Supporting Information

Lewis acid-promoted site-selective cyanation of phenols

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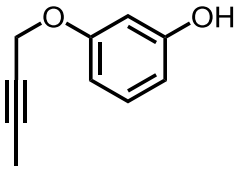
1. General information

Unless otherwise noted, all reactions were conducted in oven-dried vials with a magnetic stir bar under nitrogen atmosphere. Solvents obtained commercially were purified under nitrogen using a solvent purification system. Unless otherwise noted, all reagents and catalysts were purchased from commercial suppliers without further purification and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 MHz at 20 ^{o}C. Chemical shifts (δ) are given in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane (^{1}H NMR: $CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm. ^{13}C NMR: $CDCl_3$ at 77.00 ppm, DMSO-d_6 at 39.52 ppm). The data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet, br = broad), coupling constant J (Hz) and integration. Flash chromatography was performed with EM Science silica gel 60 (200-300 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F254 plates. Compounds were visualized with ultraviolet fluorescence. High resolution mass spectra were recorded on a Bruker Maxis System. IR spectra were collected on a Spectrum BX FTIR from Perkin-Elmer and reported in unit of cm^{-1}. Melting points were measured on an automatic melting points instrument hanon MP430 at ambient pressure.

2. Preparation of substrates

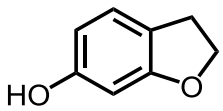
[1,1′-biphenyl]-3-ol (**1q**),[1] [1,1′-biphenyl]-3,3′-diol (**1u**)[2] and 3-hydroxy-1,3,5(10)-estratriene (**1z**)[3] were prepared according to known procedure. The data are all in accordance with the literature.

Synthesis of 3-(but-2-yn-1-yloxy) phenol (1k)



To a suspension of resorcinol (550.6 mg, 5.0 mmol) and potassium carbonate (1.38 g, 10.0 mmol) in acetone (20 mL) was added dropwise 1-bromo-2-butyne (864.5 mg, 6.5 mmol) dropwise at room temperature, and the resulting mixture was refluxed for 5 h. Upon completed, the reaction mixture was concentrated, acidified with 2 M aq. HCl and then extracted with ethyl acetate (15 mL x 3) for three times. The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate as eluent) to obtain desire product **1k** in 45% yield (365.0 mg) as yellow oil. $\mathbf{R_f}$ = 0.45 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.12 (t, J = 7.9 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 6.53-6.45 (m, 2H), 6.18 (br s, 1H), 4.60 (s, 2H), 1.83 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.9, 156.5, 130.1, 108.5, 107.2, 102.5, 84.0, 73.8, 56.5, 3.5 ppm. **HRMS (ESI$^+$):** Calcd for $C_{10}H_9O_2$ [M-H]$^-$: 161.0603; Found: 161.0609. **IR (neat, cm^{-1}):** 3449, 2921, 2868, 2231, 1597, 1490, 1460, 1369, 1147, 1024, 765.

Synthesis of 2, 3-dihydro-6-benzofuranol (1o)[4]

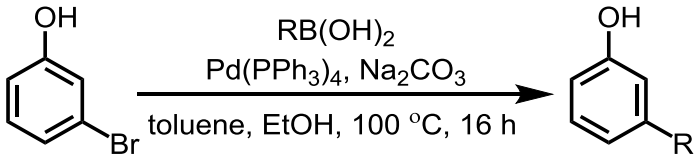


A suspension of 6-hydroxy-1-benzofuran-3-one (750.7 mg, 5.0 mmol) in 3 mL hydrazine hydrate, 29 mL diethyleneglycol and NaOH (2.18 g, 54.5 mmol) was heated to 120 ℃. After stirring at this temperature for 1 h, the temperature was increased to 190 ℃. After stirring for additional 8 h, the mixture was cooled to room temperature, acidified with 2 M aq. HCl, and then extracted with ethyl acetate (30 mL x 3) for three times. The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and

concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether-ethyl acetate as eluent) to obtain desire product **1o** in 37% yield (252.0 mg) as colorless solid. **m.p.** 59-60 ℃. **R_f** = 0.47 (PE/EA = 5:1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.00 (d, J = 8.4 Hz, 1H), 6.46 (br s, 1H), 6.39-6.32 (m, 2H), 4.57 (t, J = 8.4 Hz, 2H), 3.11 (t, J = 8.6 Hz, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 160.7, 155.9, 125.0, 118.6, 107.3, 97.6, 72.0, 28.8 ppm. **HRMS (ESI^+):** Calcd for C8H7O2 [M-H] $^-$: 135.0446; Found: 135.0453. **IR (neat, cm^{-1}):** 3372, 2966, 1621, 1608, 1499, 1460, 1182, 1136, 1092, 987, 833.

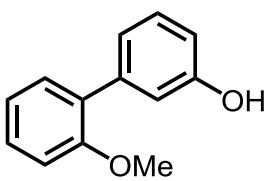
Synthesis of [1,1′-biphenyl]-3-ol derivatives

General procedure A[1]



A solution of arylboronic acid (5.5 mmol) in 15 mL ethanol was added to a mixture of 3-bromophenol (865.0 mg, 5.0 mmol), Pd $(PPh_3)_4$ (462.2 mg, 8 mol %) and Na_2CO_3 (2.33 g, 22.0 mmol) in toluene (30 mL) and H_2O (16 mL) at room temperature under N_2 atmosphere. The mixture was stirred at 100 ℃ for 16 h. Upon completed, the mixture was concentrated, acidified with 2 M aq. HCl, and then extracted with ethyl acetate (15 mL x 3) for three times. The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate as eluent = 10/1) to the corresponding products.

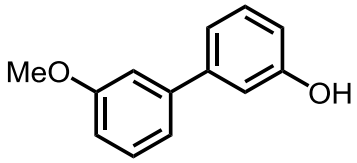
Synthesis of 2'-Methoxy-[1,1′-biphenyl]-3-ol (1r)[5]



The title compound **1r** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and (2-methoxyphenyl)boronic acid (836.0 mg, 5.5 mmol) according to the general procedure A and isolated as colorless oil with 83% yield (831.0 mg). **R_f =** 0.45 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43-7.29 (m, 3H), 7.17 (d, J =

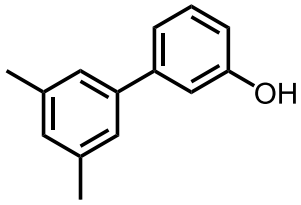
7.5 Hz, 1H), 7.13-7.01 (m, 3H), 6.86 (d, *J* = 7.9 Hz, 1H), 6.05 (br s, 1H), 3.82 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ 156.2, 155.0, 139.9, 130.7, 130.2, 129.1, 128.7, 121.9, 120.8, 116.5, 114.0, 111.4, 55.5 ppm.

Synthesis of 3′-methoxy-[1,1′-biphenyl]-3-ol (1s)[6]



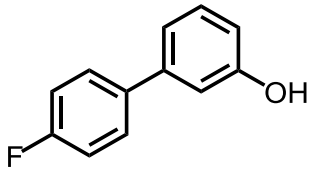
The title compound **1s** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and (3-methoxyphenyl)boronic acid (836.0 mg, 5.5 mmol) according to the general procedure A and isolated as colorless oil with 81% yield (811.0 mg). **R$_f$ =** 0.46 (PE/EA = 5/1). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.42-7.31 (m, 2H), 7.25-7.13 (m, 4H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.45 (br s, 1H), 3.89 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ 159.5, 155.7, 142.6, 142.1, 130.0, 129.7, 119.7, 119.6, 114.4, 114.1, 112.9, 112.7, 55.2 ppm.

Synthesis of 3',5′-dimethyl-[1,1′-biphenyl]-3-ol (1t)[7]



The title compound **1t** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and (3,5-dimethylphenyl)boronic acid (825.0 mg, 5.5 mmol) according to the general procedure A and isolated as light orange oil with 65% yield (645.0 mg). **R$_f$ =** 0.48 (PE/EA = 5/1). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.28 (t, *J* = 7.7 Hz, 1H), 7.18 (s, 3H), 7.08 (s, 1H), 7.00 (s, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.17 (s, 1H), 2.36 (s, 6H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ 155.5, 143.1, 140.6, 138.1, 129.8, 129.0, 124.9, 119.8, 114.11, 114.08, 21.3 ppm.

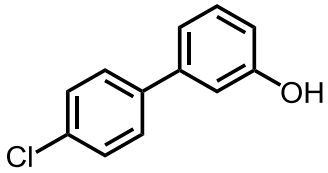
Synthesis of 4'-fluoro-[1,1′-biphenyl]-3-ol (1v)[7]



The title compound **1v** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and (4-fluorophenyl)boronic acid (770 mg, 5.5 mmol) according to the general procedure A and isolated as a colorless solid with 75% yield (706.0 mg). **m.p.** 76-77 ℃. **R$_f$ =** 0.41 (PE/EA = 5/1). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.53-7.46 (m, 2H), 7.32 (t, *J* = 7.9 Hz, 1H), 7.17-7.07 (m, 3H), 7.05 (s, 1H), 6.89-6.83 (m, 1H), 5.66 (br s, 1H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ

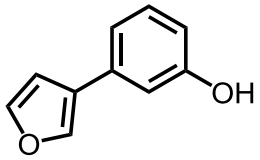
162.5 (d, *J* = 246.5 Hz), 155.6, 142.0, 136.7 (d, *J* = 3.2 Hz), 130.1, 128.6 (d, *J* = 8.1 Hz), 119.7, 115.5 (d, *J* = 21.5 Hz), 114.2, 114.0 ppm.

Synthesis of 4'-Chloro-[1,1′-biphenyl]-3-ol (1w)[7]



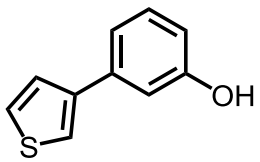
The title compound **1w** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and (4-chlorophenyl)boronic acid (860.2 mg, 5.5 mmol) according to the general procedure A and isolated as a colorless solid with 79% yield (809.0 mg). **m.p.** 75-76 ℃. **R_f = 0.39** (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.45 (d, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.18 (br s, 1H) ppm. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.5, 141.6, 138.9, 133.5, 130.2, 128.8, 128.2, 119.6, 114.5, 113.9 ppm.

Synthesis of 3-(furan-3-yl) phenol (1x)[8]



The title compound **1x** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and furan-3-ylboronic acid (615.5 mg, 5.5 mmol) according to the general procedure A and isolated as a colorless solid with 73% yield (585.0 mg). **m.p.** 55-56 ℃. **R_f =** 0.38 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (s, 1H), 7.50 (s, 1H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.01 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 5.43 (s, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.7, 143.6, 138.7, 134.1, 130.1, 126.0, 118.5, 114.0, 112.8, 108.8 ppm.

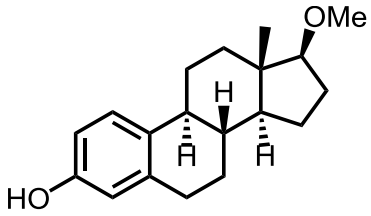
Synthesis of 3-(thiophen-3-yl) phenol (1y)[9]



The title compound **1y** was synthesized from 3-bromophenol (865.0 mg, 5.0 mmol) and thiophen-3-ylboronic acid (704.0 mg, 5.5 mmol) according to the general procedure A and isolated as a colorless solid with 70% yield (617.0 mg). **m.p.** 97-98 ℃. **R_f =** 0.37 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.49 (s, 1H), 7.46-7.40 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.14 (s, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 5.16 (s, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.8, 141.8, 137.5, 130.0, 126.3, 126.2, 120.6, 119.1,

114.1, 113.4 ppm.

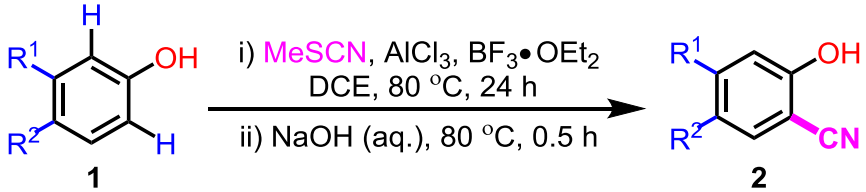
Synthesis of 17-Methoxy-1,3,5(10)-estratrien-3-ol (1aa)[10]



3,17β-Dimethoxyestra-1,3,5(10)-triene was prepared according to literature procedure using estradiol as the starting material.[11] Adopting a modified method of demethylation invented by our group, in a nitrogen-filled glovebox, to an oven-dried vial was charged with $HPPh_2$ (558.6 mg, 3.0 mmol), and ^{t}BuOK (336.6 mg, 3.0 mmol) in DMF (2.0 M) was added 3,17*β*-dimethoxyestra-1,3,5(10)-triene (450.6 mg, 1.5 mmol). The vial was sealed with a teflon-lined cap, removed out from the glovebox and heated at 80 °C for 14 h. After cooling down, the mixture was quenched with water (5 mL), acidified with 2 M HCl, and then extracted with ethyl acetate (15 mL x 3) for three times. The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to afford the desire product **1aa** in 82% yield (353.0 mg) as a colorless solid. **m.p.** 246-247 ℃. **R_f** = 0.32 (PE/EA = 4/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.98 (s, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 3.25 (s, 3H), 2.76-2.62 (m, 2H), 2.27-2.15 (m, 1H), 2.12-1.84 (m, 3H), 1.81-1.69 (m, 1H), 1.67-1.54 (m, 1H), 1.45-1.08 (m, 8H), 0.70 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 154.9, 137.1, 130.3, 126.0, 114.9, 112.8, 89.9, 57.1, 49.6, 43.4, 42.8, 38.4, 37.5, 29.1, 27.3, 26.9, 26.1, 22.7, 11.6 ppm.

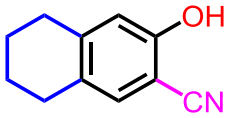
3. Lewis acid-promoted site-selective cyanation of phenols

General procedure B



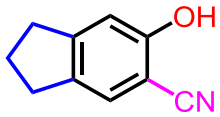
To a solution of phenol **1** (1.0 mmol), CH_3SCN (0.14 mL, 146.2 mg, 2.0 mmol), and $AlCl_3$ (133.3 mg, 1.0 mmol) in DCE (1 mL) was added BF_3•OEt_2 (0.25 mL, 283.8 mg, 2.0 mmol). The reaction mixture was stirred at 80 °C for 24 h. Upon completion, 4 M aq. NaOH (3.3 mL) was added and the mixture was refluxed for 0.5 h. After cooling, the organic layer was separated and the aqueous layer was washed with CH_2C1_2. The aqueous layer was acidified with 6 M HCl (3 mL), and then extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (eluent: dichloromethane/ethyl acetate = 20/1 to 10/1, unless otherwise noted) to afford the 2-hydroxy-4-substituted benzonitrile **2a**-**2aa**.

Synthesis of 3-hydroxy-5,6,7,8-tetrahydronaphthalene-2-carbonitrile (2a)



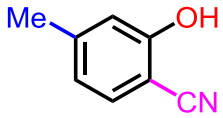
The title compound **2a** was synthesized from 5, 6, 7, 8-tetrahydronaphthalen-2-ol **1a** according to the general procedure B and isolated as a colorless solid in 87% yield (150.7 mg). **m.p.** 157-158 ℃. **R_f** = 0.48 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.59 (s, 1H), 7.23 (s, 1H), 6.67 (s, 1H), 2.72-2.55 (m, 4H), 1.72-1.60 (m, 4H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 157.4, 144.3, 132.9, 128.3, 117.4, 115.8, 96.4, 29.2, 27.5, 22.5, 22.1 ppm. **HRMS (ESI$^+$):** Calcd for $C_{11}H_{10}NO$ [M-H] $^-$: 172.0762; Found: 172.0769. **IR (neat, cm^{-1}):** 3294, 2917, 2230, 1618, 1584, 1437, 1348, 1285, 1198, 865.

Synthesis of 6-hydroxy-indene-5-carbonitrile (2b)



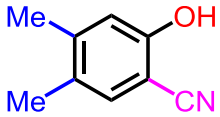
The title compound **2b** was synthesized from inden-5-ol **1b** according to the general procedure B and isolated as a colorless solid in 92% yield (146.5 mg). **m.p.** 175-176 ℃. **R_f** = 0.47 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** *δ* 10.61 (s, 1H), 7.21 (s, 1H), 6.83 (s, 1H), 2.76 (t, *J* = 7.3 Hz, 2H), 2.68 (t, *J* = 7.2 Hz, 2H), 1.97-1.86 (m, 2H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** *δ* 159.3, 151.9, 134.9, 127.7, 117.8, 112.1, 96.5, 33.0, 31.1, 25.3 ppm. **HRMS (ESI$^+$):** Calcd for $C_{10}H_8NO$ [M-H] $^-$: 158.0606; Found: 158.0612. **IR (neat, cm^{-1}):** 3260, 2921, 2231, 1615, 1588, 1491, 1429, 1276, 1182, 874.

Synthesis of 2-hydroxy-4-methylbenzonitrile (2c)[12]



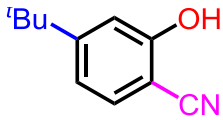
The title compound **2c** was synthesized from *m*-cresol **1c** according to the general procedure B and isolated as a colorless solid in 93% yield (123.9 mg). The data of **2c** was in accordance with the literature. **m.p.** 108-109 ℃. **R_f** = 0.47 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.91 (s, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 6.80 (s, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 2.27 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.1, 145.5, 132.9, 120.7, 117.3, 116.5, 96.0, 21.5 ppm.

Synthesis of 2-hydroxy-4, 5-dimethylbenzonitrile (2d)



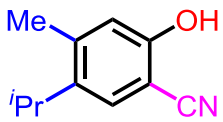
The title compound **2d** was synthesized from 3,4-dimethylphenol **1d** according to the general procedure B and isolated as a colorless solid in 96% yield (141.3 mg). **m.p.** 198-199 ℃. **R_f** = 0.46 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.59 (s, 1H), 7.21 (s, 1H), 6.77 (s, 1H), 2.14 (s, 3H), 2.06 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 158.3, 144.2, 132.8, 127.8, 117.5, 117.1, 95.9, 20.0, 18.0 ppm. **HRMS (ESI$^+$):** Calcd for C_9H_8NO [M-H] $^-$: 146.0606; Found: 146.0612. **IR (neat, cm^{-1}):**3252, 2943, 2229, 1619, 1586, 1499, 1407, 1296, 1200, 873, 669.

Synthesis of 4-*tert*-butyl-2-hydroxybenzonitrile (2e)[13]



The title compound **2e** was synthesized from 3-(*tert*-butyl) phenol **1e** according to the general procedure B and isolated as a colorless solid in 88% yield (154.2 mg). **m.p.** 130-131 ℃. **R_f** = 0.43 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.88 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 1.23 (s, 9H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.1, 158.2, 132.7, 117.21, 117.18, 112.9, 95.9, 34.9, 30.6 ppm.

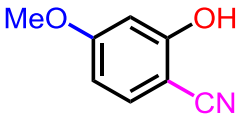
Synthesis of 2-hydroxy-5-isopropyl-4-methylbenzonitrile (2f)



The title compound **2f** was synthesized from 4-isopropyl-3-methylphenol **1f** according to the general procedure B and isolated as a colorless solid in 91% yield (159.5 mg). **m.p.** 118-119 ℃. **R_f** = 0.46 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.66 (br s, 1H), 7.35 (s,

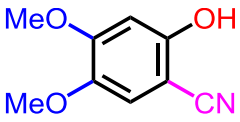
1H), 6.77 (s, 1H), 3.20-2.92 (m, 1H), 2.25 (s, 3H), 1.11 (d, *J* = 6.7 Hz, 6H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 157.7, 142.8, 138.2, 129.0, 117.51, 117.46, 96.4, 28.0, 23.0, 19.4 ppm. **HRMS (ESI$^+$):** Calcd for $C_{11}H_{12}NO$ [M-H]$^-$: 174.0919; Found: 174.0925. **IR (neat, cm^{-1}):**3303, 2960, 2870, 2229, 1614, 1587, 1503, 1379, 1289, 1146, 864.

Synthesis of 2-hydroxy-4-methoxybenzonitrile (2g)[14]



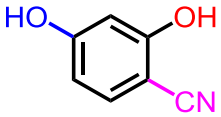
The title compound **2g** was synthesized from 3-methoxyphenol **1g** according to the general procedure B and isolated as a colorless solid in 95% yield (141.7 mg). **m.p.** 168-169 ℃. **R$_f$** = 0.45 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.05 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 6.54-6.48 (m, 2H), 3.76 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 164.1, 161.9, 134.4, 117.4, 106.7, 101.1, 91.2, 55.5 ppm.

Synthesis of 2-hydroxy-4,5-dimethoxybenzonitrile (2h)



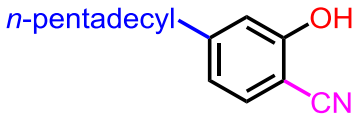
The title compound **2h** was synthesized from 3,4-dimethoxyphenol **1h** according to the general procedure B and isolated as a colorless solid in 93% yield (166.7 mg). **m.p.** 134-135 ℃. **R$_f$** = 0.45 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.58 (s, 1H), 7.05 (s, 1H), 6.55 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 156.3, 154.1, 142.1, 117.6, 114.2, 100.3, 88.4, 56.2, 55.6 ppm. **HRMS (ESI$^+$):** Calcd for $C_9H_8NO_3$ [M-H]$^-$: 178.0504; Found: 178.0511. **IR (neat, cm^{-1}):** 3247, 2981, 2834, 2222, 1613, 1525, 1469, 1212, 1116, 990, 852.

Synthesis of 2, 4-dihydroxybenzonitrile (2i)[15]



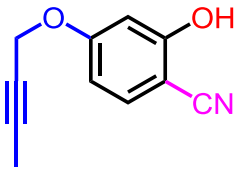
The title compound **2i** was synthesized from resorcinol **1i** according to the general procedure B and isolated as a colorless solid in 81% yield (109.4 mg). **m.p.** 183-184 ℃. **R$_f$** = 0.35 (CH_2Cl_2/EA = 5/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.76 (br s, 1H), 10.36 (br s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.42 (s, 1H), 6.32 (d, *J* = 8.5 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 163.0, 162.0, 134.5, 118.0, 108.4, 102.6, 89.7 ppm.

Synthesis of 2-hydroxy-4-pentadecylbenzonitrile (2j)



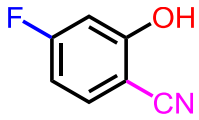
The title compound **2j** was synthesized from 3-pentadecylphenol **1j** according to the general procedure B and isolated as a colorless solid in 90% yield (296.6 mg). **m.p.** 72-73 ℃. **R_f** = 0.44 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, J = 7.8 Hz, 1H), 6.83-6.75 (m, 2H), 2.58 (t, J = 7.6 Hz, 2H), 1.66-1.51 (m, 2H), 1.31-1.21 (m, 24H), 0.88 (t, J = 6.3 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.6, 151.2, 132.5, 121.3, 116.8, 116.4, 96.5, 36.1, 31.9, 30.7, 29.72-29.57 (m, 6C), 29.5, 29.4, 29.3, 29.2, 22.7, 14.1 ppm. **HRMS (ESI$^+$):** Calcd for $C_{22}H_{34}NO$ [M-H]$^-$: 328.2640; Found: 328.2647. **IR (neat, cm^{-1}):** 3272, 2916, 2853, 2229, 1615, 1586, 1471, 1440, 1311, 875, 718.

Synthesis of 4-(but-2-yn-1-yloxy)-2-hydroxybenzonitrile (2k)



The title compound **2k** was synthesized from **1k** according to the general procedure B and isolated as a colorless solid in 55% yield (103.0 mg). **m.p.** 119-120 ℃. **R_f** = 0.40 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.10 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 6.58-6.51 (m, 2H), 4.76 (s, 2H), 1.83 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-d_6)** δ 162.2, 161.7, 134.3, 117.3, 107.3, 102.0, 91.7, 84.3, 74.0, 56.3, 3.2 ppm. **HRMS (ESI$^+$):** Calcd for $C_{11}H_8NO_2$ [M-H]$^-$: 186.0555; Found: 186.0562. **IR (neat, cm^{-1}):** 3235, 2924, 2854, 2225, 1612, 1513, 1491, 1439, 1182, 1014, 837.

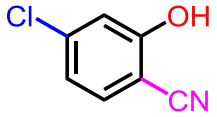
Synthesis of 4-fluoro-2-hydroxybenzonitrile (2l)



According to the modified literature procedure for 8 h,[16] the reaction was carried out with 3-fluorophenol **1l** (112.1 mg, 1 mmol), CH_3SCN (82 uL, 87.7 mg, 1.2 mmol), $AlCl_3$ (133.3 mg, 1 mmol) and BCl_3 (1.2 mL, 1.2 mmol, 1.0 M in dichloromethane). The product **21** was obtained as a colorless solid in 92% yield (126.1 mg). **m.p.** 114-115 ℃. **R_f** = 0.35 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 11.67 (br s, 1H), 7.67 (t, J = 7.5 Hz, 1H), 6.82-6.73 (m, 2H) ppm. **^{13}C NMR (100 MHz, DMSO-d_6)** δ 165.5 (d, J = 252.5 Hz), 162.4 (d, J = 12.6 Hz), 135.6 (d, J = 11.7 Hz), 116.4, 107.5 (d, J = 23.2 Hz), 103.5 (d, J = 24.6 Hz), 96.0 (d, J = 2.7 Hz) ppm. **HRMS (ESI$^+$):** Calcd for C_7H_3FNO [M-H]$^-$: 136.0199;

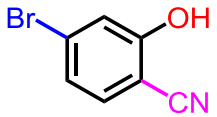
Found: 136.0205. **IR (neat, cm^{-1}):** 3276, 2233, 1606, 1598, 1514, 1446, 1366, 1284, 1101, 980, 856.

Synthesis of 4-chloro-2-hydroxybenzonitrile (2m)



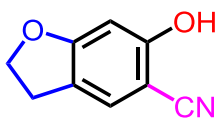
According to the modified literature procedure for 16 h,[16] the reaction was carried out with 3-chlorophenol **1m** (128.6 mg, 1 mmol), CH_3SCN (82 uL, 1.2 mmol), $AlCl_3$ (133.3 mg, 1 mmol) and BCl_3 (1.2 mL, 1.2 mmol, 1.0 M in dichloromethane). The product **2m** was obtained as a colorless solid in 84% yield (129.0 mg). **m.p.** 159-160 ℃. **R$_f$** = 0.33 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.56 (br s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 161.0, 139.0, 134.6, 119.9, 116.2, 116.1, 98.2 ppm. **HRMS (ESI$^+$):** Calcd for C_7H_3ClNO [M-H] $^-$: 151.9903; Found: 151.9910. **IR (neat, cm^{-1}):** 3159, 2242, 1601, 1592, 1499, 1427, 1259, 1086, 917, 855.

Synthesis of 4-bromo-2-hydroxybenzonitrile (2n)



According to the modified literature procedure for 20 h,[16] the reaction was carried out with 3-bromophenol **1n** (173 mg, 1 mmol), CH_3SCN (82 uL, 1.2 mmol), $AlCl_3$ (133.3 mg, 1 mmol) and BCl_3 (1.2 mL, 1.2 mmol, 1.0 M in dichloromethane). The product **2n** was obtained as a colorless solid in 76% yield (150.5 mg). **m.p.** 162-163 ℃. **R$_f$** = 0.32 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.57 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.17 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.9, 134.7, 127.8, 122.7, 119.0, 116.3, 98.5 ppm. **HRMS (ESI$^+$):** Calcd for C_7H_3BrNO [M-H] $^-$: 195.9398; Found: 195.9405. **IR (neat, cm^{-1}):** 3146, 2241, 1631, 1594, 1493, 1422, 1256, 1075, 896, 854.

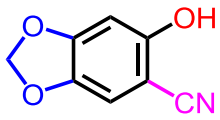
Synthesis of 6-hydroxy-2, 3-dihydrobenzofuran-5-carbonitrile (2o)



The title compound **2o** was synthesized from 6-hydroxy-2,3-dihydrobenzofuran **1o** according to the general procedure B and isolated as a colorless solid in 87% yield (140.2 mg). **m.p.** 200-201 ℃. **R$_f$** = 0.45 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.83

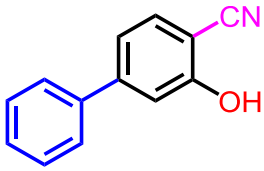
(s, 1H), 7.29 (s, 1H), 6.35 (s, 1H), 4.55 (t, *J* = 8.6 Hz, 2H), 3.04 (t, *J* = 8.6 Hz, 2H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 164.9, 161.8, 128.6, 119.5, 118.0, 97.2, 90.3, 72.8, 27.7 ppm. **HRMS (ESI$^+$):** Calcd for $C_9H_6NO_2$ [M-H] $^-$: 160.0399; Found: 160.0405. **IR (neat, cm^{-1}):** 3248, 2956, 2224, 1626, 1606, 1492, 1451, 1314, 1192, 1079, 835.

Synthesis of 6-hydroxy-benzo [1, 3] dioxole-5-carbonitrile (2p)[17]



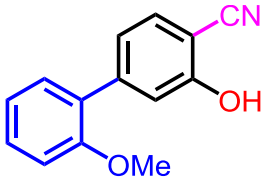
The title compound **2p** was synthesized from sesamol **1p** according to the general procedure B and isolated as a colorless solid in 56% yield (91.4 mg). **m.p.** 235-236 ℃. **R$_f$** = 0.43 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.81 (s, 1H), 7.09 (s, 1H), 6.55 (s, 1H), 6.04 (s, 2H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 157.9, 152.4, 140.2, 117.4, 109.9, 102.3, 97.8, 89.2 ppm.

Synthesis of 3-hydroxy-[1,1'-biphenyl]-4-carbonitrile (2q)



The title compound **2q** was synthesized from **1q** according to the general procedure B and isolated as a colorless solid in 72% yield (140.5 mg). **m.p.** 180-181 ℃. **R$_f$** = 0.41 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.25 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.52-7.38 (m, 3H), 7.24 (s, 1H), 7.20 (d, *J* = 7.9 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.6, 146.4, 138.7, 133.8, 129.2, 128.7, 126.9, 118.2, 117.1, 114.0, 97.9 ppm. **HRMS (ESI$^+$):** Calcd for $C_{13}H_8NO$ [M-H] $^-$: 194.0606; Found: 194.0613. **IR (neat, cm^{-1}):** 3267, 2231, 1611, 1574, 1490, 1417, 1315, 1246, 874, 756.

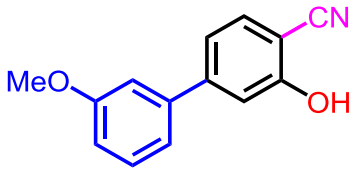
Synthesis of 3-hydroxy-2'-methoxy-[1,1'-biphenyl]-4-carbonitrile (2r)



The title compound **2r** was synthesized from **1r** according to the general procedure B and isolated as a colorless solid in 81% yield (182.5 mg). **m.p.** 144-145 ℃. **R$_f$** = 0.43 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.10 (s, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.17 (s, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 7.03 (t, *J* = 8.1 Hz, 2H), 3.77 (s, 3H) ppm. **^{13}C NMR (100 MHz,**

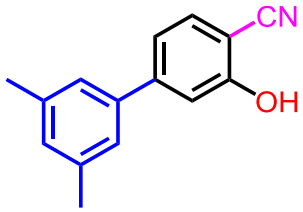
DMSO-*d*$_6$) δ 159.8, 156.1, 144.6, 132.7, 130.2, 130.0, 128.3, 121.0, 120.8, 117.2, 116.9, 112.0, 97.3, 55.6 ppm. **HRMS (ESI$^+$):** Calcd for $C_{14}H_{10}NO_2$ [M-H]$^-$: 224.0712; Found: 224.0718. **IR (neat, cm^{-1}):** 3264, 2938, 2228, 1612, 1585, 1486, 1415, 1244, 1115, 877, 754.

Synthesis of 3-hydroxy-3'-methoxy-[1,1'-biphenyl]-4-carbonitrile (2s)



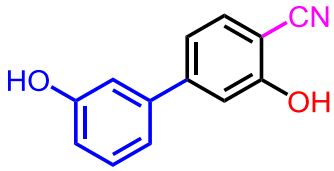
The title compound **2s** was synthesized from **1s** according to the general procedure B and isolated as a colorless solid in 80% yield (180.2 mg). **m.p.** 142-143 ℃. **R$_f$** = 0.43 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.23 (s, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.26-7.11 (m, 4H), 7.00 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.5, 159.8, 146.3, 140.2, 133.7, 130.3, 119.2, 118.4, 117.1, 114.3, 114.2, 112.4, 98.0, 55.2 ppm. **HRMS (ESI$^+$):** Calcd for $C_{14}H_{10}NO_2$ [M-H]$^-$: 224.0712; Found: 224.0718. **IR (neat, cm^{-1}):** 3259, 2940, 2228, 1609, 1574, 1485, 1283, 1035, 817, 780.

Synthesis of 3-hydroxy-3',5'-dimethyl-[1,1'-biphenyl]-4-carbonitrile (2t)



The title compound **2t** was synthesized from **1t** according to the general procedure B and isolated as a colorless solid in 83% yield (185.3 mg). **m.p.** 195-196 ℃. **R$_f$** = 0.45 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.15 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.22 (s, 1H), 7.17 (s, 2H), 7.12 (d, *J* = 8.1 Hz, 1H), 6.99 (s, 1H), 2.29 (s, 6H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.5, 146.7, 138.7, 138.2, 133.5, 130.1, 124.7, 118.2, 117.1, 114.0, 97.7, 21.0 ppm. **HRMS (ESI$^+$):** Calcd for $C_{15}H_{12}NO$ [M-H]$^-$: 222.0919; Found: 222.0926. **IR (neat, cm^{-1}):** 3250, 2917, 2230, 1612, 1580, 1483, 1443, 1404, 1244, 847, 816.

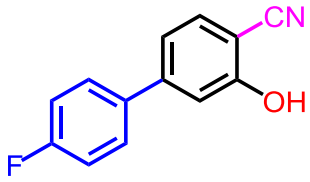
Synthesis of 3,3'-dihydroxy-[1,1'-biphenyl]-4-carbonitrile (2u)



The title compound **2u** was synthesized from **1u** according to the general procedure B and isolated as a colorless solid in 61% yield (128.8 mg). **m.p.** 222-223 ℃. **R$_f$** = 0.31 (CH_2Cl_2/EA = 5/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.21 (s, 1H), 9.69

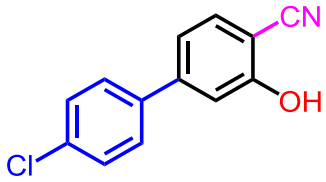
(s, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.22-7.11 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.98 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.5, 158.0, 146.6, 140.1, 133.7, 130.3, 118.1, 117.6, 117.1, 115.8, 113.9, 113.6, 97.8 ppm. **HRMS (ESI$^+$):** Calcd for $C_{13}H_8NO_2$ [M-H]$^-$: 210.0555; Found: 210.0562. **IR (neat, cm^{-1}):** 3235, 2237, 1610, 1579, 1485, 1421, 1288, 1244, 844, 781.

Synthesis of 4'-fluoro-3-hydroxy-[1,1'-biphenyl]-4-carbonitrile (2v)



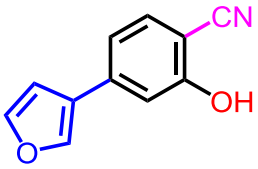
The title compound **2v** was synthesized from **1v** according to the general procedure B and isolated as a colorless solid in 81% yield (172.7 mg). **m.p.** 262-263 ℃. **R$_f$** = 0.37 (CH_2Cl_2/EA = 10:1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.26 (s, 1H), 7.67 (d, *J* = 6.2 Hz, 3H), 7.32 (t, *J* = 8.4 Hz, 2H), 7.23-7.16 (m, 2H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 162.5 (d, *J* = 246.0 Hz), 160.5, 145.3, 135.2 (d, *J* = 3.0 Hz), 133.8, 129.1 (d, *J* = 8.4 Hz), 118.2, 117.0, 116.1 (d, *J* = 21.6 Hz), 114.0, 97.9 ppm. **HRMS (ESI$^+$):** Calcd for $C_{13}H_7FNO$ [M-H]$^-$: 212.0512; Found: 212.0518. **IR (neat, cm^{-1}):** 3229, 2237, 1613, 1579, 1497, 1439, 1403, 1224, 1161, 842, 817.

Synthesis of 4'-chloro-3-hydroxy-[1,1'-biphenyl]-4-carbonitrile (2w)



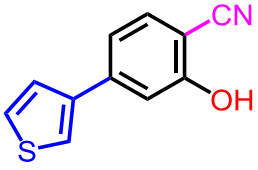
The title compound **2w** was synthesized from **1w** according to the general procedure B and isolated as a colorless solid in 74% yield (170.0 mg). **m.p.** 279-280 ℃. **R$_f$** = 0.34 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.28 (s, 1H), 7.68-7.58 (m, 3H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.21 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.6, 145.0, 137.5, 133.8, 133.7, 129.1, 128.7, 118.1, 117.0, 114.0, 98.3 ppm. **HRMS (ESI$^+$):** Calcd for $C_{13}H_7ClNO$ [M-H]$^-$: 228.0216; Found: 228.0223. **IR (neat, cm^{-1}):** 3229, 2234, 1609, 1587, 1486, 1438, 1281, 1091, 1012, 874, 804.

Synthesis of 4-(furan-3-yl)-2-hydroxybenzonitrile (2x)



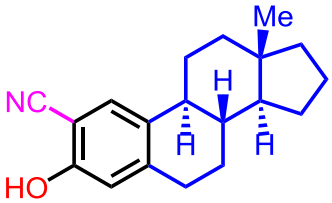
The title compound **2x** was synthesized from **1x** according to the general procedure B and isolated as a colorless solid n 51% yield (94.5 mg). **m.p.** 190-191 ℃. **R_f** = 0.37 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.13 (s, 1H), 8.25 (s, 1H), 7.78 (s, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.15 (s, 1H), 6.89 (s, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.5, 144.8, 141.0, 138.2, 133.7, 124.8, 117.2, 117.1, 112.6, 108.6, 97.2 ppm. **HRMS (ESI$^+$):** Calcd for $C_{11}H_6NO_2$ [M-H] $^-$: 184.0399; Found: 184.0405. **IR (neat, cm^{-1}):** 3198, 2233, 1616, 1568, 1430, 1369, 1227, 1163, 1057, 862, 781.

