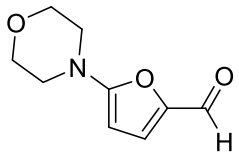
General

All reagents were obtained from commercial sources and used as received unless otherwise stated. Amberlyst® 15 was obtained from Sigma Aldrich in the hydrogen form. Analytical thin layer chromatography was performed on aluminium-backed plates coated with silica gel (Merck Kieselgel 60 F_{254}) and compounds visualised by exposure to UV light, potassium permanganate solution, phosphomolybdic acid or ninhydrin solution. Flash column chromatography was carried out using silica gel 60, SDS, 0.04–0.06 mm.

^{1}H and ^{13}C NMR spectra were recorded at 298 K at the field indicated using Avance 500 and Avance 600 machines. Chemical shifts were measured in ppm (δ) relative to the residual solvent signal (^{1}H NMR, 7.26 ppm ($CDCl_3$), 3.31 ppm (CD_3OD), 2.50 ppm ($(CD_3)_2SO$) or 2.05 ppm ($(CD_3)_2CO$); ^{13}C NMR, 77.16 ppm ($CDCl_3$), 49.00 ppm (CD_3OD), 39.52 ppm ($(CD_3)_2SO$ or 29.84 ppm ($(CD_3)_2CO$)). Coupling (*J*) constants were measured in Hertz (Hz) and splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sx), multiplet (m), broad (br), apparent (app) and combinations thereof. IR spectra were recorded on a Nicolet FT-IT spectrometer. Mass spectra were recorded on Thermo Finnegan MAT 900XP and Micro Mass Quattro LC electrospray mass spectrometers VG ZAB 2SE. Melting points were established using a Stuart SMP11 analogue apparatus and are uncorrected.

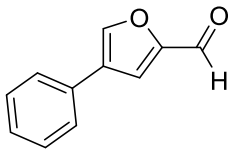
1. Preparation of Furfurals 1

5-Morpholinofuran-2-carbaldehyde 1l[1]



Synthesised according to a literature procedure.[1] R_f 0.25 (Pet. Ether 40-60/EtOAc, 1:1); IR (film, cm^{-1}) 3120, 2961, 2893, 2850, 1642, 1569, 1527; ^1H NMR ($CDCl_3$; 600 MHz) 3.37 (4H, br s, 2 x CH_2N), 3.74 (4H, m, 2 x CH_2O), 5.30 (1H, d, *J* = 3.6 Hz, 4-H), 7.18 (1H, br s, 3-H); 9.02 (1H, br s, CHO); ^{13}C NMR ($CDCl_3$; 151 MHz) 46.0 (2 x CH_2N), 65.9 (2 x CH_2O), 87.1 (C-4), 130.8 (C-3), 144.7 (C), 163.1 (C), 172.0 (CHO); *m/z* HRMS (ESI+) found $[MH]^+$ 182.0815, $C_9H_{12}NO_3$ requires 182.0817.

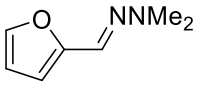
4-Phenylfuran-2-carbaldehyde 1q[2]



Synthesised according to a literature procedure.[2] R_f 0.34 (Pet. Ether 40-60/EtOAc, 9:1); ^1H NMR ($CDCl_3$; 600 MHz) 7.35 (1H, t, *J* = 7.2, Ar-H), 7.43 (2H, t, *J* = 7.2, Ar-H), 7.52 (2H, d, *J* = 7.2, Ar-H), 7.53 (1H, s, 3-H), 7.96 (1H, s, 5-H), 9.71 (1H, s, CHO); ^{13}C NMR ($CDCl_3$; 151 MHz) 119.0 (CH), 126.1 (2 x CH); 128.3 (C); 129.3 (2 x CH), 129.4 (C), 130.5 (C), 143.8 (C), 153.7 (C), 178.3 (CHO); *m/z* HRMS (ESI+) found $[M]^+$ 172.0519, $C_{11}H_8O_2$ requires 172.0524.

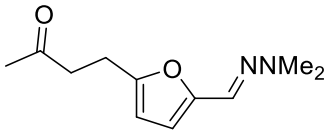
2. Preparation of Furfural Hydrazones 2

2-Furaldehyde dimethylhydrazone 2a[3]



To a solution of furfural **1a** (28.8 mg, 25.4 µL, 300 µmol) in water (6 mL), *N*,*N*-dimethylhydrazine **4** (24.0 mg, 30.4 µL, 400 µmol) was added and the mixture was stirred at rt for 40 min. The organic component was extracted with ether (3 x 30 mL), dried with $MgSO_4$, and the solvent removed under vacuum to give **2a** as a red-brown liquid (36.5 mg, 76%). R_f 0.67 (Pet. Ether 40-60/EtOAc, 1:1); IR (film, cm^{-1}) 2850, 1524, 1445; ^1H NMR ($CDCl_3$; 600 MHz) 2.95 (s, 6H, 2 x CH_3), 6.37 (1H, d, *J* = 3.3 Hz, 3-H), 6.39 (1H, dd, *J* = 3.3, 1.6 Hz, 4-H), 7.10 (1H, s, N=CH), 7.39 (1H, d, *J* = 1.6 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.7 (2 x CH_3), 107.1 (C-4), 111.2 (C-3), 123.2 (C=N), 141.8 (C-2), 152.1 (C-5);

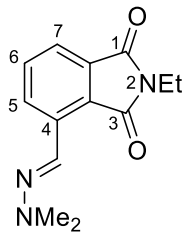
4-(5-((2,2-Dimethylhydrazono)methyl)furan-2-yl)butan-2-one 2t



To a solution of furfural **1a** (192 mg, 166 µL, 2.00 mmol) in water (10 mL), *N*,*N*-dimethylhydrazine **4** (144 mg, 183 µL, 2.40 mmol) was added and the mixture was stirred at 50 °C for 30 min. The solution was heated to reflux and methyl vinyl ketone **7d** (701 mg, 834 µL, 10 mmol) added dropwise over 5 h. The solution was stirred at reflux for a further 1 h then cooled to rt, and the organic component extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$, and the solvent removed under vacuum. The crude reaction mixture was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give **2t** as a yellow oil (162 mg, 39%). R_f 0.21 (Pet. Ether 40-60/EtOAc, 4:1); IR (film, cm^{-1}) 2925, 1713, 1674; ^1H NMR ($CDCl_3$; 600 MHz) 2.11 (3H, s, C(O)CH_3), 2.76 (2H, t, *J* = 7.5 Hz, CH_2CH_2), 2.86-2.91 (m, 8H, 2 x CH_3 and CH_2CH_2), 5.97 (1H, d, *J* = 3.3 Hz, 3-H), 6.21 (1H, d, *J* = 3.3 Hz, 4-H), 7.03 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$; 151 MHz) 22.5, 30.1, 41.9, 43.0 (2 x CH_3), 107.4 (C-3), 108.8 (C-4), 124.3 (C=N), 150.9 (5), 154.6 (C-2), 207.8 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 209.1289, $C_{11}H_{17}N_2O_2$ requires 209.1290.

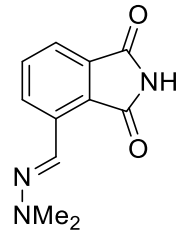
3. Preparation of Phthalimides 5

4-((2,2-Dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5a[4]



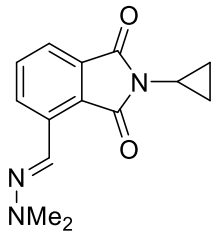
To a solution of furfural **1a** (20.0 g, 17.2 mL, 208 mmol) in water (500 mL, pH 6), *N*,*N*-dimethylhydrazine (15.0 g, 19.0 mL, 250 mmol) was added and the mixture was stirred at 50 °C for 30 min. *N*-Ethyl maleimide **3a** (26.0 g, 208 mmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 100 mL) and dried to give **5a** as yellow needles (49.6 g, 97%). R_f 0.22 (Pet. Ether 40-60/EtOAc, 17:3); M.p. 142-143 °C (water), Lit[4] 141-142 °C ($CHCl_3$); IR (film, cm^{-1}) 2920, 2875, 1755, 1695, 1590; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.27 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 3.14 (6H, s, 2 x CH_3), 3.72 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 7.55 (1H, t, *J* = 7.7 Hz, 6-H), 7.61 (1H, dd, *J* = 7.7, 1.1 Hz, 7-H), 8.14 (1H, s, N=CH), 8.22 (1H, dd, *J* = 7.7, 1.1 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 32.9 (CH_2), 42.9 (2 x CH_3), 120.9 (CH), 124.7 (N=CH), 124.9 (C), 129.0 (C), 132.6 (C), 133.4 (CH), 136.4 (C), 168.4 (C=O), 169.4 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 246.1341, $C_{13}H_{16}N_3O_2$ requires 246.1243.

4-((2,2-Dimethylhydrazono)methyl)isoindoline-1,3-dione 5b



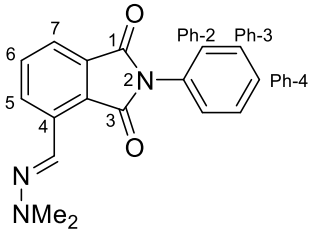
To a solution of furfural **1a** (4.81 g, 4.13 mL, 50.0 mmol) in water (100 mL, pH 6), *N*,*N*-dimethylhydrazine (3.60 g, 4.56 mL, 60.0 mmol) was added and the mixture was stirred at 50 °C for 30 min. Maleimide **3b** (7.32 g, 75.0 mmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 500 mL) and dried to give **5b** as yellow needles (9.33 g, 86%). R_f 0.41 (Pet. Ether 40-60/EtOAc, 3:2); M.p. 238-240 °C (water); IR (film, cm^{-1}) 3196, 1759, 1715, 1544; ^{1}H NMR ($CDCl_3$; 600 MHz) 3.13 (6H, s, 2 x CH_3), 7.55 (1H, s br, NH), 7.60 (1H, t, *J* = 7.4 Hz, 6-H), 7.62 (1H, dd, *J* = 7.4, 1.1 Hz, 7-H), 8.05 (1H, s, N=CH), 8.27 (1H, dd, *J* = 7.4, 1.1 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.8 (2 x CH_3), 121.2 (CH), 124.1 (N=CH), 125.1 (C), 129.4 (C), 133.0 (C), 133.8 (CH), 137.0 (C), 168.1 (C=O), 169.0 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 218.0940, $C_{11}H_{14}N_3O_2$ requires 218.0930.

2-Cyclopropyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5c



To a solution of furfural **1a** (33.7 mg, 29.0 µL, 350 µmol) in water (2 mL, pH 6), *N*,*N*-dimethylhydrazine (25.2 mg, 32.0 µL, 420 µmol) was added and the mixture was stirred at 50 °C for 30 min. *N*-Cyclopropyl maleimide **3c** (96.0 mg, 700 µmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5c** as yellow needles (72.0 mg, 80%). R_f 0.30 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 174-176 °C (water); IR (film, cm^{-1}) 2861, 1764, 1706, 1548; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.01 (4H, m, 2 x CH_2), 2.67 (1H, m, CH), 3.12 (6H, s, 2 x CH_3), 7.55 (1H, t, *J* = 7.6 Hz, 6-H), 7.59 (1H, dd, *J* = 7.6, 1.1 Hz, 7-H), 8.11 (1H, s, N=CH), 8.22 (1H, dd, *J* = 7.6, 1.1 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 5.3 (2 x CH_2), 20.9 (CH), 42.7 (2 x CH_3), 120.9 (CH), 124.4 (C), 124.7 (N=CH), 129.1 (CH), 132.2 (C), 133.5 (CH), 136.5 (C), 169.1 (C=O), 170.2 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 258.1240, $C_{14}H_{17}N_3O_2$ requires 258.1242.

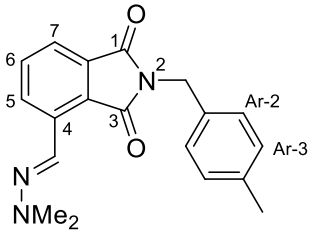
4-((2,2-Dimethylhydrazono)methyl)-2-phenylisoindoline-1,3-dione 5d[5]



To a solution of furfural **1a** (67.4 mg, 48.0 µL, 700 µmol) in water (2 mL, pH 6), *N*,*N*-dimethylhydrazine (50.4 mg, 64.0 µL, 840 µmol) was added and the mixture was stirred at 50 °C for 30 min. *N*-Phenyl maleimide **3d** (121 mg, 700 µmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5d** as yellow needles (150 mg, 73%). R_f 0.34 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 210-212 °C (water), Lit[5] 206 °C (EtOAc); IR (film, cm^{-1}) 2941, 1766, 1710, 1687; ^{1}H NMR ($CDCl_3$; 600 MHz) 3.13 (6H, s, 2 x CH_3), 7.40 (1H, tt, *J* = 7.3, 1.3 Hz, Ph-4-H), 7.43 (2H, dd, *J* = 7.3, 1.3 Hz, Ph-2-H), 7.50 (2H, t, *J* = 7.3 Hz, Ph-3-H), 7.64 (1H, t, *J* = 7.6 Hz, 6-H), 7.72 (1H, d, *J* = 7.6 Hz, 7-H), 8.16 (1H, s, N=CH), 8.31 (1H, d, *J* = 7.6 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.7 (2 x CH_3), 120.8 (C), 121.4 (CH), 124.2 (C), 124.4 (N=CH), 126.8 (CH), 128.1 (CH), 129.2 (CH), 129.4 (CH), 131.9 (C), 132.1 (C),

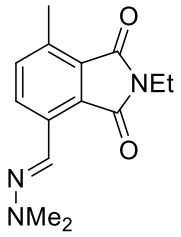
133.9 (CH), 137.0 (C), 167.5 (C=O), 168.5 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 294.1251, $C_{17}H_{16}N_3O_2$ requires 294.1243.

4-((2,2-Dimethylhydrazono)methyl)-2-(4-methylbenzyl)isoindoline-1,3-dione 5e



To a solution of furfural **1a** (67.4 mg, 48.0 µL, 700 µmol) in water (2 mL, pH 6), *N*,*N*-dimethylhydrazine (50.4 mg, 64.0 µL, 840 µmol) was added and the mixture was stirred at 50 °C for 30 min. *N*-(4-Methylbenzyl) maleimide **3e** (141 mg, 700 µmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5e** as yellow needles (153 mg, 68%). R_f 0.40 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 135-137 °C (water); IR (film, cm^{-1}) 2928, 1758, 1697; ^{1}H NMR ($CDCl_3$; 600 MHz) 2.31 (3H, s, CH_3), 3.11 (6H, s, 2 x CH_3), 4.79 (2H, s, CH_2), 7.13 (2H, d, *J* = 7.9 Hz, Ar-3-H), 7.33 (2H, d, *J* = 7.9 Hz, Ar-2-H), 7.54 (1H, t, *J* = 7.7 Hz, 6-H), 7.60 (1H, d, *J* = 7.7 Hz, 7-H), 8.12 (1H, s, N=CH), 8.21 (1H, d, *J* = 7.7 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.8 (2 x CH_3), 121.1 (CH), 124.9 (C), 125.2 (CH), 128.7 (CH), 129.1 (CH), 129.5 (CH), 132.5 (C), 133.4 (CH), 133.8 (C), 136.5 (C), 137.6 (C), 167.6 (C=O), 168.6 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 322.1567, $C_{19}H_{20}N_3O_2$ requires 322.1556.

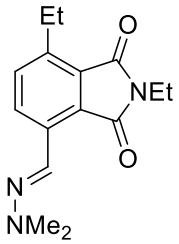
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-methylisoindoline-1,3-dione 5f[4]



To a solution of 5-methylfurfural **1f** (110 mg, 99.5 µL, 1.00 mmol) in water (4 mL, pH 6), *N*,*N*-dimethylhydrazine (72.0 mg, 91.2 µL, 1.20 mmol) was added and the mixture was stirred at 50 °C for 2 h. *N*-Ethyl maleimide **3a** (250 mg, 2.00 mmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5f** as yellow needles (260 mg, 93%). R_f 0.70 (Pet. Ether 40-60/EtOAc, 17:3); M.p. 144-146 °C ($CDCl_3$), Lit[4] 145-146 °C ($CHCl_3$); IR (film, cm^{-1}) 2976, 2937, 2868, 1750, 1685, 1590; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.26 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 2.65 (3H, s, Ar-CH_3), 3.09 (6H, s, 2 x CH_3), 3.70 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 7.32 (1H, d, *J* = 8.2 Hz, 6-H), 8.09 (1H, d, *J* = 8.2 Hz, 5-H), 8.17 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 17.7 (Ar-CH_3), 32.7 (CH_2), 42.9 (2 x CH_3), 125.3 (C),

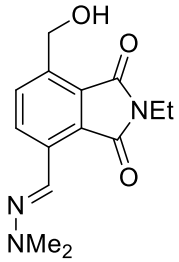
125.6 (N=CH), 128.7 (C), 128.8 (CH), 134.1 (C), 135.7 (C), 136.2 (CH), 169.1 (C=O), 169.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 260.1480, $C_{14}H_{18}N_3O_2$ requires 260.1399.

4-((2,2-Dimethylhydrazono)methyl)-2,7-diethylisoindoline-1,3-dione, 5g



To a solution of 5-ethyl-2-furaldehyde (124 mg, 1.0 mmol) in water (4 mL, pH 6) *N,N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 2.5 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a yellow precipitate forming within 5 min. After 4 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5g** as yellow needles (205 mg, 75%). R_f = 0.38 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2935, 2879, 2864, 2785, 1748, 1690, 1545, 1439; M.p. 109-111 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.26 (6H, m, 2 x CH_2CH_3), 3.08 (6H, s, 2 × CH_3), 3.09 (2H, m, CH_2CH_3), 3.70 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.36 (1H, d, *J* = 8.4 Hz, 6-H), 8.12 (1H, d, *J* = 8.4 Hz, 5-H), 8.17 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_2CH_3), 15.1 (CH_2CH_3), 24.4 (CH_2), 32.6 (CH_2), 42.8 (2 x CH_3), 125.4 (C), 125.7 (N=CH), 128.1 (C), 129.1 (CH), 134.1 (C), 134.7 (CH), 142.4 (C), 168.9 (C=O), 169.4 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 274.1559, $C_{15}H_{20}N_3O_2$ requires 274.1555.

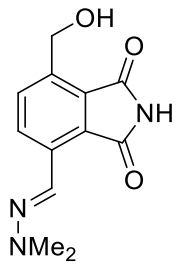
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(hydroxymethyl)isoindoline-1,3-dione 5h



To a solution of 5-hydroxymethylfurfural **1h** (126 mg, 97.8 µL, 1.00 mmol) in water (4 mL, pH 6), *N*,*N*-dimethylhydrazine (72.0 mg, 91.2 µL, 1.20 mmol) was added and the mixture was stirred at 50 °C for 2 h. *N*-Ethyl maleimide **3a** (250 mg, 2.00 mmol) was added and the reaction stirred at 50 °C for 30 min. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5h** as yellow needles (251 mg, 95%). R_f 0.14 (Pet. Ether 40-60/EtOAc, 17:3); M.p. 152-154 °C ($CDCl_3$); IR (film, cm^{-1}) 3306 (br), 2937, 2871, 1750, 1682, 1592; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.27 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.12 (6H, s, 2 x CH_3), 3.72 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 4.89 (2H, s, Ar-CH_2OH),

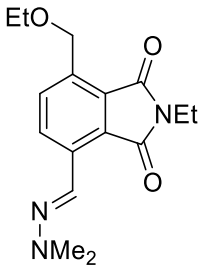
7.45 (1H, d, *J* = 8.2 Hz, 6-H), 8.14 (1H, s, N=CH), 8.18 (1H, d, *J* = 8.2 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 33.0 (CH_2), 42.7 (2 x CH_3), 62.7 (Ar-CH_2OH), 124.3 (N=CH), 125.2 (C), 129.4 (CH), 133.2 (CH), 134.3 (C), 136.0 (C), 138.5 (C), 169.2 (C=O), 170.2 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 275.1268, $C_{14}H_{18}N_3O_3$ requires 275.1270.

4-((2,2-Dimethylhydrazono)methyl)-7-(hydroxymethyl)isoindoline-1,3-dione 5i



To a solution of hydroxymethylfurfural **1h** (1.00 g, 775 µL, 7.94 mmol) in water (20 mL, pH 6), *N*,*N*-dimethylhydrazine (572 mg, 1.16 mL, 9.52 mmol) was added and the mixture was stirred at 50 °C for 40 min. Maleimide **3b** (2.33 g, 15.9 mmol) was added and the reaction stirred at 50 °C for 3 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 100 mL) and dried to give **5i** as yellow needles (1.71 g, 87%). R_f 0.50 (Pet. Ether 40-60/EtOAc, 1:2); M.p. 202-204 °C (water); IR (film, cm^{-1}) 3187 (br), 3045, 1752, 1688, 1650, 1537; ^{1}H NMR (CD_3OD; 600 MHz) 3.06 (6H, s, 2 x CH_3), 4.98 (2H, s, CH_2), 7.69 (1H, d, *J* = 8.4 Hz, 6-H), 8.05 (1H, s, N=CH), 8.14 (1H, d, *J* = 8.4 Hz, 5-H); ^{13}C NMR (CD_3OD; 151 MHz) 42.7 (2 x CH_3), 60.5 (CH_2), 125.7 (CH), 126.9 (C), 129.7 (C), 129.9 (CH), 133.2 (CH), 136.5 (C), 140.2 (C), 171.2 (C=O), 171.6 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 248.1032, $C_{12}H_{14}N_3O_3$ requires 248.1035.

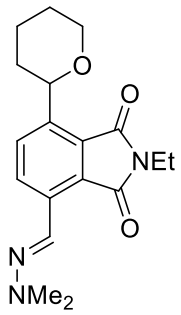
4-((2,2-Dimethylhydrazono)methyl)-7-(ethoxymethyl)-2-ethylisoindoline-1,3-dione 5j



To a solution of 5-(ethoxymethyl)-2-furaldehyde (154 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 4 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a yellow precipitate forming within 5 min. After 1 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5j** as yellow solid (217 mg, 72%). R_f = 0.40 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2980, 2938, 2870, 2795, 1751, 1692, 1543, 1437; M.p. 104-106 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.25 (3H, t, *J* = 7.2 Hz, NCH_2CH_3), 1.28 (3H, t, *J*

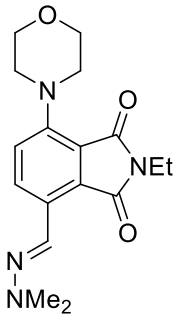
= 7.0 Hz, OCH_2CH_3), 3.11 (6H, s, 2 x CH_3), 3.64 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.69 (2H, q, *J* = 7.2 Hz, NCH_2CH_3), 4.97 (2H, s, CH_2Ar), 7.70 (1H, d, *J* = 8.4 Hz, 6-H), 8.14 (1H, s, N=CH), 8.20 (1H, d, *J* = 8.4 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 15.4 (CH_3), 32.7 (NCH_2CH_3), 42.7 (2 x CH_3), 66.6 (OCH_2CH_3), 67.4 (Ar-CH_2), 124.9 (C), 125.0 (N=CH), 127.9 (C), 129.1 (CH), 132.7 (CH), 135.3 (C), 136.4 (C), 168.7 (C=O), 169.4(C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 304.1653, $C_{16}H_{22}N_3O_3$ requires 304.1661.

4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione 5k



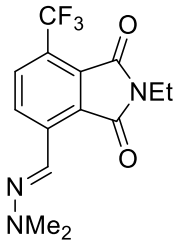
To a solution of 5-(tetrahydropyran-2-yl)-2-furaldehyde (180 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 4 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a yellow precipitate forming within 5 min. After 1 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5k** as yellow solid (278 mg, 85%). R_f = 0.42 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2931, 2857, 2833, 2780, 1754, 1697, 1545, 1438; M.p. 108-110 °C (water); ^1H NMR ($CDCl_3$; 600 MHz) 1.25 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.41 (1H, m, CH*H*), 1.60 (1H, m, CH*H*), 1.69 (1H, m, CH*H*), 1.78 (1H, m, CH*H*), 1.92 (2H, m, CH_2), 3.09 (6H, s, 2 x CH_3), 3.67 (3H, m, CH_2CH_3 + CH), 4.14 (1H, m, CH*H*), 5.31 (1H, d, *J* = 10.8 Hz, OCH), 7.75 (1H, d, *J* = 8.4 Hz, 6-H), 8.14 (1H, s, N=CH), 8.18 (1H, d, *J* = 8.4 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 24.0 (CH_2), 25.9 (CH_2), 32.7 (CH_2), 33.9 (CH_2), 42.7 (2 x CH_3), 69.0 (CH_2), 74.8 (CH), 124.6 (CH), 125.1 (C), 126.5 (CH), 129.4 (C), 131.0 (CH), 135.1 (C), 141.2 (C), 168.6 (C=O), 169.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 330.1824, $C_{18}H_{24}N_3O_3$ requires 330.1818.

4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-morpholinoisoindoline-1,3-dione 5l



To a solution of 5-morpholino-2-furaldehyde (181 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 2.5 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 5 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5l** as brown-red solid (134 mg, 41%). R_f = 0.38 (Pet. Ether 40-60/EtOAc, 9:1); IR (film cm^{-1}) 2965, 2859, 2828, 1738, 1683, 1435; M.p. 112-114 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.24 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.06 (6H, s, 2 x CH_3), 3.32 (4H, m, 2 x NCH_2), 3.68 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 3.94 (4H, m, 2 x OCH_2), 7.09 (1H, d, *J* = 9.0 Hz, 6-H), 8.15 (1H, d, *J* = 9.0 Hz, 5-H), 8.21 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$, 151 MHz) 14.1 (CH_2CH_3), 32.7 (CH_2CH_3), 42.9 (2 x CH_3), 51.7 (2 x CH_2N), 67.1 (2 x CH_2O), 117.8 (C), 123.1 (6-C), 126.4 (N=CH), 127.0 (C), 129.4 (C), 131.4 (5-C), 148.6 (C), 167.7 (C=O), 169.2 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 331.1774, $C_{17}H_{23}N_4O_3$ requires 331.1770.

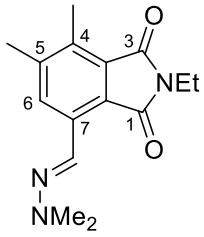
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(trifluoromethyl)isoindoline-1,3-dione 5m



To a solution of 5-(trifluoromethyl)-2-furaldehyde (164 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 4 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 24 h, the temperature was increased to 80 °C and the mixture stirred overnight. The mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5m** as yellow needles (213 mg, 88%). R_f = 0.38 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2943, 2794, 1758, 1699, 1612, 1532, 1442; M.p. 194-196 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.28 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.19 (6H, s, 2 x CH_3), 3.74 (2H, q, *J* = 7.2 Hz,

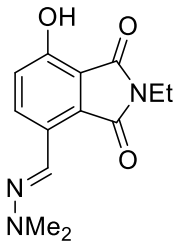
C*H*$_2$CH$_3$), 7.75 (1H, d, *J* = 8.4 Hz, 6-H), 8.11 (1H, s, N=CH), 8.29 (1H, d, *J* = 8.4 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.9 (CH_3), 33.2 (CH_2), 42.7 (2 x CH_3), 122.4 (N=CH), 122.5 (q, *J* = 273.0 Hz, CF_3), 123.4 (q, *J* = 35.5 Hz, C-3a), 125.7 (C), 128.2 (C), 128.7 (CH-5), 130.1 (q, *J* = 5.4 Hz, CH-6), 139.5 (C-4), 165.1 (C=O), 168.4 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 314.1118, $C_{14}H_{15}N_3O_2F_3$ requires 314.1118.

7-((2,2-Dimethylhydrazono)methyl)-2-ethyl-4,5-methylisoindoline-1,3-dione 5n



To a solution of 4,5-dimethylfurfural **1n** (124 mg, 122 µL, 1.00 mmol) in water (4 mL, pH 6), *N*,*N*-dimethylhydrazine (72.0 mg, 91.2 mL, 1.20 mmol) was added and the mixture was stirred at 50 °C for 2 h. *N*-Ethyl maleimide **3a** (250 mg, 2.00 mmol) was added and the reaction stirred at 50 °C for 2 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5n** as yellow needles (195 mg, 72%). R_f 0.10 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 153-154 °C ($CDCl_3$); IR (film, cm^{-1}) 2938, 2864, 1748, 1691, 1546; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.25 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 2.36 (3H, s, Ar-CH_3), 2.61 (3H, s, Ar-CH_3), 3.09 (6H, s, 2 x CH_3), 3.69 (2H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 7.97 (1H, s, 6-H), 8.15 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.9 (CH_3), 14.1 (Ar-CH_3), 20.1 (Ar-CH_3), 32.6 (CH_2), 42.8 (2 x CH_3), 123.5 (C), 126.1 (N=CH), 129.0 (C), 129.3 (CH), 133.5 (C), 135.6 (C), 144.5 (C), 169.2 (C=O), 169.6 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 274.1552, $C_{15}H_{20}N_3O_2$ requires 274.1556.

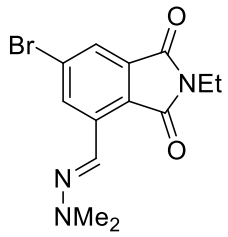
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-hydroxyisoindoline-1,3-dione 5o



To a solution of either 5-chloro-2-furaldehyde (131 mg, 1.0 mmol) or 5-bromo-2-furaldehyde (175 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 2 h *N*-ethyl maleimide (125 mg, 1.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 2 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5o** as a brown-orange solid either from 5-chloro-2-furaldehyde (101 mg, 39%) or 5-bromo-2-furaldehyde (141 mg, 54%).

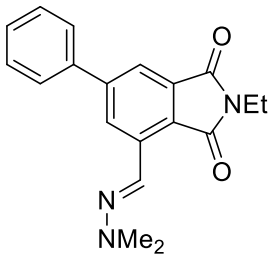
R_f = 0.45 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 3175, 2987, 2942, 2918, 1748, 1670, 1546, 1439; M.p. 164-166 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.26 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.06 (6H, s, 2 x CH_3), 3.69 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.06 (1H, d, *J* = 8.9 Hz, 6-H), 7.78 (1H, s broad, OH), 8.07 (1H, s, N=CH), 8.15 (1H, d, *J* = 8.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.0 (CH_3), 32.7 (CH_2), 42.8 (2 x CH_3), 113.5 (C), 123.2 (CH), 124.2 (C), 125.4 (C), 129.7 (C), 132.4 (CH), 153.7 (C), 168.6 (C=O), 170.4 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 262.1192, $C_{13}H_{16}N_3O_3$ requires 262.1198.

6-Bromo-4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5p



To a solution of 4-bromo-2-furaldehyde (175 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 3.5 h *N*-ethyl maleimide (125 mg, 1.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 1.5 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5p** as a yellow solid (273 mg, 84%). R_f = 0.45 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2918, 2864, 1751, 1696, 1586, 1431; M.p. 166-168 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.25 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.14 (6H, s, 2 x CH_3), 3.69 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.65 (1H, s, 6-H), 7.92 (1H, s, N=CH), 8.31 (1H, s, 7-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.0 (CH_3), 32.9 (CH_2), 42.7 (2 x CH_3), 122.3 (N=CH), 123.0 (C), 123.6 (CH), 128.3 (C), 131.1 (CH), 134.1 (C), 137.9 (C), 167.2 (C=O), 168.7 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 324.0343, $C_{13}H_{15}{}^{79}BrN_3O_2$ requires 324.0348.

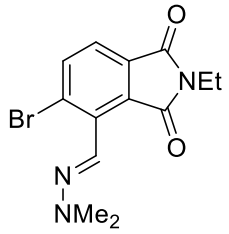
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-6-phenylisoindoline-1,3-dione 5q



To a solution of 4-phenyl-2-furaldehyde (179 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 4 h *N*-ethyl maleimide (250 mg, 2.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 4 h, the mixture was cooled

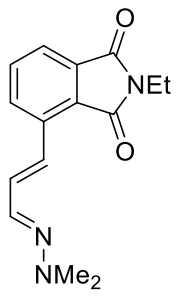
to rt and the precipitate collected by filtration, washed with cold water (100 mL), and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give **5q** as a yellow solid (260 mg, 81%). R_f = 0.34 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2979, 2921, 2868, 2850, 1752, 1694, 1549; M.p. 153-155 °C (EtOAc); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.29 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.14 (6H, s, 2 x CH_3), 3.74 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.42 (1H, t, *J* = 7.4 Hz, Ph-4-H), 7.48 (2H, t, *J* = 7.6 Hz, Ph-3-H), 7.67 (2H, d, *J* = 7.4 Hz, Ph-2-H), 7.84 (1H, d, *J* = 1.2 Hz, 7-H), 8.13 (1H, s, N=CH), 8.43 (1H, d, *J* = 1.2 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_2CH_3), 32.9 (CH_2CH_3), 42.7 (2 x CH_3), 119.7 (7-CH), 123.6 (C), 124.6 (N=CH), 127.1 (5-CH), 127.5 (CH), 128.6 (CH), 129.1 (CH), 133.5 (C), 136.6 (C), 139.7 (C), 146.6 (C), 168.4 (C=O), 169.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 322.1555, $C_{19}H_{20}N_3O_2$ requires 322.1556.

5-Bromo-4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5r



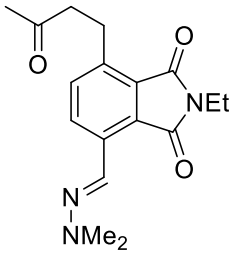
To a solution of 3-bromo-2-furaldehyde (175 mg, 1.0 mmol) in water (4 mL, pH 6) *N*,*N*-dimethylhydrazine (78 mg, 99 µL, 1.3 mmol) was added and the mixture was stirred at 50 °C. After 3.5 h *N*-ethyl maleimide (125 mg, 1.0 mmol) was added and the reaction stirred at the same temperature with a precipitate forming within 5 min. After 2.5 h, the mixture was cooled to rt and the precipitate collected by filtration, washed with cold water (100 mL), and dried in vacuo to give **5r** as a yellow solid (256 mg, 79%). R_f = 0.4 (Pet. Ether 40-60/EtOAc, 9:1); IR (film, cm^{-1}) 2921, 2864, 2792, 1758, 1693, 1546, 1437; M.p. 112-114 °C (water); ^{1}H NMR ($CDCl_3$; 600 MHz) 1.23 (3H, t, *J* = 7.2 Hz, NCH_2CH_3), 3.12 (6H, s, 2 x CH_3), 3.68 (2H, q, *J* = 7.2 Hz, OCH_2CH_3), 7.42 (1H, d, *J* = 7.8 Hz, 6-H), 7.80 (1H, s, N=CH), 7.86 (1H, d, *J* = 7.8 Hz, 7-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.0 (CH_3), 33.1 (NCH_2CH_3), 42.5 (2 x CH_3), 120.9 (CH), 123.5 (N=CH), 126.5 (C), 128.2 (C), 131.9 (CH), 135.3 (CH), 139.4 (CH), 167.4 (C=O), 167.8 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 324.0343, $C_{13}H_{15}{}^{79}BrN_3O_2$ requires 324.0348.

4-(3-(2,2-Dimethylhydrazono)prop-1-en-1-yl)-2-ethylisoindoline-1,3-dione 5s



To a solution of 2-furfurylacrolein **1k** (104 mg, 850 μmol) in water (4 mL, pH 6), *N*,*N*-dimethylhydrazine (61.3 mg, 77.6 μL, 1.02 mmol) was added and the mixture was stirred at 50 °C for 30 min. *N*-Ethyl maleimide **3a** (189 mg, 1.70 mmol) was added and the reaction stirred at 50 °C for 18 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5k** as yellow needles (147 mg, 64%). R_f 0.56 (Pet. Ether 40-60/EtOAc, 2:3); M.p. 145-146 °C ($CDCl_3$); IR (film, cm^{-1}) 2919, 2864, 1764, 1695, 1608; ^1H NMR ($CDCl_3$; 600 MHz) 1.26 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 3.00 (6H, s, 2 x CH_3), 3.72 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.12-7.19 (2H, m, $CHCHCNNMe_2$), 7.58 (1H, t, *J* = 7.3 Hz, 6-H), 7.64 (1H, d, *J* = 7.3 Hz, 7-H), 7.70 (1H, d, *J* = 14.3 Hz, N=CH), 7.88 (1H, d, *J* = 7.3 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_3), 32.9 (CH_2), 42.7 (2 x CH_3), 121.4 (CH), 123.7 (N=CH), 126.0 (C), 129.4 (CH), 132.7 (CH), 133.0 (C), 133.4 (CH), 133.6 (CH), 136.8 (C), 168.3 (C=O), 169.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 272.1403, $C_{15}H_{18}N_3O_2$ requires 272.1399.

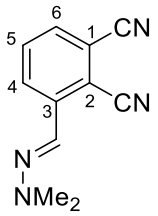
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(3-oxobutyl)isoindoline-1,3-dione 5t



To a solution of 4-(5-((2,2-dimethylhydrazono)methyl)furan-2-yl)butan-2-one **2t** (208 mg, 1.00 mmol) in water (4 mL, pH 6), *N*-ethyl maleimide **3a** (250 mg, 2.00 mmol) was added and the reaction stirred at 50 °C for 4 h. The mixture was cooled and the precipitate was collected by filtration, washed with cold water (2 x 25 mL) and dried to give **5t** as yellow needles (184 mg, 58%). R_f 0.32 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 132-133 °C (H_2O); IR (film, cm^{-1}) 2936, 1754, 1694, 1545, 1441; ^1H NMR ($CDCl_3$; 600 MHz) 1.26 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 2.16 (3H, s, $C(O)CH_3$), 2.82 (2H, t, *J* = 7.6 Hz, $CH_2C(O)Me$), 3.10 (6H, s, 2 x CH_3), 3.28 (2H, t, *J* = 7.6 Hz, $ArCH_2$), 3.70 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.37 (1H, d, *J* = 8.4 Hz, 6-H), 8.11 (1H, d, *J* = 8.4 Hz, 5-H), 8.13 (1H, s, N=CH); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.1 (CH_2CH_3), 25.8 (CH_2), 30.0 ($C(O)CH_3$), 32.7 (CH_2CH_3), 42.8 (2 x CH_3), 44.3 (CH_2), 125.2 (C), 125.4 (C), 128.6 (C), 129.2 (CH), 134.8 (CH), 135.7 (CH), 138.9 (C), 168.9 (C=O), 169.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 316.1653, $C_{17}H_{23}N_3O_3$ requires 316.1661.

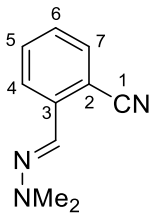
4. Preparation of Aromatics 8

3-((2,2-Dimethylhydrazono)methyl)phthalonitrile 8a[4]



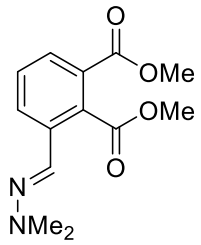
To a solution of 2-furaldehyde dimethylhydrazone **2a** (48.6 mg, 46.4 µL, 350 µmol) in water (2 mL, pH 6), fumaronitrile **7a** (54.6 mg, 700 µmol) was added and the reaction stirred at reflux for 48 h. The mixture was cooled to rt and the organic component extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$, and the solvent removed under vacuum. The crude reaction mixture was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give **8a** as pale green needles (47.6 mg, 68%). R_f 0.22 (Pet. Ether 40-60/EtOAc, 17:3); M.p. 168-169 °C (EtOAc), Lit[1] 165-166 °C ($CHCl_3$); IR (film, cm^{-1}) 2219, 1570, 1546; ^1H NMR ($CDCl_3$; 600 MHz) 3.16 (6H, s, 2 x CH_3), 7.29 (1H, s, N=CH), 7.52 (1H, dd, *J* = 7.4, 1.4 Hz, 6-H), 7.55 (1H, m, 5-H), 8.19 (1H, dd, *J* = 8.0, 1.4 Hz, 4-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.7 (2 x CH_3), 110.7 (C), 115.0 (C), 116.1 (CN), 116.2 (CN), 122.3 (CH), 128.3 (CH), 130.5 (CH), 132.4 (CH), 142.6 (C); *m/z* HRMS (ESI+) found $[MH]^+$ 199.0979, $C_{11}H_{11}N_4$ requires 199.0984.

3-((2,2-Dimethylhydrazono)methyl)benzonitrile 8b



To a solution of 2-furaldehyde dimethylhydrazone **2a** (48.6 mg, 46.4 µL, 350 µmol) in water (2 mL, pH 6), acrylonitrile **7b** (35.9 mg, 46.4 µL, 700 µmol) was added and the reaction stirred at reflux for 24 h. The mixture was cooled to rt and the organic component extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$, and the solvent removed under vacuum. The crude reaction mixture was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give **8b** as a pale green oil (8.5 mg, 24%). R_f 0.66, 0.74 (Pet. Ether 40-60/EtOAc, 3:2); IR (film, cm^{-1}) 2219, 1570; ^1H NMR ($CDCl_3$; 600 MHz) 3.09 (6H, s, 2 x CH_3), 7.21 (1H, t, *J* = 7.8 Hz, 5-H), 7.37 (1H, s, N=CH), 7.48 (1H, t, *J* = 7.8 Hz, 6-H), 7.56 (1H, d, *J* = 7.8 Hz, 7-H), 7.95 (1H, d, *J* = 7.8 Hz, 4-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.7 (2 x CH_3), 109.0 (C), 118.3 (CN), 124.4 (C), 125.7 (CH), 126.6 (CH), 132.7 (CH), 132.8 (CH), 140.4 (C); *m/z* HRMS (ESI+) found $[MH]^+$ 174.1023, $C_{10}H_{12}N_2$ requires 174.1031.

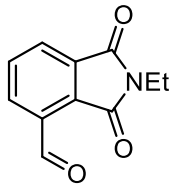
Dimethyl-3-((2,2-dimethylhydrazono)methyl)phthalate 8c



To a solution of furfural **1a** (96.1 mg, 82.9 µL, 1.00 mmol) in water (2 mL, pH 6), *N*,*N*-dimethylhydrazine (72.1 mg, 91.4 µL, 1.20 mmol) was added and the mixture was stirred at 50 °C for 30 min. Dimethyl maleate **7c** (288 mg, 250 µL, 2.00 mmol) was added and the reaction stirred at reflux for 24 h. The mixture was cooled to rt and the organic component extracted with ethyl acetate (3 x 50 mL), dried with $MgSO_4$, and the solvent removed under vacuum. The crude reaction mixture was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give **8c** as a yellow oil (44.8 mg, 19%). R_f 0.39 (Pet. Ether 40-60/EtOAc, 3:2); IR (film, cm^{-1}) 1721 (str), 1555; ^1H NMR ($CDCl_3$; 600 MHz) 2.99 (6H, s, 2 x CH_3), 3.88 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 7.12 (1H, s, N=CH), 7.40 (1H, t, *J* = 7.9 Hz, 5-H), 7.81 (1H, dd, *J* = 7.9, 1.1 Hz, 6-H), 8.02 (1H, dd, *J* = 7.9, 1.1 Hz, 4-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 42.7 (2 x CH_3), 52.6 (OCH_3), 52.7 (OCH_3), 127.1 (N=CH), 128.4 (C), 128.4 (CH), 129.3 (CH), 129.5 (CH), 132.4 (C), 134.9 (C), 136.4 (C), 166.5 (C=O), 169.7 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 265.1182, $C_{13}H_{17}N_2O_4$ requires 265.1188.

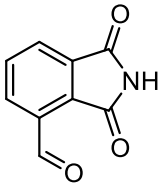
5. Preparation of Aldehydes 9

2-Ethyl-1,3-dioxoisoindoline-4-carbaldehyde 9a



To a solution of 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol) in acetone (30 mL), Amberlyst® 15 (1.00g) was added, and the mixture was stirred at rt for 3 h. The Amberlyst was removed by filtration and the solvent removed under vacuum to give **9a** as an off-white solid (192 mg, 94%). R_f 0.44 (Pet. Ether 40-60/EtOAc, 2:1); M.p. 126-127 °C (Acetone); IR (film, cm^{-1}) 1773, 1692, 1610; ^1H NMR ($CDCl_3$; 600 MHz) 1.31 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 3.80 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 7.84 (1H, t, *J* = 7.5 Hz, 6-H), 8.02 (1H, d, *J* = 7.5 Hz, 7-H), 8.24 (1H, d, *J* = 7.5 Hz, 5-H), 11.05 (1H, s, CHO); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.0 (CH_3), 33.4 (CH_2), 128.0 (CH), 131.4 (CH), 132.3 (C), 133.1 (C), 133.7 (C), 134.3 (CH), 167.3 (C=O), 167.7 (C=O), 188.9 (CHO); *m/z* HRMS (ESI+) found $[MH]^+$ 204.0652, $C_{11}H_{10}NO_3$ requires 204.0661.

1,3-Dioxoisoindoline-4-carbaldehyde 9b

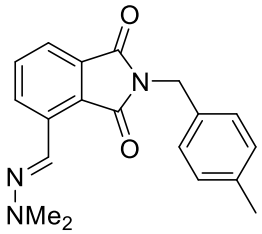


To a solution of 4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione **5b** (217 mg, 1.00 mmol) in acetone (70 mL), Amberlyst® 15 (1.00g) was added, and the mixture was stirred at rt for 3 h. The Amberlyst was removed by filtration and the solvent removed under vacuum to give **9b** as a pale yellow solid (169 mg, 97%). R_f 0.60 (Pet. Ether 40-60/EtOAc, 2:1); M.p. 226 °C (Acetone); IR (film, cm^{-1}) 3212 (br, NH), 1773, 1700, 1610; ^1H NMR (acetone-d_6; 600 MHz) 8.01 (1H, t, *J* = 7.3 Hz, 6-H), 8.13 (1H, d, *J* = 7.3 Hz, 7-H), 8.22 (1H, d, *J* = 7.3 Hz, 5-H), 10.41 (1H, s br, NH), 10.97 (1H, s, CHO); ^{13}C NMR (acetone-d_6; 151 MHz) 128.6 (CH), 131.5 (CH), 134.0 (C), 134.7 (C), 135.0 (C), 135.4 (CH), 168.5 (C=O), 169.3 (C=O), 189.3 (CHO); *m/z* HRMS (ESI+) found $[MH]^+$ 176.0344, $C_9H_6NO_3$ requires 176.0348.

6. Transamidation Reactions

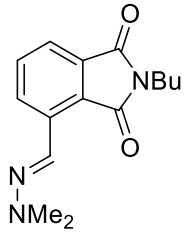
General Boric Acid Transamidation Procedure: To a solution of 4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione **5b** (229 mg, 1.00 mmol) and boric acid (6.2 mg, 0.1 mmol) in toluene (0.2 mL) and 1,4-dioxane (0.2 mL), water (36 µL, 2.0 mmol) and amine (2 or 5 mmol) were added and the mixture was stirred at 100 °C. After 72 h the mixture was cooled to rt and IRA 743 scavenger (approximately 1 g) and water (0.2 mL) were added, and the mixture stirred for a further 1 h. The scavenger resin was removed by filtration and the filtrate collected and the solvent removed under vacuum. The crude product was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95) to give the product.

4-((2,2-Dimethylhydrazono)methyl)-2-(4-methylbenzyl)isoindoline-1,3-dione 5e



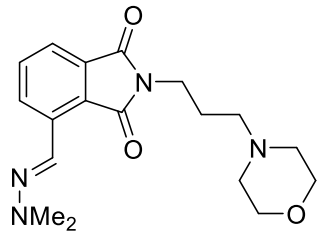
Following the general boric acid procedure with p-tolylmethanamine (255 µL, 2.00 mmol) gave **5e** as a yellow solid (241 mg, 75%). Experimental data as before.

