Supplementary Information for

N-Carboxyanhydrides Directly from Amino Acids and Carbon Dioxide and their Tandem Reactions to Therapeutic Alkaloids

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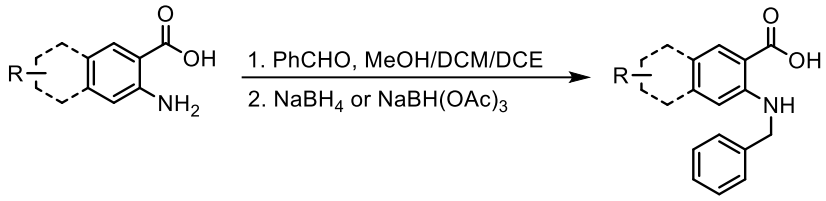
General Considerations

Reagents and Materials: 4-(Dimethylamino)pyridine (DMAP), *n*-propylphosphonic anhydride (T3P), 2-chloro-1-methylpyridinium iodide (CMPI), 1,1′-carbonyldiimidazole (CDI), triethylamine (TEA), and *N*,*N*-di-*iso*-propylethylamine (DIPEA) were purchased from Sigma Aldrich and used as received. Carbon dioxide (USP grade) was purchased from Matheson Tri-Gas Inc. or Airgas Inc. and used as received. ^{13}C labeled carbon dioxide ($^{13}CO_2$, 99.0 atom % ^{13}C) was purchased from Sigma-Aldrich Chemical Co. and used as received. The other reagents were purchased from Ambeed Inc., Alfa Aesar, AK Scientific Inc., Matrix Scientific, TCI, and Sigma-Aldrich and used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories Inc., degassed, and stored over activated molecular sieves prior to use. Solvents were purified using a two-column solid-state purification system by the method of Grubbs and transferred to the glovebox without exposure to air.[1] Acetonitrile was distilled over calcium hydride and stored over sieves prior to use.

Physical Methods: NMR spectra were acquired using JEOL (ECA-300, 400, 500, and 600) or Bruker (AV-300 and AV-500) at ambient temperature and referenced using residual solvent peaks. All ^{13}C and ^{19}F NMR spectra were proton decoupled. Gas chromatography-mass spectrometry (GC-MS) was performed using an Agilent 7890 GC/5977A MSD instrument equipped with an HP-5MS capillary column. DART-MS used a Thermo Exactive Plus MSD (Thermo Scientific) equipped with an ID-CUBE ion source and a Vapur Interface (IonSense). Both the source and MSD were controlled by Excalibur v. 3.0. The analyte was spotted onto OpenSpot sampling cards (IonSense) using chloroform as the solvent. Ionization was accomplished using He plasma with no additional ionization agents. Mass calibration was carried out using Pierce LTQ Velos ESI (+) and (-) Ion calibration solutions (Thermo Fisher Scientific).

General Procedure for the Synthesis of 2-(*N*-Benzylamino)benzoic Acids



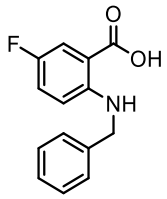
Method A: To a 200 mL round-bottom flask equipped with a magnetic stir bar, the 2-aminobenzoic acid derivative (15 mmol, 1.0 equiv.), and benzaldehyde (1530 μL, 15 mmol, 1.0 equiv.) were dissolved in methanol (100 mL). The mixture was stirred at 40 °C for 4 h. Solid $NaBH_4$ (850 mg, 22.5 mmol, 1.5 equiv.) was then added portion-wise to the reaction mixture, and the reaction was stirred at RT for an additional 3 h, giving a transparent solution. The reaction mixture was diluted with CH_2Cl_2 (100 mL) after being quenched with water. The aqueous phase was collected, then an aqueous solution of HCl (1 M, 10 mL) was added to the mixture until the pH was ~ 3, affording a cloudy solution. The aqueous suspension was evaporated to dryness. The crude solid was rinsed three times with a mixture of hexanes/ethyl acetate (3/1, *v/v*), dried under reduced pressure, and used in the next step without any further purification.

Method B: To a 200 mL round-bottom flask equipped with a magnetic stir bar, the 2-aminobenzoic acid derivative (15 mmol, 1.0 equiv.) and benzaldehyde (1530 μL, 15 mmol, 1.0 equiv.) were dissolved in CH_2Cl_2 (50 mL). The mixture was stirred at 40 °C for 3 h, which led to the formation of a precipitate. Solid $NaBH_4$ (850 mg, 22.5 mmol, 1.5 equiv.) was then added portion-wise to the reaction mixture, followed by the addition of MeOH (10 mL), and stirred at RT for an additional 2 h. Upon completion, water was added to quench the reaction and the pH of the solution was adjusted to ~ 3 using HCl (aqueous solution, 1 M, 10 mL). The product was extracted by the addition of ethyl acetate (100 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated to dryness, giving the product as a solid, which was used in the next step without any further purification.

Method C: Under N_2, the 2-aminobenzoic acid derivative (9 mmol, 1.0 equiv.) and benzaldehyde (955 mg, 9 mmol, 1.0 equiv.) were dissolved in 1,2-dicholoroethane (20 mL) in a 100 mL round-bottom flask was equipped with a magnetic stir bar. The mixture was stirred at ambient temperature for 2 h, which led to the formation of a slurry. Solid $NaBH(OAc)_3$ (2.67 g, 12.6 mmol, 1.4 equiv.) was added and the slurry was allowed to stir overnight under N_2. Upon completion, a saturated solution containing $NaHCO_3$ was added to quench the reaction. The mixture was extracted into ethyl acetate (3×100 mL) and the organic layer was separated, dried over $MgSO_4$, filtered, and evaporated to dryness. The benzylated products were obtained as solids and used in the next step without any further purification.

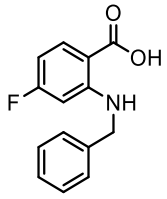
Characterization Data

2-(*N*-Benzylamino)-5-fluorobenzoic acid (1b)



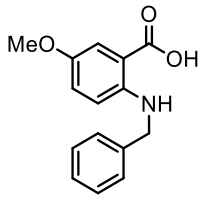
Compound **1b** was synthesized by following Method C. It was isolated as a white solid (1.54 g, 42%). This compound has been reported previously.[2] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = δ 7.48 (dd, *J* = 9.8, 3.2 Hz, 1H, Ar*H*), 7.29 (d, *J* = 4.4 Hz, 4H, Ar*H*), 7.23 – 7.14 (m, 2H, Ar*H*), 6.62 (dd, *J* = 9.3, 4.5 Hz, 1H, Ar*H*), 4.41 (s, 2H, NCH_2Ar). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 169.6 (d, *J* = 2.6 Hz, *C*OOH), 152.8 (d, *J* = 231.2 Hz, *C*F), 148.2 (d, *J* = 0.5 Hz), 139.8, 129.1, 127.6, 127.5, 122.4 (d, *J* = 22.7 Hz), 117.1 (d, *J* = 22.7 Hz), 113.7 (d, *J* = 7.0 Hz), 110.8 (d, *J* = 6.3 Hz), 46.6 (N*C*H_2Ar). ^{19}F NMR (376 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = -130.1 (ddd, *J* = 9.8, 8.1, 4.5 Hz).

2-(*N*-Benzylamino)-4-fluorobenzoic acid (1c)



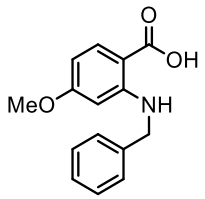
Compound **1c** was synthesized by following Method C. It was isolated as a white solid (1.83 g, 83%). This compound was reported previously.[3] ^{1}H NMR (300 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 8.48 (br, 1H, N*H*), 7.86 (dd, *J* = 8.8, 7.1 Hz, 1H, Ar*H*), 7.36 (s, 4H, Ar*H*), 7.31 – 7.23 (m, 1H, Ar*H*), 6.45 (dd, *J* = 12.7, 2.5 Hz, 1H, Ar*H*), 6.36 (td, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 4.46 (s, 2H, NCH_2Ar). ^{13}C NMR (125 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 169.3 (*C*OOH), 166.3 (d, *J* = 248.0 Hz, *C*F), 152.9 (d, *J* = 12.7 Hz), 138.8, 134.6 (d, *J* = 11.9 Hz), 128.6, 127.1, 127.1, 107.3, 101.9 (d, *J* = 22.7 Hz), 97.8 (d, *J* = 25.8 Hz), 45.9 (N*C*H_2Ar). ^{19}F NMR (282 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = -104.40 (dt, *J* = 12.7, 7.7 Hz).

2-(*N*-Benzylamino)-5-methoxybenzoic acid (1d)



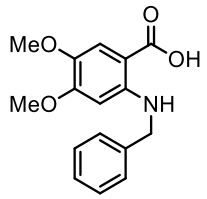
Compound **1d** was synthesized by following Method A. It was isolated as a yellow solid (2.50 g, 65%). This compound was reported previously.[3] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 8.33 (br, 1H, N*H*), 7.70 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.34 – 7.27 (m, 4H, Ar*H*), 7.22 (ddt, *J* = 8.6, 6.0, 3.3 Hz, 1H, Ar*H*), 6.13 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar*H*), 6.07 (d, *J* = 2.3 Hz, 1H, Ar*H*), 4.40 (s, 2H, NC*H*$_2$Ar), 3.64 (s, 3H, C*H*$_3$O). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 170.2 (*C*OOH), 164.7, 153.0, 139.8, 134.2, 129.1, 127.7, 127.5, 104.3, 102.3, 96.3, 55.5 (*C*H$_3$OAr), 46.5 (N*C*H$_2$Ar).

2-(*N*-Benzylamino)-4-methoxybenzoic acid (1e)



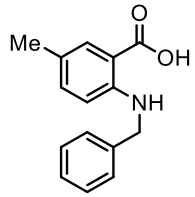
Compound **1e** was synthesized by following Method A. It was isolated as a brown solid (1.58 g, 41%). This compound was reported previously.[4] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 7.32 – 7.26 (m, 5H, Ar*H*), 7.24 – 7.17 (m, 1H, Ar*H*), 6.96 (dd, *J* = 9.1, 3.1 Hz, 1H, Ar*H*), 6.59 (d, *J* = 9.2 Hz, 1H, Ar*H*), 4.38 (s, 2H, NC*H*$_2$Ar), 3.61 (s, 3H, C*H*$_3$OAr). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 170.2 (*C*OOH), 149.3, 146.2, 140.3, 129.0, 127.6, 127.4, 123.1, 115.0, 113.8, 110.8, 55.9 (*C*H$_3$OAr), 46.8 (N*C*H$_2$Ar).

2-(*N*-Benzylamino)-4,5-dimethoxybenzoic acid (1f)



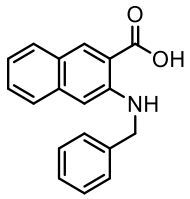
Compound **1f** was synthesized by following Method A. It was isolated as a white solid (2.80 g, 65%). This compound was reported previously.[5] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 7.35 – 7.28 (m, 4H, Ar*H*), 7.24 – 7.19 (m, 2H, Ar*H*), 6.21 (s, 1H, Ar*H*), 4.42 (s, 2H, NCH_2Ar), 3.65 (s, 3H, CH_3OAr), 3.59 (s, 3H, CH_3OAr).^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 170.1 (*C*OOH), 155.4, 148.4, 140.1, 139.2, 129.1, 127.9, 127.5, 114.9, 101.5, 96.1, 56.6 (*C*H_3OAr), 55.8 (*C*H_3OAr), 46.9 (N*C*H_2Ar).

2-(*N*-Benzylamino)-5-methylbenzoic acid (1g)



Compound **1g** was synthesized by following Method C. It was isolated as a light-yellow solid (1.52 g, 70%). This compound was reported previously.[2] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.79 (s, 1H, Ar*H*), 7.39 – 7.26 (m, 5H, Ar*H*), 7.16 (d, *J* = 8.6 Hz, 1H, Ar*H*), 6.57 (d, *J* = 8.6 Hz, 1H, Ar*H*), 4.48 (s, 2H, NCH_2Ar), 2.23 (s, 3H, CH_3). ^{13}C NMR (125 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 174.2 (*C*OOH), 149.7, 139.0, 136.9, 132.4, 128.8, 127.2, 127.0, 124.3, 112.2, 109.0, 47.2 (N*C*H_2), 20.2 (Ar*C*H_3).

3-(*N*-Benzylamino)-2-naphthanoic acid (1h)



Compound **1h** was synthesized by following Method B. It was isolated as a yellow solid (3.01 g, 72%). This compound was reported previously.[6] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 8.49 (s, 1H, Ar*H*), 7.76 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.49 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.40 – 7.29 (m, 5H, Ar*H*), 7.22 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.10 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H, Ar*H*), 6.85 (s, 1H, Ar*H*), 4.46 (s, 2H, NC*H*$_2$Ar). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 170.3 (*C*OOH), 146.9, 139.8, 137.7, 134.2, 129.7, 129.3, 129.1, 127.8, 127.5, 125.8, 125.0, 122.4, 115.2, 105.0, 46.9 (N*C*H$_2$Ar).

General Procedure for the Synthesis of *N*-Carboxyanhydrides (NCA) from 2-Aminobenzoic Acids and CO_2

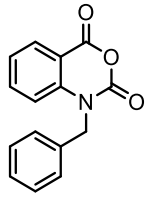
Method D: To a 350 mL stainless steel Parr reaction vessel equipped with a stir bar, the 2-aminobenzoic acid derivative (2.5 mmol, 1 equiv.), 4-(dimethylamino)pyridine (300 mg, 2.5 mmol, 1 equiv.), anhydrous acetonitrile (50 mL), and *N*,*N*-diisopropylethylamine (1.7 mL, 10 mmol, 4 equiv.) were added. The reaction vessel was sealed and purged with CO_2 three times. The CO_2 pressure was increased to 300 psi and the system was heated to 65 ^oC and stirred for 2 h. The vessel was then cooled to RT and the CO_2 pressure was reduced to below 5 psi so that propylphosphonic anhydride (4.5 mL - 50% wt in ethyl acetate, 7.5 mmol, 3 equiv.) could be injected into the reactor via syringe. The vessel was pressured with CO_2 to 300 psi and the contents were heated at 65 ^oC and stirred for another 24 h. To stop the reaction, the vessel was cooled to RT and slowly vented. The resulting mixture was then diluted with 250 mL of ethyl acetate, washed with a saturated solution of NaCl, and then washed again with cold water twice. The organic layer was collected, dried over anhydrous $MgSO_4$, and the volatiles were removed under reduced pressure to afford the NCA product as a yellow/brown solid.

Method E: To a 350 mL stainless steel Parr reaction vessel equipped with a stir bar, the 2-aminobenzoic acid derivative (2.5 mmol, 1 equiv.), 4-(dimethylamino)pyridine (300 mg, 2.5 mmol, 1 equiv.), anhydrous acetonitrile (50 mL), *N*,*N*-diisopropylethylamine (1.7 mL, 10 mmol, 4 equiv.), and propylphosphonic anhydride (4.5 mL - 50% weight in ethyl acetate, 7.5 mmol, 3 equiv.) were added. The reaction vessel was sealed and purged with CO_2 three times. The CO_2 pressure was increased to 300 psi and the contents were heated to 65 ^oC and stirred for 24 h. To stop the reaction, the vessel was cooled to RT and vented. The resulting mixture was then diluted with 250 mL of ethyl acetate, washed with a saturated NaCl solution, and then washed again with cold water twice. The organic layer was collected and dried over anhydrous $MgSO_4$. The volatiles were removed under a reduced pressure to afford the NCA product as a yellow/brown solid.

Method F: To a 350 mL stainless steel Parr reaction vessel equipped with a stir bar, 2-aminobenzoic acid derivative (2.5 mmol, 1 equiv.) and anhydrous acetonitrile (40 mL) were combined. The vessel was sealed, purged with CO_2 (300 psi), and was stirred for 30 min at RT. After releasing the pressure, the temperature went down to below 5 °C. The vessel was then opened so that *N*,*N*-diisopropylethylamine (2 mL, 10 mmol, 4 equiv.) and propylphosphonic anhydride (4.5 mL, 7.5 mmol, 3 equiv.) could be injected into the reactor. The reaction vessel was quickly sealed and purged with CO_2 three times. The CO_2 pressure was increased to 300 psi and the contents were heated to 40 °C and stirred for 15 h. To stop the reaction, the vessel was cooled to RT and vented. The resulting mixture was then diluted with 100 mL of ethyl acetate, washed with cold deionized water, and then washed again with a saturated NaCl solution. The organic layer was collected, dried over anhydrous $MgSO_4$, and the volatiles were removed under a reduced pressure to afford the NCA product as an off-white solid or brown oil.

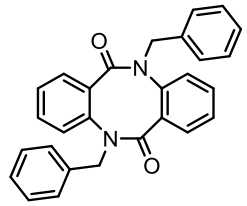
Characterization Data

1-Benzyl-3,1-benzoxazine-2,4-dione (2a)



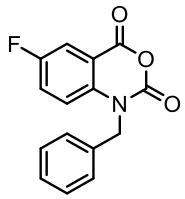
Compound **2a** was synthesized by following Method E. It was obtained as a light-yellow solid (487 mg, 77%) without any further purification needed. This compound was reported previously.[7] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.15 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.63 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H, Ar*H*), 7.38 – 7.32 (m, 2H, Ar*H*), 7.32 – 7.27 (m, 3H, Ar*H*), 7.27 – 7.23 (m, 1H, Ar*H*), 7.11 (d, *J* = 8.5 Hz, 1H, Ar*H*), 5.30 (s, 2H, NCH_2Ar). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 158.5 (Ar*C*OO), 148.6 (ArN*C*OO), 141.5, 137.3, 134.5, 131.0, 129.3, 128.3, 126.7, 124.3, 114.8, 111.9, 48.6 (N*C*H_2Ar). GC-MS: calc. for $C_{15}H_{10}NO_3$ $[M]^+$ = 253.1, found 253.1.

5,11-Bis(phenylmethyl)dibenzo[*b,f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (2a′)



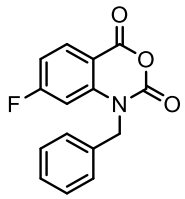
Compound **2a′** was synthesized by following the condition described in Table S2, entry 5. It was isolated as an off-white solid (300 mg, 58%) after purification by silica gel chromatography using ethyl acetate/ hexanes (3/7) as the eluent. This compound was reported previously.[8] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.31 – 7.25 (m, 8H, Ar*H*), 7.21 – 7.17 (m, 4H, Ar*H*), 7.17 – 7.13 (m, 4H, Ar*H*), 6.87 – 6.82 (m, 2H, Ar*H*), 5.06 (d, *J* = 14.3 Hz, 2H, NCH_2Ar), 4.88 (d, *J* = 14.3 Hz, 2H, NCH_2Ar). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 167.9 (Ar*C*ON), 139.1, 136.6, 135.3, 130.5, 129.1, 128.7, 128.5, 127.9, 127.9, 126.2, 53.0 (N*C*H_2Ar). GC-MS: calc. for $C_{28}H_{22}N_2O_2$ $[M]^+$ = 418.2, found 418.2.

1-Benzyl-2*H*-7-fluorobenzo[*d*][1,3]oxazine-2,4-dione (2b)



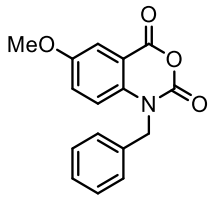
Compound **2b** was synthesized by following Method E. It was isolated as a light-yellow solid (404 mg, 55%) after purification by silica gel chromatography using ethyl acetate:hexanes (3:7) as the eluent, followed by recrystallization in CH_2Cl_2. This compound was reported previously.[9] ^{1}H NMR (300 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.84 (dd, *J* = 7.5, 3.0 Hz, 1H, Ar*H*), 7.39 – 7.28 (m, 6H, Ar*H*), 7.09 (dd, *J* = 9.2, 3.9 Hz, 1H, Ar*H*), 5.30 (s, 2H, NC*H*$_2$Ar). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 158.6 (d, *J* = 247.5 Hz, *C*F), 157.6 (d, *J* = 3.0 Hz, Ar*C*OO), 148.2 (ArN*C*O), 137.9 (d, *J* = 2.2 Hz), 134.2, 129.4, 128.4, 126.6, 125.0 (d, *J* = 23.7 Hz), 117.0 (d, *J* = 7.5 Hz), 116.4 (d, *J* = 24.3 Hz), 113.3 (d, *J* = 8.0 Hz), 49.0 (N*C*H$_2$Ar). GC-MS: calc. for $C_{15}H_{10}NO_3F$ $[M]^+$ = 271.1, found 271.1.

1-Benzyl-2*H*-6-fluorobenzo[*d*][1,3]oxazine-2,4-dione (2c)



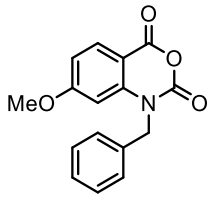
Compound **2c** was synthesized by following Method E. It was obtained as a white-yellowish solid (502 mg, 74%) without any further purification needed. This compound was reported previously.[10] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.18 (dd, *J* = 8.8, 6.1 Hz, 1H, Ar*H*), 7.38 (ddd, *J* = 7.6, 6.2, 1.3 Hz, 2H, Ar*H*), 7.35 – 7.28 (m, 3H, Ar*H*), 6.96 (ddd, *J* = 8.8, 7.8, 2.2 Hz, 1H, Ar*H*), 6.81 (dd, *J* = 10.1, 2.2 Hz, 1H, Ar*H*), 5.26 (s, 2H, NC*H*$_2$Ar). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 168.1 (d, *J* = 259.0 Hz, *C*F), 157.5 (Ar*COO*), 148.5 (ArN*C*OO), 143.8 (d, *J* = 12.3 Hz), 133.9 (d, *J* = 11.4 Hz), 133.9, 129.4, 128.5, 126.7, 112.4 (d, *J* = 22.9 Hz), 108.4 (d, *J* = 2.3 Hz), 102.6 (d, *J* = 28.1 Hz), 49.0 (N*C*H$_2$Ar). GC-MS: calc. for $C_{15}H_{10}NO_3F$ $[M]^+$ = 271.1, found 271.1.

1-Benzyl-2*H*-7-dimethoxybenzo[*d*][1,3]oxazine-2,4-dione (2d)



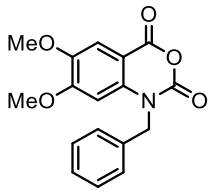
Compound **2d** was synthesized by following Method E. It was isolated as a white-yellowish solid (148 mg, 21%) after purification by silica gel chromatography using ethyl acetate:hexanes (3:7) as the eluent. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.57 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.39 – 7.27 (m, 5H, Ar*H*), 7.20 (dd, *J* = 9.1, 3.0 Hz, 1H, Ar*H*), 7.03 (d, *J* = 9.2 Hz, 1H, Ar*H*), 5.28 (s, 2H, NC*H*$_2$Ar), 3.84 (s, 3H, C*H*$_3$OAr). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 158.6 (Ar*C*OO), 156.2 (ArN*C*OO), 148.5, 135.5, 134.7, 129.3, 128.2, 126.7, 126.0, 116.4, 112.6, 111.8, 56.1 (*C*H$_3$OAr), 48.7 (N*C*H$_2$Ar). GC-MS: calc. for $C_{16}H_{13}NO_4$ $[M]^+$ = 283.1, found 283.1. ESI-MS (+): calc. for $C_{16}H_{13}NO_4$ $[M+H]^+$ = 284.09173, found 284.09272.

1-Benzyl-2*H*-6-dimethoxybenzo[*d*][1,3]oxazine-2,4-dione (2e)



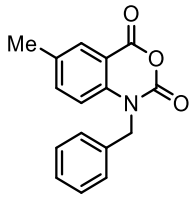
Compound **2e** was synthesized by following Method E. It was obtained as a yellow solid (587 mg, 83%) without any further purification needed. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.04 (d, *J* = 8.8 Hz, 1H, Ar*H*), 7.39 – 7.25 (m, 5H, Ar*H*), 6.75 (dd, *J* = 8.8, 1.8 Hz, 1H, Ar*H*), 6.52 (s, 1H, Ar*H*), 5.25 (s, 2H, NC*H*$_2$Ar), 3.78 (s, 3H, C*H*$_3$OAr). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 166.7 (Ar*C*OO), 158.0 (ArN*C*OO), 149.1, 143.4, 134.6, 133.0, 129.2, 128.2, 126.8, 110.7, 104.5, 100.2, 56.0 (*C*H$_3$OAr), 48.7 (N*C*H$_2$Ar). ESI-MS (+): calc. for $C_{16}H_{13}NO_4$ $[M+H]^+$ = 284.09173, found 284.09251.

1-Benzyl-2*H*-6,7-dimethoxybenzo[*d*][1,3]oxazine-2,4-dione (2f)



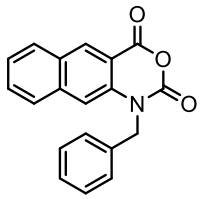
Compound **2f** was synthesized by following Method E. It was obtained as an orange solid (715 mg, 91%) without any further purification needed. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.48 (s, 1H, Ar*H*), 7.41 – 7.34 (m, 5H, Ar*H*), 6.51 (s, 1H, Ar*H*), 5.31 (s, 2H, NCH_2Ar), 3.91 (s, 3H, CH_3OAr), 3.78 (s, 3H, CH_3OAr). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 158.3 (Ar*C*OO), 156.7 (ArN*C*OO), 149.2, 146.2, 137.6, 134.9, 129.3, 128.3, 126.7, 110.1, 103.5, 98.0 (*C*H_3OAr), 56.5 (*C*H_3OAr), 48.9 (N*C*H_2Ar). ESI-MS (+): calc. for $C_{17}H_{15}NO_5$ $[M+H]^+$ = 314.10229, found 314.10234.

1-Benzyl-2*H*-7-methylbenzo[*d*][1,3]oxazine-2,4-dione (2g)



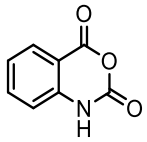
Compound **2g** was synthesized by following Method E. It was isolated as a light-yellow solid (281 mg, 42%) after purification by silica gel chromatography using ethyl acetate/hexanes (3/7) as the eluent. This compound was reported previously.[9] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.95 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.46 – 7.40 (m, 1H, Ar*H*), 7.39 – 7.27 (m, 5H, Ar*H*), 7.00 (d, *J* = 8.6 Hz, 1H, Ar*H*), 5.29 (s, 2H, NCH_2Ar), 2.37 (s, 3H, CH_3Ar). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$) δ (ppm) = 158.6 (Ar*C*OO), 148.6 (ArN*C*OO), 139.3, 138.3, 134.6, 134.3, 130.5, 129.2, 128.2, 126.7, 114.8, 111.7, 48.5 (N*C*H_2Ar), 20.5 (*C*H_3Ar). GC-MS: calc. for $C_{16}H_{13}NO_3$ $[M]^+$ = 267.1, found 267.1.

1-Benzyl-2*H*-naphtho[2,3-*d*][1,3]oxazine-2,4-dione (2h)



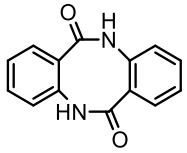
Compound **2h** was synthesized by following Method E. It was isolated as a pale-yellow solid (330 mg, 44%) after purification by silica gel chromatography using ethyl acetate/hexanes/toluene (5/20/1) as the eluent. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.80 (s, 1H, Ar*H*), 7.94 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.75 – 7.70 (m, 1H, Ar*H*), 7.60 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H, Ar*H*), 7.49 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H, Ar*H*), 7.41 – 7.33 (m, 5H, Ar*H*), 7.29 (ddd, *J* = 8.6, 5.9, 2.8 Hz, 1H, Ar*H*), 5.40 (s, 2H, NC*H*$_2$Ar). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ = 158.7 (Ar*C*OO), 148.4 (ArN*C*OO), 137.5, 136.0, 134.6, 133.9, 130.8, 129.6, 129.3, 129.2, 128.2, 127.7, 126.7, 126.7, 111.6, 111.5, 48.9 (N*C*H$_2$Ar). ESI-MS (+): calc. for $C_{19}H_{13}NO_3$ $[M+H]^+$ = 304.09682, found 304.09683.

3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic anhydride, 2i)



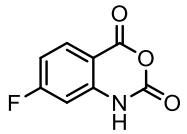
Compound **2i** was synthesized by following Method F. It was obtained as an off-white solid (400 mg, 99%) without any further purification needed. This compound was reported previously.[11] ^{1}H NMR (500 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 11.71 (s, 1H, N*H*), 7.88 (dd, *J* = 7.9, 1.1 Hz, 1H, Ar*H*), 7.76 – 7.66 (m, 1H, Ar*H*), 7.22 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.11 (d, *J* = 8.2 Hz, 1H, Ar*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 160.4 (Ar*C*OO), 147.7 (ArN*C*OO), 141.9, 137.5, 129.5, 124.1, 115.9, 110.8. GC-MS: calc. for $C_8H_5NO_3$ $[M]^+$ = 163.0, found 163.0.

Dibenzo[*b,f*][1,5]diazocine-6,12(5*H*,11*H*)-dione (2i′)



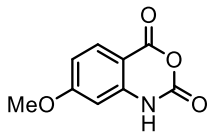
Compound **2i′** was synthesized by following the condition described in Table S8, entry 2. It was isolated as a yellow solid (190 mg, 64%) after purification by silica gel chromatography using hexanes/ethyl acetate/diethyl ether (9/3/1) as the eluent. This compound was reported previously.[12] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.23 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar*H*), 8.10 (dd, *J* = 8.4, 1.5 Hz, 1H, Ar*H*), 7.78 (m, 1H, Ar*H*), 7.60 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.58 (m, 1H, Ar*H*), 7.26 (m, 1H, Ar*H*), 6.73 (dt, *J* = 7.1, 3.4 Hz, 2H, Ar*H*), 6.48 (br, 2H, N*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 159.4 (Ar*C*ON), 158.0, 149.8, 146.7, 136.6, 133.8, 129.7, 128.7, 127.8, 126.5, 116.9, 116.8, 116.6, 110.1. GC-MS: calc. for $C_{14}H_{10}N_2O_2$ $[M]^+$ = 238.1, found 238.1.

7-Fluoro-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (2j)



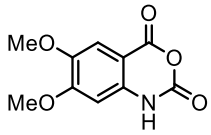
Compound **2j** was synthesized by following Method F. It was obtained as a tawny-colored solid (445 mg, 95%) without any further purification needed. This compound was reported previously.[13] ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.85 (br, 1H, N*H*), 7.96 (dd, *J* = 8.8, 6.0 Hz, 1H, Ar*H*), 7.07 (td, *J* = 8.8, 2.4 Hz, 1H, Ar*H*), 6.84 (dd, *J* = 9.7, 2.4 Hz, 1H, Ar*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 167.3 (d, *J* = 254.2 Hz, *C*F), 159.5 (Ar*C*OO), 147.5 (ArN*C*OO), 144.2 (d, *J* = 13.5 Hz), 132.9 (d, *J* = 11.6 Hz), 112.1 (d, *J* = 23.4 Hz), 107.9, 102.3 (d, *J* = 26.5 Hz). ^{19}F NMR (376 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = -99.79 – -99.87 (m). GC-MS: calc. for $C_8H_4FNO_3$ $[M]^+$ = 180.0, found 180.1.

7-Methoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (2k)



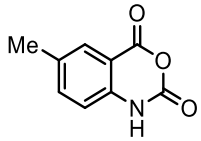
Compound **2k** was synthesized by following Method F. It was obtained as an off-white solid (390 mg, 81%) without any further purification needed. This compound was reported previously.[14] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 11.59 (br, 1H, N*H*), 7.71 (d, *J* = 8.7 Hz, 1H, Ar*H*), 6.72 (dd, *J* = 8.9, 2.3 Hz, 1H, Ar*H*), 6.48 (d, *J* = 2.3 Hz, 1H, Ar*H*), 3.78 (s, 3H, C*H*$_3$OAr). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 166.3 (Ar*C*OO), 159.7 (ArN*C*OO), 147.9, 144.1, 131.4, 112.1, 103.2, 98.9, 56.4 (*C*H$_3$OAr). GC-MS: calc. for $C_9H_7NO_4$ $[M]^+$ = 193.0, found 193.1.

6,7-Dimethoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (2l)



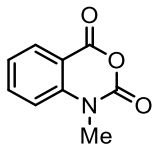
Compound **2l** was synthesized by following Method F. It was obtained as an off-white solid (435 mg, 78%) without any further purification needed. This compound was reported previously.[15] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 11.51 (br, 1H, N*H*), 7.14 (s, 1H, Ar*H*), 6.54 (s, 1H, Ar*H*), 3.80 (s, 3H, C*H*$_3$OAr), 3.74 (s, 3H, C*H*$_3$OAr). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 159.9 (Ar*C*OO), 157.0 (ArN*C*OO), 147.9, 146.1, 138.1, 108.9, 101.6, 98.1, 56.6 (*C*H$_3$OAr), 56.3 (*C*H$_3$OAr). GC-MS: calc. for $C_{10}H_9NO_5$ $[M]^+$ = 223.1, found 223.1.

6-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (2m)



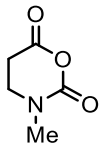
Compound **2m** was synthesized by following Method F. It was obtained as an off-white solid (341 mg, 77%) without any further purification needed. This compound was reported previously.[16] ^{1}H NMR (500 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 11.65 (br, 1H, N*H*), 7.71 (s, 1H, Ar*H*), 7.56 (dd, *J* = 8.3, 1.6 Hz, 1H, Ar*H*), 7.06 (d, *J* = 8.3 Hz, 1H, Ar*H*), 2.32 (s, 3H, C*H*$_3$Ar). ^{13}C NMR (126 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 160.0 (Ar*C*OO), 147.2 (ArN*C*OO), 139.3, 138.0, 133.0, 115.3, 110.0, 20.1 (*C*H$_3$Ar).

1-Methyl-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (2n)



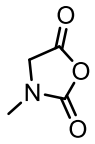
Compound **2n** was synthesized by following Method F. It was obtained as an off-white solid (335 mg, 76%) without any further purification needed. This compound was reported previously.[17] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 7.97 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.82 (t, *J* = 7.9 Hz, 1H, Ar*H*), 7.41 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.30 (t, *J* = 7.6 Hz, 1H, Ar*H*), 3.42 (s, 3H, C*H*$_3$N). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 159.6 (Ar*C*OO), 148.3 (ArN*C*OO), 142.8, 137.7, 129.9, 124.1, 115.4, 112.1, 32.2 (*C*H$_3$N). GC-MS: calc. for $C_9H_7NO_3$ $[M]^+$ = 177.0, found 177.1.

3-Methyl-1,3-oxazinane-2,6-dione (2o)



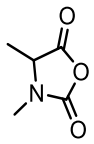
Compound **2o** was synthesized by following Method F. It was obtained as a yellowish-white solid (175 mg, 54%) without any further purification needed. This compound was reported previously.[18] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 3.43 (t, *J* = 6.6 Hz, 2H, C*H*$_2$N), 3.07 (s, 3H, C*H*$_3$N), 2.84 (t, *J* = 6.8 Hz, 2H, C*H*$_2$CO). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 165.0 (CH$_2$*C*OO), 149.5 (N*C*OO), 42.8 (*C*H$_2$N), 36.6 (*C*H$_3$N), 29.4 (*C*H$_2$CO).

3-Methyl-1,3-oxazolidine-2,5-dione (4a)



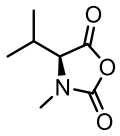
Compound **4a** was synthesized from *N*-methylglycine by following Method F. It was isolated as an off-white solid (145 mg, 51%) after trituration in cold THF/hexanes (1/10). This compound was reported previously.[19] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 4.12 (s, 2H, COC*H*$_2$N), 3.03 (s, 3H, C*H*$_3$N). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 165.4 (CH$_2$*C*OO), 152.4 (N*C*OO), 51.0 (N*C*H$_2$COO), 30.4 (*C*H$_3$N).

3,4-Dimethyl-1,3-oxazolidine-2,5-dione (4b)



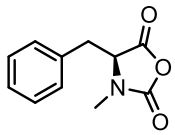
Compound **4b** was synthesized from *N*-methyl-*DL*-alanine by following Method F. It was obtained as a tawny-colored amorphous solid (180 mg, 56%) without any further purification needed. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 4.17 (q, *J* = 7.0 Hz, 1H, CH_3CHCO), 2.93 (s, 3H, CH_3N), 1.48 (d, *J* = 7.2 Hz, 3H, CH_3CHCO). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 169.6 (CHCOO), 151.7 (NCOO), 57.0 (CHCOO), 28.3 (CH_3N), 15.1 (CH_3CH). Due to the heat and moisture sensitivity of **4b**, dimerization occurred during mass spectrometric analysis.

3-Methyl-4-(1-methylethyl)-2,5-oxazolidinedione (4c)



Compound **4c** was synthesized from *N*-methyl-*L*-valine by following Method F. It was obtained as a tawny-colored amorphous solid (310 mg, 49%) without any further purification needed. This compound was reported previously.[18] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 4.01 (d, *J* = 3.4 Hz, 1H, NCHCOO), 2.96 (s, 3H, CH_3N), 2.26 (heptd, *J* = 7.1, 3.4 Hz, 1H, $(CH_3)_2CHCHCOO$), 1.15 (d, *J* = 7.1 Hz, 3H, $(CH_3)_2CHCHCOO$), 0.94 (d, *J* = 6.9 Hz, 3H, $(CH_3)_2CHCHCOO$). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 167.7 (CHCOO), 152.4 (NCOO), 66.2 (CHCOO), 28.9 ($(CH_3)_2CHCHCOO$), 28.7 ($(CH_3)_2CHCHCOO$), 17.3 ($(CH_3)_2CHCHCOO$), 16.2 ($(CH_3)_2CHCHCOO$).

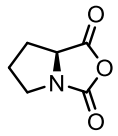
4-Benzyl-3-methyloxazolidine-2,5-dione (4d)



Compound **4d** was synthesized from *N*-methyl-*L*-phenylalanine hydrochloride by following Method F, using additional 2 equiv. of DIPEA. It was isolated as an off-white solid (230 mg, 45%) after trituration in cold THF/hexanes (1/10). This compound was reported previously.[18] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.31 – 7.27 (m, 3H), 7.11 (dd, *J* = 7.8, 1.8 Hz, 2H), 4.41 (t, *J* = 4.8 Hz, 2H, CH_2CH(CO)N), 3.19 (d, *J* = 5.0 Hz, 2H, $PhCH_2$), 2.92 (s, 3H, CH_3).^{13}C NMR (101

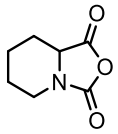
MHz, 25 °C, $CDCl_3$): δ (ppm) = 168.29 (CH*C*OO), 151.95 (N*C*OO), 133.30, 129.32, 129.19, 128.09, 62.55 (*C*HCOO), 35.24 (*C*H_3N), 29.31 (*C*H_2).

(*S*)-Proline *N*-carboxyanhydride (4e)



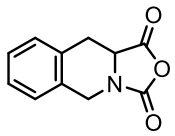
Compound **4e** was synthesized from *L*-proline by following Method F. It was obtained as an off-white colored amorphous solid (145 mg, 41%) without any further purification needed. Compound **4e** is heat-sensitive, as it will readily polymerize with gentle heating. This compound was reported previously.[20] ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ (ppm) = 4.31 (dd, *J* = 9.3, 7.5 Hz, 1H, NC*H*COO), 3.73 (dt, *J* = 11.2, 7.6 Hz, 1H, NC*H*$_2$CH$_2$), 3.29 (ddd, *J* = 11.2, 8.5, 4.6 Hz, 1H, NC*H*$_2$CH$_2$), 2.28 (dtd, *J* = 11.2, 7.3, 3.7 Hz, 1H), 2.17 (ddt, *J* = 12.6, 8.3, 4.0 Hz, 1H), 2.13 – 2.04 (m, 1H), 1.91 (dq, *J* = 12.4, 8.9 Hz, 2H). ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$): δ (ppm) = 168.9 (CH*C*OO), 155.0 (N*C*OO), 63.2 (N*C*HCOO), 46.6 (N*C*H$_2$CH$_2$), 27.7 (CH*C*H$_2$CH$_2$), 27.0 (CHCH$_2$*C*H$_2$CH$_2$N).

Tetrahydro-3*H*-oxazolo[3,4-*a*]pyridine-1,3(5*H*)-dione (4f)



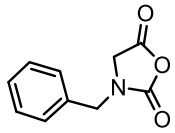
Compound **4f** was synthesized from *DL*-pipecolic acid by following Method F. It was obtained as an off-white solid (235 mg, 60%) without any further purification needed. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$): δ (ppm) = 3.98 (ddd, *J* = 17.2, 12.5, 4.5 Hz, 2H, NC*H*COO & N*C*H$_2$CH$_2$), 2.89 (td, *J* = 12.5, 3.7 Hz, 1H, N*C*H$_2$CH$_2$), 2.13 (dt, *J* = 8.5, 4.6 Hz, 1H), 1.97 (dt, *J* = 9.9, 5.0 Hz, 1H), 1.78 – 1.67 (m, 1H), 1.49 – 1.33 (m, 3H). ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$): δ (ppm) = 169.1 (NCH*C*OO), 150.2 (N*C*OO), 57.0 (N*C*HCOO), 40.5 (N*C*H$_2$CH$_2$), 27.1, 24.1, 22.3. Due to the heat and moisture sensitivity of **4f**, dimerization and oligomerization occurred during mass spectrometric analysis.

10,10*a*-Dihydro-3*H*-oxazolo[3,4-*b*]isoquinoline-1,3(5*H*)-dione (4g)



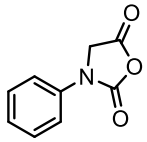
Compound **4g** was synthesized from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by following Method F. It was obtained as an off-white solid (430 mg, 85%) without any further purification needed. This compound was reported previously.[21] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.25 (ddq, *J* = 20.6, 13.3, 7.3 Hz, 4H, Ar*H*), 4.96 (d, *J* = 16.7 Hz, 1H, ArC*H*$_2$N), 4.50 (d, *J* = 16.5 Hz, 1H, ArC*H*$_2$N), 4.35 (dd, *J* = 11.8, 4.9 Hz, 1H, NC*H*COO), 3.29 (dd, *J* = 15.6, 5.0 Hz, 1H, ArC*H*$_2$CH), 3.04 (t, *J* = 13.8 Hz, 1H, ArC*H*$_2$CH). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 168.5 (CH*C*OO), 150.9 (N*C*OO), 129.8 (d, *J* = 1.9 Hz) (*C*$_{aro}$), 129.7 (*C*$_{aro}$), 128.0 (*C*$_{aro}$), 127.8 (*C*$_{aro}$), 126.8 (*C*$_{aro}$), 54.7 (*C*HCOO), 42.5 (Ar*C*H$_2$N), 30.6 (Ar*C*H$_2$O).

3-(Phenylmethyl)-2,5-oxazolidinedione (4h)



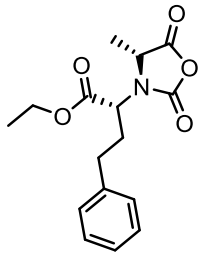
Compound **4h** was synthesized from *N*-benzylglycine by following Method F. It was obtained as an off-white solid (420 mg, 87%) without any further purification needed. This compound was reported previously.[22] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.39 – 7.31 (m, 3H, Ar*H*), 7.28 – 7.24 (m, 2H, Ar*H*), 4.51 (s, 2H, C*H*$_2$COO), 3.92 (s, 2H, C*H*$_2$COO). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 165.6 (CH$_2$*C*OO), 152.4 (N*C*OO), 134.0, 129.4, 128.8, 128.5, 48.5 (*C*H$_2$COO), 47.6 (N*C*H$_2$Ar).

3-Phenyloxazolidine-2,5-dione (4k)



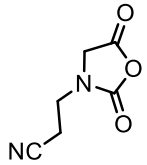
Compound **4k** was synthesized from *N*-phenylglycine by following Method F. It was obtained as an off-white solid (225 mg, 51%) after recrystallization in $CHCl_3$. This compound was reported previously.[23] ^{1}H NMR (300 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.51 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.44 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.25 (t, *J* = 7.2 Hz, 1H, Ar*H*), 4.56 (s, 2H, NC*H*$_2$COO). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 164.04 (CH$_2$*C*OO), 149.09 (ArN*C*OO), 135.80, 129.76, 125.99, 118.93, 49.59 (N*C*H$_2$COO).

Ethyl (α*S*,4*S*)-4-methyl-2,5-dioxo-α-(2-phenylethyl)-3-oxazolidineacetate (4l)



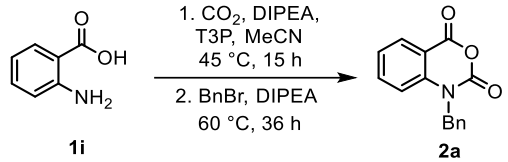
Compound **4l** was synthesized from *N*-[(*S*)-(+)-1-(ethoxycarbonyl)-3-phenylpropyl]-*L*-alanine by following Method F. It was obtained as a yellow-colored sticky wax (570 mg, 75%) without any further purification needed. This compound is heat-sensitive, as it will readily polymerize with gentle heating. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.31 – 7.17 (m, 5H, Ar*H*), 4.44 – 4.28 (m, 1H, NC*H*(CH_3)COO), 4.18 – 4.13 (m, 2H, CH_3C*H*$_2$O), 4.08 – 3.83 (m, 1H, COC*H*(CH_2)N), 2.79 – 2.68 (m, 2H, C*H*$_2$), 2.49 – 2.22 (m, 2H, C*H*$_2$), 1.50 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CH), 1.26 (t, *J* = 7.2 Hz, 3H, C*H*$_3$$CH_2$). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 169.51 (CH_2*C*OO), 152.00 (N*C*OO), 139.90 (O*C*OCH), 128.87 (*C*$_{aro}$), 128.66 (*C*$_{aro}$), 128.54 (*C*$_{aro}$), 128.45 (*C*$_{aro}$), 126.71 (*C*$_{aro}$), 126.35 (*C*$_{aro}$), 62.36 (CO*C*H(CH_2)N), 56.41 (CH_3(N)*C*HCO), 56.15 (CH_3*C*H_2COO), 32.52 (Ar*C*H_2), 31.54 (*C*H_2), 16.78 (*C*H_3), 14.19 (*C*H_3). Due to the heat and moisture sensitivity of **4l**, dimerization and oligomerization occurred during mass spectrometric analysis.

