Electronic Supplementary Information

TBHP-promoted Multicomponent Reaction to Access 2-Aminobenzoxazinones using Sodium Chlorodifluoroacetate as C1 Synthon

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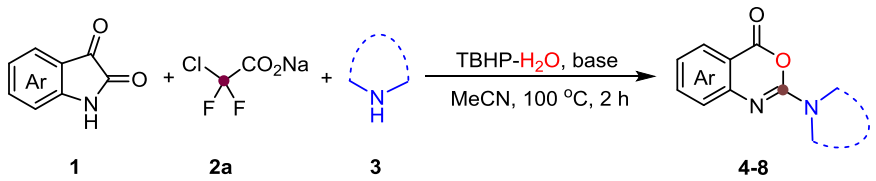
Table of Contents

1. General information

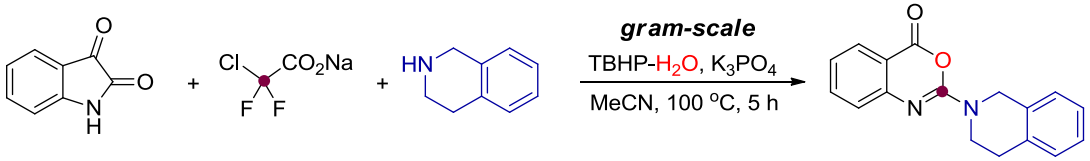
The chemicals were commercially available without further purification. Reactions were monitored by TLC analysis. Flash column chromatography was performed over silica gel (200-300 mesh). ^{1}H spectra were recorded in $CDCl_3$ on Bruker Avance II 300 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. ^{13}C spectra were recorded in $CDCl_3$ on 75 MHz NMR spectrometers and resonances (δ) are given in ppm. IR spectra were obtained as KBr pellet samples using a Nicolet 5700 FTIR spectrometer. Melting points were determined using an uncorrected X-4 apparatus. HRMS were obtained on an Agilent QTOF 6540 MS/Thermo Scientific LTQ Orbitrap XL equipped with an electrospray source. The X-ray crystal structure determination was performed using a Bruker SMART APEX CCD system.

2. General procedure for the synthesis of products 4-8



TBHP (70% in H_2O) (0.75 mmol, 1.5 equiv) was added to a mixture of isatin (**1**, 0.5 mmol, 1.0 equiv), $ClCF_2COONa$ (**2a**, 1.5 mmol, 3.0 equiv), K_3PO_4 or Cs_2CO_3 (1.0 mmol, 2.0 equiv), and amine (**3**, 0.5 mmol, 1.0 equiv) in CH_3CN (3 mL). Then the sealed tube was stirred at 100 ℃ for 2 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatograph (silica gel, petroleum ether : EtOAc = 10:1~50:1, v/v) to give the products **4-8**.

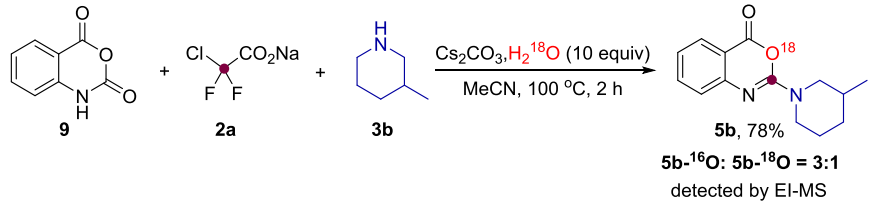
3. Scale-up synthesis of product 4a



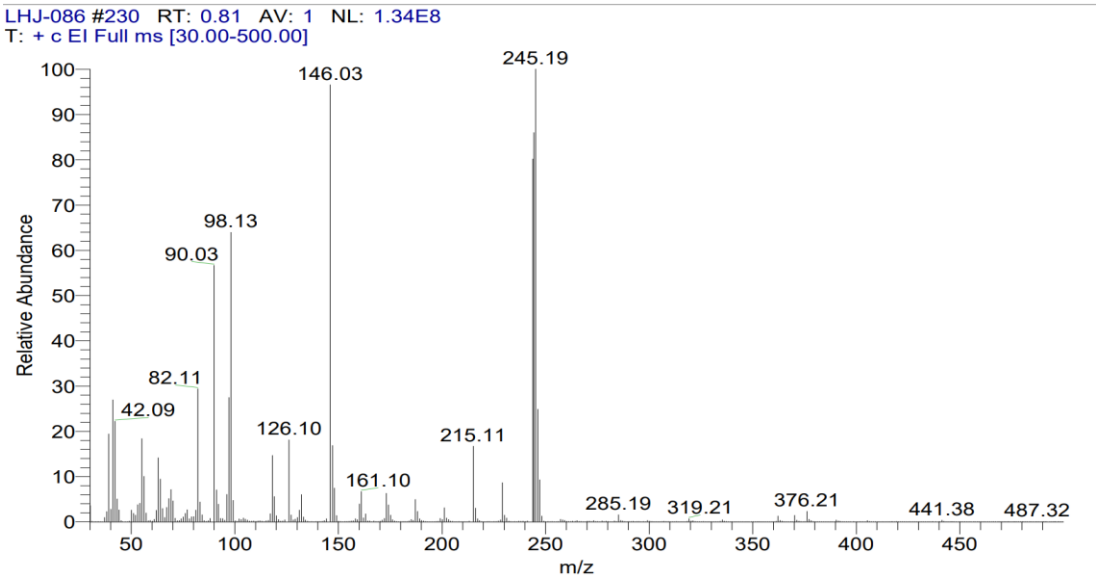
A 100 mL sealed tube was charged with isatin (**1a**) (0.74 g, 5.0 mmol), $ClCF_2COONa$ (**2a**) (2.29 g, 15.0 mmol), 1,2,3,4-tetrahydroisoquinoline (**3a**) (0.67 g, 5.0 mmol), K_3PO_4 (2.12 g, 10.0 mmol), then CH_3CN (30 mL) and TBHP (70% in H_2O) (0.97 g, 7.5 mmol) was added. The resulting mixture was stirred at 100 ℃ for 5 h. Upon completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatograph (silica gel, petroleum ether : EtOAc = 10:1, v/v) to give the desired product **4a** as a white solid (0.90 g, 65% yield).

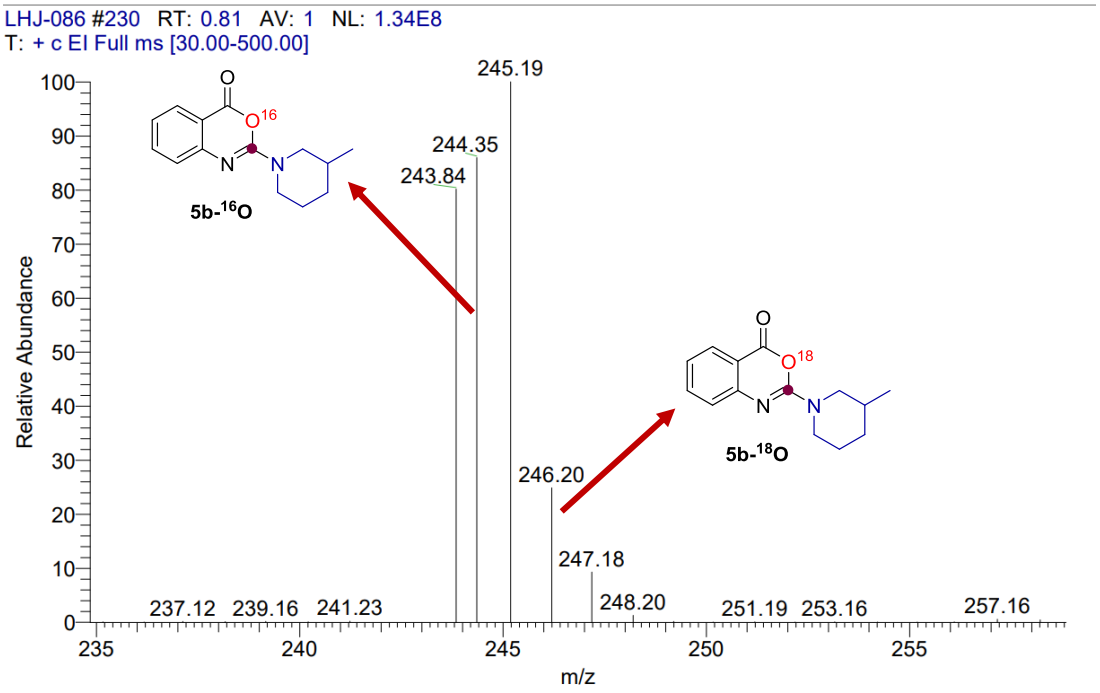
4. Evidence in support of the mechanism

The ^{18}O-labeling experiment was examined to investigate the source of oxygen of product **5b**. The experimental result suggests that $H_2{}^{18}O$ participates in this ring construction process, and the 3-position oxygen atom of lactone originates from $H_2{}^{18}O$, and the ratio of **5b-^{16}O**:**5b-^{18}O** is 3:1 determined by EI-MS.



The EI-MS Spectra is listed below:

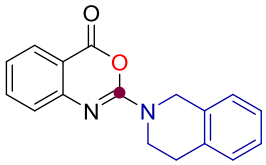




5. Crystal data of product 5a

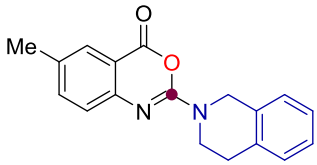
Empirical formula	$C_{13}H_{14}N_2O_2$ (**CCDC**: 2166162)
Formula weight	230.26
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 9.637(8) Å $\alpha = 90^o$
	b = 11.436(9) Å β = 113.063(18) ^{o}
	c = 11.619(9) Å $\gamma = 90^o$
Volume	1178.2 (16) $Å^3$
Z	4
Density (calculated)	1.298 mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000）	488
Crystal size	0.200×0.200×0.200 mm^3
Theta range for data collection	2.608 to 25.065 ^{o}
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 13
Reflections collected	17307
Independent reflections	2084 [R(int) = 0.0918]
Completeness to theta = 25.00^o	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.982 and 0.982
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2084/0/154
Goodness-of-fit on F^2	1.017
Final R indices [I>2sigma(I)]	R_1 = 0.0535, wR_2 = 0.1203
R indices (all data)	R_1 = 0.1328, wR_2 = 0.1597
Largest diff. peak and hole	0.150 and -0.159 e.$Å^{-3}$

6. Characterization data for products 4-8



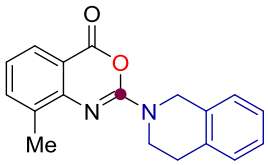
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4a)

White solid; yield 80%; 111 mg; m.p. 92−93 ^{o}C; IR (KBr, cm^{-1}) *v*: 2928, 1748, 1599, 1566, 1472, 1299, 1231, 751; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.64-7.59 (m, 1H), 7.30-7.11 (m, 6H), 4.87 (s, 2H), 3.97 (t, *J* = 5.7 Hz, 2H), 2.97 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9, 153.3, 150.8, 136.7, 134.2, 132.4, 128.7, 128.6, 126.8, 126.6, 126.4, 124.2, 123.3, 112.3, 46.1, 41.9, 28.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{15}N_2O_2$: 279.1128, found: 279.1134 $(M+H)^+$.



2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4b)

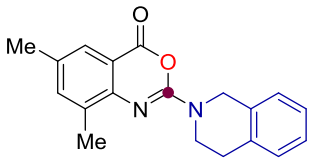
White solid; yield 70%; 102 mg; m.p. 130−131 ^{o}C; IR (KBr, cm^{-1}) *v*: 2924, 1700, 1602, 1516, 1498, 1230, 1147, 747; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80 (s, 1H), 7.43 (dd, *J* = 8.4 Hz, *J* = 2.1 Hz, 1H), 7.22-7.16 (m, 5H), 4.85 (s, 2H), 3.95 (t, *J* = 5.7 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.0, 152.9, 148.5, 138.1, 134.2, 133.1, 132.5, 128.5, 128.0, 126.8, 126.5, 126.3, 124.0, 112.0, 46.0, 41.8, 28.6, 20.8; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_2$: 293.1285, found 293.1288 $(M+H)^+$.



2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-8-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4c)

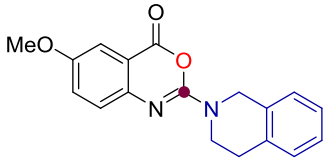
White solid; yield 78%; 114 mg; m.p. 113−114 ^{o}C; IR (KBr, cm^{-1}) *v*: 2924, 1758, 1616, 1597, 1456, 1299, 1223, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.87 (dd, *J* = 7.8 Hz, *J* = 0.6 Hz, 1H), 7.48 (dd, *J* = 7.2 Hz, *J* = 0.6 Hz, 1H) 7.23-7.18 (m, 4H),

7.03 (t, *J* = 7.8 Hz, 1H), 4.87 (s, 2H), 3.98 (t, *J* = 5.7 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5, 152.5, 149.3, 137.0, 134.3, 132.7, 132.6, 128.6, 126.8, 126.5, 126.3, 126.1, 122.6, 111.9, 46.0, 41.8, 28.5, 17.2; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_2$: 293.1285, found 293.1285 $(M+H)^+$.



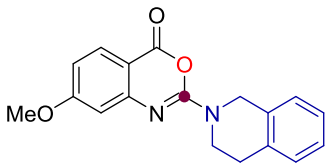
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6,8-dimethyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4d)

White solid; yield 75%; 115 mg; m.p. 132−134 ^{o}C; IR (KBr, cm^{-1}) *v*: 2922, 1751, 1603, 1455, 1298, 1223, 1150, 925, 749; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.64 (s, 1H), 7.29 (s, 1H), 7.22-7.15 (m, 4H), 4.83 (s, 2H), 3.94 (t, *J* = 6.0 Hz, 2H), 2.95 (t, *J* = 6.0 Hz, 2H), 2.39 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.6, 152.1, 147.0, 138.5, 134.3, 132.6, 132.4, 132.2, 128.6, 126.7, 126.4, 126.3, 125.4, 111.6, 46.0, 41.8, 28.5, 20.7, 17.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_2$: 307.1441, found 307.1439 $(M+H)^+$.



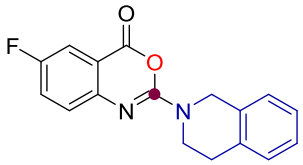
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (4e)

White solid; yield 73%; 112 mg; m.p. 135−136 ^{o}C; IR (KBr, cm^{-1}) *v*: 2973, 1782, 1714, 1509, 1455, 1235, 1045, 744; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.41 (t, *J* = 1.5 Hz, 1H), 7.26-7.17 (m, 6H), 4.85 (s, 2H), 3.96 (t, *J* = 5.7 Hz, 2H), 3.85 (s, 3H), 2.97 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1, 155.7, 152.4, 145.2, 134.3, 132.5, 128.6, 126.9, 126.8, 126.5, 126.4, 125.7, 112.3, 108.2, 55.7, 46.1, 41.9, 28.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_3$: 309.1234, found 309.1232 $(M+H)^+$.



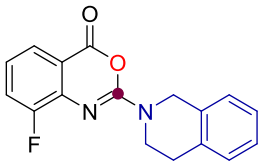
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-7-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (4f)

White solid; yield 79%; 122 mg; m.p. 117−118 ^{o}C; IR (KBr, cm^{-1}) *v*: 2929, 1744, 1605, 1564, 1456, 1302, 1211, 1027, 839, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.92 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H), 7.25-7.18 (m, 4H), 6.74-6.71 (m, 2H), 4.88 (s, 2H), 3.97 (t, J = 6.0 Hz, 2H), 3.89 (s, 3H), 2.98 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 166.6, 159.4, 153.9, 153.3, 134.2, 132.4, 130.3, 128.5, 126.8, 126.5, 126.3, 113.2, 105.4, 105.2, 55.6, 46.0, 41.8, 28.6; HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_3$: 309.1234, found 309.1232 $(M+H)^+$.



2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6-fluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (4g)

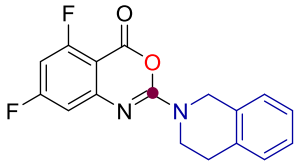
White solid; yield 78%; 115 mg; m.p. 104−105 ^{o}C; IR (KBr, cm^{-1}) *v*: 2923, 1769, 1607, 1491, 1454, 1300, 1229, 733; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.64-7.61 (m, 1H), 7.36-7.18 (m, 6H), 4.83 (s, 2H), 3.93 (t, J = 5.1 Hz, 2H), 2.95 (t, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1 (d, $J_{C\text{-}F}$ = 3.8 Hz), 158.1 (d, $J_{C\text{-}F}$ = 242.3 Hz), 152.8, 147.4, 134.1, 132.3, 128.5, 126.9, 126.5, 126.3, 126.1 (d, $J_{C\text{-}F}$ = 7.5 Hz), 125.0 (d, $J_{C\text{-}F}$ = 24.0 Hz), 113.2 (d, $J_{C\text{-}F}$ = 23.3 Hz), 112.7 (d, $J_{C\text{-}F}$ = 8.3 Hz), 46.0, 41.9, 28.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}FN_2O_2$: 297.1034, found 297.1037 $(M+H)^+$.



2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-8-fluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (4h)

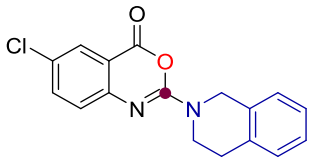
White solid; yield 80%; 118 mg; m.p. 126−127 ^{o}C; IR (KBr, cm^{-1}) *v*: 2928, 1769, 1628, 1613, 1370, 1305, 1061, 931, 755; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) δ 7.80 (d, J = 7.8 Hz, 1H), 7.40-7.34 (m, 1H), 7.26-7.21(m, 4H), 7.09-7.02 (m, 1H), 4.90 (s, 2H), 3.40 (s, 2H), 2.98 (t, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.7 (d, $J_{C\text{-}F}$ = 3.8 Hz), 154.9 (d, $J_{C\text{-}F}$ = 249.8 Hz), 153.3, 140.3 (d, $J_{C\text{-}F}$ = 12 Hz), 134.1, 132.1, 128.5, 126.9, 126.6, 126.3, 124.0 (d, $J_{C\text{-}F}$ = 4.5 Hz), 122.4 (d, $J_{C\text{-}F}$ = 7.5 Hz),

121.0 (d, $J_{C\text{-}F}$ = 18.8 Hz), 114.07 (d, $J_{C\text{-}F}$ = 3.0 Hz), 46.0, 41.9, 28.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}FN_2O_2Na$: 319.0853, found 319.0856 $(M+Na)^+$.



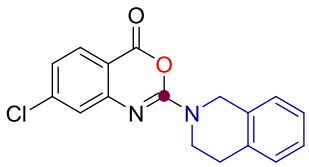
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-5,7-difluoro-4*H*-benzo[*d*][1,3]oxazin-4-one (4i)

White solid; yield 71%; 112 mg; m.p. 144−145 ^oC; IR (KBr, cm^{-1}) *v*: 3082, 2941, 1771, 1603, 1572, 1449, 1260, 1191, 990, 784; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.26-7.20 (m, 4H), 6.75 (d, *J* = 9.9 Hz, 1H), 6.58-6.51 (m, 1H), 4.87 (s, 2H), 3.97 (s, 2H), 2.97 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 167.8 (dd, $J_{C\text{-}F}$ = 255.0 Hz, $J_{C\text{-}F}$ = 15.0 Hz), 163.7 (dd, $J_{C\text{-}F}$ = 266.3 Hz, $J_{C\text{-}F}$ = 15.8 Hz), 154.6, 154.3 (d, $J_{C\text{-}F}$ = 18.7 Hz), 154.1, 134.0, 132.0, 128.5, 127.0, 126.7, 126.3, 106.0 (dd, $J_{C\text{-}F}$ = 22.5 Hz, $J_{C\text{-}F}$ = 3.8 Hz), 99.4 (dd, $J_{C\text{-}F}$ = 26.3 Hz, $J_{C\text{-}F}$ = 24.0 Hz), 98.7 (dd, $J_{C\text{-}F}$ = 8.3 Hz, $J_{C\text{-}F}$ = 2.3 Hz), 46.2, 42.0, 28.3; HRMS (ESI) *m/z* calcd for $C_{17}H_{12}F_2N_2O_2Na$: 337.0759, found 337.0753 $(M+Na)^+$.



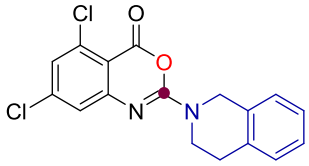
6-Chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4j)

White solid; yield 70%; 109 mg; m.p. 134−135 ^oC; IR (KBr, cm^{-1}) *v*: 3060, 2923, 1770, 1616, 1597, 1477, 1448, 1298, 1227, 913, 747; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.98 (d, *J* = 2.4 Hz, 1H), 7.56 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 1H), 7.30-7.18 (m, 5H), 4.88 (s, 2H), 3.98 (t, *J* = 6.0 Hz, 2H), 2.99 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.8, 153.2, 149.4, 136.9, 134.1, 132.2, 128.5, 128.1, 127.7, 126.9, 126.6, 126.3, 125.8, 113.1, 46.0, 41.9, 28.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}ClN_2O_2$: 313.0738, found 313.0738 $(M+H)^+$.



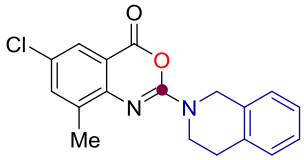
7-Chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4k)

White solid; yield 75%; 117 mg; m.p. 112−113 ^{o}C; IR (KBr, cm^{-1}) *v*: 2998, 2892, 1758, 1617, 1590, 1574, 1556, 1456, 1391, 1289, 1224, 922, 768; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.93 (d, *J* = 8.4 Hz, 1H), 7.29-7.18 (m, 5H), 7.09 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H), 4.87 (s, 2H), 3.97 (t, *J* = 5.4 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.2, 153.8, 151.9, 143.0, 134.1, 132.2, 130.0, 128.6, 127.0, 126.7, 126.4, 123.9, 123.8, 110.6, 46.1, 42.0, 28.6; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClN_2O_2Na$: 335.0558, found 335.0556 $(M+Na)^+$.



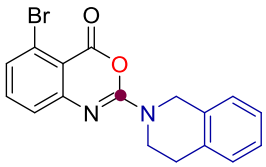
5,7-Dichloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4l)

White solid; yield 82%; 142 mg; m.p. 179−180 ^{o}C; IR (KBr, cm^{-1}) *v*: 3073, 2933, 1772, 1620, 1574, 1404, 1250, 1207, 1166, 955; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.25-7.10 (m, 6H), 4.84 (s, 2H), 3.94 (m, 2H), 2.97 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 155.7, 153.9, 153.8, 141.8, 136.7, 134.0, 132.0, 128.6, 127.0, 126.7, 126.3, 125.5, 123.0, 108.4, 45.6, 41.9, 28.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{13}Cl_2N_2O_2$: 347.0349, found 347.0349 $(M+H)^+$.



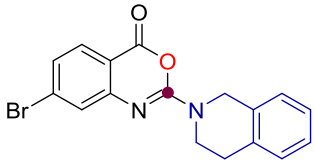
6-Chloro-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-8-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4m)

White solid; yield 77%; 126 mg; m.p. 142−143 ^{o}C; IR (KBr, cm^{-1}) *v*: 2905, 1757, 1615, 1445, 1298, 1250, 782,751; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 (d, *J* = 2.1 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.23-7.17 (m, 4H), 4.84 (s, 2H), 3.95 (t, *J* = 5.4 Hz, 2H), 2.96 (t, *J* = 5.7 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.4, 152.5, 148.0, 136.8, 135.0, 134.2, 132.3, 128.6, 127.3, 126.9, 126.5, 126.3, 125.0, 112.6, 46.0, 41.9, 28.5, 17.0; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}ClN_2O_2$: 327.0895, found 327.0901 $(M+H)^+$.



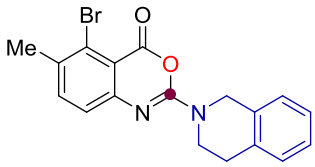
5-Bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4n)

White solid; yield 81%; 145 mg; m.p. 114−115 ^{o}C; IR (KBr, cm^{-1}) *v*: 2932, 1768, 1621, 1591, 1542, 1431, 1287, 799, 732; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38-7.34 (m, 2H), 7.24-7.16 (m, 5H), 4.85 (s, 2H), 3.95 (t, *J* = 5.7 Hz, 2H), 2.96 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.7, 153.3, 153.1, 136.1, 134.1, 132.2, 129.3, 128.6, 126.9, 126.6, 126.3, 124.0, 123.4, 111.2, 45.9, 41.8, 28.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}BrN_2O_2$: 357.0233, found 357.0234 $(M+H)^+$.



7-Bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4o)

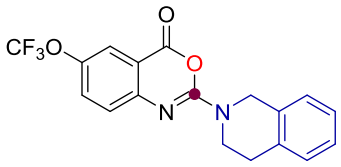
White solid; yield 79%; 141 mg; m.p. 123−124 ^{o}C; IR (KBr, cm^{-1}) *v*: 2926, 1767, 1705, 1614, 1592, 1453, 1390, 1230, 912, 745; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.25-7.18 (m, 5H), 4.86 (s, 2H), 3.96 (t, *J* = 5.4 Hz, 2H), 2.97 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3, 153.8, 151.9, 134.1, 132.2, 131.8, 129.9, 128.6, 127.0, 127.0, 126.7, 126.6, 126.3, 111.0, 46.1, 42.0, 28.5; HRMS (ESI) *m/z* calcd for $C_{17}H_{14}BrN_2O_2$: 357.0233, found 357.0233. $(M+H)^+$.



5-Bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4p)

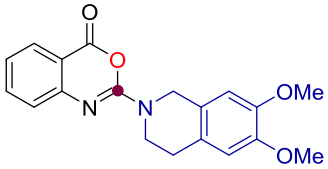
White solid; yield 80%; 148 mg; m.p. 112−113 ^{o}C; IR (KBr, cm^{-1}) *v*: 2925, 1713, 1622, 1593, 1468, 1224, 1146, 730; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 8.4 Hz, 1H), 7.23-7.15 (m, 5H), 4.84 (s, 2H), 3.94 (t, *J* = 5.7 Hz, 2H), 2.96 (t, *J* = 5.7

Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.8, 152.9, 151.2, 137.8, 134.8, 134.1, 132.2, 128.6, 126.9, 126.6, 126.3, 124.7, 123.3, 111.3, 45.9, 41.7, 28.6, 23.7; HRMS (ESI) *m/z* calcd for $C_{18}H_{16}BrN_2O_2$: 371.0390, found 371.0389 $(M+H)^+$.



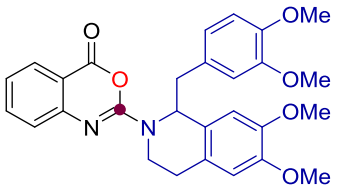
2-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-6-(trifluoromethoxy)-4*H*-benzo[*d*][1,3]oxazin-4-one (4q)

White solid; yield 75%; 136 mg; m.p. 122−123 ^{o}C; IR (KBr, cm^{-1}) *v*: 2932, 1771, 1602, 1493, 1454, 1261, 930, 750; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 (s, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 7.37-7.19 (m, 5H), 4.85 (s, 2H), 3.95 (m, 2H), 2.96 (t, *J* = 5.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.9, 153.4, 149.6, 144.1 (d, $J_{C\text{-}F}$ = 2.3 Hz), 134.1, 132.1, 130.2, 128.6, 127.0, 126.6, 126.3, 126.0, 120.4 (d, $J_{C\text{-}F}$ = 255.7 Hz), 120.2, 112.6, 46.1, 42.0, 28.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{14}F_3N_2O_3$: 363.0951, found 363.0950 $(M+H)^+$.



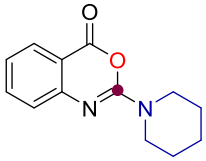
2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4s)

White solid; yield 62%; 105 mg; m.p. 149−150 ^{o}C; IR (KBr, cm^{-1}) *v*: 2986, 2865, 1743, 1622, 1591, 1451, 1273, 1120, 772; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (d, *J* = 6.9, 1H), 7.65-7.60 (m, 1H), 7.31-7.27 (m, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 6.3 Hz, 2H), 4.82 (s, 2H), 3.97 (t, *J* = 5.4 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 2.90 (t, *J* = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9, 153.3, 150.7, 147.9, 147.8, 136.7, 128.7, 126.0, 124.1, 123.3, 112.3, 111.3, 109.0, 55.9 (2C), 45.8, 42.0, 28.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_4$: 339.1339, found 339.1344 $(M+H)^+$.



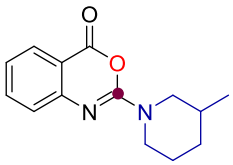
2-(1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (4t)

White solid; yield 68%; 166 mg; m.p. 155−156 ^{o}C; IR (KBr, cm^{-1}) *v*: 2959, 2934, 2833, 1747, 1602, 1438, 1270, 1140, 850, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.62 (t, *J* = 6.9 Hz, 1H), 7.30-7.27 (m, 1H), 7.16-7.11 (m, 1H), 6.73-6.64 (m, 4H), 6.38 (s, 1H), 5.70-5.50 (m, 1H), 4.43-4.11 (m, 1H), 3.87-3.72 (m, 12H), 3.62-3.59 (m, 1H), 3.20-3.03 (m, 3H), 2.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 153.1, 150.8, 148.6, 147.8, 147.7, 147.0, 136.5, 130.0, 128.5, 127.4, 125.8, 124.0, 123.0, 121.9, 112.7, 112.1, 111.1, 110.9, 110.3, 56.6, 55.8(2C), 55.7, 42.9, 41.6, 39.3, 27.5; HRMS (ESI) *m/z* calcd for $C_{28}H_{29}N_2O_6$: 489.2020, found 489.2024 $(M+H)^+$.



2-(Piperidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5a) [1]

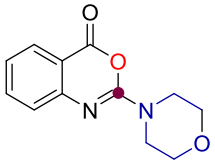
White solid; yield 82%; 94 mg; m.p. 101−102 ^{o}C; IR (KBr, cm^{-1}) *v*: 2942, 1748, 1590, 1464, 1282, 1004, 775; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.62-7.56 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.13-7.08 (m, 1H), 3.72 (d, *J* = 5.4 Hz, 4H), 1.66 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2, 153.3, 151.2, 136.6, 128.6, 124.1, 122.9, 112.1, 45.2, 25.5, 24.3; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O_2$: 231.1128, found 231.1129 $(M+H)^+$.



2-(3-Methylpiperidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5b)

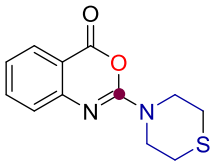
White solid; yield 83%; 101 mg; m.p. 103−104 ^{o}C; IR (KBr, cm^{-1}) *v*: 2925, 2851, 1747, 1593, 1487, 1273, 1241, 1003, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99-7.97 (m, 1H), 7.61-7.56 (m, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.12-7.07 (m, 1H),

4.43-4.34 (m, 2H), 2.96-2.87 (m, 1H), 2.64-2.56 (m, 1H), 1.87-1.54 (m, 4H), 1.22-1.11 (m, 1H), 0.96 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1, 153.2, 151.1, 136.5, 128.5, 124.0, 122.8, 112.0, 51.3, 44.6, 32.7, 30.9, 24.9, 18.8; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N_2O_2$: 245.1285, found 245.1286 $(M+H)^+$.



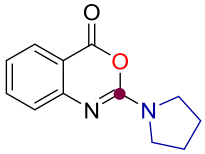
2-Morpholino-4*H*-benzo[*d*][1,3]oxazin-4-one (5c) [2]

White solid; yield 87%; 101 mg; m.p. 116−117 ^{o}C; IR (KBr, cm^{-1}) v: 2968, 1746, 1600, 1473, 1278, 1114, 993, 774; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H), 7.65-7.60 (m, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.19-7.13 (m, 1H), 3.79-3.72 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.5, 153.2, 150.4, 136.7, 128.7, 124.2, 123.6, 112.4, 66.3, 44.3; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2O_3$: 233.0921, found 233.0922 $(M+H)^+$.



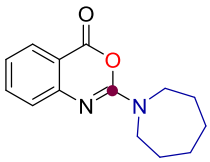
2-Thiomorpholino-4*H*-benzo[*d*][1,3]oxazin-4-one (5d)

White solid; yield 75%; 93 mg; m.p. 119−120 ^{o}C; IR (KBr, cm^{-1}) v: 2912, 2852, 1773, 1591, 1474, 1308, 1225, 1006, 757; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 6.9 Hz, 1H), 7.24-7.14 (m, 2H), 4.05 (t, J = 4.5 Hz, 4H), 2.72 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.7, 152.8, 150.5, 136.8, 128.7, 124.3, 123.6, 112.3, 46.8, 27.1; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2O_2S$: 249.0692, found 249.0696 $(M+H)^+$.



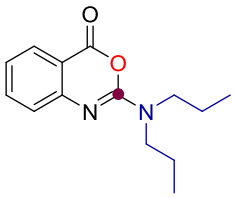
2-(Pyrrolidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5f) [3]

White solid; yield 42%; 45 mg; m.p. 108−109 ^{o}C; IR (KBr, cm^{-1}) *v*: 2971, 2876, 2760, 1594, 1328, 1304, 1018, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.00 (dd, *J* = 7.8 Hz, *J* =1.2 Hz, 1H), 7.63-7.57 (m, 1H), 7.28-7.25 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 3.63 (t, *J* = 6.6 Hz, 4H), 2.03-1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1, 152.6, 151.1, 136.6, 128.7, 123.9, 122.8, 112.1, 46.8, 25.2; HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2O_2$: 217.0972, found 217.0973 $(M+H)^+$.