2-Butyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5u



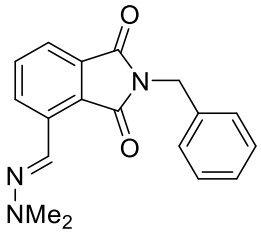
Following the general boric acid procedure with *n*-butylamine (198 µL, 2.00 mmol) gave a **5u** as a yellow solid (252 mg, 92%). R_f 0.41 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 91-92 °C (EtOAc); IR (film, cm^{-1}) 1760, 1696, 1547; ^{1}H NMR ($CDCl_3$; 600 MHz) 0.92 (3H, t, *J* = 7.3 Hz, CH_3), 1.37 (2H, sx, *J* = 7.3 Hz, CH_2), 1.65 (2H, qn, *J* = 7.3 Hz, CH_2), 3.12 (6H, s, 2 x CH_3), 3.65 (2H, t, *J* = 7.3 Hz, CH_2), 7.55 (1H, t, *J* = 7.6 Hz, 6-H), 7.60 (1H, d, *J* = 7.6 Hz, 7-H), 8.11 (1H, s, N=CH), 8.22 (1H, d, *J* = 7.6 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.8 (CH_3), 20.3 (CH_2), 30.8 (CH_2), 37.8 (CH_2), 42.7 (2 x CH_3), 120.9 (CH), 124.7 (N=CH), 124.8 (C), 128.9 (C), 132.5 (C), 133.3 (CH), 136.3 (C), 168.7 (C=O), 169.7 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 274.1551, $C_{15}H_{20}N_3O_2$ requires 274.3382.

4-((2,2-Dimethylhydrazono)methyl)-2-(3-morpholinopropyl)isoindoline-1,3-dione 5v



Following the general boric acid procedure with 3-morpholinopropylamine (292 µL, 2.00 mmol) gave **5v** as a yellow solid (269 mg, 78%). R_f 0.17 (Pet. Ether 40-60/EtOAc, 1:2); M.p. 98-99 °C (Water); IR (film, cm^{-1}) 1759, 1697, 1596, 1547; ^1H NMR ($CDCl_3$; 600 MHz) 1.87 (2H, t, *J* = 6.8 Hz, CH_2), 2.42 (6H, m, CH_2 and 2 x morpholine CH_2), 3.12 (6H, s, 2 x CH_3), 3.58 (4H, m, 2 x morpholine CH_2), 3.74 (2H, t, *J* = 6.9 Hz, CH_2), 7.56 (1H, t, *J* = 7.5 Hz, 6-H), 7.60 (1H, d, *J* = 7.5 Hz, 7-H), 8.10 (1H, s, N=CH), 8.23 (1H, d, *J* = 7.5 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.9 (CH_3), 20.4 (CH_2), 30.9 (CH_2), 37.9 (CH_2), 42.8 (2 x CH_3), 121.0 (CH), 124.8 (N=CH), 124.9 (C), 129.0 (C), 132.6 (C), 133.4 (CH), 136.4 (C), 168.8 (C=O), 169.8 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 345.1924, $C_{18}H_{24}N_4O_3$ requires 345.1927.

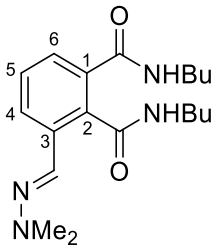
2-Benzyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5w



Following the general boric acid procedure with benzylamine (219 µL, 2.00 mmol) gave **5w** as a yellow solid (191 mg, 62%). R_f 0.29 (Pet. Ether 40-60/EtOAc, 4:1); M.p. 136-138 °C (water); IR (film, cm^{-1}) 1754, 1696, 1546; ^1H NMR ($CDCl_3$; 600 MHz) 3.12 (6H, s, 2 x CH_3), 4.83 (2H, s, CH_2), 7.27 (1H, t, *J* = 7.5 Hz, Ph-4), 7.32 (2H, t, *J* = 7.5 Hz, Ph-3), 7.43 (2H, d, *J* = 7.5 Hz, Ph-2-H), 7.56 (1H, t, *J* = 7.6 Hz, 6-H), 7.63 (1H, d, *J* = 7.6 Hz, 7-H), 8.09 (1H, s, N=CH), 8.23 (1H, d, *J* = 7.6 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 41.5 (CH_2), 42.7 (2 x CH_3), 121.0, 124.5, 124.7, 127.9, 128.6, 128.8, 129.1, 132.4, 133.5, 136.6, 136.7, 168.3 (C=O), 169.2 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 308.0831, $C_{18}H_{18}N_3O_2$ requires 308.1399.

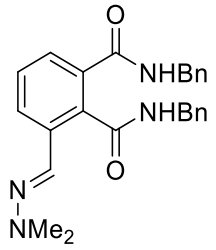
7. Preparation of Diamides 10

N,*N*-Dibutyl-3-((2,2-dimethylhydrazono)methyl)phthalamide 10a



A solution of 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol) in butylamine (4 mL) was stirred for 3 h at rt and then added to water (40 mL). A yellow precipitate formed, the solution was cooled on ice and the precipitate collected by filtration, washed with cold water (2 x 50 mL) and dried to give **10a** (313 mg, 96%) as yellow needles. R_f 0.47 (Pet. Ether 40-60/EtOAc, 2:1); M.p. 132-133 °C (water); IR (film, cm^{-1}) 3258 (br, NH), 1630, 1554, 1458; ^{1}H NMR ($CDCl_3$; 600 MHz) 0.932 (3H, t, *J* = 7.4 Hz, CH_3), 0.935 (3H, t, *J* = 7.4 Hz, CH_3), 1.379 (2H, sx, *J* = 7.4 Hz, CH_2), 1.383 (2H, sx, *J* = 7.4 Hz, CH_2), 1.53 (2H, qn, *J* = 7.4 Hz, CH_2), 1.55 (2H, qn, *J* = 7.4 Hz, CH_2), 2.98 (6H, s, 2 x CH_3), 3.35 (2H, m, NCH_2), 3.40 (2H, m, NCH_2), 6.07 (1H, br t, *J* = 5.0 Hz, NH), 6.51 (1H, br t, *J* = 5.0 Hz, NH), 7.18 (1H, s, N=CH), 7.34 (1H, t, *J* = 7.6 Hz, 5-H), 7.46 (1H, d, *J* = 7.6 Hz, 6-H), 7.95 (1H, d, *J* = 7.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.8 (CH_3), 13.9 (CH_3), 20.2 (CH_2), 20.3 (CH_2), 31.57 (CH_2), 31.61 (CH_2), 40.0 (CH_2), 40.1 (CH_2), 42.7 (2 x CH_3), 126.6 (CH), 126.9 (CH), 127.8 (CH), 129.3 (CH), 132.7 (C), 134.2 (C), 134.5 (C), 168.5 (C=O), 169.8 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 347.2442, $C_{19}H_{31}N_4O_2$ requires 347.2447.

N,*N*-Dibenzyl-3-((2,2-dimethylhydrazono)methyl)phthalamide 10b

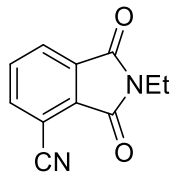


A solution of 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol) in benzylamine (4 mL) was stirred for 3 h at rt and then added to water (40 mL). A yellow precipitate formed, the solution was cooled on ice and the precipitate collected by filtration, washed with cold water (2 x 50 mL), dried, and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 95:5) to give **10b** (311mg, 75%) as yellow needles. R_f 0.53 (Pet. Ether 40-60/EtOAc, 2:1); M.p. 184-185 °C (EtOAc); IR (film, cm^{-1}) 3254 (br, NH), 1636, 1554, 1496; ^{1}H NMR ($(CD_3)_2SO$; 600 MHz) 2.73 (6H, s, 2 x CH_3), 4.33 (2H, d, *J* = 5.8 Hz, NCH_2), 4.41 (2H, d, *J* = 5.8 Hz, NCH_2), 7.01 (1H, s, N=CH); 7.23 (2H, t, *J* = 6.3 Hz, 2 x Ph-3-H) 7.27-7.40 (9H, m, 8 x Ph-H and 5-H), 7.42 (1H, d, *J* = 7.6 Hz, 6-H),

7.87 (1H, d, *J* = 7.6 Hz, 4-H), 8.61 (1H, br t, *J* = 5.8 Hz, NH), 8.81 (1H, br t, *J* = 5.8 Hz, NH); ^{13}C NMR ($(CD_3)_2SO$; 151 MHz) 42.1 (2 x CH_3), 42.5 (CH_2), 42.6 (CH_2), 125.0 (CH), 125.7 (CH), 126.7 (CH), 126.8 (CH), 127.2 (CH), 127.5 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 133.7 (C), 134.7 (C), 134.8 (C), 139.4 (C), 167.4 (C=O), 167.6 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 415.1837, $C_{25}H_{27}N_4O_2$ requires 415.2134.

8. Preparation of Nitrile 11

2-Ethyl-1,3-dioxoisoindoline-4-carbonitrile 11a

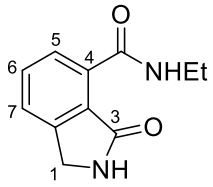


To a solution of 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol) in methanol (10 mL) on ice, magnesium monoperoxyphthalate hexahydrate (1.23 g, 2.50 mmol) was added and the reaction stirred for 5 min. To the reaction mixture, water (20 mL) was added, and the organic component extracted with ethyl acetate (3 x 100 mL), dried with $MgSO_4$, and the solvent removed under vacuum, giving **11a** as a white solid (194 mg, 97%). R_f 0.34 (Pet. Ether 40-60/EtOAc, 3:2); M.p. 158-159 °C (EtOAc); IR (film, cm^{-1}) 2239 (C≡N), 1777, 1704; ^{1}H NMR ($CDCl_3$; 600 MHz) 1.30 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 3.79 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 7.85 (1H, t, *J* = 7.6 Hz, 6-H), 7.97 (1H, dd, *J* = 7.6, 1.1 Hz, 7-H), 8.07 (1H, dd, *J* = 7.6, 1.1 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 13.9 (CH_3), 33.7 (CH_2), 107.8 (C), 114.4 (C), 127.2 (CH), 133.4 (C), 133.5 (C), 134.6 (CH), 137.8 (CH) 165.2 (C=O), 166.4 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 201.0659, $C_{11}H_9N_2O_2$ requires 201.0664.

9. Preparation of Lactams 12

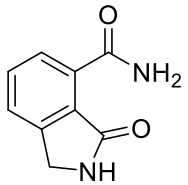
General Lactam Procedure: To a solution of phthalimide hydrazone in water, Pd/C (10%, 50% wet) was added and the reaction vessel evacuated under vacuum and filled with argon. Methanol was added and the reaction vessel evacuated once more and put under hydrogen using a balloon. Formic acid (2 equivalents) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was filtered through Celite and the solution collected. The organic component was extracted with ethyl acetate (3 x 50 mL). H_2SO_4 was added (2 equivalents) and the reaction mixture stirred for 5 min. A white precipitate formed and was collected by filtration, washed with cold ethyl acetate (100 mL), and dried in vacuo, giving the product.

_N_-Ethyl-3-oxoisoindoline-4-carboxamide 12a



Following the general lactam procedure with 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol), Pd/C (20 mg), in water (7 mL) and methanol (14 mL) gave **12a** as white crystals (188 mg, 92%). R_f 0.30 (CH_3OH/EtOAc, 4:1); M.p. decomposed at 205-210 °C; IR (film, cm^{-1}) 2879, 1769, 1697; ^1H NMR (CD_3OD; 600 MHz) 1.27 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 3.74 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 4.58 (2H, s, CH_2), 7.83 (1H, d, *J* = 7.5 Hz, 7-H), 7.86 (1H, t, *J* = 7.5 Hz, 6-H), 7.93 (1H, d, *J* = 7.5 Hz, 5-H); ^{13}C NMR (CD_3OD; 151 MHz) 14.0 (CH_3), 33.9 (CH_2), 39.8 (CH_2), 125.0 (CH), 131.3 (C), 132.4 (C), 134.2 (C), 135.9 (CH), 136.5 (CH), 168.9 (C=O), 170.0 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 205.1094, $C_{11}H_{13}N_3O_2$ requires 205.0977.

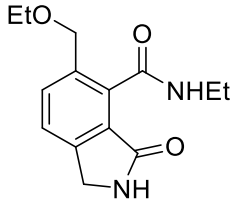
3-Oxoisoindoline-4-carboxamide 12b[6]



Following the general lactam procedure with 4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione **5b** (217 mg, 1.00 mmol), Pd/C (20 mg), in water (7 mL) and methanol (14 mL) gave **12b** as white crystals (173 mg, 98%). R_f 0.28 (CH_3OH/EtOAc, 4:1); M.p. decomposed at 205-210 °C (EtOAc); IR (film, cm^{-1}) 3038 (br), 2925 (br), 1763, 1699, 1600, 1515; ^1H NMR (CD_3OD; 600 MHz) 4.56 (2H, s, CH_2), 7.83 (1H, dd, *J* = 7.3, 1.7 Hz, 7-H), 7.86 (1H, t, *J* = 7.3 Hz, 6-H), 7.90 (1H, dd, *J* = 7.3, 1.7 Hz, 5-H); ^{13}C NMR (CD_3OD; 151 MHz) 39.9 (CH_2), 125.1

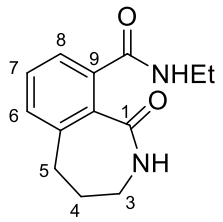
(CH), 132.0 (C), 132.5 (C), 135.1 (C), 136.0 (CH), 136.6 (CH), 170.1 (C=O), 171.3 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 177.0657, $C_9H_9N_2O_2$ requires 177.0664.

5-(Ethoxymethyl)-*N*-ethyl-3-oxoisoindoline-4-carboxamide 12c



Following the general lactam procedure with 4-((2,2-dimethylhydrazono)methyl)-7-(ethoxymethyl)-2-ethylisoindoline-1,3-dione **5j** (60.6 mg, 200 µmol), Pd/C (10 mg), in water (3 mL) and methanol (6 mL) gave **12c** as white crystals (33 mg, 62%). R_f 0.35 (CH_3OH/EtOAc, 4:1); M.p. decomposed at 115-120 °C (EtOAc);IR (film, cm^{-1}) 1764, 1697, 1598, 1504; ^1H NMR (CD_3OD; 600 MHz) 1.23-1.29 (6H, m, NCH_2CH_3 and OCH_2CH_3), 3.67 (2H, q, *J* = 7.2 Hz, NCH_2CH_3), 3.71 (2H, q, *J* = 7.3 Hz, OCH_2CH_3), 4.55 (2H, s, $ArCH_2N$), 4.99 (2H, s, $ArCH_2O$), 7.78 (1H, d, *J* = 8.0 Hz, 7-H), 7.92 (1H, d, *J* = 8.0 Hz, 6-H); ^{13}C NMR (CD_3OD; 151 MHz) 14.0 (CH_3), 15.4 (CH_3), 33.8 (CH_2), 39.8 (CH_2), 67.7 (CH_2), 68.1 (CH_2), 129.8 (C), 131.1 (C), 131.4 (C), 134.5 (CH), 136.5 (CH), 140.9 (C), 169.0 (C=O), 169.9 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 263.1389, $C_{14}H_{19}N_2O_3$ requires 263.1396.

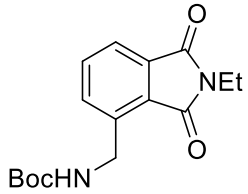
***N*-Ethyl-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepine-9-carboxamide 12d**



Following the general lactam procedure with 4-(3-(2,2-dimethylhydrazono)prop-1-en-1-yl)-2-ethylisoindoline-1,3-dione **5s** (135 mg, 500 µmol), Pd/C (20 mg), in water (3 mL) and methanol (6 mL) gave **12d** as white crystals (52 mg, 45%). R_f 0.11 (CH_3OH/EtOAc, 4:1); M.p. 124-126 °C (EtOAc); IR (film, cm^{-1}) 2942 (w, br), 1767, 1697, 1657, 1556; ^1H NMR (CD_3OD; 600 MHz) 1.23 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 2.02 (2H, qn, *J* = 7.7 Hz, 4-H_2), 2.99 (2H, t, *J* = 7.7 Hz, 5-H_2), 3.17 (2H, t, *J* = 7.7 Hz, 3-H_2), 3.68 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 7.61 (1H, dd, *J* = 6.8, 1.7 Hz, 8-H), 7.67-7.73 (2H, m, 6-H and 7-H), 8.53 (1H, br s, N*H*Et); ^{13}C NMR (CD_3OD; 151 MHz) 14.1 (CH_3), 29.0 (CH_2), 29.9 (CH_2), 33.6 (CH_2), 40.2 (CH_2), 122.5 (CH), 129.9 (C), 134.2 (C), 135.3 (CH), 136.7 (CH), 141.6 (C), 169.4 (C=O), 170.2 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 233.1285, $C_{13}H_{17}N_2O_2$ requires 233.1290.

10. Preparation of Boc-Protected Amine 13

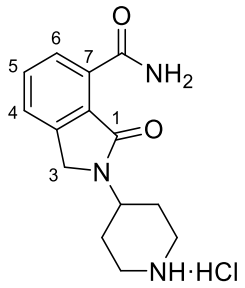
***Tert*-butyl-((2-ethyl-1,3-dioxoisoindolin-4-yl)methyl)carbamate 13**



To a solution of 4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione **5a** (245 mg, 1.00 mmol) in water (7 mL), Pd/C (10%, 50% wet, 20 mg) was added and the reaction vessel evacuated under vacuum and filled with argon. Methanol (14 mL) was added and the reaction vessel evacuated once more and put under hydrogen using a balloon. Formic acid (92.0 mg, 75.4 µL, 2.00 mmol) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was filtered through Celite and the solution collected. Solid $NaHCO_3$ was slowly added until the solution was alkaline, then di-*tert*-butyl dicarbonate (1.09 g, 1.15 mL, 5.00 mmol) added and the reaction stirred at rt for 4 h. The organic component was extracted with ethyl acetate (3 x 100 mL), dried with $MgSO_4$, and the solvent removed under vacuum. The crude product was dry-loaded onto silica and purified by flash column chromatography (Pet. Ether 40-60/EtOAc, 5:95), giving **13a** as a yellow oil (234 mg, 77%). R_f 0.46 (Pet. Ether 40-60/EtOAc, 3:2); IR (film, cm^{-1}) 1807, 1770, 1704, 1508; ^1H NMR ($CDCl_3$; 600 MHz) 1.25 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.39 (9H, s, $C(CH_3)_3$), 3.70 (2H, q, *J* = 7.3 Hz, CH_2CH_3), 4.61 (2H, d, *J* = 6.5 Hz, $ArCH_2$), 5.63 (1H, br t, *J* = 6.5 Hz, NH), 7.61 (1H, t, *J* = 7.4 Hz, 6-H), 7.66 (1H, d, *J* = 7.4 Hz, 7-H), 7.71 (1H, d, *J* = 7.4 Hz, 5-H); ^{13}C NMR ($CDCl_3$; 151 MHz) 14.0 (CH_3), 28.5 ($C(CH_3)_3$), 33.0 (CH_2CH_3), 40.9 ($ArCH_2$), 79.7 ($C(CH_3)_3$), 122.3 (CH), 128.9 (C), 132.9 (C), 134.1 (CH), 134.6 (CH), 138.5 (C), 156.0 ($C(O)O^tBu$), 168.2 (C=O), 169.1 (C=O); *m/z* HRMS (ESI+) found $[MH]^+$ 305.1493, $C_{16}H_{21}N_2O_4$ requires 305.1501.

11. Preparation of 14

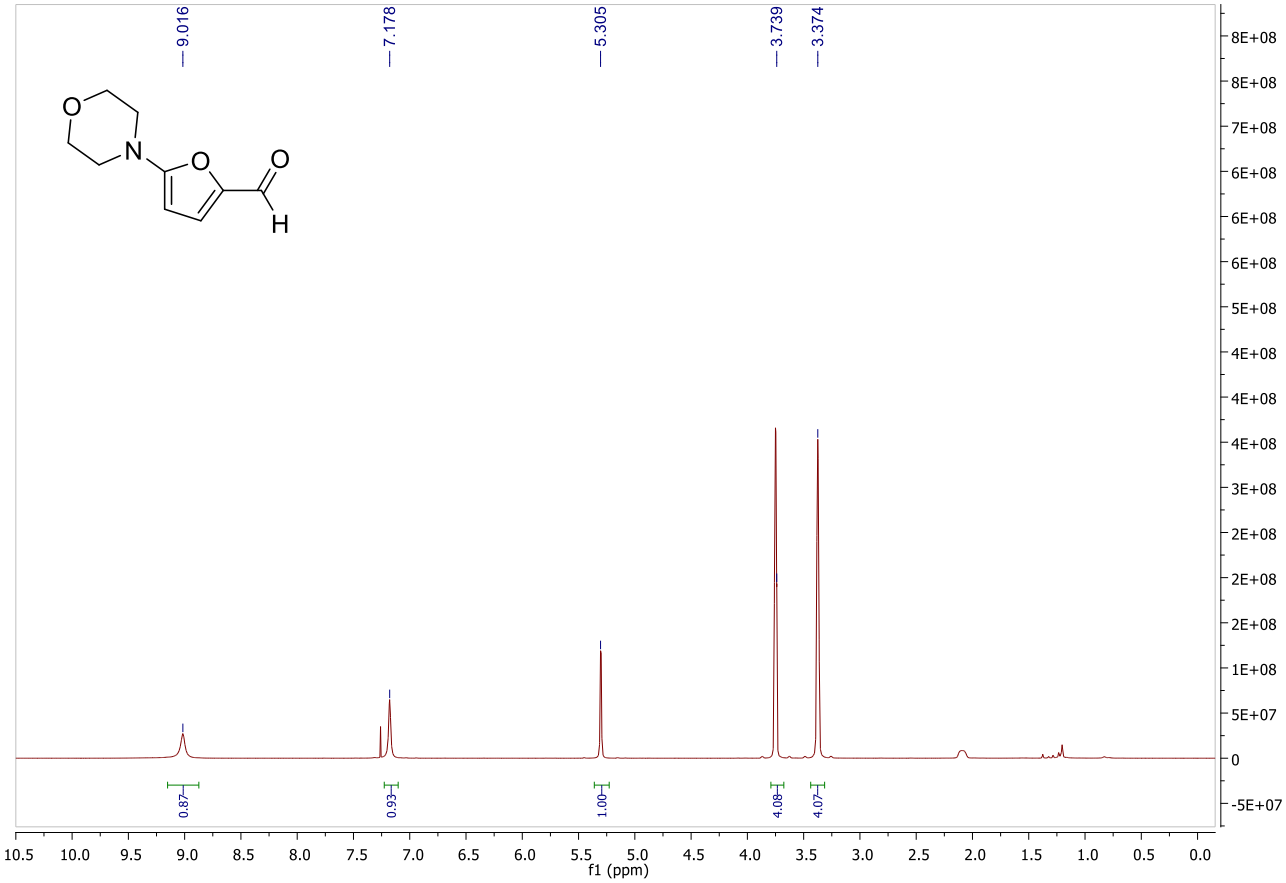
4-(7-carbamoyl-1-oxoisoindolin-2-yl)piperidin-1-ium chloride 14·HCl

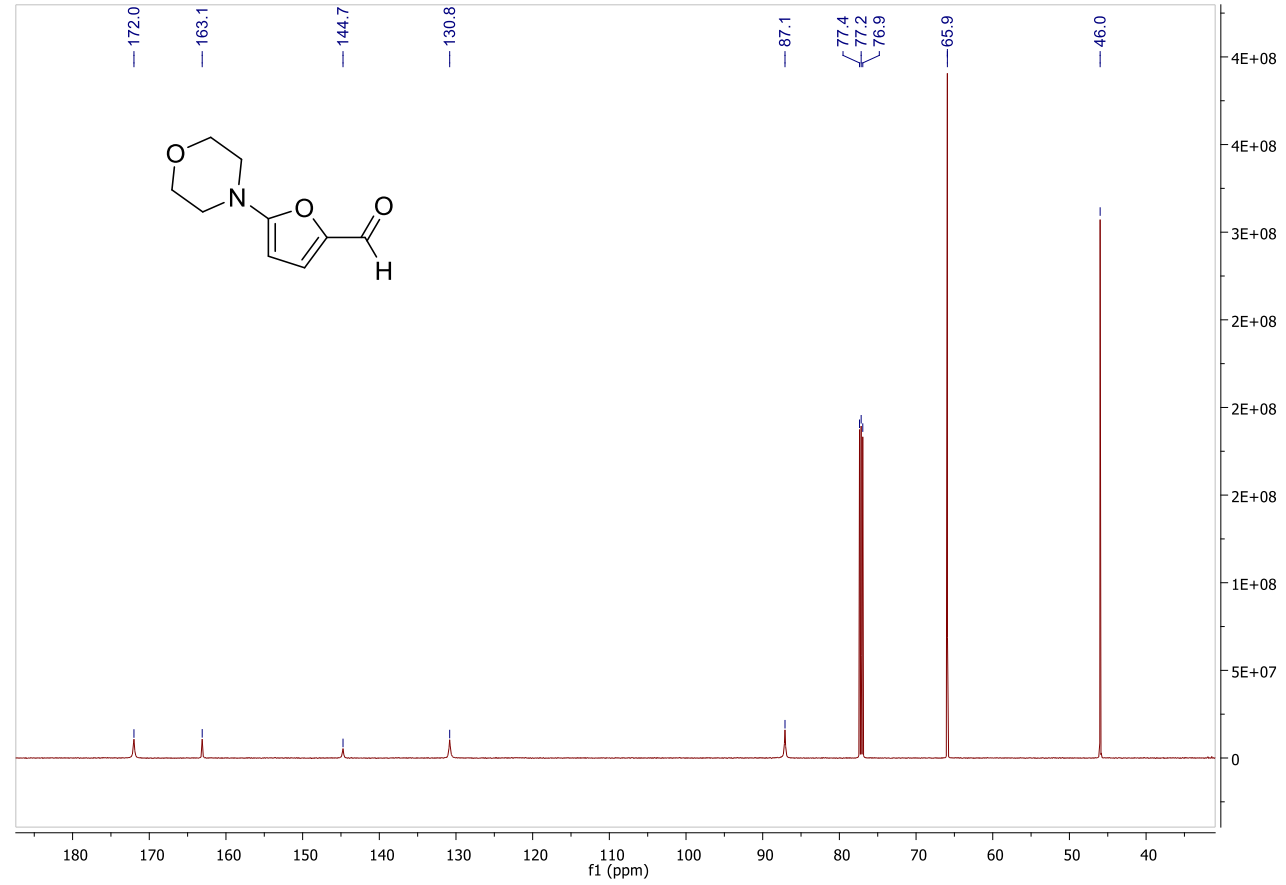


To a dry flask, 1,3-dioxoisoindoline-4-carbaldehyde **9b** (1.05 g, 6.00 mmol), *tert*-butyl 4-aminopiperidine-1-carboxylate **15** (1.20 g, 6.00 mmol), and dry THF (15 mL) were added and the flask sealed, evacuated, filled with nitrogen, and fitted with a nitrogen balloon. The mixture was stirred at rt and tris-(2,2,2-trifluoroethyl) borate (1.85 g, 1.30 mL, 6.00 mmol) added dropwise, then stirred for a further 2 h. Sodium cyanoborohydride (754 mg, 12.0 mmol) was dissolved in THF (5 mL) and added to the reaction mixture, followed by acetic acid (721 mg, 686 µL, 12.0 mmol), and the mixture stirred for a further 2 h. Hydrogen chloride solution (4 M in dioxane, 15 mL) was added slowly and the mixture stirred for 1 h. The precipitate formed was collected by filtration and washed with THF (2 x 50 mL), then recrystallized (EtOH:H_2O, 9:1), giving **14·HCl** as a colourless salt (1.32 g, 74%). M.p. decomposed at 240-250 °C (EtOH/H_2O); IR (film, cm^{-1}) 2960 (br, NH), 2706, 2592, 2517, 1758, 1720, 1701, 1587, 1549, 1455; ^{1}H NMR (D_2O; 600 MHz) 2.06 (2H, d, *J* = 13.2, 4.0 Hz, 2 x C$H_{ax}H_{eq}$), 2.60 (2H, br d, *J* = 13.2 Hz, 2 x C$H_{ax}H_{eq}$), 3.23 (2H, td, *J* = 13.2, 2.2 Hz, 2 x C$H_{ax}H_{eq}NH_2^+$), 3.71 (2H, br d, *J* = 13.2 Hz, 2 x C$H_{ax}H_{eq}NH_2^+$), 3.82 (1H, app tt, *J* = 11.8, 4.0 Hz, CHN), 4.79 (2H, s, ArCH_2), 7.92 (1H, dd, *J* = 7.4, 1.2 Hz, 4-H), 7.95 (1H, t, *J* = 7.4 Hz, 5-H), 8.02 (1H, dd, *J* = 7.4, 1.2 Hz, 6-H); ^{13}C NMR (D_2O; 151 MHz) 25.7 (2 x CH_2), 42.8 (2 x CH_2), 44.3 (CH_2), 53.5 (CH), 125.4 (CH), 129.2 (C), 130.9 (C), 133.6 (C), 136.1 (CH), 137.2 (CH), 171.0 (C=O), 171.5 (C=O); *m/z* HRMS (ESI+) found [**14**H]$^+$ 260.1398, $C_{14}H_{18}N_3O_2$ requires 260.1399.

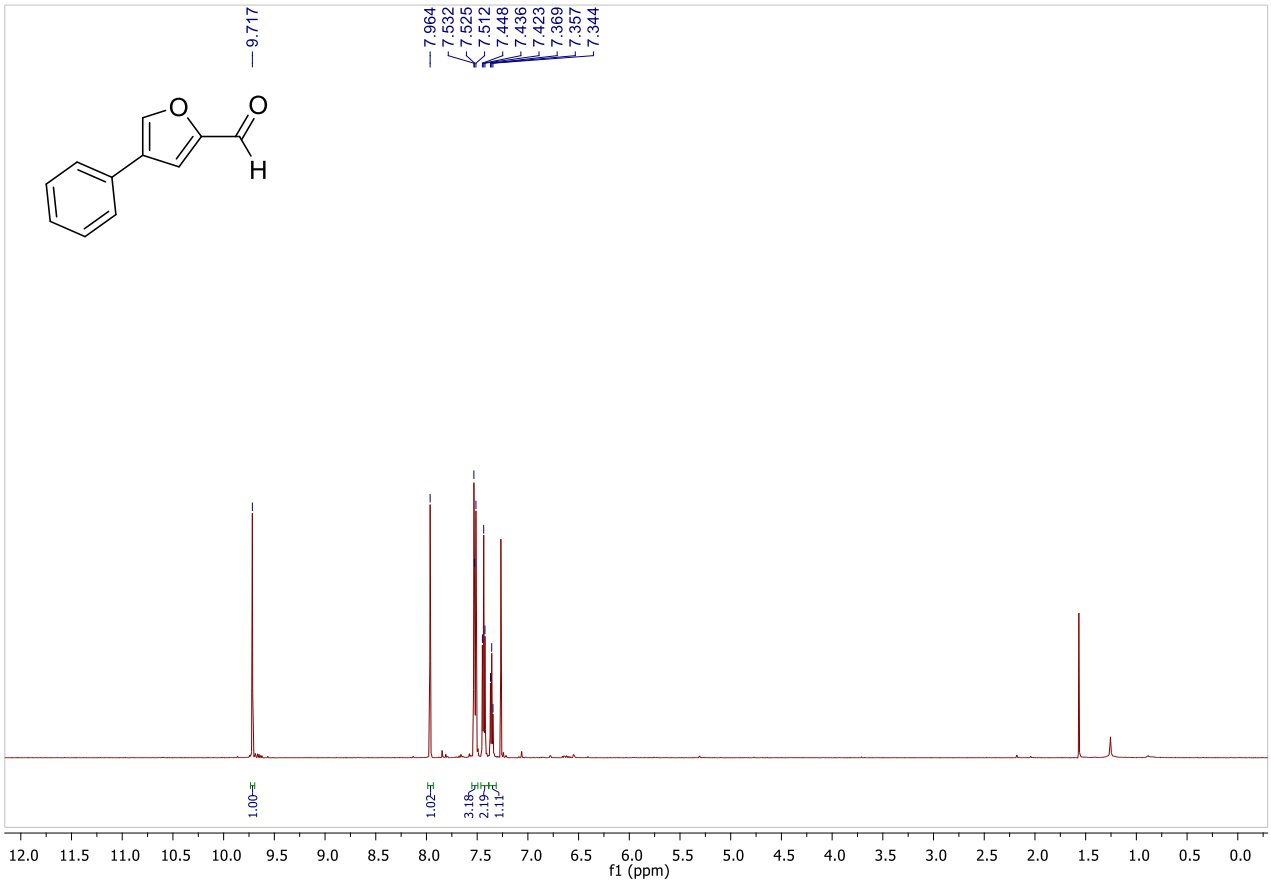
Spectra

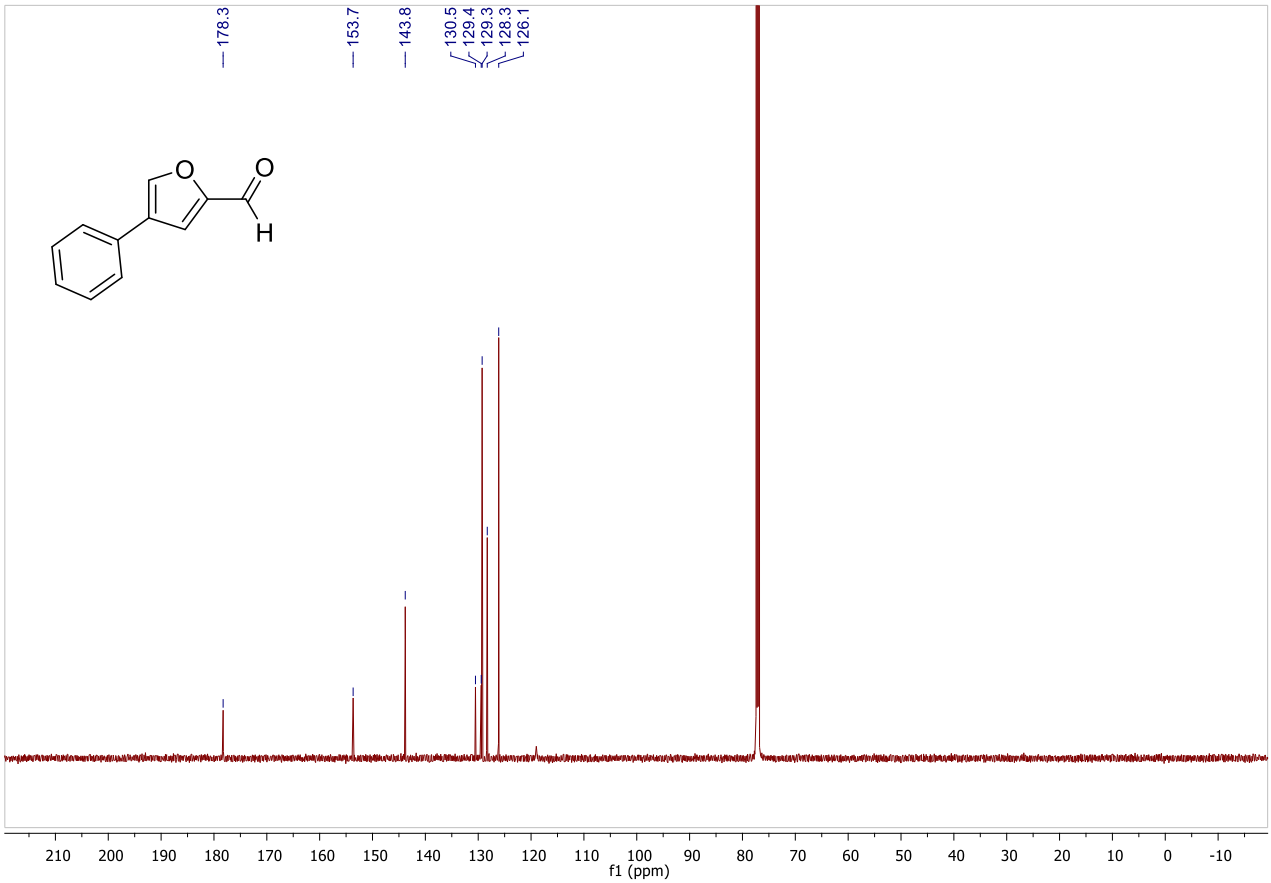
1,1-dimethyl-2-((5-nitrofuran-2-yl)methylene)hydrazine 1l