2,5-Dioxo-3-oxazolidinepropanenitrile (4m)



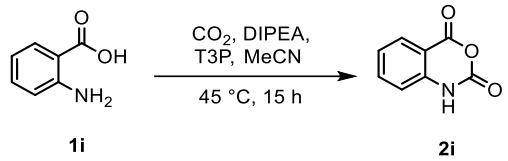
Compound **4m** was synthesized from *N*-(2-cyanoethyl)glycine by following Method F. It was obtained as a reddish oil (210 mg, 54%) without any further purification needed. This compound is heat-sensitive, as it will readily polymerize with gentle heating. ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-*d*$_6$): δ (ppm) = 4.27 (s, 2H, NC*H*$_2$CO), 3.54 (t, *J* = 6.6 Hz, 2H, C*H*$_2$N), 2.77 (t, *J* = 6.5 Hz, 2H, NCC*H*$_2$). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-*d*$_6$): δ (ppm) = 167.51 (CH_2*C*OO), 152.89 (N*C*OO), 119.33 (*C*N), 49.89 (N*C*H_2CO), 39.69 (*C*H_2N), 16.32 (NC*C*H_2). Due to the heat and moisture sensitivity of **4m**, dimerization occurred during mass spectrometric analysis.

One-pot Synthesis of 2a from 1i



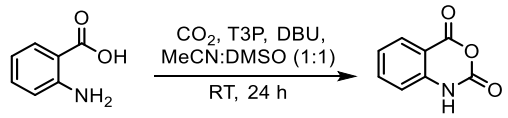
To a 350 mL stainless steel Parr reaction vessel equipped with a stir bar, **1i** (2.06 g, 15 mmol, 1 equiv.) and anhydrous acetonitrile (150 mL) were combined. The vessel was sealed, purged with CO_2 (300 psi), and was stirred for 15 min at RT. After releasing the pressure, the temperature dropped to below 5 °C. The vessel was then opened so that *N*,*N*-diisopropylethylamine (12 mL, 4 equiv.) and propylphosphonic anhydride (25 mL, 3 equiv.) could be injected into the reactor through a side arm. The reaction vessel was quickly sealed and purged with CO_2 three times. The CO_2 pressure was increased to 300 psi and the contents were heated to 45 °C and stirred for 15 h. After this time, CO_2 was released and benzyl bromide (4.5 mL, 37.5 mmol, 2.5 equiv.) and *N*,*N*-diisopropylethylamine (6 mL, 2 equiv.) were injected into the reactor. The reaction vessel was stirred for additional 36 h at 60 °C. To stop the reaction, the vessel was cooled to RT and vented. The resulting mixture was then diluted with 100 mL of ethyl acetate, washed with cold deionized water, and then washed again with a saturated NaCl solution. The organic layer was collected, dried over anhydrous $MgSO_4$, and the volatiles were removed under a reduced pressure to afford the crude product as a brown oil. A mixture of toluene/hexanes (1:20, 100 mL), was added to the flask, which resulted in the precipitation of a beige/orange solid. The resulting mixture was cooled in an ice bath and the solid was collected by filtration. The solvent residue was dried under vacuum to obtain the desired product **2a** as beige/orange colored solid (2.65 g, 70%).

Gram Scale Synthesis of 2i



Method F above was used in this synthesis. The reaction was performed on a 15 mmol scale. **1i** (2.06 g, 15 mmol, 1 equiv.), DIPEA (12 mL), propylphosphonic anhydride in ethyl acetate (25 mL), and anhydrous acetonitrile (150 mL, 0.1 M) were used. The reaction was stirred for 36 h at 45 °C. After work-up, the crude mixture was rinsed with a mixture of hexanes/dichloromethane (20:1, 10 mL). The solvent was then removed under vacuum, giving a white/beige colored solid as the desired product (1.89 g, 77%).

Synthesis of 2i Using CO_2 Balloon



1i **2i**

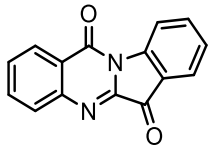
In a 25 mL round-bottom flask equipped with a magnetic stir bar, **1i** (68 mg, 0.5 mmol, 1 equiv.), and 1,8-diazabicycloundec-7-ene (310 μL, 2 mmol, 4 equiv.) were dissolved in a mixture of acetonitrile: DMSO (1:1, 8 mL). The flask was sealed with a rubber septum, and the CO_2 balloon was injected into the flask through the septum. The reaction mixture was stirred at RT for 2 h. After 2 h, propylphosphonic anhydride solution (≥50 wt. % in ethyl acetate, 500 μL, 3.0 equiv.) was injected into the mixture through the septum. The reaction was stirred continuously at RT for 22 h. Additional CO_2 balloons were required to maintain the CO_2 pressure in the reaction flask when purging and in between each injection. The work-up and purification procedures were used as described in Method F above when the reaction was complete.

General Procedure for the Tandem Synthesis of Tryptanthrin and its Derivatives from 2-Aminobenzoic Acids and CO_2

To a 350 mL Parr stainless steel reaction vessel equipped with a magnetic stir bar, compound **1** (2.5 mmol, 1.0 equiv.), compound **5** (2.25 mmol, 0.9 equiv.), DMAP (300 mg, 2.5 mmol, 1.0 equiv.), dry CH_3CN (0.05 M, 50 mL), DIPEA (10 mmol, 4.0 equiv., 2 mL), and propylphosphonic anhydride solution (≥50 wt. % in ethyl acetate, 3.0 equiv., 4.5 mL) were combined in sequence at RT. (A 0.9:1.0 mole ratio of **5**:**1** was found to be optimal because excess **5** in the reaction product was difficult to remove). The reaction vessel was sealed and purged with CO_2 three times. The CO_2 pressure was increased to 300 psi and the contents were heated to 65 ^oC and stirred for 15 h. After completion, the reaction vessel was cooled to RT and the CO_2 gas was gradually vented. The red/brown colored crude product was diluted in 50 mL of ethyl acetate, washed 3 times with brine until the aqueous layer became colorless. The combined organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to obtain a brown oil, which was purified by silica gel chromatography, using a gradient containing hexanes/ethyl acetate/diethyl ether as eluent.

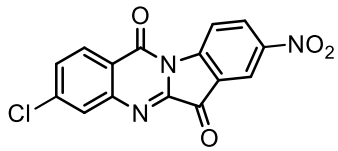
Characterization Data

Indolo[2,1-*b*]quinazoline-6,12-dione (Tryptanthrin, 6a)



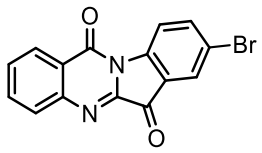
Compound **6a** was isolated by silica gel column chromatography using hexanes/ethyl acetate/diethyl ether (9/3/1) as the eluent. The product was isolated as a yellow solid (325 mg, 58%). This compound was reported previously.[24] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.61 (d, *J* = 8.1 Hz, 1H, Ar*H*), 8.44 – 8.40 (m, 1H, Ar*H*), 8.02 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.93 – 7.88 (m, 1H, Ar*H*), 7.87 – 7.82 (m, 1H, Ar*H*), 7.78 (td, *J* = 8.1, 1.3 Hz, 1H, Ar*H*), 7.69 – 7.64 (m, 1H, Ar*H*), 7.42 (td, *J* = 7.5, 0.7 Hz, 1H, Ar*H*). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 182.7 (Ar*C*OAr), 158.2 (N*C*OAr), 146.7, 146.4, 146.4, 138.4, 135.3, 130.8, 130.4, 127.7, 127.3, 125.5, 123.8, 122.0, 118.1. GC-MS: calc. for $C_{15}H_8N_2O_2$ $[M]^+$ = 248.1, found 248.1.

3-Chloro-8-nitroindolo[2,1-*b*]quinazoline-6,12-dione (3-Chloro-8-nitrotryptanthrin, 6b)



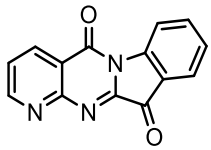
Compound **6b** was isolated by silica gel column chromatography using hexanes/toluene/ethyl acetate (4/1/1 to 2/0.1/1, *v/v/v*) as the eluent. The product was isolated as an orange solid (320 mg, 44%). This compound was reported previously.[25] ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 8.70 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar*H*), 8.62 (d, *J* = 8.7 Hz, 1H, Ar*H*), 8.53 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.31 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.10 (d, *J* = 2.1 Hz, 1H, Ar*H*), 7.79 (dd, *J* = 8.5, 2.1 Hz, 1H, Ar*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 181.11 (Ar*C*OAr), 157.92 (N*C*OAr), 149.51, 147.91, 146.90, 146.30, 140.88, 133.24, 130.93, 129.79, 129.61, 123.61, 122.21, 120.15, 118.23. GC-MS: calc. for $C_{15}H_6ClN_3O_4$ $[M]^+$ = 327.0, found 327.1.

8-Bromoindolo[2,1-*b*]quinazoline-6,12-dione (8-Bromotryptanthrin, 6c)



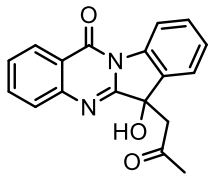
Compound **6c** was isolated by silica gel column chromatography using hexanes/ethyl acetate (3/1) as the eluent The product was isolated as a dark green solid (270 mg, 37%). This compound was reported previously.[25] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.51 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.43 – 8.39 (m, 1H, Ar*H*), 8.04 – 7.99 (m, 2H, Ar*H*), 7.90 – 7.82 (m, 2H, Ar*H*), 7.71 – 7.65 (m, 1H, Ar*H*). ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 181.4 (Ar*C*OAr), 158.0 (N*C*OAr), 146.6, 145.0, 143.9, 140.7, 135.5, 131.0, 130.7, 128.3, 127.7, 123.7, 123.5, 120.8, 119.6. GC-MS: calc. for $C_{15}H_7BrN_2O_2$ $[M]^+$ = 325.9, found 326.0.

Pyrido[2',3':4,5]pyrimido[1,2-*a*]indole-5,11-dione (4-Azatryptanthrin, 6d)



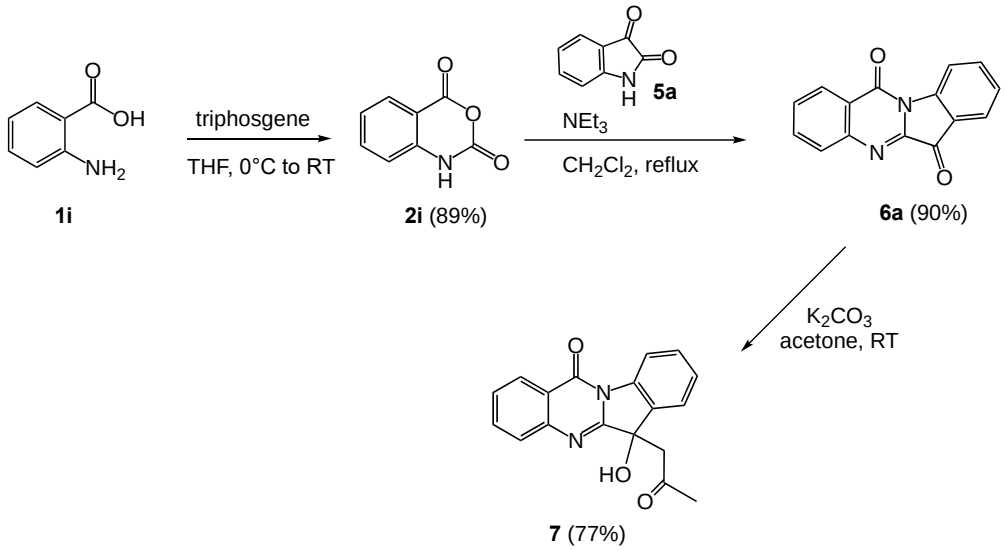
Compound **6d** was isolated by silica gel column chromatography using a gradient containing hexanes/ethyl acetate (1/3, *v/v*) to ethyl acetate/methanol (15/1, *v/v*) as the eluent. The product was isolated as a yellow solid (225 mg, 40%). This compound was reported previously.[26] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 9.09 (dd, *J* = 4.6, 2.1 Hz, 1H), 8.75 (dd, *J* = 7.9, 1.9 Hz, 1H), 8.58 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.95 – 7.90 (m, 1H), 7.80 (td, *J* = 7.8, 1.4 Hz, 1H), 7.61 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.46 (td, *J* = 7.6, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 181.73, 158.30, 157.57, 156.63, 146.93, 145.92, 138.54, 136.77, 127.87, 125.80, 124.84, 121.92, 119.76, 117.97. GC-MS: calc. for $C_{14}H_7N_3O_2$ $[M]^+$ = 249.0, found 249.1.

6-Hydroxy-6-(2-oxopropyl)indolo[2,1-*b*]quinazolin-12(6*H*)-one (Phaitanthrin A, 7)



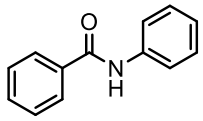
Compound **7** was synthesized using the condition described above except with the following modifications: dry acetonitrile/acetone (3/1, 40 mL) was used and the reaction was conducted at 65 °C for 48 h. The product was purified by silica gel column chromatography using hexanes/ethyl

acetate (3/1 to 1/3, *v/v*) as the eluent and isolated as a light pink solid (210 mg, 31%). This compound was reported previously.[27] ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.34 (d, *J* = 8.0 Hz, 1H, Ar*H*), 8.23 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.73 (q, *J* = 3.8, 2.4 Hz, 2H, Ar*H*), 7.51 – 7.45 (m, 2H, Ar*H*), 7.25 (d, *J* = 2.7 Hz, 2H, Ar*H*), 7.15 (t, *J* = 7.4 Hz, 1H, Ar*H*), 4.91 (s, 1H, C*H*OH), 3.54 (d, *J* = 17.6 Hz, 1H, COCH_2), 3.40 (d, *J* = 17.6 Hz, 1H, COCH_2), 2.13 (s, 3H, CH_3CO). ^{13}C NMR (126 MHz, 25 ^{o}C, DMSO-d_6): δ (ppm) = 206.35, 161.81, 159.47, 147.58, 139.79, 135.36, 134.41, 130.23, 127.97 (d, *J* = 5.1 Hz), 127.10, 126.98, 124.27, 121.84, 116.48, 75.02, 52.29, 30.58. GC-MS: calc. for $C_{18}H_{14}N_2O_3$ $[M]^+$ = 306.1, found 306.1.



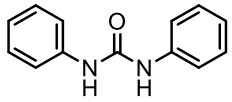
Scheme S1. Conventional (non-tandem) synthesis of **6a** and **7**.

***N*-Phenylbenzamide (11)**



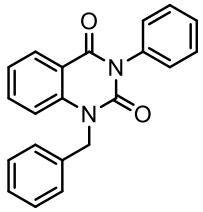
Compound **11** was reported previously.[28] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 7.90 – 7.80 (m, 3H, Ar*H* & N*H*), 7.64 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.57 – 7.52 (m, 1H, Ar*H*), 7.51 – 7.45 (m, 2H, Ar*H*), 7.37 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.15 (t, *J* = 7.4 Hz, 1H, Ar*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 165.9 (*C*O), 138.0 (N*C*$_{aro}$), 135.1 (*C*$_{aro}$CO), 132.0, 129.2, 128.9, 127.1, 124.7, 120.3.

***N,N'*-Diphenylurea (13)**



Compound **13** was reported previously.[29] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.62 (s, 2H, N*H*), 7.42 (dd, *J* = 8.6, 1.0 Hz, 4H, Ar*H*), 7.27 – 7.21 (m, 4H, Ar*H*), 6.95 – 6.90 (m, 2H, Ar*H*). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 153.1 (*C*O), 140.2 (N*C*$_{aro}$), 129.3, 122.3, 118.7.

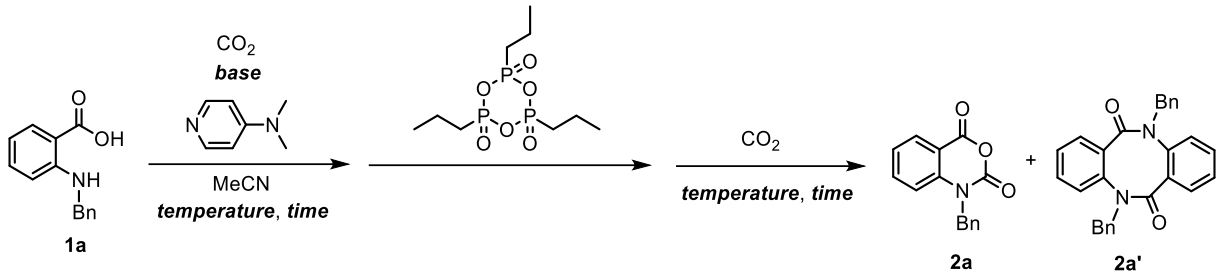
3-Phenyl-1-(phenylmethyl)-2,4(1*H*,3*H*)-quinazolinedione (14)



Compound **14** was reported previously.[30] ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 8.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.8, 7.4, 1.6 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.48 – 7.43 (m, 1H), 7.38 – 7.25 (m, 8H), 7.21 (d, *J* = 8.5 Hz, 1H), 5.40 (s, 2H). ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$): δ (ppm) = 157.27, 146.91, 135.59, 130.98, 130.87, 130.78, 124.80, 124.73, 124.35, 124.16, 123.75, 123.12, 122.07, 118.61, 111.46, 109.96, 42.87.

Reaction Studies

Table S1. Two-Step Screening Conditions for the Synthesis of *N*-Benzyl Substituted Six-Membered NCAs



Entry[a]	Temp. (°C)	Time (h)	T3P (equiv.)	DIPEA (equiv.)	Conversion (%)[b]	Yield (%)[b]	2a: 2a′[b]
1	70	20	1.5	2.2	100	30	100:80
2	70	20	1.5	2.2	64	5	100:60
3	70	20	1.5	0	78	0	N/A
4	70	20	1.5	4	95	24	100:66
5[c]	70	20	1.5	4	100	11	100:169
6[d, e]	65	20	1.5	4	90	6	100:30
7[e]	65	20	1.5	4	100	34	100:21
8[e]	65	20	3	4	100	77	100:2
9[f]	65	20	3	4	100	71	100:5

a. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (2.5 mmol), DMAP (varied), DIPEA (varied), CO_2 (300 psi), MeCN (50 mL). For step 1: preheat at 70 °C for 2 h before adding T3P (1.5 equiv.) as the activating reagent. The reactions were set up using Method D described in the experimental section.

b. Determined by ^{1}H NMR spectroscopy using ferrocene or 1,3,5-trimethoxybenzene as an internal standard.

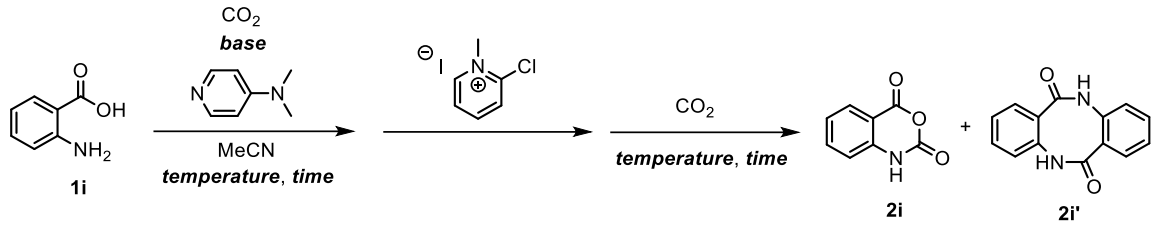
c. No CO_2 after adding T3P.

d. No CO_2 before adding T3P.

e. The reaction was preheated at 60 °C for 2 h.

f. The reaction was set up using Method E described in the experimental section (all reagents were combined in one-pot at the beginning of the reaction).

Table S2. Two-Step Screening Conditions for the Synthesis of Unsubstituted Six-Membered NCAs



Entry[a]	Temp. (°C)	Time (h)	DMAP (equiv.)	Base	Conversion (%)[b]	Yield (%)[b]	2i: 2i'[c]
1	50	20	1.4	DIPEA	91	40	N/A
2	50	20	1.05	DIPEA	81	27	1:1
3	50	40	1.4	DIPEA	80	18	100:80
4	50	20	1.4	Et_3N	98	28	100:75
5	50	12	1.4	Et_3N	94	41	100:102
6[d]	70	20	1.4	Et_3N	98	24	100:56
7[e]	50	20	1.8	DIPEA	98	25	100:56
8[e]	70	20	1.8	DIPEA	99	34[c]	100:35
9[e]	70	20	1.8	Et_3N	>99	21[c]	100:32
10[d, f]	70	20	1.5	DIPEA	>99	40[c] (11)[g]	100:9

a. Reaction conditions**:** 2-aminobenzoic acid (2.5 mmol), DMAP (varied), base (2.2 equiv.), CO_2 (300 psi), MeCN (50 mL). The reaction mixture was preheated at 50 °C for 2 h before adding CMPI (1.5 equiv.) as the activating reagent. The reactions were set up using Method D, except for the use of CMPI instead of T3P, as described in the experimental section.

b. Determined by GC-MS using a biphenyl internal standard.

c. Calculated from ^{1}H NMR spectroscopy.

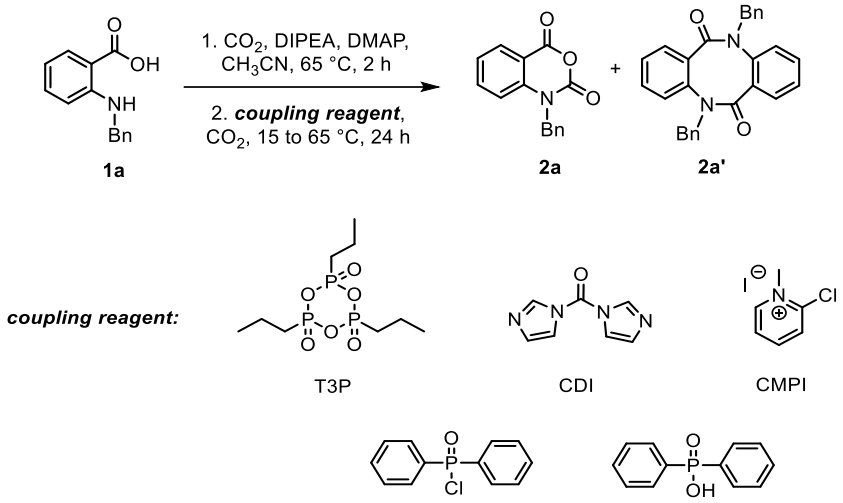
d. The reaction mixture was preheated at 70 °C for 2 h before adding CMPI.

e. Isolated solid from mixing CMPI with DMAP is used as the activating reagent without preheating in step 1. All reagents were combined at the beginning instead of adding stepwise.

f. Using T3P (50% solution in ethyl acetate, 1.5 equiv.) as activating reagent instead of CMPI with 4 equiv. of base.

g. Isolated yield.

Table S3. Screening Coupling Reagents Using Two-Step Method

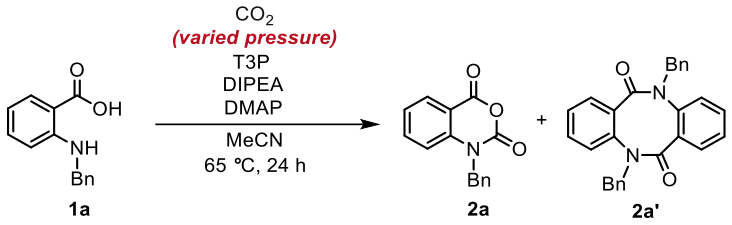


Entry[a]	**Coupling Reagent** (equiv.)	**Conversion**[b] (%)	**Isolated Yield** (%)	**2a:2a′ Ratio**[b]
1	T3P (1.5)	100	80	100:8
2	T3P (3.0)	100	82	100:1
3	CMPI (1.5)	100	54	100:20
4	CDI (1.5)	100	0	-
5	diphenylphosphinic chloride (1.5)	100	0	-
6	diphenylphosphinic acid (1.5)	100	0	-

a. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (2.5 mmol), DMAP (1 equiv.), DIPEA (4 equiv.), CO_2 (300 psi), MeCN (50 mL). The reactions were set up using Method D described in the experimental section.

b. Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table S4. Screening CO_2 Pressure Using One-Step Method[a]

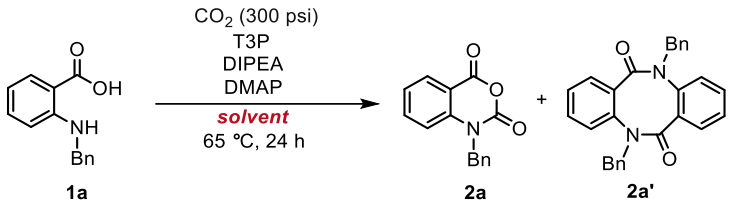


Entry	T3P (equiv.)	CO_2 (psi)	Conversion[b] (%)	Isolated Yield (%)	2a:2a′ Ratio[b]
1	1.5	300	95	56	100:1
2	3.0	300	100	85	100:0
3	3.0	150	100	84	100:0
4	3.0	100	100	88	100:1
5	3.0	50	99	68	100:7
6	3.0	20	96	53	100:20
7	9.0	50	71	62	100:0

a. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (2.5 mmol), DMAP (1 equiv), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (varied pressure), MeCN (50 mL). The reactions were set up using Method F described in the experimental section.

b. Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Table S5. One-pot Synthesis of *N*-Benzyl Substituted Six-Membered NCAs in Different Solvents

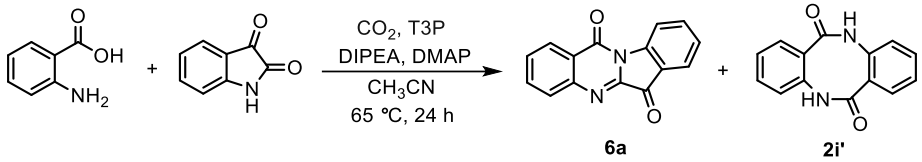


Entry[a]	Solvent	Conversion[b] (%)	Yield[b] (%)	2a: 2a'[b]
1	THF	100	-	100:40
2	MeCN	100	85	100:0
3	Ethylene carbonate	100	-	100:0
4	Propylene carbonate	100	27	100:0
5	Propylene carbonate: THF (3:7)	100	73	100:0
6	Propylene oxide	100	-	-

a. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (2.5 mmol), DMAP (1 equiv), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (300 psi), solvent (50 mL). The reactions were set up using Method F described in the experimental section.

b. Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

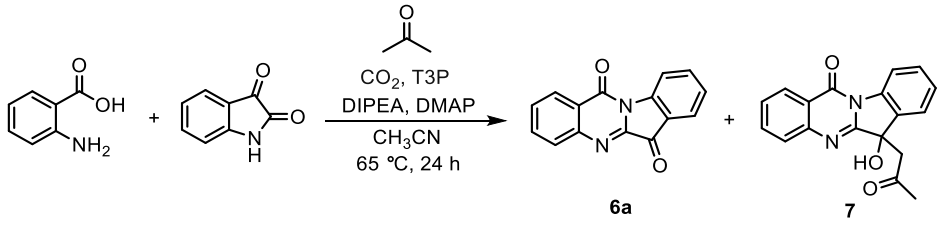
Table S6. Synthesis of Tryptanthrin (**6a**)



Entry[a]	Experiment	Yield (%)[b]	
		6a	2i′
1	Standard condition	44	0
2	Using N_2 (15 psi) instead of CO_2	13	64
3	No T3P	0	0
4	Using 1.2 equiv. of isatin	51	0
5	Using 0.9 equiv. of isatin	58	trace

a. Reaction conditions: 2-aminobenzoic acid (2.5 mmol), DMAP (1 equiv.), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (300 psi), CH_3CN (50 mL), 65 ˚C, 24 h.
b. Isolated yield.

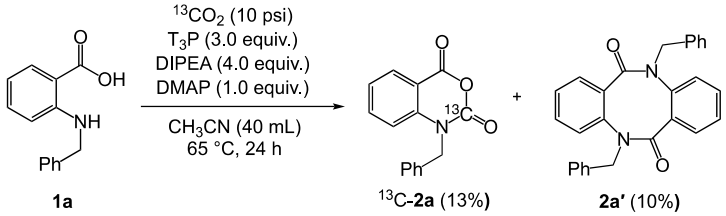
Table S7. Synthesis of Phaitanthrin A (**7**)



Entry[a]	Experiment	Yield (%)[b]	
		6a	7
1	Acetone (anhydrous, 5 mL) was added + stirred for additional 12 h at 40 °C	61	0
2	Using CH_3CN/acetone (3/1), 100 °C, 15 h	27	18
3	Using CH_3CN/acetone (3/1), 65 °C, 48 h	trace	31

a. Reaction conditions: 2-aminobenzoic acid (2.5 mmol), DMAP (1 equiv.), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (300 psi), CH_3CN (50 mL), 65 ˚C, 24 h.
b. Isolated yield.

Mechanistic Studies



Scheme S2. Synthesis of ^{13}C-**2a** using $^{13}CO_2$ under low pressure (15 psi).

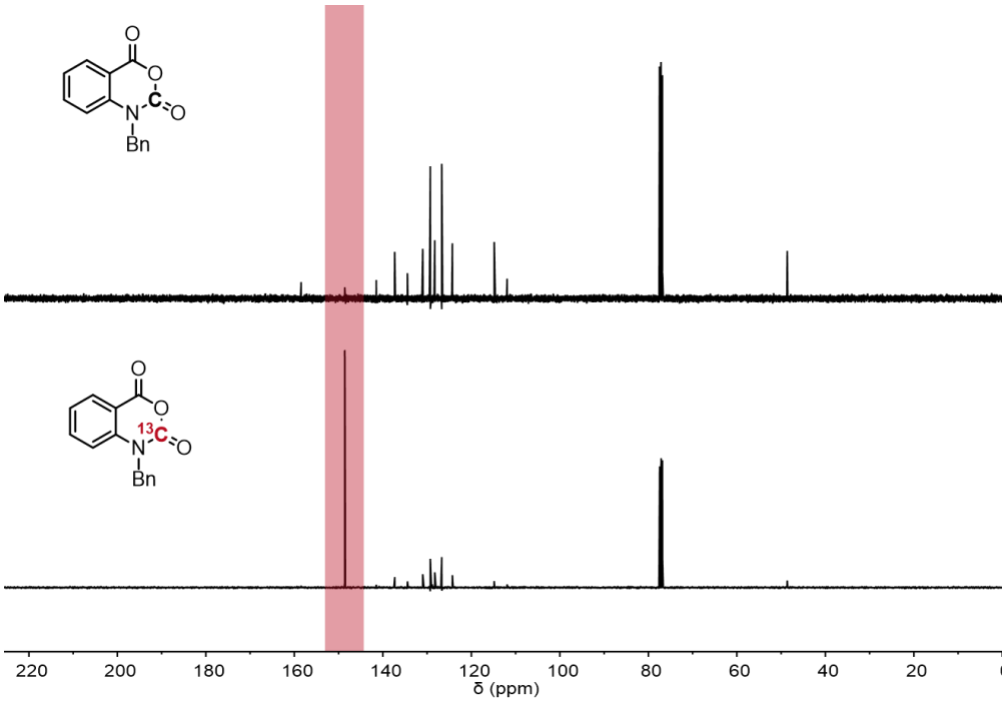
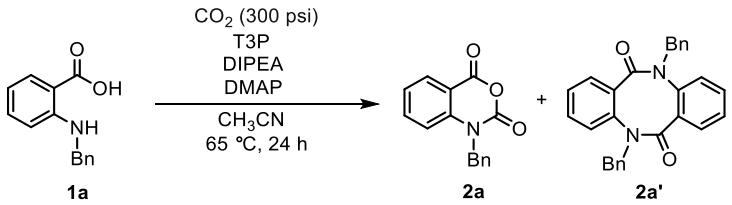


Figure S1. ^{13}C NMR spectra (101 MHz, RT, $CDCl_3$) of **2a** synthesized using CO_2 (top) and $^{13}CO_2$ (bottom). The increase in intensity of the C=O signal at 148.6 ppm strongly suggest that the source of carbon was CO_2.

Table S8. Studying the Effect of Different Reagents and Reactants

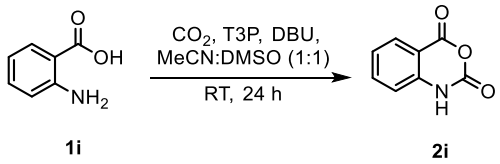


Entry[a]	Experiment	Conversion[b] (%)	Yield of 2a[b] (%)	Yield of 2a′[b] (%)	2a: 2a′[b]
1	Omitting CO_2	100	0	68	0:100
2	Omitting DIPEA	90	2.5	-	1: 16
3	Omitting DMAP	63	10	-	100: 37.5
4	Omitting T3P	42.5	0	0	0:0
5	Using 1.5 equiv. of T3P	95	56	-	100: 11
6	Using 3.0 equiv. of T3P	100	85	-	100:0

a. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (2.5 mmol), DMAP (1 equiv), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (300 psi), CH_3CN (50 mL). The reactions were set up using Method E described in the experimental section.

b. Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.

Table S9. Synthesis of **2i** Using CO_2 Balloon



Entry[a]	Experiment	Conversion (%)[b]	Yield (%)[b]
1	Standard condition	100	58
2	Performed in DMSO (0.06 M)	55	27[c]
3	Performed in DMF (0.06 M)	100	trace[c]

a. Reaction conditions: **1i** (0.5 mmol), T3P (3 equiv), DBU (4 equiv.), CO_2 balloon (15 psi), MeCN: DMSO (1:1, 8 mL). The reactions were set up as described in the experimental section.

b. Determined by GC-MS.

c. Dimer **2i′** was observed as the major product.

Computational Studies

Density functional theory (DFT) calculations were performed using the Gaussian 16 package.[31] Geometry optimization and natural bond order (NBO) calculations were performed at the B3LYP/6-311G(d,p) level of theory in acetonitrile (ε = 37.5) using the solvation model based on density (SMD).[32-34] Thermochemistry corrections and geometry verifications were performed *via* frequency calculations using the same conditions as the geometry optimizations. Energies obtained from ground state geometries were used to calculate the pk_a of the carboxylic acid moieties using reported methods.[35]

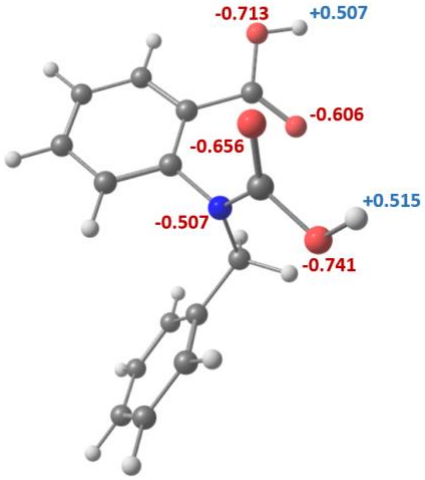
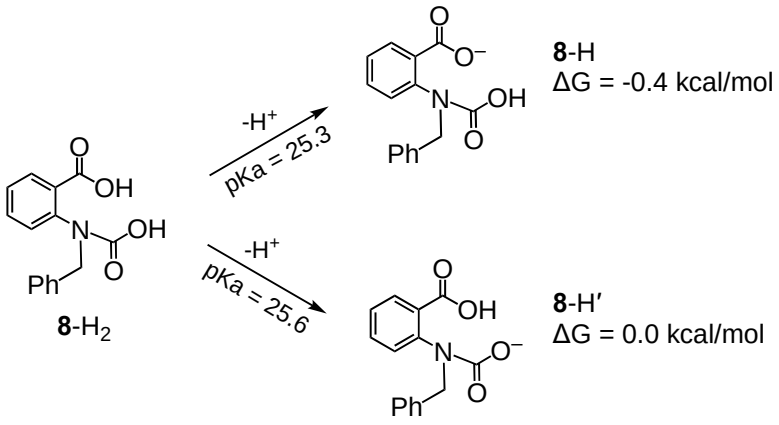
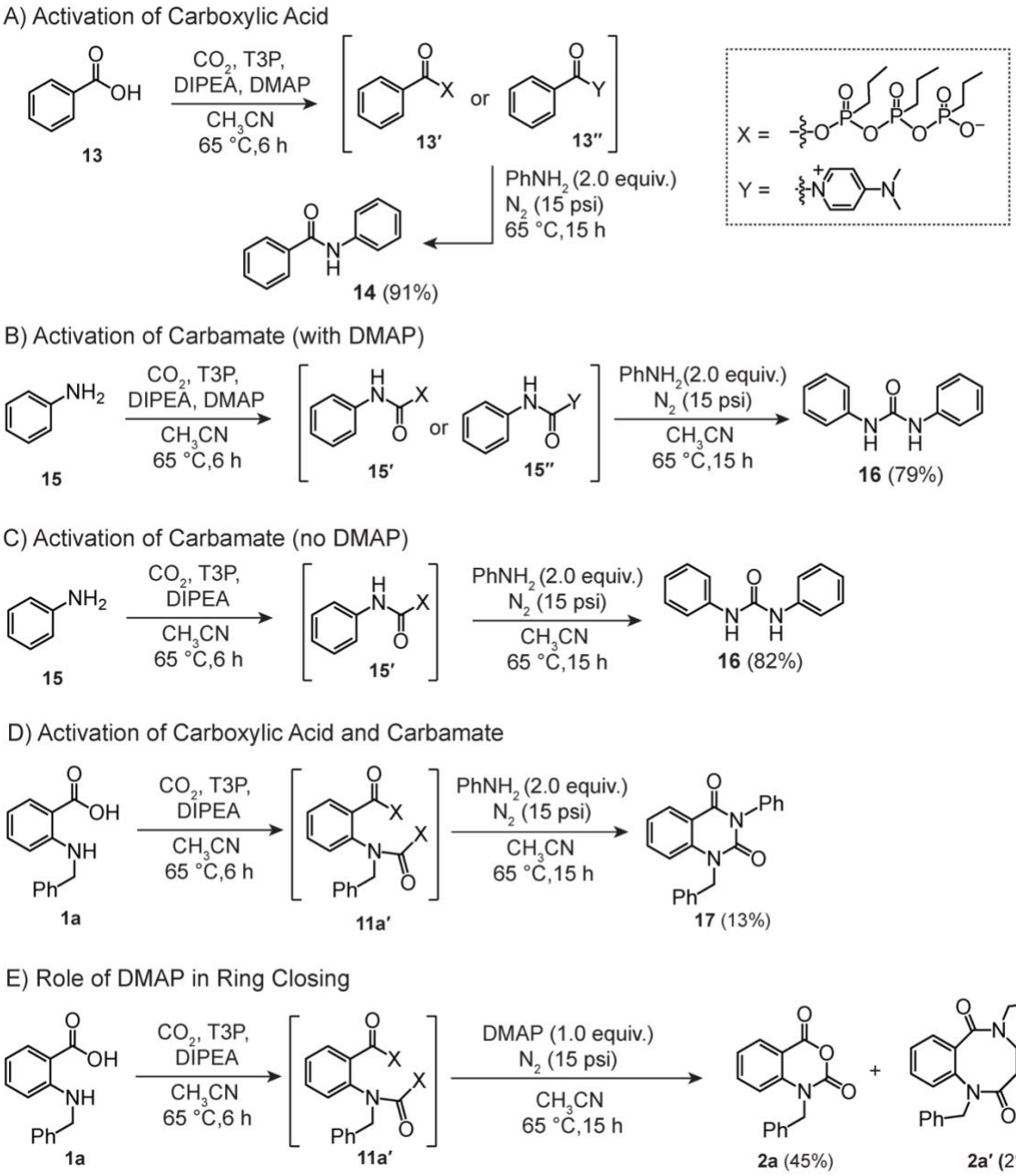


Figure S2. NBO charges of relevant atoms of **8**-H_2**.**



Scheme S3. Relative energies for deprotonation of the benzoic acid (to **8**-H) vs. carbamic acid (to **8**-H′) moieties.



Scheme S4. Studying the activation of carboxylates and carbamates. Reaction conditions: 2-(*N*-benzylamino)benzoic acid (**1a**) (or benzoic acid/aniline) (2.5 mmol), DMAP (1 equiv.), DIPEA (4 equiv.), T3P (3 equiv.), CO_2 (300 psi), CH_3CN (50 mL). The reactions were set up using Method D described in the experimental section.

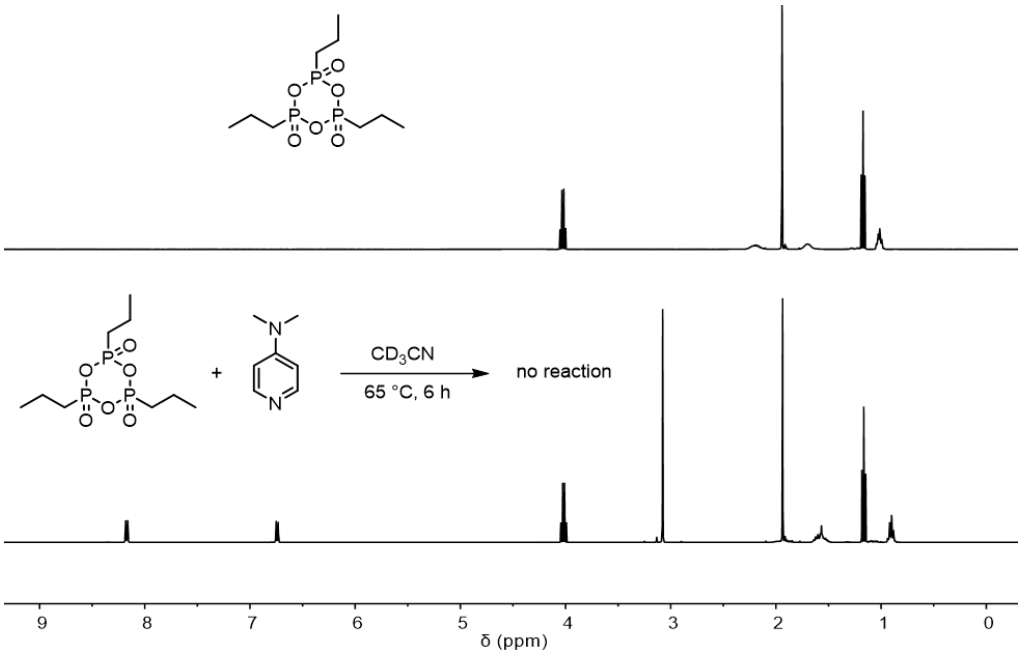


Figure S3. ^{1}H NMR spectrum (400 MHz, 25 ^{o}C, CD_3CN) of the reaction mixture obtained from combining T3P with DMAP (bottom). The top trace is the ^{1}H NMR spectrum of T3P alone. Our results indicate that T3P does not react with DMAP under these reaction conditions.

GC and GC-MS Data

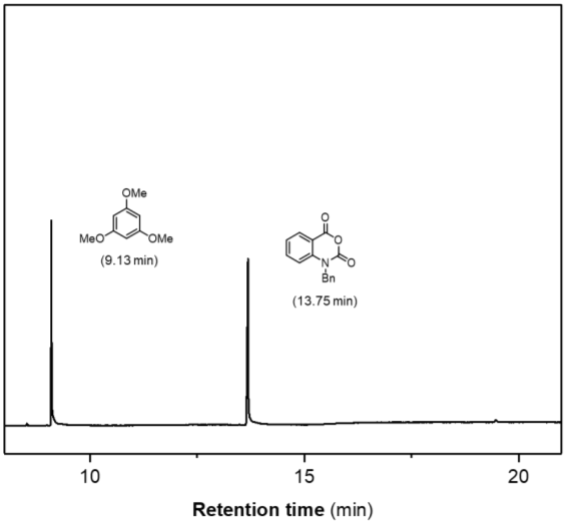


Figure S4. GC plot of product obtained from reaction of **1a**, T3P, DIPEA, and DMAP in CH_3CN at 65 °C for 24 h under 300 psi CO_2 (Table S4, entry 2). 1,3,5-trimethoxybenzene was added as an internal standard.

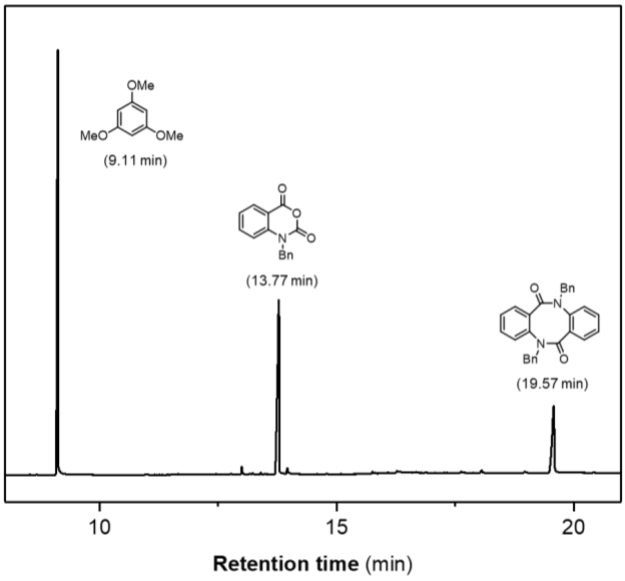


Figure S5. GC plots of product obtained from reaction of **1a**, T3P, DIPEA, and DMAP in CH_3CN at 65 °C for 24 h under 20 psi CO_2 (Table S4, entry 6). 1,3,5-trimethoxybenzene was added as an internal standard.

