Supporting information

Synthesis of Valuable Aromatics from Bioderived 5-Hydroxymethylfurfural (HMF) under Mild Conditions

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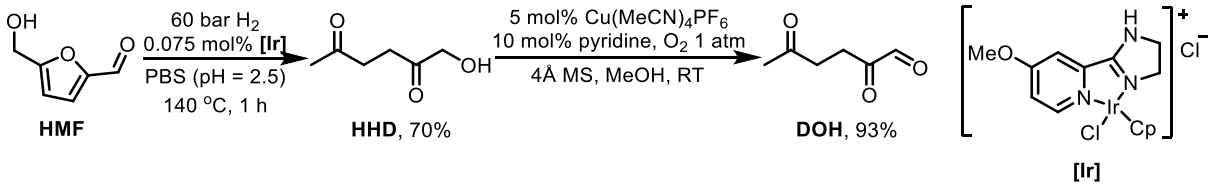
1. General remarks

5-Hydroxymethylfurfural (HMF) was purchased from AVA-Biochem BSL AG and used directly without further purification. All other commercially available reagents were purchased from Sigma-Aldrich, Strem, TCI, and ABCR. Solvents used in reactions were obtained from Acros Organics, or a solvent purification system (MBraun SPS). All solvents used for work-up or column chromatography were purchased from Walter. ^{1}H, ^{2}H and ^{13}C NMR spectra were recorded on a Bruker Fourier 300, a Bruker AV300, or a Bruker AV400 MHz spectrometer. Chemical shifts are given in ppm and related to residual solvent peaks.[1] High resolution mass spectroscopy was performed on an Agilent 6210 Time-of-Flight (SICRIT ionization, 15 kHz, 1600 V) or a Thermo Electron MAT 95-XP (EI, 70 eV).

2. Synthesis of DOH from HMF

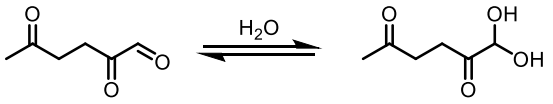


The synthesis followed the reported procedure[2]: To a 300 mL Hastelloy autoclave was added 5-HMF (2.5 g, 20.0 mmol), 100 mL phosphate-buffered saline solution (PBS) (pH = 2.49), Ir catalyst (8.0 mg, 0.075 mol%), and a magnetic stirring bar. The autoclave was flushed with N_2 three times, H_2 twice, and pressurized with 30 bar H_2. The reaction was stirred at 140 °C for 1 hour (temperature achieved after 30 mins). The reaction was allowed to cool down to room temperature and the solvent was removed by evaporation. The crude product was purified through column chromatography (silica gel) using ethyl acetate/cyclohexane (1/1 to 3/1) as eluent to give a yellow solid. Further recrystallization with CH_2Cl_2 and pentane under -20 °C gave the desired HHD (1.8 g, 70%) as yellow needles.

To a 1 L Schlenk flask was added HHD (10.0 mmol, 1.3 g), MS 4Å (powdered, 2 g), and a magnetic stirring bar. The flask was evacuated for 0.5 h and then flushed with O_2 three times. To the flask equipped with an O_2 balloon was added dry MeOH (80 mL), $Cu(CH_3CN)_4PF_6$ (5 mol%, 186 mg), and pyridine (10 mol%, 81µL). The reaction was stirred at room temperature for 100 mins. The reaction mixture was filtered and diluted with 200 ml DCM. Subsequently, this mixture was washed with 20 ml NaEDTA solution (1% in H_2O) followed by 10 ml NaEDTA solution (1% in H_2O, prepared by neutralizing 1g of EDTA in 100 ml H2O with sodium hydroxide). Then the blue-green aqueous solution was counter-extracted using DCM (2 x 50 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Removal of the solvent through evaporation afforded 1.2 g (93%) of a yellow oil.

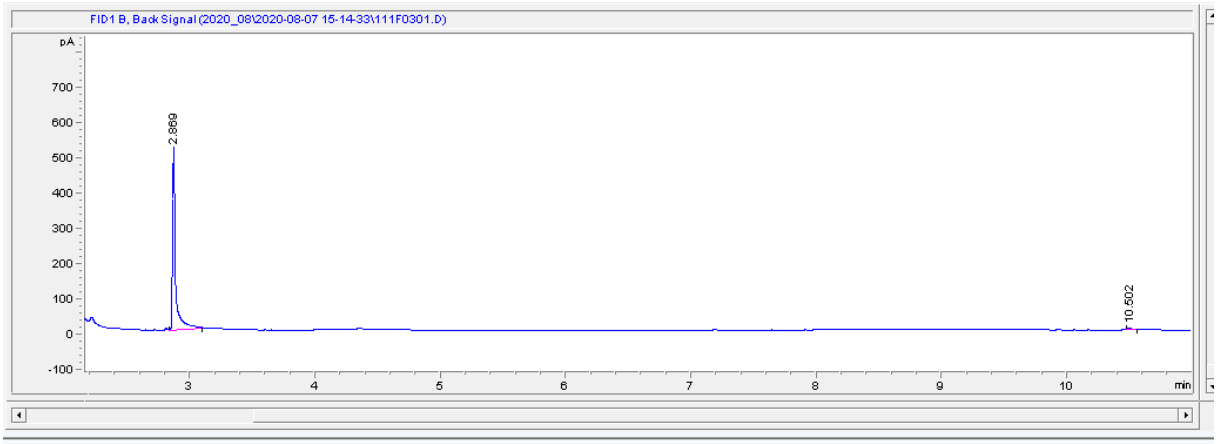
Although GC and TLC both showed high purity of DOH after purification, ^{1}H NMR spectra in $CDCl_3$, CD_2Cl_2, CD_3CN, d_6-DMSO, and d_8-THF all were ambiguous, which is due to the high reactivity of DOH. In d_8-toluene, the solubility of DOH was very poor. Under acidic conditions in the presence of H2O, DOH converted to 2,5-dioxohexane-1,1-diol (shown below), which was confirmed by GC. In

CD_3OD, recognizable NMR spectra were obtained, showing the structure of 2,5-dioxohexanediol. ^1H NMR (300 MHz, CD_3OD): δ (ppm) 4.78 (s, 1H), 3.35 (s, 2H), 2.81-2.87 (m, 2H), 2.72-2.77 (m, 2H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 209.8, 206.9, 98.5, 37.3, 32.1, 29.7.



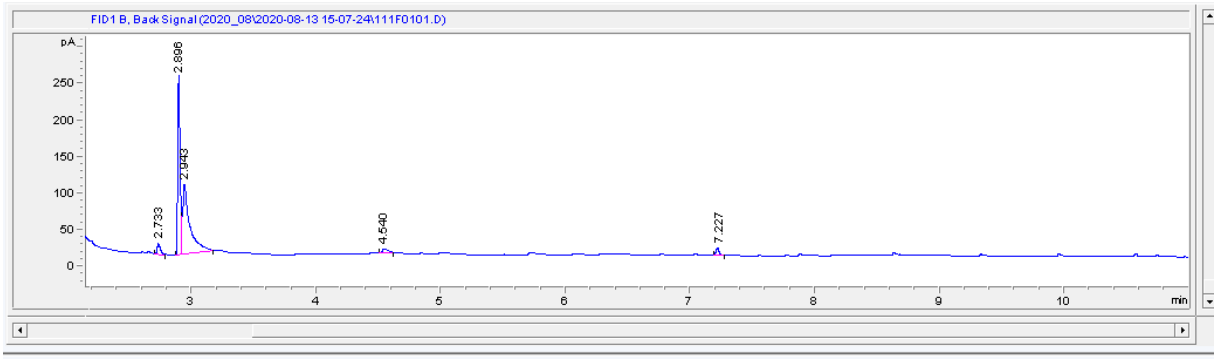
DOH 2.5-dioxohexanediol

GC of DOH



#	Time	Area	Height	Width	Area%	Symmetry
1	2.869	865.8	512.2	0.0247	98.736	0.493
2	10.502	11.1	3.9	0.0398	1.264	0.382

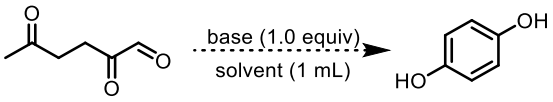
GC of DOH in acidic solution



#	Time	Area	Height	Width	Area%	Symmetry
1	2.733	25.4	14	0.0273	3.277	0.602
2	2.896	339.3	241.6	0.0214	43.685	0.655
3	2.943	377.8	94.6	0.0526	48.651	0.276
4	4.54	17.5	5.7	0.0419	2.251	0.326
5	7.227	16.6	10	0.0253	2.135	0.743

3. Base-catalyzed intramolecular aldol condensation of DOH

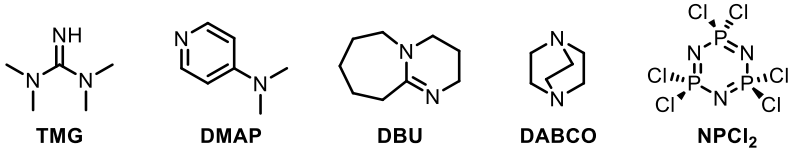
Table S1: Reactions of DOH under basic conditions



DOH, 0.2 mmol — Hydroquinone

Entry	Bases	Solvent	*T*	Time	Results[a]
1[b]	KOH	THF	RT	1.5 h	No desired product
2[b]	$NaHCO_3$			3 h	No reaction
3[b]	TMG				No reaction
4[b]	Cs_2CO_3				Levulinic acid
5[b]	DMAP			0.6 h	Complex mixture, no desired product
6[b]	Na_2CO_3			2 h	Complex mixture, no desired product
7[b]	TBD			3.5 h	No desired product
8	DMAP	Toluene	- 40 °C to RT	6 h	Complex mixture, no desired product
9		THF		7 h	
10		*i*-PrOH			
11		DCM			
12		MeOH			Levulinic acid
13	DBU	Toluene		6 h	Complex mixture, no desired product
14		THF			
15		*i*-PrOH			
16		DCM			
17		MeOH		7 h	Levulinic acid
18	DABCO	Toluene		6 h	Complex mixture, no desired product
19		THF			
20		*i*-PrOH			
21		DCM			No reaction
22		MeOH		7 h	Partly converted to levulinic acid
23	DABCO	*i*-PrOH	40 °C	2 h	No desired product
24	DMAP		40 °C		Complex mixture, no desired product
25	$(NPCl_2)_3$		80 °C		
26	*t*-BuOK		40 °C		
27	DABCO	*t*-BuOH	40 °C		
28	DMAP		40 °C		
29	$(NPCl_2)_3$		80 °C		No reaction
30	*t*-BuOK		40 °C		Complex mixture, no desired product
31[c]	K_2CO_3	MeOH	RT	0.5 h	Mixture of levulinic acid and methyl levulinate
32[c]	Cs_2CO_3				
33[c]	KOH				

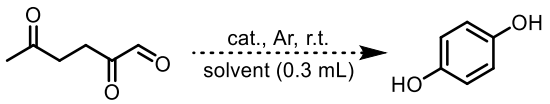
Reaction conditions: DOH (0.2 mmol), Base (1.0 equiv), solvent (1 mL), under Ar. [a]Analyzed by GC, NMR, TLC, and/or GC-MS. [b]Under air. [c]Base (16.0 equiv), MeOH (60 mL).



General procedure for Table S1: to a 4 mL vial was added DOH (0.2 mmol, 25 mg) and a magnetic stirring bar. The vial was sealed with a septum and flushed with Ar. Solvent (1 mL) and base (1.0 equiv) were added under Ar. The reaction was stirred at the specified temperature for the specified time.

4. Proline and derivatives catalyzed intramolecular aldol condensation of DOH

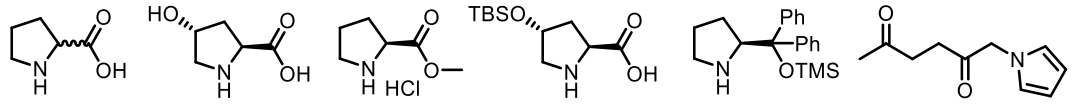
Table S2: Reactions of DOH catalyzed by proline and various derivatives



DOH, 0.3 mmol — Hydroquinone

Entry	Conditions	Solvent	Time	Results[a]
1	DL-proline (25 mol%)	*i*-PrOH	48 h	
2		DMSO		
3		DMF		
4		H_2O		
5	DL-proline (25 mol%)	DCM		
6	HOAc (0.5 equiv)	*i*-PrOH		
7		MeOH		
8		THF	19 h	No reaction
9	DL-proline (25 mol%)	DCM		
10	TFA (0.5 equiv)	*i*-PrOH		
11		MeOH		
12		THF		
13	DL-proline (25 mol%)	DCM		
14	PTSA ·H_2O (0.5 equiv)	*i*-PrOH		
15		MeOH		
16		THF		
17	**S1** (20 mol%)	DMSO	19 h	No reaction
18		DMF		No desired product, complex mixture, **S5** was observed.
19		H_2O	9 h	
20	**S1** (50 mol%)	H_2O		
21[b]	L-proline (50 mol%)	DMF/H_2O (1/1)	4 h	No reaction
22[b]	**S1** (50 mol%)			No desired product, complex mixture, **S5** was observed.
23[b]	**S2** (50 mol%)			
24	**S1** (50 mol%), 2.5 h; then PTSA (1.0 equiv), 2.5 h	H_2O	2.5 h	No reaction
25	**S1** (50 mol%), 2.5 h; then pyridine (1.0 equiv), 2.5h	H_2O		No desired product, complex mixture, **S5** was observed.
26	**S3** (50 mol%)	MeOH	17 h	
27		DCM		No desired product, complex mixture, **S5** was isolated (yield: 4%).
28	**S3** (50 mol%), pyridine	H_2O	2 h	No desired product, complex mixture, **S5** was observed.
29	(1.0 equiv)	DCM		
30	**S3** (1.0 equiv), pyridine	H_2O		
31	(1.0 equiv)	DCM		
32	**Pyrrolidine (25 mol%)**	**THF**	**19 h**	**4-pyrrolidylphenol was detected.**
33	**Pyrrolidine (1.0 equiv)**	**THF**	**2 h**	**1,4-dipyrrolidinylbenzene, 4-pyrrolidylphenol**
34	**S4** (50 mol%)	DCM	2 h	No desired product
35[c]	L-proline (2.0 equiv)	DMF	2 h	No desired product
36[c]	**S1** (2.0 equiv)			No desired product, complex mixture, **S5** was observed.
37[c]	**S3** (2.0 equiv)			

Reaction conditions: DOH (0.3 mmol), solvent (300 μL), Cat., base or acid, under Ar, stirred at room temperature. [a]Analyzed by GC, ^{1}H NMR, TLC, and GC-MS. [b]DMF (300 μL), H_2O (300 μL). [c]80 °C.

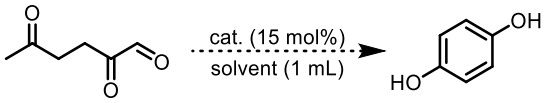


General procedure for Table S2: to a 4 mL vial was added DOH (0.3 mmol, 38 mg) and a magnetic stirring bar. The vial was sealed with a septum and flushed with Ar. Solvent (300 µL), cat., and additives were added under Ar. The reaction was stirred at room temperature (unless mentioned otherwise).

1-(1*H*-pyrrol-1-yl)hexane-2,5-dione (S5). To a 50 mL Schlenk flask under Ar was added DOH (5.0 mmol, 640 mg), a magnetic stirring bar, DCM (5 mL), and (*R*)-4-TBSO-*L*-proline **S3** (0.5 eq, 614 mg). After stirring at room temperature for 90 mins, the reaction solvent was removed through evaporation. Column chromatography (SiO_2, DCM) afforded **S5** as yellowish oil (12 mg, 4%). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.64 (t, J = 2.1 Hz, 2H), 6.09 (t, J = 2.1 Hz, 2H), 4.80 (s, 2H), 2.73-2.77 (m, 2H), 2.55-2.59 (m, 2H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 209.8, 207.5, 122.9, 109.5, 37.7, 33.5, 29.6. MS-EI (*m/z*): 179 (32%), 136 (4%), 99 (44%), 80 (100%), 71 (8%), 53 (20%), 43 (25%).

5. Thiourea catalyzed intramolecular aldol condensation of DOH

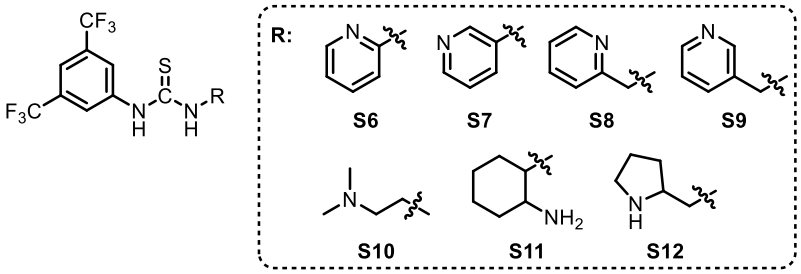
Table S3: Reactions of DOH catalyzed by thiourea catalysts



Entry	Cat.	Solvents	*T*	*t*	Results[a]
1	**S6**	DCM	RT	overnight	No reaction
2		THF	RT, 24 h; then at 40 °C, 24 h		
3		MeOH	RT	24 h	Full conversion, no desired product.
4		DCM			No reaction
5	**S7**	THF	RT, 24 h; then at 40 °C, 24 h		
6		MeOH	RT	24 h	No reaction
7		DCM			
8	**S8**	THF	RT, 24 h; then at 40 °C, 24 h		
9		MeOH	RT	24 h	Full conversion, no desired product.
10		DCM			
11	**S9**	THF	RT, 24 h; then at 40 °C, 24 h		No reaction
12		MeOH	RT	24 h	
13		DCM			Full conversion, no desired product.
14	**S10**	THF	RT, 24 h; then at 40 °C, 24 h		
15		MeOH	RT	24 h	
16		DCM			Full conversion, no desired product.
17	**S11**	THF			
18		MeOH	RT, 24 h; then at 40 °C, 24 h		

19		DCM			
20	**S12**	THF	RT	72 h	No reaction
21	**S10**	MeCN	RT	24 h	Full conversion, no desired product.
22			reflux	5 h	

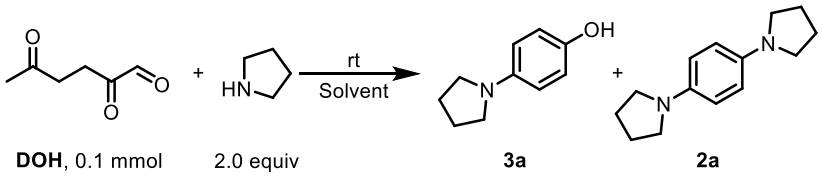
Reaction conditions: DOH (0.2 mmol), Cat. (15 mol%), solvent (1 mL). [a]Analyzed by GC, ^{1}H NMR, TLC, and/or GC-MS.



General procedure for Table S3: to a 4 mL vial was added DOH (0.2 mmol, 25 mg), cat. (15 mol%), a magnetic stirring bar, and solvent (1 mL). The vial was sealed with a cap and the reaction was stirred at the specified temperature for the specified time.

6. Condition optimization for the formation of 1,4-dipyrrolidinylbenzene (2a) and 4-pyrrolidinylphenol (3a)

Table S4. Solvent screening for 3a and 2a

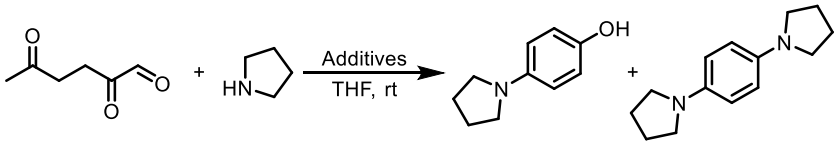


Entry	Solvent	3a (%)	2a (%)	Total (%)[a]
1	**THF**	**2**	**18**	**20**
2	Dioxane	2	18	20
3	Toluene	2	15	17
4[b]	Toluene	0	2	2
5	Et_2O	2	13	15
6	MTBE	1	9	10
7	H_2O	0	0	0
8	Acetone	0	0	0
9	DMF	9	8	17
10	DMSO	5	11	16
11	$CDCl_3$	2	3	5
12	Pyridine	1	17	18

Reaction conditions: DOH (0.1 mmol), pyrrolidine (2.0 equiv), solvent (0.5 mL), rt, overnight. [a]Yield determined by GC using dodecane as internal standard. [b]Toluene (5 mL).

General procedure for Table S4: to a 4 mL pressure tube was added DOH (0.1 mmol, 13 mg), solvent, a magnetic stirring bar, and pyrrolidine (2.0 equiv, 16 µL). The pressure tube was sealed and stirred at room temperature overnight. Then, dodecane was added as internal standard for GC measurement.

Table S5. Optimization of additives and concentration for 3a and 2a



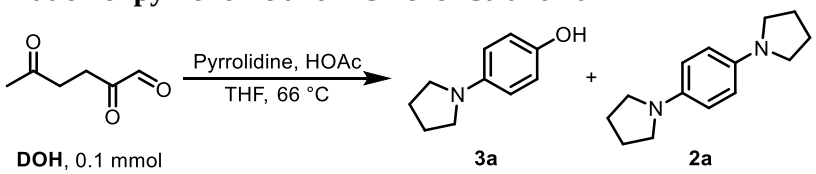
DOH, 0.1 mmol 3a 2a

Entry	Pyrrolidine (equiv)	Additives	THF	3a (%)	2a (%)	Total (%)[a]
1	2.0	-	0.5 mL	2	18	20
2[b]	2.0	-	0.5 mL	7	9	16
3	2.0	-	2 mL	3	14	17
4	2.0	-	5 mL	1	0	1
5	2.0	-	0.1 mL	2	9	11
6	2.0	-	0.2 mL	2	13	15
7	1.0	-	0.5 mL	3	5	8
8	4.0	-	0.5 mL	0	3	3
9	3.0	-	0.5 mL	0	4	4
10	2.0	HCl (aq.)	0.5 mL	1	0	1
11	2.0	TFA	0.5 mL	6	2	8
12	2.0	HOAc	0.5 mL	4	11	15
13	2.0	PTSA·H_2O	0.5 mL	4	1	5
14	2.0	pyridine	0.5 mL	1	15	16
15	2.0	Na_2CO_3	0.5 mL	2	14	16
16	2.0	DMAP	0.5 mL	1	10	11
17[b]	**2.0**	**TFA**	**0.5 mL**	**15**	**4**	**19**
18[b]	**2.0**	**HOAc**	**0.5 mL**	**9**	**21**	**30**
19[c]	2.0	TFA	0.5 mL	9	2	11
20[c]	2.0	HOAc	0.5 mL	12	11	23

Reaction conditions: DOH (0.1 mmol), pyrrolidine (2.0 equiv), THF, additives (1.0 equiv), rt, overnight. [a]Yield determined by GC using dodecane as internal standard. [b]66 °C. [c]1,4-dioxane, 101 °C.

General procedure for Table S5: to a 4 mL pressure tube was added DOH (0.1 mmol, 13 mg), THF, a magnetic stirring bar, additive (1.0 equiv), and pyrrolidine (2.0 equiv). The pressure tube was sealed and stirred at the specified temperature overnight. Then, dodecane was added as internal standard for GC measurement.

Table S6. Optimization of pyrrolidine and HOAc for 3a and 2a



DOH, 0.1 mmol 3a 2a

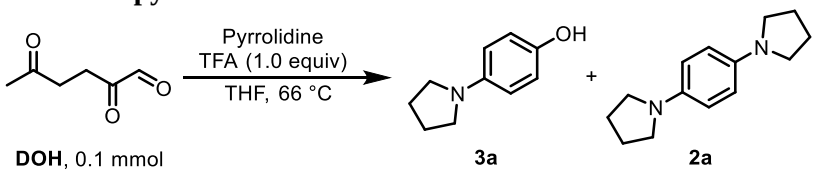
Entry	Pyrrolidine (equiv)	HOAc (equiv)	3a (%)	2a (%)	Total (%)[a]
1	1.5	1.0	10	7	17
2	2.0	1.0	13	7	20
3	2.25	1.0	7	14	21
4	3.0	1.0	7	21	28
5	4.0	1.0	8	31	39
6	5.0	1.0	8	32	40
7	6.0	1.0	8	33	41
8	8.0	1.0	6	31	37

9	10.0	1.0	5	33	38
10	12.0	1.0	4	30	34
11	6.0	0.5	4	28	32
12	6.0	2.0	10	37	47
13	6.0	4.0	18	36	54
14	6.0	6.0	19	19	38
15	6.0	8.0	21	10	31
16[b]	6.0	2.0	14	35	49

Reaction conditions: 1st step) pyrrolidine, THF (0.2 mL), HOAc, rt, 5 mins; 2nd step) DOH (0.1 mmol), THF (0.3 mL), 66 °C, overnight. [a]Yield determined by GC using dodecane as internal standard. [b]1,4-dioxane as solvent instead of THF.

General procedure for Table S6: to a 4 mL vial was added pyrrolidine, THF (0.2 mL), and HOAc. After stirring at room temperature for 5 mins, the mixture was injected to the solution of DOH (0.1 mmol, 13 mg) in THF (0.3 mL) at 66 °C. The reaction was stirred at 66 °C overnight. After cooling down to room temperature, dodecane was added as internal standard for GC measurement.

Table S7. Optimization of pyrrolidine and TFA for 3a and 2a



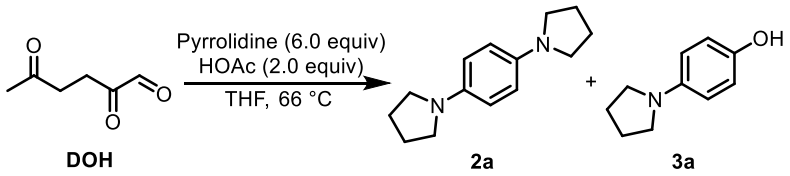
Entry	Pyrrolidine (equiv)	TFA (equiv)	3a (%)	2a (%)	Total (%)[a]
1	1.0	1.0	6	1	7
2	2.0	1.0	9	2	11
3	3.0	1.0	25	6	31
4	4.0	1.0	32	10	42
5	6.0	1.0	41	25	66
6	8.0	1.0	18	23	41
7	10.0	1.0	16	26	42
8	12.0	1.0	13	23	36
11[b]	4.0	1.0	36	5	41
12[b]	6.0	1.0	61	11	72
13	2.0	2.0	6	1	7
14	4.0	2.0	20	5	25
15	6.0	2.0	31	13	44
16	8.0	2.0	29	22	51
17	10.0	2.0	24	19	43
18	12.0	2.0	12	25	37

Reaction conditions: 1st step) pyrrolidine, THF (0.2 mL), TFA, rt, 5 mins; 2nd step) DOH (0.1 mmol), THF (0.3 mL), 66 °C, overnight. [a]Yield determined by GC using dodecane as internal standard. [b]1,4-dioxane, 101 °C.

General procedure for Table S7: to a 4 mL vial was added pyrrolidine, THF (0.2 mL), and TFA. After stirring at room temperature for 5 mins, the mixture was injected to the solution of DOH (0.1 mmol, 13 mg) in THF (0.3 mL) at 66 °C. The reaction was stirred at 66 °C overnight. After cooling down to room temperature, dodecane was added as internal standard for GC measurement.

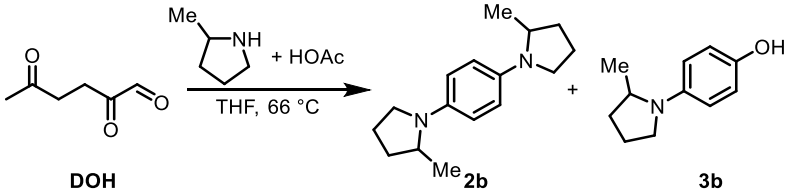
7. General procedures for the reactions of DOH and Amines

7.1. Reactions of DOH and amines catalyzed by HOAc



1,4-Dipyrrolidinylbenzene (2a). To a 4 mL vial was added pyrrolidine (6.0 equiv., 480 µL), a magnetic stirring bar, THF (2 mL), and HOAc (2.0 equiv., 120 µL). After stirring at room temperature for 5 mins, the mixture was added to the solution of DOH in THF (3 mL) in a 35 mL pressure tube at 66 °C. The reaction was stirred at 66 °C overnight. After cooling down to room temperature, the solvent was evaporated. Column chromatography (SiO_2, EA/cyclohexane = 2/23) afforded the desired **2a** as a white solid in 42% yield (90 mg). ^{1}H NMR (300 MHz, d_8-toluene): δ (ppm) 6.64 (brs, 4H), 3.02 (brs, 8H), 1.66-1.62 (m, 8H). HRMS (ESI) *m/z* calcd. for $C_{14}H_{21}N_2^+$ $[M+H]^+$: 217.1705, found: 217.1702. Because of the facile oxidation of **2a** to the radical cation analogous to the formation of Würster's salt,[3] its NMR spectroscopy cannot be properly conducted. To the solution of **2a** in acetone was added two drops of HCl (aq. 37%). **2a**·2HCl was obtained as needle crystal after evaporation. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.54 (brs, 4H), 3.71-3.66 (m, 8H), 2.28-2.23 (m, 8H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 141.0, 121.7, 57.0, 25.1. ^{1}H NMR (300 MHz, d_8-toluene): δ (ppm) 6.64 (brs, 4H), 3.02 (brs, 8H), 1.66-1.62 (m, 8H). HRMS (ESI) *m/z* calcd. for $C_{14}H_{21}N_2^+$ $[M+H]^+$: 217.1705, found: 217.1702. Because of the facile oxidation of **2a** to the radical cation analogous to the formation of Würster's salt,[3] its NMR spectroscopy cannot be properly conducted. To the solution of **2a** in acetone was added two drops of HCl (aq. 37%). **2a**·2HCl was obtained as needle crystal after evaporation. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.54 (brs, 4H), 3.71-3.66 (m, 8H), 2.28-2.23 (m, 8H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 141.0, 121.7, 57.0, 25.1.

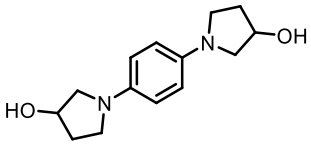
4-Pyrrolidinylphenol (3a). From the above-mentioned reaction mixture, column chromatography (SiO_2, EA/cyclohexane = 3/17) furthermore afforded the desired **3a** as yellow crystals (18 mg, yield: 11%). ^{1}H NMR (300 MHz, d_6-DMSO) δ (ppm) 8.42 (s, 1H), 6.63-6.60 (m, 2H), 6.41-6.38 (m, 2H), 3.12-3.08 (m, 4H), 1.93-1.88 (m, 4H). ^{13}C NMR (75 MHz, d_6-DMSO) δ (ppm) 147.9, 141.8, 115.8, 112.8, 48.0, 24.8. HRMS (ESI) *m/z* calculated for $C_{10}H_{14}NO^+$ $[M+H]^+$: 164.1075, Found 164.1075.



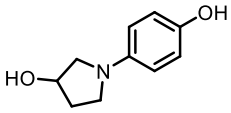
4-Bis(2-methylpyrrolidinyl)benzene (2b). To a 35 mL pressure tube was added 2-methylpyrrolidine (4.0 equiv., 1632 µL), a magnetic stirring bar, THF (8 mL), and HOAc (2.0 equiv., 480 µL). After stirring at room temperature for 5 mins, the mixture was added to the solution of DOH (4.0 mmol, 532 mg) in THF (12 mL) in a 35 mL pressure tube at 66 °C. The reaction was stirred at 66 °C overnight.

After cooling down to room temperature, the solvent was evaporated. Column chromatography (SiO_2, EA/cyclohexane = 2/23) afforded the desired 4-bis(2-methylpyrrolidinyl)benzene as a yellow solid (mixture of diastereomers, 80 mg, yield: 8%). ^{1}H NMR (300 MHz, d_6-benzene) δ (ppm) 6.74-6.73 (s, 4H), 3.71-3.62 (m, 2H), 3.32-3.26 (m, 2H), 3.03-2.95 (m, 2H), 1.84-1.70 (m, 4H), 1.64-1.54 (m, 2H), 1.40-1.34 (m, 2H), 1.11-1.08 (d, 6H). ^{13}C NMR (300 MHz, d_6-benzene) δ (ppm) 140.0, 114.4, 54.3, 49.5, 33.5, 23.6, 20.0. HRMS (ESI) *m/z* calculated for $C_{16}H_{25}N_2^+$ $[M+H]^+$: 245.2018, Found 245.2014.

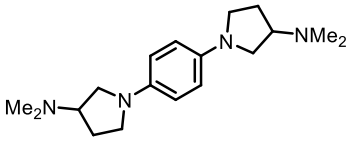
4-(2-Methylpyrrolidinyl)phenol (3b). From the above reaction mixture, column chromatography (SiO_2, EA/cyclohexane = 3/17) furthermore afforded desired 4-(2-methylpyrrolidinyl)phenol as orange crystals (53 mg, yield: 7%). ^{1}H NMR (300 MHz, d_6-DMSO) δ (ppm) 8.40 (s, 1H), 6.63-6.59 (m, 2H), 6.39 (d, J = 8.8 Hz, 2H), 3.74-3.64 (m, 1H), 3.30-3.24 (m, 1H), 3.01-2.93 (m, 1H), 2.02-1.85 (m, 3H), 1.63-1.58 (m, 1H), 1.05 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, d_6-DMSO) δ (ppm) 148.2, 141.2, 116.3, 113.3, 53.9, 49.0, 33.2, 23.3, 19.8. HRMS (ESI) *m/z* calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1232, Found 178.1236.



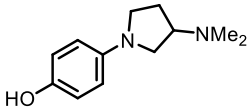
1,1'-(1,4-Phenylene)bis(pyrrolidin-3-ol) (2c). From reaction of DOH (0.5 mmol, 64 mg) and (*R*)-3-pyrroldinol (**1c**, 6.0 equiv, 240 µL) in 1,4-dioxane (2.5 mL) at 101 °C overnight, 40 mg (32%) of white crystal **2c** was obtained after column chromatography (SiO_2, EA). To the solution of **2c** in acetone was added two drops of HCl (aq. 37%). **2c**·2HCl was obtained after evaporation. ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 7.20 (s, 4H), 4.69 – 4.60 (m, 2H), 3.79 – 3.68 (m, 4H), 3.67 – 3.58 (m, 2H), 3.48 – 3.41 (m, 2H), 2.40 – 2.25 (m, 2H), 2.19 – 2.10 (m, 2H). ^{13}C NMR (75 MHz, d_6-DMSO) δ (ppm) 138.8, 117.3, 69.2, 60.7, 51.7, 34.0. HRMS (ESI) *m/z* calculated for $C_{14}H_{21}N_2O_2^+$ $[M+H]^+$: 249.1603, Found 249.1606.



1-(4-hydroxyphenyl)pyrrolidin-3-ol (3c). From the same reaction for the preparation of **2c** from DOH (0.5 mmol, 64 mg) and (*R*)-3-pyrroldinol (**1c**, 6.0 equiv, 240 µL) in 1,4-dioxane (2.5 mL) at 101 °C overnight, 30 mg (34%) of orange crystal **3c** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/1). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.79 – 6.63 (m, 2H), 6.55 – 6.39 (m, 2H), 4.52 – 4.45 (m, 1H), 3.49 – 3.32 (m, 2H), 3.26 – 3.14 (m, 1H), 3.14 – 3.03 (m, 1H), 2.22 – 2.08 (m, 1H), 2.01 – 1.90 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 149.2, 143.9, 116.9, 114.2, 71.9, 47.6, 35.0. HRMS (ESI) *m/z* calculated for $C_{10}H_{14}NO_2^+$ $[M+H]^+$: 180.1024, Found 180.1026.