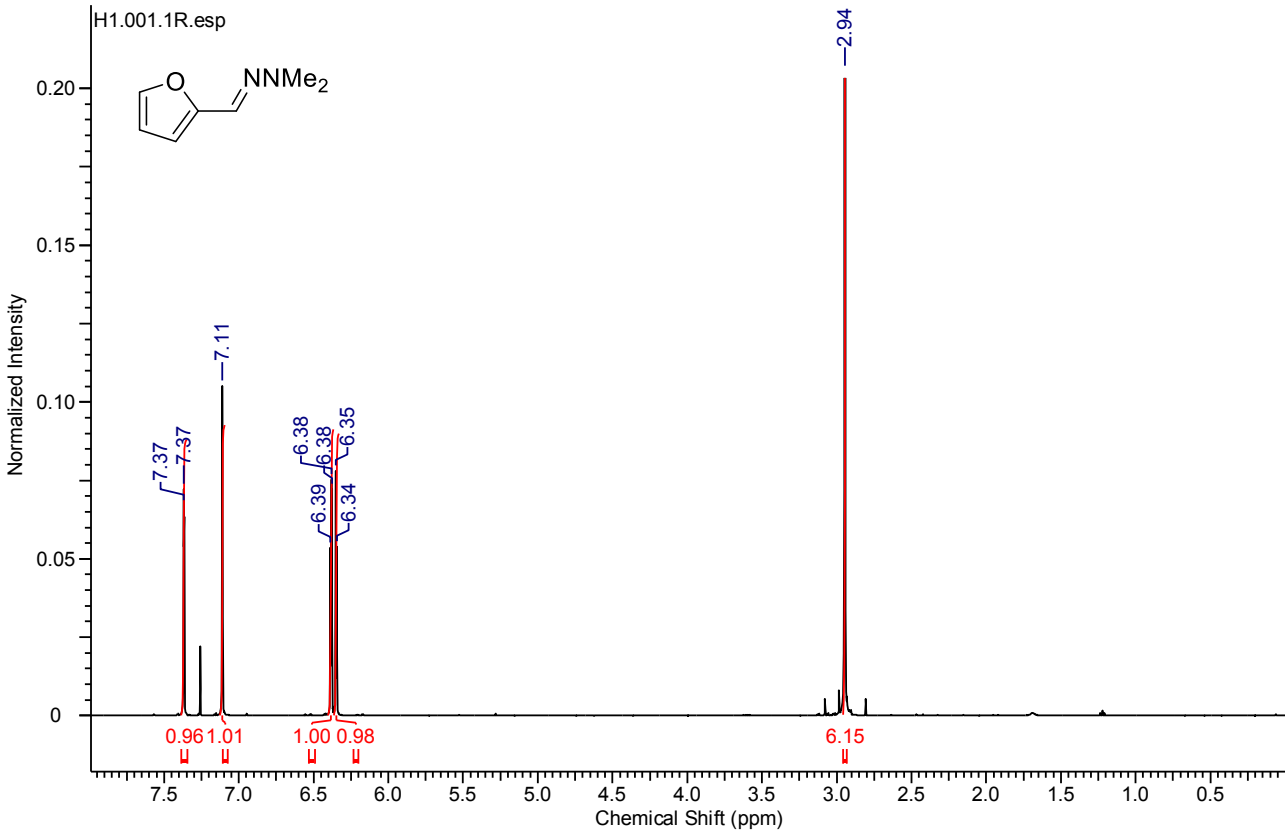


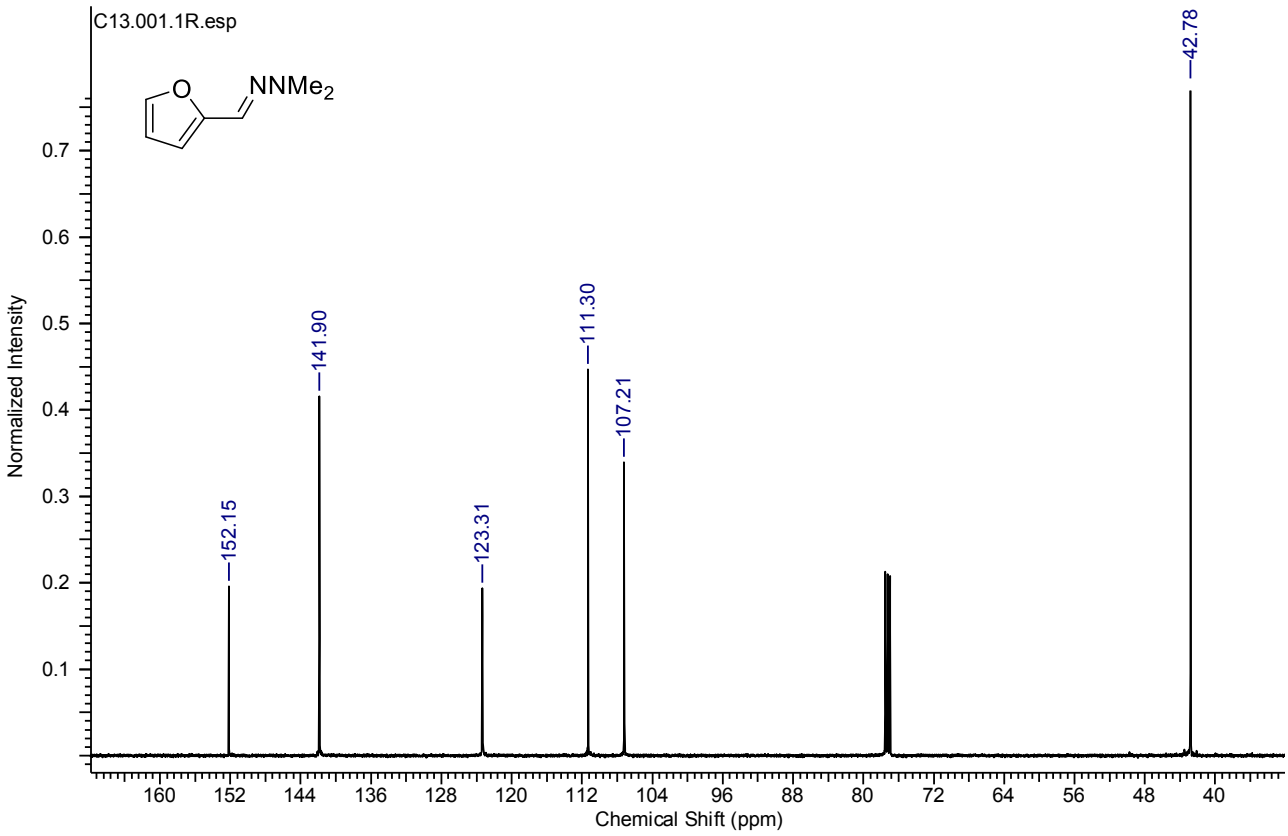
4-Phenylfuran-2-carbaldehyde 1q



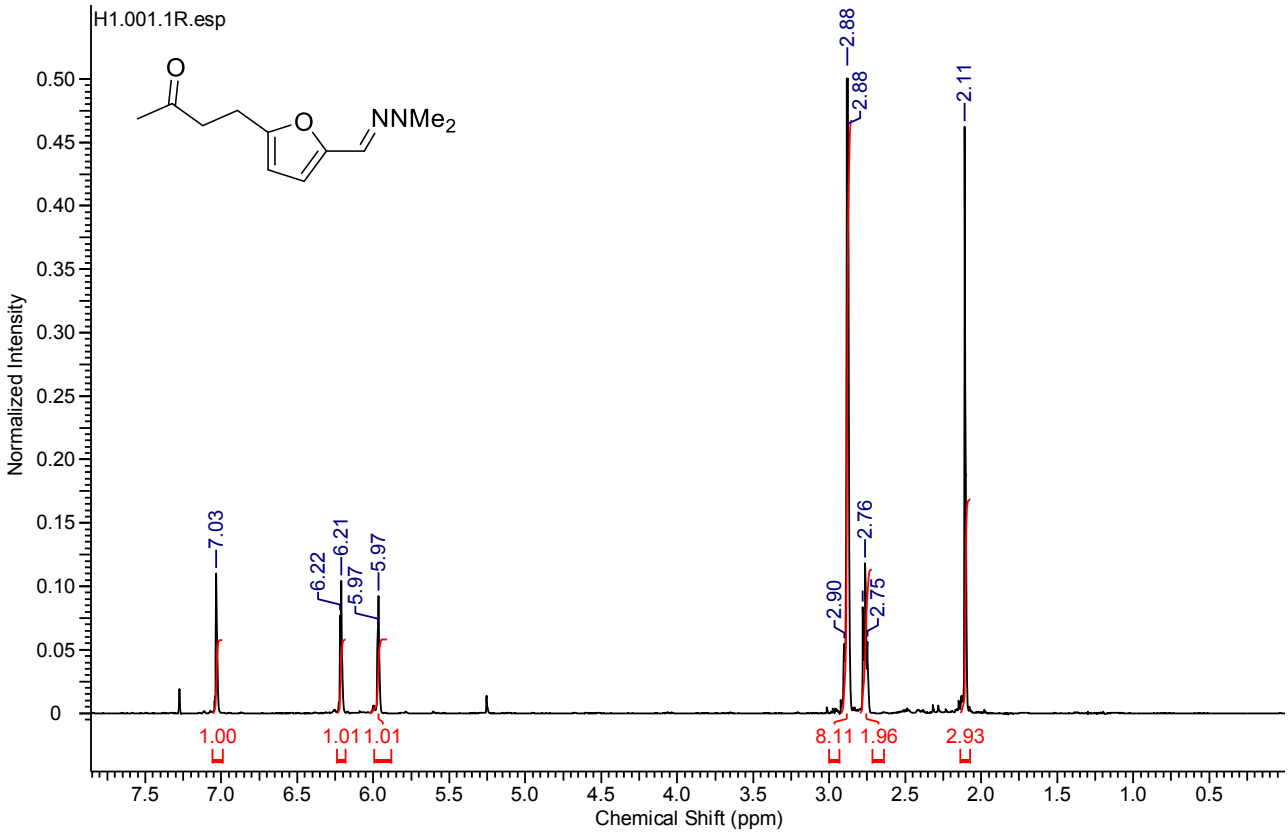


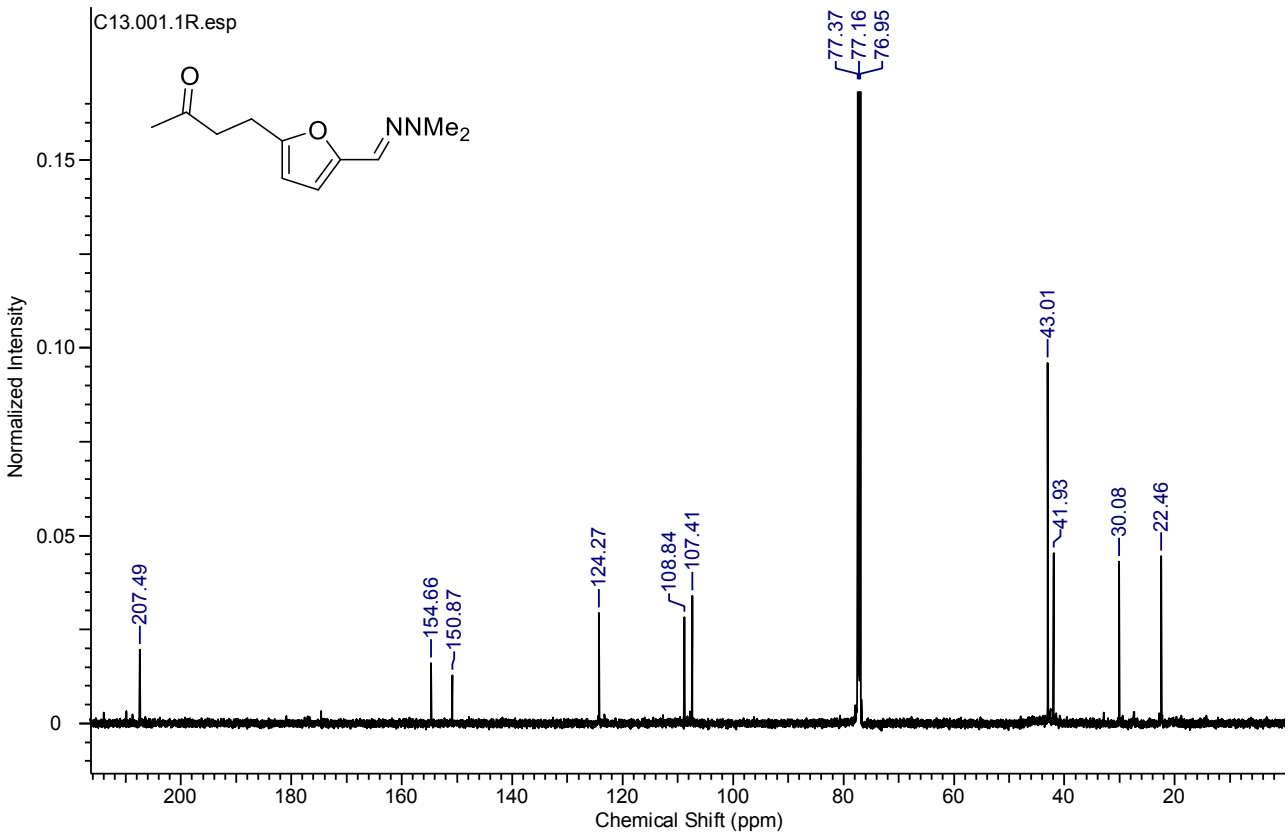
2-Furaldehyde dimethylhydrazone 2a



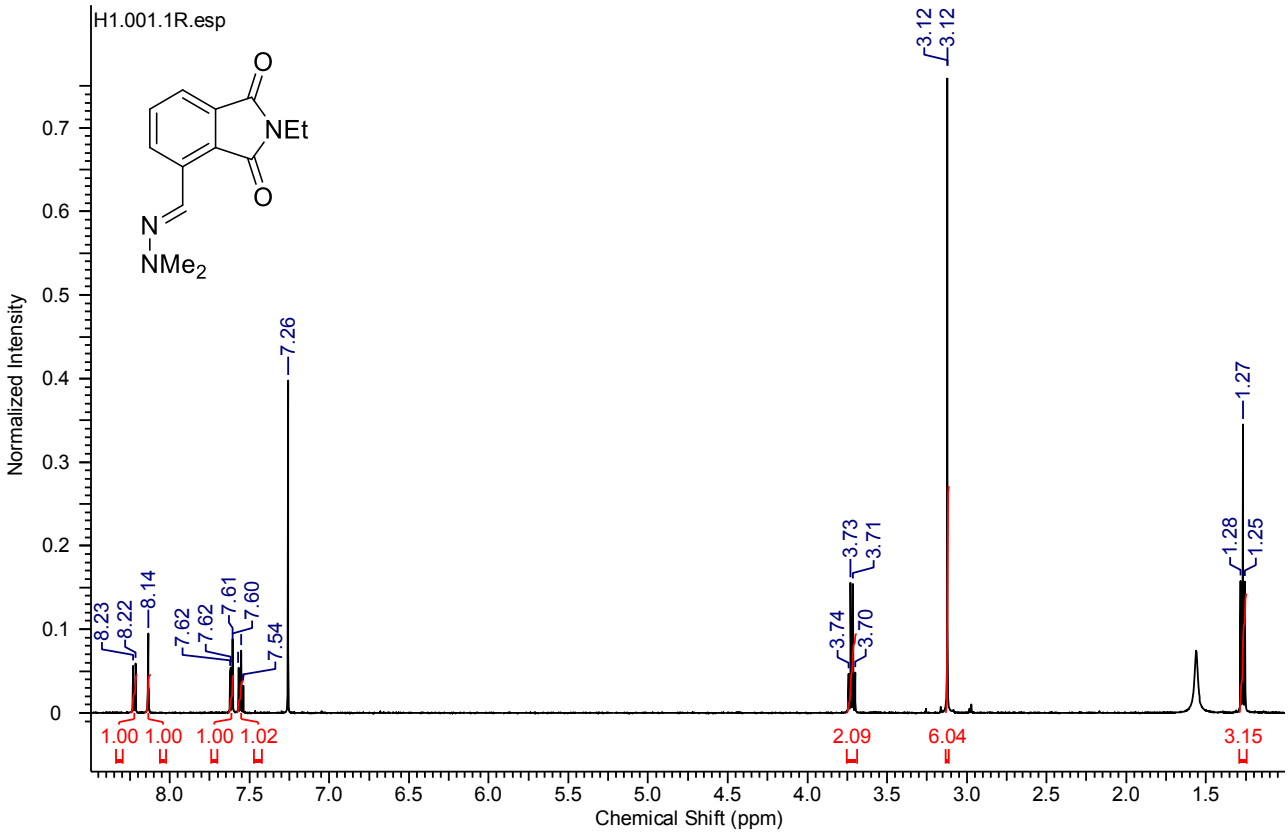


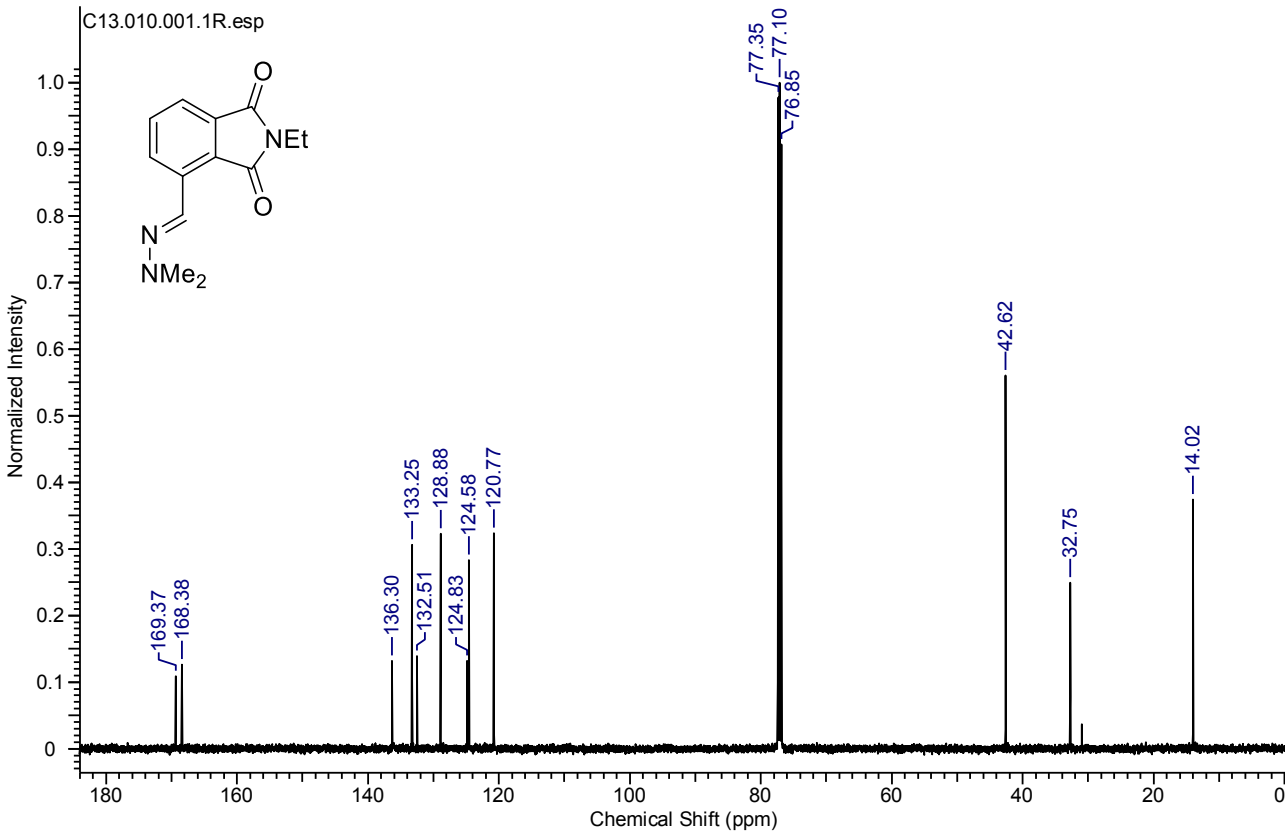
4-(5-((2,2-Dimethylhydrazono)methyl)furan-2-yl)butan-2-one 2t



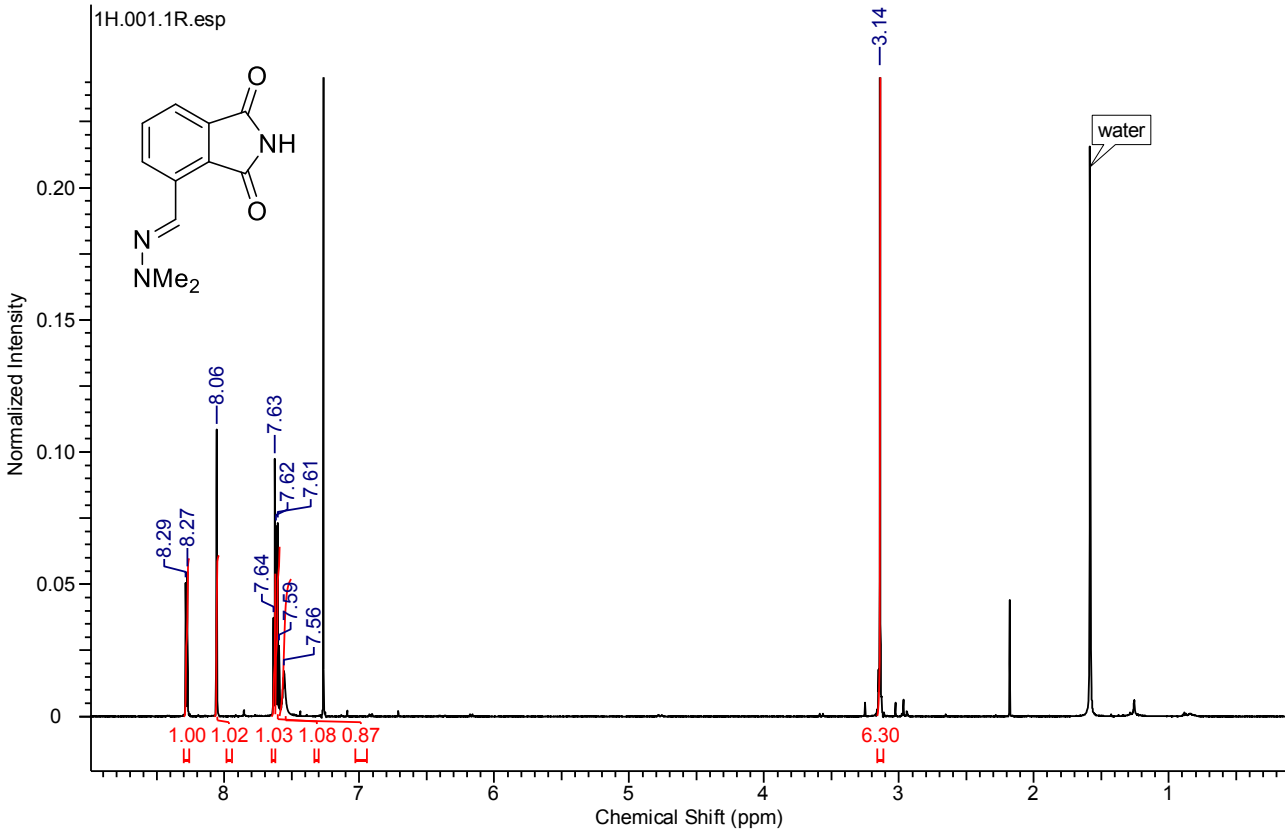


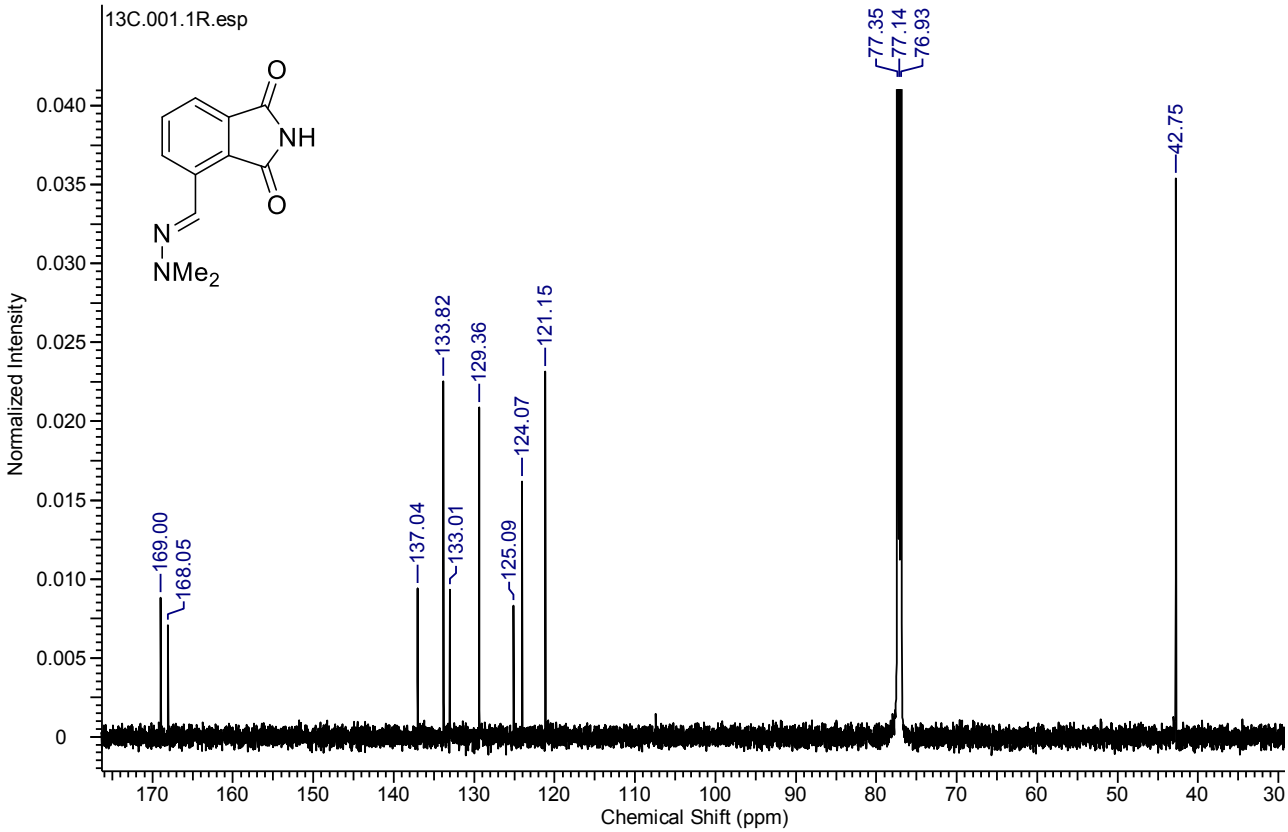
4-((2,2-Dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5a



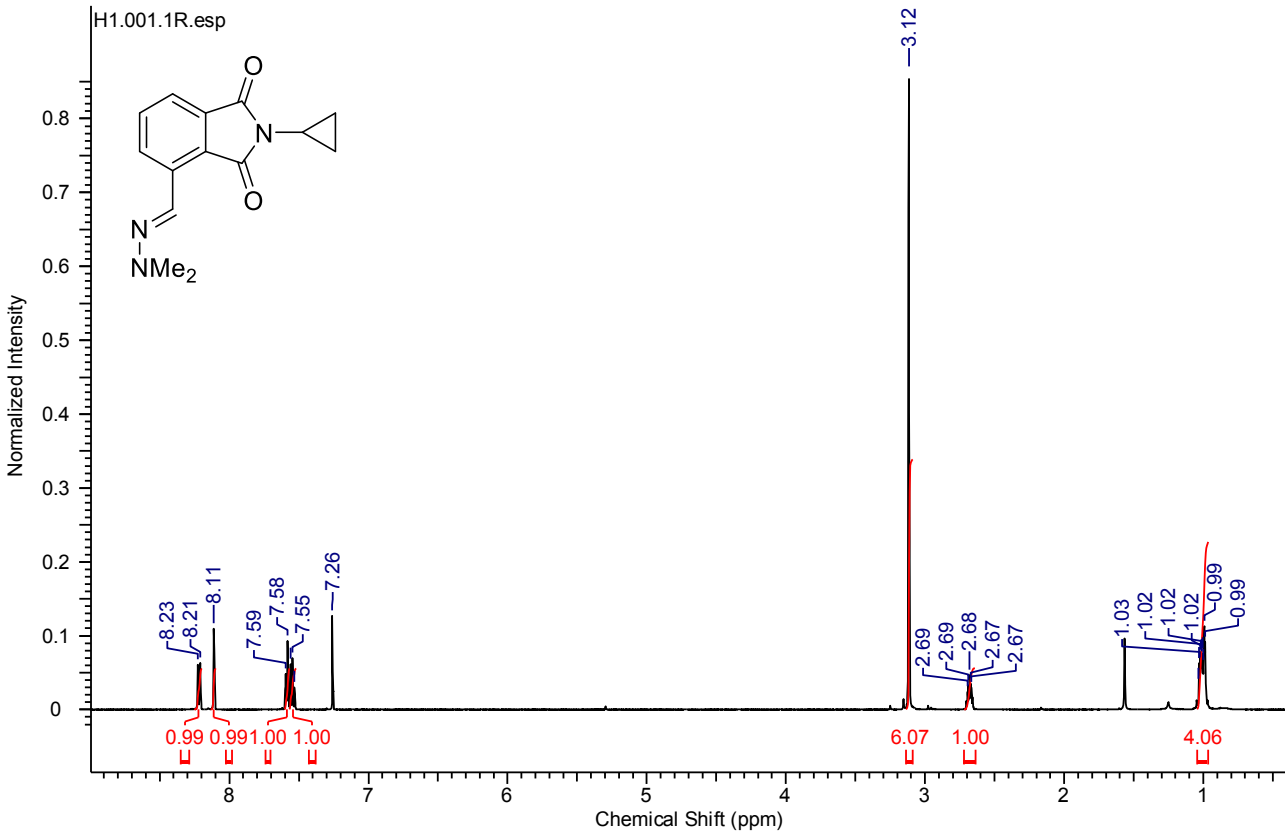


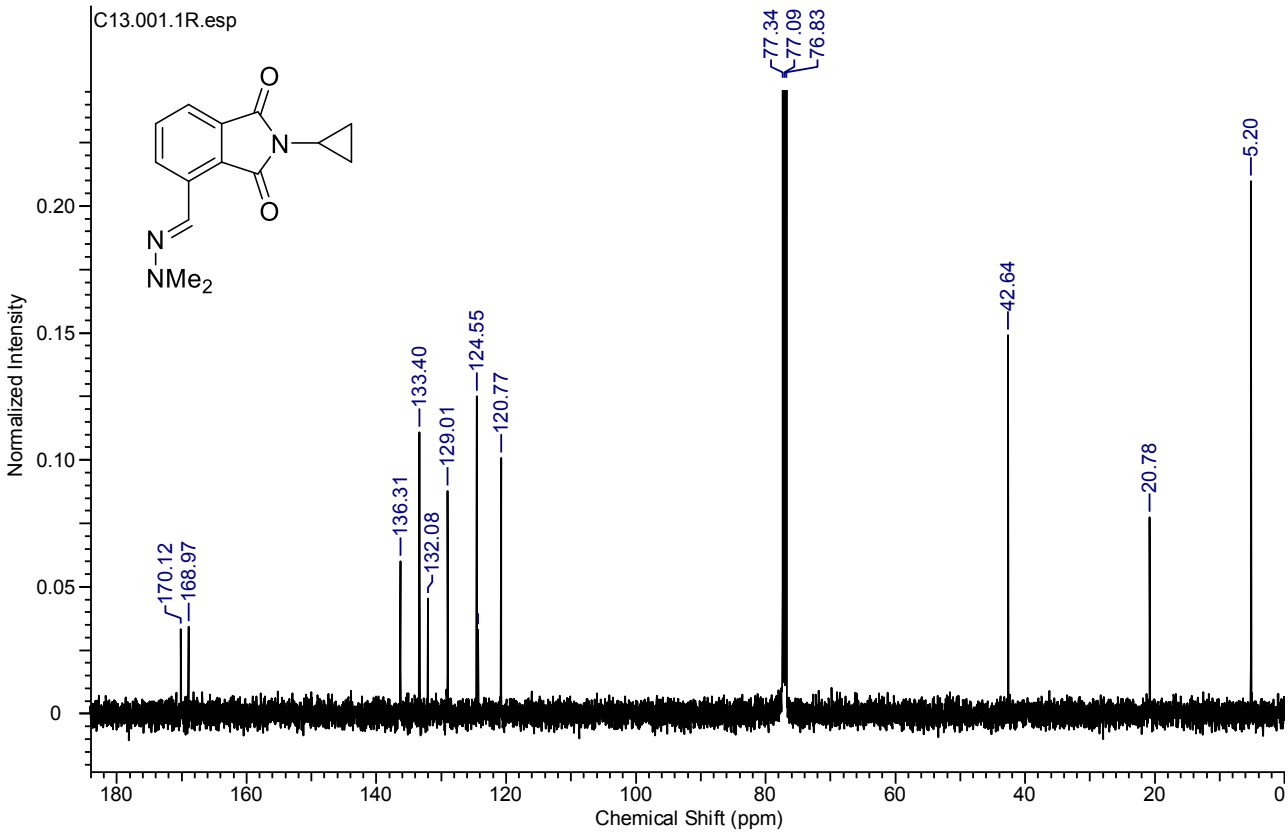
4-((2,2-Dimethylhydrazono)methyl)isoindoline-1,3-dione 5b



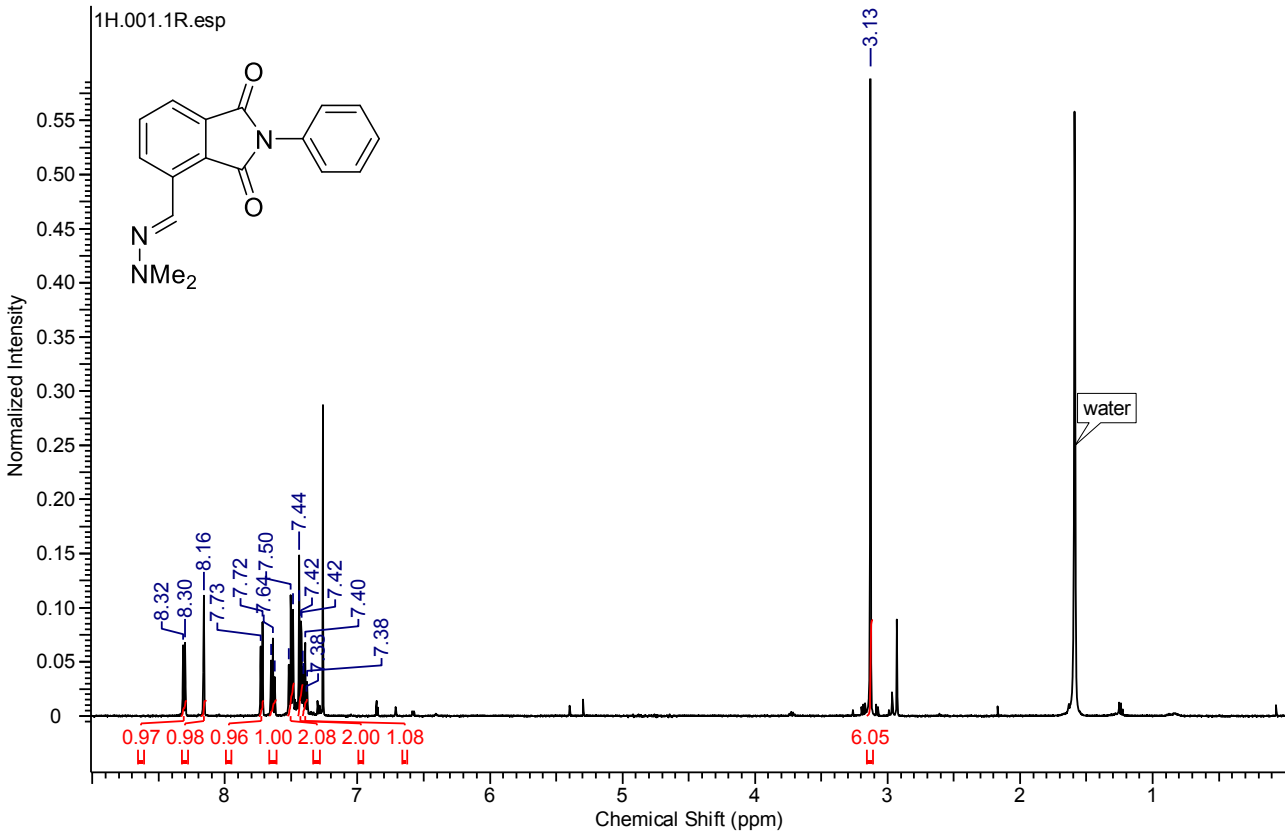


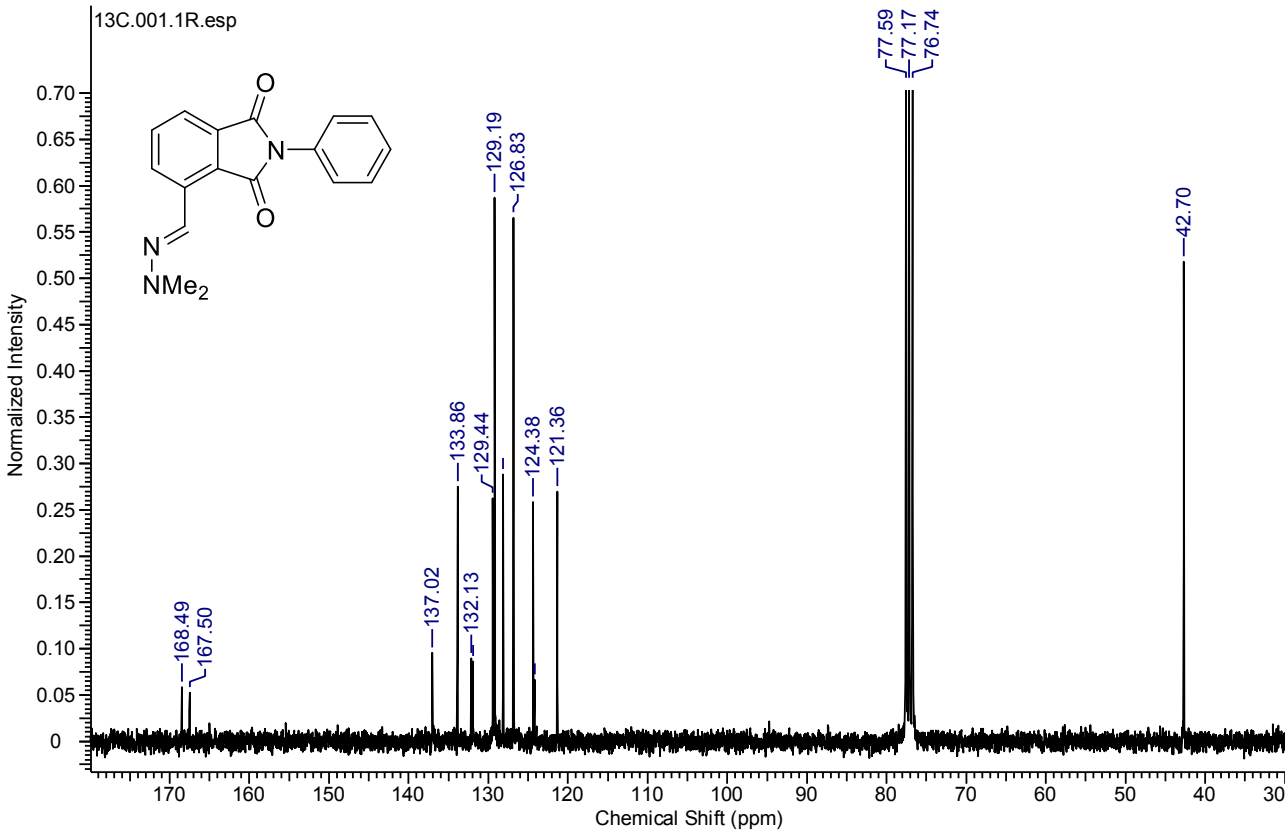
2-Cyclopropyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5c



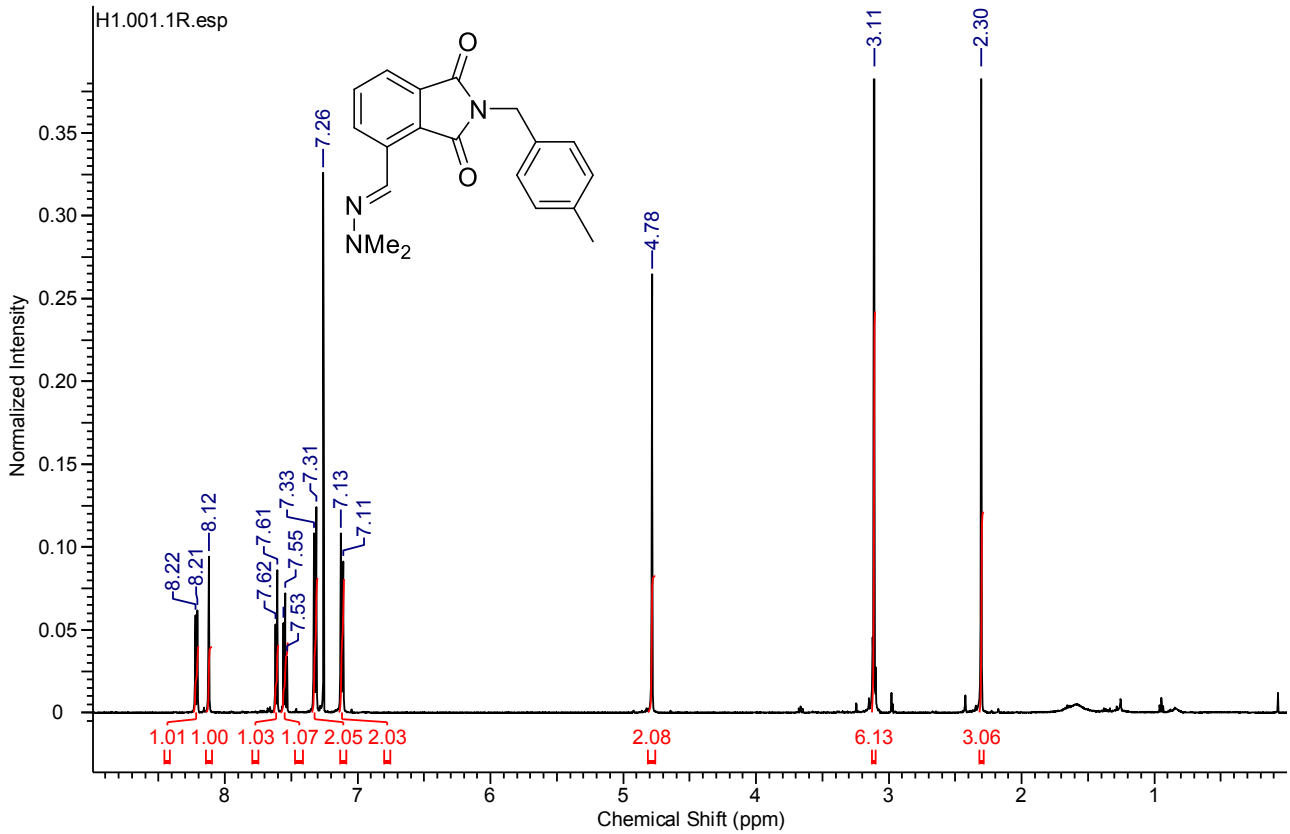


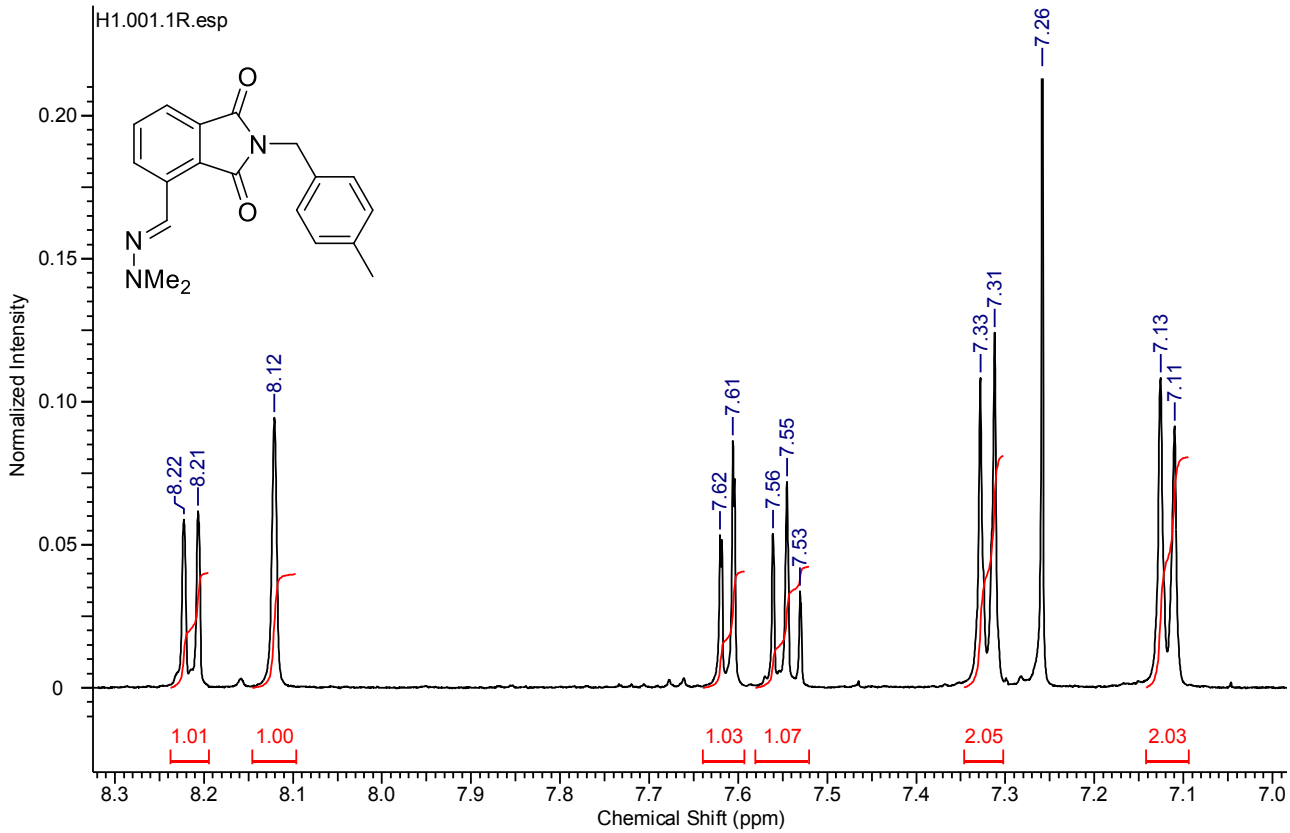
4-((2,2-Dimethylhydrazono)methyl)-2-phenylisoindoline-1,3-dione 5d

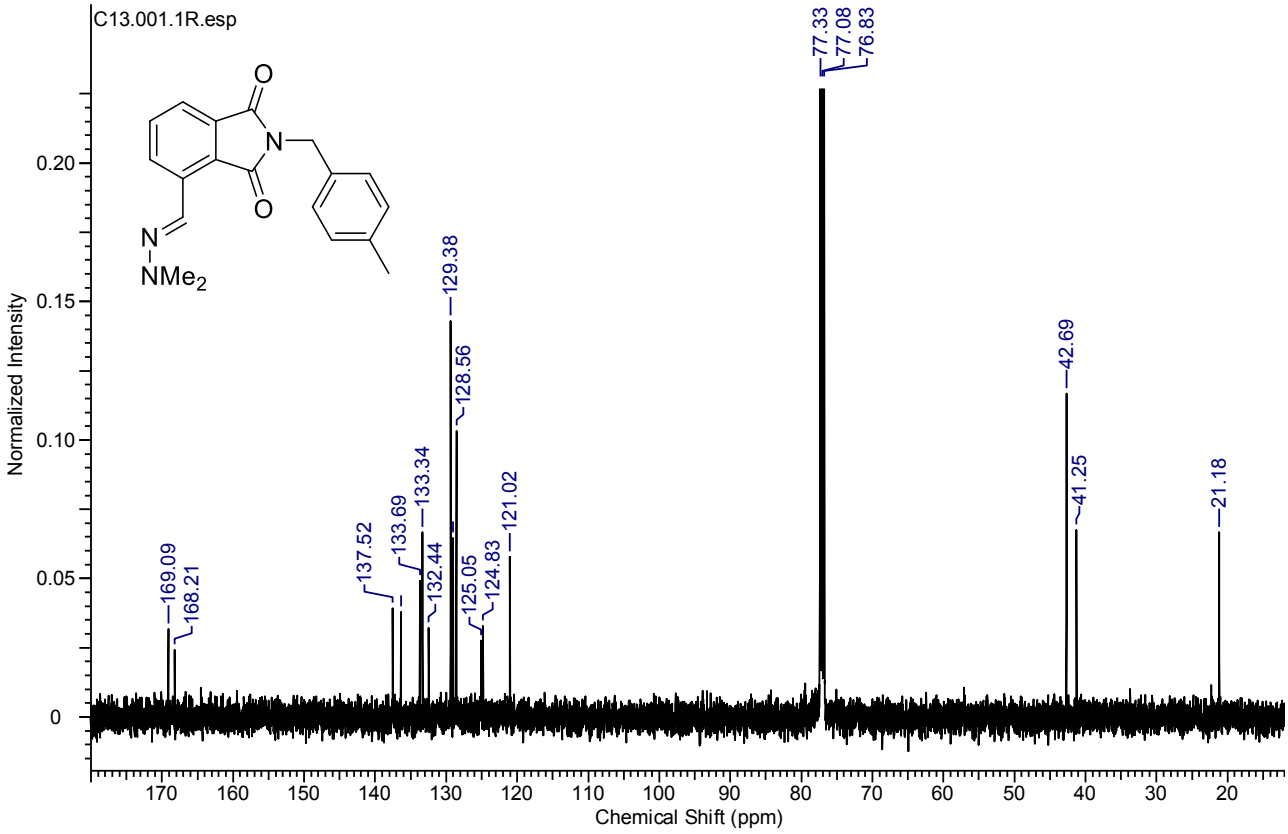




4-((2,2-Dimethylhydrazono)methyl)-2-(4-methylbenzyl)isoindoline-1,3-dione 5e



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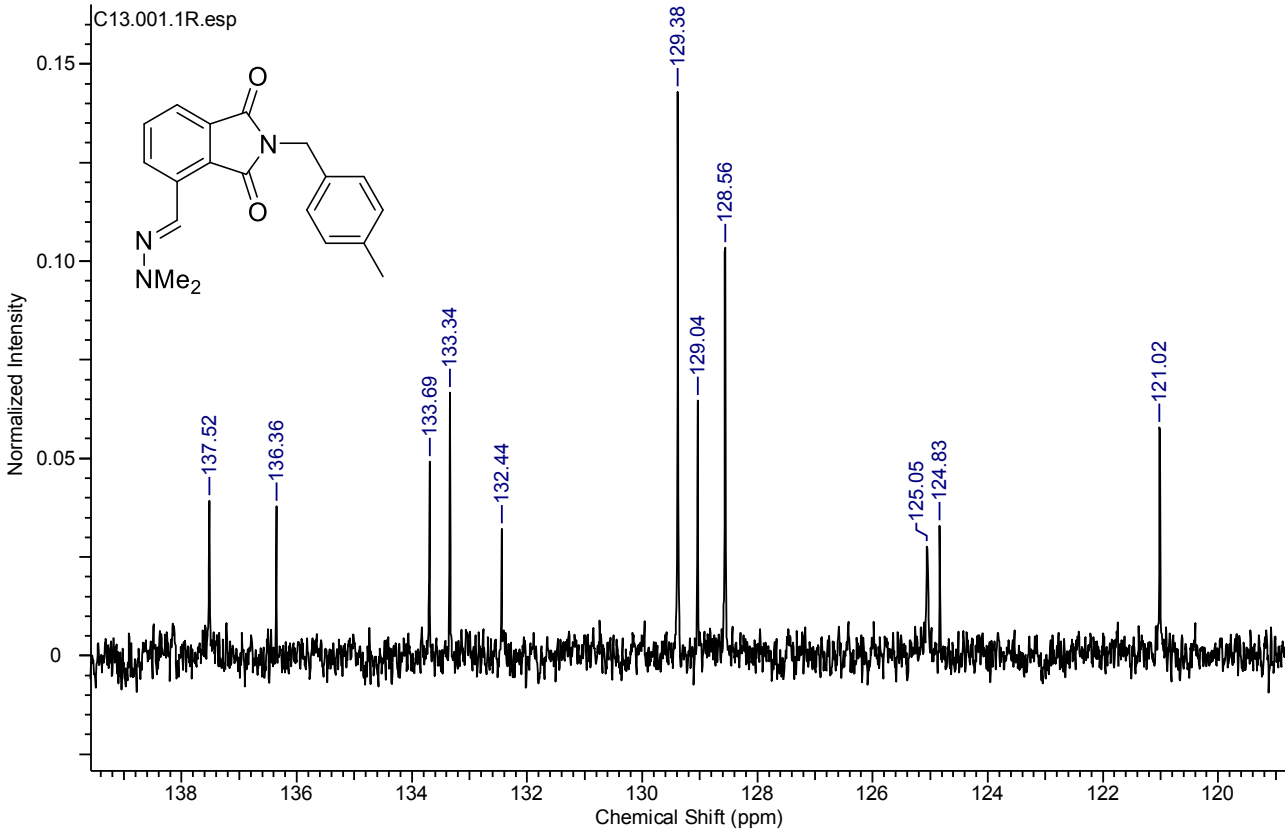
169.09
168.21
Normalized Intensity
Chemical Shift (ppm)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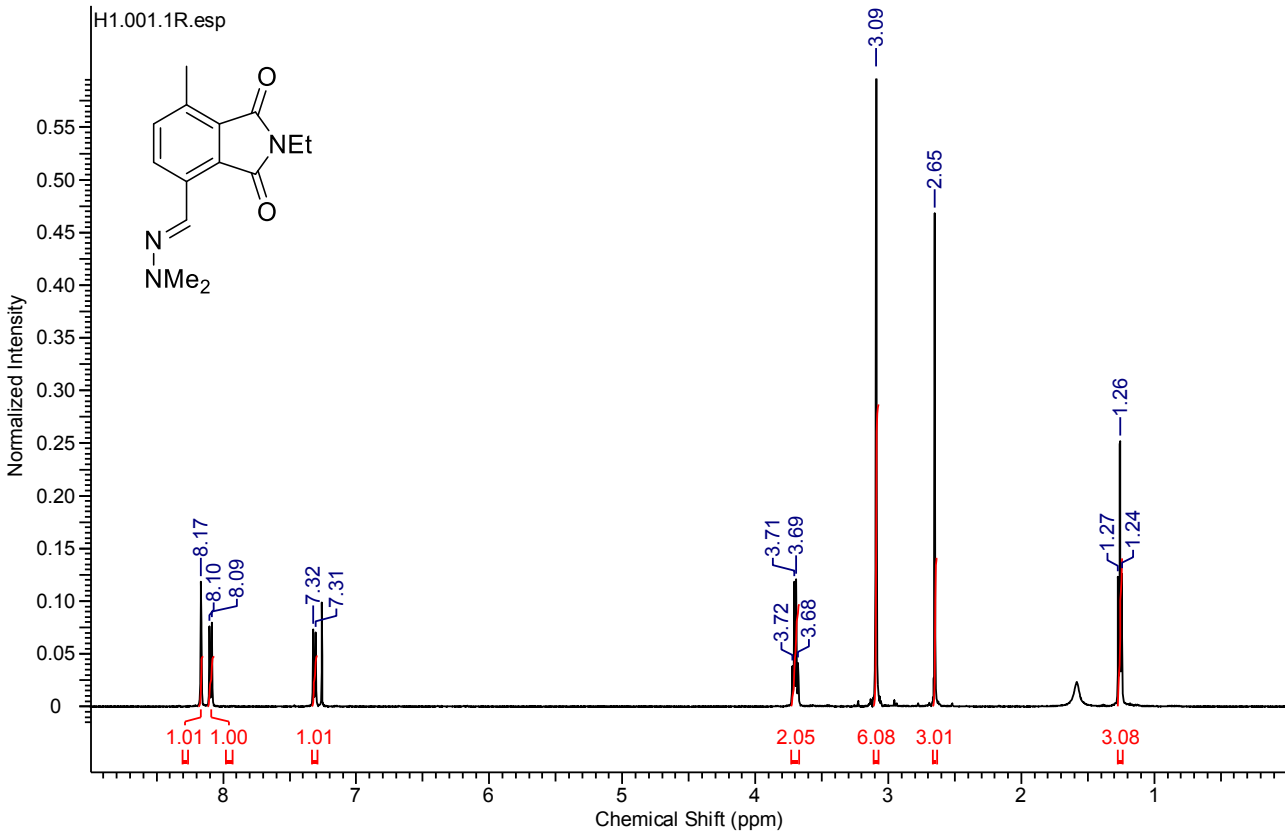
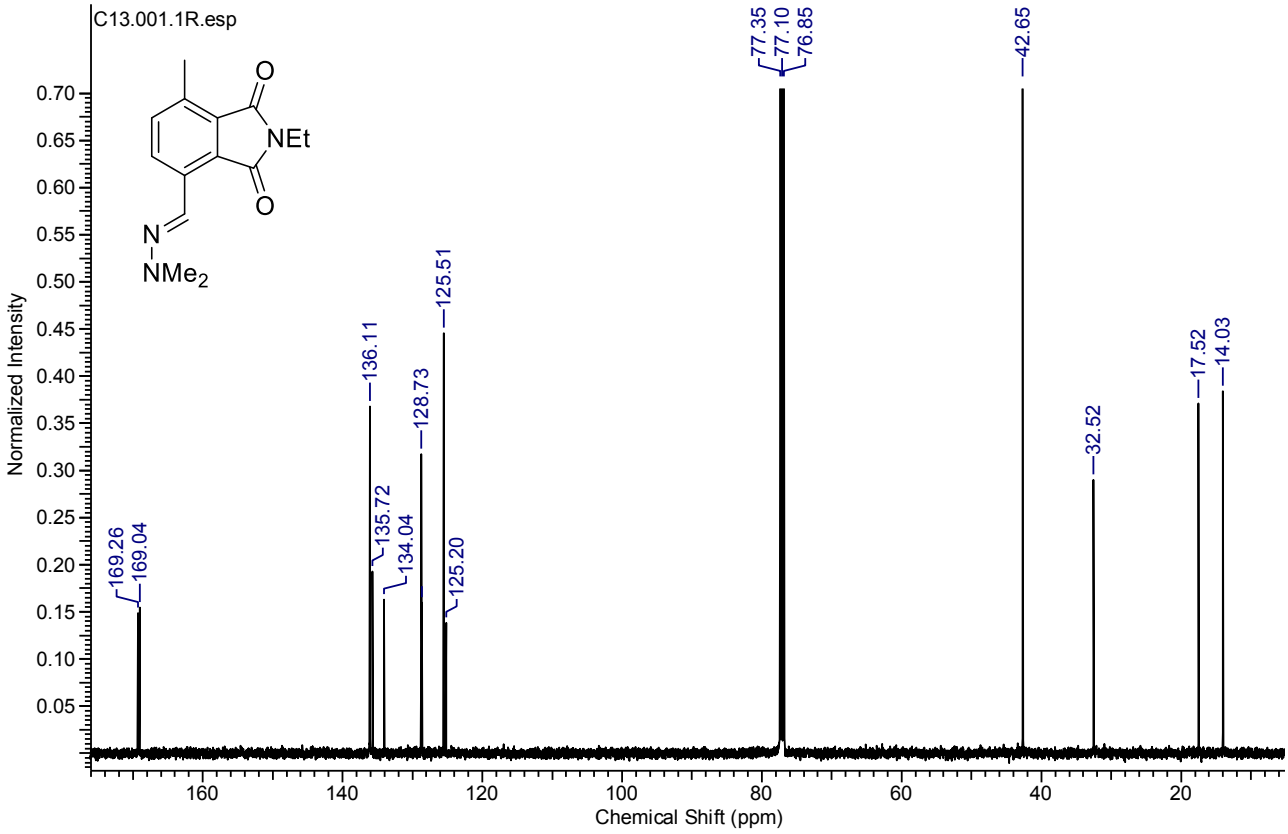
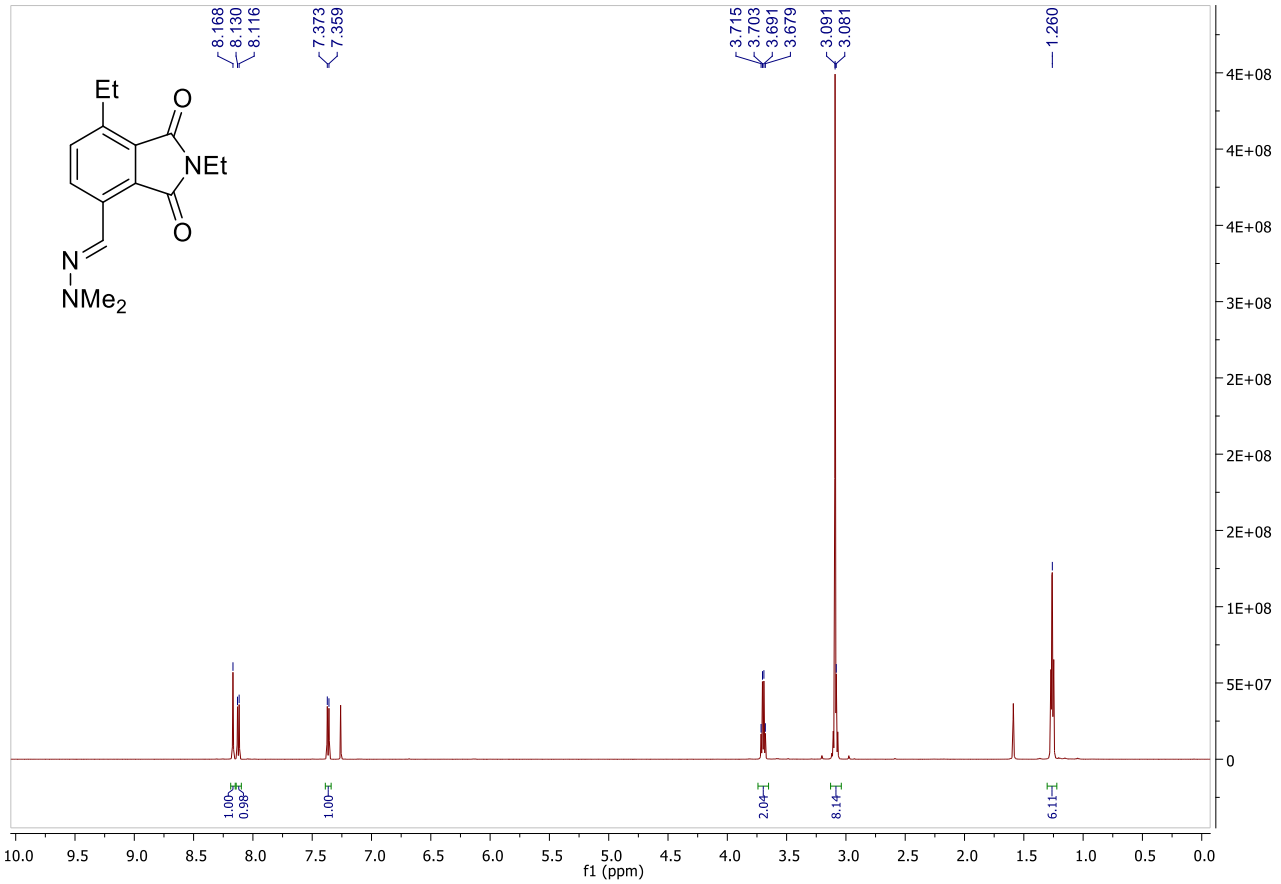
124.83
121.02
Normalized Intensity
Chemical Shift (ppm)