Synthesis of 2-hydroxy-4-(thiophen-3-yl)benzonitrile (2y)



The title compound **2y** was synthesized from **1y** according to the general procedure B and isolated as a colorless solid in 86% yield (173.1 mg). **m.p.** 202-203 ℃. **R_f** = 0.38 (CH_2Cl_2/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.18 (s, 1H), 7.89 (s, 1H), 7.65-7.56 (m, 2H), 7.47 (d, *J* = 4.7 Hz, 1H), 7.29 (s, 1H), 7.24 (d, *J* = 8.1 Hz, 1H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 160.6, 141.0, 140.0, 133.7, 127.7, 126.0, 123.5, 117.7, 117.2, 113.2, 97.5 ppm. **HRMS (ESI$^+$):** Calcd for $C_{11}H_6NOS$ [M-H] $^-$: 200.0170; Found: 200.0177. **IR (neat, cm^{-1}):** 3205, 2232, 1610, 1581, 1443, 1378, 1230, 1120, 948, 851, 782.

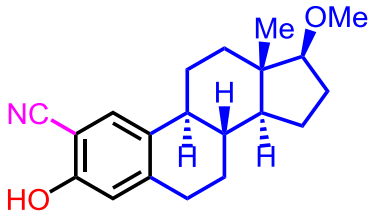
Synthesis of 3-hydroxy-estra-1,3,5(10)-triene-2-carbonitrile (2z)



The title compound **2z** was synthesized from **1z** according to the general procedure B and isolated as a colorless solid in 74% yield (208.2 mg) using petroleum ether-ethyl acetate (v/v, from 4/1 to 2/1) as an eluent. **m.p.** 207-208 ℃. **R_f** = 0.47 (PE/EA = 2/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.59 (s, 1H), 7.32 (s, 1H), 6.66 (s, 1H), 2.78-2.69 (m, 2H), 2.25-2.14 (m, 1H), 2.06-1.93 (m, 1H), 1.81-1.71 (m, 2H), 1.70-1.48 (m, 3H), 1.46-1.07 (m, 7H), 1.06-0.94 (m, 1H), 0.64 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 157.6, 144.0, 132.0, 129.5, 117.5, 115.7, 96.3, 52.9, 42.9, 40.5, 40.0, 38.3, 38.1, 29.4, 27.1, 26.0, 24.7, 20.2, 17.2

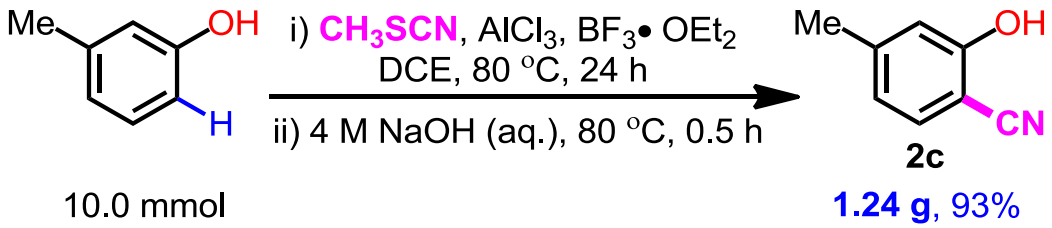
ppm. **HRMS (ESI$^+$):** Calcd for $C_{19}H_{22}NO$ [M-H]$^-$: 280.1701; Found: 280.1708. **IR (neat, cm^{-1}):** 3262, 2930, 2228, 1613, 1585, 1503, 1451, 1419, 1282, 1185, 890.

Synthesis of 17-Methoxy-3-hydroxy-estra-1,3,5(10)-triene-2-carbonitrile (2aa)



The title compound **2aa** was synthesized from **1aa** according to the general procedure B and isolated as a colorless solid in 73% yield (227.3 mg) using petroleum ether-ethyl acetate (v/v, from 4/1 to 2/1) as an eluent. **m.p.** 246-247 ℃. **R$_f$** = 0.49 (PE/EA = 2/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.63 (s, 1H), 7.31 (s, 1H), 6.65 (s, 1H), 3.22 (s, 3H), 3.20-3.14 (m, 1H), 2.76-2.66 (m, 2H), 2.22-2.10 (m, 1H), 2.01-1.81 (m, 3H), 1.76-1.63 (m, 1H), 1.61-1.46 (m, 1H), 1.39-1.11 (m, 6H), 1.06-0.96 (m, 1H), 0.62 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 157.7, 144.1, 131.8, 129.5, 117.5, 115.8, 96.4, 89.8, 57.2, 49.5, 42.8, 42.7, 37.8, 37.3, 29.3, 27.3, 26.3, 25.7, 22.6, 11.4 ppm. **HRMS (ESI$^+$):** Calcd for $C_{20}H_{24}NO_2$ [M-H]$^-$: 310.1807; Found: 310.1814. **IR (neat, cm^{-1}):** 3436, 2931, 2232, 1612, 1552, 1502, 1421, 1288, 1096, 966.

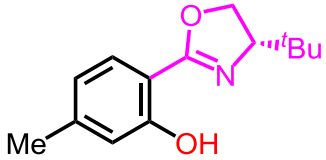
4. Product transformations



To a solution of *meta*-methyl phenol **1c** (10 mmol, 1.08 g), CH_3SCN (1.35 mL, 1.46 g, 20 mmol) and $AlCl_3$ (1.33 g, 10 mmol) in DCE (10 mL) was added BF_3•OEt_2 (2.5 mL, 2.84 g, 20 mmol). The reaction mixture was stirred at 80 °C for 24 h. Upon completed, 4 M aq. NaOH (33 mL) was added and refluxed for 0.5 h. After cooled, the organic layers were separated and the aqueous layer was washed with CH_2C1_2. The aqueous layer was acidified with 6.0 M HC1 (30 mL), and then extracted with ethyl acetate (30 x 3). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography

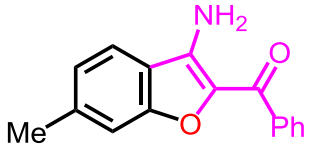
on silica gel (dichloromethane-ethyl acetate as eluent) to the desired cyanated product **2c** (1.24 g, 93%).

Synthesis of (*S*)-2-(4-(*tert*-butyl)-4, 5-dihydrooxazol-2-yl)-5-methylphenol (3a)[18]



An oven-dried vial equipped with a magnetic stir bar was charged with **2c** (66.6 mg, 0.5 mmol). The vial was then moved into a N_2-filled glovebox. (*S*)-2-amino-3,3-dimethylbutan-1-ol (117.2 mg, 1.0 mmol), $ZnCl_2$ (68.2 mg, 0.5 mmol), and PhCl (2 mL) were added to the vial. The vial was capped, and the resulting reaction mixture was stirred at 131 ℃ for 3 days. The reaction was quenched with water, and extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel to afford (*S*)-2-(4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl)-5-methylphenol **3a** in 88% yield (102.7 mg) as colorless oil. $\mathbf{R_f}$ = 0.51 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 12.36 (br s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.36-4.29 (m, 1H), 4.20 (t, *J* = 8.2 Hz, 1H), 4.13-4.06 (m, 1H), 2.35 (s, 3H), 0.94 (s, 9H).ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 165.0, 159.9, 144.1, 127.7, 119.6, 116.9, 108.0, 74.8, 67.9, 33.7, 25.7, 21.7 ppm. **HRMS (ESI$^+$):** Calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1499; Found: 234.1489. **IR (neat, cm^{-1}):** 2959, 2870, 1650, 1578, 1480, 1359, 1263, 1147, 1079, 965, 790.

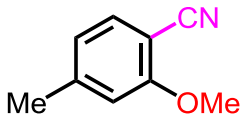
Synthesis of (3-amino-6-methylbenzofuran-2-yl) (phenyl) methanone (3b)[19]



To a suspension of **2c** (66.6 mg, 0.5 mmol) and potassium carbonate (138.2 mg, 1.0 mmol) in acetone (1 mL) was added α-bromoacetophenone (99.6 mg, 0.5 mmol). The resulting reaction mixture was refluxed for 8 h. After cooled to room temperature, the reaction mixture was diluted with ethyl acetate (15 mL), and washed with water and brine, respectively. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to afford **3b** in 90% yield (113.1 mg) as a yellow solid. **m.p.** 155-156 ℃. $\mathbf{R_f}$ = 0.41 (PE/EA = 3/1). **^{1}H NMR (400 MHz,**

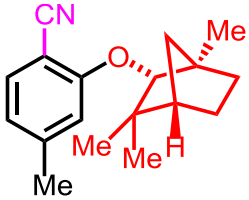
CDCl$_3$) δ 8.28 (d, J = 6.5 Hz, 2H), 7.63-7.49 (m, 4H), 7.26 (s, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.20 (br s, 2H), 2.50 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ 182.5, 155.0, 142.6, 140.9, 137.8, 135.0, 131.6, 129.1, 128.1, 123.9, 119.7, 118.3, 112.5, 22.0 ppm. **HRMS (ESI$^+$):** Calcd for $C_{16}H_{14}NO_2$ [M+H]$^+$: 252.1018; Found: 252.1019. **IR (neat, cm^{-1}):** 3410, 3293, 1612, 1589, 1513, 1479, 1407, 1355, 1310, 1181, 808.

Synthesis of 2-methoxy-4-methylbenzonitrile (3c)[20]



The title compound **3c** was synthesized by the known literature procedure.[21] A suspension of 2-hydroxy-4-methylbenzonitrile **2c** (666.0 mg, 5.0 mmol) and potassium carbonate (1.38 g, 10.0 mmol) in DMF (15 mL) was stirred for 30 min at room temperature, and then CH_3I (0.62 mL, 10.0 mmol) was added dropwise. After stirring at 60 °C for 5 h, the reaction was quenched with saturated aqueous ammonium chloride (20 mL), and extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give the desired product **3c** in 94% yield (692.0 mg) as a colorless solid. **m.p.** 72-73 ℃. **R$_f$** = 0.53 (PE/EA = 5/1). **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.42 (d, J = 7.8 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.76 (s, 1H), 3.90 (s, 3H), 2.40 (s, 3H) ppm. **^{13}C NMR (100 MHz, CDCl$_3$)** δ 161.2, 145.7, 133.4, 121.6, 116.8, 112.0, 98.8, 55.8, 22.2 ppm.

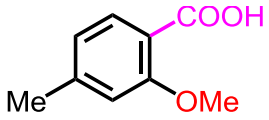
Synthesis of 4-methyl-2-(((1*R*, 2*S*, 4*S*)-1, 3, 3-trimethylbicyclo [2.2.1] heptan-2-yl) oxy) benzonitrile (3d)



The title compound **3d** was synthesized by the known literature procedure.[22] An oven-dried vial equipped with a magnetic stir bar was charged with **3c** (73.6 mg, 0.5 mmol), and the vial was then moved into a N_2-filled glovebox. ^{t}BuOK (112.2 mg, 1.0 mmol), (+)-fenchol (1.0 mmol), and 1,4-dioxane (0.5 mL) were added to the vial. The vial was capped, and the reaction mixture was stirred at 80 ℃ for 16 h. The mixture was diluted with Et_2O (3 mL), filtered through a plug of silica gel, and washed with THF. The filtrate was concentrated in *vacuo* and purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to provide **3d** as

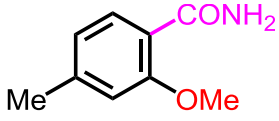
colorless oil in 69% yield (92.9 mg). **R_f** = 0.50 (PE/EA = 5/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, J = 8.1 Hz, 1H), 6.76-6.71 (m, 2H), 3.98 (s, 1H), 2.36 (s, 3H), 2.21-2.11 (m, 1H), 1.84-1.72 (m, 2H), 1.60 (d, J = 10.3 Hz, 1H), 1.54-1.45 (m, 1H), 1.29-1.21 (m, 2H), 1.19 (s, 3H), 1.11 (s, 3H), 0.86 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.8, 145.2, 133.4, 121.2, 117.0, 114.1, 99.5, 91.0, 49.7, 49.0, 41.4, 40.1, 30.5, 26.3, 25.8, 22.3, 20.4, 19.8 ppm. **HRMS (ESI$^+$):** Calcd for $C_{18}H_{24}NO$ $[M+H]^+$: 270.1853; Found: 270.1852. **IR (neat, cm^{-1}):** 2957, 2873, 2225, 1606, 1568, 1499, 1462, 1286, 1161, 1044, 808.

Synthesis of 2-methoxy-4-methylbenzoic acid (3e)[23]



The title compound **3e** was synthesized by the known literature procedure.[23] A Schlenk tube equipped with a magnetic stir bar was charged with **3c** (73.6 mg, 0.5 mmol). EtOH (4 mL) and KOH (4 mL, 34% aqueous solution) were added *via* syringe. The resulting reaction mixture was heated to 80 ºC and stirred overnight. The reaction mixture was quenched and acidified with HCl (2 M), and then extracted with ethyl acetate (15 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to afford **3e** as a colorless solid in 85% yield (70.6 mg). **m.p.** 102-103 ℃.**R_f** = 0.50 (PE/EA = 2.5/1). **^{1}H NMR (400 MHz, DMSO-d_6)** δ 12.40 (br s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 6.93 (s, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.79 (s, 3H), 2.32 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-d_6)** δ 167.1, 158.5, 143.8, 131.1, 120.7, 118.0, 113.1, 55.7, 21.4 ppm.

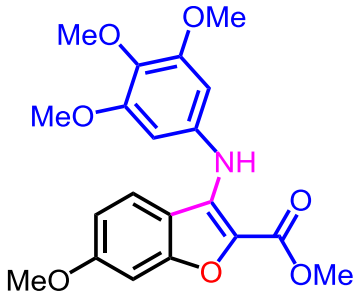
Synthesis of 2-methoxy-4-methylbenzamide (3f)



The title compound **3f** was synthesized *via* the hydrolysis of 2-methoxy-4-methylbenzonitrile **3c** by a modified literature procedure.[24] To a solution of **3c** (73.6 mg, 0.5 mmol) in ^{t}BuOH (10 mL) was added solid KOH (420.8 mg, 7.5 mmol) in a N_2-filled glovebox. The reaction was heated to 60 ºC and stirred overnight. Upon completion, the mixture was diluted with ethyl acetate (20 mL), and washed with water and brine, respectively. The organic layer

was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to afford **3f** as a colorless solid in 81% yield (66.9 mg). **m.p.** 143-144 ℃. **R_f** = 0.35 (PE/EA = 1/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.60 (br s, 1H), 7.48 (br s, 1H), 6.95 (s, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H) ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 166.1, 157.3, 143.0, 131.0, 121.2, 119.5, 112.5, 55.8, 21.2 ppm. **HRMS (ESI$^+$):** Calcd for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0863; Found: 166.0863. **IR (neat, cm^{-1}):** 3450, 3157, 1666, 1598, 1467, 1422, 1371, 1274, 1176, 1032, 805.

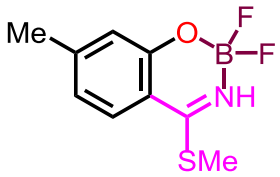
Synthesis of methyl 6-methoxy-3-((3, 4, 5-trimethoxyphenyl) amino) benzofuran-2-carboxylate (3g)[25]



2-Hydroxy-4-methoxybenzonitrile **2g** was prepared on a gram scale (94% yield, 1.40 g). Methyl 3-(3,4,5-trimethoxyphenylamino)-6-methoxybenzofuran -2-carboxylate **3g'** was synthesized by the known procedure.[26] Under N_2, a dry Schlenk tube equipped with a magnetic stir bar was charged with **3g'** (110.6 mg, 0.5 mmol), $Pd(OAc)_2$ (6.7 mg, 6 mol %), rac-BINAP (37.0 mg, 12 mol %), $CsCO_3$ (230.0 mg, 0.7 mmol), 5-bromo-1,2,3-trimethoxybenzene (148.0 mg, 0.6 mmol), and dry toluene (5 mL). The reaction mixture was stirred at 120 ℃ for 18 h. After cooling, the mixture was diluted with ethyl acetate (10 mL), filtered through a plug of silica gel, and washed with ethyl acetate (10 mL). The filtrate was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, concentrated under *vacco*. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1 to 2/1) to give **3g** in 75% yield (145.3 mg) as a yellow solid. **m.p.** 138-139 ℃. **R_f** = 0.49 (PE/EA = 2/1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (s, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.71 (dd, *J* = 8.9 and 2.3 Hz, 1H), 6.41 (s, 2H), 3.95 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.76 (s, 6H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 161.8, 161.2, 156.1, 153.5, 137.2, 136.6, 134.7, 126.9, 123.9,

113.9, 112.1, 99.6, 95.7, 61.0, 56.0, 55.6, 51.5 ppm.

Synthesis of 2,2-difluoro-7-methyl-4-(methylthio)-2*H*-2λ^4-benzo[*e*][1,3,2] oxazaborinine (4)



To a solution of *m*-cresol **1c** (108.1 mg, 1.0 mmol), CH_3SCN (0.14 mL, 146.2 mg, 2.0 mmol), and $AlCl_3$ (133.3 mg, 1.0 mmol) in DCE (1 mL) was added BF_3•OEt_2 (0.25 mL, 283.8 mg, 2.0 mmol). The reaction mixture was stirred at 80 °C for 24 h. Upon completion, the mixture was diluted with ethyl acetate, and then concentrated under *vacco*. The residue was purified by flash column chromatography on silica gel using dichloromethane-ethyl acetate (v/v, from 20/1 to 10/1) as an eluent to give the desired product **4** in 87% yield (199.3 mg) as a white solid. **m.p.** 276-277 ℃. R_f = 0.49 (DCM/EA = 10/1). **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.42 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 2.73 (s, 3H), 2.32 (s, 3H) ppm. **^{19}F NMR (376 MHz, DMSO-*d*$_6$)** δ -133.70 ppm. **^{13}C NMR (100 MHz, DMSO-*d*$_6$)** δ 176.8, 156.3, 148.6, 126.9, 121.2, 119.4, 113.0, 21.4, 12.8 ppm. **HRMS (EI$^+$):** Calcd for $C_9H_{10}BF_2NOS$ [M] $^+$: 229.0539; Found: 229.0542. IR (neat, cm^{-1}): 3325, 2933, 1621, 1593, 1498, 1444, 1325, 1280, 1222, 1156, 1046, 938.

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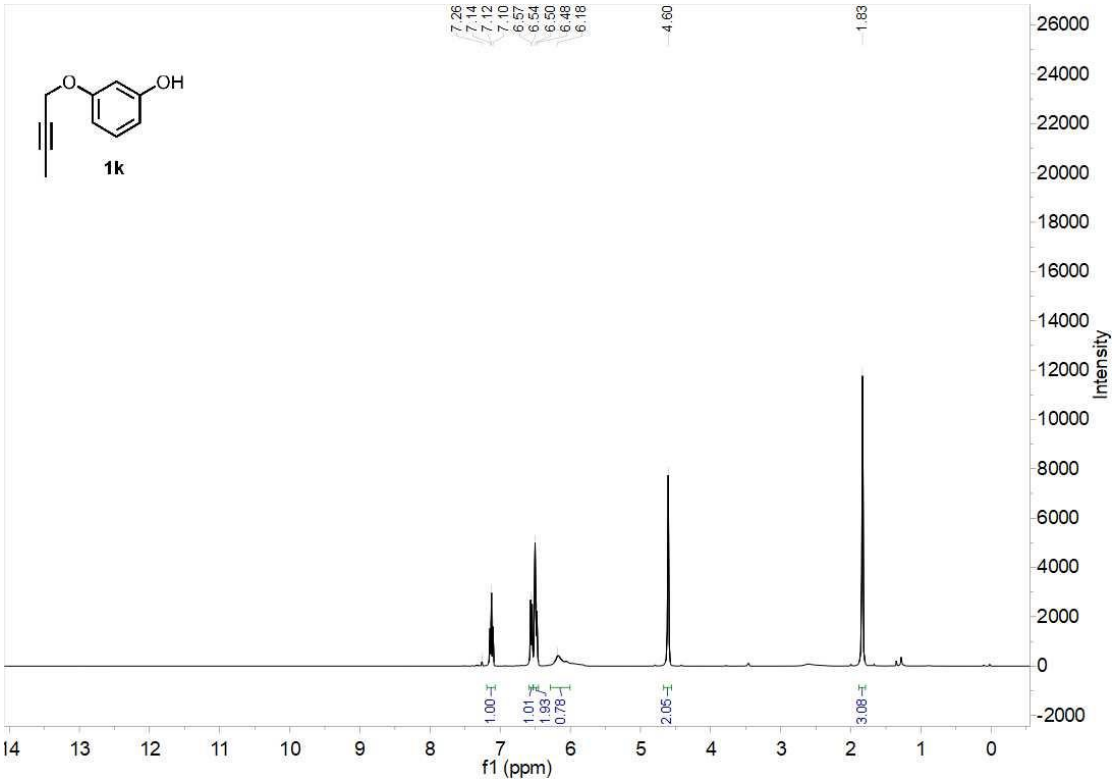
6. Copies of ^{1}H NMR and ^{13}C NMR spectra

^{1}H NMR spectrum of **1k** (400 MHz, $CDCl_3$)



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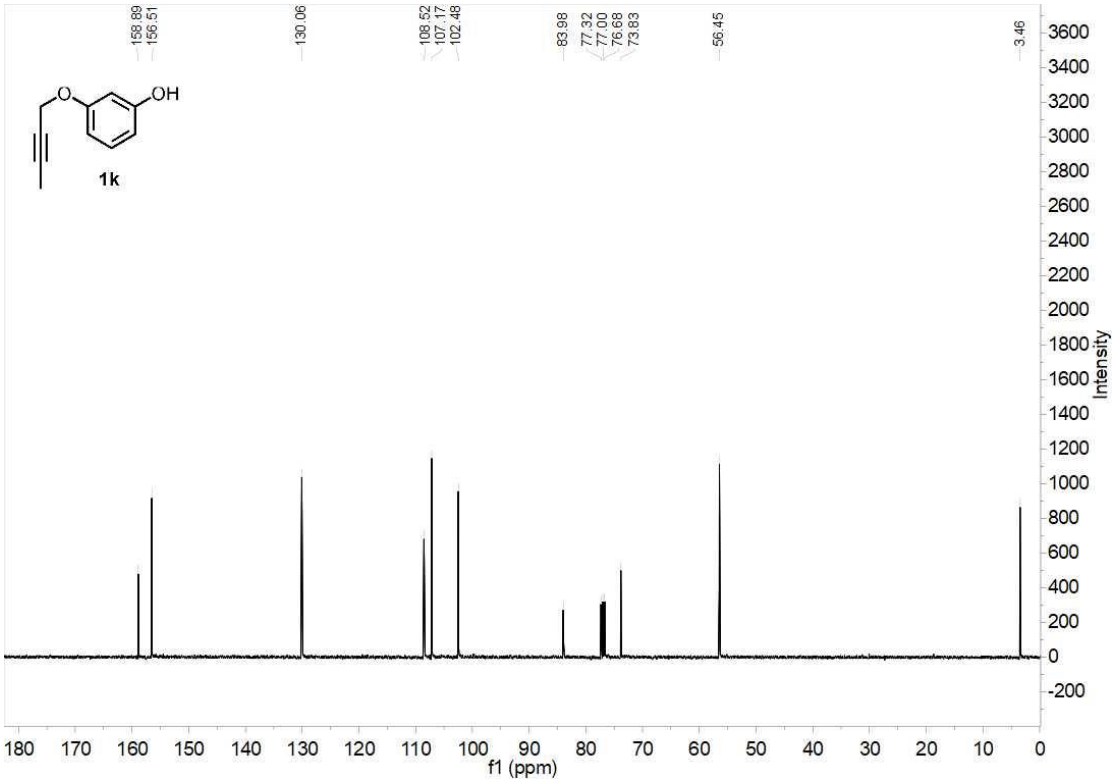

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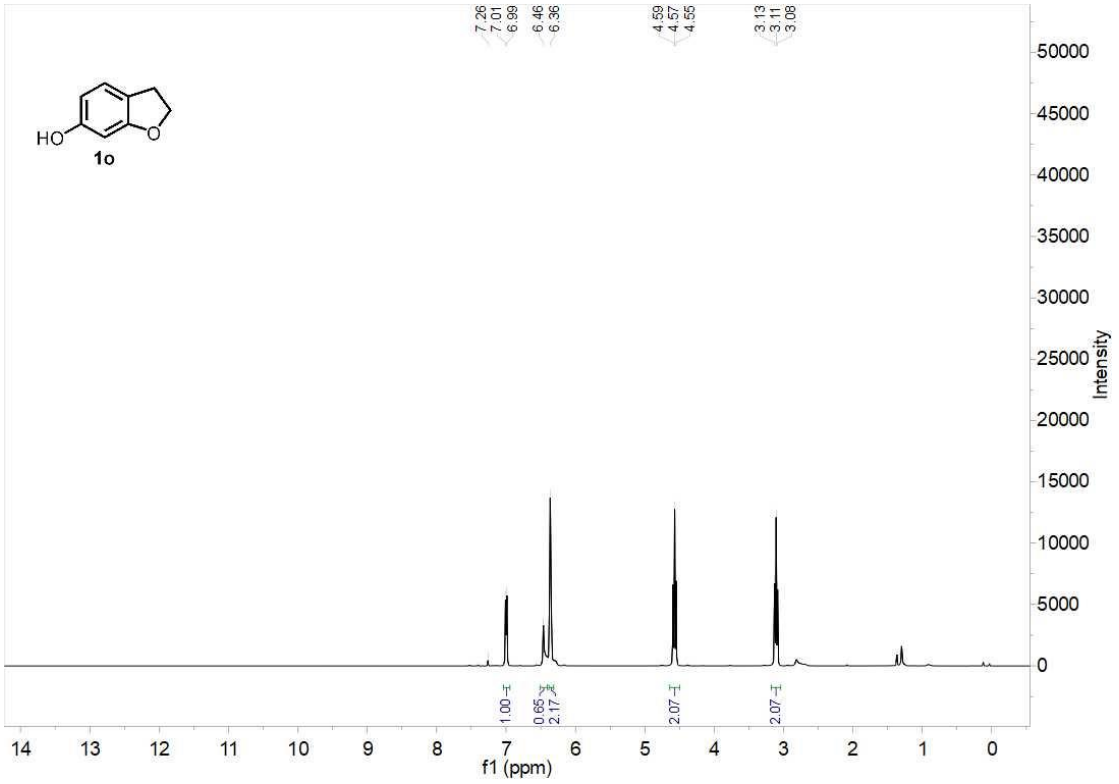

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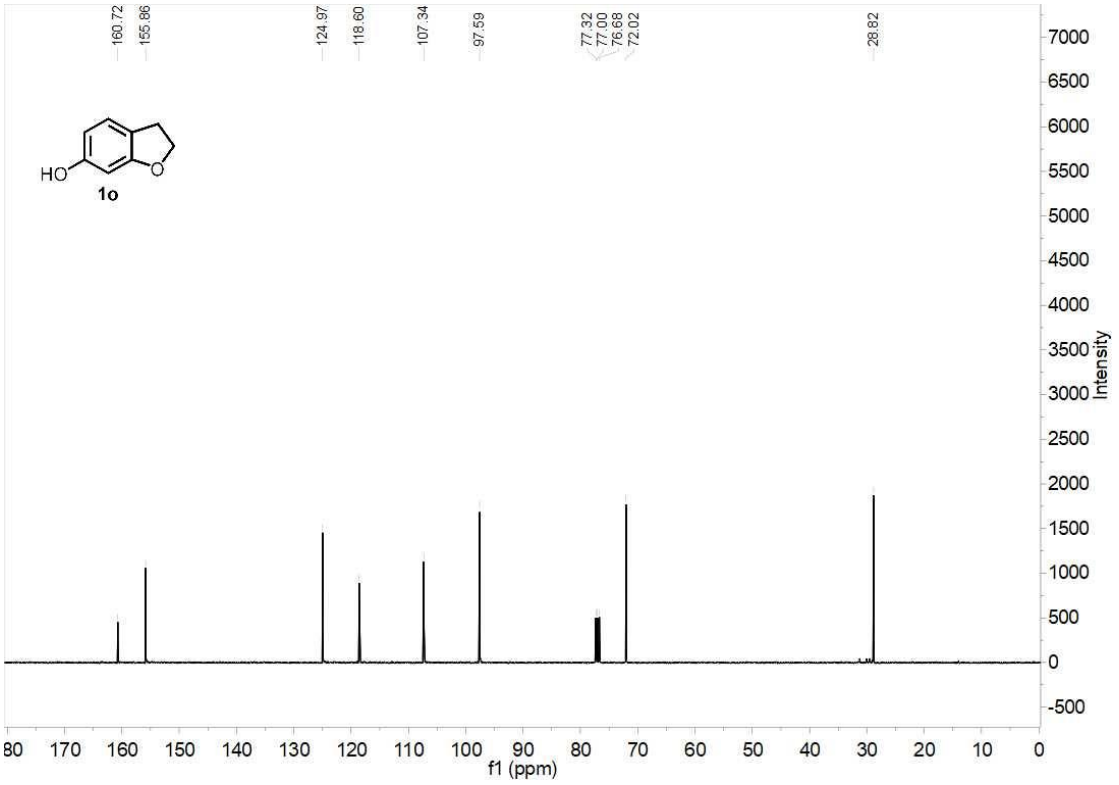

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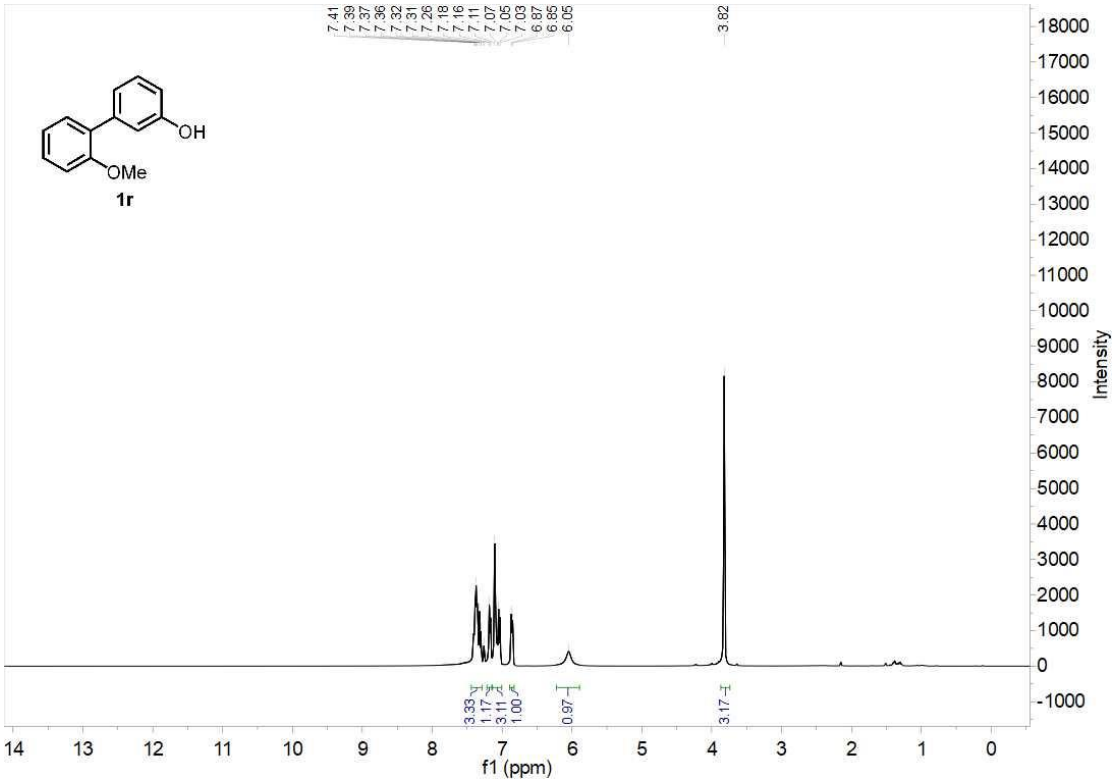

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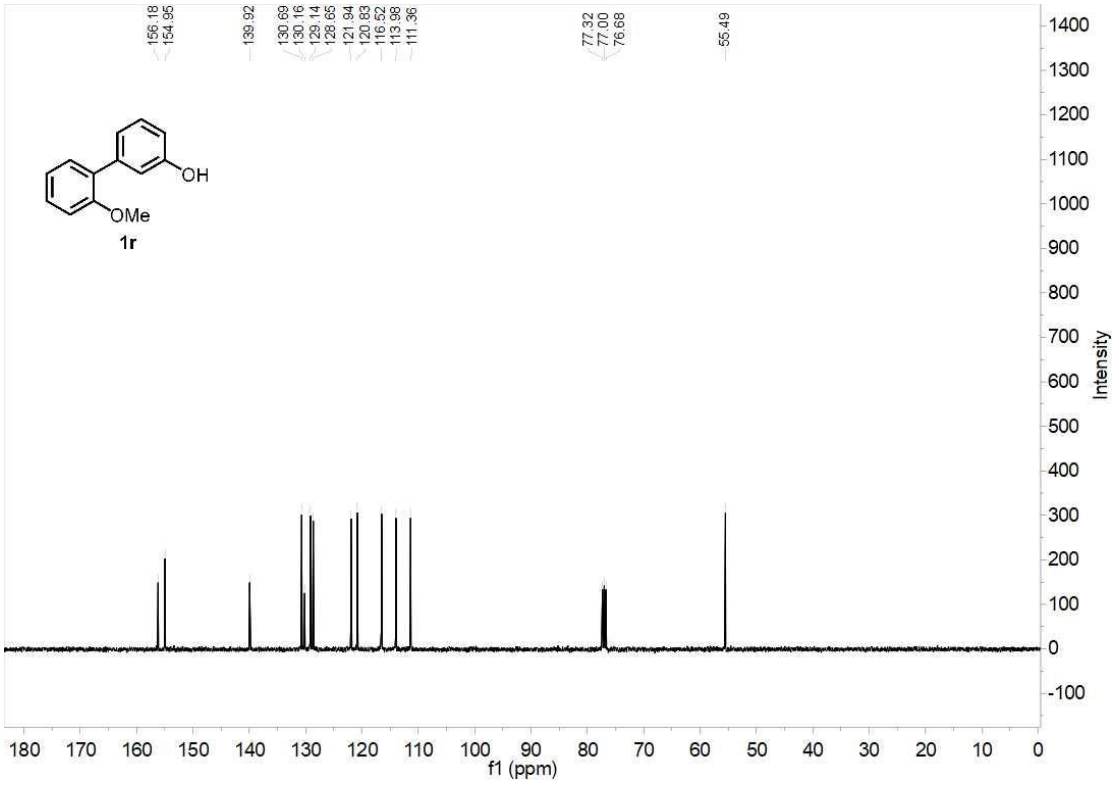

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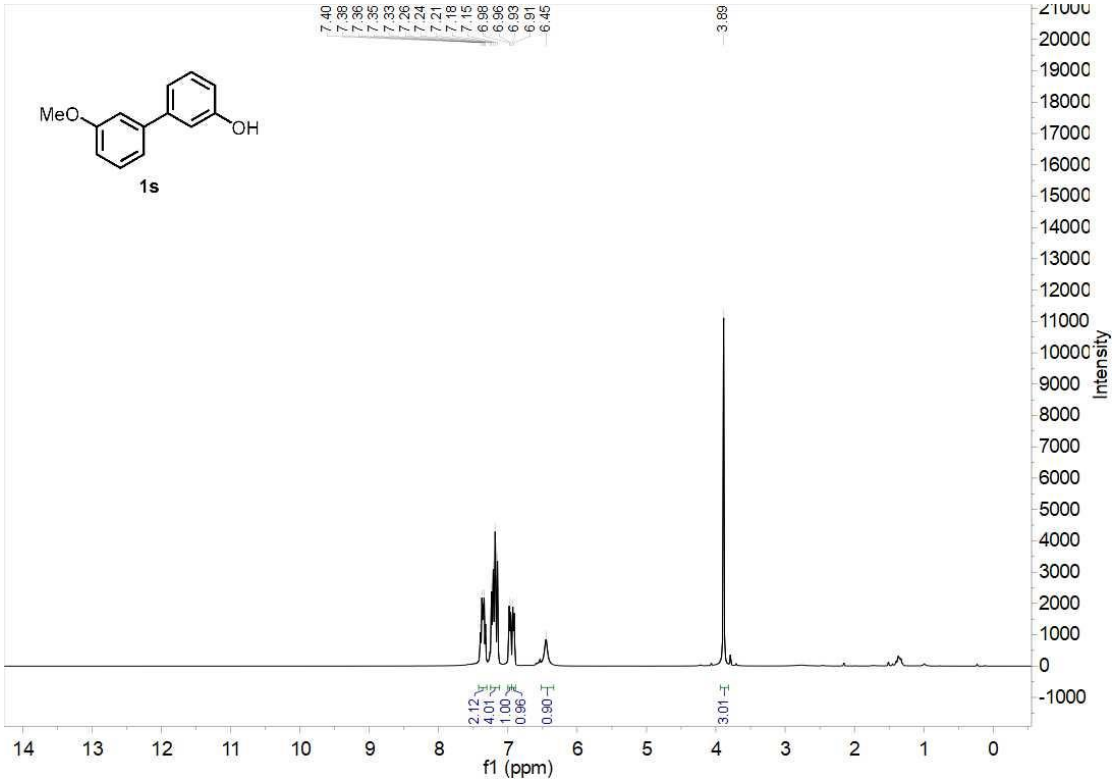

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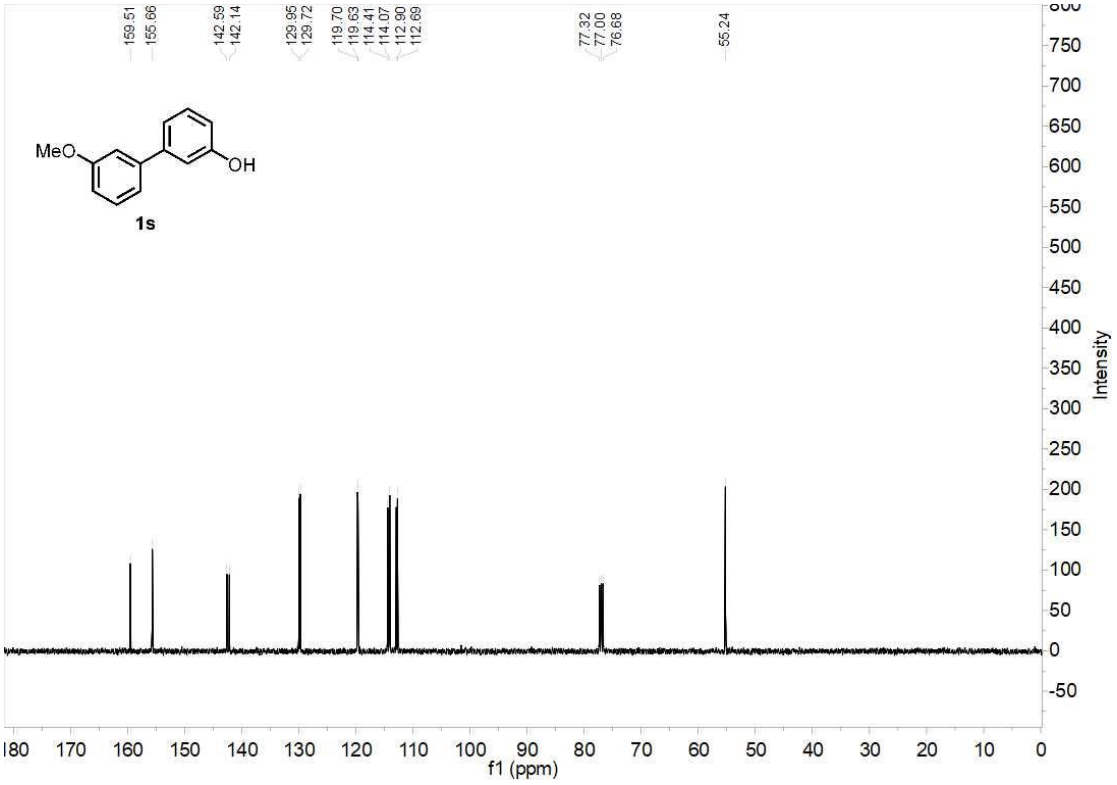