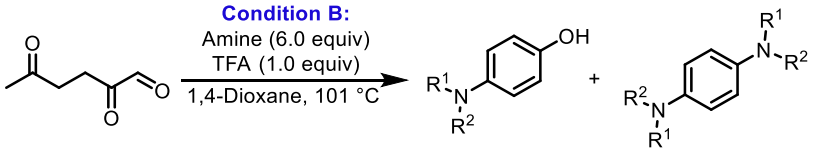


1,1'-(1,4-Phenylene)bis(N,N-dimethylpyrrolidin-3-amine) (2d). From the reaction of DOH (0.5 mmol, 64 mg) and *N*,*N*-dimethylpyrrolidin-3-amine (**1d**, 6.0 equiv, 381 µL) in 1,4-dioxane (2.5 mL) at 101 °C overnight, 120 mg (57%) of brown oil **2d**·HOAc was obtained after column chromatography (reverse-SiO_2, methanol). ^{1}H NMR (300 MHz, d_8-toluene) δ (ppm) 10.43 (s, 2H), 6.56 (s, 4H), 3.25 – 3.14 (m, 4H), 3.14 – 3.06 (m, 2H), 3.04 – 2.94 (m, 2H), 2.68 – 2.54 (m, 2H), 2.04 (s, 12H), 1.89 (s, 6H), 1.81 – 1.70 (m, 4H). ^{13}C NMR (75 MHz, d_8-toluene) δ (ppm) 174.2, 140.8, 113.7, 65.4, 52.3, 47.8, 42.8, 29.1, 21.5. HRMS (ESI) *m/z* calculated for $C_{18}H_{31}N_4^+$ $[M+H]^+$: 303.2549, Found 303.2549.

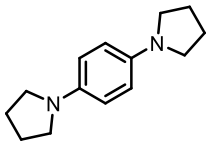


4-(3-(dimethylamino)pyrrolidin-1-yl)phenol (3d). From the same reaction for the preparation of **2d** from DOH (0.5 mmol, 64 mg) and *N*,*N*-dimethylpyrrolidin-3-amine (**1d**, 6.0 equiv, 381 µL) in 1,4-dioxane (2.5 mL) at 101 °C overnight, 11 mg (11%) of orange crystal **3d** was obtained after column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1/19). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.76 – 6.63 (m, 2H), 6.57 – 6.42 (m, 2H), 3.41 (dd, J = 8.8, 7.2 Hz, 1H), 3.35 – 3.28 (m, 1H), 3.27 – 3.17 (m, 1H), 3.12-3.04 (m, 1H), 3.02 – 2.87 (m, 1H), 2.33 (s, 6H), 2.27 – 2.16 (m, 1H), 1.98 – 1.80 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 149.5, 143.6, 116.9, 114.3, 66.8, 53.8, 48.8, 44.1, 30.6. HRMS (ESI) *m/z* calculated for $C_{12}H_{19}N_2O^+$ $[M+H]^+$: 207.1497, Found 207.1501.

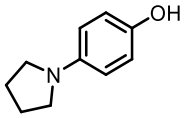
7.2. Reactions of DOH and amines catalyzed by TFA



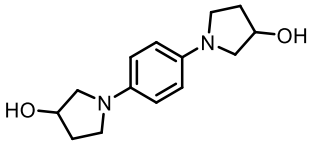
General procedures: To a 35 mL pressure tube was added DOH (1.0 mmol, 128 mg), a magnetic stirring bar, and 1,4-dioxane (5 mL). To the solution was added amine (6.0 equiv) and TFA (1.0 equiv, 80 µL). The reaction was stirred at 101 °C overnight. After cooling down to room temperature and removal of solvent by evaporation, the reaction mixture was purified by column chromatography (SiO_2).



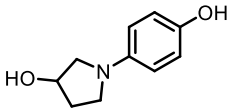
1,4-Dipyrrolidinylbenzene (2a). From reaction of DOH and pyrrolidine (**1a**, 6.0 equiv, 480 µL), 35 mg (13%) of white solid **2a** was obtained after column chromatography (SiO_2, EA/cyclohexane = 2/23).



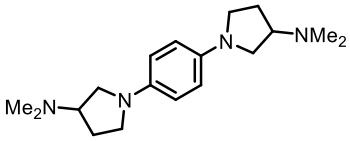
4-Pyrrolidinylphenol (3a). From the same reaction for the preparation of **2a** from DOH and pyrrolidine (**1a**, 6.0 equiv, 480 µL), 95 mg (58%) of yellow crystal **3a** was obtained after furthermore column chromatography (SiO_2, EA/cyclohexane = 3/17).



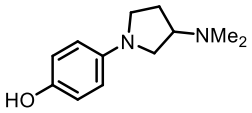
1,1'-(1,4-Phenylene)bis(pyrrolidin-3-ol) (2c). From reaction of DOH and (*R*)-3-pyrroldinol (**1c**, 6.0 equiv, 480 µL), 43 mg (13%) of white crystal **2c** was obtained after column chromatography (SiO_2, EA).



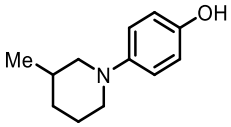
1-(4-hydroxyphenyl)pyrrolidin-3-ol (3c). From the same reaction for the preparation of **2c** from DOH and (*R*)-3-pyrroldinol (**1c**, 6.0 equiv, 480 µL), 105 mg (59%) of orange crystal **3c** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/1).



1,1'-(1,4-Phenylene)bis(N,N-dimethylpyrrolidin-3-amine) (2d). From the reaction of DOH (0.5 mmol, 64 mg) and *N*,*N*-dimethylpyrrolidin-3-amine (**1d**, 6.0 equiv, 381 µL), 50 mg (33%) of brown oil **2d** was obtained after column chromatography (reverse-SiO_2, methanol).

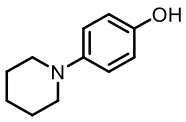


4-(3-(dimethylamino)pyrrolidin-1-yl)phenol (3d). From the same reaction for the preparation of **2d** from DOH (0.5 mmol, 64 mg) and *N*,*N*-dimethylpyrrolidin-3-amine (**1d**, 6.0 equiv, 381 µL), 57 mg (55%) of orange crystal **3d** was obtained after column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1/19).

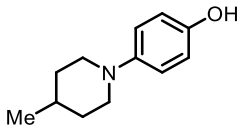


4-(3-Methylpiperidin-1-yl)phenol (3e). From the reaction of DOH and 3-methylpiperidine (**1e**, 6.0 equiv, 710 µL), 85 mg (45%) of white solid **3e** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/4). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.92 – 6.85 (m, 2H), 6.74 – 6.67 (m, 2H), 3.37 – 3.26 (m, 2H), 2.54 – 2.41 (m, 1H), 2.17 (dd, J = 11.7, 10.3 Hz, 1H), 1.86 – 1.65 (m, 4H), 1.06 – 0.95 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 153.1, 146.7, 121.0, 116.6,

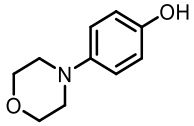
61.8, 53.8, 33.8, 32.4, 26.6, 19.9. HRMS (ESI) *m/z* calculated for $C_{12}H_{18}NO^+$ $[M+H]^+$: 192.1388, Found 192.1390.



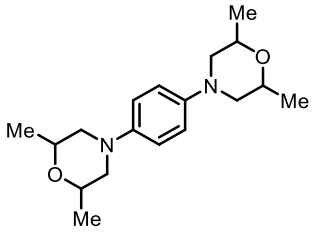
4-(Piperidin-1-yl)phenol (3f). From the reaction of DOH and piperidine (**1f**, 6.0 equiv, 533 µL), 37 mg (21%) of white crystal **3f** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.87 (d, J = 9.1 Hz, 2H), 6.71 (d, J = 9.1 Hz, 2H), 3.01 (t, J = 5.4 Hz, 4H), 1.78 – 1.67 (m, 4H), 1.60 – 1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 150.0, 146.6, 119.4, 116.0, 52.8, 26.1, 24.2. HRMS (ESI) *m/z* calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1232, Found 178.1233.



4-(4-Methylpiperidin-1-yl)phenol (3g). From the reaction of DOH and 4-methylpiperidine (**1g**, 6.0 equiv, 710 µL), 32 mg (21%) of yellow oil **3g** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/4). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.99 – 6.81 (m, 2H), 6.82 – 6.60 (m, 2H), 3.41 – 3.32 (m, 2H), 2.66 – 2.48 (m, 2H), 1.83 – 1.68 (m, 2H), 1.46 – 1.25 (m, 3H), 0.98 (d, J = 6.2 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 153.1, 146.6, 121.0, 116.6, 53.8, 35.4, 31.7, 22.2. HRMS (ESI) *m/z* calculated for $C_{12}H_{18}NO^+$ $[M+H]^+$: 192.1388, Found 192.1389.

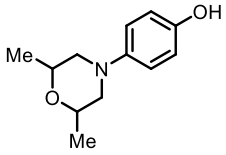


4-Morpholinophenol (3h). From the reaction of DOH and morpholine (**1h**, 6.0 equiv, 517 µL), 84 mg (21%) of white crystal **3h** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/3). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.89 – 6.80 (m, 2H), 6.76 – 6.69 (m, 2H), 3.82 – 3.76 (m, 4H), 2.99 – 2.93 (m, 4H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 152.9, 146.0, 119.6, 116.7, 68.01 52.6. HRMS (ESI) *m/z* calculated for $C_{10}H_{14}NO_2^+$ $[M+H]^+$: 180.1024, Found 180.1022.

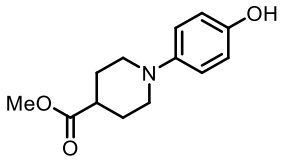


1,4-bis(2,6-dimethylmorpholino)benzene (2i). From the reaction of DOH and morpholine (**1i**, mixture of *cis* and *trans* isomers, 6.0 equiv, 740 µL), 29 mg (10%) of yellow solid **2i** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/9). ^{1}H NMR (300 MHz, C_6D_6, isomer **2ia**) δ (ppm) 6.87 (s, 4H), 3.80 – 3.68 (m, 4H), 3.22 – 3.14 (m, 4H), 2.30 (dd, J = 11.9, 10.2 Hz, 4H), 1.13 (d, J = 6.3 Hz, 12H). ^{13}C NMR (75 MHz, C_6D_6, isomer **2ia**) δ (ppm) 145.9, 118.0, 72.0, 56.7, 19.3. ^{1}H NMR (300 MHz, C_6D_6, isomer **2ib**) δ (ppm) δ 6.90 – 6.79 (m, 4H), 4.08 – 3.95 (m, 2H), 3.79 – 3.66 (m, 2H), 3.17 (ddd,

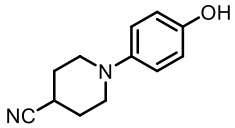
J = 10.8, 2.4, 1.1 Hz, 2H), 2.95 (ddd, *J* = 11.4, 3.3, 1.0 Hz, 2H), 2.61 (ddd, *J* = 11.6, 5.9, 1.1 Hz, 2H), 2.34 – 2.23 (m, 2H), 1.23 (d, *J* = 6.4 Hz, 6H), 1.12 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (75 MHz, C_6D_6, isomer **2ib**) δ (ppm) 146.6, 146.0, 118.3, 118.1, 71.9, 66.6, 56.7, 56.2, 19.3, 18.3. HRMS (ESI) *m/z* calculated for $C_{18}H_{29}N_2O_2^+$ $[M+H]^+$: 305.2229, Found 305.2232.



4-(2,6-Dimethylmorpholino)phenol (3i). From the reaction for the preparation of **2i** from DOH and morpholine (**1i**, mixture of *cis* and *trans* isomers, 6.0 equiv, 740 µL), 96 mg (47%, 21 mg and 76 mg respectively) of yellow oil **3i** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/9). ^{1}H NMR (300 MHz, CD_3OD, isomer **3ia**) δ (ppm) 6.87 – 6.77 (m, 2H), 6.77 – 6.64 (m, 2H), 4.17 – 4.04 (m, 2H), 3.02 (ddd, *J* = 11.6, 3.3, 1.1 Hz, 2H), 2.71 (ddd, *J* = 11.6, 5.9, 1.1 Hz, 2H), 1.29 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (75 MHz, CD_3OD, isomer **3ia**) δ (ppm) 152.6, 146.6, 119.8, 116.7, 68.1, 57.6, 18.2. HRMS (ESI) *m/z* calculated for $C_{12}H_{18}NO_2^+$ $[M+H]^+$: 208.1337, Found 208.1333. ^{1}H NMR (300 MHz, CD_3OD, isomer **3ib**) δ (ppm) 6.88 – 6.80 (m, 2H), 6.75 – 6.68 (m, 2H), 3.85 – 3.70 (m, 2H), 3.30 – 3.24 (m, 2H), 2.31 – 2.18 (m, 2H), 1.19 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (75 MHz, CD_3OD, isomer **3ib**) 152.9, 145.7, 119.8, 116.7, 73.1, 58.2, 19.2. HRMS (ESI) *m/z* calculated for $C_{12}H_{18}NO_2^+$ $[M+H]^+$: 208.1337, Found 208.1335.

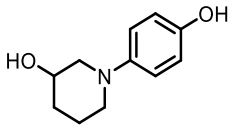


Methyl 1-(4-hydroxyphenyl)piperidine-4-carboxylate (3j). From the reaction of DOH and methyl piperidine-4-carboxylate (**1j**, 6.0 equiv, 810 µL), 81 mg (35%) of white crystal **3j** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/4). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.96 – 6.82 (m, 2H), 6.80 – 6.61 (m, 2H), 3.69 (s, 3H), 3.42 – 3.33 (m, 2H), 2.65 (ddd, *J* = 12.2, 11.1, 2.8 Hz, 2H), 2.44 (tt, *J* = 11.3, 4.1 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.92 – 1.73 (m, 2H).^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 177.1, 153.2, 146.4, 121.0, 116.6, 52.8, 52.2, 41.8, 29.5. HRMS (ESI) *m/z* calculated for $C_{13}H_{18}NO_3^+$ $[M+H]^+$: 236.1286, Found 236.1292.

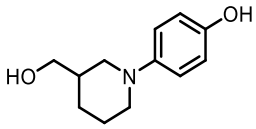


1-(4-Hydroxyphenyl)piperidine-4-carbonitrile (3k). From the reaction of DOH and piperidine-4-carbonitrile (**1k**, 6.0 equiv, 670 µL), 98 mg (35%) of white crystal **3k** was obtained after column chromatography (SiO_2, EA/cyclohexane = 7/13). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.91 – 6.82 (m, 2H), 6.75 – 6.67 (m, 2H), 3.26 – 3.14 (m, 2H), 2.94 – 2.80 (m, 3H), 2.11 – 2.00 (m, 2H), 1.98 – 1.85 (m,

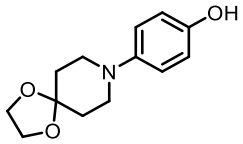
2H).[13]C NMR (75 MHz, CD_3OD) δ (ppm) 153.3, 146.2, 122.9, 121.0, 116.6, 51.4, 30.0, 26.9. HRMS (ESI) *m/z* calculated for $C_{12}H_{15}N_2O^+$ $[M+H]^+$: 203.1184, Found 203.1188.



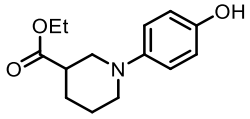
1-(4-Hydroxyphenyl)piperidin-3-ol (3l). From the reaction of DOH and piperidin-3-ol (**1l**, 6.0 equiv, 610 mg), 82 mg (42%) of white crystal **3l** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/1). [1]H NMR (300 MHz, CD_3OD) δ (ppm) 6.91 – 6.84 (m, 2H), 6.74 – 6.66 (m, 2H), 3.85 – 3.73 (m, 1H), 3.40 – 3.33 (m, 1H), 3.23 – 3.14 (m, 1H), 2.60 (ddd, *J* = 11.7, 10.5, 3.1 Hz, 1H), 2.50 (dd, *J* = 11.1, 8.8 Hz, 1H), 2.02 – 1.91 (m, 1H), 1.91 – 1.80 (m, 1H), 1.75 – 1.59 (m, 1H), 1.41 – 1.30 (m, 1H). [13]C NMR (75 MHz, CD_3OD) δ (ppm) 153.0, 146.4, 121.0, 116.6, 68.1, 60.6, 53.3, 33.7, 24.4. HRMS (ESI) *m/z* calculated for $C_{11}H_{16}NO_2^+$ $[M+H]^+$: 194.1181, Found 194.1184.



4-(3-(Hydroxymethyl)piperidin-1-yl)phenol (3m). From the reaction of DOH and piperidin-3-ylmethanol (**1m**, 6.0 equiv, 690 mg), 51 mg (25%) of yellowish solid **3m** was obtained after column chromatography (SiO_2, EA/cyclohexane = 3/2). [1]H NMR (300 MHz, CD_3OD) δ (ppm) 6.95 – 6.86 (m, 2H), 6.76 – 6.67 (m, 2H), 3.55 – 3.38 (m, 3H), 3.38 – 3.31 (m, 1H), 2.61 – 2.49 (m, 1H), 2.32 (dd, *J* = 11.6, 10.3 Hz, 1H), 1.96 – 1.83 (m, 1H), 1.83 – 1.67 (m, 3H), 1.14 – 1.00 (m, 1H). [13]C NMR (75 MHz, CD_3OD) δ (ppm) 153.1, 146.8, 121.0, 116.6, 66.3, 57.3, 54.2, 40.3, 28.1, 26.1. HRMS (ESI) *m/z* calculated for $C_{12}H_{18}NO_2^+$ $[M+H]^+$: 208.1337, Found 208.1337.

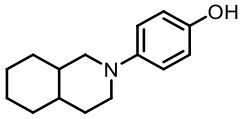


4-(1,4-Dioxa-8-azaspiro[4.5]decan-8-yl)phenol (3n). From the reaction of DOH and 1,4-dioxa-8-azaspiro[4.5]decane (**1n**, 6.0 equiv, 769 µL), 56 mg (24%) of yellow crystal **3n** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/3). [1]H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.90 – 6.81 (m, 2H), 6.76 – 6.63 (m, 2H), 3.98 (s, 4H), 3.16 (t, *J* = 5.7 Hz, 4H), 1.87 (t, *J* = 5.8 Hz, 4H). [13]C NMR (75 MHz, $CDCl_3$) δ (ppm) 150.3, 145.2, 119.6, 116.0, 107.2, 64.4, 49.8, 34.8. HRMS (ESI) *m/z* calculated for $C_{13}H_{18}NO_3^+$ $[M+H]^+$: 236.1286, Found 236.1292.

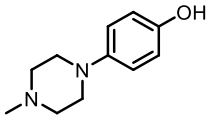


Ethyl 1-(4-hydroxyphenyl)piperidine-3-carboxylate (3o). From the reaction of DOH and ethyl piperidine-3-carboxylate (**1o**, 6.0 equiv, 932 µL), 67 mg (27%) of yellow solid **3o** was obtained after column chromatography (SiO_2, EA/cyclohexane = 1/4). [1]H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.97 – 6.82 (m, 2H), 6.82 – 6.69 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.59 – 3.49 (m, 1H), 3.30 (dd, *J* = 12.2, 3.9

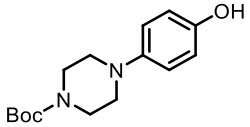
Hz, 1H), 2.90 (dd, *J* = 11.9, 9.8 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.07 – 1.97 (m, 1H), 1.91 – 1.69 (m, 2H), 1.69 – 1.55 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 174.5, 150.6, 145.7, 119.8, 116.0, 60.8, 54.2, 51.9, 41.8, 26.8, 24.5, 14.3. HRMS (ESI) *m/z* calculated for $C_{14}H_{20}NO_3^+$ $[M+H]^+$: 250.1443, Found 250.1447.



4-(Octahydroisoquinolin-2(1H)-yl)phenol (3p). From the reaction of DOH and decahydroisoquinoline (**1p**, 6.0 equiv, 890 µL), 92 mg (25%) of yellow crystal **3p** was obtained after column chromatography (SiO_2, EA/cyclohexane = 3/17). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.93 – 6.85 (m, 2H), 6.75 – 6.65 (m, 2H), 3.42 (ddt, *J* = 11.6, 4.1, 2.3 Hz, 1H), 3.25 (ddd, *J* = 11.3, 3.7, 2.1 Hz, 1H), 2.59 (ddd, *J* = 12.7, 11.7, 2.9 Hz, 1H), 2.24 (t, *J* = 11.2 Hz, 1H), 1.81 – 1.74 (m, 2H), 1.71 – 1.57 (m, 3H), 1.51 – 1.40 (m, 1H), 1.39 – 1.27 (m, 4H), 1.12 – 0.95 (m, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 153.1, 146.54 121.0, 116.6, 60.2, 54.3, 43.1, 42.8, 34.1, 34.1, 31.6, 27.5, 27.2. HRMS (ESI) *m/z* calculated for $C_{15}H_{22}NO^+$ $[M+H]^+$: 232.1701, Found 232.1701.



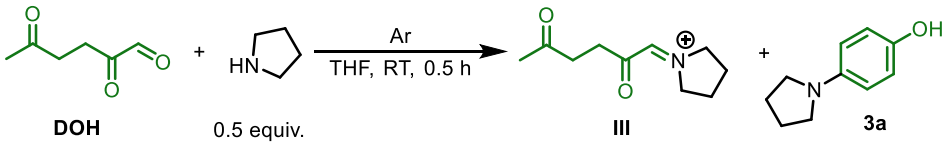
4-(4-Methylpiperazin-1-yl)phenol (3q). From the reaction of DOH (0.5 mmol, 64 mg) and 1-methylpiperazine (**1q**, 6.0 equiv, 335 µL), 35 mg (36%) of yellow crystal **3q** was obtained after column chromatography (SiO_2, MeOH/CH_2Cl_2 = 1/9). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.90 – 6.83 (m, 2H), 6.75 – 6.68 (m, 2H), 3.10 – 3.01 (m, 4H), 2.68 – 2.60 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 153.1, 145.7, 120.1, 116.7, 56.0, 51.8, 46.0. HRMS (ESI) *m/z* calculated for $C_{11}H_{17}N_2O^+$ $[M+H]^+$: 193.1341, Found 193.1346.



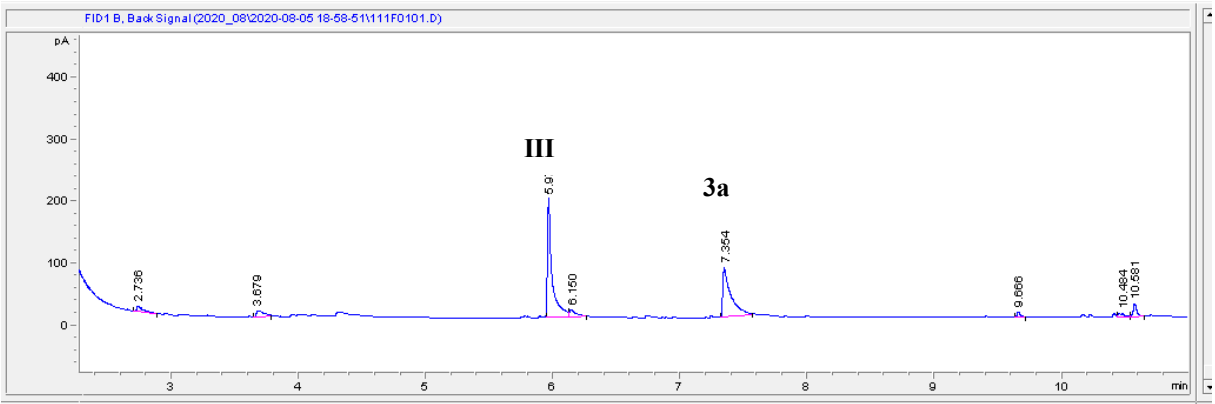
***tert*-Butyl 4-(4-hydroxyphenyl)piperazine-1-carboxylate (3r).** From the reaction of DOH and tert-butyl piperazine-1-carboxylate (**1r**, 6.0 equiv, 1.1 g), 89 mg (32%) of yellow oil **3r** was obtained after column chromatography (SiO_2, EA/cyclohexane = 3/17). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.90 – 6.82 (m, 2H), 6.77 – 6.66 (m, 2H), 3.54 (t, *J* = 5.2 Hz, 4H), 2.97 – 2.91 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 156.4, 153.3, 146.0, 120.6, 116.7, 81.3, 52.6, 28.7. HRMS (ESI) *m/z* calculated for $C_{15}H_{23}N_2O_3^+$ $[M+H]^+$: 279.1709, Found 279.1714.

8. Mechanism studies

8.1. The reaction of DOH and pyrrolidine at room temperature



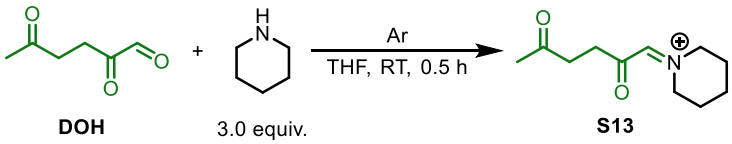
DOH 0.5 equiv. **III** **3a**



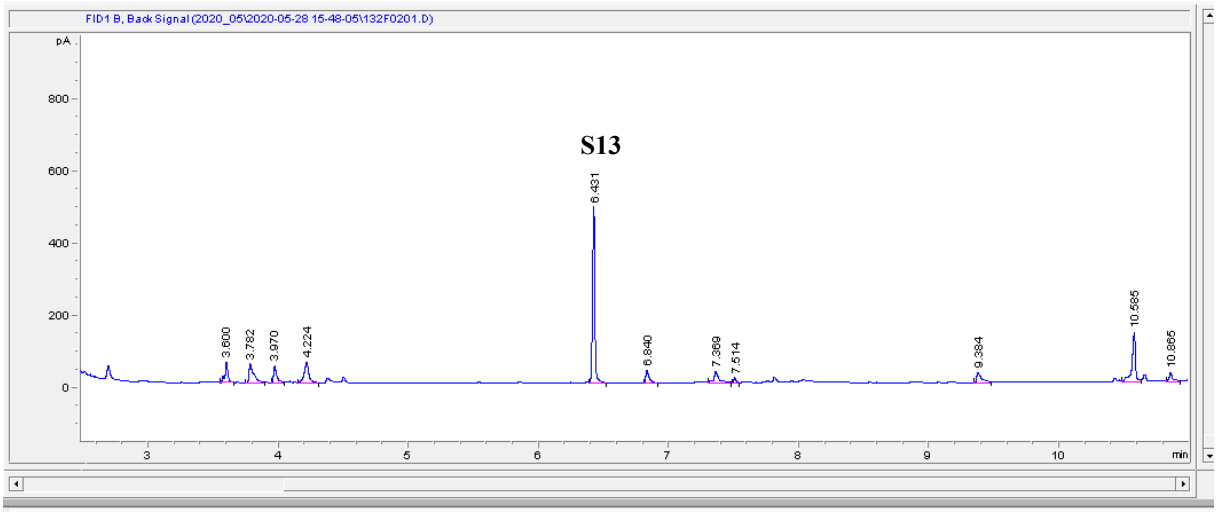
#	Time	Area	Height	Width	Area%	Symmetry
1	2.736	29.4	9	0.0461	2.921	0.208
2	3.679	40.8	9.6	0.0555	4.049	0.241
3	5.973	481.2	190.5	0.0355	47.799	0.31
4	6.15	41.7	10.8	0.0522	4.141	0.359
5	7.354	343.4	79.5	0.0564	34.105	0.211
6	9.666	14.2	7.9	0.027	1.408	0.619
7	10.484	17.4	5.4	0.0424	1.725	1.556
8	10.581	38.8	20.8	0.0278	3.853	0.713

GC-MS for **III**:

8.2. The reaction of DOH and piperidine at room temperature

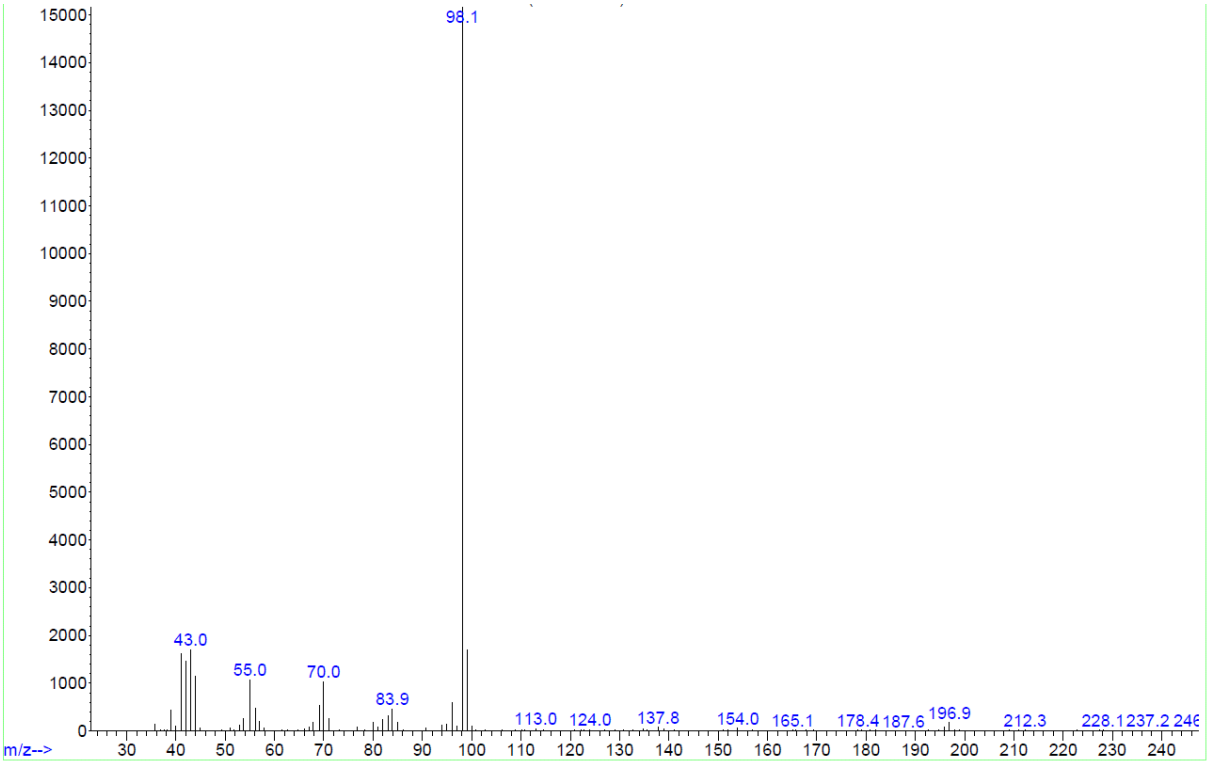


DOH 3.0 equiv. **S13**

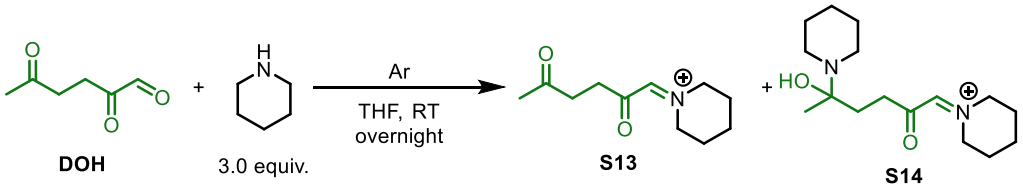


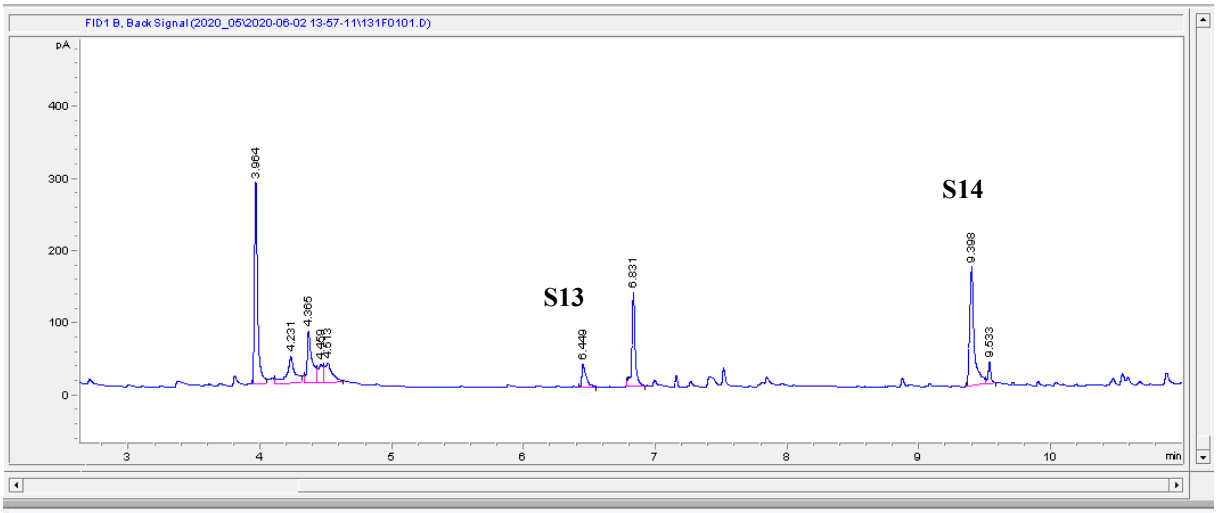
#	Time	Area	Height	Width	Area%	Symmetry
1	3.6	87.1	55	0.0225	5.446	1.189
2	3.782	128.6	51.3	0.0353	8.037	0.32
3	3.97	74.4	44.9	0.0244	4.652	0.501
4	4.224	139.6	56.1	0.037	8.726	1.068
5	6.431	604.1	486	0.0185	37.760	1.065
6	6.84	66.2	34.5	0.0274	4.136	0.46
7	7.369	86.3	31.3	0.0372	5.394	0.635
8	7.514	16.9	13.2	0.019	1.059	0.861
9	9.384	73.7	26.2	0.0397	4.604	0.355
10	10.585	267.5	136.1	0.0289	16.723	1.768
11	10.865	55.4	25.7	0.0302	3.462	0.62

GC-MS for **S13**:



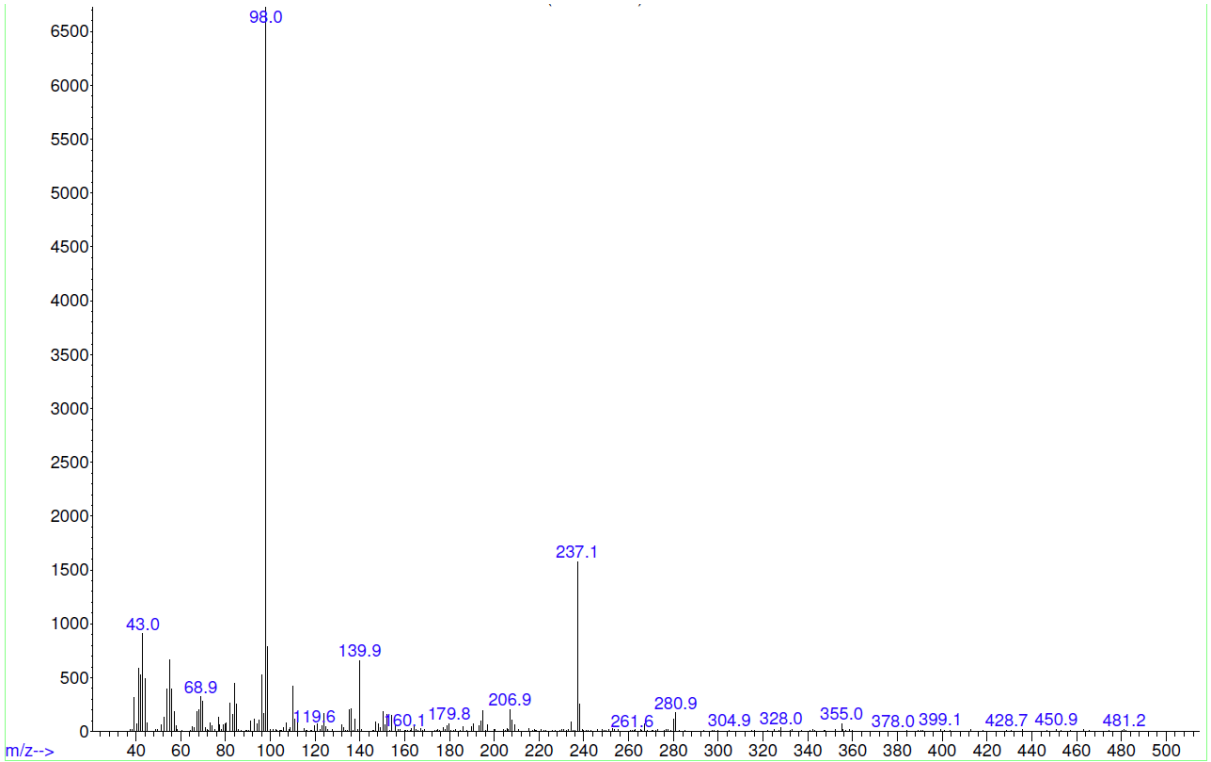
8.3. The reaction of DOH and piperidine at 40°C





#	Time	Area	Height	Width	Area%	Symmetry
1	3.964	465.4	278.4	0.0255	27.185	0.606
2	4.231	161.8	36.2	0.0591	9.452	0.956
3	4.365	190.6	71.1	0.0363	11.133	0.357
4	4.459	60.7	24.5	0.0339	3.543	0.943
5	4.513	103.2	26.8	0.0499	6.031	0.66
6	6.449	71.7	32.2	0.031	4.188	0.377
7	6.831	224.8	129.1	0.0253	13.131	0.825
8	9.398	391.6	163.4	0.035	22.878	0.67
9	9.533	42.1	29.7	0.0205	2.458	0.956

GC-MS for **S14**:



9. Drug molecules containing *N*-phenylpiperizinyl moiety[4-7]

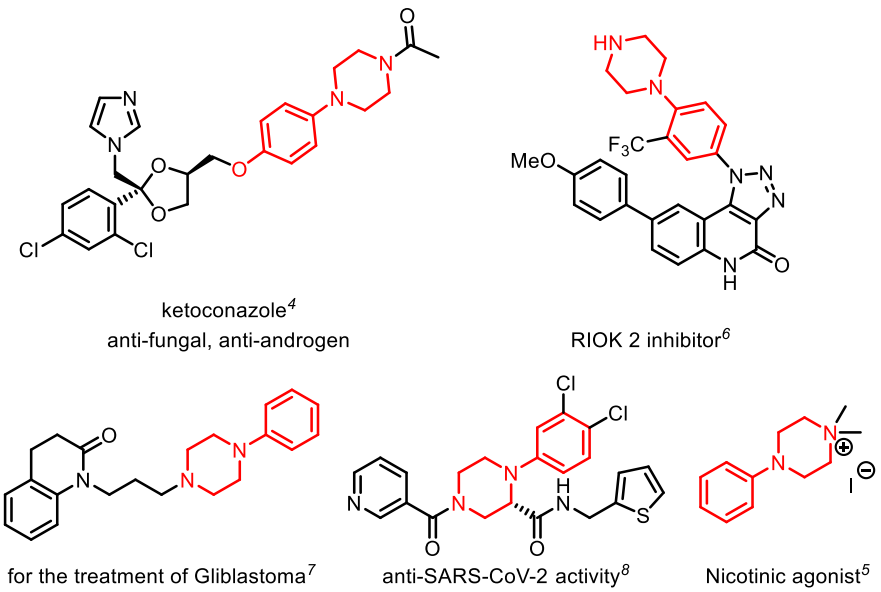
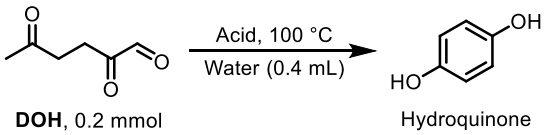


Fig. S1. Drug molecules containing *N*-phenylpiperizinyl moiety.

