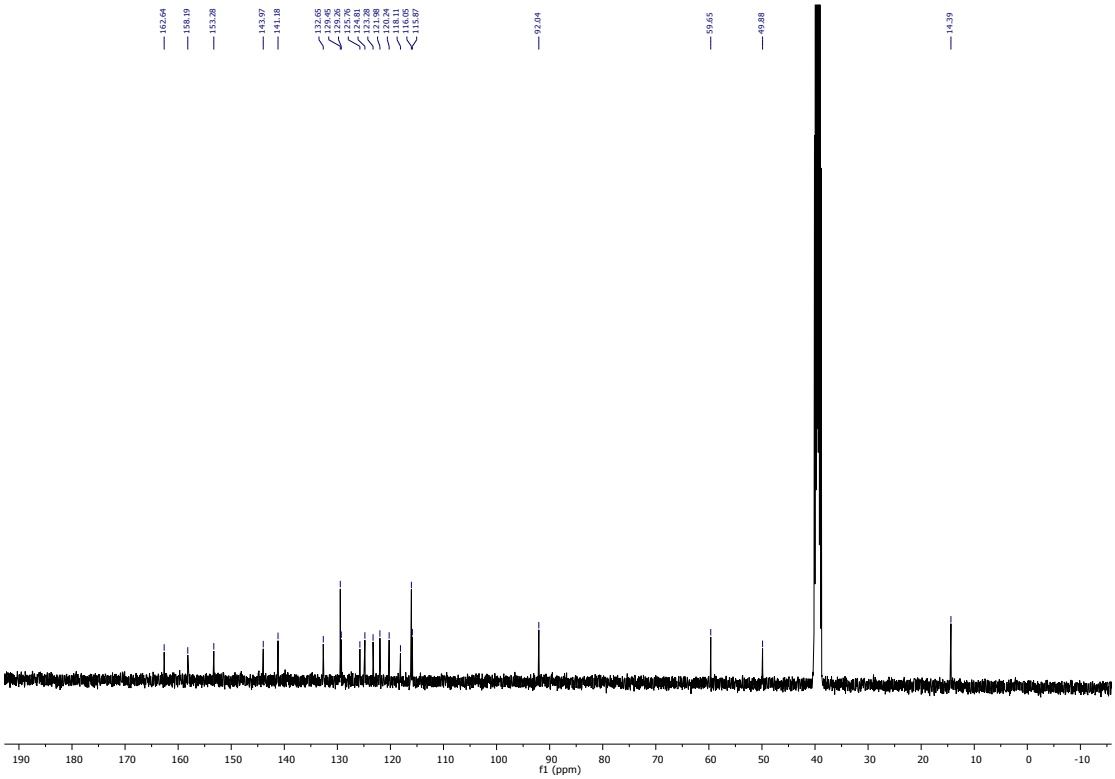
^{1}H NMR (400 MHz) spectrum of compound **3q** in DMSO-d_6



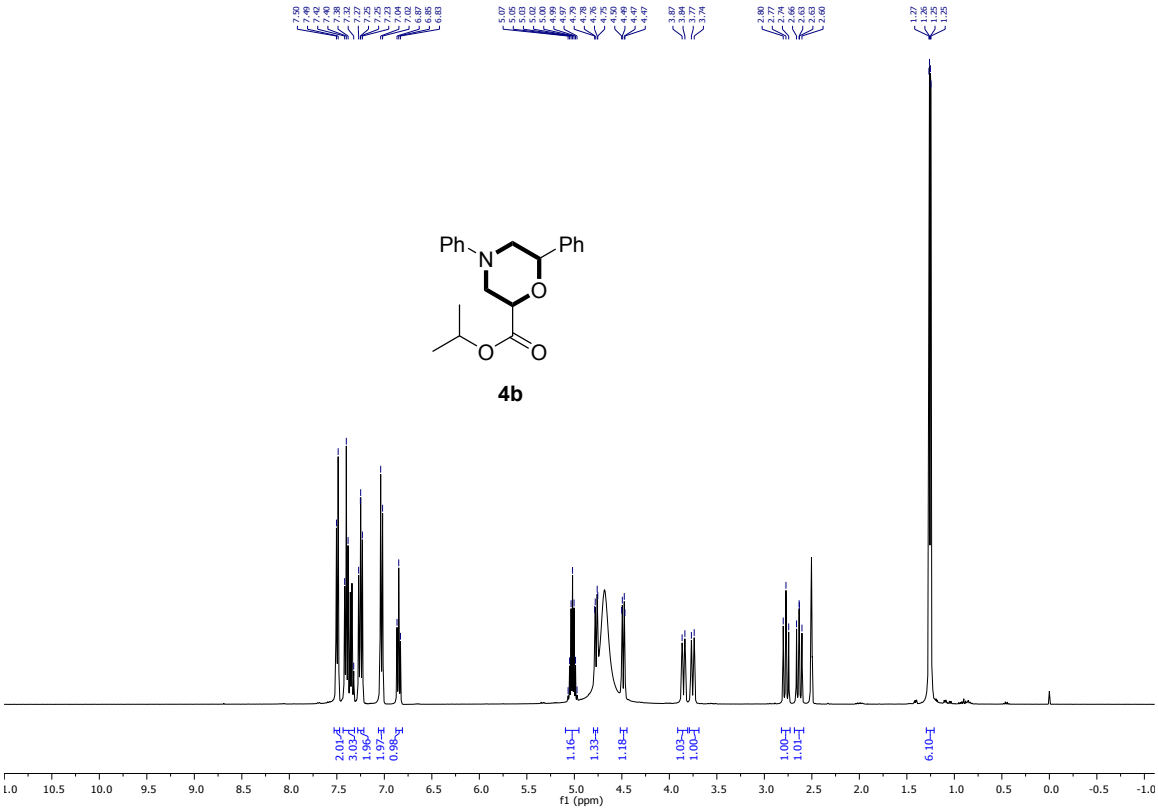
^{13}C NMR (101 MHz) spectrum of compound **3q** in DMSO-d_6



