Electronic Supplementary Information

for

Iridium-catalyzed *N*-methylation of drug molecules

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Contents

1. General Information

Unless otherwise noted, all starting materials were purchased from commercial suppliers. Column chromatography was performed using silica gel (normal phase, 200–300 mesh) from Anhui Liangchen Silicon Material Co. Ltd, with petroleum ether (60–90 ℃ fraction), dichloromethane, and ethyl acetate as eluents. Reactions were monitored by thin-layer chromatography (TLC) on GF_{254} silica gel plates (0.2 mm) from Anhui Liangchen Silicon Material Co. Ltd. The plates were visualized under UV light, as well as other TLC stains (1.5 g of $KMnO_4$, 10 g of K_2CO_3, and 1.25 mL of 10 % NaOH in 200 mL water. ^1H, ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$, or dimethyl sulfoxide-d_6, with tetramethylsilane (TMS) as an internal standard. The chemical shifts (δ) are reported in parts per million (ppm), and multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), dd (double doublet), tt (triple triplet), dq (double quartet), m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). HRMS measurements were carried out on an Agilent LC/MSD TOF mass spectrometer. Melting points were obtained on a Yanaco MP-500 melting point apparatus and are uncorrected. PE, EtOAc, DCM, THF, DMSO and HFIP are abbreviations for petroleum ether, ethyl acetate, dichloromethane, dimethyl sulfoxide, and hexafluoroisopropanol, respectively.

The solvents used are chosen according to the CHEM21 selection guide of solvents established by Prat and coworkers (D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadad and P. J. Dunn, *Green Chem.*, 2016, **18**, 288-296.). Even so, in very rare cases we had to use the problematic or hazardous solvents (dichloromethane, methanol and petroleum ether for some column chromatography purifications). The poor solubility and/or large polarity of some cyclized and *N*-monomethylated products makes the use of these solvents almost unavoidable. Although we had checked alternative recommended low-boiling-point green solvents (EtOH, i-PrOH, EtOAc, i-PrOAc) and recommended or problematic solvent acetone, they did not give good purification results.

The substrates are listed in Figures S1 and S2.

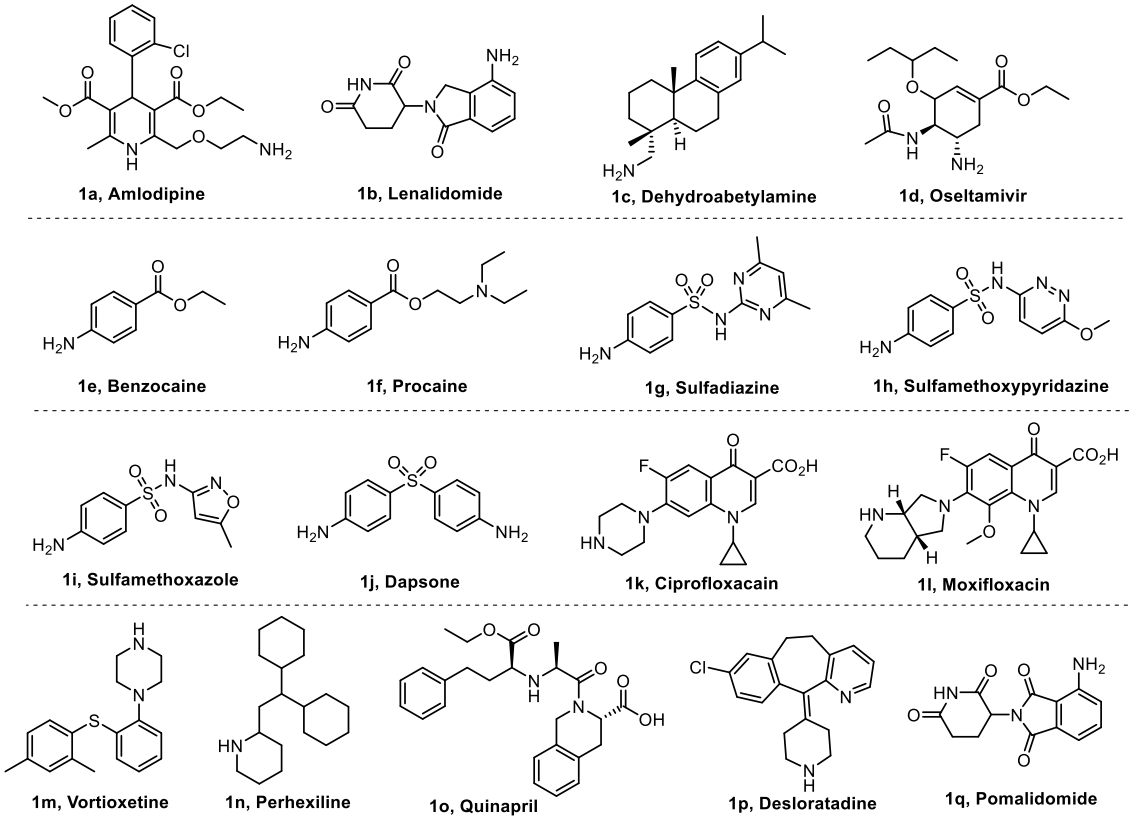


Figure S1. The drug molecules

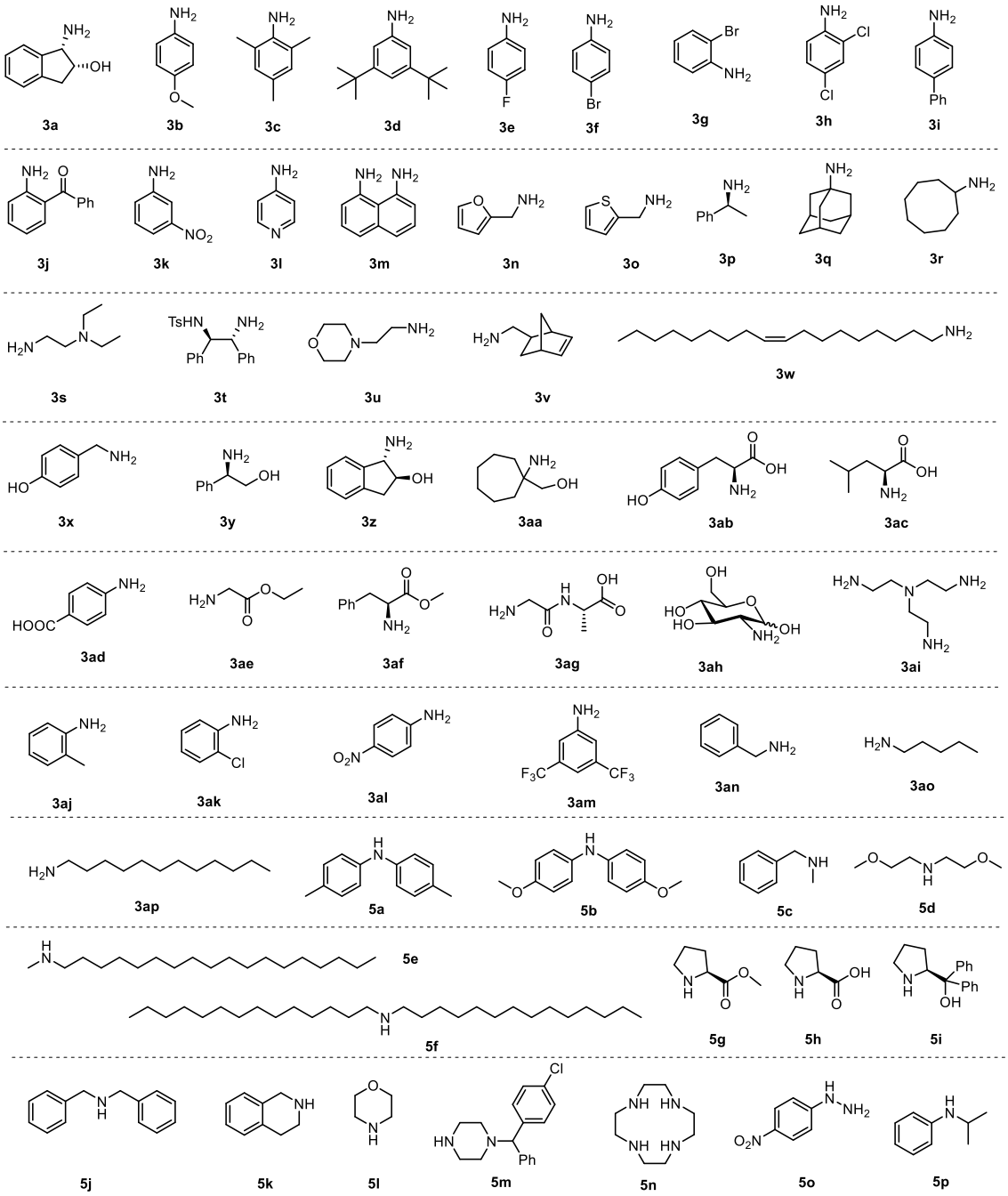
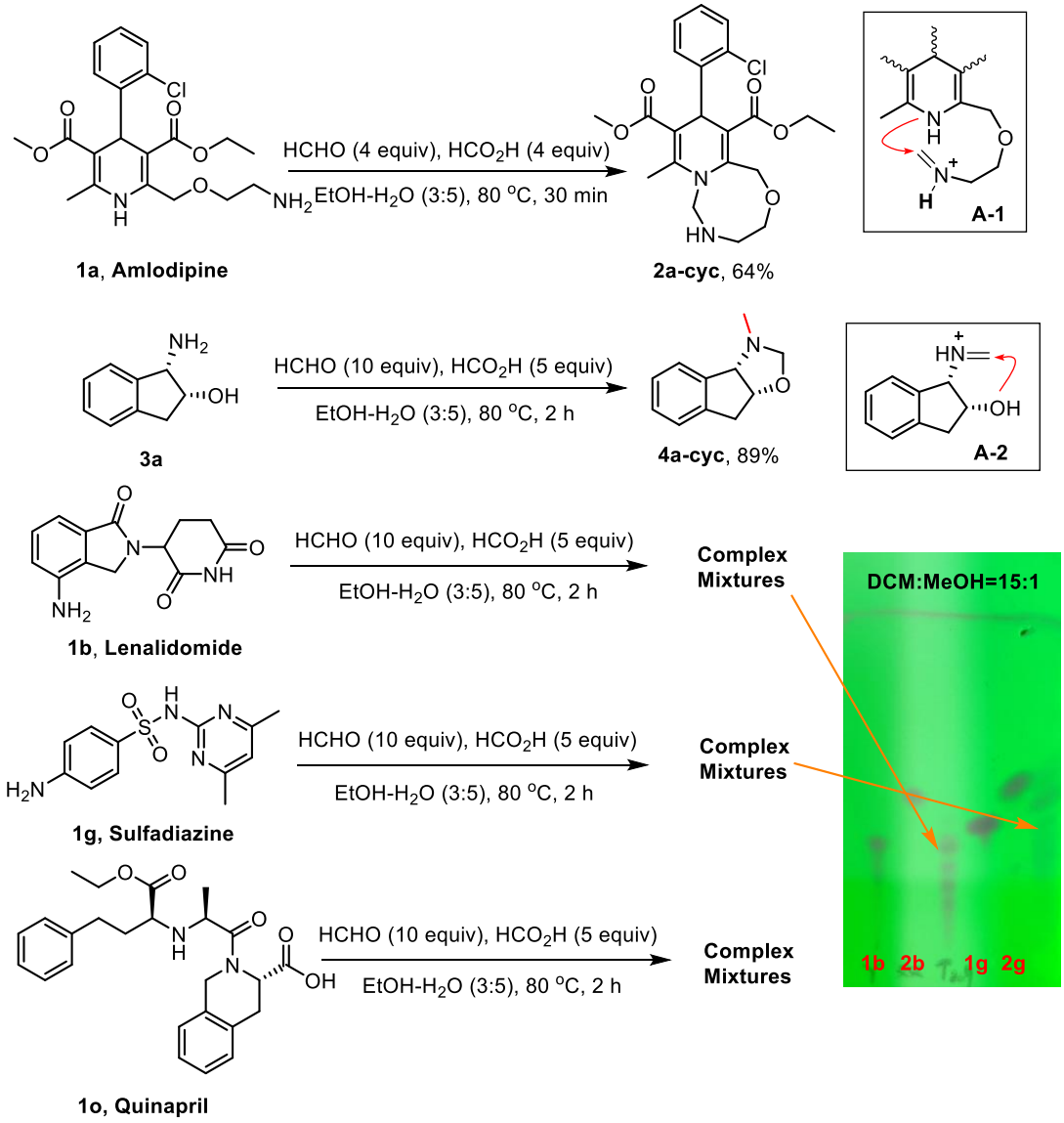


Figure S2. The primary and secondary amines

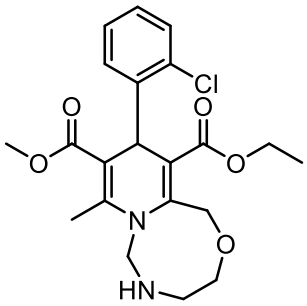
2 Classic Eschweiler-Clarke methylation of drug molecules



Scheme S1. The example of failure in classic Eschweiler-Clarke methylation

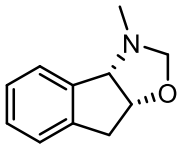
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added amine (0.2 mmol), ethanol (0.6 mL), HCHO (60 μL, 0.8 mmol, 4 equiv; 150 μL, 2 mmol, 10 equiv, w = 37-40%), HCO_2H (30 μL, 0.8 mmol, 4 equiv; 37.5 μL, 1 mmol, 5 equiv) and H_2O (1mL). The mixture was stirred for 2 h at 80 °C in a heating block. The reaction process was monitored by TLC. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL), and extracting with ethyl acetate (2 mL × 3), concentration of the organic phase under reduced pressure followed by purification by column chromatography on silica gel afforded desired products.

Note: With mixtures of recommended low-boiling-point green solvents (EtOH, i-PrOH, EtOAc, i-PrOAc) and recommended or problematic solvent acetone, **2a-cyc** or **4a-cyc** could not be well purified.



11-Ethyl 9-methyl 10-(2-chlorophenyl)-8-methyl-1,3,4,5,6,10-hexahydropyrido[2,1-*c*][1,4,6]oxadiazocine-9,11-dicarboxylate (2a-cyc)

Yellow oil, 0.2 mmol scale, yield: 53.7 mg, 64%, R_f = 0.60 (EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.36 (m, 1H), 7.36 – 7.32 (m, 1H), 7.22 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.11 (td, *J* = 7.4, 1.4 Hz, 1H), 7.03 (dd, *J* = 7.6, 1.8 Hz, 1H), 5.40 (s, 1H), 4.73 (q, *J* = 16.5 Hz, 2H), 4.10 – 3.99 (m, 2H), 3.62 (m, 5H), 3.55 (s, 2H), 2.80 (d, *J* = 4.8 Hz, 2H), 2.33 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 168.0, 167.2, 145.6, 145.6, 143.9, 132.5, 131.6, 129.4, 127.4, 126.7, 103.9, 101.4, 74.8, 69.7, 68.1, 59.8, 52.3, 50.8, 37.5, 19.4, 14.3. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{26}ClN_2O_5^+$, 421.1525; found, 421.1525.



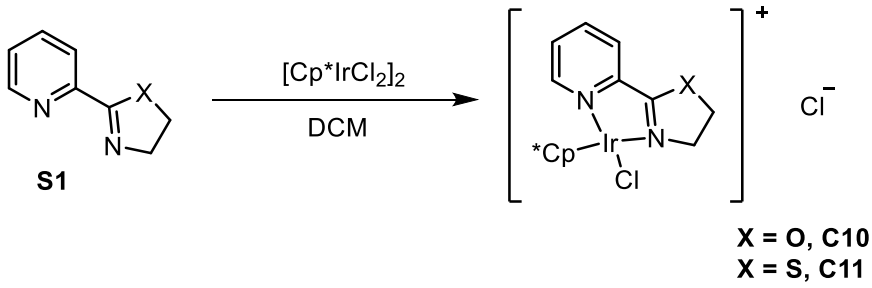
(3*aS*,8*aR*)-3-Methyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazole (4a-cyc)

Yellow oil, 0.2 mmol scale, yield: 31.2 mg, 89%, R_f = 0.70 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (dd, *J* = 5.2, 3.5 Hz, 1H), 7.28 – 7.14 (m, 3H), 4.86 (td, *J* = 5.3, 2.5 Hz, 1H), 4.55 (dd, *J* = 5.5, 2.4 Hz, 1H), 4.32 (dd, *J* = 6.2, 1.4 Hz, 1H), 3.97 (dd, *J* = 6.2, 1.6 Hz, 1H), 3.23 – 3.08 (m, 2H), 2.63 (d, *J* = 2.0 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.2, 140.6, 128.4, 127.1, 125.7, 124.8, 87.5, 76.5, 76.0, 43.5, 39.3. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{14}NO^+$, 176.1070; found, 176.1073.

3. Preparation of new catalysts

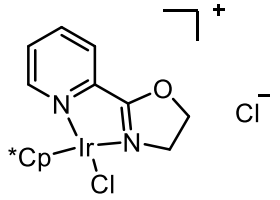
The catalysts (**C1**–**C9**, **C12**–**16, C18**) were synthesized according to our previous publications, [1] and their solution in water at different concentrations were also prepared according to our previous publication. [1] Herein, we also report a greener procedure with ethanol as the solvent.

3.1. Synthesis of C10, C11 and C17

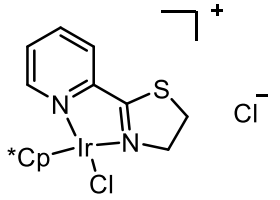


Scheme S2. Preparation of **C10** and **C11** catalysts

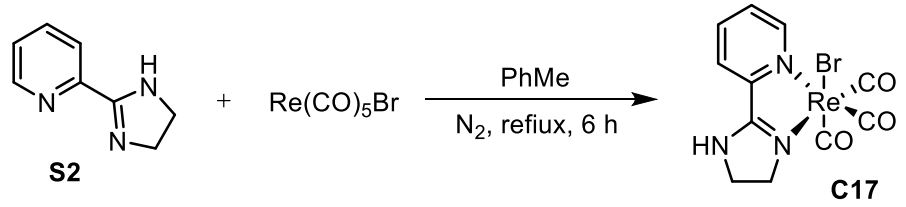
To a solution of ligand **S1** (0.11 mmol, 16.3 mg for X = O, 18.1 mg for X = S) in 5 mL of DCM was added the powder of $[Cp^*IrCl_2]_2$ (0.05 mmol, 40 mg). The resultant red solution was stirred overnight. DCM was removed under reduced pressure, and the resulting red solid was dissolved in minimum amount of DCM. Then a large amount of EtOAc slowly was added to precipitate a bright yellow powder as desired product, which was isolated by reduced-pressure filtration and further dried under vacuum at room temperature.



Light yellow solid, 51.5 mg, yield 90%, m.p. > 300 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.93 (d, *J* = 5.3 Hz, 1H), 8.18 (t, *J* = 7.5 Hz, 1H), 8.04 – 7.93 (m, 2H), 5.47 (q, *J* = 9.5 Hz, 1H), 5.06 (q, *J* = 8.2 Hz, 1H), 4.90 (m, 1H), 4.15 – 4.01 (m, 1H), 1.82 (s, 15H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.4, 152.5, 143.6, 140.4, 131.0, 126.8, 89.2, 74.4, 52.2, 9.5. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{18}H_{23}ClIrN_2O^+$, 511.1123; found, 511.1123.

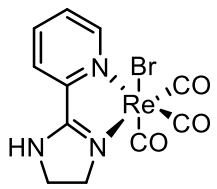


Light yellow solid, 52.8 mg, yield 94%, m.p. > 300 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.03 (d, *J* = 5.5 Hz, 1H), 8.24 (t, *J* = 7.7 Hz, 1H), 8.03 (t, *J* = 6.7 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 5.20 – 5.08 (m, 1H), 4.48 – 4.29 (m, 2H), 3.96 (td, *J* = 10.0, 6.7 Hz, 1H), 1.82 (s, 15H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.6, 152.3, 150.7, 140.6, 130.9, 128.1, 89.8, 62.9, 34.9, 9.5. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{18}H_{23}ClIrN_2S^+$, 527.0894; found, 527.0894.



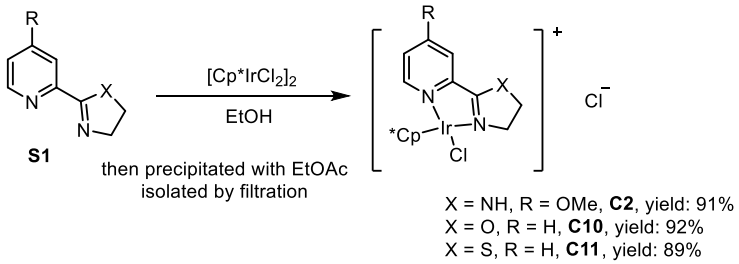
Scheme S3. Preparation of **C17** catalysts

To a mixture of ligand **S2** (30.8 mg, 0.21 mmol) and $Re(CO)_5Br$ (81.2 mg, 0.20 mmol) was added 15 mL of toluene. The mixture was refluxed under N_2 atmosphere for 6 h. After cooling, the solvent was removed by evaporation. The product was purified by recrystallization from PE:DCM (1:1 *v*/*v*), isolated by reduced-pressure filtration, and dried under vacuum at room temperature.



Light yellow solid, 88 mg, yield 89%, m.p. > 300 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 – 8.91 (m, 2H), 8.34 (t, *J* = 7.4 Hz, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.87 – 7.73 (m, 1H), 4.08 (q, *J* = 10.7 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.89 (q, *J* = 9.2, 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 198.1, 197.8, 189.7, 169.0, 154.4, 146.9, 140.8, 129.4, 125.6, 55.7, 45.9. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{11}H_9N_3O_3Re^+$, 418.0196; found, 418.0196. FT-IR $\tilde{\upsilon}$ (cm^{-1}): 2025 (s, CO), 1901 (s, CO), 1872 (s, CO).

3.2. Improved synthesis of catalysts in ethanol

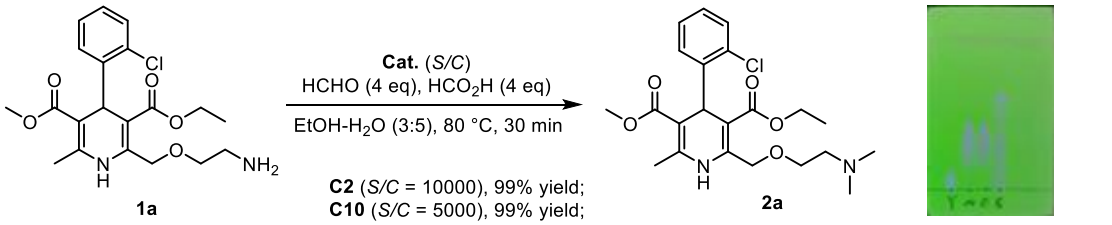


Scheme S4. Process diagrams of **C10** and **C11** catalysts preparation by new method

To a solution of ligand **S1** (0.11 mmol; 19.5 mg for X = NH, R = OMe; 16.3 mg for X = O, R = H; 18.1 mg for X = S, R = H) in 1 mL of EtOH was added the powder of $[Cp^*IrCl_2]_2$ (0.05 mmol, 40 mg). The resultant red solution was stirred overnight. EtOH was removed under reduced pressure, and the resulting red solid was dissolved in minimum amount of EtOH. Then a large amount of EtOAc slowly was added to precipitate a bright yellow powder as desired product, which was isolated by reduced-pressure filtration and further dried under vacuum at room temperature. These catalysts display identical NMR data with those prepared in dichloromethane.

3.3 Catalyst activity test

The catalytic activity of freshly prepared catalysts **C2**, **C10**, and **C11** in ethanol were measured. The **C2** catalyst showed the same activity as that prepared in dichloromethane (both >99% conversion at *S/C* = 10000). The **C10** and **C11** catalysts showed slightly higher activity, as compared with the results listed in Table 1 in the manuscript.



Scheme S5. Catalyst activity test experimental reaction

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Amlodipine (**1a**, 41 mg, 0.1 mmol), EtOH (0.3 mL), HCHO (30 μL, 0.4 mmol, 4 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 4 equiv) and 0.5 mL of catalyst solution (**C2**, 0.00002 mol/L for *S/C* = 10000, **C10** and **C11**, 0.00004 mol/L for *S/C* = 5000 dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The ^1H NMR yields of the crude residues were determined using 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol) as an internal standard.

4. Optimization of reaction conditions of dimethylation of primary amines

4. 1. Optimization of catalysts in entries 1-18, Table 1.

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Amlodipine (**1a**, 41 mg, 0.1 mmol), EtOH (0.3 mL), HCHO (30 μL, 0.4 mmol, 4 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 4 equiv) and 0.5 mL of catalyst solution (**C1-C18**, 0.00002 mol/L for *S/C* = 10000 dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The ^{1}H NMR yields of the crude residues were determined using 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol) as an internal standard.

4. 2. Optimization of catalyst loading in entries 19-30, Table 1.

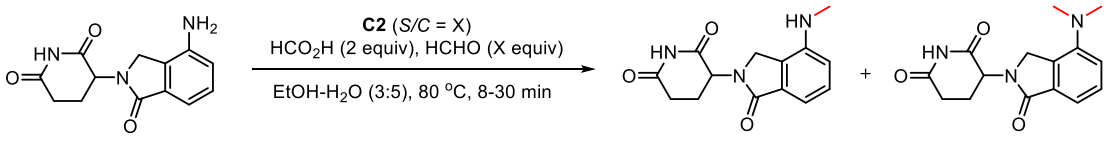
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Amlodipine (**1a**, 41 mg, 0.1 mmol), EtOH (0.3 mL), HCHO (30 μL, 0.4 mmol, 4 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 4 equiv) and 0.5 mL of catalyst solution (0.00004 mol/L for *S/C* = 5000, **C9-C12** in entries 19-22; 0.0002 mol/L for *S/C* = 1000, **C13-C18** in entries 23-28; 0.00001 mol/L for *S/C* = 20000, **C2** in entry 29; 0.000004 mol/L for *S/C* = 50000, **C2** in entry 30, dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. The ^{1}H NMR yields of the crude residues were determined using 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol) as an internal standard.

4. 3. Optimization of equivalents of HCHO and HCO_2H in entries 31-34, Table 1.

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Amlodipine (**1a**, 41 mg, 0.1 mmol), EtOH (0.3 mL), HCHO (15 μL, 0.2 mmol, 2 equiv; 45 μL, 0.6 mmol, 6 equiv, w = 37-40%), HCO_2H (7.5 μL, 0.2 mmol, 2 equiv; 22.5 μL, 0.6 mmol, 6 equiv) and 0.5 mL of catalyst solution (0.00001 mol/L for *S/C* = 20000, **C2** dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. The ^{1}H NMR yields of the crude residues were determined using 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol) as an internal standard.

5. Optimization of *N*-monomethylation of primary amines

Table S1. Optimization of reaction conditions of *N*-Monomethylation



1b **7b** **2b**

entry	cat.	*S/C*	HCHO (equiv.)	HCO_2H (equiv.)	Time (min)	yield / 7b (%) [b]	yield / 2b (%) [b]
1	**C2**	5000	1	2	30	12	33
2	**C2**	10000	1	2	30	19	22
3	**C2**	20000	1	2	30	28	16
4	**C2**	20000	0.8	2	30	35	10
5	**C2**	20000	0.6	2	30	47	8
6	**C2**	20000	0.6	2	15	50	0
7	**C2**	20000	0.6	2	10	41	0
8	**C2**	**20000**	**1**	**2**	**15**	**59**	**0**

[a] Reactions conditions: **1b** (0.2 mmol), **C2**, EtOH (0.6 mL), H_2O (1 mL), HCO_2H (15 uL, 2 equiv), 80℃, 8-30 min.

[b] Isolated yield.

5. 1. Optimization of catalyst loading in entries 1-3, Table S1.

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Lenalidomide (**1b**, 52 mg, 0.2 mmol), EtOH (0.6 mL), HCHO (15 μL, 0.2 mmol, 1 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 2 equiv) and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 20000; 0.0004 mol/L for *S/C* = 5000; 0.00002 mol/L for *S/C* = 10000, **C2** in entries 1-3, dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. Then, the isolated yield is obtained through silica gel column chromatography.

5. 2. Optimization of equivalents of for HCHO in entries 3-5, Table S1.

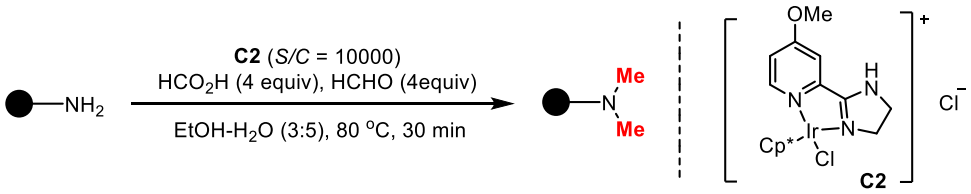
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Lenalidomide (**1b**, 52 mg, 0.2 mmol), EtOH (0.6 mL), HCHO (15 μL, 0.2 mmol, 1 equiv; 12 μL, 0.16 mmol, 0.8 equiv; 9 μL, 0.12 mmol, 0.6 equiv, w = 37-40% in entries 3-5), HCO_2H (15 μL, 0.4 mmol, 2 equiv) and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 20000, **C2** dissolved in deionized water).

The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. Then, the isolated yield is obtained through silica gel column chromatography.

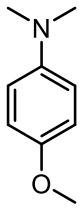
5. 3. Optimization of reaction time in entries 5-7, Table S1.

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added Lenalidomide (**1b**, 52 mg, 0.2 mmol), EtOH (0.6 mL), HCHO (15 μL, 0.2 mmol, 1 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 2 equiv) and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 20000, **C2** dissolved in deionized water). The mixture was stirred for 30 (15 or 10 in entries 5-7) min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. Then, the isolated yield is obtained through silica gel column chromatography.

6. Procedure for methylation of primary and secondary amines and NMR (and HRMS) data of products

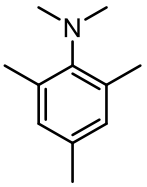


To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added amine (0.2 mmol), ethanol (0.6 mL), HCHO (60 μL, 0.8 mmol, 4 equiv, w = 37-40%), HCO_2H (30 μL, 0.8 mmol, 4 equiv) and 1 mL of the **C2** catalyst solution in deionized water (0.00002 mol/L for *S/C* = 10000). The mixture was stirred for 30 min at 80 °C in a heating block. The reaction process was monitored by TLC. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3) and drying over Na_2SO_4, concentration of the organic phase under reduced pressure followed by purification by column chromatography on silica gel with afforded desired products.



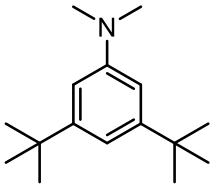
4-Methoxy-*N*, *N*-dimethylaniline (4b) [2] [CAS:701-56-4]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 25 mg, 83%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.90 – 6.85 (m, 2H), 6.82 – 6.76 (m, 2H), 3.79 (s, 3H), 2.90 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 152.1, 145.8, 115.1, 114.7, 55.9, 42.0.



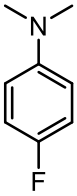
***N*,*N*,2,4,6-Pentamethylaniline (4c)** [3] [CAS:13021-15-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 32 mg, 98%, R_f = 0.5 (PE/EtOAc = 20:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.85 (s, 2H), 2.84 (s, 6H), 2.30 (s, 6H), 2.28 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 147.2, 137.1, 134.3, 129.6, 42.7, 20.8, 19.1.



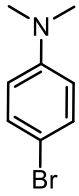
3,5-Di-tert-butyl-*N*,*N*-dimethylaniline (4d) [2] [CAS:53172-38-6]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 42 mg, 90%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.93 (s, 1H), 6.72 (s, 2H), 3.03 (s, 6H), 1.41 (s, 18H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 151.5, 150.4, 112.0, 107.8, 41.2, 35.2, 31.7.



4-Fluoro-*N*,*N*-dimethylaniline (4e) [2] [CAS:403-46-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 29 mg, 99%, R_f = 0.35 (PE/EtOAc = 20:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.95 (t, *J* = 8.7 Hz, 2H), 6.69 (dd, *J* = 9.0, 4.3 Hz, 2H), 2.90 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 155.8 (d, *J* = 235.6 Hz), 147.7 (this carbon is not split by the fluorine atom), 115.5 (d, *J* = 14.6 Hz), 114.1 (d, *J* = 4.9 Hz), 41.5.

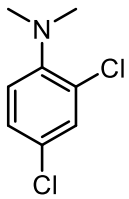


4-Bromo-*N*, *N*-dimethylaniline (4f) [2] [CAS: 586-77-6]

Purified by extraction with ethyl acetate, drying over Na2SO4, and concentration under reduced pressure. White solid, m.p. 53-55 °C, 0.2 mmol scale, yield: 39.4 mg, 99%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.35 (m, 2H), 6.69 – 6.60 (m, 2H), 2.99 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 149.6, 131.8, 114.2, 108.5, 40.6.

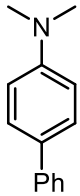
2-Bromo-*N*,*N*-dimethylaniline (4g) [4] [CAS: 698-00-0]

Purified by extraction with ethyl acetate, drying over Na2SO4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 39.2 mg, 99%, R_f = 0.4 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.55 (m, 1H), 7.27 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.10 (dt, *J* = 8.1, 1.6 Hz, 1H), 6.90 (tt, *J* = 7.5, 1.5 Hz, 1H), 2.82 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 151.9, 133.9, 128.2, 124.0, 120.6, 119.2, 44.3.



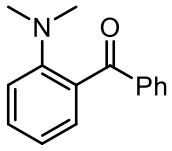
2,4-Dichloro-*N*,*N*-dimethylaniline (4h) [5] [CAS:35113-90-7]

Purified by extraction with ethyl acetate, drying over Na2SO4, and concentration under reduced pressure. Brown solid, m.p. 169-171 °C, 0.2 mmol scale, yield: 26 mg, 70%, R_f = 0.3 (PE/EtOAc = 20:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 2.81 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 149.3, 130.4, 128.9, 127.6, 127.5, 120.8, 43.8.



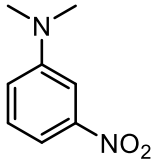
***N,N*-Dimethyl-(1,1'-biphenyl)-4-amine (4i)** [6] [CAS:1137-79-7]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 112-114 °C, 0.2 mmol scale, yield: 39 mg, 98%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (dd, *J* = 20.5, 8.1 Hz, 4H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 3.06 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 150.1, 141.3, 129.3, 128.8, 127.8, 126.4, 126.1, 112.9, 40.7.



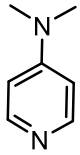
(2-(Dimethylamino)phenyl)(phenyl)methanone (4j) [7] [CAS:36648-32-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 30 mg, 67%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.89 – 7.82 (m, 2H), 7.60 – 7.53 (m, 1H), 7.48 – 7.39 (m, 3H), 7.34 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.93 (td, *J* = 7.4, 1.0 Hz, 1H), 2.73 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 198.3, 151.8, 137.9, 132.8, 131.6, 130.9, 130.1, 129.3, 128.2, 119.0, 116.6, 43.6.



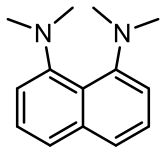
***N,N*-Dimethyl-3-nitroaniline (4k)** [8] [CAS:619-31-8]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 93-95 °C, 0.2 mmol scale, yield: 25 mg, 75%, R_f = 0.40 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 – 7.47 (m, 2H), 7.34 (t, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 8.3, 2.5 Hz, 1H), 3.05 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 150.9, 149.5, 129.6, 117.7, 110.8, 106.2, 40.5.



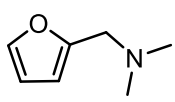
***N,N*-Dimethylpyridin-4-amine (4l)** [9] [CAS: 1122-58-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 110-112 °C, 0.2 mmol scale, yield: 23.9 mg, 98%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.83 (m, 2H), 6.16 – 6.06 (m, 2H), 2.58 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 153.8, 149.4, 106.3, 38.6.



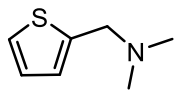
***N1,N1,N8,N8*-Tetramethylnaphthalene-1,8-diamine (4m)** [2] [CAS: 20734-58-1]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 180-182 °C, 0.2 mmol scale, yield: 41.5 mg, 97%, R_f = 0.6 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.15 – 7.10 (m, 2H), 2.99 (s, 12H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 150.9, 138.0, 125.6, 121.9, 120.8, 112.9, 44.6.

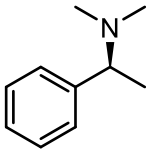


1-(Furan-2-yl)-*N,N*-dimethylmethanamine (4n) [10] [CAS: 14496-34-5]

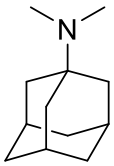
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Red oil, 0.5 mmol scale, yield: 55 mg, 88%, R_f = 0.4 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 1.5 Hz, 1H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.27 (dt, *J* = 3.3, 1.9 Hz, 1H), 4.04 (s, 2H), 2.55 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 167.0, 144.3, 113.6, 111.0, 52.3, 41.8.



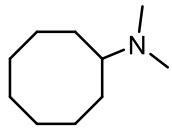
***N*,*N*-Dimethyl-1-(thiophen-2-yl)methanamine (4o)** [10] [CAS: 26019-17-0]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 25.6 mg, 97%, R_f = 0.3 (PE/EtOAc = 5:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.04 – 6.88 (m, 2H), 3.67 (s, 2H), 2.29 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 142.0, 126.4, 126.0, 125.0, 58.3, 45.0.



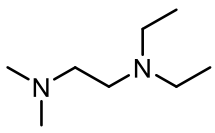
(*S*)-*N*-Dimethyl-1-phenylmethanamine (4p) [11] [CAS: 17279-31-1]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 21 mg, 74%, R_f = 0.40 (PE/EtOAc/TEA = 5:1:4%, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.23 (m, 5H), 3.28 (q, *J* = 6.7 Hz, 1H), 2.23 (s, 6H), 1.40 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 144.0, 128.3, 127.7, 127.1, 66.1, 43.3, 20.3.



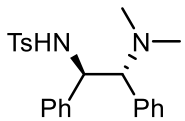
(3s,5s,7s)-*N*,*N*-Dimethyladamantan-1-amine (4q) [11] [CAS:3717-40-6]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.5 mmol scale, yield: 88.4 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.22 (s, 6H), 2.03 (s, 3H), 1.67 – 1.51 (m, 12H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 53.4, 37.9, 37.0, 36.8, 29.5.



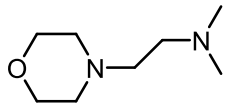
***N*,*N*-Dimethylcyclooctanamine (4r)** [11] [CAS: 17630-21-6]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 30.7 mg, 98%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.52 (t, *J* = 6.6 Hz, 1H), 2.22 (s, 6H), 1.78 – 1.66 (m, 4H), 1.60 (d, *J* = 11.3 Hz, 3H), 1.51 – 1.39 (m, 7H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 63.7, 40.8, 28.9, 26.7, 26.5, 25.5.



***N1*,*N1*-Diethyl-*N2*,*N2*-dimethylethane-1,2-diamine (4s)** [12] [CAS:123-10-4]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 28 mg, 97%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.66 – 2.58 (m, 6H), 2.47 (dd, *J* = 8.6, 6.0 Hz, 2H), 2.28 (s, 6H), 1.05 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 56.9, 50.4, 47.2, 45.7, 11.2.

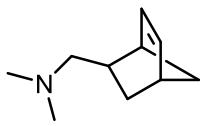


***N*-((1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (4t)**
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 54.4 mg, 69%, R_f = 0.6 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.02 – 6.96 (m, 4H), 6.95 – 6.89 (m, 3H), 6.28 (s, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 3.72 (d, *J* = 11.1 Hz, 1H), 2.34 (s, 3H), 2.19 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 142.7, 137.7, 137.3, 130.6, 129.9, 128.9, 128.3, 128.1, 127.9, 127.7, 127.3, 127.1, 73.1, 57.5, 40.1, 21.4. HRMS (ESI): *m/z* calcd for: $C_{23}H_{27}N_2O_2S^+$ $[M+H]^+$: 395.1788, found: 395.1792.



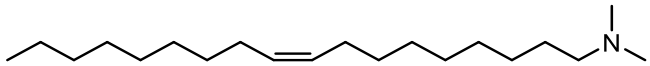
***N*,*N*-Dimethyl-2-morpholinoethan-1-amine (4u)** [13] [CAS:4385-05-1]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 31 mg, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): δ 3.72 – 3.65 (m, 4H), 2.51 – 2.38 (m, 8H), 2.24 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 66.9, 57.1, 56.6, 54.2, 45.9.



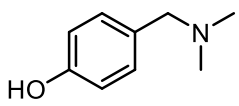
1-((1*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)-*N*,*N*-dimethylmethanamine (4v) [14] [CAS: 6537-01-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.5 mmol scale, yield: 74.7 mg, 99%, R_f = 0.4 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.26 (dd, *J* = 5.7, 3.1 Hz, 1H), 6.06 (dd, *J* = 5.7, 2.8 Hz, 1H), 3.10 (s, 1H), 2.97 – 2.92 (m, 1H), 2.85 (s, 6H), 2.71 – 2.63 (m, 1H), 2.55 (ddq, *J* = 14.5, 7.3, 3.8 Hz, 1H), 2.09 (ddd, *J* = 12.5, 9.0, 3.8 Hz, 1H), 1.53 (dd, *J* = 8.5, 2.1 Hz, 1H), 1.33 (d, *J* = 8.6 Hz, 2H), 0.77 (ddd, *J* = 11.7, 4.0, 2.7 Hz, 1H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 139.0, 131.5, 62.8, 49.8, 45.5, 42.6, 34.7, 32.1.



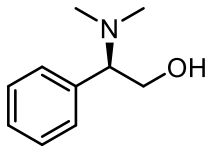
(*Z*)-*N*,*N*-Dimethyloctadec-9-en-1-amine (4w) [15] [CAS: 14727-68-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 58.4 mg, 99%, R_f = 0.5 (PE/EA+Et_3N = 2:1:4%, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.28 (t, *J* = 4.8 Hz, 2H), 2.18 (d, *J* = 7.3 Hz, 2H), 2.15 (s, 6H), 1.96 (q, *J* = 6.6 Hz, 3H), 1.39 (p, *J* = 7.1 Hz, 2H), 1.33 – 1.13 (m, 23H), 0.83 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 129.8, 129.7, 59.9, 45.4, 31.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.3, 29.2, 27.8, 27.5, 27.1, 22.6, 22.5, 14.0.



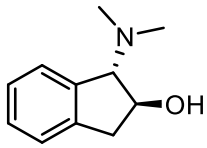
4-((Dimethylamino)methyl)phenol (4x) [16] [CAS:103-87-7]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 108-110 °C, 0.2 mmol scale, yield: 30 mg, 98%, R_f = 0.25 (PE/EtOAc/TEA = 2:1:4%, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.40 (s, 1H), 7.09 – 7.02 (m, 2H), 6.74 – 6.65 (m, 2H), 3.24 (s, 2H), 2.09 (s, 6H).^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ (ppm): 156.3, 129.9, 129.0, 114.8, 63.0, 44.8.



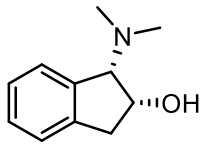
(*S*)-2-(Dimethylamino)-2-phenylethan-1-ol (4y) [17] [CAS: 2202-65-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 30 mg, 91%, R_f = 0.3 (PE/EtOAc/TEA = 2:1:4%, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (dddd, *J* = 10.5, 6.7, 4.4, 2.4 Hz, 3H), 7.25 – 7.19 (m, 2H), 3.96 (dd, *J* = 10.8, 8.9 Hz, 1H), 3.71 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.59 (dd, *J* = 8.9, 5.3 Hz, 1H), 3.20 (s, 1H), 2.22 (s, 6H).^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 135.8, 129.1, 128.3, 127.9, 70.3, 61.5, 41.5.



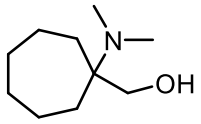
(1*S*,2*S*)-1-(Dimethylamino)-2,3-dihydro-1*H*-inden-2-ol (4z) [18] [CAS:1571103-71-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 30 mg, 85%, R_f = 0.35 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 – 7.19 (m, 4H), 4.66 (s, 1H), 4.49 (q, *J* = 7.9 Hz, 1H), 4.11 (d, *J* = 7.9 Hz, 1H), 3.29 (dd, *J* = 16.4, 8.2 Hz, 1H), 2.83 (dd, *J* = 16.3, 7.7 Hz, 1H), 2.32 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 141.8, 138.3, 128.7, 126.6, 126.5, 125.7, 69.9, 69.8, 43.2, 41.3.



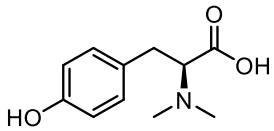
(1*S*,2*R*)-1-(Dimethylamino)-2,3-dihydro-1*H*-inden-2-ol (4a) [18]. [CAS: 245085-46-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 31.5 mg, 89%, R_f = 0.35 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.14 (m, 4H), 5.07 – 4.74 (m, 1H), 4.46 (q, *J* = 7.8 Hz, 1H), 4.04 (q, *J* = 7.3 Hz, 1H), 3.23 (td, *J* = 13.8, 11.6, 7.5 Hz, 1H), 2.82 (dd, *J* = 16.3, 7.6 Hz, 1H), 2.29 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 141.6, 138.4, 128.5, 126.4, 125.5, 70.0, 69.9, 43.1, 41.2.



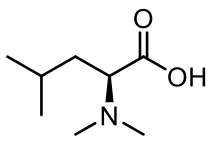
1-(Dimethylamino)cycloheptyl)methanol (4aa) [CAS:1554358-67-6]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 32 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.88 (s, 1H), 3.47 (s, 2H), 2.34 (s, 6H), 1.79 (dd, *J* = 14.5, 9.5 Hz, 2H), 1.61 – 1.43 (m, 10H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 66.2, 64.0, 38.5, 31.3, 31.2, 24.1.



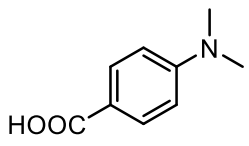
***N*,*N*-Dimethyl-*L*-tyrosine (4ab)** [19] [CAS: 17350-74-2]

Purified by recrystallization from water (may contain small amount of ethanol) after concentration under reduced pressure. White solid, m.p. 248-249 °C, 0.5 mmol scale, yield: 103.4 mg, 99%, R_f = 0.35 (DCM/MeOH = 1:1, *v/v*). ^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.13 – 7.03 (m, 2H), 6.81 – 6.73 (m, 2H), 3.67 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.14 (dd, *J* = 13.9, 5.8 Hz, 1H), 2.94 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.82 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Deuterium Oxide) δ 172.3, 154.6, 130.5, 126.9, 115.6, 72.2, 42.6, 40.4, 33.1.

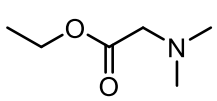


Dimethyl-*L*-leucine (4ac) [20] [CAS: 174785-98-9]

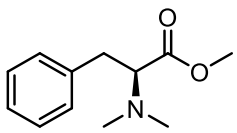
Purified by recrystallization from water (may contain small amount of ethanol) after concentration under reduced pressure. White solid, m.p. 182-183 °C, 0.5 mmol scale, yield: 77.9 mg, 98%. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.47 (dd, *J* = 9.8, 4.5 Hz, 1H), 2.78 (d, *J* = 8.0 Hz, 6H), 1.59 (m, 3H), 0.86 (t, *J* = 5.4 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, Deuterium Oxide) δ 173.4, 70.2, 42.3, 40.9, 36.7, 25.1, 22.7, 20.6.



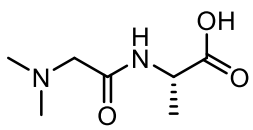
4-(Dimethylamino)benzoic acid (4ad) [21] [CAS: 619-84-1]
Purified by recrystallization from water (may contain small amount of ethanol) after concentration under reduced pressure. White solid, m.p. 240-242 °C, 0.2 mmol scale, yield: 32.4 mg, 98%, R_f = 0.40 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 7.83 – 7.71 (m, 2H), 6.73 – 6.62 (m, 2H), 2.95 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 168.0, 153.5, 131.4, 117.4, 111.1, 40.0



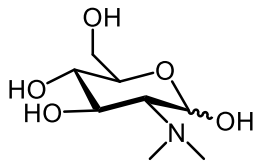
Ethyl dimethylglycinate (4ae) [22] [CAS: 33229-89-9]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.5 mmol scale, yield: 64.2 mg, 98%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.13 (s, 2H), 2.32 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 170.6, 60.6, 60.5, 45.3, 14.2.



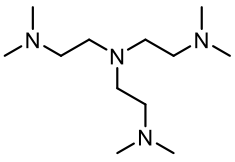
Methyl dimethyl-*L*-phenylalaninate (4af) [23] [CAS:27720-05-4]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.5 mmol scale, yield: 102.4 mg, 99%, R_f = 0.25 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.25 (m, 2H), 7.21 (dq, *J* = 9.0, 2.3 Hz, 3H), 3.61 (s, 3H), 3.45 (dd, *J* = 9.4, 5.7 Hz, 1H), 3.07 (dd, *J* = 13.4, 9.5 Hz, 1H), 2.95 (dd, *J* = 13.4, 5.7 Hz, 1H), 2.40 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 171.8, 138.2, 129.1, 128.4, 126.4, 69.6, 51.0, 41.9, 35.8.



Dimethylglycyl-*L*-alanine (4ag) [24] [CAS: 1227930-17-7]
Purified by removing water and ethanol under reduced pressure, followed by washing with small portion of EtOAc. Yellow oil, 0.5 mmol scale, yield: 79.2 mg, 91%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (d, *J* = 6.5 Hz, 1H), 7.05 (s, 1H), 4.14 (t, *J* = 7.2 Hz, 1H), 3.25 (s, 2H), 2.43 (s, 6H), 1.25 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 175.1, 167.3, 60.8, 48.8, 44.7, 18.4.

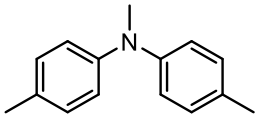


***N*, *N*-Dimethyl-*D*-glucosamine (4ah)** [25] [CAS: 2161394-97-2]
Purified by removing water and ethanol under reduced pressure, followed by washing with small portion of EtOAc. Yellow oil, 0.5 mmol scale, yield: 88.6 mg, 86%, α:β = 5:3. ^{1}H NMR (400 MHz, DMSO-d_6) data for the α-anomer δ 9.52 (s, 1H), 5.36 (d, 2.4 Hz, 1H), 3.86 – 3.77 (m, 1H), 3.57 (d, *J* = 13.0 Hz, 1H), 3.53 – 3.36 (m, 2H), 3.23 (s, 1H), 3.11 (d, *J* = 10.6 Hz, 1H), 2.8 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) data for the α-anomer δ 88.7, 72.4, 71.1, 68.0, 65.9, 60.9, 41.6, 41.1.



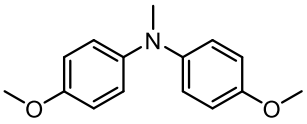
***N1*,*N1*-Bis(2-(dimethylamino)ethyl)-*N2*,*N2*-dimethylethane-1,2-diamine (4ai)** [26] [CAS:33527-91-2]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 21 mg, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.60 (dd, *J* = 8.4, 6.1 Hz,

6H), 2.38 (dd, *J* = 8.6, 6.1 Hz, 6H), 2.22 (s, 18H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 57.5, 53.0, 45.9.



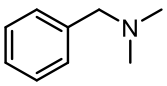
_N_,4-Dimethyl-_N_-(p-tolyl)aniline (6a) [3] [CAS:3480-97-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 37 mg, 86%, R_f = 0.35 (PE/EtOAc = 20:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.14 (d, *J* = 8.3 Hz, 4H), 6.98 (d, *J* = 8.4 Hz, 4H), 3.33 (s, 3H), 2.37 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 147.2, 130.6, 129.8, 120.5, 40.6, 20.8.



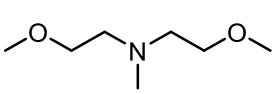
4-Methoxy-_N_-(4-methoxyphenyl)-_N_-methylaniline(6b) [3] [CAS:27151-57-1]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 96-97 °C, 0.2 mmol scale, yield: 42 mg, 88%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.95 – 6.88 (m, 4H), 6.86 – 6.80 (m, 4H), 3.79 (s, 6H), 3.22 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 154.5, 143.8, 121.7, 114.7, 55.7, 41.2.



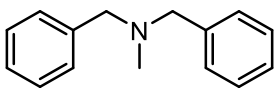
***N*,*N*-Dimethyl-1-phenylmethanamine (6c)** [2] [CAS:103-83-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 21 mg, 78%, R_f = 0.35 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 – 7.23 (m, 5H), 3.47 (s, 2H), 2.28 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 138.6, 129.3, 128.4, 127.3, 64.4, 45.4.



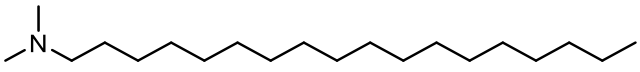
2-Methoxy-_N_-(2-methoxyethyl)-_N_-methylethan-1-amine (6d) [27] [CAS: 92260-33-8]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2mmol scale, yield: 29.1mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.71 (s, 4H), 3.32 (s, 6H), 3.26 (s, 4H), 2.82 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 67.4, 58.8, 55.5, 41.5.



***N*-Benzyl-*N*-methyl-1-phenylmethanamine (6e)** [2] [CAS:102-05-6]

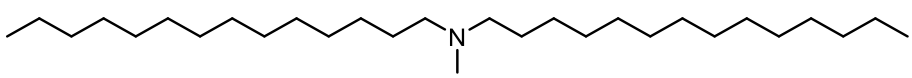
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 41.79 mg, 99%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.40 (m, 8H), 7.37 (t, *J* = 6.7 Hz, 2H), 3.66 (s, 4H), 2.32 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 139.5, 129.1, 128.4, 127.1, 62.0, 42.4.



***N*,*N*-Dimethyloctadecan-1-amine (6f)** [28] [CAS: 124-28-7]

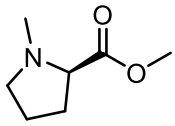
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 58.8 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.20 (d, *J* = 7.4 Hz, 1H), 2.17 (s, 6H), 1.47 – 1.36 (m, 2H), 1.24 (d, *J* = 11.3 Hz, 31H), 0.84 (t, *J* =

6.8 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 59.9, 45.5, 31.9, 29.7, 29.6, 29.4, 27.8, 27.5, 22.7, 14.0.



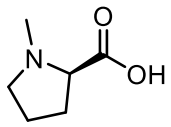
***N*-Methyl-*N*-tetradecyltetradecan-1-amine (6g)** [29] [CAS: 41961-81-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 82.1 mg, 97%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.34 – 2.27 (m, 4H), 2.21 (s, 3H), 1.46 (p, *J* = 6.7, 5.8 Hz, 4H), 1.27 (s, 44H), 0.89 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 58.0, 42.4, 31.9, 29.7, 29.7, 29.4, 27.7, 27.4, 22.7, 14.1.



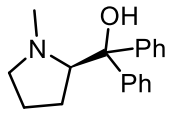
Methyl methyl-*D*-prolinate (6h) [30] [CAS: 114883-82-8]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.5 mmol scale, yield: 70.1 mg, 98%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.69 (s, 3H), 3.13 – 3.05 (m, 1H), 2.95 – 2.87 (m, 1H), 2.35 (s, 3H), 2.26 (td, *J* = 8.9, 7.7 Hz, 1H), 2.16 – 2.03 (m, 1H), 1.96 – 1.82 (m, 2H), 1.80 – 1.68 (m, 1H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 174.2, 67.5, 56.3, 51.8, 40.9, 29.6, 23.1.



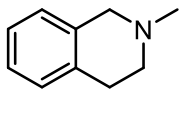
Methyl-*D*-proline (6i) [31] [CAS: 475-11-6]

Purified by recrystallization from water (may contain small amount of ethanol) after concentration under reduced pressure. White solid, m.p. 114-116 °C, 0.5 mmol scale, yield: 63.2 mg, 98%. ^{1}H NMR (400 MHz, Deuterium Oxide) δ 3.80 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.65 (ddd, *J* = 11.7, 7.4, 4.4 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.85 (s, 3H), 2.48 – 2.36 (m, 1H), 2.13 – 1.84 (m, 3H). ^{13}C NMR{^{1}H} (101 MHz, Deuterium Oxide) δ 173.6, 70.6, 56.3, 40.7, 28.7, 22.8.



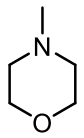
(*R*)-(1-Methylpyrrolidin-2-yl)diphenylmethanol (6j) [32] [CAS:144119-12-0]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 52 mg, 98%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 – 7.63 (m, 2H), 7.57 (dt, *J* = 8.4, 1.7 Hz, 2H), 7.29 (ddt, *J* = 8.1, 6.7, 2.0 Hz, 4H), 7.20 – 7.12 (m, 2H), 3.65 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.17 – 3.09 (m, 1H), 2.46 (ddd, *J* = 10.0, 9.1, 6.5 Hz, 1H), 1.96 – 1.88 (m, 1H), 1.84 (s, 3H), 1.77 – 1.61 (m, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 148.4, 146.8, 128.1, 126.2, 125.6, 125.5, 77.6, 72.1, 59.3, 43.1, 30.0, 24.2.



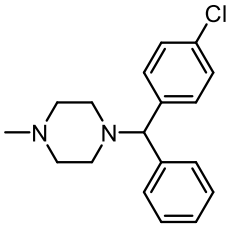
2-Methyl-1,2,3,4-tetrahydroisoquinoline (6k) [13] [CAS:1612-65-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 29 mg, 99%, R_f = 0.3 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21 – 7.09 (m, 3H), 7.08 – 7.01 (m, 1H), 3.61 (s, 2H), 2.96 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 134.8, 133.9, 128.8, 126.5, 126.2, 125.7, 58.1, 53.0, 46.2, 29.3.



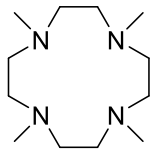
4-Methylmorpholine (6l) [33] [CAS: 109-02-4]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.5 mmol scale, yield: 50.1 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.68 – 3.46 (m, 4H), 2.25 (s, 4H), 2.19 – 2.05 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 66.7, 55.3, 46.3.



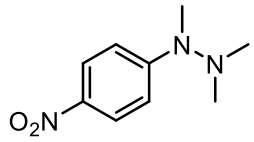
4-((4-Chlorophenyl)(phenyl)methyl)-1-methylpiperidine (6m) [34] [CAS: 109-02-4]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 59.5 mg, 99%, R_f = 0.5 (DCM/MeOH = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.37 (m, 4H), 7.32 – 7.18 (m, 5H), 4.22 (s, 1H), 2.46 (s, 8H), 2.30 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 142.3, 141.5, 132.5, 129.2, 128.7, 128.6, 127.8, 127.1, 75.5, 55.4, 51.9, 46.0.



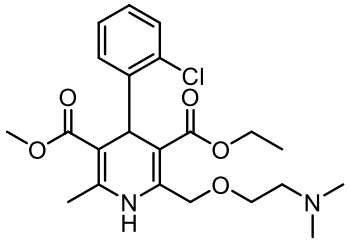
1,4,7,10-Tetramethyl-1,4,7,10-tetraazacyclododecane (6n) [35] [CAS: 76282-33-2]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.5 mmol scale, yield: 112.7 mg, 99%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.45 (s, 16H), 2.16 (s, 12H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 55.9, 44.6.



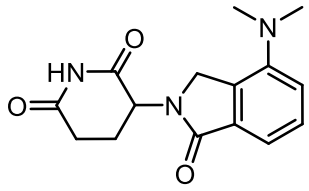
1,1,2-Trimethyl-2-(4-nitrophenyl)hydrazine (6o)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Green solid, m.p. 68-70 °C, 0.2 mmol scale, yield: 38.2 mg, 98%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.06 (m, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 2.94 (s, 3H), 2.53 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 154.6, 137.8, 126.0, 110.5, 41.7, 26.5. HRMS (ESI): *m/z* calcd for : $C_9H_{14}N_3O_2^+$ [M+H]$^+$: 196.1081, found: 196.1089



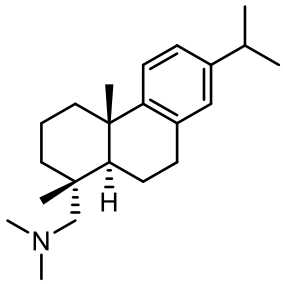
3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(dimethylamino)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a) [9] [CAS:84157-10-8]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 112-114 °C, 0.2 mmol scale, yield: 86 mg, 99%, R_f = 0.4 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (s, 1H), 7.36 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.21 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.11 (td, *J* = 7.5, 1.4 Hz, 1H), 7.02 (td, *J* = 7.5, 1.7 Hz, 1H), 5.39 (s, 1H), 4.83 – 4.65 (m, 2H), 4.03 (qd, *J* = 7.1, 3.1 Hz, 2H), 3.51-3.63 (m, 5H), 2.53 (qtd, *J* = 12.4, 6.5, 4.0 Hz, 2H), 2.32 (s, 3H), 2.30 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 168.2, 167.4, 146.7, 146.0, 144.8, 132.4, 131.6, 129.2, 127.3, 126.8, 103.5, 101.0, 69.2, 68.3, 59.7, 59.0, 50.7, 45.6, 37.5, 18.9, 14.3.



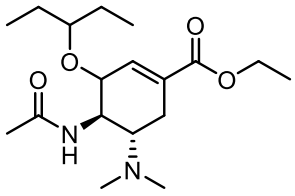
3-(4-(Dimethylamino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b) [36] [CAS:905952-53-6]

Purified by recrystallization from water (may contain small amount of ethanol) after concentration under reduced pressure. White solid, m.p. 248-249 °C, 0.2 mmol scale, yield: 46 mg, 80%, R_f = 0.50 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.97 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 4.41 (d, *J* = 17.0 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.90 (s, 6H), 2.68-2.57 (m, 1H), 2.53 – 2.42 (m, 1H), 2.08-1.98 (m, 1H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 178.2, 176.3, 173.5, 153.0, 138.4, 134.9, 134.3, 123.0, 118.7, 56.7, 53.0, 47.1, 36.4, 27.6.



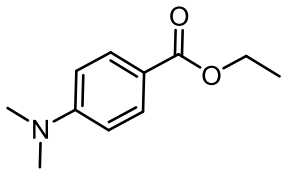
1-((1*R*,4*aS*,10*aR*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)-*N*,*N*-dimethylmethanamine (2c) [37] [CAS:54234-82-1]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 58 mg, 92%, R_f = 0.45 (DCM/MeOH = 25:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 (d, *J* = 8.1 Hz, 1H), 7.01 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.91 (d, *J* = 2.0 Hz, 1H), 2.97 – 2.79 (m, 3H), 2.31 (m, 8H), 1.99 (d, *J* = 14.1 Hz, 1H), 1.88 – 1.78 (m, 2H), 1.78 – 1.75 (m, 1H), 1.75 – 1.69 (m, 2H), 1.59 (td, *J* = 13.3, 4.0 Hz, 1H), 1.48 (dd, *J* = 12.9, 3.7 Hz, 1H), 1.38 (dtd, *J* = 12.8, 3.4, 1.6 Hz, 1H), 1.27 (s, 3H), 1.25 (d, *J* = 1.1 Hz, 6H), 0.88 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 147.8, 145.3, 134.8, 126.8, 124.2, 123.7, 71.1, 49.2, 44.2, 38.8, 38.5, 37.4, 36.4, 33.5, 30.2, 25.7, 24.0, 19.1, 19.0, 18.9.



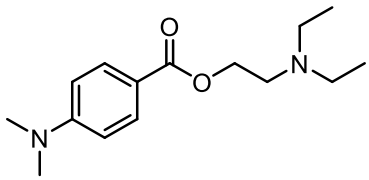
Ethyl(4*R*,5*S*)-4-acetamido-5-(dimethylamino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d) [38] [CAS:2230050-50-5]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 62 mg, 91%, R_f = 0.45 (DCM/MeOH = 25:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.73 (s, 1H), 5.71 (d, *J* = 7.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.04 (d, *J* = 8.8 Hz, 1H), 3.90 (dt, *J* = 11.4, 8.8 Hz, 1H), 3.29 (p, *J* = 5.6 Hz, 1H), 2.98 – 2.87 (m, 1H), 2.53 (dd, *J* = 17.3, 4.6 Hz, 1H), 2.27 (s, 6H), 2.24-2.21 (m, 1H), 2.00 (s, 3H), 1.48 (dt, *J* = 13.0, 7.1 Hz, 4H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.86 (dt, *J* = 14.9, 7.4 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 170.6, 166.7, 138.2, 129.5, 82.1, 77.8, 60.9, 60.8, 53.4, 40.2, 26.1, 25.6, 23.9, 21.8, 14.3, 9.7, 9.2.



Ethyl 4-(dimethylamino)benzoate (2e) [2] [CAS:10287-53-3]

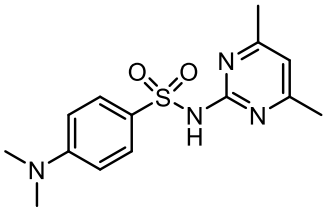
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Colorless oil, 0.2 mmol scale, yield: 34 mg, 95%, R_f = 0.30 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.91 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.03 (s, 6H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 167.1, 153.3, 131.3, 117.4, 110.8, 60.2, 40.2, 14.6.



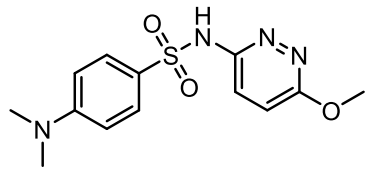
2-(Diethylamino)ethyl-4-(dimethylamino)benzoate (2f) [39] [CAS:10367-92-7]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White oil, 0.2 mmol scale, yield: 52 mg, 98%, R_f = 0.45 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.96 – 7.87 (m, 2H), 6.70 – 6.60 (m, 2H), 4.36 (t, *J* = 6.3 Hz, 2H), 3.04 (s, 6H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.65 (q, *J* = 7.1 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 167.1, 153.4, 131.4, 117.2, 110.8, 62.7, 51.2, 47.9, 40.1, 12.2.

4-(Dimethylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (2g)

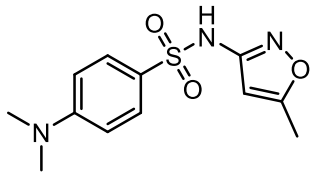


Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White soild, m.p. 189-190 °C, 0.2 mmol scale, yield: 54.5 mg, 89%, R_f = 0.6 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.44 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 6.68 – 6.56 (m, 3H), 3.03 (s, 6H), 2.39 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 168.2, 156.6, 153.1, 130.8, 124.6, 114.7, 110.1, 40.1, 23.7. HRMS (ESI): *m/z* calcd for : $C_{14}H_{19}N_4O_2S^+$ $[M+H]^+$: 307.1223, found: 307.1228.



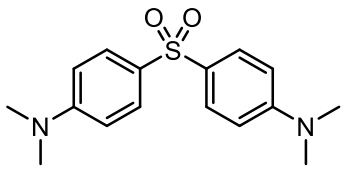
4-(Dimethylamino)-*N*-(6-methoxypyridazin-3-yl)benzenesulfonamide (2h)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Green solid, m.p. 175-176 °C, 0.2 mmol scale, yield: 60.4 mg, 98%. R_f = 0.5 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 3H), 7.25 (d, *J* = 9.1 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 2H), 3.85 (s, 3H), 2.95 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 152.8, 152.6, 128.6, 127.3, 127.2, 125.1, 125.0, 111.2, 54.8, 40.1. HRMS (ESI): *m/z* calcd for : $C_{13}H_{17}N_4O_3S^+$ $[M+H]^+$: 309.1016, found: 309.1017.



4-(Dimethylamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (2i) [40] [CAS: 2543698-83-3]

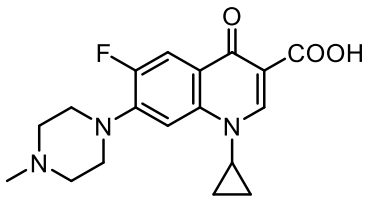
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 205-207 °C, 0.2 mmol scale, yield: 54.5 mg, 97%, R_f = 0.6 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.11 (s, 1H), 2.98 (s, 6H), 2.28 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 175.1, 163.2, 158.0, 133.6, 129.5, 116.0, 100.5, 44.8, 17.2.



4,4'-Sulfonylbis(*N*,*N*-dimethylaniline) (2j) [41] [CAS: 33871-62-4]

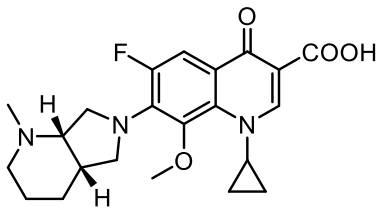
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 257-259 °C, 0.2 mmol scale, yield: 57.8 mg, 97%, R_f = 0.5 (PE/EtOAc

= 2:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (d, *J* = 8.5 Hz, 4H), 6.73 (d, *J* = 8.7 Hz, 4H), 2.96 (s, 12H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 152.9, 128.7, 128.6, 111.6, 40.1.



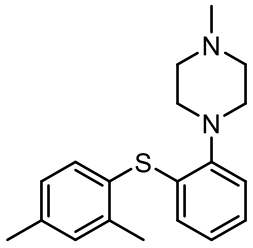
1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (2k) [42] [CAS:86483-46-7]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 241-243 °C, 0.2 mmol scale, yield: 61 mg, 88%, R_f = 0.50 (DCM/MeOH/HCOOH=5:1:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm): 8.76 (s, 1H), 7.99 (d, *J* = 13.1 Hz, 1H), 7.37 (d, *J* = 7.1 Hz, 1H), 3.57 (tt, *J* = 7.4, 4.0 Hz, 1H), 3.38 (t, *J* = 4.8 Hz, 4H), 2.67 (t, *J* = 4.8 Hz, 4H), 2.41 (s, 3H), 1.40 (t, *J* = 6.7 Hz, 2H), 1.22 (dd, *J* = 6.2, 3.9 Hz, 2H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 176.9, 166.9, 153.6 (d, *J* = 251.5 Hz), 147.3, 145.8 (d, *J* = 10.3 Hz), 139.1, 119.5 (d, *J* = 7.6 Hz), 112.1 (d, *J* = 23.4 Hz), 107.9, 104.8 (d, *J* = 3.2 Hz), 54.7, 49.7 (d, *J* = 5.1 Hz), 49.6, 46.1, 35.3, 8.2. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.7.



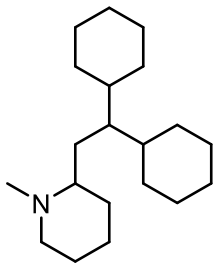
1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-methyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2l) [43] [CAS: 721970-37-2]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 137-139 °C, 0.2 mmol scale, yield: 79 mg, 95%, R_f = 0.50 (DCM/MeOH/HCOOH=5:1:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (s, 1H), 7.66 (d, *J* = 13.9 Hz, 1H), 3.98 (tt, *J* = 7.6, 4.0 Hz, 1H), 3.85 (t, *J* = 9.5 Hz, 1H), 3.70 (q, *J* = 11.2 Hz, 2H), 3.53 (s, 3H), 3.41 (d, *J* = 8.6 Hz, 1H), 2.80 – 2.65 (m, 2H), 2.38 (m, 1H), 2.22 (s, 3H), 2.13 (t, *J* = 10.0 Hz, 1H), 1.82 (d, *J* = 12.1 Hz, 1H), 1.67 (s, 2H), 1.56 (d, *J* = 9.8 Hz, 1H), 1.20 (s, 1H), 1.13 – 0.95 (m, 2H), 0.86 (s, 1H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 176.6, 167.2, 153.6 (d, *J* = 250.8 Hz), 149.4, 140.3 (d, *J* = 7.4 Hz), 137.7 (d, *J* = 10.9 Hz), 134.5, 117.7 (d, *J* = 8.4 Hz), 107.6, 107.4 (d, *J* = 3 Hz), 64.4, 61.0, 54.3 (d, *J* = 6.1 Hz), 54.2, 53.2 (d, *J* = 6.5 Hz), 44.2, 40.6, 37.6, 23.1, 22.0, 10.1, 8.9. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.7.

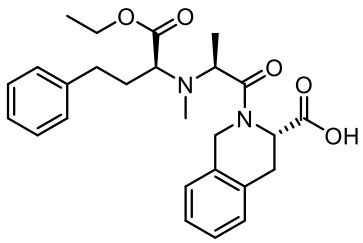


1-(2-((2,4-Dimethylphenyl)thio)phenyl)-4-methylpiperazine (2m) [44] [CAS:1293489-87-8]

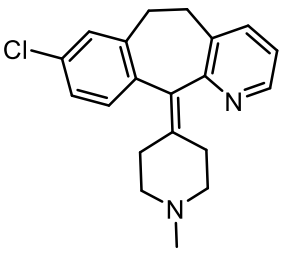
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 69-71 °C, 0.2 mmol scale, yield: 62 mg, 99%, R_f = 0.50 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 7.13 – 7.08 (m, 2H), 7.08 – 7.02 (m, 1H), 6.88 (ddd, *J* = 8.3, 6.0, 2.6 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 1H), 3.14 (s, 4H), 2.67 (s, 4H), 2.40 (s, 3H), 2.38 (s, 3H), 2.35 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, CDCl3) δ (ppm): 149.3, 142.6, 139.3, 136.4, 134.7, 131.7, 128.1, 127.9, 126.2, 125.5, 124.4, 120.0, 55.6, 51.7, 46.3, 21.3, 20.7.



2-(2,2-Dicyclohexylethyl)-1-methylpiperidine (2n) [45] [CAS:81321-04-2]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 57 mg, 98%, R_f = 0.3 (DCM/MeOH = 20:1, *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.84 (dtd, *J* = 11.8, 3.7, 1.4 Hz, 1H), 2.31 (s, 3H), 2.17 – 2.04 (m, 1H), 1.85 (tt, *J* = 9.7, 3.0 Hz, 1H), 1.78 – 1.53 (m, 14H), 1.50 – 1.43 (m, 1H), 1.39 (dq, *J* = 13.9, 2.8 Hz, 1H), 1.30 – 0.95 (m, 15H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ (ppm): 63.1, 57.2, 45.6, 43.0, 40.7, 39.5, 32.4, 31.5, 31.3, 31.2, 29.4, 27.3, 27.2, 27.1, 26.9, 26.8, 26.8, 25.8, 24.4.

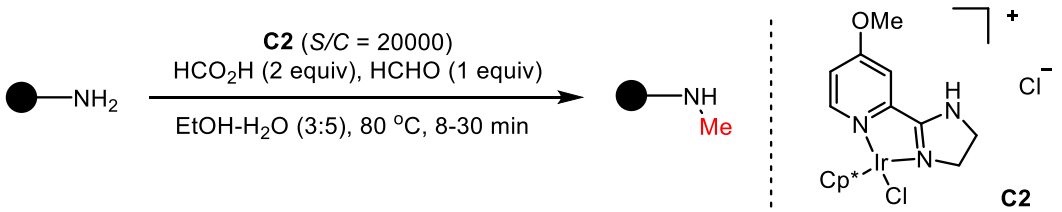


(*S*)-2-(*N*-((*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl)-*N*-methyl-L-alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2o) [46] [CAS:103733-45-5]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.1 mmol scale, yield: 61.3 mg, 98%, R_f = 0.3 (PE/EtOAc = 1:2, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 2H), 7.20 (d, *J* = 7.1 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 2H), 7.10 – 6.99 (m, 3H), 6.97 – 6.91 (m, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 4.64 (t, *J* = 5.4 Hz, 1H), 4.44 (d, *J* = 14.9 Hz, 1H), 4.12 – 4.04 (m, 1H), 4.02 – 3.93 (m, 1H), 3.80 (q, *J* = 6.3 Hz, 1H), 3.39-3.33 (m, 1H), 3.08 (dd, *J* = 15.4, 6.1 Hz, 1H), 2.92 (dd, *J* = 15.3, 5.6 Hz, 1H), 2.56 (t, *J* = 7.9 Hz, 2H), 2.18 (s, 3H), 2.07 (dq, *J* = 16.2, 8.0 Hz, 1H), 1.84 (dq, *J* = 13.7, 8.0 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, $CDCl_3$) δ 177.6, 173.5, 173.0, 141.5, 135.0, 134.0, 128.4, 128.4, 127.9, 126.9, 126.0, 125.6, 77.3 64.1, 60.4, 59.4, 55.8, 45.2, 32.7, 31.9, 31.1, 14.2, 11.8.



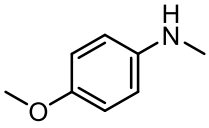
8-Chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2p) [47] [CAS:38092-89-6]
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Pink solid, m.p. 108-110 °C, 0.2 mmol scale, yield: 63.5 mg, 98%, R_f = 0.3 (DCM/MeOH = 10:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (tt, *J* = 4.6, 1.7 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 6.4 Hz, 3H), 6.98 (h, *J* = 4.5 Hz, 1H), 3.42 – 3.21 (m, 2H), 2.82 – 2.57 (m, 4H), 2.52-2.44 (m, 1H), 2.46-2.26 (m, 3H), 2.18 (s, 3H), 2.03-1.96 (m, 2H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 157.5, 146.5, 139.5, 138.2, 137.8, 137.2, 133.3, 132.8, 132.6, 130.7, 128.9, 125.9, 122.0, 77.4, 56.8, 46.0, 31.8, 31.4, 31.0, 30.8.

7. Procedure for *N*-Monomethylation of primary amines and NMR (and HRMS) data of products



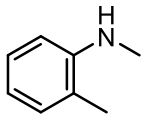
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added primary amine (0.2 mmol), ethanol (0.6 mL), HCHO (15 uL, 0.2 mmol, 1 equiv, w = 37-40%), HCO_2H (15 μL, 0.4 mmol, 2 equiv) and 1 mL of the **C2** catalyst solution in deionized water (0.00001 mol/L for *S/C* = 20000). The mixture was stirred for 8-30 min at 80 °C in a heating block. The reaction process was monitored by TLC. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3) and drying over Na_2SO_4, concentration of the organic phase under reduced pressure followed by purification by column chromatography on silica gel with afforded desired products.

Note: The very similar polarity of starting materials and *N*-monomethylated and *N*,*N*-dimethylated products makes the use of recommended low-boiling-point green solvents (EtOH, i-PrOH, EtOAc, i-PrOAc) unreliable in the column chromatography process, and they did not give good purification results. Thus, for the products with low polarity, the mixture of PE and EtOAc were used. For the products with very high polarity, the mixture of DCM and MeOH were used.



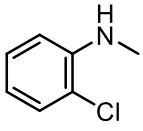
4-Methoxy-*N*-methylaniline (5b) [11] [CAS: 5961-59-1]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Black oil, 0.2 mmol scale, yield: 19.7 mg, 72%, R_f = 0.55 (PE/EtOAc = 10:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.90 (dd, *J* = 8.7, 1.3 Hz, 2H), 6.68 – 6.63 (m, 2H), 3.83 (s, 3H), 3.55 (s, 1H), 2.85 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 152.1, 143.9, 115.0, 113.6, 55.8, 31.6.



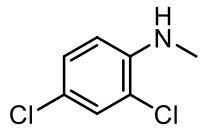
***N*-Methyl-o-methylaniline (5aj)** [11] [CAS: 611-21-2]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Gray oil, 0.2 mmol scale, yield: 17.2 mg, 71%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 (t, *J* = 7.6 Hz, 1H), 7.36 (s, 1H), 7.06 – 6.96 (m, 1H), 6.91 (dd, *J* = 7.7, 2.6 Hz, 1H), 3.78 (s, 1H), 3.14 (d, *J* = 2.6 Hz, 3H), 2.41 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 147.6, 130.2, 127.5, 122.1, 117.1, 109.4, 31.0, 17.6.



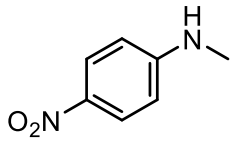
2-Chloro-*N*-methylaniline (5ak) [48] [CAS: 932-32-1]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 20.5 mg, 73%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.14 (m, 1H), 6.82 (dt, *J* = 9.3, 4.9 Hz, 1H), 6.67 (dp, *J* = 4.1, 2.0 Hz, 1H), 6.58 – 6.51 (m, 1H), 3.79 (s, 1H), 2.84 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 150.7, 135.0, 130.3, 116.9, 112.0, 110.9, 30.5.



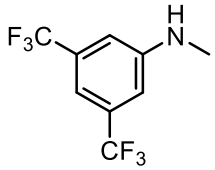
***N*-Methyl-2,4-dichloro (5h)** [11] [CAS: 35113-88-3]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 23.8 mg, 68%, R_f = 0.6 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.57 (d, *J* = 8.7 Hz, 1H), 4.34 (s, 1H), 2.90 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 143.8, 128.5, 127.8, 120.9, 119.2, 111.1, 30.4.



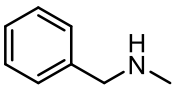
***N*-Methyl-4-nitroaniline (5al)** [11] [CAS: 100-15-2]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Yellow solid, m.p. 147-149 °C, 0.2 mmol scale, yield:17.94 mg, 59%, R_f = 0.5 (PE/EtOAc = 5:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.01 (m, 2H), 6.62 – 6.49 (m, 2H), 4.65 (s, 1H), 2.96 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 154.2, 137.9, 126.4, 110.7, 30.2.



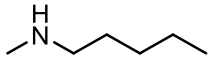
***N*-Methyl-3,5-bis(trifluoromethyl)aniline (5am)** [13] [CAS: 42450-72-6]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Yellow oil, 0.2 mmol scale, yield: 29.5 mg, 61%, R_f = 0.5 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (s, 1H), 6.95 (s, 2H), 4.19 (s, 1H), 2.93 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 149.7, 132.3 (q, *J* = 32.7 Hz), 123.6 (q, *J* = 273.6 Hz), 111.4 (2C), 109.9, 30.3.



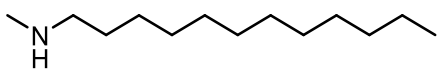
***N*-Methylbenzylamine (5an)** [13] [CAS: 103-67-3]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 14.2 mg, 59%, R_f = 0.6 (PE/EtOAc = 10:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.31 (m, 4H), 7.26 (ddt, *J* = 8.5, 6.5, 3.2 Hz, 1H), 3.75 (d, *J* = 1.8 Hz, 2H), 2.46 (d, *J* = 2.4 Hz, 3H), 1.48 (s, 1H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 140.3, 128.4, 128.2, 126.9, 56.1, 36.1.



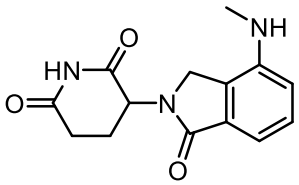
***N*-Methylpentylamine (5ao)** [49] [CAS: 25419-06-1]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 11.5 mg, 57%, R_f = 0.45 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.25 (ddt, *J* = 9.4, 7.2, 2.7 Hz, 2H), 2.13 (td, *J* = 6.8, 5.5, 3.8 Hz, 3H), 1.31 – 1.11 (m, 3H), 1.11 – 0.89 (m, 4H), 0.60 (qt, *J* = 7.1, 2.7 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 51.9, 36.1, 29.3, 29.2, 22.3, 13.6.



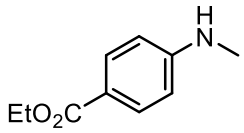
***N*-Methyldodecylamine (5ap)** [50] [CAS: 7311-30-0]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 20.71 mg, 52%, R_f = 0.3 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.46 (td, *J* = 7.2, 2.6 Hz, 2H), 2.33 (s, 3H), 1.37 (qt, *J* = 7.4, 3.2 Hz, 2H), 1.28 – 1.05 (m, 19H), 0.78 (td, *J* = 6.7, 2.6 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 52.2, 36.4, 31.8, 29.9, 29.6, 29.5, 29.3, 27.3, 22.6, 13.9.



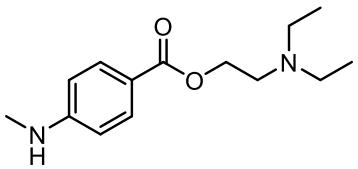
3-(4-(Methylamino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (7b) [51] [CAS: 2197421-58-0]

Purified by column chromatography on silica gel with dichloromethane and methanol. White solid, m.p. 267-268 ºC, 0.2 mmol scale, yield: 32.2 mg, 59%, R_f = 0.45 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.96 (d, *J* = 7.3 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 5.79 – 5.64 (m, 1H), 5.12 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.23 (d, *J* = 17.1 Hz, 1H), 4.13 (d, *J* = 17.1 Hz, 1H), 2.93 (ddd, *J* = 18.3, 13.6, 6.0 Hz, 1H), 2.79 (d, *J* = 4.9 Hz, 3H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.31 (qd, *J* = 13.2, 4.3 Hz, 1H), 2.10 – 1.97 (m, 1H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 173.4, 171.7, 169.4, 145.1, 132.4, 129.8, 126.9, 111.8, 110.4, 52.0, 46.1, 31.7, 30.1, 23.3



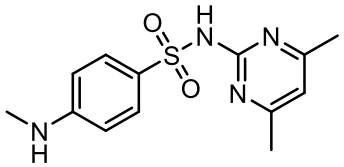
Ethyl 4-(methylamino)benzoate (7e) [33] [CAS: 10541-82-9]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Yellow solid, m.p. 52-53 ºC, 0.2 mmol scale, yield: 26.5 mg, 74%, R_f = 0.4 (PE/EtOAc = 5:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.82 (m, 2H), 6.62 – 6.45 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 3H), 2.87 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 167.0, 152.9, 131.4, 118.4, 111.0, 60.2, 30.1, 14.5.



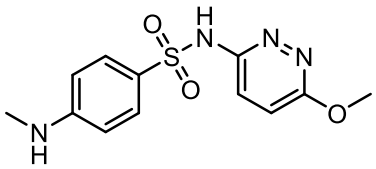
2-(Diethylamino)ethyl 4-(methylamino)benzoate (7f) [52] [CAS: 16488-52-1]

Purified by column chromatography on silica gel with petroleum ether and ethyl acetate. Colorless oil, 0.2 mmol scale, yield: 21.1 mg, 42%, R_f = 0.3 (PE/EtOAc = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.37 (t, *J* = 6.3 Hz, 2H), 4.22 (s, 1H), 2.90 (s, 3H), 2.87 (t, *J* = 6.3 Hz, 2H), 2.67 (q, *J* = 7.1 Hz, 4H), 1.09 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 166.8, 152.9, 131.5, 118.3, 111.1, 62.5, 51.0, 47.7, 30.1, 12.0.



***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(methylamino)benzenesulfonamide (7g)** [53] [CAS: 50520-02-0]

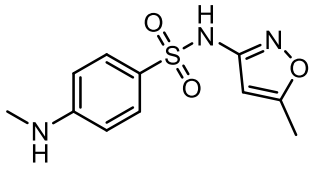
Purified by column chromatography on silica gel with dichloromethane and methanol. White solid, m.p. 82-83 ºC, 0.2 mmol scale, yield: 36.1 mg, 67%, R_f = 0.5 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.95 (s, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 6.59 (s, 1H), 6.50 (d, *J* = 8.8 Hz, 2H), 4.54 (s, 1H), 2.79 (s, 3H), 2.37 (s, 6H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 168.3, 156.6, 153.0, 131.0, 125.4, 114.8, 110.5, 29.9, 23.6.



***N*-(6-Methoxypyridazin-3-yl)-4-(methylamino)benzenesulfonamide (7h)** [53] [CAS: 50519-98-7]

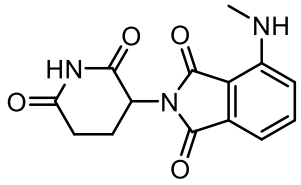
Purified by column chromatography on silica gel with dichloromethane and methanol. Yellow oil, 0.2 mmol scale,

yield: 32.9 mg, 56%, R_f = 0.3 (DCM/MeOH = 15:1, *v/v*).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 9.6 Hz, 1H), 6.97 (d, *J* = 9.7 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H), 2.86 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 158.6, 152.5, 151.2, 129.9, 128.5, 128.0, 124.6, 111.3, 54.8, 30.1.



4-(Methylamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7i) [53] [CAS: 204636-74-8]

Purified by column chromatography on silica gel with dichloromethane and methanol. White solid, m.p. 142-143 °C, 0.2 mmol scale, yield: 22.9 mg, 43%, R_f = 0.5 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H), 7.54 (d, *J* = 8.6 Hz, 2H), 6.65 (q, *J* = 4.9 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 2H), 6.10 (s, 1H), 2.71 (d, *J* = 4.7 Hz, 3H), 2.29 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, DMSO-d_6) δ 170.3, 158.4, 153.8, 129.2, 124.4, 111.0, 95.7, 29.6, 12.5.



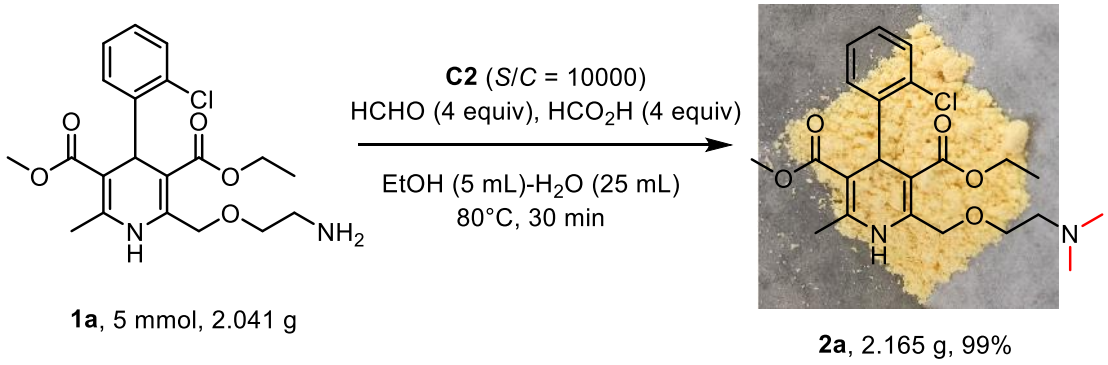
2-(2,6-Dioxopiperidin-3-yl)-4-(methylamino)isoindoline-1,3-dione (7q) [CAS: 2934571-12-5]

Purified by column chromatography on silica gel with dichloromethane and methanol. Green solid, m.p. 275-277 °C, 0.2 mmol scale, yield: 26.4 mg, 46%, R_f = 0.55 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (s, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.63 (s, 1H), 5.06 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.90 (s, 3H), 2.69 – 2.41 (m, 3H), 2.14 – 1.94 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.3, 170.6, 169.2, 167.9, 147.5, 136.7, 132.6, 117.4, 110.7, 109.6, 49.0, 31.5, 29.7, 22.6.

8. Large-scale reactions

8. 1. Gram-scale preparation of 2a.

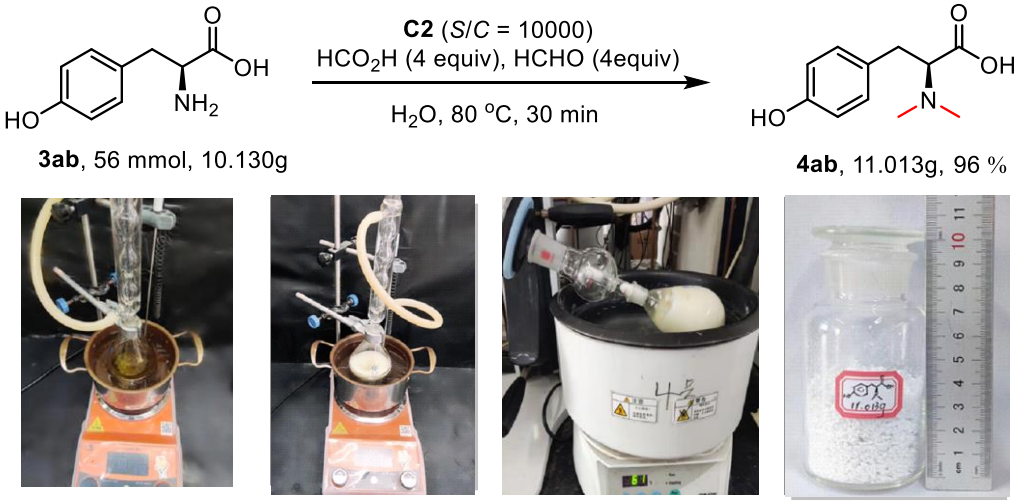
To a 100-mL round bottom flask charged with a magnetic stirring bar was sequentially added Amlodipine (**1a**, 5 mmol, 2.041 g), ethanol (5 mL), HCHO (1.5 mL, 20 mmol, w = 37-40%), HCO_2H (0.75 mL, 20 mmol), **C2** (0.28 mg, *S/C* = 10000) and H_2O (25 mL). The mixture was stirred for 30 min at 80 °C in the oil bath. The reaction process was monitored by TLC. Upon cooling the system to room temperature, part of ethanol was removed under reduced pressure. The resulting mixture was neutralized with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (25 mL x 3). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, yielding **2a** as a yellow solid (2.16 g, 99%).



Scheme S6. Gram-scale preparation of **2a**.

8. 2. Decagram-scale preparation of 4ab.

To a 250-mL round bottom flask charged with a magnetic stirring bar was sequentially added *L*-tyrosine (**3ab**, 56 mmol, 10.14 g), H_2O (50 mL), HCHO (16.8 mL, 224 mmol, w = 37-40%), HCO_2H (8.4 mL, 224 mmol) and **C2** (3.19 mg, *S/C* = 10000). The mixture was stirred for 30 min at 80 °C in the oil bath. The reaction process was monitored by TLC. After the reaction was completed, the water was removed under reduced pressure at 60 °C. The solid mixture was washed with ethanol (3 × 15 mL) and then dried to obtain **4ab** (white solid, 11.013 g, yield 96%)

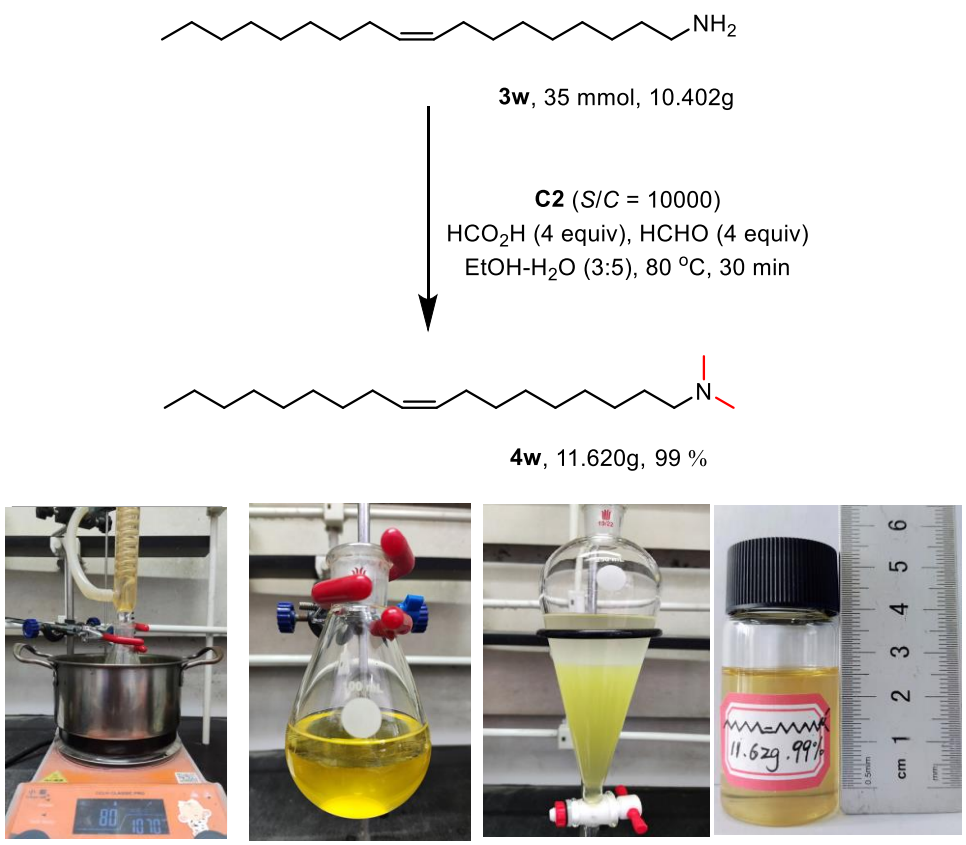


Scheme S7. Decagram-scale preparation of **4ab**.

8. 3. Decagram-scale preparation of 4w.

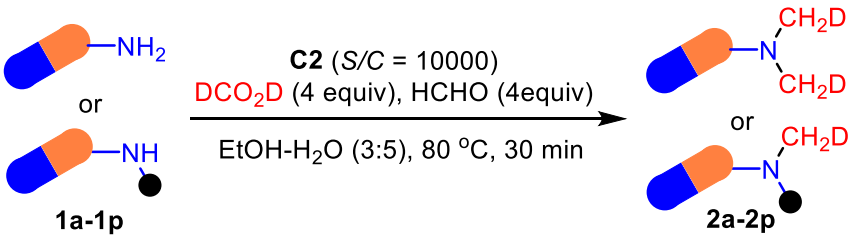
To a 100-mL round bottom flask charged with a magnetic stirring bar was sequentially added oleylamine (**3w**, 35 mmol, 10.40 g), ethanol (10 mL), HCHO (10.5 mL, 140 mmol, w = 37-40%), H_2O (20 mL), HCO_2H (5.25 mL, 140 mmol) and **C2** (1.96 mg, *S/C* = 10000). The mixture was stirred for 30 min at 80 °C in the oil bath. The reaction process was monitored by TLC. Upon cooling the system to room temperature, ethanol was removed under reduced pressure. The resulting mixture

was neutralized with saturated sodium bicarbonate (10 mL) and extracted with ethyl acetate (25 mL x 3). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, yielding **4w** as a yellow oil (11.62 g, 99%).



Scheme S8. Decagram-scale preparation of **4w**.