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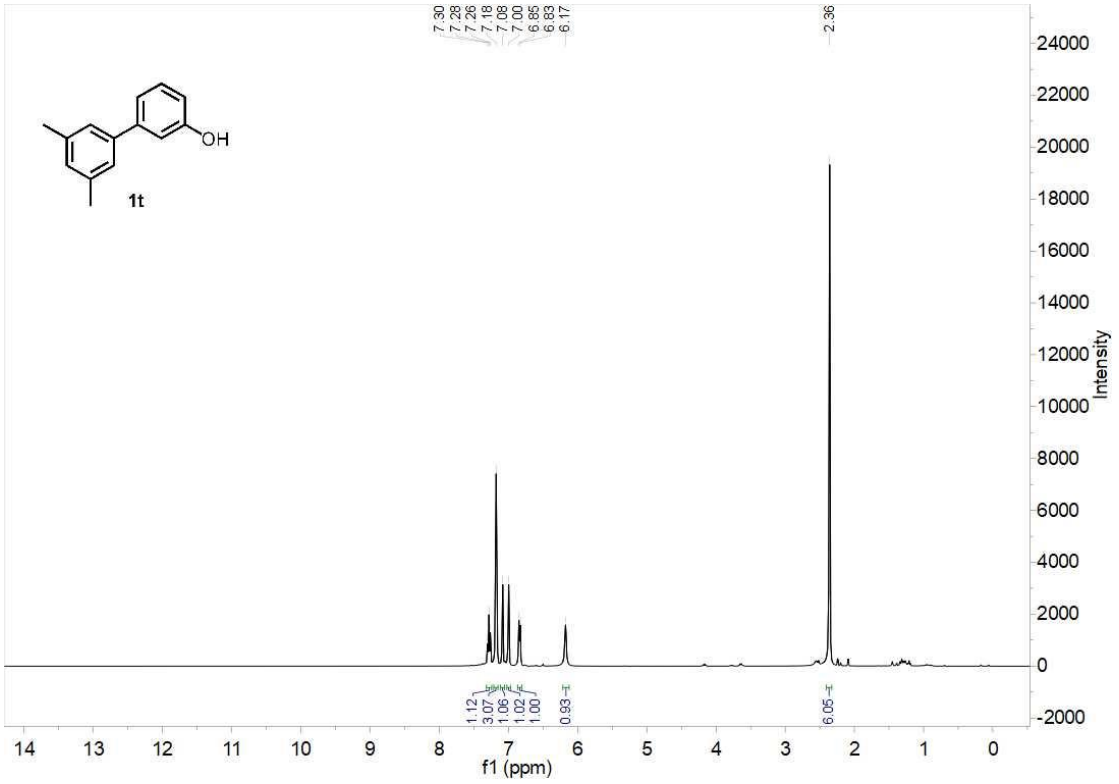

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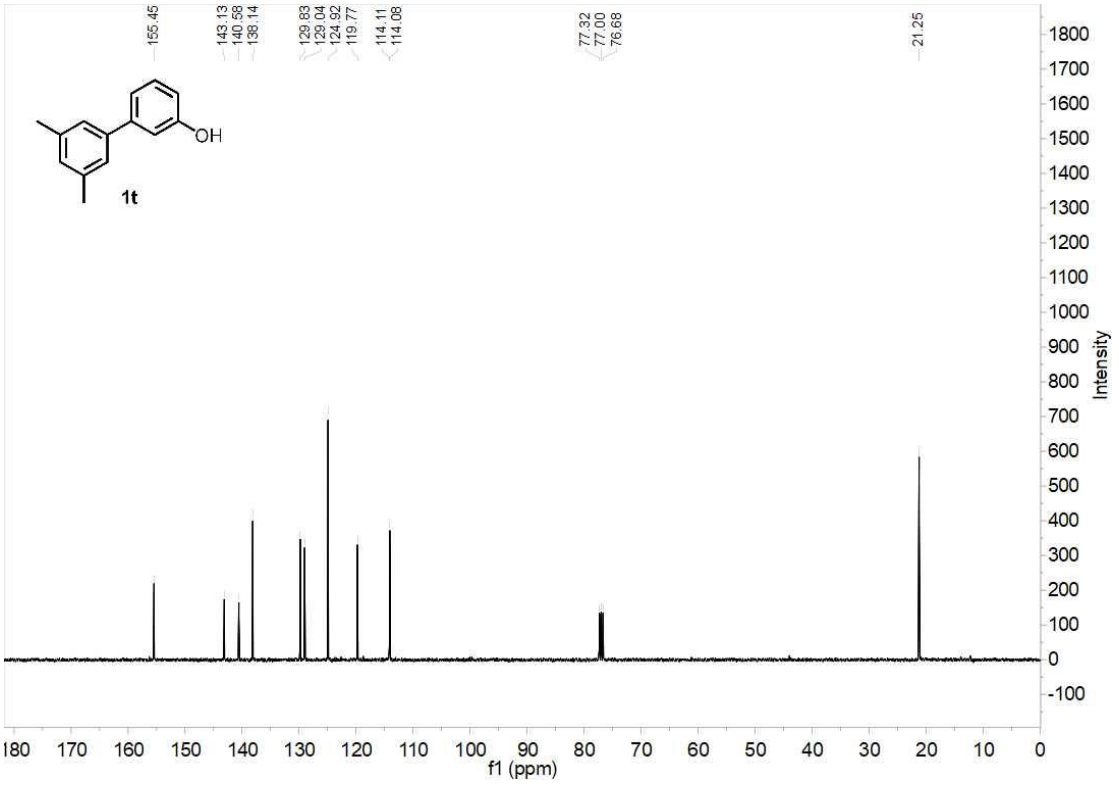

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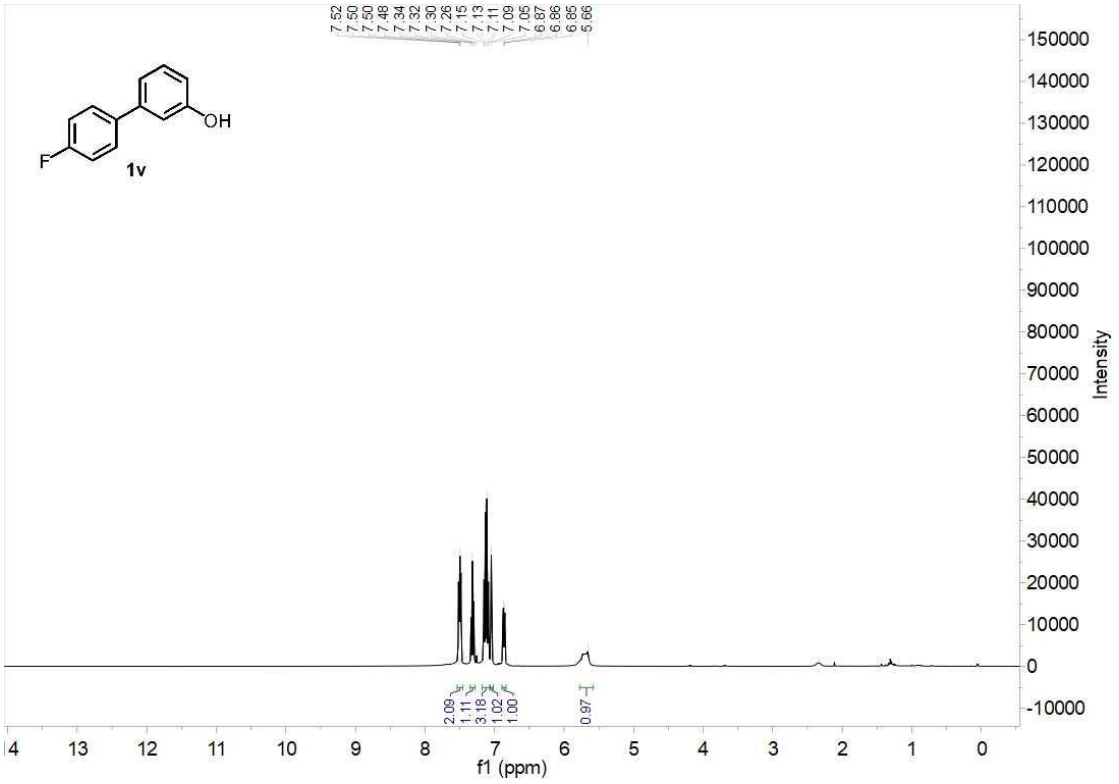

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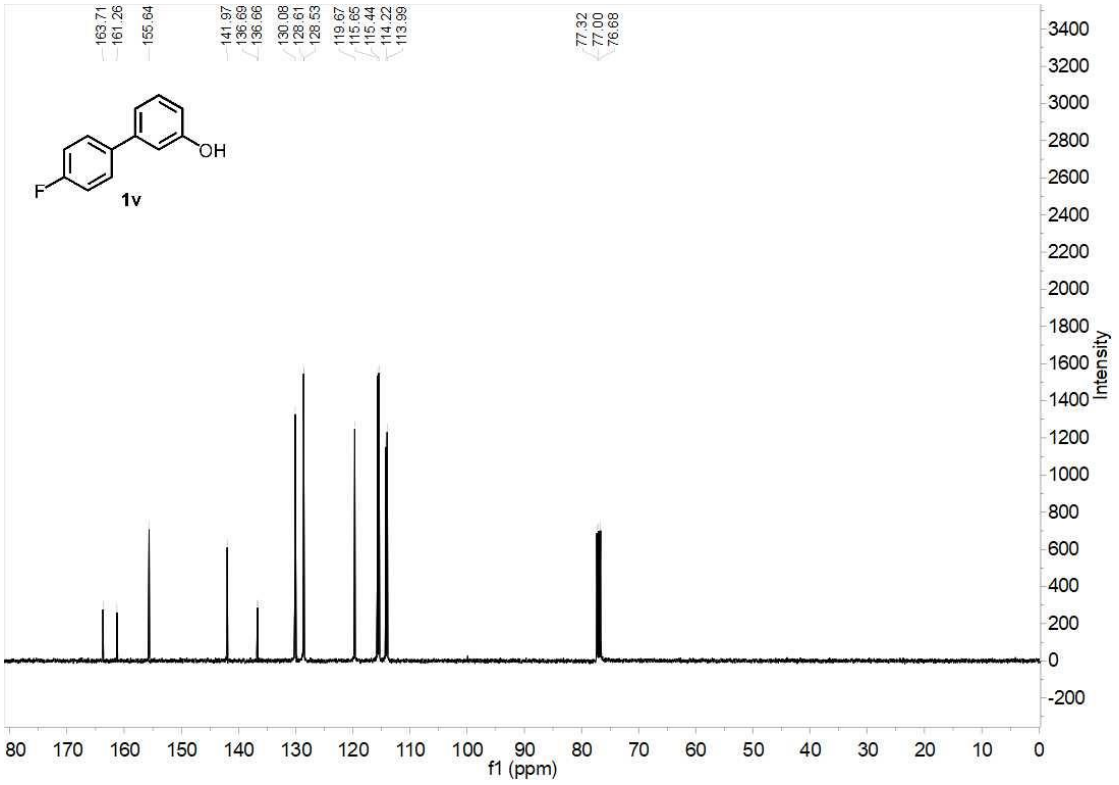

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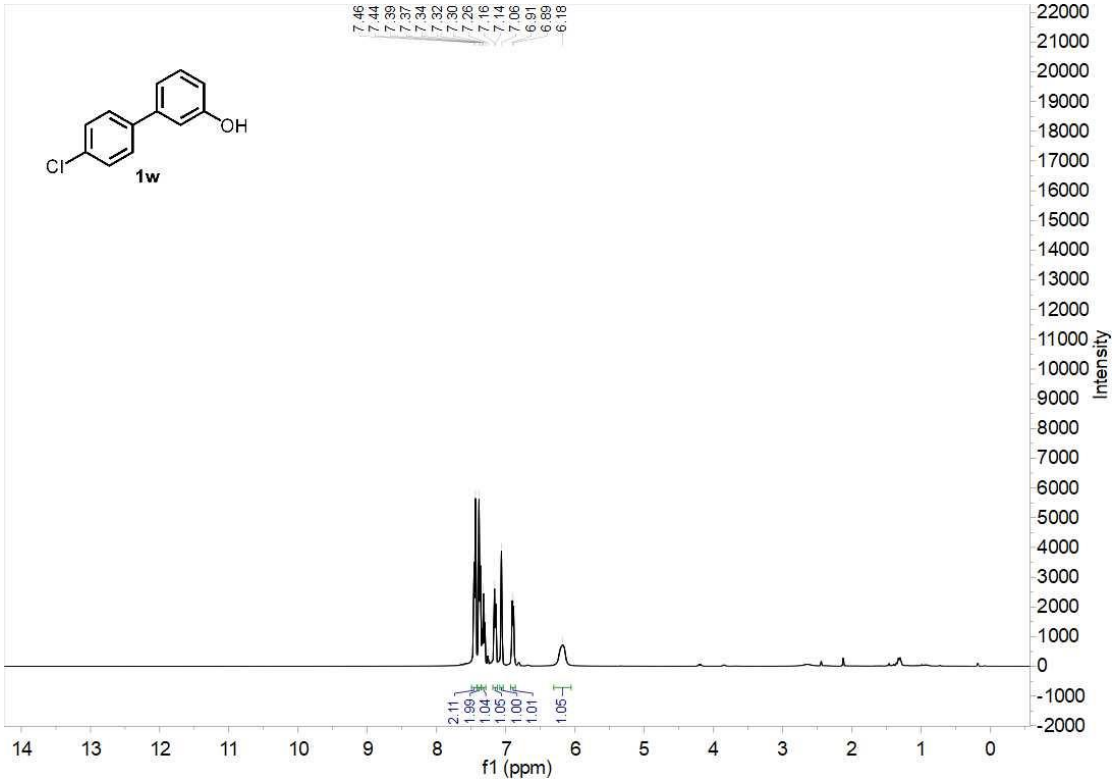

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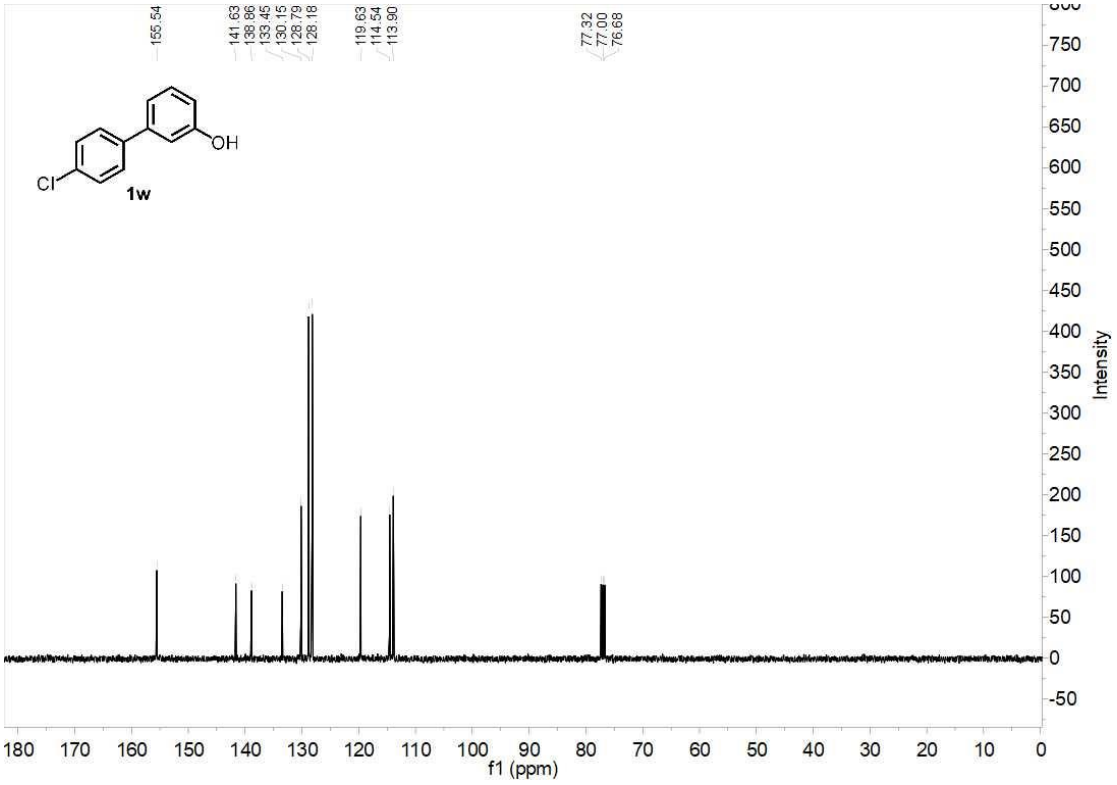

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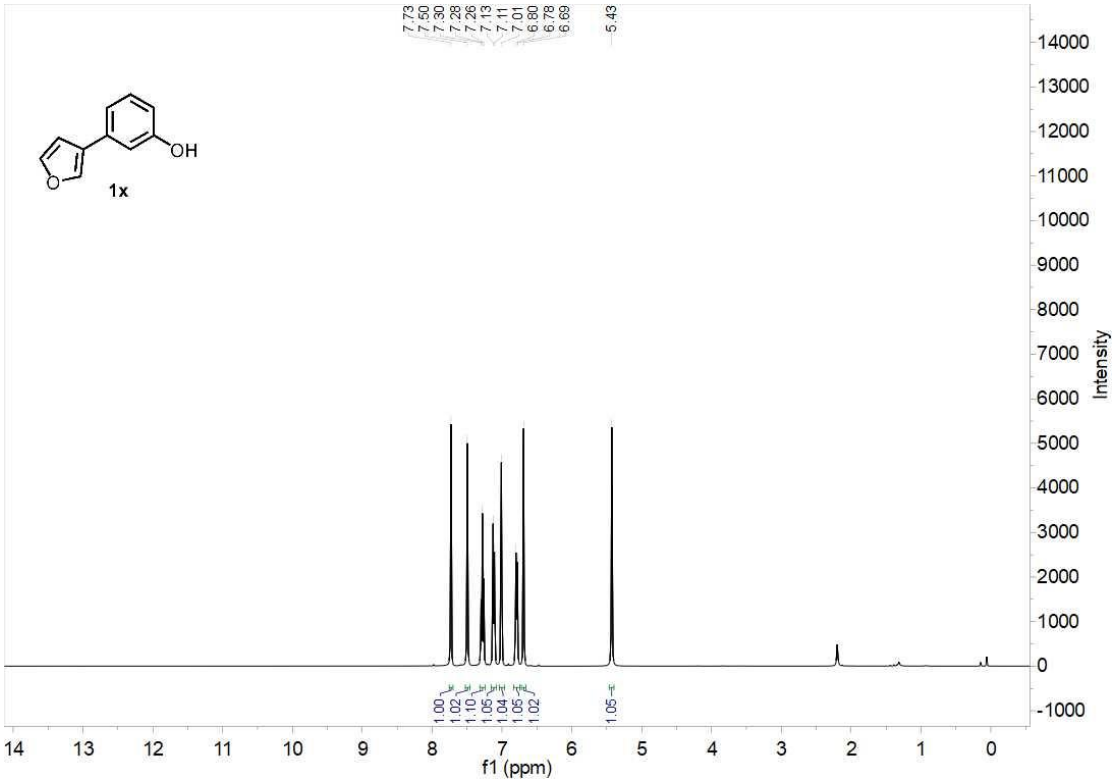

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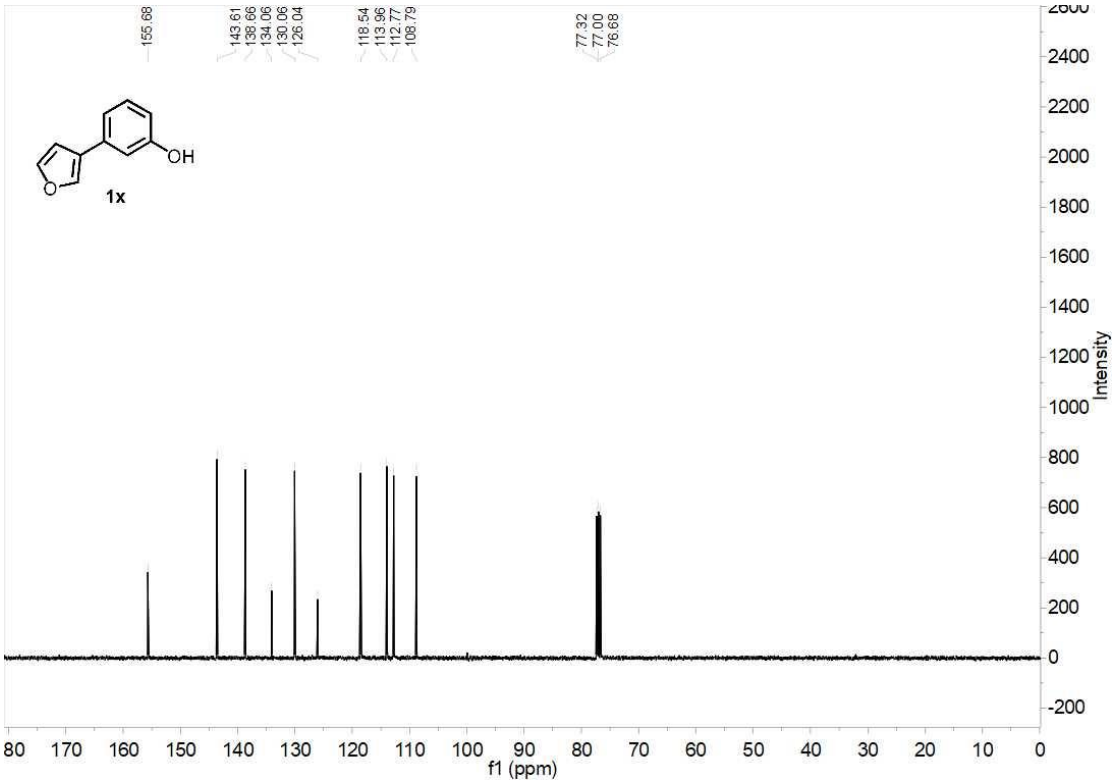

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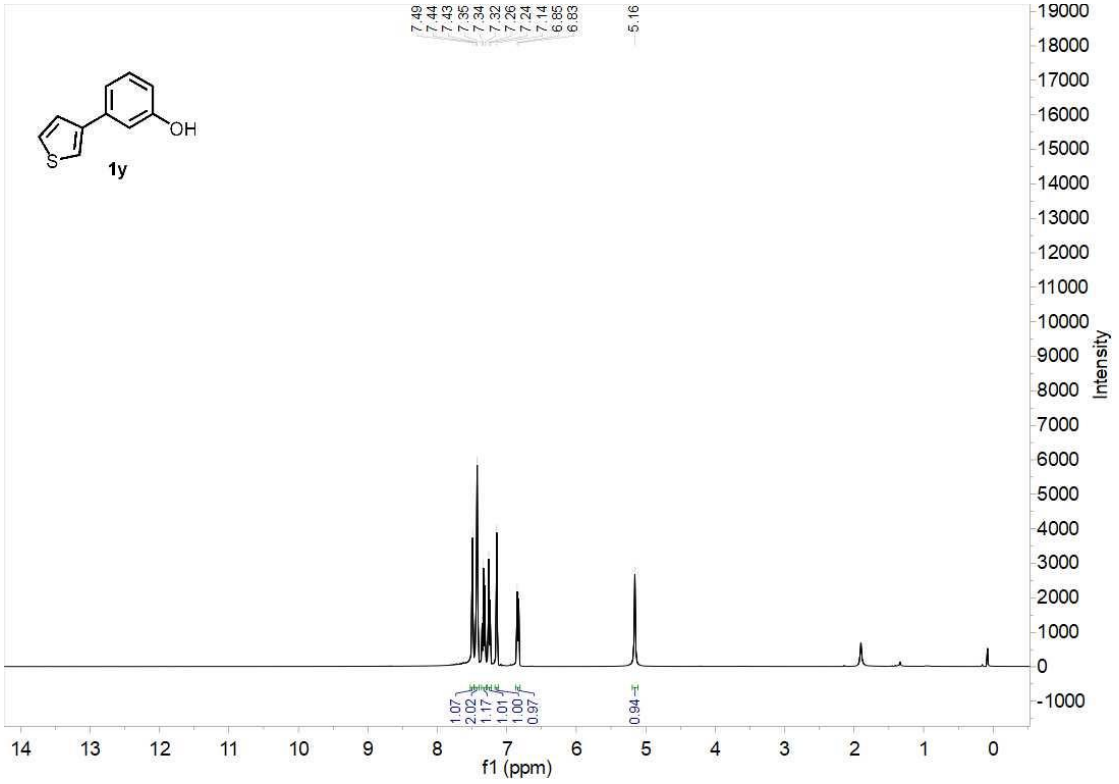

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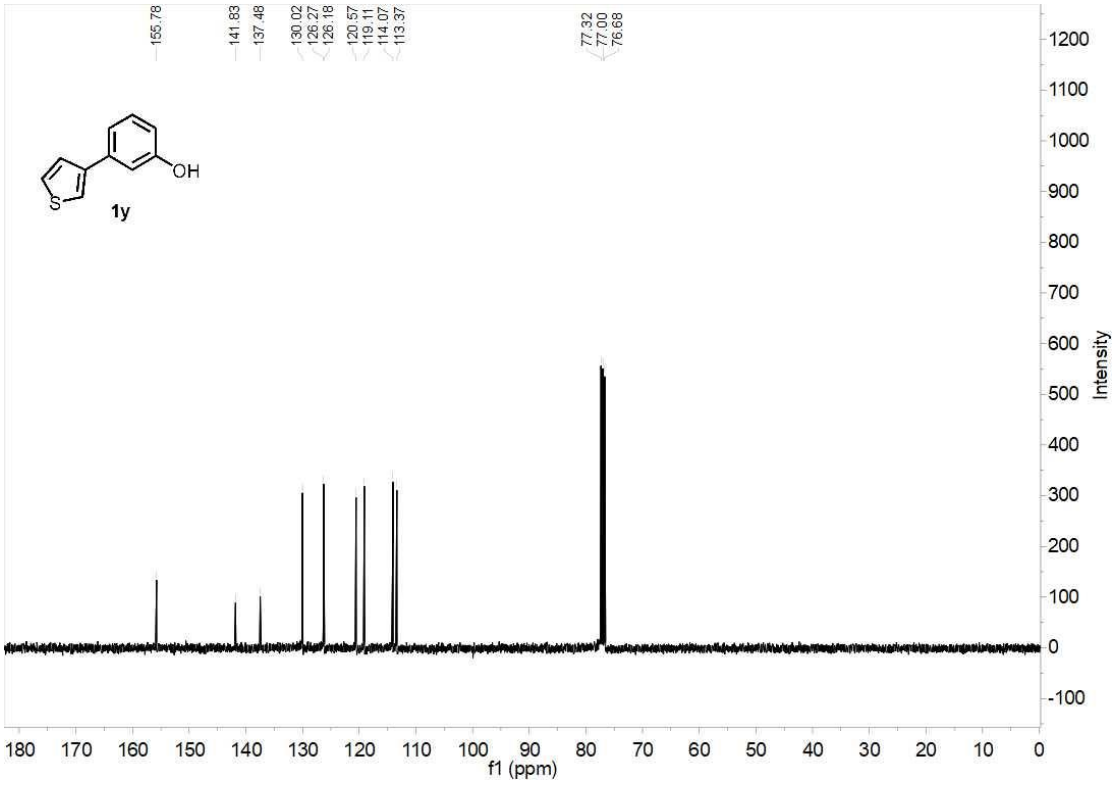
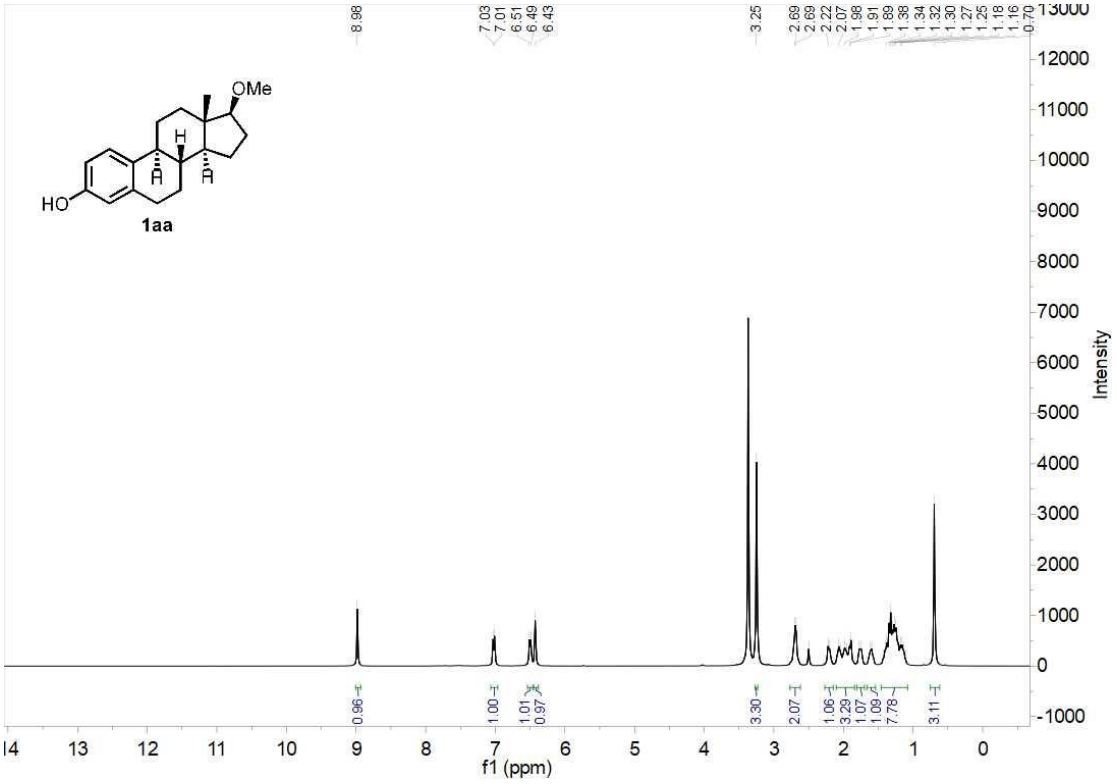


^{1}H NMR spectrum of **1aa** (400 MHz, DMSO-d_6)



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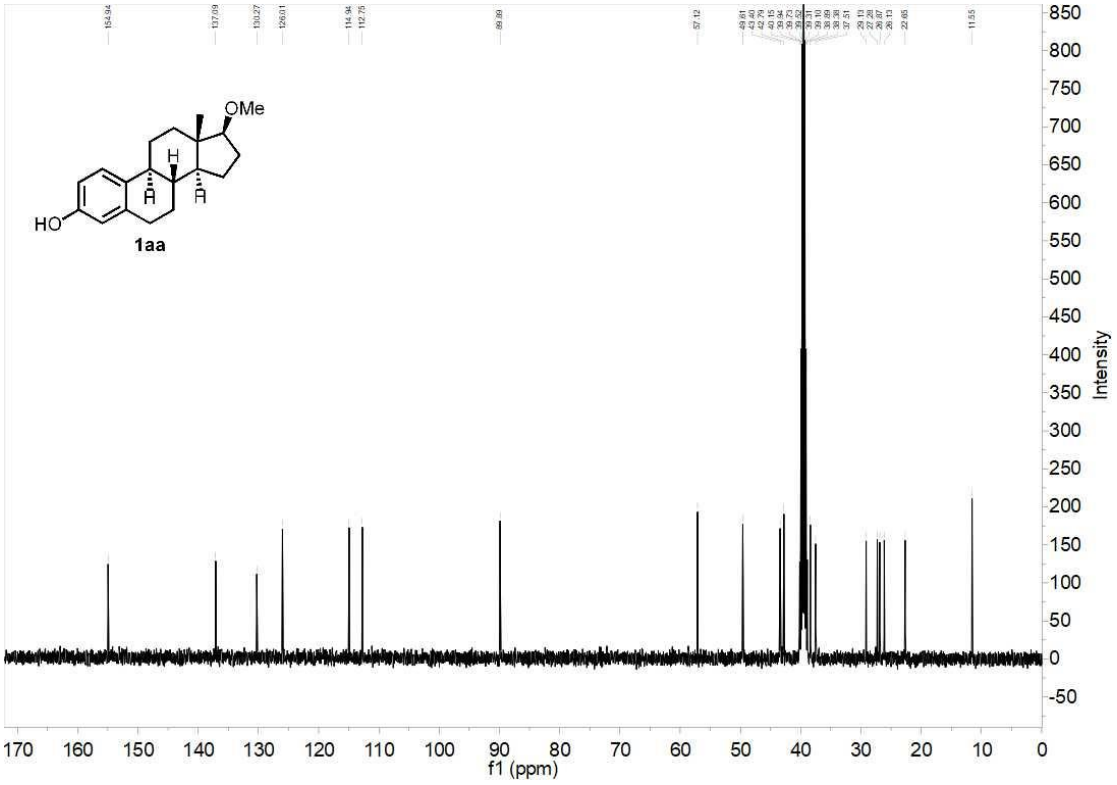

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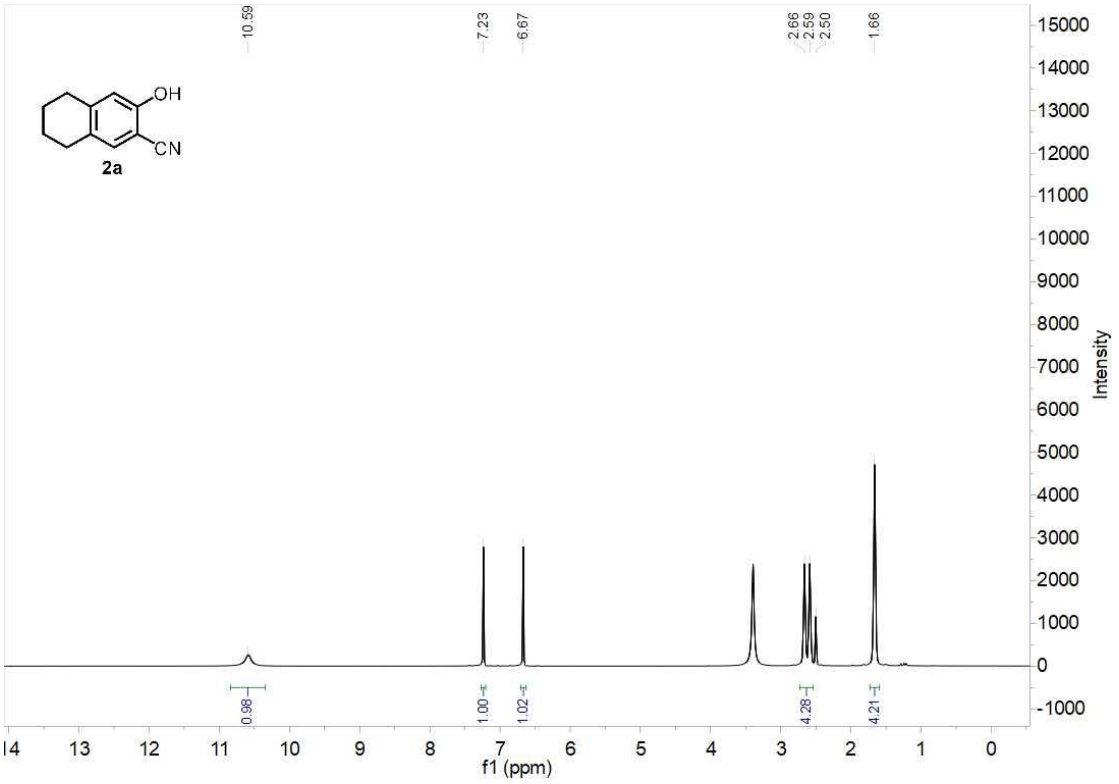