10. Acid-catalyzed intramolecular Aldol condensation of DOH

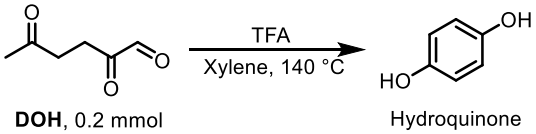
Table S8: Screening of various acids for intramolecular aldol condensation of DOH



Entry	Acid	*t*	Yield[a]
1	$BF_3 \cdot 2H_2O$, 2.0 equiv	5 h	2%
2	$Sc(OTf)_3$, 1.0 equiv	1.5 h	n.d.
3	$Yb(OTf)_3$, 1.0 equiv	1.5 h	n.d.
4	$In(OTf)_3$, 1.0 equiv	1.5 h	n.d.
5	HCOOH, 2.0 equiv	26 h	1%
6	HOAc, 2.0 equiv	1 h	n.d.
7	TFA, 2.0 equiv	26 h	5%
8	HCl, 2.0 equiv	24 h	2%
9[b]	$Sc(OTf)_3$, 10 mol%	19 h	n.d.
10[b]	$Yb(OTf)_3$, 10 mol%	19 h	n.d.
11[b]	$In(OTf)_3$, 10 mol%	19 h	n.d.
12[b]	$Cu(OTf)_2$, 2.0 equiv	19 h	n.d.
13[c]	Amberlyst-15, 50% (w/w)	8 h	n.d.
14[d]	HOTf, 0.2 equiv	22 h	n.d.
15[e]	PTSA, 2.0 equiv	1 h	n.d.

Reaction conditions: DOH (0.2 mmol, 0.5 M), Acid, H_2O (0.4 mL), 100 °C. [a]Yield determined by ^1H NMR using 1,4-dinitrobenzene as reference. [b]DOH (0.2 M). [c]DOH (0.1 M). [d]DOH (0.02 M). [e]Xylene (1.0 mL) instead of H_2O, 140 °C.

Table S9: Effect of the concentration of DOH/TFA for intramolecular aldol condensation of DOH



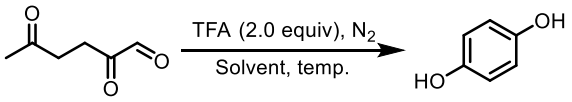
Entry	Conc. (DOH)	Conc. (TFA)	*t* (h)	Yield (%)[a]
1	0.2 M	0.4 M	0.5	14 (12)[b]
2	0.2 M	0.4 M	1	19
3	0.1 M	0.2 M	0.5	17
4	0.02 M	0.2 M	1	20
5	0.01 M	0.2 M	1	32
6	0.003M	0.2 M	1	28
7	0.003M	0.2 M	16	26

Reaction conditions: DOH (0.2 mmol), TFA, Xylene, 140 °C. [a]Yield was measured by ^1H NMR using 1,4-dinitrobenzene as reference. [b]Isolated yield in 2.0 mmol scale.

General procedure for Table S8-9: to a 4 mL pressure tube was added DOH (0.2 mmol, 26 mg), solvent, a magnetic stirring bar, and acid. The pressure tube was sealed and stirred at the specified temperature. After cooling down to room temperature, the solvent was evaporated. 1,4-dinitrobenzene was added as reference, and the mixture was analyzed *via* ^1H NMR measurement.

Hydroquinone (2.0 mmol scale reaction in entry 2). To a 35 mL pressure tube was added DOH (2.0 mmol, 256 mg), xylene (10 mL), and a magnetic stirring bar. To the solution was added TFA (2.0 equiv., 306 μL), and the reaction was stirred at 140 °C for 30 mins. After cooling down to room temperature, the solvent was evaporated. Column chromatography (SiO_2, EA/cyclohexane = 1/4) afforded hydroquinone as a white solid (26 mg, yield: 12%). ^{1}H NMR (300 MHz, CD_3OD): δ (ppm) 6.62 (s, 4H). HRMS (EI): calculated for $C_6H_6O_2$ 110.03623, Found 110.03602.

Table S10: TFA-catalyzed intramolecular aldol condensation of DOH under high temperature

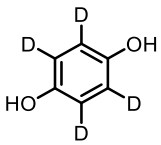


DOH, 0.1 mmol Hydroquinone

Entry	*T* (°C)	*P* (N_2)	*t*	Yield (%)[a]
1[b]	100	1.01 bar	19 h	7
2	150	30 bar	1 h	9
3	200	16 bar	1 h	19
4	200	16 bar	2 h	23
5	250	40 bar	1 h	27
6	265	56 bar	1 h	32
7[c]	150	30 bar	1 h	16
8[c]	207	5 bar	1 h	23

Reaction conditions: DOH (0.05 M), TFA (2.0 equiv), H_2O (2 mL), temp. N_2. [a]Yield determined by ^{1}H NMR using 1,4-dinitrobenzene as reference. [b]DOH (0.1 M), Ar instead of N_2. [c]Xylene (2 mL).

General procedure for Table S10: to a 4 mL vial was added DOH (0.1 mmol, 13 mg), a magnetic stirring bar, solvent, and TFA (2.0 equiv). The vial was sealed by an open-top cap (phenolic) with a septum (PTFE-faced styrene butadiene rubber) pierced with a needle. The vial was placed inside a 300 mL autoclave. The autoclave was flushed with N_2 three times and was subsequently charged with the desired pressure of N_2. The reaction was stirred at the specified temperature. After cooling down to room temperature, the solvent was evaporated. 1,4-dinitrobenzene was added as reference, and the mixture was analyzed *via* ^{1}H NMR measurement.



***d*$_4$-Hydroquinone**. To a custom-made autoclave glass insert (height: 6 cm, screw neck: 2 cm, diameter: 6 cm) was added DOH (1.0 mmol, 128 mg), a magnetic stirring bar, D_2O (20 mL), and TFA (2.0 eq., 160 μL). The insert was sealed by an open-top cap (phenolic) with a septum (PTFE-faced styrene butadiene rubber) pierced with a needle, and then placed inside a 300 mL autoclave. The autoclave was flushed with N_2 three times and charged with 40 bar N_2. The reaction was stirred at 250 °C (the heating mantle was preheated to 250 °C.) for 1 hours. After cooling down to room temperature and removal of the solvent, column chromatography (SiO_2, EA/cyclohexane = 1/4) afforded desired *d*$_4$-hydroquinone

as yellow solid (9 mg, 8%). ^{2}H NMR (400 MHz, DMSO): δ (ppm) 6.58 (s, 4H). HRMS (EI): calculated for $C_6H_2D_4O_2$ 114.06134, Found 114.06182.

11. Condition optimization for the conversion of DOA to catechol

Scheme S1. Conversion of HMF to MCO[8-10]

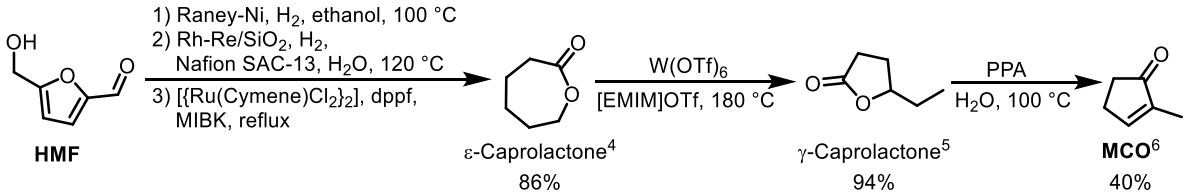
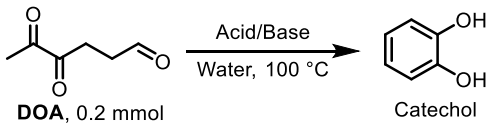


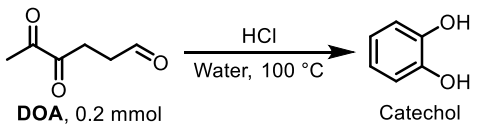
Table S11. Screen of various acids for the conversion of DOA to catechol



Entry	Acid/Base	Time	Yield (%)[a]
1	PTSA·H_2O, 2.0 equiv	24 h	16
2	HCl, 2.0 equiv	24 h	18
3	TFA, 2.0 equiv	3 h	6
4	HOAc, 2.0 equiv	5 h	n.d.
5	HOTf, 2.0 equiv	5 h	n.d.
6	H_2SO_4, 1.0 equiv	24 h	n.d.
7	H_3PO_4, 1.0 equiv	24 h	n.d.
8	HBF_4, 1.0 equiv	24 h	<1
9	CH_3SO_3H, 1.0 equiv	24 h	n.d.
10	$ClSO_3H$, 1.0 equiv	24 h	n.d.
11	BF_3·$2H_2O$, 2.0 equiv	24 h	n.d.
12[b]	L-proline, 25 mol%	24 h	n.d.
13[c]	TBD, 25 mol%	24 h	n.d.

Reaction conditions: DOA (0.2 mmol, 25 mg), H_2O (2 mL), acid or base, 100 °C, under Ar. [a]Yield was determined by ^{1}H NMR using 1,4-dinitrobenzene as reference. [b]H_2O (1 mL), rt. [c]H_2O (4 mL), rt.

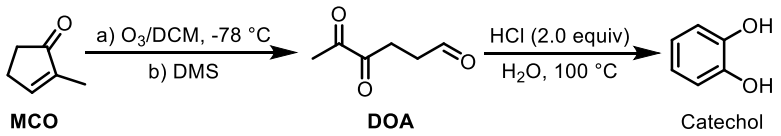
Table S12. The effects of solvent and concentration on the conversion of DOA to catechol



Entry	Conc. (DOA)	HCl	Solvent	Yield (%)[a]
1	0.1 M	0.5 equiv	H_2O	8
2	0.1 M	1.0 equiv	H_2O	10
3	0.1 M	2.0 equiv	H_2O	18
4	0.1 M	3.0 equiv	H_2O	15
5	0.1 M	4.0 equiv	H_2O	14
6	0.05 M	1.0 equiv	H_2O	22
7	**0.05 M**	**2.0 equiv**	**H_2O**	**34**

8	0.05 M	4.0 equiv	H_2O	28
9	0.01 M	2.0 equiv	H_2O	24
10[b]	0.05 M	2.0 equiv	Xylene	0
11	0.05 M	2.0 equiv	Dioxane	3
12[c]	0.05 M	2.0 equiv	1,2-diethoxyethane	2
13[d]	0.05 M	-	pH = 1.0	14
14[d]	0.05 M	-	pH = 1.5	16
15[d,e]	0.05 M	-	pH = 1.5	26
16[d]	0.05 M	-	pH = 2.0	12
17[f]	0.05 M	-	pH =2.5 (PBS)	5
18	0.05 M	2.0 equiv	H_2O/dioxane	13
19[g]	0.05 M	2.0 equiv	H_2O	35
20[h]	0.05 M	2.0 equiv	H_2O	32

Reaction conditions: DOA (0.2 mmol, 25 mg), solvent, HCl, 100 °C, 24 h, under Ar. [a]Yield was determined by ^{1}H NMR using 1,4-dinitrobenzene as reference. [b]140 °C. [c]125 °C. [d]Buffer solution were prepared by KCl and HCl (0.2 M) in H_2O. [e]5 days. [f]Phosphate buffer solution (0.1 mol/L). [g]*L*-proline (20 mol%). [h] **S1** (20 mol%).

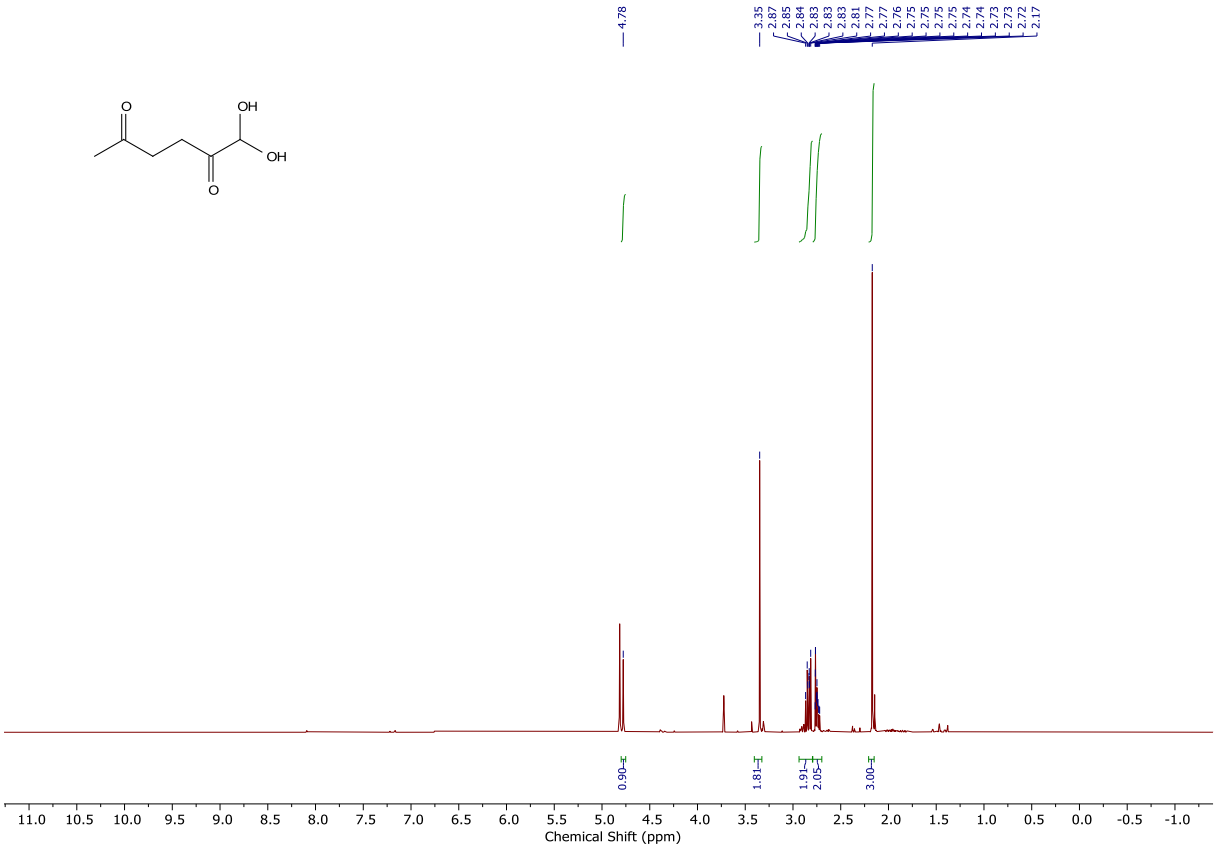


Catechol. To a 25 mL Schlenk flask was added 2-methylcyclopent-2-en-1-one (MCO, 1.0 mmol, 98 µL), a magnetic stirring bar, DCM (2.5 mL), and a trace amount of Sudan III. A glass pipette (ozone inlet) was inserted into the Schlenk flask and a tube was connected as a gas outlet. The mixture was cooled down to -78 °C and ozone (generated by one Erwin Sander@ ozonisator 301.7, flow rate of inlet compressed air was 150 L/h) was bubbled through the reaction. The reaction was stirred at -78 °C for 5 mins until the red reaction solution turned blue. Compressed air was bubbled into the reaction mixture until the solution turned yellow, followed by addition of dimethyl sulfide (200 µL). After stirring at room temperature for 2 hours, the reaction mixture was diluted with DCM and washed with brine twice. The organic layer was dried over Na_2SO_4 and concentrated to around 1 mL. The obtained DOA solution was used directly for the next step.

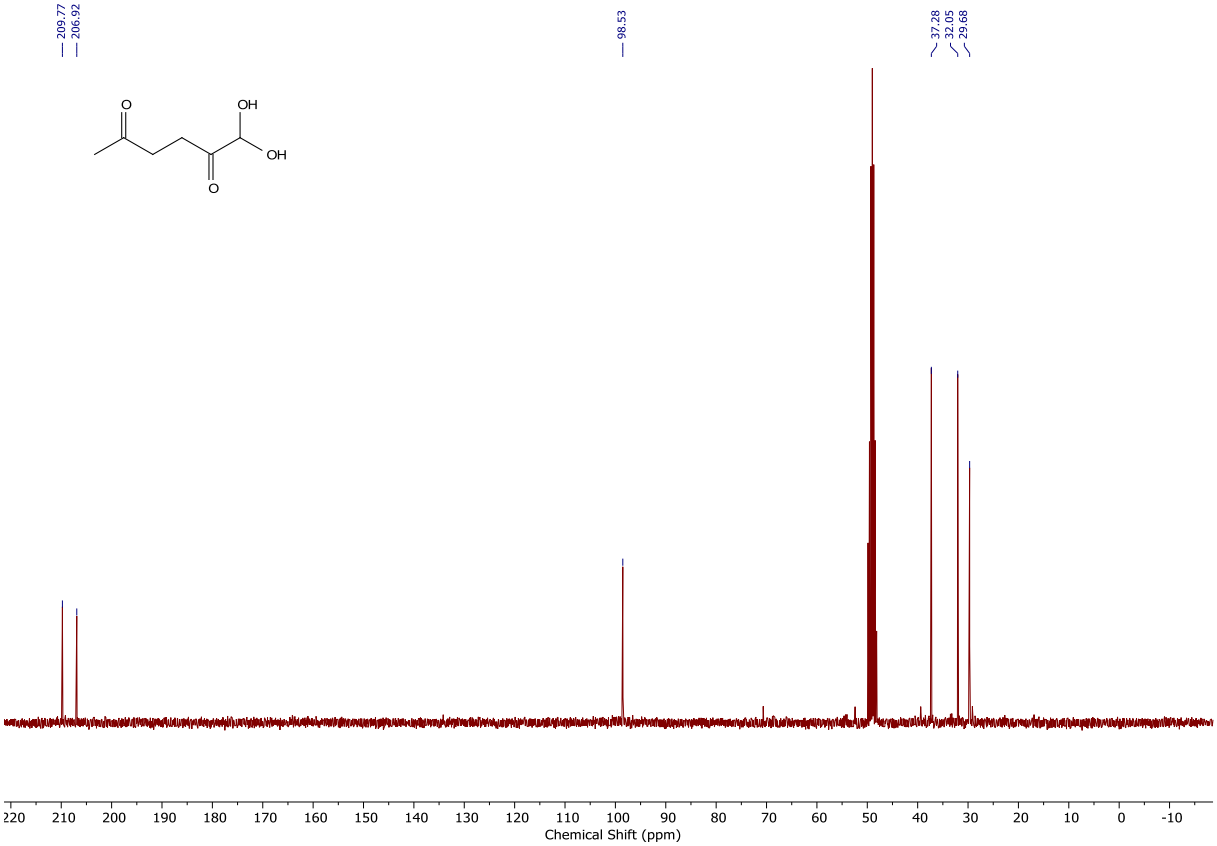
To a 50 mL Schlenk flask was added a magnetic stirring bar, degassed H_2O (20 mL), and HCl (37%, 2 equiv, 200 µL) under Ar. The above solution of DOA was added into the stirred aqueous solution. The reaction was stirred at 100 °C for 24 hours. After cooling down to room temperature and removal of all volatiles *in vacuo*, column chromatography (SiO_2, EA/cyclohexane = 1/4) afforded catechol as a white solid (46 mg, yield: 42%). ^{1}H NMR (300 MHz, CD_3OD) δ (ppm) 6.78-6.72 (m, 2H), 6.68-6.62 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ (ppm) 146.3, 120.9, 116.4. HRMS (EI): calculated for $C_6H_6O_2$ 110.03623, Found 110.03592.

Appendix I: NMR spectra

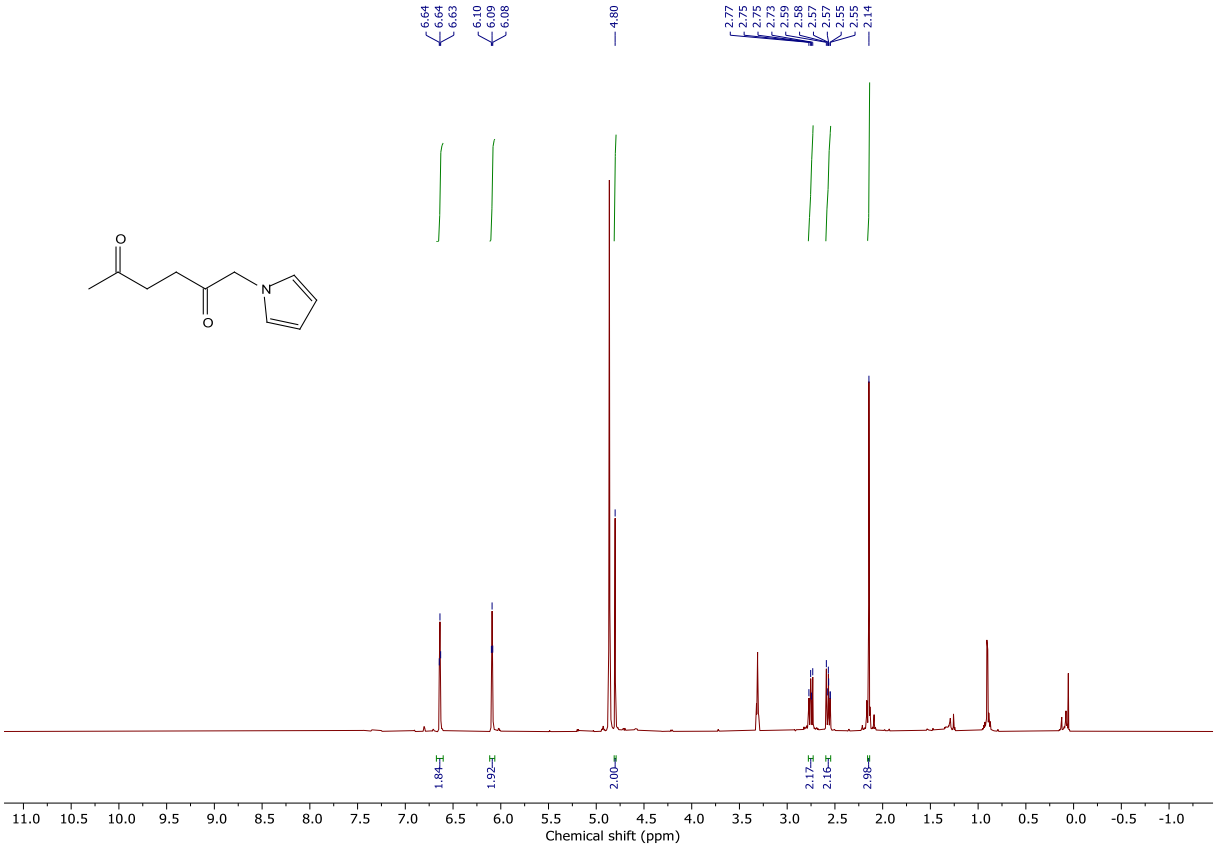
^{1}H-NMR (300 MHz, CD_3OD)



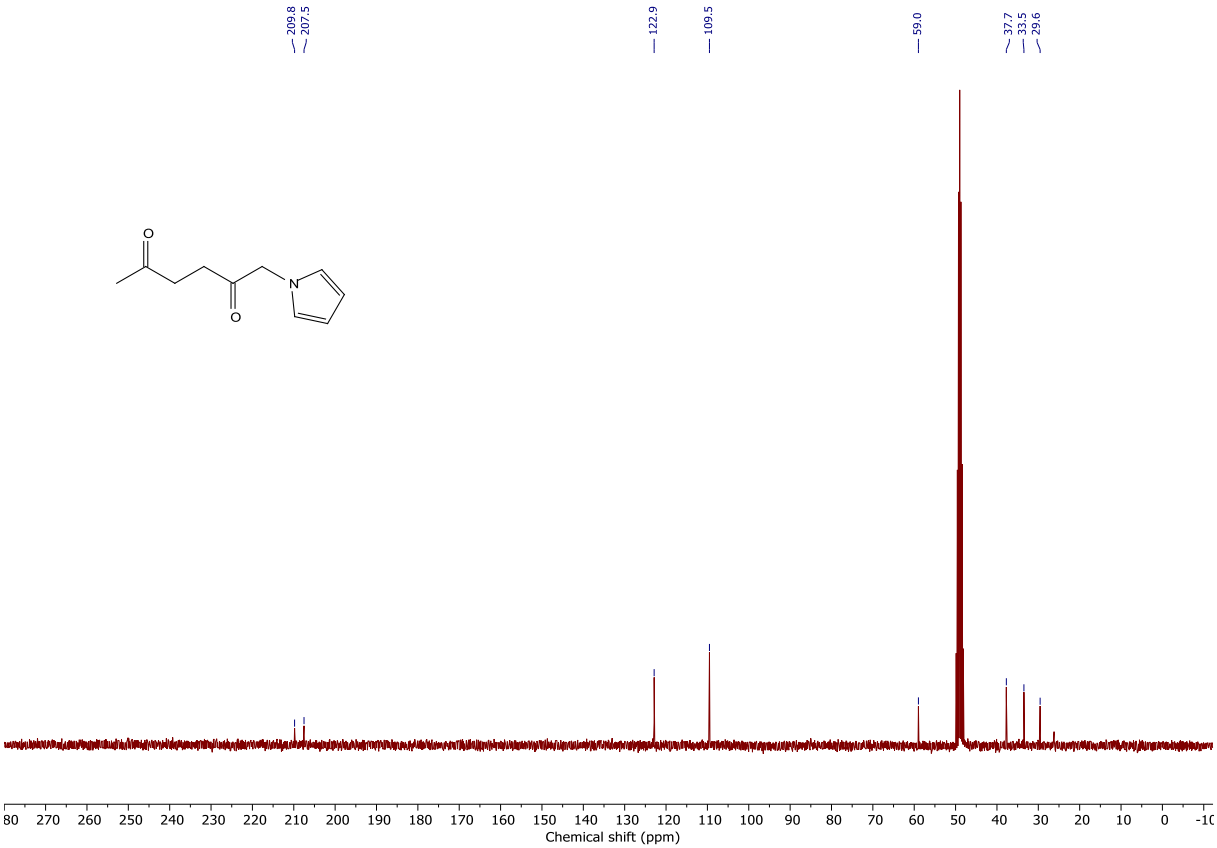
^{13}C-NMR (75 MHz, CD_3OD)



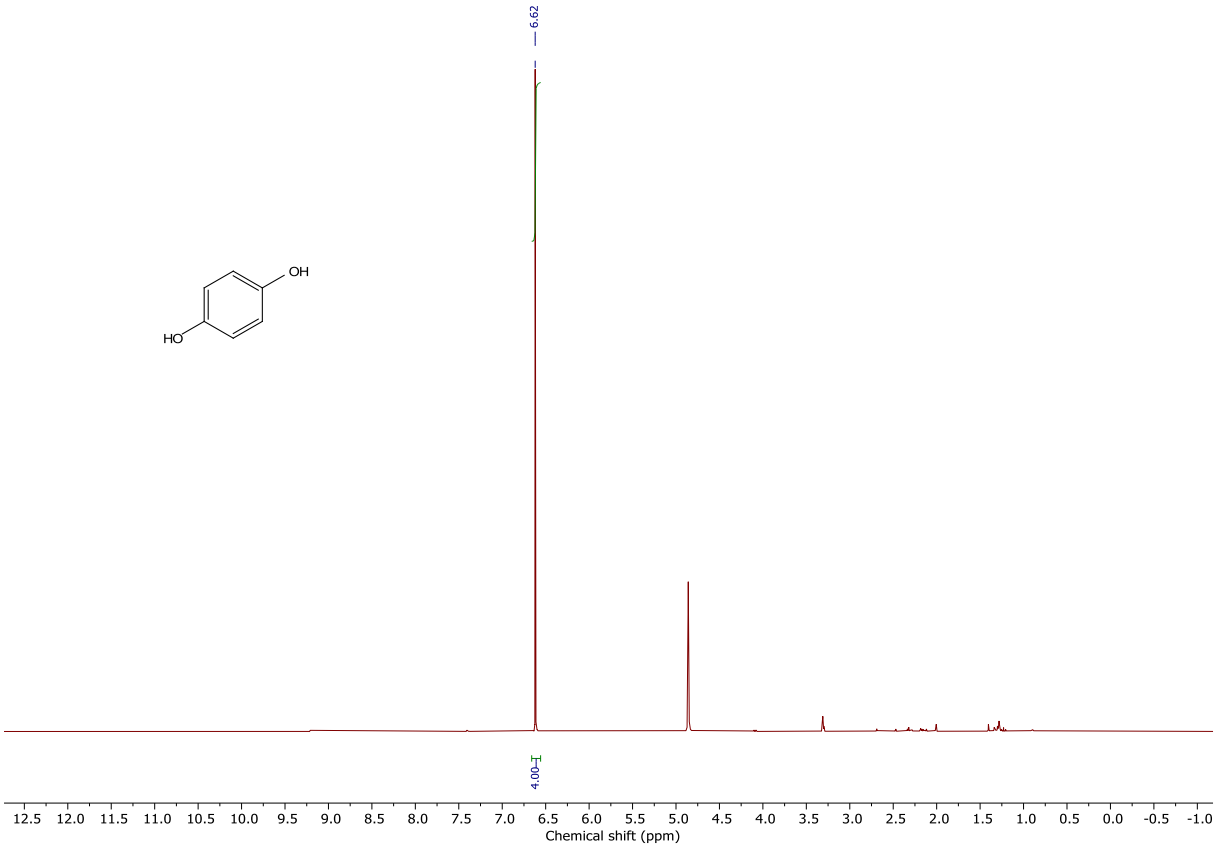
^{1}H-NMR (300 MHz, CD_3OD)



