Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

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Double Heteroatom Functionalization of Arenes Using Benzyne Three-Component Coupling**

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Supporting Information

General Remarks

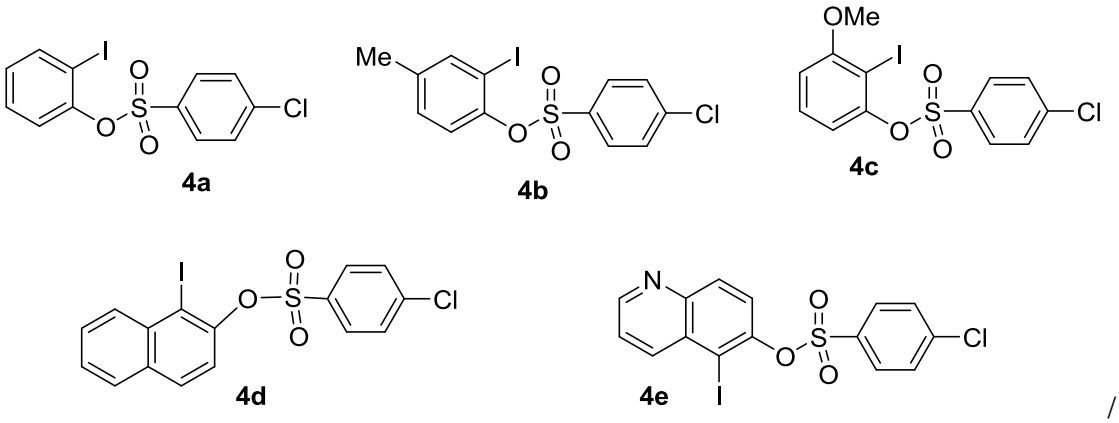
Nuclear Magnetic Resonance (NMR) spectra were recorded on a 500 or 400 MHz Bruker NMR spectrometers in $CDCl_3$ at 298 K (unless stated otherwise). All chemical shift values are reported in parts per million (ppm) with coupling constant (*J*) values reported in Hz. All spectra were referenced to $CDCl_3$ the residual solvent peak $CHCl_3$ (δ = 7.26 ppm) for ^1H NMR and the $CDCl_3$ solvent peak (δ = 77.16 ppm) for $^{13}C\{^1H\}$ NMR. The notation of signals is: Proton: δ chemical shift in ppm (number of protons, multiplicity, *J* value(s), proton assignment). Carbon: δ chemical shift in ppm (carbon assignment). Fluorine: δ chemical shift in ppm (Fluorine assignment). Splitting patterns are assigned s = singlet, b = broad, d = doublet, td = triplet of doublet, dt = doublet of triplet, t = triplet, q = quartet. Catalytic reactions were carried out on a 1 mmol scale under N_2 using pre-dried glassware. THF was freshly distilled over sodium/benzophenone and stored under N_2. Other solvents, unless otherwise stated, were purchased in reagent grade or anhydrous quality and used as received. Dry $ZnCl_2$ (1M solution in THF) and ^{i}PrMgCl (2 M solution in THF) were purchased from Sigma-Aldrich. ^{i}PrMgCl was titrated with I_2 prior to use. TLC plates Alugram® Sil G/UV254. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Silica gel (Sigma Aldrich, 40-63 μ, 60 Å). High Resolution Mass Spectrometry (HRMS) were recorded on Thermo Finnigan MAT95XP. Melting points were determined using a Buchi M565 melting point apparatus.

Synthesis of starting materials

All the *O*-benzoyl *N*-hydroxylamine derivatives were prepared from the corresponding commercially available amines and benzoyl peroxide following literature procedures.[1,2] The aryne precursors **4a-e** were prepared from the corresponding 2-iodo phenols according to previoulsy reported methods.[3] 4-Methyl 2-iodo-phenol and 1-iodo-2-naphthol were obtained by iodination of 4-methyl phenol and 2-naphthol.[4]

Procedure A. Representative synthesis of *O*-benzoyl *N*-hydroxylamines.[1,2] Benzoyl peroxide (3.88 g, 12 mmol, 1.00 equiv) and K_2HPO_4 (3.17 g, 18.0 mmol, 1.50 equiv) were suspended in *N*,*N*-dimethylformamide (30 mL). The mixture was cooled to 0 ºC and *N*,*N*-dimethylamine (commercially available 40% water solution) (1.22 mL, 14.4 mmol, 1.2 equiv) was added via syringe in one portion. After 5 min the cooling bath was removed and the mixture was stirred for 1.5 h at room temperature. Deionized water (200 mL) was added, and the contents were stirred vigorously for several minutes until all solids dissolved. The reaction mixture was extracted with 150 mL of ethyl acetate. The organic phase was collected and washed with two 100 mL portions of saturated aqueous $NaHCO_3$ solution. All the aqueous fractions were combined and extracted with three 100 mL portions of ethyl acetate. All the organic fractions were combined and washed with three 100 mL portions of deionized water and 100 mL of brine, dried over $MgSO_4$, and concentrated by rotatory evaporation. The resulting crude product was purified by flash column chromatography (eluent EtOAc/Pet. Ether 1:5) to afford *O*-benzoyl *N*,*N*-dimethyl hydroxylamine as a colorless oil (1.21 g, 7.33 mmol, 61%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.7 Hz, 1 H), 7.41 (t, *J* = 7.7 Hz, 2 H), 2.88 (s, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9 (C_q), 132.9 (CH), 129.3 (CH), 129.2 (C_q), 128.3 (CH), 48.5 (CH_3).

Chart of starting 2-iodoaryl 4-chlorobenzenesulfonate derivatives (4).



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Synthesis of 2-iodo-3-methoxyphenol precursor for compound 4c. **A)** NaH (60% in mineral oil, 1440 mg, 36 mmol) was slowly added to a stirred solution of 3-methoxyphenol (1975 mg, 18 mmol) in dry THF (30 mL) and the mixture was stirred for 1.5 h. A solution of N,N-diethylcarbamoyl chloride (5.45 mL, 27 mmol) in THF (5 mL) was added and the resulting mixture was stirred overnight at room temperature. Water (50 mL) was added and subsequent extraction with CH_2Cl_2 (3 × 50 mL) was carried out. The organic layers were combined, dried over anhydrous Mg_2SO_4 and filtered. The crude was purified by column chromatography (eluent: Pet. Ether/EtOAc 1:1) to afford 3-methoxyphenyl *N*,*N*-diethyl carbamate as a pale yellow oil (2.29 g, 13.2 mmol, 73% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 7.8 Hz, 1H), 6.78 (m, 2 H), 6.73 (t, *J* = 2.1 Hz, 1 H), 3.84 (s, 3 H), 3.46 (m, 4 H), 1.27 (m, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3 (C_q), 154.1 (C_q), 152.5 (C_q), 129.5 (CH), 113.4 (CH), 111.1 (CH), 107.6 (CH), 55.3 (CH_3), 42.2 (CH_2), 41.8 (CH_2), 14.2 (CH_3), 13.4 (CH_3).

B) 11.3 mL of 1.17 M solution of *n*-BuLi in THF was added dropwise to a solution of 3-methoxyphenyl *N*,*N*-diethyl carbamate (2924 mg, 13 mmol) in dry THF (50 mL) at -78 ºC under N_2 atmosphere and the mixture was stirred at that temperature for 2 h. Then, a solution of I_2 (3960 mg, 15.7 mmol) in dry THF (30 mL) was added dropwise and the stirring continued at low temperature for further 30 min. The reaction mixture was then allowed to warm to room temperature followed by quenching with water (30 mL) and saturated $Na_2S_2O_3$ aqueous solution (25 mL). The mixture was extracted with EtOAc (3 × 50 mL), the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The crude was purified by column chromatography (eluent: Pet.Ether/EtOAc 9:1) on silica gel to afford the desired 3-methoxy 2-iodophenyl *N*,*N*-diethyl carbamate (1.7 g, 4.9 mmol, 37%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.67 (dd, *J* = 8.3, 1.1 Hz, 1H), 3.89 (s, 3 H, MeO), 3.54 (q, *J* = 7.1 Hz, 2 H, CH_2), 3.40 (q, *J* = 7.1 Hz, 2 H, CH_2), 1.33 (t, *J* = 7.1 Hz, 3 H, Me), 1.22 (t, *J* = 7.1 Hz, 3 H, Me). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C_q), 153.08 (C_q), 153.01 (C_q), 129.5 (CH), 115.9 (CH), 107.7 (CH), 83.8 (C_q), 56.7 (CH_3), 42.2 (CH_2), 42.0 (CH_2), 14.4 (CH_3), 13.3 (CH_3).

C) 3-Methoxy 2-iodophenyl *N*,*N*-diethyl carbamate was dissolved in EtOH (50 mL) and excess of NaOH (1.3 g, 33 mmol) was added. The mixture was refluxed for 8 h. Most of the EtOH was evaporated under reduced pressure, Et_2O (50 mL) was added and the excess of NaOH was neutralized at 0 ºC using a 1M HCl solution. The aqueous solution was extracted with Et_2O (3 × 30 mL) and the combined organic phase was washed with brine, dried (anhydrous $MgSO_4$), and evaporated under reduced pressure. The crude was purified by column chromatography (eluent: hexane/EtOAc) to afford 3-methoxy 2-iodo phenol (960 mg, 3.84 mmol, 78% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.1 Hz, 1 H), 6.68 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.40 (dd, *J* = 8.1, 1.1 Hz,

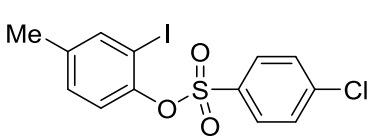
1 H), 5.51 (s, 1 H, OH), 3.89 (s, 3 H, MeO). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (C_q), 156.1 (C_q), 130.1 (CH), 107.9 (CH), 103.0 (CH), 78.07 (C_q), 56.5 (CH_3).

Synthesis of 5-iodo 6-quinolinol precursor for 4e. A 15% solution of iodine (8.27 mmol) in 20% aqueous KI (20 ml) was added dropwise to a stirred solution of 6-quinolinol (1.05 g, 6.9 mmol) in 2 N NaOH (aq) (15 mL). The reaction was stirred for 3 h at room temperature and then was acidified with acetic acid to pH 3. The resulting suspension was filtered and the precipitate was washed with water, and dried under vacuum overnight to afford 5-iodo 6-quinolinol as a black solid (1.85 g, 99 % yield). M.p: 168 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 11.11 (s, 1 H, OH), 8.74 (d, J = 3.5 Hz, 1H), 8.40 (d, J = 8.2 Hz, 1 H), 7.94 (d, J = 9.0 Hz, 1H), 7.62 (dd, J = 8.4, 4.0 Hz, 1H), 7.5 (d, 9.0 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3 (C_q), 148.8 (CH), 142.0 (CH), 139.5 (C_q), 131.0 (CH), 129.4 (C_q), 123.2 (CH), 121.2 (CH), 82.9 (C_q). HR-MS (EI) *m/z* calcd for C_9H_6INO $[M]^+$ 270.9489, found 270.9489.

Procedure B. Representative synthesis of *2* -iodoaryl 4-chlorobenzenesulfonate derivatives.[3] A 100 mL round–bottom flask was charged with 1-iodonapthol (3.6 g, 13.3 mmol) and dry pyridine (15 mL) was added. 4-Chloro benzenesulfonyl chloride (3.3 g, 15.7 mmol) was added in portions and the reaction mixture was stirred at room temperature overnight. Pyridine was evaporated *in vacuo* and water (50 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined and washed with sat. aq. Na_2CO_3 (100 mL) and brine (100 mL), and then dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. Recrystallization from CH_2Cl_2 and ethanol yielded the aryne precursor **4d** as a white solid (5.5 g, 12.3 mmol, 93% yield).

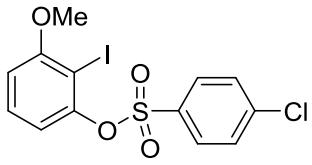
Spectroscopic data for novel starting materials (4).

Compound 4b. Prepared according to procedure **B** from 4-methyl 2-iodo phenol in 84% yield.



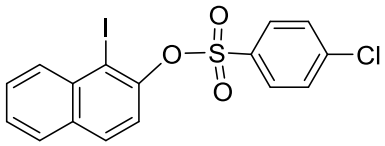
White solid, m.p.: 108 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.6 Hz, 2H), 7.57 (bs, 1 H), 7.51 (d, J = 8.6 Hz, 2 H), 7.21 (d, J = 8.3, 1H), 7.13 (dd, J = 8.3, 1.1 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (C_q), 141.2 (C_q), 140.4 (CH), 138.9 (C_q), 134.1 (C_q), 130.3 (2 CH), 129.5(CH), 122.6 (CH), 89.6 (C_q), 20.4 (CH_3). HR-MS (EI) *m/z* calcd for $C_{13}H_{10}O_3ClIS$ $[M]^+$ 407.9078, found 407.9073.

Compound 4c. Prepared according to procedure **B** from 3-methoxy 2-iodo phenol in 82% yield.



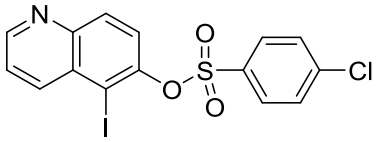
White solid, m.p: 114 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2 H), 7.31 (t, *J* = 8.2, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H) 3.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8 (C_q) , 150.8 (C_q), 141.3 (C_q), 134.2 (C_q), 130.2 (CH), 129.9 (CH), 129.5 (CH), 115.2 (CH), 109.1 (CH), 83.0 (C_q), 56.8 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{13}H_{10}O_4ClISNa$ $[M+Na]^+$ 446.8931, found 446.8951.

Compound 4d. Prepared according to procedure **B** from 2 iodo-naphthol in 93% yield. White solid,



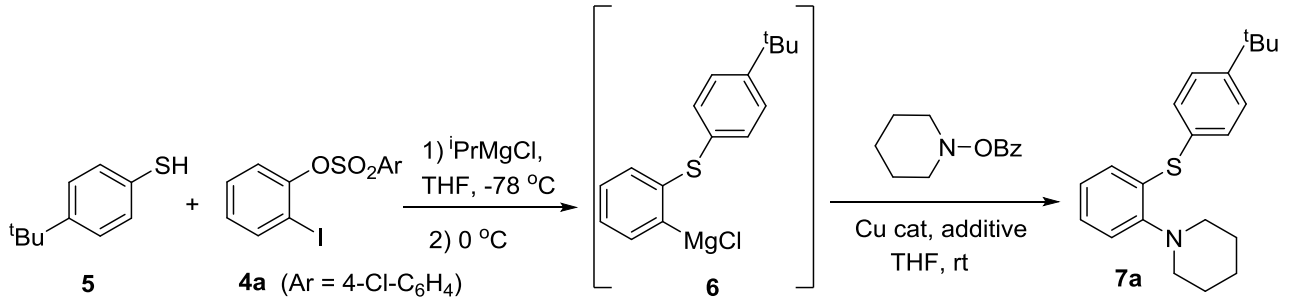
m.p: 146 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 1H), 7.91 (m, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.82 (d, *J* = 7.7, 1H), 7.61 (td, *J* = 7.0, 1.4 Hz, 1H), 7.57-7.50 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.6 (C_q), 141.4 (C_q), 135.4 (C_q), 134.4 (C_q), 132.7 (CH), 132.3 (C_q), 130.5 (CH), 130.3 (CH), 129.6 (CH), 128.6 (CH), 128.4 (CH), 127. (CH) 1, 120.9 (CH), 94.9 (C_q).HR-MS (EI) *m/z* calcd for $C_{16}H_{10}ClIO_3S$ $[M]^+$ 443.9078, found 443.9069.

Compound 4e. Prepared according to procedure **B** from 5-iodo 6-quinolinol in 67% yield after



purification by column chromatography (eluent: gradient Et_2O/Pet. Ether, 20 to 90%). Pale orange solid, m.p: 164 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.90 (dd, *J* = 4.1, 1.4 Hz, 1H), 8.41 (bd, *J* = 8.7 Hz, 1 H), 8.12 (d, *J* = 9.1 Hz, 1H), 7.91 (m, 2 H), 7.72 (d, *J* = 9.1 Hz, 1H), 7.53 (m, 2 H), 7.50 (dd, 8.7, 4.2 Hz, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (CH), 148.8 (C_q), 146.9 (C_q), 141.6 (C_q), 140.9 (CH), 132.2 (C_q), 131.9 (CH), 131.0 (C_q), 130.3 (CH), 129.7 (CH), 124.3 (CH), 123.4 (CH), 94.2 (C_q). HR-MS (EI) *m/z* calcd for $C_{15}H_9ClINO_3S$ $[M]^+$ 444.9031, found 444.9033.

Optimization study: Representative procedure for the synthesis of 1-(2-((4-(*tert*-butyl)phenyl)thio)phenyl)piperidine (7a).



5 **4a** (Ar = 4-Cl-C_6H_4) **6** **7a**

An oven-dried 5 mL microwave glass vial was charged with *p-tert*-butyl-benzenethiol **5** (87 µL, 0.50 mmol, 1.00 equiv) and a teflon-coated stirrer bar. The vial was sealed with an aluminium crimp cap and vacuum/N_2 cycle was applied three times to the vial to ensure the removal of air from the reaction vessel. Dry THF (2 mL) was added and the solution was cooled to -78 °C for 5 min in an acetone/dry ice bath. ^{i}PrMgCl (2 M solution in THF) (mmol)[1] was added via syringe, and the mixture was stirred at that temperature for 15 min before adding a solution of benzyne precursor **4a** (mmol)[1] in dry THF (2 mL) under N_2. The reaction mixture was stirred at -78 °C for 45 min. After that time, the vial was warmed to 0 °C in an ice bath and stirred for 15 min. The cooling bath was removed and the solution was taken out of the vial in a syringe and added dropwise (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of Cu salt (mol%),[1] ligand (mol%),[1] and *O*-benzoyl *N*-hydroxyl piperidine (mmol)[1] in dry THF (2 mL) under N_2 at 25-30 °C. After the addition was finished the mixture was strirred for additional 1 h and the solvent was taken to dryness. The crude was dissolved in CH_2Cl_2 (50 mL) and extracted with 10 % aq NH_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). All the organic layers were combined, dried with anhydrous $MgSO_4$, filtered and taken to dryness. The yield of the reaction was determined either by NMR using as internal standard 1,3,5-trimethoxybenzene or by column chromatography (silica, petroleum ether) to isolate the product **7a**.

1-See the amounts in the optimization table below

Optimization table

Entry	Benzyne precursor (equiv)	^{i}PrMgCl (equiv)	piperidine-OBz (equiv)	Copper source (mol %)	Additives (mol %)	Yield[a] (%)
1	1	2	1	$CuCl_2$ (5)	-	35[b]
2	1	2	1.1	$CuBr_2$ (5)	-	32
3	1	2	1.4	CuCl (5)	-	21
4	1	2	1	CuCl (50)	-	20
5	1	2	1	CuCl (100)	-	traces
6	1	2	1	$CuCl_2$ (5)	-[c]	40
7	1	2	1	$CuCl_2$ (5)	phen (5)	43
8	1	2	1	CuTC (5)	-	15
9	1	2	1	$CuCl_2$ (10)	phen(10)	62
10	1	2	1	CuCN (10)	phen(10)	traces
11	1	2	1	$CuCl_2$ (5)	$ZnCl_2$(20)	45
12	1	2	1	$CuCl_2$ (5)	$ZnCl_2$(100)	20
13	1	2	1	$CuCl_2$ (10)	TMEDA (10)	45
14	1	2	1	$CuCl_2$ (10)	DTBPY (10)	40
15	1	2	1	$CuCl_2$ (10)	Diimine (10)	38
16	1	2	2	$CuCl_2$ (10)	Diimine (10)	45
17	1	2	2	$CuCl_2$ (10)	BINAP (10)	42
18	1	2	1.5	$CuCl_2$ (10)	phen(10)	51
19	1	2	1	CuCl (10)	phen(10)	60
20	1	2	1.5	CuCl (10)	phen(10)[d]	52[b]
21	1.2	2.2	1.5	CuCl (10)	phen(10)[d]	76[b]
22	1.3	2.5	1.5	CuCl (10)	phen(10)[d]	55
23	1	2	1	-	phen(10)	-
24	1.2	2.2	1.5	CuCl (15)	phen(15)	65

Reactions were carried out using 0.5 mmol (1 equiv) of *p-tert*-butyl-benzenethiol, in dry THF as described above. *a*: NMR yields. *b*: isolated yield. *c*: After addition of the intermediate Grignard to the piperidine-OBz solution, the mixture was heated at 50 ^{o}C for 8 h. *d*: 3 mg of 60% NaH dispersion in mineral oil was added to remove any moisture present in the added copper salt or the 1,10-phenanthroline, CuTC: Copper(I) thiophen-2-carboxylate, phen: 1,10-phenanthroline, TMEDA: tetramethylethylenediamine, DTBPY: 4,4'-di-*tert*-butyl-2,2'-bipyridine. Diimine: (2E,3E)-N2,N3-dimesitylbutane-2,3-diimine.

Representative procedure C for the synthesis of *ortho*-thioaminated compounds 7a–j, 7m, 7o, 7p, and compounds 8a and 8b.

An oven-dried 20 mL microwave glass vial was charged with *p*-MeO-benzenethiol (123 µL, 1 mmol, 1.00 equiv) and a teflon-coated stirrer bar. The vial was sealed with an aluminium crimp cap and vacuum/N_2 cycle was applied three times to the vial to ensure the removal of air from the reaction vessel. Dry THF (4 mL) was added and the solution was cooled to -78 °C for 5 min in an acetone/dry ice bath. ^{i}PrMgCl (2 M solution in THF) (1.1 mL, 2.2 mmol, 2.2 equiv) was added dropwise via syringe and the mixture was stirred at that temperature for 15 min. A solution of benzyne precursor **4a** (474 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 atmosphere was added dropwise, while the mixture was vigorously stirred. The reaction mixture was stirred at -78 °C for 45 min. After that time, the vial was warmed to 0 °C in an ice bath and stirred for 15 min. The cooling bath was removed and the solution was taken out of the vial in a syringe and added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (10 mg, 10 mol%), 1,10-phenanthroline (18 mg, 10 mol%) NaH (60 % in mineral oil) (3 mg, 0.07 mmol) and *O*-benzoyl *N*-methyl *N*-benzyl hydroxylamine (362 mg, 1.5 mmol, 1.5 equiv) in dry THF (4 mL) under N_2 at 25-30 °C. After the addition was finished the mixture was strirred for additional 1 h and the solvent was taken to dryness. The crude was dissolved in CH_2Cl_2 (50 mL) and extracted with 10 % aq NH_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). All the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The filtrate was taken to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 95% Pet. Ether/5% Et_2O) to afford the product **7e** (250 mg, 0.75 mmol, 75% yield). In the cases where the *O*-benzoyl *N*-Boc *N*-hydroxyl piperazine was used (products **7n** and **12**), a slightly different protocol using $ZnCl_2$ as an additive was followed, see below the synthesis of vortioxetine.

The synthesis of compounds **8a** and **8b** was carried out starting form 0.5 mmol of thiol following the scaled-down fisrt part of procedure **C**. After warming the reaction mixture to 0 °C in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl and the corresponding electrophile reagent (see below).

Representative procedure D for the synthesis of *ortho*-thioaminated compounds containing *N*-Boc moiety (7n, 12) and secondary amines (7k, 7l). Synthesis of *N*-Boc-vortioxetine. An oven-dried 20 mL microwave glass vial was charged with 2,4-dimethyl benzenethiol (142 µL, 1 mmol, 1.00 equiv) and a teflon-coated stirrer bar. The vial was sealed with an aluminium crimp cap and vacuum/N_2 cycle was applied three times to the vial to ensure the removal of air from the reaction vessel. Dry THF (4 mL) was added and the solution was cooled to -78 °C for 5 min in an acetone/dry

ice bath. ^{i}PrMgCl (2 M solution in THF) (1.1 mL, 2.2 mmol, 2.2 equiv) was added dropwise via syringe and the mixture was stirred at that temperature for 15 min. A solution of benzyne precursor **4a** (474 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 atmosphere was added dropwise, while the mixture was vigorously stirred. The reaction mixture was stirred at -78 °C for 45 min. After that time, the vial was warmed to 0 °C in an ice bath and stirred for 15 min. The cooling bath was removed and the solution was warmed to room temperature. Dry $ZnCl_2$ in THF solution (0.5 mL of a 1 M solution, 0.5 mmol, 0.5 equiv) was dropwise added and the solution was stirred at room temperature for 30 min. After this time, the solution was taken out of the vial in a syringe and added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (2.5 mg, 2.5 mol%) and *O*-benzoyl *N*-Boc *N*-hydroxyl piperazine (365 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 at 25-30 ^{o}C. After the addition was finished the mixture was strirred for additional 1 h, the solvent was taken to dryness and the crude was purified by column chromatography (silica. Pet. Ether/ diethyl ether, 10:1) to afford *N*-Boc-vortioxetine **12** (310 mg, 0.78 mmol, 78% yield).

Representative procedure E for the synthesis of *ortho*-diaminated compounds 10a-f, 10k, 10l, and compounds 11a and 11b.

An oven-dried 20 mL microwave glass vial was charged with *N*-methyl aniline (109 µL, 1 mmol, 1.00 equiv) and a teflon-coated stirrer bar. The vial was sealed with an aluminium crimp cap and vacuum/N_2 cycle was applied three times to the vial to ensure the removal of air from the reaction vessel. Dry THF (4 mL) was added and the solution was cooled to approx. -15 °C in an ice/salt bath for 5 min. ^{i}PrMgCl (2 M solution in THF) (0.55 mL, 1.1 mmol, 1.1 equiv) was added dropwise via syringe and the mixture was stirred at that temperature for 30 min. The vial was then cooled to -78 °C and a second portion of ^{i}PrMgCl (0.55 mL, 1.1 mmol, 1.1 equiv) was added, followed by the dropwise additon of a solution of benzyne precursor **4a** (474 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 atmosphere, while the mixture was vigorously stirred. The reaction mixture was stirred at -78 ^{o}C for 45 min. After that time, the vial was warmed to 0 °C in an ice bath and stirred for 15 min. The cooling bath was removed and the solution was taken out of the vial in a syringe and added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (10 mg, 10 mol%), 1,10-phenanthroline (18 mg, 10 mol%), NaH (60 % in mineral oil) (3 mg, 0.07 mmol) and *O*-benzoyl *N*-morpholine hydroxylamine (362 mg, 1.5 mmol, 1.5 equiv) in dry THF (4 mL) under N_2 at 25-30 ^{o}C. After the addition was finished the mixture was strirred for additional 1 h and the solvent was taken to dryness. The crude was dissolved in CH_2Cl_2 (50 mL) and extracted with 10 % aq NH_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). All the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The filtrate was taken

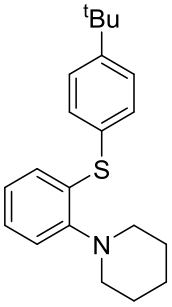
to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 95% Pet. Ether/5% Et_2O) to afford the product **10a** (171 mg, 0.64 mmol, 64% yield).

The synthesis of compounds **11a** and **11b** was carried out starting form 0.5 mmol of thiol following the scaled-down first part of procedure **E**. After warming the reaction mixture to 0 ^oC in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl and the corresponding electrophile reagent (see below).

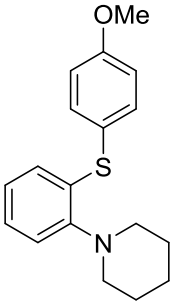
Representative procedure F for the synthesis of *ortho*-diaminated compounds 10g-j. An oven-dried 20 mL microwave glass vial was charged with *N*-methyl aniline (109 µL, 1 mmol, 1.00 equiv) and a teflon-coated stirrer bar. The vial was sealed with an aluminium crimp cap and vacuum/N_2 cycle was applied three times to the vial to ensure the removal of air from the reaction vessel. Dry THF (4 mL) was added and the solution was cooled to approx. -15 °C in an ice/salt bath for 5 min. ^{i}PrMgCl (2 M solution in THF) (0.55 mL, 1.1 mmol, 1.1 equiv) was added dropwise via syringe and the mixture was stirred at that temperature for 30 min. The vial was then cooled to -78 °C and a second portion of ^{i}PrMgCl (0.55 mL, 1.1 mmol, 1.1 equiv) was added, followed by the dropwise additon of a solution of benzyne precursor **4a** (474 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 atmosphere, while the mixture was vigorously stirred. The reaction mixture was stirred at -78 °C for 45 min. After that time, the vial was warmed to 0 °C in an ice bath and stirred for 15 min. The cooling bath was removed and the solution and warmed to room temperature. Dry $ZnCl_2$ in THF solution (0.5 mL of a 1 M solution, 0.5 mmol, 0.5 equiv) was dropwise added and the solution was stirred at room temperature for 30 min. After this time, the solution was taken out of the vial in a syringe and added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (2.5 mg, 2.5 mol%) and *O*-benzoyl *N*-Boc *N*-hydroxyl piperazine (365 mg, 1.2 mmol, 1.2 equiv) in dry THF (4 mL) under N_2 at 25-30 ^oC. After the addition was finished the mixture was strirred for additional 1 h, the solvent was taken to dryness and the crude was purified by column chromatography (silica. Pet. Ether/ Et_2O, 10:1) to afford compound **10h** (265 mg, 0.72 mmol, 72% yield).

Spectroscopic data for compounds 7 and 8.

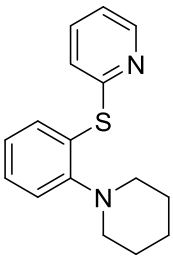
Compound 7a. Prepared according to procedure **C** (247 mg, 0.76 mmol, 76%). White solid, m.p.: 82 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45-7.38 (m, 4H), 7.12-7.04 (m, 2H), 6.90-6.86 (td, J=8.0, 1.6 Hz, 1H), 6.79 (dd, J=8.0, 1.2 Hz, 1H), 3.00-2.97 (m, 4H), 1.76-1.73 (m, 4H), 1.59-1.57 (m, 2H), 1.35 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.32 (C_q), 150.89 (C_q), 135.04 (C_q), 134.17 (CH), 129.77 (C_q), 127.45 (CH), 126.42 (CH), 125.79 (CH), 123.72 (CH), 119.77 (CH), 53.45 (CH_2), 34.69 (C_q), 31.32 (CH_3), 26.42 (CH_2), 24.35 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{21}H_{28}NS$ $[M+H]^+$ 326.1942, found 326.1953.



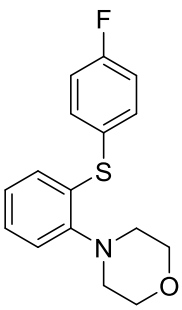
Compound 7b. Prepared according to procedure **C** (201 mg, 0.67 mmol, 67%). White solid, m.p.: 102 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.50-7.48 (m, 2H), 7.07-7.04 (m, 2H), 6.96-6.94 (m, 2H), 6.89-6.85 (m, 1H), 6.64 (d, J=8.0 Hz, 1H), 3.85 (s, 3H), 3.01-2.98 (m, 4H), 1.81-1.75 (m, 4H), 1.62-1.58 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.14 (C_q), 150.17 (C_q), 137.15 (CH), 136.39 (C_q), 126.05 (CH), 125.30 (CH), 123.83 (CH), 123.09 (C_q), 119.70 (CH), 115.11 (CH), 55.37 (CH_3), 53.46 (CH_2), 26.49 (CH_2), 24.38 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{22}NOS$ $[M+H]^+$ 300.1422, found 300.1429.



Compound 7c. Prepared according to procedure **C** (178 mg, 0.66 mmol, 66%). Dense pale yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, J=4.0 Hz, 1H), 7.47-7.41 (m, 2H), 7.32 (t, J=8.0 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 7.03-6.99 (m, 2H), 6.92 (d, J=8.0 Hz, 1H), 2.95 (br m, 4H), 1.71 (br s, 2H), 1.52-1.46 (m, 4H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.93 (C_q), 155.08 (C_q), 149.28 (CH), 136.27 (CH), 135.32 (CH), 129.64 (CH), 127.30 (C_q), 123.40 (CH), 122.40 (CH), 120.64 (CH), 119.88 (CH), 55.27 (CH_2), 26.20 (CH_2), 24.19 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{16}H_{19}N_2S$ $[M+H]^+$ 271.1269, found 271.1260.

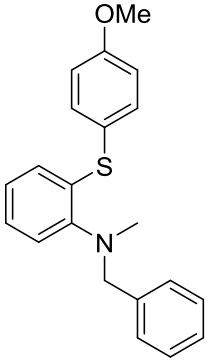


Compound 7d. Prepared according to procedure **C** (227 mg, 0.76 mmol, 76%). White solid, m.p.: 88 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47-7.44 (m, 2H), 7.16 (t, J=8.0 Hz, 1H), 7.11-7.07 (m, 3H), 6.96 (t, J=8.0 Hz, 1H), 6.77 (d, J=8.0 Hz, 1H), 3.87-3.84 (m, 4H), 3.07-3.05 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.88 (d, J_{CF}=247 Hz, C_q), 149.30 (C_q), 136.17 (d, J_{CF}=8 Hz, CH), 134.41 (C_q), 128.24 (d, J_{CF}=3 Hz, C_q), 127.89 (CH), 126.48 (CH), 124.62 (CH), 120.03 (CH), 116.63 (d, J_{CF}=20 Hz, CH),



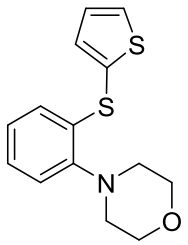
67.34 (CH_2), 52.10 (CH_2). ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.99 (s). HR-MS (+ESI) *m/z* calcd for $C_{16}H_{17}FNOS$ $[M+H]^+$ 290.1009, found 290.1011.

Compound 7e. Prepared according to procedure **C** (252 mg, 0.75 mmol, 75%). Dense colorless oil.



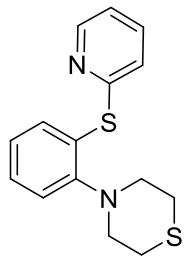
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.51-7.49 (m, 4H), 7.35 (t, J=8.0 Hz, 2H), 7.30-7.26 (m, 1H), 7.13-7.06 (m, 2H), 6.98 (d, J=12.0 Hz, 2H), 6.91 (td, J=8.0, 1.6 Hz, 1H), 6.70 (dd, J=8.0, 1.2 Hz, 1H), 4.17 (s, 2H), 3.86 (s, 3H), 2.68 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.16 (C_q), 149.54 (C_q), 138.71 (C_q), 137.05 (CH), 136.53 (C_q), 128.79 (CH), 128.22 (CH), 127.06 (CH), 126.57 (CH), 125.32 (CH), 124.35 (CH), 123.07 (C_q), 120.95 (CH), 115.15 (CH), 61.00 (CH_2), 55.39 (CH_3), 40.67 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{21}H_{22}NOS$ $[M+H]^+$ 336.1422, found 336.1408.

Compound 7f. Prepared according to procedure **C** (170 mg, 0.61 mmol, 61%). Pale yellow solid, m.p.: 103-104 ^{o}C.



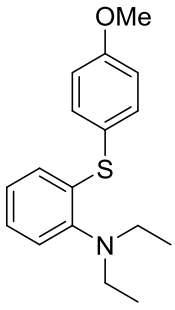
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.54 (dd, J=5.4, 1.2 Hz, 1H), 7.30 (dd, J=3.4, 1.3 Hz, 1H), 7.14-7.07 (m, 3H), 6.98-6.95 (m, 1H), 6.72 (dd, J=8.0, 1.3 Hz, 1H), 3.91-3.89 (m, 4H), 3.06-3.04 (m, 4H).^{13}C NMR (126 MHz, $CDCl_3$) δ = 148.26 (C_q), 137.10 (CH), 136.42 (C_q), 131.85 (CH), 129.96 (C_q), 128.22 (CH), 125.91 (CH), 125.62 (CH), 125.03 (CH), 119.94 (CH), 67.37 (CH_2), 52.27 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{14}H_{16}NOS_2$ $[M+H]^+$ 278.0673, found 278.0685.

Compound 7g. Prepared according to procedure **C** (160 mg, 0.55 mmol, 55%). Pale yellow solid, m.p.: 86-87 ^{o}C.



^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.45-8.44 (ddd, J=4.8, 1.9, 0.9 Hz, 1H), 7.48-7.44 (m, 2H), 7.34 (td, J=8.0, 1.8 Hz, 1H), 7.09-7.05 (m, 2H), 7.04-7.01 (m, 1H), 6.93 (dt, J=8.0, 1.1 Hz, 1H), 3.24 (m, 4H), 2.57-2.55 (m, 4H).^{13}C-NMR (126 MHz, $CDCl_3$): δ = 160.41 (C_q), 154.48 (C_q), 149.47 (CH), 136.32 (CH), 135.15 (CH), 129.73 (CH), 128.11 (C_q), 124.36 (CH), 122.42 (CH), 121.50 (CH), 120.11 (CH), 54.19 (CH_2), 28.08 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{15}H_{17}N_2S_2$ $[M+H]^+$ 289.0833, found 289.0847.

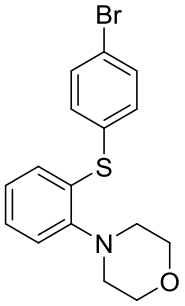
Compound 7h. Prepared according to procedure **C** (201 mg, 0.70 mmol, 70%). White solid, m.p.: 48 ^{o}C.



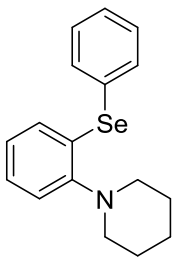
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39-7.36 (m, 2H), 6.98 (dt, J=7.8, 1.7 Hz, 2H), 6.87-6.85 (m, 2H), 6.81 (dd, J=7.8, 1.7 Hz, 1H), 6.66 (dd, J=8.0, 1.4 Hz, 1H), 3.76 (s, 3H), 3.02 (q, J=7.2 Hz, 4H), 0.99 (t, J=7.2 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.04 (C_q), 146.99 (C_q), 139.21 (C_q), 137.03 (CH), 126.30 (CH), 124.80 (CH), 124.46 (CH), 123.76 (C_q), 122.75 (CH), 115.04 (CH), 55.35 (CH_3),

47.68 (CH_2), 12.43 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{17}H_{21}NOS$ $[M+H]^+$ 288.1432, found 288.1422.

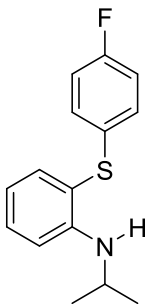
Compound 7i. Prepared according to procedure **C** (179 mg, 0.51 mmol, 51%). White solid, m.p.: 114 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.47-7.45 (m, 2H), 7.27-7.25 (m, 2H), 7.20 (td, J=8.0, 2.0 Hz, 1H), 7.08 (td, J=8.0, 2.0 Hz, 1H), 6.99-6.92 (m, 2H), 3.81-3.78 (m, 4H), 3.05-3.03 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.30 (C_q), 134.24 (CH), 133.37 (C_q), 132.45 (C_q), 132.39 (CH), 129.79 (CH), 127.38 (CH), 124.56 (CH), 121.78 (C_q), 120.19 (CH), 67.28 (CH_2), 52.07 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{16}H_{17}BrNOS$ $[M+H]^+$ 350.0214, found 350.0216.



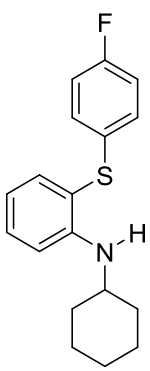
Compound 7j. Prepared according to procedure **C** (187 mg, 0.59 mmol, 59%). Pale yellow solid, m.p.: 48 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, J=8.0, 1.6 Hz, 2H), 7.41-7.35 (m, 3H), 7.15-7.07 (m, 2H), 7.87 (td, J=8.0, 1.6 Hz, 1H), 6.77 (dd, J=8.0, 1.6 Hz, 1H), 2.97-2.94 (m, 4H), 1.79-1.74 (m, 4H), 1.60-1.56 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.49 (C_q), 136.92 (CH), 133.49 (C_q), 129.49 (CH), 128.59 (C_q), 128.48 (CH), 128.21 (CH), 126.24 (CH), 124.93 (CH), 120.61 (CH), 53.94 (CH_2), 26.59 (CH_2), 24.29 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{17}H_{20}NSe$ $[M+H]^+$ 318.0761, found 318.0750.



Compound 7k. Prepared according to procedure **D** (117 mg, 0. 44 mmol, 44%). Dense colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, J=7.6 Hz, 1H), 7.29 (t, J=7.6 Hz, 1H), 7.07-7.04 (m, 2H), 6.92 (t, J=8.6 Hz, 2H), 6.68-6.63 (m, 2H), 4.67 (br s, 1H), 3.64 (br s, 1H), 1.11 (d, J=6.3 Hz, 6H).^{13}C-NMR (126 MHz, $CDCl_3$): δ = 161.14 (d, J_{CF}=245 Hz, C_q), 148.49 (C_q), 137.45 (CH), 131.87 (d, J_{CF}=3 Hz, C_q), 131.33 (CH), 128.47 (d, J_{CF}=8 Hz, CH), 116.39 (CH), 115.45 (d, J_{CF}=20 Hz, CH), 114.38 (C_q), 111.18 (CH), 43.92 (CH), 22.72 (CH_3).^{19}F-NMR (470 MHz, $CDCl_3$): δ = -117.32 (s). HR-MS (+ESI) *m/z* calcd for $C_{15}H_{17}FNS$ $[M+H]^+$ 262.1066, found 262.1071.

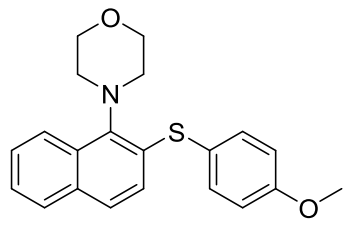


Compound 7l. Prepared according to procedure **D** (139 mg, 0. 46 mmol, 46%). Dense colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ =7.45 (dd, J=7.5, 1.7 Hz, 1H), 7.29-7.26 (m, 1H), 7.07-7.04 (m, 2H), 6.94-6,90 (m, 2H), 6.68 (d, J=8.0 Hz, 1H), 6.63 (td, J=7.5, 1.4 Hz, 1H), 4.79 (br s, 1H), 3.28 (br s, 1H), 1.91-1.88 (m, 2H), 1.65-1.62 (m, 2H), 1.60-1.56 (m, 1H), 1.36-1.29 (m, 2H), 1.22-1.17 (m, 1H), 1.13-1.05 (m, 2H). ^{13}C-NMR (126 MHz, $CDCl_3$): δ =160.65 (d, J_{CF}=254 Hz, C_q), 148.31 (C_q), 137.50 (CH), 131.87 (d, J_{CF}=4



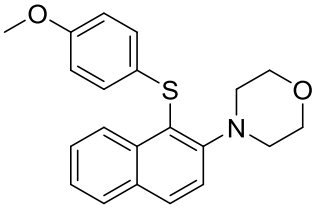
Hz, C_q), 131.30 (CH), 128.47 (d, J_{CF}=8 Hz, CH), 116.21 (CH), 116.44 (d, J_{CF}=23 Hz, CH), 114.20 (C_q), 111.05 (CH), 50.98 (CH), 32.84 (CH_2), 25.75 (CH_2), 24.57 (CH_2).^{19}F-NMR (470 MHz, $CDCl_3$): δ = -117.34 (s). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{21}FNS$ $[M+H]^+$ 302.1379, found 302.1389.

