Supporting Information for:

Detosylative (Deutero)alkylation of Indoles and Phenols with (Deutero)alkoxides

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General Information and Materials

Unless otherwise stated, all reactions were carried out in oven-dried Schlenk glassware under an atmosphere of dry argon or in a glovebox. Reactions were monitored by thin-layer chromatography (TLC). TLC was performed using Huanghai 8±0.2μm precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, $KMnO_4$, *p*-anisaldehyde, or phosphomolybdic acid staining. Huanghai silica gel (particle size 300–400 or 200–300 mesh) was used for silica gel chromatography. ^{1}H NMR spectra were recorded at room temperature on a Bruker ADVANCE III 400 MHz spectrometer or Oxford NMR AS600 600 MHz spectrometer and were reported relative to $CDCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on a Bruker ADVANCE III 400 MHz spectrometer and were reported relative to $CDCl_3$ (δ 77.16 ppm). Data for ^{1}H NMR were reported as chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration) using standard abbreviations for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, and br = broad signal. Data for ^{13}C NMR were reported in terms of chemical shifts (δ ppm). GC-MS analyses were carried out on an Agilent 7890B gas chromatograph equipped with a HP-5 (5%-phenyl)-methylpolysiloxane capillary column (Agilent) and an Agilent 5977A quadrupole mass-selective detector (MSD) in an electron ionization (EI) mode. High resolution mass spectra (HRMS) were obtained by use of Thermo Fisher Scientific LTQ FTICR-MS spectrometer or Bruker Compact TOF mass spectrometer in an electrospray ionization mode (ESI+) or an atmospheric pressure chemical ionization (APCI+).

Unless otherwise noted, all reagents were purchased commercially and used without further purification. Petroleum ether (60–90 ^{o}C) was used as eluent for silica gel chromatography. Dry solvents were purchased commercially or were dried by passage through an activated alumina column under argon.

Scheme S1. Debrominative Deuteration vs Detosylative Methylation.

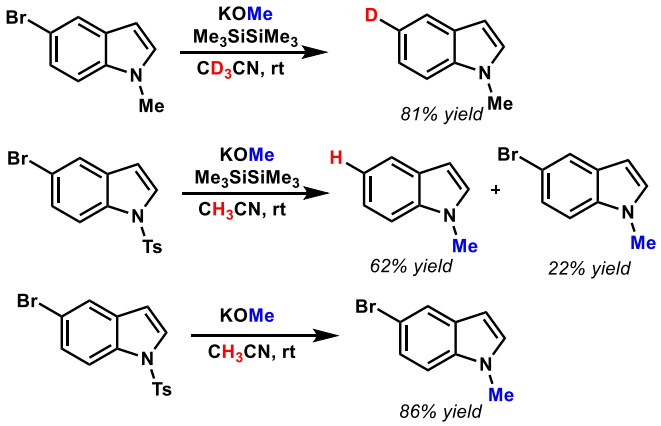
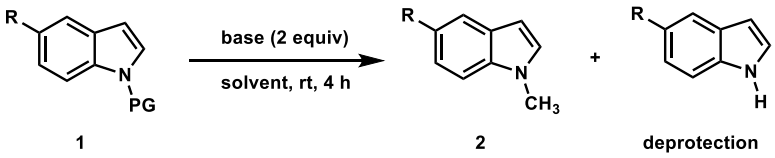


Table S1. Reaction Condition Optimizations for N-Methylation of *N*-Tosylindole.

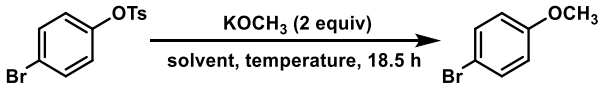


entry[a]	R; PG	solvent	base	**2** (yield)	deprotection (yield)
1	R = H; PG = Ts	CH_3CN	$KOCH_3$	**2a**, 95%[b]	N.D.
2	R = H; PG = Ts	THF	$KOCH_3$	**2a**, 95%[b]	N.D.
3	R = H; PG = Ts	toluene	$KOCH_3$	**2a**, 94%[b]	N.D.
4	R = H; PG = Ts	DMF	$KOCH_3$	**2a**, 81%[b]	N.D.
5	R = H; PG = Ts	DCM	$KOCH_3$	**2a**, 72%[b]	N.D.
6	R = H; PG = Ts	CH_3CN	$LiOCH_3$	**2a**, N.D.	N.D.
7	R = H; PG = Ts	CH_3CN	$NaOCH_3$	**2a**, 84%[c]	N.D.
8	R = H; PG = Ts	CH_3CN	$KOCH_3$	**2a**, 92%[c]	N.D.
9	R = H; PG = $PhSO_2$	CH_3CN	$KOCH_3$	**2a**, 96%[c]	N.D.
10	R = H; PG = Tf	CH_3CN	$KOCH_3$	**2a**, N.D.	77%[c]
11	R = Br; PG = Ac	CH_3CN	$KOCH_3$	**2d**, N.D.	20%[c] (68%[d])

[a]Reactions were conducted with 0.2 mmol **1**, 0.4 mmol base in 0.7 mL solvent. [b]Yield was determined by GC using dodecane as an internal standard. [c]Isolated yield. [d]Recovered starting material. N.D. = not detected.

General Procedure for Condition Optimizations (Table S1): To a screw-capped vial equipped with a magnetic stirring bar were added 1-tosyl-1*H*-indole **1a** (54.2 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) and 0.7 mL solvent. The vial was sealed and stirred until the completion of the reaction as monitored by TLC. Then the vial was removed from the glove box. H_2O (10 mL) was added to quench the reaction and the mixture was extracted with DCM (5 mL × 3). The organic layers were washed with brine and dried over anhydrous Na_2SO_4, then filtered and evaporated under reduced pressure. The desired product was purified by silica gel chromatography.

Table S2. Reaction Condition Optimizations for O-Methylation of *O*-Tosylphenol.



1n 2n

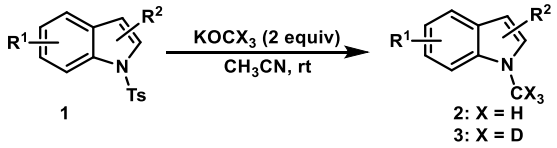
entry[a]	solvent	temperature	yield
1	DCM	rt	39%
2	THF	rt	30%
3	CH_3CN	rt	41%
4	CH_3CN	45 °C	82%

[a]Reactions were conducted with 0.2 mmol 4-bromophenyl 4-methylbenzenesulfonate (**1n**), 0.4 mmol $KOCH_3$ in 2 mL solvent for 18.5 h. [b]Isolated yield.

General Procedure for Condition Optimizations (Table S2): To a screw-capped vial equipped with a magnetic stirring bar were added 4-bromophenyl 4-methylbenzenesulfonate **1n** (65.4 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) and 2 mL solvent. The vial was sealed and stirred at indicated temperature for 18.5 h. Then the vial

was removed from the glove box. The reaction mixture was filtered through a short pad of Celite, and washed by Et_2O (diethyl ether) (about 4 – 5 mL). The filtrate was concentrated under reduced pressure. The desired product was purified by silica gel chromatography.

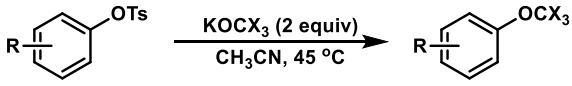
General Procedure and Spectroscopic Data for Detosylation/(Deutero)alkylation of Indoles and Phenols with (Deutero)alkoxides



1

2: X = H
3: X = D

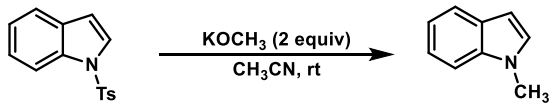
General procedure A: To a dry schlenk tube equipped with a magnetic stirring bar were added tosylated heterocycles **1** (1.0 equiv), $KOCH_3$ or $KOCD_3$ (2.0 equiv) and CH_3CN under an atmosphere of dry argon. The mixture was stirred at room temperature until the substrate **1** was completely consumed as monitored by TLC. The reaction was quenched with H_2O (10 mL) and extracted with DCM (10 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Then the desired product was purified by silica gel chromatography.



1

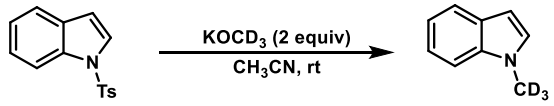
2: X = H
3: X = D

General procedure B: To a dry schlenk tube equipped with a magnetic stirring bar were added *p*-toluenesulfonylphenolic esters **1** (1.0 equiv), $KOCH_3$ or $KOCD_3$ (2.0 equiv), and CH_3CN under an atmosphere of dry argon. The mixture was stirred at 45 °C until the substrate **1** was completely consumed as monitored by TLC. Then, the reaction mixture was filtered through a short pad of Celite, and washed with Et_2O. The filtrate was concentrated under reduced pressure at 0 °C. The crude mixture was purified by silica gel chromatography to give the desired product.



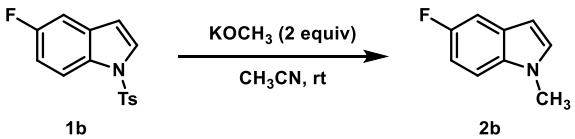
1a 2a

1-Methyl-1*H*-indole (2a): The general procedure A was followed. The reaction was performed with 1-tosyl-1*H*-indole **1a** (54.3 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2a** (24.0 mg, 92% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.18 – 7.09 (m, 1H), 7.07 (d, *J* = 2.8 Hz, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 3.81 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[1]



1a 3a

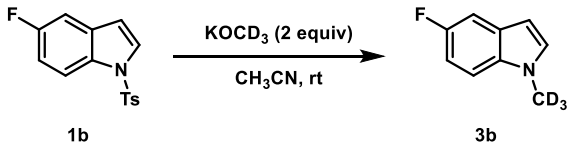
1-Trideuteromethyl-1*H*-indole (3a): The general procedure A was followed. The reaction was performed with 1-tosyl-1*H*-indole **1a** (135.6 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3a** (59.1 mg, 88% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.27 – 7.18 (m, 1H), 7.12 (d, *J* = 2.9 Hz, 1H), 6.60 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 128.8, 128.5, 121.5, 120.9, 119.3, 109.3, 100.9, 32.2 (m); GCMS: calc'd for $C_9H_6D_3N$ $[M]^+$: 134.09, found: 134.10.



1b 2b

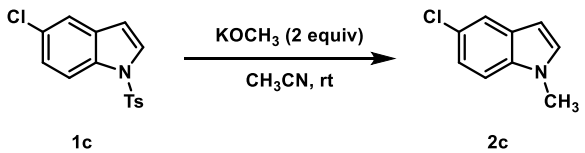
5-Fluoro-1-methyl-1*H*-indole (2b): The general procedure A was followed. The reaction was performed with 5-fluoro-1-tosyl-1*H*-indole **1b** (57.9 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2b** (28.1 mg, 94% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.29 – 7.26 (m, 1H), 7.23 (dd, *J* = 8.9, 4.3 Hz, 1H), 7.09 (d, *J* = 2.9 Hz, 1H), 6.98 (td, *J* = 9.1, 2.5 Hz, 1H), 6.45 (dd, *J* = 3.2, 1.0 Hz, 1H), 3.79 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]



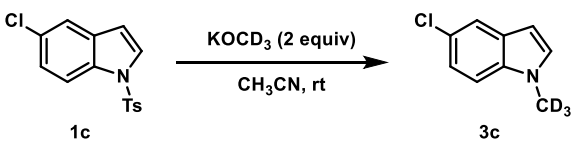
1b 3b

5-Fluoro-1-Trideuteromethyl-1*H*-indole (3b): The general procedure A was followed. The reaction was performed with 5-fluoro-1-tosyl-1*H*-indole **1b** (144.6 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3b** (64.8 mg, 86% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 9.7, 2.5 Hz, 1H), 7.15 (dd, *J* = 8.8, 4.3 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.91 (td, *J* = 9.1, 2.5 Hz, 1H), 6.38 (dd, *J* = 3.1, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 (d, *J* = 233.4 Hz), 133.5, 130.5, 128.7 (d, *J* = 10.3 Hz), δ 110.0 (d, *J* = 12.8 Hz), 109.8 (d, *J* = 3.8 Hz), 105.6 (d, *J* = 23.3 Hz), 100.9 (d, *J* = 4.8 Hz), 32.5 (m); GCMS: calc'd for $C_9H_5D_3FN$ $[M]^+$: 152.08, found: 152.10.



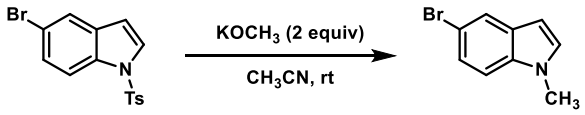
1c 2c

5-Chloro-1-methyl-1*H*-indole (2c): The general procedure A was followed. The reaction was performed with 5-chloro-1-tosyl-1*H*-indole **1c** (61.0 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2c** (29.6 mg, 89% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 2.1 Hz, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.17 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.07 (d, *J* = 3.0 Hz, 1H), 6.42 (d, *J* = 3.0 Hz, 1H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]



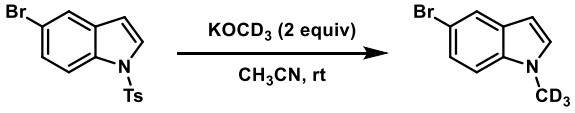
1c 3c

5-Chloro-1-trideuteromethyl-1*H*-indole (3c): The general procedure A was followed. The reaction was performed with 5-chloro-1-tosyl-1*H*-indole **1c** (152.9 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3c** (72.9 mg, 86% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.1 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.20 (dd, *J* = 8.7, 1.9 Hz, 1H). 7.08 (d, *J* = 3.1 Hz, 1H), 6.45 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 130.2, 129.5, 125.1, 121.8, 120.2, 110.3, 100.6, 32.4 (m); GCMS: calc'd for $C_9H_5D_3ClN$ $[M]^+$: 168.05, found: 168.05.



1d 2d

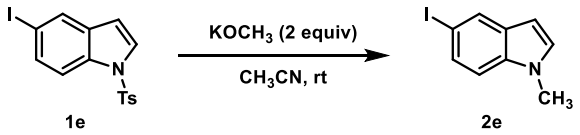
5-Bromo-1-methyl-1*H*-indole (2d): The general procedure A was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (70.1 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2d** (36.3 mg, 86% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.42 (d, *J* = 3.2 Hz, 1H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]



1d 3d

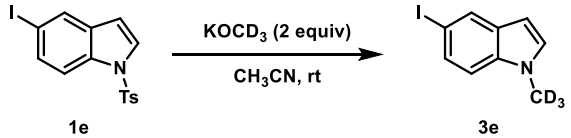
5-Bromo-1-trideuteromethyl-1*H*-indole (3d): The general procedure A was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.1 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3d** (96.4 mg, 91% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.8 Hz, 1H), 7.31 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 3.1 Hz, 1H), 6.44 (dd, *J* = 3.2, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 135.4, 130.2, 130.0, 124.3, 123.3, 112.7, 110.8, 100.6, 32.4 (m); GCMS: calc'd for $C_9H_5D_3BrN$ $[M]^+$: 212.00, found: 211.95.



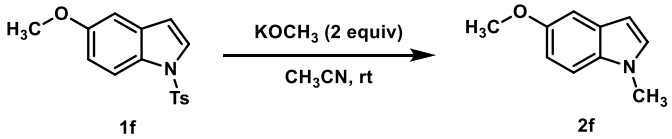
1e 2e

5-Iodo-1-methyl-1*H*-indole (2e): The general procedure A was followed. The reaction was performed with 5-iodo-1-tosyl-1*H*-indole **1e** (79.4 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2e** (42.3 mg, 82% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.9 Hz, 1H), 7.46 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.03 – 6.97(m, 1H), 6.43 – 6.38 (m, 1H), 3.77 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]



1e 3e

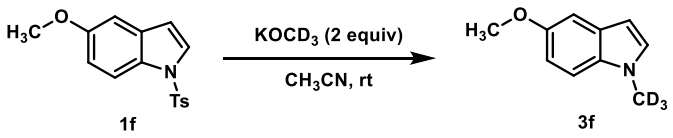
5-Iodo-1-trideuteromethyl-1*H*-indole (3e): The general procedure A was followed. The reaction was performed with 5-iodo-1-tosyl-1*H*-indole **1e** (198.6 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3e** (121.7 mg, 94% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.42 (dd, *J* = 3.1, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 131.0, 129.8, 129.7, 129.6, 111.3, 100.3, 82.9, 32.3 (m); GCMS: calc'd for $C_9H_5D_3IN$ $[M]^+$: 259.99, found: 259.95.



1f 2f

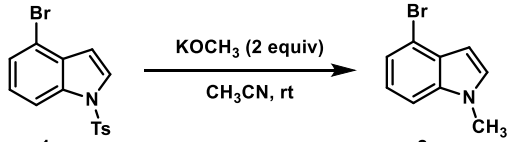
5-Methoxy-1-methyl-1*H*-indole (2f): The general procedure A was followed. The reaction was performed with 5-methoxy-1-tosyl-1*H*-indole **1f** (150.7 mg, 0.5 mmol), $KOCH_3$ (70.0

mg, 1.0 mmol) in 1 mL CH_3CN. The desired product **2f** (73.7 mg, 91% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H), 7.02 (s, 1H), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.40 (s, 1H), 3.85 (s, 3H), 3.77 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]



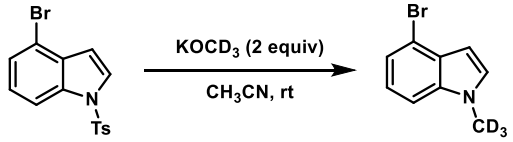
1f 3f

5-Methoxy-1-trideuteromethyl-1*H*-indole (3f): The general procedure A was followed. The reaction was performed with 5-methoxy-1-tosyl-1*H*-indole **1f** (150.7 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 1 mL CH_3CN. The desired product **3f** (64.6 mg, 79% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.9 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.44 (dd, *J* = 3.0, 0.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 132.1, 129.3, 128.8, 111.9, 110.0, 102.5, 100.4, 56.0, 32.3 (m); GCMS: calc'd for $C_{10}H_8D_3NO$ $[M]^+$: 164.10, found: 164.10.



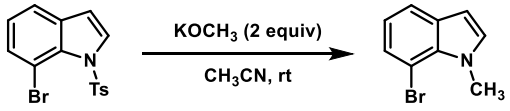
1g 2g

4-Bromo-1-methyl-1*H*-indole (2g): The general procedure A was followed. The reaction was performed with 4-bromo-1-tosyl-1*H*-indole **1g** (70.1 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2g** (37.4 mg, 89% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.13 – 7.03 (m, 2H), 6.54 (d, *J* = 3.1 Hz, 1H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[3]

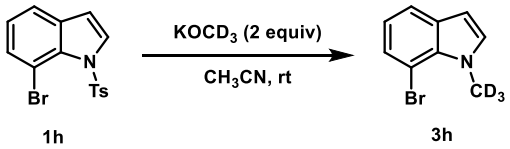


1g 3g

4-Bromo-1-trideuteromethyl-1*H*-indole (3g): The general procedure A was followed. The reaction was performed with 4-bromo-1-tosyl-1*H*-indole **1g** (70.0 mg, 0.2 mmol), $KOCD_3$ (29.3 mg, 0.4 mmol) in 1 mL CH_3CN. The desired product **3g** (75.5 mg, 71% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 1H), 7.28 – 7.26 (m, 1H), 7.11 (d, *J* = 3.3 Hz, 1H), 7.07 (d, *J* = 8.3 Hz, 1H), 6.53 (dd, *J* = 3.1, 0.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 129.4, 129.2, 122.5, 122.3, 114.9, 108.5, 101.4, 32.6 (m); GCMS: calc'd for $C_9H_5D_3NBr$ $[M]^+$: 212.00, found: 211.95.

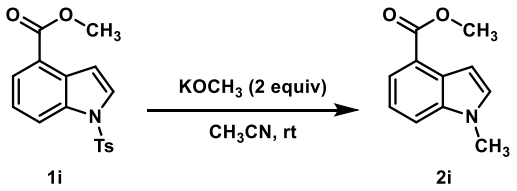


7-Bromo-1-methyl-1*H*-indole (2h): The general procedure A was followed. The reaction was performed with 7-bromo-1-tosyl-1*H*-indole **1h** (70.1 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2h** (31.9 mg, 76% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.91 (t, *J* = 7.7 Hz, 1H), 6.46 (dd, *J* = 3.1, 0.9 Hz, 1H), 4.16 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[2]

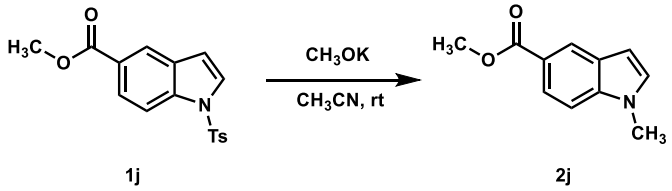


7-Bromo-1-trideuteromethyl-1*H*-indole (3h): The general procedure A was followed. The reaction was performed with 7-bromo-1-tosyl-1*H*-indole **1h** (175.1 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3h** (97.2 mg, 92% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 3.1 Hz, 1H), 6.92 (t, *J* = 7.7 Hz, 1H), 6.47 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2,

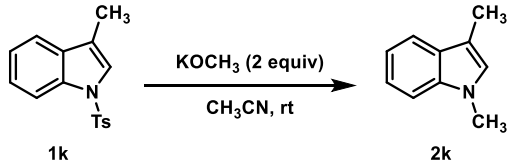
131.84, 131.75, 126.6, 120.6, 120.5, 104.0, 101.3, 36.1 (m); GCMS: calc'd for $C_9H_5D_3NBr$ $[M]^+$: 212.00, found: 211.95.



