Heterogeneous Co-catalyzed dehydrogenative aromatization of cyclohex-2-enone and amines to 1,4- phenylenediamine

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1. General information

All chemicals were obtained from commercial suppliers and used without further purification unless specified. The commercial silicotungstic acid ($H_4SiW_{12}O_{40}$) was dried at 120 ºC for 3 h, which was labeled as H_4SiW. Analytical thin-layer chromatography (TLC) was performed on silica gel GF 254 plates and visualized under UV light (254 nm). All NMR spectra were measured at room temperature using a Bruker 400 (400 MHz for ^1H, 101 MHz for ^{13}C and 377 MHz for ^{19}F) NMR spectrometer in $CDCl_3$ with internal solvent signals (for ^1H and ^{13}C) as reference (7.26 ppm, 77.2ppm). All the NMR spectra were processed in MestReNova software. High-resolution mass spectra (HRMS) were acquired on a Thermo Fisher Q Exactive mass spectrometer with electrospray ionization (ESI). X-ray diffraction (XRD) patterns were collected on a Philips X'Pert Pro diffractometer with Co Kα radiation (λ = 1.79 Å). Fourier-transform infrared (FT-IR) spectra (4000–400 cm^{-1}) were recorded on a Thermo Nicolet iS10 spectrometer. X-ray photoelectron spectroscopy (XPS) analyses were conducted using a Thermo Scientific ESCALAB 250 Xi spectrometer with monochromatic Al Kα radiation.

2. Preparation of catalysts

Transition metal-exchanged H_4SiW catalysts were synthesized via a literature-adapted procedure. In a typical synthesis, H_4SiW (5 g, 1.73 mmol) was dissolved in a 1:4 deionized water/ethanol solvent mixture (20 mL) under vigorous stirring at room temperature. An aqueous solution of the cobalt chloride ($CoCl_2$) was added dropwise to the H_4SiW suspension. The resulting mixture was continuously stirred and heated at 90 ºC for 12 h, followed by evaporation of the solvent under reduced pressure. The residue was aged at 25 ºC for 12 h to facilitate crystallization. The precipitated solid was dried at 120 ºC for 3 h and subsequently calcined in air at varied temperatures (150 ºC, 200 ºC, 250 ºC, 300 ºC) for 3 h. The final catalysts were designated as CoSiW-T (T: calcination temperature). For comparison, the other catalysts were also prepared based on the above-mentioned process at 300 ºC for 3 h, which were designated as MSiW-T (M: La, Ag, Fe, Cu, Ni).

3. Characterization data for catalysts

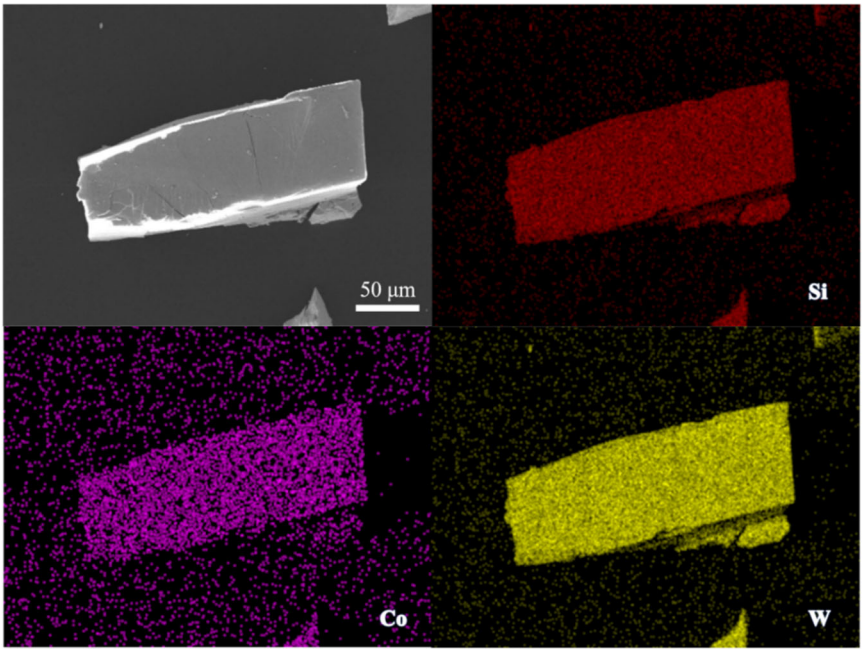


Fig. S1. EDS spectra of CoSiW-300.

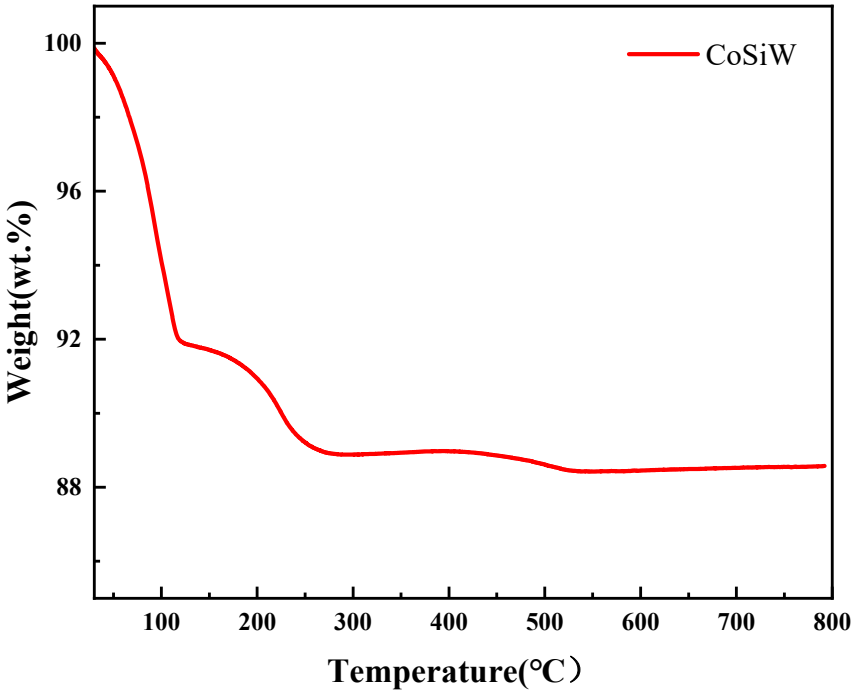


Fig. S2. TGA spectra of CoSiW

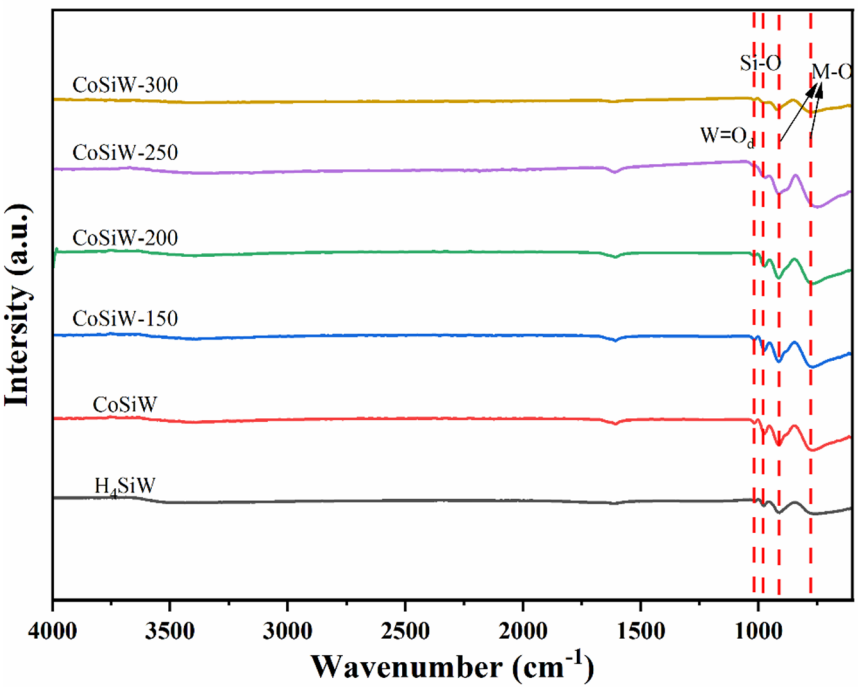


Fig. S3. FT-IR spectra of CoSiW-T and H_4SiW

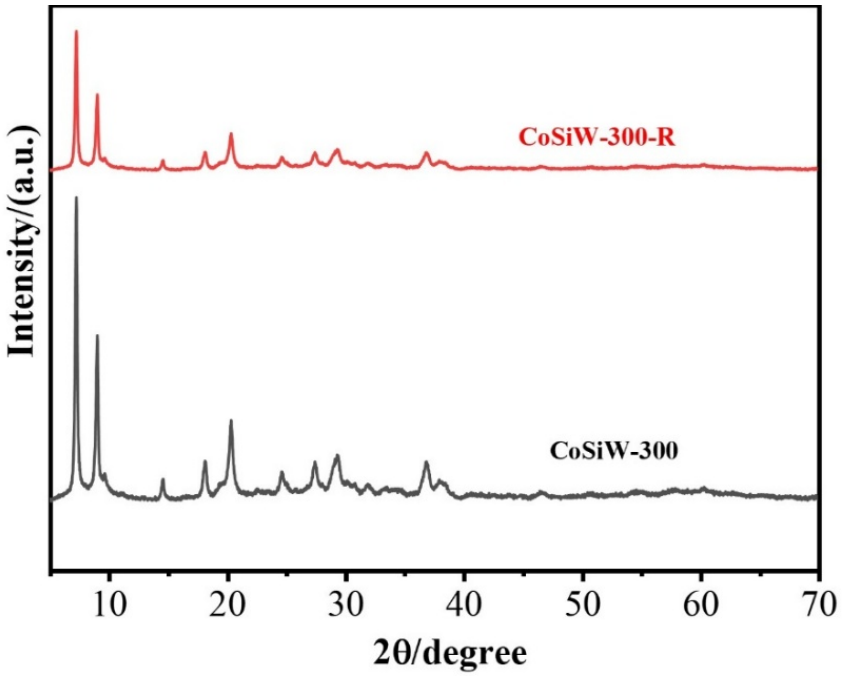


Fig. S4. XRD patterns of CoSiW-300 and recovered CoSiW-300

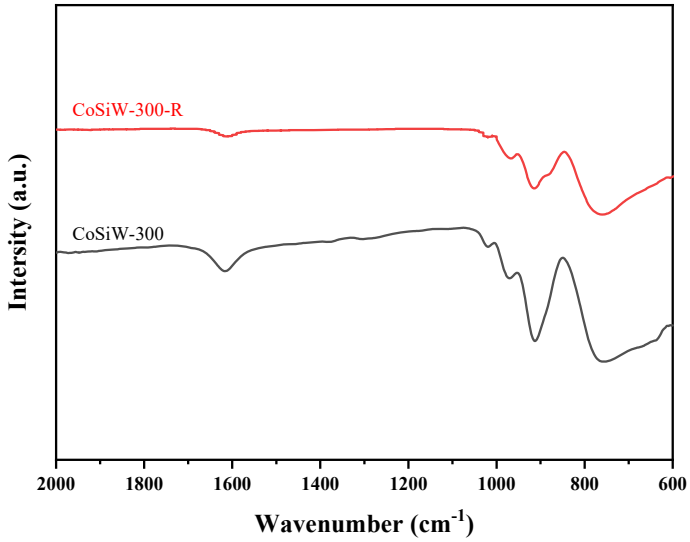
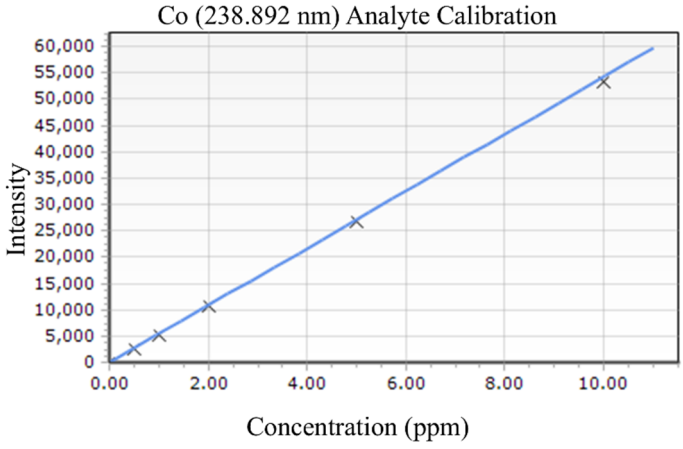


Fig. S5. FT-IR spectra of CoSiW-300 and recovered CoSiW-300

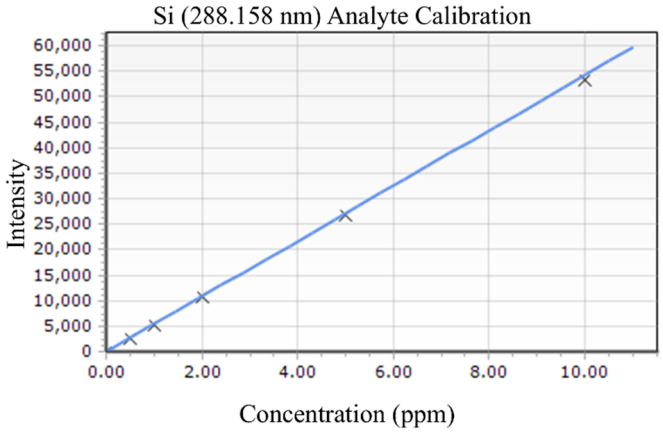
ICP-OES of CoSiW-300

Co、Si and W content in the optimal into CoSiW-300 were determined using an inductively coupled plasma optical emission spectrometry (ICP-OES, Agilent 5800). The CoSiW-300 sample was dissolved in nitric acid and analyzed at 238.892 nm, 288.158 mn and 207.912 nm, respectively. The good linear relationship between Co、Si and W concentration and intensity (R2>0.99) for the calibration curve showed the accuracy as follow,



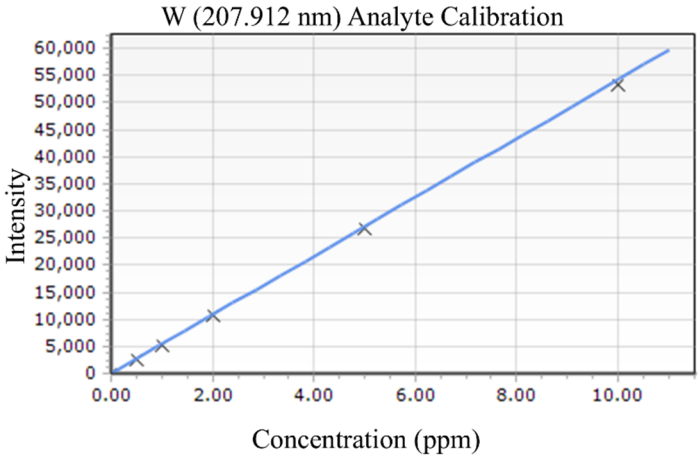
Y=5423.61599679*X+26.88799968
Correlation coefficient: 0.99998
%RSE: 1.28864981

Fig. S6 Calibration curve relative to the presence of Co element detected by ICP-OES



Y=899.54022211*X+330.82899180
Correlation coefficient: 0.99998
%RSE: 3.11993700

Fig. S7 Calibration curve relative to the presence of Si element detected by ICP-OES



Y=1598.62499595*X+15.19253575
Correlation coefficient: 0.99997
%RSE: 0.94779156

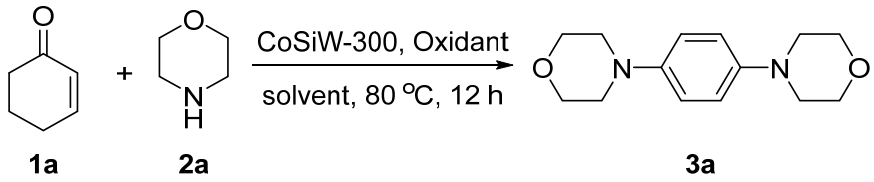
Fig. S8 Calibration curve relative to the presence of W element detected by ICP-OES

Table S1. Contents of different elements in CoSiW-300 catalysts

CoSiW-300	Elements content (wt%, ICP-OES)
Co	3.20%
Si	1.01%
W	73.86%

4. Optimization of Reaction Conditions

Table S2. Optimization of Oxidant and Solvent [a]

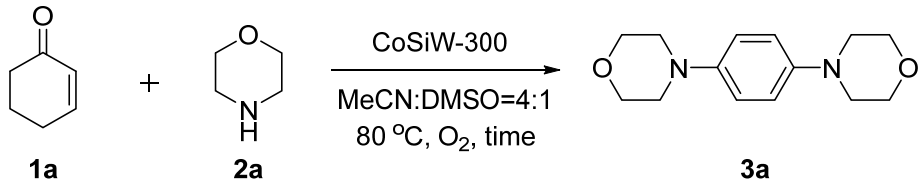


1a **2a** **3a**

Entry	Oxidant	Solvent	Yield [b] (%)
1	O_2	MeCN	52
2	O_2	DMSO	60
3	O_2	DMF	trace
4	O_2	DCE	trace
5	O_2	toluene	trace
6	O_2	PhCl	trace
7	O_2	dioxane	trace
8	O_2	THF	trace
9	O_2	MeCN:DMSO (4:1)	86
10	air	MeCN:DMSO (4:1)	28
11	N_2	MeCN:DMSO (4:1)	trace
12	H_2O_2	MeCN:DMSO (4:1)	42
13	TBHP	MeCN:DMSO (4:1)	50
14	Oxone	MeCN:DMSO (4:1)	trace
15	$K_2S_2O_8$	MeCN:DMSO (4:1)	53
16	DTBP	MeCN:DMSO (4:1)	70

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), CoSiW-300 (1 mol%), solvent (0.5 mL), 80 °C, oxidant (2.0 equiv.), 12 h. [b] Isolated yield.

Table S3. Optimization of Reaction Time[a]



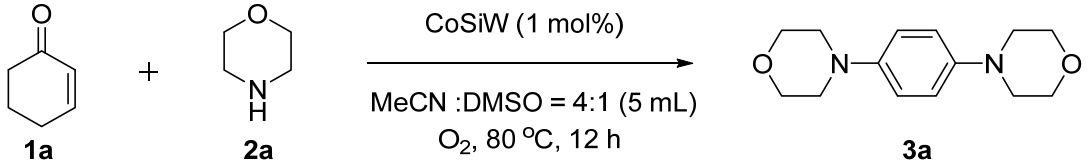
Entry	Time (h)	Atmosphere	Yield[b]（%）
1	6	O_2	65
2	12	O_2	82
3	18	O_2	82
7	24	O_2	83

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), CoSiW-300 (1 mol%), MeCN: DMSO = 4:1 (0.5 mL), 80 °C, O_2, 12 h. [b] Isolated yield.

5. General procedure for the oxidative coupling of C-N bonds of cyclohexenones and amines.

The C–N oxidative cross-coupling reactions were conducted in 10 mL sealed reaction tubes. A representative procedure: cyclohexenone (0.2 mmol), amine (0.6 mmol), a mixed solvent of acetonitrile and dimethyl sulfoxide (0.5 mL), and Co_2SiW-300 catalyst (10 mg, 4 mol% Co) were charged into the reactor. The system was purged with O_2 (three evacuation-refill cycles) to establish an inert-free oxidative atmosphere. The reaction mixture was heated to the target temperature under vigorous stirring (800 rpm). Reaction progress was monitored by gas chromatography (GC-FID), and product identity was confirmed via GC-MS. Post-reaction, the mixture was diluted with acetonitrile (10 mL), and the catalyst was recovered via centrifugation (12,000 rpm, 5 min) for reuse. The supernatant was concentrated by rotary evaporation, followed by extraction with ethyl acetate (4 × 20 mL) and water (5 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Pure products (>95% by GC) were isolated and characterized by $^1H/^{13}C$ NMR spectroscopy.

6. 2.0 mmol Scale Reactions



A 100 mL round-bottom flask was charged with **1a** (2 mmol), **2a** (6 mmol), CoSiW-300 (0.2 mmol, 1 mol%), MeCN (4 mL), and DMSO (1 mL). Upon reaction completion,

the mixture was quenched with acetonitrile (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography on neutral alumina (200–300 mesh, petroleum ether/ethyl acetate = 5:1) afforded the target product as a white solid (282 mg, 67% isolated yield).

7. Crude NMR spectra and GC-MS

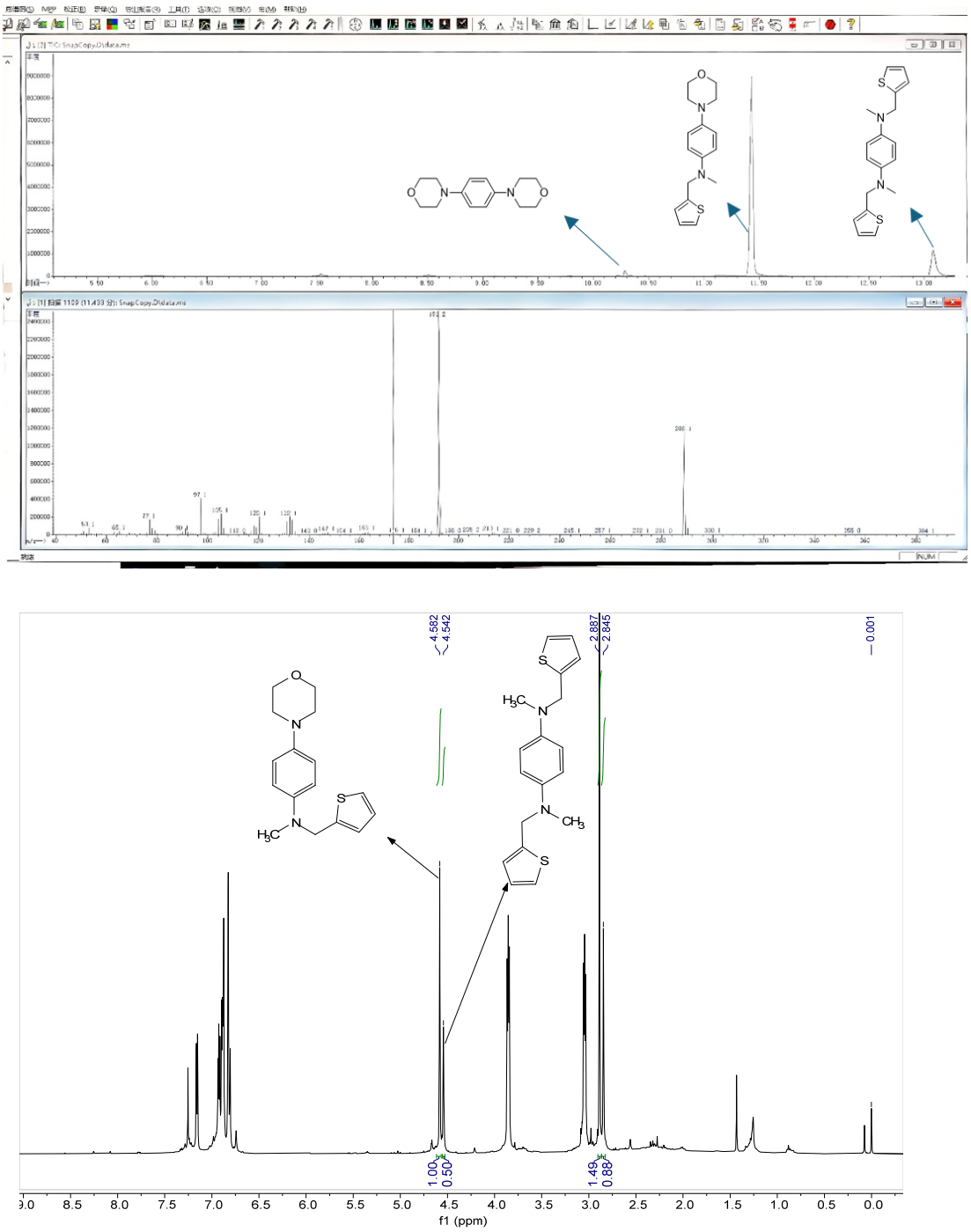


Fig. S9 Crude NMR spectra and GC-MS of 4g

8. Calculation of green chemistry metrics

Green chemistry metrics has been calculated for our optimized reaction on the basis of following parameters.

(1) Atom economy (AE) (%) $=\frac{\text{molecular mass of desired product}}{\text{Molecular mass of all reactants}} \times 100$

(2) Reaction mass efficiency (RME) (%) $=\frac{\text{mass of desired product}}{\text{mass of all reactants}} \times 100$

(3) Carbon efficiency (CE) (%) $= \frac{\text{amount of carbon in desired product total}}{\text{producttotal amount of carbon presented in all reactants}} \times 100$

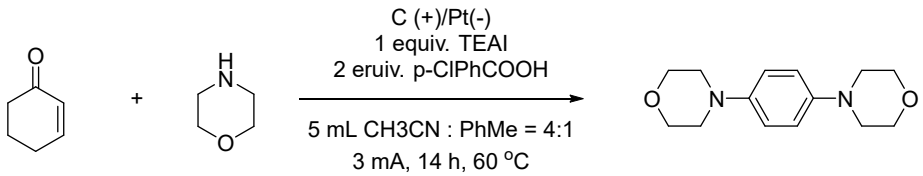
(4) Atom efficiency(AE_f) (%) =(% yield of product × % atom economy)×100

(5) Environmental factor (E-factor) $= \frac{\text{Amount of waste}}{\text{Amount of product}}$

(6) Optimumefficiency(OE) $=\frac{\text{RME}}{\text{AE}} \times 100$

(7) Productmassintensity(PMI) $=\frac{\text{mass of all reactants + solvent}}{\text{mass of product}}$

(a) *Green Chem.,* 2024**, 26,** 4684**.**



0.3 mmol
28.82mg
C_6H_8O
96.06

1.8 mmol
156.73mg
C_4H_9NO
87.07

0.225mmol
55.83mg
$C_{14}H_{20}N_2O_2$
248.15

Reactant **1a**	cyclohex-2-en-1-one	28.82 mg	0.3 mmol FW 96.06
Reactant **2a**	morpholine	156.73mg	1.8 mmol FW 87.07
Solvent	CH_3CN	3144mg	76.6mmol FW 41.05
	PhMe	867mg	9.4mmol FW 92.14
Product **3a**	1,4-dimorpholinobenzene	55.83mg	0.225mmol FW 248.15
Yield of product **3a** =75%			

(1) AE= $\frac{248.15}{96.06+87.07\times2} \times 100\% = 91.83\%$

(2) RME= $\frac{55.83}{28.82+156.73} \times 100\% = 30.08\%$

(3) CE= $\frac{0.75\times14}{6+4\times2} \times 100\% = 75\%$

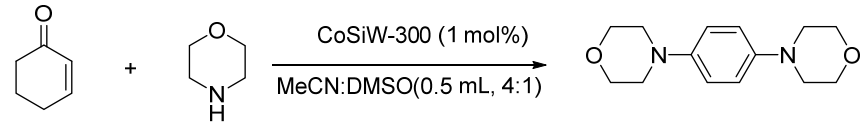
(4) AE_f=(0.75×0.9183)×100%=68.87%

(5) E-factor=$\frac{(28.82+156.73+3144+867+77+94)-55.83}{55.83}$=77.2

(6) OE=$\frac{30.08}{91.83} \times 100\% = 32.75\%$

(7) PMI=$\frac{28.82+156.73+3144+867}{55.83}$=75.16

(b) Our approach:



0.2 mmol
19.21mg
C_6H_8O
96.06

0.6 mmol
52.24mg
C_4H_9NO
87.07

82% yield
40.70mg
$C_{14}H_{20}N_2O_2$
248.15

Reactant **1a**	cyclohex-2-en-1-one	19.21 mg	0.2 mmol FW 96.06
Reactant **2a**	morpholine	52.24mg	0.6 mmol FW 87.07
Solvent	MeCN DMSO	314mg 110mg	76.6mmol FW 41.05 1.4mmol FW 78.13
Product **3a**	1,4-dimorpholinobenzene	40.70mg	0.164mmol FW 248.15
Yield ofproduct **3a** =82%			

(1) AE= $\frac{248.15}{96.06+87.07\times2}\times100\%=91.83\%$

(2) RME= $\frac{40.70}{19.21+52.24}\times100\%=56.96\%$

(3) CE= $\frac{0.82\times14}{6+4\times2}\times100\%=82\%$

(4) $AE_f=(0.82\times0.9183)\times100\%=75.30\%$

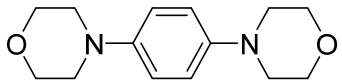
(5) E-factor=$\frac{(19.21+52.24+314+110+6)-40.70}{40.70}=11.3$

(6) OE=$\frac{56.96}{91.83}\times100\%=62.02\%$

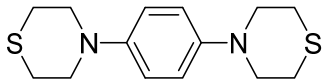
(7) PMI=$\frac{19.21+52.24+314+110}{40.70}=12.17$

No.	*E*-Factor	PMI	AE (%)	RME (%)	CE (%)	AE_f (%)	OE (%)
Ideal value	0	1	100	100	100	100	100
Reported method[8]	77.2	75.2	91.8	30.1	75.0	68.9	32.7
This work	11.3	12.2	91.8	57.0	82	75.4	62.0

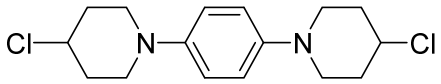
8. Characterization data of products



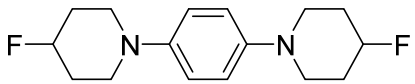
1,4-dimorpholinobenzene (3a)： pale yellow solid was obtained with 82% isolated yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 4H), 3.88 – 3.84 (m, 8H), 3.11 – 3.05 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 117.3, 66.9, 50.4.



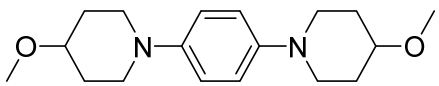
1,4-dithiomorpholinobenzene (3b): white solid was obtained with 67% isolated yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 4H), 3.42 – 3.36 (m, 8H), 2.80 – 2.74 (m, 8H).^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 119.1, 53.2, 27.4.



