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for

One-step hydroxylation of aryl and heteroaryl fluorides using mechanochemistry

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1. General contents

All reagents were purchased from commercial suppliers and used in analytical grades without further purification.

KOH in powder was purchased from Sigma-Aldrich, with a minimum purity of 85%.

Mechanochemical reactions were carried out using a Retsch MM 400 Mixer Mill, with milling jars made of ZrO_2 (10 mL in internal volume) and 15 milling balls made of the same material (each weighing 0.4 g, total mass: 6 g). The mill was operated at a frequency of 30 Hz for the corresponding indicated time.

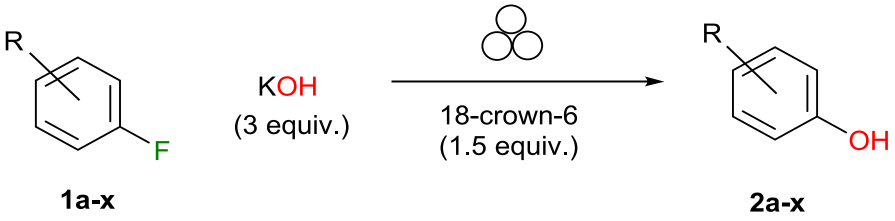
Purifications were carried out through Automated Flash Chromatography on a CombiFlash Rf + Teledyne ICSO system using prepacked RediSepRf Gold Silica columns (4g, 13 mL/min, max. pressure 600 psi, 20−400 mg sample), unless otherwise specified. Detection was performed with DAD and/or ELSD.

^1H, ^{13}C and ^{19}F NMR spectra were recorded at 23 °C on Bruker Avance III 500 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to traces of $CHCl_3$ (7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR) or DMSO (2.51 ppm for ^1H NMR and 40.0 ppm for ^{13}C NMR) in the corresponding deuterated solvent.

Melting points were determined with a Melting Point Apparatus B-545 (Büchi, Flawil, Switzerland) and were uncorrected. The heating rate was 5°C/min.

High-resolution mass spectra were obtained on a Bruker timsTOF device.

2. General procedure for the formation of phenols 2a-x



The corresponding aryl or heteroaryl fluoride **1a-x** (0.15 mmol), potassium hydroxide in powder (25.2 mg, 0.45 mmol, 3 equiv.) and ether 18-crown-6 (59.5 mg, 0.225 mmol, 1.5 equiv.) are weighed in a 10 mL ZrO_2 vessel and 15 balls of 5 mm were added (total ball mass ca. 6 g). The vial was closed, sealed, and placed in the Mixer Mill at 30 Hz for the indicated time (usually 1 hour, unless otherwise specified, see Scheme 2 in the manuscript).

Figure S1. ZrO_2 milling jar prior to milling arylfluoride **1a,** to afford phenol **2a.**

Figure S2. ZrO_2 milling jar after 1h milling at 30 Hz, containing phenol **2a** as product.

Then, the crude reaction mixture was dissolved in AcOEt and water (ca. 3 mL each) by adding them to the vessel and everything was homogenizing by manual shaking. The pH of the water was adjusted to a value of 5-6 with a 1M HCl solution to ensure protonation of the corresponding phenol. The mixture was transferred to an extraction funnel and extracted twice. The combined organic phases were washed with brine, dried over $MgSO_{4,}$ filtrated and the solvent was removed under reduced pressure.

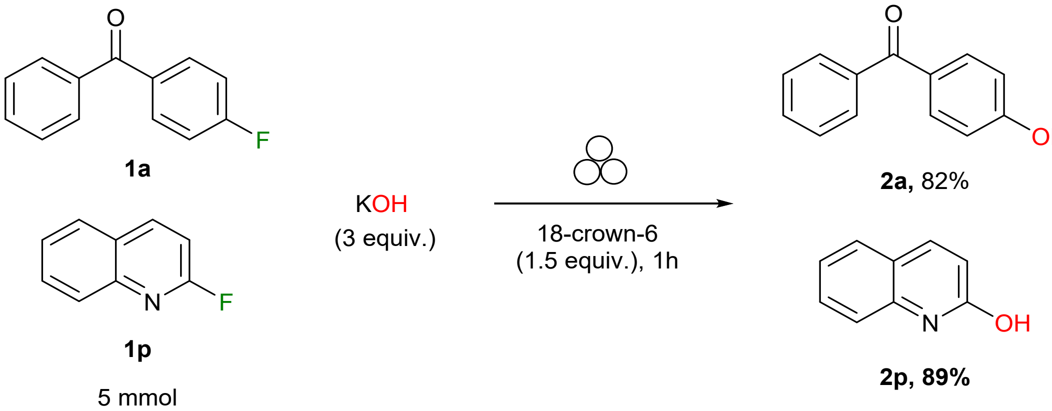
Alternatively, the crude reaction mixture can be dissolved in DCM in the milling jar, and directly injected into the Automated Flash Chromatography system.

All crude reaction mixtures were purified through Automated Flash Chromatography to afford the corresponding phenols **2a-x.**

- For the determination of conversions and NMR yields (Table 1)

1,3,5-trimethoxybenzene (16.8 mg, 0.1 mmol) was added to the reaction mixture. Everything was dissolved in AcOEt and water (ca. 3 mL each) by adding them to the vessel, homogenizing by manual shaking. The pH of the water was adjusted to a value of 5-6 with a 1M HCl solution to ensure protonation of the corresponding phenol. The mixture was transferred to an extraction funnel and extracted twice. The combined organic phases were washed with brine, dried over $MgSO_{4,}$ filtrated and the solvent was removed under reduced pressure. The crude was dissolved in $CDCl_3$ and integration was carried out in the ^1H NMR spectra.

- For the scale up:



The corresponding aryl or heteroaryl fluoride **1a** or **1p** (1 gram for **1a**; 736 mg for **1p**, 5 mmol), potassium hydroxide in powder (842 mg, 15 mmol, 3 equiv.) and ether 18-crown-6 (1.98 g, 7.5 mmol, 1.5 equiv.) were weighed in a 10 mL ZrO_2 vessel and 15 balls of 5 mm were added (total ball mass ca. 6 g). The vial was closed, sealed, and placed in the Mixer Mill at 30 Hz for 1h. Then, the crude reaction mixture was dissolved in DCM in the milling jar, and directly injected in the Automated Flash Chromatography

809 mg (Yield: 82%) of 4-hydroxybenzophenone **2a** were obtained.

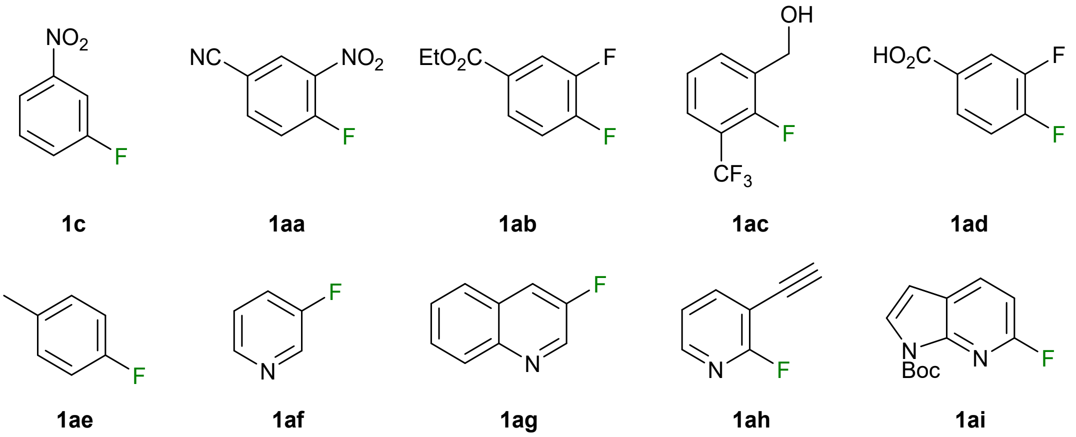
643 mg (Yield: 89%) of quinolin-2-ol **2p** were obtained.

- For the comparison in solution:

The corresponding aryl or heteroaryl fluoride **1j** or **1k** (0.15 mmol), potassium hydroxide in powder (25.2 mg, 0.45 mmol, 3 equiv.) and ether 18-crown-6 (59.5 mg, 0.225 mmol, 1.5 equiv.) were weighed in a flask, and dry DMSO (1.5 mL) was added. After 90 min, internal standard (1,3,5-trimethoxybenzene: 0.1 mmol, 16.8 mg), AcOEt (10 mL) and water (10 mL) were added to the flask. The pH of the water was carefully adjusted to a value of 5-6 with some drops of a 1M HCl solution to ensure protonation of the corresponding phenol. The mixture was transferred to an extraction funnel and extracted twice with AcOEt. The combined organic phases were washed with water, brine, dried over $MgSO_{4,}$ filtrated and the solvent was removed under reduced pressure. The crude was directly analysed by ^{1}H NMR.

The substrates shown in Figure S3 were also chosen to investigate the scope but did not afford the desired hydroxylated product in good yields.

Meta-activated compound **1c**, only gave traces of the desired phenol. In the case of nitrile **1aa**, mostly hydrolysis of the nitrile moiety was observed, yielding the corresponding carboxylic acid. Same issue was observed for ester **1ab**. The presence of acidic protons was also an expected limitation, due to the basicity of the hydroxide anion. Free alcohols or carboxylic acids (**1ac** and **1ad**) didn't yield the product under the standard conditions. A non-deactivated ring such as **1ae**, didn't show any conversion. 3-subtituted pyridine **1af** and quinoline **1ag** only gave traces of the hydroxylated product. The presence of a terminal triple bond (pyridine **1ah**) led to a complex mixture, probably due to polymerization. Finally, 7-azaindole **1ai** was also sluggish, as the loss of the Boc group and no reaction at position 2 were observed.

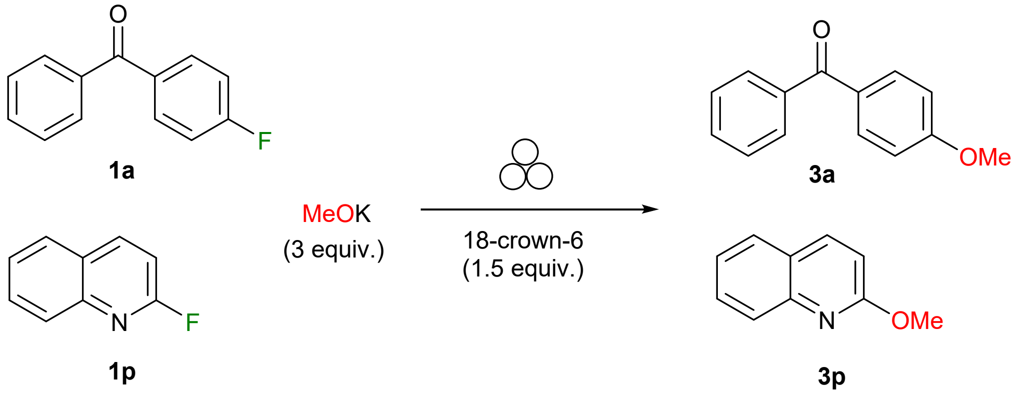


1c **1aa** **1ab** **1ac** **1ad**

1ae **1af** **1ag** **1ah** **1ai**

Figure S3. Substrates that did not give hydroxylated products in good yields.

3. General procedure for the formation of ethers 3a and 3p

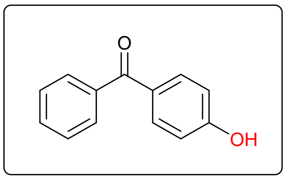


The corresponding aryl or heteroaryl fluoride **1a** or **1p** (30.0 or 22.1 mg, 0.15 mmol), potassium methoxide (31.6 mg, 0.45 mmol, 3 equiv.) and ether 18-crown-6 (59,5 mg, 0.225 mmol, 1.5 equiv.) were weighed in a 10 mL ZrO_2 vessel and 15 balls of 5 mm were added (total ball mass ca. 6 g).

The vial was closed, sealed, and placed in the Mixer Mill at 30 Hz for 1h. Then, the crude reaction mixture was directly dissolved in DCM, injected into the Automated Flash Chromatography system, to afford the corresponding phenols **3a** and **3p.**

4. Characterization of phenols 2a-x

4-Hydroxybenzophenone (2a)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 60% AcOEt).

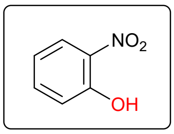
White solid (mp = 133-134°C). 25.8 mg (Yield: 87%). When the reaction was scaled up (See page S5), 809 mg (Yield: 82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80-7.72 (m, 4H), 7.59-7.55 (m, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.04, 160.96, 138.01, 133.18, 132.26, 129.88, 129.45, 128.29, 115.44.

HRMS (ESI): calculated for $C_{13}H_{11}O_2$ $(M + H)^+$: 199.0754; found: 199.0762.

2-Nitrophenol (2b)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 60% AcOEt).

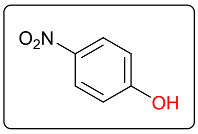
Yellow oil. 15.3 mg (Yield: 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.59 (s, 1H), 8.12 (dd, *J* = 8.5 and 1.7 Hz, 1H), 7.66 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H), 7.17 (dd, *J* = 8.5 and 1.3 Hz, 1H), 7.00 (ddd, *J* = 8.5, 7.2 and 1.3 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.15, 137.54, 133.73, 125.09, 120.23, 119.99.

HRMS (ESI): calculated for $C_6H_4NO_3$ $(M - H)^-$: 138.0197; found: 138.0196.

4-Nitrophenol (2d)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 60% AcOEt).

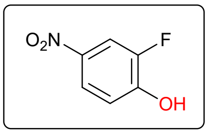
White solid (mp = 114-116°C). 17.4 mg (Yield: 83%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.09 (bs, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.36, 140.07, 126.66, 116.26.

HRMS (ESI): calculated for $C_6H_4NO_3$ $(M - H)^-$: 138.0197; found: 138.0195.

2-Fluoro-4-nitrophenol (2e)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 70% AcOEt).

White solid (mp = 118-119°C). 20.6 mg (Yield: 87%).

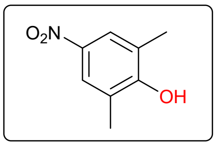
^{1}H NMR (500 MHz, DMSO): δ 11.60 (bs, 1H), 8.10 (dd, *J* = 11.1 and 2.7 Hz, 1H), 8.01 (ddd, *J* = 1.2, 2.7 and 8.9 Hz, 1H), 7.16 (t, *J* = 8.9 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 152.66 (C, d, *J* = 11.8 Hz), 150.23 (CF, d, *J* = 246 Hz), 139.39 (C, d, *J* = 7.6 Hz), 121.95 (CH, d, *J* = 3.2 Hz), 117.74 (CH, d, *J* = 3.5 Hz), 112.93 (CH, d, *J* = 22.8 Hz).

^{19}F NMR (471 MHz, DMSO): δ -133.33.

HRMS (ESI): calculated for $C_6H_3FNO_3$ $(M - H)^-$: 156.0102; found: 156.0090.

2,6-Dimethyl-4-nitrophenol (2f)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 80% AcOEt)

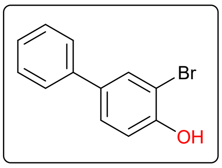
White solid (mp = 163-165°C). 20.0 mg (Yield: 80%).

^{1}H NMR (500 MHz, DMSO): δ 9.86 (bs, 1H), 7.89 (s, 2H), 2.25 (s, 6H).

^{13}C NMR (125 MHz, DMSO): δ 160.49, 139.60, 125.56, 124.46, 16.95.

HRMS (ESI): calculated for $C_8H_8NO_3$ $(M - H)^-$: 166.0509; found: 166.0499.

3-bromo-[1,1'-biphenyl]-4-ol (2g)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 40% AcOEt)

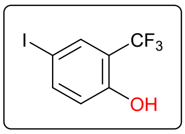
White solid (mp = 70-71 °C). 12.2 mg (Yield: 33%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (t, *J* = 1.9 Hz, 1H), 7.47-7.38 (m, 4H), 7.27 (t, *J* = 7.9 Hz, 1H), 6.93 - 6.86 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.56, 142.89, 132.48, 130.22, 129.75, 129.61, 128.42, 125.29, 122.87, 115.79.

HRMS (ESI): calculated for $C_{12}H_8BrO$ $(M - H)^-$: 246.9764; found: 246.9764.

4-Iodo-2-[(trifluoromethyl)phenol)] (2h)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 50% AcOEt).

White solid (mp = 63-64°C). 35.5 mg (Yield: 82%).

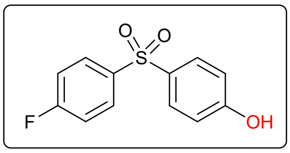
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.5 and 2.1 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 2H), 5.97 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.61, 142.17, 135.40 (CH, q, *J* = 4.9 Hz), 122.94 (CF_3, q, *J* = 272 Hz), 119.91, 118.74 (C, q, *J* = 31 Hz), 81.55.

^{19}F NMR (471 MHz, $CDCl_3$): δ -61.41

HRMS (ESI): calculated for $C_7H_3F_3IO$ $(M - H)^-$: 286.9186; found: 286.9185.

4-[(4-fluorophenyl)sulphonyl]phenol (2i)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 0 to 70% AcOEt)

White solid (mp = 154-155°C). 23.3 mg (Yield: 62%).

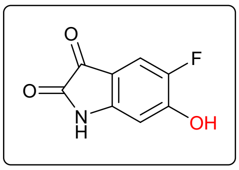
^{1}H NMR (500 MHz, DMSO): δ 10.66 (s, 1H), 8.00-7.93 (m, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 7.43 (dd, *J* = 9.7 and 8.1 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (125 MHz, DMSO): δ 164.97 (CF, d, *J* = 253 Hz), 162.65, 139.16, 131.06, 130.50 (2 CH, d, *J* = 9.6 Hz), 130.37, 117.27 (2 CH, d, *J* = 23 Hz), 116.65.

^{19}F NMR (471 MHz, DMSO): δ -105.68.

HRMS (ESI): calculated for $C_{12}H_{10}FO_3S$ (M + H)$^+$: 253.0329; found: 253.0337.

5-Fluoro-6-hydroxyindoline-2,3-dione (2j)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 30% MeOH).

Orange solid (mp = 301-303°C). 17.8 mg (Yield: 66%).

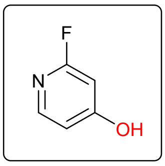
^{1}H NMR (500 MHz, DMSO): δ 10.77 (bs, 1H), 7.37 (d, *J* = 9.6 Hz, 1H), 6.47 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 181.73, 161.03, 155.99 (C, d, *J* = 14.1 Hz), 150.19, 148.06 (CF, d, *J* = 239 Hz), 113.11 (CH, d, *J* = 20.0 Hz), 108.43 (C, d, *J* = 5.8 Hz), 101.32.

^{19}F NMR (471 MHz, DMSO): δ -143.89.

HRMS (ESI): calculated for $C_8H_3FNO_3$ (M - H)$^-$: 180.0102; found: 180.0100.

2-Fluoro-4-hydroxypyridine (2k)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 20% MeOH).

Pale brown solid (mp = 148-150°C). 12.2 mg (Yield: 72%).

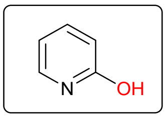
^{1}H NMR (500 MHz, DMSO): δ 7.91 (d, *J* = 5.7 Hz, 1H), 6.71 (dt, *J* = 5.7, 1.9 Hz, 1H), 6.39 (d, *J* = 1.9 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 168.97 (C, d, *J* = 12.1 Hz), 165.23 (CF, d, *J* = 231 Hz), 148.42 (CH, d, *J* = 19.0 Hz), 111.19 (CH, d, *J* = 3.4 Hz), 95.90 (CH, d, *J* = 40.0 Hz).

^{19}F NMR (471 MHz, DMSO): δ -68.88

HRMS (ESI): calculated for C_5H_5FNO (M + H)$^+$: 114.0350; found: 144.0355.

2(1*H*)-Pyridinone (2l)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 20% MeOH).

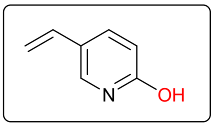
White solid (mp = 106-108°C). 10.4 mg (Yield: 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 13.44 (bs, 1H), 7.48 (ddd, *J* = 9.2, 6.6 and 2.1 Hz, 1H), 7.41 (ddd, *J* = 6.6, 2.1 and 1.1 Hz, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 6.30 (td, *J* = 6.6 and 1.1 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 165.51, 141.75, 134.73, 120.22, 106.98.

HRMS (ESI): calculated for C_5H_6NO $(M + H)^+$: 96.0444; found: 96.0448.

2-Hydroxy-5-vinyl-pyridine (2m)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 15% MeOH).

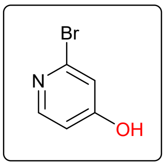
Pale brown solid (mp = 117-118°C). 14.0 mg (Yield: 77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 9.5 and 2.6 Hz, 1H), 7.33 (d, *J* = 2.6 Hz, 1H), 6.61 (d, *J* = 9.5 Hz, 1H), 6.45 (dd, *J* = 17.5 and 11.0 Hz, 1H), 5.49 (d, *J* = 17.5 Hz, 1H), 5.16 (d, *J* = 11.0 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.96, 138.62, 132.76, 131.46, 120.32, 118.35, 112.14.

HRMS (ESI): calculated for C_7H_8NO $(M + H)^+$: 122.0601; found: 122.0604.

2-Bromo-4-hydroxypyridine (2n)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 30% MeOH).

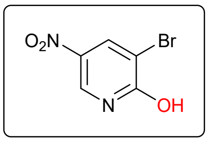
Pale yellow solid (mp = 171-173°C). 17.0 mg (Yield: 65%).

^{1}H NMR (500 MHz, DMSO): δ 11.21 (s, 1H), 8.06 (d, *J* = 5.7 Hz, 1H), 6.96 (d, *J* = 2.2 Hz, 1H), 6.81 (dd, *J* = 5.7 and 2.2 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 166.11, 151.46, 142.54, 115.14, 112.36.

HRMS (ESI): calculated for C_5H_5BrNO $(M + H)^+$: 173.9549; found: 173.9557.

3-Bromo-2-hydroxy-5-nitropyridine (2o)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 10% MeOH).

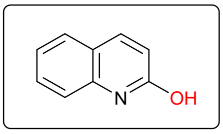
Orange solid (mp = 212-214 °C). 24.2 mg (Yield: 74%).

^{1}H NMR (500 MHz, DMSO): δ 13.18 (bs, 1H), 8.73 (d, *J* = 2.9 Hz, 1H), 8.57 (d, *J* = 2.9 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 158.93, 138.13, 136.14, 130.60, 114.86.

HRMS (ESI): calculated for $C_5H_4BrN_2O_3$ (M + H)$^+$: 218.9400; found: 218.9408.

2-Hydroxyquinoline (2p)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 20 to 100% AcOEt)

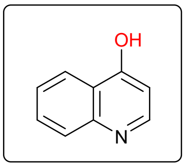
White solid (mp = 197-198°C). 20.8 mg (Yield: 96%).

^{1}H NMR (500 MHz, DMSO): δ 11.74 (s, 1H), 7.90 (d, *J* = 9.5 Hz, 1H), 7.65 (dd, *J* = 7.8 and 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.5, 7.3 and 1.4 Hz, 1H), 7.32 (dd, *J* = 8.2 and 1.1 Hz, 1H), 7.17 (ddd, *J* = 8.2, 7.3 and 1.1 Hz, 1H), 6.50 (d, *J* = 9.5 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 162.39, 140.68, 139.35, 130.79, 128.32, 122.38, 122.19, 119.57, 115.58.

HRMS (ESI): calculated for C_9H_8NO (M + H)$^+$: 146.0601; found: 146.0605.

4-Hydroxyquinoline (2q)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 30% MeOH)

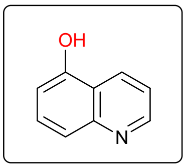
White solid (mp = 186-188 °C). 19.9 mg (Yield: 91%).

^{1}H NMR (500 MHz, DMSO): δ 11.77 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.04 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 177.35, 140.51, 139.85, 132.07, 126.29, 125.41, 123.51, 118.73, 109.14.

HRMS (ESI): calculated for C_9H_8NO (M + H)$^+$: 146.0601; found: 146.0608.

5-Hydroxyquinoline (2r)



Purified through Combiflash System from ISCO (Cyclohexane:AcOEt, 20 to 100% AcOEt)

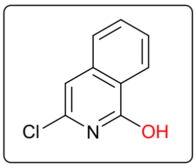
White solid (mp = 220-221 °C). 10.5 mg (Yield: 48%).

^{1}H NMR (500 MHz, DMSO): δ 10.46 (s, 1H), 8.89 - 8.83 (m, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.49 - 7.40 (m, 2H), 6.94 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (125 MHz, DMSO): δ 153.72, 150.92, 149.38, 130.98, 130.27, 120.47, 120.08, 119.82, 108.85.

HRMS (ESI): calculated for C_9H_8NO (M + H)$^+$: 146.0601; found: 146.0607.

3-Chloro-1-Hydroxyisoquinoline (2s)



Purified through Combiflash (Cyclohexane:AcOEt, 0 to 100% AcOEt).