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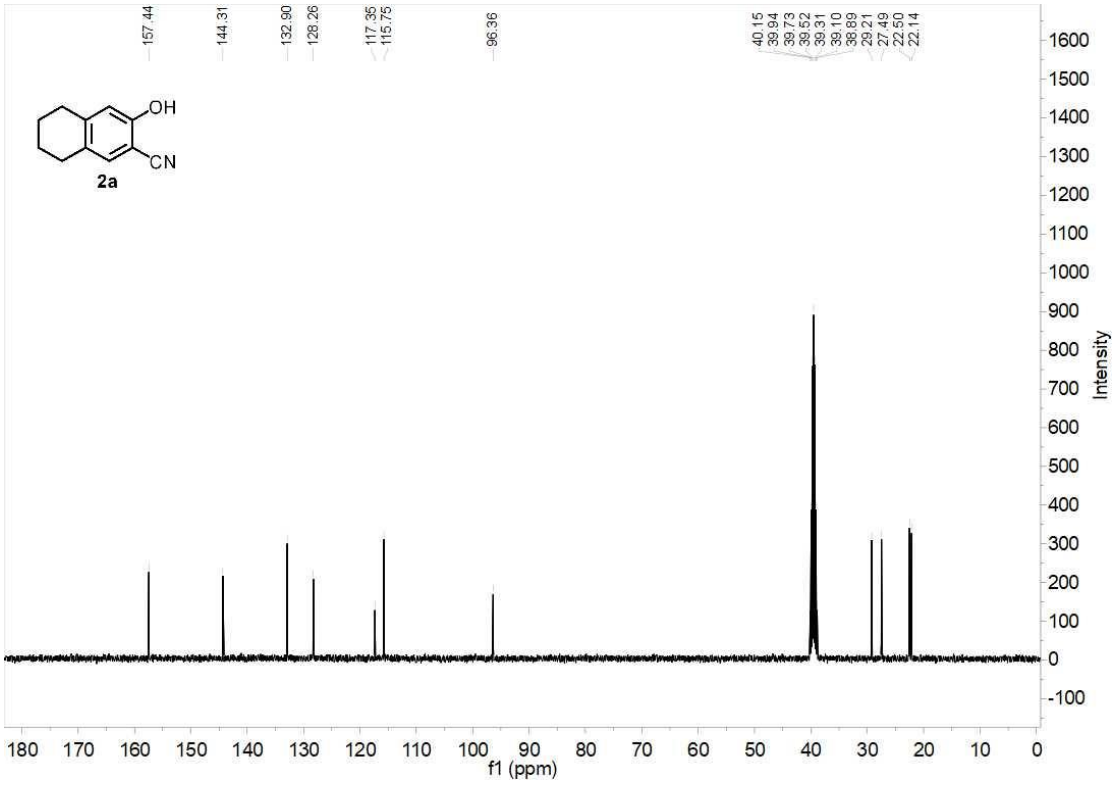
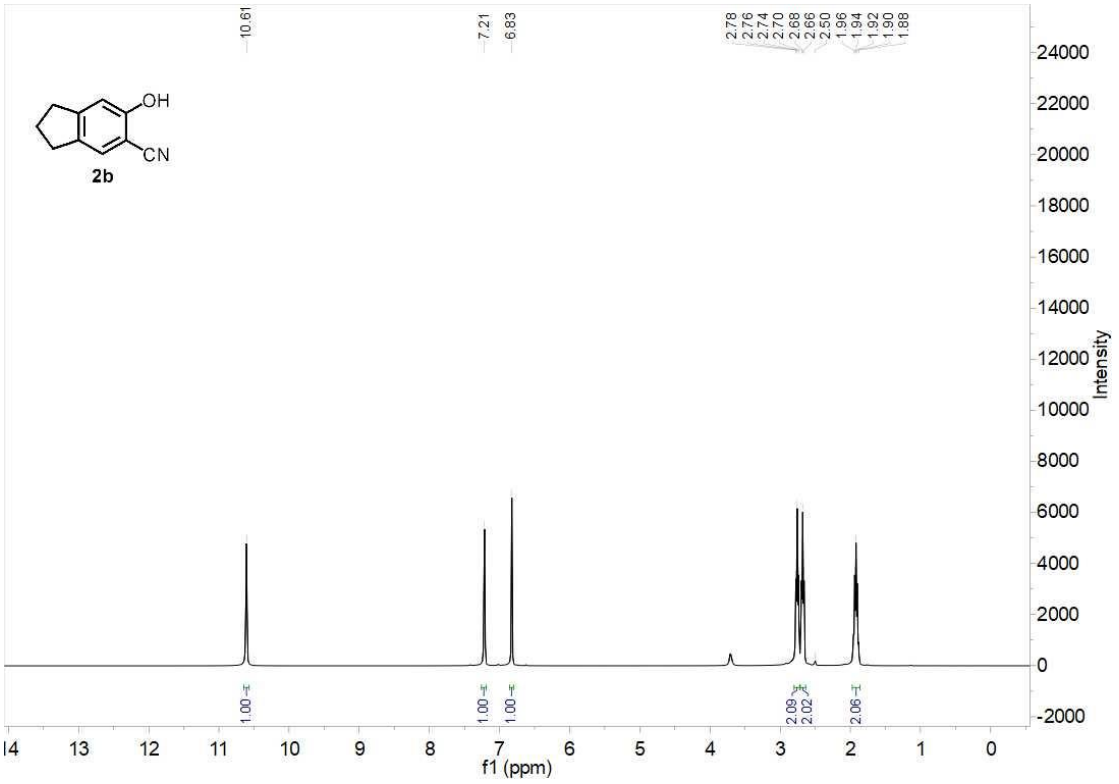


^{1}H NMR spectrum of **2b** (400 MHz, DMSO-d_6)



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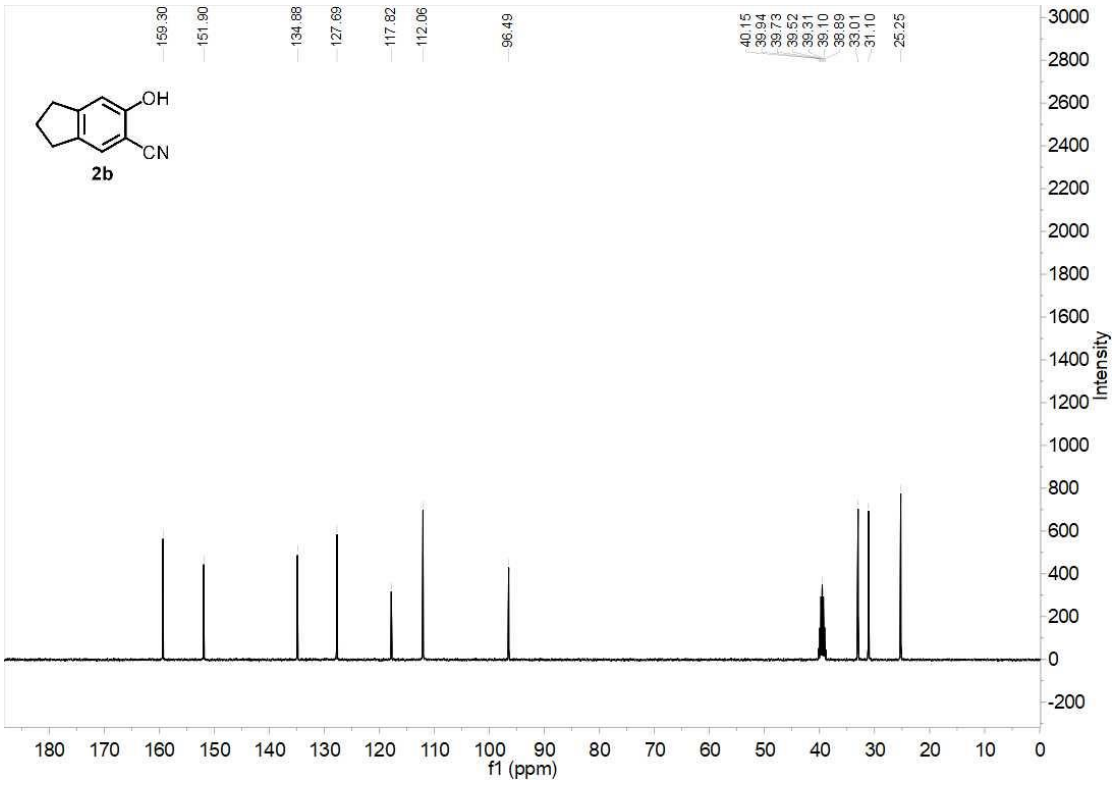

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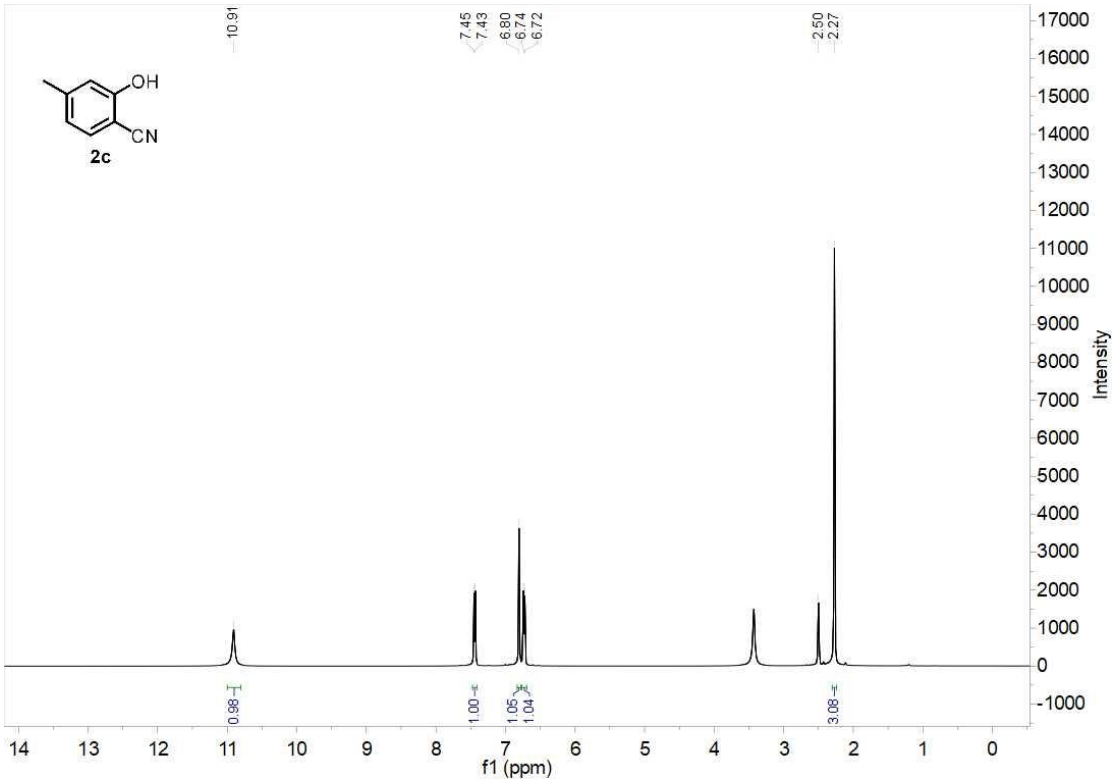

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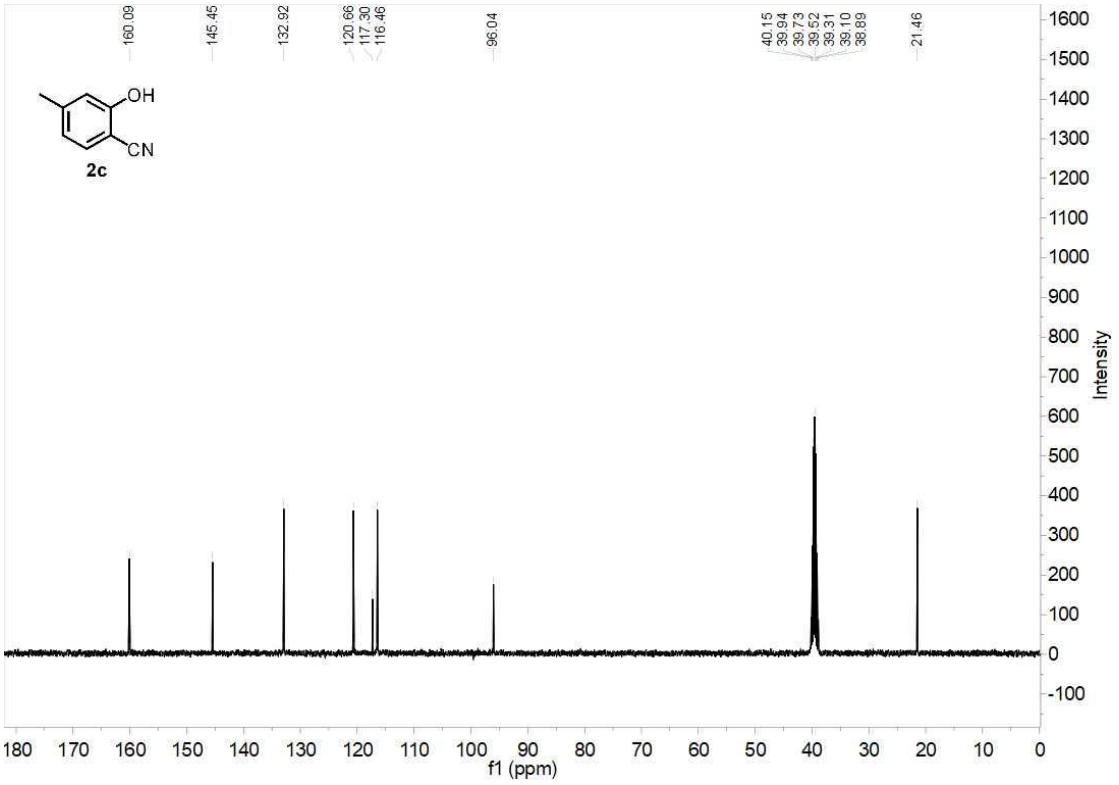

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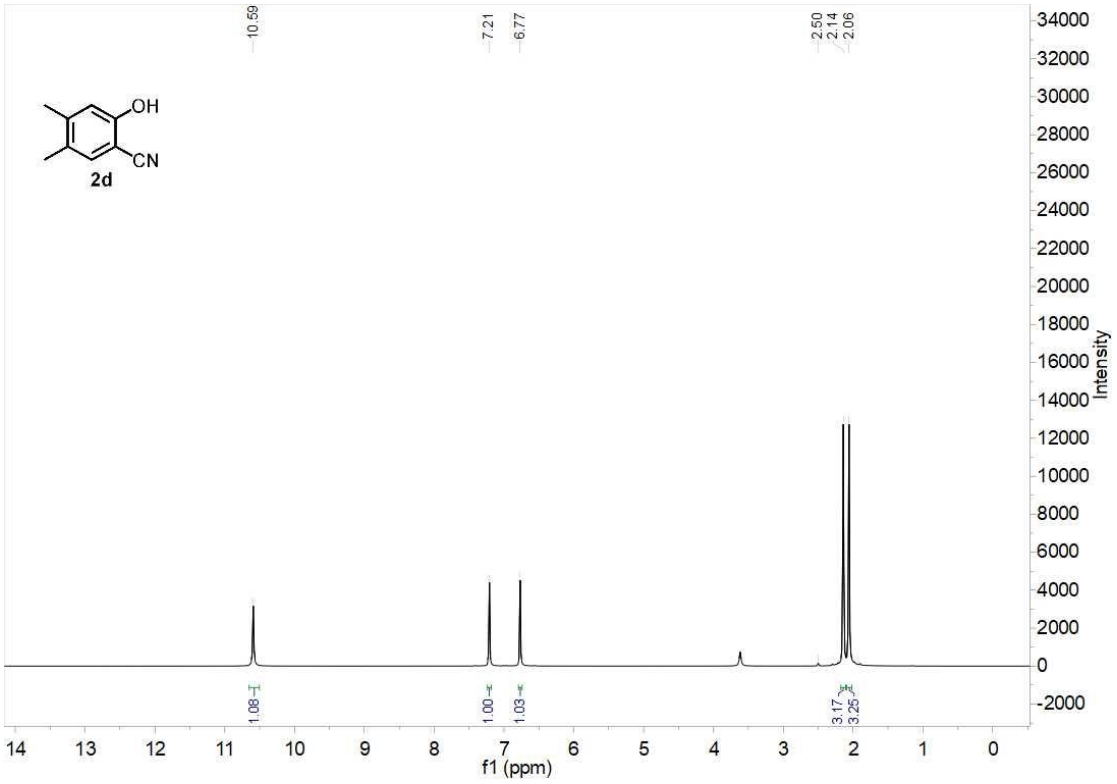

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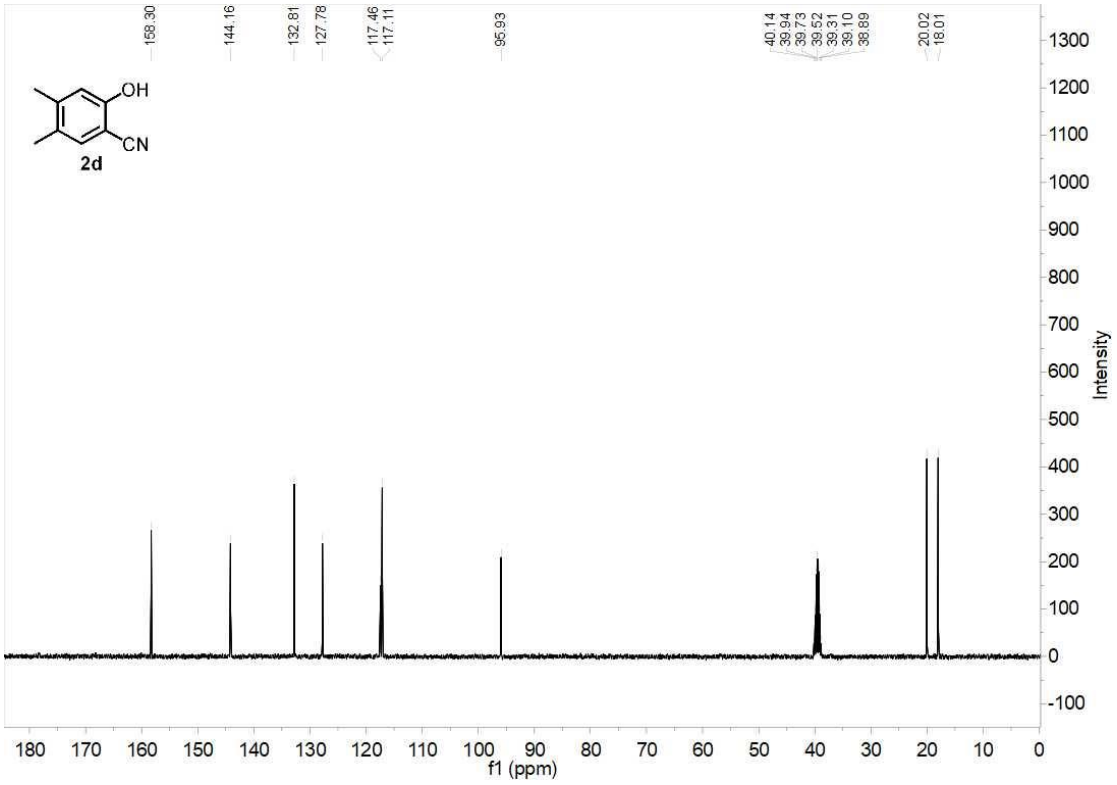

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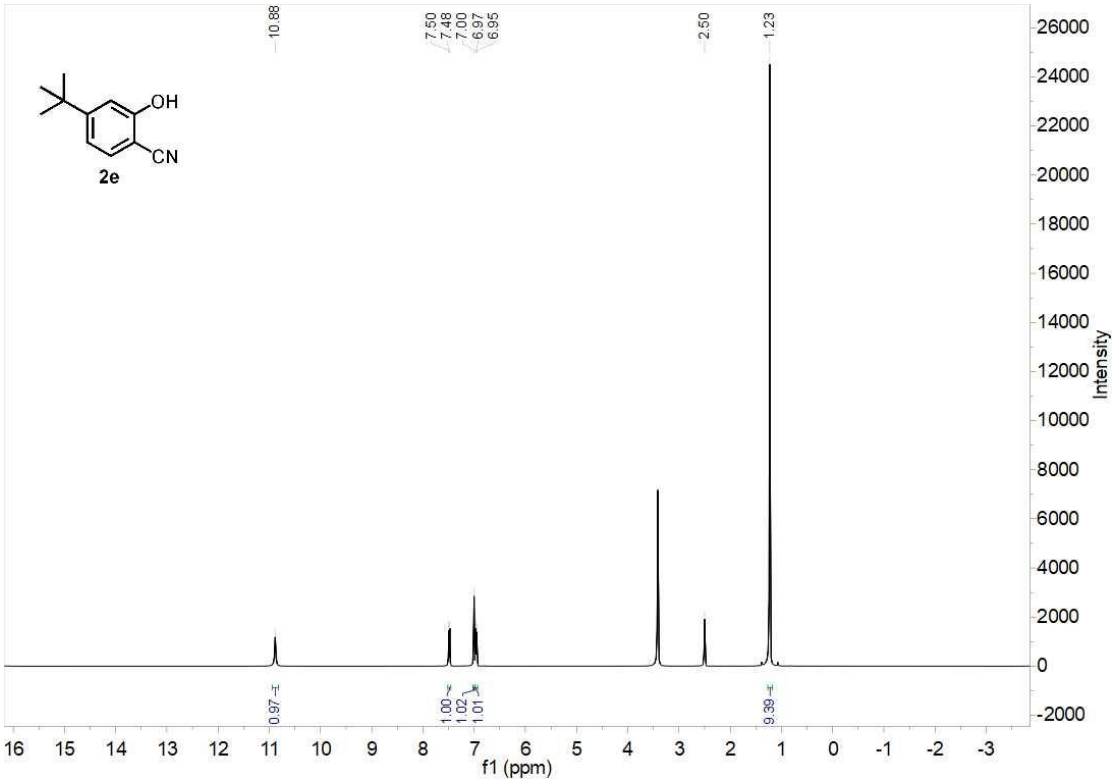

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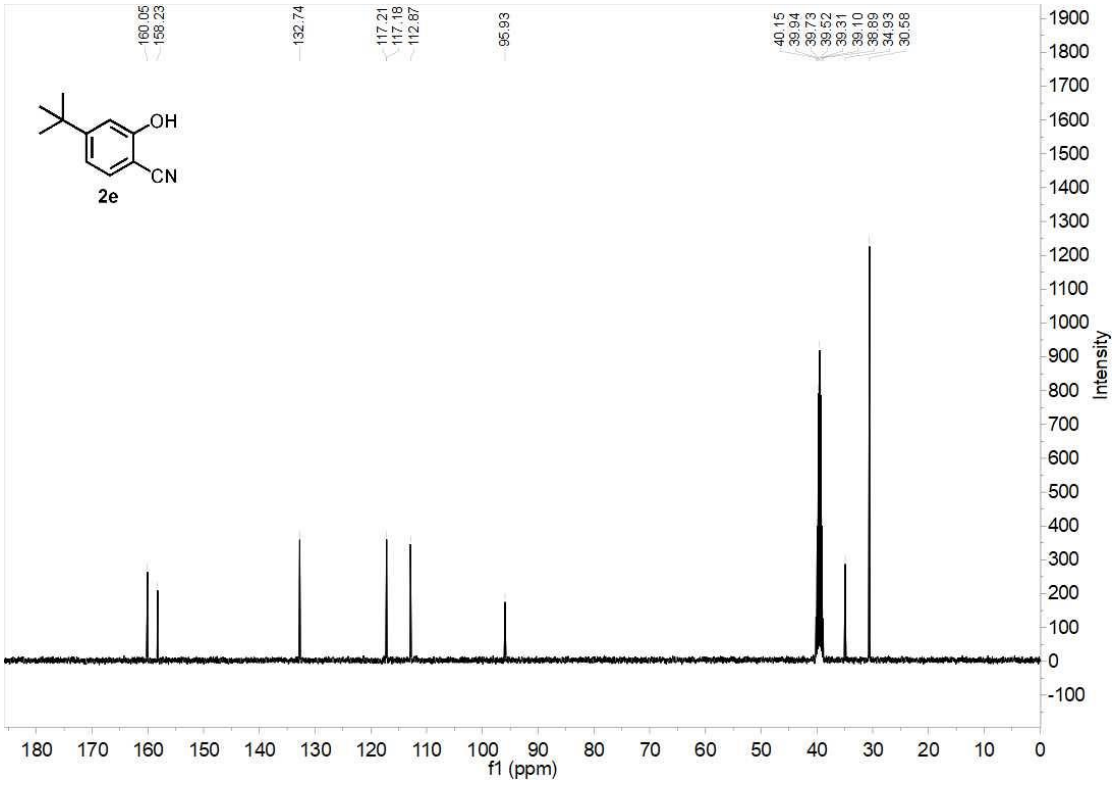
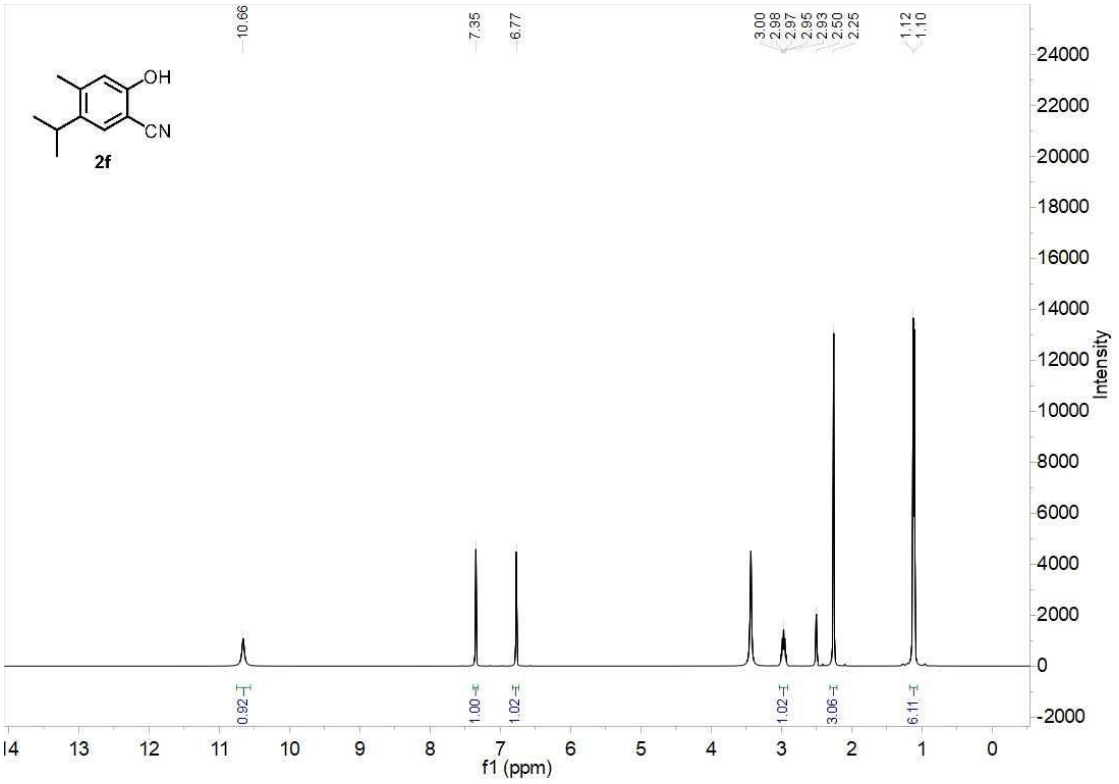
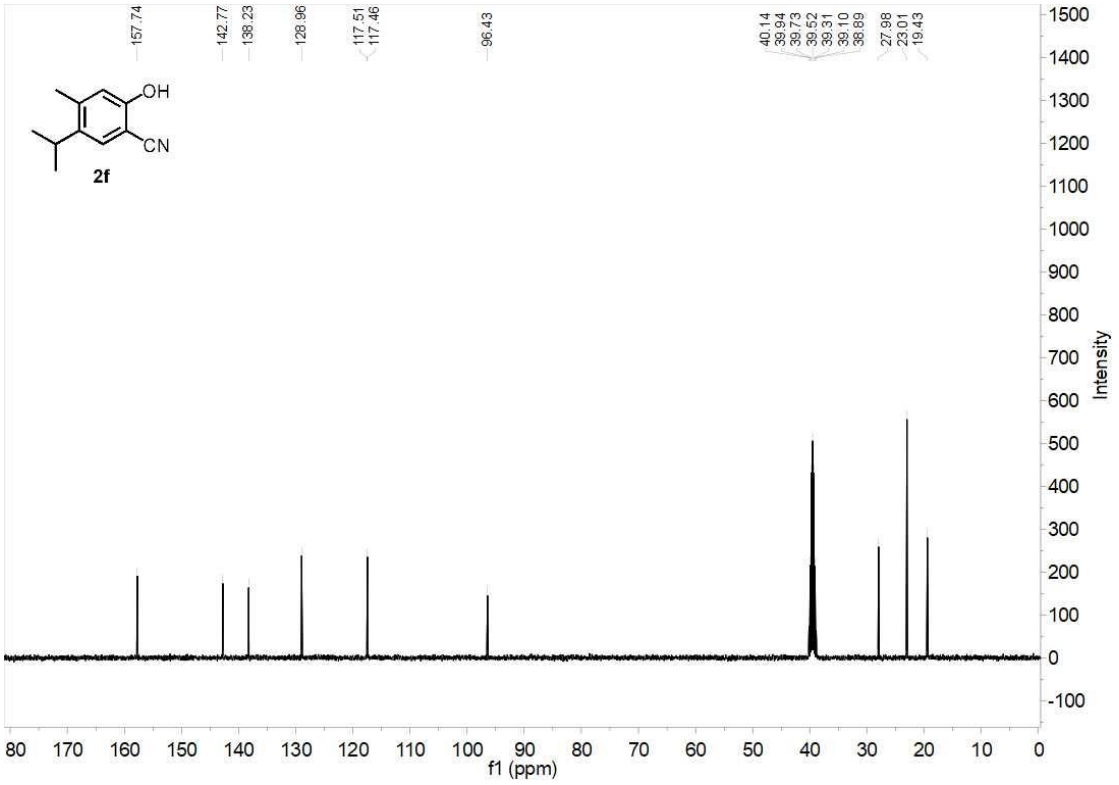


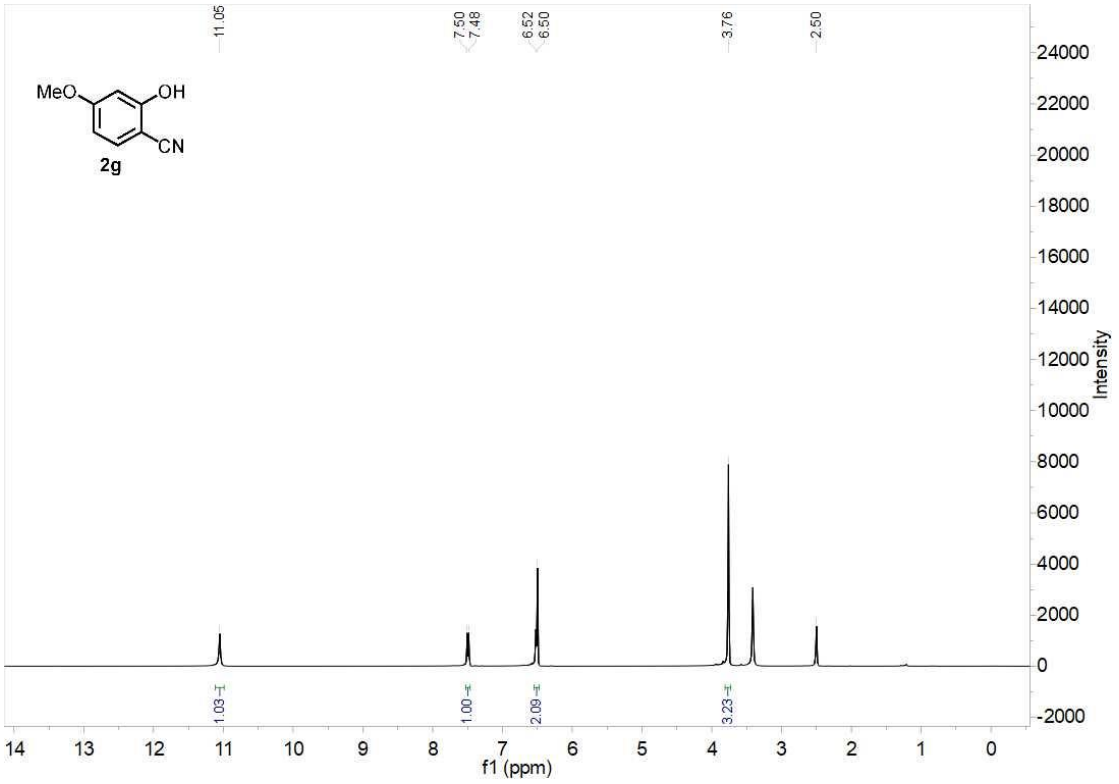
^{1}H NMR spectrum of **2f** (400 MHz, DMSO-d_6)



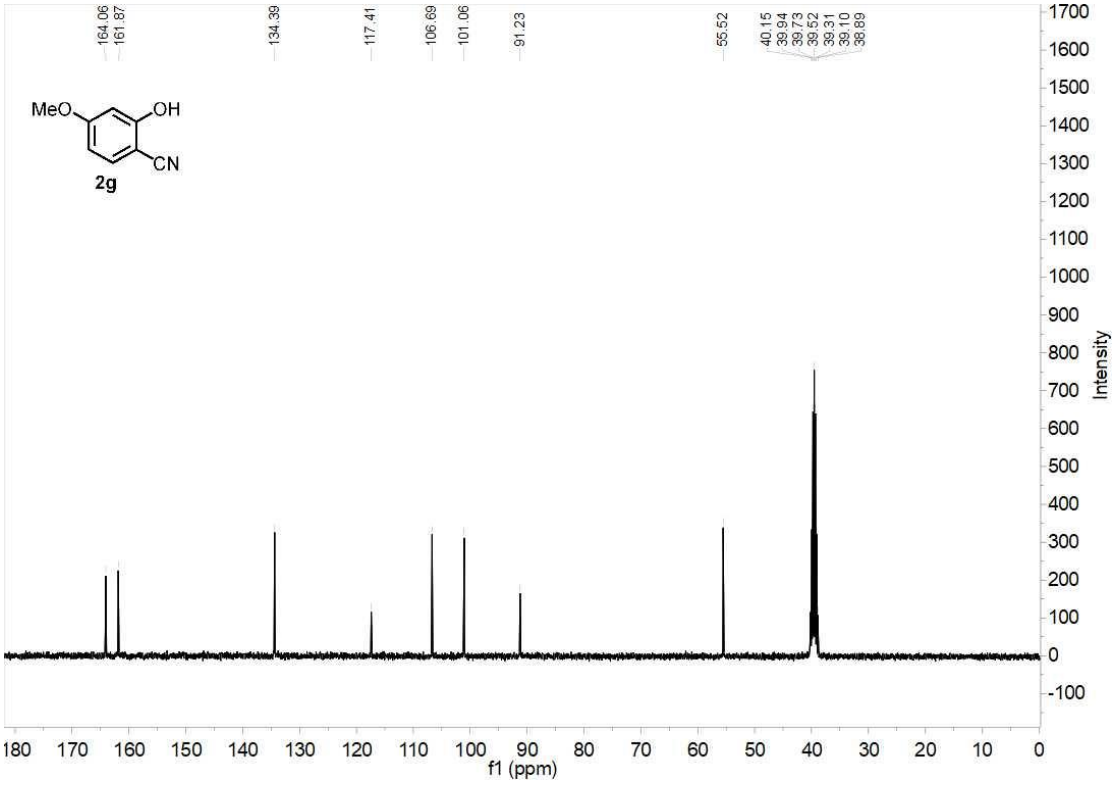
^{13}C NMR spectrum of **2f** (100 MHz, DMSO-d_6)



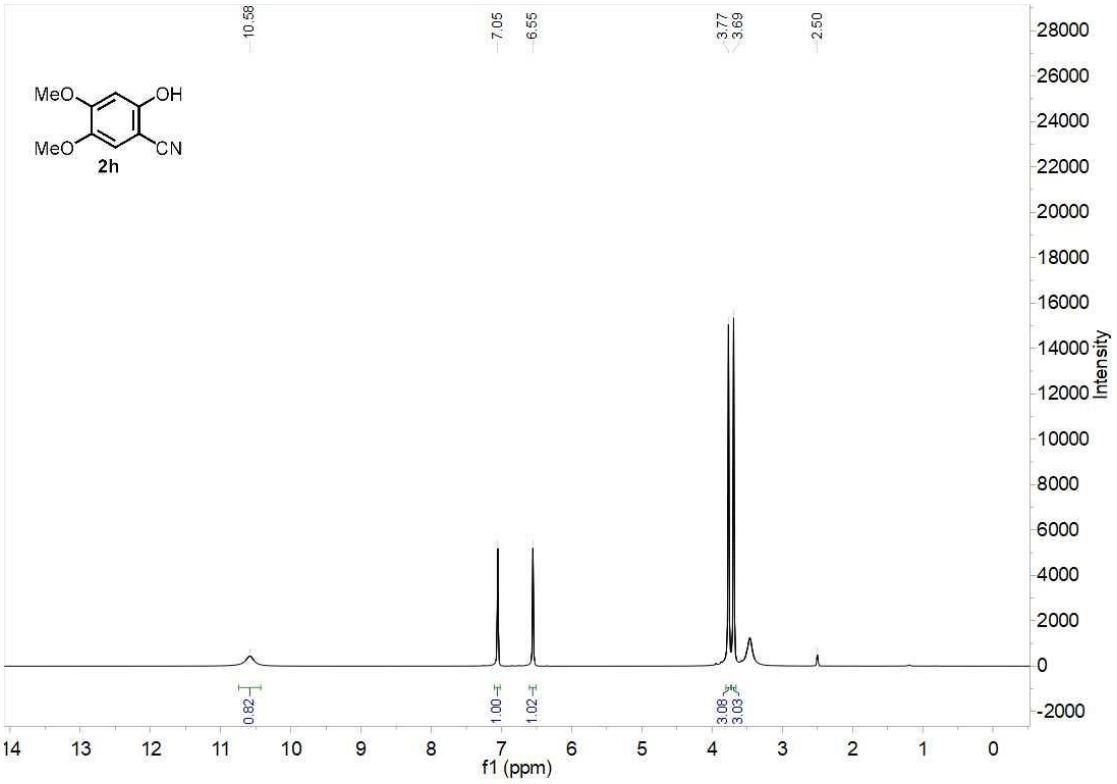
^{1}H NMR spectrum of **2g** (400 MHz, DMSO-d_6)



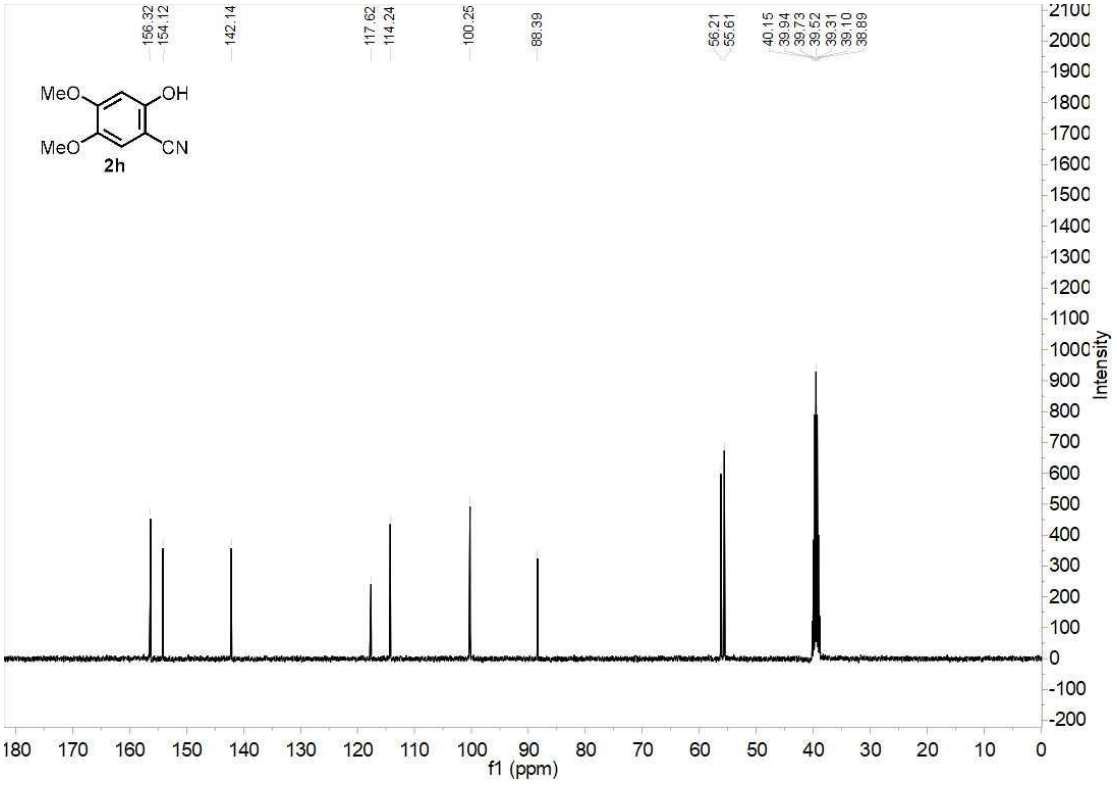
^{13}C NMR spectrum of **2g** (100 MHz, DMSO-d_6)