1,4-bis(4-chloropiperidin-1-yl)benzene (3c): brown solid was obtained with 52% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 4H), 4.22 – 4.13 (m, 2H), 3.45 – 3.35 (m, 4H), 3.00 – 2.89 (m, 4H), 2.26 – 2.16 (m, 4H), 2.08 – 1.96 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 118.2, 57.1, 48.6, 35.3.

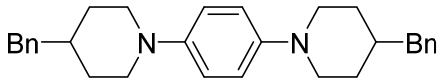


1,4-bis(4-fluoropiperidin-1-yl)benzene (3d): colourless solid was obtained with 66% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 4H), 4.88 – 4.81 (m, 1H), 4.76 – 4.68 (m, 1H), 3.31 – 3.21 (m, 4H), 3.10 – 3.00 (m, 4H), 2.11 – 1.94 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 118.3, 89.2, 87.5, 47.2, 47.1, 31.4, 31.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -180.94.

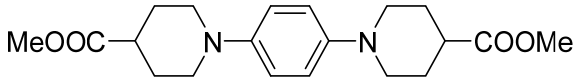


1,4-bis(4-methoxypiperidin-1-yl)benzene (3e): Pale yellow solid was obtained with 40% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 4H), 3.44 – 3.29 (m, 12H),

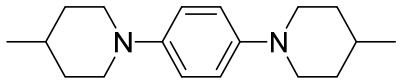
2.85 – 2.77 (m, 4H), 2.07 – 1.98 (m, 4H), 1.75 – 1.69 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 118.2, 76.2, 55.5, 48.6, 30.9.



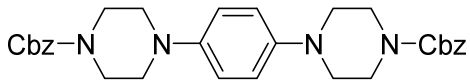
1,4-bis(4-benzylpiperidin-1-yl)benzene (3f): white solid was obtained with 42% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.4 Hz, 4H), 7.23 – 7.14 (m, 6H), 6.88 (s, 4H), 3.55 – 3.45 (m, 4H), 2.63 – 2.51 (m, 8H), 1.78 – 1.71 (m, 4H), 1.68 – 1.63 (m, 2H), 1.48 – 1.38 (m, 4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 140.6, 129.1, 128.2, 125.8, 118.2, 51.3, 43.2, 37.7, 32.2.



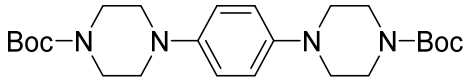
dimethyl 1,1'-(1,4-phenylene)bis(piperidine-4-carboxylate) (3g): pink solid was obtained with 56% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 4H), 3.70 (s, 6H), 3.54 – 3.47 (m, 4H), 2.69 (td, *J* = 11.8, 2.7 Hz, 4H), 2.45 – 2.36 (m, 2H), 2.06 – 1.98 (m, 4H), 1.94 – 1.83 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 145.7, 118.2, 51.7, 50.4, 40.8, 28.3.



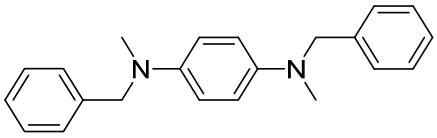
1,4-bis(4-methylpiperidin-1-yl)benzene (3h): brown solid was obtained with 40% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 4H), 3.49 (d, *J* = 11.7 Hz, 4H), 2.60 (t, *J* = 11.4 Hz, 4H), 1.73 (d, *J* = 12.6 Hz, 4H), 1.48 – 1.33 (m, 6H), 0.97 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 118.1, 51.3, 34.4, 30.6, 21.9.



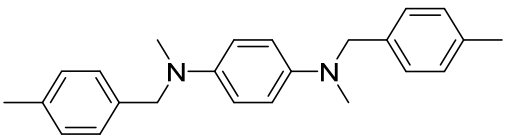
dibenzyl 4,4'-(1,4-phenylene)bis(piperazine-1-carboxylate) (3i): Off-white solid was obtained with 61% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 10H), 6.89 (s, 4H), 5.16 (s, 4H), 3.66 (t, J = 5.1 Hz, 8H), 3.04 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 136.6, 128.5, 128.1, 127.9, 118.3, 67.2, 50.4. 43.8.



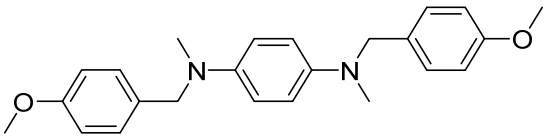
di-tert-butyl 4,4'-(1,4-phenylene)bis(piperazine-1-carboxylate) (3j): Brownish-gray solid was obtained with 45% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 4H), 3.57 (t, J = 5.0 Hz, 8H), 3.03 (t, J = 5.1 Hz, 8H), 1.48 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 145.6, 118.2, 79.8, 50.4, 28.4.



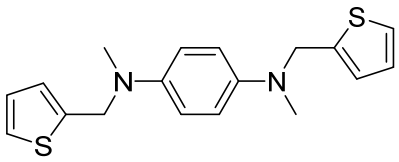
***N*^{1},*N*^{4}-dibenzyl-*N*^{1},*N*^{4}-dimethylbenzene-1,4-diamine (3k):** green solid was obtained with 56% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 10H), 6.76 (s, 4H), 4.37 (s, 4H), 2.86 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 139.4, 128.4, 127.3, 126. 8, 115.2, 58.4, 39.1.



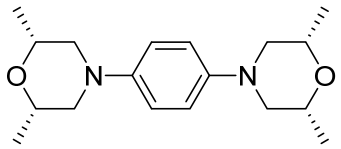
***N*^{1},*N*^{4}-dimethyl-*N*^{1},*N*^{4}-bis(4-methylbenzyl)benzene-1,4-diamine (3l):** Pale green solid was obtained with 65% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 8H), 6.76 (s, 4H), 4.33 (s, 4H), 2.84 (s, 6H), 2.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9, 136.3, 129.0, 127.3, 115.1, 58.0, 38.9, 21.1.



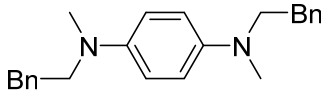
***N*^{1},*N*^{4}-bis(4-methoxybenzyl)-*N*^{1},*N*^{4}-dimethylbenzene-1,4-diamine (3m):** Dark green solid was obtained with 63% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 4H), 6.84 (d, J = 8.6 Hz, 4H), 6.77 (s, 4H), 4.30 (s, 4H), 3.79 (s, 6H), 2.82 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 143.0, 131.3, 128.5, 115.4, 113.7, 57.8, 55.2, 38.8.



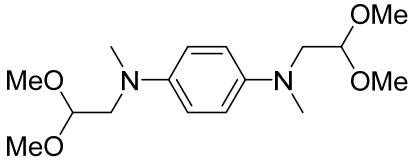
***N*^{1},*N*^{4}-dimethyl-*N*^{1},*N*^{4}-bis(thiophen-2-ylmethyl)benzene-1,4-diamine (3n):** black solid was obtained with 59% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 5.0, 1.3 Hz, 2H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 2H), 6.88 (d, *J* = 3.4 Hz, 2H), 6.83 (s, 4H), 4.54 (s, 4H), 2.85 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 142.3, 126.5, 125.1, 124.3, 116.0, 53.6, 38.7.



1,4-bis((2R,6S)-2,6-dimethylmorpholino)benzene (3o): green solid was obtained with 87% isolated yield, m.p.133–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 4H), 3.89 – 3.76 (m, 4H), 3.33 (d, J = 11.6 Hz, 4H), 2.36 (t, J = 11.0 Hz, 4H), 1.25 (s, 6H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 117.4, 71.7, 56.0, 19.0. HRMS (ESI): m/z calcd. for $C_{18}H_{29}N_2O_2$ $[M+H]^+$: 305.2224, found: 305.2221.

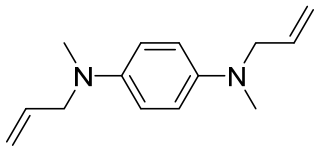


***N*^{1},*N*^{4}-dimethyl-*N*^{1},*N*^{4}-diphenethylbenzene-1,4-diamine (3p):** green solid was obtained with 53% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 4H), 7.23 – 7.18 (m, 6H), 6.79 (s, 4H), 3.50 – 3.43 (m, 4H), 2.88 – 2.80 (m, 10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 128.8, 128.4, 126.0, 115.3, 56.1, 39.2, 32.7.

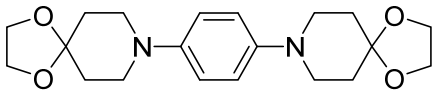


***N*^{1},*N*^{4}-bis(2,2-dimethoxyethyl)-*N*^{1},*N*^{4}-dimethylbenzene-1,4-diamine (3q):** colorless oil was obtained with 43% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 4H),

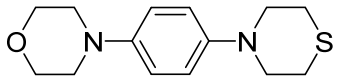
4.50 (t, J = 5.1 Hz, 2H), 3.39 (s, 12H), 3.34 (s, 4H), 2.92 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 114.7, 103.4, 56.6, 54.3, 39.9.



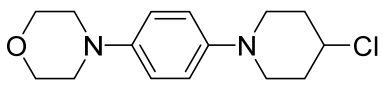
***N*^{1},*N*^{4}-diallyl-*N*^{1},*N*^{4}-dimethylbenzene-1,4-diamine (3r):** colorless oil was obtained with 34% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (s, 4H), 5.93 – 5.79 (m, 2H), 5.21 – 5.11 (m, 4H), 3.79 (s, 4H), 2.83 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 134.7, 116.4, 115.4, 57.0, 38.8.



1,4-di(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)benzene (3s): white solid was obtained with 48% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 4H), 3.99 (s, 8H), 3.23 – 3.18 (m, 8H), 1.88 – 1.83 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 118.3, 107.1, 64.2, 49.0, 34.7.

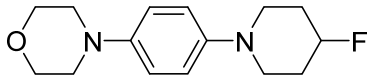


4-(4-thiomorpholinophenyl)morpholine(4a): Pale yellow solid was obtained with 70% isolated yield, m.p.130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.7 Hz, 4H), 3.85 (dd, *J* = 5.9, 3.6 Hz, 4H), 3.38 (dd, *J* = 6.4, 3.6 Hz, 4H), 3.10 – 3.05 (m, 4H), 2.80 – 2.75 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 145.6, 119.3, 117.2, 67.0, 53.4, 50.3, 27.5. HRMS (ESI): m/z calcd. for $C_{14}H_{21}N_2OS$ $[M+H]^+$: 265.1369, found: 265.1363.

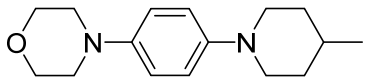


4-(4-(4-chloropiperidin-1-yl)phenyl)morpholine (4b): yellow solid was obtained with 39% isolated yield, m.p.114–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 – 6.84 (m, 4H), 4.21 – 4.13 (m, 1H), 3.94 – 3.78 (m, 4H), 3.45 – 3.35 (m, 2H), 3.14 – 3.01 (m,

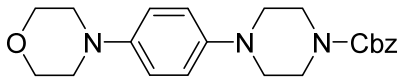
4H), 2.99 – 2.90 (m, 2H), 2.26 – 2.17 (m, 2H), 2.06 – 1.97 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 145.4, 118.4, 117.3, 67.0, 57.2, 50.4, 48.7, 35.3. HRMS (ESI): m/z calcd. for $C_{15}H_{22}ClN_2O$ $[M+H]^+$: 281.1415, found: 281.1413.



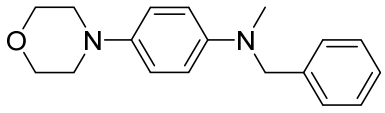
4-(4-(4-fluoropiperidin-1-yl)phenyl)morpholine (4c): white solid was obtained with 44% isolated yield, m.p.121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.90 (m, 2H), 6.90 – 6.85 (m, 2H), 4.88 – 4.81 (m, 1H), 4.76 – 4.69 (m, 1H), 3.90 – 3.82 (m, 4H), 3.31 – 3.21 (m, 2H), 3.11 – 3.01 (m, 6H), 2.08 – 1.95 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 145.3, 118.4, 117.2, 89.2, 87.5, 67.0, 50.4, 47.2, 47.1, 31.4, 31.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -180.96.HRMS (ESI): m/z calcd. for $C_{15}H_{22}FN_2O$ $[M+H]^+$: 265.1711, found: 265.1707.



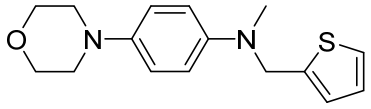
4-(4-(4-methylpiperidin-1-yl)phenyl)morpholine (4d): colourless solid was obtained with 43% isolated yield, m.p.117–119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.90 (m, 2H), 6.90 – 6.85 (m, 2H), 3.89 – 3.81 (m, 4H), 3.55 – 3.47 (m, 2H), 3.10 – 3.02 (m, 4H), 2.66 – 2.57 (m, 2H), 1.76 – 1.70 (m, 2H), 1.52 – 1.43 (m, 1H), 1.43 – 1.34 (m, 2H), 0.97 (d, J = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 144.9, 118.2, 117.2, 67.0, 51.2, 50.5, 34.3, 30.6, 21.9. HRMS (ESI): m/z calcd. for $C_{16}H_{25}N_2O$ $[M+H]^+$: 261.1962, found: 261.1961.



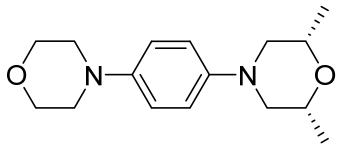
benzyl 4-(4-morpholinophenyl)piperazine-1-carboxylate (4e): white solid was obtained with 40% isolated yield, m.p.143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 6.89 (d, J = 2.5 Hz, 4H), 5.16 (s, 2H), 3.89 – 3.82 (m, 4H), 3.66 (t, J = 5.1 Hz, 4H), 3.10 – 2.99 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 145.8, 145.2, 136.6, 128.5, 128.0, 127.9, 118.4, 117.2, 67.2, 67.0, 50.5, 50.3, 43.9. HRMS (ESI): m/z calcd. for $C_{22}H_{28}N_3O_3$ $[M+H]^+$: 382.2125, found: 382.2119.



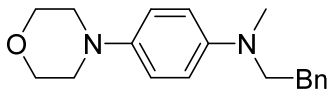
***N*-benzyl-*N*-methyl-4-morpholinoaniline (4f):** grey solid was obtained with 47% isolated yield, m.p.95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 6.7 Hz, 2H), 7.26 – 7.21 (m, 3H), 6.91 – 6.85 (m, 2H), 6.78 – 6.72 (m, 2H), 4.45 (s, 2H), 3.90 – 3.82 (m, 4H), 3.08 – 3.00 (m, 4H), 2.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9, 142.9, 139.2, 128.4, 127.0, 126.8, 118.1, 114.0, 67.1, 57.5, 51.1, 38.8. HRMS (ESI): m/z calcd. for $C_{18}H_{23}N_2O$ $[M+H]^+$: 283.1805, found: 283.1795.



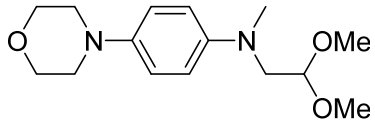
***N*-methyl-4-morpholino-*N*-(thiophen-2-ylmethyl)aniline (4g):** black solid was obtained with 72% isolated yield, m.p.92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.94 – 6.91 (m, 1H), 6.91 – 6.86 (m, 3H), 6.84 – 6.79 (m, 2H), 4.59 (s, 2H), 3.88 – 3.83 (m, 4H), 3.08 – 3.02 (m, 4H), 2.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 143.6, 142.2, 126.6, 125.0, 124.3, 117.8, 115.1, 67.1, 53.0, 50.9, 38.5. HRMS (ESI): m/z calcd. for $C_{16}H_{21}N_2OS$ $[M+H]^+$: 289.1369, found: 289.1361.



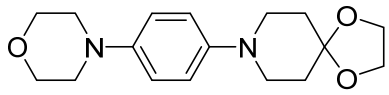
(2*R*,6*S*)-2,6-dimethyl-4-(4-morpholinophenyl)morpholine (4h): brown solid was obtained with 61% isolated yield, m.p.88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 4H), 3.88 – 3.84 (m, 4H), 3.38 – 3.30 (m, 2H), 3.10 – 3.01 (m, 4H), 2.36 (t, *J* = 11.0 Hz, 2H), 1.25 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2, 145.2, 117.4, 117.3, 71.7, 67.0, 55.9, 50.4, 19.0. HRMS (ESI): m/z calcd. for $C_{16}H_{25}N_2O_2$ $[M+H]^+$: 277.1911, found: 277.1907.



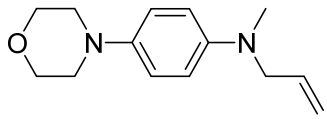
***N*-methyl-4-morpholino-*N*-phenethylaniline (4i):** grey solid was obtained with 78% isolated yield, m.p.78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.23 – 7.17 (m, 3H), 6.94 – 6.88 (m, 2H), 6.76 – 6.71 (m, 2H), 3.89 – 3.84 (m, 4H), 3.54 – 3.47 (m, 2H), 3.07 – 3.02 (m, 4H), 2.86 (s, 3H), 2.85 – 2.79 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 142.6, 139.9, 128.7, 128.4, 126.1, 118.2, 113.8, 67.1, 55.4, 51.1, 38.8, 32.7. HRMS (ESI): m/z calcd. for $C_{19}H_{25}N_2O$ $[M+H]^+$: 297.1962, found: 297.1952.



***N*-(2,2-dimethoxyethyl)-*N*-methyl-4-morpholinoaniline (4j):** black solid was obtained with 45% isolated yield, m.p.49–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 – 6.85 (m, 2H), 6.78 – 6.69 (m, 2H), 4.50 (t, J = 5.1 Hz, 1H), 3.89 – 3.80 (m, 4H), 3.39 (m, 8H), 3.06 – 3.00 (m, 4H), 2.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 142.7, 118.1, 113.4, 103.3, 67.1, 56.0, 54.4, 51.1, 39.5. HRMS (ESI): m/z calcd. for $C_{15}H_{25}N_2O_3$ $[M+H]^+$: 281.186, found: 281.1855.

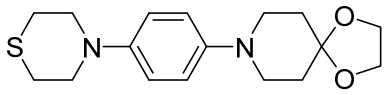


8-(4-morpholinophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (4K): yellow solid was obtained with 53% isolated yield, m.p.152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 – 6.9 (m, 2H), 6.9 – 6.8 (m, 2H), 4.0 (s, 4H), 3.4 – 3.3 (m, 4H), 3.3 – 3.2 (m, 4H), 2.8 – 2.7 (m, 4H), 1.9 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.9, 145.7, 119.2, 118.3, 107.1, 64.3, 53.4, 48.9, 34.7, 27.5. HRMS (ESI): m/z calcd. for $C_{17}H_{25}N_2O_2S$ $[M+H]^+$: 321.1631, found: 321.1626.

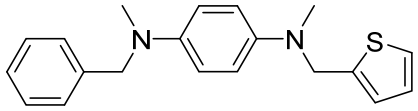


***N*-allyl-*N*-methyl-4-morpholinoaniline (4l):** brown oil was obtained with 38% isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) 6.91 – 6.84 (m, 2H), 6.76 – 6.70 (m, 2H),

5.90 – 5.78 (m, 1H), 5.21 – 5.11 (m, 2H), 3.89 – 3.82 (m, 6H), 3.06 – 3.00 (m, 4H), 2.87 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 142.9, 134.2, 118.0, 116.4, 114.2, 67.1, 56.2, 51.1, 38.4. HRMS (ESI): m/z calcd. for $C_{14}H_{21}N_2O$ $[M+H]^+$: 233.1649, found: 233.1642.



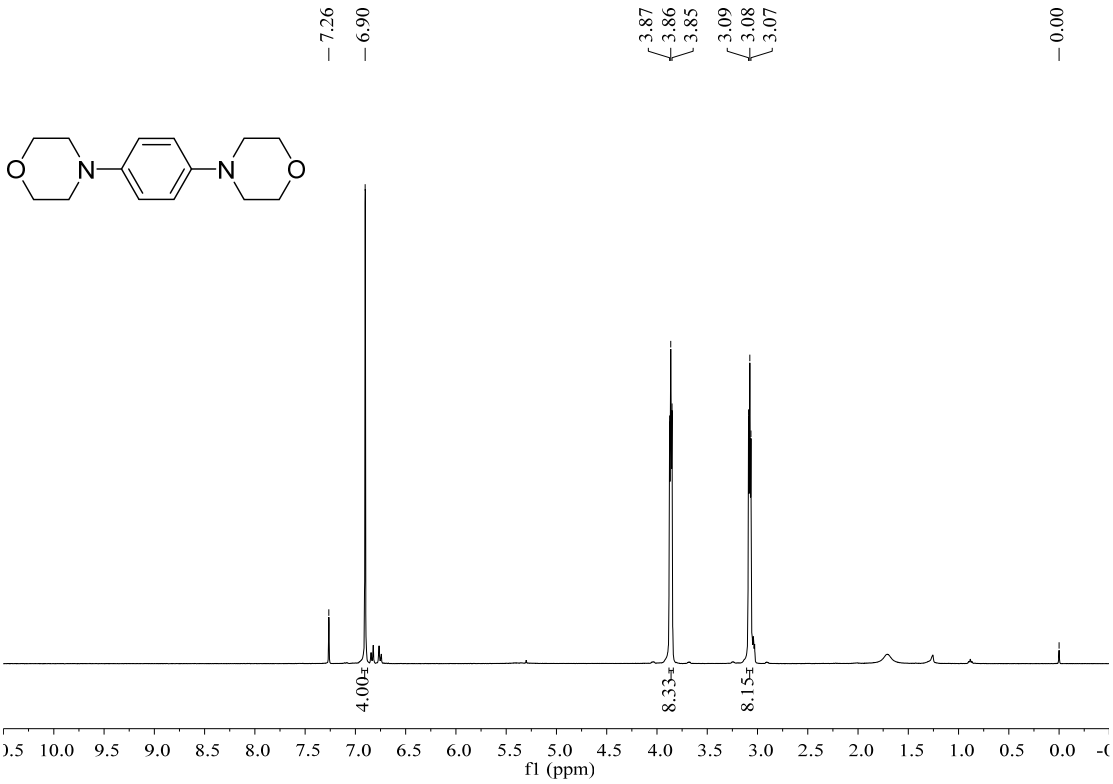
8-(4-thiomorpholinophenyl)-1,4-dioxa-8-azaspiro[4.5]decane (4m): yellow solid was obtained with 46% isolated yield, m.p.152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 – 6.84 (m, 4H), 3.99 (s, 4H), 3.41 – 3.34 (m, 4H), 3.24 – 3.16 (m, 4H), 2.80 – 2.74 (m, 4H), 1.89 – 1.83 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 145.6, 119.2, 118.3, 107.06, 64.3, 53.4, 48.8, 34.7, 27.5. HRMS (ESI): m/z calcd. for $C_{17}H_{25}N_2O_2S$ $[M+H]^+$: 321.1631, found: 321.1626.



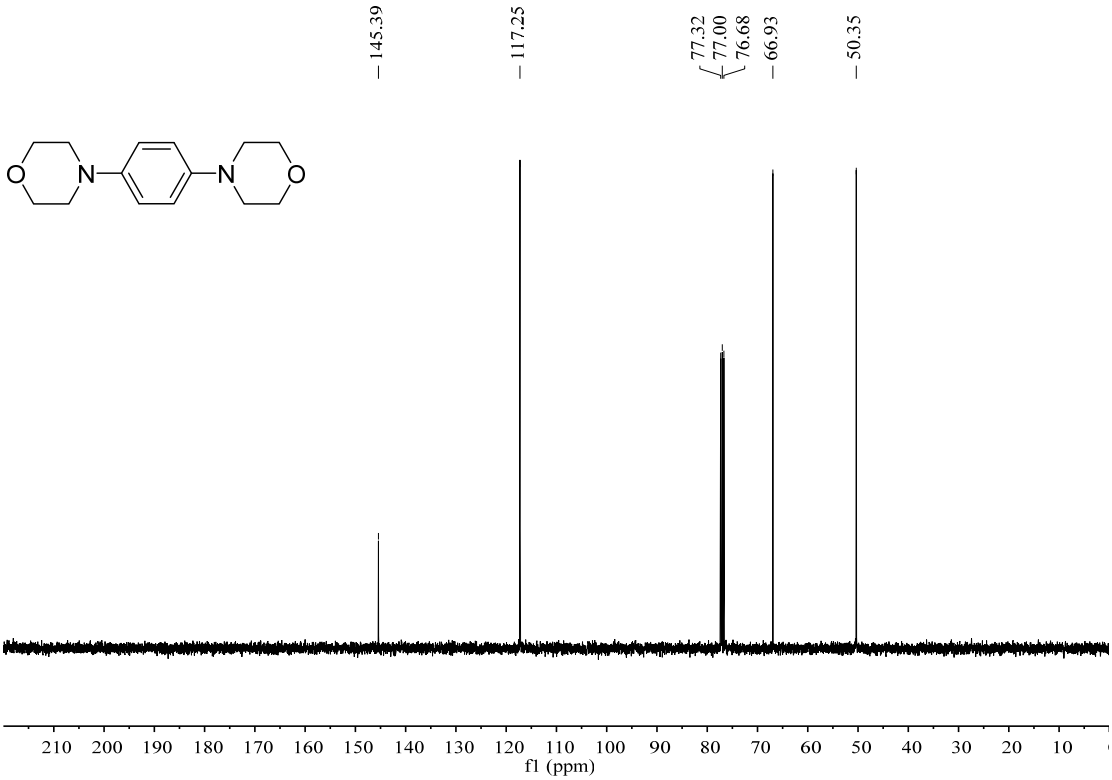
***N*^{1}-benzyl-*N*^{1},*N*^{4}-dimethyl-*N*^{4}-(thiophen-2-ylmethyl)benzene-1,4-diamine (4n):** black solid was obtained with 32% isolated yield, m.p.81–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 77.33 – 7.23 (m, 5H), 7.16 (d, *J* = 5.0 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.90 – 6.87 (m, 1H), 6.87 – 6.67 (m, 4H), 4.52 (s, 2H), 4.40 (s, 2H), 2.86 (d, *J* = 22.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 142.4, 142.0, 139.4, 128.4, 127.2, 126.8, 126.5, 125.1, 124.29, 116.4, 114.8, 58.1, 53.8, 38.9, 38.9. HRMS (ESI): m/z calcd. for $C_{20}H_{23}N_2S$ $[M+H]^+$: 323.1577, found: 323.1561.

