Supporting Information

Metal-free C(sp^3)–H functionalization: Oxidative carbo-oxygenation of α-diazo carbonyls *via* radical dediazotization

Nan-Nan Wang,[a] Wen-Juan Hao,[a] Tian-Shu Zhang,[a] Guigen Li,*[,b,c] Ya-Nan Wu,[a] Shu-Jiang Tu,*[,a] and Bo Jiang*[,a,b]

[a]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, P. R. China. Email: laotu@jsnu.edu.cn (SJT.); jiangchem@jsnu.edu.cn (B.J.).

[b]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA email: guigen.li@ttu.edu;

[c]Institute of Chemistry & BioMedical Sciences, Nanjing University, Nanjing 210093, P. R. China.

Context

Experimental

General Information

^{1}H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 MHz spectrometer in $CDCl_3$ (DMSO-d_6) with chemical shift (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz)]. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

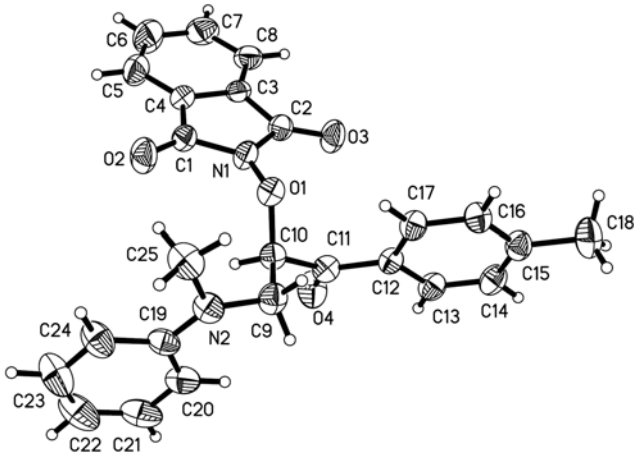
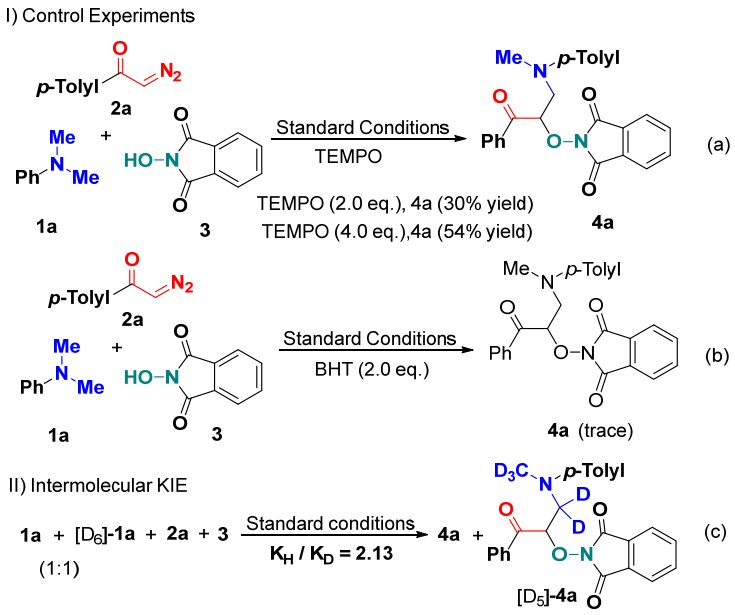


Figure 1 The ORTEP Drawing of **4a** (Thermal ellipsoids are set at 30% probability level)

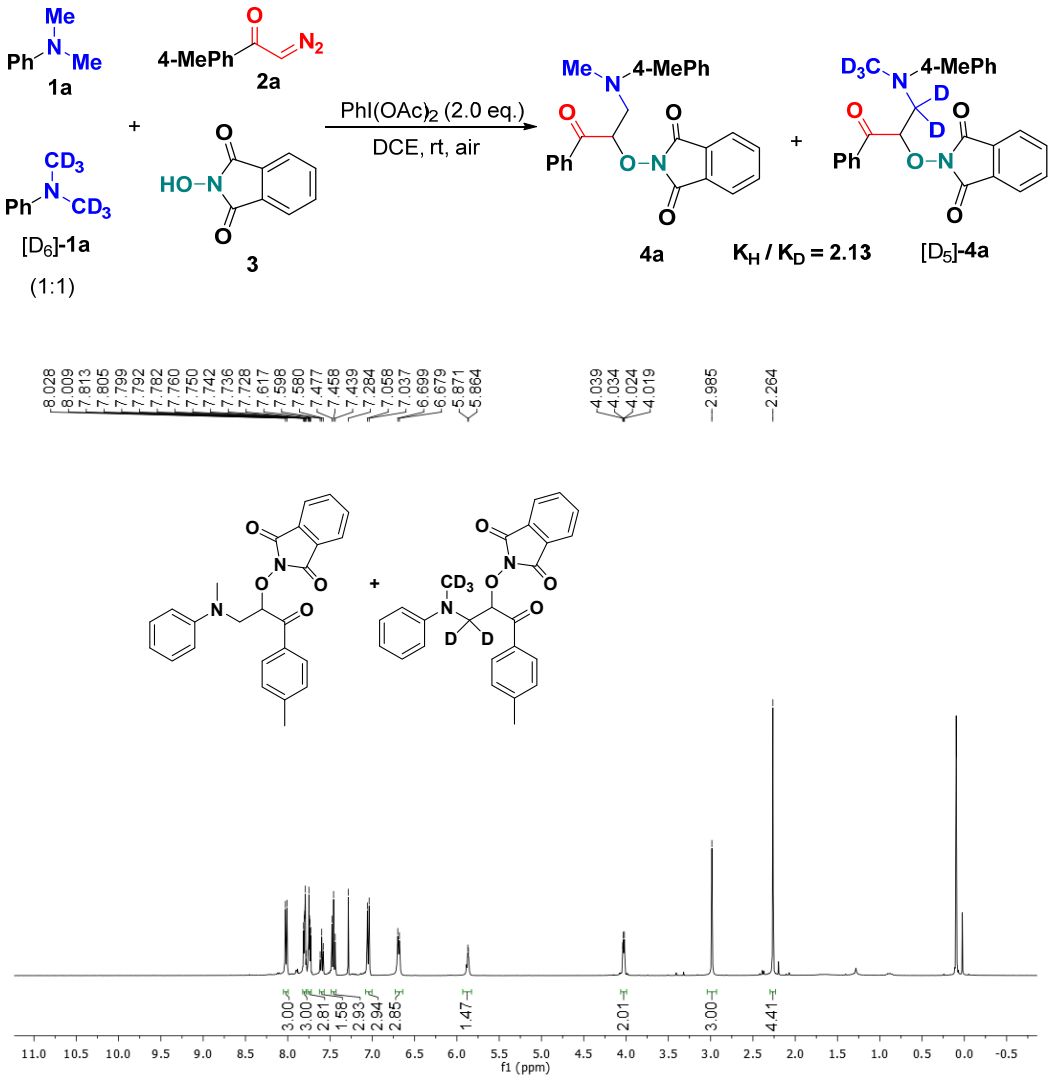


Scheme 1. Control experiments

Competing Kinetic Isotope Effect (KIE) Experiment:

KIE experimental procedure:

A mixture of *N*,*N*-dimethyl aniline (**1a**, 0.5 mmol, 1.0 equiv.), [D$_6$]-*N*,*N*-dimethyl aniline ([D$_6$]-**1a**, 0.5 mmol, 1.0 equiv.), *N*-hydroxyphthalimide (**3**, 0.50 mmol, 1.0 equiv.), 2-diazo-1-(*p*-tolyl)ethan-1-one (**2a**, 1.0 mmol, 2.0 equiv.), and phenyliodine diacetate (PIDA, 1.0 mmol, 2.0 equiv.) in dry 1,2-dichloroethane (DCE, 2.0 mL) was stirred at room temperature for about 12 hour. After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography to afford a mixture of products **4a** and [D$_5$]-**4a**. The KIE value was determined by ^{1}H NMR spectra of the mixture of **4a** and [D$_5$]-**4a**, which has been described in details as follows.



^{1}H NMR spectra of products **4a** and [D$_5$]-**4a**

Note: The value of k_H/k_D was calculated from the ^{1}H NMR spectra above. K_H/K_D = 2.13

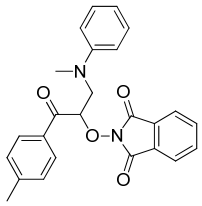
K_H/K_D = 1/(1.47-1) = 2.13

General procedure for the synthesis of 4

Example for the synthesis of **4a**

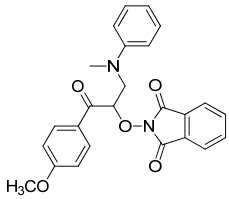
N,*N*-Dimethyl aniline (**1a**, 1.0 mmol, 2.0 equiv.), *N*-hydroxyphthalimide (**3**, 0.50 mmol, 1.0 equiv.) and 2-diazo-1-(*p*-tolyl)ethan-1-one (**2a**, 1.0 mmol, 2.0 equiv.) were introduced in a 10-mL Schlenk tube, dry 1,2-dichloroethane (DCE, 2.0 mL) and phenyliodine diacetate (PIDA, 1.0 mmol, 2.0 equiv.) were then successively added and the mixture stirred at room temperature for about 12 hours (monitored by TLC). After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography (petroleum ether/ethyl acetate) to afford the desired product **4a**.

*2-(1-(Methyl(phenyl)amino)-3-oxo-3-(p-tolyl)propoxy)isoindoline-1,3-dione (**4a**)*



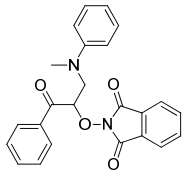
Yellow solid, mp 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.07–7.62 (m, 6H), 7.29–7.12 (m, 4H), 6.77 (d, J = 8.4 Hz, 3H), 5.84 (s, 1H), 4.06-4.02 (m, 2H), 3.01 (s, 3H), 2.40 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$; δ, ppm) 195.0, 163.2, 148.2, 145.1, 134.6, 132.9, 129.5, 129.3, 129.1, 128.7, 123.7, 117.3, 112.7, 84.9, 53.9, 39.7, 21.8; IR (KBr, ν, cm^{-1}) 3067, 2910, 1791, 1739, 1660, 1505, 1376, 1182, 1082, 973, 836, 699; HRMS (APCI) m/z Calcd. For $C_{25}H_{22}N_2O_4Na$, 437.1477 $[M+Na]^+$, found 437.1488.

*2-((1-(4-Methoxyphenyl)-3-(methyl(phenyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4b**)*



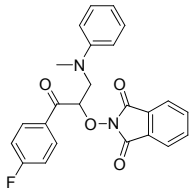
Yellow solid, mp 119-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.07-7.99 (m, 2H), 7.83-7.71 (m, 4H), 7.28-7.24 (m, 2H), 6.95-6.90 (m, 2H), 6.94-6.90 (m, 2H), 5.85 (s, 1H), 4.08-4.04 (m, 2H), 3.88 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.7, 164.2, 163.2, 146.3, 134.6, 131.4, 129.8, 128.8, 128.4, 126.5, 123.7, 113.9, 113.1, 84.8, 55.5, 54.2, 39.8, 20.3; IR (KBr, ν, cm-1) 3054, 2931, 1792, 1732, 1677, 1597, 1348, 1254, 1171, 973, 873, 700; HRMS (APCI) m/z Calcd. For $C_{25}H_{22}N_2O_5Na$, 453.1426 [M+Na], found 453.1428.

*2-((3-(Methyl(phenyl)amino)-1-oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione (**4c**)*



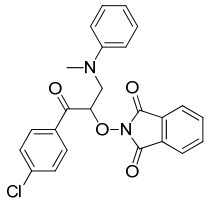
Yellow solid, mp 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.06-7.98 (m, 2H), 7.77-7.75 (m, 4H), 7.60-7.59 (m, 1H), 7.46 (m, 2H), 7.31-7.20 (m, 2H), 6.83-6.72 (m, 3H), 5.87-5.85 (m, 1H), 4.08-4.04 (m, 2H), 3.02 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.6, 163.2, 148.2, 135.3, 134.9, 134.7, 134.0, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.7, 123.9, 123.7, 117.4, 112.7, 85.0, 53.9, 39.7; IR (KBr, v, cm^{-1}) 3065, 2911, 1785, 1727, 1690, 1597, 1507, 1375, 1185, 977, 880, 750, 690; HRMS (APCI) m/z Calcd. For $C_{24}H_{20}N_2O_4Na$, 423.1321 $[M+Na]^+$, found 423.1302.

*2-((1-(4-Fluorophenyl)-3-(methyl(phenyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4d**)*



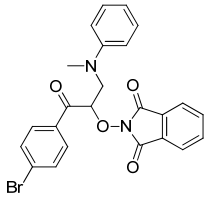
Yellow solid, mp 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.02-7.93 (m, 2H), 7.72-7.63 (m, 4H), 7.15-6.99 (m, 4H), 6.68-6.66 (m, 3H), 5.66 (t, J = 6.0 Hz 1H), 3.99-3.95 (m, 2H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.0, 166.2 (J = 255.2 Hz), 163.2, 148.1, 134.7, 134.3, 131.9 (J = 9.5 Hz), 131.7 (J = 3.0 Hz), 129.4, 128.7, 123.8, 123.6, 117.6, 115.9 (J = 21.8), 112.8, 85.2, 53.9, 39.8; IR (KBr, v, cm^{-1}) 3055, 2924, 1774, 1687, 1596, 1508, 1352, 1230, 1081, 975, 701; HRMS (APCI) m/z Calcd. For $C_{24}H_{19}FN_2O_4Na$, 441.1227 $[M+Na]^+$, found 441.1206.

*2-((1-(4-Chlorophenyl)-3-(methyl(phenyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4e**)*



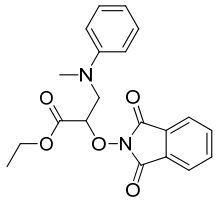
Yellow solid, mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.03-7.95 (m, 2H), 7.90-7.89 (m, 1H), 7.83-7.74 (m, 5H), 7.44-7.42 (m, 1H), 7.26-7.23 (m, 2H), 6.76 (d, J = 8.0 Hz, 2H), 5.76-5.72 (m, 1H), 4.09-4.05 (m, 2H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.4, 167.8, 163.2, 140.6, 134.8, 134.4, 133.6, 132.6, 130.5, 129.4, 129.1, 128.7, 123.8, 123.6, 117.7, 112.9, 85.3, 53.9, 39.9; IR (KBr, v, cm^{-1}) 3199, 2920, 1737, 1604, 1500, 1373, 1185, 969, 875, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{19}ClN_2O_4Na$, 457.0931 $[M+Na]^+$, found457.0924.

*2-((1-(4-Bromophenyl)-3-(methyl(phenyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4f**)*



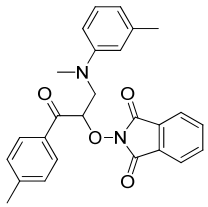
Yellow solid, mp 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.94-7.88 (m, 2H), 7.83-7.73 (m, 4H), 7.63-7.54 (m, 2H), 7.28-7.22 (m, 2H), 6.79-6.75 (m, 3H), 5.72 (d, J = 6.0 Hz, 1H), 4.09-4.05 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.7, 163.2, 148.1, 134.8, 134.3, 134.0, 132.0, 130.5, 129.4, 128.6, 123.8, 123.6, 117.5, 112.7, 85.4, 53.8, 39.8; IR (KBr, v, cm^{-1}) 3054, 1793, 1774, 1686, 1507, 1350, 1257, 1061, 972, 873, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{19}N_2O_4BrNa$, 501.0426 $[M+Na]^+$, found 501.0420.

*Ethyl 2-((1,3-dioxoisoindolin-2-yl)oxy)-3-(methyl(phenyl)amino)propanoate (**4g**)*



Yellow solid, mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82-7.72 (m, 4H), 7.29-7.25 (m, 2H), 6.84-6.67 (m, 3H), 4.98-4.95 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.99-3.95 (m, 2H), 3.12 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 168.6, 162.9, 148.4, 134.7, 129.3, 128.8, 123.7, 117.2, 112.6, 84.0, 62.0, 53.2, 39.4, 14.0; IR (KBr, v, cm^{-1}) 2996, 1792, 1730, 1599, 1508, 1374, 1264, 1121, 1025, 971, 878, 701; HRMS (APCI) m/z Calcd. For $C_{20}H_{20}N_2O_5Na$, 391.1270 $[M+Na]^+$, found 391.1274.

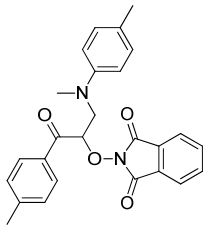
*2-((3-(Methyl(m-tolyl)amino)-1-oxo-1-(p-tolyl)propan-2-yl)oxy)isoindoline-1,3-dione (**4h**)*



Yellow solid; mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.94 (d, J = 8.4 Hz, 2H), 7.83-7.72 (m, 4H), 7.26 (d, J = 8.0 Hz, 2H), 7.14 (m, 1H), 6.60 (d, J = 7.6 Hz, 3H), 5.87 (t, J = 5.6 Hz,, 1H), 4.05-4.03 (m, 2H), 3.01 (s, 3H), 2.42 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.9, 167.9, 163.2, 148.3, 145.1, 139.0, 134.6, 134.3, 132.8, 132.6, 129.5, 129.2, 129.1, 128.7, 123.7, 123.6, 118.2, 113.5, 110.0, 85.0, 53.9, 39.7, 29.7, 21.9, 21.8; IR (KBr, v, cm^{-1}) 3199,

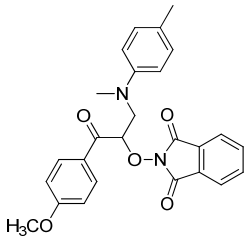
1791, 1737, 1655, 1604, 1500, 1185, 1053, 969, 875, 700; HRMS (APCI) m/z Calcd. For $C_{26}H_{24}N_2O_4Na$, 451.1634 $[M+Na]^+$, found 451.1633.

*2-((3-(Methyl(p-tolyl)amino)-1-oxo-1-(p-tolyl)propan-2-yl)oxy)isoindoline-1,3-dione (**4i**)*



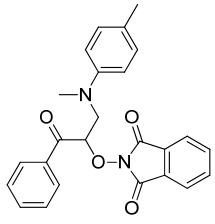
Yellow solid; mp 138-139 ^oC; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.93 (d, J = 8.0 Hz, 2H), 7.80-7.78 (m, 4H), 7.26 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 5.85 (t, *J* = 6.0 Hz,, 1H), 4.03-4.01 (m, 2H), 2.99 (s, 3H), 2.42 (s, 3H), 2.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.0, 163.2, 146.3, 145.0, 134.6, 132.9, 129.8, 129.5, 129.1, 128.7, 126.6, 123.7, 113.1, 85.0, 54.2, 39.8, 21.8, 20.3; IR (KBr, *v*, cm^{-1}) 2910, 1736, 1664, 1522, 1372, 1261, 1187, 1121, 970, 810, 702; HRMS (APCI) m/z Calcd. For $C_{26}H_{24}N_2O_4Na$, 451.1634 $[M+Na]^+$, found 451.1631.

*2-((1-(4-Methoxyphenyl)-3-(methyl(p-tolyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4j**)*



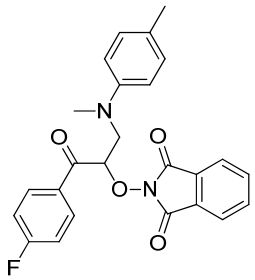
Yellow solid, mp 126-127 ^oC; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.02 (d, J = 8.8 Hz, 2H), 7.83-7.70 (m, 4H), 7.05 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.70 (d, J = 7.2 Hz, 2H), 5.83 (s, 1H), 4.03-4.01 (m, 2H), 3.88 (s, 3H), 2.98 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.7, 164.2, 163.2, 148.3, 134.6, 131.4, 129.3, 128.7, 128.4, 123.7, 117.2, 114.0, 112.6, 84.7, 55.5, 53.7, 39.6; IR (KBr, *v*, cm^{-1}) 2912, 1735, 1600, 1522, 1256, 1174, 970, 842, 702 ; HRMS (APCI) m/z Calcd. For $C_{26}H_{24}N_2O_5Na$, 467.1583 $[M+Na]^+$, found 467.1555.

*2-((3-(Methyl(p-tolyl)amino)-1-oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione (**4k**)*



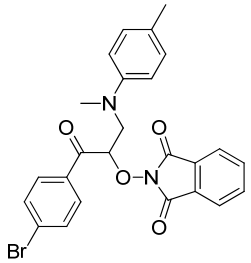
Yellow solid; mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.06-7.99 (m, 2H), 7.81-7.72 (m, 4H), 7.60 (s, 1H), 7.48-7.44 (m, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.87 (t, *J* = 6.0 Hz, 1H), 4.04-4.02 (m, 2H), 2.98 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.6, 167.9, 163.2, 146.2, 135.3, 134.6, 134.3, 133.9, 132.6, 129.8, 129.0, 128.7, 126.7, 123.7, 123.6, 113.2, 85.1, 54.2, 39.8, 20.3; IR (KBr, *v*, cm^{-1}) 2911, 1774, 1736, 1667, 1523, 1377, 1257, 1156, 970, 877, 701, 634; HRMS (APCI) m/z Calcd. for $C_{25}H_{22}N_2O_4Na$, 437.1477 $[M+Na]^+$, found 437.1476.

*2-((1-(4-Fluorophenyl)-3-(methyl(p-tolyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4l**)*



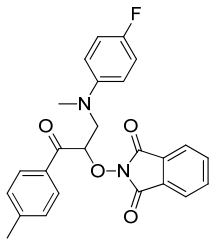
Yellow solid; mp 141-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.10-8.07 (m, 2H), 7.85-7.69 (m, 4H), 7.19-6.98 (m, 4H), 6.68 (d, *J* = 7.9 Hz, 2H), 5.77 (t, *J* = 6.0 Hz, 1H), 4.05-4.02 (s, 2H), 2.97 (s, 3H), 2.26 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$; *δ*, ppm) 194.0, 166.2 (J_{CF} = 255.0 Hz), 163.2, 146.1, 134.7, 134.3, 131.9 (J_{CF} = 9.5 Hz), 131.7 (J_{CF} = 2.9 Hz), 129.9, 128.7, 123.7, 123.6, 115.9 (J_{CF} = 21.8), 113.2, 85.3, 54.2, 39.9, 20.3; IR (KBr, v, cm^{-1}) 3199, 2909, 1774, 1736, 1666, 1596, 1522, 1307, 1186, 1053, 971, 804, 714; HRMS (APCI): m/z Calcd. for $C_{25}H_{21}FN_2O_4Na$, 455.1383 $[M+Na]^+$, found 455.1377.

*2-((1-(4-Bromophenyl)-3-(methyl(p-tolyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4m**)*



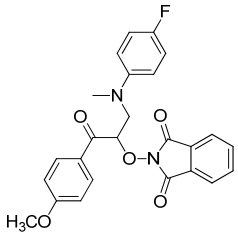
Yellow solid; mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$; *δ*, ppm) 7.92-7.89 (m, 2H), 7.82-7.74 (m, 4H), 7.60 (d, J = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 7.6 Hz, 2H), 5.73 (t, *J* = 6.0 Hz, 1H), 4.04-4.02 (m, 2H), 2.97 (s, 3H), 2.26 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$; *δ*, ppm) 194.7, 167.9, 163.2, 134.7, 134.3, 134.0, 132.6, 132.0, 130.5, 129.9, 129.3, 128.7, 123.8, 123.6, 113.2, 85.4, 54.2, 40.0, 20.3; IR (KBr, v, cm^{-1}) 3067, 2911, 1791, 1735, 1660, 1596, 1520, 1375, 1186, 1053, 971, 714; HRMS (APCI): m/z Calcd. for: $C_{25}H_{21}BrN_2O_4$, 515.0582 $[M+Na]^+$, found 515.0580.