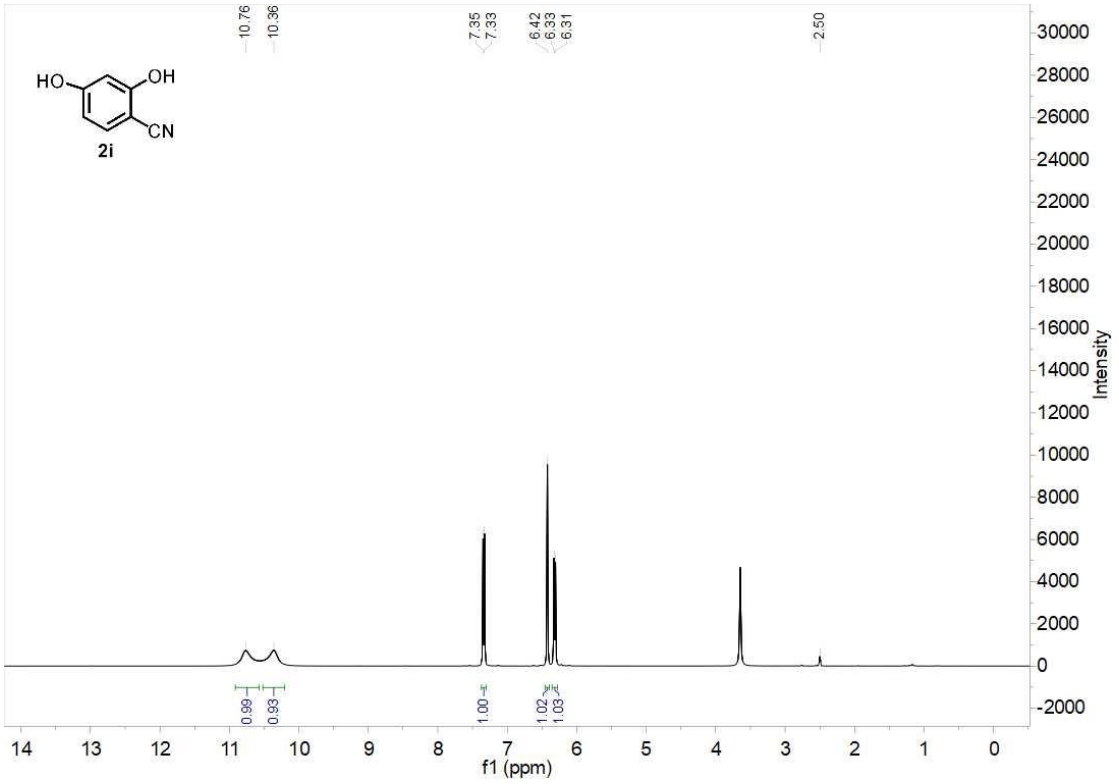
^{1}H NMR spectrum of **2h** (400 MHz, DMSO-d_6)



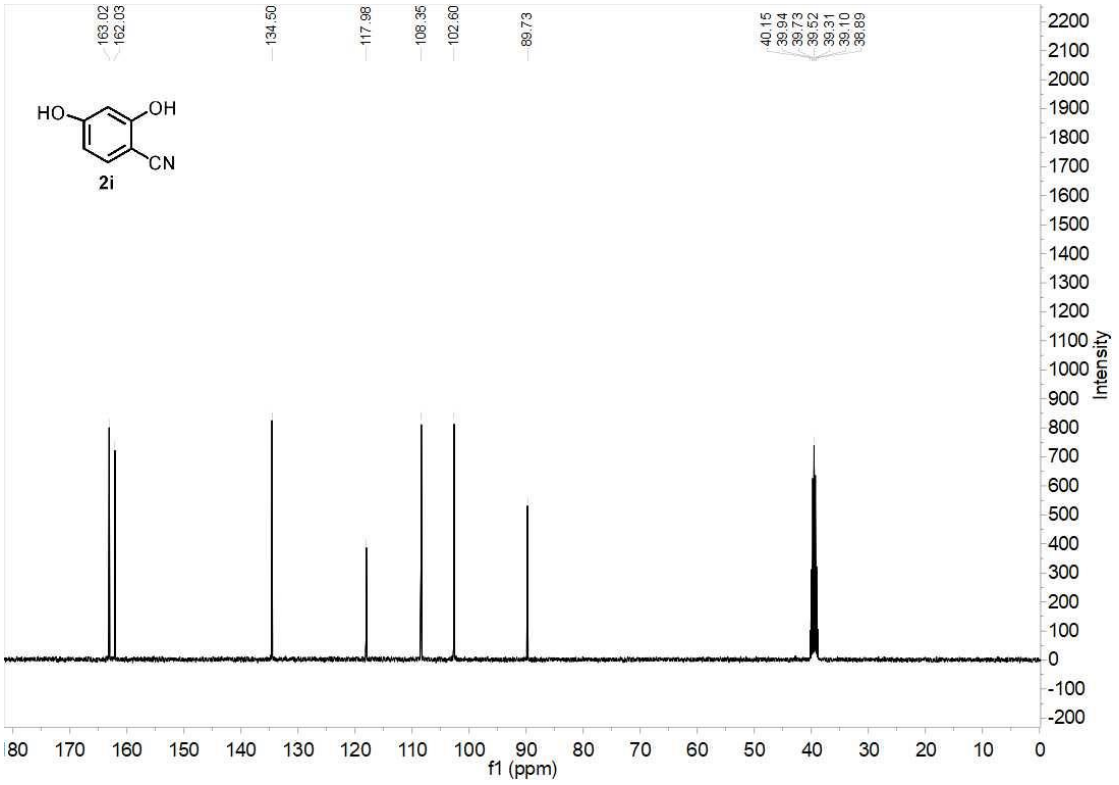
^{13}C NMR spectrum of **2h** (100 MHz, DMSO-d_6)



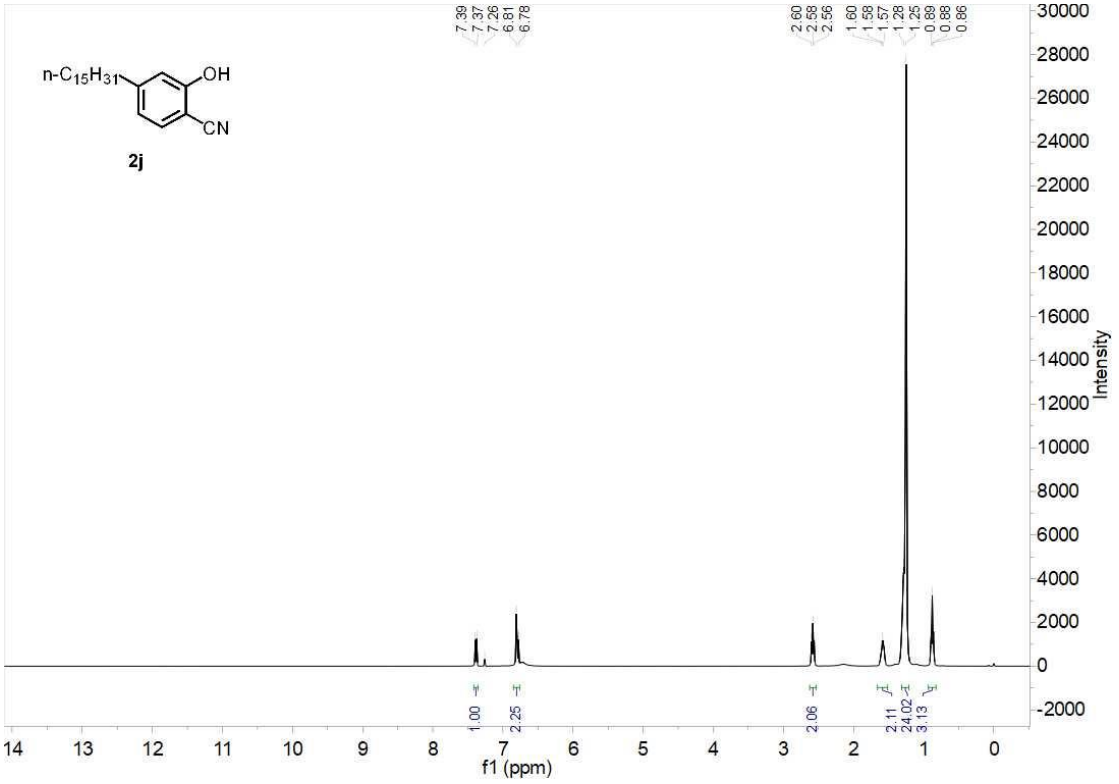
^{1}H NMR spectrum of **2i** (400 MHz, DMSO-d_6)



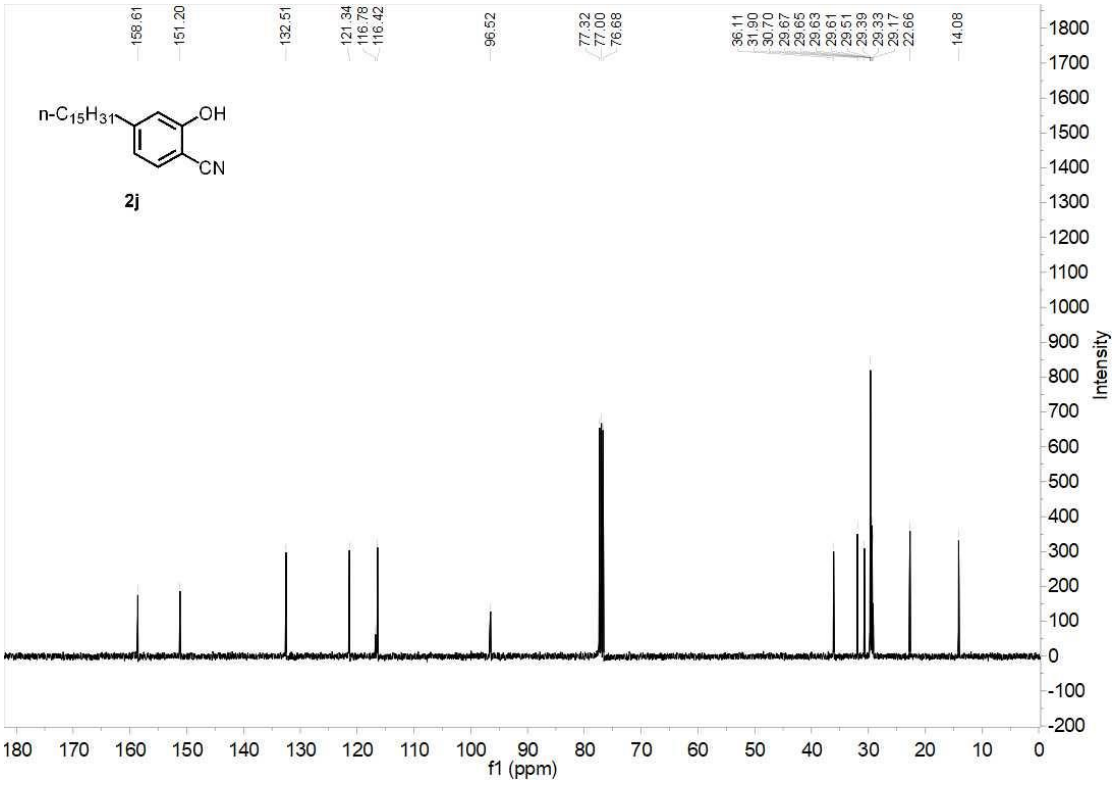
^{13}C NMR spectrum of **2i** (100 MHz, DMSO-d_6)



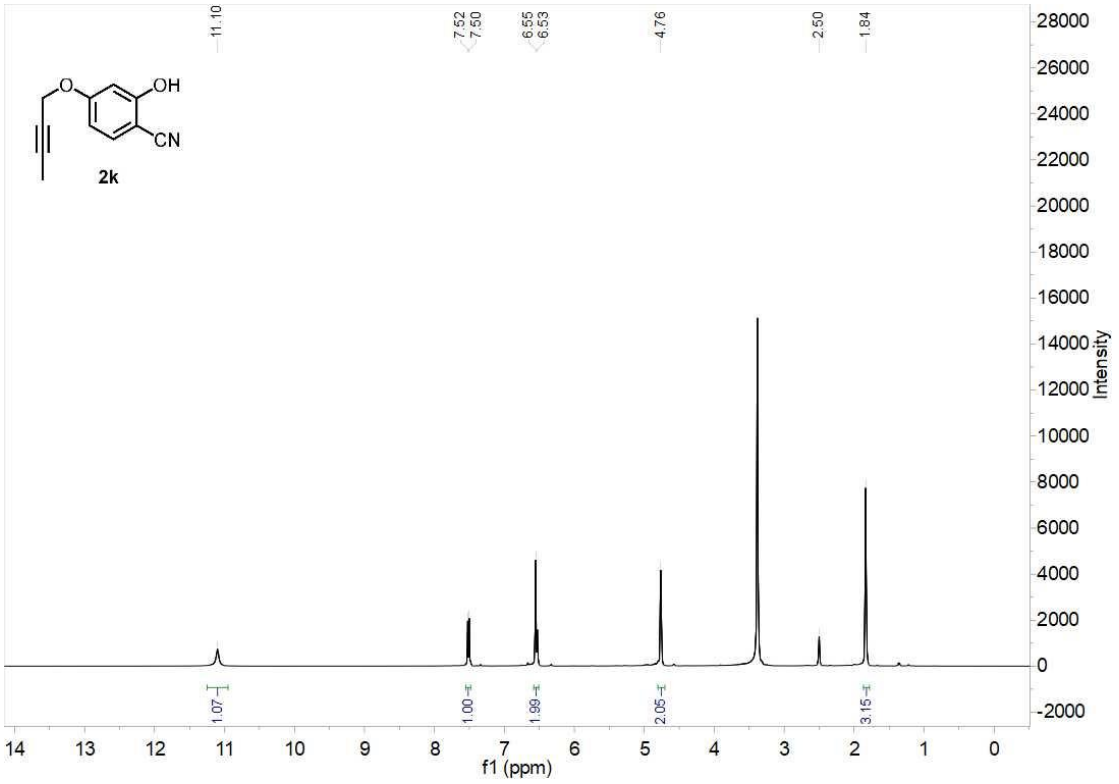
^{1}H NMR spectrum of **2j** (400 MHz, $CDCl_3$)



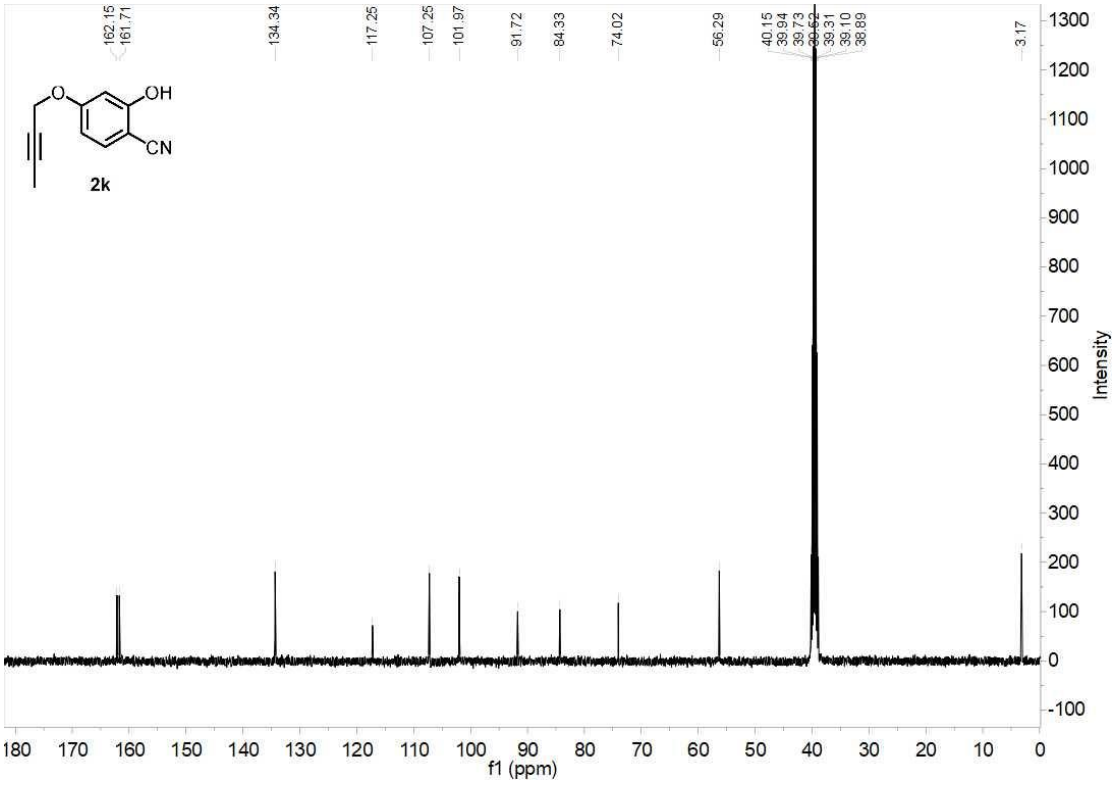
^{13}C NMR spectrum of **2j** (100 MHz, $CDCl_3$)



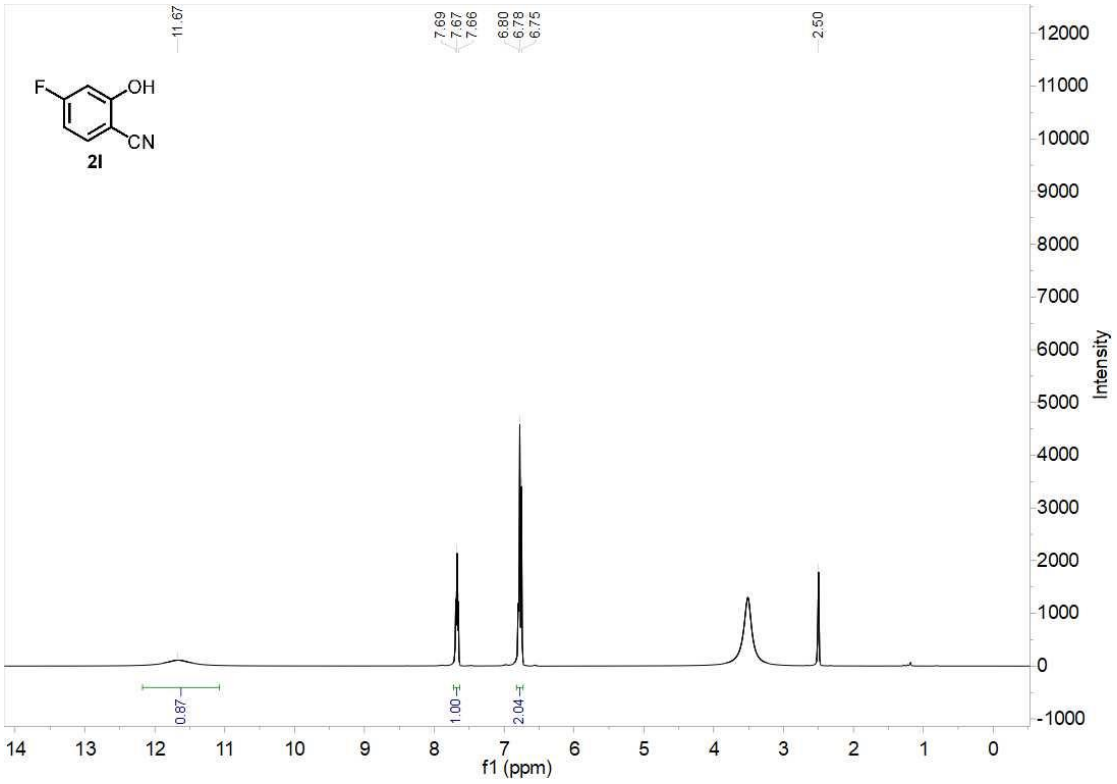
^{1}H NMR spectrum of **2i** (400 MHz, DMSO-d_6)



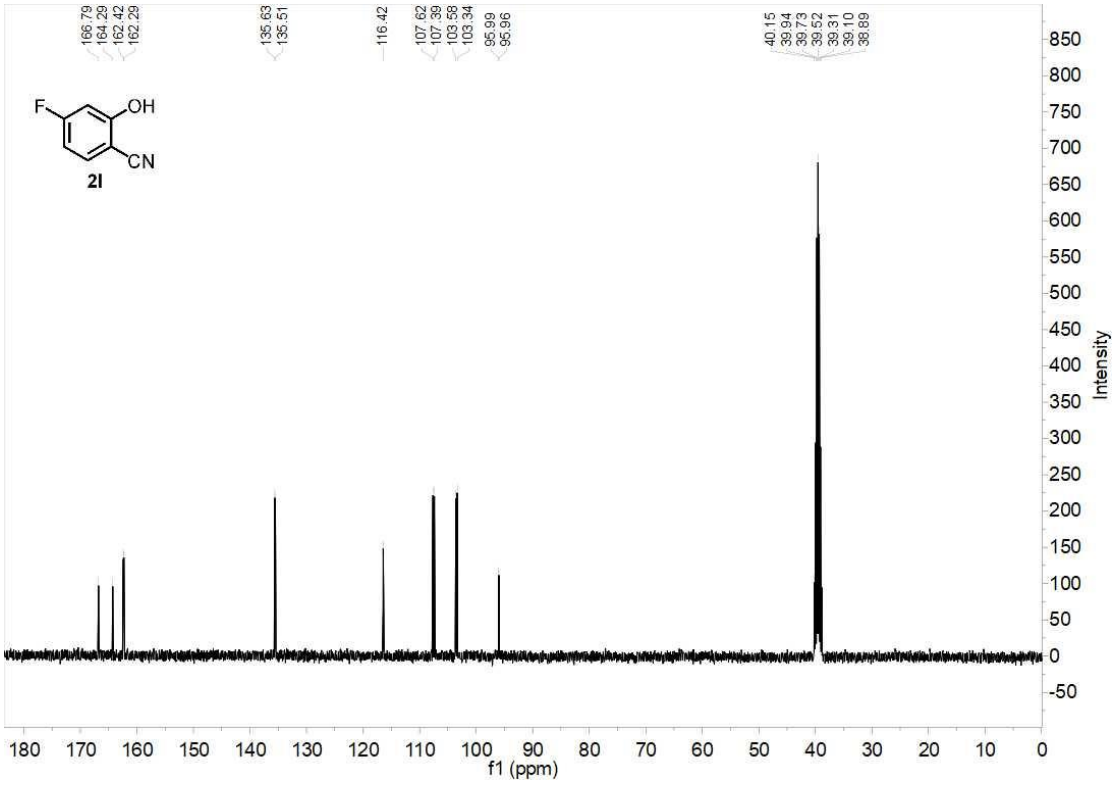
^{13}C NMR spectrum of **2k** (100 MHz, DMSO-d_6)



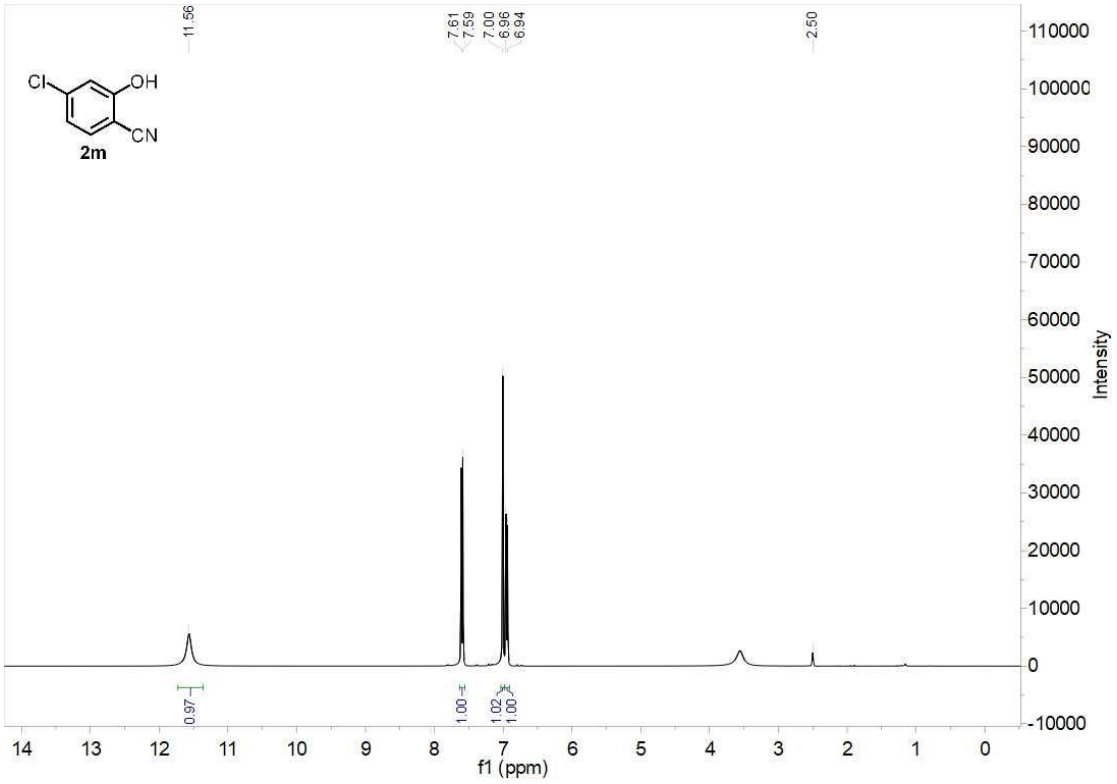
^{1}H NMR spectrum of **2l** (400 MHz, DMSO-d_6)



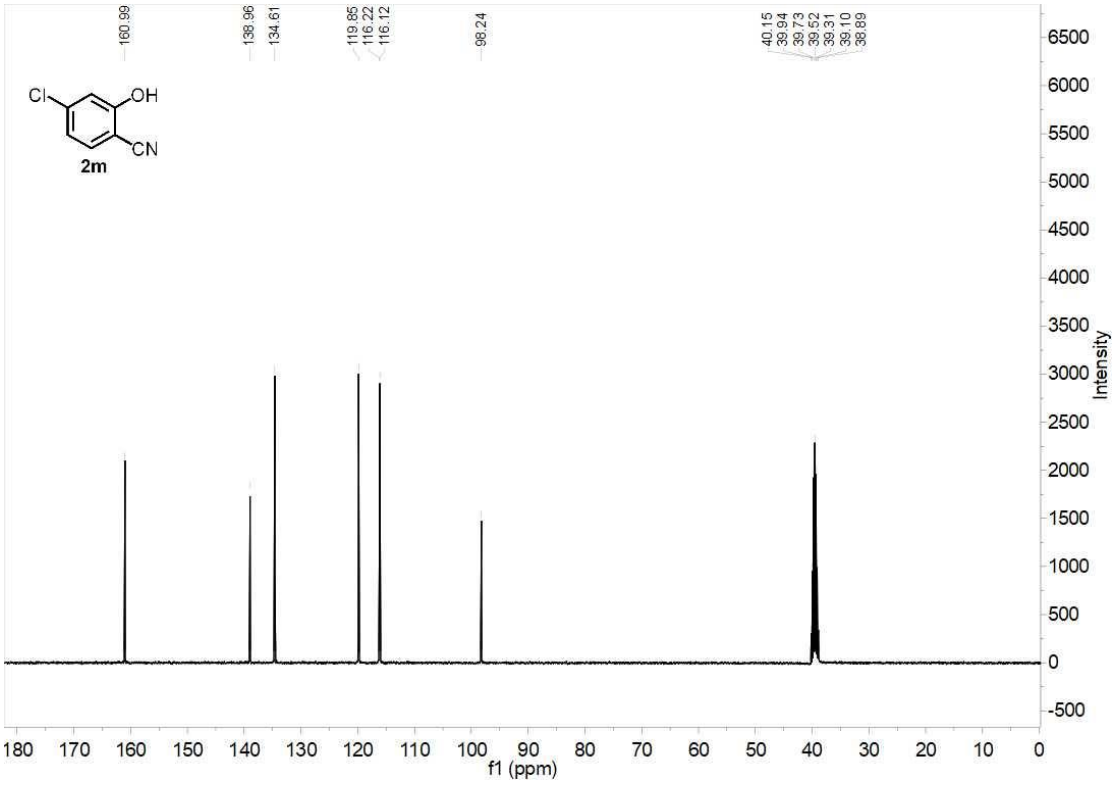
^{13}C NMR spectrum of **2l** (100 MHz, DMSO-d_6)



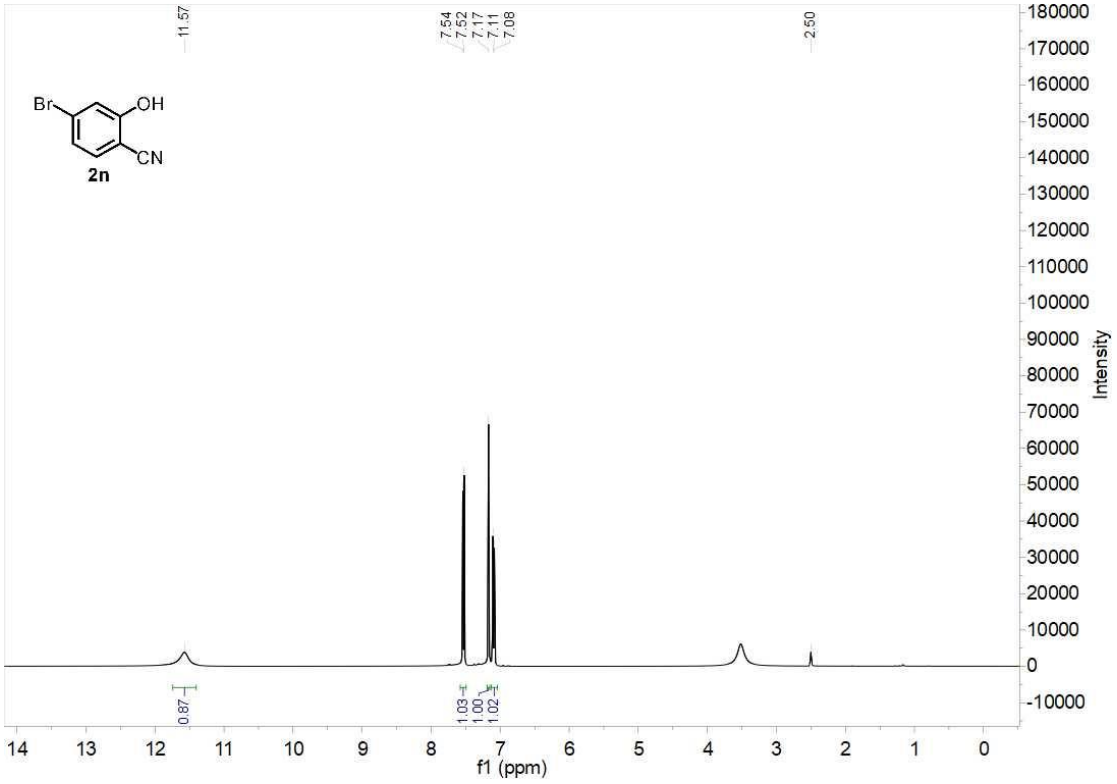
^{1}H NMR spectrum of **2m** (400 MHz, DMSO-d_6)



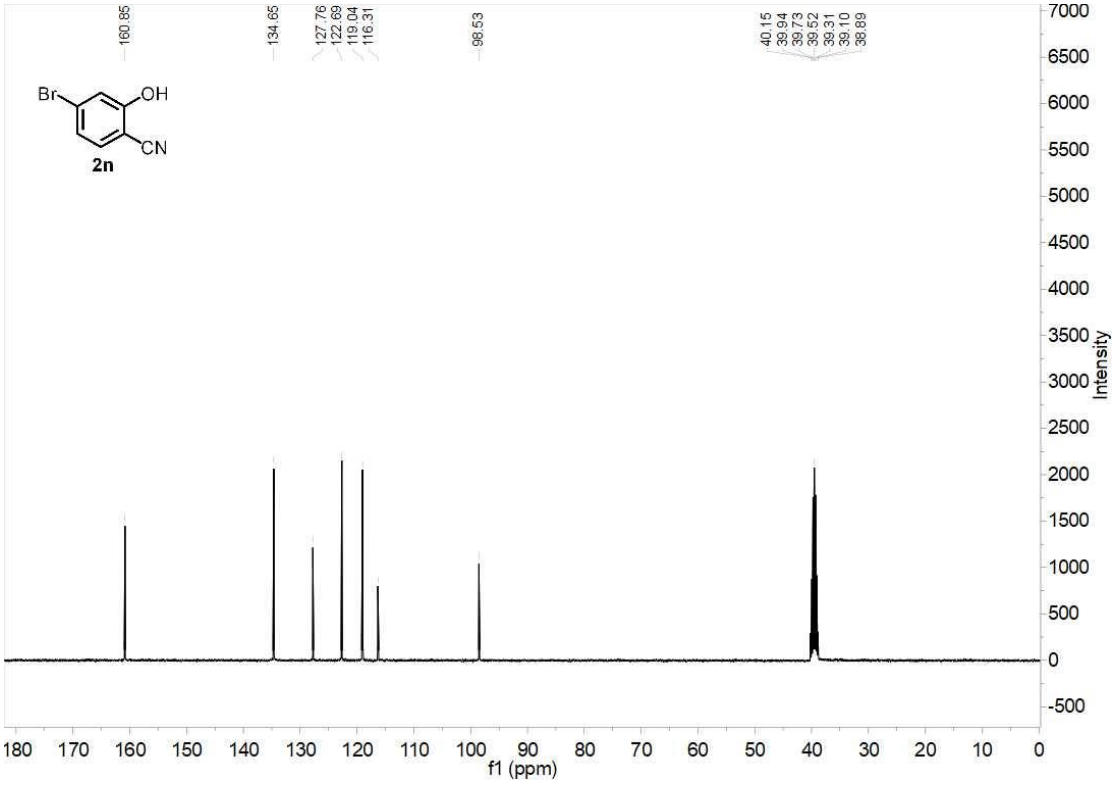
^{13}C NMR spectrum of **2m** (100 MHz, DMSO-d_6)



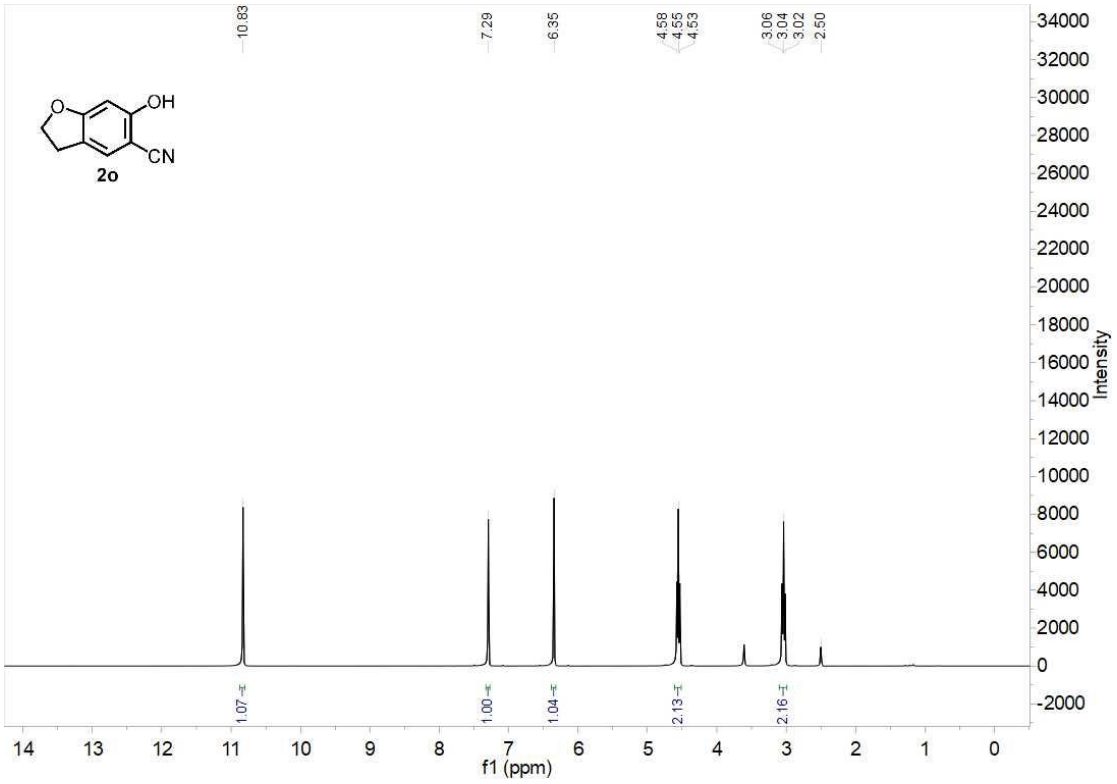
^{1}H NMR spectrum of **2n** (400 MHz, DMSO-d_6)