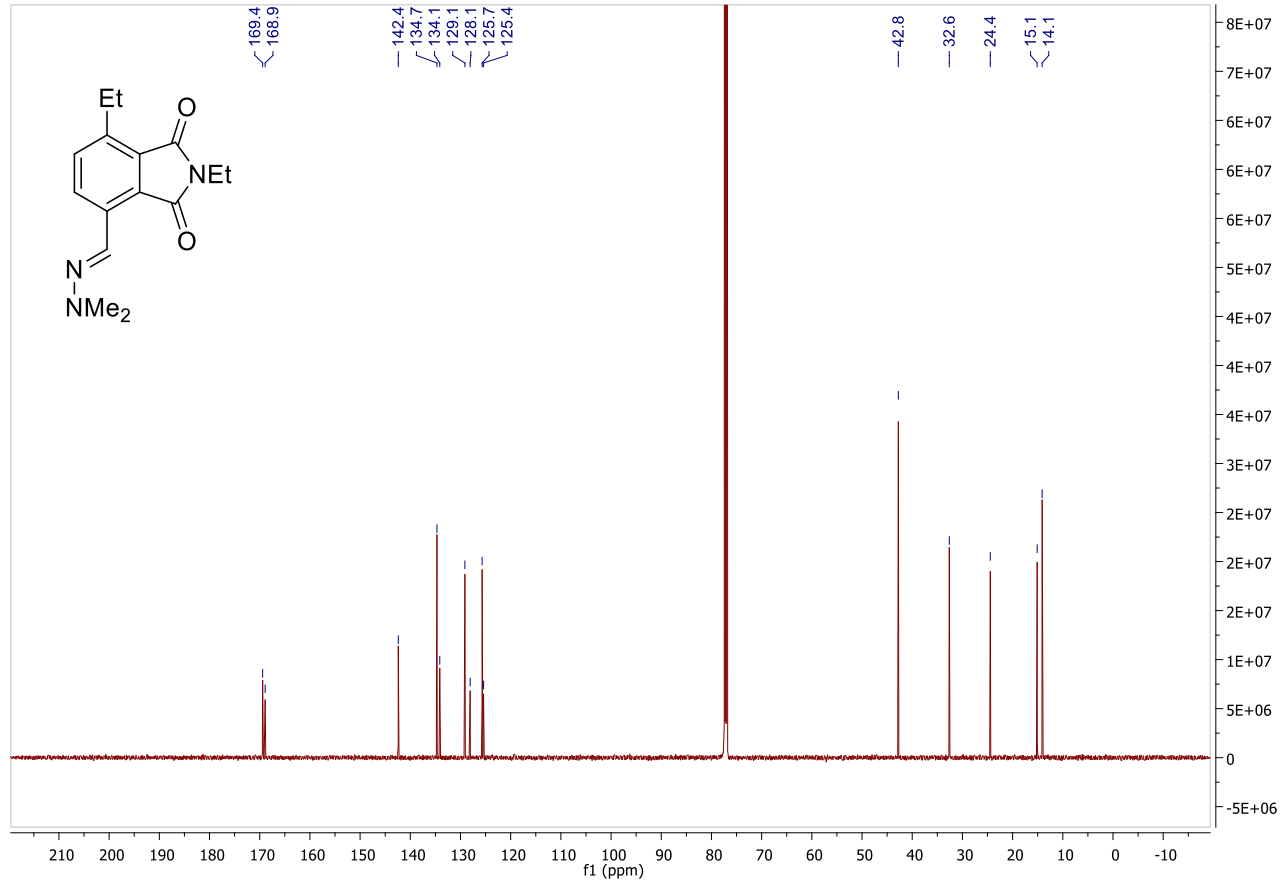
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-methylisoindoline-1,3-dione 5f



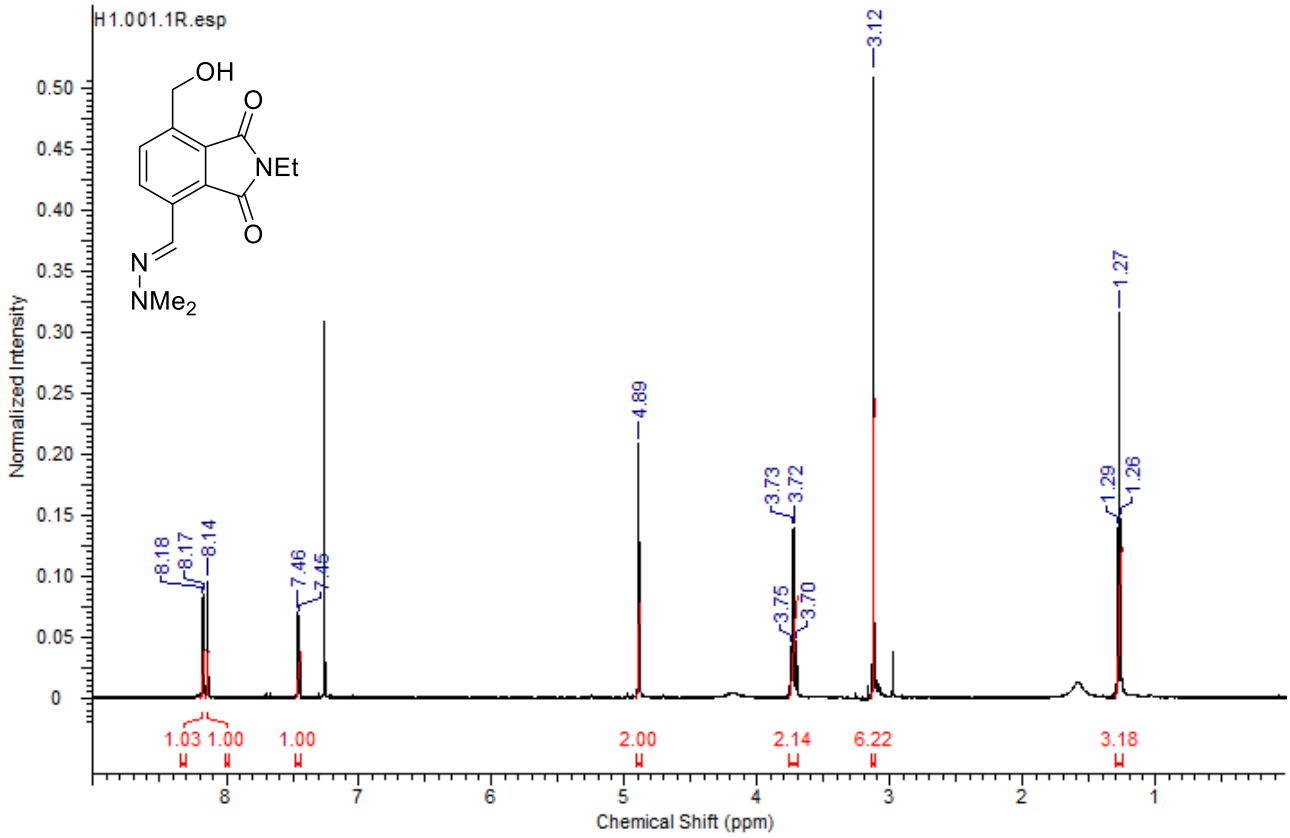


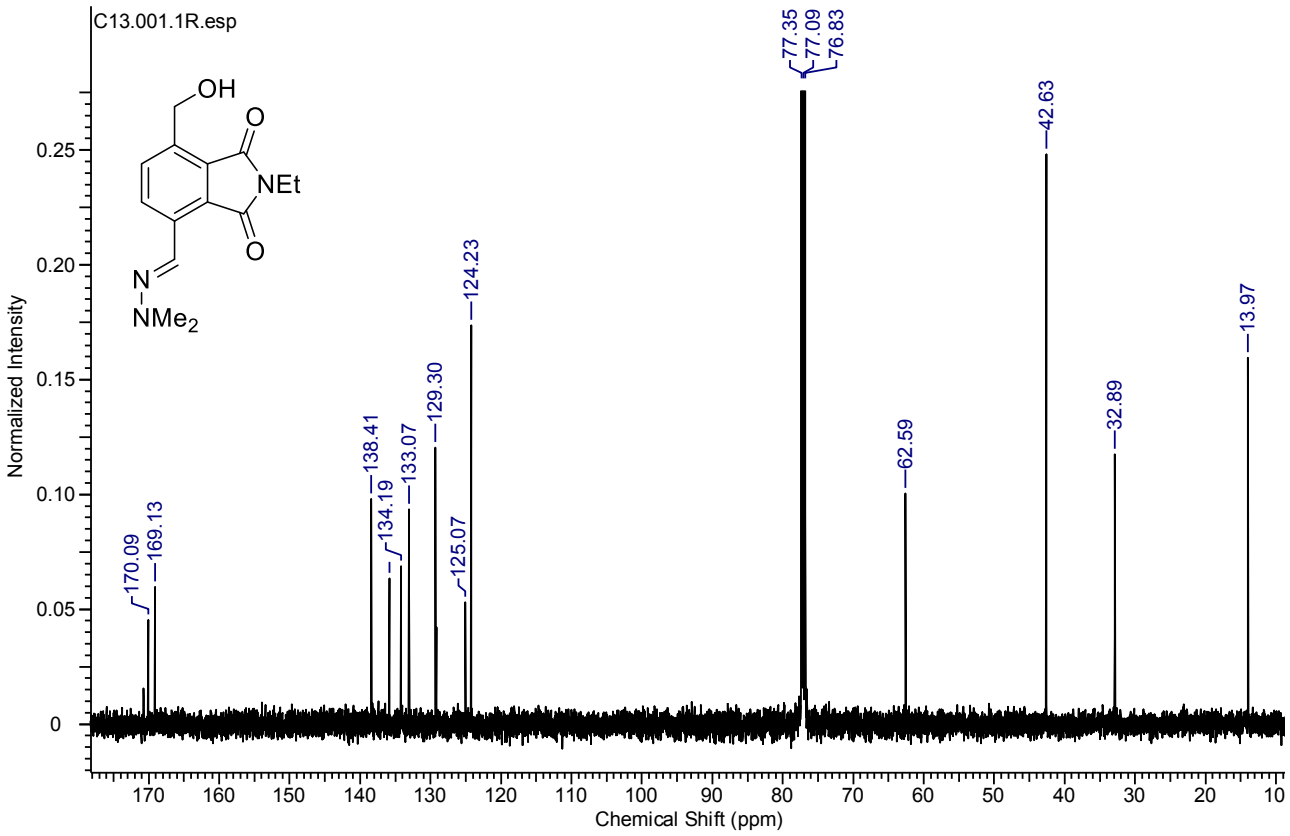
4-((2,2-dimethylhydrazono)methyl)-2,7-diethylisoindoline-1,3-dione 5g



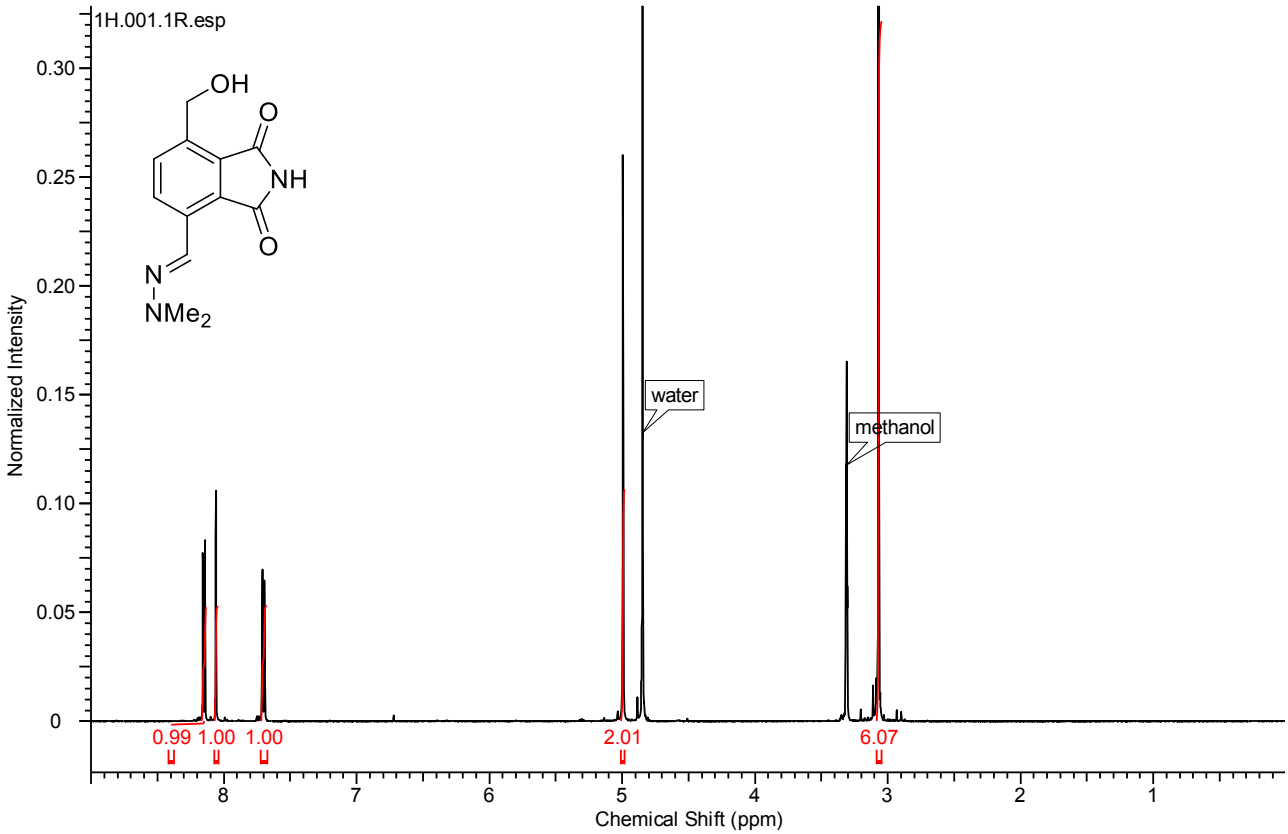


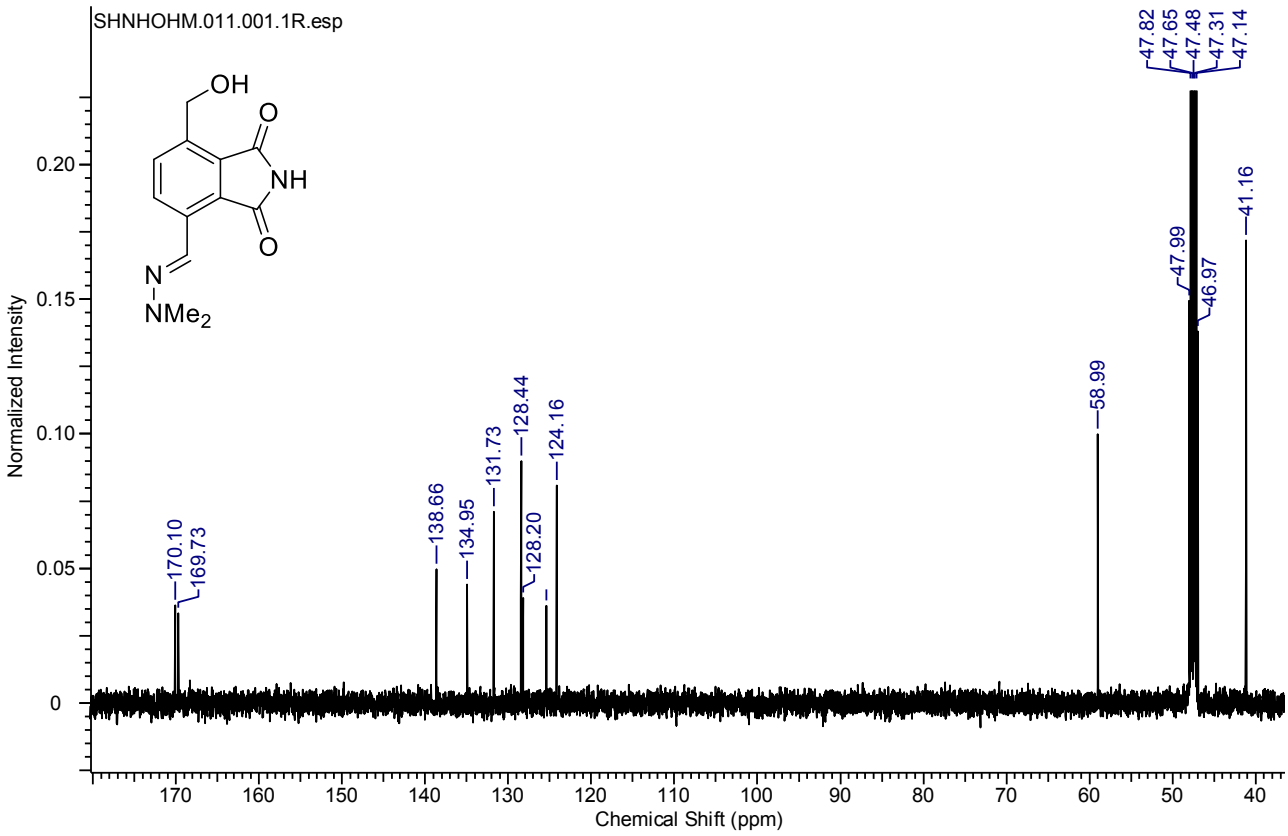
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(hydroxymethyl)isoindoline-1,3-dione 5h



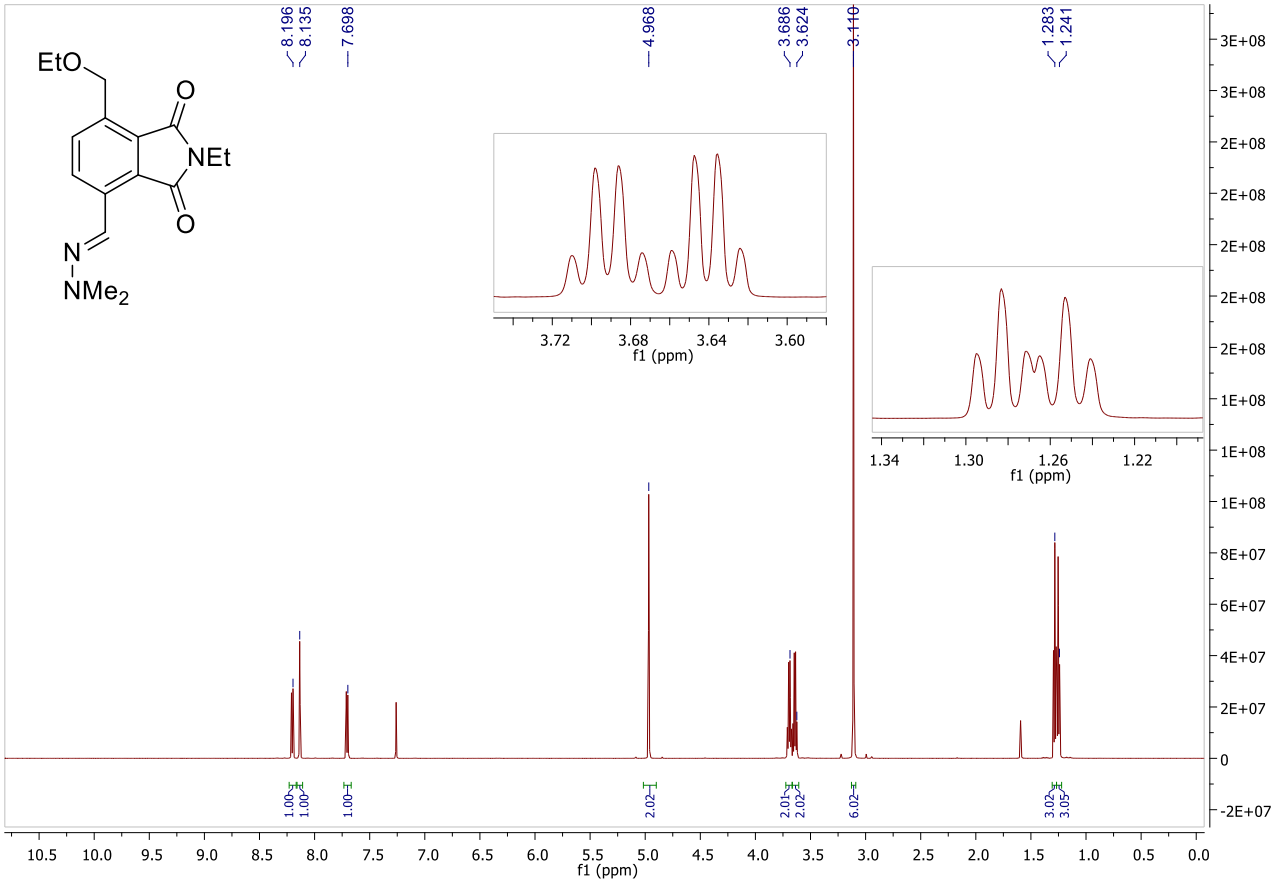


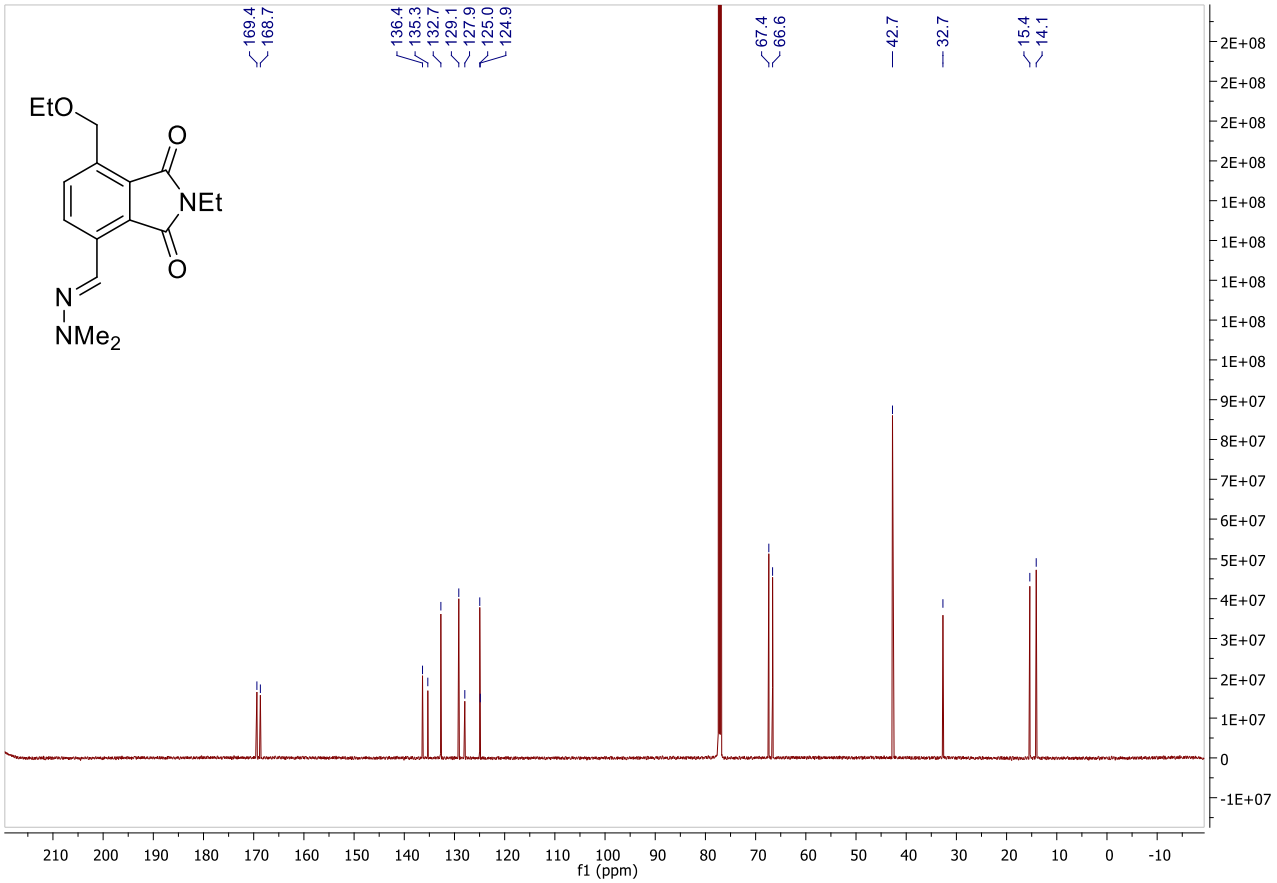
4-((2,2-Dimethylhydrazono)methyl)-7-(hydroxymethyl)isoindoline-1,3-dione 5i



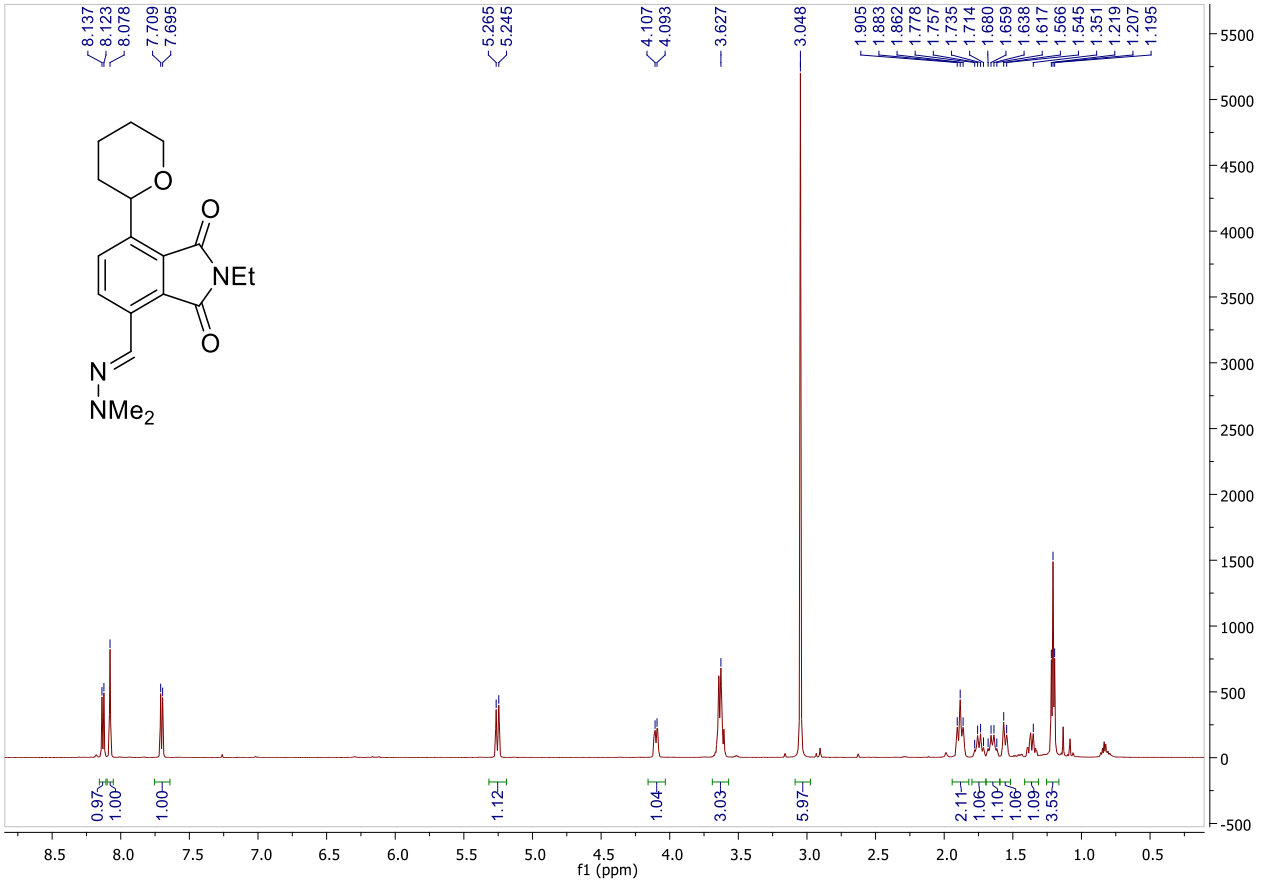


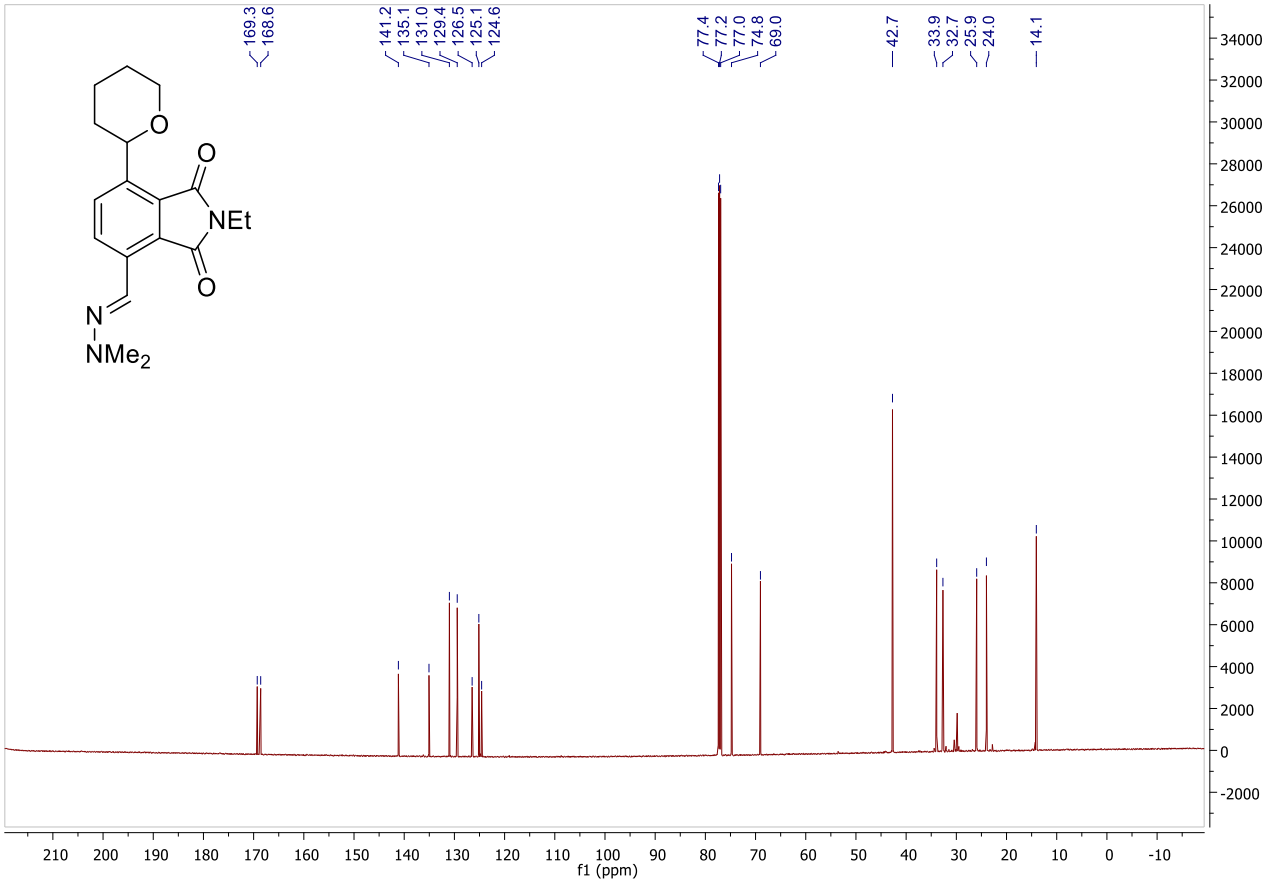
4-((2,2-Dimethylhydrazono)methyl)-7-(ethoxymethyl)-2-ethylisoindoline-1,3-dione 5j



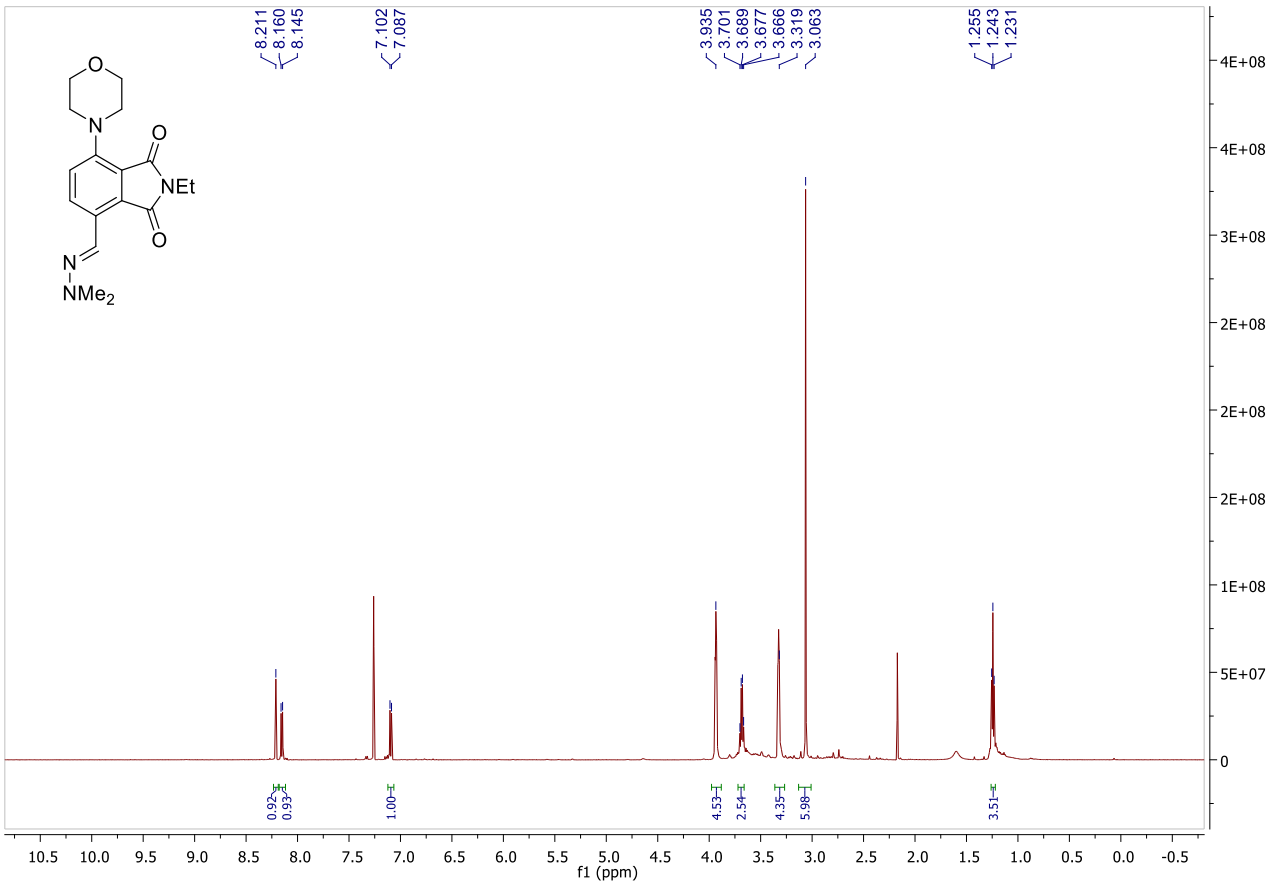


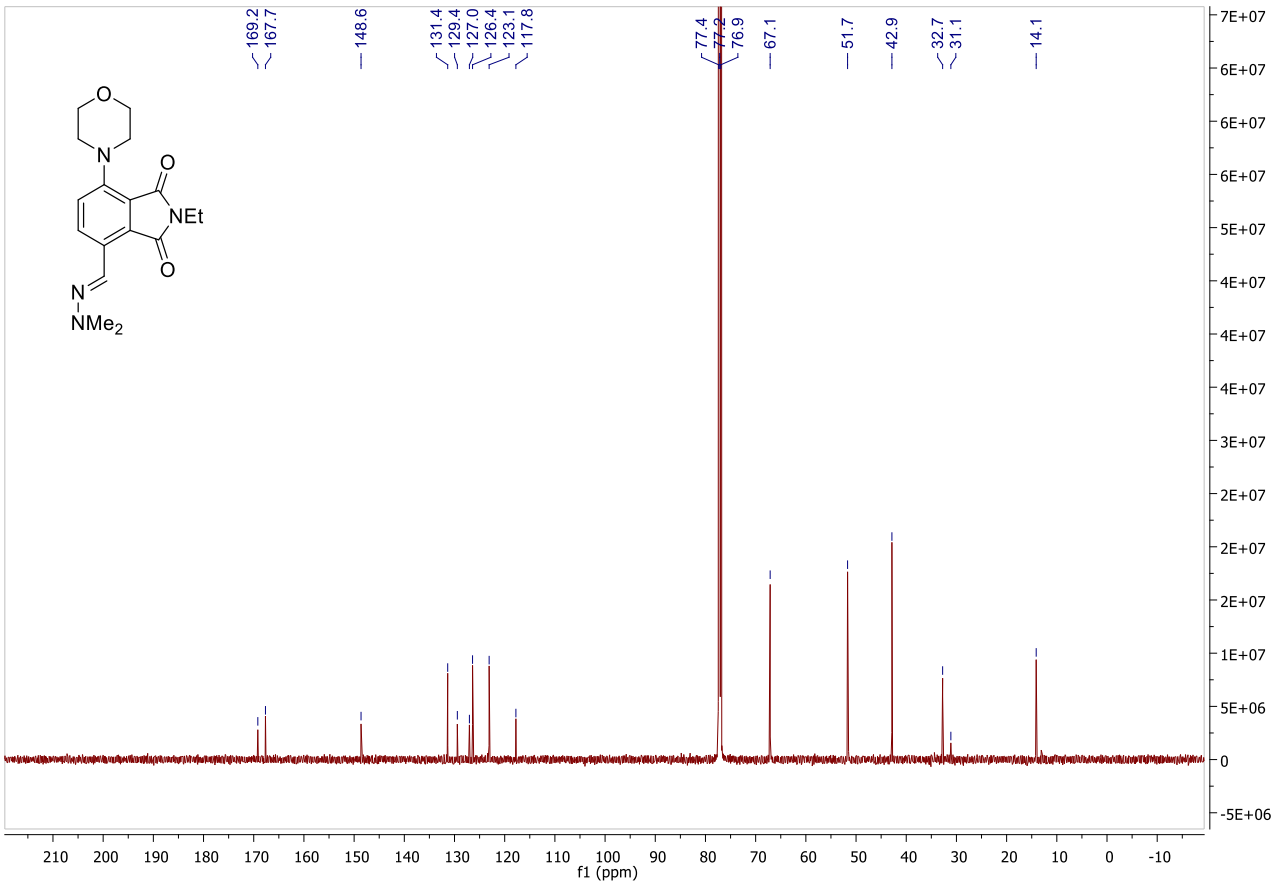
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(tetrahydro-2H-pyran-2-yl)isoindoline-1,3-dione 5k