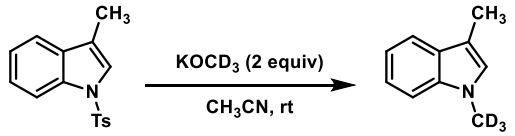
Methyl 1-Methyl-1*H*-indole-4-carboxylate (2i): The general procedure A was followed. The reaction was performed with methyl 1-tosyl-1*H*-indole-4-carboxylate **1i** (65.9 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2i** (24.7 mg, 65% yield) was obtained after purification by silica gel chromatography (10% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.53 (d, *J* = 9.1 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 3.1 Hz, 1H), 7.11 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.98 (s, 3H), 3.84 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[4]



Methyl 1-Methyl-1*H*-indole-5-carboxylate (2j): The general procedure A was followed. The reaction was performed with methyl 1-tosyl-1*H*-indole-5-carboxylate **1j** (65.9 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2j** (33.3 mg, 90% yield) was obtained after purification by silica gel chromatography (10% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.0 Hz, 1H), 7.93 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 6.59 (dd, *J* = 3.2, 0.9 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[5]

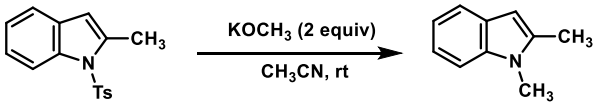


1,3-Dimethyl-1*H*-indole (2k): The general procedure A was followed. The reaction was performed with 3-methyl-1-tosyl-1*H*-indole **1k** (57.1 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2k** (25.2 mg, 87% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.83 (s, 1H), 3.74 (s, 3H), 2.33 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[6]



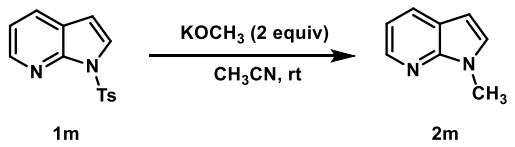
1k 3i

3-Methyl-1-trideuteromethyl-1*H*-indole (3i): The general procedure A was followed. The reaction was performed with 3-methyl-1-tosyl-1*H*-indole **1k** (142.7 mg, 0.5 mmol), $KOCD_3$ (73.2 mg, 1.0 mmol) in 2 mL CH_3CN. The desired product **3i** (71.1 mg, 97% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.06 – 7.00 (m, 1H), 6.73 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.7, 126.6, 121.5, 119.0, 118.6, 110.1, 109.1, 31.9 (m), 9.7; GCMS: calc'd for $C_{10}H_8D_3N$ $[M]^+$: 148.11, found: 148.10.

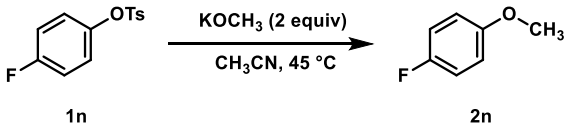


1l 2l

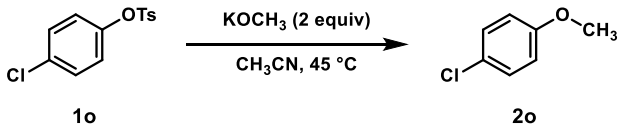
1,2-Dimethyl-1*H*-indole (2l): The general procedure A was followed. The reaction was performed with 2-methyl-1-tosyl-1*H*-indole **1l** (57.1 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2l** (14.7 mg, 51% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^1H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H). 3.66 (s, 3H), 2.43 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[7]



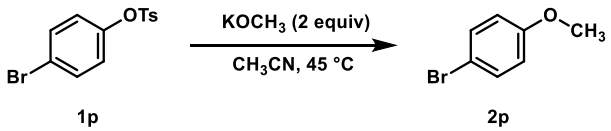
1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine (2m): The general procedure A was followed. The reaction was performed with 1-tosyl-1*H*-pyrrolo[2,3-*b*]pyridine **1m** (54.5 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN. The desired product **2m** (22.5 mg, 85% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.18 (d, *J* = 3.4 Hz, 1H), 7.06 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.45 (d, *J* = 3.4 Hz, 1H), 3.90 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[8]



1-Fluoro-4-methoxybenzene (2n): The general procedure B was followed. The reaction was performed with 4-fluorophenyl 4-methylbenzenesulfonate **1n** (132.8 mg, 0.5 mmol), $KOCH_3$ (70.5 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2n** (49.0 mg, 76% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 – 6.94 (m, 2H), 6.86 – 6.80 (m, 2H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[9]

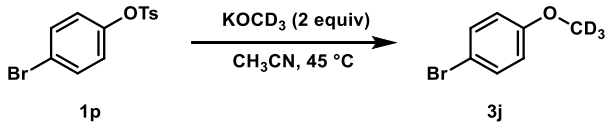


1-Chloro-4-methoxybenzene (2o): The general procedure B was followed. The reaction was performed with 4-chlorophenyl 4-methylbenzenesulfonate **1o** (141.3 mg, 0.5 mmol), $KOCH_3$ (70.3 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2o** (53.4 mg, 75% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 6.86 – 6.80 (m, 2H), 3.79 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[10]



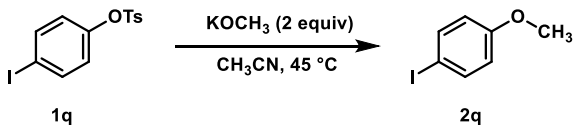
1p 2p

1-Bromo-4-methoxybenzene (2p): The general procedure B was followed. The reaction was performed with 4-bromophenyl 4-methylbenzenesulfonate **1p** (64.4 mg, 0.2 mmol), $KOCH_3$ (28.8 mg, 0.4 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2p** (30.2 mg, 82% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[10]



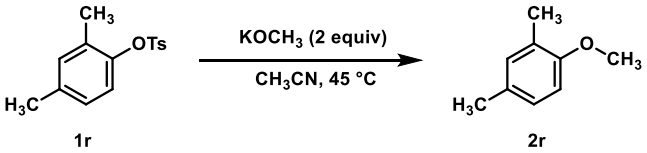
1p 3j

1-Bromo-4-trideuteromethoxybenzene (3j): The general procedure B was followed. The reaction was performed with 4-bromophenyl 4-methylbenzenesulfonate **1p** (65.4 mg, 0.2 mmol), $KOCD_3$ (29.2 mg, 0.4 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **3j** (25.1 mg, 66% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 9.1 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 132.4, 115.8, 112.9. These spectroscopic data were consistent with those reported in the literature.[11]



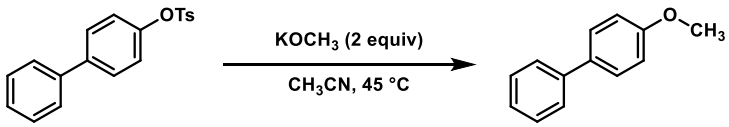
1q 2q

1-Iodo-4-methoxybenzene (2q): The general procedure B was followed. The reaction was performed with 4-iodophenyl 4-methylbenzenesulfonate **1q** (186.2 mg, 0.5 mmol), $KOCH_3$ (69.9 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2q** (85.3 mg, 73% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.9 Hz, 2H), 6.68 (d, *J* = 8.9 Hz, 2H), 3.78 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[10]



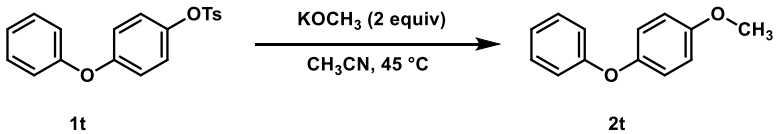
1r 2r

1-Methoxy-2,4-dimethylbenzene (2r): The general procedure B was followed. The reaction was performed with 2,4-dimethylphenyl 4-methylbenzenesulfonate **1r** (137.9 mg, 0.5 mmol), $KOCH_3$ (70.5 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2r** (47.6 mg, 70% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 – 6.93 (m, 2H), 6.72 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 2.26 (s, 3H), 2.19 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[12]



1s 2s

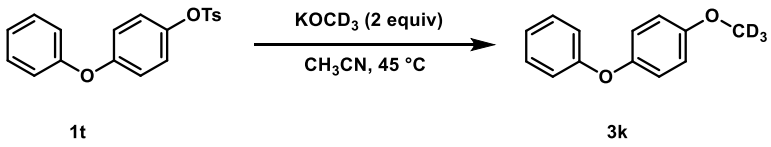
4-Methoxy-1,1'-biphenyl (2s): The general procedure B was followed. The reaction was performed with [1,1'-biphenyl]-4-yl 4-methylbenzenesulfonate **1s** (64.8 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2s** (19.9 mg, 54% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.50 (m, 4H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[13]



1t 2t

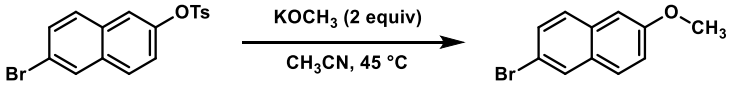
1-Methoxy-4-phenoxybenzene (2t): The general procedure B was followed. The reaction was performed with 4-phenoxyphenyl 4-methylbenzenesulfonate **1t** (170.6 mg, 0.5 mmol), $KOCH_3$ (70.8 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **2t** (56.2 mg, 56% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.05 (td, *J* = 7.4, 1.0 Hz, 1H), 7.00 (d,

J = 9.2 Hz, 2H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 3.81 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[14]



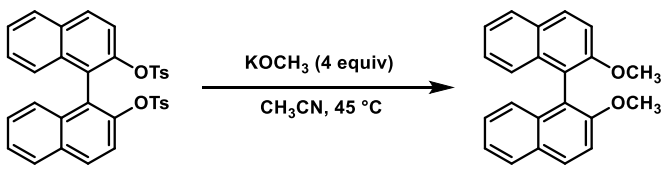
1t 3k

1-Trideuteromethoxy-4-phenoxybenzene (3k): The general procedure B was followed. The reaction was performed with 4-phenoxyphenyl 4-methylbenzenesulfonate **1t** (170.8 mg, 0.5 mmol), $KOCD_3$ (73.8 mg, 1.0 mmol) in 2 mL CH_3CN for 18.5 h. The desired product **3k** (46.9 mg, 46% yield) was obtained after purification by silica gel chromatography (2% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 2H), 7.04 (t, *J* = 7.3 Hz, 1H), 7.02 – 6.97 (m, 2H), 6.95 (dd, *J* = 8.8, 1.1 Hz, 2H), 6.89 (d, *J* = 9.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 156.0, 150.2, 129.7, 122.5, 121.0, 117.7, 114.9; HRMS (APCI+): calc'd for $C_{13}H_{10}D_3O_2$ $[M+H]^+$: 204.1098, found: 204.1097



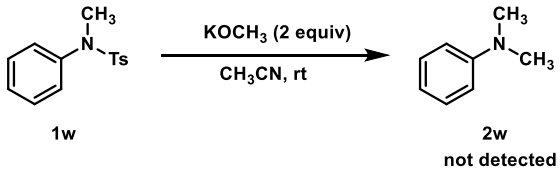
1u 2u

2-Bromo-6-methoxynaphthalene (2u): The general procedure A was followed. The reaction was performed with 6-bromonaphthalen-2-yl 4-methylbenzenesulfonate **1u** (30.3 mg, 0.08 mmol), $KOCH_3$ (11.2 mg, 0.2 mmol) in 0.4 mL CH_3CN. The desired product **2u** (13.2 mg, 70% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.10 (s, 1H), 3.92 (s, 2H). These spectroscopic data were consistent with those reported in the literature.[15]

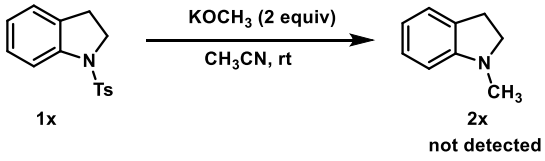


1v 2v

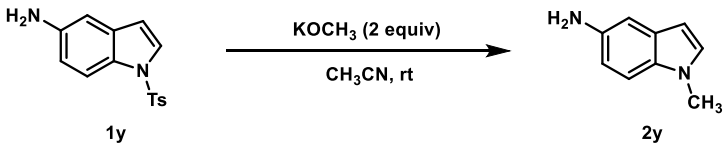
2,2'-Dimethoxy-1,1'-binaphthalene (2v): The general procedure A was followed. The reaction was performed with [1,1'-binaphthalene]-2,2'-diyl bis(4-methylbenzenesulfonate) **1v** (118.9 mg, 0.2 mmol), $KOCH_3$ (56.0 mg, 0.8 mmol) in 0.8 mL CH_3CN. The desired product **2v** (42.0 mg, 67% yield) was obtained after purification by silica gel chromatography (7% EA in PE). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.10 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 6H). These spectroscopic data were consistent with those reported in the literature.[16]



***N, N*-Dimethylaniline (2v)**: The general procedure A was followed. The reaction was performed with *N*,4-dimethyl-*N*-phenylbenzenesulfonamide **1v** (131.0 mg, 0.5 mmol), $KOCH_3$ (77.0 mg, 1.1 mmol) in 2 mL CH_3CN overnight. The desired product **2v** was not detected.



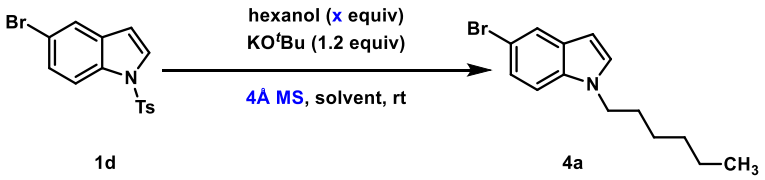
1-Methylindoline (2x): The general procedure A was followed. The reaction was performed with 1-tosylindoline **1x** (54.7 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 0.7 mL CH_3CN overnight. The desired product **2x** was not detected.



1-Methyl-1*H*-indol-5-amine (2y): The general procedure A was followed. The reaction was performed with 1-tosyl-1*H*-indol-5-amine **1y** (57.3 mg, 0.2 mmol), $KOCH_3$ (28.0 mg, 0.4 mmol) in 3.0 mL CH_3CN. The desired product **2y** (24.4 mg, 84% yield) was obtained

after purification by silica gel chromatography (33% EA in PE). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 1H), 6.98 (m, 2H), 6.73 (d, *J* = 8.5 Hz, 1H), 6.30 (d, *J* = 3.1 Hz, 1H), 3.74 (s, 3H). These spectroscopic data were consistent with those reported in the literature.[17]

Table S3. Reaction Condition Optimizations for N-Alkylation of Indoles with Alcohols



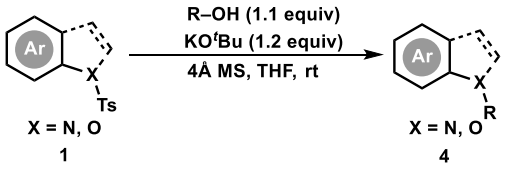
1d 4a

entry[a]	solvent	alcohol (x equiv)	4Å MS	yield
1	DMF	2	w/o	21%[b]
2	DCE	2	w/o	trace
3	DCM	2	w/o	36%[b]
4	toluene	2	w/o	53%[b](51%[c])
5	Et_2O	2	w/o	44%[b]
6	DMSO	2	w/o	22%[b]
7	THF	2	w/o	75%[b](60%[c])
8	THF	2	w	78%[b](67%[c])
9	THF	1	w	74%[c]
10	THF	1.1	w	87%[c]
11	THF	1.2	w	83%[c]
12	THF	2.5	w	43%[c]
13	THF	3	w	37%[c]

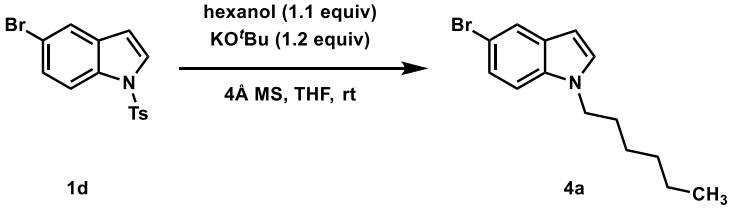
[a]Reactions were conducted with 0.2 mmol of **1d**, 50 mg 4Å MS in 2 mL of solvent for the suitable time monitored by TLC. [b]^{1}H NMR yield. [c]Isolated yield. w = with, w/o = without.

General Procedure for Condition Optimizations (Table S3): To a screw-capped vial equipped with a magnetic stirring bar were added hexanol (x equiv), KO^{t}Bu (1.2 equiv), 4Å MS (50 mg) and 2 mL solvent. The mixture was stirred at room temperature for 1 h. Then *N*-tosyl-5-bromoindole **1d** (70.0 mg, 0.2 mmol) was added and stirred at room temperature and the reaction was monitored by TLC until the completion. Then the vial was removed from the glove box. The reaction mixture was filtered through a short pad of Celite, washed with EA (about 4 – 5 mL). The filtrate was concentrated under reduced pressure. Internal standard 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol) was added to the residue and the yield was determined by the crude ^{1}H NMR. Then the desired product was purified by silica gel chromatography (1% EA in PE).

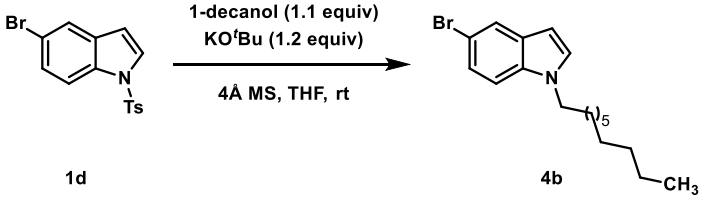
General Procedure and Spectroscopic Data for N-Alkylation of Indoles and Heterocyclic Compounds using Alcohols



General procedure C: To a dry Schlenk tube or screw-capped vial equipped with a magnetic stirring bar, ROH (1.1 equiv), KO^{t}Bu (1.2 equiv), 4Å MS (250 mg per 1 mmol substrate) and solvent (0.1 mmol/mL) were added under an atmosphere of dry argon. After the mixture was stirred at room temperature for 1 h, substrate **1** (1 equiv) were added and stirred at room temperature until the completion of the reaction as monitored by TLC. Then the reaction mixture was filtered through a short pad of Celite, washed with EA (5 mL) and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography to give the desired product.

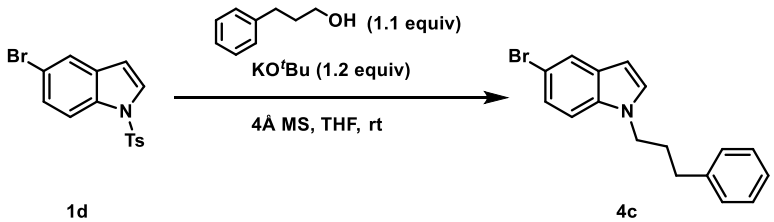


5-Bromo-1-hexyl-1*H*-indole (4a): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (70.0 mg, 0.2 mmol), hexanol (22.3 mg, 0.22 mmol), KO^{t}Bu (27.2 mg, 0.24 mmol) and 4Å MS (50.0 mg) in 2 mL THF for 1 h. The desired product **4a** (48.9 mg, 87% yield) was obtained after purification by silica gel chromatography (1% CH_2Cl_2 in PE). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.31 – 7.24 (m, 1H), 7.23 – 7.18 (m, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.42 (d, *J* = 3.1 Hz, 1H), 4.08 (t, *J* = 7.1 Hz, 2H), 1.92 – 1.75 (m, 2H), 1.35 – 1.20 (m, 6H), 0.87 (t, *J* = 6.2 Hz, 3H). These spectroscopic data were consistent with those reported in the literature.[18]



1d 4b

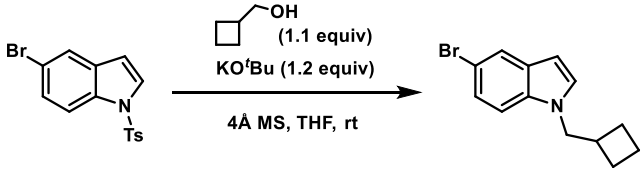
5-Bromo-1-decyl-1*H*-indole(4b): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (176.8 mg, 0.5 mmol), 1-decanol (86.9 mg, 0.55 mmol), KO^{t}Bu (67.8 mg, 0.61 mmol) and 4Å MS (125.0 mg) in 5 mL THF for 1 h. The desired product **4b** (153.1 mg, 90% yield) was obtained after purification by silica gel chromatography (1% CH_2Cl_2 in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.8 Hz, 1H), δ 7.30 – 7.24 (m, 1H), 7.22 – 7.17 (m, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.42 (d, *J* = 3.1 Hz, 1H), 4.08 (t, *J* = 7.1 Hz, 2H), 1.75 – 1.86 (m, 2H), 1.26 (m, 14H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 130.3, 129.1, 124.3, 123.5, 112.6, 111.0, 100.6, 46.7, 32.0, 30.3, 29.64, 29.61, 29.40, 29.35, 27.1, 22.8, 14.3; HRMS (APCI+) calc'd for $C_{18}H_{27}BrN$ $[M+H]^+$: 336.1321, found 336.1328.



1d 4c

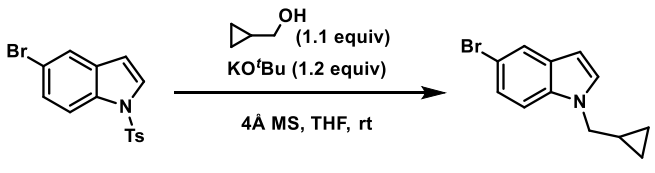
5-Bromo-1-(3-phenylpropyl)-1*H*-indole (4c): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (189.7 mg, 0.5 mmol), 3-

phenylpropan-1-ol (81.1 mg, 0.60 mmol), KO^{t}Bu (74.4 mg, 0.66 mmol) and 4Å MS (125.0 mg) in 5 mL THF for 1 h. The desired product **4c** (129.7 mg, 76% yield) was obtained after purification by silica gel chromatography (1% CH_2Cl_2 in PE to 3% CH_2Cl_2 in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.25 (m, 3H), 7.25 – 7.18 (m, 1H), 7.18 – 7.12 (m, 3H), 7.09 (d, *J*= 3.1 Hz, 1H), 6.44 (dd, *J* = 3.1, 0.8 Hz, 1H), 4.10 (t, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 7.6 Hz, 2H), δ 2.18 (quint, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 134.8, 130.4, 129.0, 128.7, 128.5, 126.4, 124.4, 123.5, 112.7, 111.0, 100.9, 45.9, 33.0, 31.5; HRMS (APCI+) calc'd for $C_{17}H_{17}BrN$ $[M+H]^+$:314.0539, found: 314.0545.