Compound 7m. Procedure **C** afforded a 1:1 separable mixture of isomers **7m** and **7m'**. Data for



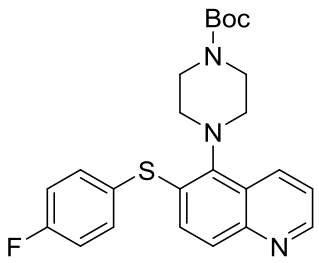
compound **7m**: (98 mg, 0.28 mmol, 28%). Pale orange solid, m.p.: 114 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, J=8.0 Hz, 1H), 7.76 (d, J=8.0 Hz, 1H), 7.51-7.47 (m, 2H), 7.45-7.43 (m, 2H), 7.39 (td, J=8.0, 2.0 Hz, 1H), 6.96-6.94 (m, 2H), 6.88 (d, J=8.0 Hz, 1H), 4.04-3.94 (m, 4H), 3.85 (s, 3H), 3.55-3.49 (m, 2H), 3.39-3.34 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.96 (C_q), 142.07 (C_q), 137.40 (C_q), 136.17 (CH), 133.00 (C_q), 132.66 (C_q), 128.61 (CH), 126.88 (CH), 126.27 (CH), 125.53 (CH), 124.97 (CH), 124.34 (C_q), 123.48 (CH), 115.14 (CH), 68.24 (CH_2), 55.40 (CH_3), 50.36 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{21}H_{22}O_2NS$ $[M+H]^+$ 352.1366, found 352.1361.

Compound 7m'. Procedure **C** afforded a 1:1 separable mixture of isomers **7m** and **7m'**. Data for



compound **7m'**: (98 mg, 0.28 mmol, 28%). Pale orange solid, m.p.: 66 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, J=8.0 Hz, 1H), 7.89 (d, J=8.0 Hz, 1H), 7.80 (d, J=8.0 Hz, 1H), 7.47 (td, J=8.0, 1.2 Hz, 1H), 7.42-7.36 (m, 2H), 6.99-6.95 (m, 2H), 6.72-6.69 (m, 2H), 3.77-3.75 (m, 4H), 3.72 (s, 3H), 3.15-3.13 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 157.53 (C_q), 153.51 (C_q), 136.18 (C_q), 131.06 (C_q), 130.88 (CH), 129.41 (C_q), 128.34 (CH), 128.17 (CH), 127.23 (CH), 126.15 (CH), 124.77 (CH), 122.57 (C_q), 119.96 (CH), 114.41 (CH), 67.23 (CH_2), 55.31 (CH_3), 52.48 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{21}H_{22}O_2NS$ $[M+H]^+$ 352.1366, found 352.1369.

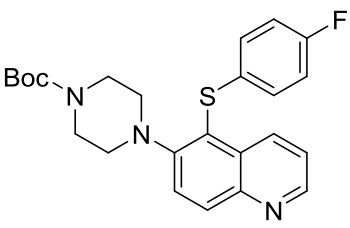
Compound 7n. Procedure **D** afforded a 1:1 separable mixture of isomers **7n** and **7n'**. Data for



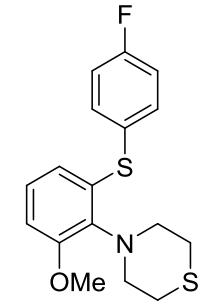
compound **7n**: (124 mg, 0.28 mmol, 28%). Dense yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.43 (dd, J=4.0, 1.2 Hz, 1H), 8.50 (d, J=8.0 Hz, 1H), 7.83 (d, J=12.0 Hz, 1H), 7.46-7.39 (m, 3H), 7.14 (d, J=8.0 Hz, 1H), 7.09 (t, J=8.0 Hz, 2H), 3.72-3.62 (m, 4H), 3.42-3.37 (m, 2H), 3.30-3.25 (m, 2H), 1.47 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 162.90 (d, J_{CF}=248 Hz, C_q), 154.97 (C_q), 149.44 (CH), 147.79 (C_q), 143.15 (C_q), 136.35 (C_q), 135.71 (d, J_{CF}=5 Hz, CH), 132.14 (CH), 129.88 (CH), 128.86 (d, J_{CF}=3 Hz, C_q), 128.18 (CH), 127.88 (C_q), 121.32 (CH), 116.81 (d, J_{CF}=22 Hz, CH), 79.87 (C_q), 50.36 (br s, CH_2), 45.45 (br s, CH_2), 44.42 (br s, CH_2),

28.50 (CH_3). ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.56 (s). HR-MS (+ESI) *m/z* calcd for $C_{19}H_{18}N_3FS$ $[M\text{-Boc}+H]^+$ 339.1200, found 339.1189.

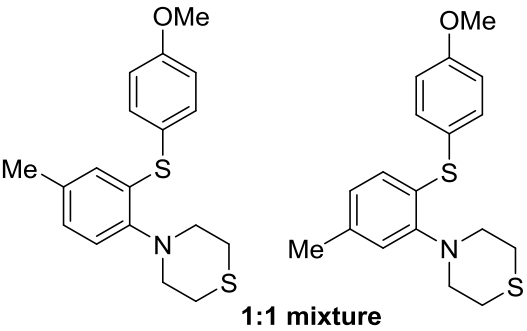
Compound 7n'. Procedure **D** afforded a 1:1 separable mixture of isomers **7n** and **7n'**. Data for compound **7n'**: (123 mg, 0.28 mmol, 28%). Yellow solid, m.p.: 126 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.83 (dd, J=4.0, 1.6 Hz, 1H), 8.75 (d, J=12.0 Hz, 1H), 8.19 (d, J=8.0 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.39 (dd, J=8.0, 4.0 Hz, 1H), 6.94-6.90 (m, 2H), 6.85 (t, J=8.0 Hz, 2H), 3.48-3.46 (m, 4H), 3.12-3.09 (m, 4H), 1.47 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.91 (d, J_{CF}=244 Hz, C_q), 154.80 (C_q), 154.11 (C_q), 148.94 (CH), 145.54 (Cq), 134.46 (CH), 132.88 (d, J_{CF}=3 Hz, C_q), 132.22 (CH), 131.55 (C_q), 128.16 (d, J_{CF}=8 Hz, CH), 123.75 (CH), 122.16 (CH), 121.41 (C_q), 116.09 (d, J_{CF}=22 Hz, CH), 79.90 (C_q), 51.96 (CH_2), 44.39 (br s, CH_2), 43.38 (br s, CH_2), 28.44 (CH_3). ^{19}F-NMR (376 MHz, $CDCl_3$): δ = -117.09 (s). HR-MS (+ESI) *m/z* calcd for $C_{19}H_{18}N_3FS$ $[M\text{-Boc}+H]^+$ 339.1200, found 339.1196.



Compound 7o. Prepared according to procedure **C** (187 mg, 0.56 mmol, 56%). White solid, m.p.: 147-148 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.51-7.48 (m, 2H), 7.10 (t, J=10.0 Hz, 2H), 6.92 (t, J=10.0 Hz, 1H), 6.63 (dd, J=8.0, 1.2 Hz, 1H), 6.14 (dd, J=8.0, 1.2 Hz, 1H), 3.81 (s, 3H), 3.59-3.54 (m, 2H), 3.17-3.09 (m, 4H), 2.49-2.47 (m, 2H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 163.03 (d, J_{CF}=248 Hz, C_q), 158.27 (C_q), 141.84 (C_q), 137.51 (d, J_{CF}=8 Hz, CH), 136.06 (C_q), 128.45 (d, J_{CF}=4 Hz, C_q), 126.70 (CH), 117.19 (CH), 116.65 (d, J_{CF}=22 Hz, CH), 108.38 (CH), 55.20 (CH_3), 51.89 (CH_2), 28.96 (CH_2).^{19}F-NMR (376 MHz, $CDCl_3$): δ = -112.64 (s). HR-MS (+ESI) *m/z* calcd for $C_{17}H_{19}FNOS_2$ $[M+H]^+$ 336.0892, found 336.0905.

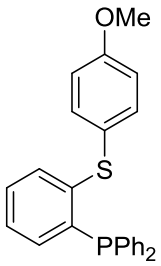


Compound 7p. Prepared according to procedure **C** (219 mg, 0.66 mmol, 66%) as a 1:1 mixture of isomers. White solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46 (m, 4H), 6.97-6.92 (m, 5H), 6.90-6.86 (m, 2H), 6.74 (d, J=8.0 Hz, 1H), 6.59 (d, J=8.0 Hz, 1H), 6.45 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.28-3.23 (m, 8H), 2.85-2.83 (m, 8H), 2.28 (s, 3H), 2.14 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 160.12 (C_q), 159.97 (C_q), 149.96 (C_q), 147.39 (C_q), 136.92 (CH), 136.45 (CH), 136.40 (C_q), 135.66 (C_q), 134.41 (C_q), 132.61 (C_q), 126.88 (CH), 126.68 (CH), 126.21 (CH), 125.34 (CH), 123.33 (C_q), 122.73 (C_q), 121.47 (CH), 120.46 (CH), 115.15 (CH), 115.09 (CH), 55.40 (2 C_q, OCH_3), 54.46



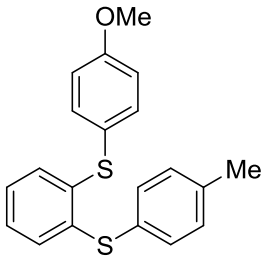
(CH_2), 54.37 (CH_2), 28.55 (CH_2), 28.49 (CH_2), 21.09 (CH_3), 21.05 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{22}NOS_2$ $[M+H]^+$ 332.1143, found 332.1127.

Compound 8a. The synthesis of compound **8a** was carried out starting form 0.5 mmol of thiol



following the scaled-down fisrt part of procedure **C**. After warming the reaction mixture to 0 °C in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (1 mg, 2 mol%), PPh_2Cl (103 µL, 0.6 mmol, 1.2 equiv) in dry THF (2 mL) under N_2 at 25 °C. After the addition was finished the mixture was strirred for additional 2.5 h at 50 °C. The solvent was taken to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 95% Pet. Ether/5% Et_2O) to afford the product **8a** (147 mg, 0.367 mmol, 73% yield). Colorless solid, m.p.: 104-106 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.30 (m, 12H), 7.17 (td, J=7.2, 1.0 Hz, 1H), 7.07-7.03 (m, 2H), 6.86-6.79 (m, 3H), 3.80 (s, 3H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.70 (C_q), 144.15 (d, J_{CP}= 27.9 Hz, C_q), 136.92 (d, J_{CP}= 10.52 Hz, C_q), 136.40 (d, J_{CP}= 10.40 Hz, C_q), 135.25 (CH), 134.02 (d, J_{CP}= 20.1 Hz, CH), 133.28 (CH), 129.42 (d, J_{CP}= 3.81 Hz, CH), 129.27 (CH), 128.75 (CH), 128.54 (d, J_{CP}= 6.54 Hz, CH), 126.0 (CH), 125.0 (d, J_{CP}= 7.7 Hz, C_q), 114.87 (CH), 55.30 (CH_3). ^{31}P-NMR (162.29 MHz, $CDCl_3$): -13.46 ppm. HR-MS (+ESI) *m/z* calcd for $C_{25}H_{22}OPS$ $[M+H]^+$ 401.1129, found 401.1127.

Compound 8b. The synthesis of compound **8b** was carried out starting form 0.5 mmol of thiol

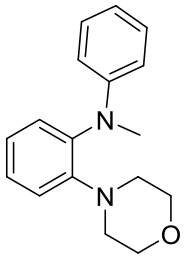


following the scaled-down fisrt part of procedure **C**. After warming the reaction mixture to 0 °C in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (5 mg, 10 mol%), *p*-tolyl disulfide (148 mg, 0.6 mmol, 1.2 equiv) in dry THF (2 mL) under N_2 at 25 °C. After the addition was finished the mixture was strirred for additional 12 h at R.T. The crude was dissolved in CH_2Cl_2 (50 mL) and extracted with 10 % aq NH_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). All the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The filtrate was taken to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 90% Pet. Ether/10% Et_2O) to afford the product **8b** (104 mg, 0.31 mmol, 62% yield). Colorless solid, m.p.: 98-100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.45-7.42 (m, 2H), 7.32-7.29 (m, 2H), 7.17 (d, J=8.0, 2H), 7.13-7.11 (m, 1H), 7.09-7.01 (m, 2H), 6.95-6.91 (m, 3H), 3.84 (s, 3H), 2.37 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 159.91 (C_q), 139.95 (C_q), 137.46 (C_q), 135.62 (CH), 135.12 (C_q), 131.82 (CH), 131.15 (CH), 130.71 (C_q),

130.08 (CH), 128.58 (CH), 127.24 (CH), 126.19 (CH), 123.30 (C_q), 115.06 (CH), 55.23 (CH_3), 21.12 (CH_3). HR-MS (EI) *m/z* calcd for $C_{20}H_{18}OS_2$ $[M]^+$ 338.0794, found 338.0795.

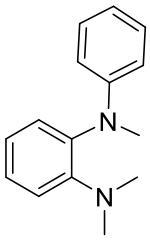
Spectroscopic data for compounds 10 and 11.

Compound 10a. Prepared according to procedure **E** (172 mg, 0.64 mmol, 64%). Dense colorless oil.



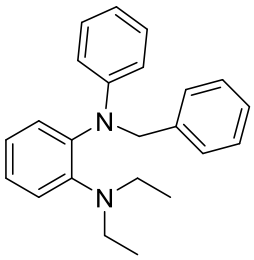
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24-7.17 (m, 4H), 7.03-6.99 (m, 2H), 6.80-6.76 (m, 3H), 3.71-3.69 (m, 4H), 3.28 (s, 3H), 3.04-3.02 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.39 (C_q), 147.86 (C_q), 140.72 (C_q), 128.81 (CH, 2C), 126.14 (CH), 123.01 (CH), 118.98 (CH), 117.69 (CH), 114.29 (CH), 67.47 (CH_2), 50.49 (CH_2), 37.71 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1654, found 269.1646.

Compound 10b. Prepared according to procedure **E** (excluding the addition of NaH) (95 mg, 0.42 mmol, 42%). Dense colorless oil.



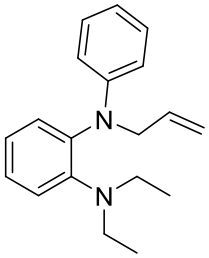
^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.22-7.17 (m, 2H), 7.14 (t, J=8.0 Hz, 2H), 7.00 (dd, J=8.0. 1.2 Hz, 1H), 6.89 (td, J=8.0, 1.2 Hz, 1H), 6.76-6.72 (m, 3H), 3.18 (s, 3H), 2.74 (s, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.25 (C_q), 148.53 (C_q), 139.03 (C_q), 129.22 (CH), 128.81 (CH), 126.16 (CH), 121.18 (CH), 118.21 (CH), 117.00 (CH), 113.51 (CH), 42.23 (CH_3), 37.19 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1548, found 227.1547. The data are in agreement with those reported in the literature.[5]

Compound 10c. Prepared according to procedure **E** (132 mg, 0.40 mmol, 40%) (excluding the addition of NaH). Dense colorless oil.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 7H), 7.17-7.06 (m, 4H), 6.94 (t, J=8.0 Hz, 1H), 6.75 (d, J=8.0 Hz, 2H), 5.00 (s, 2H), 3.12 (q, J=8.0 Hz, 4H), 1.00 (t, J=8.0 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.56 (C_q), 146.61 (C_q), 139.95 (C_q), 139.67 (C_q), 131.04 (CH), 128.83 (CH), 128.36 (CH), 126.87 (CH), 126.38 (CH), 125.71 (CH), 122.44 (CH), 122.17 (CH), 117.11 (CH), 113.75 (CH), 52.41 (CH_2), 45.08 (CH_2), 11.97 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{23}H_{27}N_2$ $[M+H]^+$ 331.2174, found 331.2160.

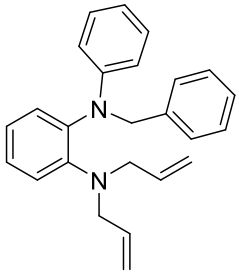
Compound 10d. Prepared according to procedure **E** (excluding the addition of NaH). (129 mg, 0.46 mmol, 46%). Dense colorless oil.



^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18-7.11 (m, 4H), 7.04 (dd, J=8.0, 1.6 Hz, 1H), 6.91 (td, J=8.0, 1.6 Hz, 1H), 6.74-6.88 (m, 3H), 5.98-5.88 (m, 1H), 5.21 (dd, J=16.0, 1.6 Hz, 1H), 5.13 (dd, J=8.0, 1.6 Hz, 1H), 4.32-4.30 (m, 2H), 3.09 (q, J=8.0 Hz, 4H), 0.98 (t, J=8.0 Hz, 6H). ^{13}C-NMR (100

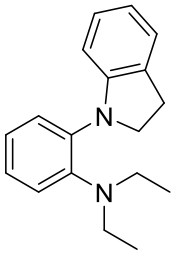
MHz, $CDCl_3$): δ = 148.23 (C_q), 146.89 (C_q), 139.87 (C_q), 135.05 (CH), 130.63 (CH), 128.75 (CH), 125.67 (CH), 121.90 (CH), 116.95 (CH), 116.11 (CH_2), 114.01 (CH), 77.24 (CH), 51.48 (CH_2), 45.06 (CH_2), 12.05 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{19}H_{25}N_2$ $[M+H]^+$ 281.2018, found 228.2012.

Compound 10e. Prepared according to procedure **E** (124 mg, 0.35 mmol, 35%). Dense colorless oil.



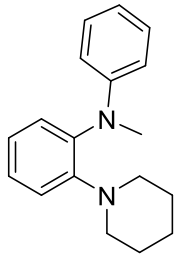
^{1}H-NMR (400 MHz, $CDCl_3$): δ =7.32-7.28 (m, 3H), 7.24-7.17 (m, 2H), 7.12-7.06 (m, 4H), 7.01 (d, J=8.0 Hz, 1H), 6.92 (t, J=8.0 Hz, 1H), 6.73-6.67 (m, 3H), 5.74-5.64 (m, 2H), 5.10 (d, J=4.0 Hz, 2H), 5.05 (s, 2H), 4.99 (s, 2H), 3.65 (d, J=8.0 Hz, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.26 (C_q), 146.64 (C_q), 139.68 (C_q), 139.18 (C_q), 134.74 (CH), 130.84 (CH), 128.88 (CH), 128.41 (CH), 126.87 (CH), 126.48 (CH), 125.79 (CH), 122.61 (CH), 122.57 (CH), 120.64 (CH), 117.68 (CH), 117.40 (CH_2), 113.97 (CH), 53.88 (CH_2), 52.58 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{25}H_{27}N_2$ $[M+H]^+$ 355.2169, found 355.2156.

Compound 10f. Prepared according to procedure **E** (excluding the addition of NaH) (112 mg, 0.42 mmol, 42%). Dense colorless oil.



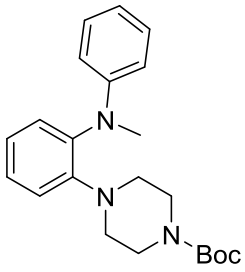
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, J=8.0, 1.2 Hz, 1H), 7.14 (d, J=8.0 Hz, 1H), 7.08 (dd, J=8.0, 1.6 Hz, 1H), 7.05-6.98 (m, 2H), 6.94 (td, J=8.0, 1.6 Hz, 1H), 6.66 (td, J=8.0, 1.2 Hz, 1H), 6.55 (d, J=8.0 Hz, 1H), 3.91 (br s, 2H), 3.15-3.10 (m, 6H), 1.01 (t, J=8.0 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.33 (C_q), 146.17 (C_q), 138.63 (C_q), 130.14 (C_q), 126.88 (CH), 124.77 (CH), 124.55 (CH), 124.15 (CH), 121.73 (CH), 121.40 (CH), 117.36 (CH), 108.25 (CH), 52.06 (CH_2), 45.15 (CH_2), 28.81 (CH_2), 12.17 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{23}N_2$ $[M+H]^+$ 267.1861, found 267.1866.

Compound 10g. Prepared according to procedure procedure **F** (178 mg, 0.67 mmol, 67%). Procedure **E** afforded a 40% yield. Pale yellow solid, m.p.: 70 ^{o}C.

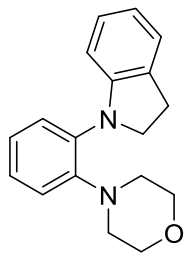


^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, J=8.0 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 7.01 (d, J=8.0 Hz, 1H), 6.92 (td, J=8.0, 1.2 Hz, 1H), 6.76-6.31 (m, 3H), 3.25 (s, 3H), 2.94-2.92 (m, 4H), 1,56-1.53 (m, 4H), 1.49-1.47 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.52 (C_q), 148.63 (C_q), 140.79 (C_q), 128.66 (CH), 128.64 (CH), 125.90 (CH), 122.16 (CH), 119.56 (CH), 117.12 (CH), 114.00 (CH), 51.61 (CH_2), 37.51 (CH_3), 26.64 (CH_2), 24.47 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{23}N_2$ $[M+H]^+$ 267.1861, found 267.1862.

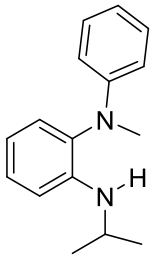
Compound 10h. Prepared according to procedure **F** (268 mg, 0.73 mmol, 73%). Pale orange solid, m.p.: 72 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20-7.13 (m, 4H), 6.99 (t, J=8.0 Hz, 2H), 6.77-6.71 (m, 3H), 3.37 (br s, 4H), 3.25 (s, 3H), 2.94 (br s, 4H), 1.44 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.75 (C_q), 148.36 (C_q), 147.99 (C_q), 140.96 (C_q), 128.75 (CH), 128.68 (CH), 126.07 (CH), 123.21 (CH), 119.42 (CH), 117.65 (CH), 114.24 (CH), 79.66 (C_q), 50.04 (br s, CH_2), 44.50 (br s, CH_2), 43.45 (br s, CH_2), 37.94 (CH_3), 28.43 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{17}H_{21}N_3$ $[M\text{-Boc} + H]^+$ 267.1730, found 267.1731.



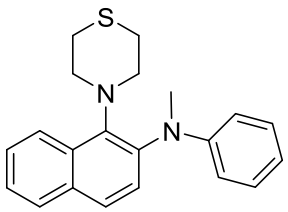
Compound 10i. Prepared according to Procedure **F** (165 mg, 0.60 mmol, 60%). Procedure **E** afforded a 54% yield. Pale orange solid, m.p.: 78 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J=8.0 Hz, 1H), 7.17-7.12 (m, 2H), 7.04-6.99 (m, 3H), 6.70 (t, J=8.0 Hz, 1H), 6.58 (d, J=8.0 Hz, 1H), 3.97 (br s, 2H), 3.75-3.73 (m, 4H), 3.14 (t, J=8.0 Hz, 2H), 3.07 (br s, 4H).^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.51 (C_q), 147.07 (C_q), 137.73 (C_q), 130.26 (C_q), 126.83 (CH), 125.36 (CH), 124.65 (CH), 123.84 (CH), 122.81 (CH), 118.75 (CH), 117.96 (CH), 109.12 (CH), 67.40 (CH_2), 52.13 (CH_2), 50.49 (CH_2), 28.80 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{21}N_2O$ $[M+H]^+$ 281.1654, found 281.1640.



Compound 10j. Prepared according to procedure **F** (144 mg, 0.60 mmol, 60%), using 1.5 equiv of *O*-benzoyl *N*-isopropyl hydroxylamine. Dense colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24-7.16 (m, 3H), 7.01 (d, J=8.0 Hz, 1H), 6.81-6.76 (m, 2H), 6.70-6.67 (m, 3H), 4.12 (br s, 1H), 3.69 (sep, 1H), 3.16 (s, 3H), 1.18 (d, J=4.0 Hz, 6H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.49 (C_q), 144.72 (C_q), 134.59 (C_q), 128.98 (CH), 127.81 (CH), 127.63 (CH), 117.66 (CH), 116.92 (CH), 113.83 (CH), 111.76 (CH), 43.94 (CH), 38.69 (CH_3), 23.04 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{16}H_{21}N_2$ $[M+H]^+$ 241.1705, found 241.1714.

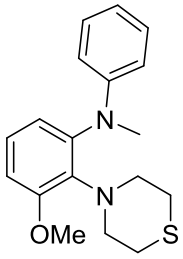


Compound 10k. Prepared according to procedure **E** (177 mg, 0.53 mmol, 53%). Dense colorless liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, J=8.0 Hz, 1H), 7.83 (d, J=8.0 Hz, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.56-7.48 (m, 2H), 7.19 (t, J=8.0 Hz, 2H), 7.13 (d, J=8.0 Hz, 1H), 6.75 (t, J=8.0 Hz, 1H), 6.60 (d, J=8.0 Hz, 2H), 3.43-3.40 (m, 4H), 3.27 (s, 3H), 3.15-3.08 (m, 2H), 2.48-2.45 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.37 (C_q), 146.23 (C_q), 140.34 (C_q), 133.52 (C_q), 132.58 (C_q), 128.89 (CH), 128.25 (CH), 128.17 (CH), 126.63 (CH), 126.02 (CH), 125.93 (CH), 124.40 (CH),

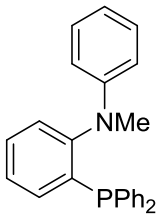


117.18 (CH), 113.49 (CH), 53.45 (CH_2), 41.30 (CH_3), 28.77 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{21}H_{23}N_2S$ $[M+H]^+$ 335.1582, found 335.1573.

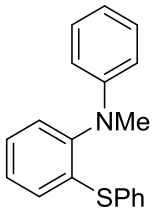
Compound 10l. Prepared according to procedure **E** (94 mg, 0.30 mmol, 30%). White solid, m.p.: 108 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.15 (t, J=8.0 Hz, 2H), 7.10 (t, J=8.0 Hz, 1H), 6.80 (t, J=8.0 Hz, 2H), 6.70 (t, J=8.0 Hz, 1H), 6.59 (d, J=8.0 Hz, 2H), 3.84 (s, 3H), 3.21 (s, 3H), 3.19 (br s, 4H), 2.41-2.39 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 158.89 (C_q), 149.77 (C_q), 146.05 (C_q), 139.08 (C_q), 128.71 (CH), 125.85 (CH), 121.67 (CH), 116.88 (CH), 113.30 (CH), 109.76 (CH), 55.57 (CH_3), 52.64 (CH_2), 39.94 (CH_3), 28.32 (CH_2). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{22}N_2OSNa$ $[M+ Na]^+$ 337.1351, found 337.1348.



Compound 11a. The synthesis of compound **11a** was carried out starting form 0.5 mmol of *N*-methyl aniline following the scaled-down fisrt part of procedure **E**. After warming the reaction mixture to 0 °C in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (1 mg, 2 mol%), PPh_2Cl (103 µL, 0.6 mmol, 1.2 equiv) in dry THF (2 mL) under N_2 at 25 °C. After the addition was finished the mixture was strirred for additional 2.5 h at 50 °C and the solvent was taken to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 95% Pet. Ether/5% Et_2O) to afford the product **11a** (121 mg, 0.329 mmol, 66% yield). Pale yellow solid, m.p.: 70-72 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.29 (td, J=7.6, 1.5 Hz, 1H), 7.21 (br m, 10H), 7.12 (t, J=7.5 Hz, 1H), 7.06-6.95 (m, 4H), 6.60 (t, J=7.4 Hz, 1H), 6.39 (d, J=8.1 Hz, 2H), 2.83 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 152.54 (d, J_{CP}= 23.3 Hz, C_q), 149.36 (C_q), 139.18 (d, J_{CP}= 11.4 Hz, C_q), 137.05 (d, J_{CP}= 12.3 Hz, C_q), 134.51 (CH), 133.97 (d, J_{CP}= 20.4 Hz, CH), 130.82 (CH), 128.67 (d, J_{CP}= 2.79 Hz, CH), 128.54 (CH), 128.50 (CH), 128.32 (d, J_{CP}= 6.90 Hz, CH), 126.9 (CH), 117.3 (CH), 113.63 (CH), 39.92 (d, J_{CP}= 3.93 Hz, CH_3). ^{31}P-NMR (162.29 MHz, $CDCl_3$): -15.01 ppm. MS (+ESI) *m/z* calcd for $C_{25}H_{22}NP$ $[M+H]^+$ 368.1568, found 368.1566.



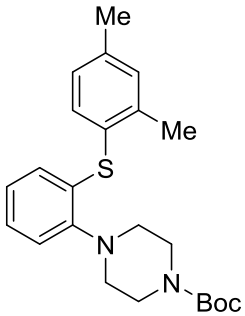
Compound 11b. The synthesis of compound **11b** was carried out starting form 0.5 mmol of *N*-methyl aniline following the scaled-down first part of procedure **E**. After warming the reaction mixture to 0 °C in an ice bath for 15 min, it was added dropwise using a syringe pump (0.05 mmol/min) to a vigorously stirred and previously prepared mixture of CuCl (5 mg, 10 mol%), phenyl disulfide (148 mg, 0.6 mmol, 1.2 equiv) in



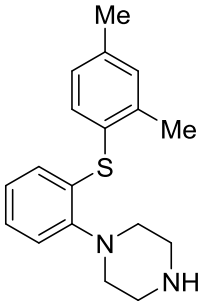
dry THF (2 mL) under N_2 at 25 ^oC. After the addition was finished the mixture was stirred for additional 12 h at R.T. The crude was disluted in CH_2Cl_2 (50 mL) and extracted with 10 % aq NH_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). All the organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The filtrate was taken to dryness and the crude product was purified by column chromatography (silica, gradient from 100% Pet. Ether to 95% Pet. Ether/5% Et_2O) to afford the product **11b** (103 mg, 0.354 mmol, 71% yield). Colorless solid, m.p.: 38-40 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.48-7.45 (m, 2H), 7.38-7.33 (m, 3H), 7.24-7.18 (m, 4H), 7.15-7.11 (m, 1H), 7.02 (m, 1H), 6.78 (tt, J=7.3, 1.0 Hz, 1H), 6.66-6.62 (m, 2H), 3.25 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.83 (C_q), 145.83 (C_q), 138.64 (C_q), 133.93 (CH), 133.32 (C_q), 129.33 (CH), 129.31 (CH), 128.85 (CH), 128.81 (CH), 128.08 (CH), 127.19 (CH), 127.03 (CH), 117.58 (CH), 113.51 (CH), 38.93 (CH_3). MS (+ESI) *m/z* calcd for $C_{19}H_{18}NS$ $[M+H]^+$ 292.1160, found 292.1174. This compound has been previously reported in the literature.[8]

Spectroscopic data for compounds 12 and vortioxetine 13.

Compound 12. Prepared according to procedure **D** (311 mg, 0.78 mmol, 78%). Procedure **C** afforded a 48% isolated yield. Pale yellow solid, m.p.: 80 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J=8.0 Hz, 1H), 7.15 (s, 1H), 7.10-7.01 (m, 3H), 6.87 (t, J=8.0 Hz, 1H), 6.52 (d, J=8.0 Hz, 1H), 3.62-3.60 (m, 4H), 3.02-3.00 (m, 4H), 2.36 (s, 3H), 2.32 (s, 3H), 1,49 (s, 9H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 154.95 (C_q), 148.97 (C_q), 142.39 (C_q), 139.27 (C_q),136.16 (CH), 134.64 (C_q), 131.71 (CH), 127.83 (CH), 127.79 (C_q), 126.24 (CH), 125.50 (CH), 124.60 (CH), 119.88 (CH), 79.69 (C_q), 51.62 (CH_2), 43.77 (br s, CH_2), 28.49 (CH_3), 21.22 (CH_3), 20.62 (CH_3). HR-MS (+ESI) *m/z* calcd for $C_{18}H_{22}N_2S$ $[M\text{-Boc }+H]^+$ 298.1498, found 298.1496. This compound has been previously reported in the literature.[6]



Synthesis of vortioxetine 13. A glass vial was charged with *N*-Boc vortioxetine **11** (91mg, 0.23 mmol) and a magnetic stirer. Dry CH_2Cl_2 (0.5 mL) and trifluoroacetic acid (0.5 mL) were added and the solution was stirred for 1h at room temperature. The solvent was removed, the residue was disolved in CH_2Cl_2 (20 mL) and extracted with sat. $NaHCO_3$aq (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford vortioxetine (63 mg, 0.22 mmol, 95%). Pale yellow solid, m.p: 100 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, J=8.0 Hz, 1H), 7.15 (br s, 1H), 7.08-7.01 (m, 3H), 6.88-6.84 (m, 1H), 6.51 (d, J=8.0 Hz, 1H), 3.08-3.05 (m, 8H), 2.36 (s, 3H), 2.32 (s, 3H), 1.89 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 149.62 (C_q),



142.46 (C_q), 139.19 (C_q), 136.23 (CH), 134.65 (C_q), 131.67 (CH), 128.01 (C_q), 127.79 (CH), 126.10 (CH), 125.44 (CH), 124.29 (CH), 119.88 (CH), 53.05 (CH_2), 46.49 (CH_2), 21.22 (CH_3), 20.62 (CH_3). MS (EI) *m/z* calcd for $C_{18}H_{22}N_2S$ $[M]^+$ 298.4, found 298.1. This compound has been previously reported in the literature.[7]

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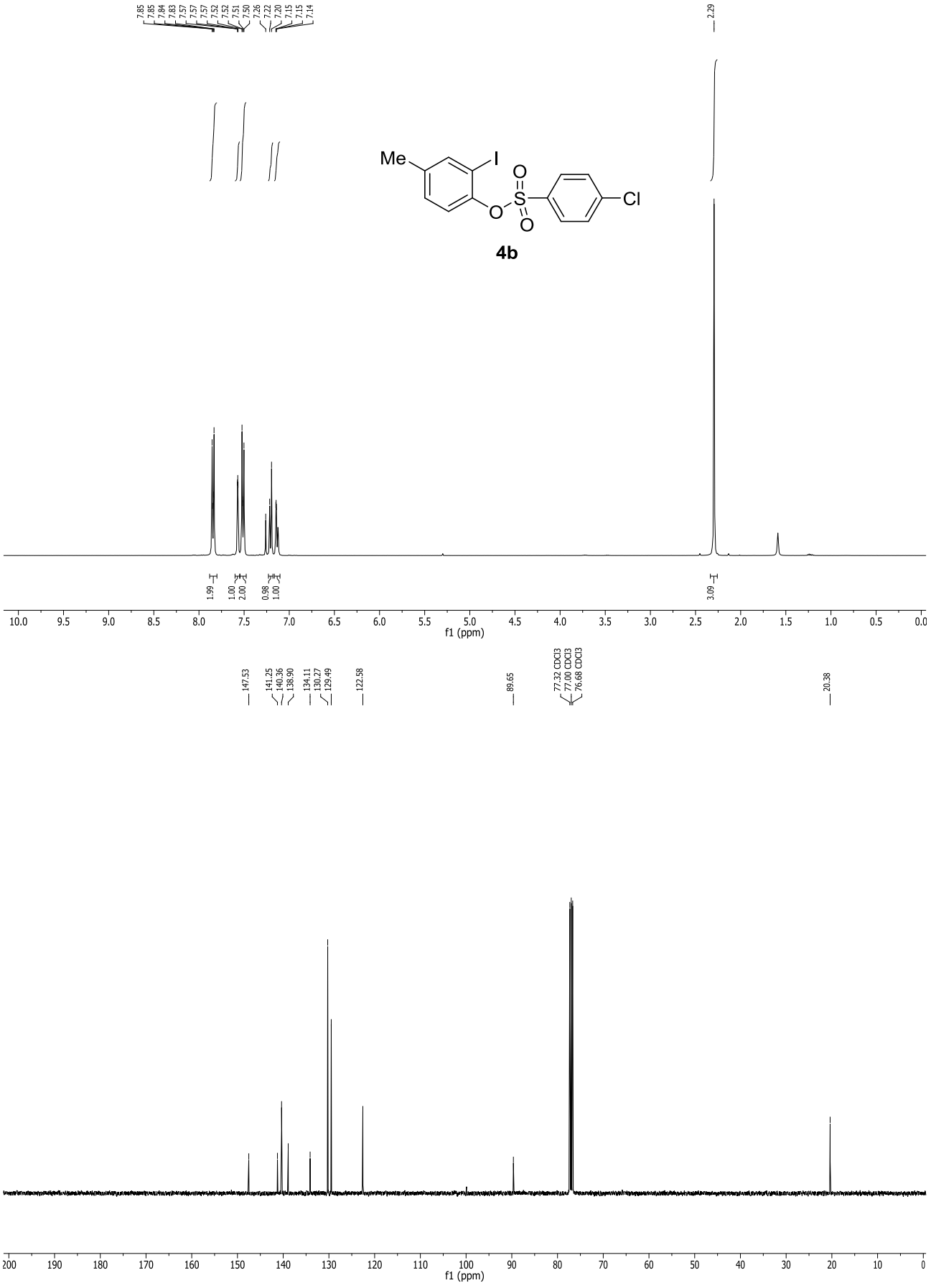
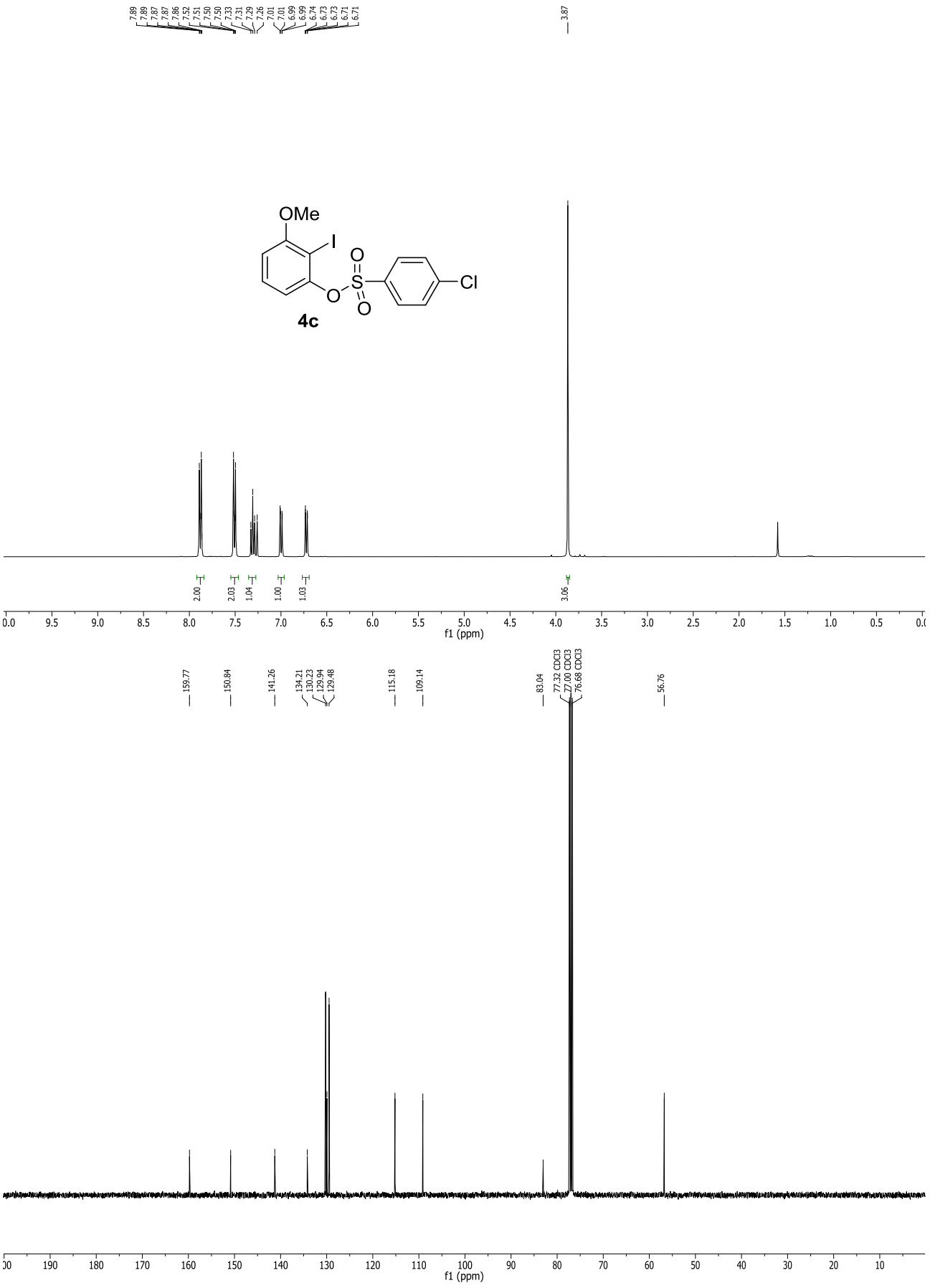
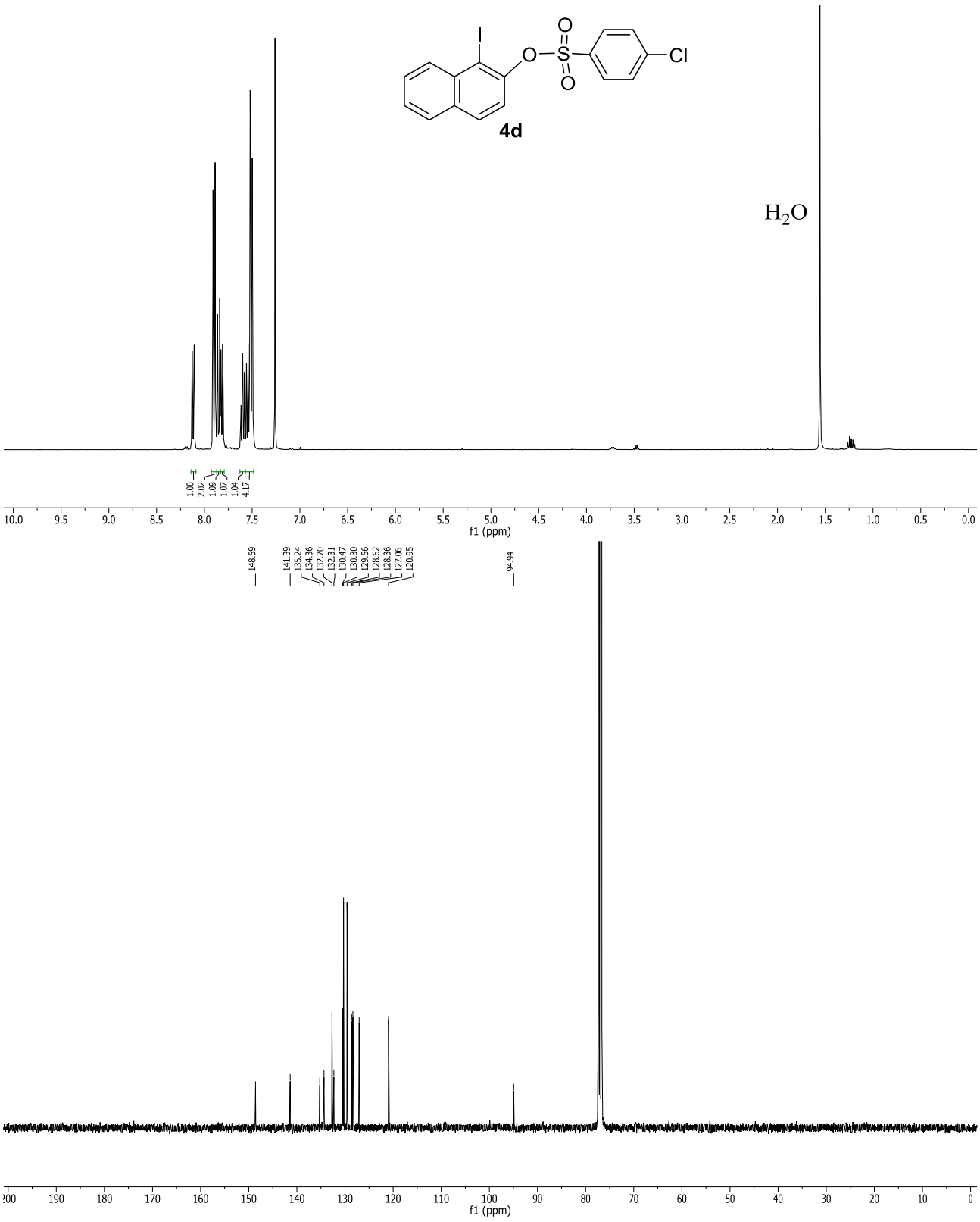
^{1}H and ^{13}C NMR data of compound **4b** (400 and 100 MHz respectively, $CDCl_3$).



