Formylation of Phenols using Formamidine Acetate

S. Hessam M. Mehr, Hannah Depmeier, Katsuya Fukuyama, Mahboobeh Maghami, and Mark J. MacLachlan*

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1 CANADA

mmaclach@chem.ubc.ca

Materials

All reagents and solvents were obtained from standard suppliers and used without purification. Formamidine acetate was prepared by the literature procedure.[1]

Instrumentation

All reactions were carried out under air unless otherwise noted. High-resolution ESI mass spectra were obtained on a Waters/Micromass LCT time-of-flight (TOF) mass spectrometer. Infrared spectroscopy was carried out on a Thermo Scientific Nicolet 6700 (ATR) FT-IR instrument using the SmartOrbit attenuated total reflectance (ATR) accessory. UV-visible spectra were collected on a Varian Cary 5000 UV-Vis-NIR spectrophotometer.

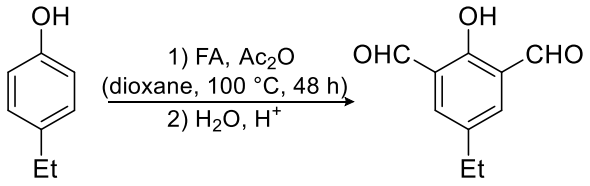
All ^{1}H and ^{13}C NMR spectra were measured on a 400 MHz Bruker spectrometer equipped with a SmartProbe™ using a flip angle of 30° pulses for proton acquisition. To speed up longitudinal relaxation, the UDEFT pulse sequence[2] of Piotto and coworkers was used for ^{13}C acquisition. We made use of ^{13}C–^{1}H HSQC/HMBC data in cases where ^{13}C peaks were difficult to assign with certainty.

All NMR experiments were carried out using Bruker TopSpin™ software and the data subsequently processed using ACD/Labs NMR Processor. Exponential window functions with a line-broadening factor (LB) of 1.0 and 2.5 Hz were applied to all ^{1}H and ^{13}C spectra, respectively.

Experimental

Formamidine acetate is denoted by the abbreviation FA in the schemes.

Preparation of 5



5 (69%)

Formamidine acetate (681 mg, 6.56 mmol, 8.0 equiv) was stirred in dioxane (15 mL) at 100 °C, in a round-bottom flask. Acetic anhydride (1.23 mL, 13.1 mmol, 16.0 equiv) was added once the target temperature had been reached and stirring continued until the formamidine acetate fully dissolved (typically 30 min). At this point, 4-ethylphenol (100 mg, 0.820 mmol, 1.0 equiv) was added in one portion. The flask was subsequently capped and the reaction allowed to proceed for 2 d.

The reaction was worked up by evaporating dioxane solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (15 mL) at 60 °C for 2 h. Aqueous hydrochloric acid (1 M, 15 mL, 15 mmol, 18.3 equiv) was added next and stirring continued for 18 h.

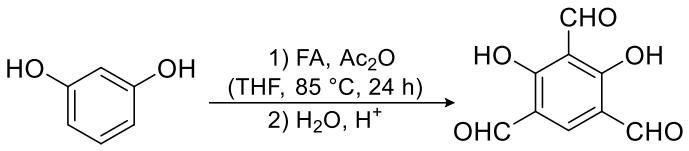
The product was extracted into dichloromethane (5 × 5 mL), which was dried over Na_2SO_4 and evaporated to give **5** as a yellow oil.

Crude **5** was purified by column chromatography using CH_2Cl_2 (100%) as eluent. Evaporation

of the second fraction (R_f = 0.6) gave pure product of **5** as yellow crystals (100 mg, 0.562 mmol, 69%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.47 (s, 1H; OH), 10.23 (s, 2H; CHO), 7.80 (s, 2H; Ar), 2.68 (q, $^3J_{HH}$ = 7.7 Hz, 2H; CH_2), 1.27 ppm (t, $^3J_{HH}$ = 7.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CD_3CN) δ 193.9 (CO), 162.4 (COH), 138.0 (CH), 137.2 (*C*CH_2), 124.0 (*C*CHO), 28.1 (CH_2), 15.8 ppm (CH_3). UV-Vis (CH_2Cl_2) λ_{max} (ε) = 206 (3.7×10^4), 236 (5.8×10^4), 354 (1.36×10^4) nm (cm^{-1} mol^{-1} L). IR (neat) *v* = 3138 (br), 2965, 2930, 2872, 2776, 1660, 1596, 1455, 1443, 1402, 1377, 1325, 1296, 1267, 1200, 1065, 1002, 971, 938, 927, 907, 789, 742, 649, 630, 609, 541, 486 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**5** - H]$^-$ Calcd for $C_{10}H_9O_3$ 177.0552; Found 177.0555.

Preparation of 6



6 (82%)

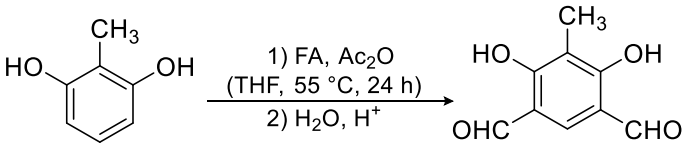
Formamidine acetate (374 mg, 3.63 mmol, 4.0 equiv), acetic anhydride (0.72 mL, 7.3 mmol, 8.0 equiv) and resorcinol (100 mg, 0.909 mmol, 1.0 equiv) were combined in THF (15 mL) in an autoclave. The reaction was heated to 85 °C and allowed to proceed for 1 d.

The reaction was worked up by evaporating THF solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in a solution of ethanol (2 mL) in water (5 mL) at r.t. for 2 h. Aqueous hydrochloric acid (1 M, 10 mL, 10 mmol, 11.0 equiv) was added next and stirring continued for 18 h.

During the hydrolysis step the product precipitated as a salmon colored powder and was isolated by filtration and washing with water. This step gave pure **6** as a salmon colored powder (144 mg, 0.742 mmol, 82%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H; CHO), 10.09 (s, 2H; CHO), 8.37 ppm (s, 1H; Ar). ^{13}C NMR (100 MHz, DMSO-d_6) δ 193.9 (CHO), 190.0 (CHO), 170.0 (COH), 140.6 (CH), 115.8 (*C*CHO), 110.0 ppm (*C*CHO). UV-Vis (CH_2Cl_2) λ_{max} (ε) = 248 (4.6×10^4), 344 (7.5×10^3) nm (cm^{-1} mol^{-1} L). IR (neat) *v* = (br), 1640, 1591, 1436, 1366, 1322, 1273, 1247, 1218, 1147, 987, 864, 938, 805, 775, 748, 602 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**6** - H]$^-$ Calcd for $C_9H_5O_5$ 193.0137; Found 193.0128.

Preparation of 7



7 (80%)

Formamidine acetate (335 mg, 3.23 mmol, 4.0 equiv) and 2-methylresorcinol (100 mg, 0.806 mmol, 1.0 equiv) were combined in THF (15 mL) in a round-bottom-flask. Once the reaction was heated up to 55 °C, acetic anhydride (0.61 mL, 6.45 mmol, 8.0 equiv) was added. The flask was

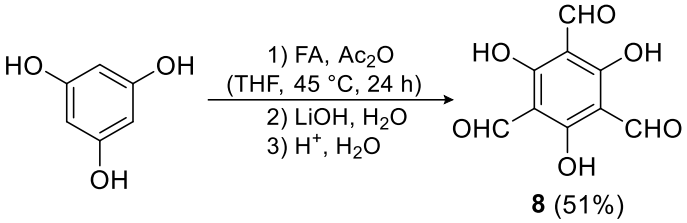
subsequently capped and the reaction allowed to proceed for 1 d.

The reaction was worked up by evaporating THF solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (10 mL) at r.t. for 2 h. Aqueous hydrochloric acid (1 M, 10 mL, 10 mmol, 12.4 equiv) was added next and stirring continued for 18 h.

During the hydrolysis step the product precipitated as salmon colored powder and was isolated by filtration and washing with water first and then with hexanes. This step gave pure **7** as a salmon colored powder (116 mg, 0.644 mmol, 80%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 2H; OH), 9.94 (s, 2H; CHO), 8.20 (s, 1H; Ar), 2.05 ppm (s, 3H; CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.1 (CHO), 164.8 (COH), 139.3 (CH), 115.3 (*C*CHO), 111.7 (*C*CH_3), 6.9 ppm (CH_3). UV-Vis (CH_2Cl_2) λ_{max} (ε) = 207 (1.3×10^4), 259 (4.9×10^4) nm (cm^{-1} mol^{-1} L). IR (neat) ν = (br), 3038, 2931, 2865, 1633, 1607, 1508, 1468, 1446, 1375, 1337, 1303, 1223, 1007, 905, 891, 864, 775, 764, 724, 646, 532, 510 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**7** - H]$^-$ Calcd for $C_9H_7O_4$ 179.0344; Found 179.0342.