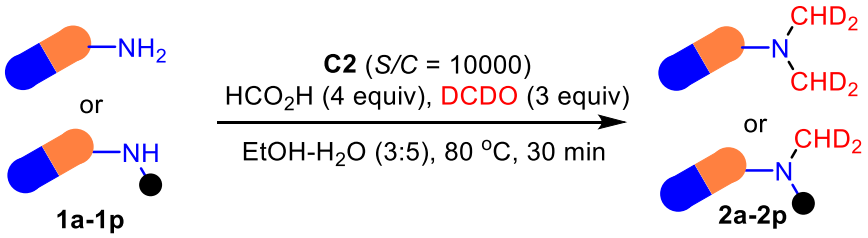
9. Deuteration labelling and calculation of deuterium incorporation



Scheme S9. Deuteration experiment of **1a-1p**.

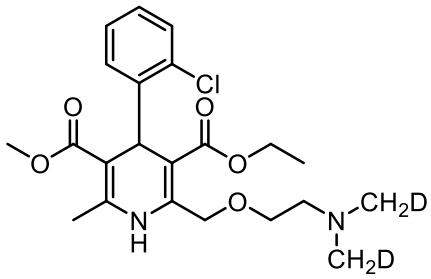
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added drug molecules (**1a-1p**, 0.1 mmol), EtOH (0.3 mL), HCHO (30 μL, 0.4 mmol, 4 equiv, dissolved in H_2O, wt% = 37-40%), DCO_2D (15 μL, 0.4 mmol, 4 equiv), and 0.5 mL of catalyst solution (0.00002 mol/L for *S/C* = 10000, **C2** dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium

bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The product was submitted to ^{1}H NMR and HRMS determination.



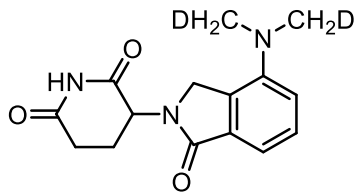
Scheme S10. Deuteration experiment of **1a-1p**.

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added drug molecules (**1a-1p**, 0.1 mmol), EtOH (0.3 mL), DCDO (30 μL, 0.3 mmol, 3 equiv, dissolved in D_2O, wt% = 30%), HCO_2H (15 μL, 0.4 mmol, 4 equiv), and 1 mL of catalyst solution (0.00002 mol/L for *S/C* = 10000, **C2** dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The product was submitted to ^{1}H NMR and HRMS determination.



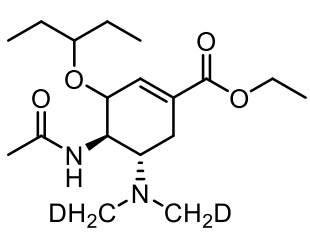
3-Mthyl 5-methyl 2-((2-(bis(methyl-*d*)amino)ethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-*d*$_2$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 97-99 °C, 0.2 mmol scale, yield: 42.9 mg, 99%, R_f = 0.4 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (s, 1H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 5.40 (s, 1H), 4.79 (d, *J* = 17.0 Hz, 1H), 4.70 (d, *J* = 16.9 Hz, 1H), 4.07-4.00 (m, 2H), 3.69 – 3.55 (m, 5H), 2.62 – 2.47 (m, 2H), 2.33 (s, 3H), 2.30 (s, 4H), 1.22 – 1.13 (m, 3H).^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 168.1, 167.3, 146.7, 145.9, 144.7, 132.4, 131.6, 129.2, 127.2, 126.7, 103.5, 100.9, 69.3, 68.3, 59.6, 58.9, 50.7, 45.3 (t, *J* = 20.5 Hz), 37.5, 18.9, 14.3. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}D_2ClN_2O_5^+$, 439.1963; found, 439.1961.



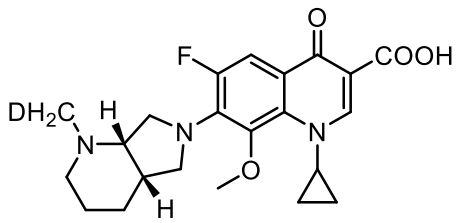
3-(4-(Bis(methyl-*d*)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b-*d*$_2$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 251-252 °C, 0.2 mmol scale, yield: 46.2 mg, 80%, R_f = 0.50 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.0 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 4.42 (d, *J* = 17.0 Hz, 1H), 2.99 – 2.89 (m, 1H), 2.88 (s, 4H), 2.61 (d, *J* = 17.6 Hz, 1H), 2.57 – 2.41 (m, 1H), 2.03-1.98 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 171.5, 168.7, 148.2, 133.6, 130.2, 129.5, 118.2, 113.8, 52.0, 48.2, 42.1 (t, *J* = 20.7 Hz), 31.7, 22.9. HRMS (ESI): *m/z* calcd for : $C_{15}H_{16}D_2N_3O_3^+$ $[M+H]^+$: 290.1468, found: 290.1470.



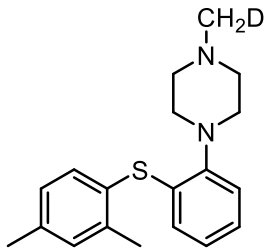
Ethyl-(4*R*,5*S*)-4-acetamido-5-(bis(methyl-*d*)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d-d_2)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 67.0 mg, 98%, R_f = 0.35 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.70 (s, 1H), 6.06 – 5.86 (m, 1H), 4.25 – 4.10 (m, 2H), 4.02 (d, *J* = 7.3 Hz, 1H), 3.95 – 3.81 (m, 1H), 3.28 (p, *J* = 5.3 Hz, 1H), 2.95 – 2.78 (m, 1H), 2.50 (d, *J* = 15.2 Hz, 1H), 2.21 (s, 5H), 1.97 (d, *J* = 2.1 Hz, 3H), 1.46 (p, *J* = 7.3 Hz, 4H), 1.25 (td, *J* = 7.1, 1.6 Hz, 3H), 0.92 – 0.77 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.4, 166.6, 138.0, 129.5, 81.9, 77.3, 76.8, 60.7, 60.6, 53.3, 39.8 (t, *J* = 20.2 Hz), 25.9, 25.4, 23.7, 21.7, 14.2, 9.5, 9.1. HRMS (ESI): *m/z* calcd for : $C_{18}H_{31}D_2N_2O_4^+$ $[M+H]^+$: 343.2560, found: 343.2564.



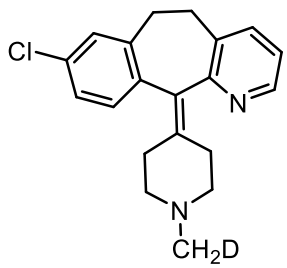
1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-(methyl-*d*)octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2d-*d*)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 170-171 °C, 0.2 mmol scale, yield: 82.4 mg, 99%, R_f = 0.50 (DCM/MeOH/HCOOH=5:1:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.74 (s, 1H), 7.72 (d, *J* = 13.9 Hz, 1H), 4.04-3.99 (m, 1H), 3.89 (td, *J* = 9.7, 3.3 Hz, 1H), 3.83 – 3.67 (m, 2H), 3.57 (s, 3H), 3.46 (ddd, *J* = 9.9, 7.5, 2.3 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.46-2.38 (m, 1H), 2.24 (s, 2H), 2.22 – 2.11 (m, 1H), 1.91-1.81 (m, 1H), 1.77-1.66 (m, 2H), 1.65 – 1.54 (m, 1H), 1.24 (tt, *J* = 9.2, 4.6 Hz, 1H), 1.19 – 1.00 (m, 2H), 0.95 – 0.83 (m, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.7, 167.2, 154.8 (d, *J* = 251.6 Hz), 149.4, 140.2 (d, *J* = 6.9 Hz), 137.6 (d, *J* = 9.8 Hz), 134.5, 117.7 (d, *J* = 8.6 Hz), 107.7, 107.4 (d, *J* = 3.5 Hz), 64.4, 61.0, 54.4 (d, *J* = 6.1 Hz), 54.2, 53.2 (d, *J* = 6.5 Hz), 43.9 (t, *J* = 30.2 Hz), 40.5, 37.6, 23.1, 22.0, 10.1, 8.8. ^{19}F NMR (376 MHz, Chloroform-*d*) δ -120.68. HRMS (ESI): *m/z* calcd for : $C_{22}H_{26}DFN_3O_4^+$ $[M+H]^+$: 417.2043, found: 417.2043.



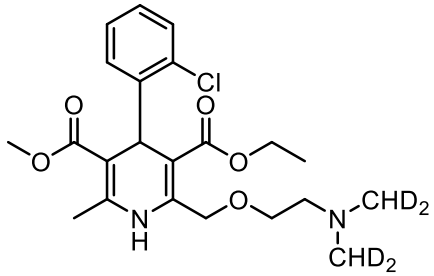
1-(2-((2,4-dimethylphenyl)thio)phenyl)-4-(methyl-*d*)piperazine (2m-*d*) [54] [CAS: 2492423-51-3]

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 71-72 °C, 0.2 mmol scale, yield: 62 mg, 97%, R_f = 0.50 (EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.09 (dd, *J* = 6.6, 1.3 Hz, 2H), 7.07 – 7.02 (m, 1H), 6.87 (ddd, *J* = 8.1, 6.3, 2.1 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 3.15 (s, 4H), 2.66 (s, 4H), 2.38 (s, 5H), 2.36 (s, 3H). ^{13}C NMR{^{1}H} (101 MHz, Chloroform-*d*) δ 149.2, 142.4, 139.1, 136.3, 134.6, 131.7, 128.1, 127.8, 126.1, 125.5, 124.3, 119.9, 55.5, 51.7, 45.9 (t, *J* = 20.2 Hz), 21.2, 20.7. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{24}DN_2S^+$, 314.1796; found, 314.1801.



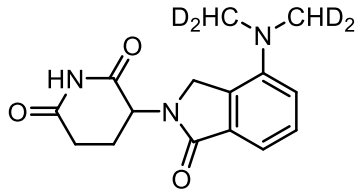
8-Chloro-11-(1-(methyl-*d*)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2m-*d*)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Pink oil, 0.2 mmol scale, yield: 63.5 mg, 98%, R_f = 0.3 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.16 – 7.09 (m, 3H), 7.05 (ddd, *J* = 7.5, 4.8, 1.4 Hz, 1H), 3.46 – 3.28 (m, 2H), 2.88 – 2.74 (m, 2H), 2.73-2.65 (m, 2H), 2.53 (ddd, *J* = 14.3, 10.2, 4.4 Hz, 1H), 2.45 – 2.30 (m, 3H),2.22 (s, 2H), 2.09-2.01 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.6, 146.6, 139.5, 138.3, 137.9, 137.2, 133.4, 132.8, 132.6, 130.8, 128.9, 126.0, 122.1, 77.3, 56.9, 46.0, 45.8 (t, *J* = 20.1 Hz), 31.8, 31.4, 31.0, 30.8. HRMS (ESI): *m/z* calcd for : $C_{20}H_{21}DClN_2^+$ $[M+H]^+$: 326.1529, found: 326.1534.



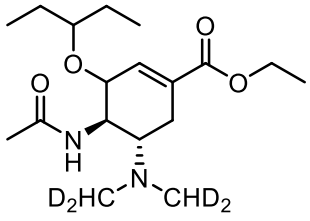
3-Ethyl 5-methyl 2-((2-(bis(methyl-*d*$_2$)amino)ethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-*d*$_4$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 92-93 °C, 0.2 mmol scale, yield: 87.1 mg, 99%, R_f = 0.4 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (s, 1H), 7.38 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.12 (td, *J* = 7.5, 1.4 Hz, 1H), 7.03 (td, *J* = 7.6, 1.7 Hz, 1H), 5.40 (s, 1H), 4.89 – 4.62 (m, 2H), 4.04 (qd, *J* = 7.1, 2.7 Hz, 2H), 3.71 – 3.51 (m, 5H), 2.62 – 2.46 (m, 2H), 2.33 (s, 3H), 2.27 (s, 2H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 168.2, 167.3, 146.7, 145.9, 144.7, 132.4, 131.6, 129.2, 127.2, 126.7, 103.5, 100.9, 69.3, 68.3, 59.6, 58.9, 50.7, 44.9 (quint, *J* = 21.0 Hz), 37.5, 18.9, 14.3. HRMS (ESI): *m/z* calcd for : $C_{22}H_{25}D_4ClN_2O_5^+$ $[M+H]^+$: 441.2089, found: 441.2086.



3-(4-(Bis(methyl-*d*$_2$)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b-*d*$_4$)

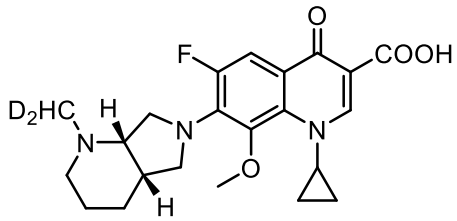
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. White solid, m.p. 250-251 °C, 0.2 mmol scale, yield: 46.2 mg, 79%, R_f = 0.50 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.99 (s, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.21 – 7.14 (m, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.56 (d, *J* = 17.0 Hz, 1H), 4.42 (d, *J* = 17.0 Hz, 1H), 2.99 – 2.87 (m, 1H), 2.86 (s, 2H), 2.61 (d, *J* = 17.8 Hz, 1H), 2.55 – 2.42 (m, 1H), 2.04-1.97 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.4, 171.5, 168.7, 148.2, 133.7, 130.1, 129.5, 118.1, 113.8, 52.0, 48.2, 41,7 (quint, *J* = 20.8 Hz), 31.7, 22.9. HRMS (ESI): *m/z* calcd for : $C_{15}H_{14}D_4N_3O_3^+$ $[M+H]^+$: 292.1594, found: 292.1600.



Ethyl (4*R*,5*S*)-4-acetamido-5-(bis(methyl-*d*$_2$)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d-*d*$_4$) [CAS: 2230279-52-2]

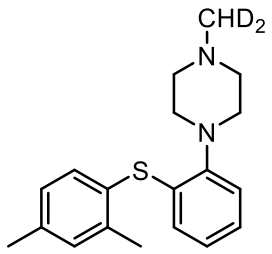
Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow oil, 0.2 mmol scale, yield: 66.8 mg, 97%, R_f = 0.35 (DCM/MeOH = 15:1, *v/v*). ^{1}H NMR

(400 MHz, Chloroform-*d*) δ 6.70 (s, 1H), 6.08 – 5.83 (m, 1H), 4.24 – 4.10 (m, 2H), 4.02 (d, *J* = 8.3 Hz, 1H), 3.89 (q, *J* = 9.5, 9.0 Hz, 1H), 3.40 – 3.19 (m, 1H), 2.89-2.81 (m, 1H), 2.49 (d, *J* = 17.3 Hz, 1H), 2.19 (s, 3H), 1.97 (d, *J* = 3.8 Hz, 3H), 1.46 (m, 4H), 1.28-1.23 (m, 3H), 0.88-0.80 (m, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.4, 166.6, 138.0, 129.5, 81.9, 77.7, 60.7, 60.6, 53.3, 39.4 (quint, *J* = 18.8 Hz), 25.9, 25.4, 23.7, 21.7, 14.2, 9.5, 9.1. HRMS (ESI): *m/z* calcd for : $C_{18}H_{29}D_4N_2O_4^+$ $[M+H]^+$: 345.2686, found: 345.2690.



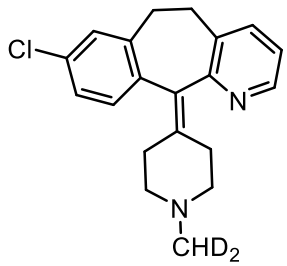
1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-(methyl-*d*$_2$)octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2l-*d*$_2$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 168-169 °C, 0.2 mmol scale, yield: 81.2 mg, 97%, R_f = 0.50 (DCM/MeOH/HCOOH=5:1:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.73 (s, 1H), 7.71 (d, *J* = 13.9 Hz, 1H), 4.01 (s, 1H), 3.87 (d, *J* = 10.1 Hz, 1H), 3.83 – 3.65 (m, 2H), 3.57 (s, 3H), 3.45 (t, *J* = 8.9 Hz, 1H), 2.86 – 2.64 (m, 2H), 2.41 (s, 1H), 2.21-2.13 (m, 2H), 1.84 (t, *J* = 11.4 Hz, 1H), 1.70-1.58 (m, 3H), 1.24 (s, 1H), 1.18 – 0.99 (m, 2H), 0.89 (s, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 176.6, 167.2, 153.5 (d, *J* = 251.6 Hz), 149.4, 140.3 (d, *J* = 7.2 Hz), 137.6 (d, *J* = 9.9 Hz), 134.5, 117.7 (d, *J* = 8.8 Hz), 107.7, 107.4 (d, *J* = 3.4 Hz), 64.4, 61.0, 54.4 (d, *J* = 5.8 Hz), 54.2, 53.2 (d, *J* = 6.6 Hz), 43.6 (quint, *J* = 12.4 Hz), 40.5, 37.6, 23.1, 22.0, 10.1, 8.9. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -120.68. HRMS (ESI): *m/z* calcd for : $C_{22}H_{25}D_2FN_3O_4^+$ $[M+H]^+$: 418.2106, found: 418.2106.



1-(2-((2,4-Dimethylphenyl)thio)phenyl)-4-(methyl-*d*$_2$)piperazine (2m-*d*$_2$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Yellow solid, m.p. 73-74 °C, 0.2 mmol scale, yield: 62.2 mg, 99%, R_f = 0.5 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 7.8 Hz, 1H), 7.17 (s, 1H), 7.14 – 7.01 (m, 3H), 6.88 (ddd, *J* = 8.3, 6.2, 2.5 Hz, 1H), 6.54 (d, *J* = 7.4 Hz, 1H), 3.15 (s, 4H), 2.67 (s, 4H), 2.38 (s, 3H), 2.36 (d, *J* = 3.8 Hz, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 149.2, 142.5, 139.2, 136.3, 134.6, 131.7, 128.1, 127.8, 126.1, 125.4, 124.3, 119.9, 55.5, 51.6, 45.6 (quint, *J* = 20.8 Hz), 21.2, 20.6. HRMS (ESI): *m/z* calcd for : $C_{19}H_{23}D_2N_2S^+$ $[M+H]^+$: 315.1858, found: 315.1860.

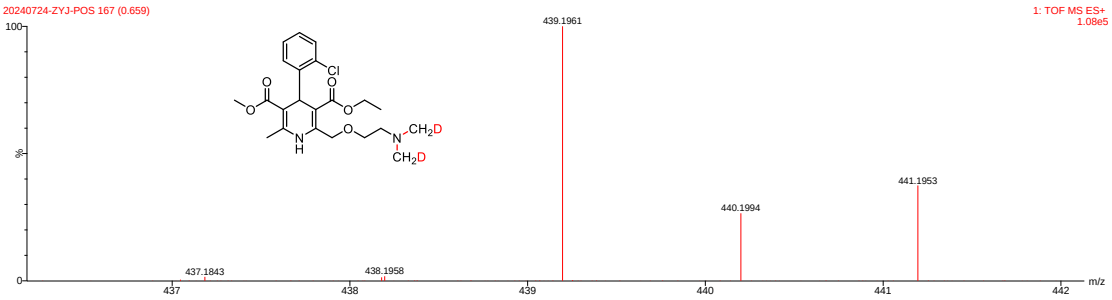


8-Chloro-11-(1-(methyl-*d*$_2$)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2p-*d*$_2$)

Purified by extraction with ethyl acetate, drying over Na_2SO_4, and concentration under reduced pressure. Pink oil, 0.2 mmol scale, yield: 63.9 mg, 99%, R_f = 0.3 (DCM/MeOH = 10:1, *v/v*). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 – 8.33 (m, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.07 – 7.01 (m, 1H), 3.46 – 3.27 (m, 2H), 2.84-2.74 (m, 2H), 2.73 – 2.63 (m, 2H), 2.56-2.49 (m, 1H), 2.45 – 2.29 (m, 3H), 2.19 (s, 1H), 2.08-2.01 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.6, 146.6, 139.5, 138.3, 137.9, 137.2, 133.3, 132.8, 132.6,

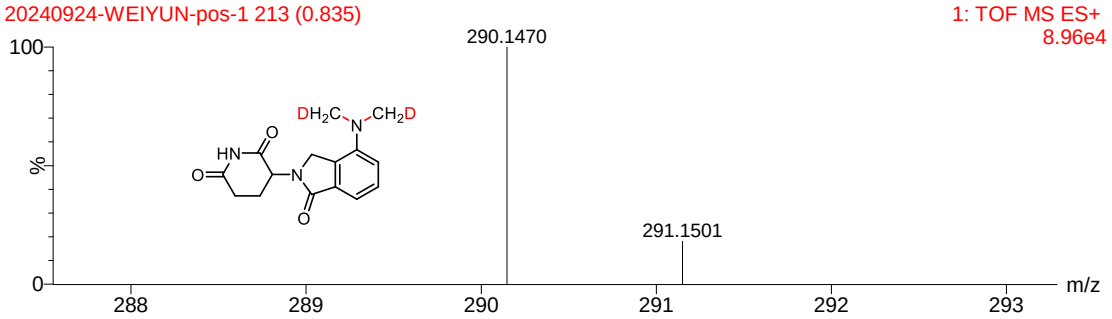
130.8, 128.9, 126.0, 122.1, 77.4, 56.9, 45.7 (quint, J = 22.2 Hz), 31.8, 31.4, 31.0, 30.8. HRMS (ESI): *m/z* calcd for : $C_{20}H_{20}D_2ClN_2^+$ $[M+H]^+$: 327.1592, found: 327.1596.

Table S2. Determining the deuterium incorporation ratio ([D]) of **2a**-d_2 by HRMS analysis.



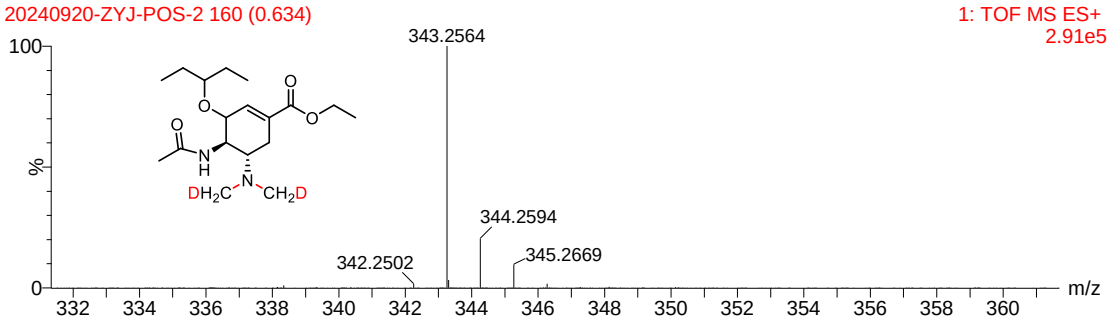
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2a	[M+H]	100%	1641	1641	1.5
	[M+H]+2	32%	108000	525	
2a-d_2	[M'+H]	100%	(in sum)	107475	98.5
[D] = 107475/(107475 + 1641) = 98.5%					

Table S3. Determining the deuterium incorporation ratio ([D]) of **2b**-d_2 by HRMS analysis.



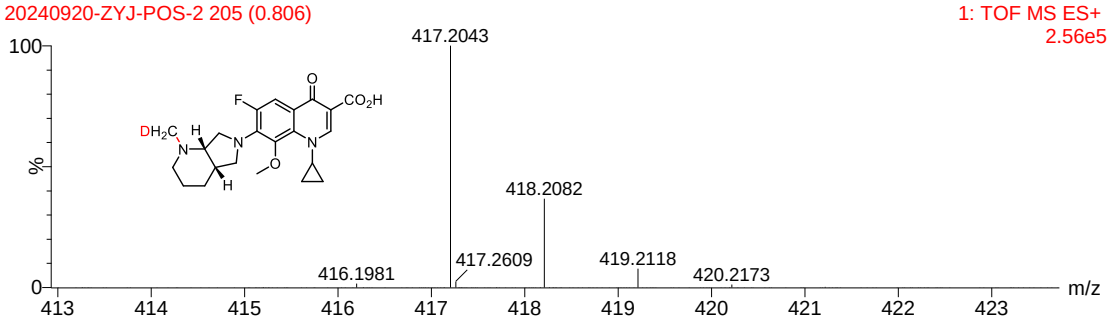
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2b	[M+H]	100%	101	101	0.1
	[M+H]+2	1.2%	94490	1.2	
2b-d_2	[M'+H]	100%	(in sum)	94488.8	99.9
[D] = 94488.8/(94488.8 + 101) = 99.9%					

Table S4. Determining the deuterium incorporation ratio ([D]) of **2d**-d_2 by HRMS analysis.



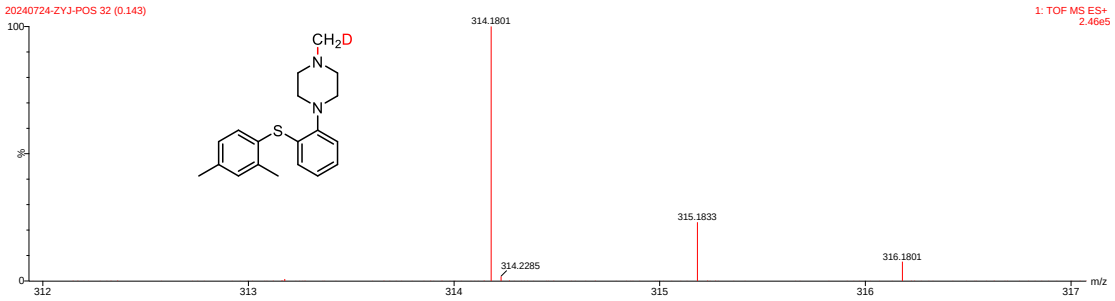
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2d	[M+H]	100%	45	45	0.1
	[M+H]+2	1.8%	169100	0.81	
2d-d_2	[M'+H]	100%	(in sum)	169099	99.9
[D] = 169099/(169099 + 45) = 97.4%					

Table S5. Determining the deuterium incorporation ratio ([D]) of **2l**-*d* by HRMS analysis.



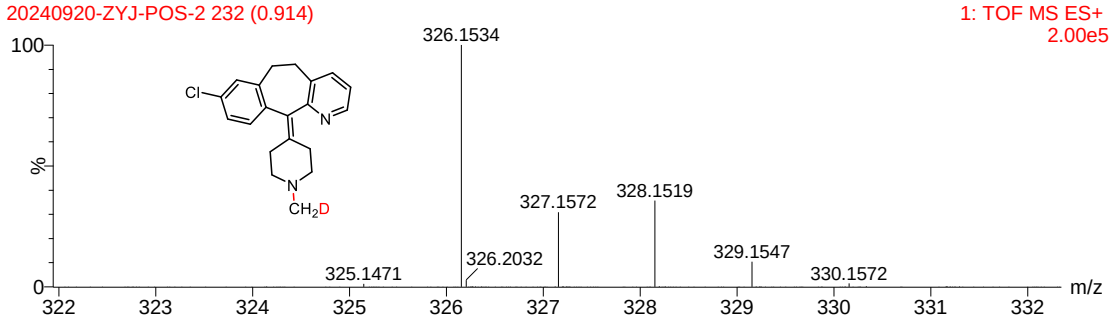
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2l	[M+H]	100%	3976	3976	1.6
	[M+H]+1	23.8%	255700	946	
2l-*d*	[M'+H]	100%	(in sum)	254754	98.4
[D] = 254754/(254754 + 3976) = 98.4%					

Table S6. Determining the deuterium incorporation ratio ([D]) of **2m**-*d* by HRMS analysis.



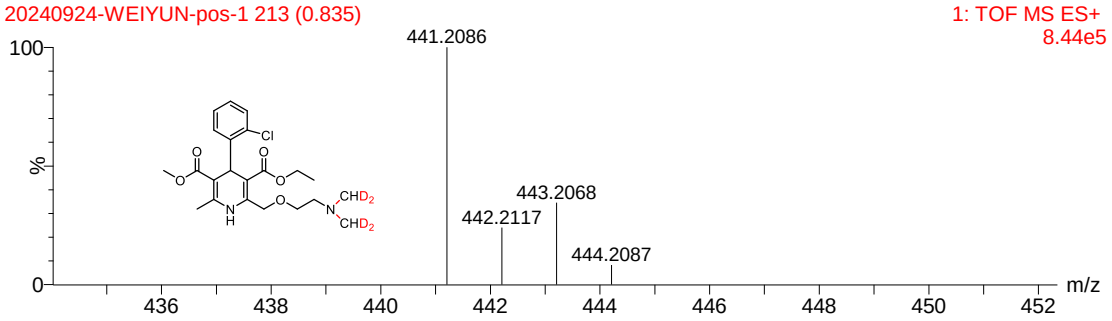
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2m	[M+H]	100%	1797	1797	0.7
	[M+H]+1	20.5%	246400	368	
2m-*d*	[M'+H]	100%	(in sum)	246032	99.3
[D] = 246032/(246032 + 1797) = 99.3%					

Table S7. Determining the deuterium incorporation ratio ([D]) of **2p**-*d* by HRMS analysis.



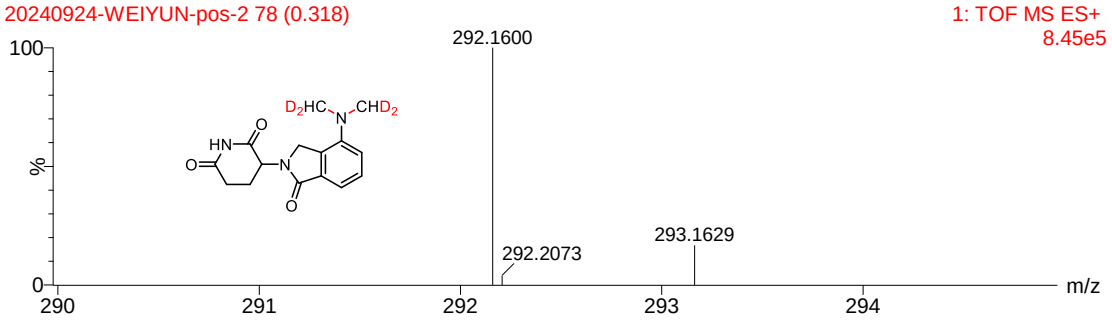
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2p	[M+H]	100%	2228	2228	1.1
	[M+H]+1	21.6%	199700	481	
2p-*d*	[M'+H]	100%	(in sum)	199219	98.9
[D] = 199219/(199219 + 2228) = 98.9%					

Table S8. Determining the deuterium incorporation ratio ([D]) of **2a**-d_4 by HRMS analysis.



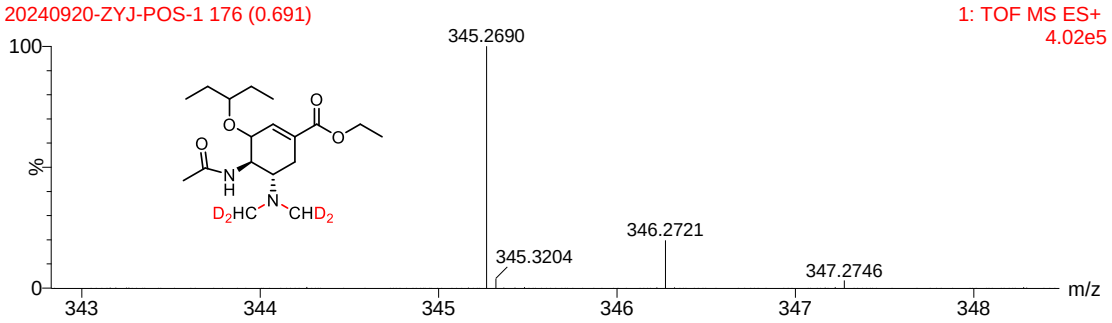
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2a	[M+H]	100%	145	145	0.1
	[M+H]+4	<1%	442000	<10	
2a-d_4	[M'+H]	100%	(in sum)	442000	99.9
[D] = 442000/(442000 + 145) = 99.9%					

Table S9. Determining the deuterium incorporation ratio ([D]) of **2b**-d_4 by HRMS analysis.



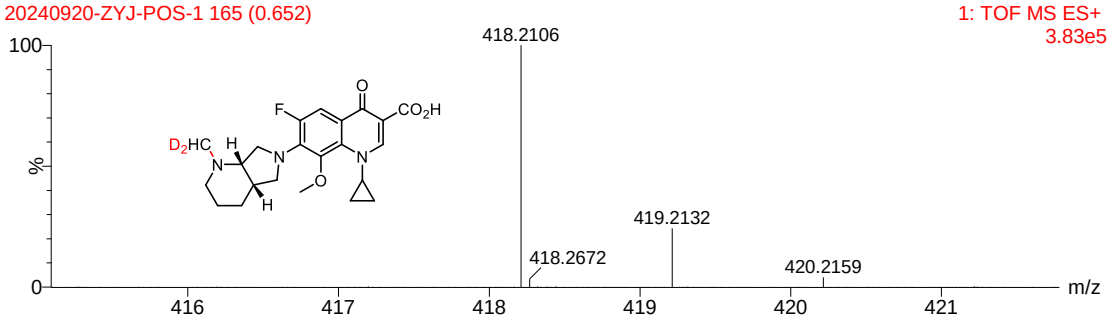
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2b	[M+H]	100%	235	235	0.1
	[M+H]+4	<1%	845000	<10	
2b-d_4	[M'+H]	100%	(in sum)	845000	99.9
[D] = 845000/(845000 + 145) = 99.9%					

Table S10. Determining the deuterium incorporation ratio ([D]) of **2d**-d_4 by HRMS analysis.



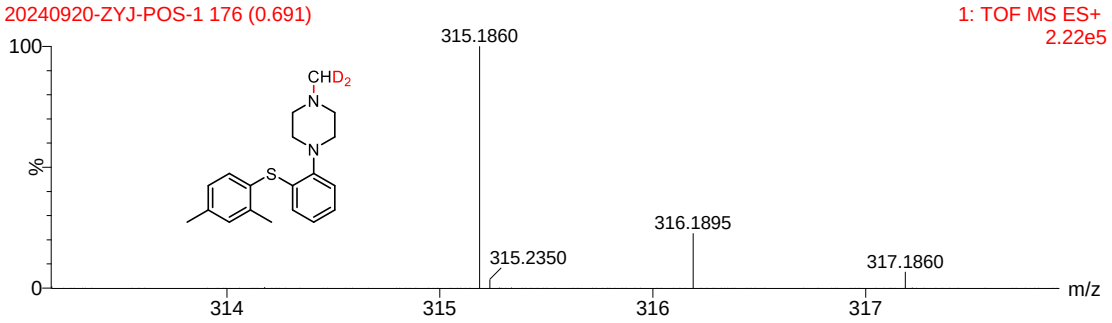
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2d	[M+H]	100%	389	389	0.1
	[M+H]+4	<1%	401800	<10	
2d-d_4	[M'+H]	100%	(in sum)	401800	99.9
[D] = 401800/(401800 + 389) = 99.9%					

Table S11. Determining the deuterium incorporation ratio ([D]) of **2l**-d_2 by HRMS analysis.



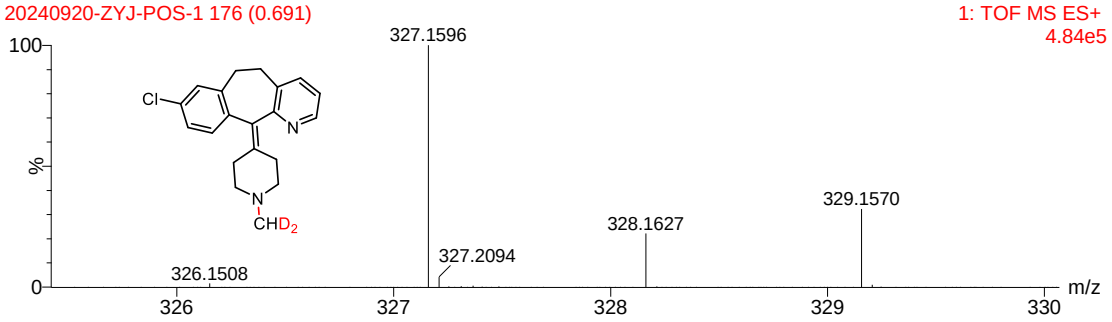
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2l	[M+H]	100%	134	134	0.1
	[M+H]+2	2.7%	383500	4	
2l-d_2	[M'+H]	100%	(in sum)	383496	99.9
[D] = 383496/(383496 + 134) = 99.9%					

Table S12. Determining the deuterium incorporation ratio ([D]) of **2m**-d_2 by HRMS analysis.



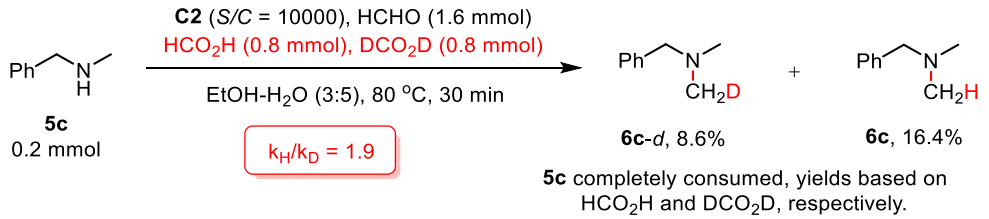
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2m	[M+H]	100%	1225	1225	0.5
	[M+H]+2	2.0%	221800	25	
2m-d_2	[M'+H]	100%	(in sum)	221775	99.5
[D] = 221775/(221775 + 1225) = 99.5%					

Table S13. Determining the deuterium incorporation ratio ([D]) of **2p**-d_2 by HRMS analysis.



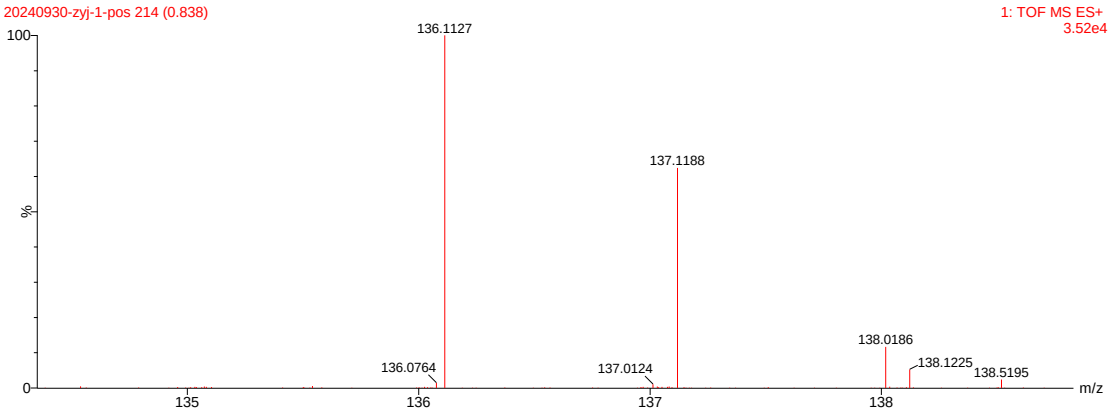
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
2p	[M+H]	100%	1278	1278	0.3
	[M+H]+2	32%	486500	409	
2p-d_2	[M'+H]	100%	(in sum)	486091	99.7
[D] = 486091/(486091 + 1278) = 99.7%					

10. Kinetic isotope effect

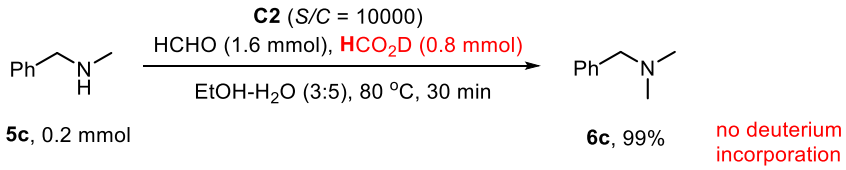


Scheme S11. Kinetic isotope effect of **5c**

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added **5c** (0.2 mmol, 24.2 mg), EtOH (0.6 mL), HCHO (120 μL, 1.6 mmol, 8 equiv, wt% = 37-40%), HCO_2H (30 μL, 0.8 mmol, 4 equiv), DCO_2D (30 μL, 0.8 mmol, 4 equiv), and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 10000, **C2** dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The product was submitted to HRMS analysis to determine the H/D ratio.



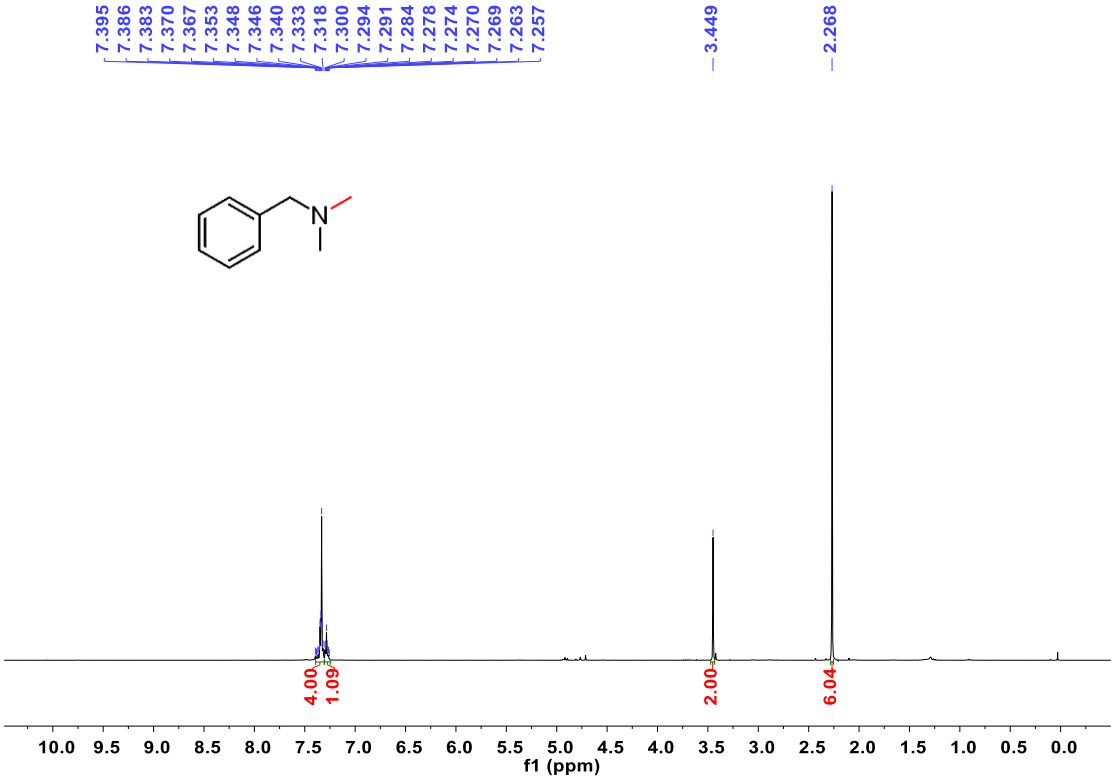
m/z		Relative Natural Abundance (%)	Observed Abundance (%)	Corrected Abundance (%)	Isotopic Enrichment Relative (%)
6c	[M+H]	100%	35210	35210	65.6
	[M+H]+1	9.7%	21970	3415.4	
6c-*d*	[M'+H]	100%	(in sum)	18554.6	34.5
[D] = 18554.6/(18554.6 + 35210) = 34.5% H/D = 65.6÷34.5 = 1.9					

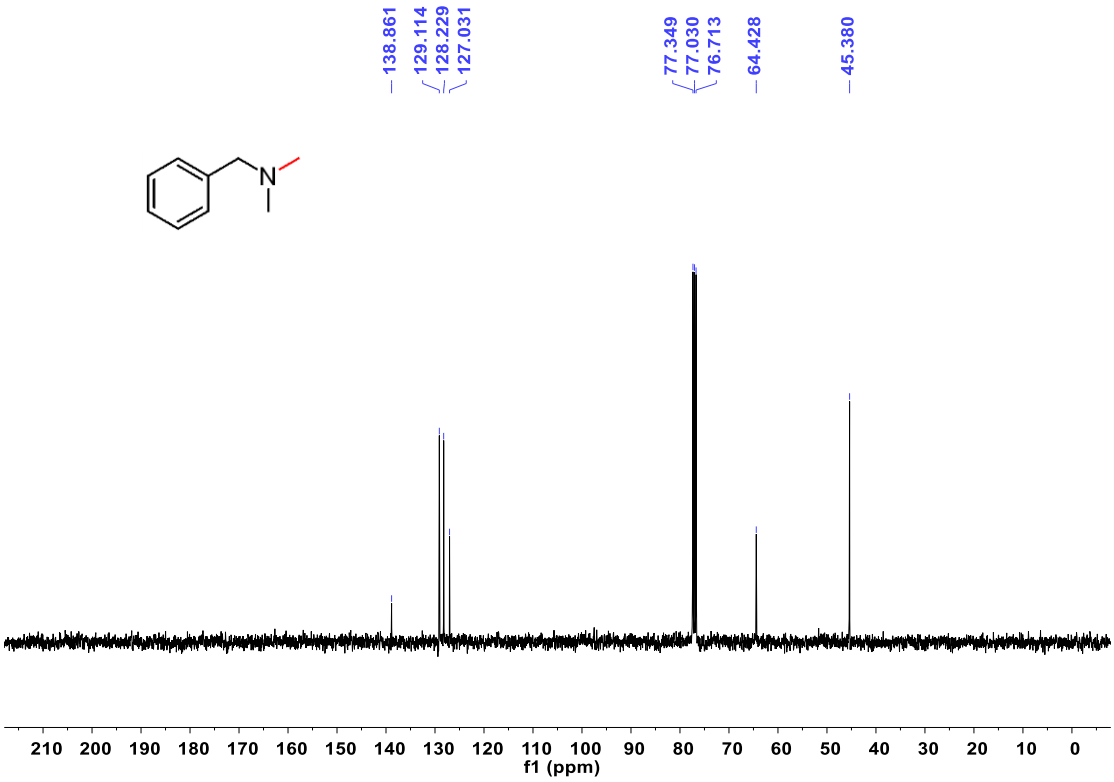


Scheme S12. Kinetic isotope effect of **5c**

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added **5c** (0.2 mmol, 24.2 mg), EtOH (0.6 mL), HCHO (120 μL, 1.6 mmol, 8 equiv, wt% = 37-40%), HCO_2D (30 μL, 0.8 mmol, 4 equiv), and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 10000, **C2** dissolved in deionized water). The mixture was stirred for 30 min at 80 °C in a heating block. After cooling to room temperature, neutralizing with saturated sodium bicarbonate (2 mL) and extracting with ethyl acetate (2 mL × 3), the organic solvent was evaporated under reduced pressure. The product was submitted to NMR determination, and almost no deuterium incorporation was observed.

The ^{1}H and ^{13}C NMR spectrum of 6c





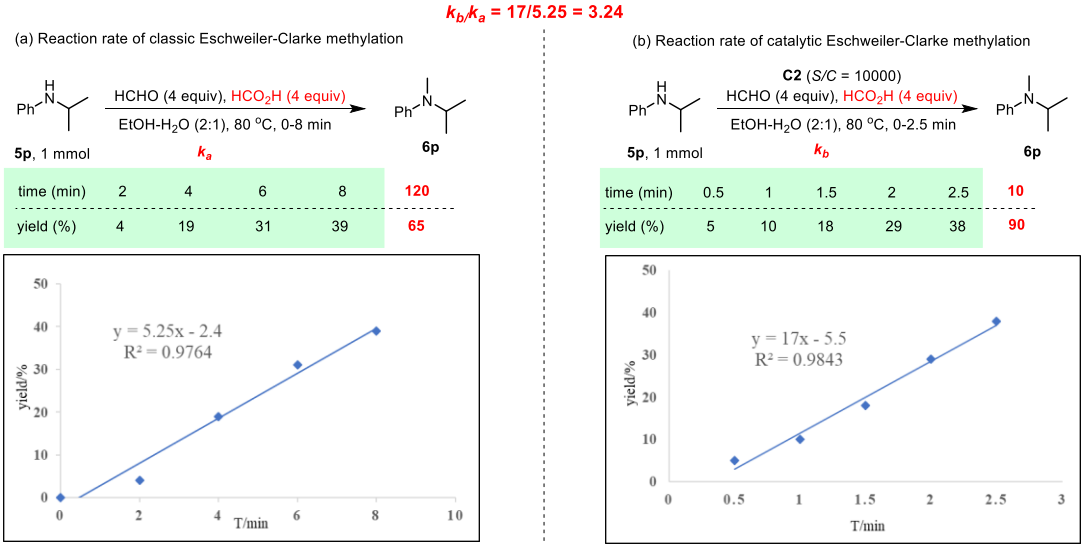
11.Reaction rate comparison

(a) Reaction rate of classic Eschweiler-Clarke methylation

To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added *N*-isopropylaniline **5p** (1 mmol, 135 mg), EtOH (2 mL), 1-bromo-4-methoxybenzene (1 mmol, 185 mg, used as internal standard), HCHO (300 μL, 4 mmol, 4 equiv, wt% = 37-40%), HCO_2H (150 μL, 4 mmol, 4 equiv), and H_2O (1 mL). The mixture was stirred at 80 °C in a heating block. At 2 min intervals a small aliquot of the clear solution was taken out, and was immediately neutralized with saturated sodium bicarbonate (2 mL) followed by extraction with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. The ^{1}H NMR yield of each crude residue was determined using 1-bromo-4-methoxybenzene as internal standard.

(b) Reaction rate of catalytic Eschweiler-Clarke methylation

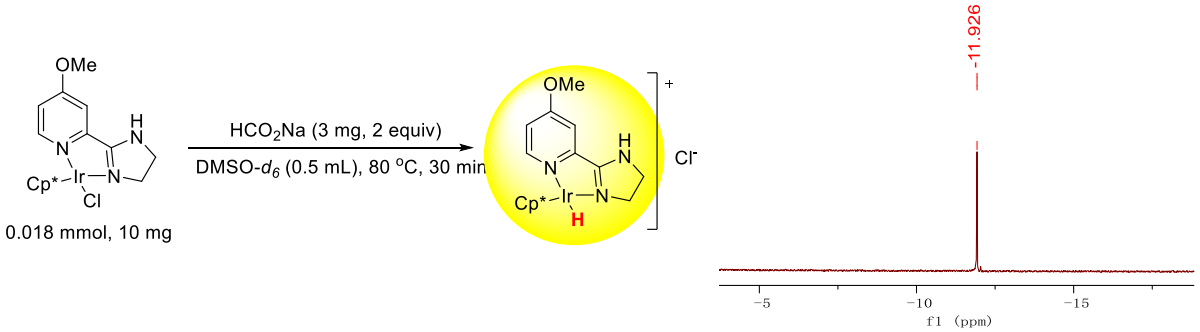
To a 10-mL reaction tube charged with a magnetic stirring bar was sequentially added *N*-isopropylaniline **5p** (1 mmol, 135 mg), EtOH (2 mL), 1-bromo-4-methoxybenzene (1 mmol, 185 mg, used as internal standard), HCHO (300 μL, 4 mmol, 4 equiv, wt% = 37-40%), HCO_2H (150 μL, 4 mmol, 4 equiv) and 1 mL of catalyst solution (0.00001 mol/L for *S/C* = 10000, **C2** dissolved in deionized water). The mixture was stirred at 80 °C in a heating block. At 2 min intervals a small aliquot of the clear solution was taken out, and was immediately neutralized with saturated sodium bicarbonate (2 mL) followed by extraction with ethyl acetate (2 mL × 3). The organic solvent was evaporated under reduced pressure. The ^{1}H NMR yield of each crude residue was determined using 1-bromo-4-methoxybenzene as internal standard.



Scheme S13. Reaction rate comparison of **5p**

12.Observation of the iridium hydride species

To a NMR tube was sequentially added **C2** (0.018 mmol, 10 mg), HCO_2Na (3 mg, 0.036 mmol, 2 equiv) and DMSO-d_6 (0.5 mL). The mixture was heated for 30 min at 80 °C in the oil bath. After cooling to room temperature, submitting to ^{1}H NMR determination



Scheme S14. Observation of the iridium hydride species

13.Reference

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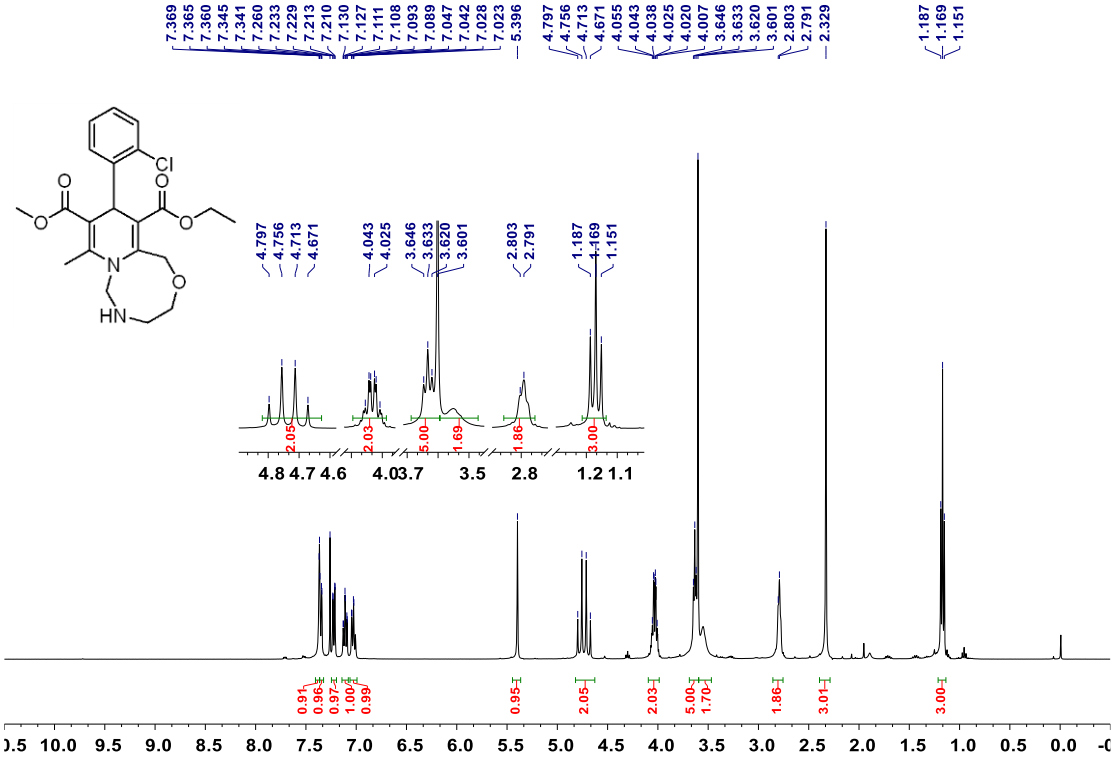
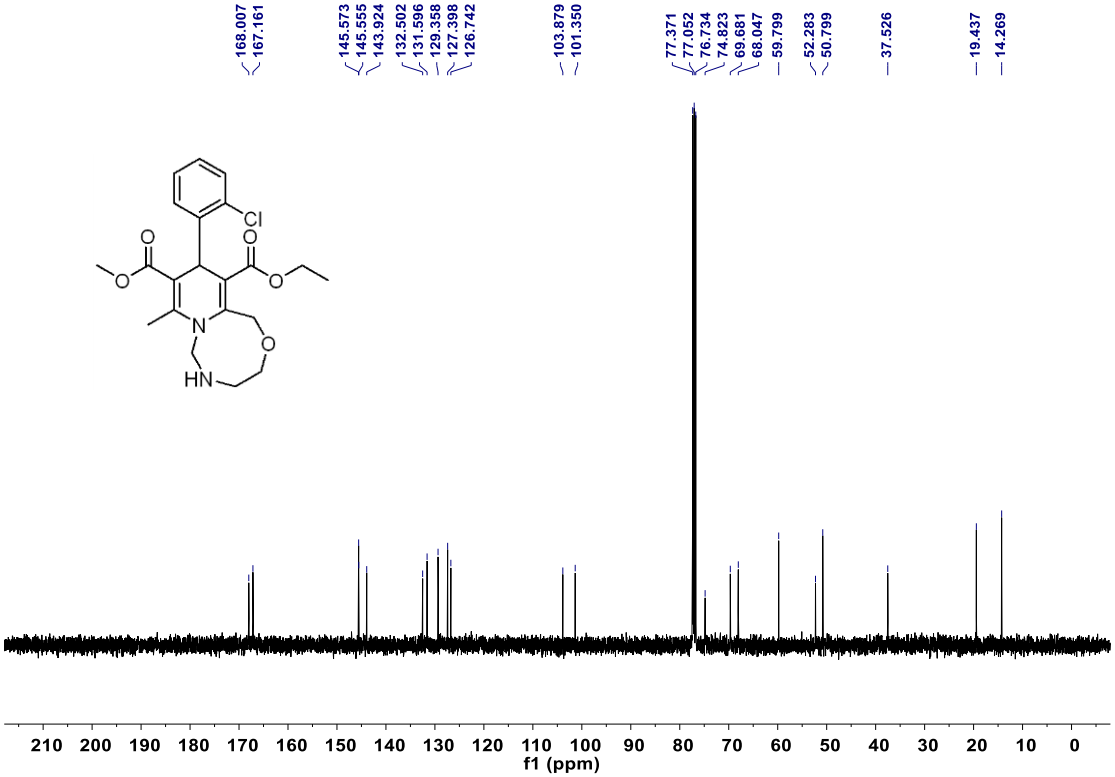
14.Copies of ^{1}H and ^{13}C NMR and HRMS spectra

11-Ethyl 9-methyl 10-(2-chlorophenyl)-8-methyl-1,3,4,5,6,10-hexahydropyrido[2,1-c][1,4,6]oxadiazocine-9,11-dicarboxylate (2a-cyc)

^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



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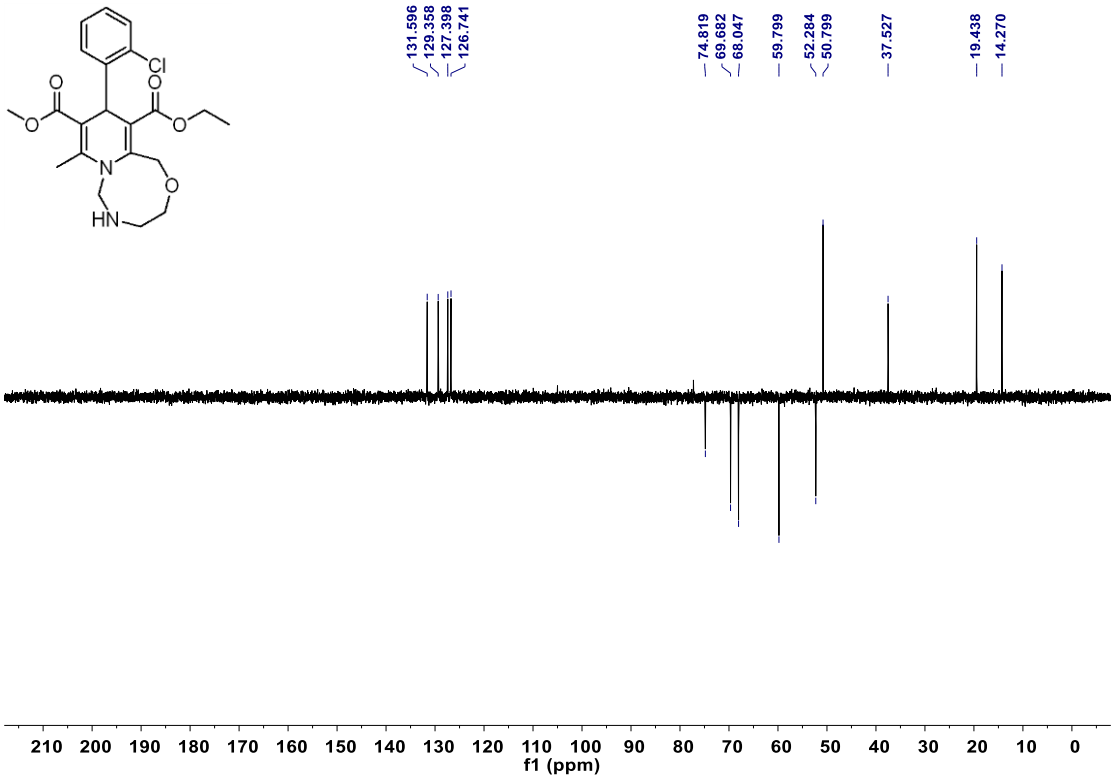
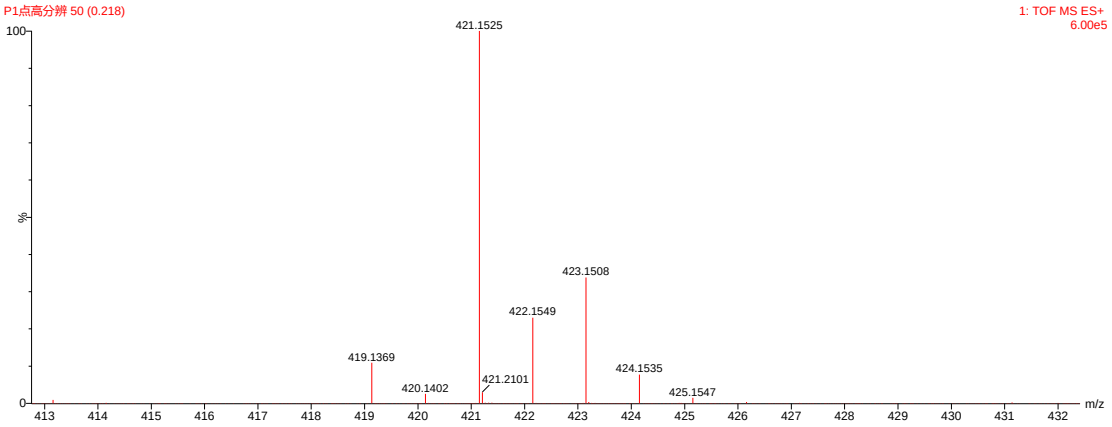
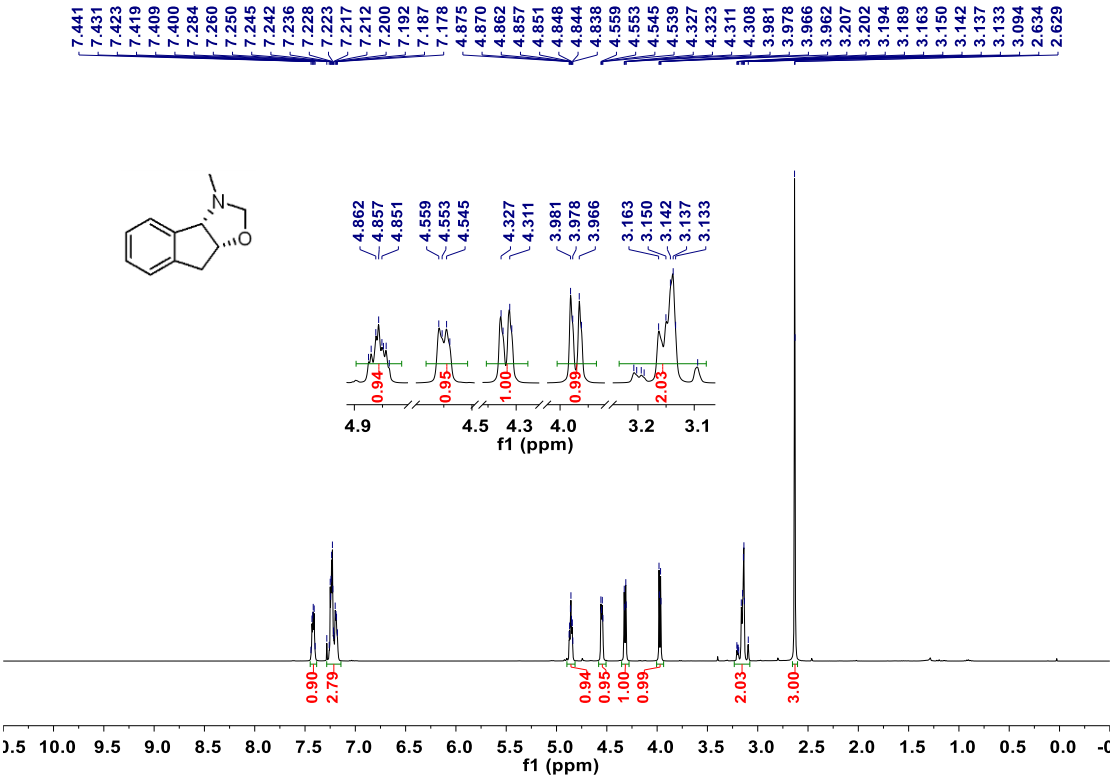


HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{26}ClN_2O_5^+$, 421.1525; found, 421.1525.

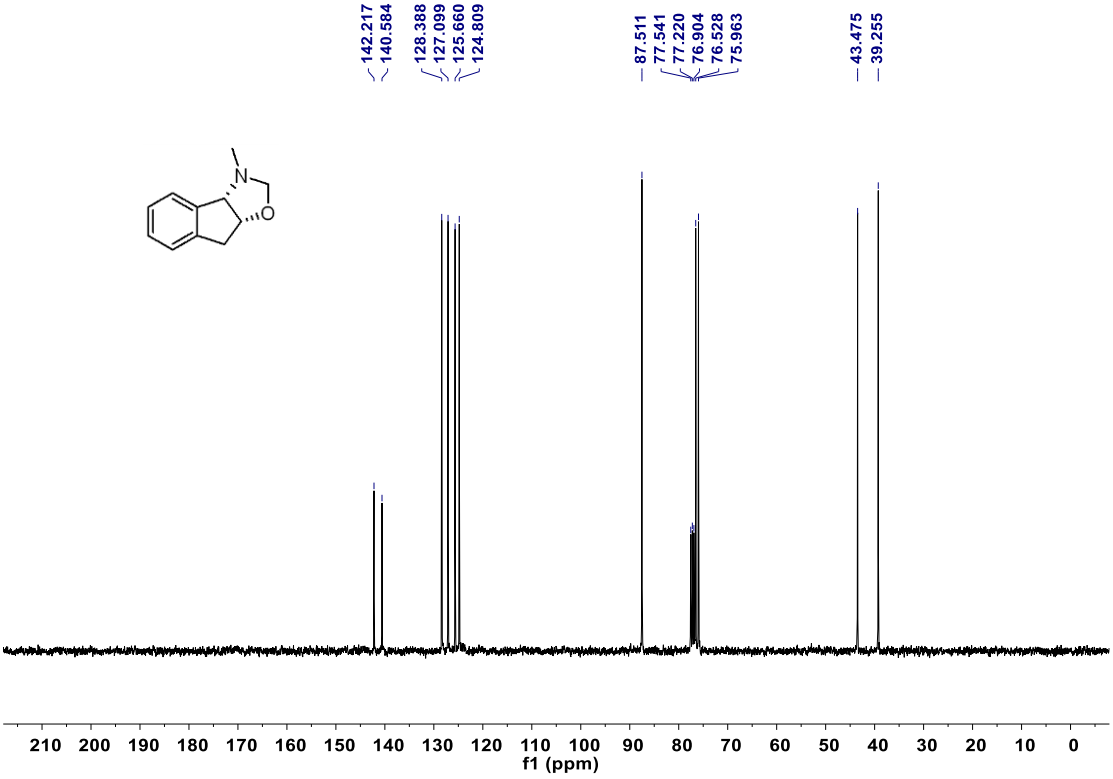


(3*aS*,8*aR*)-3-Methyl-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-d]oxazole (4a-cyc)

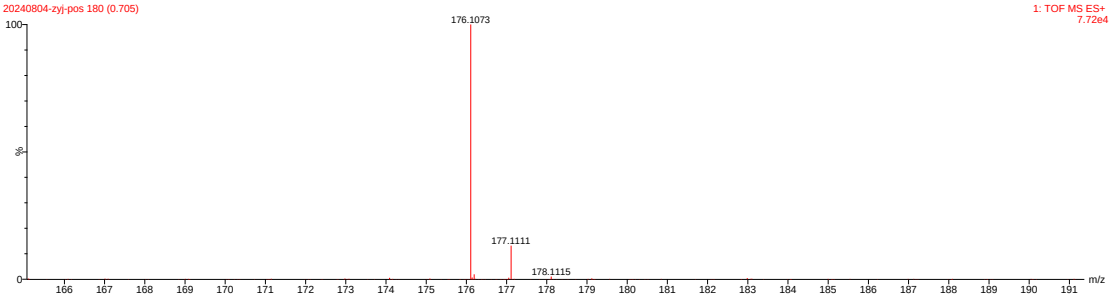
^{1}H NMR (400 MHz, $CDCl_3$)



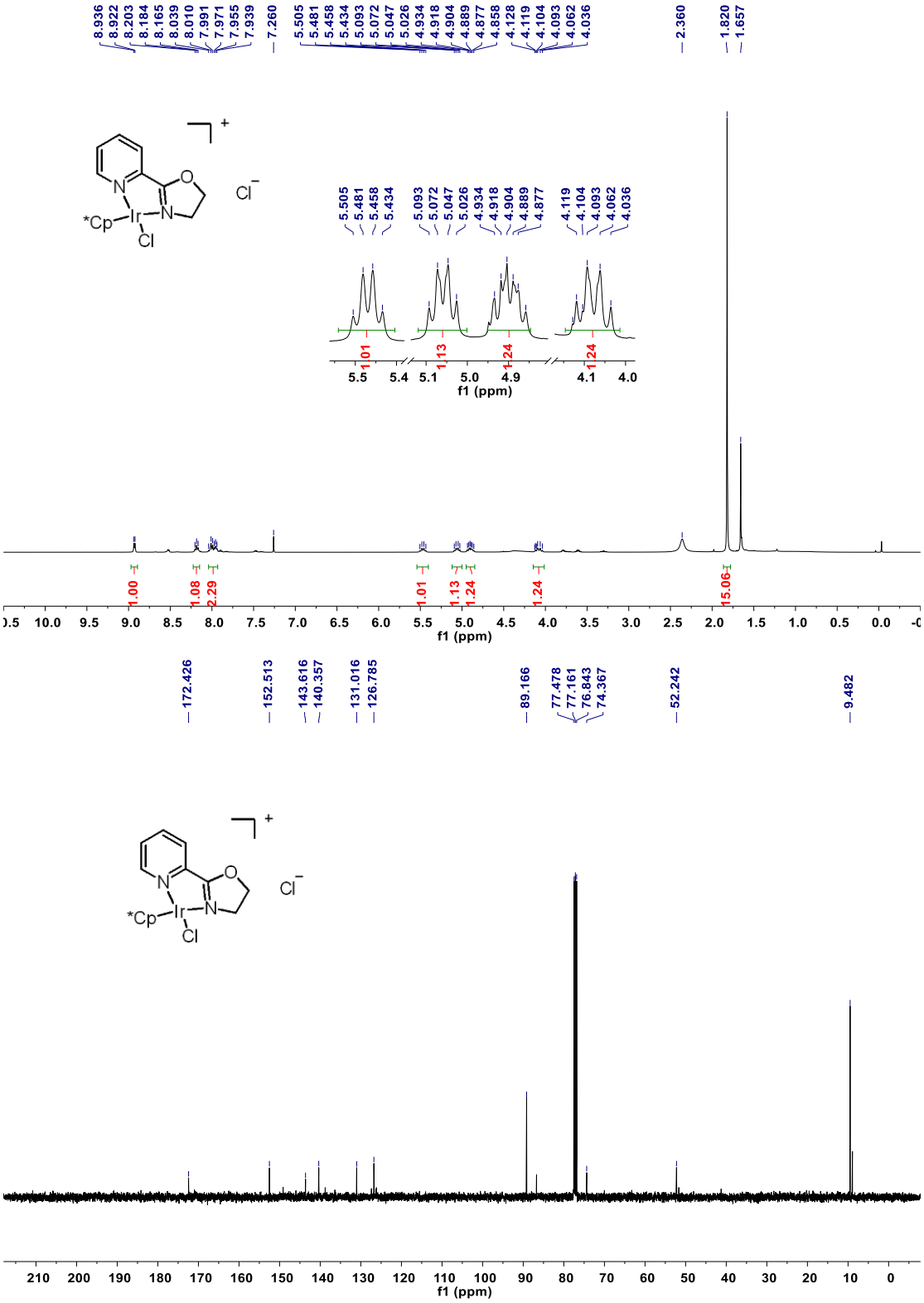
^{13}C NMR (101 MHz, $CDCl_3$)



HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{14}NO^+$, 176.1070; found, 176.1073.



The ^{1}H and ^{13}C NMR spectrum of C10



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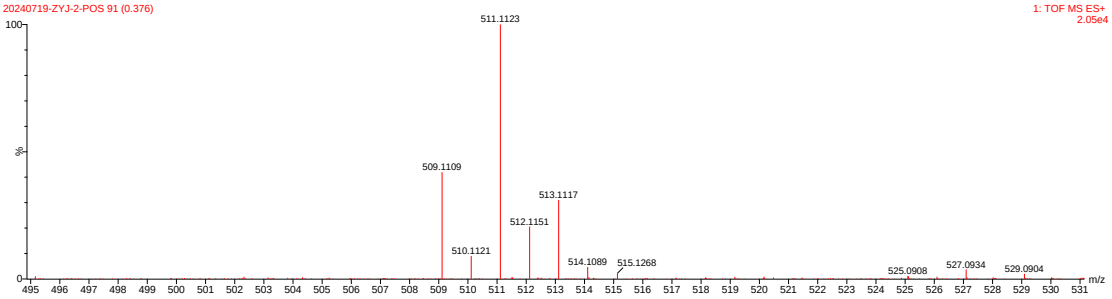
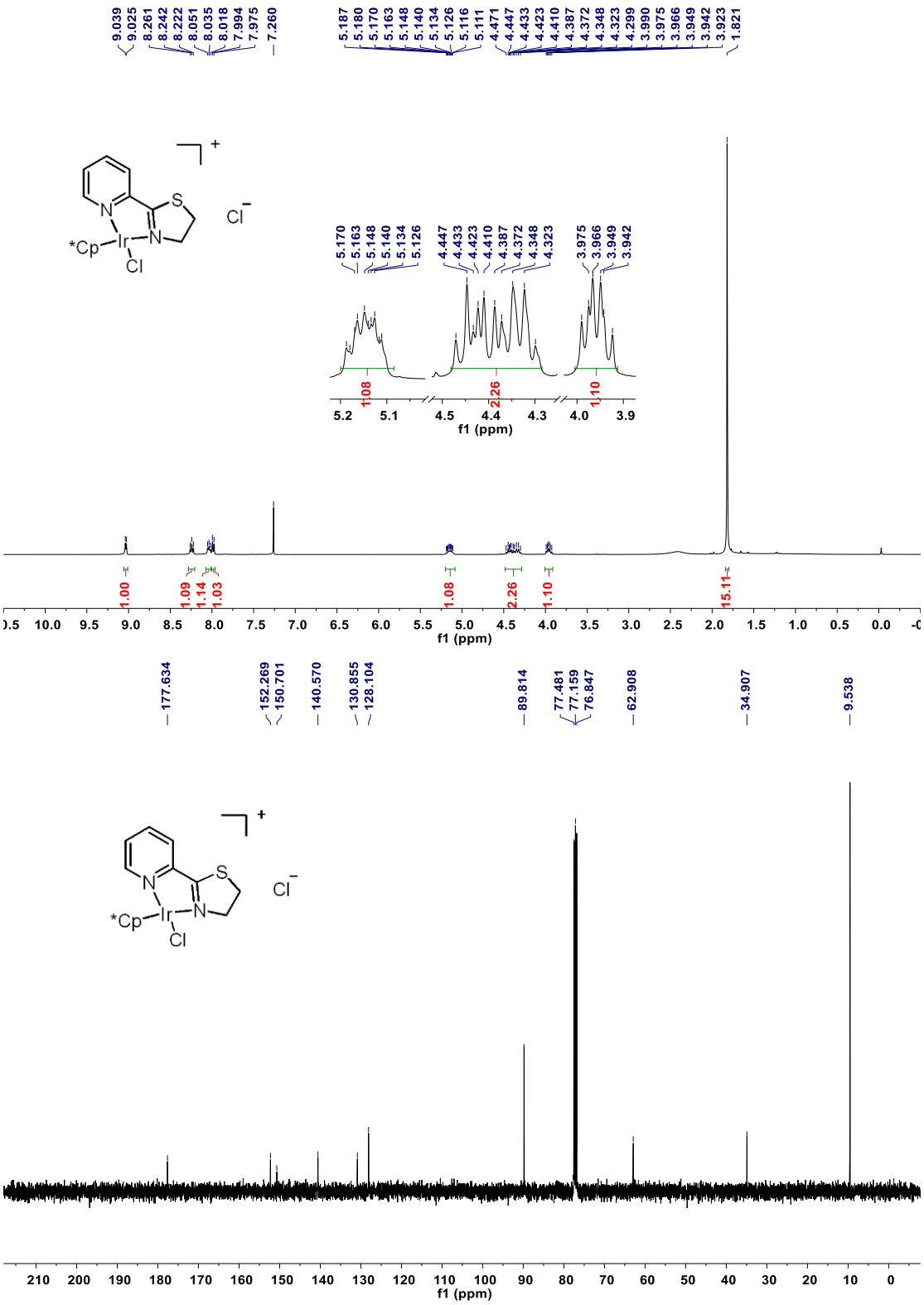
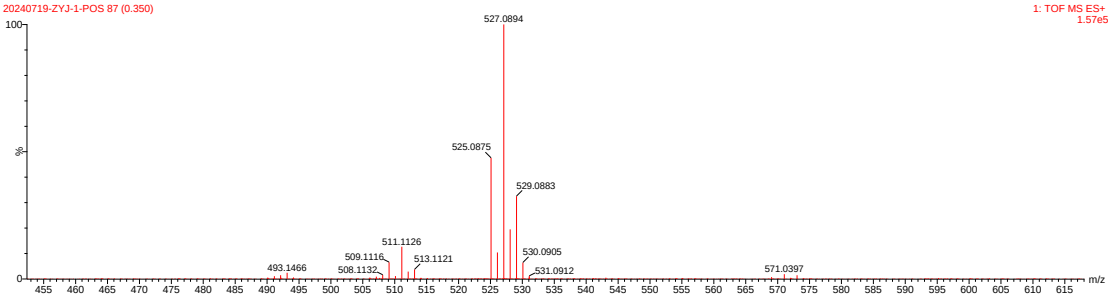


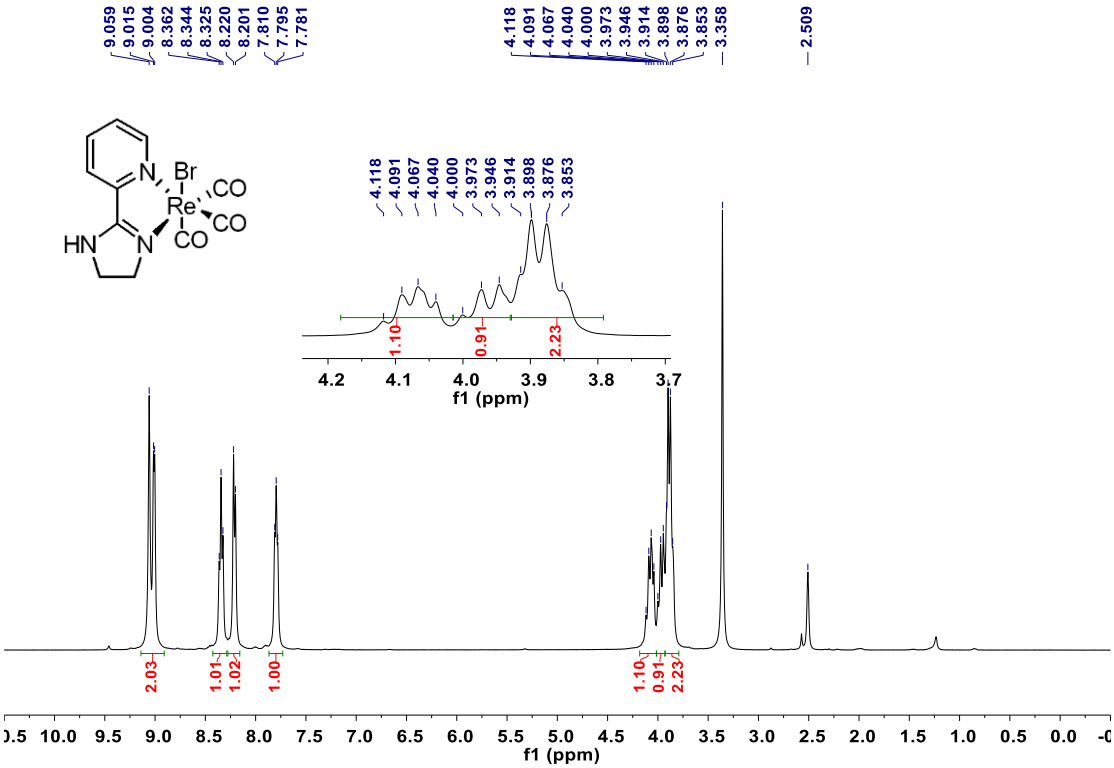
The ^{1}H and ^{13}C NMR spectrum of C11

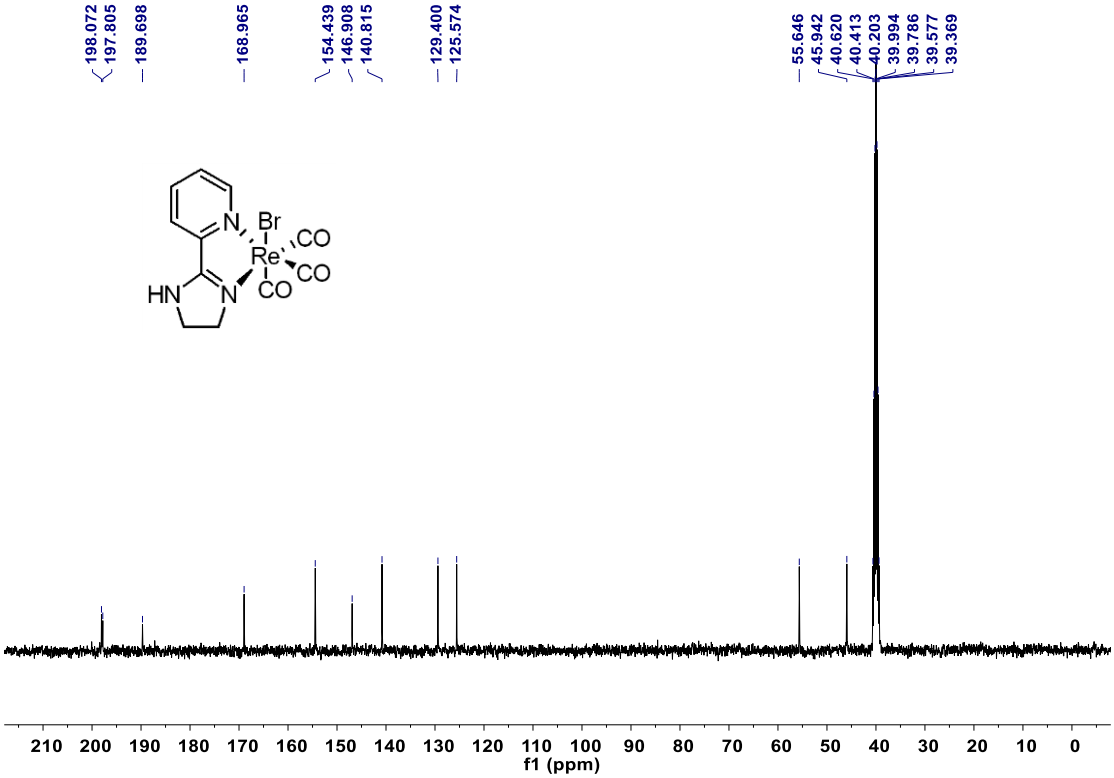


HRMS (ESI) of C11 *m/z*: $[M]^+$ calcd for $C_{18}H_{23}ClIrN_2S^+$, 527.0894; found, 527.0894.

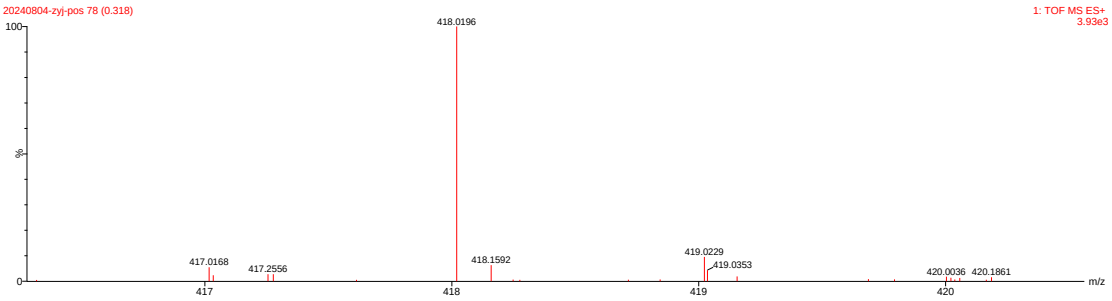


The ^{1}H and ^{13}C NMR spectrum of C17

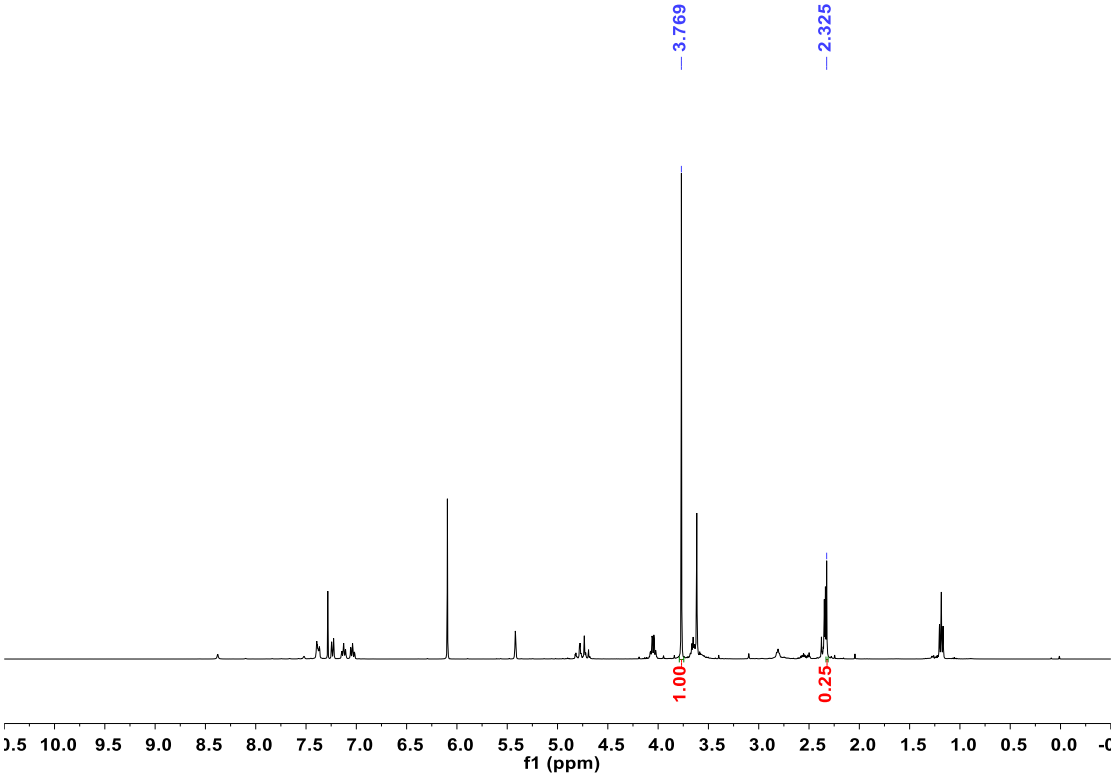




HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{11}H_9N_3O_3Re^+$, 418.0196; found, 418.0196.