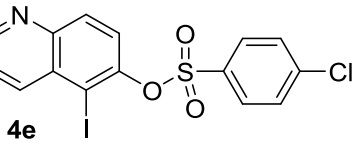
^{1}H and ^{13}C NMR data of compound **4c** (400 and 100 MHz respectively, $CDCl_3$).



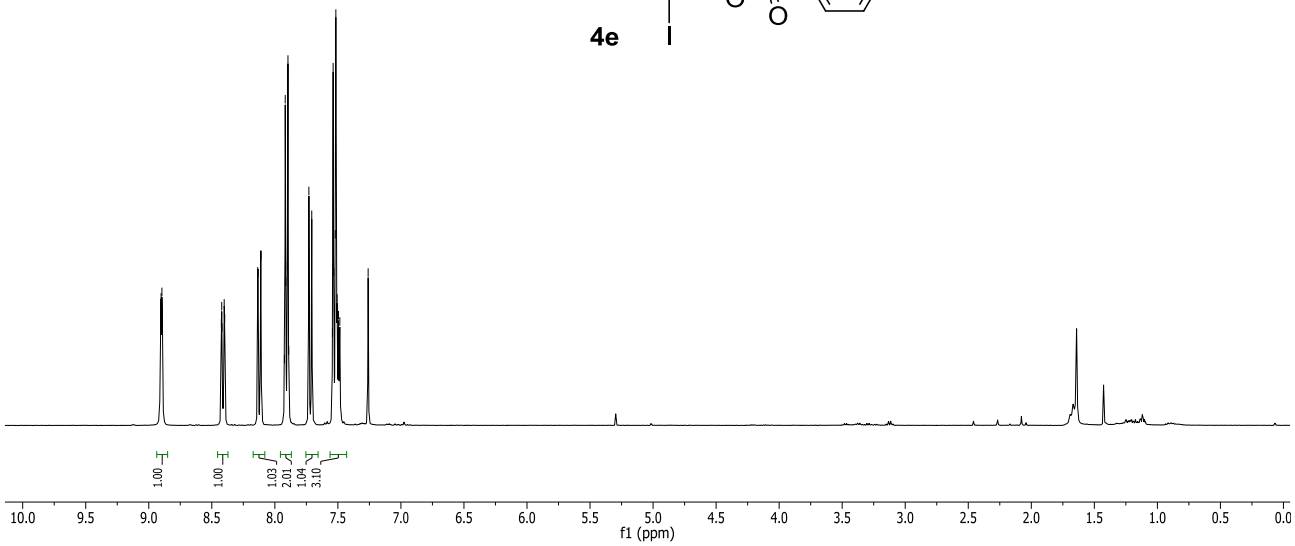
^{1}H and ^{13}C NMR data of compound **4d** (400 and 100 MHz respectively, $CDCl_3$).

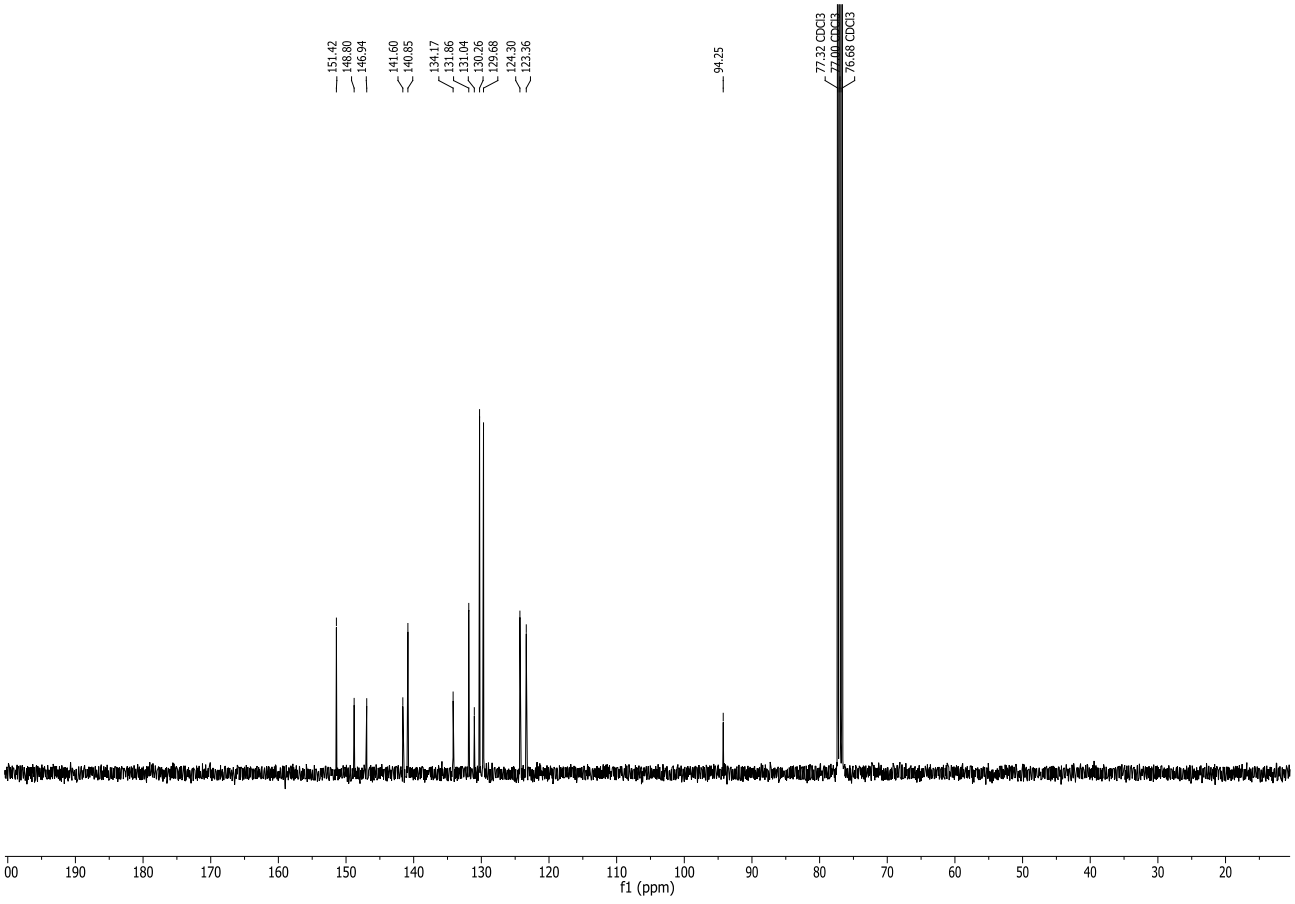


^{1}H and ^{13}C NMR data of compound **4e** (400 and 100 MHz respectively, $CDCl_3$).

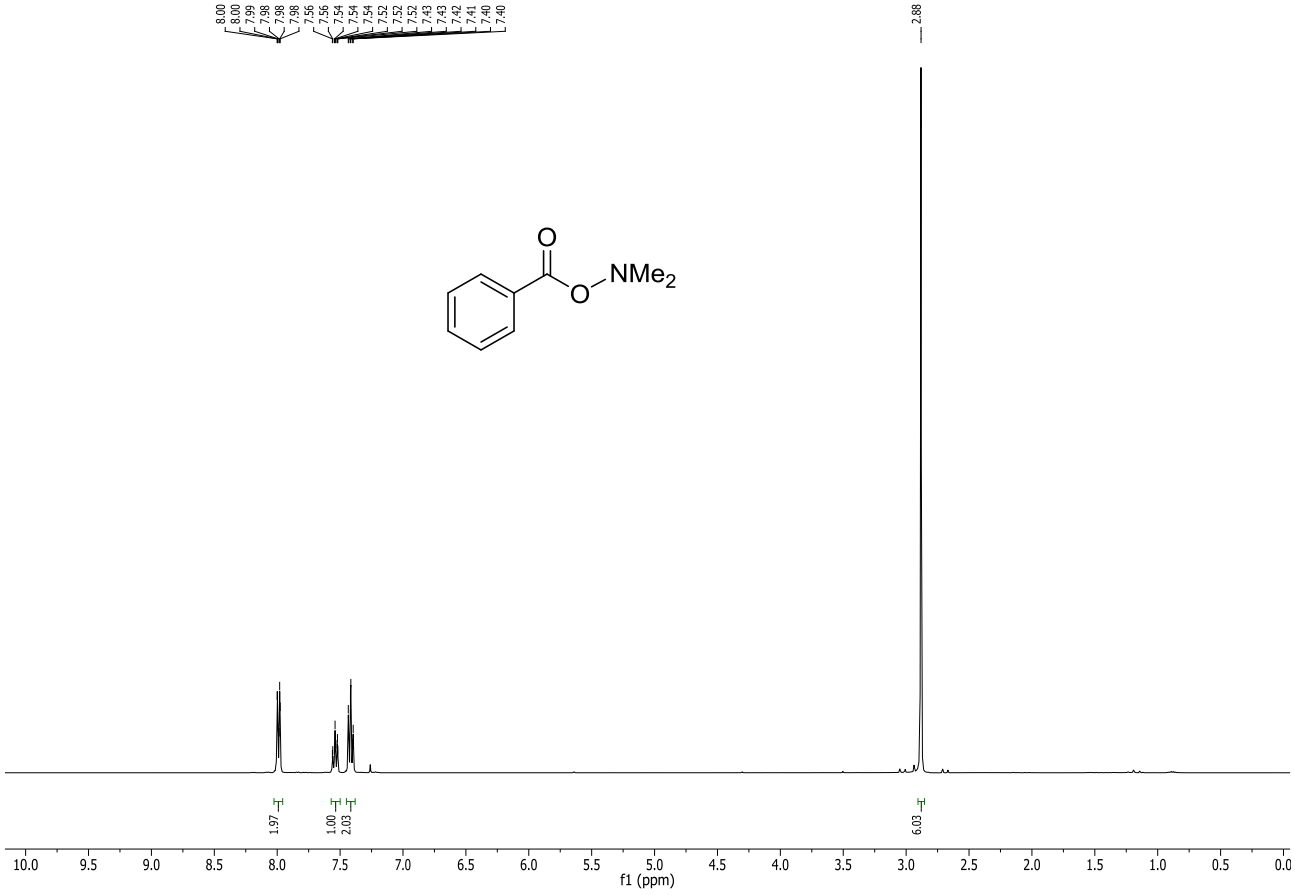


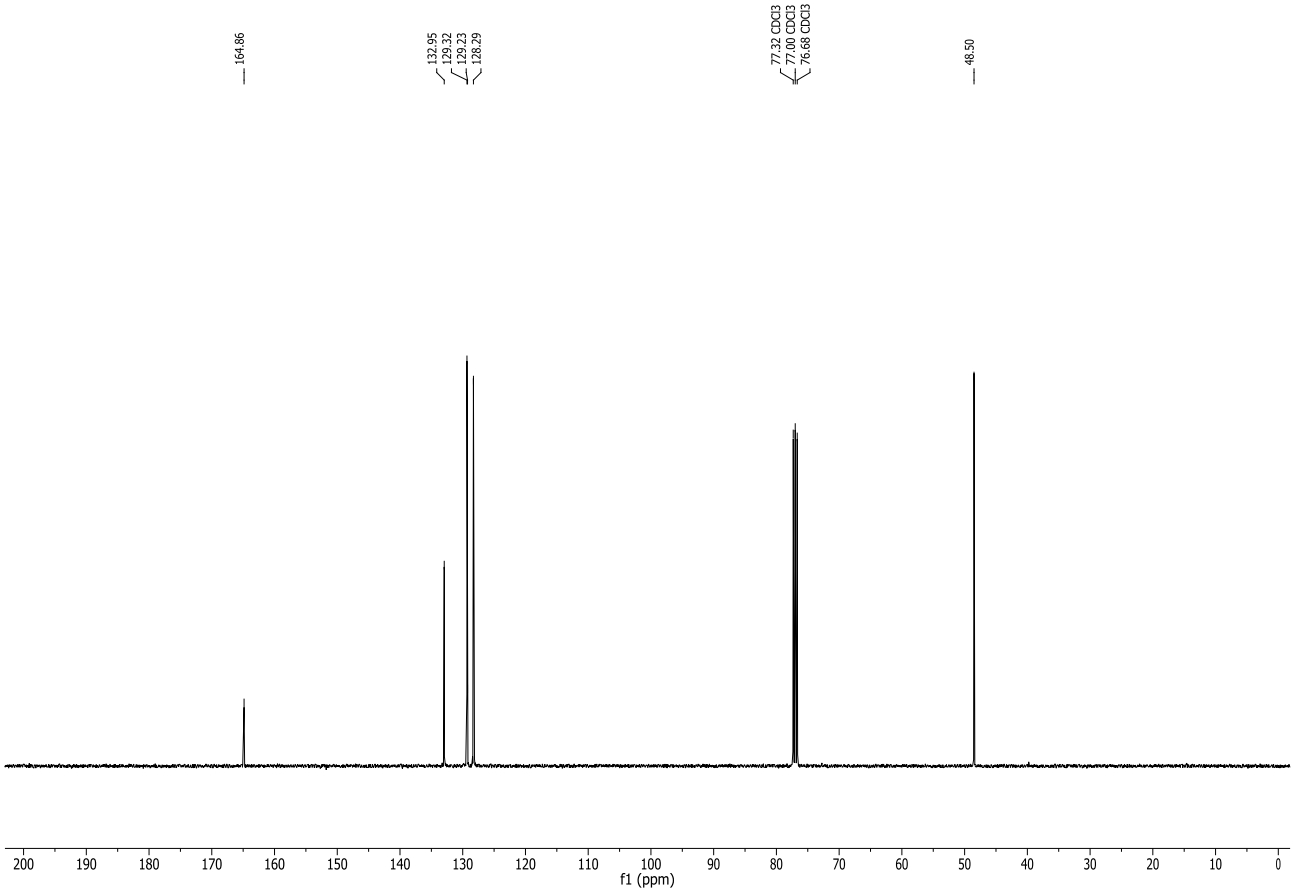
4e



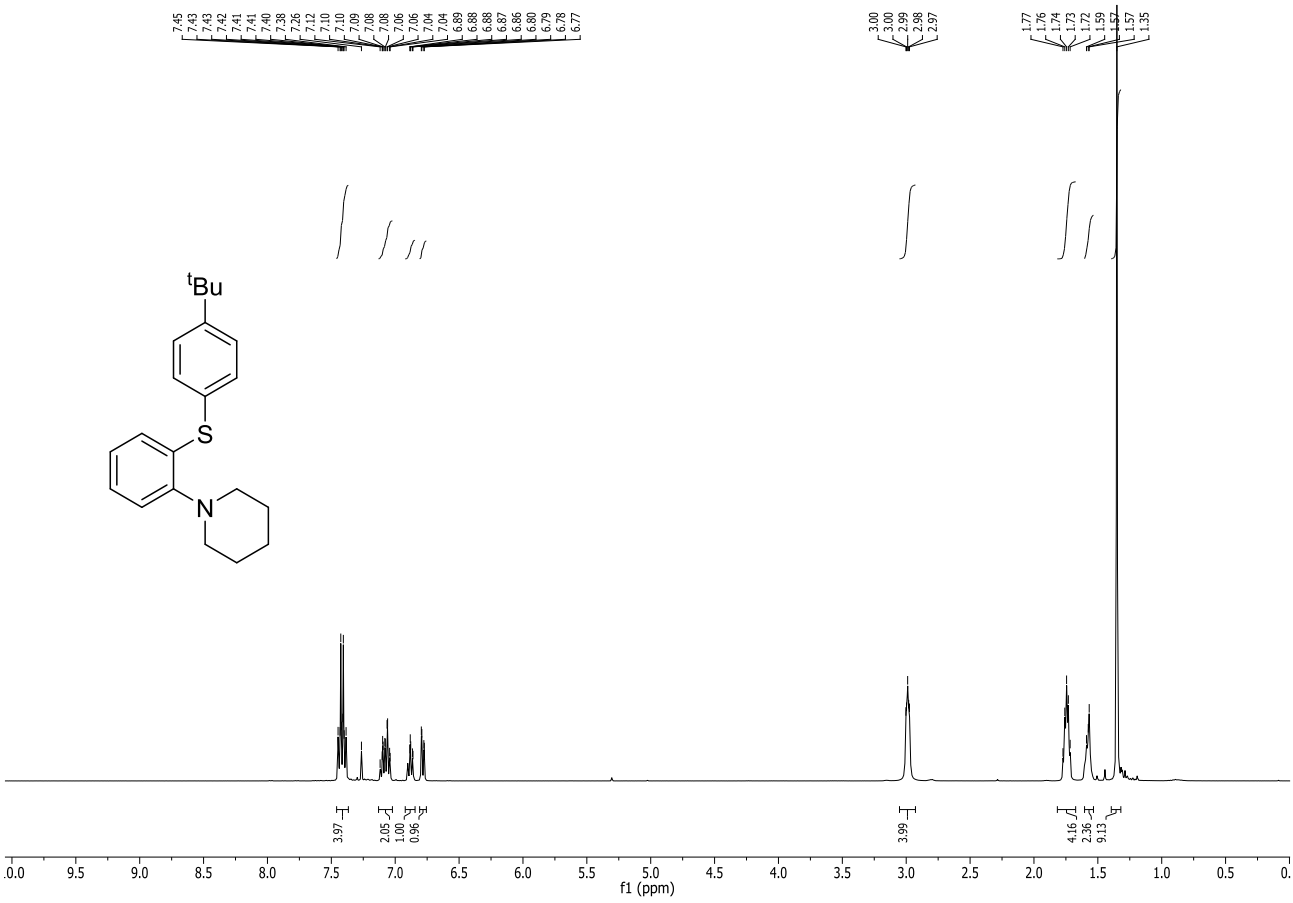


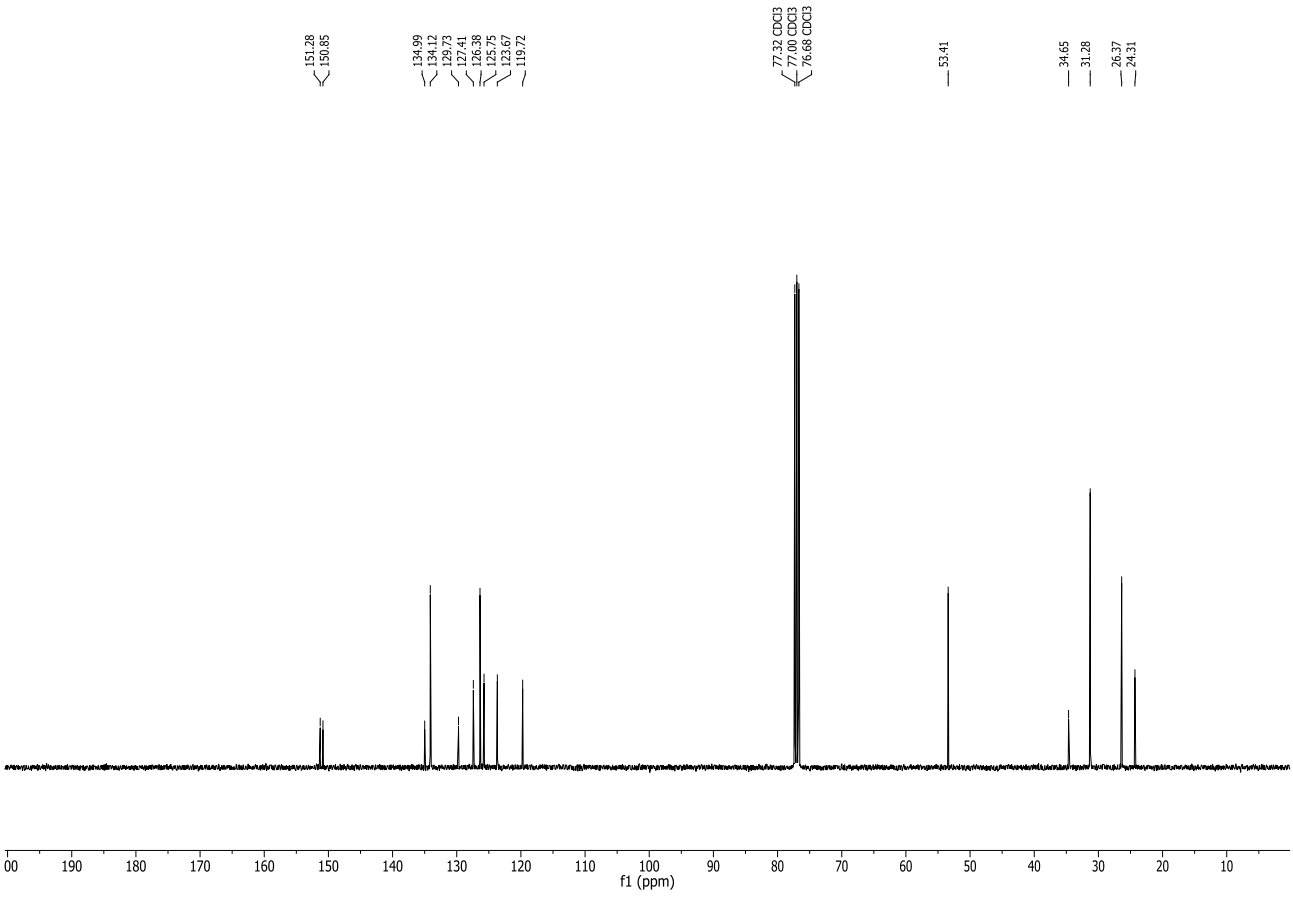
^{1}H and ^{13}C NMR data of *O*-benzoyl *N*,*N*-dimethyl hydroxylamine (400 and 100 MHz respectively, $CDCl_3$).



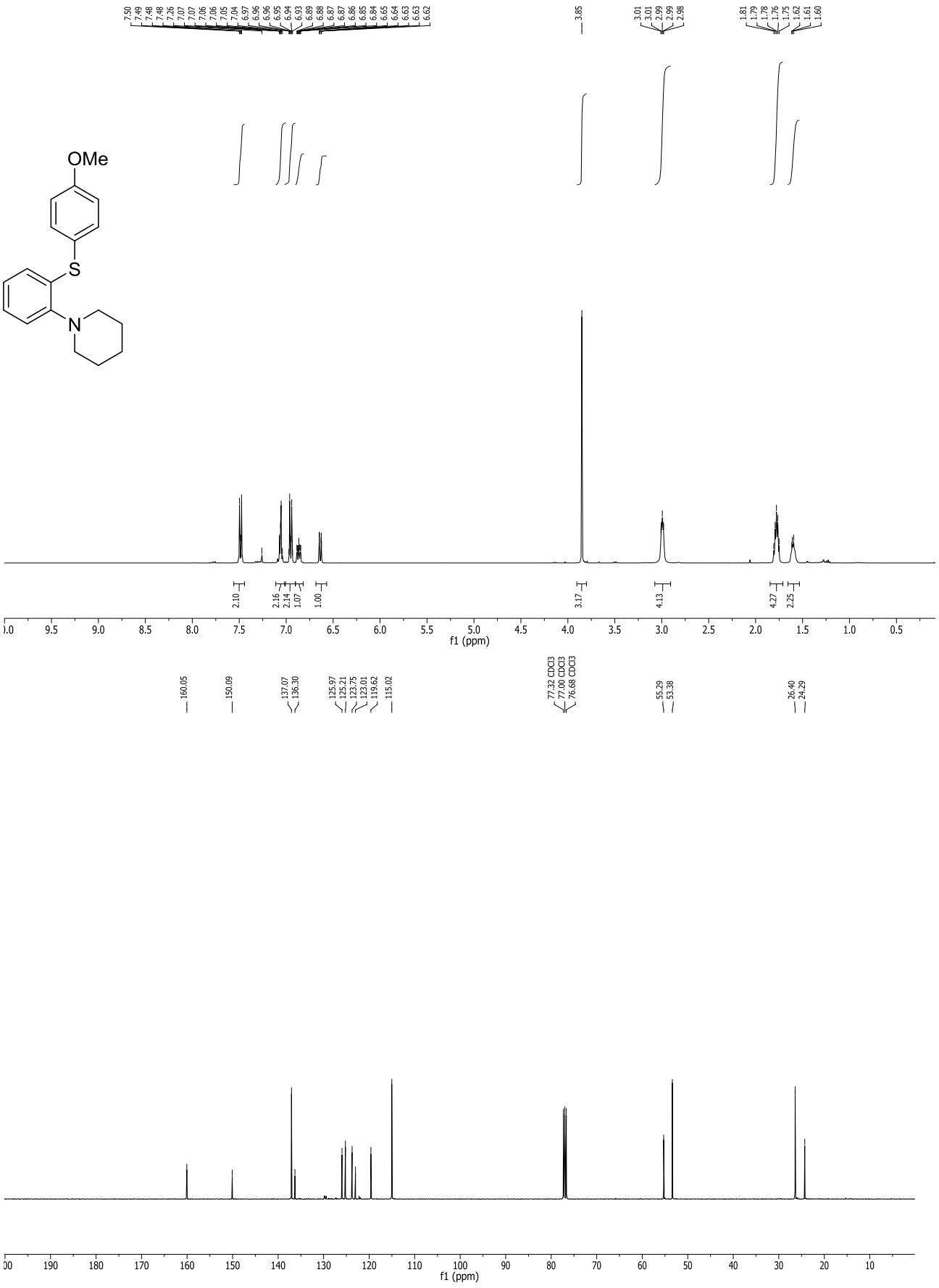


^{1}H and ^{13}C NMR data of compound **7a** (400 and 100 MHz respectively, $CDCl_3$).

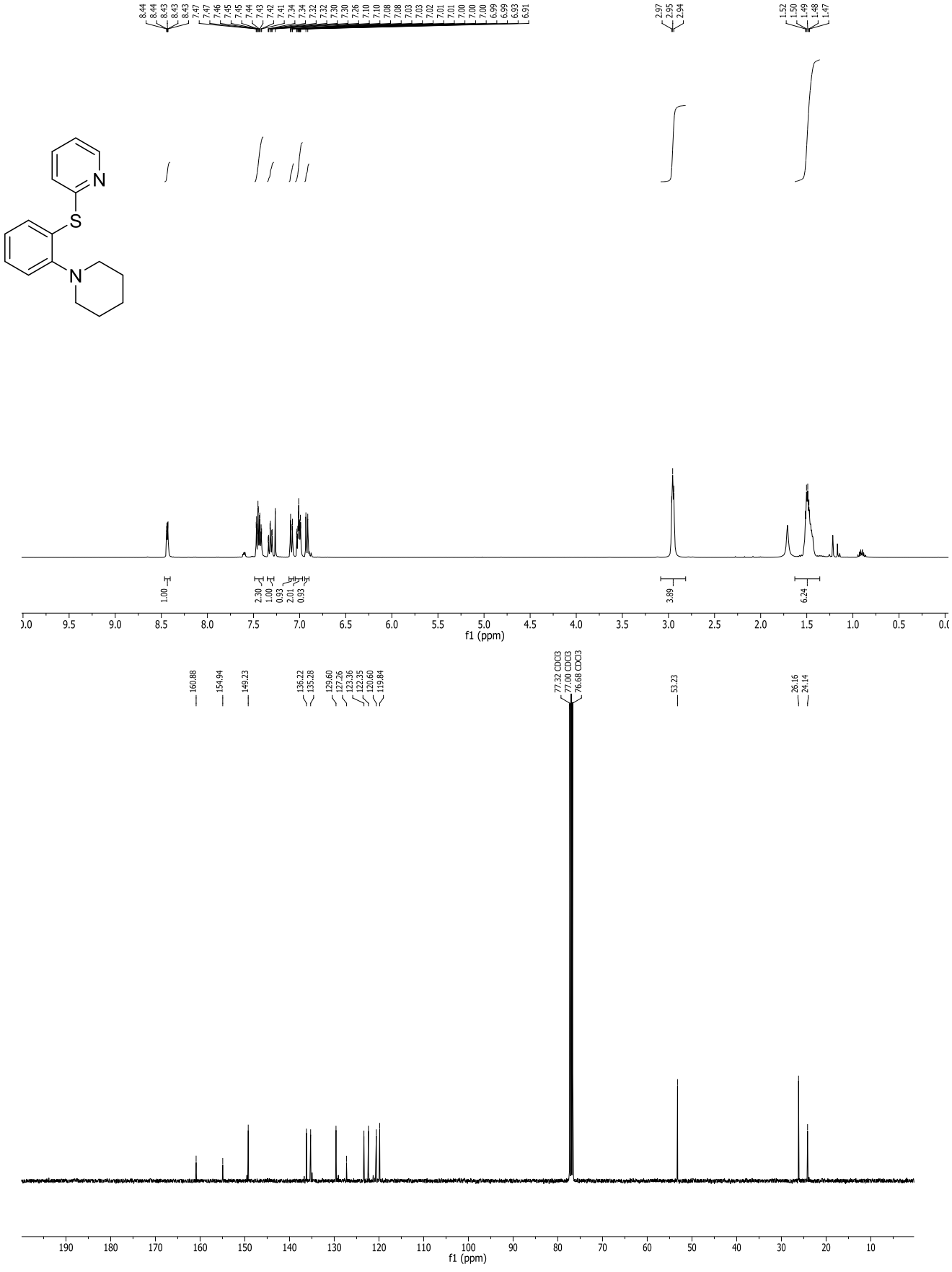




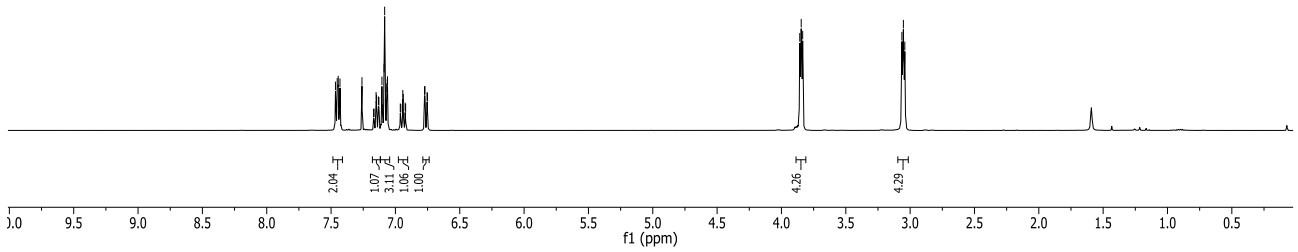
^{1}H and ^{13}C NMR data of compound **7b** (400 and 100 MHz respectively, $CDCl_3$).

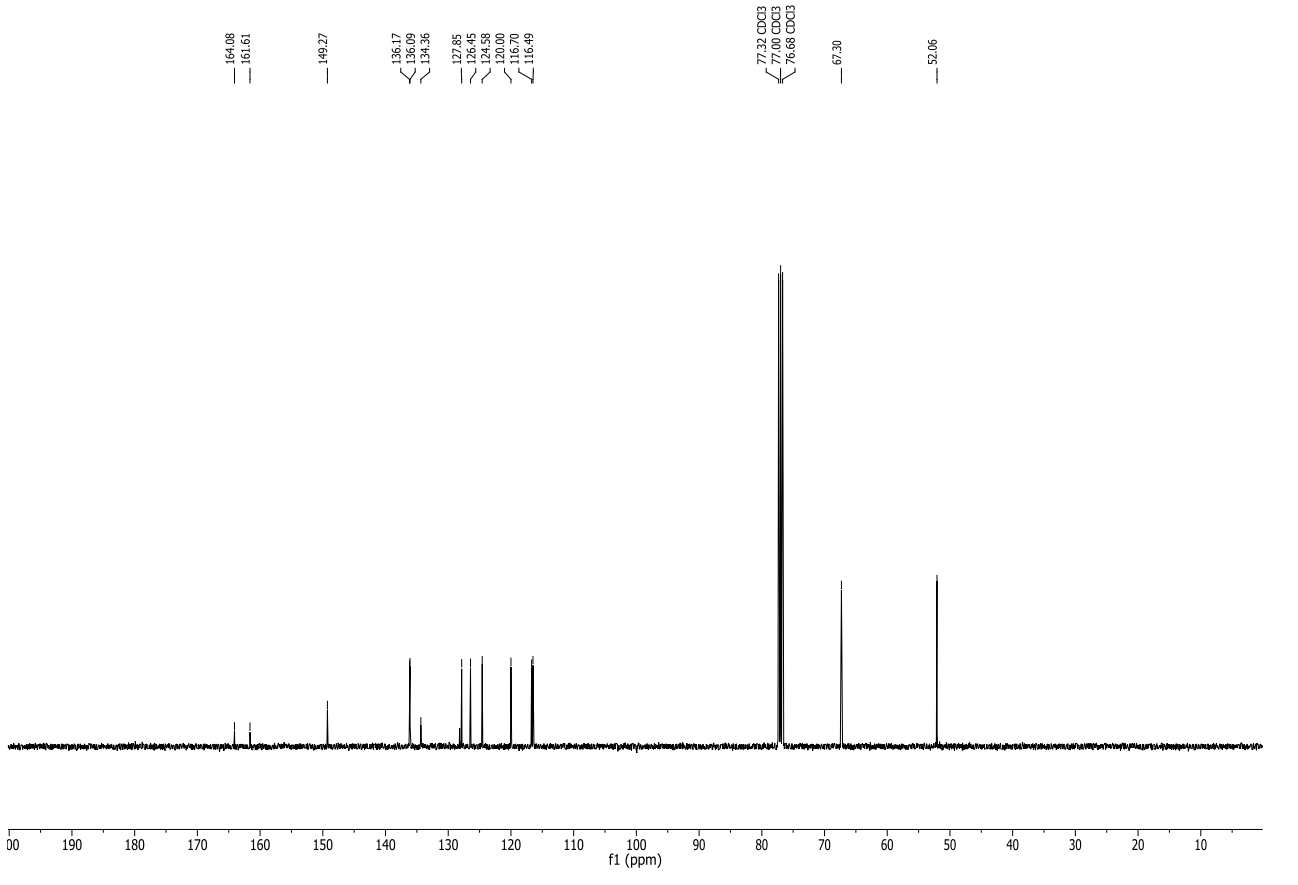


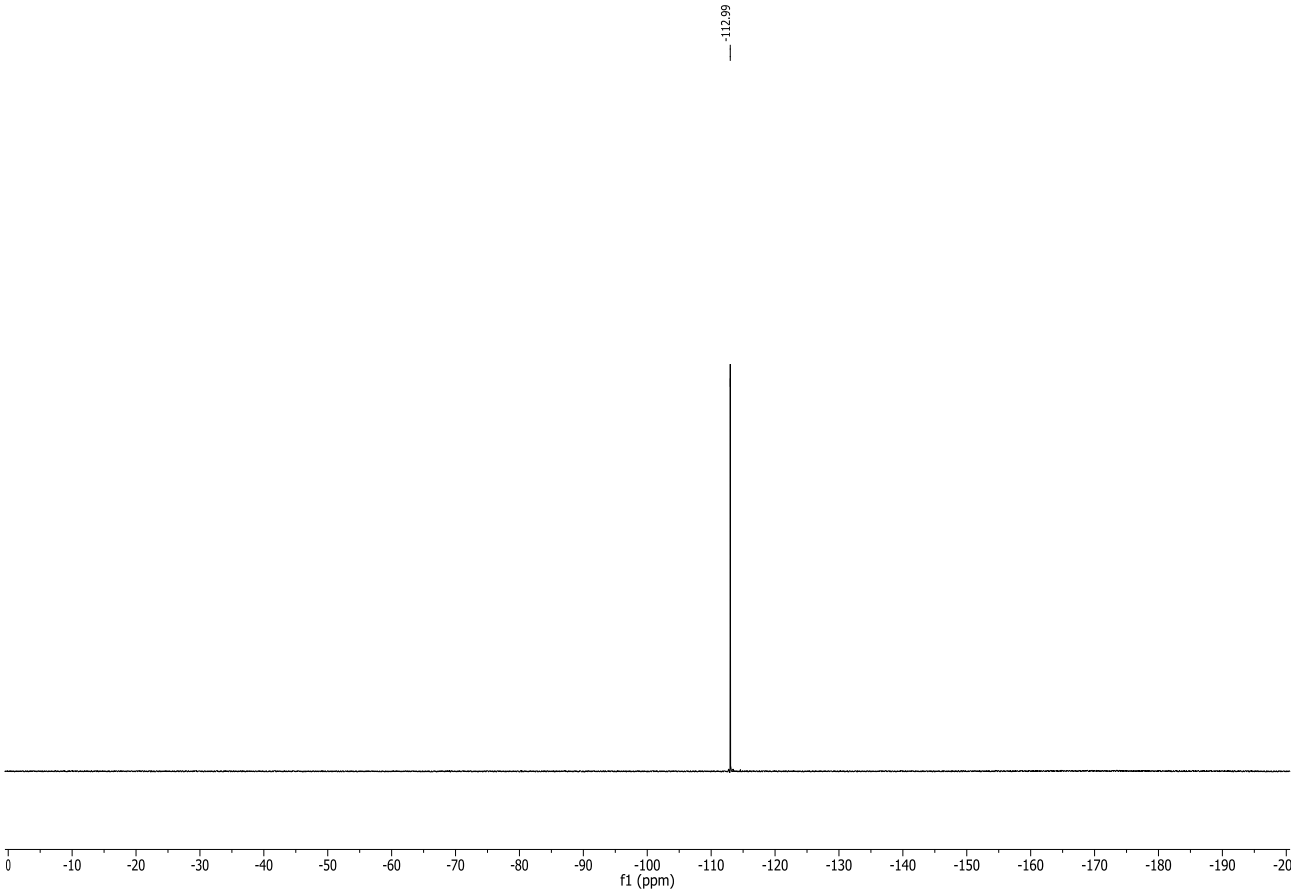
^{1}H and ^{13}C NMR data of compound **7c** (400 and 100 MHz respectively, $CDCl_3$).



^{1}H, ^{13}C NMR and ^{19}F data of compound **7d** (400, 100 and 376 MHz respectively, $CDCl_3$).