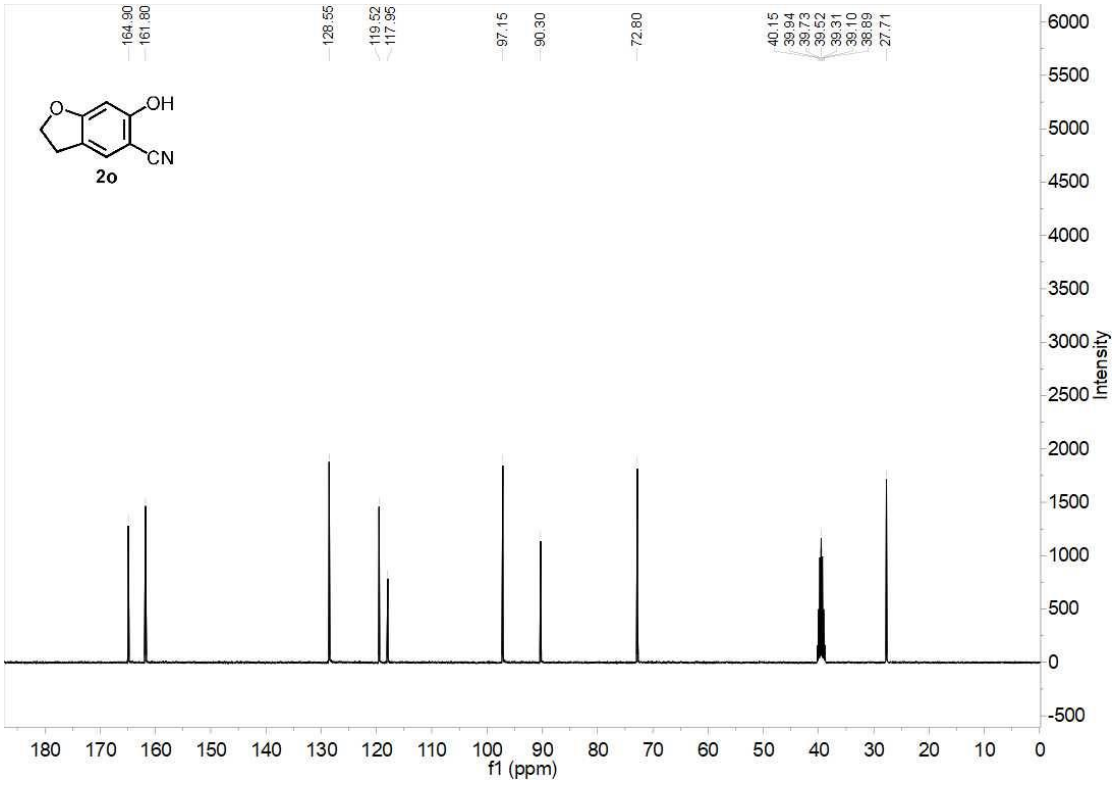
^{13}C NMR spectrum of **2n** (100 MHz, DMSO-d_6)



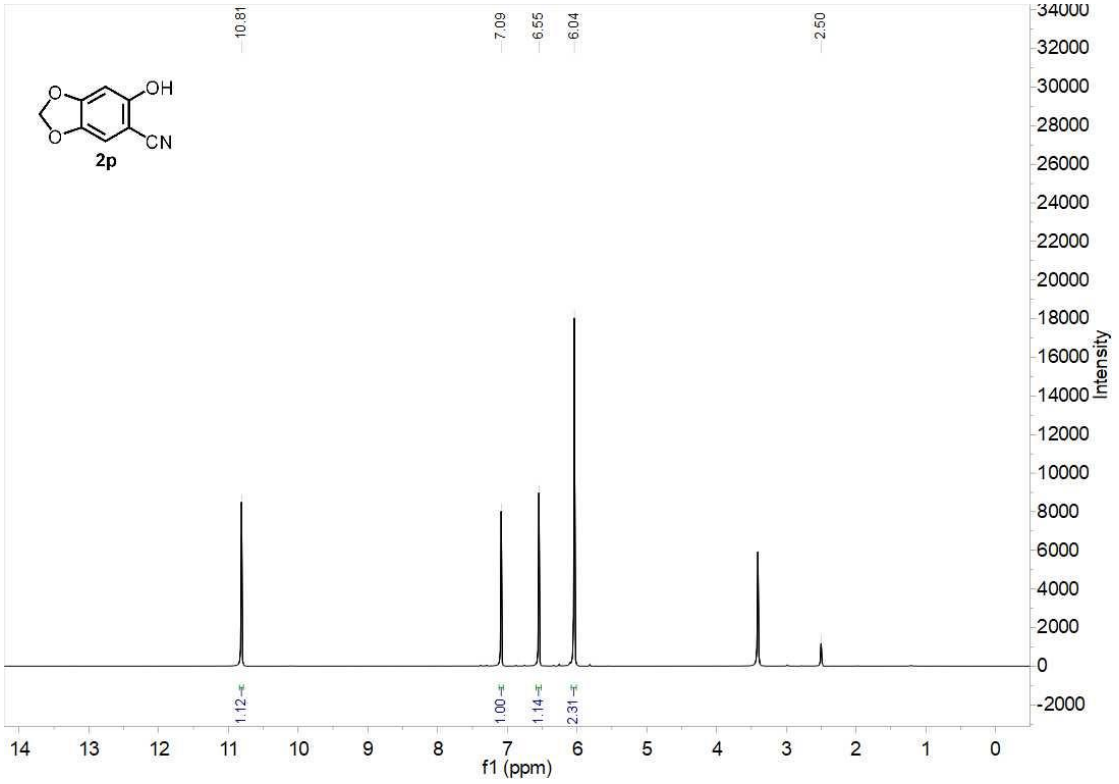
^{1}H NMR spectrum of **2o** (400 MHz, DMSO-d_6)



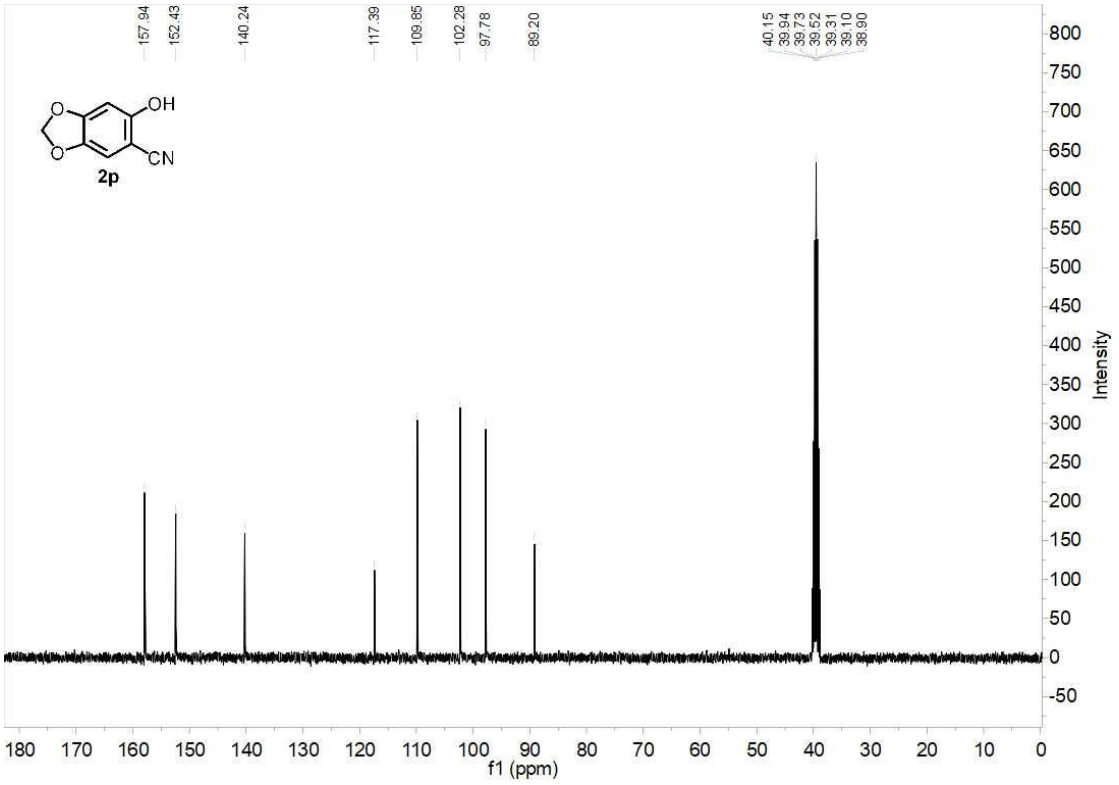
^{13}C NMR spectrum of **2o** (100 MHz, DMSO-d_6)



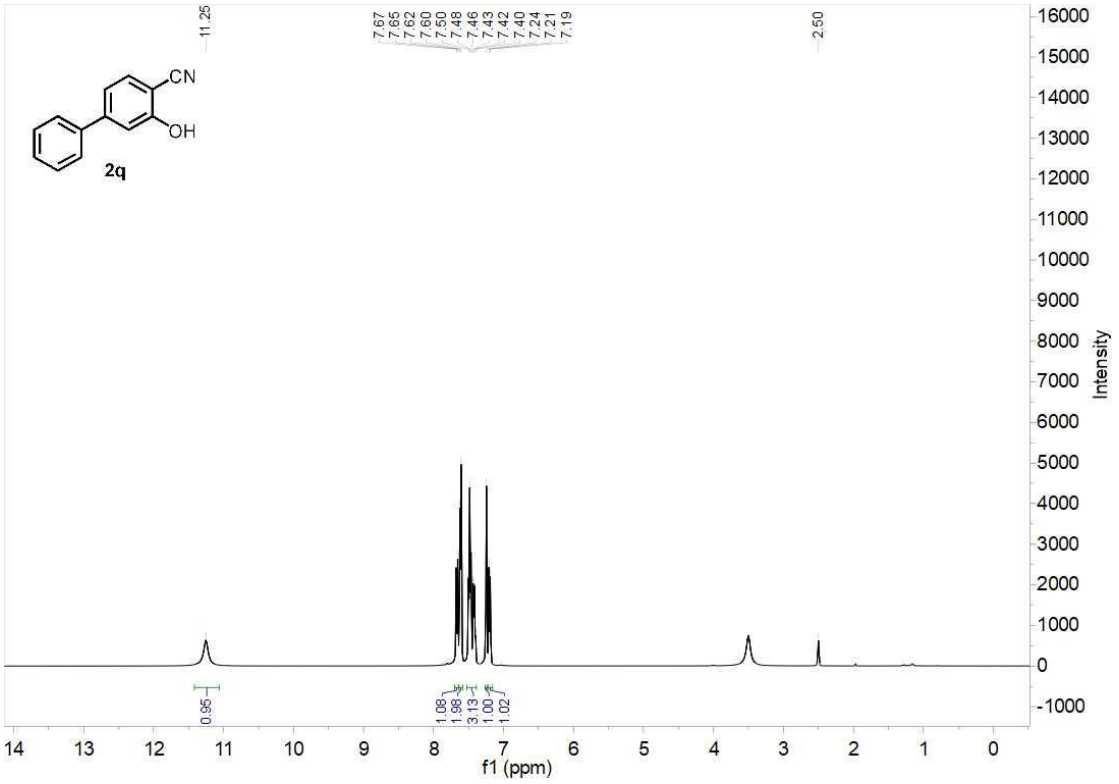
^{1}H NMR spectrum of **2p** (400 MHz, DMSO-d_6)



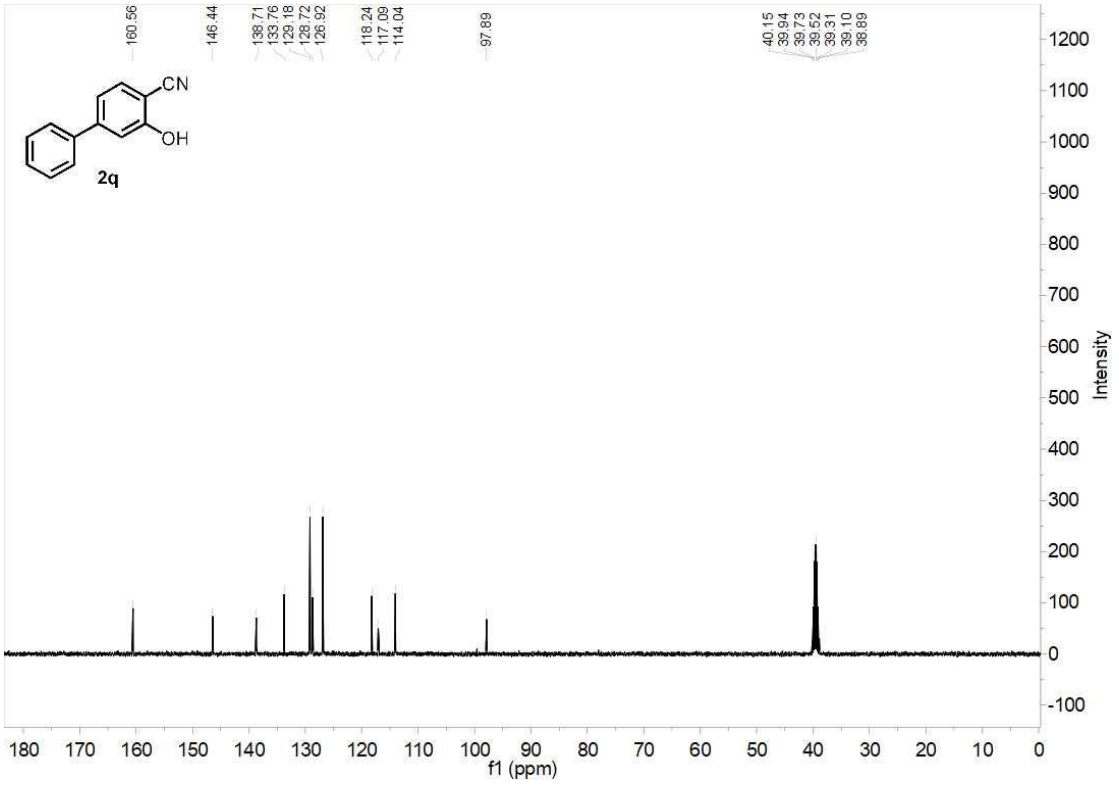
^{13}C NMR spectrum of **2p** (100 MHz, DMSO-d_6)



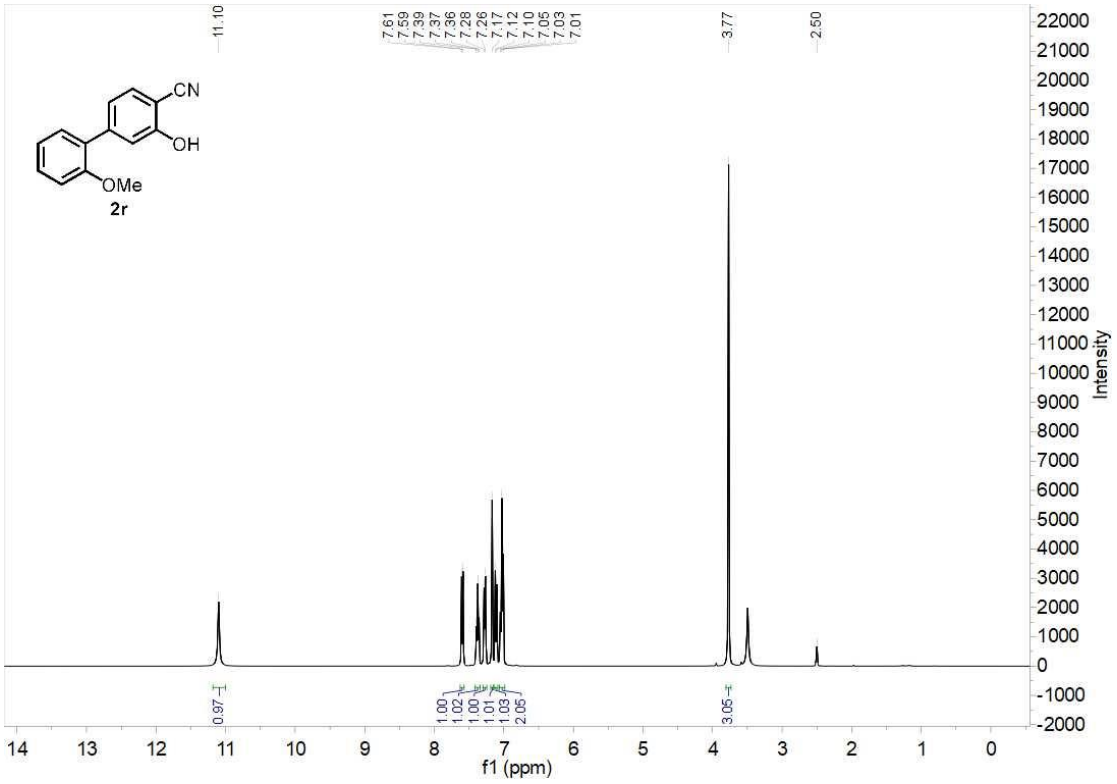
^{1}H NMR spectrum of **2q** (400 MHz, DMSO-d_6)



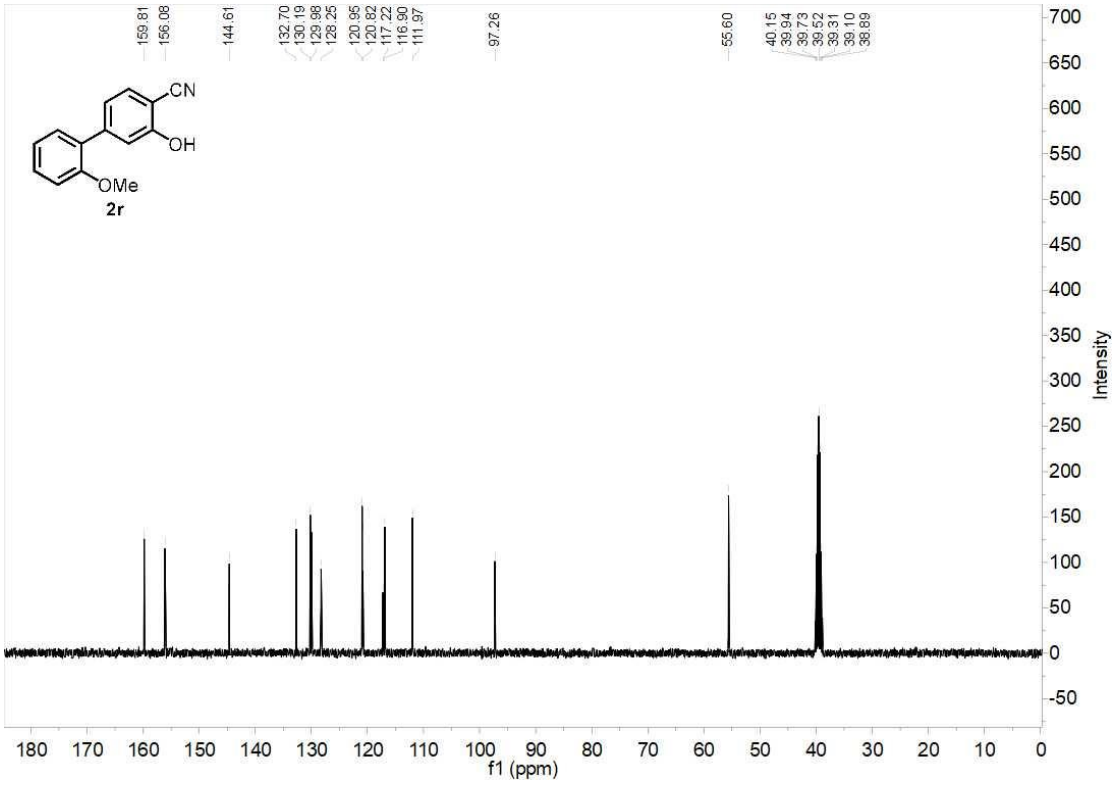
^{13}C NMR spectrum of **2q** (100 MHz, DMSO-d_6)



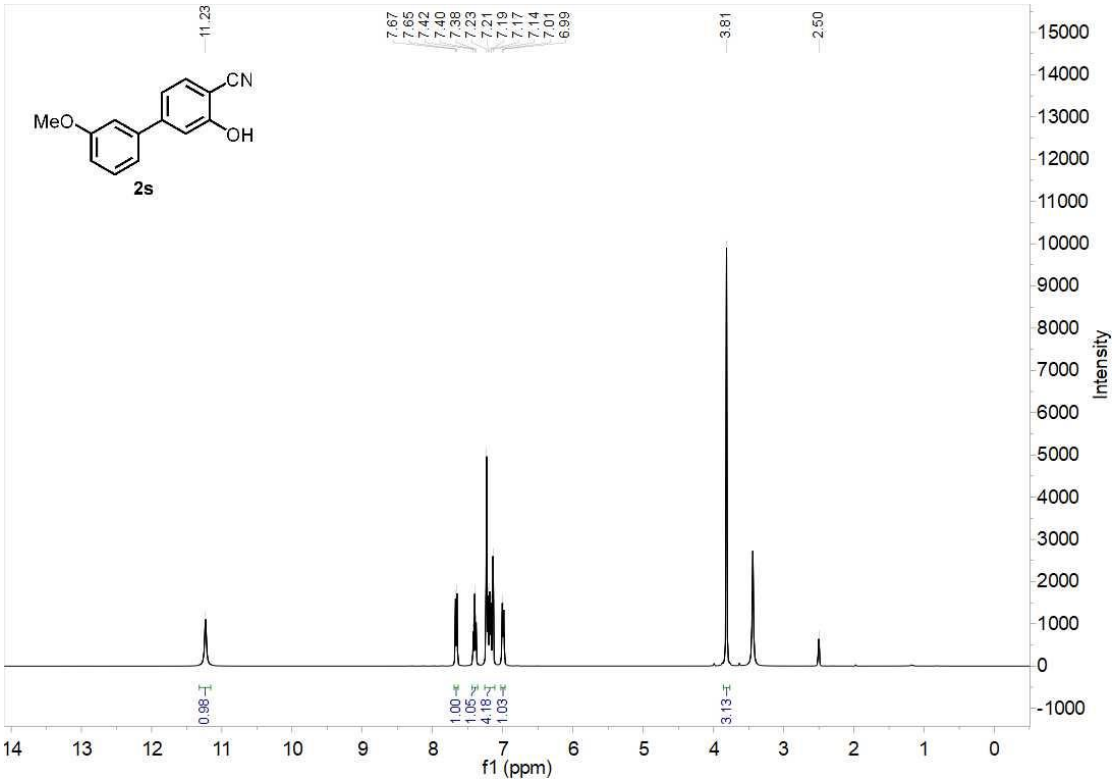
^{1}H NMR spectrum of **2r** (400 MHz, DMSO-d_6)



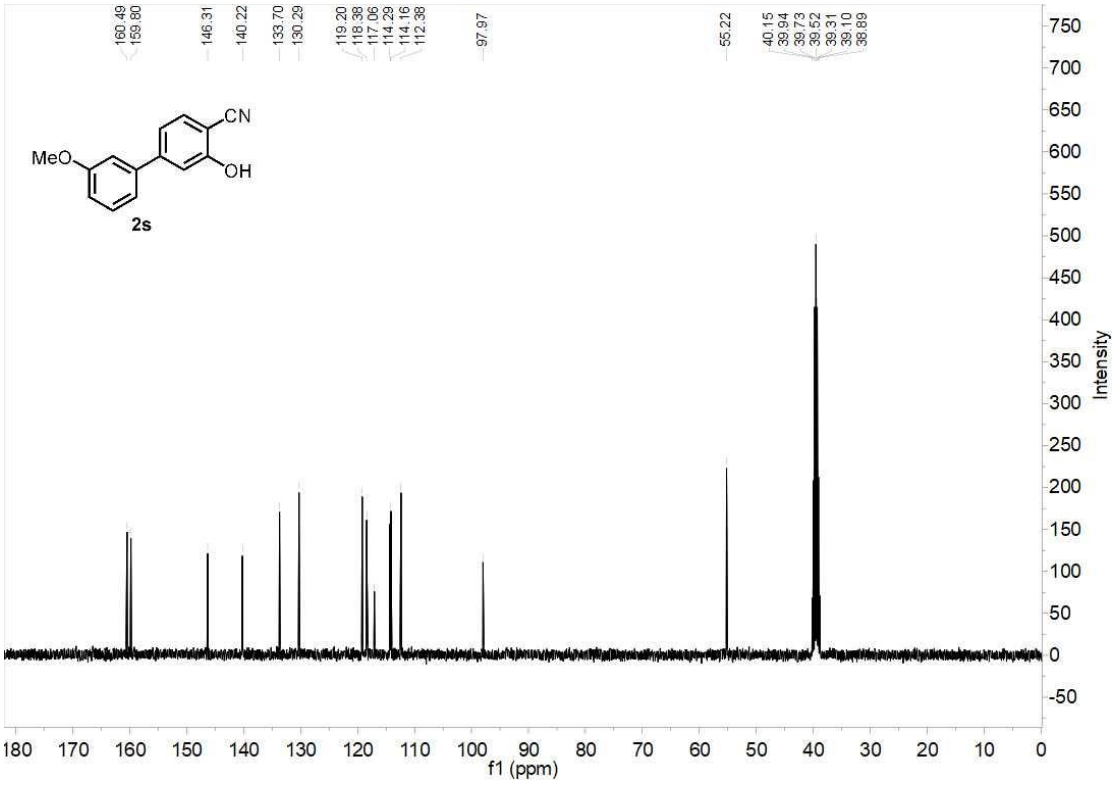
^{13}C NMR spectrum of **2r** (100 MHz, DMSO-d_6)



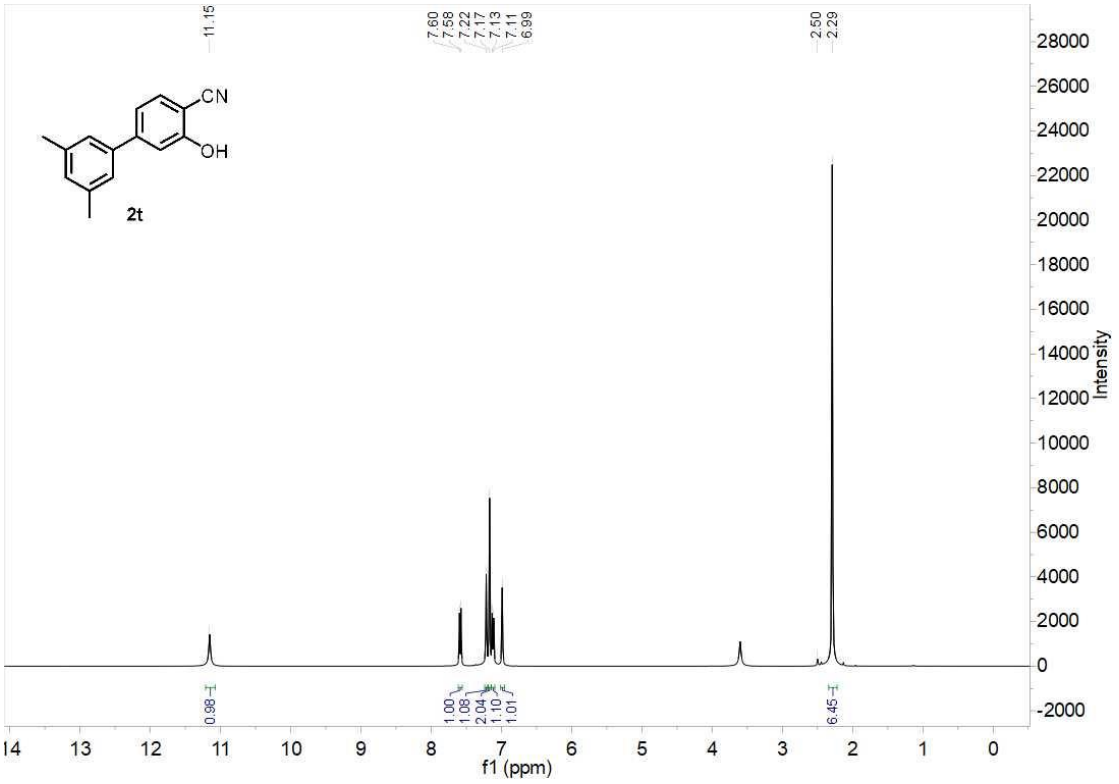
^{1}H NMR spectrum of **2s** (400 MHz, DMSO-d_6)



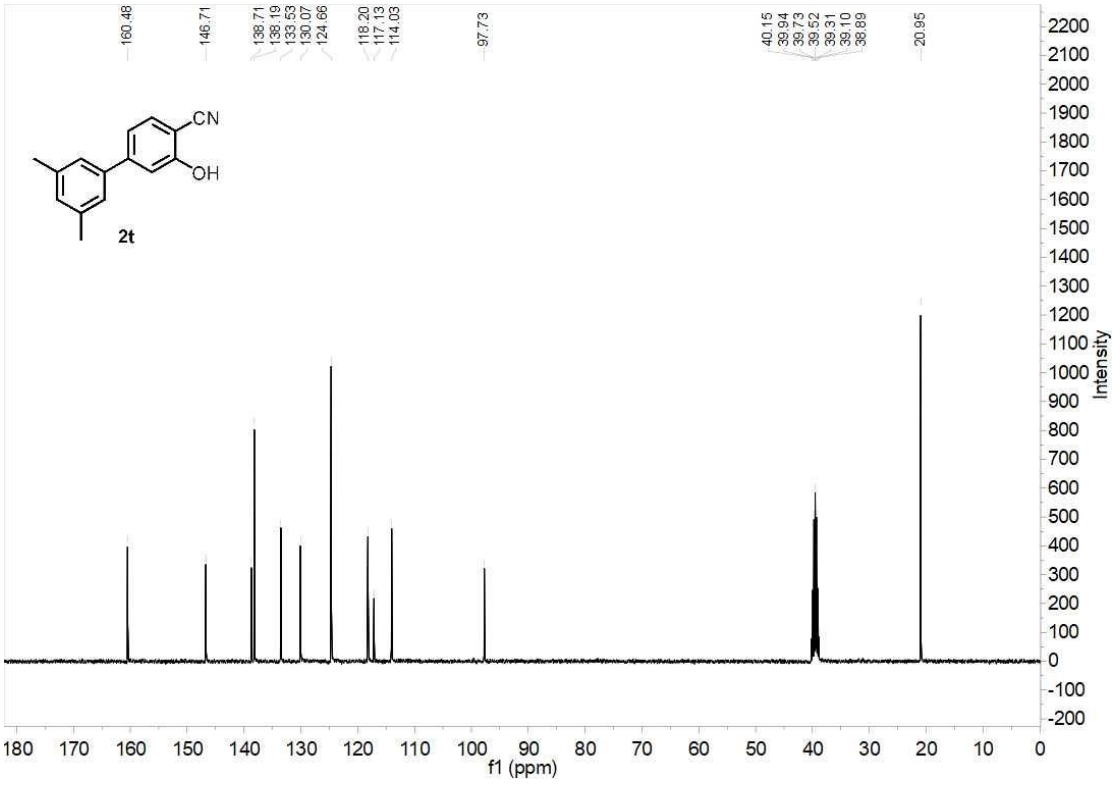
^{13}C NMR spectrum of **2s** (100 MHz, DMSO-d_6)



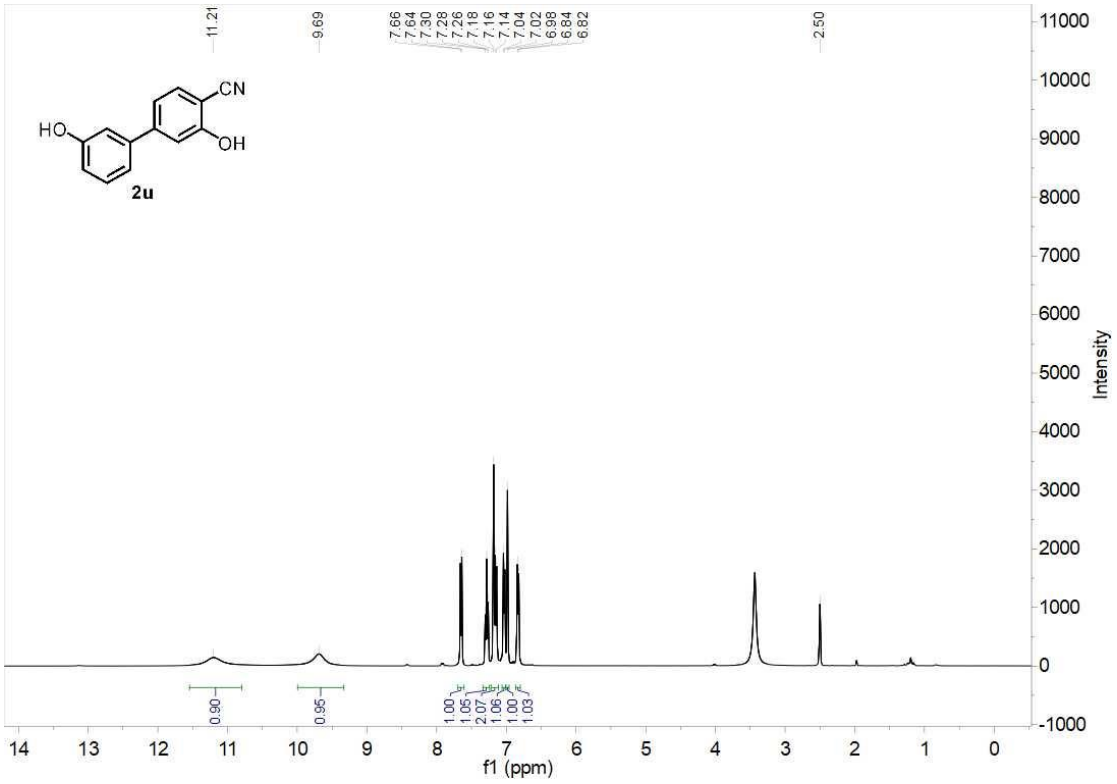
^{1}H NMR spectrum of **2t** (400 MHz, DMSO-d_6)



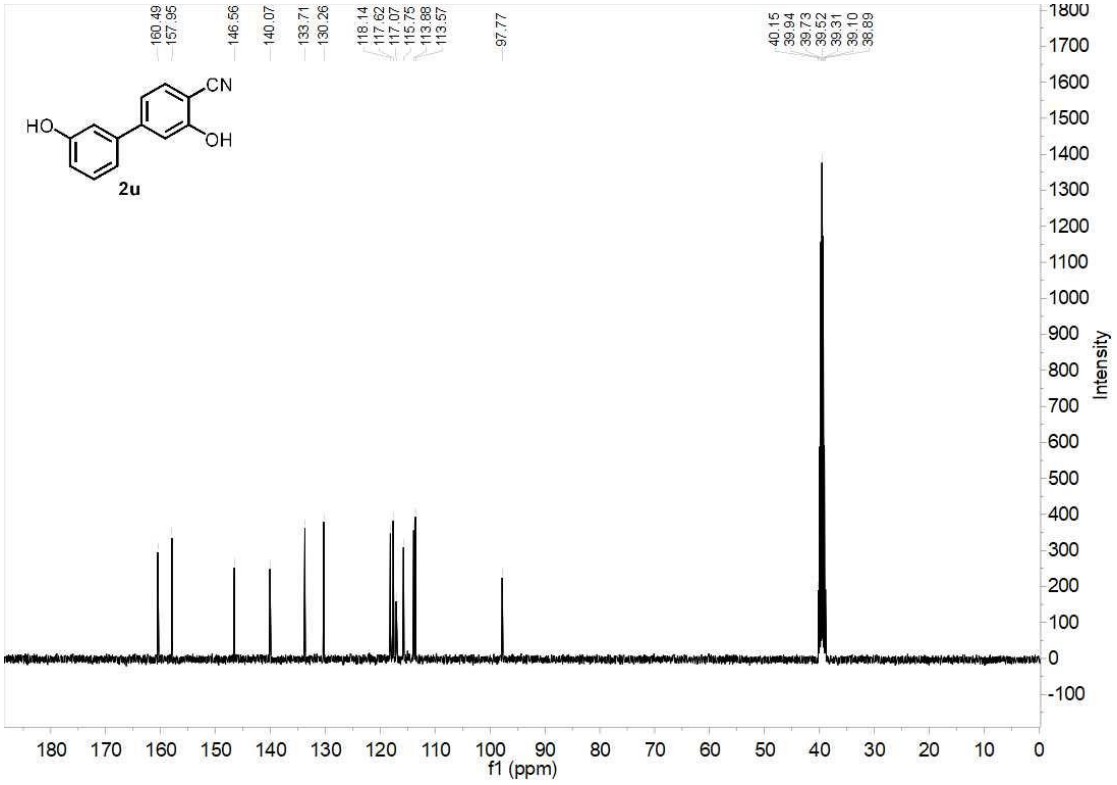
^{13}C NMR spectrum of **2t** (100 MHz, DMSO-d_6)



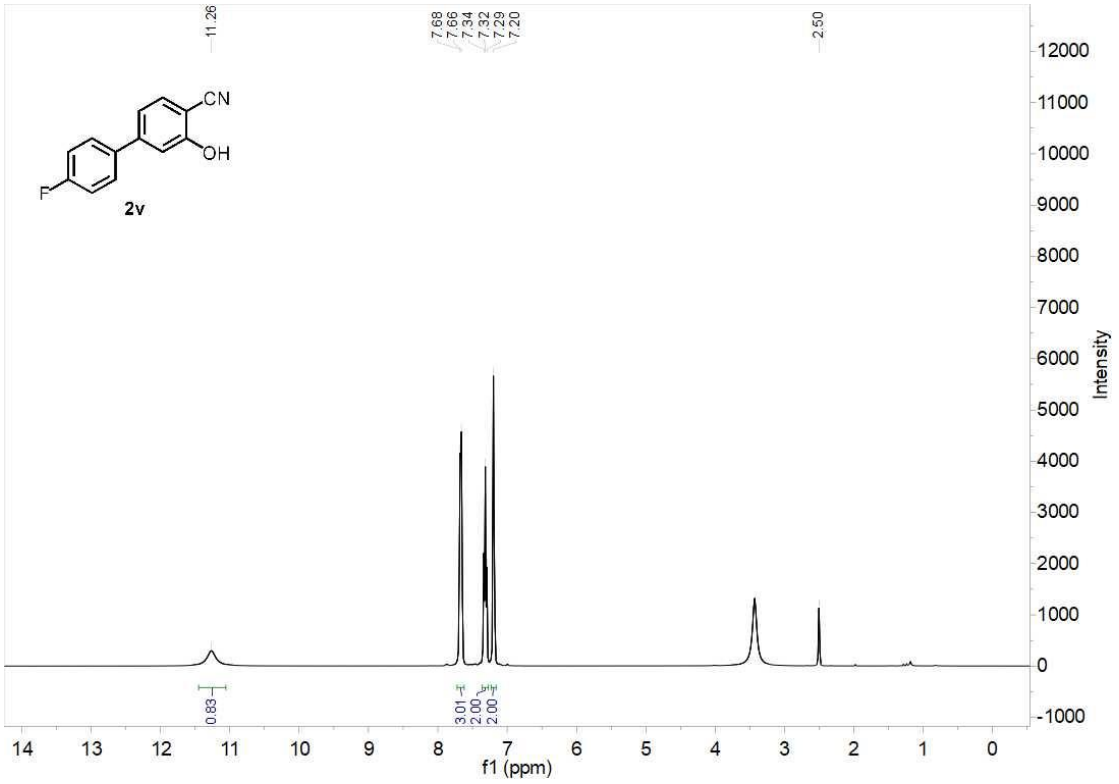
^{1}H NMR spectrum of **2u** (400 MHz, DMSO-d_6)