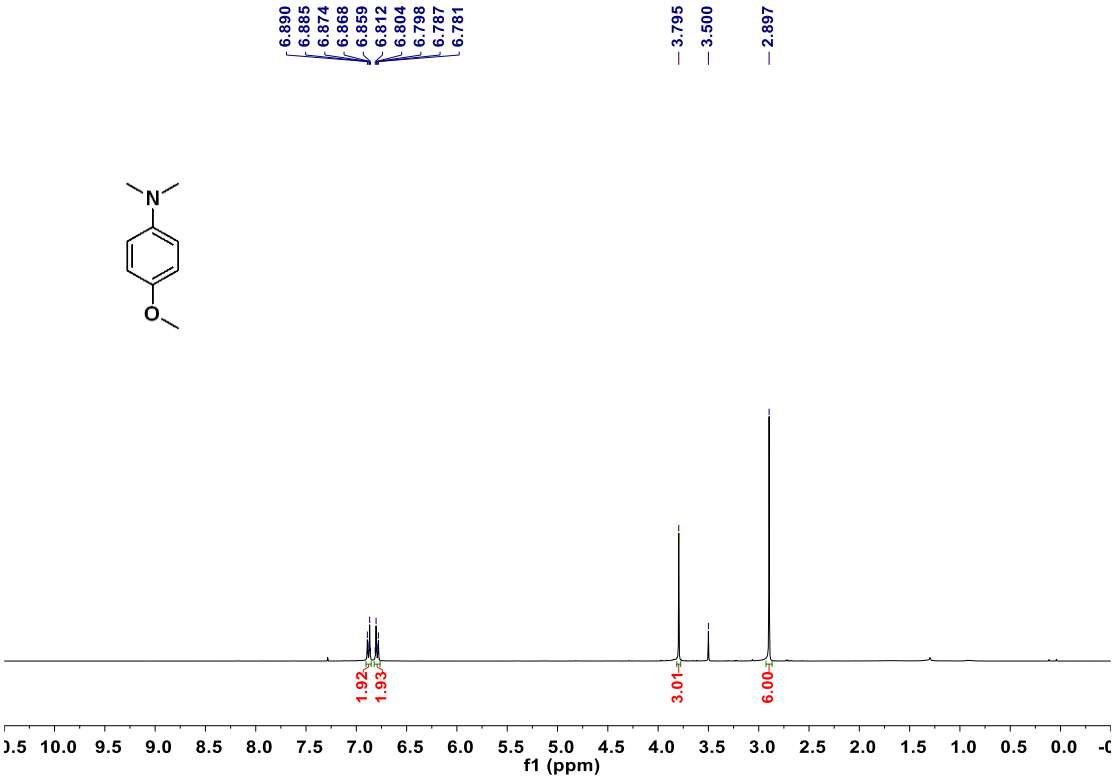


The ^{1}H spectrum of C11 catalyst activity test

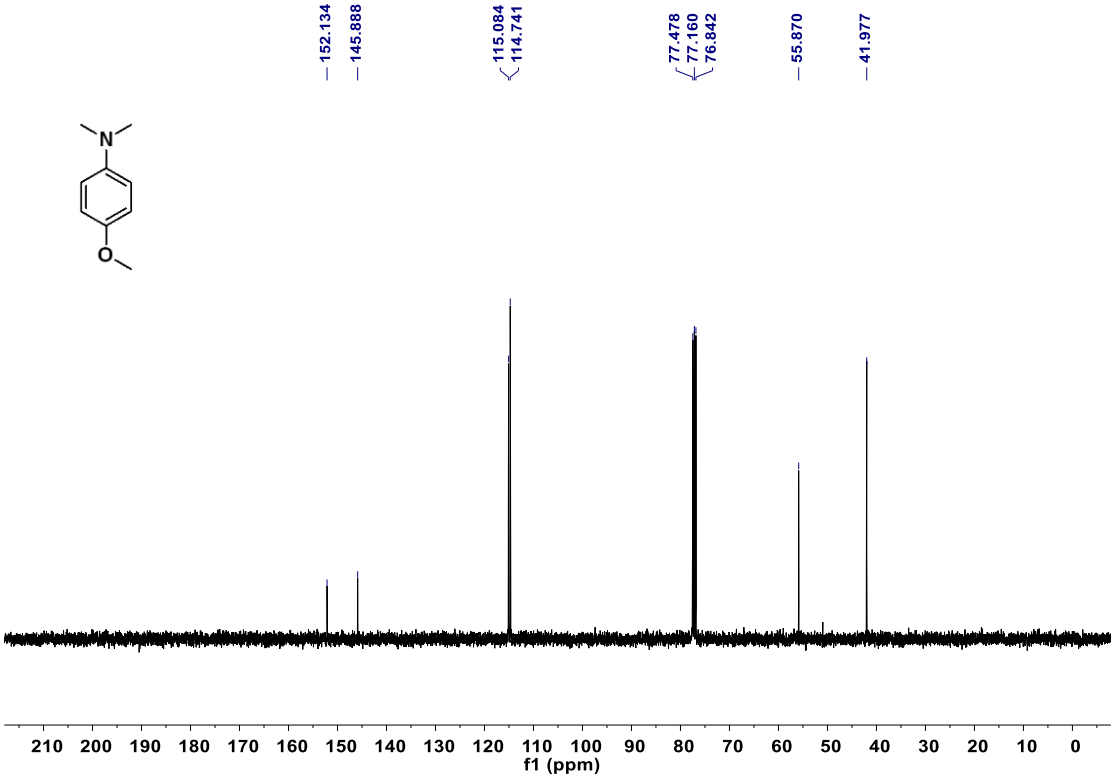


4-Methoxy-*N*,*N*-dimethylaniline (4b)

^{1}H NMR (400 MHz, $CDCl_3$)

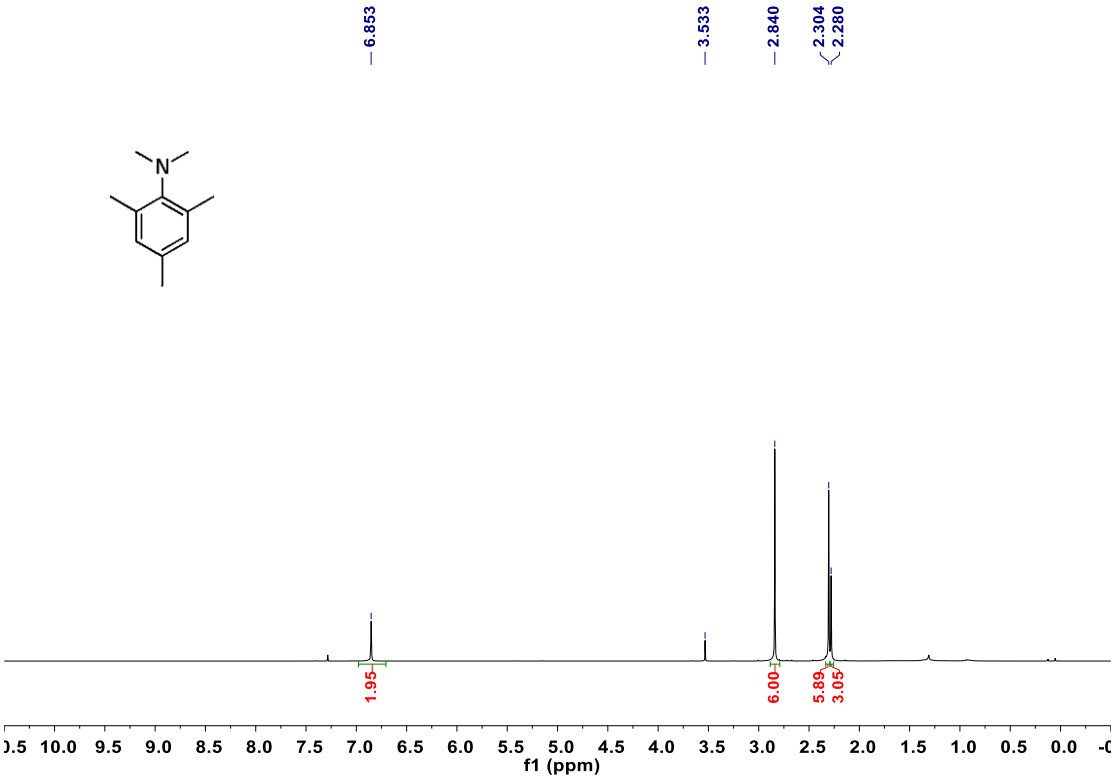


^{13}C NMR (101 MHz, $CDCl_3$)

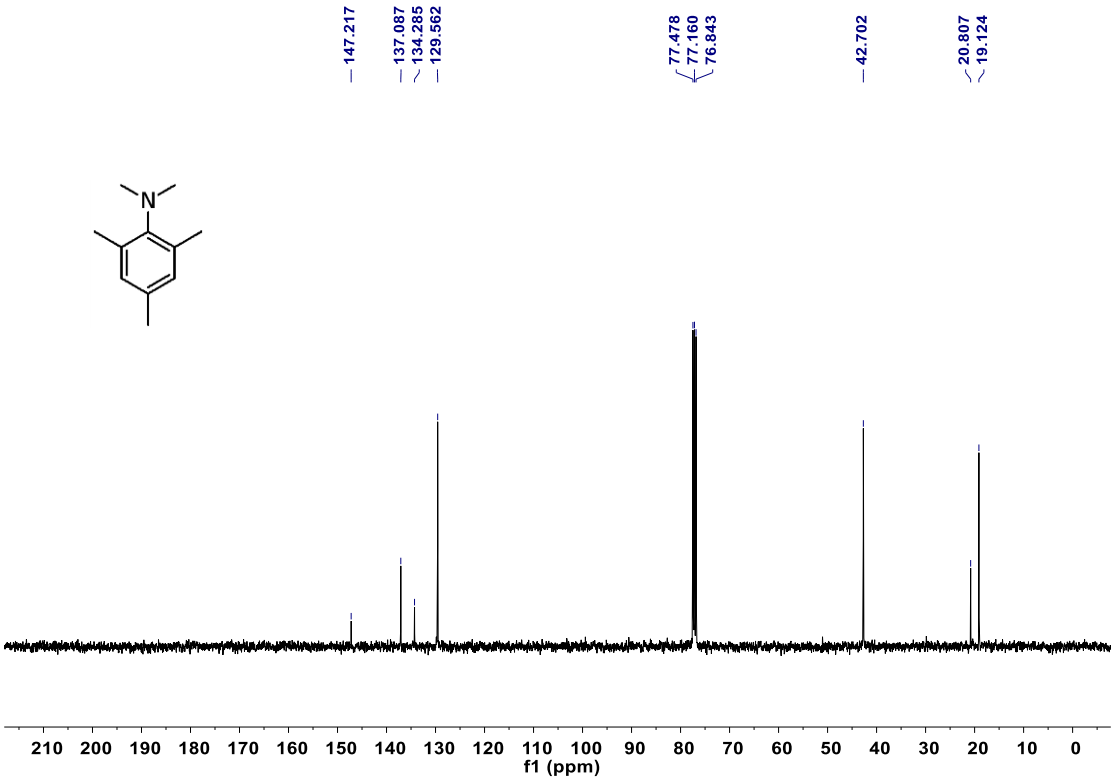


***N*,*N*,2,4,6-Pentamethylaniline (4c)**

^{1}H NMR (400 MHz, $CDCl_3$)

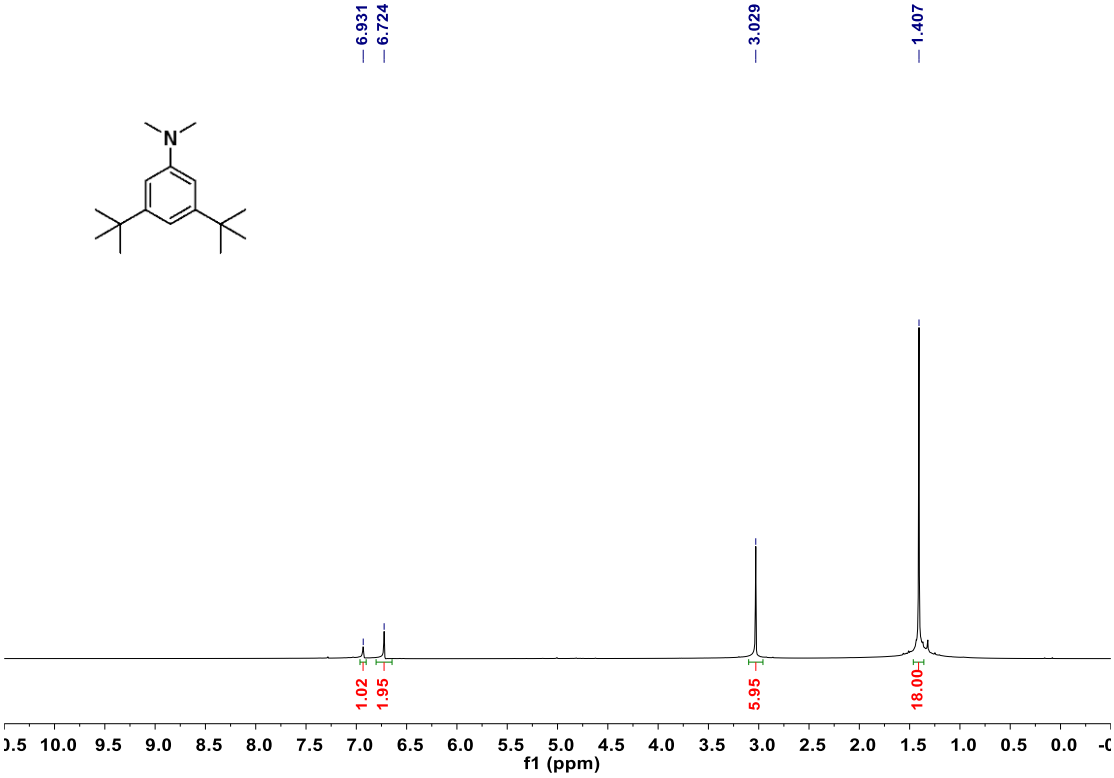


^{13}C NMR (101 MHz, $CDCl_3$)

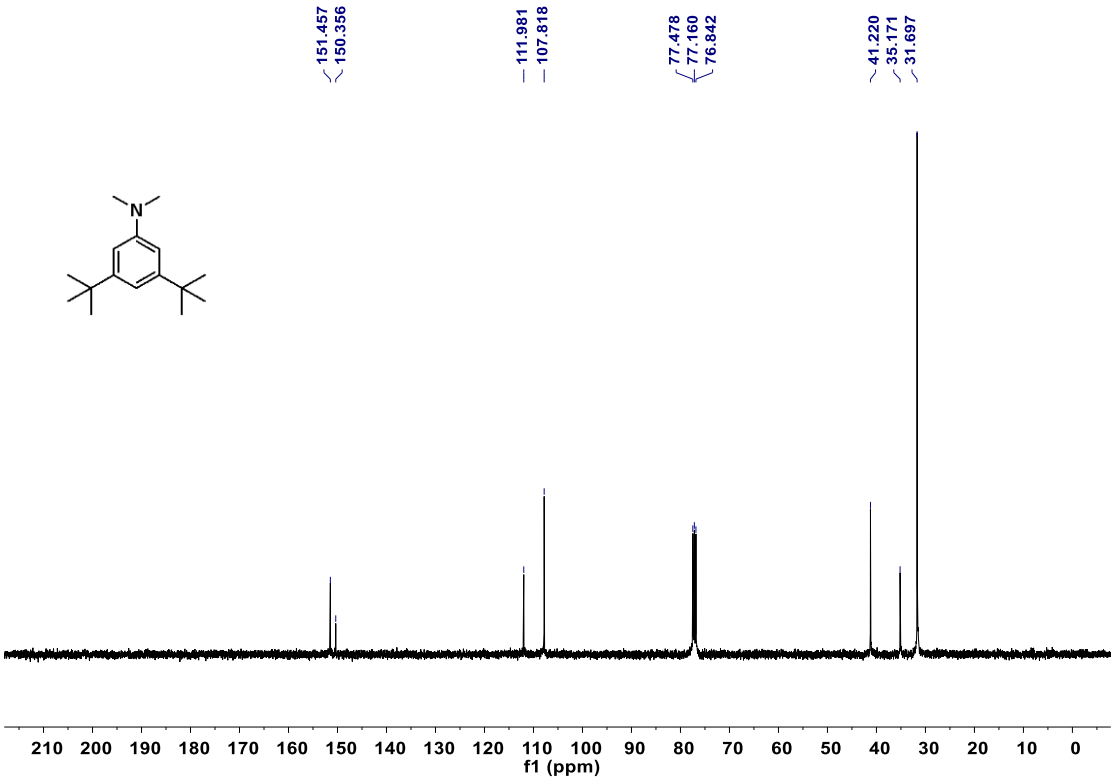


3,5-Di-tert-butyl-*N*,*N*-dimethylaniline (4d)

^{1}H NMR (400 MHz, $CDCl_3$)

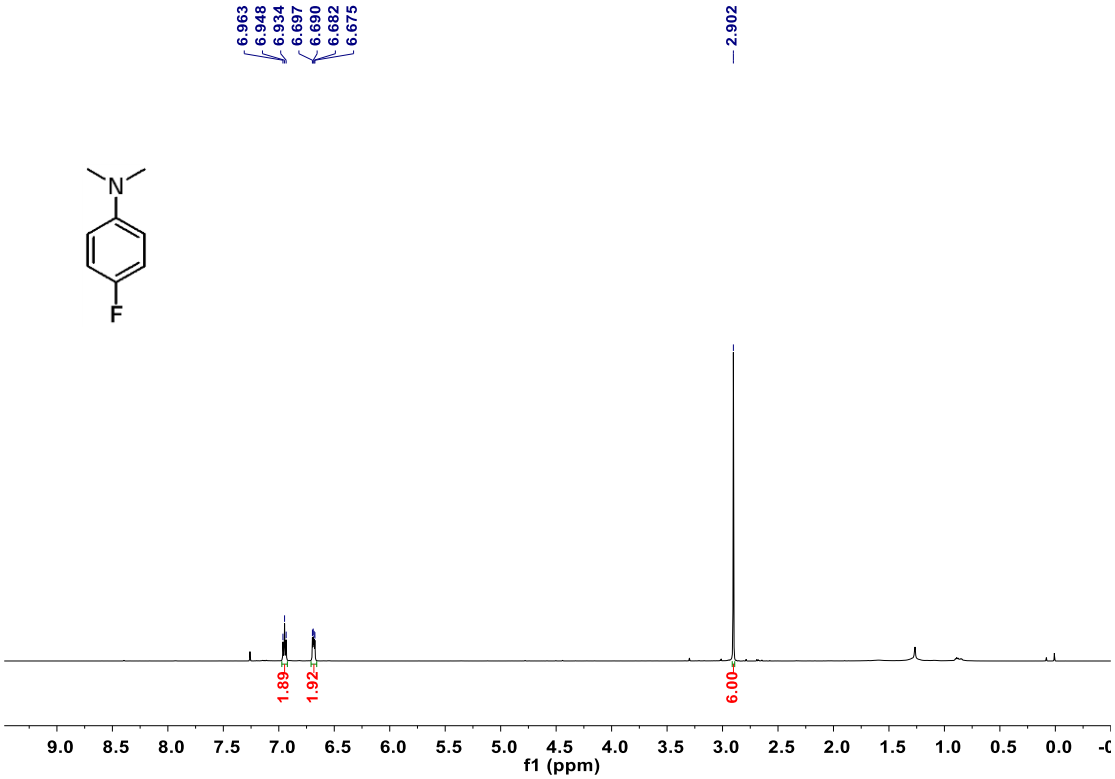


^{13}C NMR (101 MHz, $CDCl_3$)

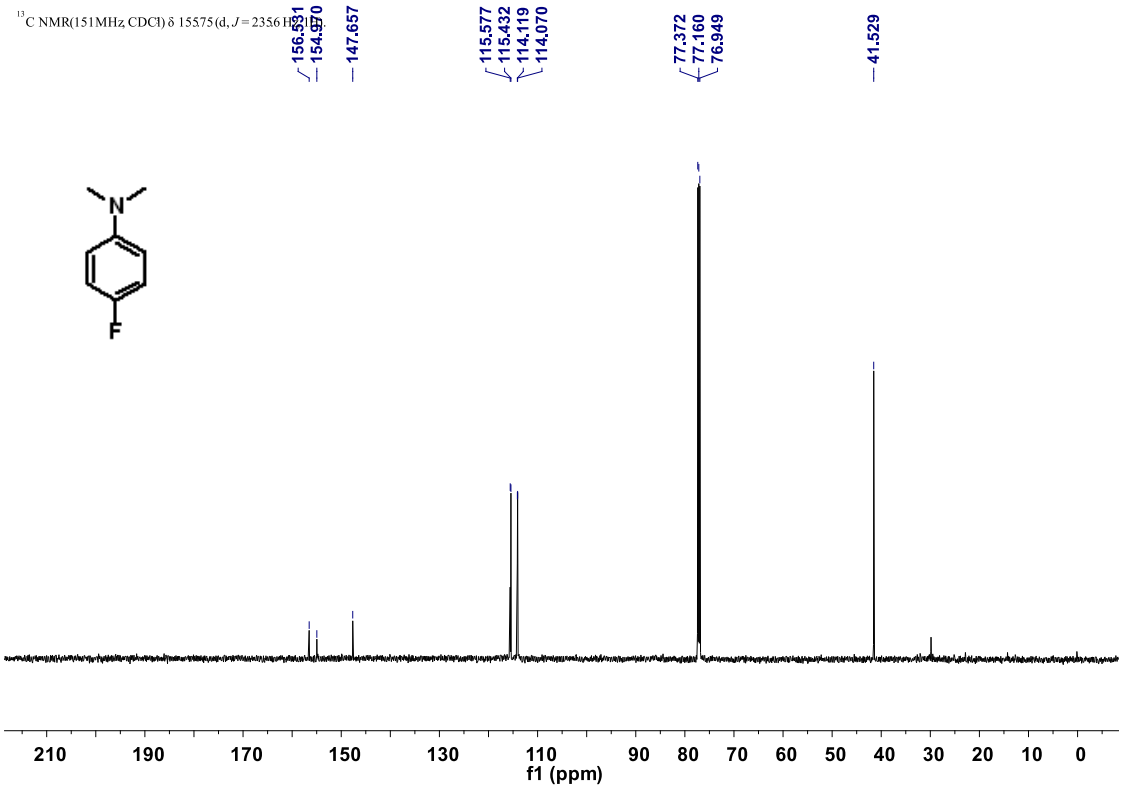


4-Fluoro-*N*,*N*-dimethylaniline (4e)

^{1}H NMR (400 MHz, $CDCl_3$)

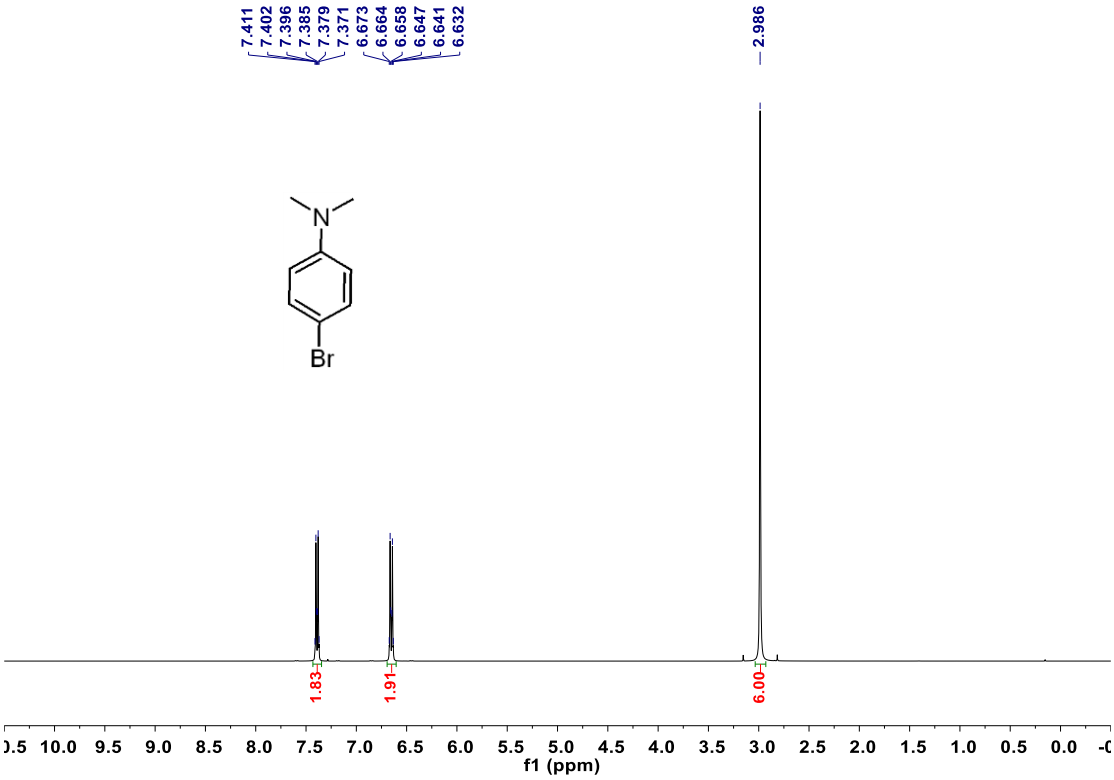


^{13}C NMR (101 MHz, $CDCl_3$)

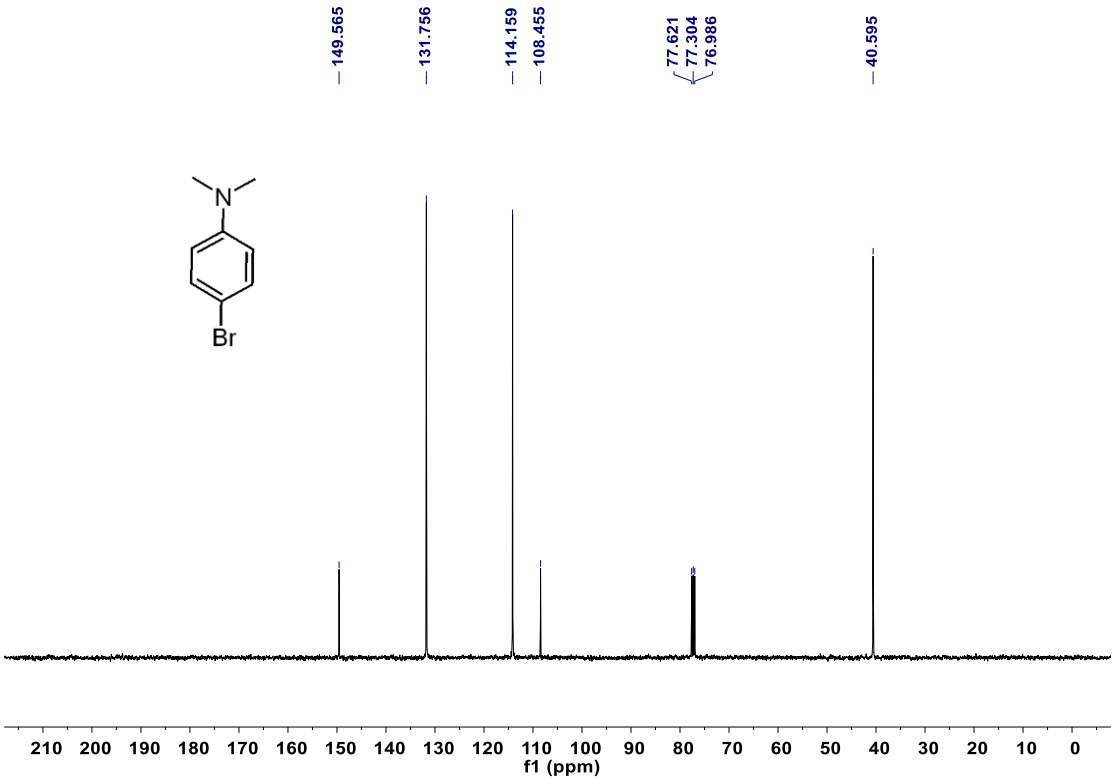


4-Bromo-*N*,*N*-dimethylaniline (4f)

^{1}H NMR (400 MHz, $CDCl_3$)

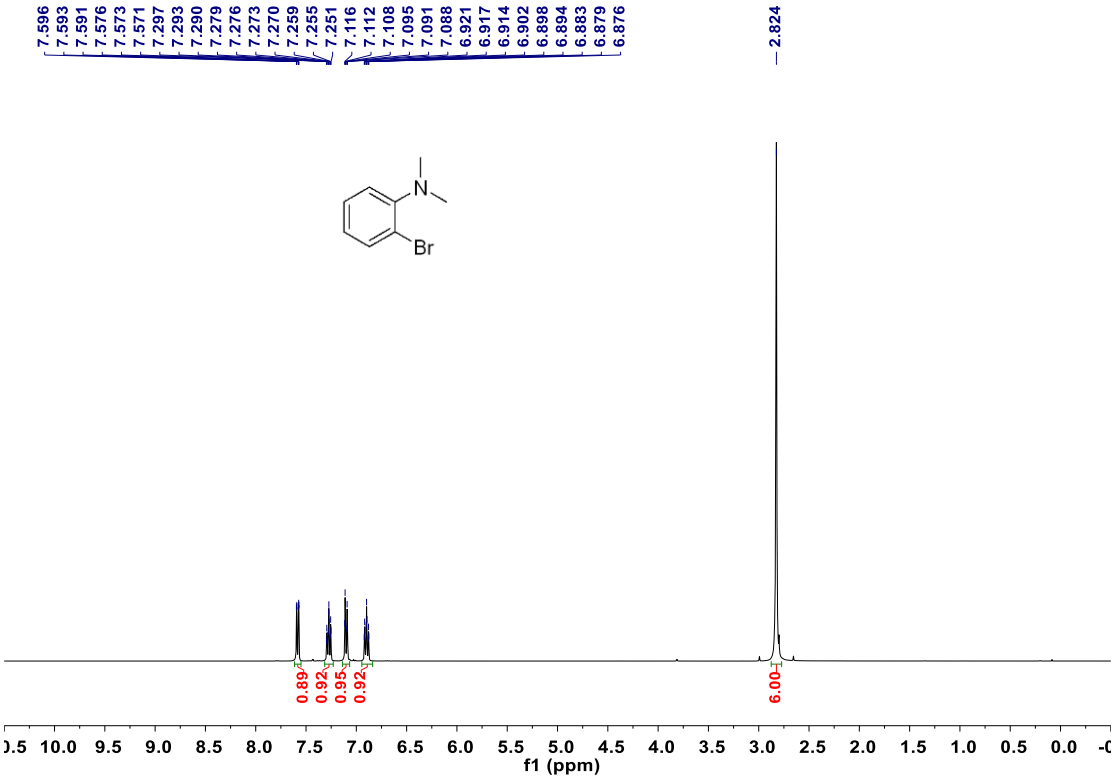


^{13}C NMR (101 MHz, $CDCl_3$)

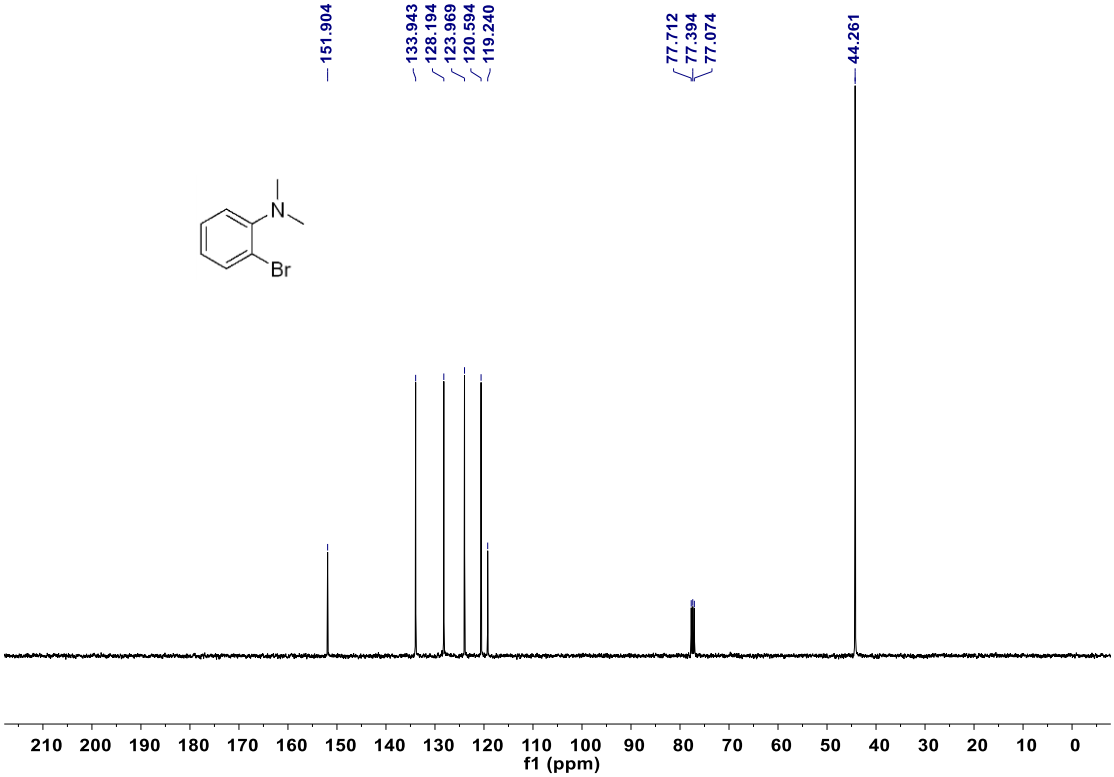


2-Bromo-*N*,*N*-dimethylaniline (4g)

^{1}H NMR (400 MHz, $CDCl_3$)

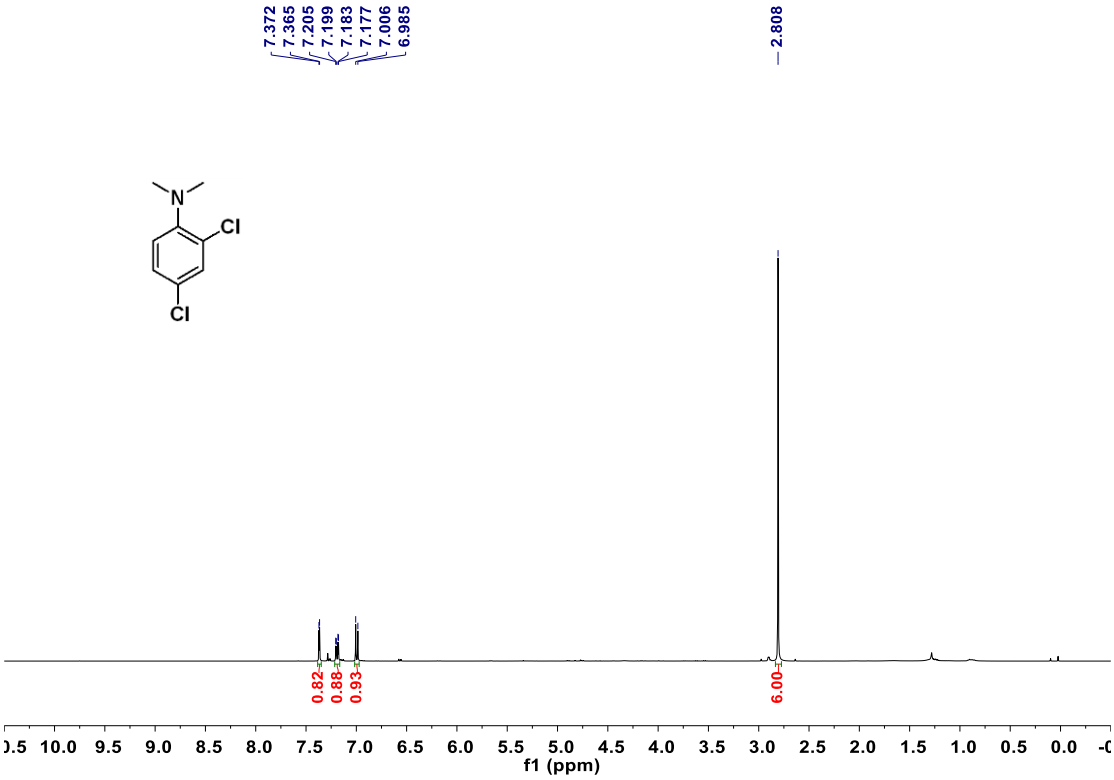


^{13}C NMR (101 MHz, $CDCl_3$)

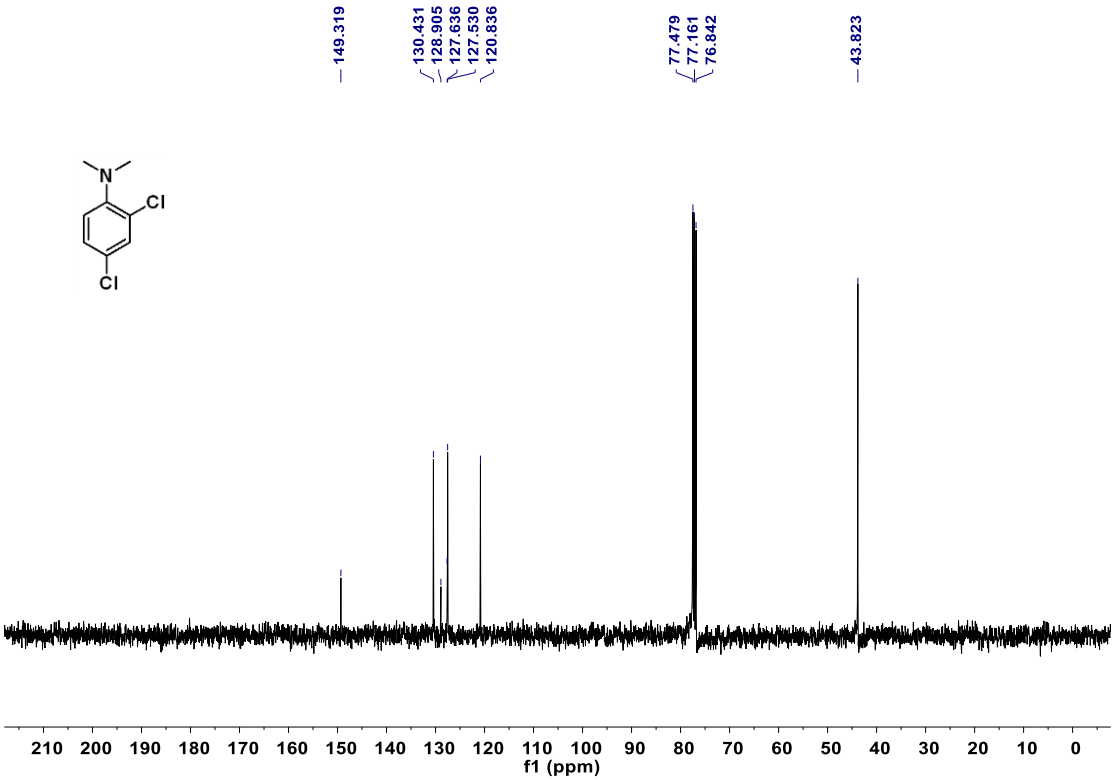


4-Dichloro-*N*,*N*-dimethylaniline (4h)

^{1}H NMR (400 MHz, $CDCl_3$)

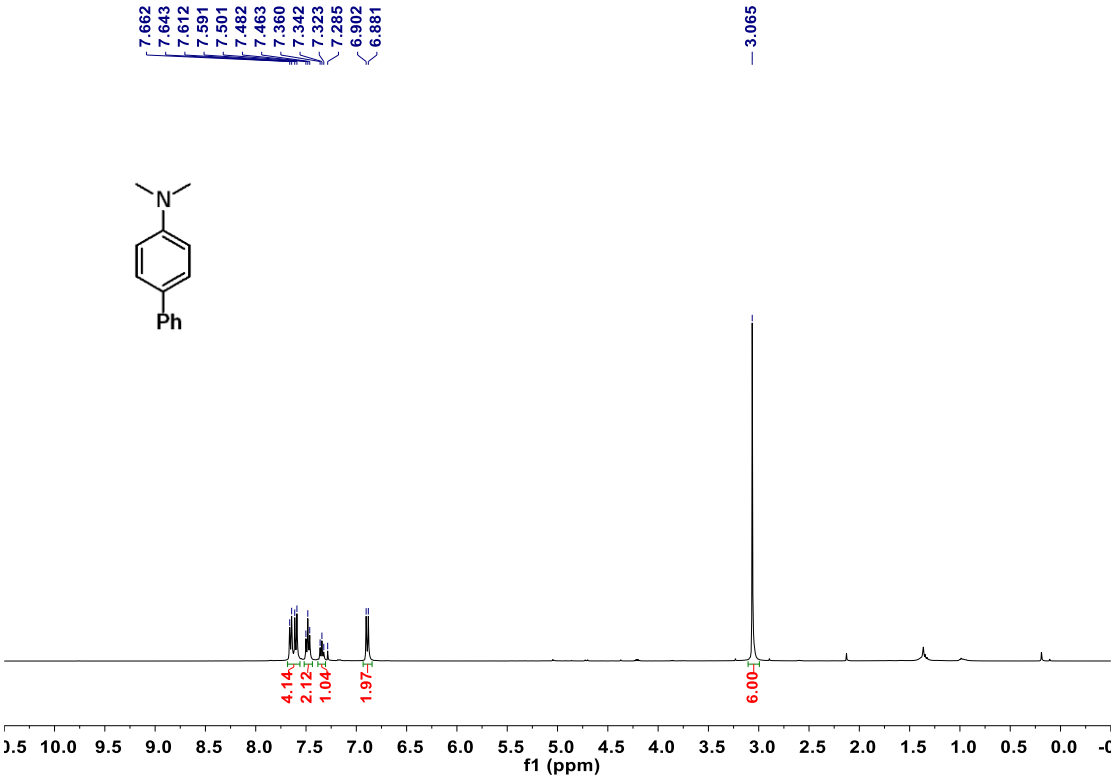


^{13}C NMR (101 MHz, $CDCl_3$)

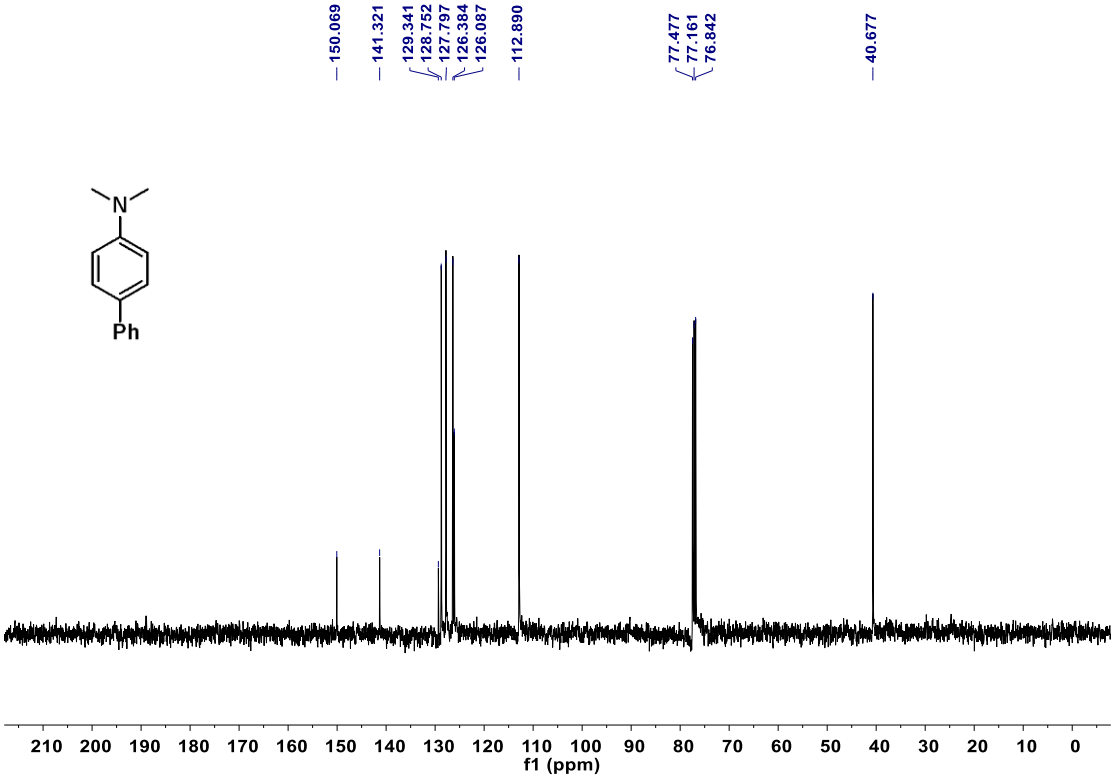


***N*,*N*-Dimethyl-(1,1'-biphenyl)-4-amine (4i)**

^{1}H NMR (400 MHz, $CDCl_3$)

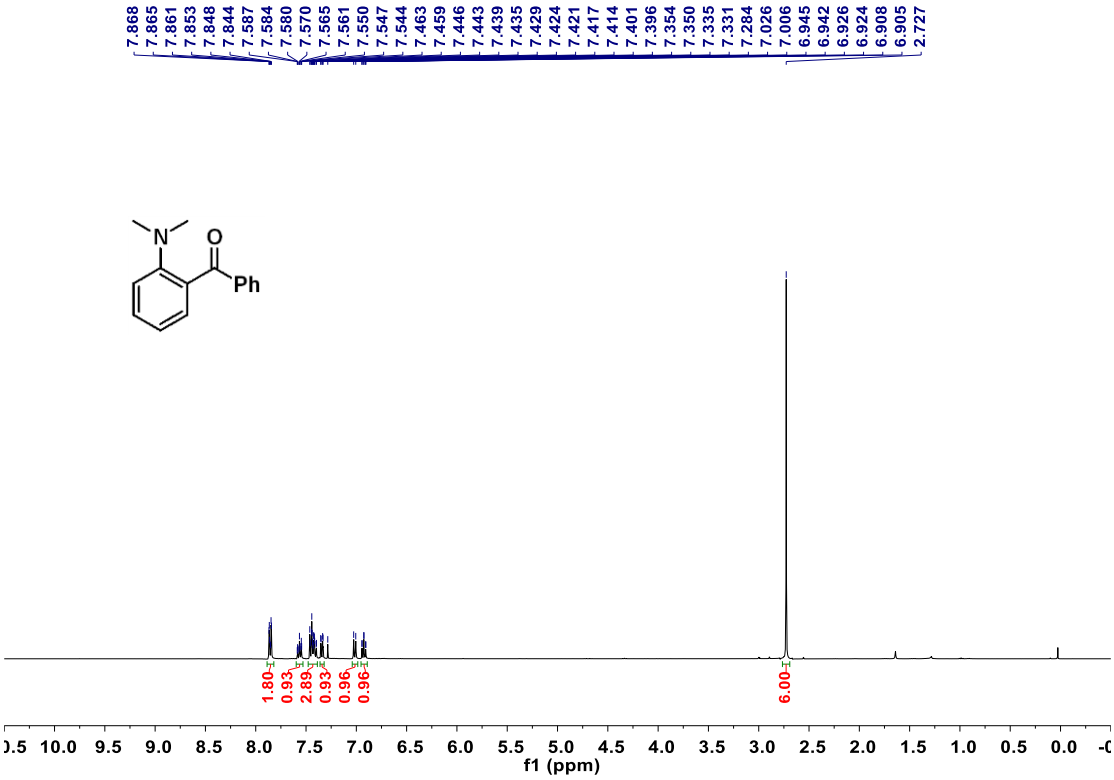


^{13}C NMR (101 MHz, $CDCl_3$)

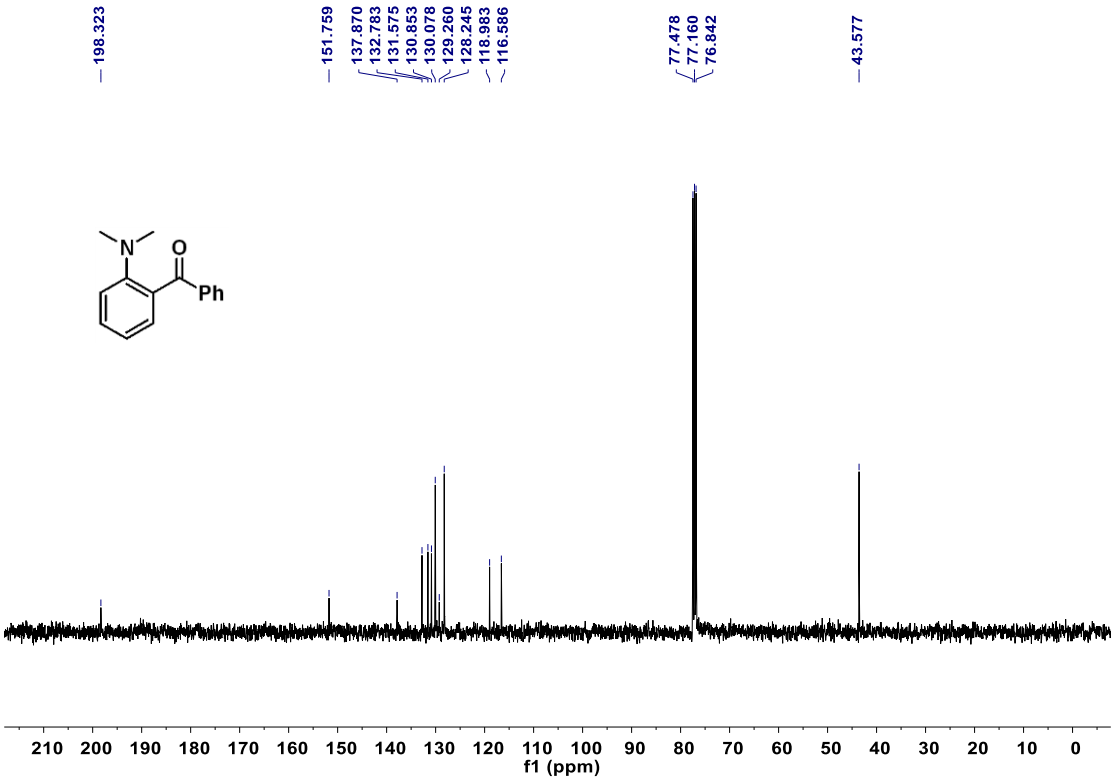


(2-(Dimethylamino)phenyl)(phenyl)methanone (4j)

^{1}H NMR (400 MHz, $CDCl_3$)

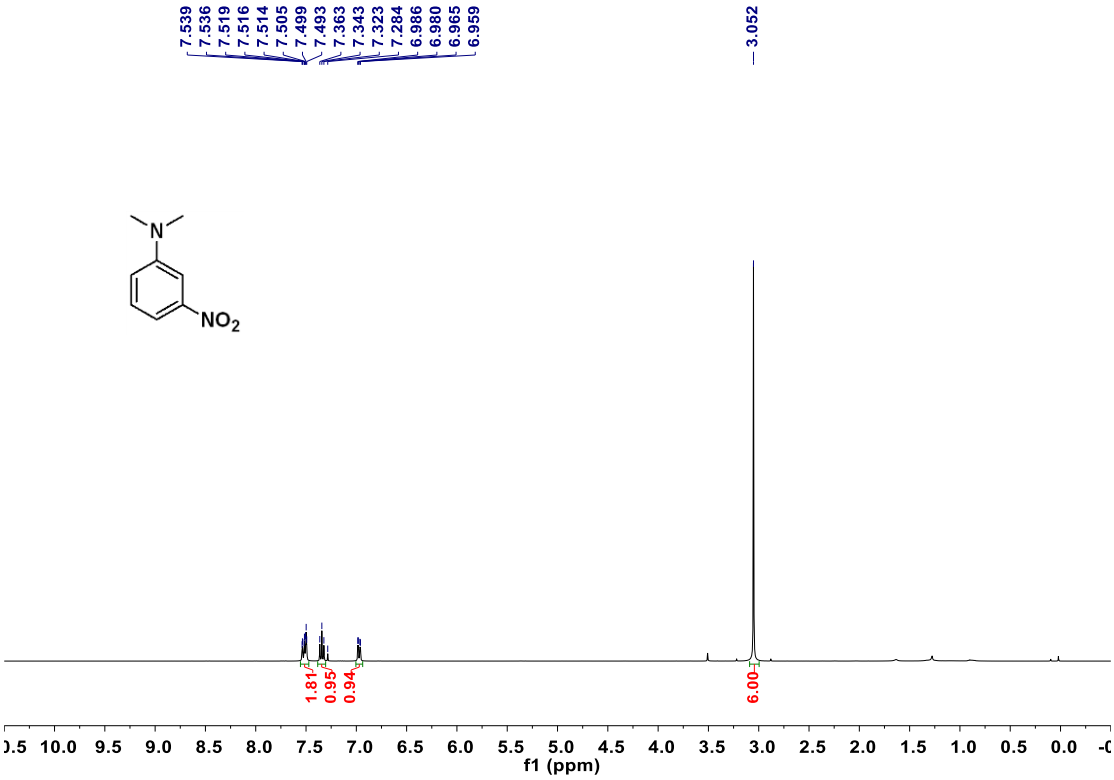


^{13}C NMR (101 MHz, $CDCl_3$)

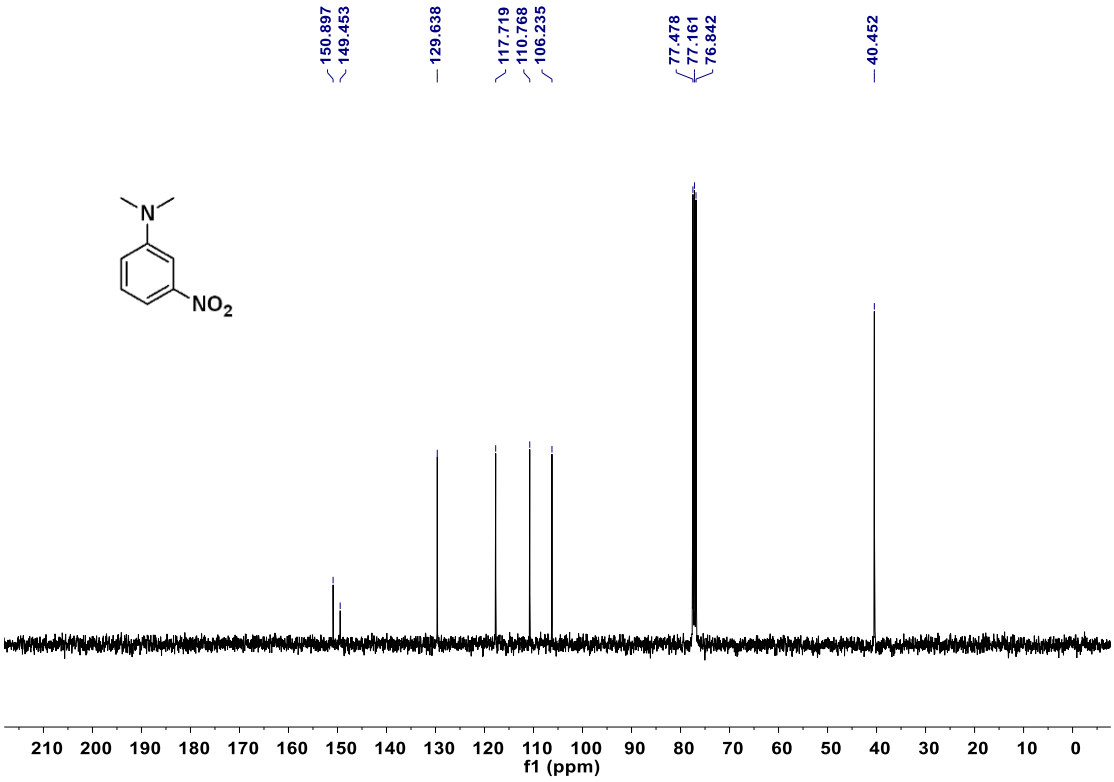


***N*,*N*-Dimethyl-3-nitroaniline (4k)**

^{1}H NMR (400 MHz, $CDCl_3$)

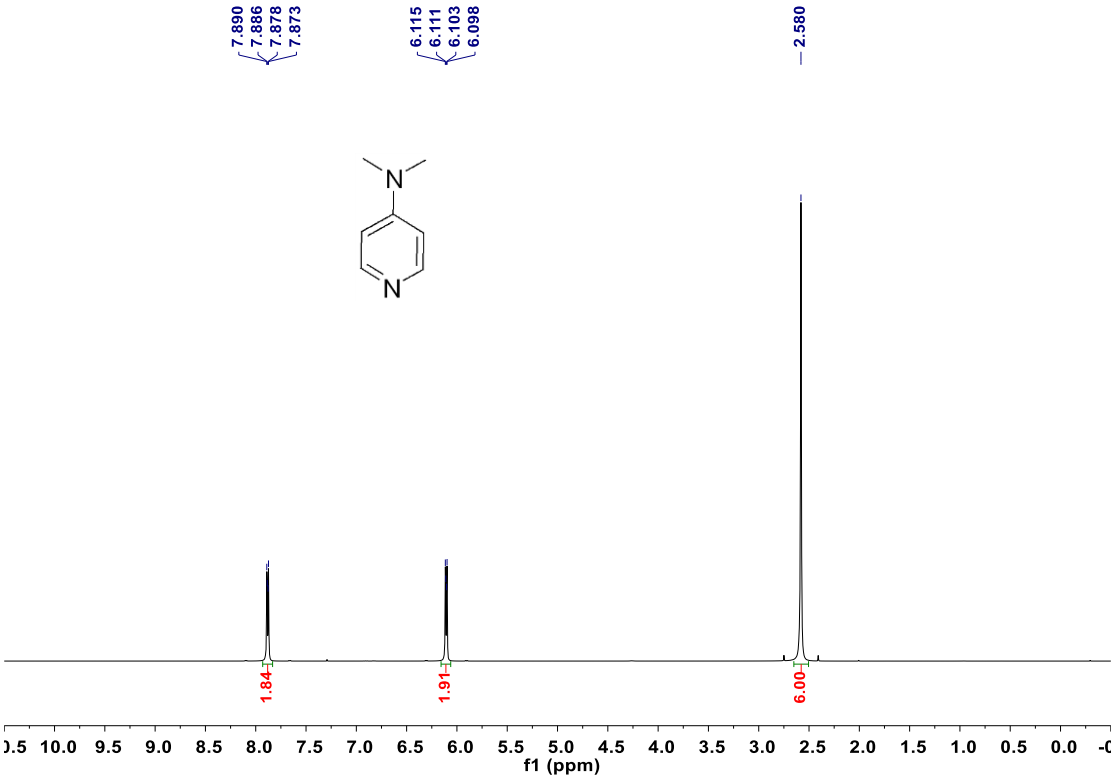


^{13}C NMR (101 MHz, $CDCl_3$)

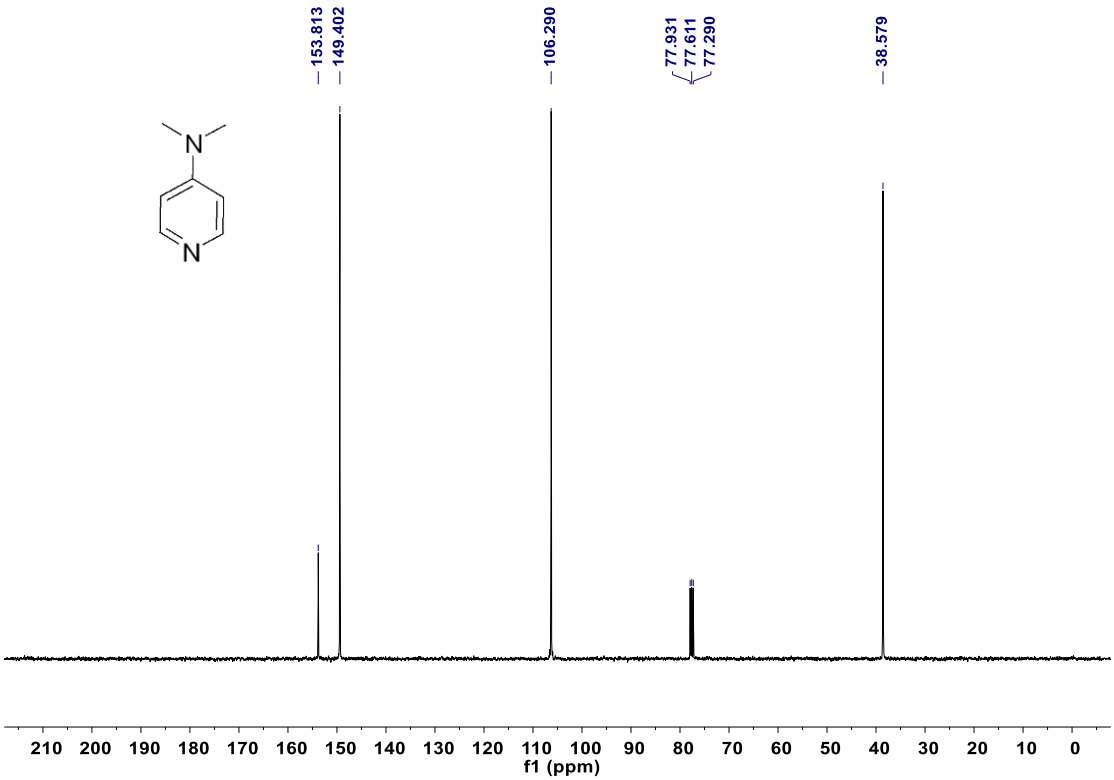


***N*,*N*-Dimethylpyridin-4-amine (4l)**

^{1}H NMR (400 MHz, $CDCl_3$)

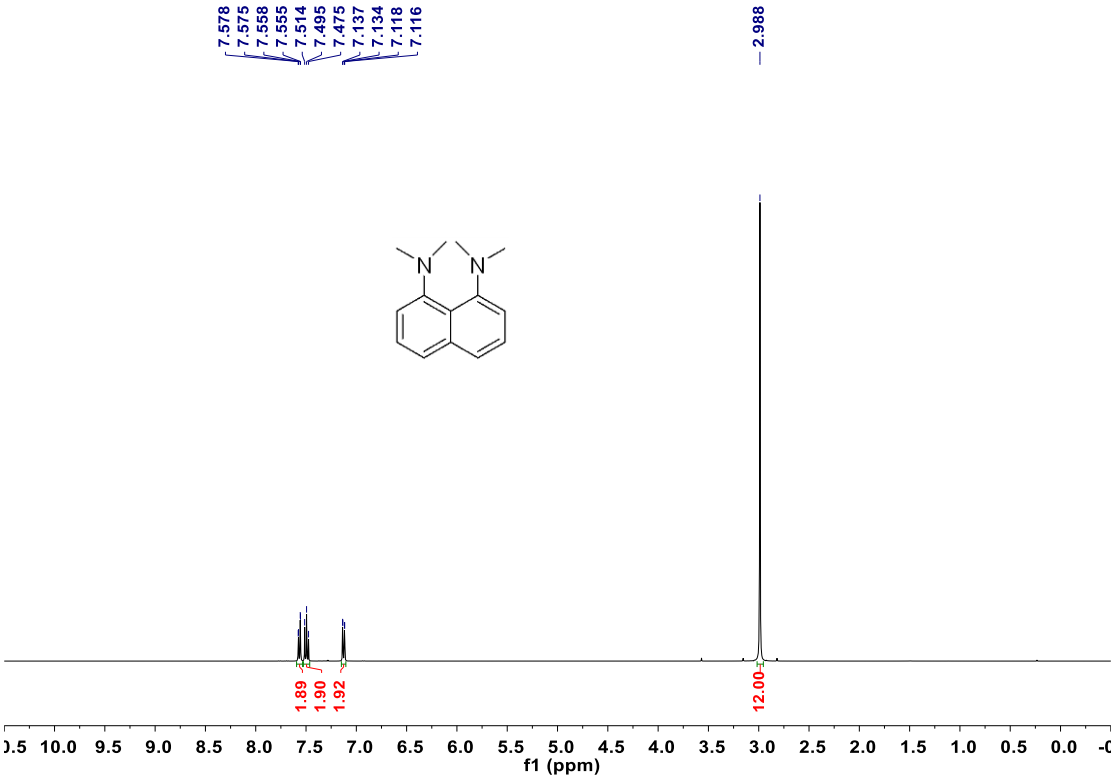


^{13}C NMR (101 MHz, $CDCl_3$)

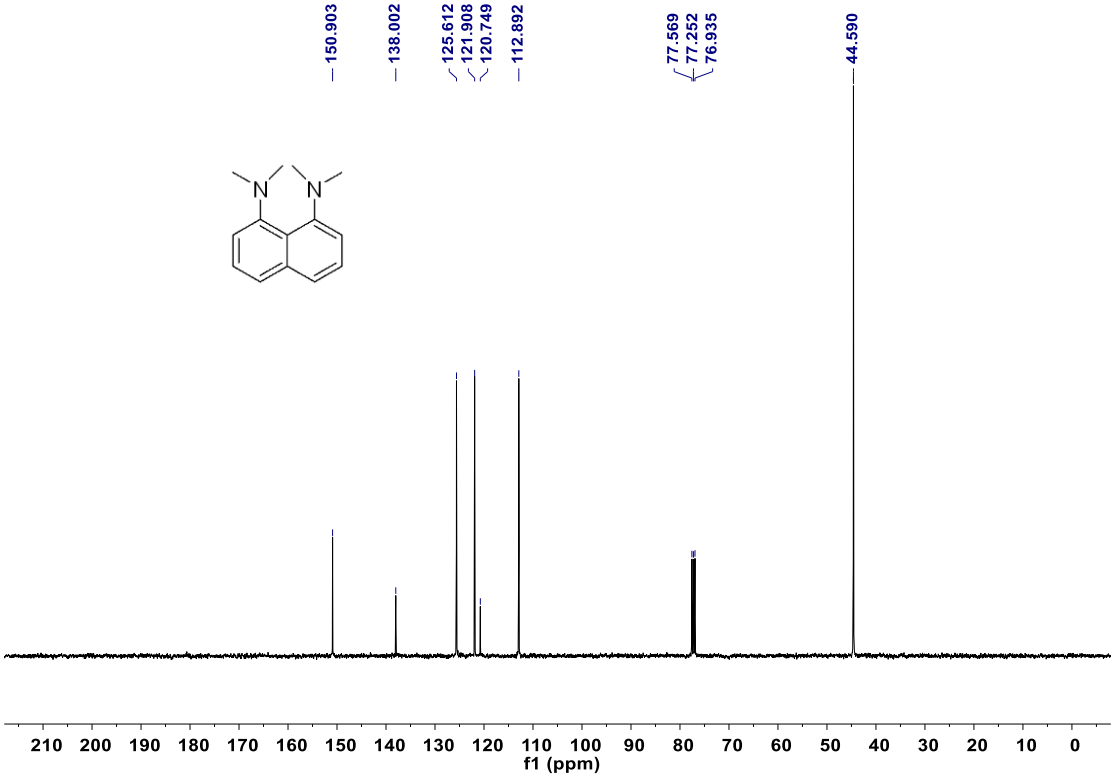


***N*1, *N1*, *N8*, *N8*-Tetramethylnaphthalene-1,8-diamine (4m)**

^{1}H NMR (400 MHz, $CDCl_3$)

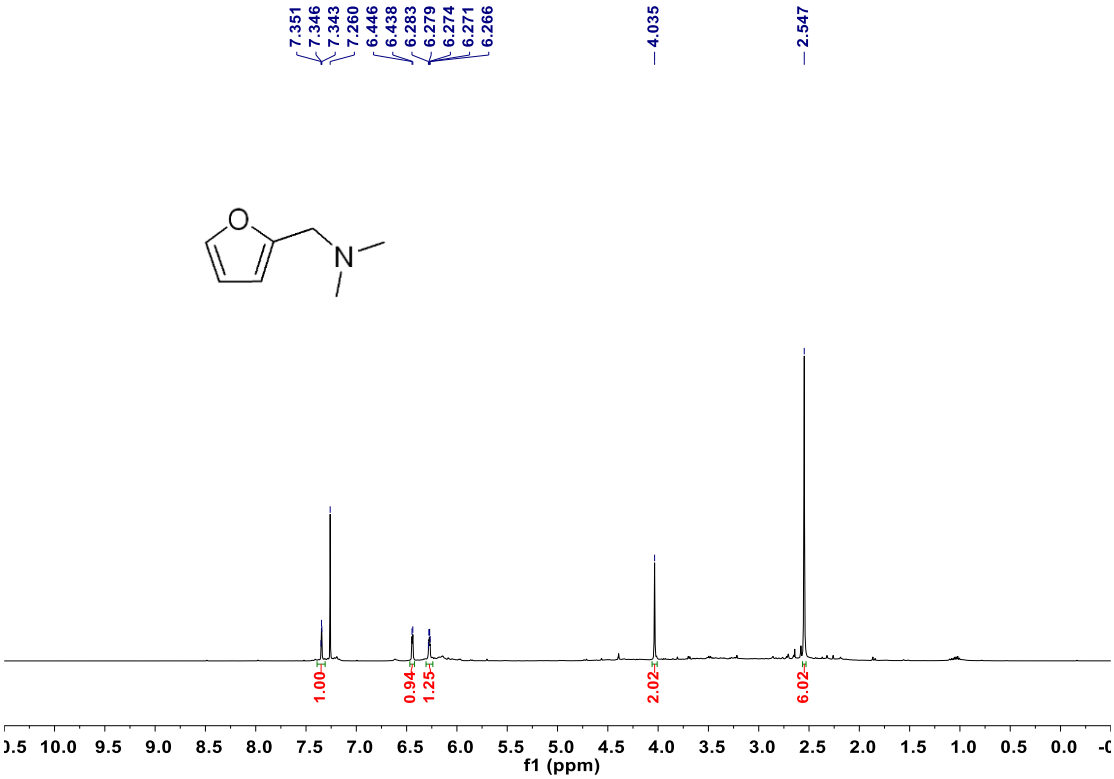


^{13}C NMR (101 MHz, $CDCl_3$)

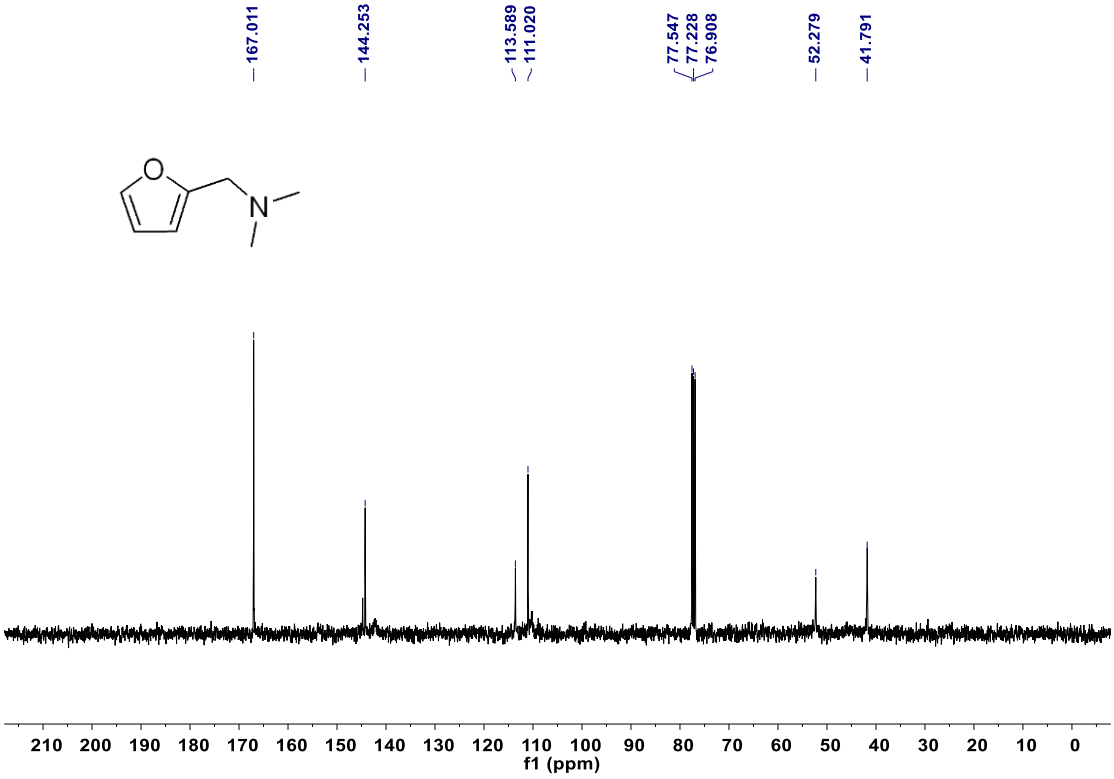


1-(Furan-2-yl)-*N*,*N*-dimethylmethanamine (4n)

^{1}H NMR (400 MHz, $CDCl_3$)

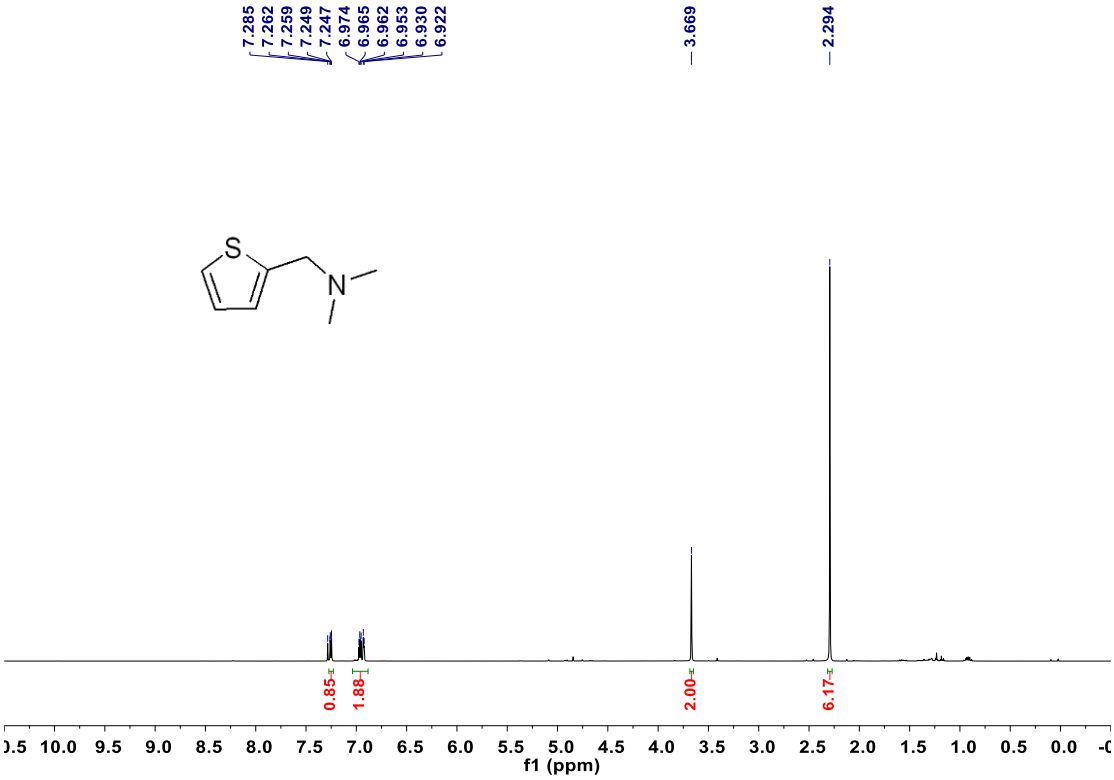


^{13}C NMR (101 MHz, $CDCl_3$)

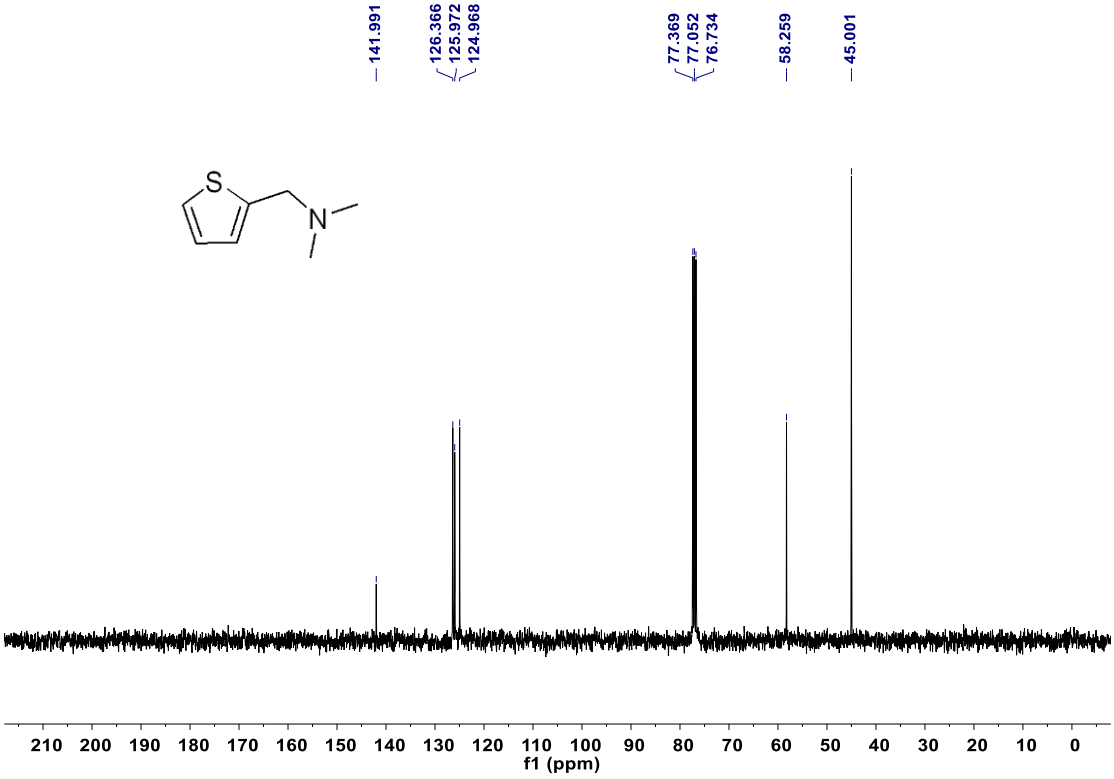


***N*,*N*-Dimethyl-1-(thiophen-2-yl)methanamine (4o)**

^{1}H NMR (400 MHz, $CDCl_3$)

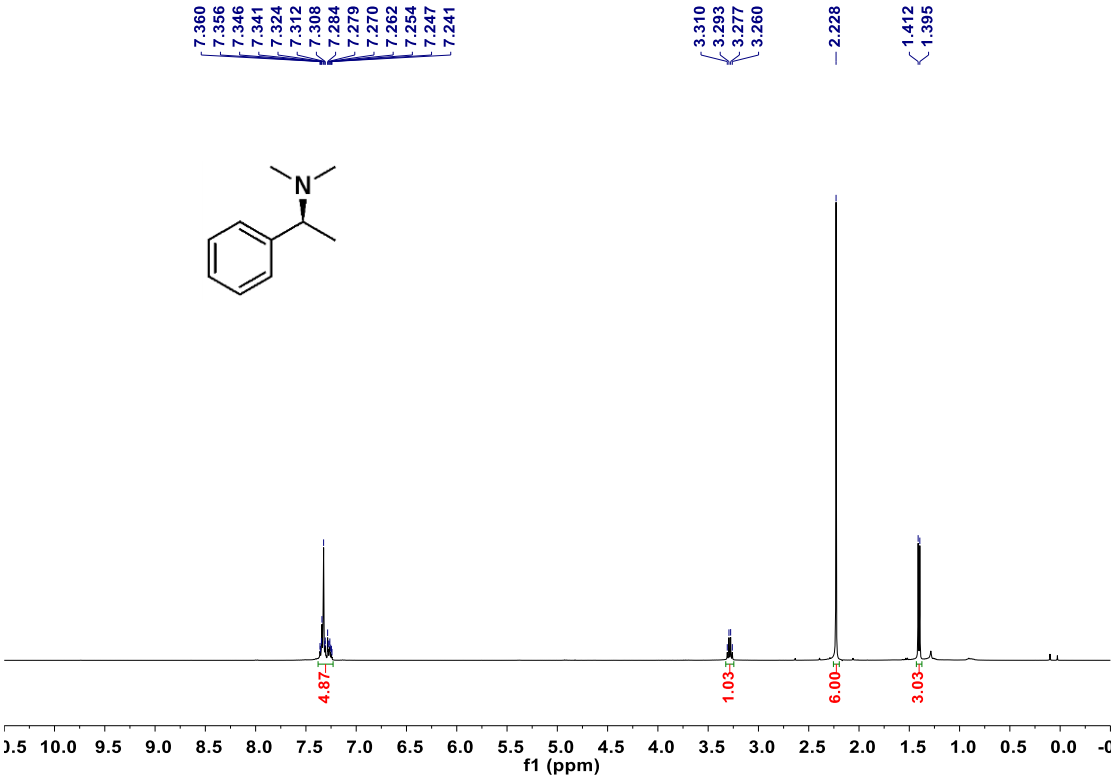


^{13}C NMR (101 MHz, $CDCl_3$)

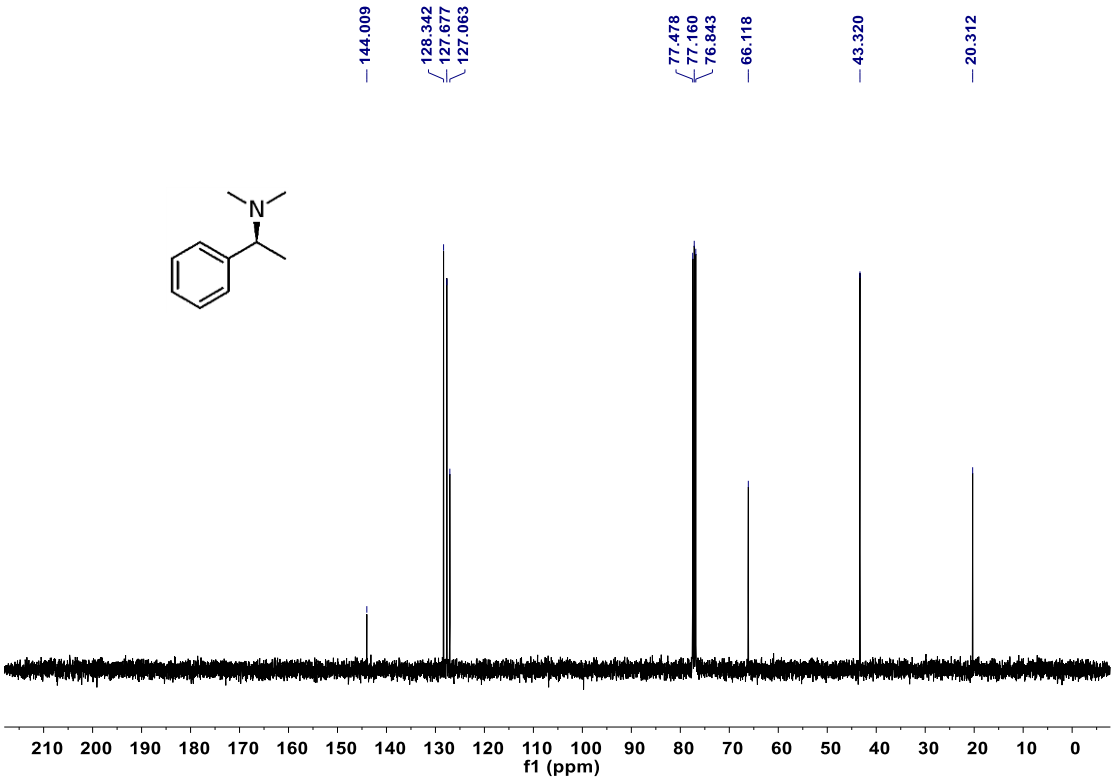


***N*,*N*-Dimethyl-1-phenylmethanamine (4p)**

^{1}H NMR (400 MHz, $CDCl_3$)

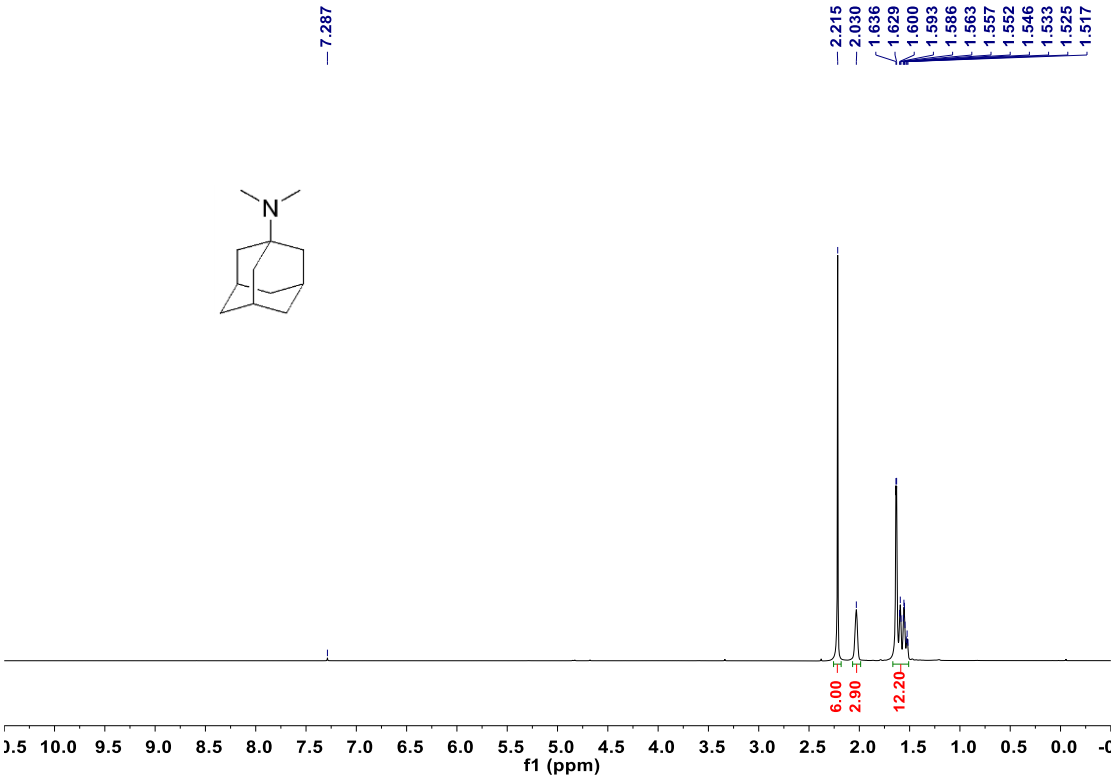


^{13}C NMR (101 MHz, $CDCl_3$)

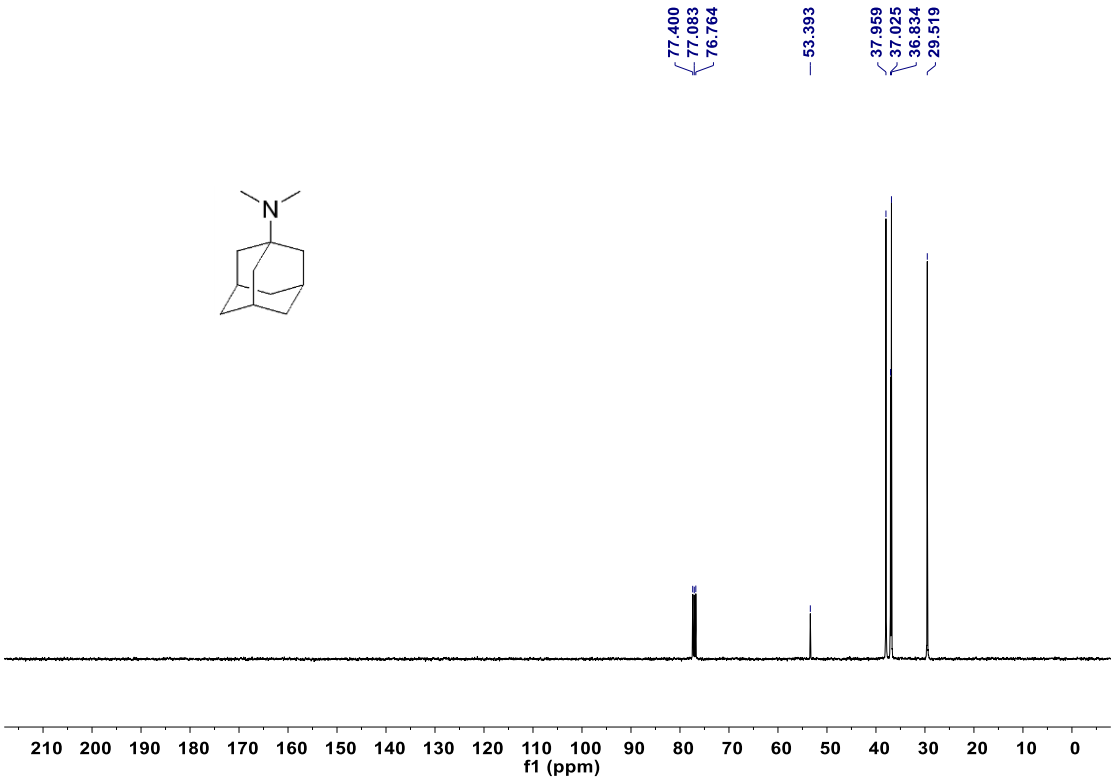


(3s,5s,7s)-*N*,*N*-Dimethyladamantan-1-amine (4q)

^{1}H NMR (400 MHz, $CDCl_3$)

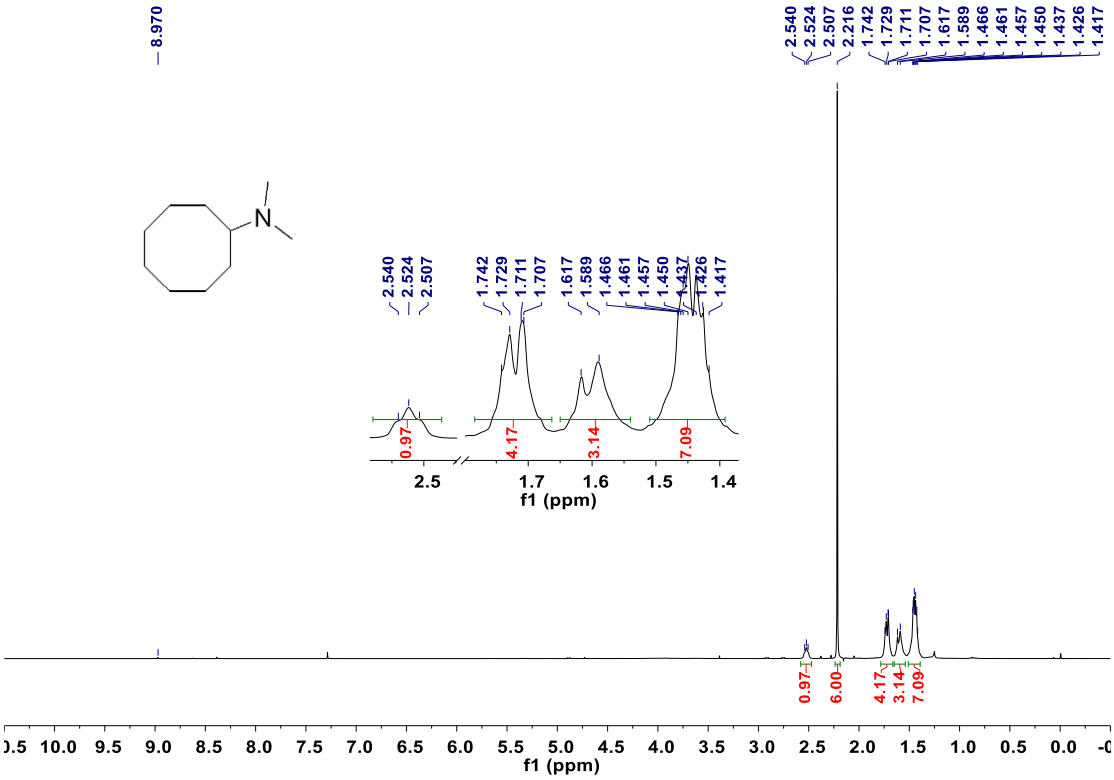


^{13}C NMR (101 MHz, $CDCl_3$)

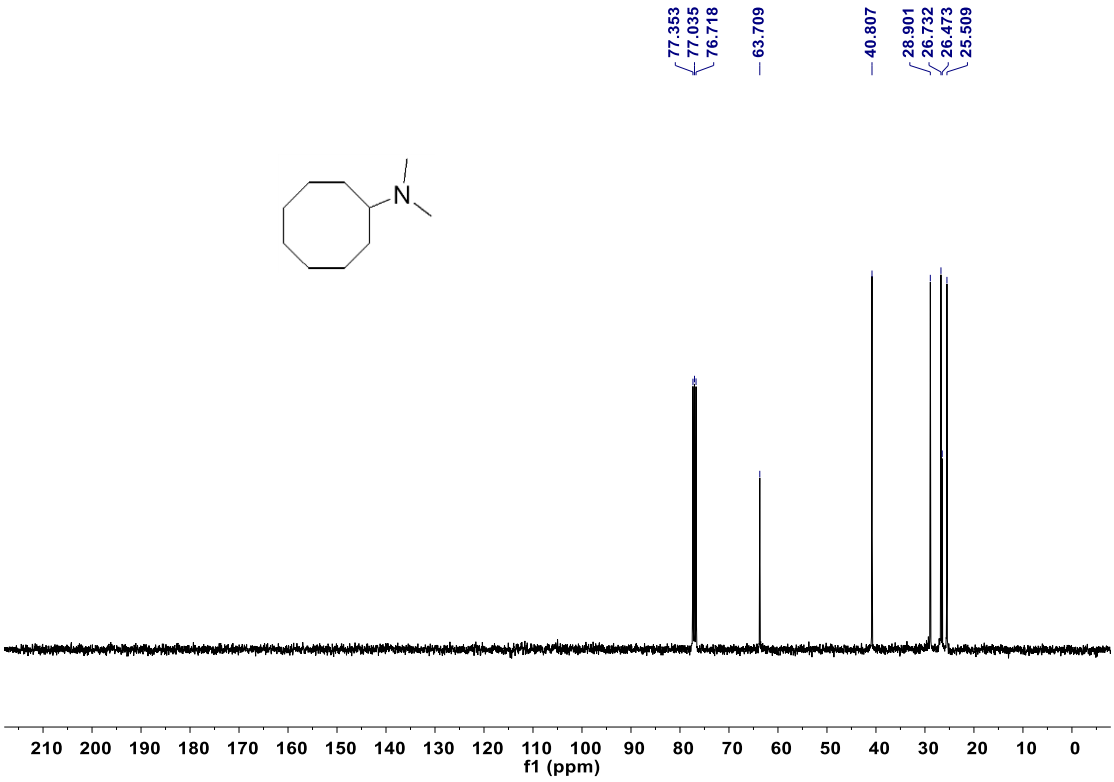


***N*,*N*-Dimethylcyclooctanamine (4r)**

^{1}H NMR (400 MHz, $CDCl_3$)

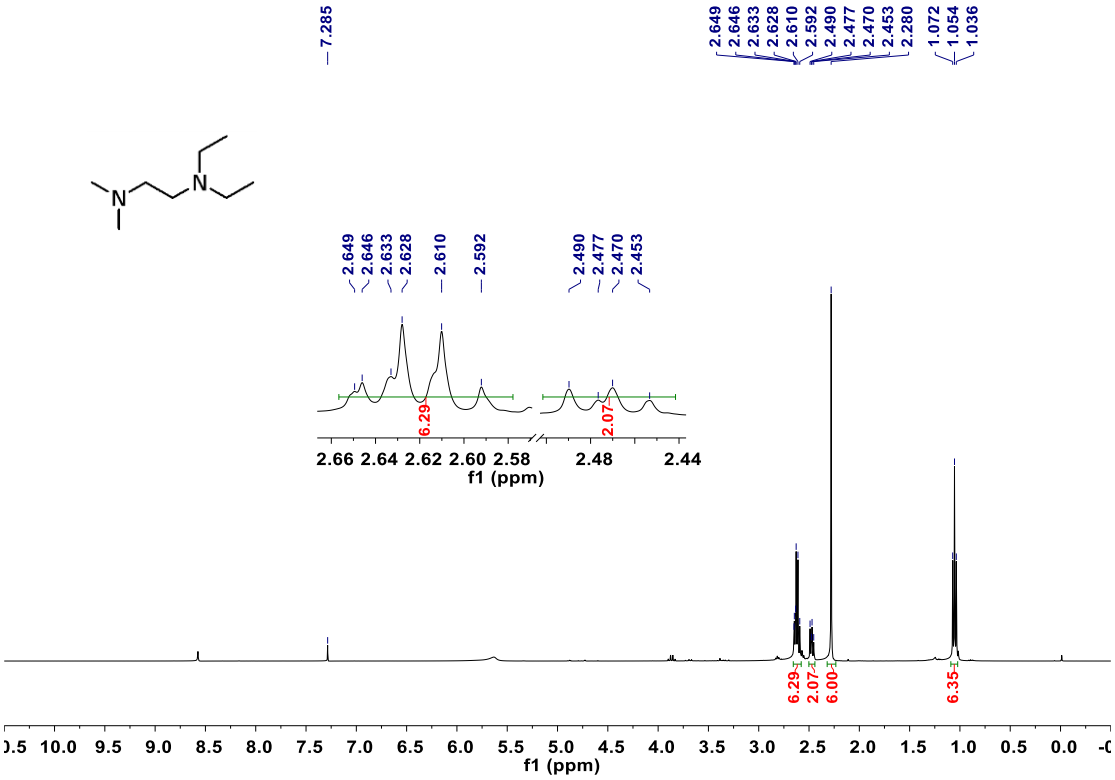


^{13}C NMR (101 MHz, $CDCl_3$)

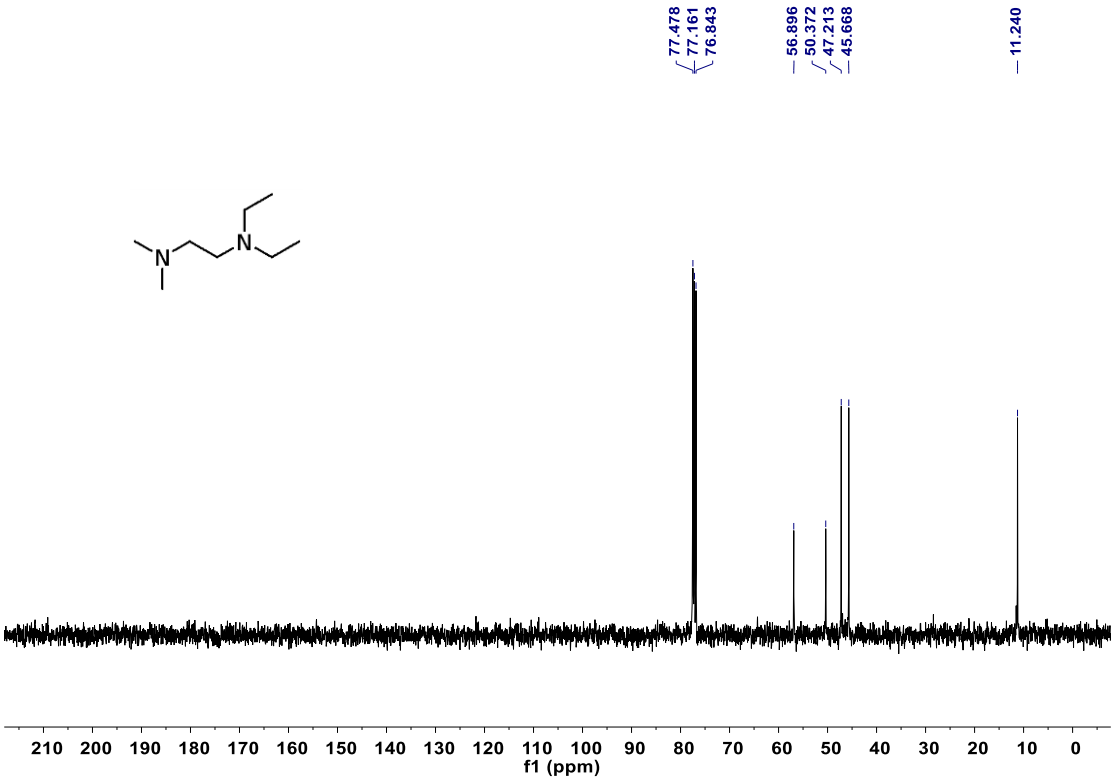


***N1*,*N1*-Diethyl-*N2*,*N2*-dimethylethane-1,2-diamine (4s)**

^{1}H NMR (400 MHz, $CDCl_3$)

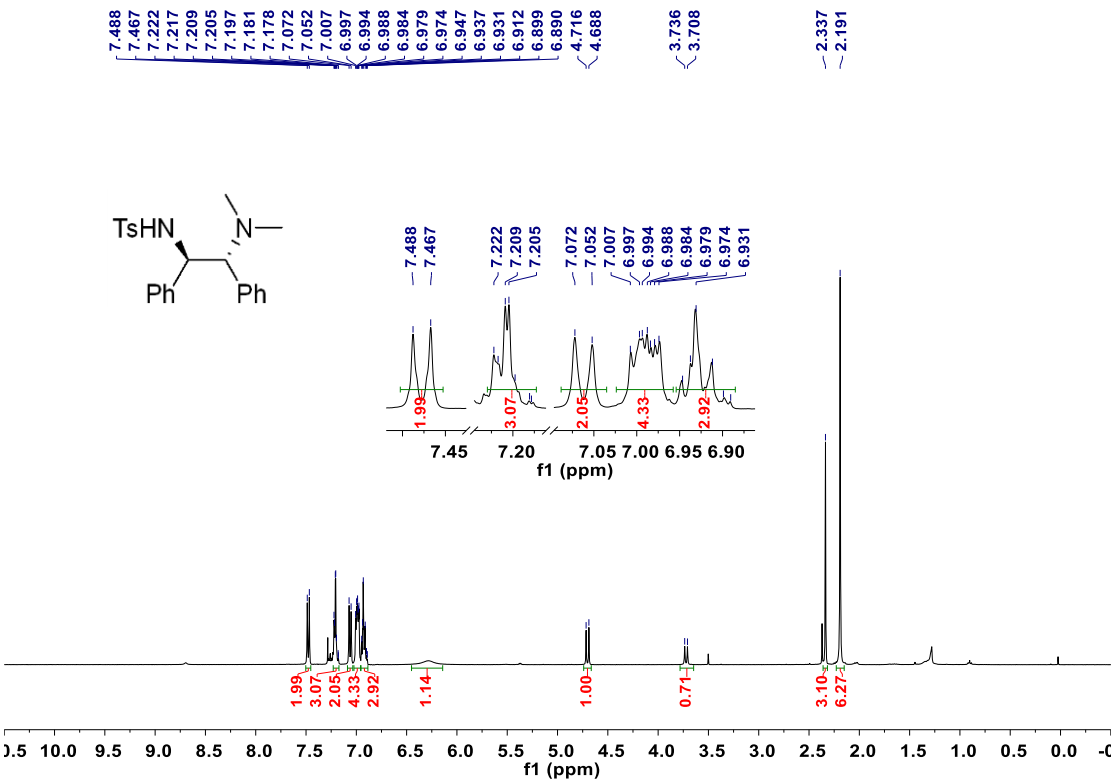


^{13}C NMR (101 MHz, $CDCl_3$)

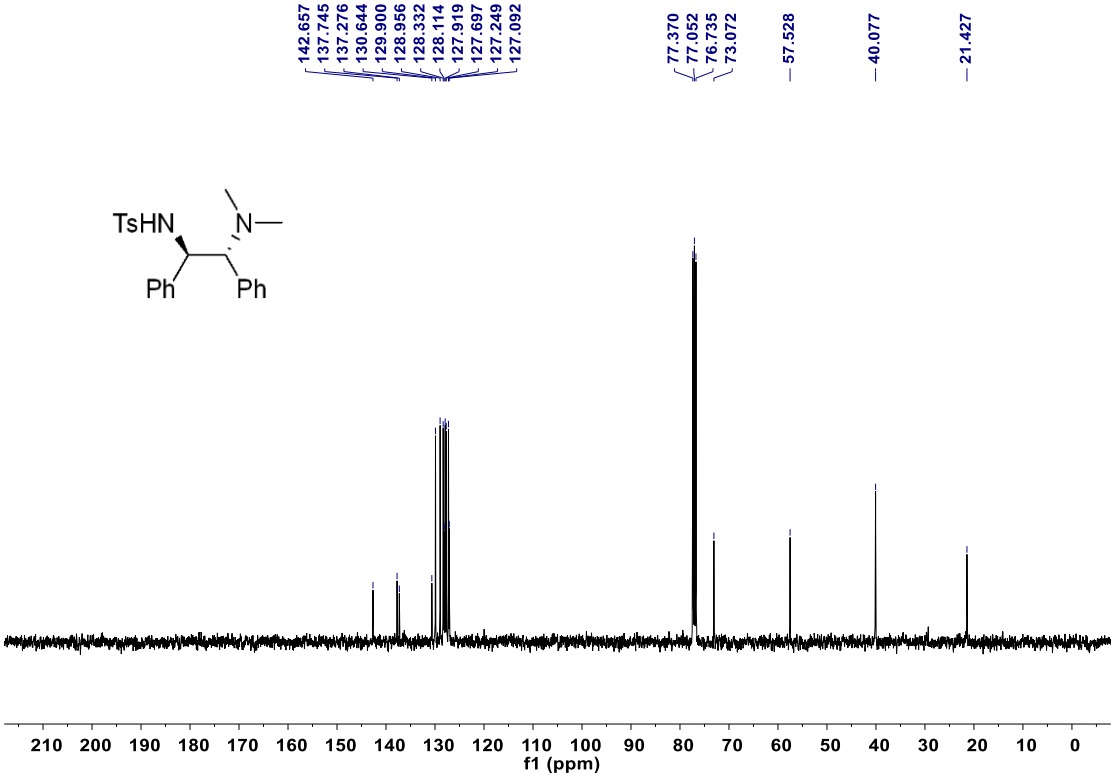


***N*-((1*R*,2*R*)-2-(Dimethylamino)-1,2-diphenylethyl)-4-methylbenzenesulfonamide (4t)**

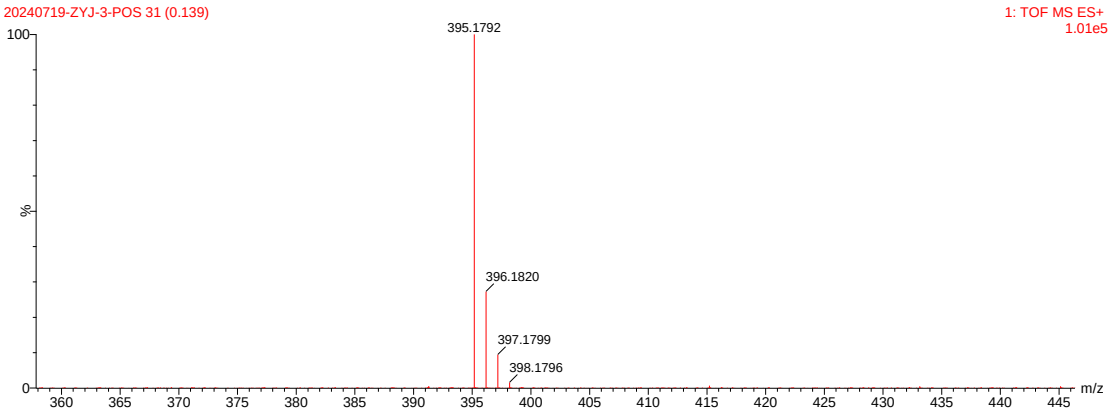
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

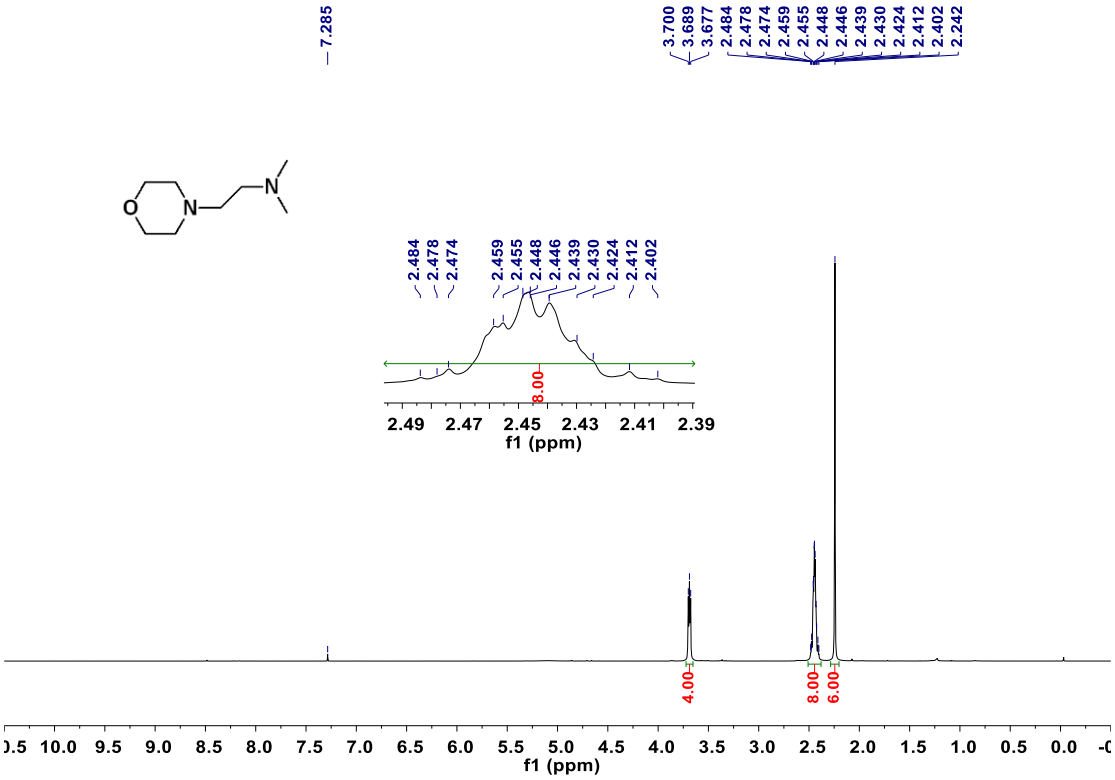


HRMS (ESI): *m/z* calcd for : $C_{23}H_{27}N_2O_2S^+$ $[M+H]^+$: 395.1788, found: 395.1792.