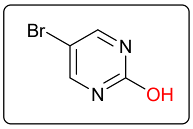
White solid (mp = 216-218 °C). 22.2 mg (Yield: 82%).

^{1}H NMR (500 MHz, DMSO): δ 12.27 (bs, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.72 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.50 (ddd, J = 8.2, 7.0 and 1.4 Hz, 1H), 6.77 (s, 1H).

^{13}C NMR (125 MHz, DMSO): δ 162.69, 137.96, 133.50, 127.25, 127.20, 126.34.

HRMS (ESI): calculated for C_9H_7ClNO (M + H)$^+$: 180.0211; found: 180.0220.

5-Bromo-1-hydroxypyrimidine (2t)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 50% MeOH)

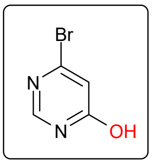
White solid (mp = 216-218°C). 16.0 mg (Yield: 61%).

^{1}H NMR (500 MHz, DMSO): δ 12.32 (bs, 1H), 8.46 (s, 2H)

^{13}C NMR (125 MHz, DMSO): δ 158.13, 157.56, 99.39.

HRMS (ESI): calculated for $C_4H_4BrN_2O$ (M + H)$^+$: 174.9502; found: 174.9506.

4-Bromo-6-hydroxypyrimidine (2u)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 20% MeOH)

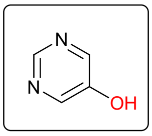
Yellow solid (mp = 215-217°C). 16.7 mg (Yield: 64%).

^{1}H NMR (500 MHz, DMSO): δ 13.01 (bs, 1H), 8.14 (s, 1H), 6.70 (s, 1H)

^{13}C NMR (125 MHz, DMSO): δ 160.66, 150.98, 149.88, 118.42.

HRMS (ESI): calculated for $C_4H_2BrN_2O$ (M - H)$^+$: 172.9356; found: 172.9350.

5-Hydroxypyrimidine (2v)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 20% MeOH)

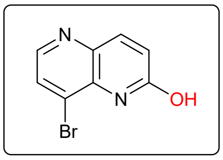
Brown solid (mp = 208-210°C). 11.0 mg (Yield: 76%).

^{1}H NMR (500 MHz, DMSO): δ 10.54 (bs, 1H), 8.66 (s, 1H), 8.34 (s, 2H).

^{13}C NMR (125 MHz, DMSO): δ 152.48, 150.31, 144.67.

HRMS (ESI): calculated for $C_4H_5N_2O$ (M + H)$^+$: 97.0397; found: 97.0401.

8-Bromo-2-hydroxy-1,5-naphthyridine (2w)



Purified through Combiflash System from ISCO (DCM:MeOH, 0 to 6% MeOH).

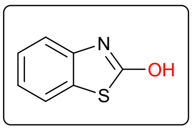
White solid (mp = 205-206°C). 23.5 mg (Yield: 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (bs, 1H), 8.34 (d, *J* = 5.0 Hz, 1H), 7.94 (d, *J* = 9.8 Hz, 1H), 7.65 (d, *J* = 5.0 Hz, 1H), 6.90 (d, *J* = 9.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.42, 145.05, 141.91, 138.39, 132.98, 127.75, 126.94, 118.98.

HRMS (ESI): calculated for $C_8H_6BrN_2O$ $(M + H)^+$: 224.9658; found: 224.9664.

2-Hydroxybenzo[*d*]thiazol (2x)



Purified through Combiflash (Cyclohexane:AcOEt, 0 to 100% AcOEt).

White solid (mp = 137-138°C). 17.5 mg (Yield: 77%).

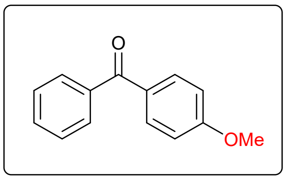
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (bs, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.30-7.25 (m, 1H), 7.18-7.12 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.96, 135.34, 126.52, 123.93, 123.28, 122.56, 111.73.

HRMS (ESI): calculated for C_7H_4NOS $(M - H)^-$: 150.0019; found: 150.0011.

5. Characterization of phenols 3a and 3p

4-Methoxybenzopheone (3a)



Purified through Combiflash (Cyclohexane:AcOEt, 0 to 50% AcOEt).

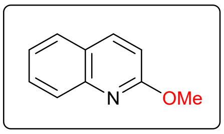
White solid (mp = 57-59°C). 27.1 mg (Yield: 85%).

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.79 - 7.73 (m, 2H), 7.63 - 7.53 (m, 1H), 7.47 (dd, *J* = 8.4 and 7.0 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H).

^{13}**C NMR** (125 MHz, $CDCl_3$): δ 195.56, 163.22, 138.28, 132.56, 131.88, 130.14, 129.72, 128.18, 113.55, 55.49.

HRMS (ESI): calculated for $C_{14}H_{13}O_2$ $(M + H)^+$: 213.0910; found: 213.0914.

2-Methoxyquinoline (3p)



Purified through Combiflash (Cyclohexane:AcOEt, 0 to 50% AcOEt).

White solid (mp = 217-219 °C). 18.5 mg (Yield: 77%).

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.8 Hz, 1H), 7.85 (dd, *J* = 8.3 and 1.1 Hz, 1H), 7.71 (dd, *J* = 8.0 and 1.5 Hz, 1H), 7.62 (ddd, *J* = 8.3, 6.9 and 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.0, 6.9 and 1.1 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 4.08 (s, 3H).

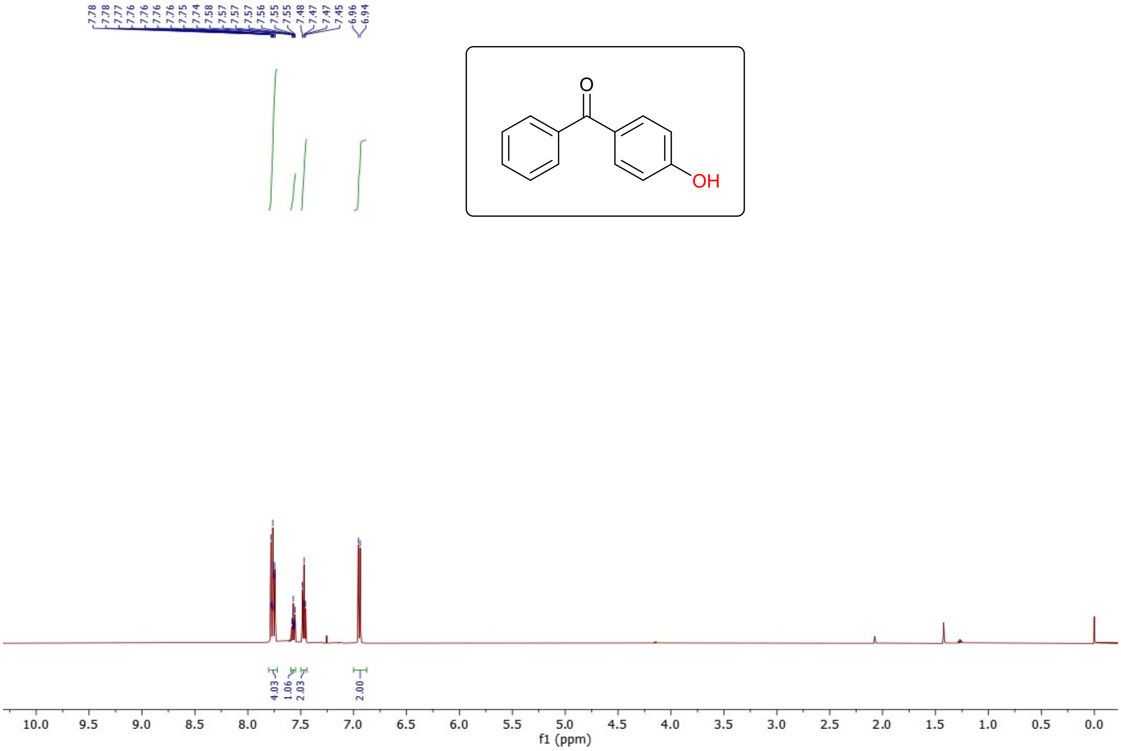
^{13}**C NMR** (125 MHz, $CDCl_3$): δ 162.42, 146.59, 138.66, 129.47, 127.43, 127.23, 125.08, 123.97, 113.07, 53.37.

HRMS (ESI): calculated for C_9H_8NO $((M + H) - CH_3)^+$: 146.0601; found: 146.0607.

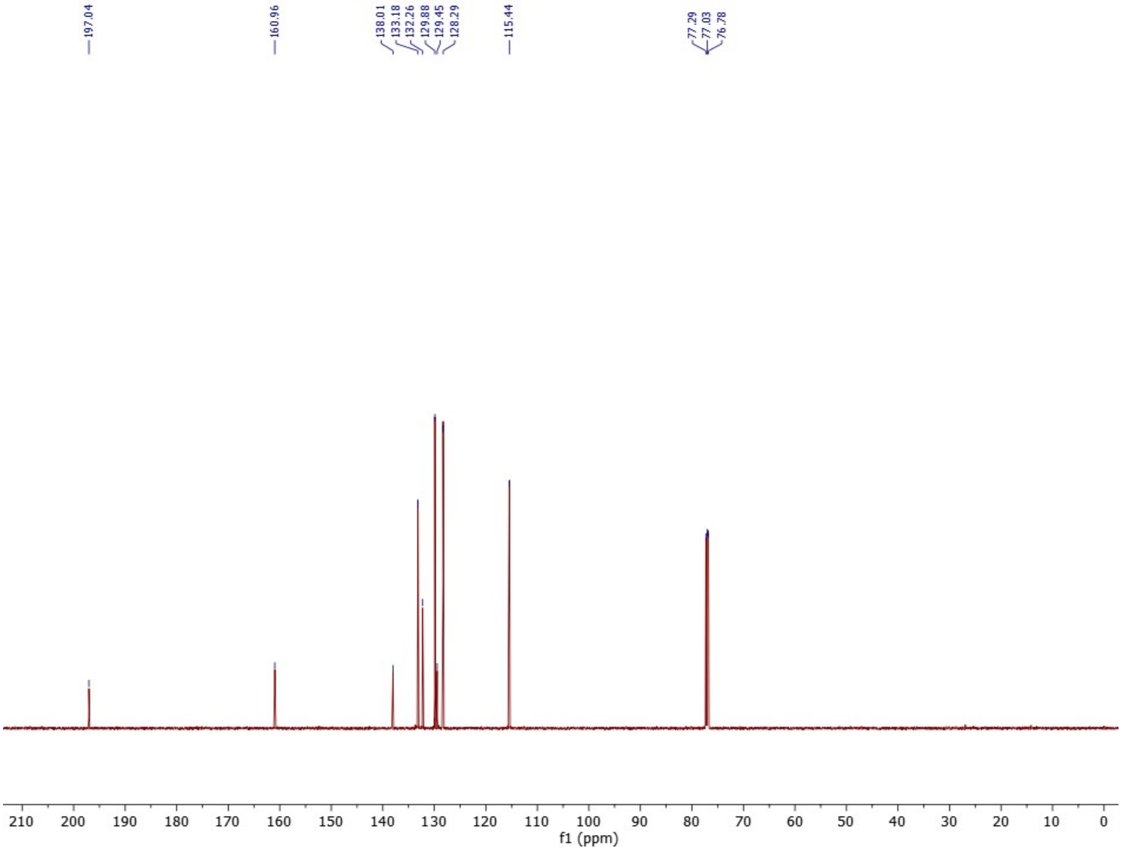
6. ^{1}H, ^{13}C and ^{19}F spectra of phenols 2a-x and ethers 3a and 3p

4-Hydroxybenzophenone (2a)

^{1}H NMR (500 MHz, $CDCl_3$)

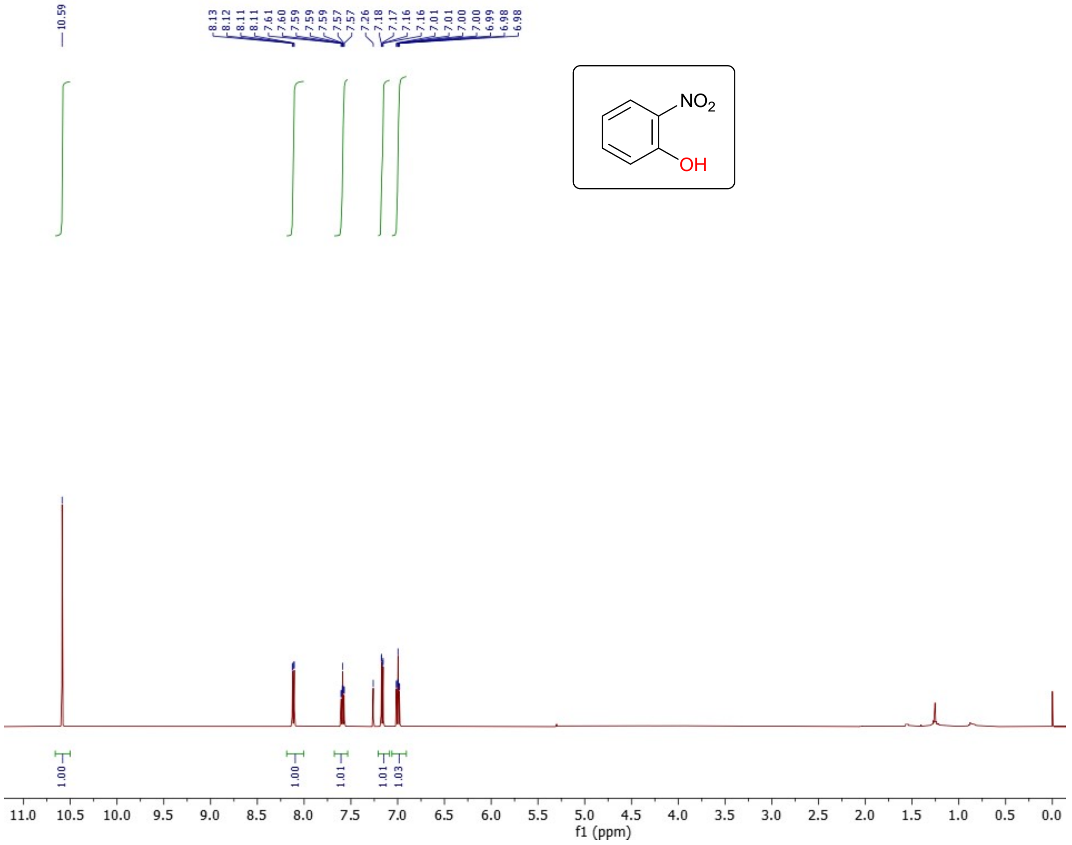


^{13}C NMR (125 MHz, $CDCl_3$)

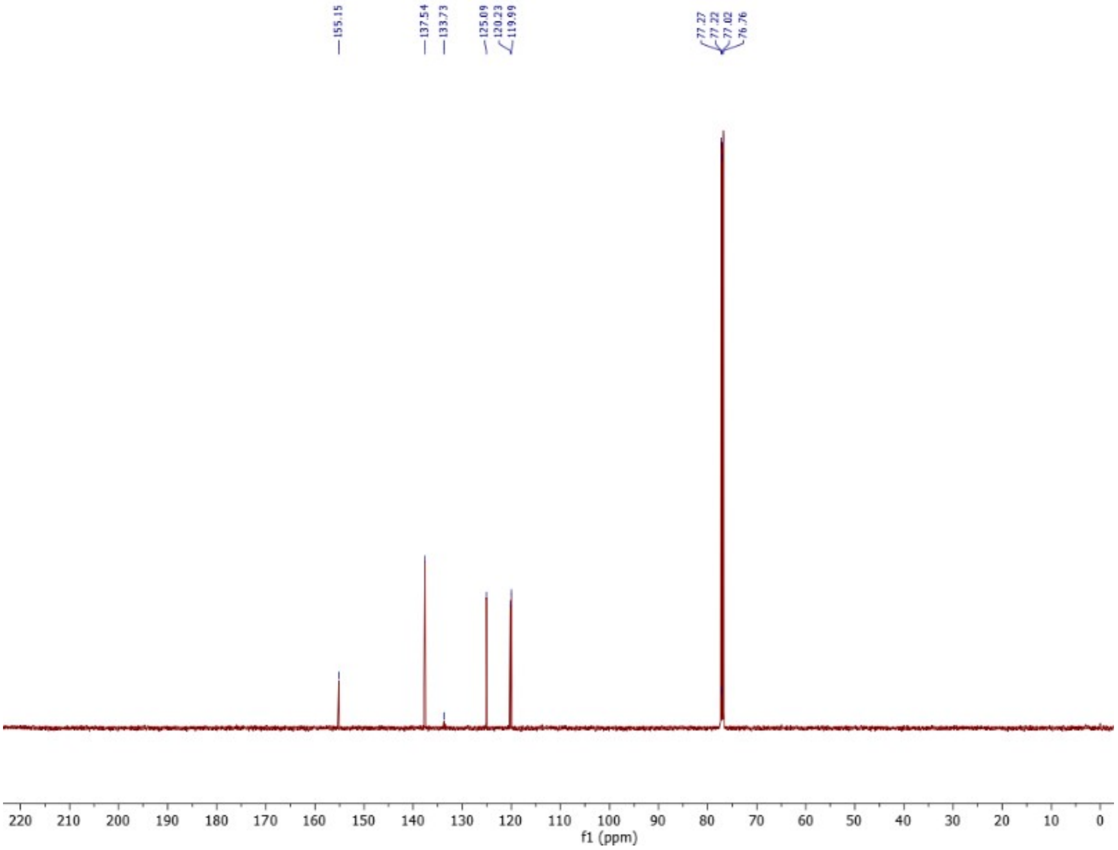


2-Nitrophenol (2b)

^{1}H NMR (500 MHz, $CDCl_3$)

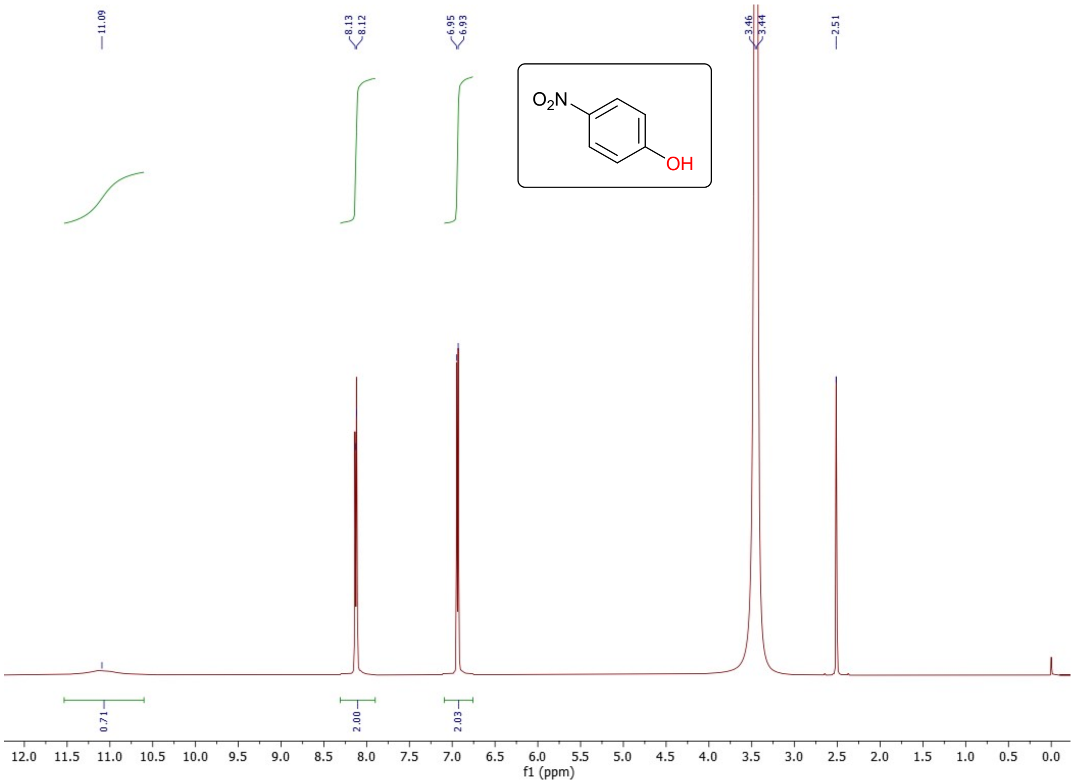


^{13}C NMR (125 MHz, $CDCl_3$)

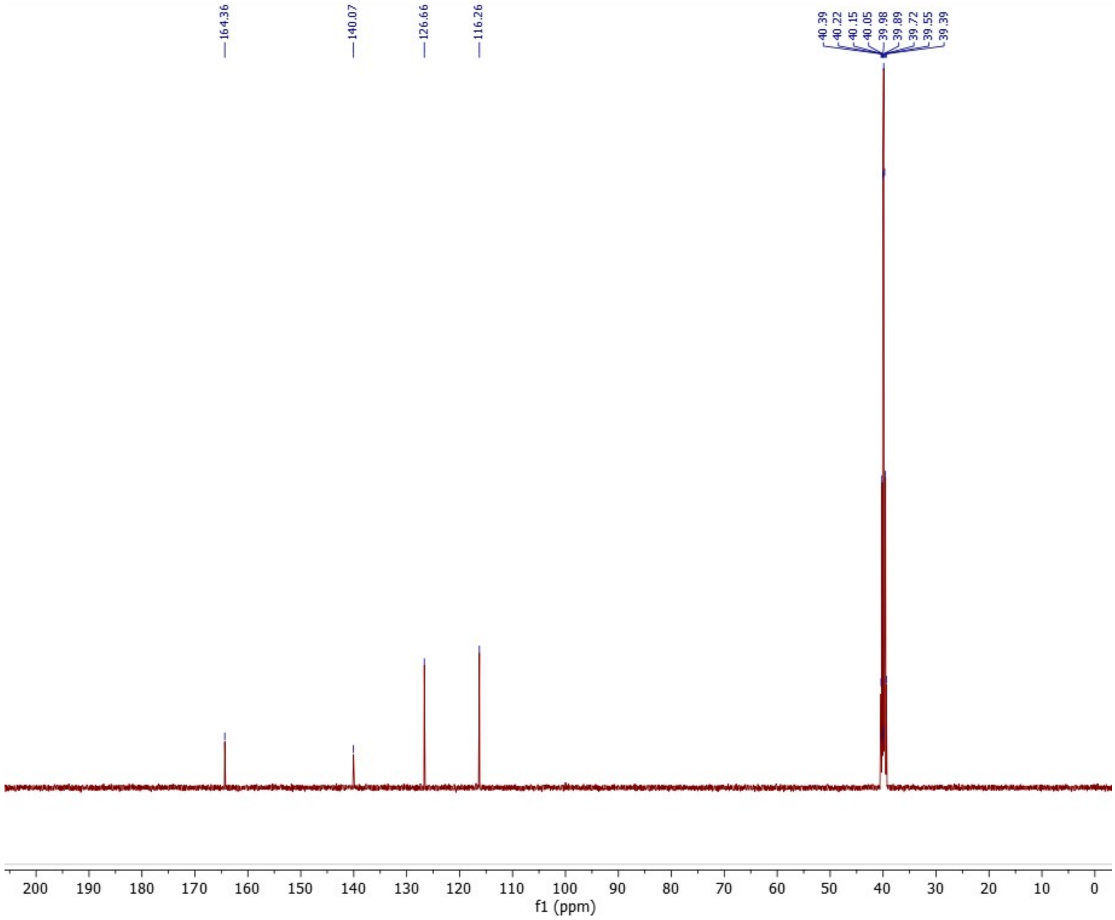


4-Nitrophenol (2d)

^{1}H NMR (500 MHz, DMSO)