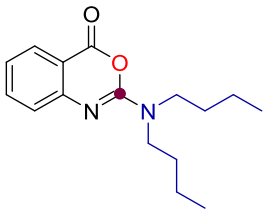
2-(Azepan-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5g)

White solid; yield 81%; 99 mg; m.p. 95−96 ^{o}C; IR (KBr, cm^{-1}) *v*: 2926, 2850, 1743, 1592, 1435, 1311, 774; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.00 (dd, *J* = 7.8 Hz, *J* = 1.2 Hz, 1H), 7.60-7.57 (m, 1H), 7.26 (d, *J* = 6.3 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 3.70 (s, 4H), 1.82 (s, 4H), 1.62-1.59 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2, 153.8, 151.3, 136.5, 128.5, 124.0, 122.6, 112.0, 47.7, 46.7, 28.3, 27.4, 26.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N_2O_2$: 245.1285, found 245.1285 $(M+H)^+$.



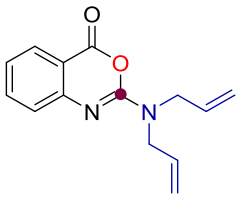
2-(Dipropylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5h)

White solid; yield 74%; 91 mg; m.p. 44−45 ^{o}C; IR (KBr, cm^{-1}) *v*: 3291, 2938, 1745, 1636, 1604, 1475, 1232, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (dd, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 7.59-7.56 (m, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.12-7.09 (m, 1H), 3.46 (t, *J* = 7.5, 4H), 1.73-1.65 (m, 4H), 0.96 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2, 153.9, 151.3, 136.5, 128.6, 124.1, 122.7, 112.1, 49.5, 21.2, 11.2; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}N_2O_2$: 247.1441, found 247.1438 $(M+H)^+$.



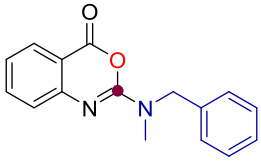
2-(Dibutylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5i) [1]

White solid; yield 77%; 106 mg; m.p. 48−49 ^{o}C; IR (KBr, cm^{-1}) *v*: 2958, 2932, 1763, 1597, 1473, 1291, 1000, 760, 686; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (dd, *J* = 8.1 Hz, *J* = 1.5 Hz, 1H), 7.61-7.55 (m, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.11-7.06 (m, 1H), 3.48 (t, *J* = 7.2 Hz, 4H), 1.66-1.59 (m, 4H), 1.41-1.34 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.3, 153.8, 151.3, 136.5, 128.6, 124.1, 122.6, 112.1, 47.5, 30.1, 20.0, 13.8; HRMS (ESI) *m/z* calcd for $C_{16}H_{23}N_2O_2$: 275.1754, found 275.1756 $(M+H)^+$



2-(Diallylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5j)

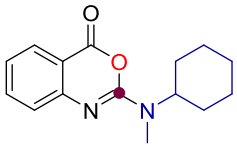
Yellow oil; yield 72%; 87 mg; IR (KBr, cm^{-1}) *v*: 3080.8, 2983.2, 2923.8, 1762.3, 1586.9, 1473.4, 1239.7, 998.7, 764.2, 688.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (d, *J* = 7.8, 1H), 7.62-7.57 (m, 1H), 7.24 (d, *J* = 8.1 Hz 1H), 7.12 (t, *J* = 7.2 Hz, 1H), 5.93-5.80 (m, 2H), 5.26-5.21 (m, 4H), 4.14 (d, *J* = 3.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8, 153.6, 150.8, 136.5, 132.3, 128.5, 124.2, 123.1, 117.8, 112.2, 48.9; HRMS (ESI) *m/z* calcd for $C_{14}H_{15}N_2O_2$: 243.1128, found 243.1129 $(M+H)^+$.



2-(Benzylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5k) [4]

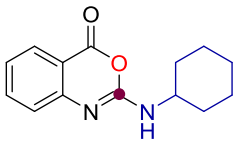
White solid; yield 71%; 94 mg; m.p. 118−119 ^{o}C; IR (KBr, cm^{-1}) *v*: 3057, 2922, 1767, 1624, 1473, 1308, 1002, 731; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 7.2 Hz, 1H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.32-7.24 (m, 6H), 7.13 (t, *J* = 7.5 Hz, 1H), 4.76 (s,

2H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9, 154.3, 150.9, 136.6, 136.3, 128.7, 128.6, 127.7, 124.2, 123.1, 112.2, 52.5, 34.5; HRMS (ESI) *m/z* calcd for $C_{16}H_{15}N_2O_2$: 267.1128, found 267.1132 $(M+H)^+$.



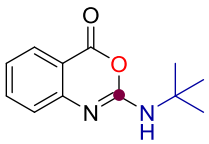
2-(Cyclohexyl(methyl)amino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5l)[5]

White solid; yield 69%; 89 mg; m.p. 127−128 ^{o}C; IR (KBr, cm^{-1}) *v*: 2946, 2922, 2854, 1770, 1592, 1402, 1304, 1008, 759, 685; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.99 (d, *J* = 7.8 Hz, 1H), 7.61-7.56 (m, 1H), 7.27-7.23 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 4.34 (s, 1H), 3.02 (s, 3H), 1.87-1.69 (m, 5H), 1.56-1.38 (m, 4H), 1.14-1.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.3, 153.9, 151.3, 136.5, 128.6, 124.1, 122.7, 112.1, 54.9, 30.0, 28.9, 25.5, 25.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}N_2O_2$: 259.1441, found 259.1444 $(M+H)^+$.



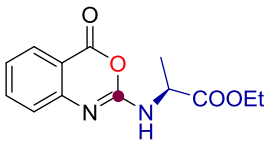
2-(Cyclohexylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5m) [6]

White solid; yield 75%; 92 mg; m.p. 207−208 ^{o}C; IR (KBr, cm^{-1}) *v*: 3291, 2920, 2853, 1745, 1636, 1604, 1475, 1232, 759; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (d, *J* = 7.8 Hz, 1H), 7.65-7.59 (m, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 4.85 (s, 1H), 3.87-3.77 (m, 1H), 2.08-2.05 (m, 2H), 1.78-1.63 (m, 3H), 1.50-1.38 (m, 2H), 1.32-1.17 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.0, 153.0, 150.5, 136.7, 128.7, 124.1, 123.4, 113.1, 50.2, 32.9, 25.4, 24.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{17}N_2O_2$: 245.1285, found 245.1285 $(M+H)^+$.



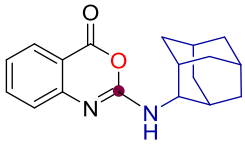
2-(*Tert*-butylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5n) [6]

Yellow solid; yield 53%; 58 mg; m.p. 129−130 ^{o}C; IR (KBr, cm^{-1}) *v*: 3299, 2972, 1742, 1631, 1606, 1475, 1278, 1071, 762; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.63-7.58 (m, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.17-7.12 (m, 1H), 5.06 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1, 152.2, 150.3, 136.4, 128.5, 124.4, 123.3, 113.2, 51.9, 28.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{15}N_2O_2$: 219.1128, found 219.1129 $(M+H)^+$.



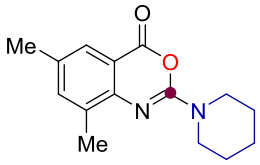
Ethyl (4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)alaninate (5o) [1]

White solid; yield 73%; 96 mg; m.p. 132−133 ^{o}C; IR (KBr, cm^{-1}) *v*: 3342, 2979, 2938, 1769, 1630, 1472, 1219, 767; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.03 (d, *J* = 6.9 Hz 1H), 7.66-7.61 (m, 1H), 7.28-7.17 (m, 2H), 5.57 (s, 1H), 4.63 (d, *J* = 6.6 Hz, 1H), 4.26 (q, *J* = 6.9 Hz, 2H), 1.55 (d, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 172.5, 159.5, 152.7, 149.8, 136.7, 128.7, 124.4, 124.0, 113.4, 61.7, 50.0, 18.3, 14.1; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O_4$: 263.1026, found 263.1030 $(M+H)^+$.



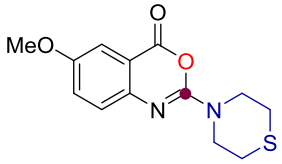
2-(((1R,3S,5r,7r)-Adamantan-2-yl)amino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5p)[6]

Yellow solid; yield 65%; 96 mg; m.p. 198−199 ^{o}C; IR (KBr, cm^{-1}) *v*: 3277, 2902, 2848, 1736, 1629, 1477, 1280, 1058, 763; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.01 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.26-7.24 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 4.81 (s, 1H), 2.12 (m, 9H), 1.72 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.0, 152.0, 150.2, 136.5, 128.6, 124.3, 123.4, 113.3, 52.5, 41.6, 36.2, 29.5; HRMS (ESI) *m/z* calcd for $C_{18}H_{21}N_2O_2$: 297.1598, found 297.1606 $(M+H)^+$.



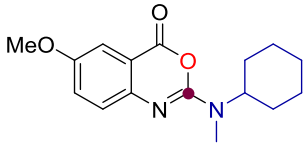
6,8-Dimethyl-2-(piperidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5q)

Yellow solid; yield 77%; 99 mg; m.p. 92−93 ^{o}C; IR (KBr, cm^{-1}) *v*: 2944, 2864, 2360, 1746, 1602, 1490, 1299, 786; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.62 (s, 1H), 7.26 (s, 1H), 3.69 (d, *J* = 5.1 Hz, 4H), 2.34 (s, 3H), 2.34 (s, 3H), 1.66 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.8, 152.2, 147.3, 138.3, 132.2, 131.8, 125.3, 111.3, 45.0, 25.4, 24.2, 20.7, 16.9; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}N_2O_2$: 259.1441, found 259.1445 $(M+H)^+$.



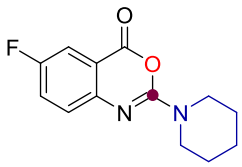
6-Methoxy-2-thiomorpholino-4*H*-benzo[*d*][1,3]oxazin-4-one (5r)

White solid; yield 81%; 113 mg; m.p. 158−159 ^{o}C; IR (KBr, cm^{-1}) *v*: 2912, 2837, 2360, 1762, 1495, 1308, 1032, 822, 786; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40 (d, *J* = 2.4 Hz, 1H), 7.28-7.19 (m, 2H), 4.04-4.01 (m, 4H), 3.85 (s, 3H), 2.72-2.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8, 155.9, 151.9, 144.8, 126.9, 125.7, 112.4, 108.2, 55.8, 46.9, 27.0; HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O_3S$: 279.0798, found 279.0806 $(M+H)^+$.



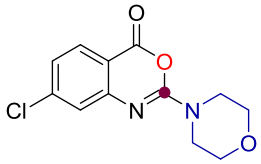
2-(Cyclohexyl(methyl)amino)-6-methoxy-4*H*-benzo[*d*][1,3]oxazin-4-one (5s)

White solid; yield 83%; 120 mg; m.p. 126−127 ^{o}C; IR (KBr, cm^{-1}) *v*: 2927, 2853, 1752, 1604, 1297, 1038, 836, 776; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.38 (s, 1H), 7.27-7.18 (m, 2H), 4.30 (s, 1H), 3.84 (s, 3H), 3.00 (s, 3H), 1.86-1.68 (m, 5H), 1.56-1.38 (m, 4H), 1.18-1.11 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.4, 155.3, 153.0, 145.8, 126.8, 125.6, 112.0, 108.0, 55.7, 54.9, 30.0, 28.8, 25.6, 25.4; HRMS (ESI) *m/z* calcd for $C_{16}H_{21}N_2O_3$: 289.1547, found 289.1553 $(M+H)^+$.



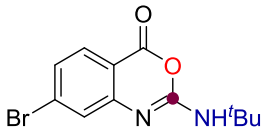
6-Fluoro-2-(piperidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5t)

Brown solid; yield 80%; 99 mg; m.p. 91−92 ^{o}C; IR (KBr, cm^{-1}) *v*: 2947, 2860, 1767, 1607, 1489, 1208, 935, 830; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J = 7.8 Hz, 1H), 7.34-7.18 (m, 2H), 3.69 (s, 4H), 1.67 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6, 159.4 (d, $J_{C\text{-}F}$ = 3.75 Hz) 154.6 (d, $J_{C\text{-}F}$ = 267.0 Hz), 147.7, 126.0 (d, $J_{C\text{-}F}$ = 7.5 Hz), 124.9 (d, $J_{C\text{-}F}$ = 23.6 Hz) 113.1 (d, $J_{C\text{-}F}$ = 23.5 Hz) 112.4 (d, $J_{C\text{-}F}$ = 8.6 Hz), 45.2, 25.4, 24.2; HRMS (ESI) *m/z* calcd for $C_{13}H_{14}FN_2O_2$: 249.1034, found 249.1035 $(M+H)^+$.



7-Chloro-2-morpholino-4*H*-benzo[*d*][1,3]oxazin-4-one (5u)

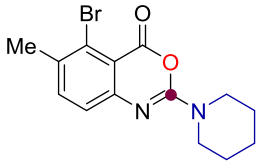
White solid; yield 76%; 101 mg; m.p. 181−182 ^{o}C; IR (KBr, cm^{-1}) *v*: 2977, 2870, 1765, 1590, 1434, 1290, 878, 771; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91 (d, J = 8.4 Hz, 1H), 7.24-7.23 (m, 1H), 7.12-7.08 (m, 1H), 3.76 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 158.8, 153.7, 151.6, 143.1, 130.0, 124.1, 123.9, 110.7, 66.3, 44.4; HRMS (ESI) *m/z* calcd for $C_{12}H_{12}ClN_2O_3$: 267.0531, found 267.0537 $(M+H)^+$.



7-Bromo-2-(*tert*-butylamino)-4*H*-benzo[*d*][1,3]oxazin-4-one (5v)

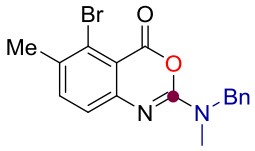
Yellow solid; yield 68%; 101 mg; m.p. 176−177 ^{o}C; IR (KBr, cm^{-1}) *v*: 3308, 2976, 2960, 2360, 1738, 1439, 1210, 769; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.84 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 1.5 Hz, 1H), 7.27-7.24 (m, 1H), 5.04 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.4, 152.6, 151.2, 131.5, 129.8, 127.3, 126.8,

112.0, 52.2, 28.7; HRMS (ESI) *m/z* calcd for $C_{12}H_{14}BrN_2O_2$: 297.0233, found 297.0231 $(M+H)^+$.



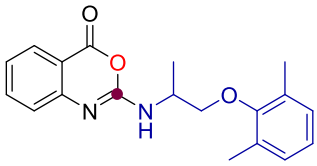
5-Bromo-6-methyl-2-(piperidin-1-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (5w)

White solid; yield 81%; 131 mg; m.p. 103−104 °C; IR (KBr, cm^{-1}) *v*: 2938, 2854, 2360, 1768, 1590, 1447, 1267, 1017, 825, 688; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.40 (d, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 3.69 (d, *J* = 5.7 Hz, 4H), 2.42 (s, 3H), 1.64 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 157.1, 152.9, 151.7, 137.6, 134.3, 124.6, 123.2, 111.1, 45.0, 25.5, 24.2, 23.6; HRMS (ESI) *m/z* calcd for $C_{14}H_{16}BrN_2O_2$: 323.0390, found 323.0390 $(M+H)^+$.



2-(Benzyl(methyl)amino)-5-bromo-6-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (5x)

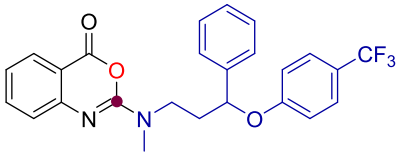
White solid; yield 90%; 162 mg; m.p. 97−98 °C; IR (KBr, cm^{-1}) *v*: 2954, 2360, 1771, 1627, 1464, 1293, 1050, 841, 724; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.43 (d, *J* = 8.4 Hz, 1H), 7.37-7.29 (m, 5H), 7.14 (d, *J* = 8.4 Hz, 1H), 4.74 (s, 2H), 3.10 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 156.9, 153.9, 151.5, 137.7, 136.2, 134.6, 128.7, 127.7, 124.7, 123.4, 111.3, 52.4, 34.4, 23.7; HRMS (ESI) *m/z* calcd for $C_{17}H_{16}BrN_2O_2$: 359.0390, found 359.0397 $(M+H)^+$.



2-((1-(2,6-Dimethylphenoxy)propan-2-yl)amino)-4*H*-benzo[*d*][1,3]oxazin-4-one (6)

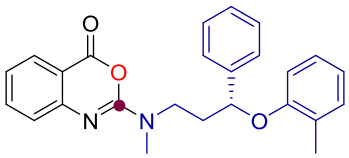
White solid; yield 72%; 117 mg; m.p. 154−155 °C; IR (KBr, cm^{-1}) *v*: 3280, 3054, 2991, 1742, 1637, 1478, 1196, 1019, 762; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.05

(d, *J* = 7.8 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.29-7.17 (m, 2H), 7.02-6.91 (m, 3H), 5.42 (s, 1H), 4.42 (s, 1H), 3.91-3.85 (m, 2H), 2.28 (s, 6H), 1.54 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8, 154.8, 153.1, 150.2, 136.7, 130.7, 129.0, 128.8, 124.3, 124.2, 123.8, 113.3,73.4, 47.7, 17.7, 16.2; HRMS (ESI) *m/z* calcd for $C_{19}H_{21}N_2O_3$: 325.1547, found 325.1546 $(M+H)^+$.



2-(Methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)amino)-4*H*-benzo[*d*][1,3]oxazin-4-one (7)

White solid; yield 71%; 161 mg; m.p. 94−95 ^{o}C; IR (KBr, cm^{-1}) *v*: 2925, 2843, 1763, 1370, 1369, 1260, 912, 694; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.91 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.35-7.27 (m, 7H), 7.08 (t, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.32 (q, *J* = 3.0 Hz, 1H), 3.83-3.81 (m, 2H), 3.17 (s, 3H), 2.38-2.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.0, 159.8, 154.1, 150.6, 140.5, 136.5, 130.0, 128.9, 128.5, 126.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 126.0, 124.3 (q, $J_{C\text{-}F}$ = 269.4 Hz), 124.0, 123.1, 115.5, 112.0, 78.0, 46.7, 36.5, 35.3; HRMS (ESI) *m/z* calcd for $C_{25}H_{22}F_3N_2O_3$: 455.1557, found 455.1582 $(M+H)^+$.



(*R*)-2-(Methyl(3-phenyl-3-(o-tolyloxy)propyl)amino)-4*H*-benzo[*d*][1,3]oxazin-4-one (8)

Yellow oil; yield 74%; 148 mg; IR (KBr, cm^{-1}) *v*: 2923.5, 2606.2, 1759.2, 1598.7, 1473.9, 1237.5, 1000.9, 751.2, 700.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.95 (dd, *J* = 8.1 Hz, *J* = 1.2 Hz, 1H), 7.58-7.53 (m, 1H), 7.36-7.28 (m, 4H), 7.26-7.21 (m, 1H), 7.16-7.06 (m, 3H), 6.93-6.88 (m, 1H), 6.76-6.71 (m, 1H), 6.58-6.55 (m, 1H), 5.26 (q, *J* = 3.9, 1H), 3.88-3.74 (m, 2H), 3.13 (s, 3H), 2.38 (s, 3H), 2.35-2.23 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.8, 155.5, 153.9, 150.8, 141.3, 136.5, 130.6, 128.7, 128.5, 127.6, 126.8, 126.5, 125.6, 124.0, 122.9, 120.3, 112.4, 112.0, 46.8, 36.6, 35.4, 16.5; HRMS (ESI) *m/z* calcd for $C_{25}H_{25}N_2O_3$: 401.1860, found 401.1872 $(M+H)^+$.

References

[1] Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464–479.

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[4] Steinebach, C.; Schulz-Fincke, A. C.; Schnakenburg, G.; Gütschow, M. *RSC Adv.* **2016**, *6*, 15430–15440.

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[6] Zhang, Y.; Yin, Z., Wang, H.; Wu, X.-F. *Org. Lett.* **2019**, *21*, 3242–3246.

7. NMR spectroscopic data for products 4-8

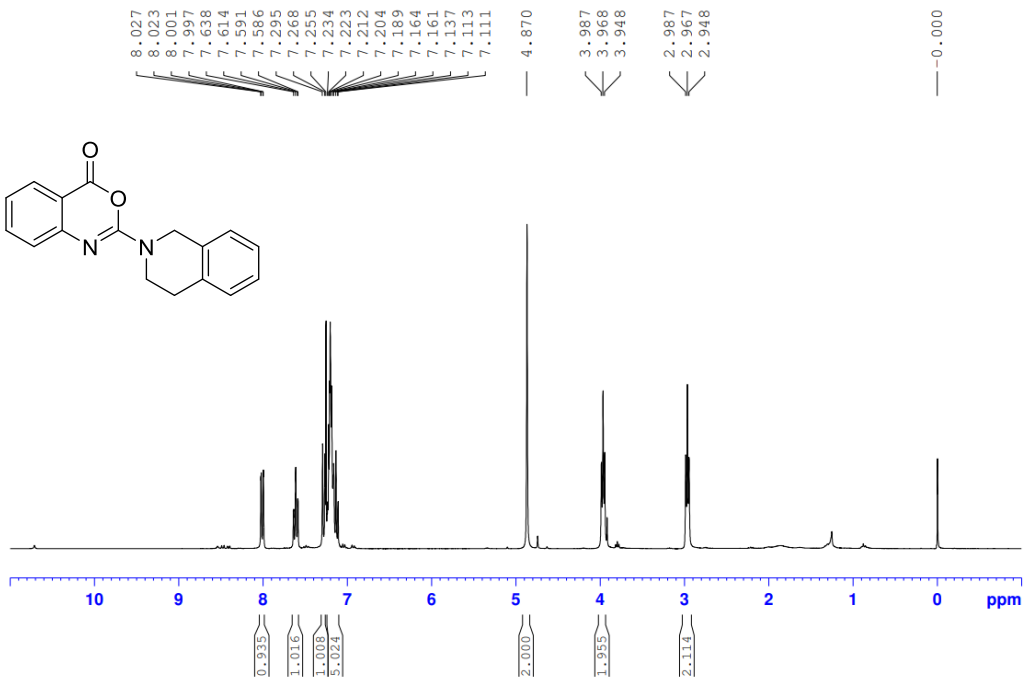

Figure S-1 ^{1}H NMR spectrum of compound **4a** (300 MHz, $CDCl_3$)

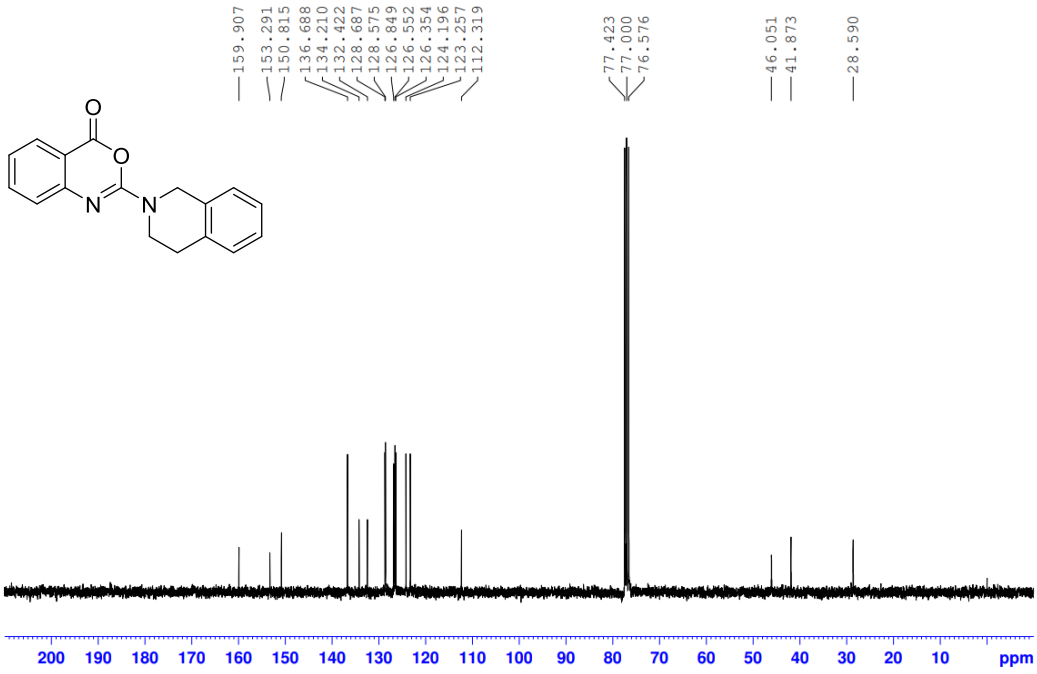

Figure S-2 ^{13}C NMR spectrum of compound **4a** (75 MHz, $CDCl_3$)

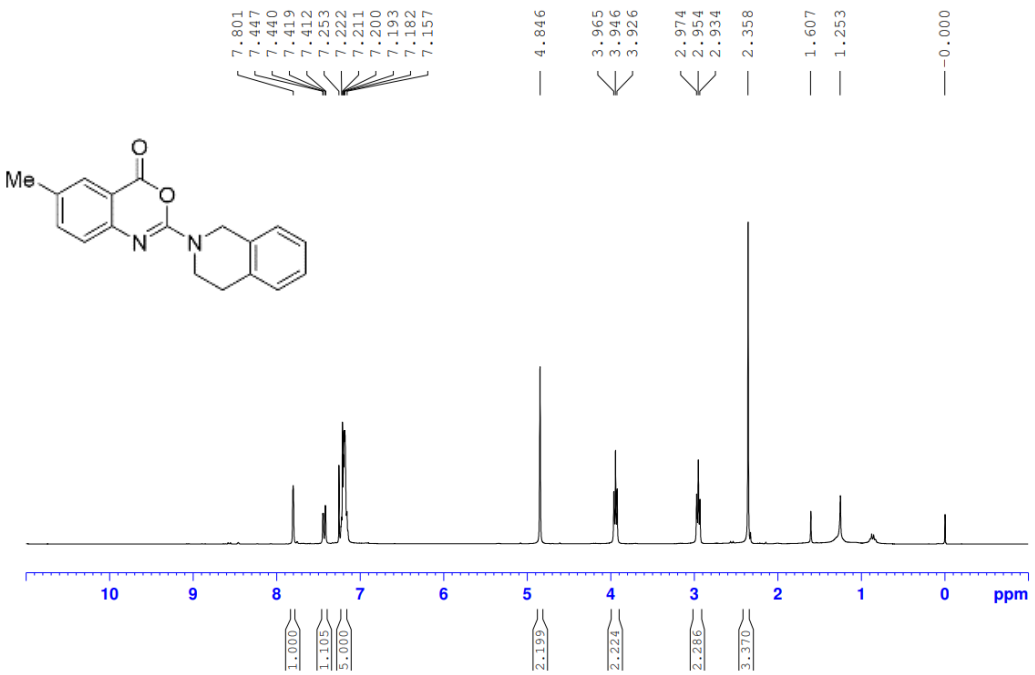

Figure S-3 ^{1}H NMR spectrum of compound **4b** (300 MHz, $CDCl_3$)

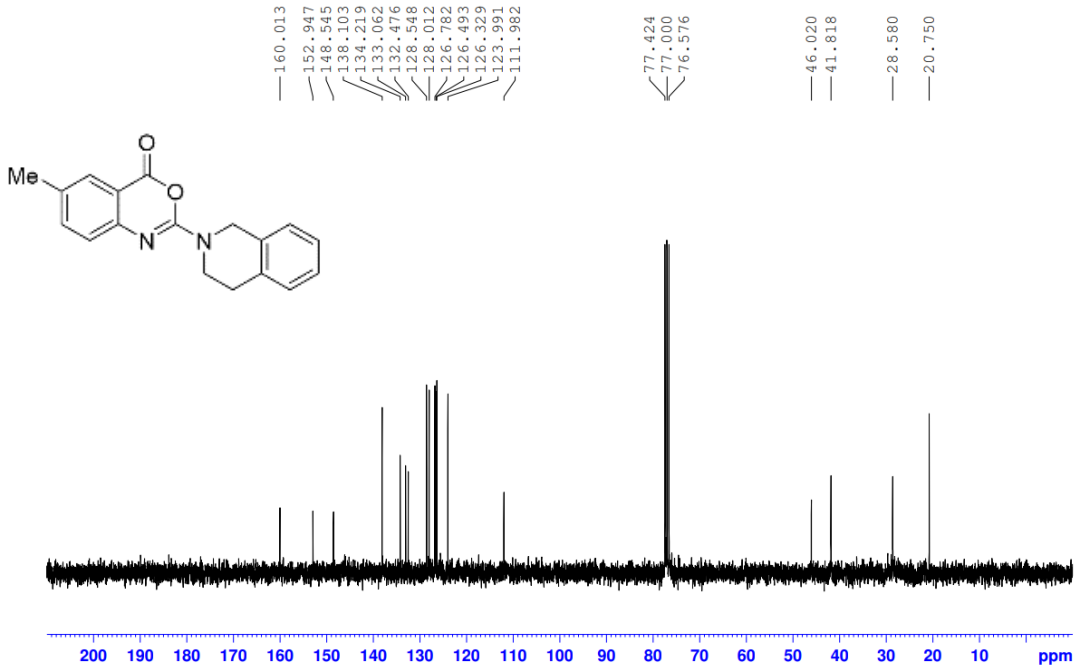

Figure S-4 ^{13}C NMR spectrum of compound **4b** (75 MHz, $CDCl_3$)

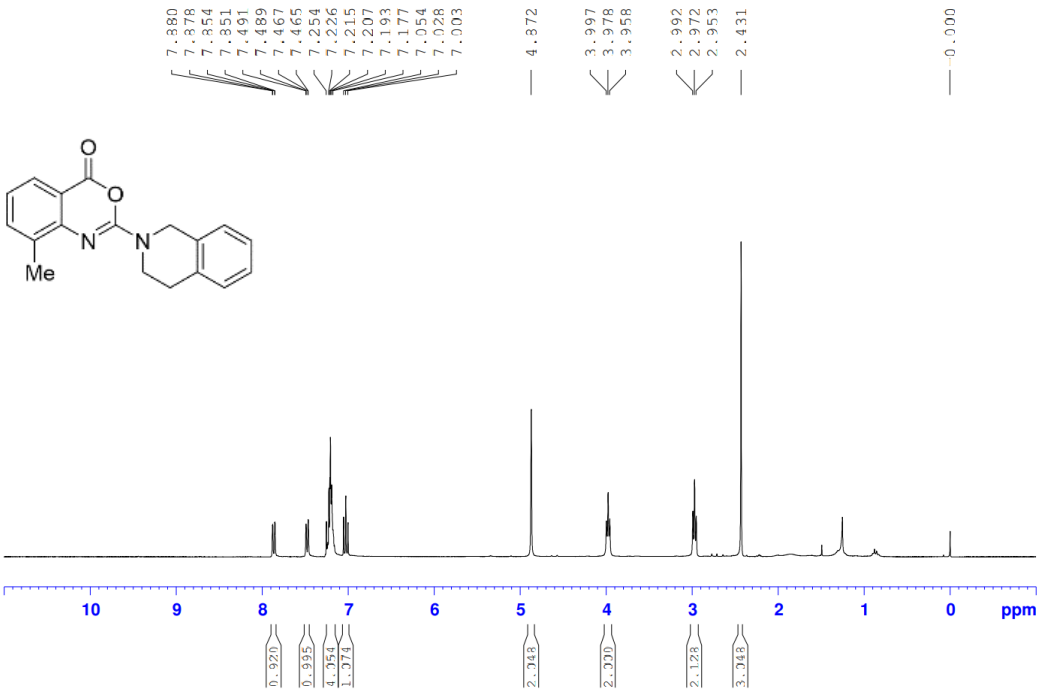

Figure S-5 ^{1}H NMR spectrum of compound **4c** (300 MHz, $CDCl_3$)

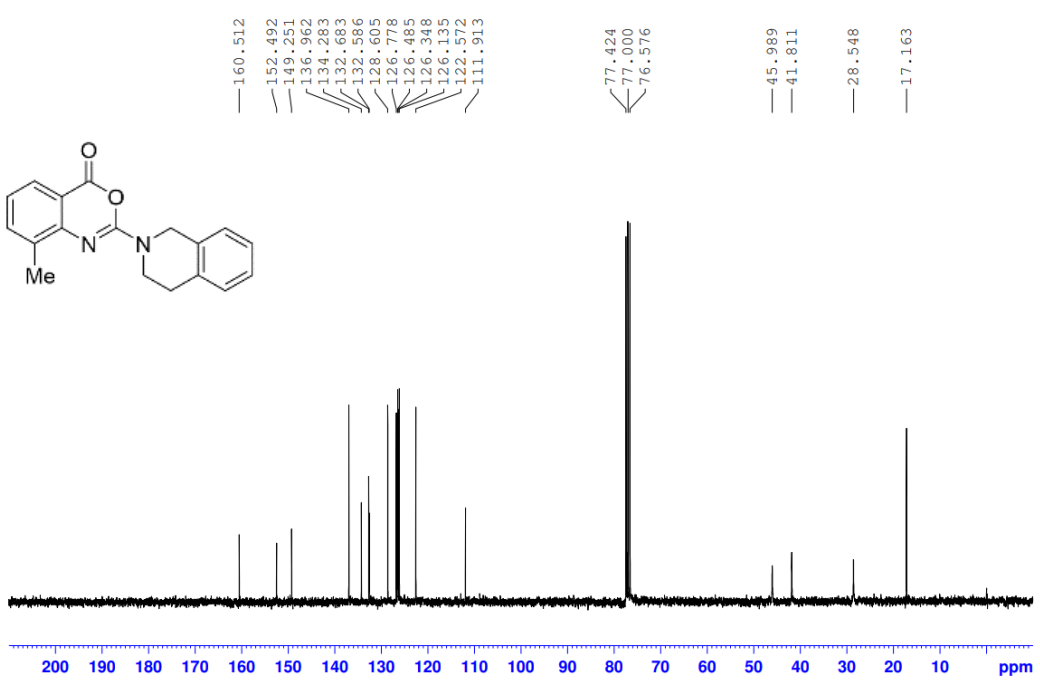

Figure S-6 ^{13}C NMR spectrum of compound **4c** (75 MHz, $CDCl_3$)