*2-((3-((4-Fluorophenyl)(methyl)amino)-1-oxo-1-(p-tolyl)propan-2-yl)oxy)isoindoline-1,3-dione (**4n**)*



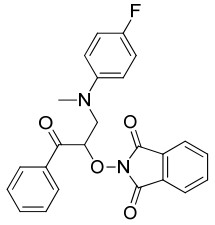
Yellow solid; mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.91 (d, J = 8.4 Hz, 2H), 7.85-7.65 (m, 4H), 7.28 (d, J = 6.8 Hz, 2H), 6.99-6.87 (m, 2H), 6.77-6.66 (m, 2H), 5.83 (t, J = 6.0 Hz, 1H), 4.02-4.00 (m, 2H), 2.99 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.8, 163.2, 156.0 (J_{CF} = 236.4 Hz), 145.2, 144.9 (J_{CF} = 1.0 Hz), 134.6, 132.8, 129.5, 129.0, 128.7, 123.7, 115.7 (J_{CF} = 21.9 Hz), 114.3 (J_{CF} = 6.3 Hz), 84.9, 54.7, 40.1, 21.8; IR (KBr, v, cm^{-1}) 2913, 1791, 1738, 1663, 1510, 1226, 1124, 971, 817, 689; HRMS (APCI) m/z Calcd. For $C_{25}H_{21}N_2O_4$ Na, 455.1383 $[M+Na]^+$, found 455.1382.

*2-((3-((4-Fluorophenyl)(methyl)amino)-1-(4-methoxyphenyl)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4o**)*



Yellow solid, mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.05-7.92 (m, 2H), 7.781-7.73 (m, 4H), 7.10-6.80 (m, 4H), 6.78-6.63 (m, 2H), 5.80 (t, J = 6.0 Hz, 1H), 4.02-4.00 (m, 2H), 3.88 (s, 3H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.5, 164.3, 163.2, 156.0 (J_{CF} = 235.0 Hz), 145.0 (J_{CF} = 5.9 Hz), 134.7, 131.4, 128.7, 128.3, 123.7, 115.7 (J_{CF} = 22.0 Hz), 114.2 (J_{CF} = 5.6 Hz), 114.0, 84.7, 55.6, 54.7, 40.1; IR (KBr, v, cm^{-1}) 2912, 1790, 1738, 1599, 1511, 1255, 1023, 971, 816, 701; HRMS (APCI) m/z Calcd. For $C_{25}H_{21}N_2O_5FNa$, 471.1332 $[M+Na]^+$, found 471.1335.

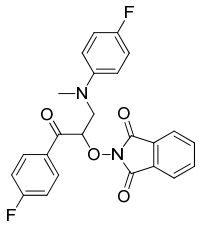
*2-((3-((4-Fluorophenyl)(methyl)amino)-1-oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione (**4p**)*



Yellow solid, mp 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.02-8.00 (m, 2H), 7.86-7.71 (m, 4H), 7.65-7.56 (m, 1H), 7.49-7.48 (m, 2H), 6.96-6.92 (m, 2H), 6.75-6.71 (m, 2H), 5.86 (t, J = 6.0 Hz, 1H), 4.04-4.01 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.4, 163.2, 156.0 (J_{CF} = 235.6 Hz), 144.9 (J_{CF} = 0.9 Hz), 135.3, 134.7, 134.0, 128.9, 128.8, 128.7, 123.7, 115.9 (J_{CF} =

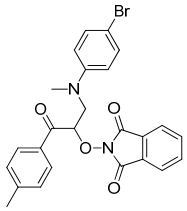
21.8 Hz), 114.4 (J_{CF} = 7.2 Hz), 85.0, 54.6, 40.1; IR (KBr, *v*, cm^{-1}) 3067, 2912, 1791, 1738, 1599, 1511, 1255, 1228, 1173, 971, 816, 701; HRMS (APCI) m/z Calcd. For $C_{24}H_{19}N_2O_4FNa$, 441.1227 $[M+Na]^+$, found 441.1219.

*2-((1-(4-Fluorophenyl)-3-((4-fluorophenyl)(methyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-di one (**4q**)*



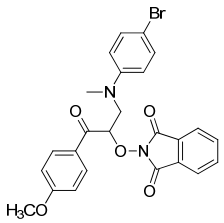
Yellow solid, mp 123-124 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.10-8.06 (m, 2H), 7.87-7.72 (m, 4H), 7.14 (m, 2H), 6.96-6.91 (m, 2H), 6.76-6.63 (m, 2H), 5.72 (t, *J* = 6.0 Hz,, 1H), 4.03-4.01 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.9, 166.2 (J_{CF} = 255.3 Hz), 163.2, 156.0 (J_{CF} = 235.2 Hz), 145.0 (J_{CF} = 1.6 Hz), 134.8, 131.8 (J_{CF} = 9.5 Hz), 131.7 (J_{CF} = 3.0 Hz), 128.6, 123.8, 115.9 (J_{CF} = 22.3 Hz), 115.7 (J_{CF} = 22.5 Hz), 114.3 (J_{CF} = 7.4 Hz), 85.4, 54.6, 40.2; IR (KBr, *v*, cm^{-1}) 2911, 1790, 1737, 1664, 1595, 1512, 1230, 969, 817, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{18}N_2O_4F_2Na$, 459.1132 $[M+Na]^+$, found 459.1146.

*2-((3-((4-Bromophenyl)(methyl)amino)-1-oxo-1-(p-tolyl)propan-2-yl)oxy)isoindoline-1,3-dione (**4r**)*



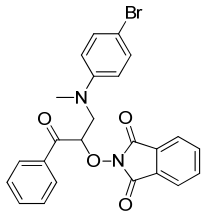
Yellow solid, mp 159-160 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.96-7.71 (m, 6H), 7.35-7.29 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.73-6.56 (m, 2H), 5.81-5.78 (m, 1H), 4.04-4.00 (m, 2H), 3.00 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.8, 163.2, 147.2, 145.3, 134.7, 132.7, 132.0, 129.5, 129.0, 128.7, 123.7, 114.3, 109.4, 84.8, 53.8, 39.8, 21.8; IR (KBr, *v*, cm^{-1}) 2912, 1735, 1659, 1591, 1498, 1257, 1121, 970, 810, 701; HRMS (APCI) m/z Calcd. For $C_{25}H_{21}N_2O_4BrNa$, 515.0582 $[M+Na]^+$, found 515.0585.

*2-((3-((4-Bromophenyl)(methyl)amino)-1-(4-methoxyphenyl)-1-oxopropan-2-yl)oxy)isoindoline-1,3 -dione (**4s**)*



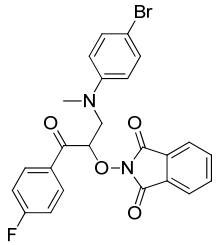
Yellow solid; mp 146-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.04-7.99 (m, 2H), 7.83-7.72 (m, 4H), 7.36-7.30 (m, 2H), 6.97-6.91 (m, 2H), 6.71 (d, J = 8.8 Hz, 2H), 5.83 (t, *J* = 6.0 Hz, 1H), 4.05-4.01 (m, 2H), 3.88 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.5, 164.3, 163.2, 147.2, 134.7, 132.0, 131.4, 128.7, 123.7, 114.2, 114.0, 100.0, 84.6, 55.6, 53.8, 39.7; IR (KBr, *v*, cm^{-1}) 2932, 1735, 1598, 1499, 1373, 1255, 1174, 1027, 968, 810, 701; HRMS (APCI) m/z Calcd. For $C_{25}H_{21}N_2O_5BrNa$, 508.0634 $[M+Na]^+$, found 503.0635.

*2-((3-((4-Bromophenyl)(methyl)amino)-1-oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione (**4t**)*



Yellow solid, mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.10-7.97 (m, 2H), 7.94-7.68 (m, 4H), 7.66-7.51 (m, 1H), 7.51-7.40 (m, 2H), 7.33-7.29 (m, 2H), 6.76-6.50 (m, 2H), 5.82 (t, *J* = 6.0 Hz, 1H), 4.06-4.02 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.3, 163.2, 147.2, 135.2, 134.7, 134.1, 132.0, 128.9, 128.8, 128.7, 1238, 114.4, 109.5, 84.9, 53.8, 39.7; IR (KBr, *v*, cm^{-1}) 3068, 2914, 1789, 1735, 1666, 1499, 1256, 1016, 968, 812, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{19}N_2O_4BrNa$, 501.0426 $[M+Na]^+$, found 501.0401.

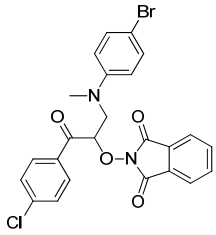
*2-((3-((4-Bromophenyl)(methyl)amino)-1-(4-fluorophenyl)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4u**)*



Yellow solid; mp 166-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.13-7.99 (m, 2H), 7.93-7.69 (m, 4H), 7.42-7.30 (m, 2H), 7.17-7.13 (m, 2H), 6.68 (d, *J* = 9.2 Hz, 2H), 5.74 (t, *J* = 6.0 Hz, 1H), 4.18-3.88 (m, 2H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.8, 166.3 (J_{CF} = 255.8 Hz), 163.2, 147.2, 135.0, 134.8, 134.2, 131,6 (J_{CF} = 3.1 Hz), 132.0, 130.1 (J_{CF} = 8.9 Hz), 128.6, 123.8, 116.0 (J_{CF} = 21.8 Hz), 114.3, 85.3, 53.7, 39.8; IR (KBr, *v*, cm^{-1}) 2913, 1788, 1735, 1664,

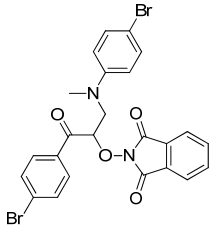
1592, 1498, 969, 810, 709; HRMS (APCI) m/z Calcd. For $C_{24}H_{18}N_2O_4BrFNa$, 519.0332 $[M+Na]^+$, found 519.0340.

*2-((3-((4-Bromophenyl)(methyl)amino)-1-(4-chlorophenyl)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4v**)*



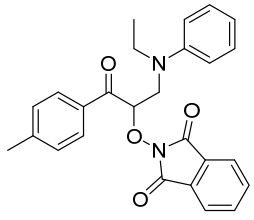
Yellow solid, mp 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.06-7.96 (m, 2H), 7.91-7.66 (m, 4H), 7.53-7.40 (m, 2H), 7.38-7.29 (m, 2H), 6.66 (d, J = 9.2 Hz, 2H), 5.69 (t, J = 6.0 Hz, 1H), 4.06-4.03 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.2, 163.2, 147.0, 140.7, 134.8, 133.5, 132.1, 130.5, 129.1, 128.6, 123.8, 114.5, 85.4, 53.8, 39.9; IR (KBr, v, cm^{-1}) 2911, 1735, 1666, 1587, 1497, 1258, 969, 875, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{18}N_2O_4BrClNa$, 535.0036 $[M+Na]^+$, found 535.0040.

*2-((1-(4-Bromophenyl)-3-((4-bromophenyl)(methyl)amino)-1-oxopropan-2-yl)oxy)isoindoline-1,3-dione (**4w**)*

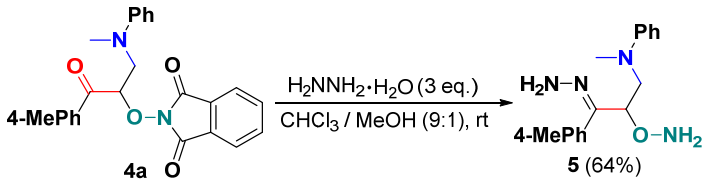


Yellow solid; mp 147-148 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.95-7.88 (m, 2H), 7.85-7.73 (m, 4H), 7.66-7.59 (m, 2H), 7.35-7.26 (m, 3H), 6.66 (d, J = 9.0 Hz, 2H), 5.68 (t, J = 6.0 Hz, 1H), 4.06-4.02 (s, 2H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 194.5, 163.2, 147.0, 134.8, 133.9, 132.1, 132.1, 130.5, 129.6, 128.6, 123.8, 114.4, 109.7, 85.4, 53.8, 39.9; IR (KBr, v, cm^{-1}) 2911, 1735, 1666, 1587, 1497, 1258, 969, 875, 700; HRMS (APCI) m/z Calcd. For $C_{24}H_{18}N_2O_4Br_2Na$, 578.9531 $[M+Na]^+$, found 578.9533.

*2-((3-(Ethyl(phenyl)amino)-1-oxo-1-phenylpropan-2-yl)oxy)isoindoline-1,3-dione (**4x**) (major)*



Yellow solid; mp 99-100 °C; ^{1}H NMR (400 MHz, CDCl; δ, ppm) 7.94–7.71 (m, 7H), 7.27-7.22 (m, 3H), 6.79-6.73 (m, 3H), 5.88-5.85 (m, 1H), 4.09-3.94 (m, 2H), 3.46-3.33 (m, 2H), 2.41 (s, 3H), 1.10 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 195.1, 163.2, 147.0, 145.1, 134.6, 133.0, 129.4, 129.1, 128.7, 123.7, 123.6, 117.1, 113.0, 84.1, 51.6, 46.0, 21.8, 11.7. IR (KBr, v, cm^{-1}): 3060, 2965, 1791, 1736, 1661, 1604, 1506, 1353, 1187, 1080, 971, 876, 702; HRMS (APCI): m/z Calcd. For: $C_{26}H_{24}N_2O_4$, 451.1634 [M+Na], found: 451.1635.

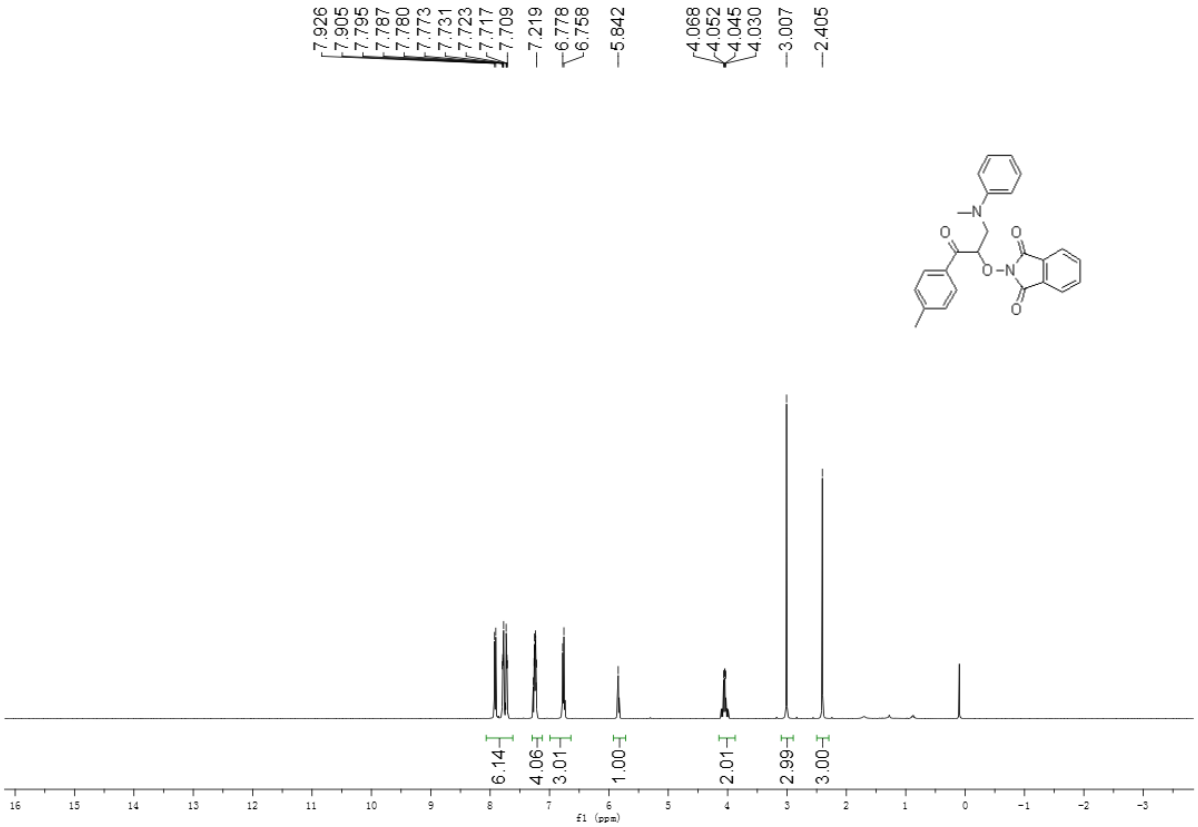


Scheme 2. Further synthetic transformations

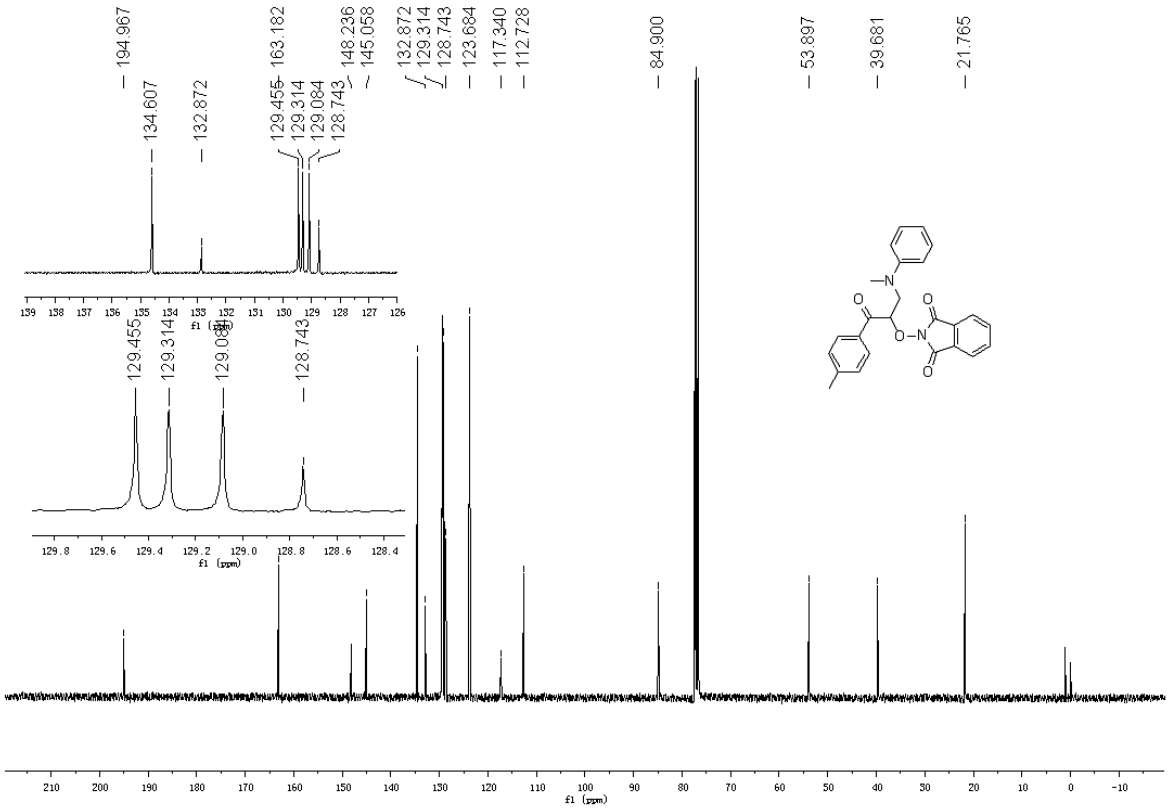
To a solution of **4a** (53 mg, 0.2 mmol) in a mixed solvent of MeOH and $CHCl_3$ (2.0 mL V/V = 9:1), hydrazine monohydrate (80% in water, 0.03 mL, 0.6 mmol) was added. The reaction mixture was stirred at room temperature for about 16 hours. After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography to afford a product **5** as a colorless oil (64%).

^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.93 (d, J = 8.0 Hz, 2H), 7.42-7.18 (m, 5H), 6.82 (s, 2H), 5.65 (s, 1H), 4.06– 3.73 (m, 2H), 3.00 (s, 3H), 2.43 (s, 3H), 1.84 (s, 2H), 1.80 (s, 2H). IR (KBr, v, cm^{-1}) 3350, 3320, 3257, 3107, 1601, 1523, 1432, 1080, 965, 821; HRMS (APCI) m/z Calcd. for $C_{17}H_{21}N_4O$, 297.1715 [M-H]$^-$, found 297.1721.

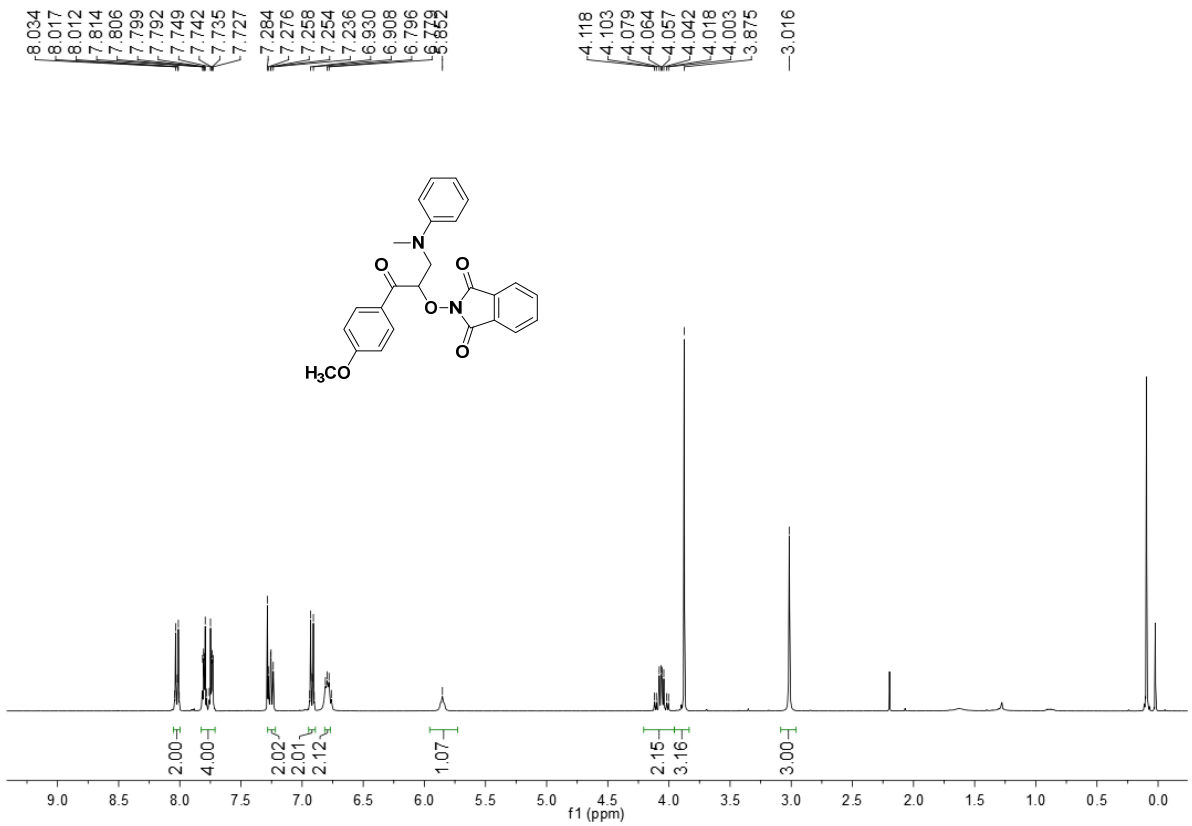
Copies of ^{1}H NMR and ^{13}C NMR of compounds