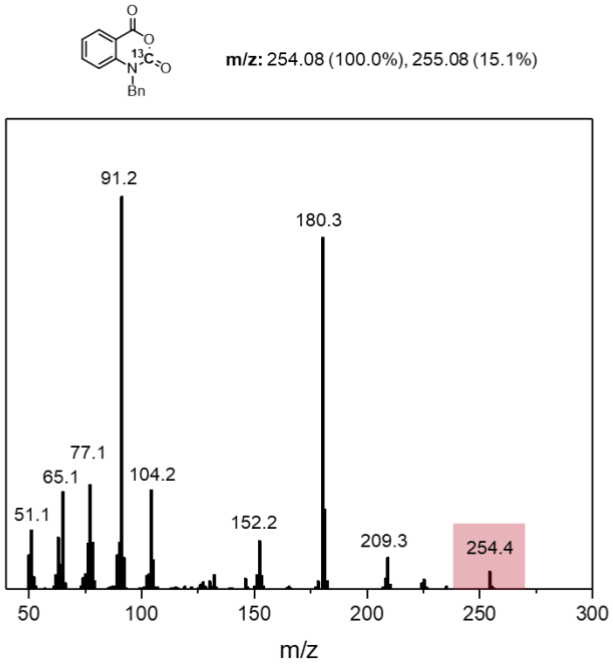


Figure S6. Mass spectrum of compound ^{13}C-**2a** synthesized using $^{13}CO_2$.

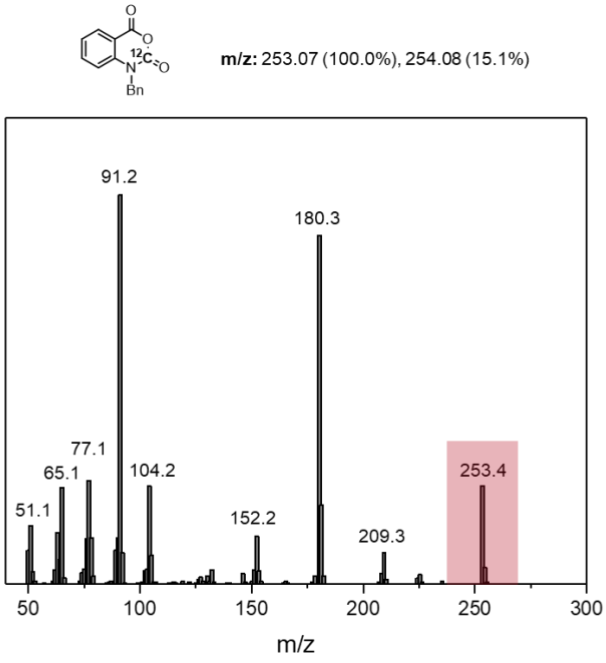


Figure S7. Mass spectrum of compound **2a** synthesized using unlabeled CO_2.

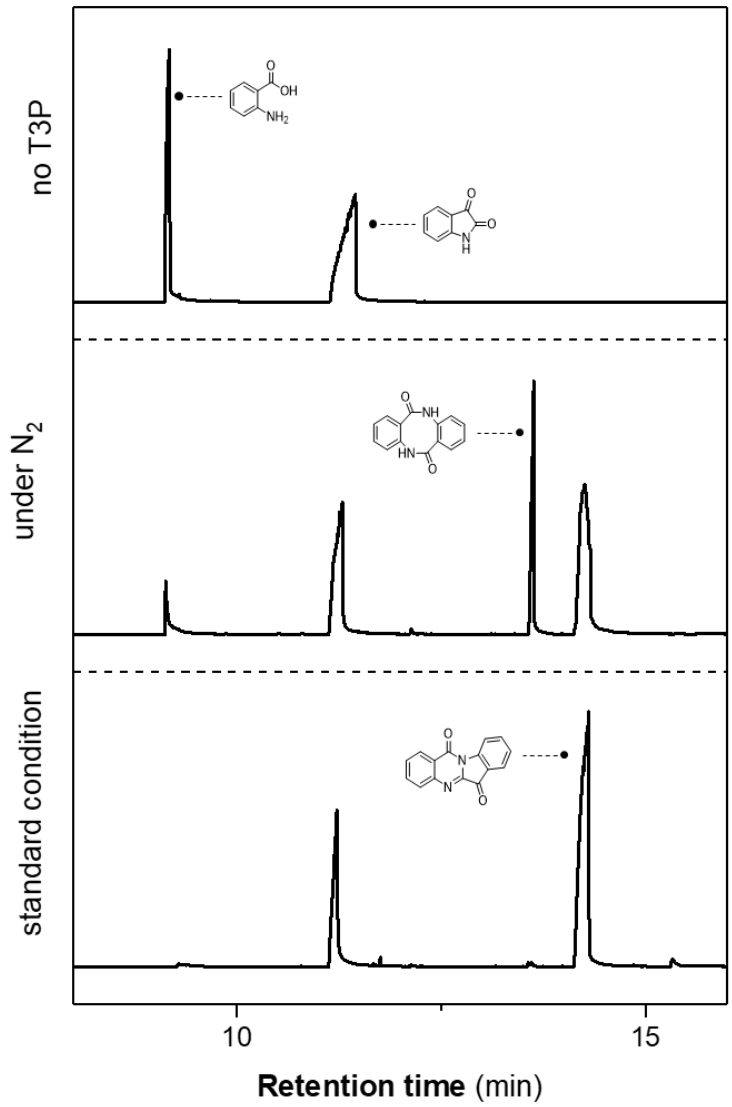


Figure S8. Representative GC plots of products obtained from the reactions shown in Table S6.

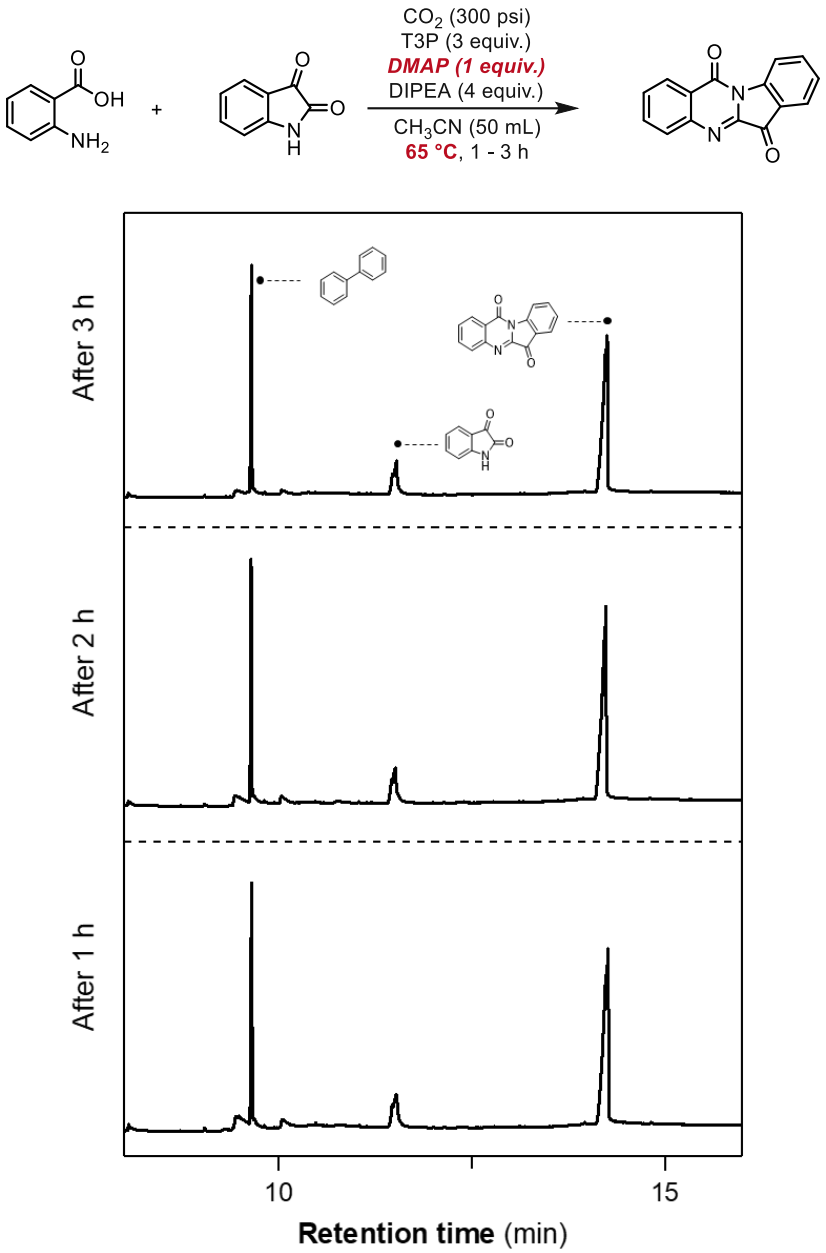
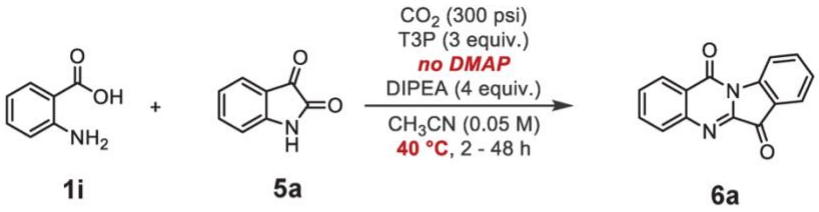
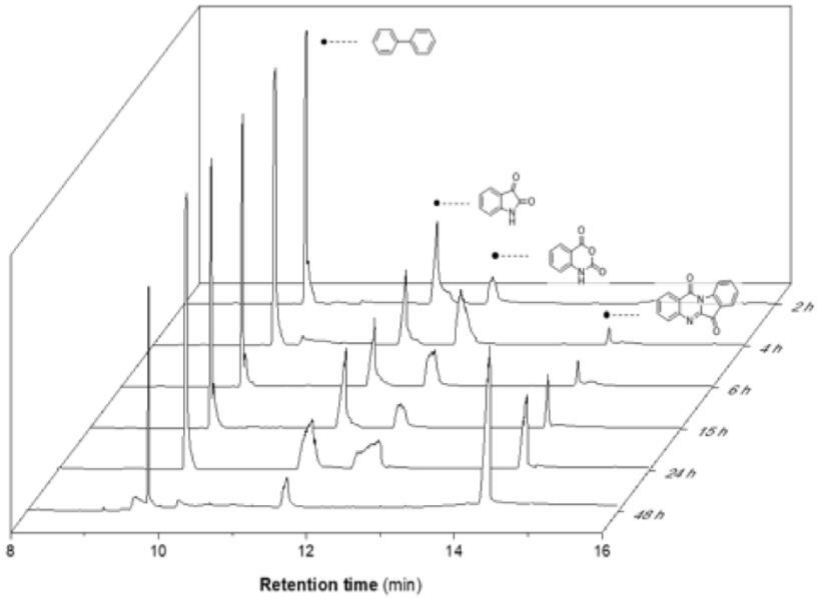


Figure S9. Representative GC plots for the synthesis of tryptanthrin in the presence of DMAP at 65 °C. Under this condition, the reaction was too fast to observe the formation of **2i**.



A) GC Traces from Time Study



B) Plot of Relative Percentage of Various Species Over Time

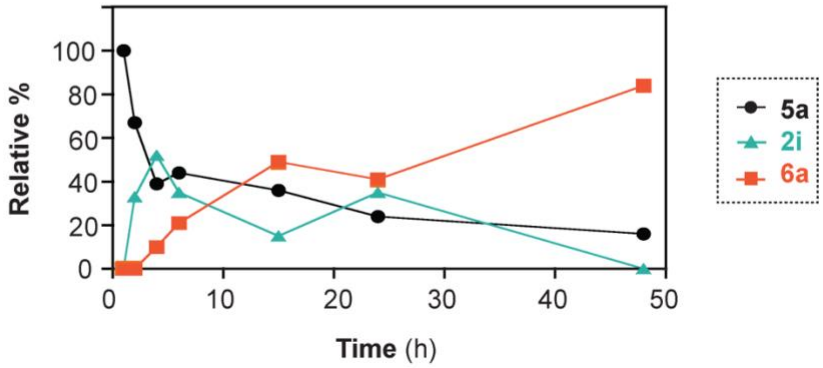


Figure S10. GC traces (A) and plot (B) showing changes in the relative ratios of **5a**, **2i** (NCA intermediate), and **6a** over the course of 48 h. These data show the growth and disappearance of **2i** as the reaction progressed, which suggests that the NCA is an intermediate in the tandem reaction.

NMR Spectroscopic Data

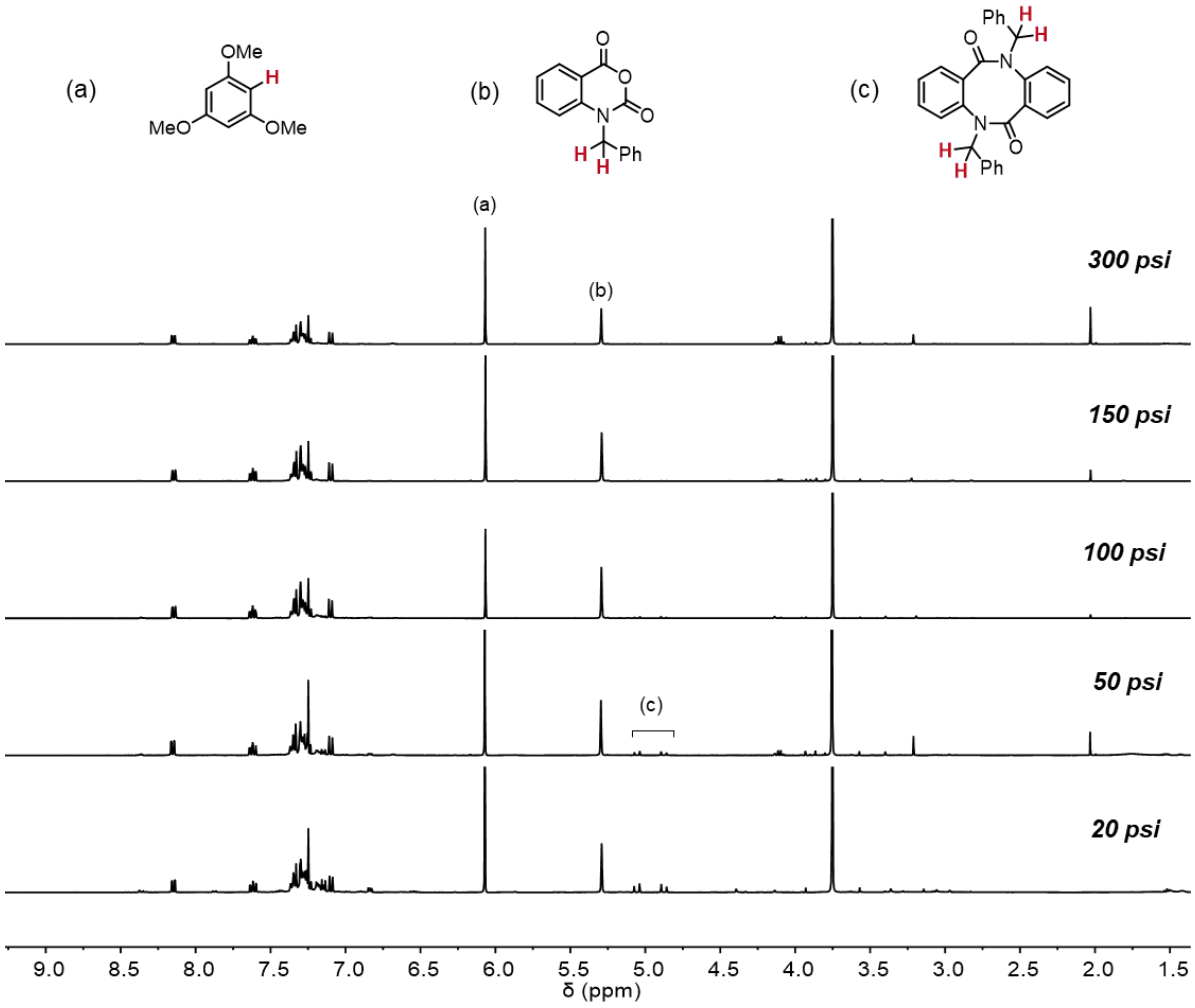


Figure S11. ^{1}H NMR spectra (400 MHz, 25 ^{o}C, $CDCl_3$) of the products obtained (after work-up) from reactions at different CO_2 pressures. The presence of **2a′** was observed only when the CO_2 pressure was at 20 or 50 psi.

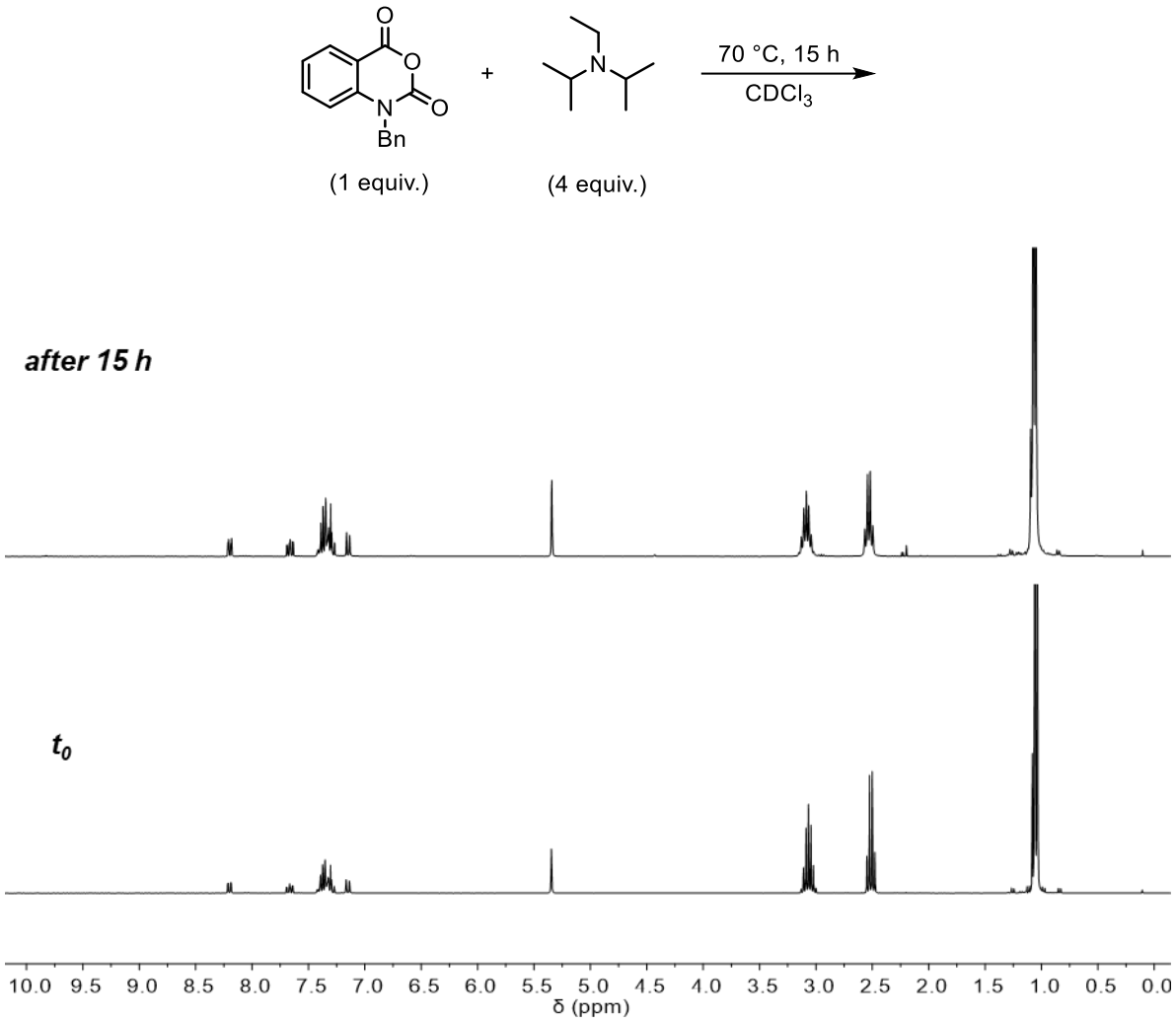


Figure S12. ^{1}H NMR spectrum (400 MHz, 25 ^{o}C, $CDCl_3$) of a solution containing compound **2a** and DIPEA. After 15 h (top trace), no reaction had occurred.

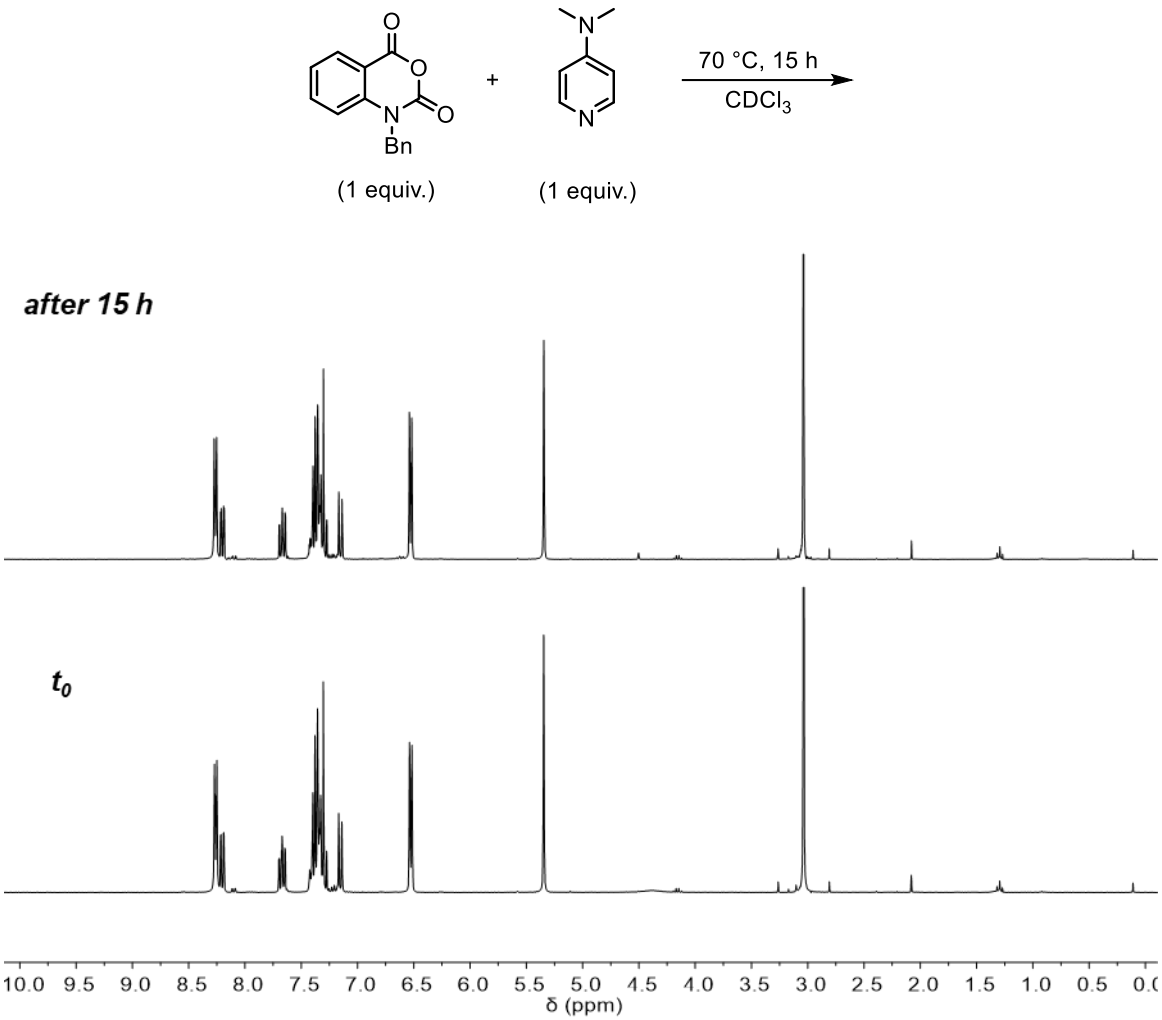


Figure S13. ^{1}H NMR spectrum (400 MHz, 25 ºC, $CDCl_3$) of a solution containing **2a** and DMAP. After 15 h (top trace), no reaction had occurred.

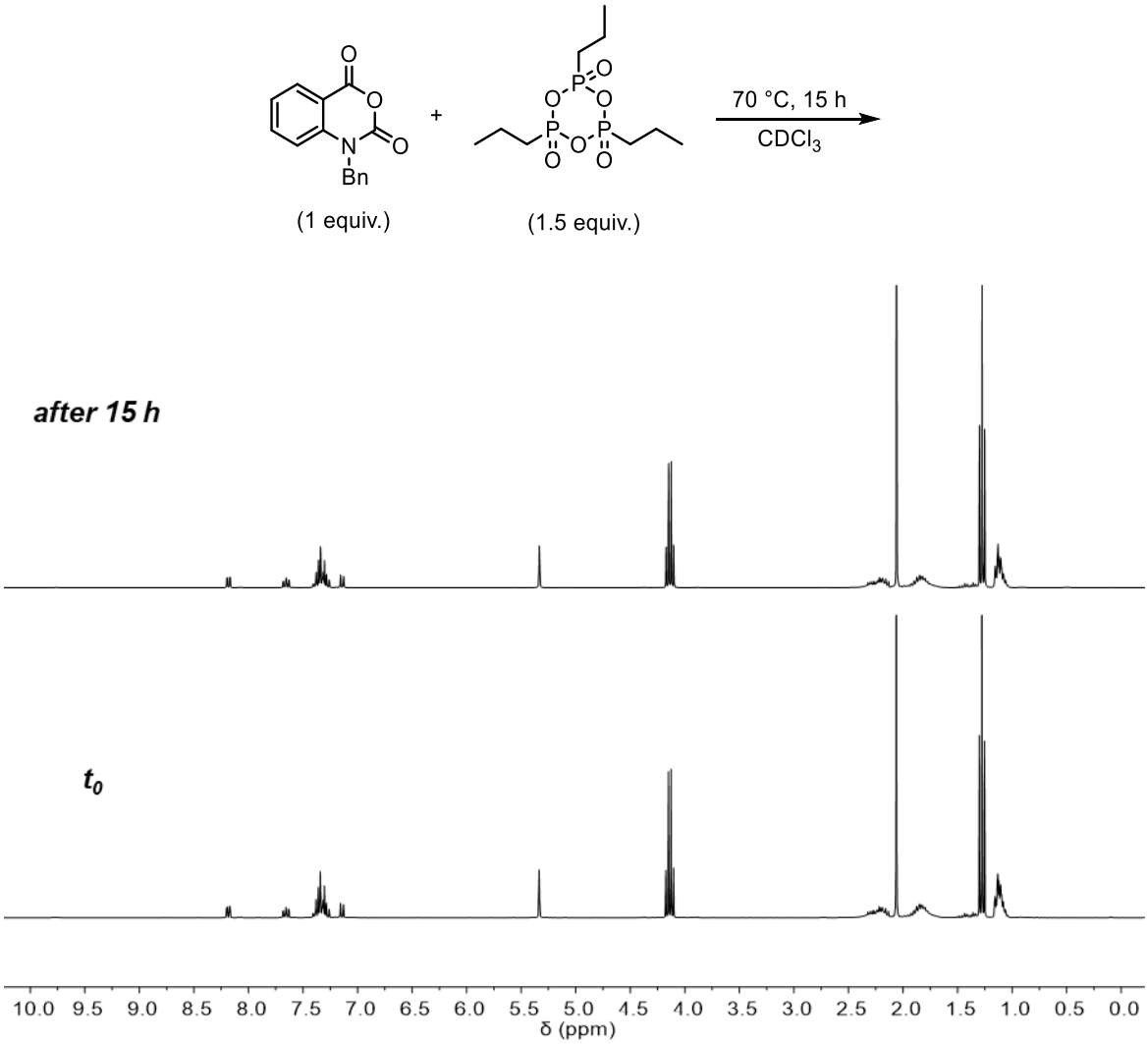


Figure S14. ^{1}H NMR spectrum (400 MHz, 25 ºC, $CDCl_3$) of a solution containing **2i** and T3P. After 15 h (top trace), no reaction had occurred.

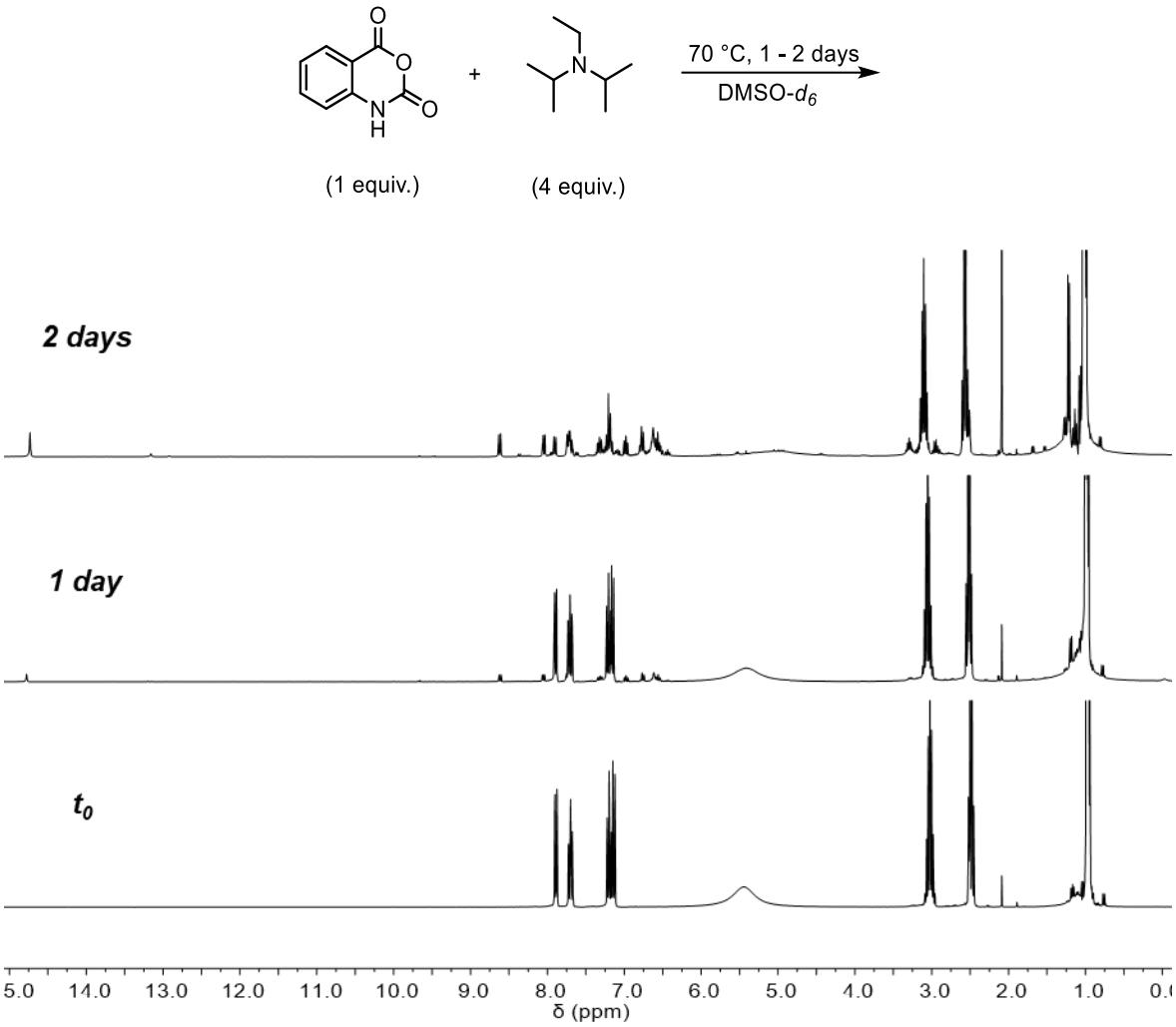


Figure S15. ^{1}H NMR spectrum (400 MHz, 25 ºC, DMSO-d_6,) of a solution containing **2i** and DIPEA. After 2 d, compound **2i** had converted to dimer **2i′**.

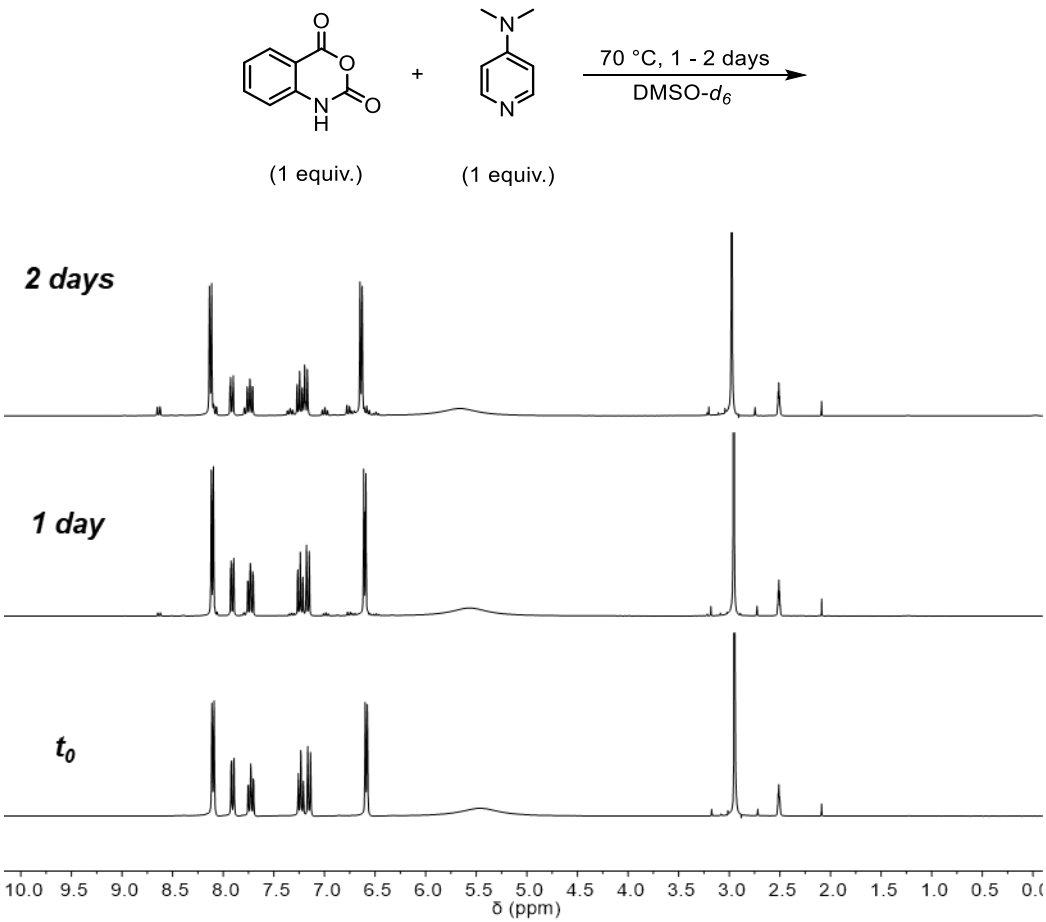


Figure S16. ^{1}H NMR spectrum (400 MHz, 25 °C, DMSO-d_6,) of solution containing **2i** and DMAP. After 2 d, a small amount of dimer **2i′** had appeared.

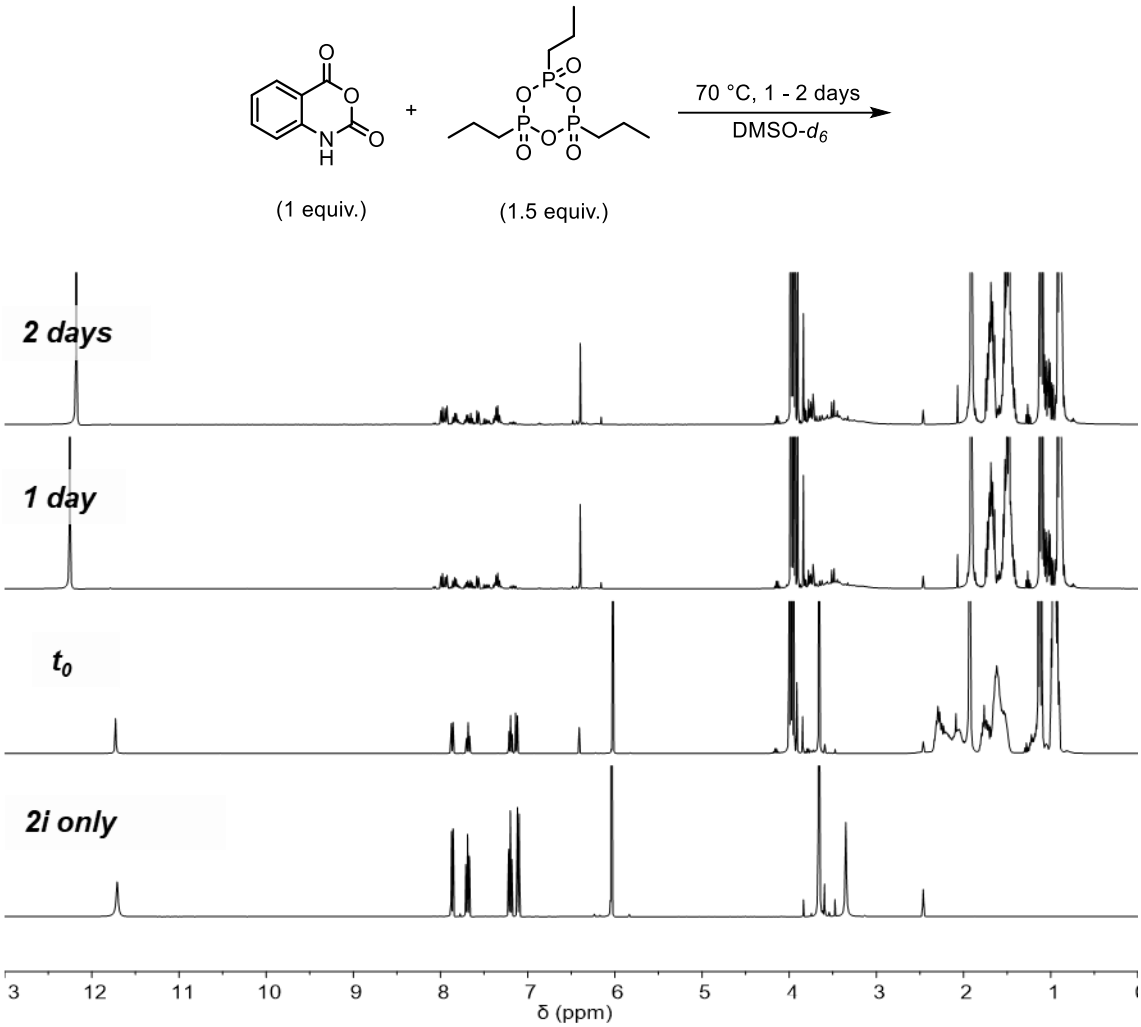


Figure S17. ^{1}H NMR spectrum (400 MHz, 25 °C, DMSO-d_6,) of a solution containing **2i** and T3P. Peaks at 11.73 ppm and 12.18 ppm belong to N*H* of **2i** and **2i′,** respectively. After 1 d, compound **2i** had converted to dimer **2i′**.

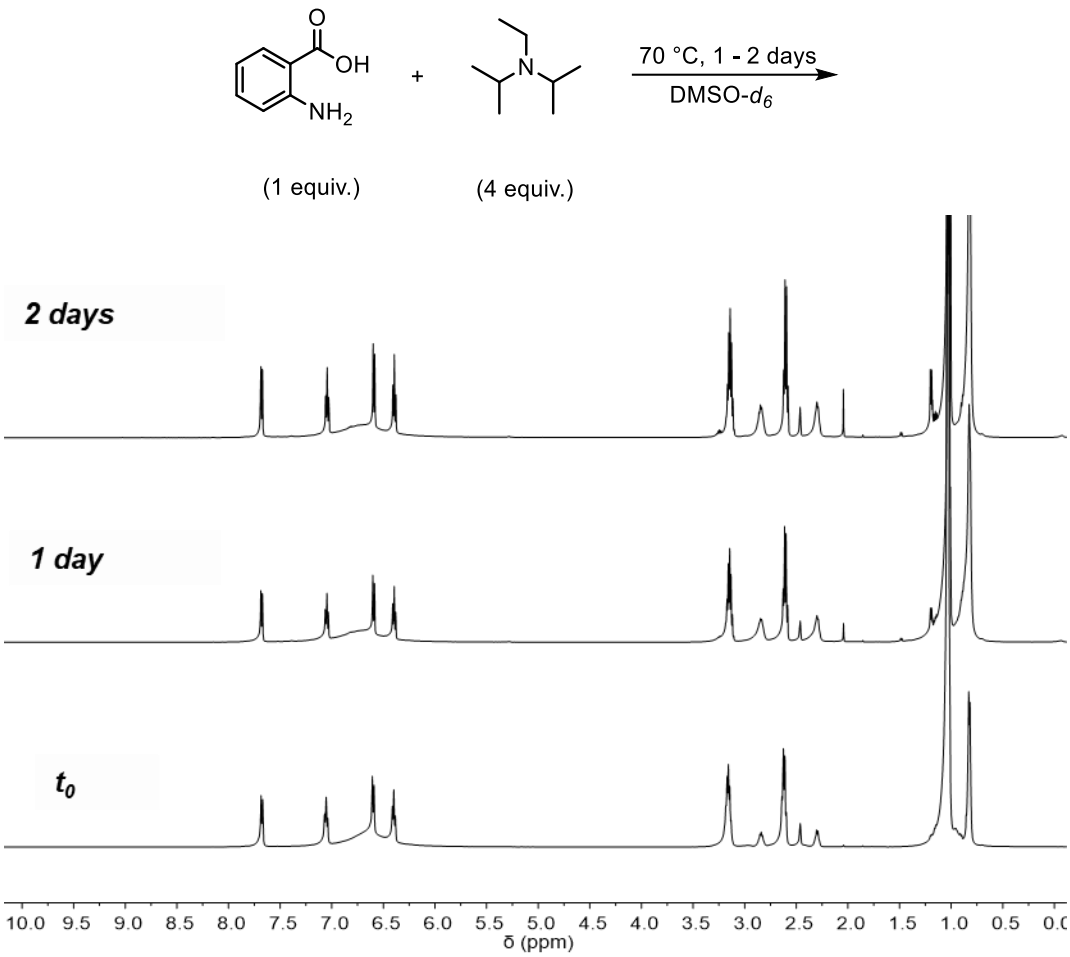


Figure S18. ^{1}H NMR spectrum (400 MHz, 25 ^{o}C, DMSO-d_6,) of a solution containing anthranilic acid and DIPEA. After 2 d, no reactions had occurred.

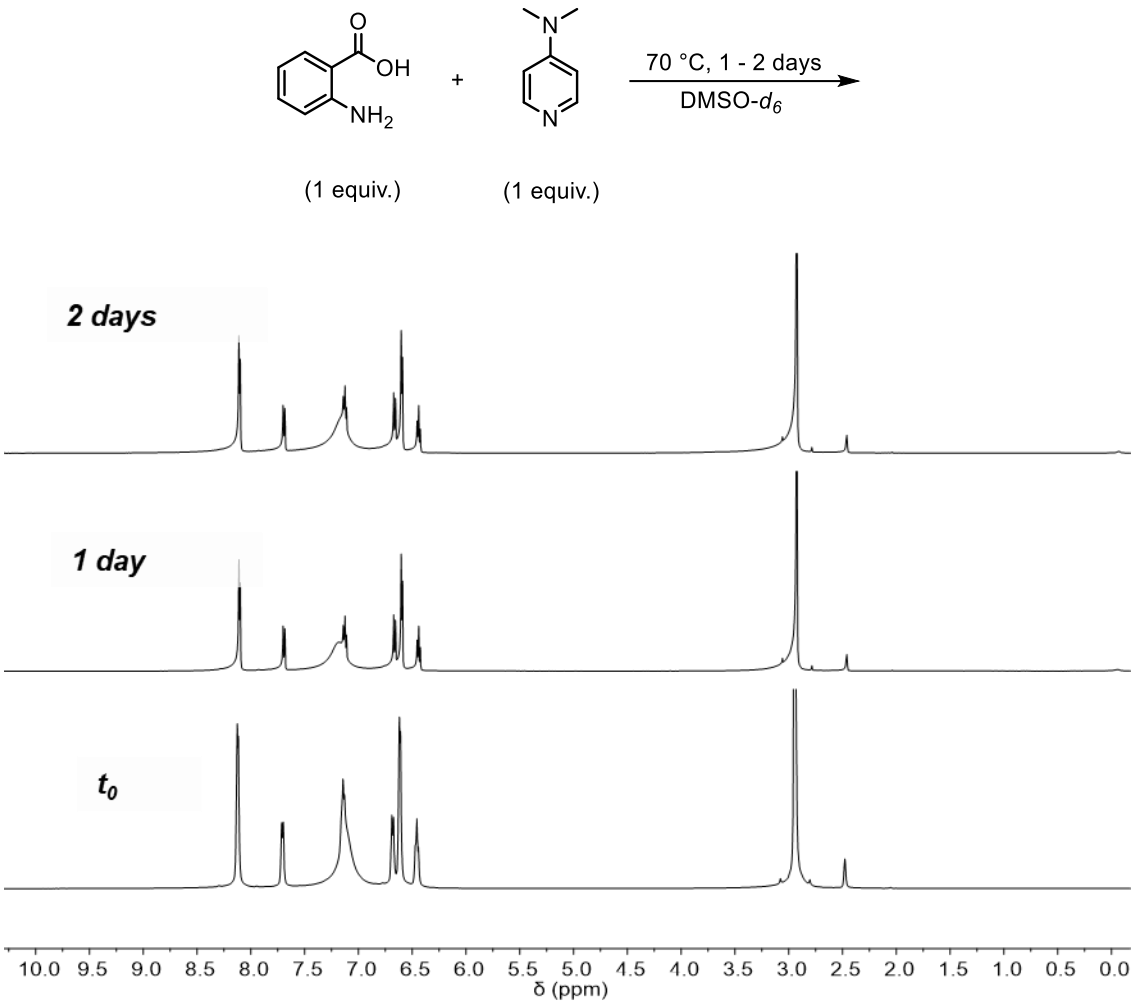


Figure S19. ^{1}H NMR spectrum (400 MHz, 25 ºC, DMSO-d_6,) of solution containing anthranilic acid and DMAP. After 2 d, no reactions had occurred.