Preparation of 8



8 (51%)

Formamidine acetate (8.25 g, 79.4 mmol, 5.0 equiv) and phloroglucinol (2.00 g, 15.9 mmol, 1.0 equiv) were combined in THF (200 mL) at 45 °C, in a round-bottom flask and stirring continued until the target temperature was reached. At this point acetic anhydride (14.7 mL, 159 mmol, 10.0 equiv) was added, the flask was subsequently capped and the reaction allowed to proceed for 1 d.

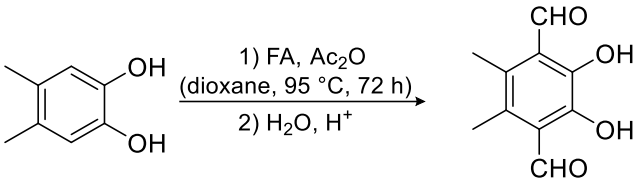
The reaction was worked up by evaporating THF solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (200 mL) at 40 °C for 2 h.

Aqueous LiOH (2 M, 600.0 mL, 1200 mmol, 75.6 eq) was added slowly, then stirring continued for 18 h. Aqueous hydrochloric acid (2 M, 300 mL, 600 mmol, 37.8 equiv) was added next to re-acidify the solution, causing a very pale salmon-coloured powder to precipitate.

The product was extracted into dichloromethane (4 × 60 mL), which was dried over Na_2SO_4 and evaporated to give pure **8** as an off-white powder (1.71 g, 8.14 mmol, 51%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 3H; CHO), 5.39 ppm (s, 3H; OH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.4 (CHO), 173.3 (COH), 103.2 ppm (*C*CHO). UV-Vis (CH_2Cl_2) λ_{max} (ε) = 264 (5.3×10^4), 289 (2.6×10^4) nm (cm^{-1} mol^{-1} L). IR (neat) ν = 2888 (br), 1635, 1585, 1427, 1389, 1246, 1189, 1104, 964, 868, 806, 781, 602, 543 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**8** - H]$^-$ Calcd for $C_9H_5O_6$ 209.0086; Found 209.0080.

Preparation of 9



9 (51%)

Formamidine acetate (2.81 g, 27.0 mmol, 5.0 equiv) was stirred in dioxane (150 mL) at 95 °C, in a round-bottom flask. Acetic anhydride (5.1 mL, 54 mmol, 10 equiv) was added once the target temperature had been reached and stirring continued until the formamidine acetate fully dissolved (typically 30 min). At this point, 4,5-dimethylcatechol (745 mg, 5.40 mmol, 1.0 equiv) was added in one portion. The flask was subsequently capped and the reaction allowed to proceed for 3 d.

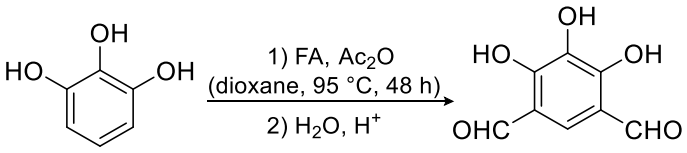
The reaction was worked up by evaporating dioxane solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C followed by stirring in water (80 mL) at 60 °C for 2 h. Aqueous hydrochloric acid (1 M, 80 mL, 80 mmol, 14.9 equiv) was added next and stirring continued for 18 h.

The product was extracted into dichloromethane (5 × 20 mL), which was dried over Na_2SO_4 and evaporated to give the crude product as a brown solid.

Crude **9** was purified by column chromatography using diethyl ether:hexanes (20:80) as eluent. Evaporation of the second fraction (R_f = 0.2) gave pure **9** as orange powder (533 mg, 2.75 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.91 (s, 2H; OH), 10.48 (s, 2H; CHO), 2.51 ppm (s, 6H; CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9 (CHO), 151.1 (COH), 128.1 (*C*CHO), 121.9 (*C*CH_3), 13.5 ppm (CH_3). UV-Vis (CH_2Cl_2) λ_{max} (ε) = 218 (1.9×10^4), 295 (1.9×10^4), 424 (3.2×10^3) nm (cm^{-1} mol^{-1} L). IR (neat) ν = 3045, 2924 (br), 1641, 1611, 1556, 1487, 1439, 1380, 1316, 1275, 1244, 1099, 1028, 924, 743, 706, 664, 596, 516 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**9** - H]$^-$ Calcd for $C_{10}H_9O_4$ 193.0501; Found 193.0493.

Preparation of 10



10 (76%)

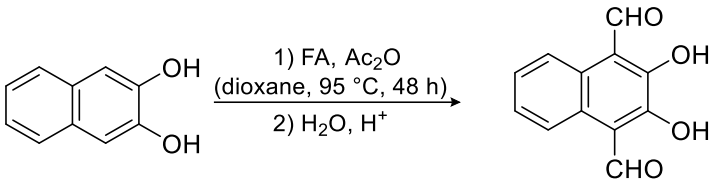
Formamidine acetate (330 mg, 3.17 mmol, 4.0 equiv) was stirred in dioxane (15 mL) at 95 °C, in a round-bottom flask. Acetic anhydride (0.59 mL, 6.3 mmol, 16.0 equiv) was added once the target temperature had been reached and stirring continued until the formamidine acetate fully dissolved (typically 30 min). At this point, pyrogallol (100 mg, 0.79 mmol, 1.0 equiv) was added in one portion. The flask was subsequently capped and the reaction allowed to proceed for 2 d.

The reaction was worked up by evaporating dioxane solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (20 mL) at 40 °C for 2 h. Aqueous hydrochloric acid (0.5 M, 10 mL, 5 mmol, 6.3 equiv) was added next and stirring continued for 18 h.

The product was extracted into dichloromethane (5 × 5 mL) and the combined extractions dried over Na_2SO_4 to give a light orange solid upon evaporation. This solid was stirred in MeOH (with one drop of trifluoroacetic acid added) at 60 °C for 18 h. The salmon-colored residue left after solvent evaporation was washed with 1 mL $CHCl_3$, leaving pure **10** (109 mg, 0.600 mmol, 76%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.20 (br s, 2H; OH), 10.02 (s, 2H; CHO), 7.75 ppm (s, 1H; Ar).^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 192.3 (CHO), 155.2 (COH), 132.5 (COH), 126.9 (CH), 116.3 (*C*CHO) ppm. UV-Vis (MeOH) λ_{max} (ε) = 267 (6.1×10^4), 203 (1.7×10^4) nm ($cm^{-1}\,mol^{-1}$ L). IR (neat) *v* = (br) 3254, 2859, 1639, 1620, 1488, 1456, 1380, 1239, 1197, 1144, 1061, 915, 885, 916, 885, 794, 777, 737, 663, 643, 543, 512 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**10** - H]$^-$ Calcd for $C_8H_5O_5$ 181.0137; Found 181.0138.

Preparation of 11



11 (52%)

Formamidine acetate (520 mg, 5.00 mmol, 8.0 equiv) was stirred in dioxane (15 mL) at 95 °C, in a round-bottom flask. Acetic anhydride (0.95 mL, 10 mmol, 16.0 equiv) was added once the target temperature had been reached and stirring continued until the formamidine acetate fully dissolved (typically 30 min). At this point, 2,3-naphthalenediol (100 mg, 0.625 mmol, 1.0 equiv) was added in one portion. The flask was subsequently capped and the reaction allowed to proceed for 2 d.

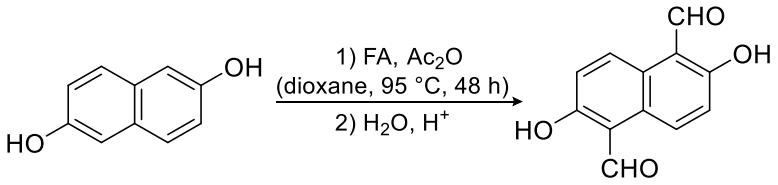
The reaction was worked up by evaporating dioxane solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (15 mL) at 60 °C for 2 h. Aqueous hydrochloric acid (1 M, 15 mL, 15 mmol, 24 equiv) was added next and stirring continued for 18 h.

During the hydrolysis step the product precipitated as yellow-brownish powder and was isolated by filtration and washing with hexanes.