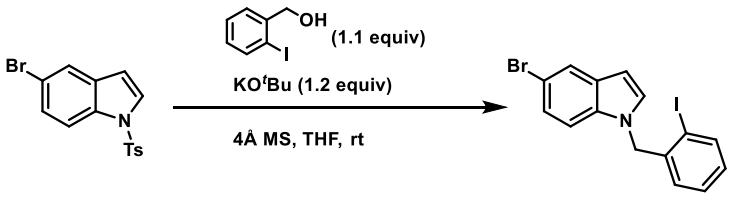
1d 4d

5-Bromo-1-(cyclobutylmethyl)-1*H*-indole (4d): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.3 mg, 0.5 mmol), cyclobutylmethanol (47.3 mg, 0.55 mmol), KO^{t}Bu (67.8 mg, 0.61 mmol) and 4Å MS (125.0 mg) in 5 mL THF for 3 h. The desired product **4d** (88.3 mg, 67% yield) was obtained after purification by silica gel chromatography (100% PE). ^{1}H NMR (400 MHz, CDCl3) δ 7.74 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), δ 6.41 (d, *J* = 2.6 Hz, 1H), 4.08 (d, *J* = 7.2 Hz, 2H), 2.81 (quint, *J* = 7.6 Hz, 1H), 2.16 – 1.97 (m, 2H), 1.97 – 1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.0, 130.2, 129.1, 124.2, 123.4, 112.6, 111.0, 100.6, 51.8, 36.1, 26.5, 18.3; HRMS (APCI+) calc'd for $C_{13}H_{15}BrN$ $[M+H]^+$: 264.0382, found 264.0378.

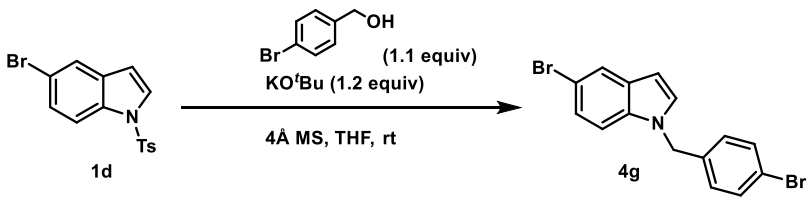


1d 4e

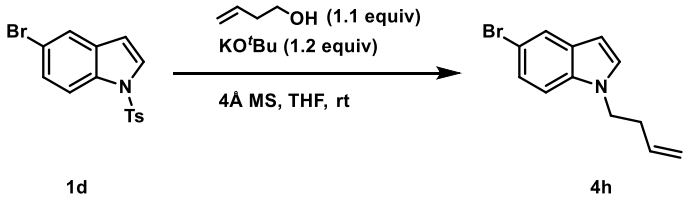
5-Bromo-1-(cyclopropylmethyl)-1*H*-indole (4e): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (364.0 mg, 1 mmol), cyclopropylmethanol (82.5 mg, 1.14 mmol), KO^{t}Bu (141.1 mg, 1.21 mmol) and 4Å MS (249.7 mg) in 5 mL THF for 1 h. The desired product **4e** (191.9 mg, 74% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.25 (m, 2H), 6.44 (dd, *J* = 3.1, 0.6 Hz, 1H), 3.96 (d, *J* = 6.8 Hz, 2H), 1.32 – 1.17 (m, 1H), 0.70 – 0.57 (m, 2H), 0.30 – 0.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 130.3, 128.7, 124.3, 123.5, 112.7, 111.0, 100.7, 51.0, 11.3, 4.2; HRMS (APCI+) calc'd for $C_{12}H_{13}BrN$ $[M+H]^+$: 250.0226, found 250.0230.



5-Bromo-1-(2-iodobenzyl)-1*H*-indole (4f): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.4 mg, 0.5 mmol), (2-iodophenyl)methanol (128.8 mg, 0.55 mmol), KO^{t}Bu (67.8 mg, 0.61 mmol) and 4Å MS (125.0 mg) in 5 mL THF for 3 h. The desired product **4f** (150.8 mg, 73% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.18 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.09 (td, *J* = 7.6, 1.1 Hz, 1H), 7.03 (d, *J* = 3.2 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 6.46 (d, *J* = 3.1 Hz, 1H), 6.36 (d, *J* = 7.7 Hz, 1H). 5.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.1, 135.0, 130.4, 129.6, 128.8, 127.6, 124.9, 123.7, 113.3, 111.3, 101.8, 97.3, 55.4; HRMS (APCI+) calc'd for $C_{15}H_{12}BrIN$ $[M+H]^+$: 411.9192, found 411.9205.

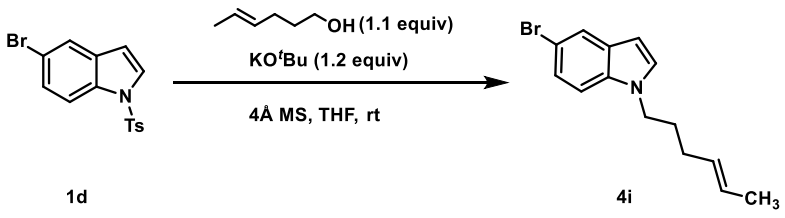


5-Bromo-1-(4-bromobenzyl)-1*H*-indole (4g): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.0 mg, 0.5 mmol), (4-bromophenyl)methanol (104.2 mg, 0.56 mmol), KO^{t}Bu (69.4 mg, 0.62 mmol) and 4Å MS (129.4 mg) in 5 mL THF for 3 h. The desired product **4g** (142.5 mg, 78% yield) was obtained after purification by silica gel chromatography (2% EA in PE to 5% EA inPE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.11 (d, *J* = 3.2 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 2H), 6.50 (dd, *J* = 3.2, 0.8 Hz, 1H), 5.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 134.9, 132.1, 130.6, 129.5, 128.4, 124.8, 123.7, 121.8, 113.2, 111.2, 101.7, 49.8; HRMS (APCI+) calc'd for $C_{15}H_{12}Br_2N$ $[M+H]^+$: 363.9331, found 363.9338.



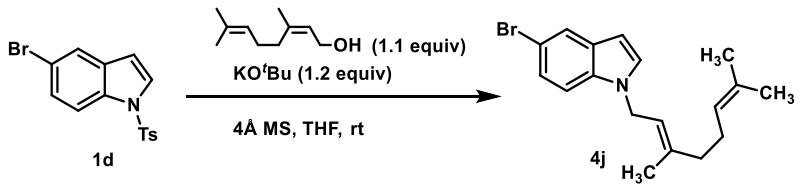
1d 4h

5-Bromo-1-(but-3-en-1-yl)-1*H*-indole (4h): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.3 mg, 0.5 mmol), but-3-en-1-ol (40.2 mg, 0.55 mmol), KO^{t}Bu (67.8 mg, 0.61 mmol) and 4Å MS (125.0 mg) in 5 mL THF for 1 h. The desired product **4h** (81.3 mg, 65% yield) was obtained after purification by silica gel chromatography (1% CH_2Cl_2 in PE to 2% CH_2Cl_2 in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.3 Hz, 1H), 7.29 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.42 (dd, *J* = 3.1, 0.7 Hz, 1H), 5.09 – 5.02 (m, 2H), 4.16 (t, *J* = 7.1 Hz, 2H), 2.60 – 2.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 134.4, 130.3, 128.9, 124.3, 123.4, 117.7, 112.6, 110.8, 100.7, 46.2, 34.5; HRMS (APCI+) calc'd for $C_{12}H_{13}BrN$ $[M+H]^+$: 250.0226, found: 250.0229.

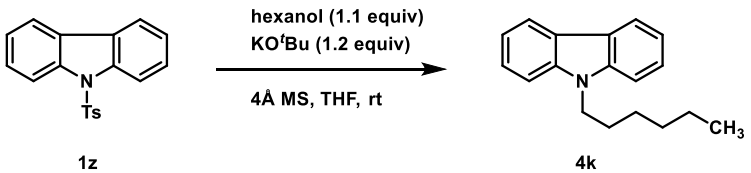


1d 4i

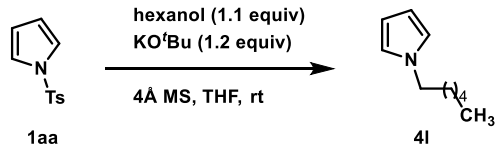
(*E*)-5-Bromo-1-(hex-4-en-1-yl)-1*H*-indole (4i): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.9 mg, 0.5 mmol), (*E*)-hex-4-en-1-ol (57.7 mg, 0.58 mmol), KO^{t}Bu (69.4 mg, 0.62 mmol) and 4Å MS (131.9 mg) in 5 mL THF for 1 h. The desired product **4i** (102.6 mg, 73% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.9 Hz, 1H), 7.28 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.20 (d, *J* = 8.7 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 5.68 – 5.23 (m, 2H), 4.08 (t, *J* = 6.9 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.93 – 1.80 (m, 2H), 1.67 (d, *J* = 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 130.4, 129.7, 129.1, 126.5, 124.2, 123.5, 112.6, 111.0, 101.0, 45.9, 29.9, 29.8, 18.1; HRMS (APCI+) calc'd for $C_{14}H_{17}BrN$ $[M+H]^+$: 278.0539, found: 278.0545.



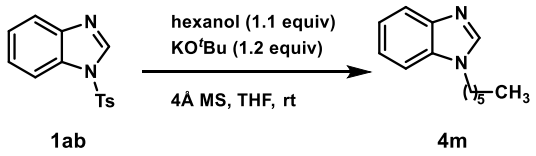
(*E*)-5-Bromo-1-(3,7-dimethylocta-2,6-dien-1-yl)-1*H*-indole (4j): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.1 mg, 0.5 mmol), (Z)-3,7-dimethylocta-2,6-dien-1-ol (89.0 mg, 0.58 mmol), KO^{t}Bu (70.3 mg, 0.62 mmol) and 4Å MS (131.8 mg) in 5 mL THF for 5 h. The desired product **4j** (78.0 mg, 47% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 1.8 Hz, 1H), 7.26 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 7.10 (d, *J* = 3.1 Hz, 1H), 6.41 (d, *J* = 3.1 Hz, 1H), 5.35 (t, *J* = 6.8 Hz, 1H), 5.14 (t, *J* = 7.1 Hz, 1H), 4.66 (dd, *J* = 6.8, 1.3 Hz, 2H), 2.28 – 2.20 (m, 2H), 2.20 – 2.12 (m, 2H), 1.77 (d, *J* = 1.4 Hz, 3H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 134.7, 132.6, 130.5, 128.7, 124.2, 123.6, 123.4, 120.3, 112.7, 111.1, 100.7, 44.2, 32.3, 26.5, 25.9, 23.4, 17.9; HRMS (APCI+) calc'd for $C_{18}H_{23}BrN$ $[M+H]^+$: 332.1008, found: 332.1010.



9-Hexyl-9*H*-carbazole (4k): The general procedure C was followed. The reaction was performed with 9-tosyl-9*H*-carbazole **1z** (161.0 mg, 0.5 mmol), hexanol (55.3 mg, 0.55 mmol), KO^{t}Bu (68.2 mg, 0.61 mmol) and 4Å MS (128.3 mg) in 5 mL THF for 5 h. The desired product **4k** (80.1 mg, 64% yield) was obtained after purification by silica gel chromatography (1% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.7 Hz, 2H), 7.53 – 7.34 (m, 4H), 7.25 – 7.20 (m, 2H), 4.30 (t, *J* = 7.3 Hz, 2H), 1.87 (quint, *J* = 7.4 Hz, 2H), 1.49 – 1.17 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). These spectroscopic data were consistent with those reported in the literature.[19]

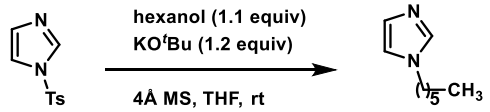


1-Hexyl-1*H*-pyrrole (4l): The general procedure C was followed. The reaction was performed with 1-tosyl-1*H*-pyrrole **1aa** (88.3 mg, 0.4 mmol), hexanol (44.8 mg, 0.44 mmol), KO^{t}Bu (54.4 mg, 0.48 mmol) and 4Å MS (100.6 mg) in 4 mL THF for 2.5 h. The desired product **4l** (36.2 mg, 60% yield) was obtained after purification by silica gel chromatography (1% EA in PE, the product is volatile and dried under vacuum at – 20 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (t, *J* = 2.1 Hz, 2H), 6.14 (t, *J* = 2.1 Hz, 2H), 3.87 (t, *J* = 7.2 Hz, 2H), 1.83 – 1.71 (m, 2H), 1.36 – 1.24 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.6, 107.9, 49.8, 31.7, 31.5, 26.6, 22.7, 14.2; HRMS (APCI+) calc'd for $C_{10}H_{18}N$ $[M+H]^+$: 152.1434, found: 152.1435.

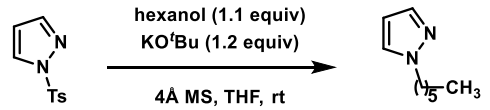


1-Hexyl-1*H*-benzo[*d*]imidazole (4m): The general procedure C was followed. The reaction was performed with 1-tosyl-1*H*-benzo[*d*]imidazole **1ab** (109.0 mg, 0.4 mmol), hexanol (45.9 mg, 0.44 mmol), KO^{t}Bu (55.4 mg, 0.48 mmol) and 4Å MS (100.1 mg) in 4 mL THF for 2 h. The desired product **4m** (40.1 mg, 50% yield) was obtained after purification by silica gel chromatography (40% EA in PE to 50% EA

in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.81 (dd, *J* = 6.4, 2.3 Hz, 1H), 7.40 (dd, *J* = 6.5, 2.3 Hz, 1H), 7.35 – 7.23 (m, 2H), 4.16 (t, *J* = 7.2 Hz, 2H), 1.87 (quint, *J* = 7.2 Hz, 2H), 1.41 – 1.14 (m, 6H), 0.86 (t, *J* =7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 143.0, 133.9, 122.9, 122.2, 120.4, 109.8, 45.3, 31.4, 29.9, 26.6, 22.6, 14.1; HRMS (ESI+) calc'd for $C_{13}H_{19}N_2$ $[M+H]^+$: 203.1543, found: 203.1548.

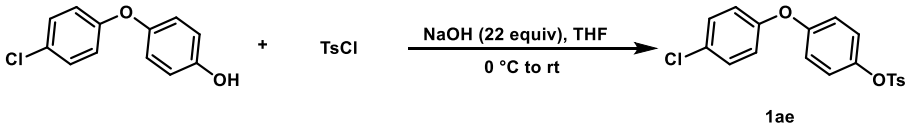


1-Hexyl-1*H*-imidazole (4n): The general procedure C was followed. The reaction was performed with 1-tosyl-1*H*-imidazole **1ac** (89.0 mg, 0.4 mmol), hexanol (44.7 mg, 0.44 mmol), KO^{t}Bu (54.3 mg, 0.48 mmol) and 4Å MS (100.5 mg) in 4 mL THF for 2 h. The desired product **4n** (25.2 mg, 41% yield) was obtained after purification by silica gel chromatography (100% DCM to 50% EA in DCM, the product is volatile and dried under vacuum at –20 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.04 (s, 1H), 6.90 (s, 1H), 3.91 (t, *J* = 7.2 Hz, 2H), 1.89 – 1.68 (m, 2H), 1.41 – 1.11 (m, 6H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 129.3, 118.9, 47.2, 31.4, 31.2, 26.3, 22.6, 14.1; HRMS (ESI+) calc'd for $C_9H_{17}N_2$ $[M+H]^+$: 153.1386, found: 153.1382.



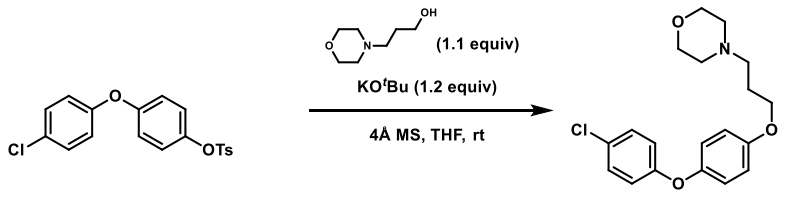
1-Hexyl-1*H*-pyrazole (4o): The general procedure C was followed. The reaction was performed with 1-tosyl-1*H*-pyrazole **1ad** (88.8 mg, 0.4 mmol), hexanol (45.4 mg, 0.44 mmol), KO^{t}Bu (54.6 mg, 0.48 mmol) and 4Å MS (100.1 mg) in 4 mL THF for 2.5 h. The desired product **4o** (51.0 mg, 84% yield) was obtained after purification by silica gel chromatography (1% EA in PE, the product is volatile and dried under vacuum at –20 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.4 Hz, 1H), 7.37 (d, *J* = 2.1 Hz, 1H), 6.23 (t, *J* = 2.0 Hz, 1H), 4.12 (t, *J* = 7.2 Hz, 2H), 1.90 – 1.79 (m, 2H), 1.36 – 1.15 (m, 6H), 0.87 (t, *J*

= 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 129.0, 105.3, 52.3, 31.4, 30.5, 26.4, 22.6, 14.1; HRMS (ESI+) calc'd for $C_9H_{17}N_2$ $[M+H]^+$: 153.1386, found: 153.1394.



1ae

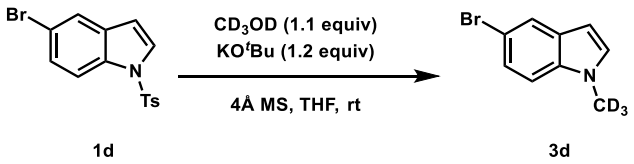
4-(4-Chlorophenoxy)phenyl 4-methylbenzenesulfonate (1ae)[20]: To a dry Schlenk flask equipped with a magnetic stirring bar, 4-(4-chlorophenoxy)phenol (1.10 g, 5 mmol), NaOH (4.4 g, 110 mmol) and 10 ml of THF were added under an atmosphere of dry argon and stirred for 15 minutes at room temperature. Then TsCl (1.05g, 5.5 mmol, 1.1 equiv, in 10 mL THF) was slowly added within 15 min at 0 °C. The reaction mixture was stirred at room temperature for 12 h, and then quenched with H_2O (20 mL) and extracted with EA (20 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. Then the desired product **1ae** (1.29 g, 69% yield) was obtained after purification by silica gel chromatography (10% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.11 (m, 4H), 7.11–6.53 (m, 6H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 155.3, 145.6, 145.1, 132.3, 130.0, 129.9, 129.0, 128.67, 124.0, 120.5, 119.4, 21.9. HRMS (ESI+) calc'd for $C_{19}H_{15}ClSO_4Na$ $[M+Na]^+$: 397.0272, found: 397.0284.



1ae 4p

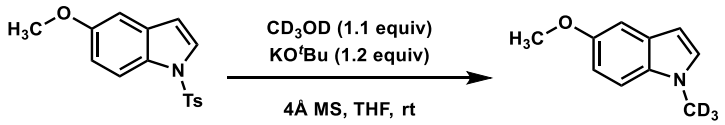
4-(3-(4-(4-Chlorophenoxy)phenoxy)propyl)morpholine (**4p)**: The general procedure C was followed. The reaction was performed with 4-(4-chlorophenoxy)phenyl 4-methylbenzenesulfonate **1ae** (74.8 mg, 0.2 mmol), 3-morpholinopropan-1-ol (86.9 mg, 0.22 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (200.0 mg) in 2 mL THF for 12 h. The desired product **4p** (38.4 mg, 55% yield) was obtained after purification by silica gel chromatography (rinsed the silica gel with 0.2% Et_3N in PE, then with 25% EA in PE as

the eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 2H), 6.91 – 6.82 (m, 4H), 4.00 (t, *J* = 6.3 Hz, 2H), 3.73 (t, *J* = 4.7 Hz, 4H), 2.61 – 2.36 (m, 6H), 2.03 –1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 155.6, 149.8, 129.7, 127.4, 120.9, 118.8, 115.7, 67.1, 66.7, 55.7, 53.9, 26.6; HRMS (ESI+) calc'd for $C_{19}H_{23}ClNO_3$ $[M+H]^+$: 348.1361, found: 348.1366.



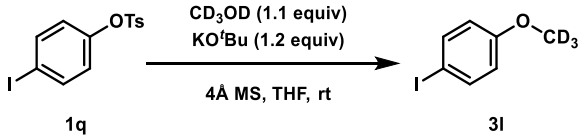
1d 3d

5-Bromo-1-trideuteromethyl-1*H*-indole (3d): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (175.1 mg, 0.5 mmol), CD_3OD (19.9 mg, 0.55 mmol), KO^{t}Bu (67.2 mg, 0.60 mmol) and 4Å MS (200.0 mg) in 5 mL THF for 3 h. The desired product **3d** (103.9 mg, 98% yield) was obtained after purification by silica gel chromatography (5% EA in PE).



1f 3f

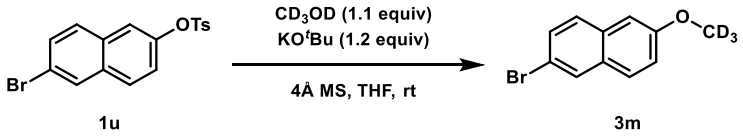
5-Methoxy-1-trideuteromethyl-1*H*-indole (3f): The general procedure C was followed. The reaction was performed with 5-methoxy-1-tosyl-1*H*-indole **1f** (60.3 mg, 0.2 mmol), CD_3OD (8.0 mg, 0.22 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (100.0 mg) in 3 mL THF overnight. The desired product **3f** (28.3 mg, 86% yield) was obtained after purification by silica gel chromatography (5% EA in PE).



1q 3l

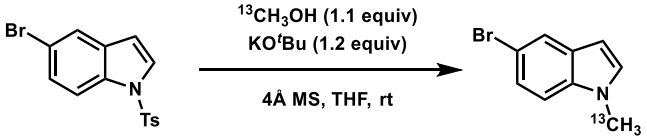
1-Iodo-4-trideuteromethoxybenzene (3l): The general procedure C was followed. The reaction was performed with, 4-iodophenyl 4-methylbenzenesulfonate **1q** (74.6 mg, 0.2 mmol), CD_3OD (8.0 mg, 0.11 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (100 mg)

in 3 mL THF overnight. The desired product **3l** (28.3 mg, 60% yield) was obtained after purification by silica gel chromatography (5% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 6.71 – 6.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 138.3, 116.5, 82.8; HRMS (APCI+): calc'd for $C_7H_4D_3IO$ $[M+H]^+$: 237.9803, found: 237.9802.