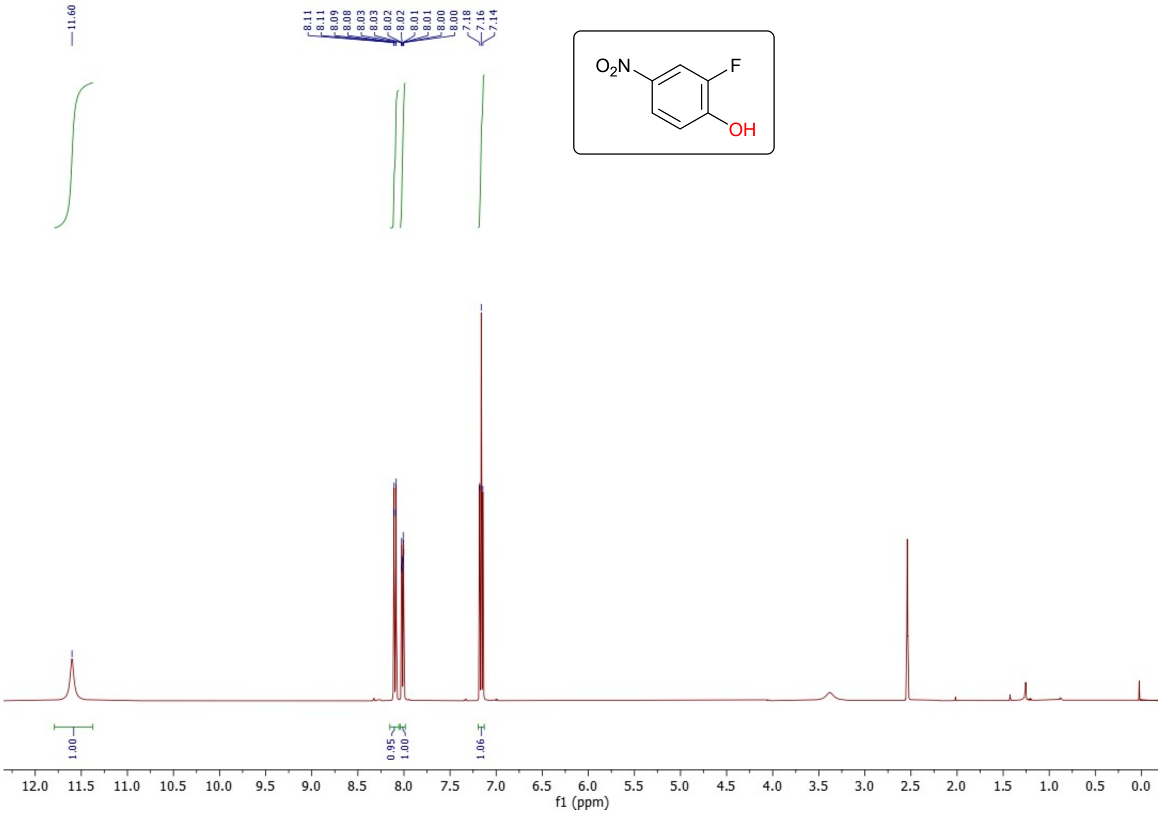


^{13}C NMR (125 MHz, DMSO)

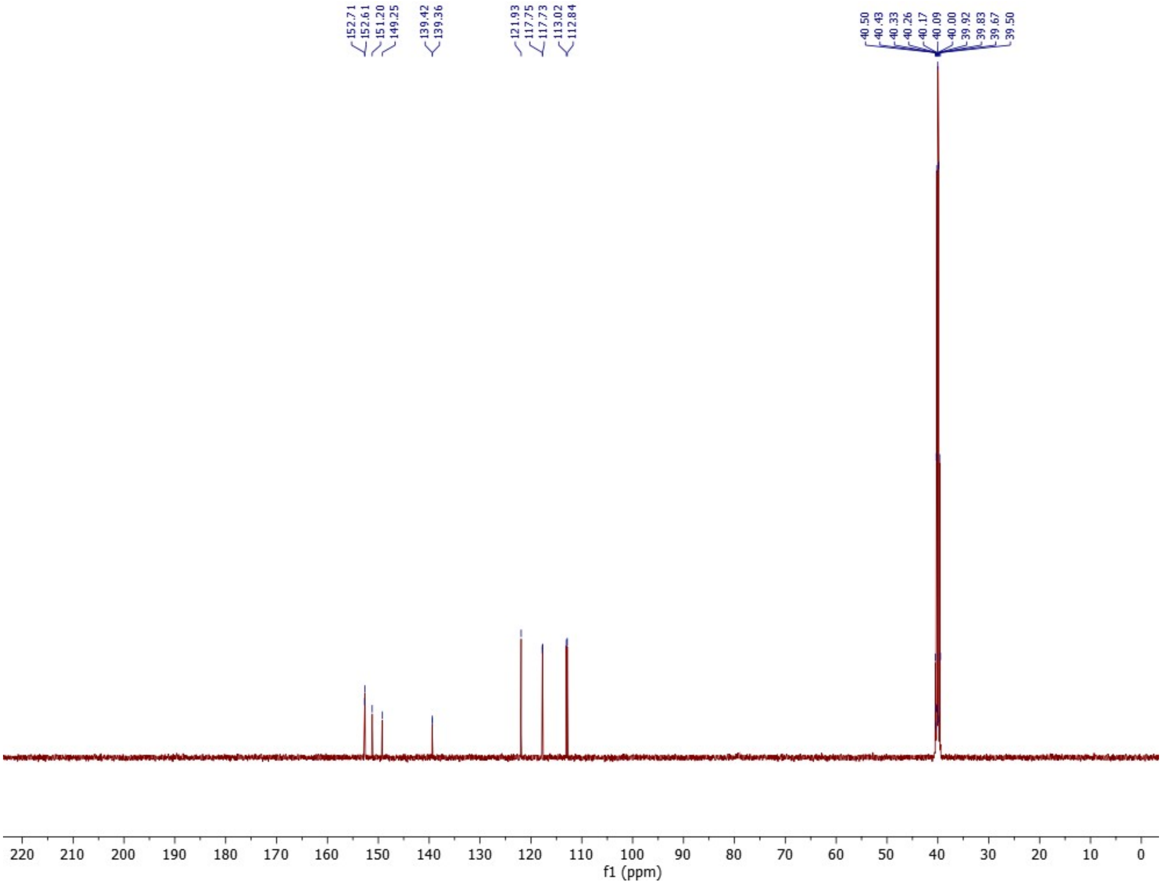


2-Fluoro-4-nitrophenol (2e)

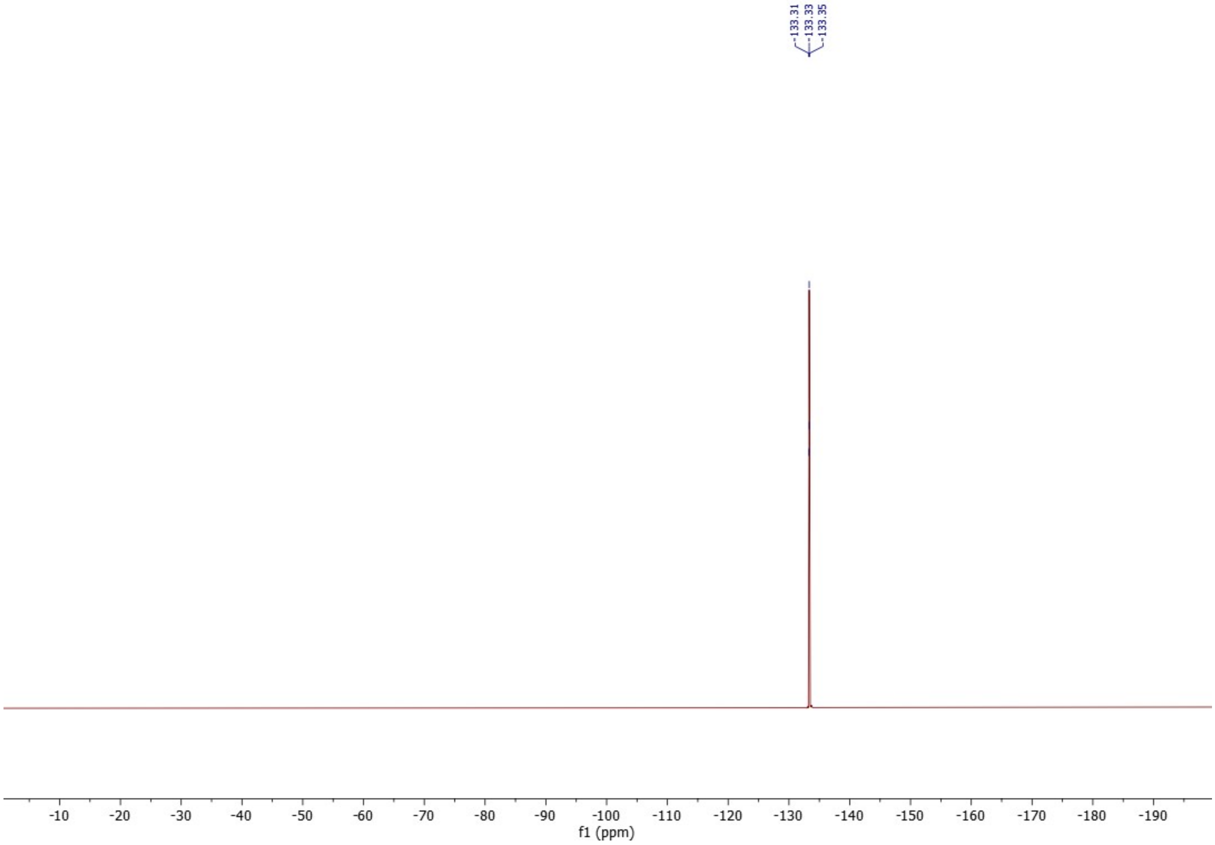
^{1}H NMR (500 MHz, DMSO)



^{13}C NMR (125 MHz, DMSO)

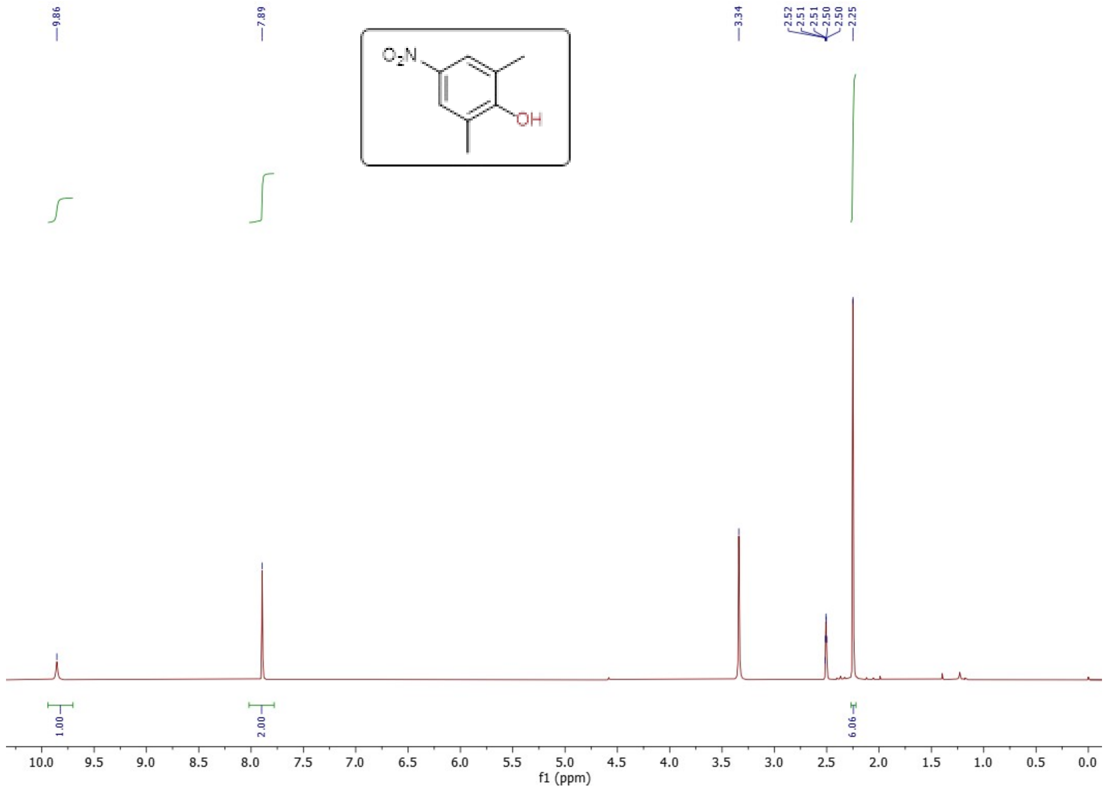


^{19}F NMR (471 MHz, DMSO)

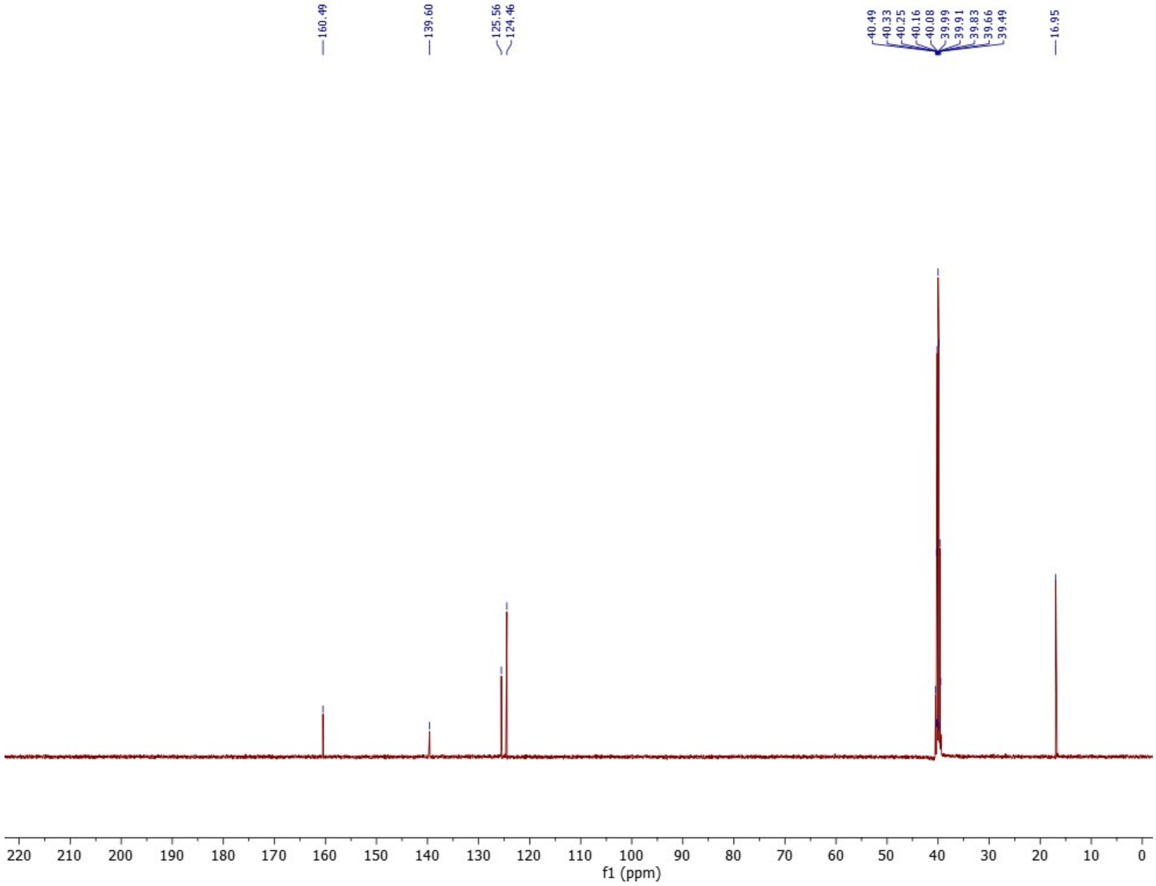


2,6-Dimethyl-4-nitrophenol (2f)

^{1}H NMR (500 MHz, DMSO)

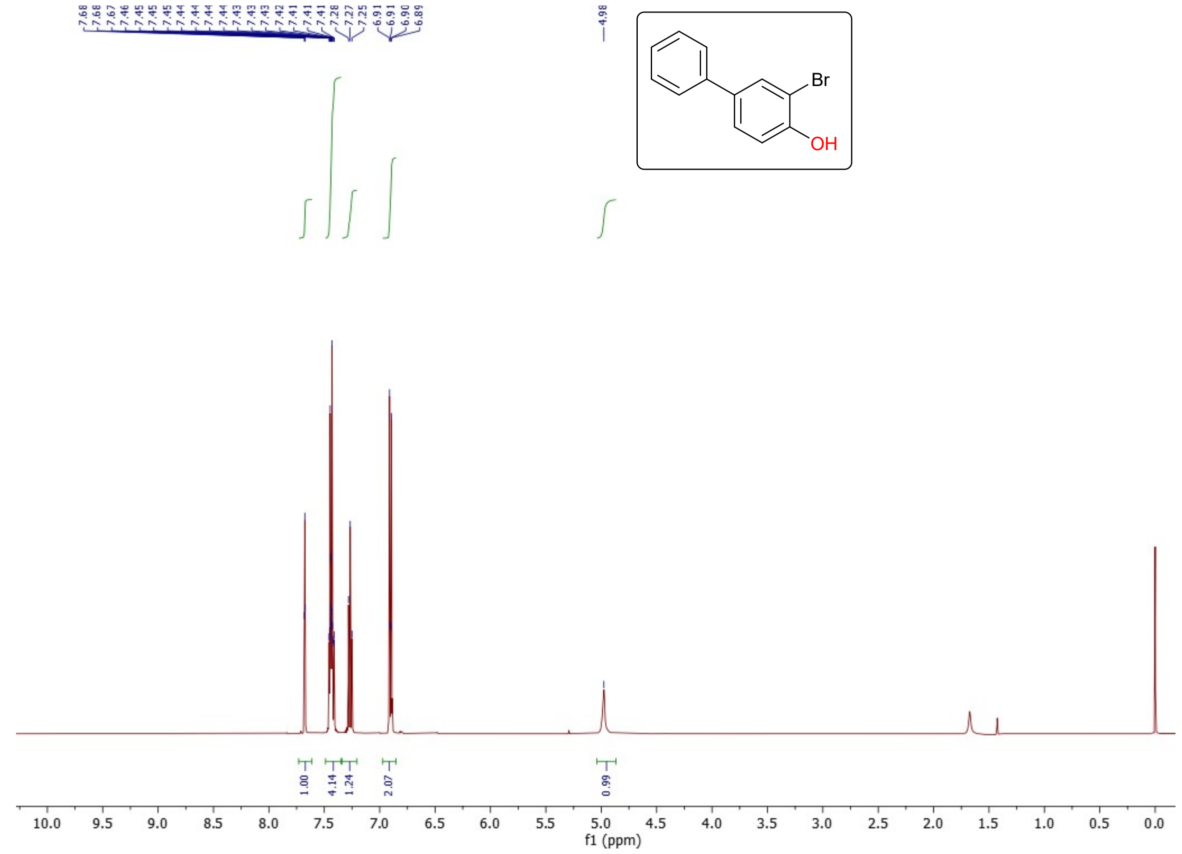


^{13}C NMR (125 MHz, DMSO)

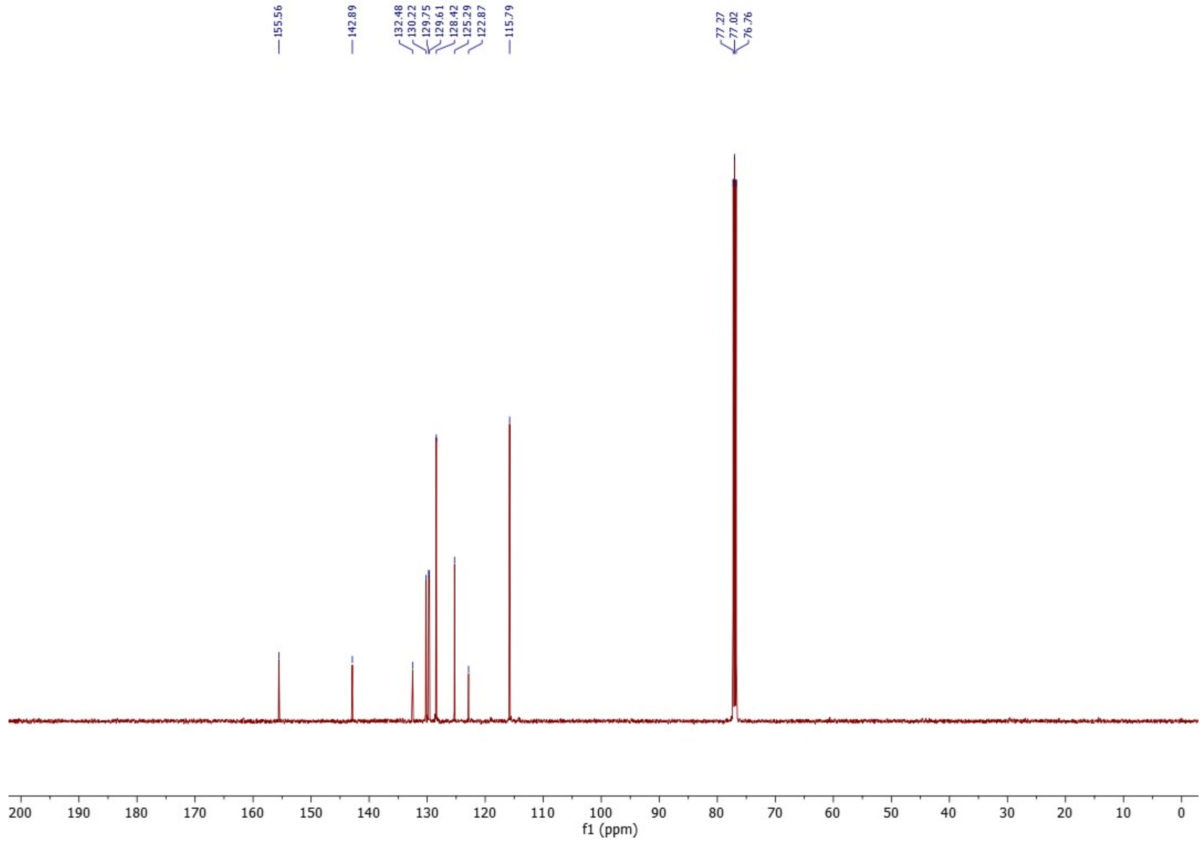


3-bromo-[1,1'-biphenyl]-4-ol (2g)

^{1}H NMR (500 MHz, CDCl$_3$)

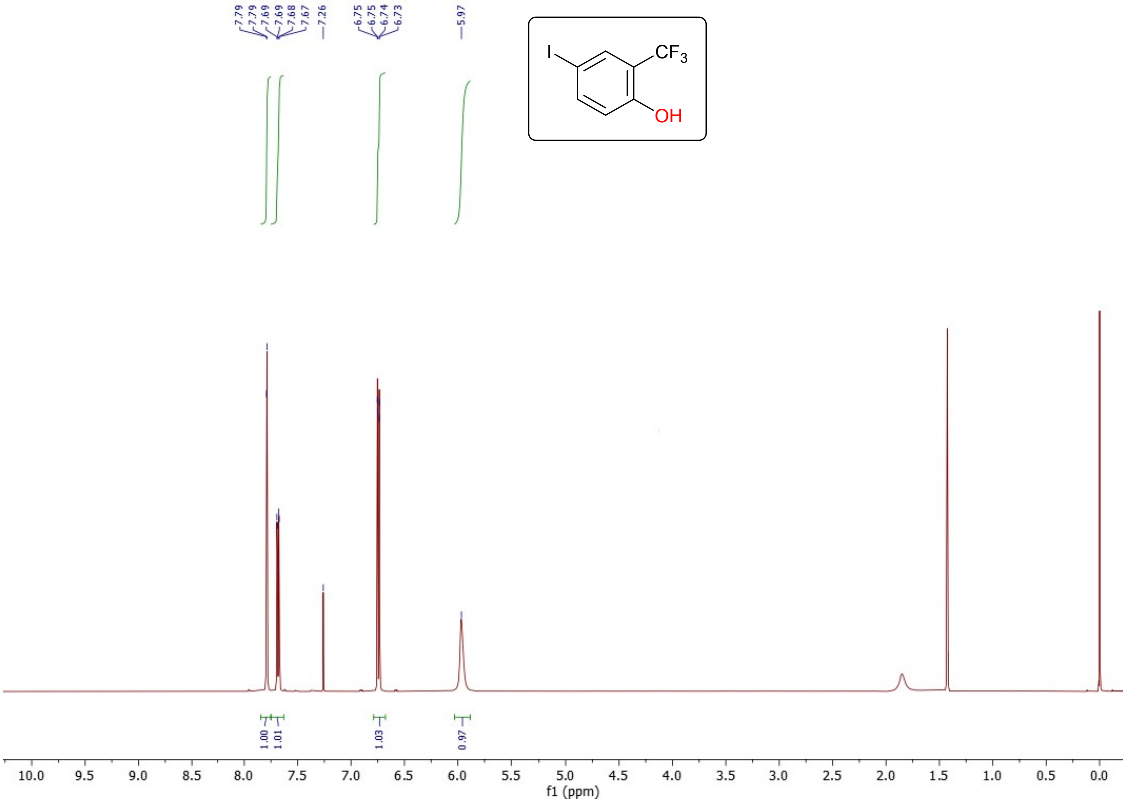


^{13}C NMR (125 MHz, CDCl$_3$)