Crude **11** was purified by column chromatography using dichloromethane (100%) as eluent. Evaporation of the first fraction (R_f = 0.25) gave pure product as a yellow powder (70 mg, 0.32 mmol, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 13.00 (s, 2H; OH), 10.92 (s, 2H; CHO), 8.40 (dd, $^3J_{HH}$=6.4 Hz, $^4J_{HH}$=3.1 Hz, 2H; Ar), 7.62 (dd, $^3J_{HH}$=6.4 Hz, $^4J_{HH}$=3.1 Hz, 2H; Ar) ppm. ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 194.2 (CHO), 154.3 (COH), 126.8 (Ar), 126.3 (Ar), 122.3 (Ar), 117.0 (*C*CHO) ppm. UV-Vis (CH_2Cl_2) λ_{max} (ε) = 225 (5.2×10^4), 372 (1.1×10^4) nm ($cm^{-1}\,mol^{-1}$ L). IR (neat) *v* = 3152, 2919 (br), 1672, 1635, 1608, 1549, 1520, 1450, 1402, 1373, 1304, 1258, 1240, 1213, 1120, 1050, 1001, 965, 916, 853, 798, 738, 698, 663, 597, 568, 505 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**11** - H]$^-$ Calcd for $C_{12}H_7O_4$ 215.0344; Found 215.0353.

Preparation of 12



12 (89%)

Formamidine acetate (520 mg, 5.00 mmol, 8.0 equiv) was stirred in dioxane (15 mL) at 95 °C, in a round-bottom flask. Acetic anhydride (0.95 mL, 10 mmol, 16.0 equiv) was added once the target temperature had been reached and stirring continued until the formamidine acetate fully dissolved (typically 30 min). At this point, 2,6-naphthalenediol (100 mg, 0.625 mmol, 1.0 equiv) was added in one portion. The flask was subsequently capped and the reaction allowed to proceed for 2 d.

The reaction was worked up by evaporating dioxane solvent and leftover acetic anhydride and acetic acid under reduced pressure at 50 °C, followed by stirring in water (15 mL) at 60 °C for 2 h. Aqueous hydrochloric acid (1 M, 15 mL, 15 mmol, 24 equiv) was added next and stirring continued for 18 h.

The product was extracted into dichloromethane (5 × 5 mL), which was dried over Na_2SO_4 and evaporated to give **12** as orange-brownish solid.

Crude **12** was purified by column chromatography using dichloromethane:hexanes (50%:50%) as eluent. Evaporation of the second fraction (R_f = 0.25) gave pure product as a yellow powder (120 mg, 0.556 mmol, 89%).

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.59 (s, 2H; OH), 10.77 (s, 2H; CHO), 9.16 (d, $^3J_{HH}$=9.4 Hz, 2H; Ar), 7.37 (d, $^3J_{HH}$=9.4 Hz, 2H; Ar) ppm. ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 192.7 (CHO), 161.6 (COH), 132.4 (CH), 125.9 (Ar), 121.4 (CH), 113.3 (*C*CHO) ppm. UV-Vis (CH_2Cl_2) λ_{max} (ε) = 400 (6.6×10^3), 385 (1.1×10^4), 314 (1.2×10^4), 302 (1.2×10^4) nm ($cm^{-1}\,mol^{-1}\,L$). IR (neat) *v* = 2917 (br), 1633, 1584, 1502, 1409, 1359, 1262, 1212, 1163, 1039, 836, 776, 731, 703, 653, 483, 450 cm^{-1}. HRMS (ESI/TOF-Q) *m/z*: [**12** - H]$^-$ Calcd for $C_{12}H_7O_4$ 215.0344; Found 215.0342.

^{1}H and ^{13}C NMR Spectra

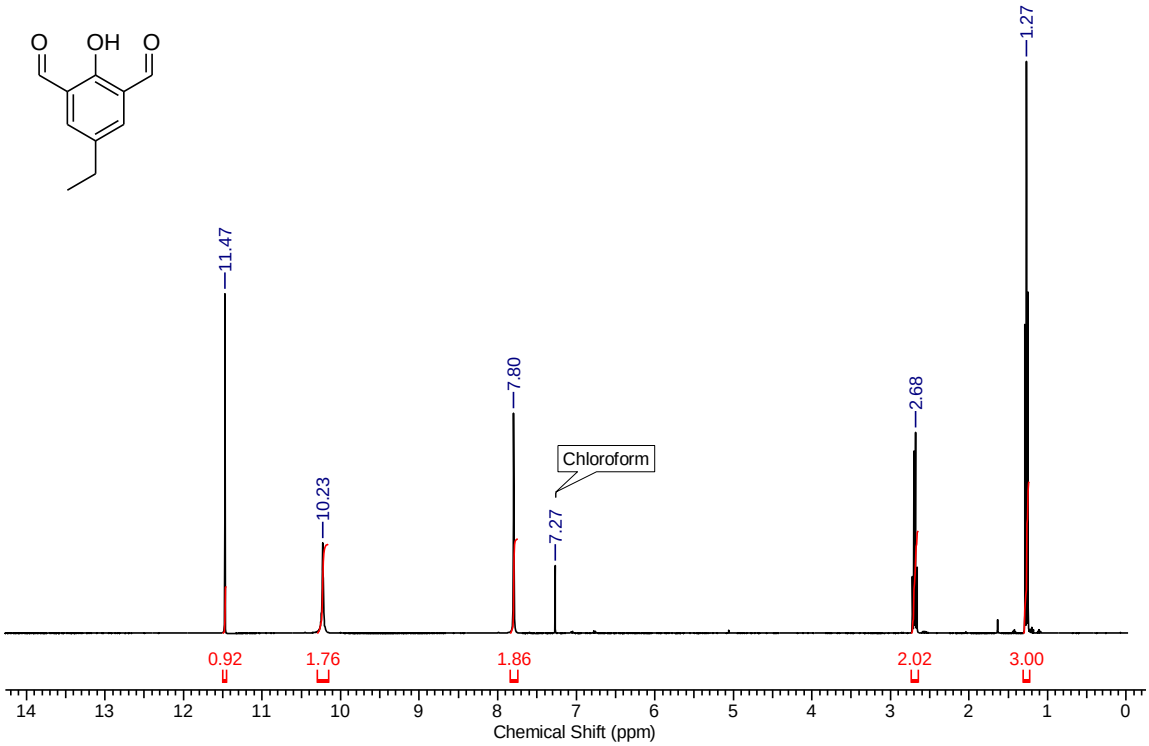


Figure S1. ^{1}H NMR spectrum for **5** ($CDCl_3$, 400 MHz).

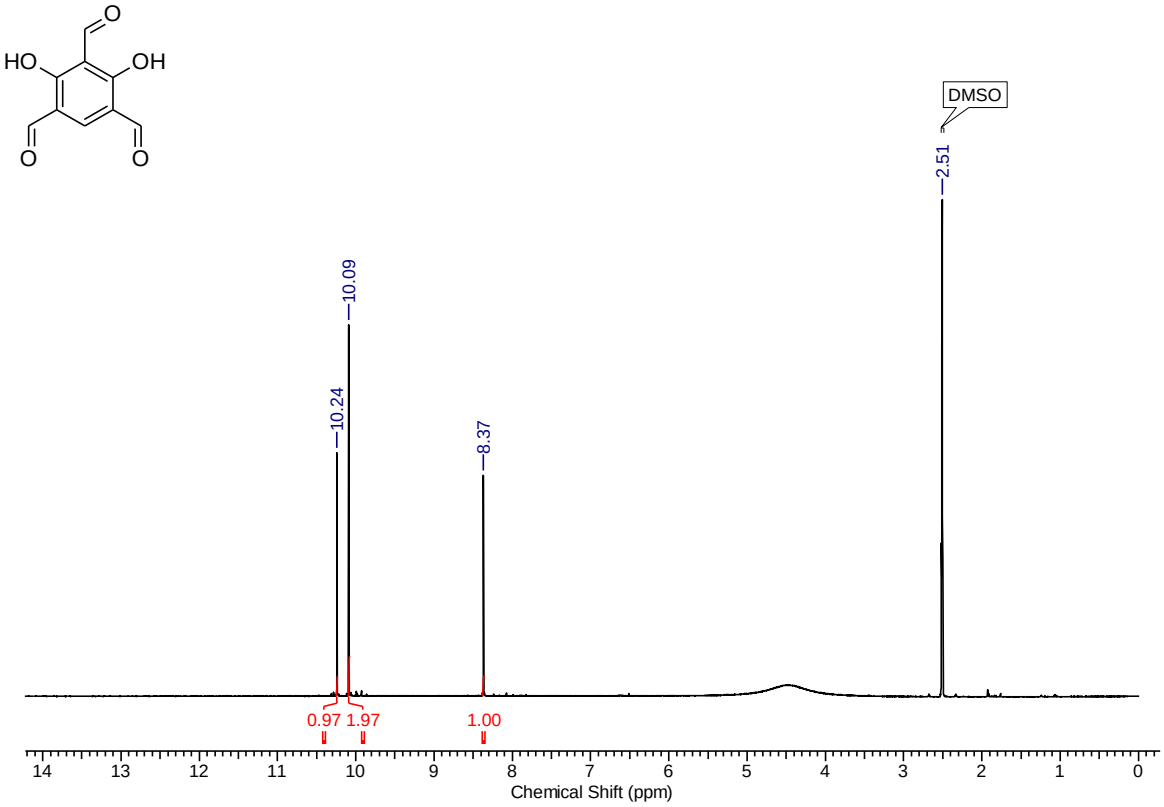


Figure S2. ^{1}H NMR spectrum for **6** (DMSO-d_6, 400 MHz).