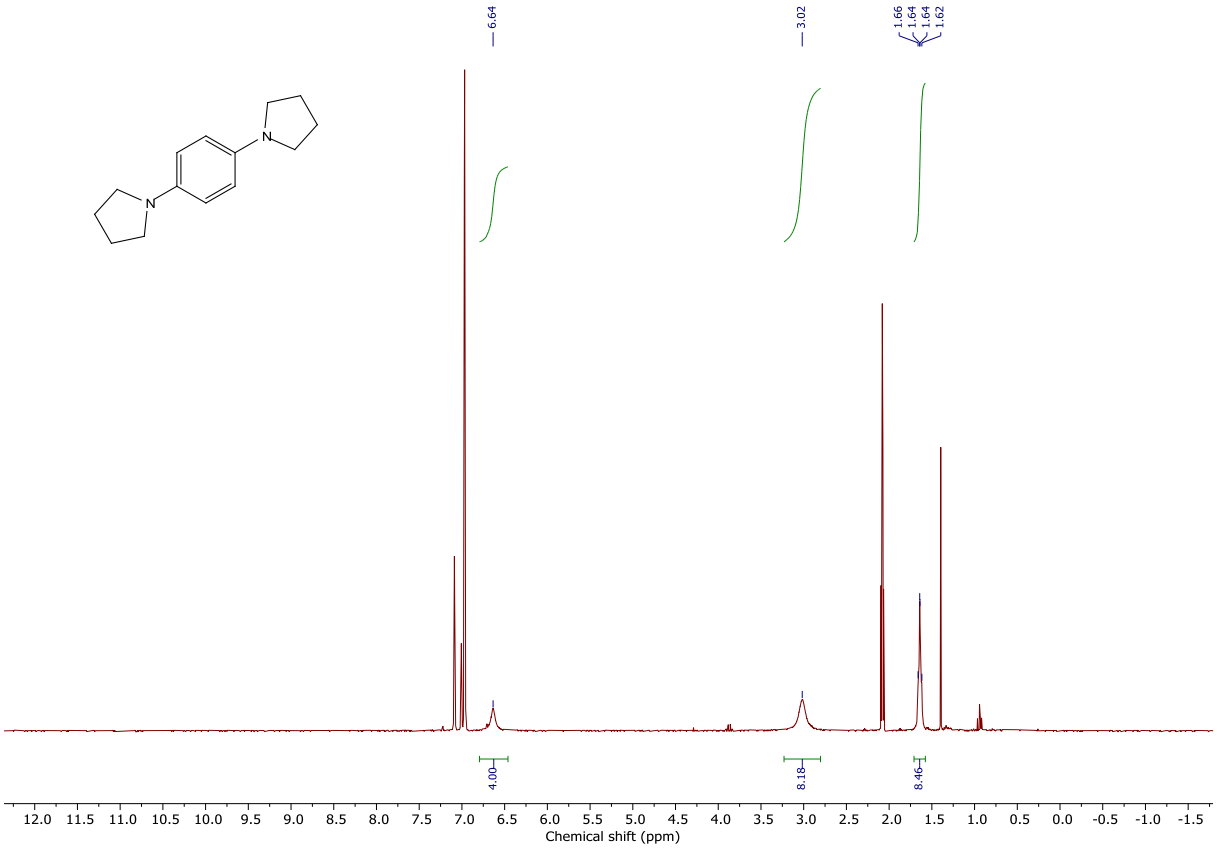
^{13}C-NMR (75 MHz, CD_3OD)



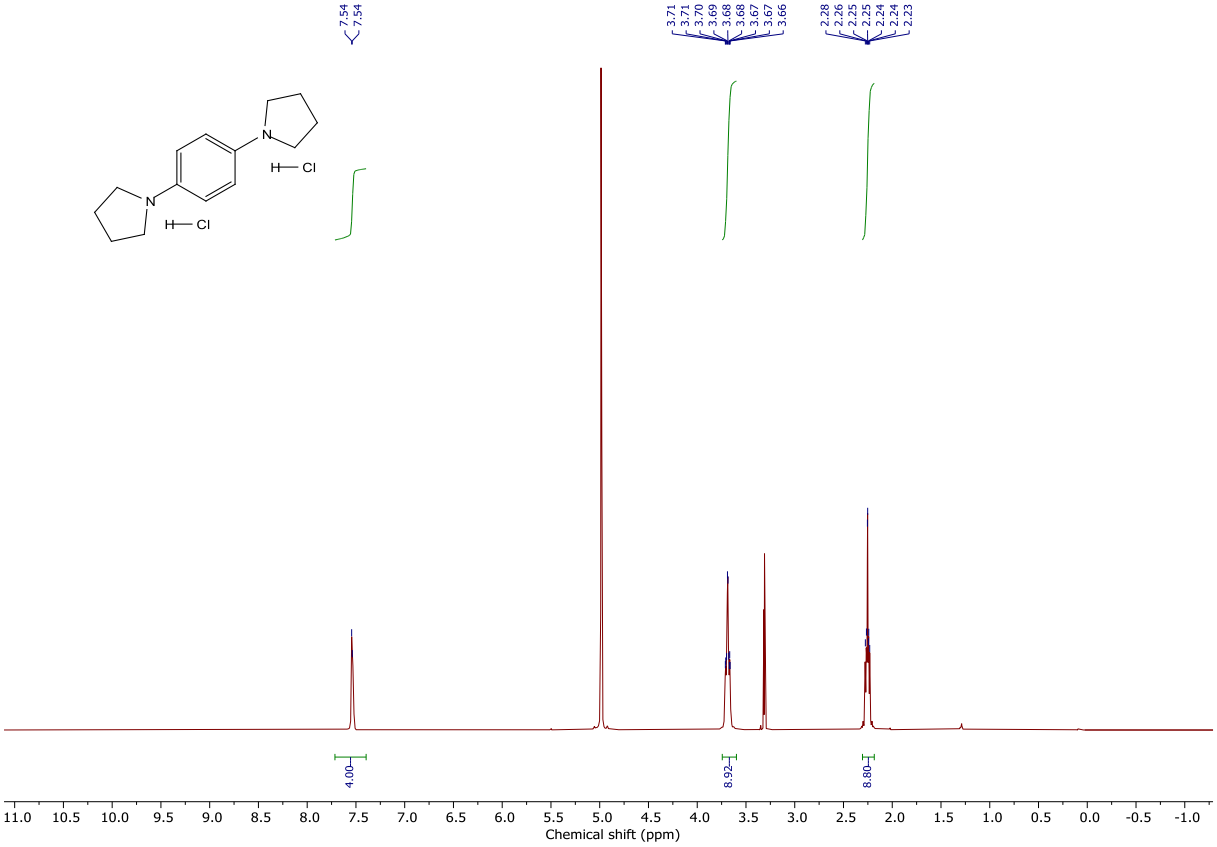
^{1}H-NMR (300 MHz, CD_3OD)



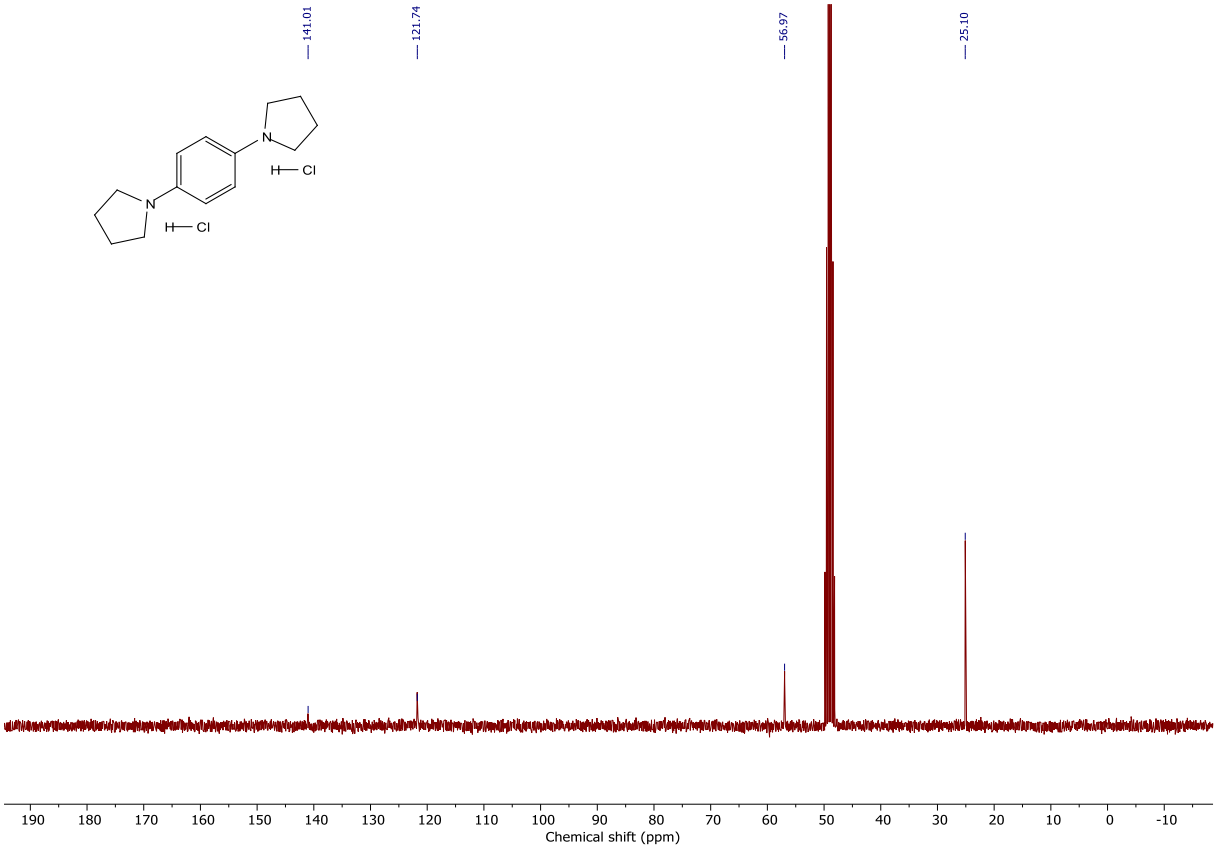
^{1}H-NMR (300 MHz, d_8-toluene)



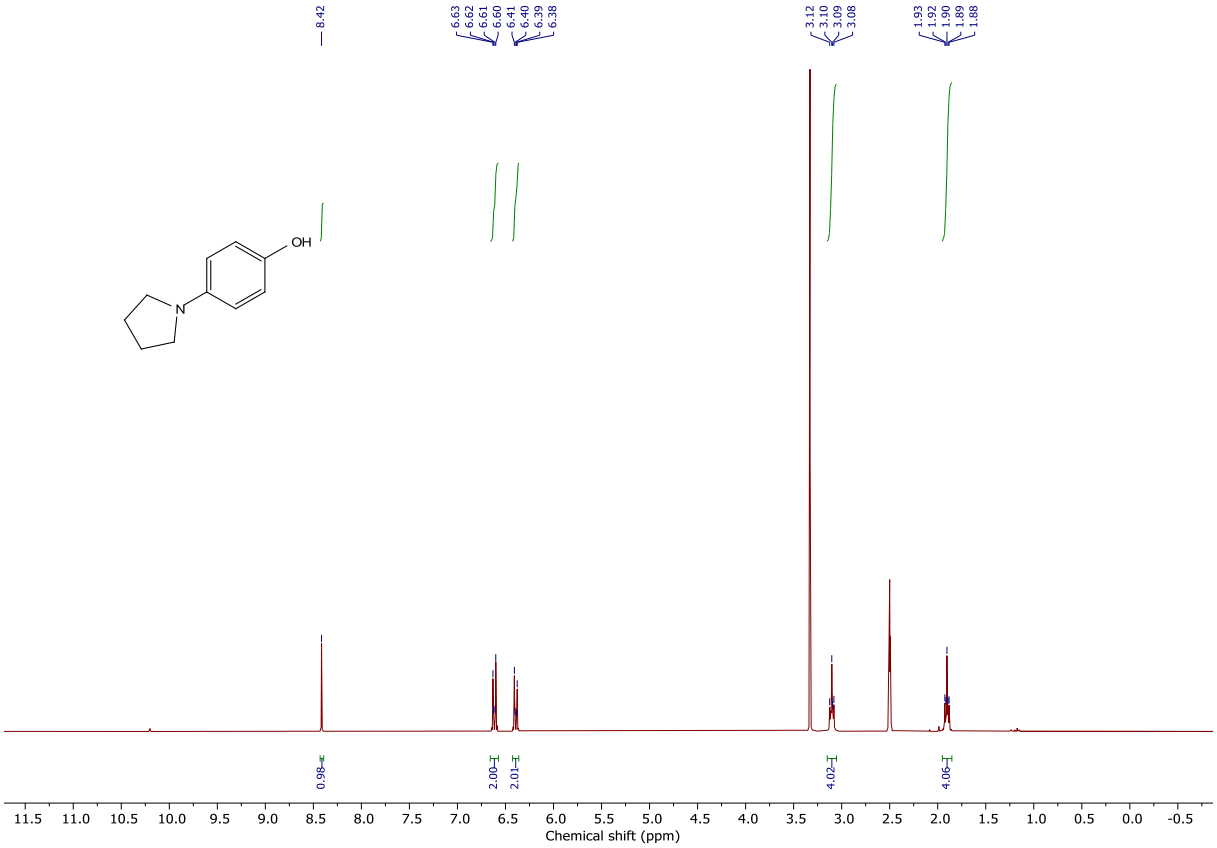
^{1}H-NMR (300 MHz, CD_3OD)



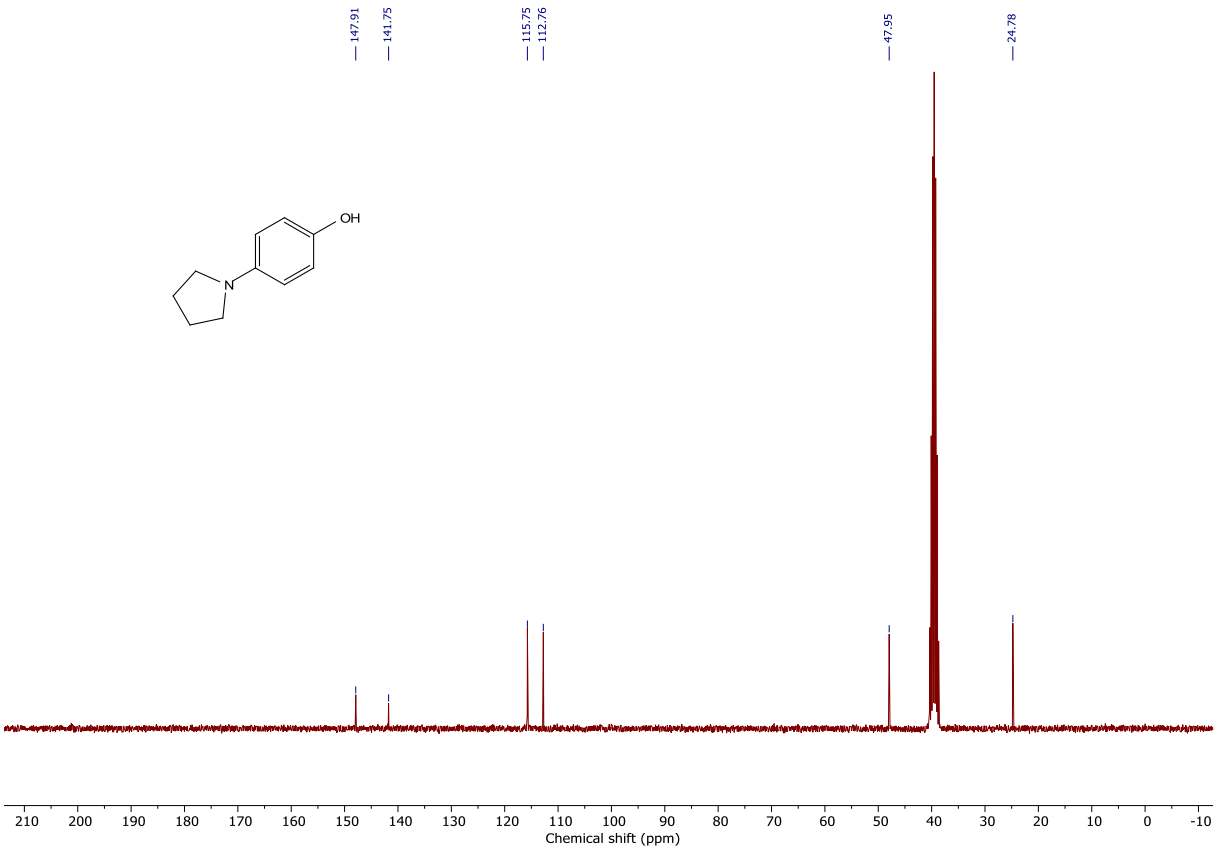
^{13}C-NMR (75 MHz, CD_3OD)



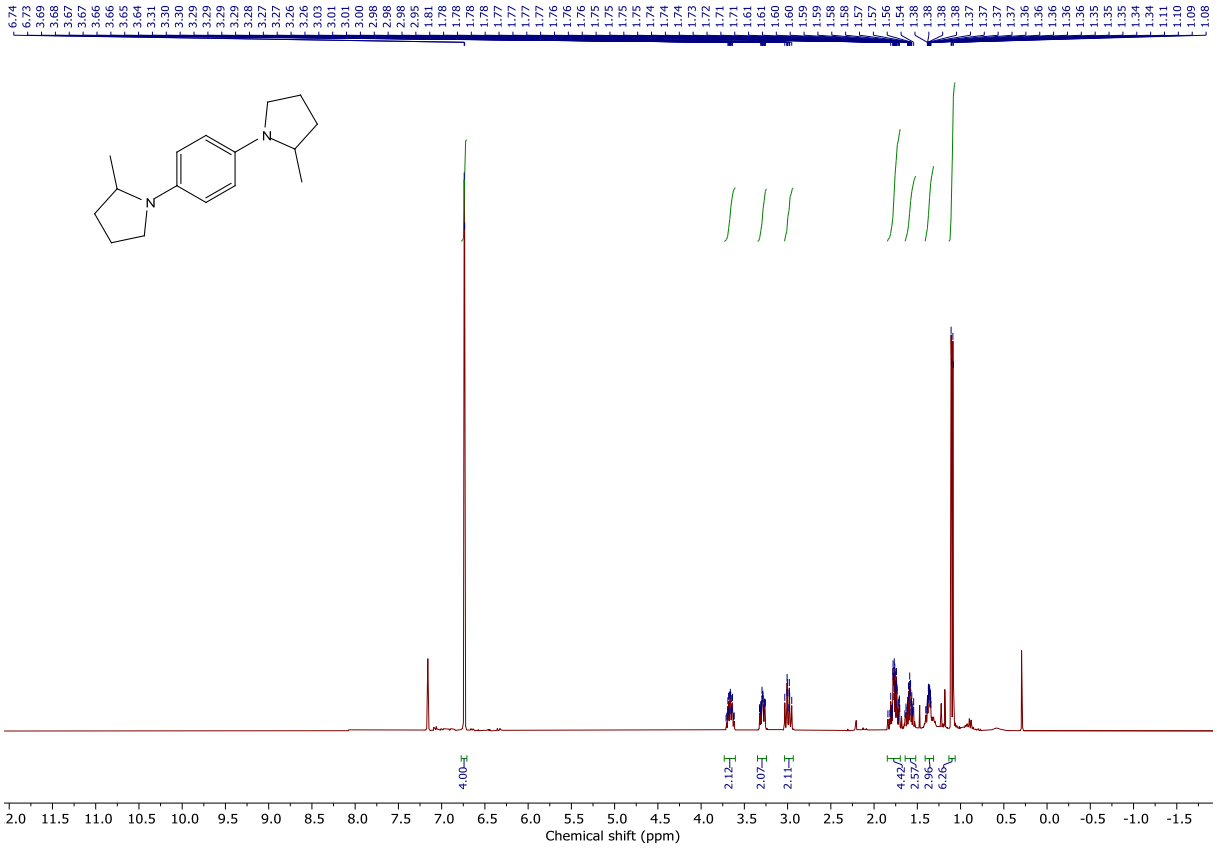
^{1}H-NMR (300 MHz, d_6-DMSO)



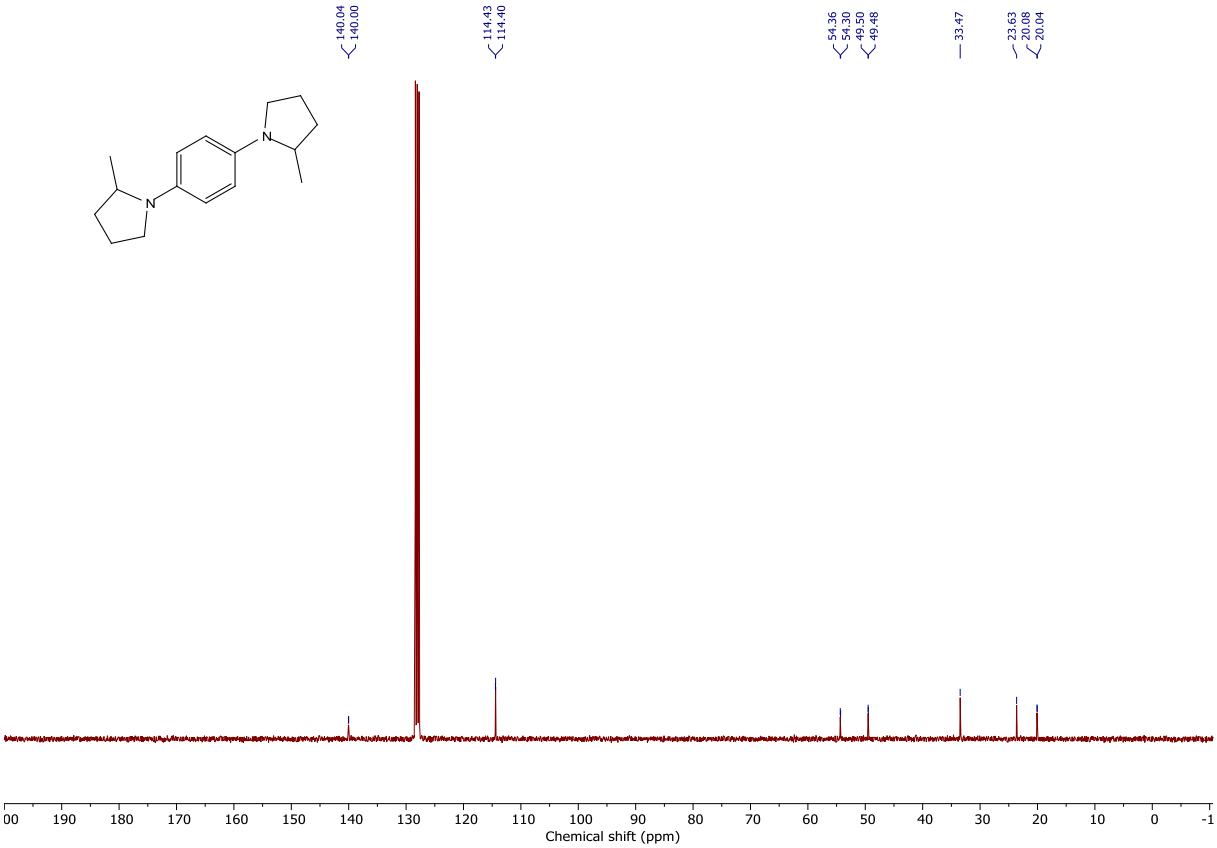
^{13}C-NMR (75 MHz, d_6-DMSO)



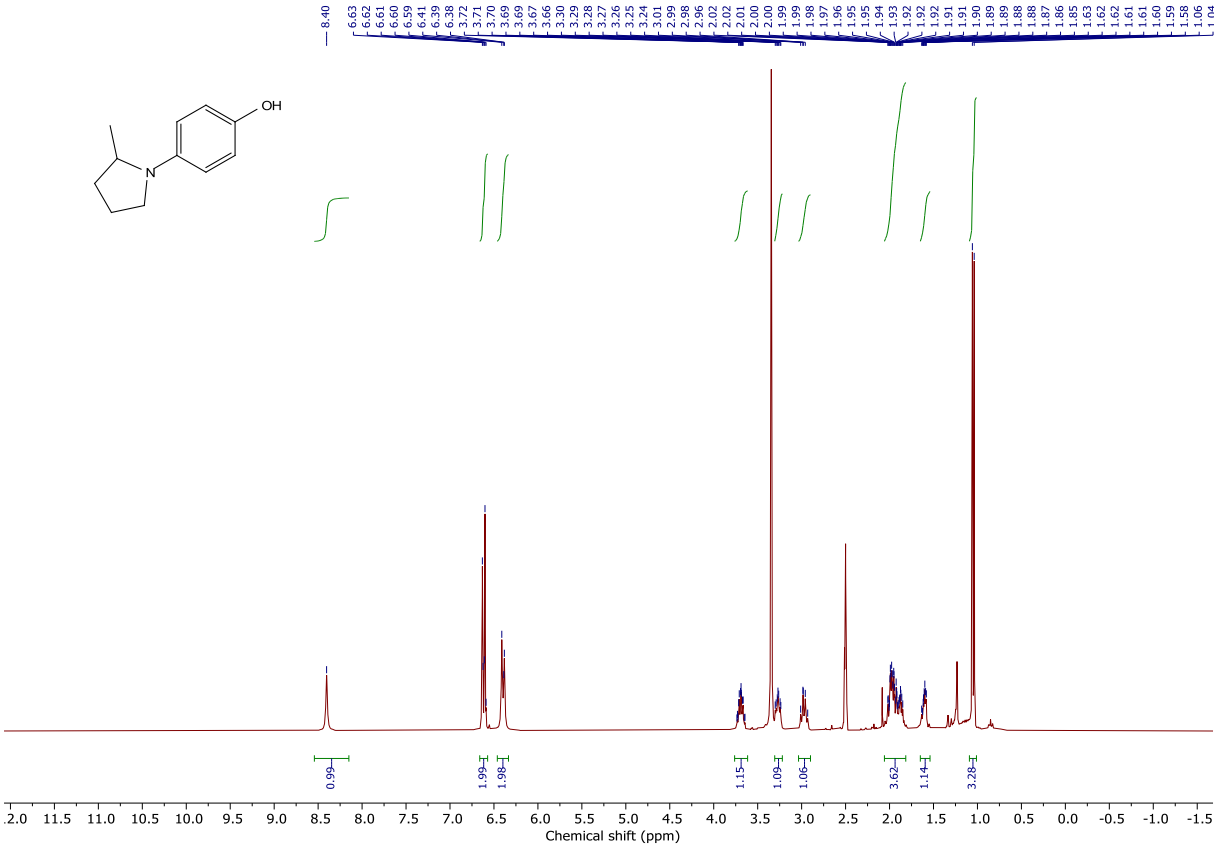
^{1}H-NMR (300 MHz, d_6-benzene)



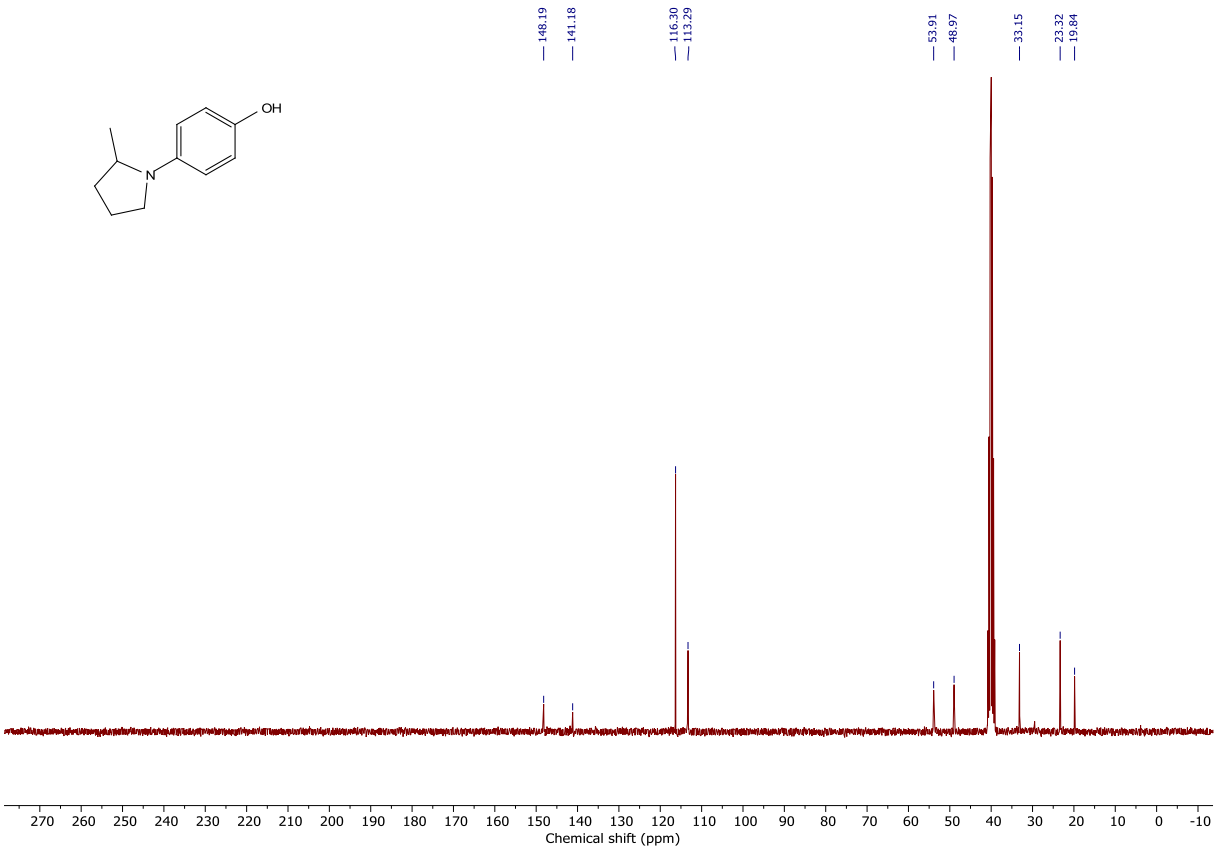
^{13}C-NMR (300 MHz, d_6-benzene)



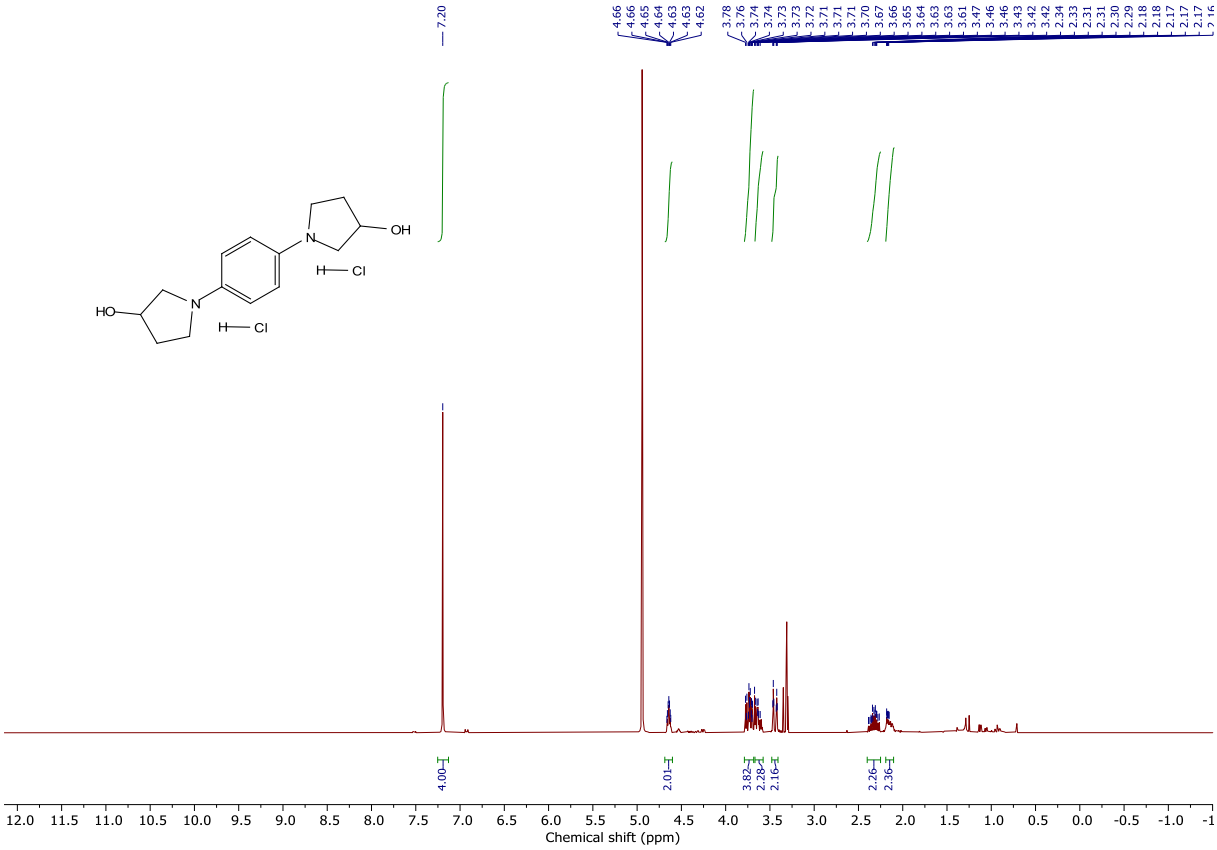
^{1}H-NMR (300 MHz, d_6-DMSO)



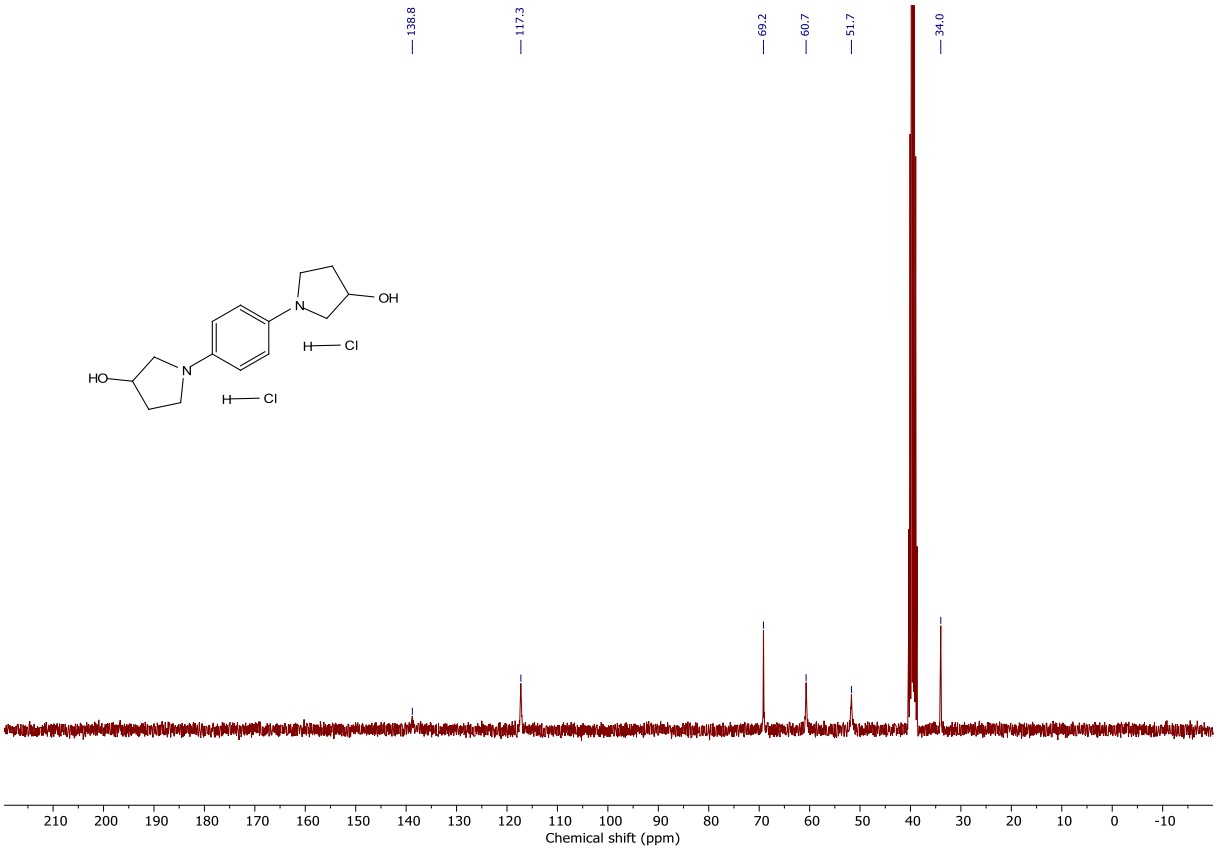
^{13}C-NMR (75 MHz, d_6-DMSO)