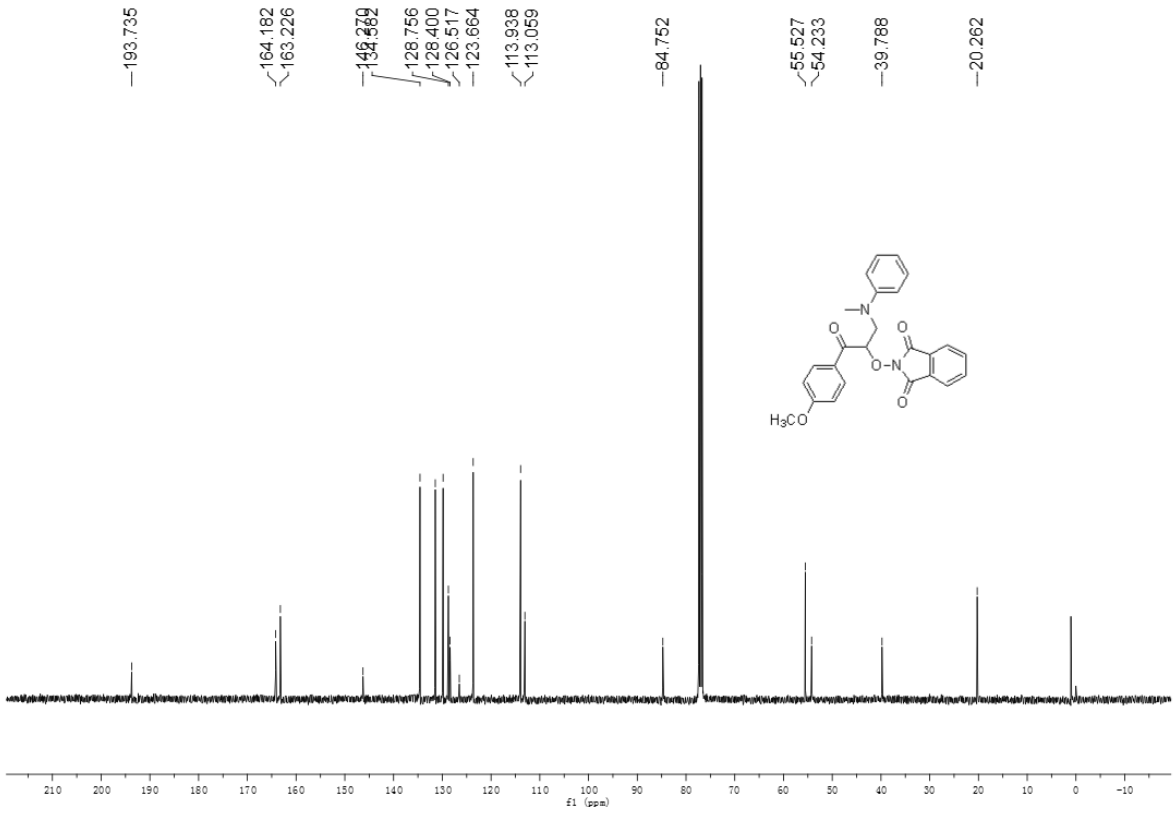
^{1}H NMR Spectrum of Compound 4a



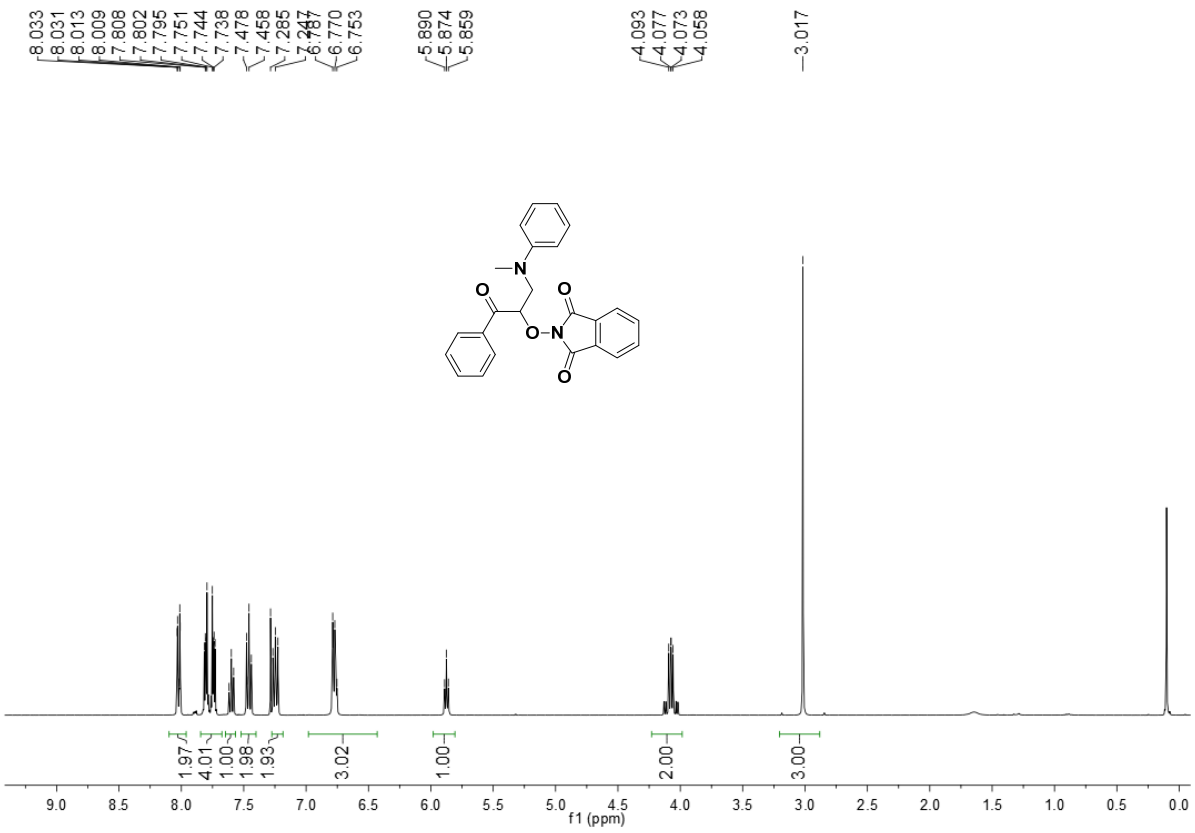
^{13}C NMR Spectrum of Compound 4a



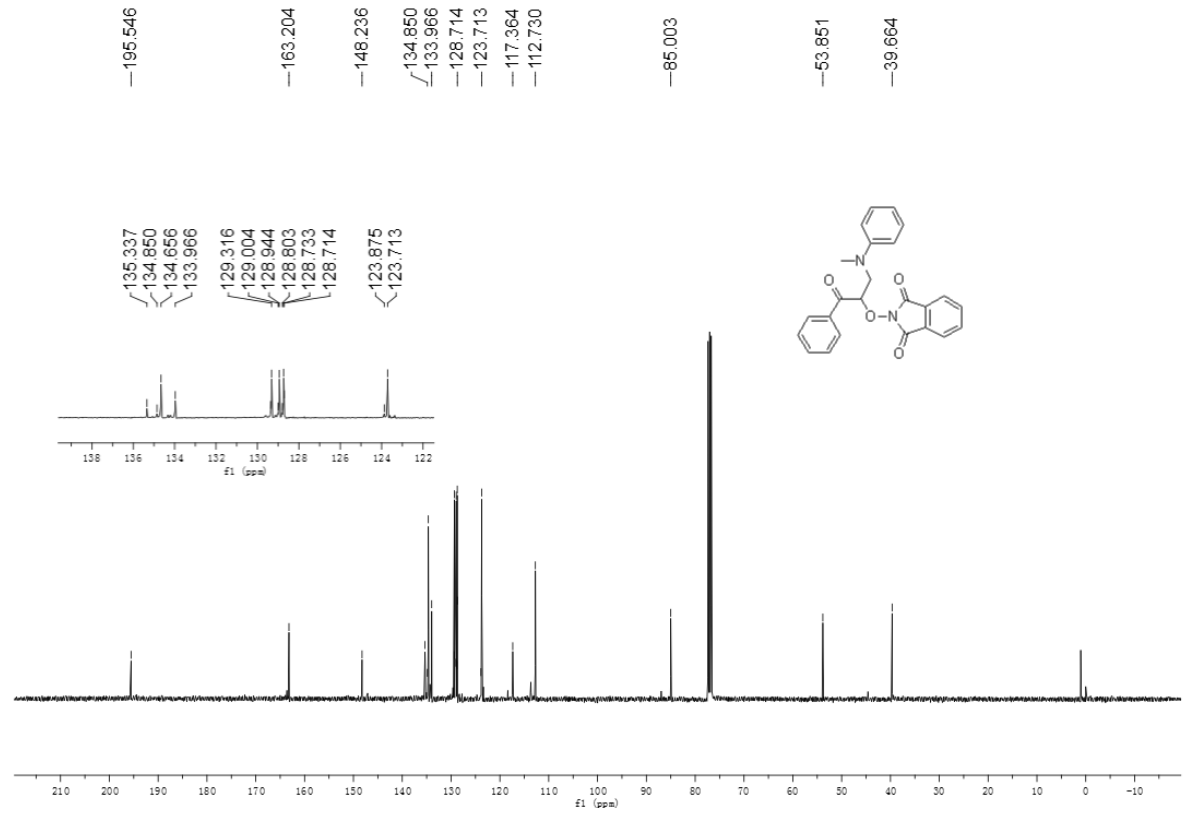
[1]H NMR Spectrum of Compound 4b



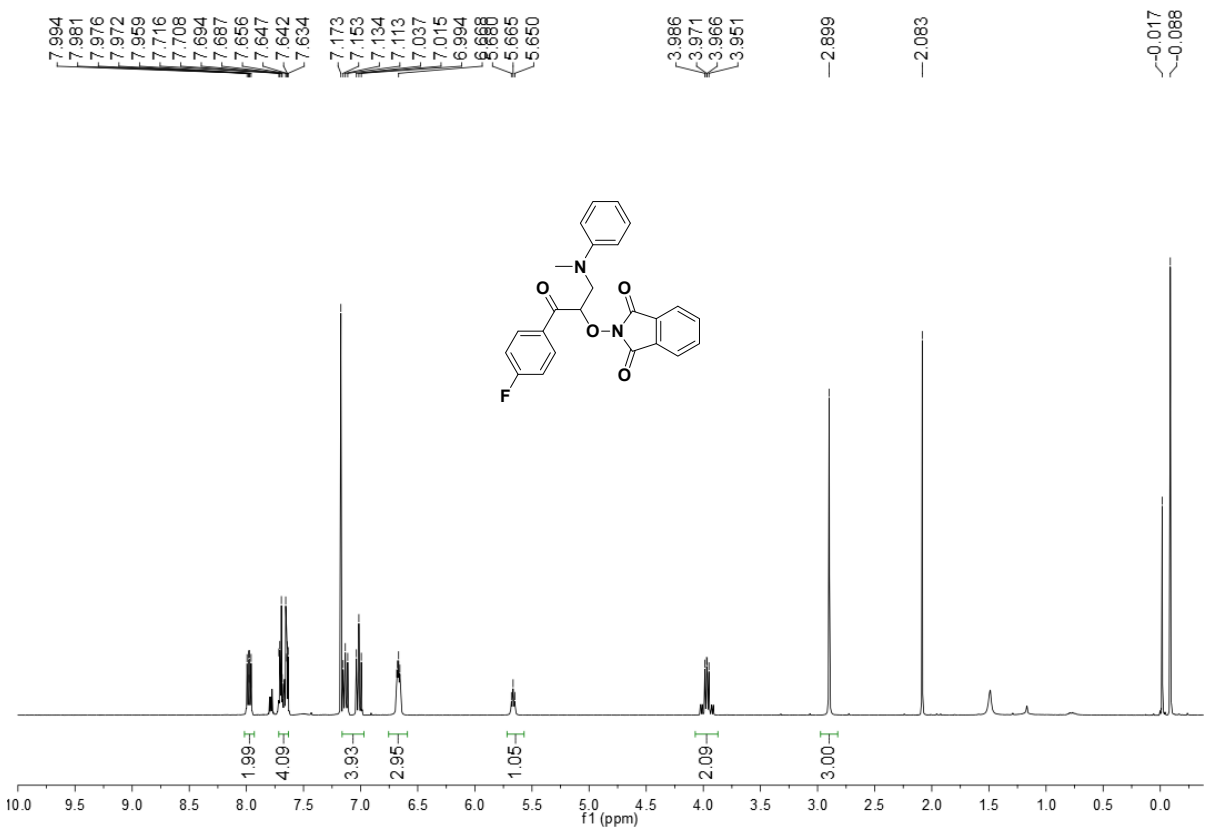
[13]C NMR Spectrum of Compound 4b



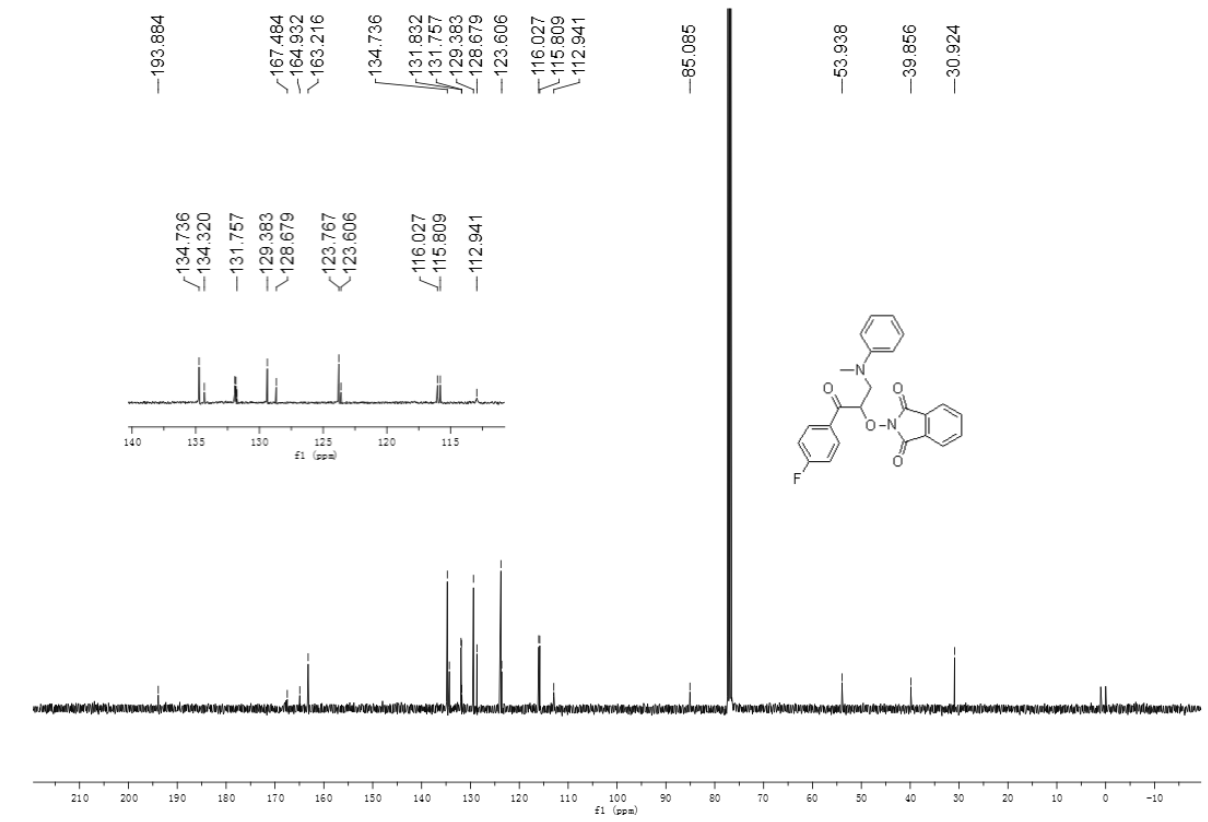
^{1}H NMR Spectrum of Compound 4c



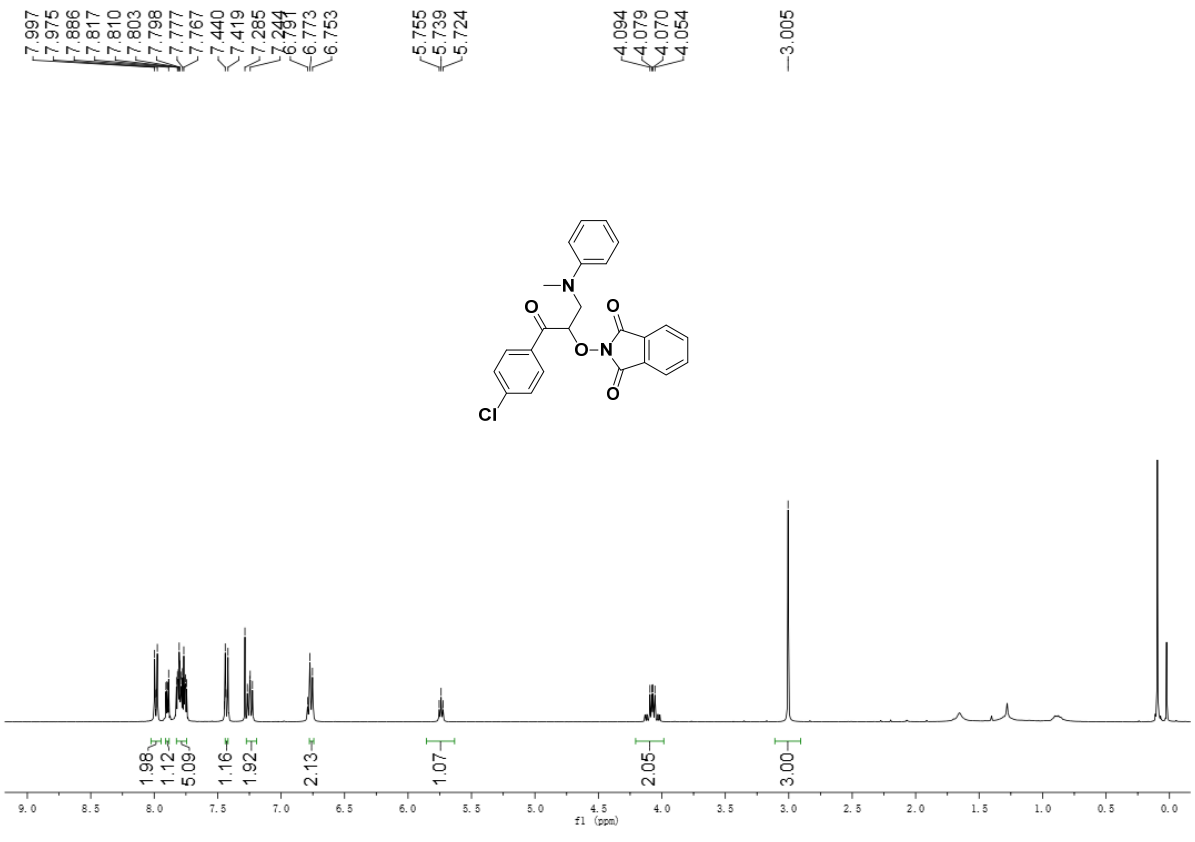
^{13}C NMR Spectrum of Compound 4c



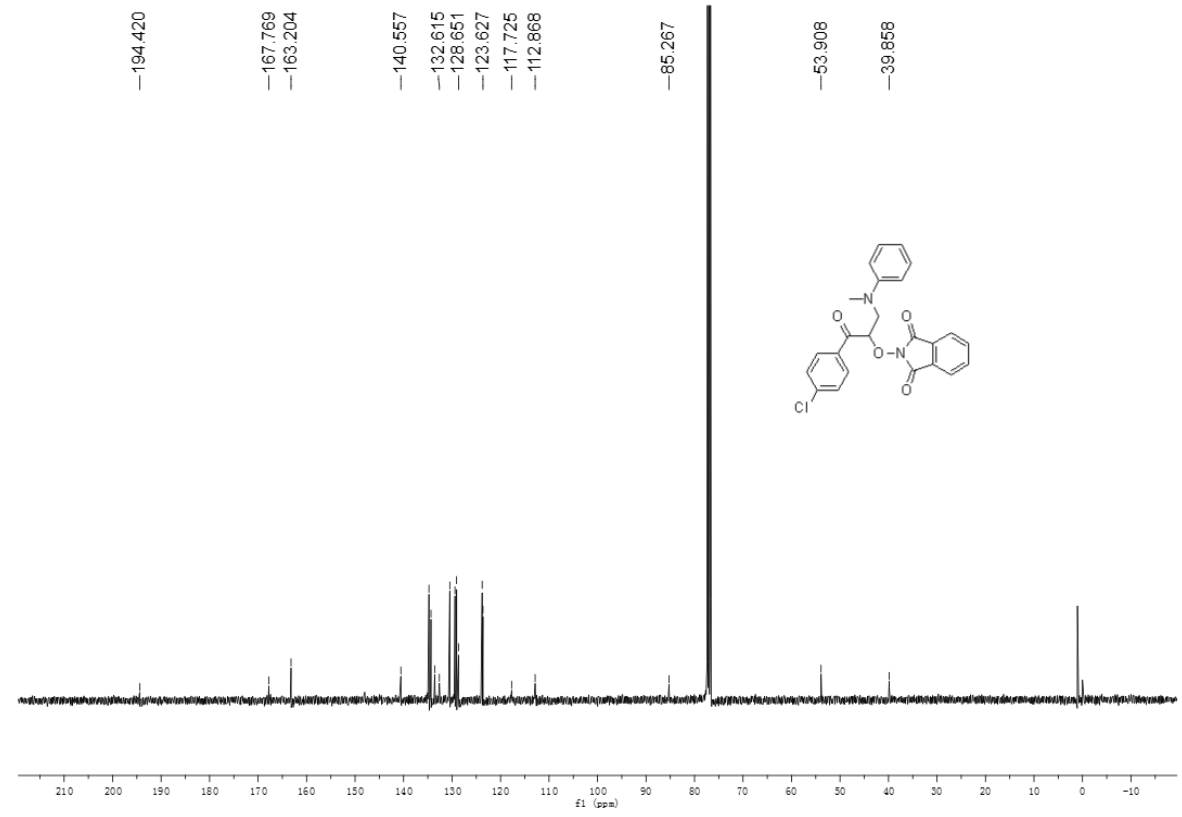
^{1}H NMR Spectrum of Compound 4d



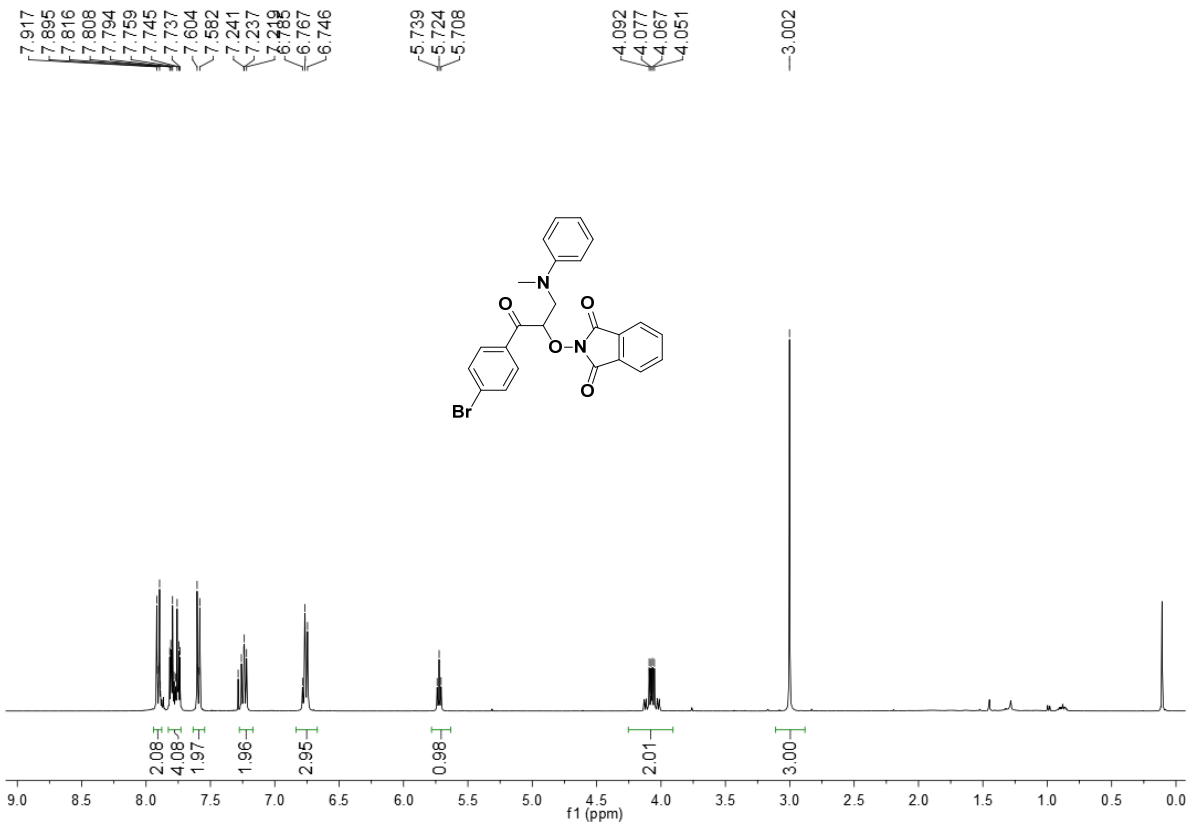
^{13}C NMR Spectrum of Compound 4d