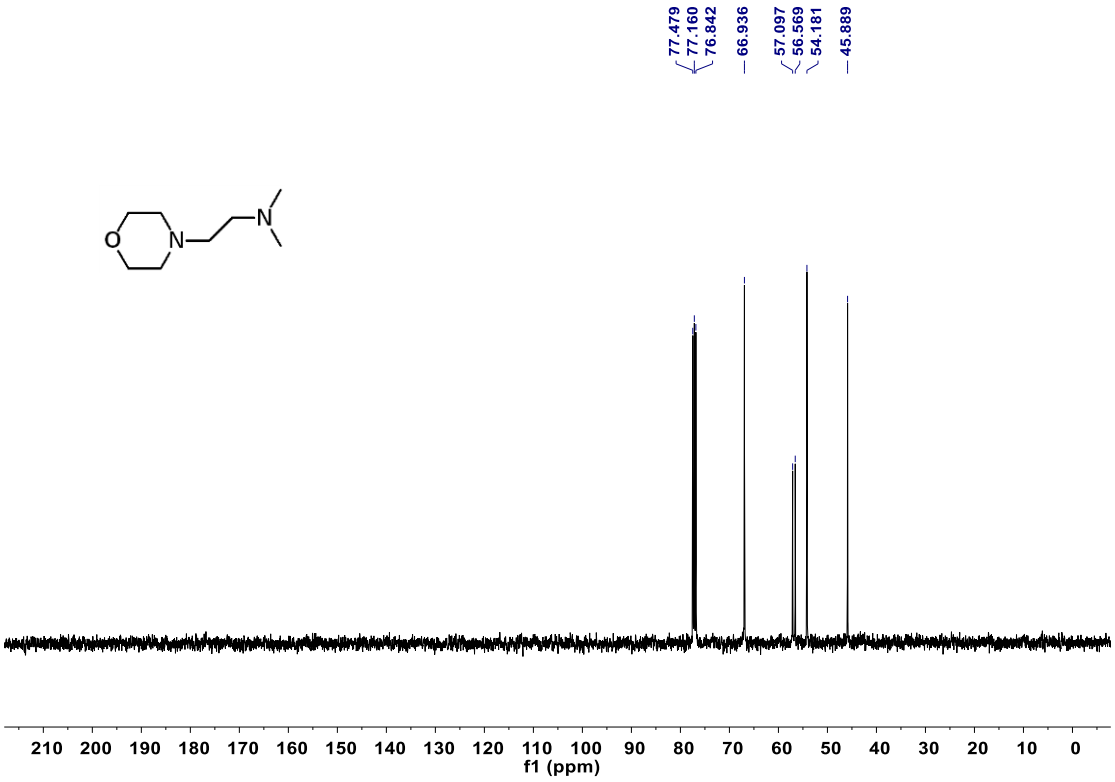


***N*,*N*-Dimethyl-2-morpholinoethan-1-amine (4u)**

^{1}H NMR (400 MHz, $CDCl_3$)

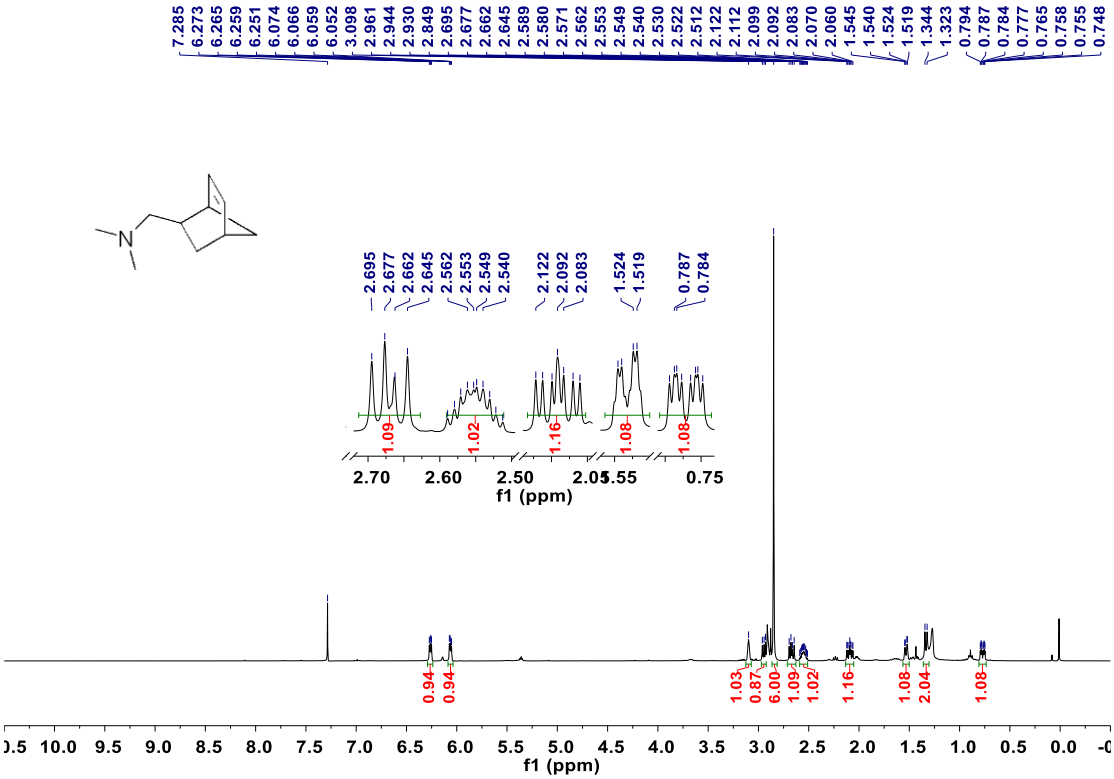


^{13}C NMR (101 MHz, $CDCl_3$)

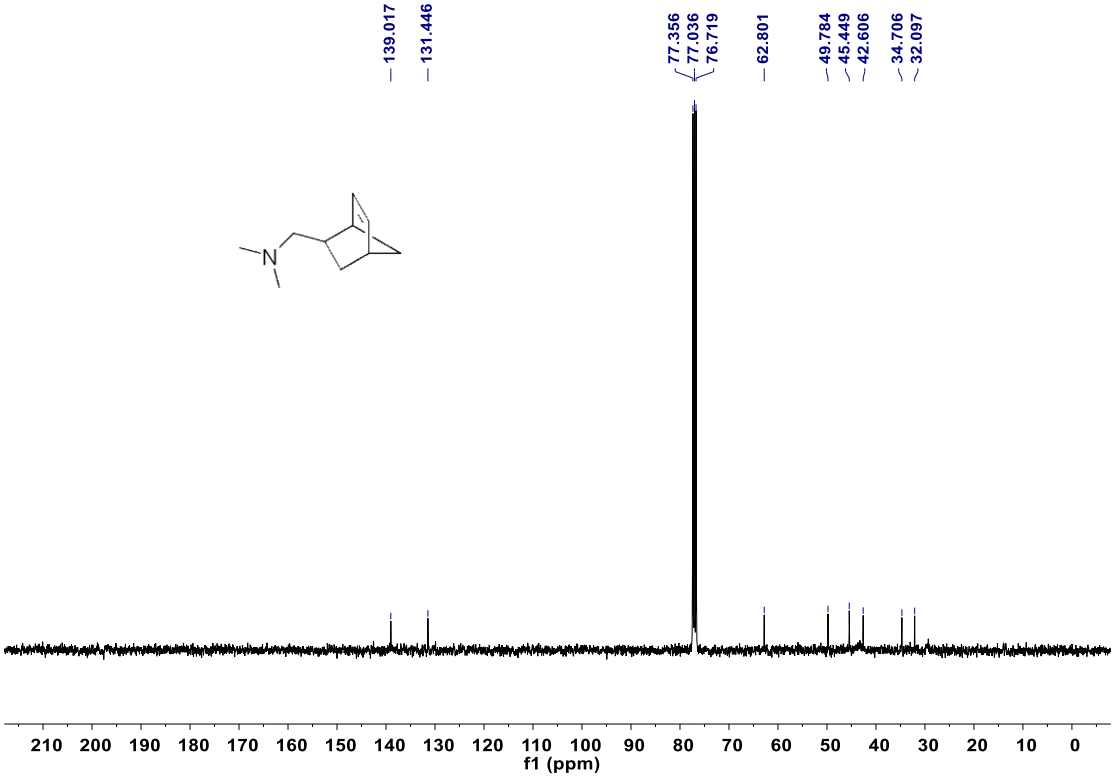


1-((1*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)-*N*,*N*-dimethylmethanamine (4v)

^{1}H NMR (400 MHz, $CDCl_3$)

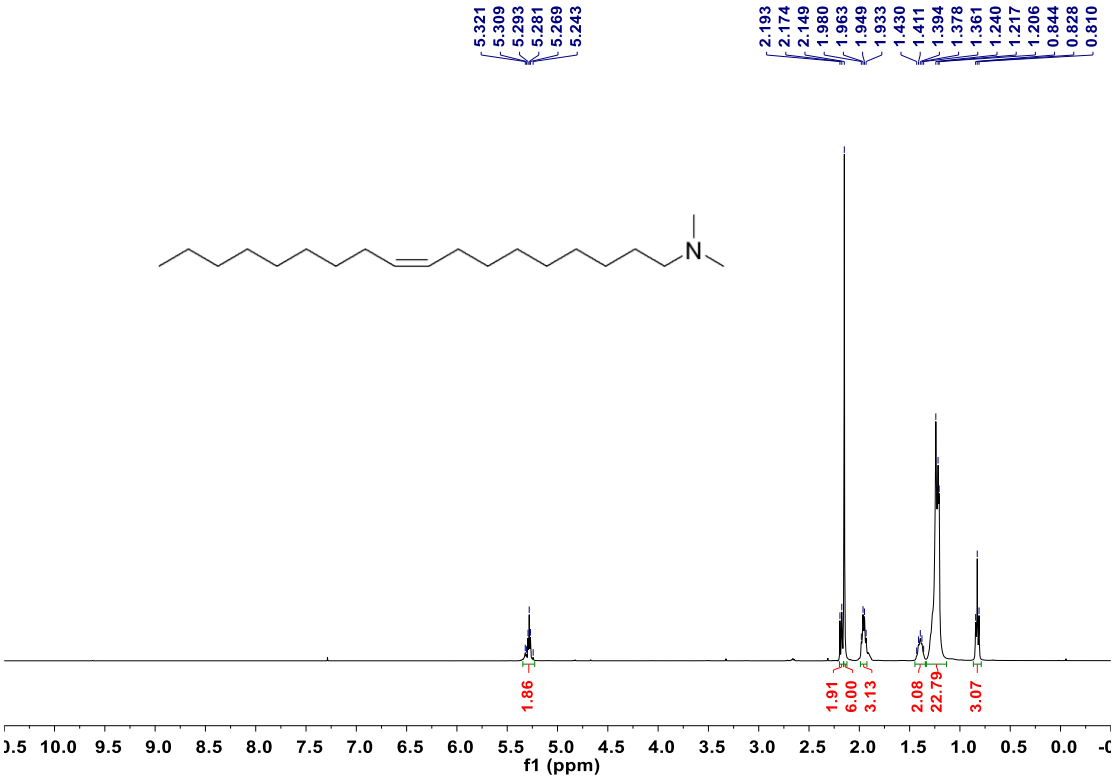


^{13}C NMR (101 MHz, $CDCl_3$)

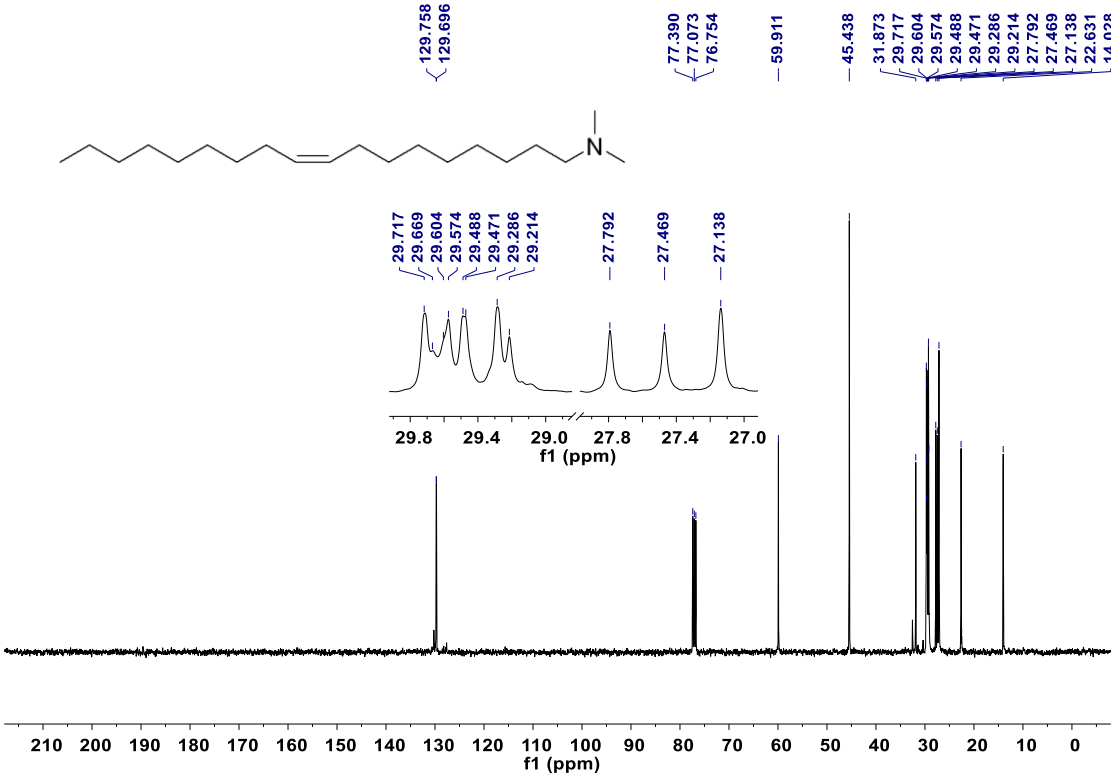


(*Z*)-*N*,*N*-Dimethyloctadec-9-en-1-amine (4w)

^{1}H NMR (400 MHz, $CDCl_3$)

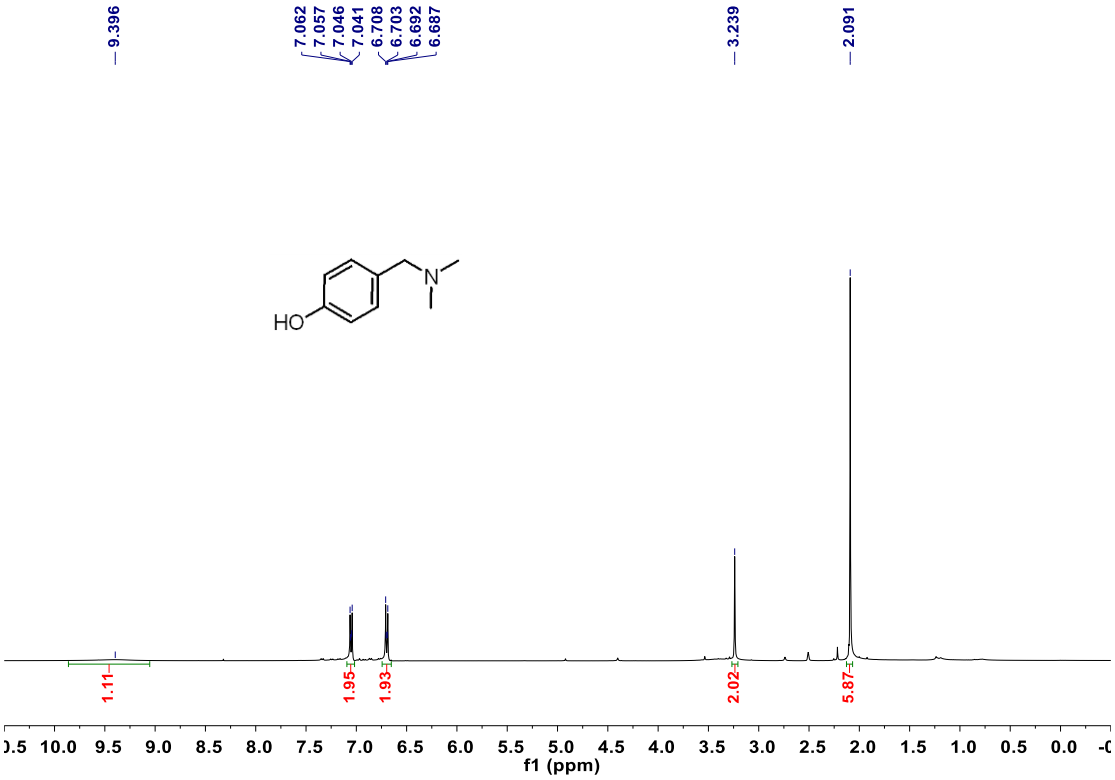


^{13}C NMR (101 MHz, $CDCl_3$)

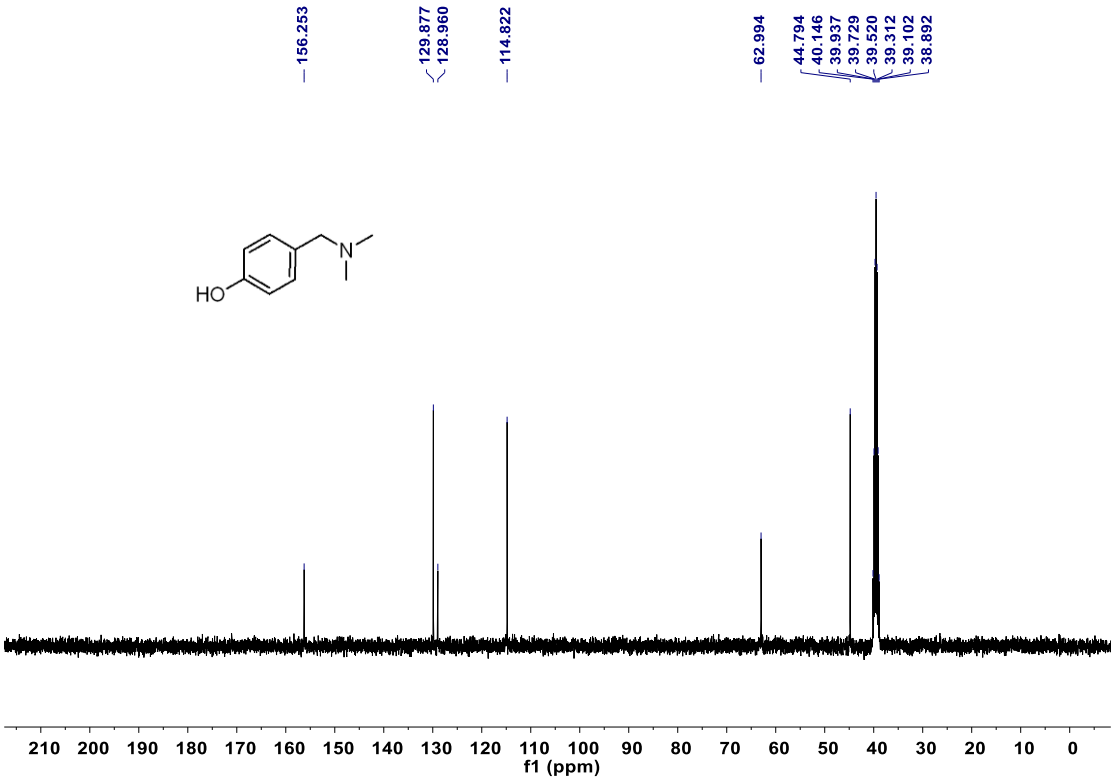


4-((Dimethylamino)methyl)phenol (4x)

^{1}H NMR (400 MHz, DMSO)

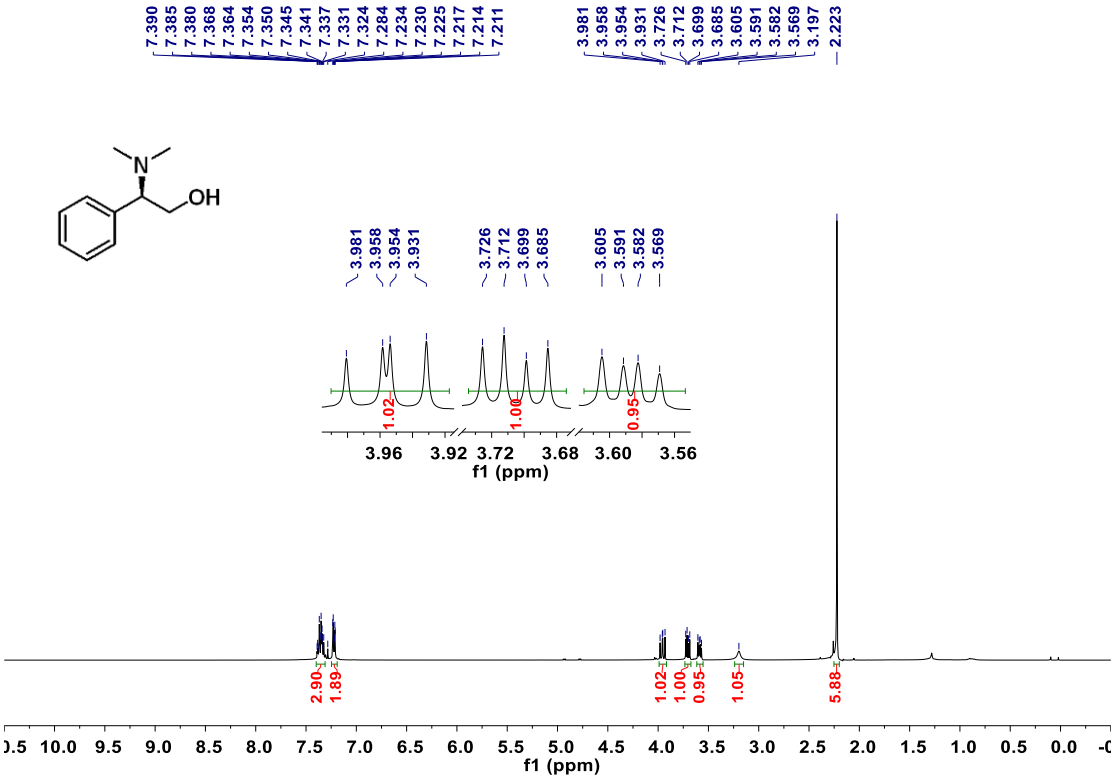


^{13}C NMR (101 MHz, DMSO)

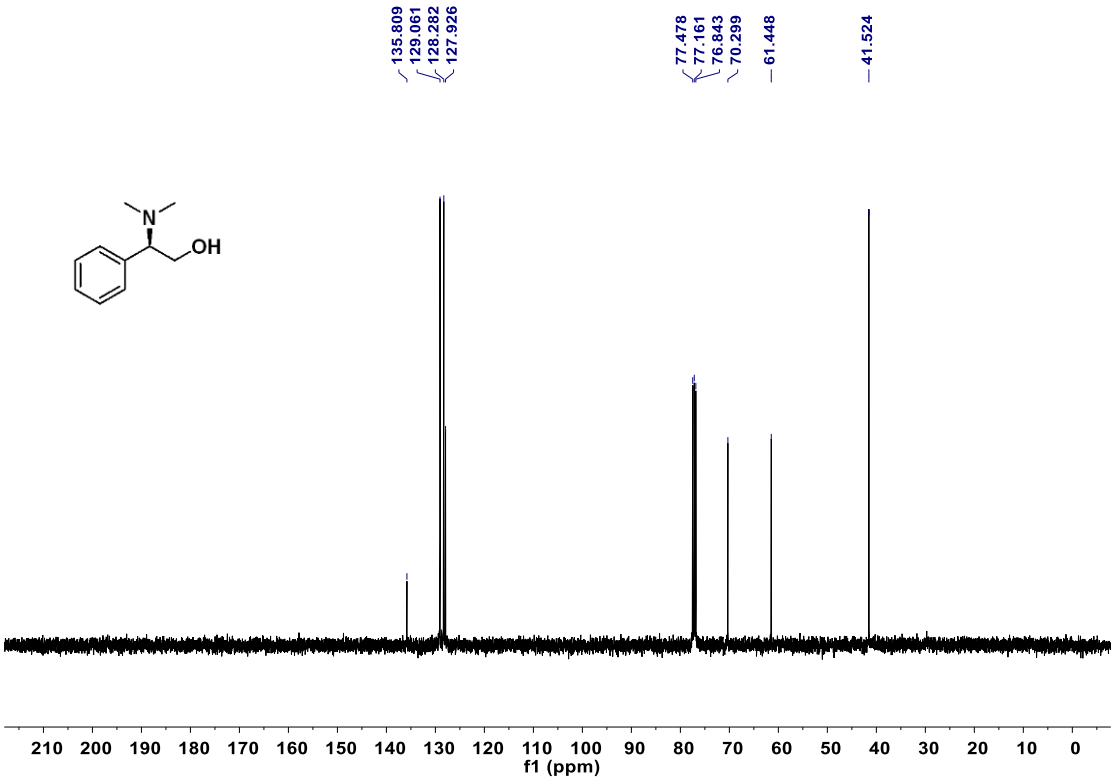


(*S*)-2-(Dimethylamino)-2-phenylethan-1-ol (4y)

^{1}H NMR (400 MHz, $CDCl_3$)

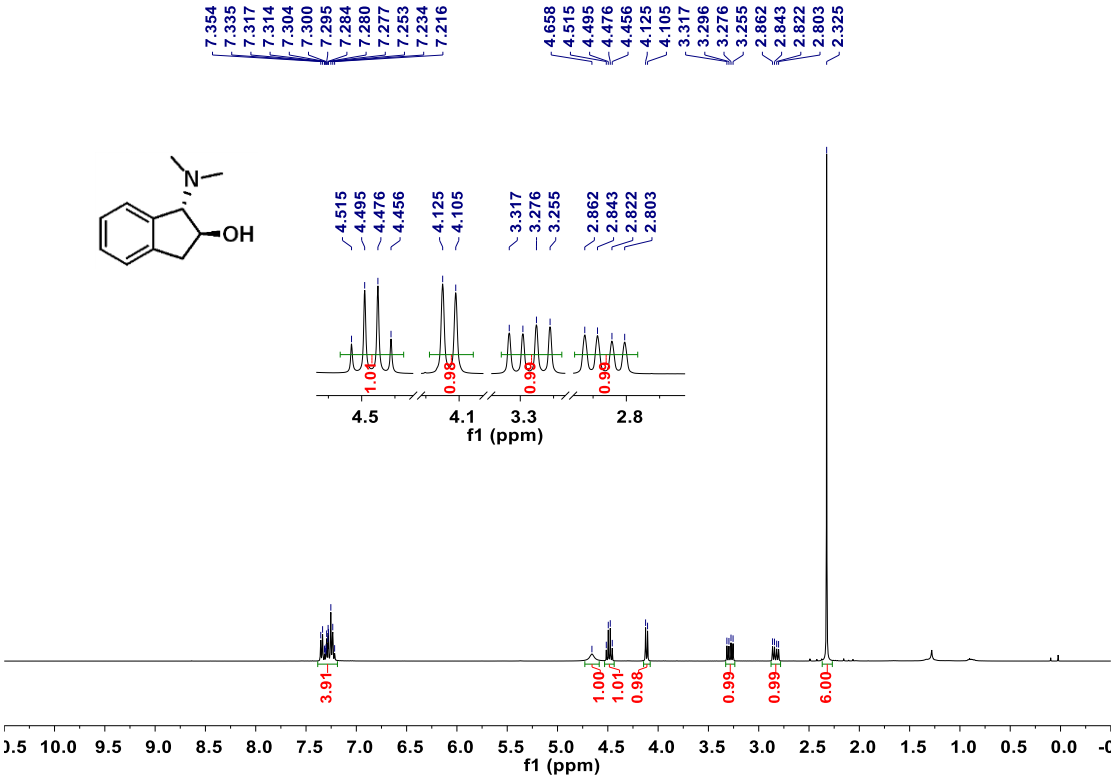


^{13}C NMR (101 MHz, $CDCl_3$)

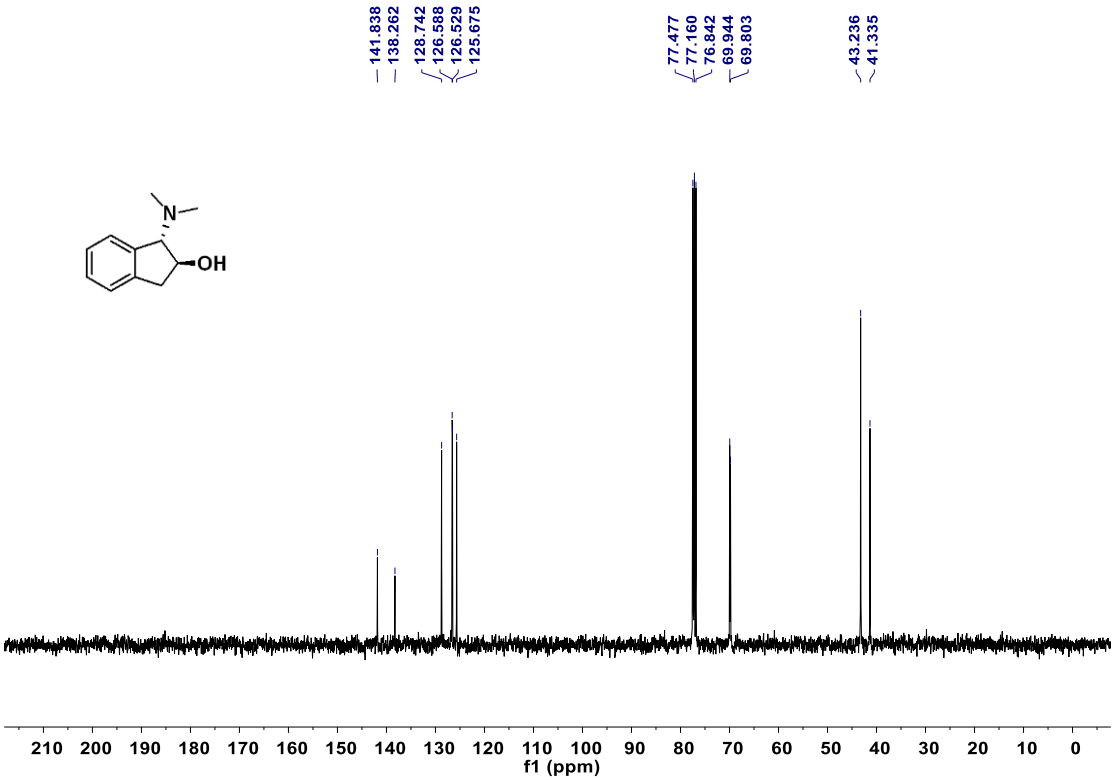


(1*S*,2*S*)-1-(Dimethylamino)-2,3-dihydro-1*H*-inden-2-ol (4z)

^{1}H NMR (400 MHz, $CDCl_3$)

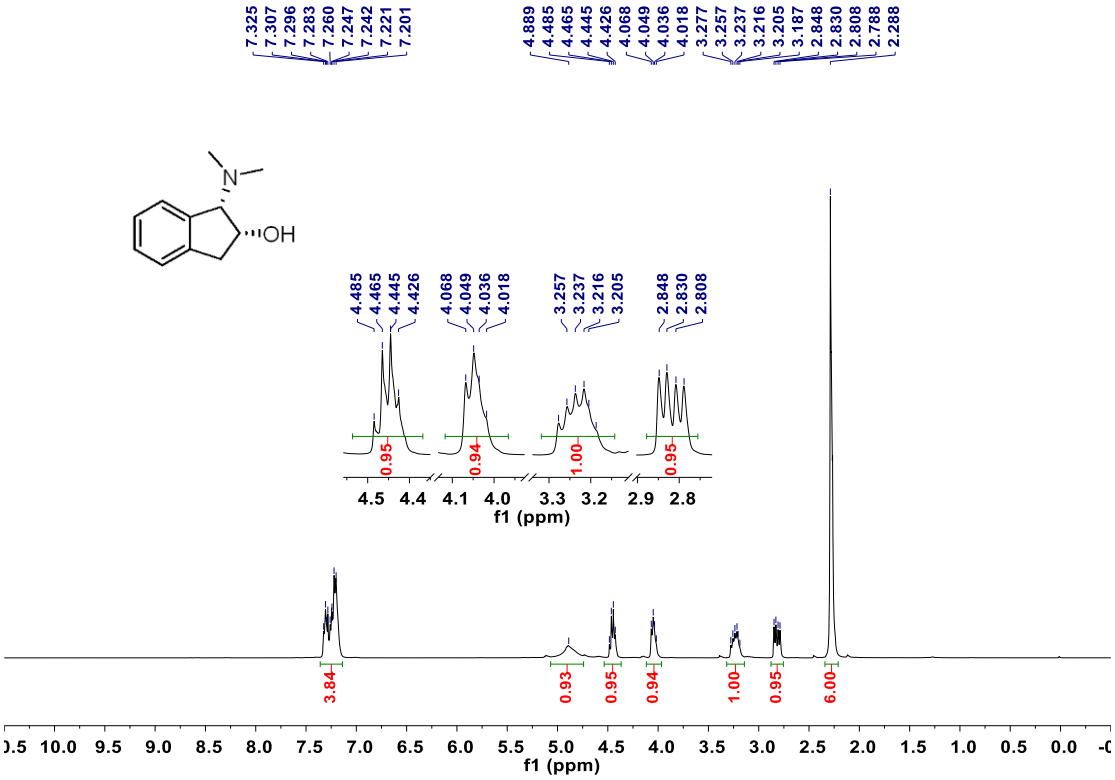


^{13}C NMR (101 MHz, $CDCl_3$)

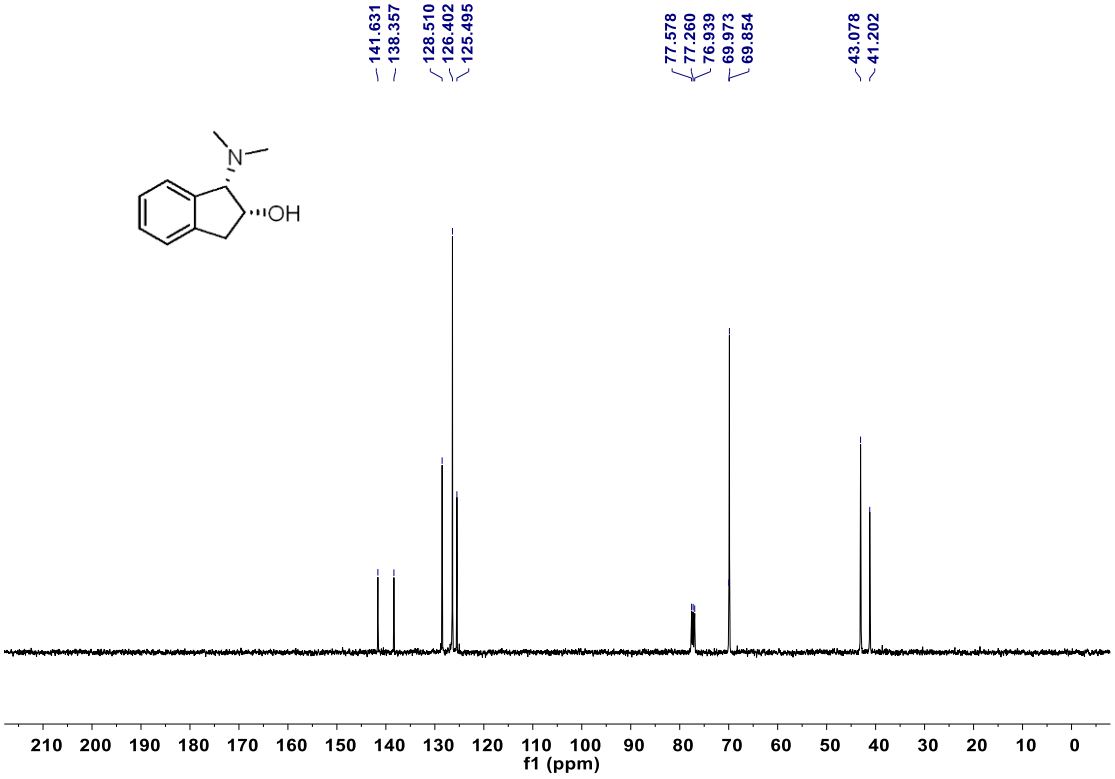


(1*S*,2*R*)-1-(Dimethylamino)-2,3-dihydro-1*H*-inden-2-ol (4a)

^{1}H NMR (400 MHz, $CDCl_3$)

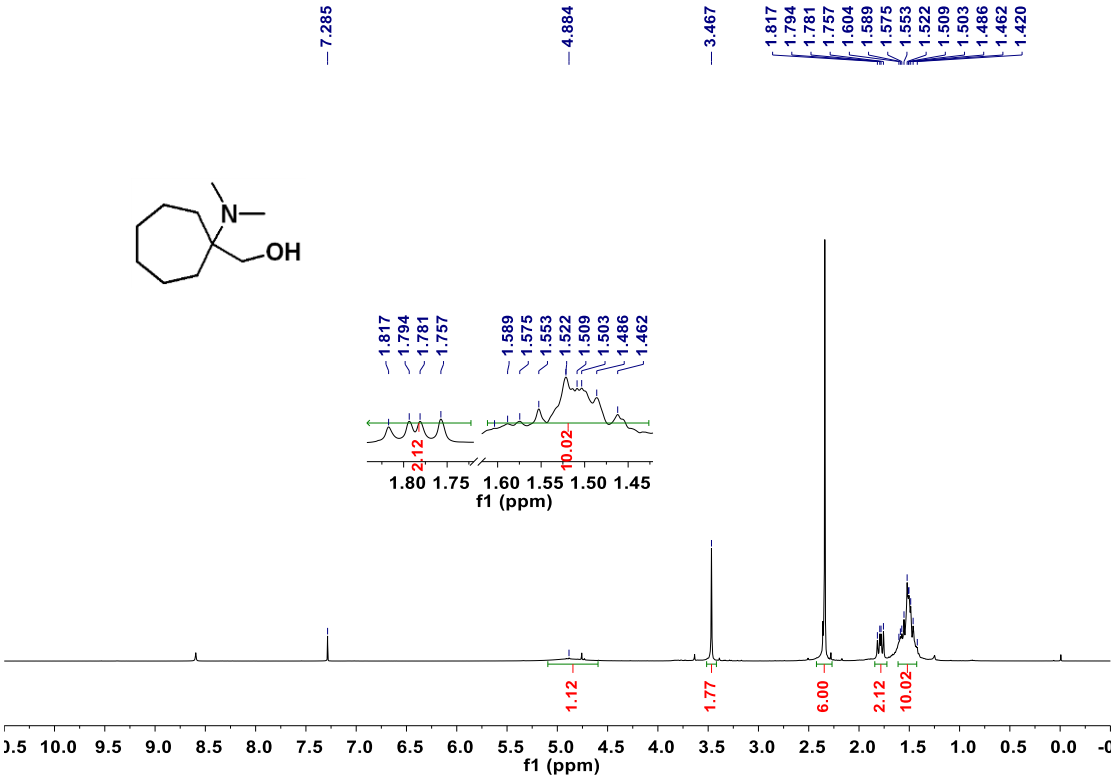


^{13}C NMR (101 MHz, $CDCl_3$)

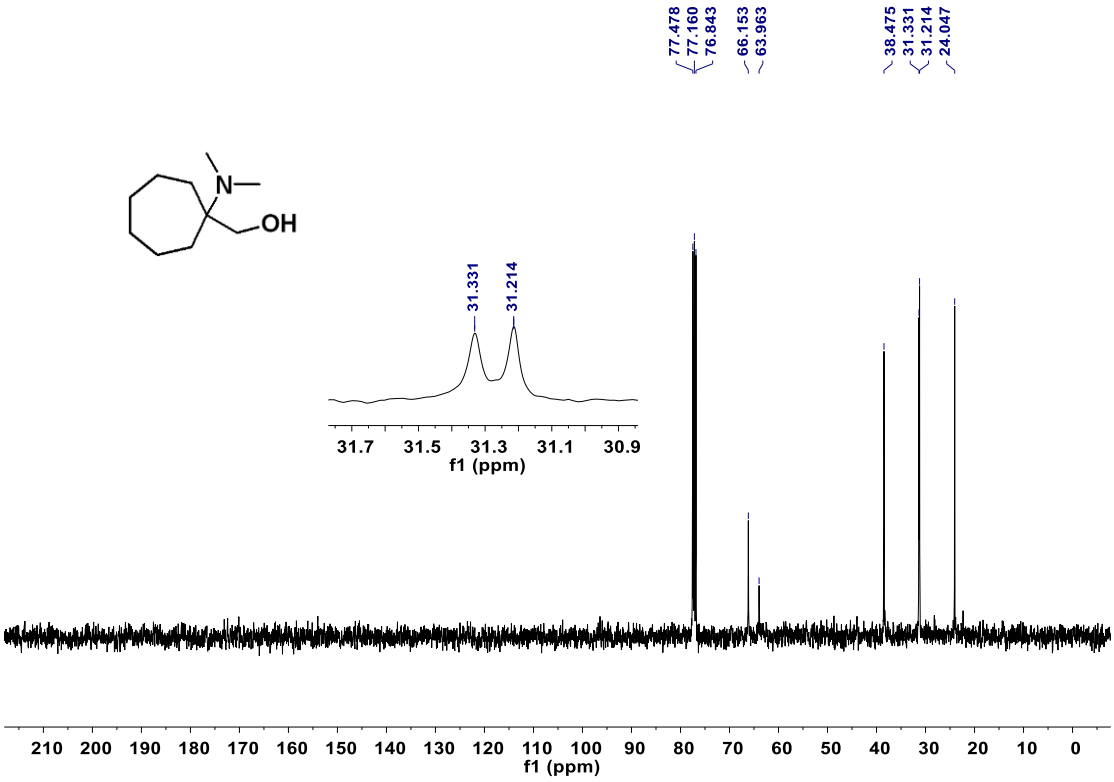


(1-(Dimethylamino)cycloheptyl)methanol (4aa)

^{1}H NMR (400 MHz, $CDCl_3$)

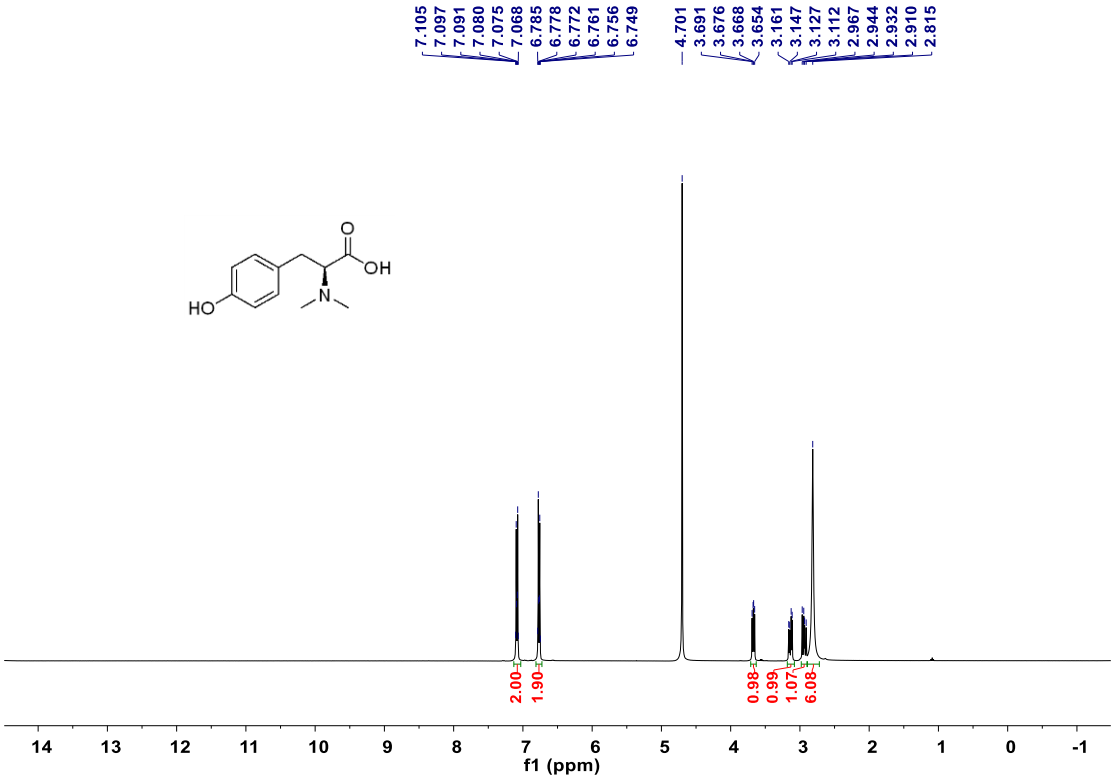


^{13}C NMR (101 MHz, $CDCl_3$)

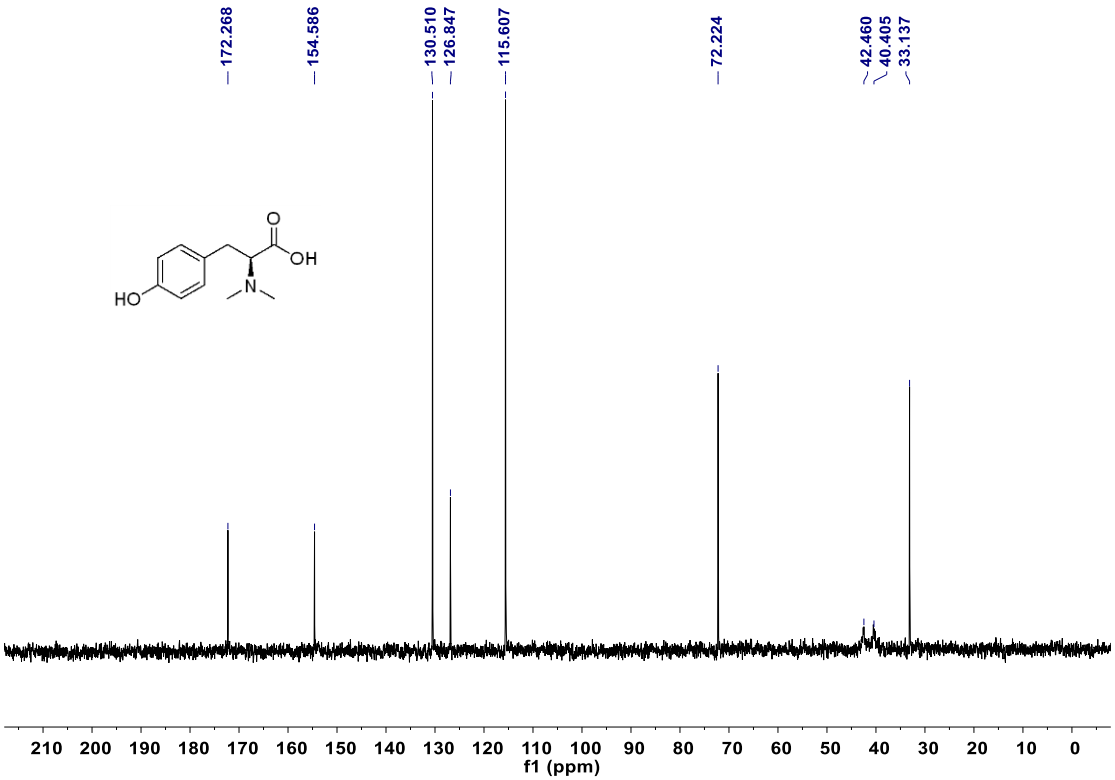


***N*,*N*-Dimethyl-*L*-tyrosine (4ab)**

^{1}H NMR (400 MHz, D_2O)

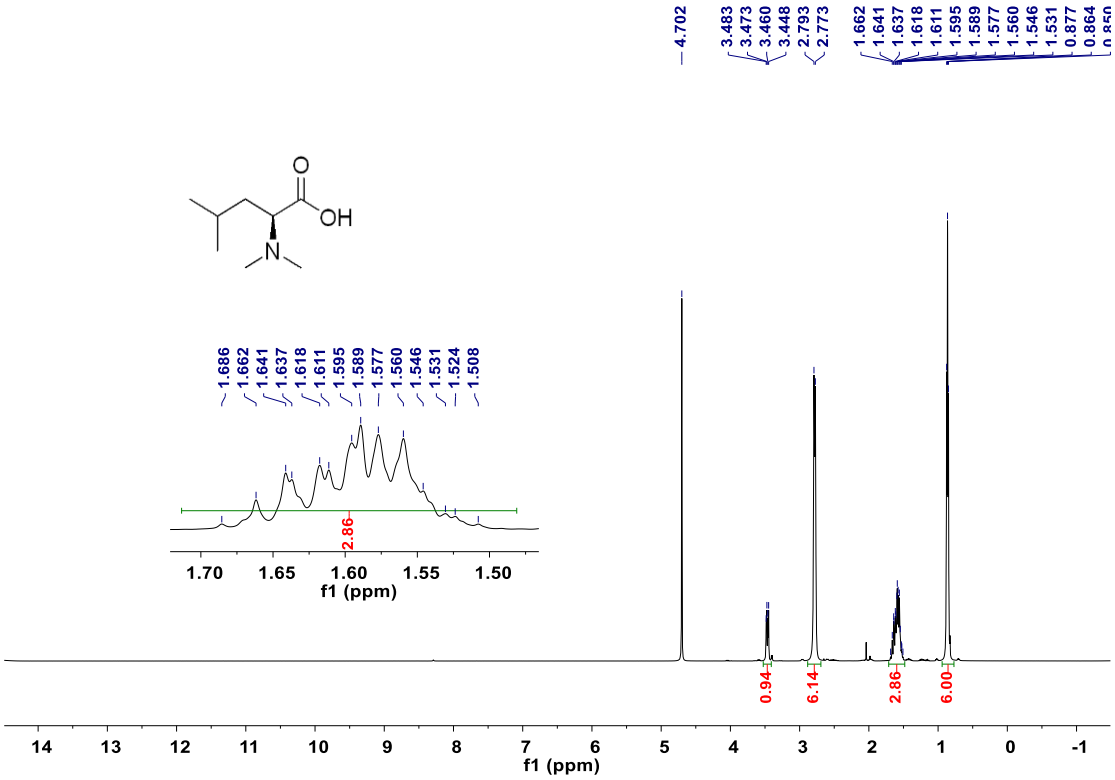


^{13}C NMR (101 MHz, D_2O)

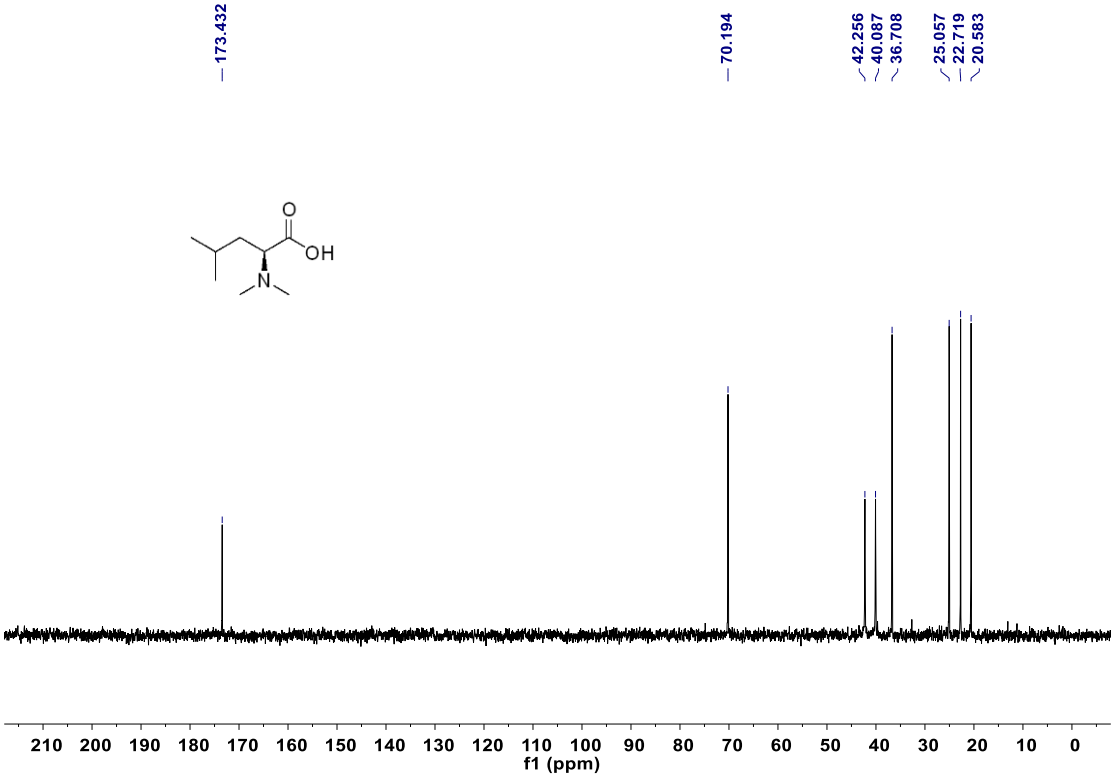


Dimethyl-*L*-leucine (4ac)

^{1}H NMR (400 MHz, D_2O)

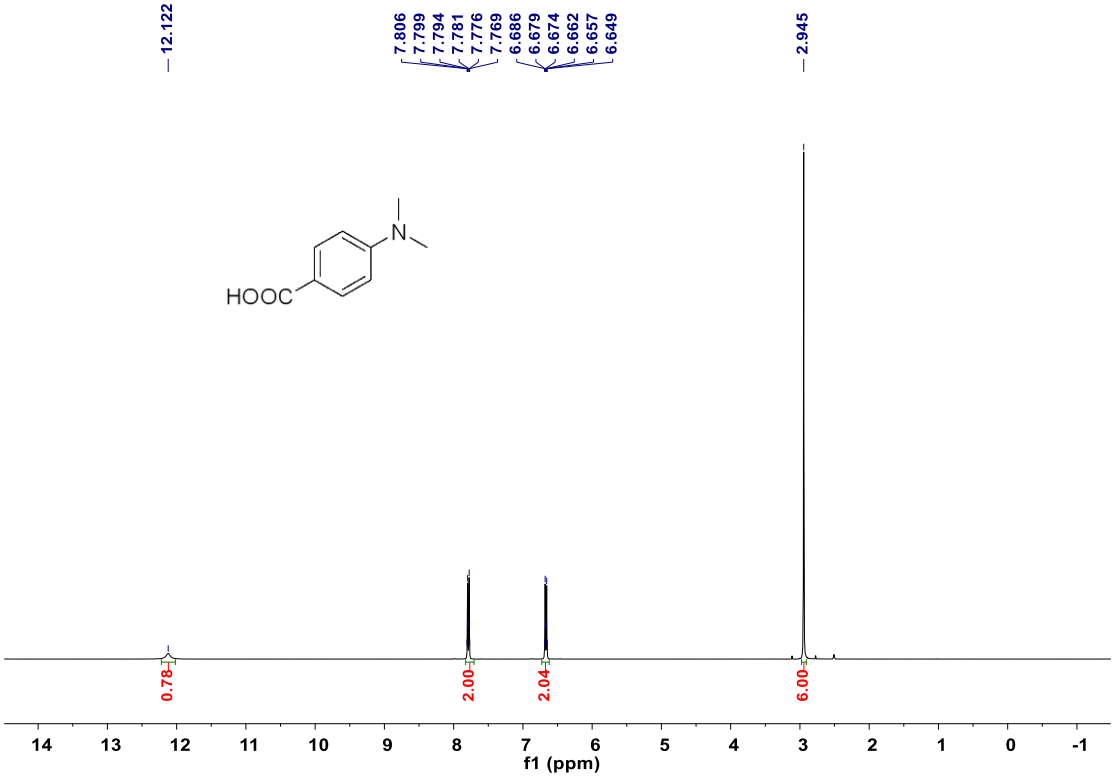


^{13}C NMR (101 MHz, D_2O)

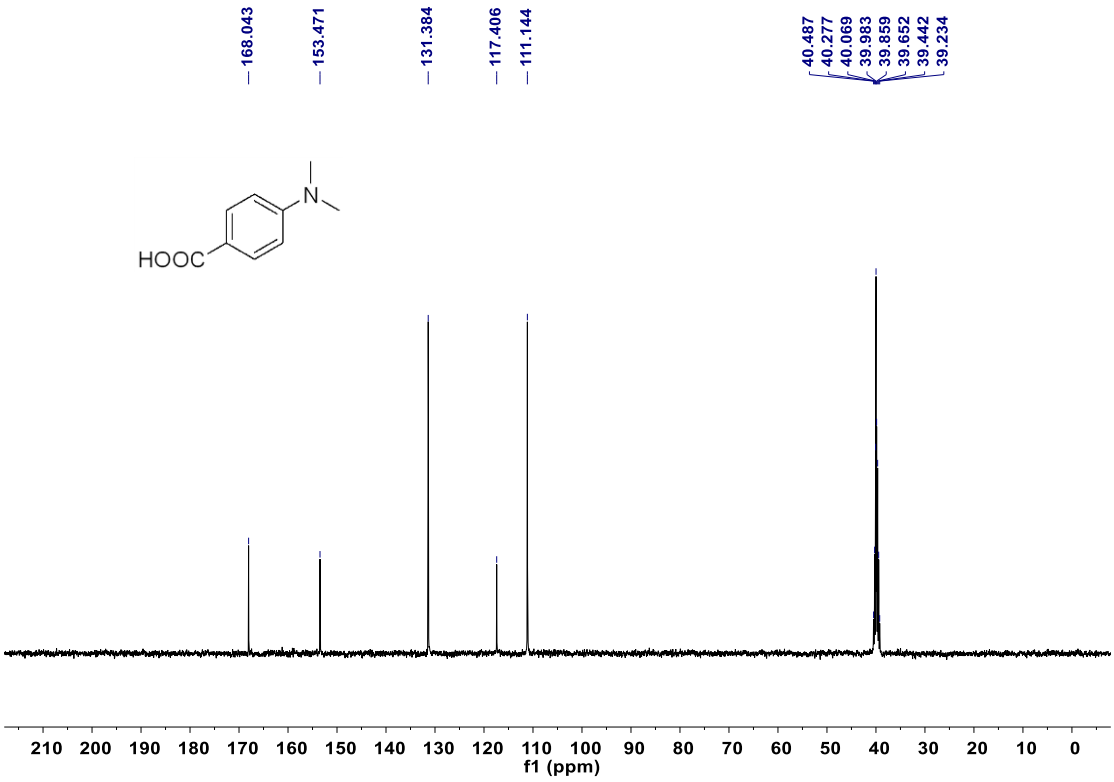


4-(Dimethylamino)benzoic acid (4ad)

^{1}H NMR (400 MHz, DMSO-d_6)

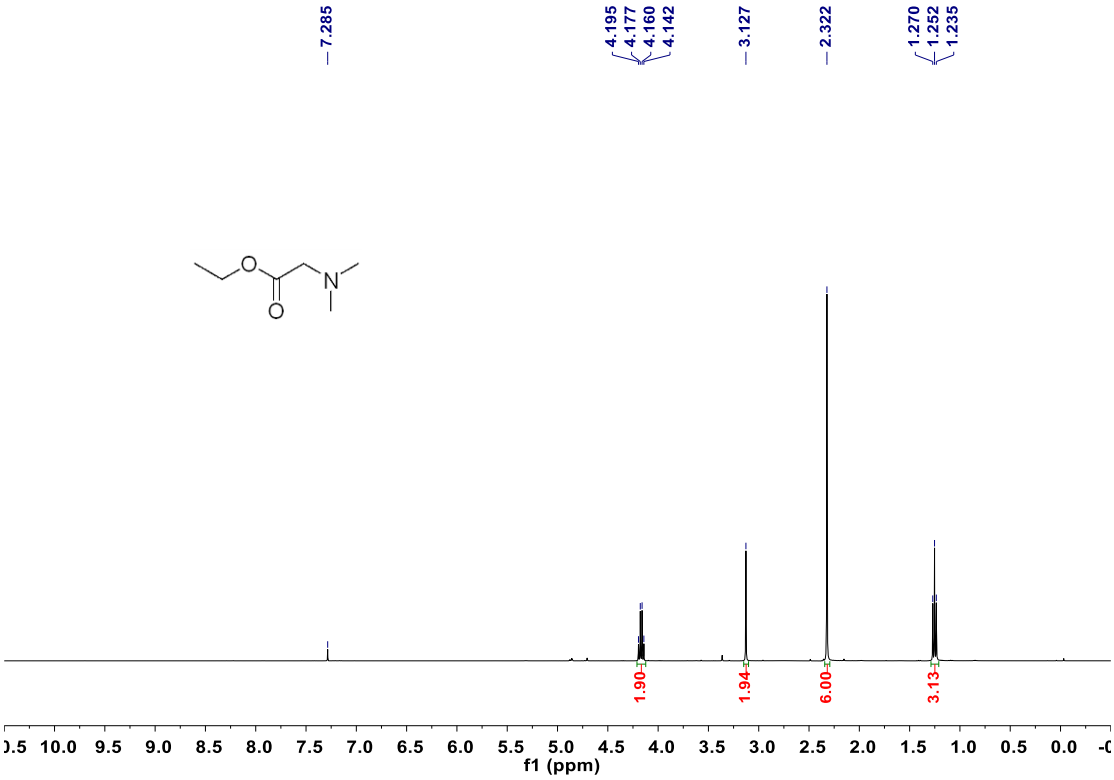


^{13}C NMR (101 MHz, DMSO-d_6)

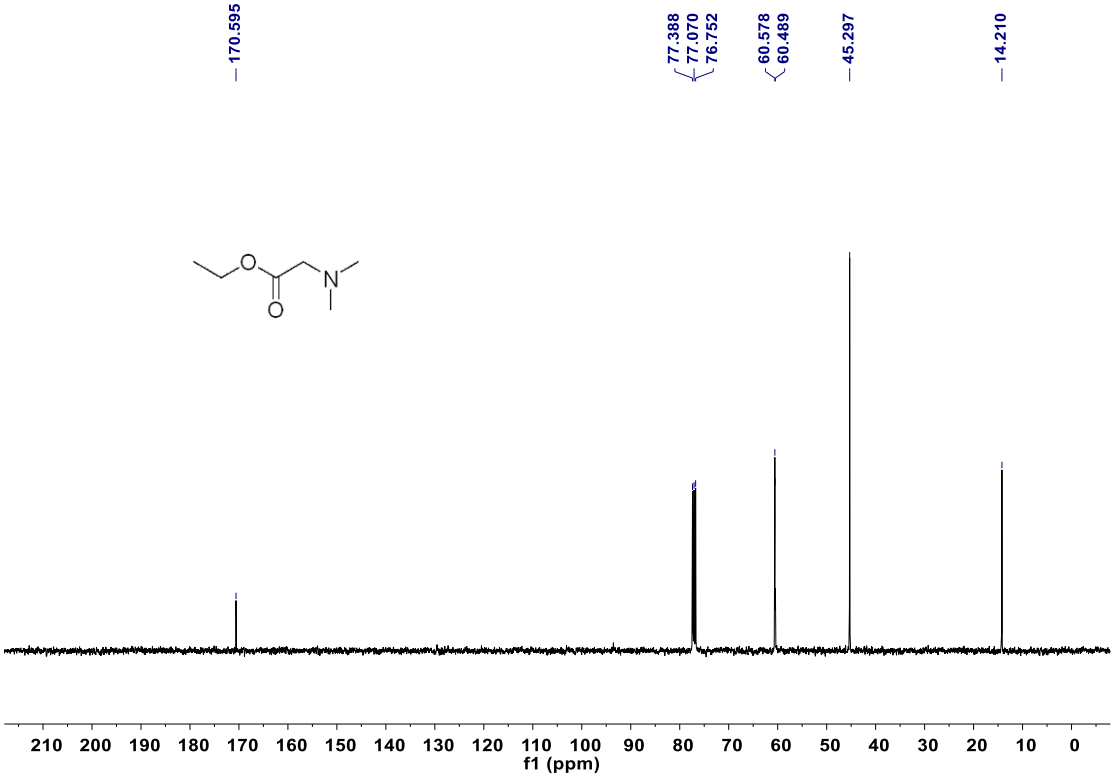


Ethyl dimethylglycinate (4ae)

^{1}H NMR (400 MHz, $CDCl_3$)

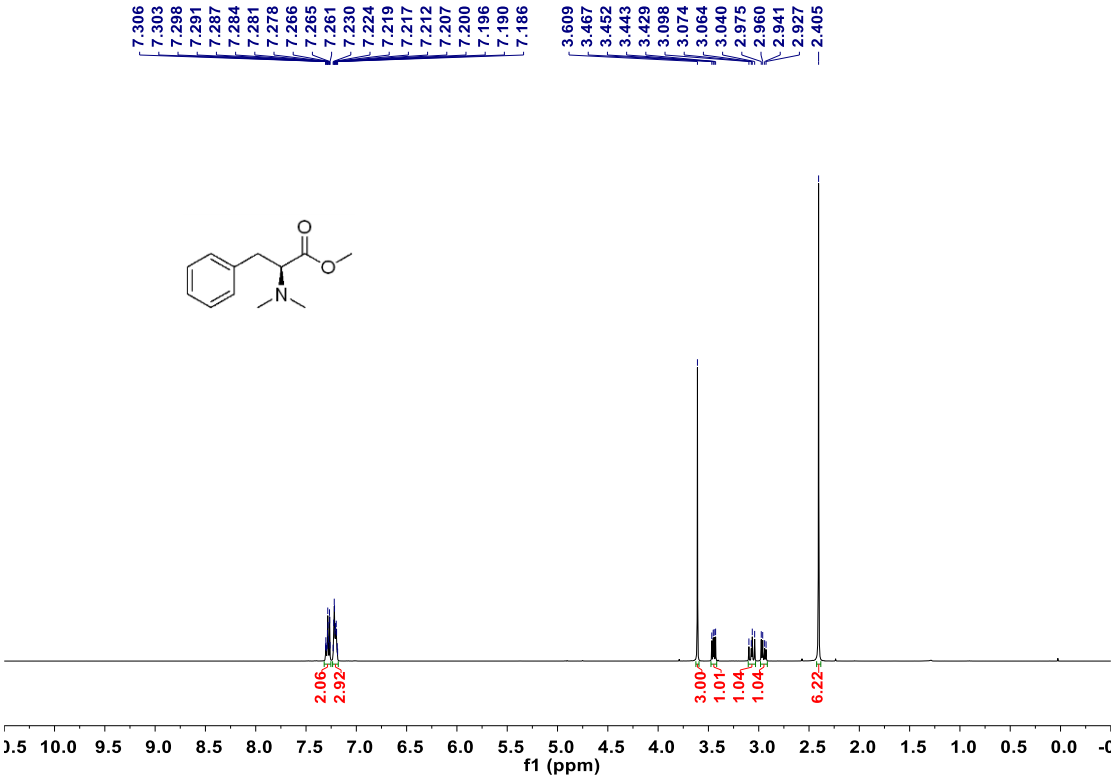


^{13}C NMR (101 MHz, $CDCl_3$)

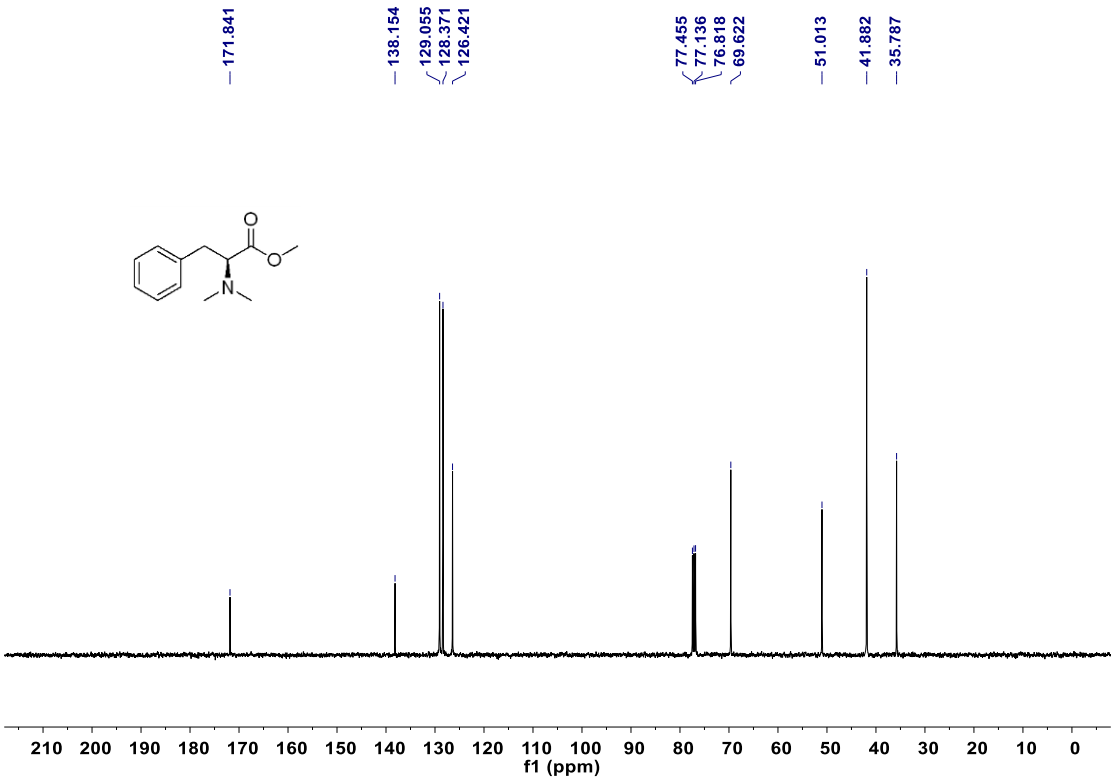


Methyl dimethyl-*L*-phenylalaninate (4af)

^{1}H NMR (400 MHz, $CDCl_3$)

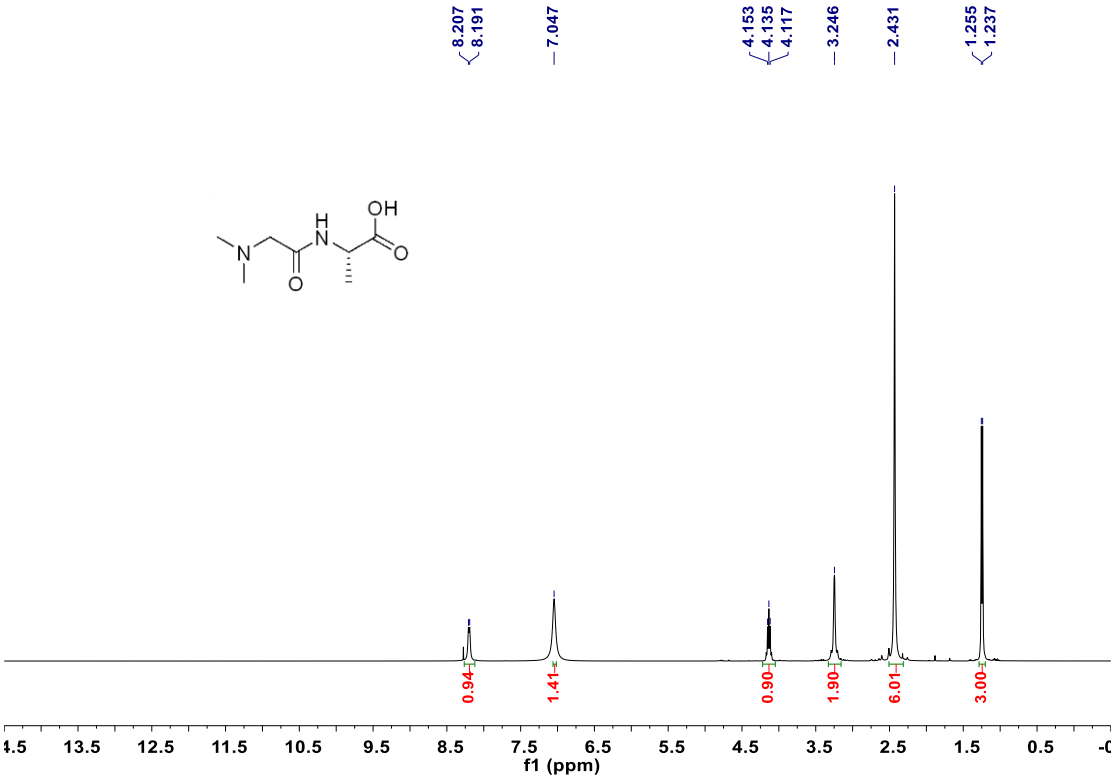


^{13}C NMR (101 MHz, $CDCl_3$)

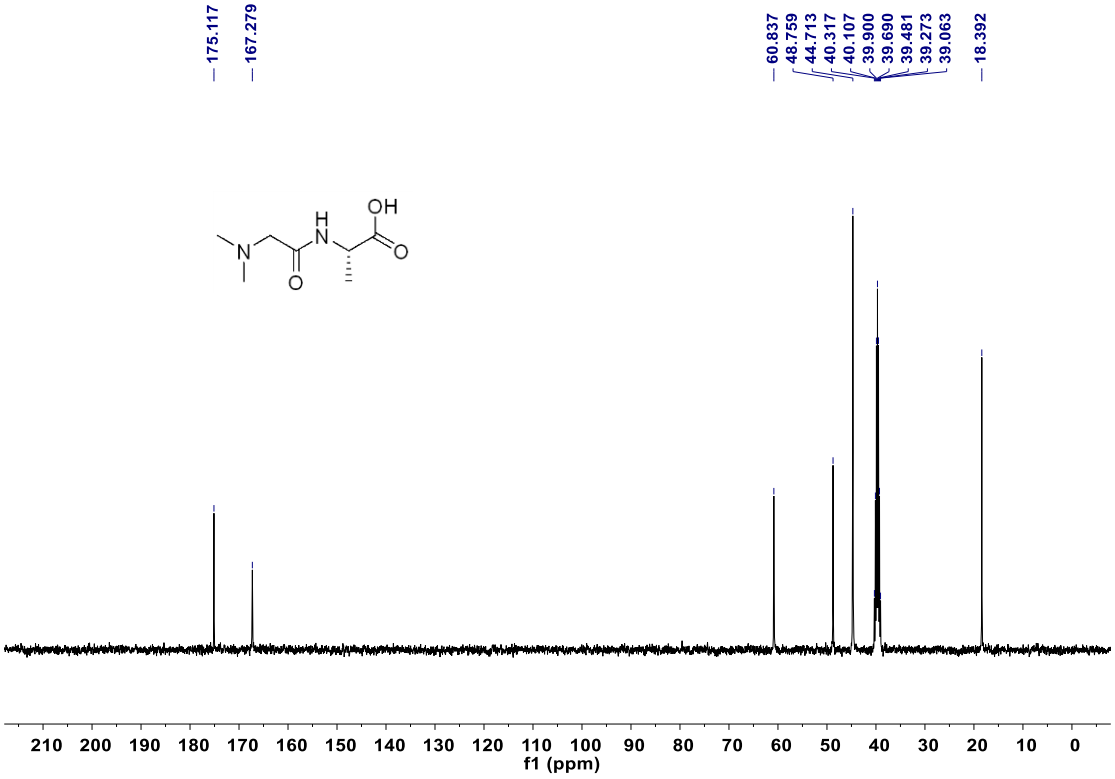


Dimethylglycyl-*L*-alanine (4ag)

^{1}H NMR (400 MHz, DMSO-d_6)

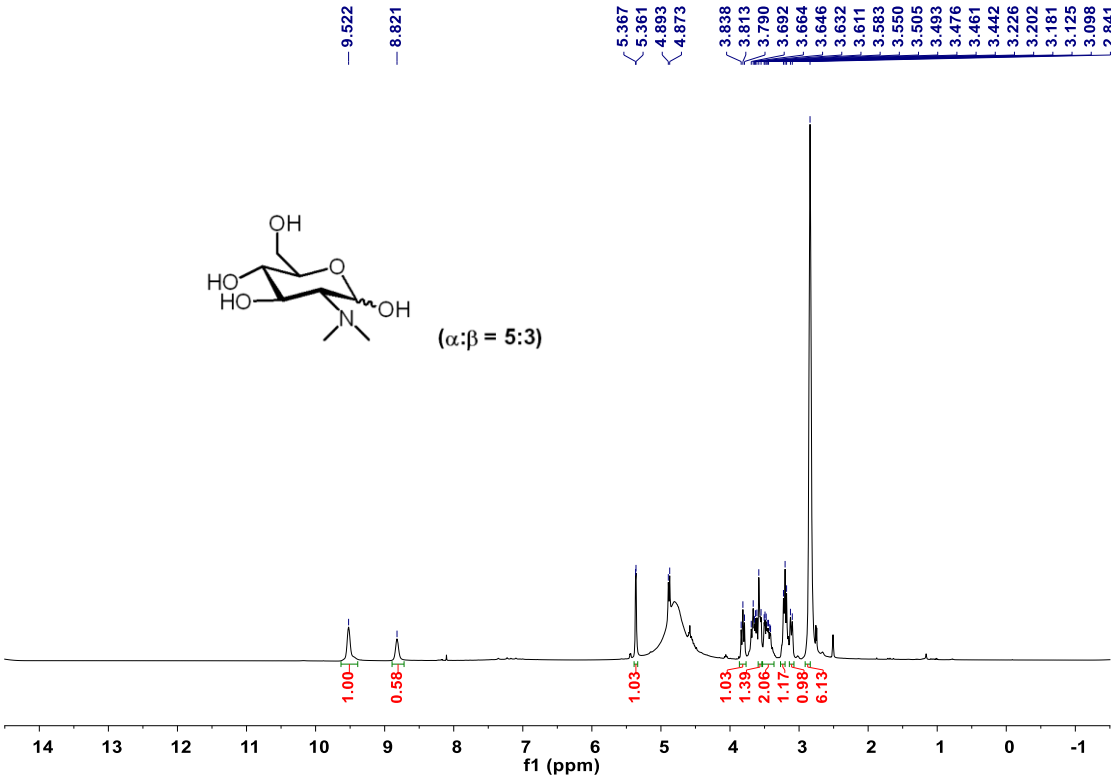


^{13}C NMR (101 MHz, DMSO-d_6)

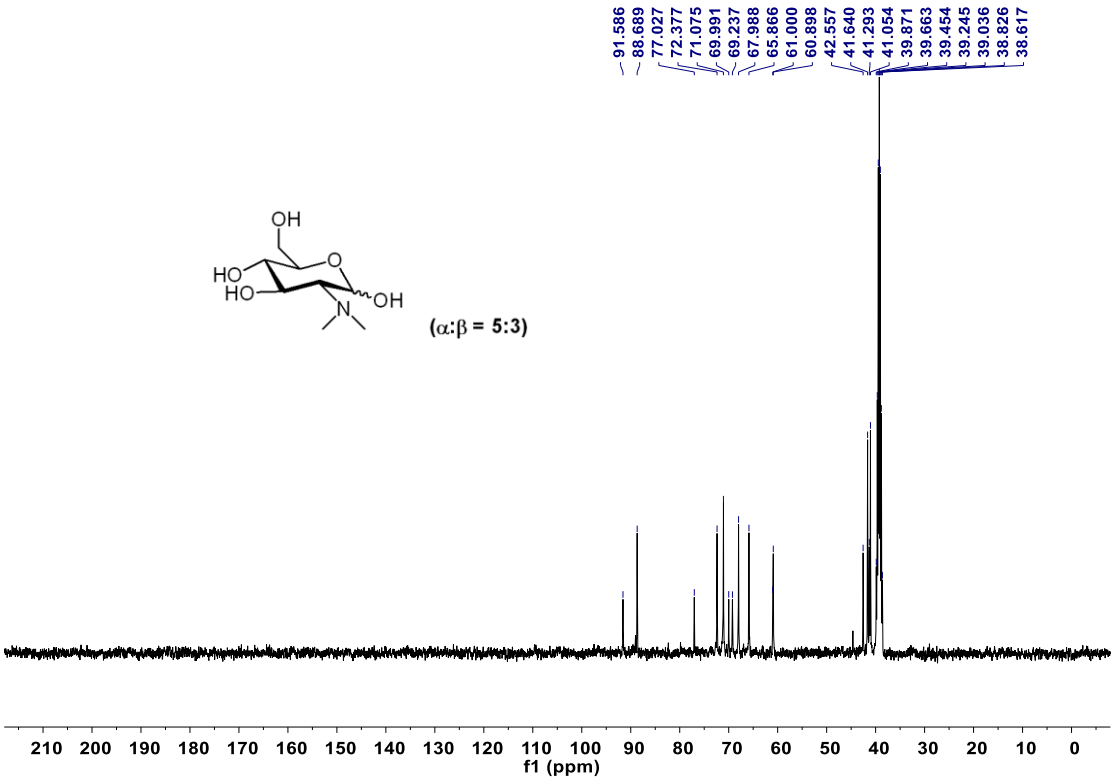


***N*,*N*-Dimethyl-*D*-glucosamine (4ah)**

^{1}H NMR (400 MHz, DMSO-d_6)

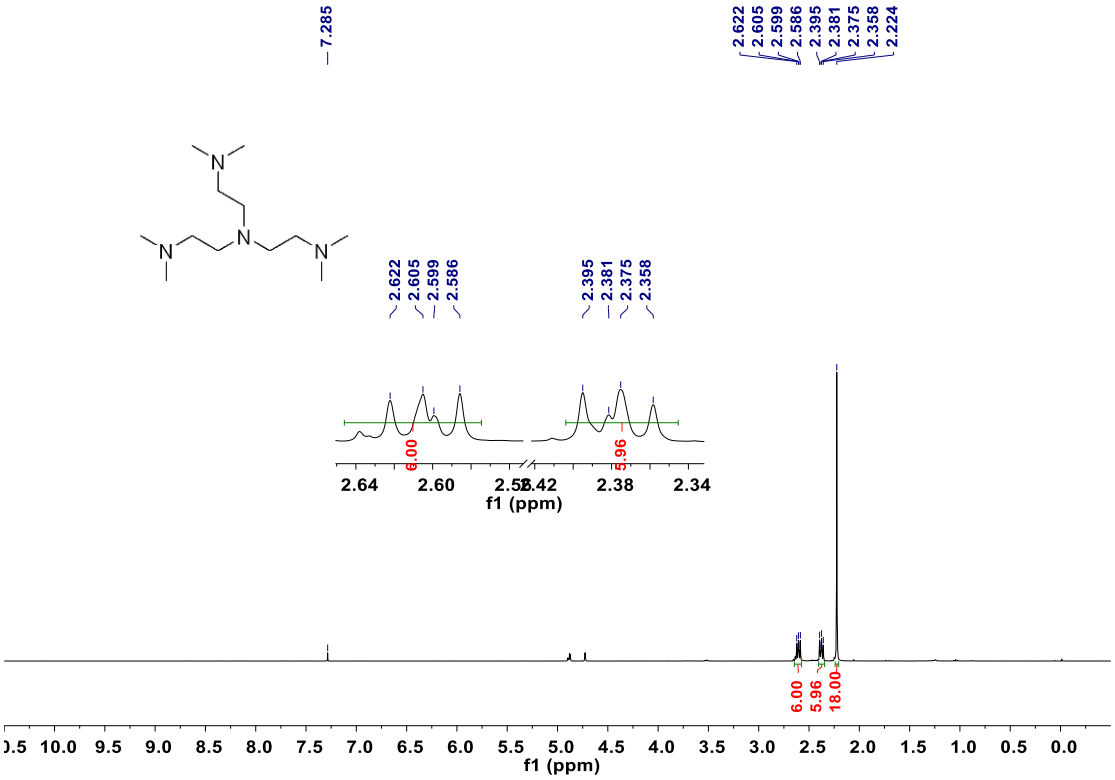


^{13}C NMR (101 MHz, DMSO-d_6)

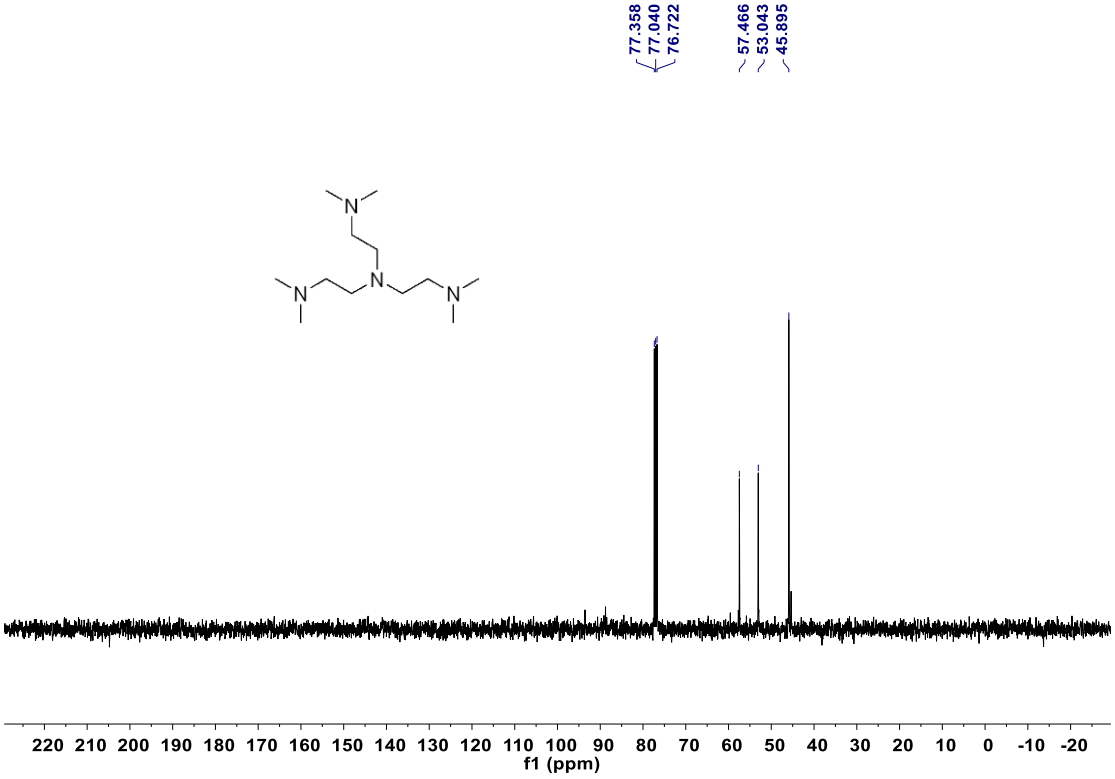


***N1*,*N1*-Bis(2-(dimethylamino)ethyl)-*N2*,*N2*-dimethylethane-1,2-diamine (4ai)**

^{1}H NMR (400 MHz, $CDCl_3$)

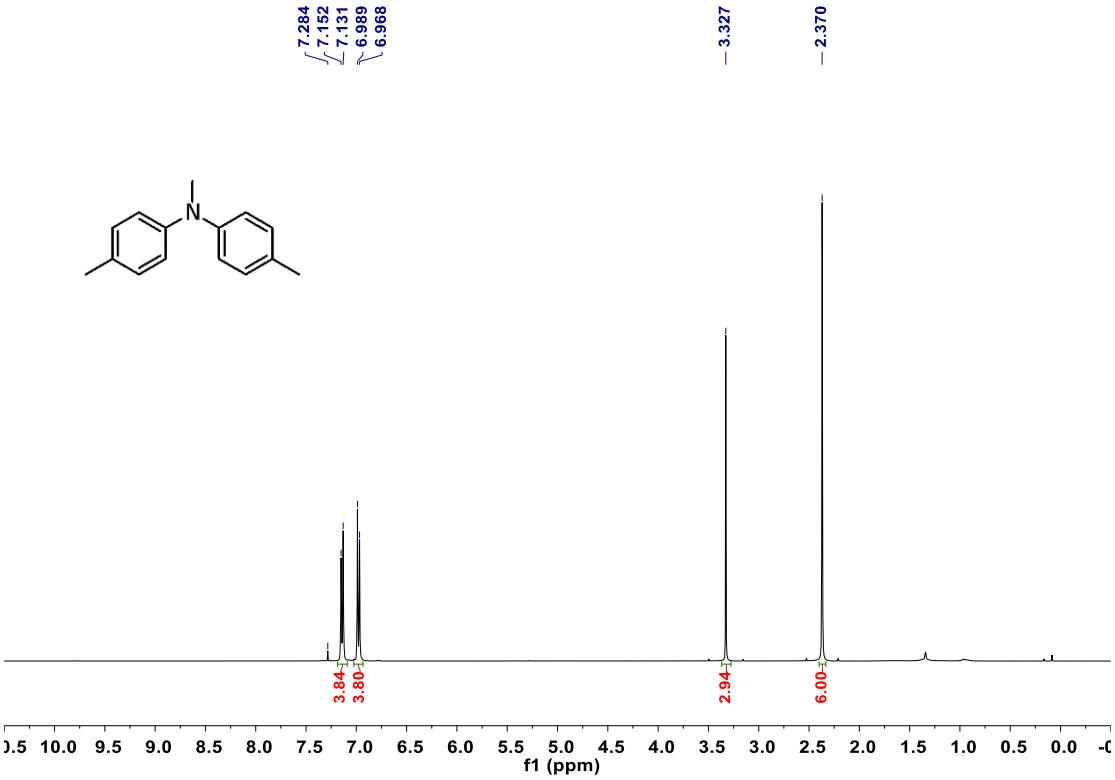


^{13}C NMR (101 MHz, $CDCl_3$)

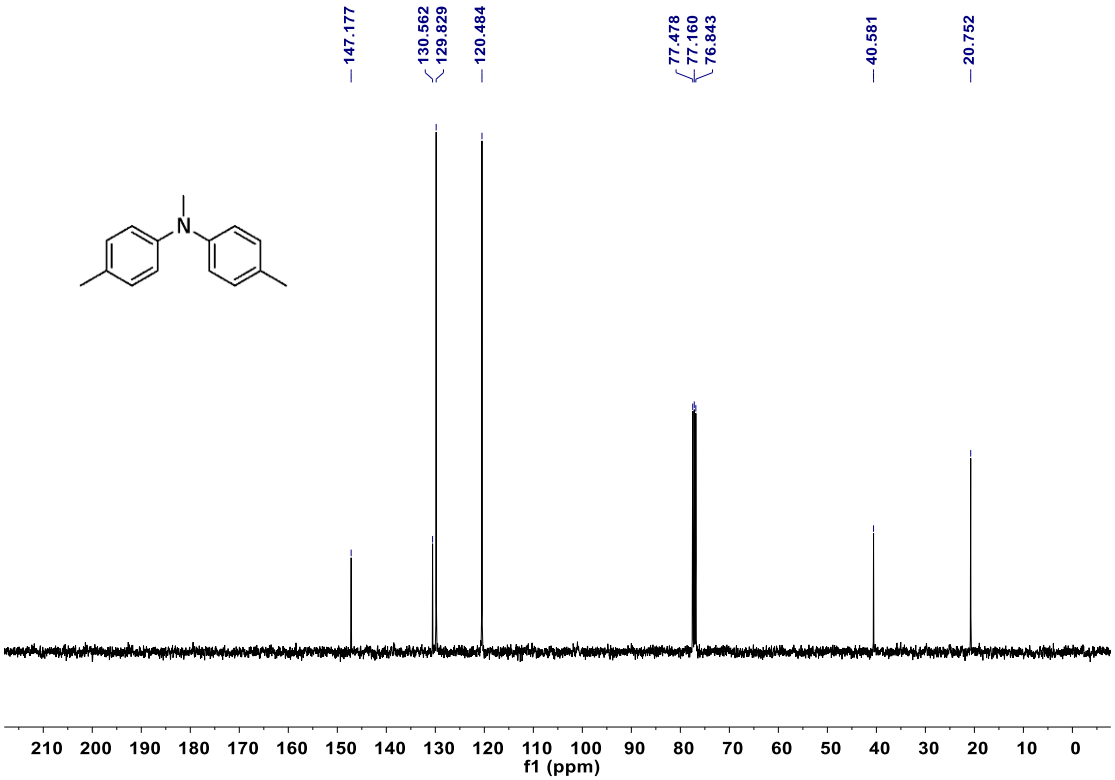


***N*,4-Dimethyl-*N*-(p-tolyl)aniline (6a)**

^{1}H NMR (400 MHz, $CDCl_3$)

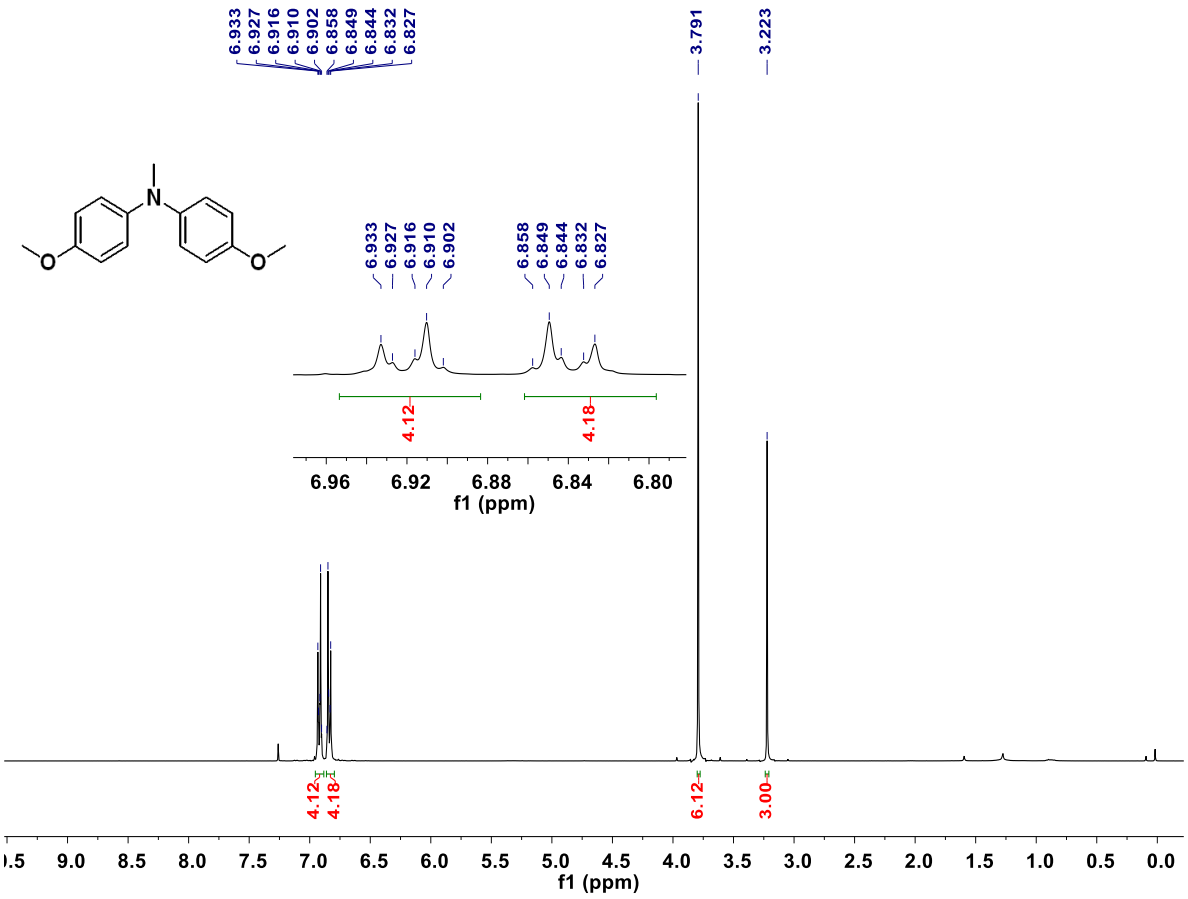


^{13}C NMR (101 MHz, $CDCl_3$)