1u 3m

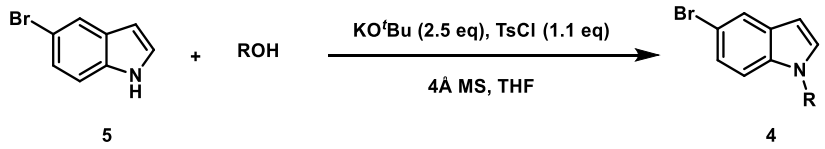
2-bromo-6-trideuteromethoxynaphthalene (3m): The general procedure C was followed. The reaction was performed with 6-bromonaphthalen-2-yl 4-methylbenzenesulfonate **1u** (75.5 mg, 0.2 mmol), CD_3OD (8.0 mg, 0.11 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (100 mg) in 3 mL THF overnight. The desired product **3m** (27.4 mg, 57% yield) was obtained after purification by silica gel chromatography (5% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.50 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.16 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 133.2, 130.1, 129.8, 129.7, 128.6, 128.5, 119.9, 117.1, 105.8; HRMS (APCI+): calc'd for $C_{11}H_6D_3BrO$ $[M+H]^+$: 240.0097, found: 240.0103.



1d 3d'

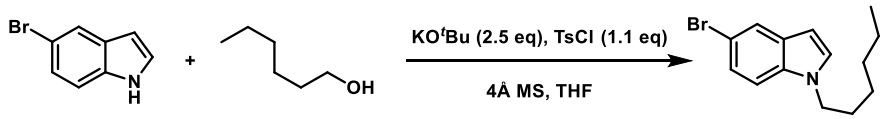
5-Bromo-1-methyl-1*H*-indole (3d'): The general procedure C was followed. The reaction was performed with 5-bromo-1-tosyl-1*H*-indole **1d** (71.1 mg, 0.2 mmol), $^{13}CH_3OH$ (7.8 mg, 0.11 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (80.0 mg) in 3 mL THF for 3 h. The desired product **3d'** (42.4 mg, 99% yield) was obtained after purification by silica gel chromatography (5% EA in PE). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 1.9 Hz, 1H), 7.30 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.05 (dd, *J* = 3.1, 2.0 Hz, 1H), 6.43 (dd, *J* = 3.1, 0.8 Hz, 1H), 3.77 (d, *J* = 138.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 130.2, 130.1 (d, *J* = 2.3 Hz), 124.5, 123.4, 112.8, 110.8, 100.7 (d, J = 2.3 Hz), 33.14; GCMS: calc'd for $C_8{}^{13}CH_8BrN$ $[M]^+$: 209.99, found: 210.00.

General Procedure for One-pot Reaction of N-Alkylation of Indoles



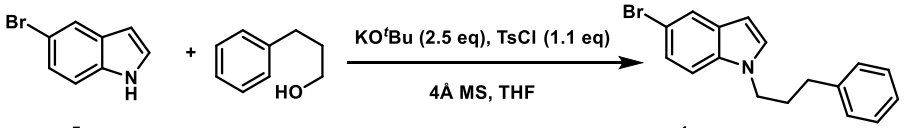
5 4

General procedure D: To a dry Schlenk tube equipped with a magnetic stirring bar, 5-bromo-1*H*-indole (1 equiv), TsCl (1.1 equiv), ROH (1.1 equiv), KO^{t}Bu (2.5 equiv), 4Å MS and THF were added under an atmosphere of dry argon. Then tube was stirred at room temperature until the completion of the reaction as monitored by TLC. After finished, the reaction mixture was filtered through a short pad of Celite, then washed with EA (10 mL). Then the filtrate was concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography to give the desired product.



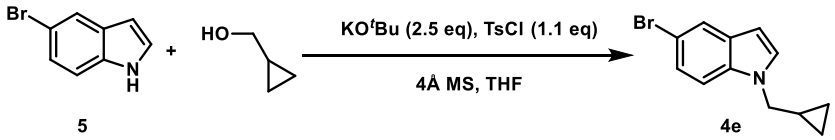
5 4a

5-Bromo-1-hexyl-1*H*-indole (4a): The general procedure D was followed. The reaction was performed with 5-bromo-1*H*-indole **5** (98.0 mg, 0.5 mmol), TsCl (105.0 mg, 0.55 mol), hexanol (61.2 mg, 0.6 mmol), KO^{t}Bu (140.0 mg, 1.25 mmol), 4Å MS (250 mg) in 5 mL THF. The desired product **4a** (102.3 mg, 73% yield) was obtained after purification by silica gel chromatography (1% CH_2Cl_2 in PE).



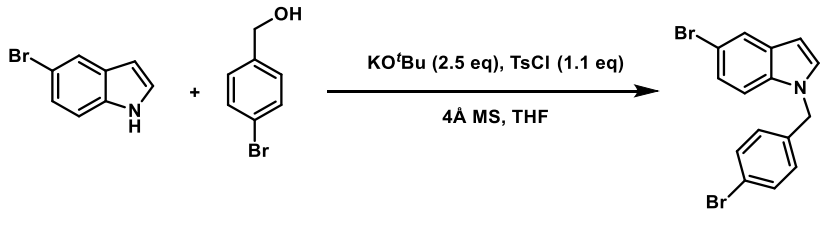
5 4c

5-Bromo-1-(3-phenylpropyl)-1*H*-indole (4c): The general procedure D was followed. The reaction was performed with 5-bromo-1*H*-indole **5** (39.3 mg, 0.2 mmol), 3-phenylpropan-1-ol (30.0 mg, 0.22 mmol), KO^{t}Bu (58.3 mg, 0.5 mmol) and 4Å MS (200 mg) in 2 mL THF. The desired product **4c** (31.4 mg, 50% yield) was obtained after purification by silica gel chromatography (5% PE in EA).



5 4e

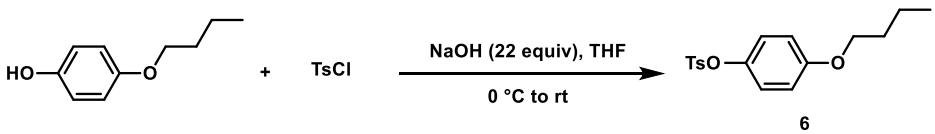
5-Bromo-1-(cyclopropylmethyl)-1*H*-indole(4e): The general procedure D was followed. The reaction was performed with 5-bromo-1*H*-indole **5** (39.3 mg, 0.2 mmol), cyclopropylmethanol (15.8 mg, 0.22 mmol), KO^{t}Bu (58.3 mg, 0.5 mmol) and 4Å MS (200 mg) in 2 mL THF. The desired product **4e** (30.7 mg, 61% yield) was obtained after purification by silica gel chromatography (5% PE in EA).



5 4g

5-Bromo-1-(4-bromobenzyl)-1*H*-indole (4g): The general procedure ***D*** was followed. The reaction was performed with 5-bromo-1*H*-indole **5** (39.3 mg, 0.2 mmol), (4-bromophenyl)methanol (41.1 mg, 0.22 mmol), KO^{t}Bu (58.3 mg, 0.5 mmol) and 4Å MS (200 mg) in 2 mL THF. The desired product **4g** (39.5 mg, 54% yield) was obtained after purification by silica gel chromatography (5% PE in EA).

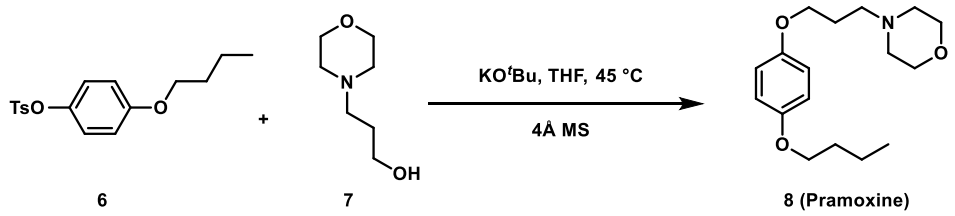
Synthesis of 8 (Pramoxine) and 8-*d* (Deuterated Pramoxine)



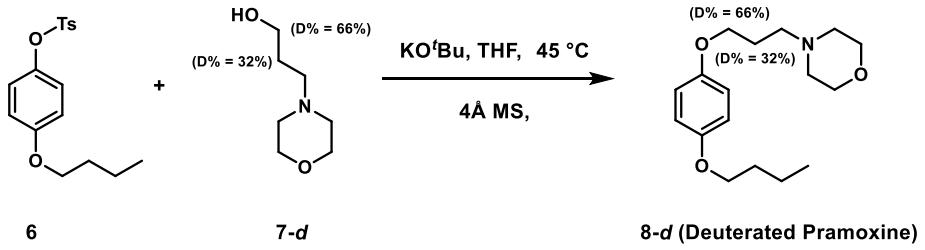
6

4-Butoxyphenyl 4-methylbenzenesulfonate (6): To a dry Schlenk flask equipped with a magnetic stirring bar, 4-butoxyphenol (0.16 g, 1 mmol), NaOH (0.88 g, 22 mmol) and 10 mL THF were added under an atmosphere of dry argon and stirred for 15 minutes at room temperature. Then TsCl (0.21 g, 1.1 mmol, 1.1 equiv, in 10 mL THF) was slowly added within 15 min at 0 °C. The reaction mixture was stirred at room temperature for 12 h, then quenched with H_2O (20 mL) and extracted with EA (20 mL × 3). The combined organic

layers were washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed under reduced pressure. The desired product **6** (0.32 g, 99 % yield) was obtained after purification by silica gel chromatography (4% EA in PE) to get the corresponding product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 2H), 3.89 (t, *J* = 6.5 Hz, 2H), 2.44 (s, 3H), 1.85 – 1.63 (m, 2H), 1.52 – 1.34 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 145.3, 143.0, 132.4, 129.8, 128.7, 123.4, 115.1, 68.2, 31.4, 21.9, 19.3, 14.0; HRMS (ESI+) calc'd for $C_{17}H_{20}SO_4K$ $[M+K]^+$: 359.0714, found: 359.0717.



4-(3-(4-Butoxyphenoxy)propyl)morpholine (8): The general procedure C was followed. The reaction was performed with 4-butoxyphenyl 4-methylbenzenesulfonate **6** (64.1 mg, 0.2 mmol), 3-morpholinopropan-1-ol **7** (31.9 mg, 0.22 mmol), KO^{t}Bu (26.9 mg, 0.24 mmol) and 4Å MS (200.0 mg) in 2 mL THF for 12 h. The desired product **8** (34.3 mg, 62% yield) was obtained after purification by silica gel chromatography (5% methanol in DCM). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.82 (s, 4H), 3.96 (t, *J* = 6.3 Hz, 2H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.74 – 3.65 (m, 4H), 2.56 – 2.43 (m, 6H), 1.98 –1.88 (m, 2H), 1.79 – 1.69 (m, 2H), 1.54 – 1.40 (m, 2H), 0.96 (t, *J* = 6.9 Hz, 3H). These spectroscopic data were consistent with those reported in the literature.[21]



4-(3-(4-Butoxyphenoxy)propyl-2,3,3-*d*$_3$)morpholine (8-*d*): The general procedure C was followed. The reaction was performed with 4-butoxyphenyl 4- methylbenzenesulfonate **6**

(48.1 mg, 0.15 mmol), 3-morpholinopropan-1,1,2-d_3-1-ol **7-*d*** (23.5 mg, 0.16 mmol), KO^{t}Bu (20.2 mg, 0.18 mmol) and 4Å MS (100.0 mg) in 2 mL THF for 12 h. The desired product **8-*d*** (33.9 mg, 76% yield) was obtained after purification by silica gel chromatography (rinsed the silica gel with 0.2% Et_3N in PE, then with 25% EA in PE as the eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 4H), 3.96 (t, *J* = 6.0 Hz, 0.69H), 3.90 (t, *J* = 6.5 Hz, 2H), 3.73 (t, *J* = 4.6 Hz, 4H), 2.58 – 2.40 (m, 6H), 1.98 – 1.88 (m, 1.39H), 1.77 – 1.68 (m, 2H), 1.53 –1.41 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 153.1, 115.5, 68.4, 67.1, 55.7, 53.9, 31.6, 26.4, 19.4, 14.0; HRMS (ESI+) calc'd for $C_{17}H_{25}D_3NO_3$ $[M+H]^+$: 297.2252, found: 297.2245.

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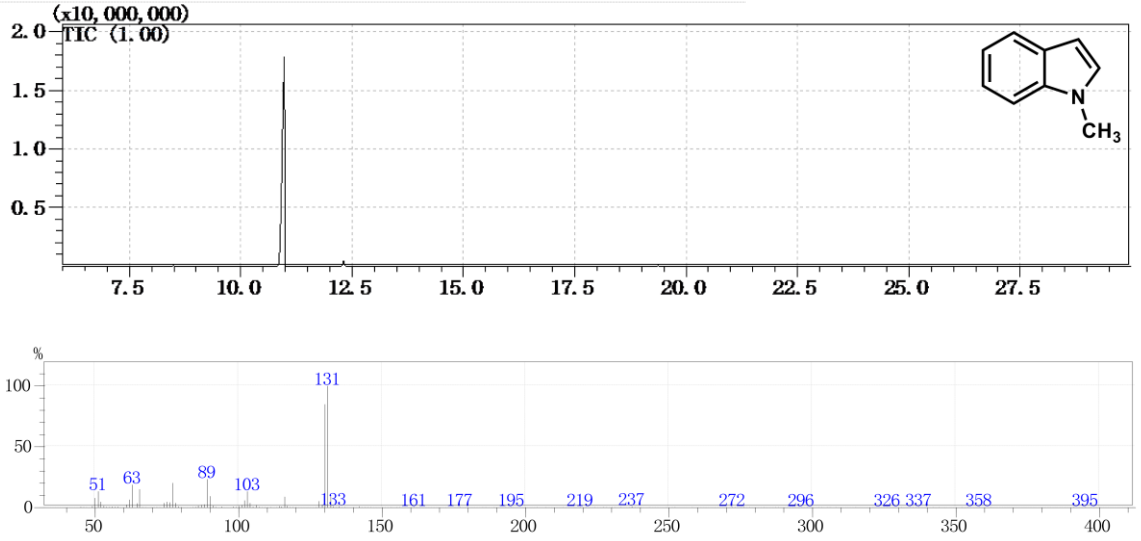
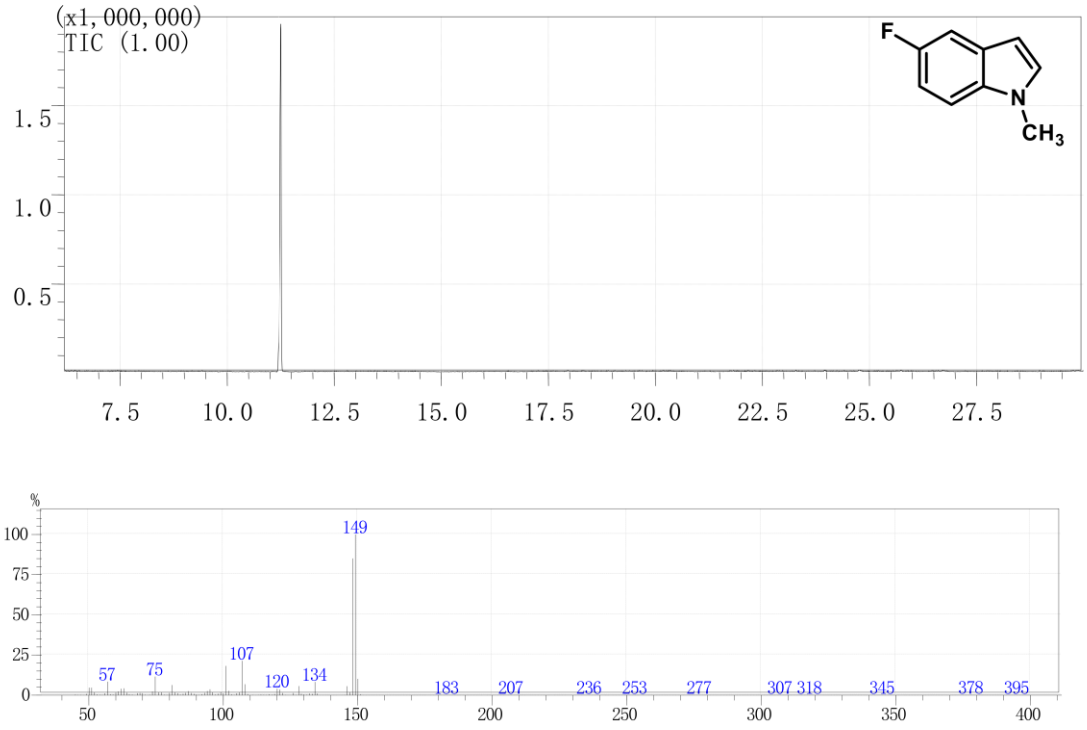
GC-MS Spectra



GC-MS of **2a**



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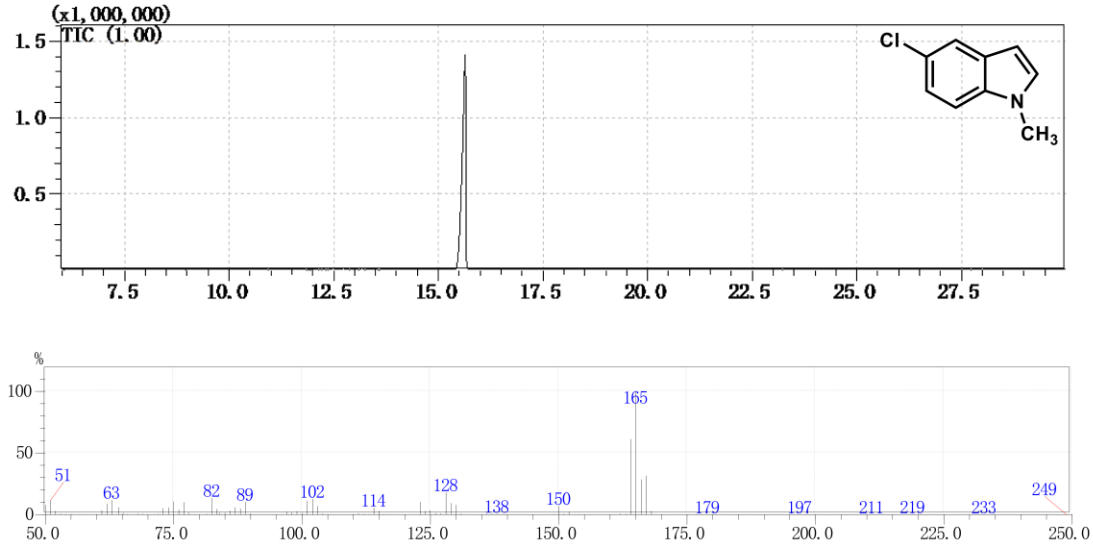

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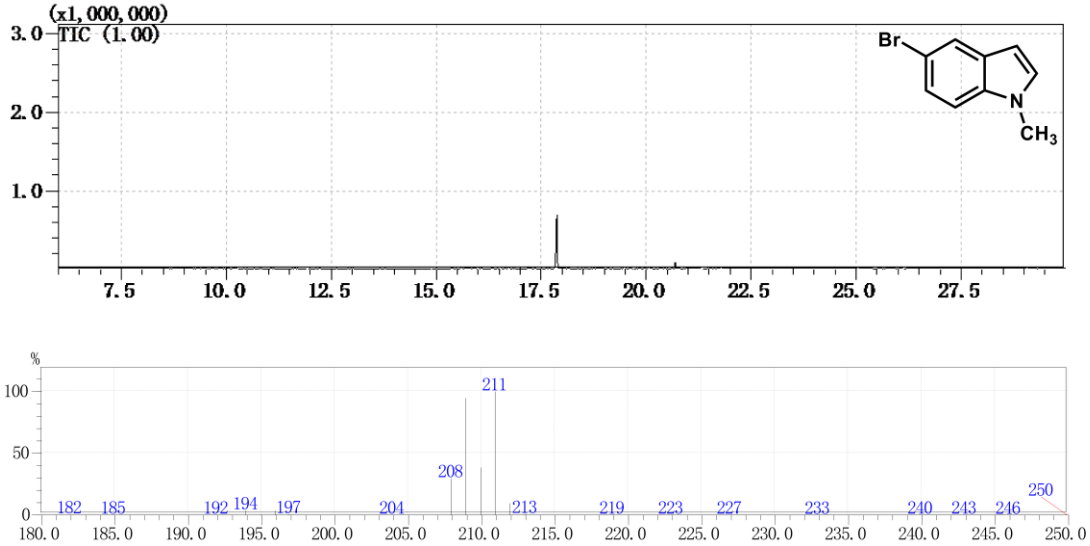