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-150
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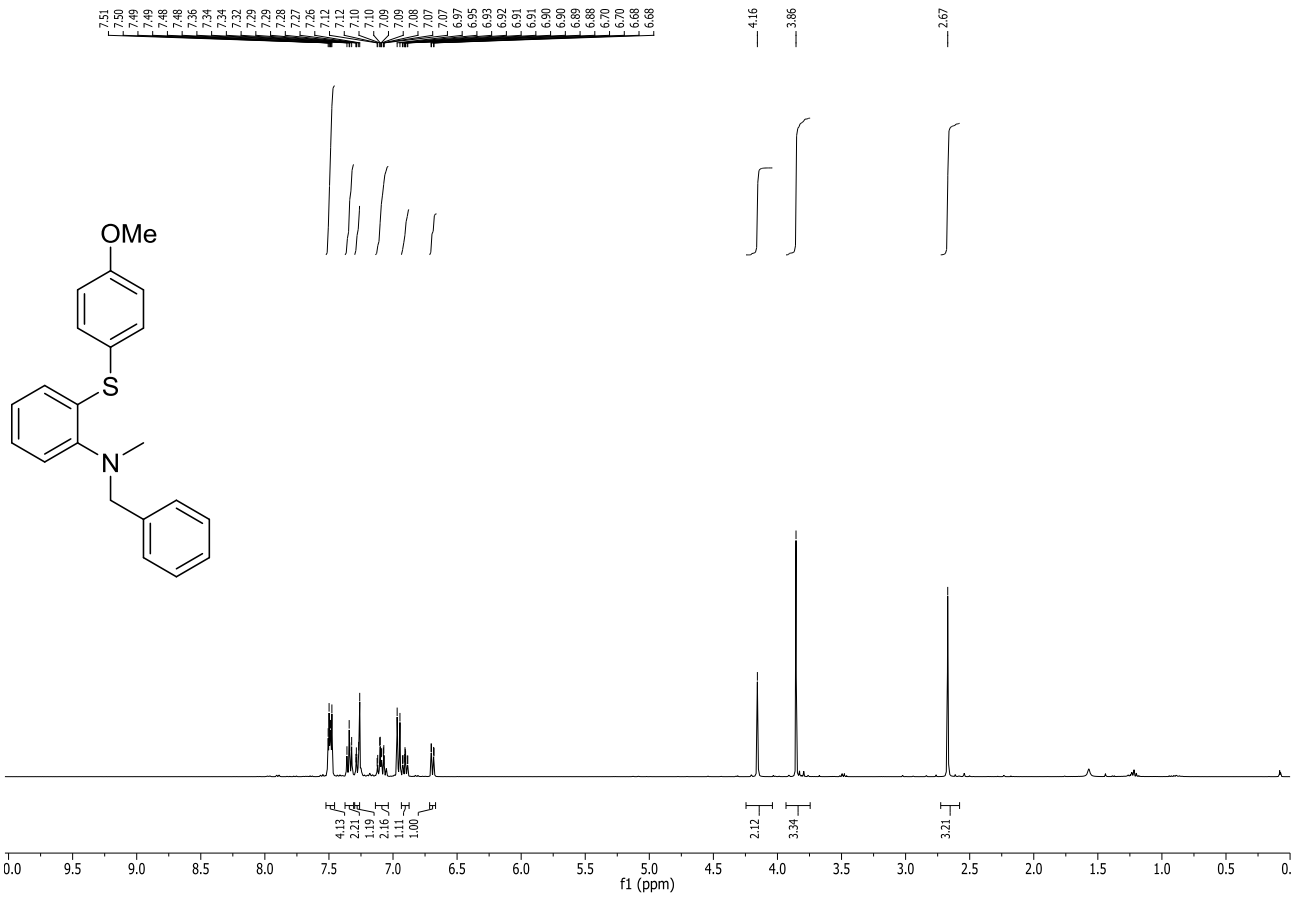
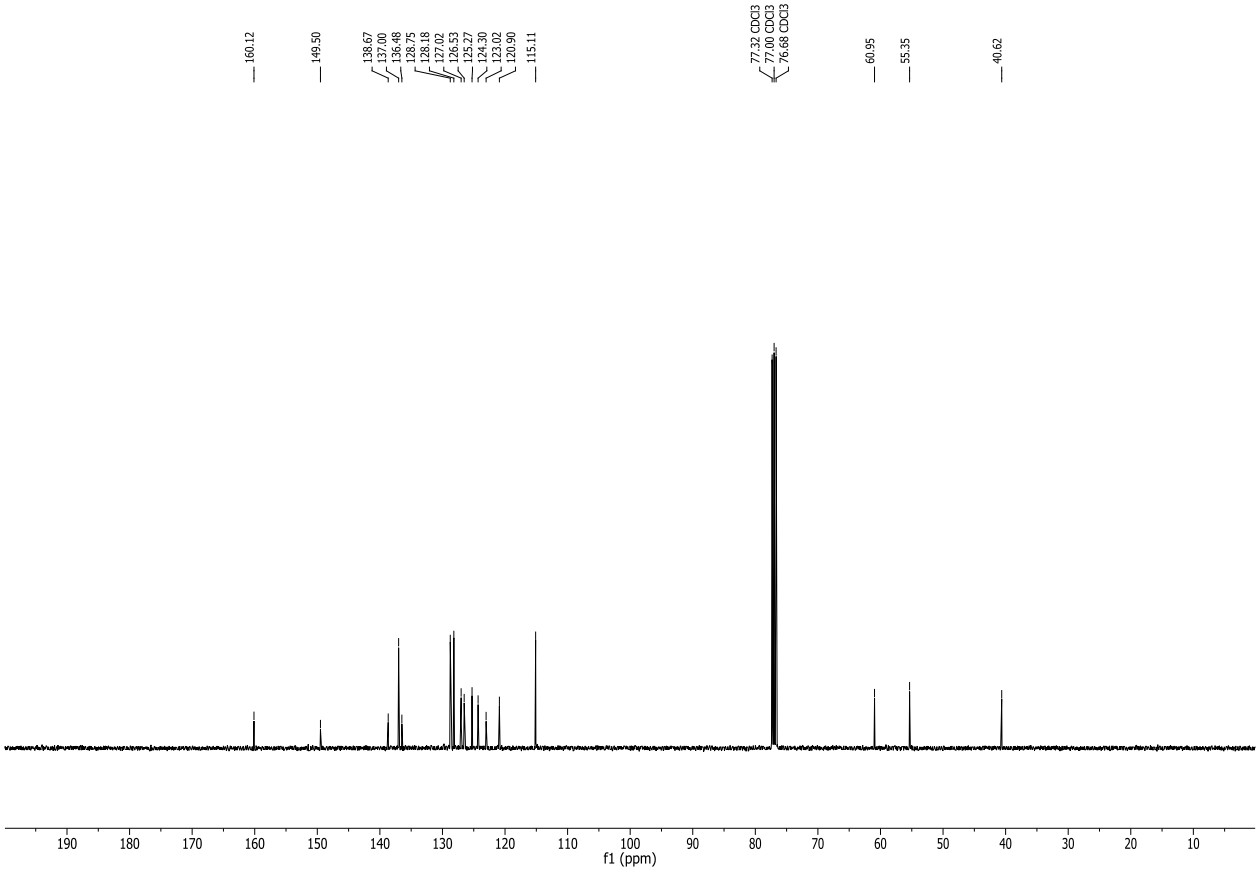
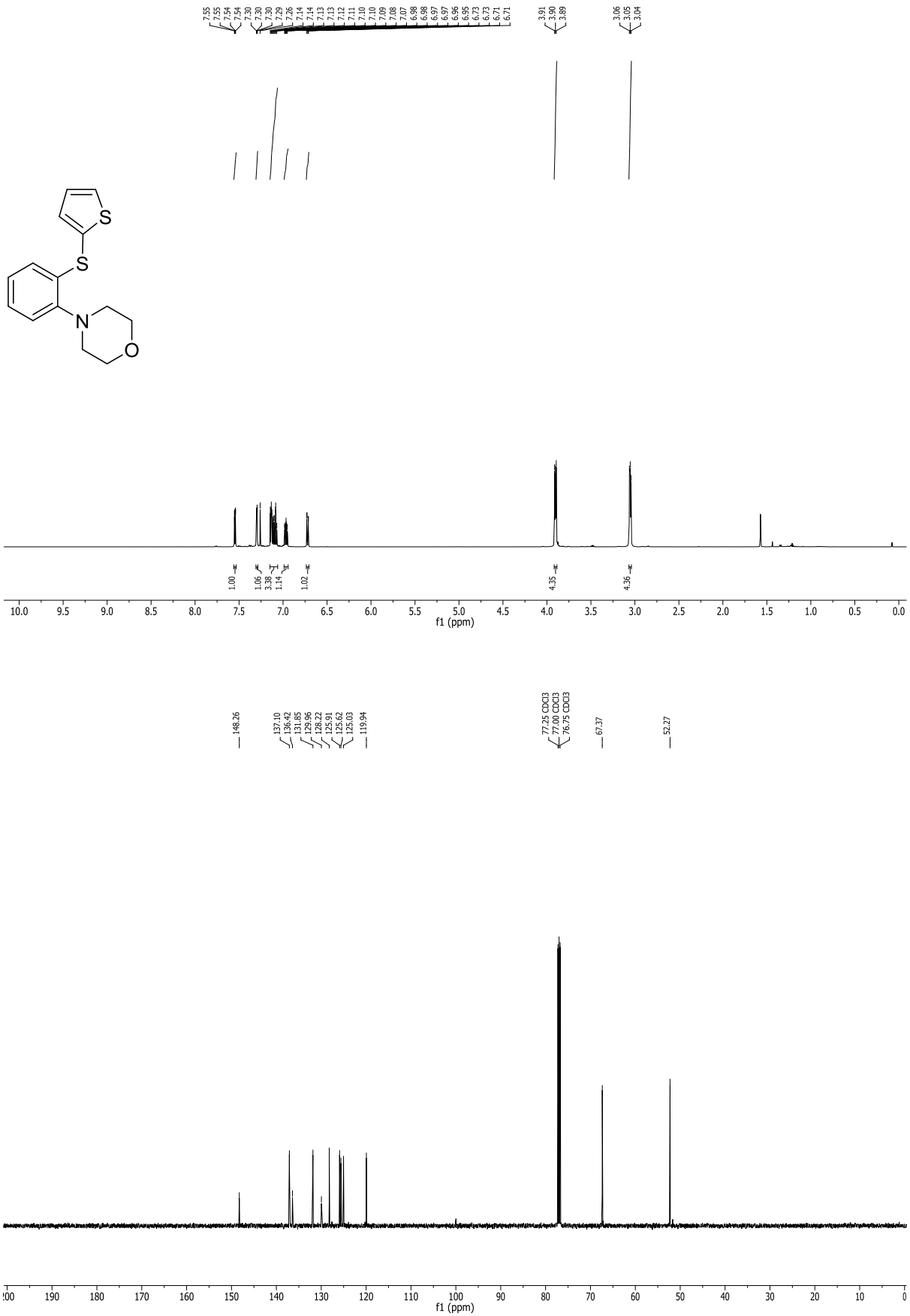
-20
f1 (ppm)

^{1}H and ^{13}C NMR data of compound **7e** (400 and 100 MHz respectively, $CDCl_3$).

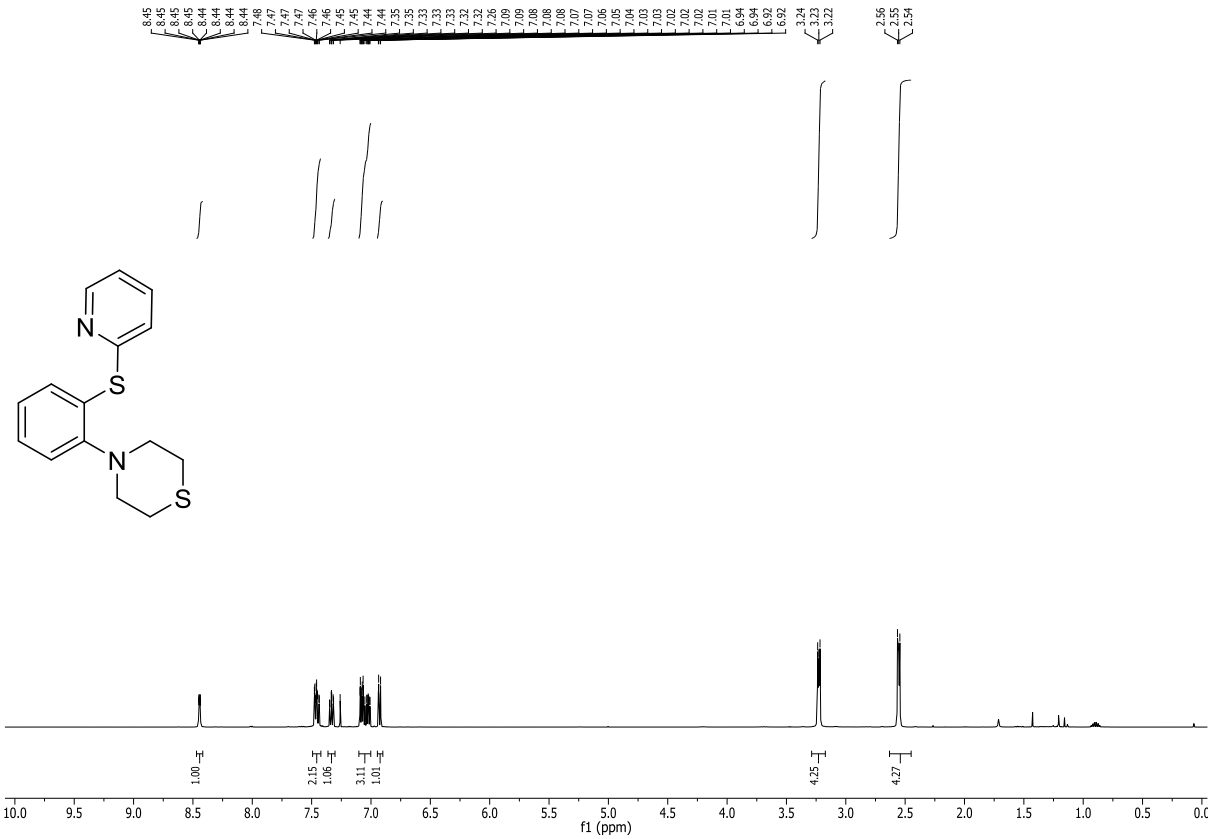


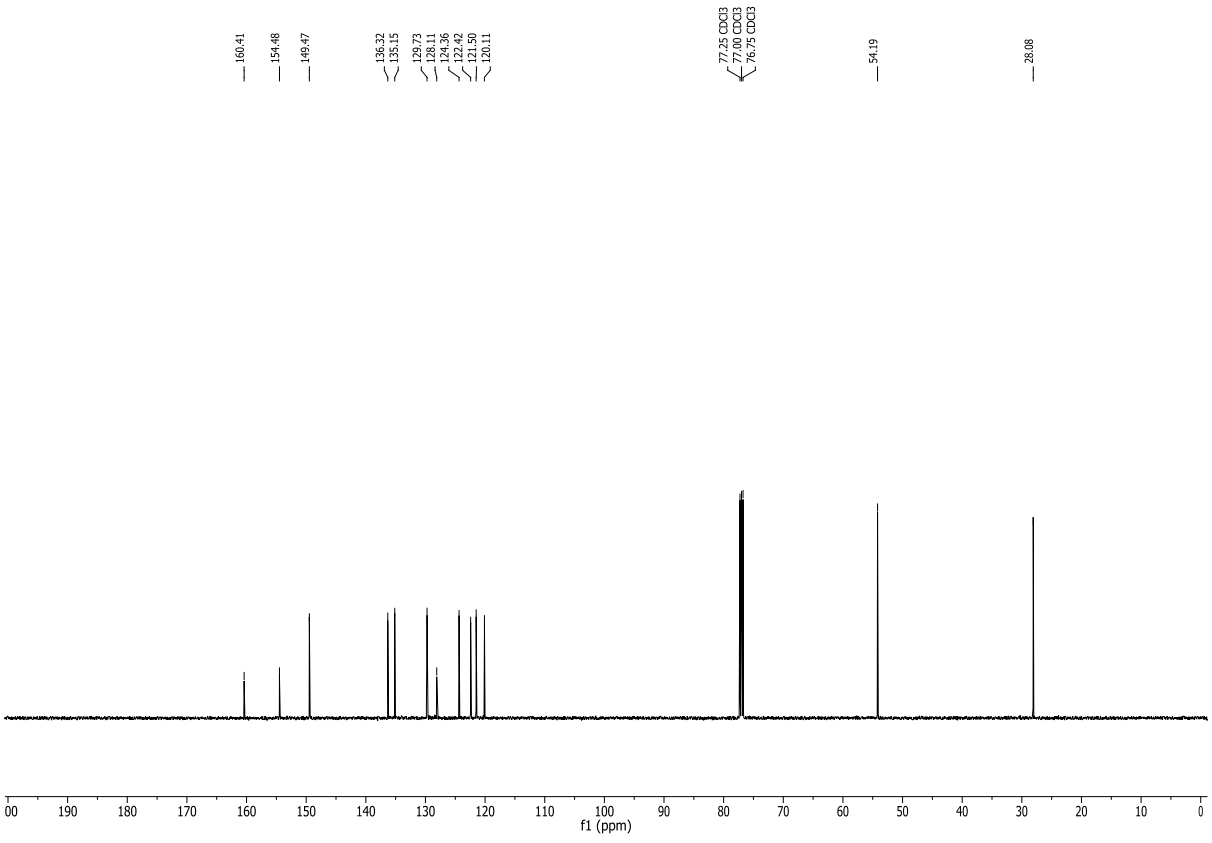


^{1}H and ^{13}C NMR data of compound **7f** (500 and 126 MHz respectively, $CDCl_3$).

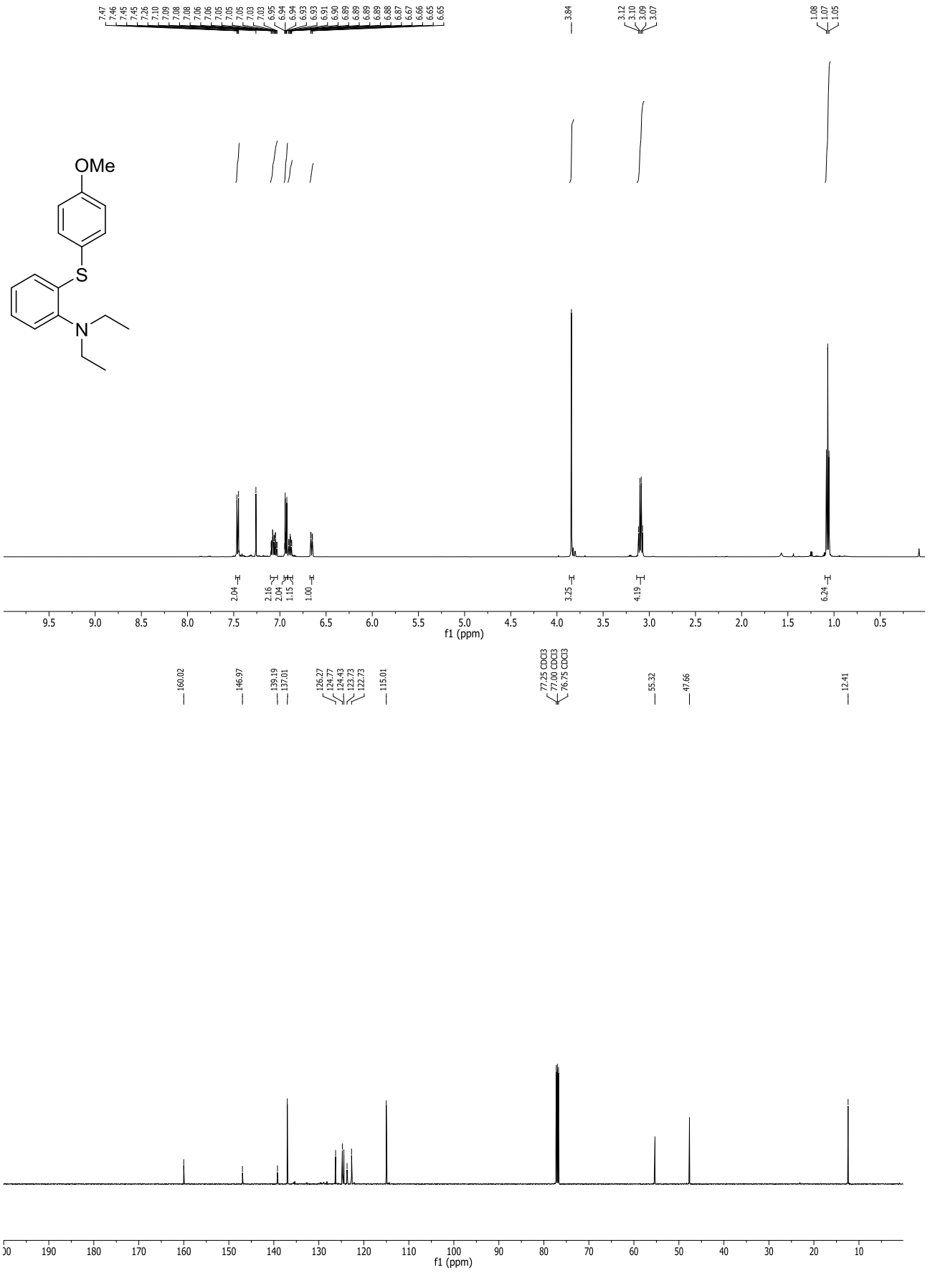


^{1}H and ^{13}C NMR data of compound **7g** (500 and 126 MHz respectively, $CDCl_3$).

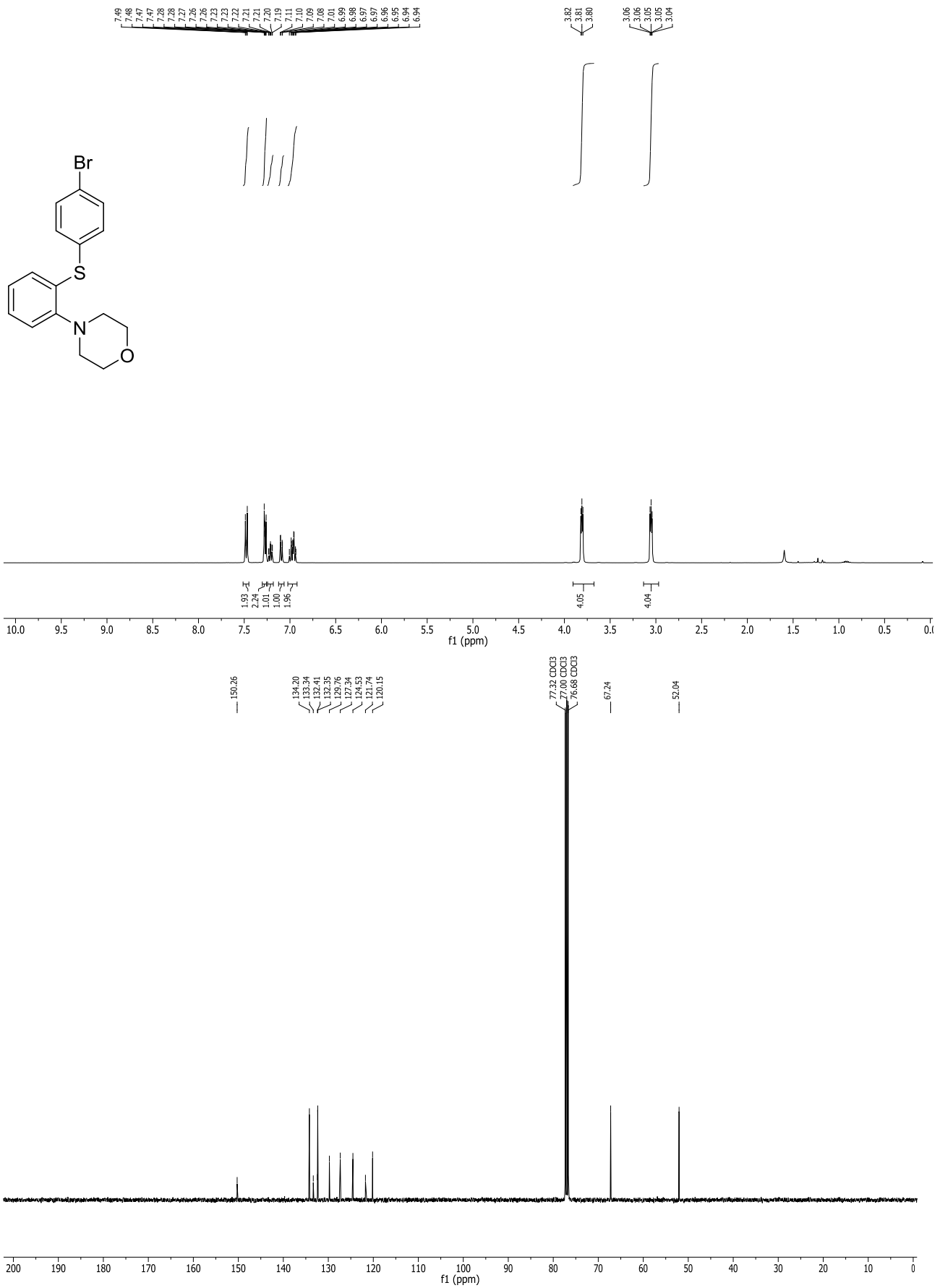




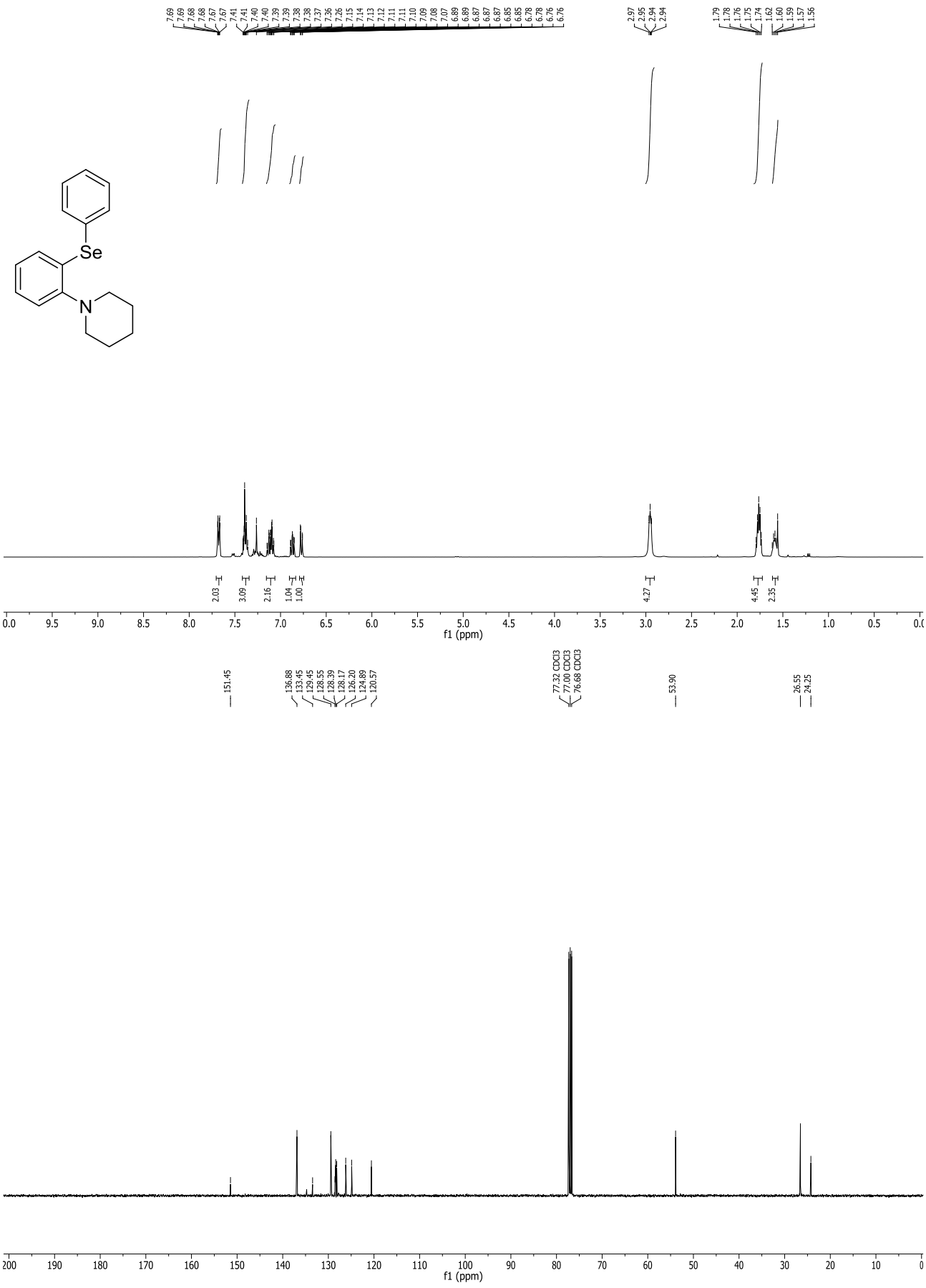
^{1}H and ^{13}C NMR data of compound **7h** (400 and 100 MHz respectively, $CDCl_3$).



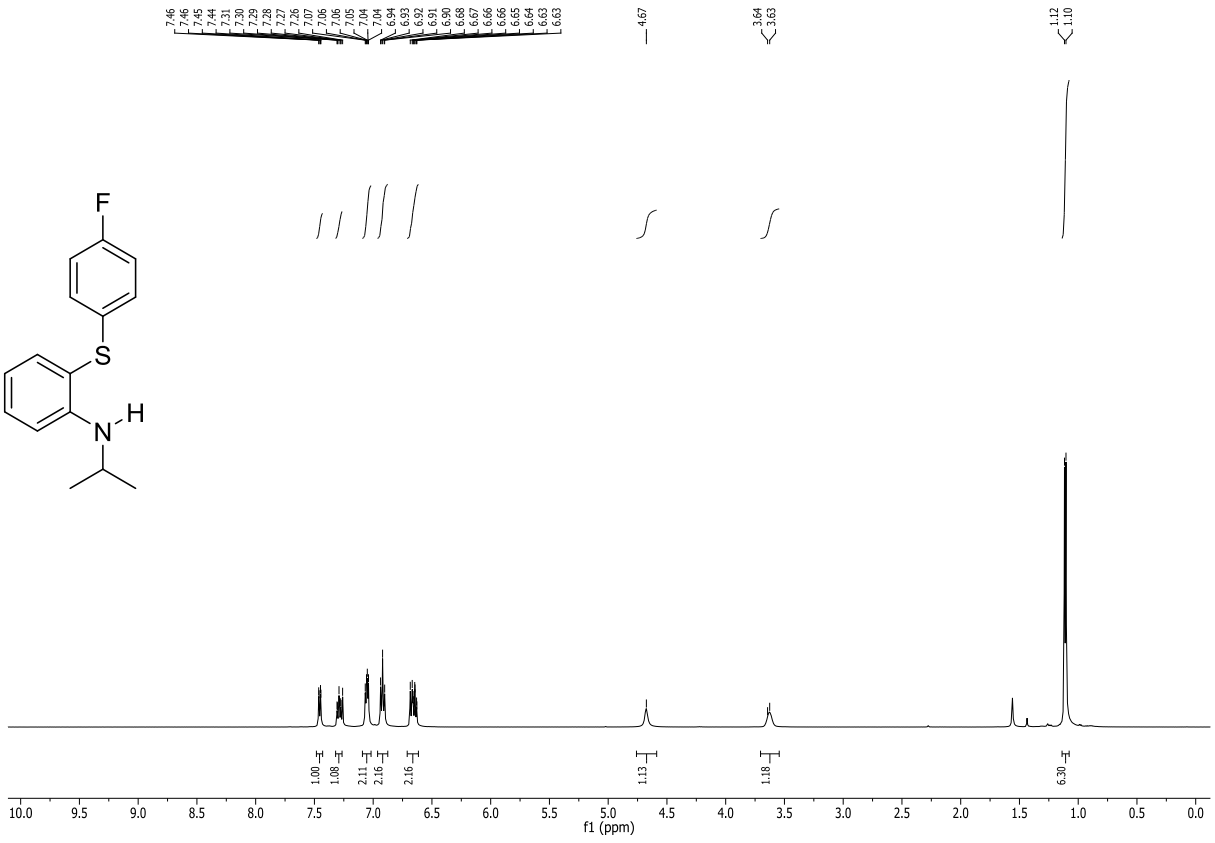
^{1}H and ^{13}C NMR data of compound **7i** (400 and 100 MHz respectively, $CDCl_3$).

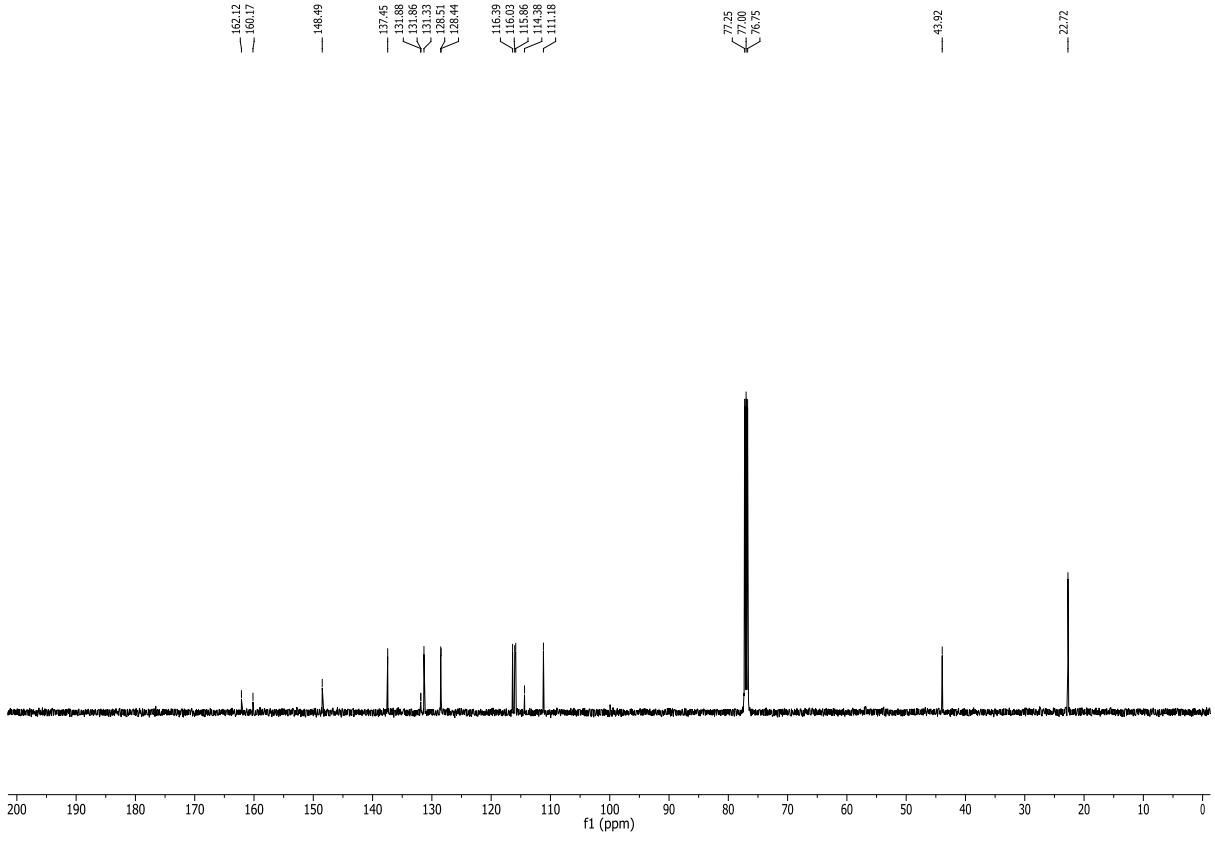


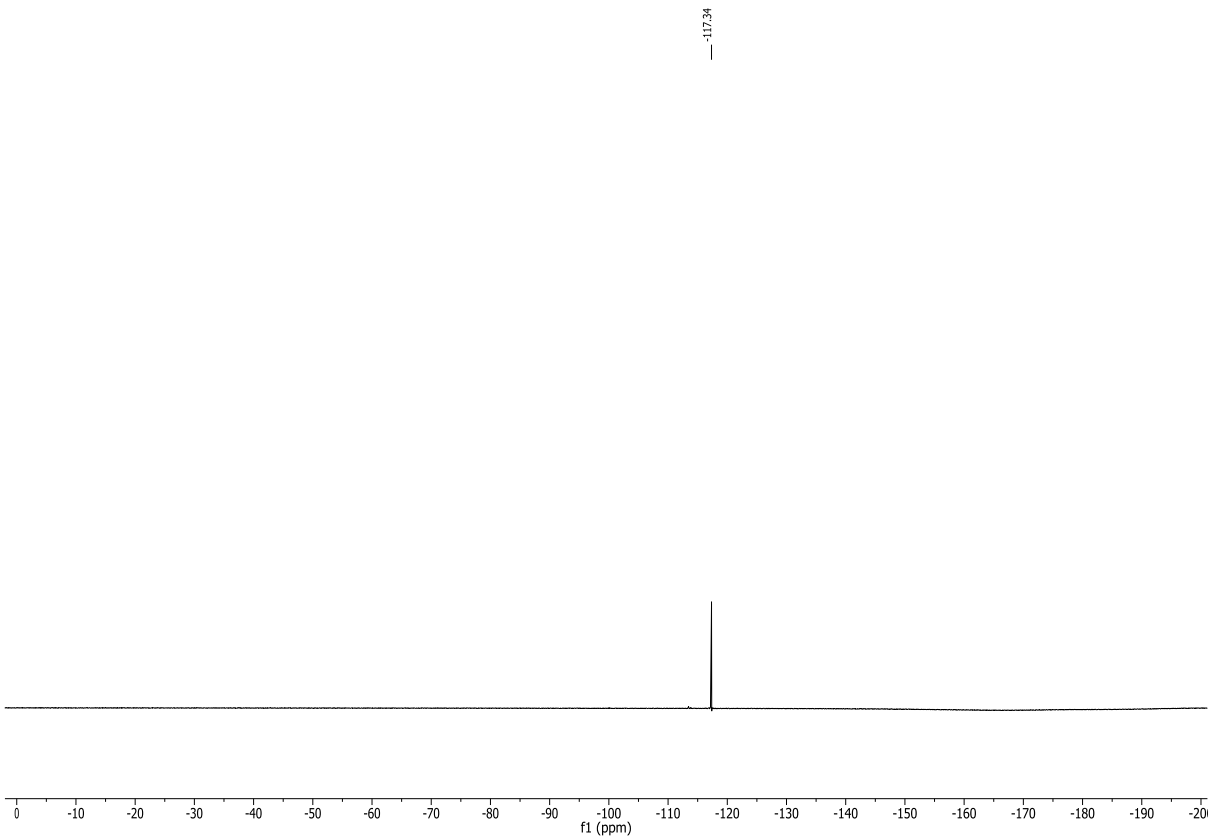
^{1}H and ^{13}C NMR data of compound **7j** (400 and 100 MHz respectively, $CDCl_3$).



^{1}H and ^{13}C NMR and ^{19}F data of compound **7k** (500, 126 and 470 MHz respectively, $CDCl_3$).



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-120
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-140
-150
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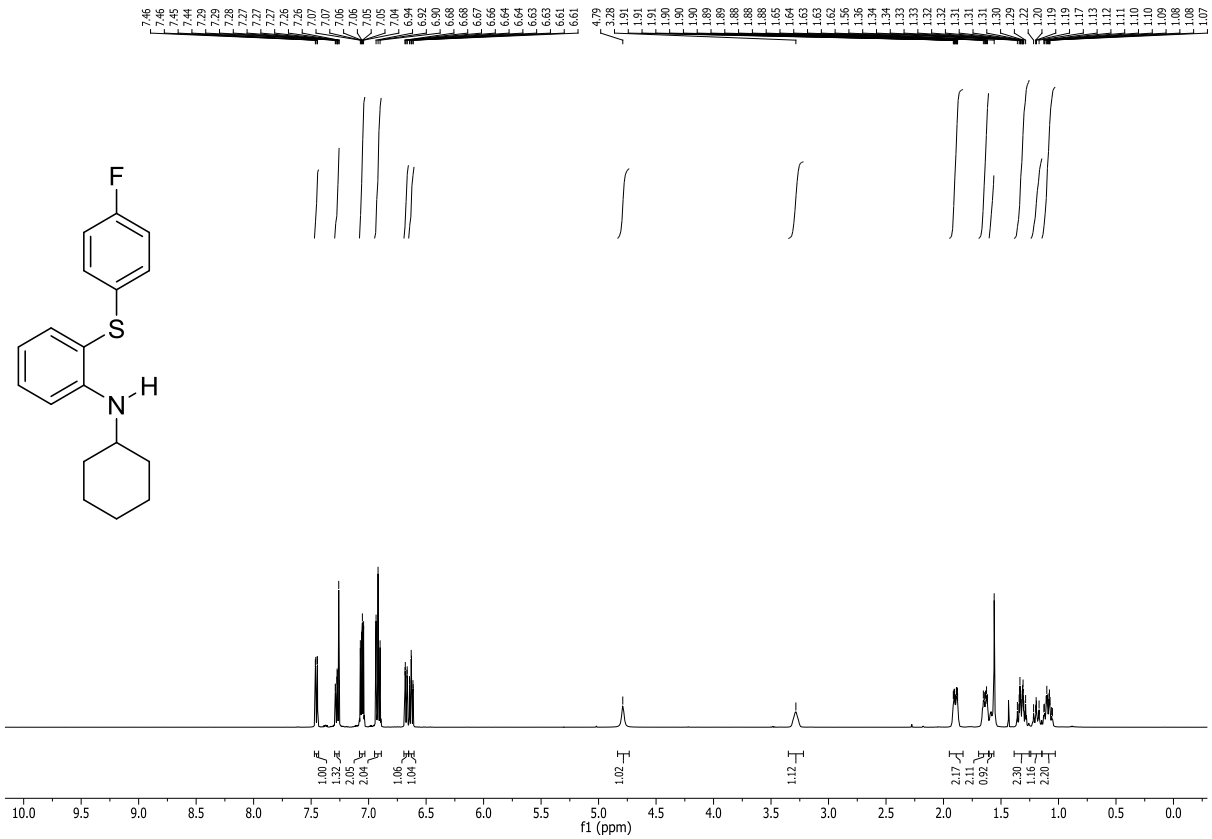
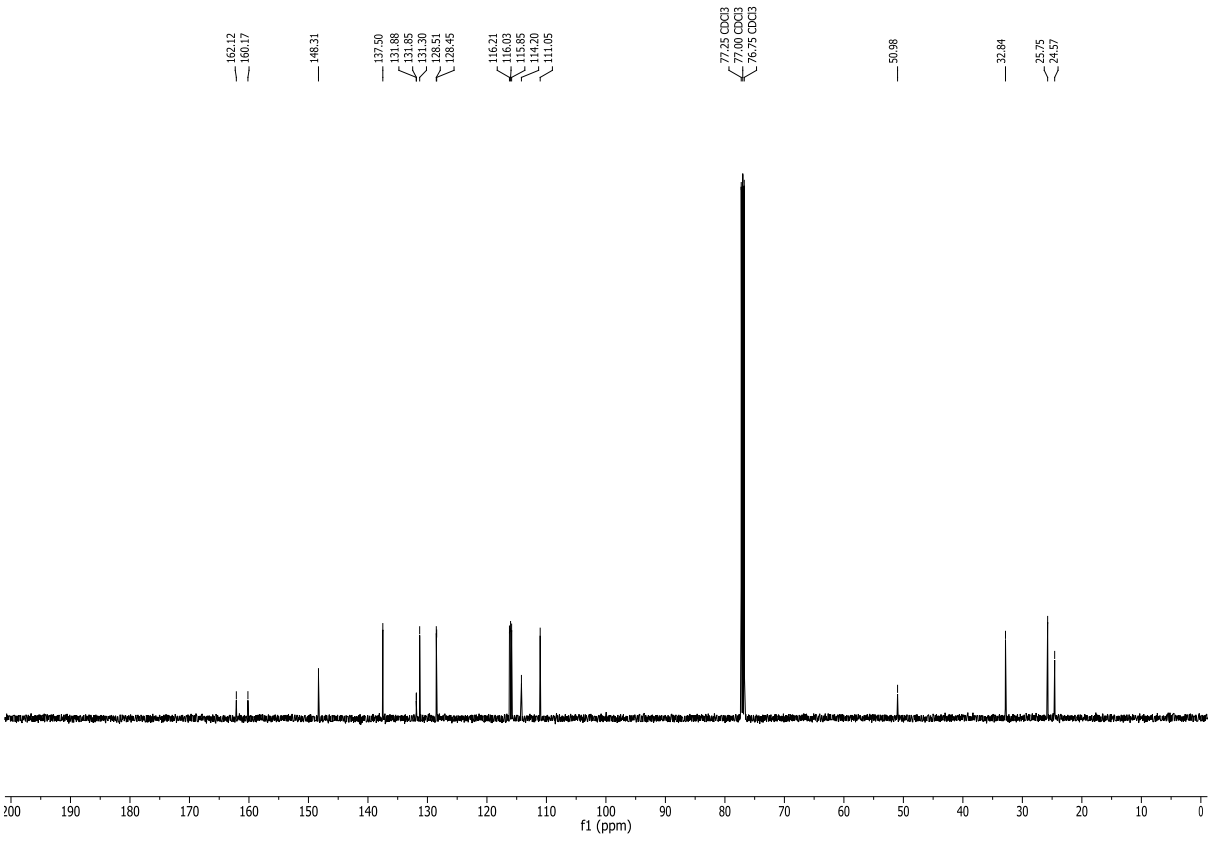
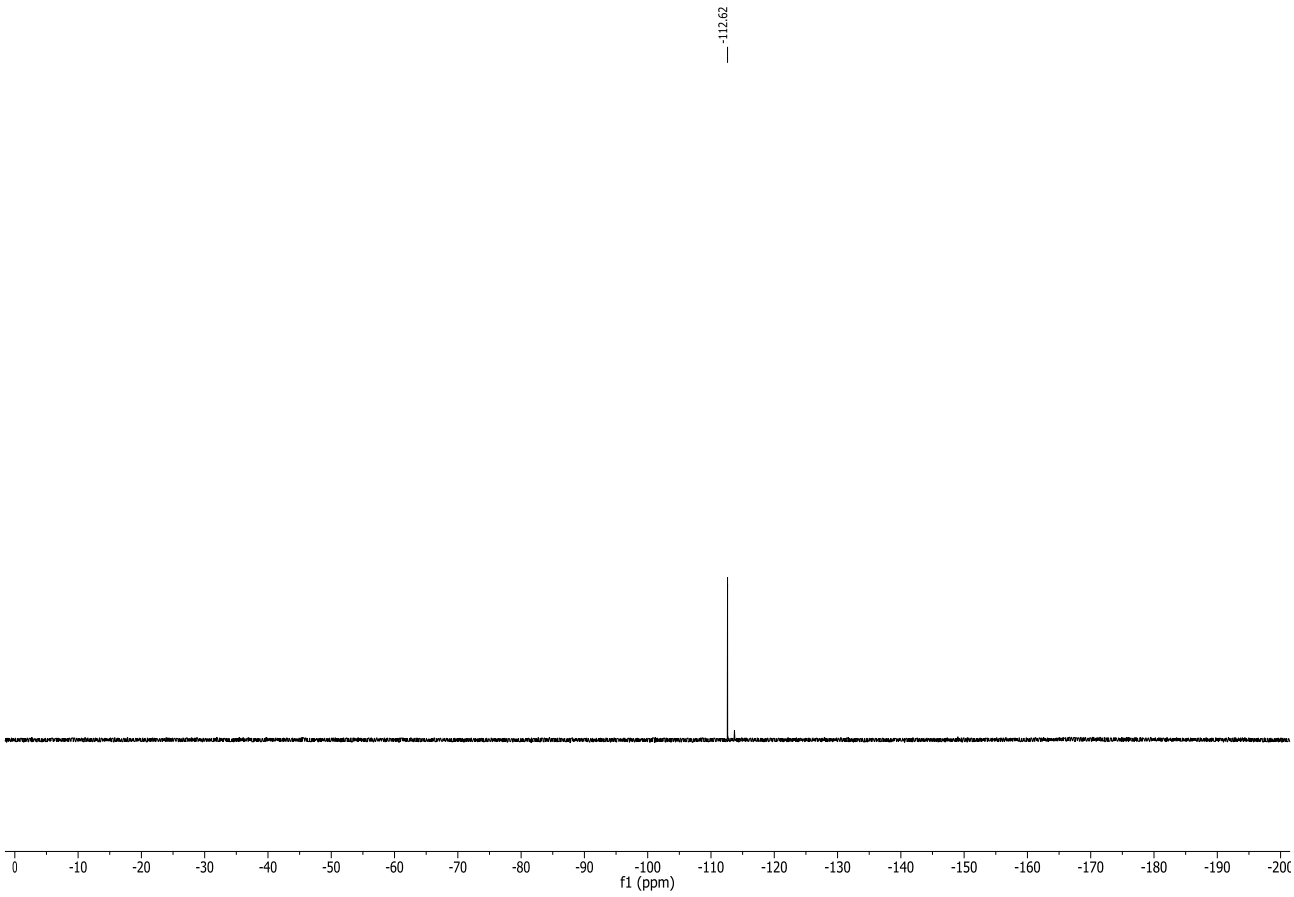
-170
-180
-190
f1 (ppm)

^{1}H and ^{13}C NMR and ^{19}F data of compound **7l** (500, 126 and 470 MHz respectively, $CDCl_3$).