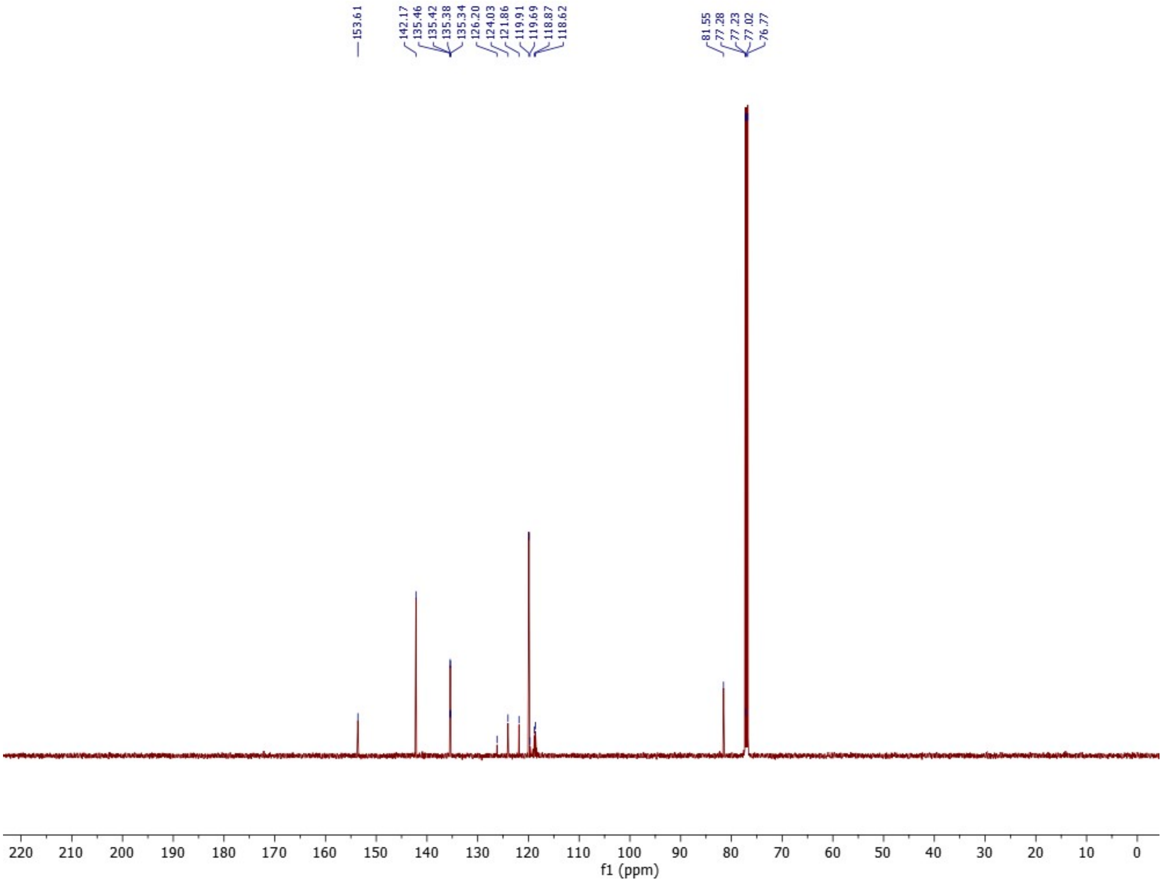


4-Iodo-2-[(trifluoromethyl)phenol] (2h)

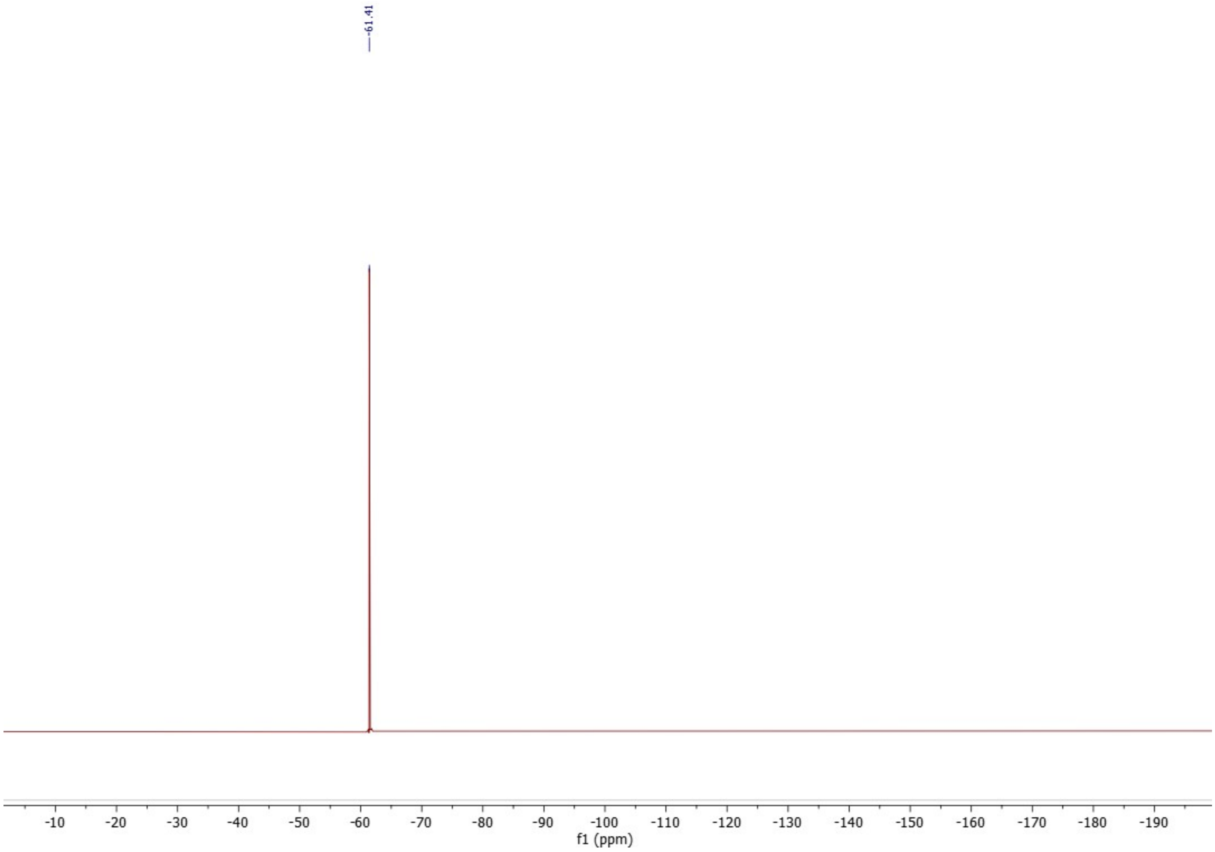
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

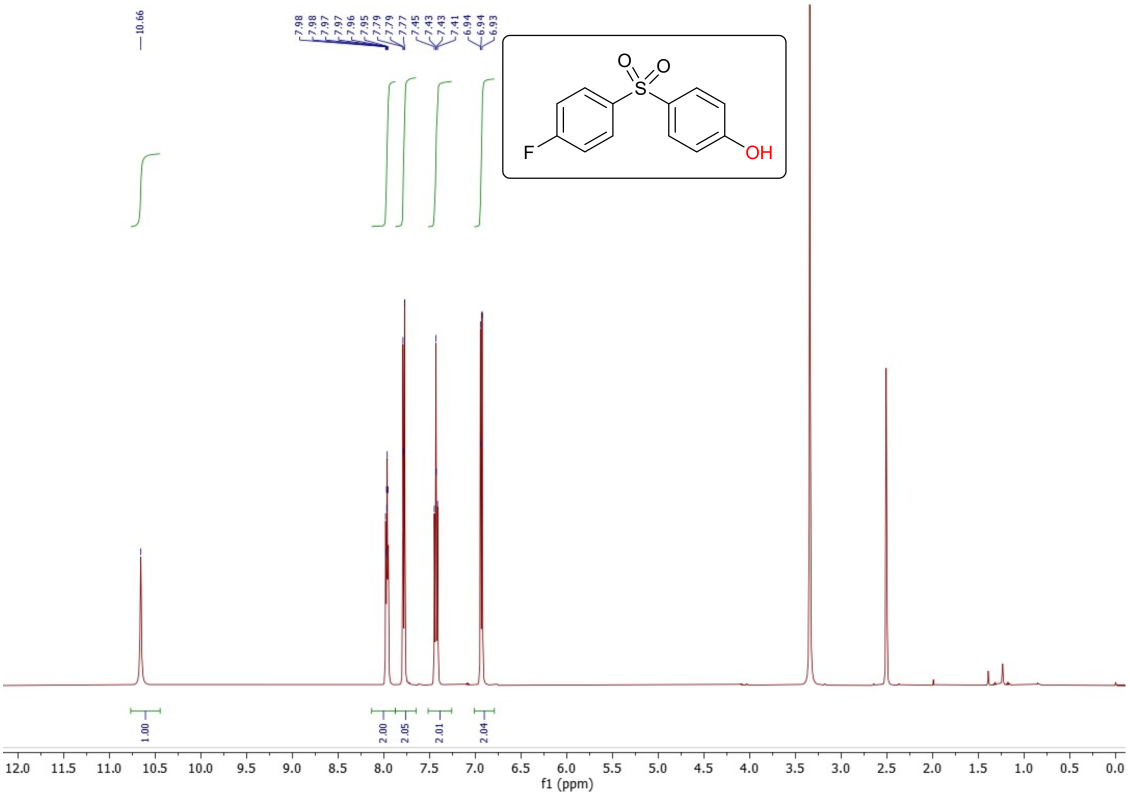


^{19}F NMR (471 MHz, CDCl$_3$)

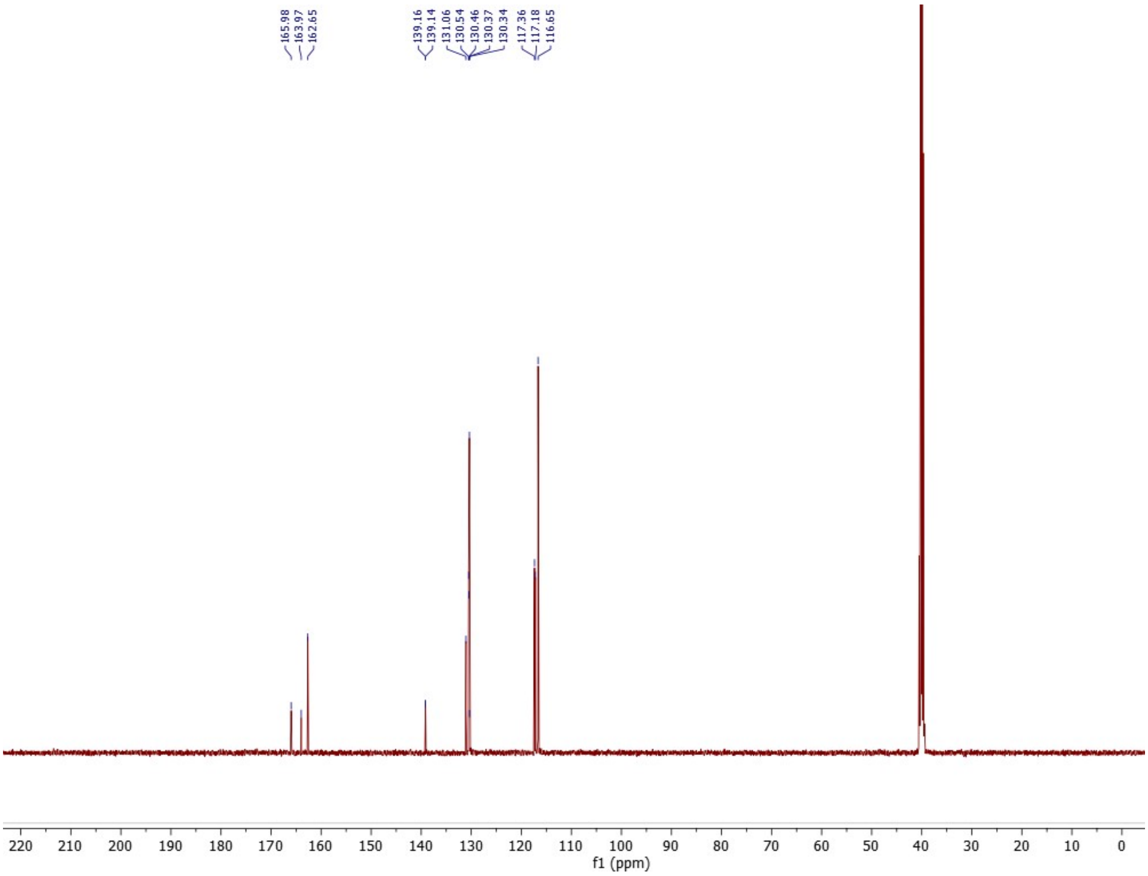


4-[(4-fluorophenyl)sulphonyl]phenol (2i)

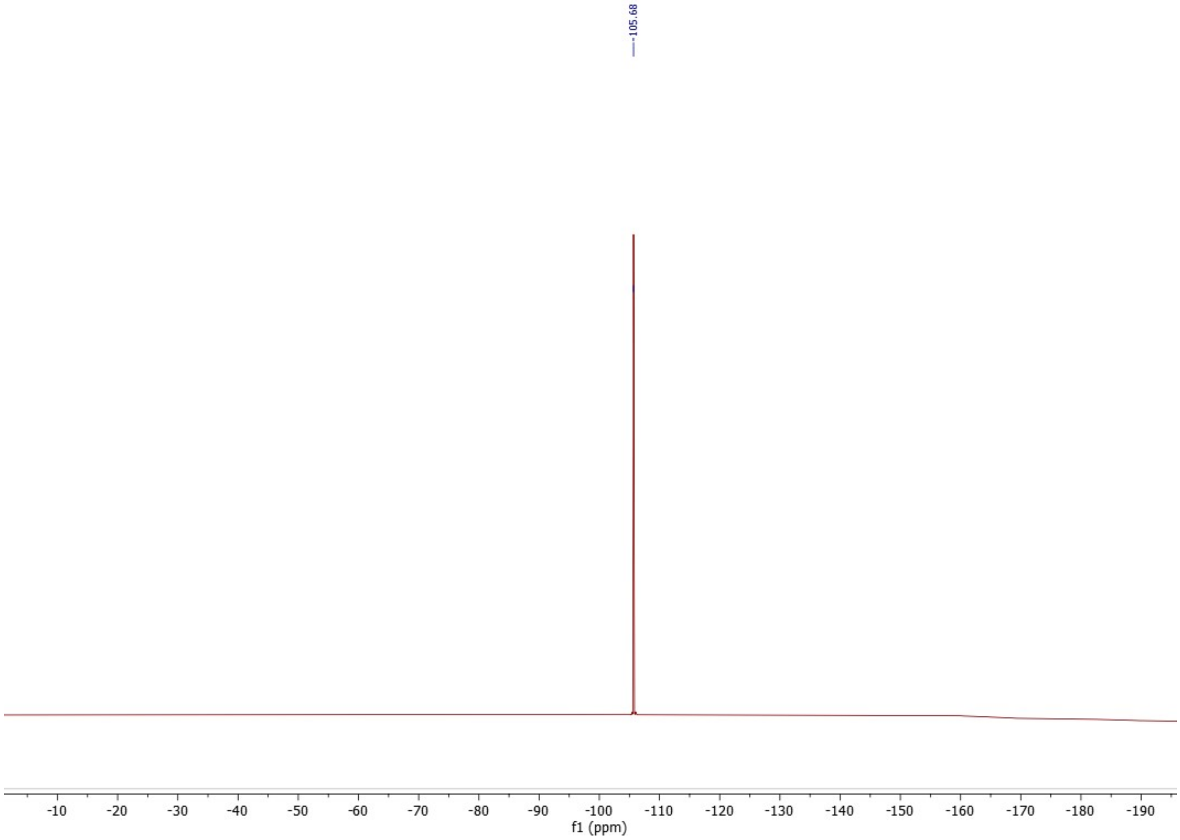
^{1}H NMR (500 MHz, DMSO)



^{13}C NMR (125 MHz, DMSO)

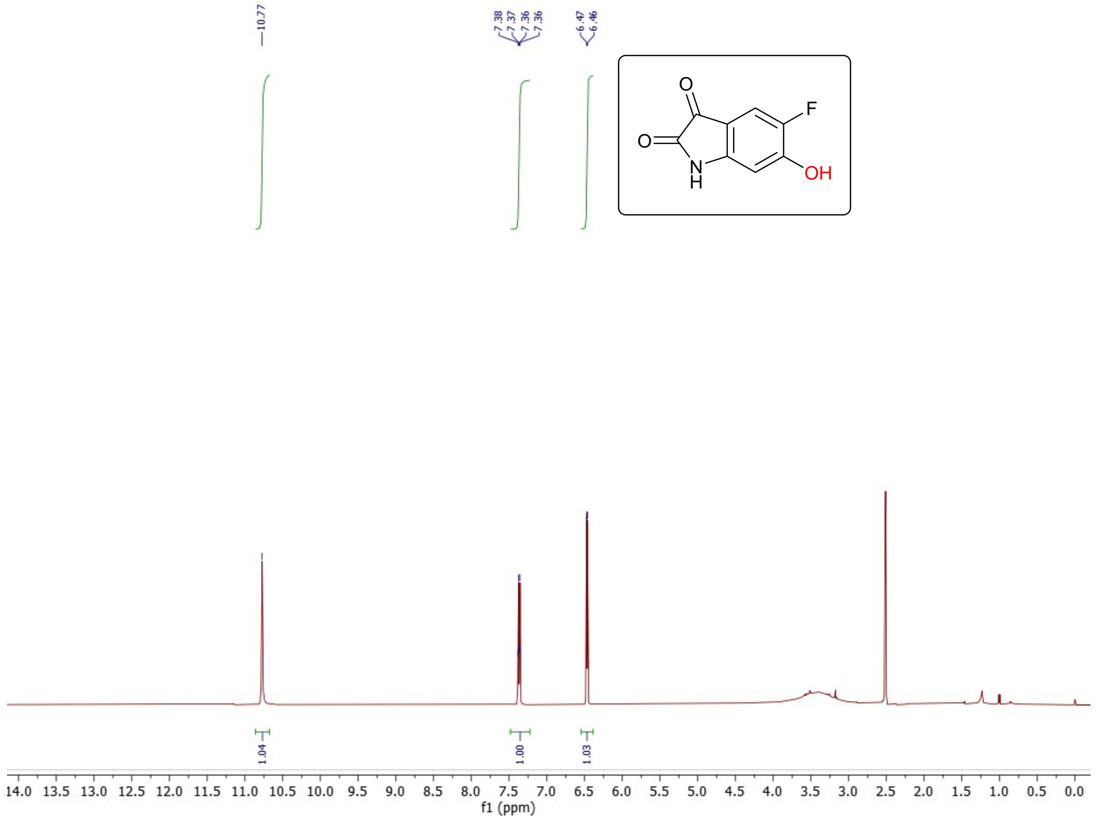


^{19}F NMR (471 MHz, DMSO)

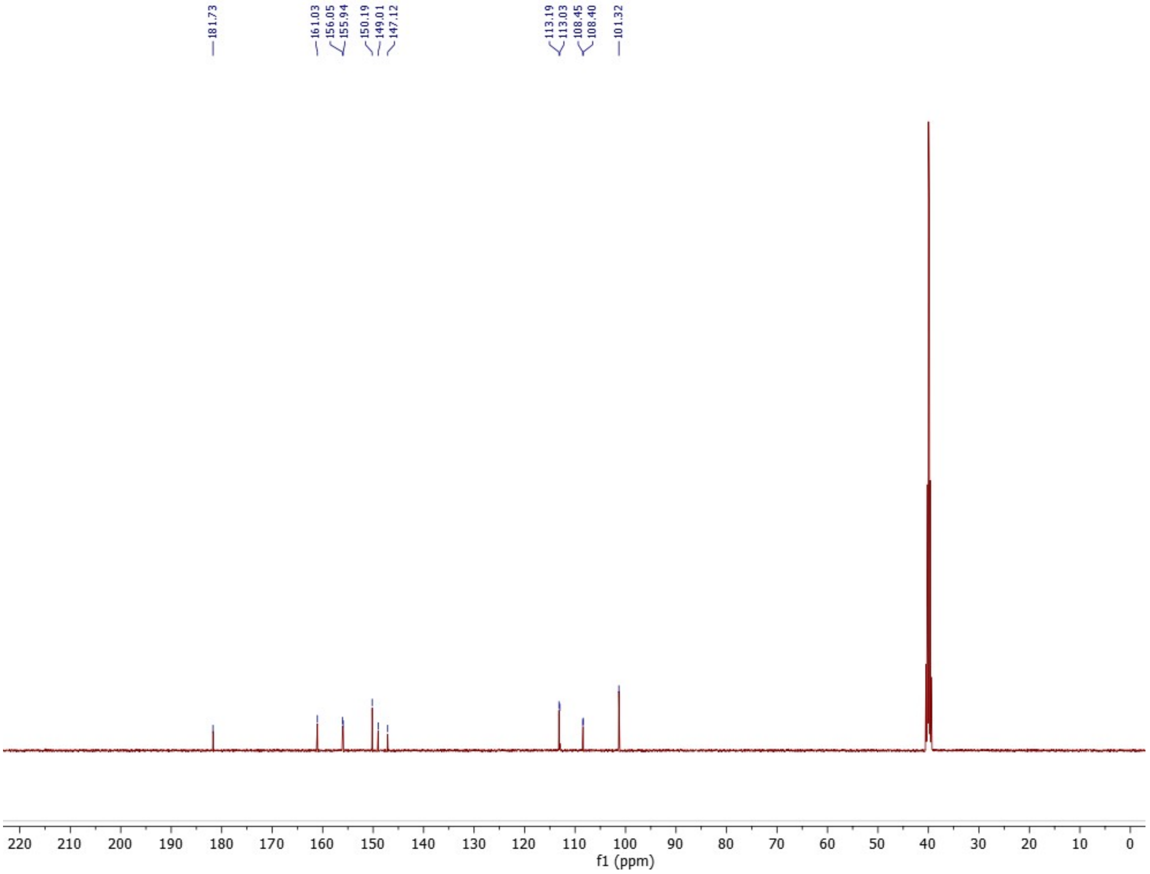


5-Fluoro-6-hydroxyindoline-2,3-dione (2j)

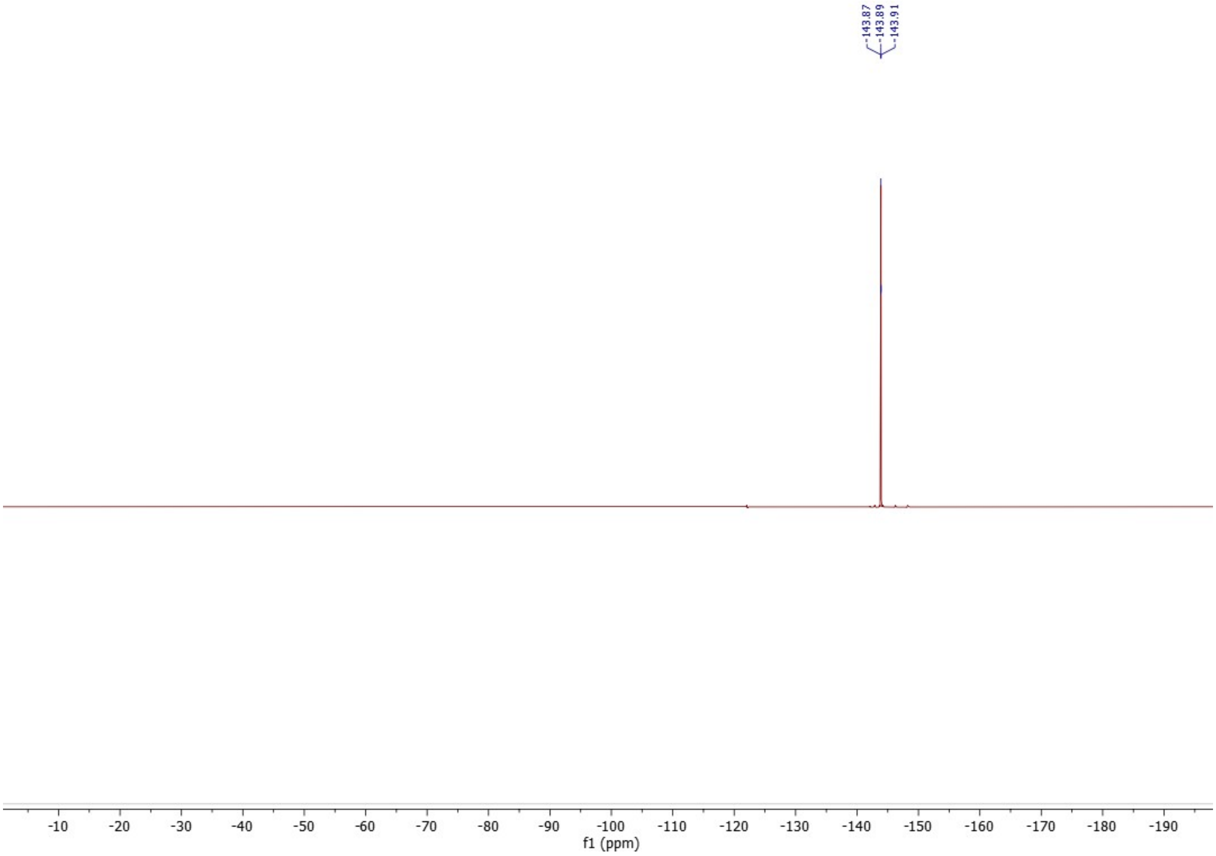
^{1}H NMR (500 MHz, DMSO)



^{13}C NMR (125 MHz, DMSO)