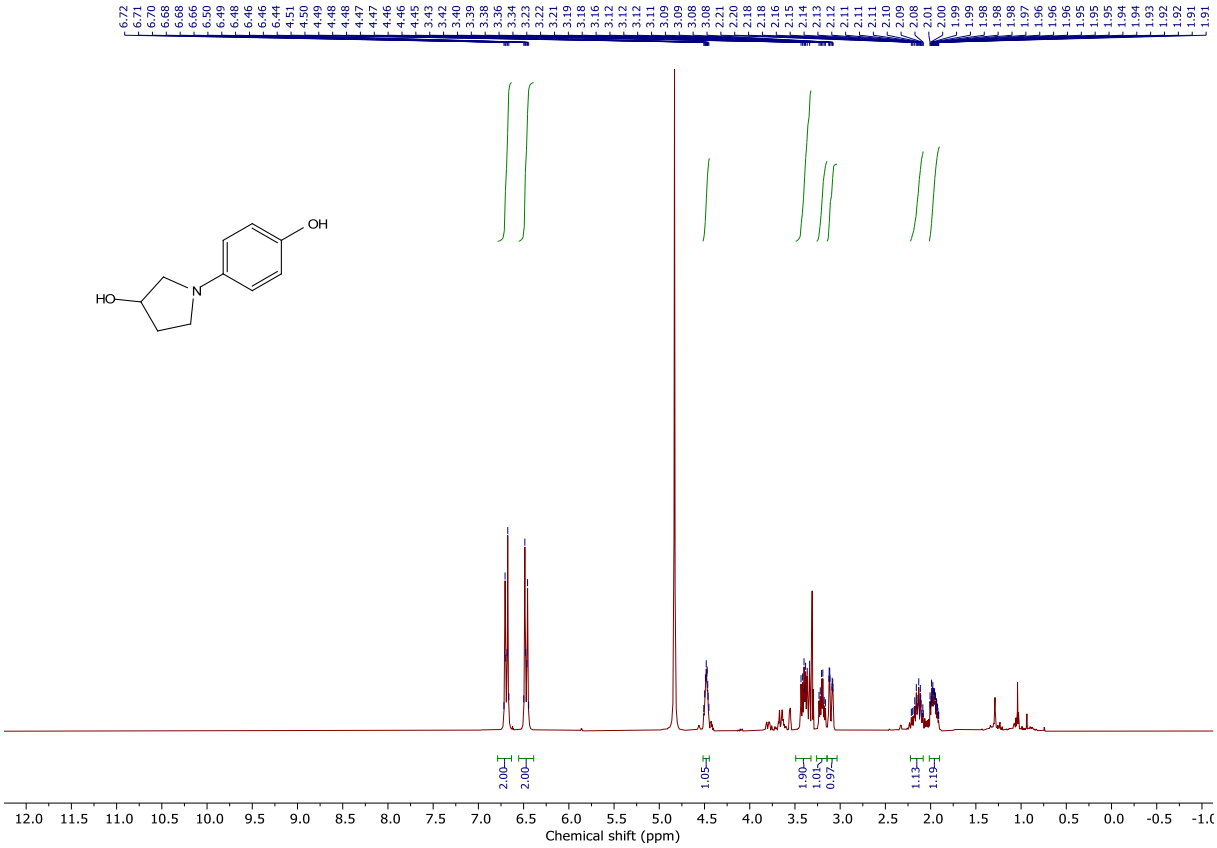
^{1}H-NMR (300 MHz, CD_3OD)



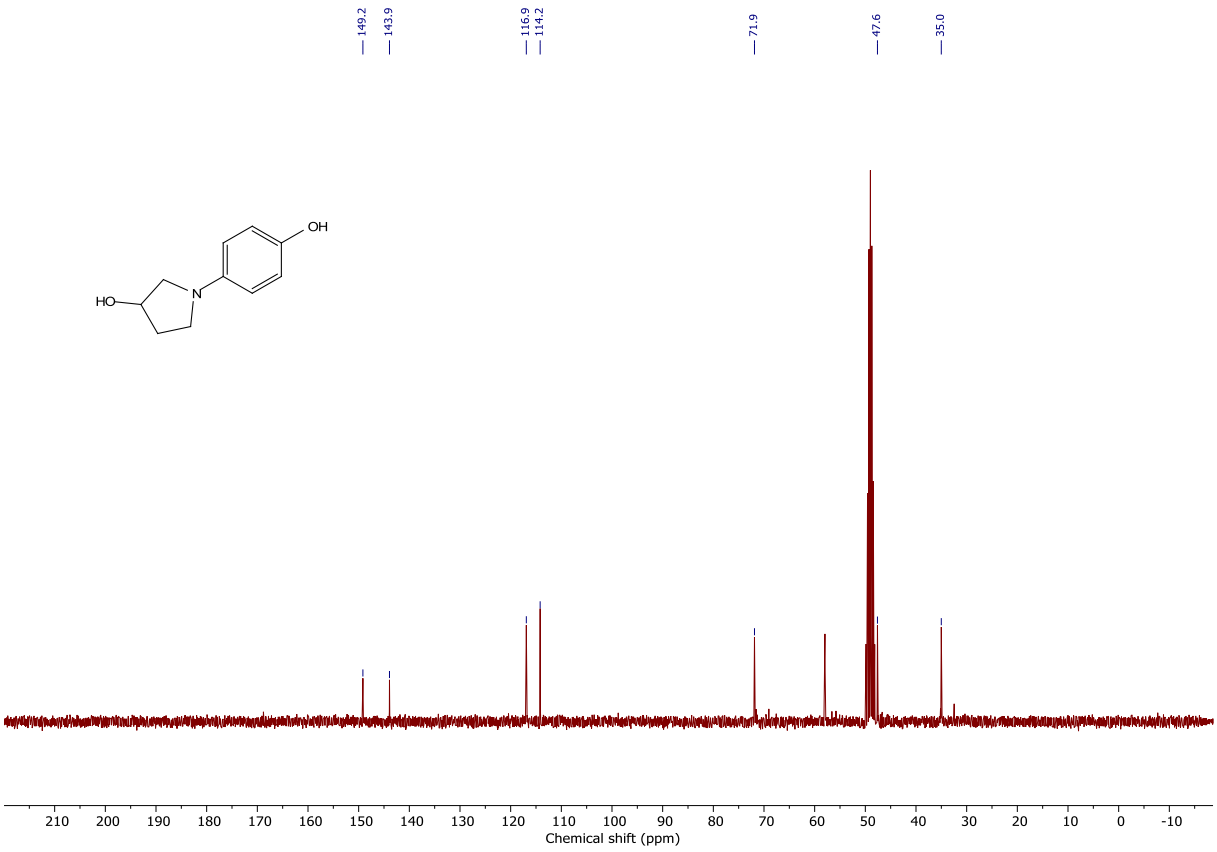
^{13}C-NMR (75 MHz, d_6-DMSO)



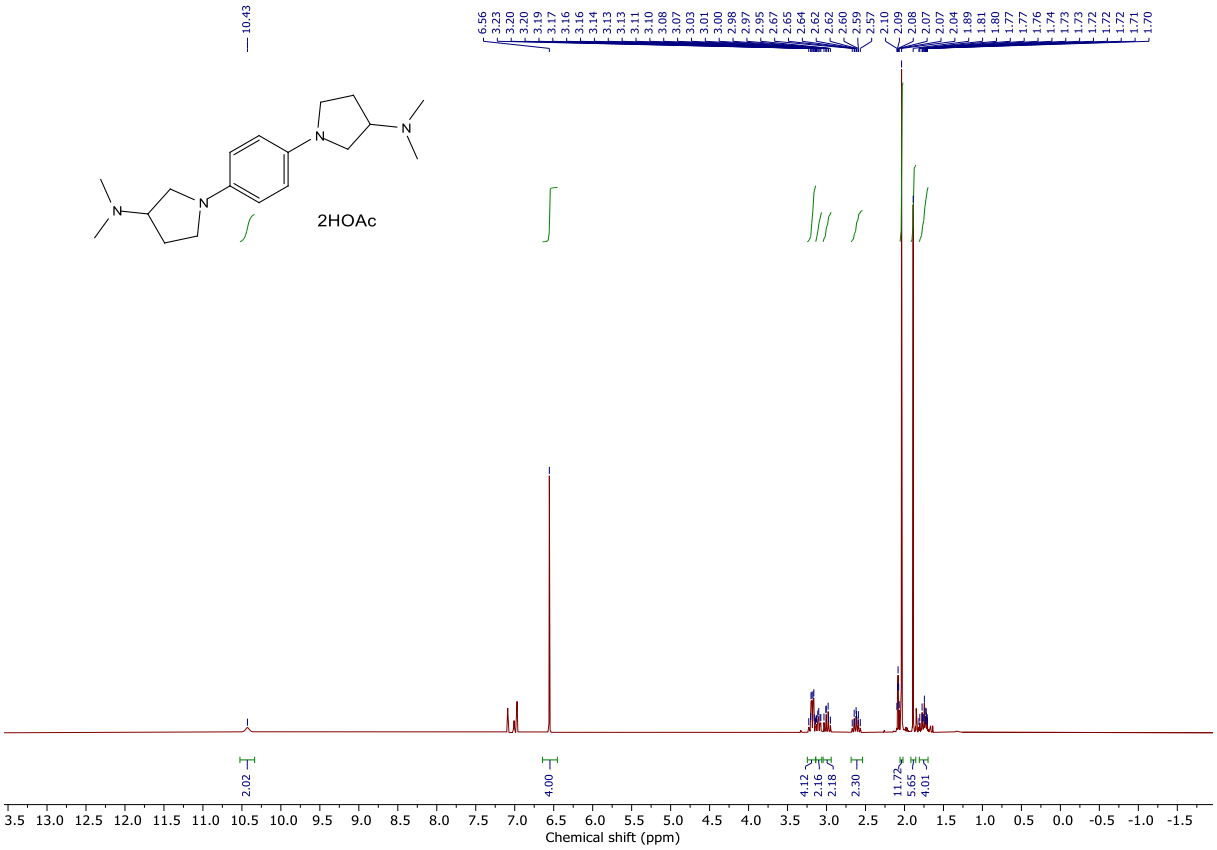
^{1}H-NMR (300 MHz, CD_3OD)



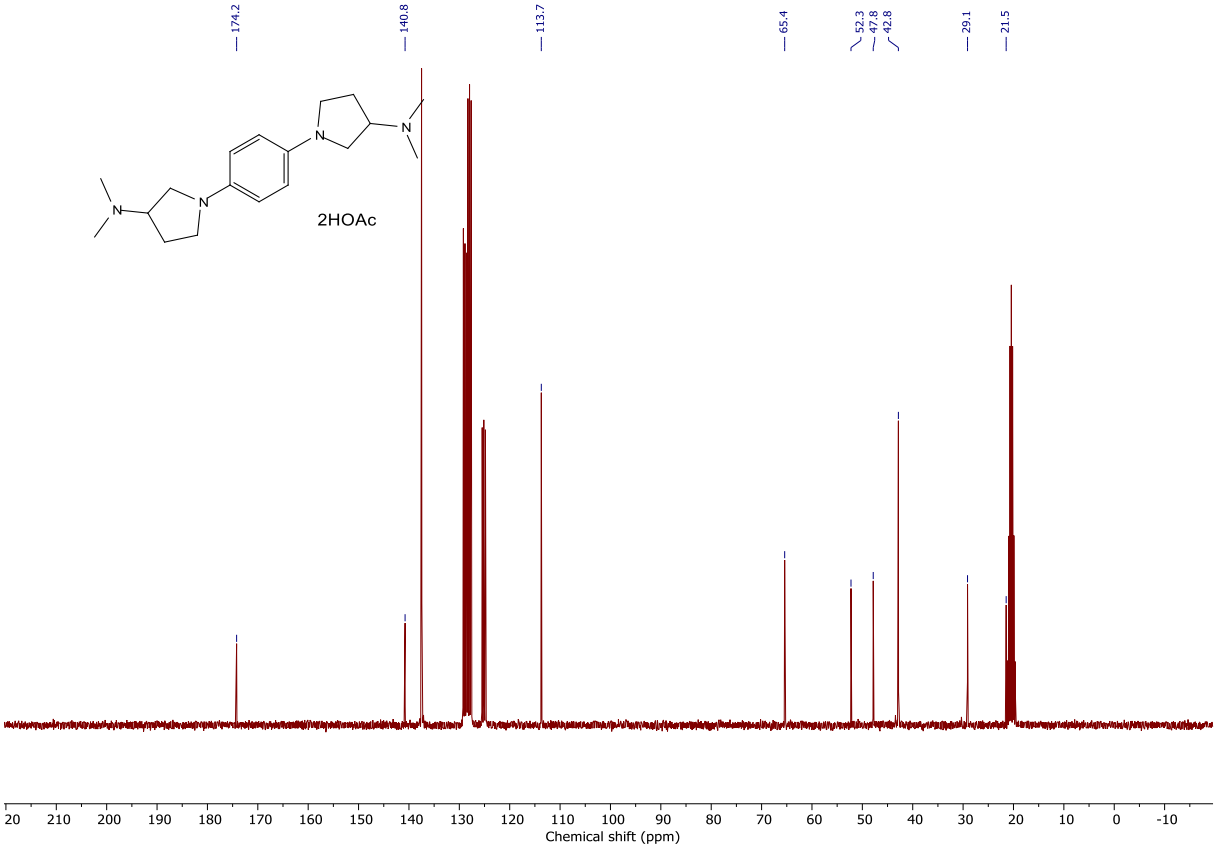
^{13}C-NMR (75 MHz, CD_3OD)



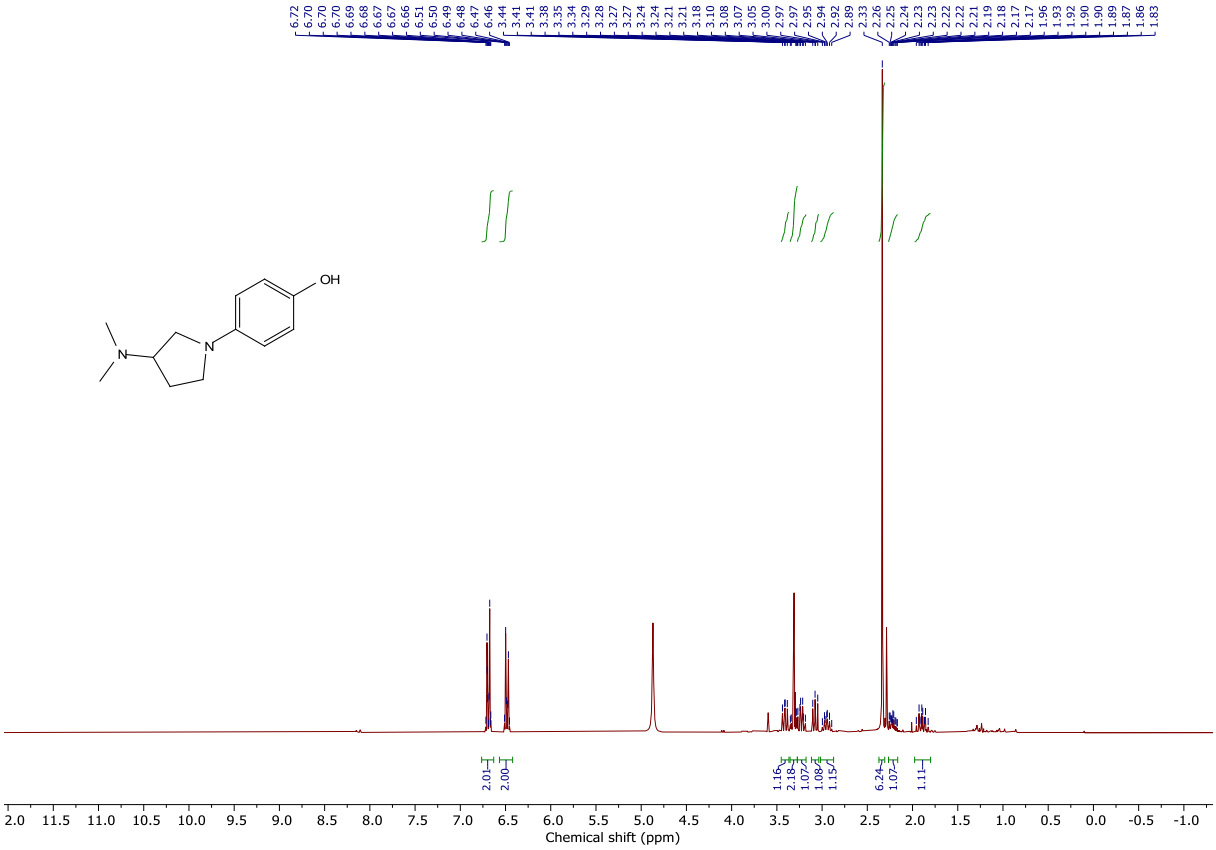
^{1}H-NMR (300 MHz, d_8-toluene)



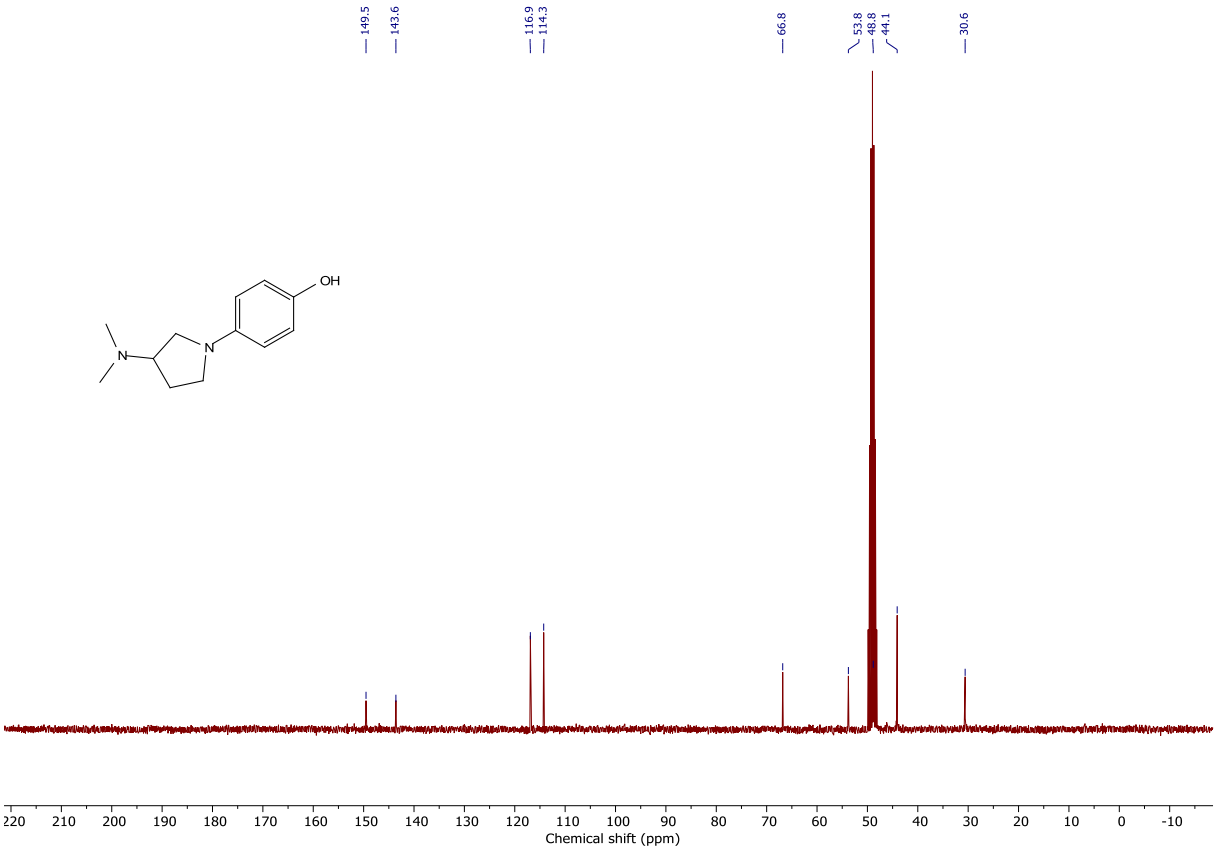
^{13}C-NMR (75 MHz, d_8-toluene)



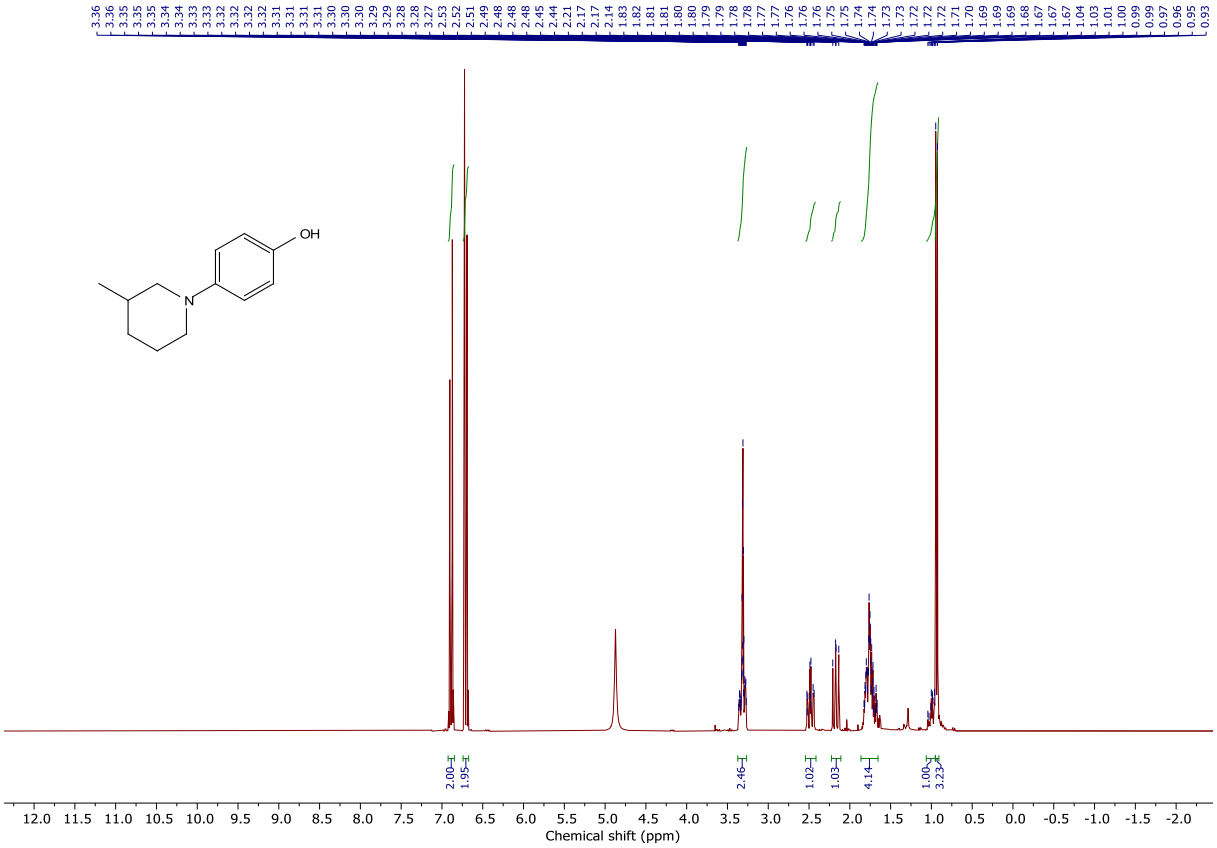
^{1}H-NMR (300 MHz, CD_3OD)



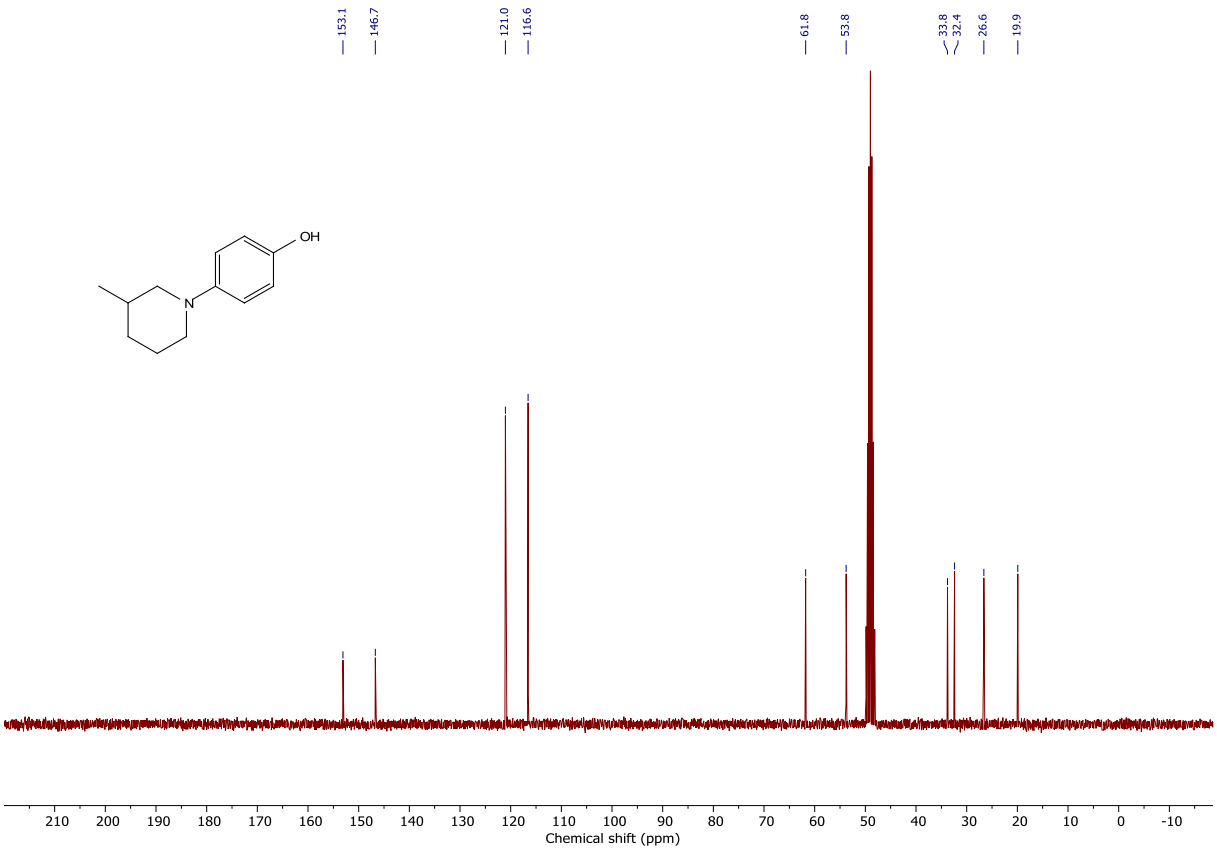
^{13}C-NMR (75 MHz, CD_3OD)



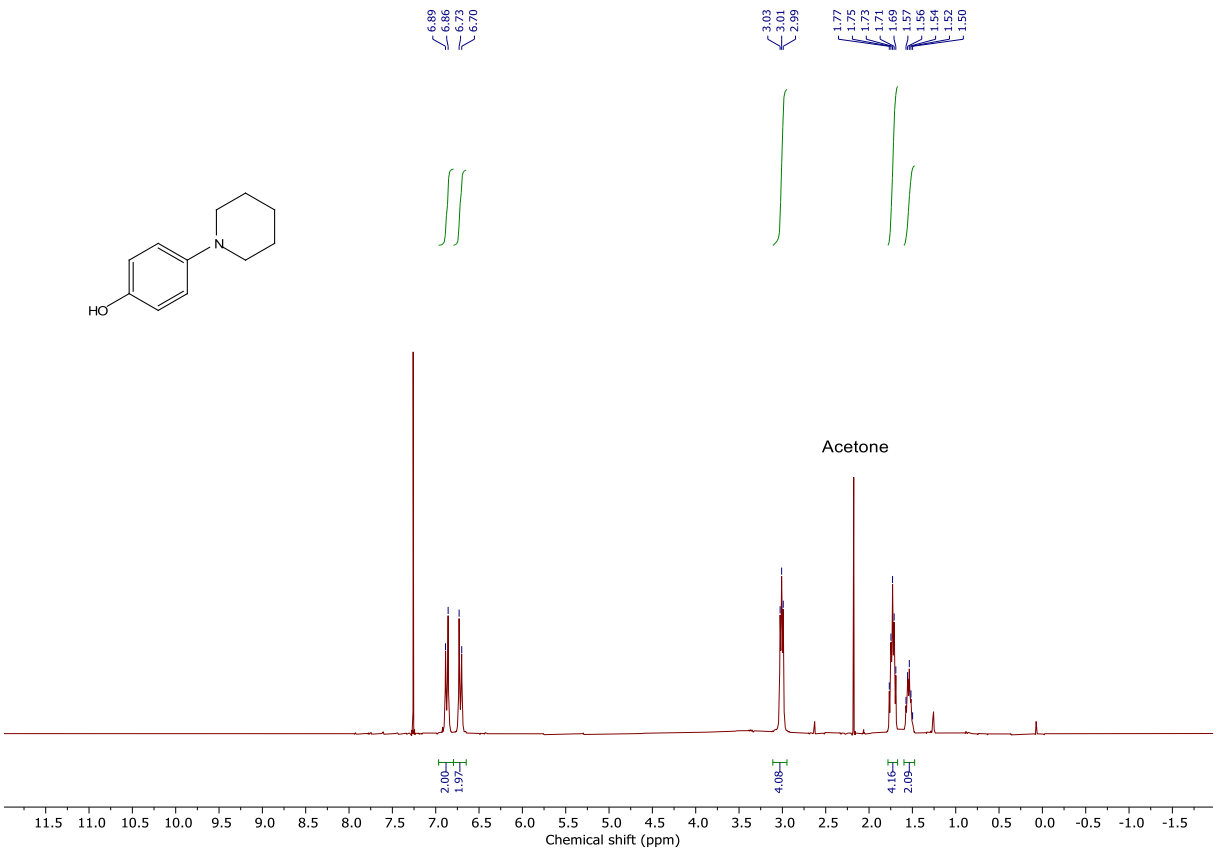
^{1}H-NMR (300 MHz, CD_3OD)



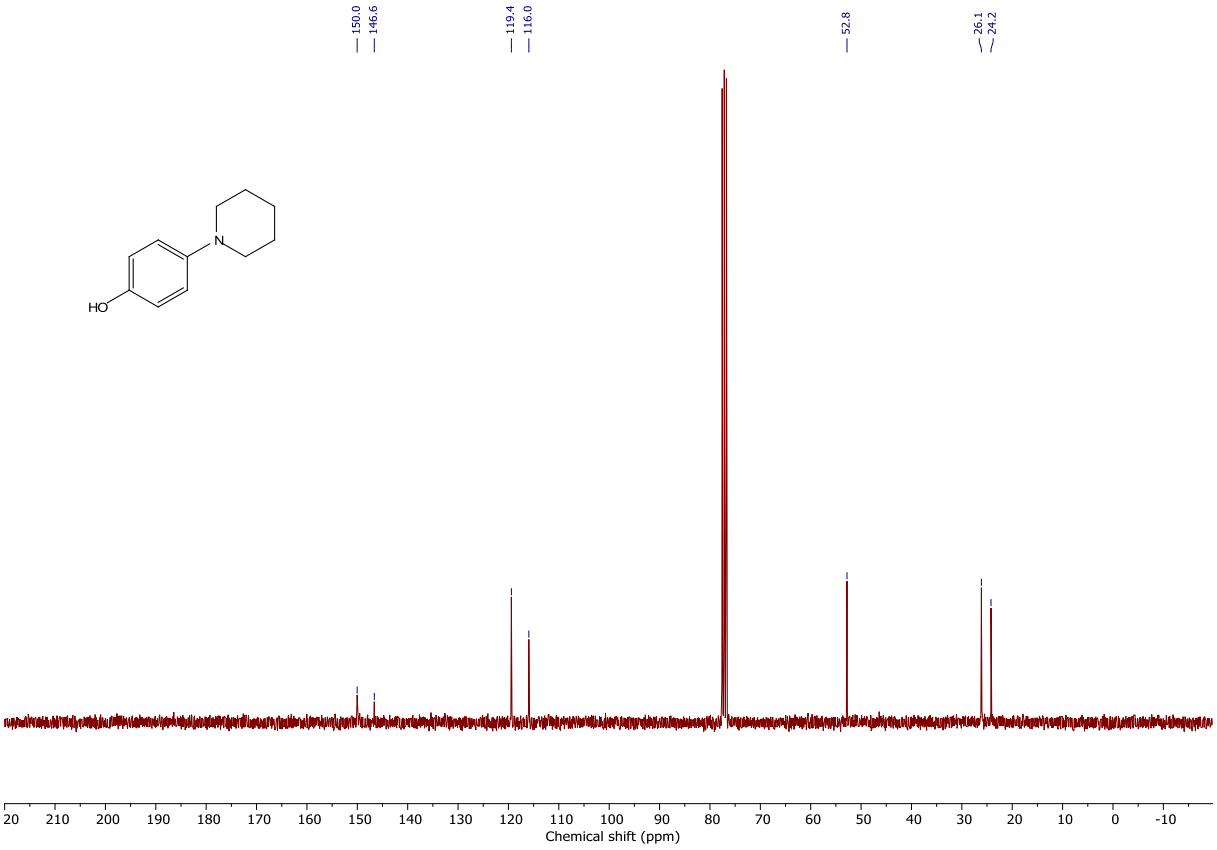
^{13}C-NMR (75 MHz, CD_3OD)