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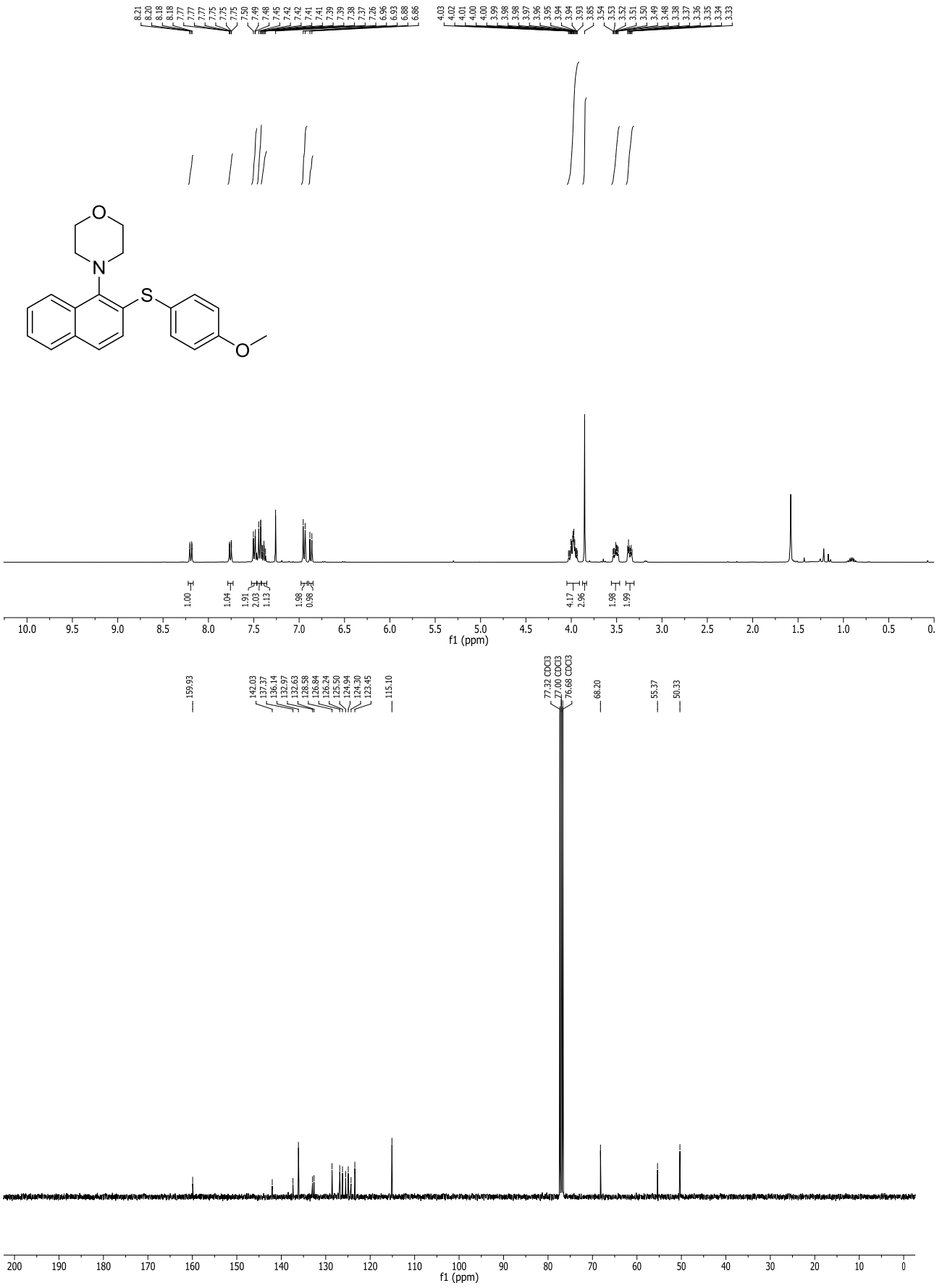
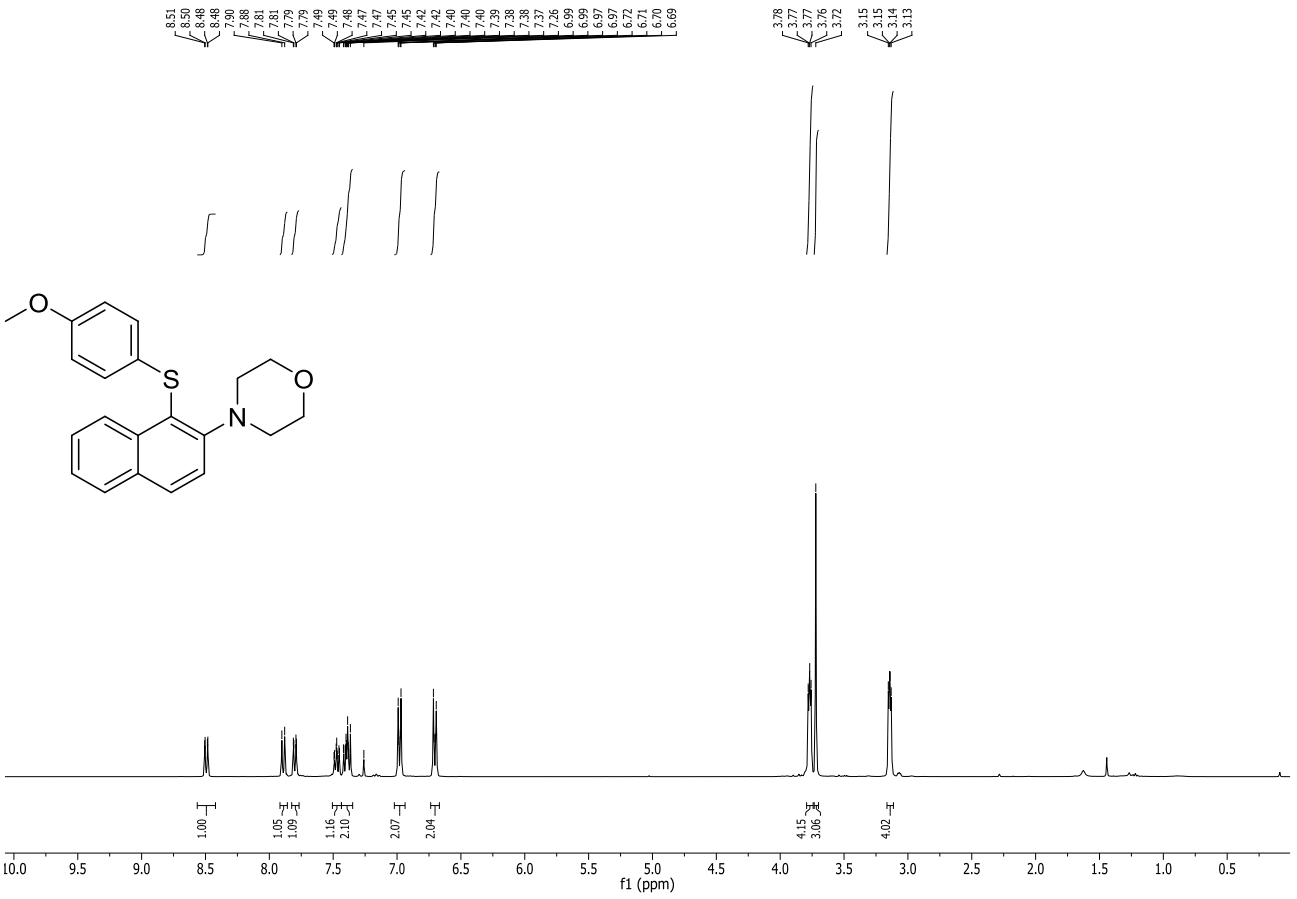
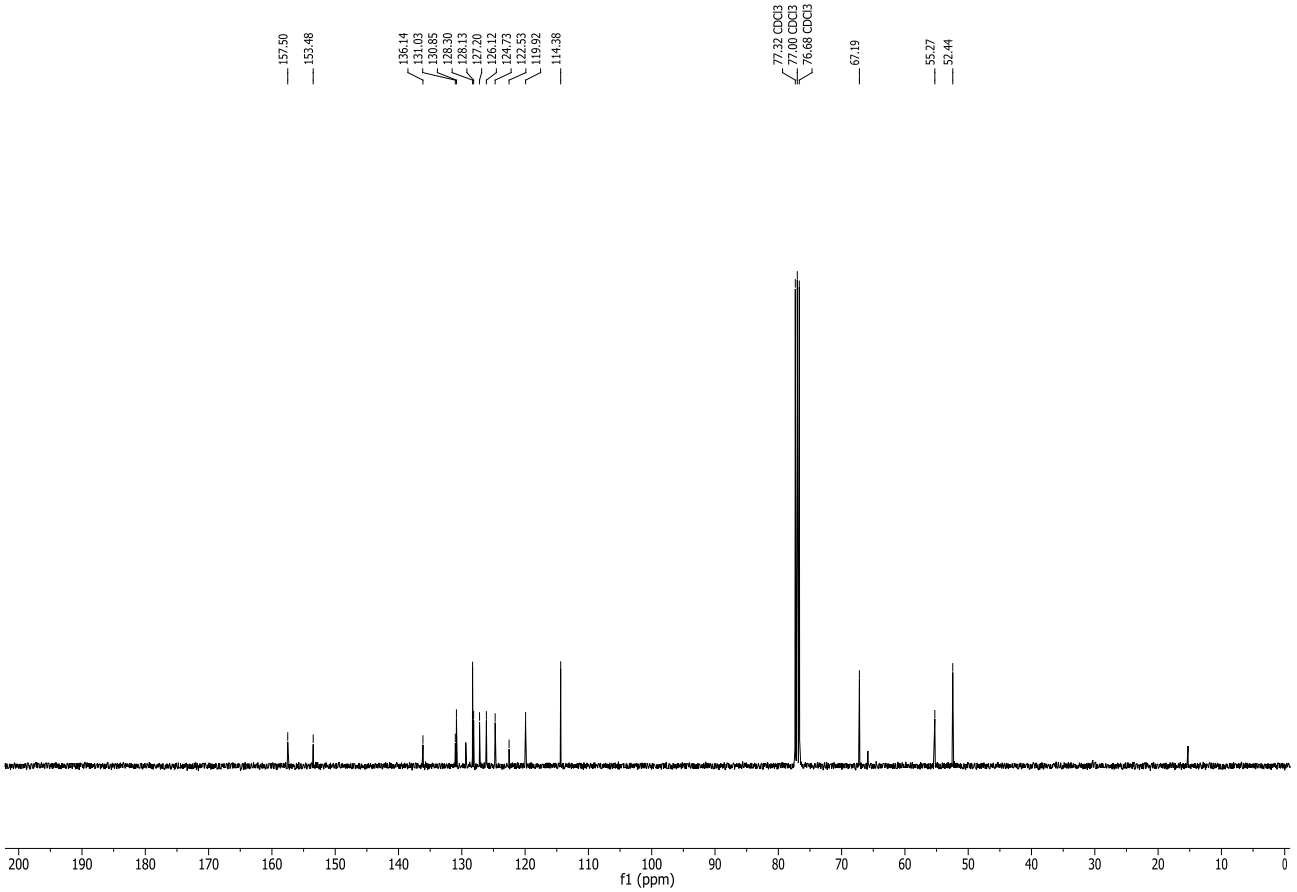
-200
f1 (ppm)

^{1}H and ^{13}C NMR data of compound **7m** (400 and 100 MHz respectively, $CDCl_3$).

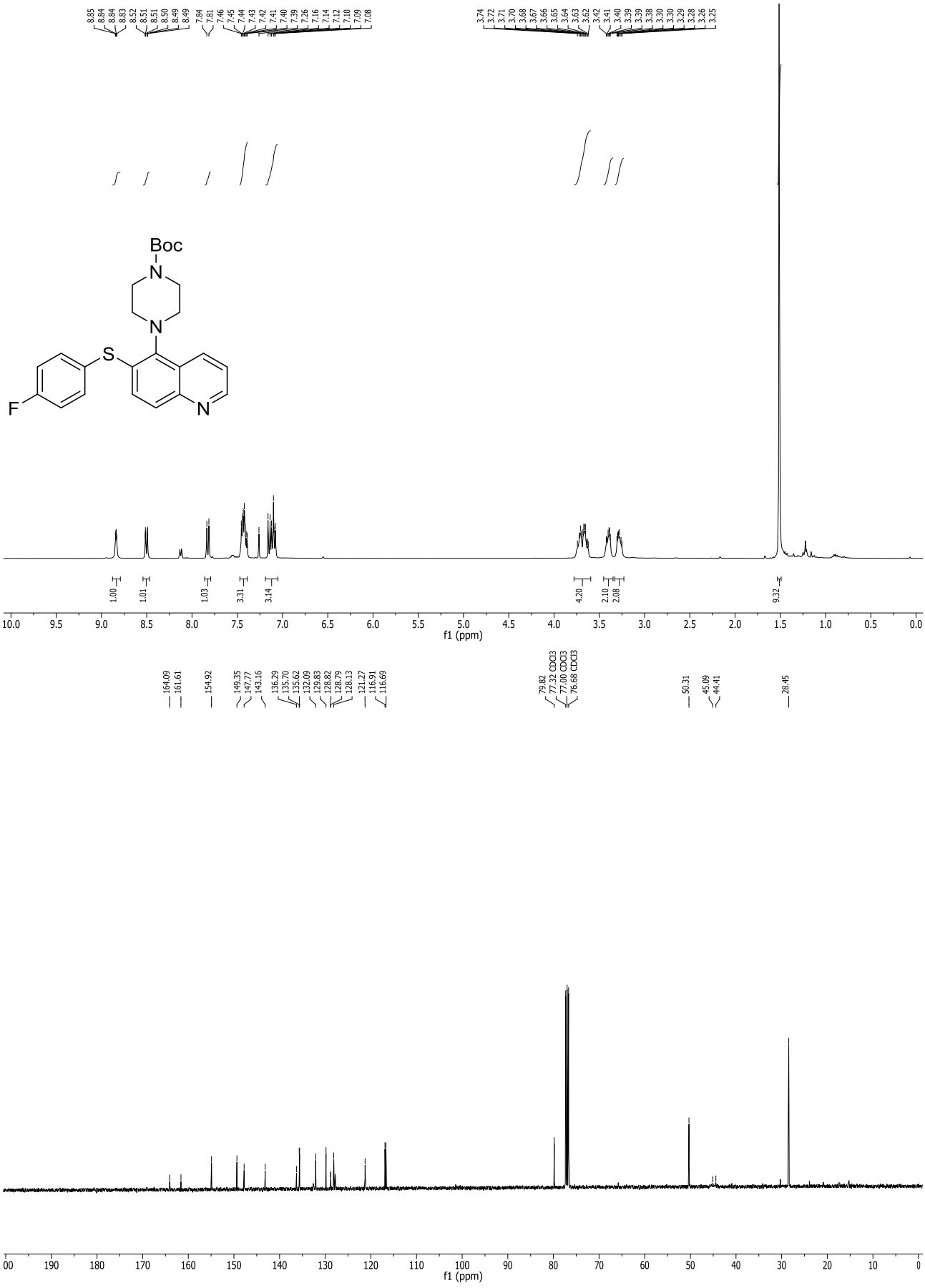


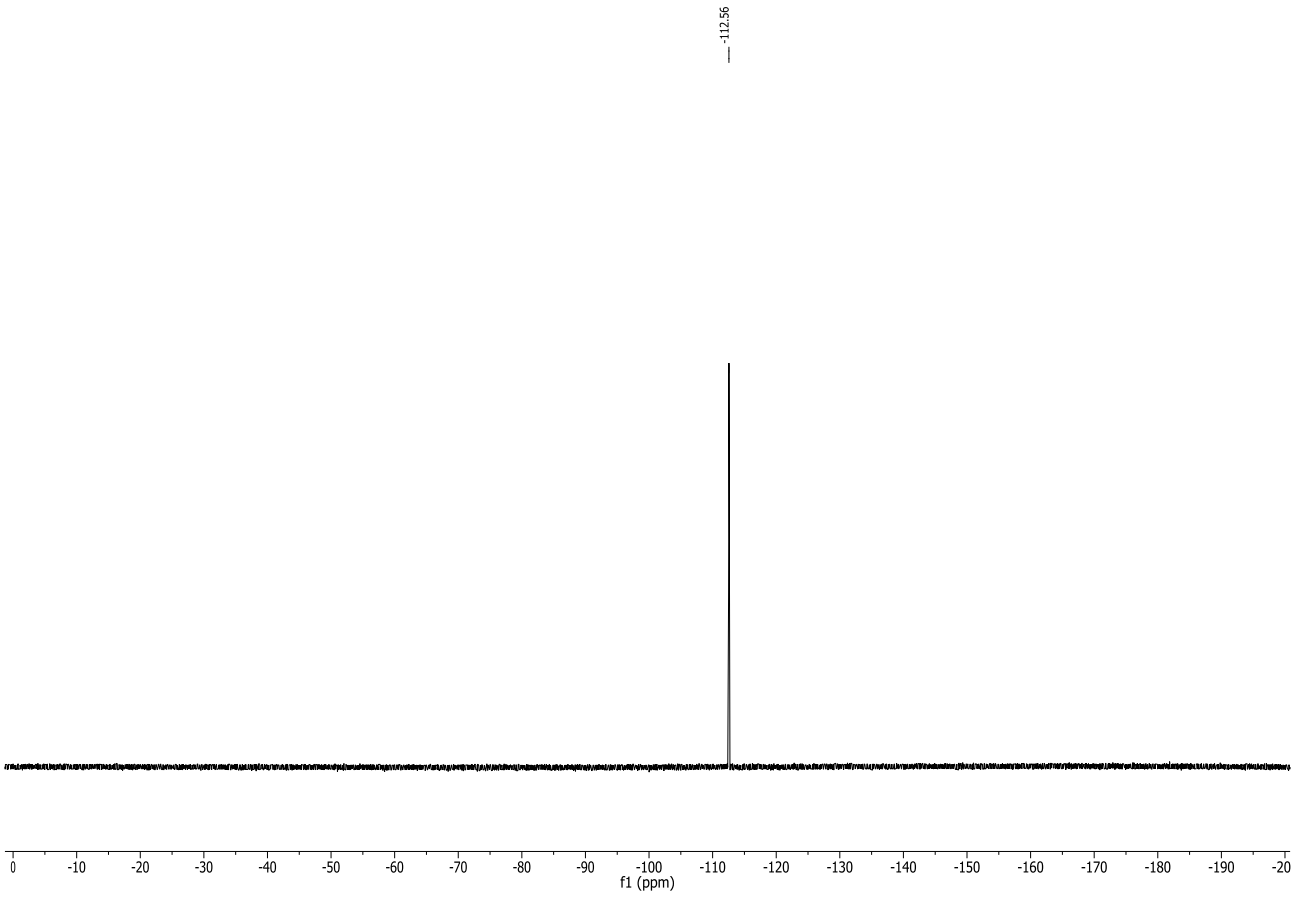
^{1}H and ^{13}C NMR data of compound **7m'** (400 and 100 MHz respectively, $CDCl_3$).





^{1}H, ^{13}C NMR and ^{19}F data of compound **7n** (400, 100 and 376 MHz respectively, $CDCl_3$).

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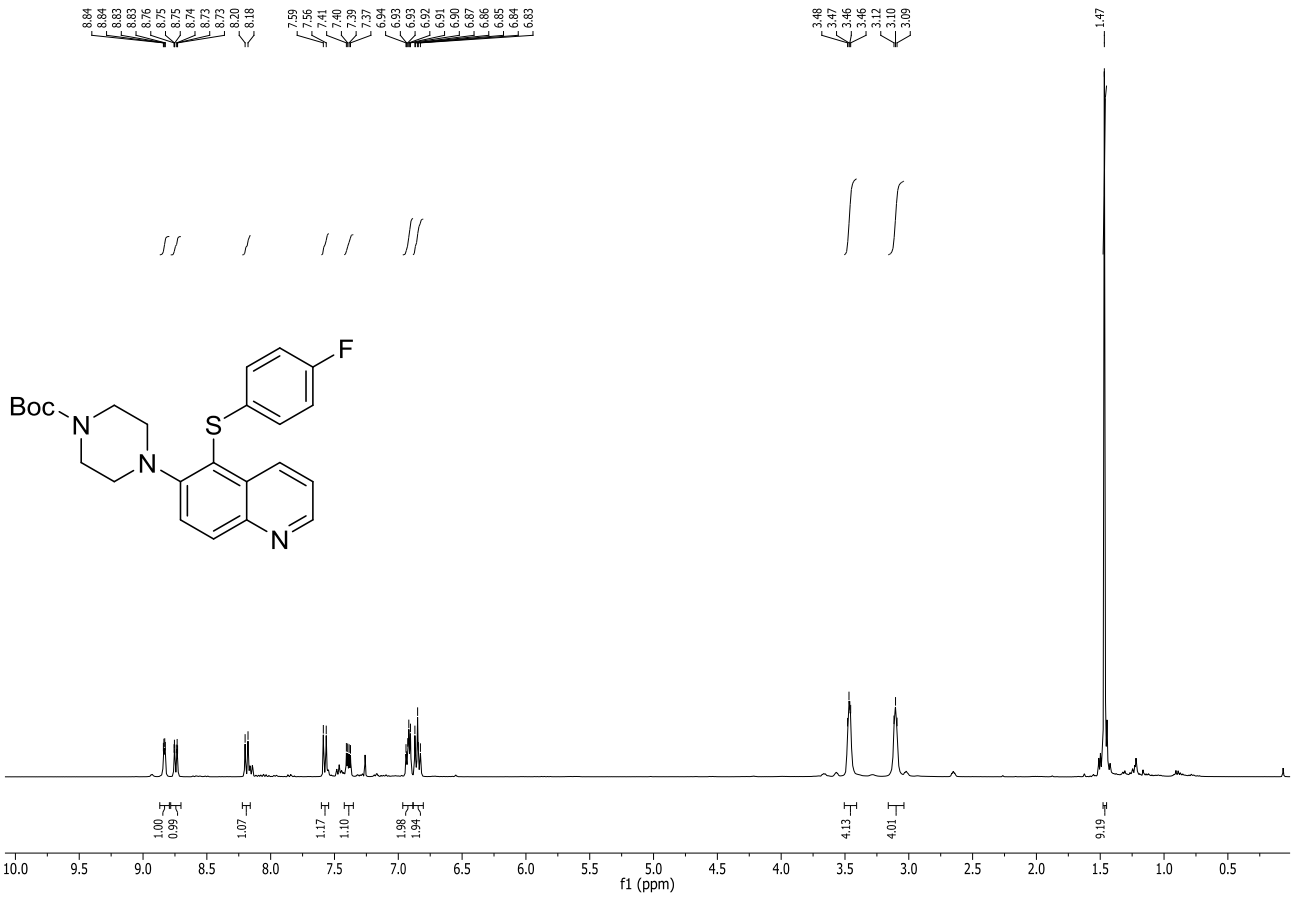
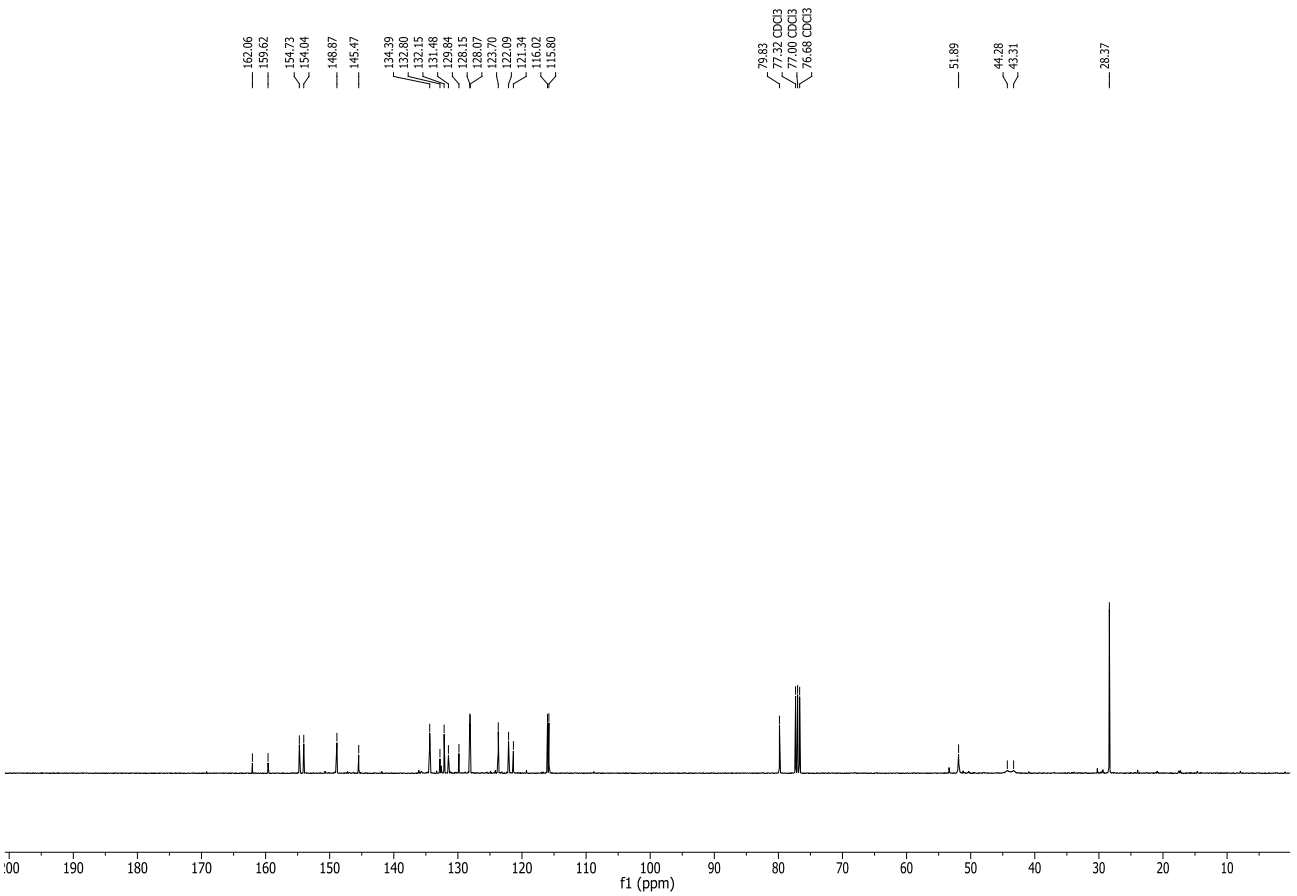
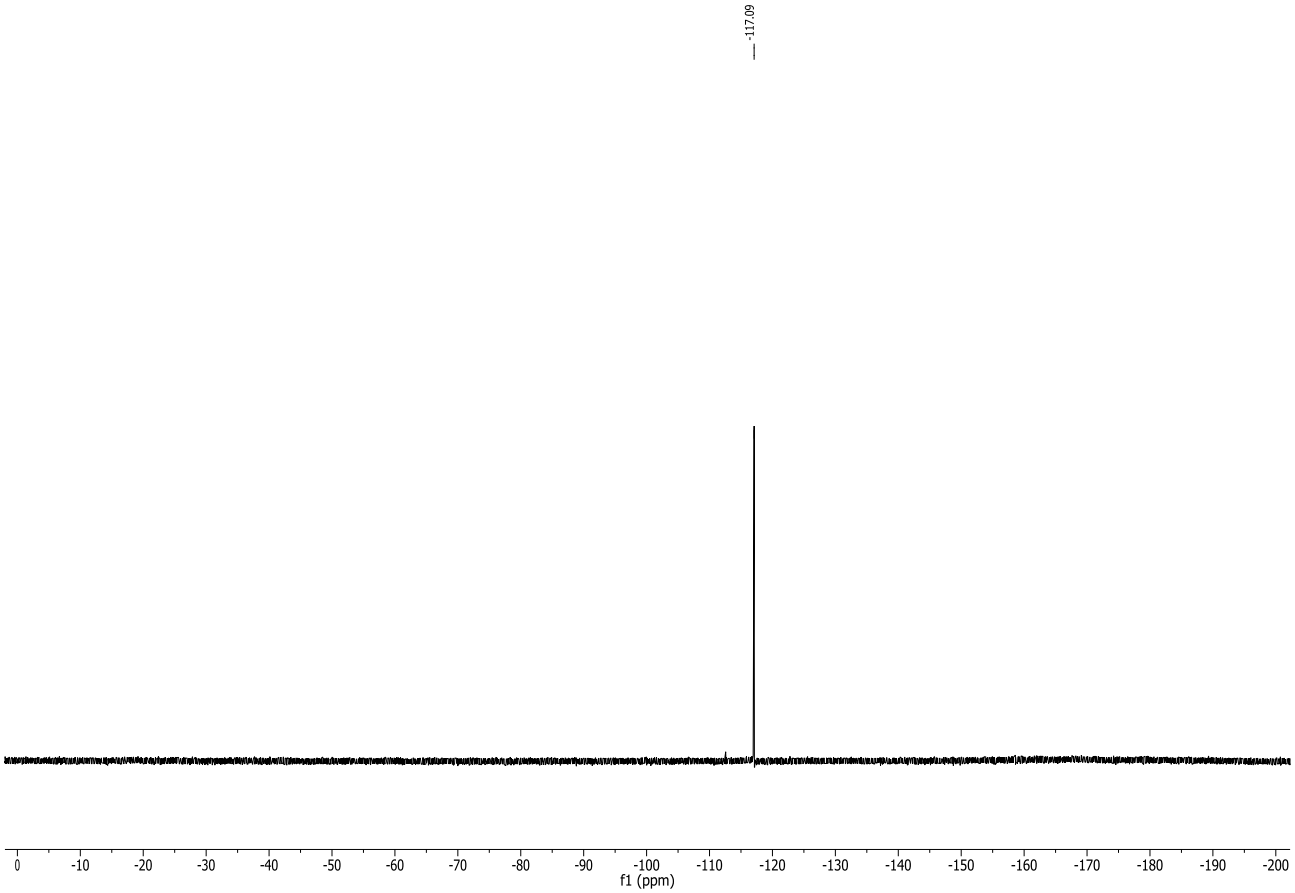
f1 (ppm)

^{1}H, ^{13}C NMR and ^{19}F data of compound **7n'** (400, 100 and 376 MHz respectively, $CDCl_3$).



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-70
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-160
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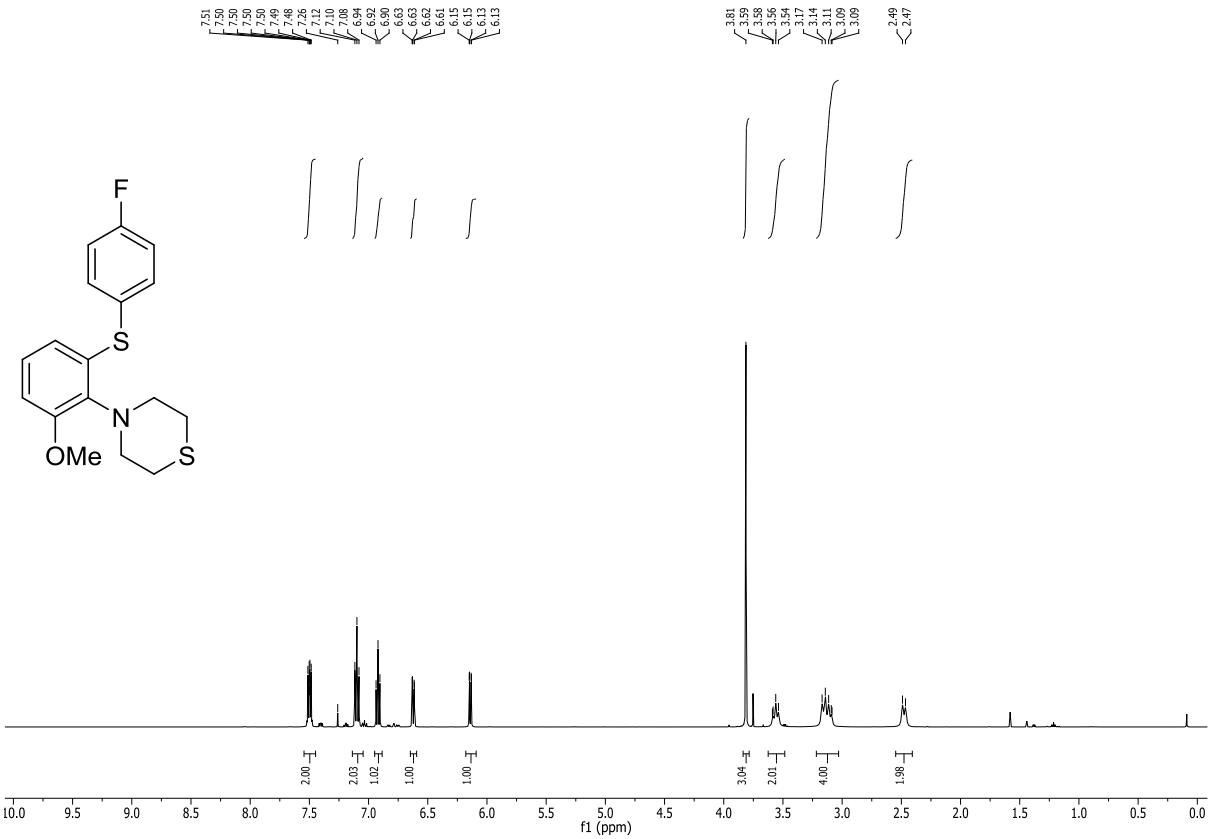
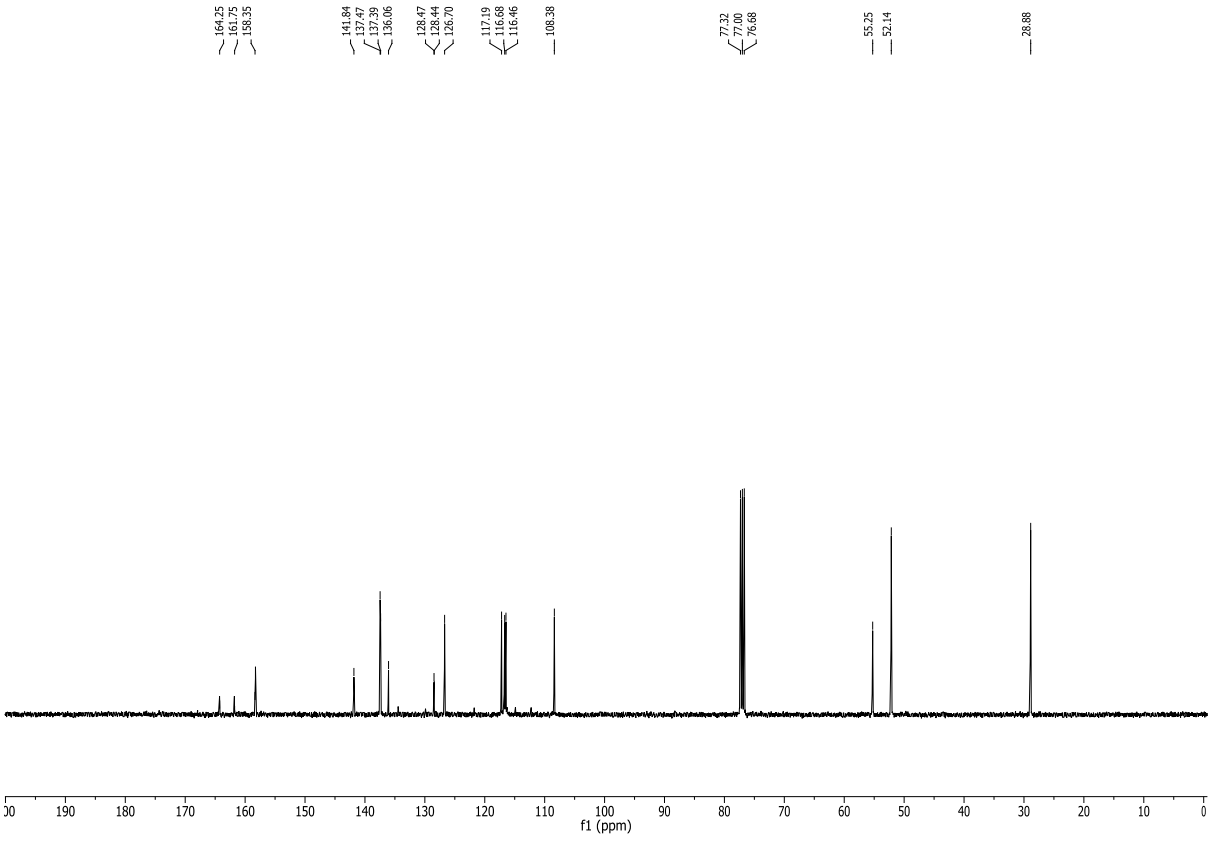
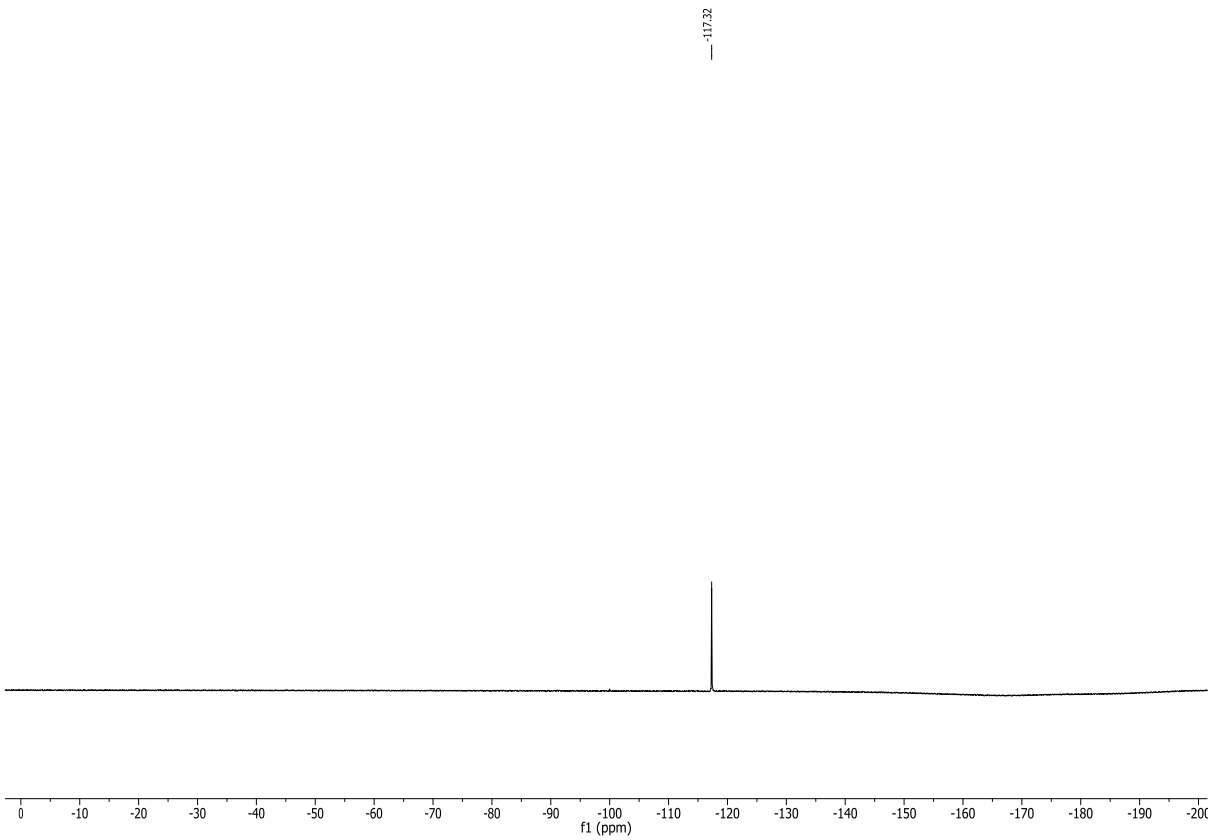
-200
f1 (ppm)

^{1}H and ^{13}C NMR and ^{19}F data of compound **7o** (500, 126 and 470 MHz respectively, $CDCl_3$).