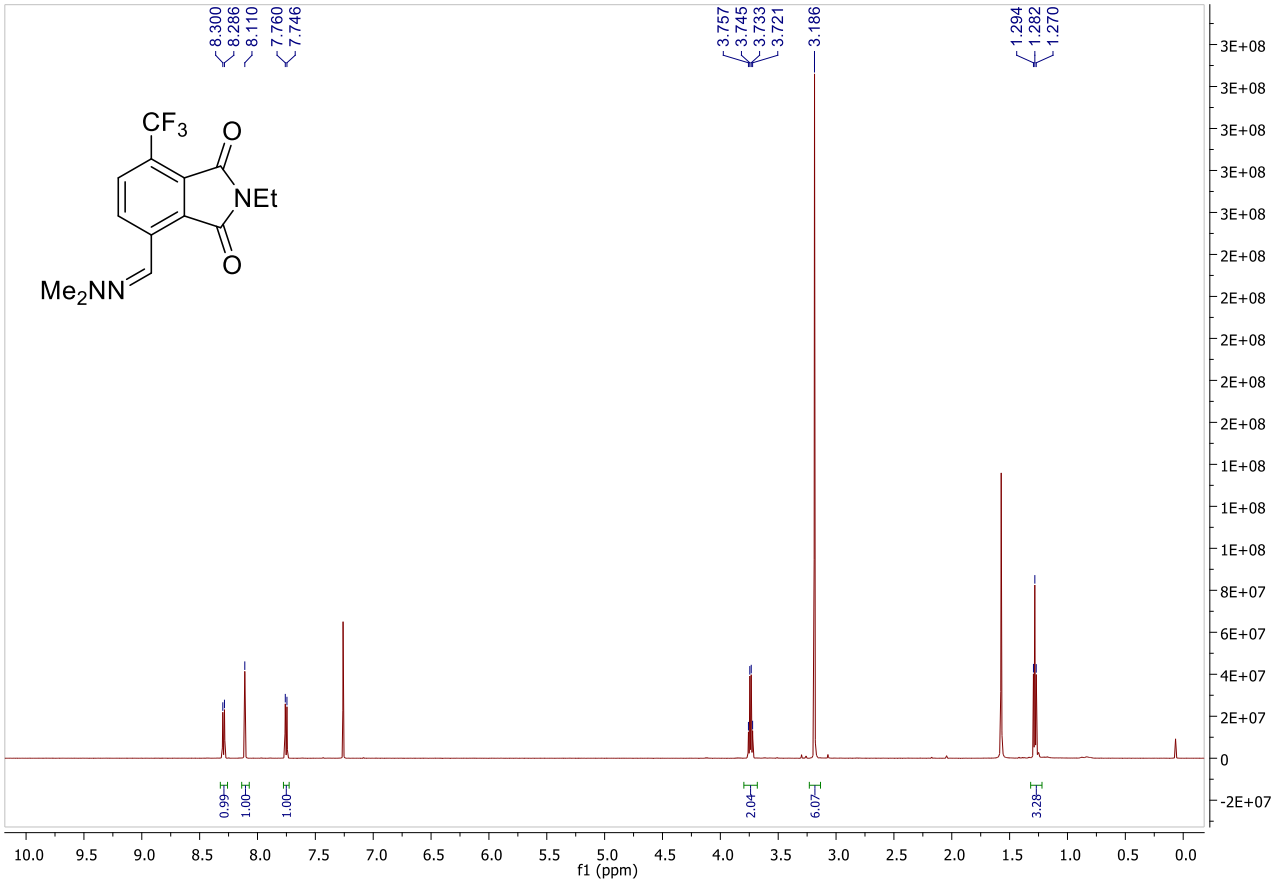


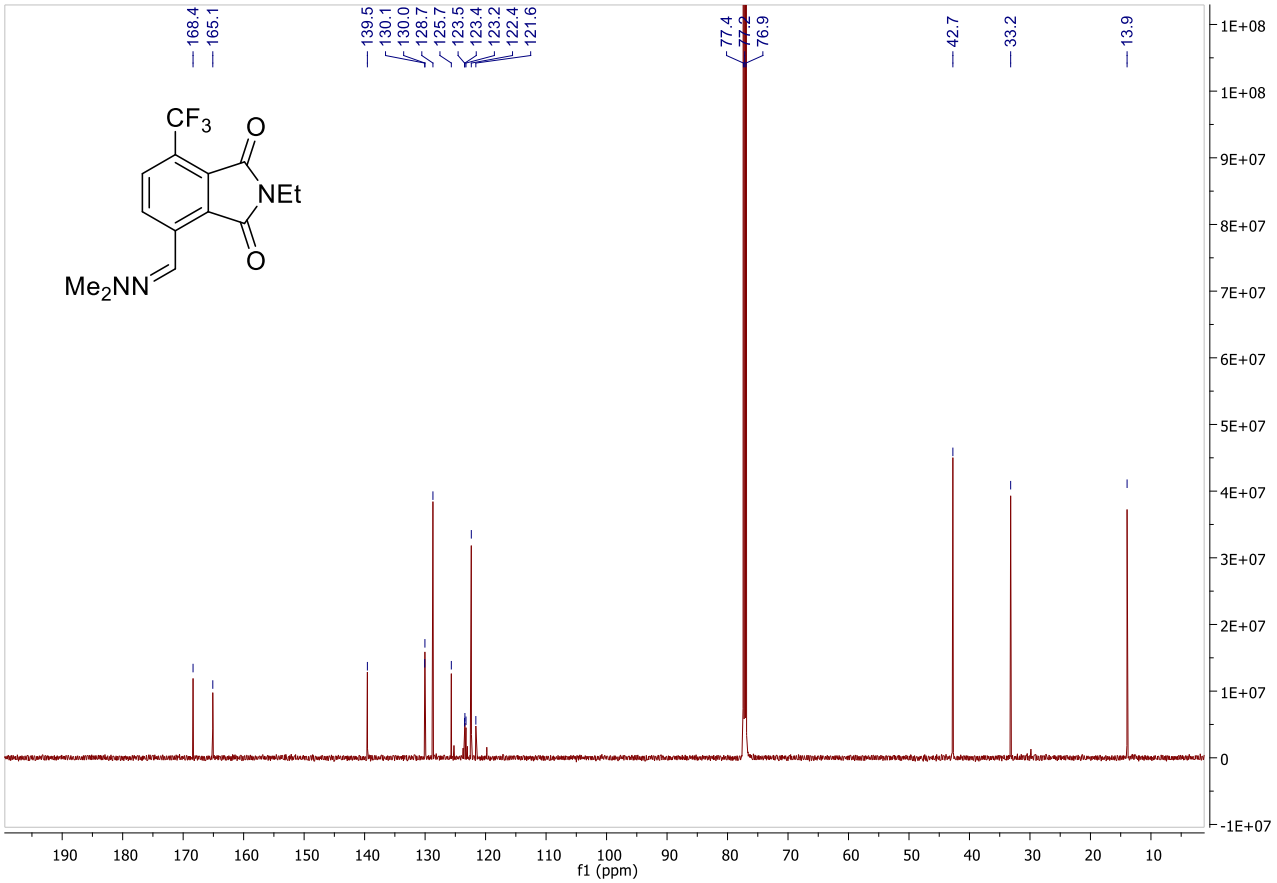
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-morpholinoisoindoline-1,3-dione 5l



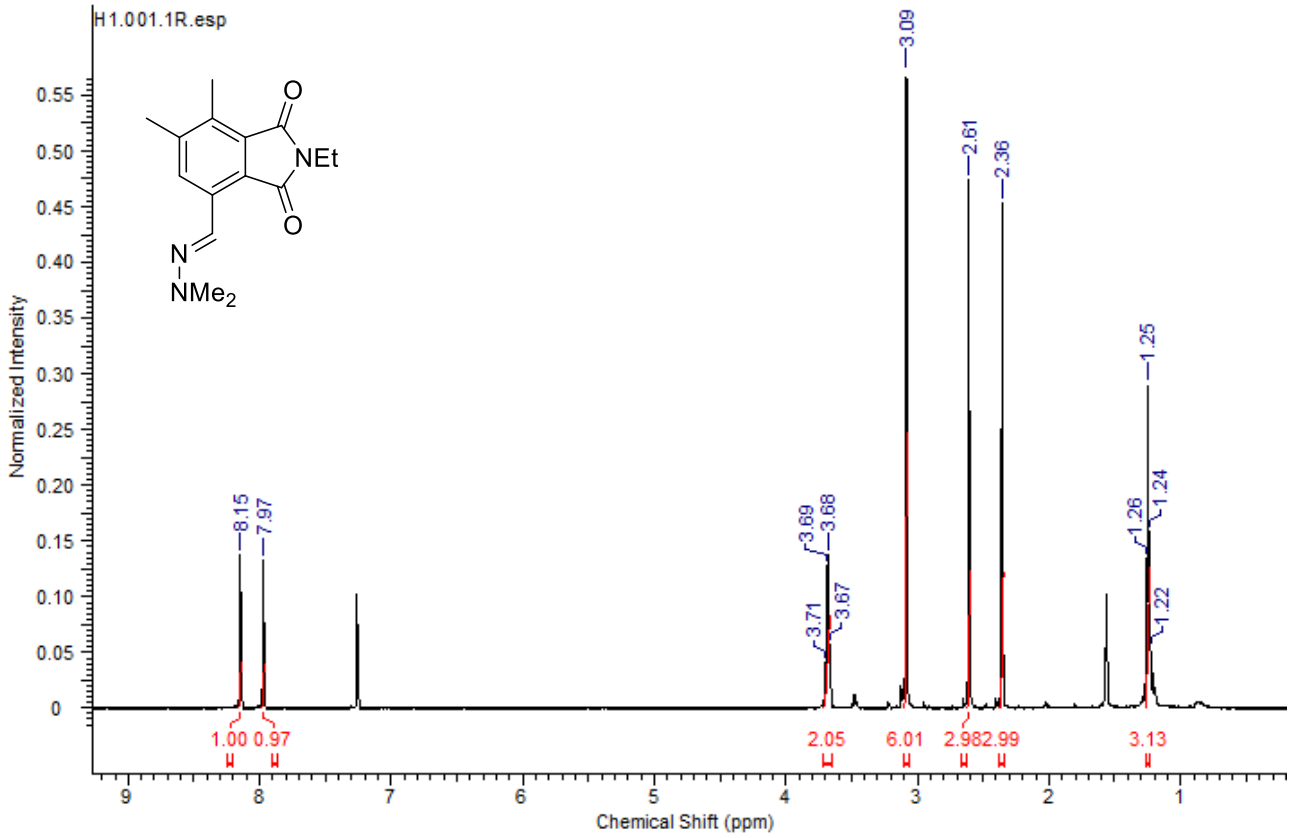


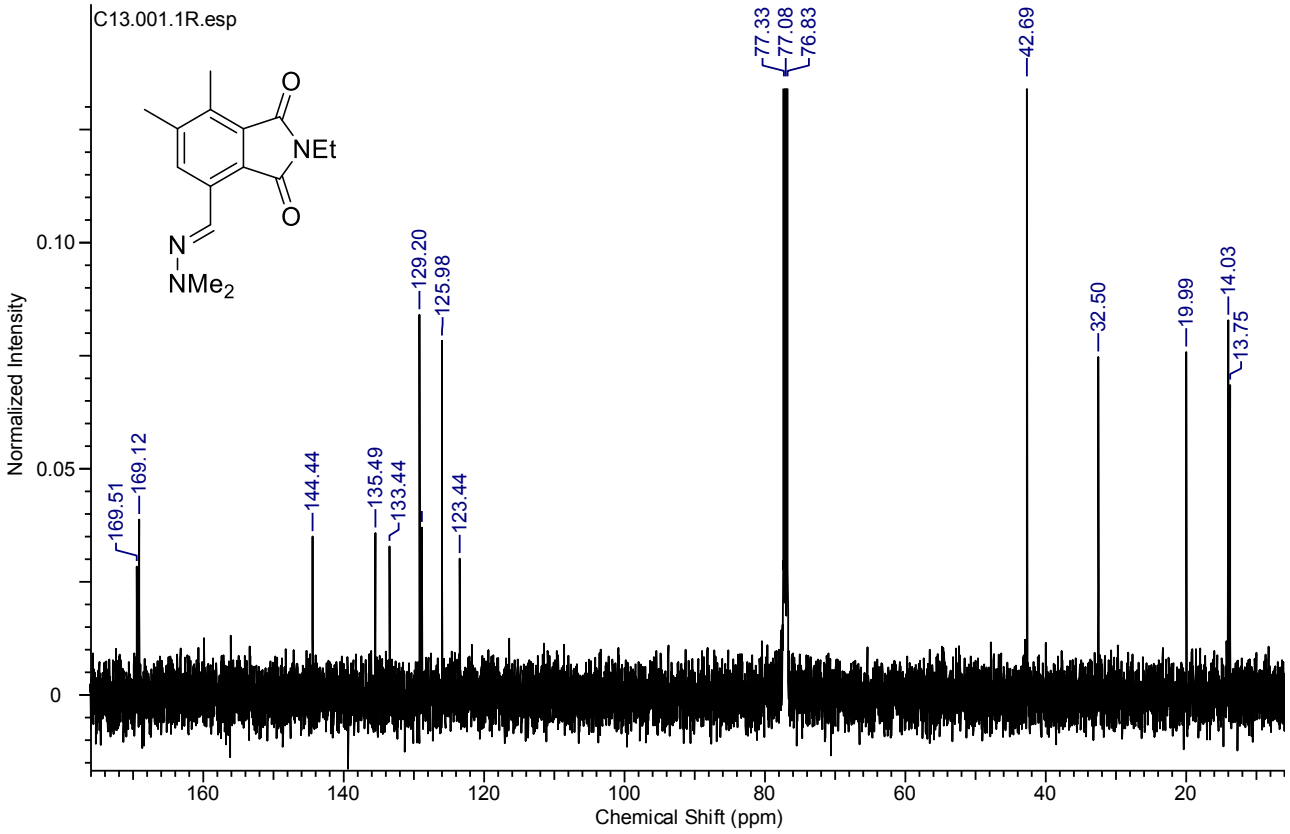
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(trifluoromethyl)isoindoline-1,3-dione 5m



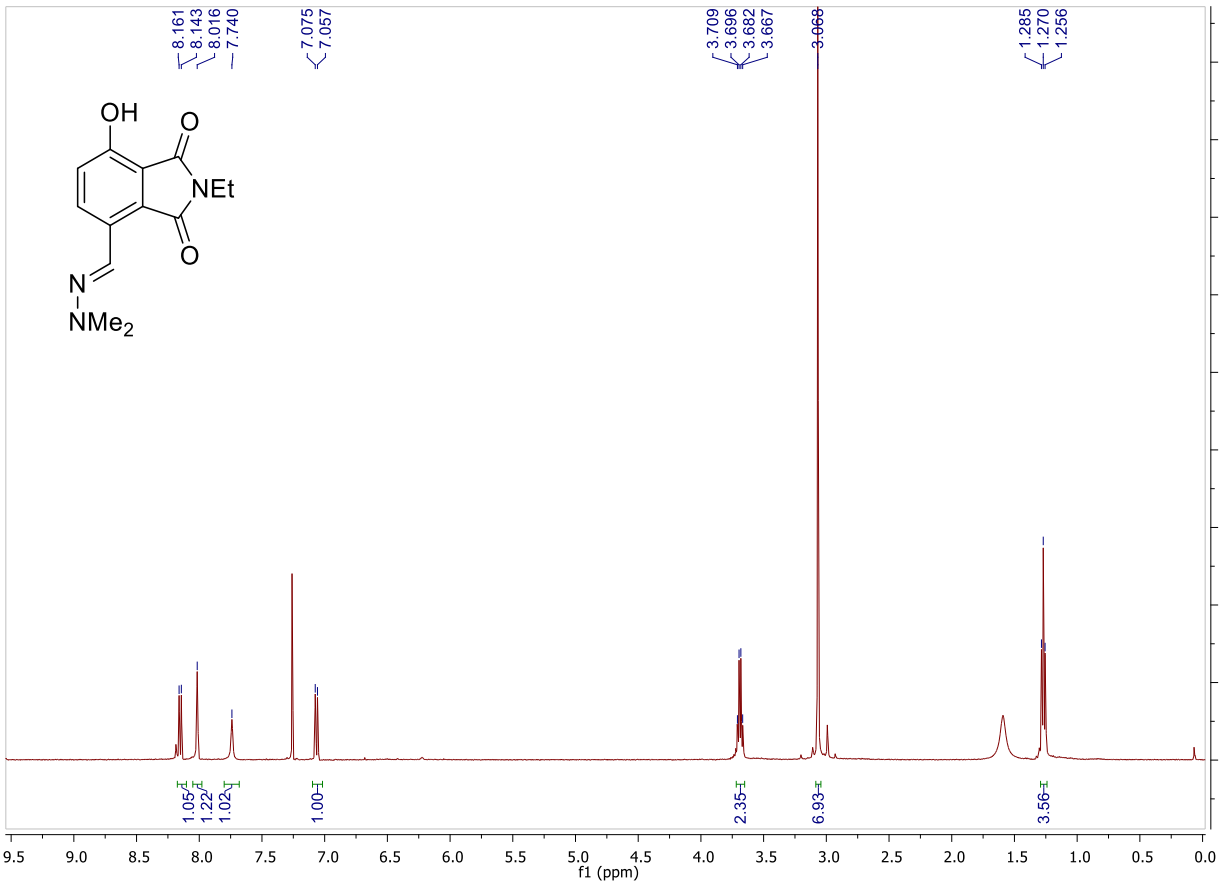


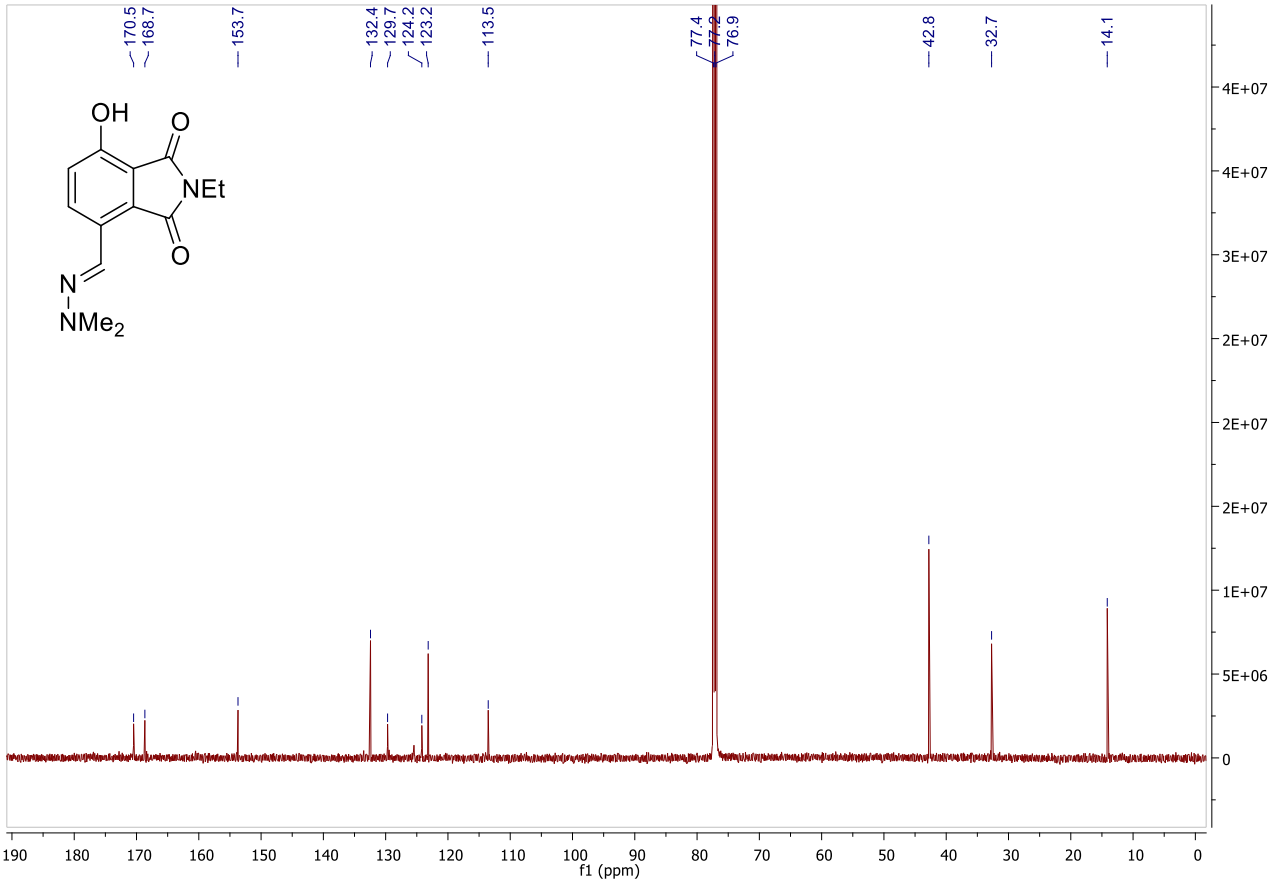
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-4,5-methylisoindoline-1,3-dione 5n



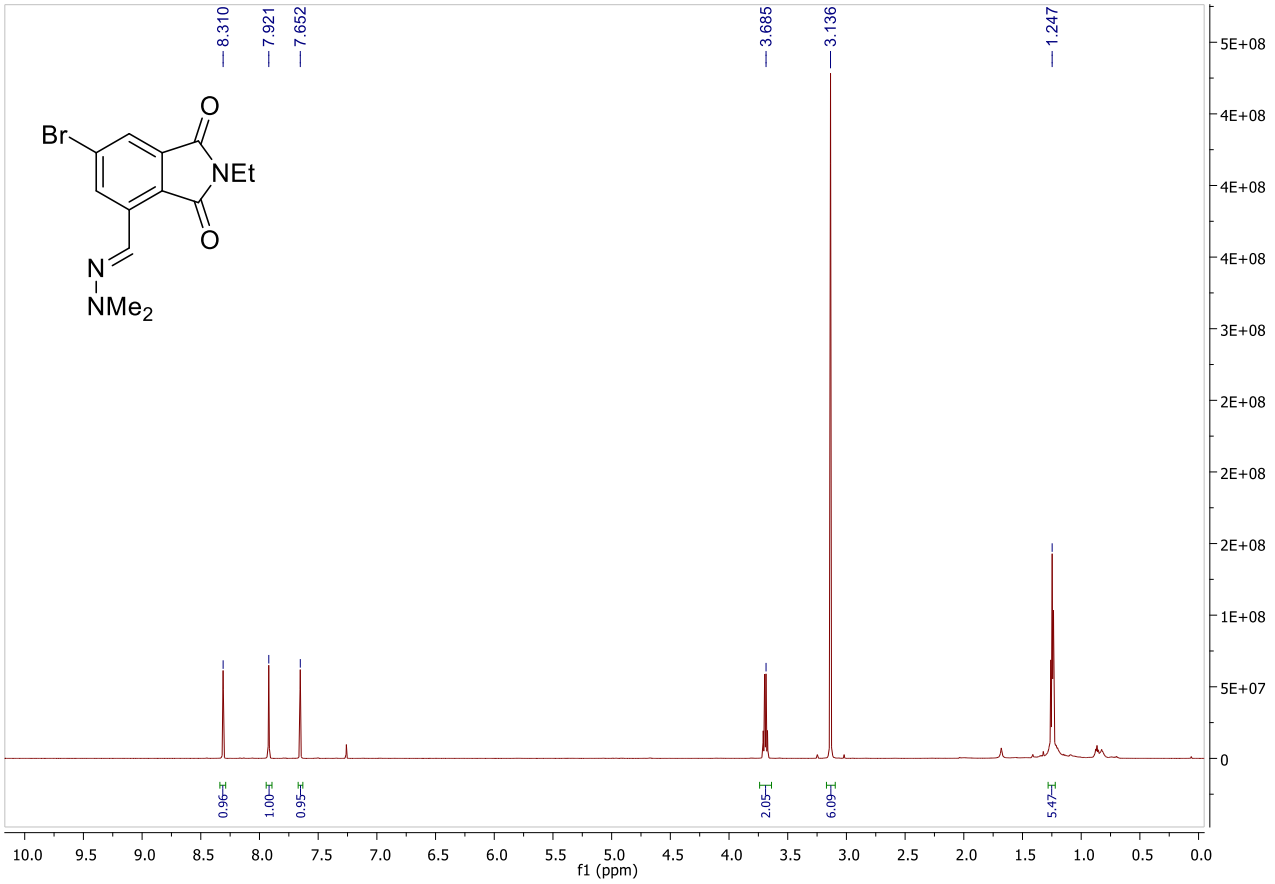


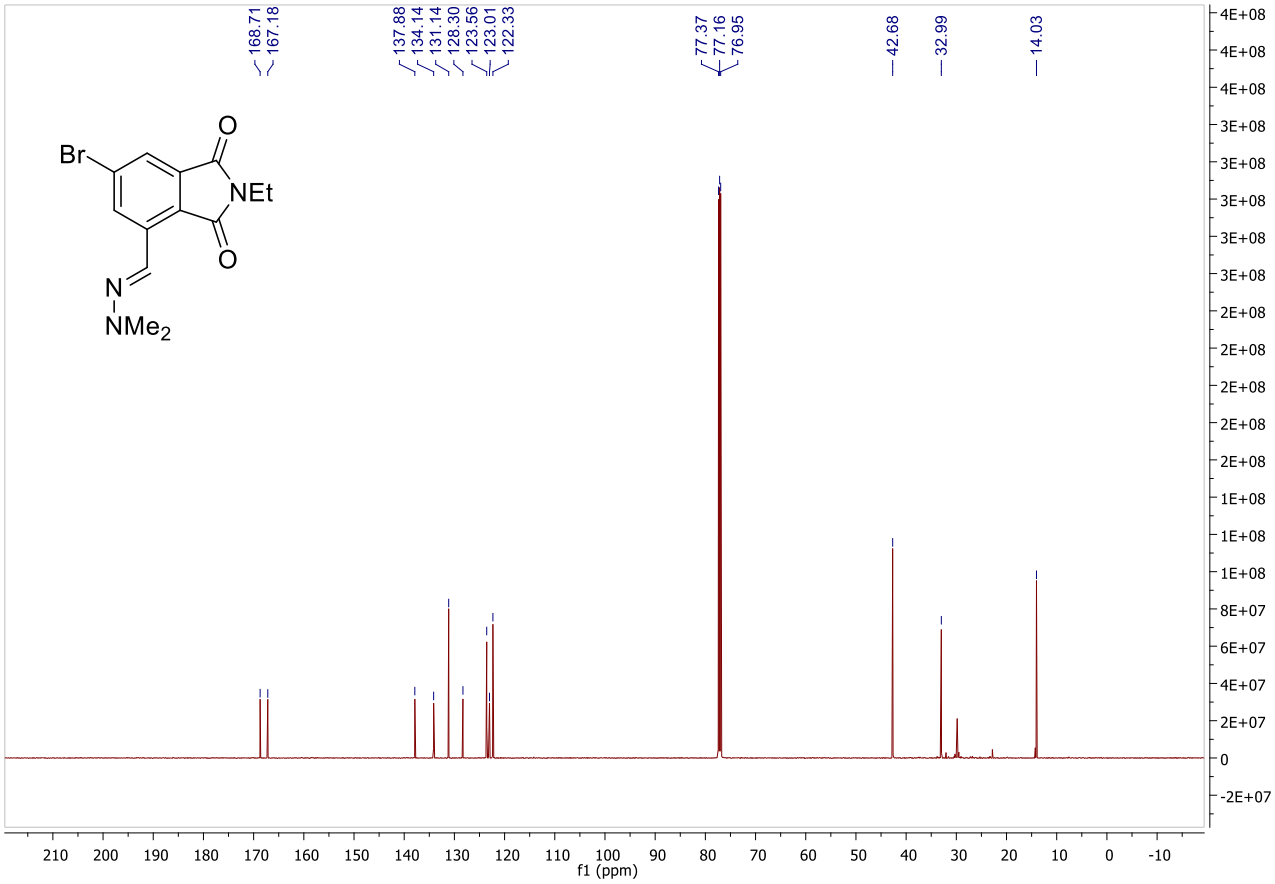
4-((2,2-dimethylhydrazono)methyl)-2-ethyl-7-hydroxyisoindoline-1,3-dione 5o



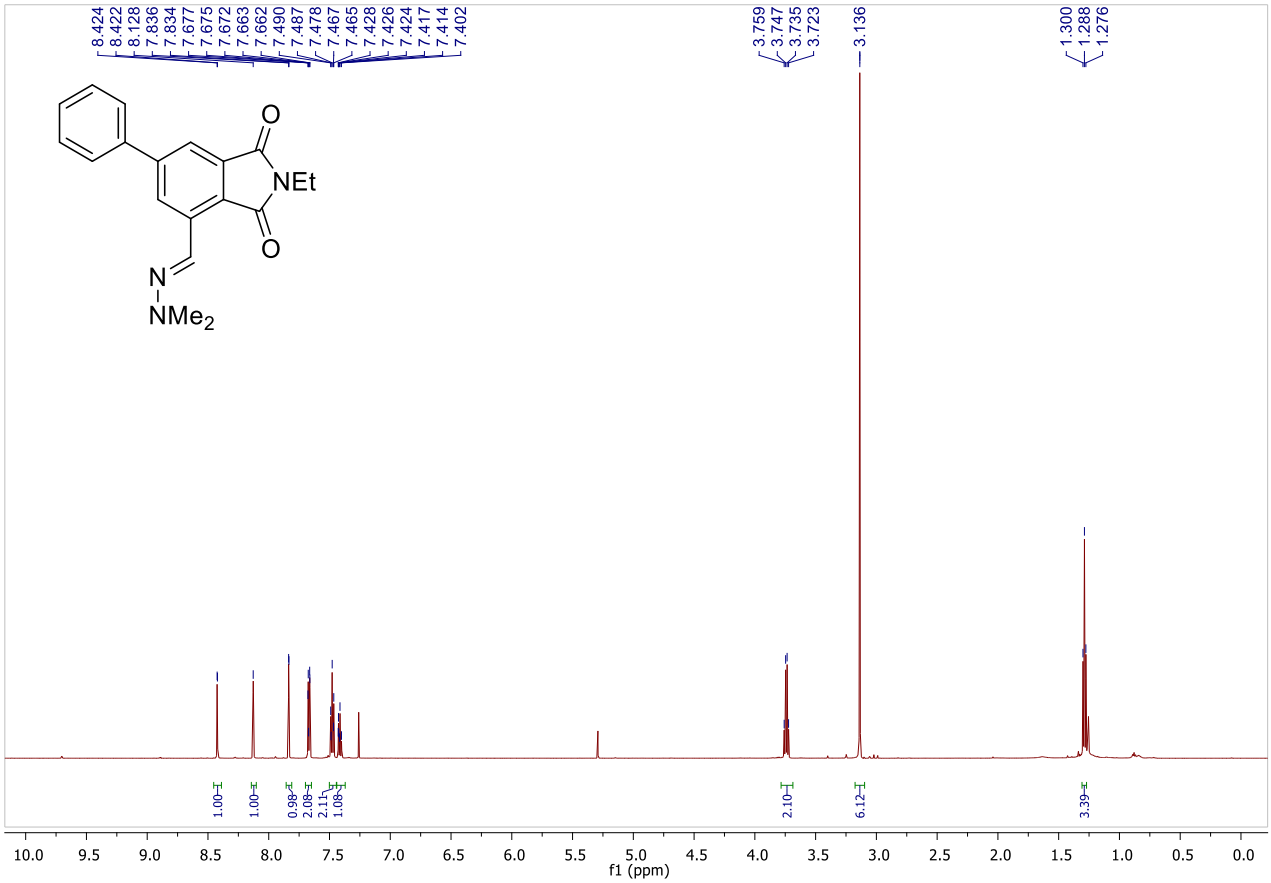


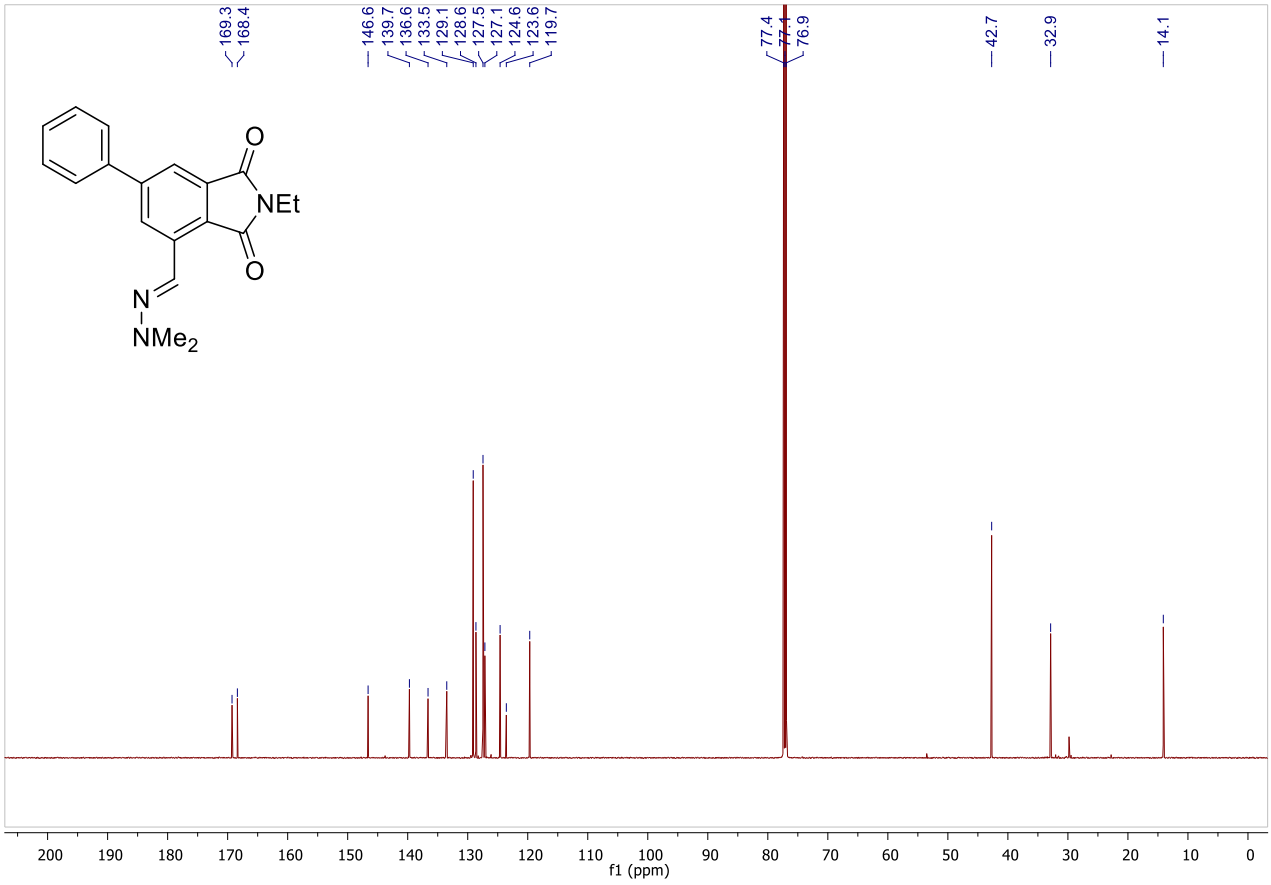
6-Bromo-4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5p



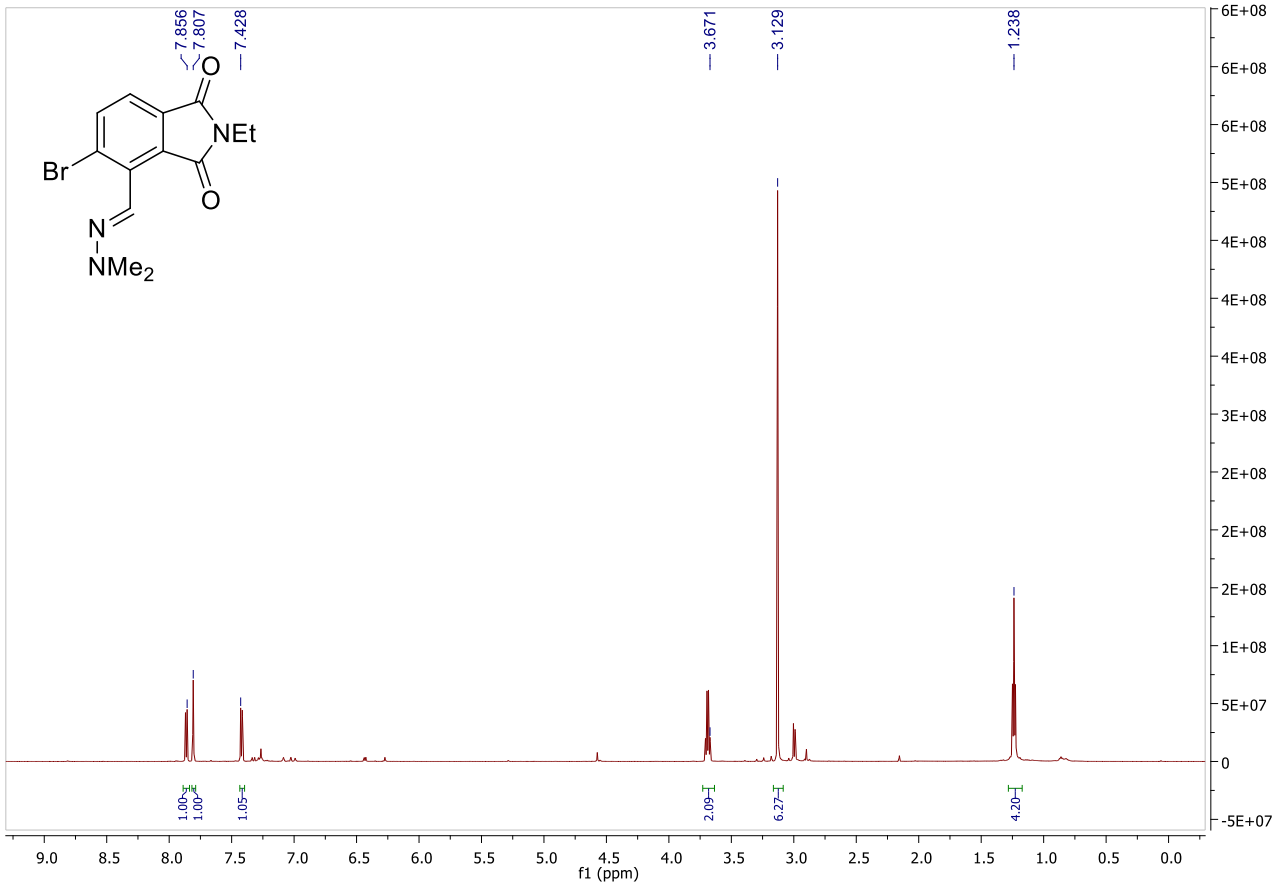


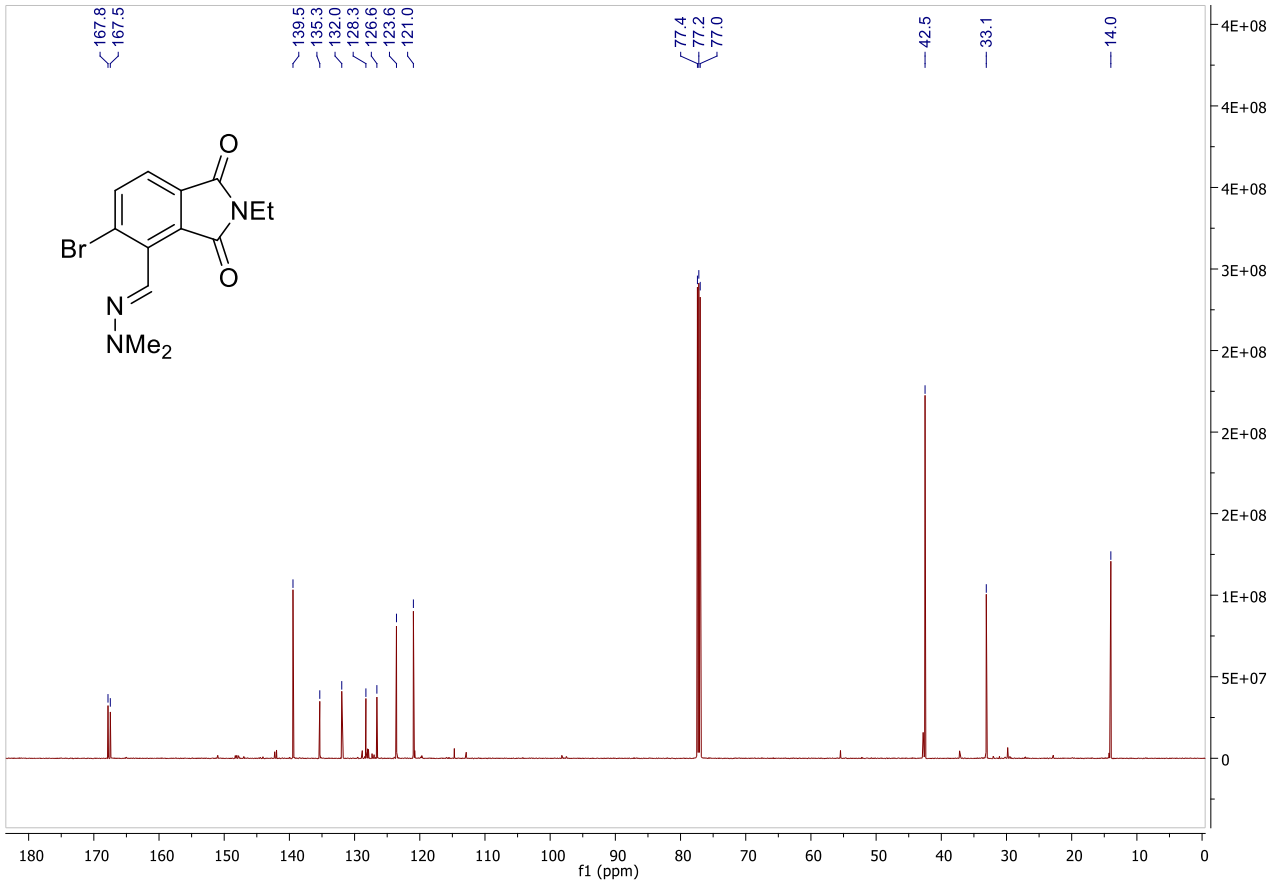
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-6-phenylisoindoline-1,3-dione 5q



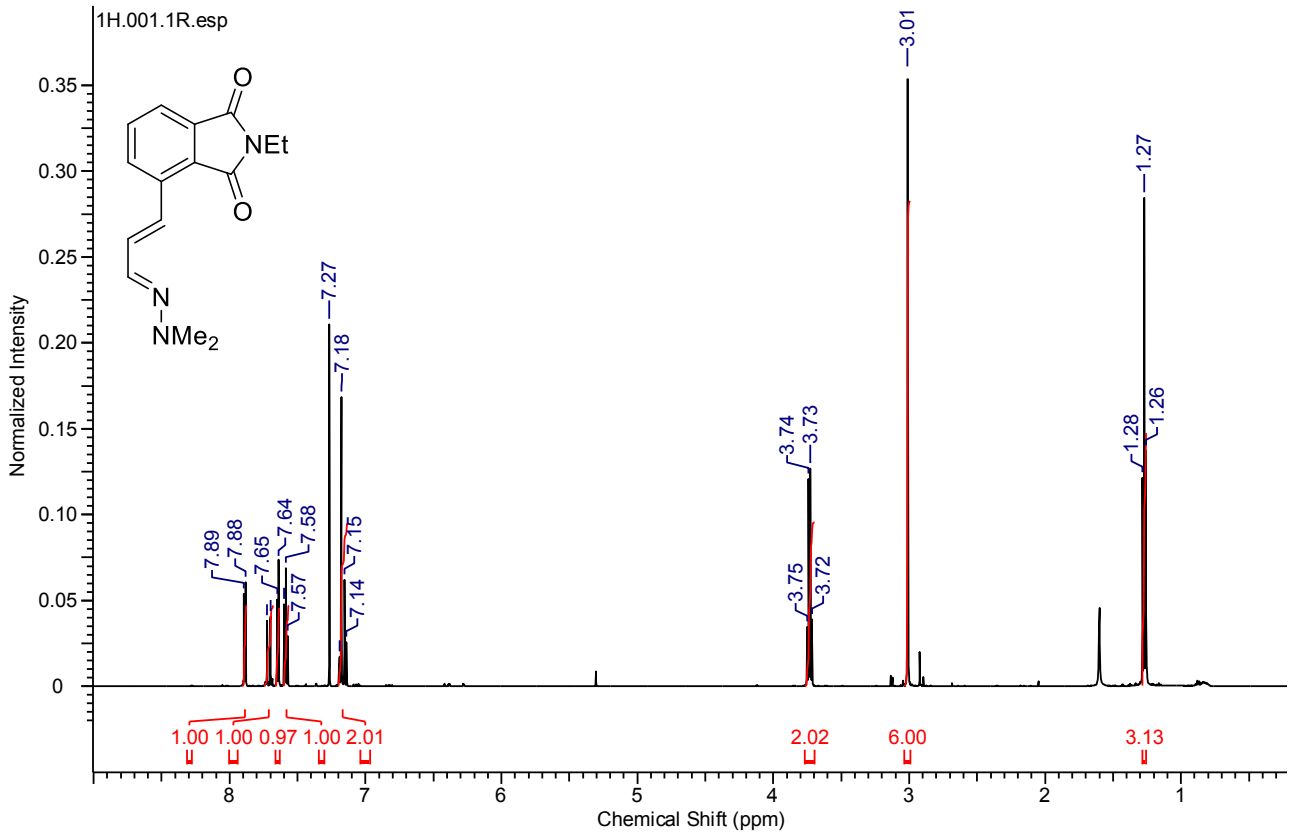


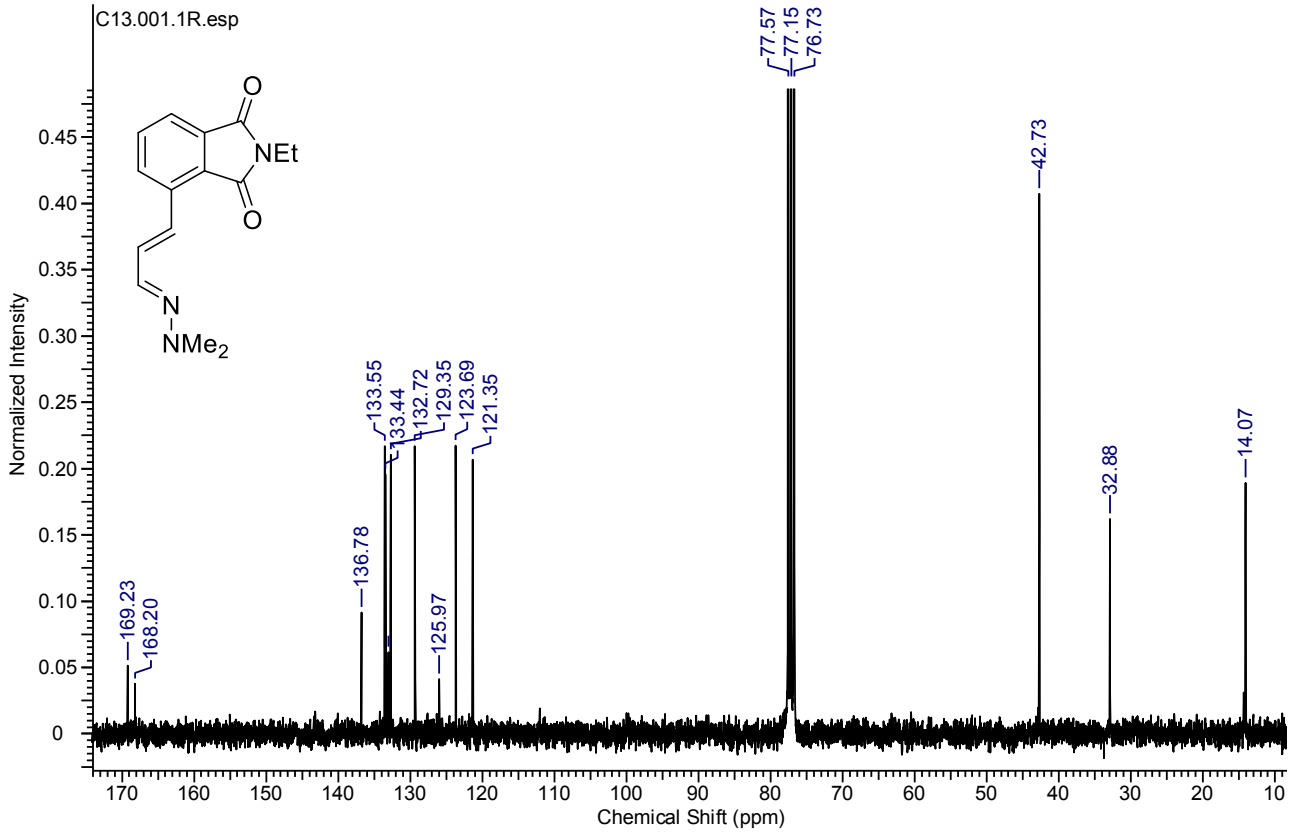
5-Bromo-4-((2,2-dimethylhydrazono)methyl)-2-ethylisoindoline-1,3-dione 5r