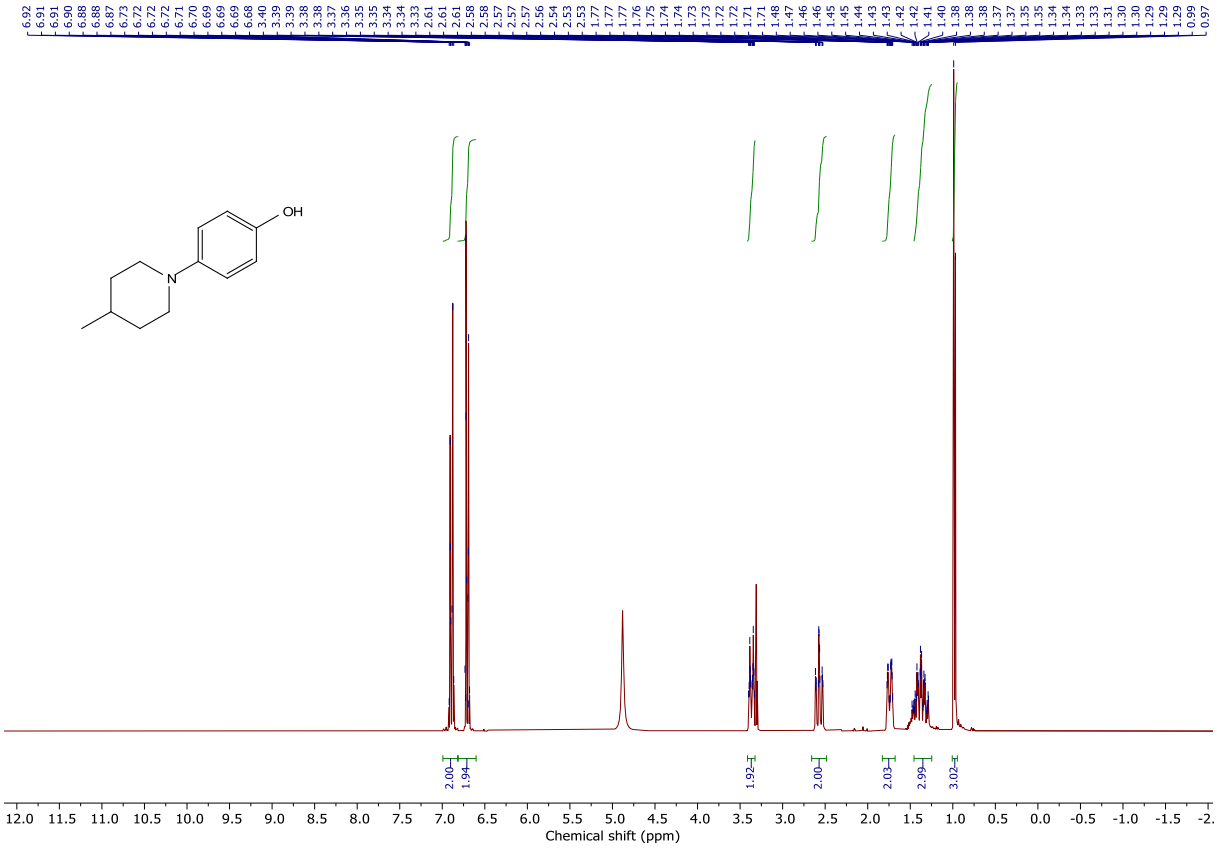
^{1}H-NMR (300 MHz, $CDCl_3$)



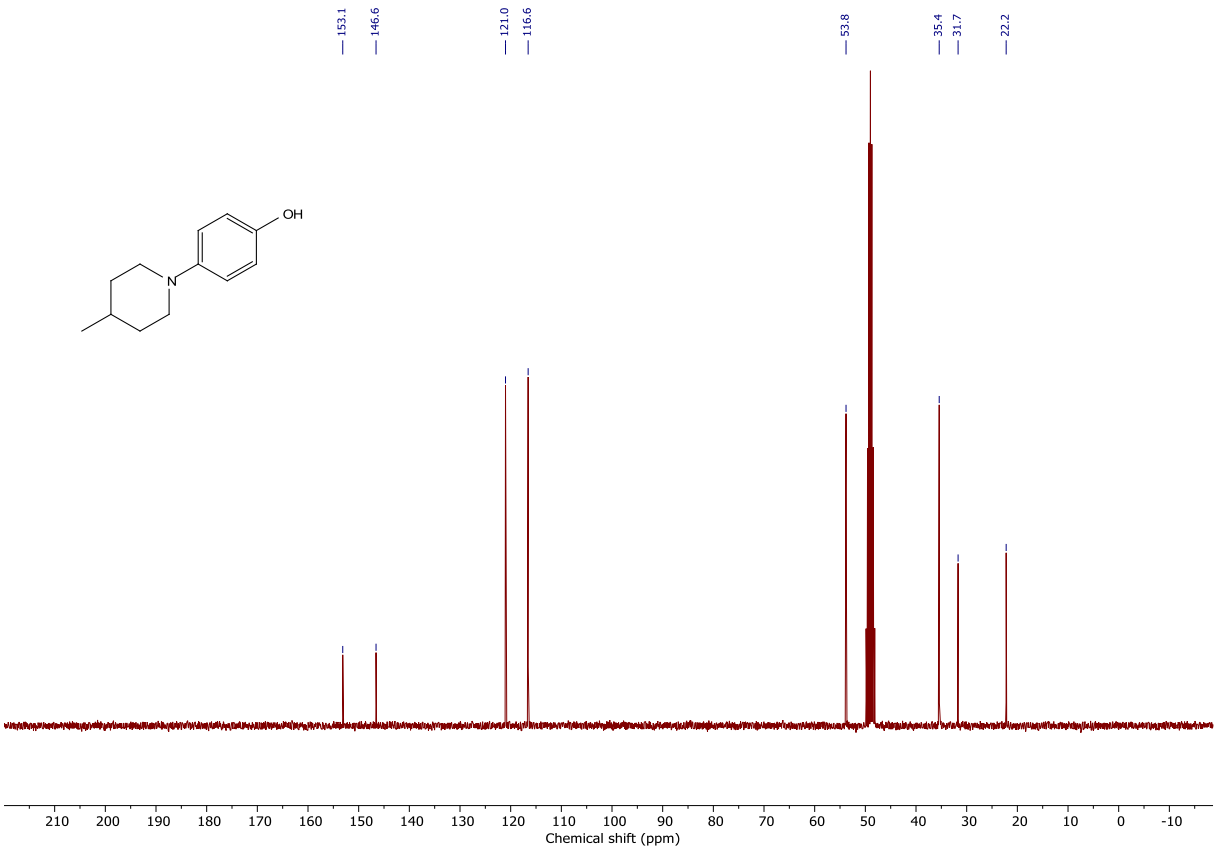
^{13}C-NMR (75 MHz, $CDCl_3$)



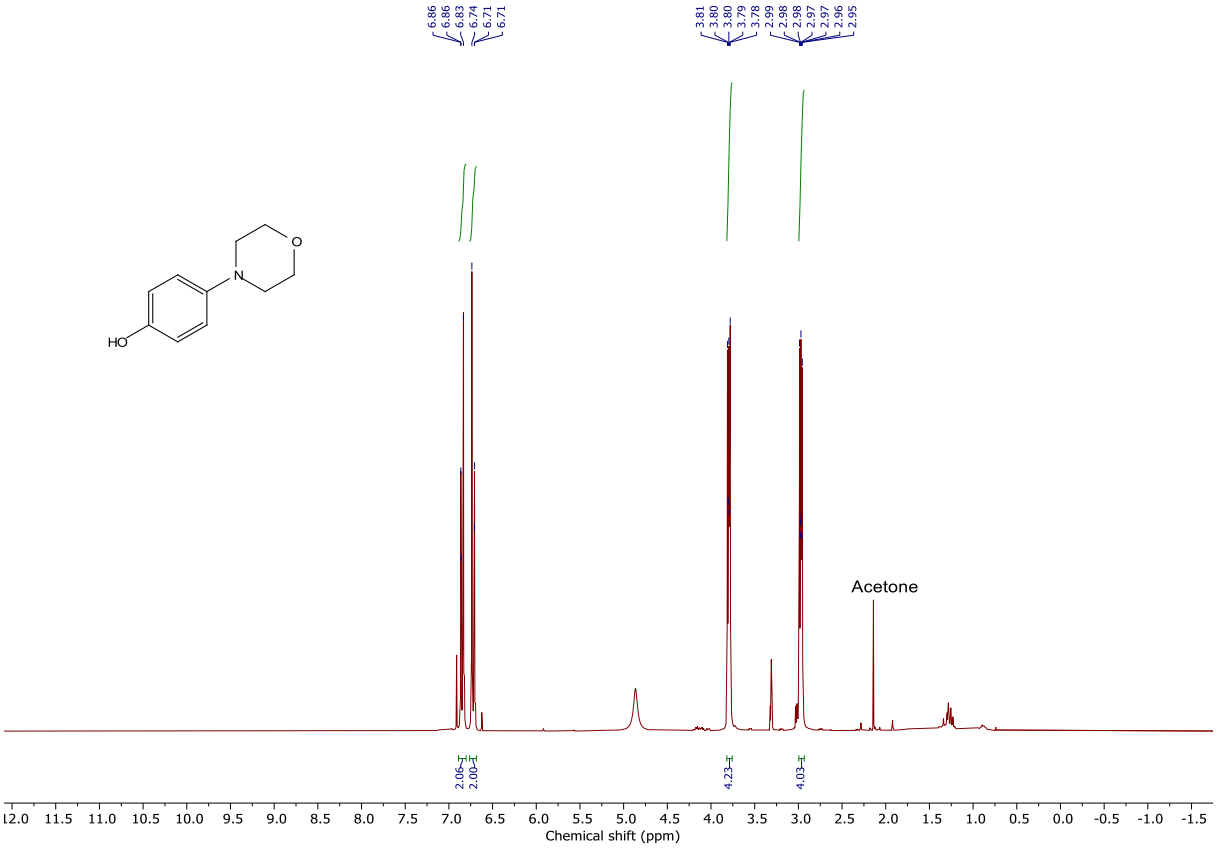
^{1}H-NMR (300 MHz, CD_3OD)



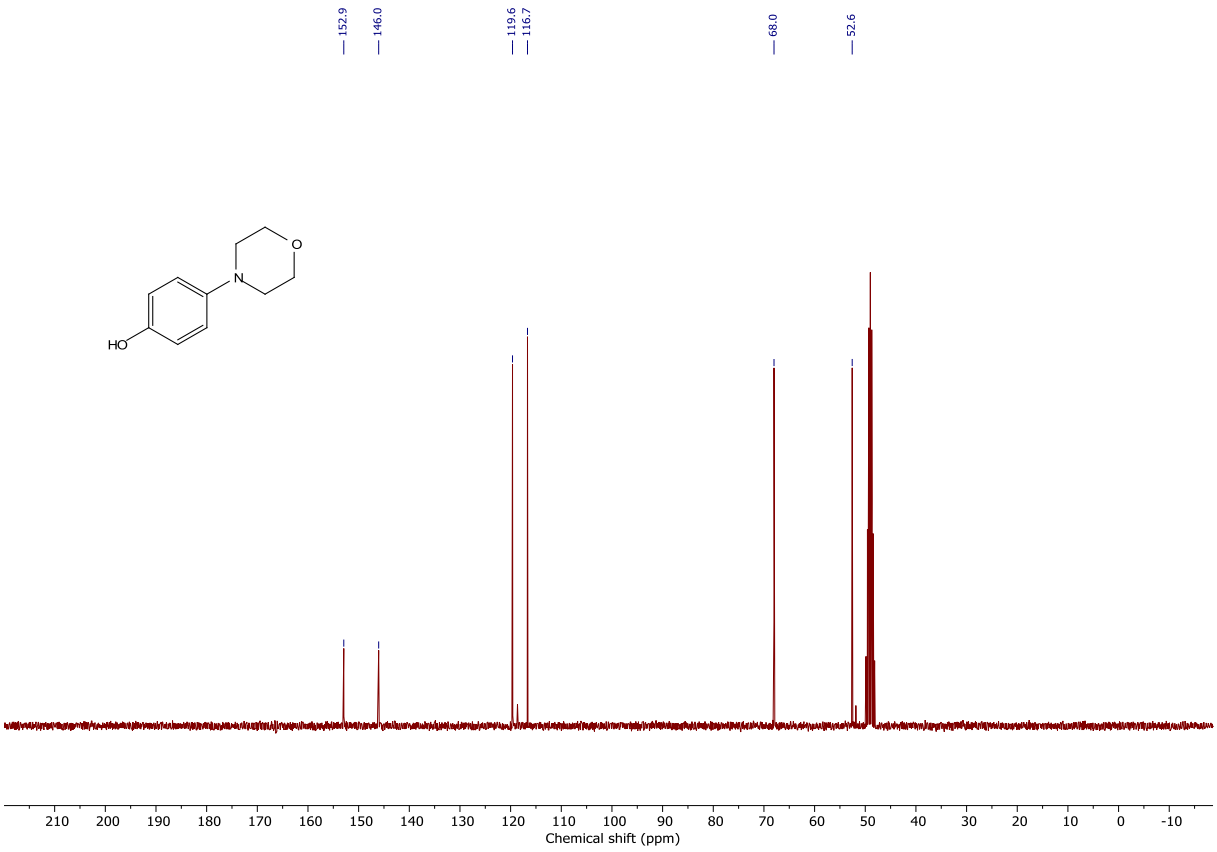
^{13}C-NMR (75 MHz, CD_3OD)



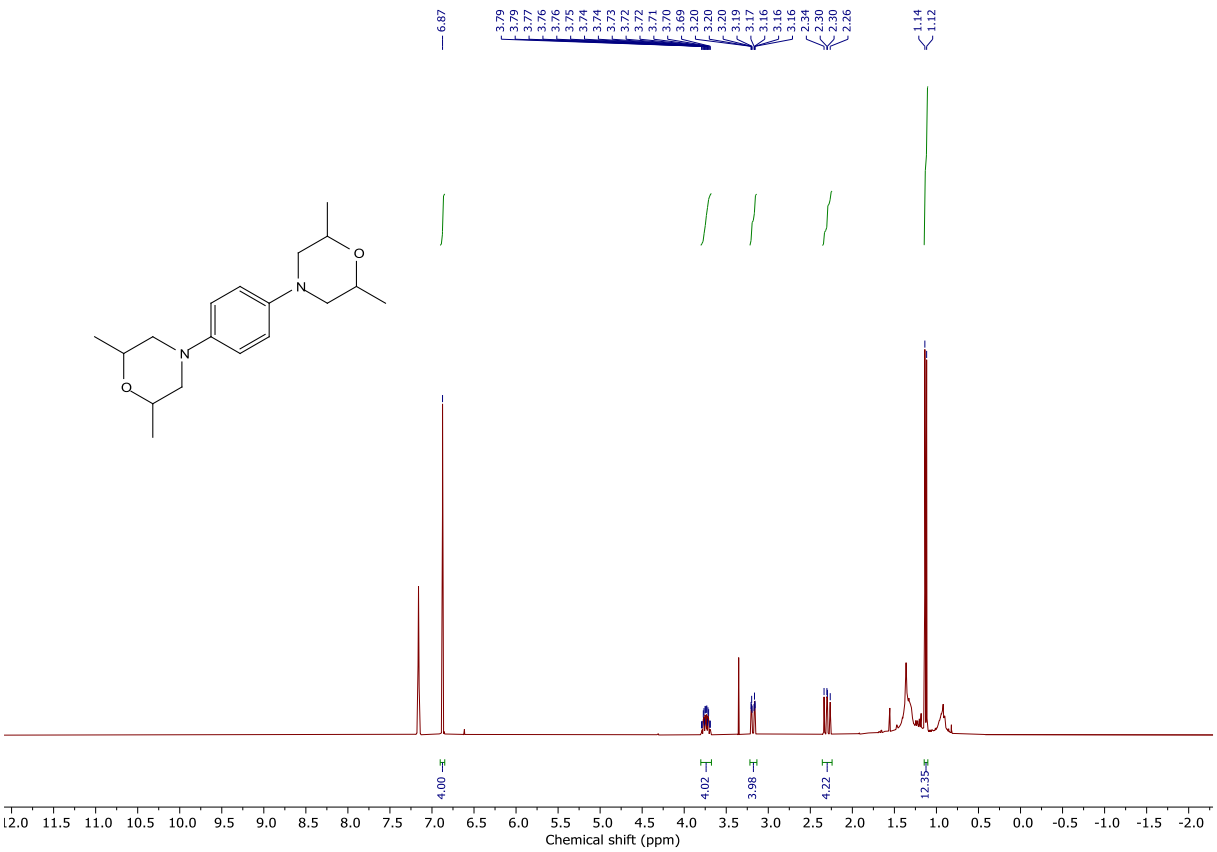
^{1}H-NMR (300 MHz, CD_3OD)



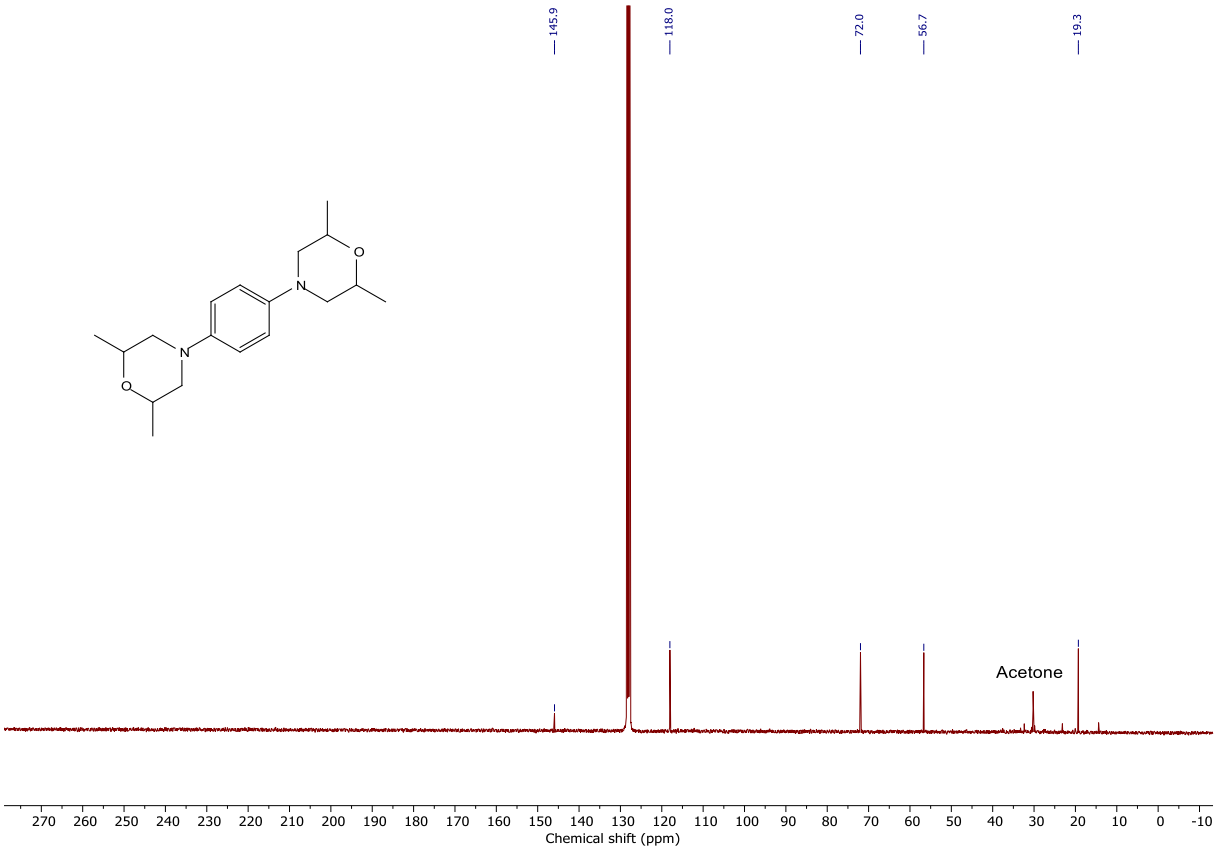
^{13}C-NMR (75 MHz, CD_3OD)



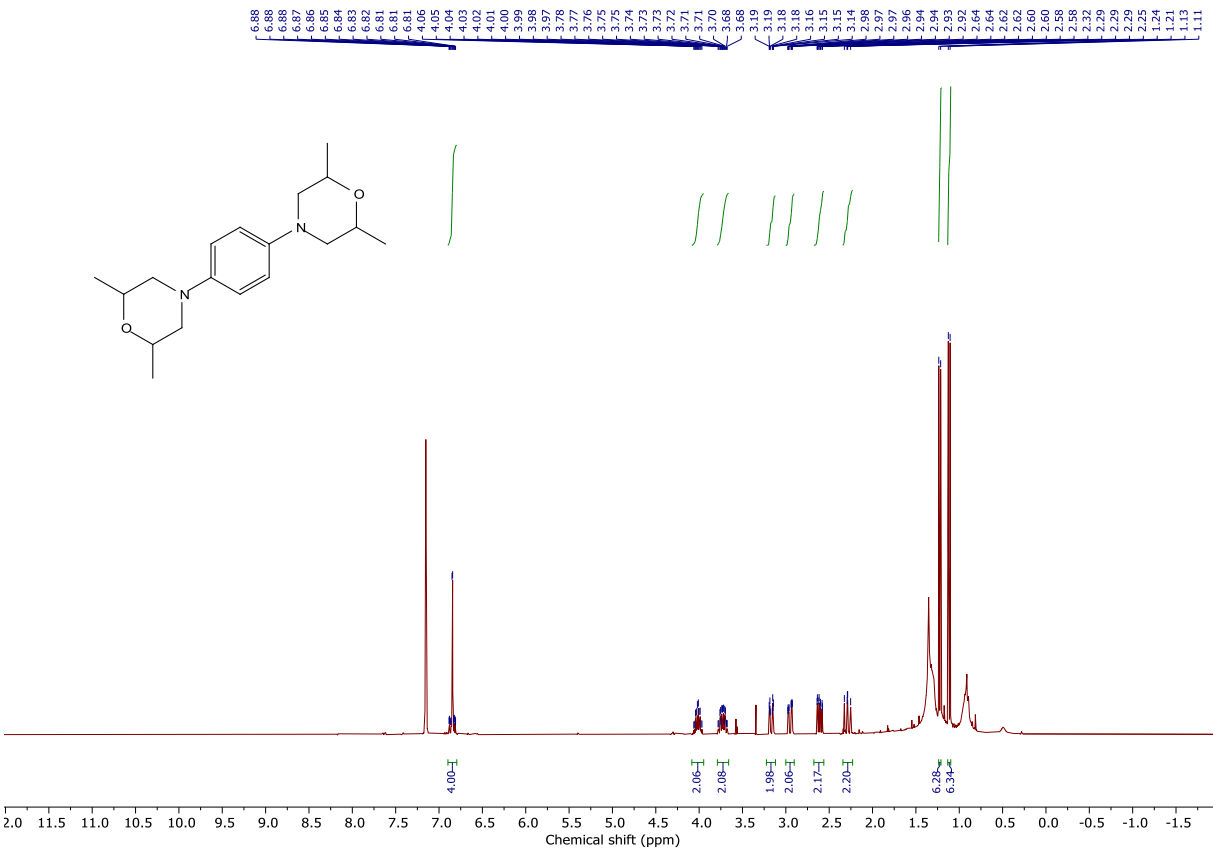
^{1}H-NMR (300 MHz, C_6D_6)



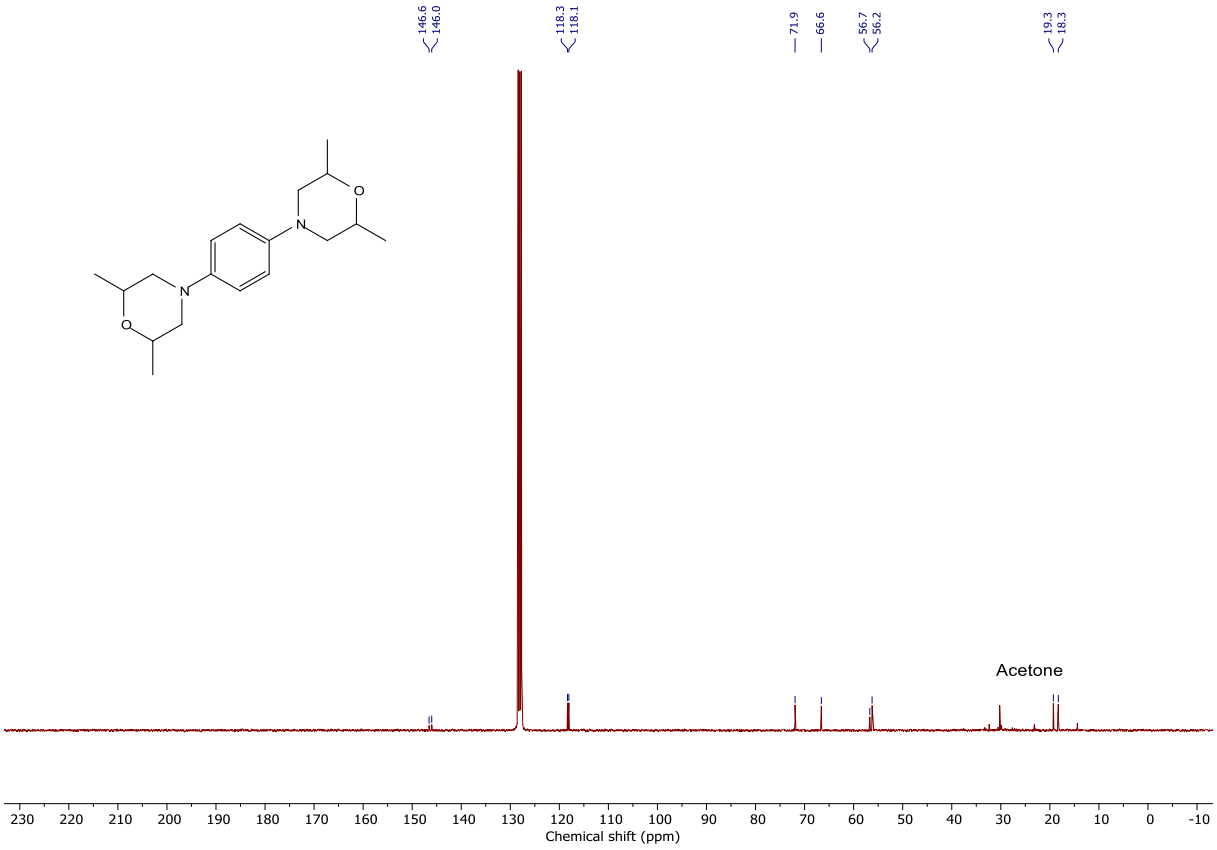
^{13}C-NMR (75 MHz, C_6D_6)



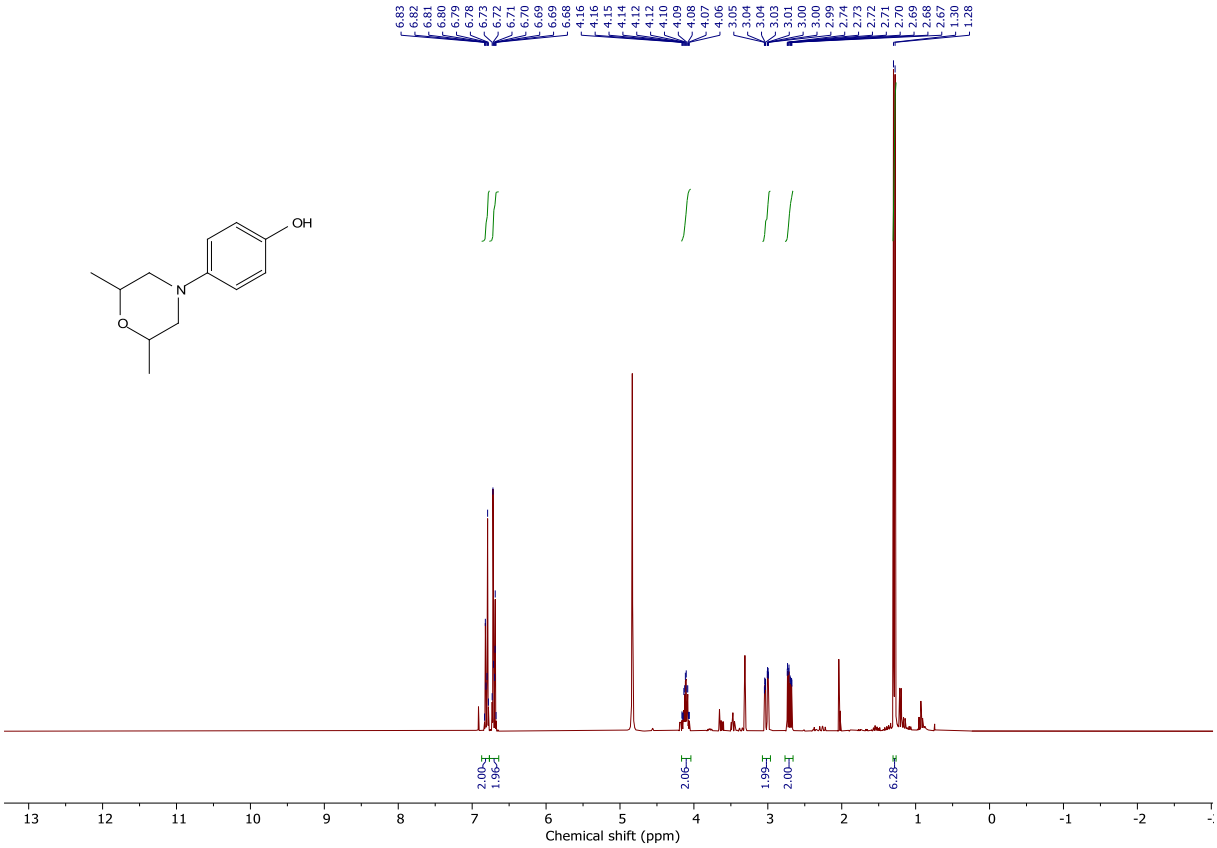
^{1}H-NMR (300 MHz, C_6D_6)



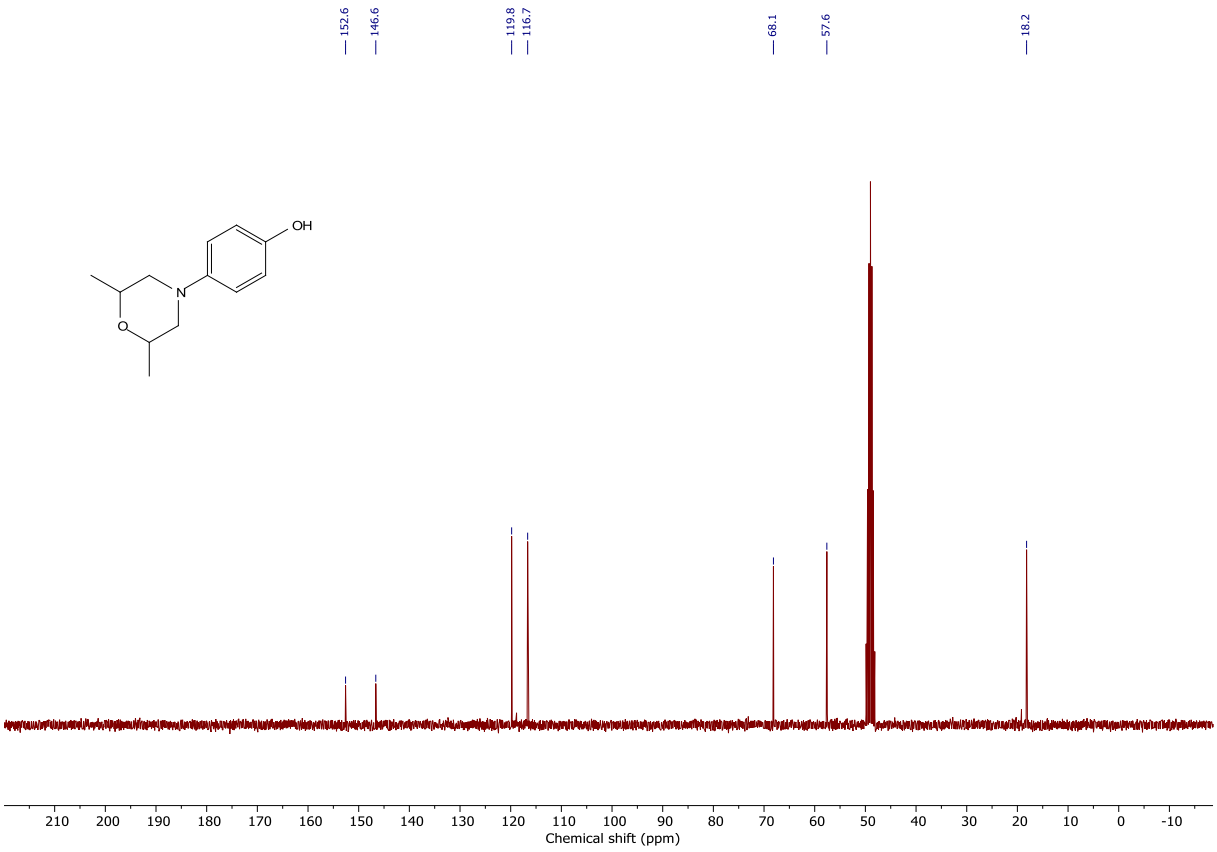
^{13}C-NMR (75 MHz, C_6D_6)



^{1}H-NMR (300 MHz, CD_3OD)



^{13}C-NMR (75 MHz, CD_3OD)



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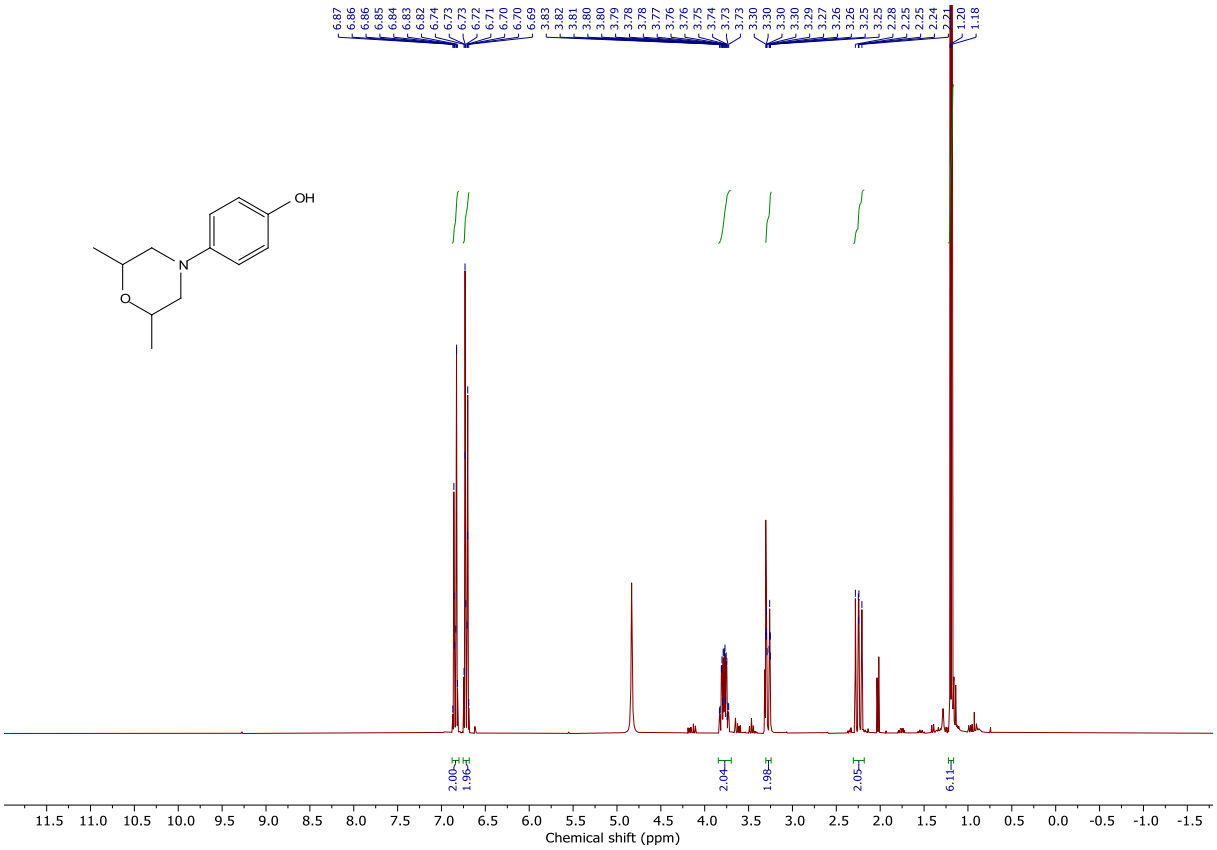