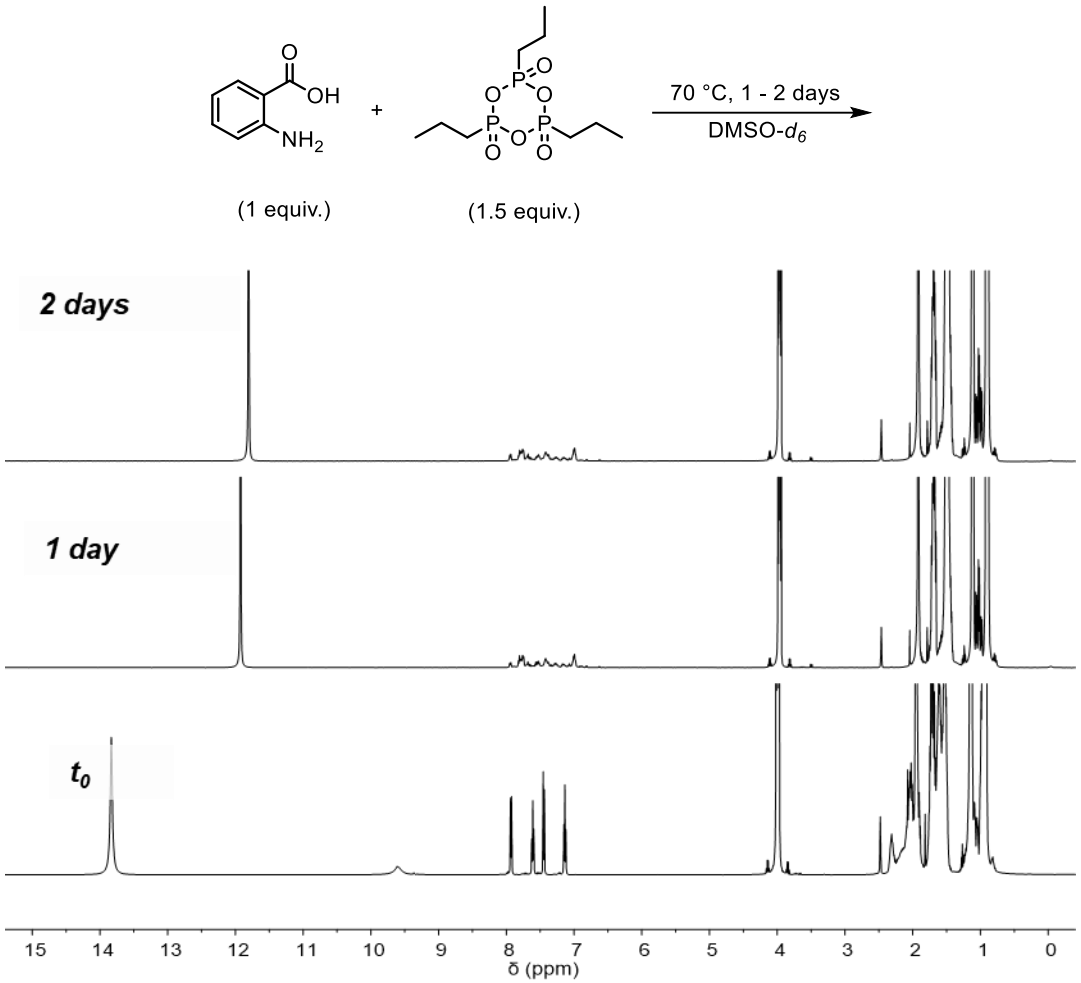
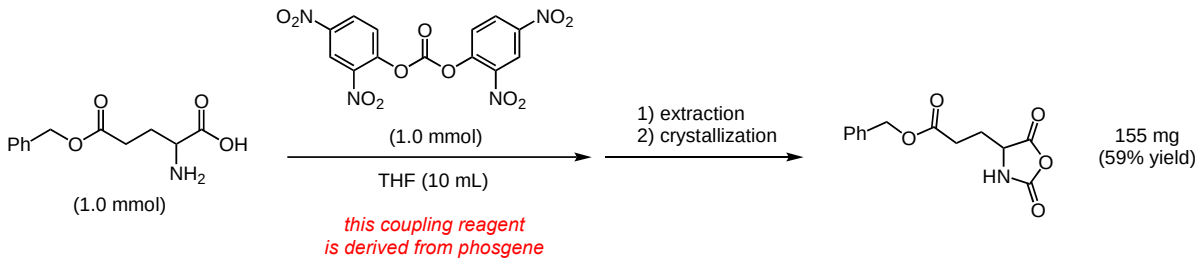
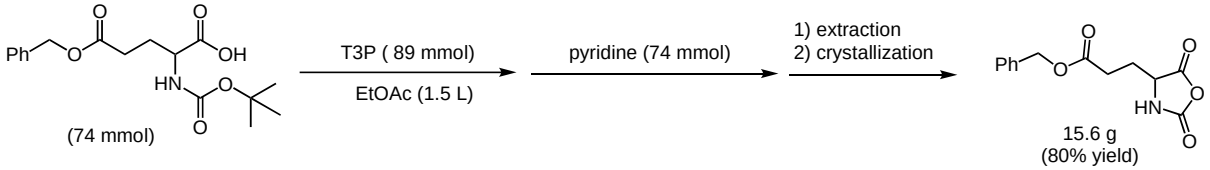


Figure S20. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of a solution containing anthranilic acid and T3P. After 1 d, the formation of a new product was observed. The ^{31}P NMR spectra of the reaction after 1 and 2 d contained numerous peaks that could not be assigned. The T3P-activated species are too unstable to be isolated and purified for further analysis.

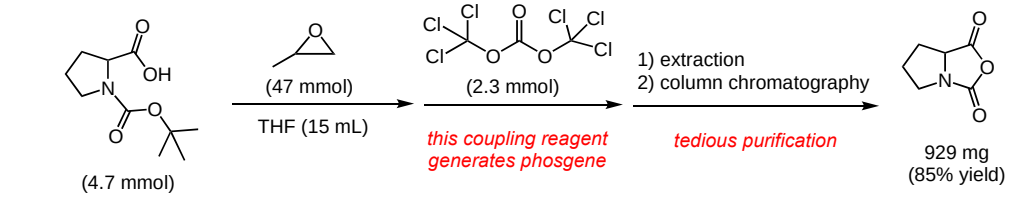
A) Method I (Endo and coworkers, *J. Polym*. Sci. *A: Poly. Chem.*, **2007**, *45*, 5365)



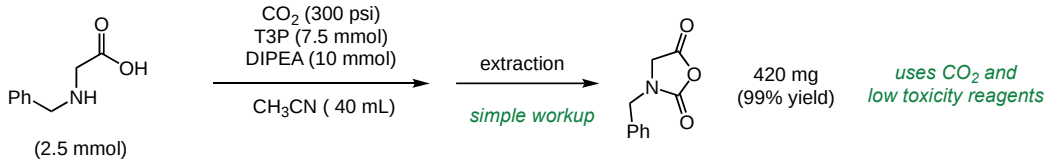
B Method II (Laconde, Martinez, and coworker, *Org. Lett.*, **2021**, *23*, 6412)



C) Method III (Lu and coworkers, *Nat. Commun*., **2021**, *12*, 8510)



D) Method IV (*this work*)



Scheme S5. Comparison of different methods reported for preparing five membered ring NCAs. Methods I, II, and III all require starting materials or reagents that are derived from the highly poisonous gas phosgene. Our approach (Method IV) uses earth abundant CO_2 and low toxicity reagents and provides NCAs with high purity after simple workup.

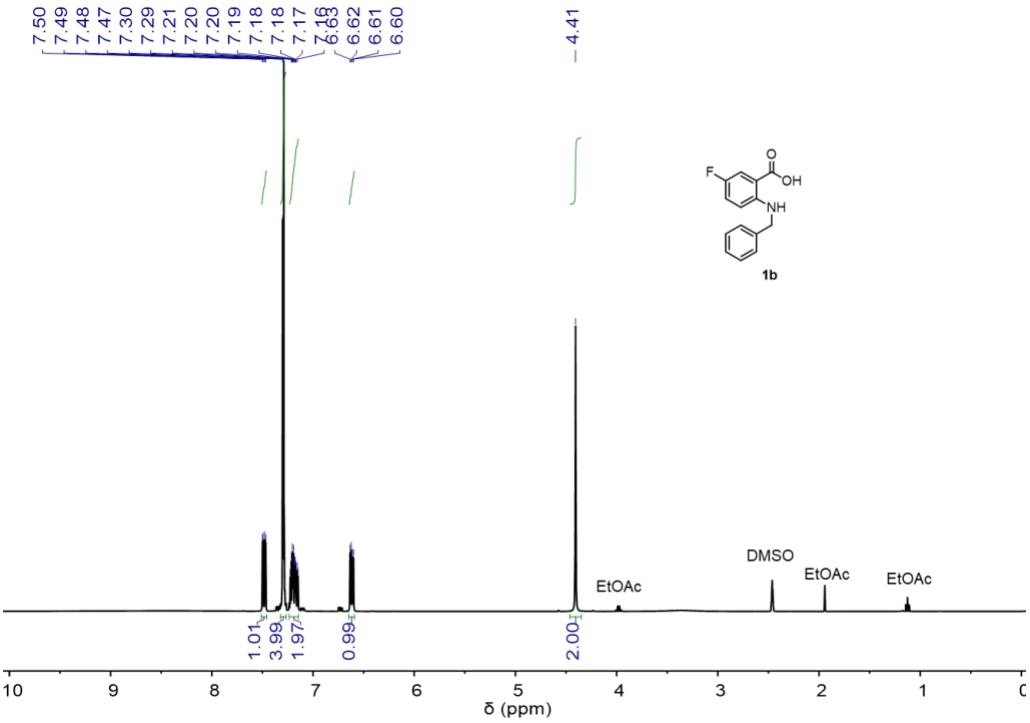


Figure S21. ^{1}H NMR (400 MHz, 25 ºC, DMSO-d_6) spectrum of compound **1b**.

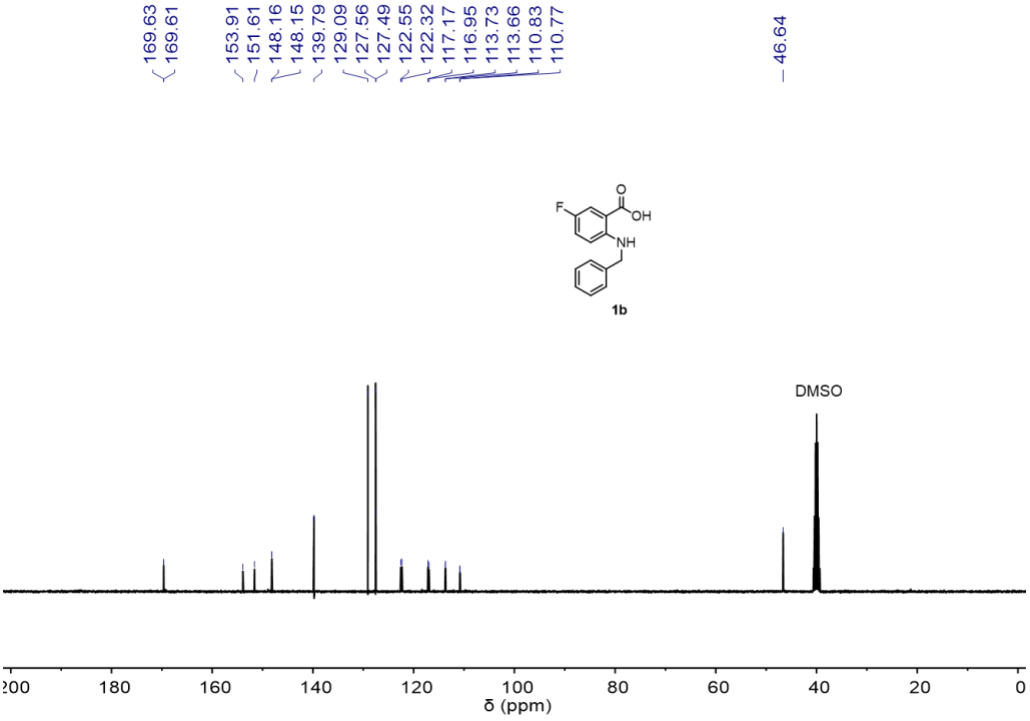


Figure S22. ^{13}C NMR (101 MHz, 25 ºC, DMSO-d_6) spectrum of compound **1b**.

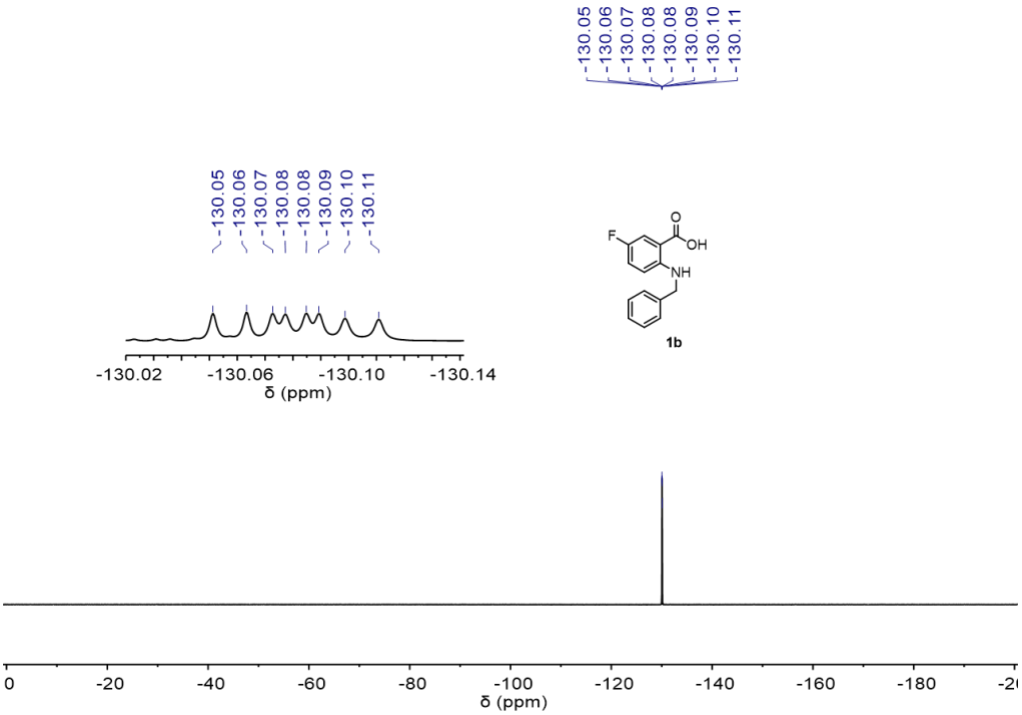


Figure S23. ^{19}F NMR (376 MHz, 25 °C, DMSO-d_6) spectrum of compound **1b**.

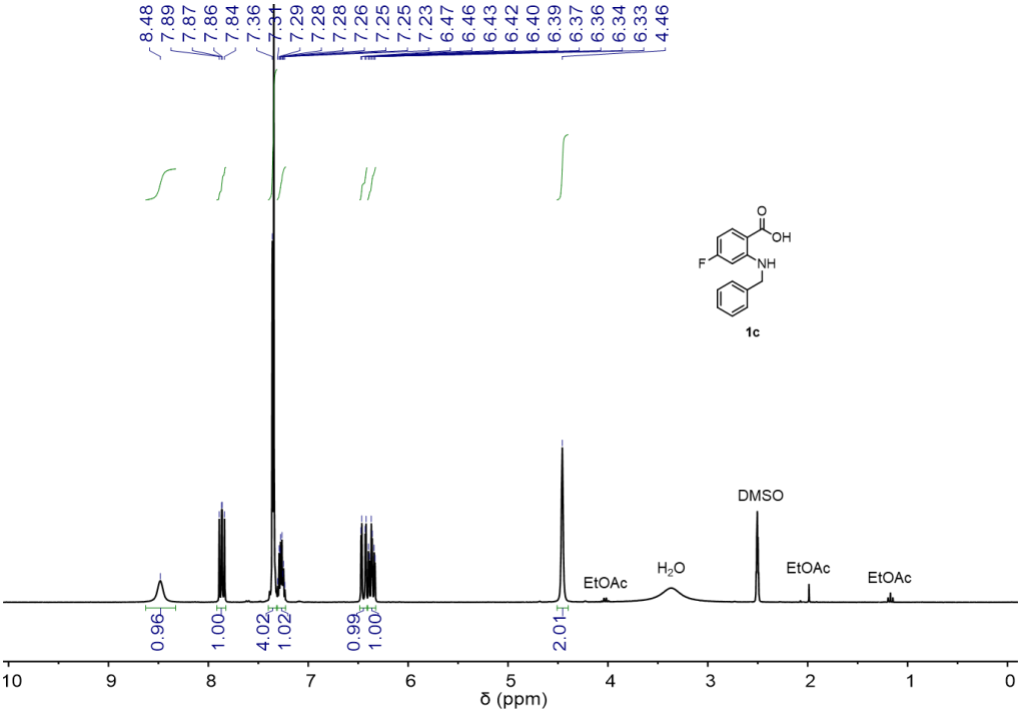


Figure S24. ^{1}H NMR (300 MHz, 25 °C, DMSO-d_6) spectrum of compound **1c**.

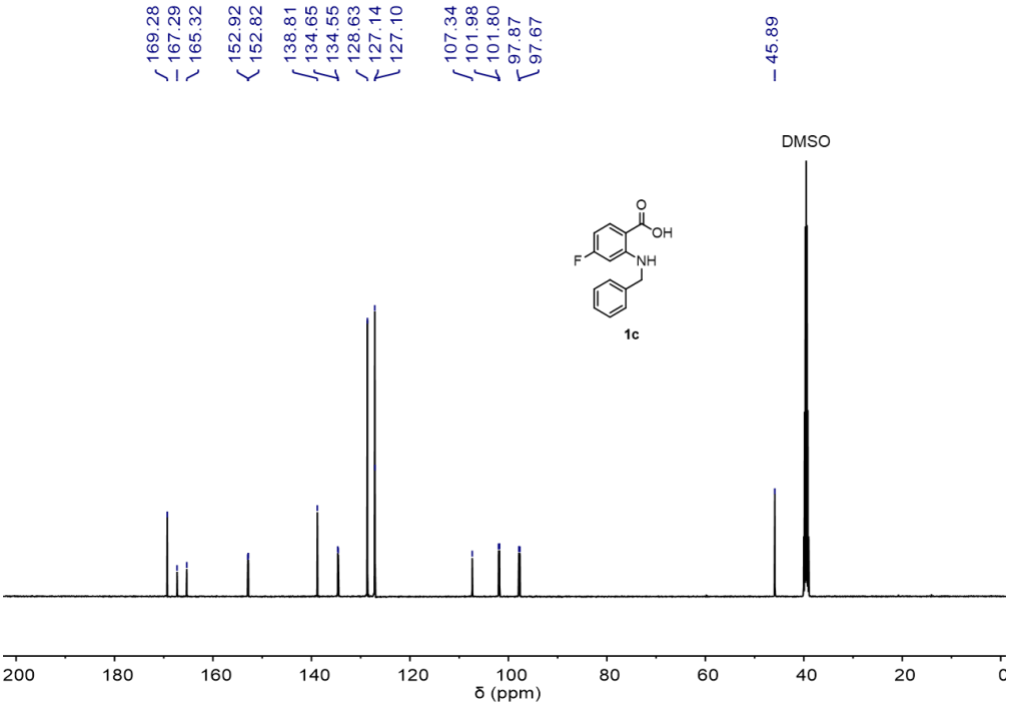


Figure S25. ^{13}C NMR (125 MHz, 25 °C, DMSO-d_6) spectrum of compound **1c**.

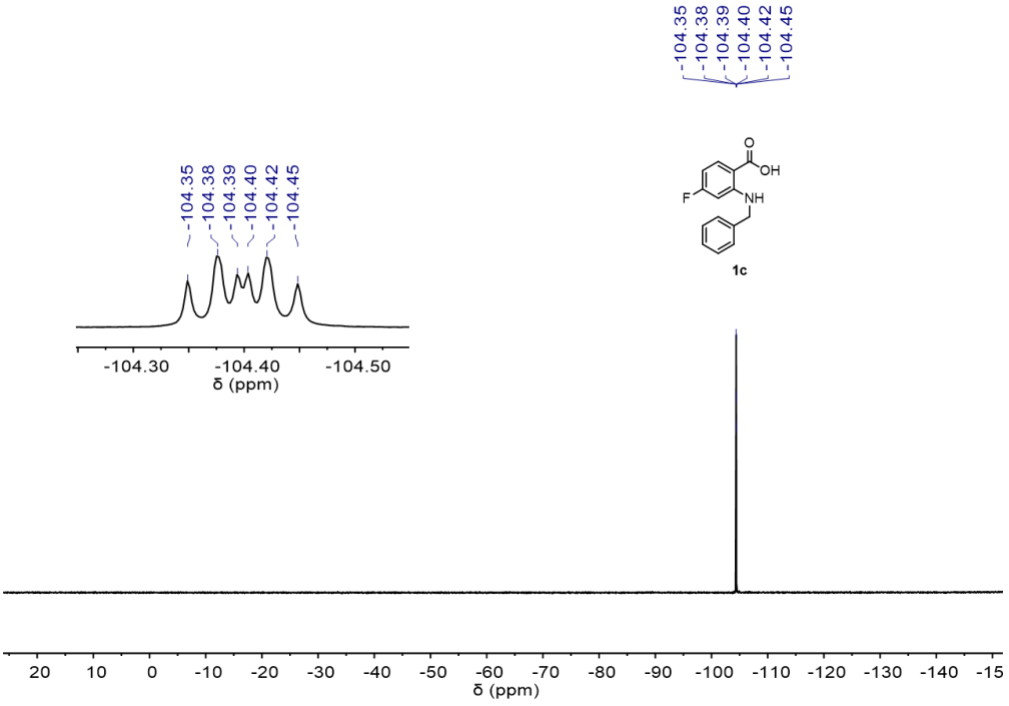


Figure S26. ^{19}F NMR (282 MHz, 25 °C, DMSO-d_6) spectrum of compound **1c**.

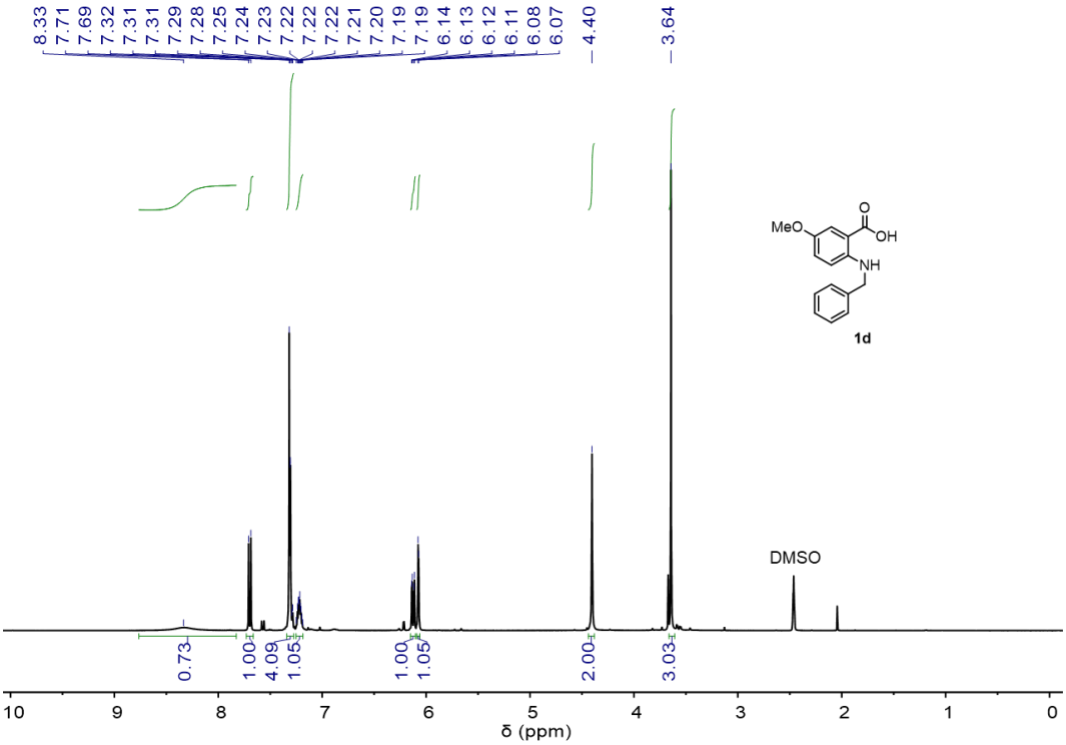


Figure S27. ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **1d**.

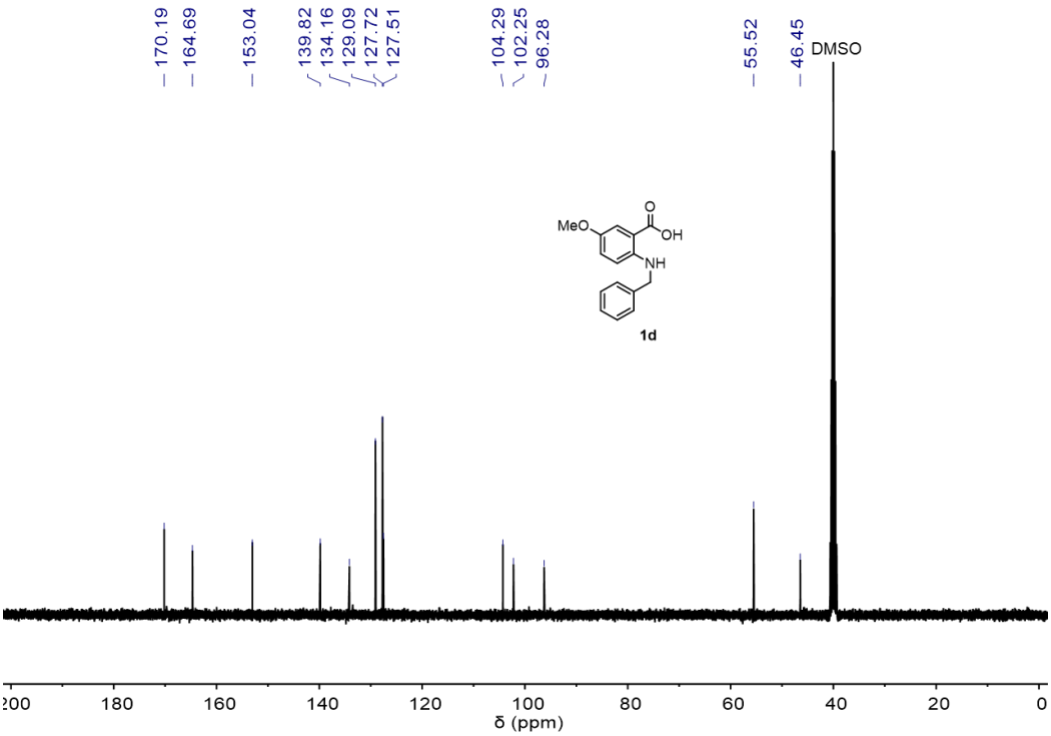


Figure S28. ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **1d**.

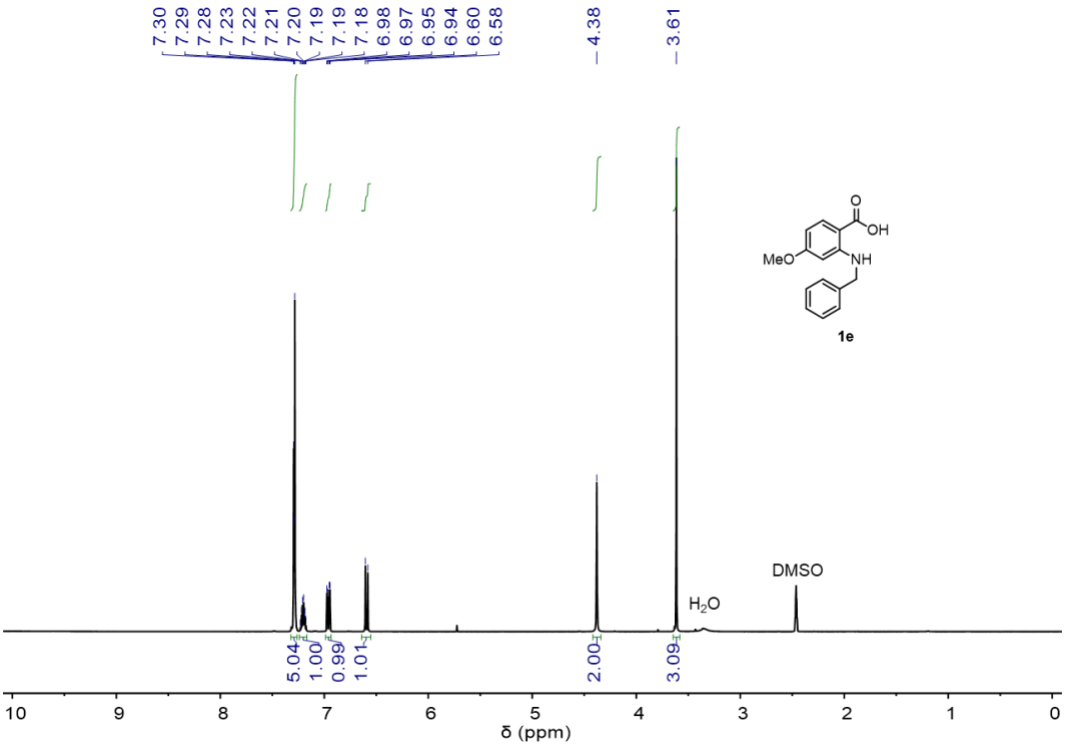


Figure S29. ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **1e**.

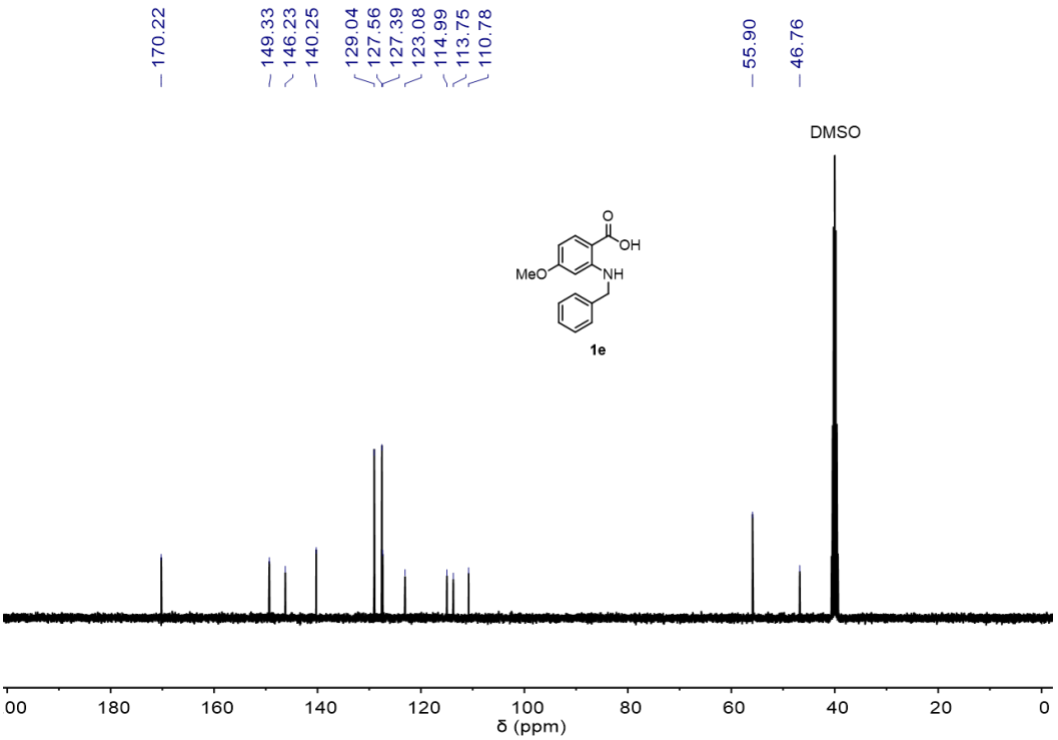


Figure S30. ^{13}C NMR (101 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **1e**.

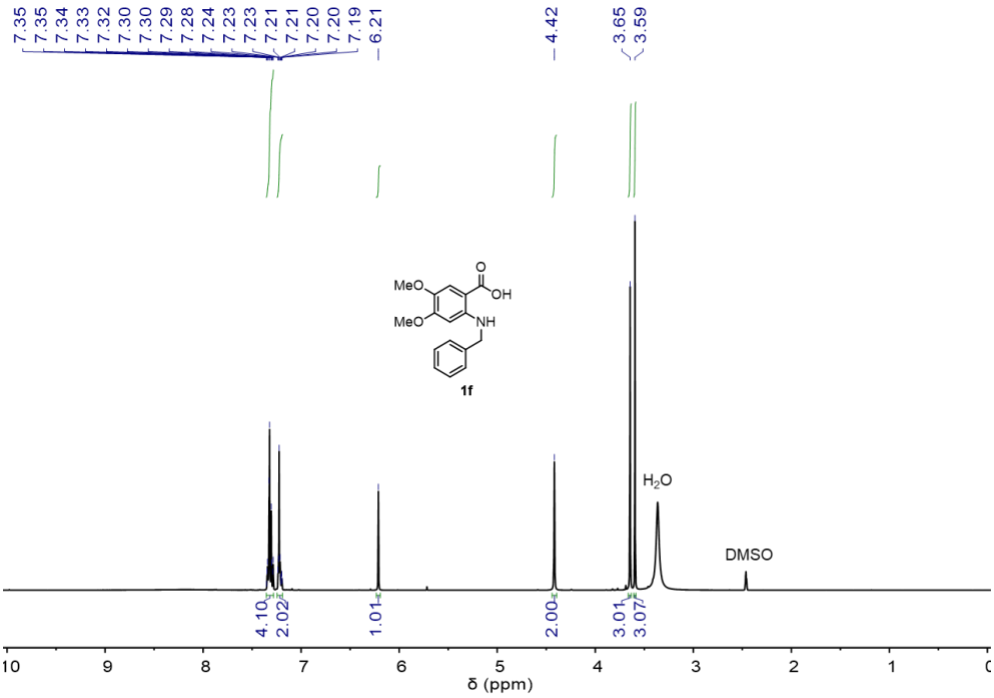


Figure S31. ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6) spectrum of compound **1f**.

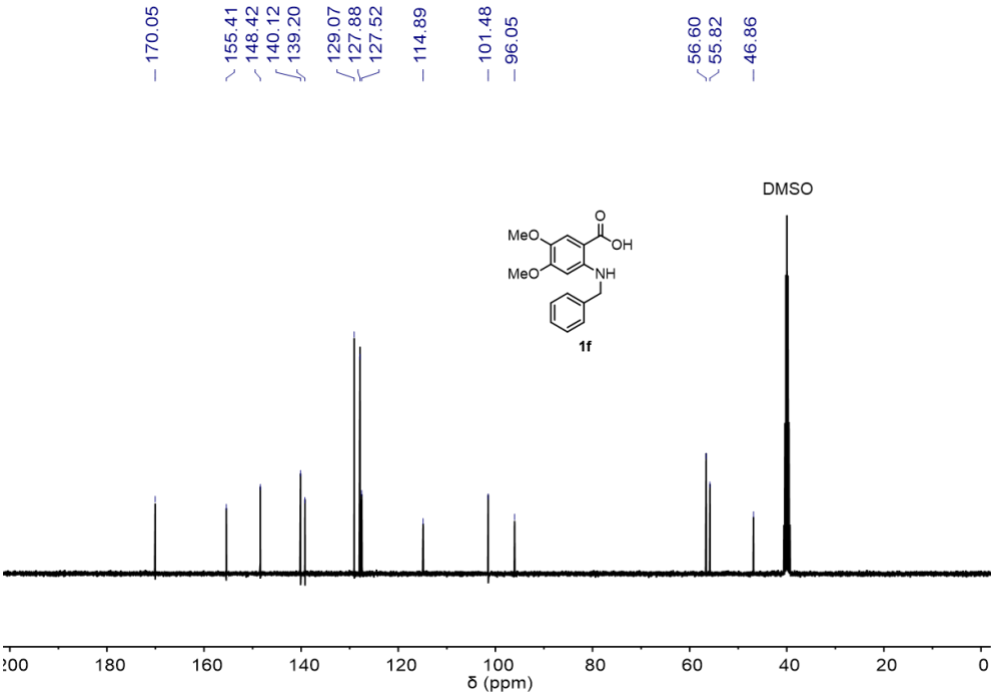


Figure S32. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **1f**.

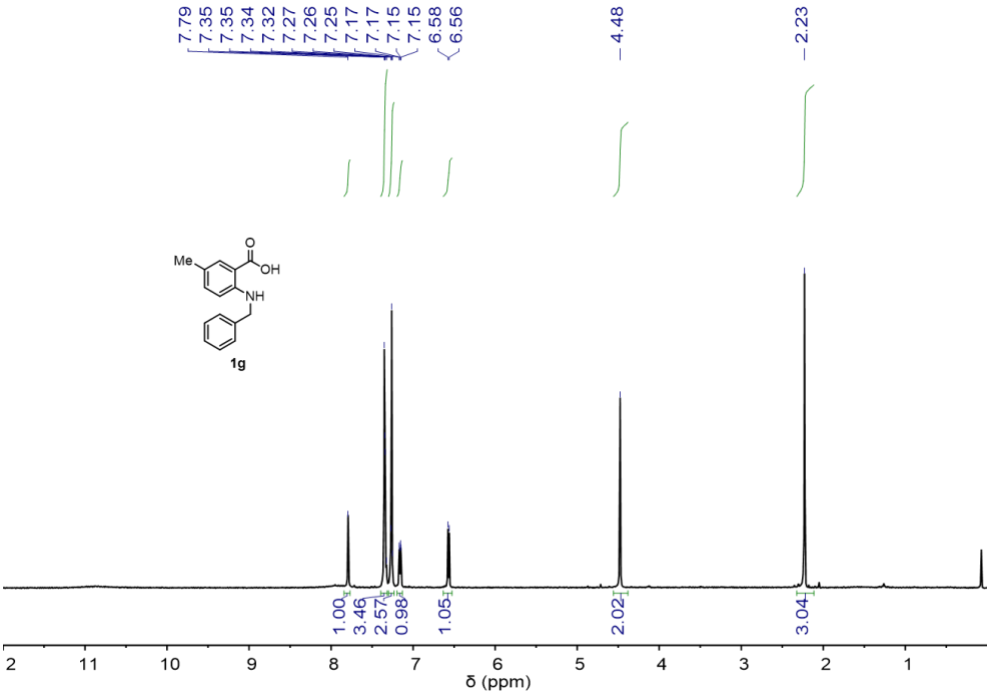


Figure S33. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **1g**.

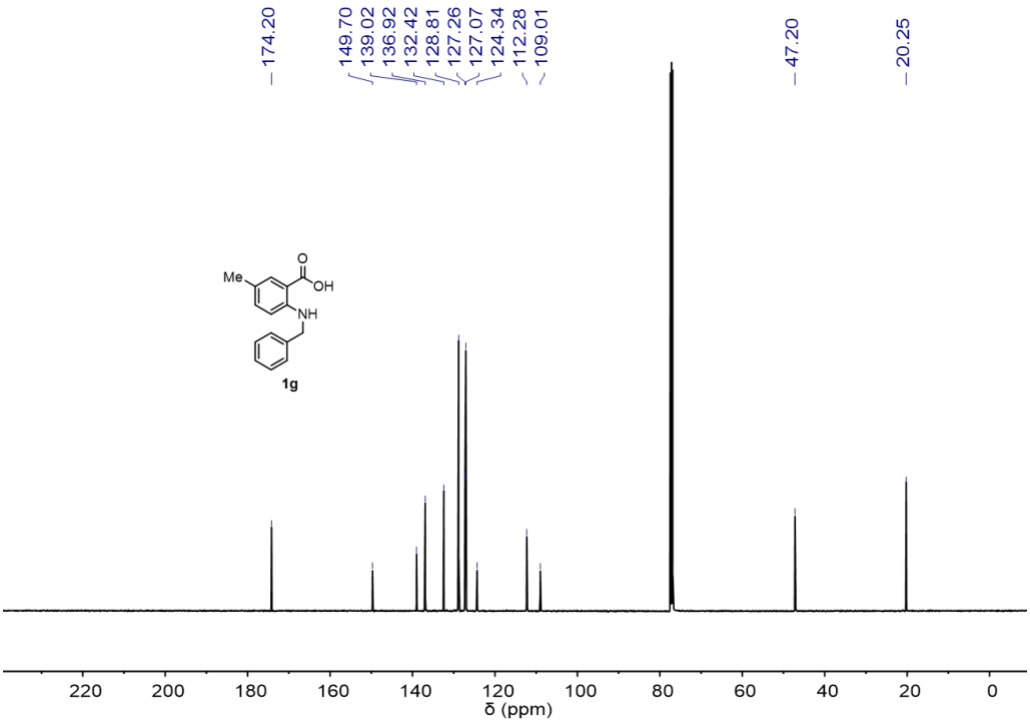


Figure S34. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **1g**.

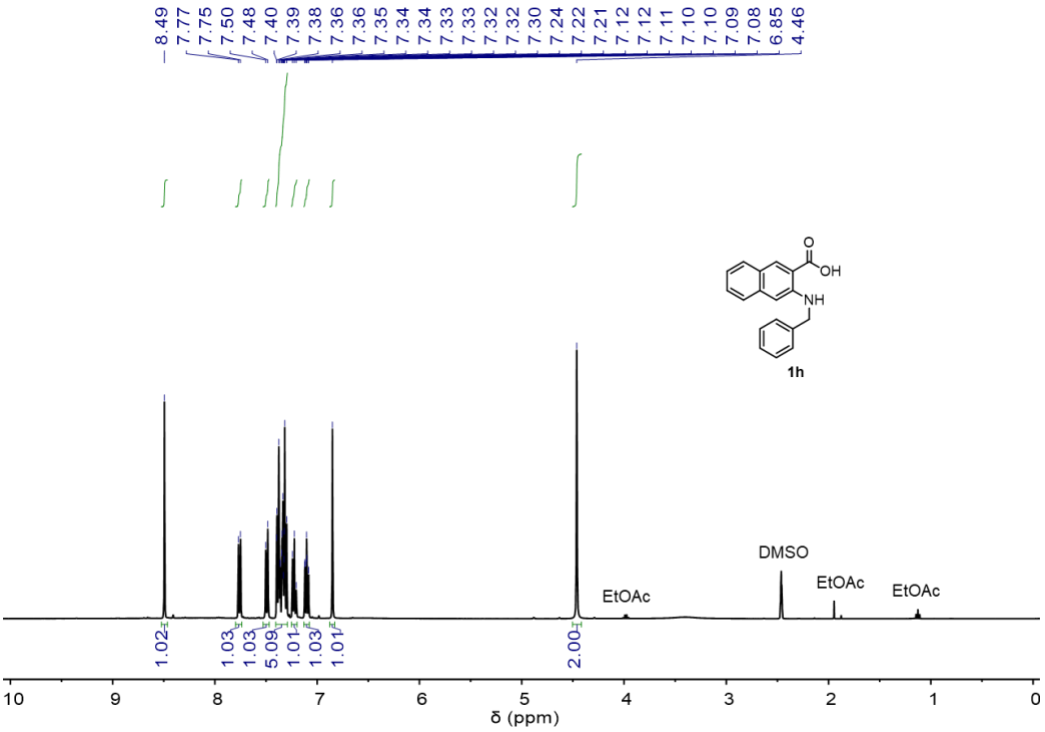


Figure S35. ^{1}H NMR (500 MHz, 25 °C, DMSO-d_6) spectrum of compound **1h**.

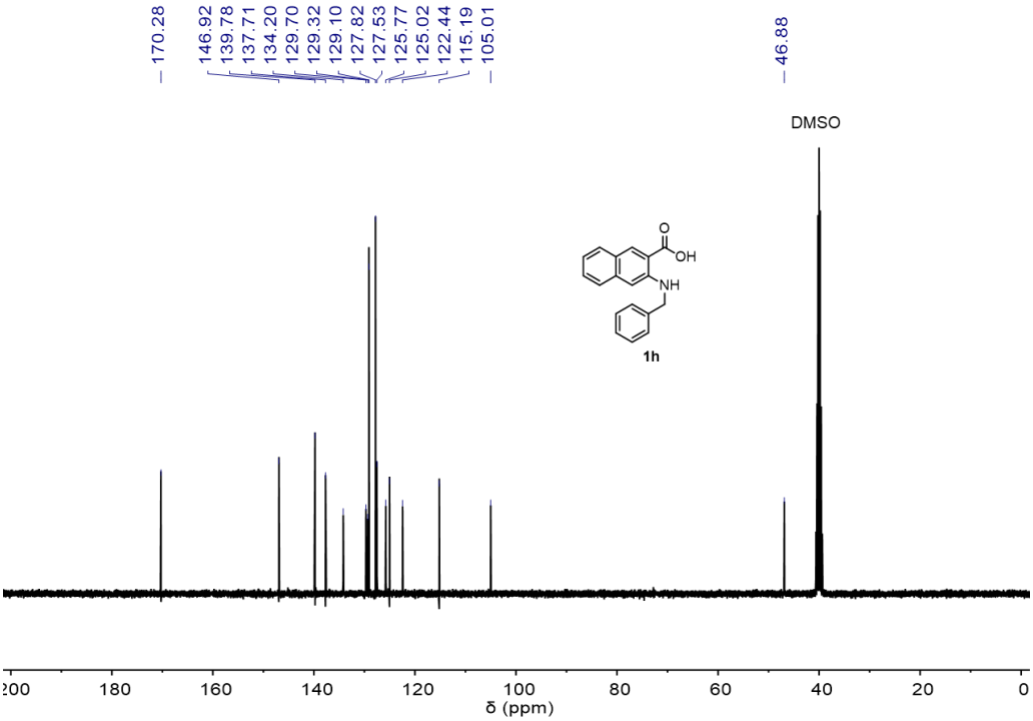


Figure S36. ^{13}C NMR (126 MHz, 25 °C, DMSO-d_6) spectrum of compound **1h**.