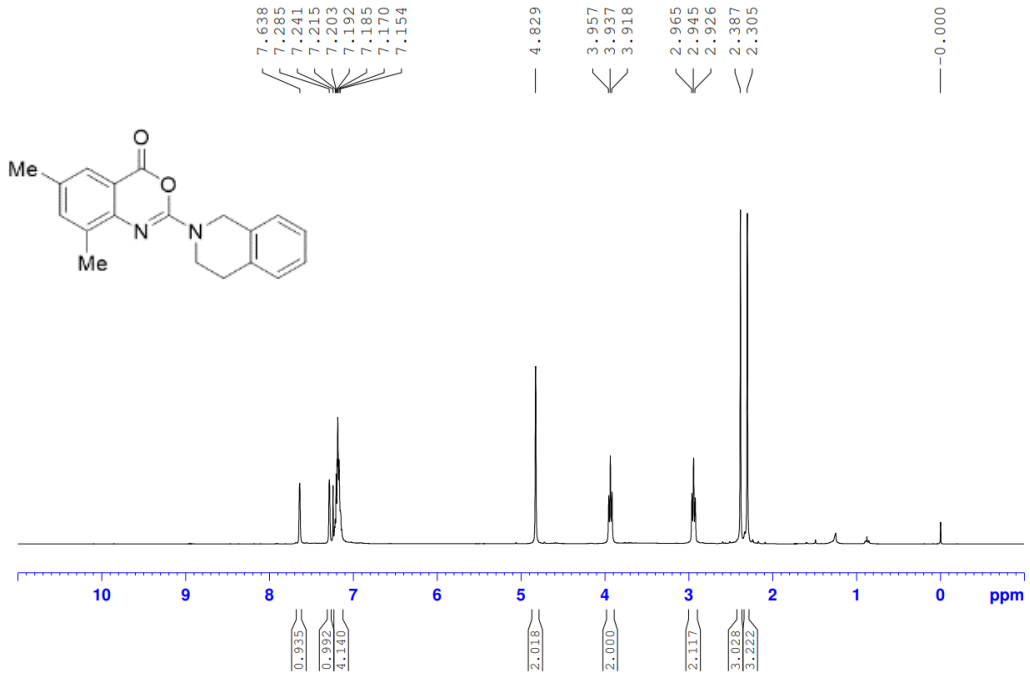

Figure S-7 ^{1}H NMR spectrum of compound **4d** (300 MHz, $CDCl_3$)

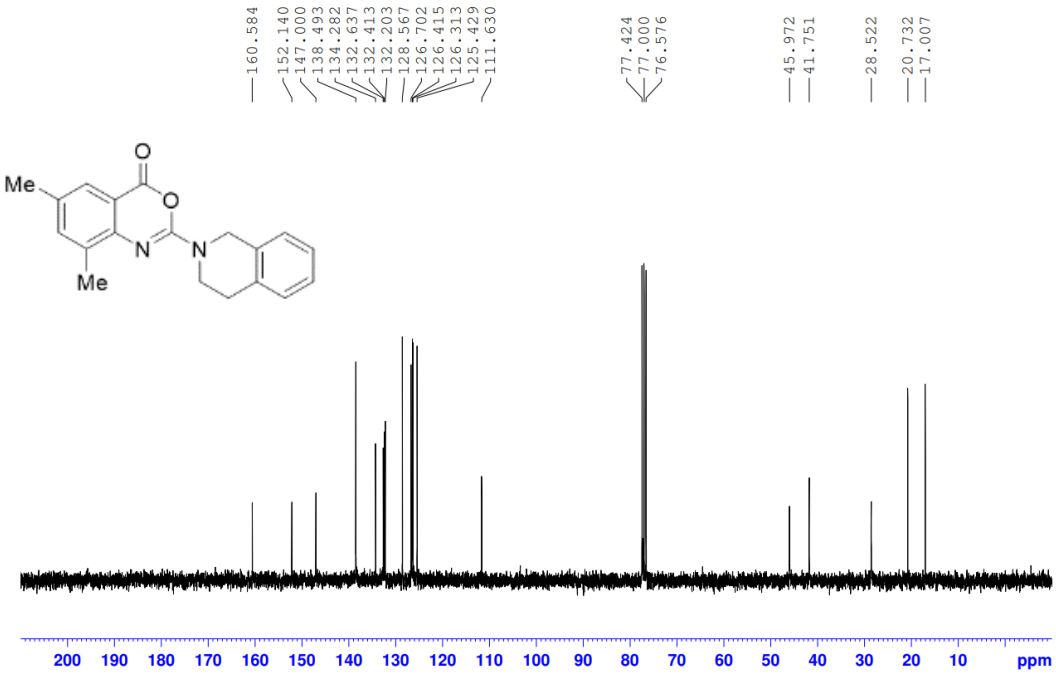

Figure S-8 ^{13}C NMR spectrum of compound **4d** (75 MHz, $CDCl_3$)

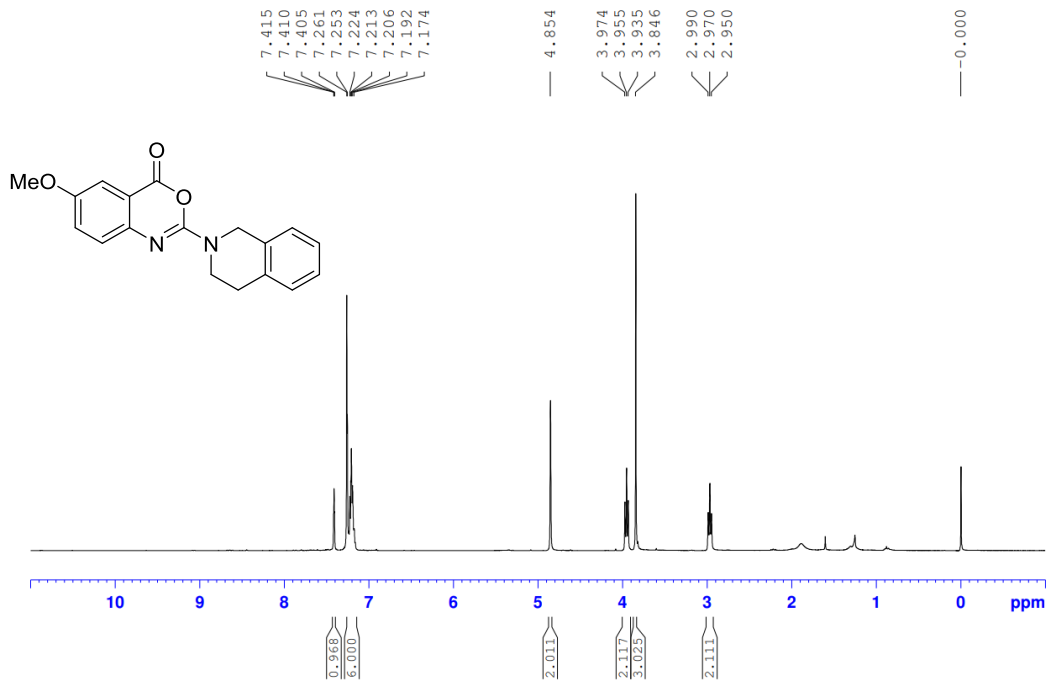

Figure S-9 ^{1}H NMR spectrum of compound **4e** (300 MHz, $CDCl_3$)

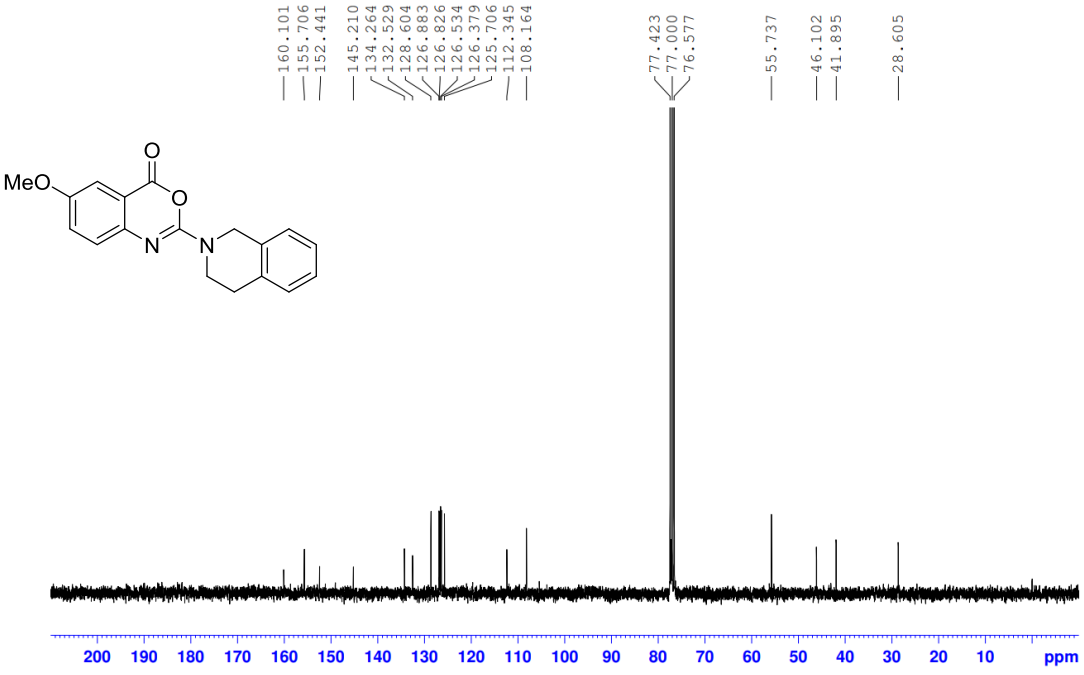

Figure S-10 ^{13}C NMR spectrum of compound **4e** (75 MHz, $CDCl_3$)

Figure S-11 ^{1}H NMR spectrum of compound **4f** (300 MHz, $CDCl_3$)

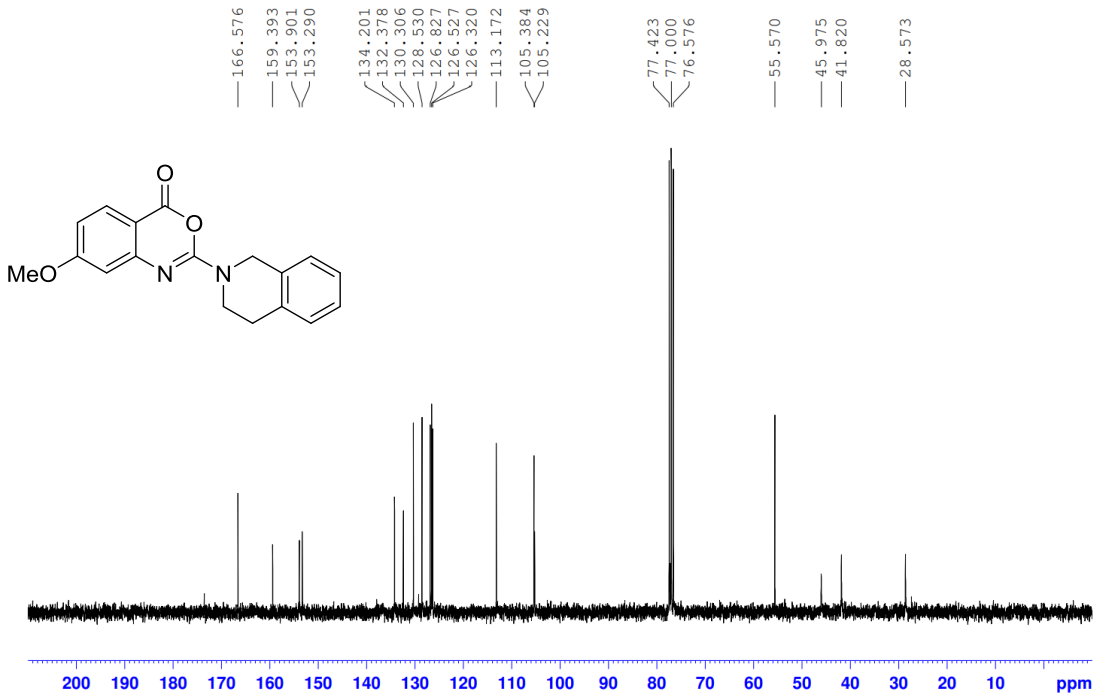

Figure S-12 ^{13}C NMR spectrum of compound **4f** (75 MHz, $CDCl_3$)

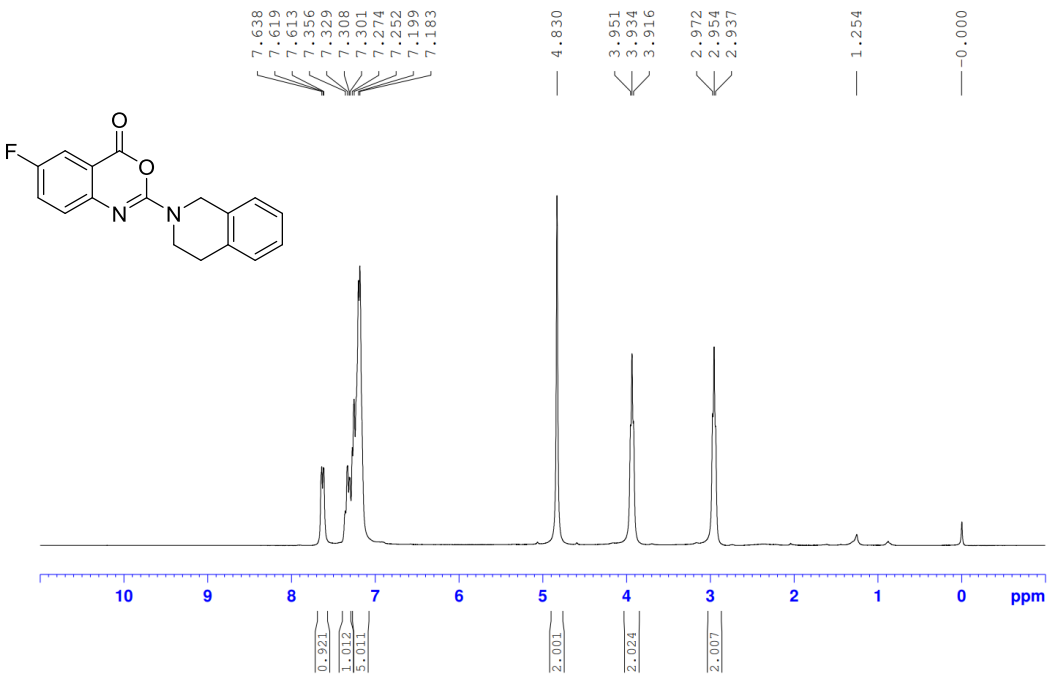

Figure S-13 ^{1}H NMR spectrum of compound **4g** (300 MHz, $CDCl_3$)

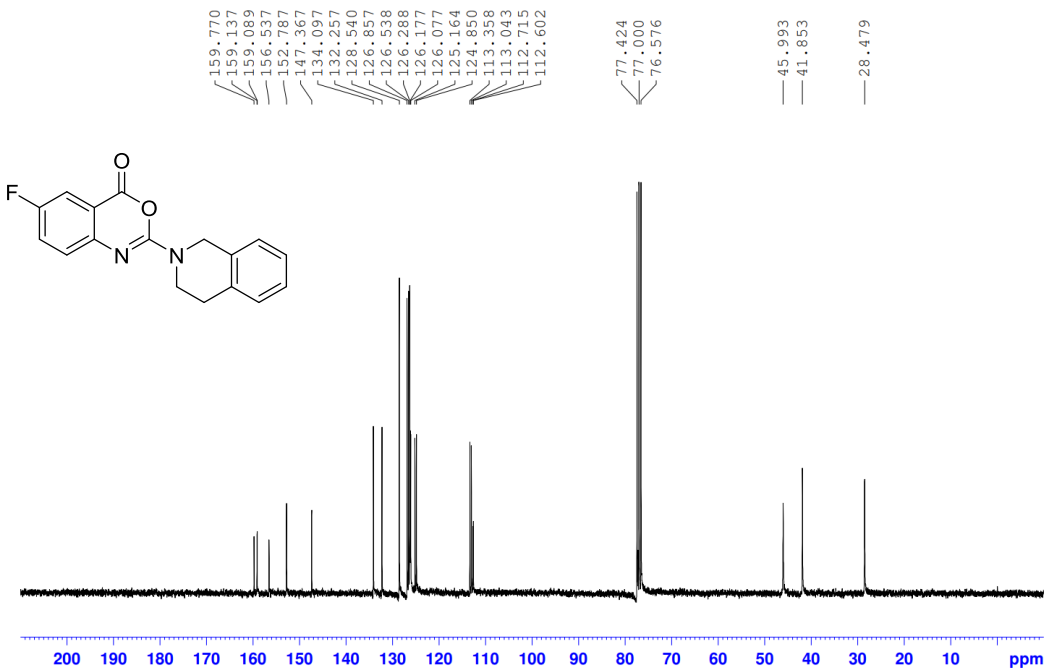

Figure S-14 ^{13}C NMR spectrum of compound **4g** (75 MHz, $CDCl_3$)

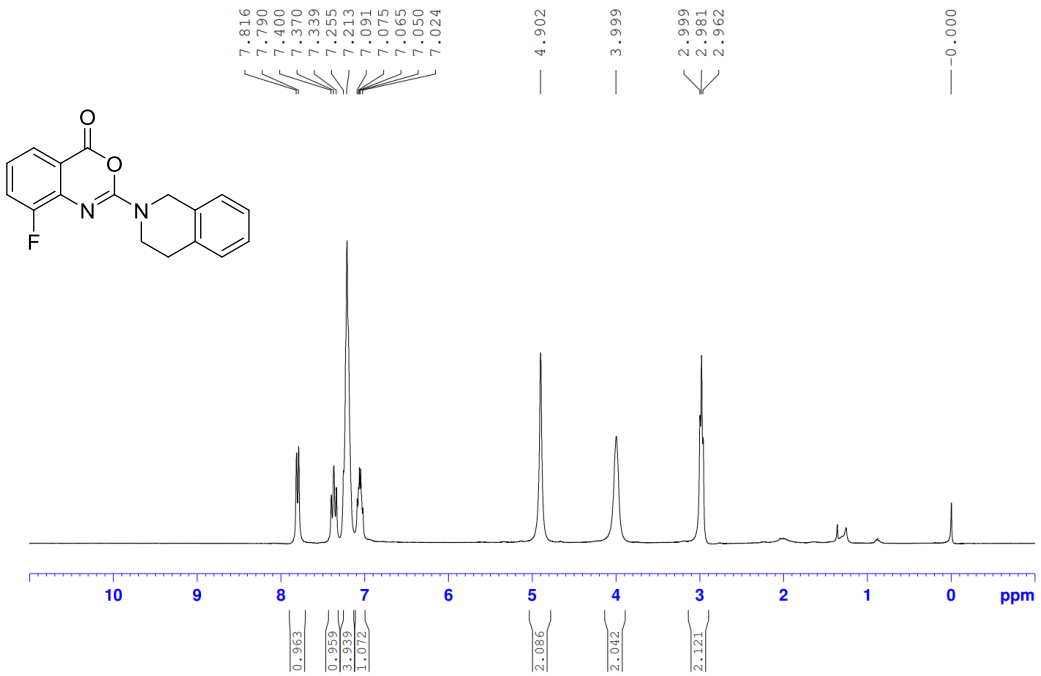

Figure S-15 ^{1}H NMR spectrum of compound **4h** (300 MHz, $CDCl_3$)

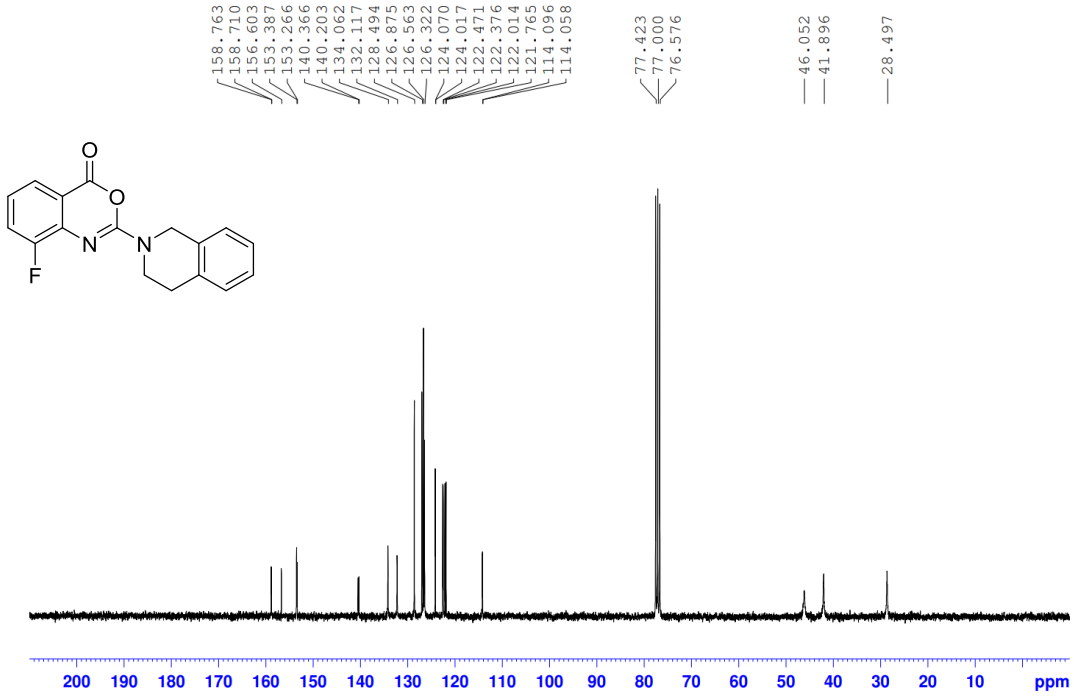

Figure S-16 ^{13}C NMR spectrum of compound **4h** (75 MHz, $CDCl_3$)

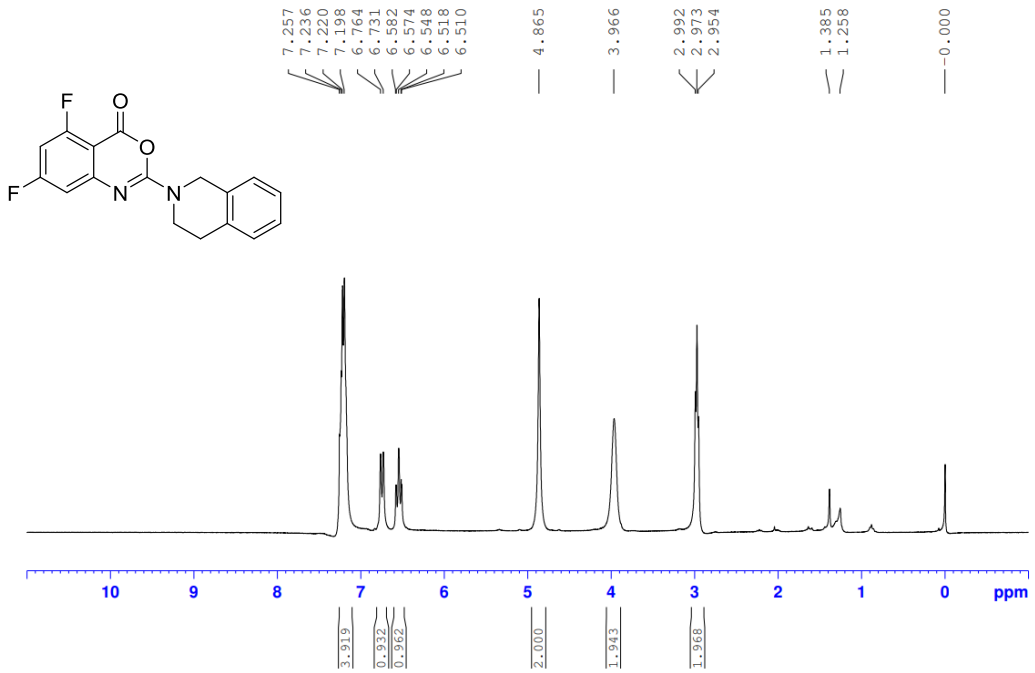

Figure S-17 ^{1}H NMR spectrum of compound **4i** (300 MHz, $CDCl_3$)

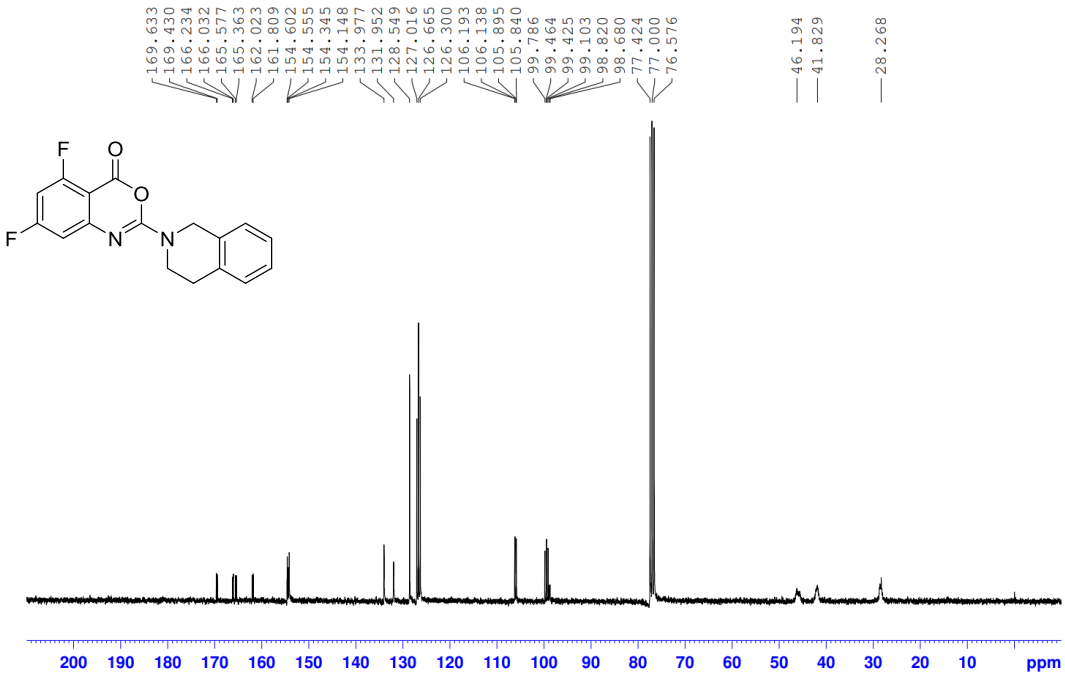

Figure S-18 ^{13}C NMR spectrum of compound **4i** (75 MHz, $CDCl_3$)

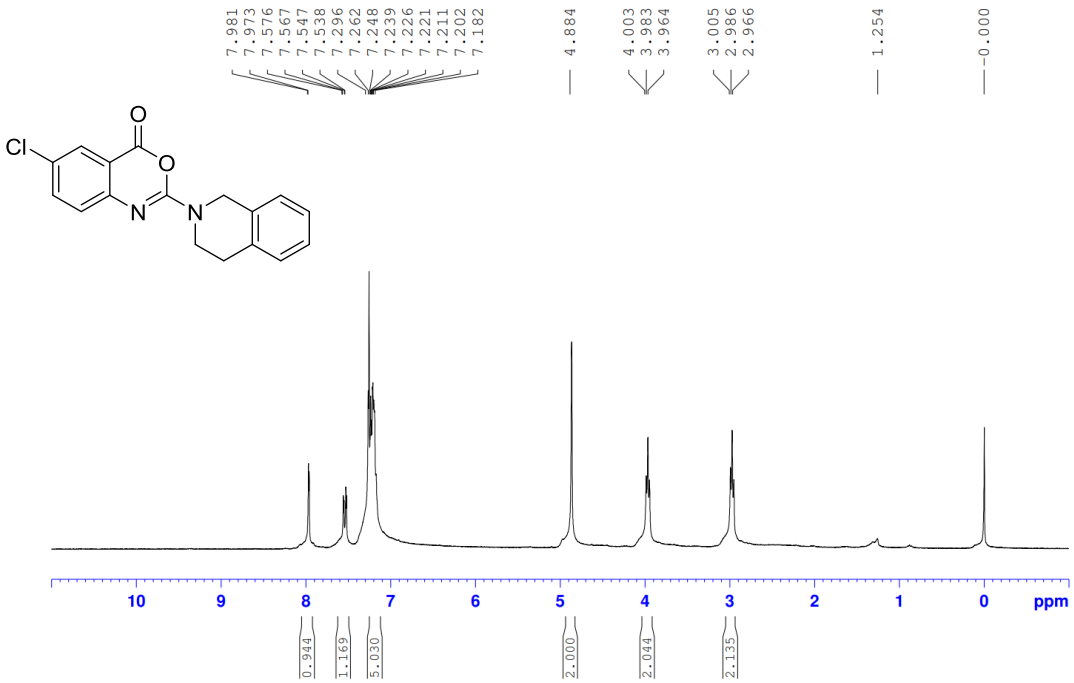

Figure S-19 ^{1}H NMR spectrum of compound **4j** (300 MHz, $CDCl_3$)

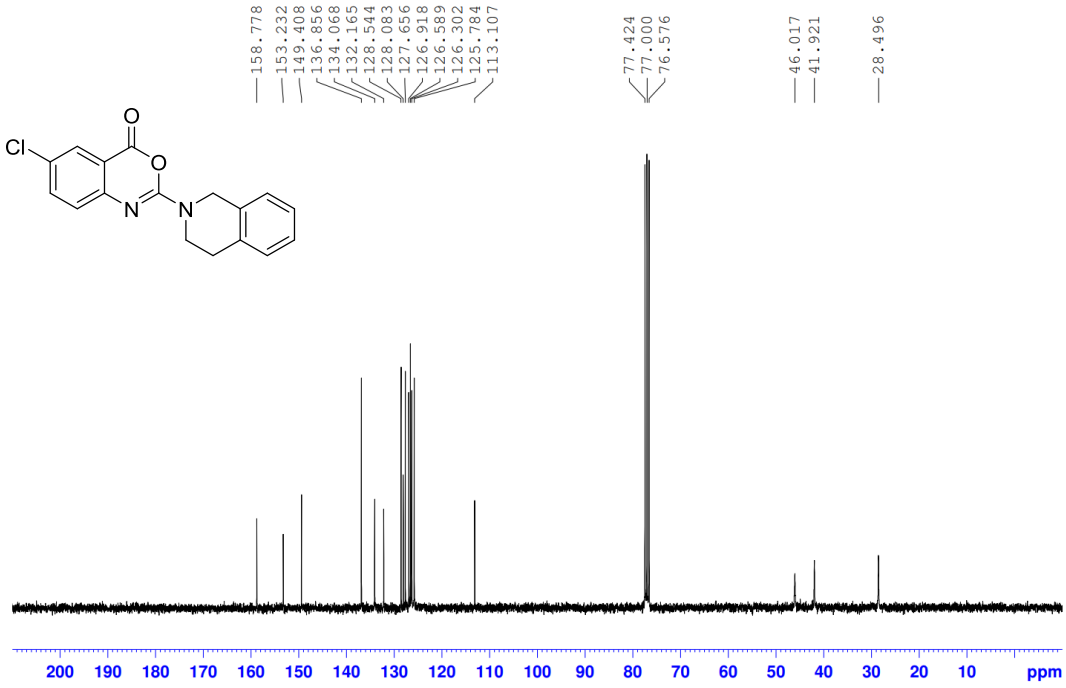

Figure S-20 ^{13}C NMR spectrum of compound **4j** (75 MHz, $CDCl_3$)

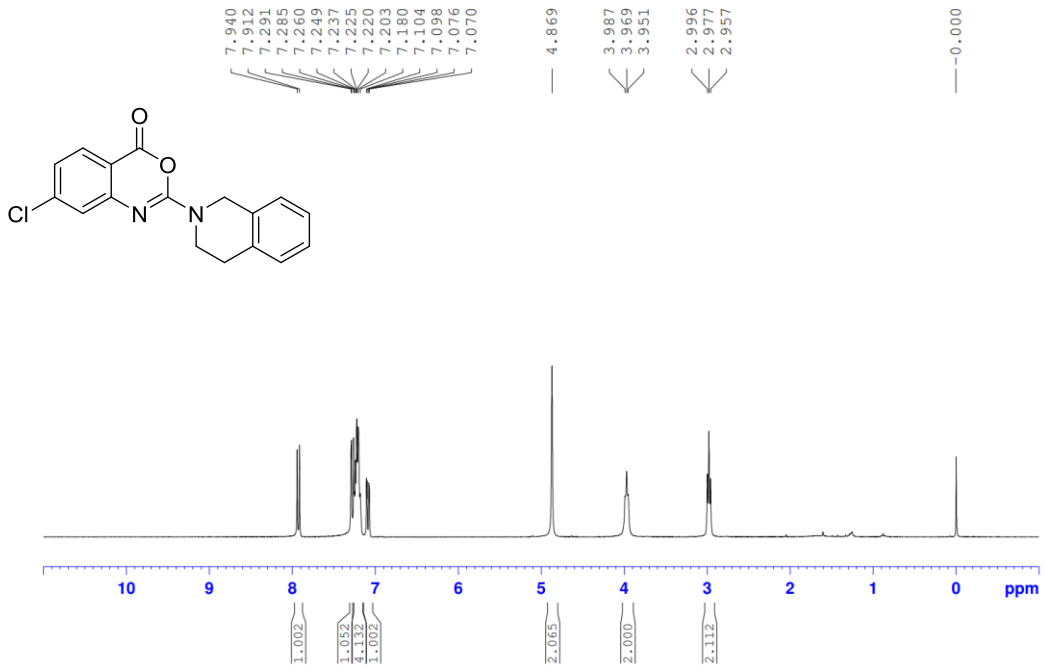

Figure S-21 ^{1}H NMR spectrum of compound **4k** (300 MHz, $CDCl_3$)