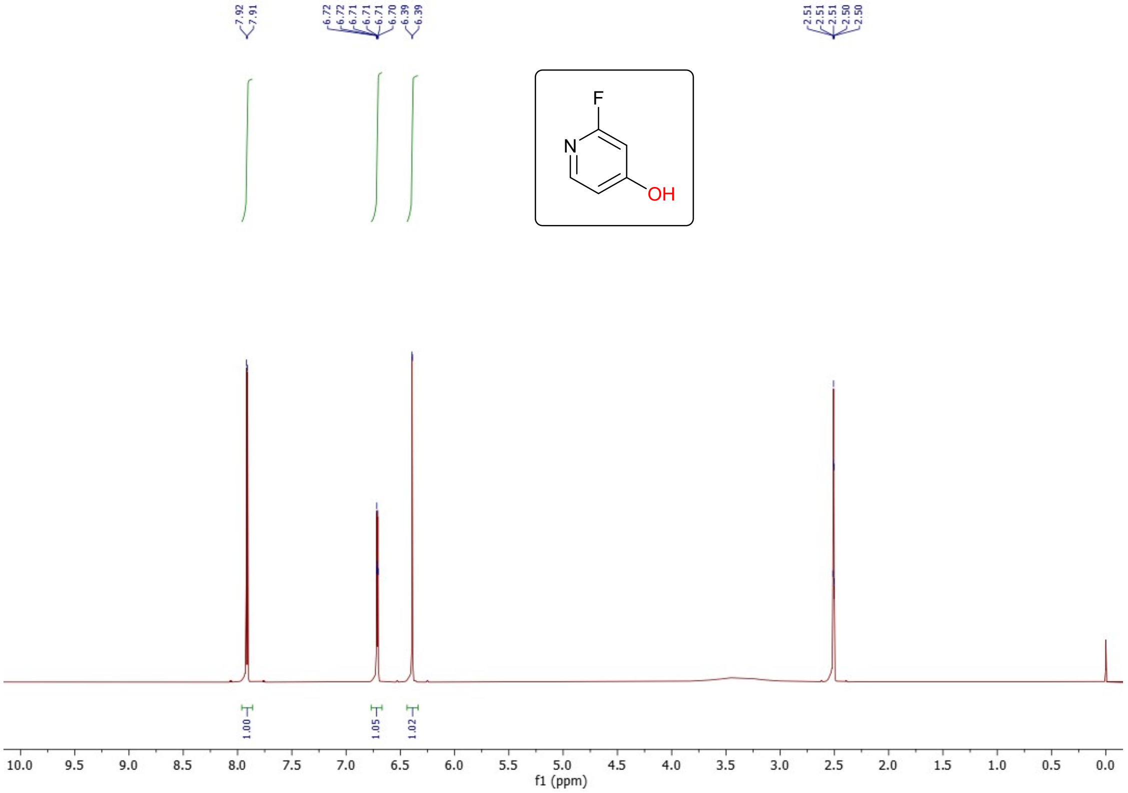


^{19}F NMR (471 MHz, DMSO)

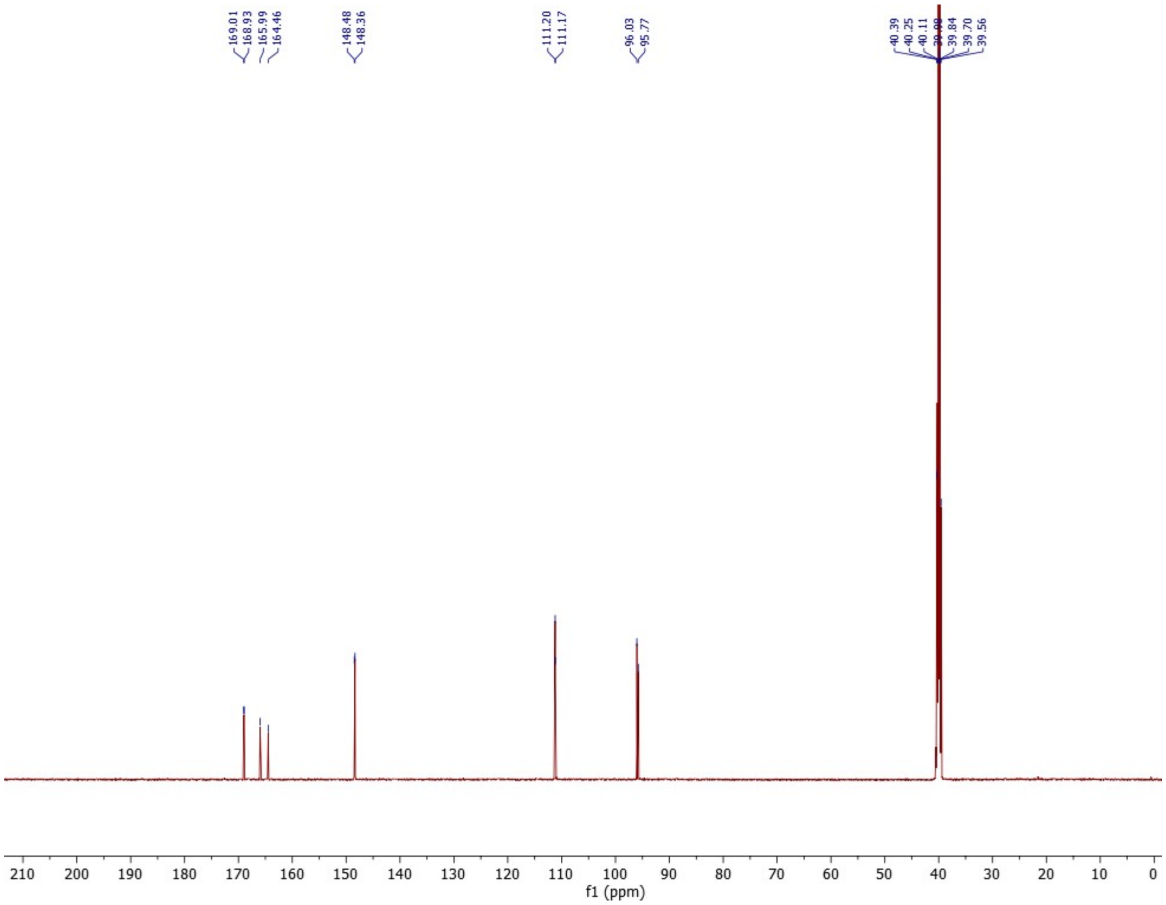


2-Fluoro-4-hydroxypyridine (2k)

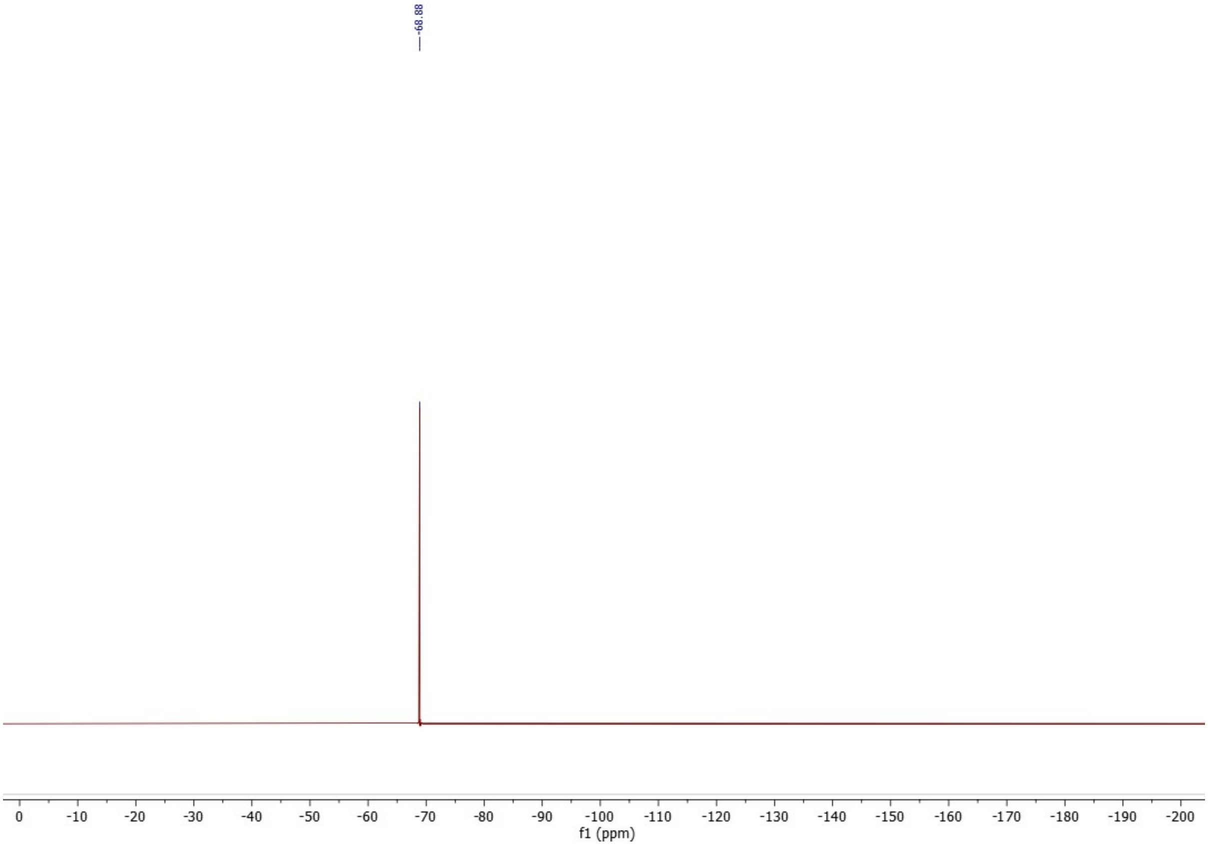
^{1}H NMR (500 MHz, DMSO)



^{13}C NMR (125 MHz, DMSO)

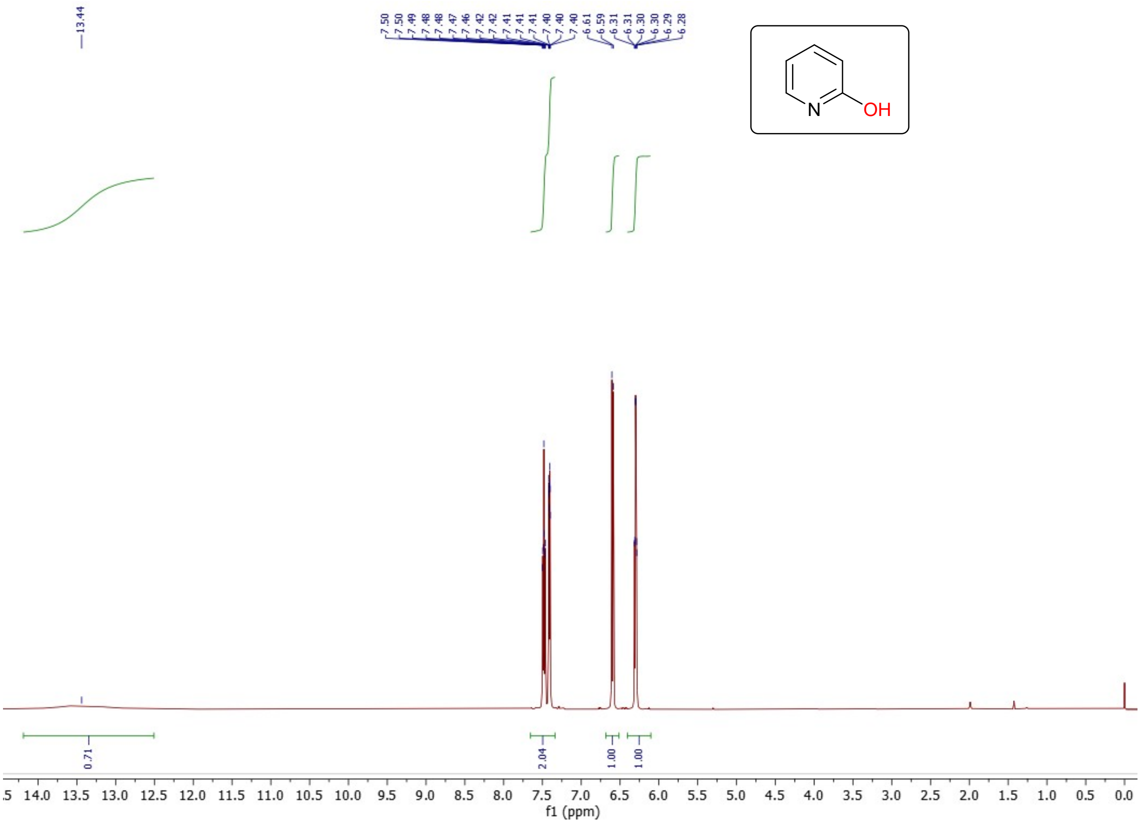


^{19}F NMR (471 MHz, DMSO)

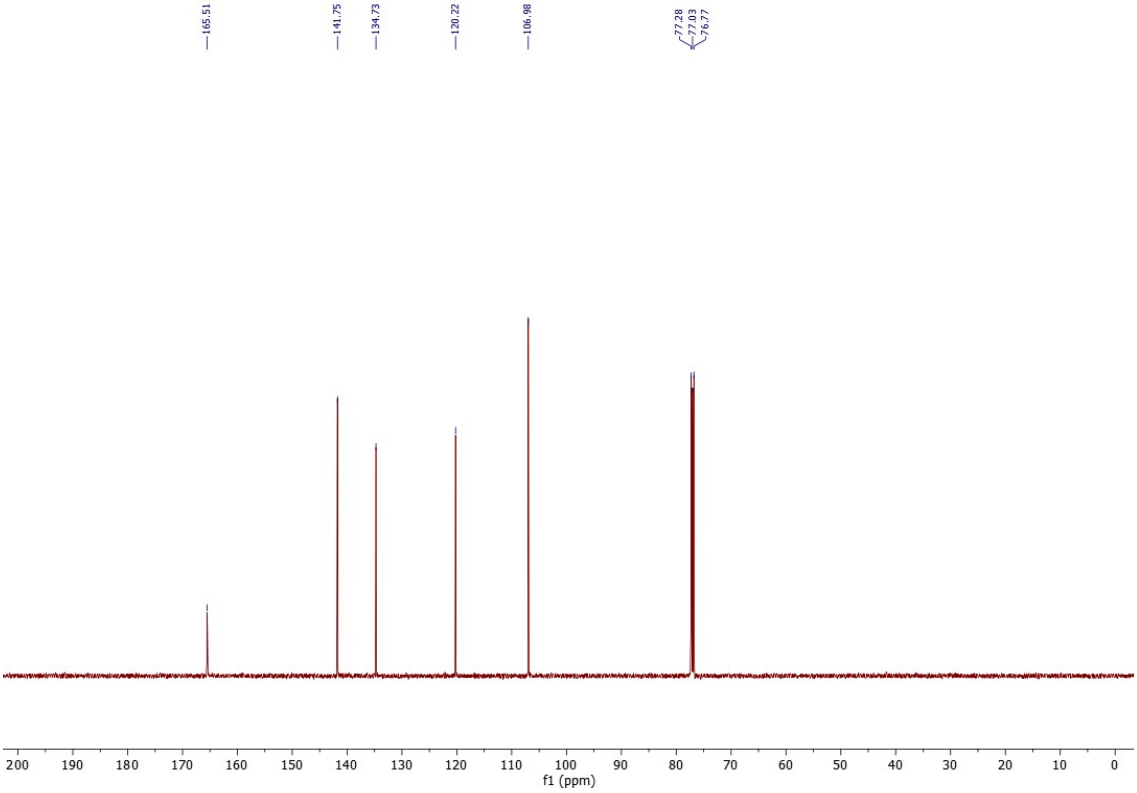


2(1*H*)-Pyridinone (2l)

^{1}H NMR (500 MHz, CDCl$_3$)

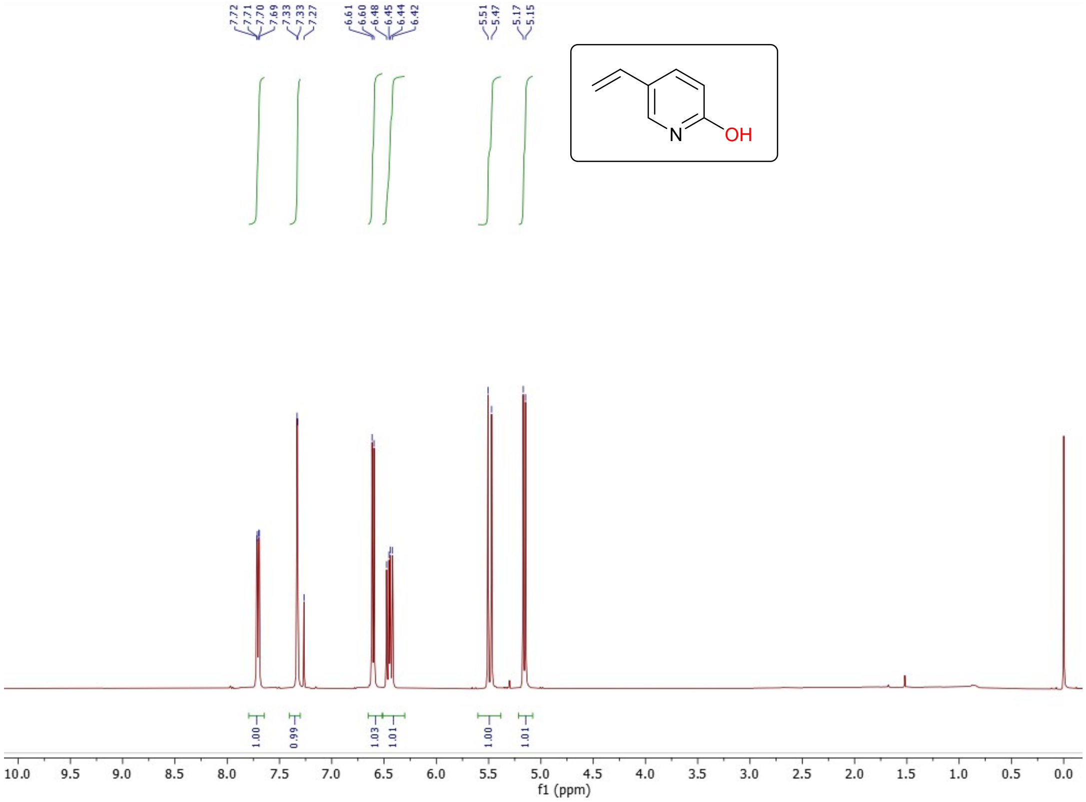


^{1}H NMR (125 MHz, CDCl$_3$)

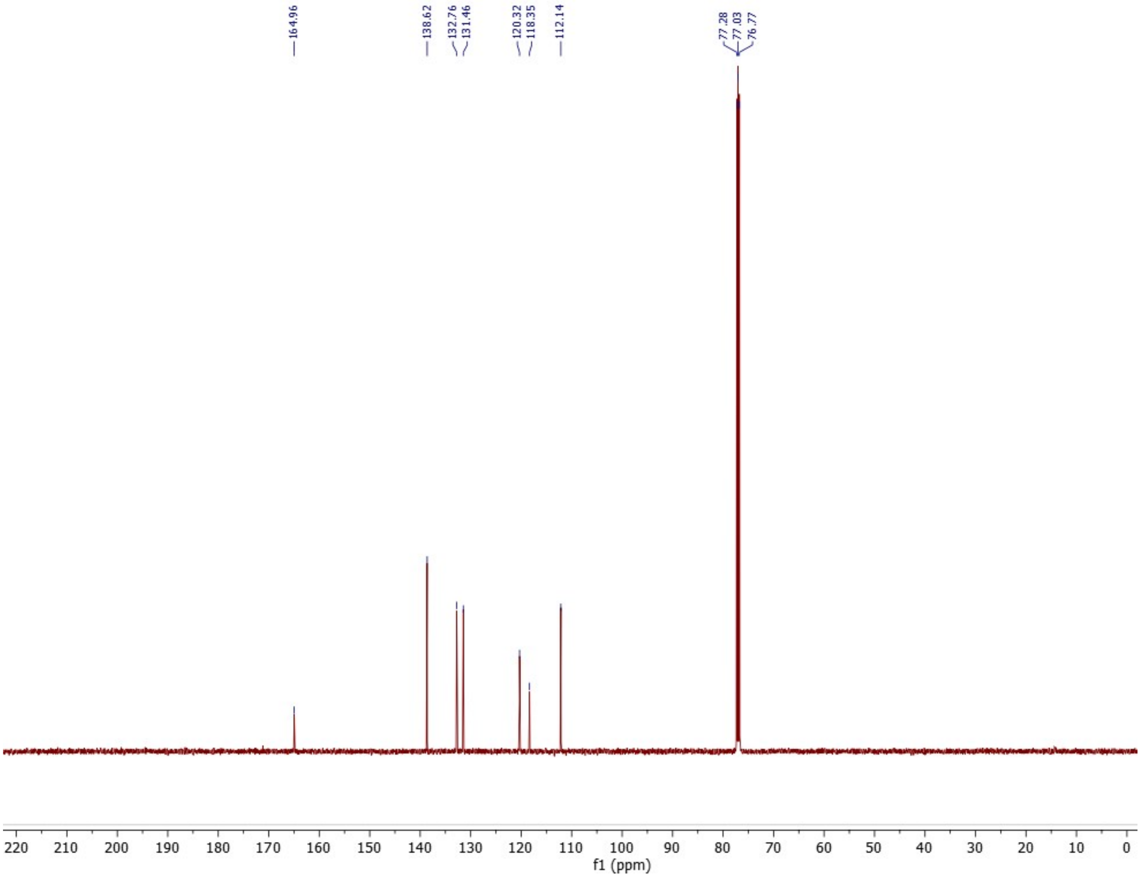


2-Hydroxy-5-vinyl-pyridine (2m)

^{1}H NMR (500 MHz, $CDCl_3$)

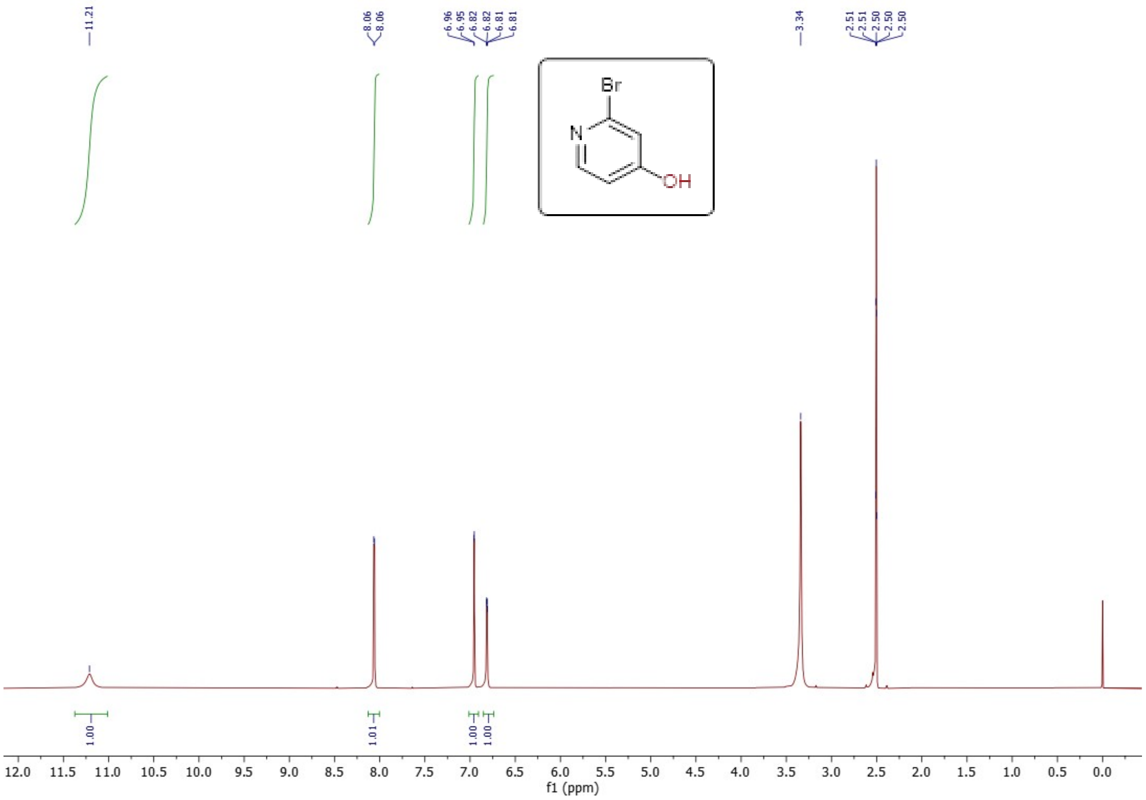


^{13}C NMR (125 MHz, $CDCl_3$)