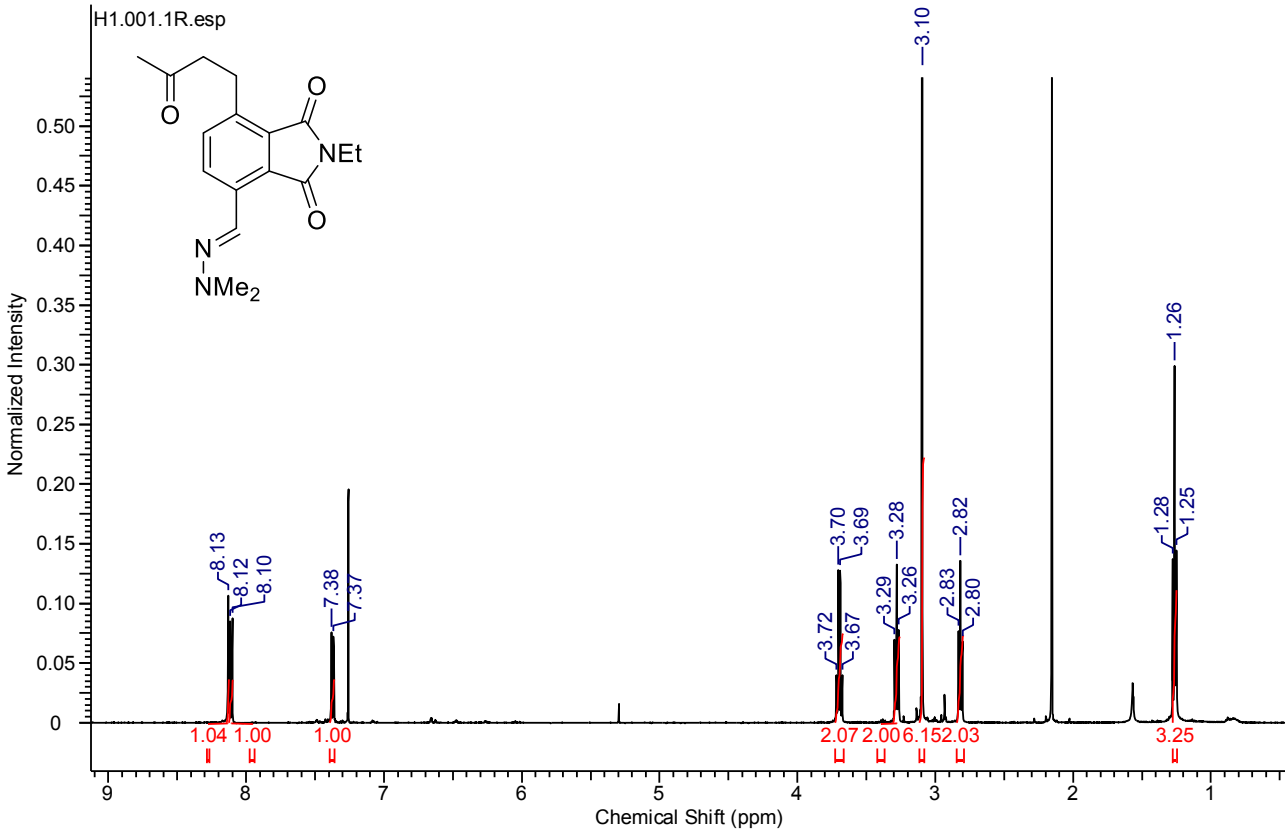


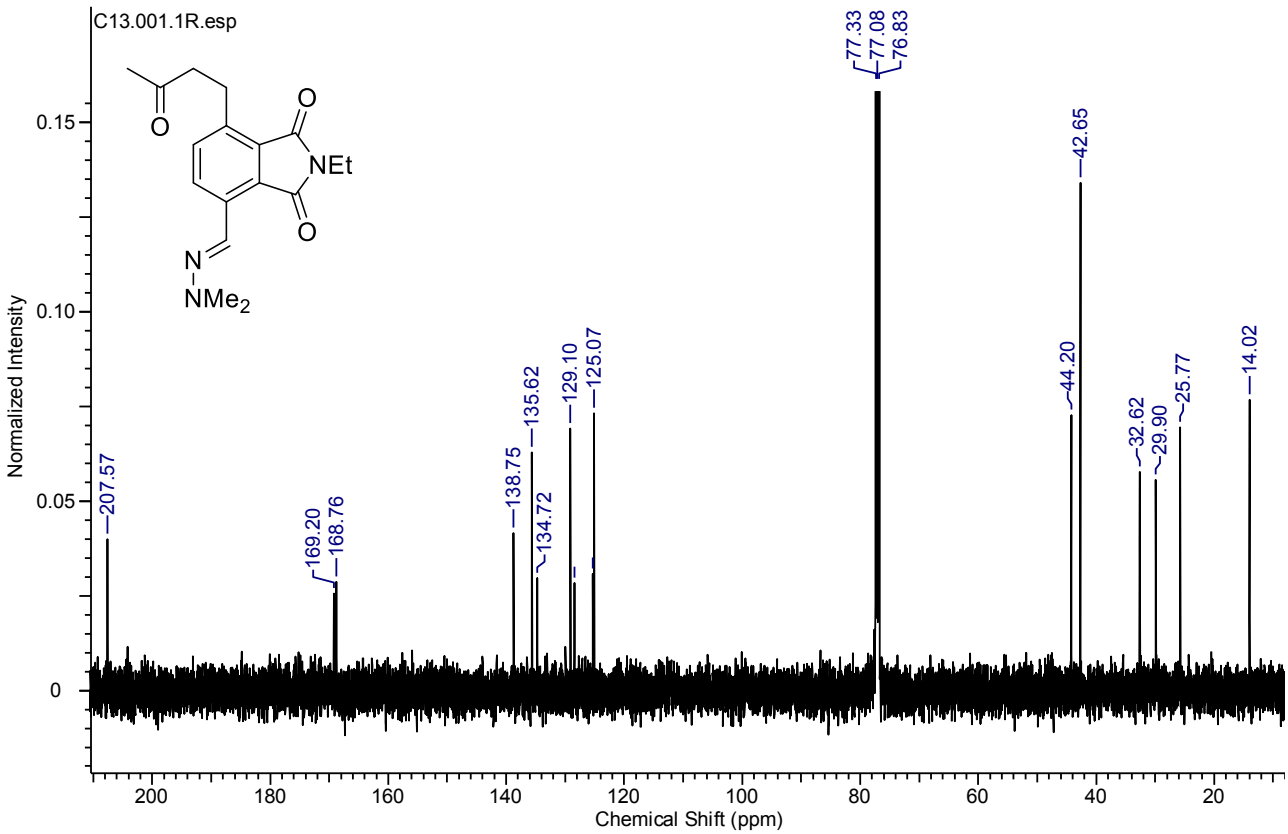
4-(3-(2,2-Dimethylhydrazono)prop-1-en-1-yl)-2-ethylisoindoline-1,3-dione 5s



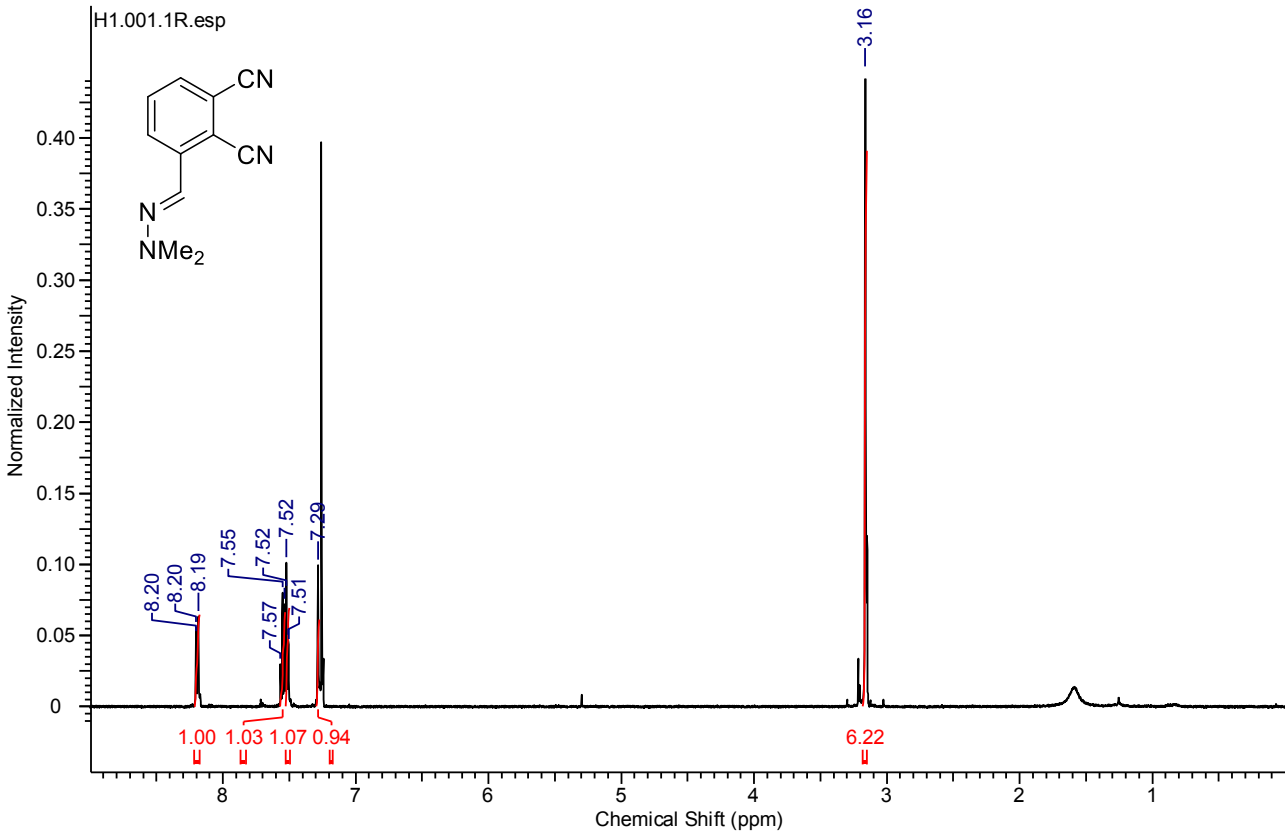


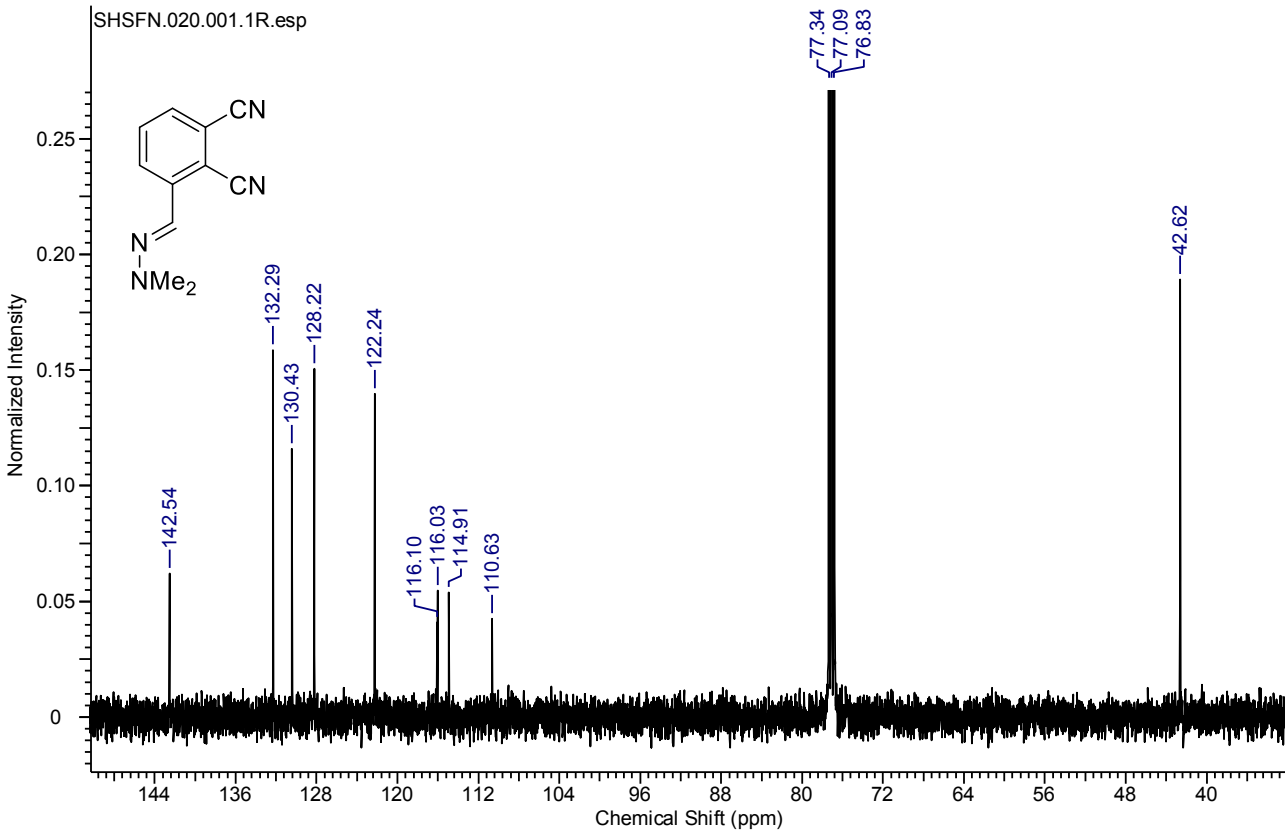
4-((2,2-Dimethylhydrazono)methyl)-2-ethyl-7-(3-oxobutyl)isoindoline-1,3-dione 5t



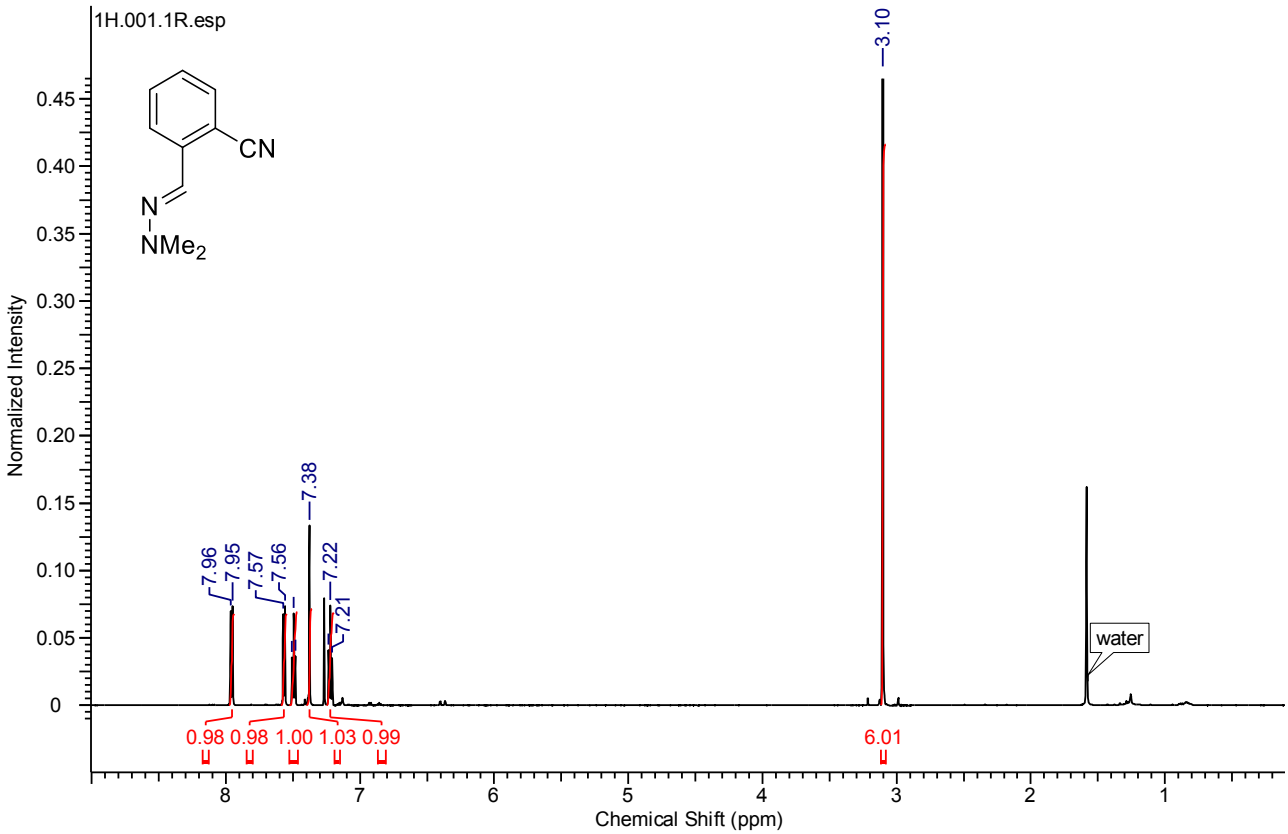


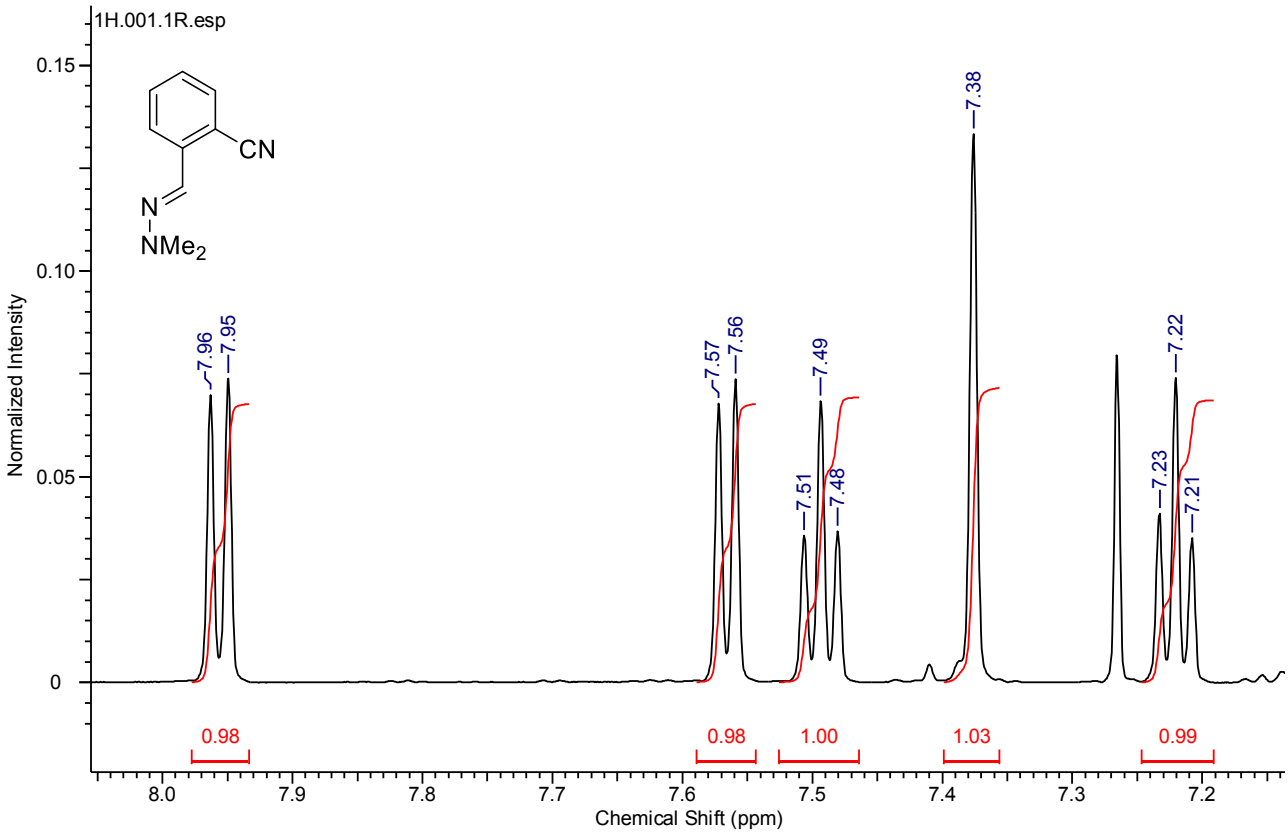
3-((2,2-Dimethylhydrazono)methyl)phthalonitrile 8a

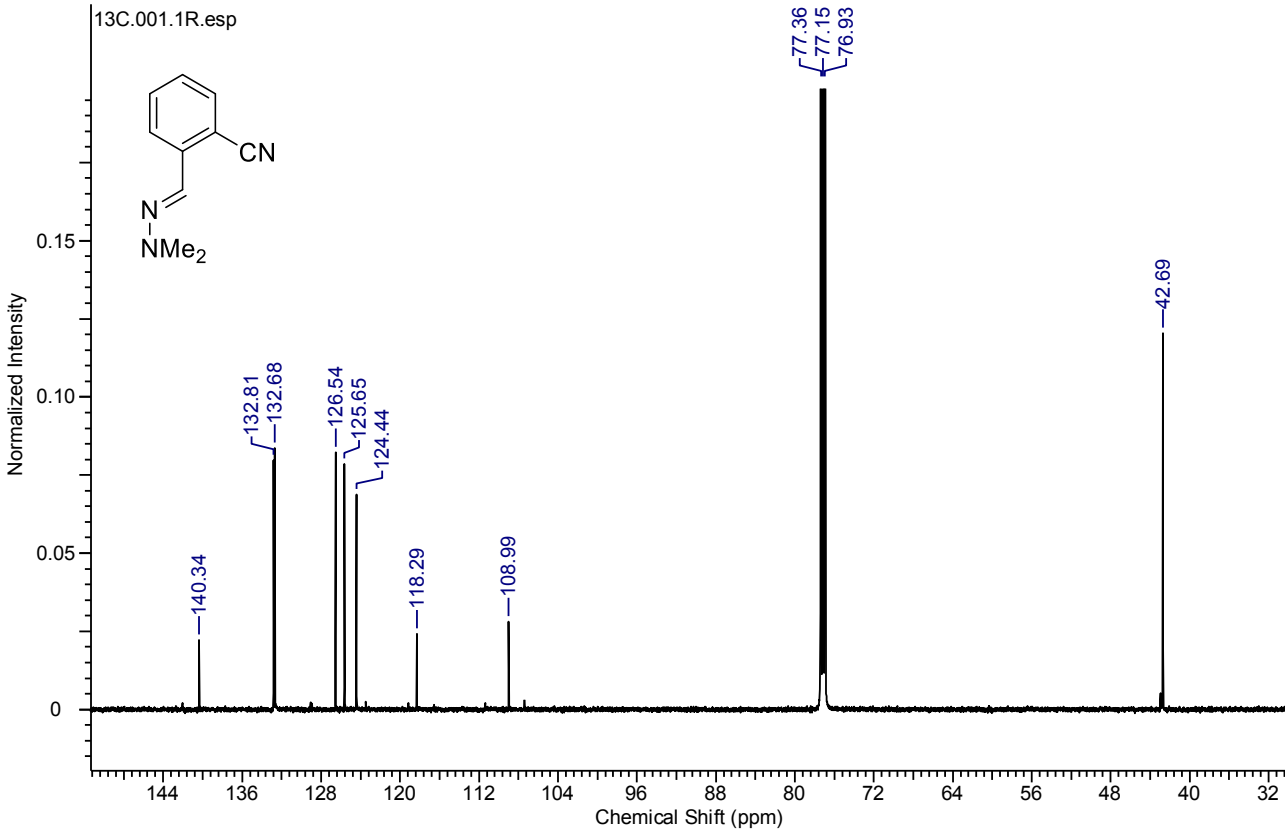




3-((2,2-Dimethylhydrazono)methyl)benzonitrile 8b



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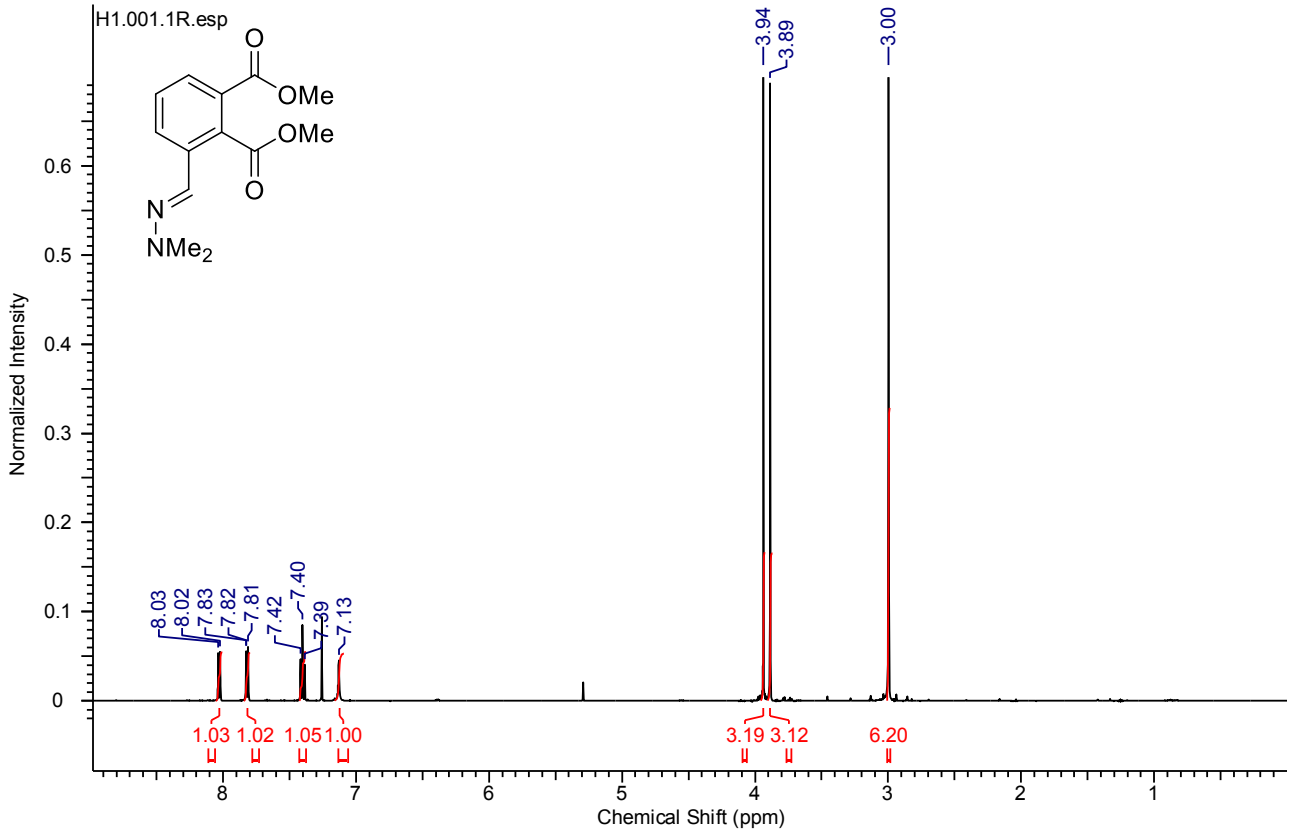
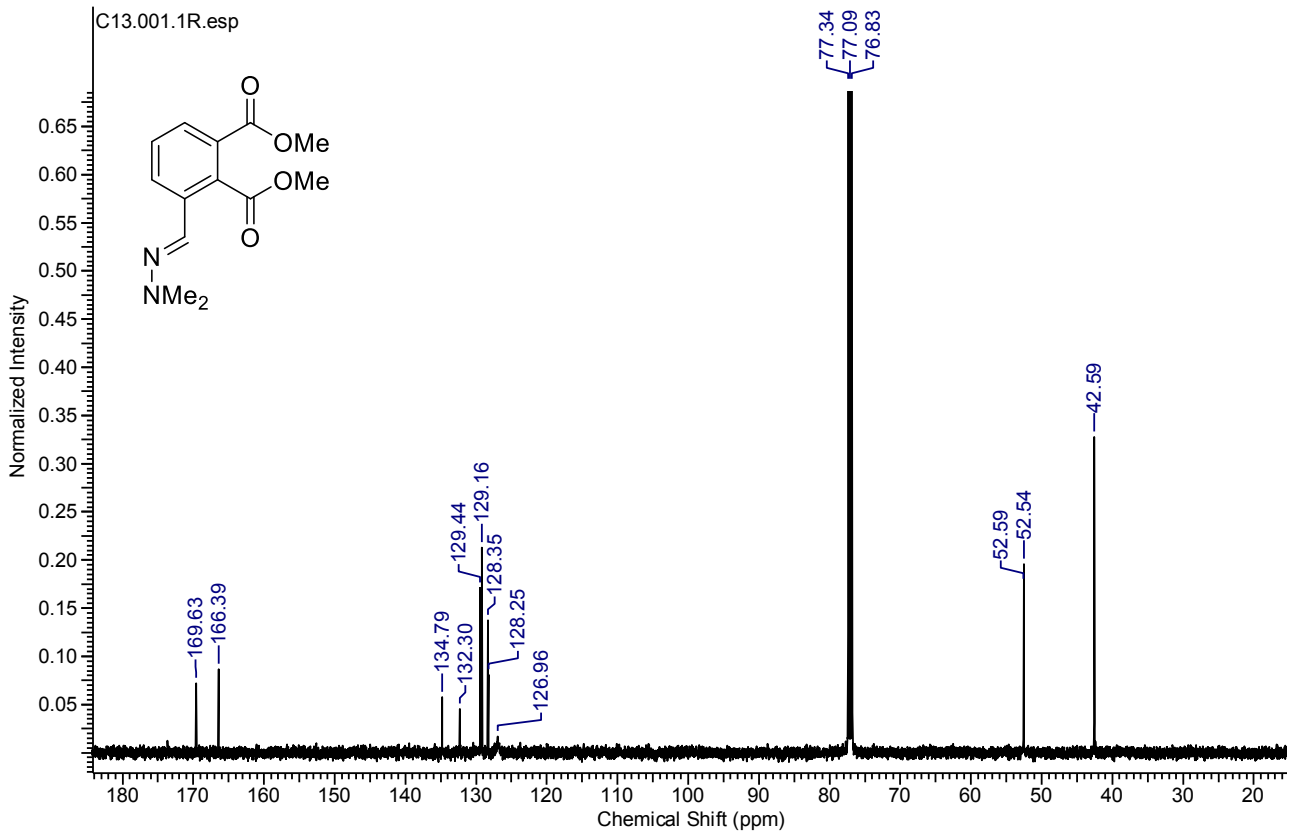
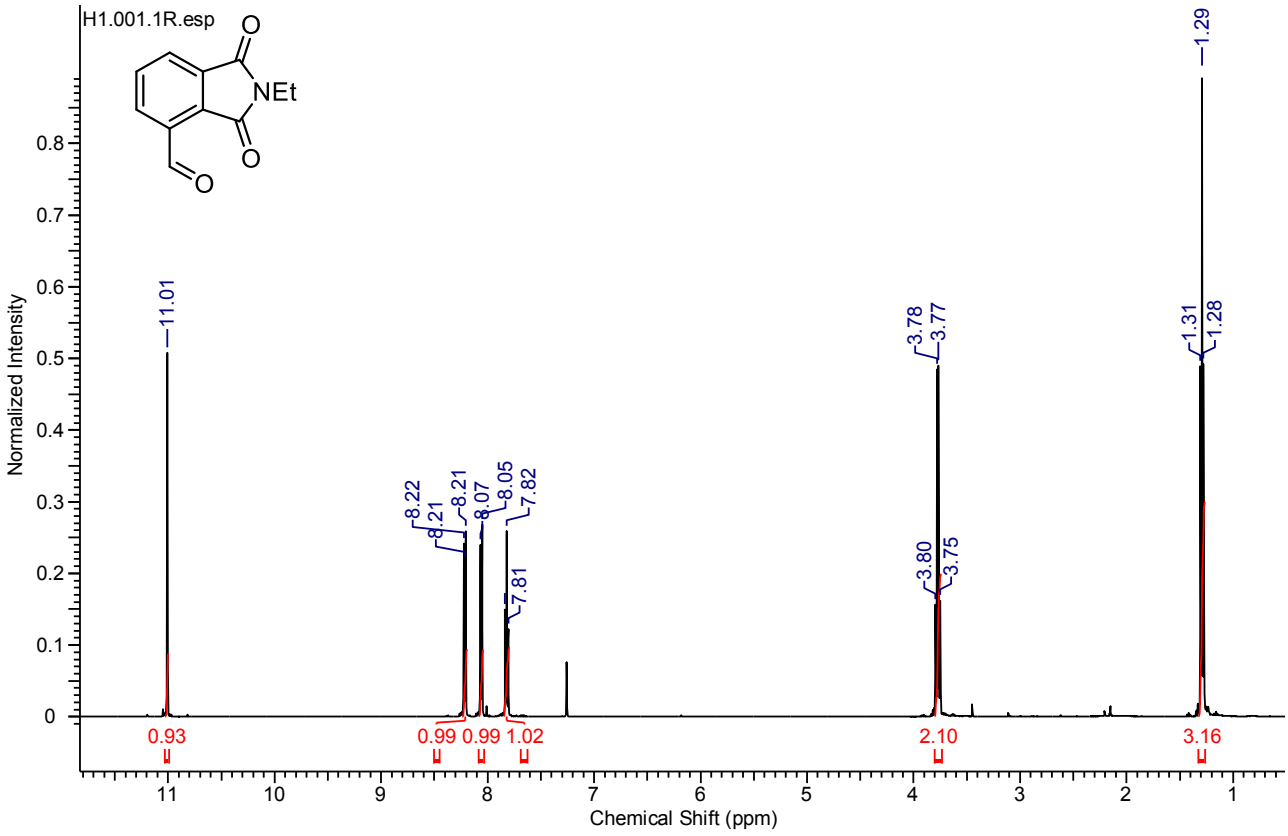
N
NMe2
77.36
77.15
76.93
42.69
132.81
132.68
126.54
125.65
124.44
140.34
118.29
108.99
Normalized Intensity
0.15
0.10
0.05
0
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)

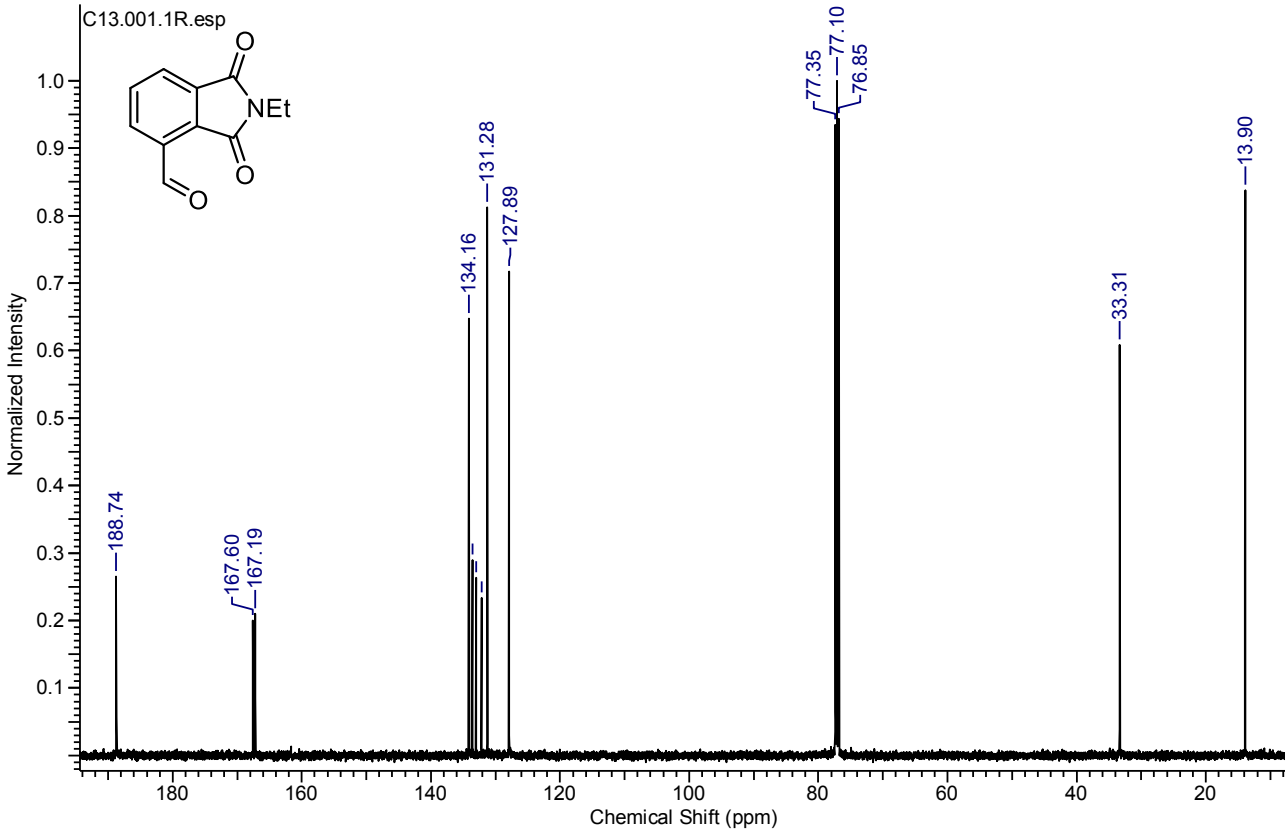
Dimethyl-3-((2,2-dimethylhydrazono)methyl)phthalate 8c



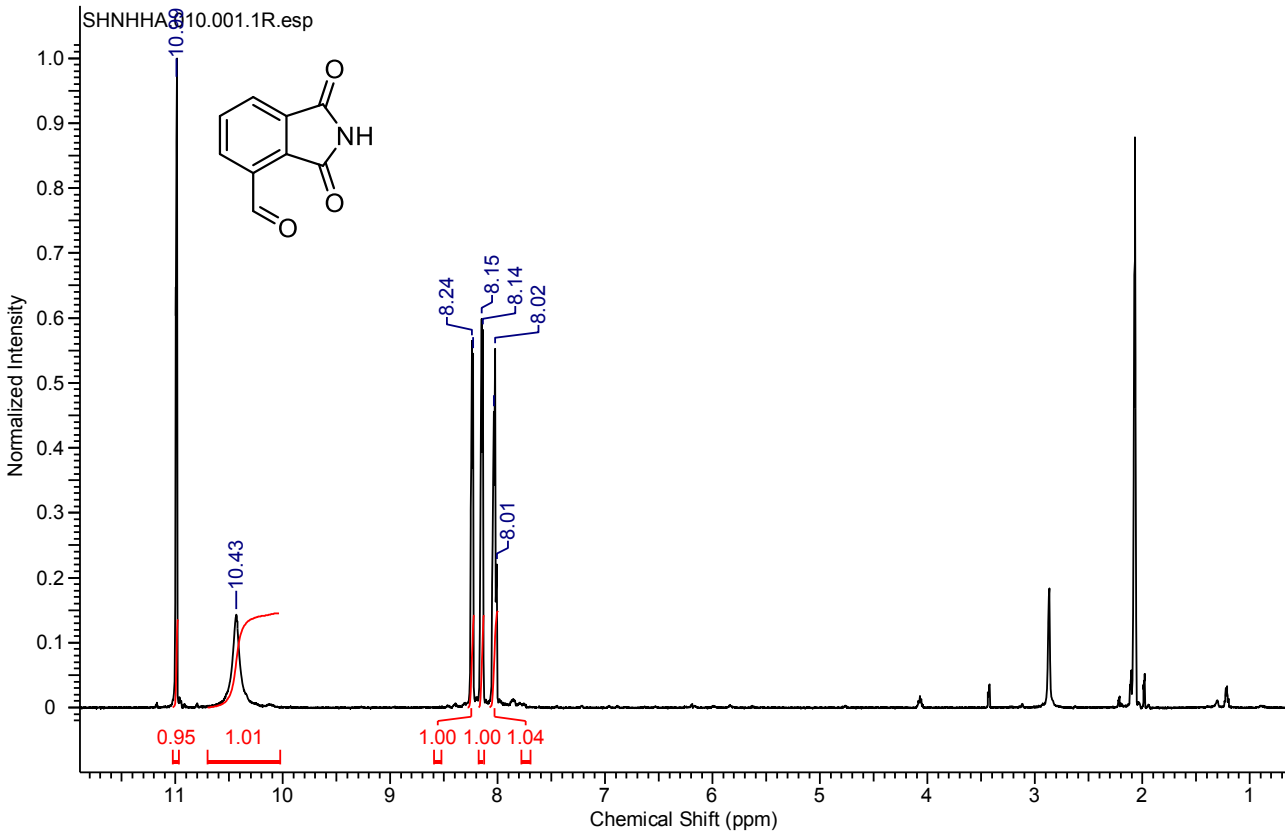


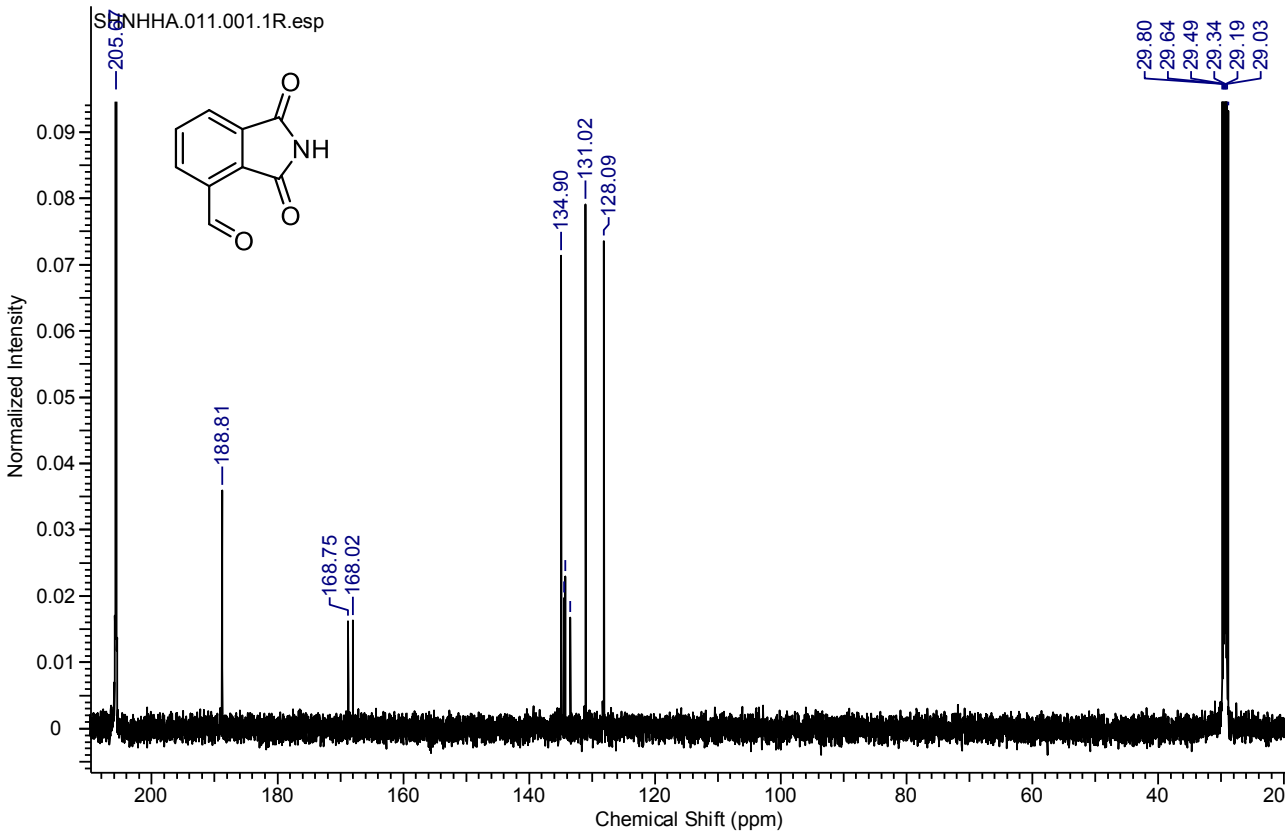
2-Ethyl-1,3-dioxoisoindoline-4-carbaldehyde 9a