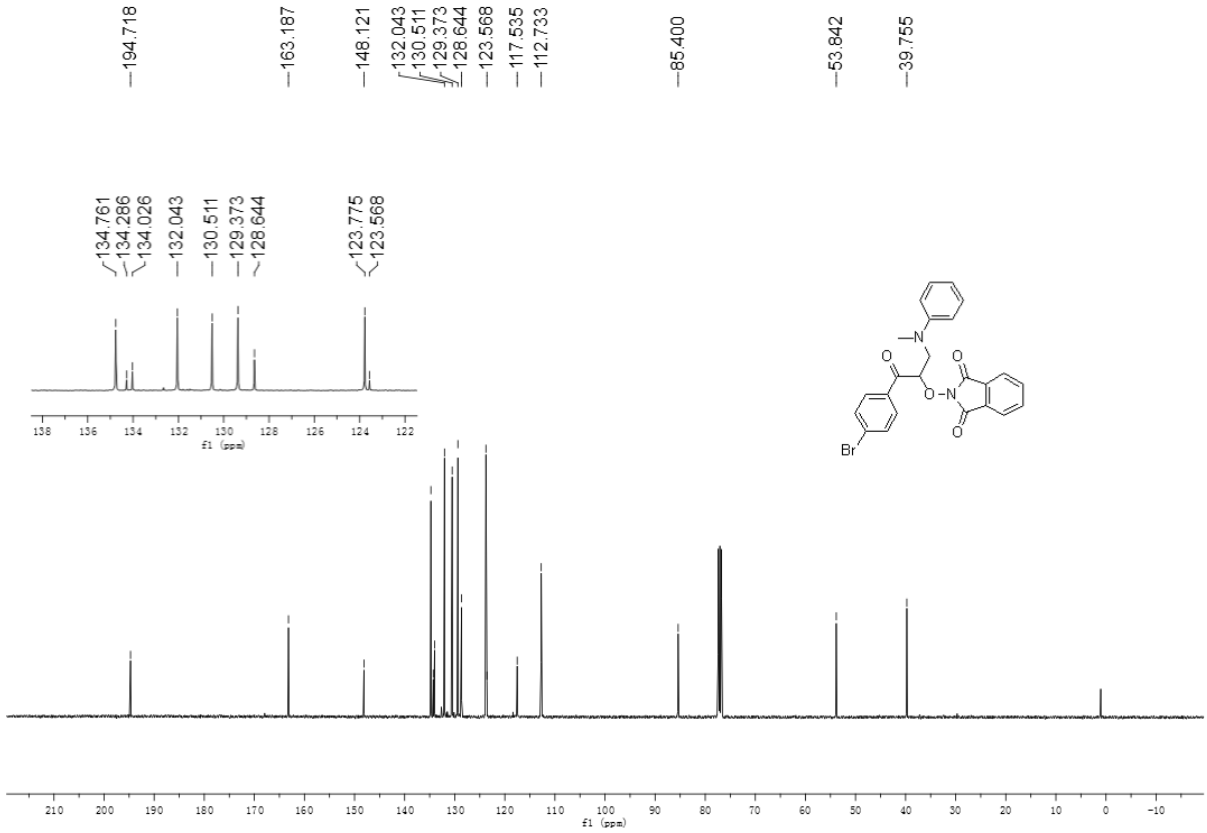
^{1}H NMR Spectrum of Compound 4e



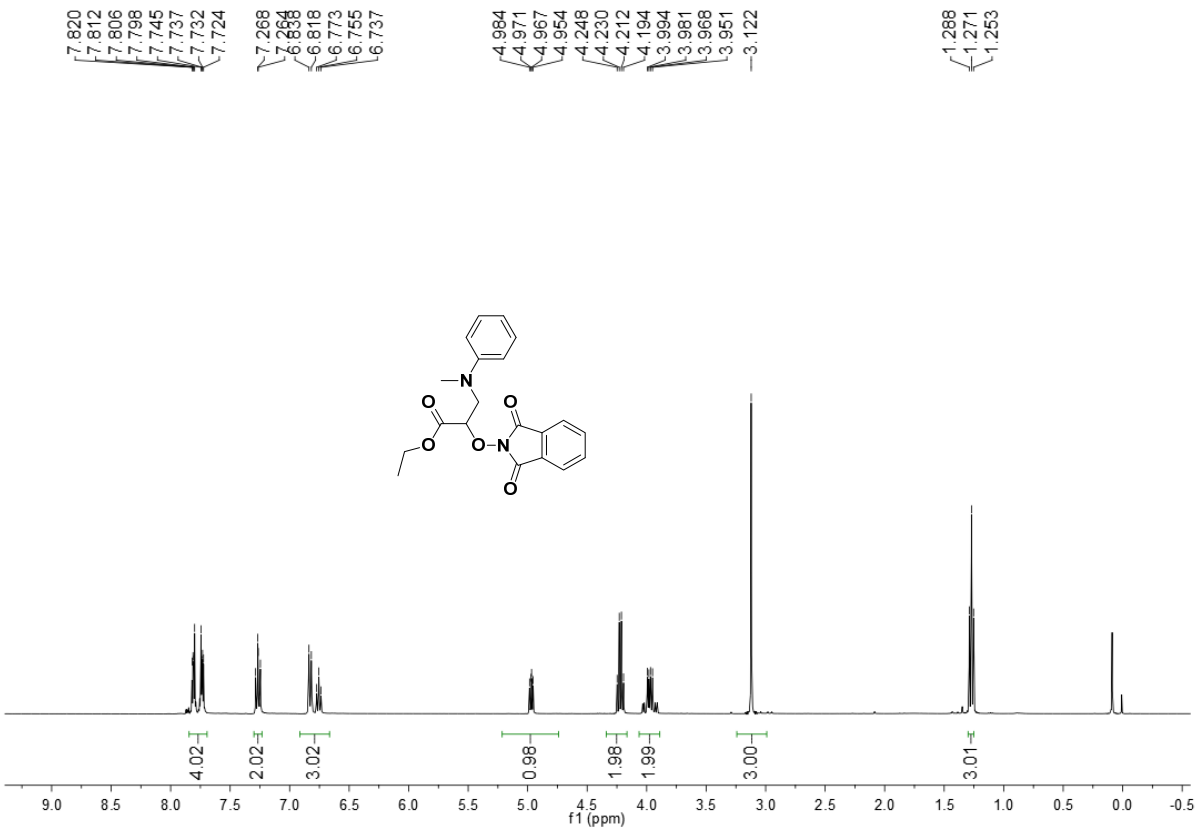
^{13}C NMR Spectrum of Compound 4e



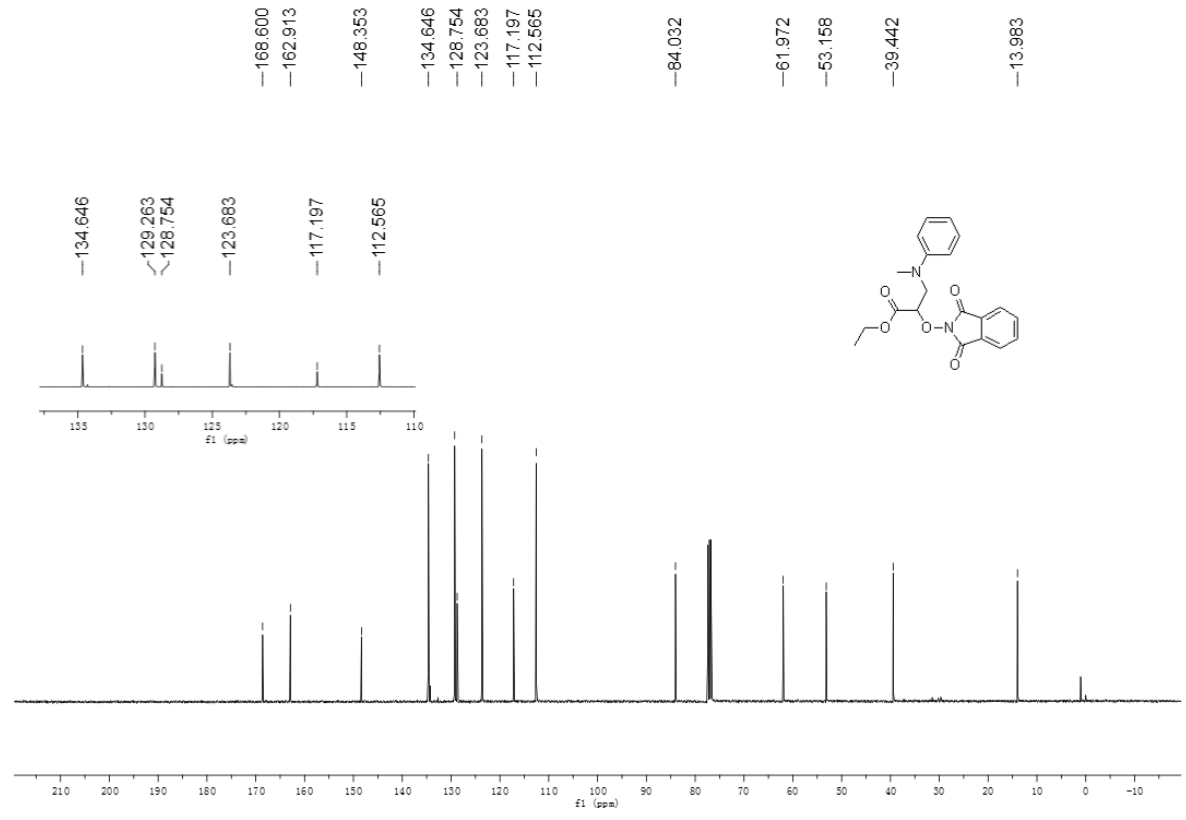
^{1}H NMR Spectrum of Compound 4f



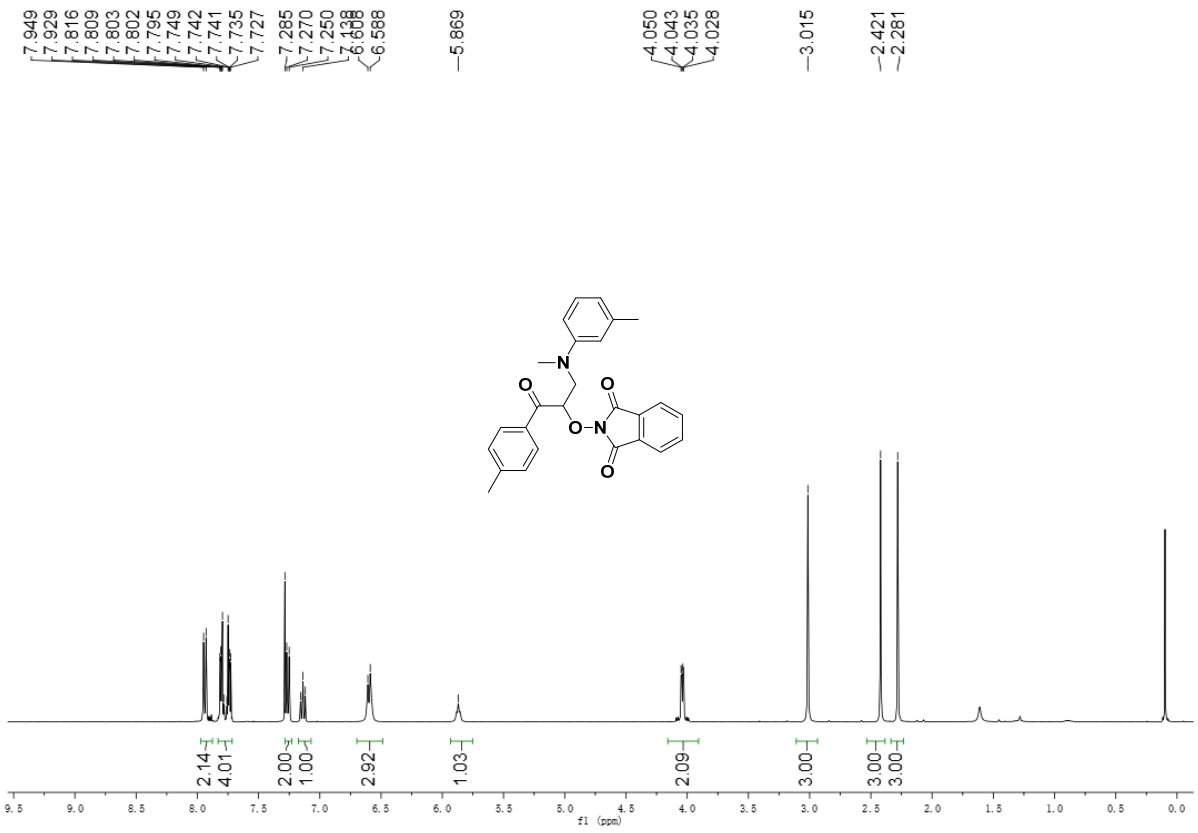
^{13}C NMR Spectrum of Compound 4f



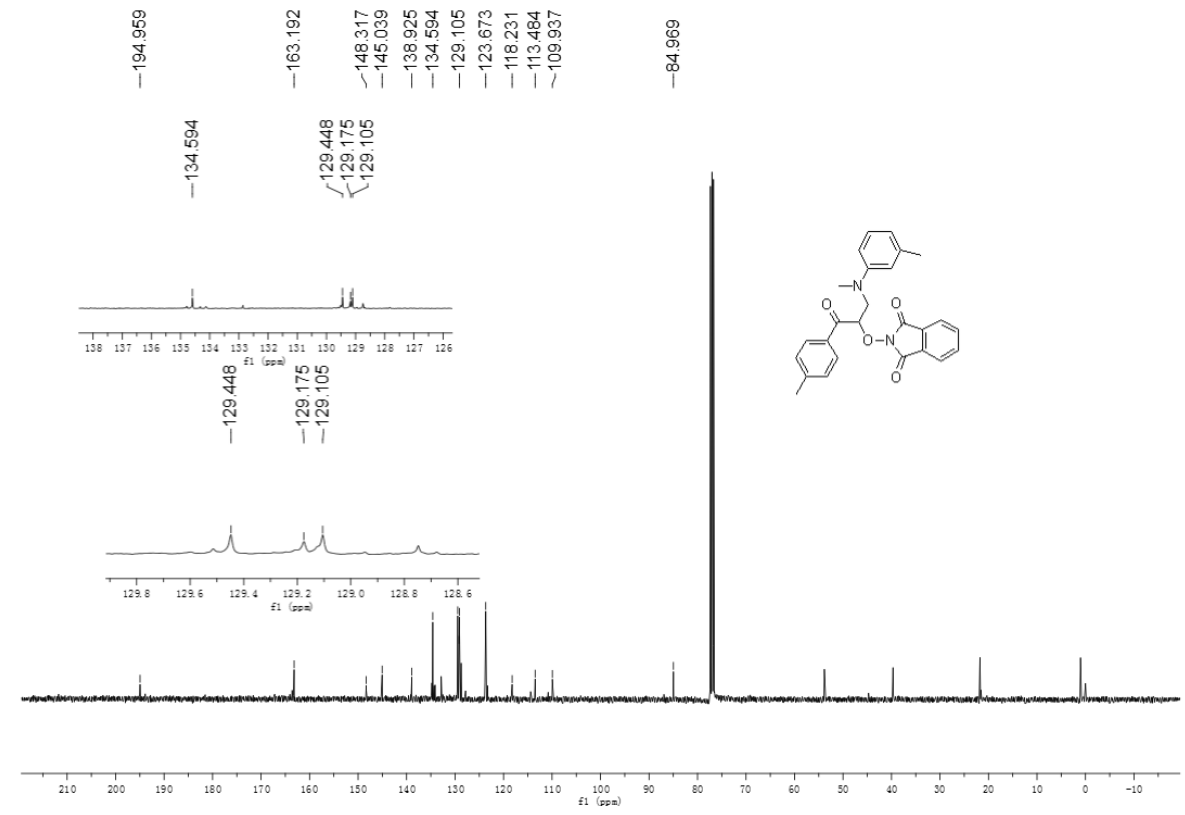
[1]H NMR Spectrum of Compound 4g



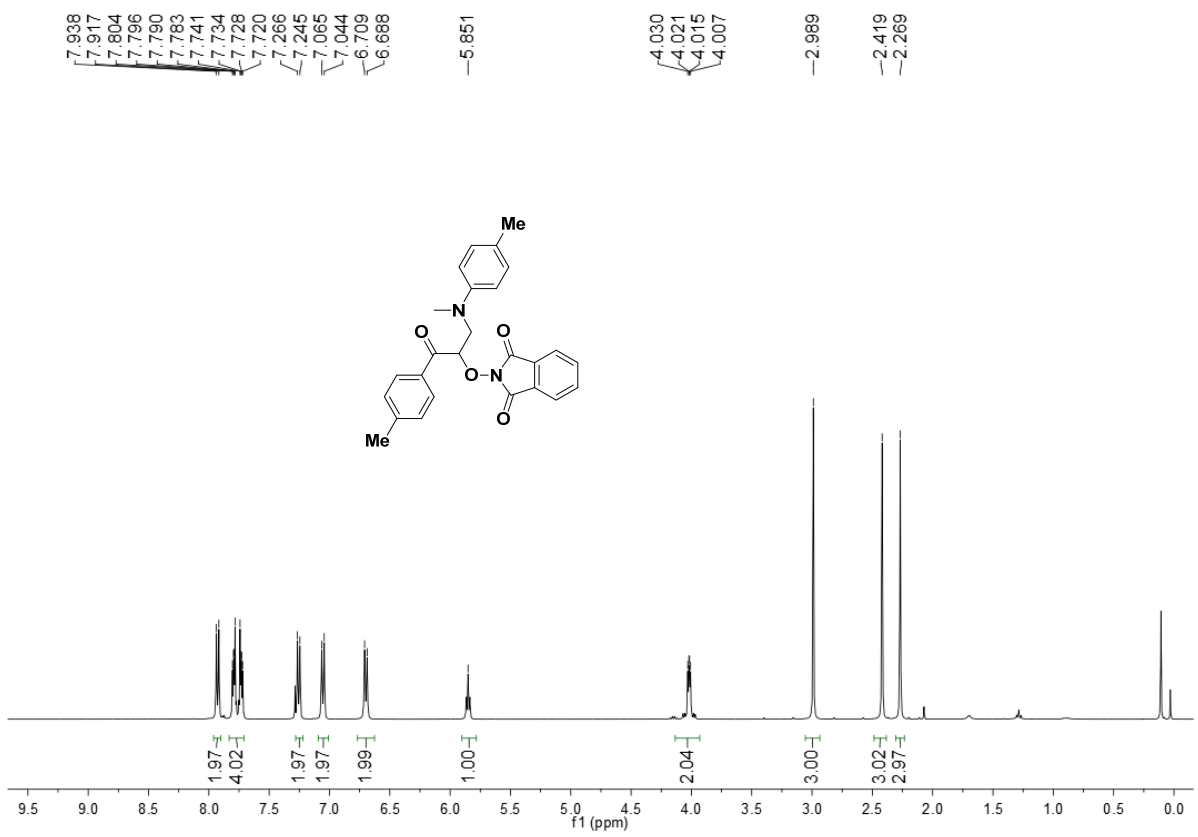
[13]C NMR Spectrum of Compound 4g



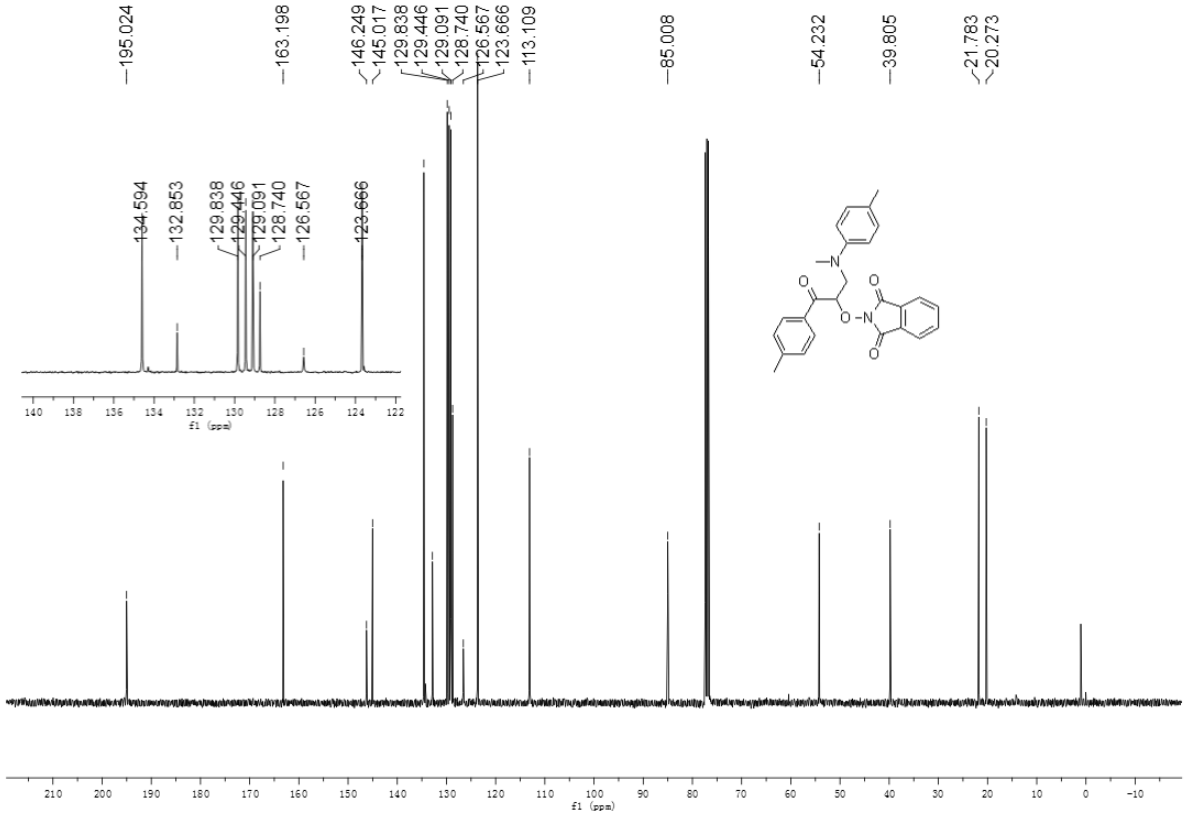
^{1}H NMR Spectrum of Compound 4h



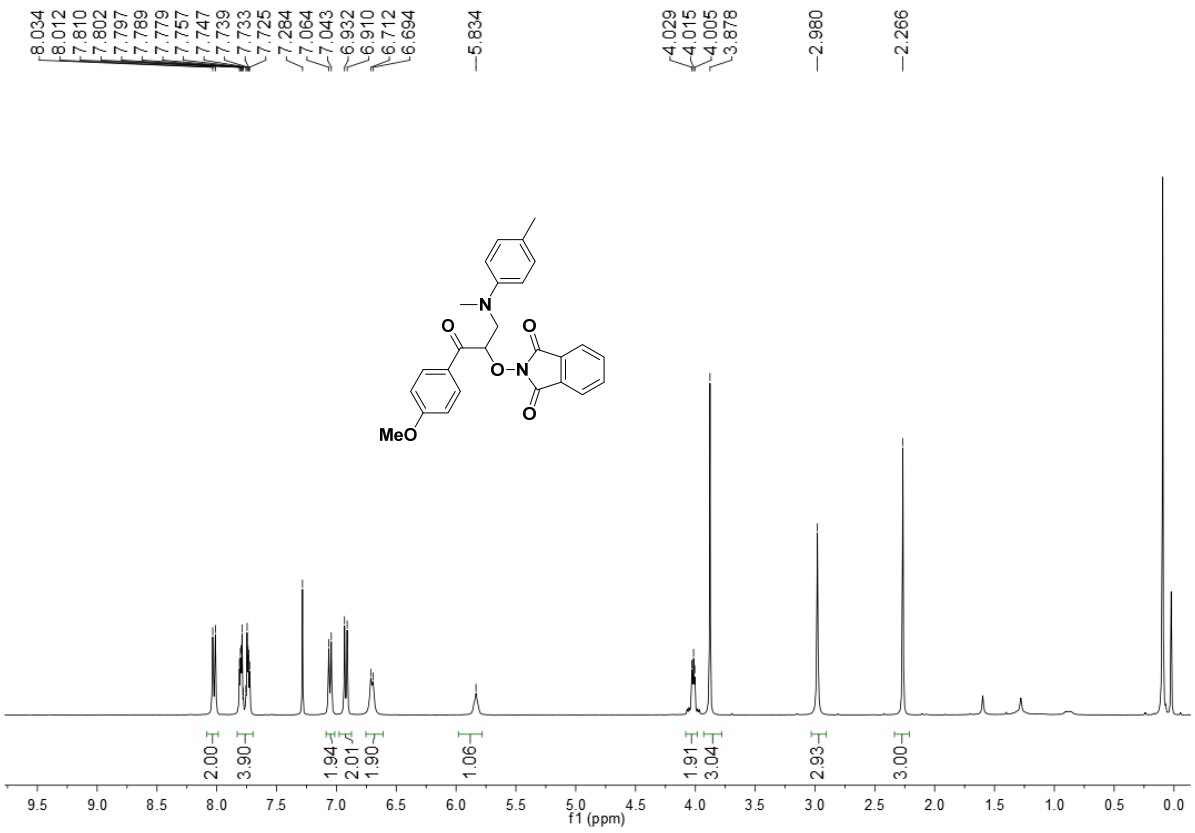
^{13}C NMR Spectrum of Compound 4h