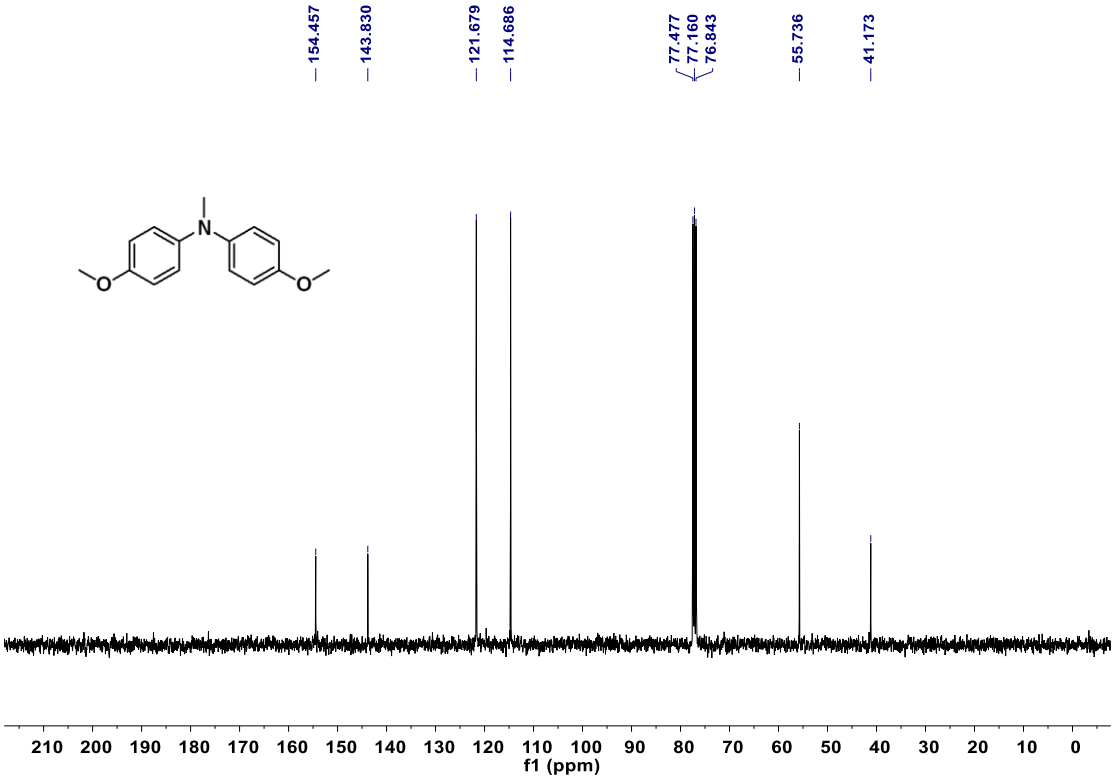


4-Methoxy-*N*-(4-methoxyphenyl)-*N*-methylaniline (6b)

^{1}H NMR (400 MHz, $CDCl_3$)

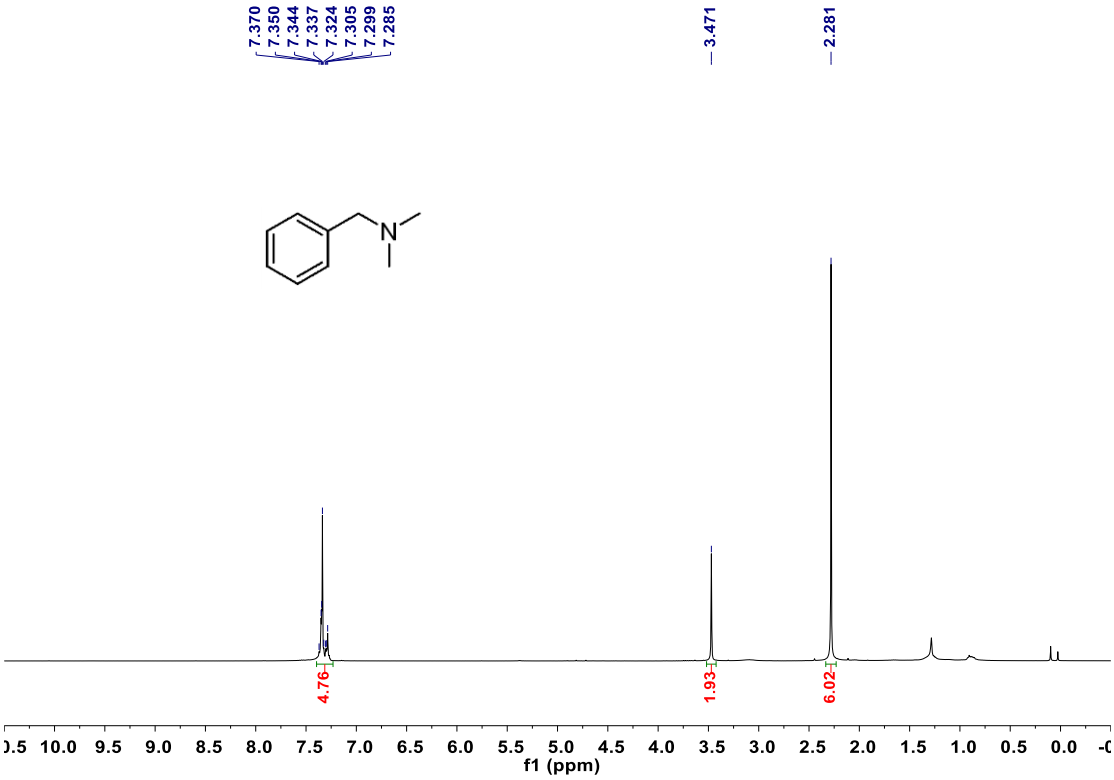


^{13}C NMR (101 MHz, $CDCl_3$)

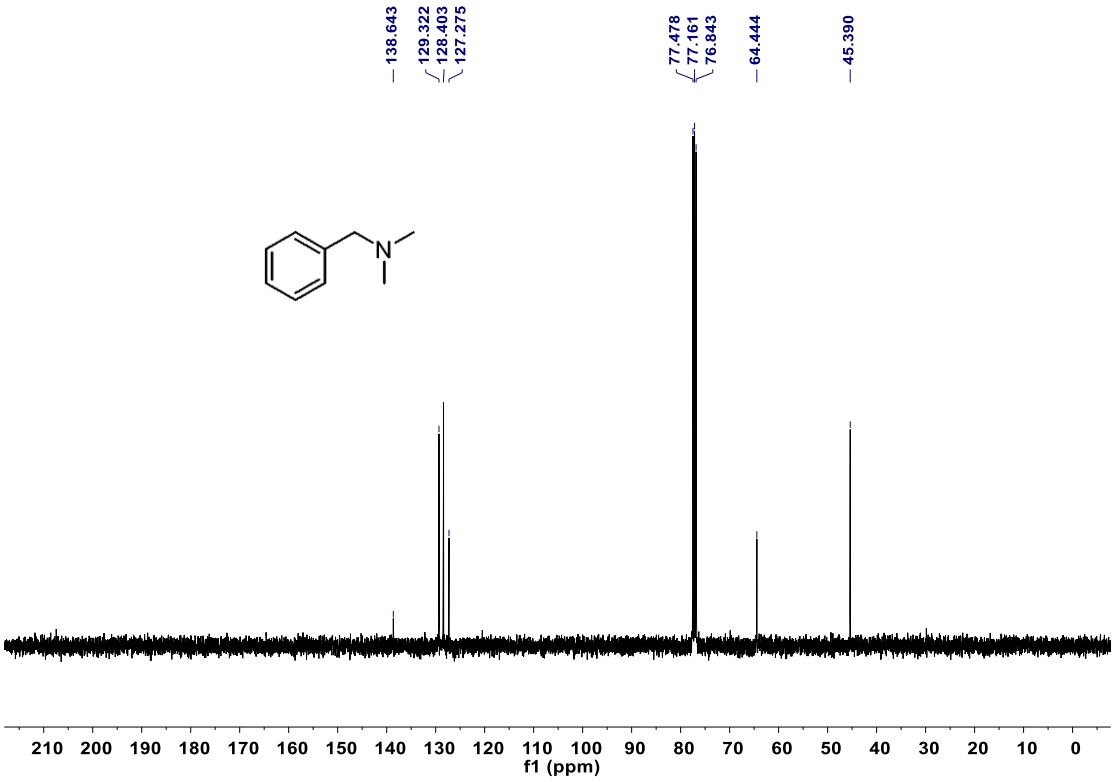


***N*,*N*-Dimethyl-1-phenylmethanamine (6c)**

^{1}H NMR (400 MHz, $CDCl_3$)

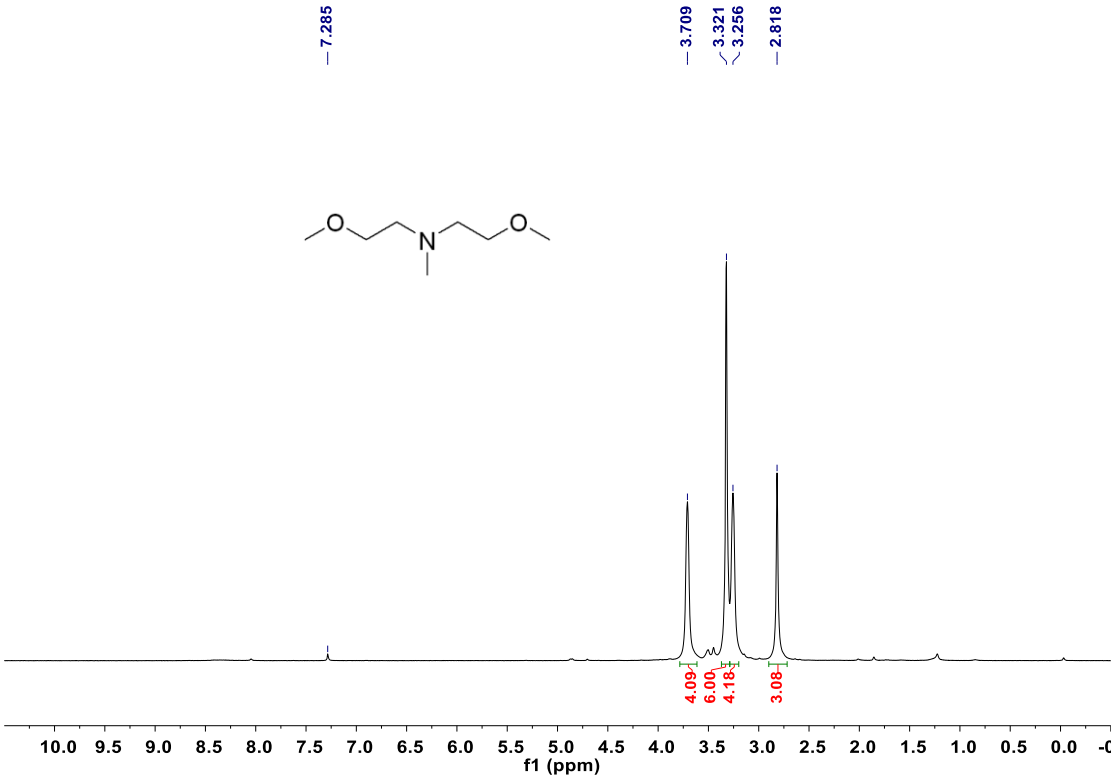


^{13}C NMR (101 MHz, $CDCl_3$)

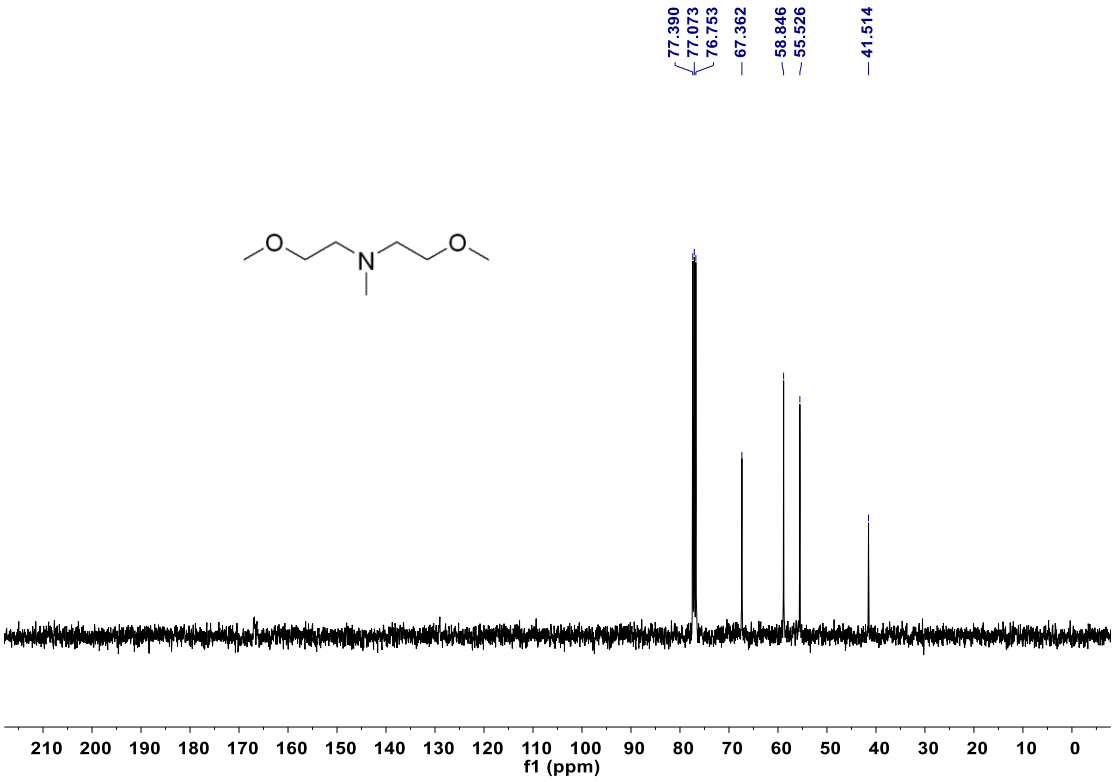


2-Methoxy-*N*-(2-methoxyethyl)-*N*-methylethan-1-amine (6d)

^{1}H NMR (400 MHz, $CDCl_3$)

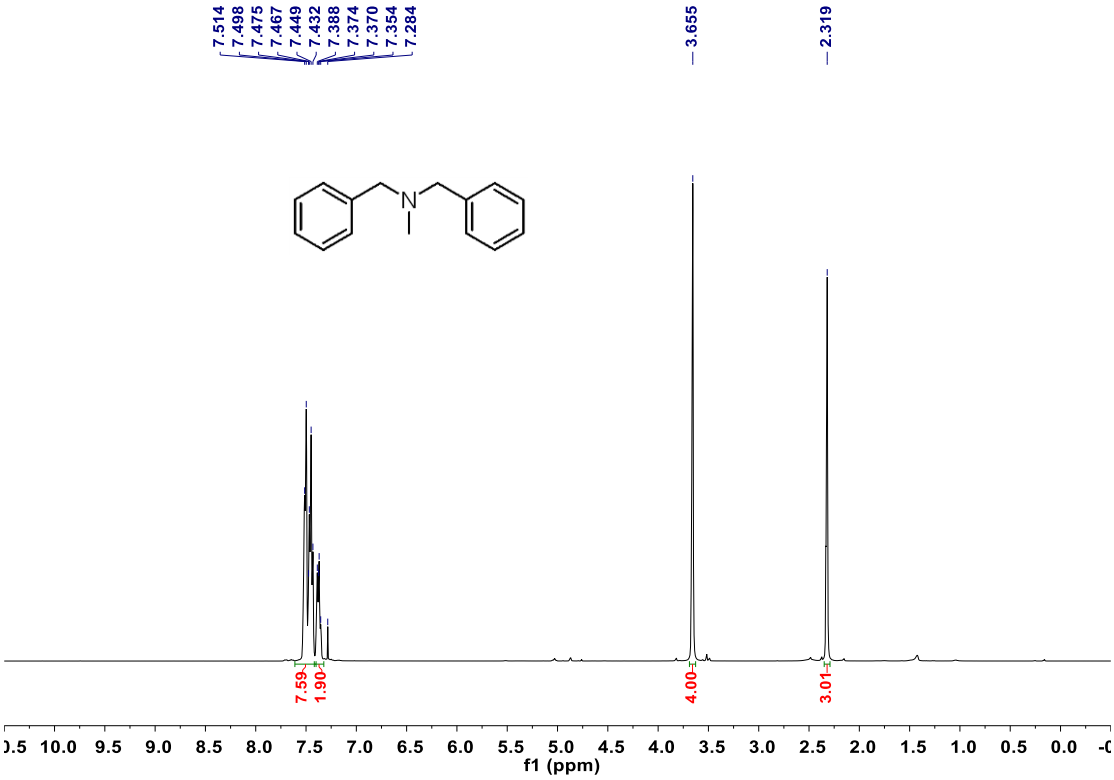


^{13}C NMR (101 MHz, $CDCl_3$)

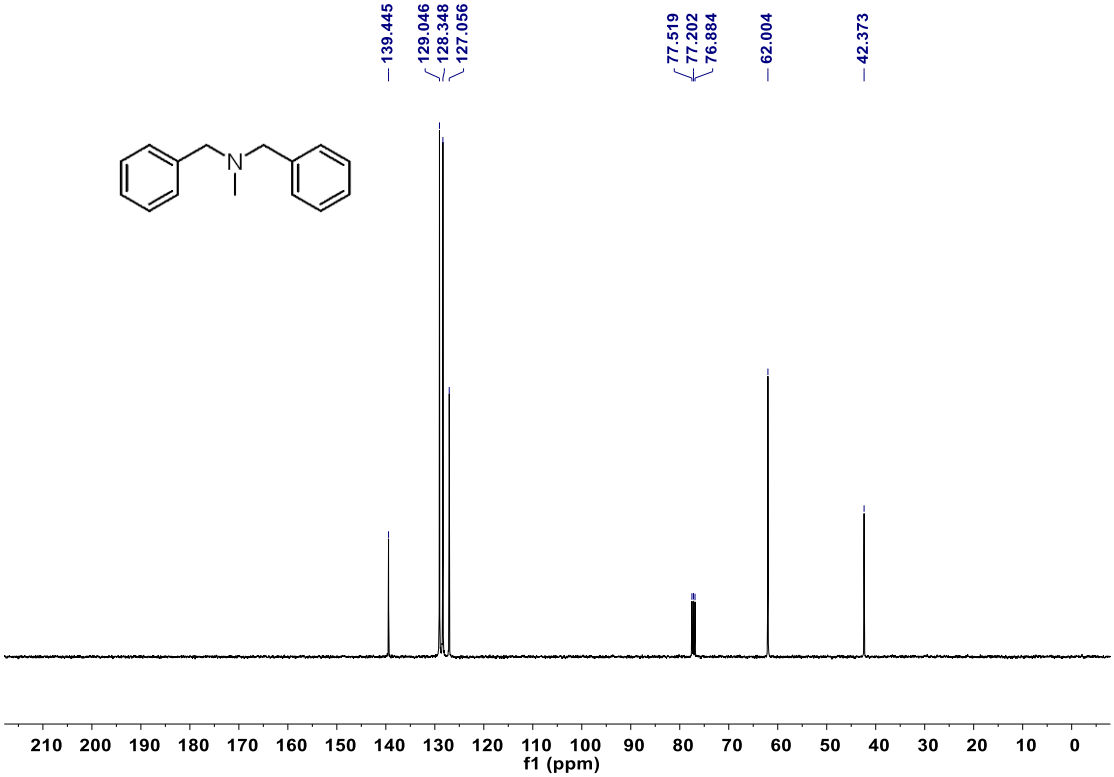


***N*-Benzyl-*N*-methyl-1-phenylmethanamine (6e)**

^{1}H NMR (400 MHz, $CDCl_3$)

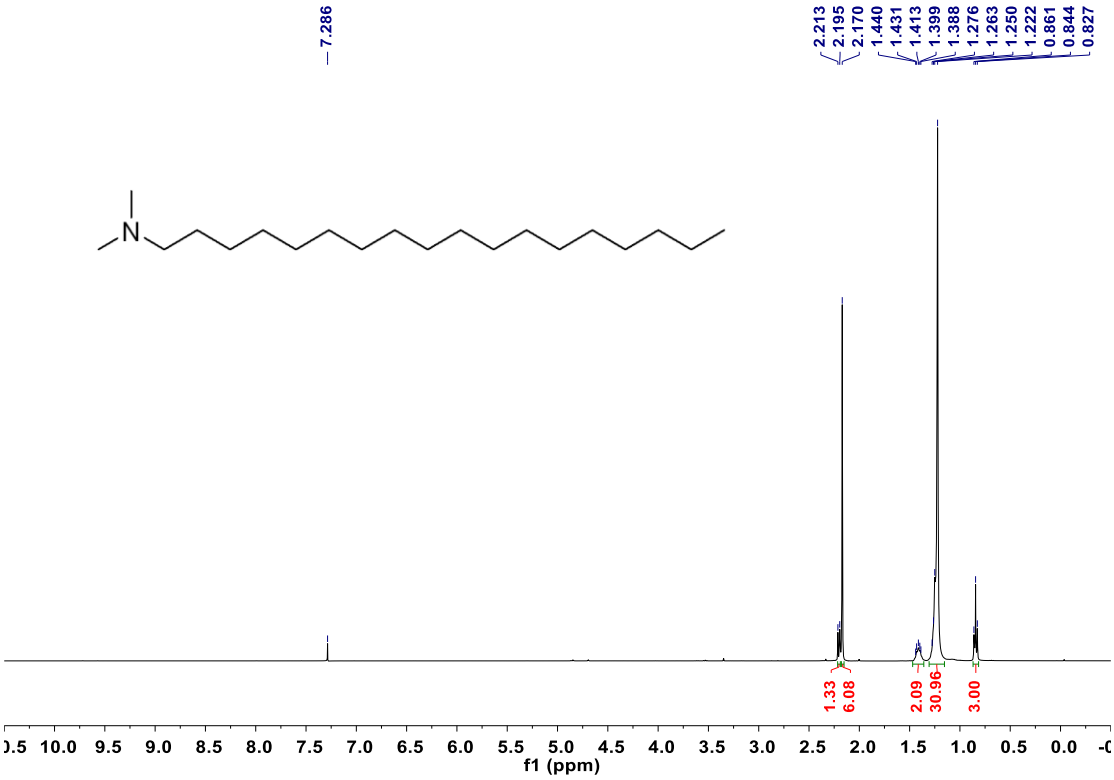


^{13}C NMR (101 MHz, $CDCl_3$)

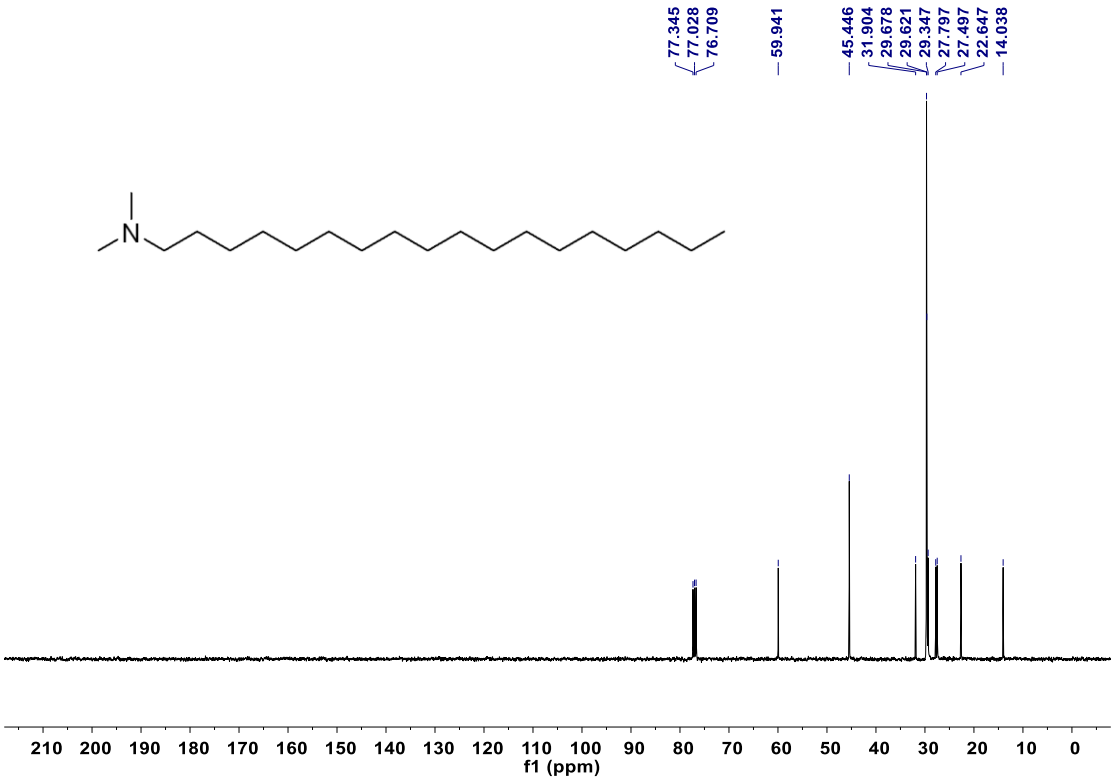


***N*,*N*-Dimethyloctadecan-1-amine (6f)**

^{1}H NMR (400 MHz, $CDCl_3$)

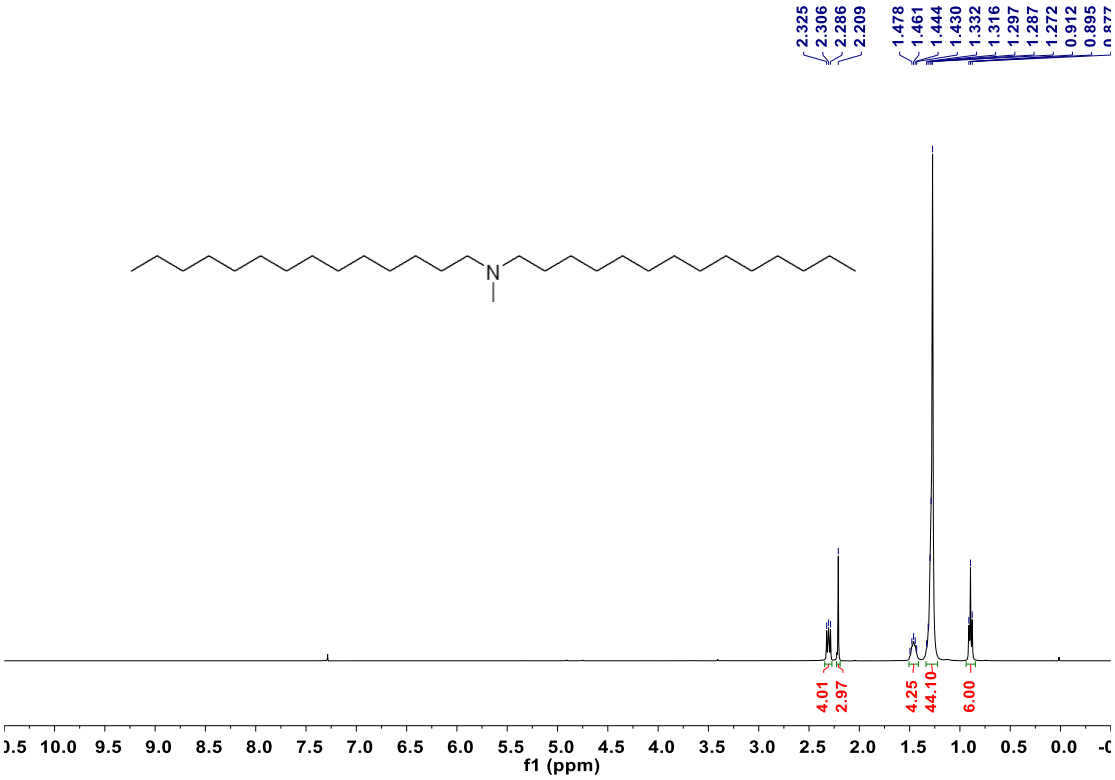


^{13}C NMR (101 MHz, $CDCl_3$)

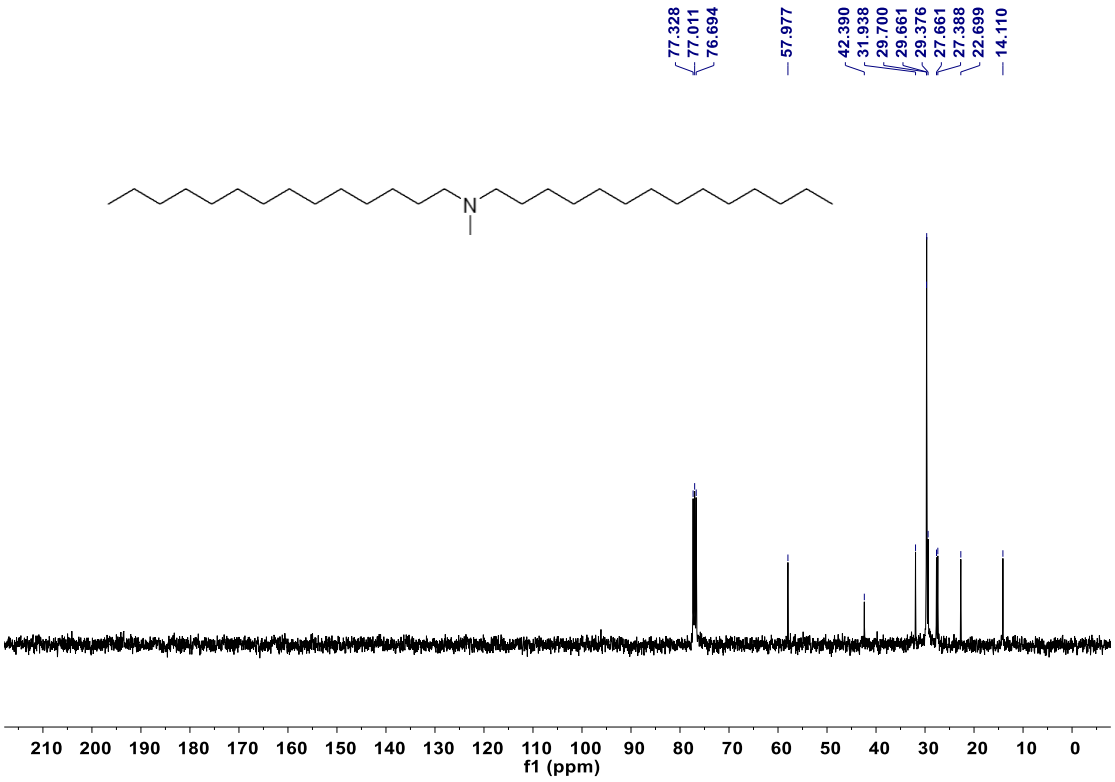


***N*-Methyl-*N*-tetradecyltetradecan-1-amine (6g)**

^{1}H NMR (400 MHz, $CDCl_3$)

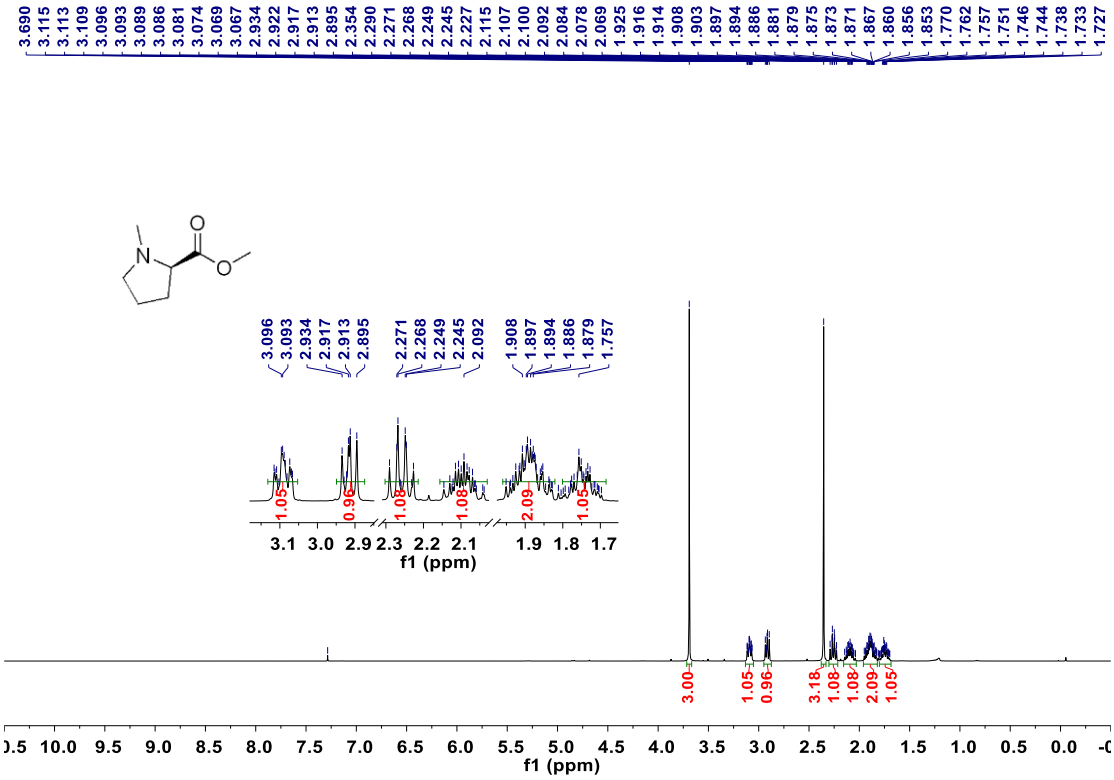


^{13}C NMR (101 MHz, $CDCl_3$)

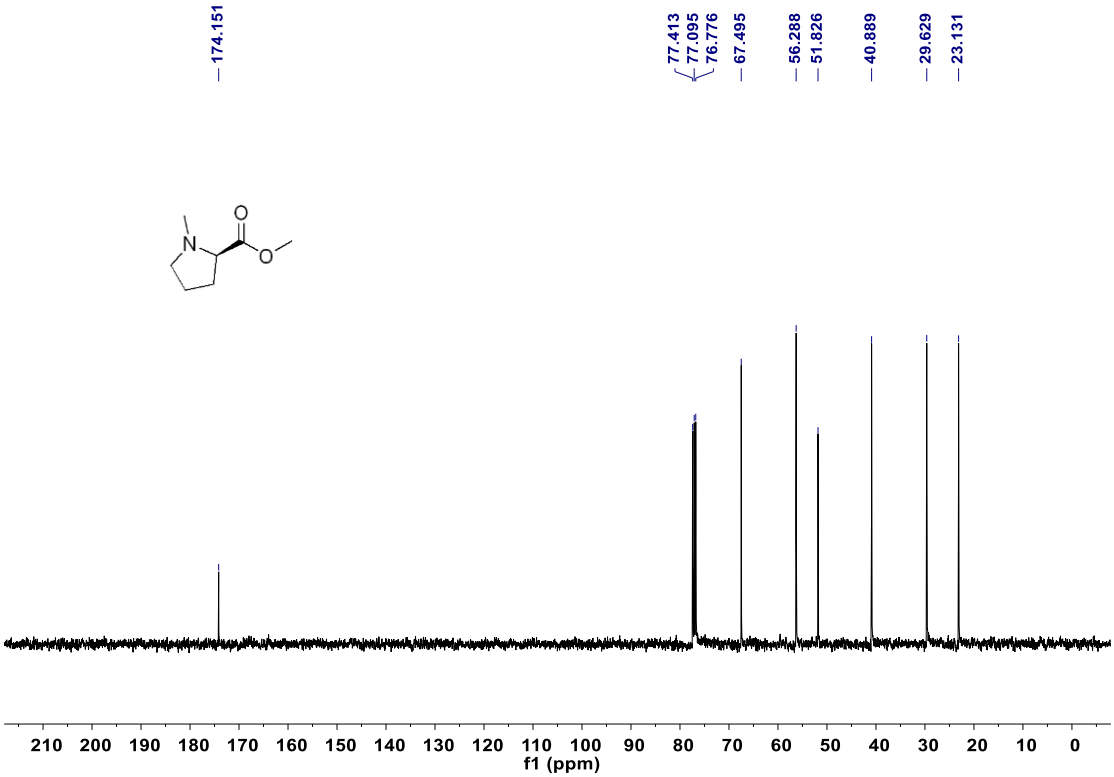


Methyl methyl-*D*-prolinate (6h)

^{1}H NMR (400 MHz, $CDCl_3$)

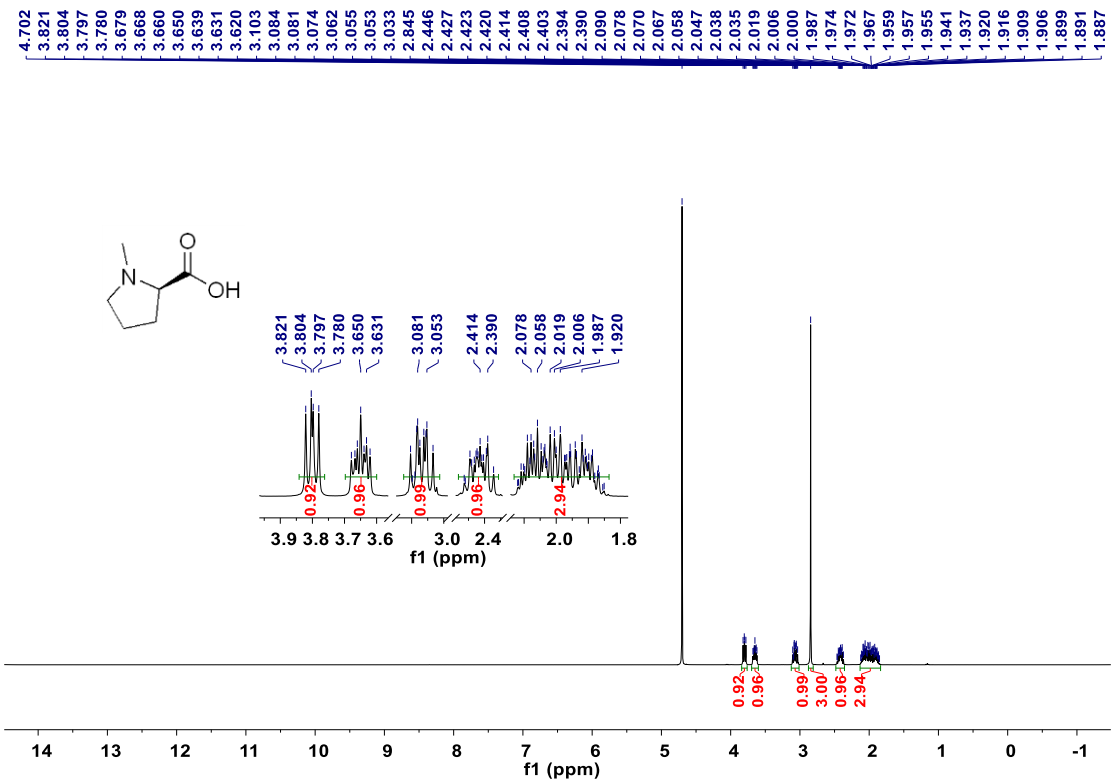


^{13}C NMR (101 MHz, $CDCl_3$)

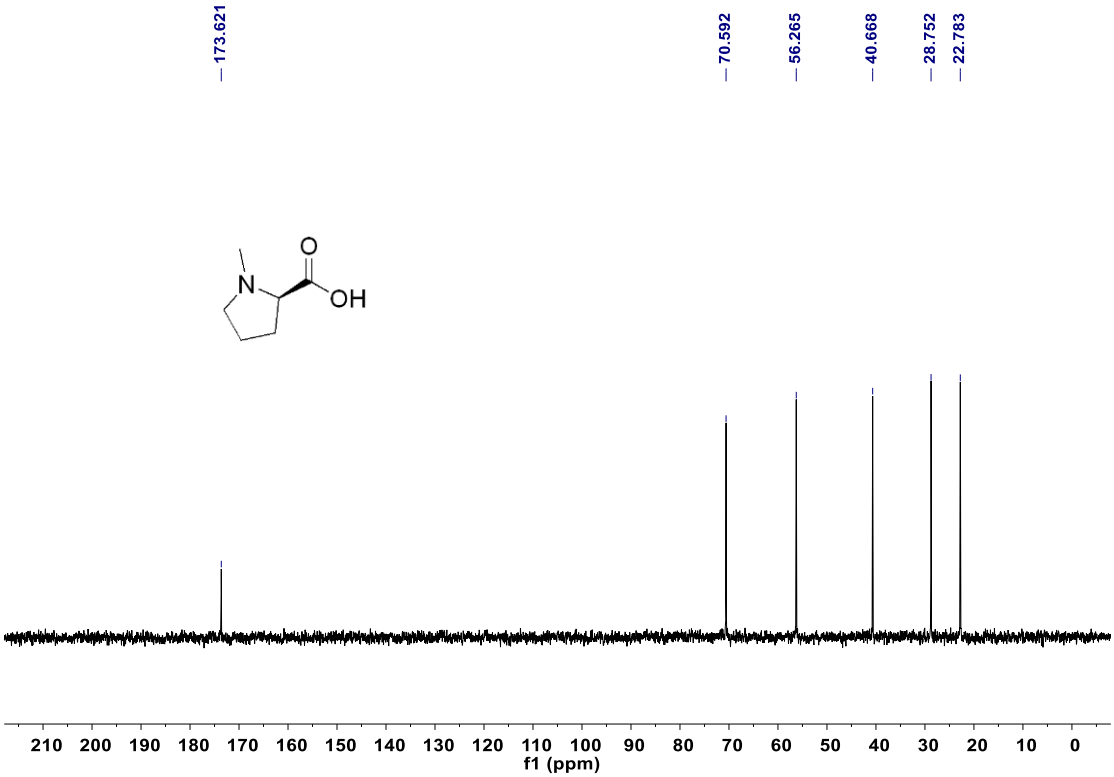


Methyl-*D*-proline (6i)

^{1}H NMR (400 MHz, D_2O)

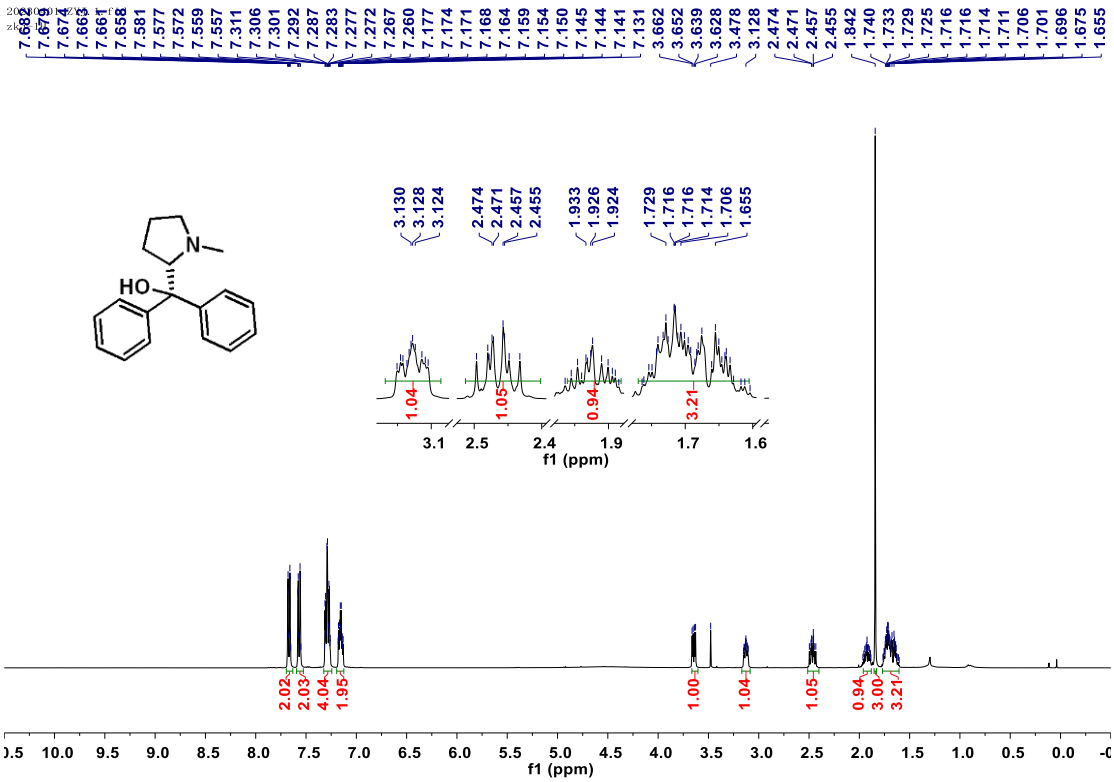


^{13}C NMR (101 MHz, D_2O)

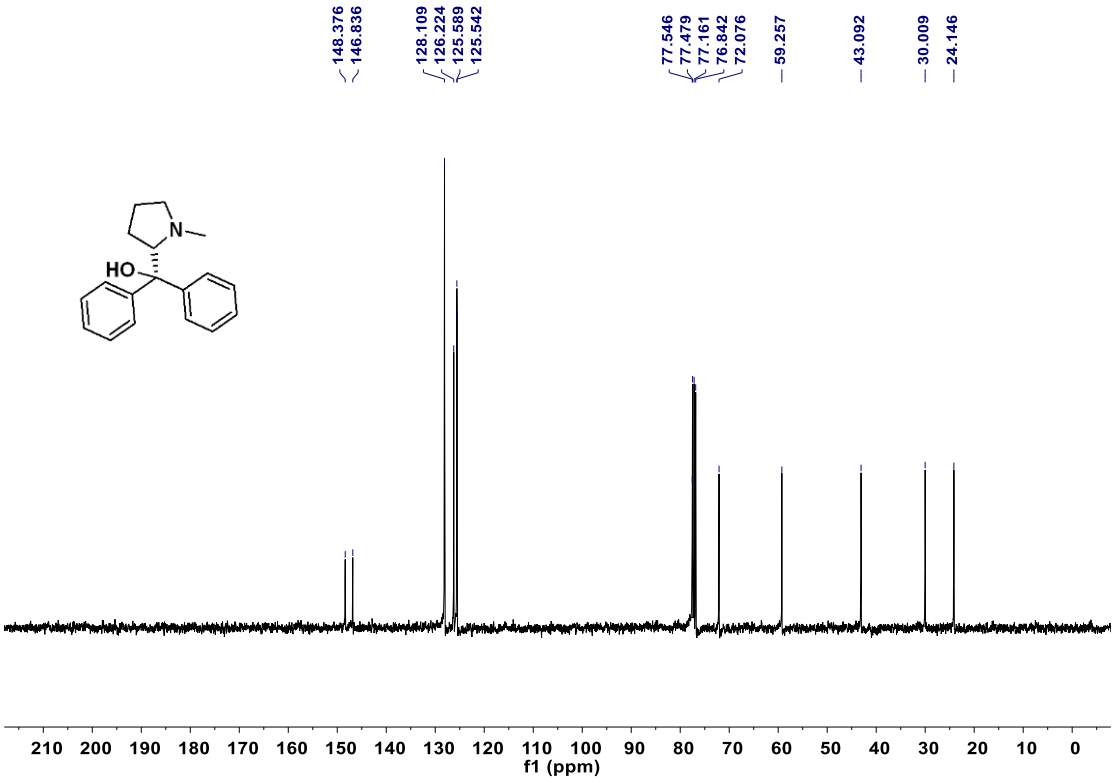


(*R*)-(1-Methylpyrrolidin-2-yl)diphenylmethanol (6j)

^{1}H NMR (400 MHz, $CDCl_3$)

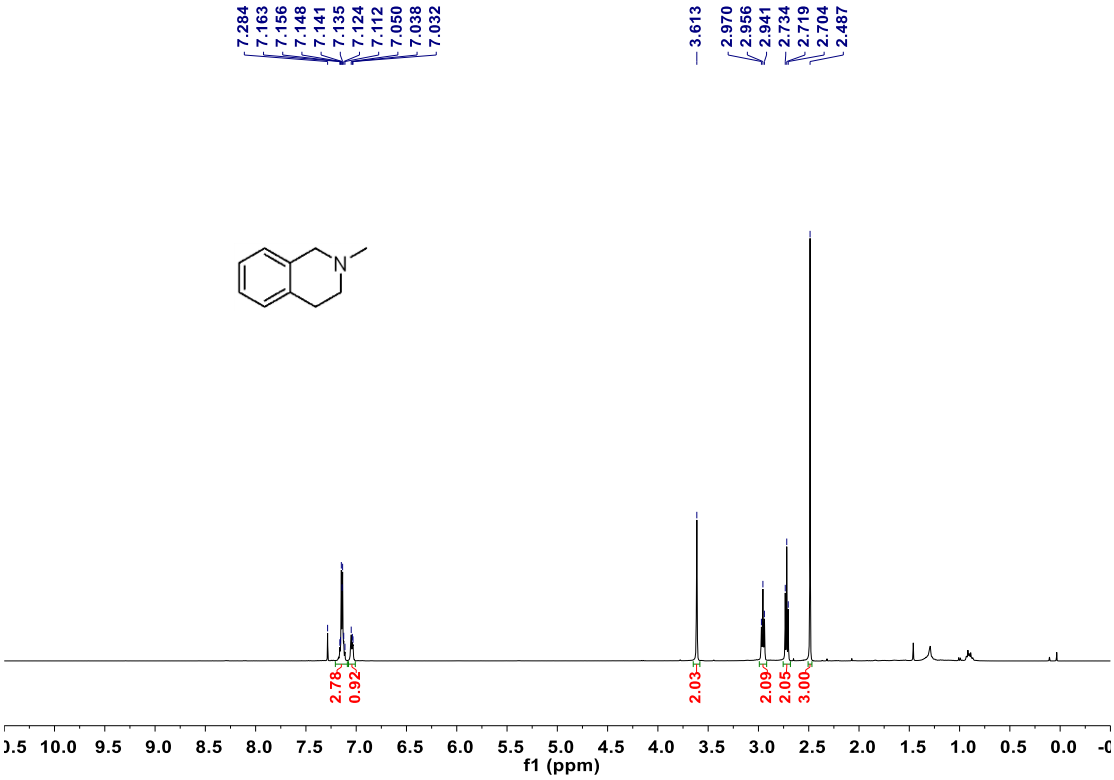


^{13}C NMR (101 MHz, $CDCl_3$)

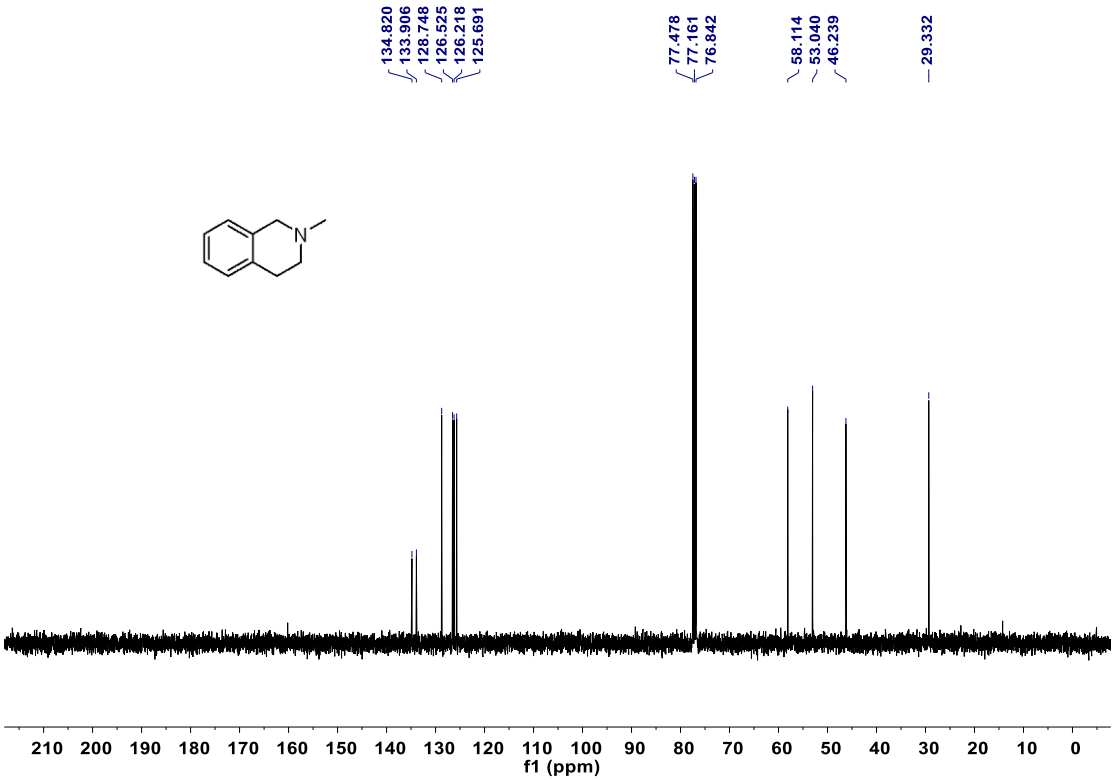


2-Methyl-1,2,3,4-tetrahydroisoquinoline (6k)

^{1}H NMR (400 MHz, $CDCl_3$)

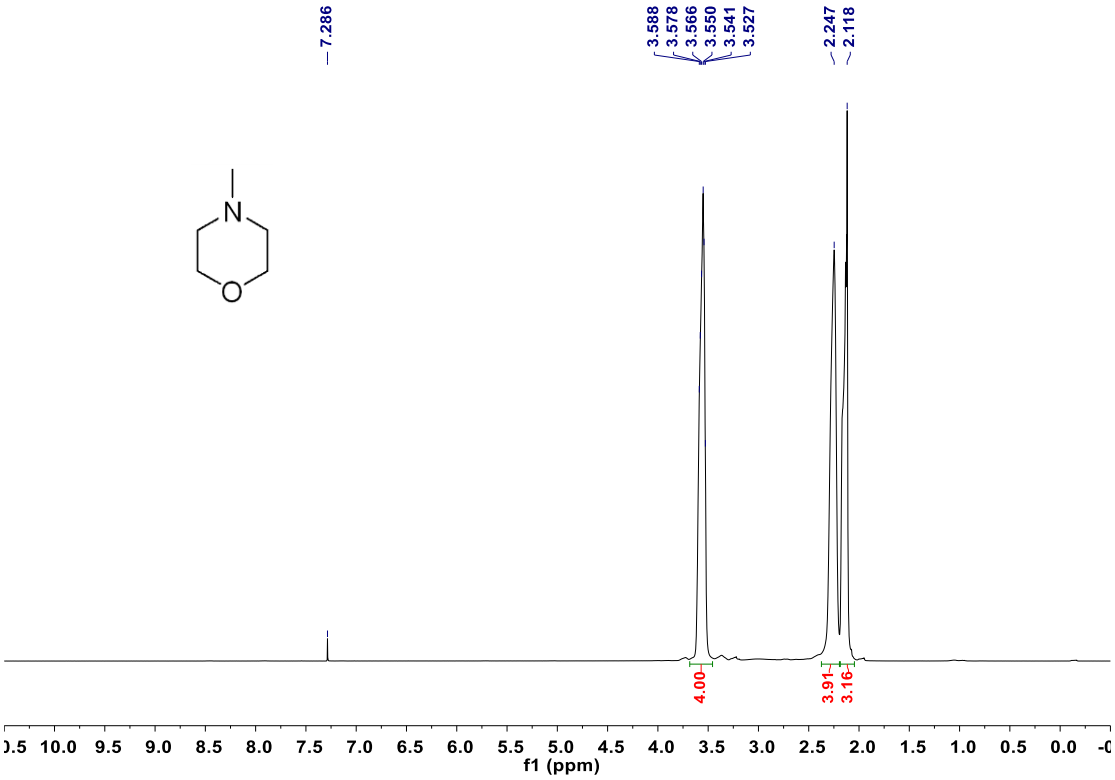


^{13}C NMR (101 MHz, $CDCl_3$)

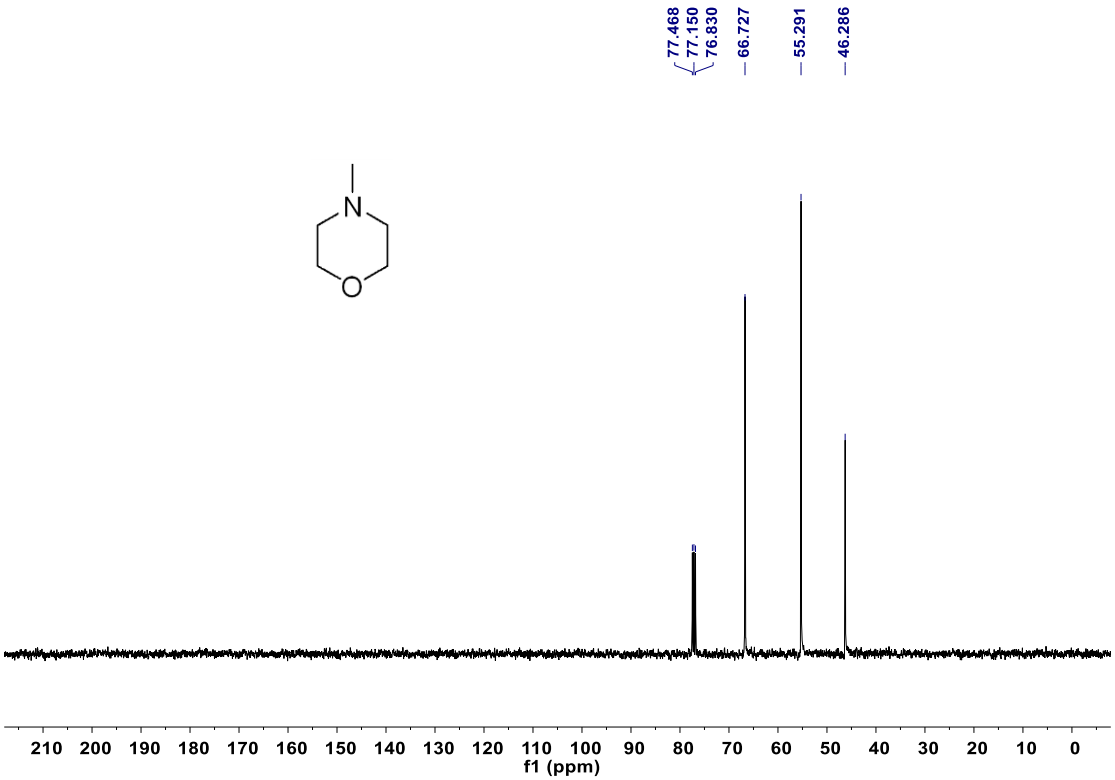


4-Methylmorpholine (6l)

^{1}H NMR (400 MHz, $CDCl_3$)

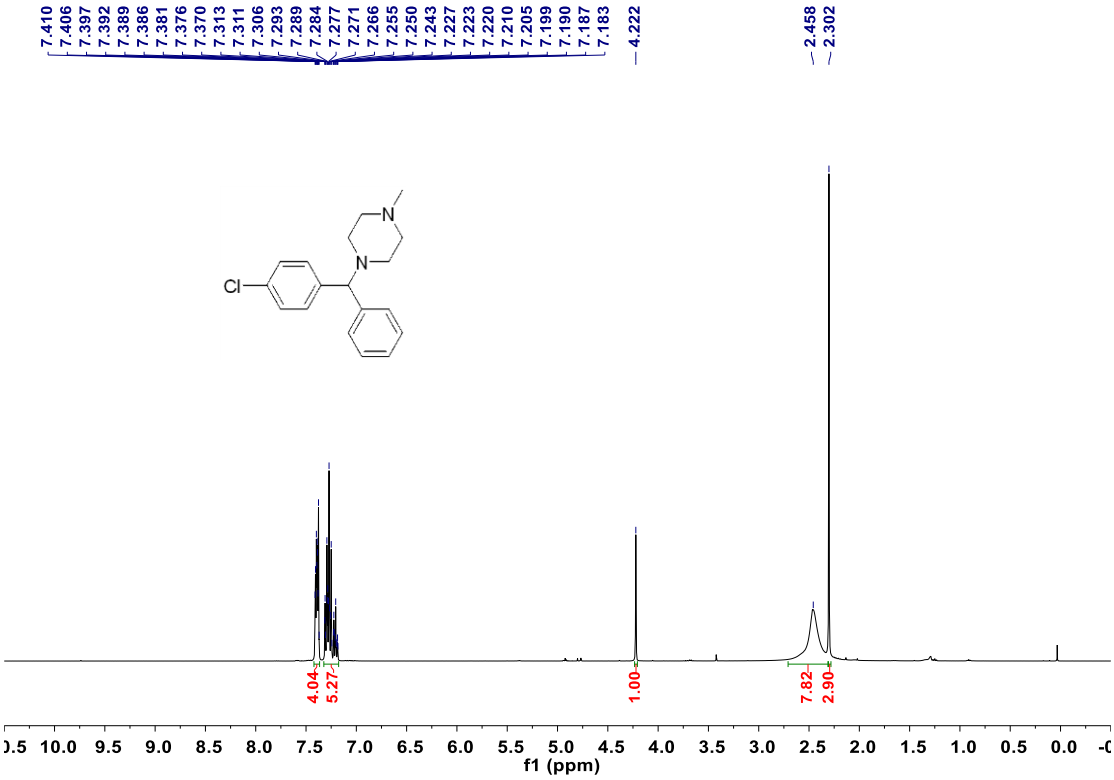


^{13}C NMR (101 MHz, $CDCl_3$)

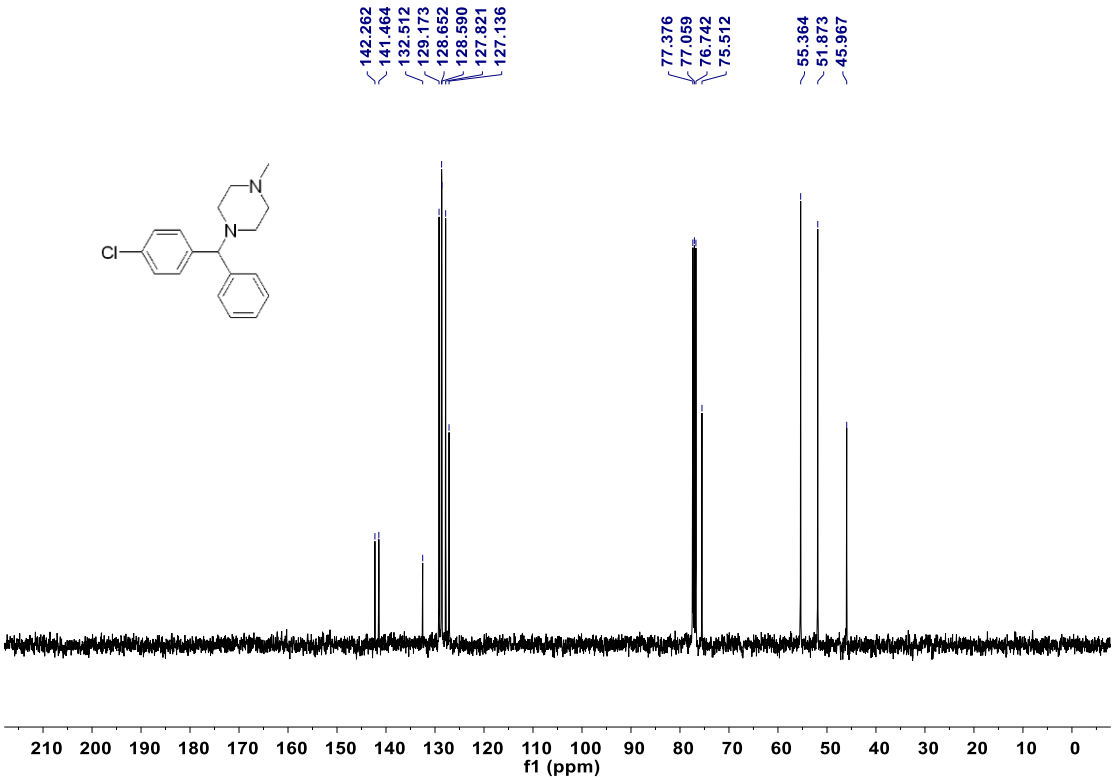


4-((4-Chlorophenyl)(phenyl)methyl)-1-methylpiperidine (6m)

^{1}H NMR (400 MHz, $CDCl_3$)

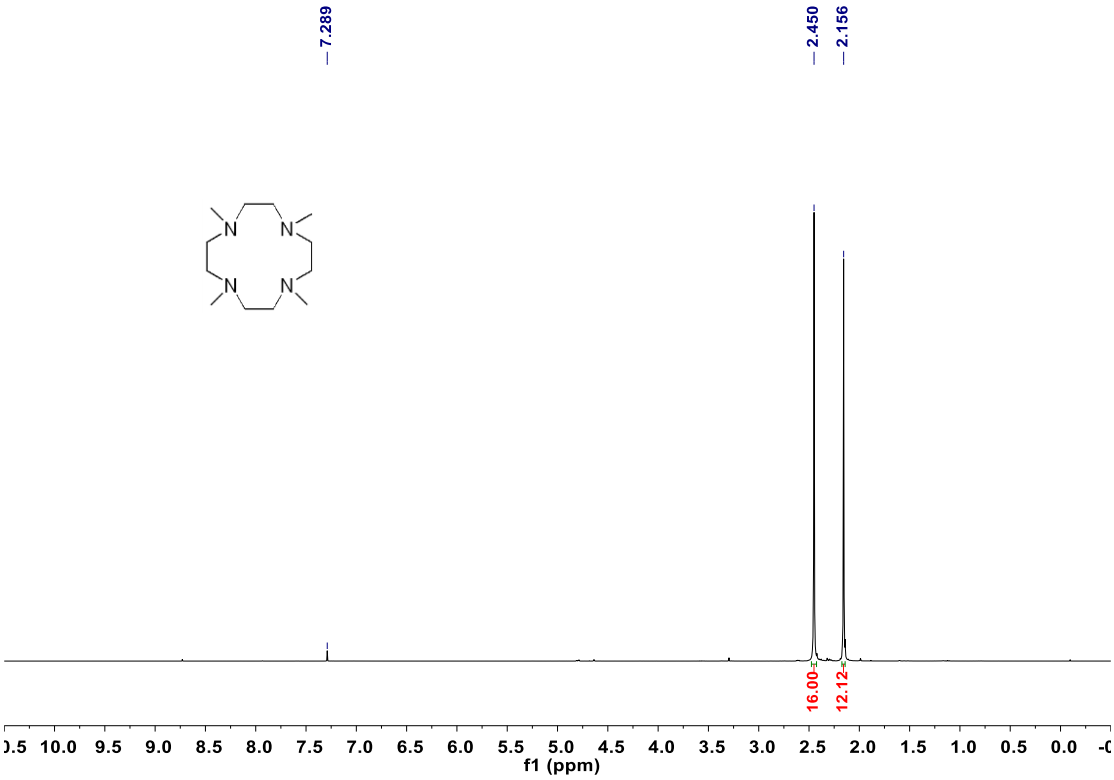


^{13}C NMR (101 MHz, $CDCl_3$)

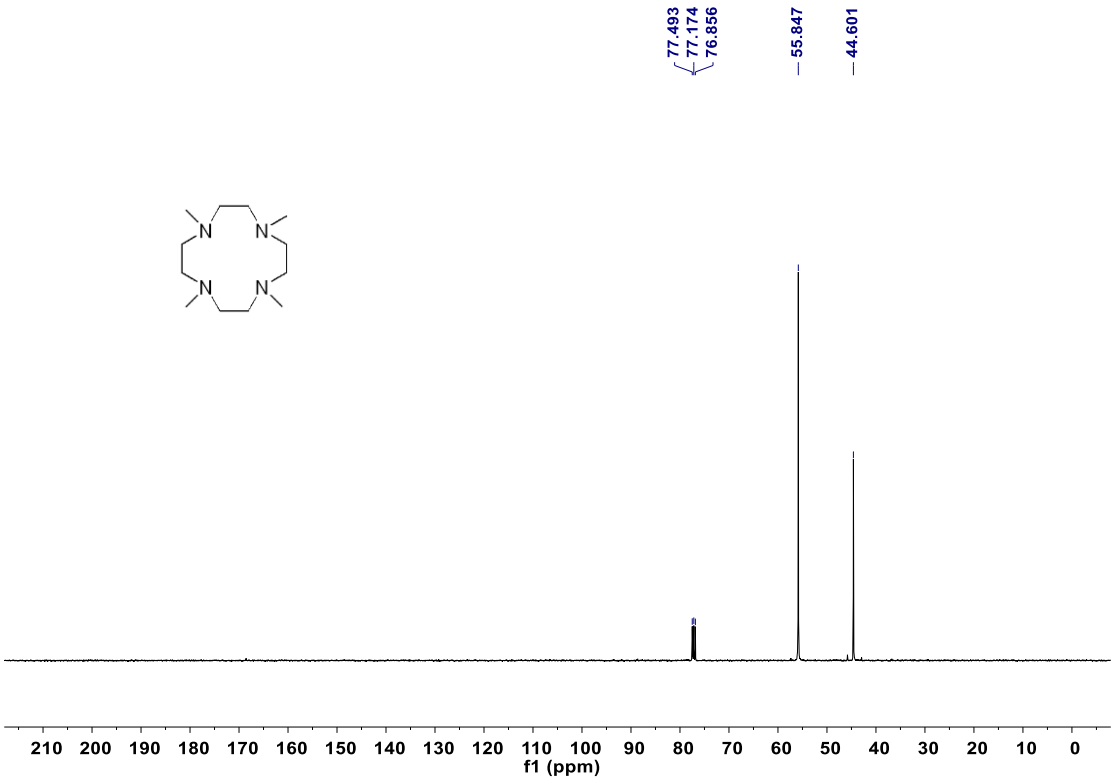


1,4,7,10-Tetramethyl-1,4,7,10-tetraazacyclododecane (6n)

^{1}H NMR (400 MHz, $CDCl_3$)

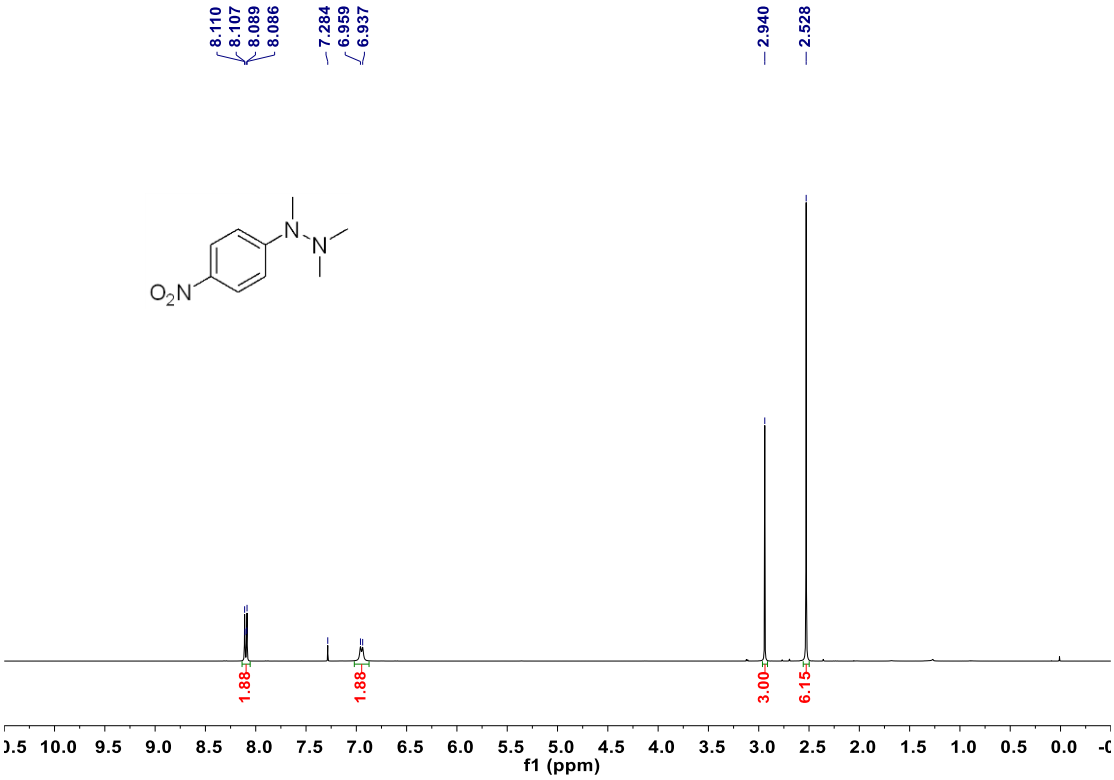


^{13}C NMR (101 MHz, $CDCl_3$)

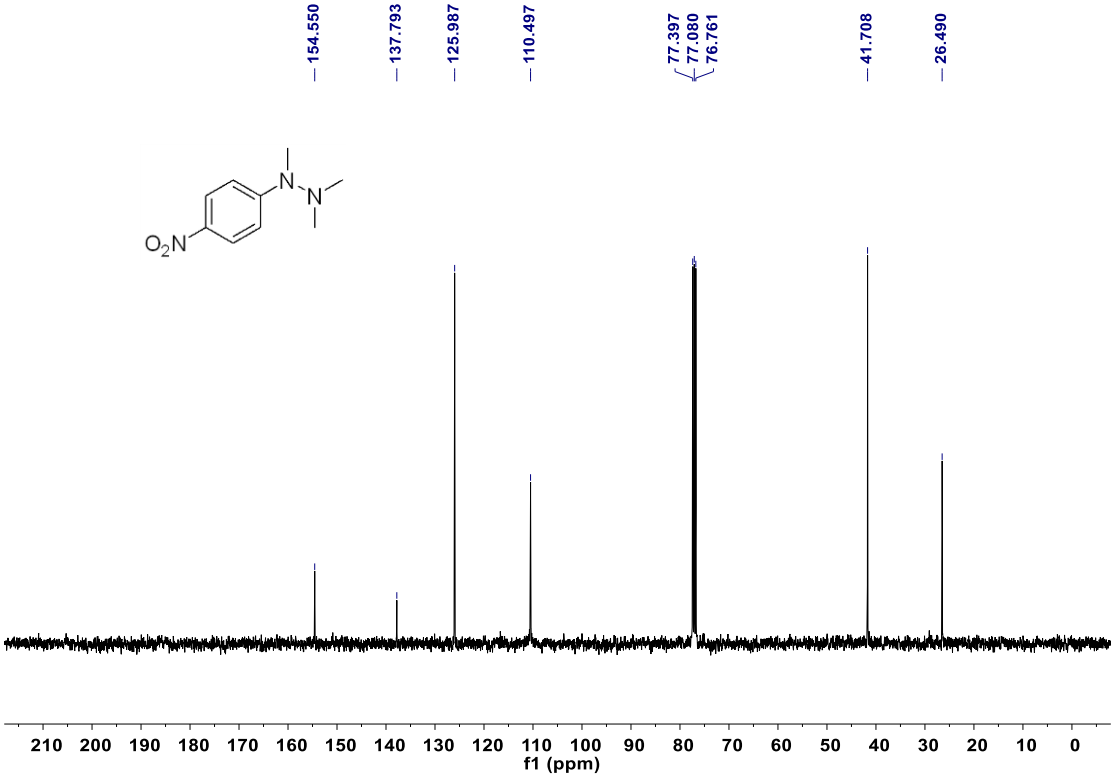


1,1,2-Trimethyl-2-(4-nitrophenyl)hydrazine (6o)

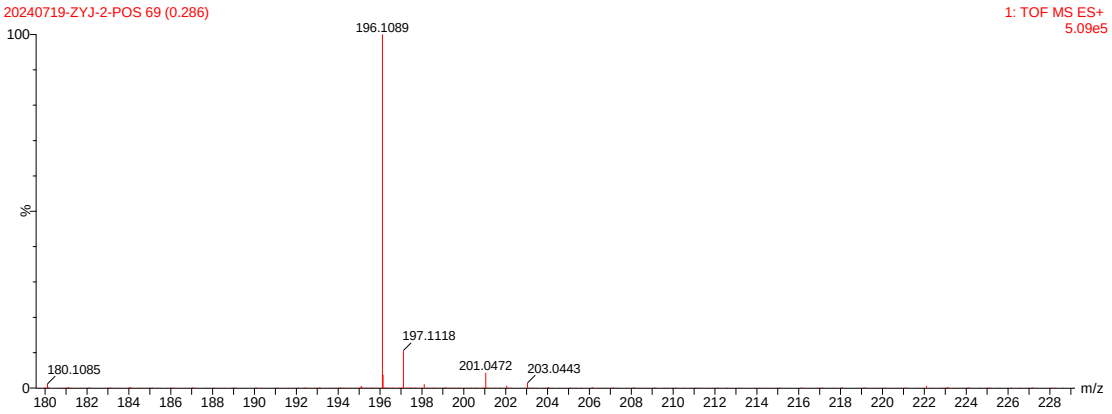
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

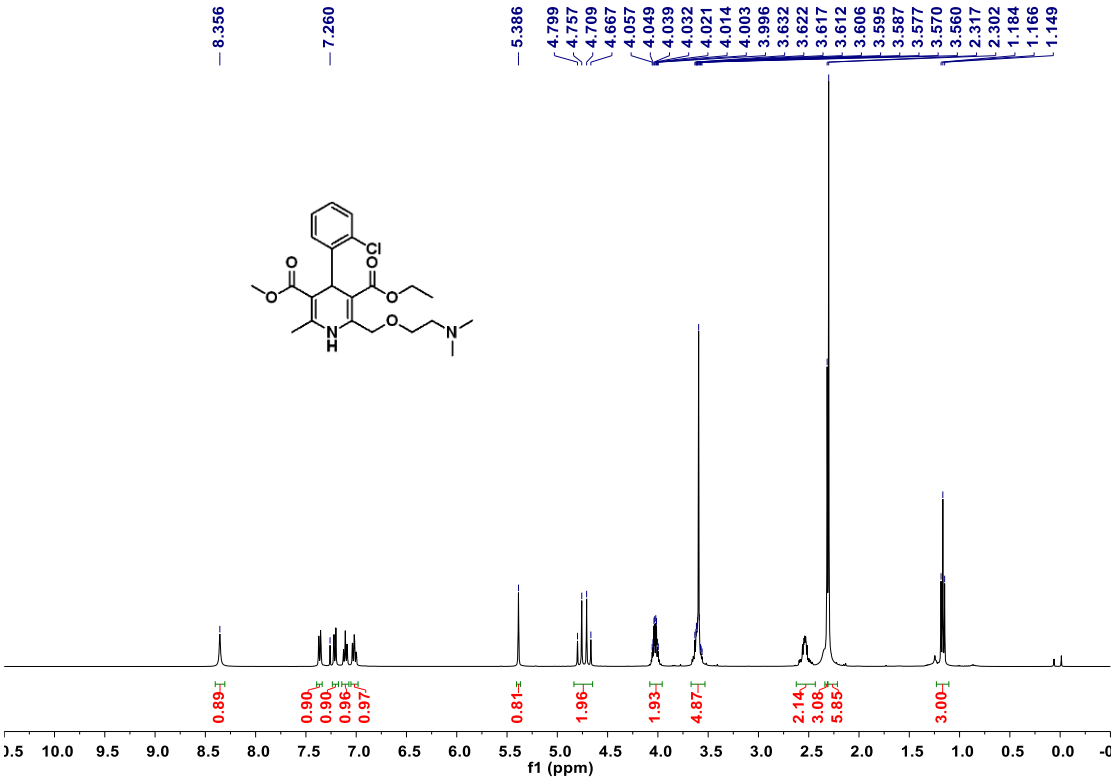


HRMS (ESI): ***m/z*** **calcd for : $C_9H_{14}N_3O_2^+$ $[M+H]^+$: 196.1081, found: 196.1089**

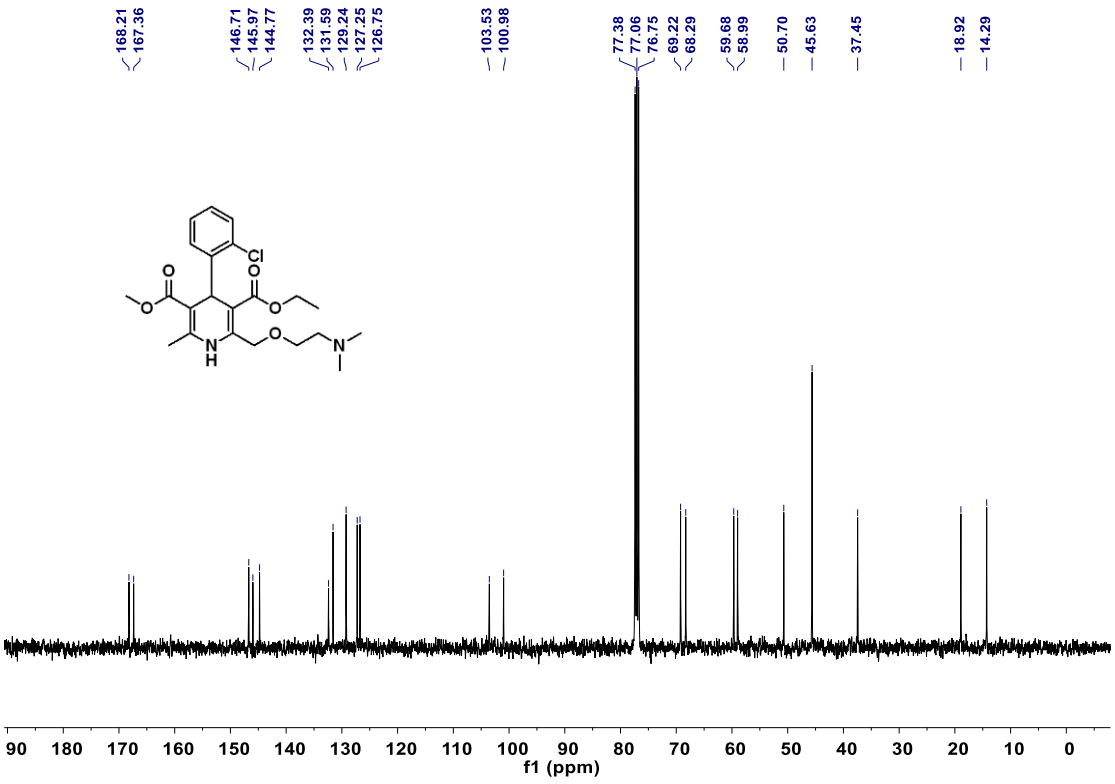


3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(dimethylamino)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a)

^{1}H NMR (400 MHz, $CDCl_3$)

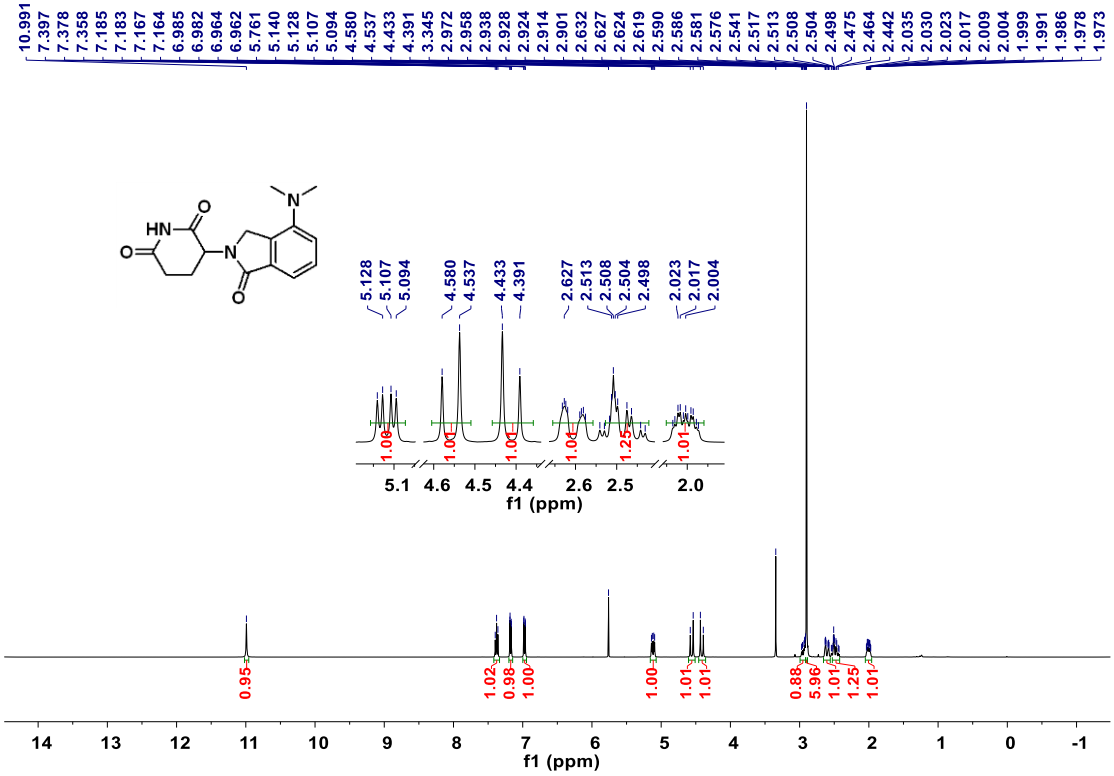


^{13}C NMR (101 MHz, $CDCl_3$)

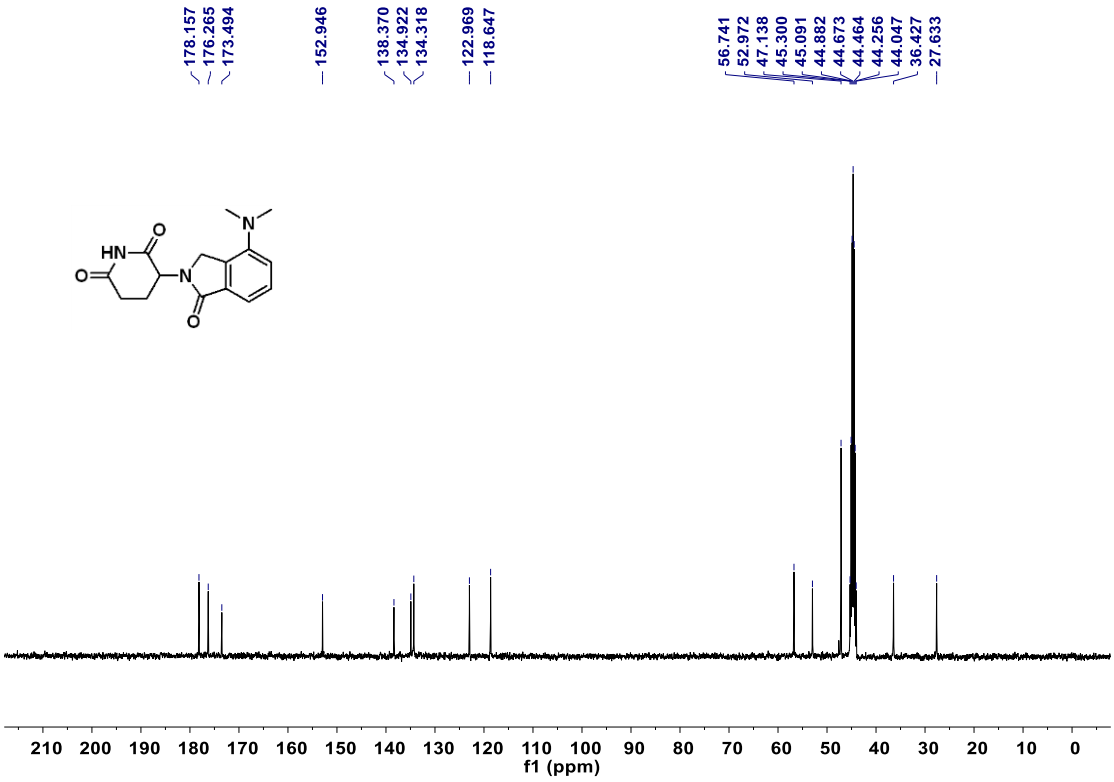


3-(4-(Dimethylamino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b)

^{1}H NMR (400 MHz, DMSO-d^{6})

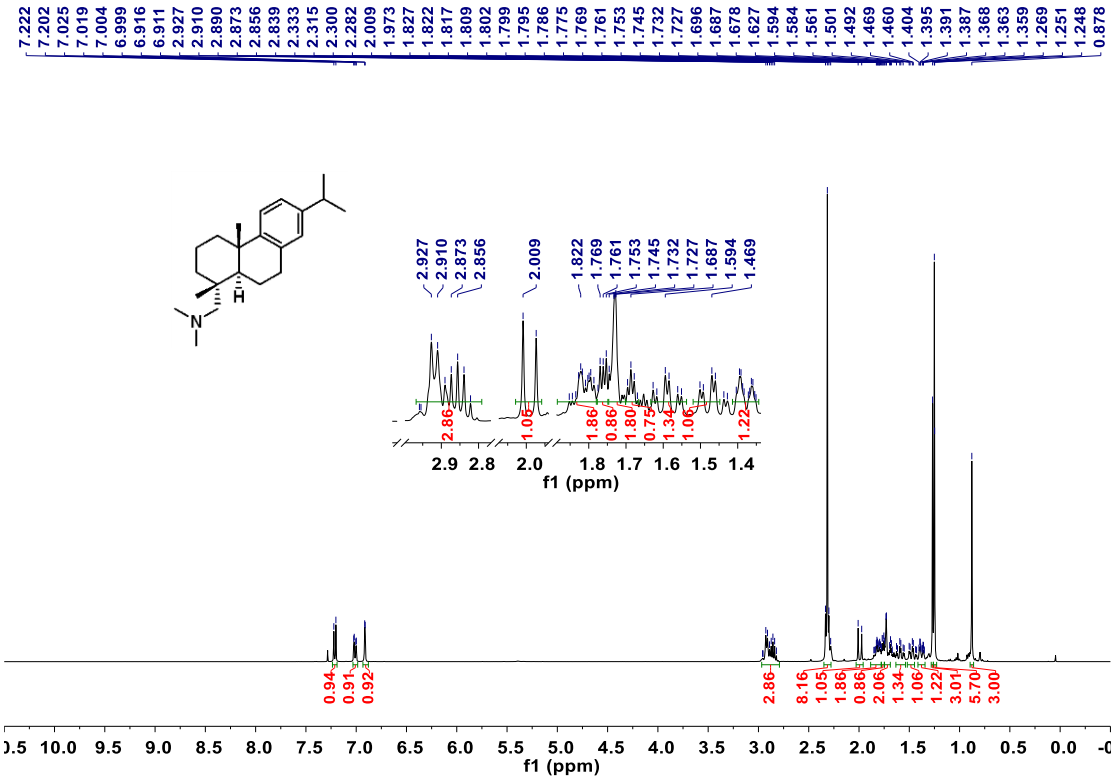


^{13}C NMR (101 MHz, DMSO-d^{6})

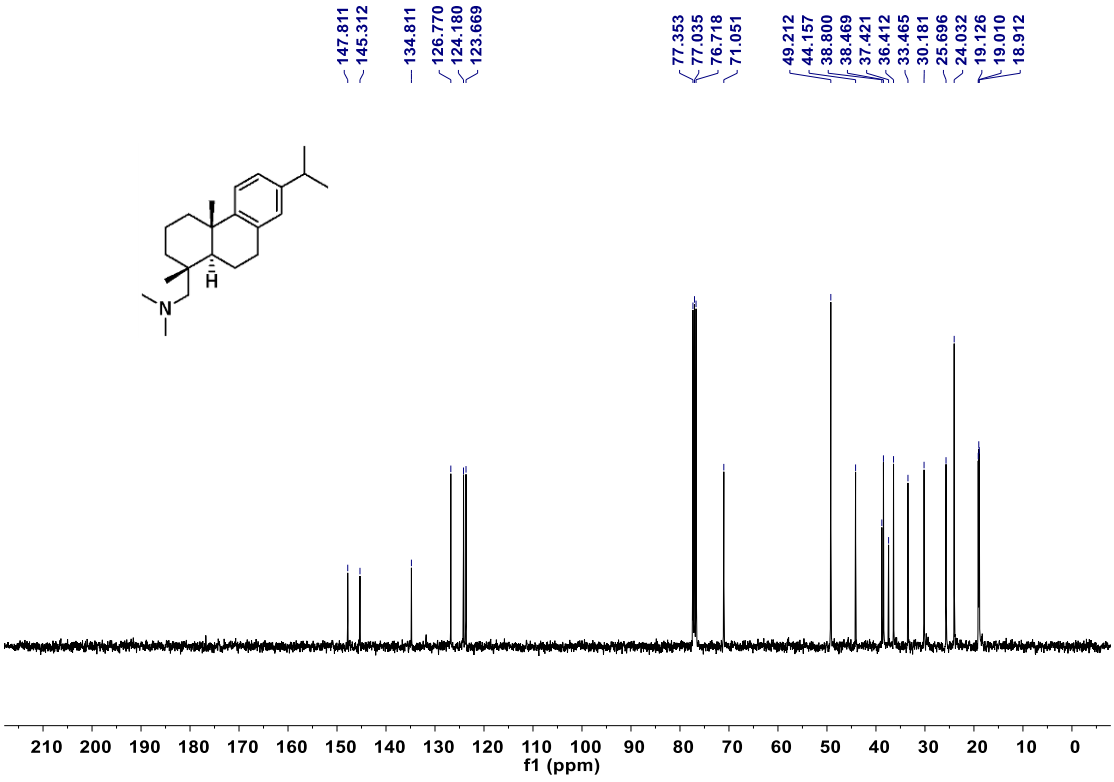


1-((1*R*,4*aS*,10*aR*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)-*N*,*N*-dimethylmethanamine (2c)

^{1}H NMR (400 MHz, $CDCl_3$)

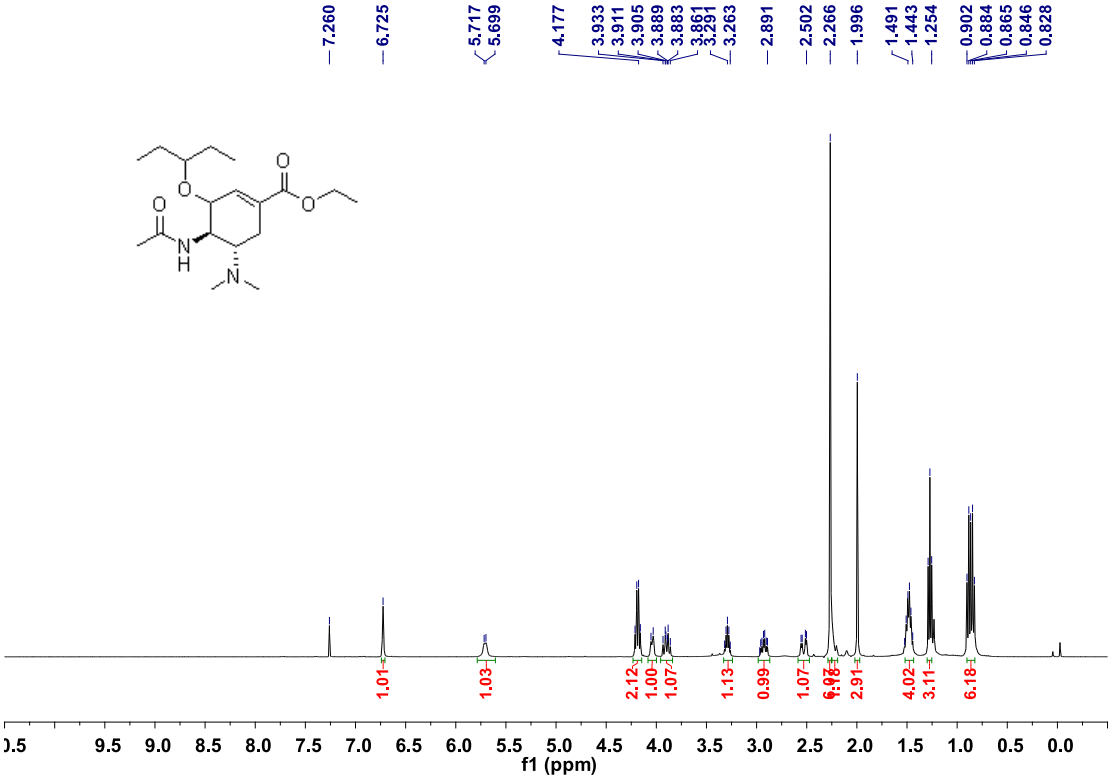


^{13}C NMR (101 MHz, $CDCl_3$)

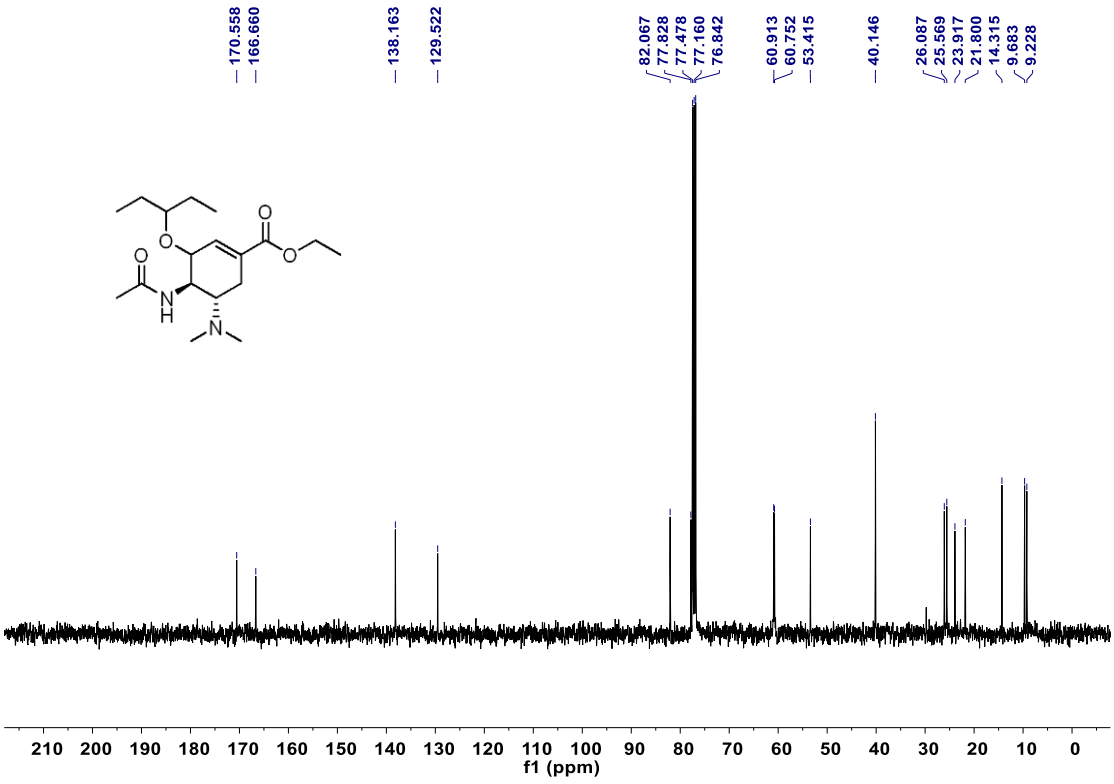


Ethyl(4*R*,5*S*)-4-acetamido-5-(dimethylamino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d)