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-150
-160
-170
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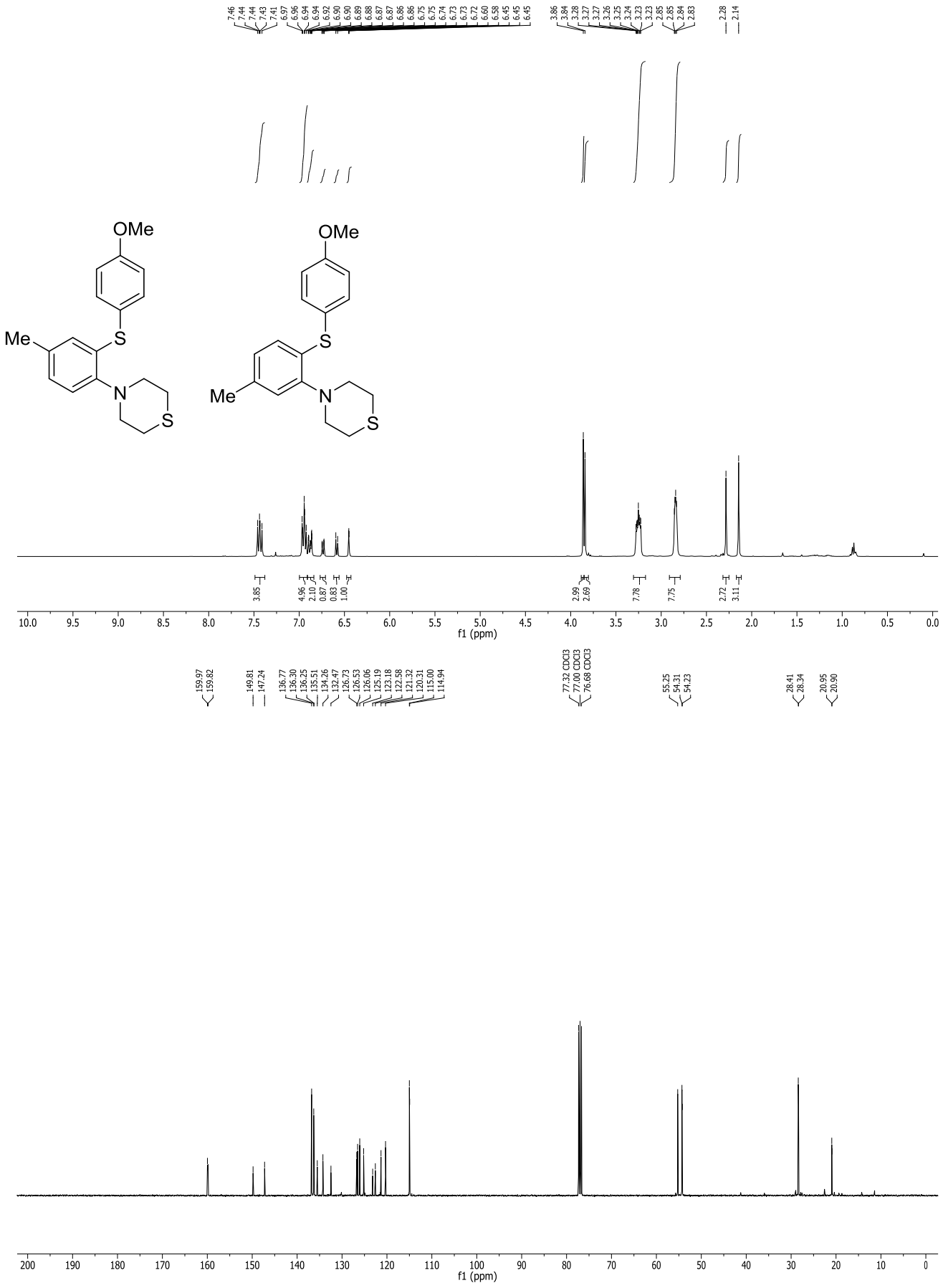
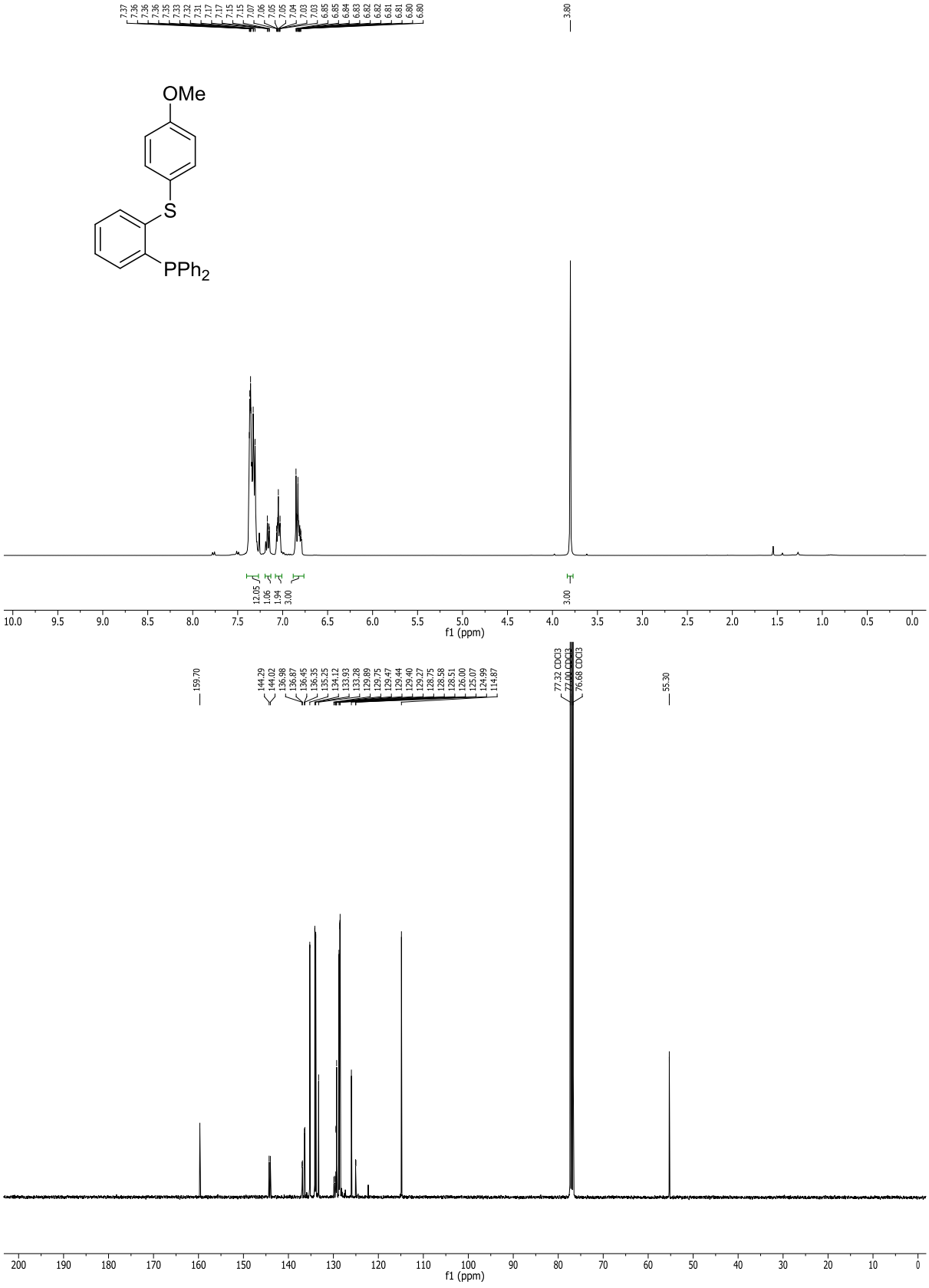
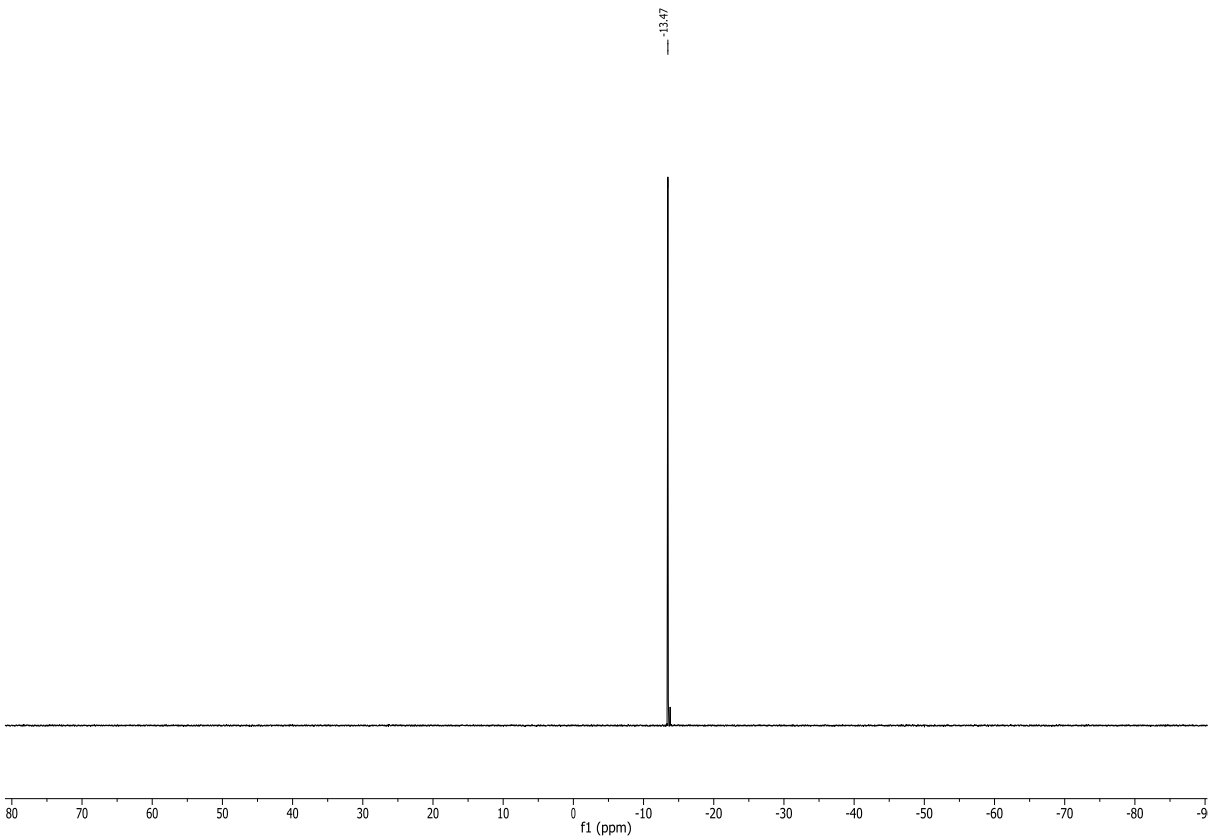
-190
-200
f1 (ppm)

^{1}H and ^{13}C NMR data of compound **7p** as 1:1 mixture of isomers (400 and 100 MHz respectively, $CDCl_3$).



^{1}H,^{13}C and ^{31}P NMR data of compound **8a** (400, 100 and 162.3 MHz respectively, $CDCl_3$).

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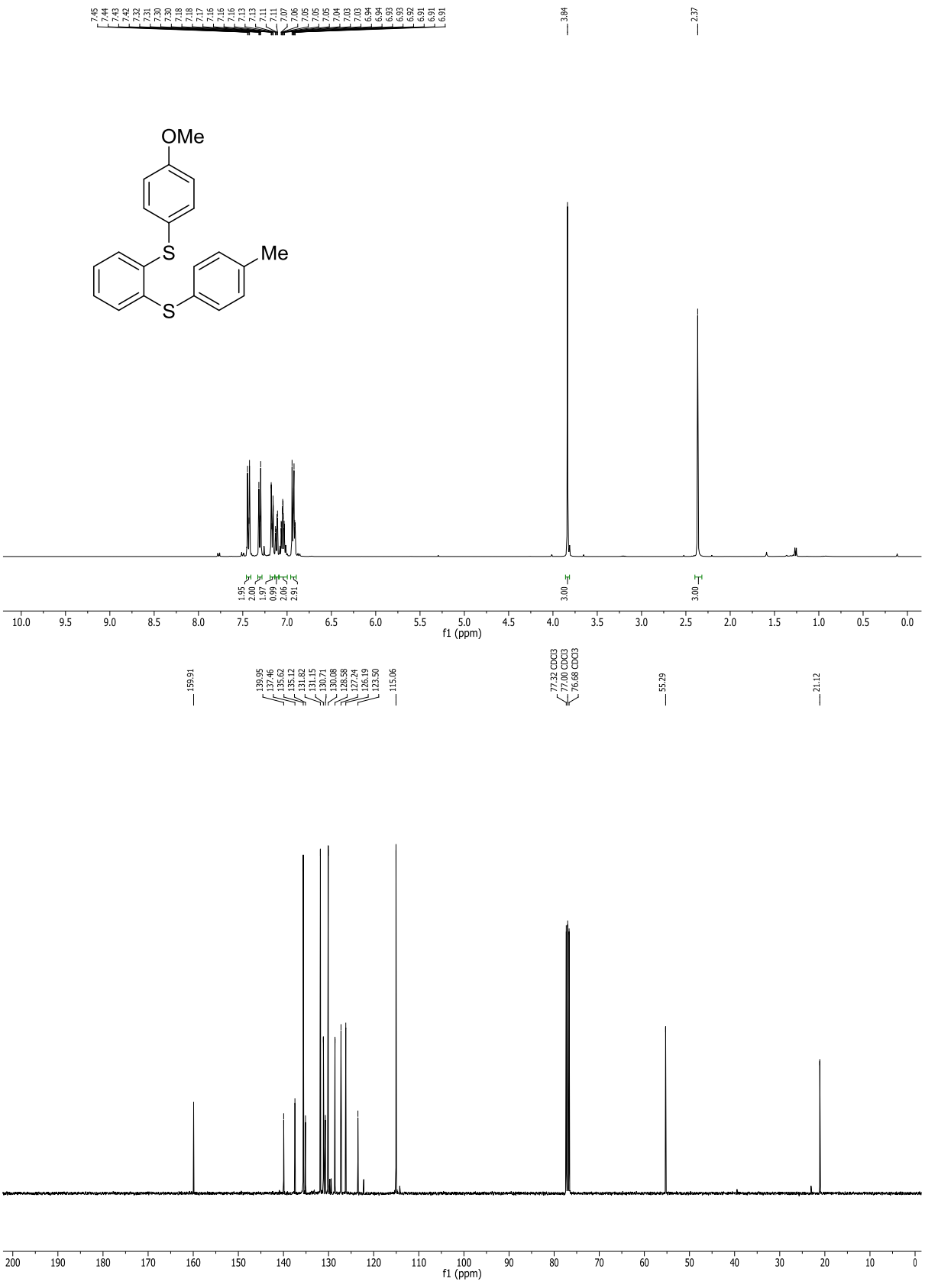
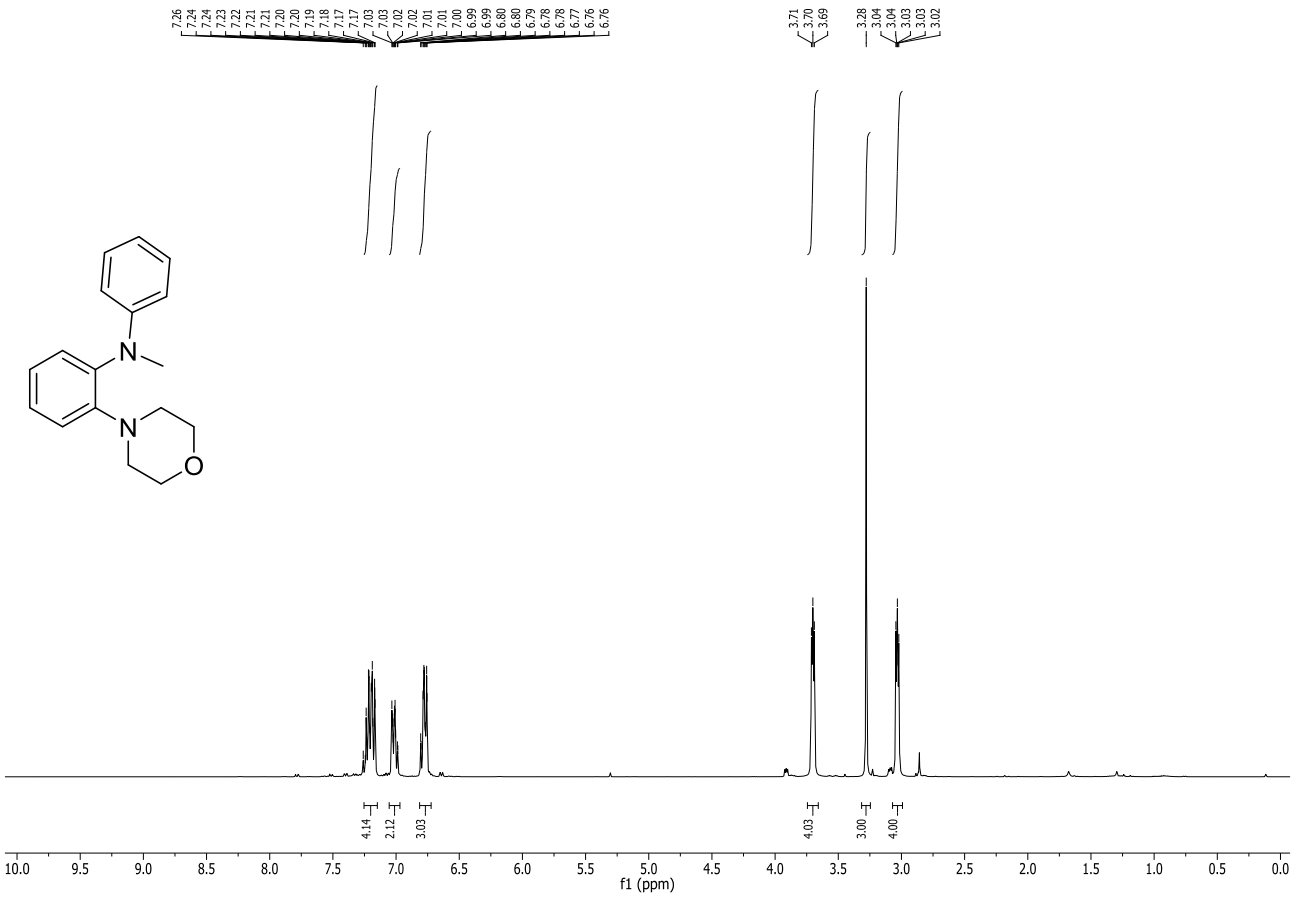
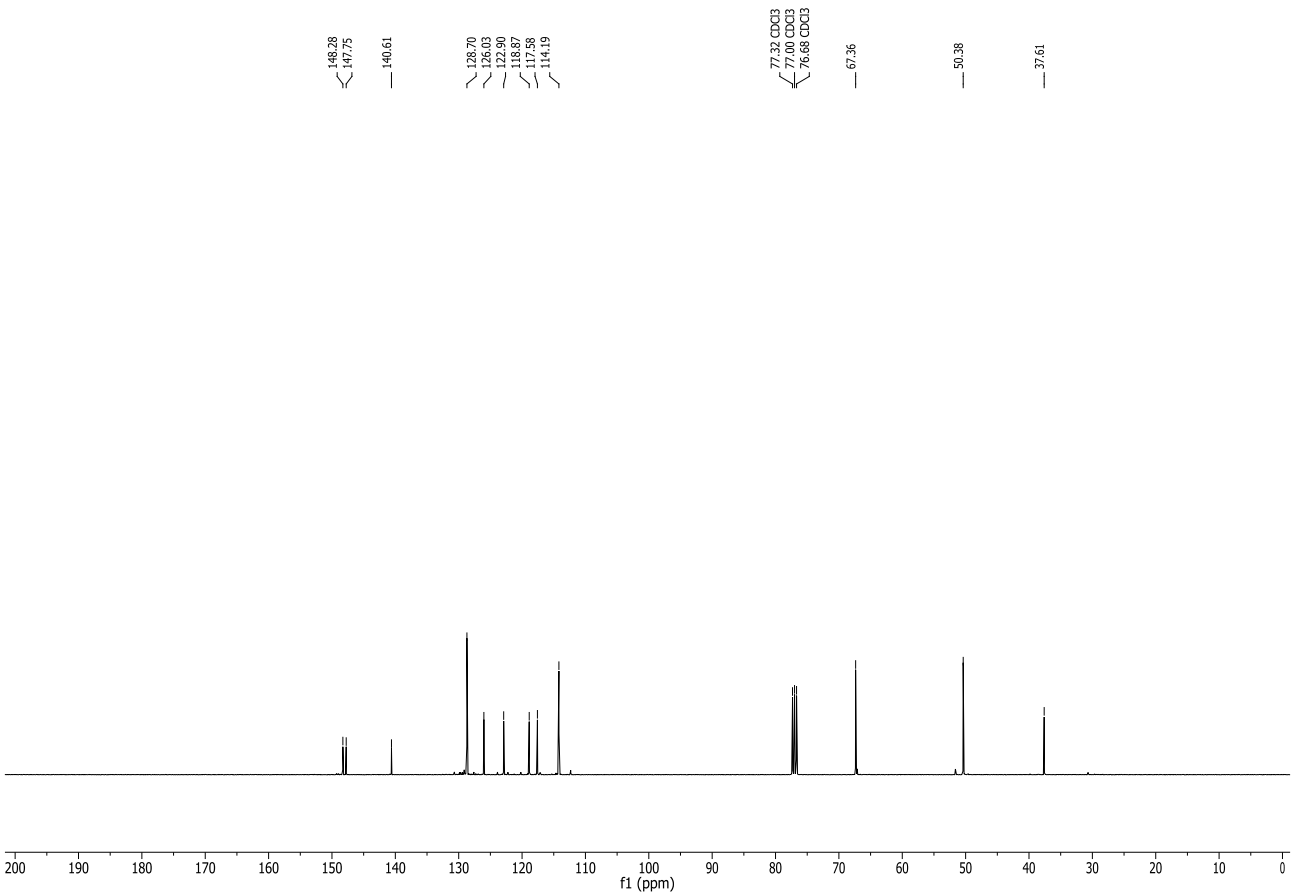
0
-10
-20
-30
-40
-50
-60
-70
-80
-9
f1 (ppm)

^{1}H and ^{13}C-NMR data of compound **8b** (400 and 100 MHz respectively, $CDCl_3$).

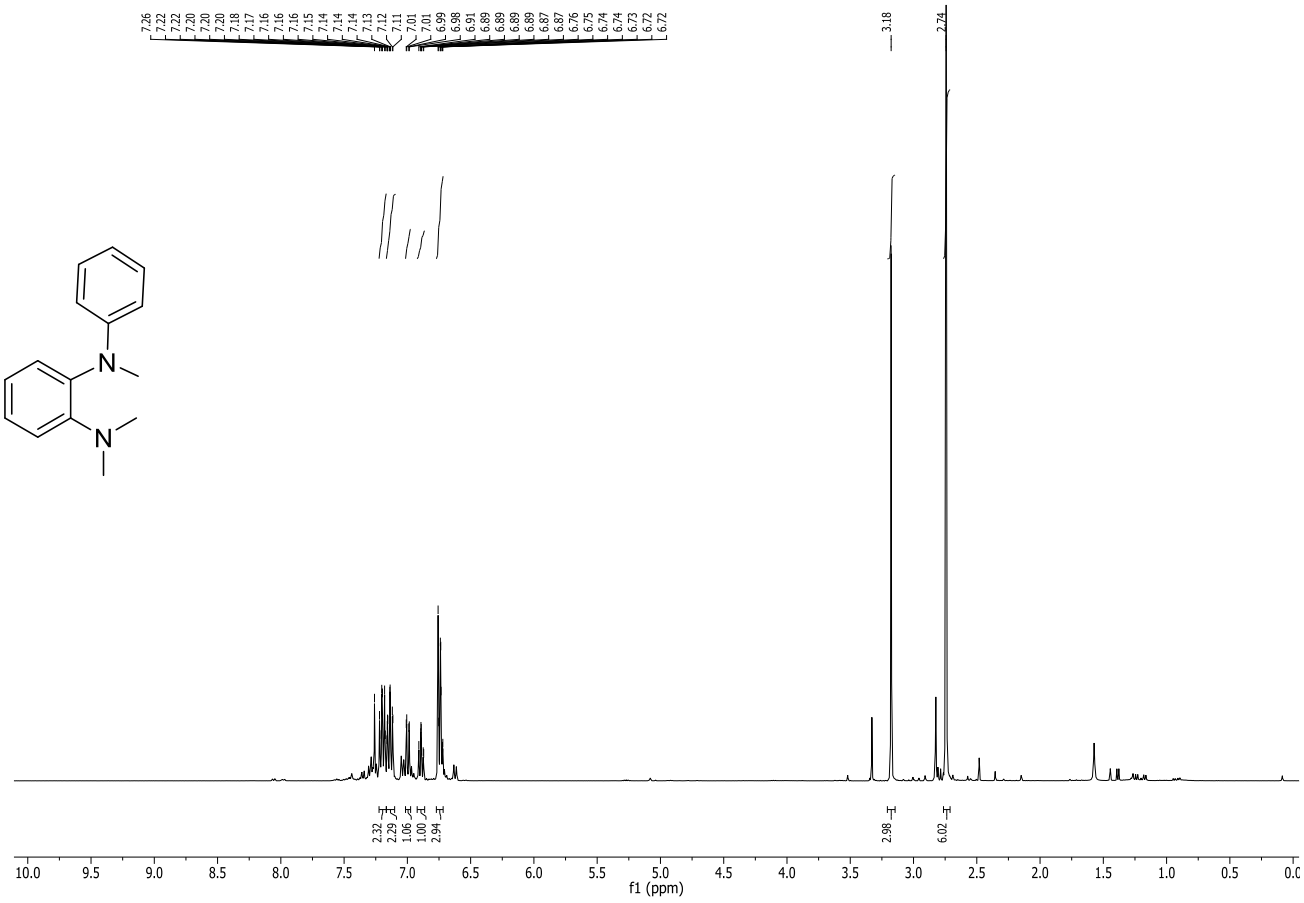


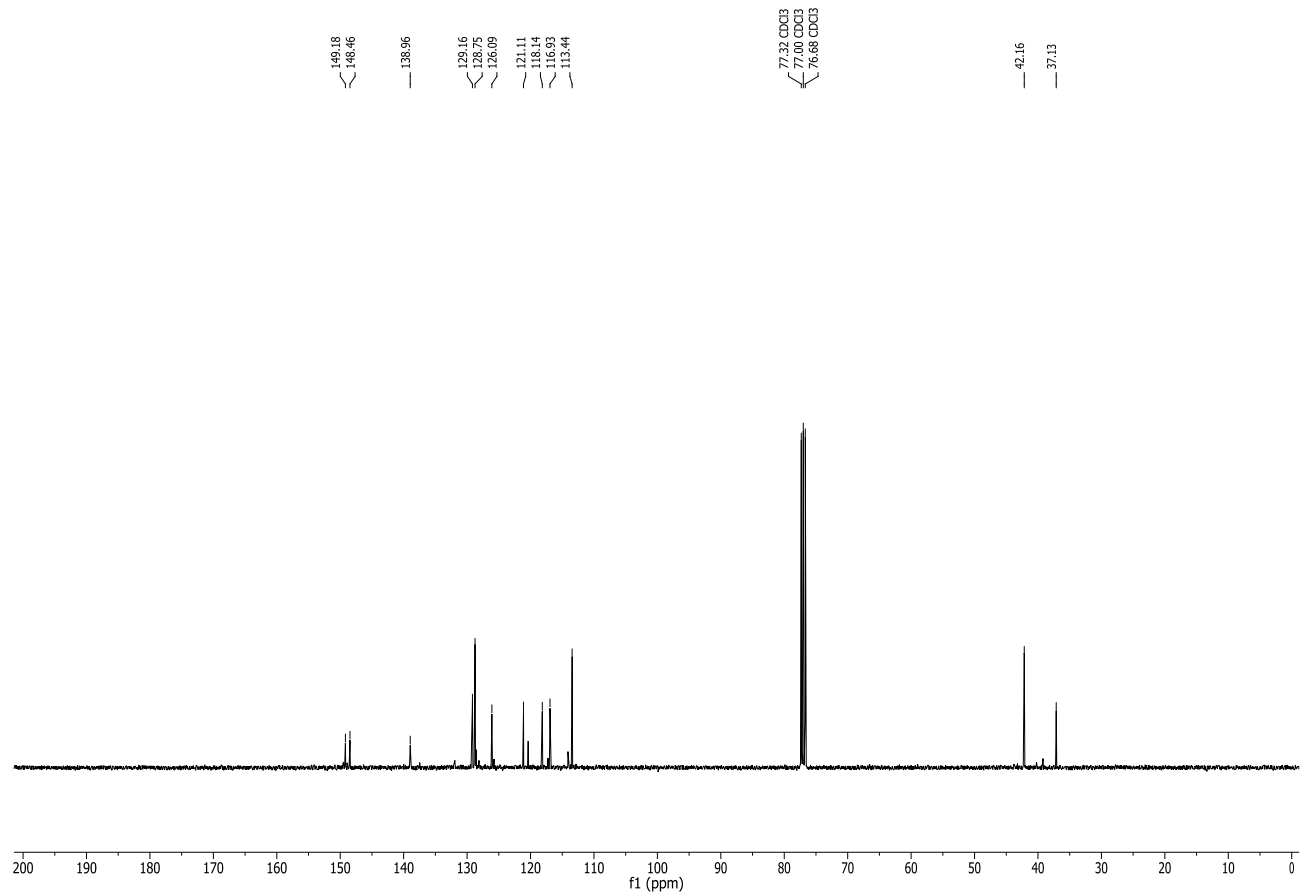
^{1}H and ^{13}C NMR data of compound **10a** (400 and 100 MHz respectively, $CDCl_3$).



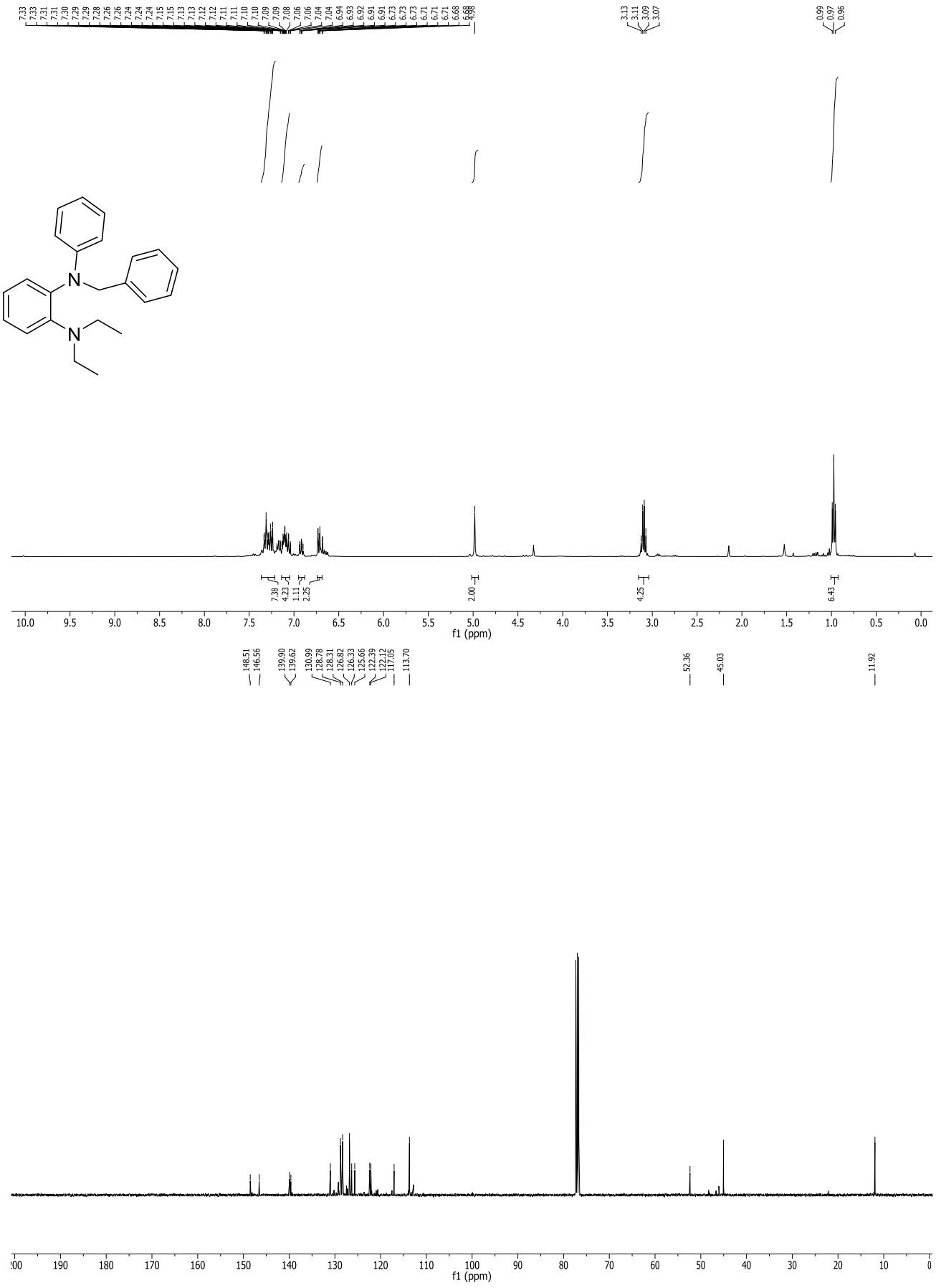


^{1}H and ^{13}C NMR data of compound **10b** (400 and 100 MHz respectively, $CDCl_3$).

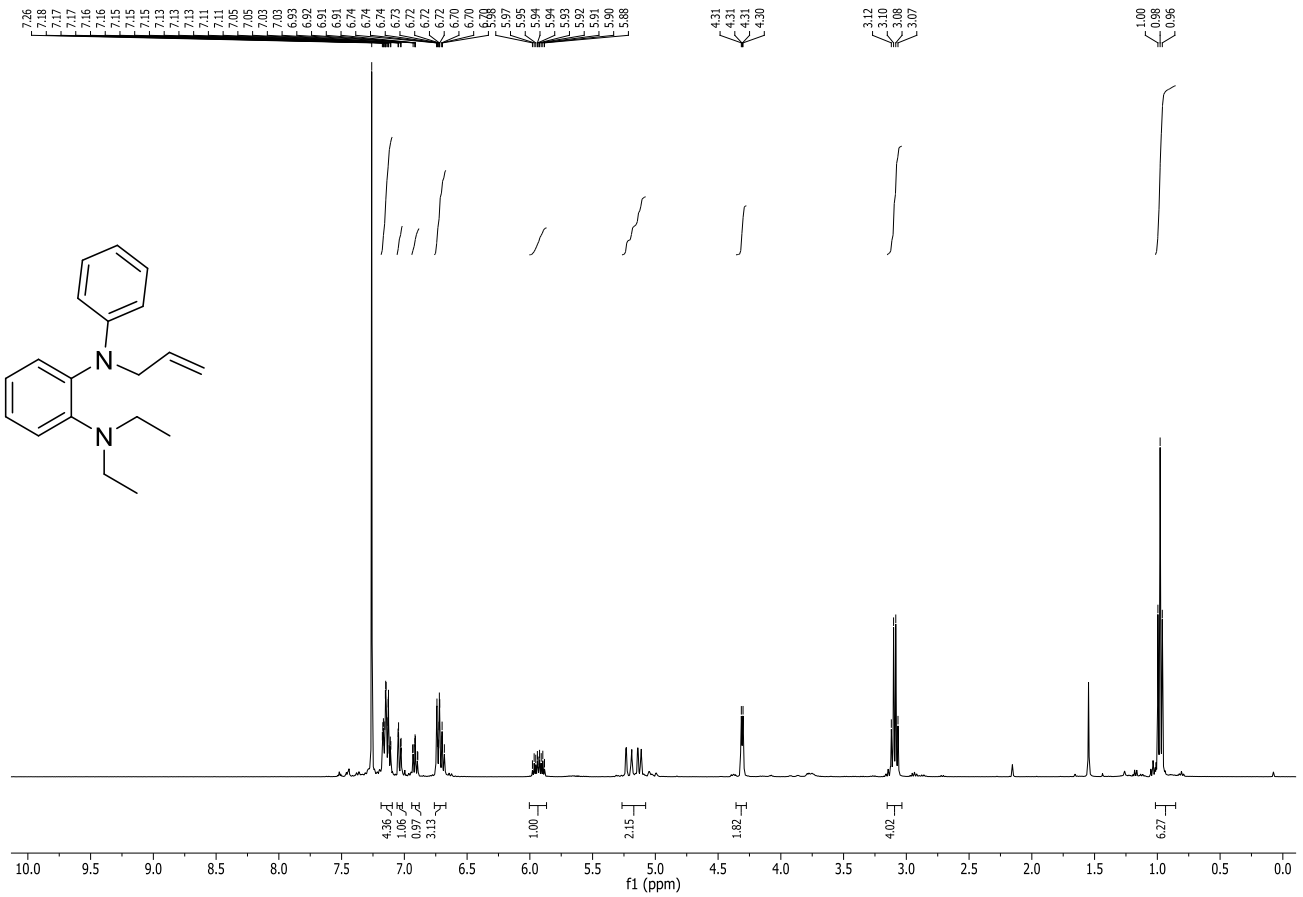


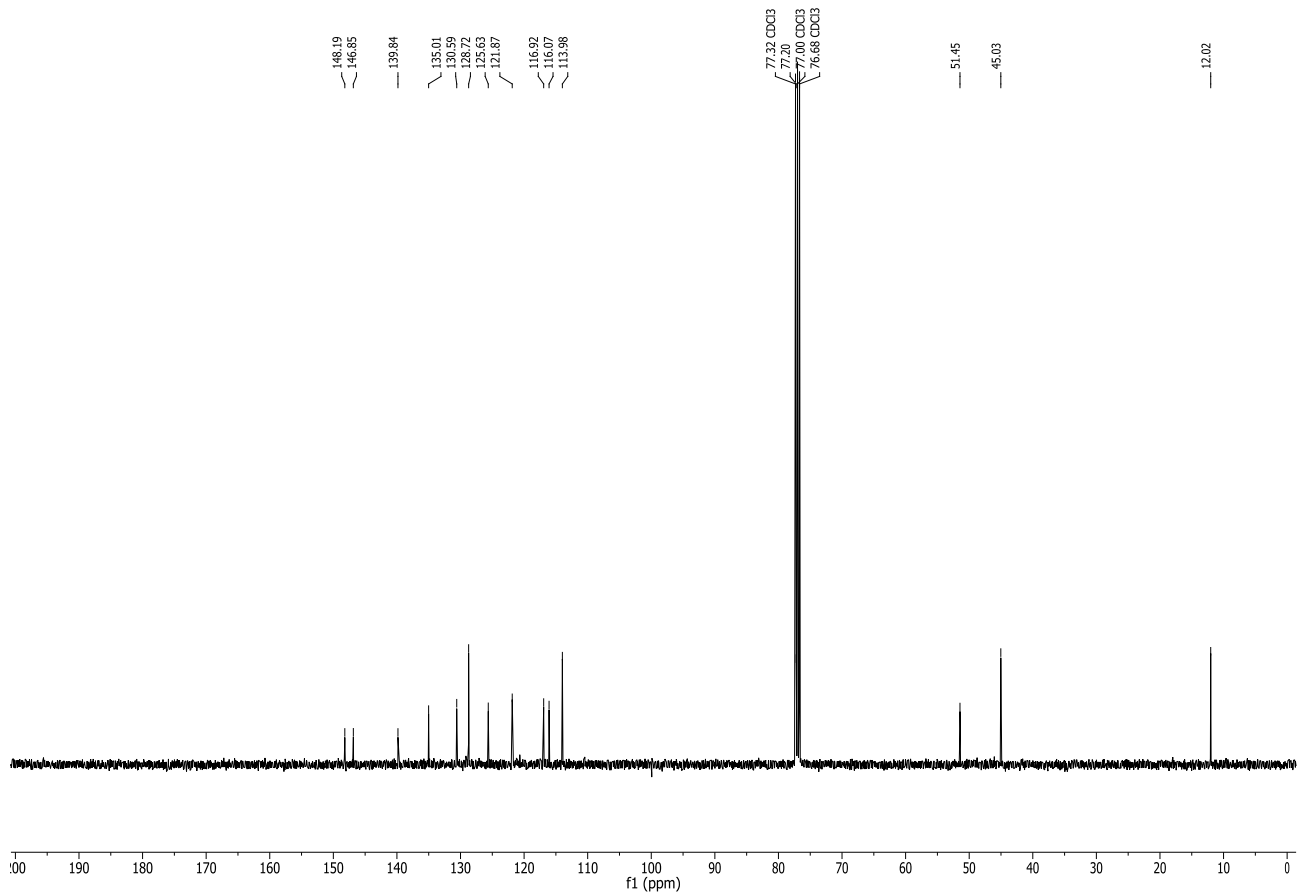


^{1}H and ^{13}C NMR data of compound **10c** (400 and 100 MHz respectively, $CDCl_3$).