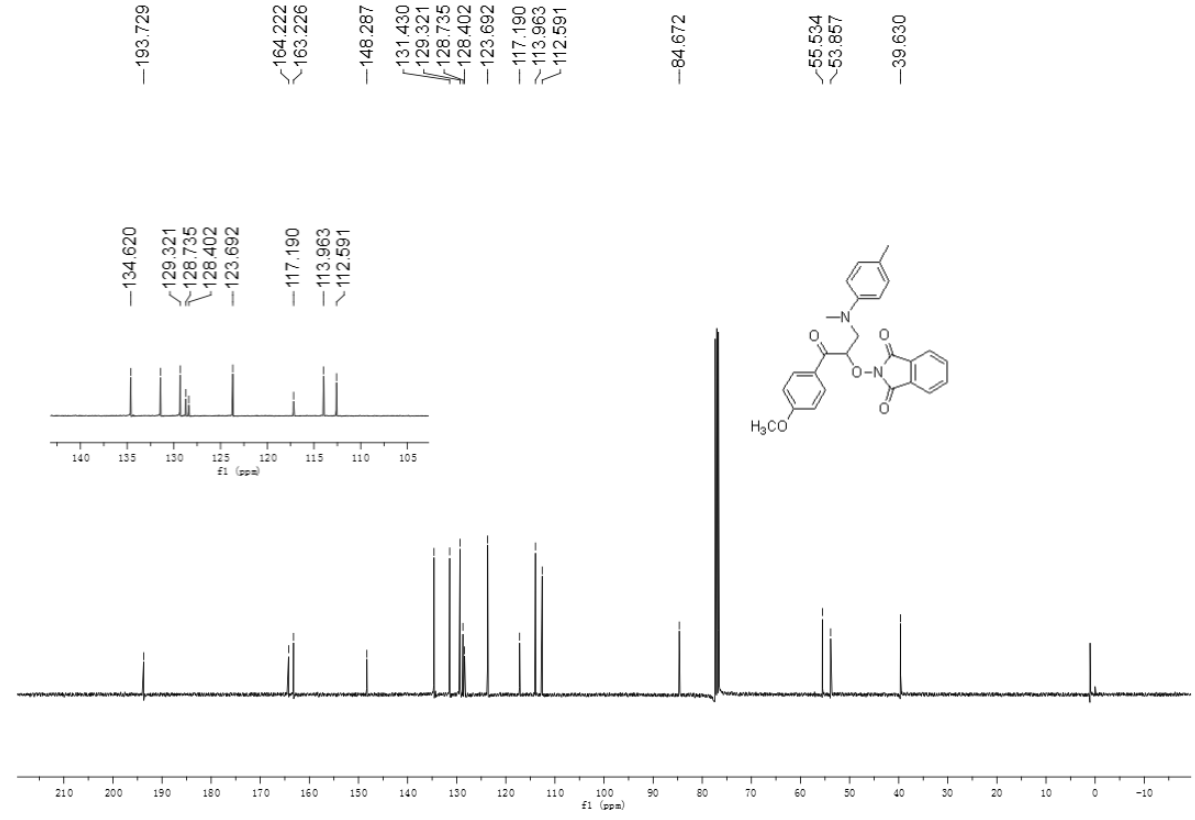
^{1}H NMR Spectrum of Compound 4i



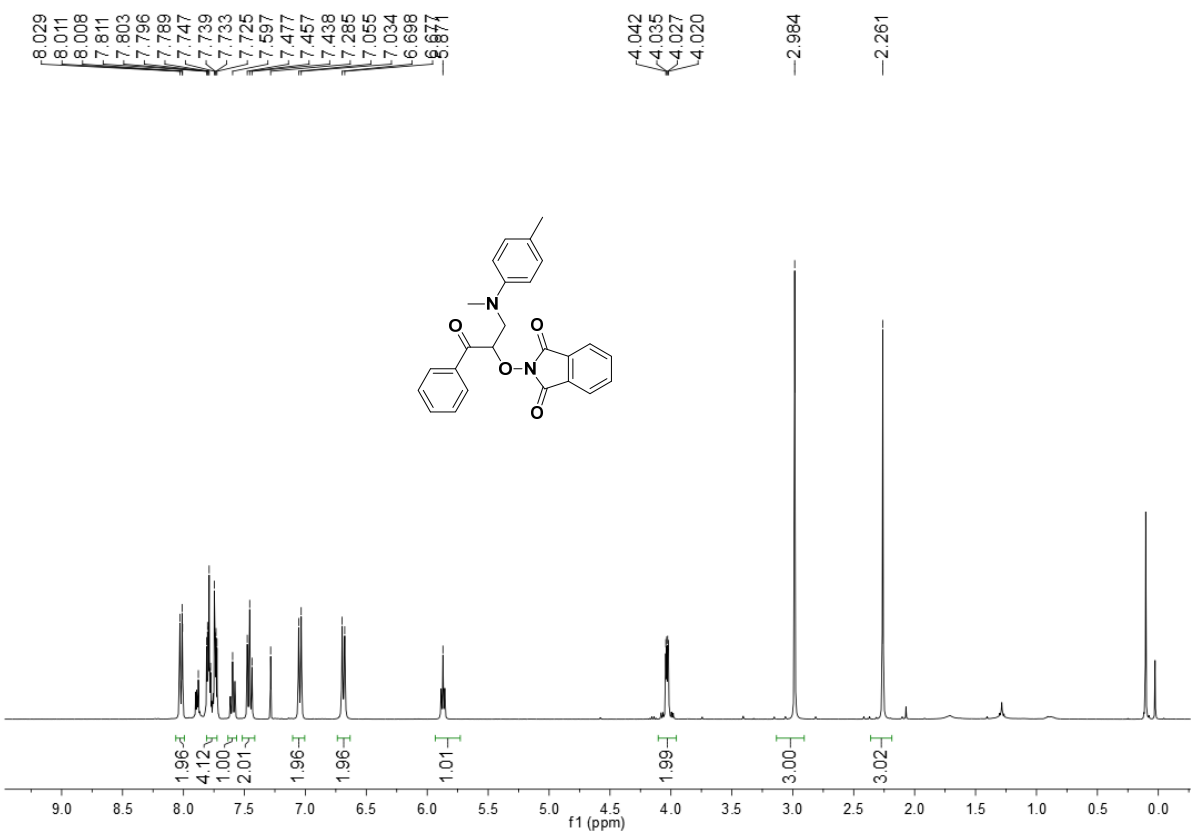
^{13}C NMR Spectrum of Compound 4i



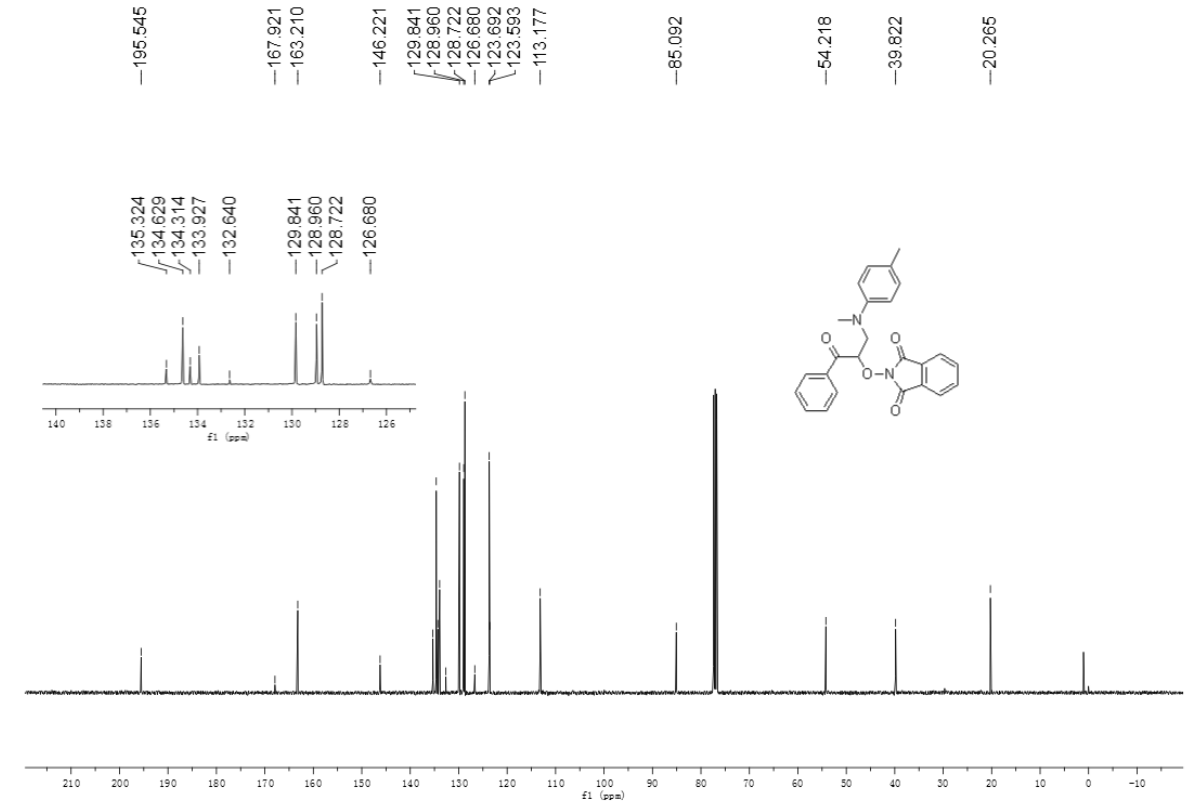
^{1}H NMR Spectrum of Compound 4j



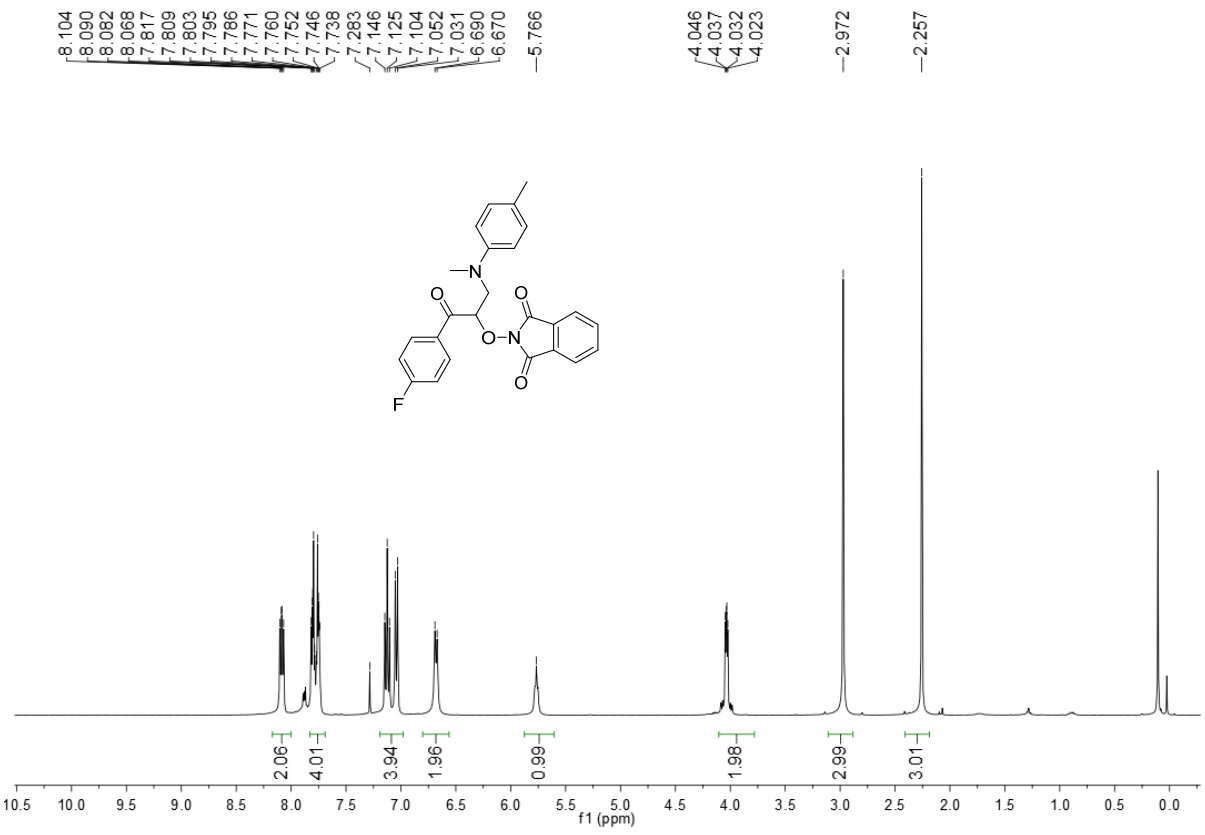
^{13}C NMR Spectrum of Compound 4j



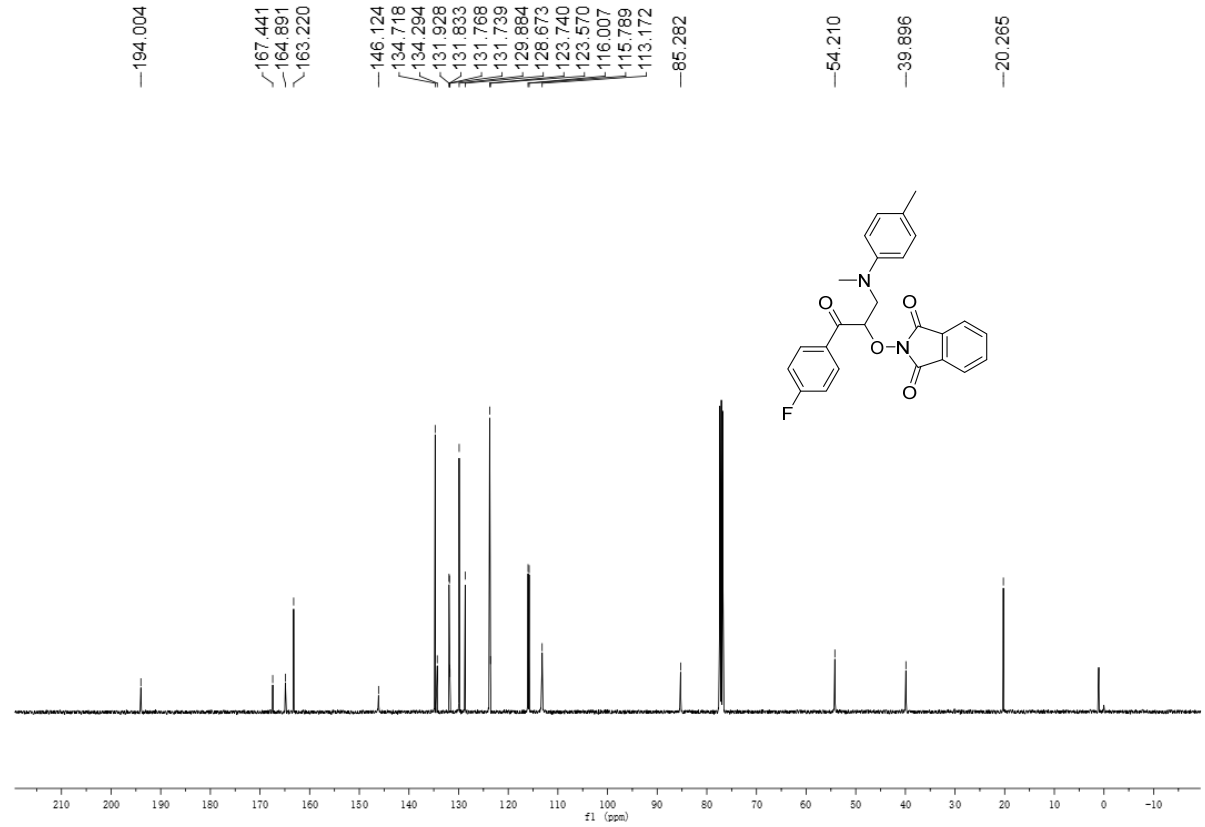
^{1}H NMR Spectrum of Compound 4k



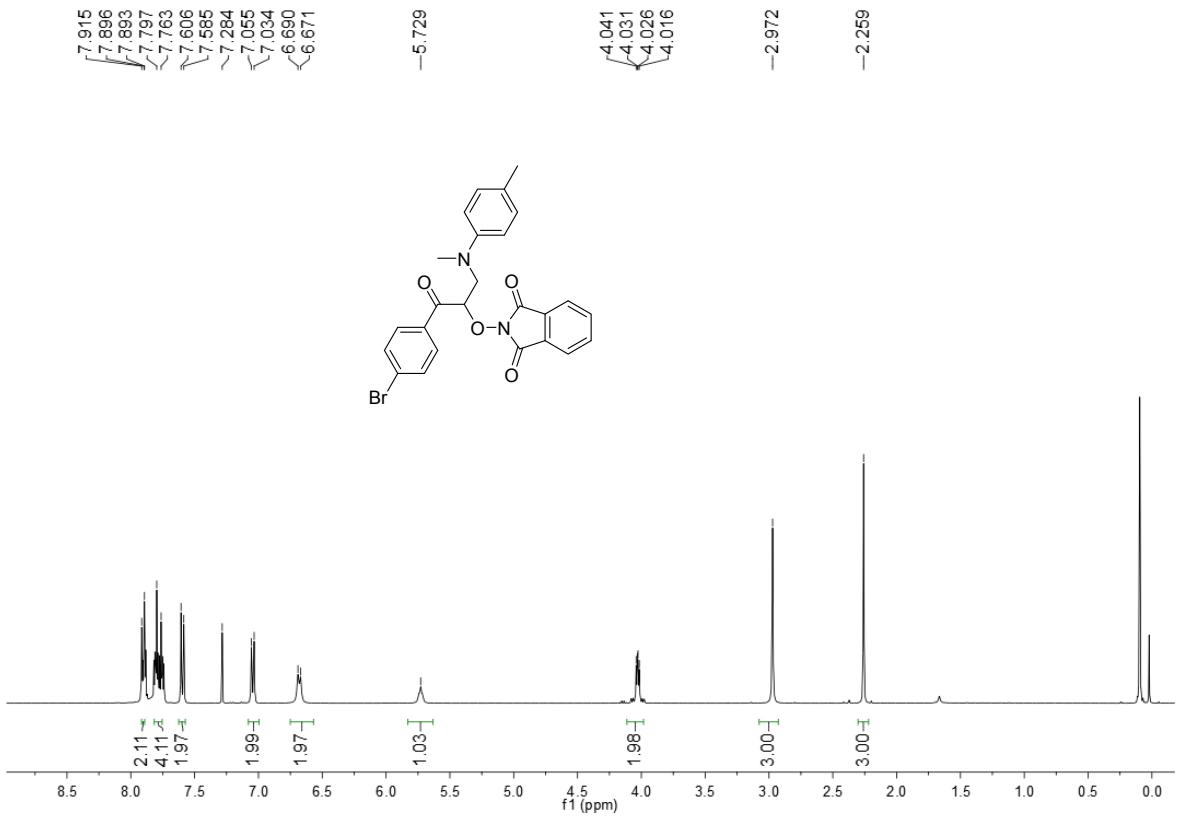
^{13}C NMR Spectrum of Compound 4k



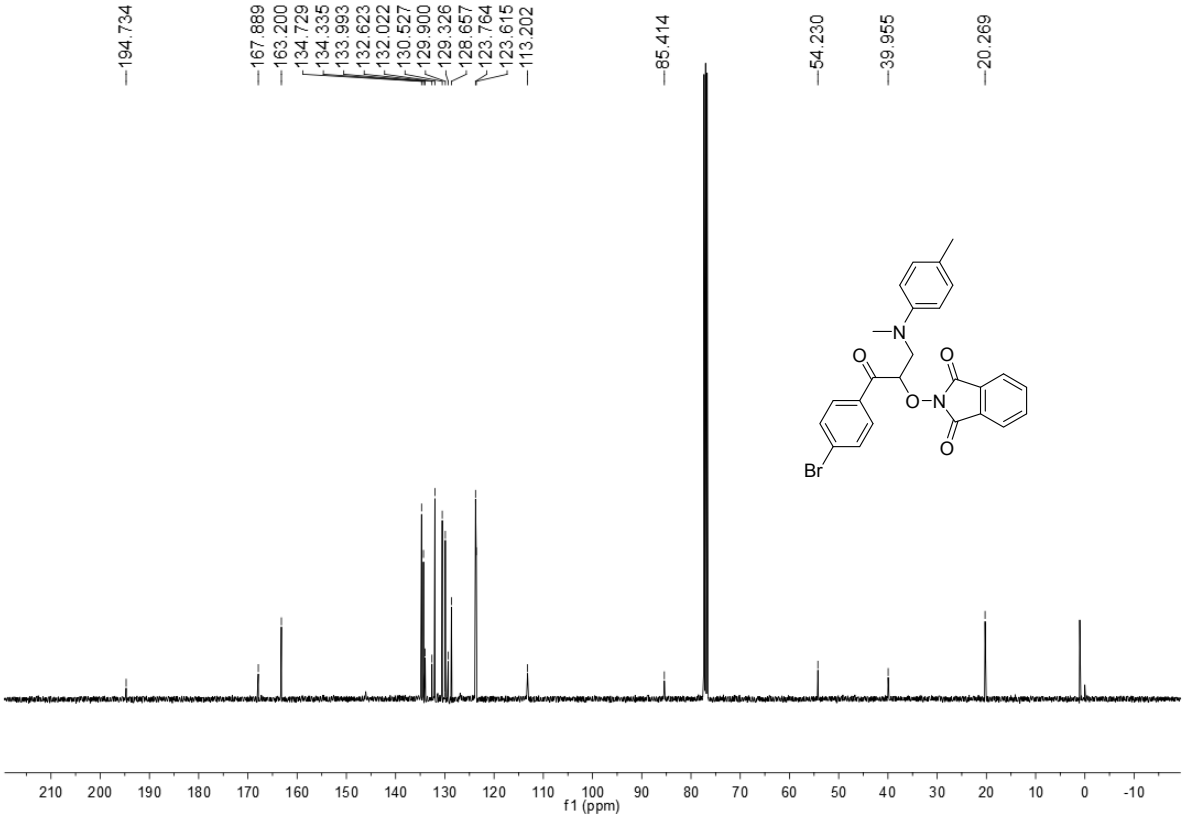
^{1}H NMR Spectrum of Compound 4l



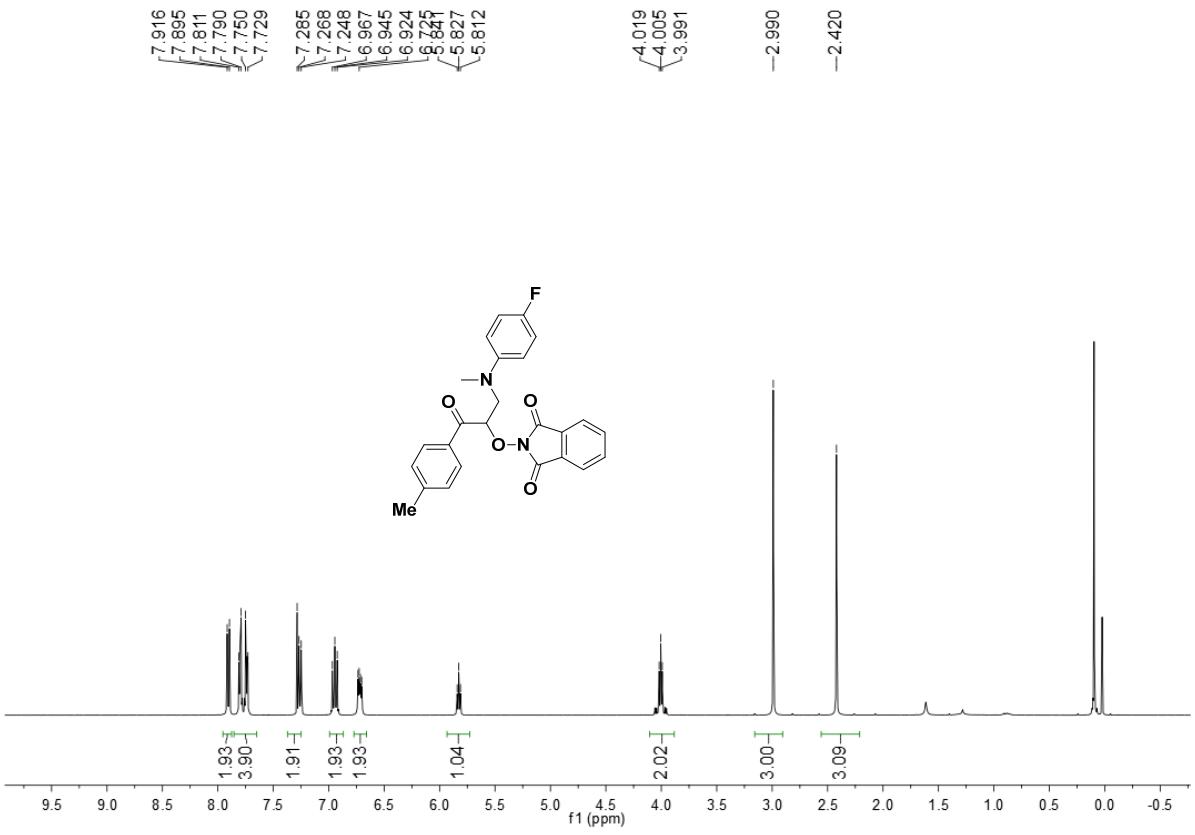