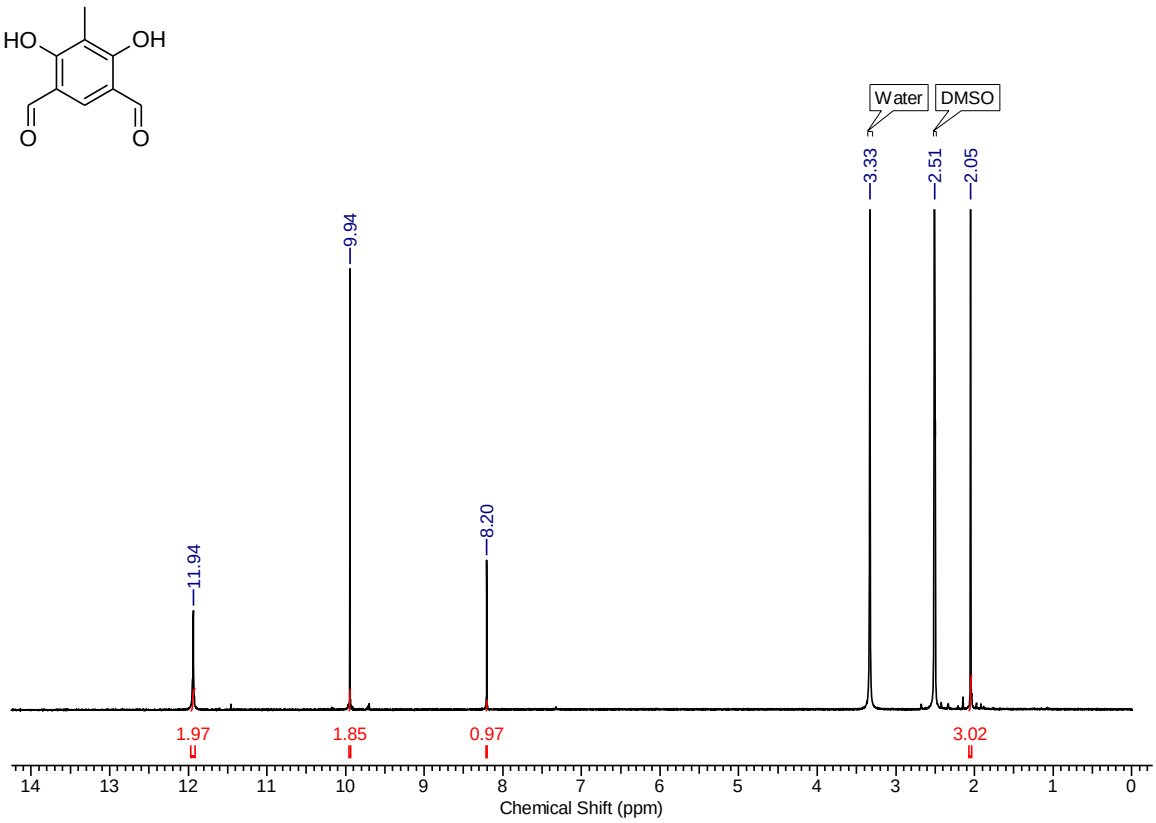


Figure S3. ^{1}H NMR spectrum for **7** (DMSO-d_6, 400 MHz).

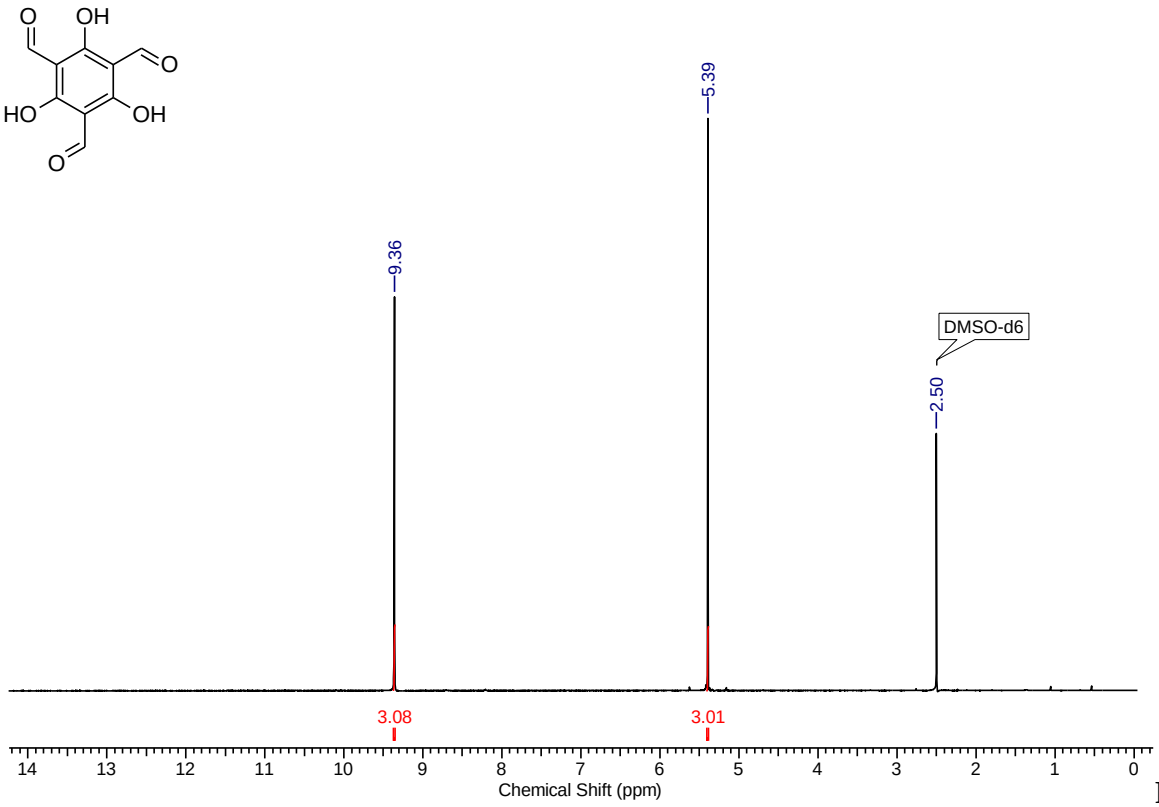


Figure S4. ^{1}H NMR spectrum for **8** (DMSO-d_6, 400 MHz).

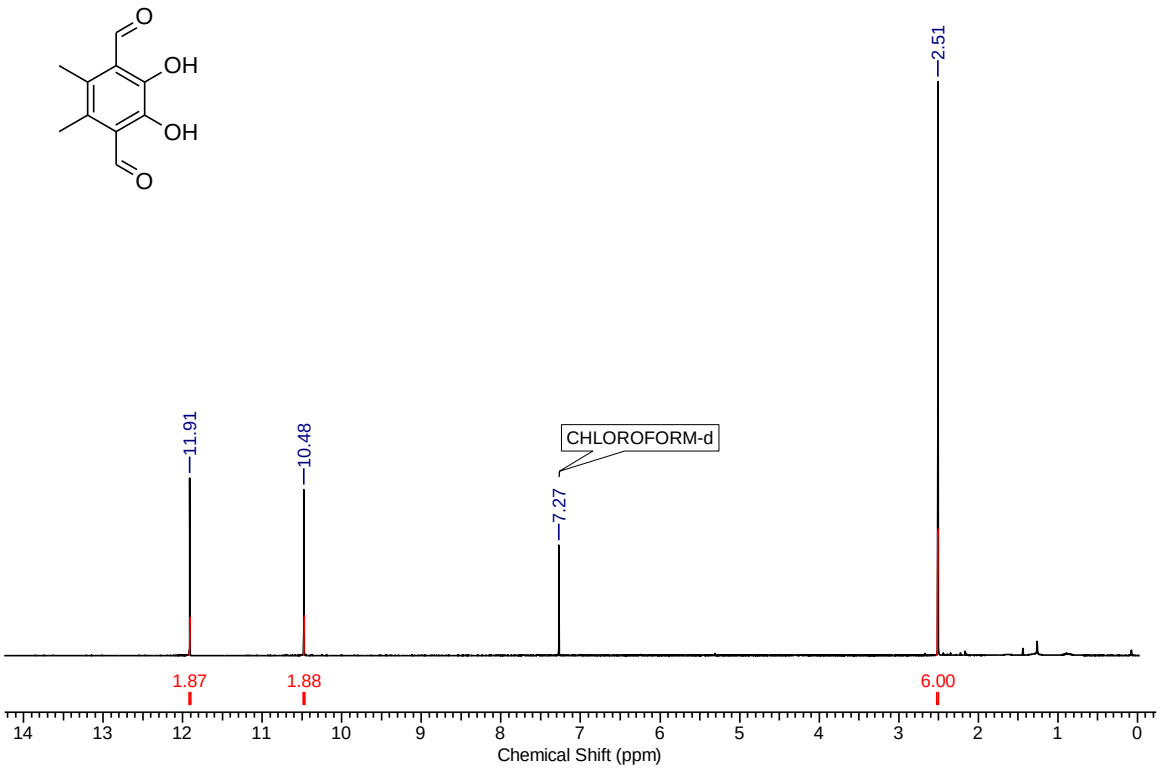


Figure S5. ^{1}H NMR spectrum for **9** ($CDCl_3$, 400 MHz).