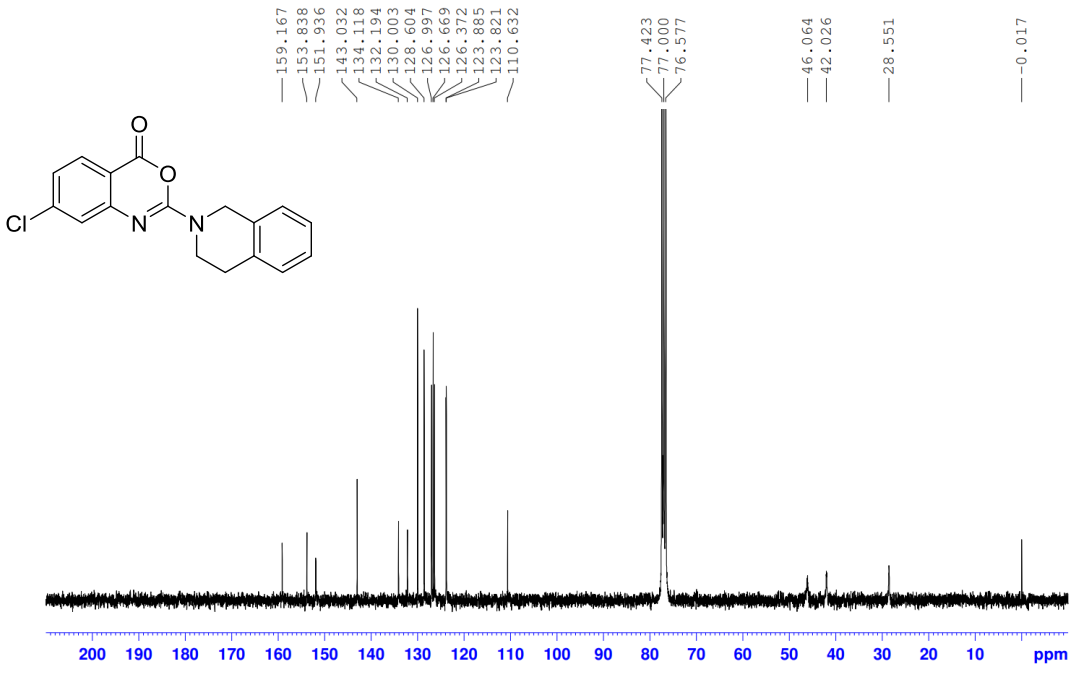

Figure S-22 ^{13}C NMR spectrum of compound **4k** (75 MHz, $CDCl_3$)

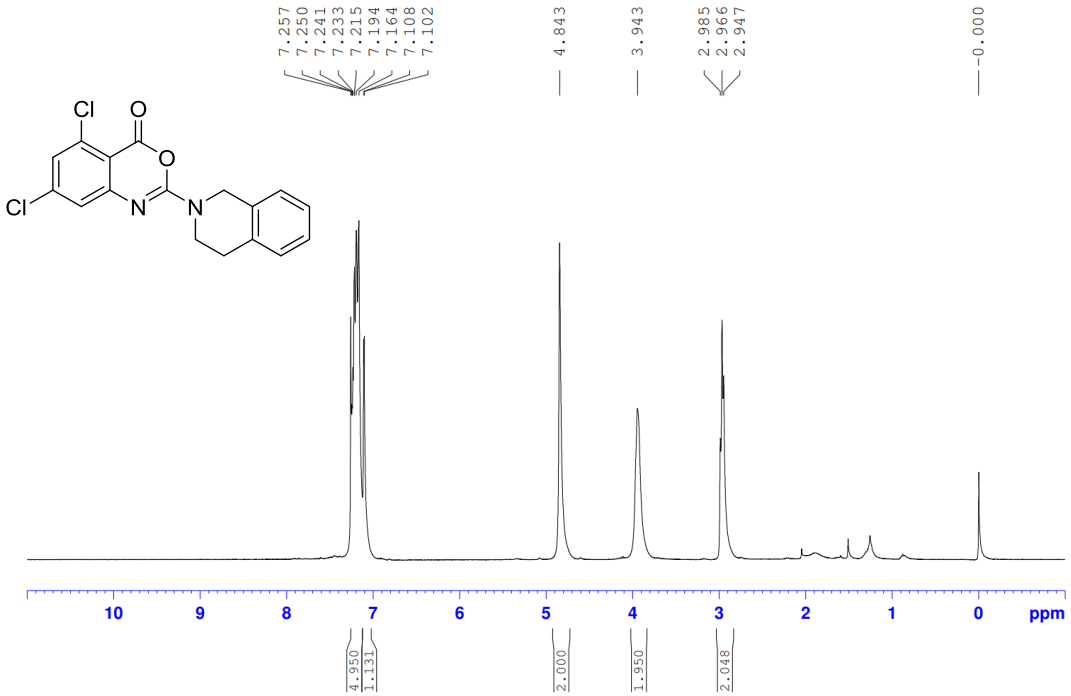

Figure S-23 ^{1}H NMR spectrum of compound **4l** (300 MHz, $CDCl_3$)

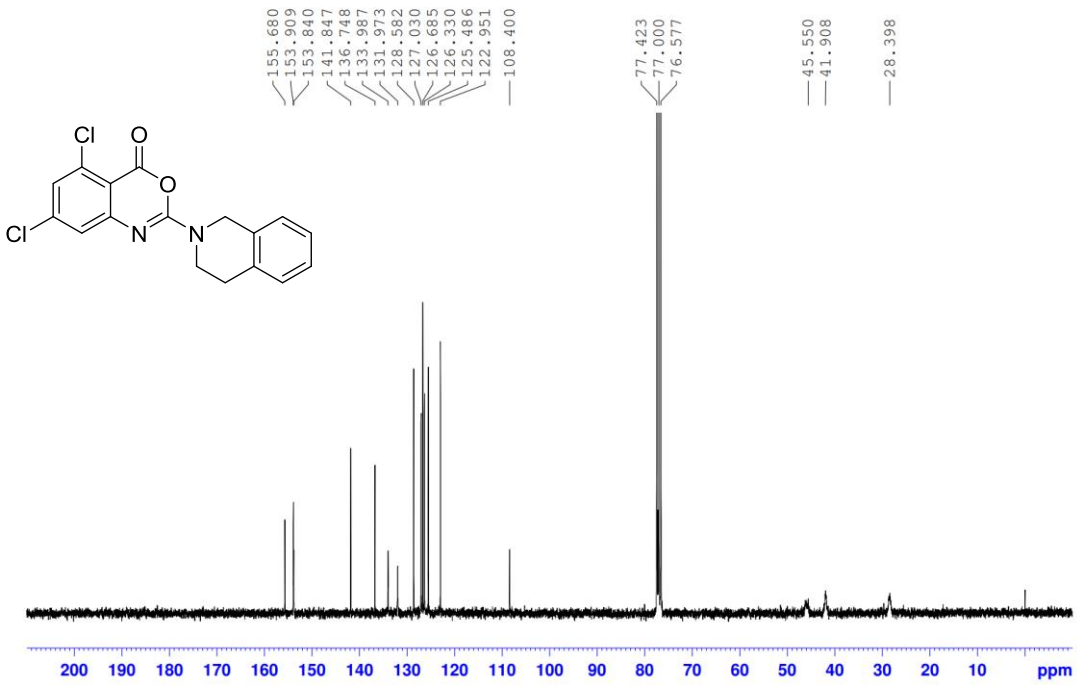

Figure S-24 ^{13}C NMR spectrum of compound **4l** (75 MHz, $CDCl_3$)

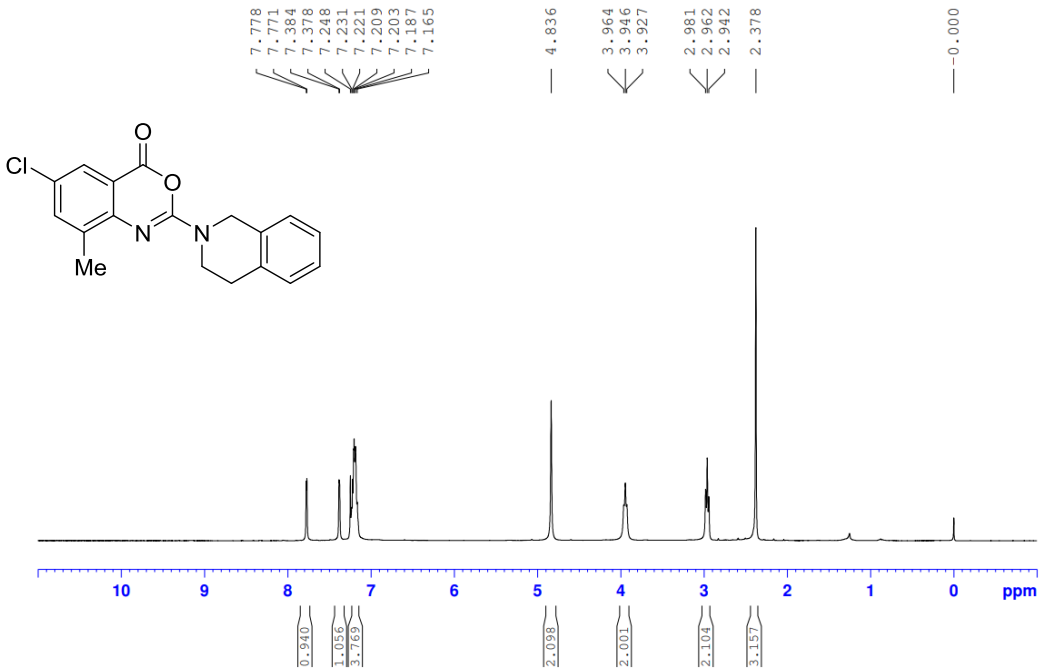

Figure S-25 ^{1}H NMR spectrum of compound **4m** (300 MHz, $CDCl_3$)

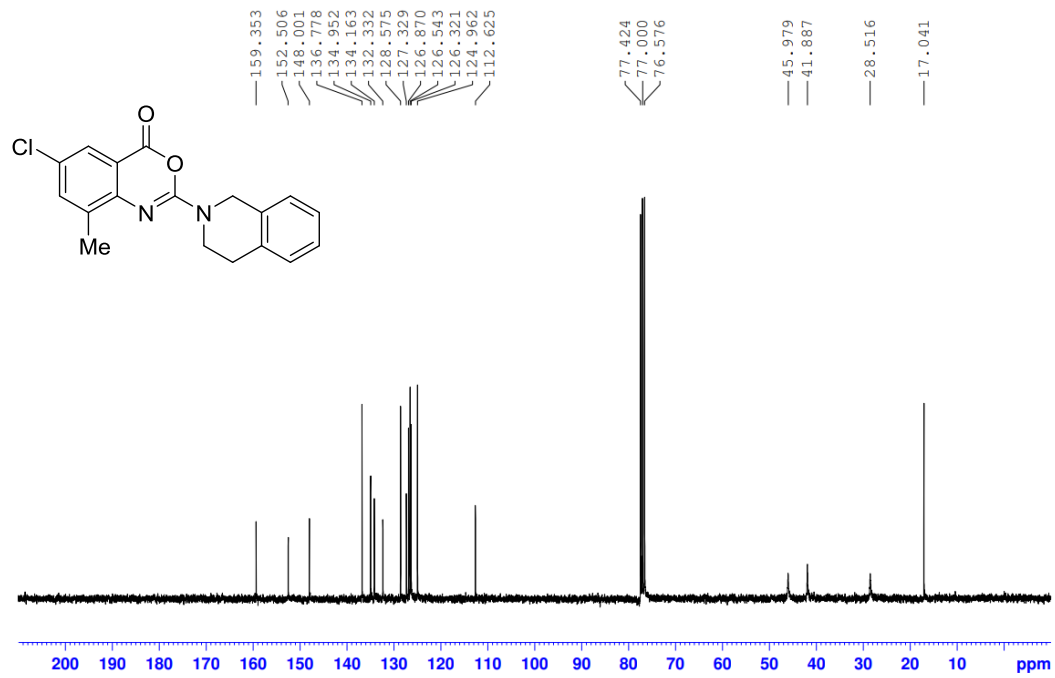

Figure S-26 ^{13}C NMR spectrum of compound **4m** (75 MHz, $CDCl_3$)

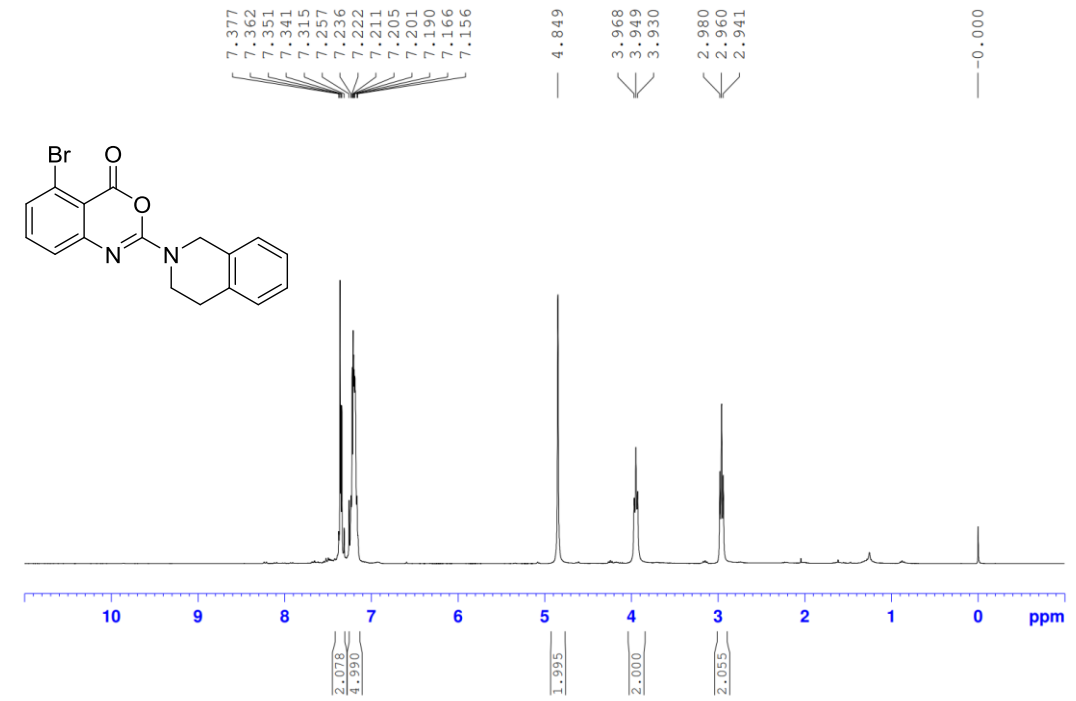

Figure S-27 ^{1}H NMR spectrum of compound **4n** (300 MHz, $CDCl_3$)

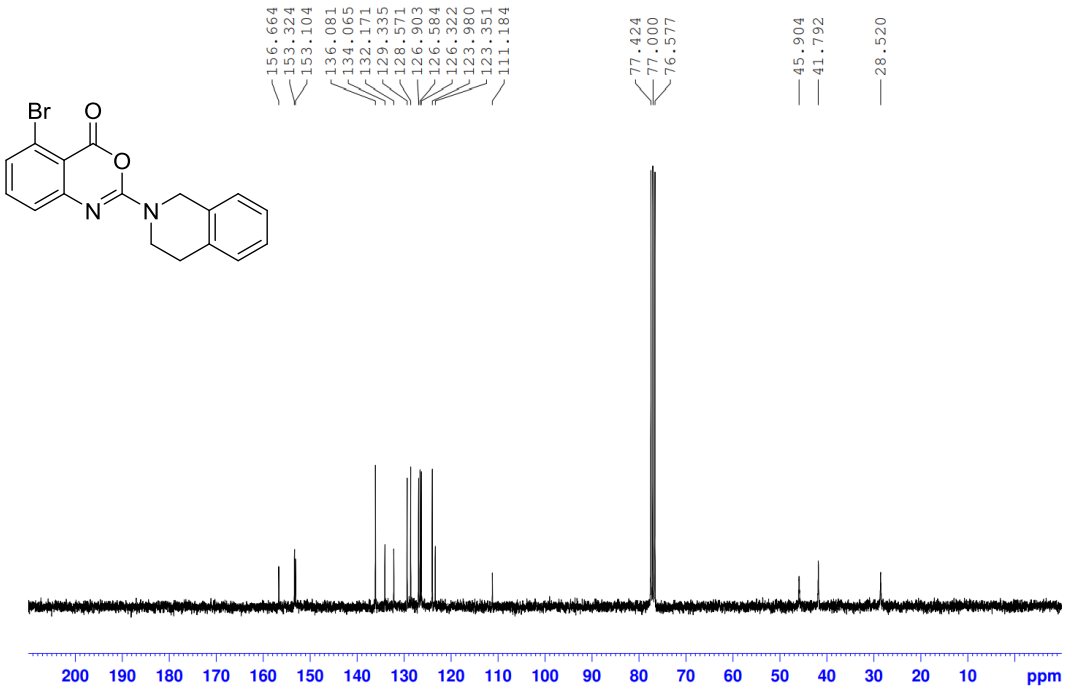

Figure S-28 ^{13}C NMR spectrum of compound **4n** (75 MHz, $CDCl_3$)

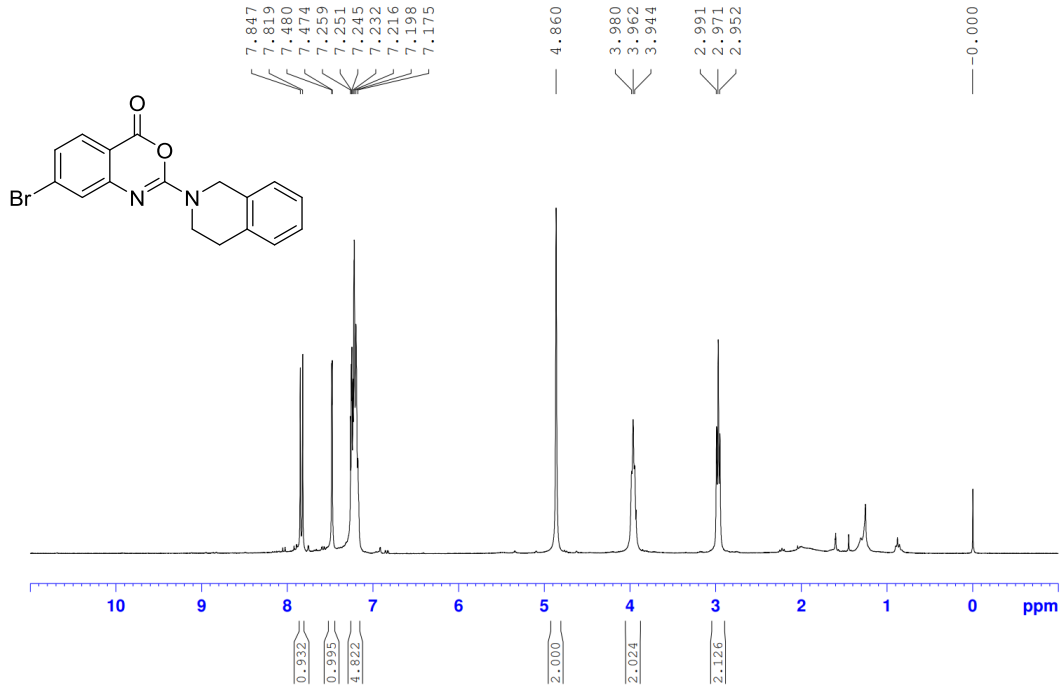

Figure S-29 ^{1}H NMR spectrum of compound **4o** (300 MHz, $CDCl_3$)

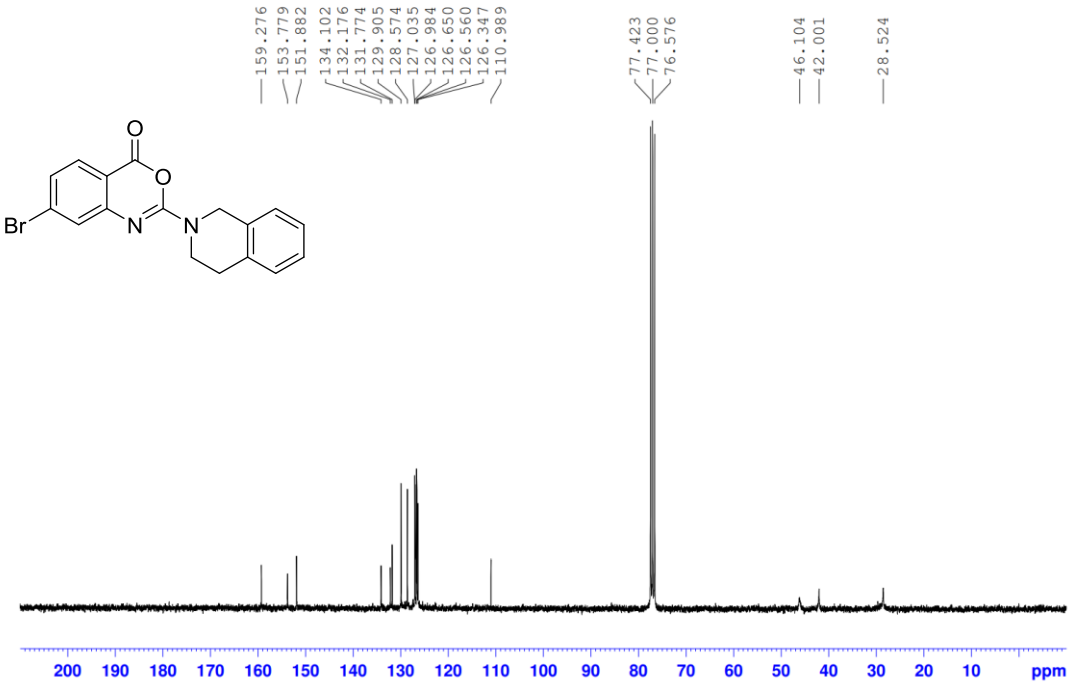

Figure S-30 ^{13}C NMR spectrum of compound **4o** (75 MHz, $CDCl_3$)

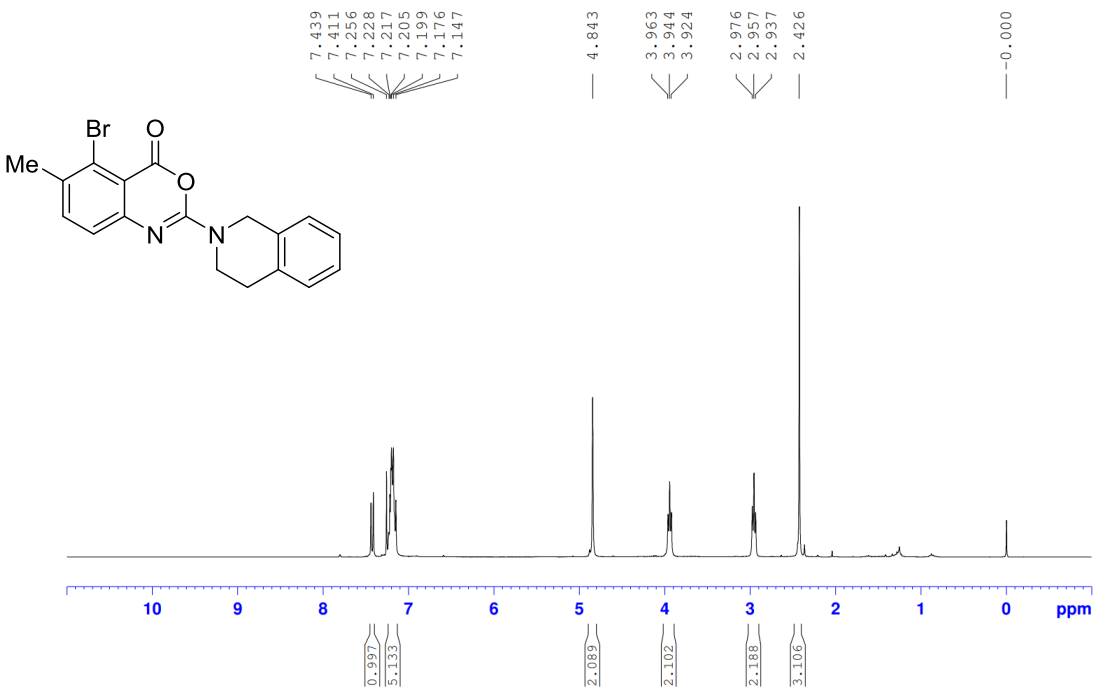

Figure S-31 ^{1}H NMR spectrum of compound **4p** (300 MHz, $CDCl_3$)

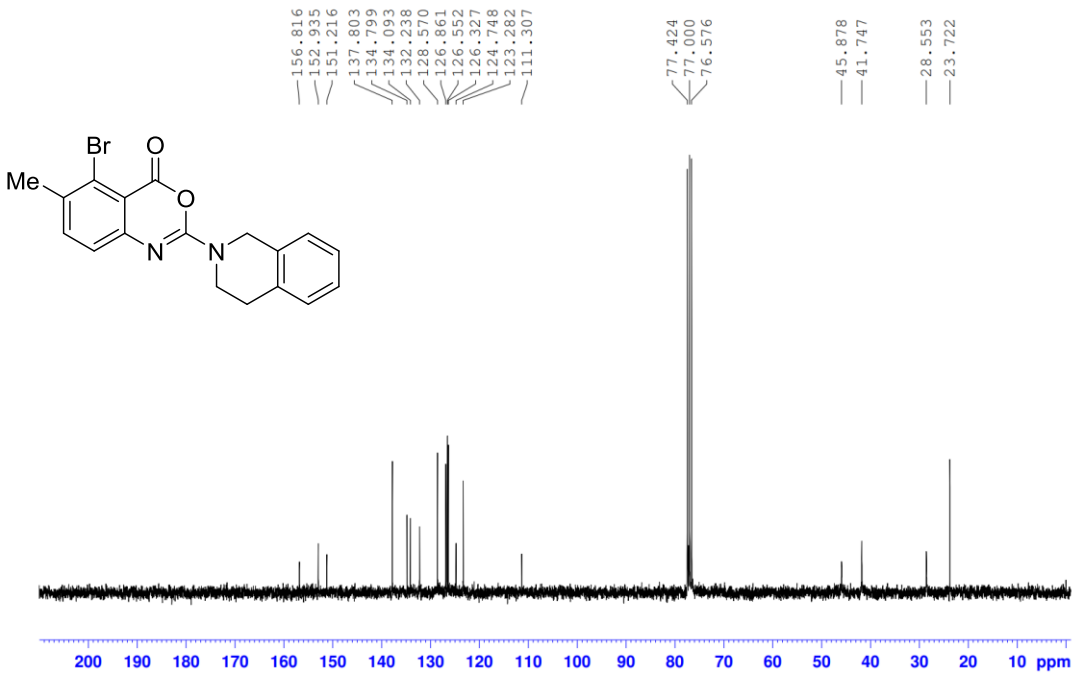

Figure S-32 ^{13}C NMR spectrum of compound **4p** (75 MHz, $CDCl_3$)

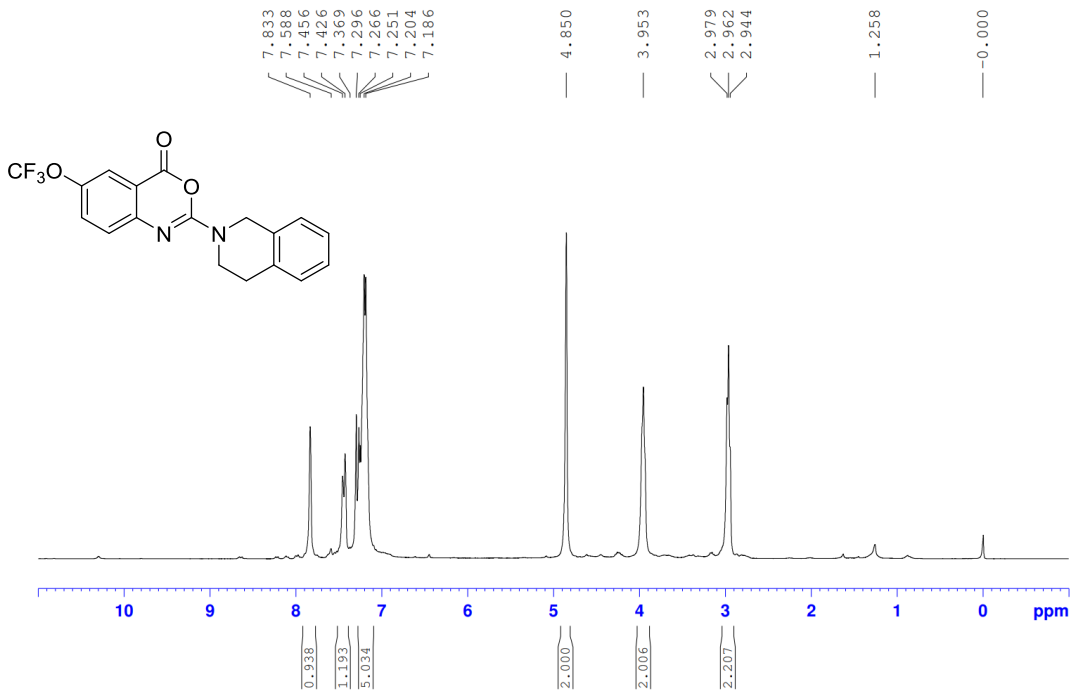

Figure S-33 ^{1}H NMR spectrum of compound **4q** (300 MHz, $CDCl_3$)

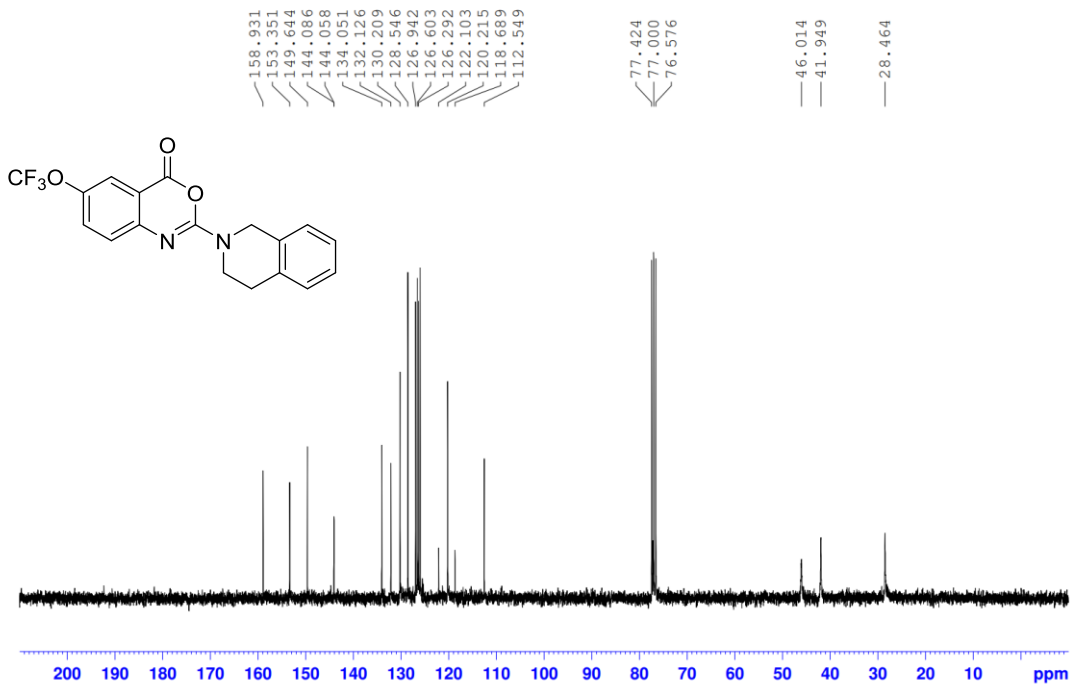

Figure S-34 ^{13}C NMR spectrum of compound **4q** (75 MHz, $CDCl_3$)

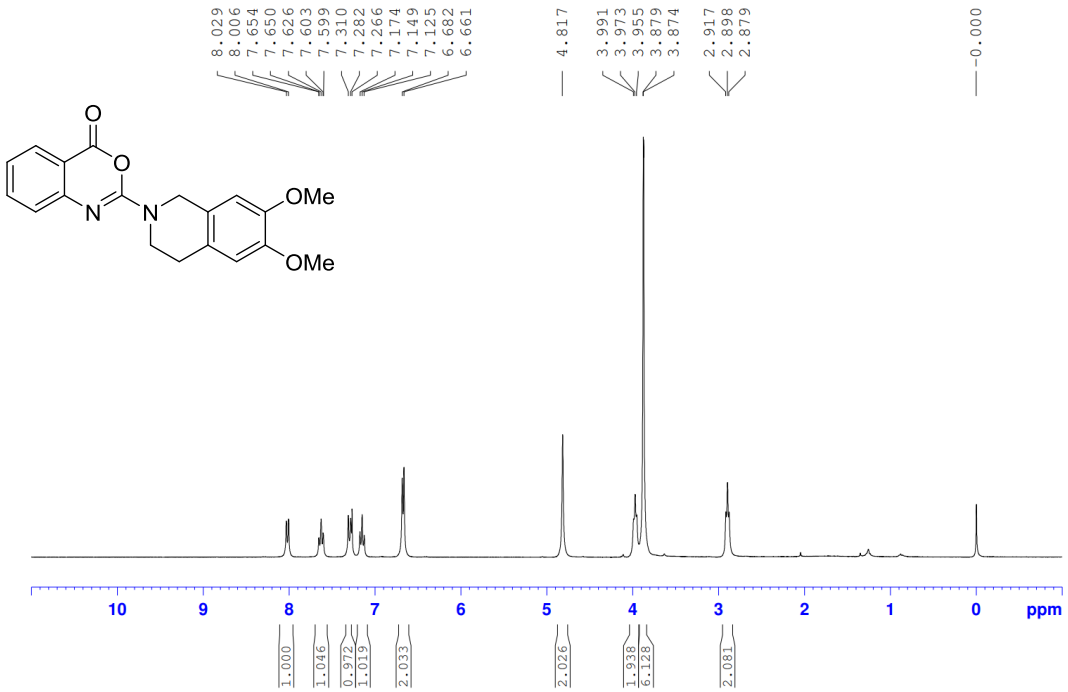

Figure S-35 ^{1}H NMR spectrum of compound **4s** (300 MHz, $CDCl_3$)