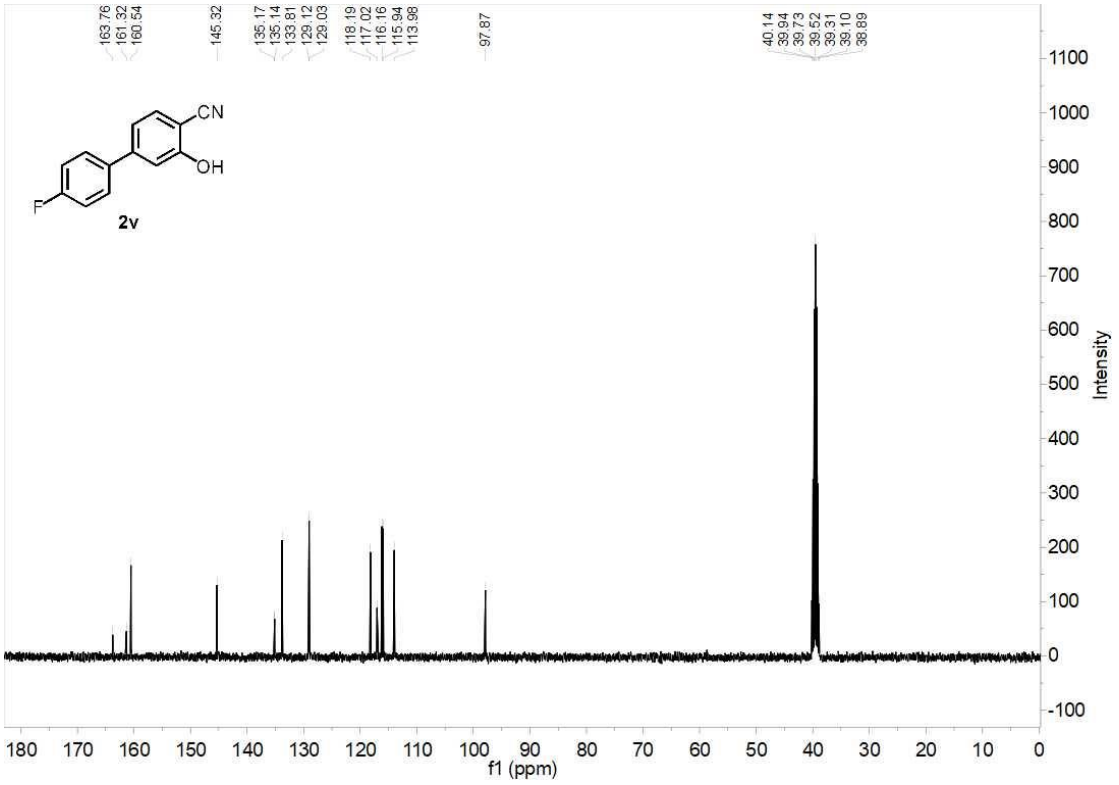
^{13}C NMR spectrum of **2u** (100 MHz, DMSO-d_6)



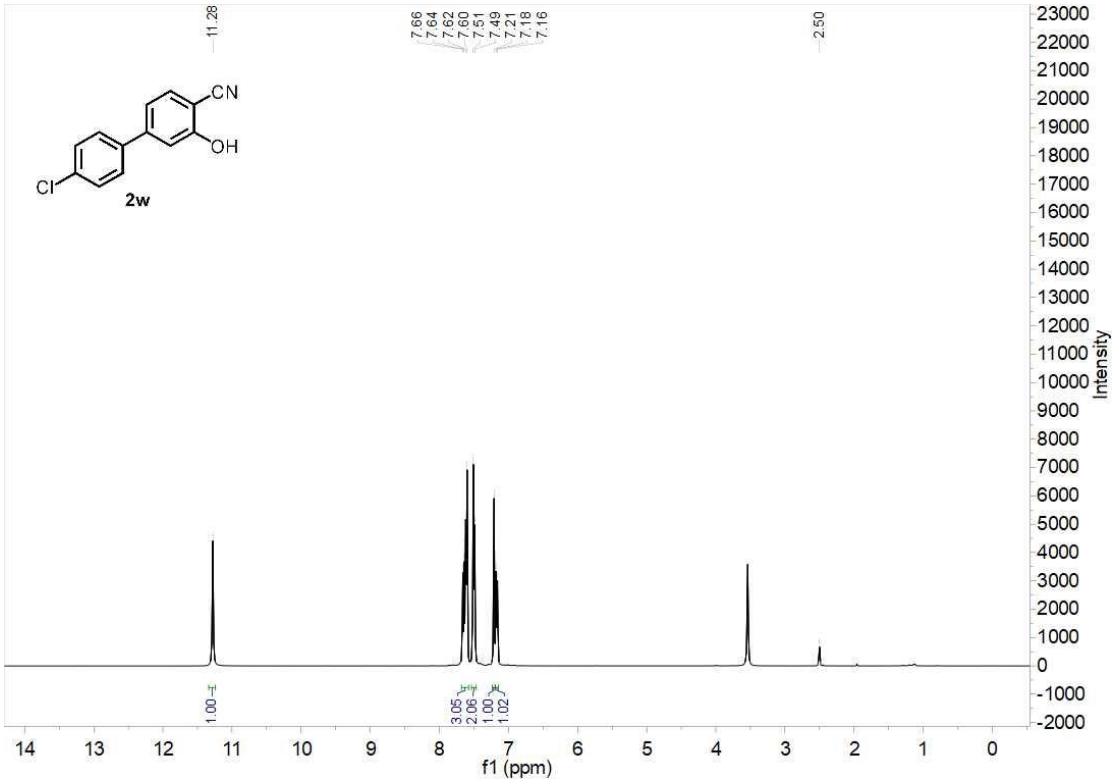
^{1}H NMR spectrum of **2v** (400 MHz, DMSO-d_6)



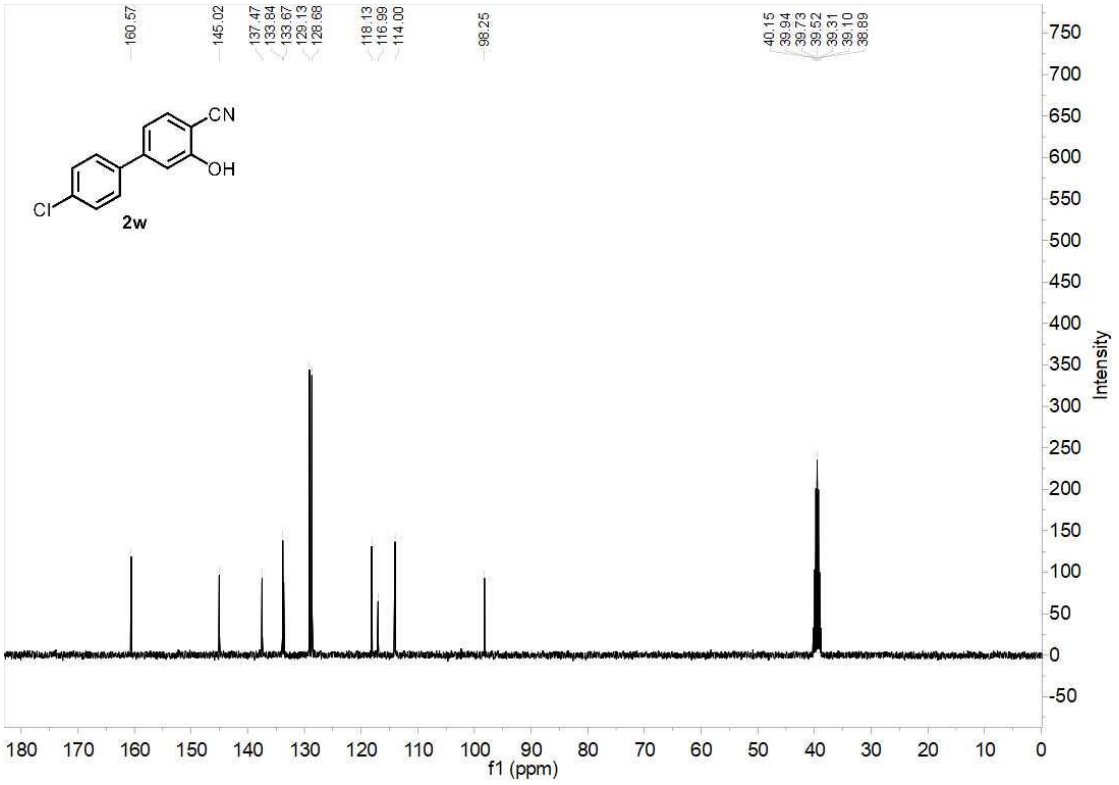
^{13}C NMR spectrum of **2v** (100 MHz, DMSO-d_6)



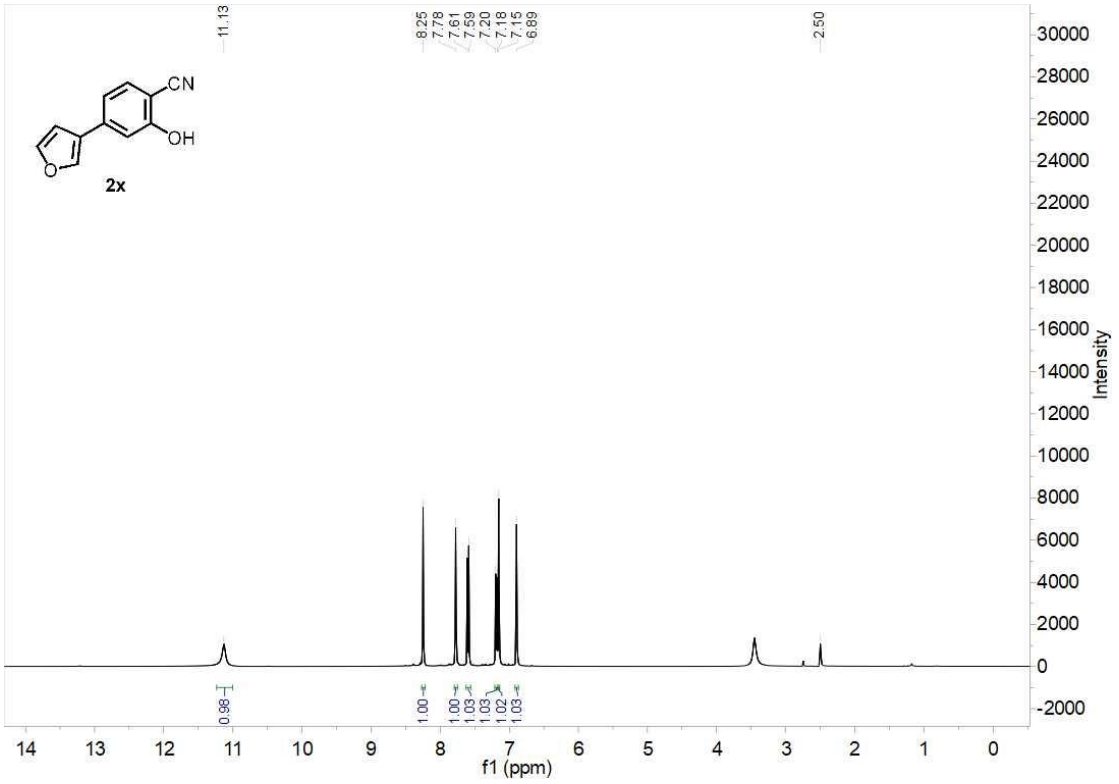
^{1}H NMR spectrum of **2w** (400 MHz, DMSO-d_6)



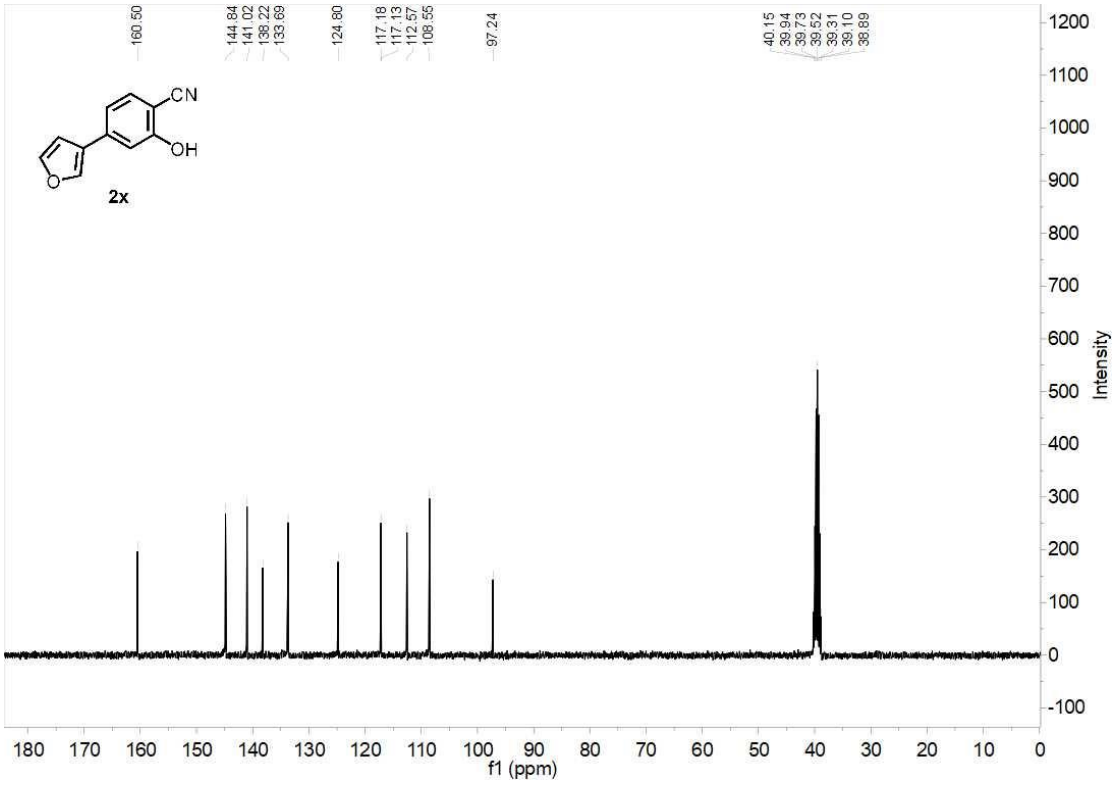
^{13}C NMR spectrum of **2w** (100 MHz, DMSO-d_6)



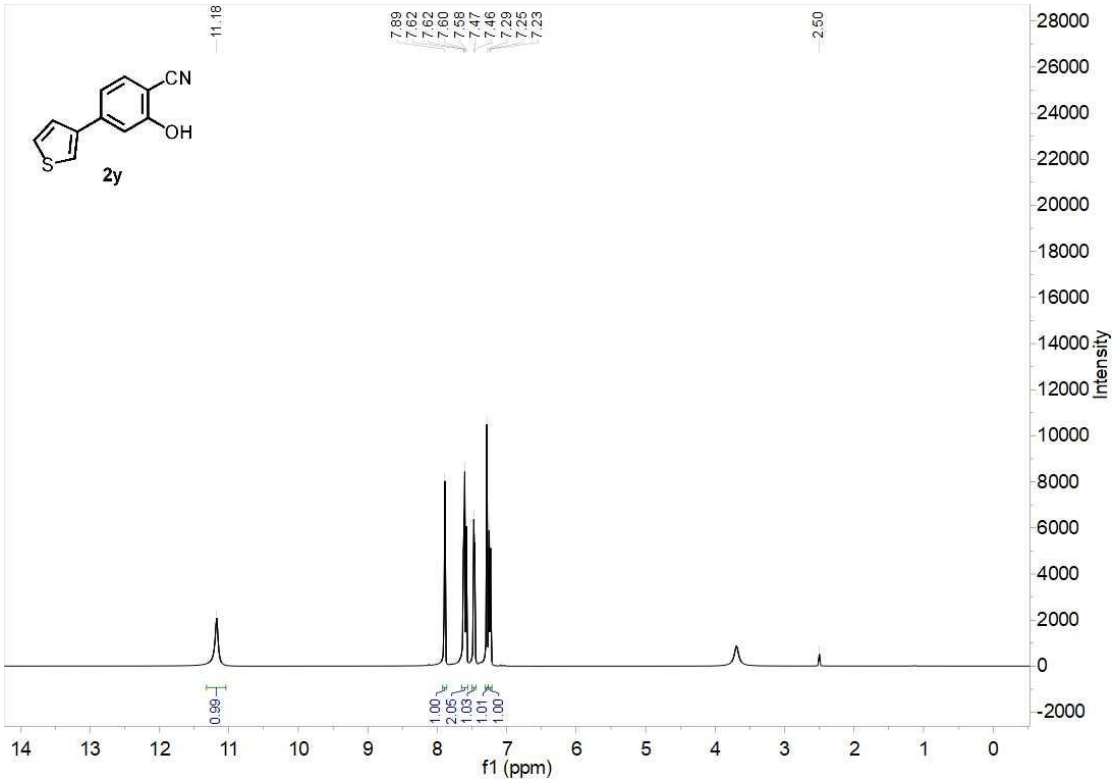
^{1}H NMR spectrum of **2x** (400 MHz, DMSO-d_6)



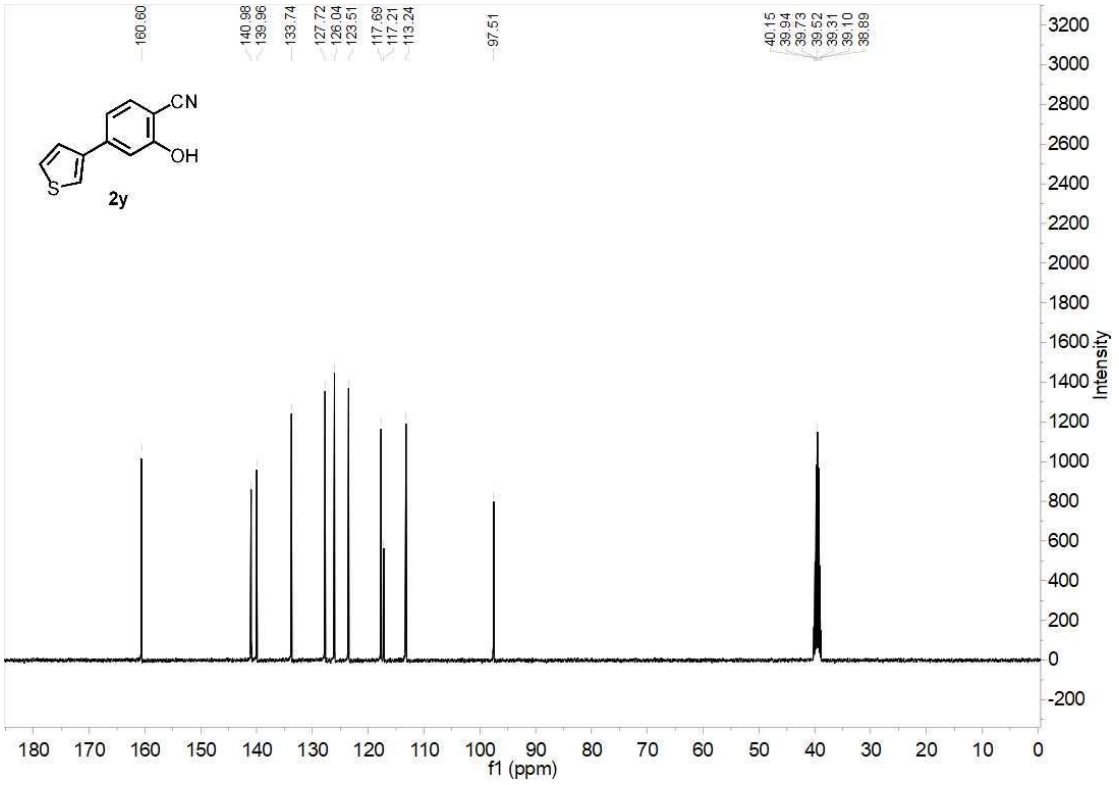
^{13}C NMR spectrum of **2x** (100 MHz, DMSO-d_6)



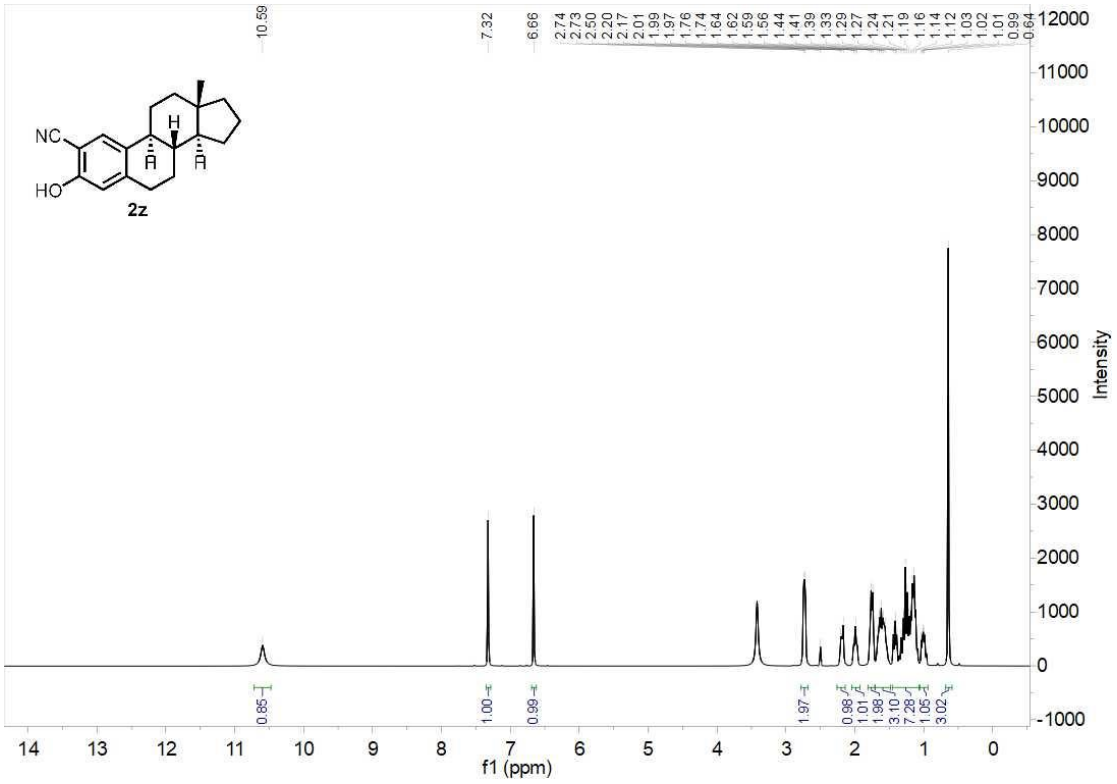
^{1}H NMR spectrum of **2y** (400 MHz, DMSO-d_6)



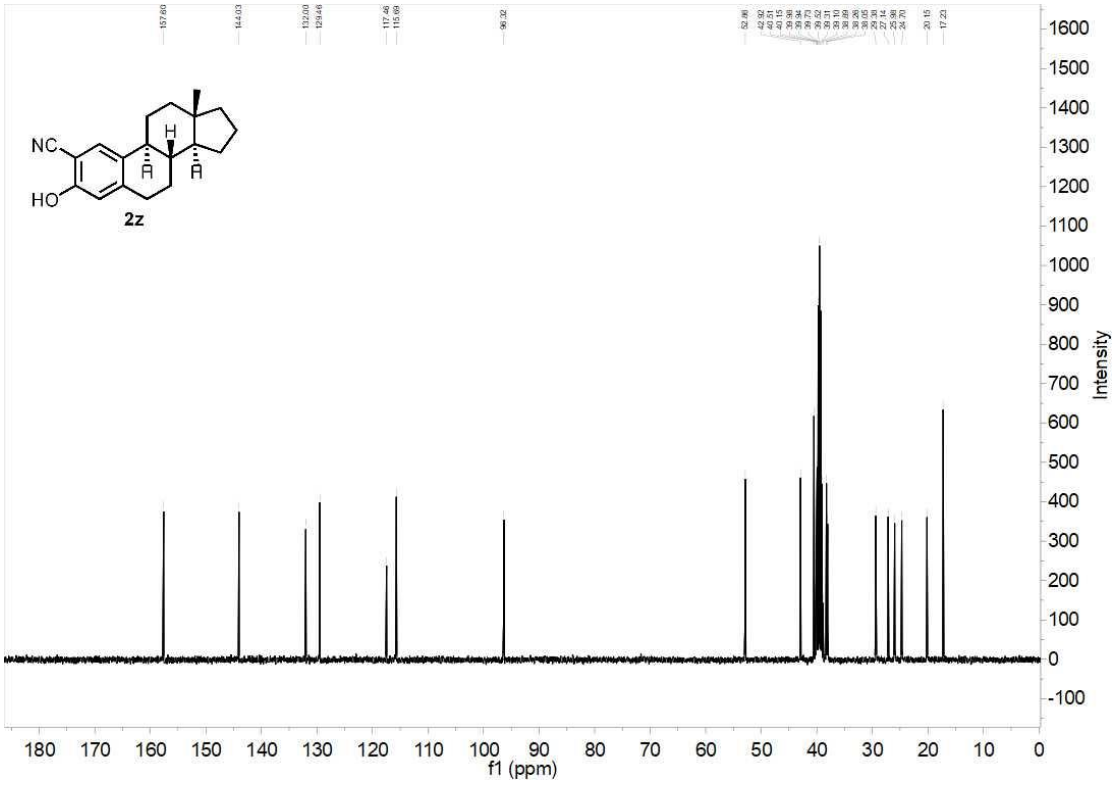
^{13}C NMR spectrum of **2y** (100 MHz, DMSO-d_6)



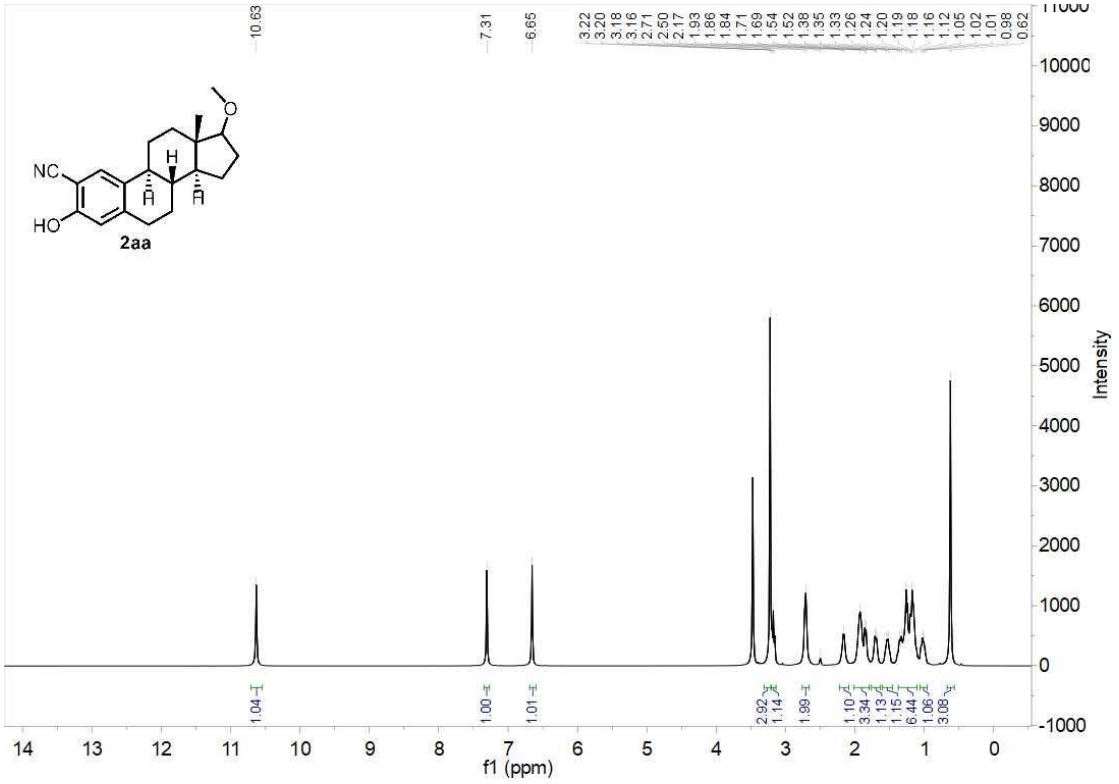
^{1}H NMR spectrum of **2z** (400 MHz, DMSO-d_6)



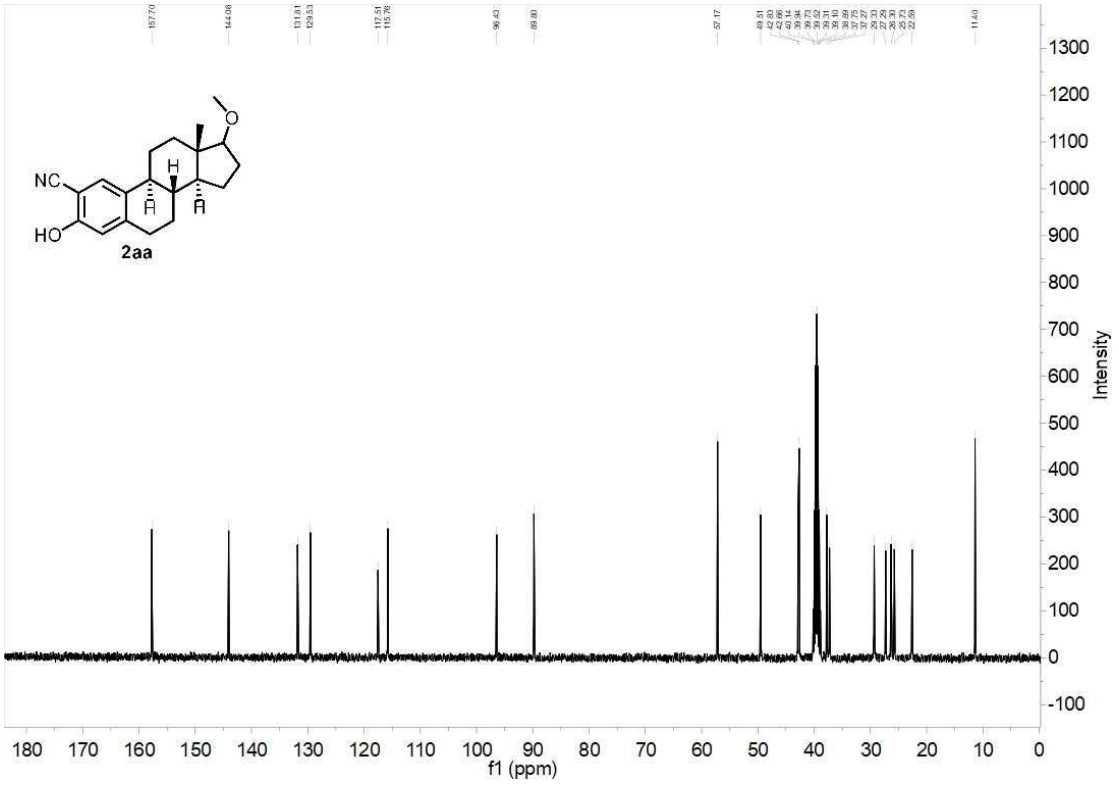
^{13}C NMR spectrum of **2z** (100 MHz, DMSO-d_6)



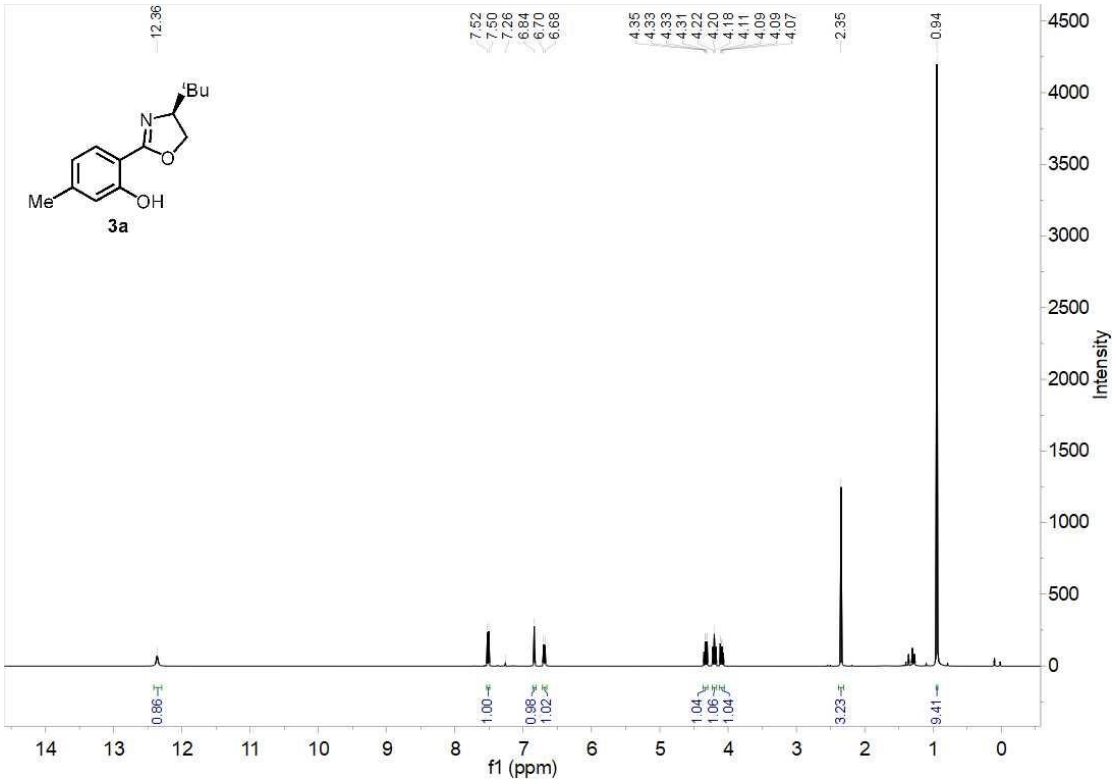
^{1}H NMR spectrum of **2aa** (400 MHz, DMSO-d_6)



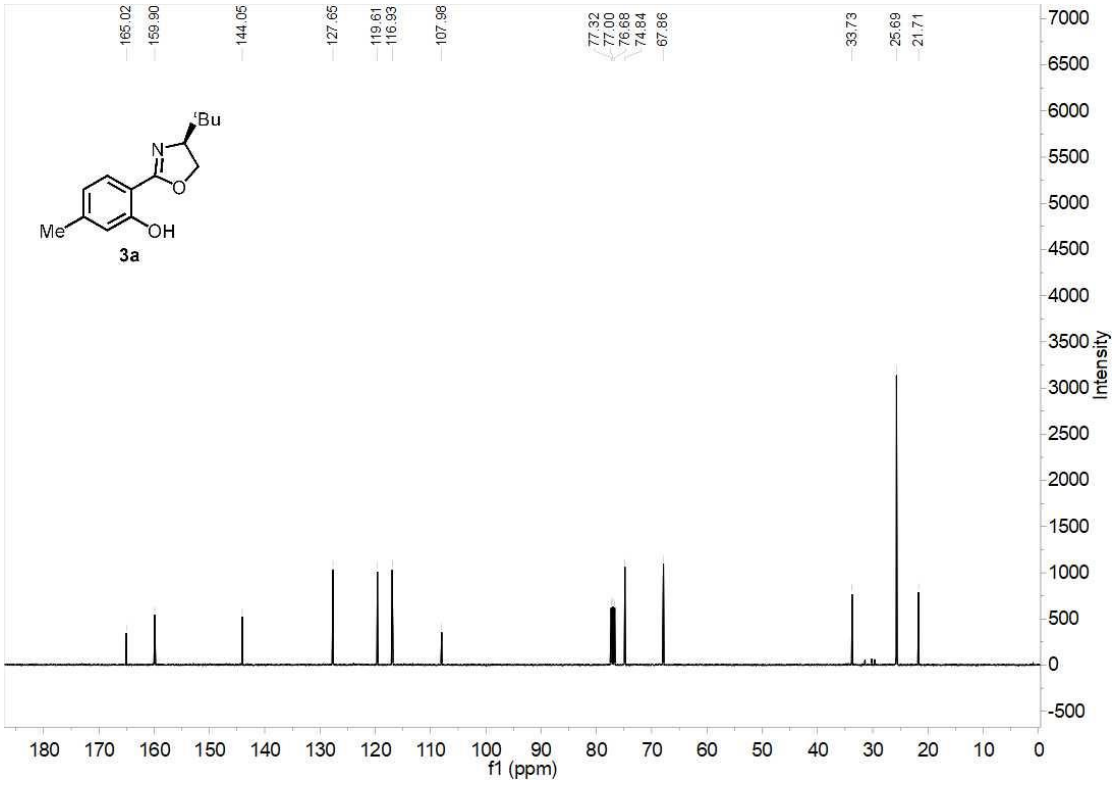
^{13}C NMR spectrum of **2aa** (100 MHz, DMSO-d_6)