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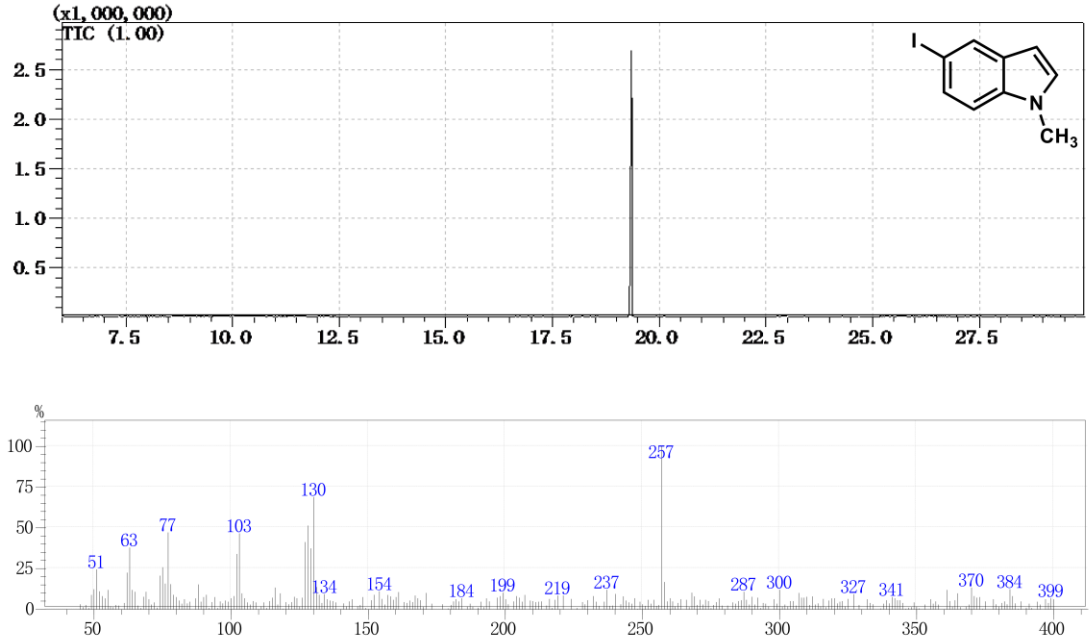
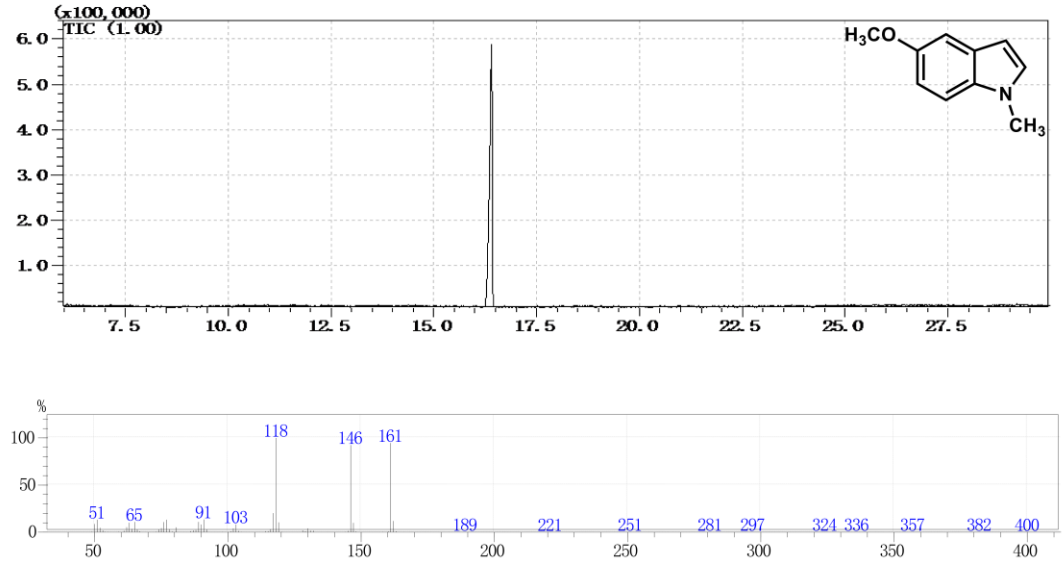


GC-MS of **2e**



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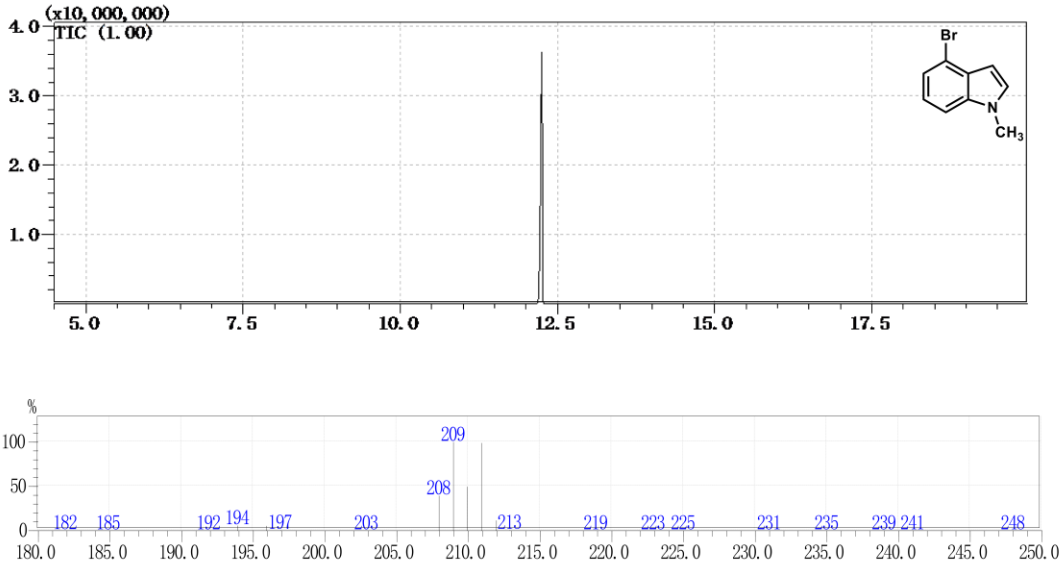

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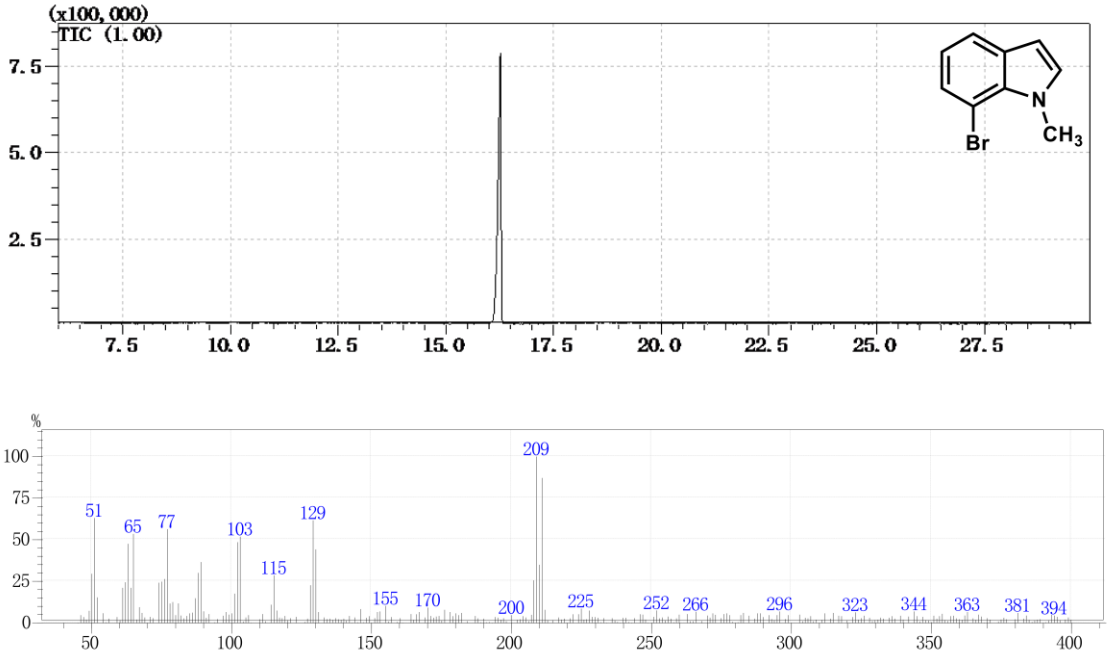

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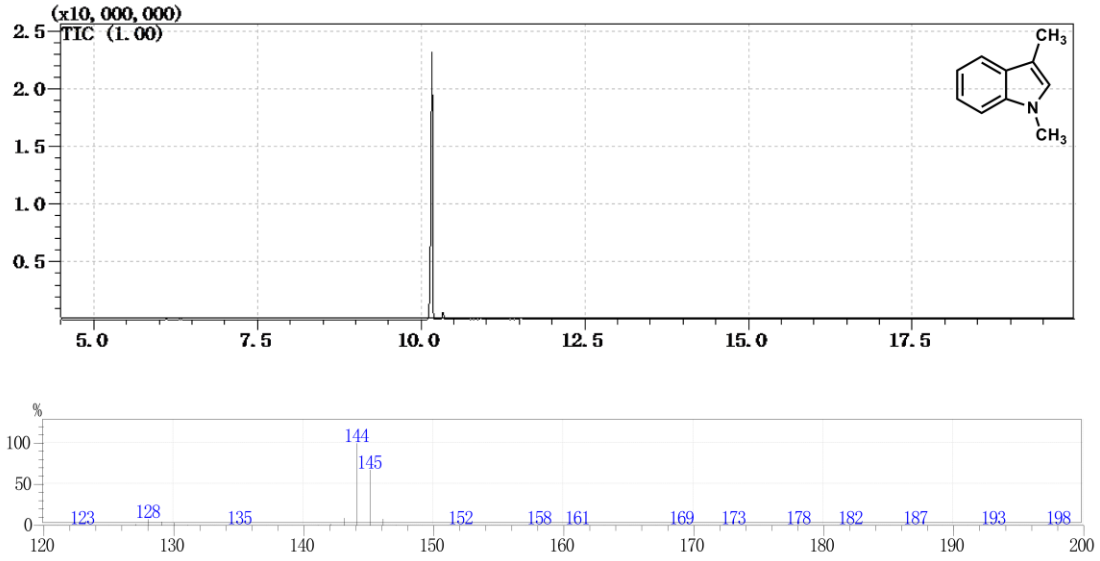

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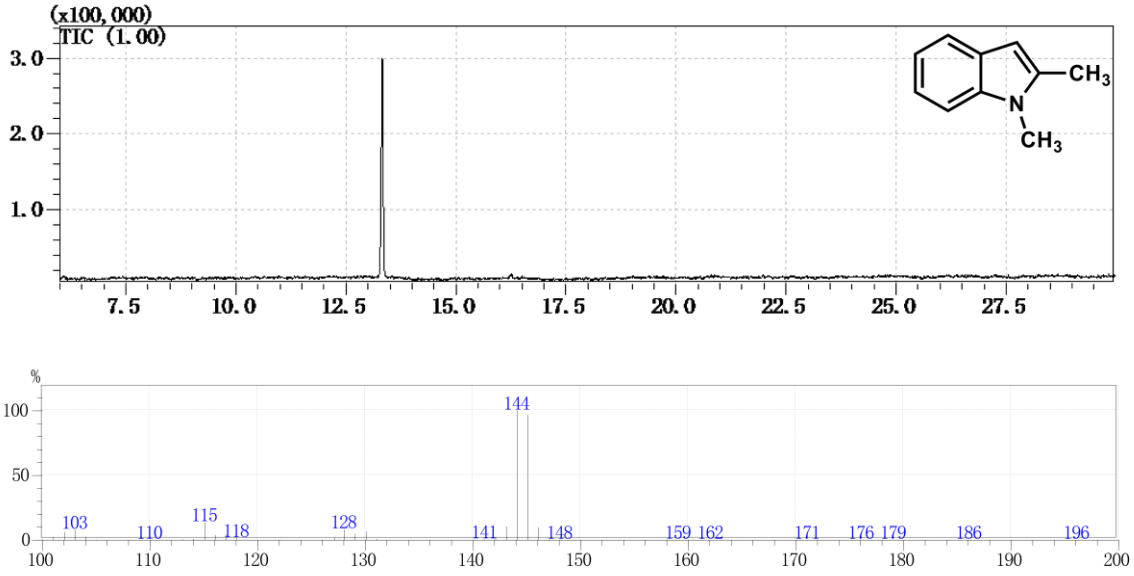

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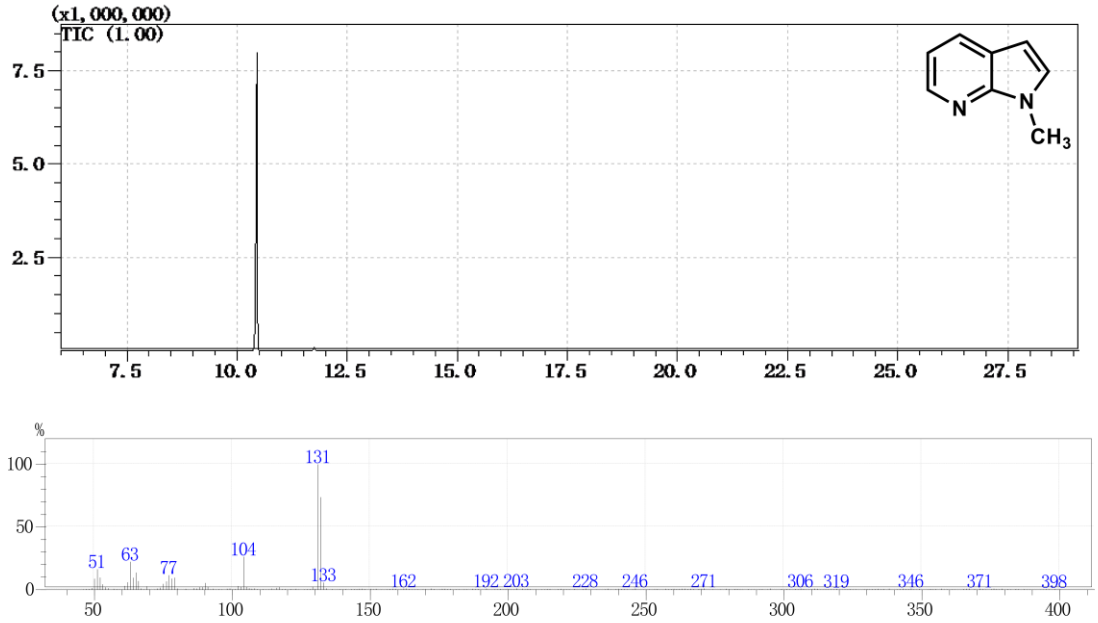
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7.5
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17.5
20.0
22.5
25.0
27.5
N
N
CH3
%
100
50
0
131
51
63
77
104
133
162
192
203
228
246
271
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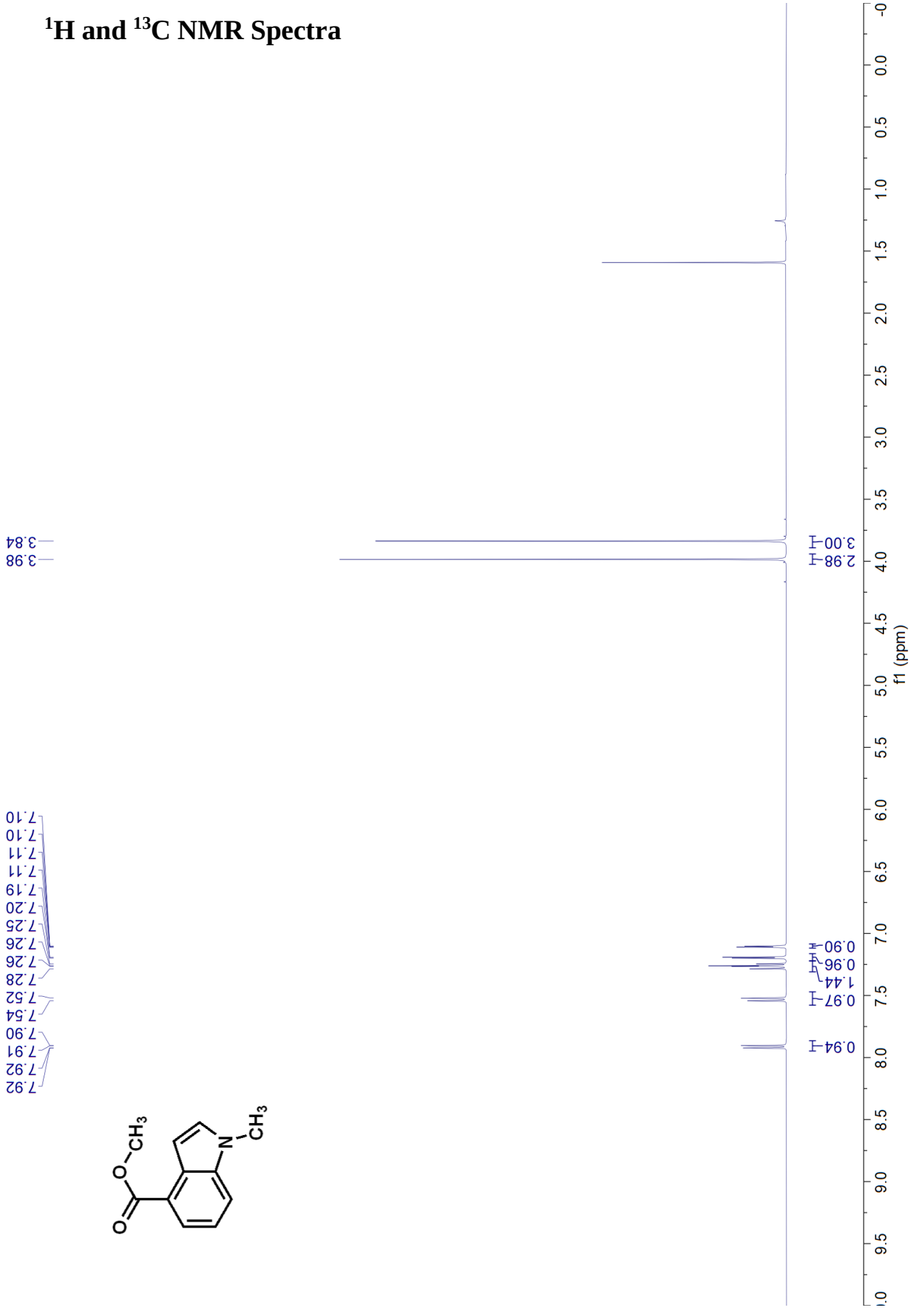
GC-MS of **2m**

^{1}H and ^{13}C NMR Spectra



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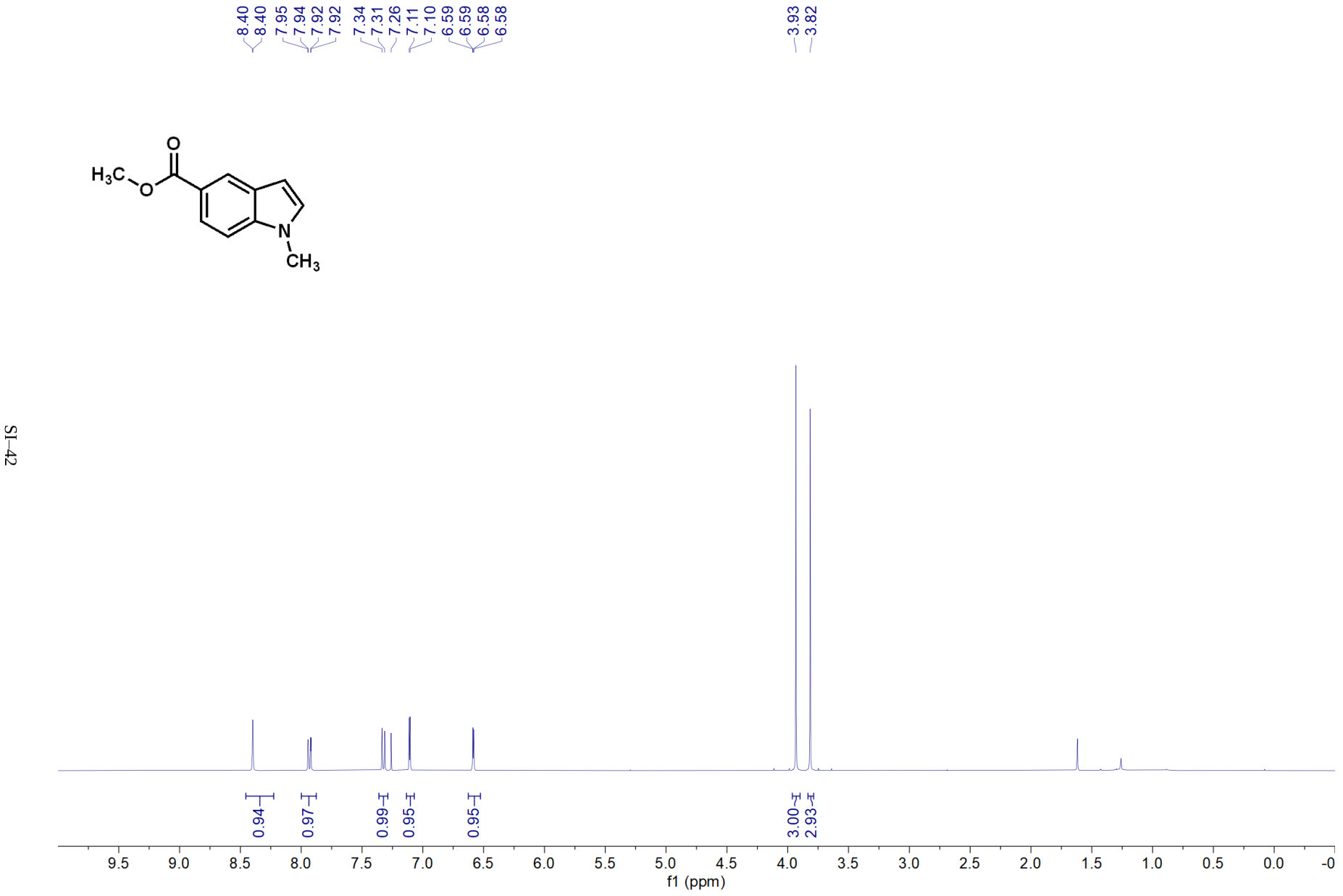