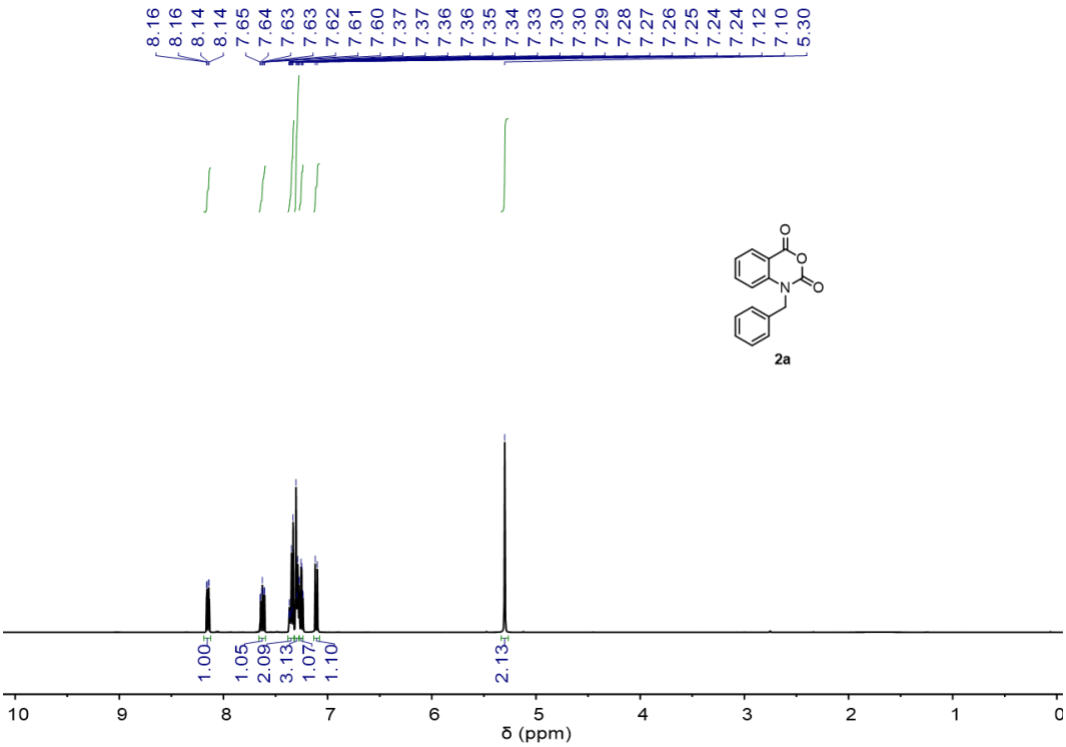


Figure S37. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2a**.

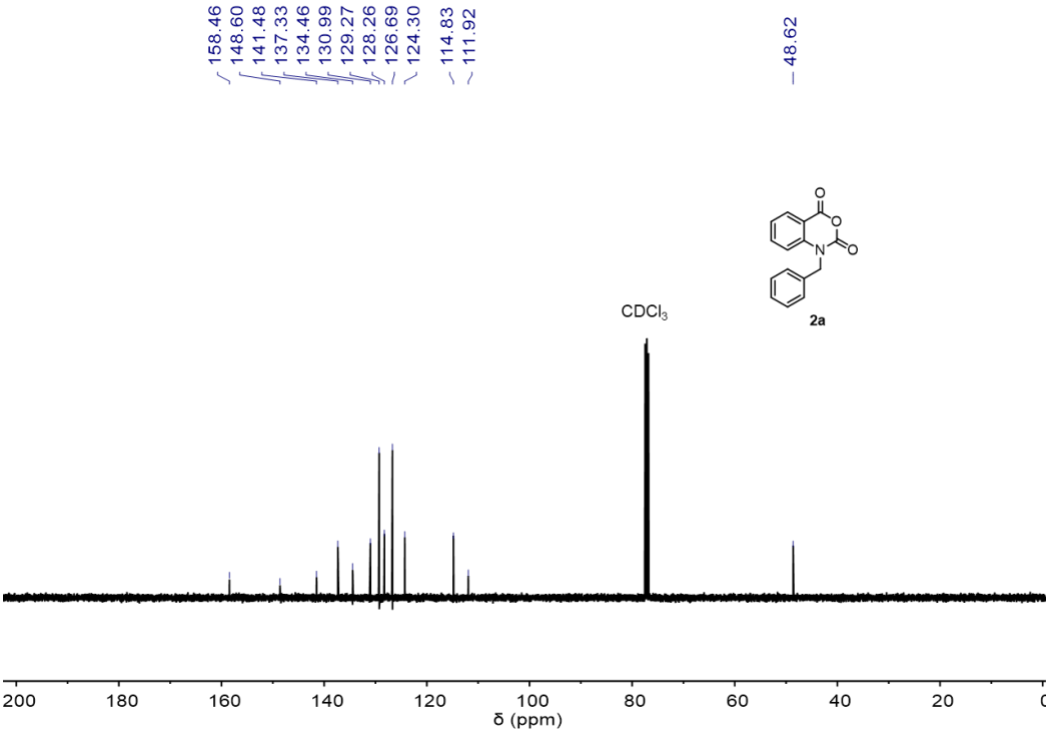


Figure S38. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2a**.

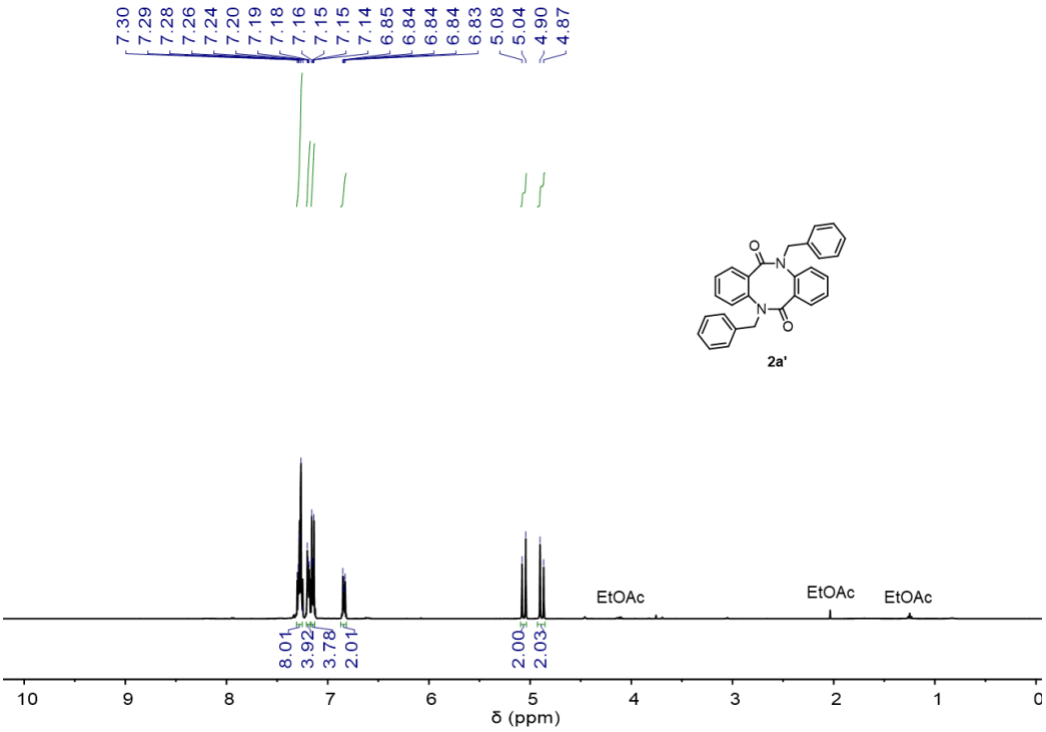


Figure S39. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2a′**.

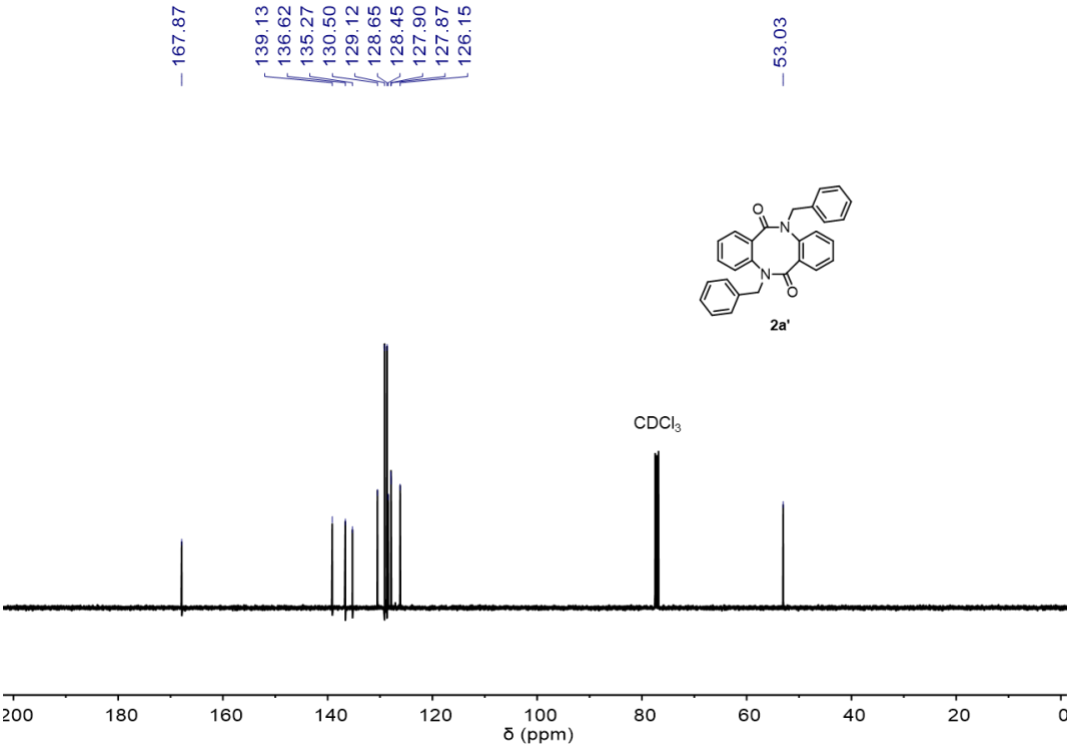


Figure S40. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2a′**.

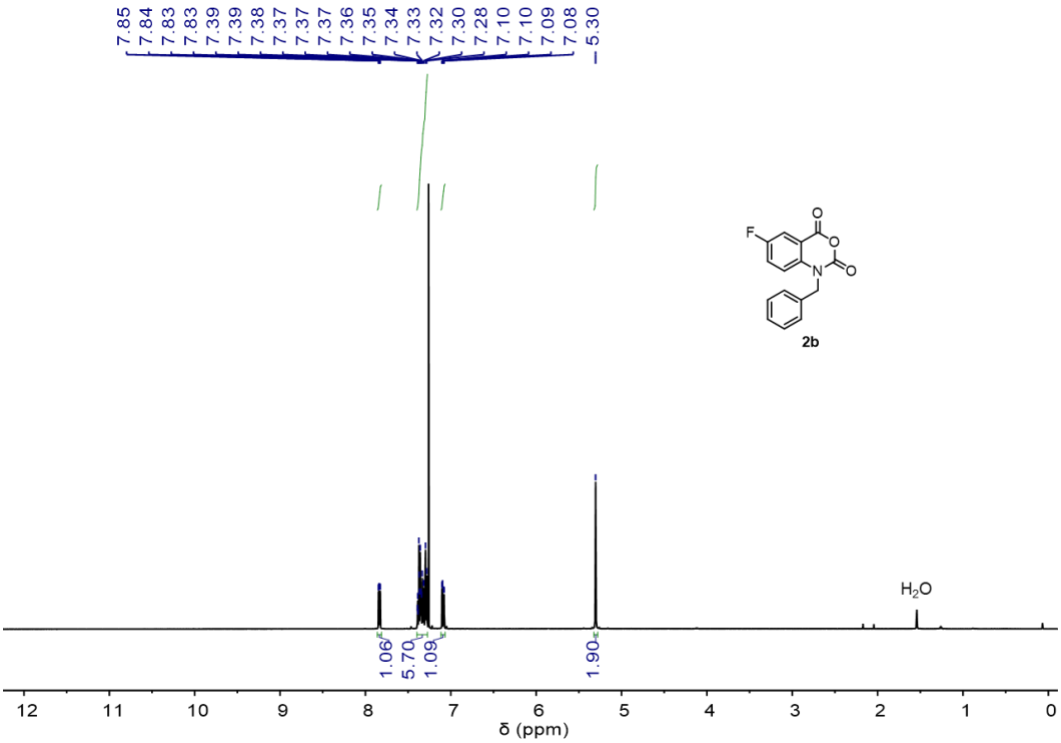


Figure S41. ^{1}H NMR (300 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2b**.

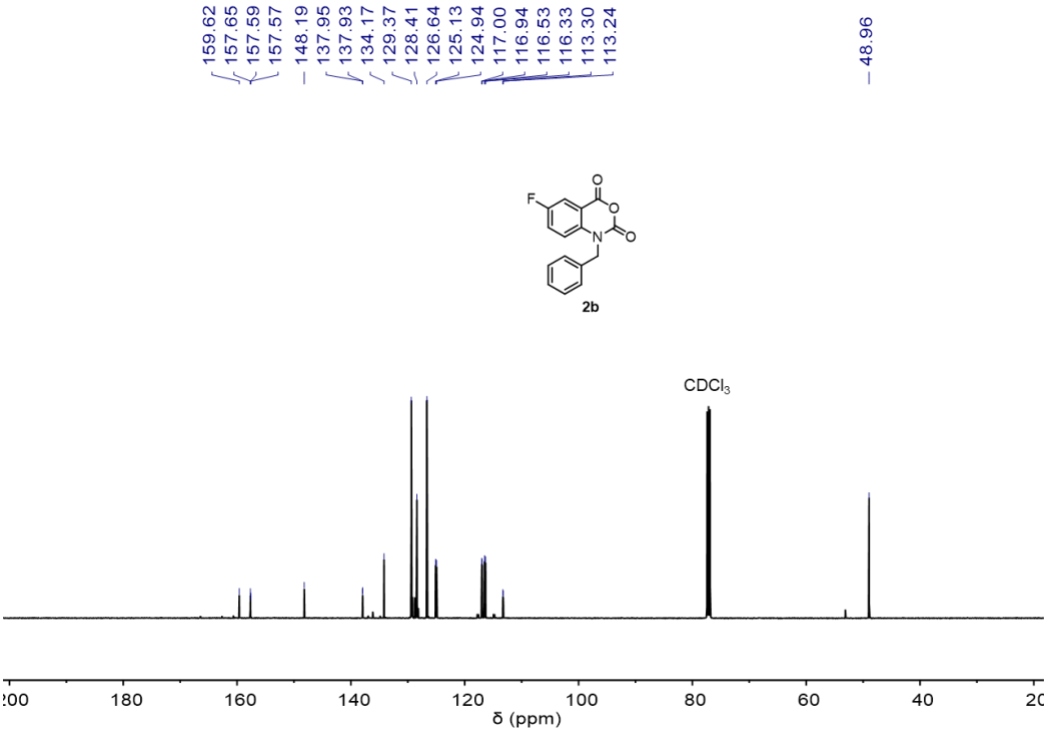


Figure S42. ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2b**.

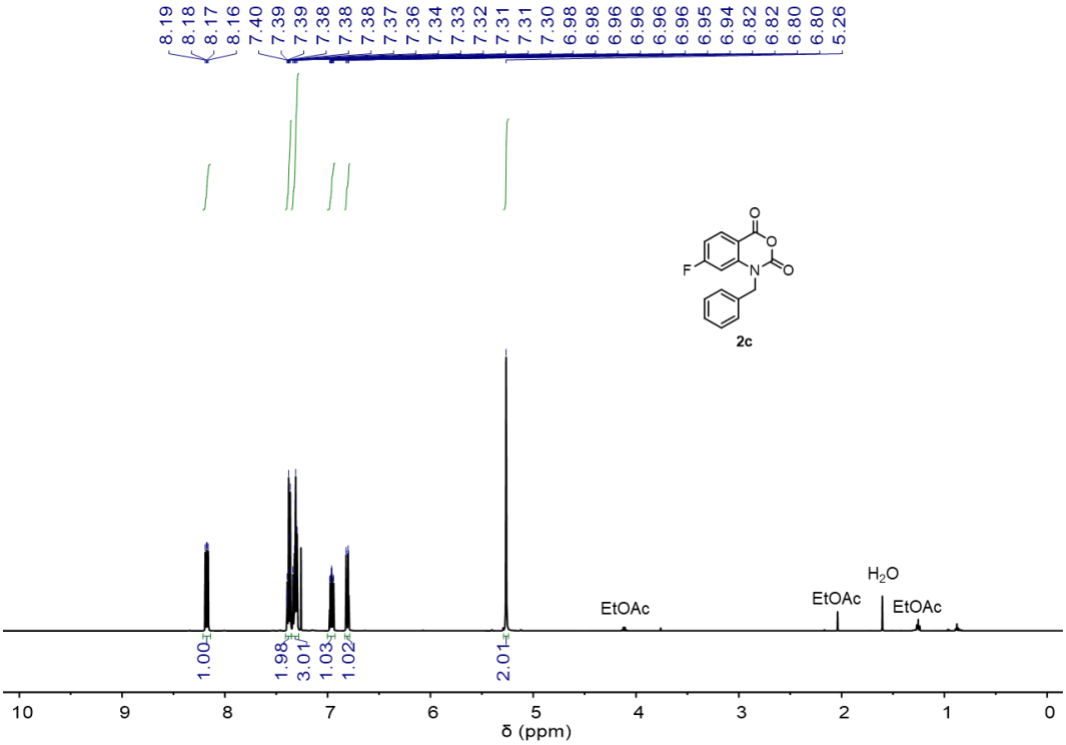


Figure S43. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2c**.

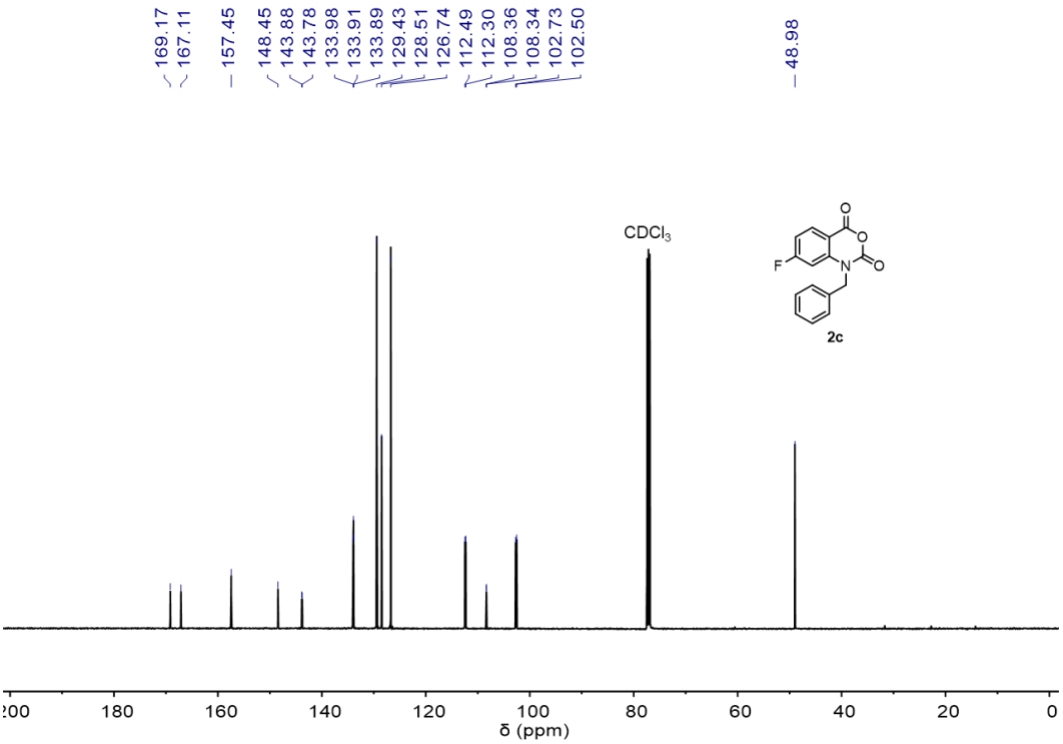


Figure S44. ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2c**.

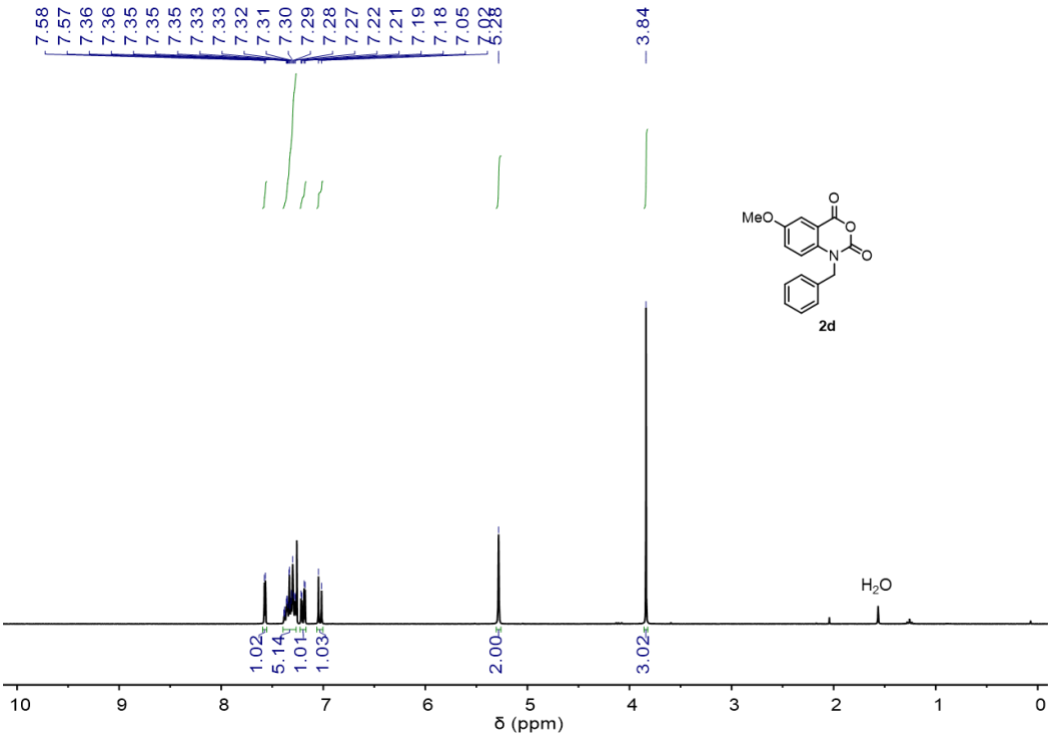


Figure S45. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **2d**.

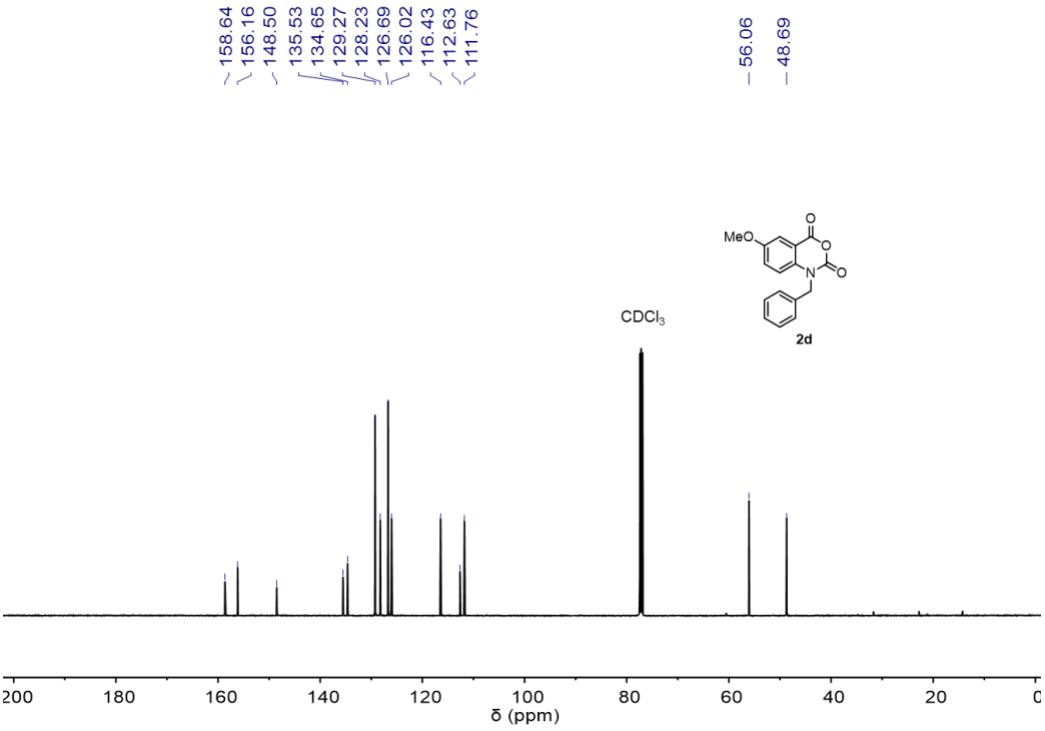


Figure S46. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **2d**.

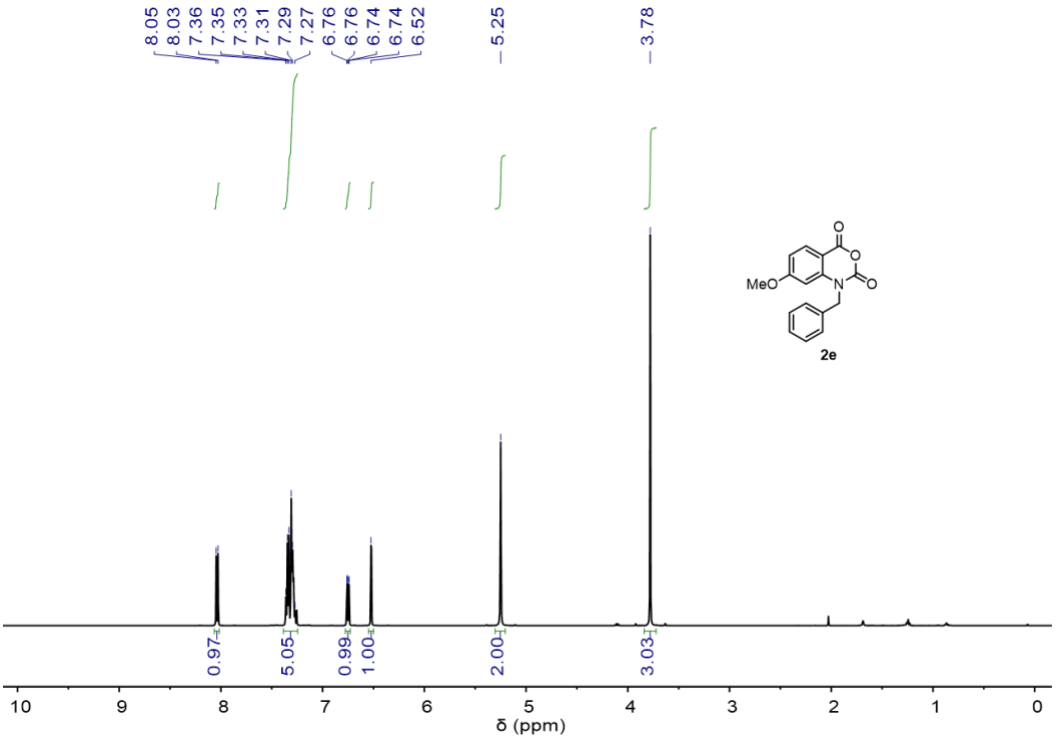


Figure S47. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **2e**.

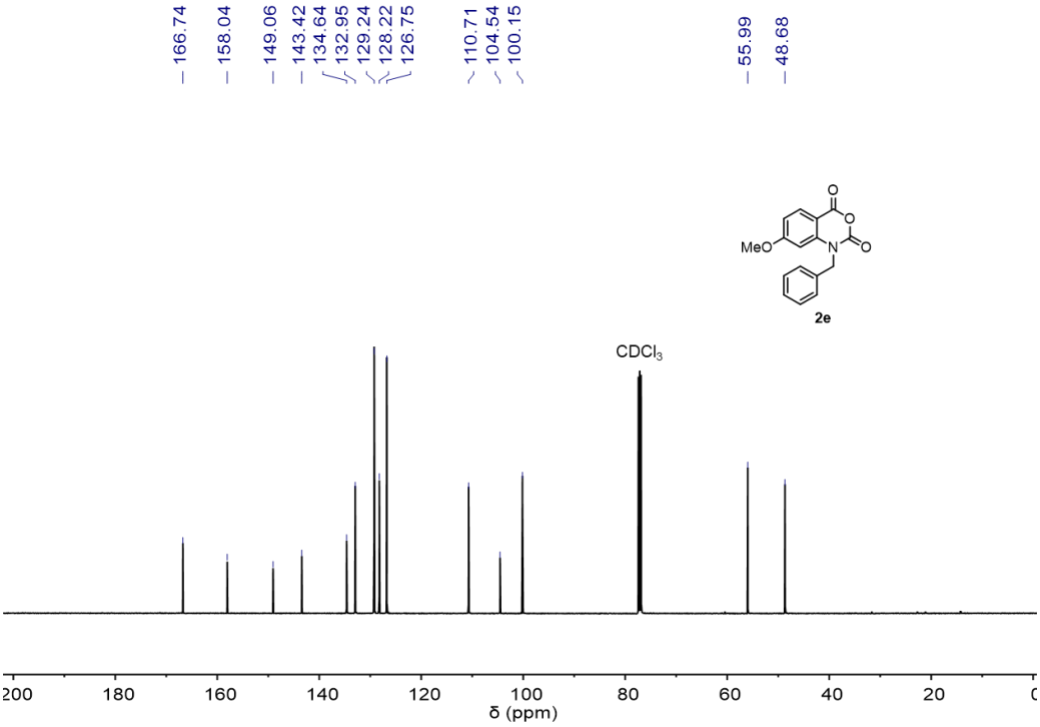


Figure S48. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **2e**.

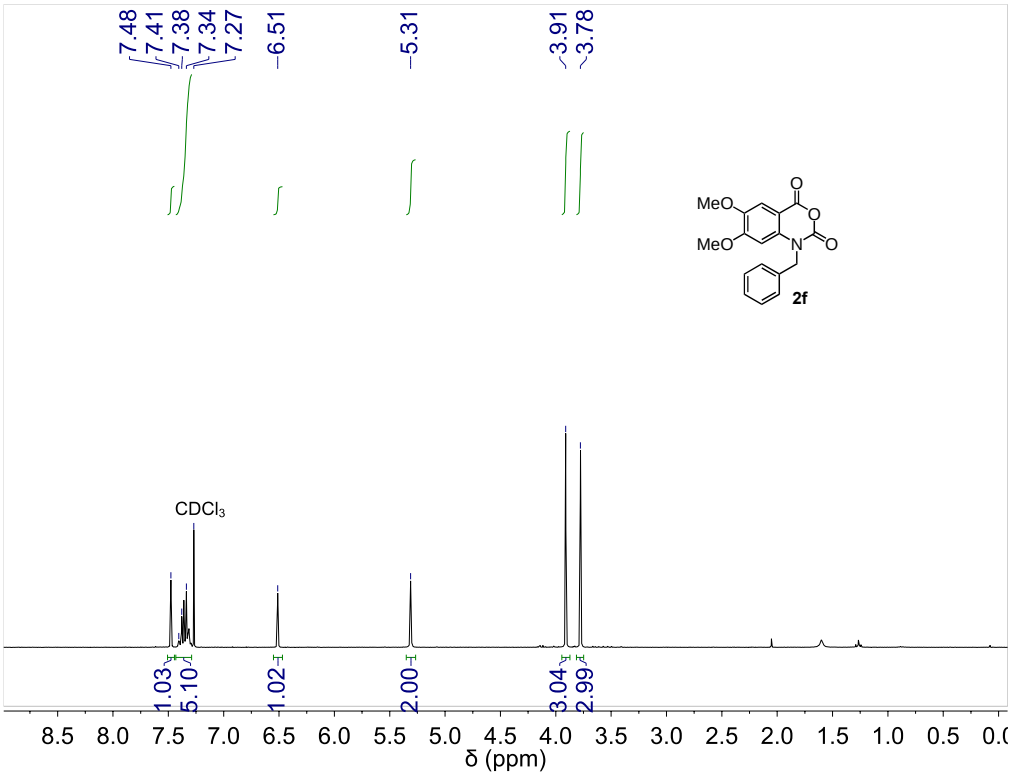


Figure S49. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **2f**.

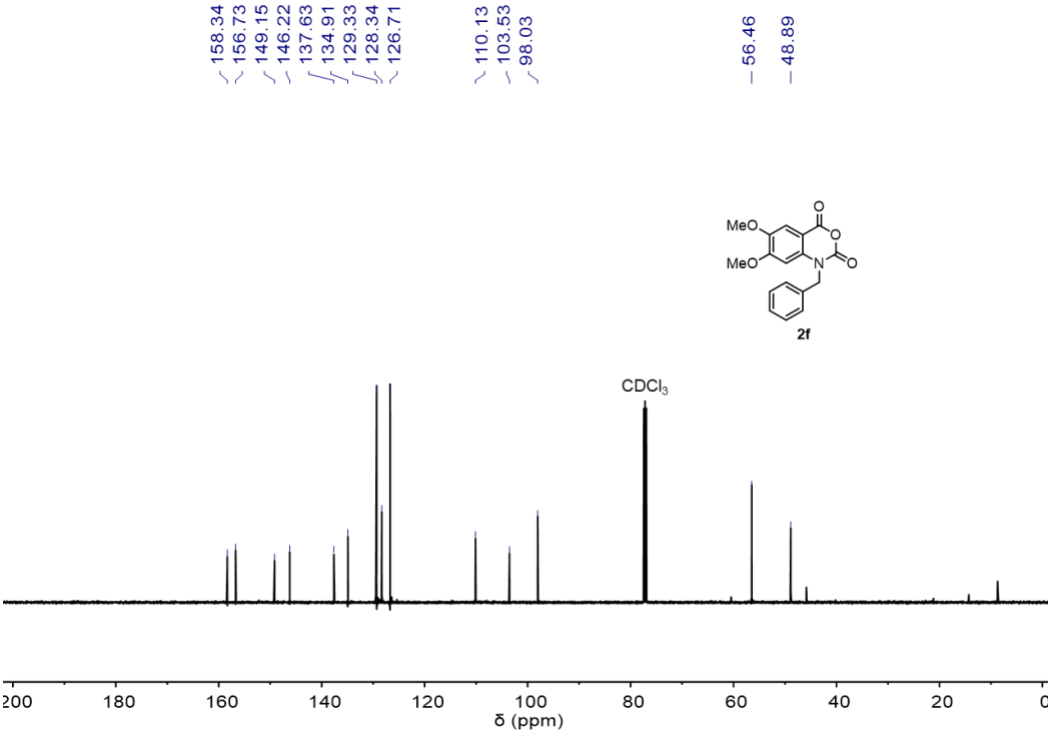


Figure S50. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **2f**.

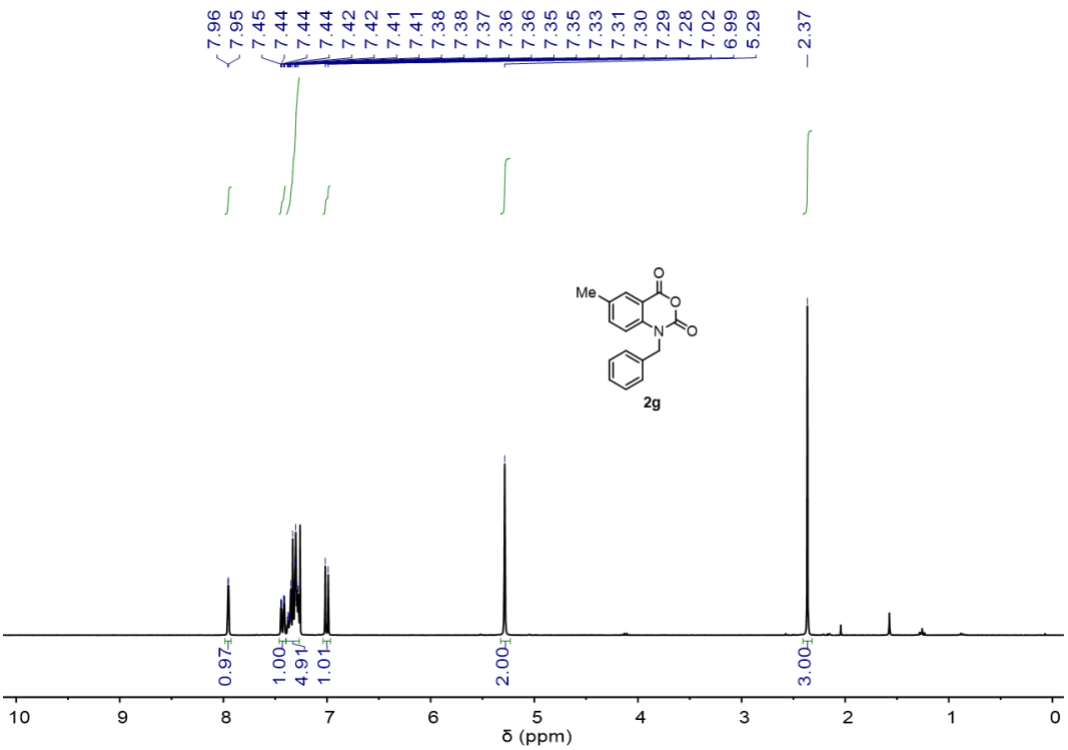


Figure S51. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **2g**.

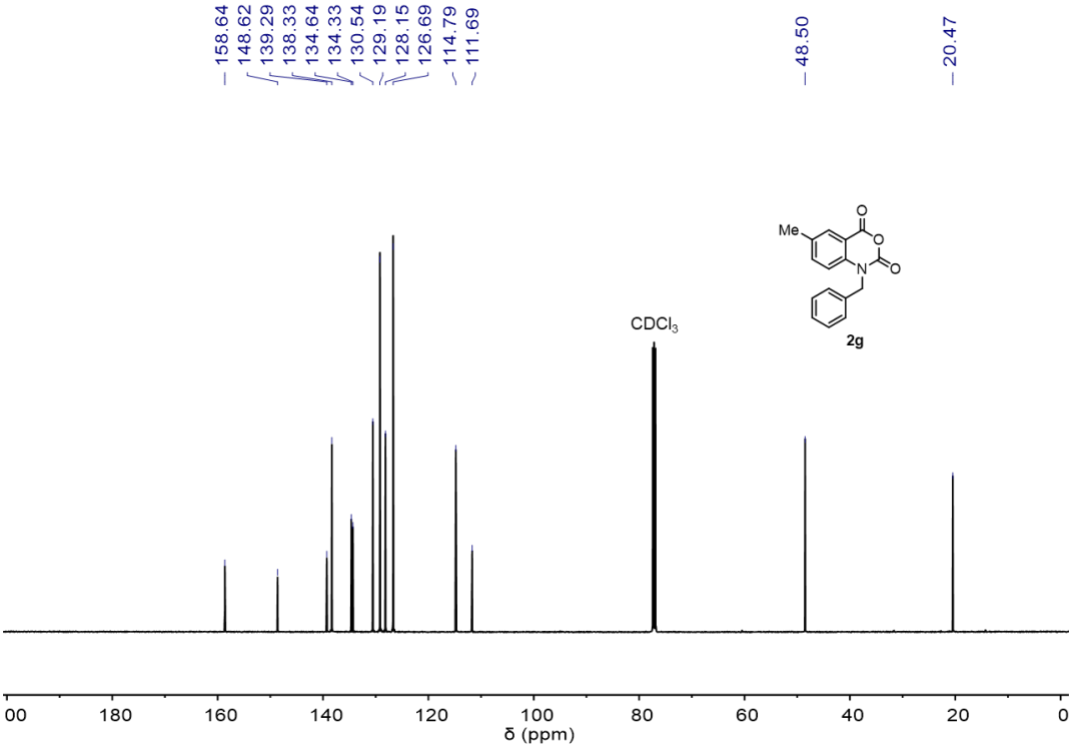


Figure S52. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **2g**.

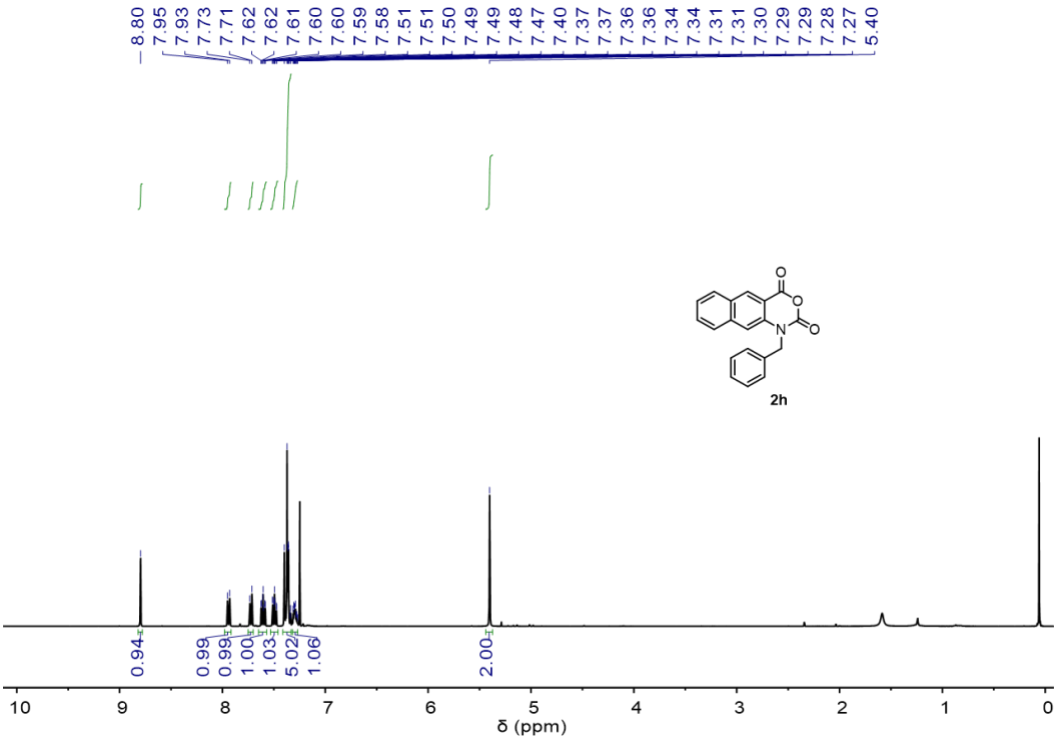


Figure S53. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **2h**.

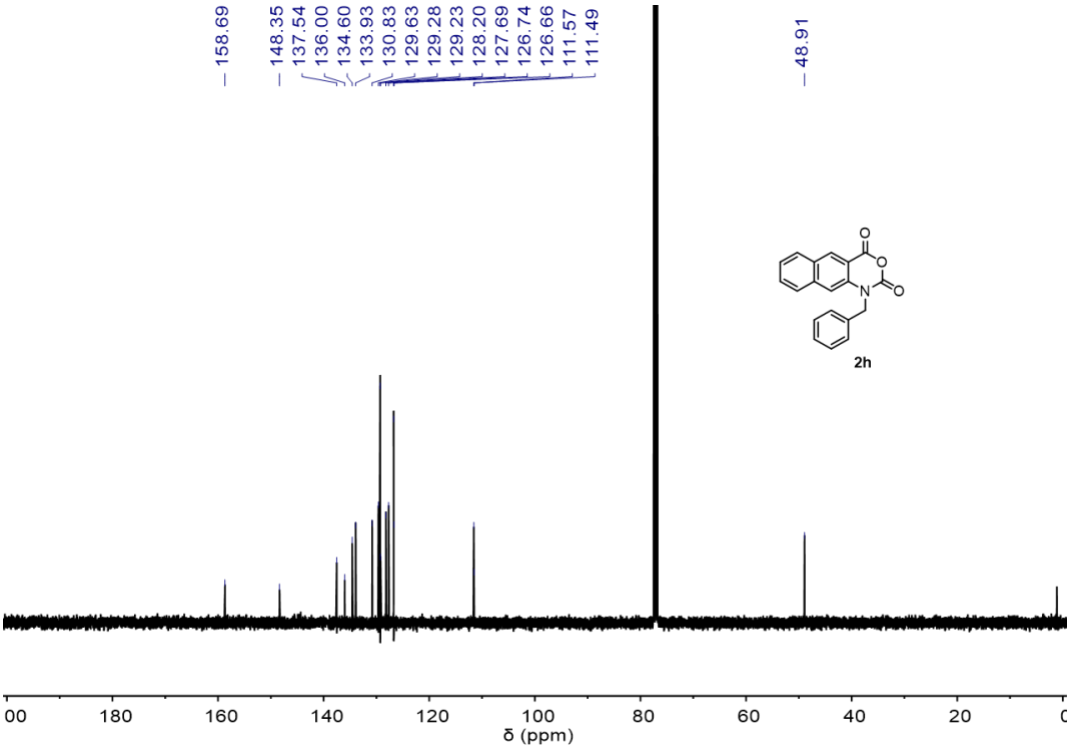


Figure S54. ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$) spectrum of compound **2h**.