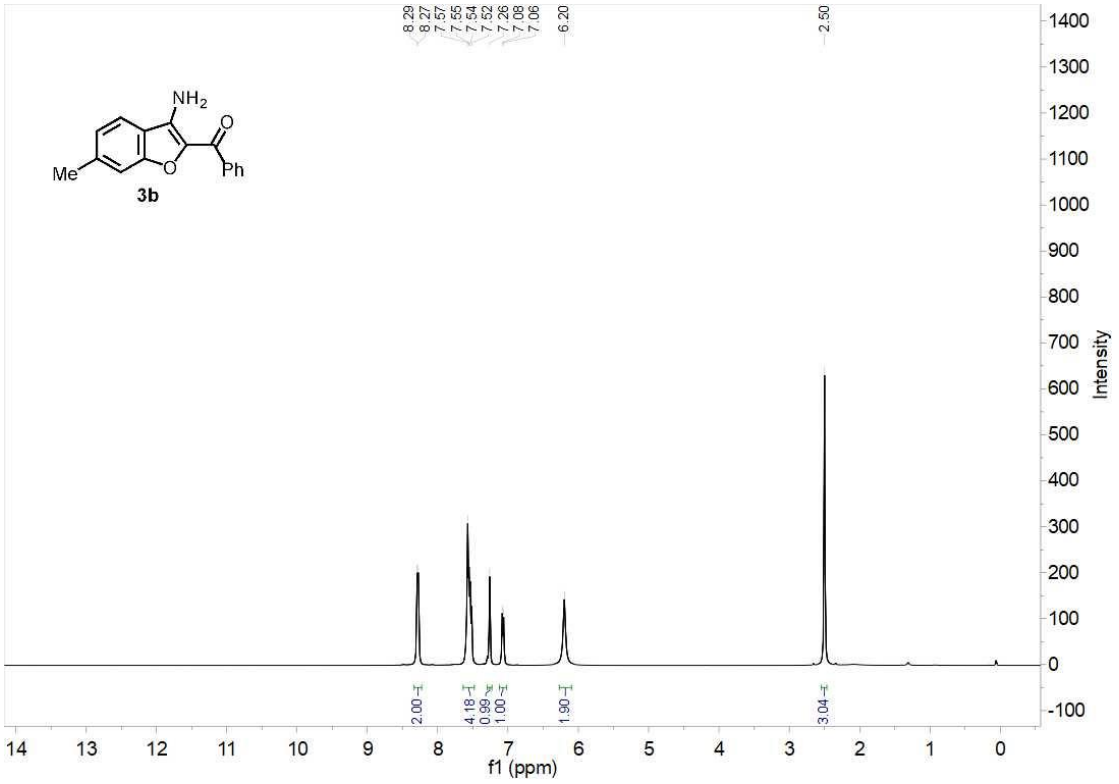
^{1}H NMR spectrum of **3a** (400 MHz, $CDCl_3$)



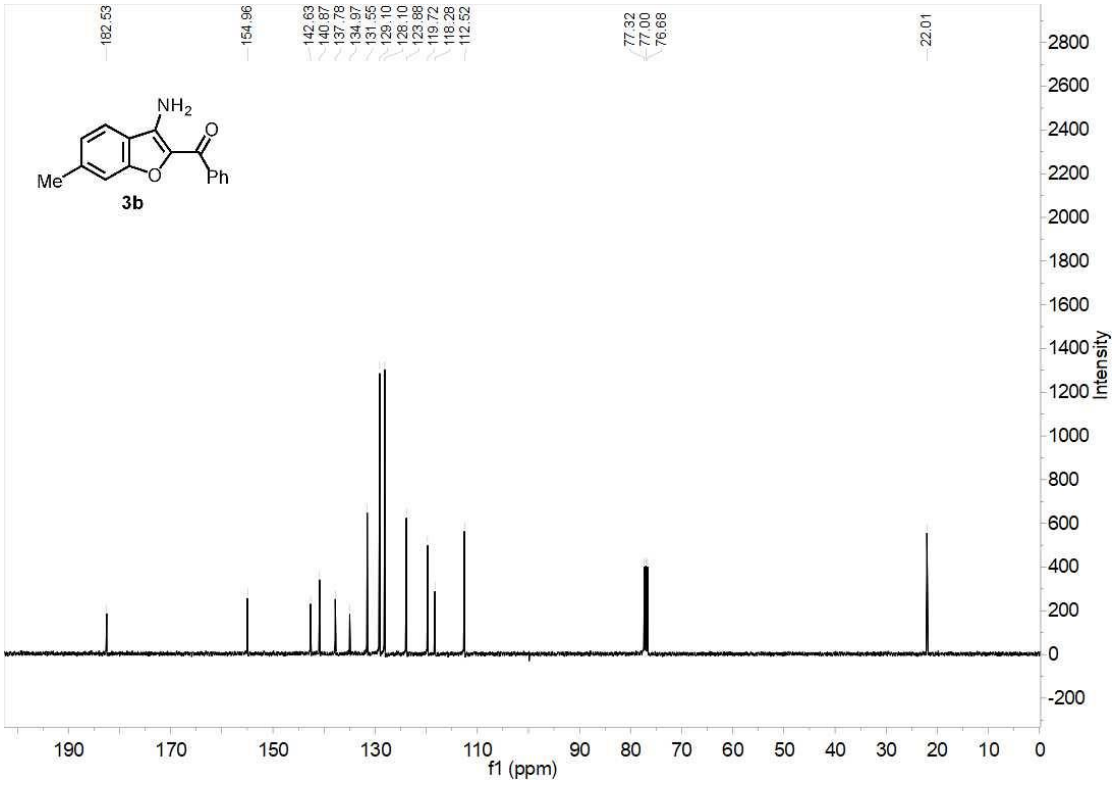
^{13}C NMR spectrum of **3a** (100 MHz, $CDCl_3$)



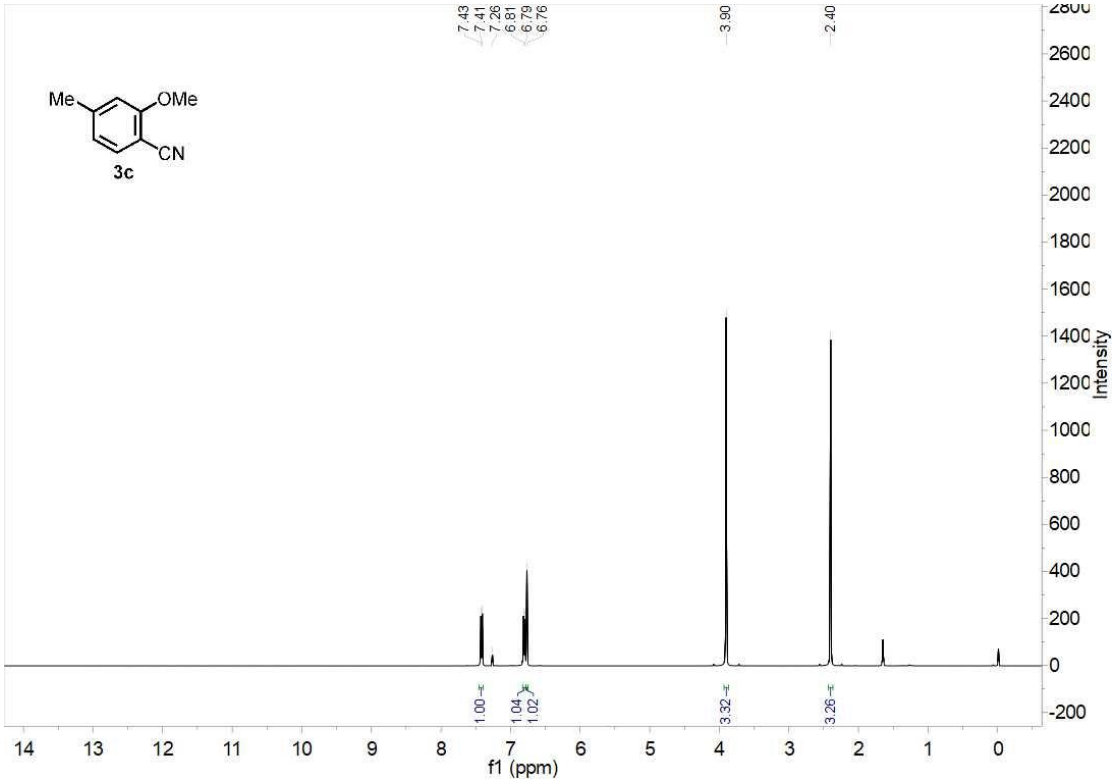
^{1}H NMR spectrum of **3b** (400 MHz, $CDCl_3$)



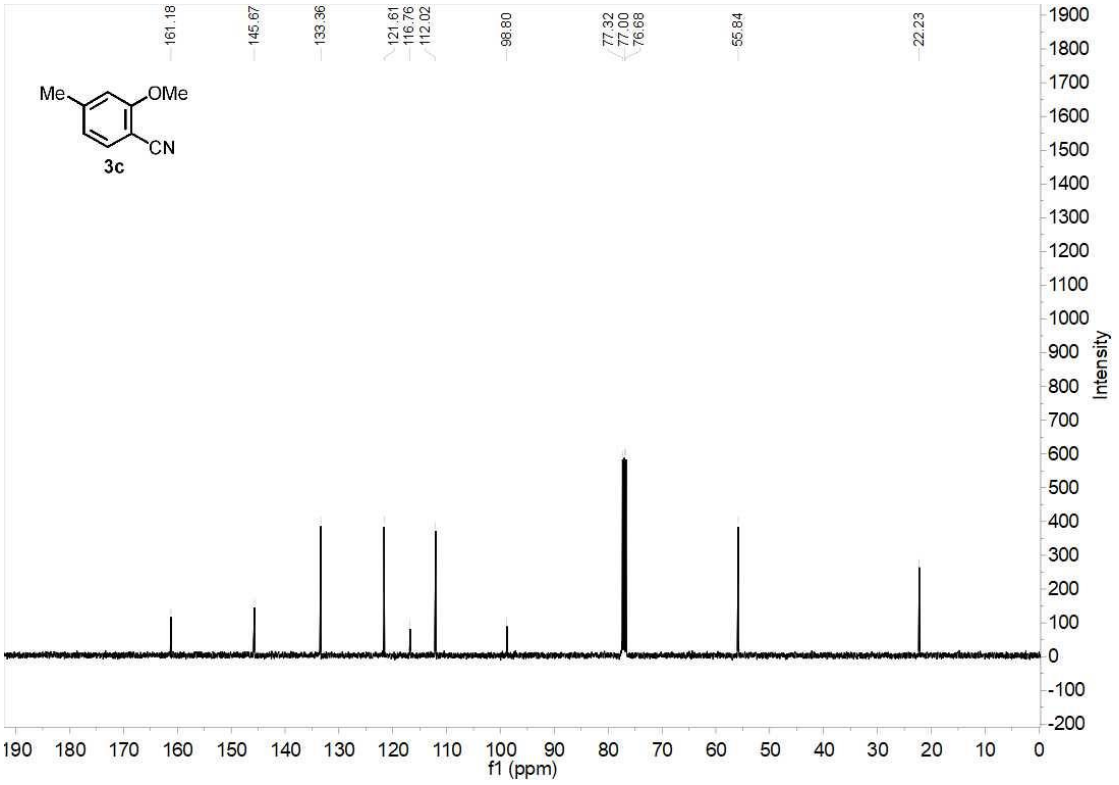
^{13}C NMR spectrum of **3b** (100 MHz, $CDCl_3$)



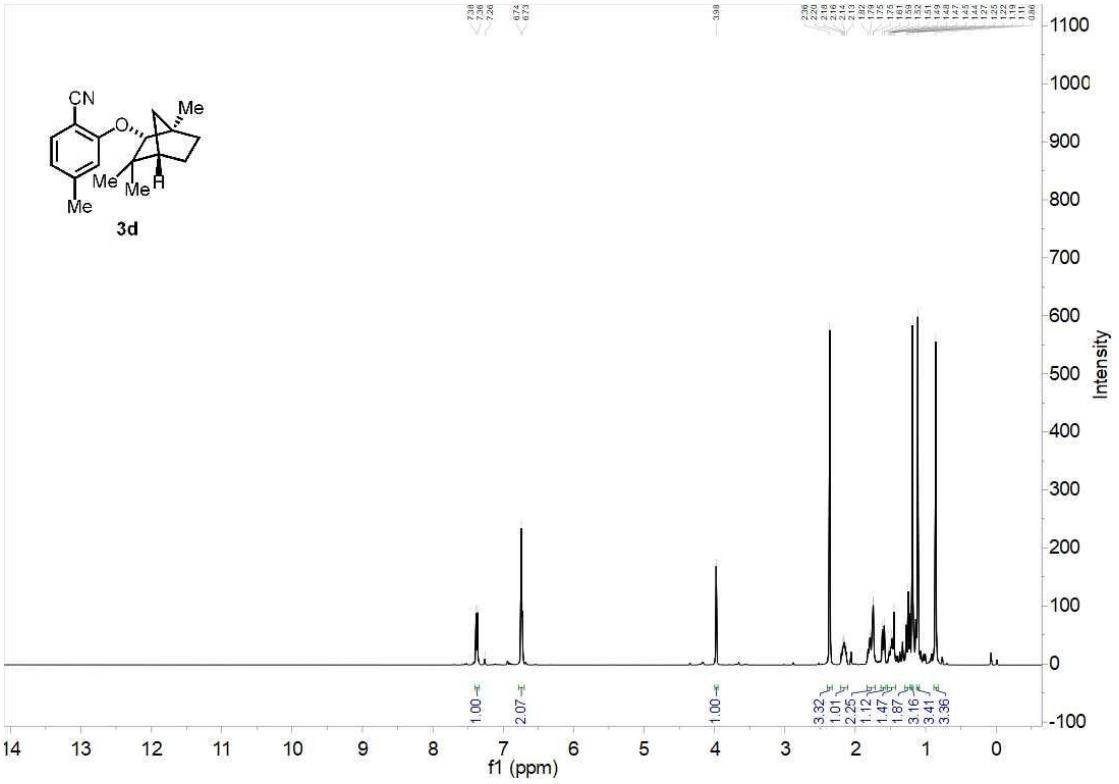
^{1}H NMR spectrum of **3c** (400 MHz, $CDCl_3$)



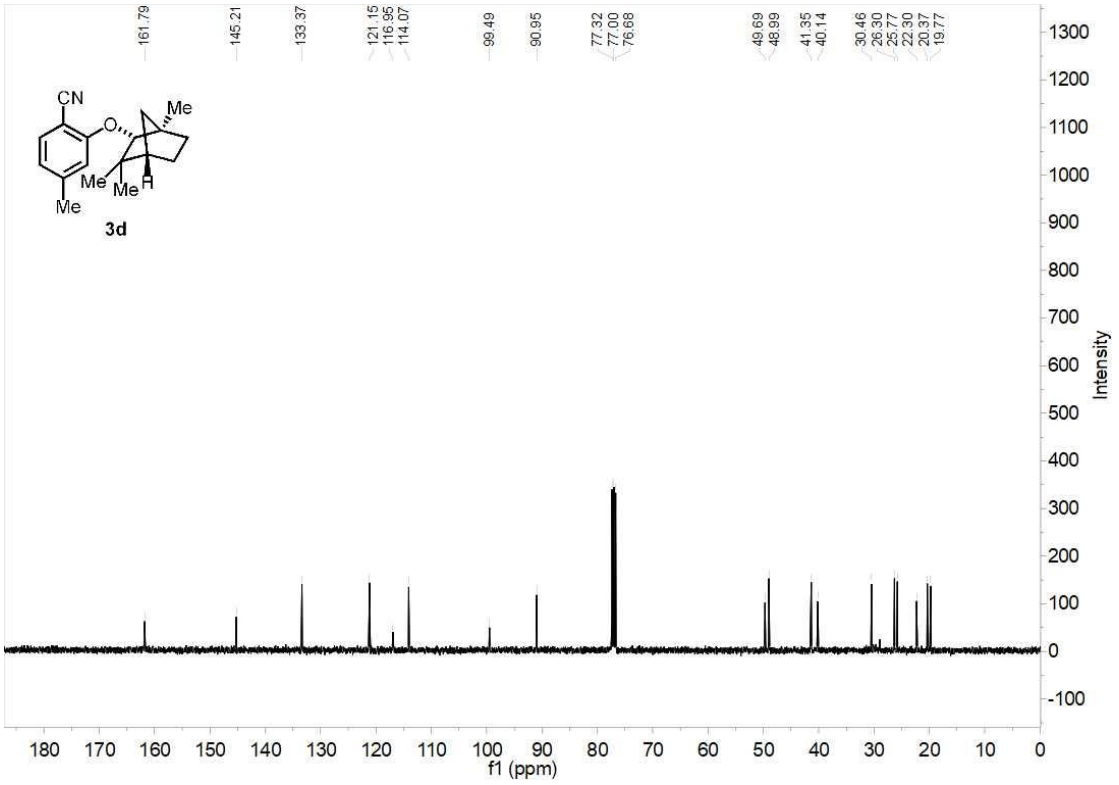
^{13}C NMR spectrum of **3c** (100 MHz, $CDCl_3$)



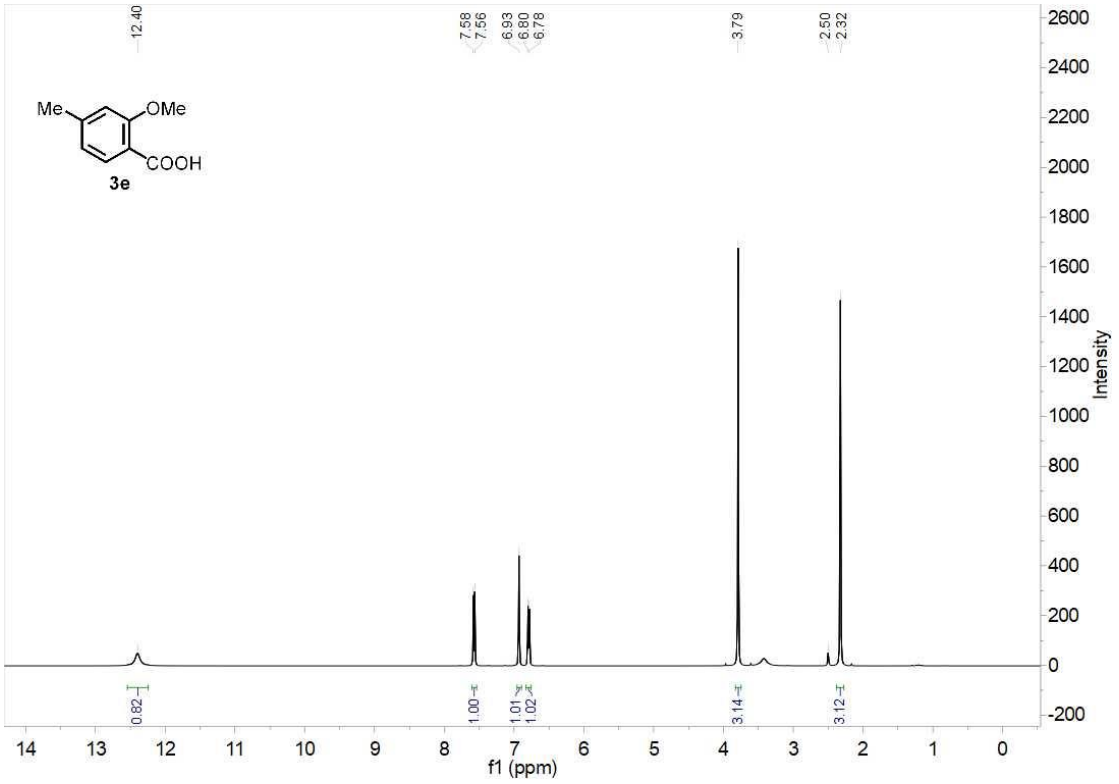
^{1}H NMR spectrum of **3d** (400 MHz, $CDCl_3$)



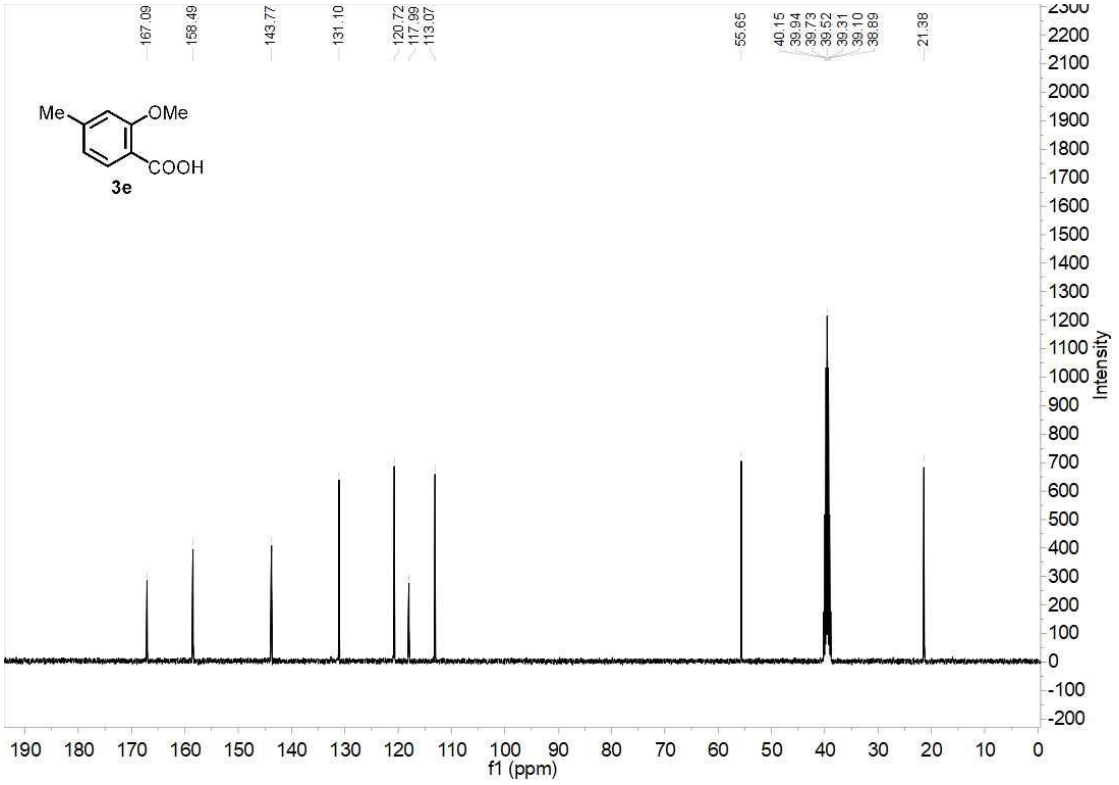
^{13}C NMR spectrum of **3d** (100 MHz, $CDCl_3$)



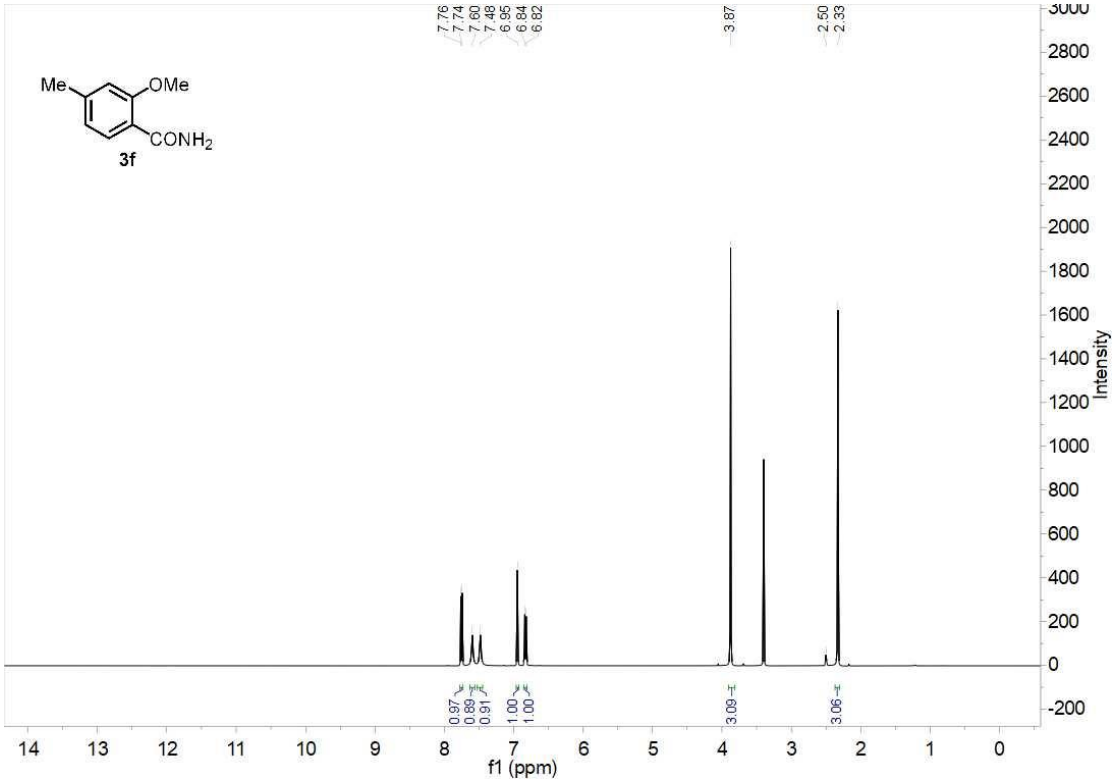
^{1}H NMR spectrum of **3e** (400 MHz, DMSO-d_6)



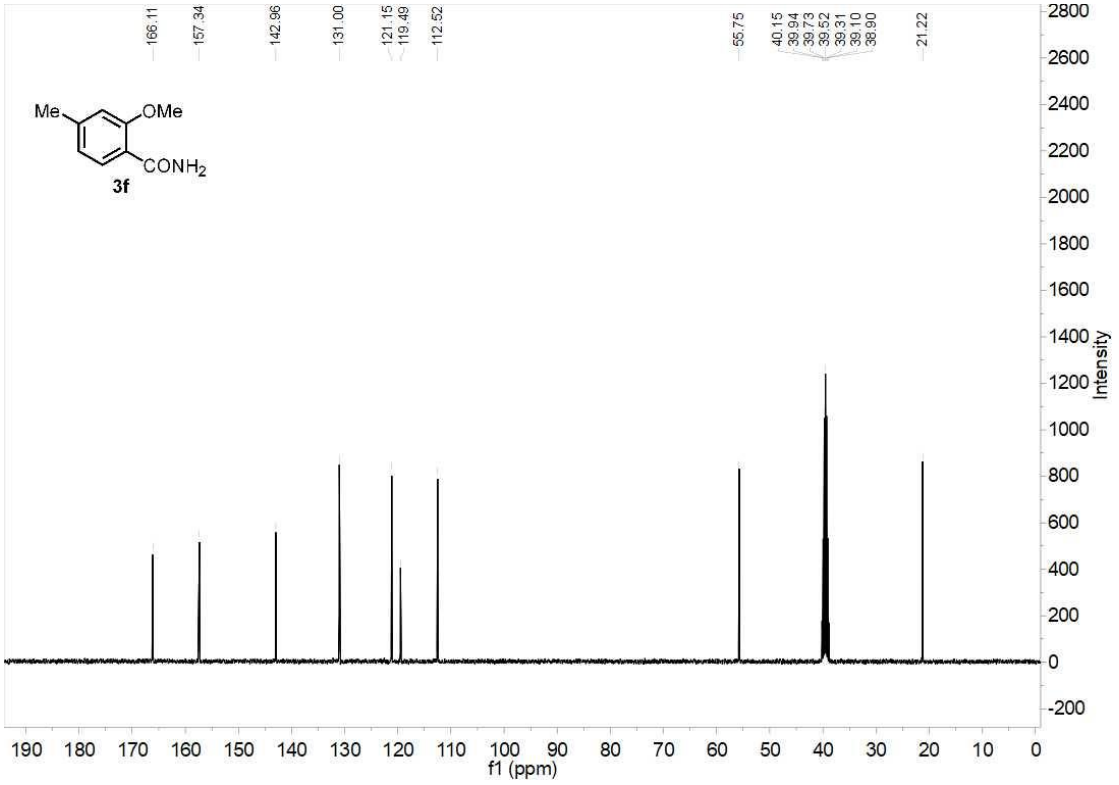
^{13}C NMR spectrum of **3e** (100 MHz, DMSO-d_6)



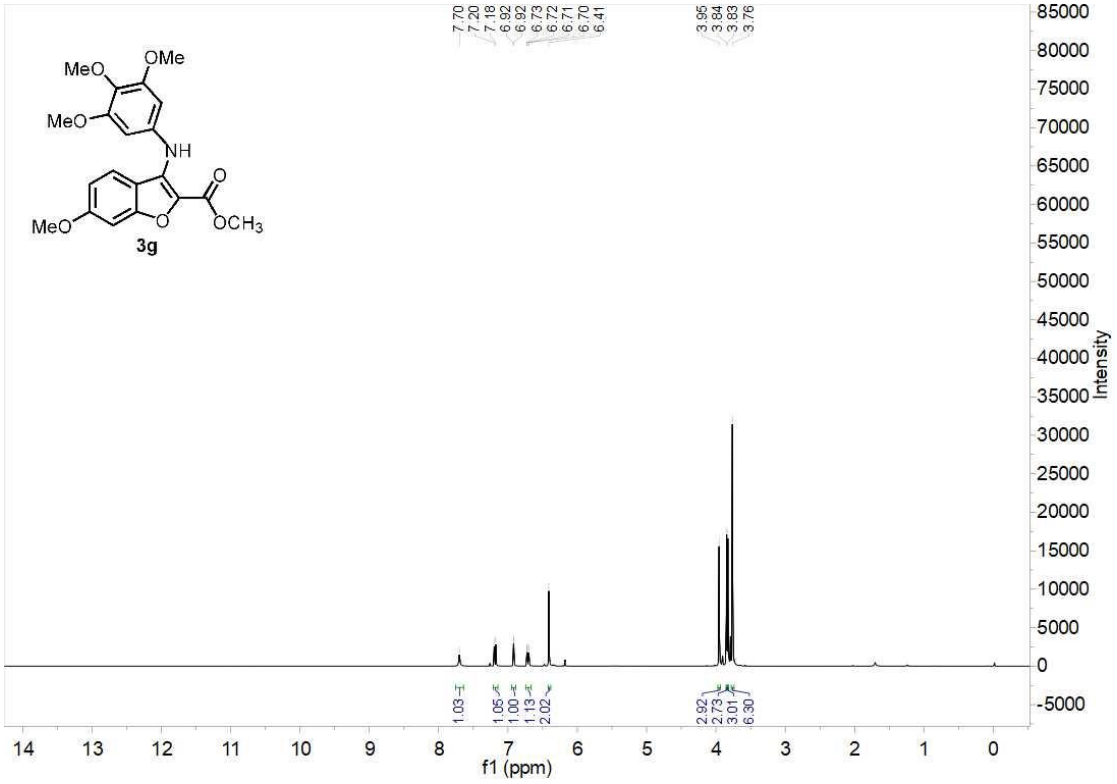
^{1}H NMR spectrum of **3f** (400 MHz, DMSO-d_6)



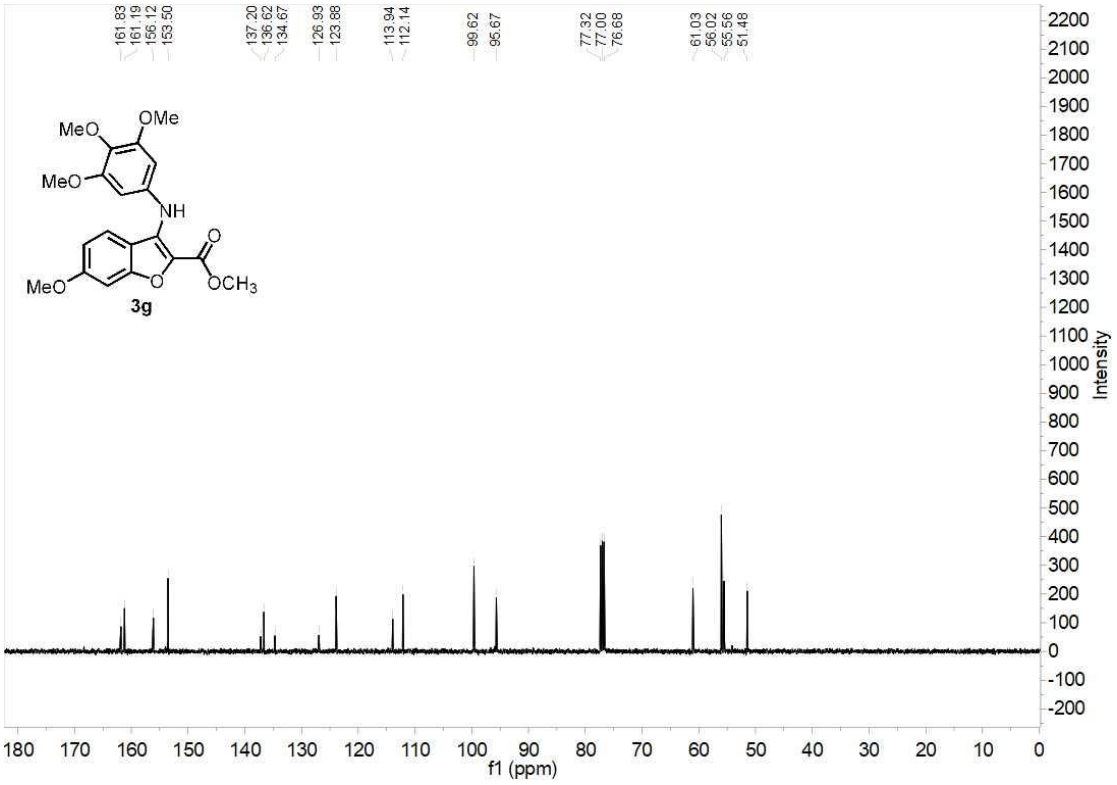
^{13}C NMR spectrum of **3f** (100 MHz, DMSO-d_6)



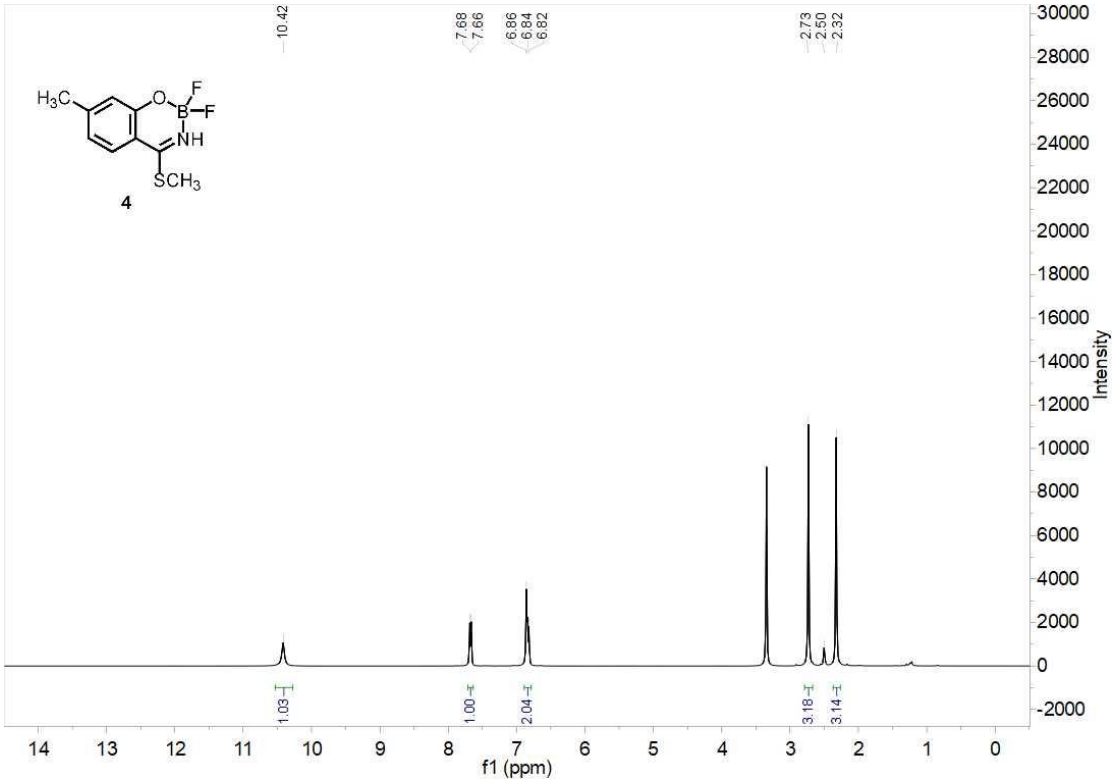
^{1}H NMR spectrum of **3g** (400 MHz, $CDCl_3$)



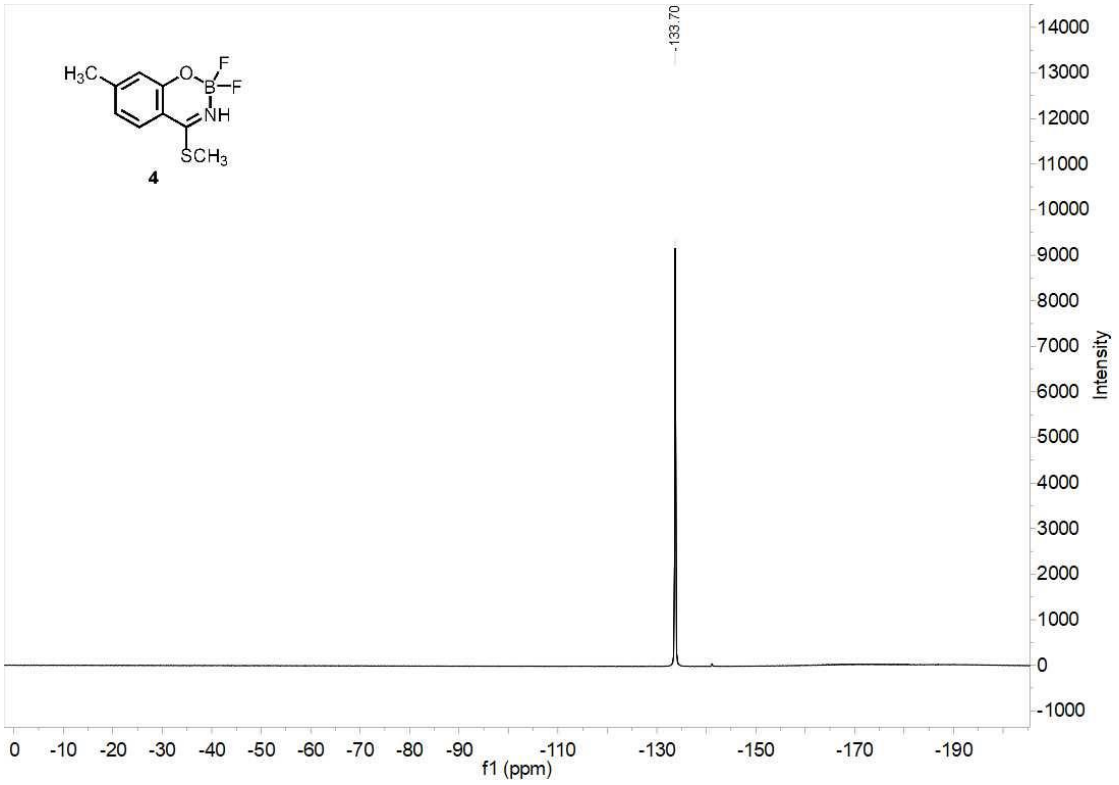
^{13}C NMR spectrum of **3g** (100 MHz, $CDCl_3$)



^{1}H NMR spectrum of **4** (400 MHz, DMSO-d_6)



^{19}F NMR spectrum of **4** (376 MHz, DMSO-d_6)



^{13}C NMR spectrum of **4** (100 MHz, DMSO-d_6)