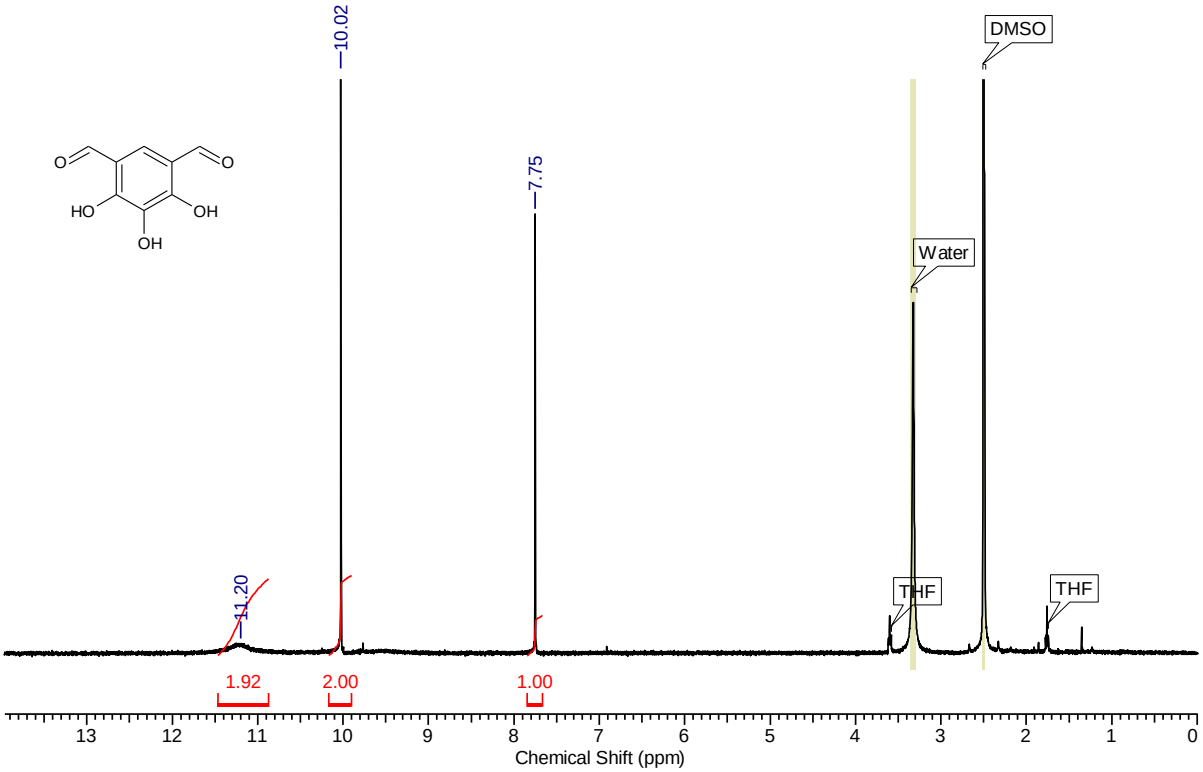


Figure S6. ^{1}H NMR spectrum for **10** (DMSO-d_6, 400 MHz).

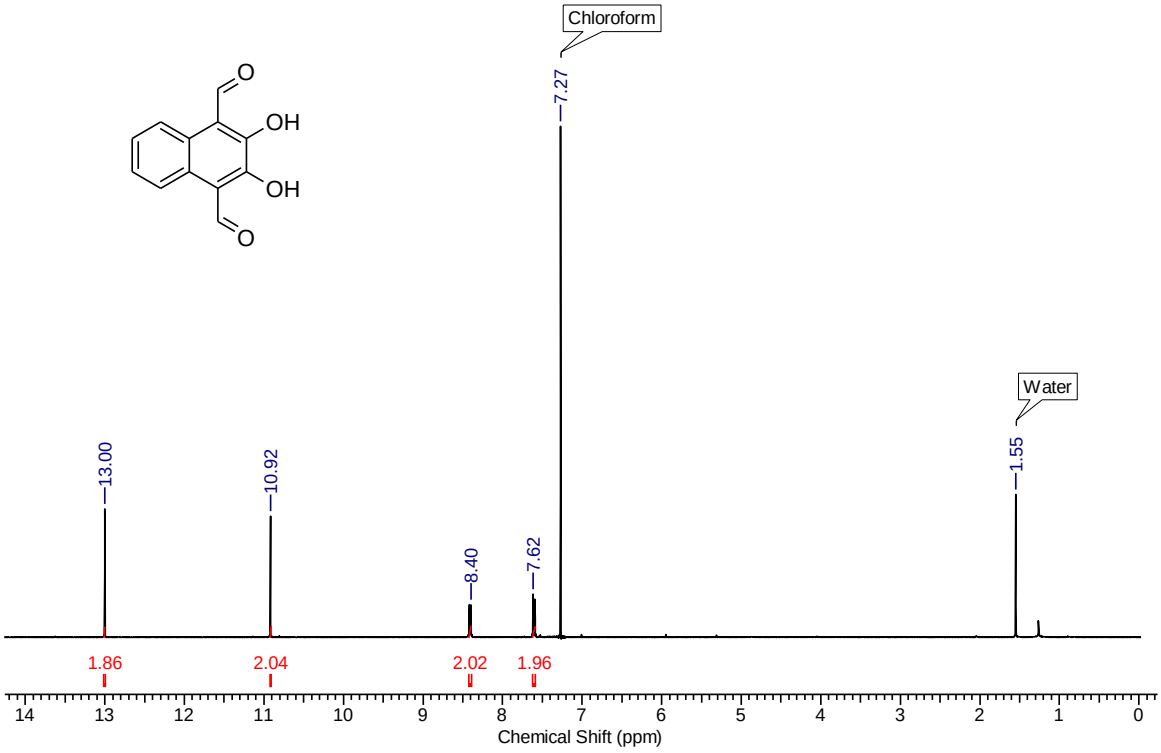


Figure S7. ^{1}H NMR spectrum for **11** ($CDCl_3$, 400 MHz).