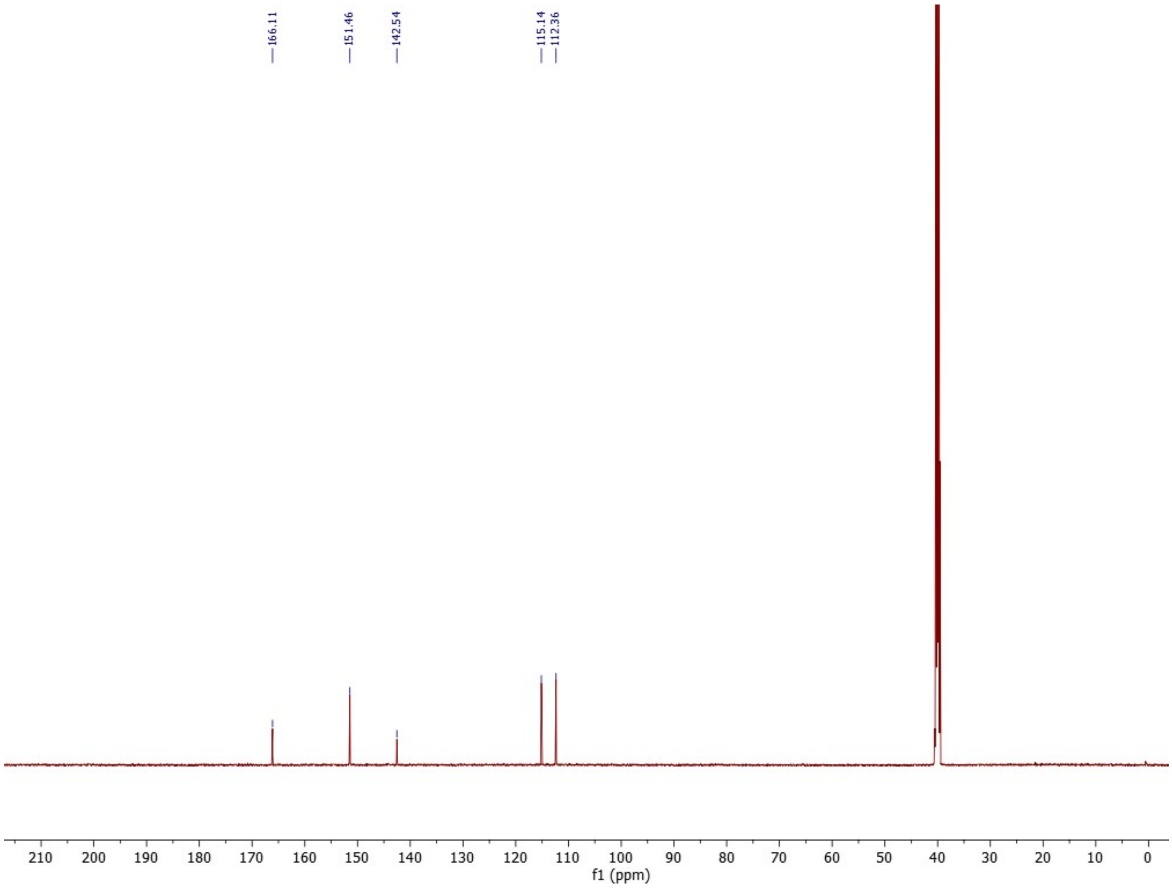


2-Bromo-4-pyridine (2n)

^{1}H NMR (500 MHz, DMSO)

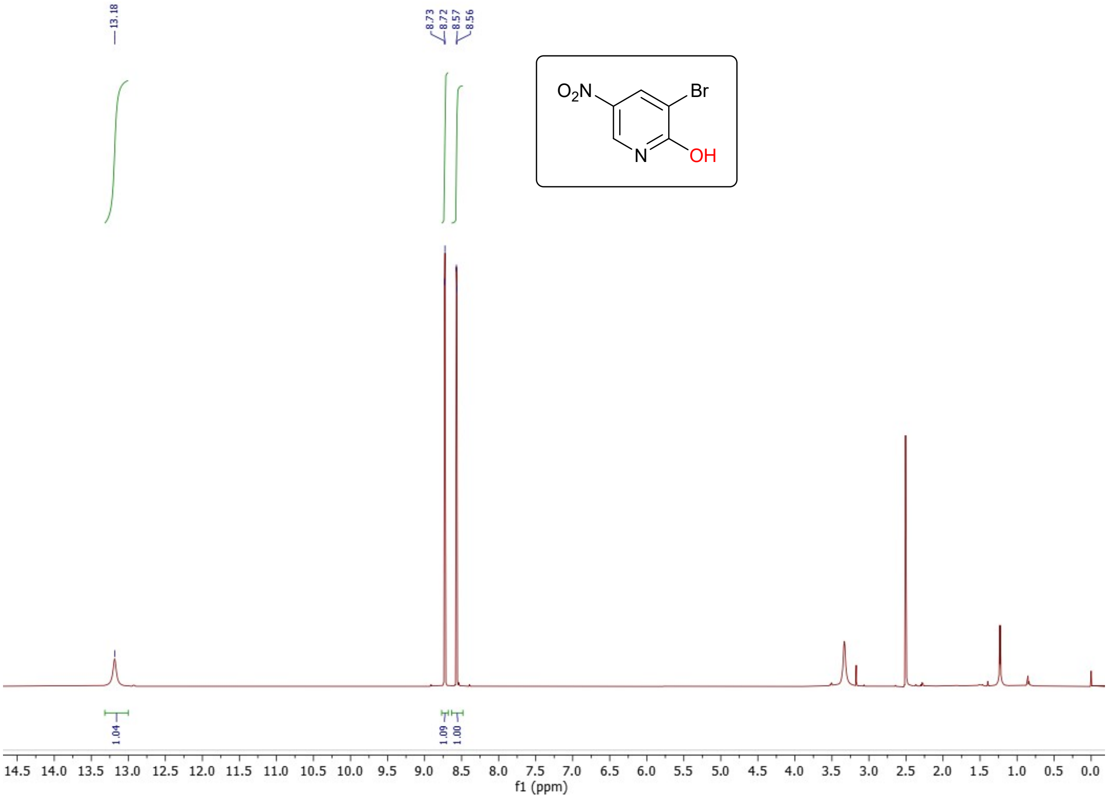


^{13}C NMR (125 MHz, DMSO)

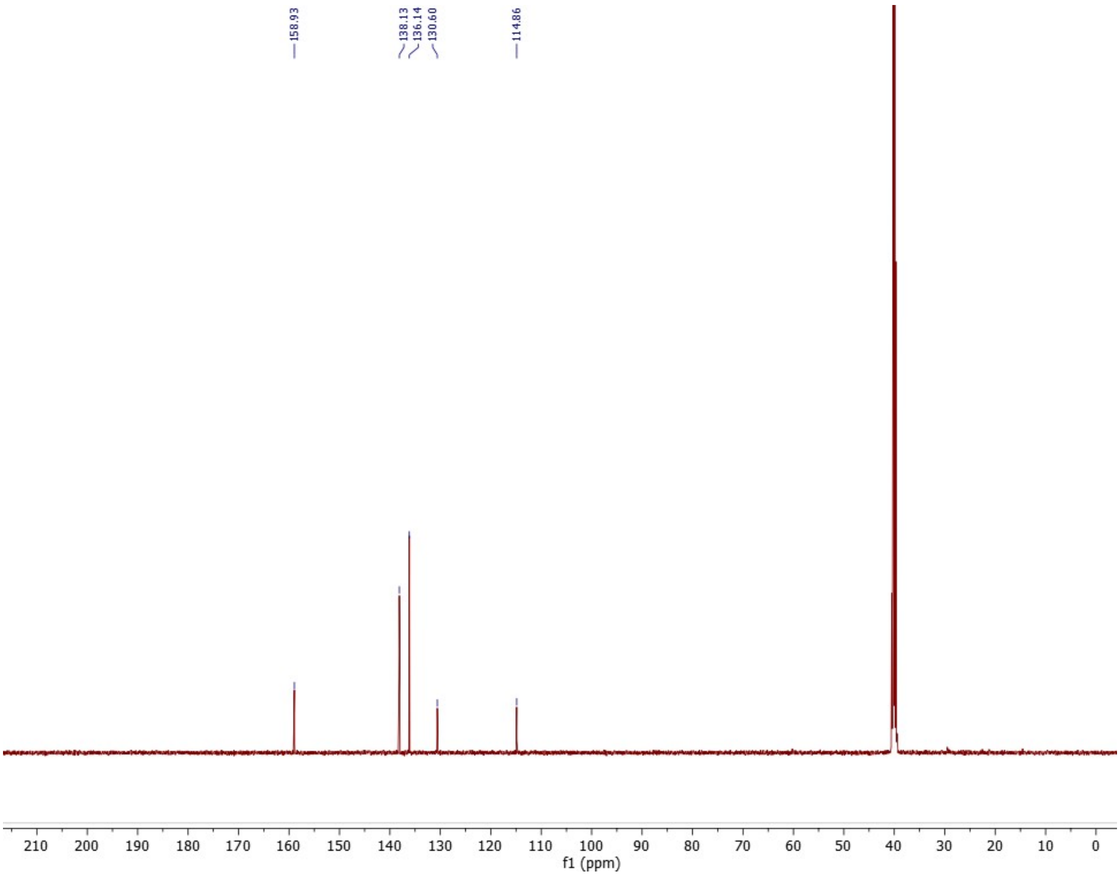


3-Bromo-2-hydroxy-5-nitropyridine (2o)

^{1}H NMR (500 MHz, DMSO)

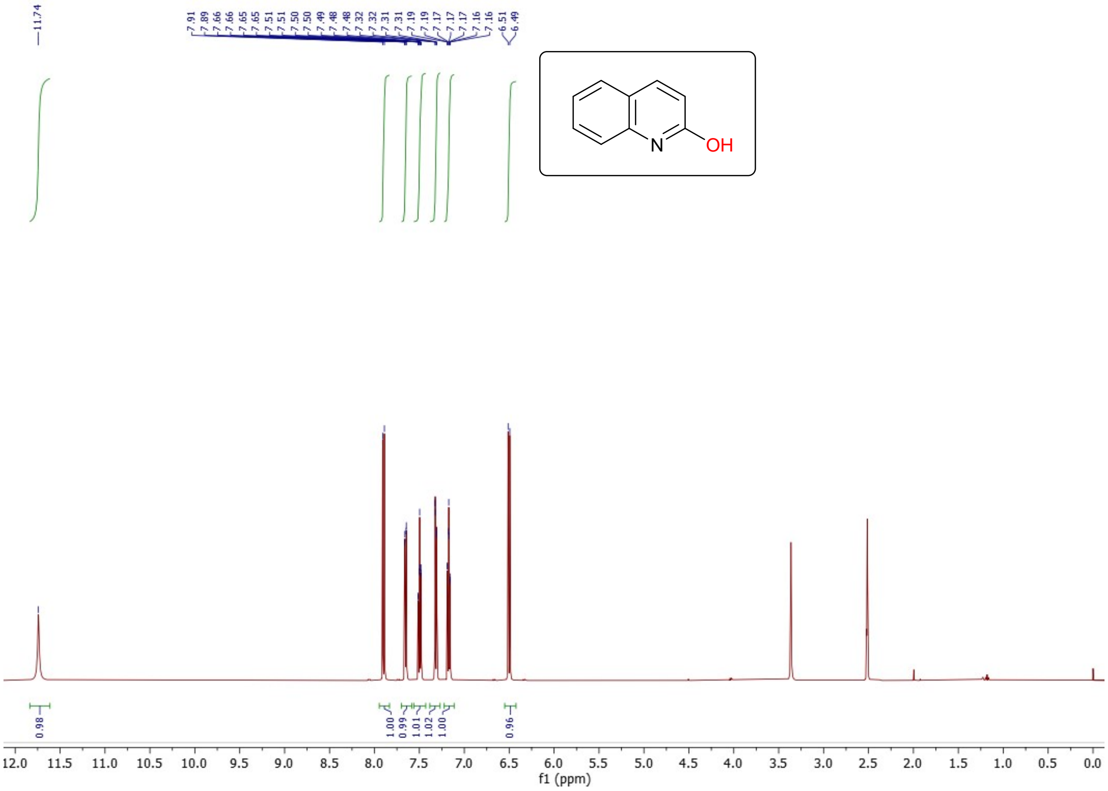


^{13}C NMR (125 MHz, DMSO)

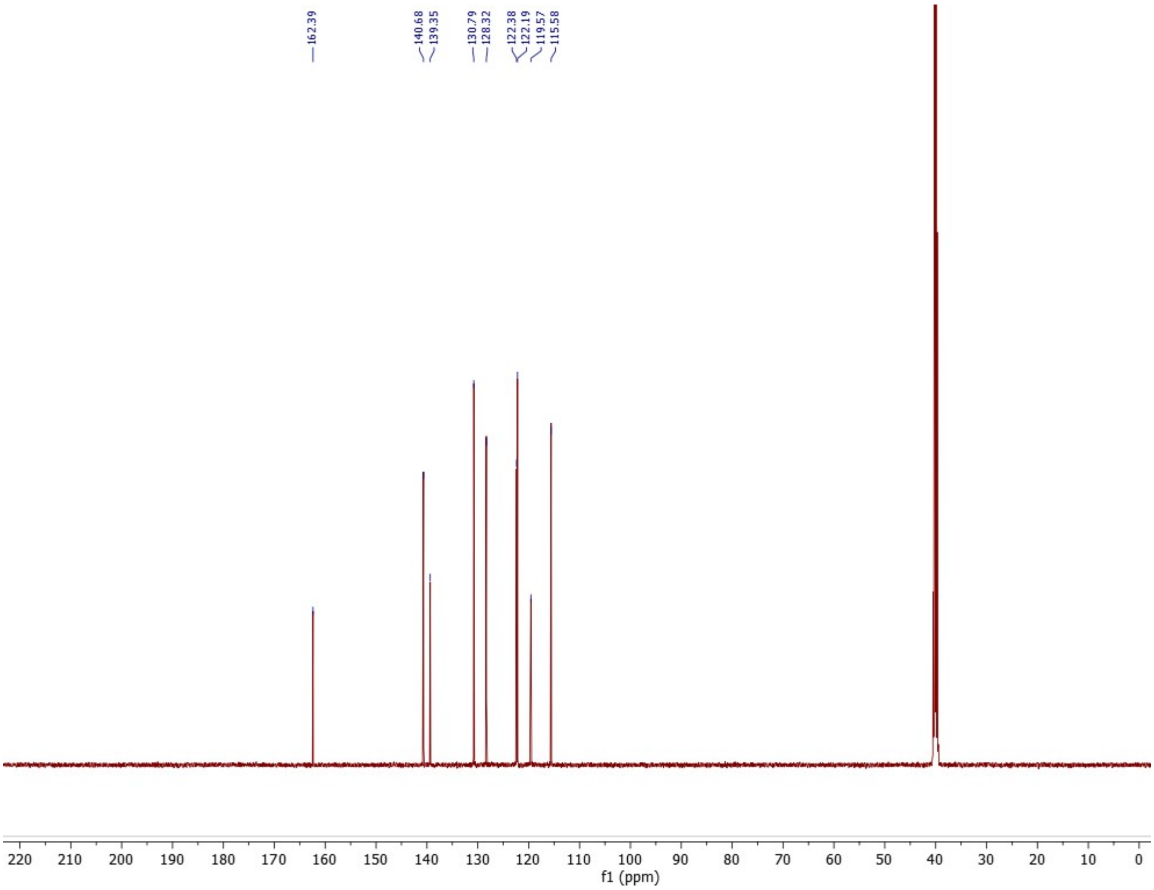


2-hydroxyquinoline (2p)

^{1}H NMR (500 MHz, DMSO)

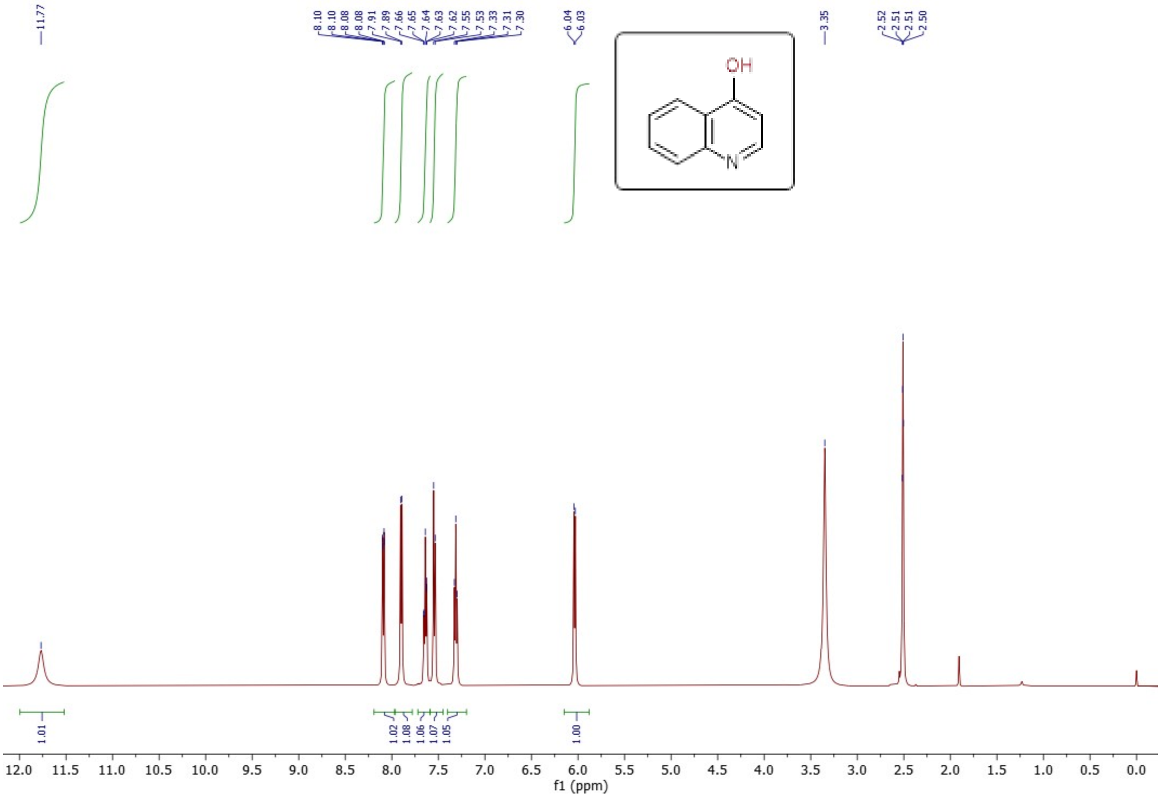


^{13}C NMR (125 MHz, DMSO)

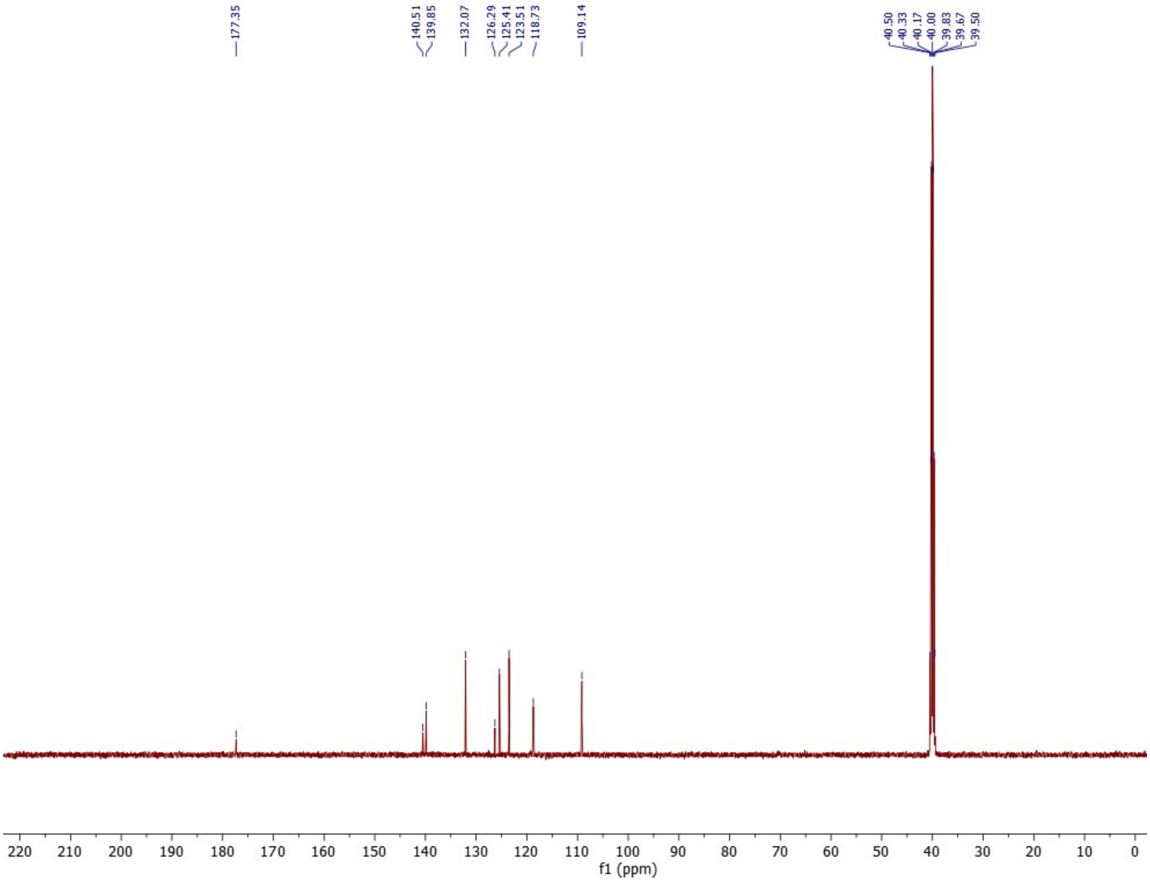


4-hydroxyquinoline (2q)

^{1}H NMR (500 MHz, DMSO)

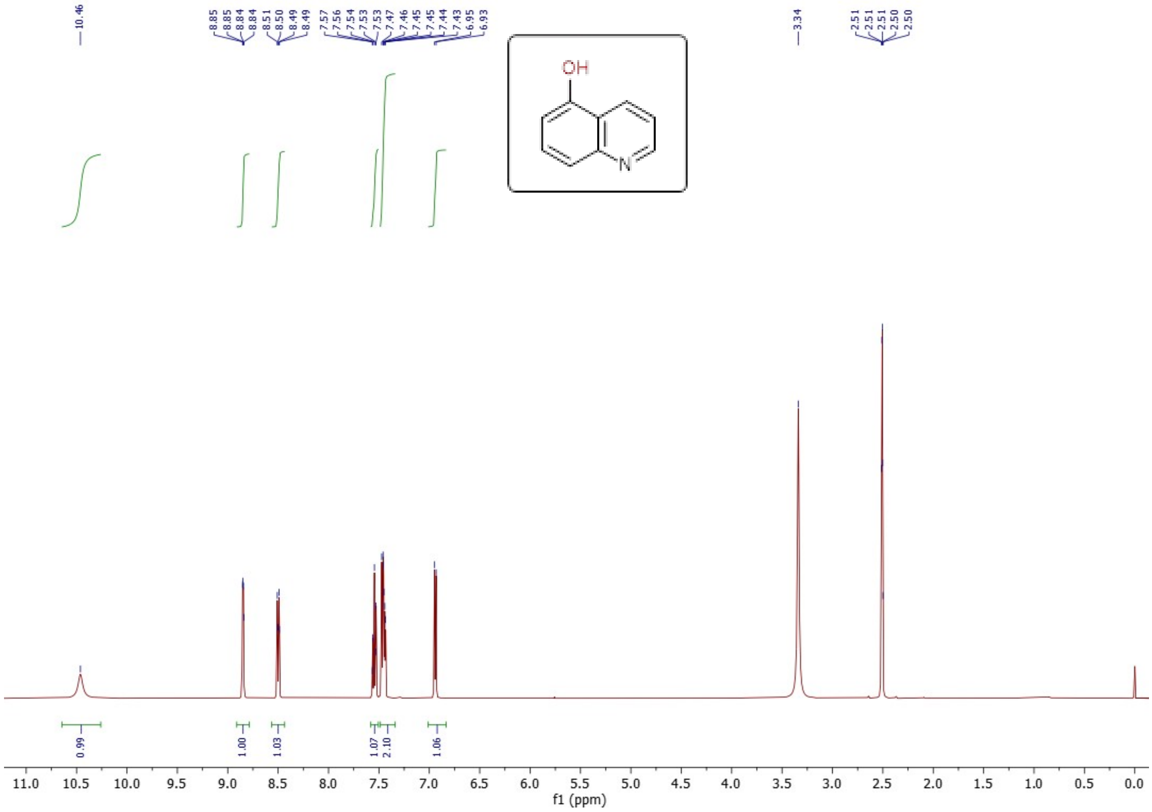


^{13}C NMR (125 MHz, DMSO)