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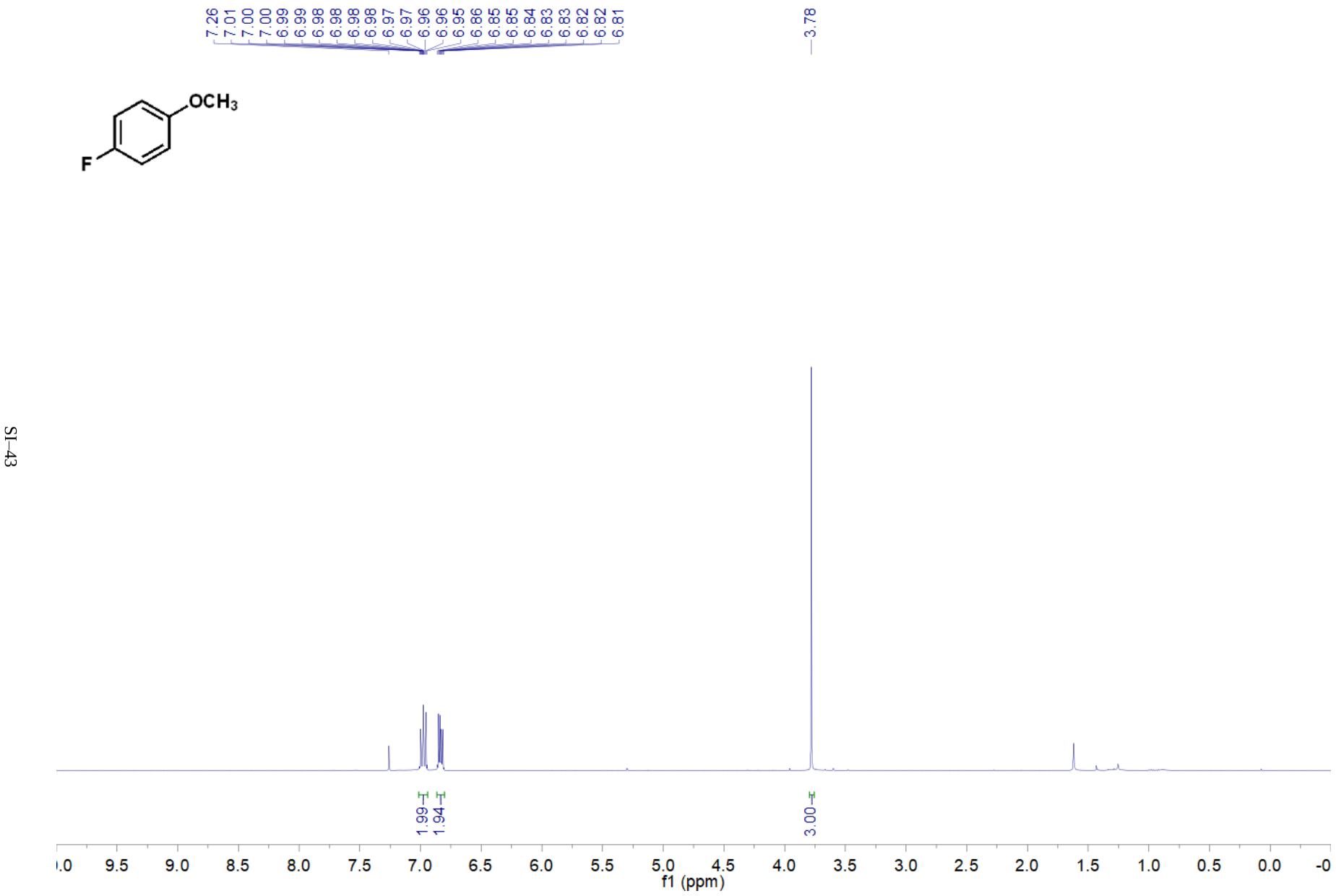

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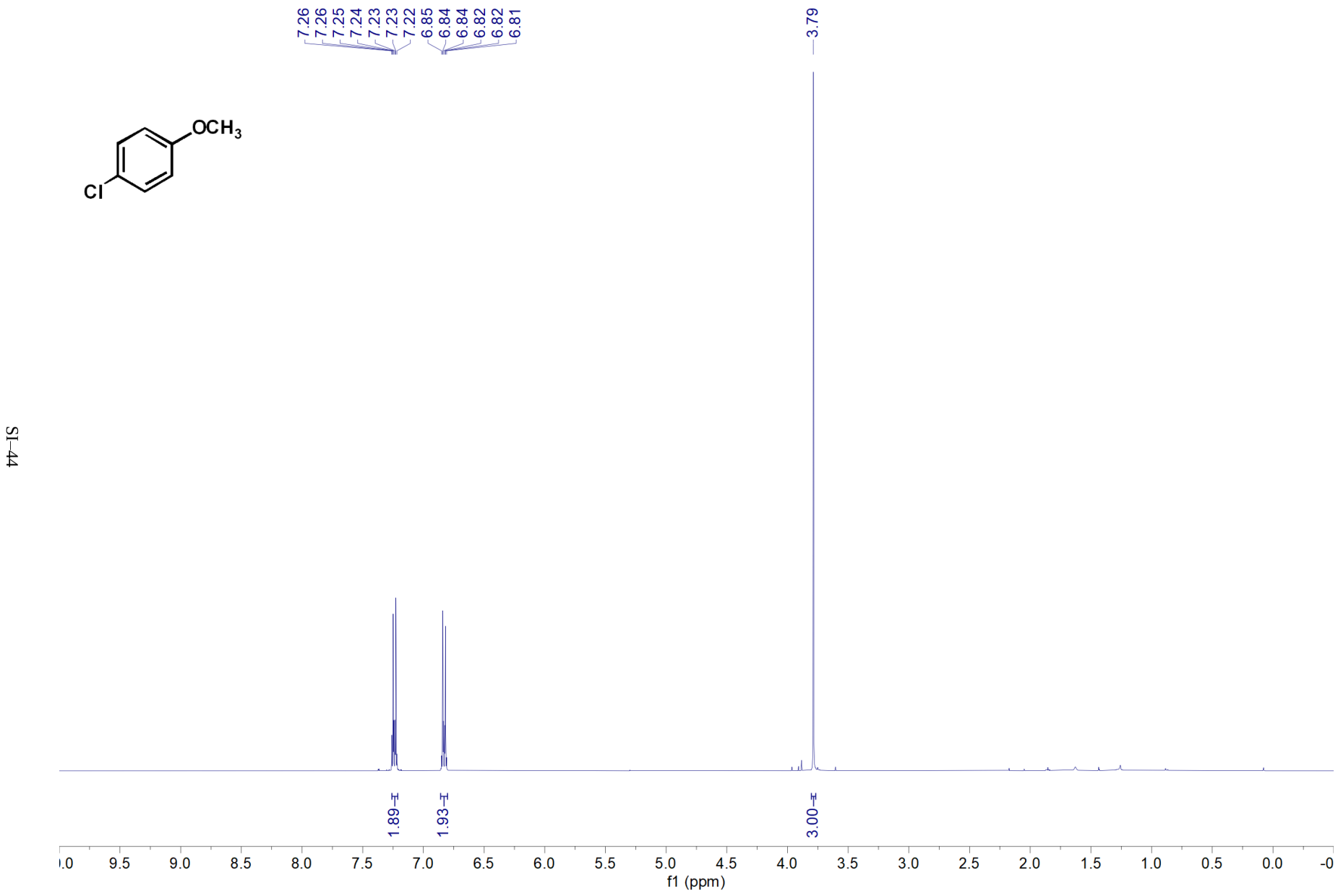
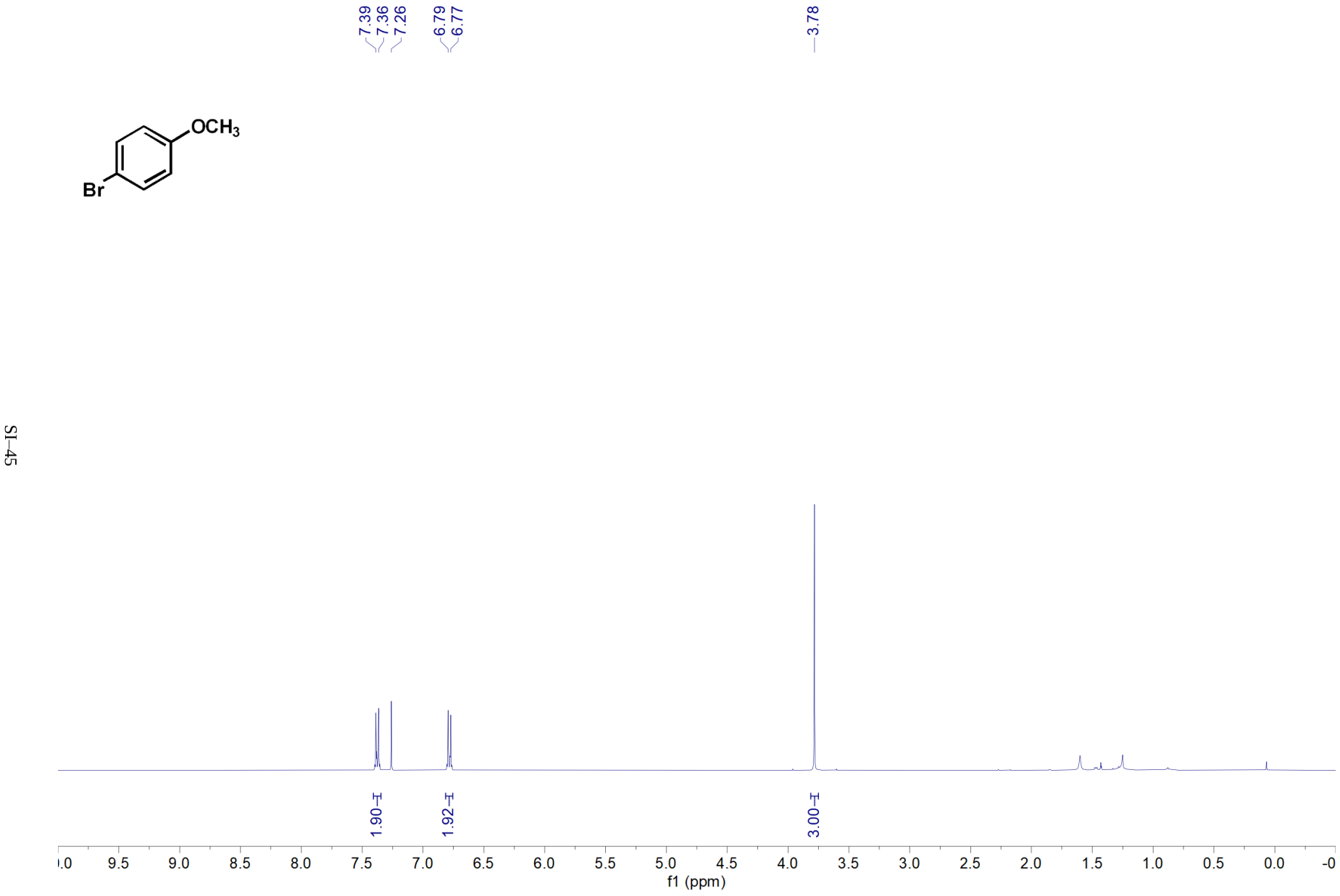


^{1}H NMR (400 MHz, $CDCl_3$) of **2o**



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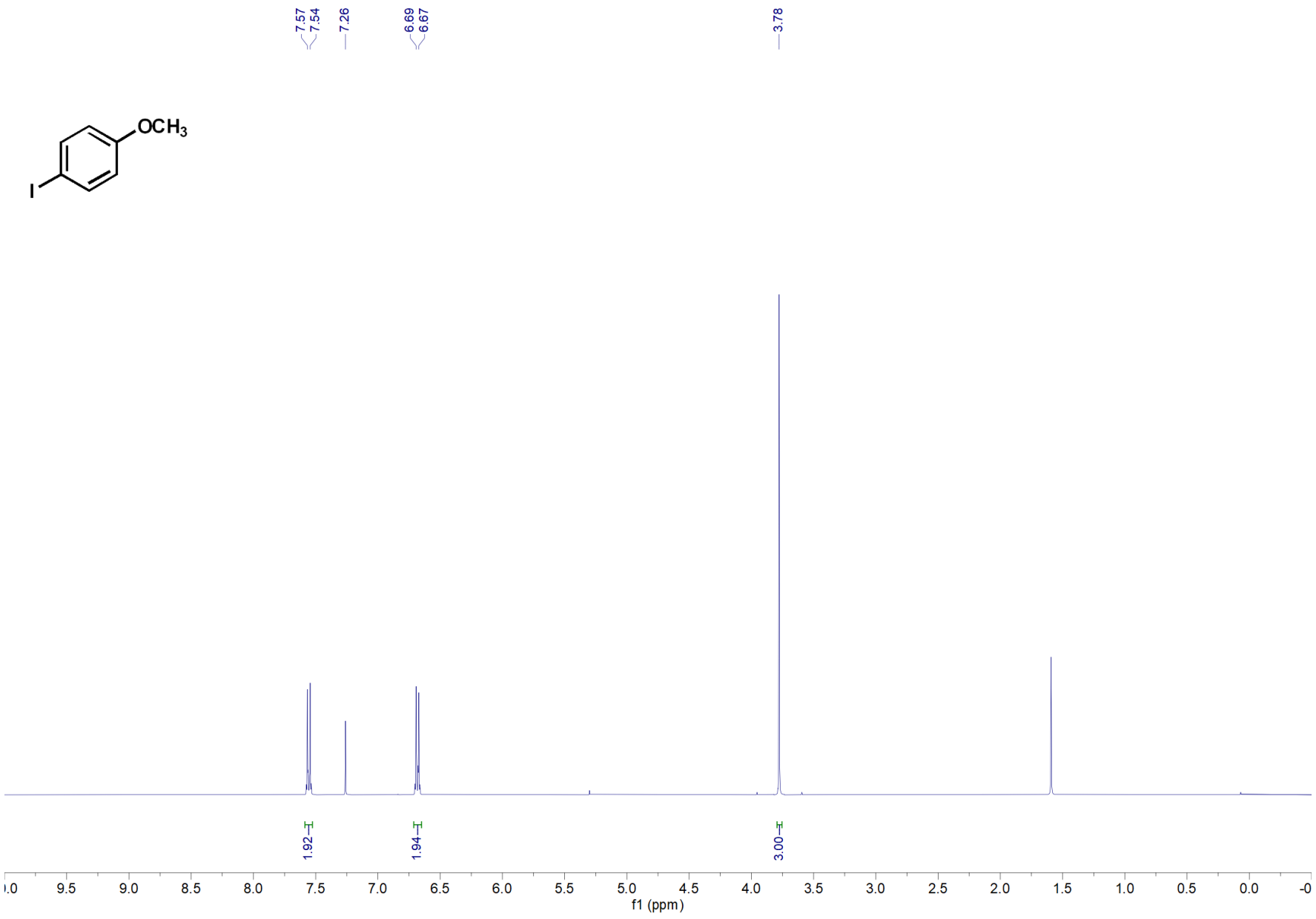
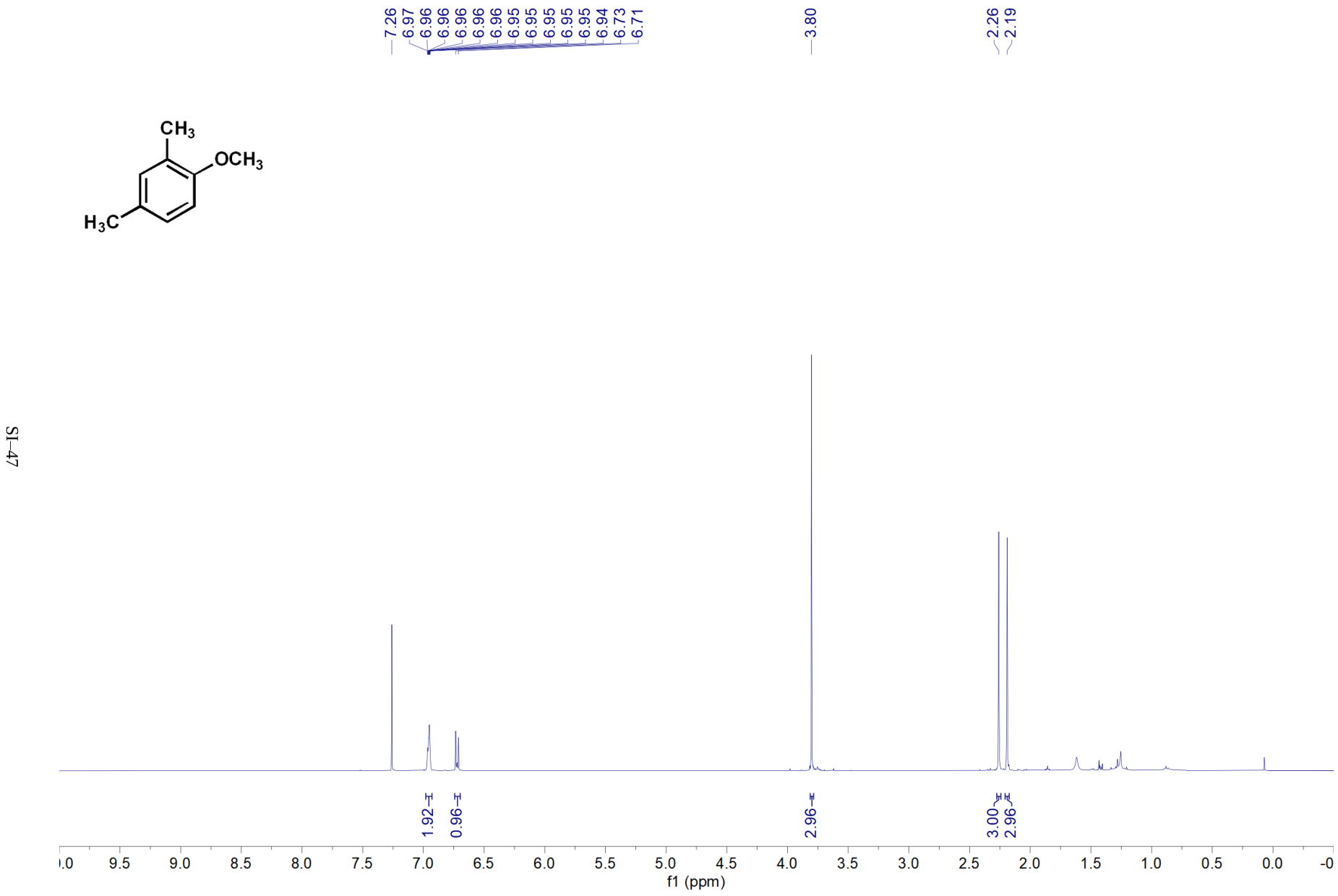


^{1}H NMR (400 MHz, $CDCl_3$) of **2q**



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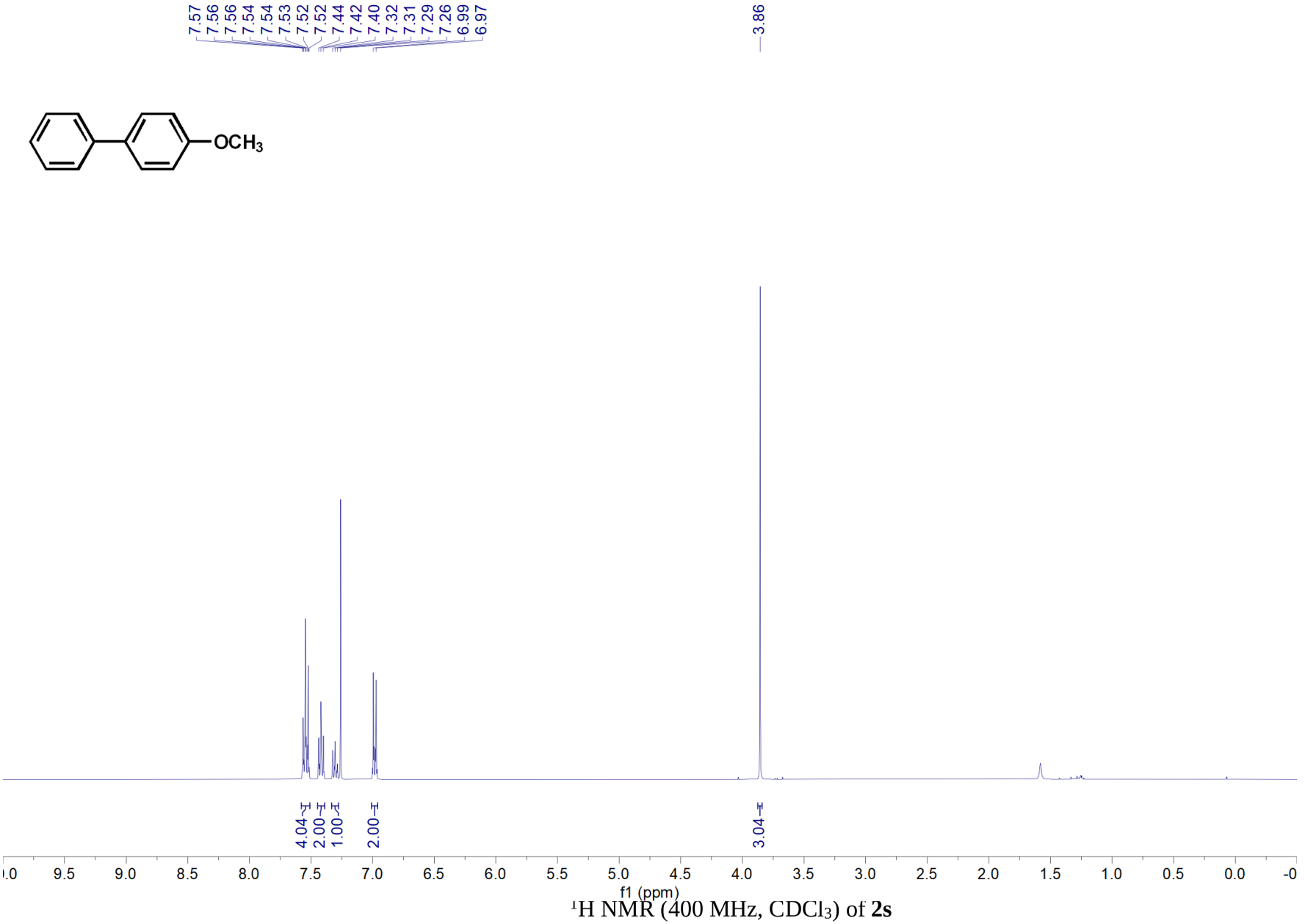