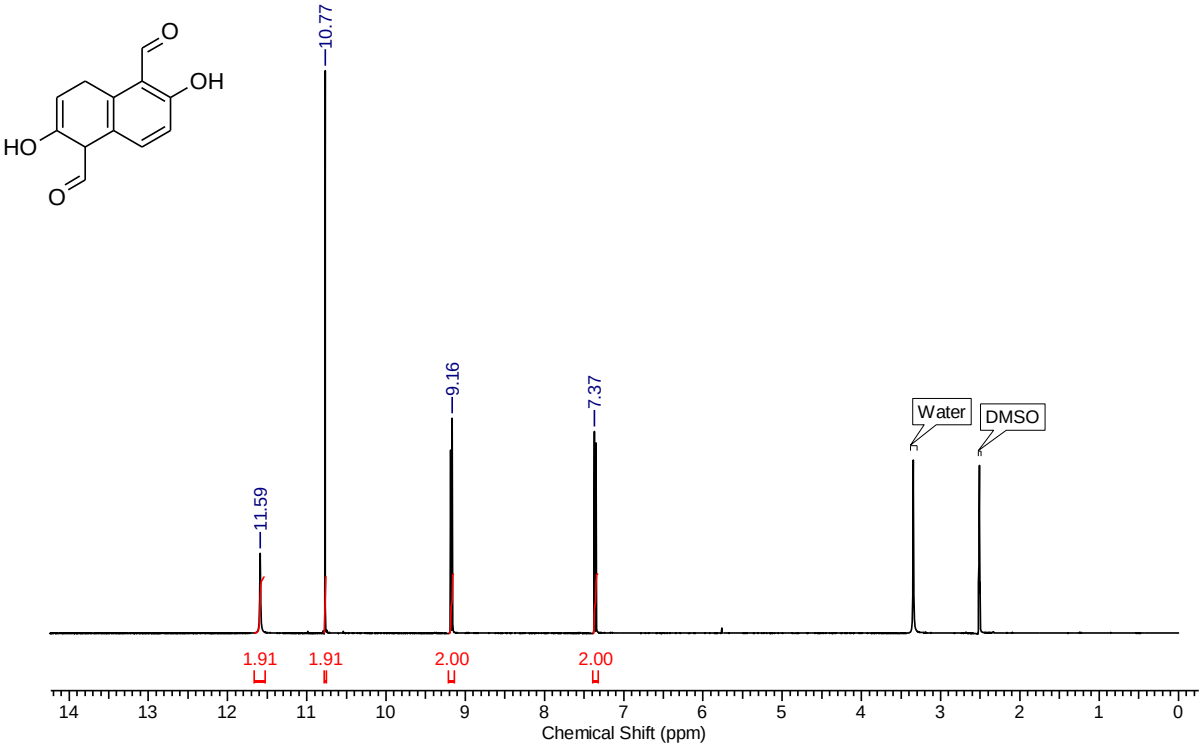


Figure S8. ^{1}H NMR spectrum for **12** (DMSO-d_6, 400 MHz).

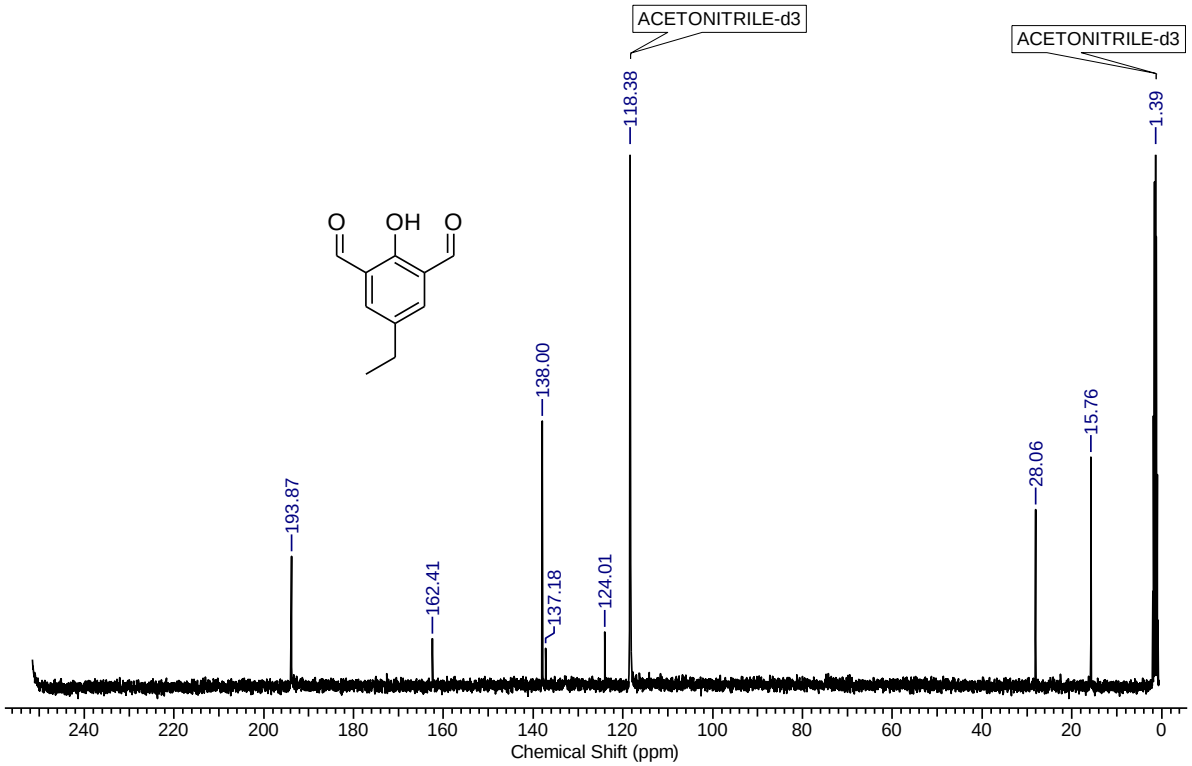


Figure S9. ^{13}C NMR spectrum for **5** (CD_3CN, 100 MHz).

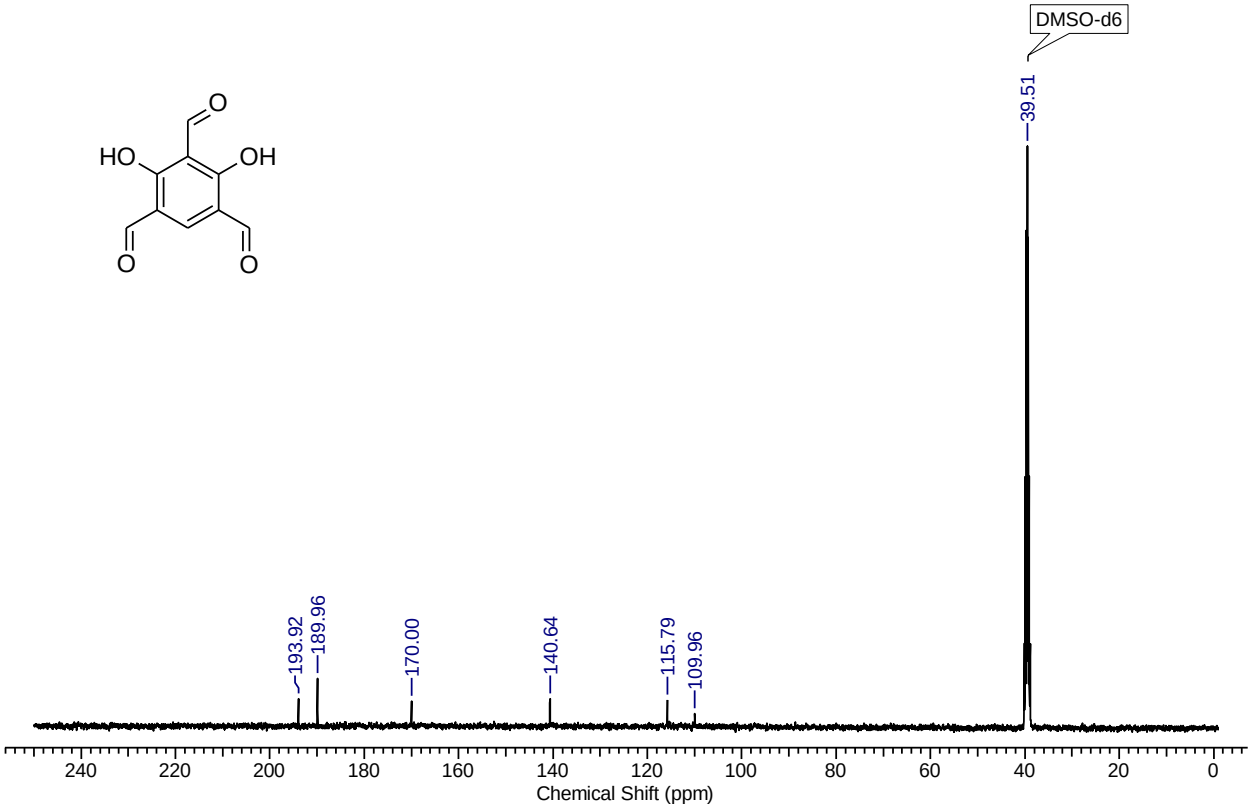


Figure S10. ^{13}C NMR spectrum for **6** (DMSO-d_6, 100 MHz).