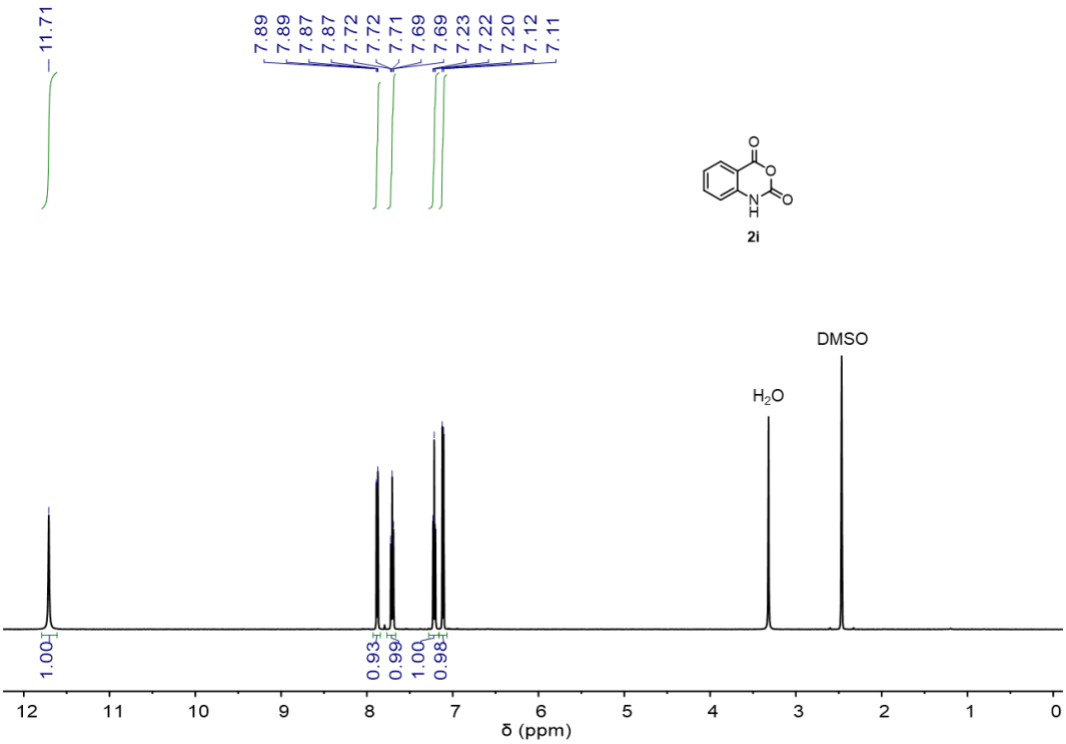


Figure S55. ^{1}H NMR (500 MHz, 25 °C, DMSO-d_6) spectrum of compound **2i**.

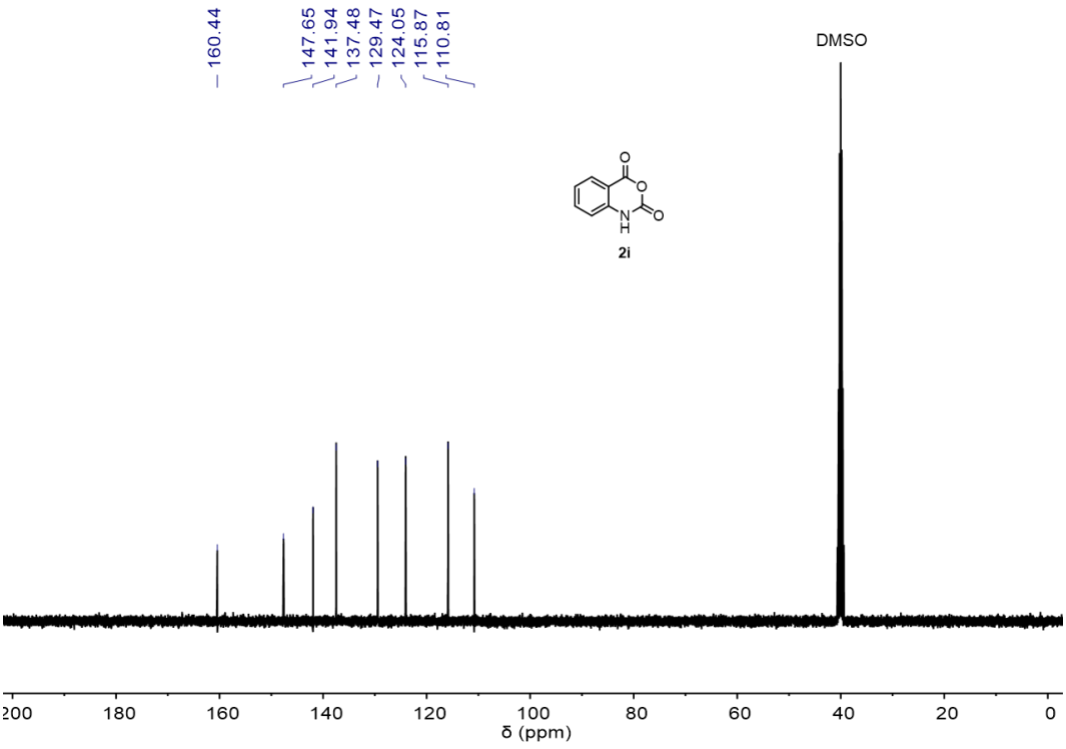


Figure S56. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2i**.

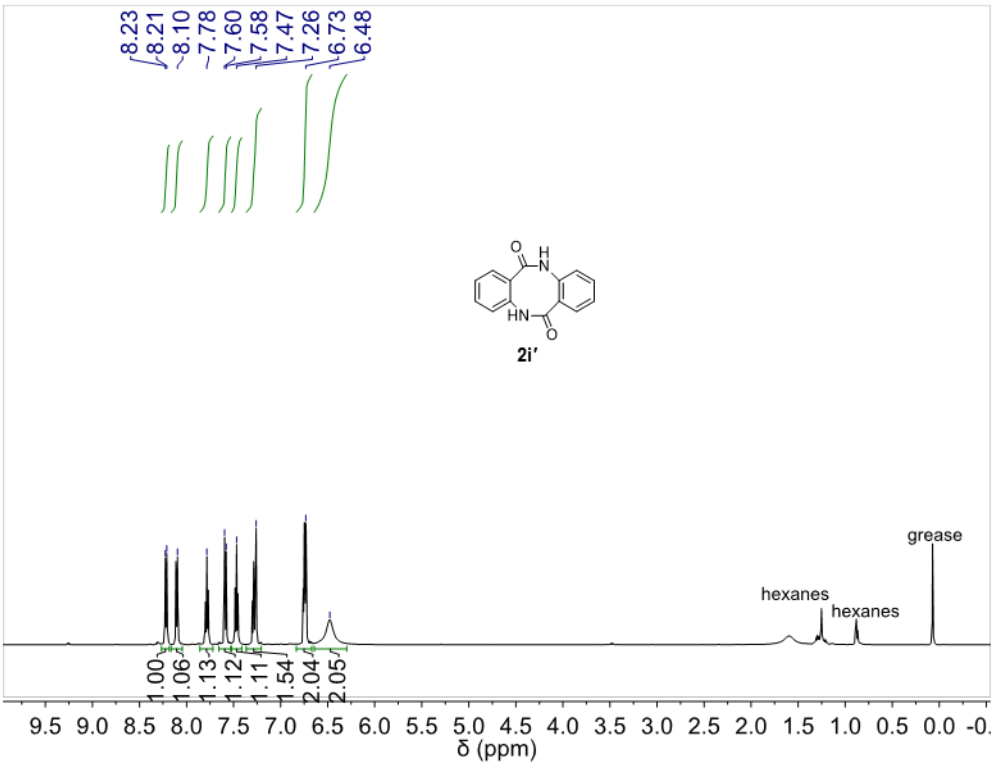


Figure S57. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2i′**.

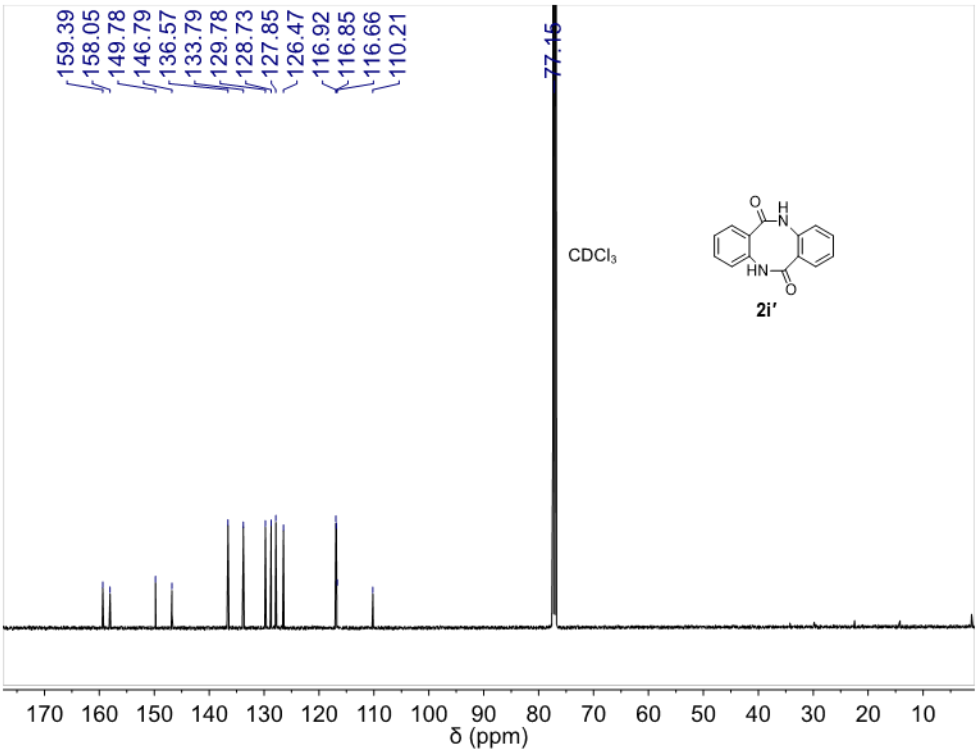


Figure S58. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **2i′**.

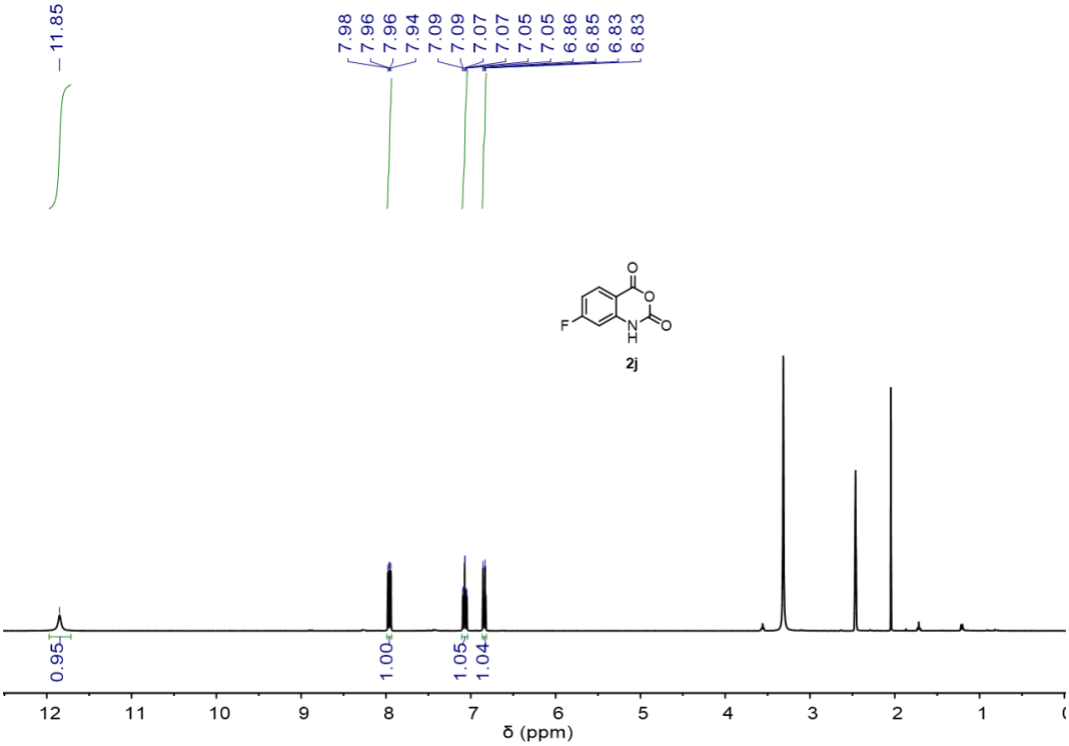


Figure S59. ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6) spectrum of compound **2j**.

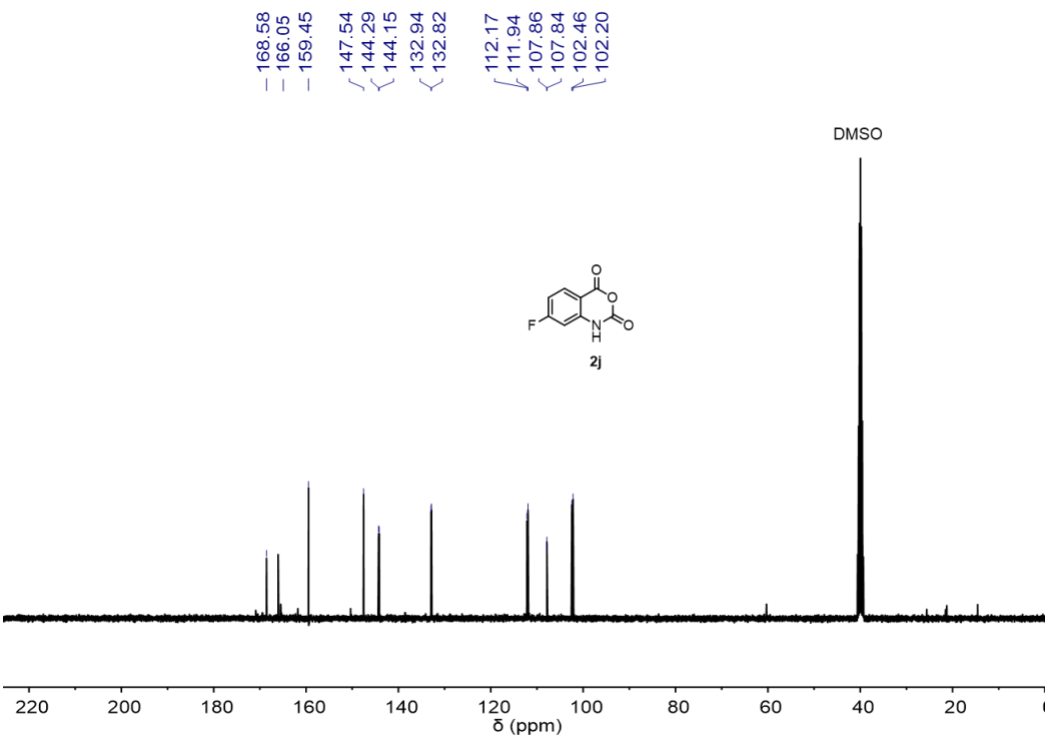


Figure S60. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2j**.

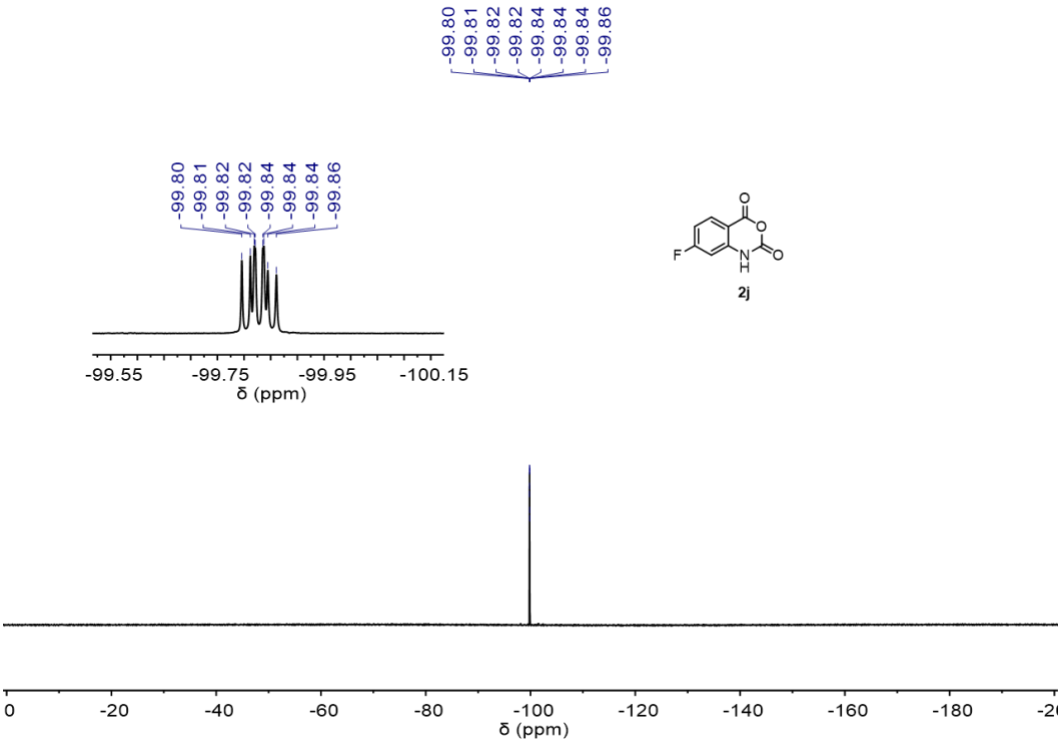


Figure S61. ^{19}F NMR (376 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **2j**.

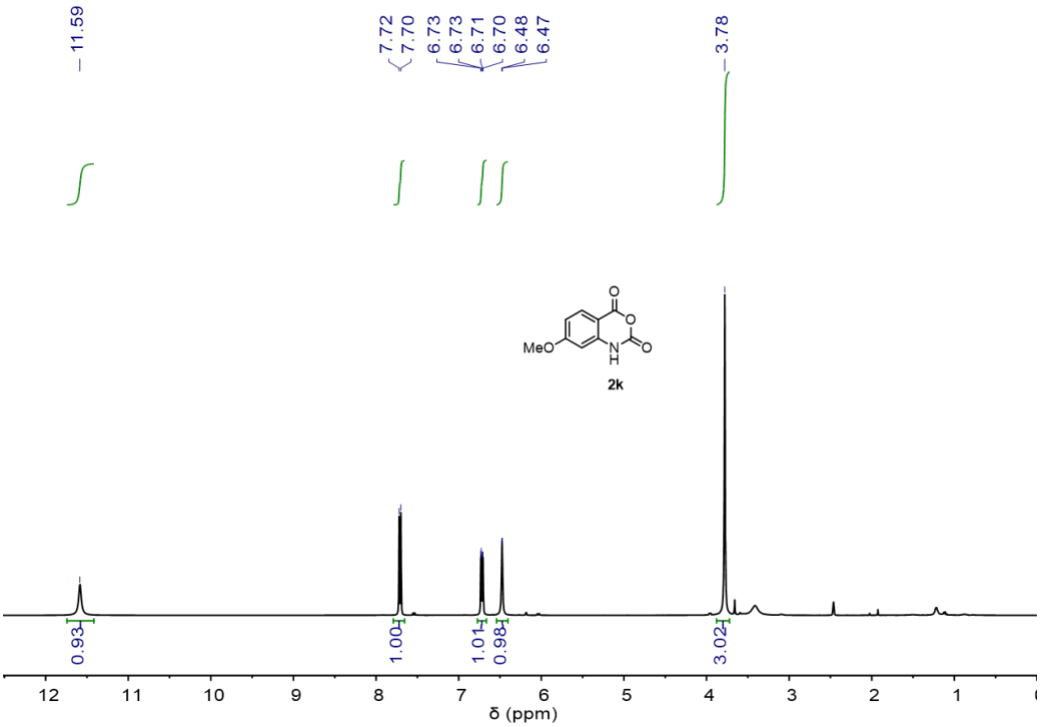


Figure S62. ^{1}H NMR (400 MHz, 25 ^{o}C, DMSO-d_6) spectrum of compound **2k**.

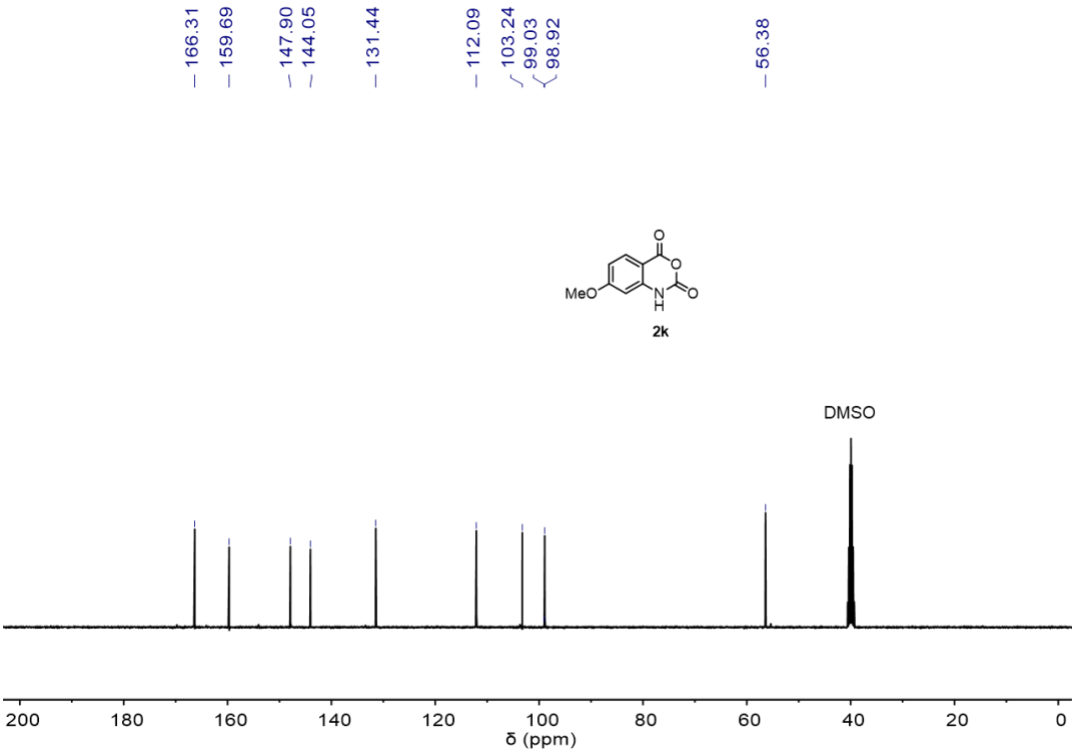


Figure S63. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2k**.

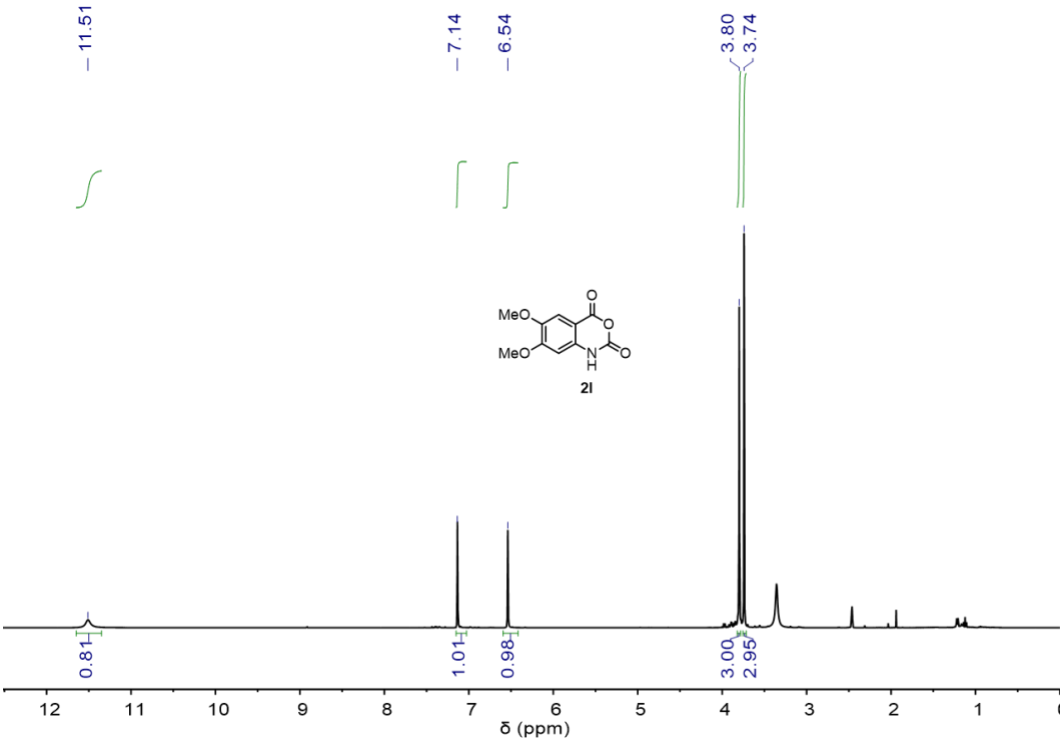


Figure S64. ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6) spectrum of compound **2l**.

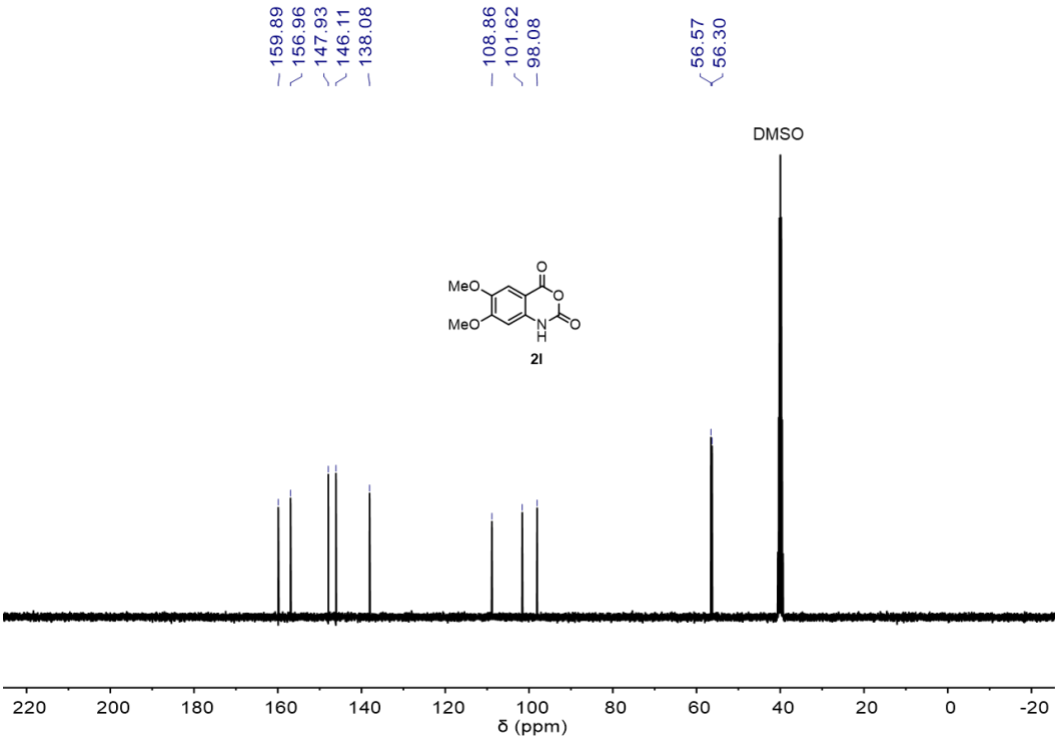


Figure S65. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2l**.

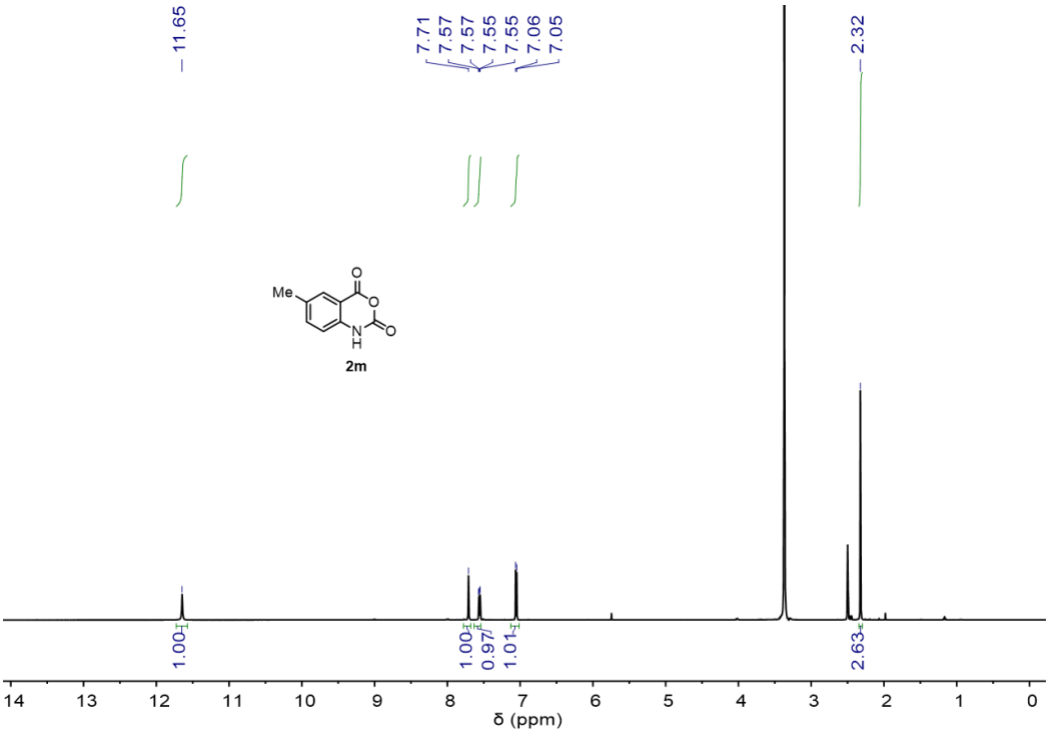


Figure S66. ^{1}H NMR (500 MHz, 25 °C, DMSO-d_6) spectrum of compound **2m**. The peak at ~3.4 ppm is water.

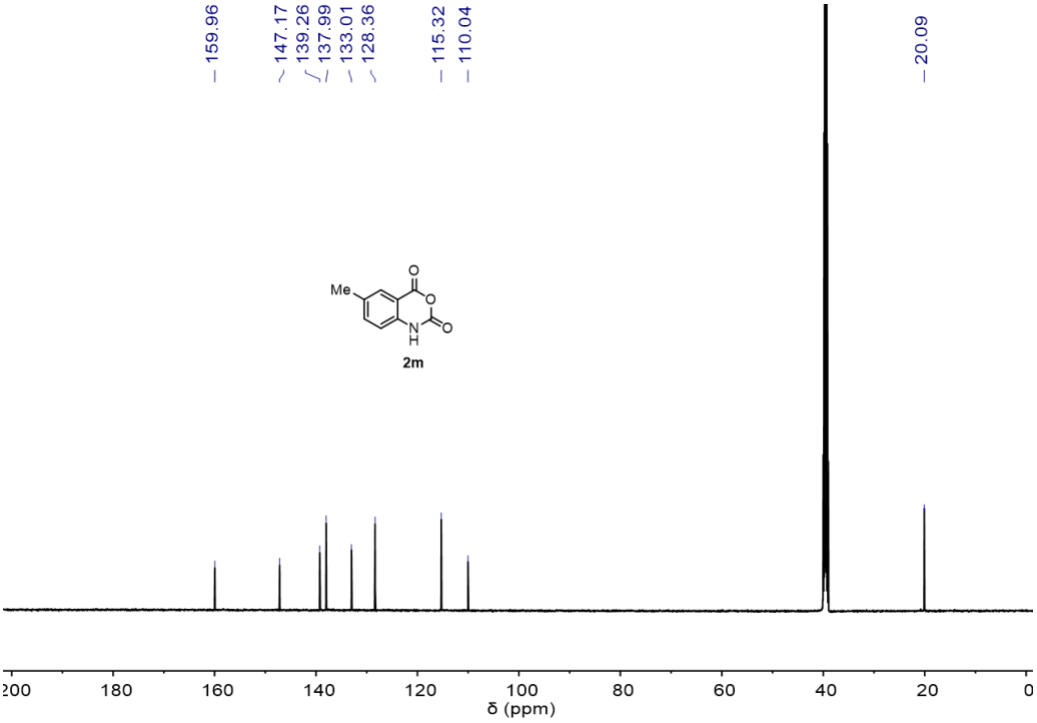


Figure S67. ^{13}C NMR (126 MHz, 25 °C, DMSO-d_6) spectrum of compound **2m**.

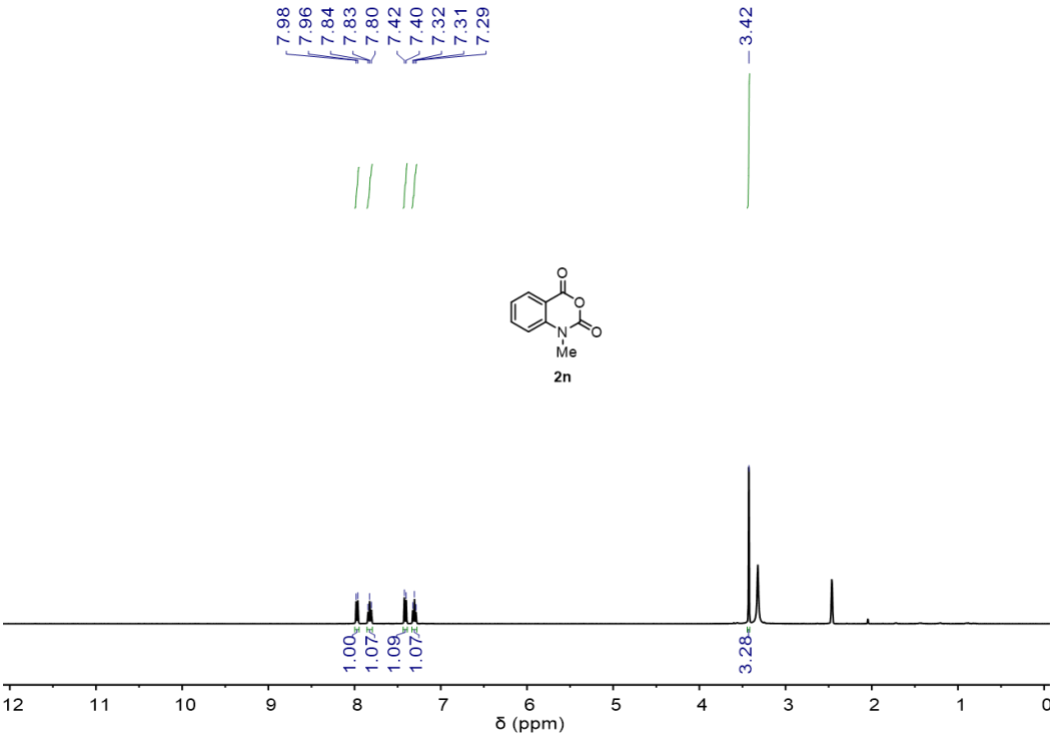


Figure S68. ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6) spectrum of compound **2n**.

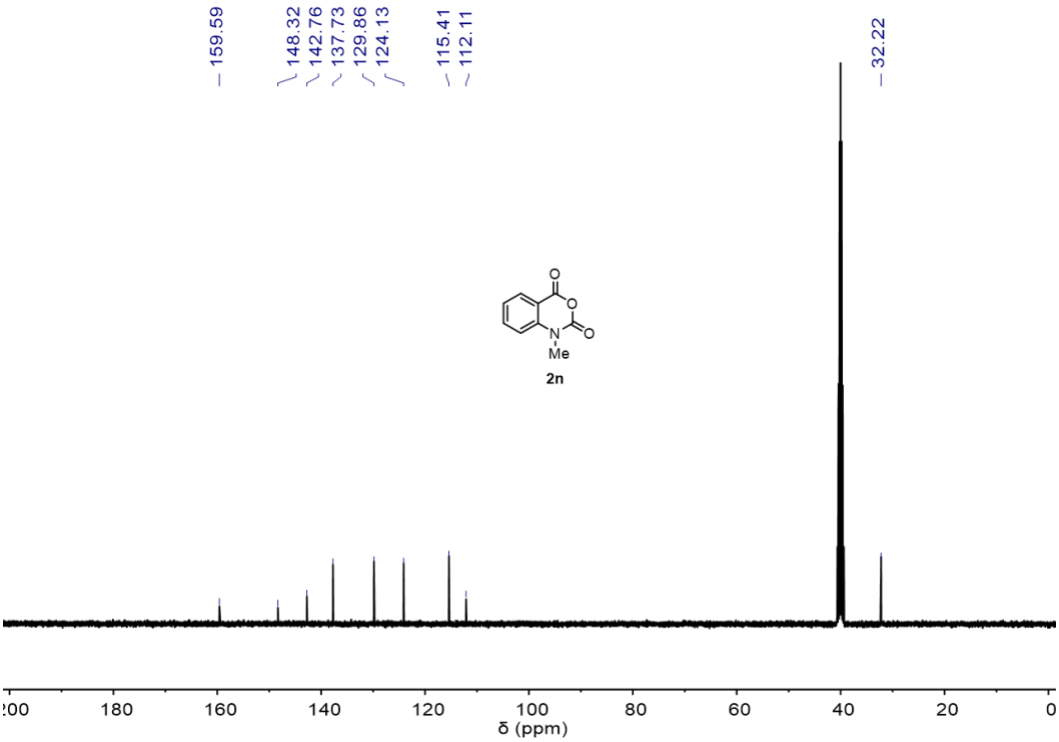


Figure S69. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2n**.

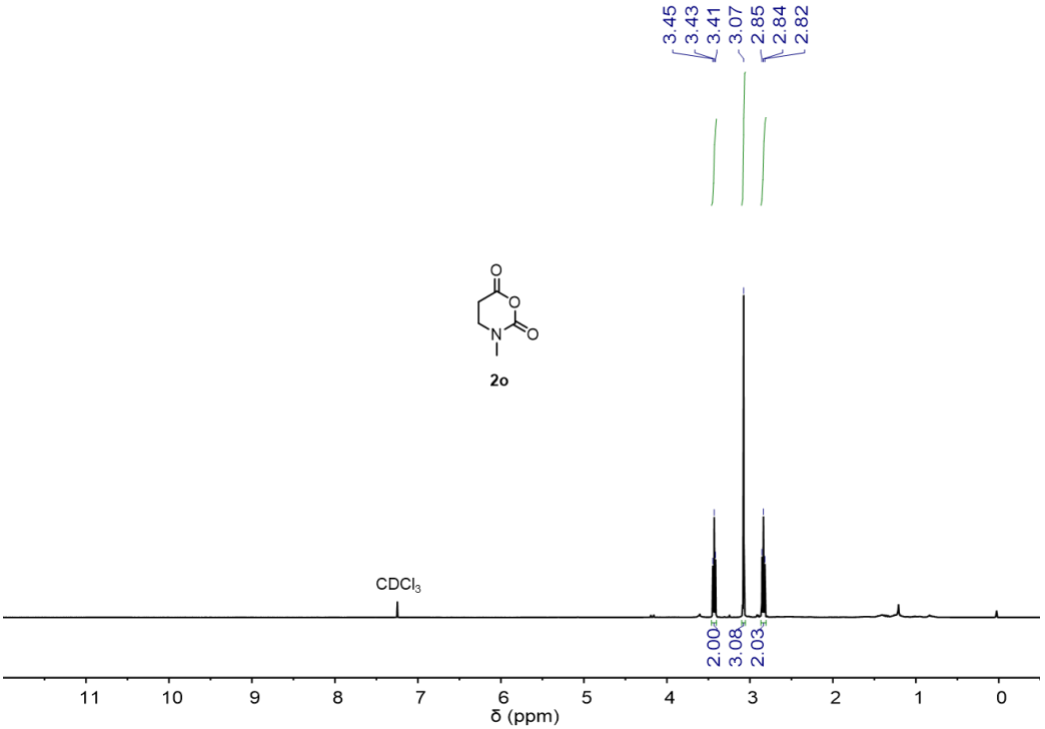


Figure S70. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **2o**.

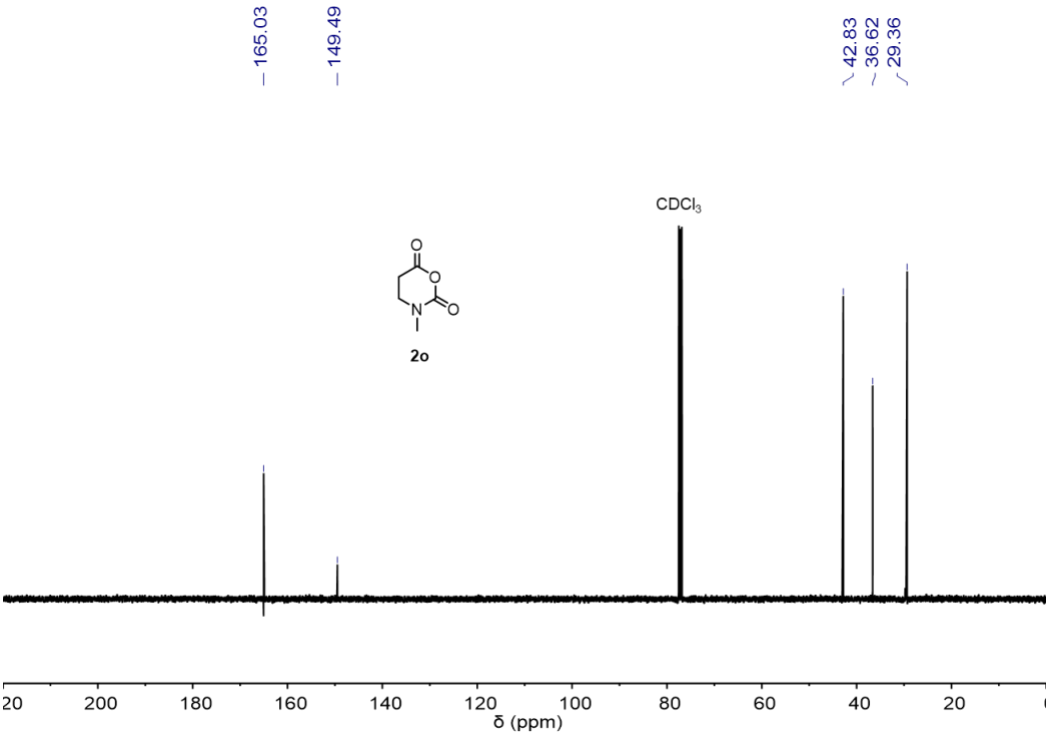


Figure S71. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **2o**.

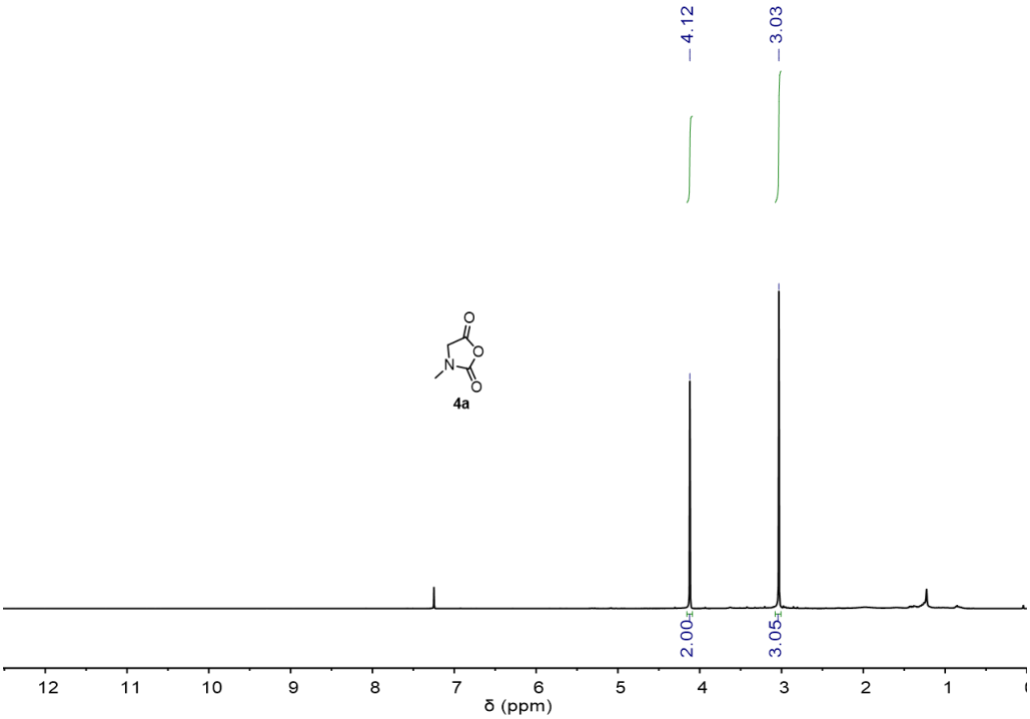


Figure S72. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **4a**.

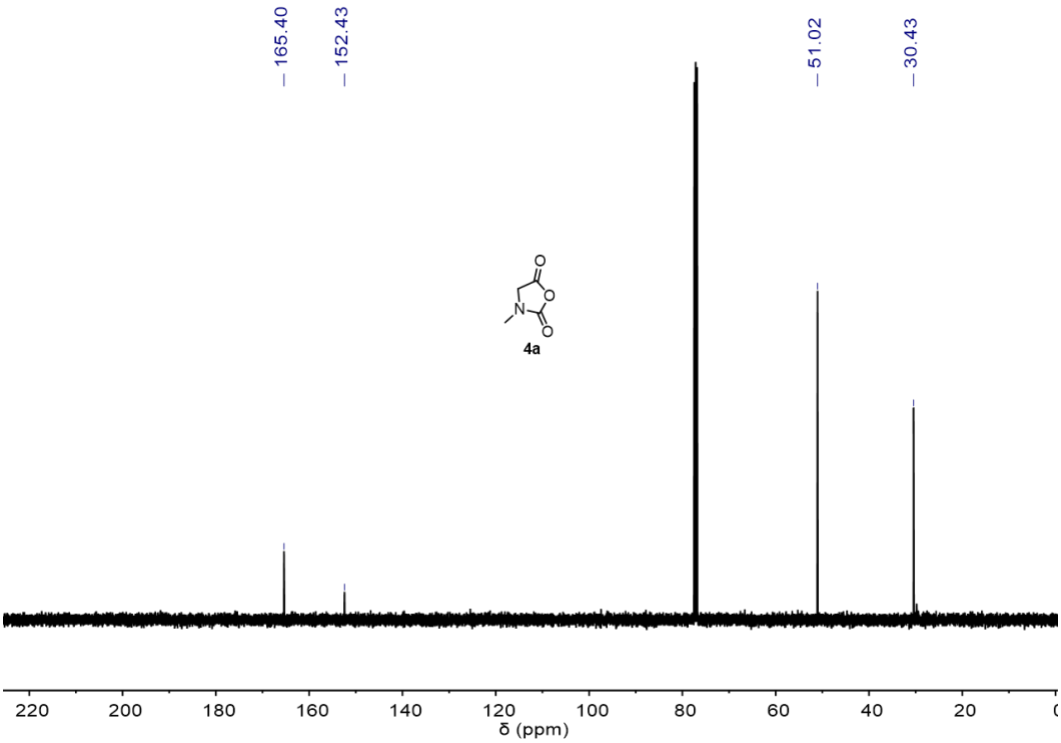


Figure S73. ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$) spectrum of compound **4a**.