9.Copies of NMR spectra of all products

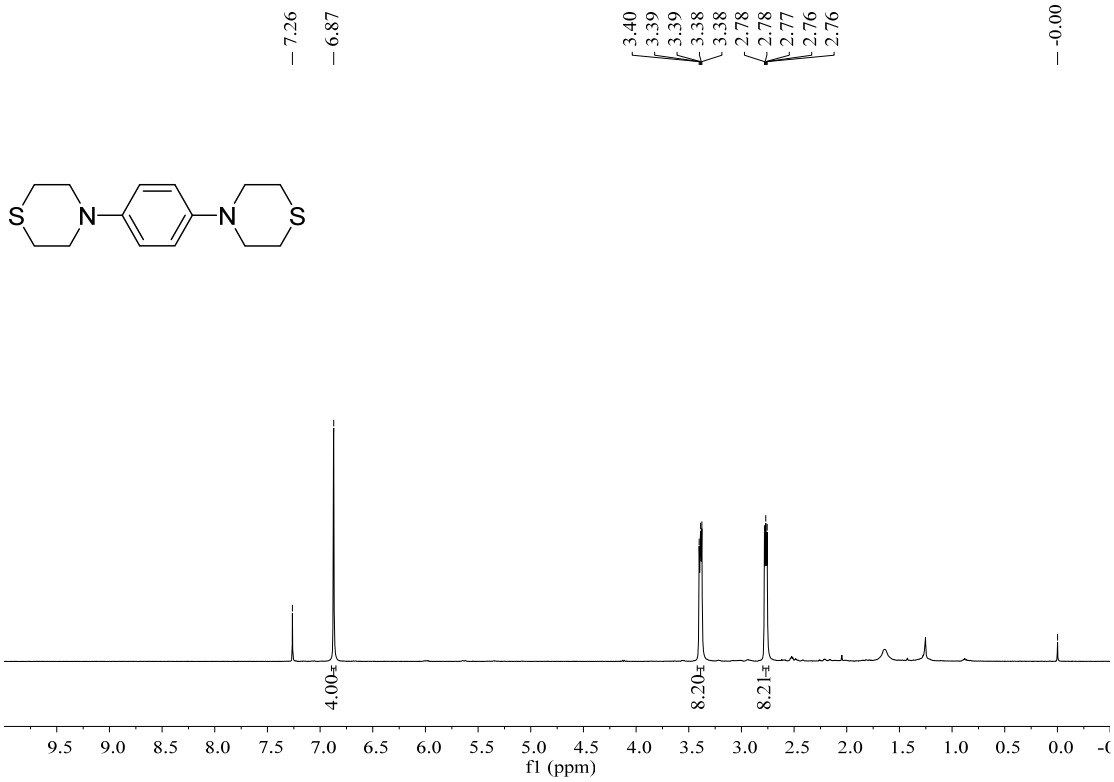
^{1}H NMR spectra of **3a** (400 MHz, $CDCl_3$)



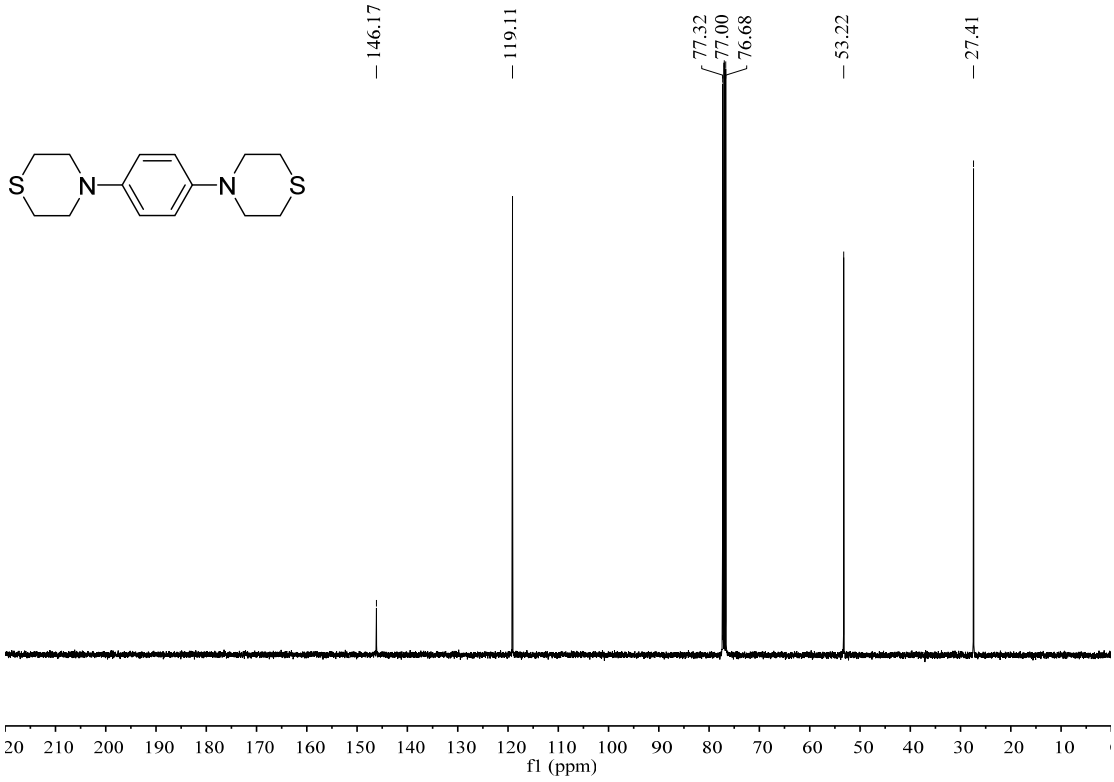
^{13}C NMR spectra of **3a** (100 MHz, $CDCl_3$)



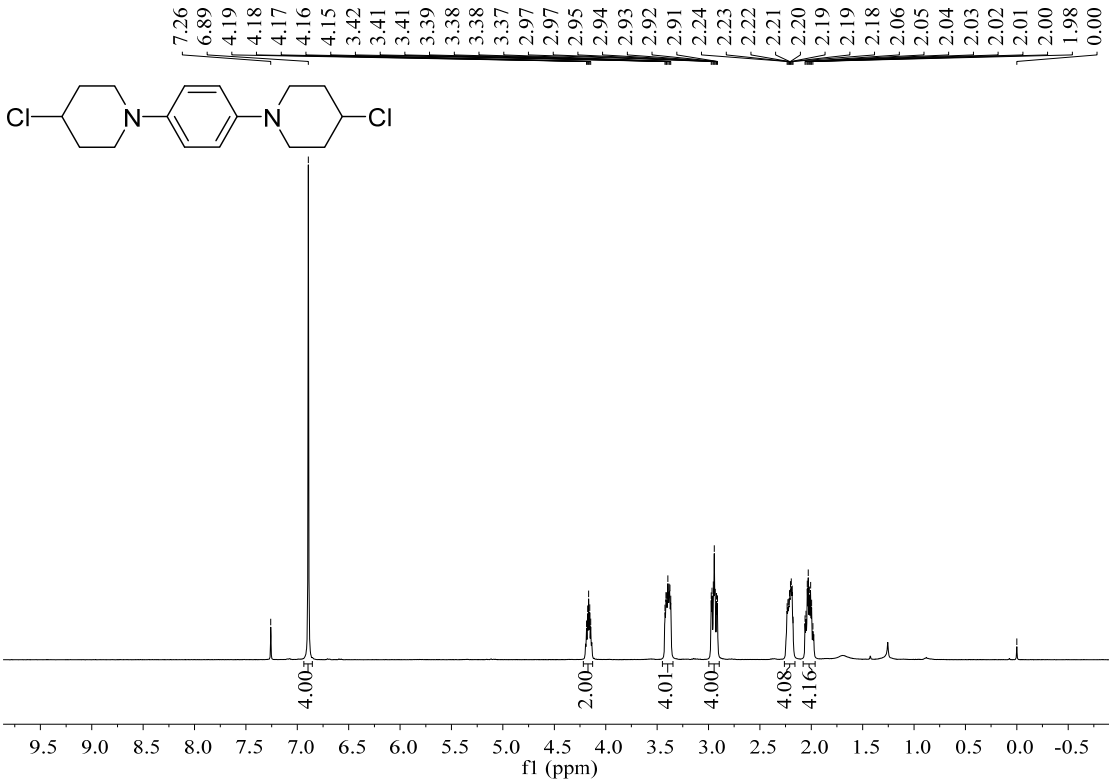
^{1}H NMR spectra of **3b** (400 MHz, $CDCl_3$)



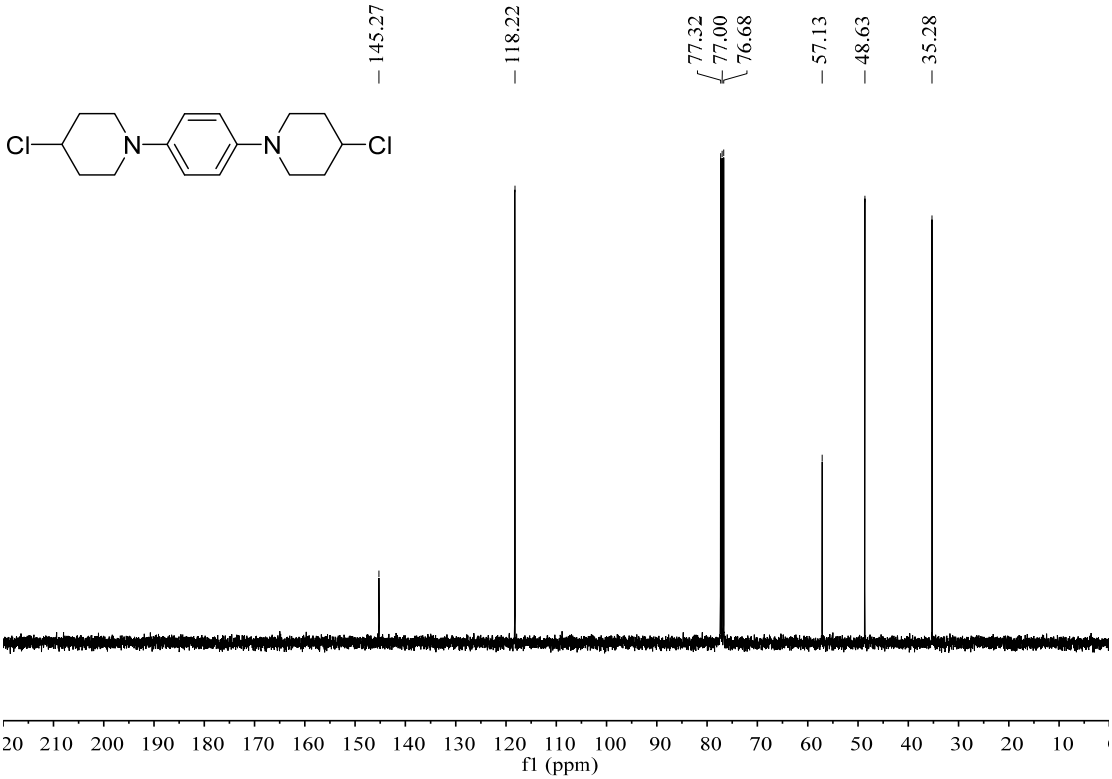
^{13}C NMR spectra of **3b** (100 MHz, $CDCl_3$)



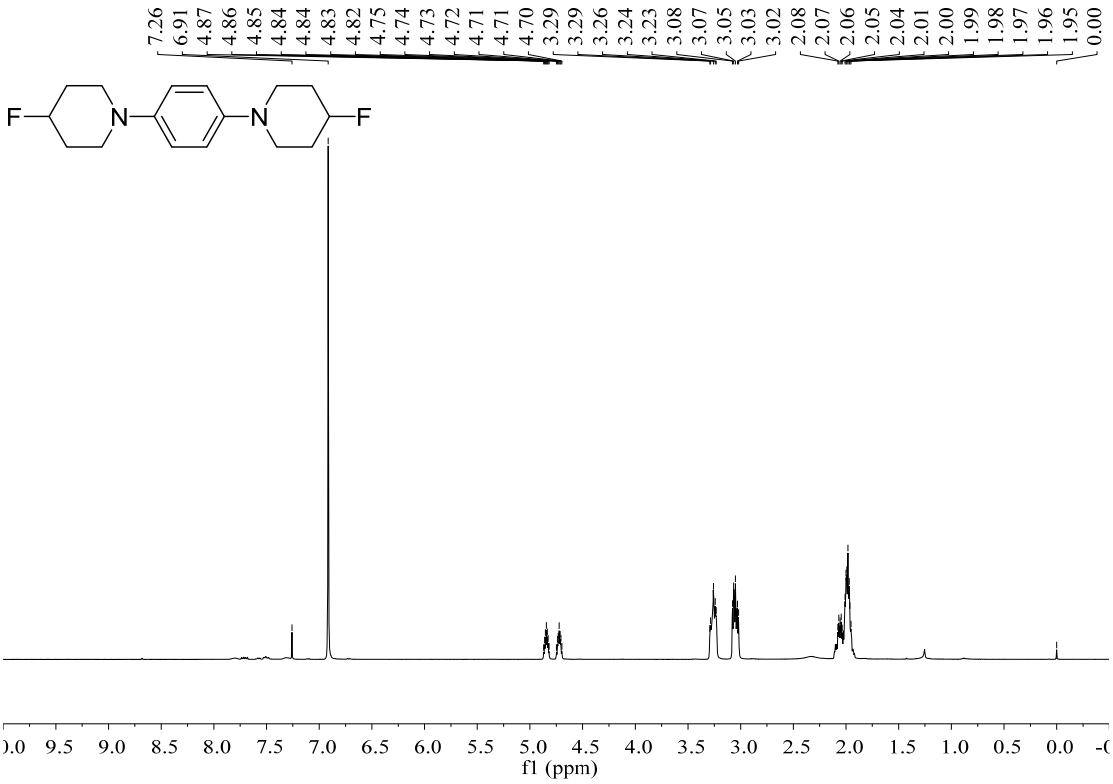
^{1}H NMR spectra of **3c** (400 MHz, $CDCl_3$)



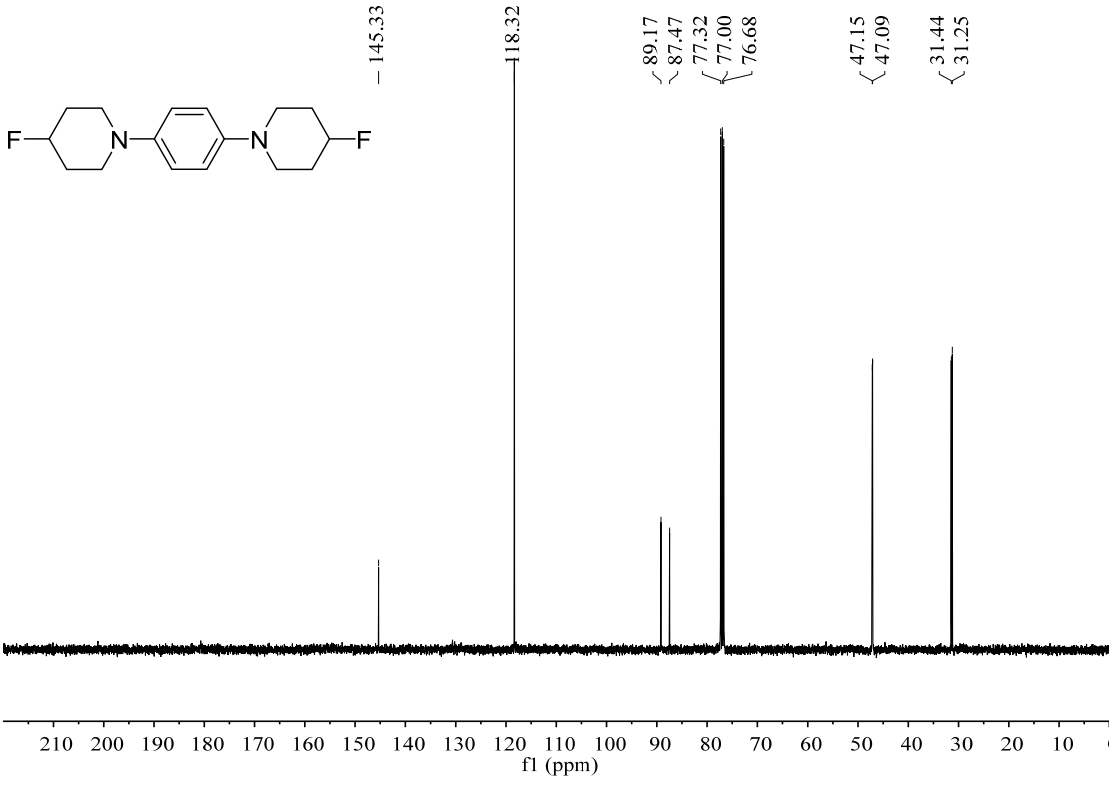
^{13}C NMR spectra of **3c** (100 MHz, $CDCl_3$)



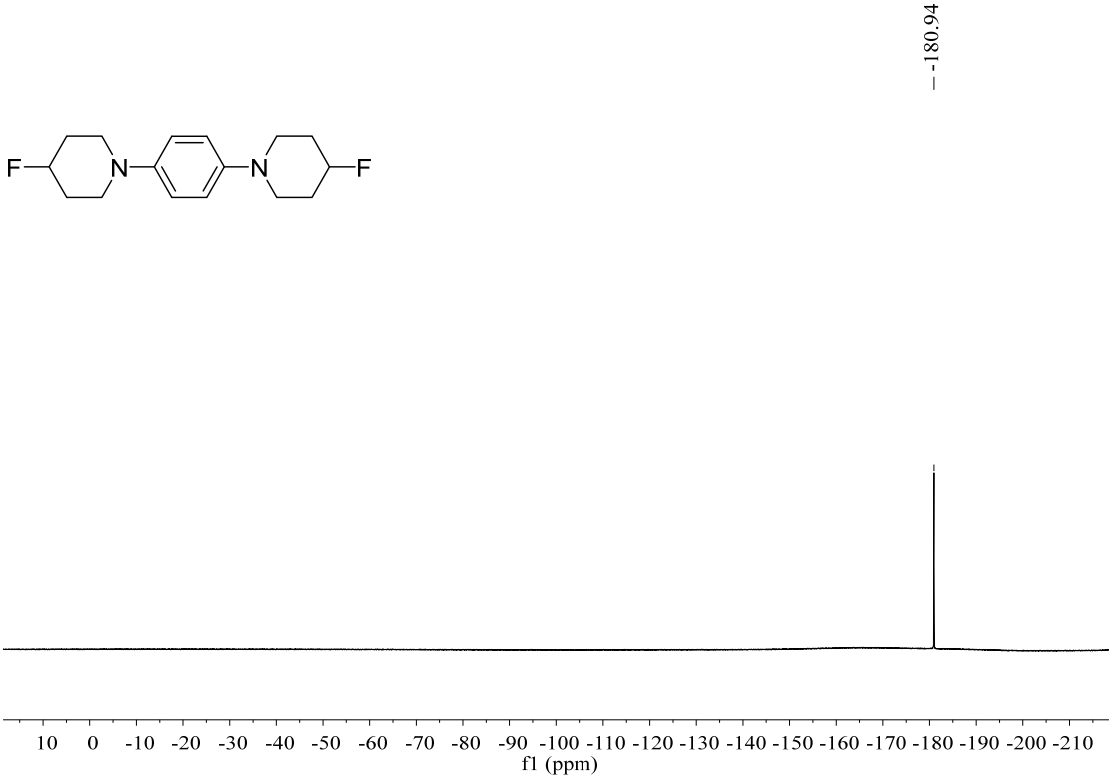
^{1}H NMR spectra of **3d** (400 MHz, $CDCl_3$)



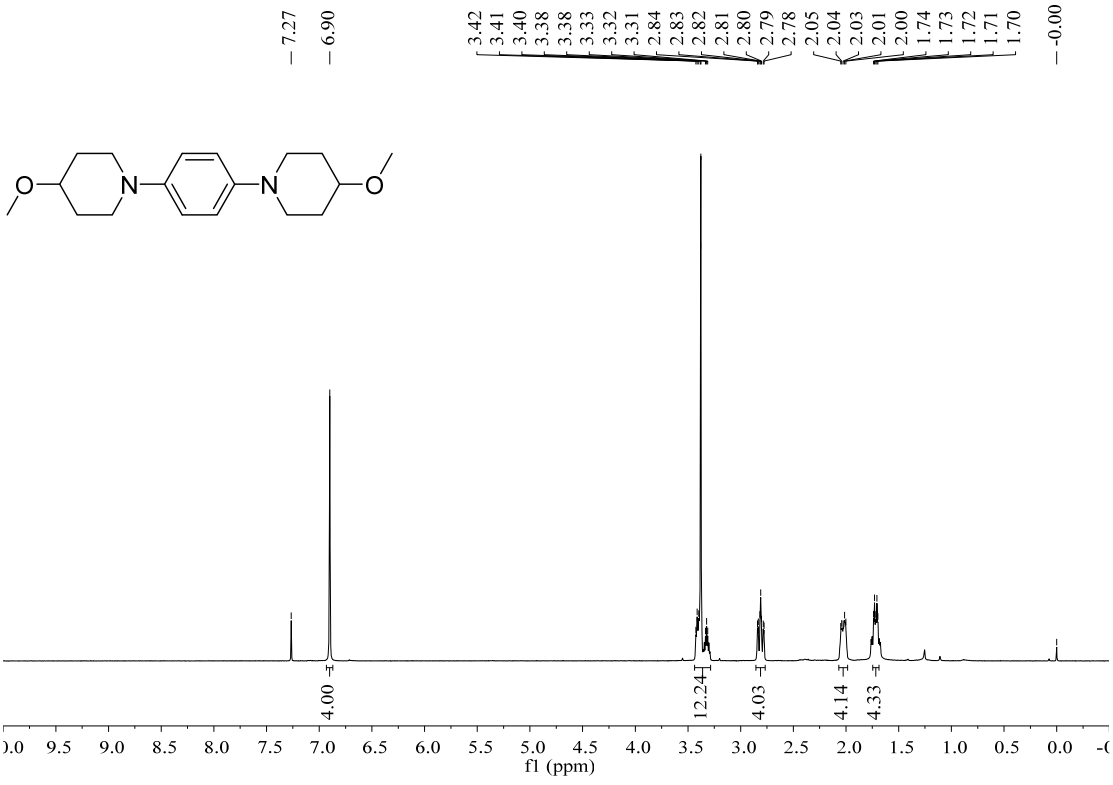
^{13}C NMR spectra of **3d** (100 MHz, $CDCl_3$)



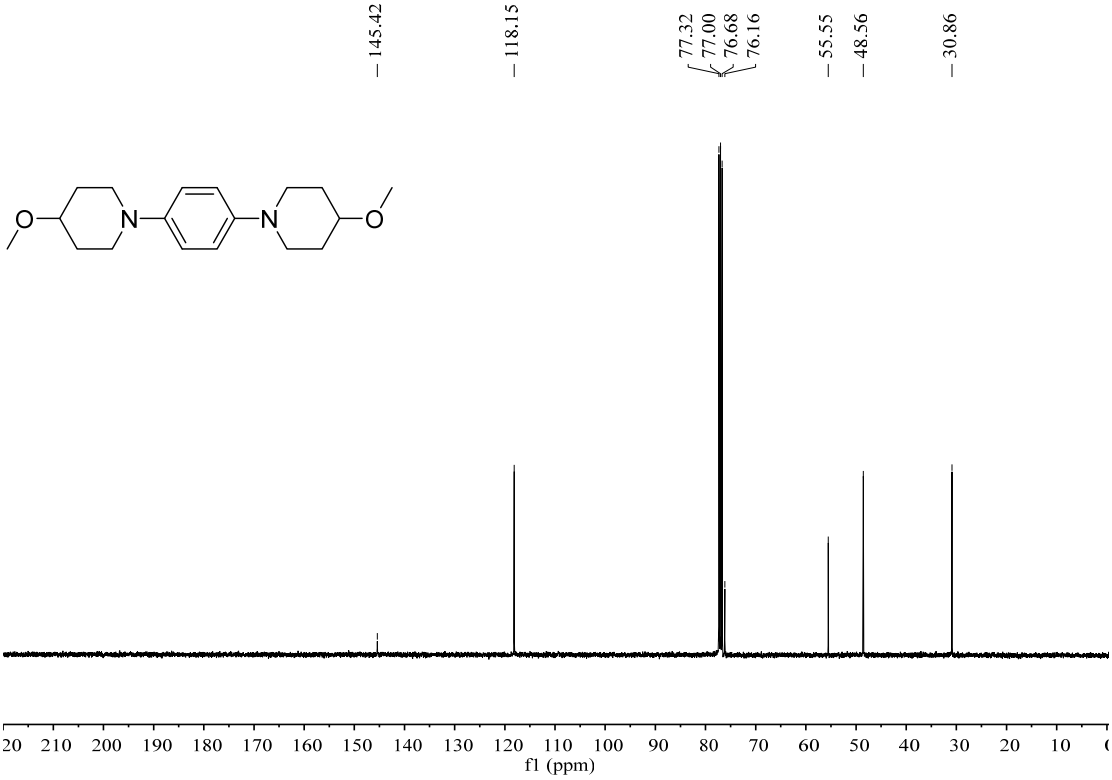
^{19}F NMR spectra of **3d** (376 MHz, $CDCl_3$)



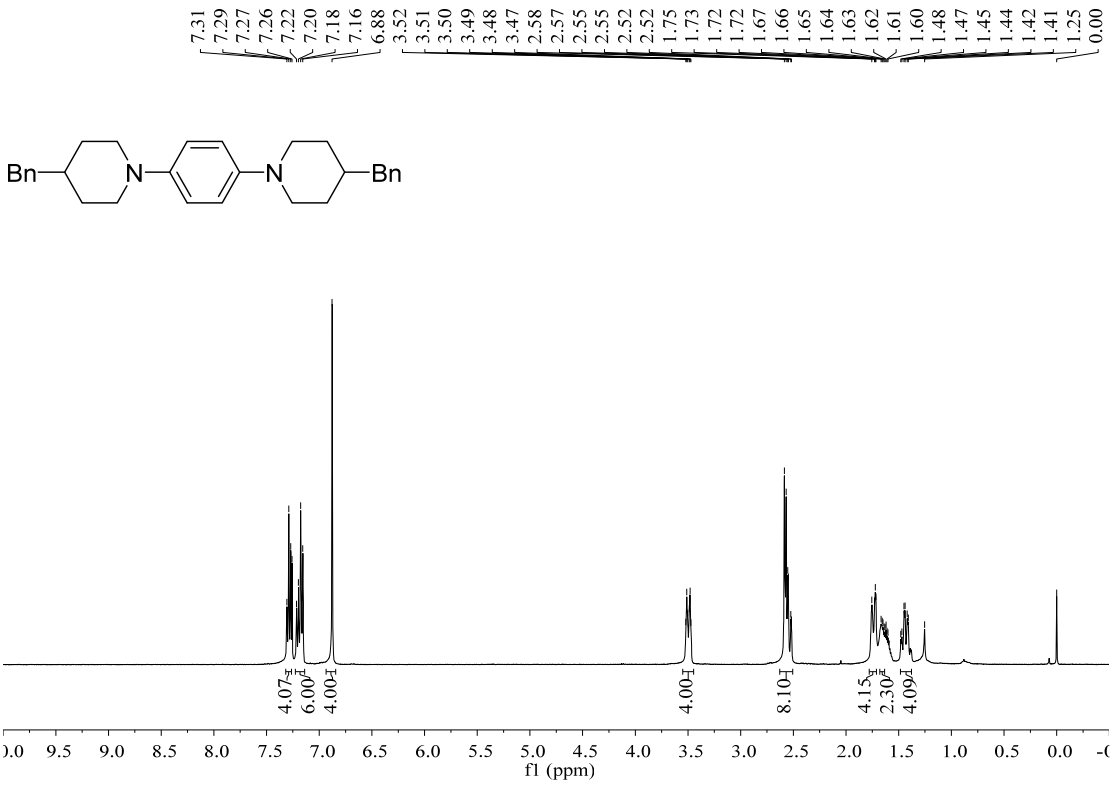
^{1}H NMR spectra of **3e** (400 MHz, $CDCl_3$)



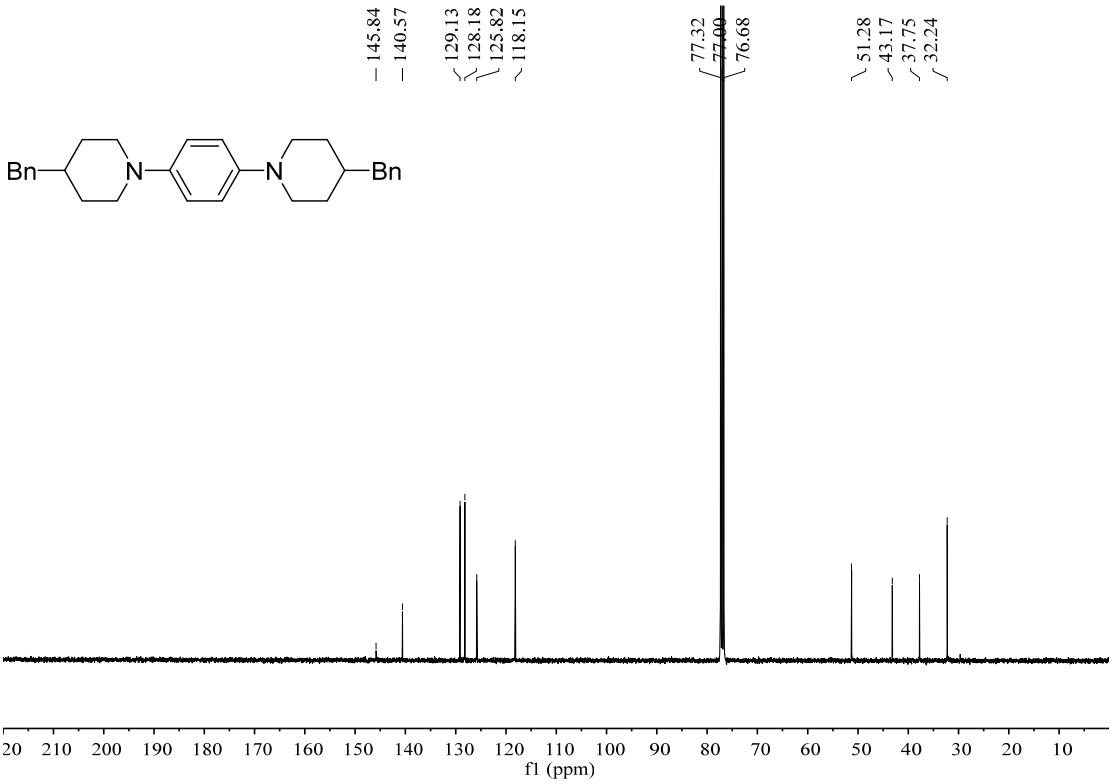
^{13}C NMR spectra of **3e** (100 MHz, $CDCl_3$)



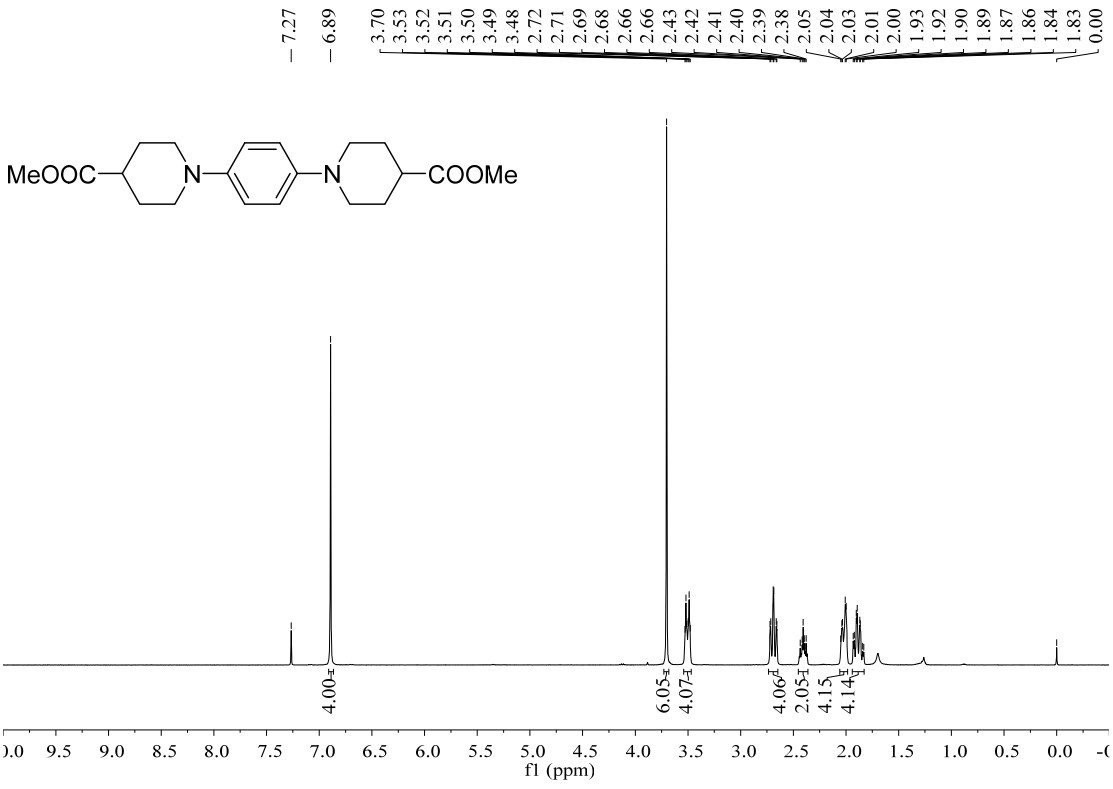
^{1}H NMR spectra of **3f** (400 MHz, $CDCl_3$)