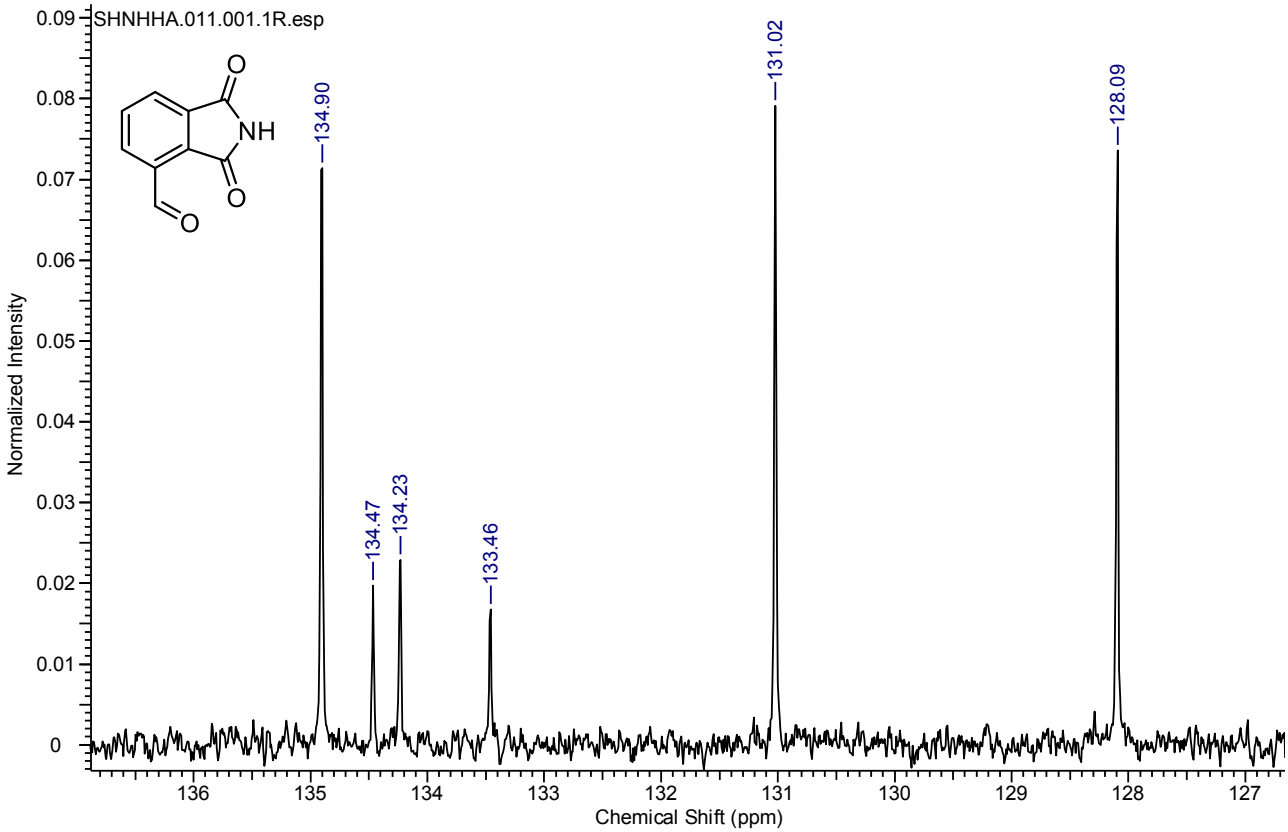




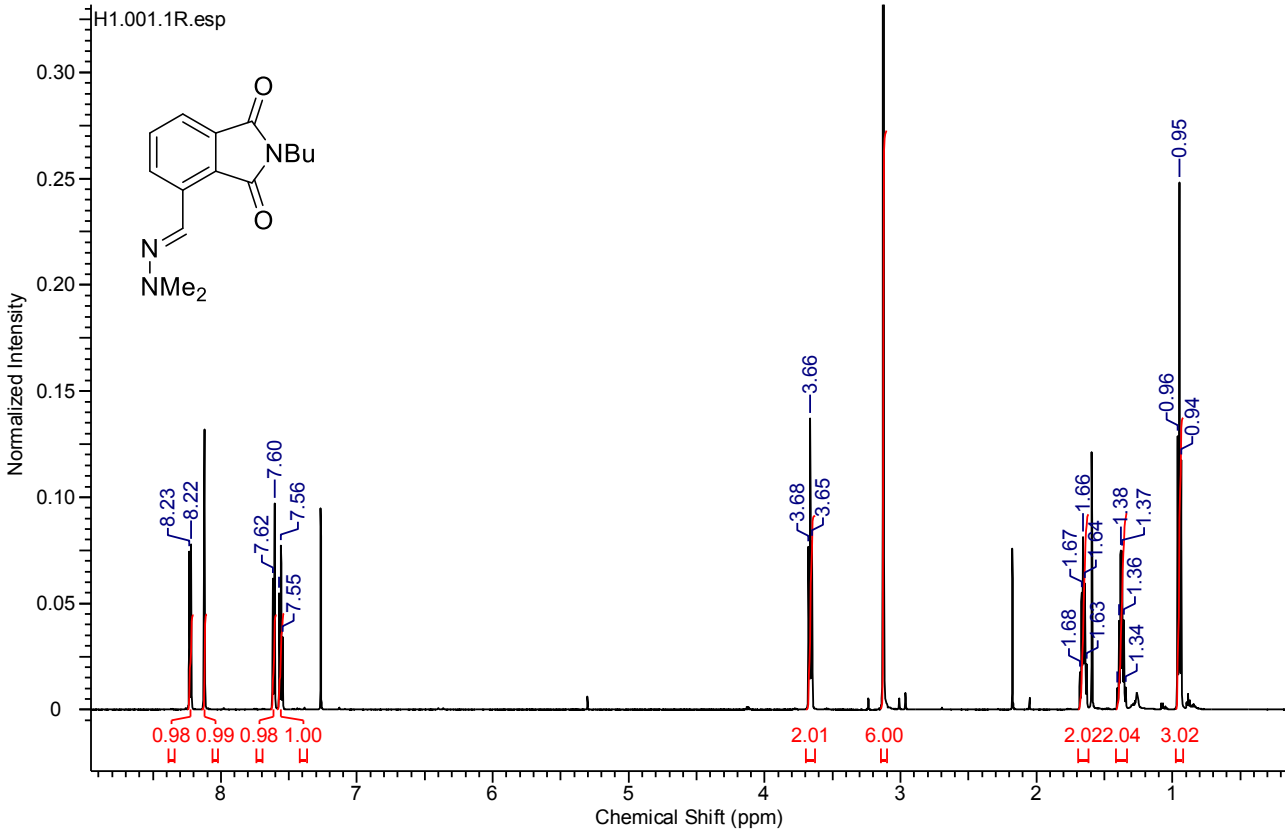
1,3-Dioxoisoindoline-4-carbaldehyde 9b

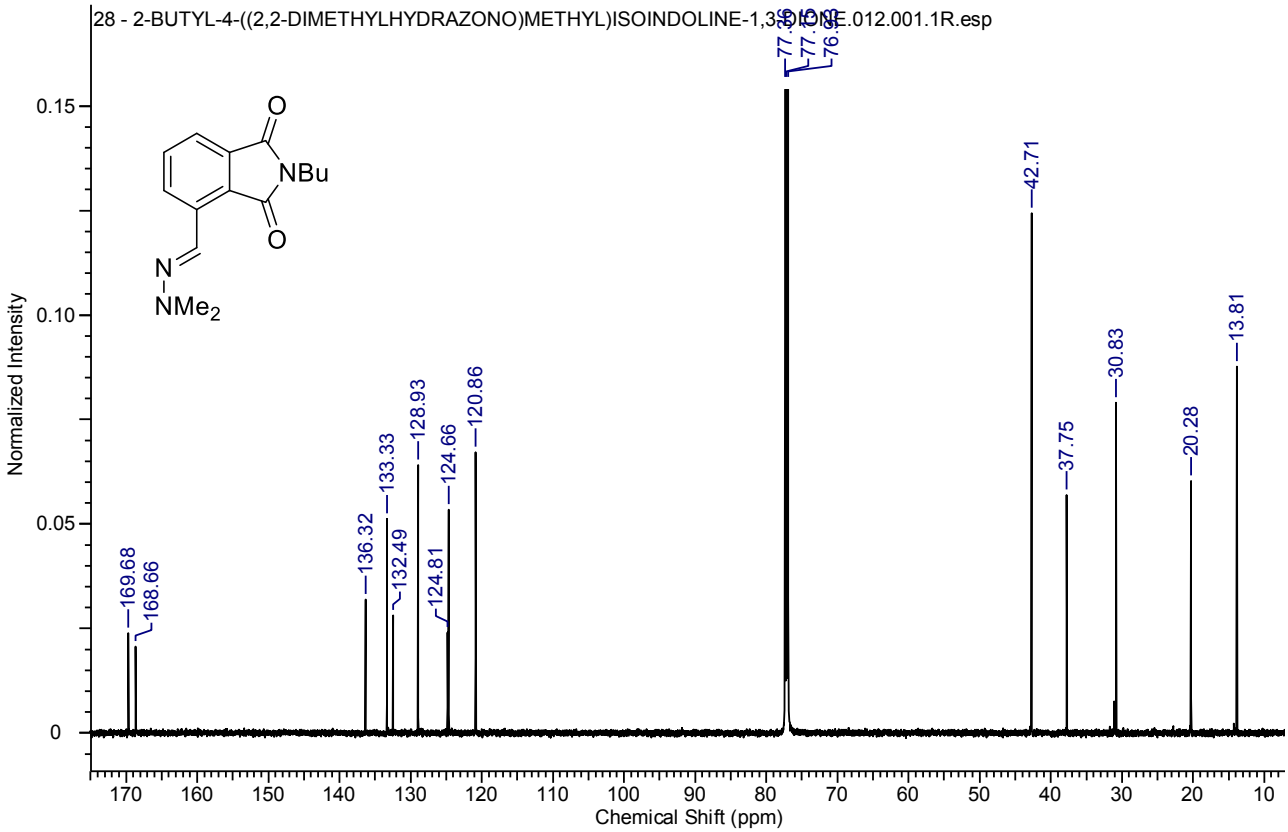




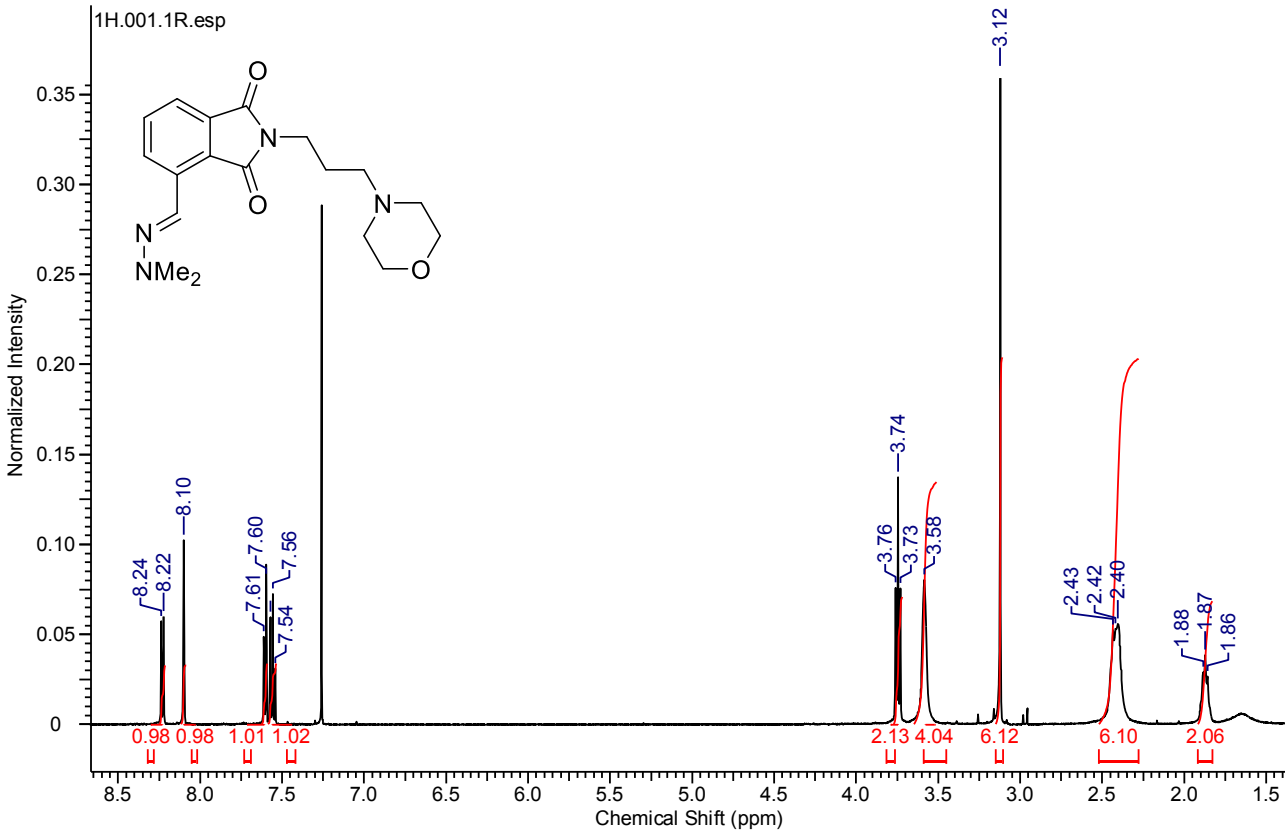

SHNHHA.011.001.1R.esp
O
NH
O
O
134.90
131.02
128.09
134.47
134.23
133.46
Normalized Intensity
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
136
135
134
133
132
131
130
129
128
127
Chemical Shift (ppm)

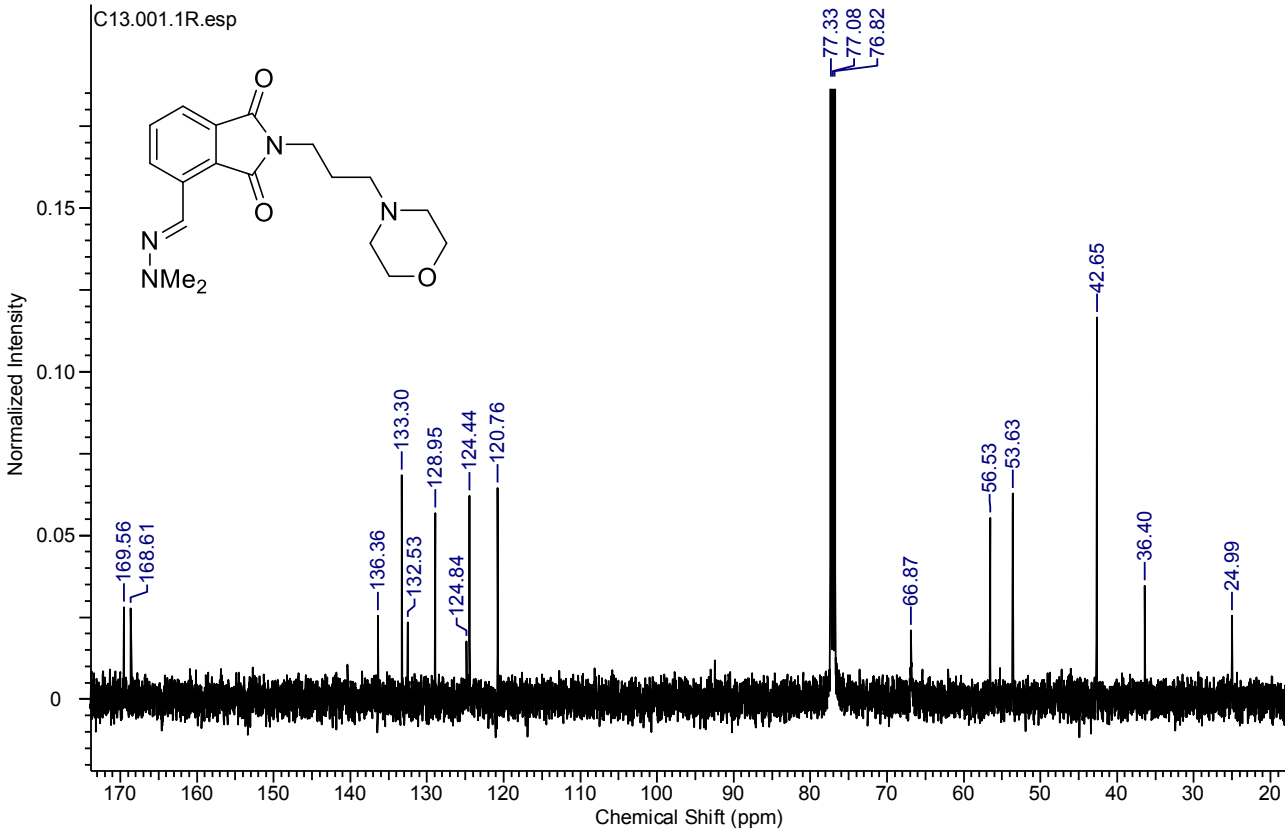
2-Butyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5u



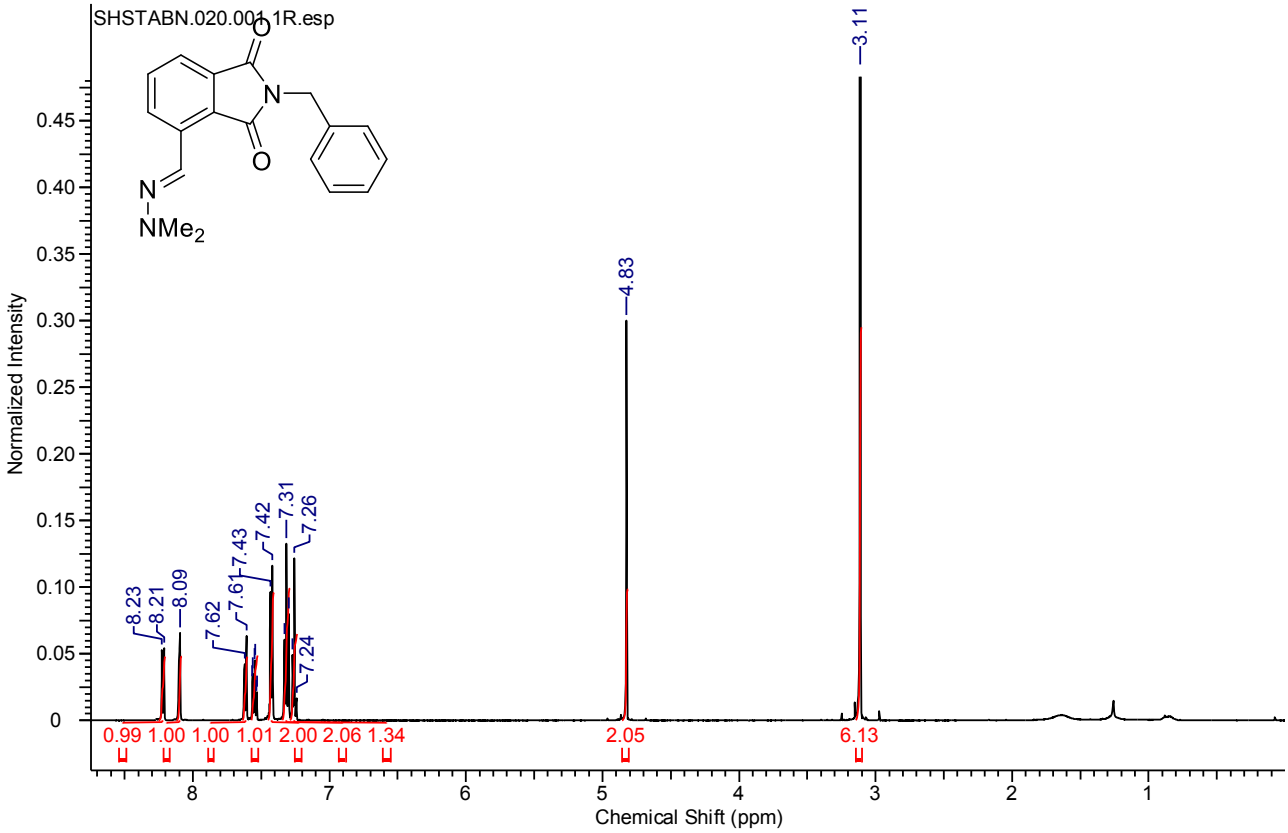


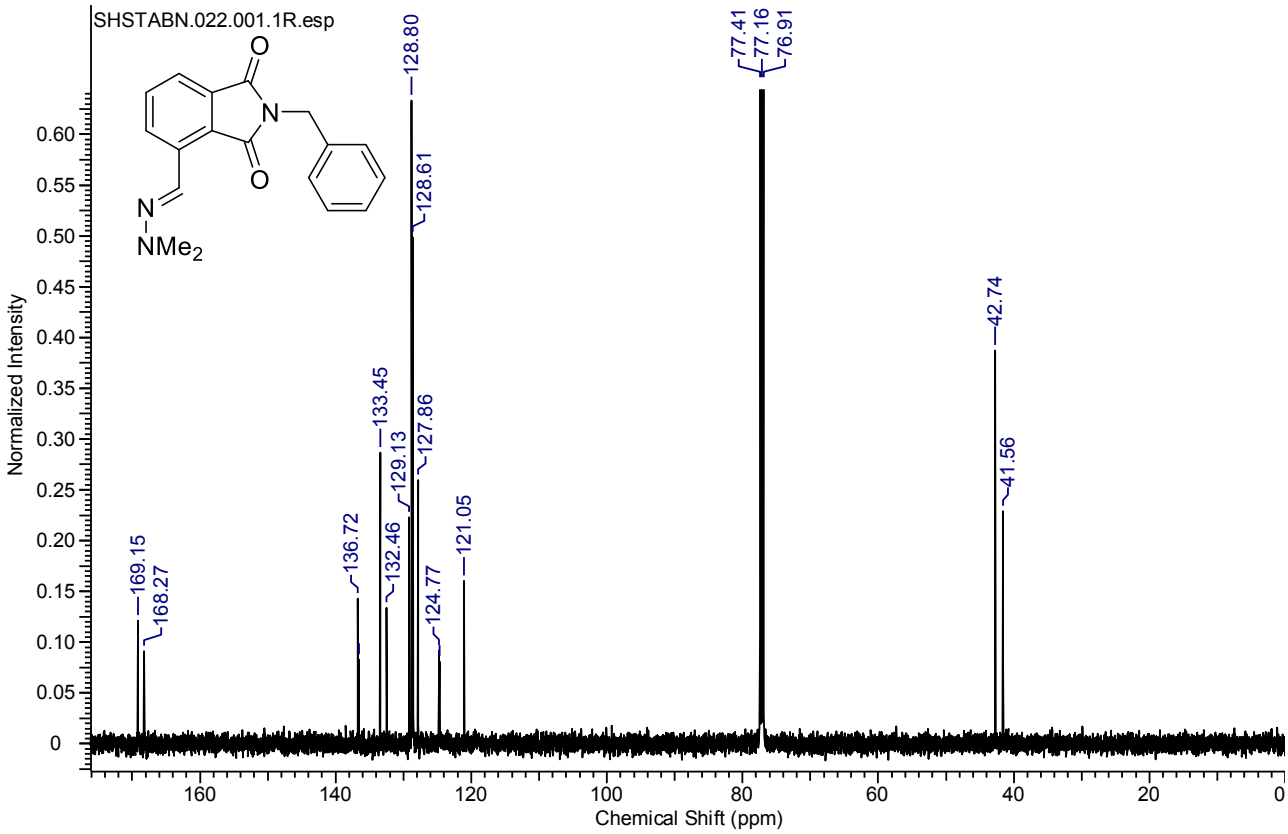
4-((2,2-Dimethylhydrazono)methyl)-2-(3-morpholinopropyl)isoindoline-1,3-dione 5v



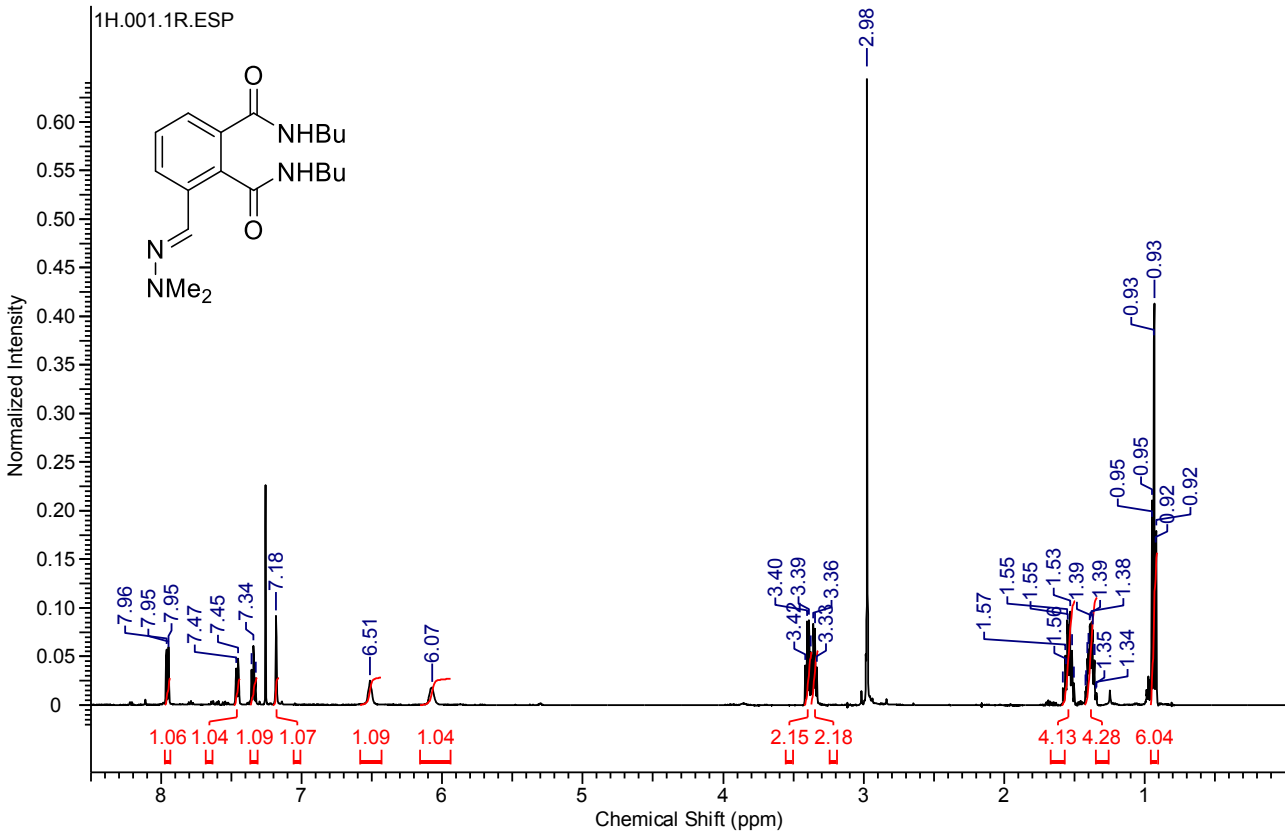


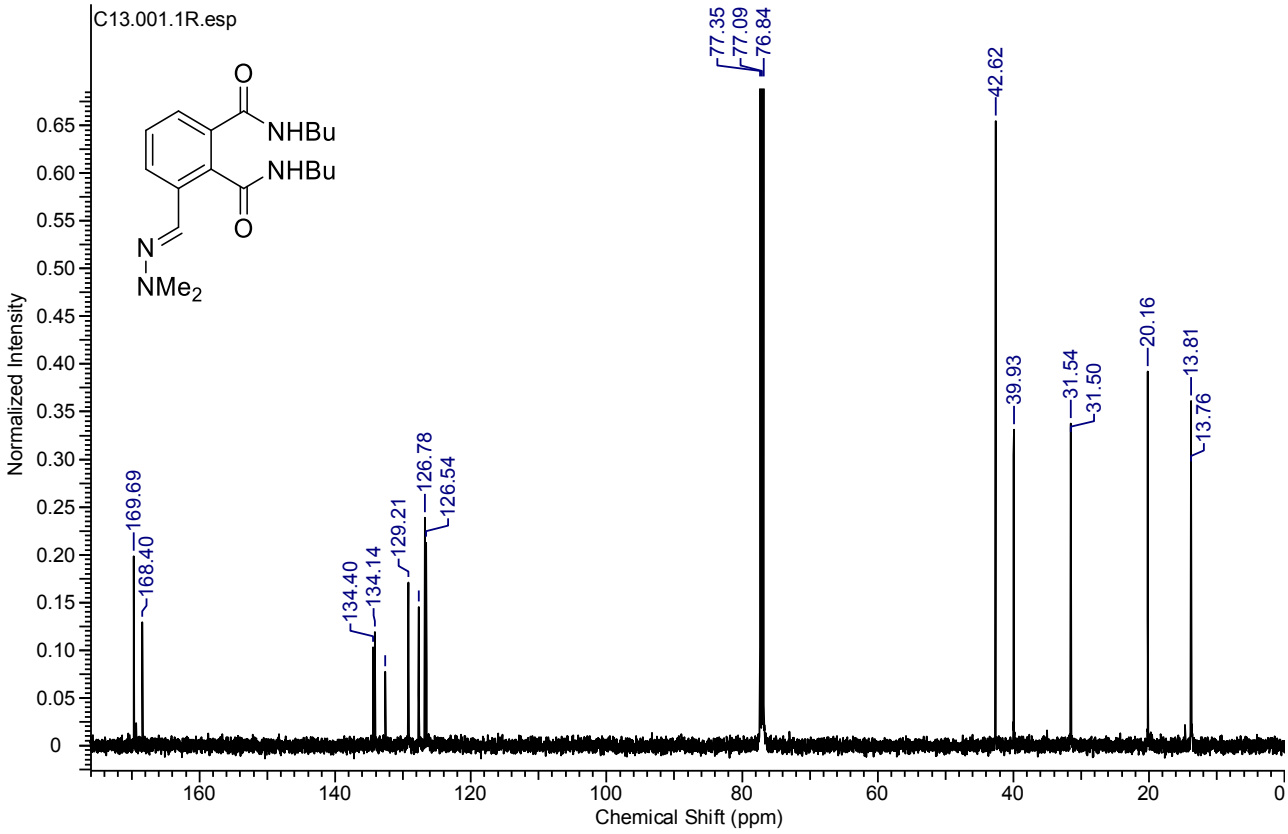
2-Benzyl-4-((2,2-dimethylhydrazono)methyl)isoindoline-1,3-dione 5w

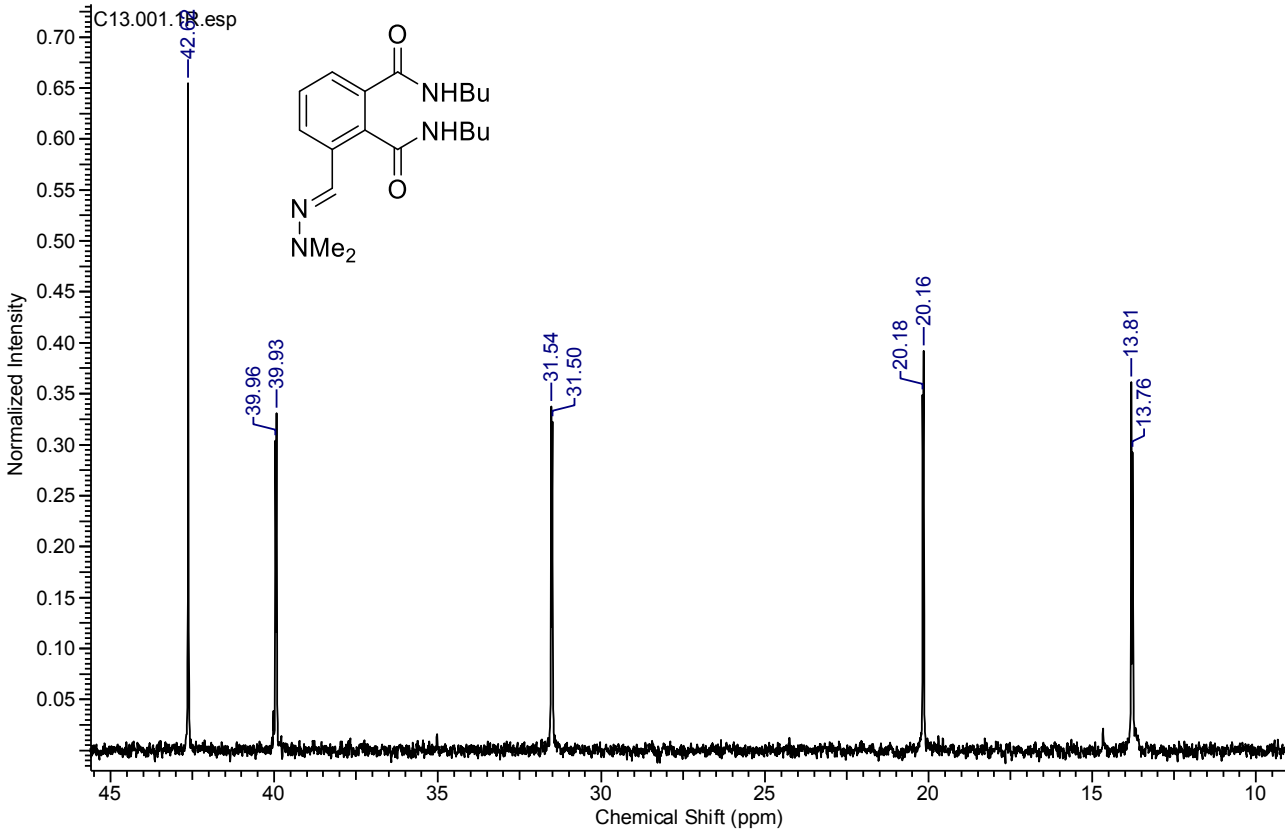




N,N-Dibutyl-3-((2,2-dimethylhydrazono)methyl)phthalamide 10a






C13.001.1.esp
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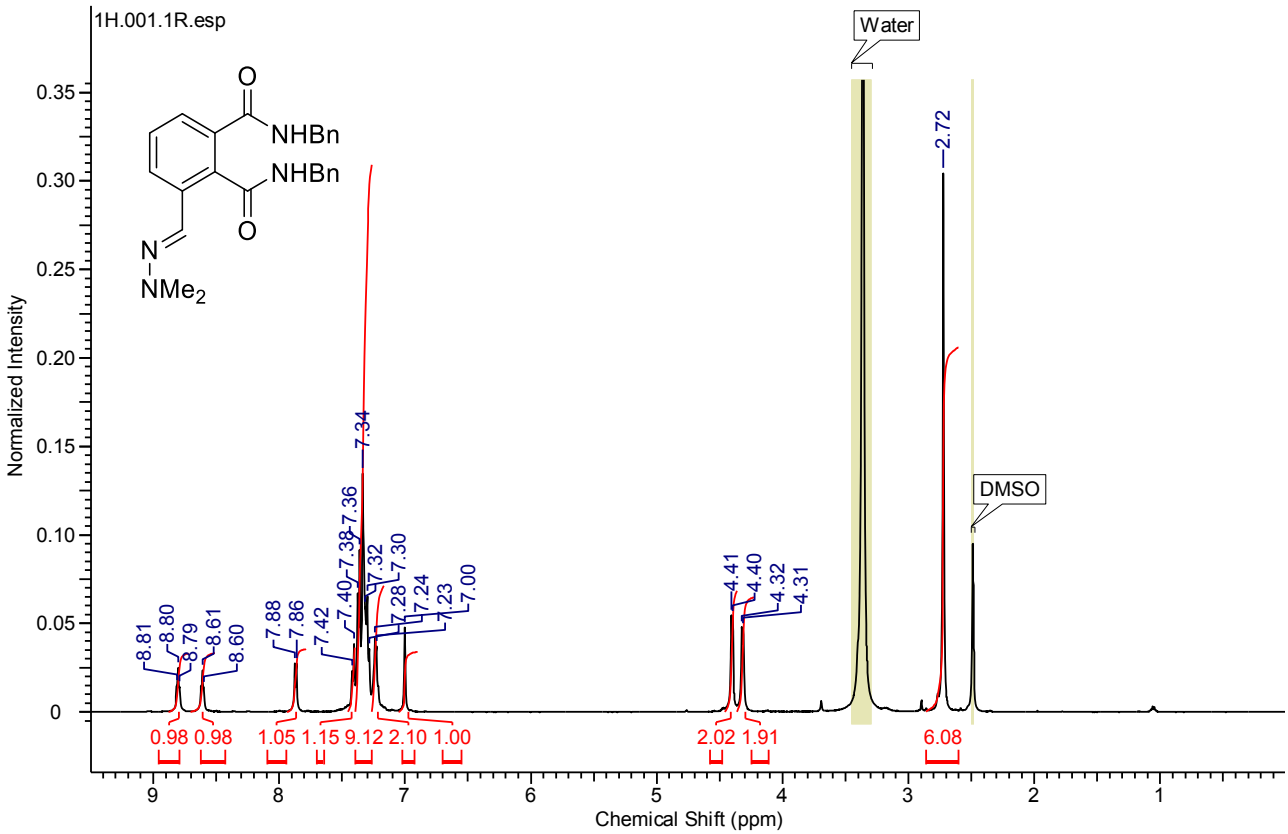
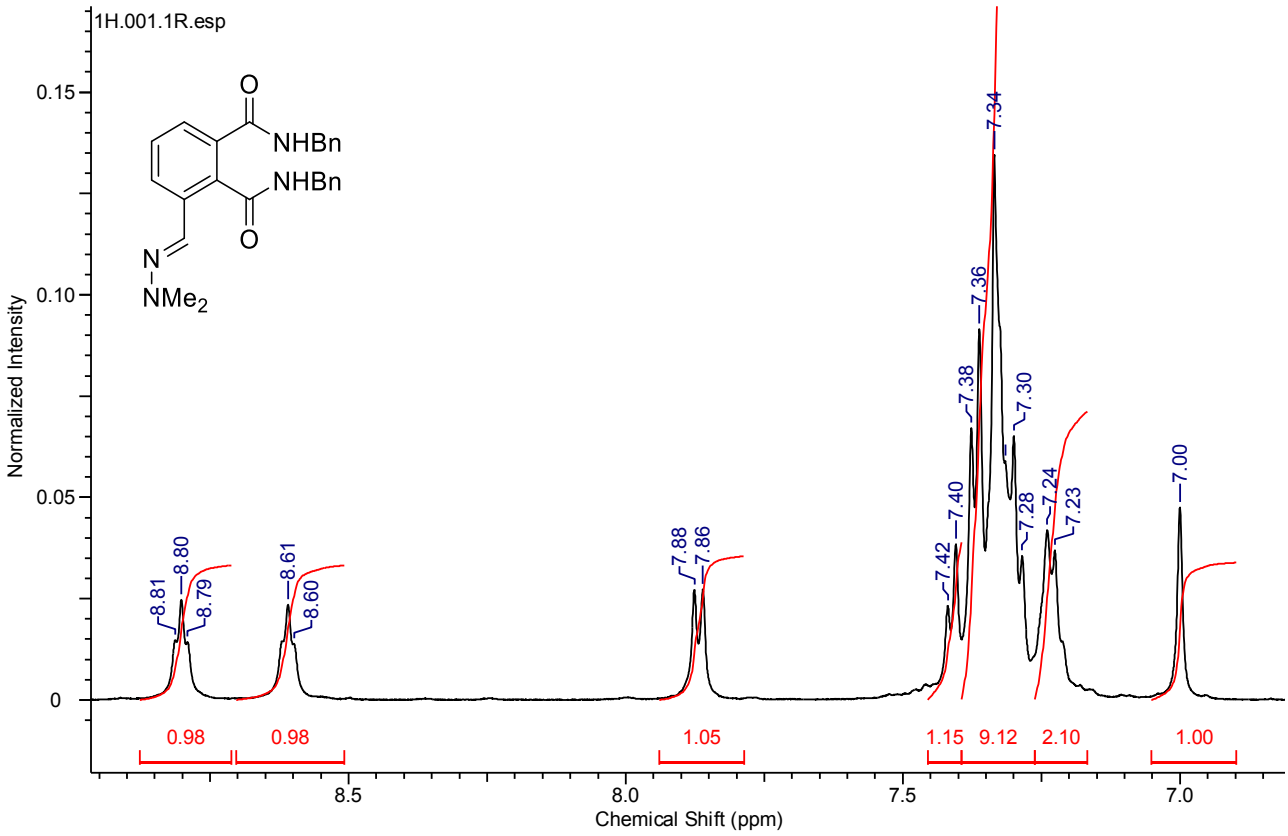
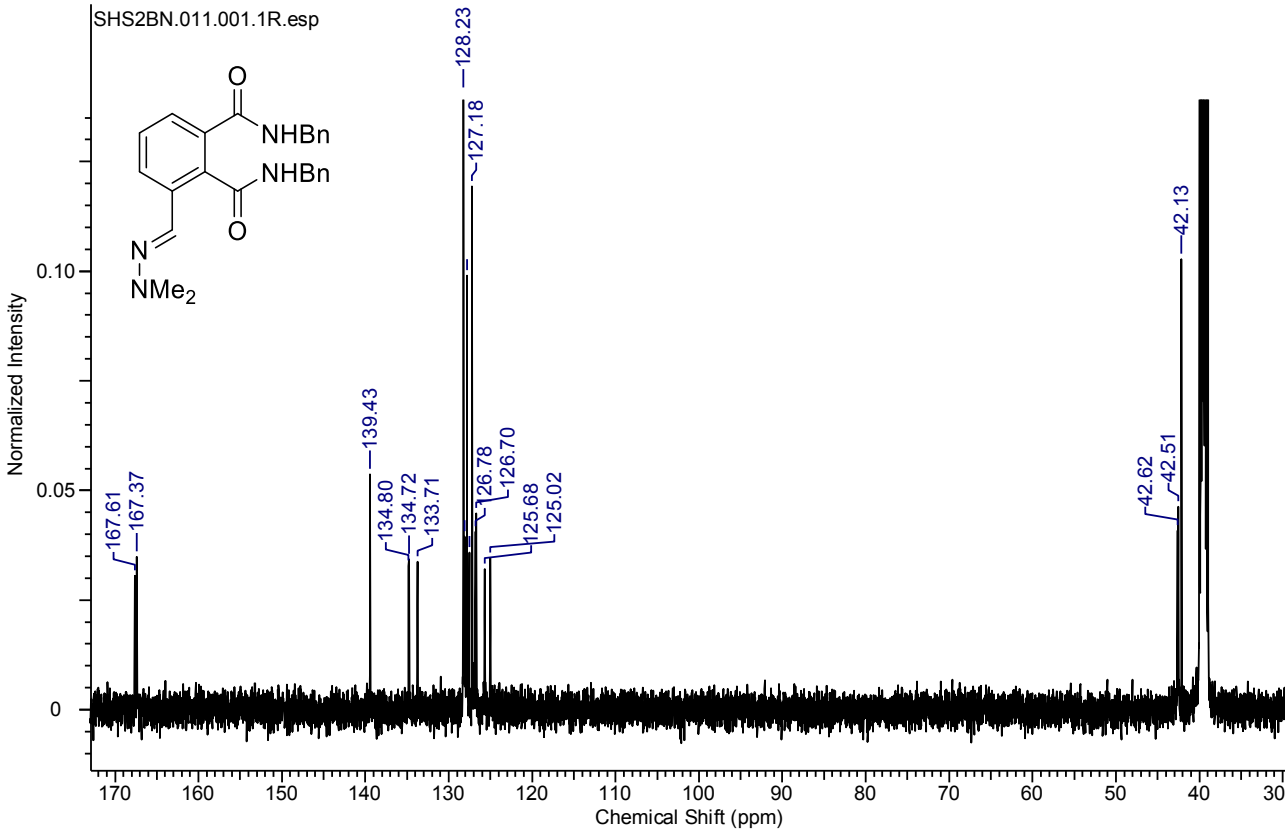
39.96
39.93
31.54
31.50
20.18
20.16
13.81
13.76
O
NHBu
NHBu
O
N
NMe2
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
45
40
35
30
25
20
15
10
Chemical Shift (ppm)

N,N-Dibenzyl-3-((2,2-dimethylhydrazono)methyl)phthalamide 10b



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NHBn
O
O
O
N
NMe2
Normalized Intensity
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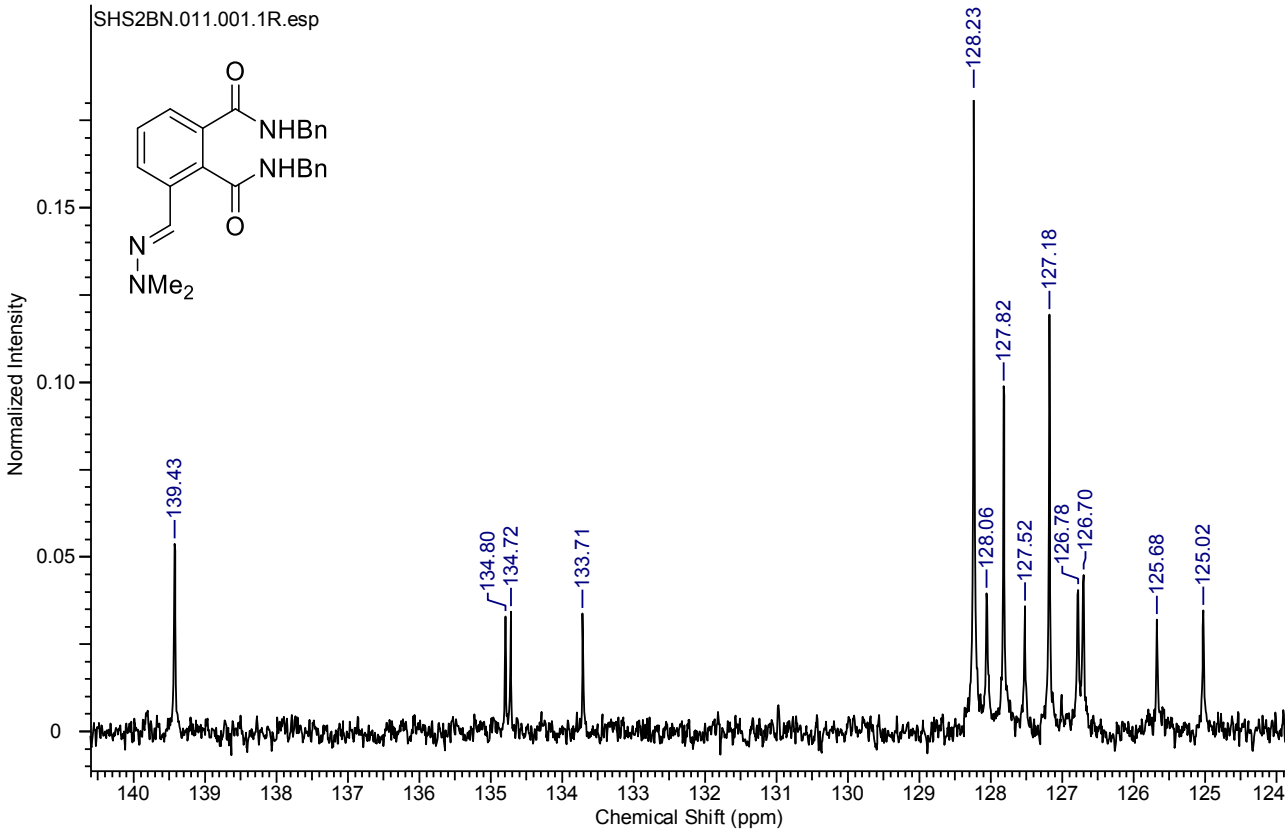
0.05
0
128.23
127.18
42.13
139.43
134.80
134.72
133.71
126.78
126.70
125.68
125.02
167.61
167.37
42.62
42.51
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)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NHBn
O
O
O
N
NMe2
Normalized Intensity
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0.05
0
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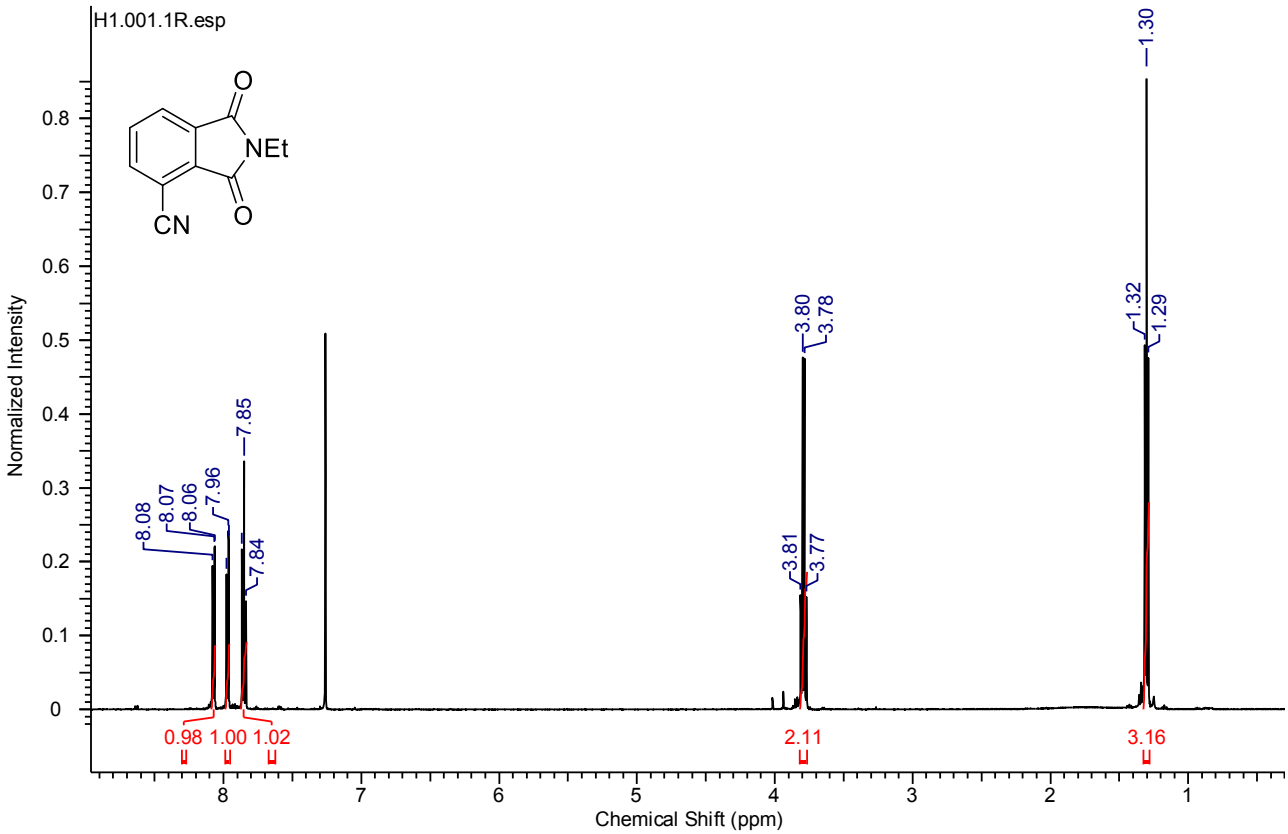
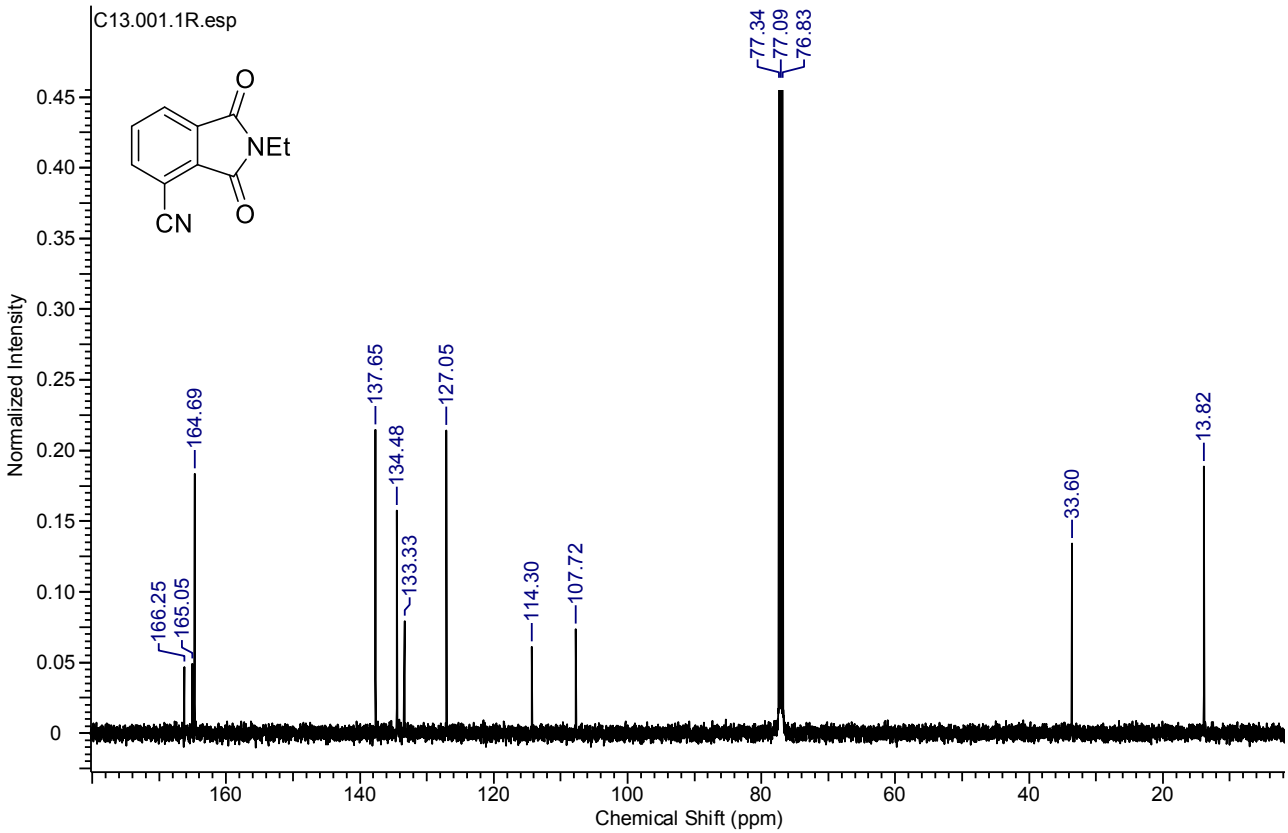
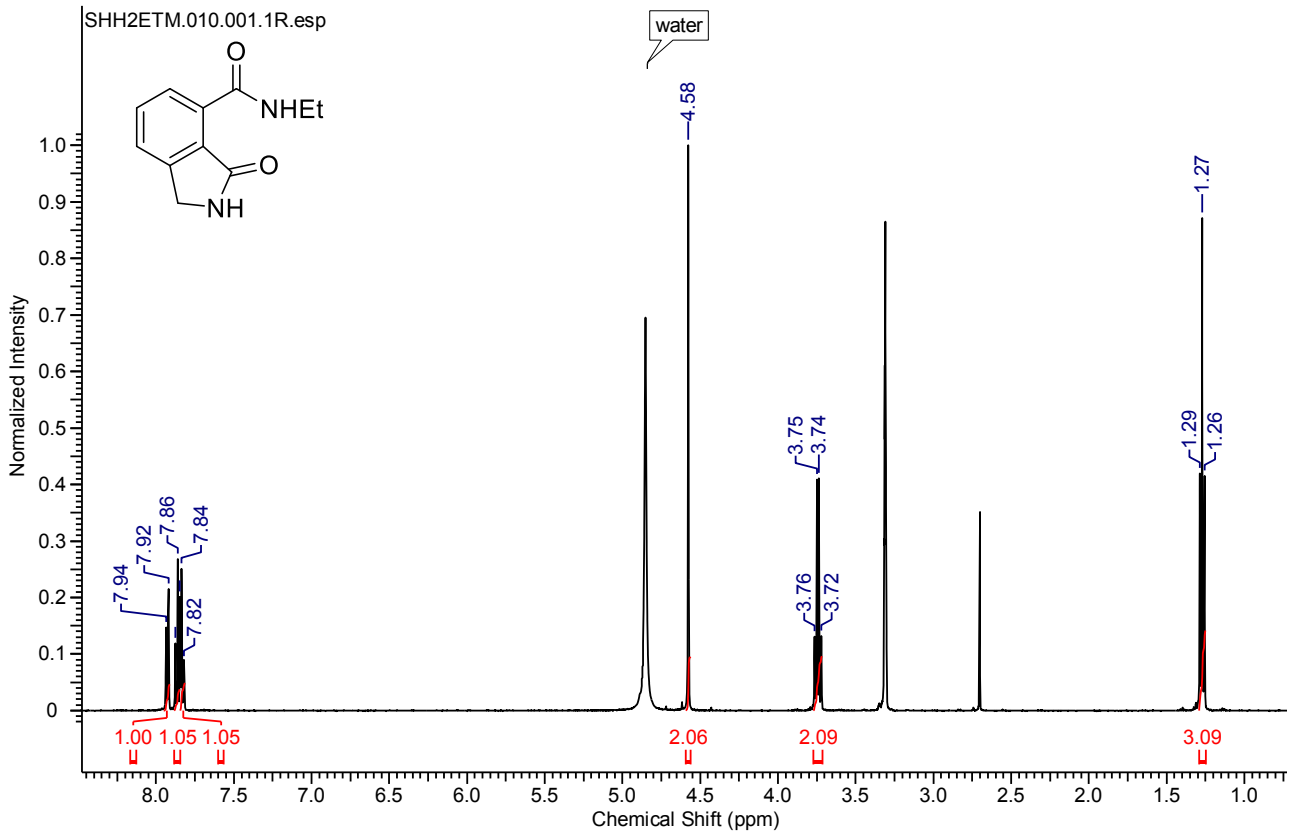
127.82
127.18
139.43
128.06
127.52
126.78
126.70
125.68
125.02
134.80
134.72
133.71
140
139
138
137
136
135
134
133
132
131
130
129
128
127
126
125
124
Chemical Shift (ppm)