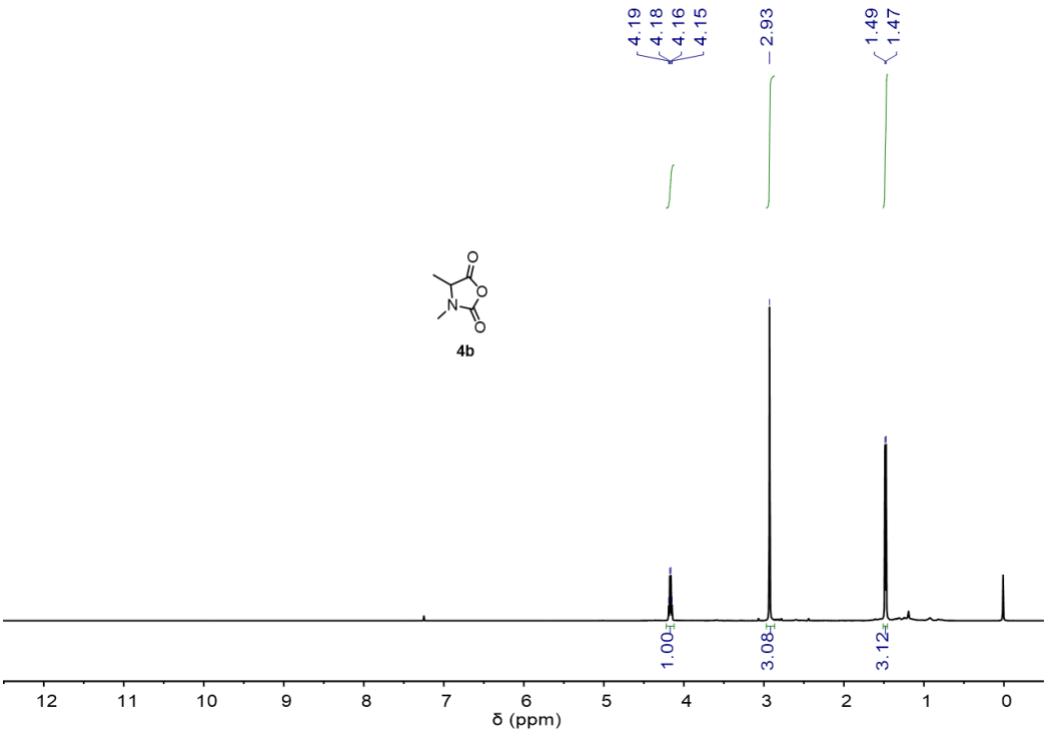


Figure S74. ^{1}H NMR (500 MHz, 25 °C, $CDCl_3$) spectrum of compound **4b**.

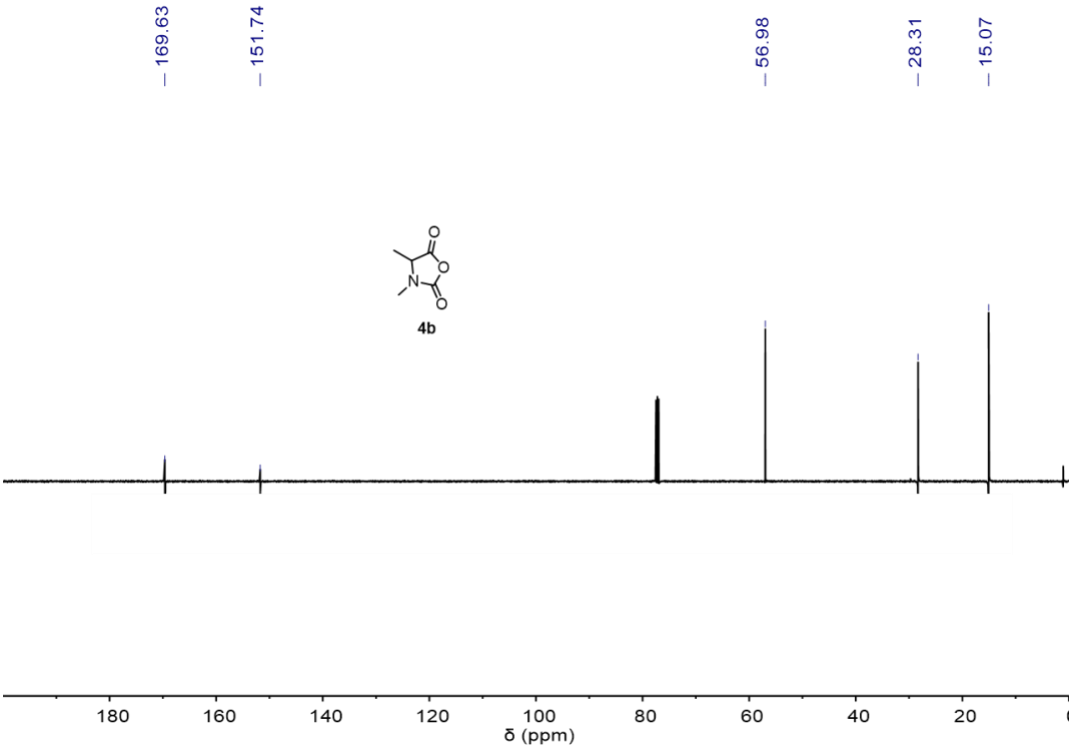


Figure S75. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **4b**.

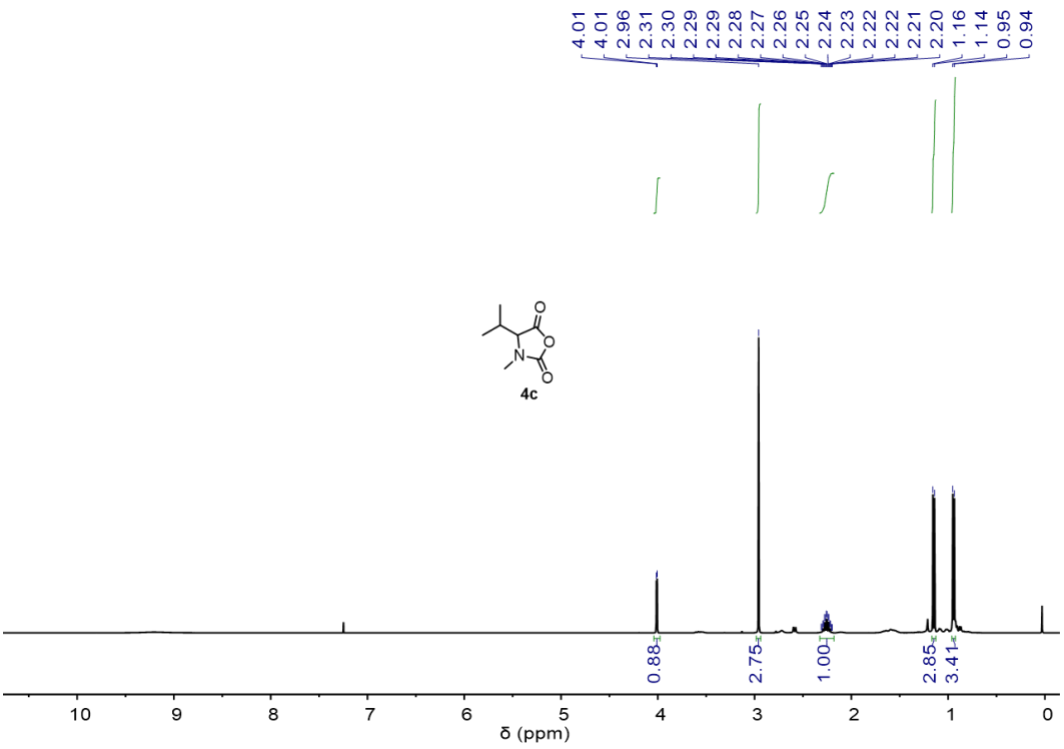


Figure S76. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **4c**.

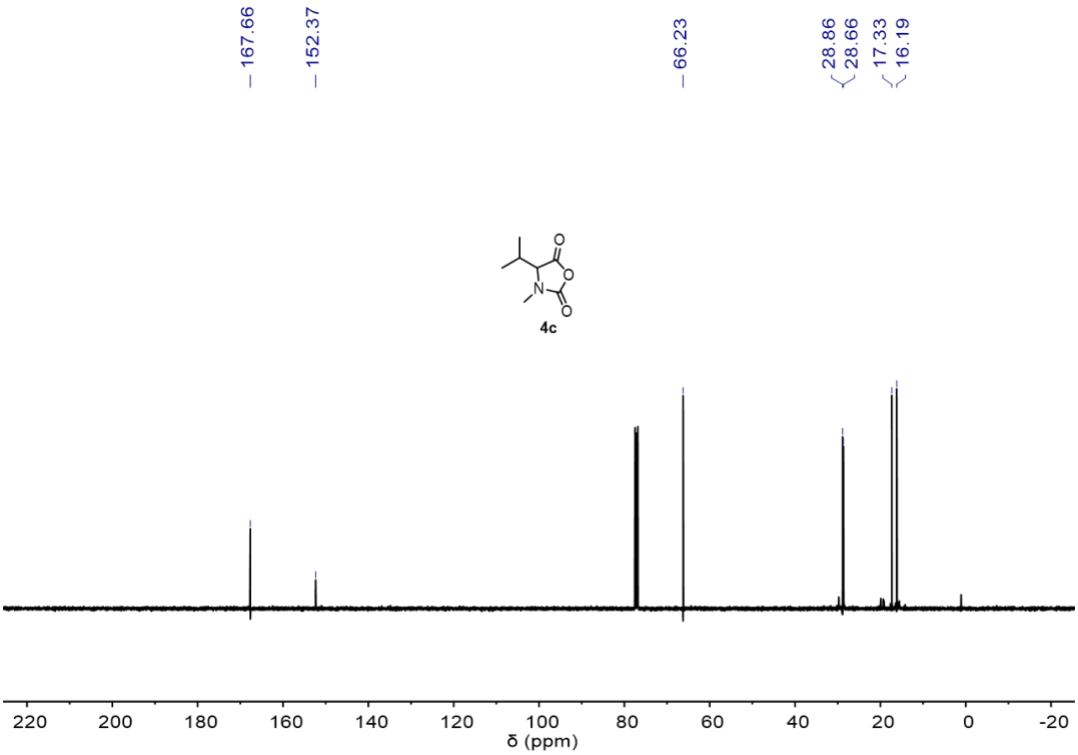


Figure S77. ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$) spectrum of compound **4c**.

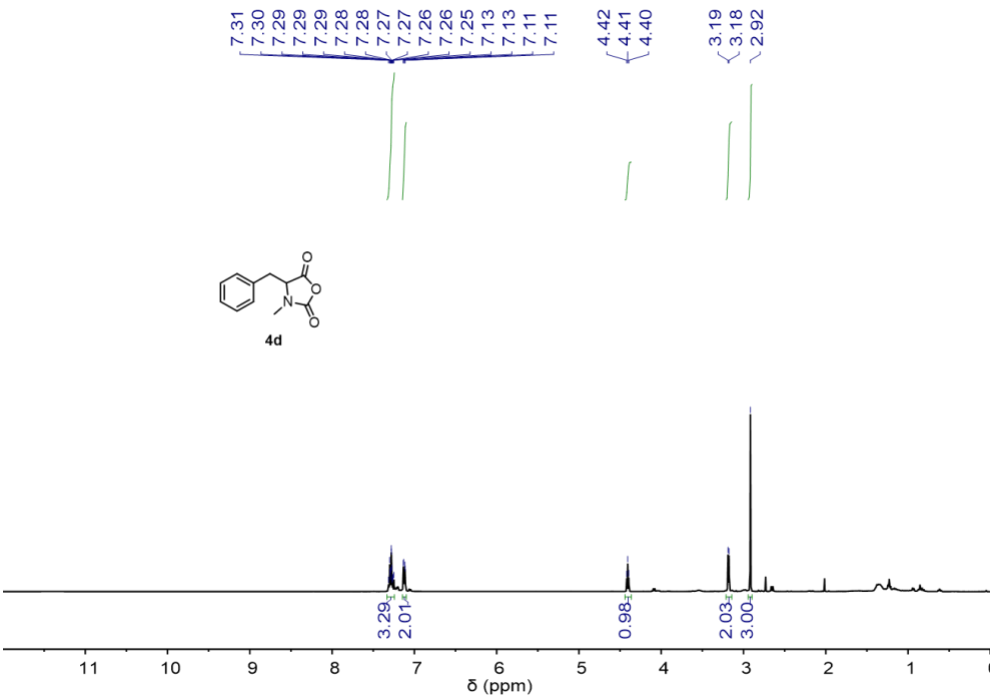


Figure S78. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4d.** This compound is prone to polymerization.

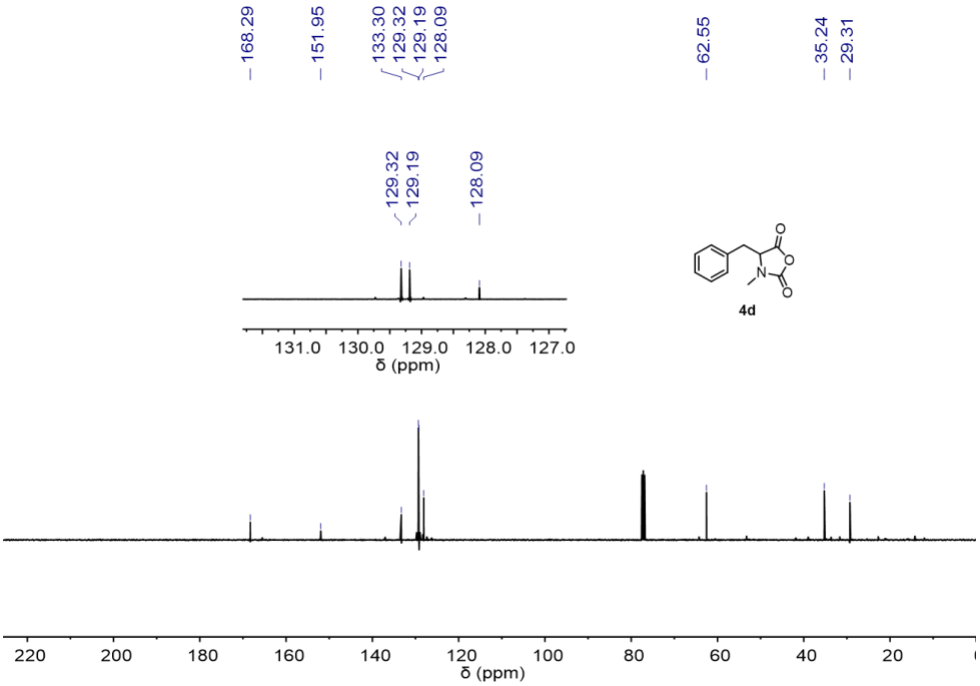


Figure S79. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4d**. This compound is prone to polymerization.

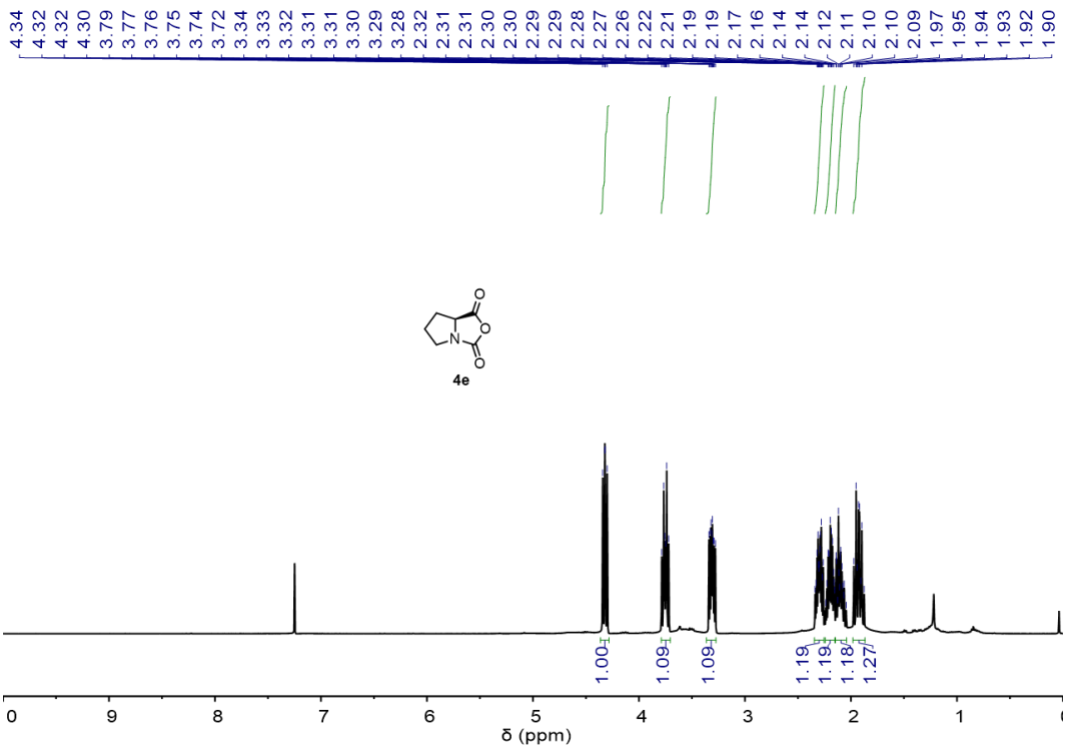


Figure S80. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4e**.

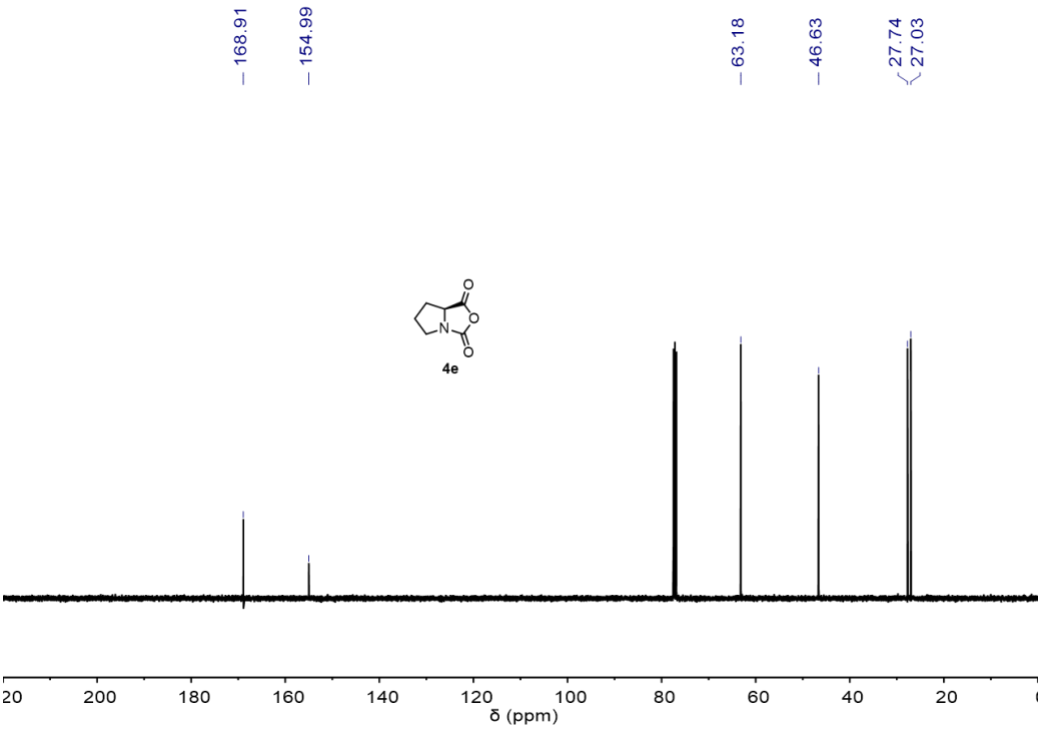


Figure S81. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4e**.

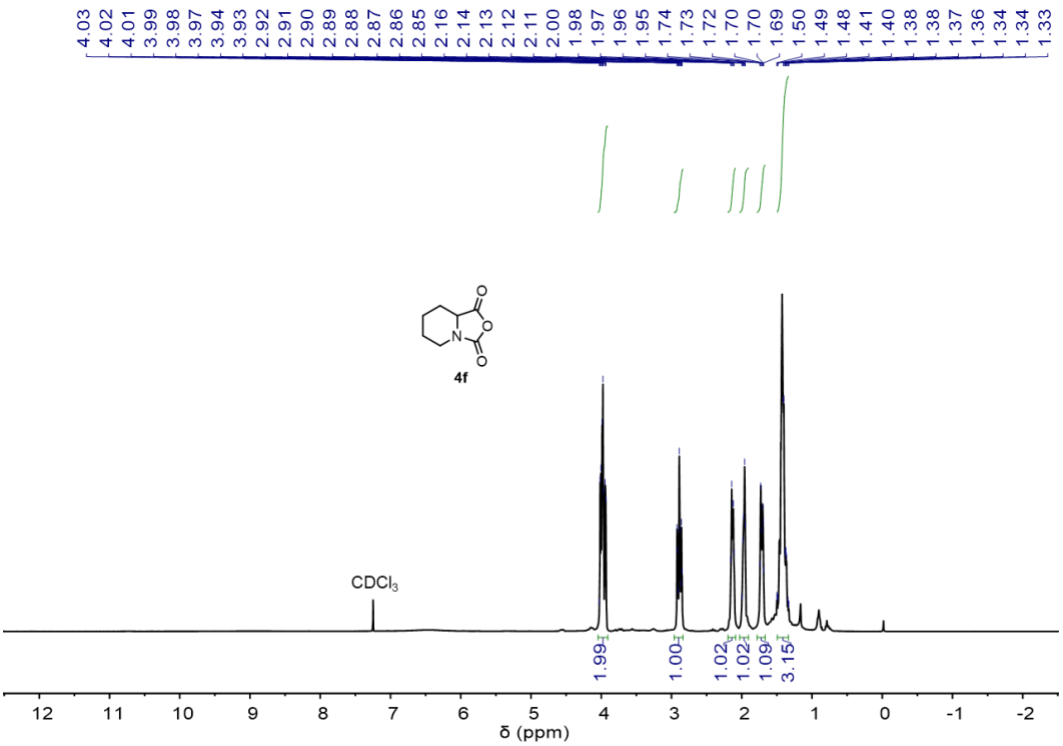


Figure S82. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4f**.

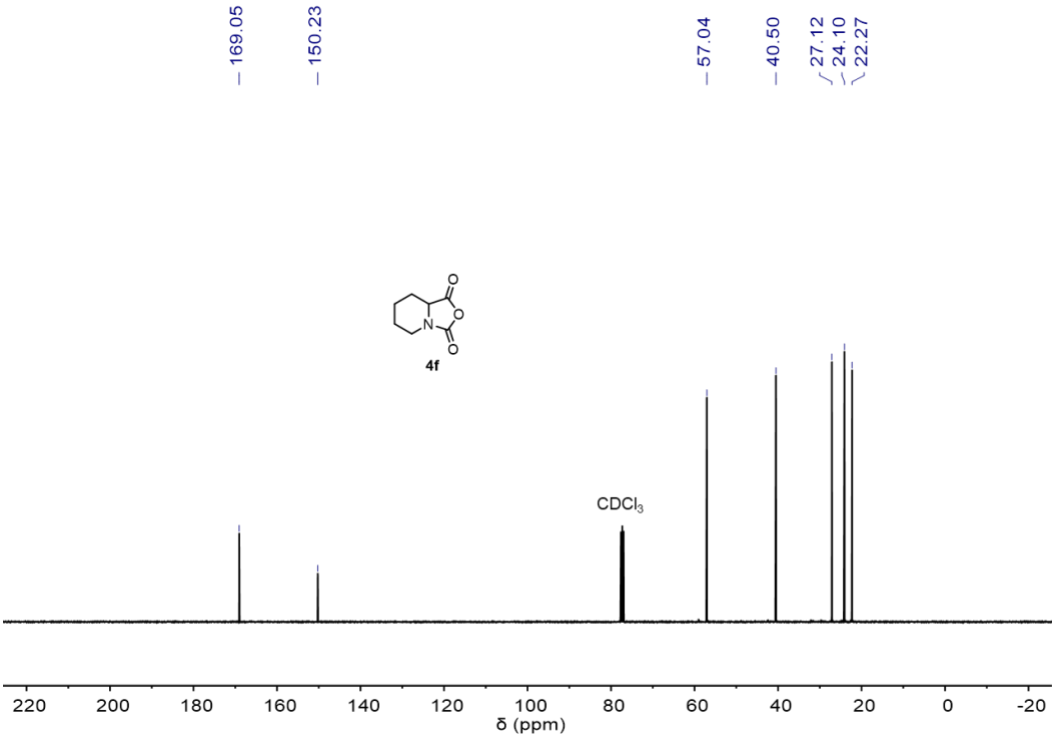


Figure S83. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4f**.

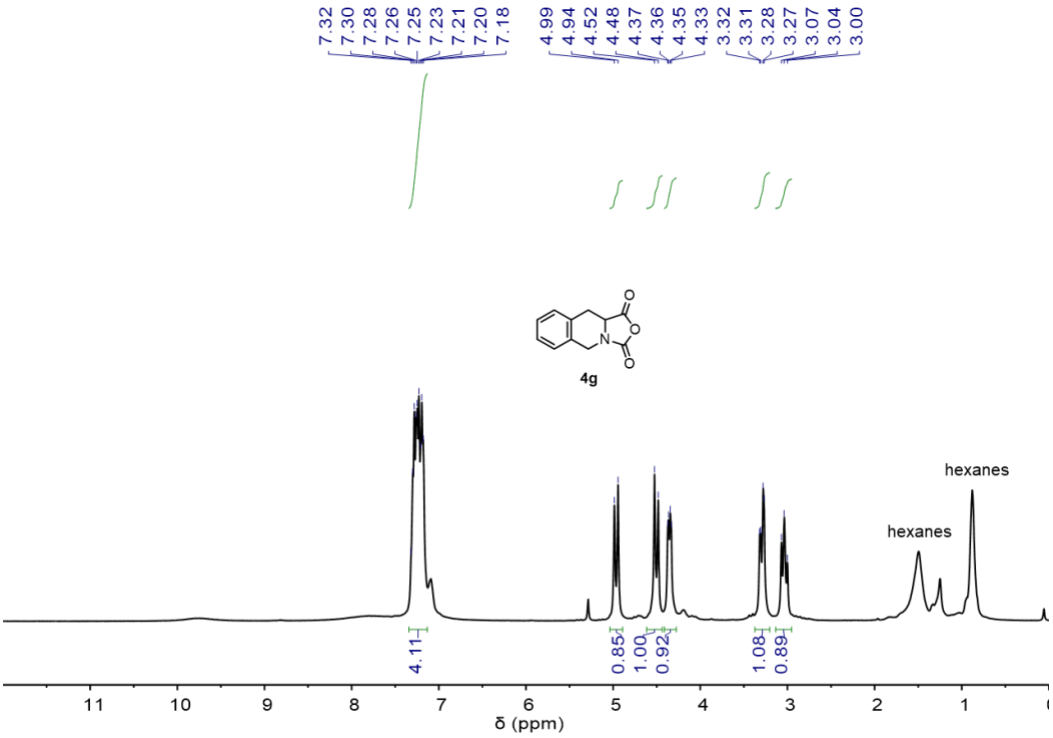


Figure S84. ^{1}H NMR (400 MHz, 25 ºC, $CDCl_3$) spectrum of compound **4g**.

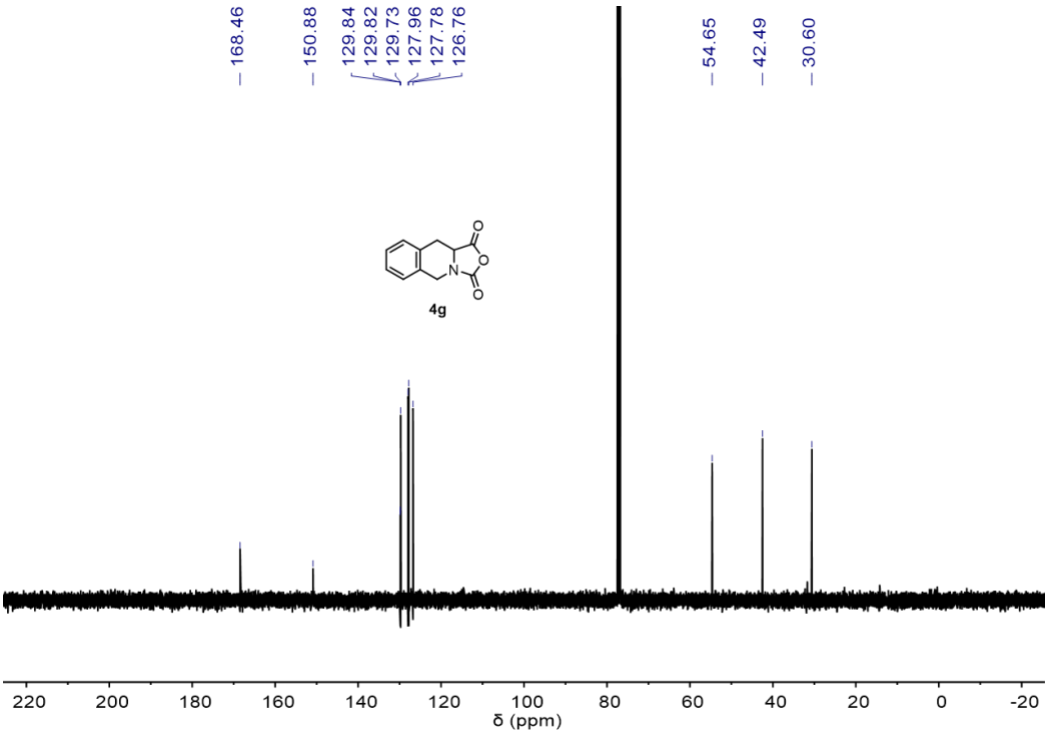


Figure S85. ^{13}C NMR (101 MHz, 25 ºC, $CDCl_3$) spectrum of compound **4g**.

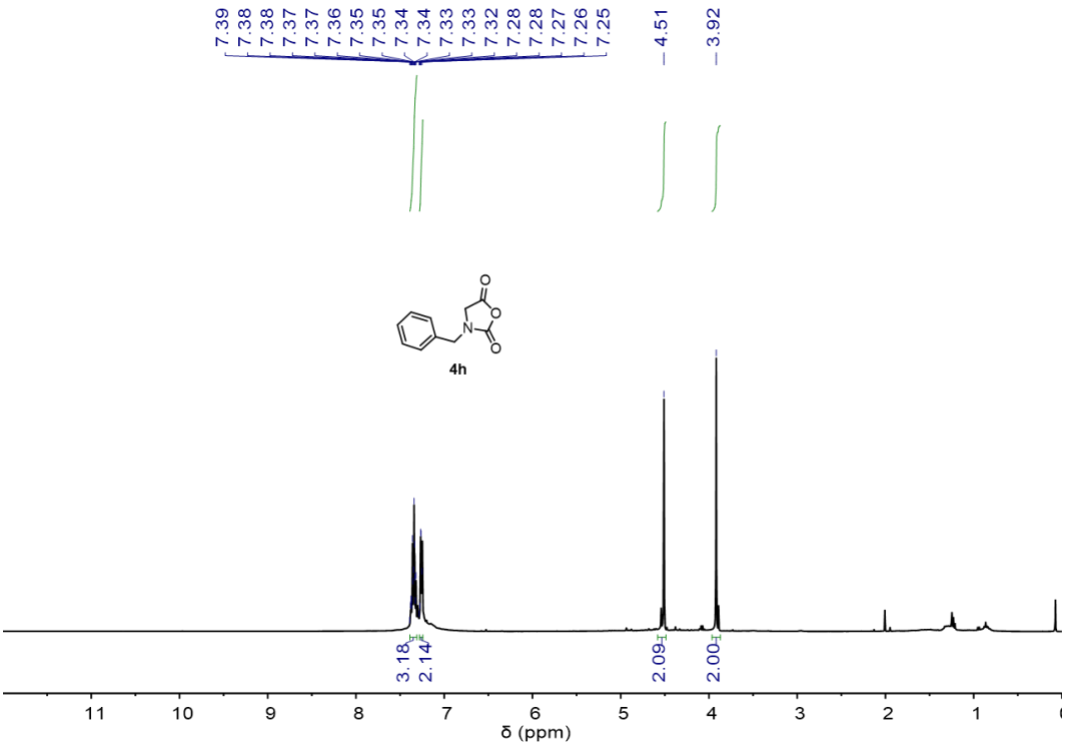


Figure S86. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4h**.

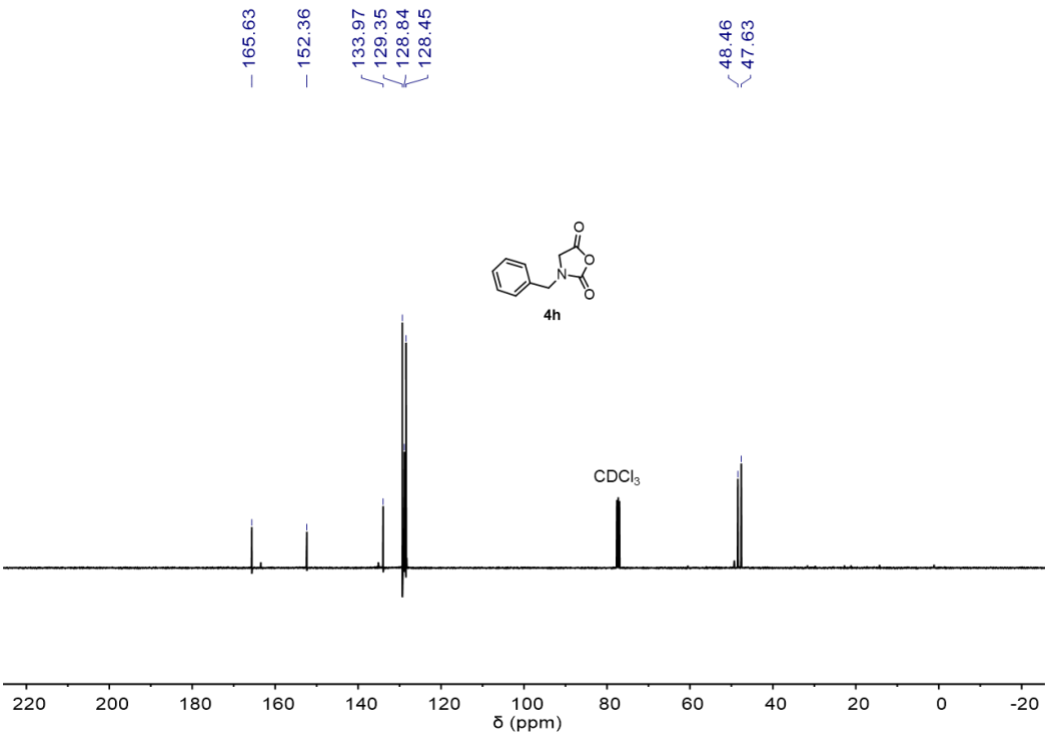


Figure S87. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4h**.

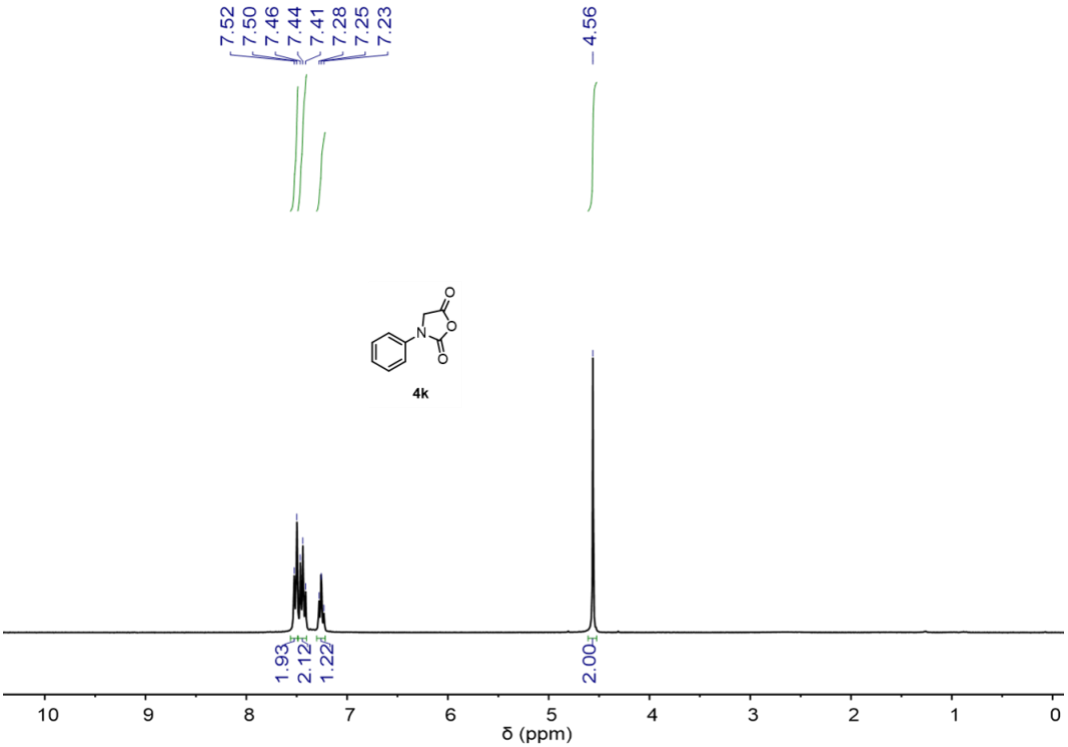


Figure S88. ^{1}H NMR (300 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4k**.

Fg

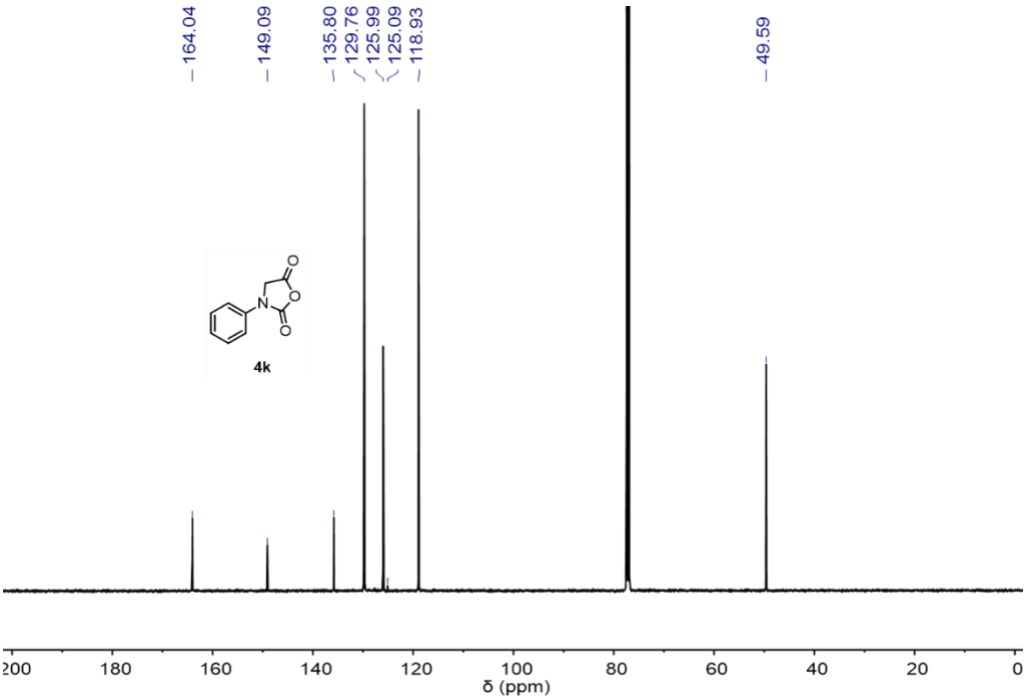


Figure S89. ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **4k**.

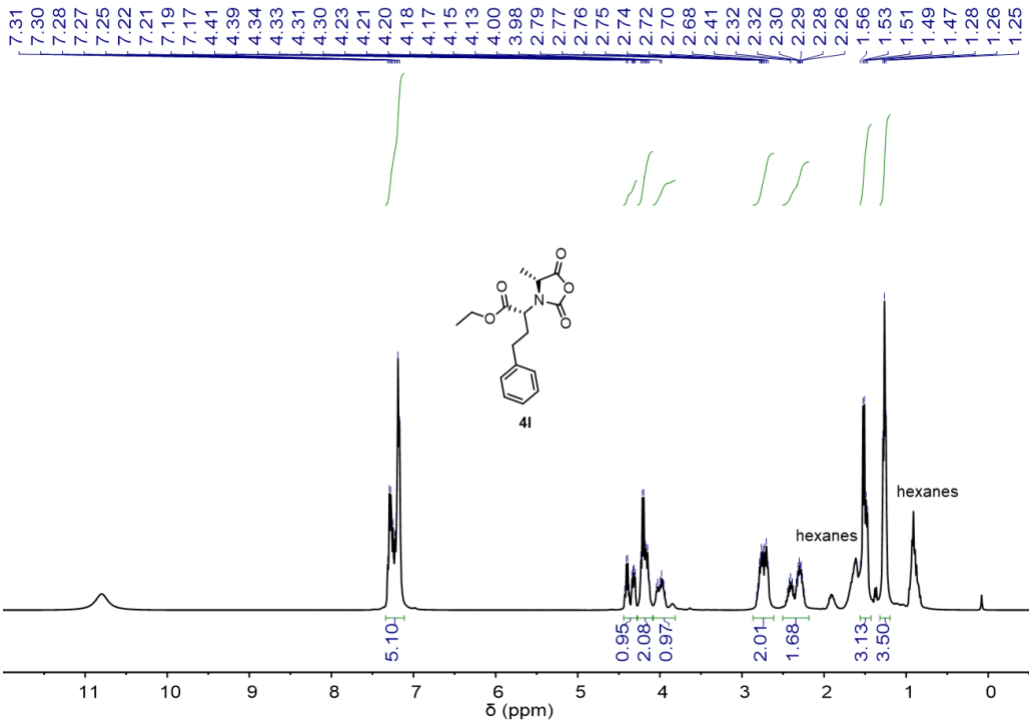


Figure S90. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **4l**. This product may contain a small amount of the epimerized diastereomer.

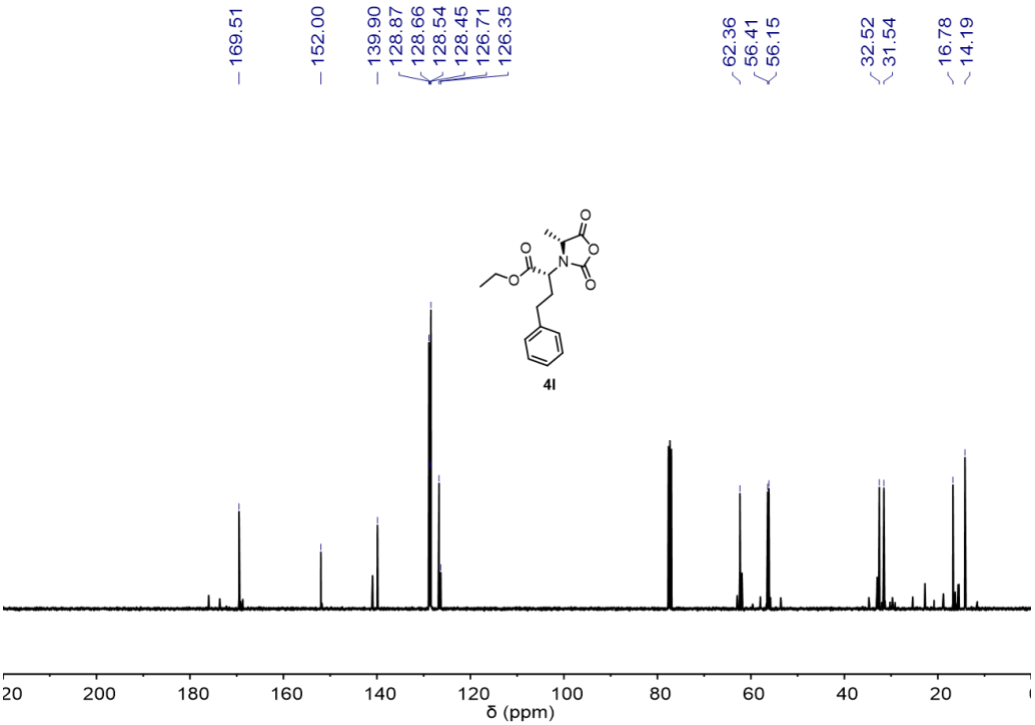


Figure S91. ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$) spectrum of compound **4l**. This product may contain a small amount of the epimerized diastereomer.