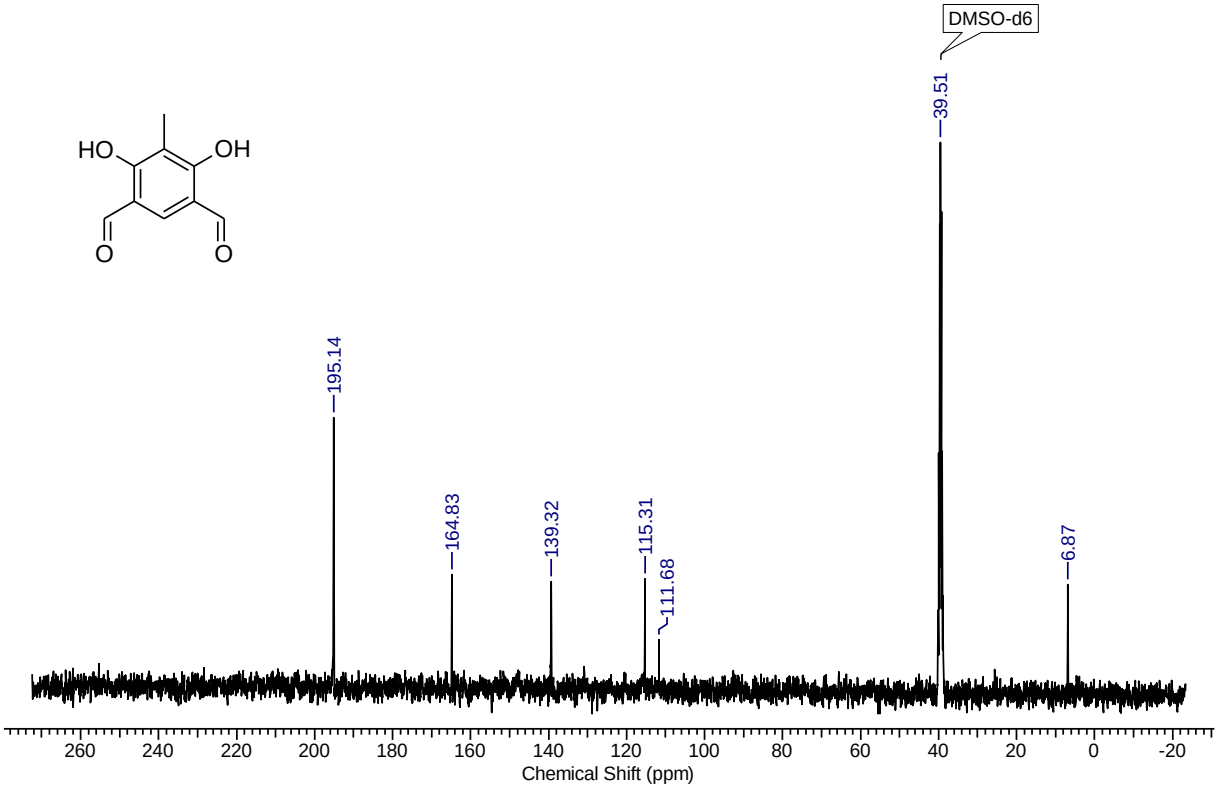


Figure S11. ^{13}C NMR spectrum for **7** (DMSO-d_6, 100 MHz).

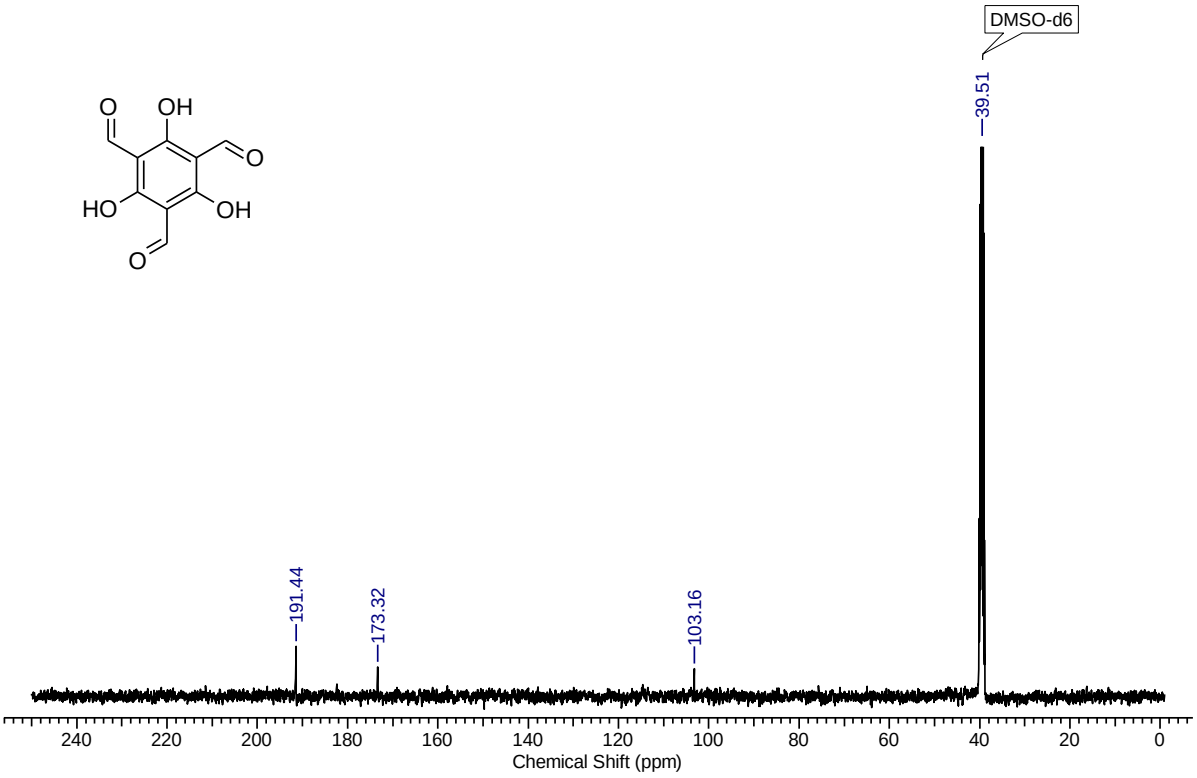


Figure S12. ^{13}C NMR spectrum for **8** (DMSO-d_6, 100 MHz).

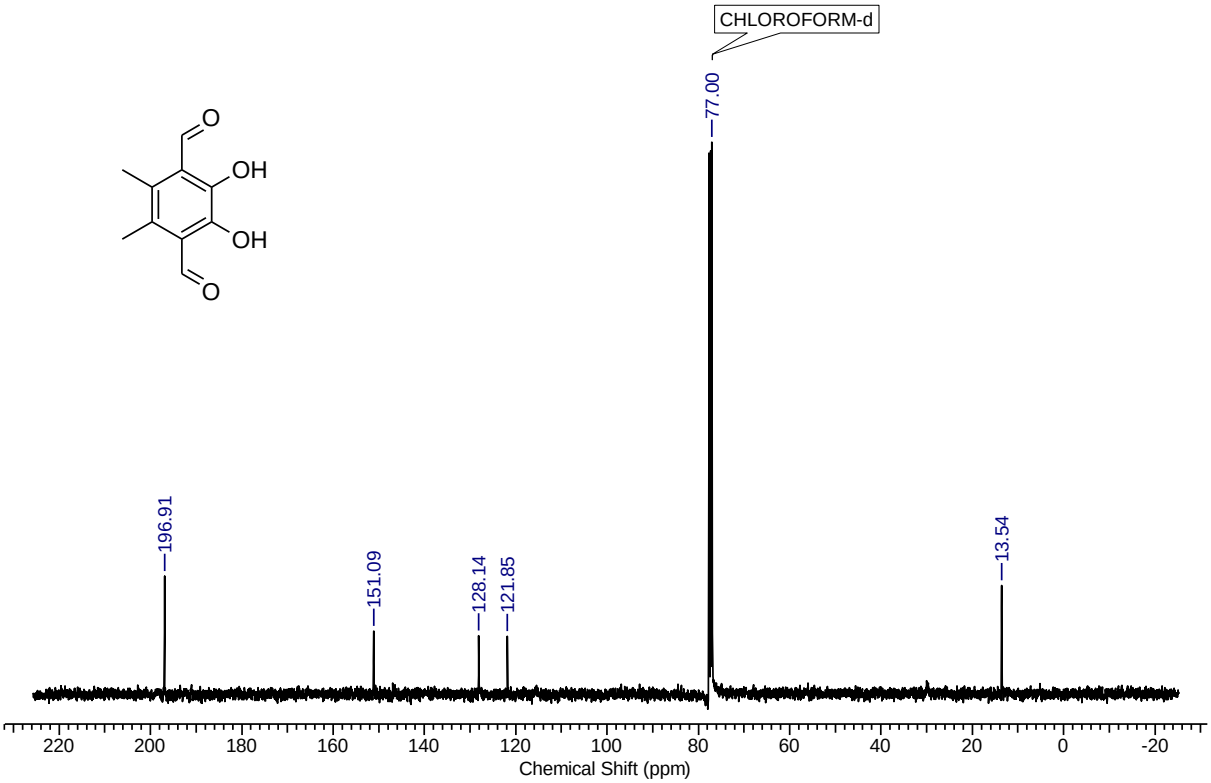


Figure S13. ^{13}C NMR spectrum for **9** ($CDCl_3$, 100 MHz).