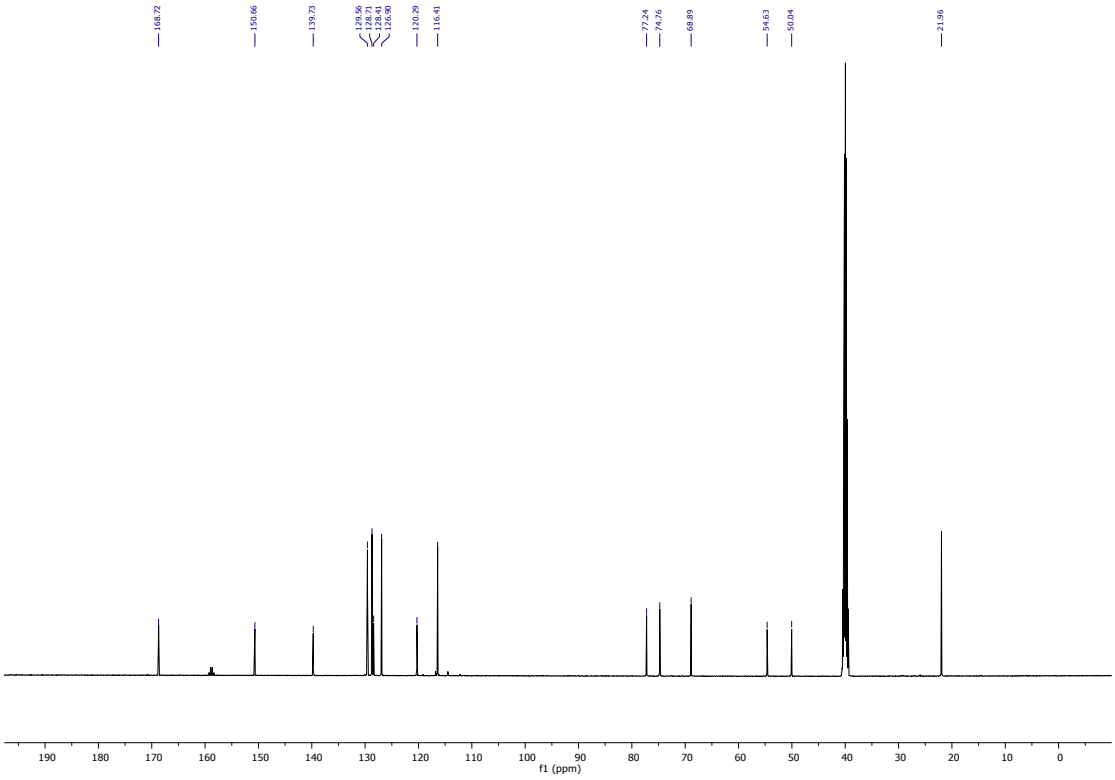
^{1}H NMR (400 MHz) spectrum of compound **3r** in DMSO-d_6



^{13}C NMR (101 MHz) spectrum of compound **3r** in DMSO-d_6



^{1}H NMR (400 MHz) spectrum of compound **4b** in DMSO-d_6



^{13}C NMR (126 MHz) spectrum of compound **4b** in DMSO-d_6

Cytotoxicity Data