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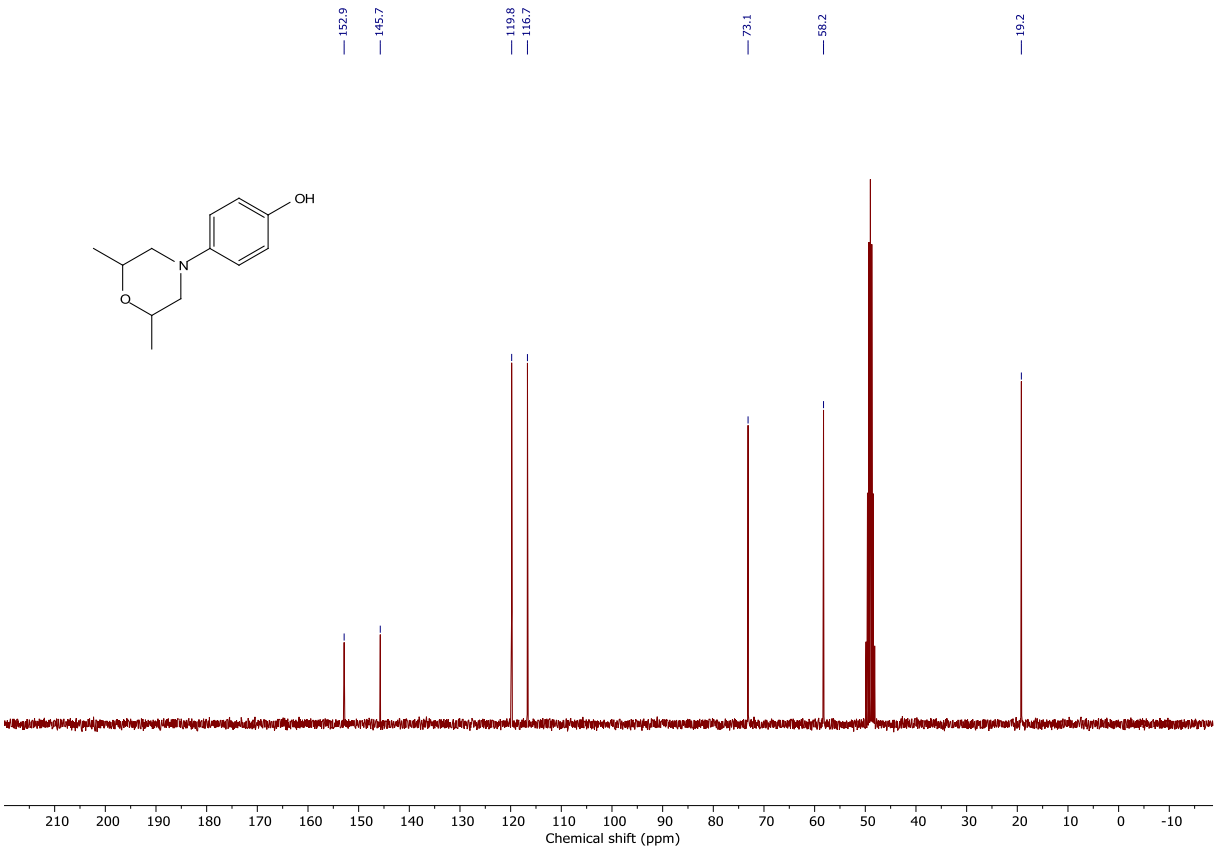

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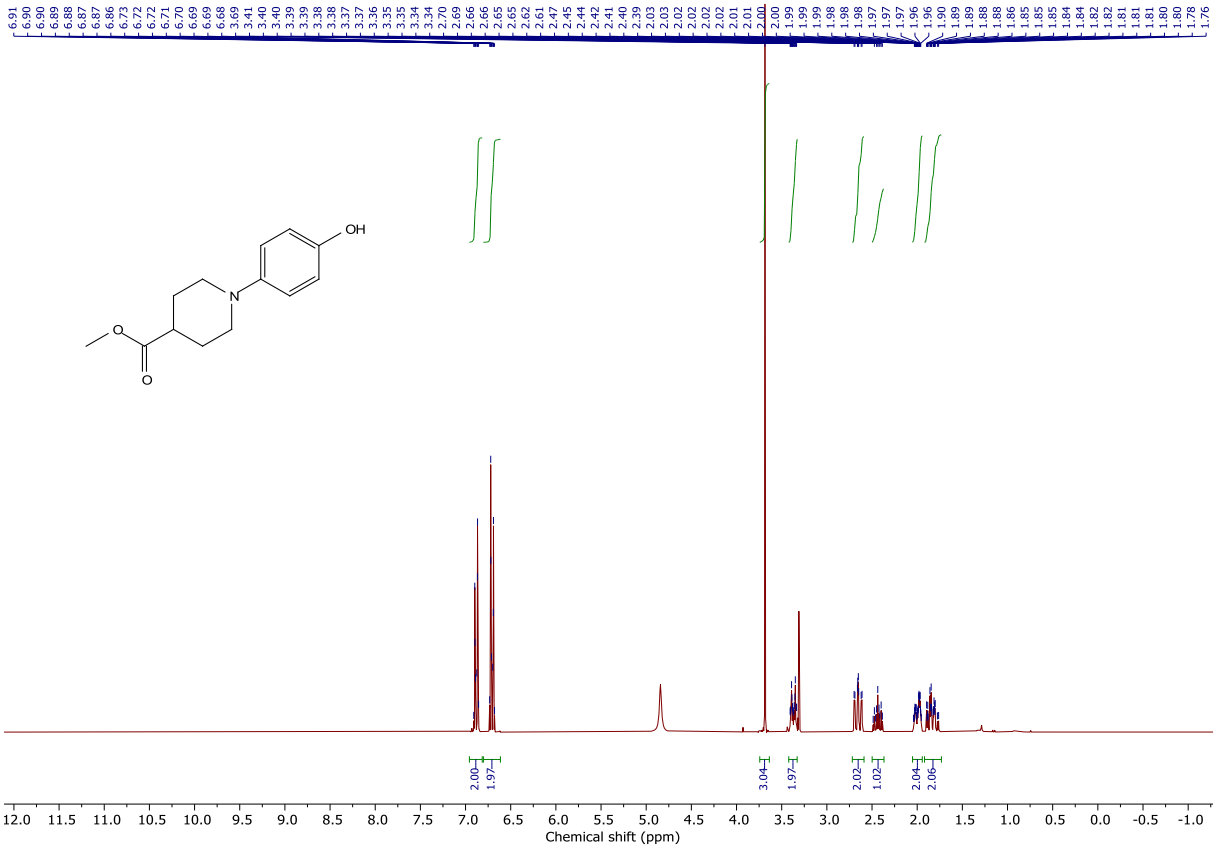

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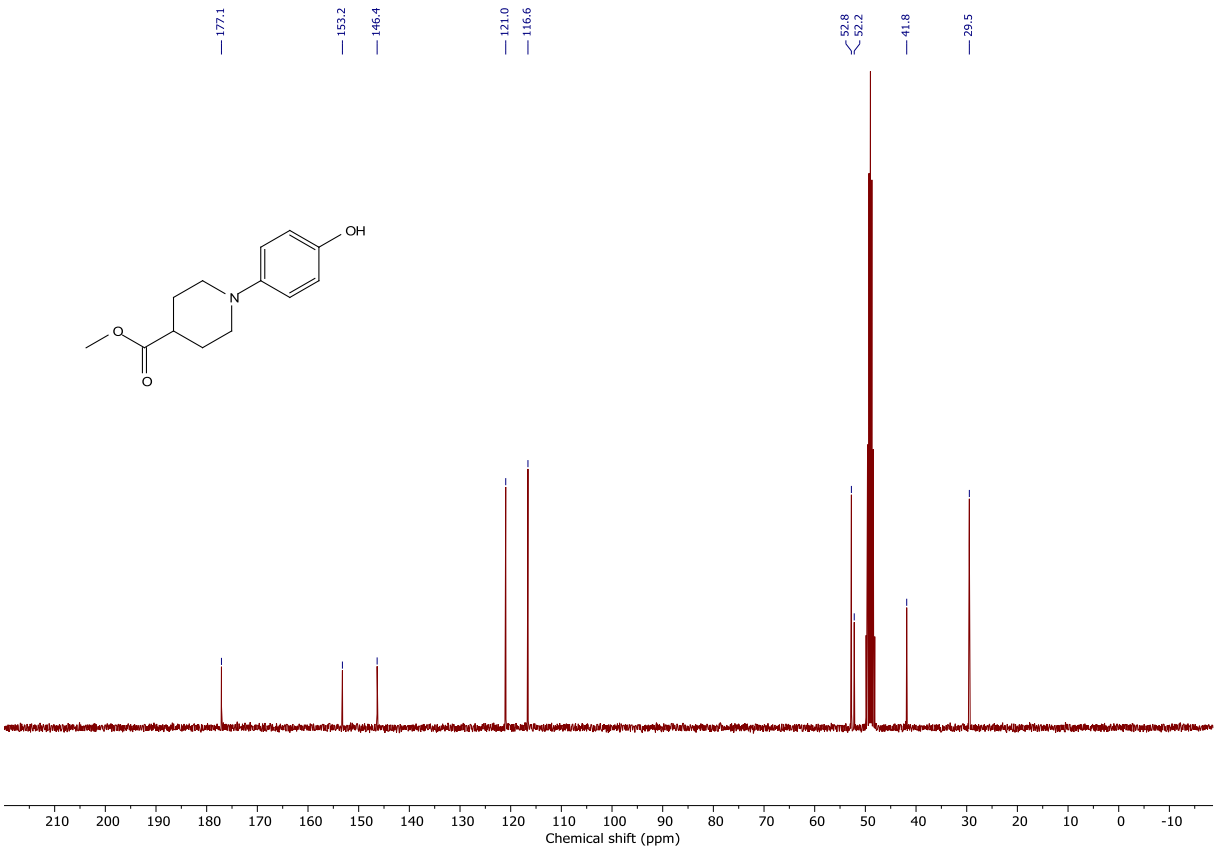

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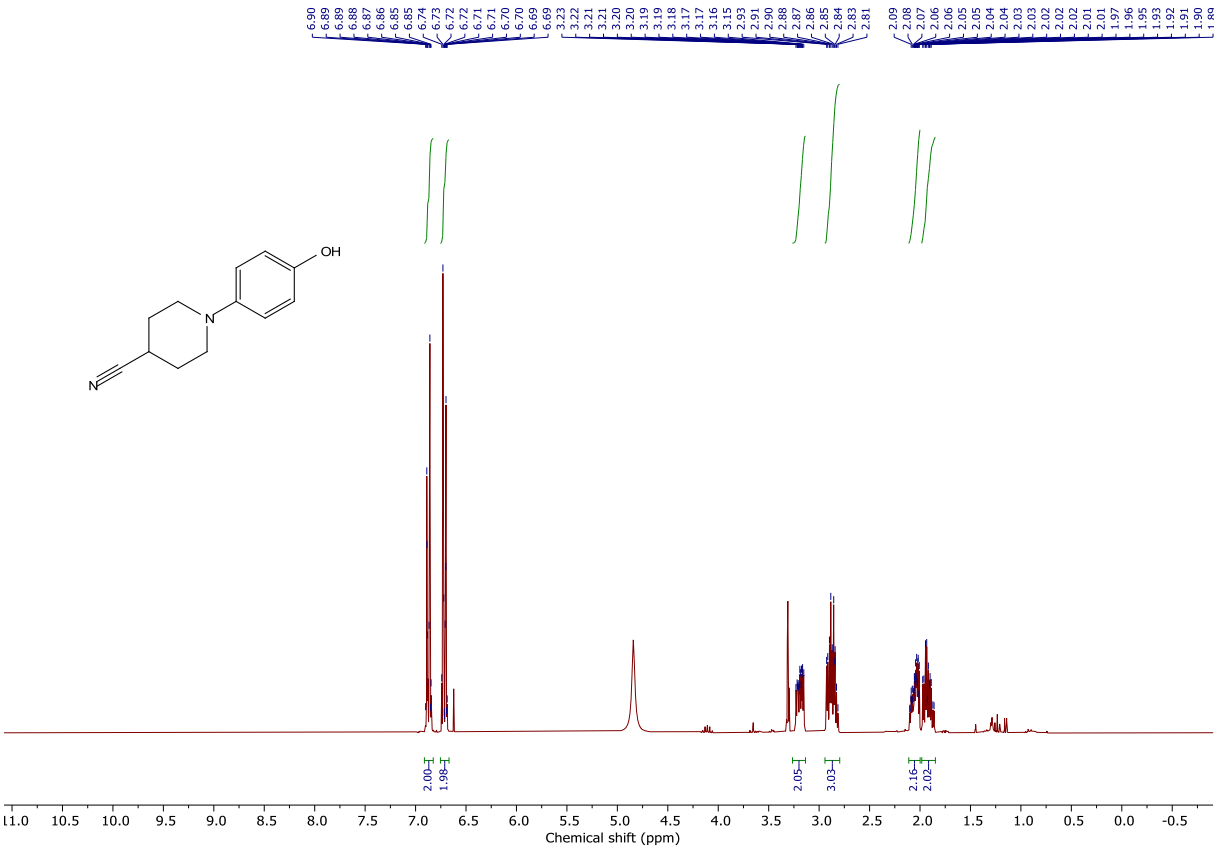

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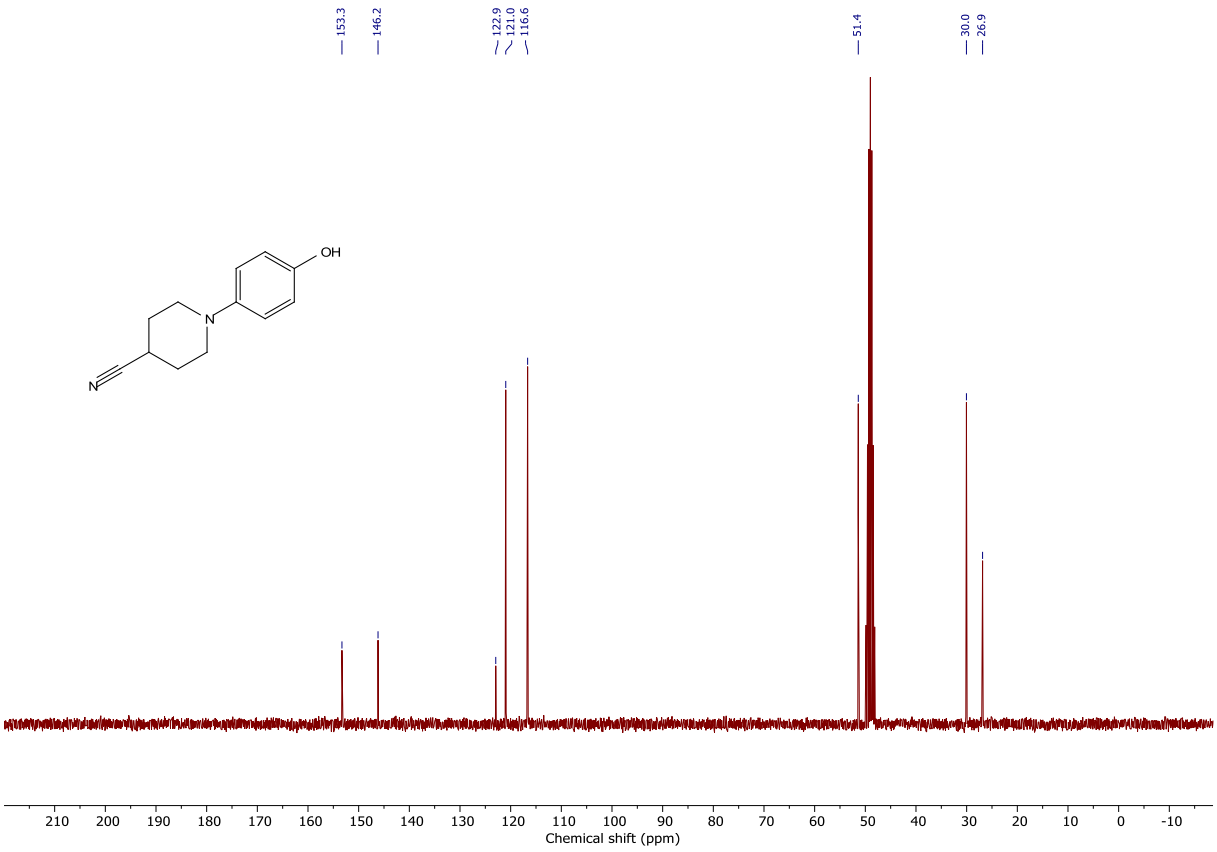

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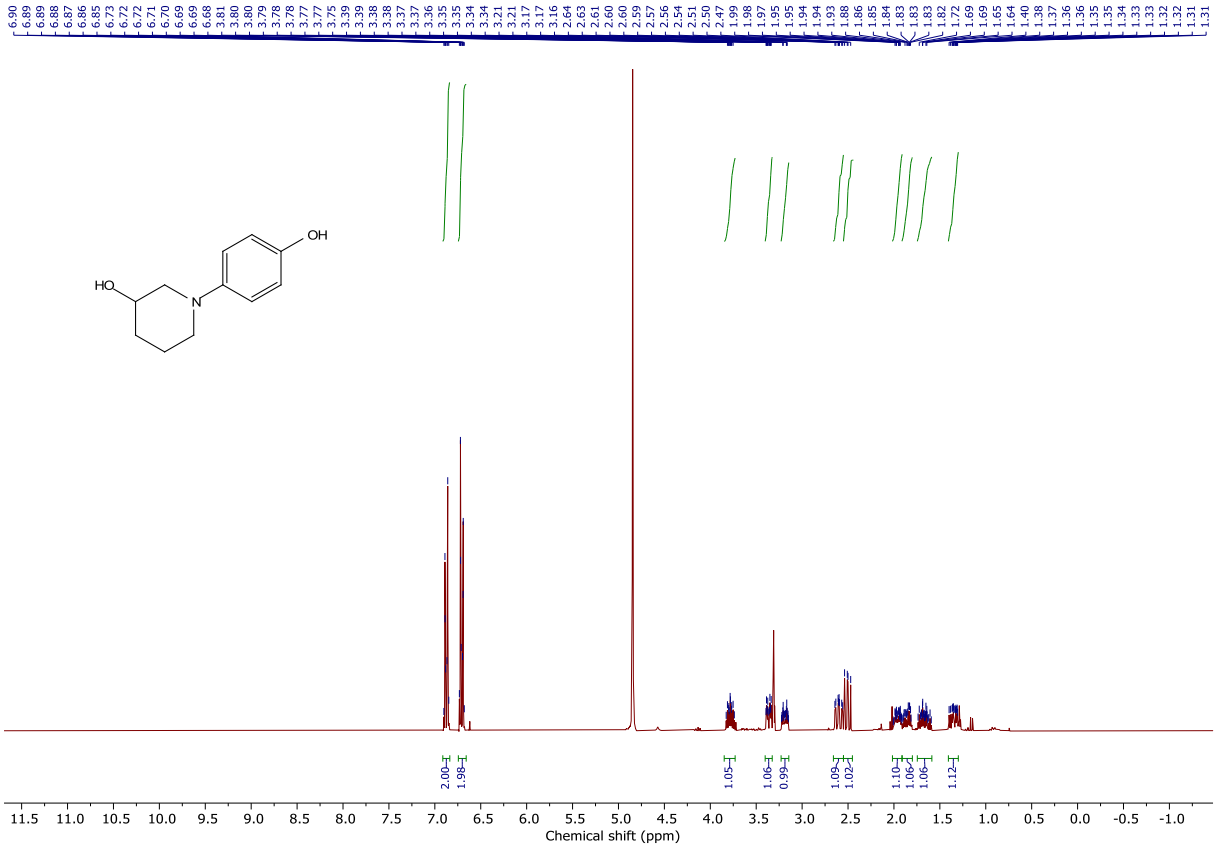

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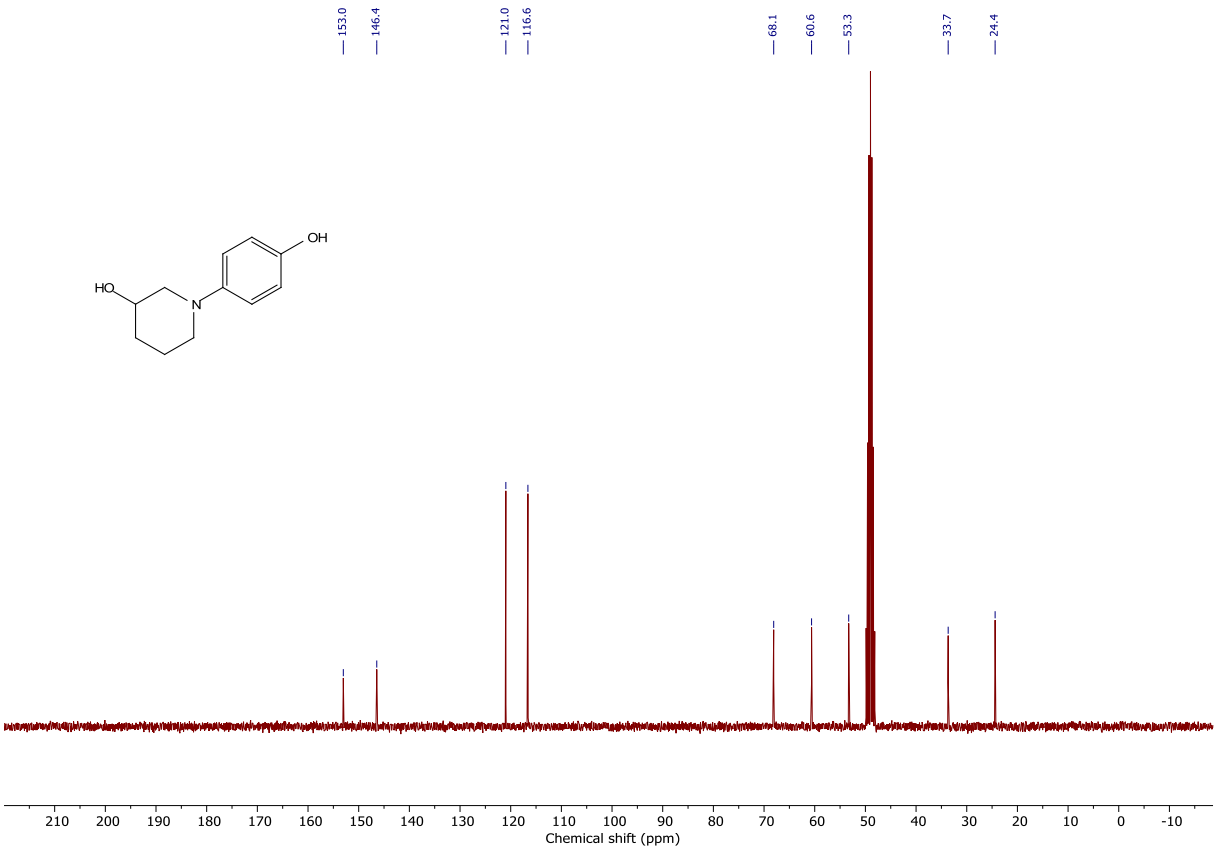

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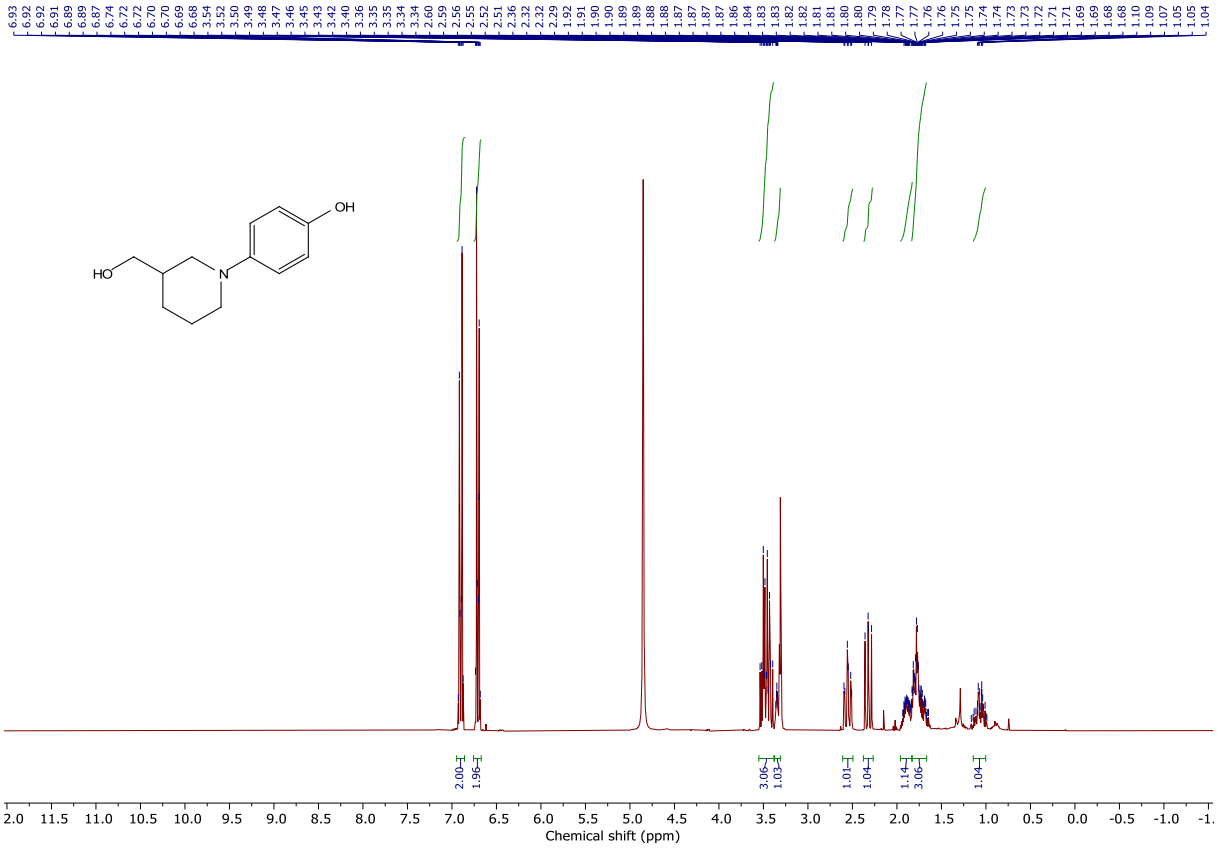

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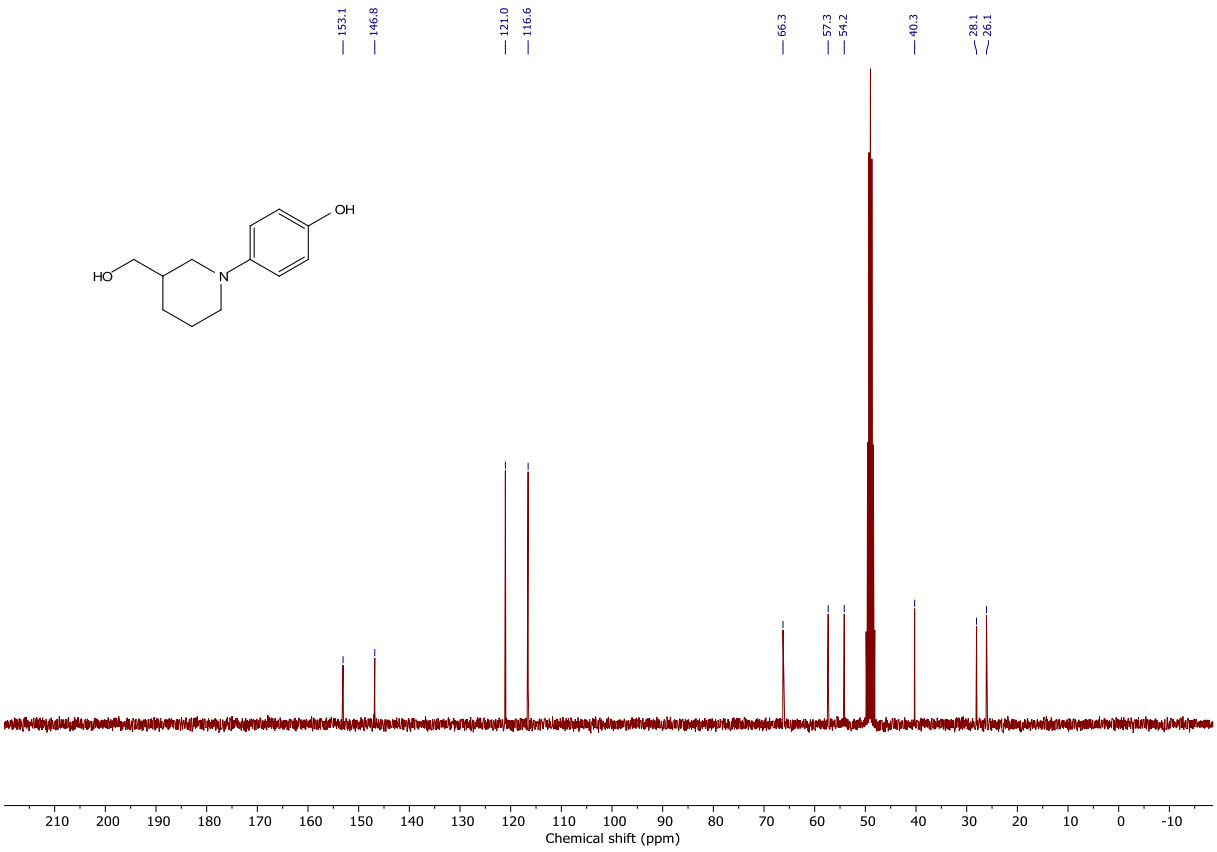

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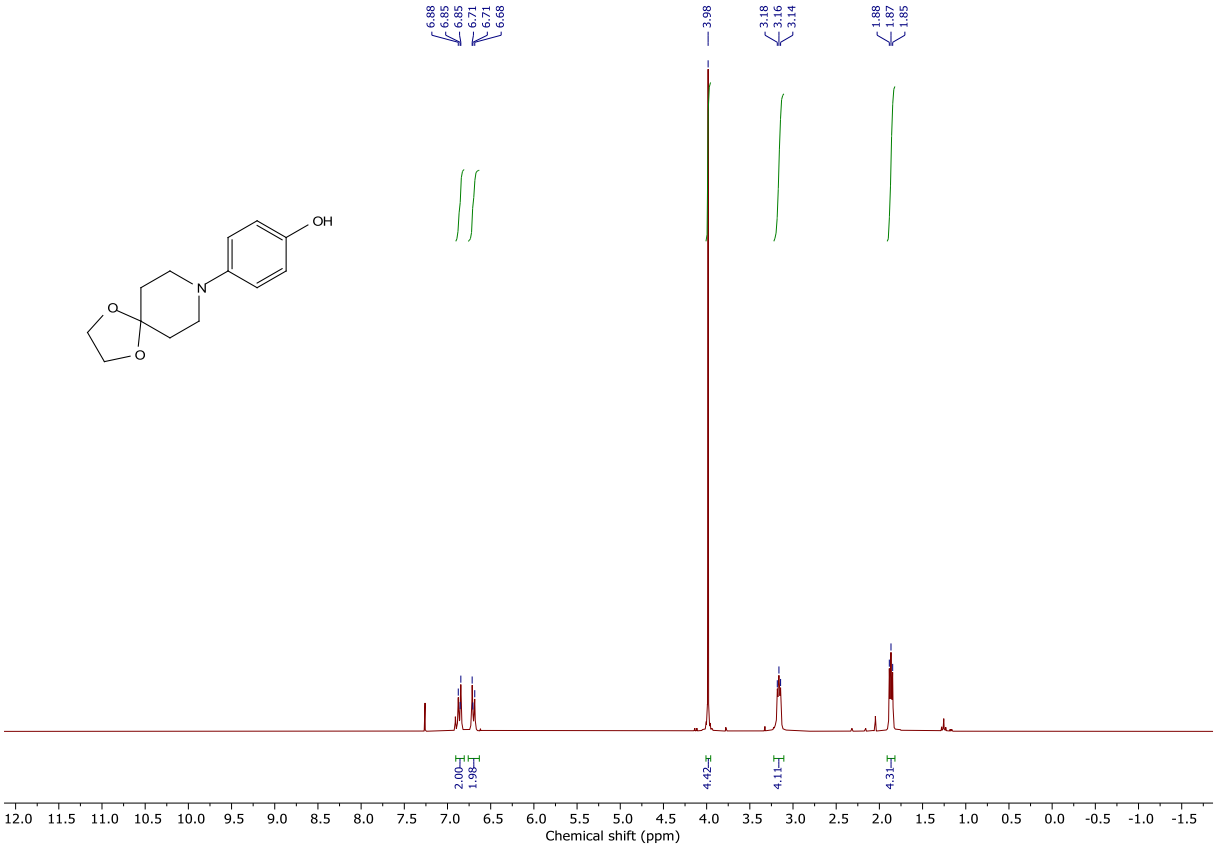