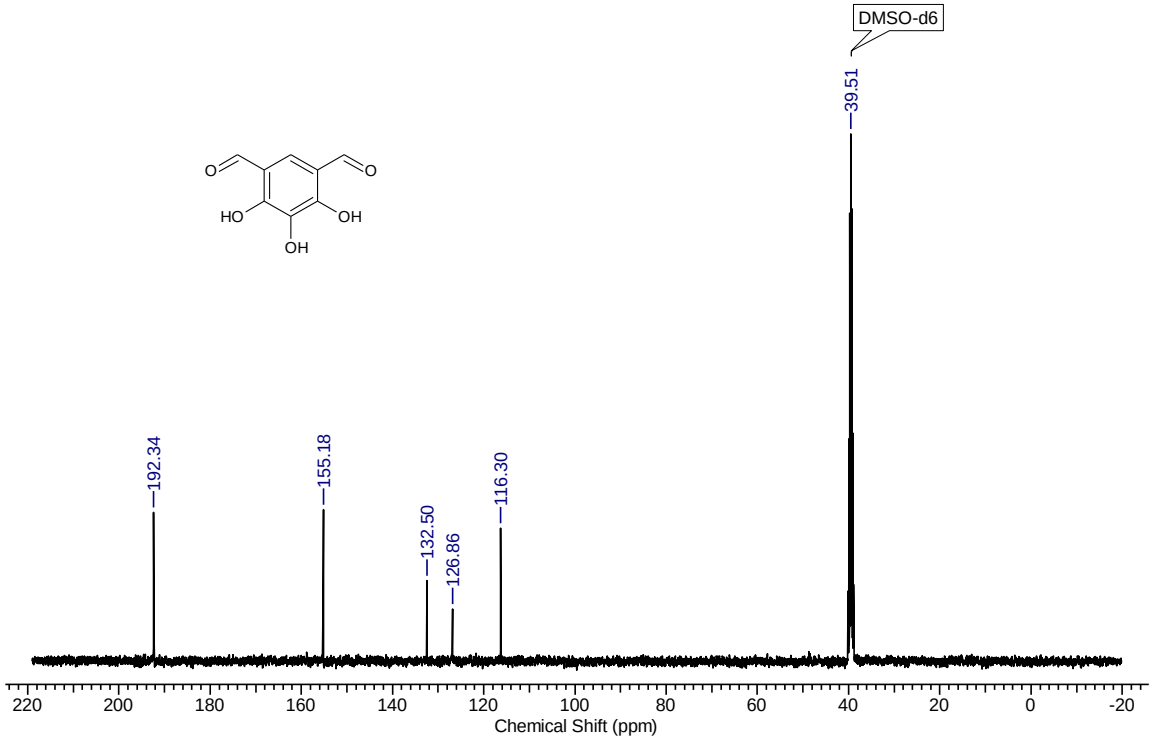


Figure S14. ^{13}C NMR spectrum for **10** (DMSO-d_6, 100 MHz).

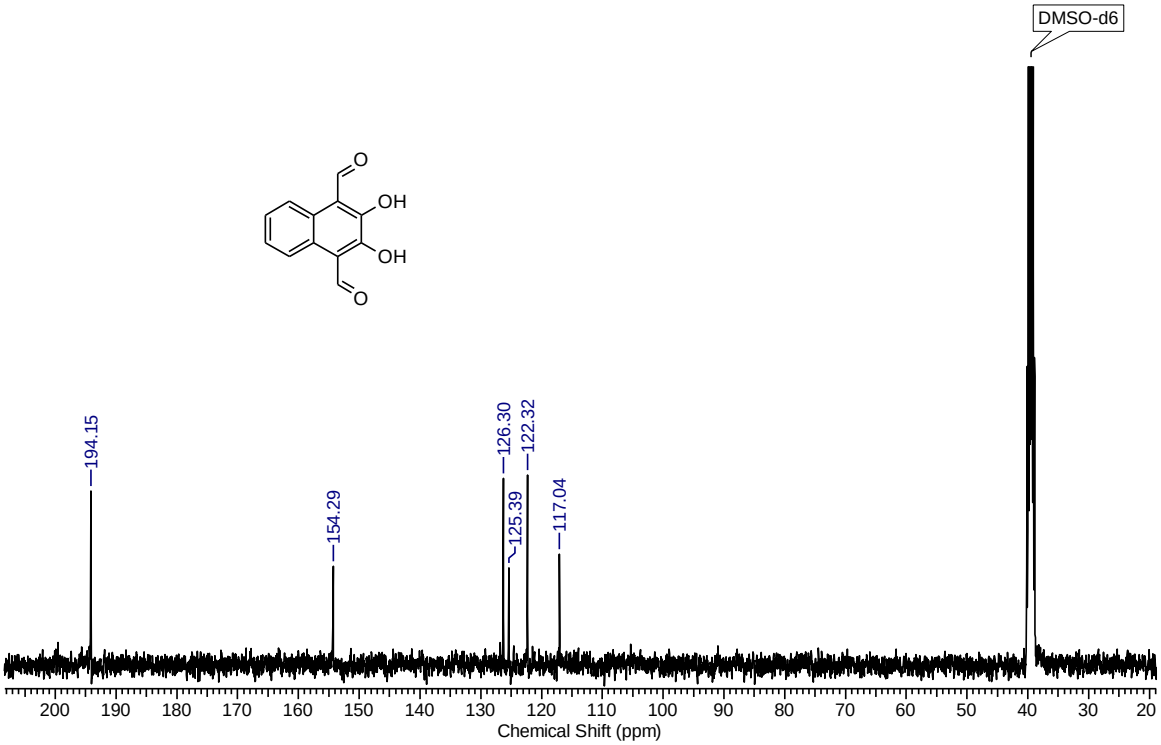


Figure S15. ^{13}C NMR spectrum for **11** (DMSO-d_6, 100 MHz).

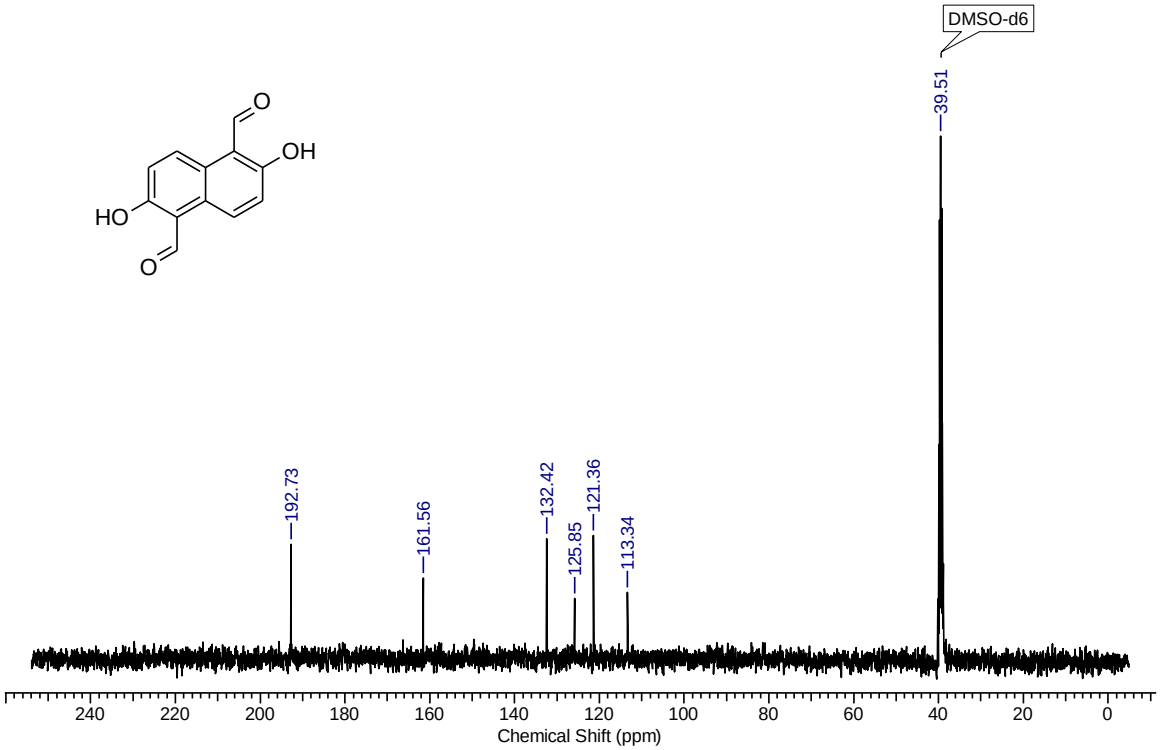


Figure S16. ^{13}C NMR spectrum for **12** (DMSO-d_6, 100 MHz).