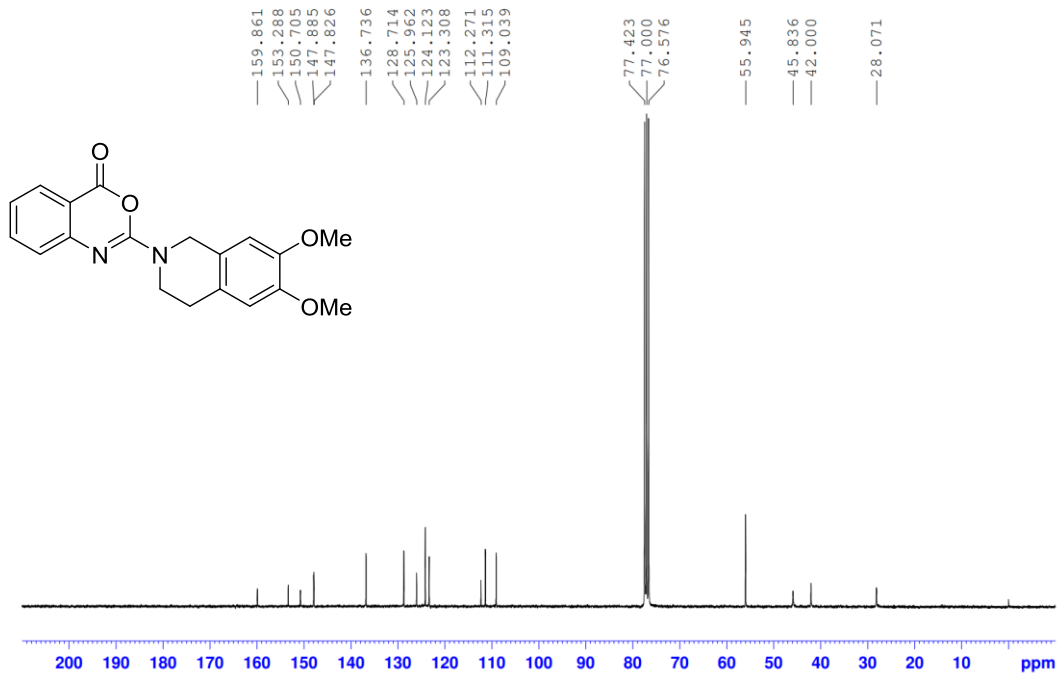

Figure S-36 ^{13}C NMR spectrum of compound **4s** (75 MHz, $CDCl_3$)

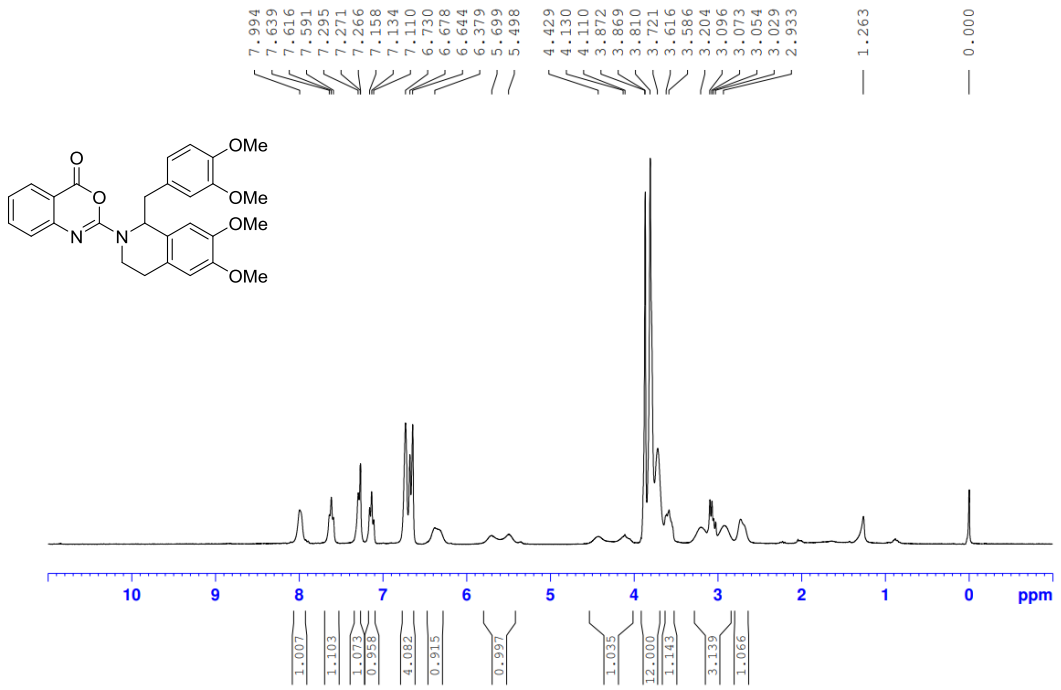

Figure S-37 ^{1}H NMR spectrum of compound **4t** (300 MHz, $CDCl_3$)

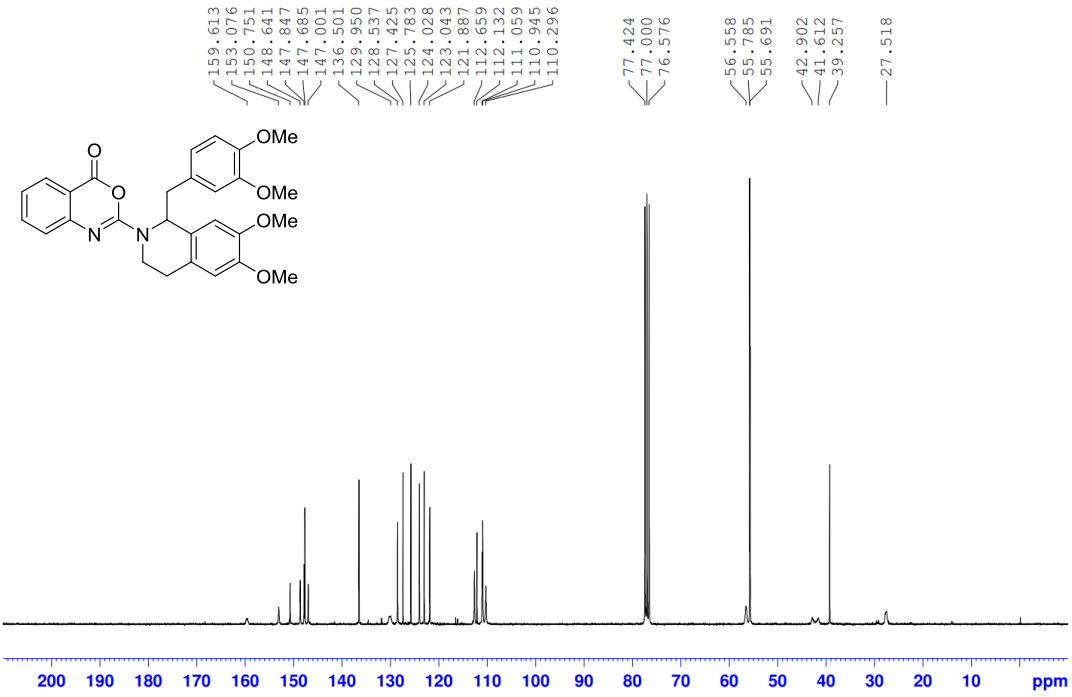

Figure S-38 ^{13}C NMR spectrum of compound **4t** (75 MHz, $CDCl_3$)

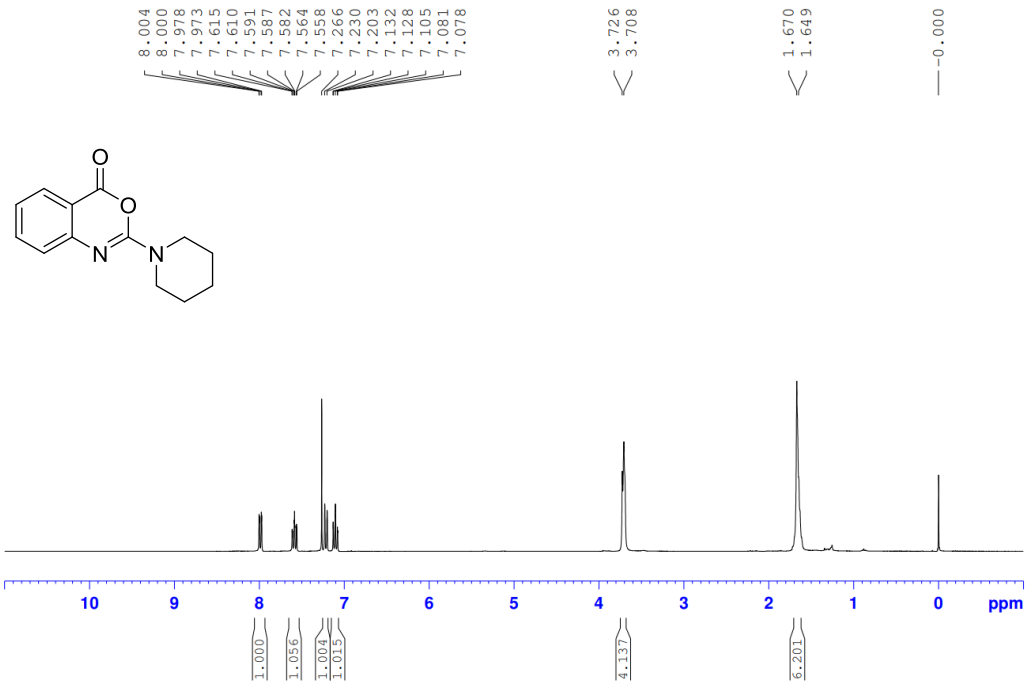

Figure S-39 ^{1}H NMR spectrum of compound **5a** (300 MHz, $CDCl_3$)

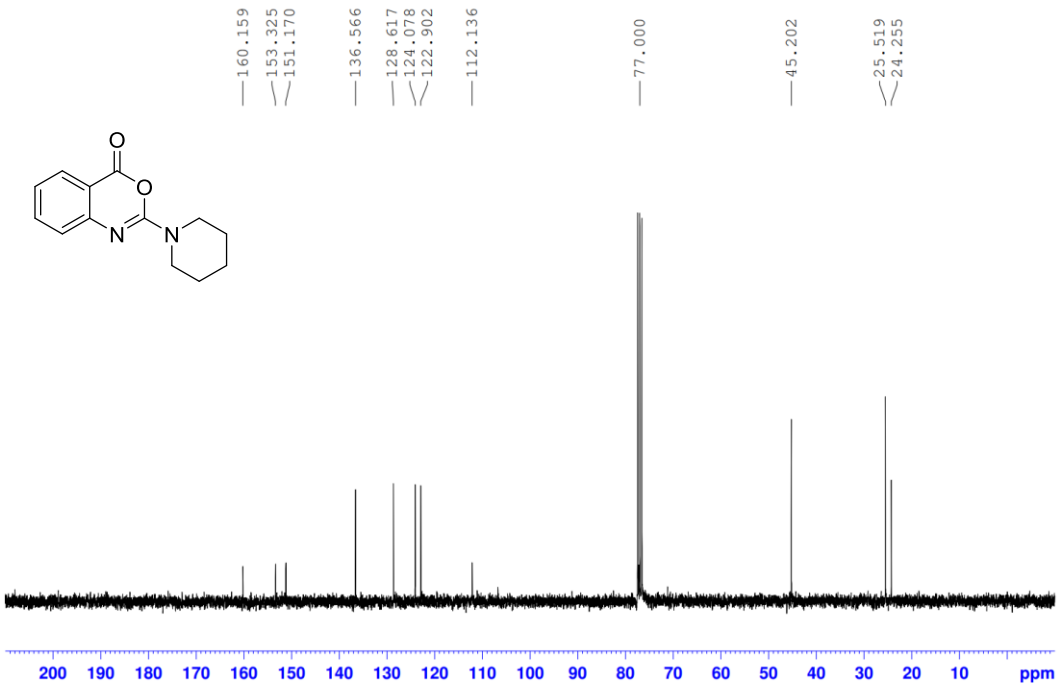

Figure S-40 ^{13}C NMR spectrum of compound **5a** (75 MHz, $CDCl_3$)

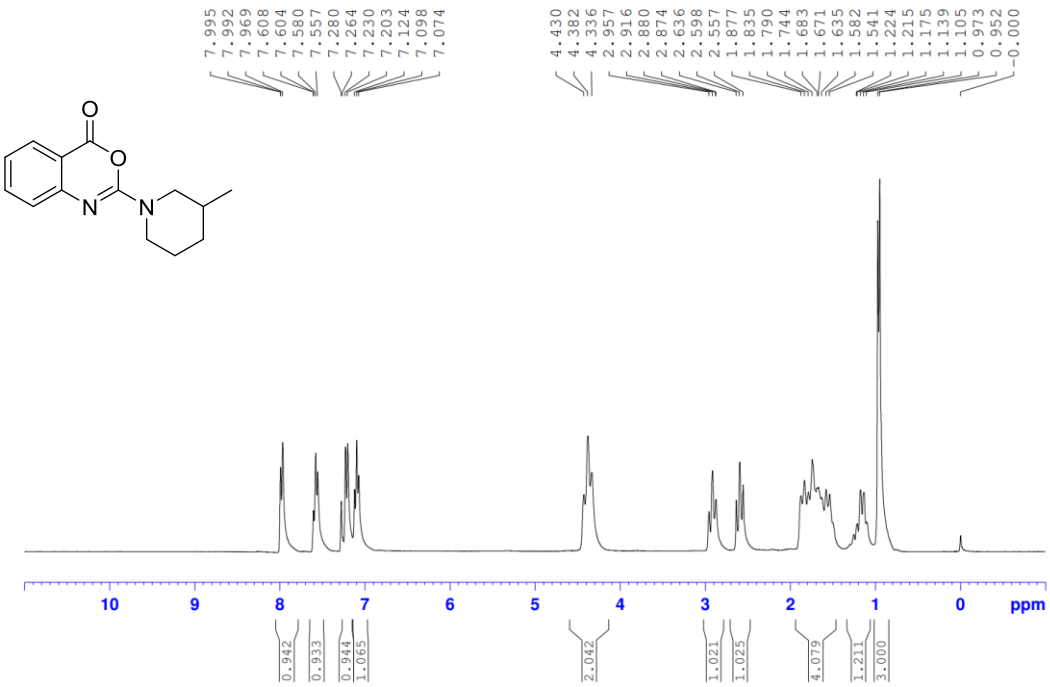

Figure S-41 ^{1}H NMR spectrum of compound **5b** (300 MHz, $CDCl_3$)

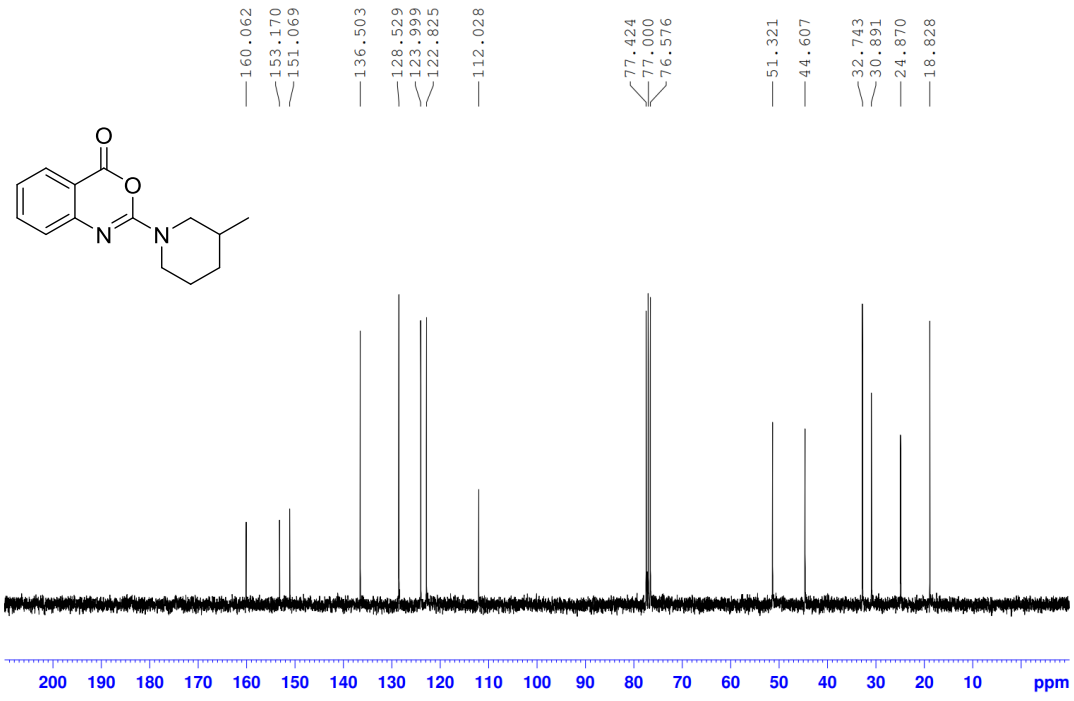

Figure S-42 ^{13}C NMR spectrum of compound **5b** (75 MHz, $CDCl_3$)

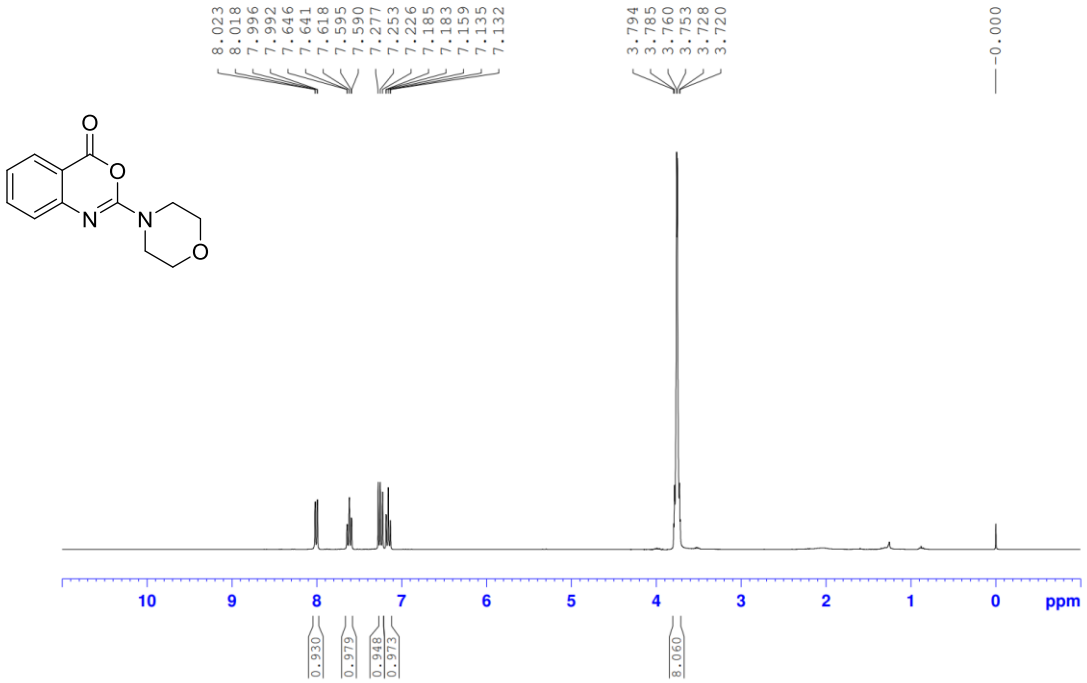

Figure S-43 ^{1}H NMR spectrum of compound **5c** (300 MHz, $CDCl_3$)

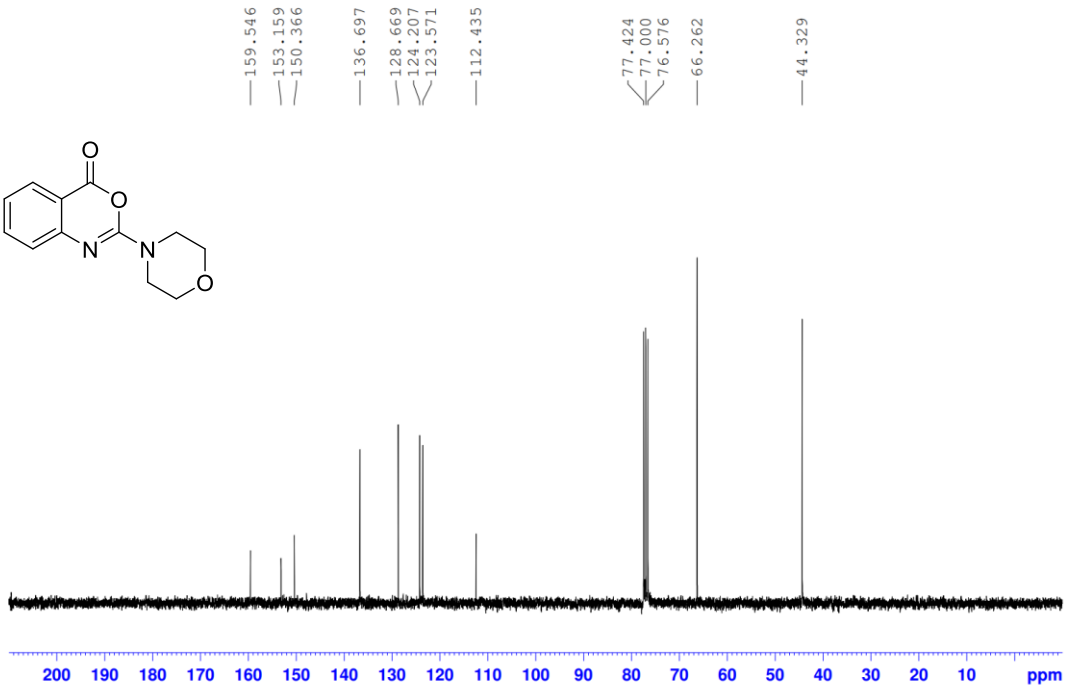

Figure S-44 ^{13}C NMR spectrum of compound **5c** (75 MHz, $CDCl_3$)

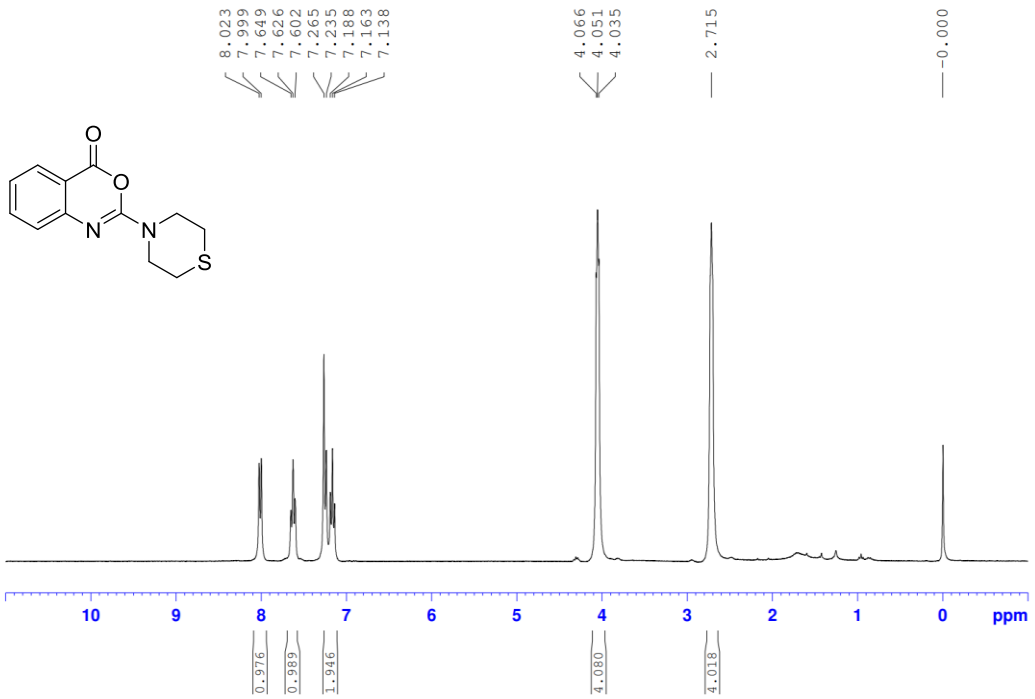

Figure S-45 ^{1}H NMR spectrum of compound **5d** (300 MHz, $CDCl_3$)

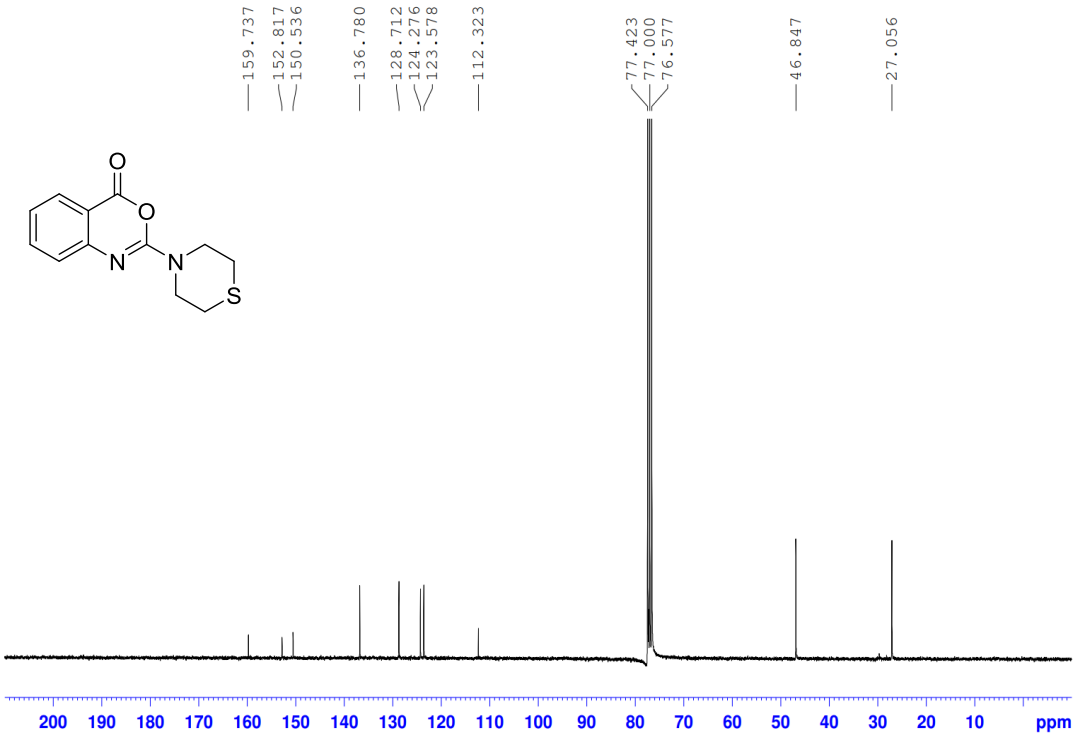

Figure S-46 ^{13}C NMR spectrum of compound **5d** (75 MHz, $CDCl_3$)

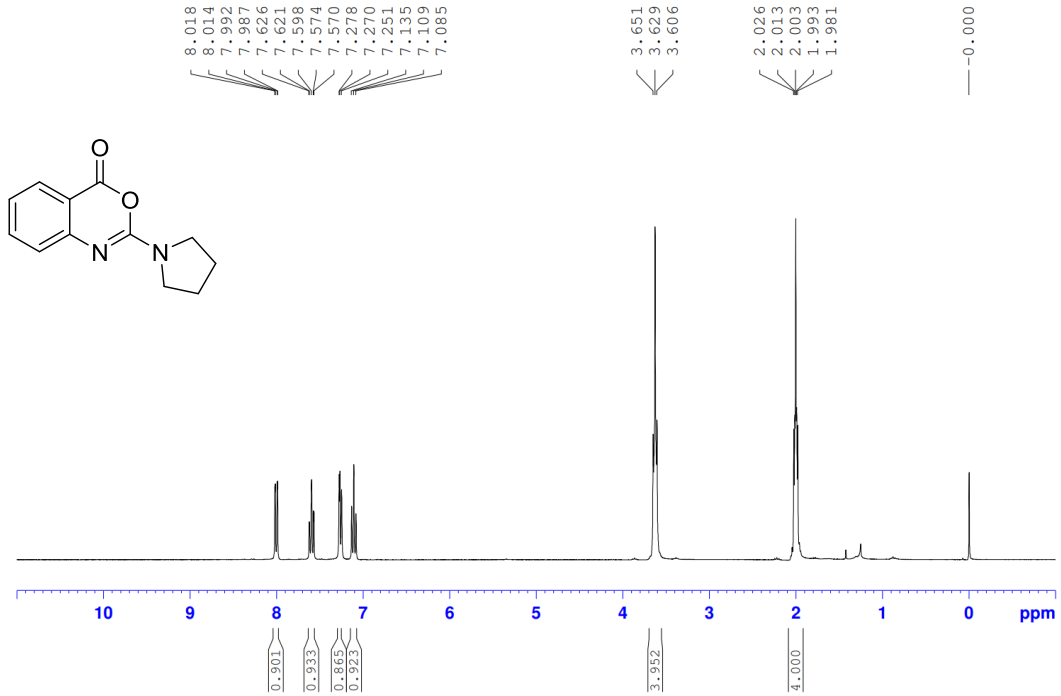

Figure S-47 ^{1}H NMR spectrum of compound **5f** (300 MHz, $CDCl_3$)

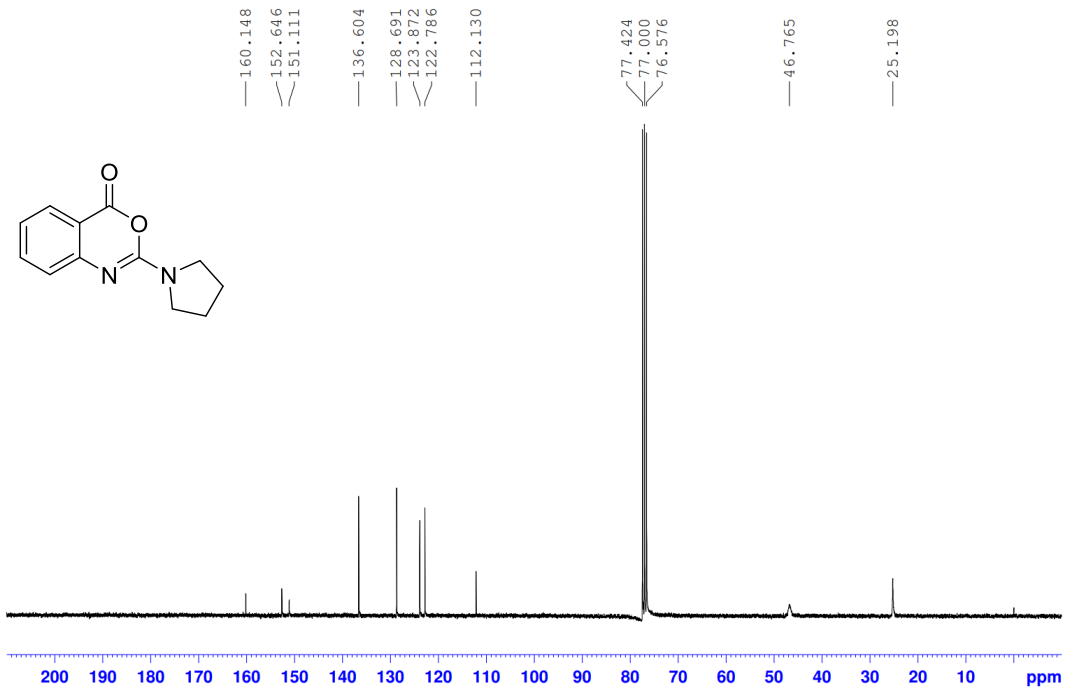

Figure S-48 ^{13}C NMR spectrum of compound **5f** (75 MHz, $CDCl_3$)