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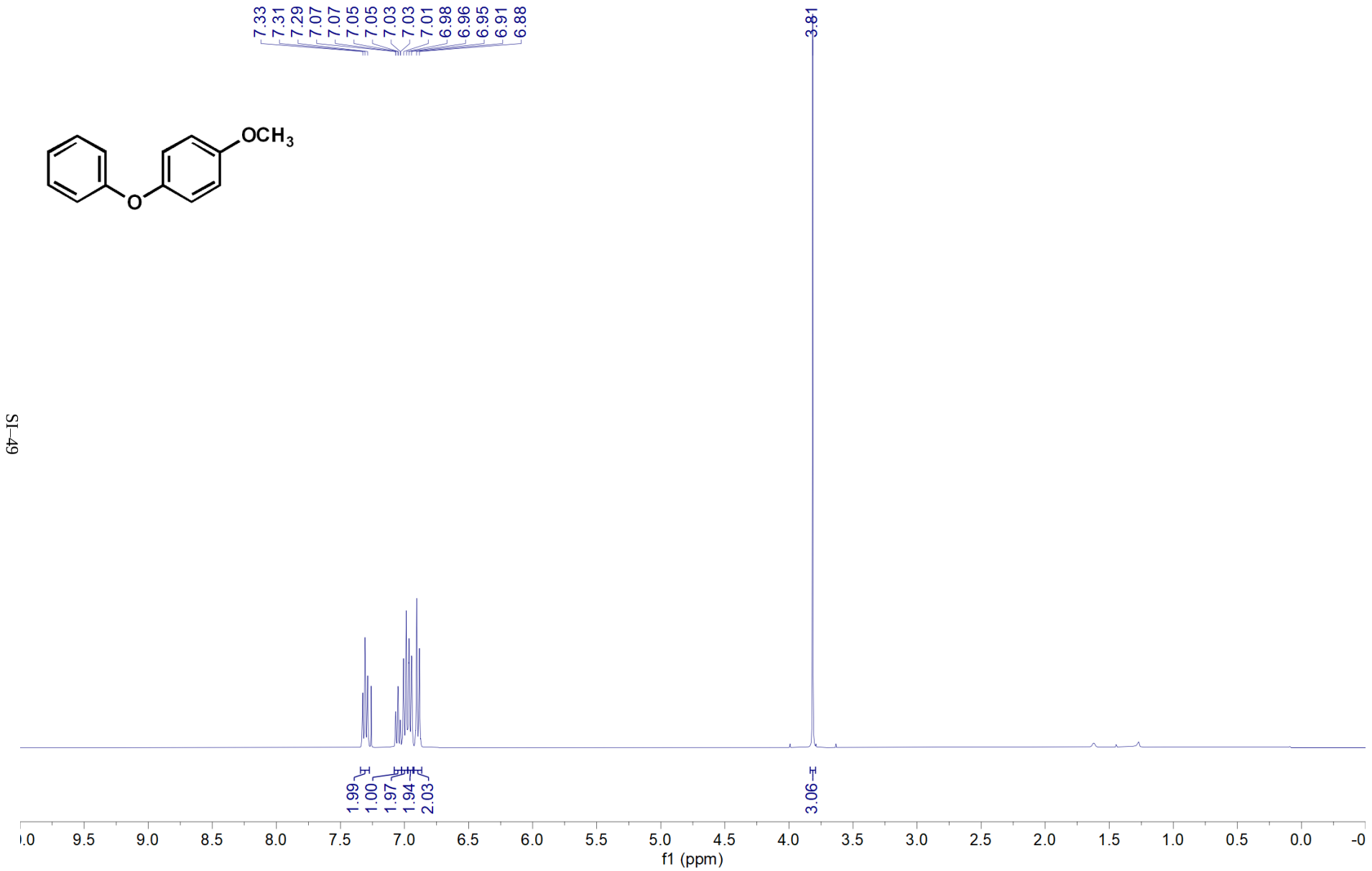

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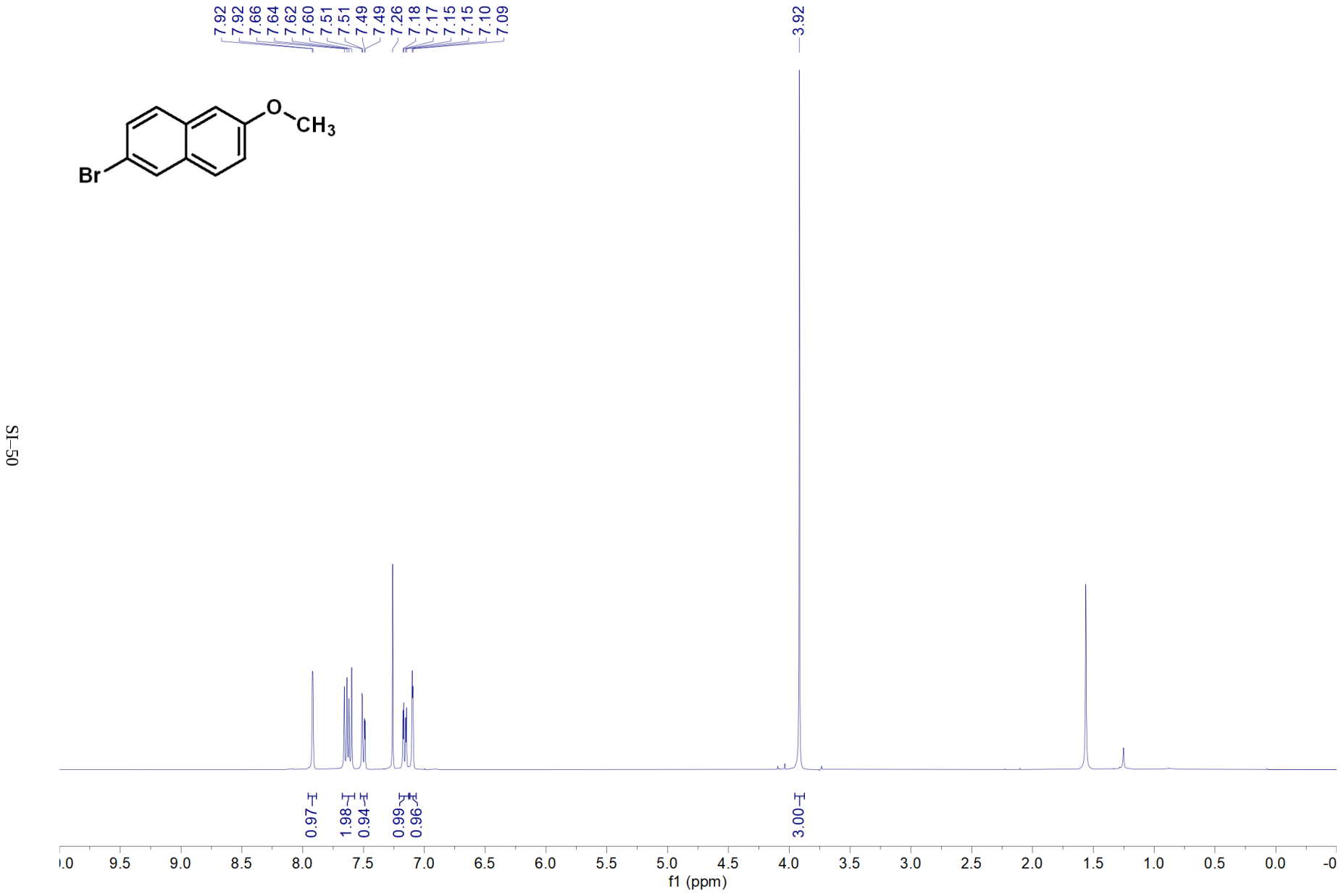

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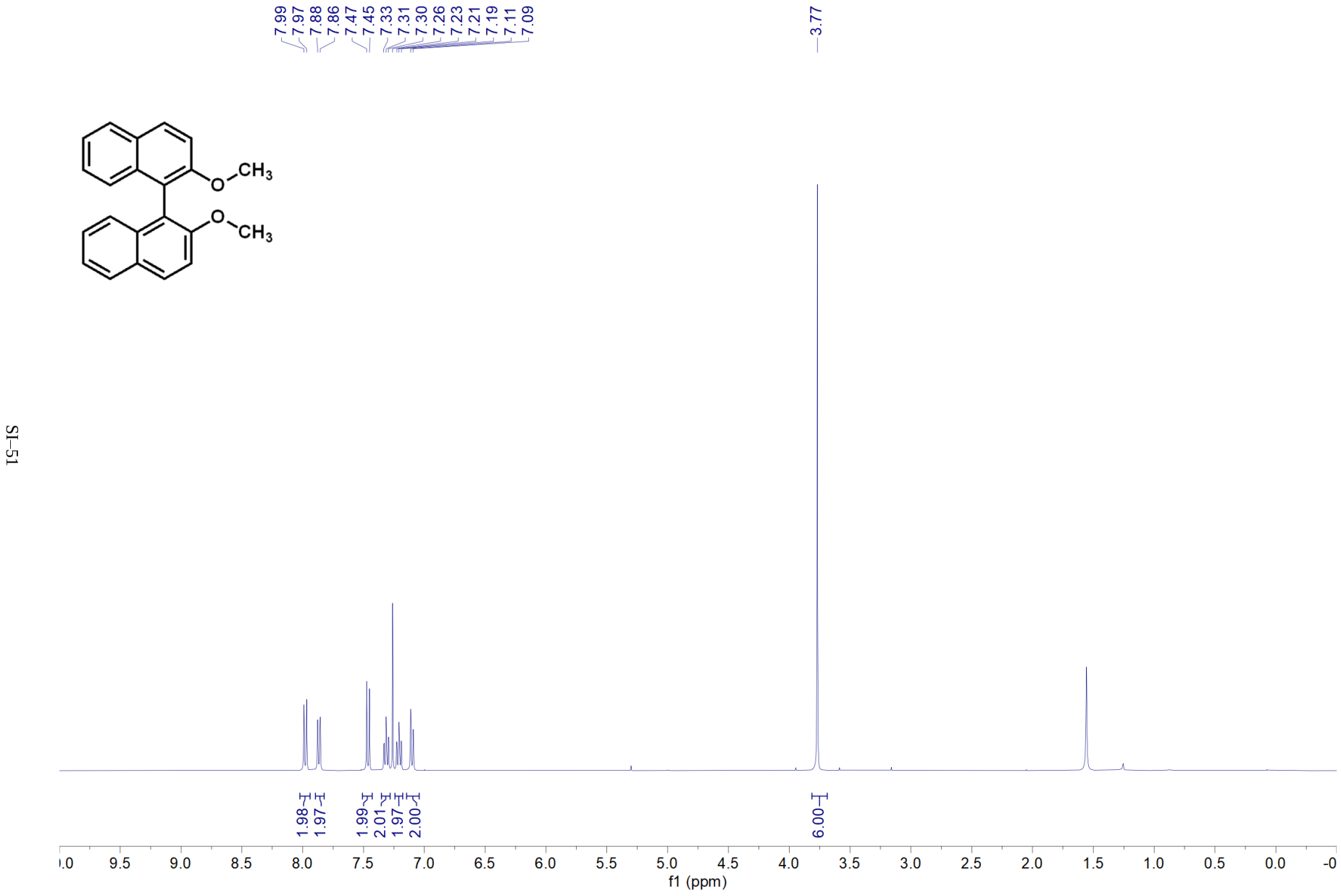
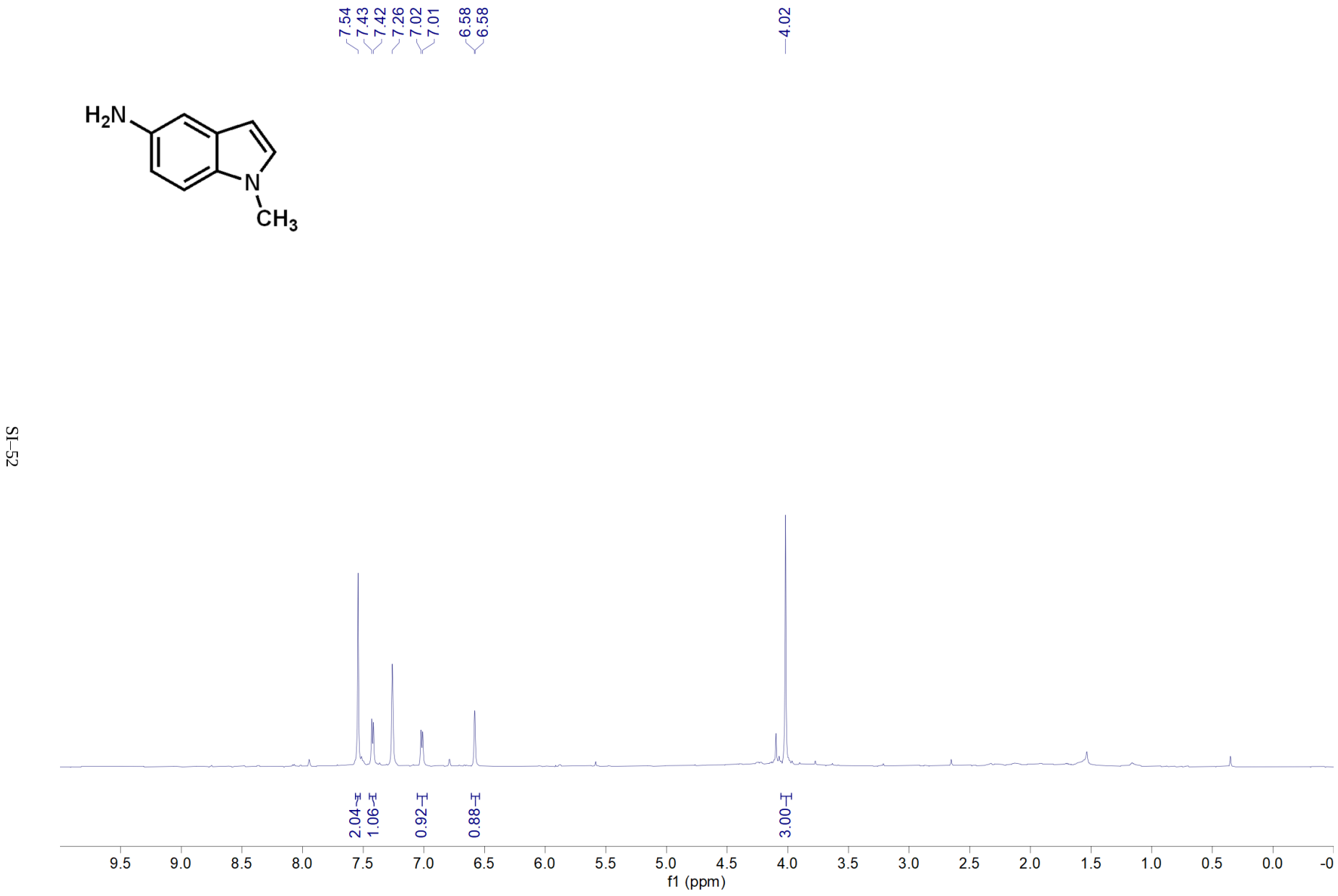
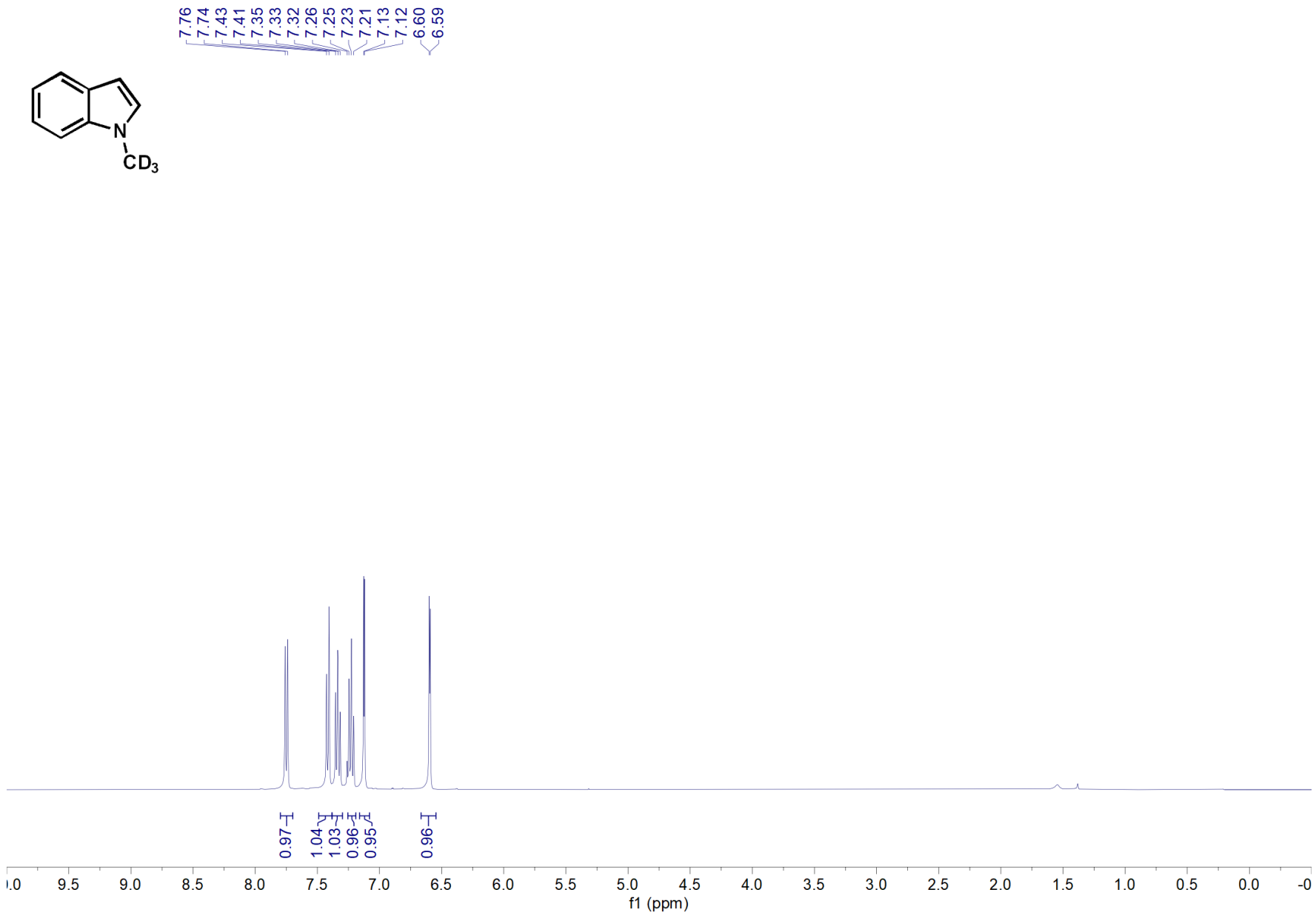