^{13}C NMR Spectrum of Compound 4l



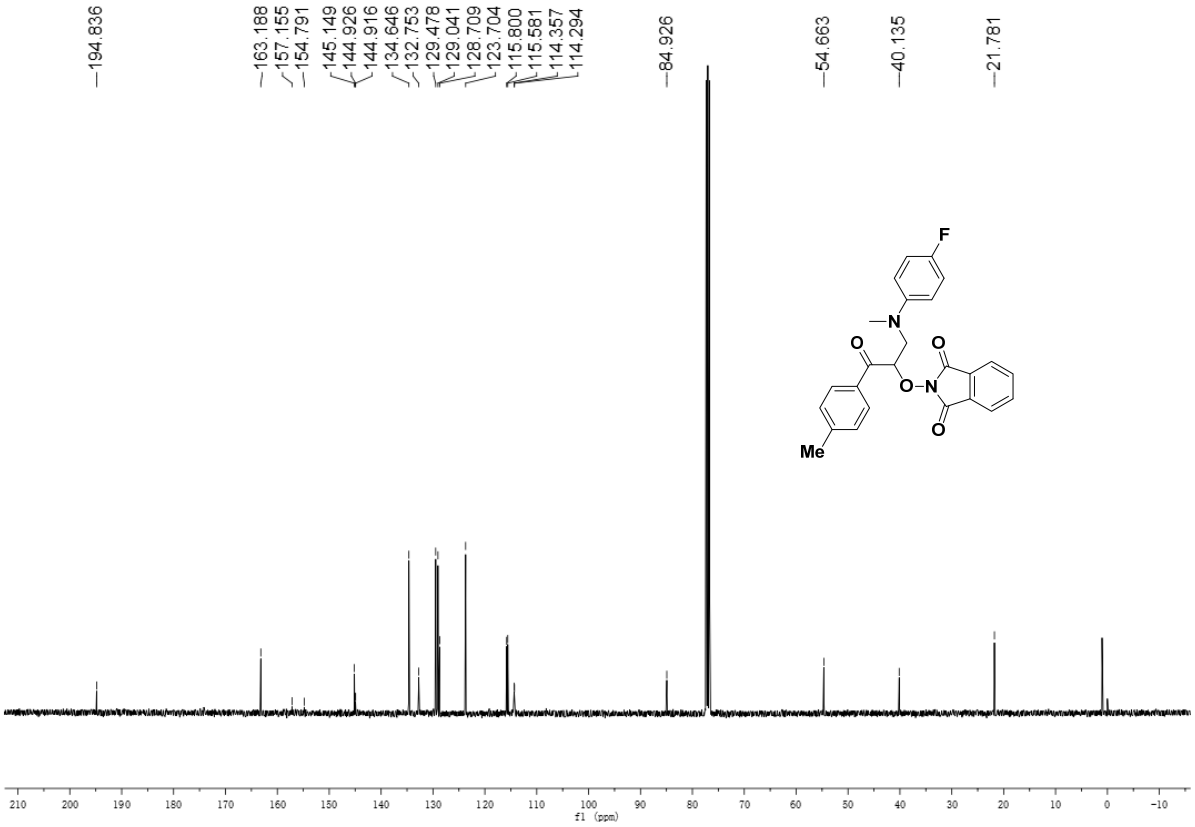
^{1}H NMR Spectrum of Compound 4m



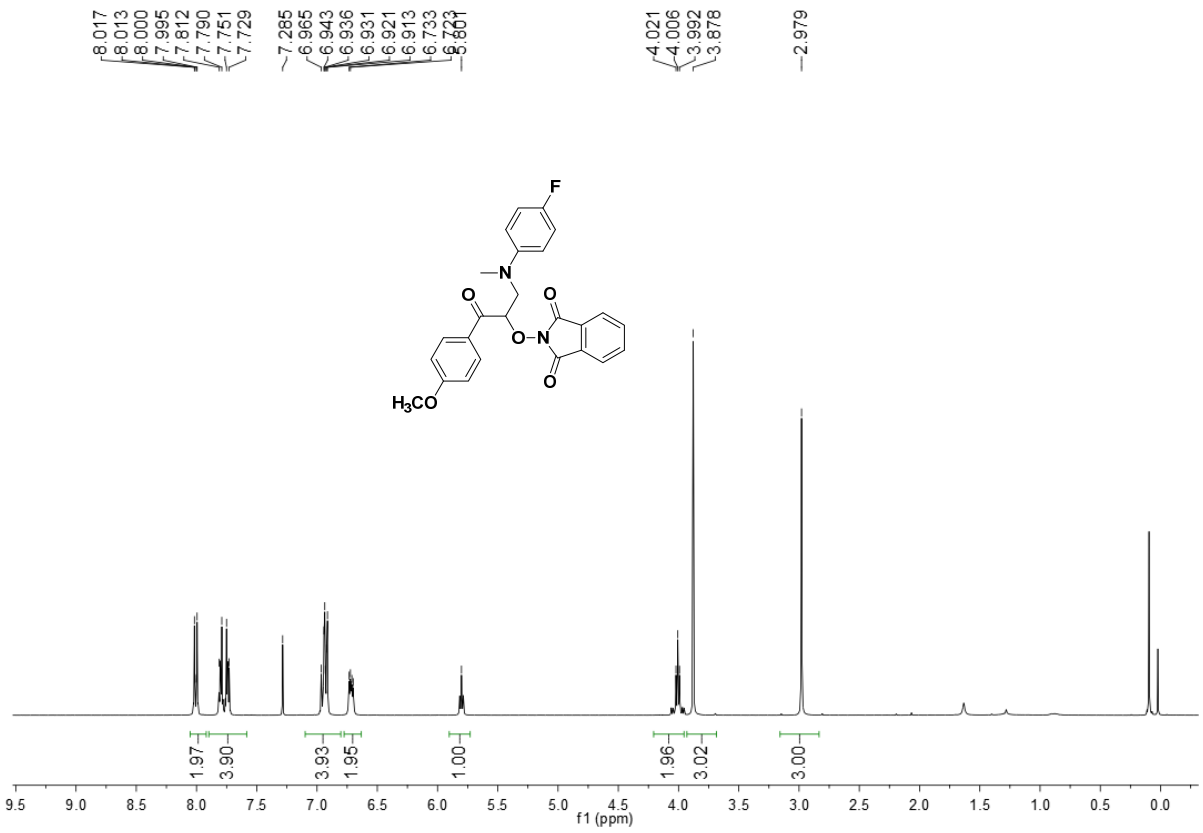
^{13}C NMR Spectrum of Compound 4m



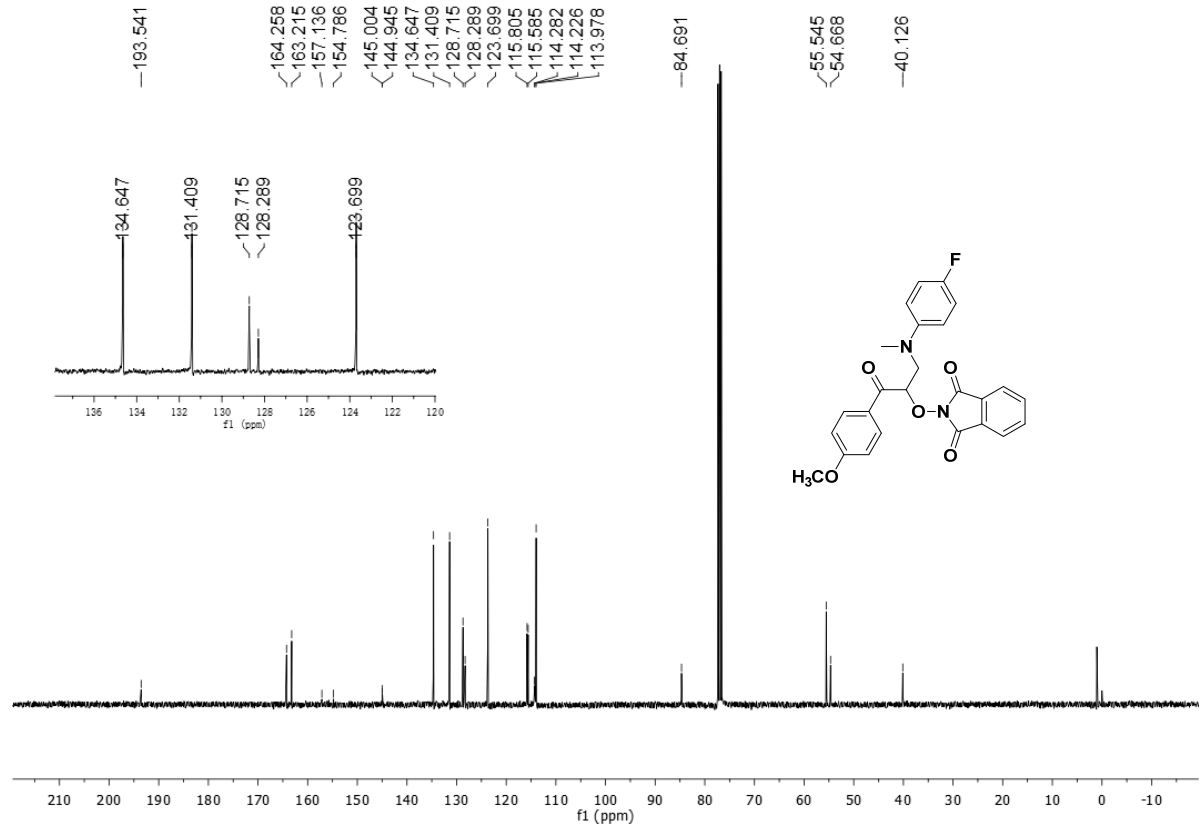
^{1}H NMR Spectrum of Compound 4n



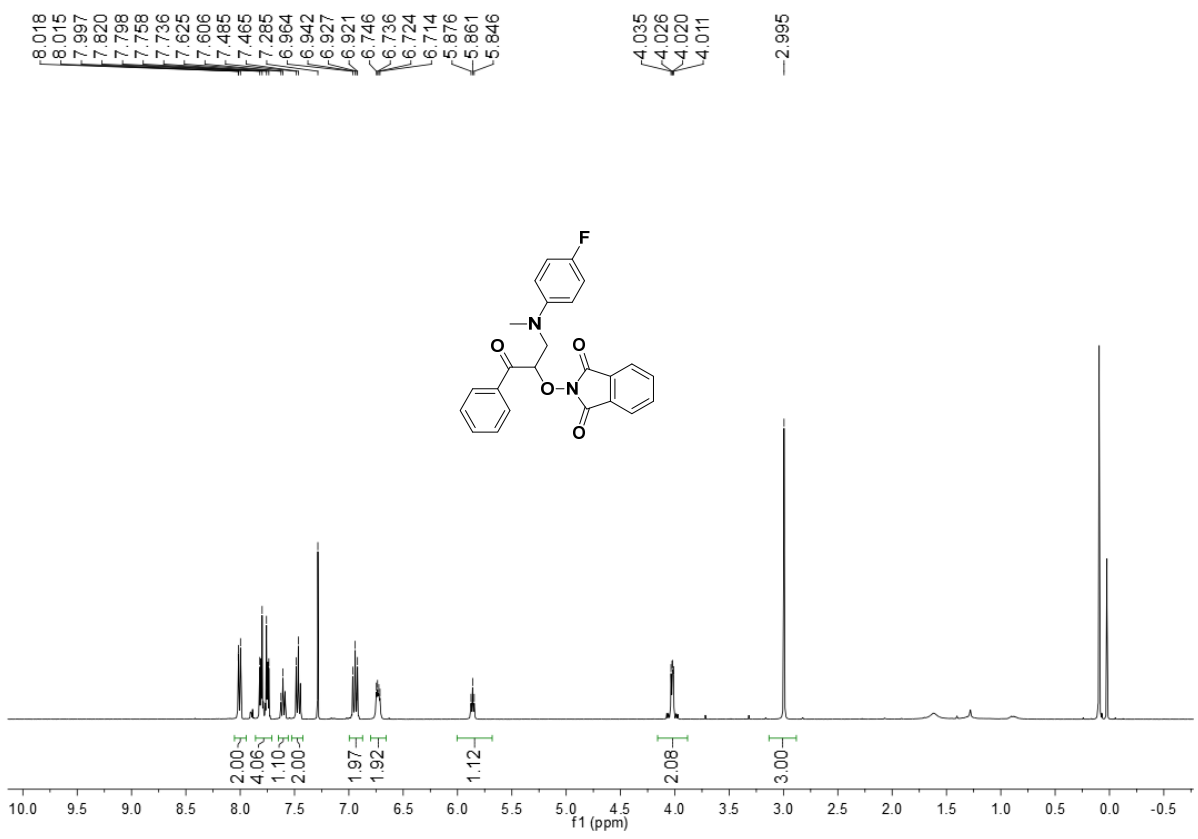
^{13}C NMR Spectrum of Compound 4n



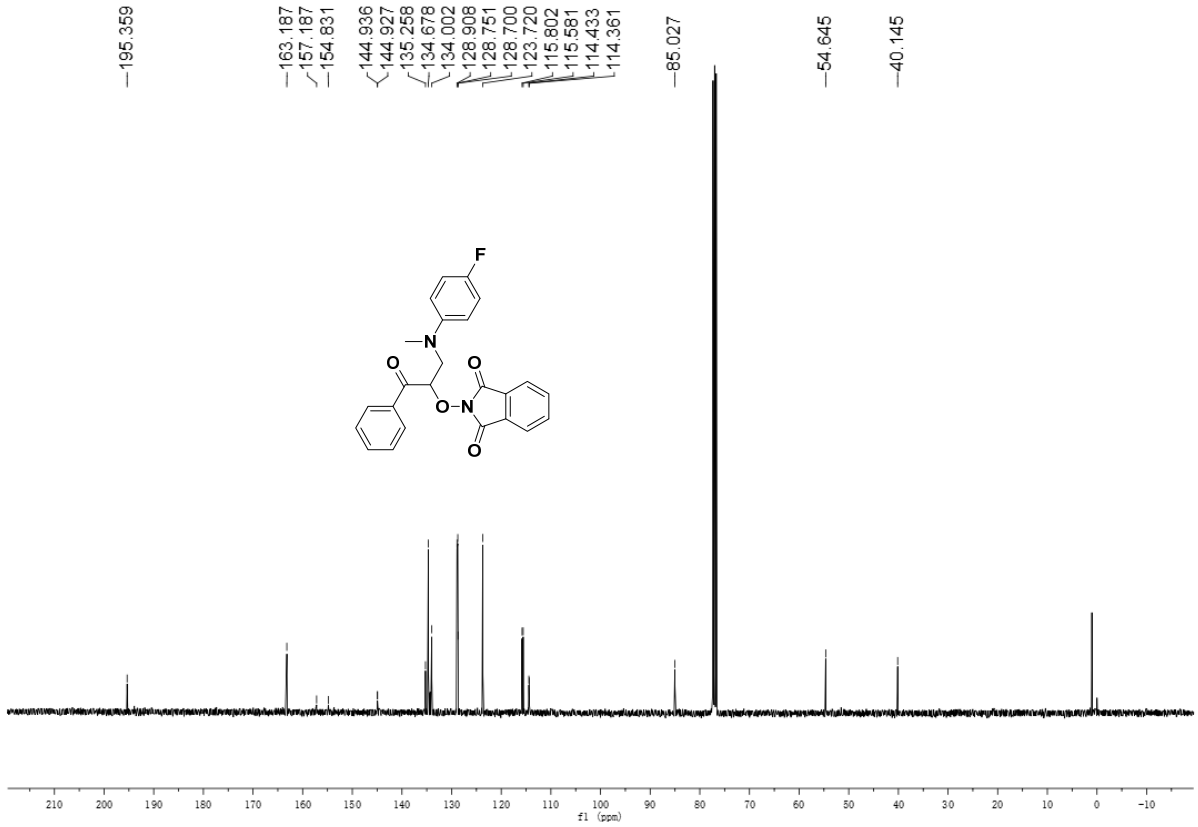
^{1}H NMR Spectrum of Compound 4o



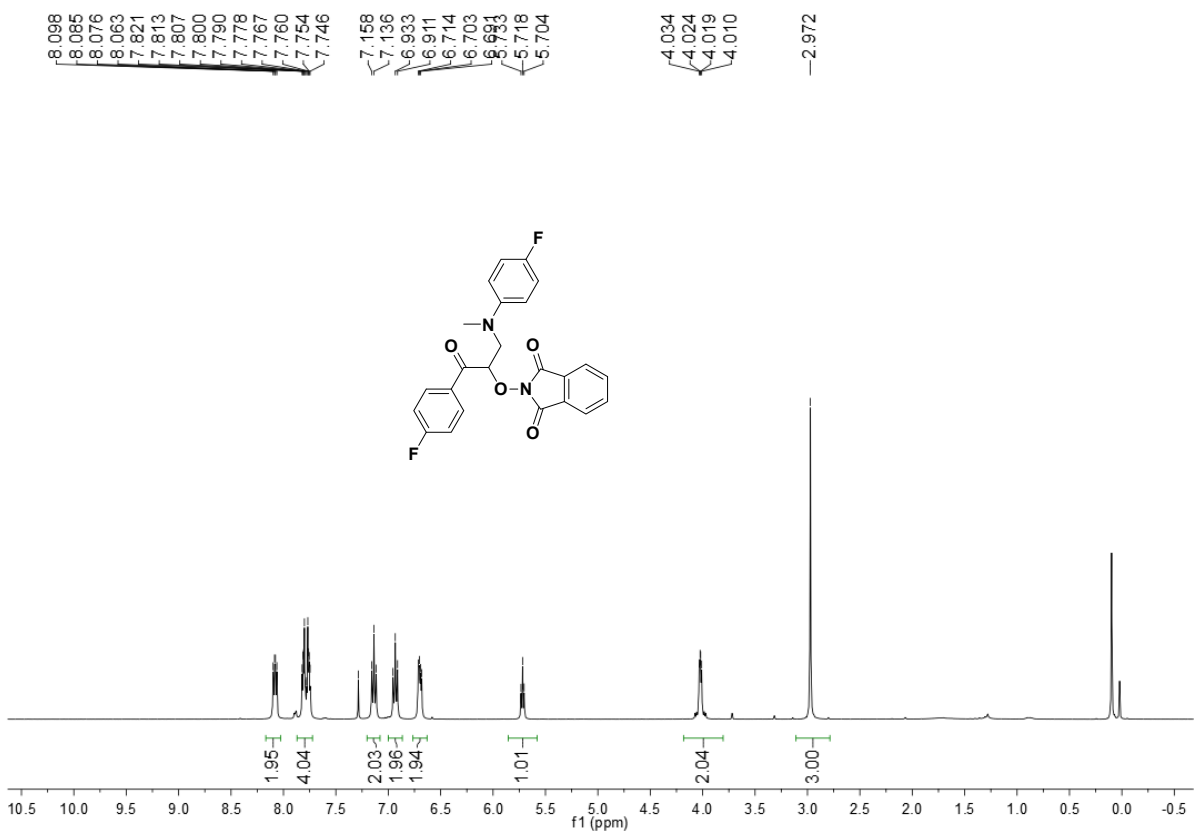
^{13}C NMR Spectrum of Compound 4o



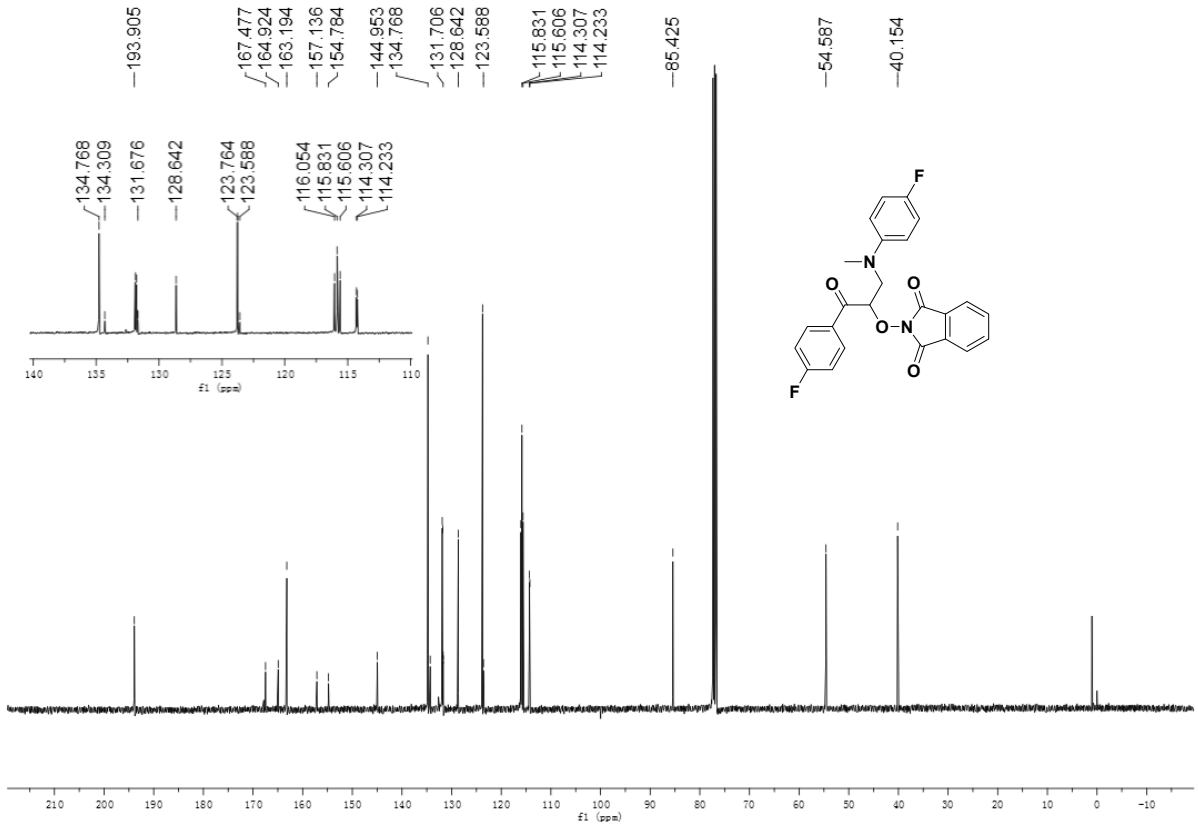
^{1}H NMR Spectrum of Compound 4p



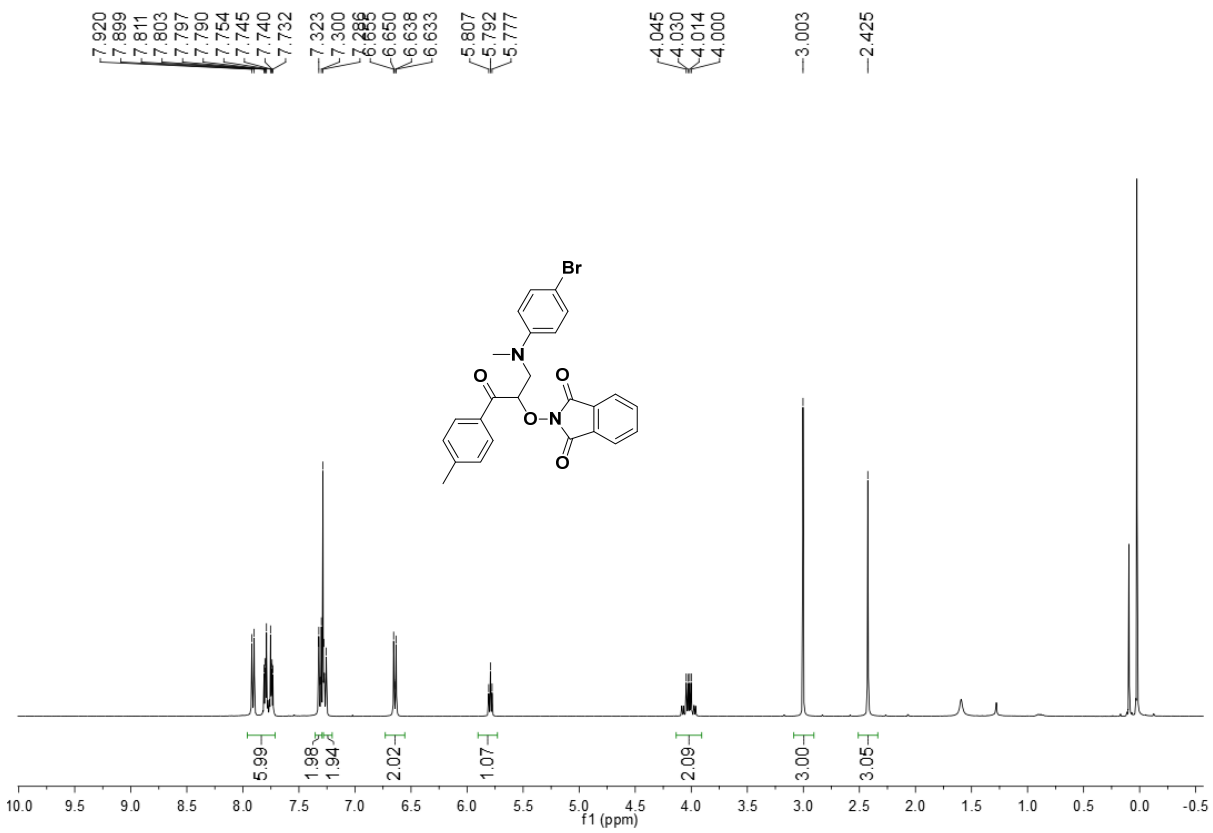