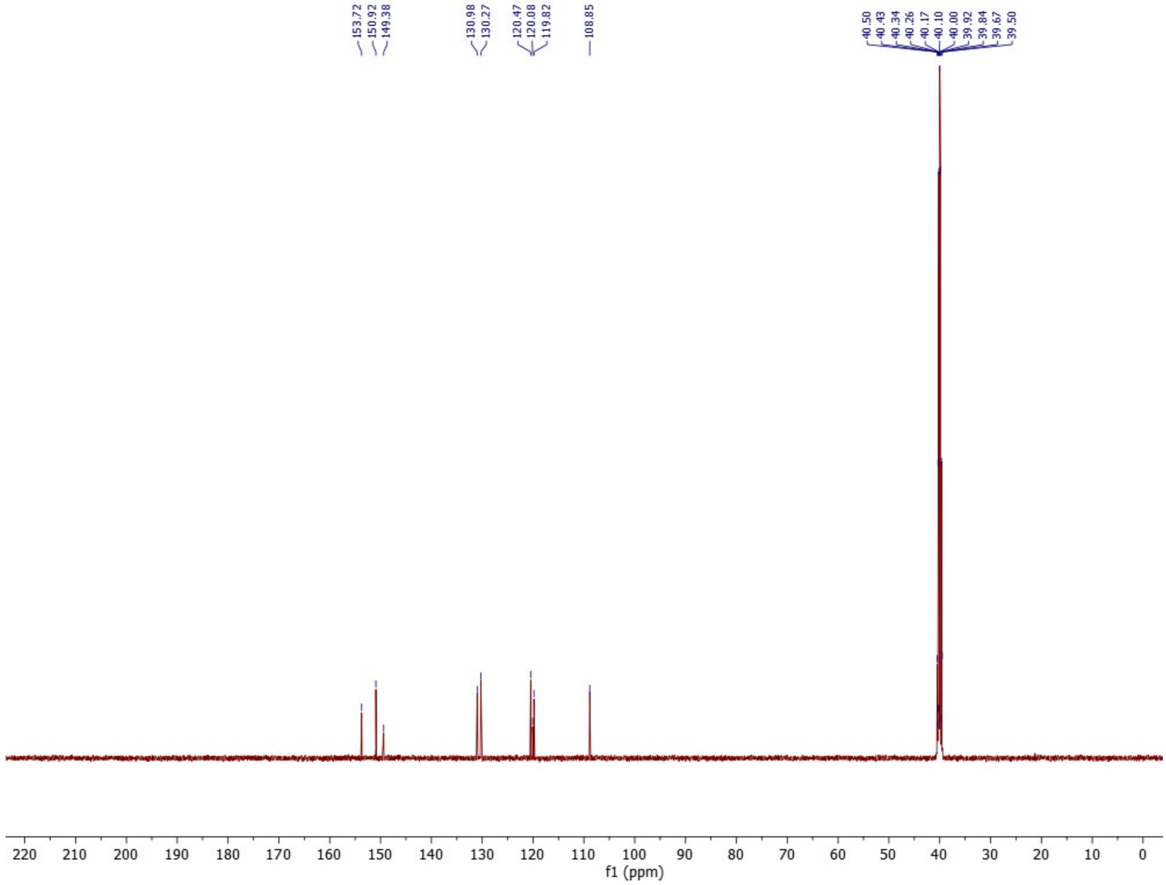


5-hydroxyquinoline (2r)

^{1}H NMR (500 MHz, DMSO)

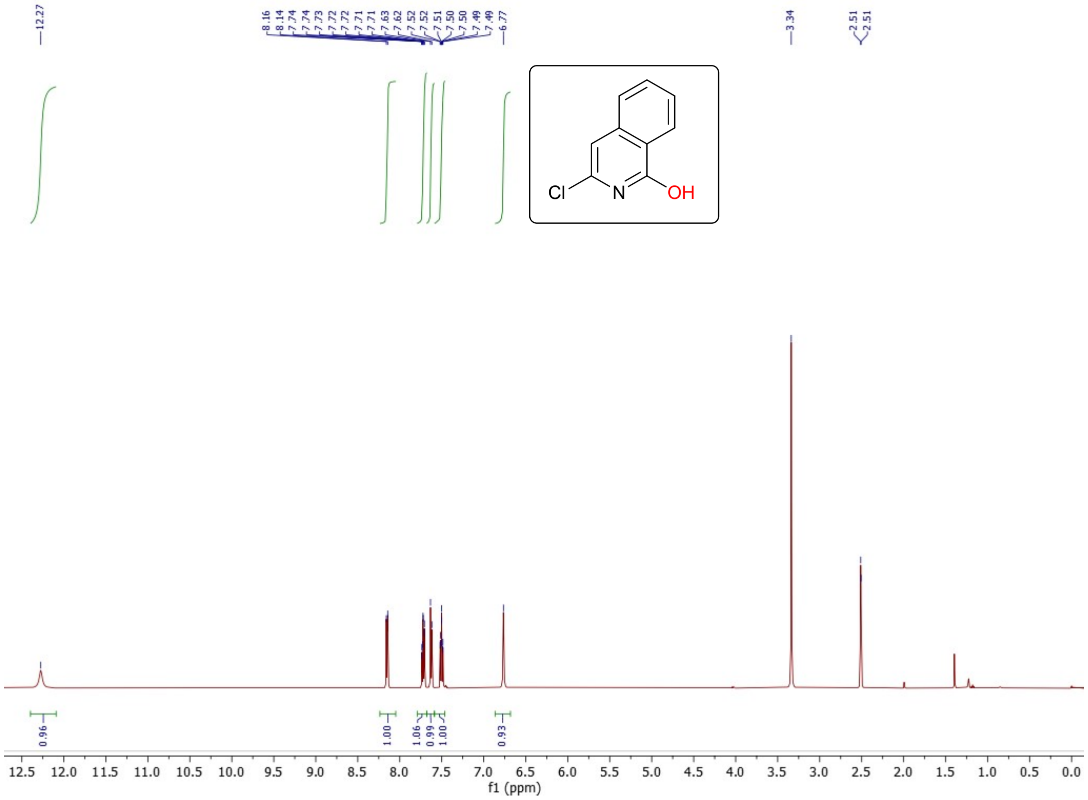


^{13}C NMR (125 MHz, DMSO)

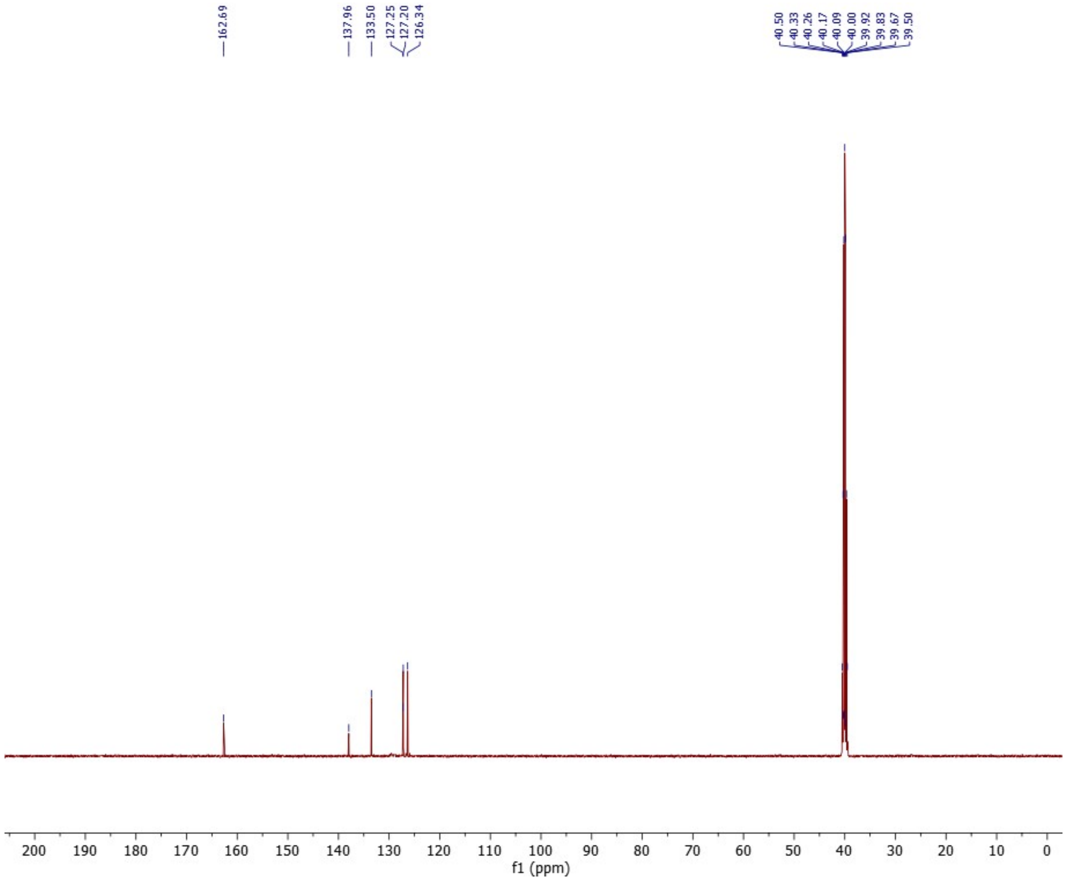


3-Chloro-1-hydroxyisoquinoline (2s)

^{1}H NMR (500 MHz, DMSO)

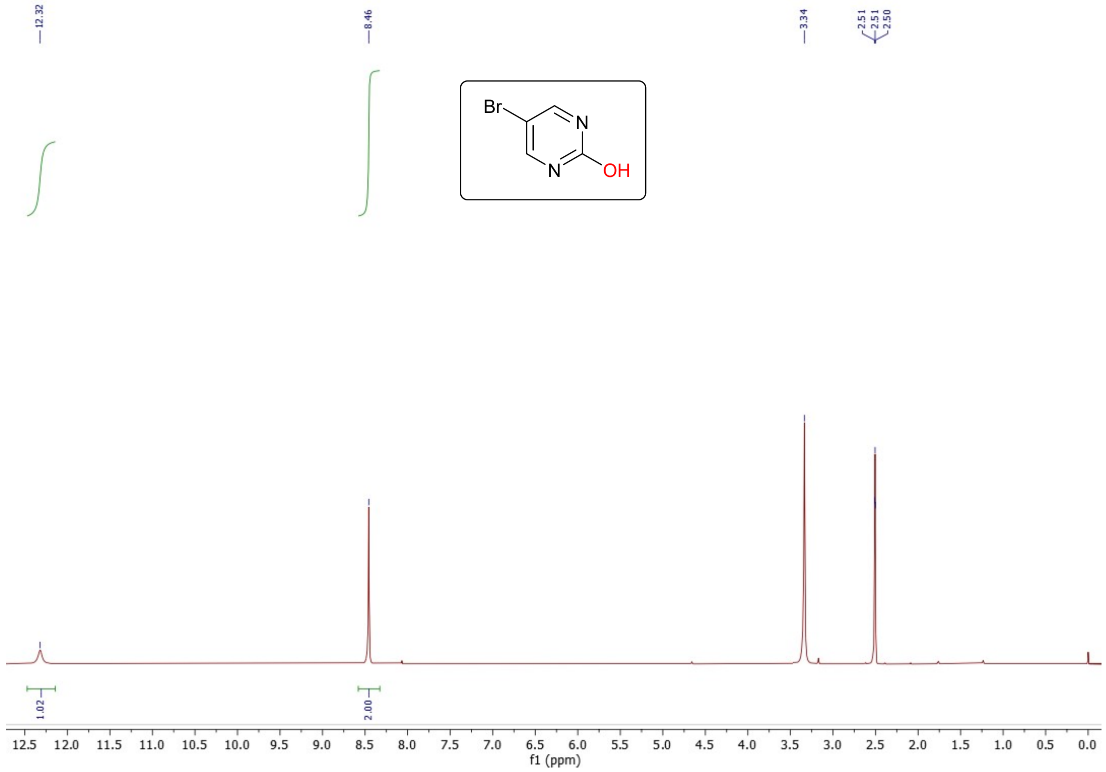


^{13}C NMR (125 MHz, DMSO)

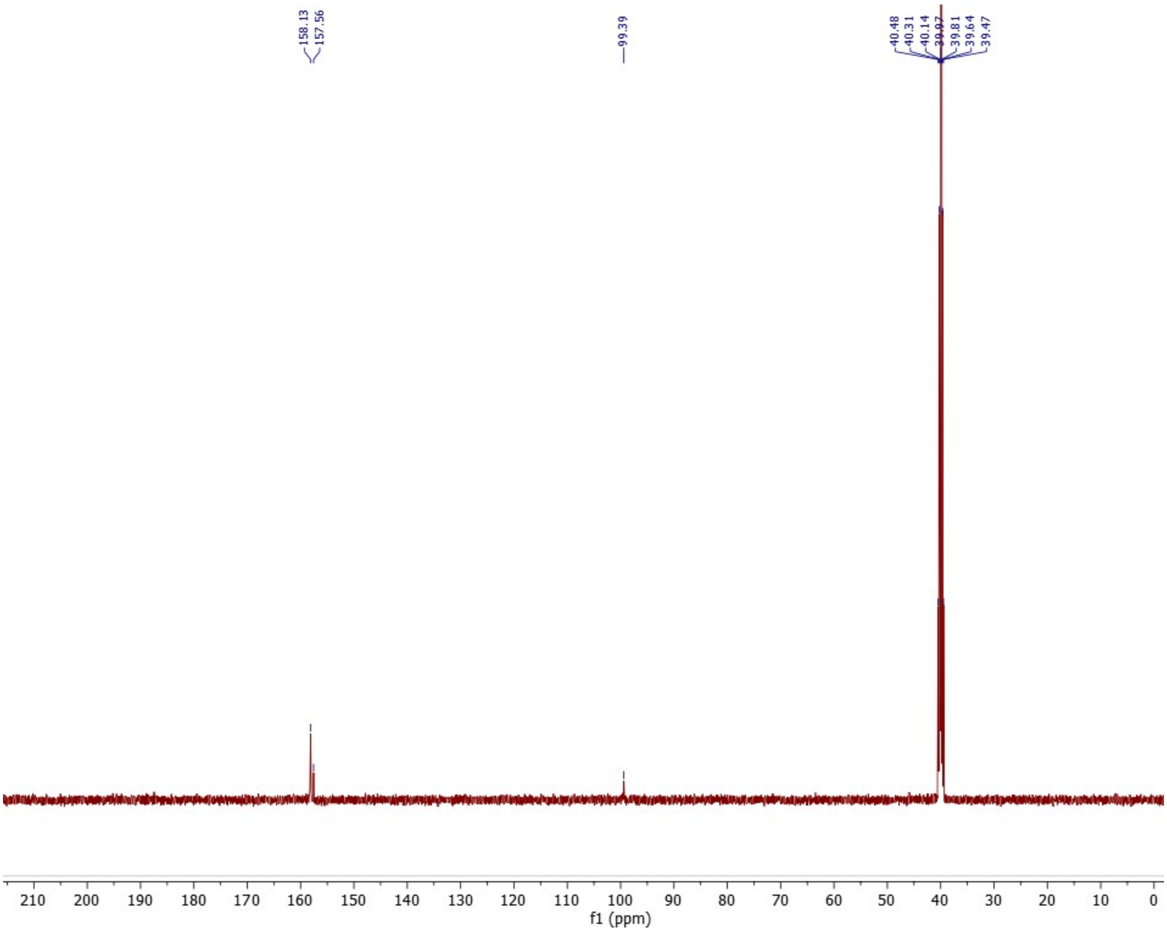


5-Bromo-2-hydroxypyrimidine (2t)

^{1}H NMR (500 MHz, DMSO)

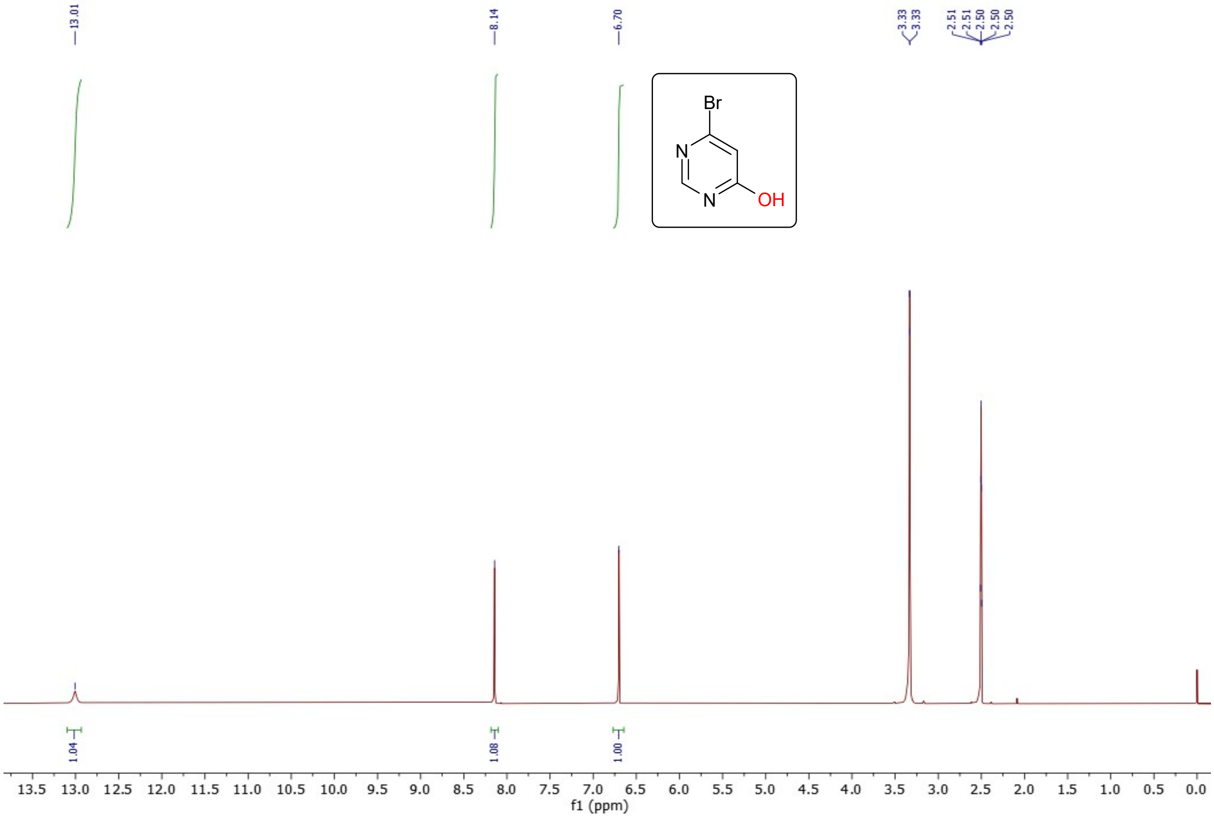


^{13}C NMR (125 MHz, DMSO)

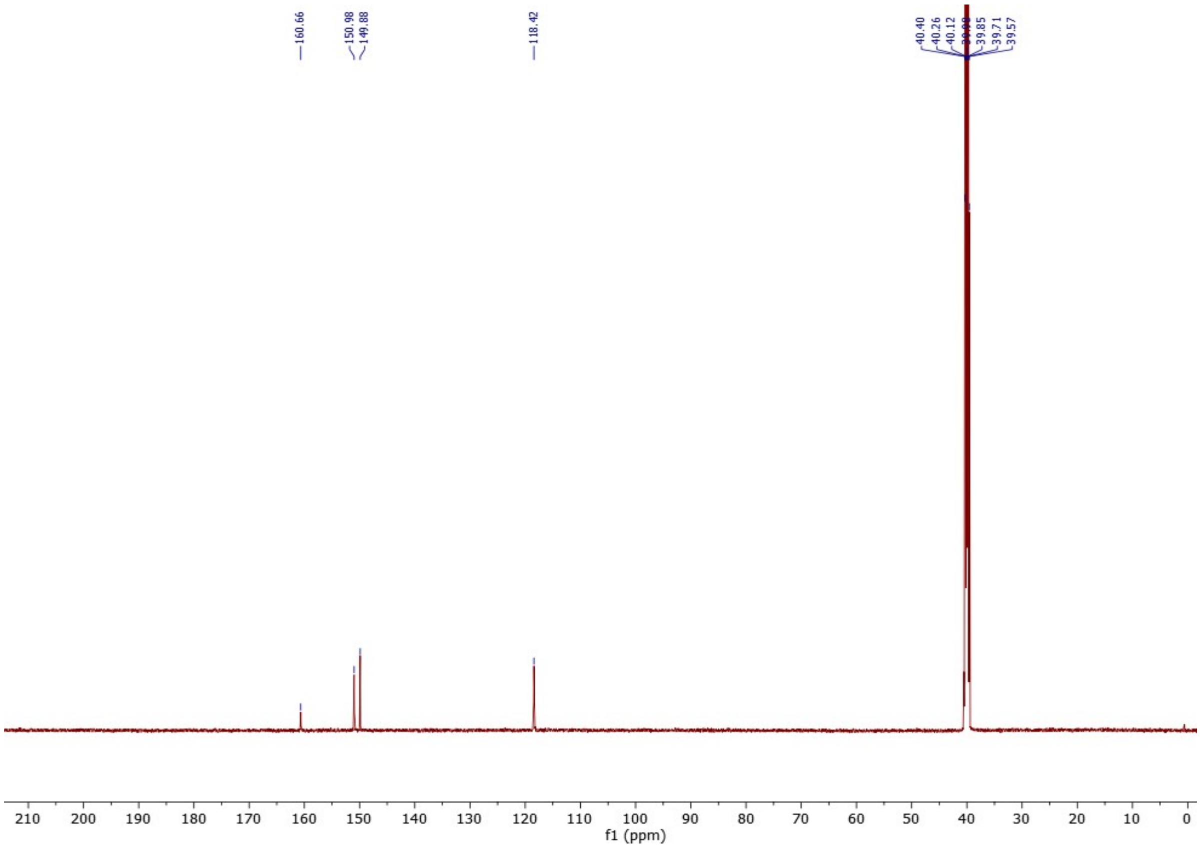


4-Bromo-6-hydroxypyrimidine (2u)

^{1}H NMR (500 MHz, DMSO)

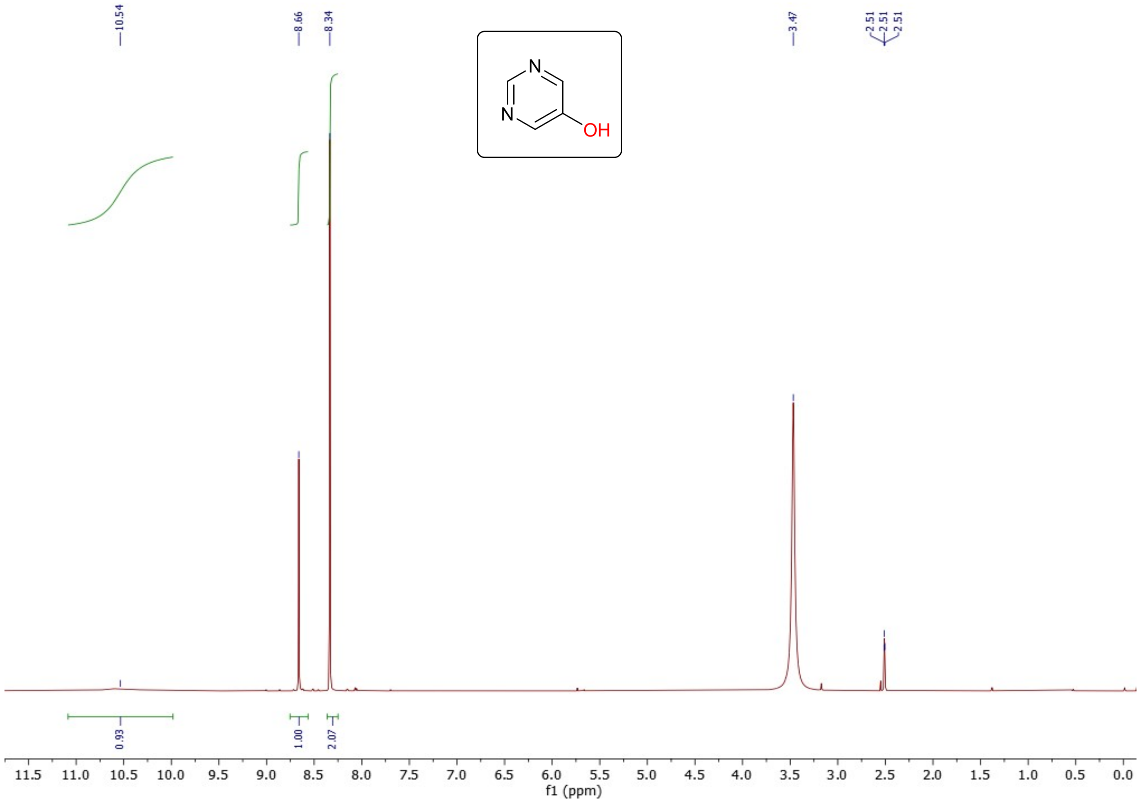


^{13}C NMR (125 MHz, DMSO)