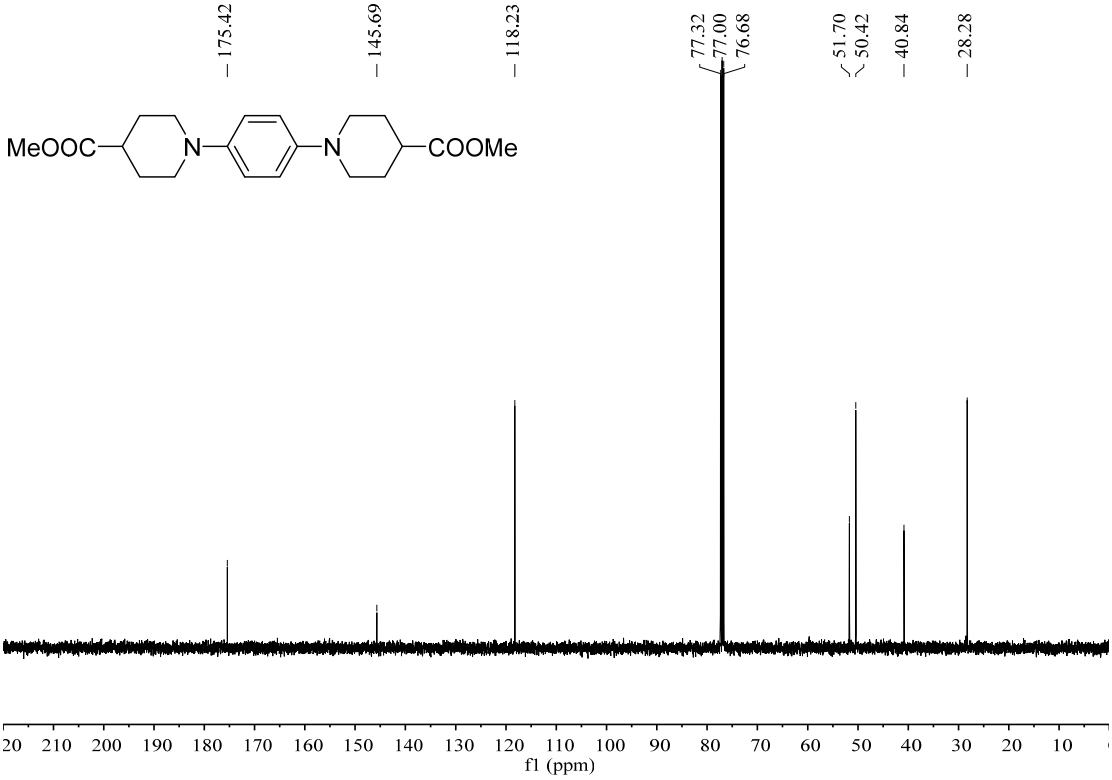
^{13}C NMR spectra of **3f** (100 MHz, $CDCl_3$)



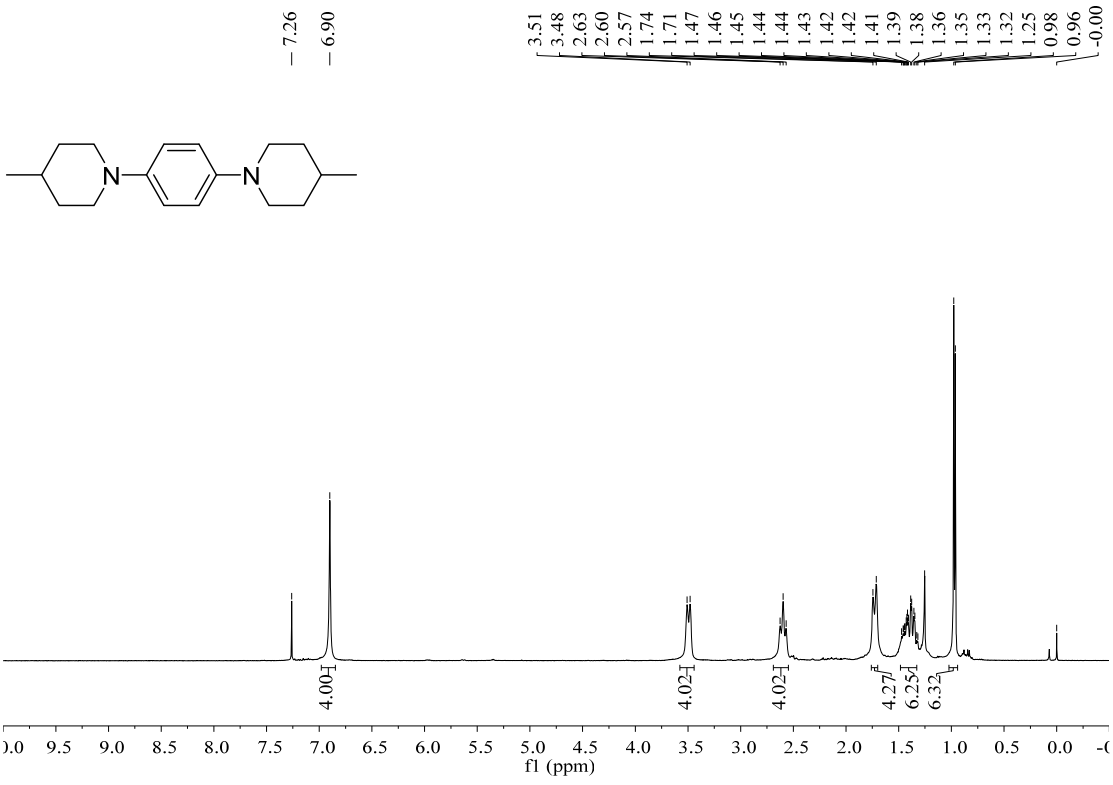
^{1}H NMR spectra of **3g** (400 MHz, $CDCl_3$)



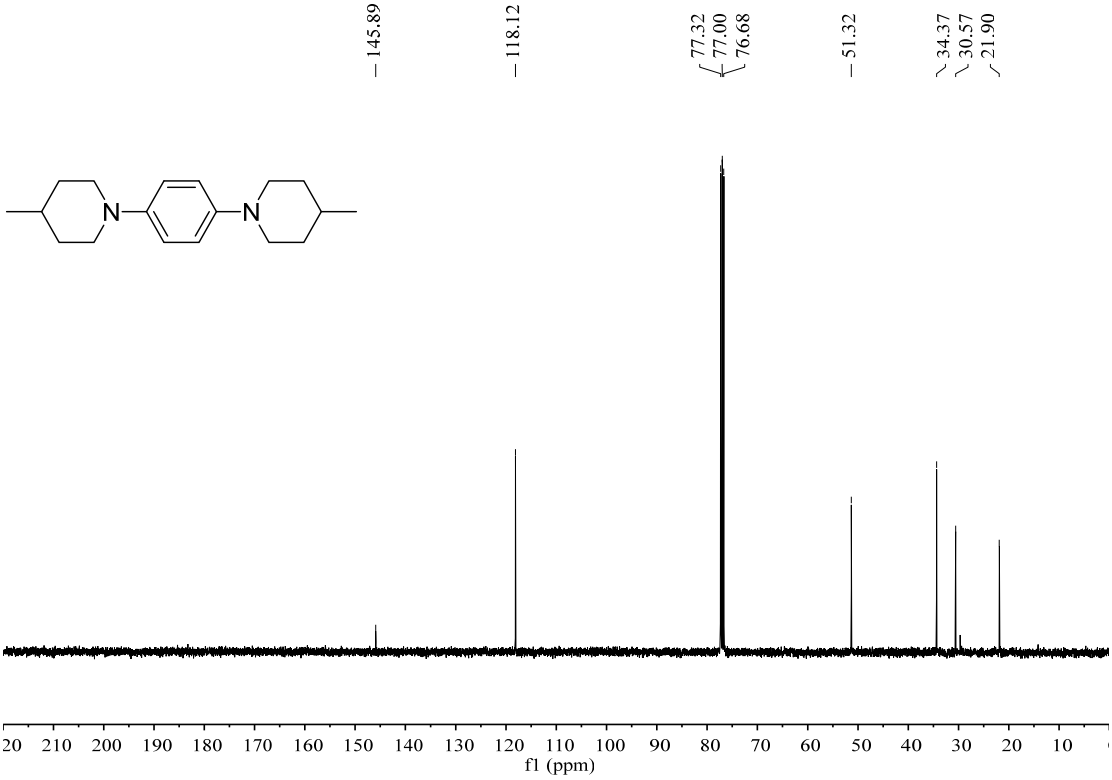
^{13}C NMR spectra of **3g** (100 MHz, $CDCl_3$)



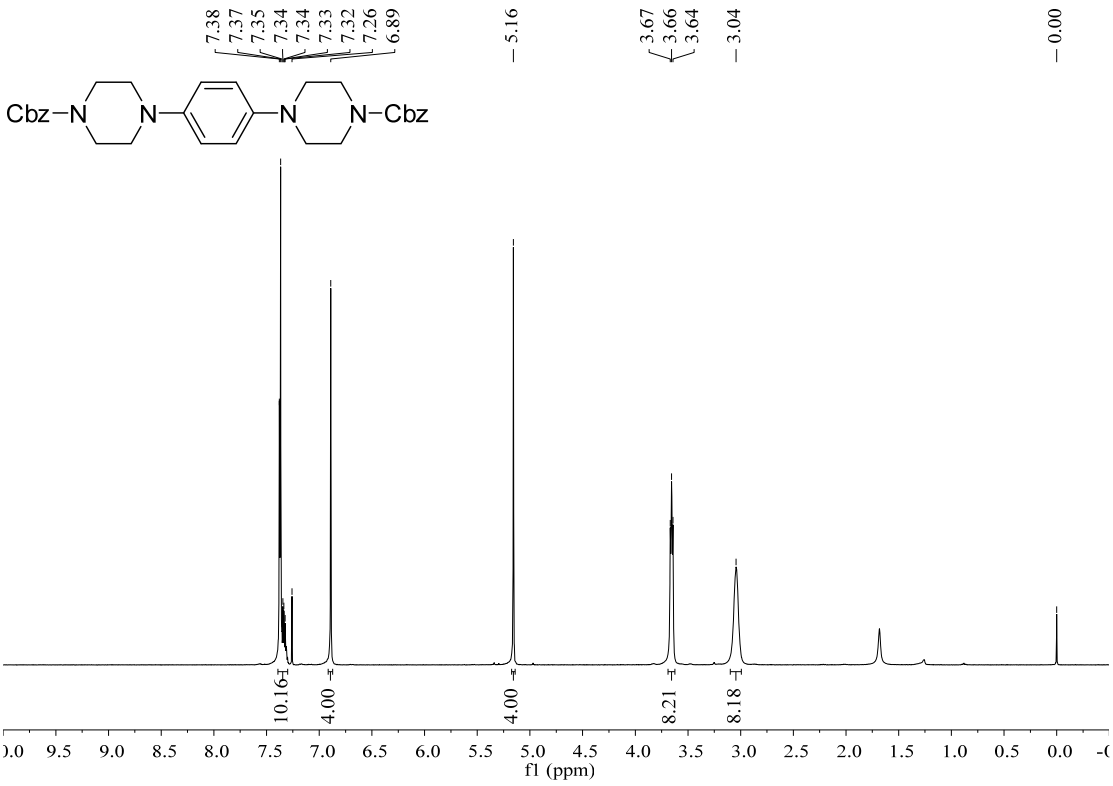
^{1}H NMR spectra of **3h** (400 MHz, $CDCl_3$)



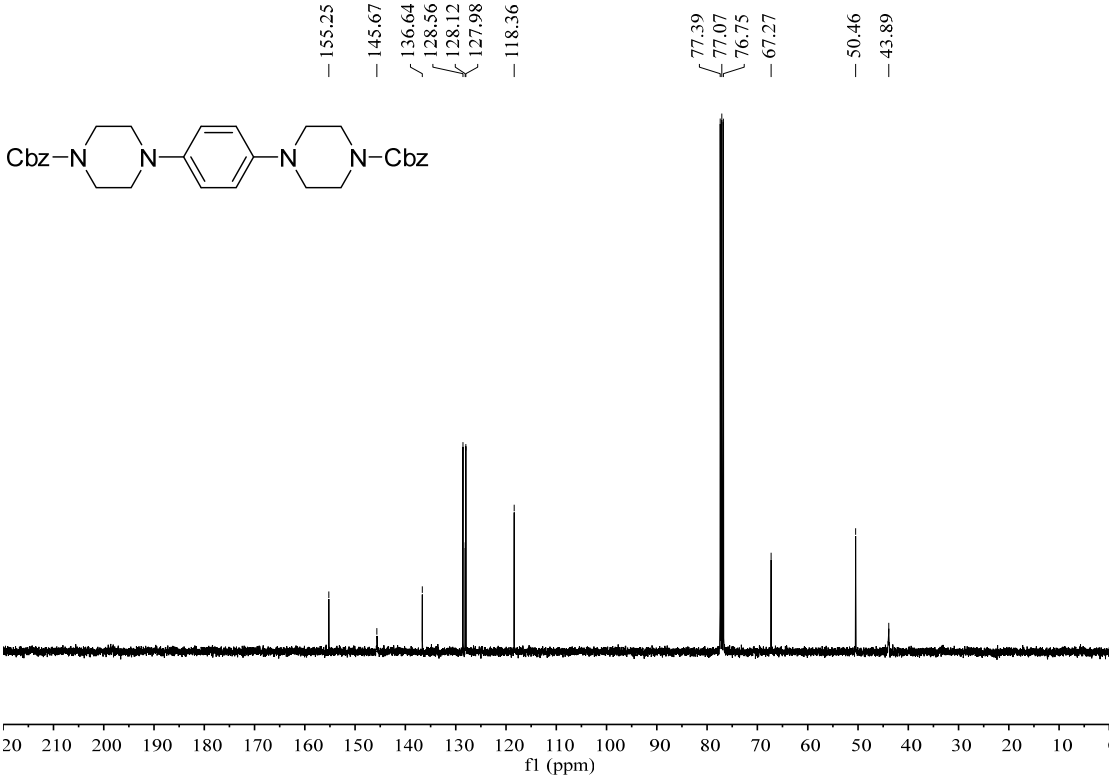
^{13}C NMR spectra of **3h** (100 MHz, $CDCl_3$)



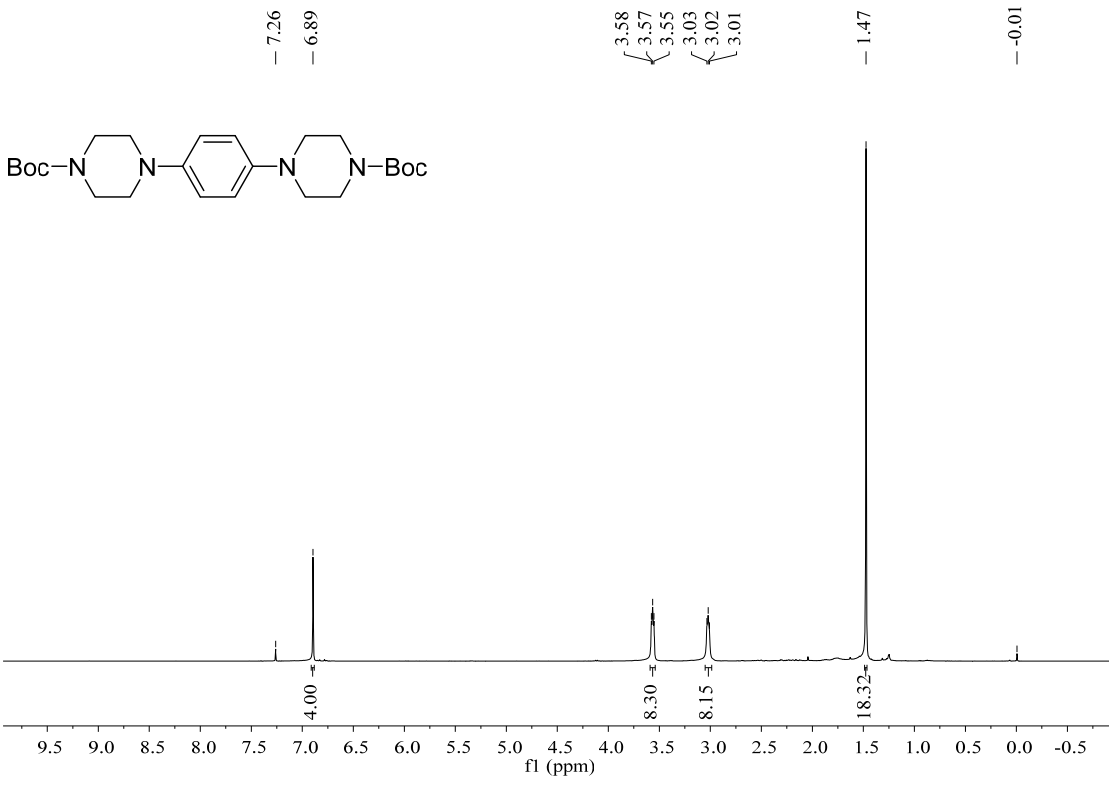
^{1}H NMR spectra of **3i** (400 MHz, $CDCl_3$)



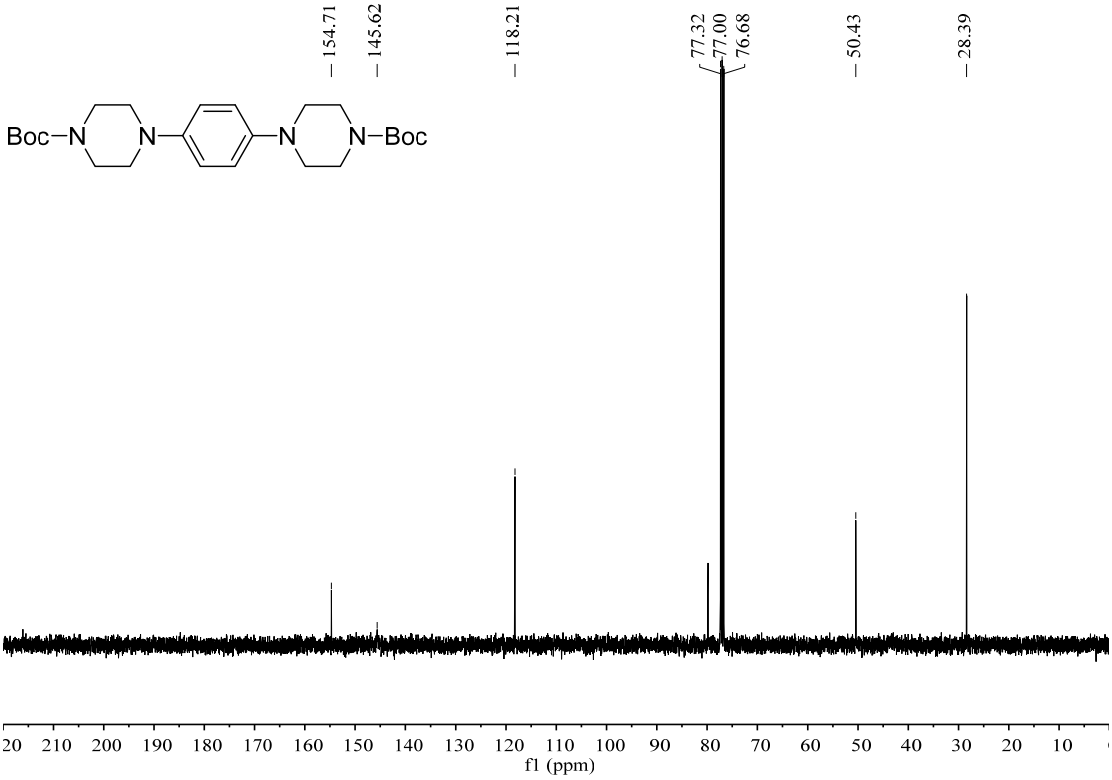
^{13}C NMR spectra of **3i** (100 MHz, $CDCl_3$)



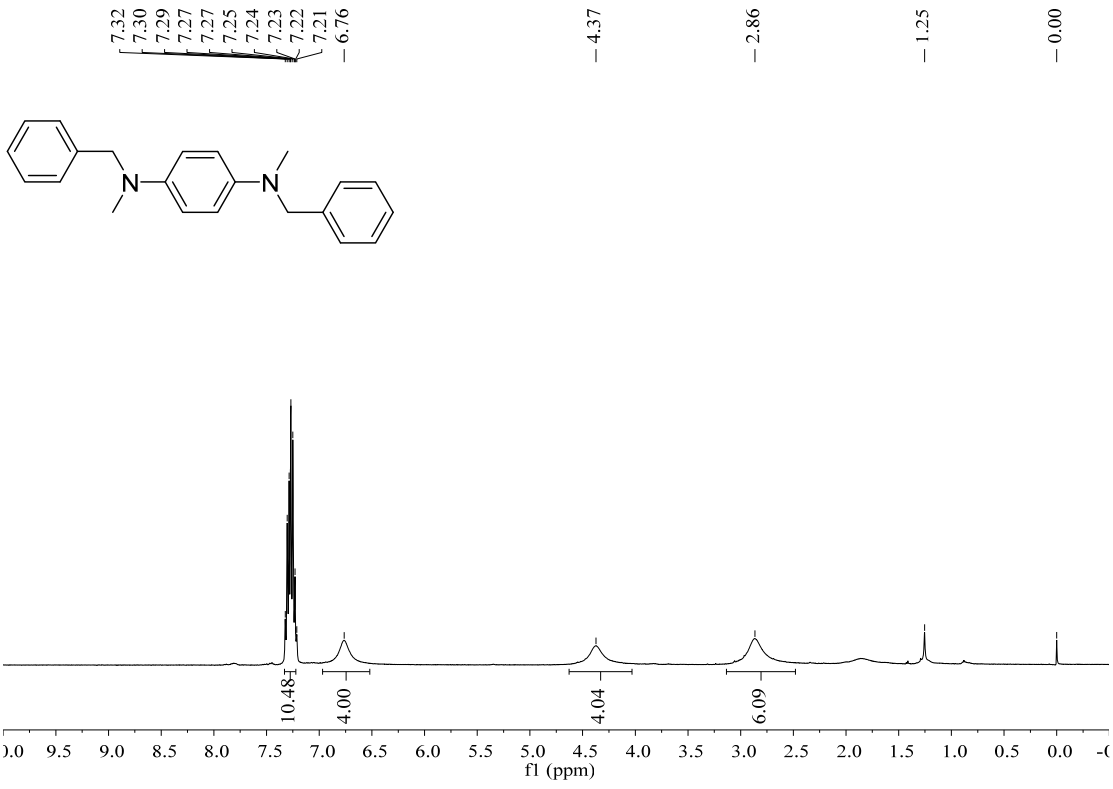
^{1}H NMR spectra of **3j** (400 MHz, $CDCl_3$)



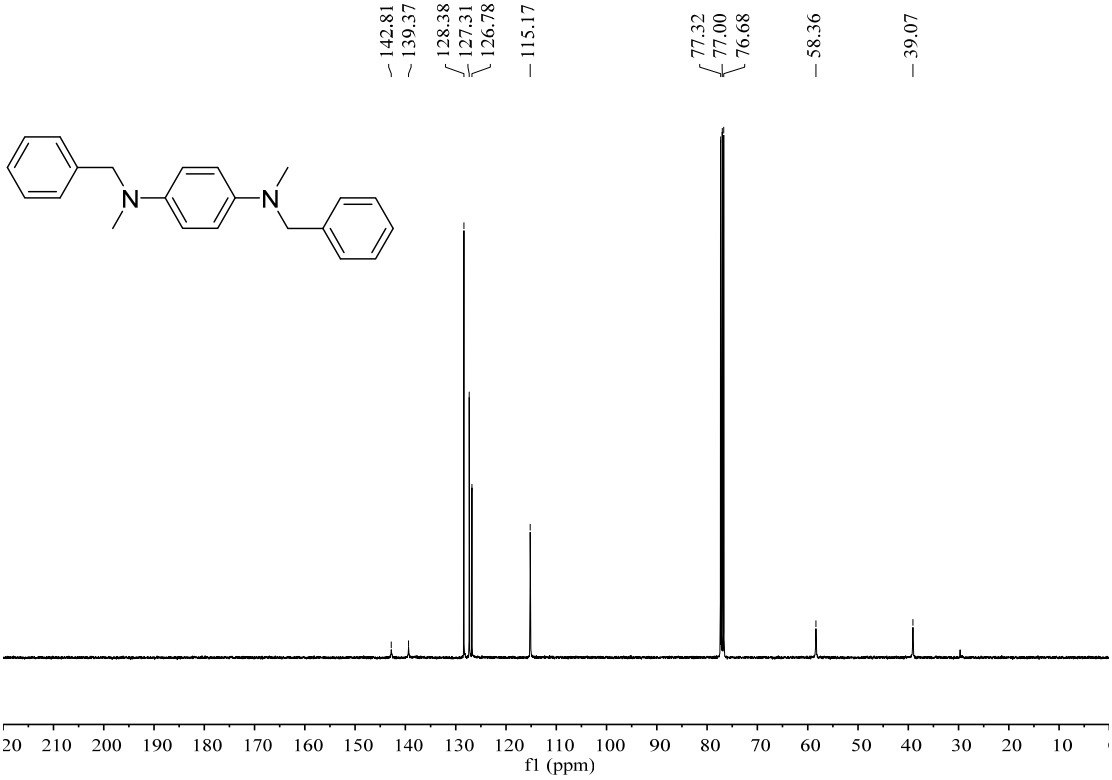
^{13}C NMR spectra of **3j** (100 MHz, $CDCl_3$)



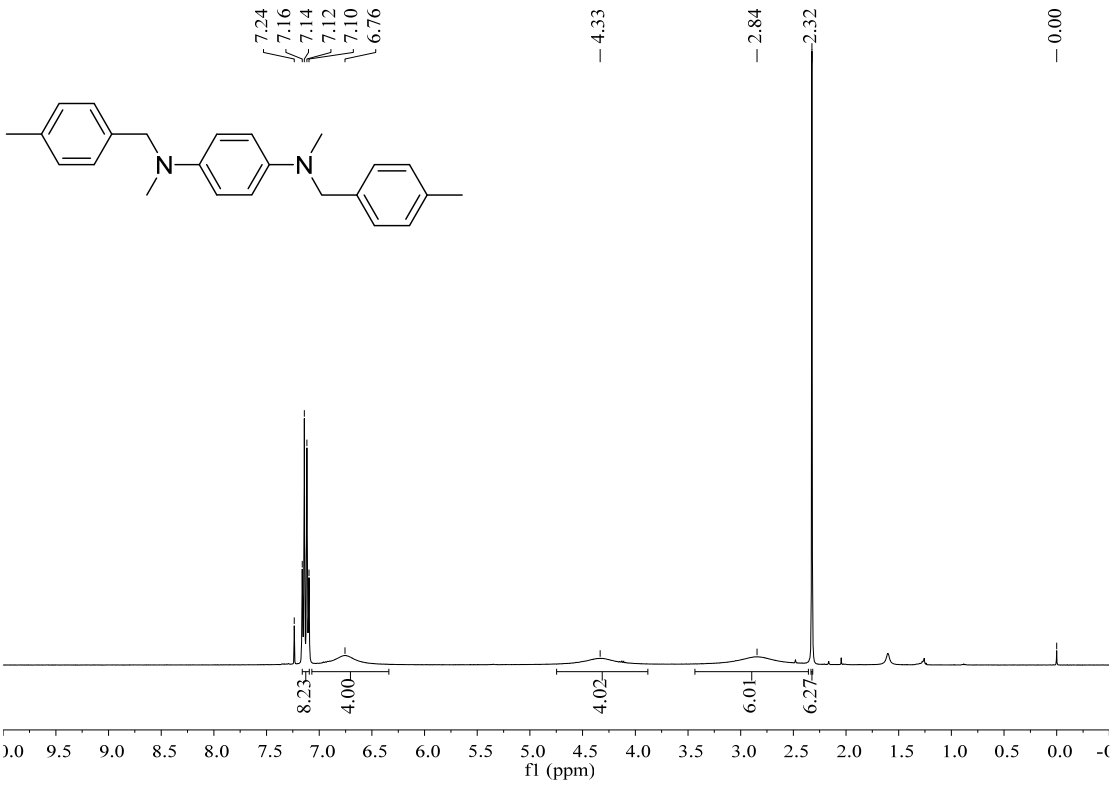
^{1}H NMR spectra of **3k** (400 MHz, $CDCl_3$)



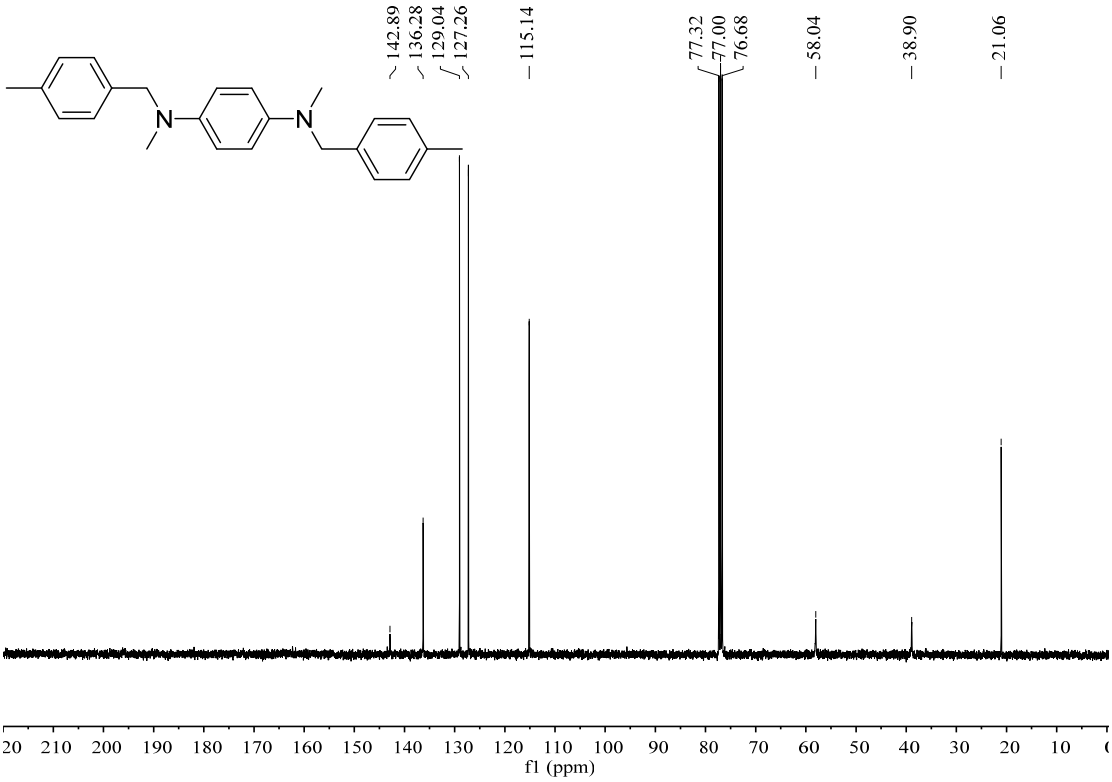
^{13}C NMR spectra of **3k** (100 MHz, $CDCl_3$)