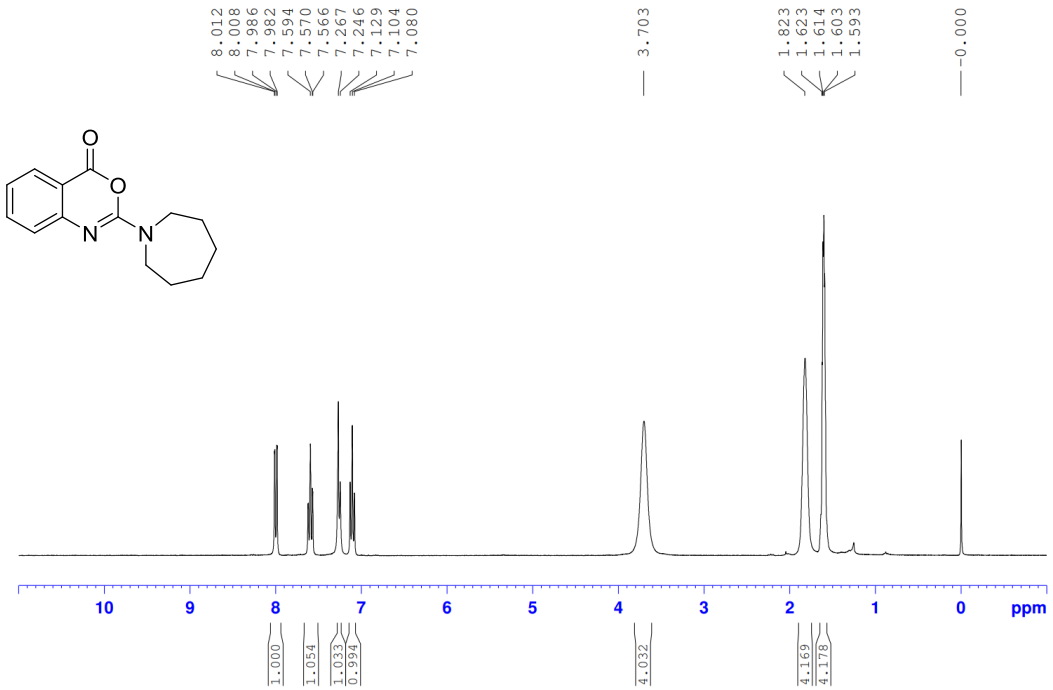

Figure S-49 ^{1}H NMR spectrum of compound **5g** (300 MHz, $CDCl_3$)

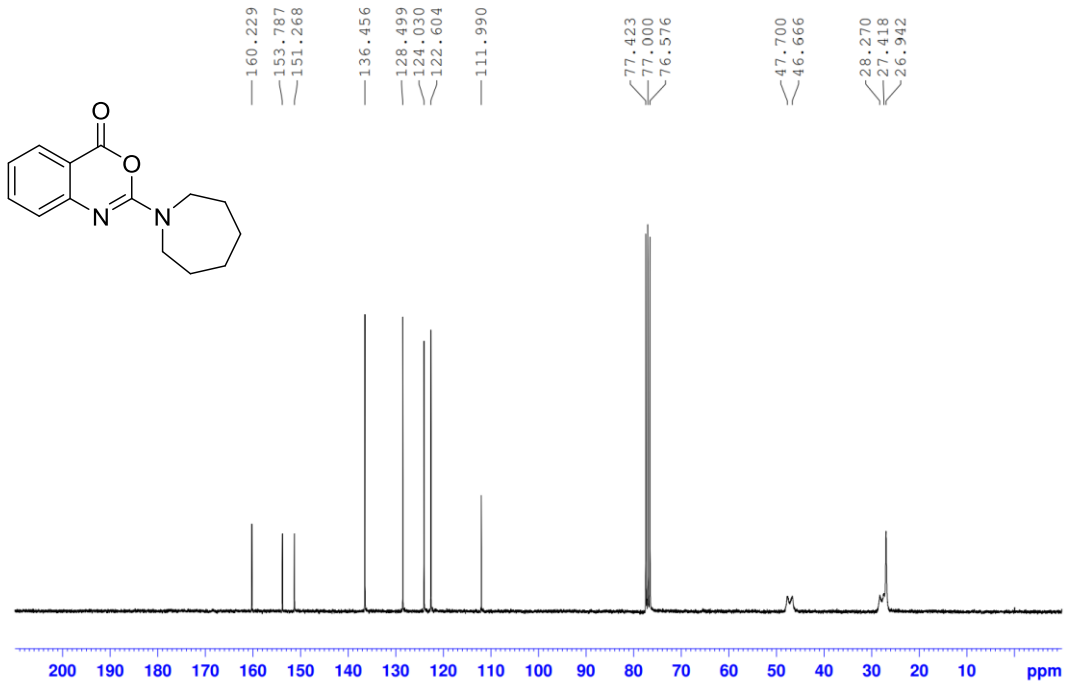

Figure S-50 ^{13}C NMR spectrum of compound **5g** (75 MHz, $CDCl_3$)

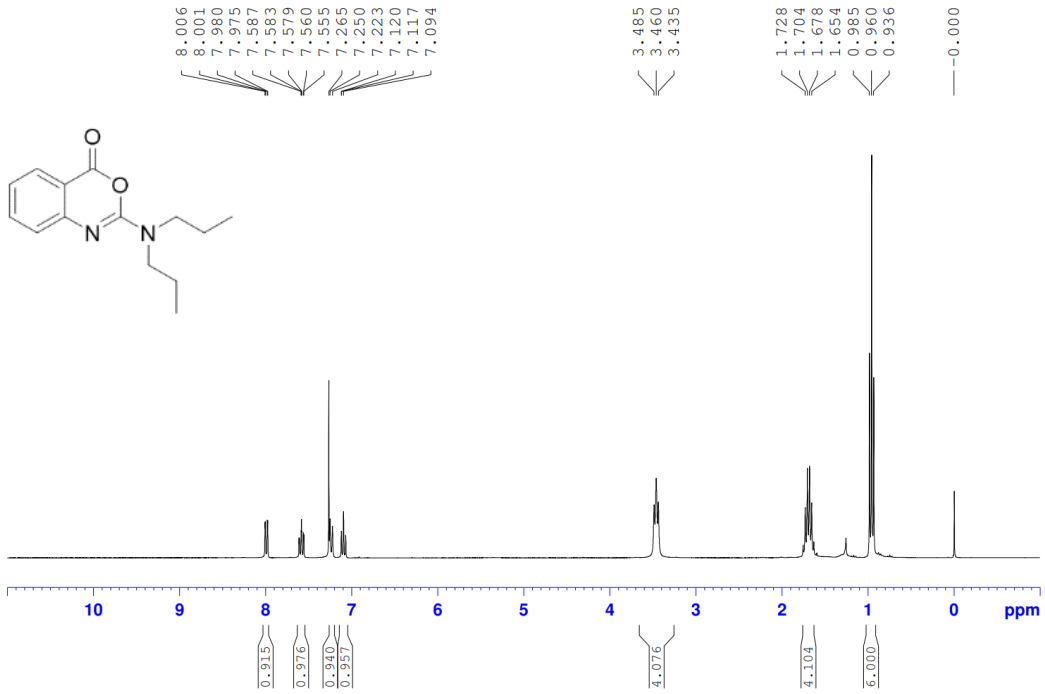

Figure S-51 ^{1}H NMR spectrum of compound **5h** (300 MHz, $CDCl_3$)

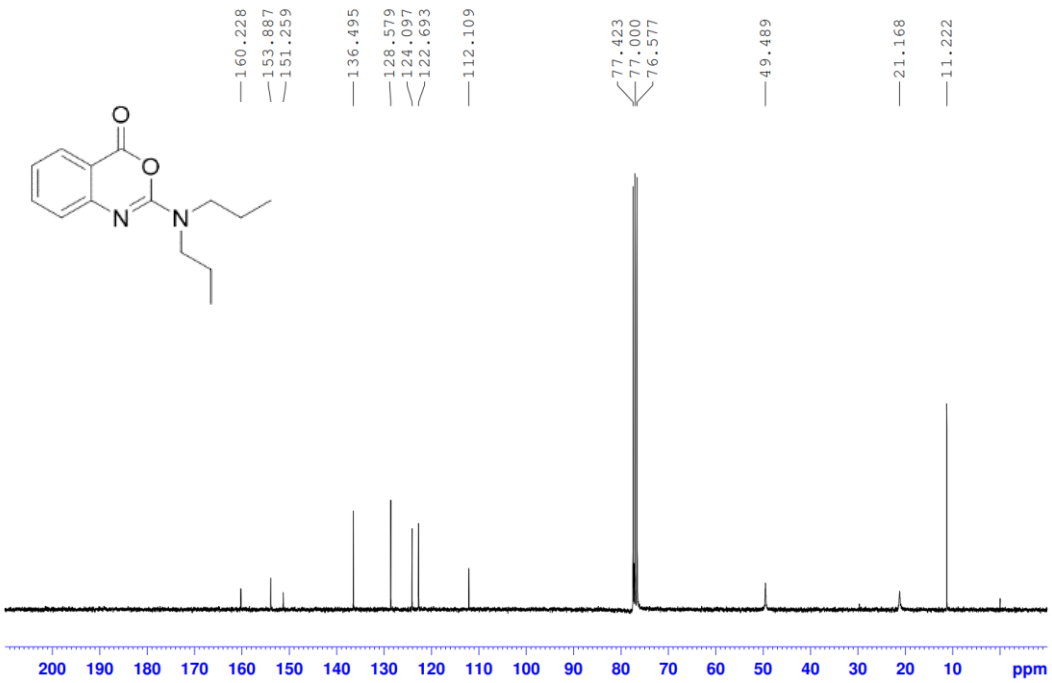

Figure S-52 ^{13}C NMR spectrum of compound **5h** (75 MHz, $CDCl_3$)

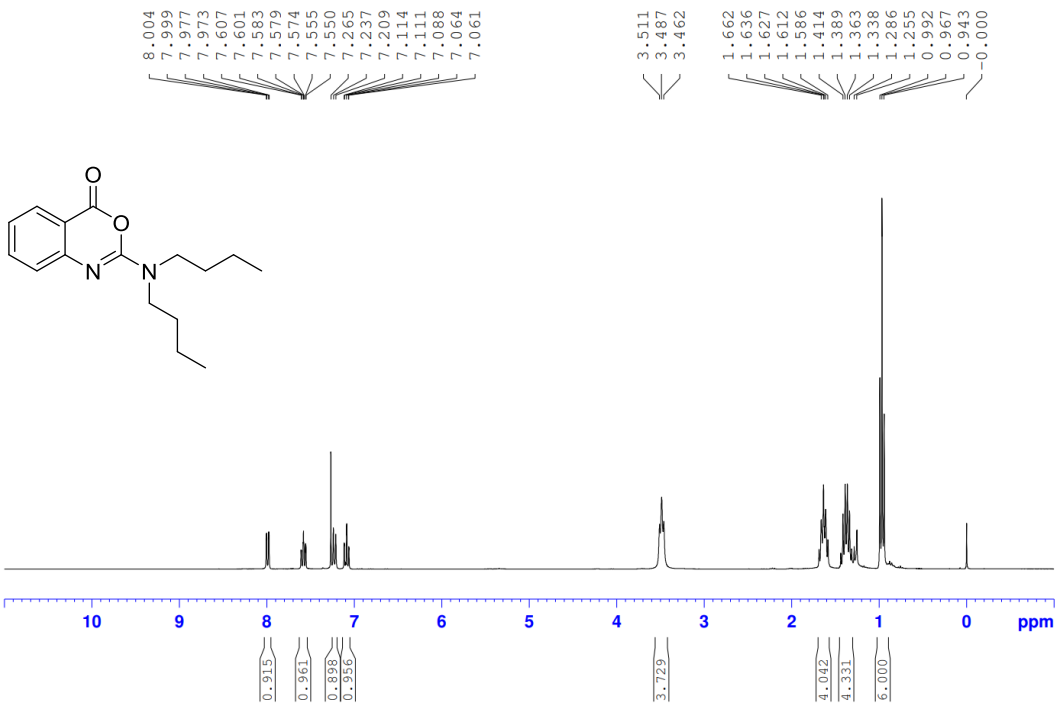

Figure S-53 ^{1}H NMR spectrum of compound **5i** (300 MHz, $CDCl_3$)

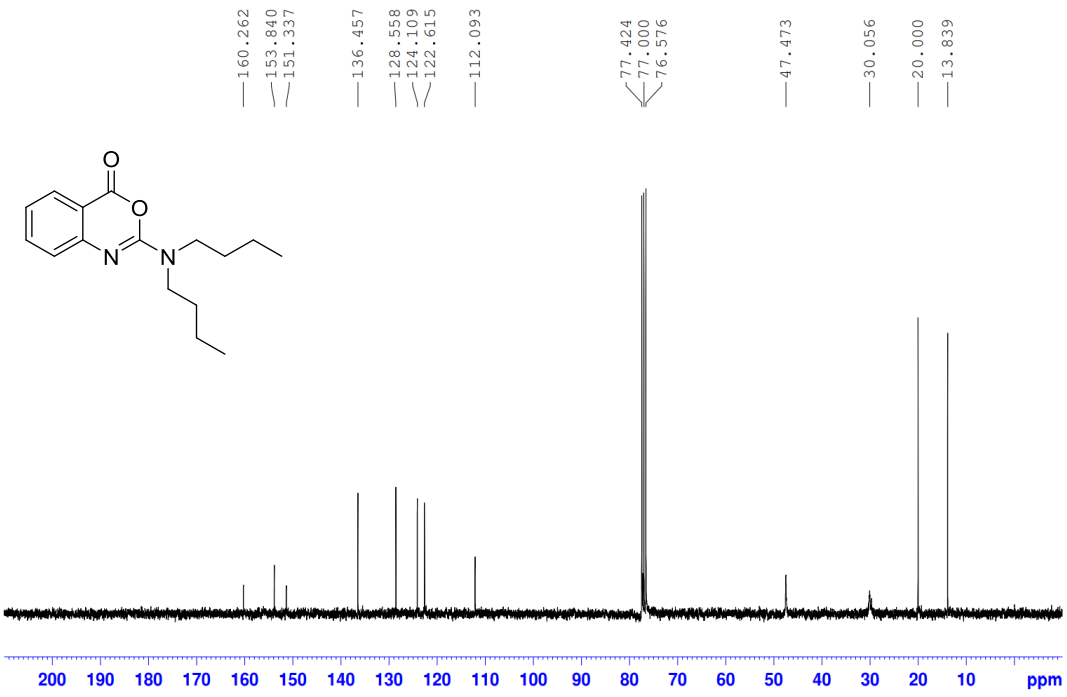

Figure S-54 ^{13}C NMR spectrum of compound **5i** (75 MHz, $CDCl_3$)

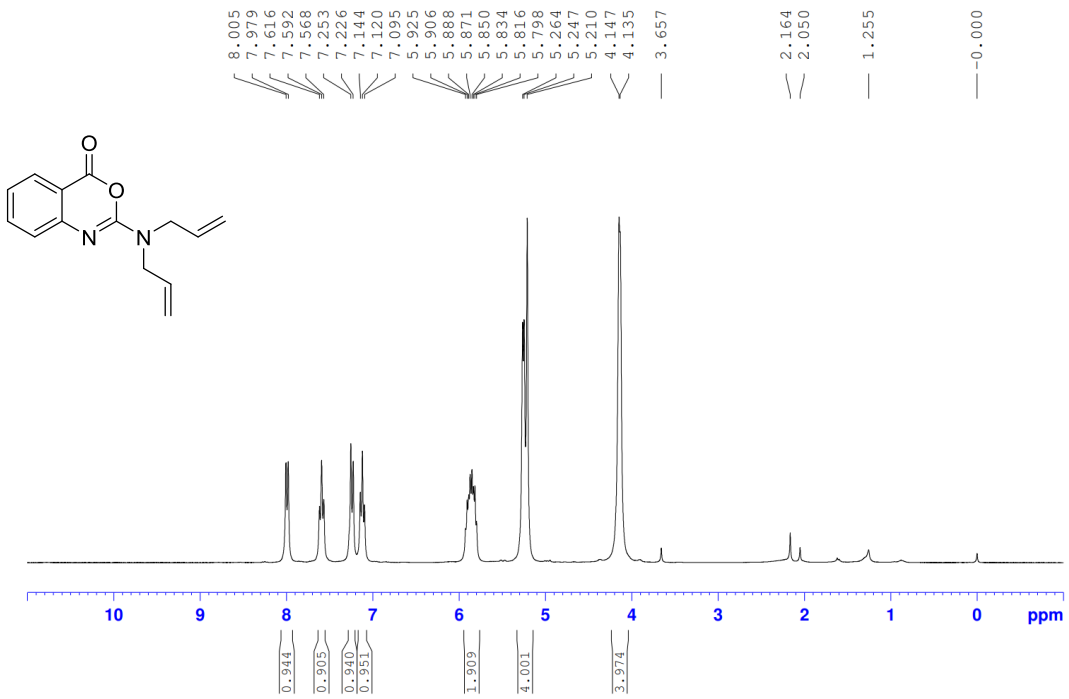

Figure S-55 ^{1}H NMR spectrum of compound **5j** (300 MHz, $CDCl_3$)

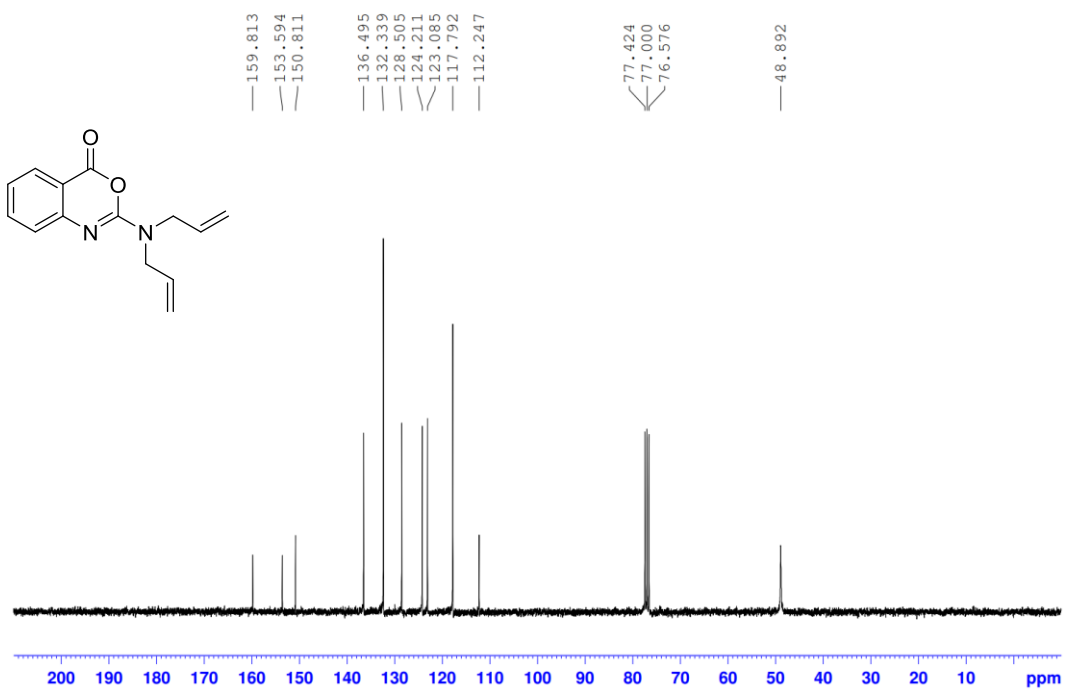

Figure S-56 ^{13}C NMR spectrum of compound **5j** (75 MHz, $CDCl_3$)

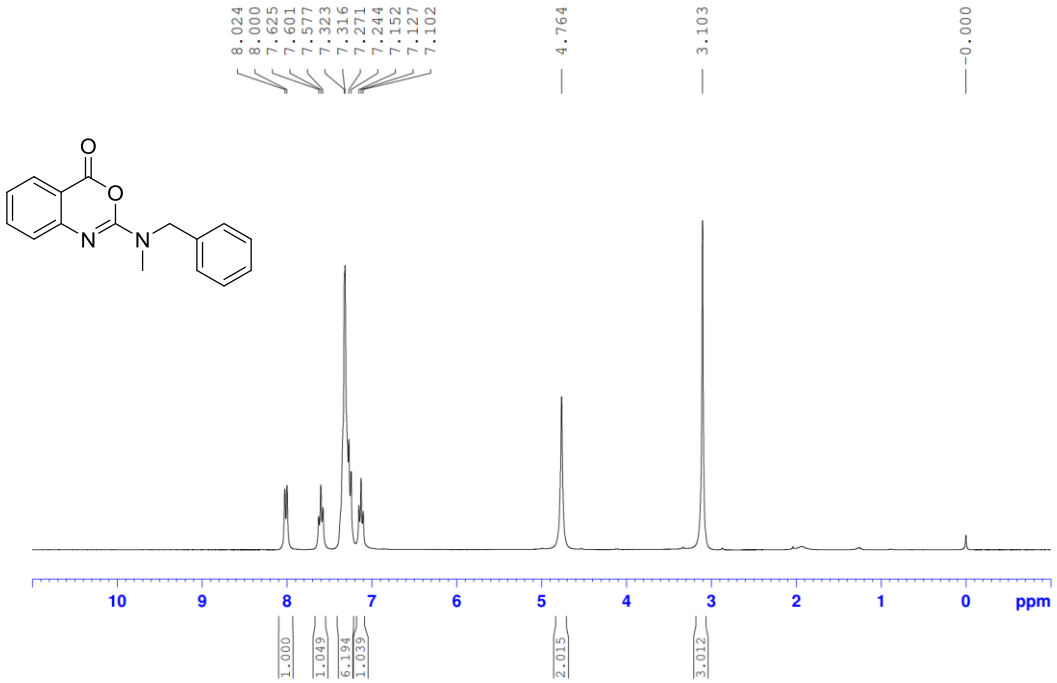

Figure S-57 ^{1}H NMR spectrum of compound **5k** (300 MHz, $CDCl_3$)

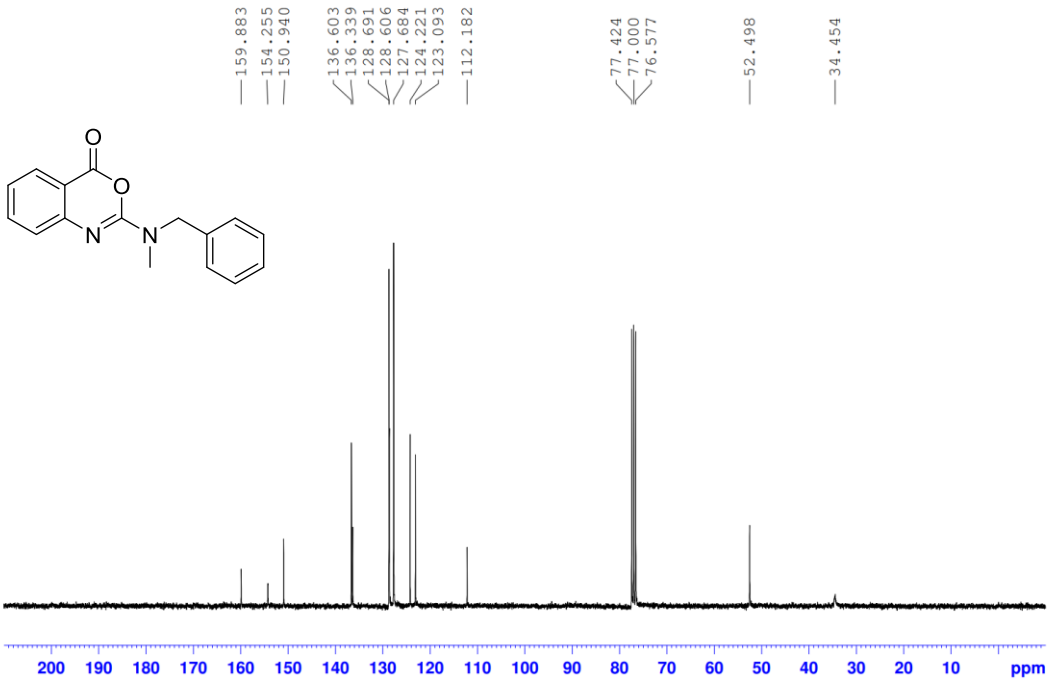

Figure S-58 ^{13}C NMR spectrum of compound **5k** (75 MHz, $CDCl_3$)

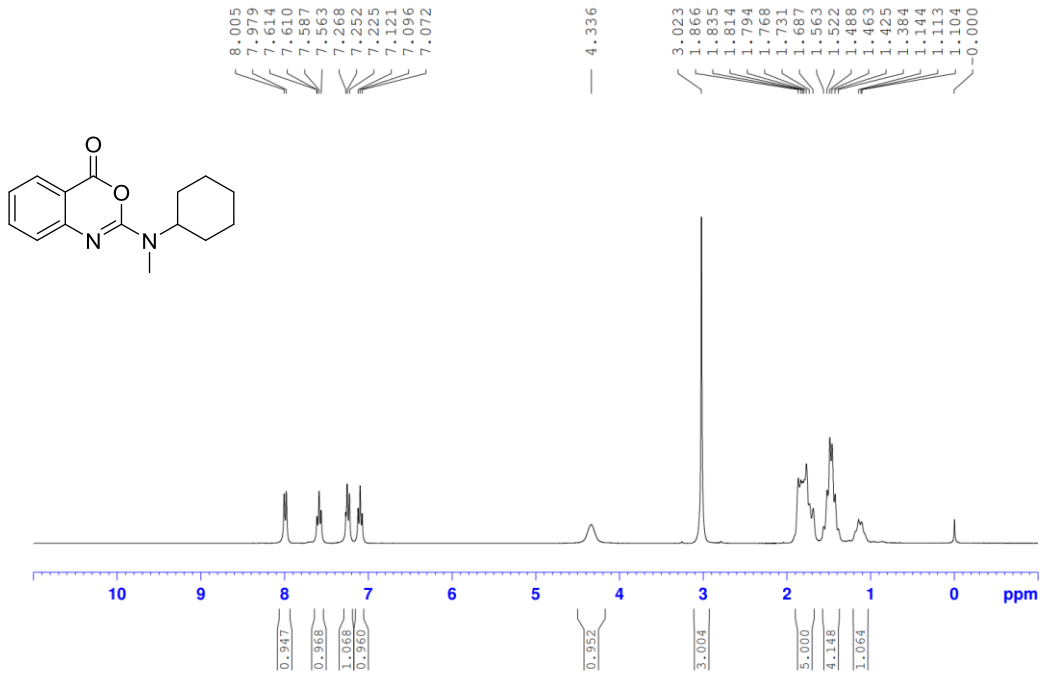

Figure S-59 ^{1}H NMR spectrum of compound **5l** (300 MHz, $CDCl_3$)

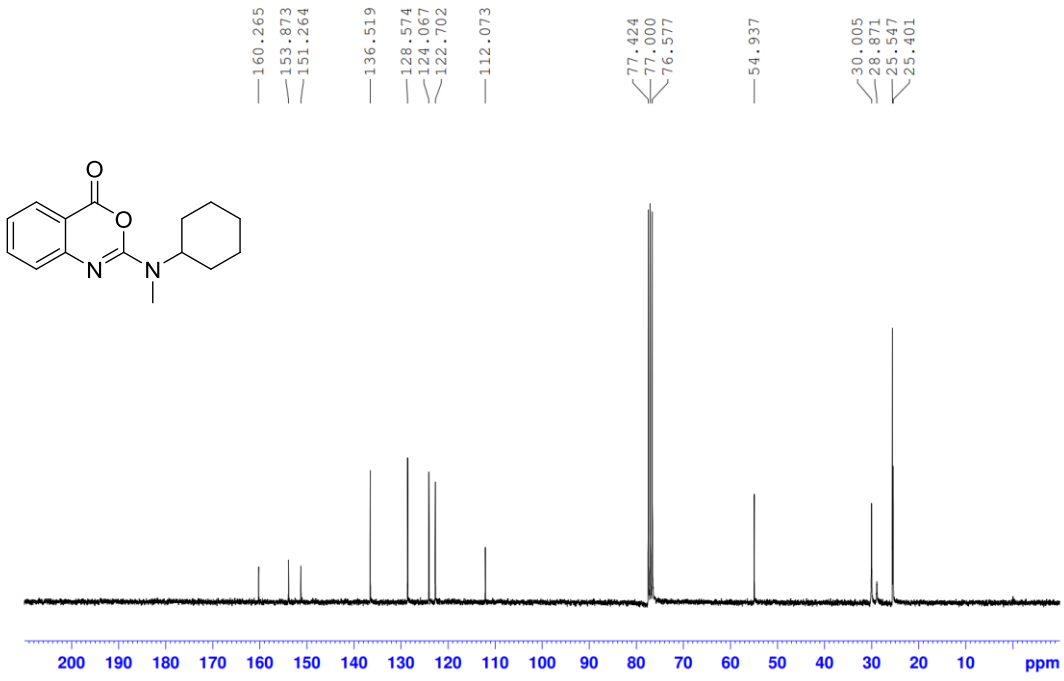

Figure S-60 ^{13}C NMR spectrum of compound **5l** (75 MHz, $CDCl_3$)

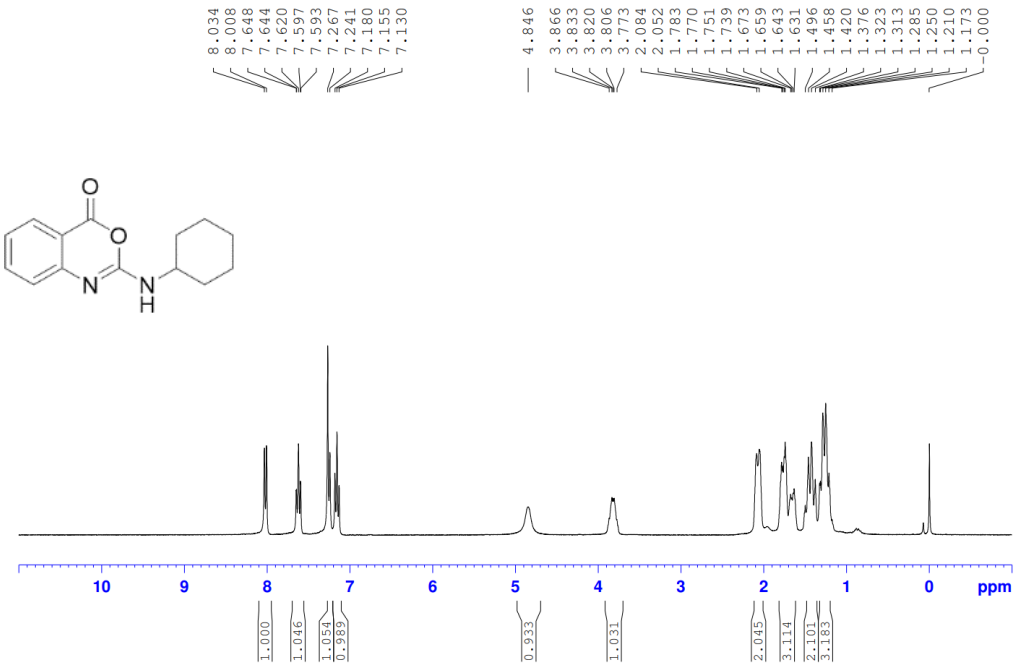

Figure S-61 ^{1}H NMR spectrum of compound **5m** (300 MHz, $CDCl_3$)

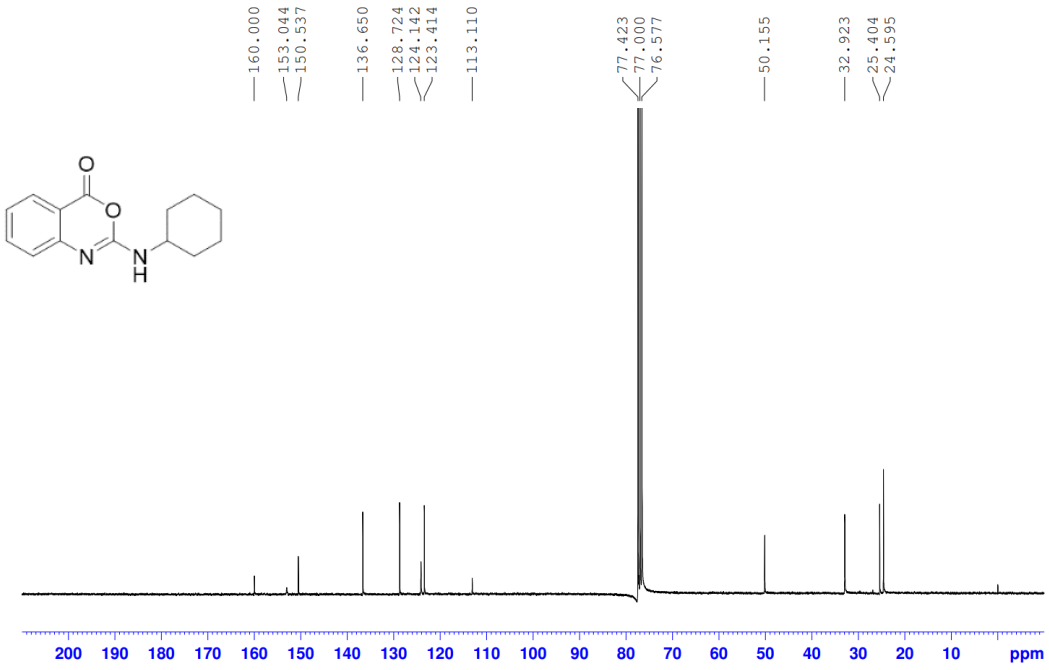

Figure S-62 ^{13}C NMR spectrum of compound **5m** (75 MHz, $CDCl_3$)