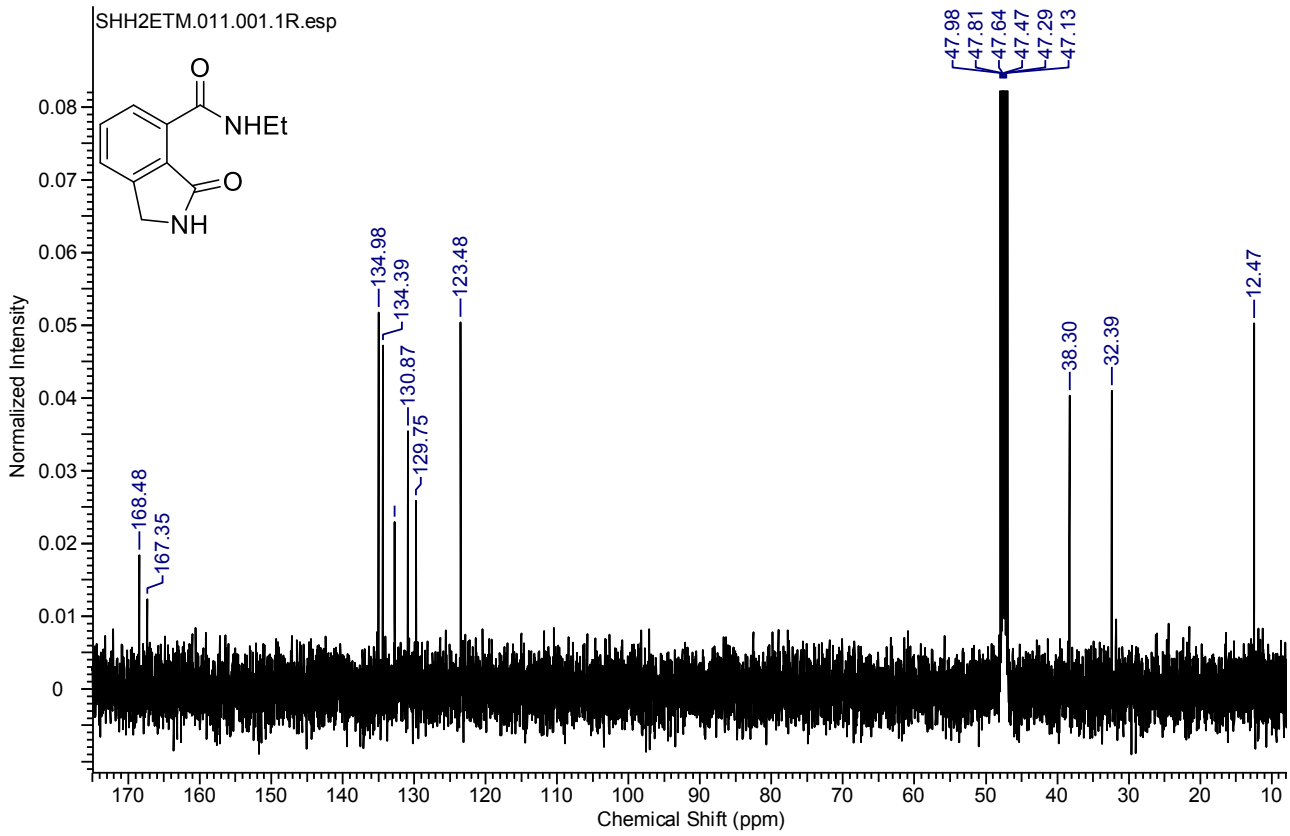
2-Ethyl-1,3-dioxoisoindoline-4-carbonitrile 11



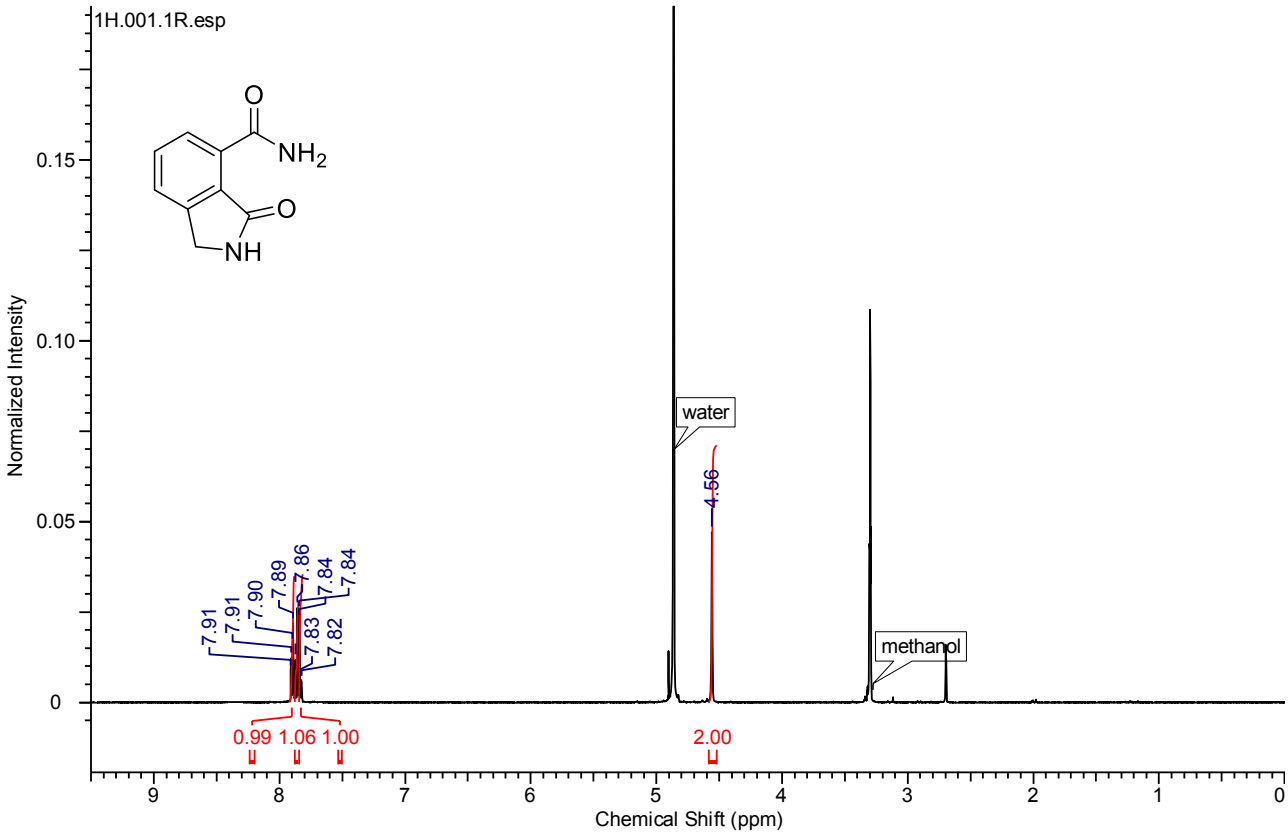


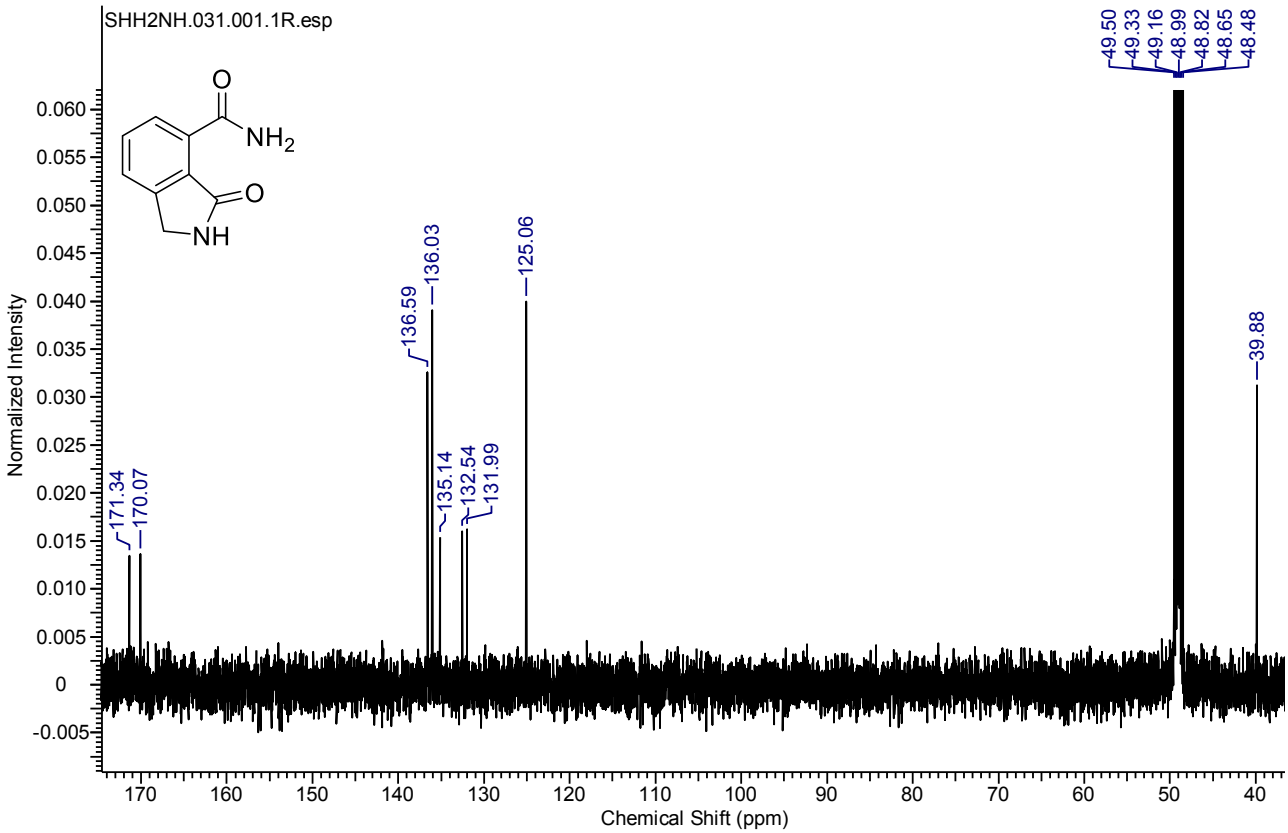
N-Ethyl-3-oxoisoindoline-4-carboxamide 12a



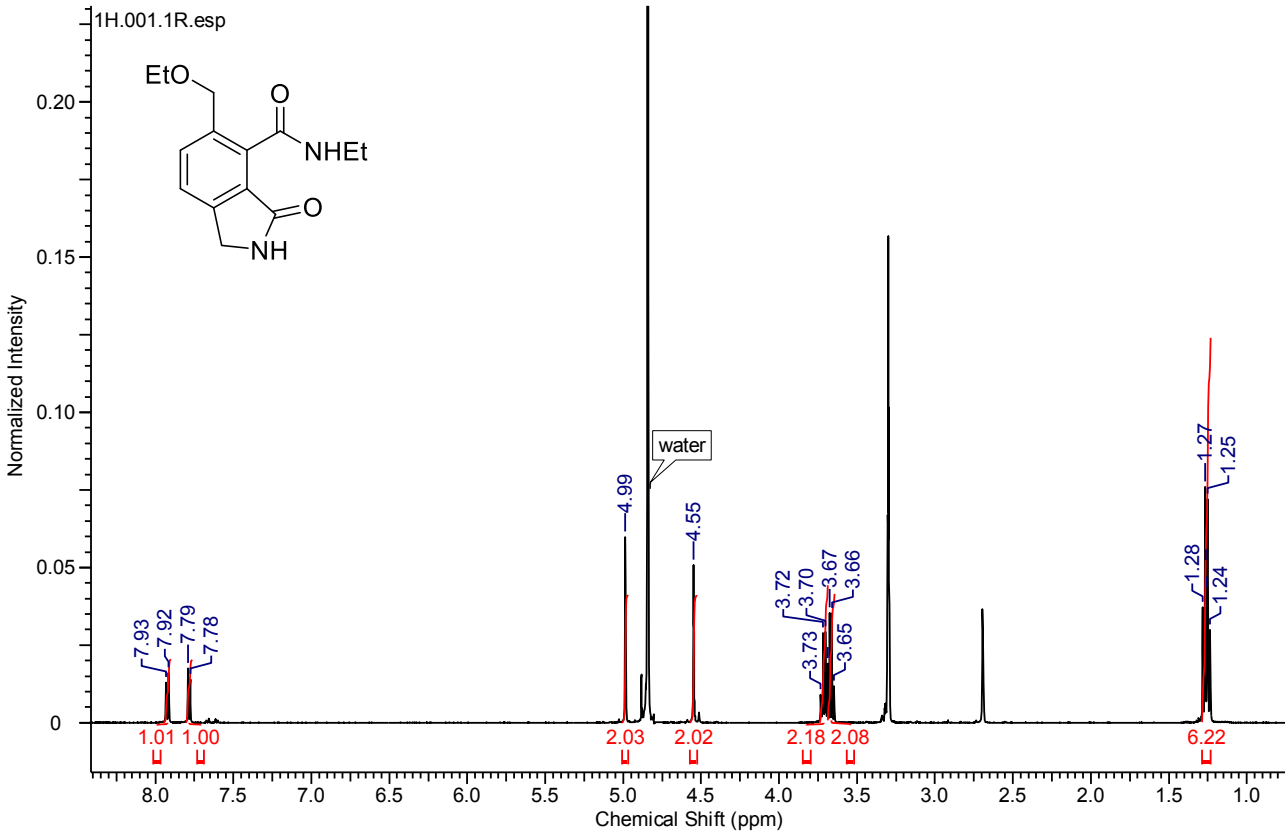


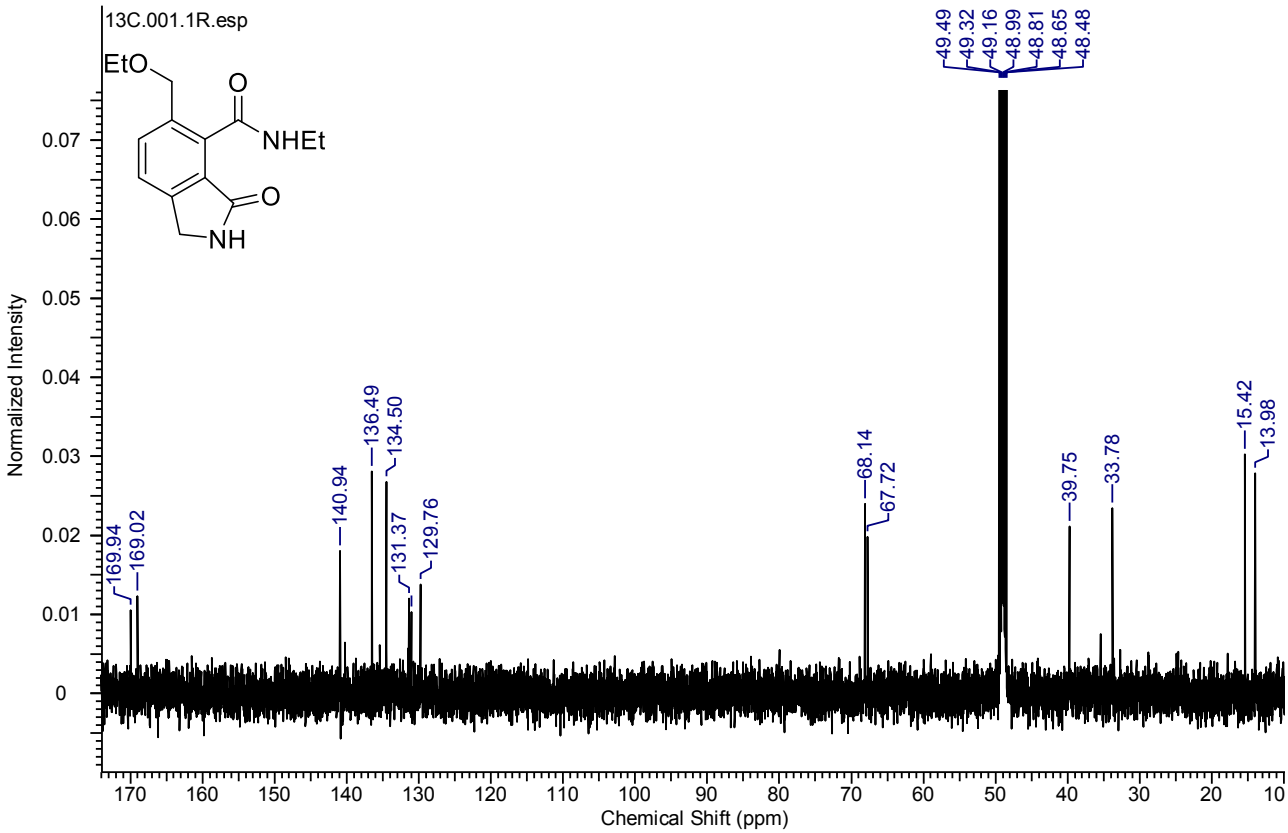
3-Oxoisoindoline-4-carboxamide 12b



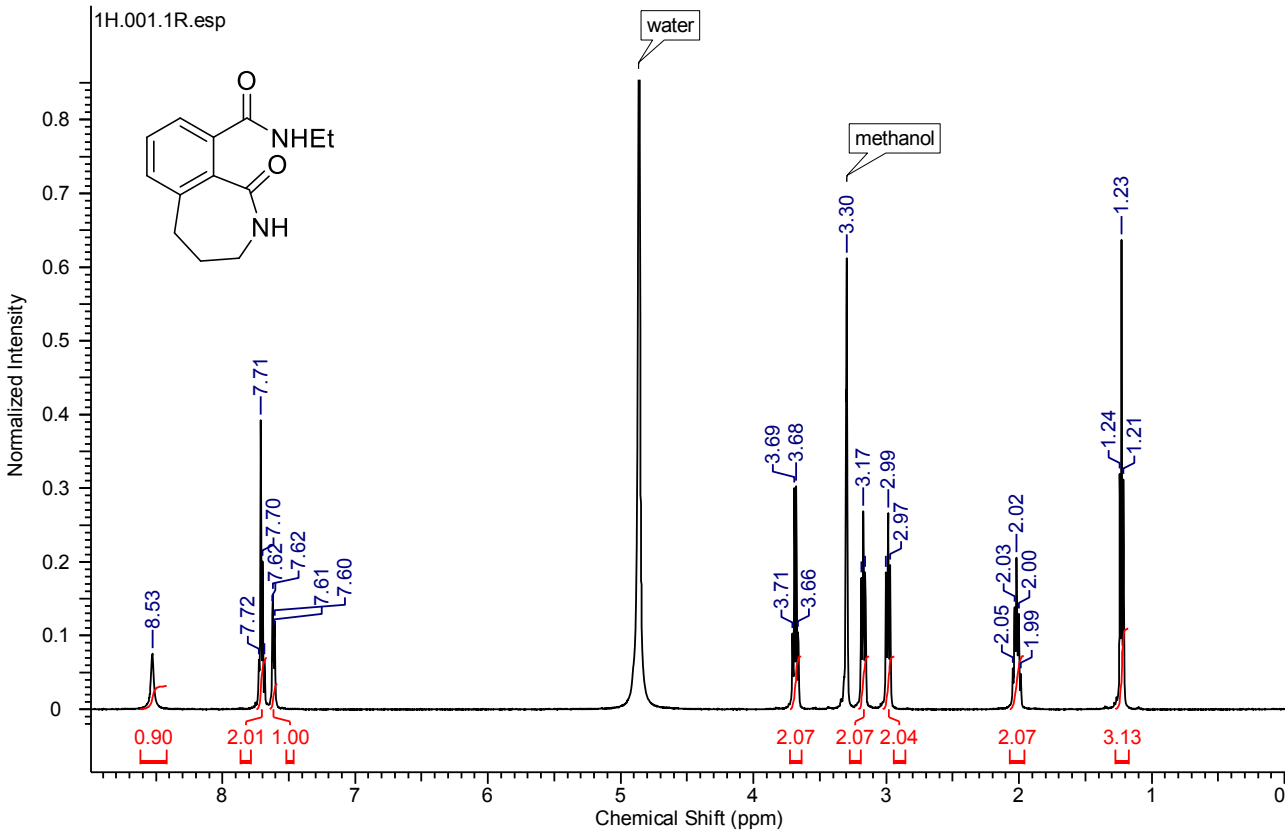


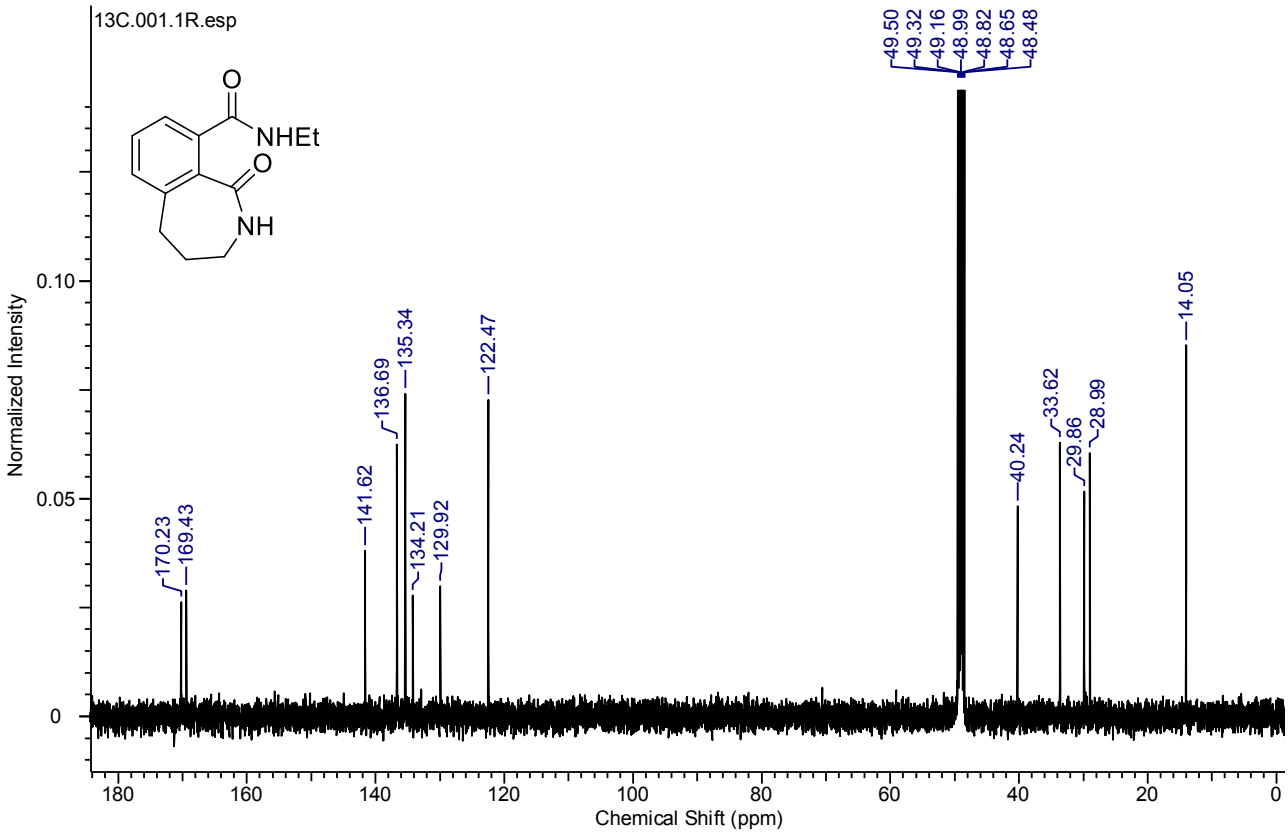
5-(Ethoxymethyl)-N-ethyl-3-oxoisoindoline-4-carboxamide 12c



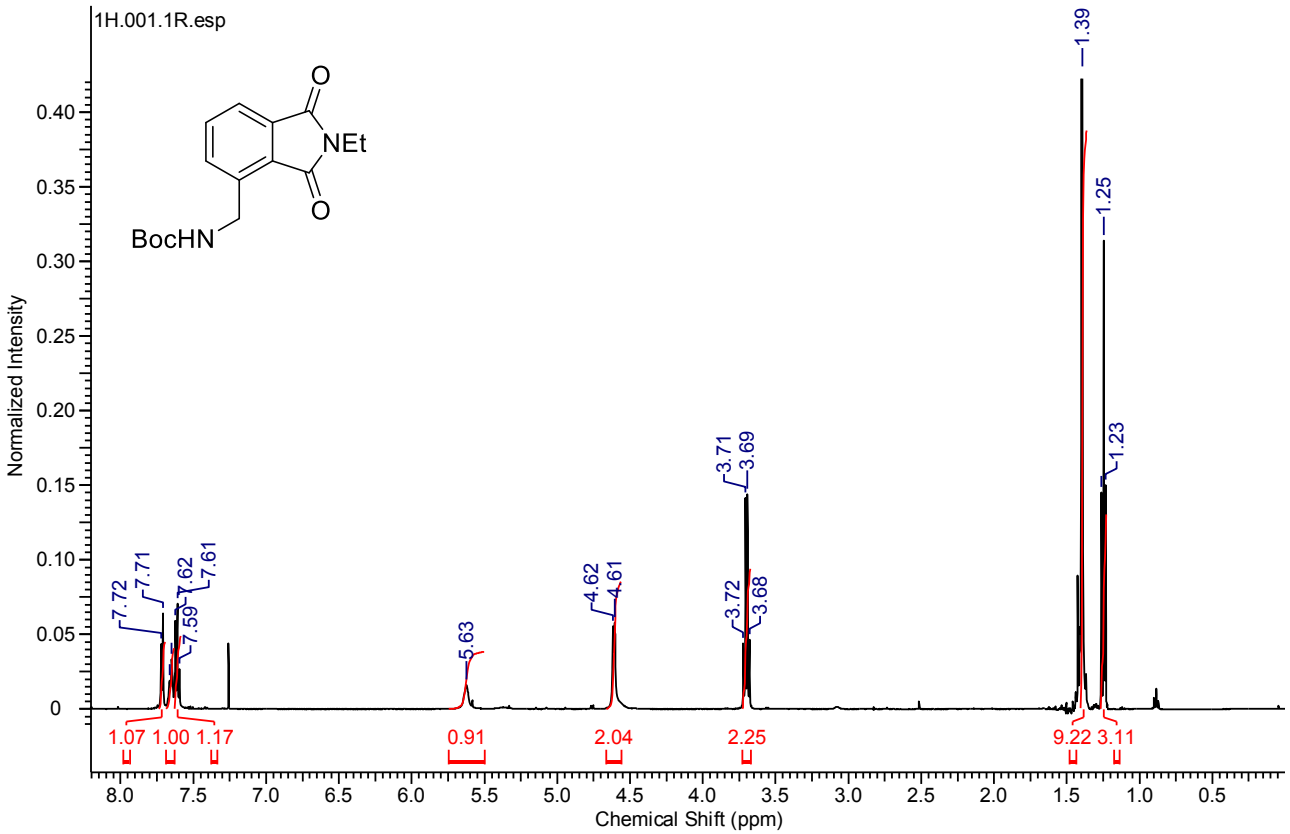


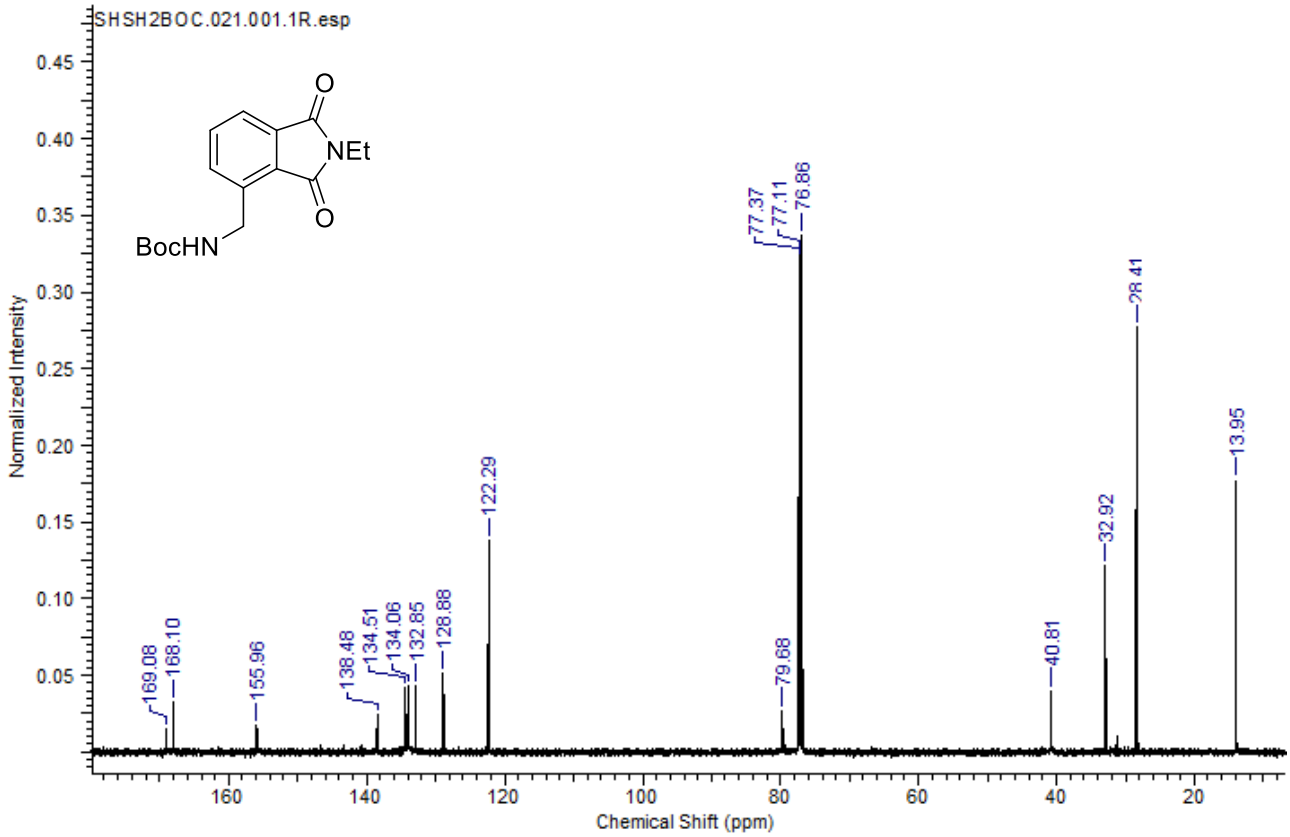
N-Ethyl-1-oxo-2,3,4,5-tetrahydro-1H-benzo[c]azepine-9-carboxamide 12d



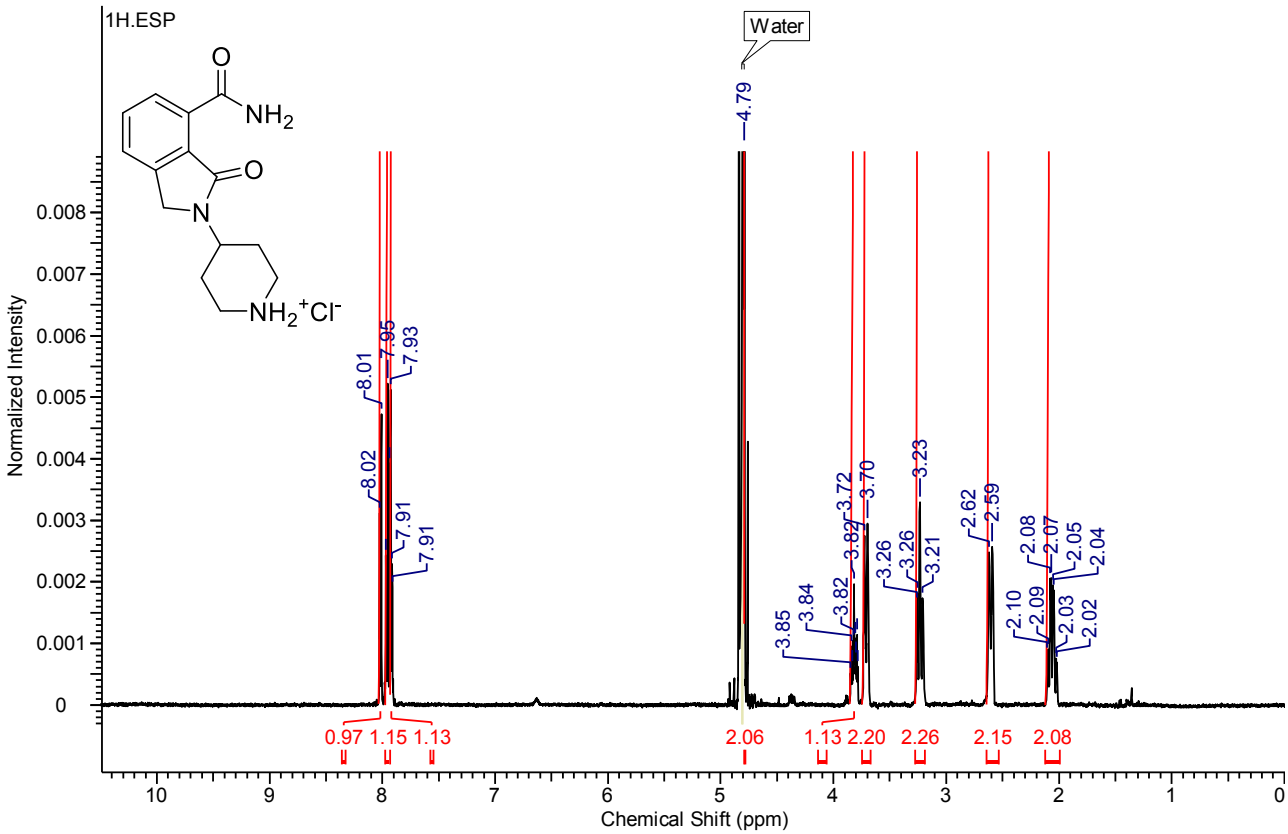


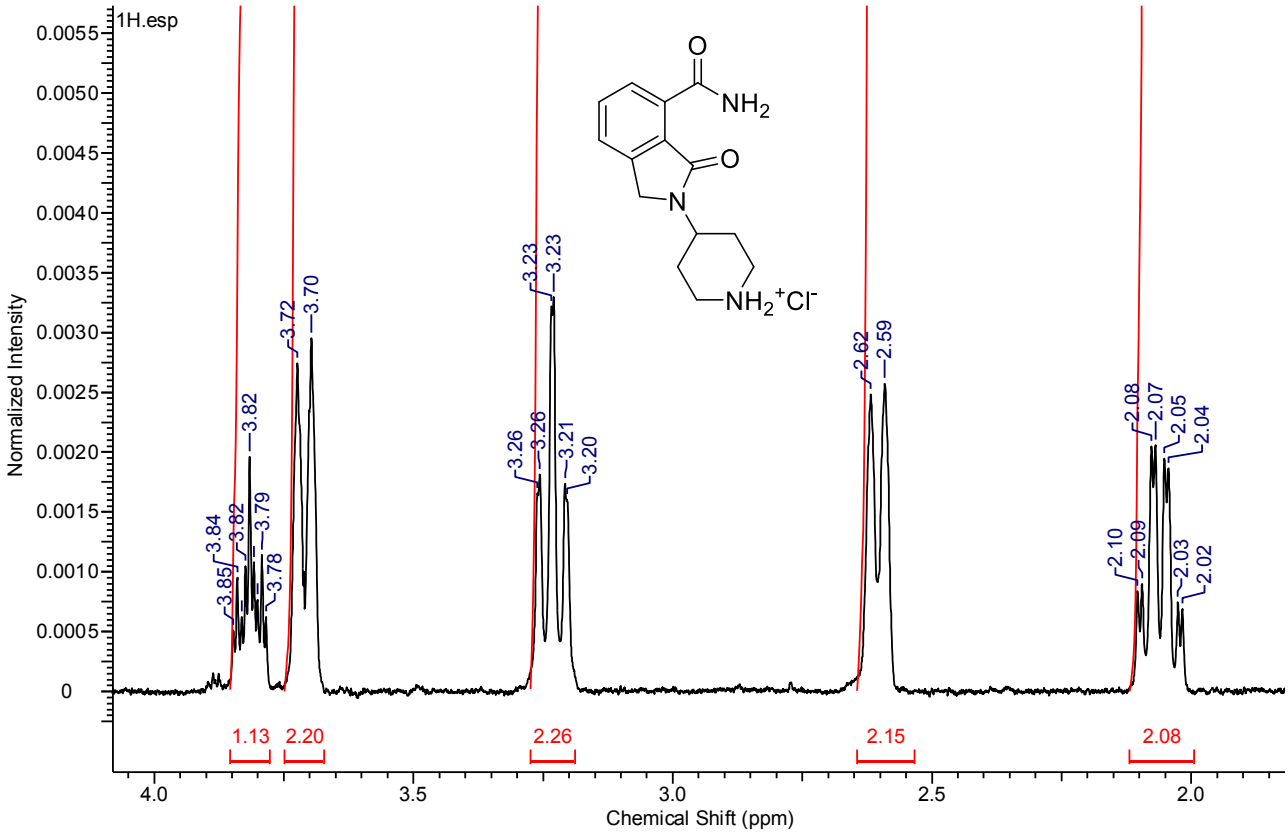
Tert-butyl-((2-ethyl-1,3-dioxoisoindolin-4-yl)methyl)carbamate 13

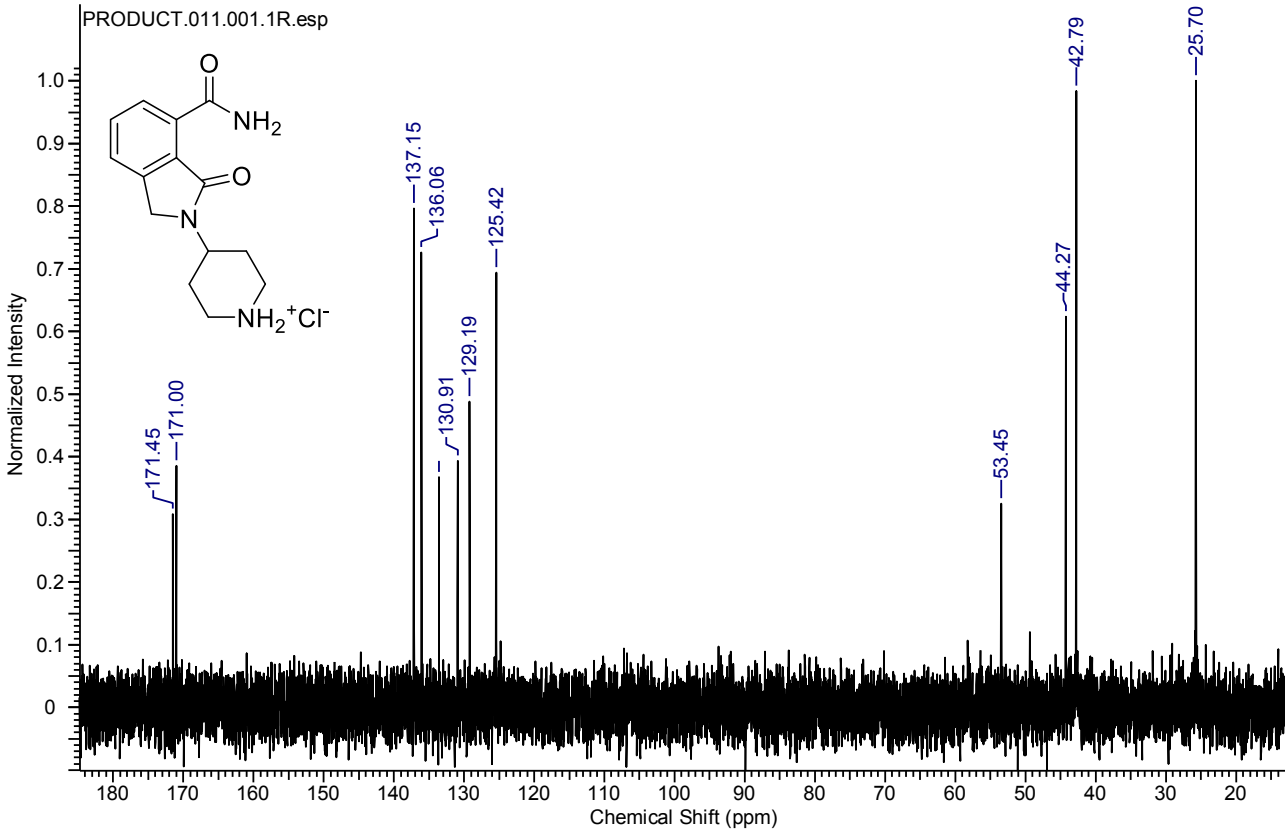




4-(7-carbamoyl-1-oxoisoindolin-2-yl)piperidin-1-ium chloride 14·HCl






PRODUCT.011.001.1R.esp
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NH2
O
N
NH2+Cl-
Normalized Intensity
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0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
171.45
171.00
137.15
136.06
130.91
129.19
125.42
53.45
44.27
42.79
25.70
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

References

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