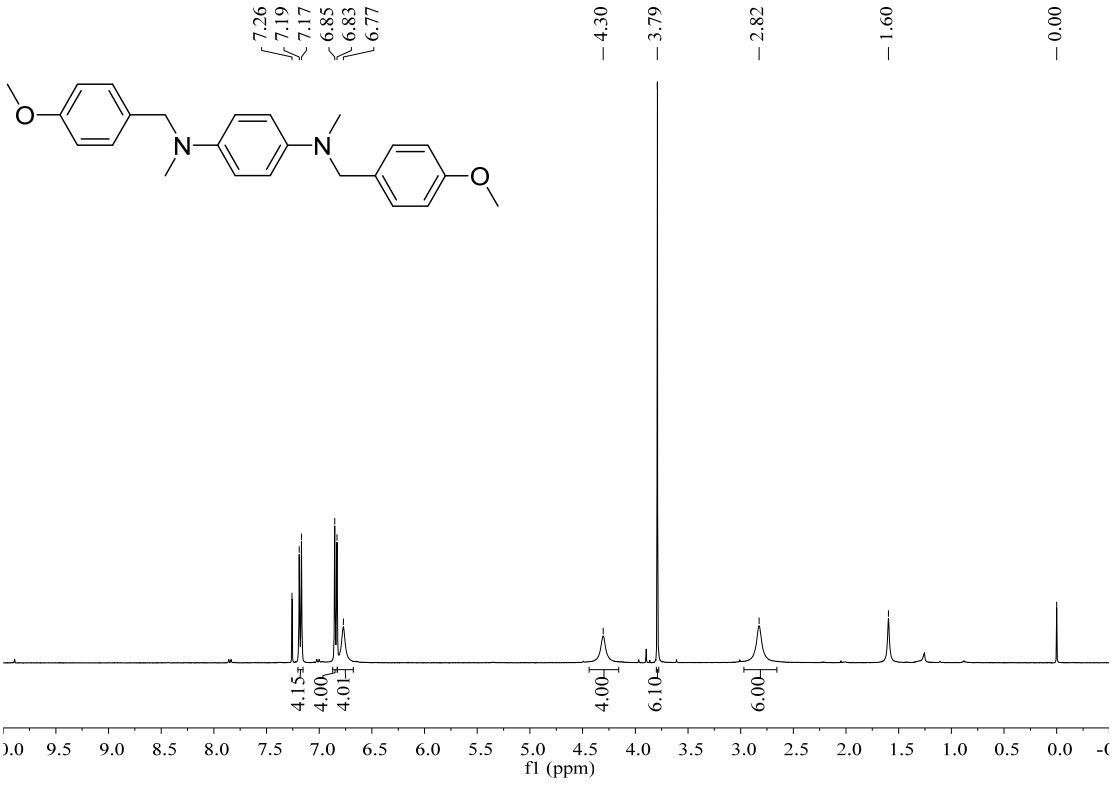
^{1}H NMR spectra of **3l** (400 MHz, $CDCl_3$)



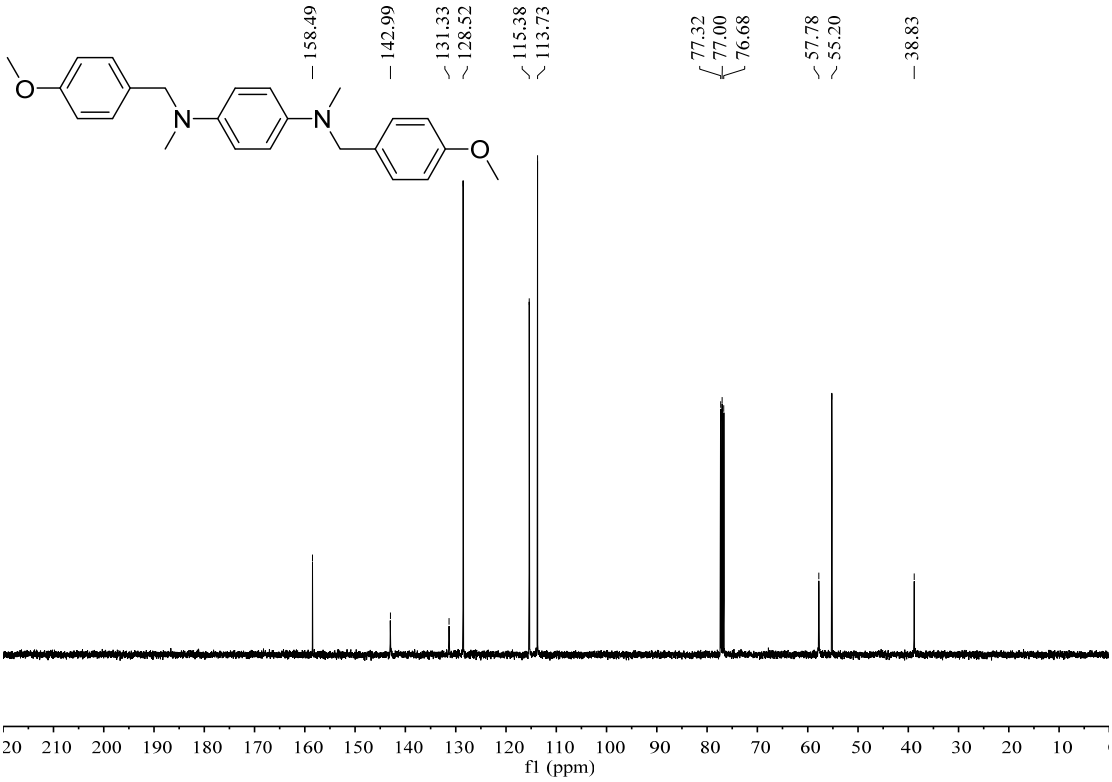
^{13}C NMR spectra of **3l** (100 MHz, $CDCl_3$)



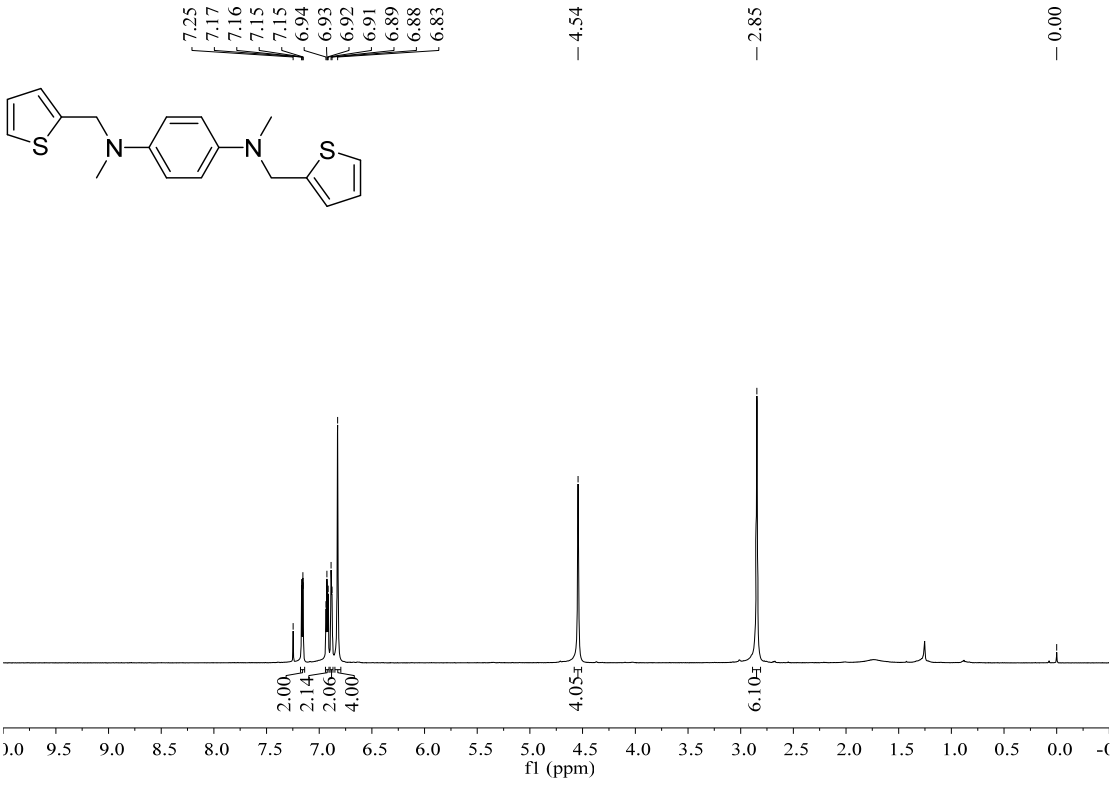
^{1}H NMR spectra of **3m** (400 MHz, $CDCl_3$)



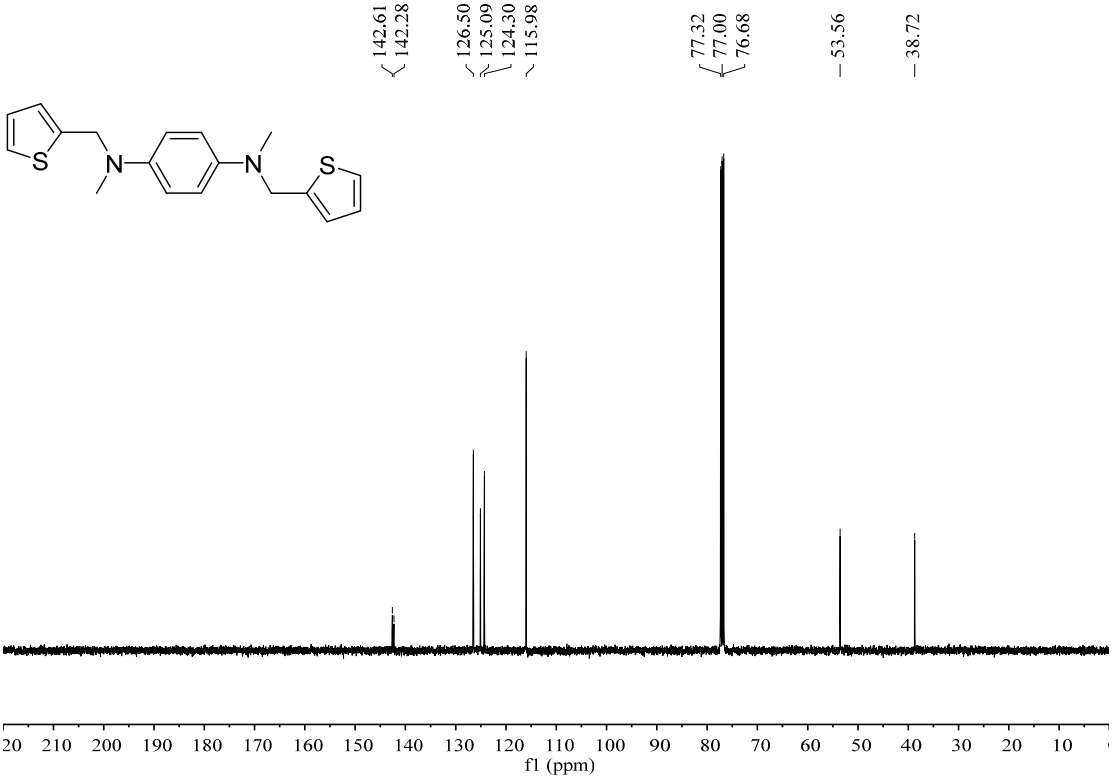
^{13}C NMR spectra of **3m** (100 MHz, $CDCl_3$)



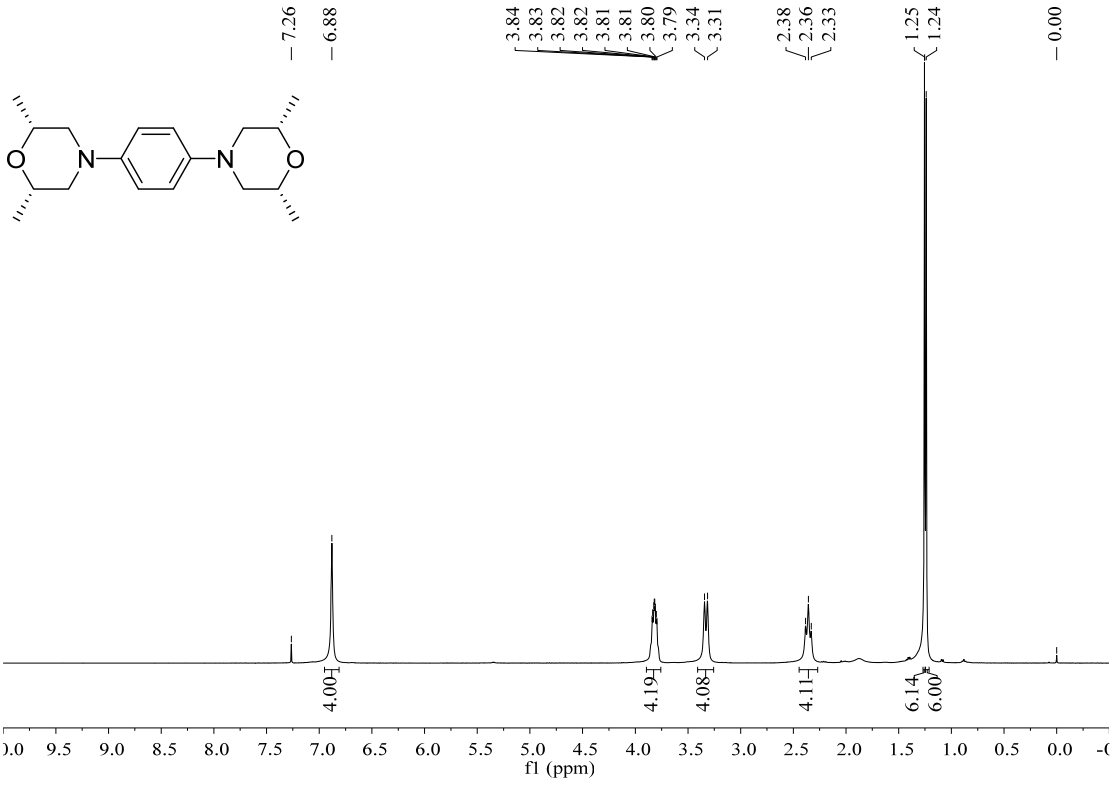
^{1}H NMR spectra of **3n** (400 MHz, $CDCl_3$)



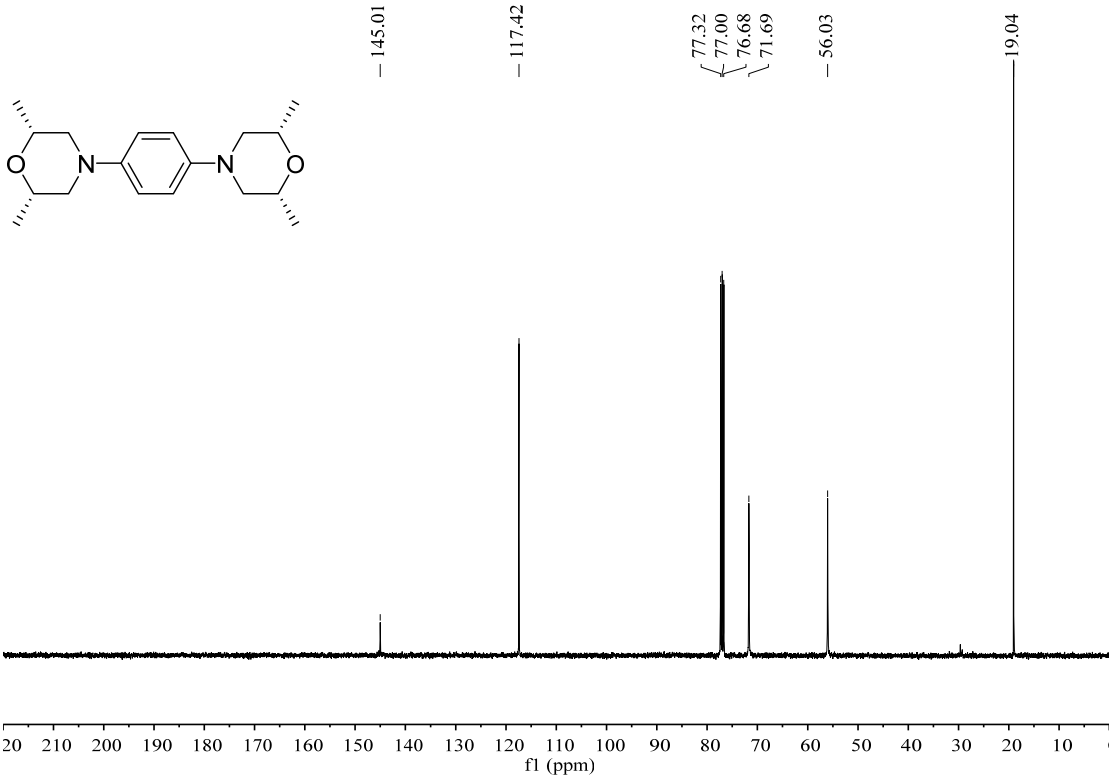
^{13}C NMR spectra of **3n** (100 MHz, $CDCl_3$)



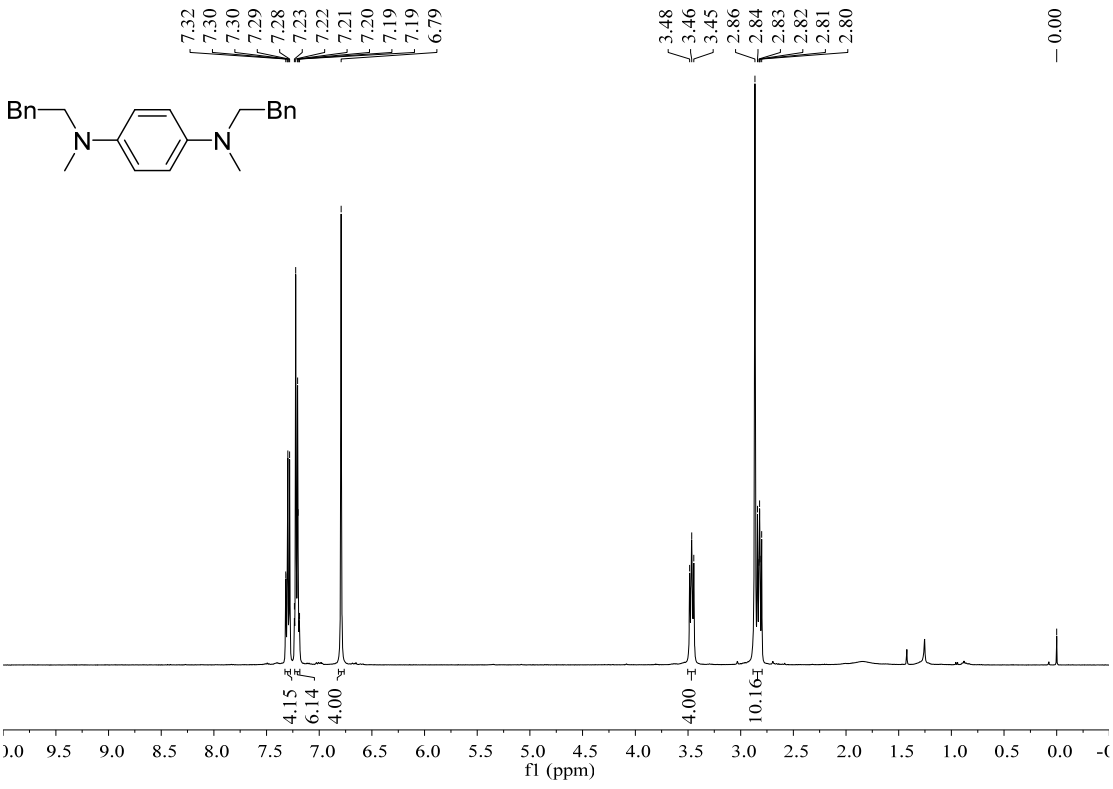
^{1}H NMR spectra of **3o** (400 MHz, $CDCl_3$)



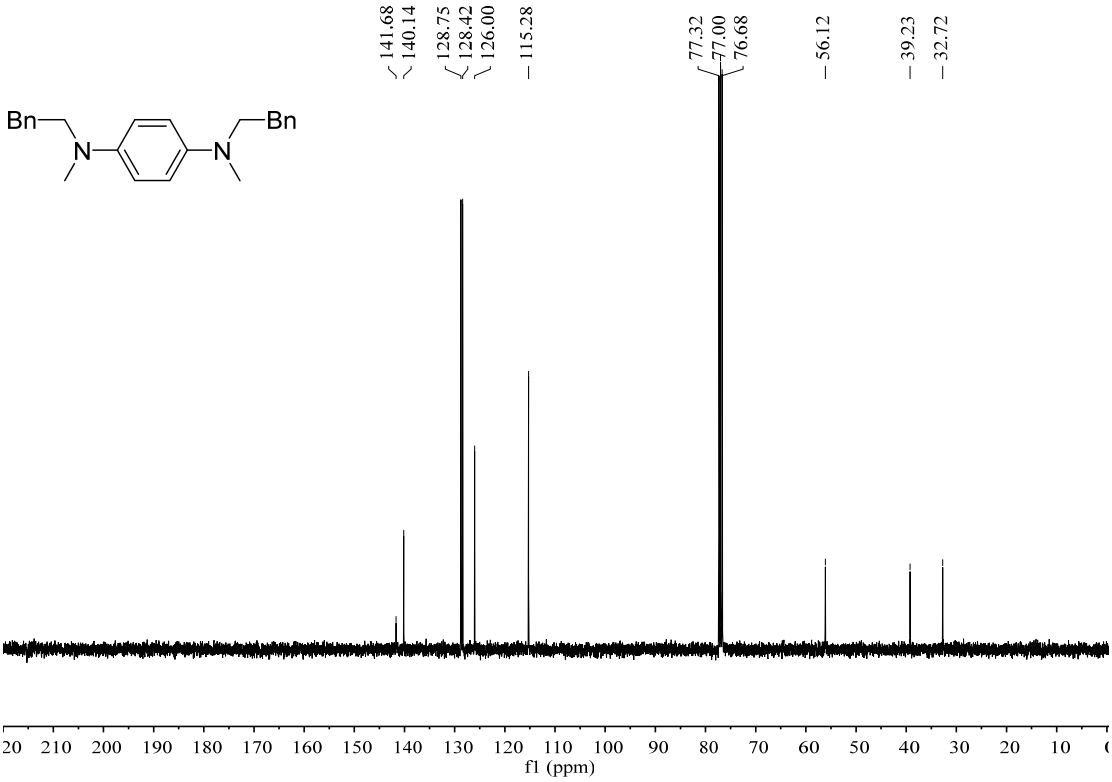
^{13}C NMR spectra of **3n** (100 MHz, $CDCl_3$)



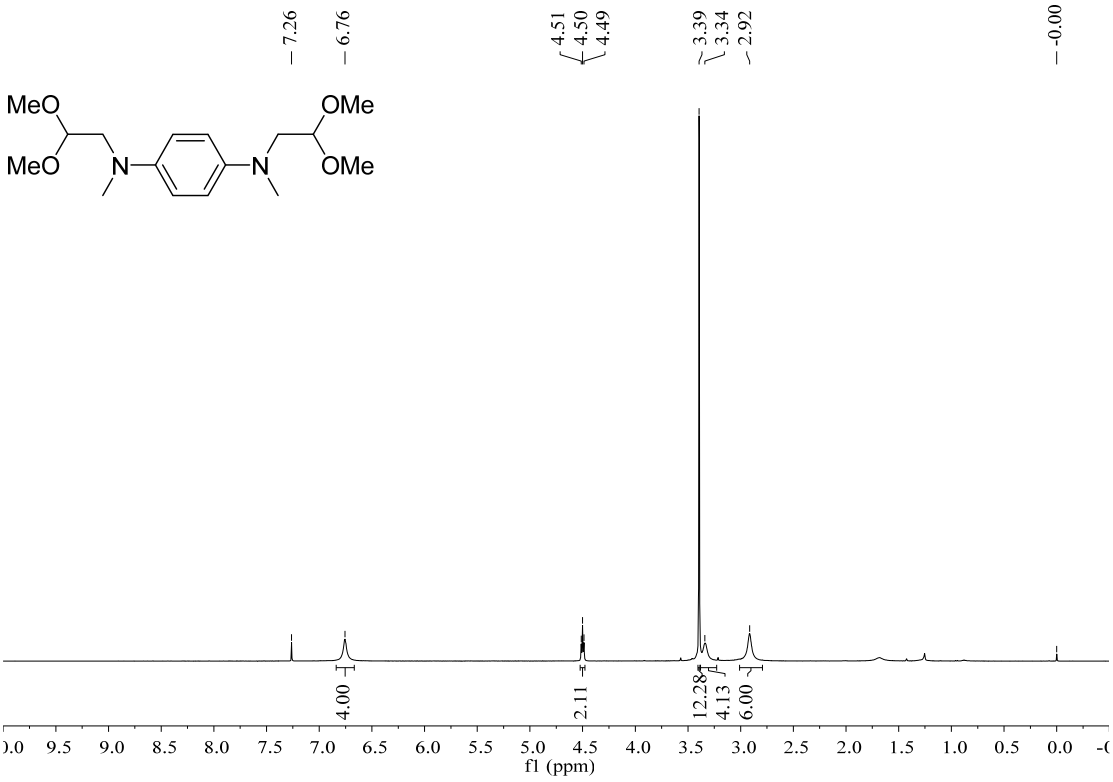
^{1}H NMR spectra of **3p** (400 MHz, $CDCl_3$)



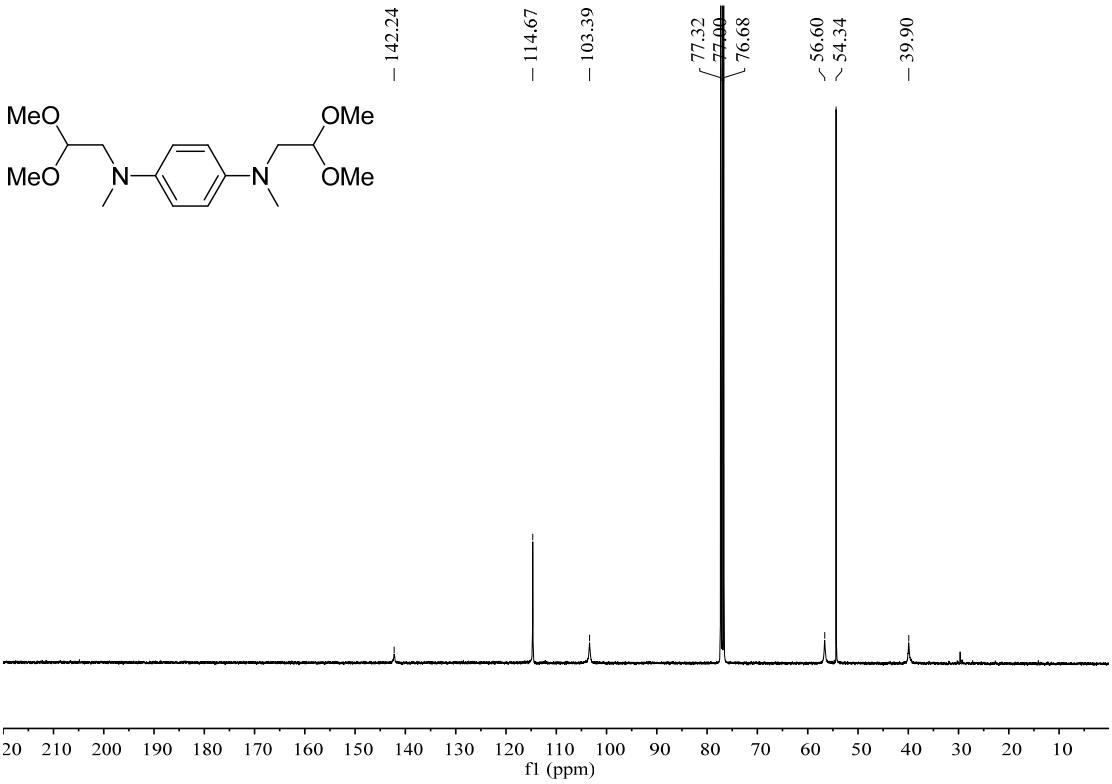
^{13}C NMR spectra of **3p** (100 MHz, $CDCl_3$)