^{1}H NMR (400 MHz, $CDCl_3$)

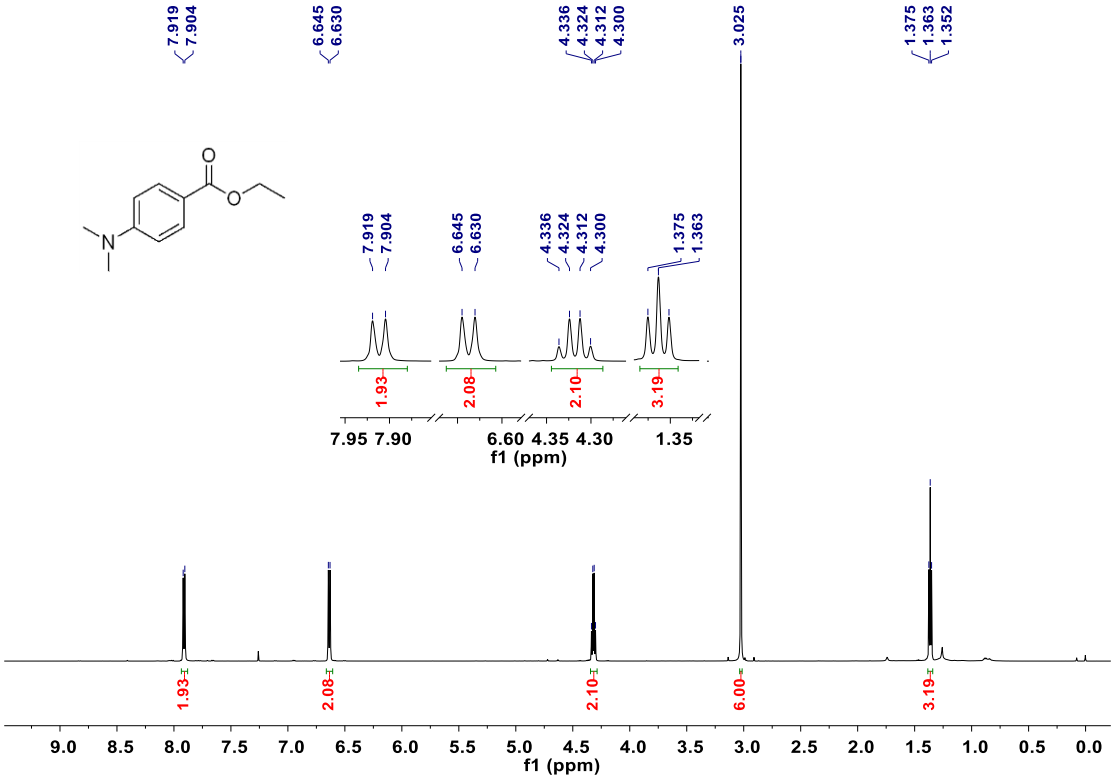


^{13}C NMR (101 MHz, $CDCl_3$)

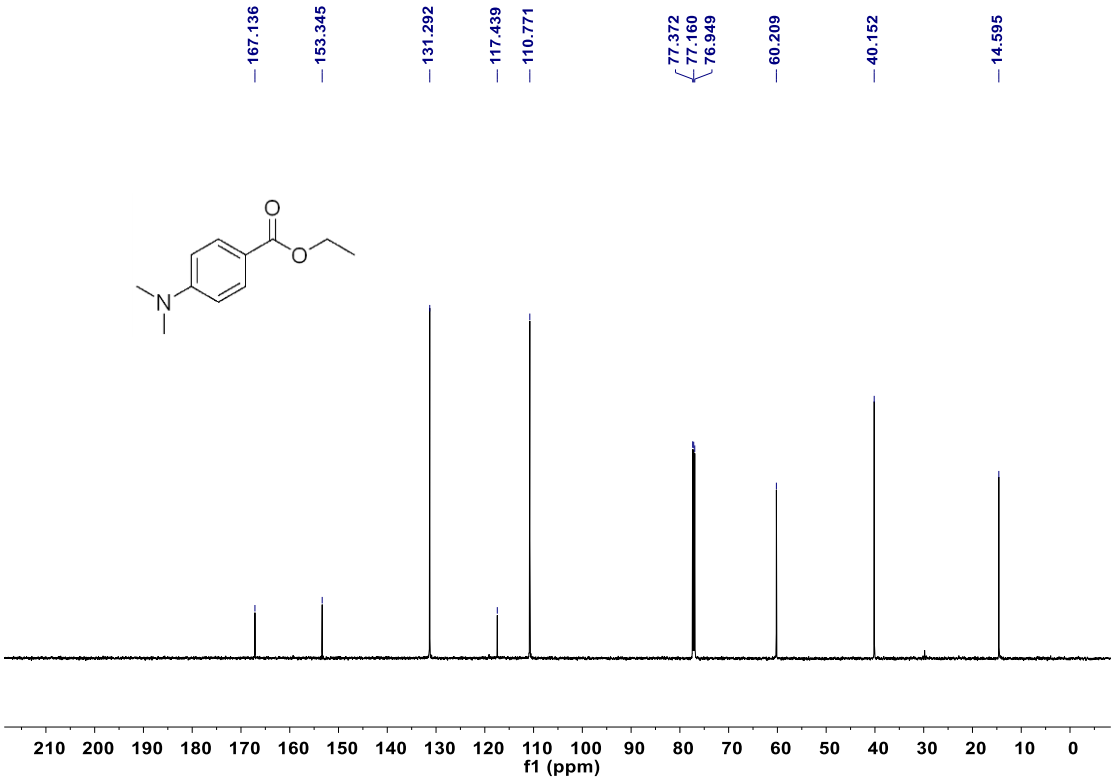


Ethyl 4-(dimethylamino)benzoate (2e)

^{1}H NMR (600 MHz, $CDCl_3$)

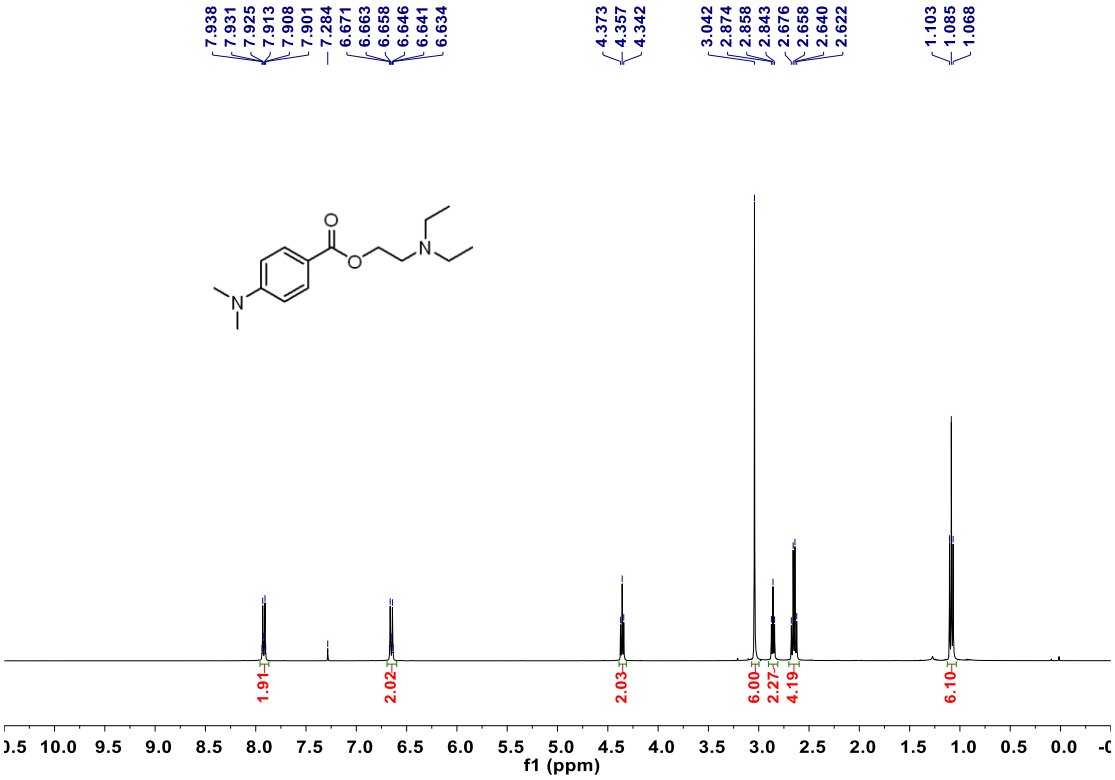


^{13}C NMR (151 MHz, $CDCl_3$)

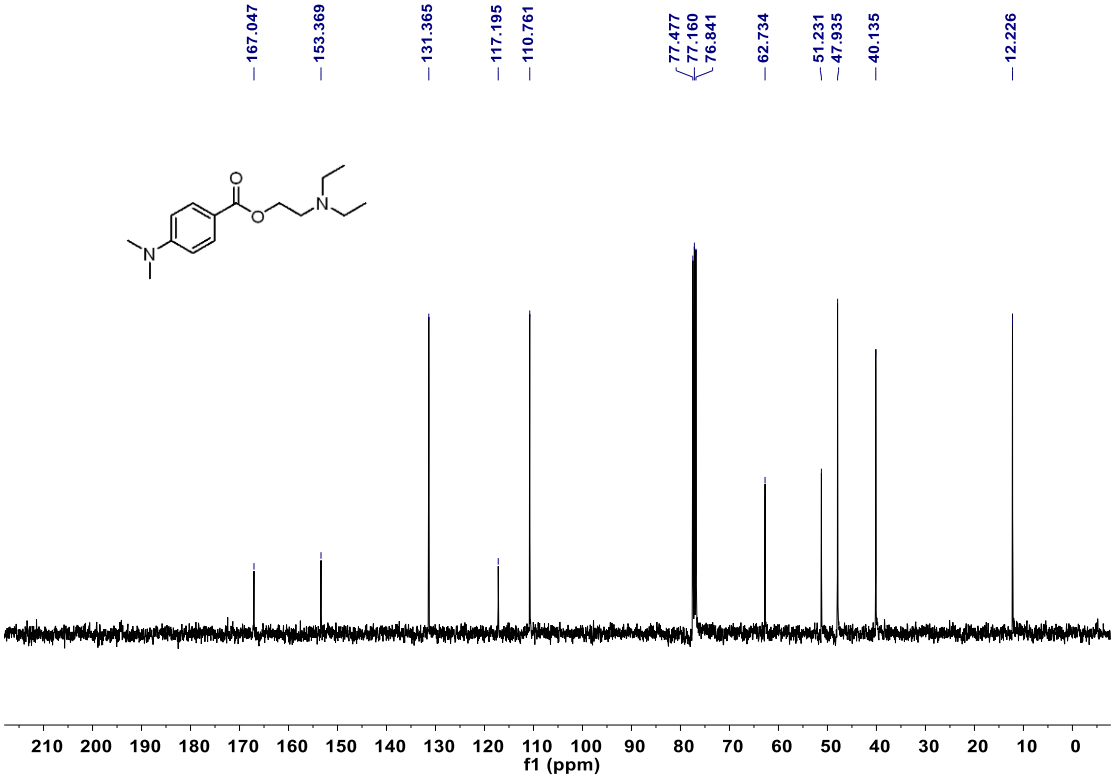


2-(Diethylamino)ethyl 4-(dimethylamino)benzoate (2f)

^{1}H NMR (400 MHz, $CDCl_3$)

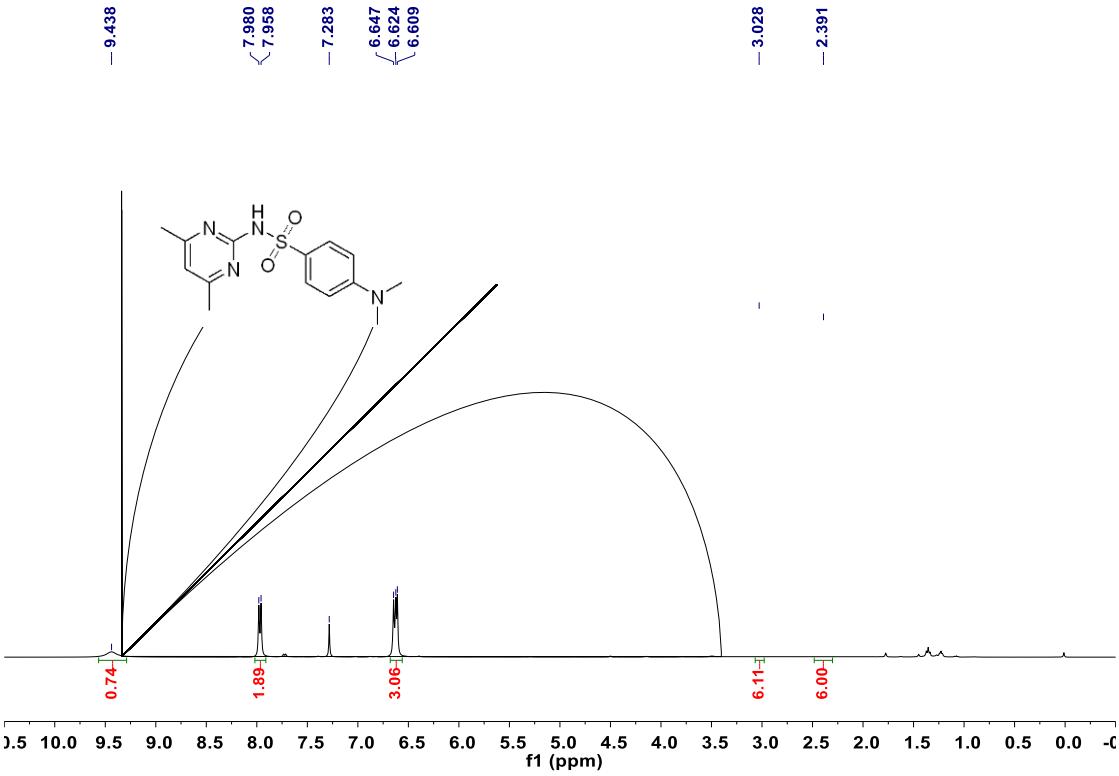


^{13}C NMR (101 MHz, $CDCl_3$)

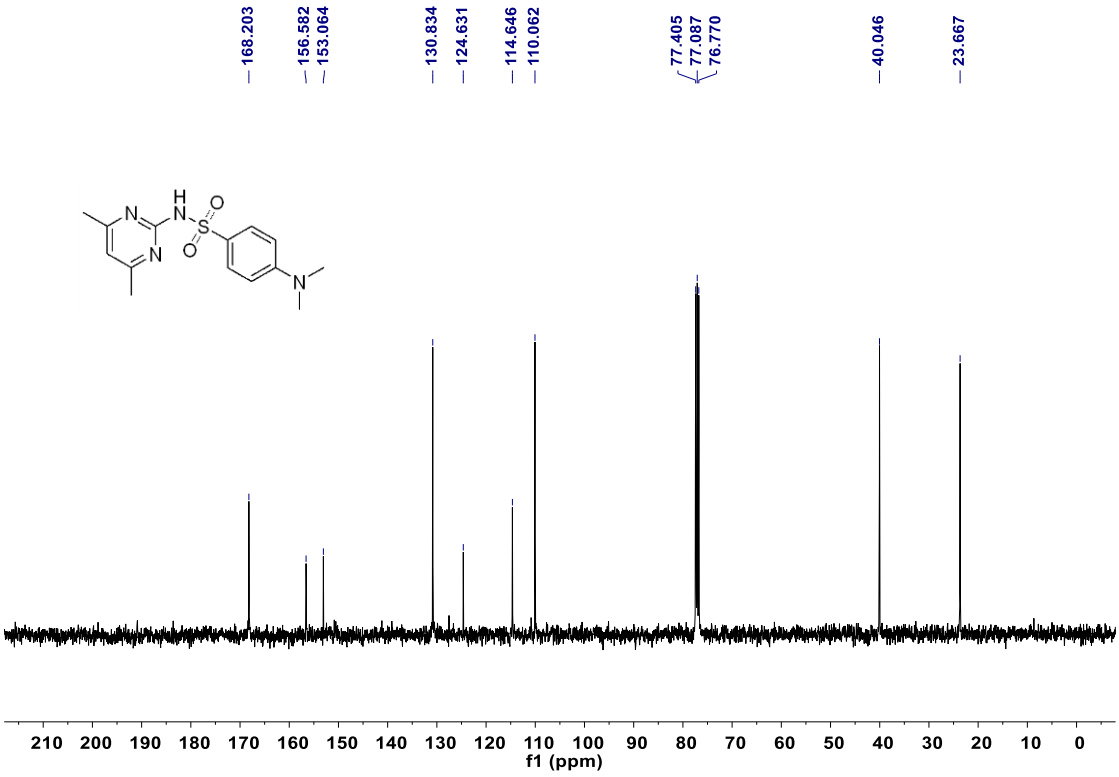


4-(Dimethylamino)-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (2g)

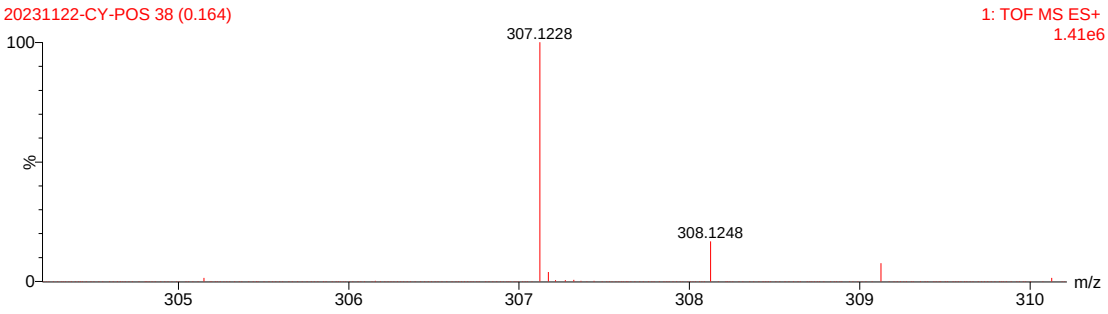
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

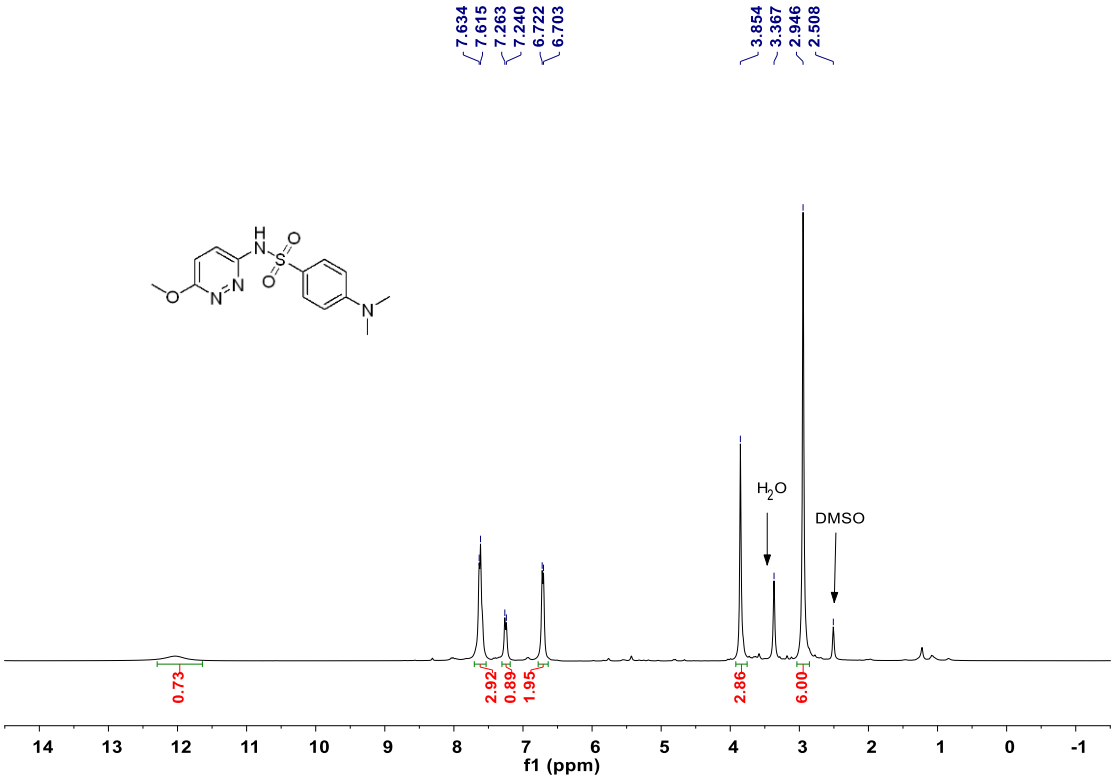


HRMS (ESI): ***m/z*** **calcd for : $C_{14}H_{19}N_4O_2S^+$ $[M+H]^+$: 307.1223, found: 307.1228**

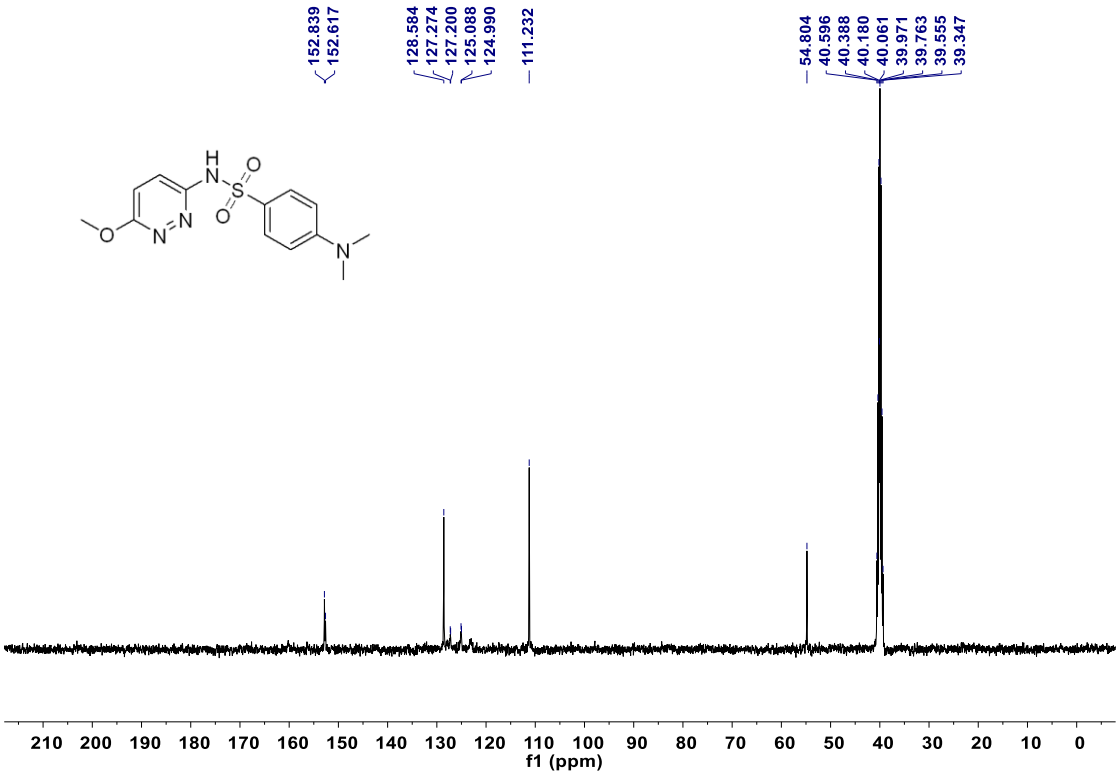


4-(Dimethylamino)-*N*-(6-methoxypyridazin-3-yl)benzenesulfonamide (2h)

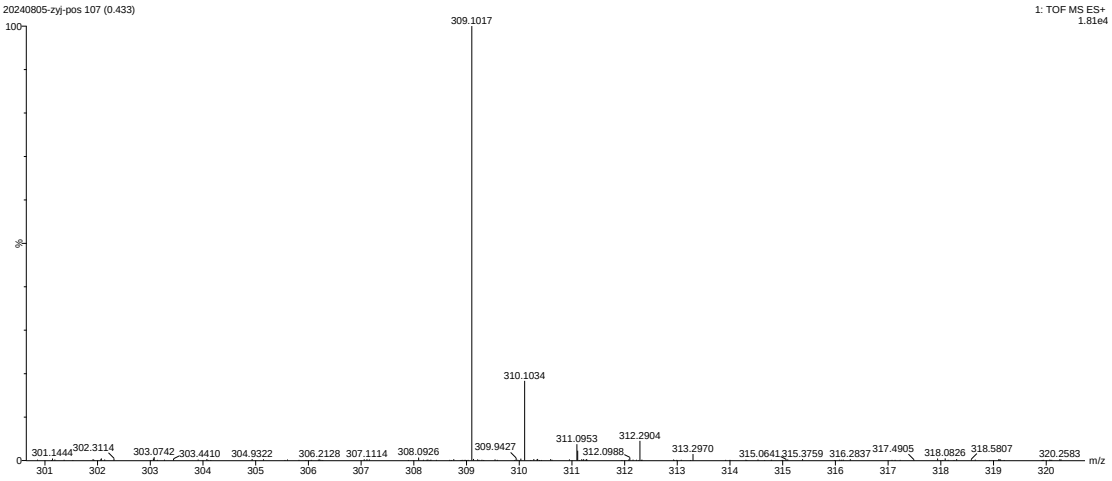
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (101 MHz, DMSO-d_6)

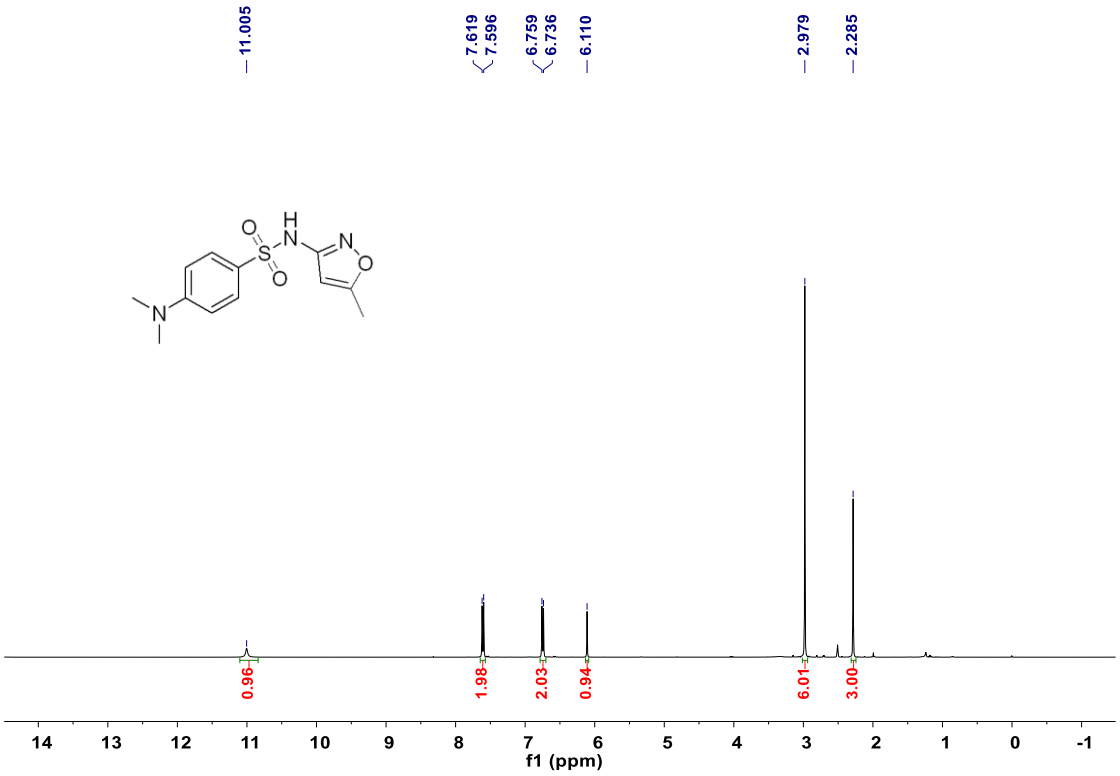


HRMS (ESI): *m/z* calcd for : $C_{13}H_{17}N_4O_3S^+$ [M+H]$^+$: 309.1016, found: 309.1017.

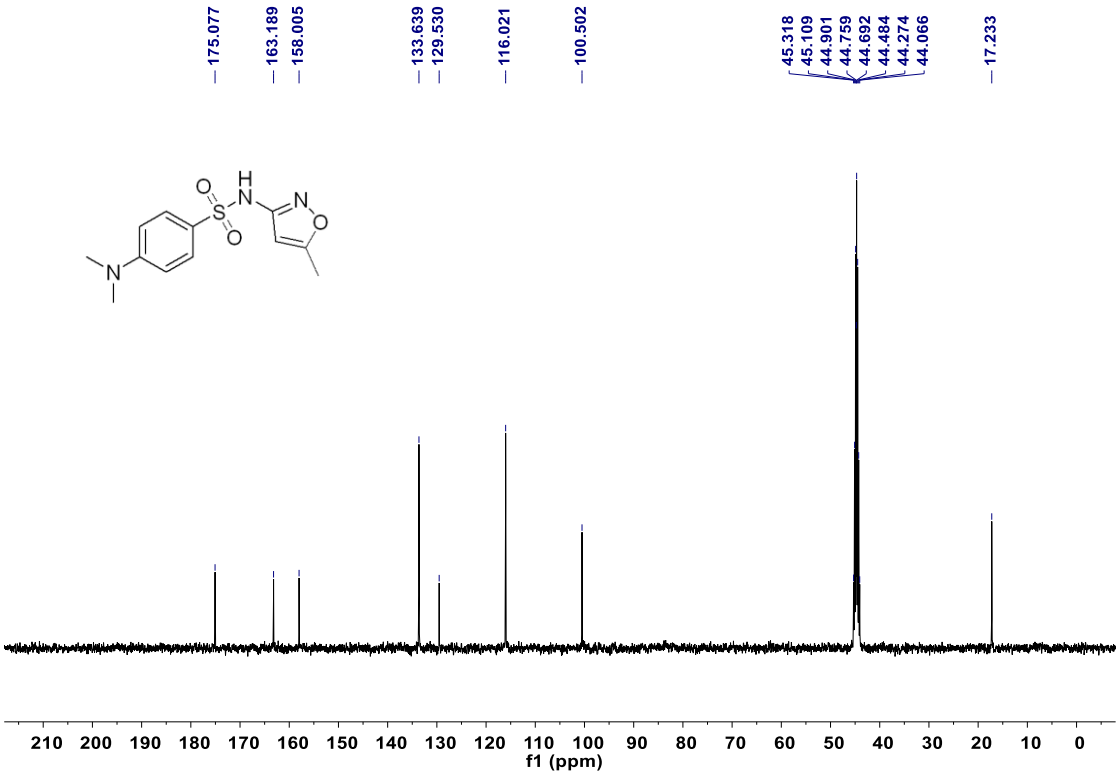


4-(Dimethylamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (2i)

^{1}H NMR (400 MHz, DMSO-d_6)

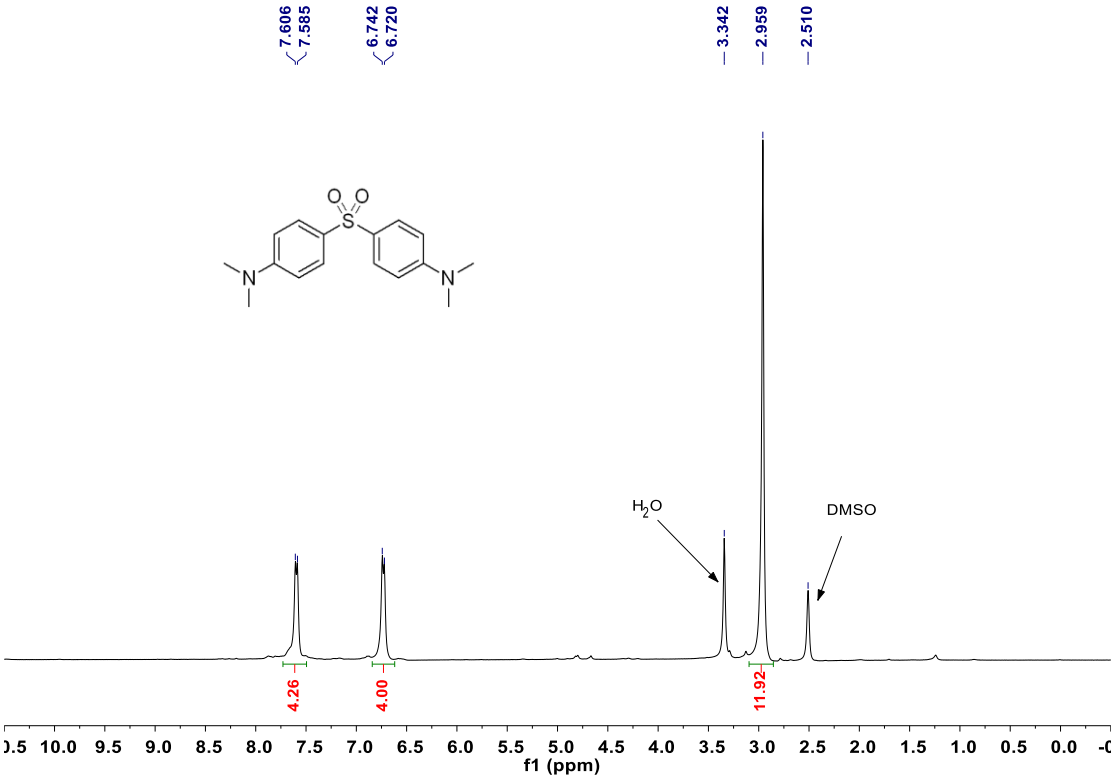


^{13}C NMR (101 MHz, DMSO-d_6)

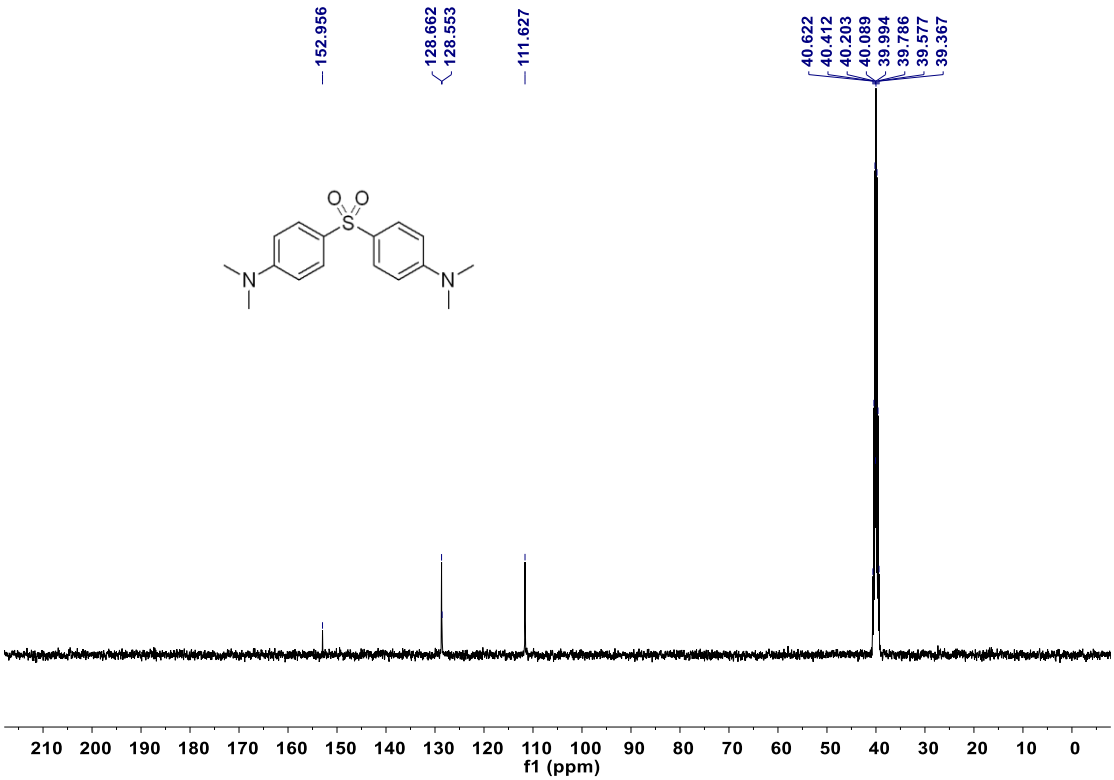


4,4'-Sulfonylbis(*N*,*N*-dimethylaniline) (2j)

^{1}H NMR (400 MHz, DMSO-d_6)

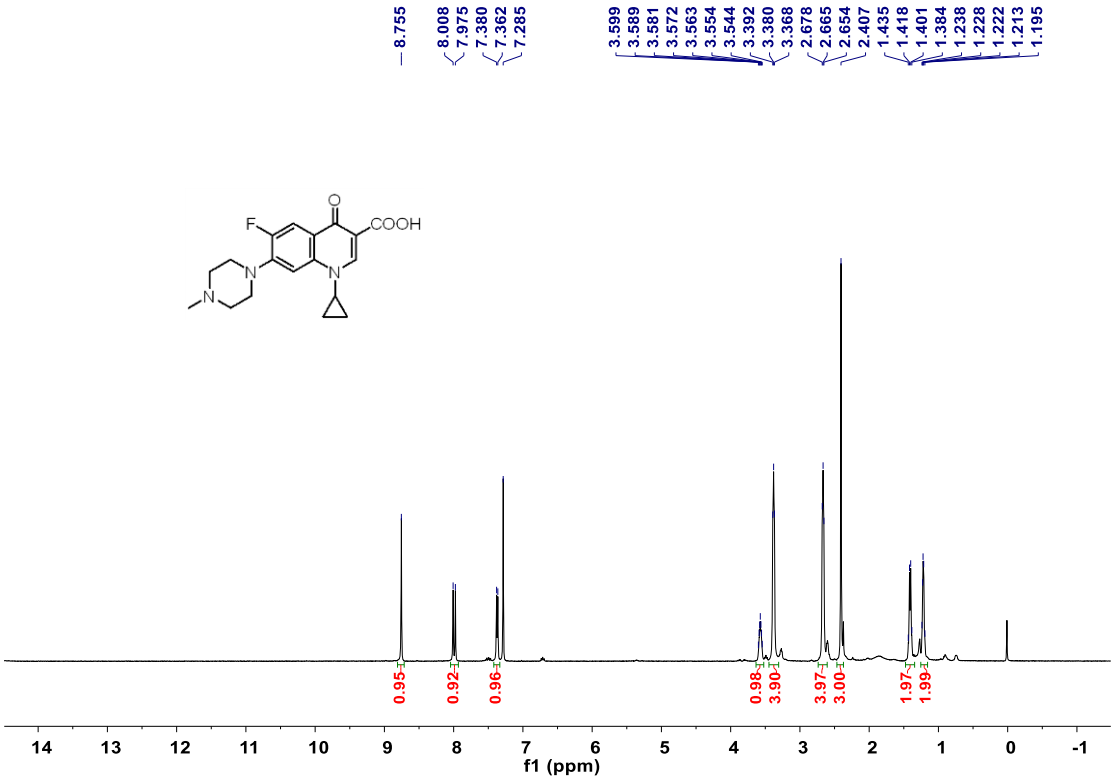


^{13}C NMR (101 MHz, DMSO-d_6)

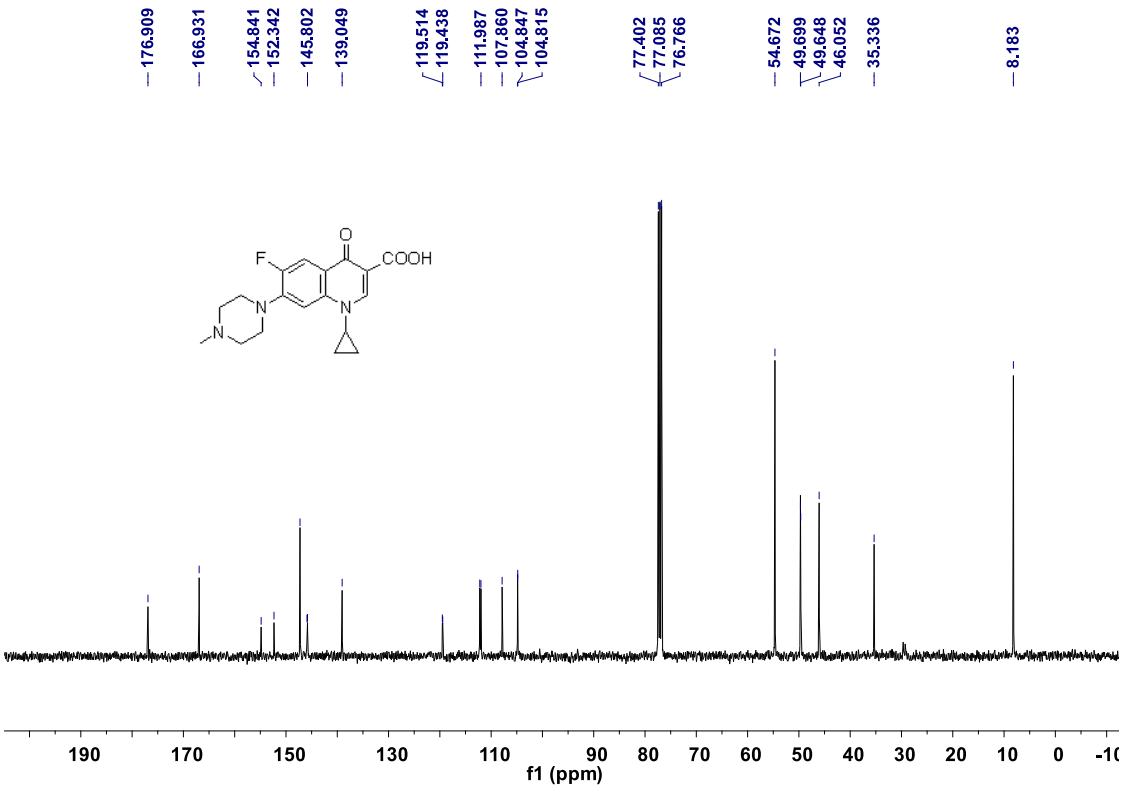


1-Cyclopropyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid (2k)

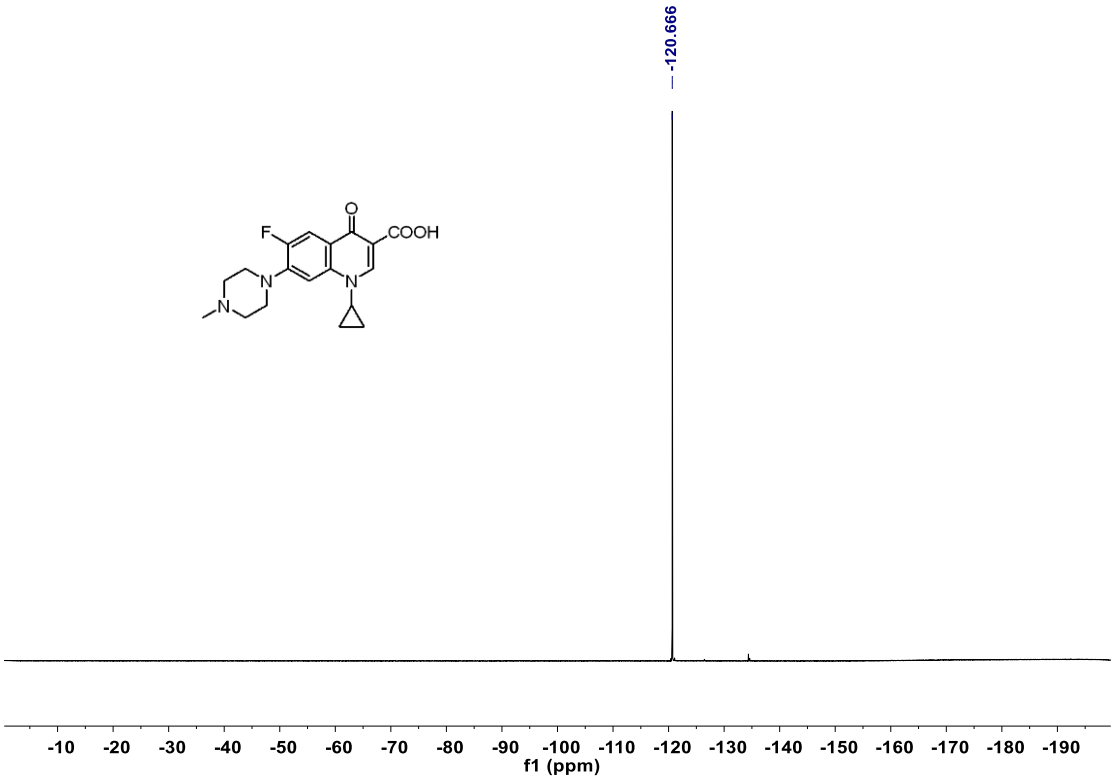
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

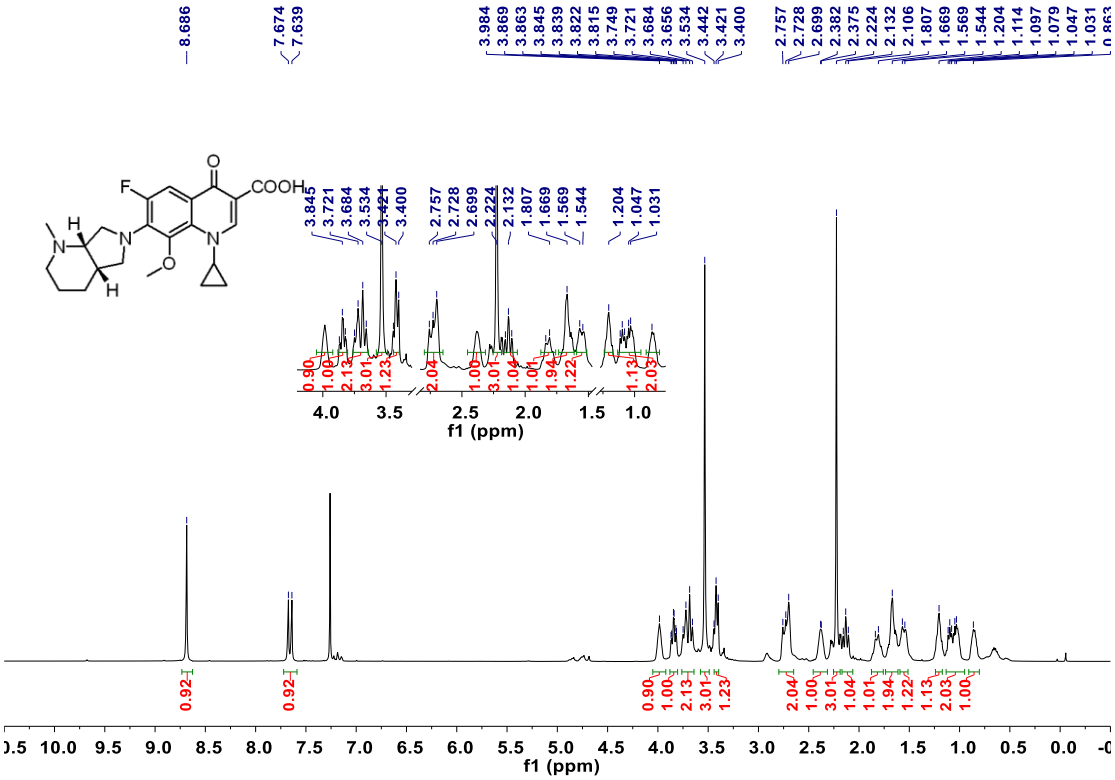


^{19}F NMR (376 MHz, $CDCl_3$)

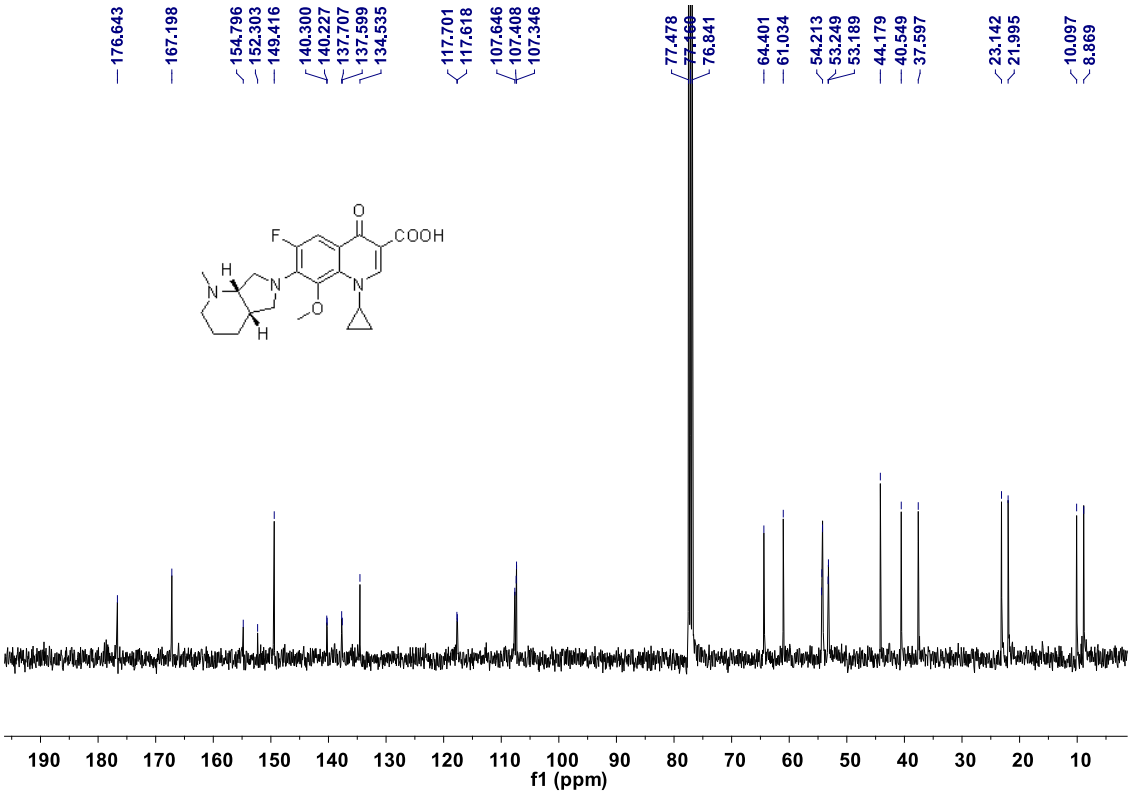


1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-methyloctahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2l)

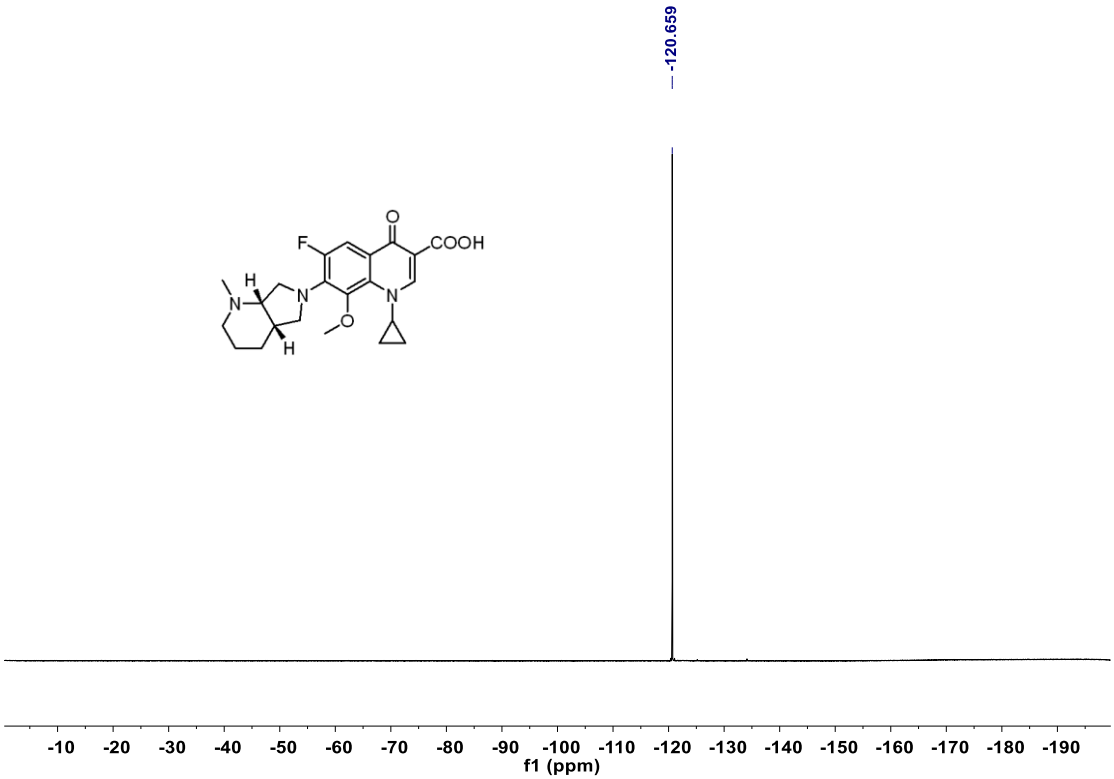
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

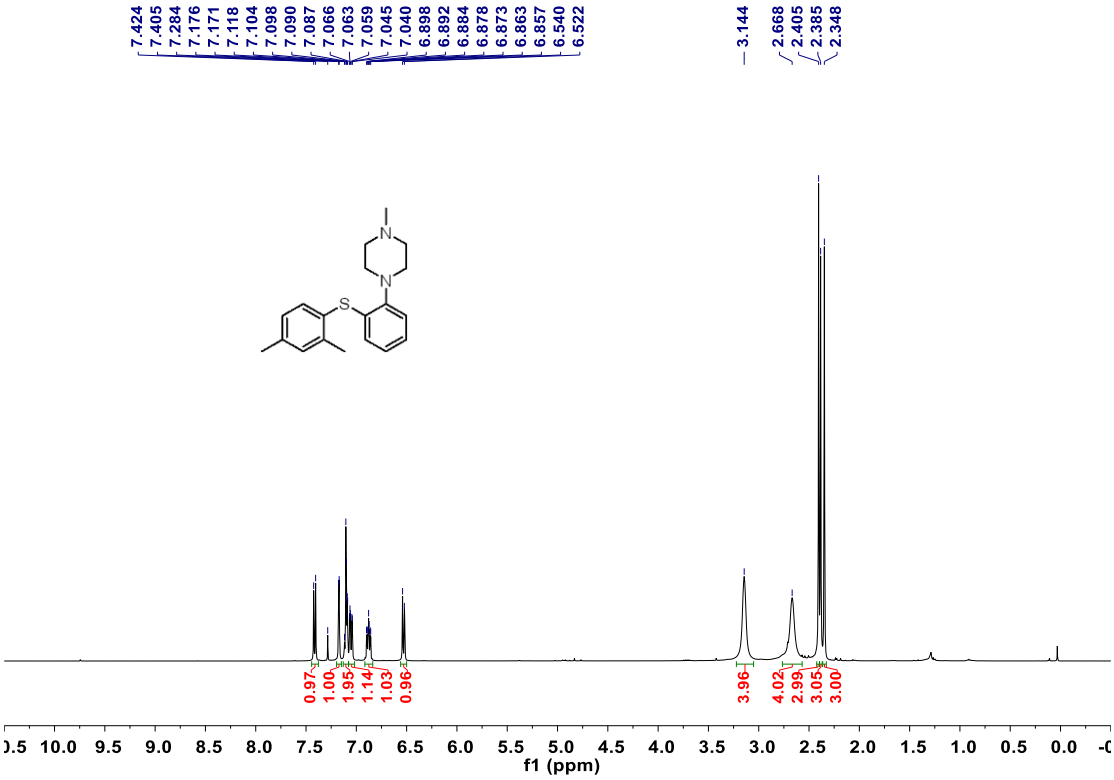


^{19}F NMR (376 MHz, $CDCl_3$)

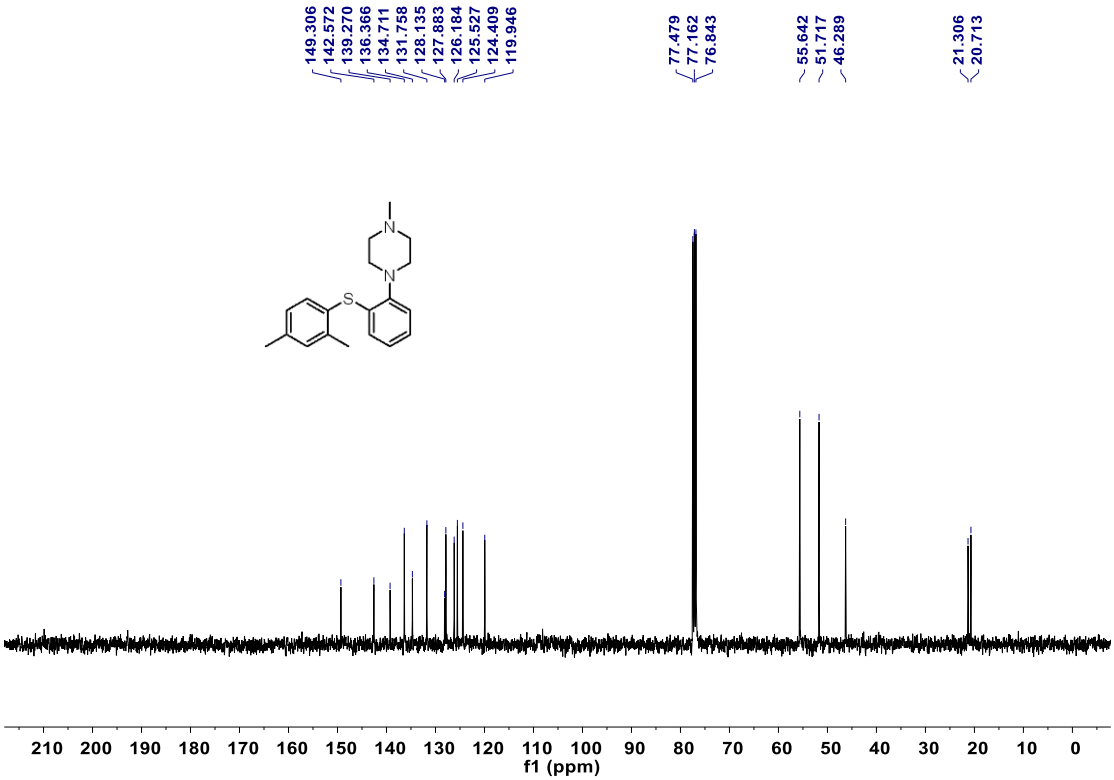


1-(2-((2,4-Dimethylphenyl)thio)phenyl)-4-methylpiperazine (2m)

^{1}H NMR (400 MHz, $CDCl_3$)

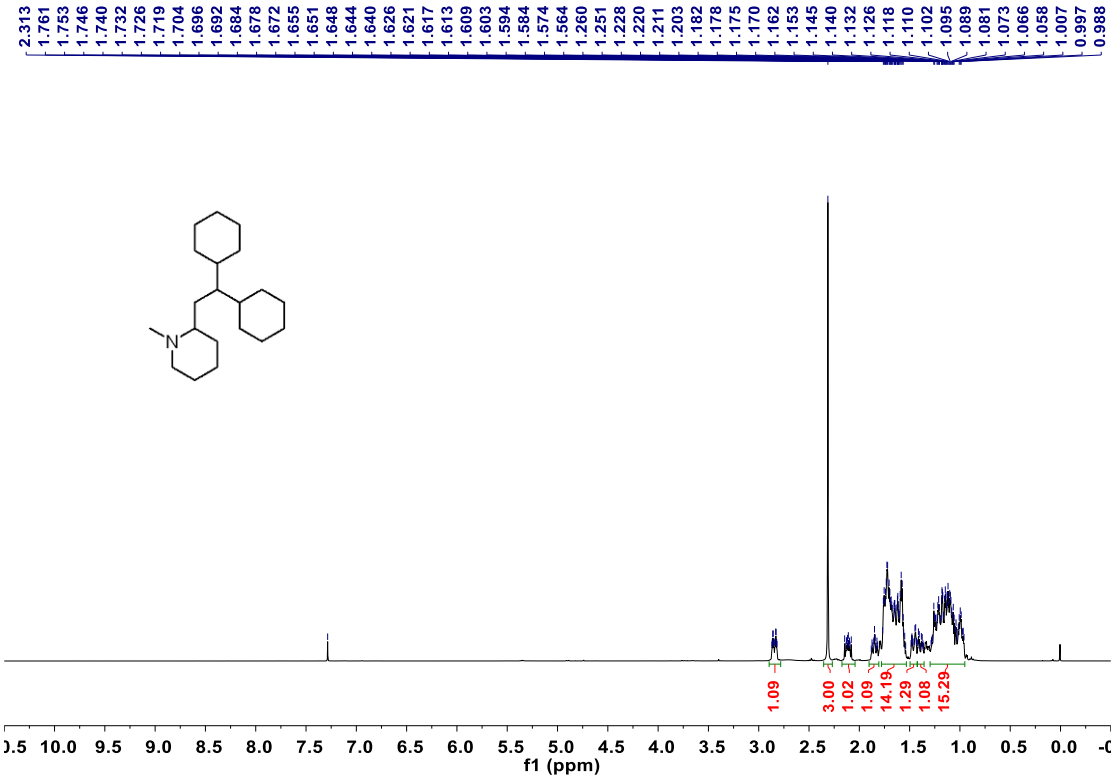


^{13}C NMR (101 MHz, $CDCl_3$)

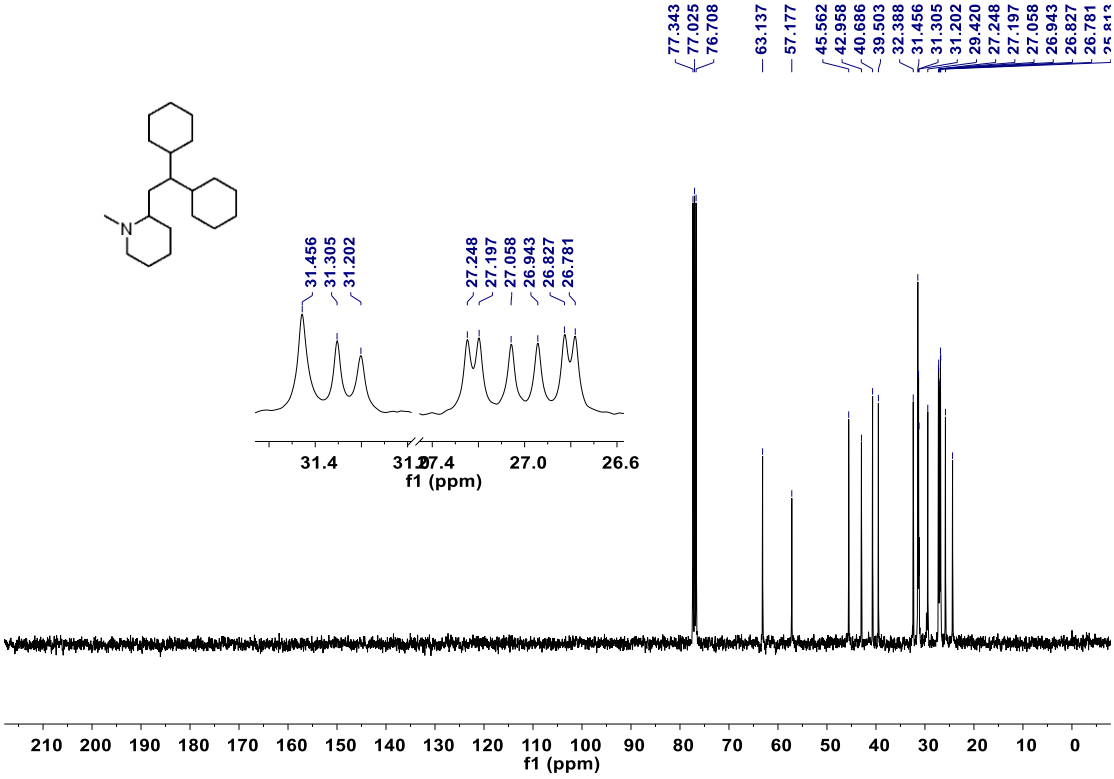


2-(2,2-Dicyclohexylethyl)-1-methylpiperidine (2n)

^{1}H NMR (400 MHz, $CDCl_3$)

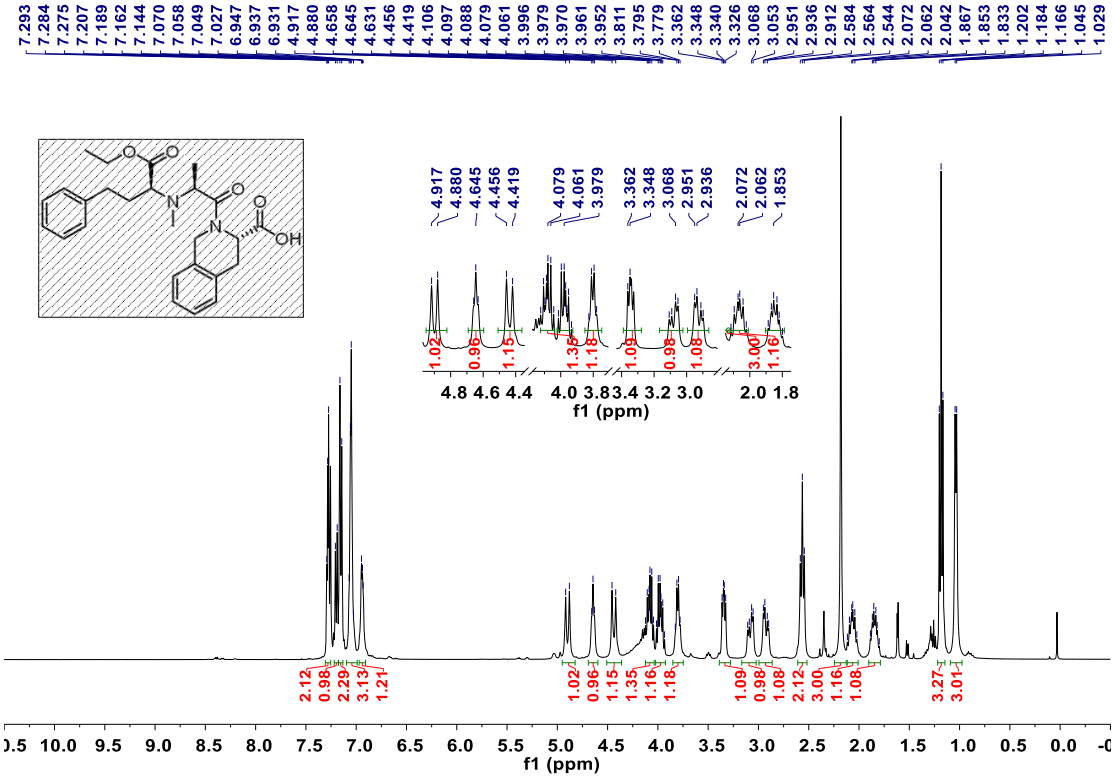


^{13}C NMR (101 MHz, $CDCl_3$)

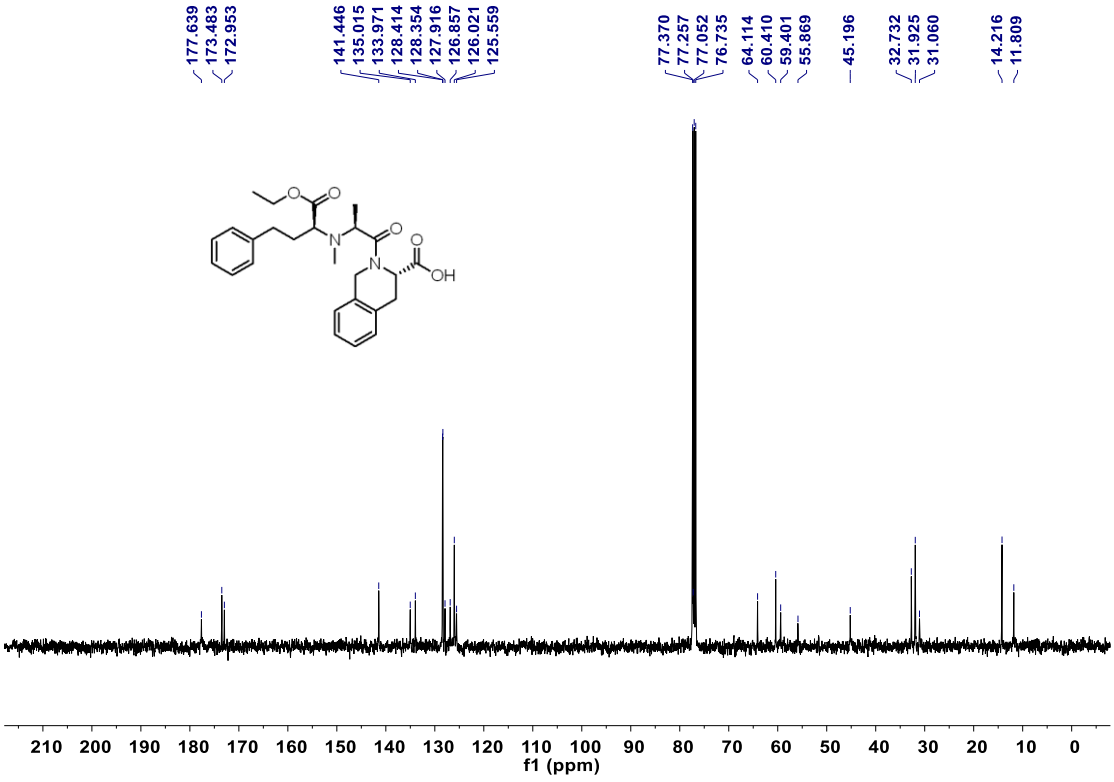


(*S*)-2-(*N*-((*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl)-*N*-methyl-*L*-alanyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2o)

^{1}H NMR (400 MHz, $CDCl_3$)

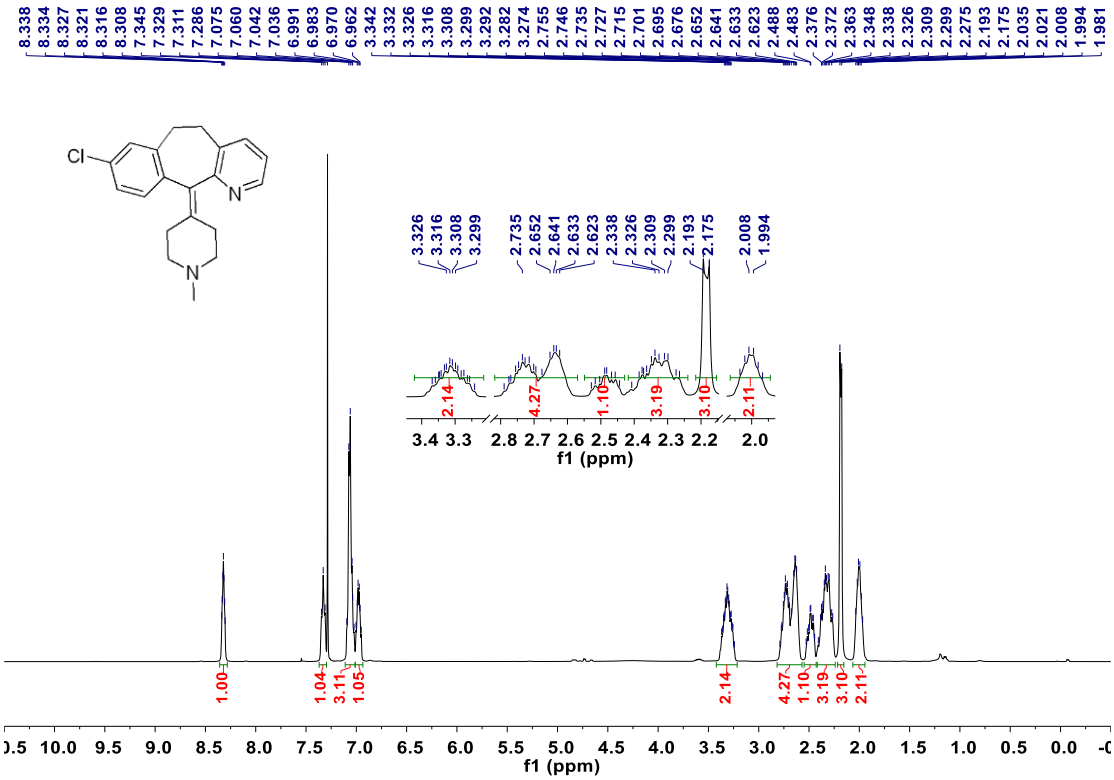


^{13}C NMR (101 MHz, $CDCl_3$)

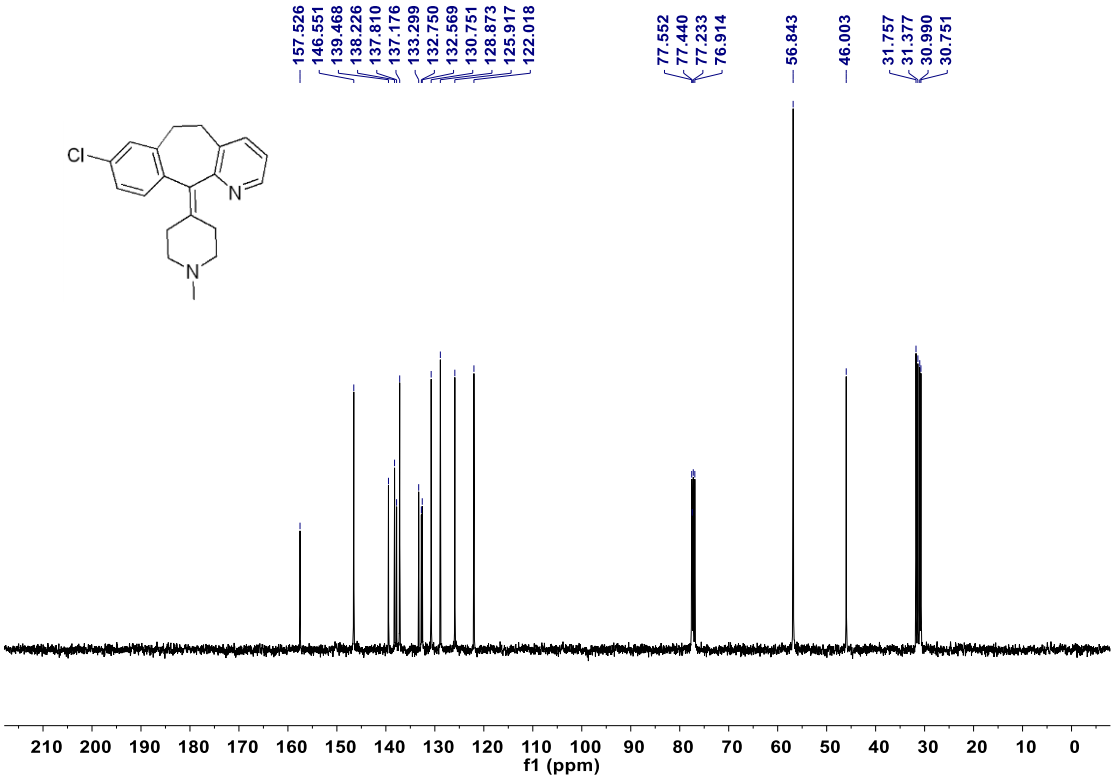


8-Chloro-11-(1-methylpiperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2p)

^{1}H NMR (400 MHz, $CDCl_3$)

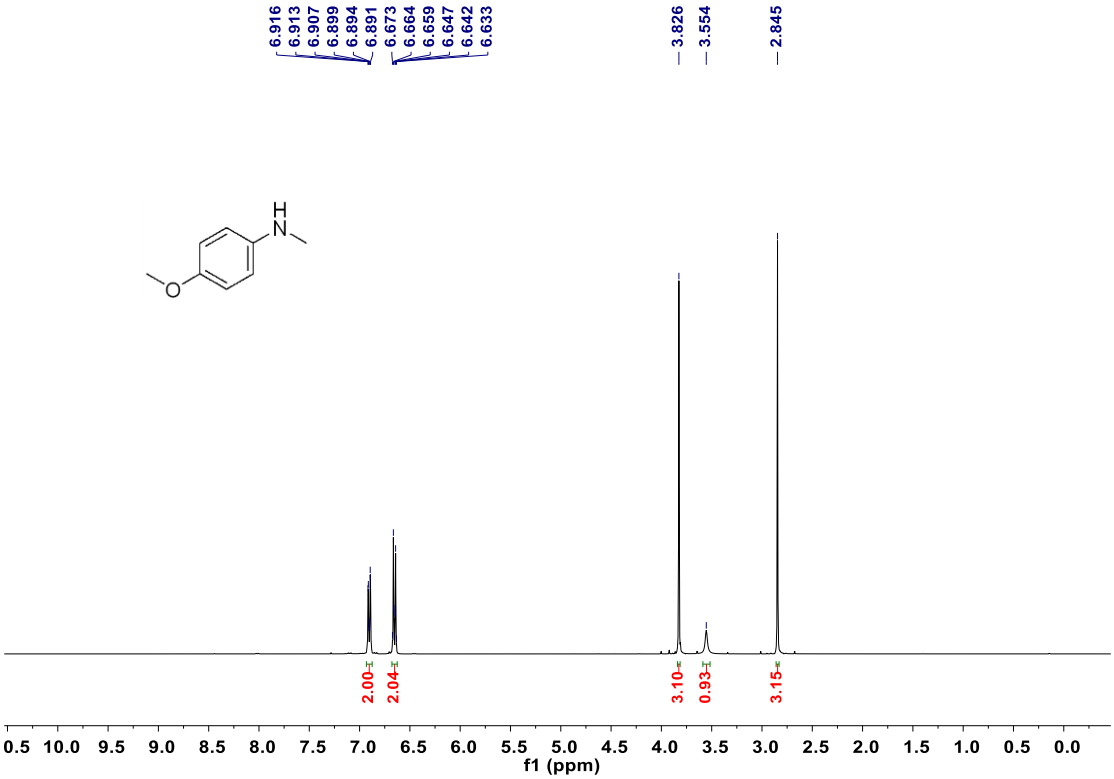


^{13}C NMR (101 MHz, $CDCl_3$)

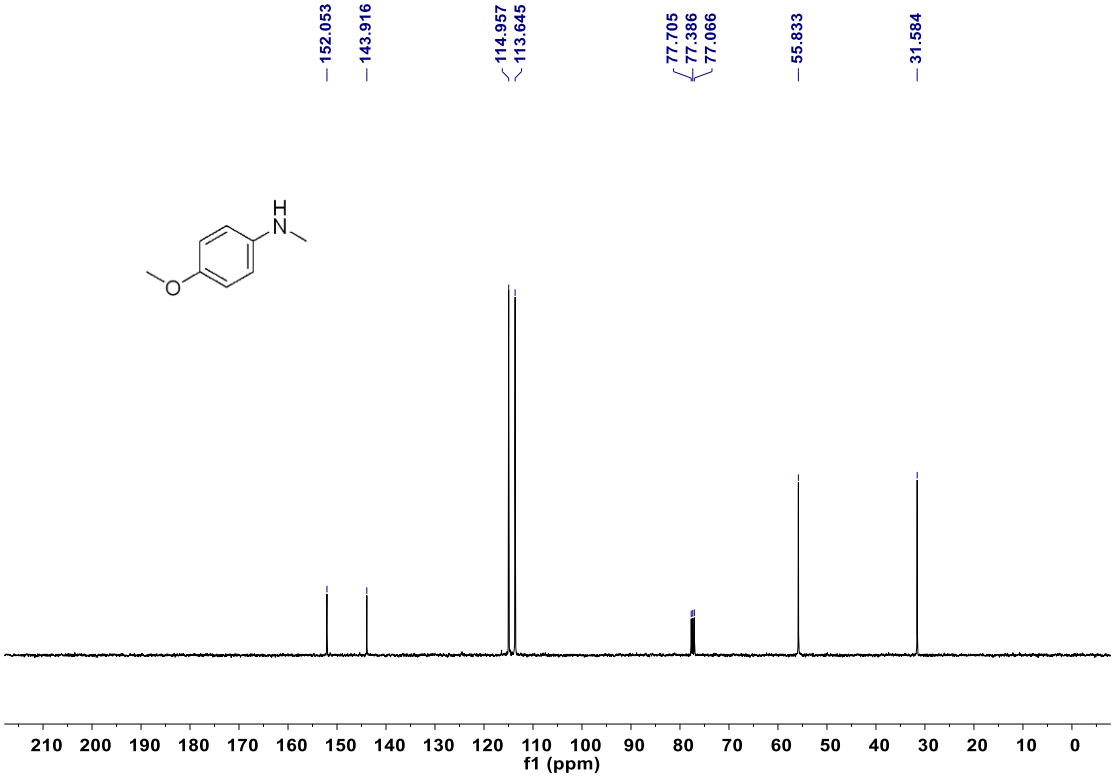


4-Methoxy-*N*-methylaniline (5b)

^{1}H NMR (400 MHz, $CDCl_3$)

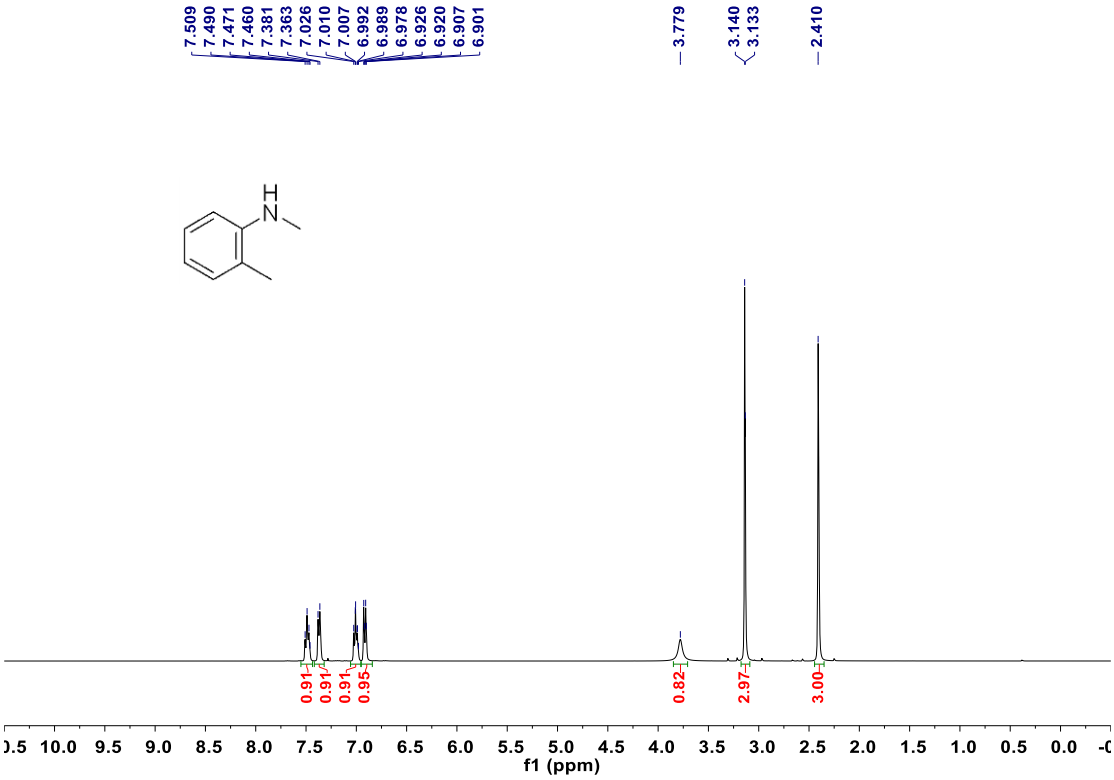


^{13}C NMR (101 MHz, $CDCl_3$)

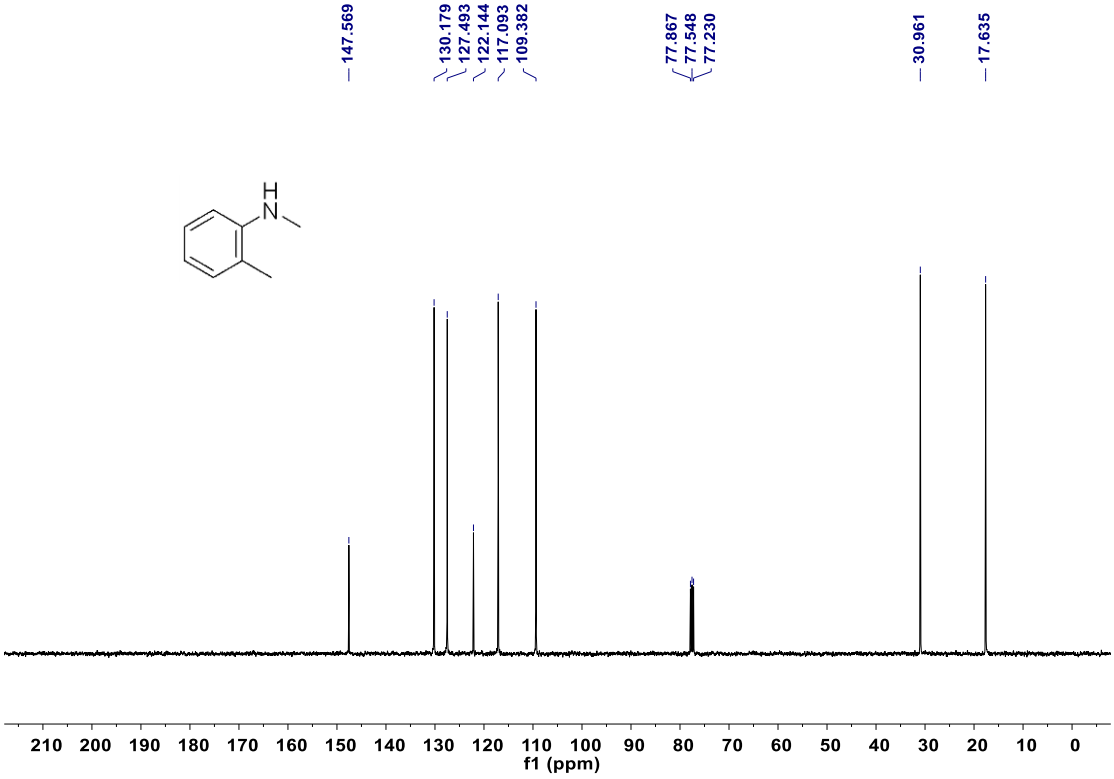


***N*,2-Dimethylaniline (5aj)**

^{1}H NMR (400 MHz, $CDCl_3$)

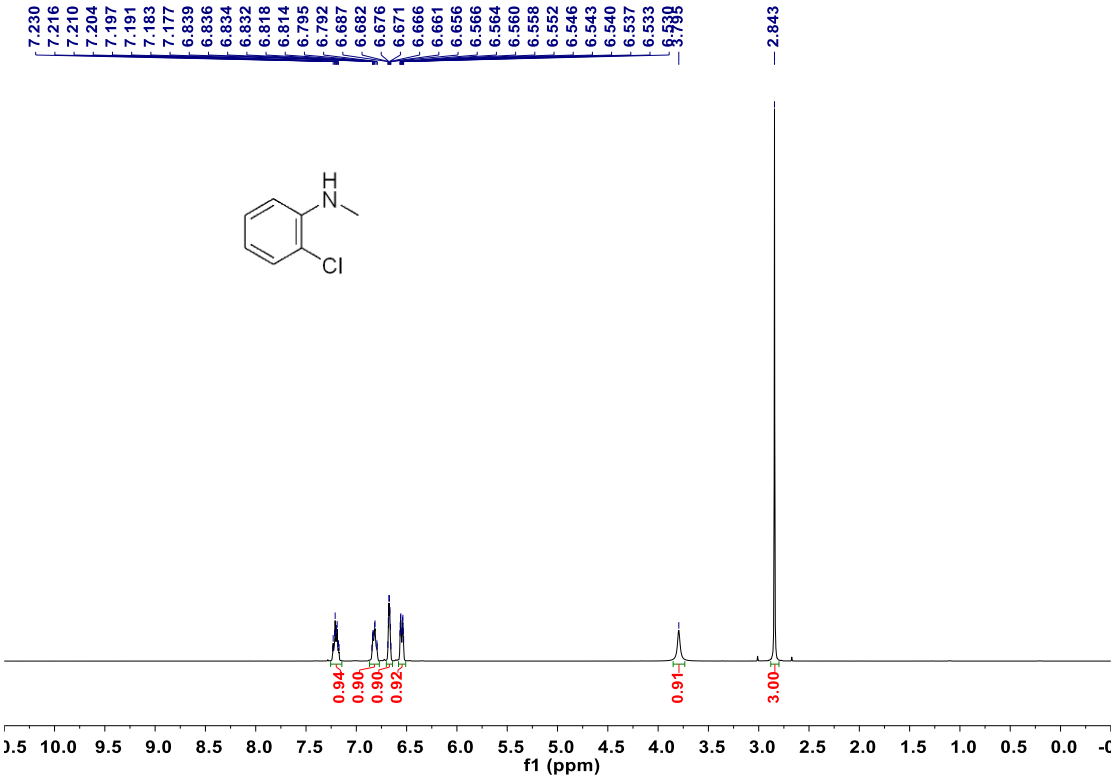


^{13}C NMR (101 MHz, $CDCl_3$)

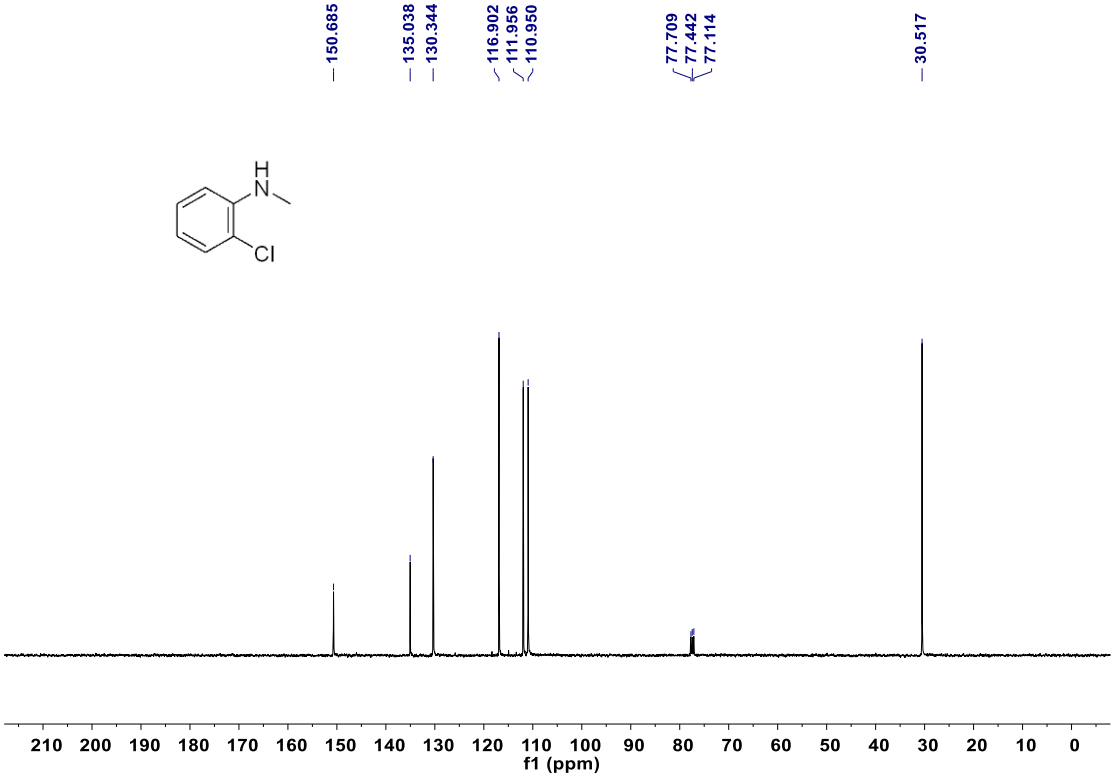


2-Chloro-*N*-methylaniline (5ak)

^{1}H NMR (400 MHz, $CDCl_3$)

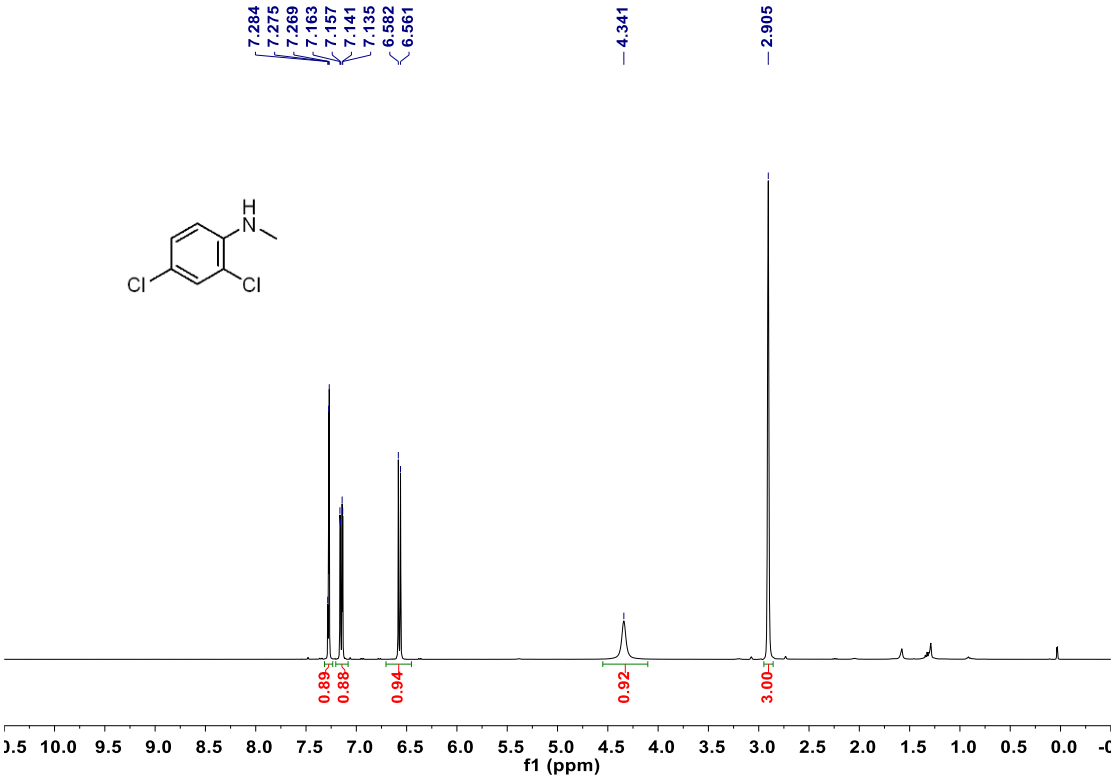


^{13}C NMR (101 MHz, $CDCl_3$)

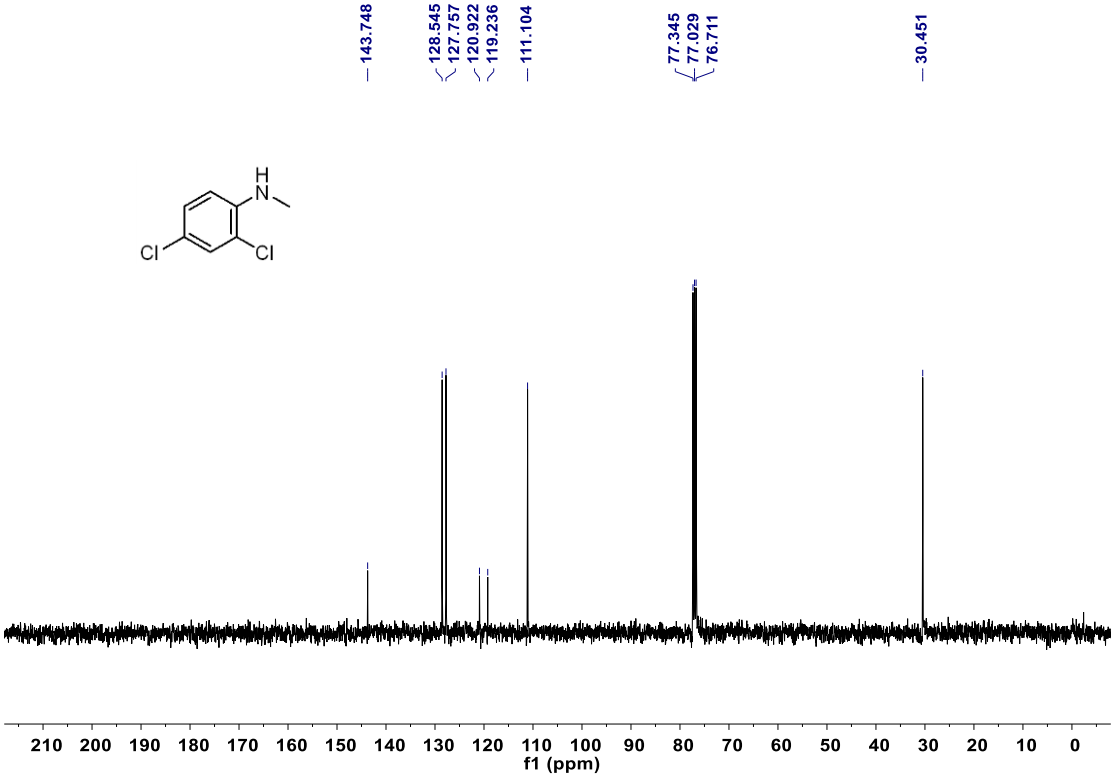


2,4-Dichloro-*N*-methylaniline (5h)