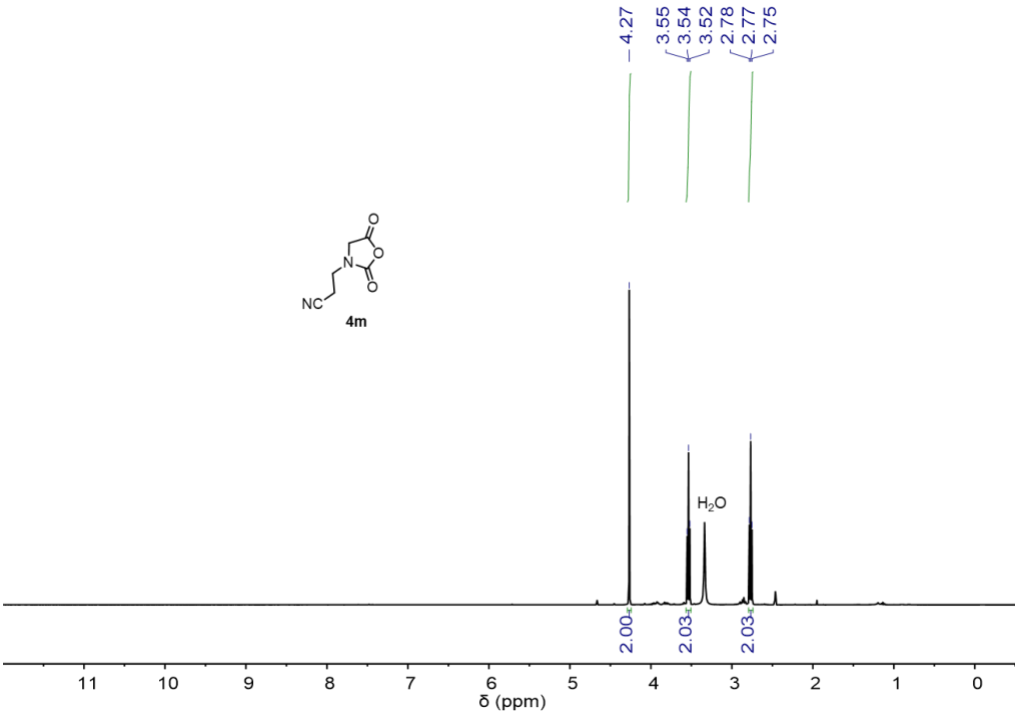


Figure S92. ^{1}H NMR (400 MHz, 25 °C, DMSO-d_6) spectrum of compound **4m**.

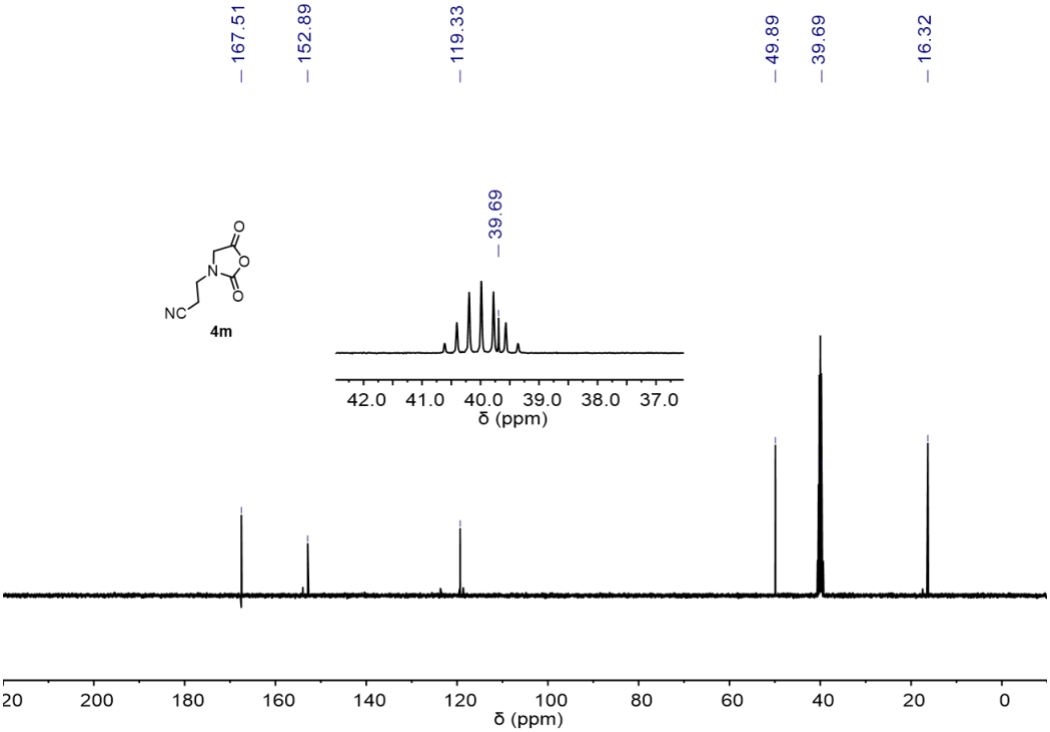


Figure S93. ^{13}C NMR (101 MHz, 25 °C, DMSO-d_6) spectrum of compound **4m**.

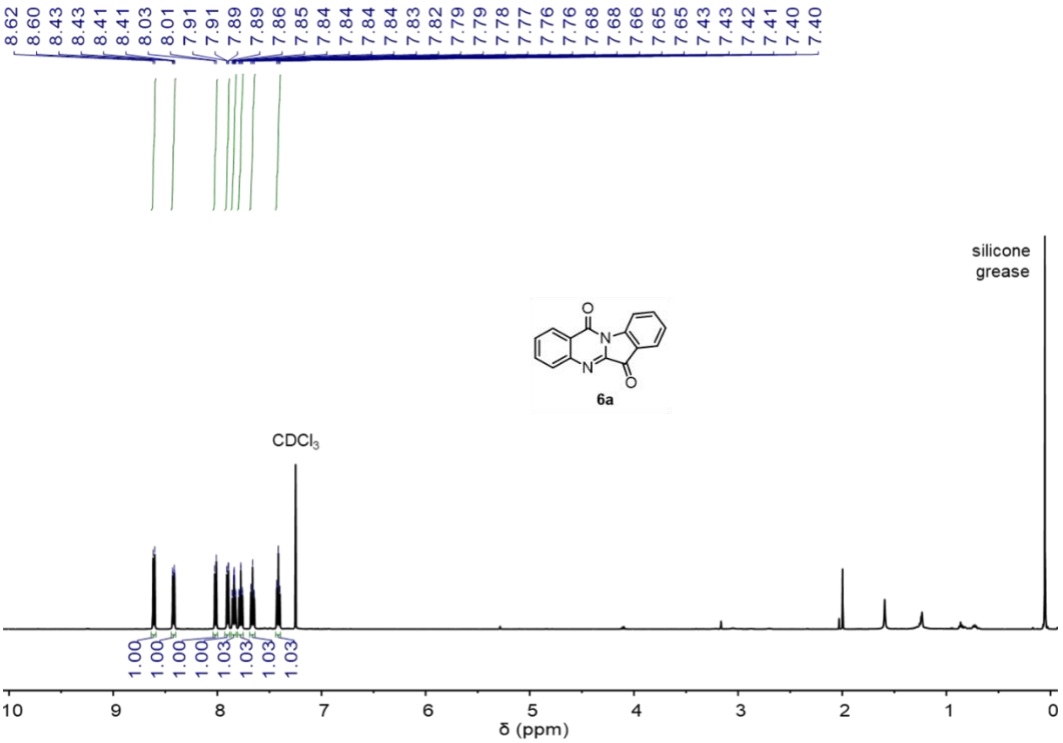


Figure S94. ^{1}H NMR (500 MHz, 25 ºC, $CDCl_3$) spectrum of compound **6a**.

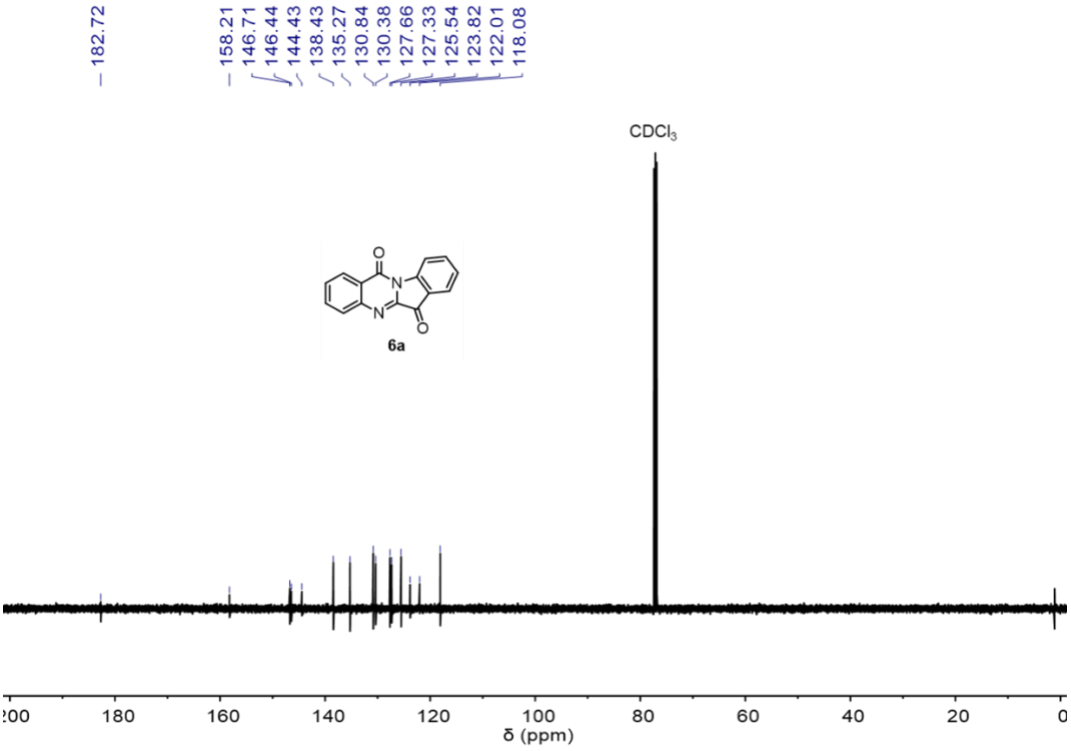


Figure S95. ^{13}C NMR (126 MHz, 25 ºC, $CDCl_3$) spectrum of compound **6a**.

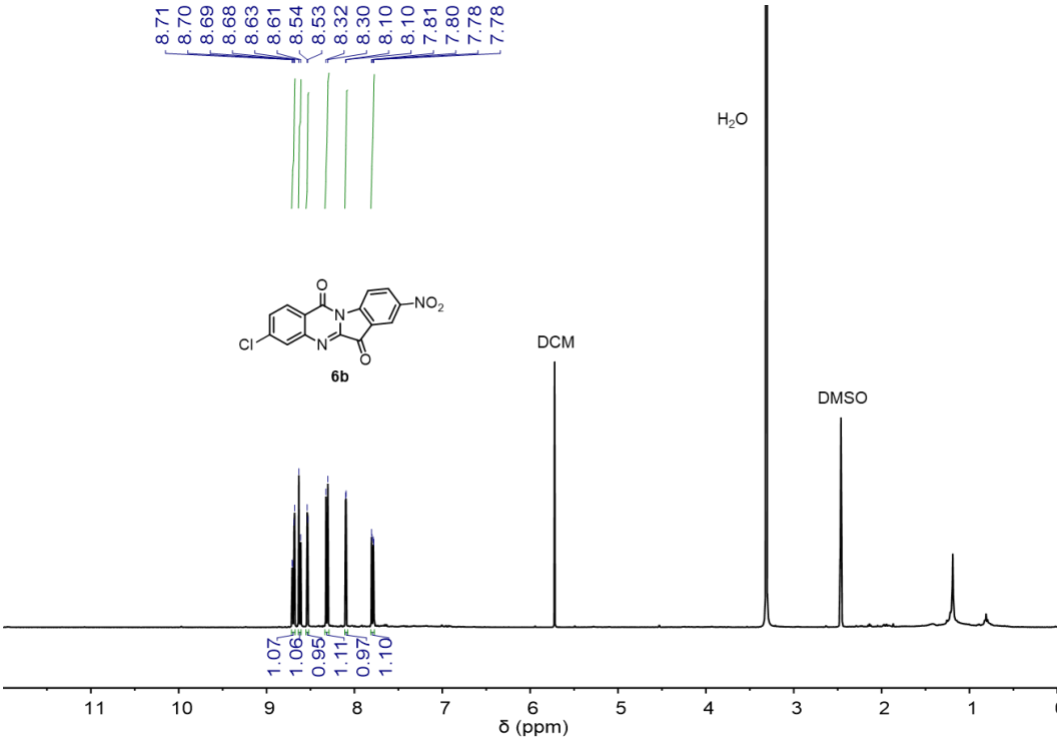


Figure S96. ^{1}H NMR (500 MHz, 25 ºC, $CDCl_3$) spectrum of compound **6b**.

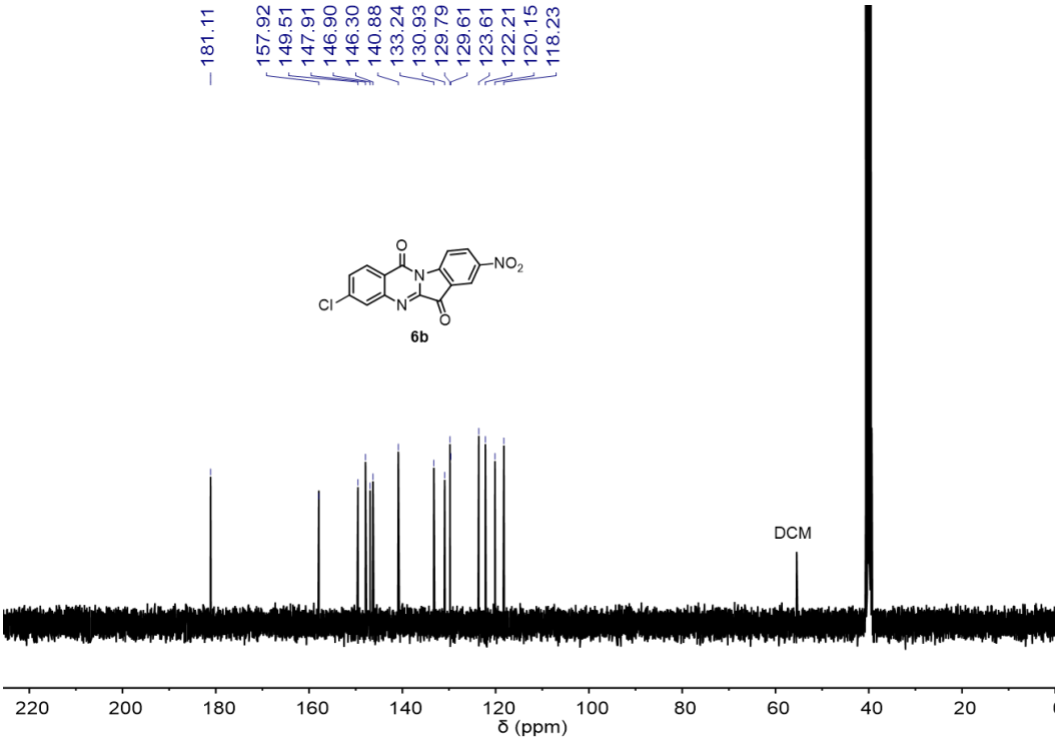


Figure S97. ^{13}C NMR (126 MHz, 25 ºC, $CDCl_3$) spectrum of compound **6b**.

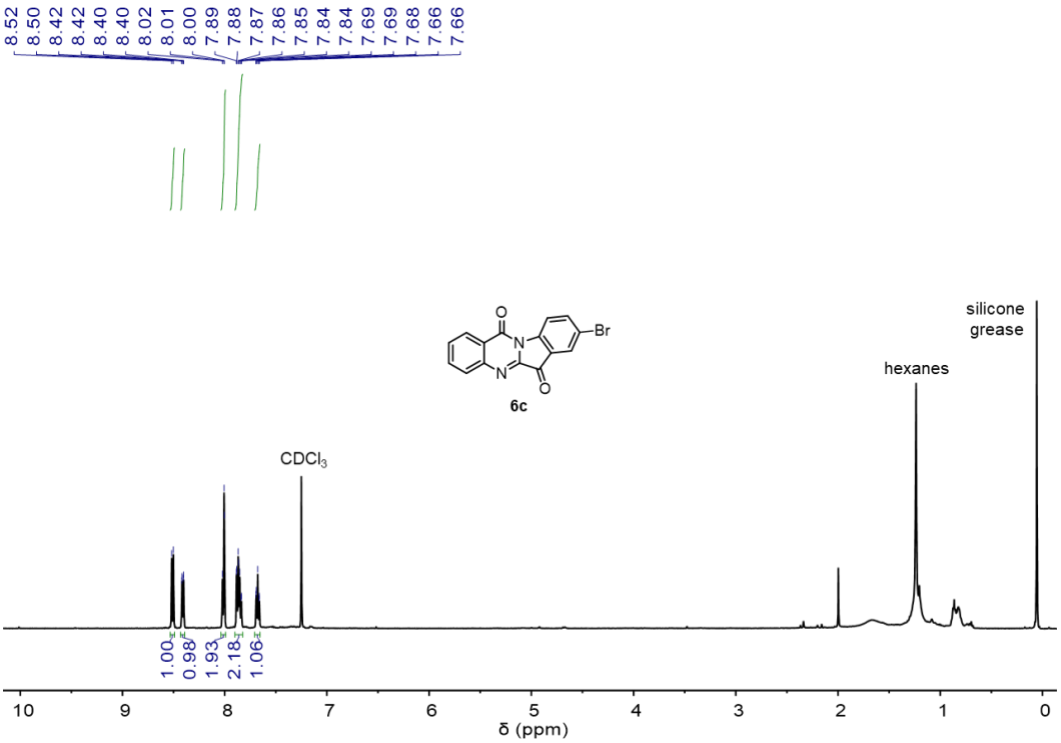


Figure S98. ^{1}H NMR (500 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **6c**.

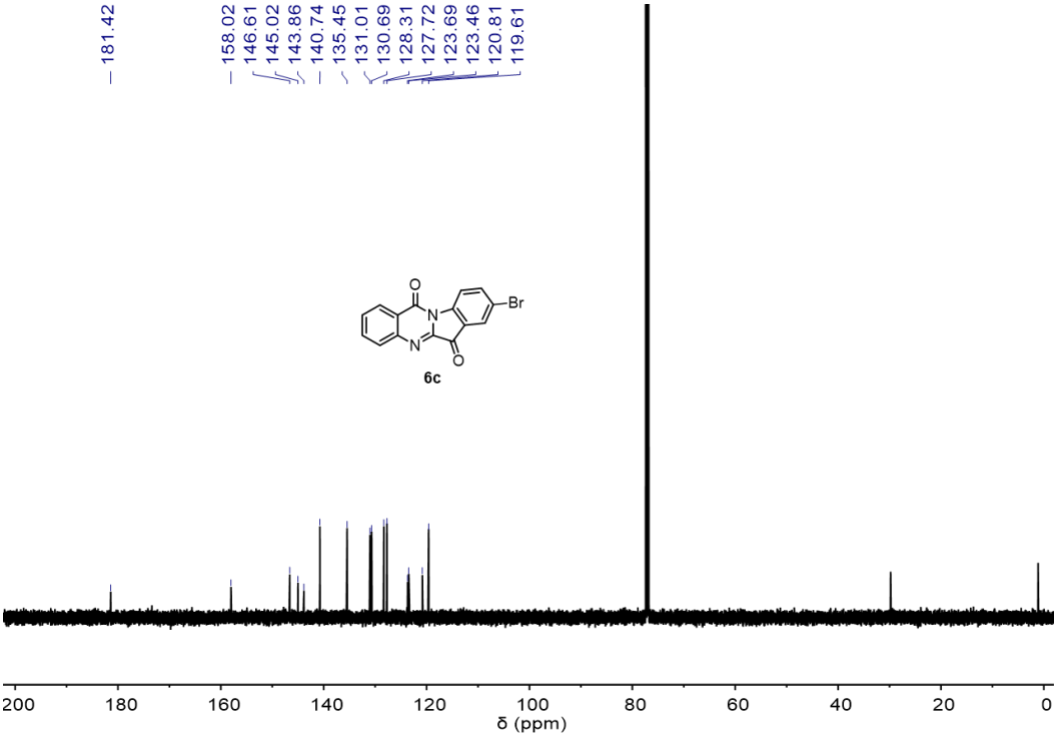


Figure S99. ^{13}C NMR (126 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **6c**.

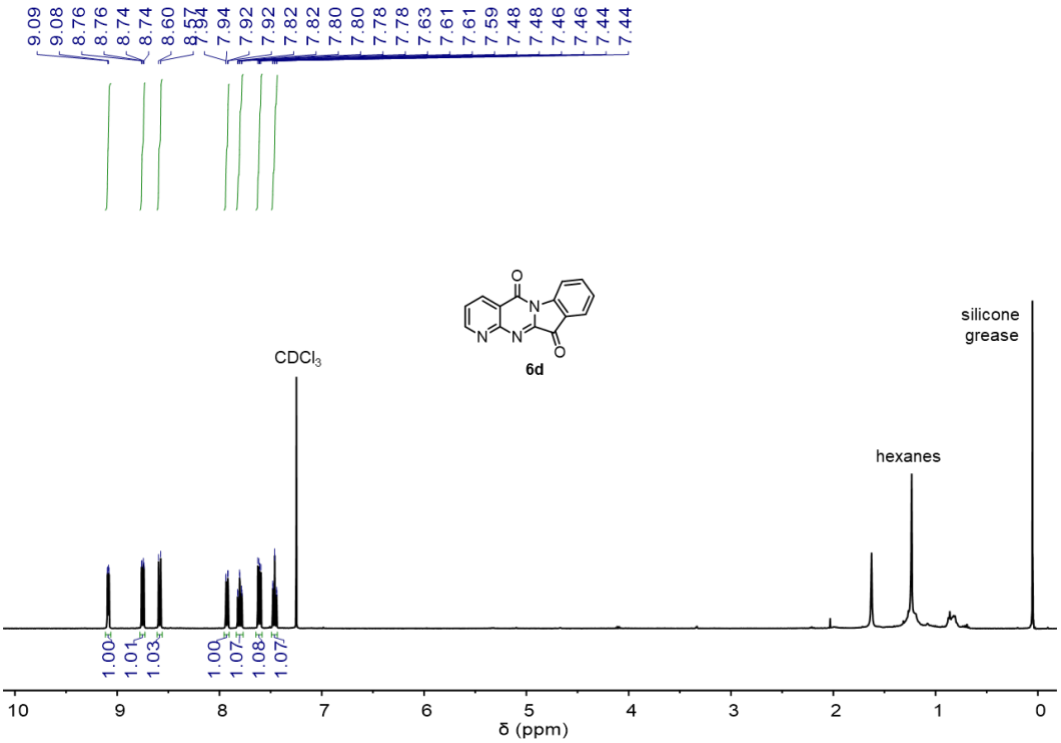


Figure S100. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **6d**.

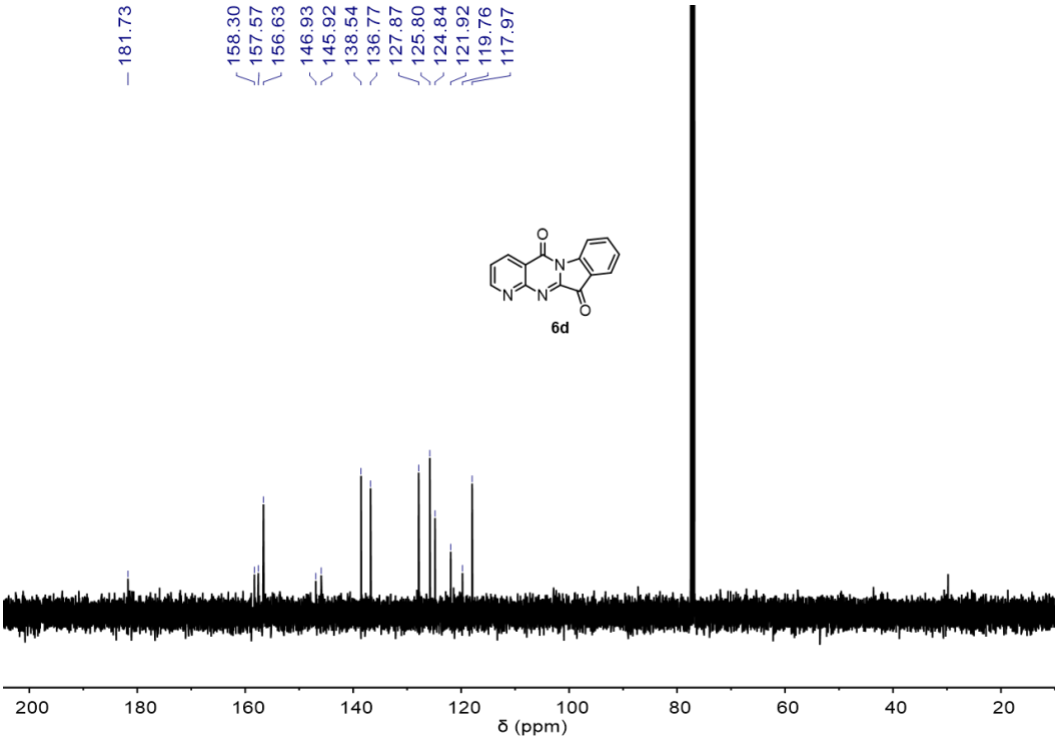


Figure S101. ^{13}C NMR (126 MHz, 25 °C, $CDCl_3$) spectrum of compound **6d**.

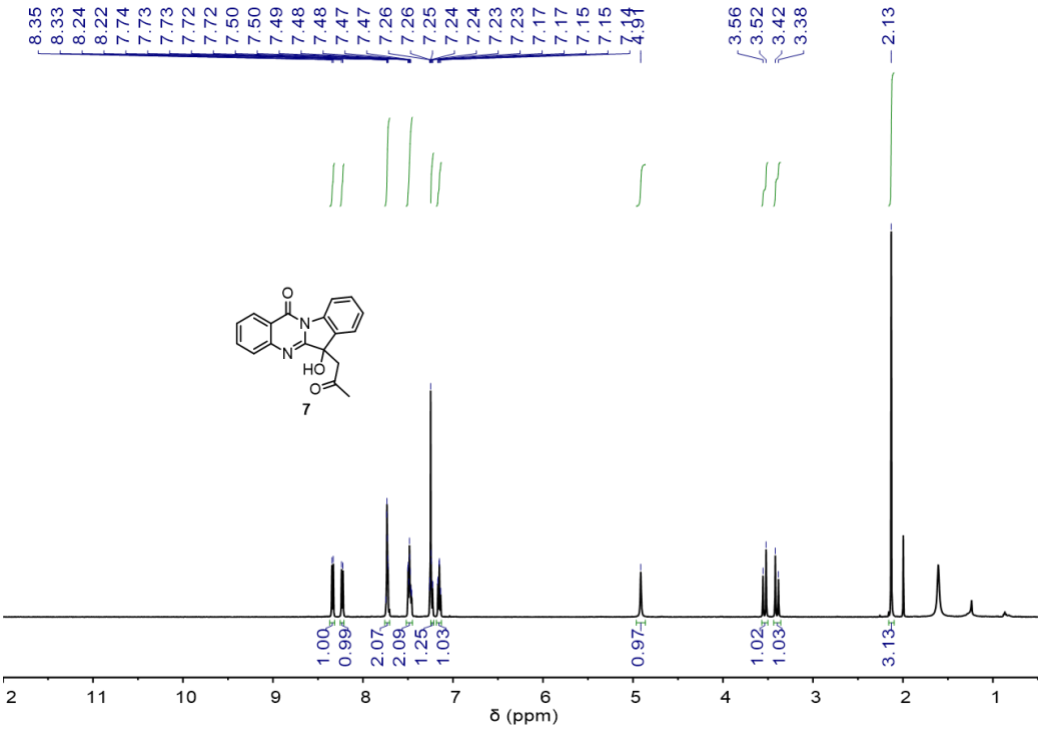


Figure S102. ^{1}H NMR (500 MHz, 25 ºC, $CDCl_3$) spectrum of compound **7**.

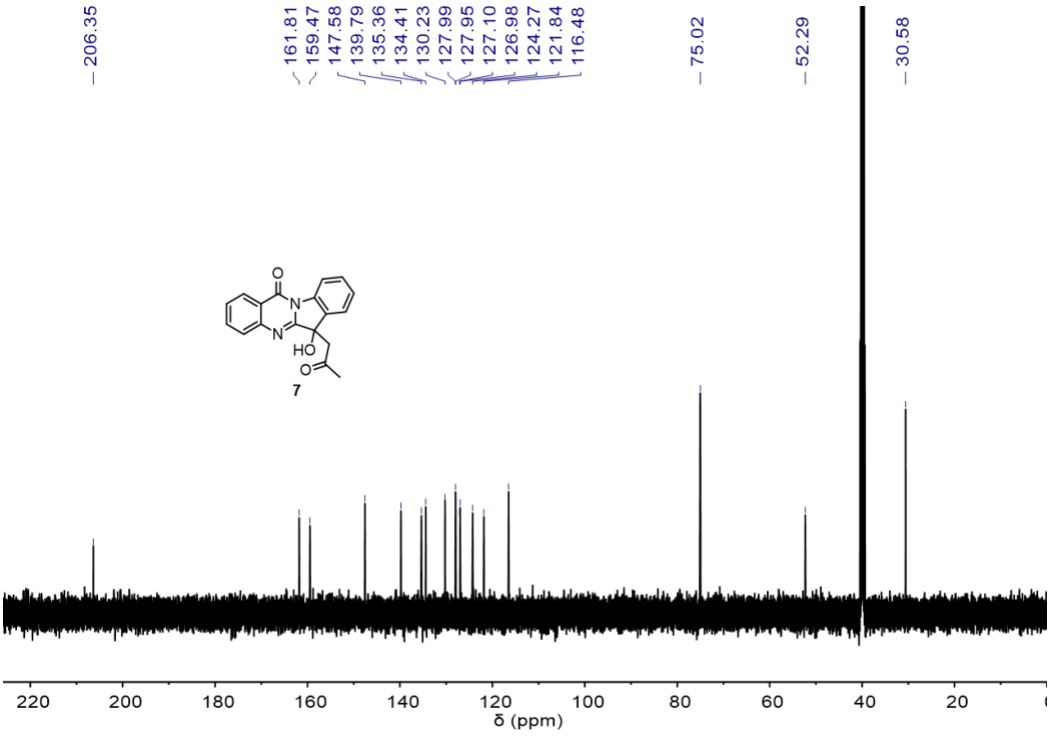


Figure S103. ^{13}C NMR (126 MHz, 25 ºC, $CDCl_3$) spectrum of compound **7**.

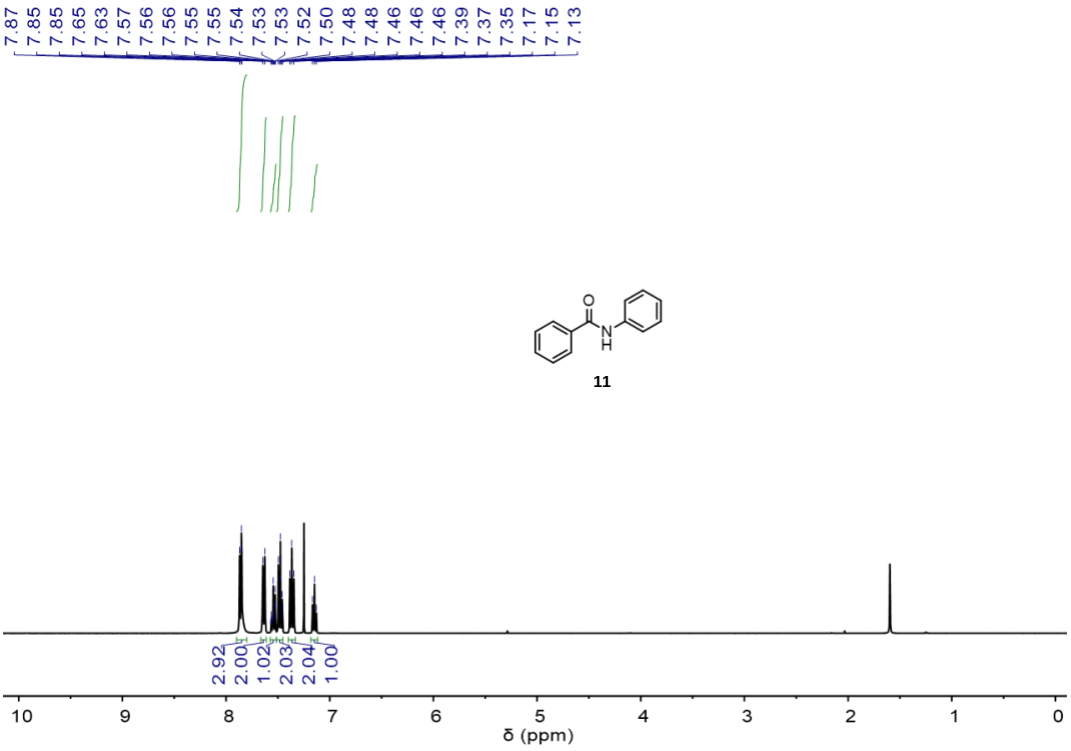


Figure S104. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **11**.

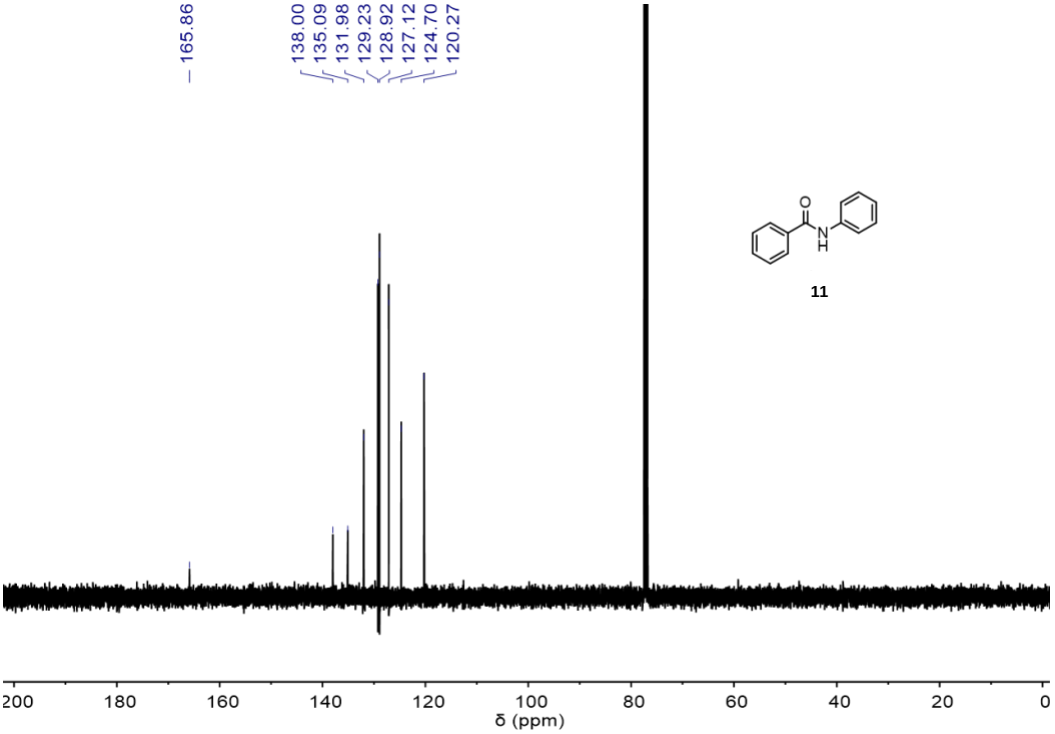


Figure S105. ^{13}C NMR (101 MHz, 25 °C, $CDCl_3$) spectrum of compound **11**.

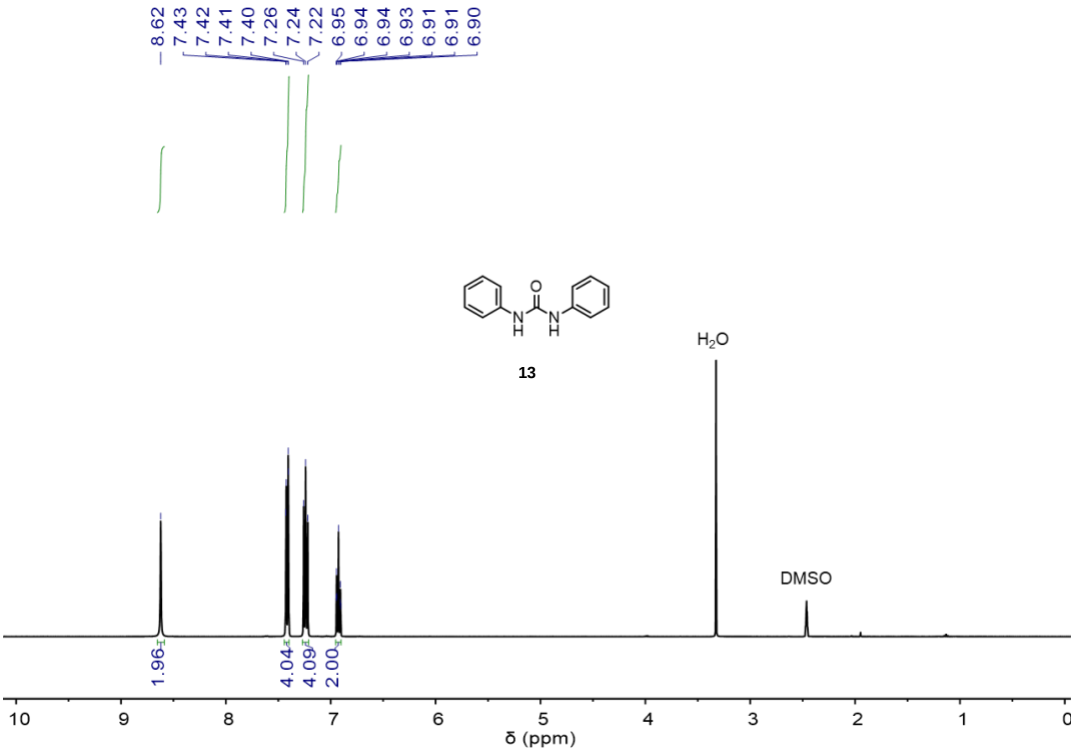


Figure S106. ^{1}H NMR (400 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **13**.

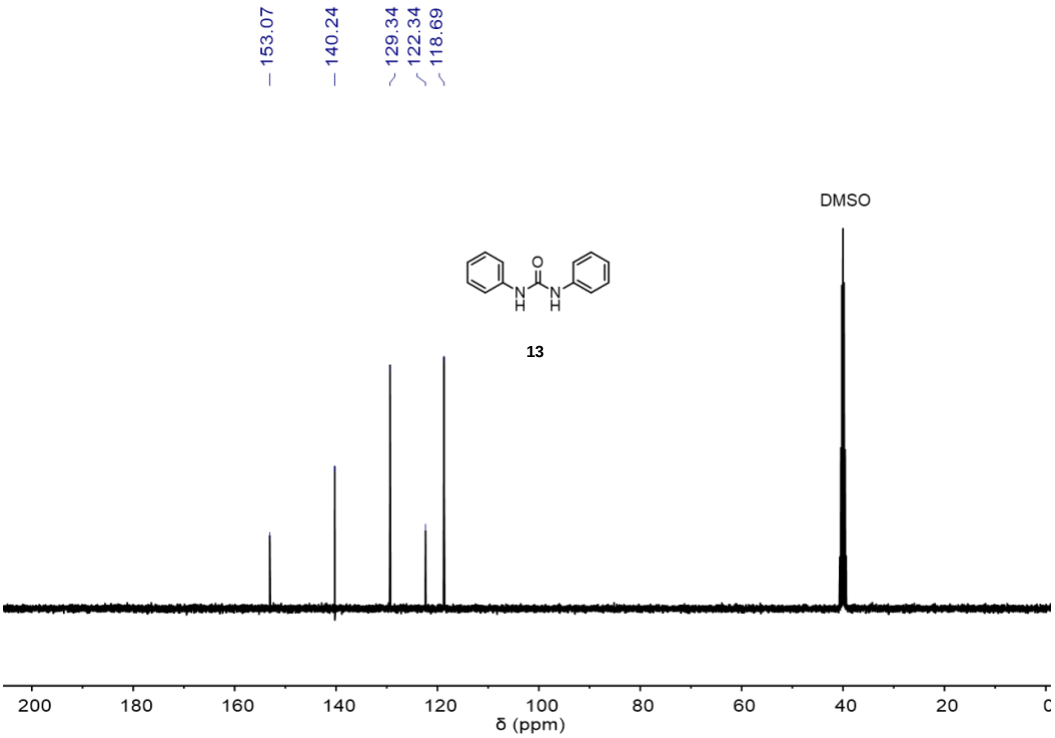


Figure S107. ^{13}C NMR (101 MHz, 25 ^{o}C, $CDCl_3$) spectrum of compound **13**.

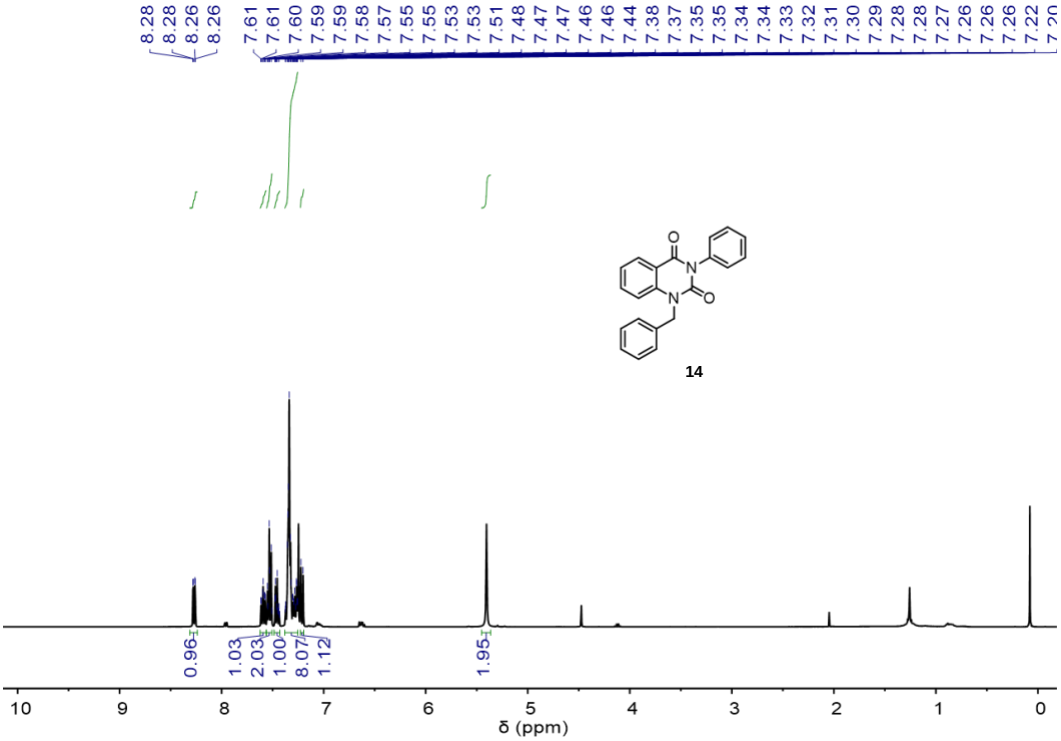


Figure S108. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **14**.

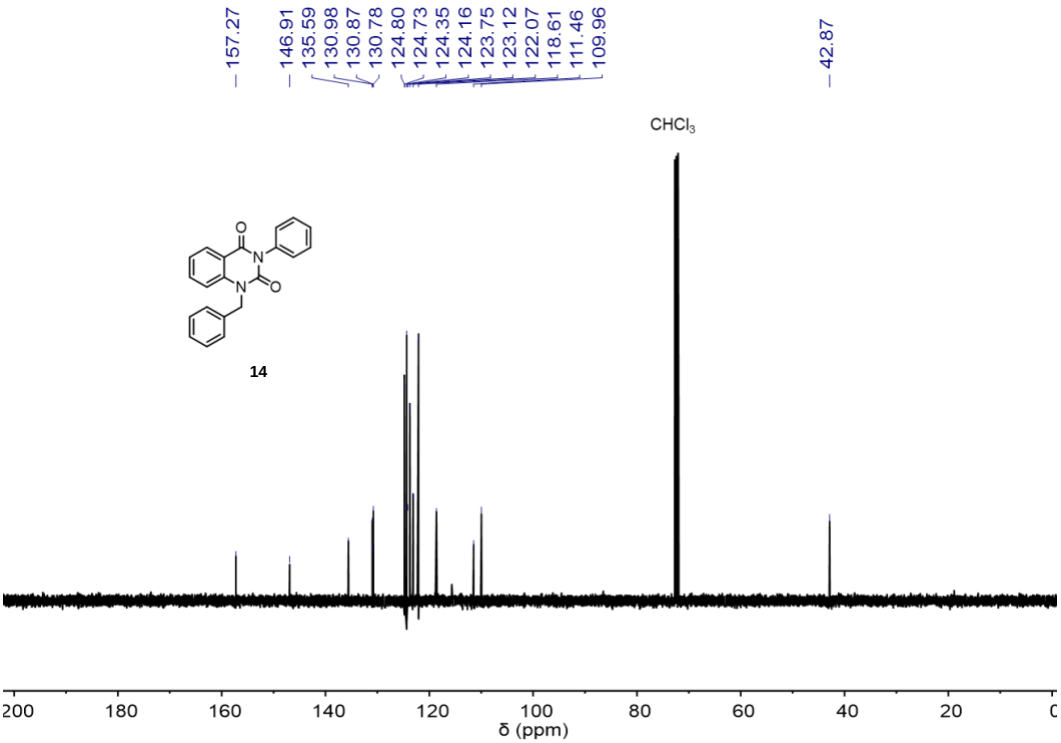


Figure S109. ^{1}H NMR (400 MHz, 25 °C, $CDCl_3$) spectrum of compound **14**.

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