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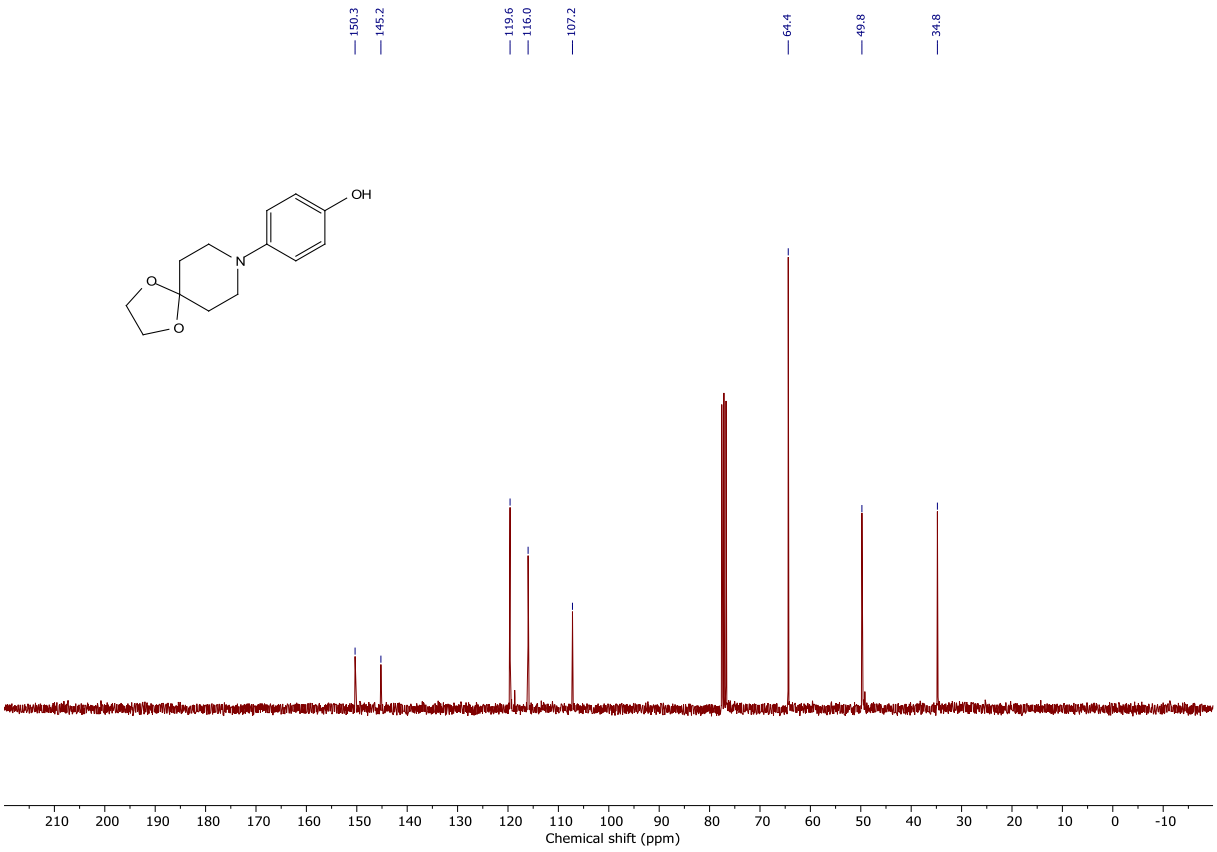
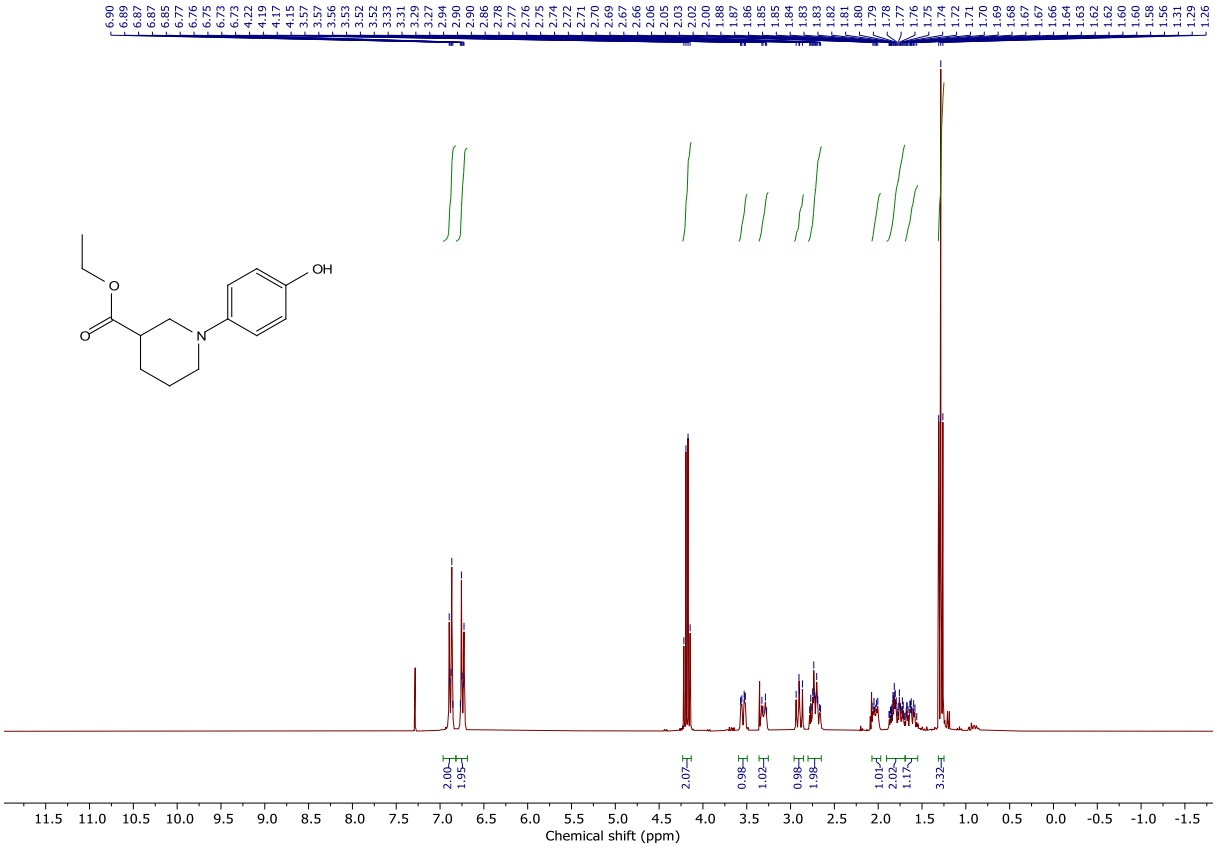


^{1}H-NMR (300 MHz, $CDCl_3$)



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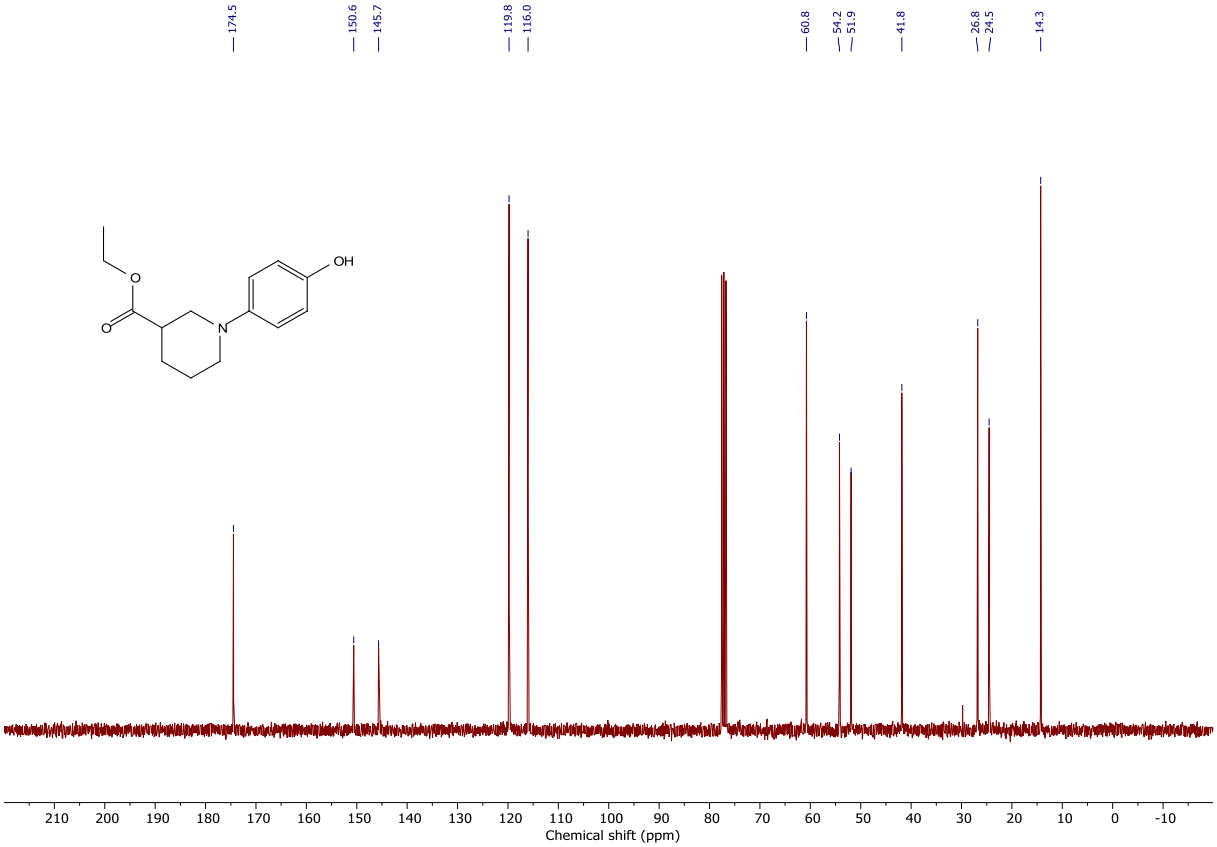
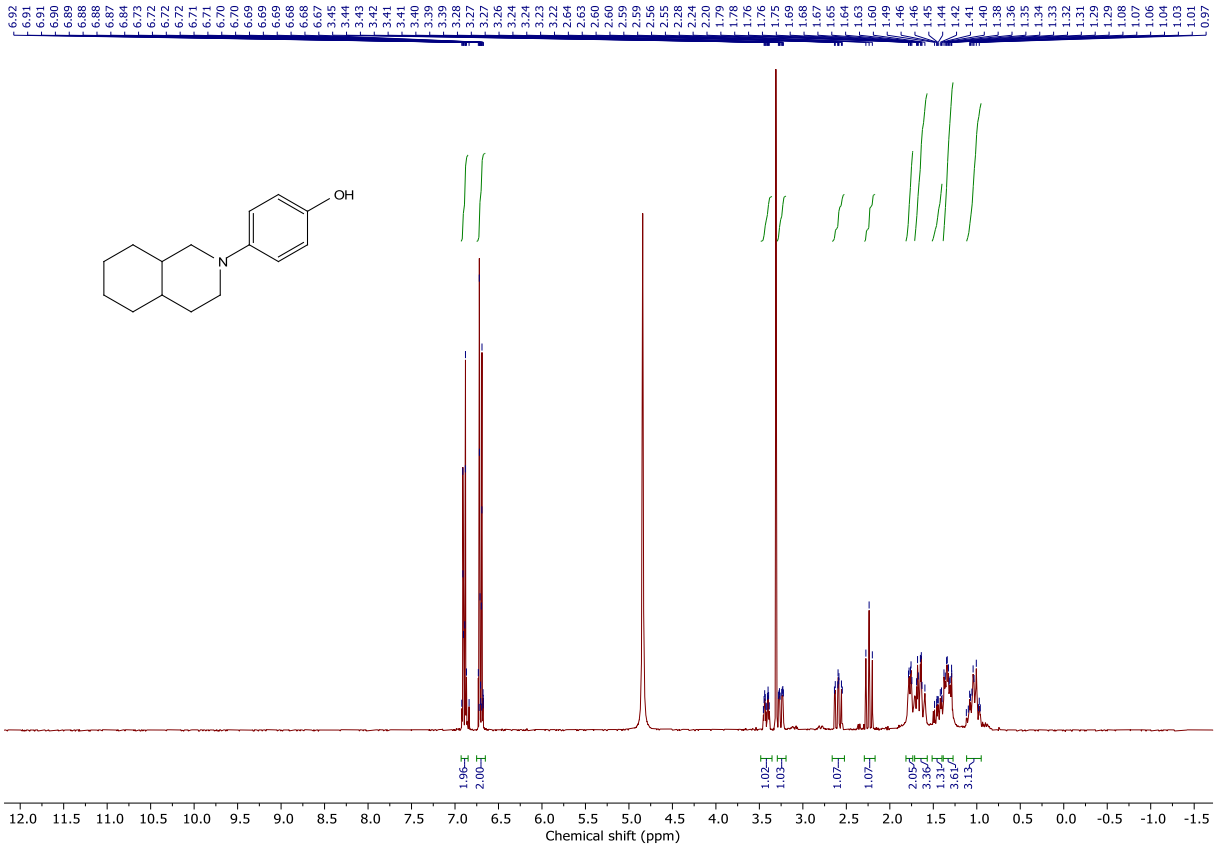


^{1}H-NMR (300 MHz, CD_3OD)



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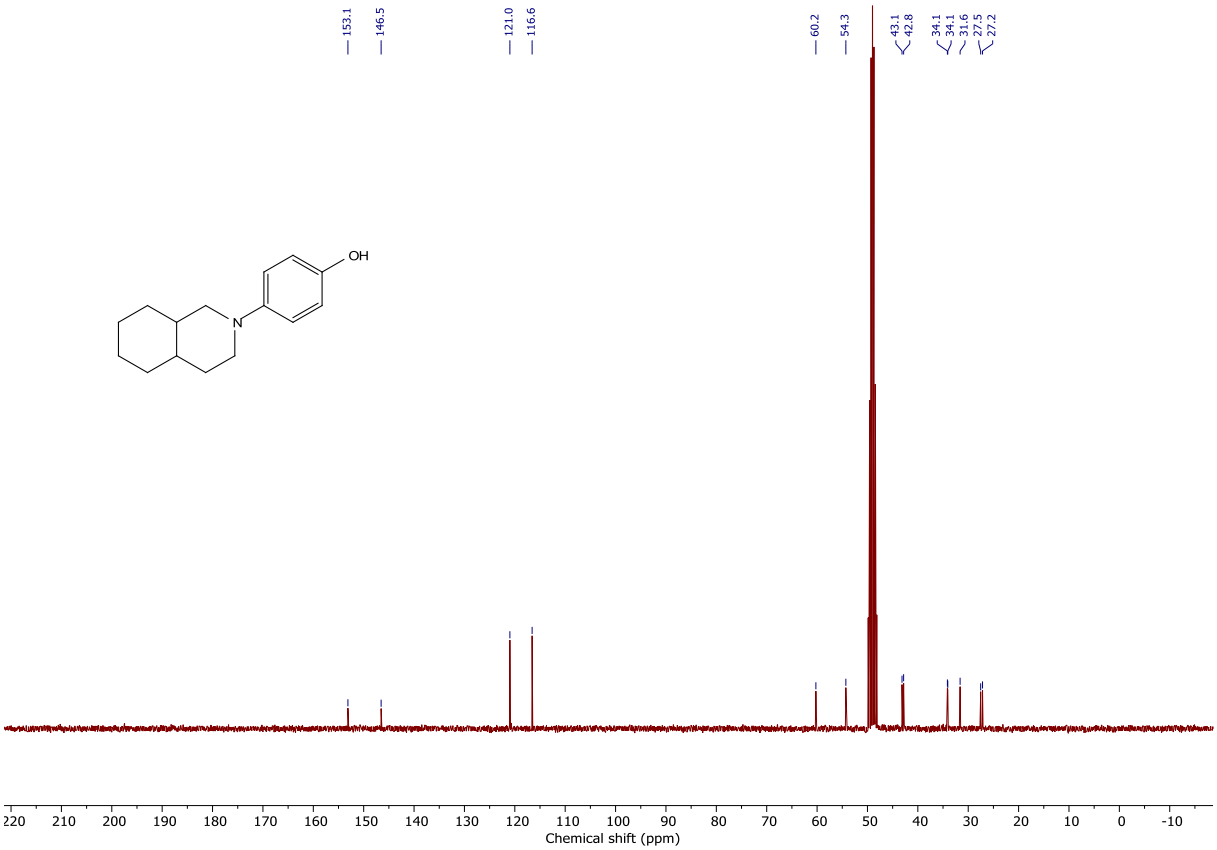

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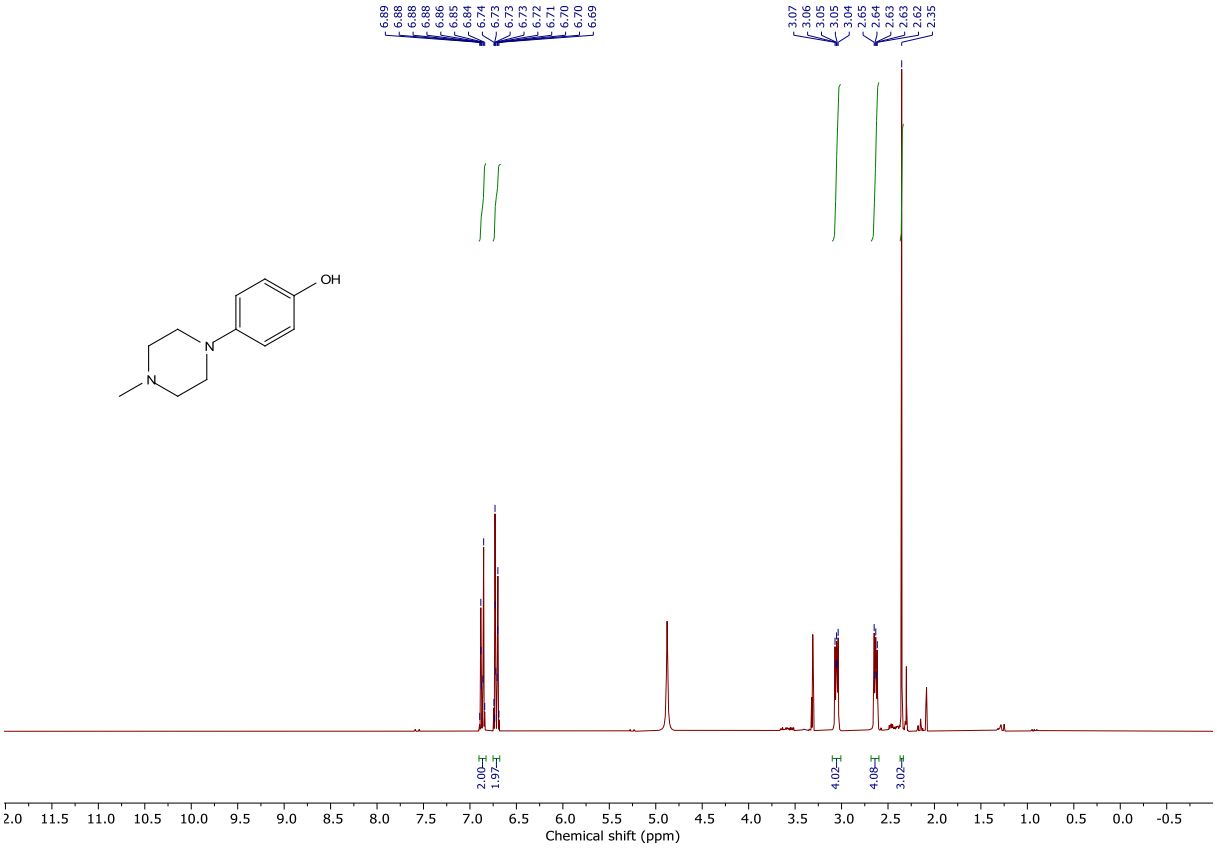

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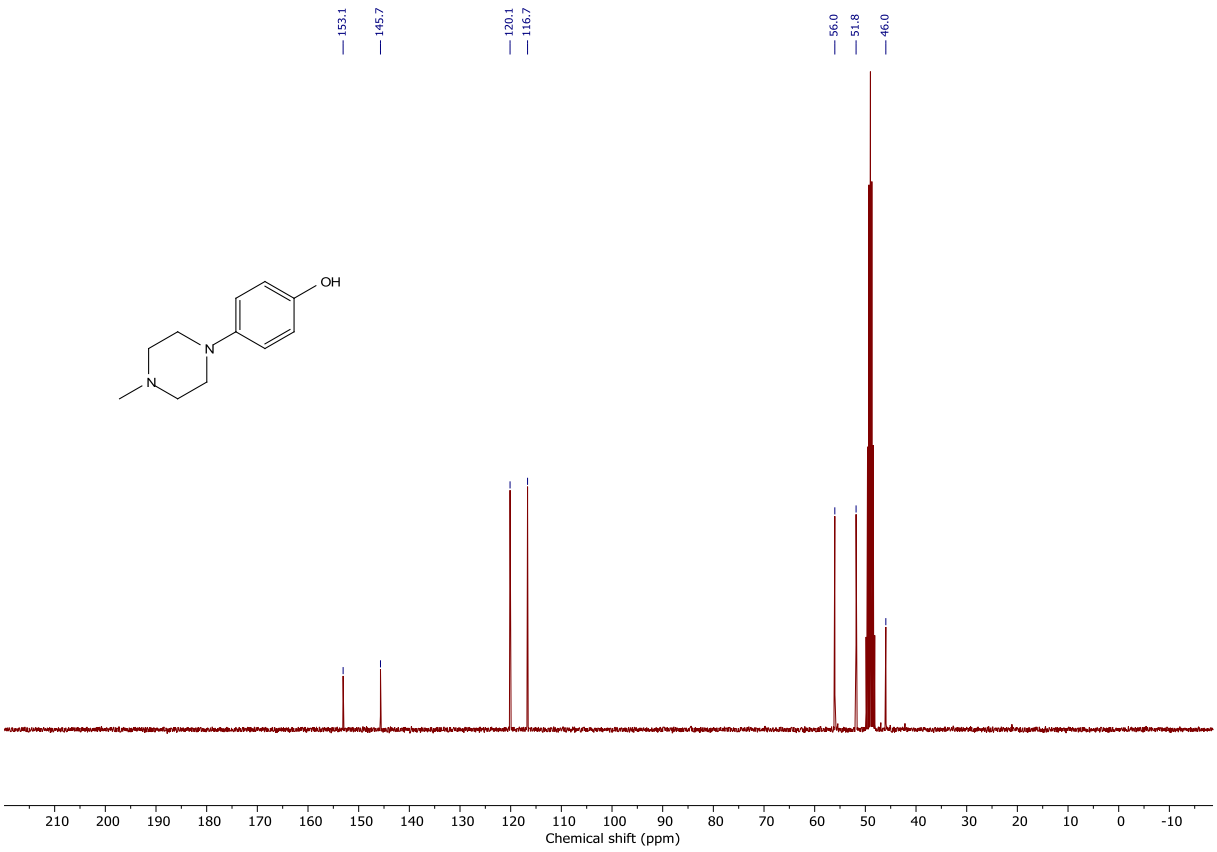

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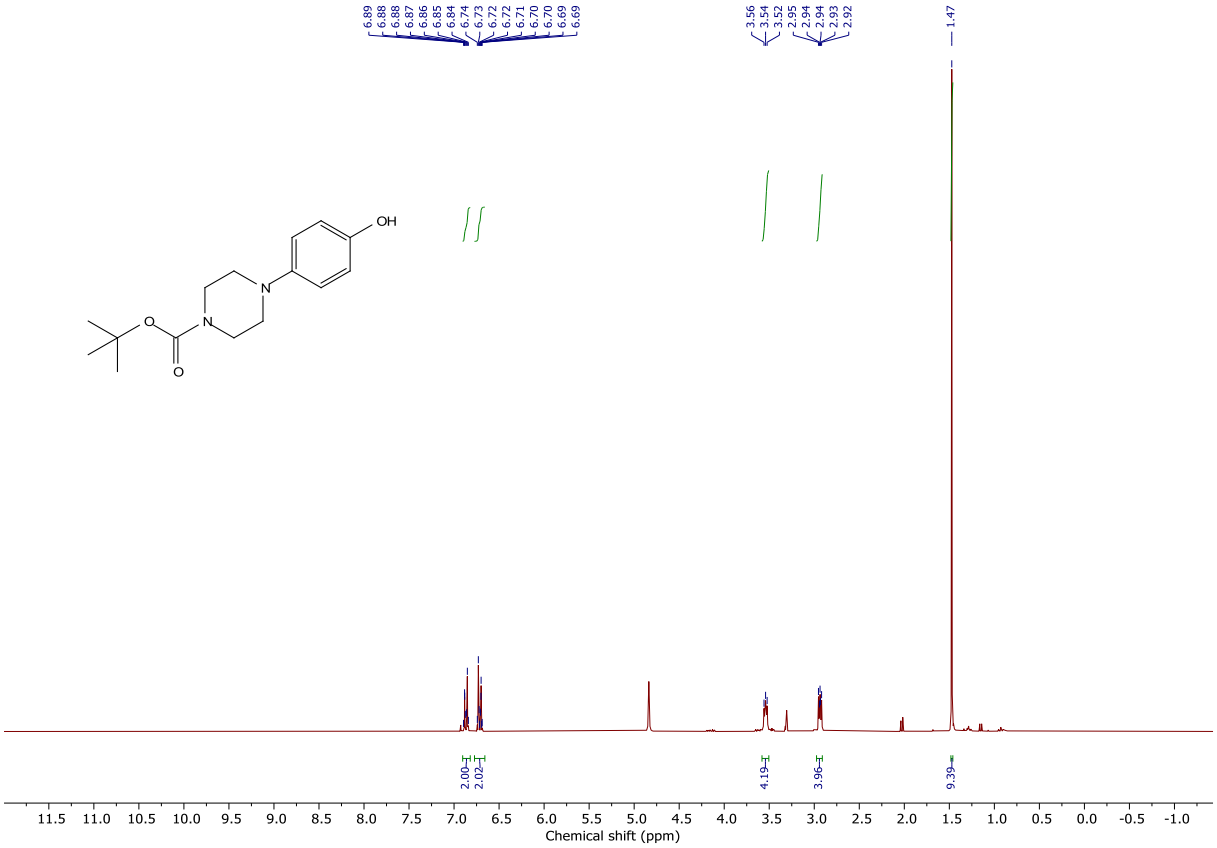

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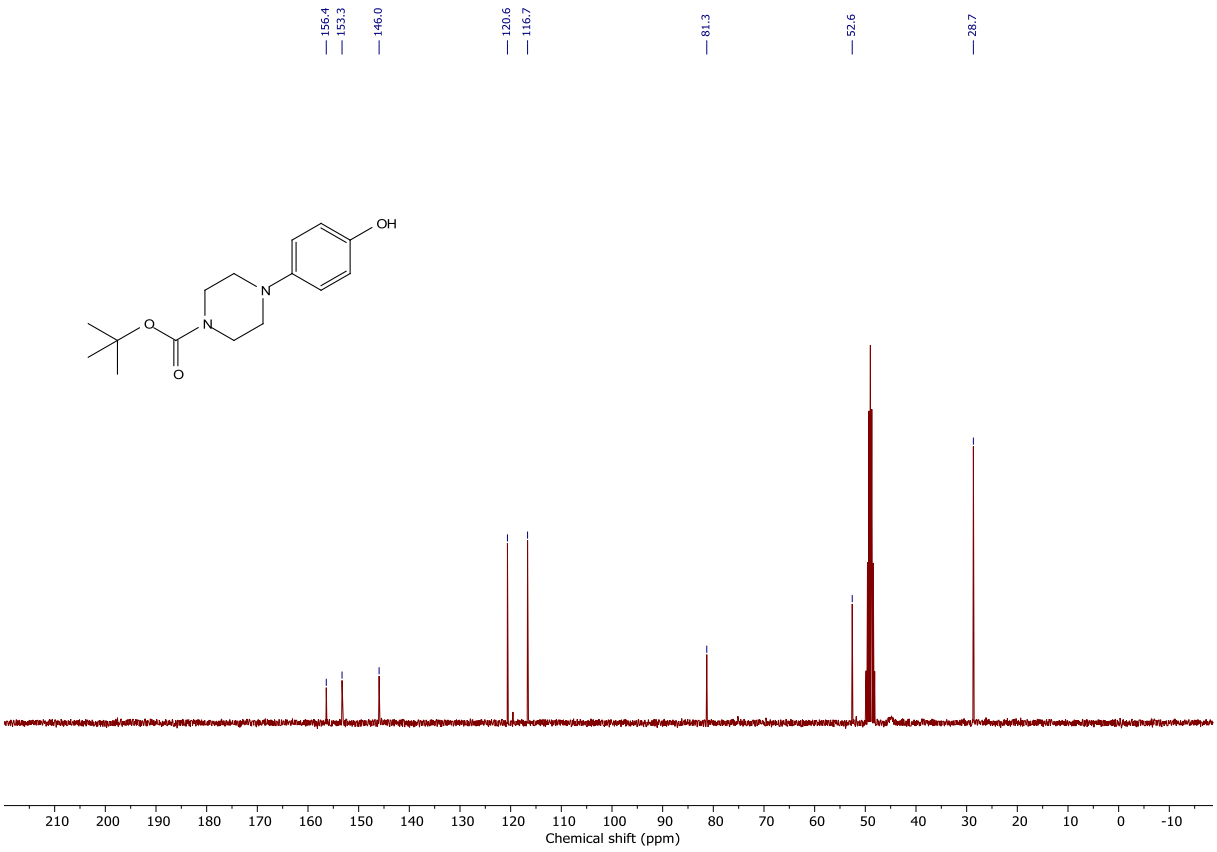

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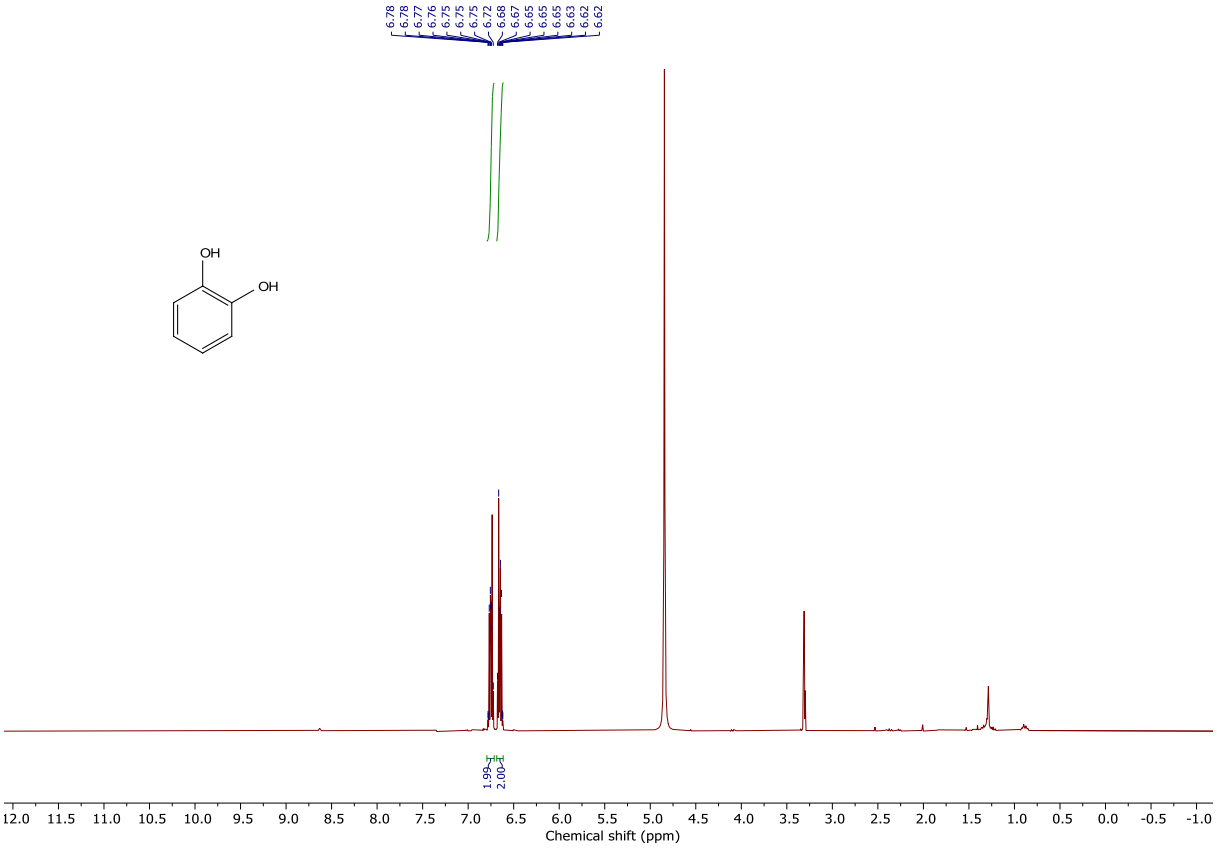

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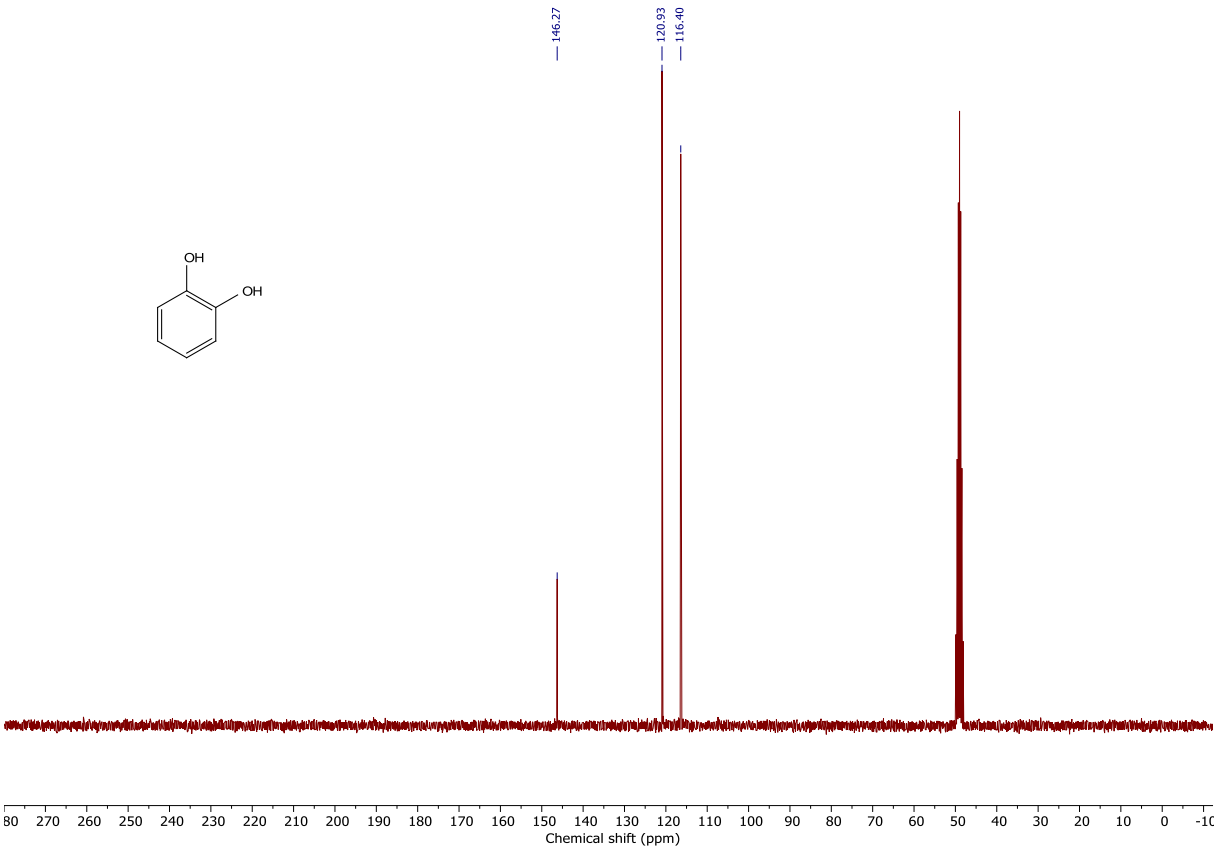

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