^{1}H NMR (400 MHz, $CDCl_3$)

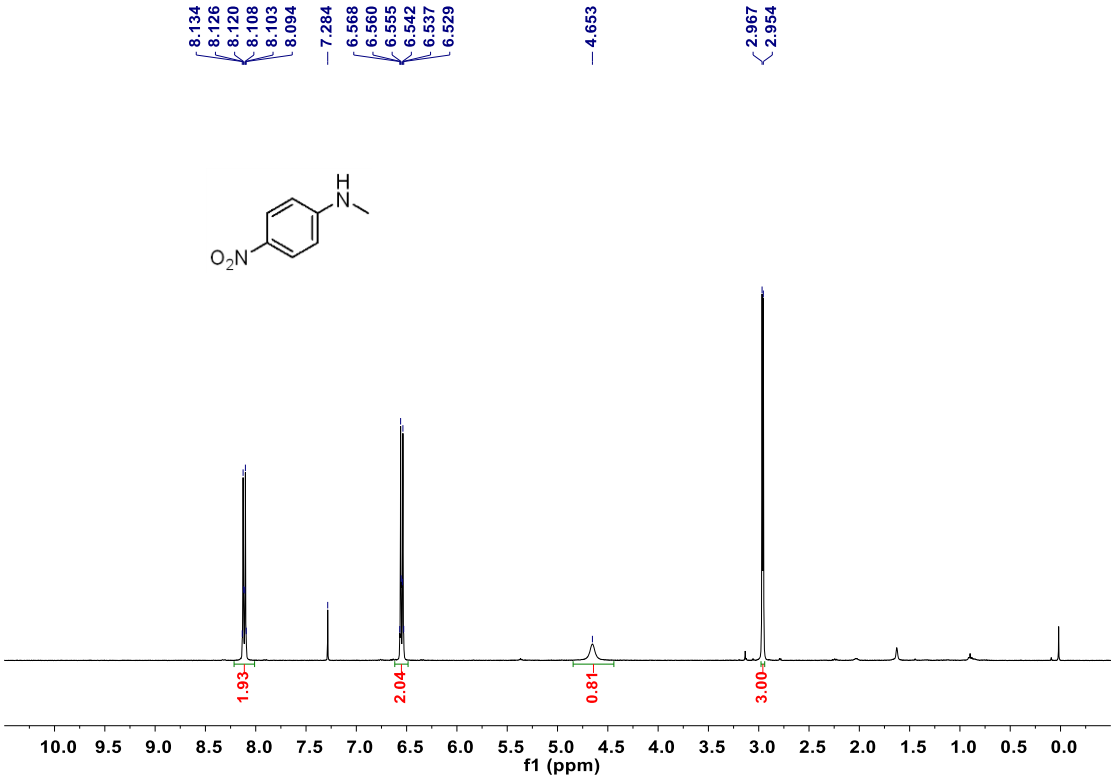


^{13}C NMR (101 MHz, $CDCl_3$)

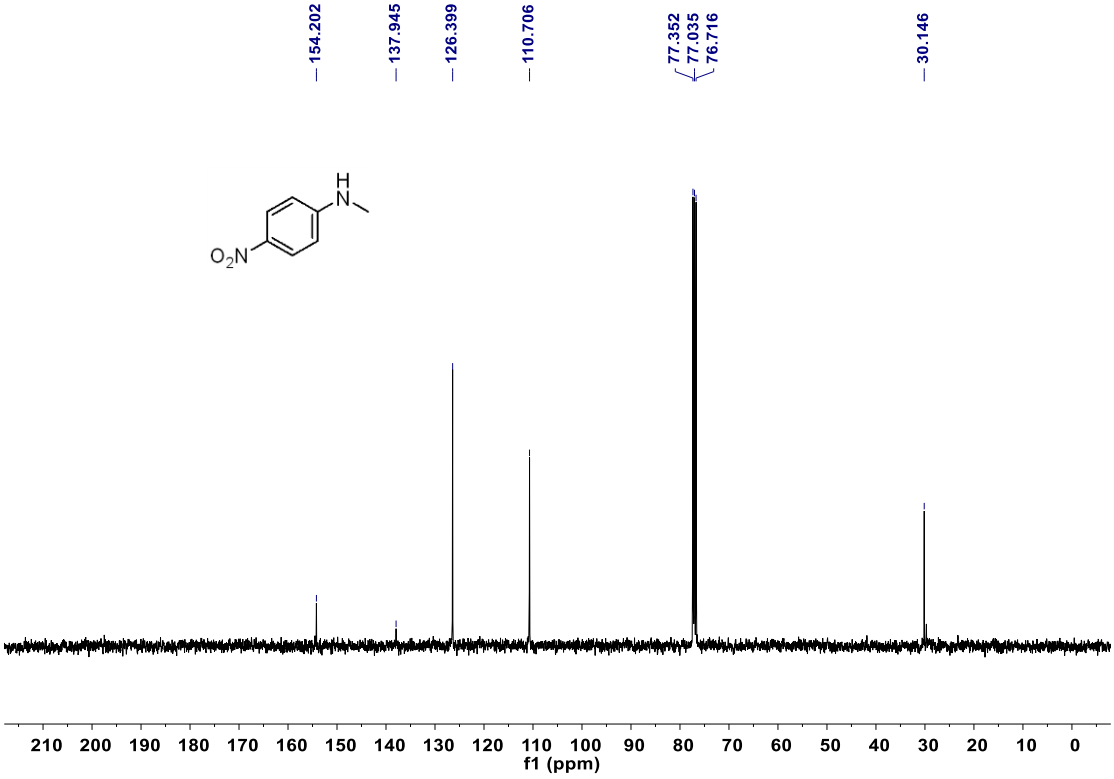


***N*-Methyl-4-nitroaniline (5al)**

^{1}H NMR (400 MHz, $CDCl_3$)

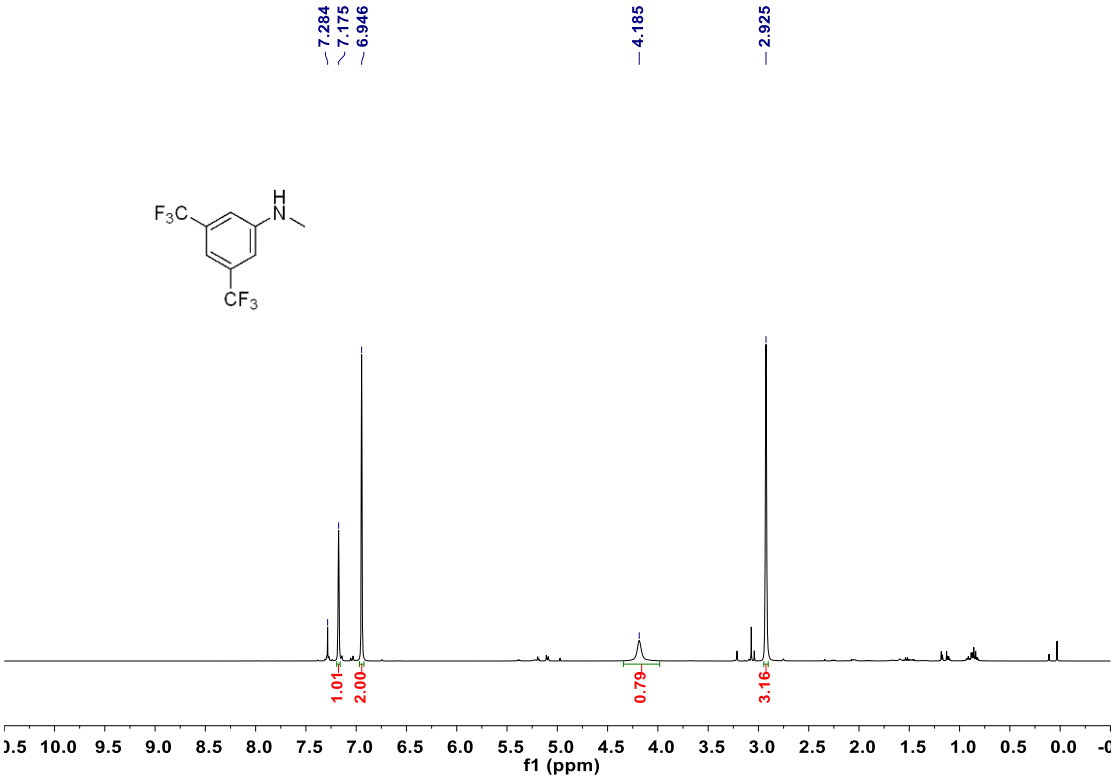


^{13}C NMR (101 MHz, $CDCl_3$)

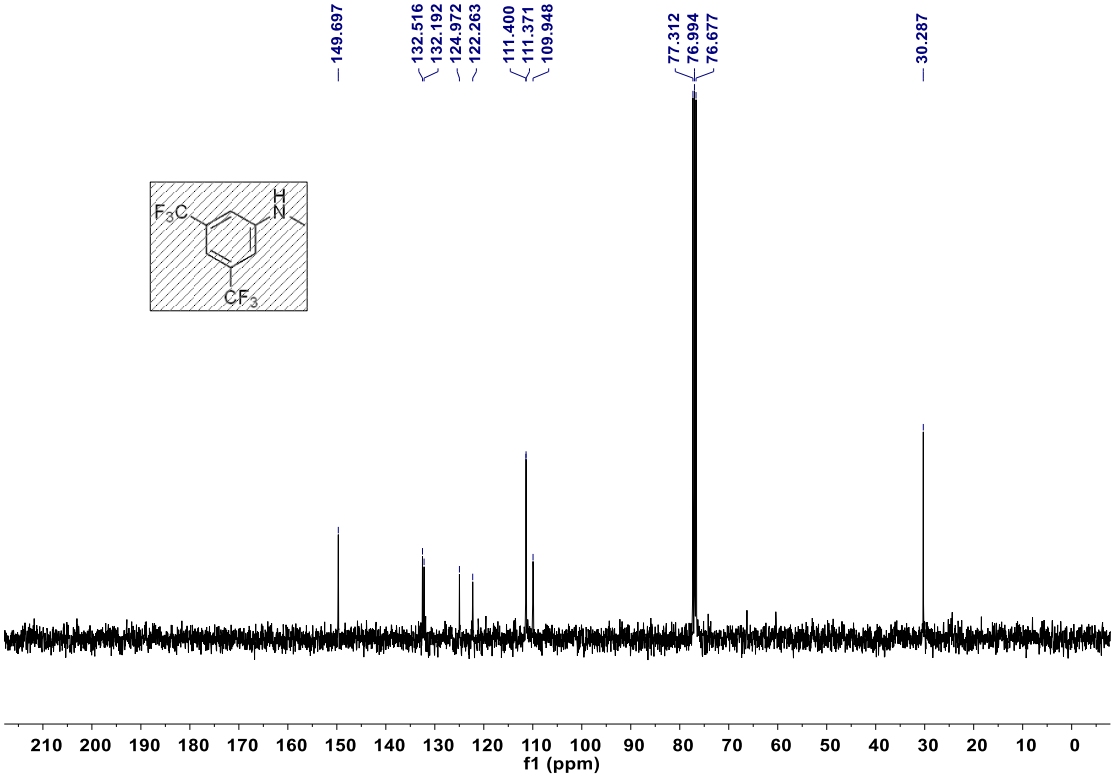


***N*-Methyl-3,5-bis(trifluoromethyl)aniline (5am)**

^{1}H NMR (400 MHz, $CDCl_3$)

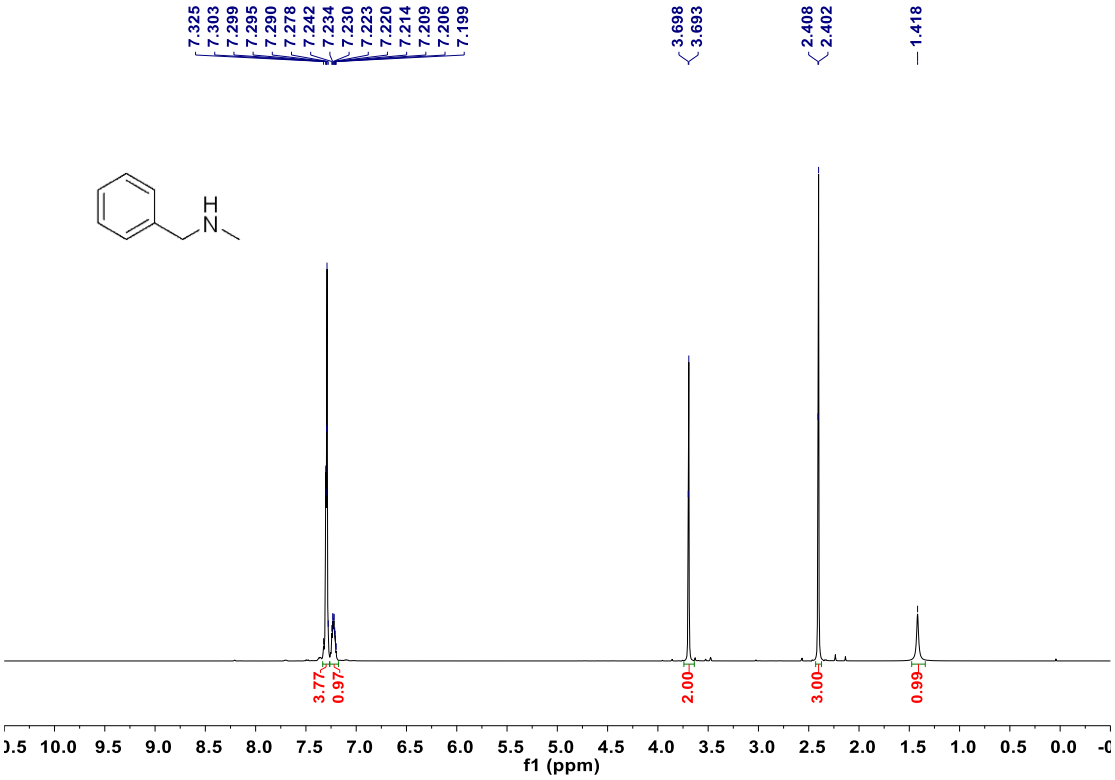


^{13}C NMR (101 MHz, $CDCl_3$)

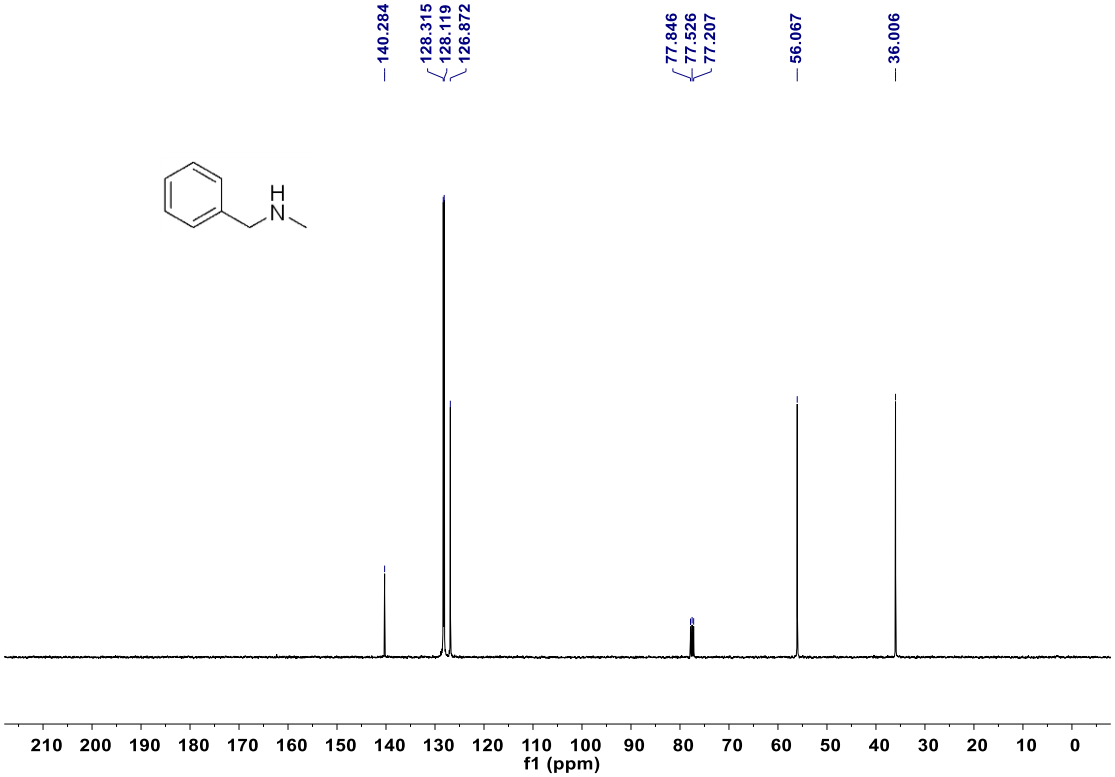


***N*-Methyl-1-phenylmethanamine (5an)**

^{1}H NMR (400 MHz, $CDCl_3$)

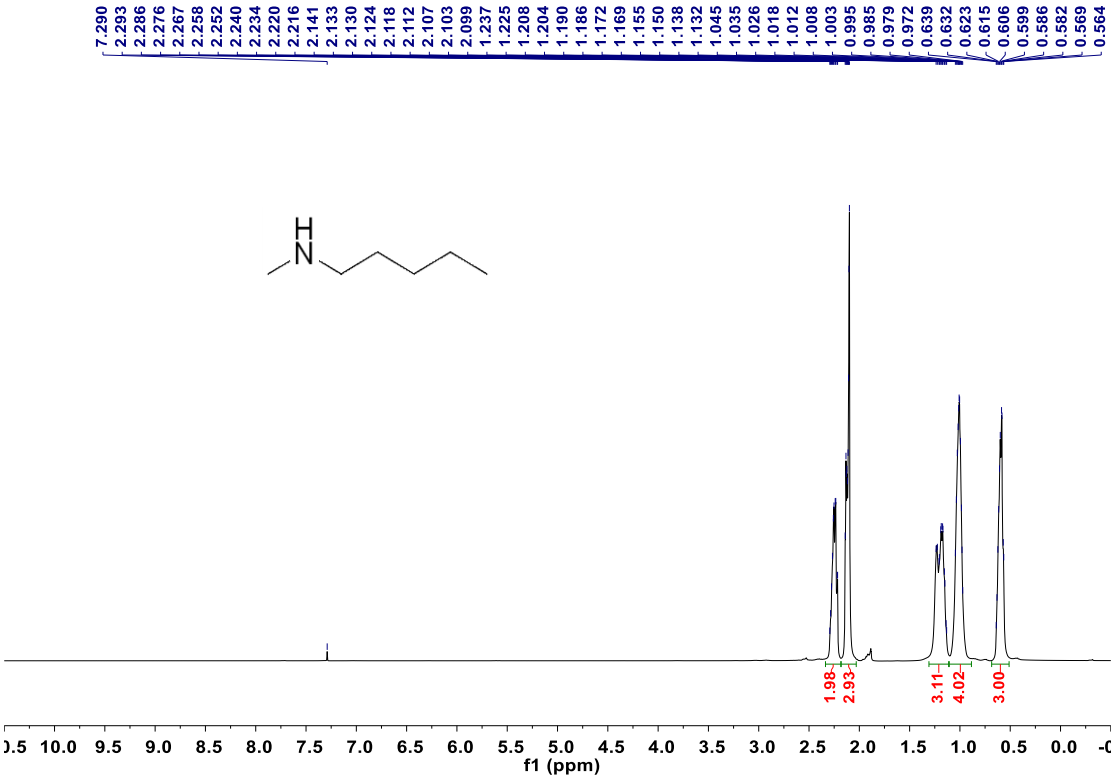


^{13}C NMR (101 MHz, $CDCl_3$)

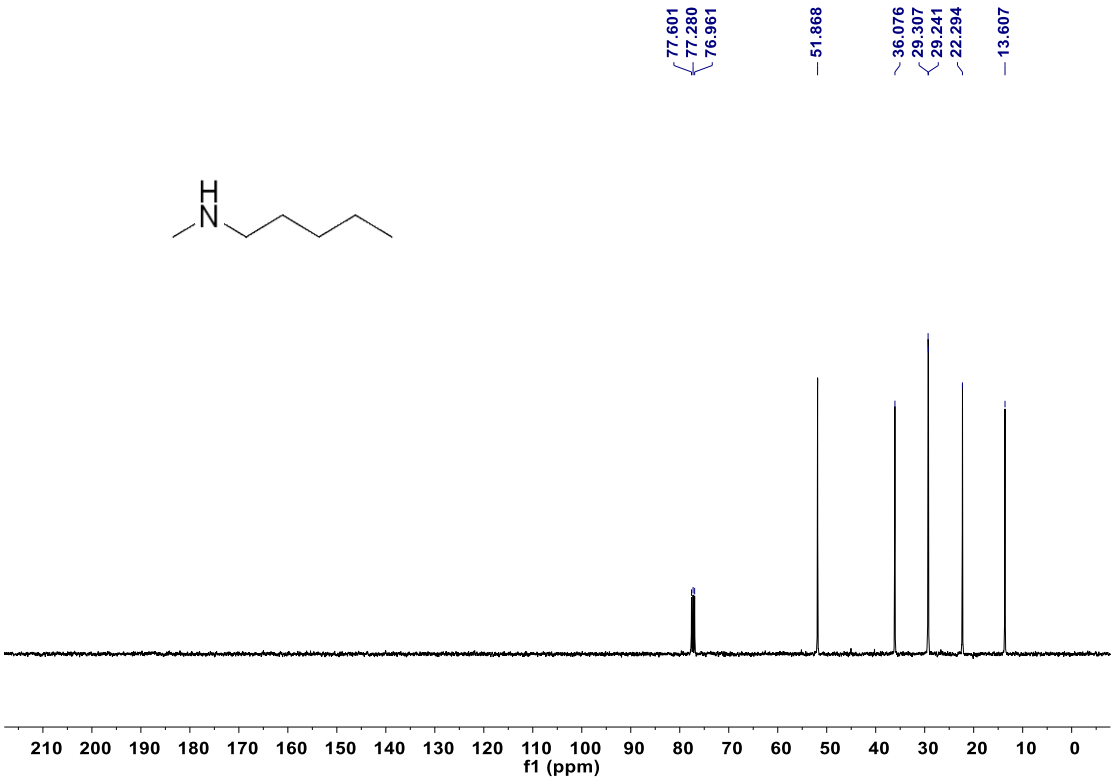


***N*-Methylpentan-1-amine (5ao)**

^{1}H NMR (400 MHz, $CDCl_3$)

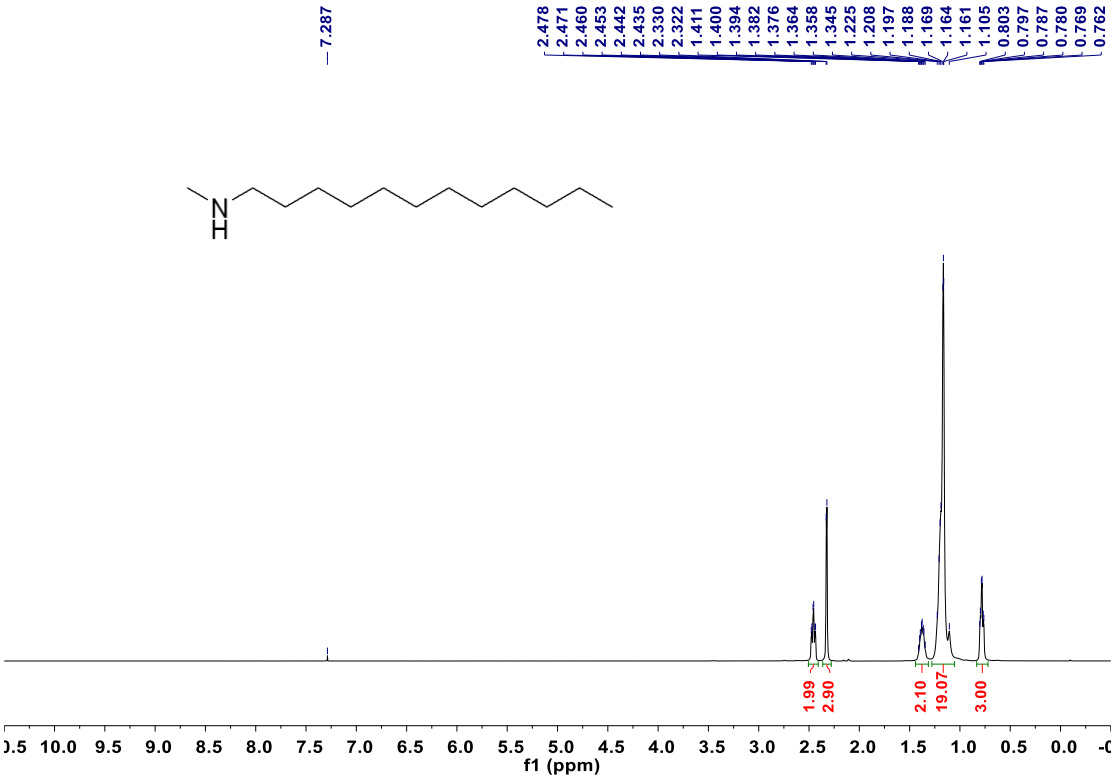


^{13}C NMR (101 MHz, $CDCl_3$)

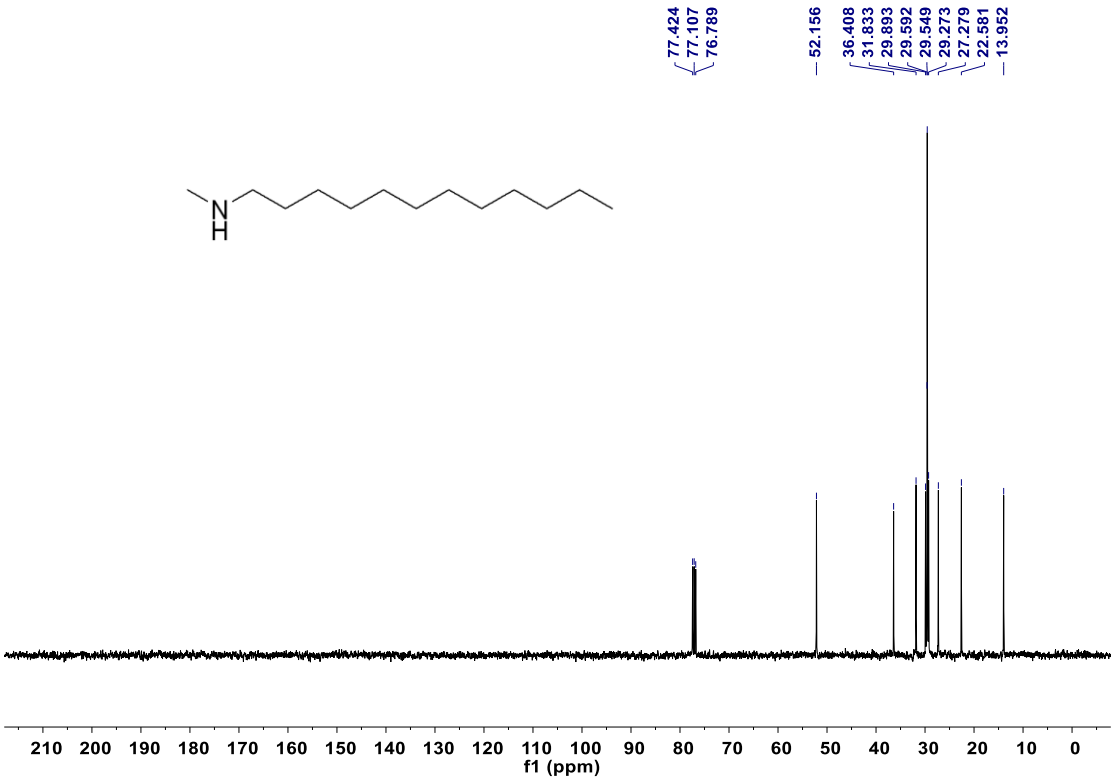


***N*-Methyldodecan-1-amine (5ap)**

^{1}H NMR (400 MHz, $CDCl_3$)

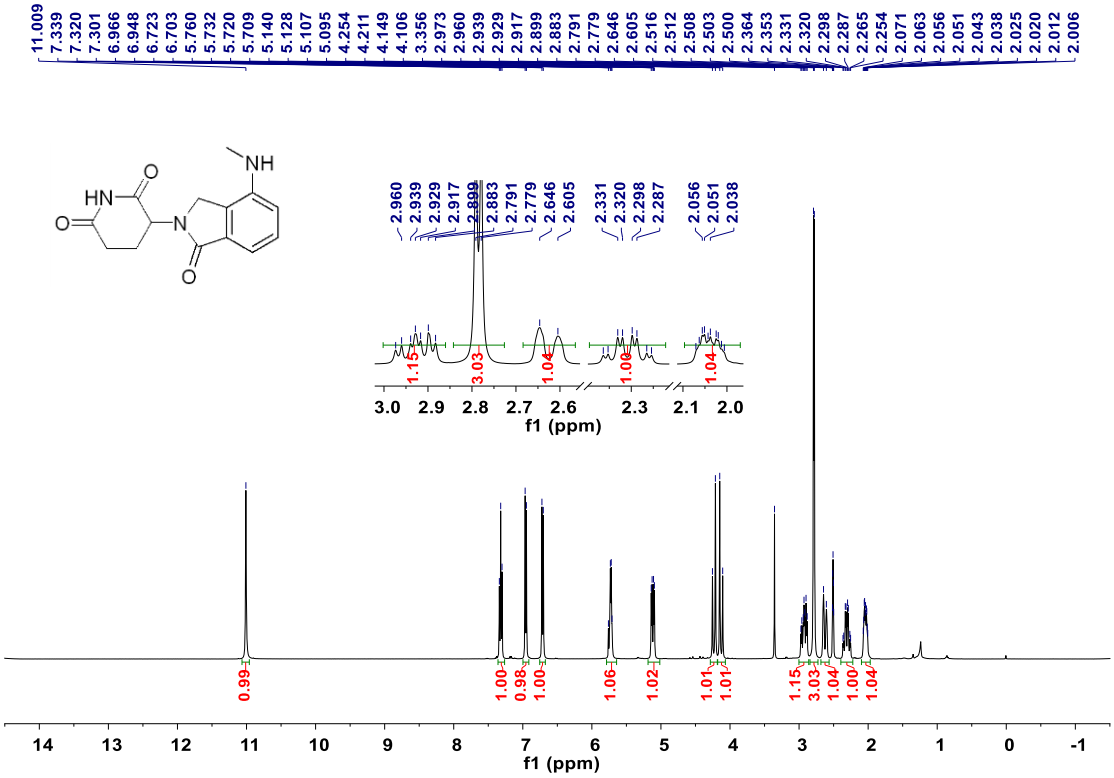


^{13}C NMR (101 MHz, $CDCl_3$)

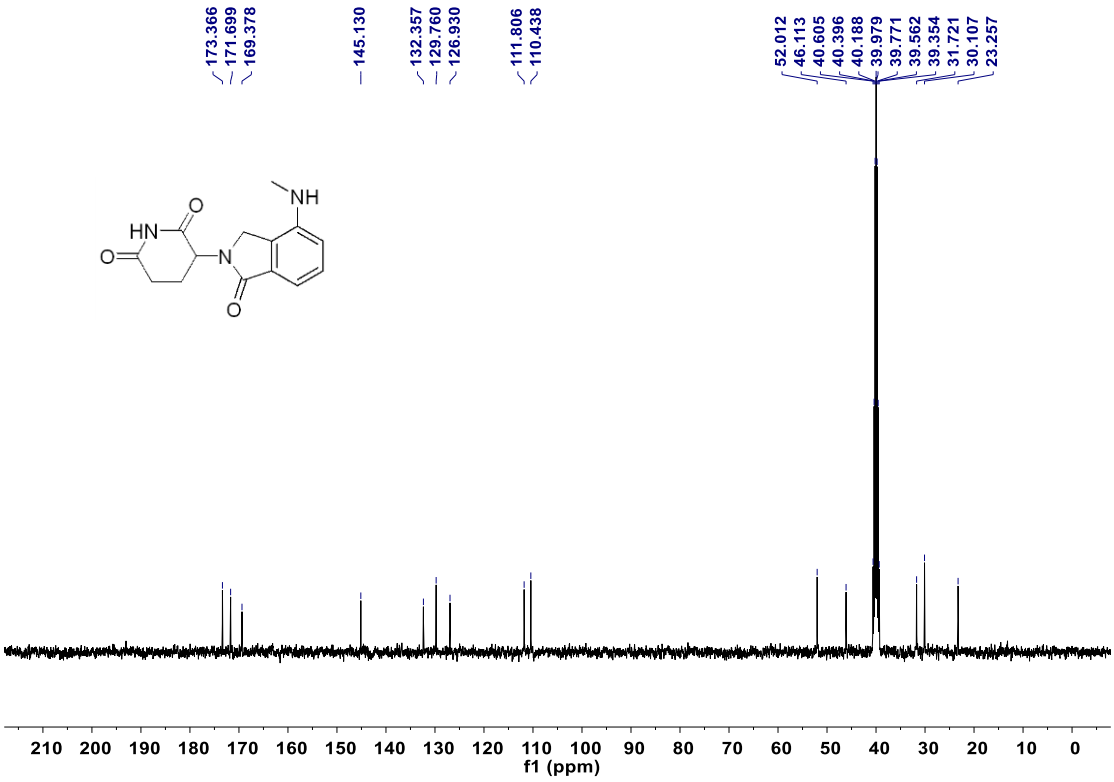


3-(4-(Methylamino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (7b)

^{1}H NMR (400 MHz, DMSO-d_6)

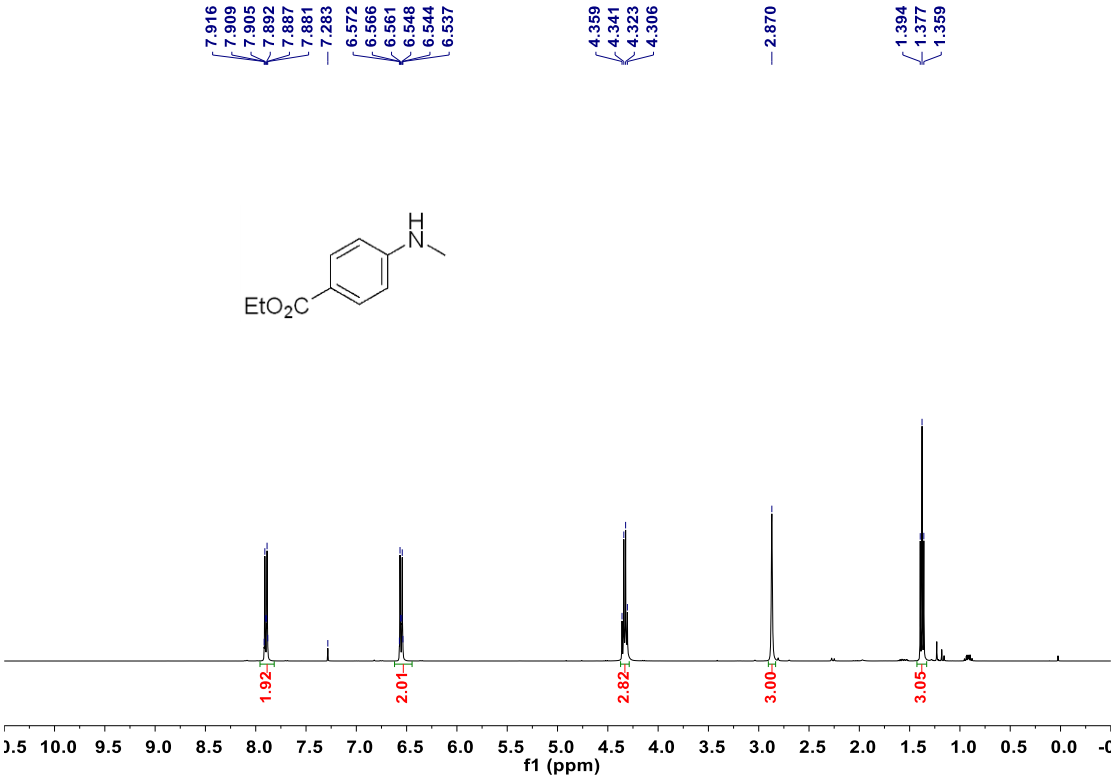


^{13}C NMR (101 MHz, DMSO-d_6)

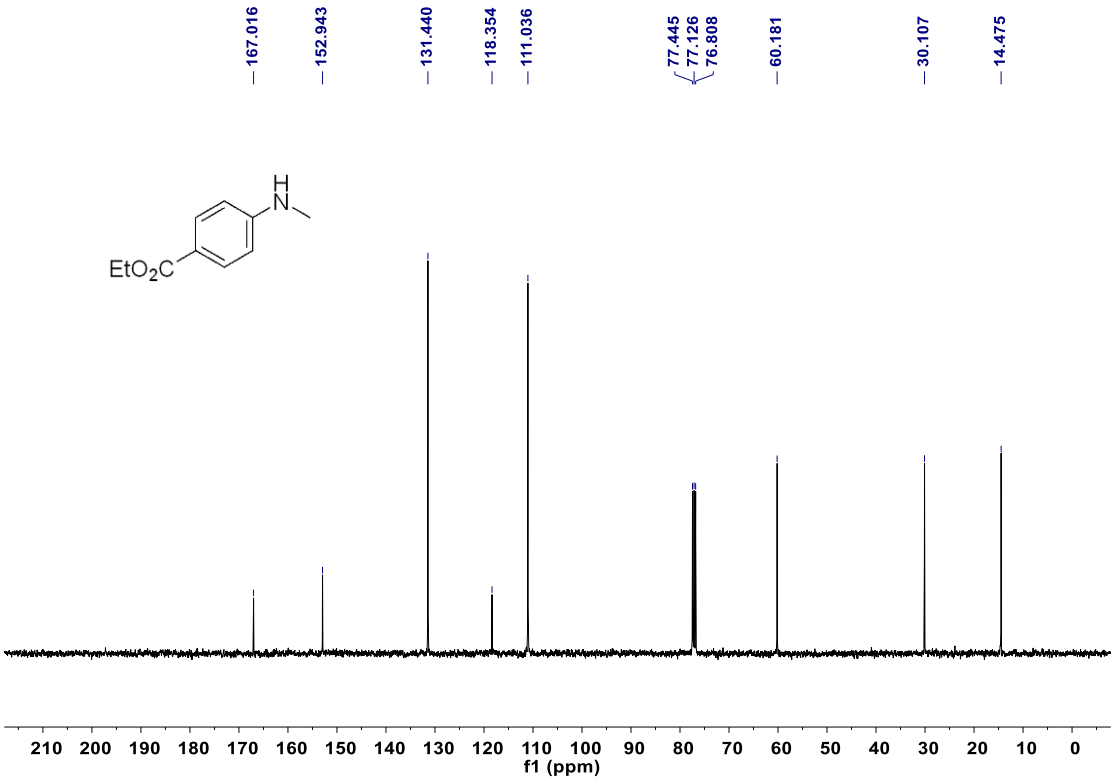


Ethyl 4-(methylamino)benzoate (7e)

^{1}H NMR (400 MHz, $CDCl_3$)

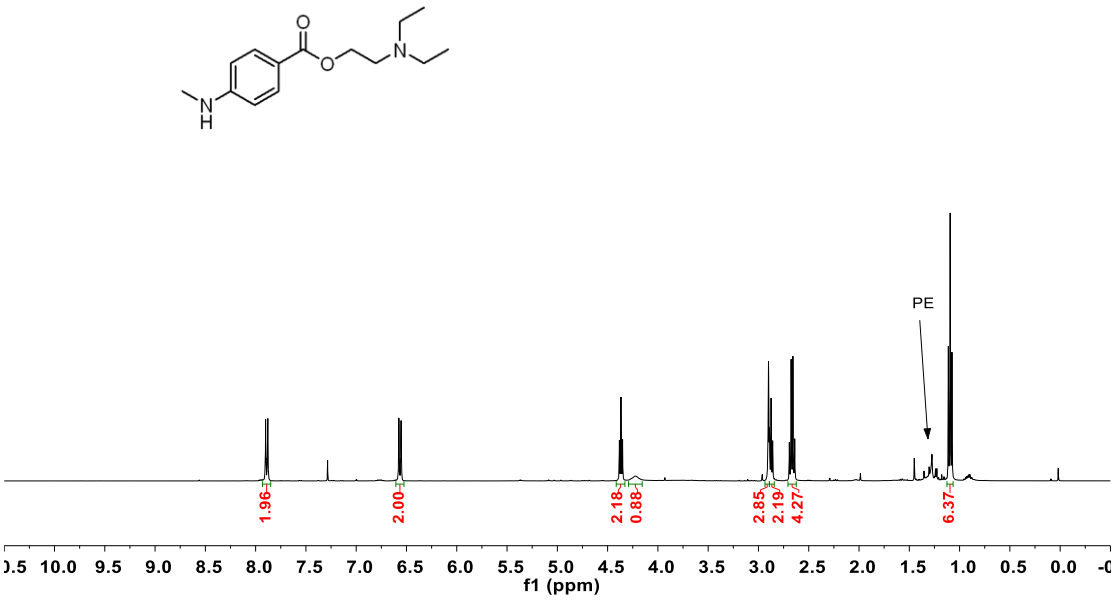


^{13}C NMR (101 MHz, $CDCl_3$)

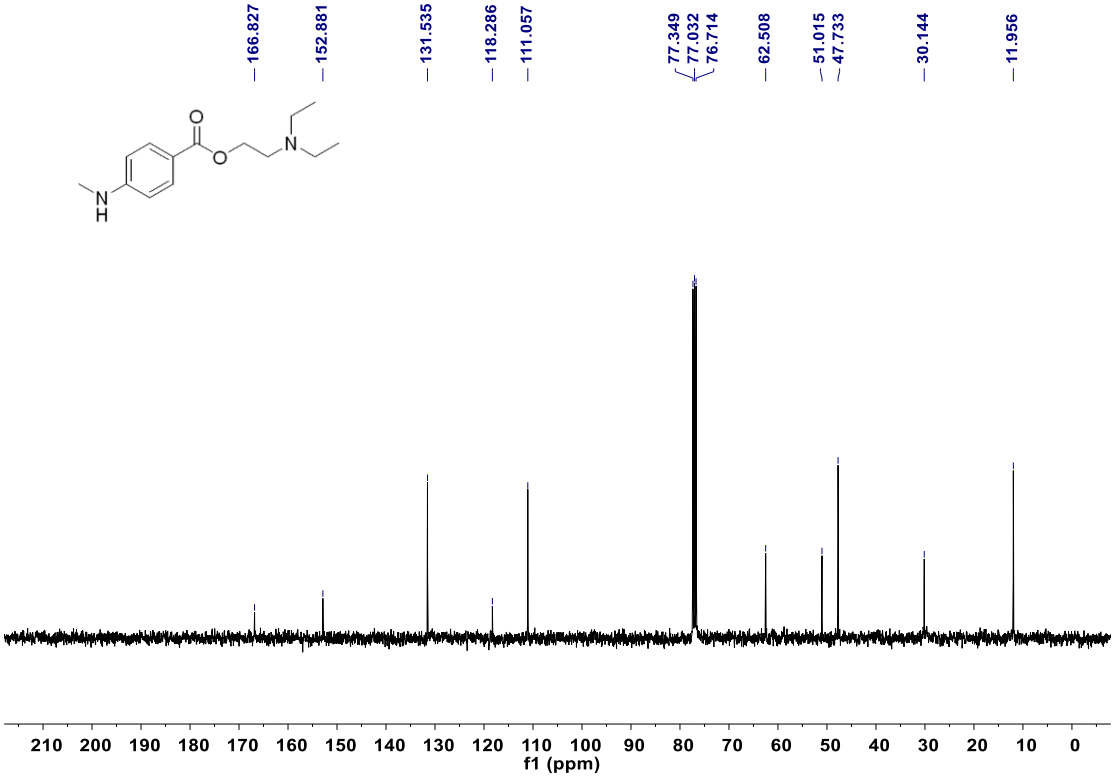


2-(Diethylamino)ethyl 4-(methylamino)benzoate (7f)

^{1}H NMR (400 MHz, $CDCl_3$)

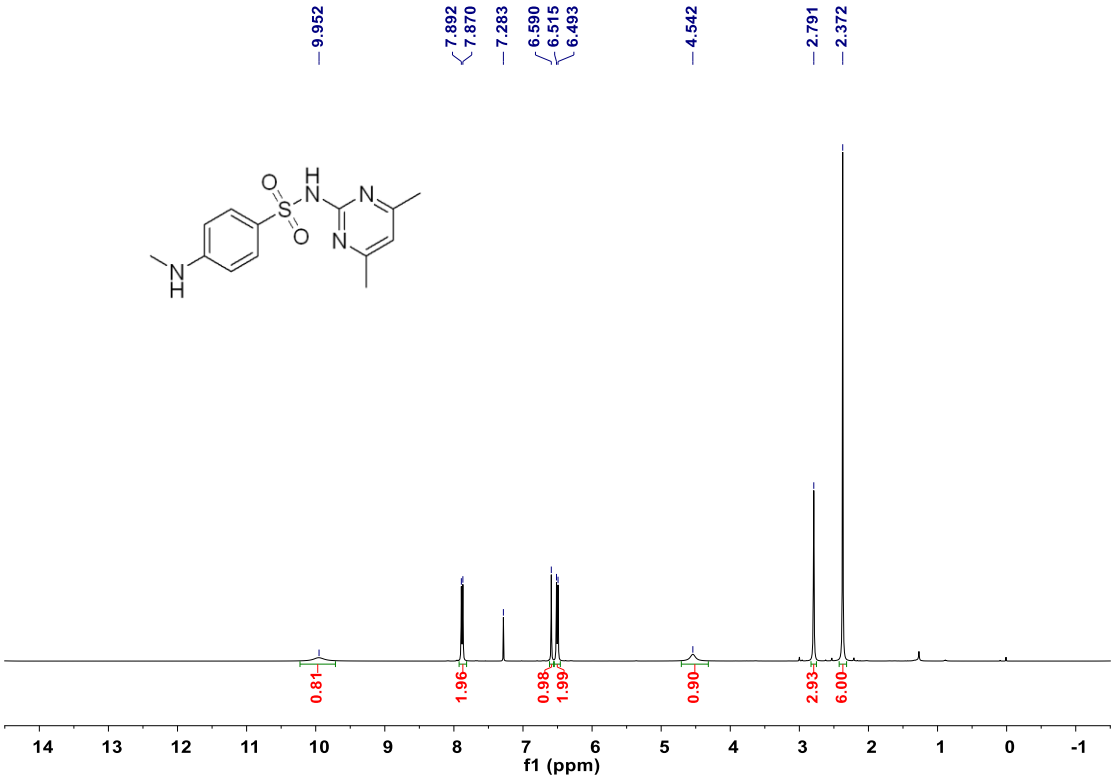


^{13}C NMR (101 MHz, $CDCl_3$)

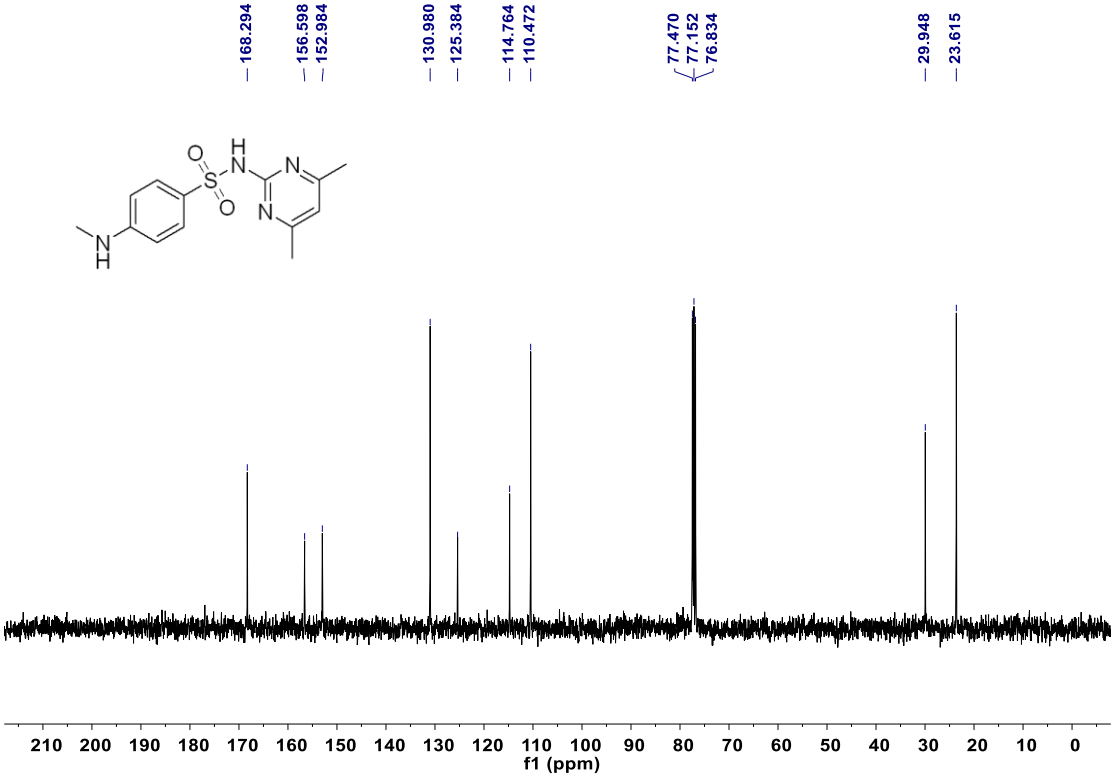


***N*-(4,6-Dimethylpyrimidin-2-yl)-4-(methylamino)benzenesulfonamide (7g)**

^{1}H NMR (400 MHz, $CDCl_3$)

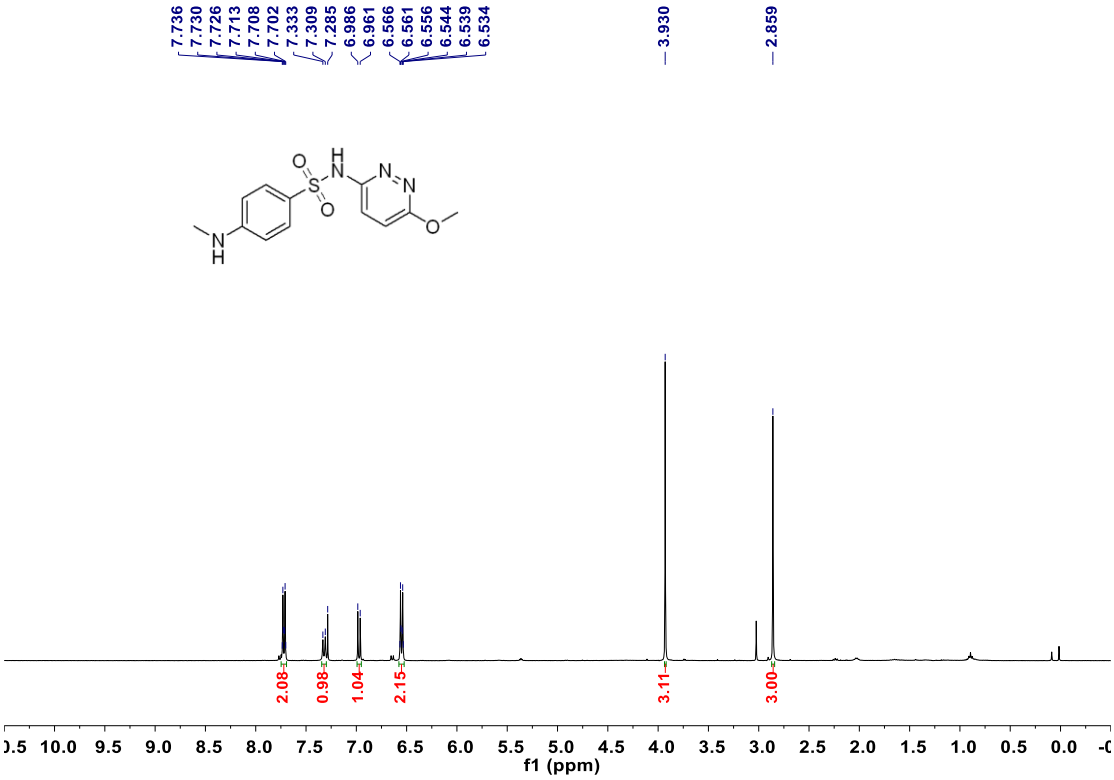


^{13}C NMR (101 MHz, $CDCl_3$)

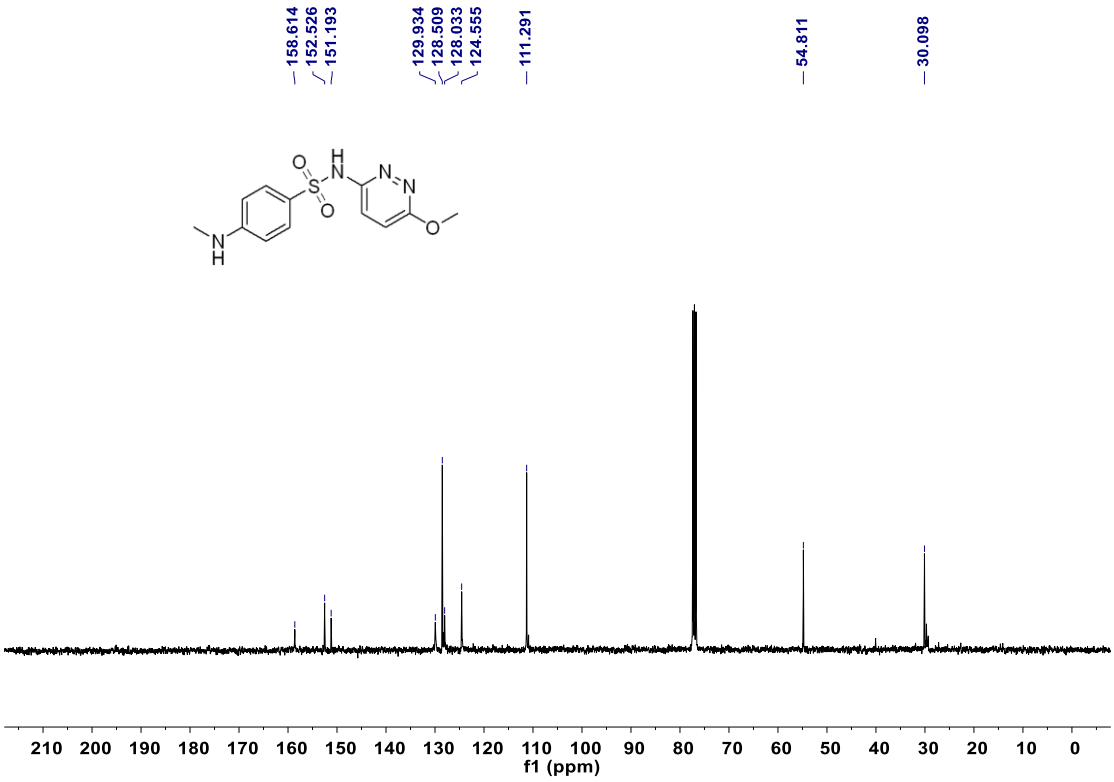


***N*-(6-Methoxypyridazin-3-yl)-4-(methylamino)benzenesulfonamide (7h)**

^{1}H NMR (400 MHz, $CDCl_3$)

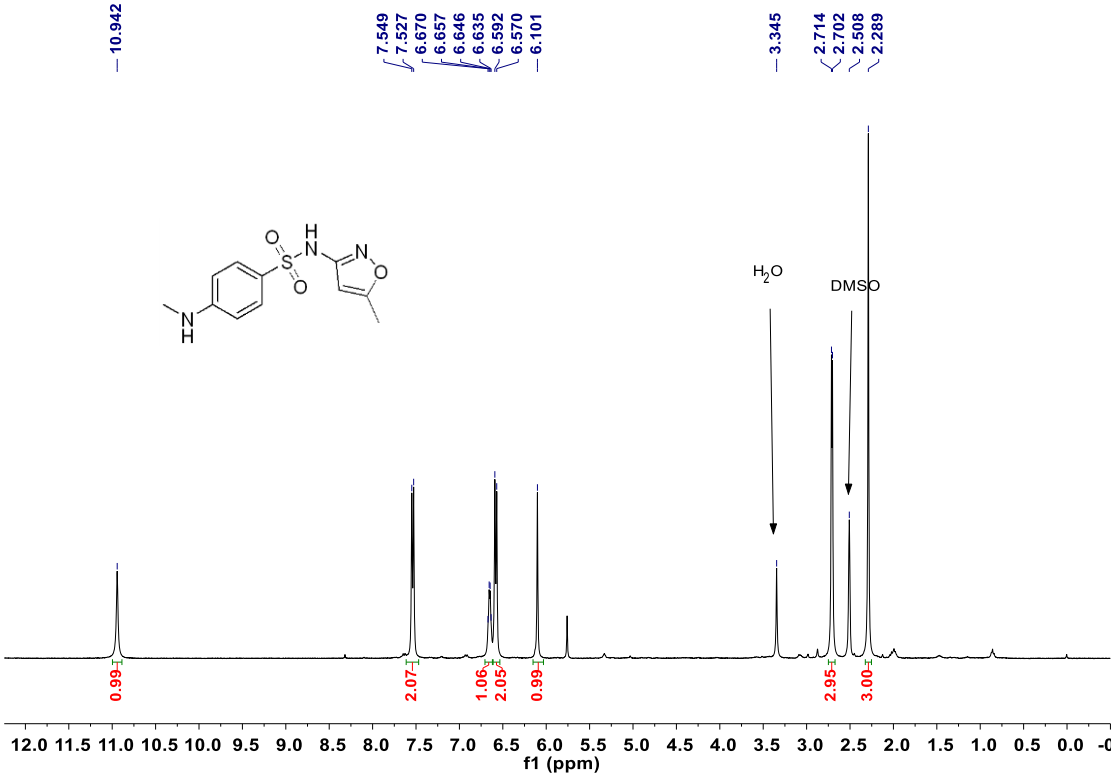


^{13}C NMR (101 MHz, $CDCl_3$)

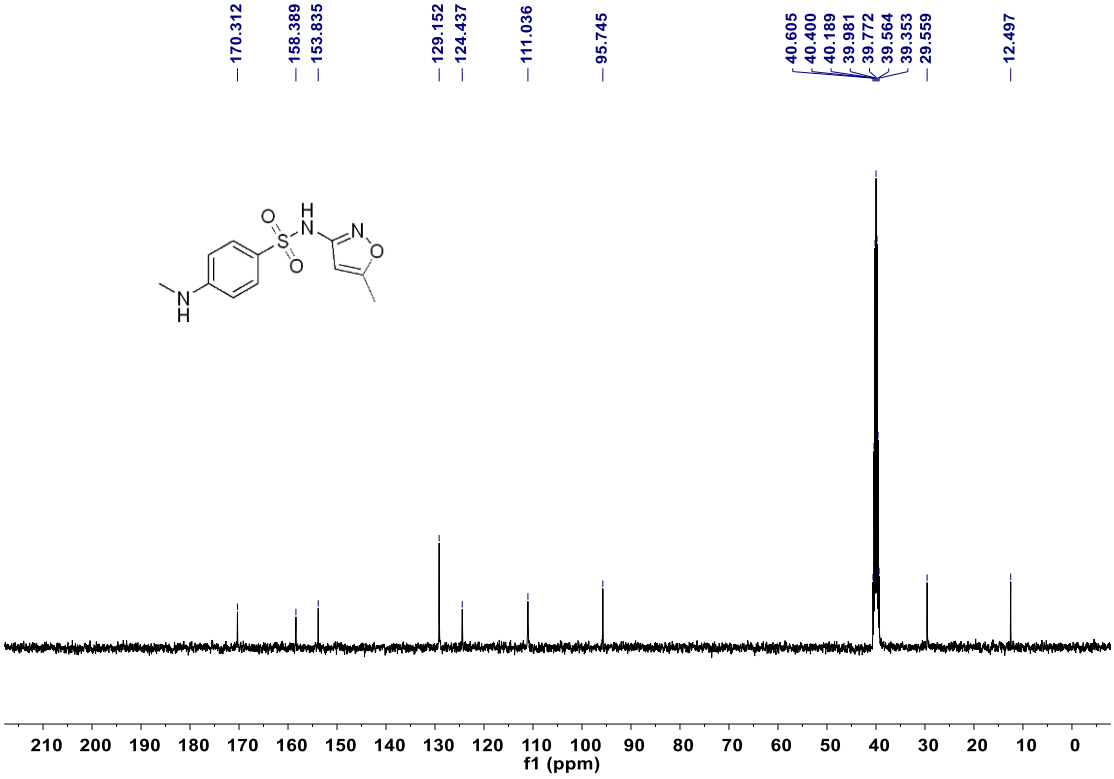


4-(Methylamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide (7i)

^{1}H NMR (400 MHz, DMSO-d_6)

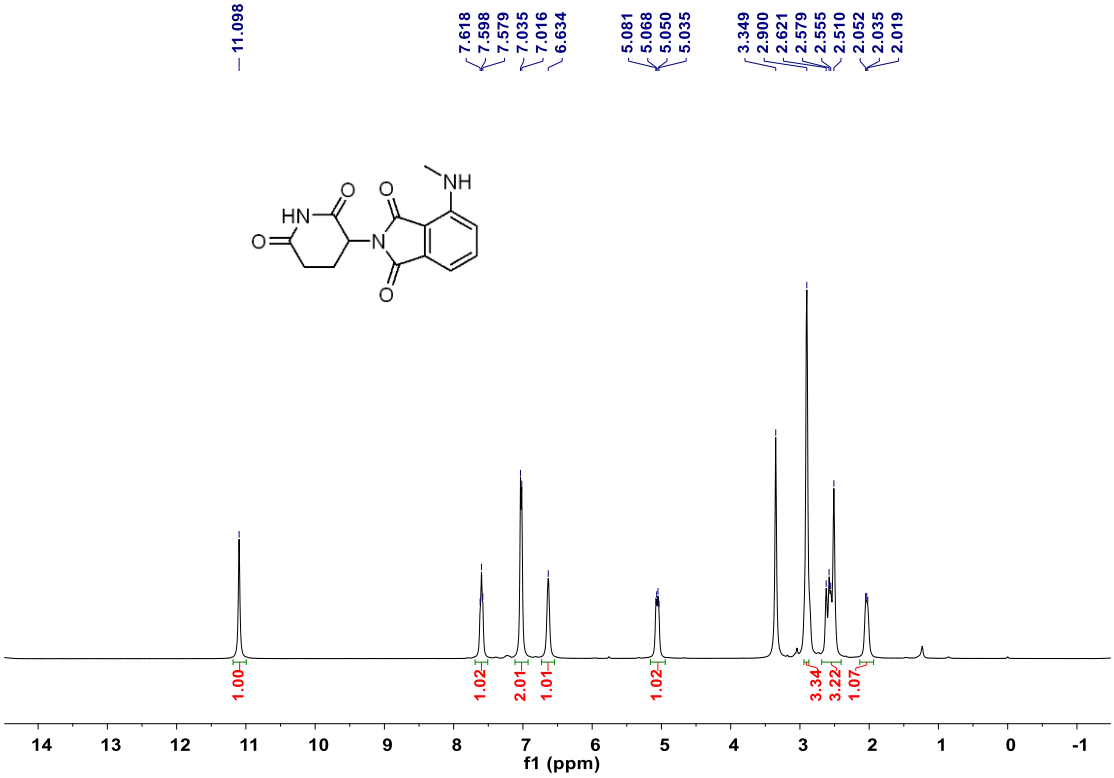


^{13}C NMR (101 MHz, DMSO-d_6)

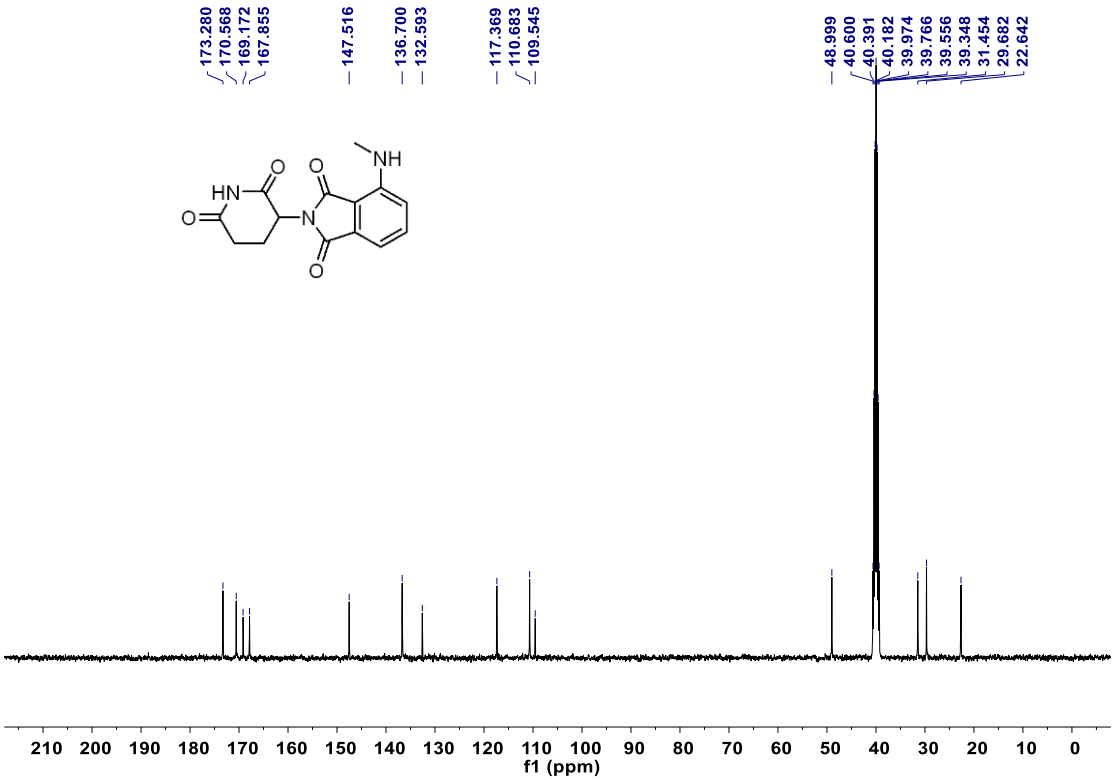


2-(2,6-Dioxopiperidin-3-yl)-4-(methylamino)isoindoline-1,3-dione (7q)

^{1}H NMR (400 MHz, DMSO-d_6)

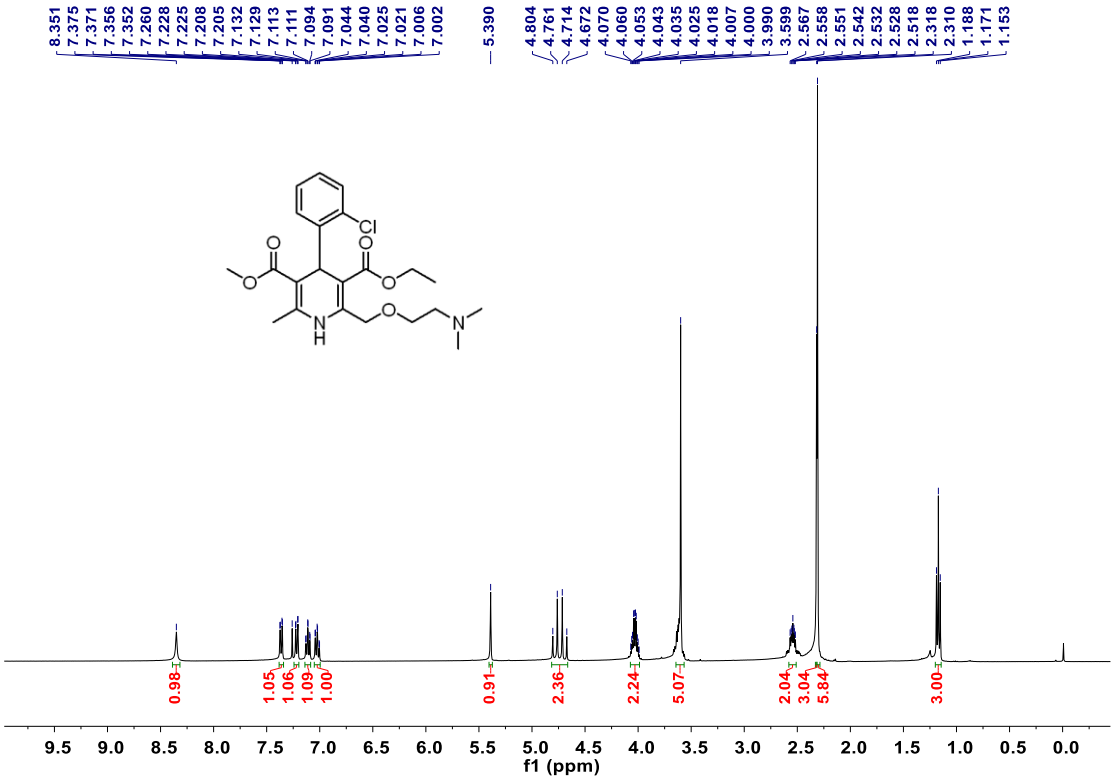


^{13}C NMR (101 MHz, DMSO-d_6)



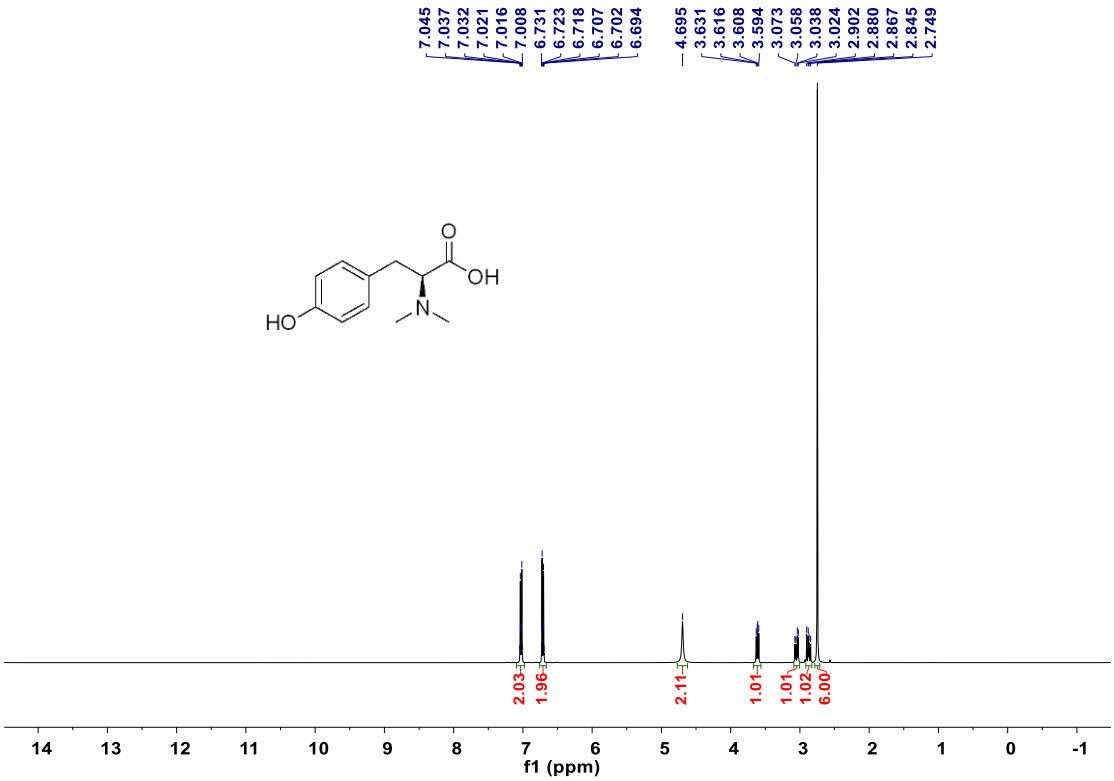
3-Ethyl-5-methyl-4-(2-chlorophenyl)-2-((2-(dimethylamino)ethoxy)methyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a) (Gram-level reaction)

^{1}H NMR (400 MHz, $CDCl_3$)



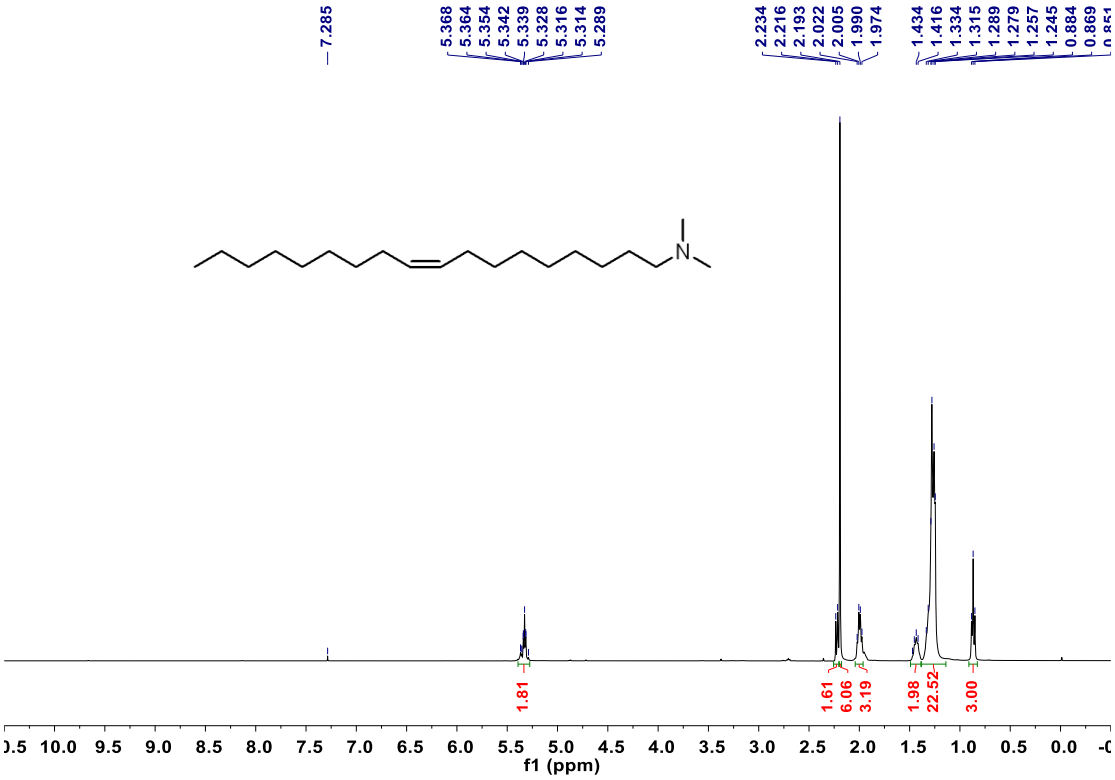
***N*,*N*-Dimethyl-*L*-tyrosine (4ab) (Decagram-level reaction)**

^{1}H NMR (400 MHz, D_2O)



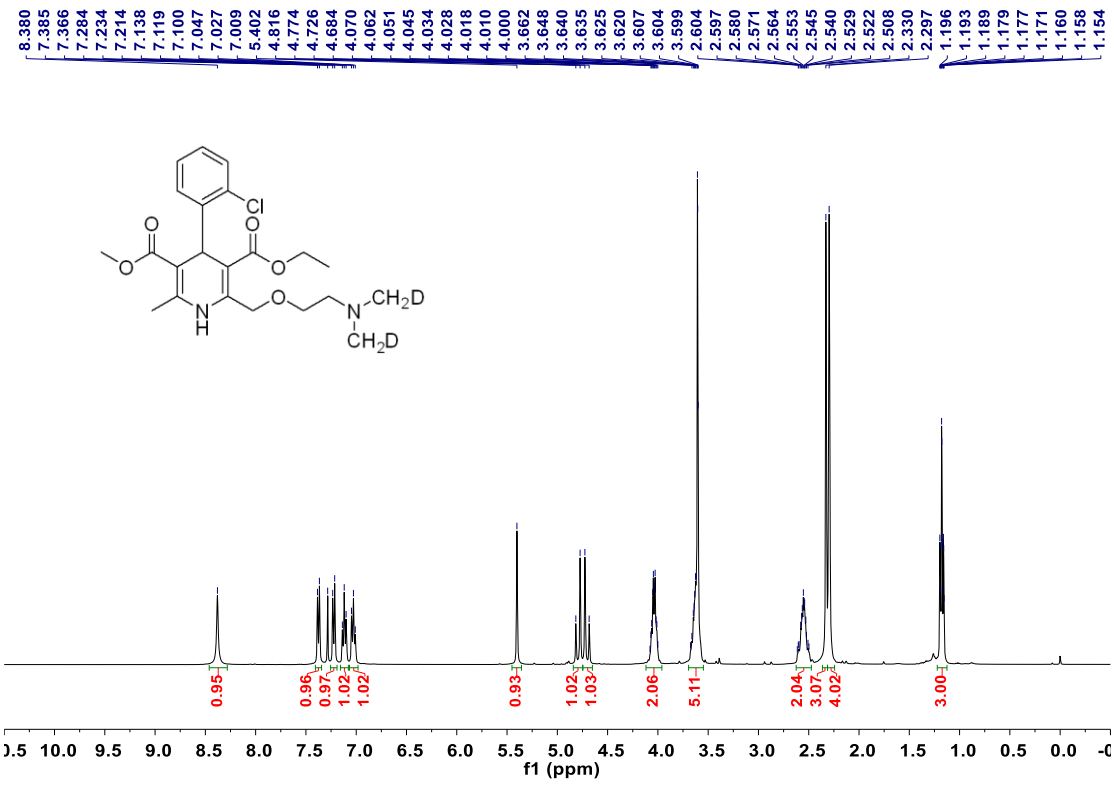
(*Z*)-*N*,*N*-Dimethyloctadec-9-en-1-amine (4w) (Decagram-level reaction)

^{1}H NMR (400 MHz, $CDCl_3$)

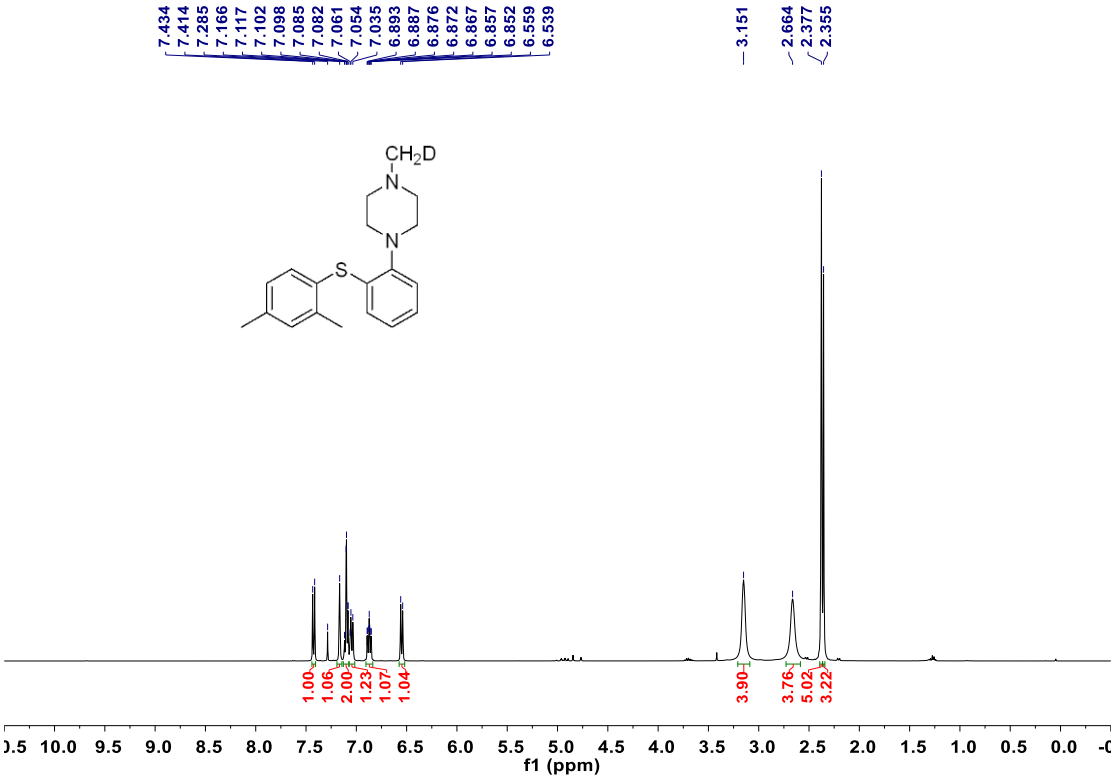


3-Ethyl 5-methyl 2-((2-(bis(methyl-*d*)amino)ethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-d_2)

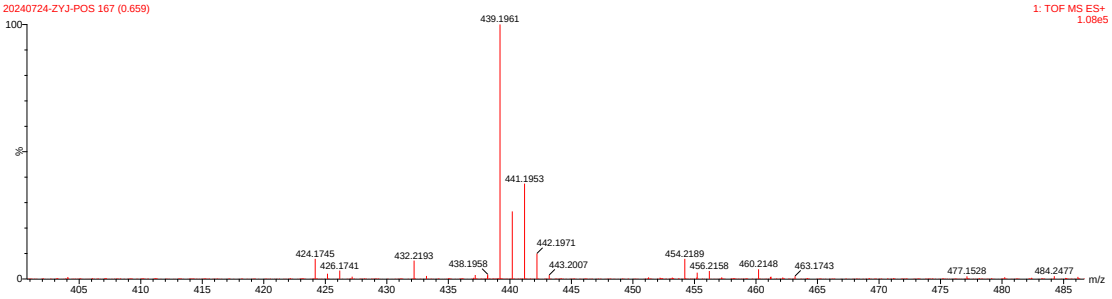
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

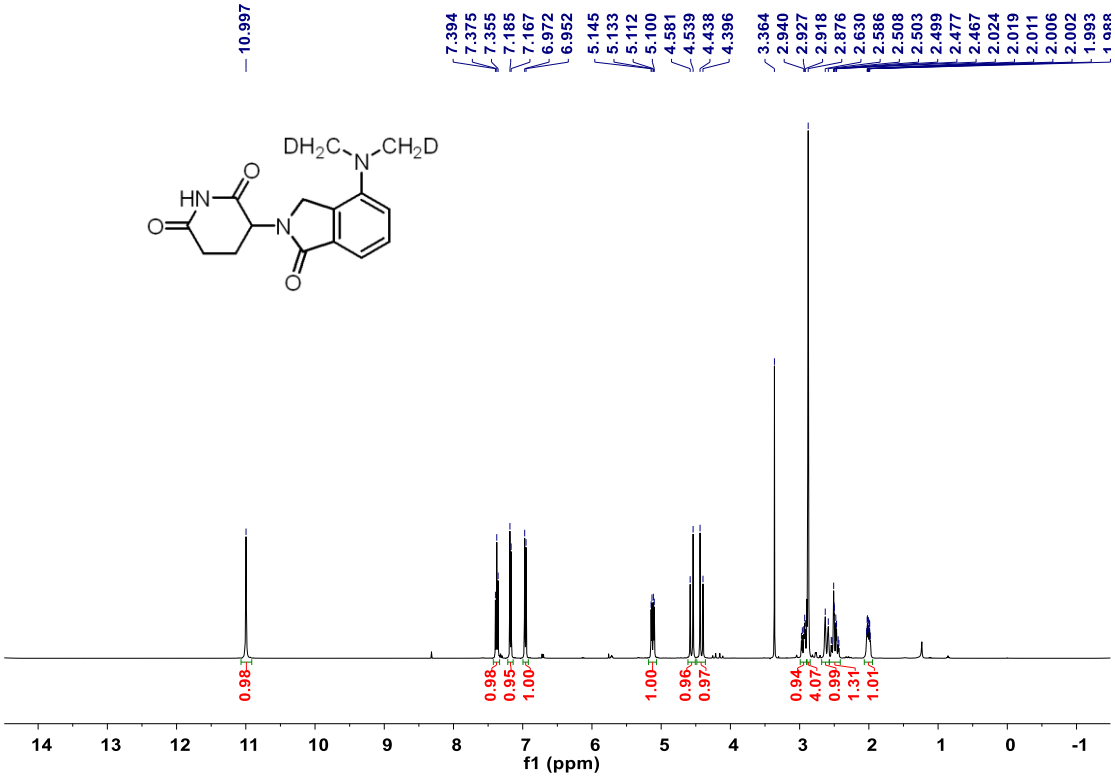


HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}D_2ClN_2O_5^+$, 439.1963; found, 439.1961.

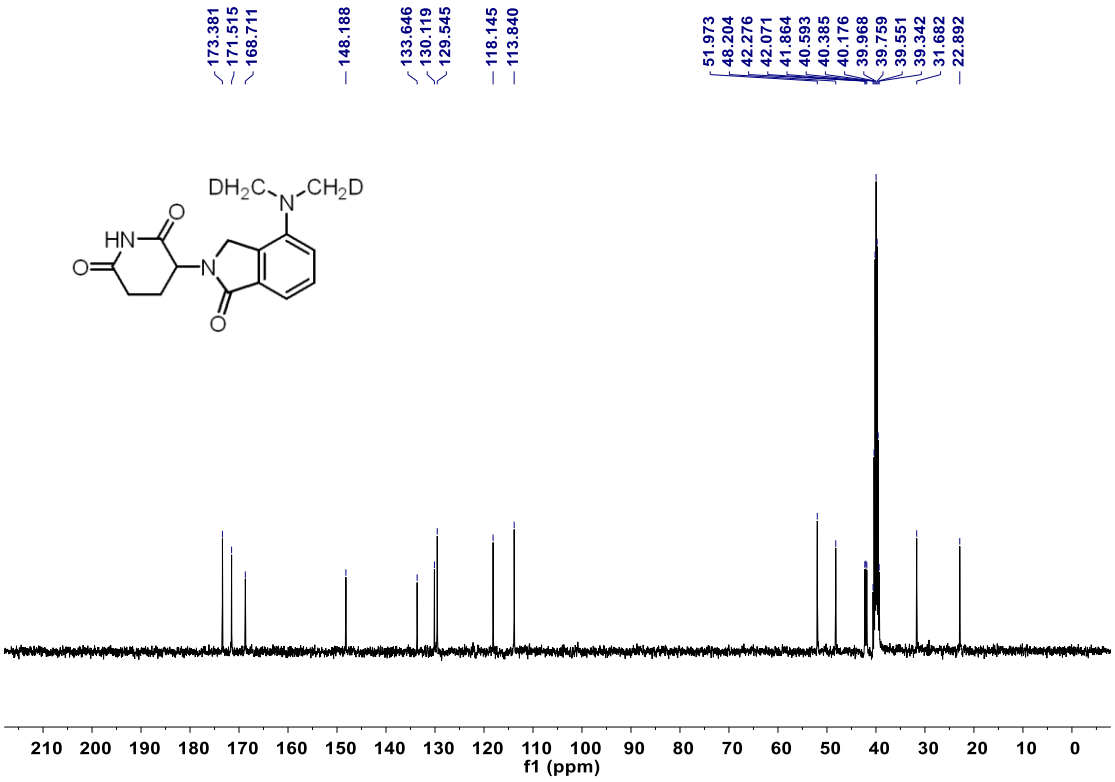


3-(4-(Bis(methyl-*d*)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b-d_2)

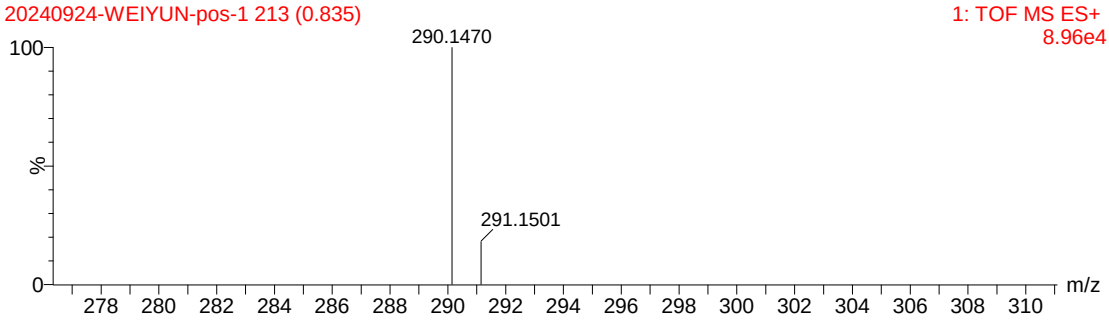
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (101 MHz, DMSO-d_6)

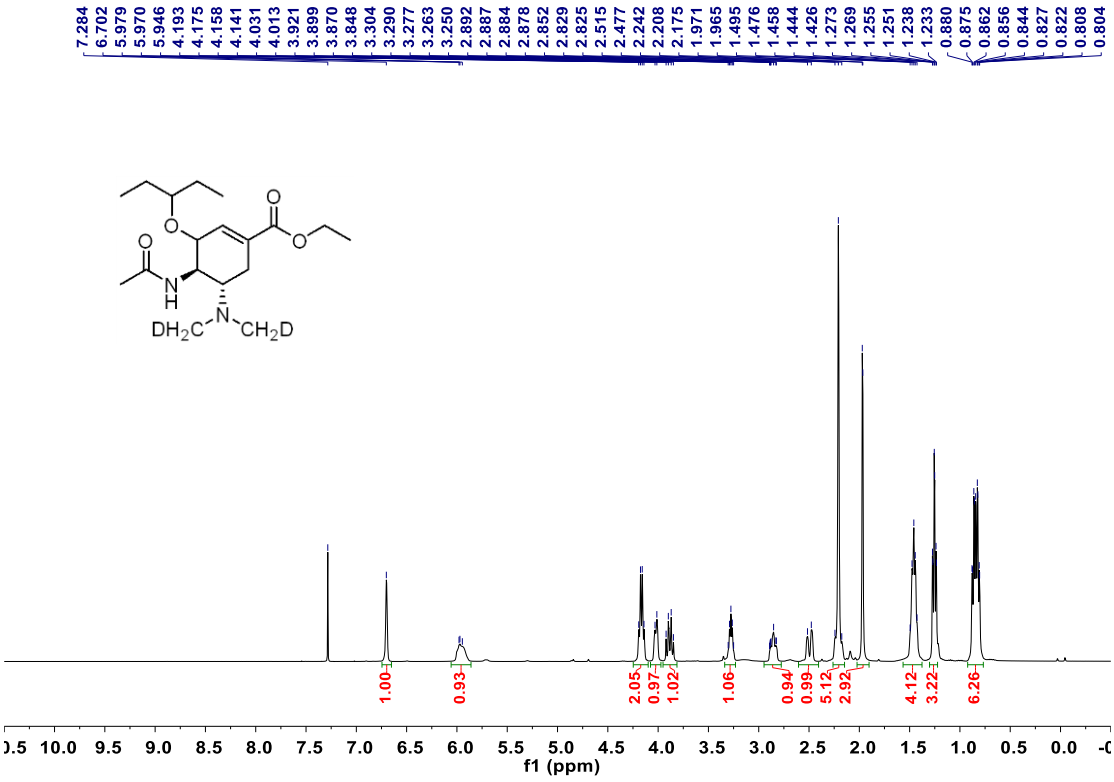


HRMS (ESI): *m/z* calcd for : $C_{15}H_{16}D_2N_3O_3^+$ $[M+H]^+$: 290.1468, found: 290.1470.

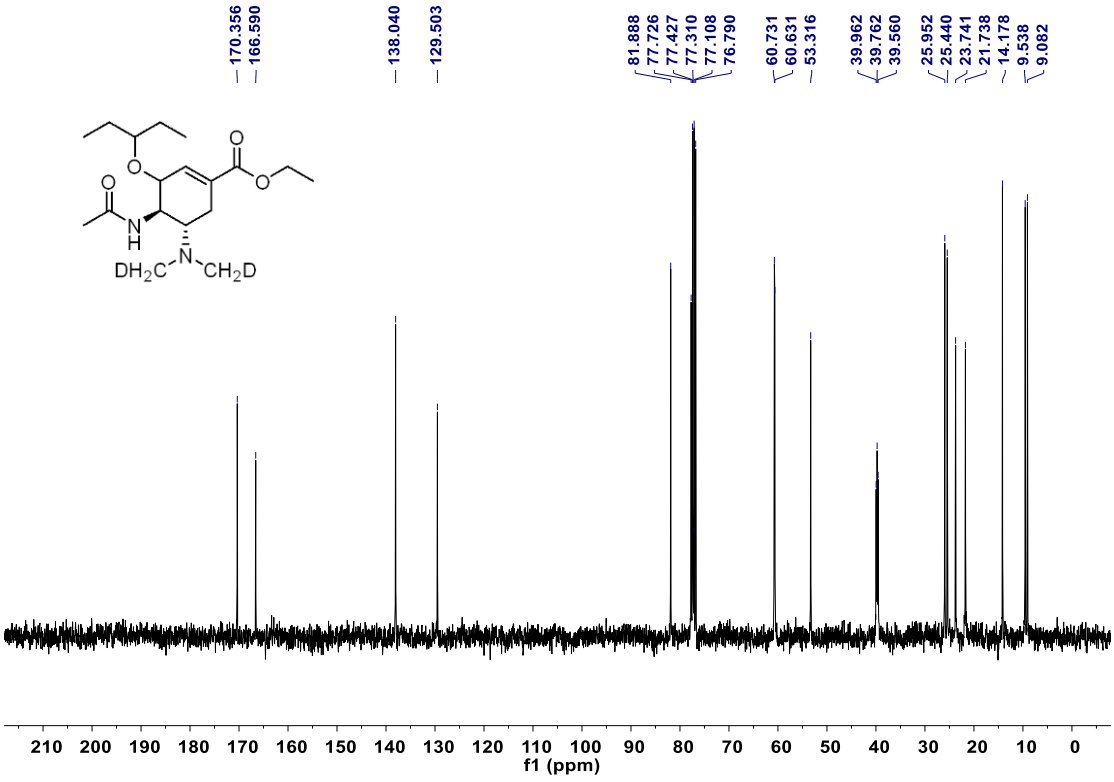


Ethyl (4*R*,5*S*)-4-acetamido-5-(bis(methyl-*d*)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d-d_2)

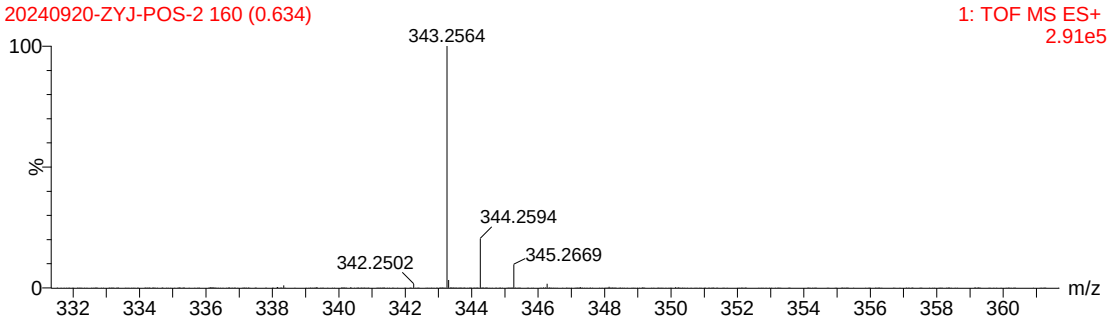
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

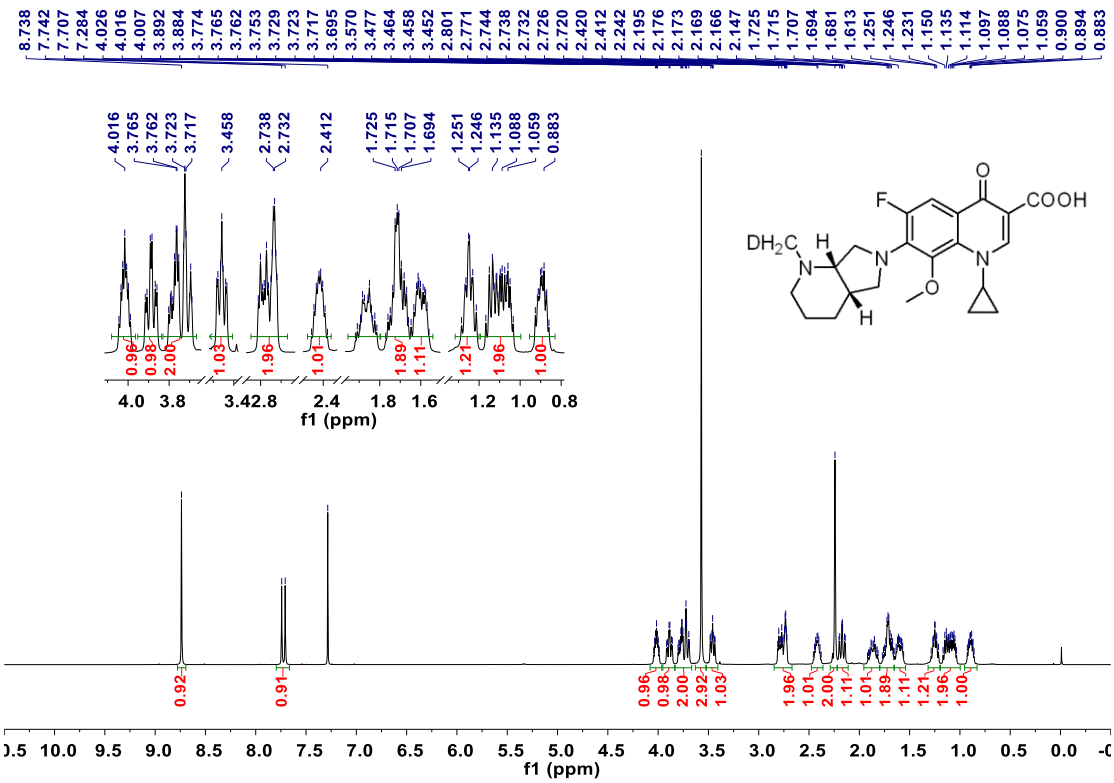


HRMS (ESI): *m/z* calcd for: $C_{18}H_{31}D_2N_2O_4^+$ $[M+H]^+$: 343.2560, found: 343.2564.