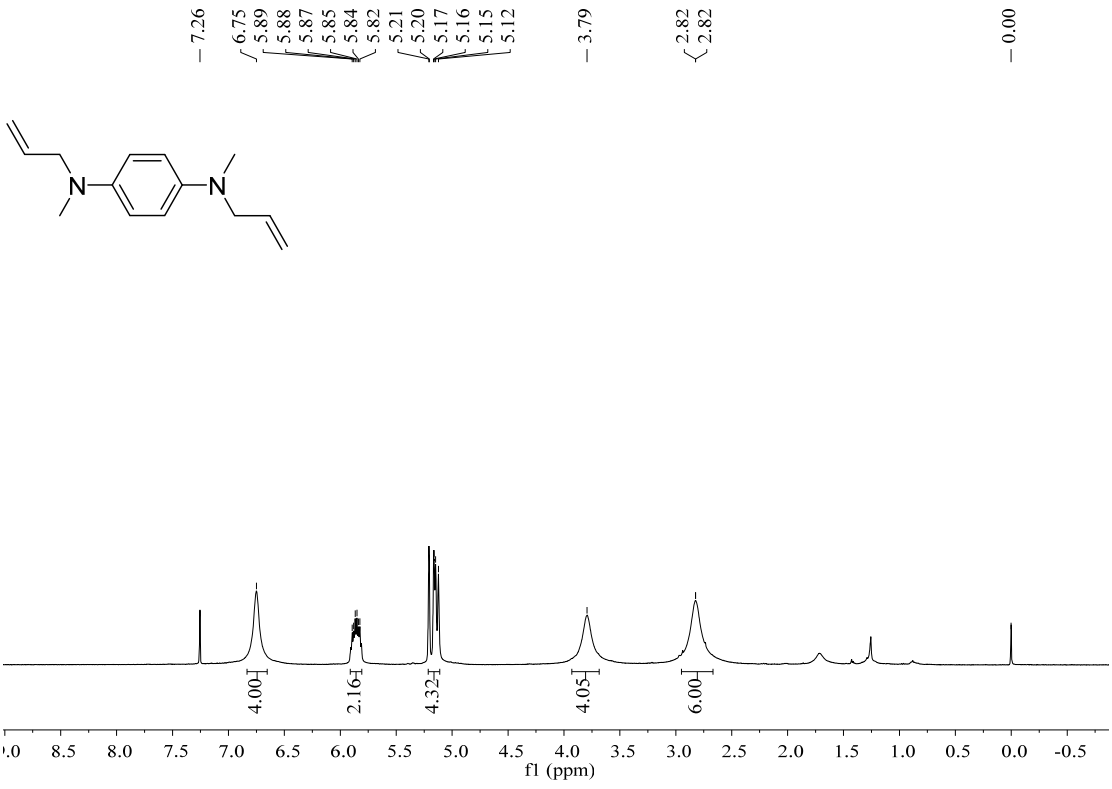
^{1}H NMR spectra of **3q** (400 MHz, $CDCl_3$)



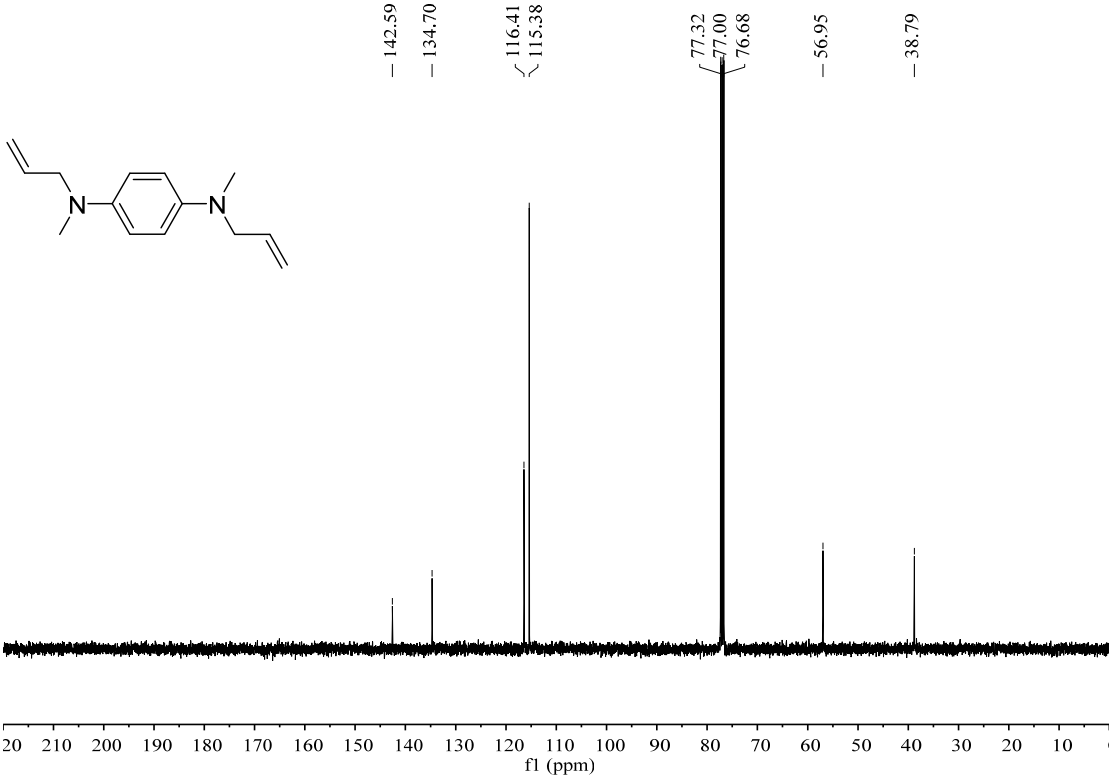
^{13}C NMR spectra of **3q** (100 MHz, $CDCl_3$)



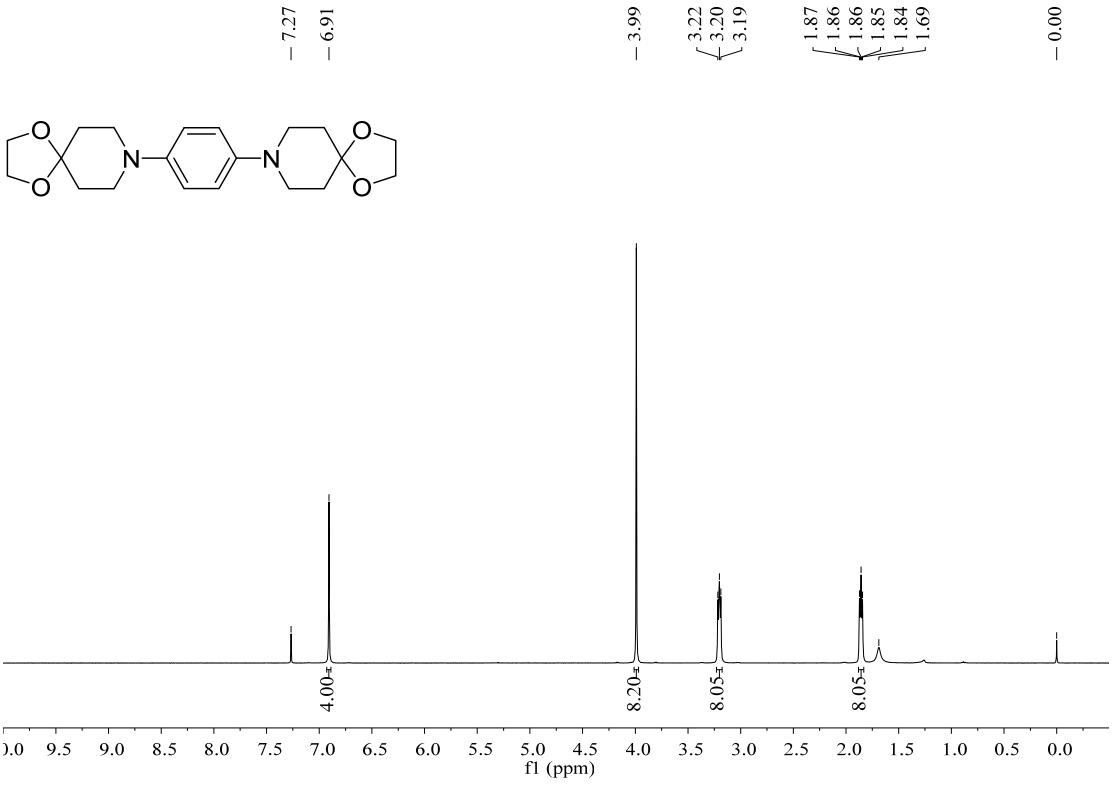
^{1}H NMR spectra of **3r** (400 MHz, $CDCl_3$)



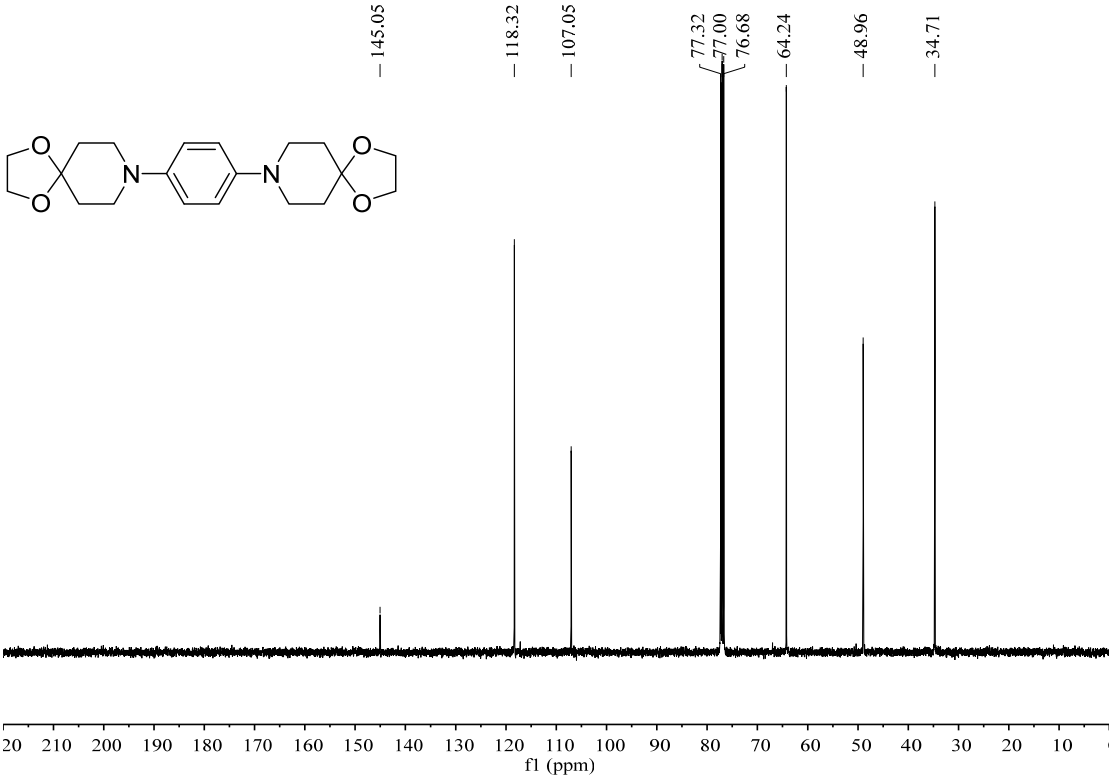
^{13}C NMR spectra of **3r** (100 MHz, $CDCl_3$)



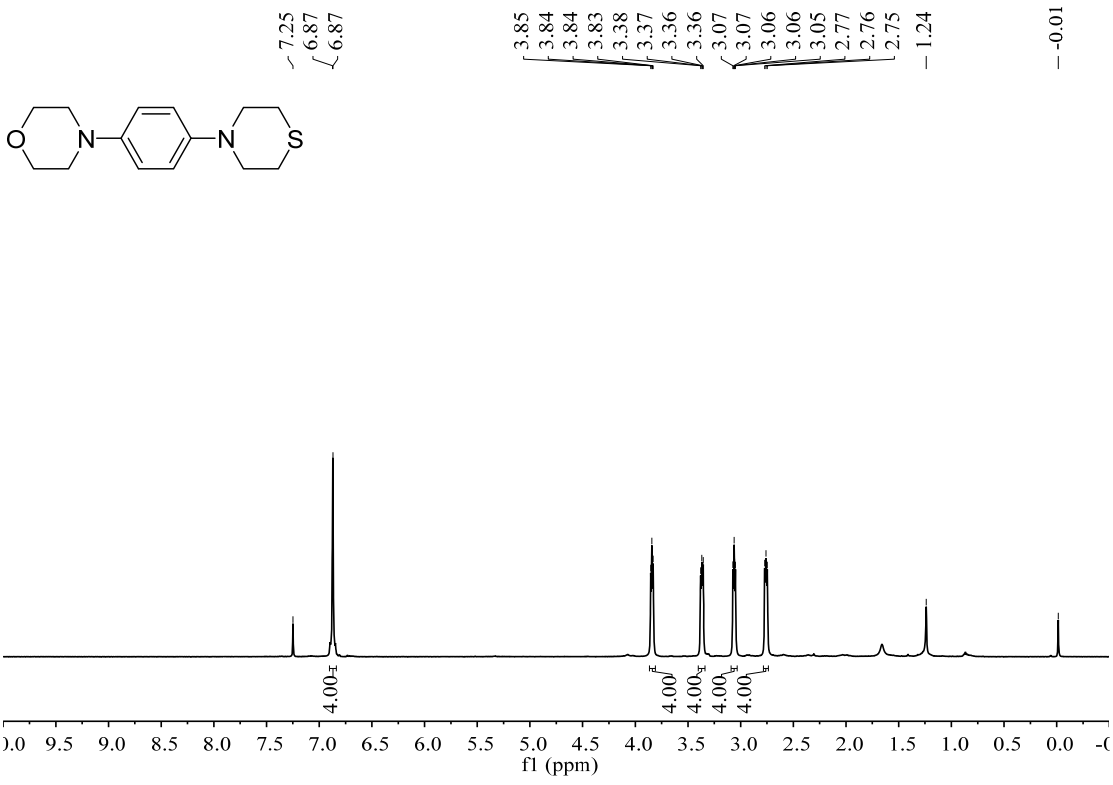
^{1}H NMR spectra of **3s** (400 MHz, $CDCl_3$)



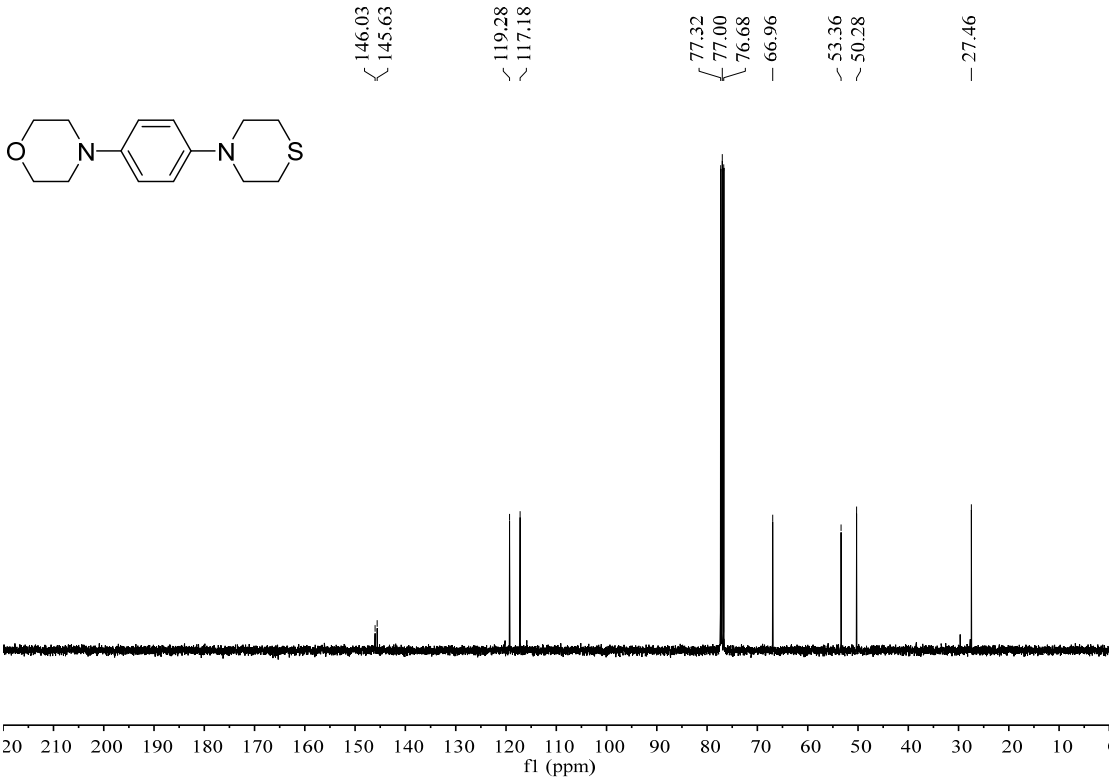
^{13}C NMR spectra of **3s** (100 MHz, $CDCl_3$)



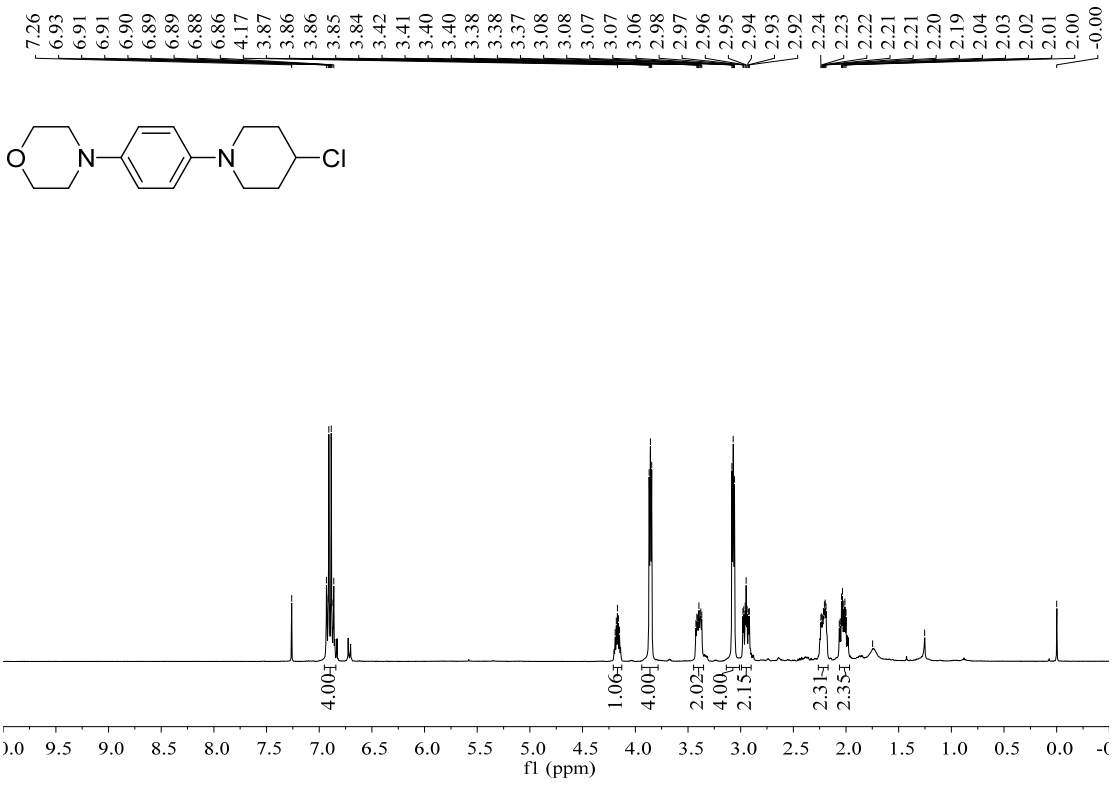
^{1}H NMR spectra of **4a** (400 MHz, $CDCl_3$)



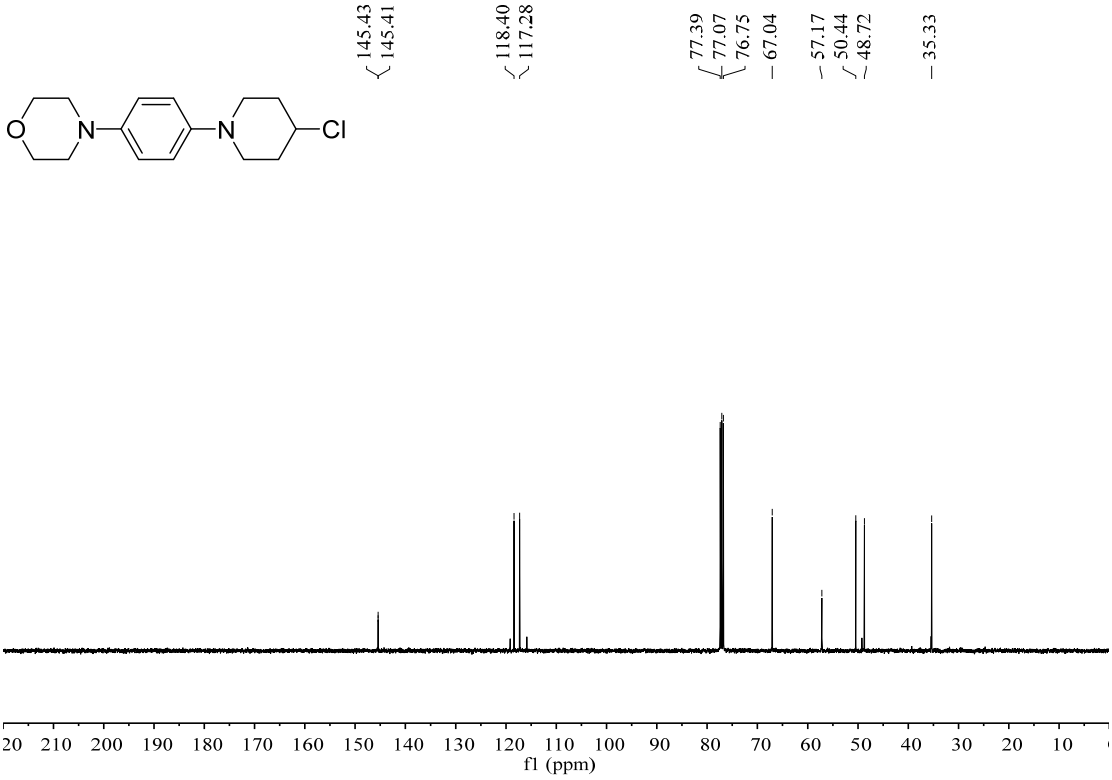
^{13}C NMR spectra of **4a** (100 MHz, $CDCl_3$)



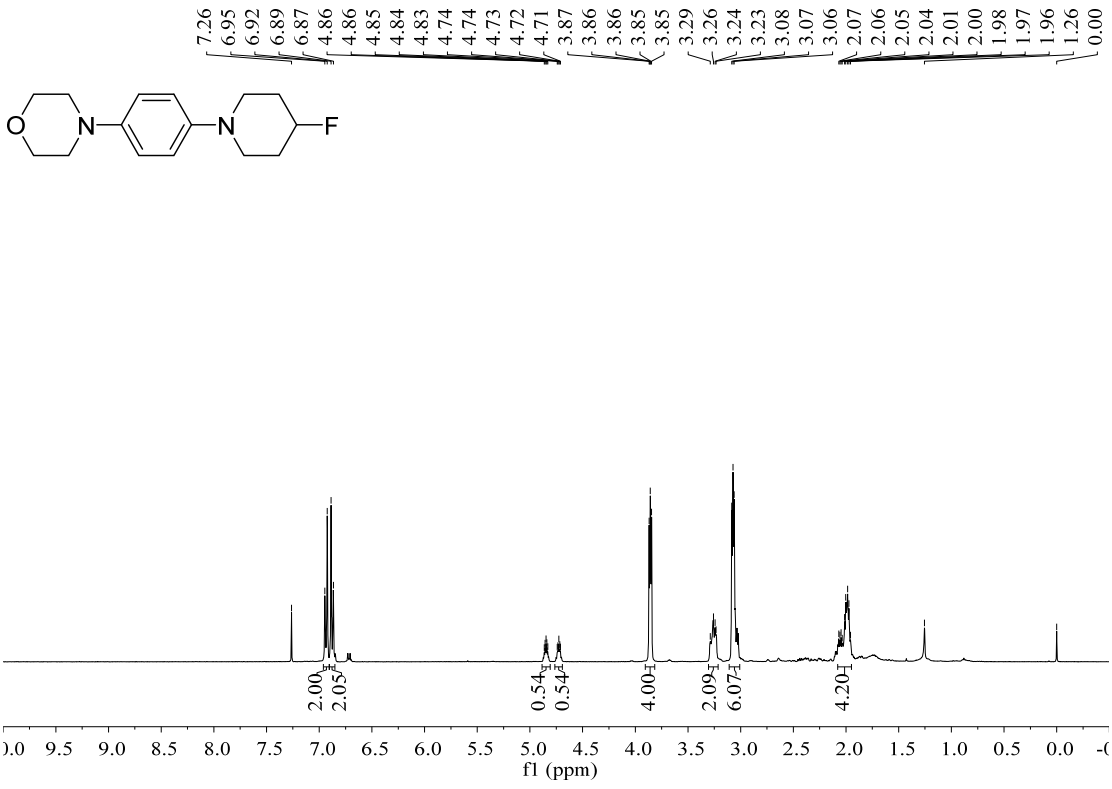
^{1}H NMR spectra of **4b** (400 MHz, $CDCl_3$)



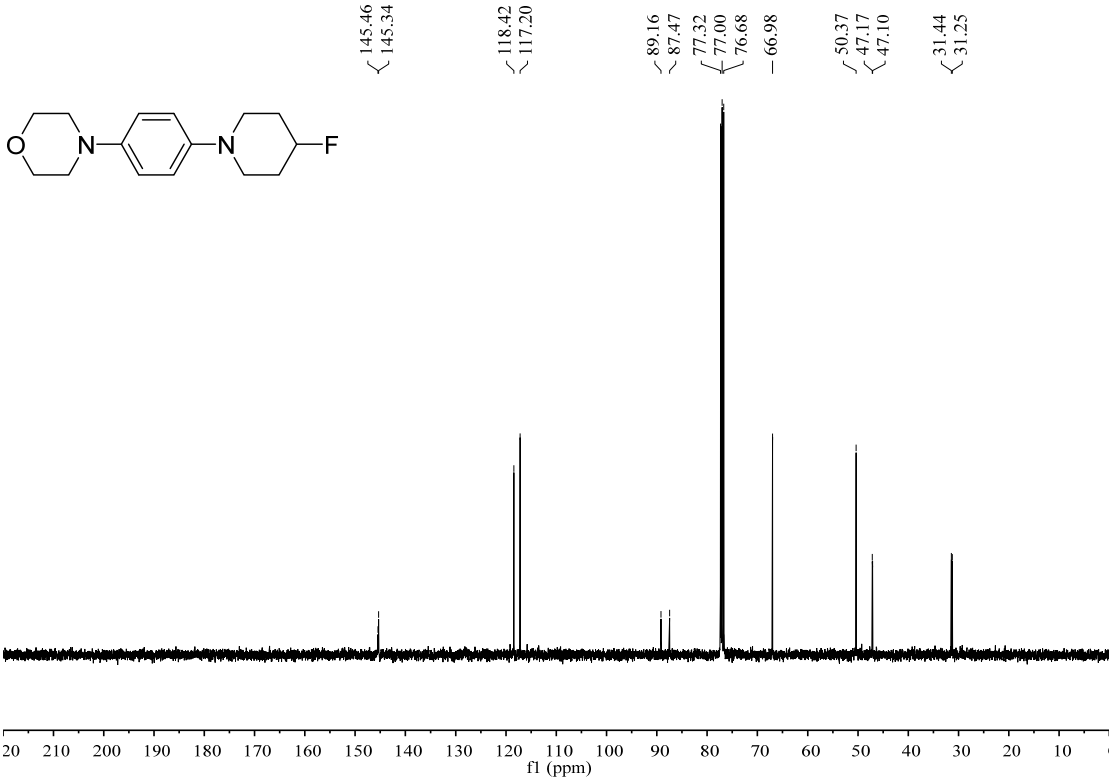
^{13}C NMR spectra of **4c** (100 MHz, $CDCl_3$)



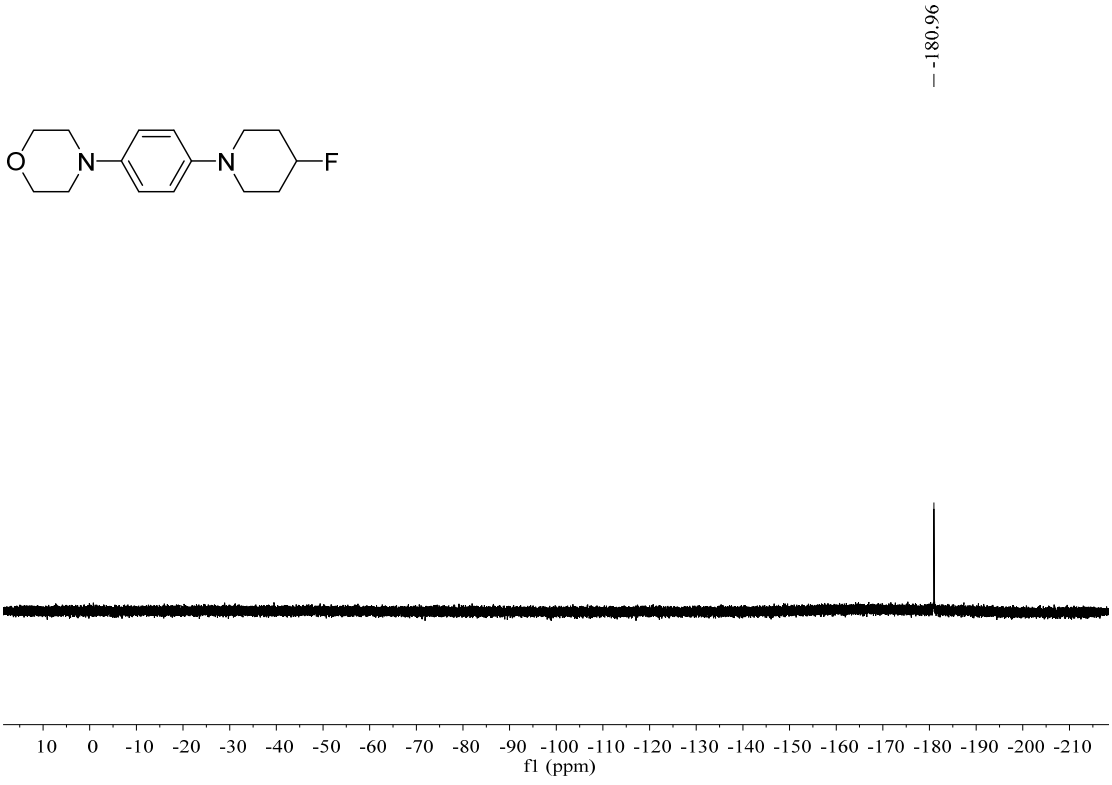
^{1}H NMR spectra of **4c** (400 MHz, $CDCl_3$)