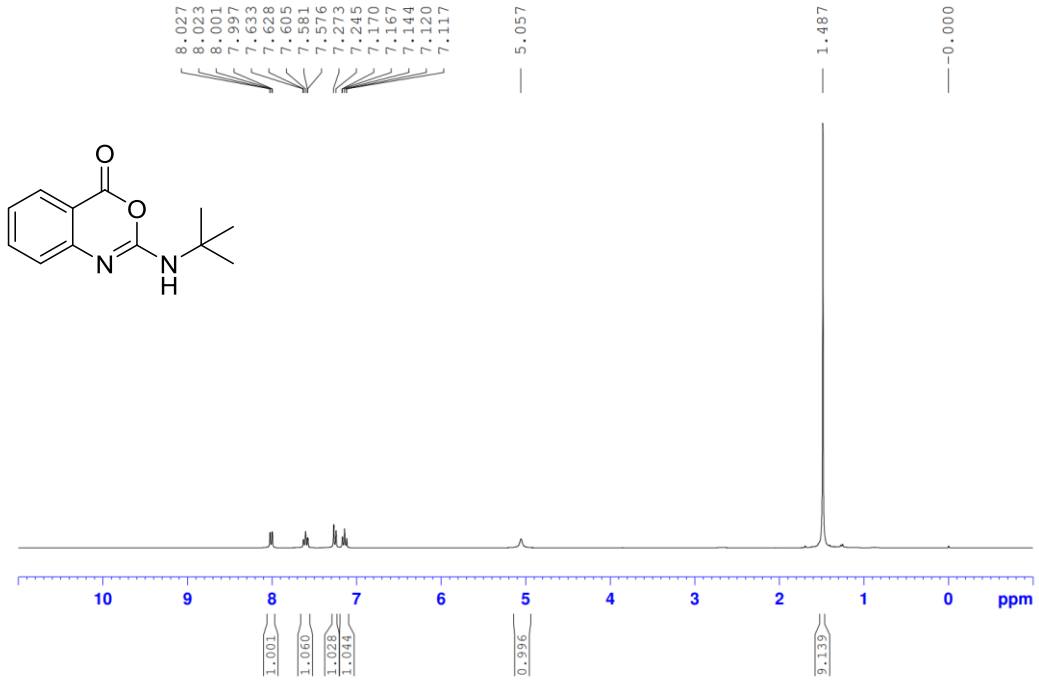

Figure S-63 ^{1}H NMR spectrum of compound **5n** (300 MHz, $CDCl_3$)

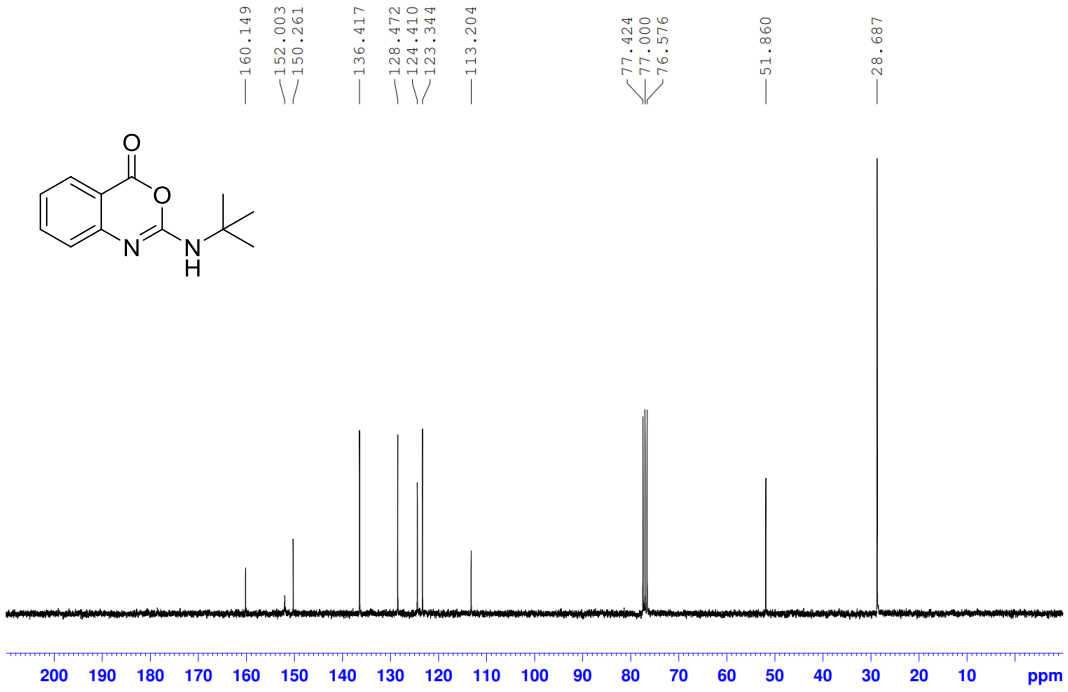

Figure S-64 ^{13}C NMR spectrum of compound **5n** (75 MHz, $CDCl_3$)

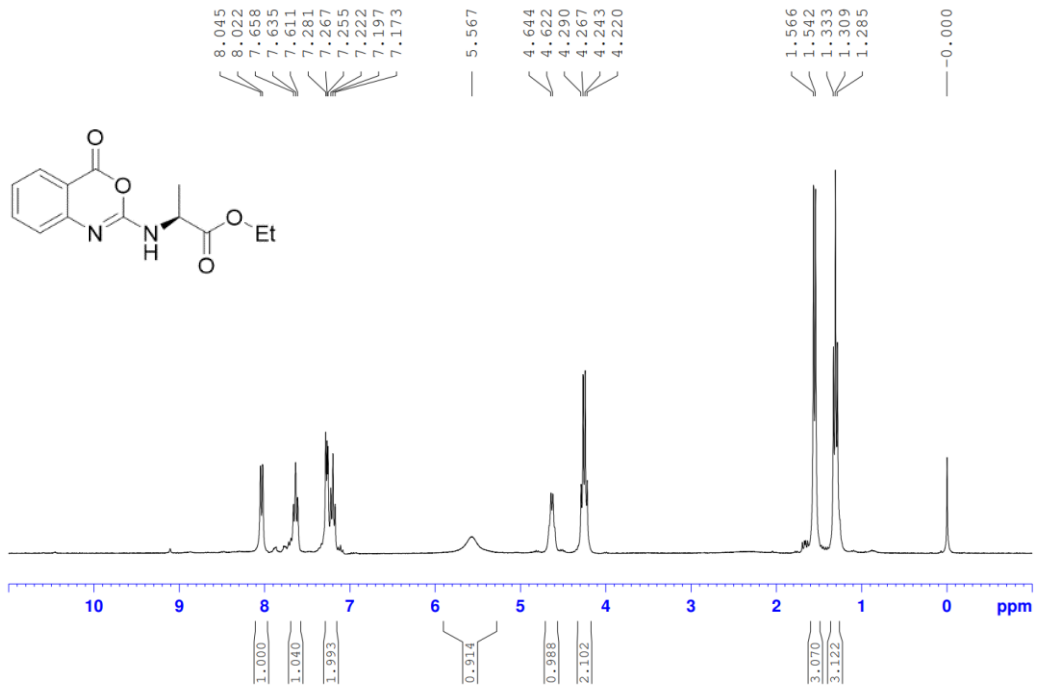

Figure S-65 ^{1}H NMR spectrum of compound **5o** (300 MHz, $CDCl_3$)

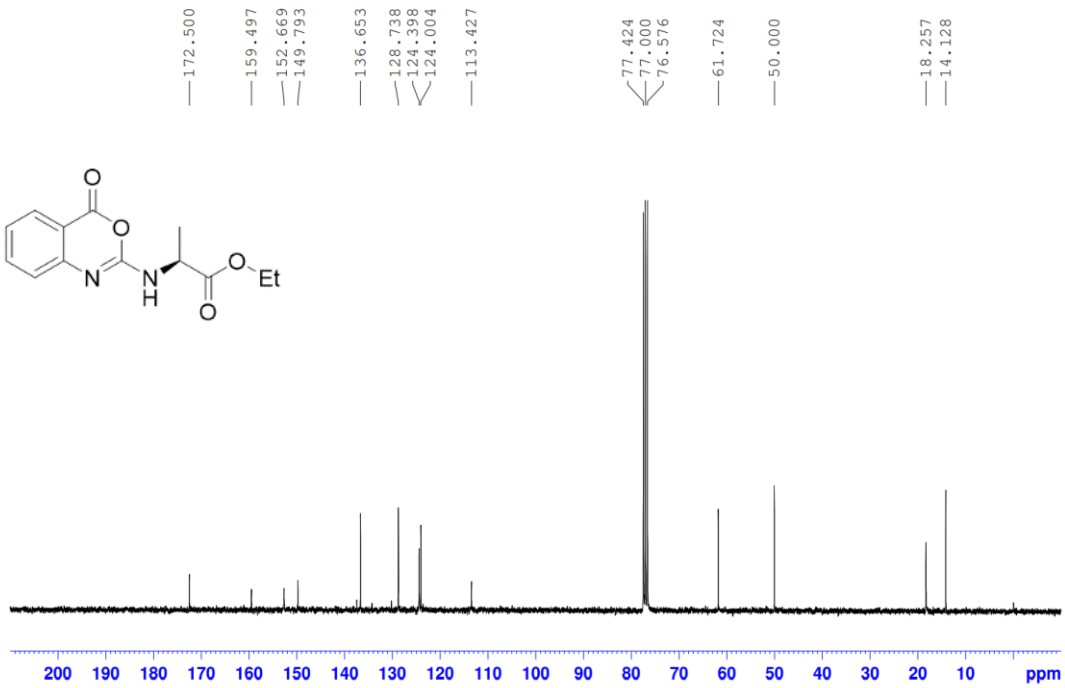

Figure S-66 ^{13}C NMR spectrum of compound **5o** (75 MHz, $CDCl_3$)

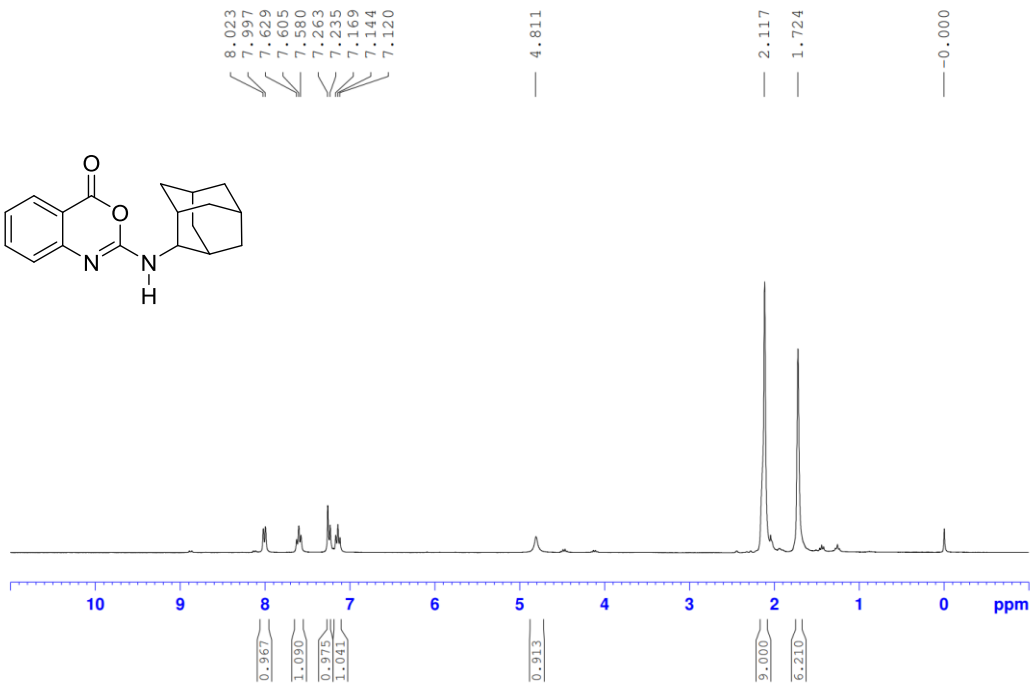

Figure S-67 ^{1}H NMR spectrum of compound **5p** (300 MHz, $CDCl_3$)

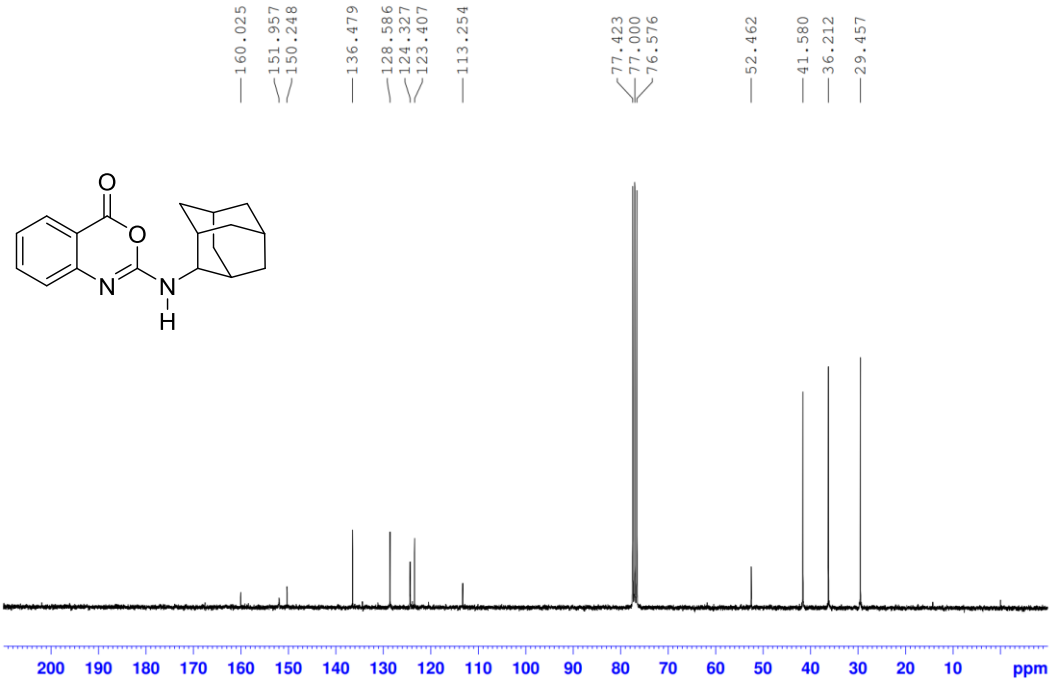

Figure S-68 ^{13}C NMR spectrum of compound **5p** (75 MHz, $CDCl_3$)

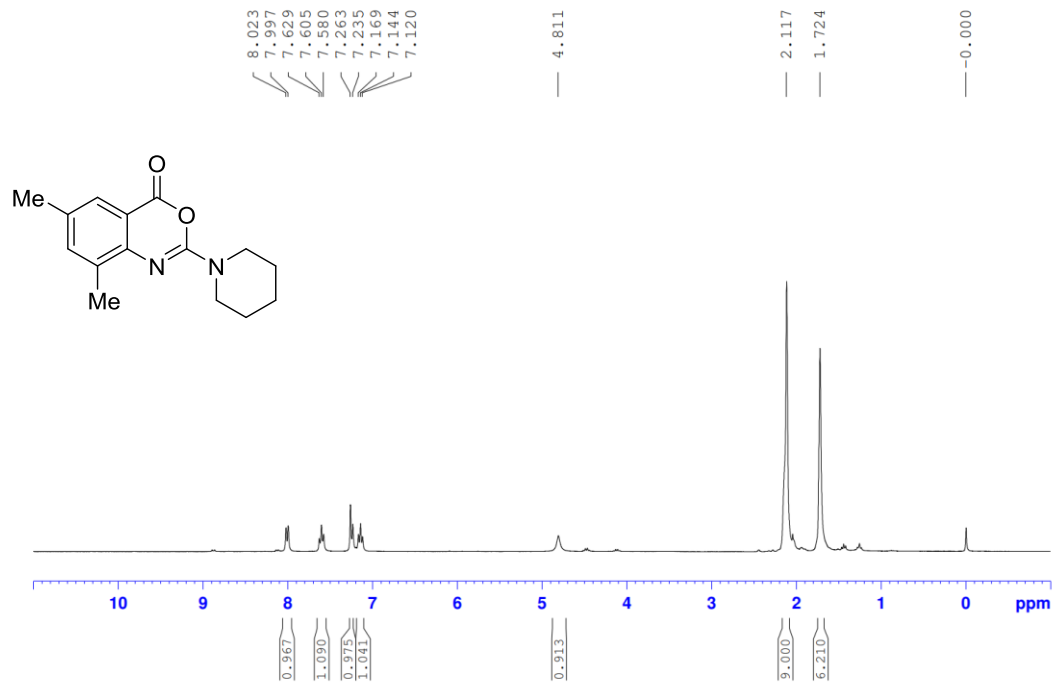

Figure S-69 ^{1}H NMR spectrum of compound **5q** (300 MHz, $CDCl_3$)

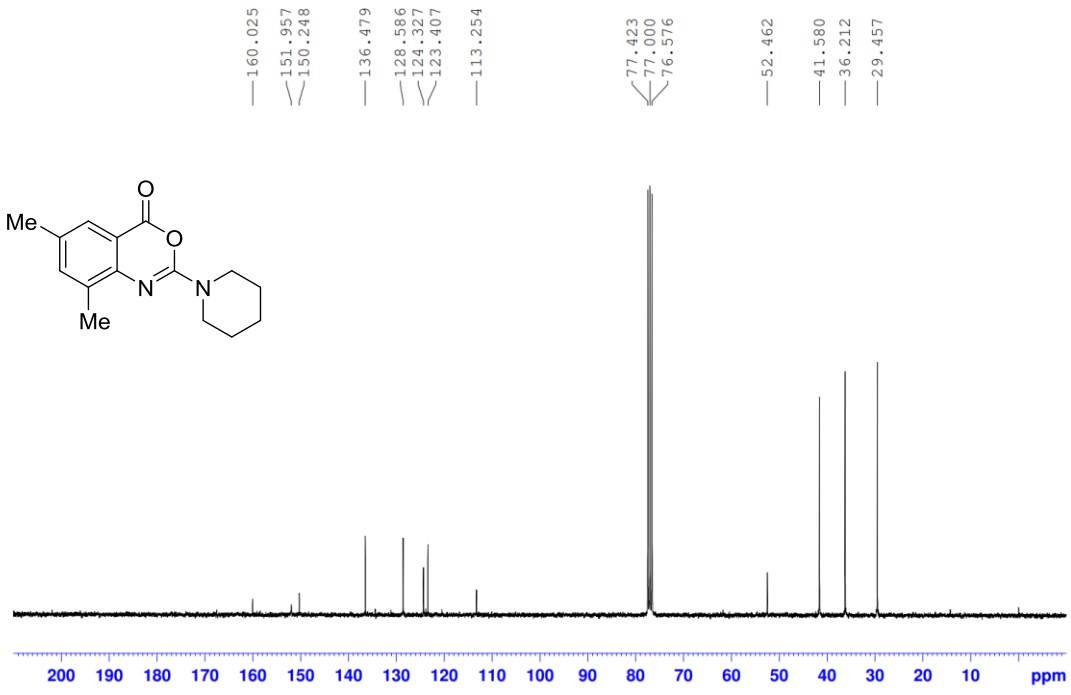

Figure S-70 ^{13}C NMR spectrum of compound **5q** (75 MHz, $CDCl_3$)

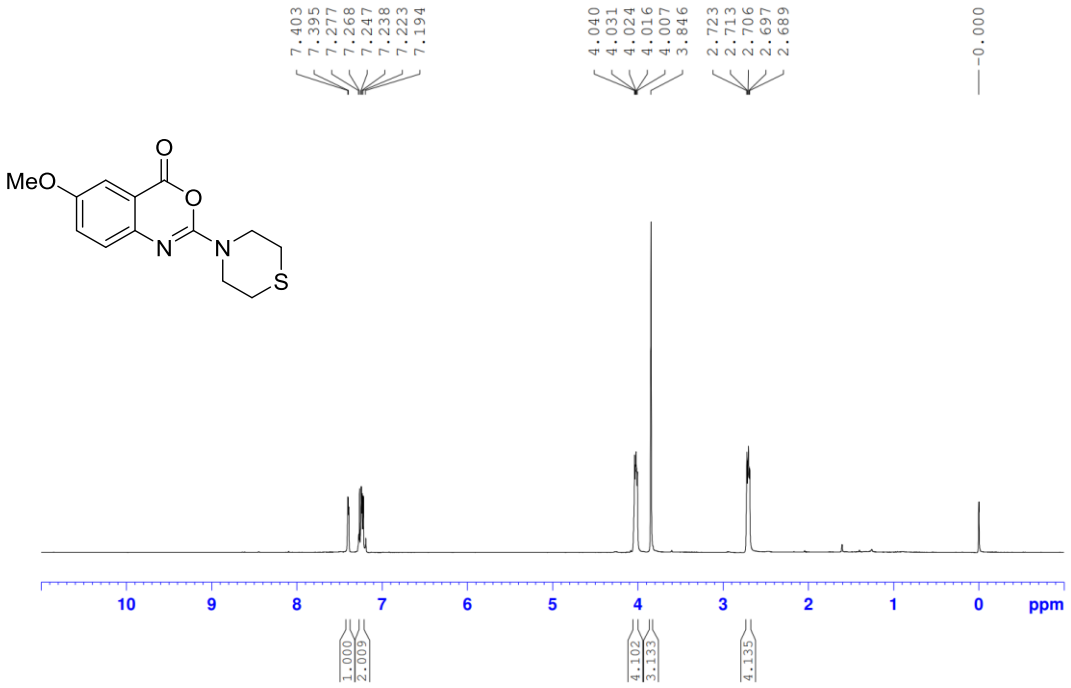

Figure S-71 ^{1}H NMR spectrum of compound **5r** (300 MHz, $CDCl_3$)

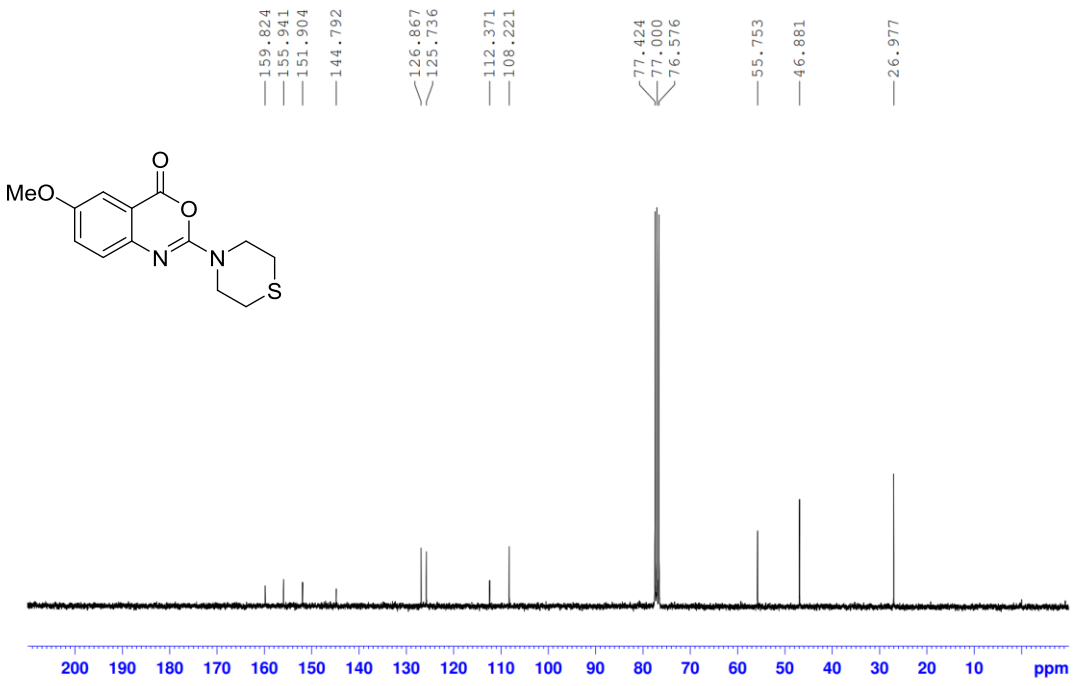

Figure S-72 ^{13}C NMR spectrum of compound **5r** (75 MHz, $CDCl_3$)

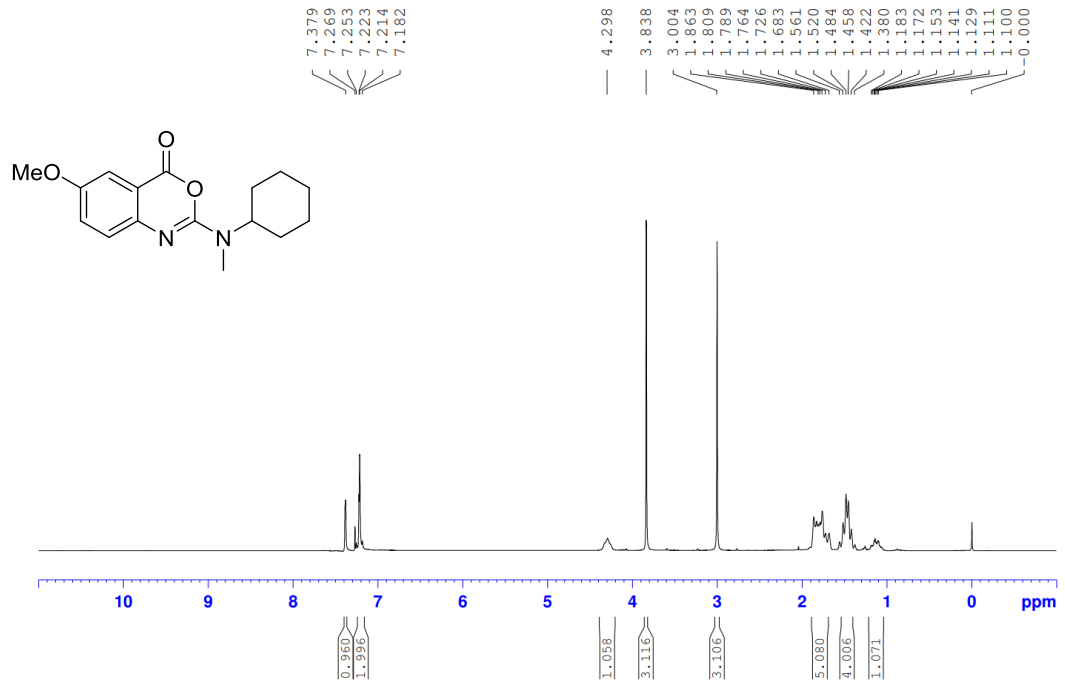

Figure S-73 ^{1}H NMR spectrum of compound **5s** (300 MHz, $CDCl_3$)

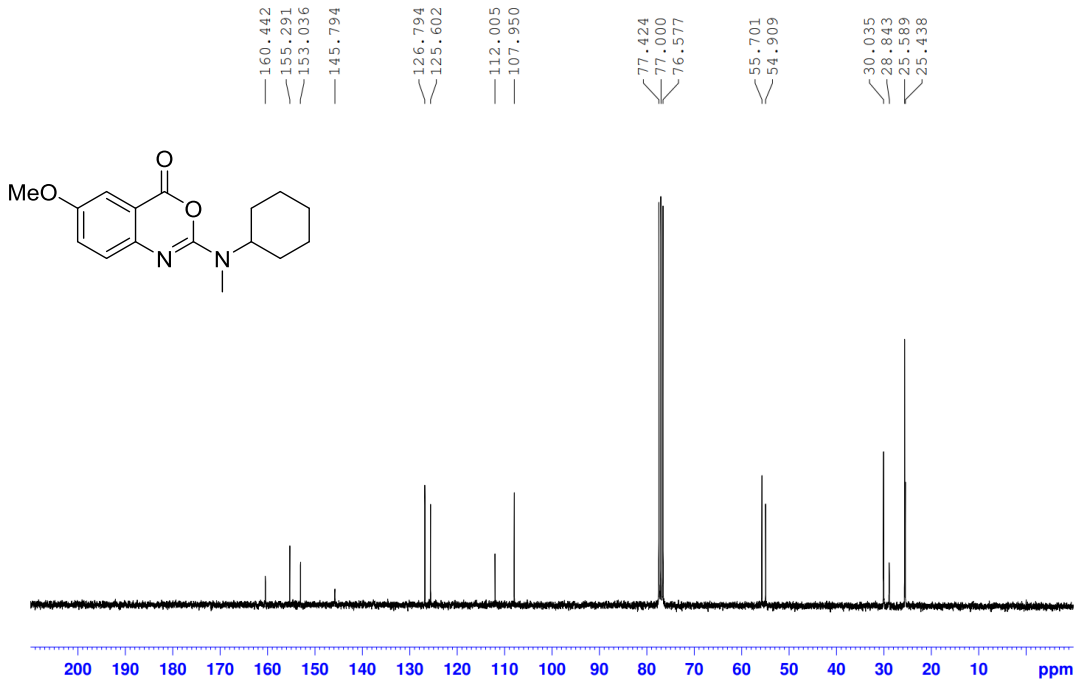

Figure S-74 ^{13}C NMR spectrum of compound **5s** (75 MHz, $CDCl_3$)

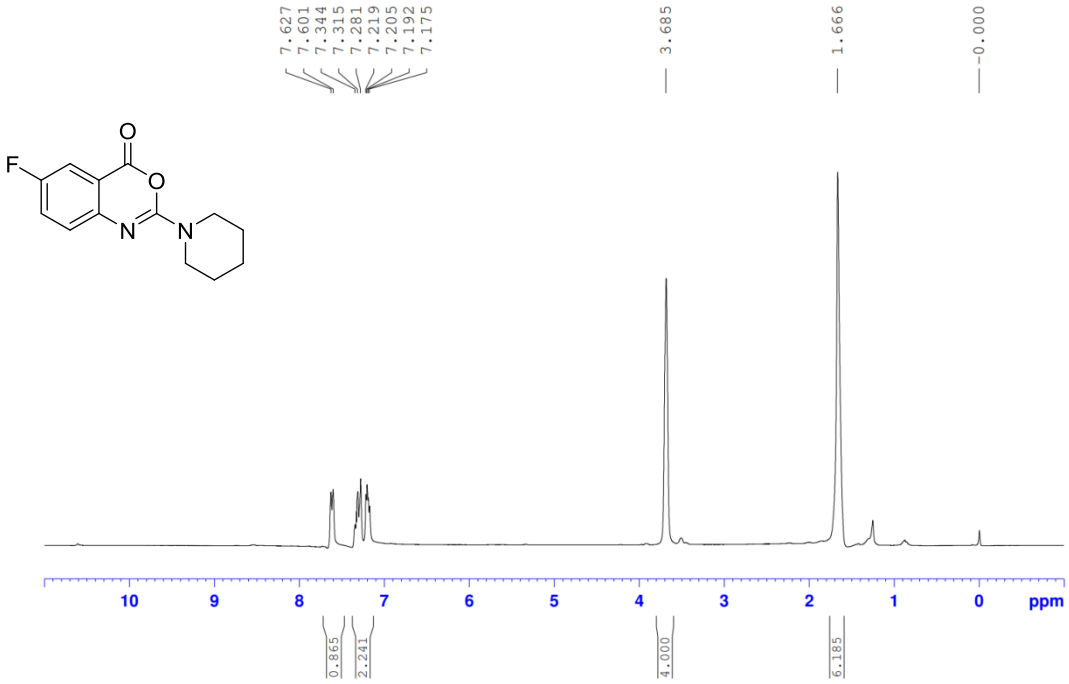

Figure S-75 ^{1}H NMR spectrum of compound **5t** (300 MHz, $CDCl_3$)

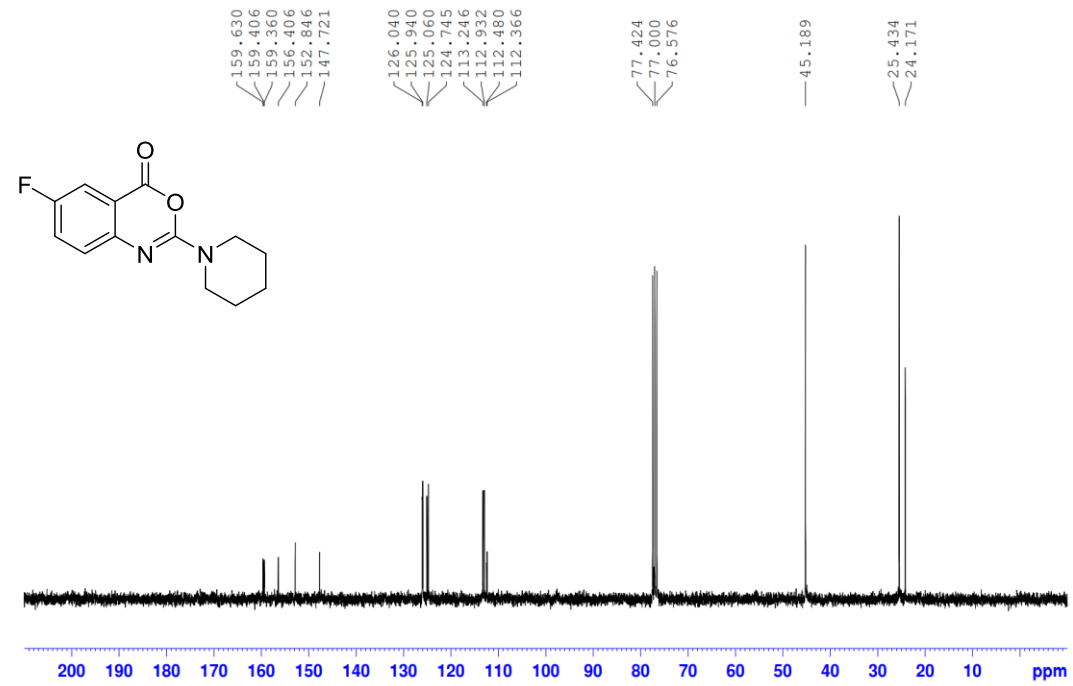

Figure S-76 ^{13}C NMR spectrum of compound **5t** (75 MHz, $CDCl_3$)