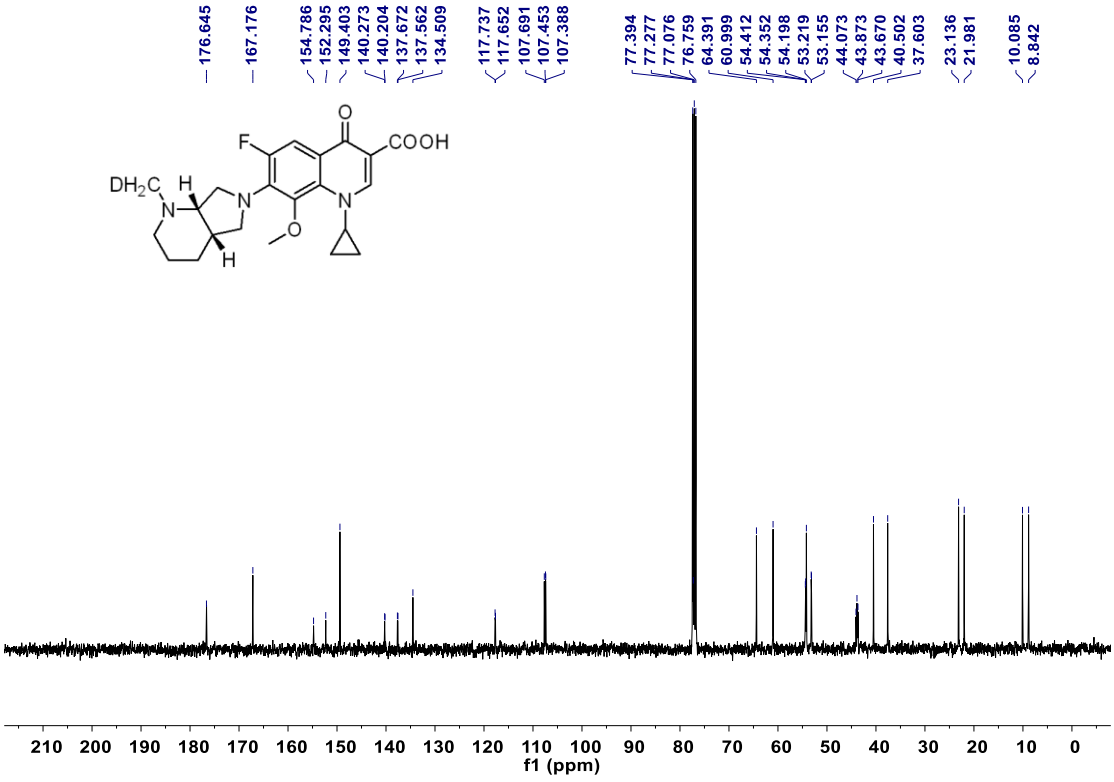


1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-(methyl-*d*)octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2l-*d*)

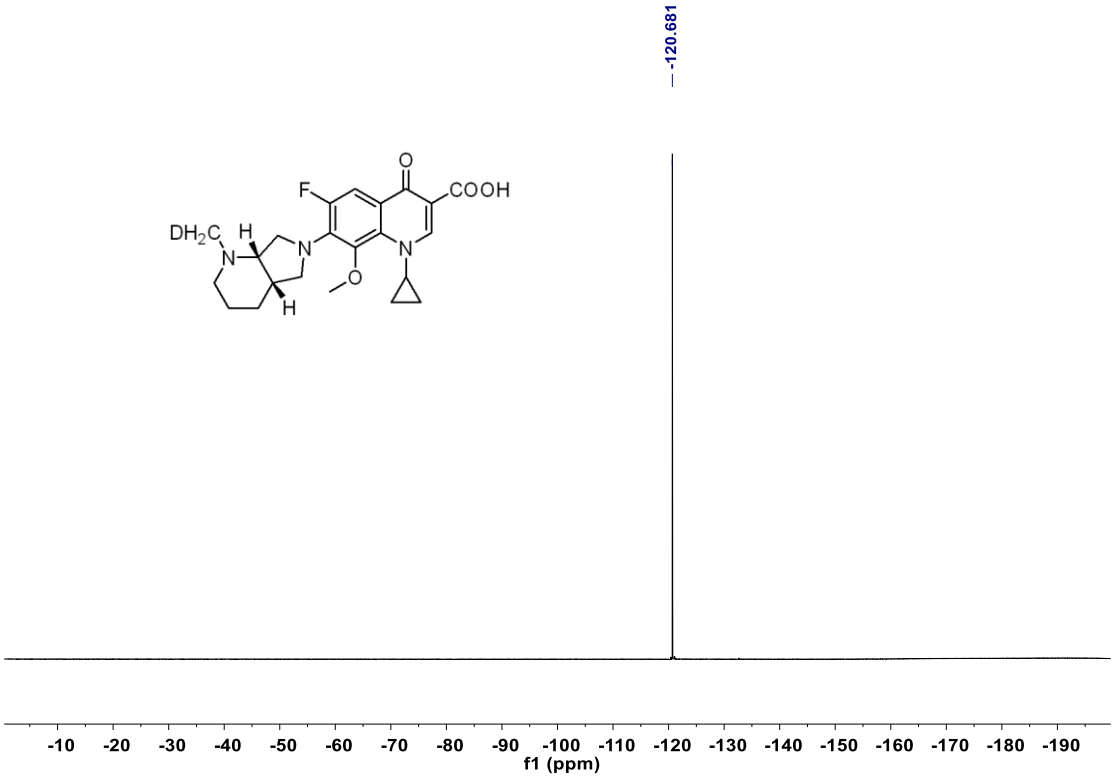
^{1}H NMR (400 MHz, $CDCl_3$)



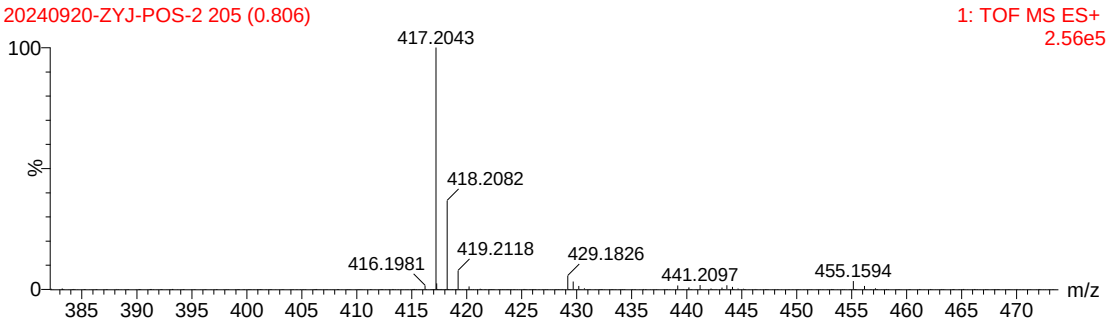
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

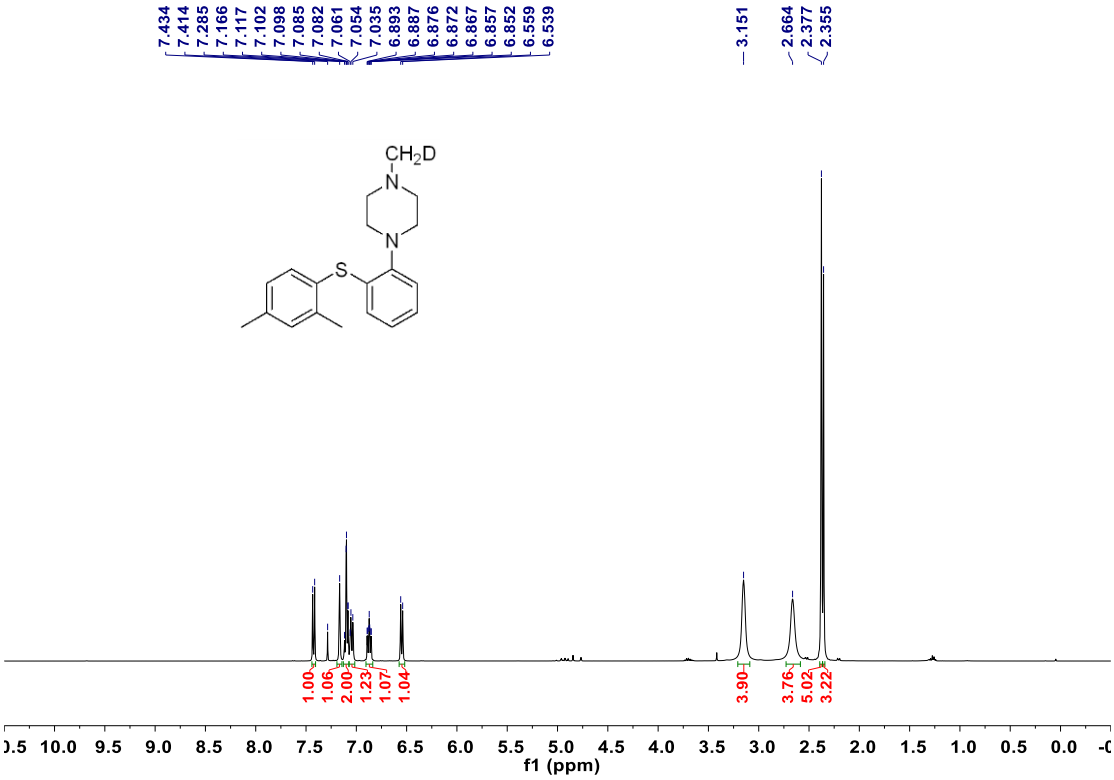


HRMS (ESI): *m/z* calcd for : $C_{22}H_{26}DFN_3O_4^+$ [M+H]$^+$: 417.2043, found: 417.2043.

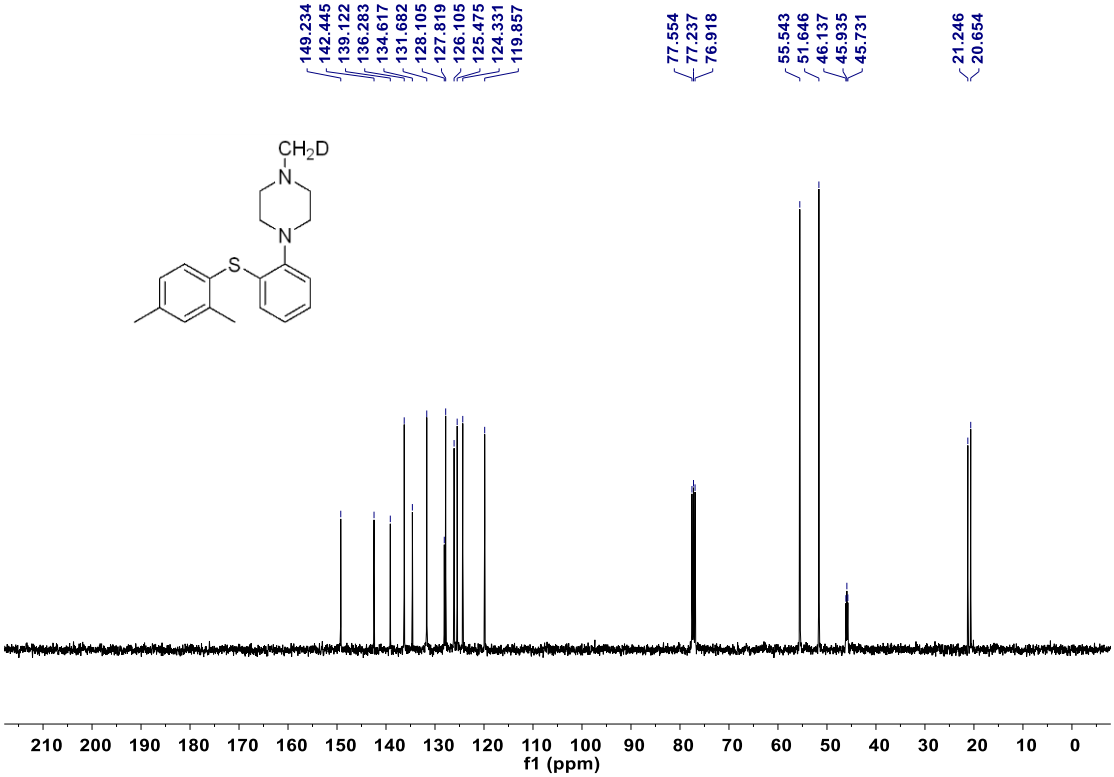


1-(2-((2,4-Dimethylphenyl)thio)phenyl)-4-(methyl-*d*)piperazine (2m-*d*)

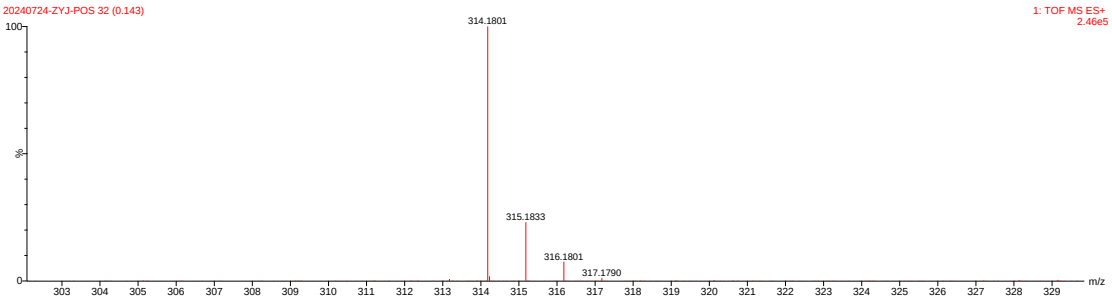
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

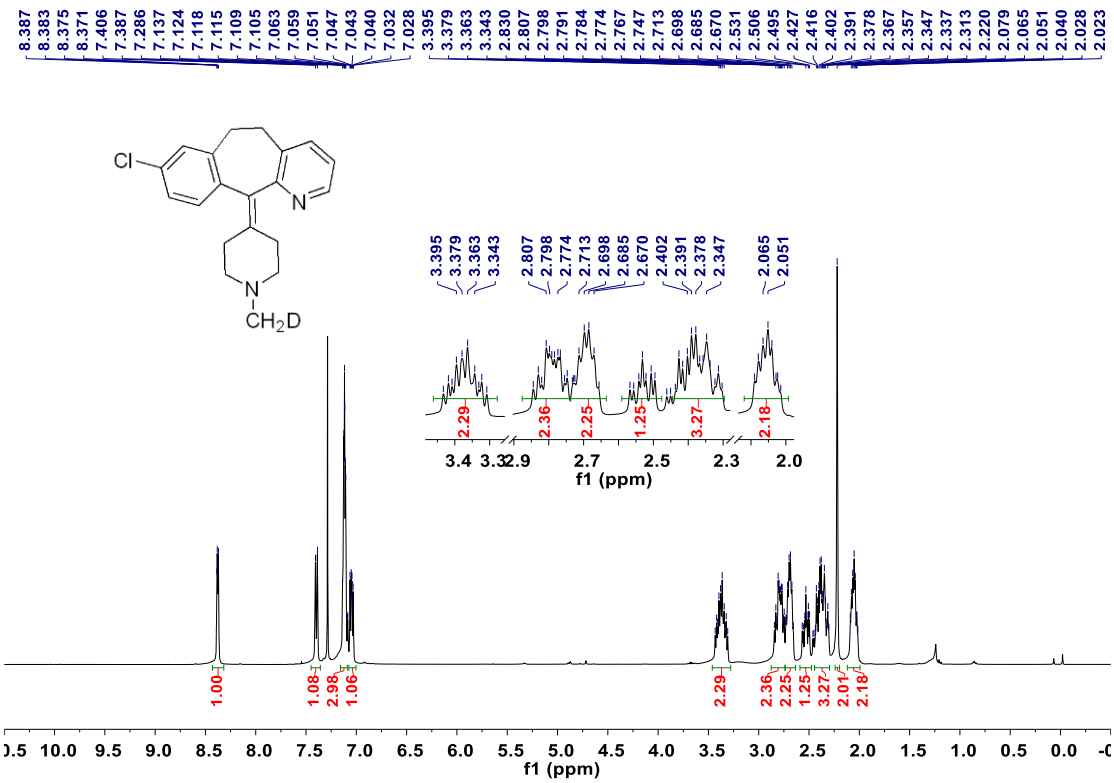


HRMS (ESI): *m/z* calcd for: $C_{19}H_{24}DN_2S^+$ $[M+H]^+$: 314.1796; found, 314.1801.

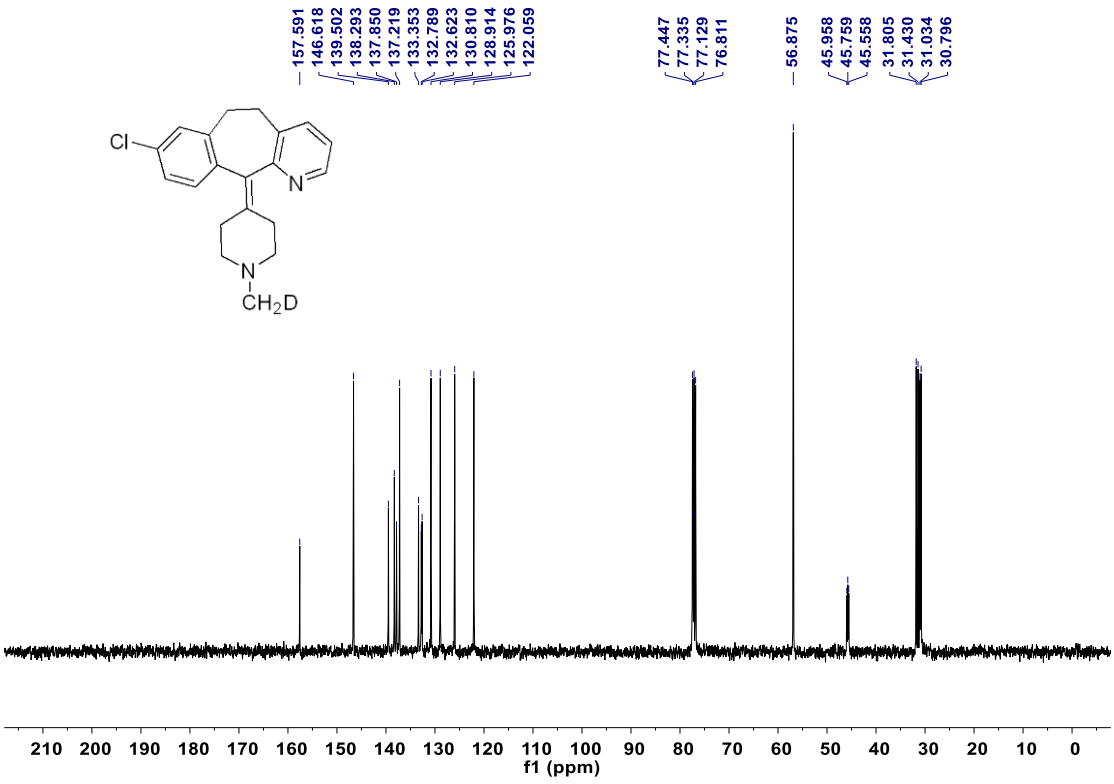


8-Chloro-11-(1-(methyl-*d*)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2p-*d*)

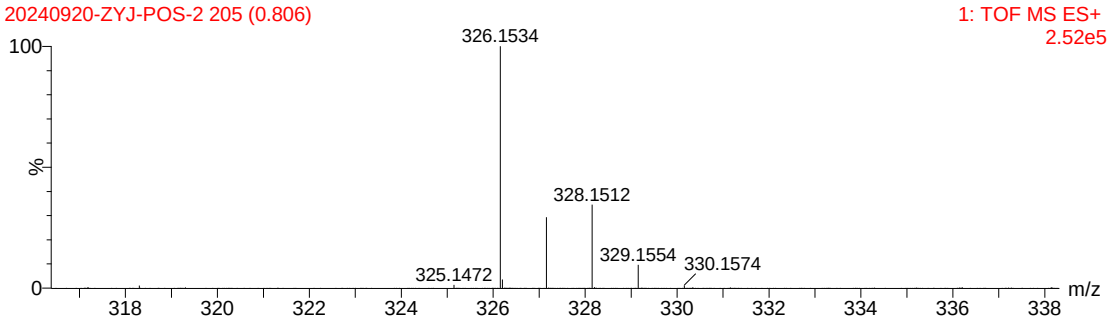
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

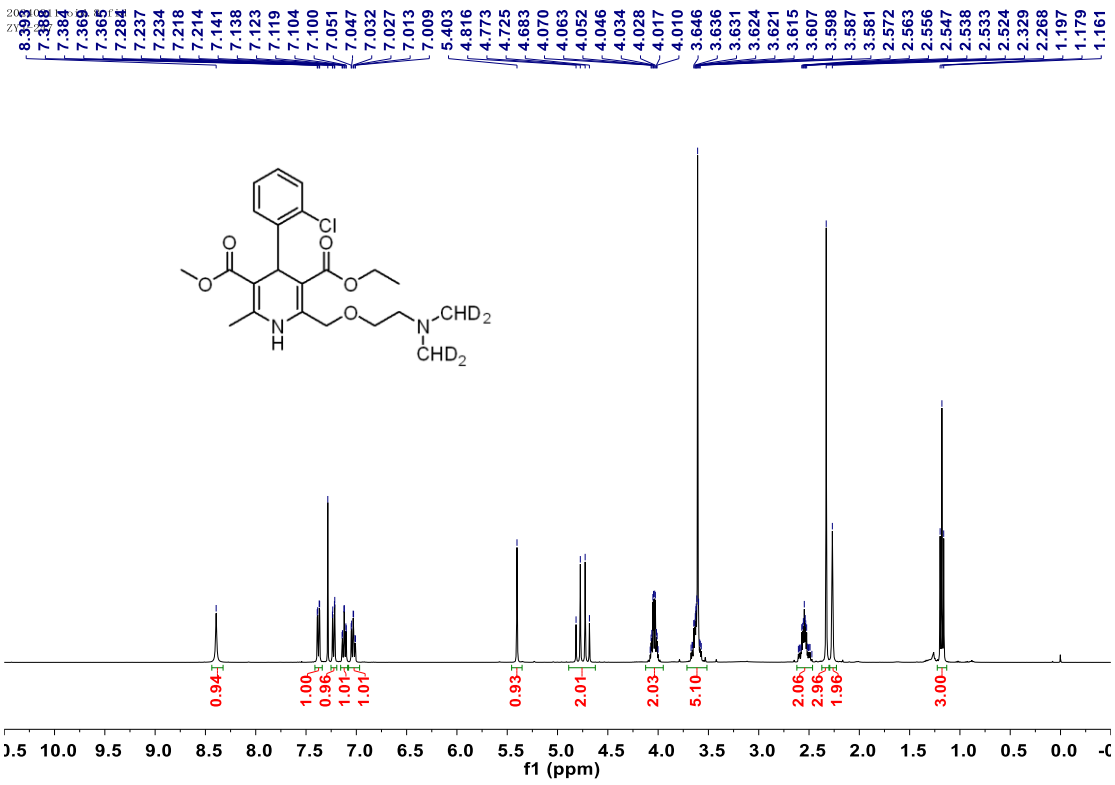


HRMS (ESI): *m/z* calcd for: $C_{20}H_{21}DClN_2^+$ $[M+H]^+$: 326.1529, found: 326.1534.

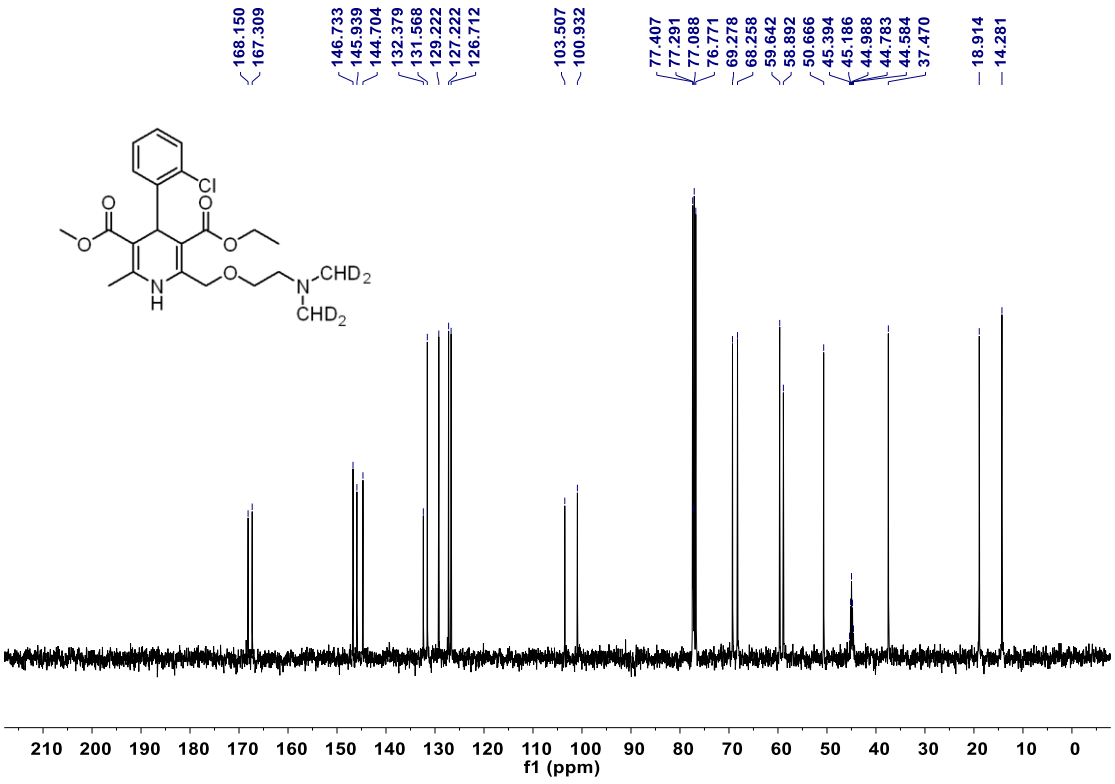


3-Ethyl-5-methyl-2-((2-(bis(methyl-d_2)amino)ethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-d_4)

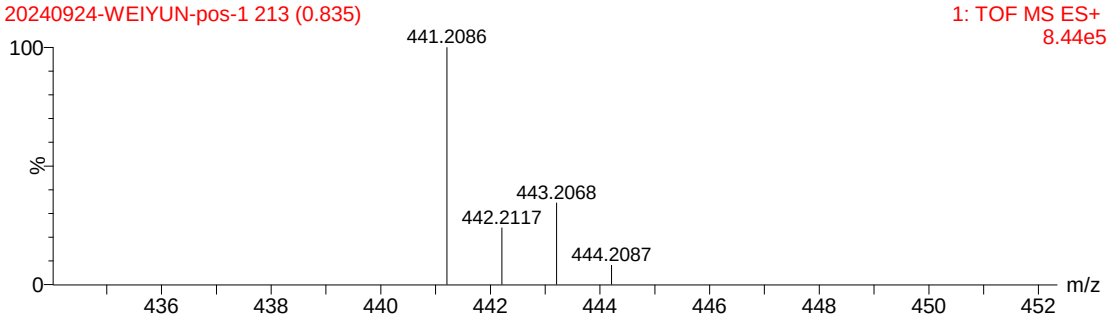
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

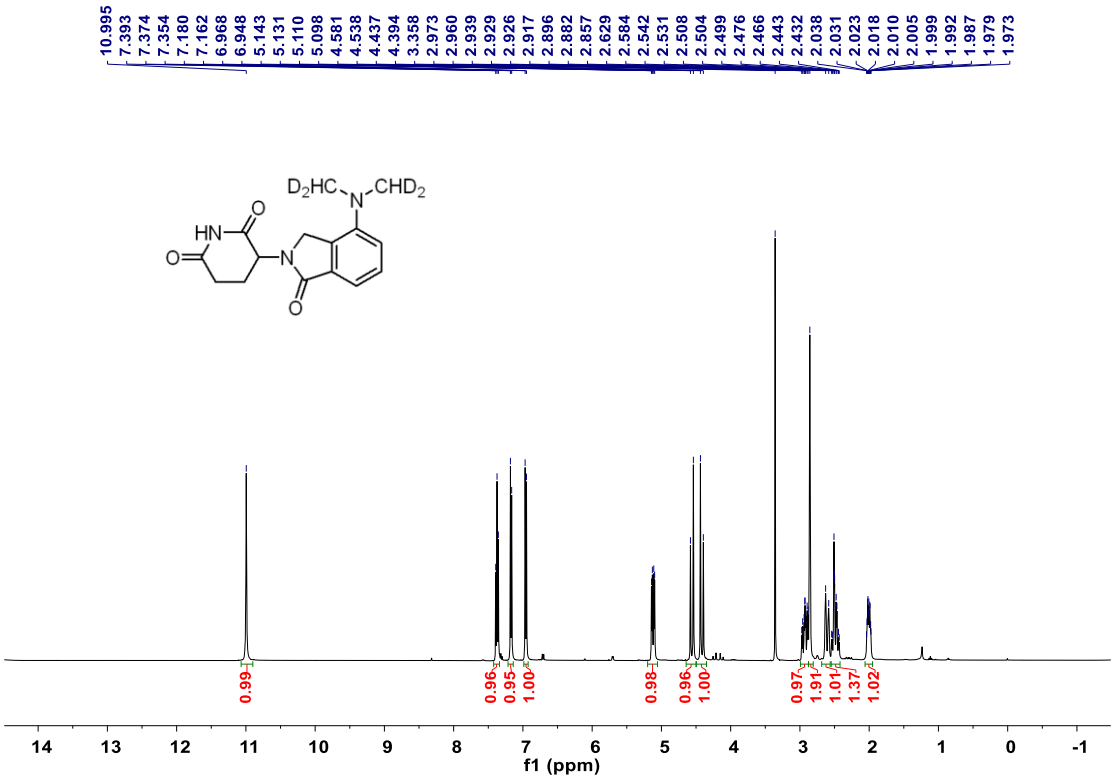


HRMS (ESI): *m/z* calcd for : $C_{22}H_{25}D_4ClN_2O_5^+$ $[M+H]^+$: 441.2089, found: 441.2086

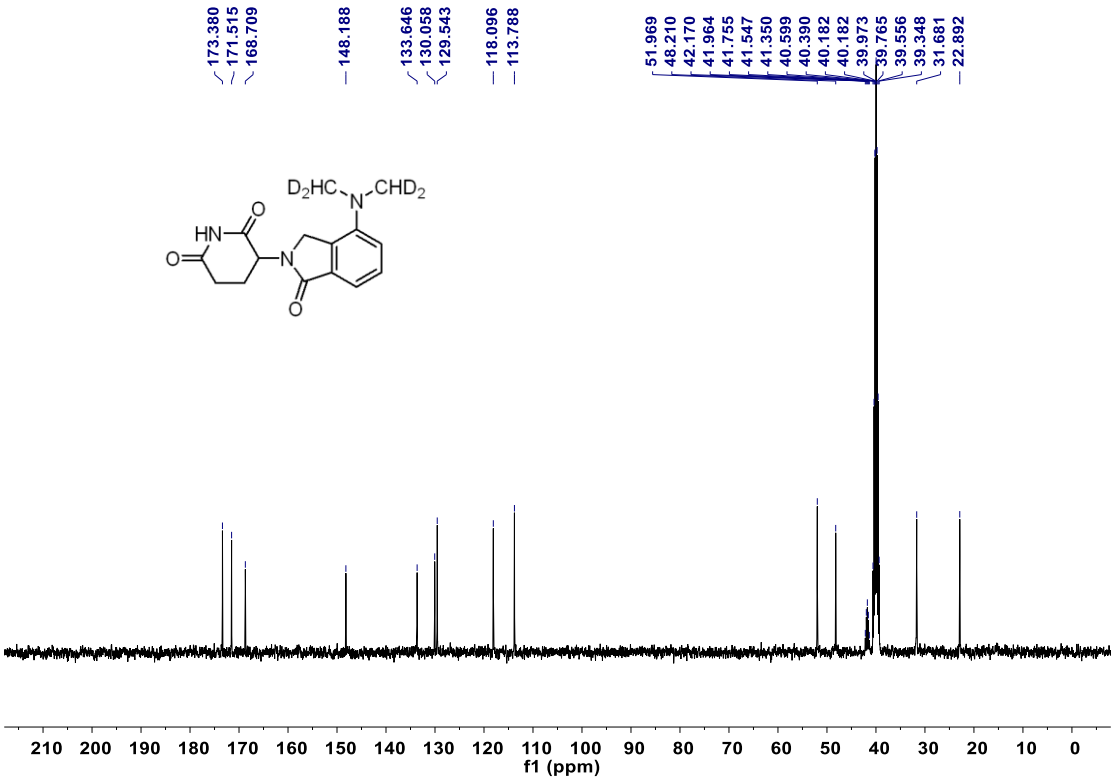


3-(4-(Bis(methyl-d_2)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2b-d_4)

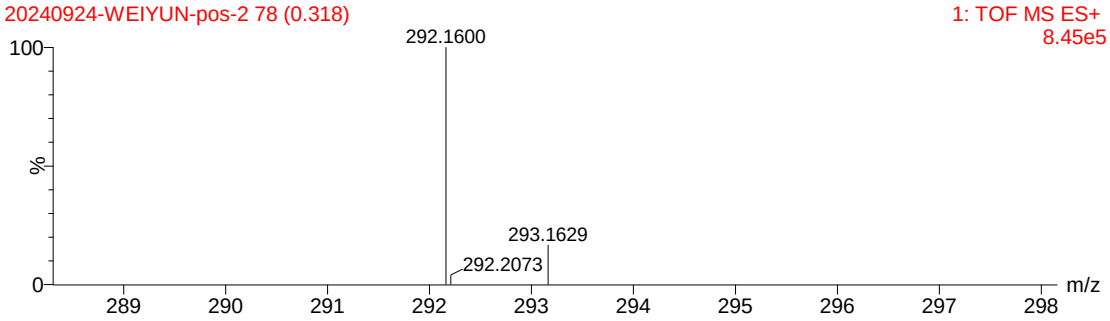
^{1}H NMR (400 MHz, DMSO-d_6)



^{13}C NMR (101 MHz, DMSO-d_6)

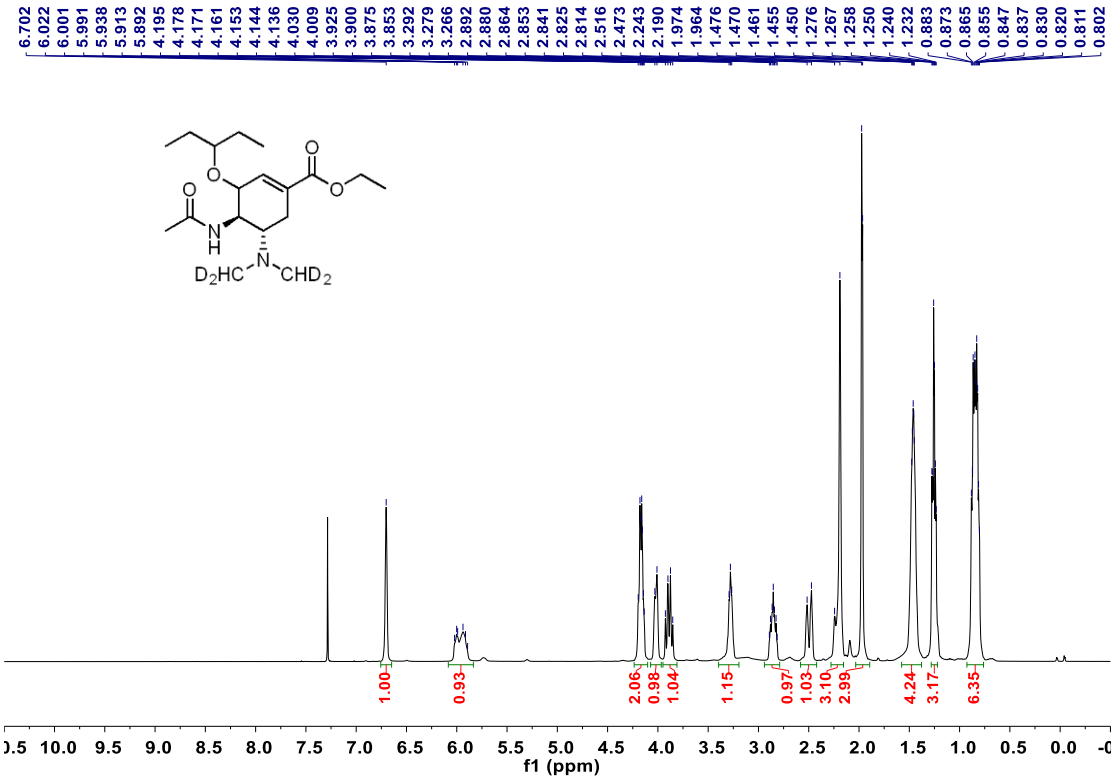


HRMS (ESI): *m/z* calcd for: $C_{15}H_{14}D_4N_3O_3^+$ $[M+H]^+$: 292.1594, found: 292.1600.

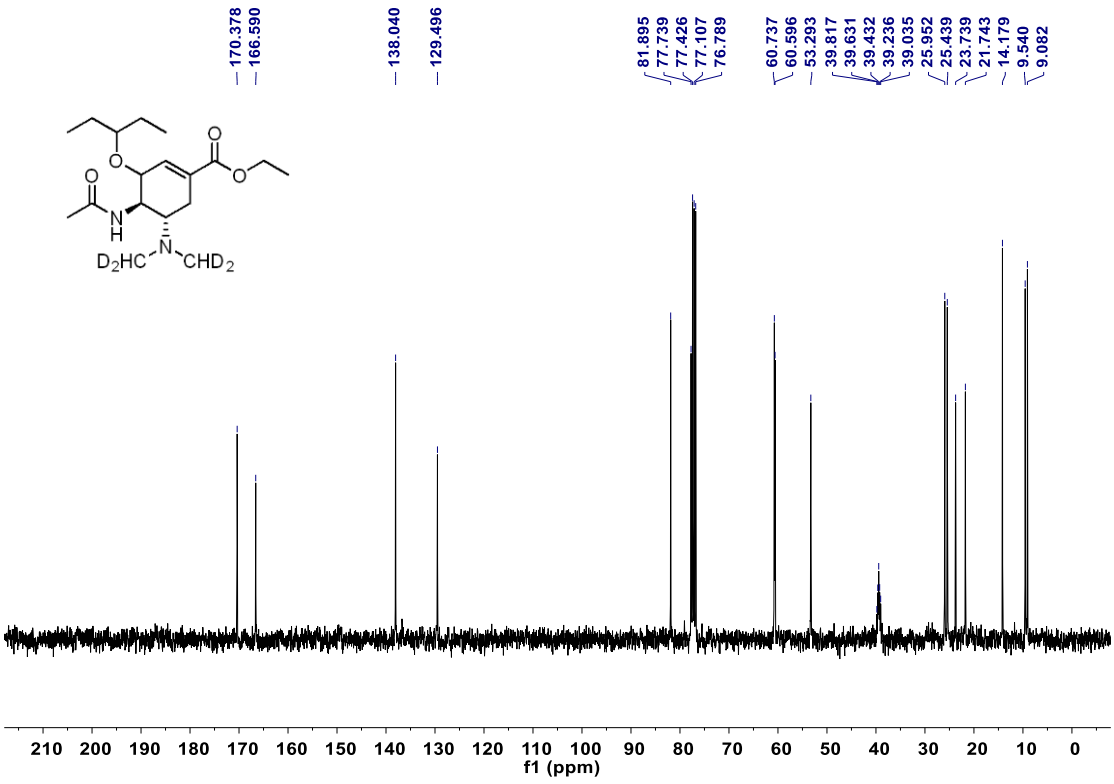


Ethyl (4*R*,5*S*)-4-acetamido-5-(bis(methyl-d_2)amino)-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (2d-d_4)

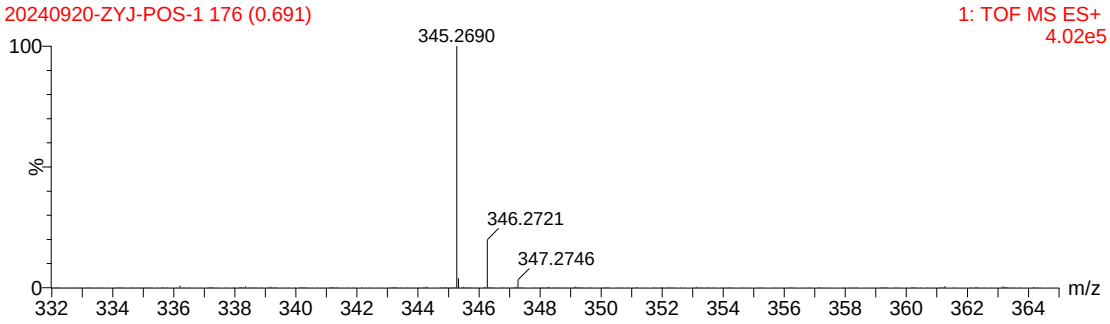
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

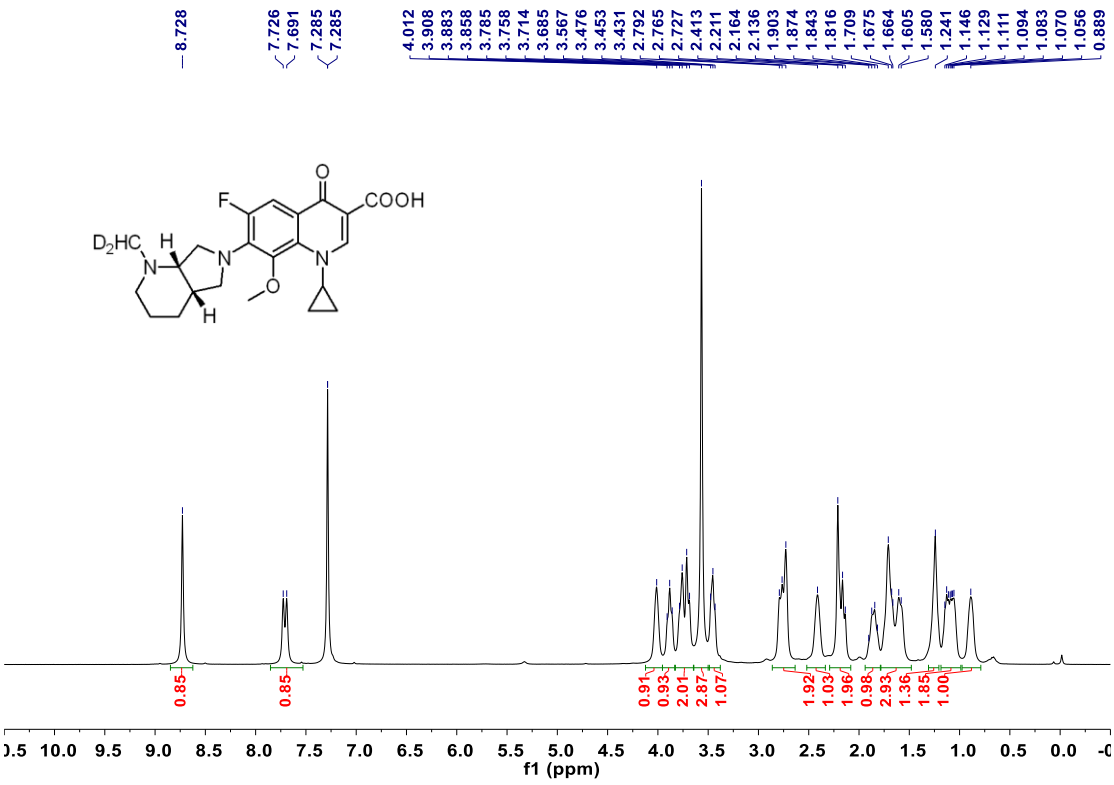


HRMS (ESI): *m/z* calcd for: $C_{18}H_{29}D_4N_2O_4^+$ $[M+H]^+$: 345.2686, found: 345.2690.

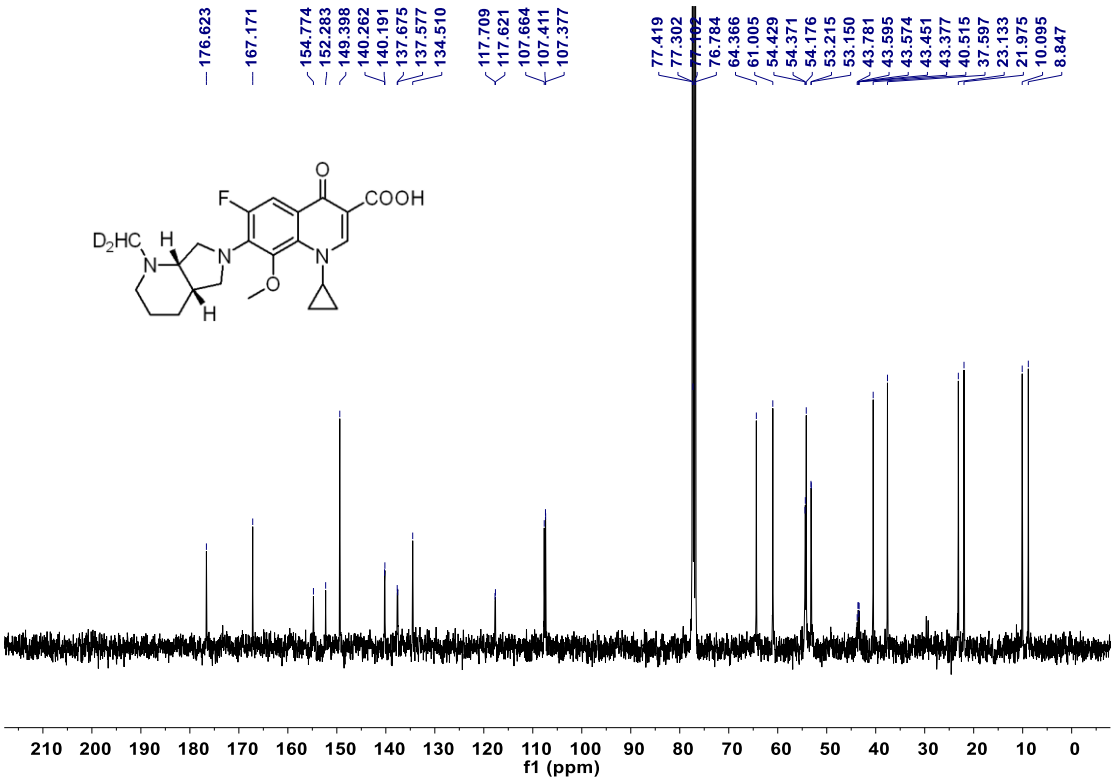


1-Cyclopropyl-6-fluoro-8-methoxy-7-((4*aS*,7*aS*)-1-(methyl-d_2)octahydro-6*H*-pyrrolo[3,4-b]pyridin-6-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (2l-d_2)

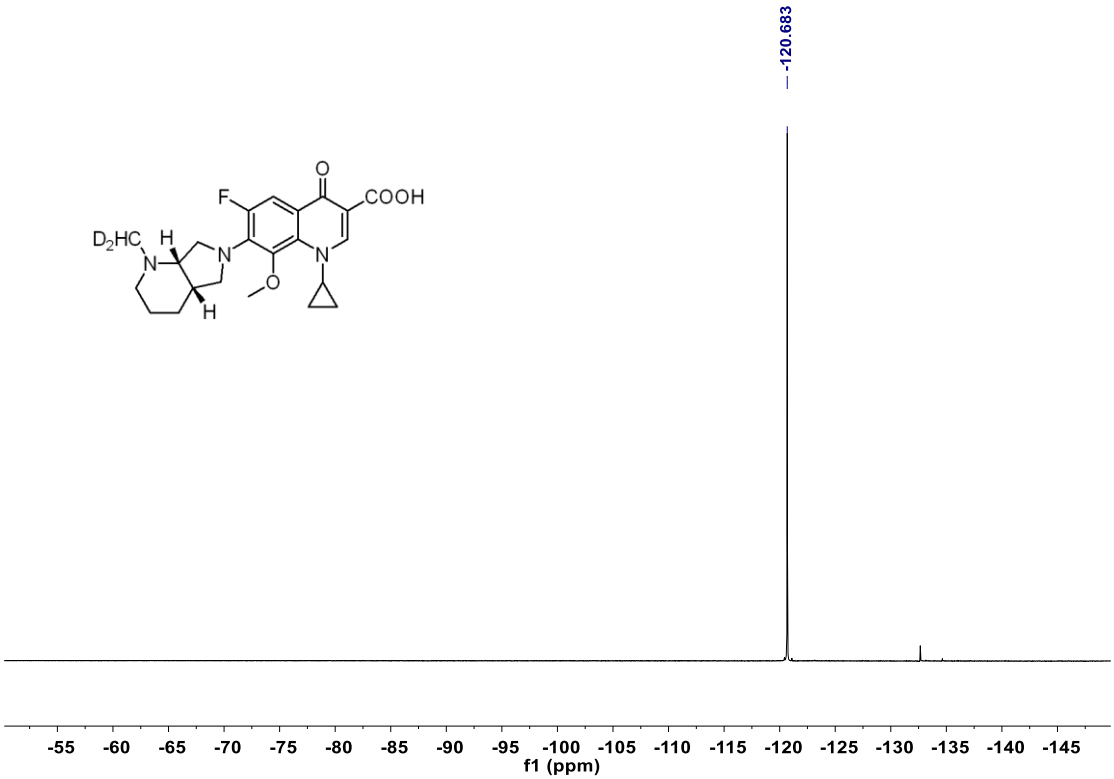
^{1}H NMR (400 MHz, $CDCl_3$)



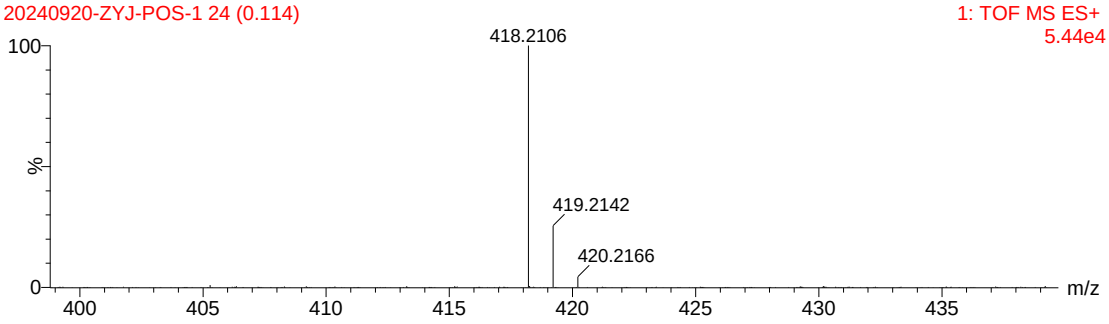
^{13}C NMR (101 MHz, $CDCl_3$)



^{19}F NMR (377 MHz, $CDCl_3$)

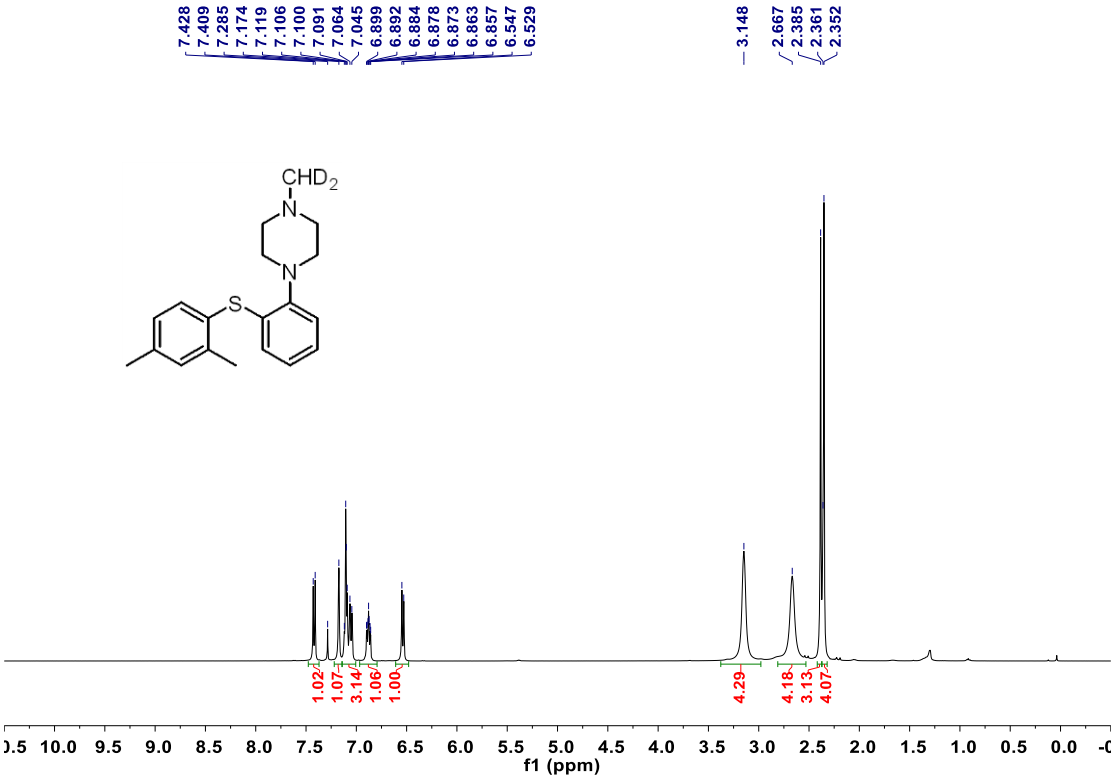


HRMS (ESI): *m/z* calcd for: $C_{22}H_{25}D_2FN_3O_4^+$ $[M+H]^+$: 418.2106, found: 418.2106.

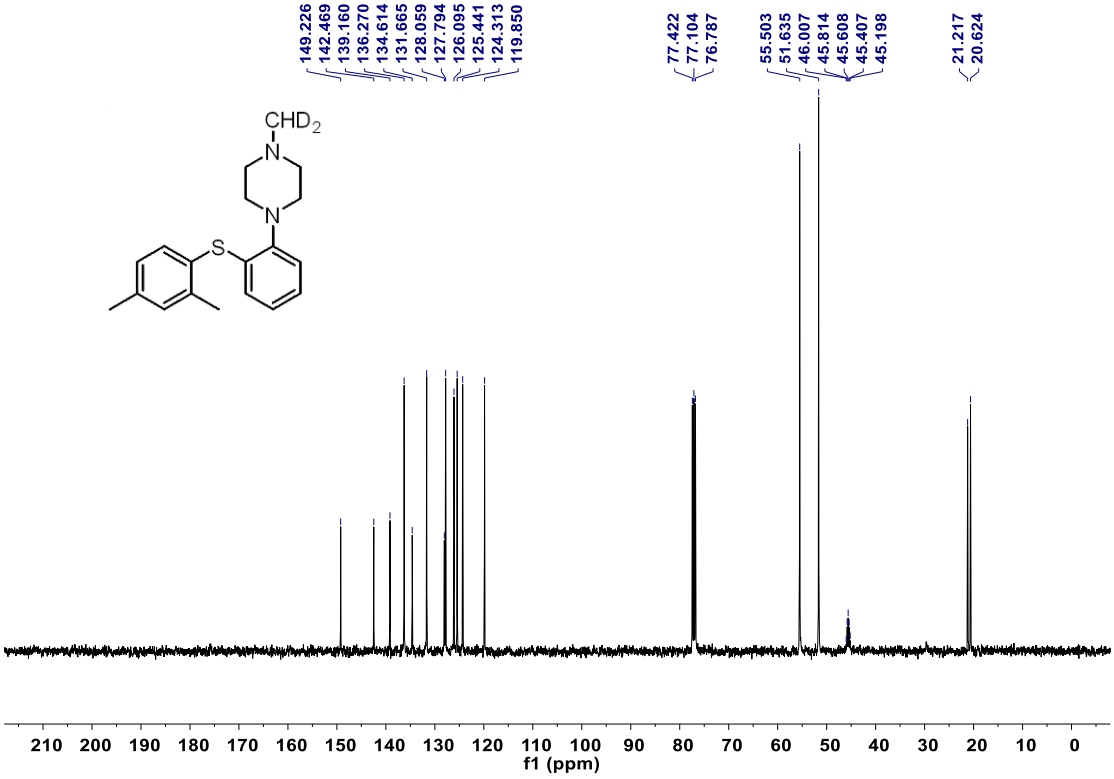


1-(2-((2,4-Dimethylphenyl)thio)phenyl)-4-(methyl-d_2)piperazine (2m-d_2)

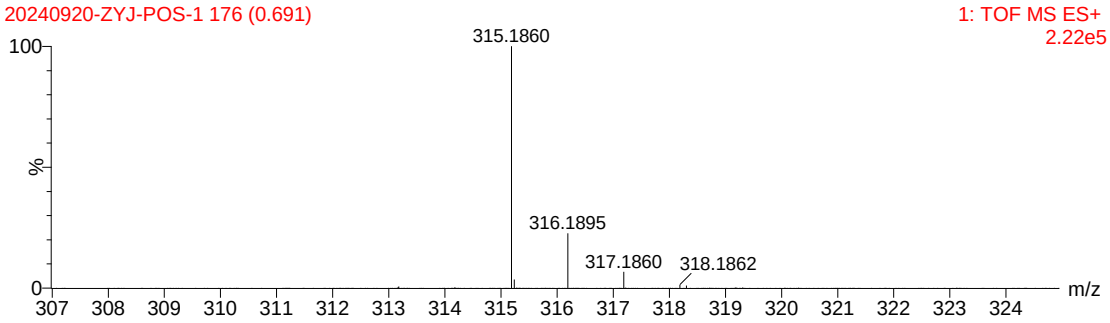
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)

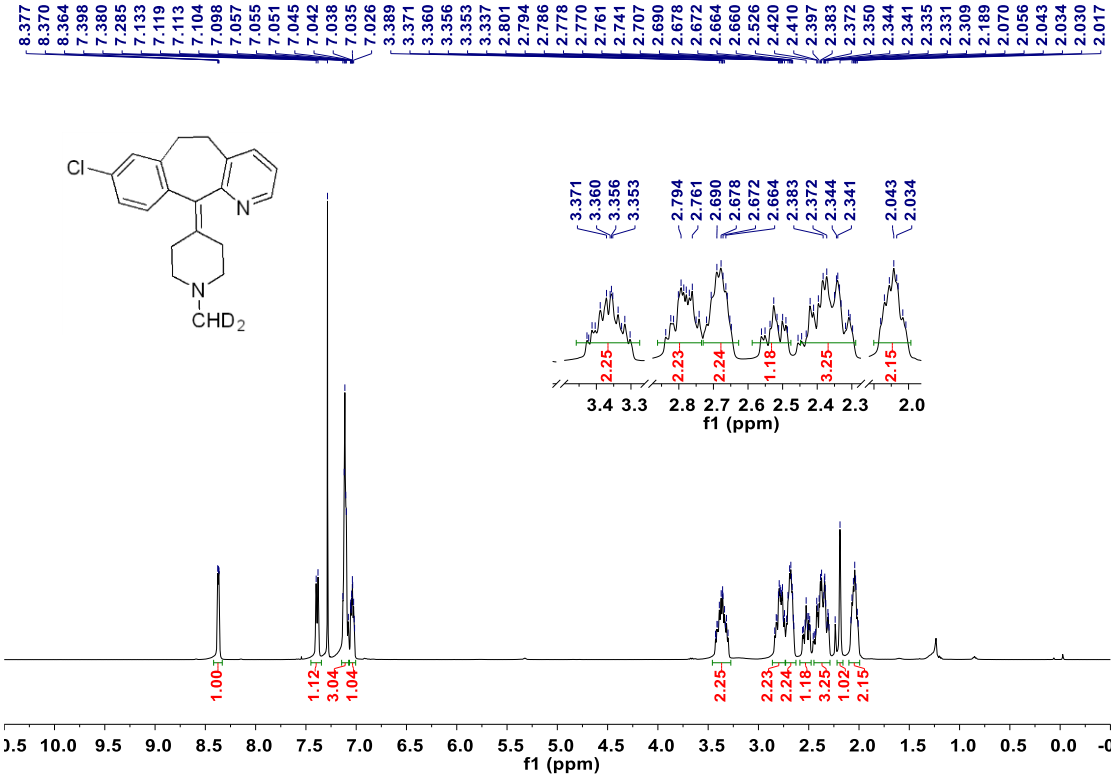


HRMS (ESI): *m/z* calcd for: $C_{19}H_{23}D_2N_2S^+$ $[M+H]^+$: 315.1858, found: 315.1860.

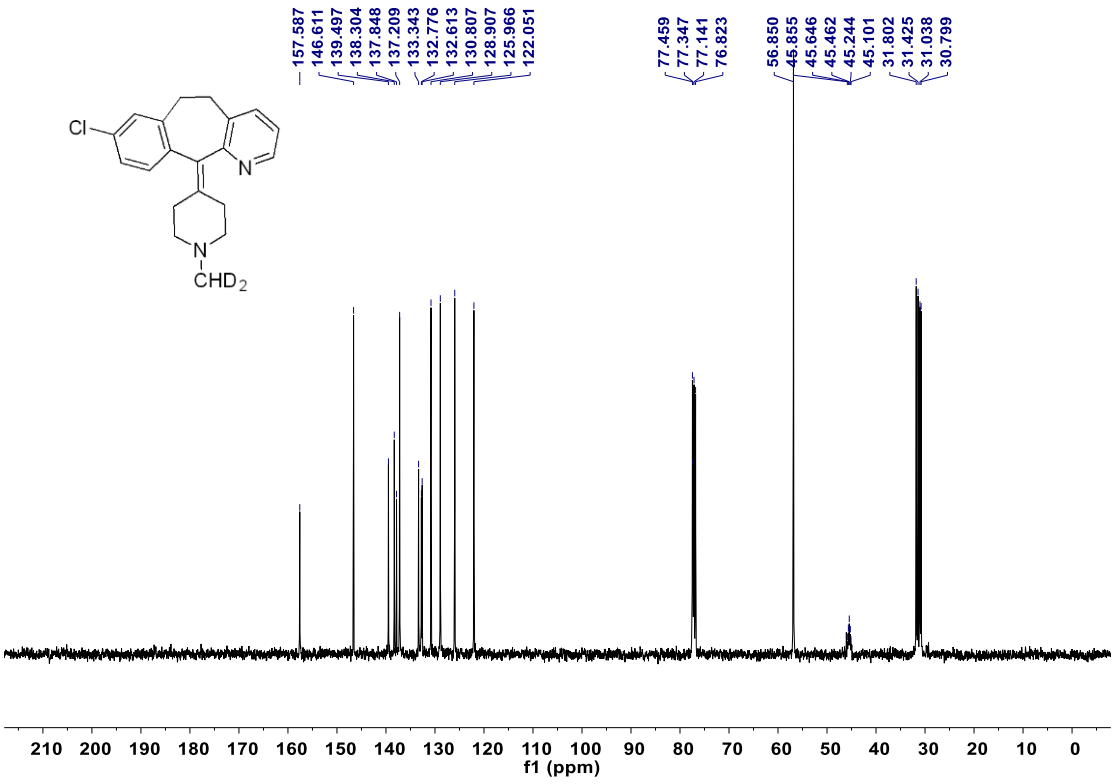


8-Chloro-11-(1-(methyl-d_2)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-b]pyridine (2p-d_2)

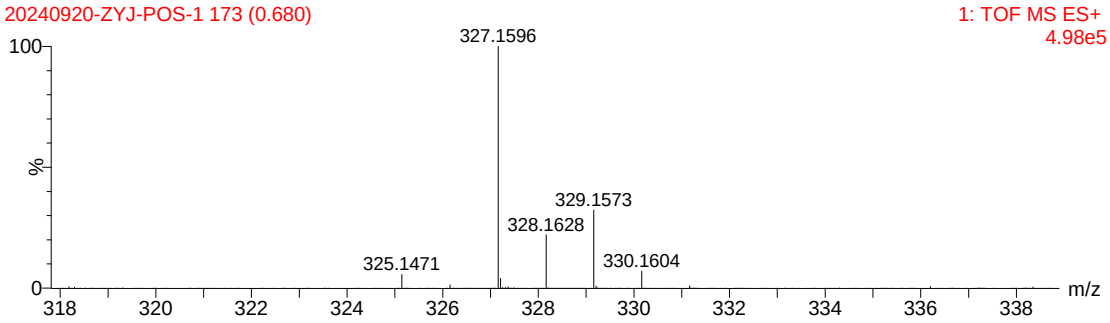
^{1}H NMR (400 MHz, $CDCl_3$)



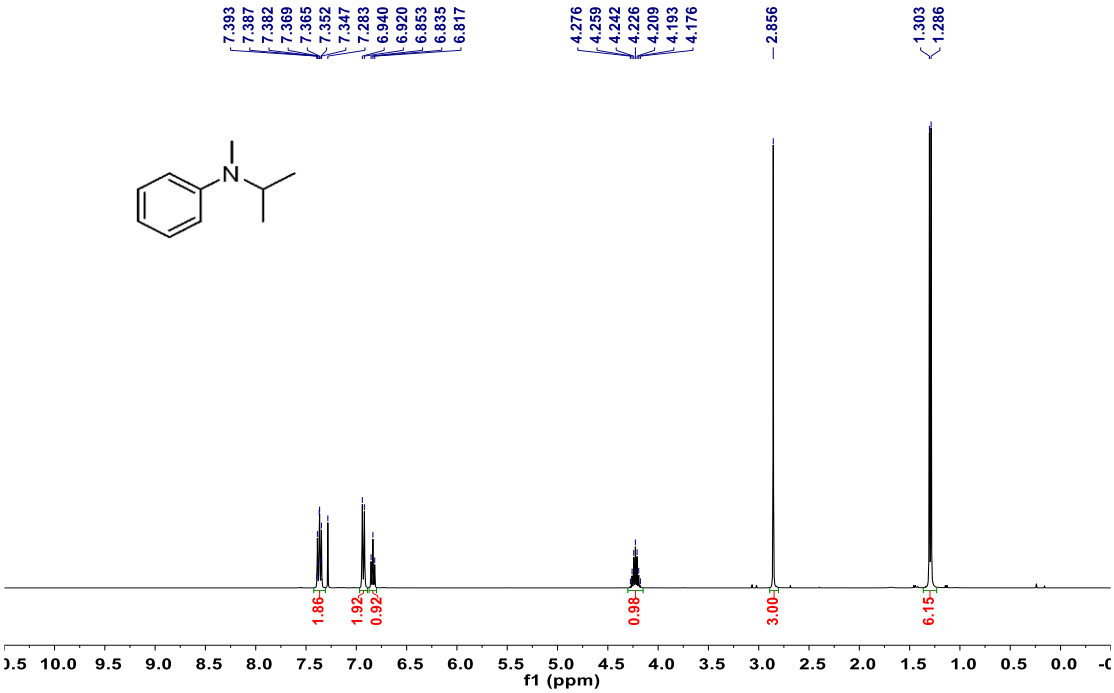
^{13}C NMR (101 MHz, $CDCl_3$)



HRMS (ESI): *m/z* calcd for: $C_{20}H_{20}D_2ClN_2^+$ $[M+H]^+$: 327.1592, found: 327.1596.

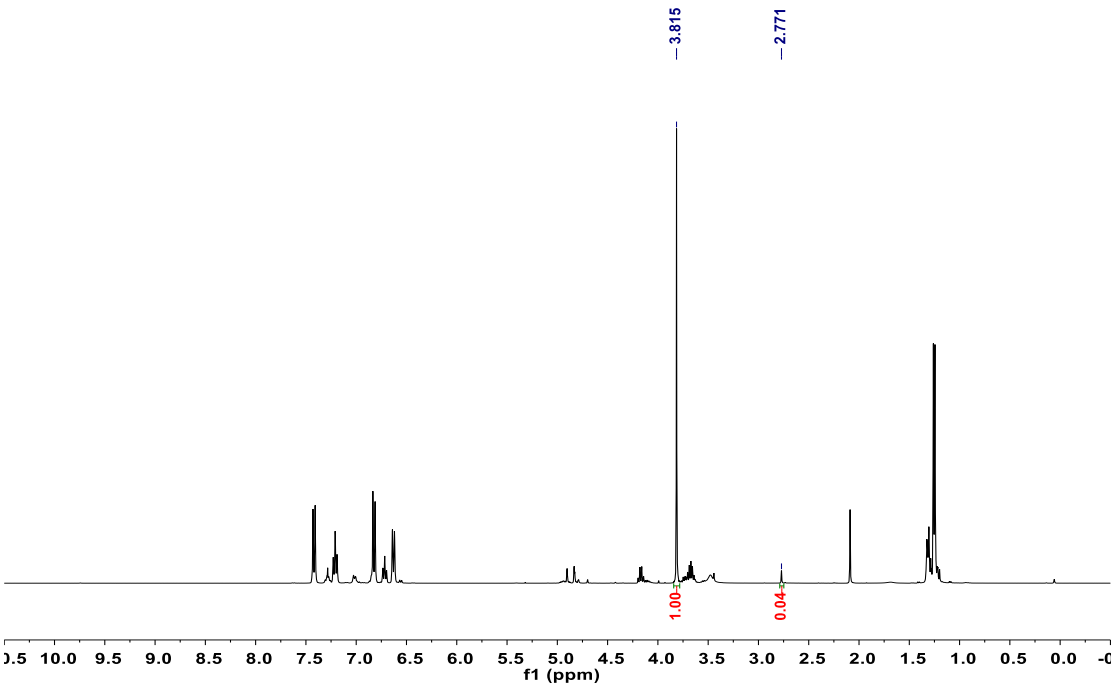


15.The ^{1}H NMR of crude reaction mixtures for the reaction rate comparison studies

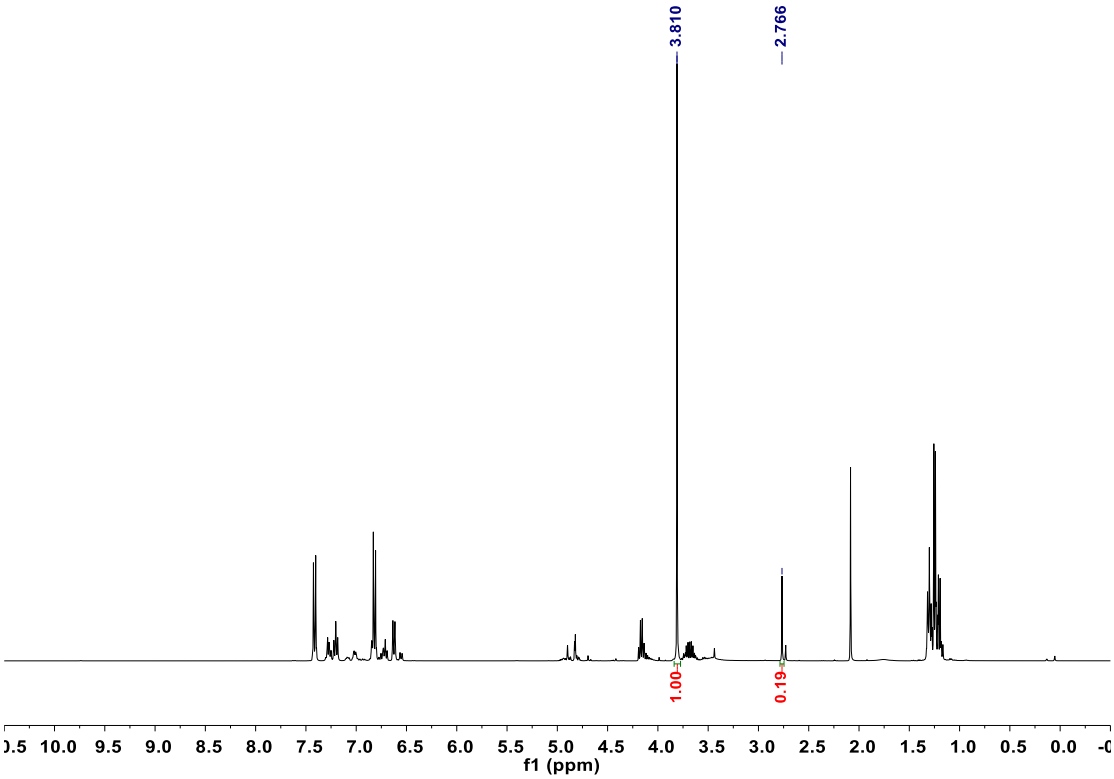


The ^{1}H NMR spectrum of *N*-isopropyl-*N*-methylaniline (**6p**)

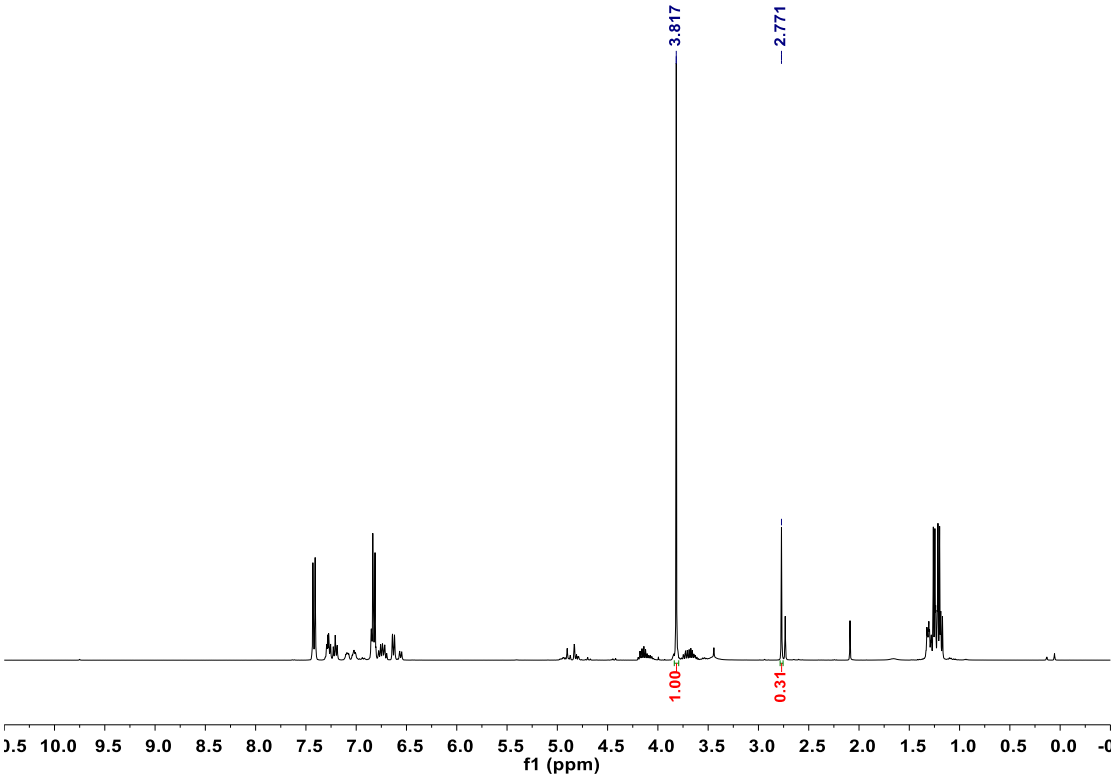
(a) Reaction rate of classic Eschweiler-Clarke methylation



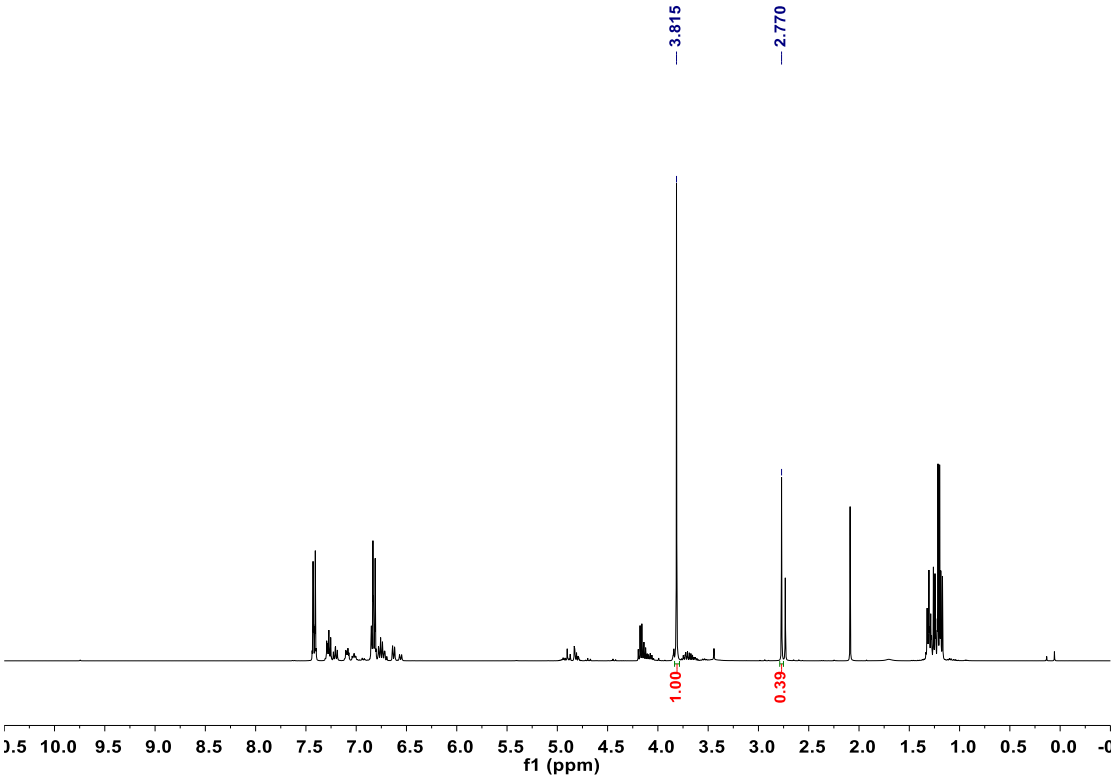
The ^{1}H NMR yield of the crude residues 5p for 2-minute reaction.



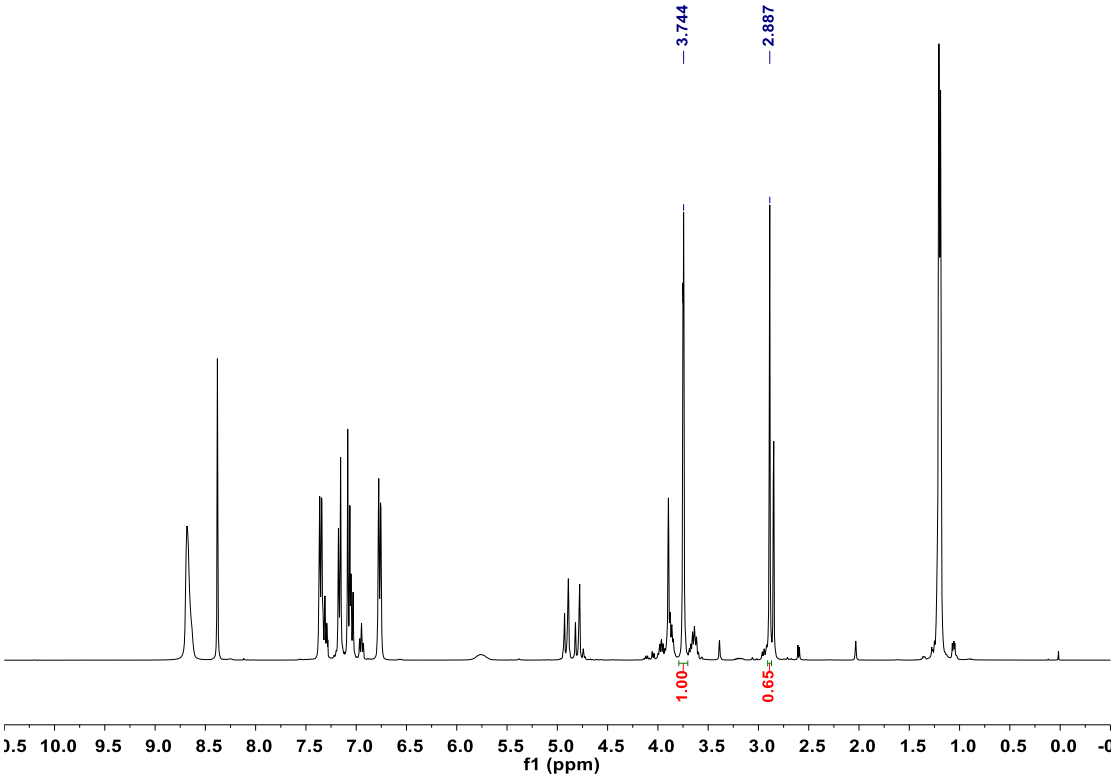
The ^{1}H NMR yield of the crude residues 5p for 4-minute reaction.



The ^{1}H NMR yield of the crude residues 5p for 6-minute reaction.

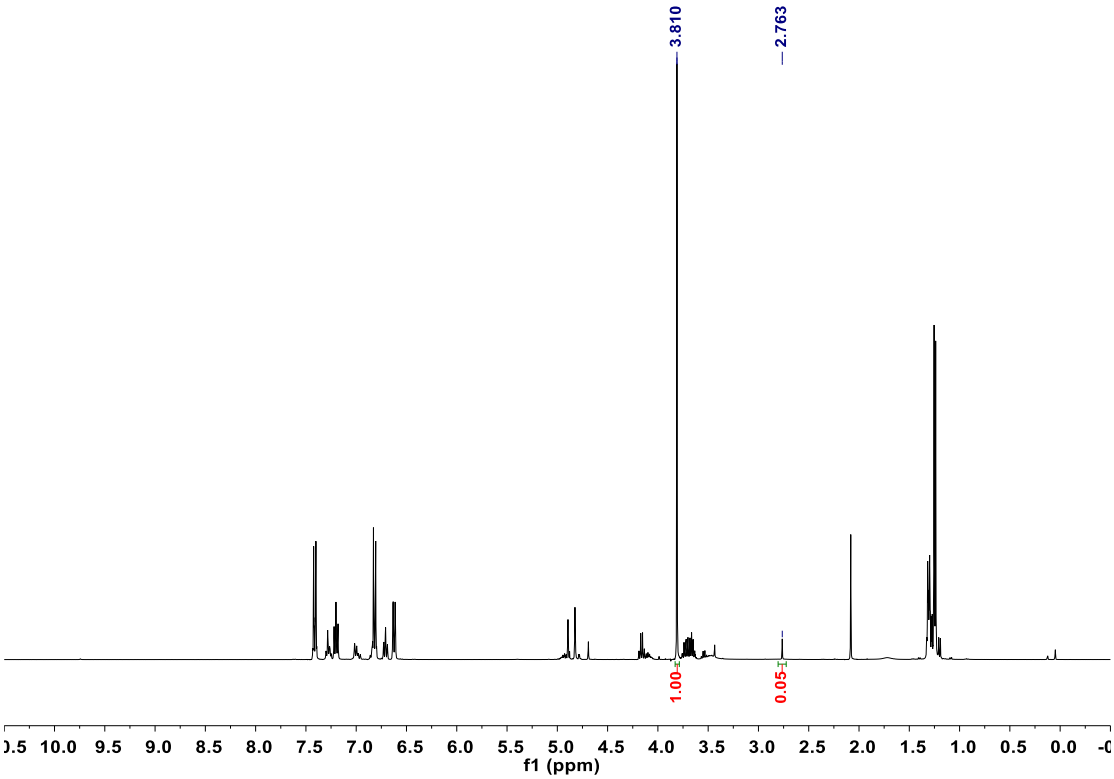


The ^{1}H NMR yield of the crude residues 5p for 8-minute reaction.

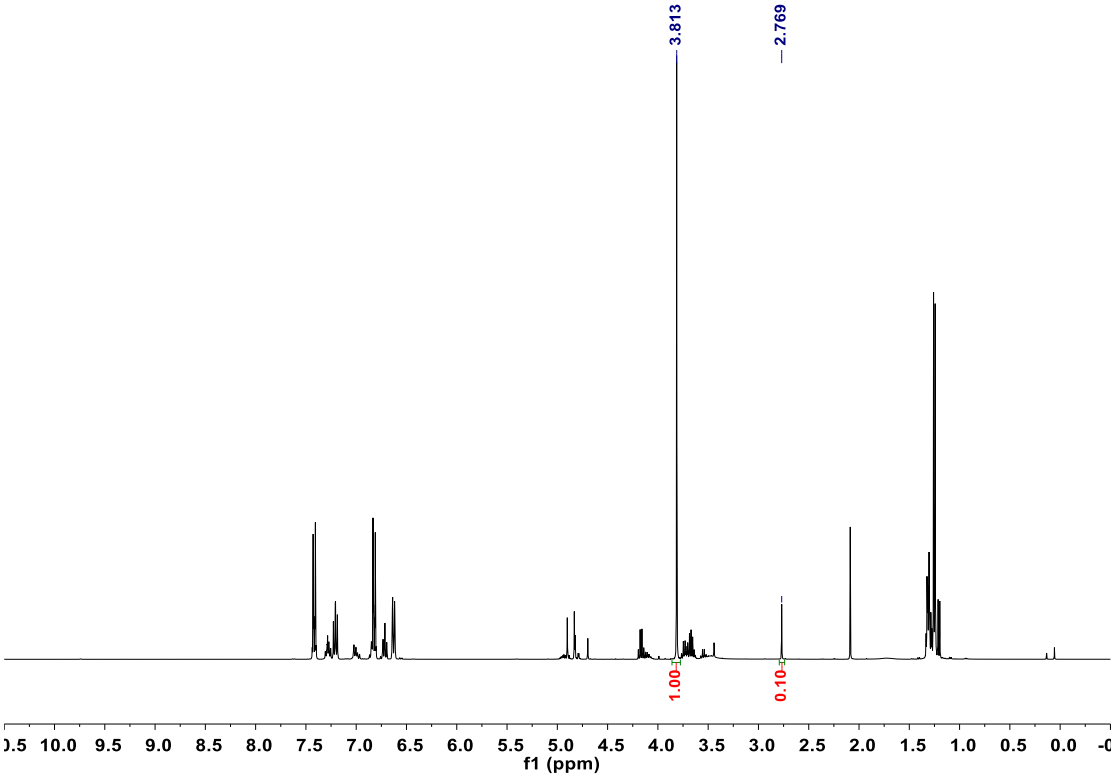


The ^{1}H NMR yield of the crude residues 5p for 2 h reaction.

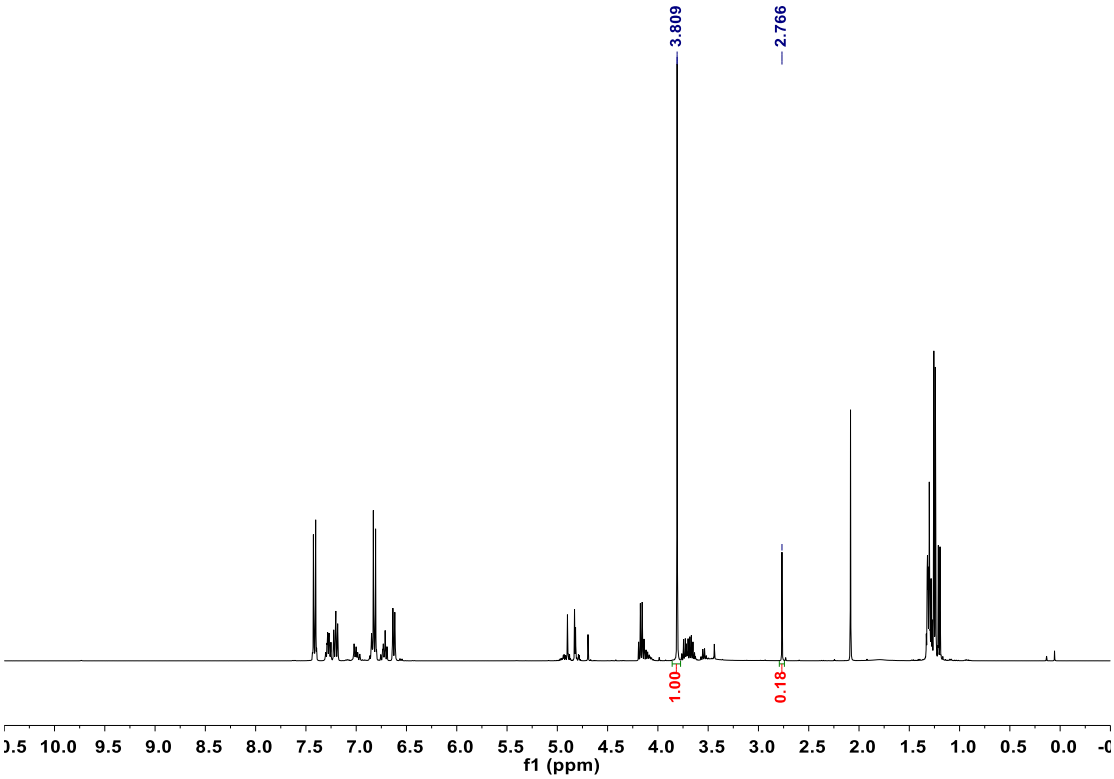
(b) Reaction rate of catalytic Eschweiler-Clarke methylation



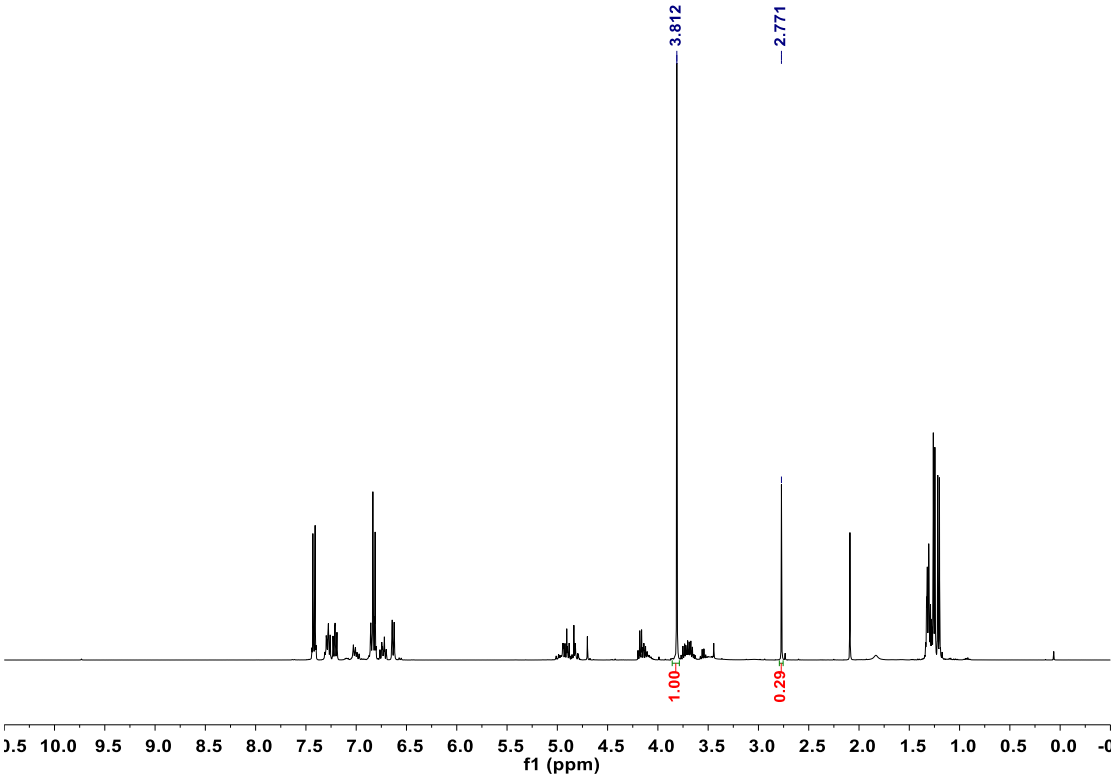
The ^{1}H NMR yield of the crude residues 5p for 0.5-minute reaction.



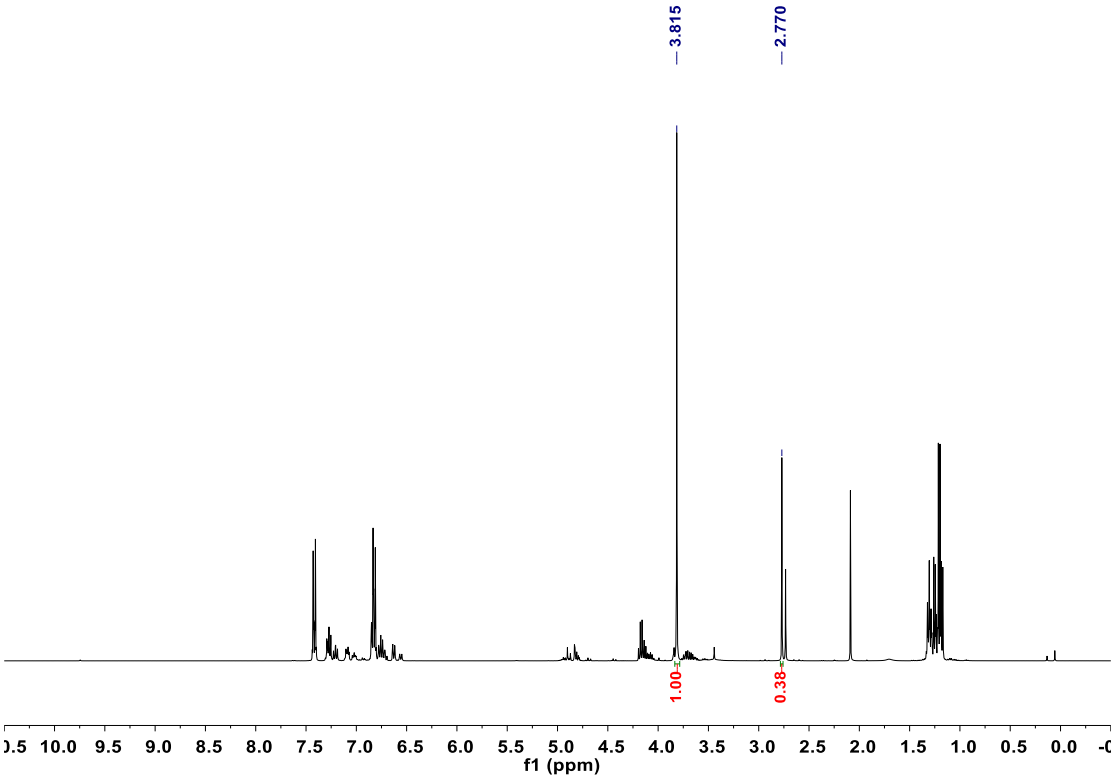
The ^{1}H NMR yield of the crude residues 5p for1-minute reaction.



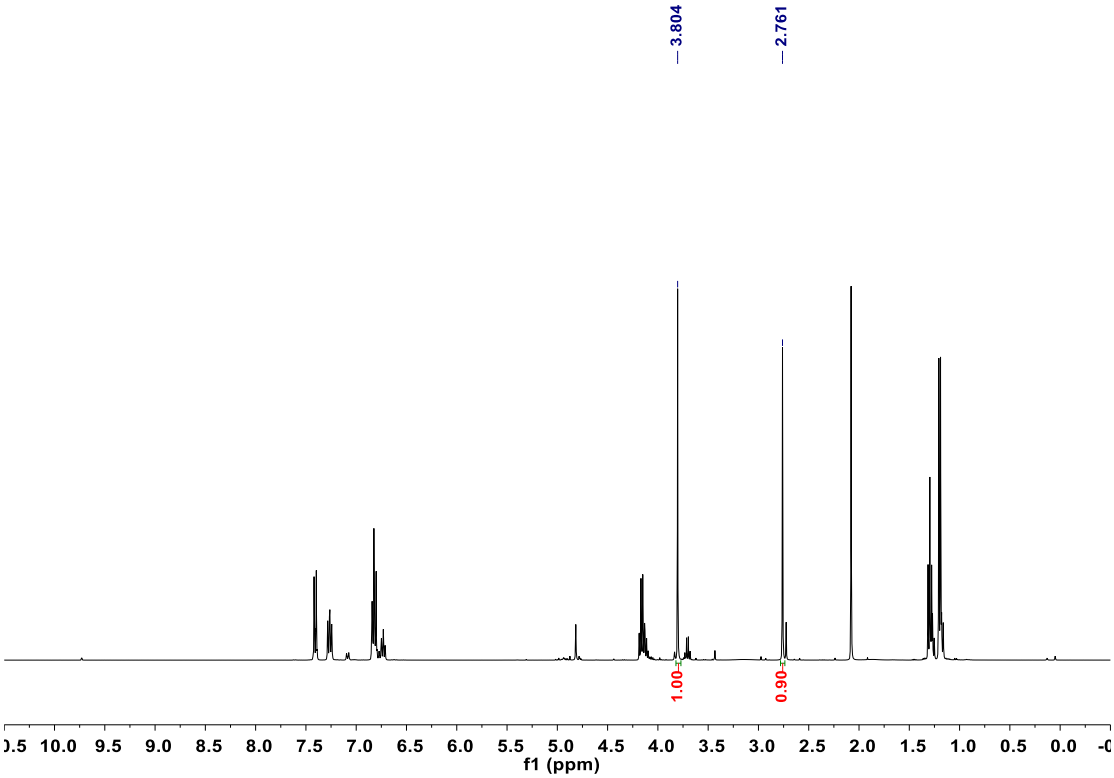
The ^{1}H NMR yield of the crude residues 5p for1.5-minute reaction.



The ^{1}H NMR yield of the crude residues 5p for 2-minute reaction.



The ^{1}H NMR yield of the crude residues 5p for 2.5-minute reaction.



The ^{1}H NMR yield of the crude residues 5p for 10-minute reaction.