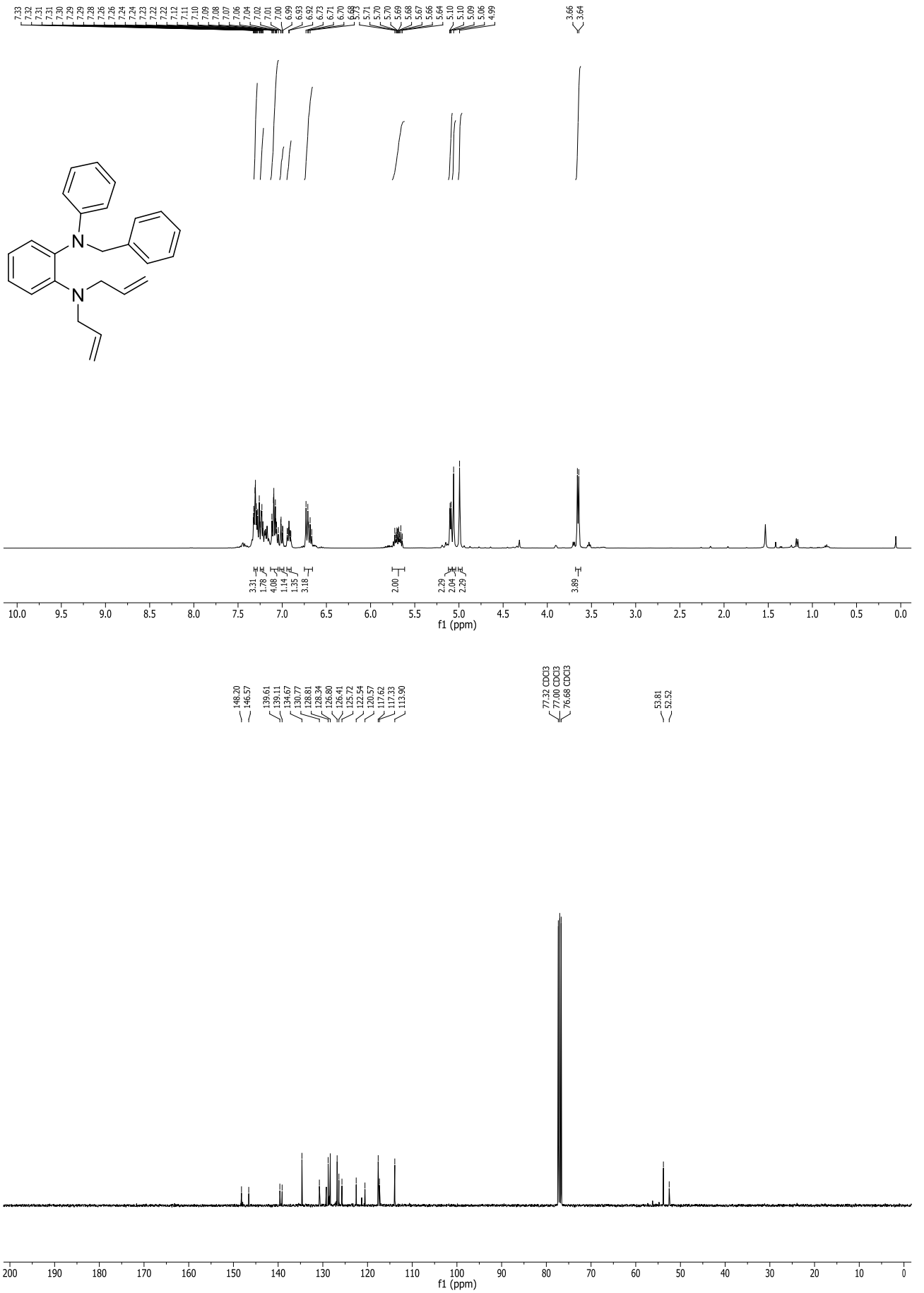


^{1}H and ^{13}C NMR data of compound **10d** (400 and 100 MHz respectively, $CDCl_3$).

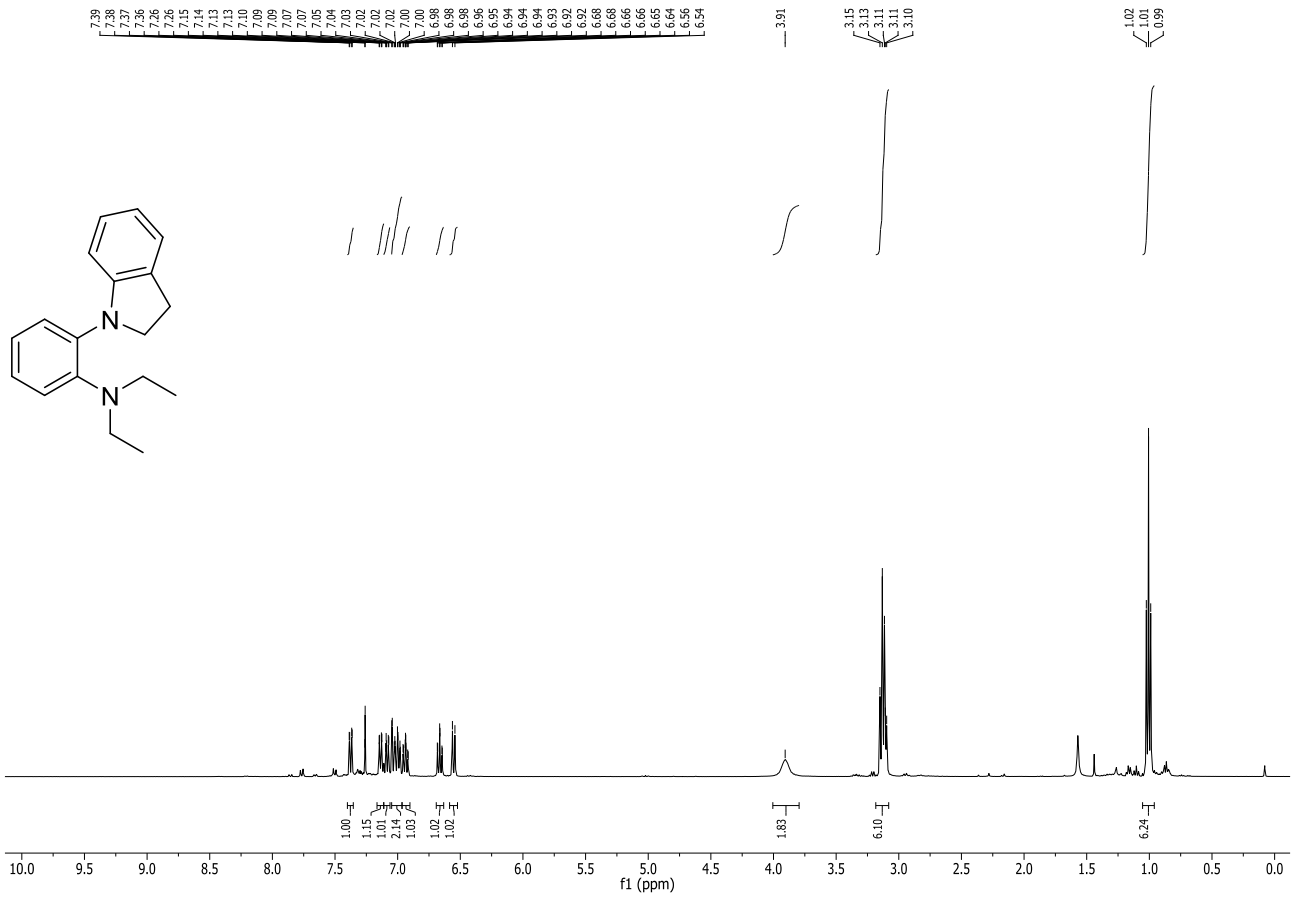


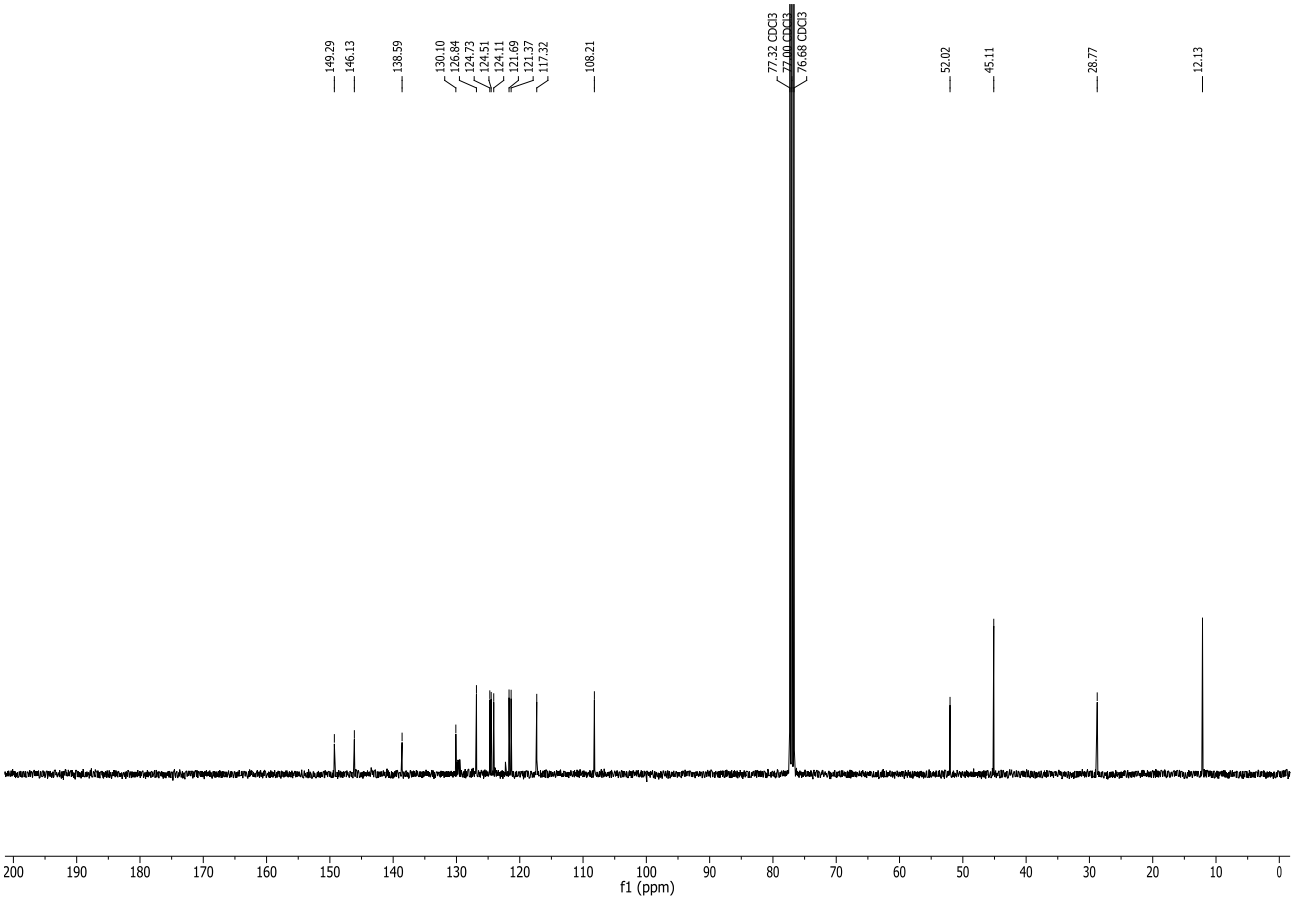


^{1}H and ^{13}C NMR data of compound **10e** (400 and 100 MHz respectively, $CDCl_3$).

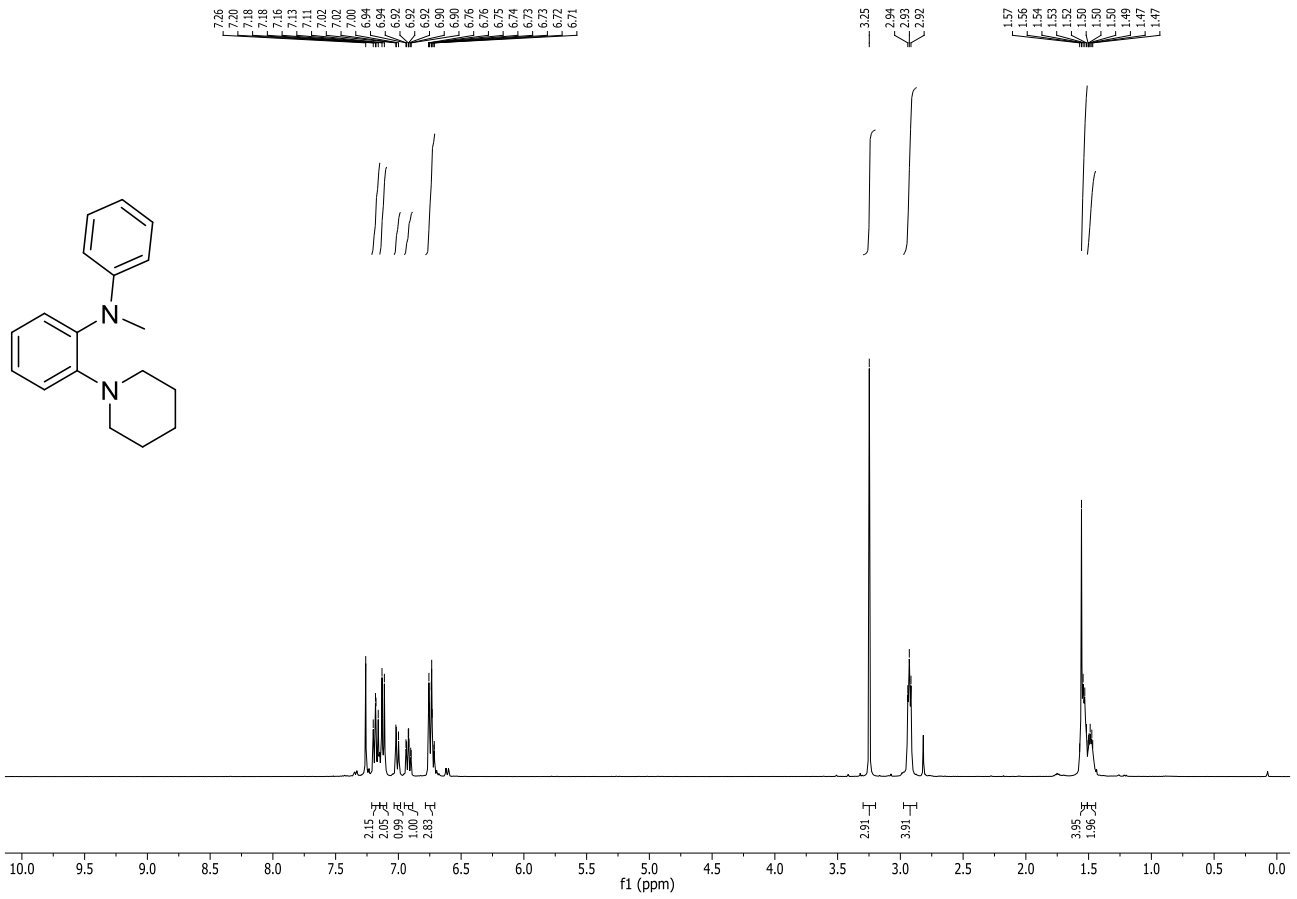


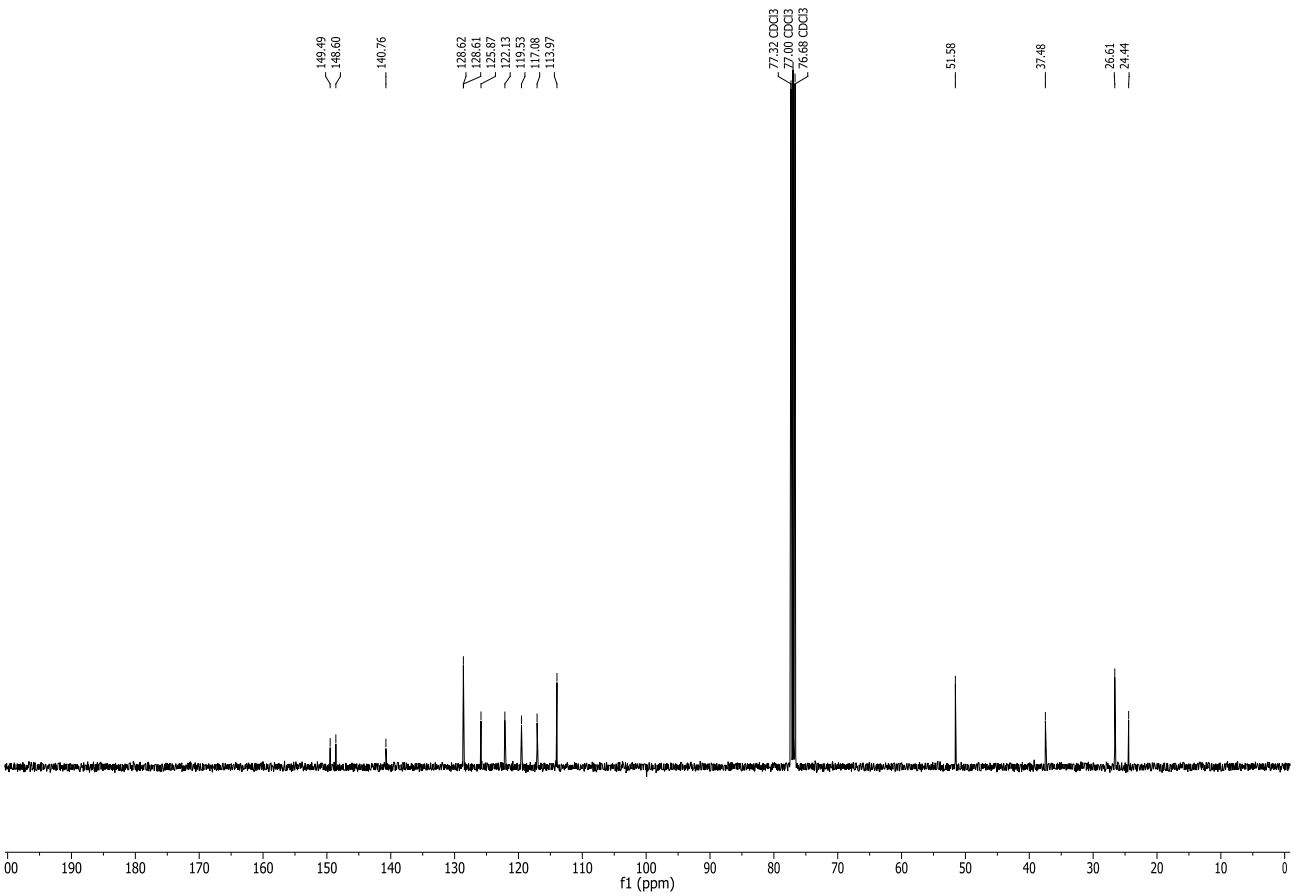
^{1}H and ^{13}C NMR data of compound **10f** (400 and 100 MHz respectively, $CDCl_3$).



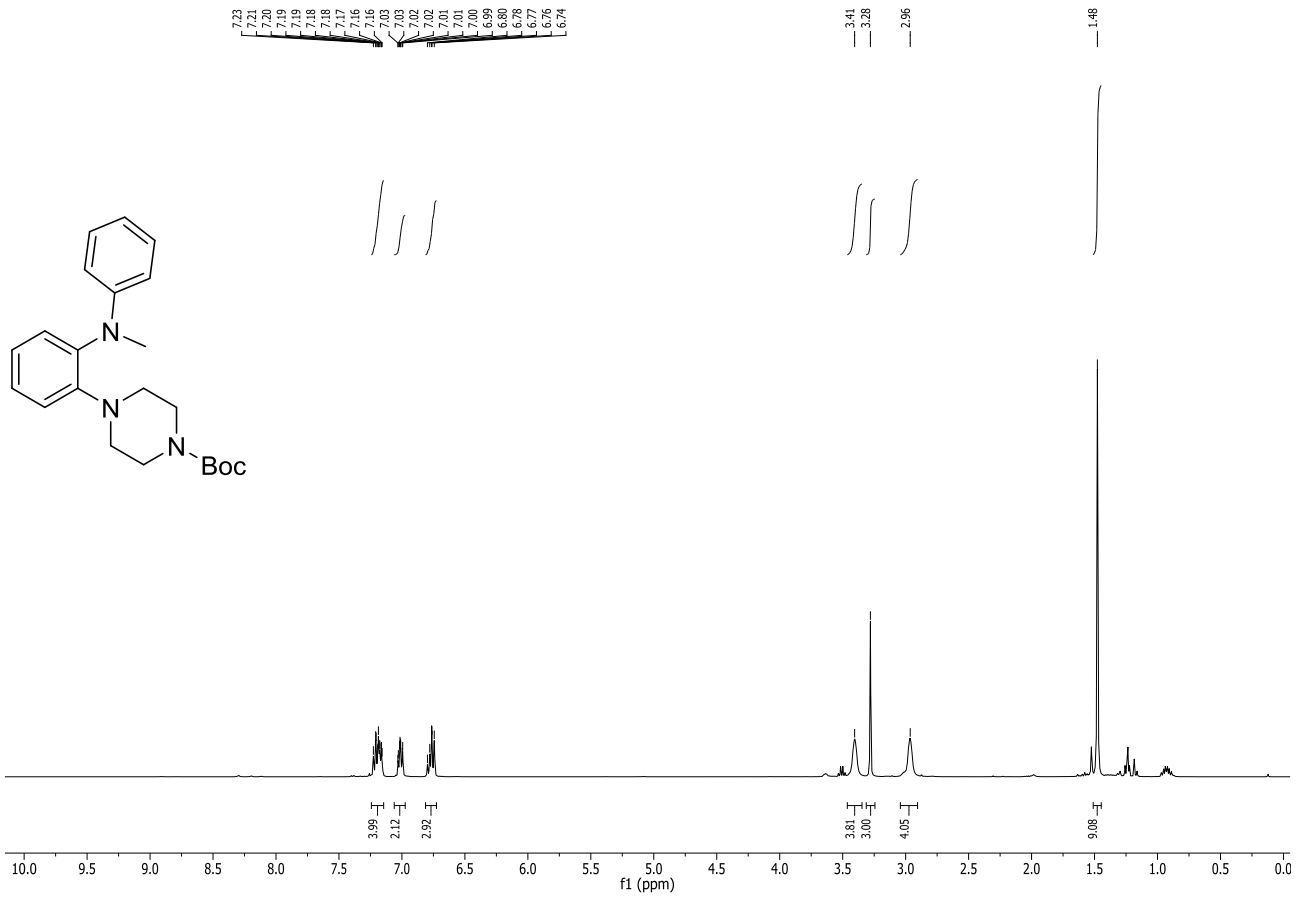


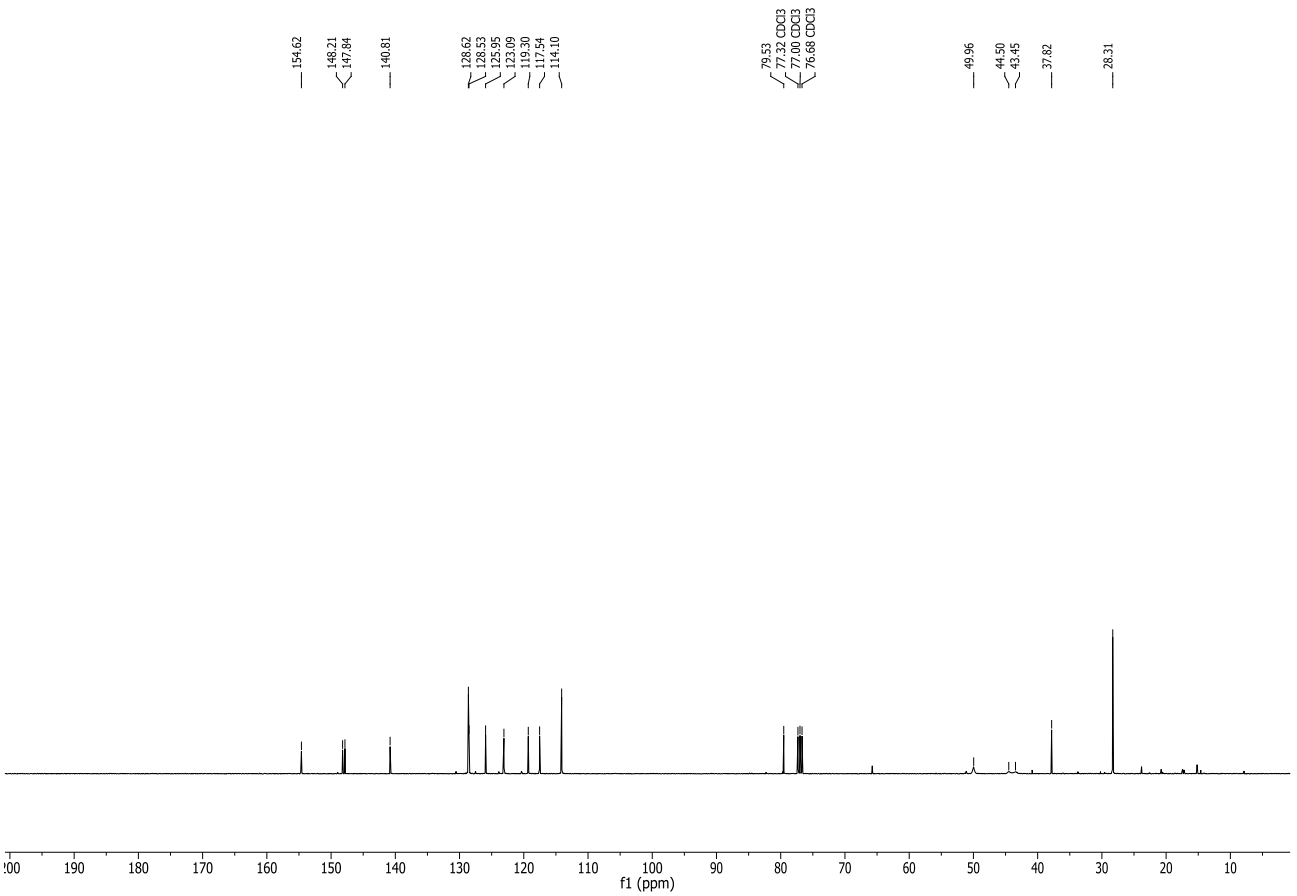
^{1}H and ^{13}C NMR data of compound **10g** (400 and 100 MHz respectively, $CDCl_3$).



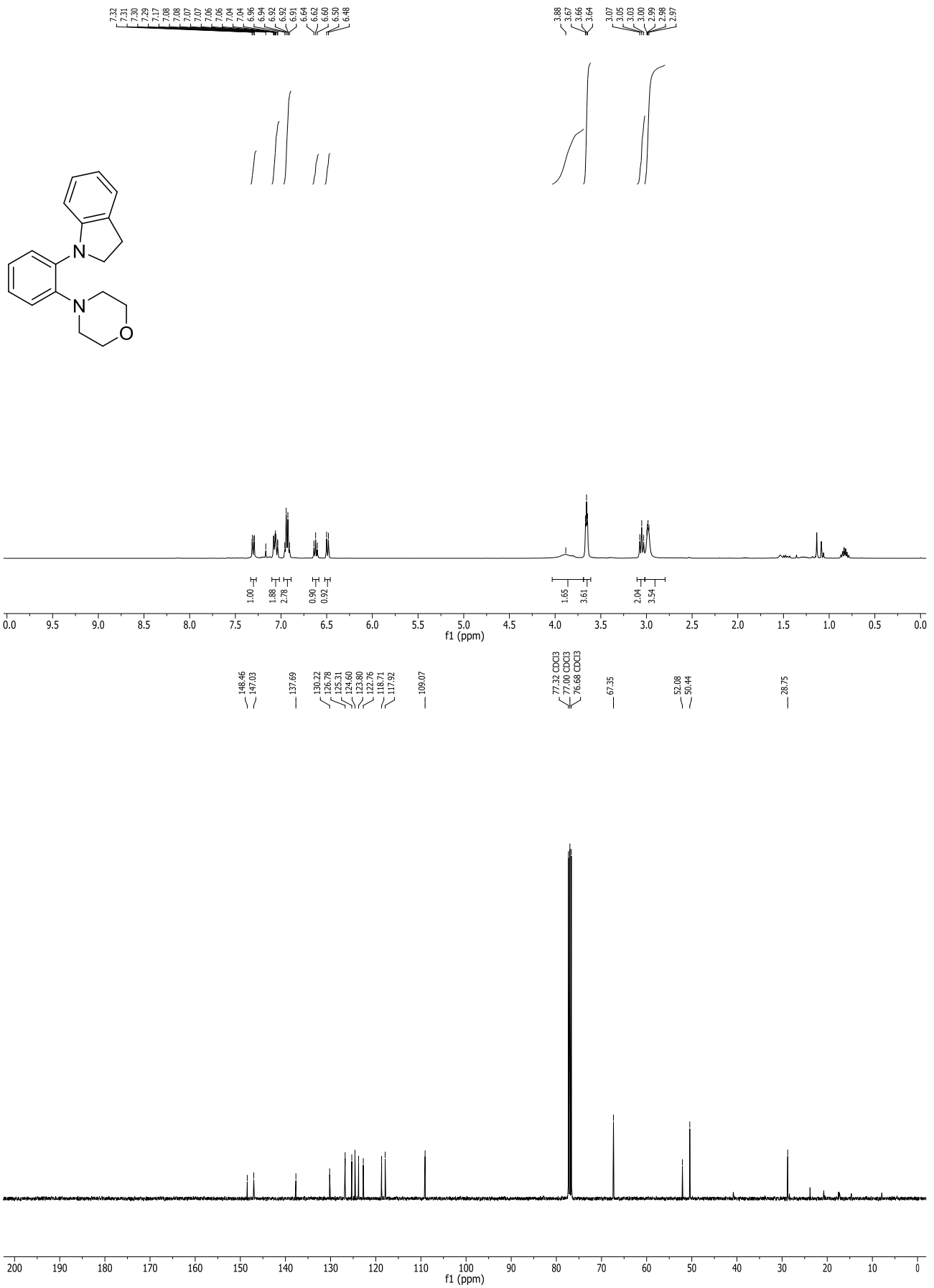


^{1}H and ^{13}C NMR data of compound **10h** (400 and 100 MHz respectively, $CDCl_3$).

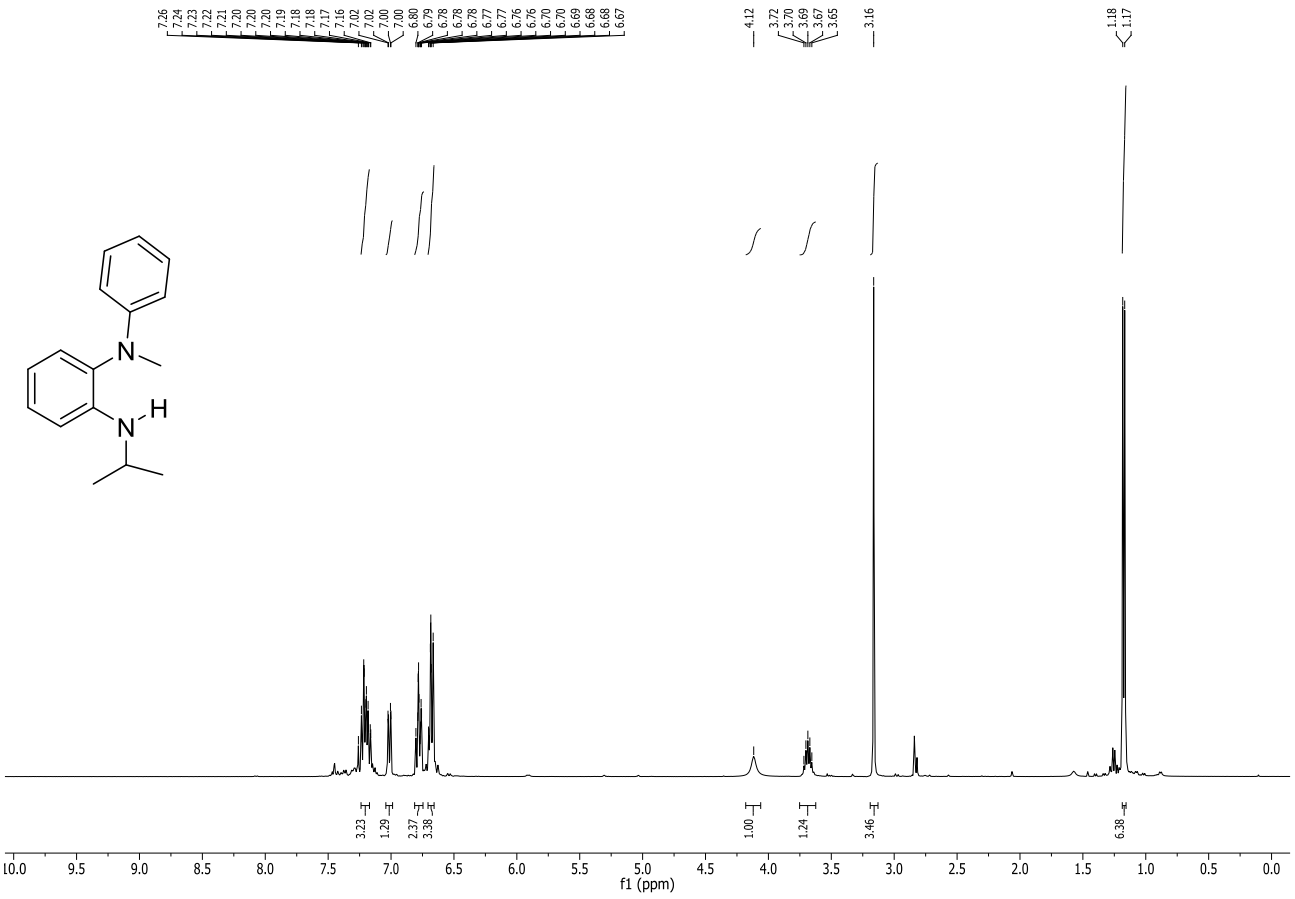


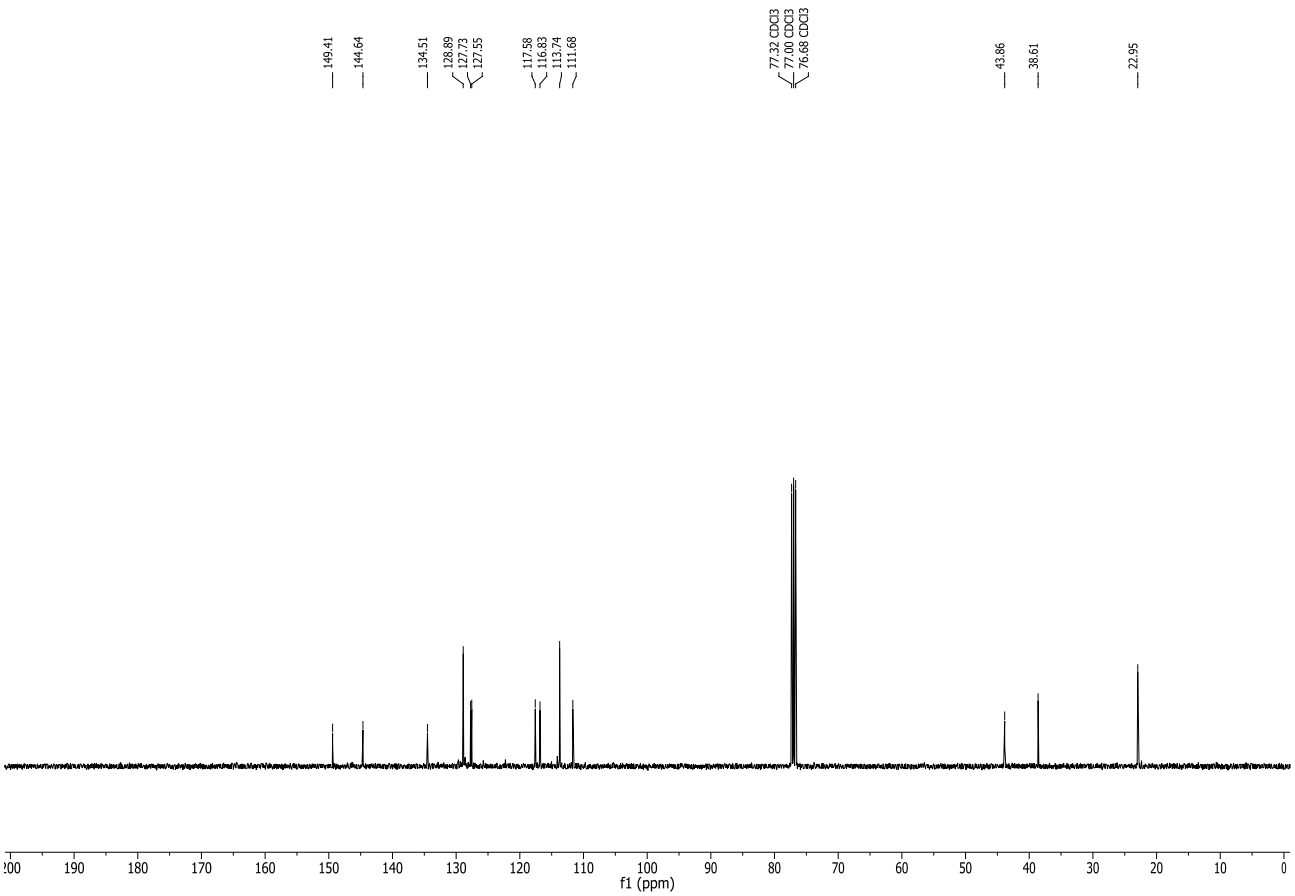


^{1}H and ^{13}C NMR data of compound **10i** (400 and 100 MHz respectively, $CDCl_3$).

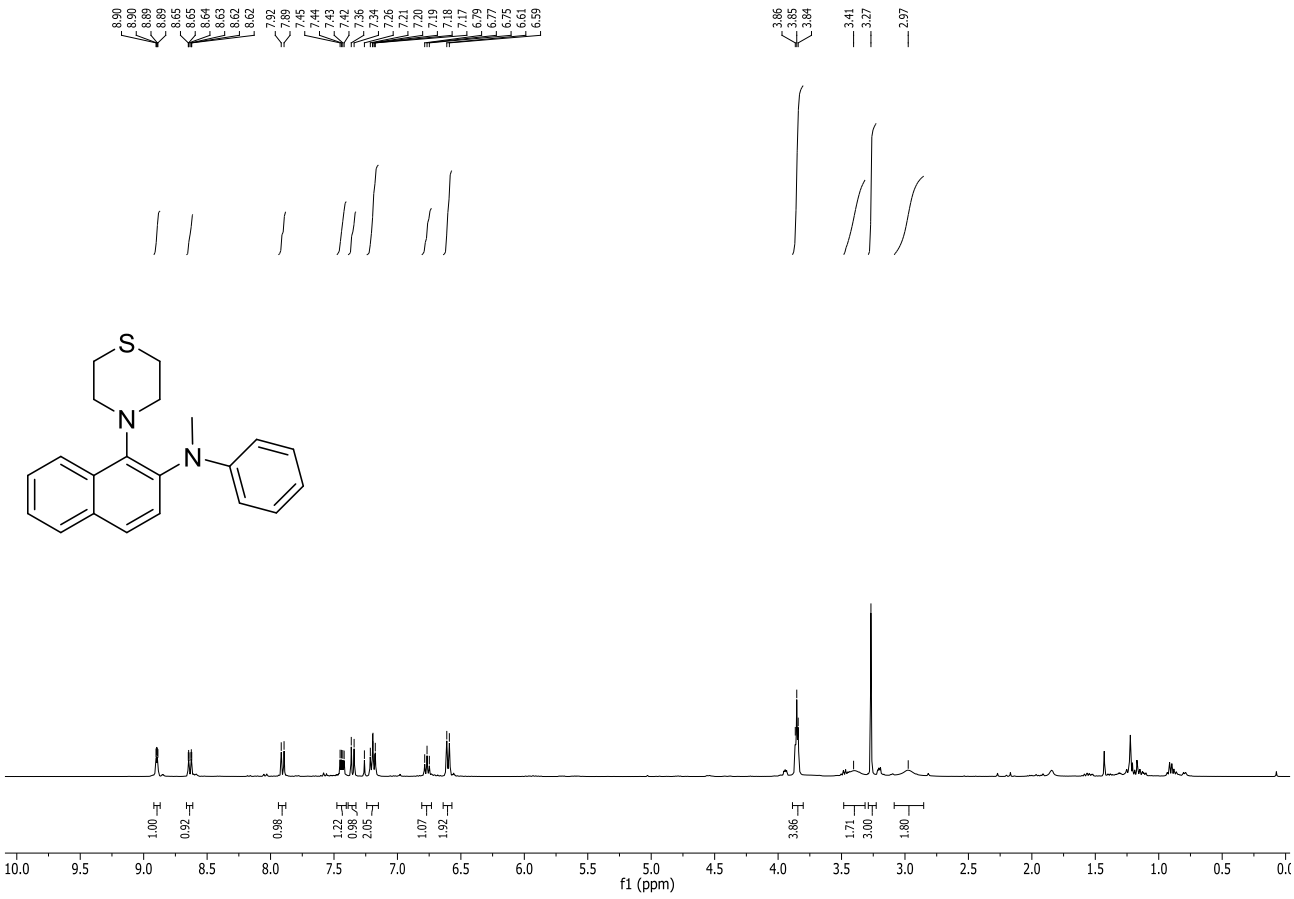


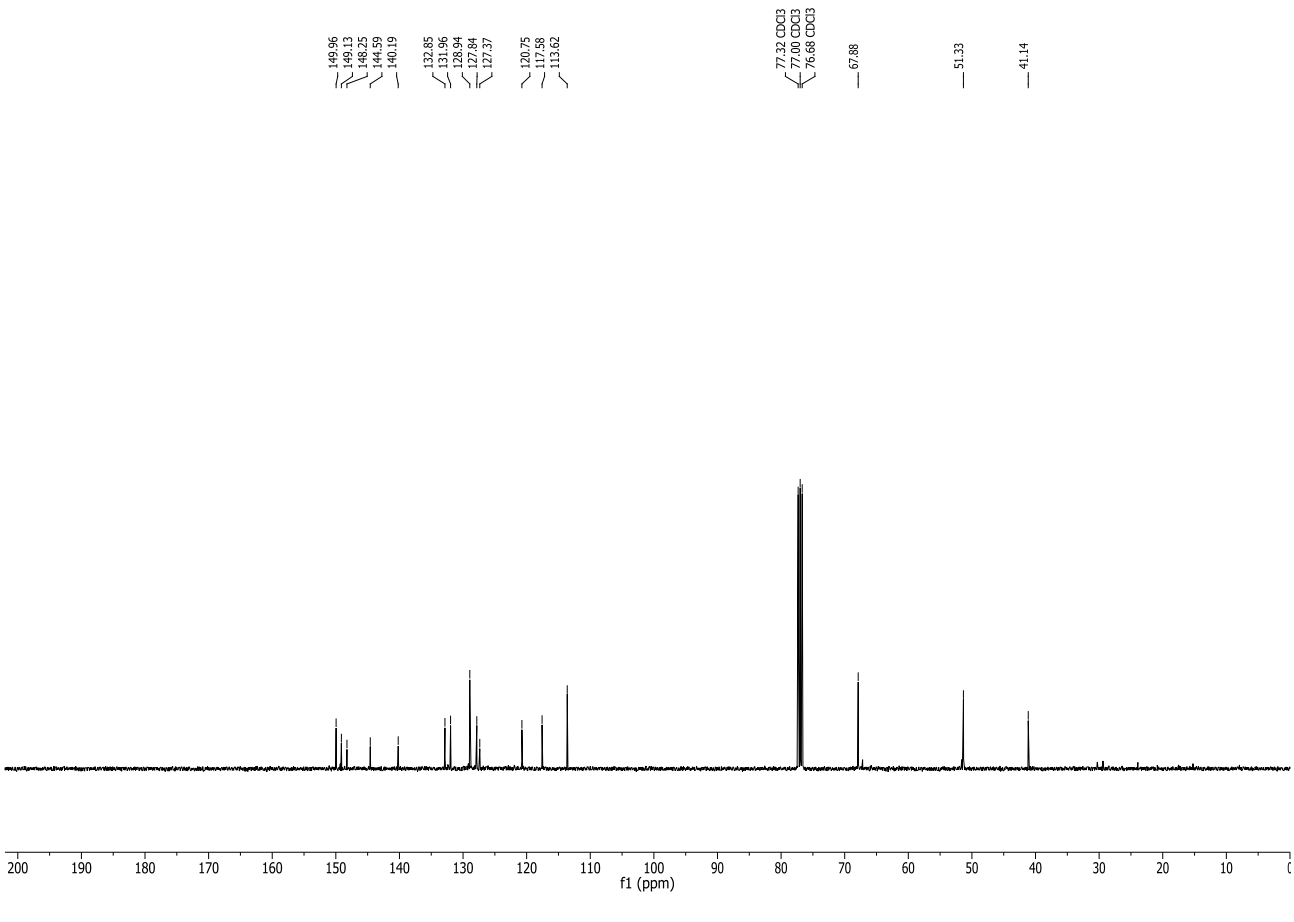
^{1}H and ^{13}C NMR data of compound **10j** (400 and 100 MHz respectively, $CDCl_3$).