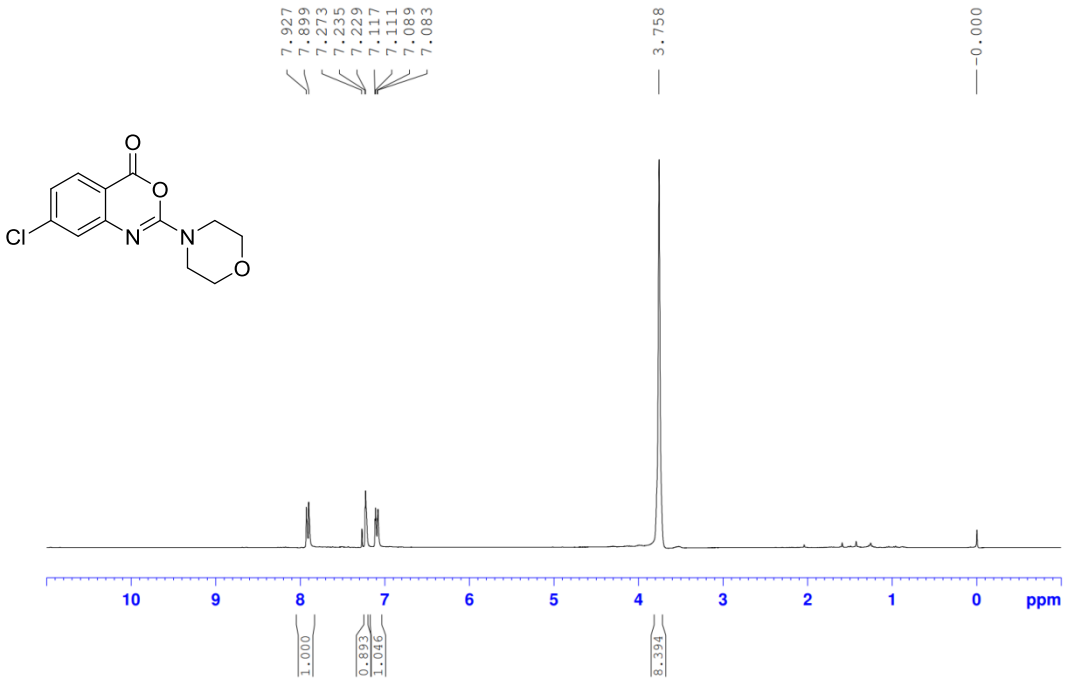

Figure S-77 ^{1}H NMR spectrum of compound **5u** (300 MHz, $CDCl_3$)

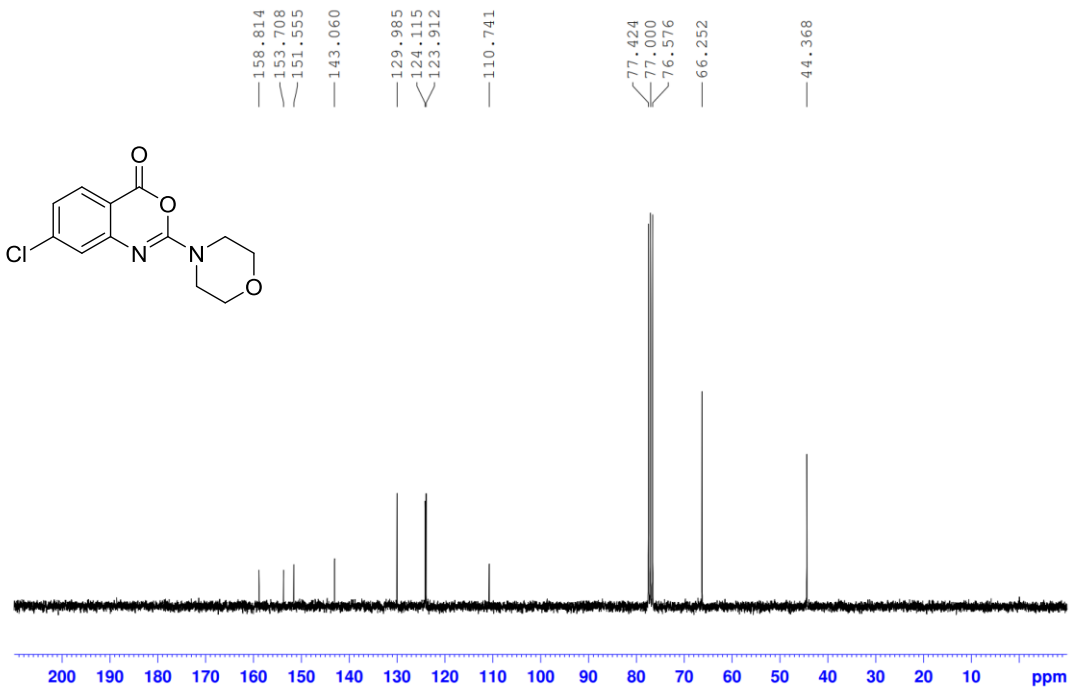

Figure S-78 ^{13}C NMR spectrum of compound **5u** (75 MHz, $CDCl_3$)

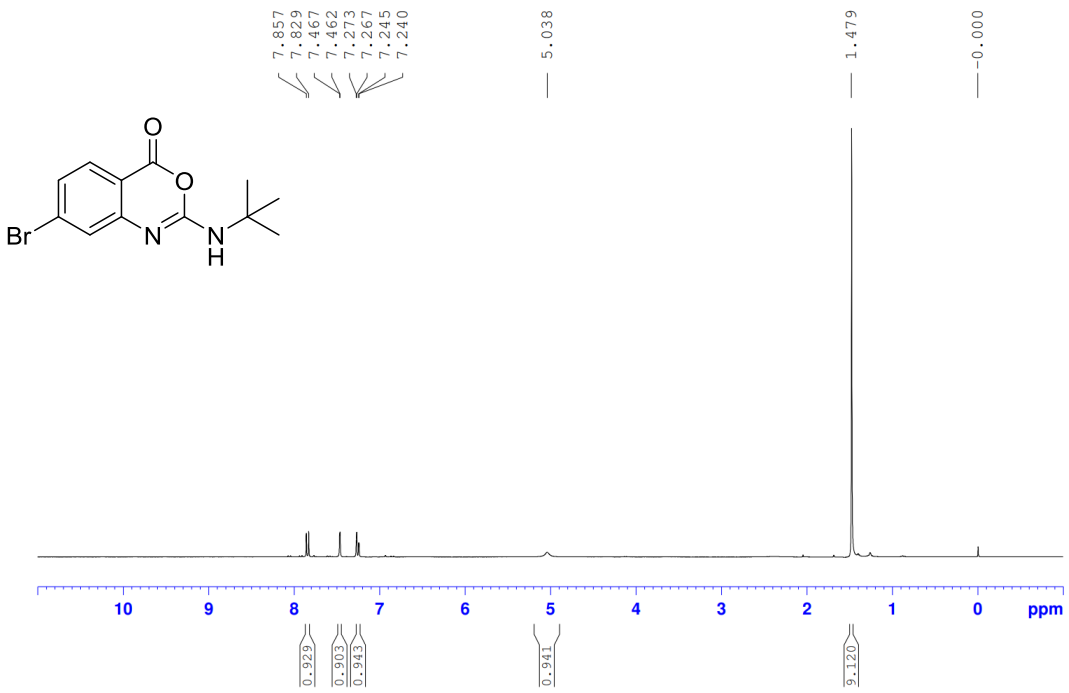

Figure S-79 ^{1}H NMR spectrum of compound **5v** (300 MHz, $CDCl_3$)

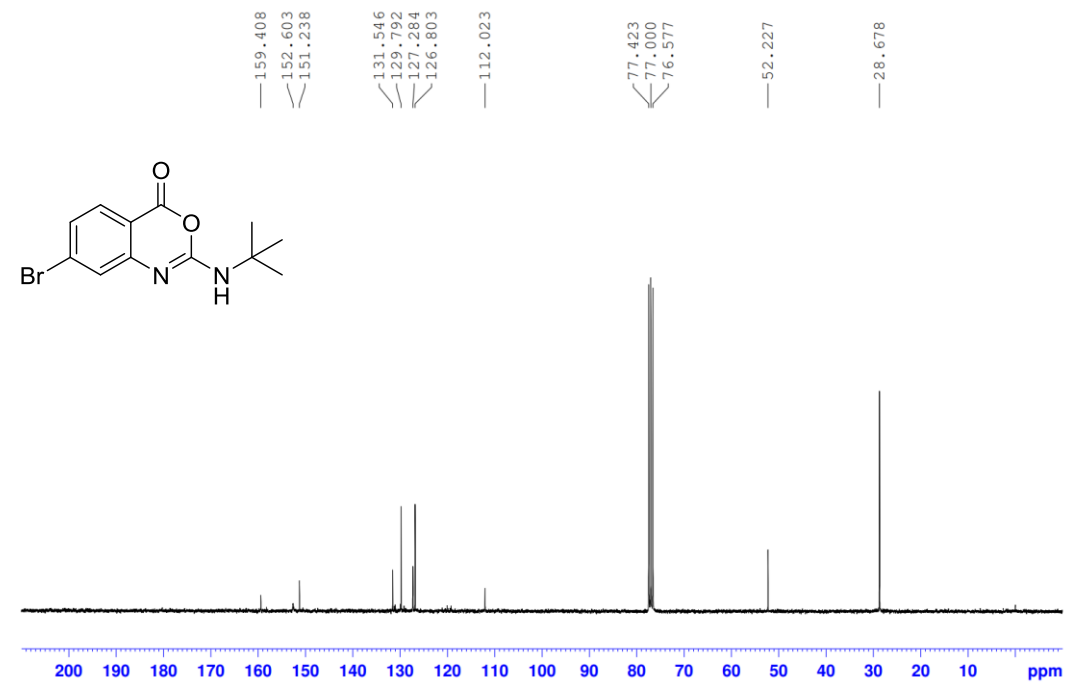

Figure S-80 ^{13}C NMR spectrum of compound **5v** (75 MHz, $CDCl_3$)

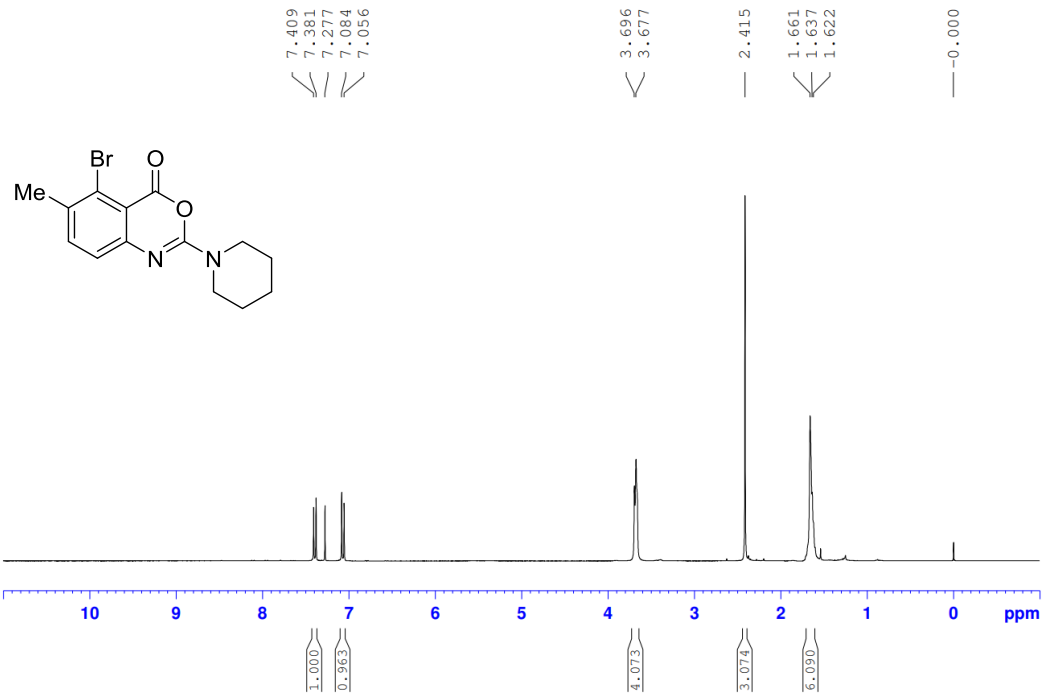

Figure S-81 ^{1}H NMR spectrum of compound **5w** (300 MHz, $CDCl_3$)

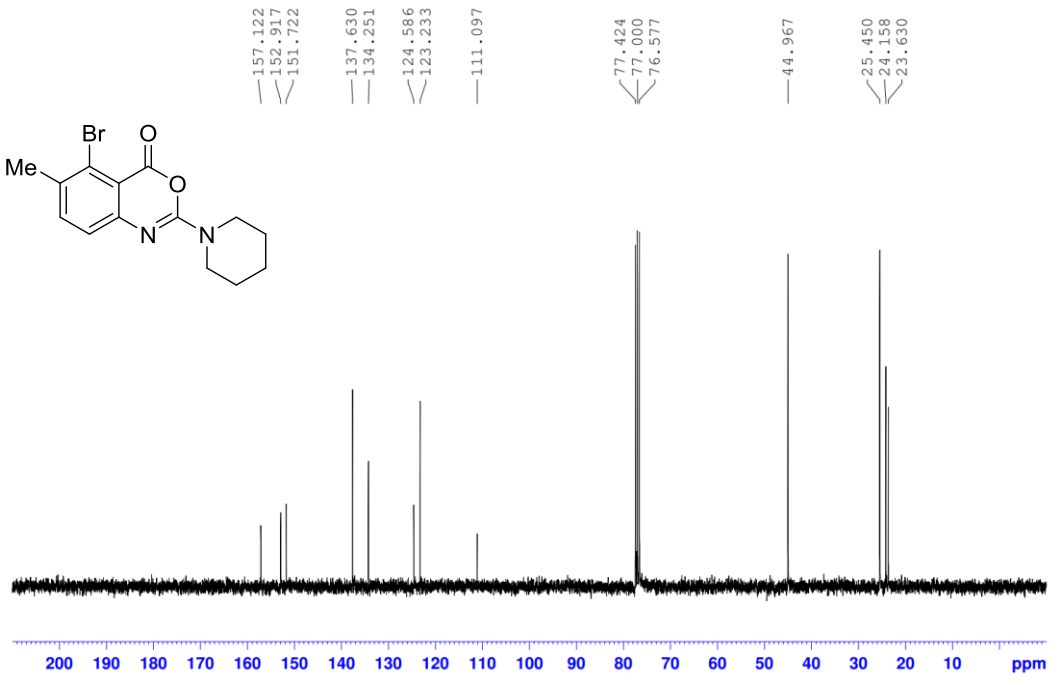

Figure S-82 ^{13}C NMR spectrum of compound **5w** (75 MHz, $CDCl_3$)

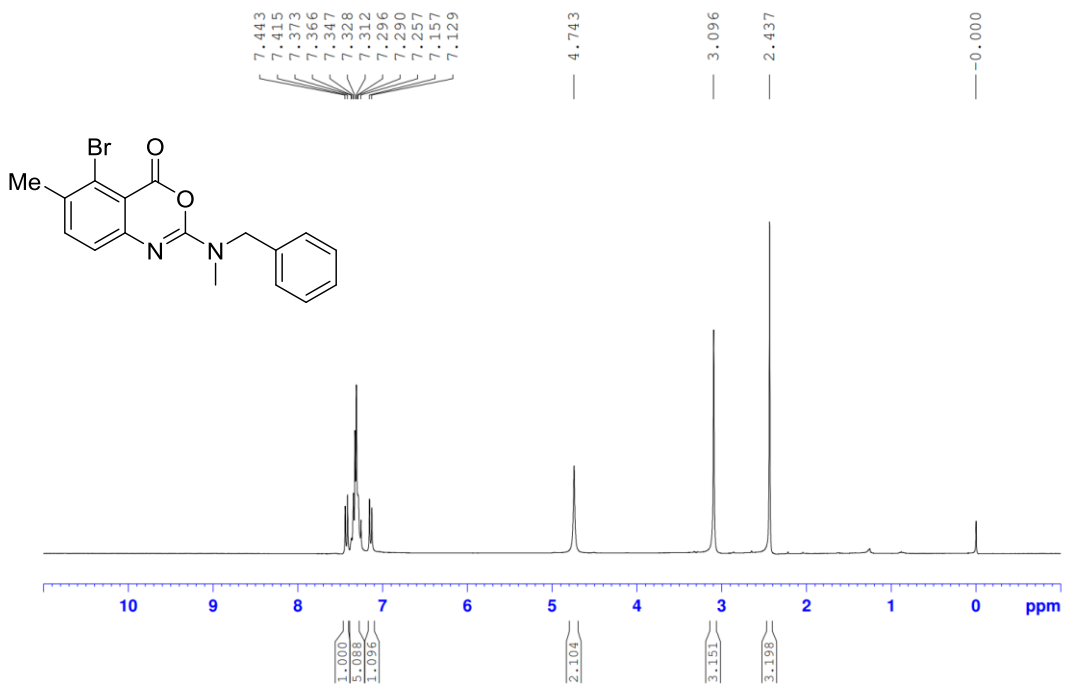

Figure S-83 ^{1}H NMR spectrum of compound **5x** (300 MHz, $CDCl_3$)

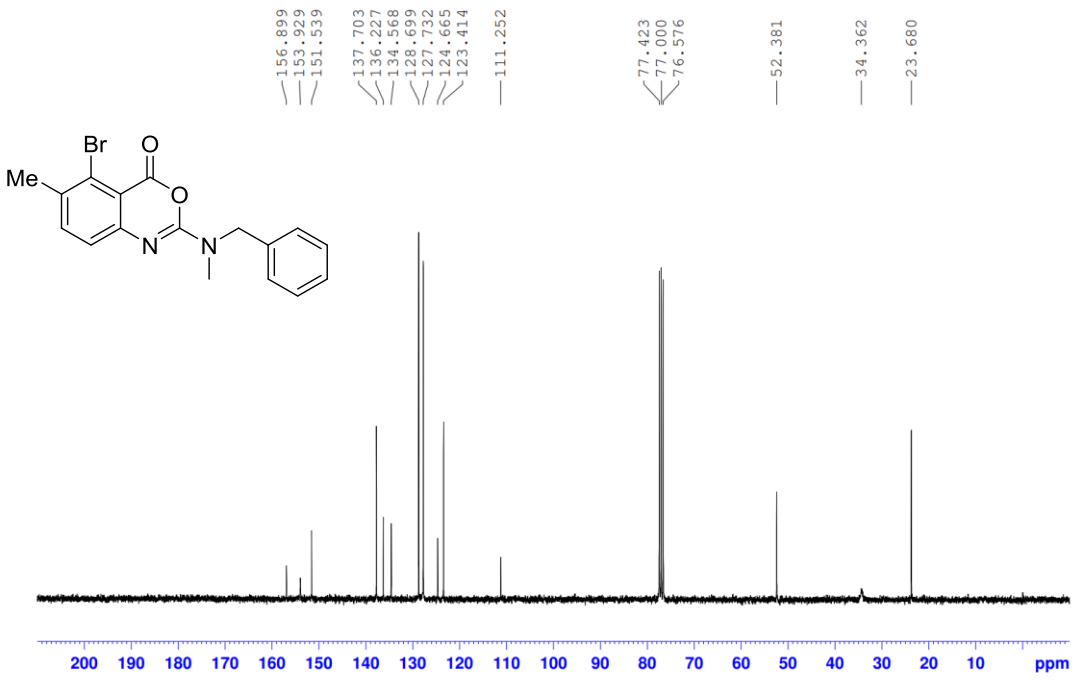

Figure S-84 ^{13}C NMR spectrum of compound **5x** (75 MHz, $CDCl_3$)

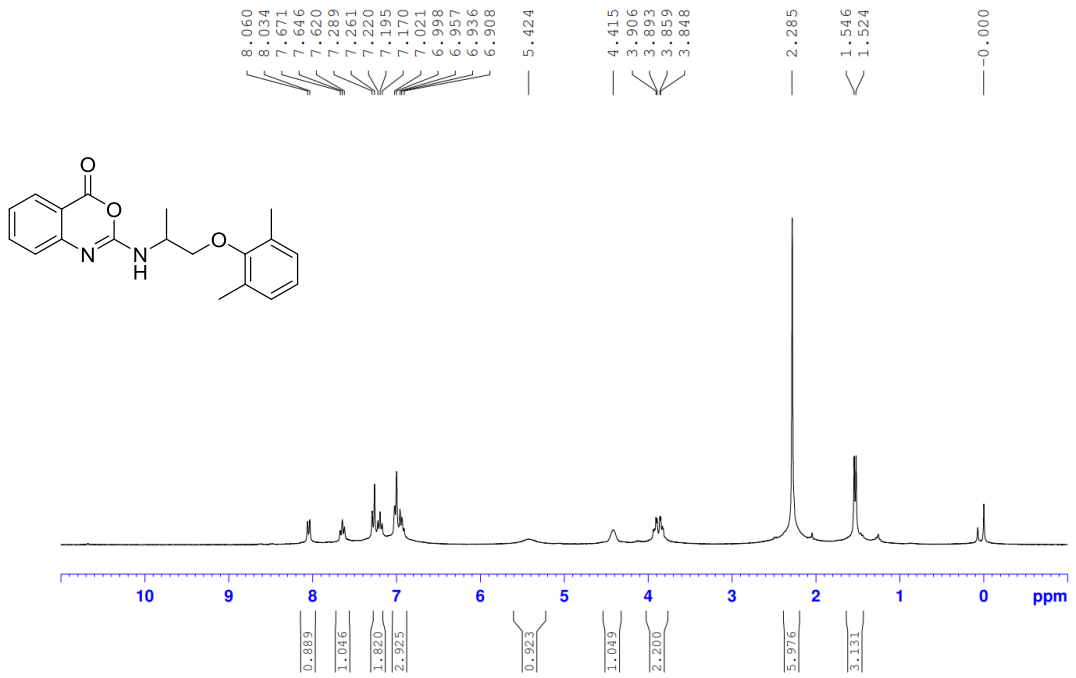

Figure S-85 ^{1}H NMR spectrum of compound **6** (300 MHz, $CDCl_3$)

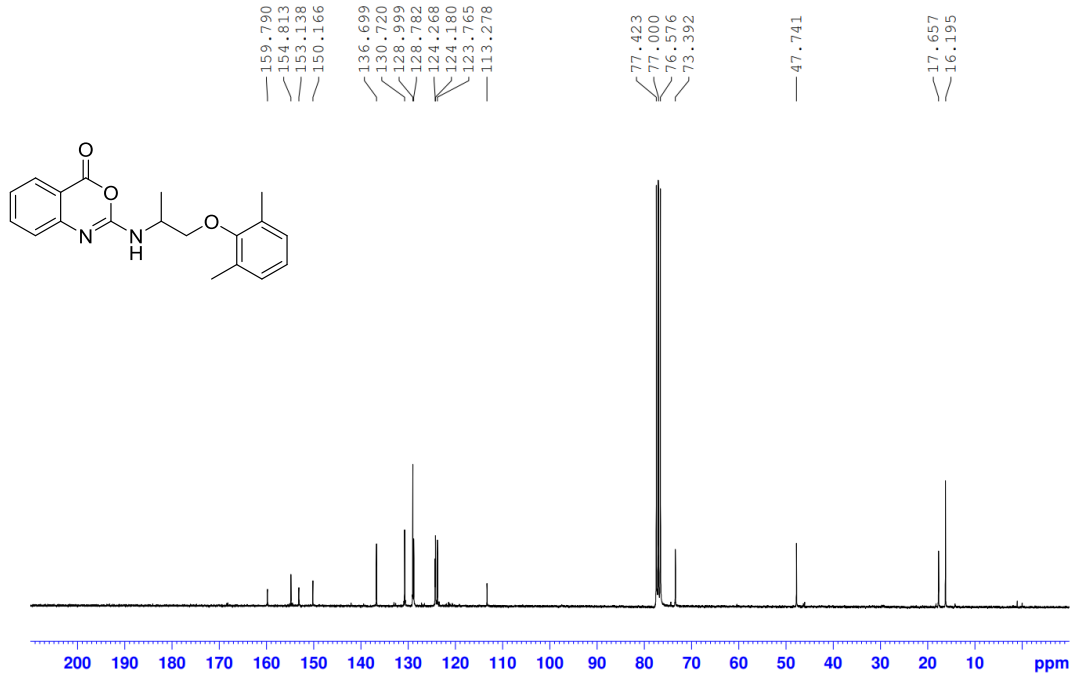

Figure S-86 ^{13}C NMR spectrum of compound **6** (75 MHz, $CDCl_3$)

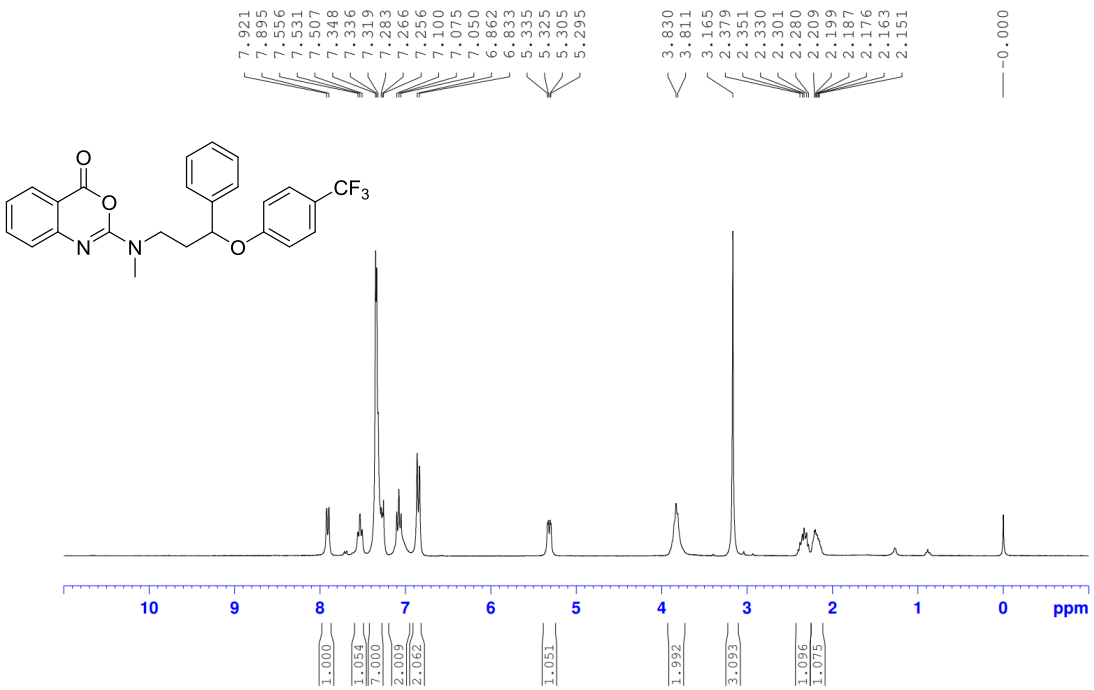

Figure S-87 ^{1}H NMR spectrum of compound **7** (300 MHz, $CDCl_3$)

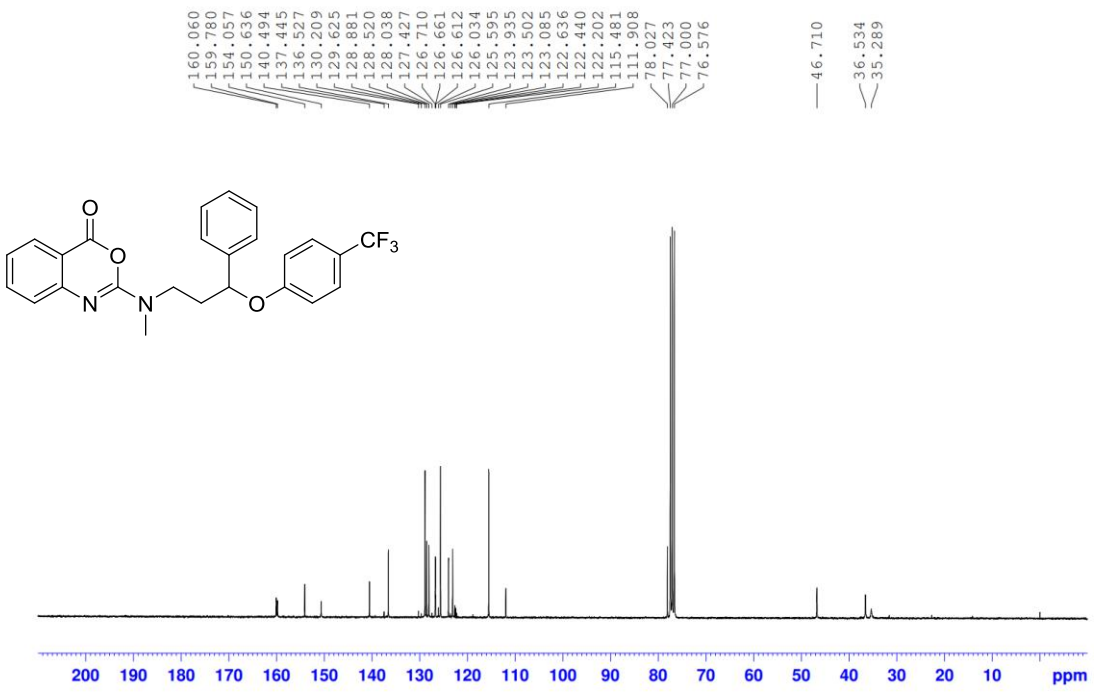

Figure S-88 ^{13}C NMR spectrum of compound **7** (75 MHz, $CDCl_3$)

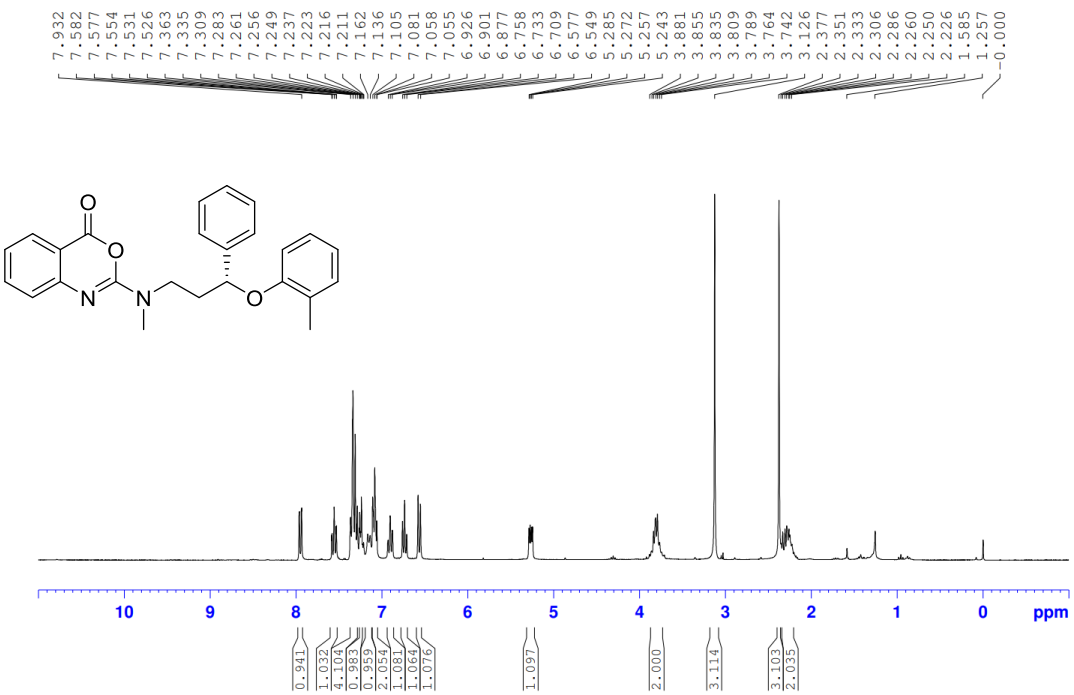

Figure S-89 ^{1}H NMR spectrum of compound **8** (300 MHz, $CDCl_3$)

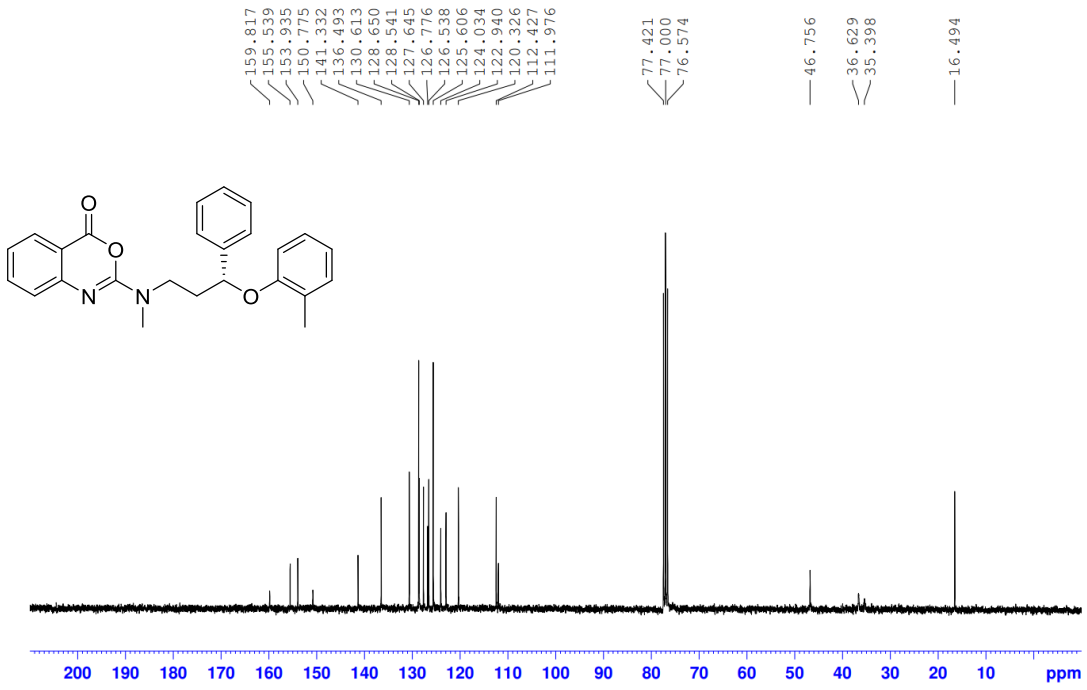

Figure S-90 ^{13}C NMR spectrum of compound **8** (75 MHz, $CDCl_3$)