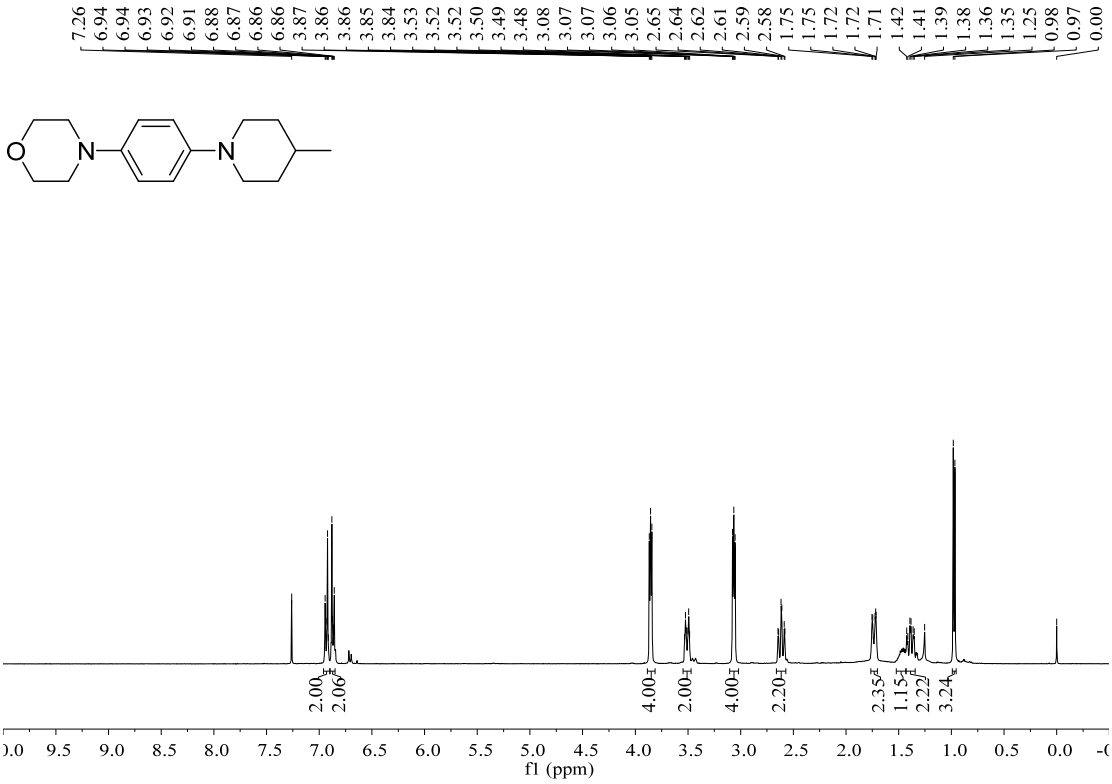
^{13}C NMR spectra of **4c** (100 MHz, $CDCl_3$)



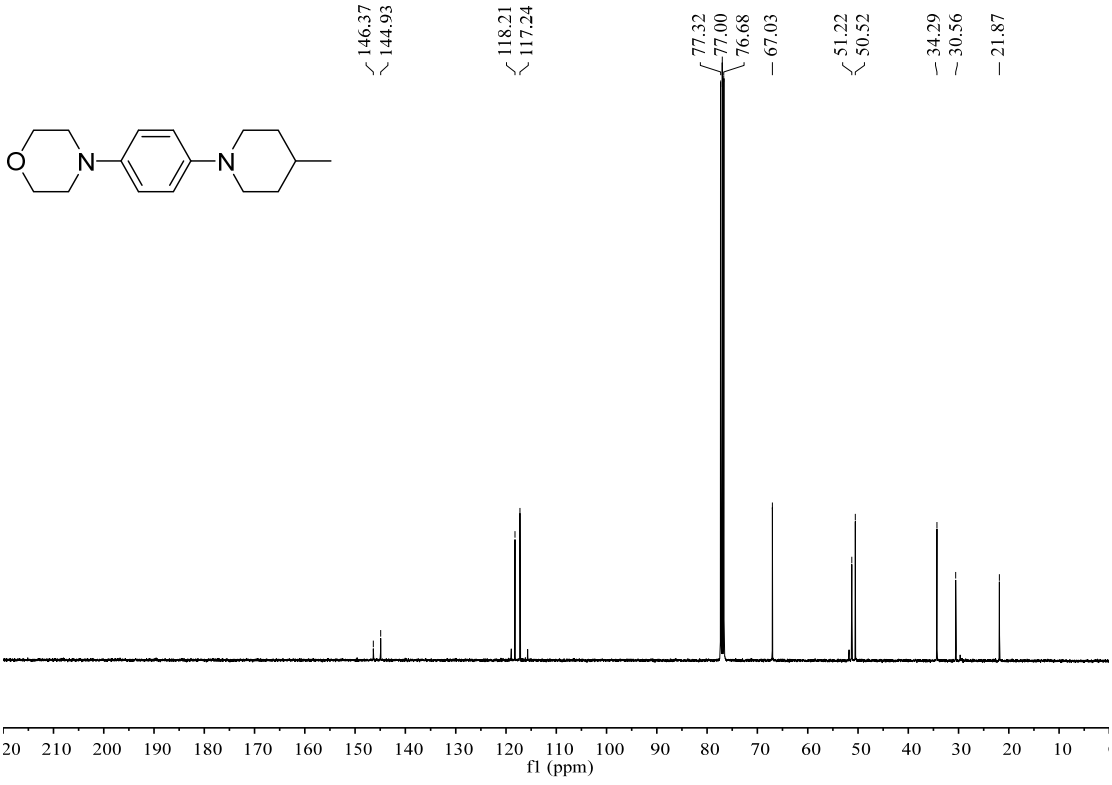
^{19}F NMR spectra of **4c** (376 MHz, $CDCl_3$)



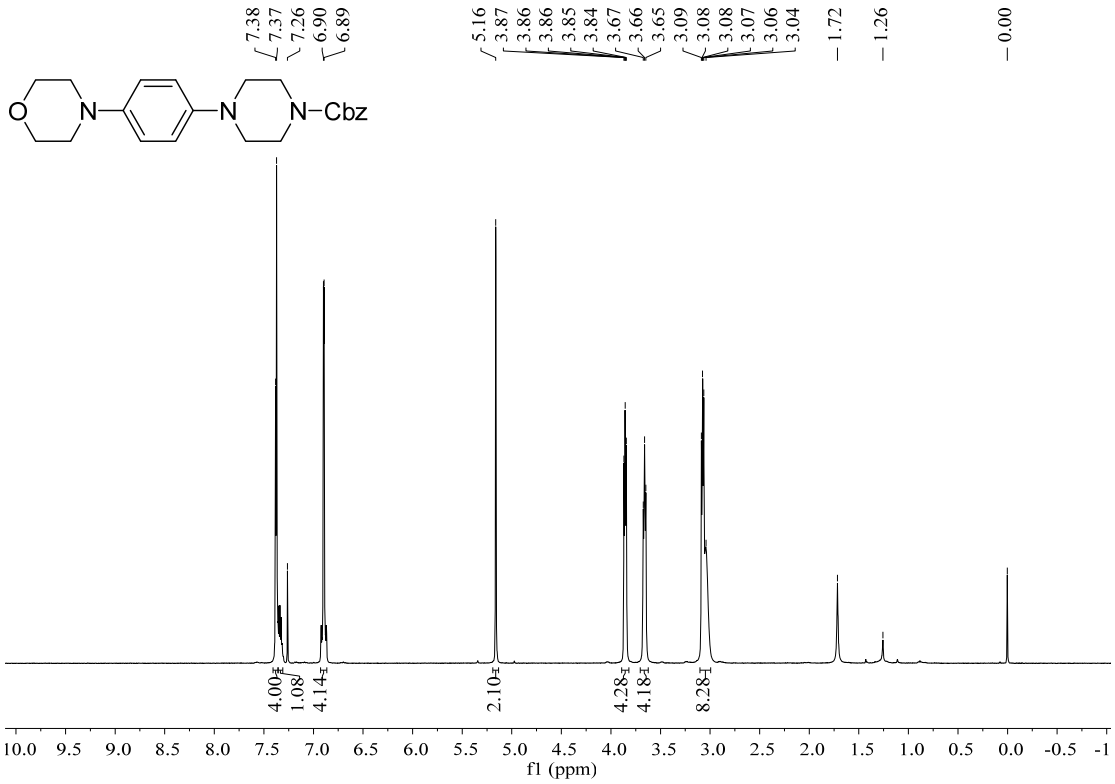
^{1}H NMR spectra of **4d** (400 MHz, $CDCl_3$)



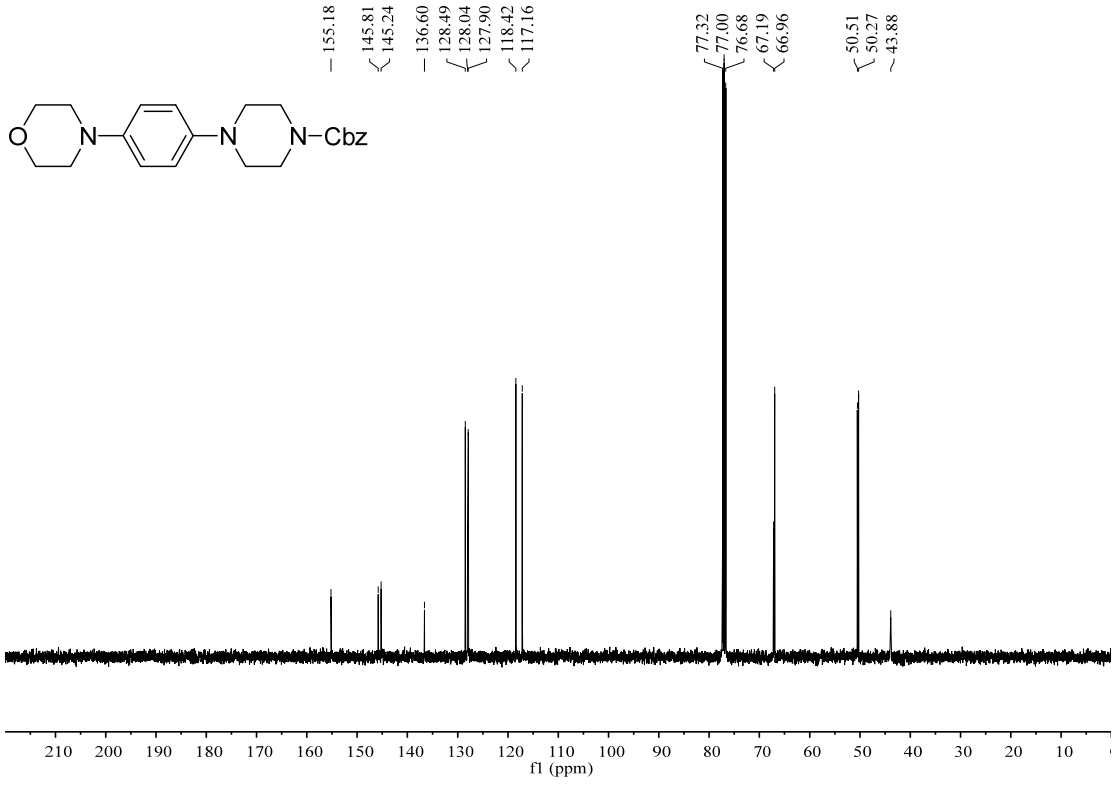
^{13}C NMR spectra of **4d** (100 MHz, $CDCl_3$)



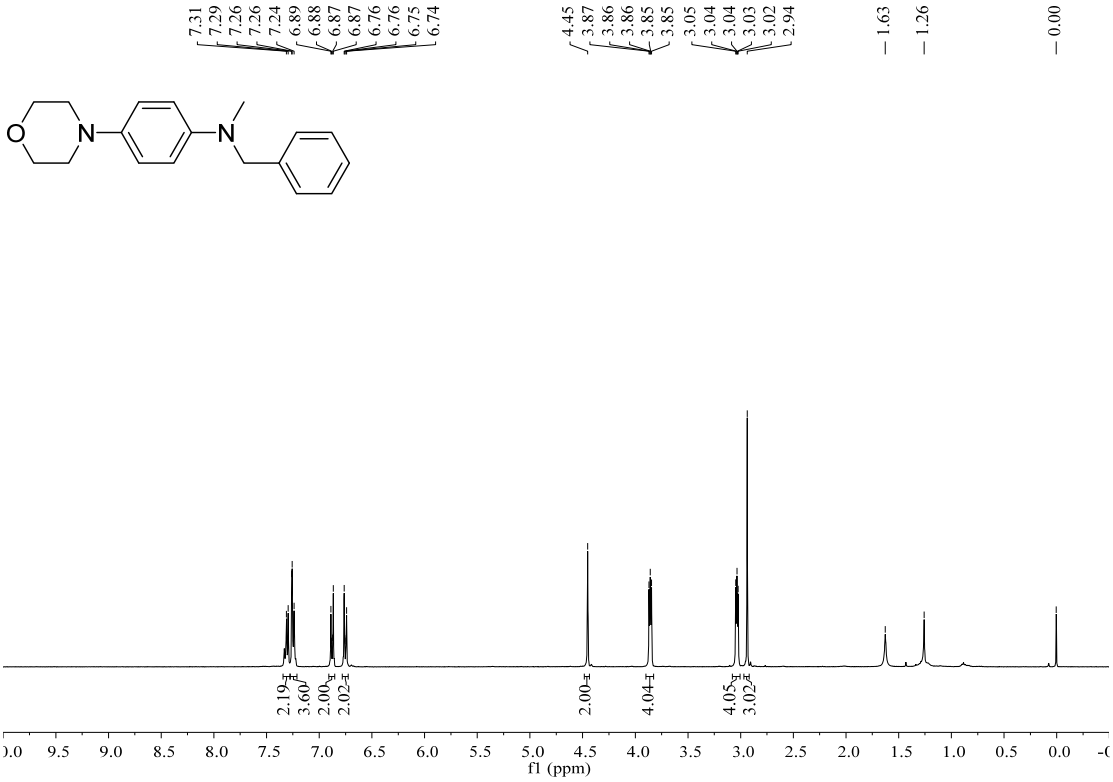
^{1}H NMR spectra of **4e** (400 MHz, $CDCl_3$)



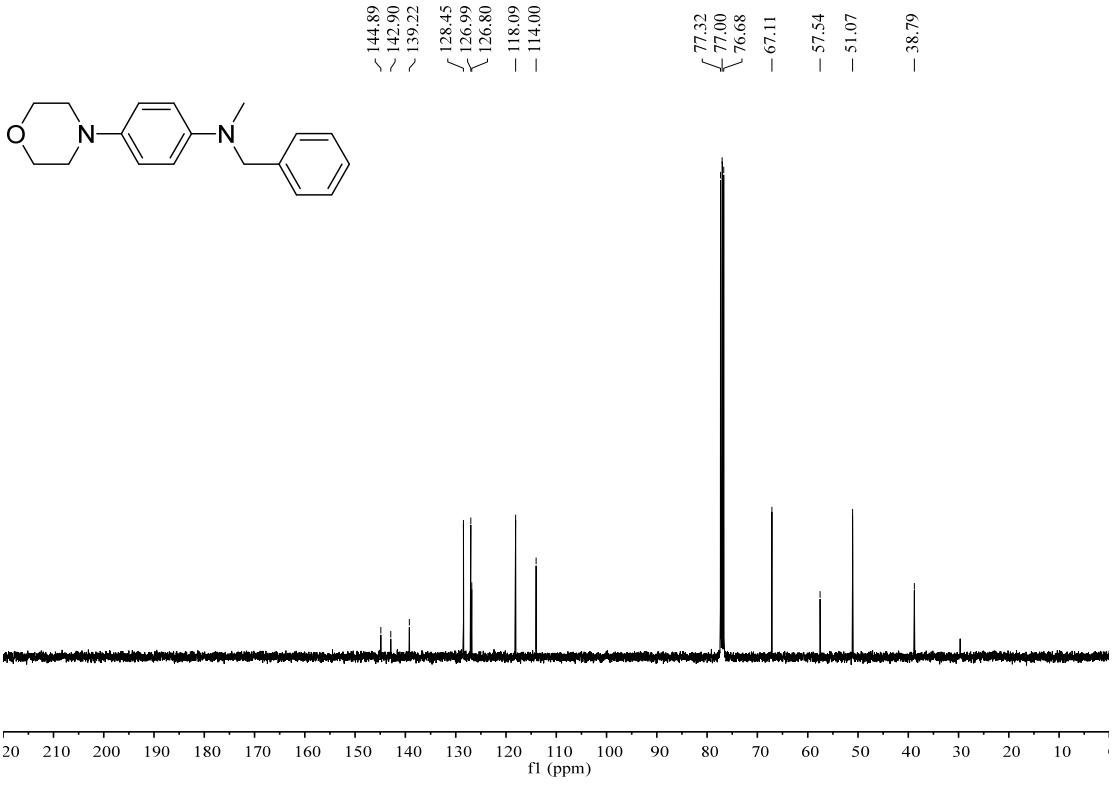
^{13}C NMR spectra of **4e** (100 MHz, $CDCl_3$)



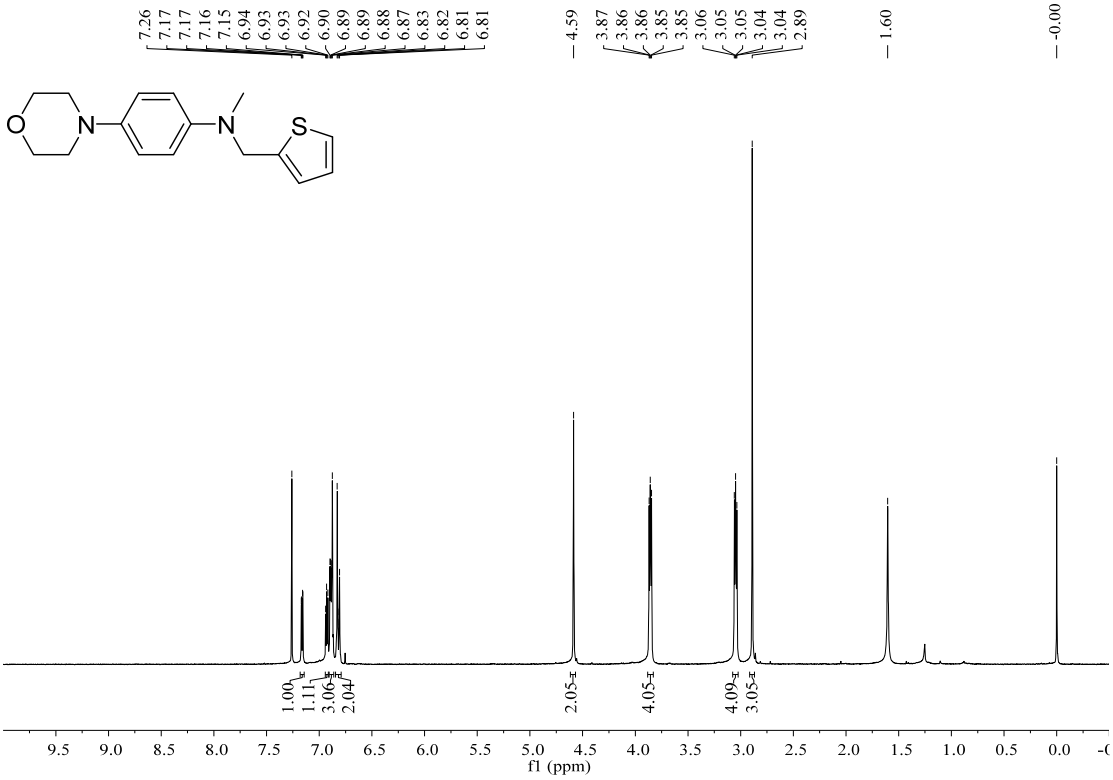
^{1}H NMR spectra of **4f** (400 MHz, $CDCl_3$)



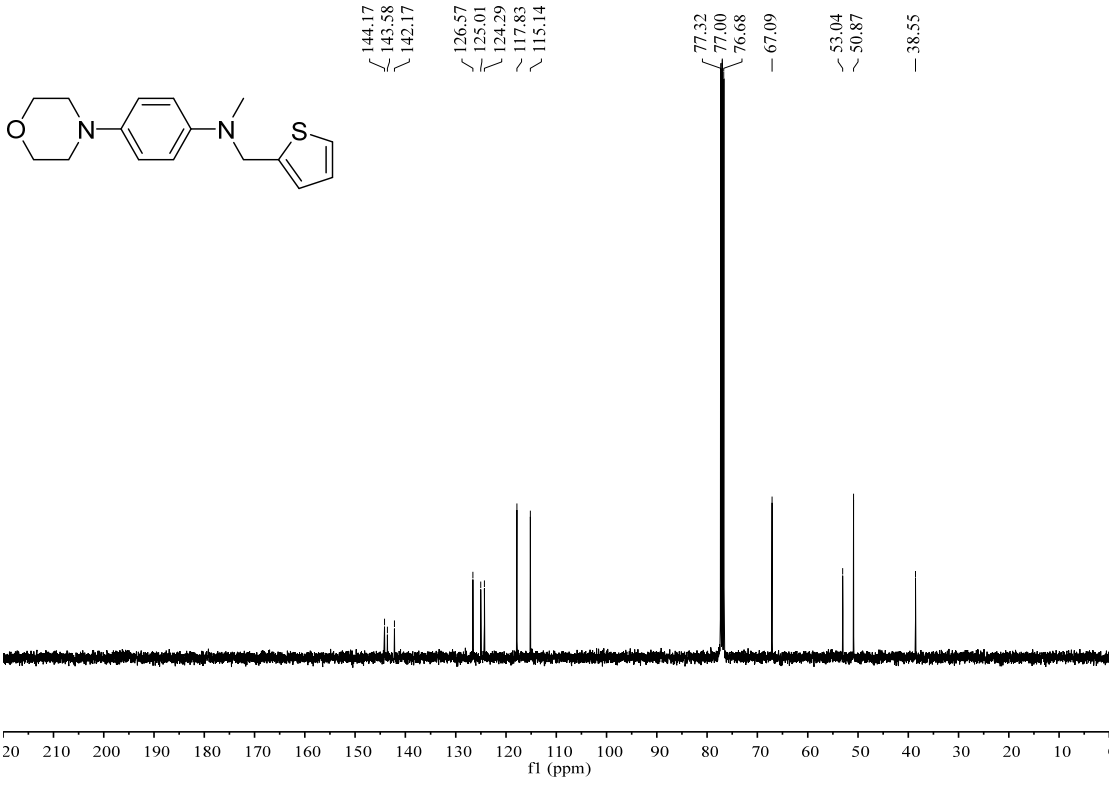
^{13}C NMR spectra of **4f** (100 MHz, $CDCl_3$)



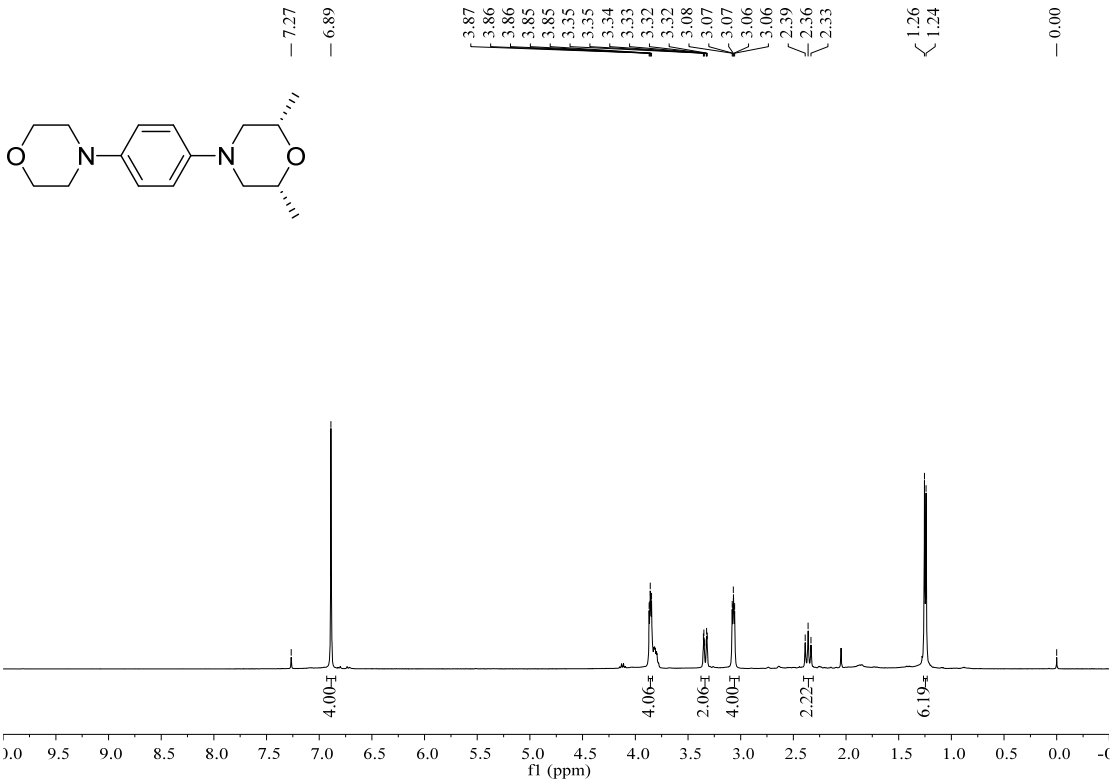
^{1}H NMR spectra of **4g** (400 MHz, $CDCl_3$)



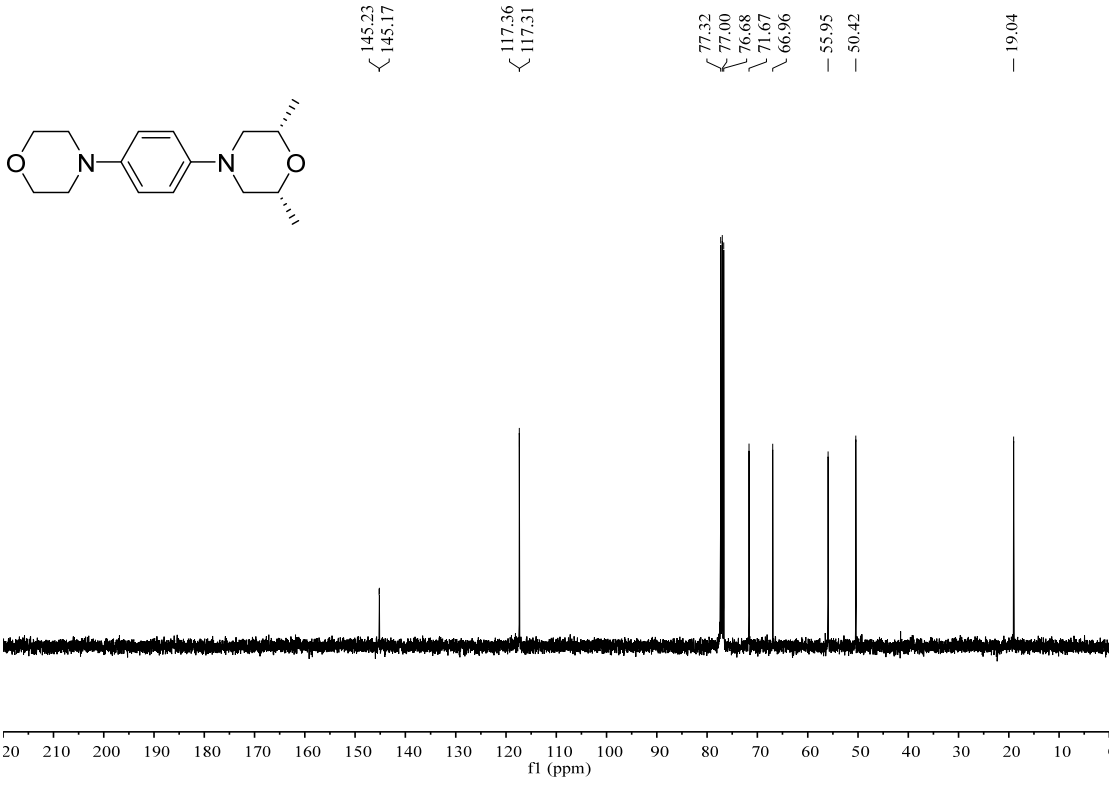
^{13}C NMR spectra of **4g** (100 MHz, $CDCl_3$)