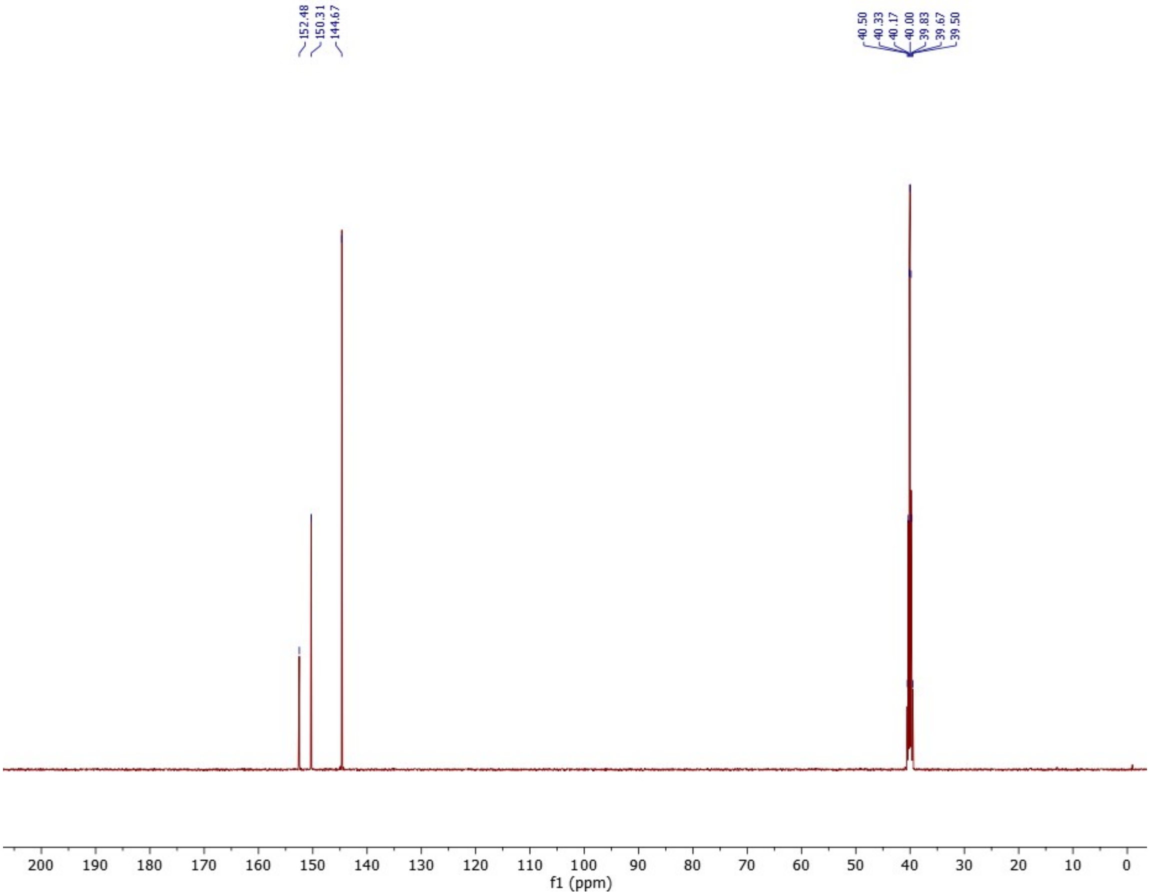


5-Hydroxypyrimidine (2v)

^{1}H NMR (500 MHz, DMSO)

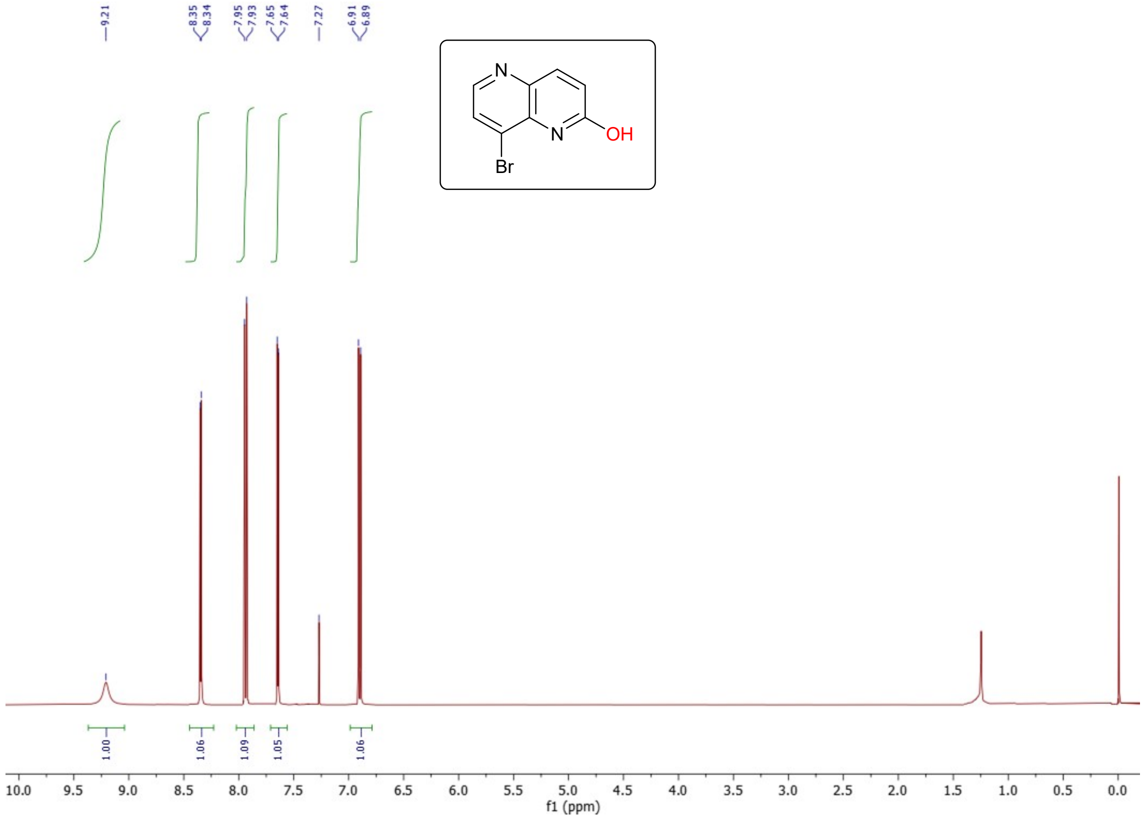


^{13}C NMR (125 MHz, DMSO)

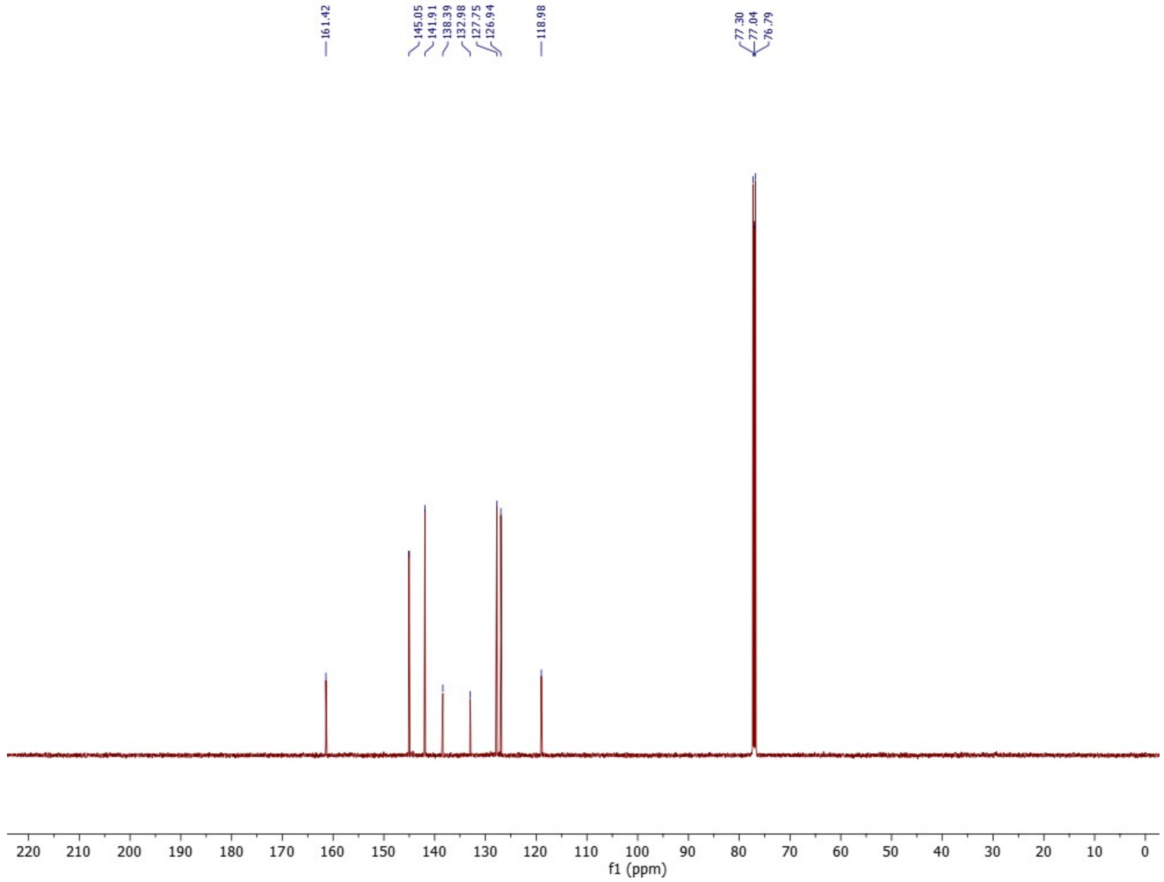


8-Bromo-2-hydroxy-1,5-naphthyridine (2w)

^{1}H NMR (500 MHz, CDCl$_3$)

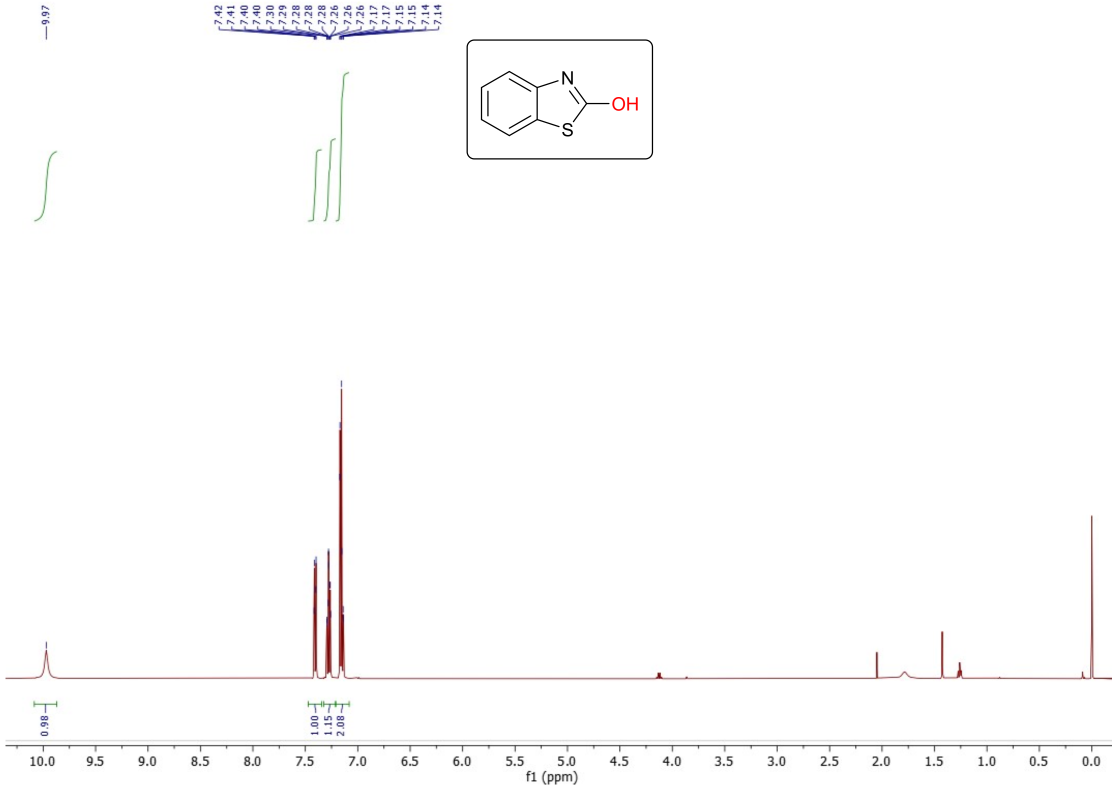


^{13}C NMR (125 MHz, CDCl$_3$)

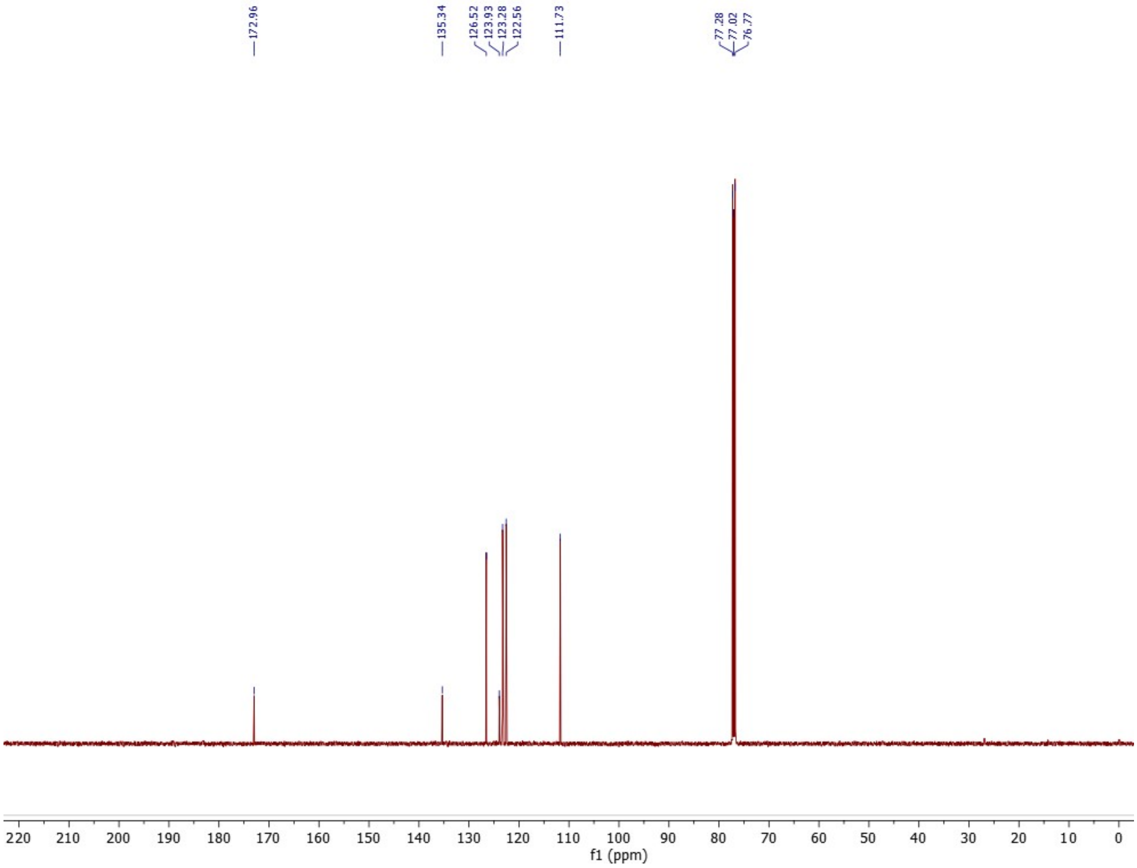


2-Hydroxybenzo[*d*]thiazole (2x)

^{1}H NMR (500 MHz, CDCl$_3$)

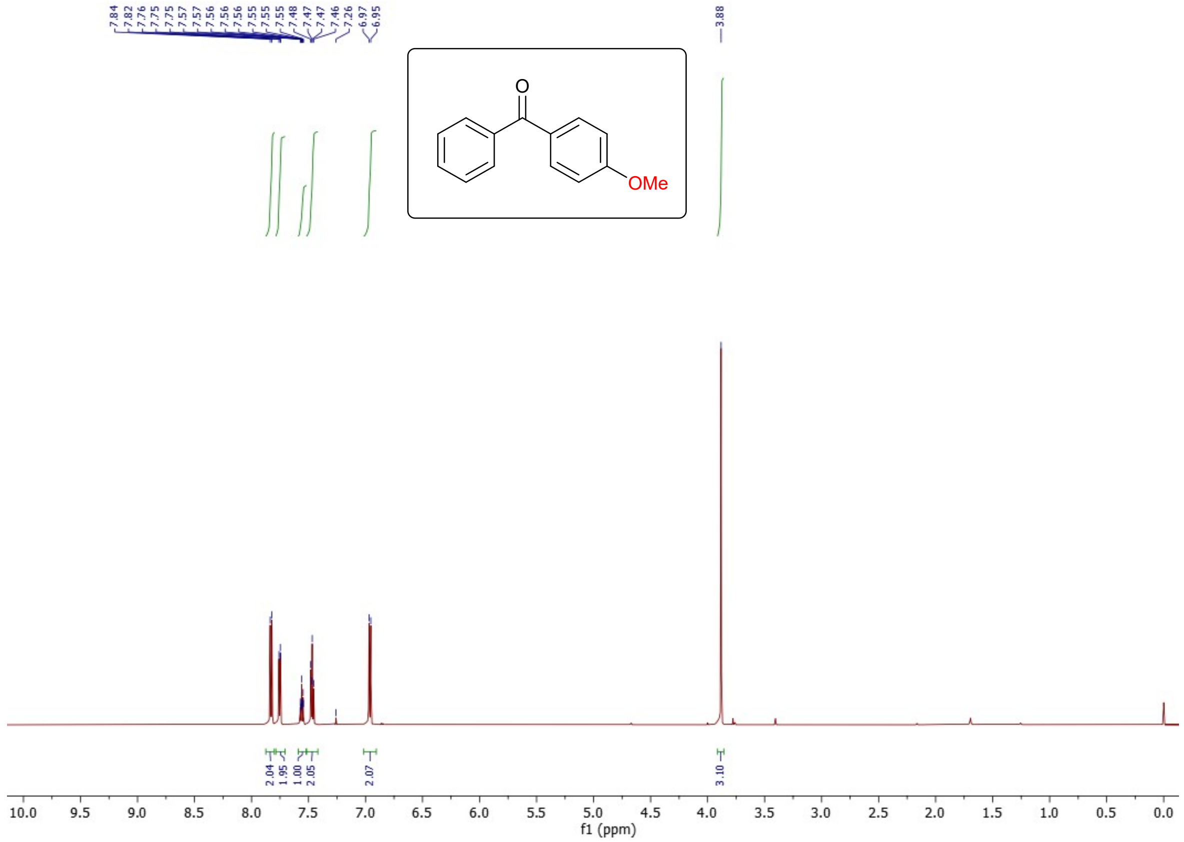


^{13}C NMR (125 MHz, CDCl$_3$)

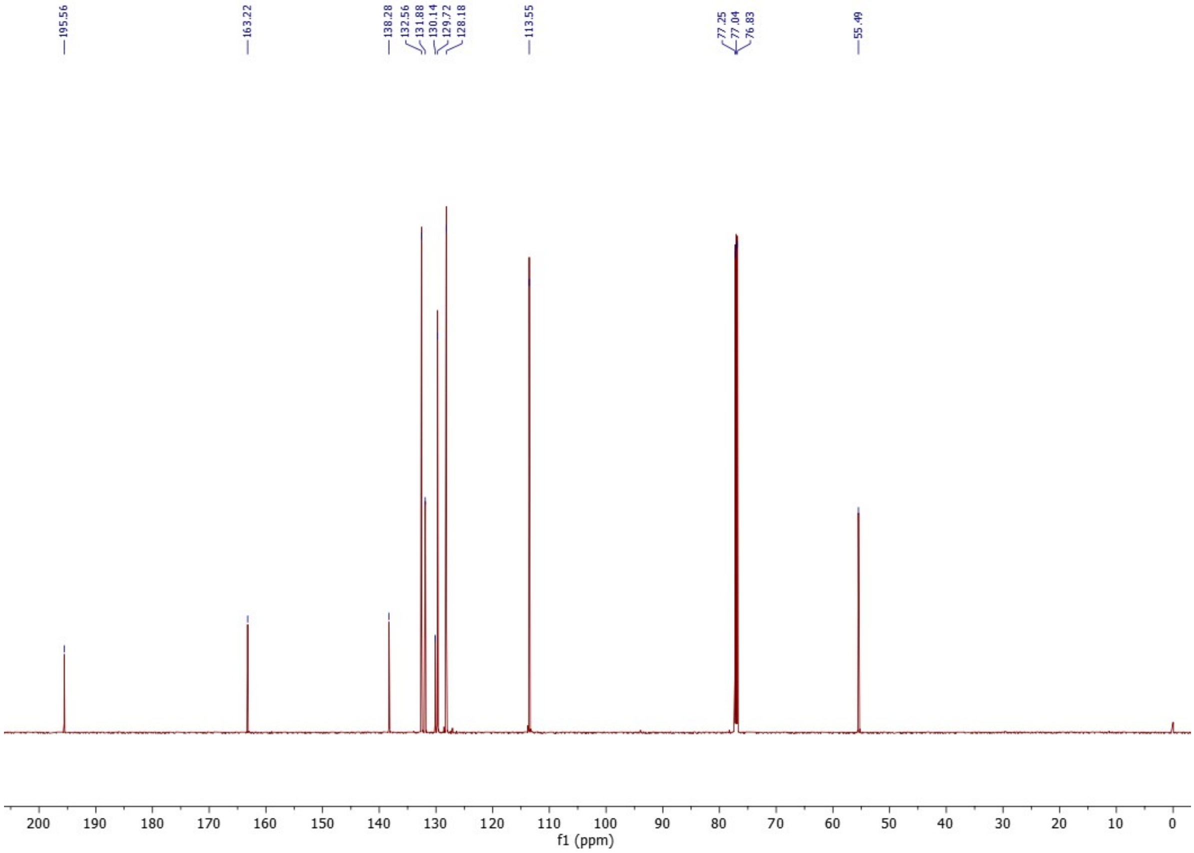


4-Methoxybenzophenone (3a)

^{1}H NMR (500 MHz, $CDCl_3$)

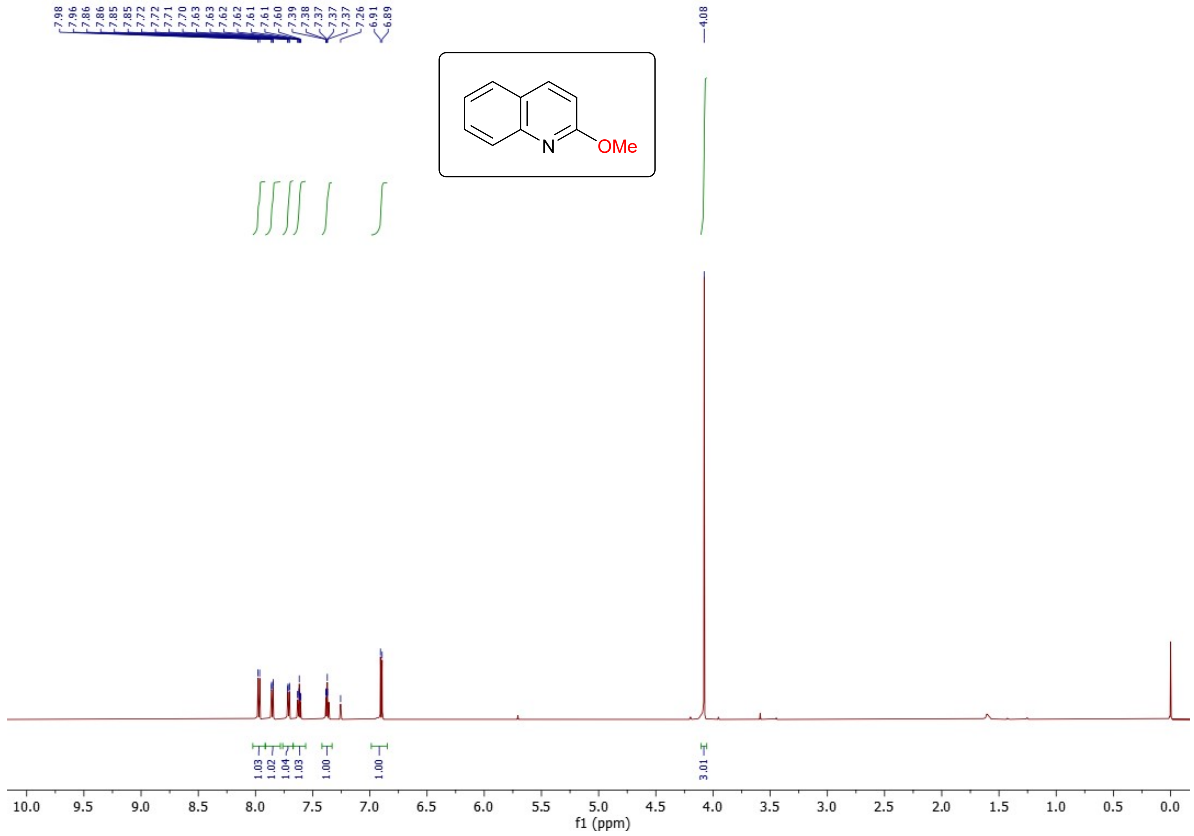


^{13}C NMR (125 MHz, $CDCl_3$)



2-Methoxyquinoline (3p)

^{1}H NMR (500 MHz, CDCl$_3$)



^{13}C NMR (125 MHz, CDCl$_3$)