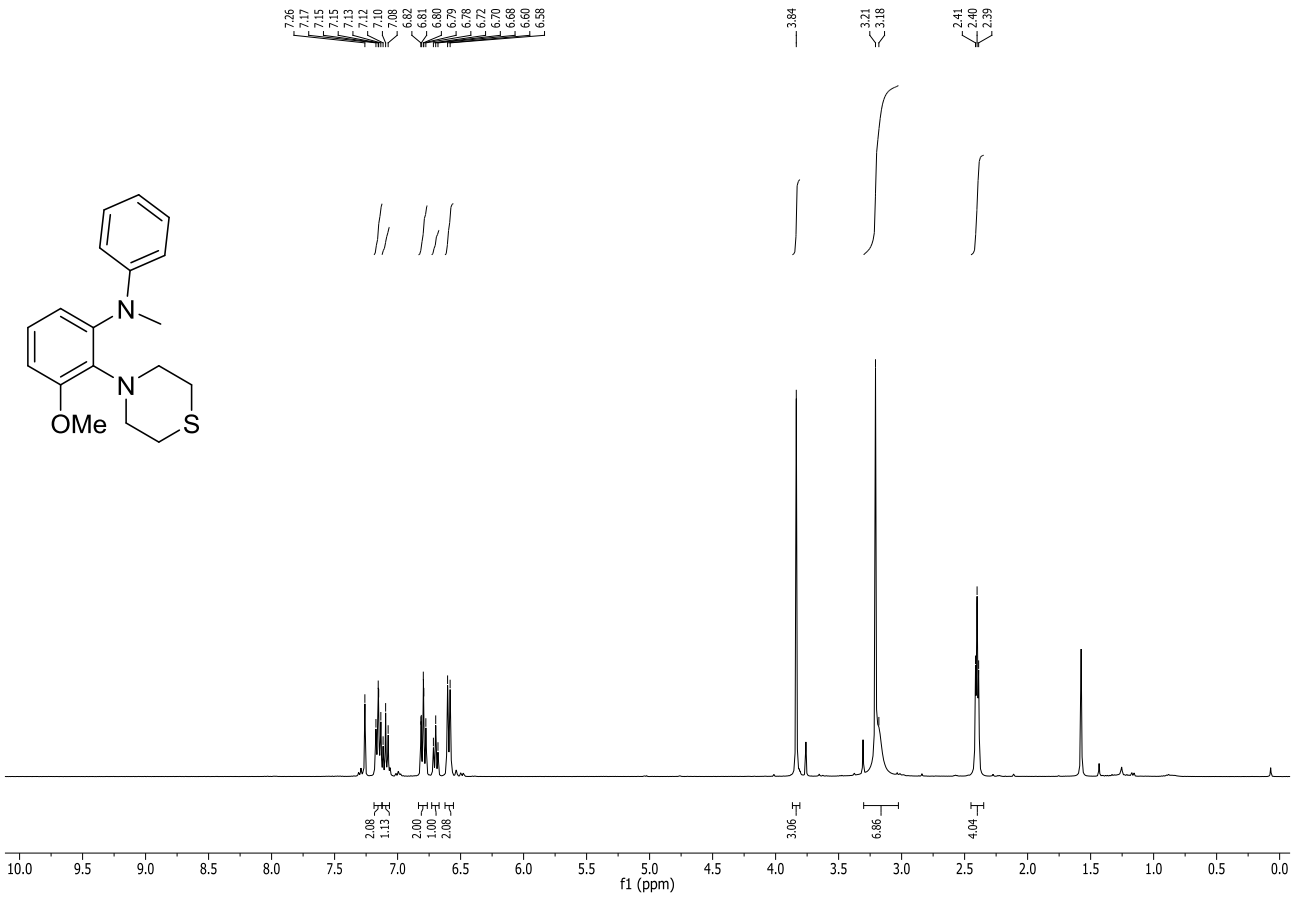


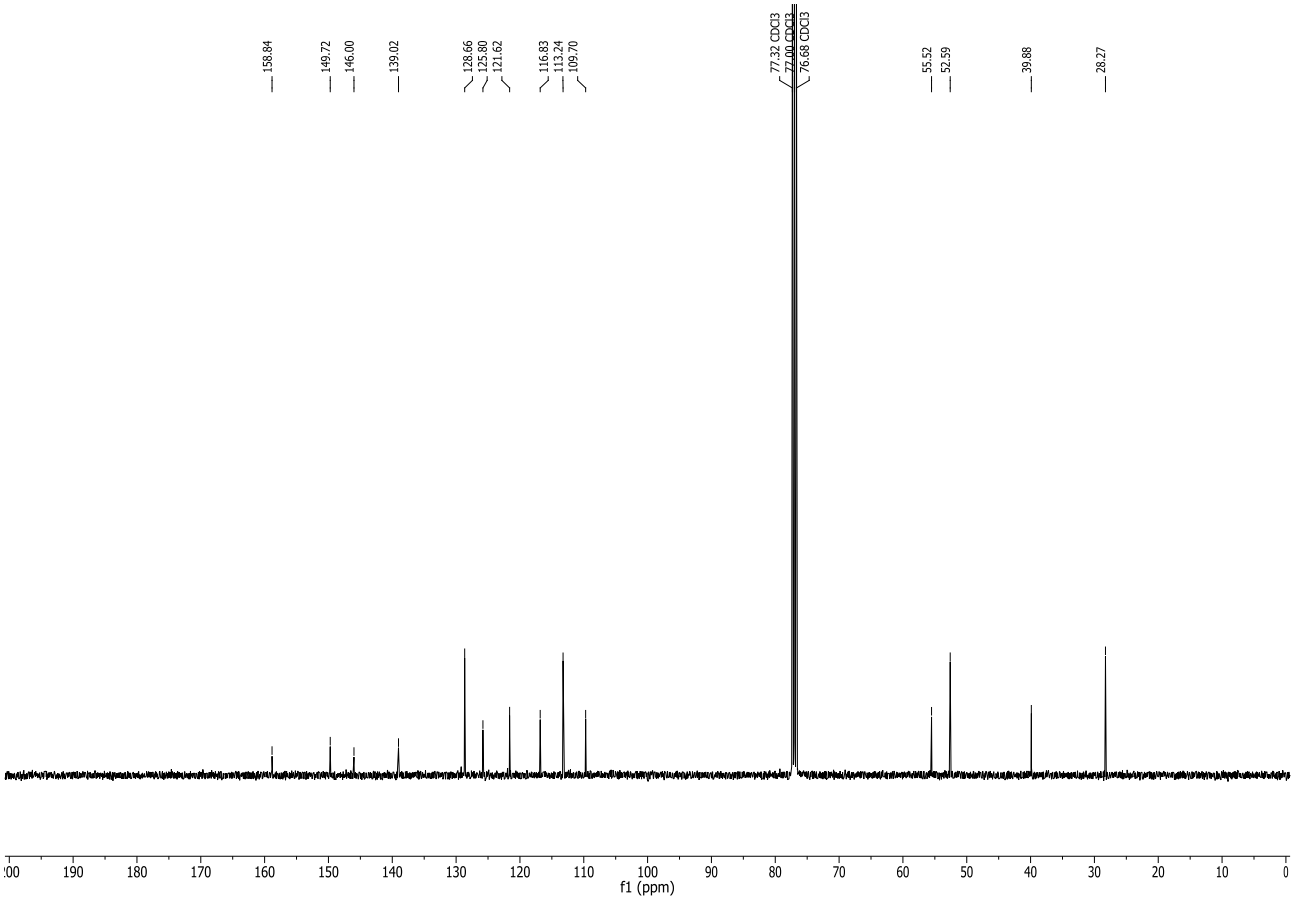
^{1}H and ^{13}C NMR data of compound **10k** (400 and 100 MHz respectively, $CDCl_3$).



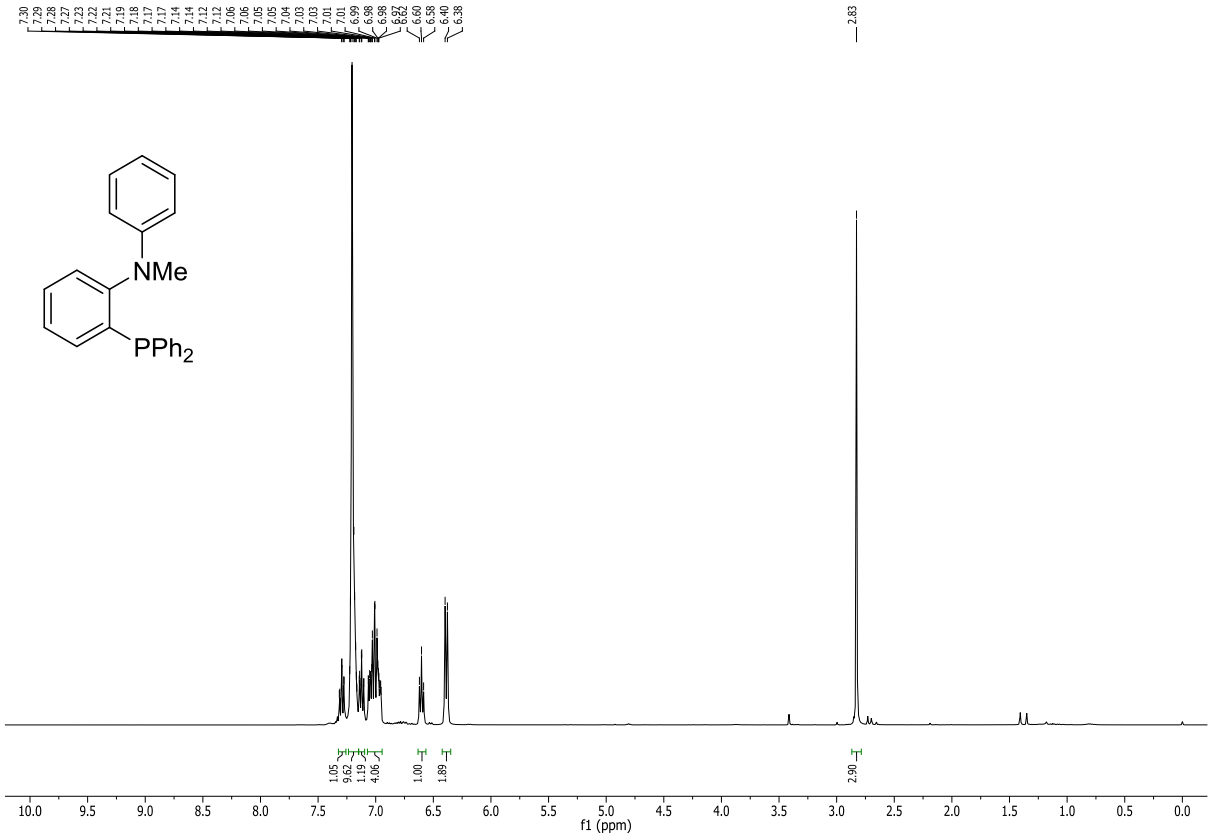


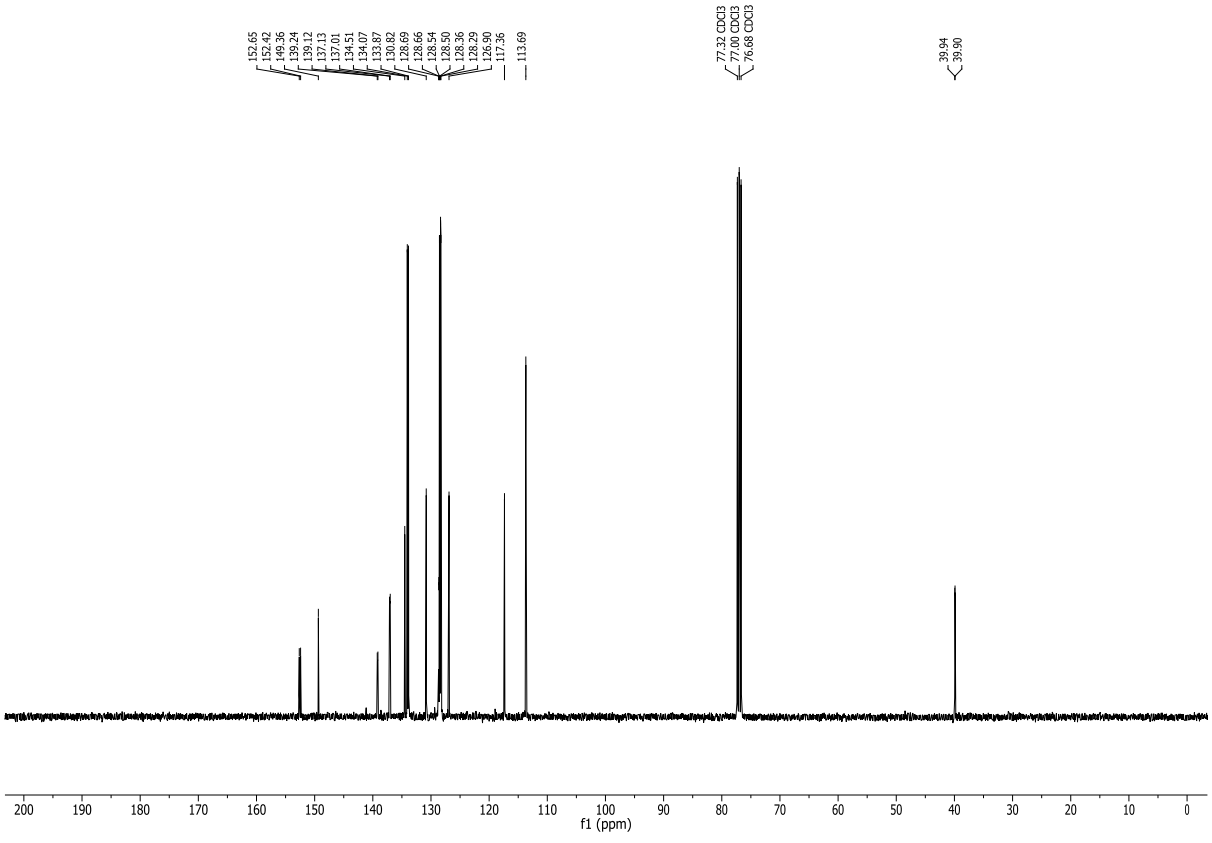
^{1}H and ^{13}C NMR data of compound **10l** (400 and 100 MHz respectively, $CDCl_3$).

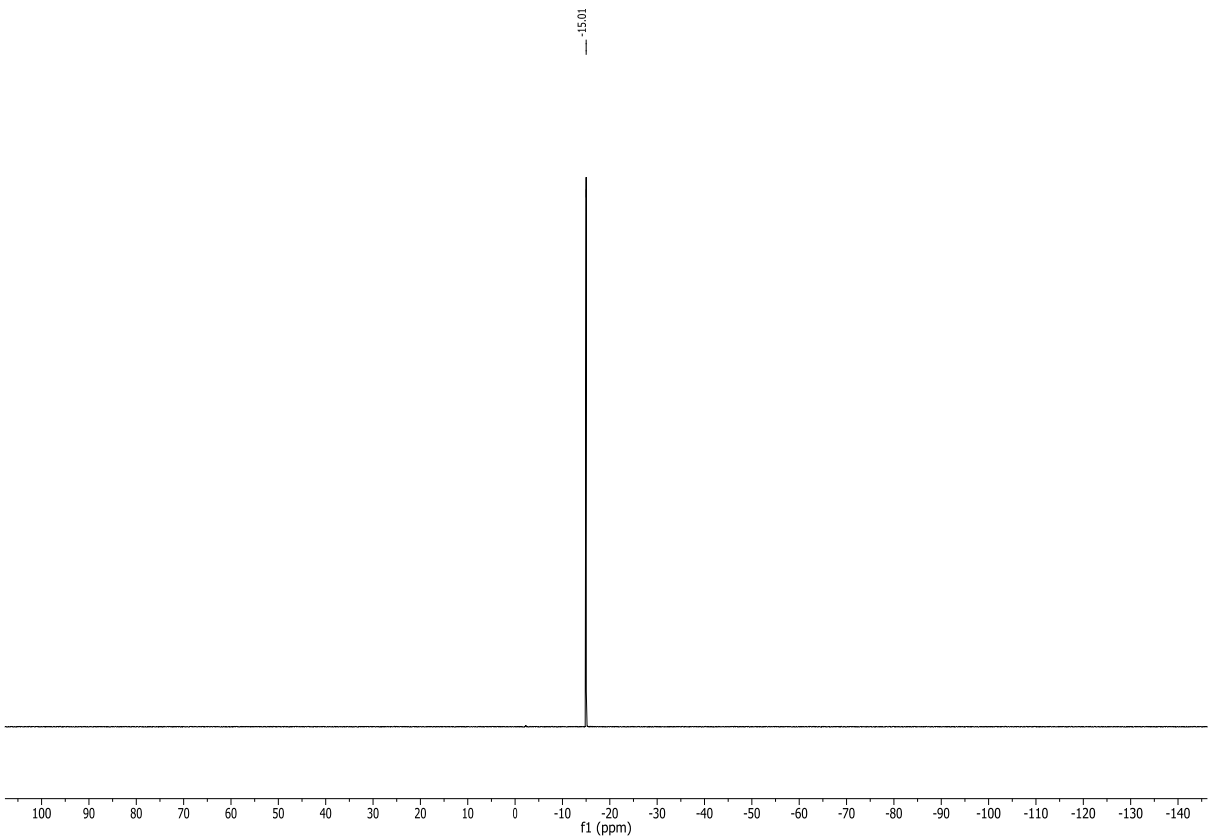




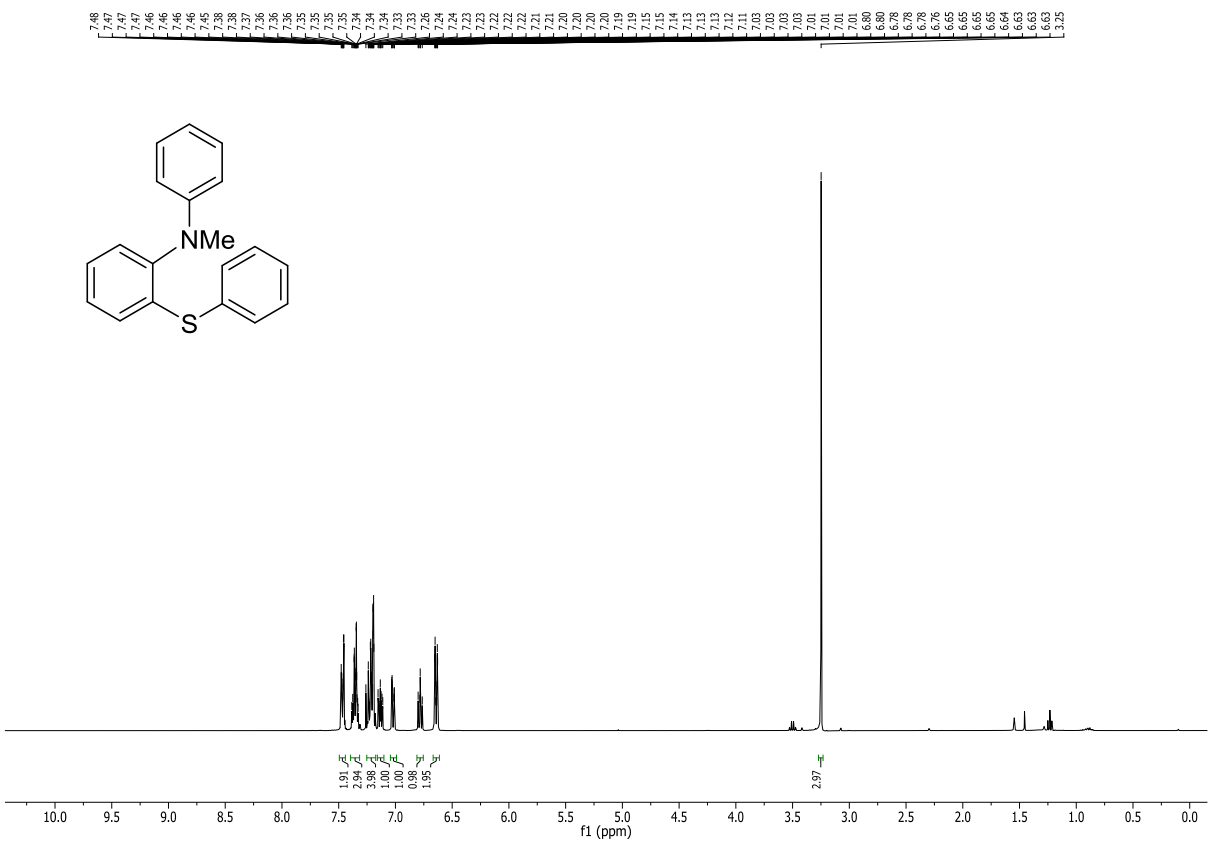
^{1}H,^{13}C and ^{31}P NMR data of compound **11a** (400, 100 and 162.3 MHz respectively, $CDCl_3$).

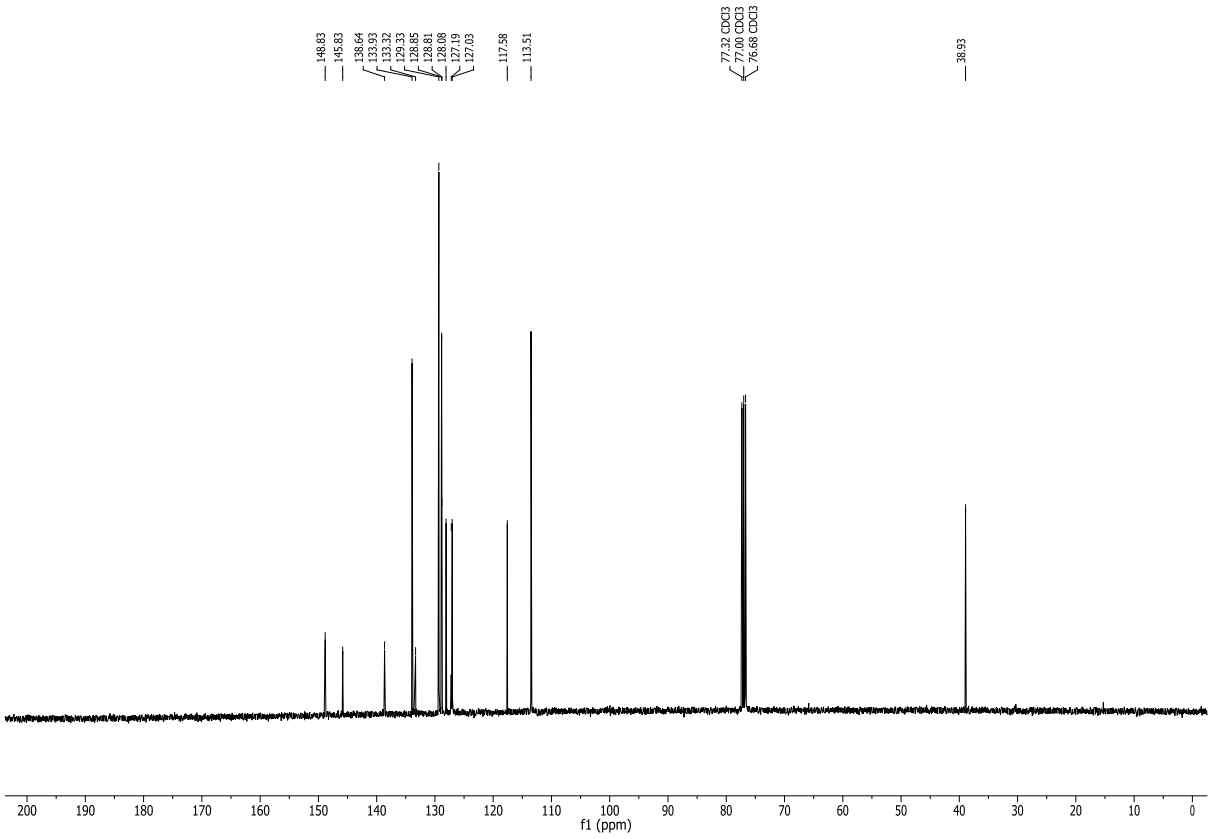




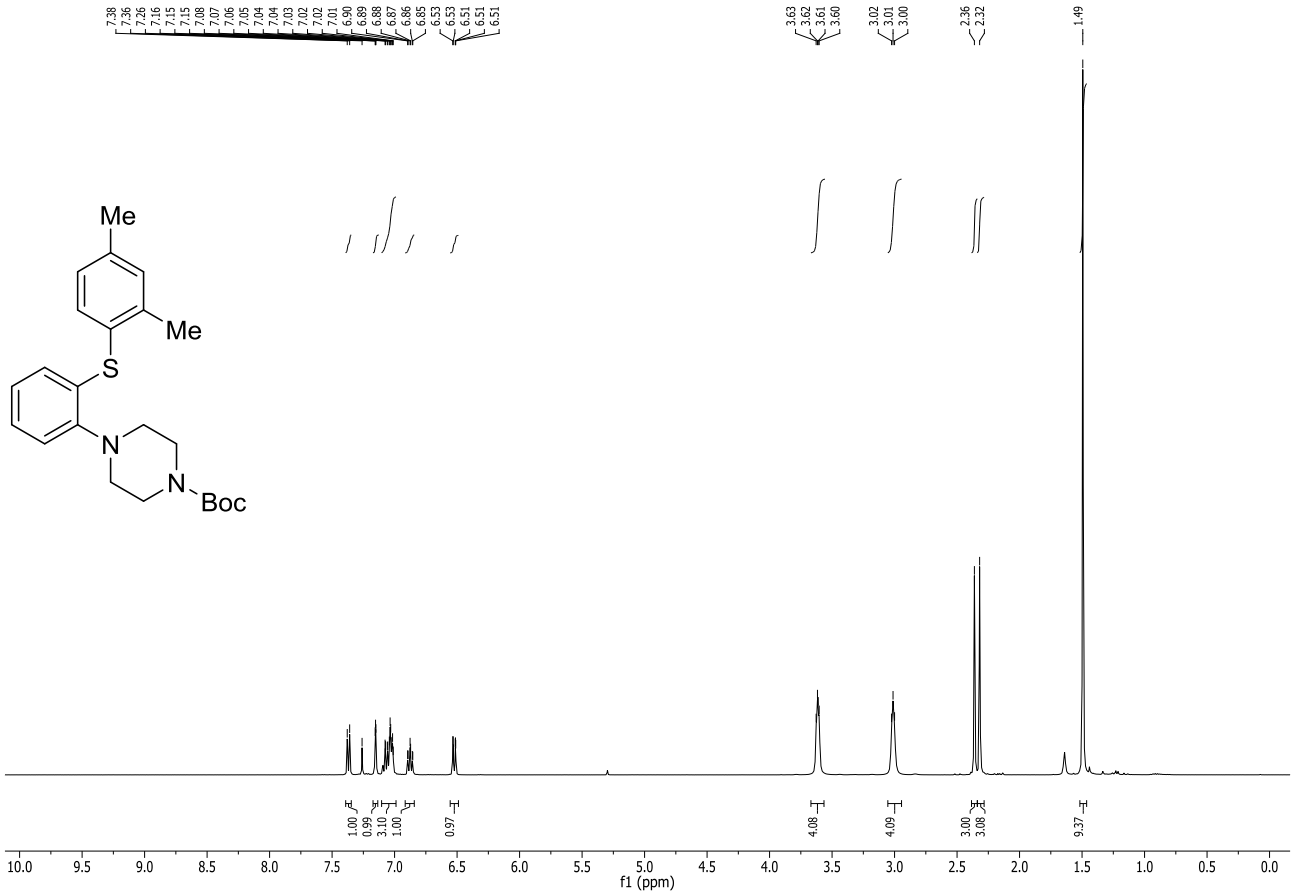

-15.01
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
f1 (ppm)

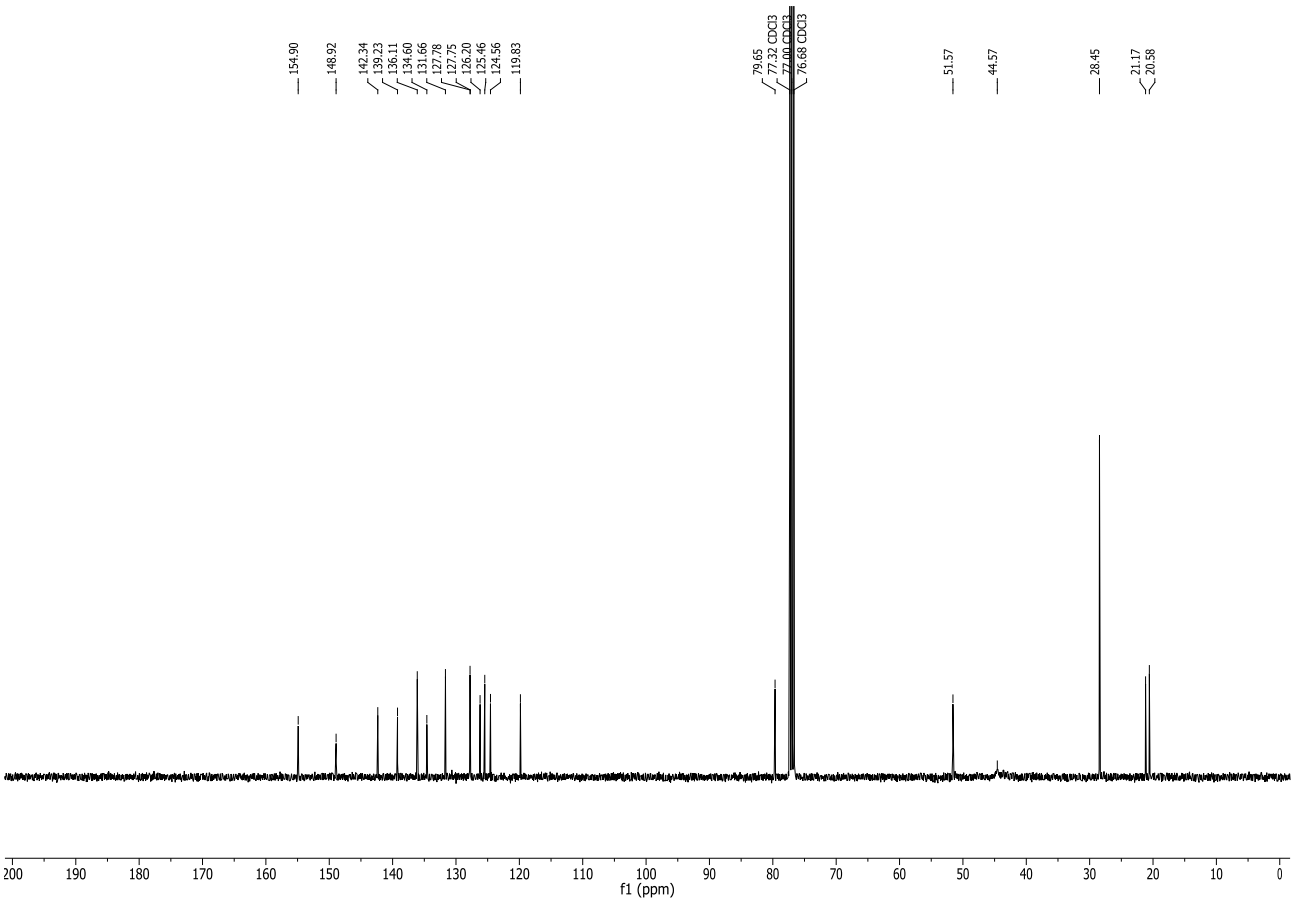
^{1}H and ^{13}C-NMR data of compound **11b** (400 and 100 MHz respectively, $CDCl_3$).



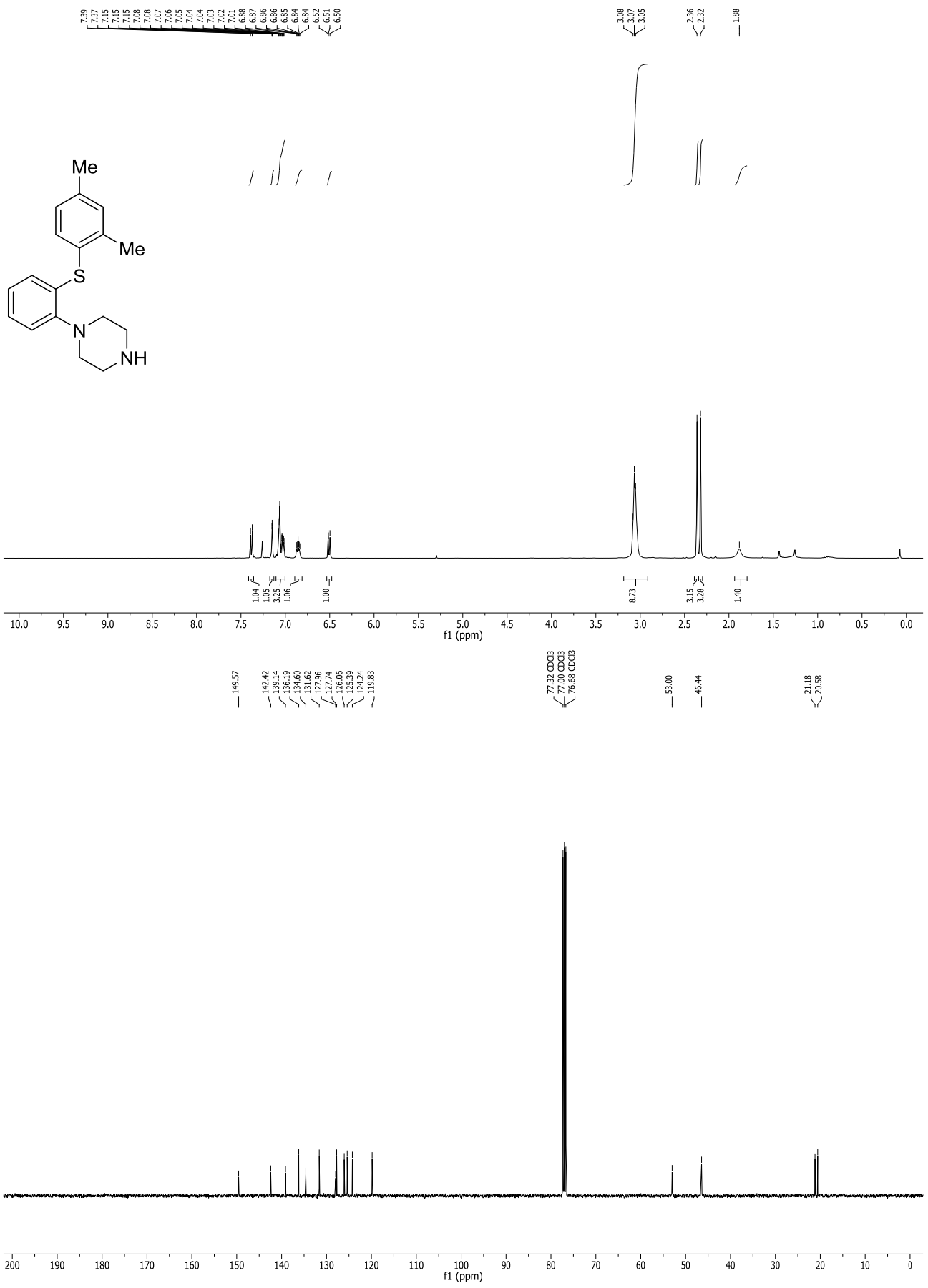


^{1}H and ^{13}C NMR data of compound **12** (400 and 100 MHz respectively, $CDCl_3$).



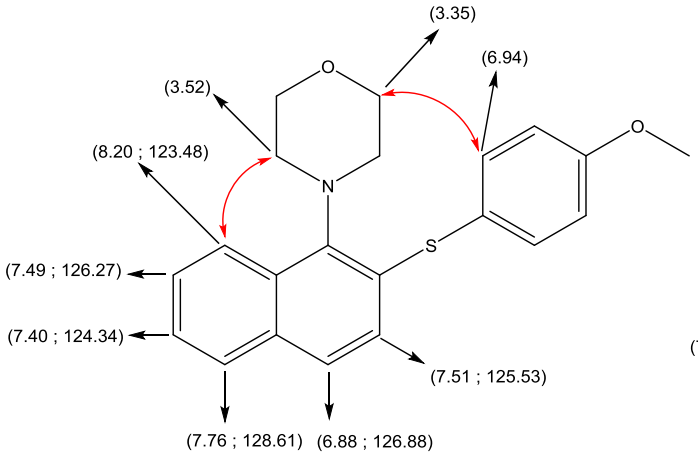


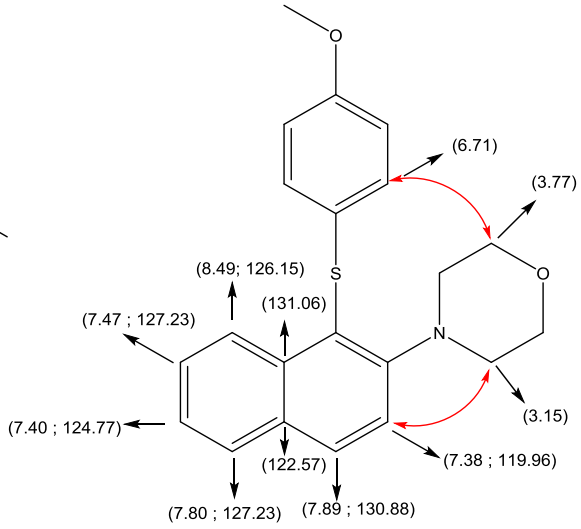
^{1}H and ^{13}C NMR data of vortioxetine **13** (400 and 100 MHz respectively, $CDCl_3$).



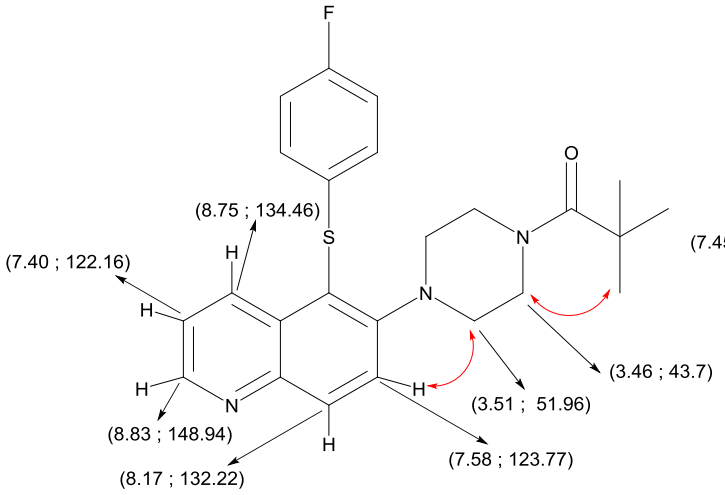
NMR assignments for compounds 7m, m', 7n, n', 9k and 9l (red arrows show selected NOESY correlatios).

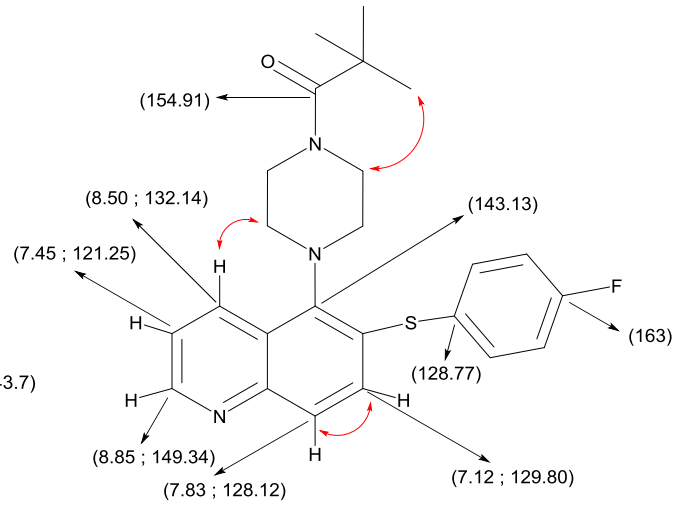
Compounds 7m and 7m'





Compounds 7n and 7n'





Compound 9k and 9l