^{13}C NMR Spectrum of Compound 4p



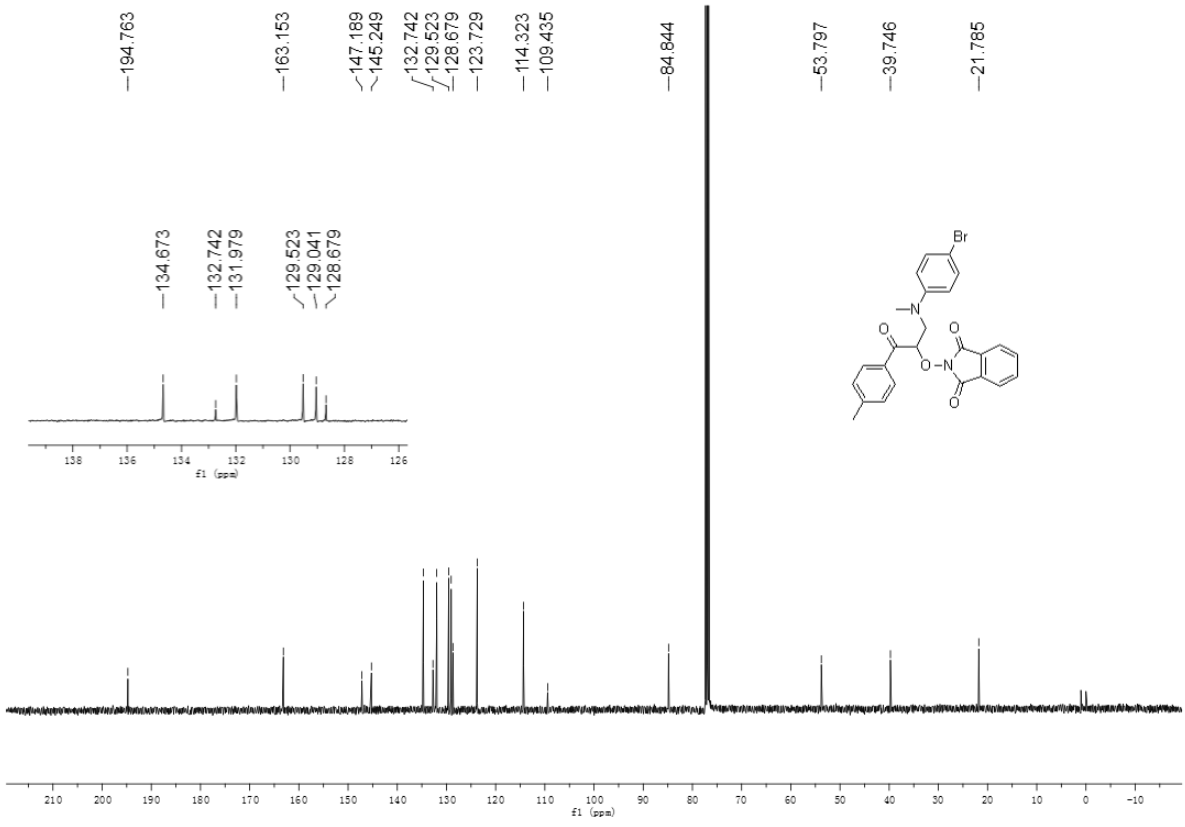
^{1}H NMR Spectrum of Compound 4q



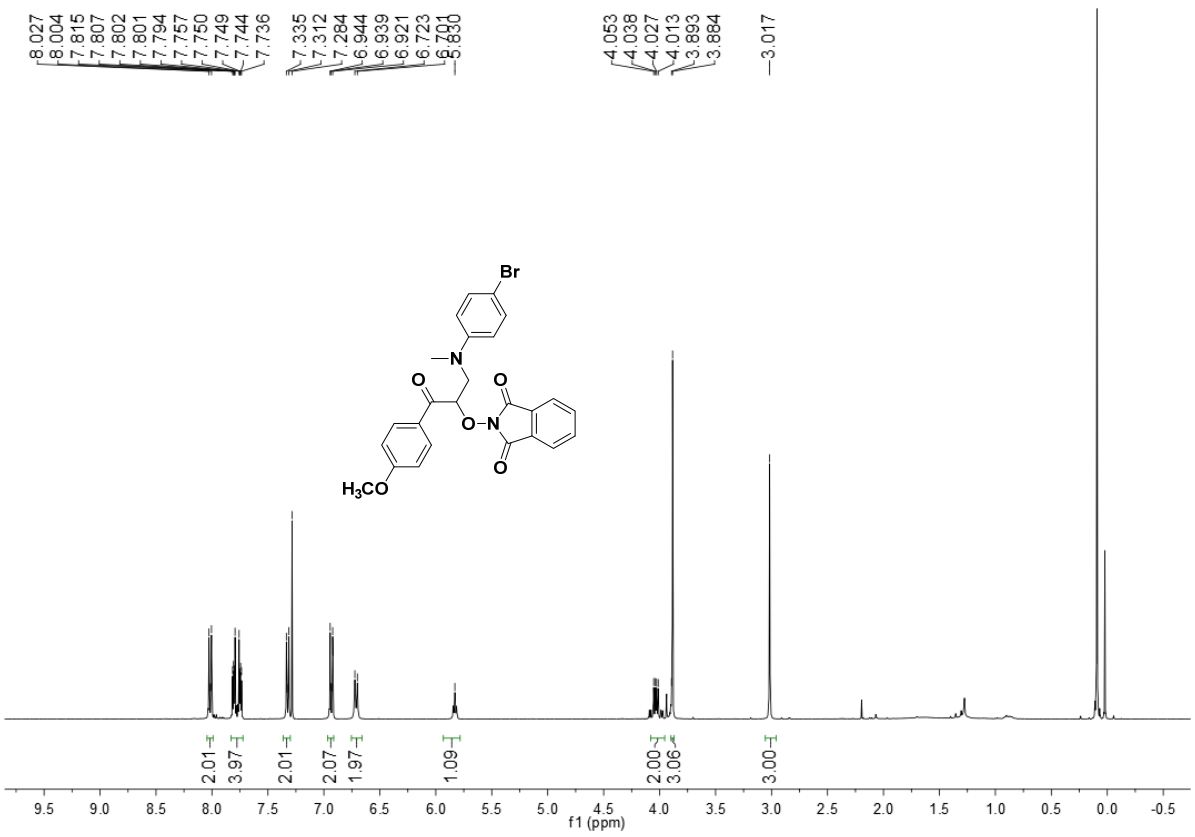
^{13}C NMR Spectrum of Compound 4q



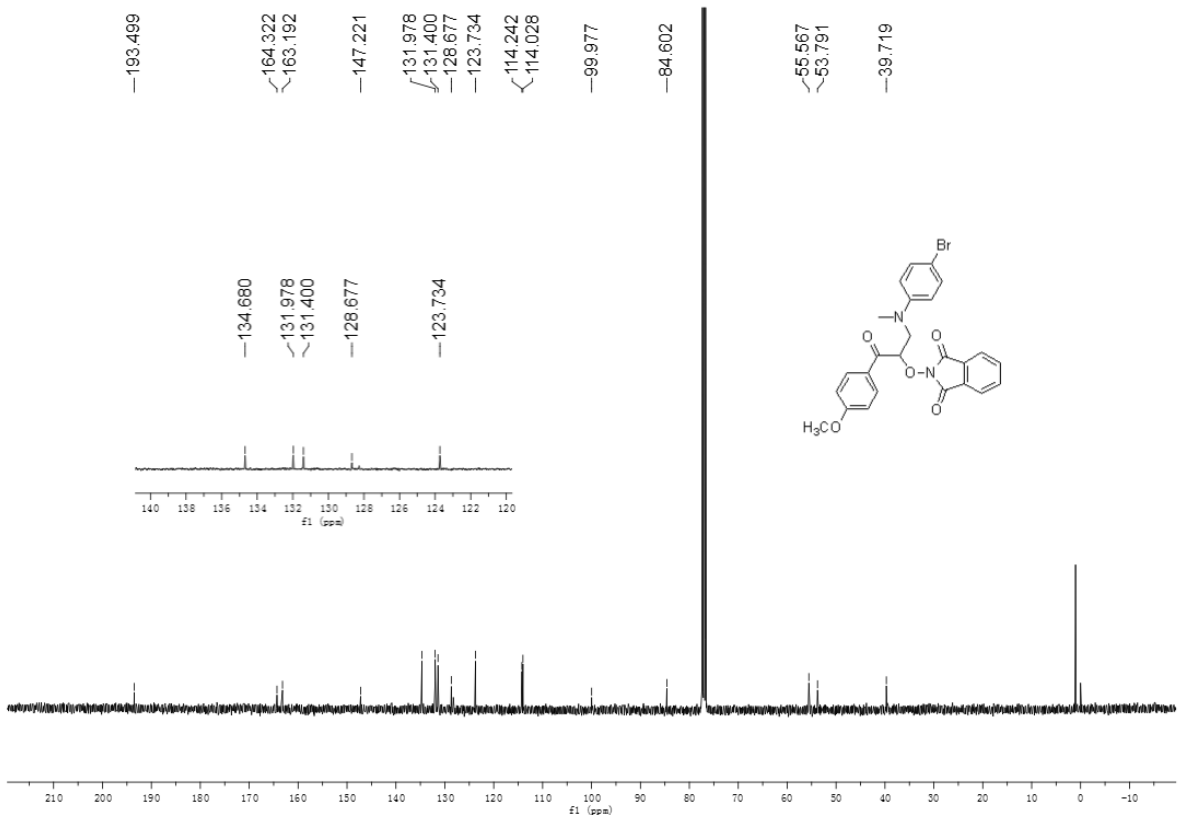
^{1}H NMR Spectrum of Compound 4r



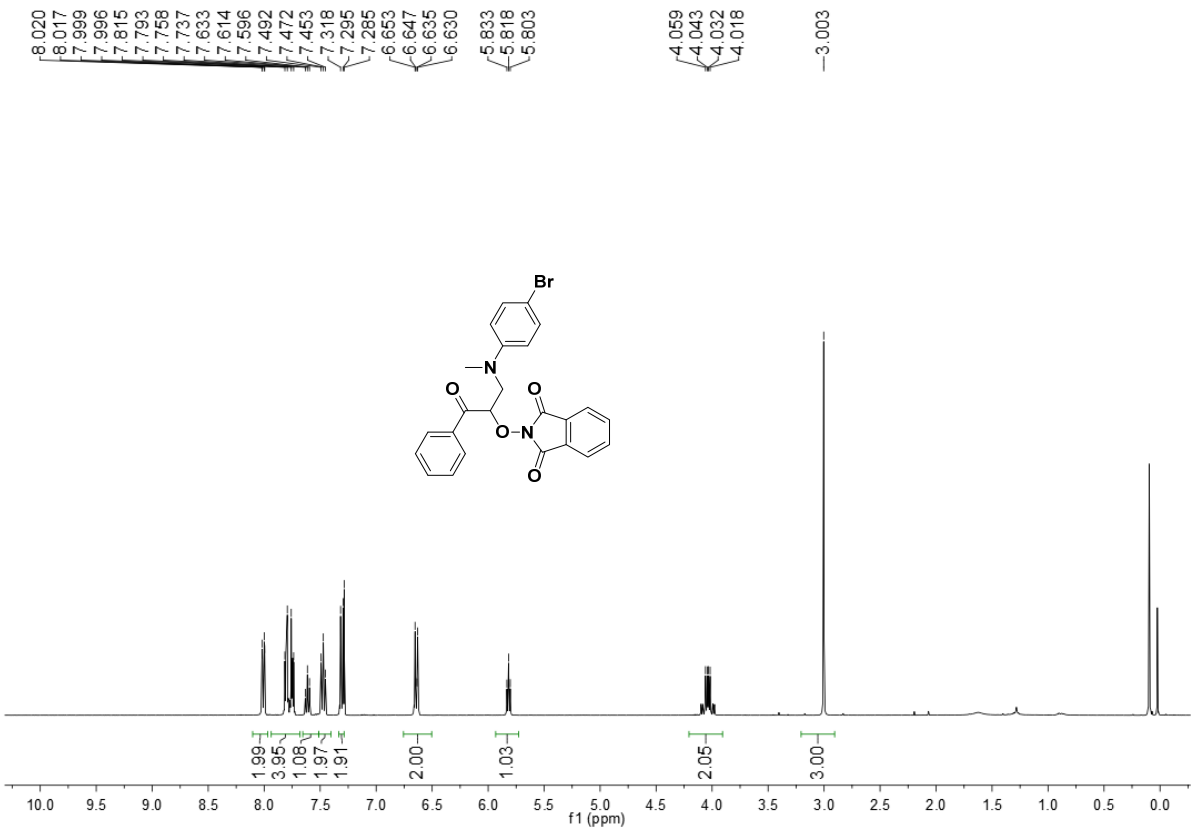
^{13}C NMR Spectrum of Compound 4r



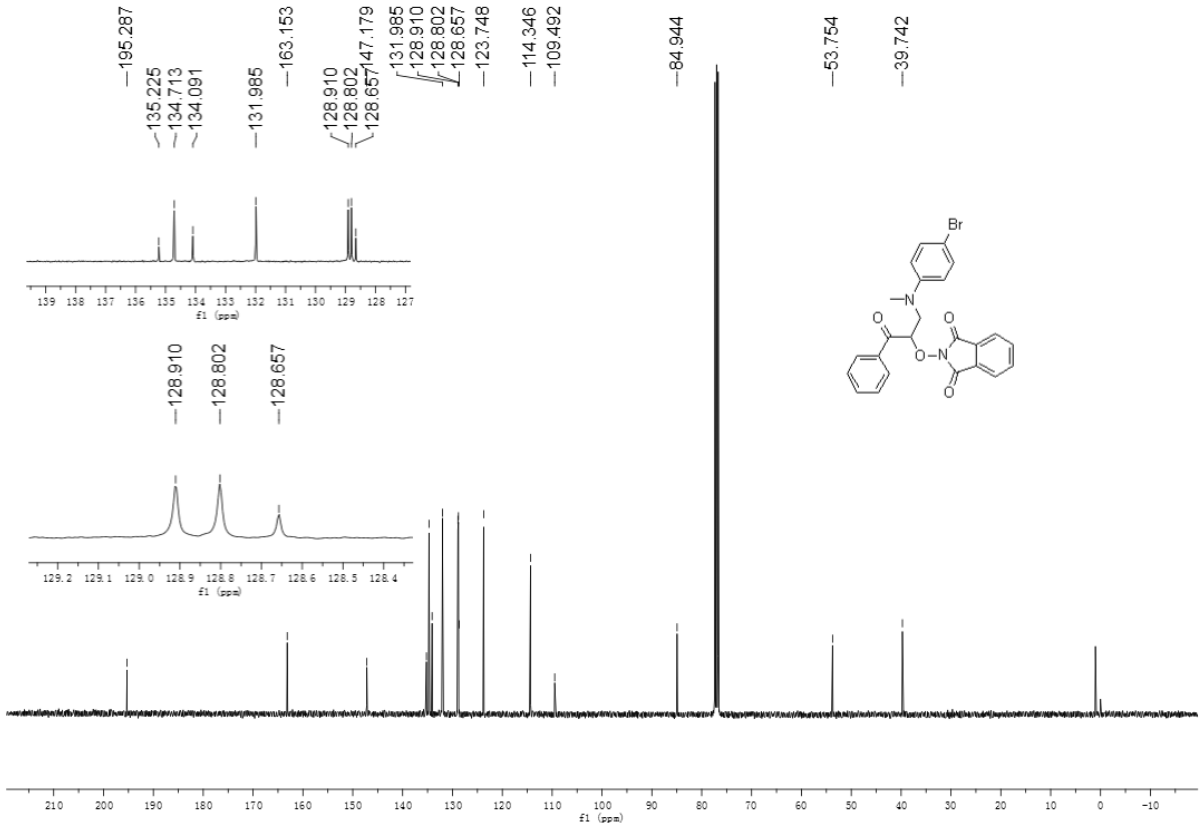
^{1}H NMR Spectrum of Compound 4s



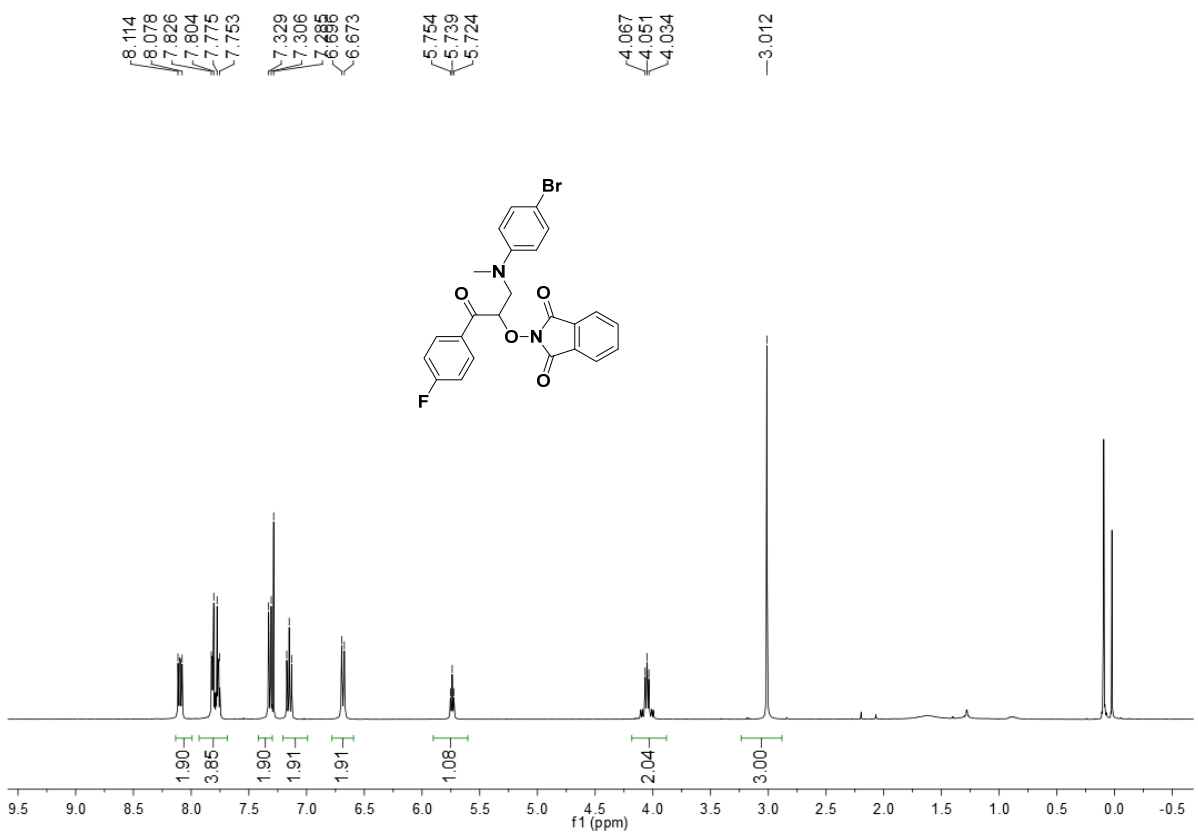
^{13}C NMR Spectrum of Compound 4s



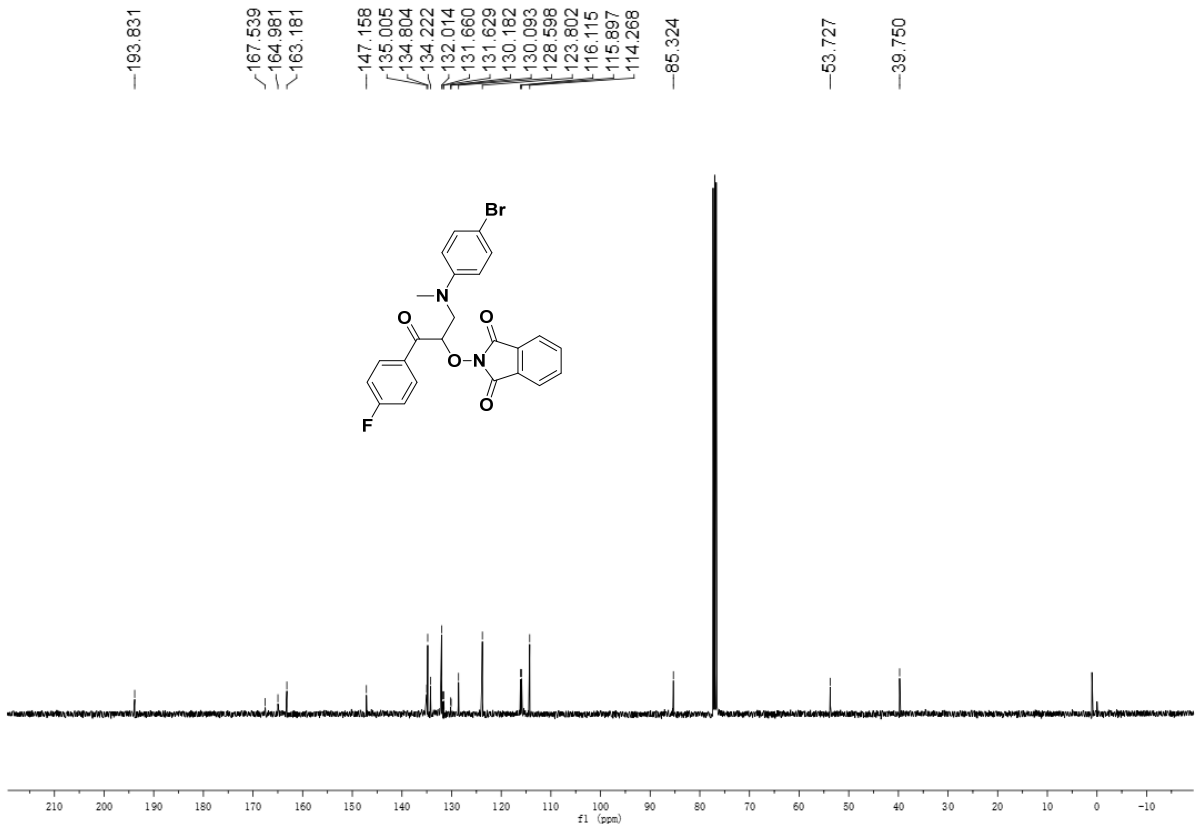
[1]H NMR Spectrum of Compound 4t



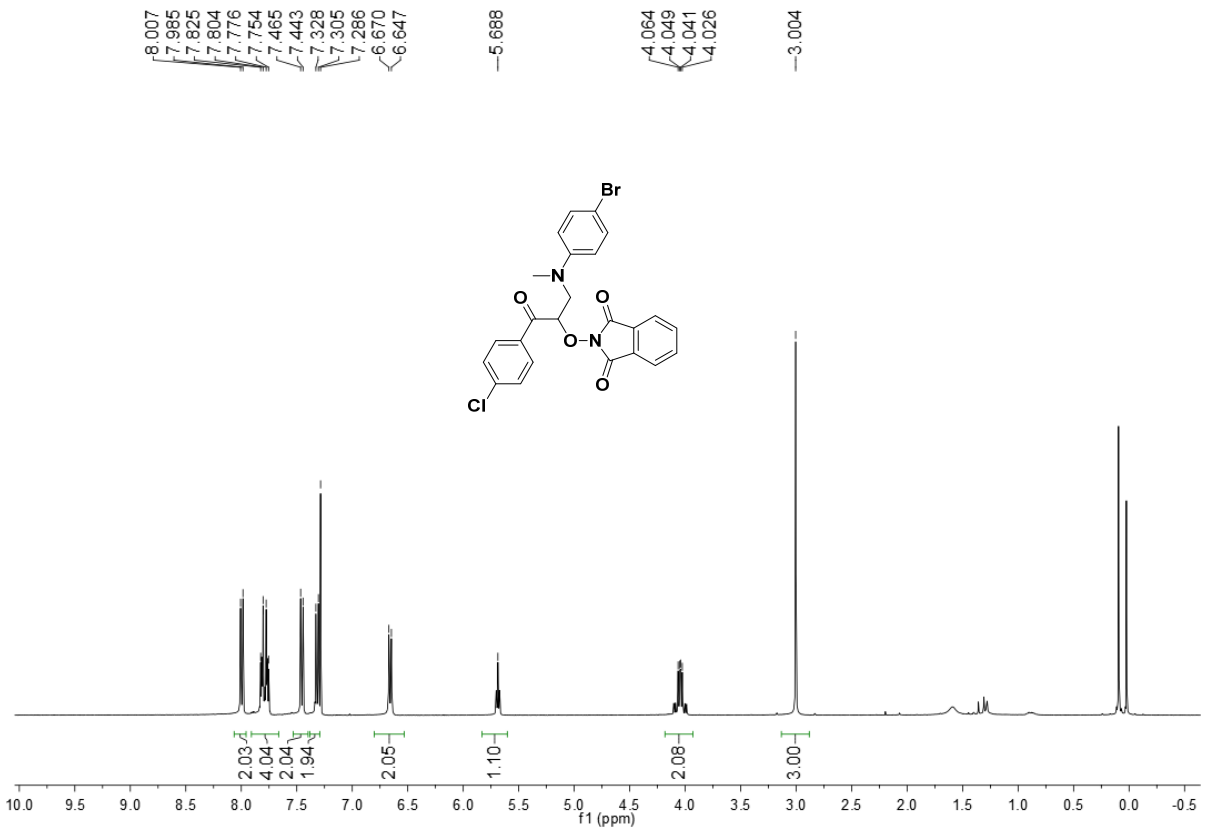