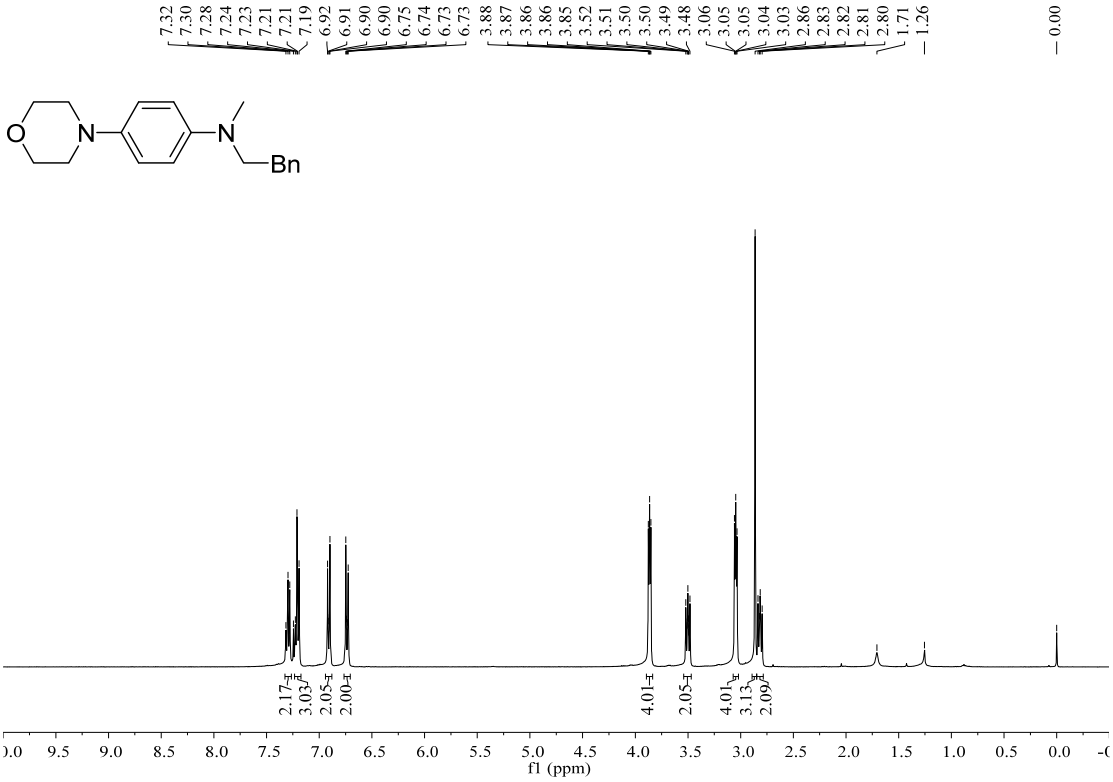
^{1}H NMR spectra of **4h** (400 MHz, $CDCl_3$)



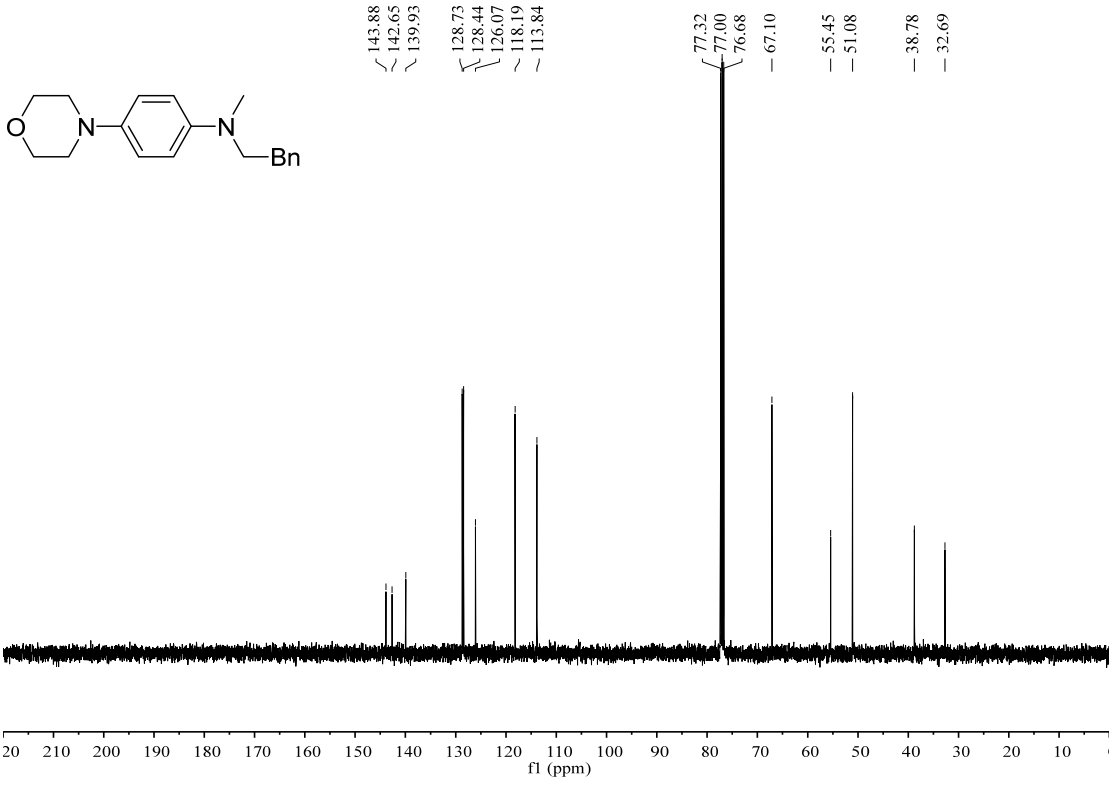
^{13}C NMR spectra of **4h** (100 MHz, $CDCl_3$)



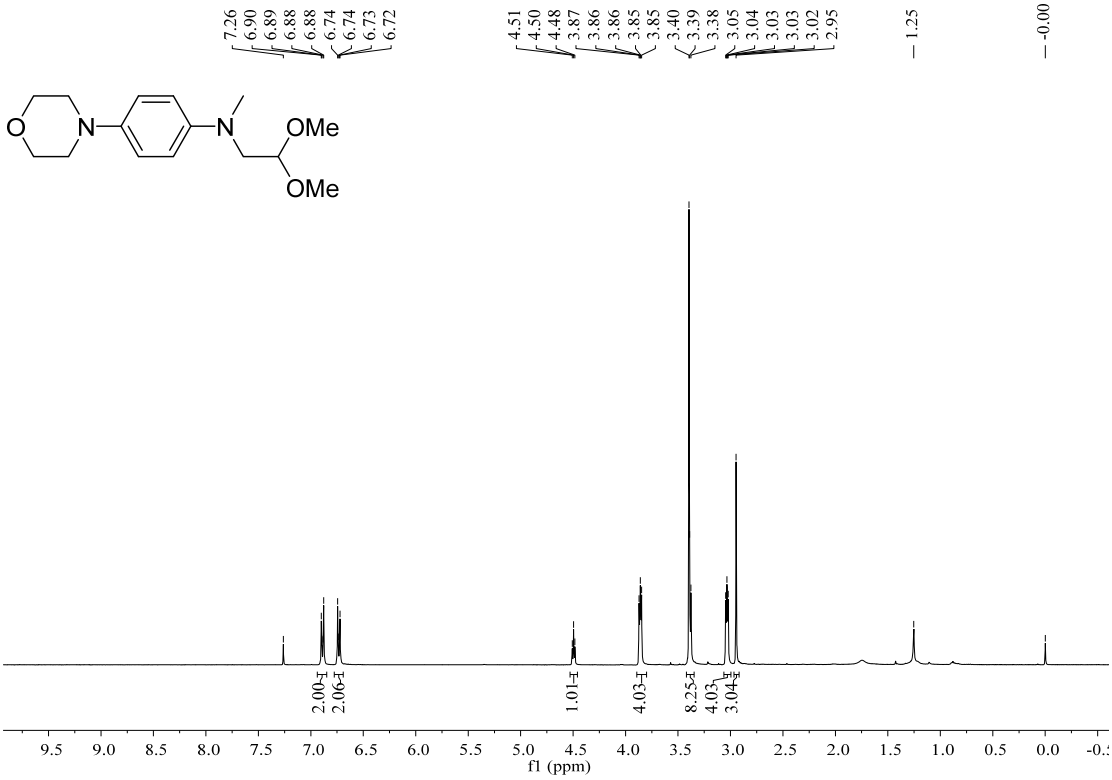
^{1}H NMR spectra of **4i** (400 MHz, $CDCl_3$)



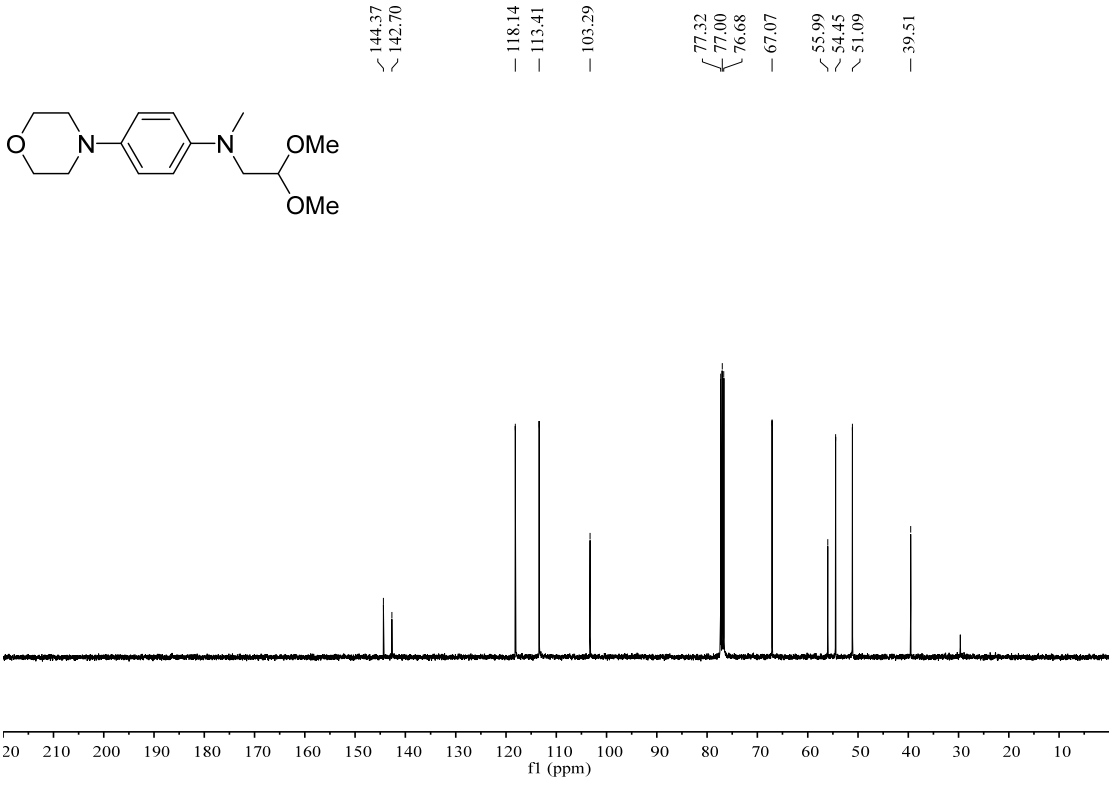
^{13}C NMR spectra of **4i** (100 MHz, $CDCl_3$)



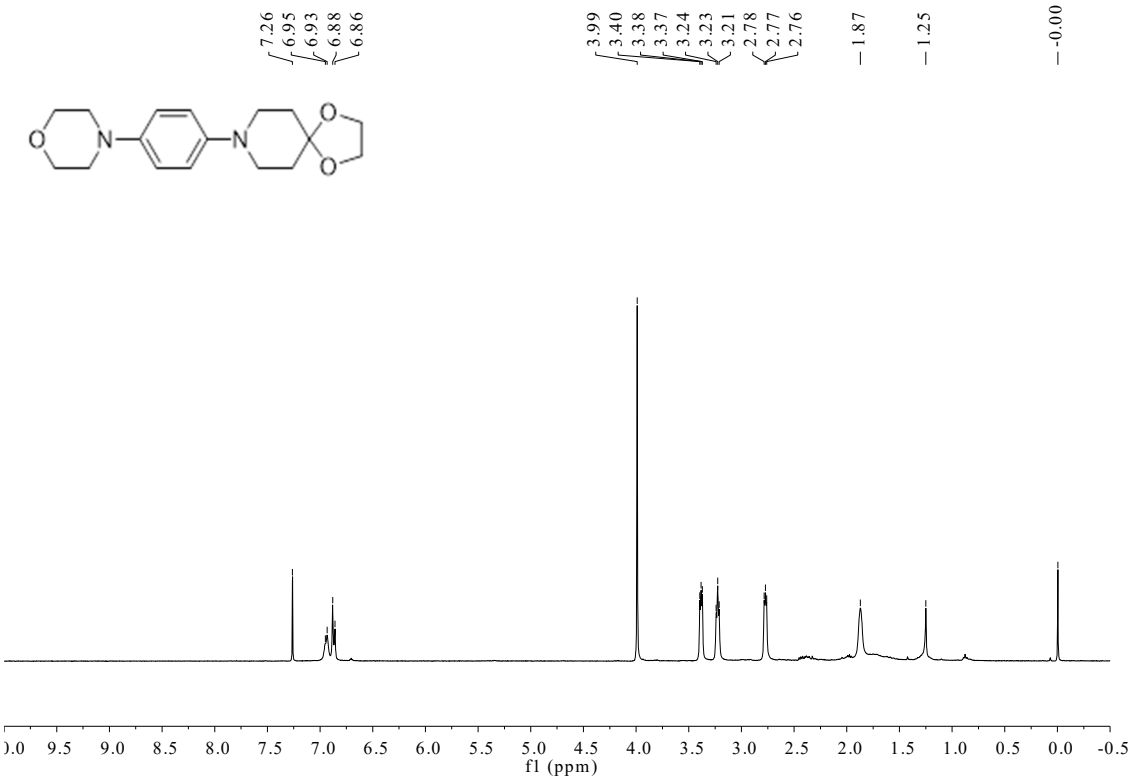
^{1}H NMR spectra of **4j** (400 MHz, $CDCl_3$)



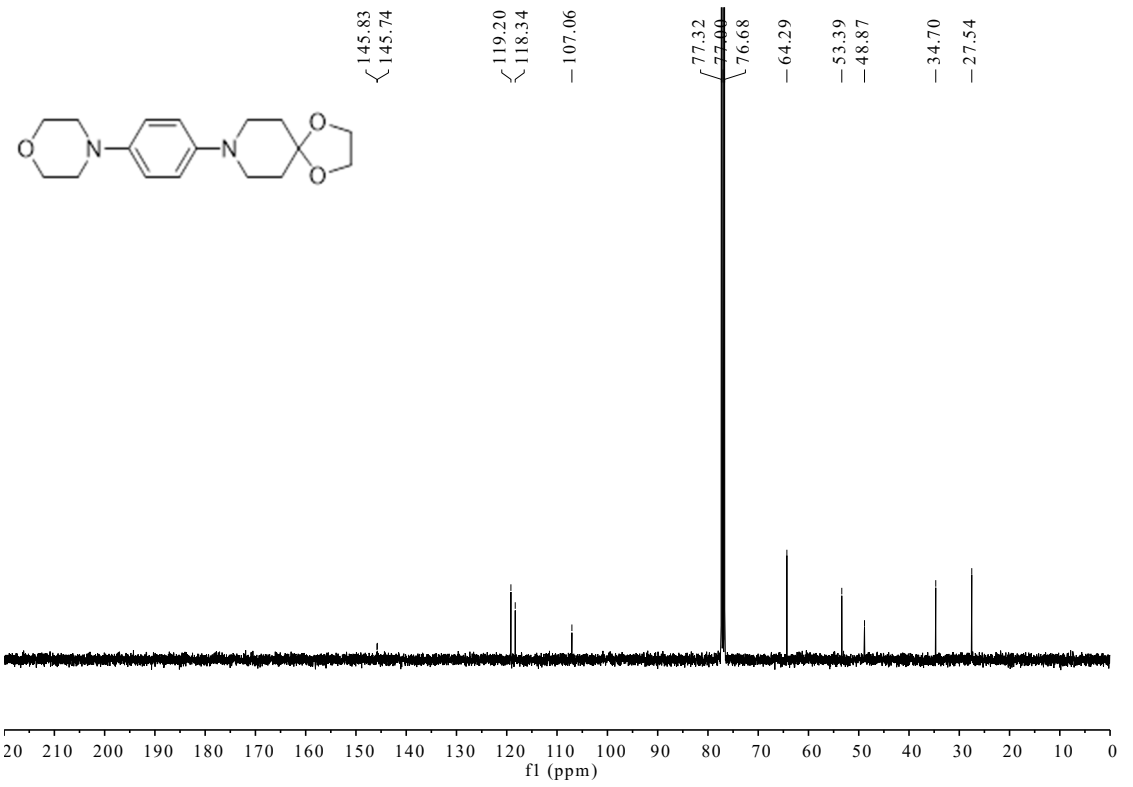
^{13}C NMR spectra of **4j** (100 MHz, $CDCl_3$)



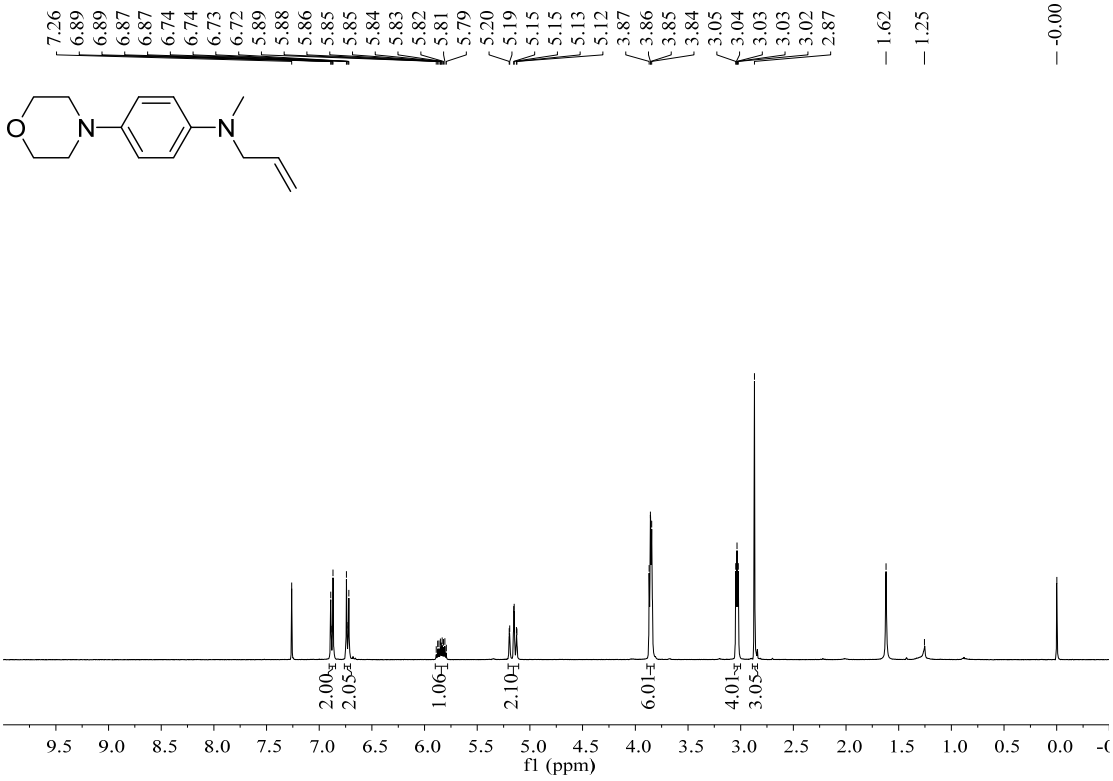
^{1}H NMR spectra of **4k** (400 MHz, $CDCl_3$)



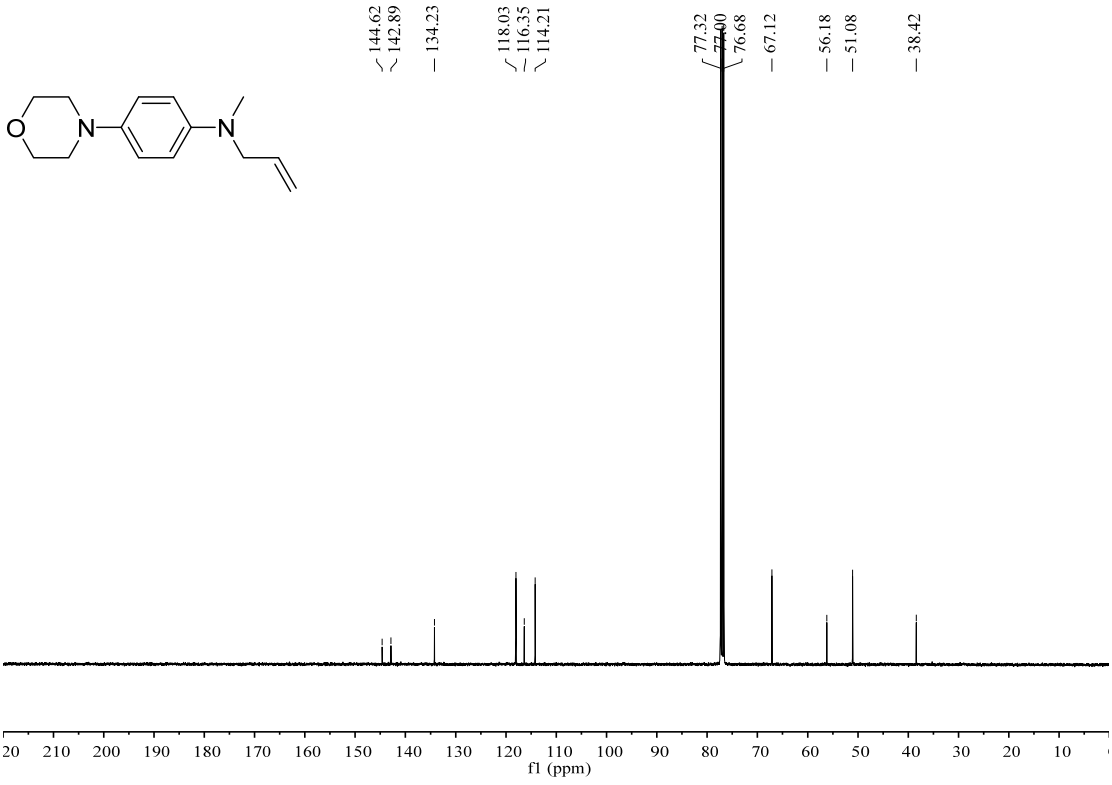
^{13}C NMR spectra of **4k** (100 MHz, $CDCl_3$)



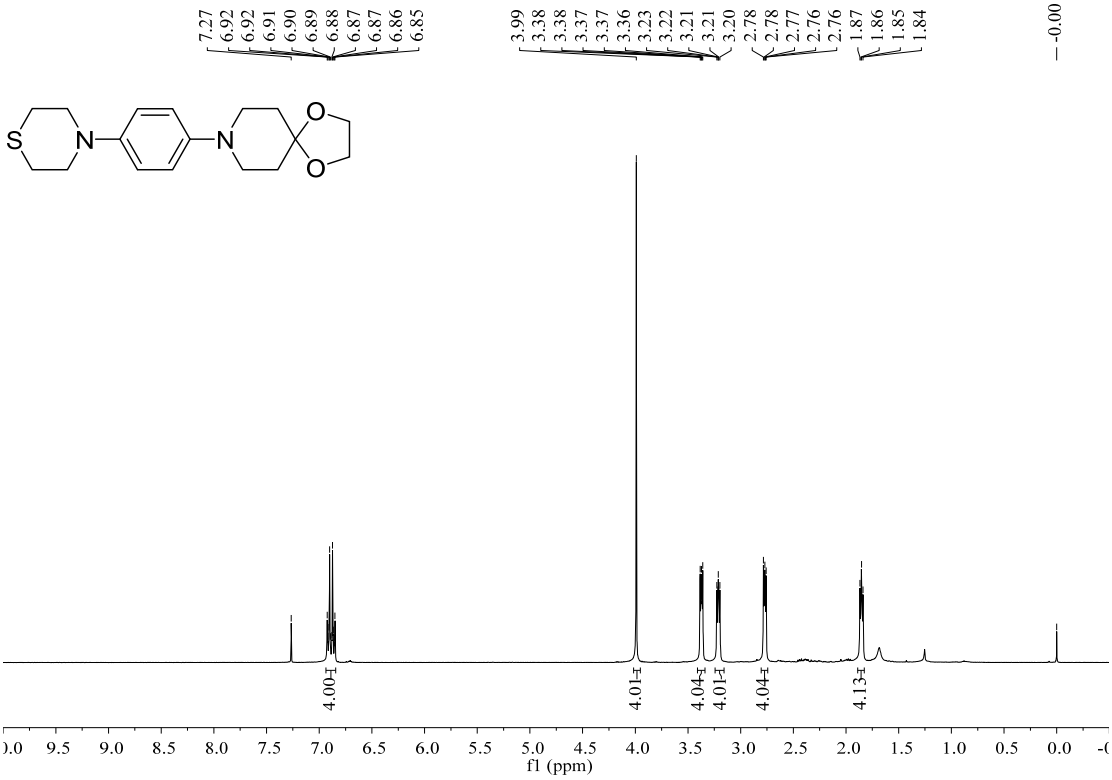
^{1}H NMR spectra of **4l** (400 MHz, $CDCl_3$)



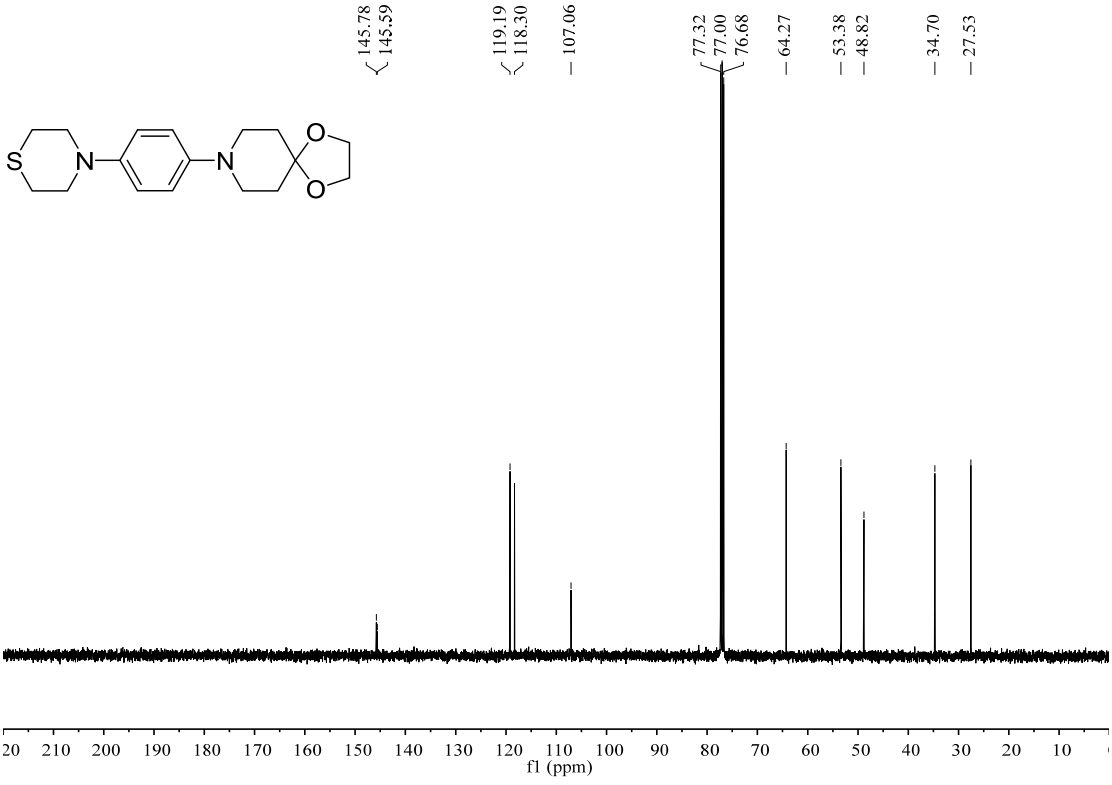
^{13}C NMR spectra of **4l** (100 MHz, $CDCl_3$)



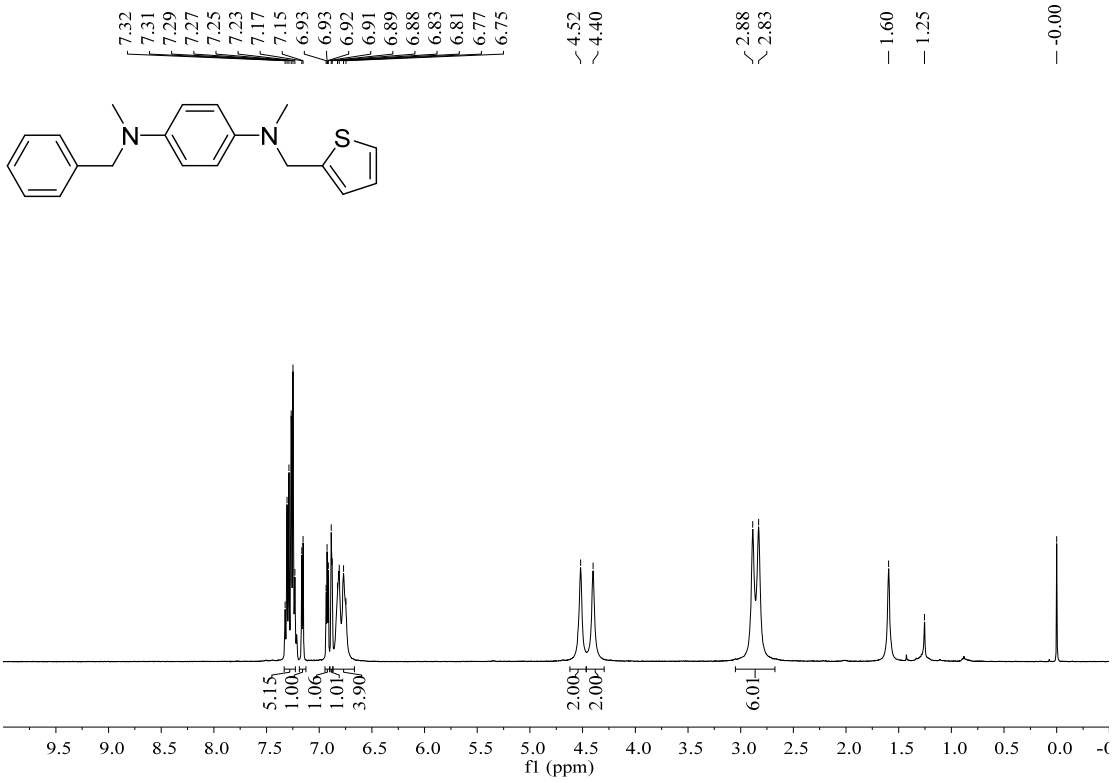
^{1}H NMR spectra of **4m** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of **4m** (100 MHz, $CDCl_3$)



^{1}H NMR spectra of **4n** (400 MHz, $CDCl_3$)



^{13}C NMR spectra of **4n** (100 MHz, $CDCl_3$)