[13]C NMR Spectrum of Compound 4t



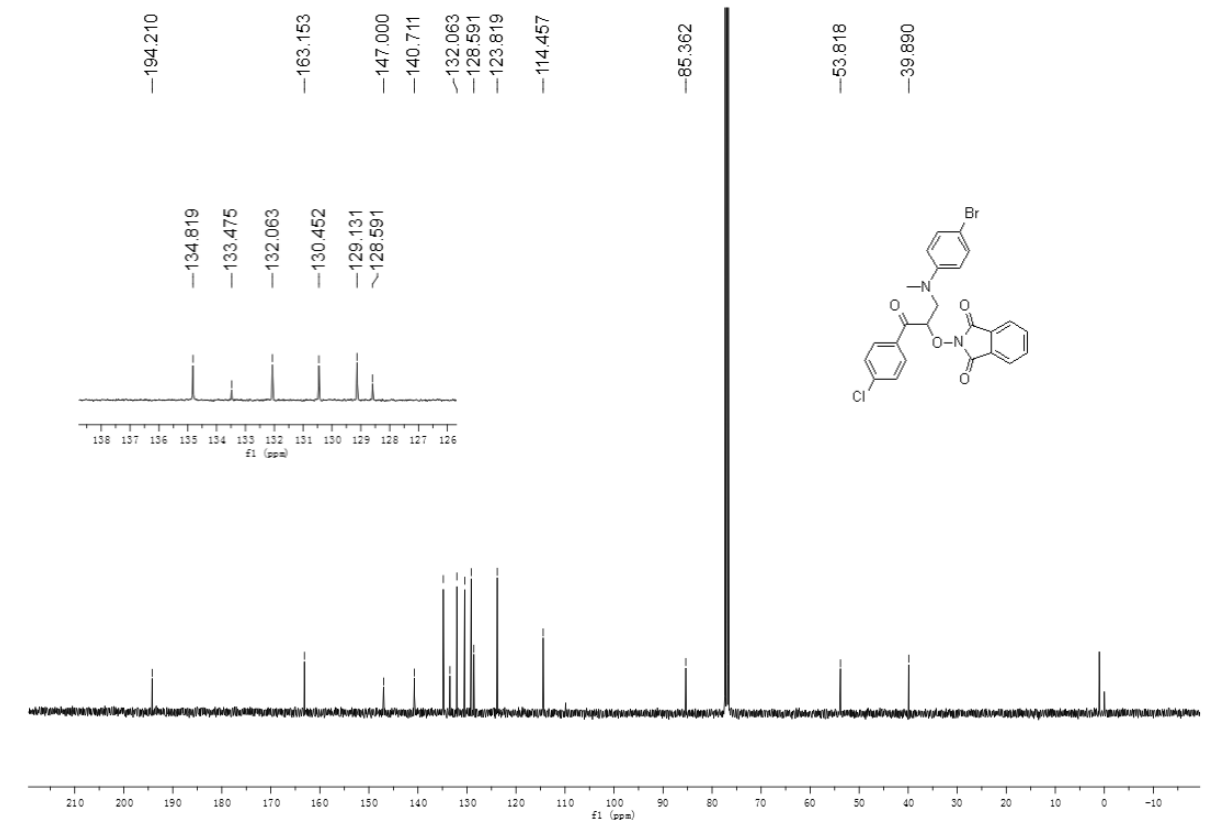
^{1}H NMR Spectrum of Compound 4u



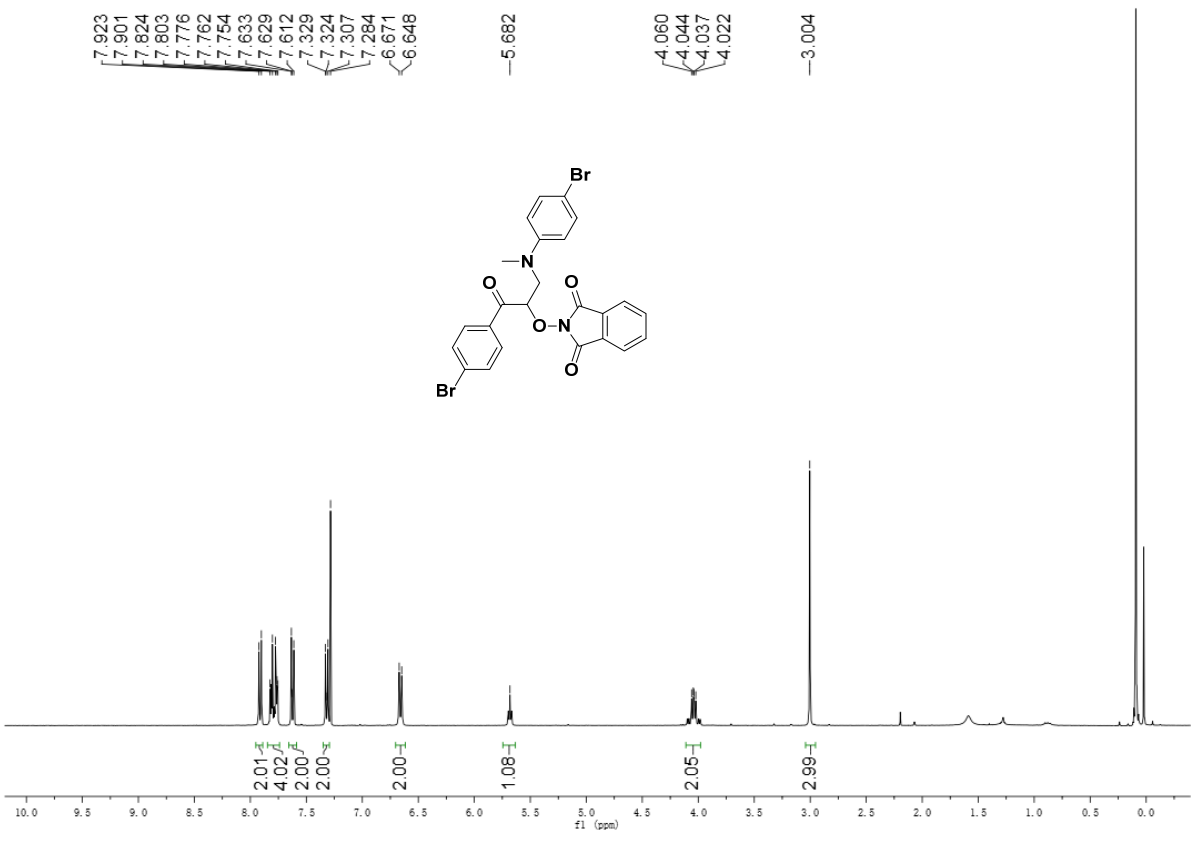
^{13}C NMR Spectrum of Compound 4u



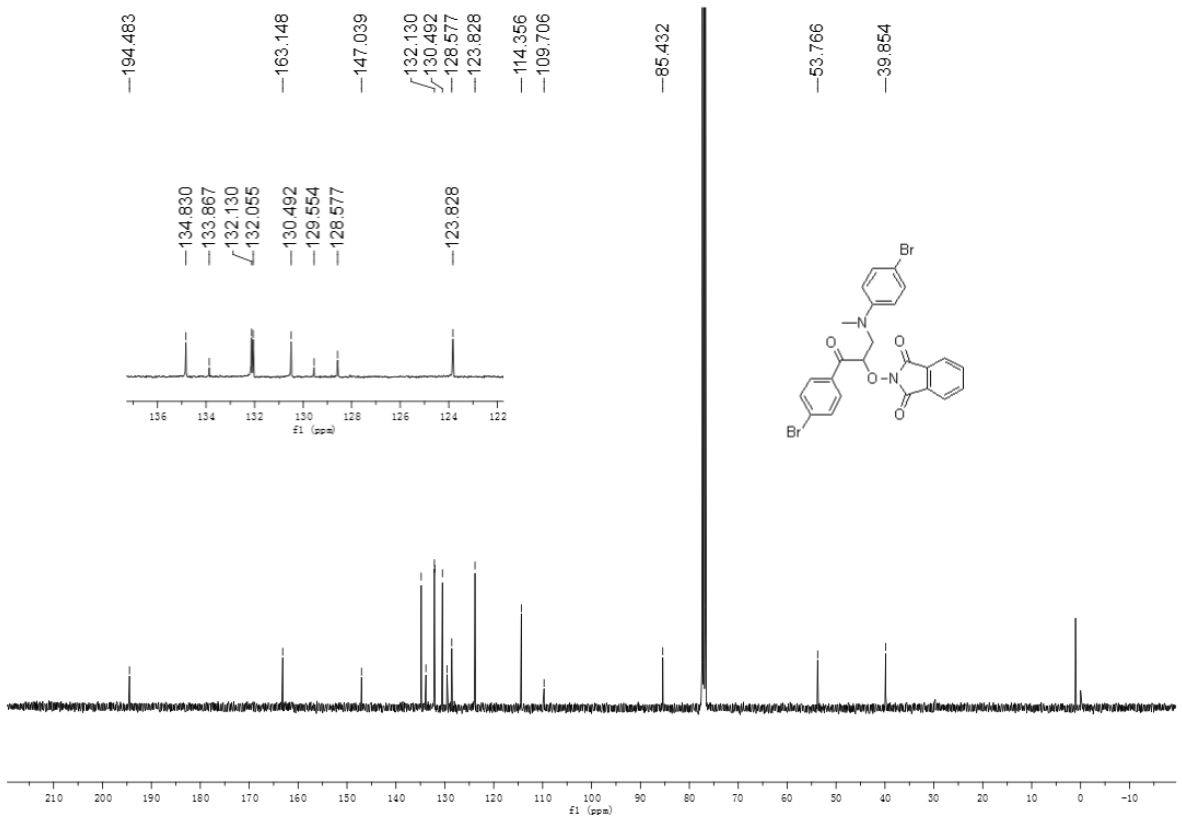
^{1}H NMR Spectrum of Compound 4v



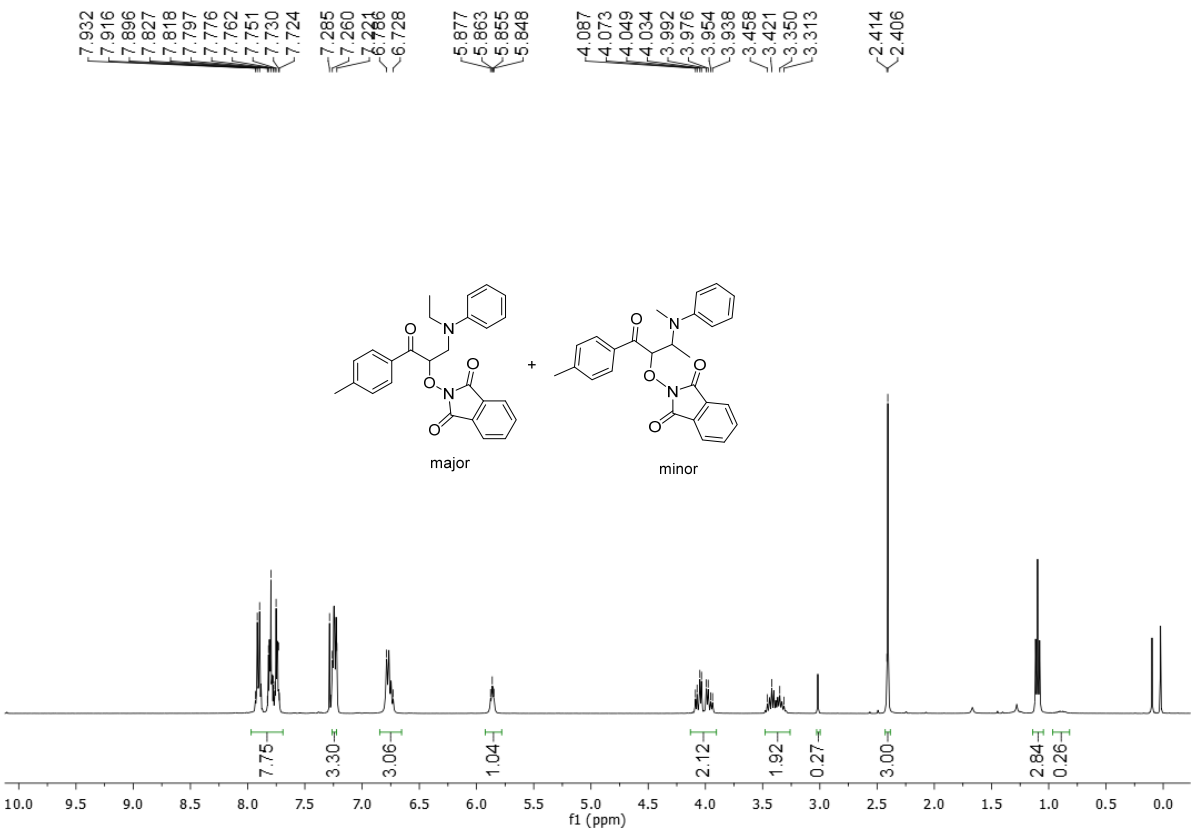
^{13}C NMR Spectrum of Compound 4v



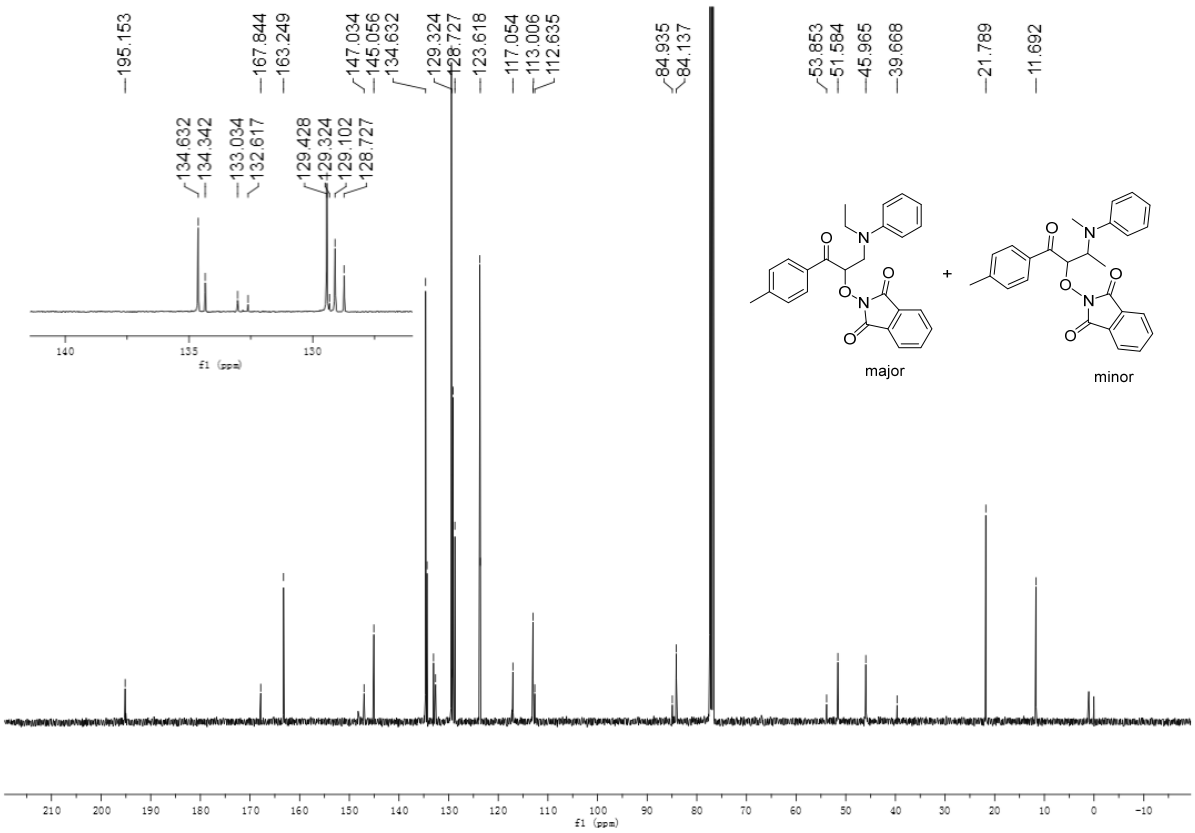
^{1}H NMR Spectrum of Compound 4w



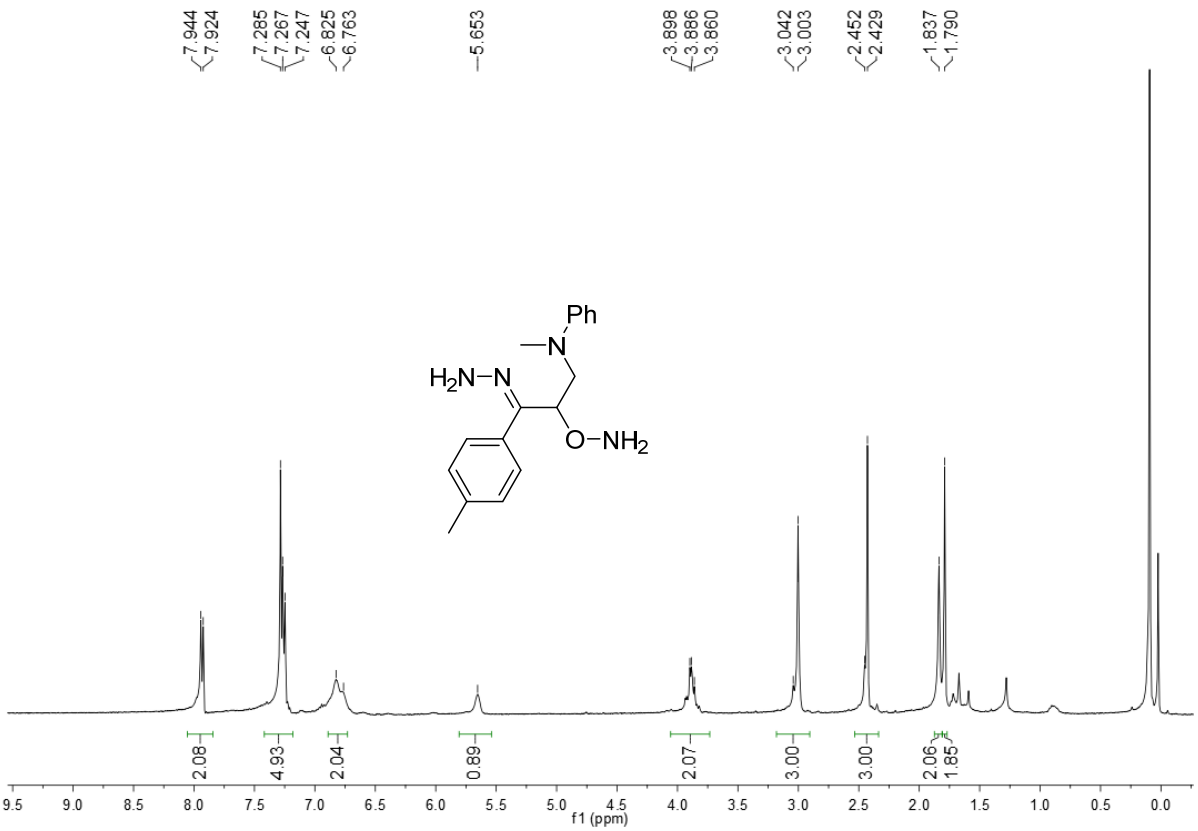
^{13}C NMR Spectrum of Compound 4w



^{1}H NMR Spectrum of Compound 4x



^{13}C NMR Spectrum of Compound 4x



^{1}H NMR Spectrum of Compound 5