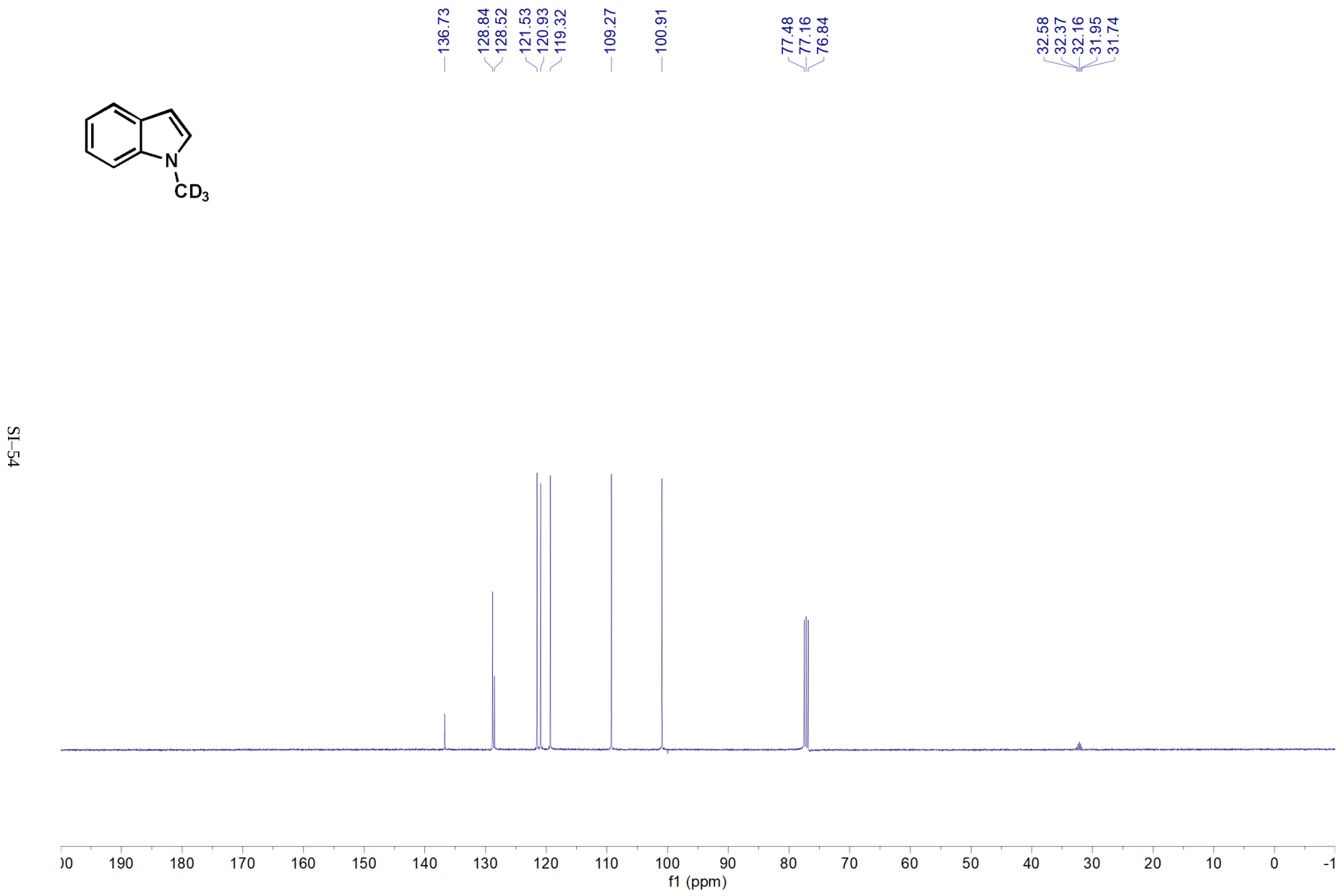
^{1}H NMR (600 MHz, $CDCl_3$) of **2v**



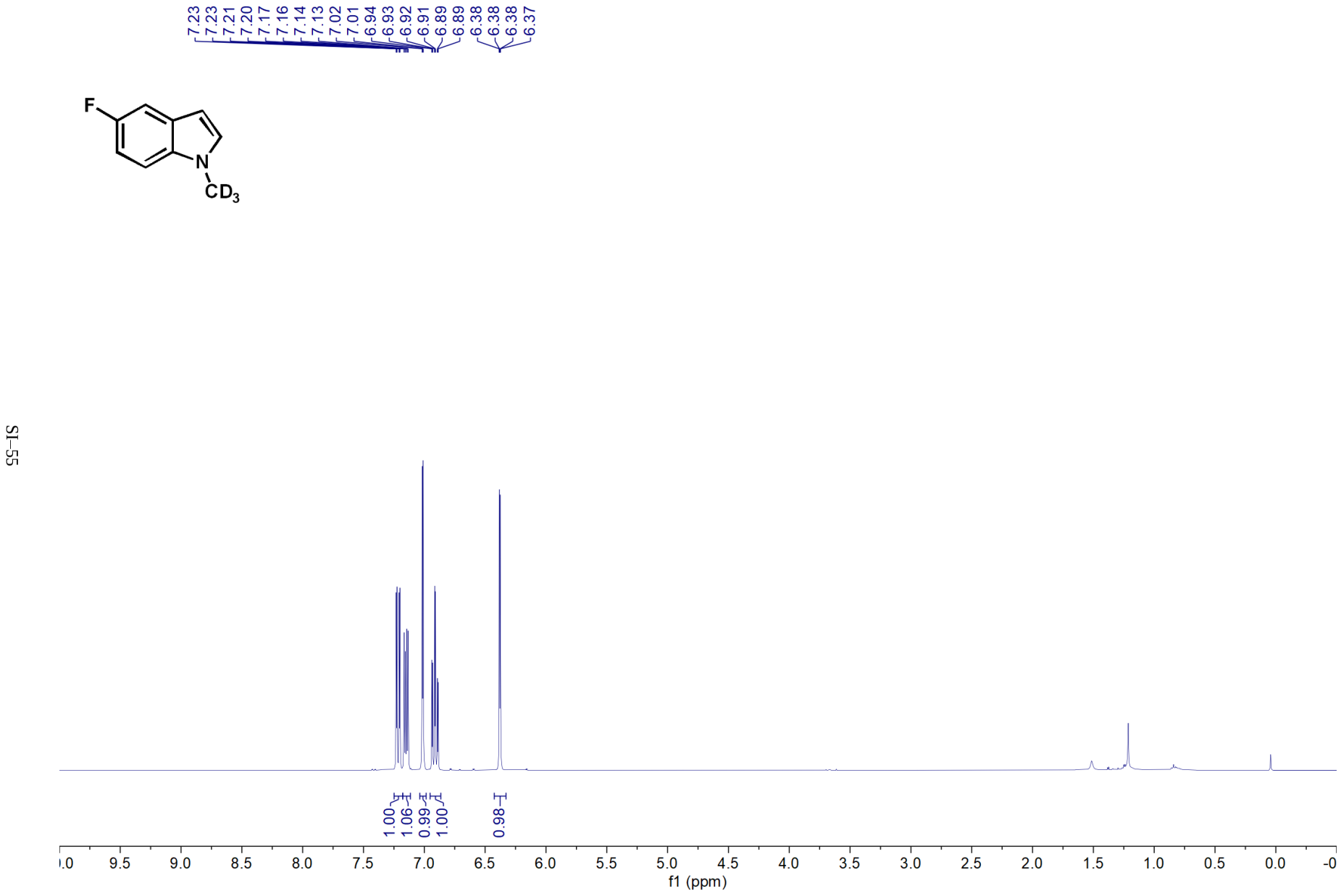
^{1}H NMR (600 MHz, $CDCl_3$) of **2y**



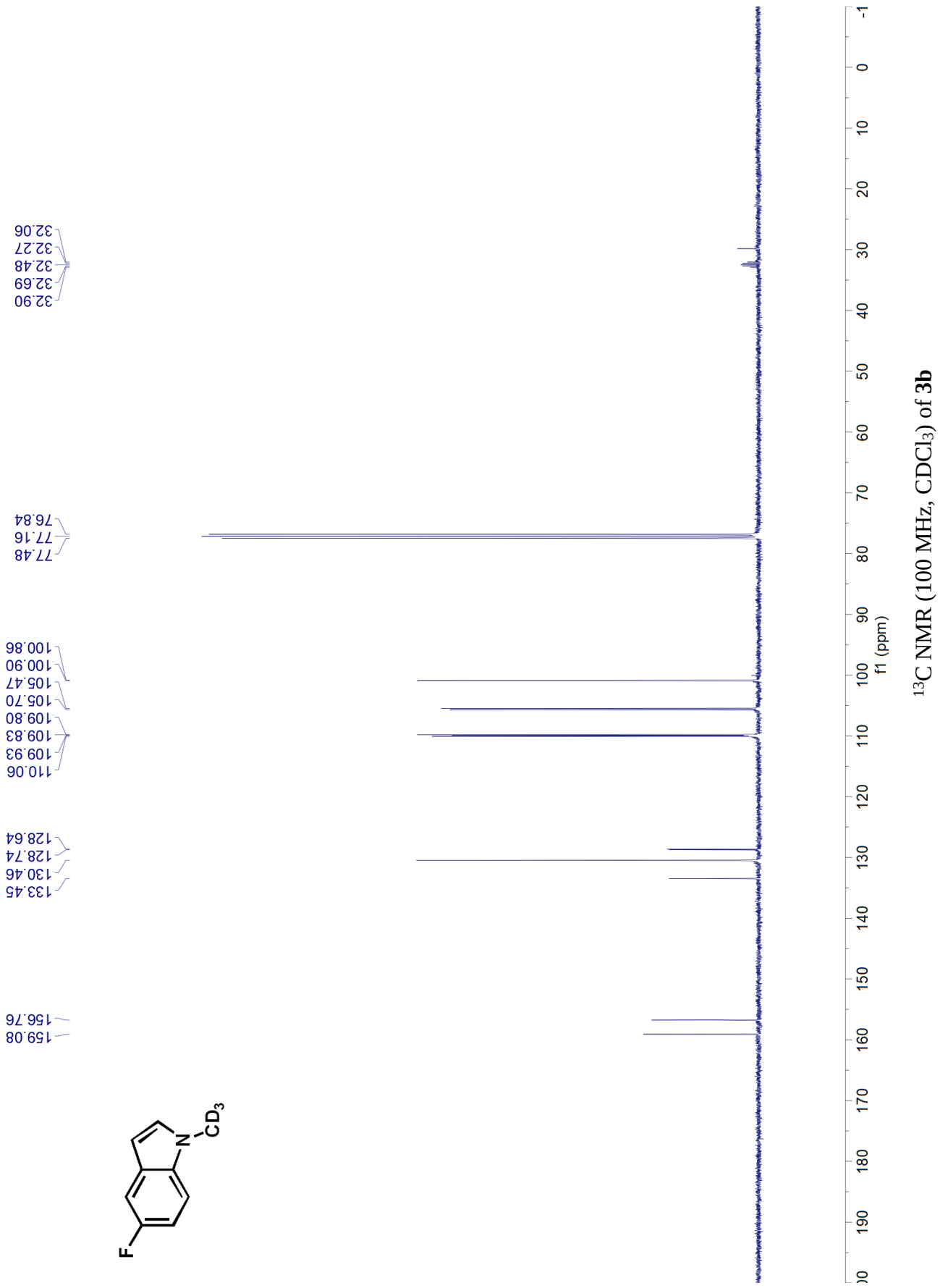
^{1}H NMR (400 MHz, $CDCl_3$) of **3a**



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



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



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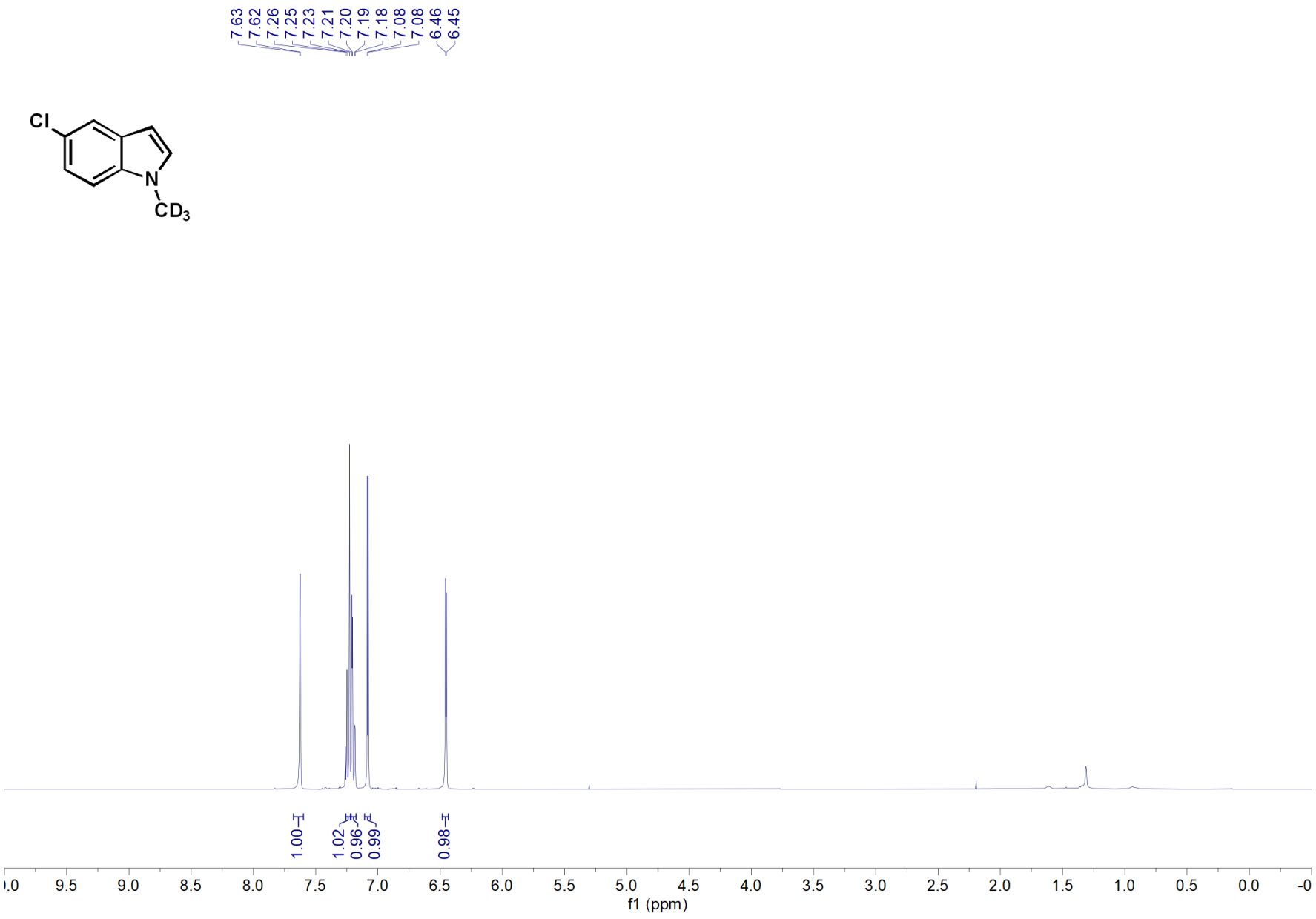

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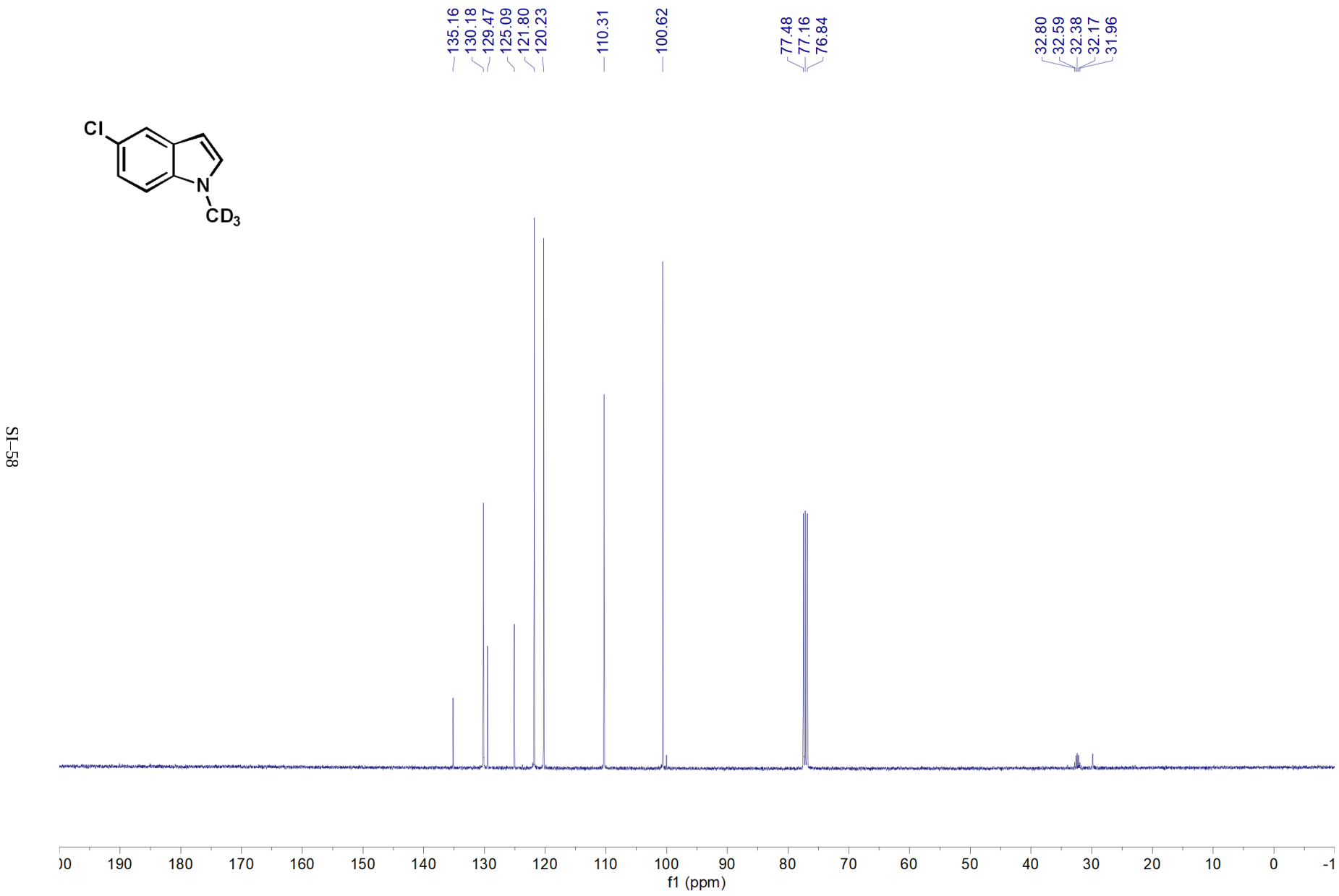
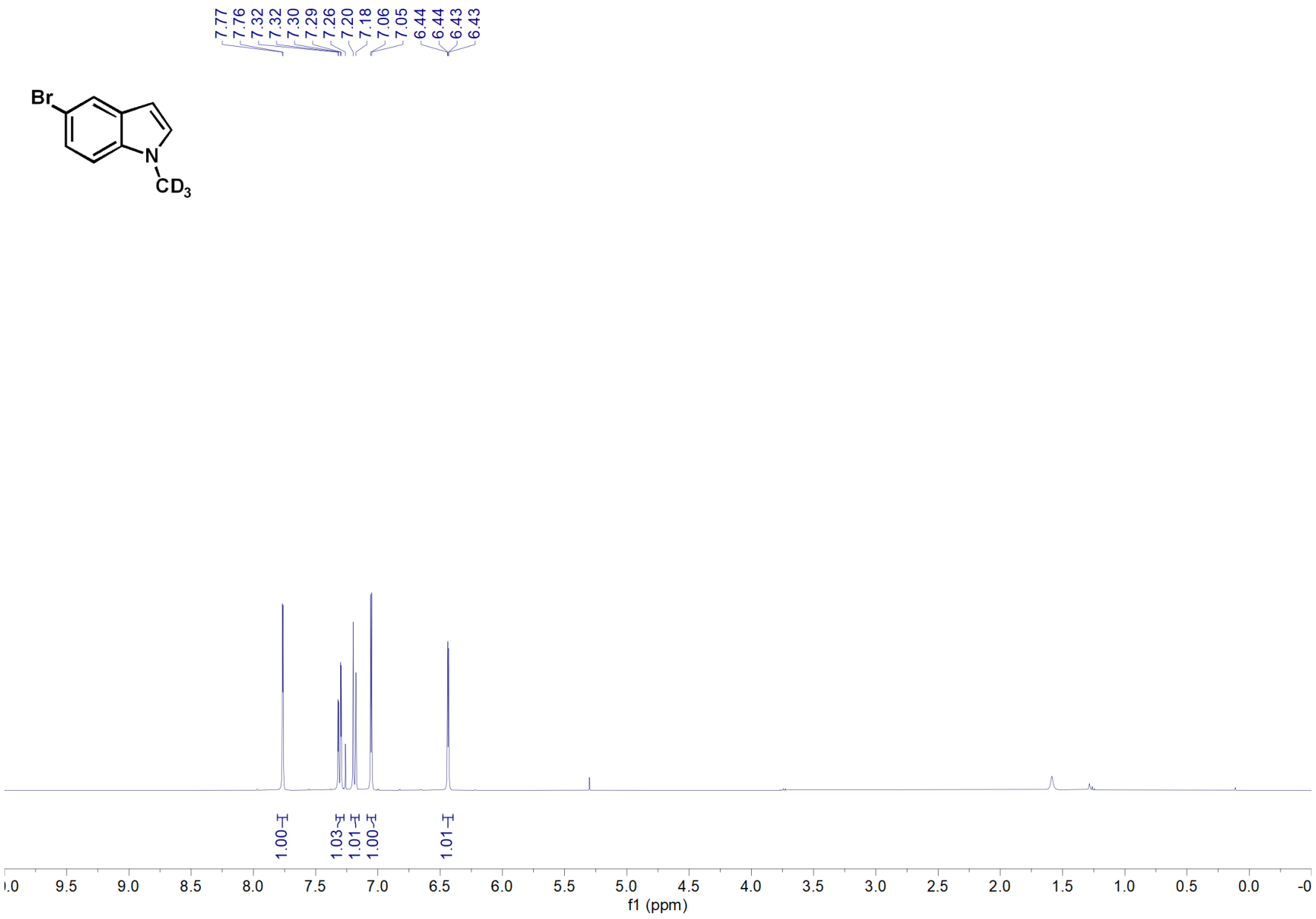
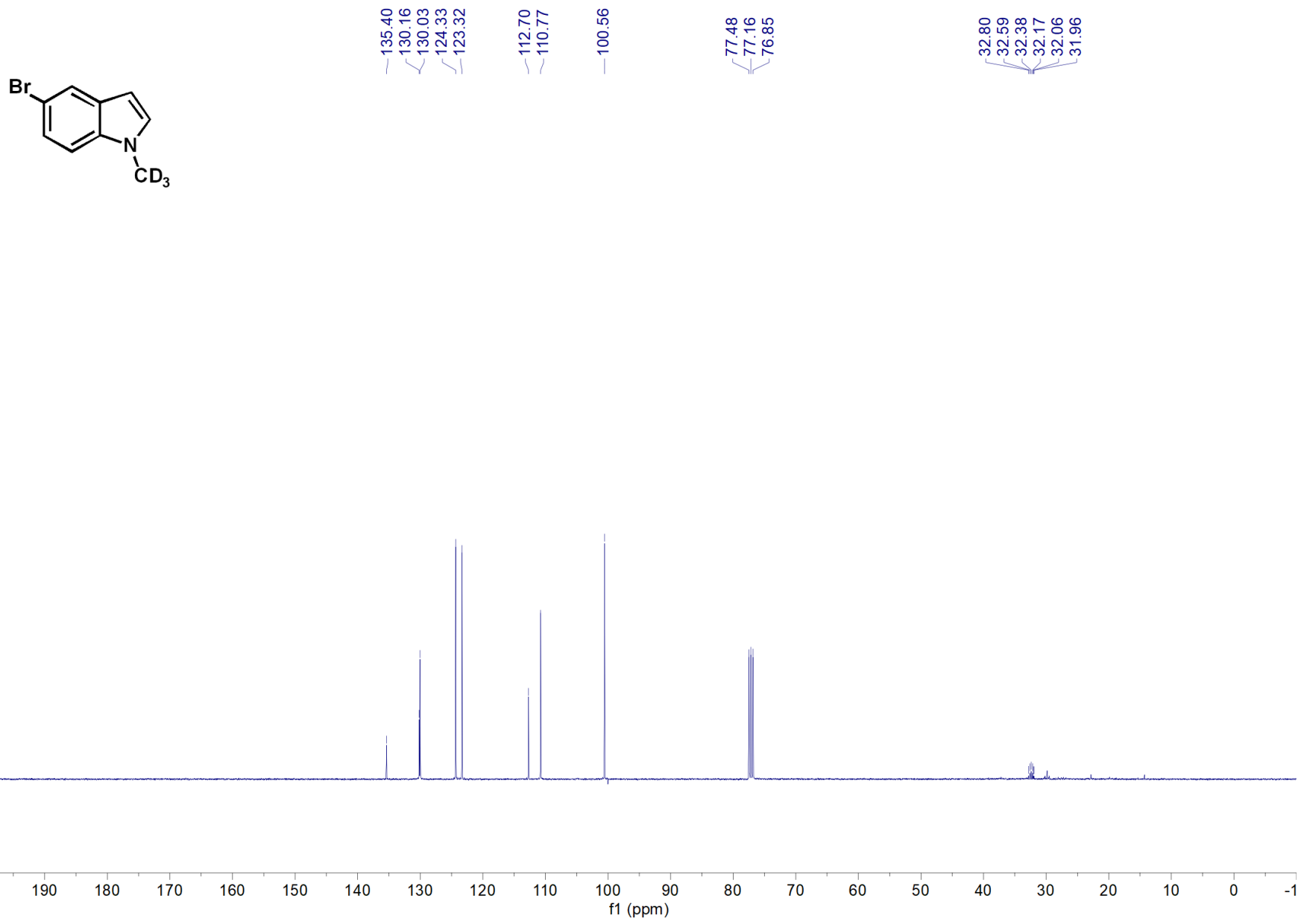


^{13}C NMR (100 MHz, $CDCl_3$) of **3c**



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



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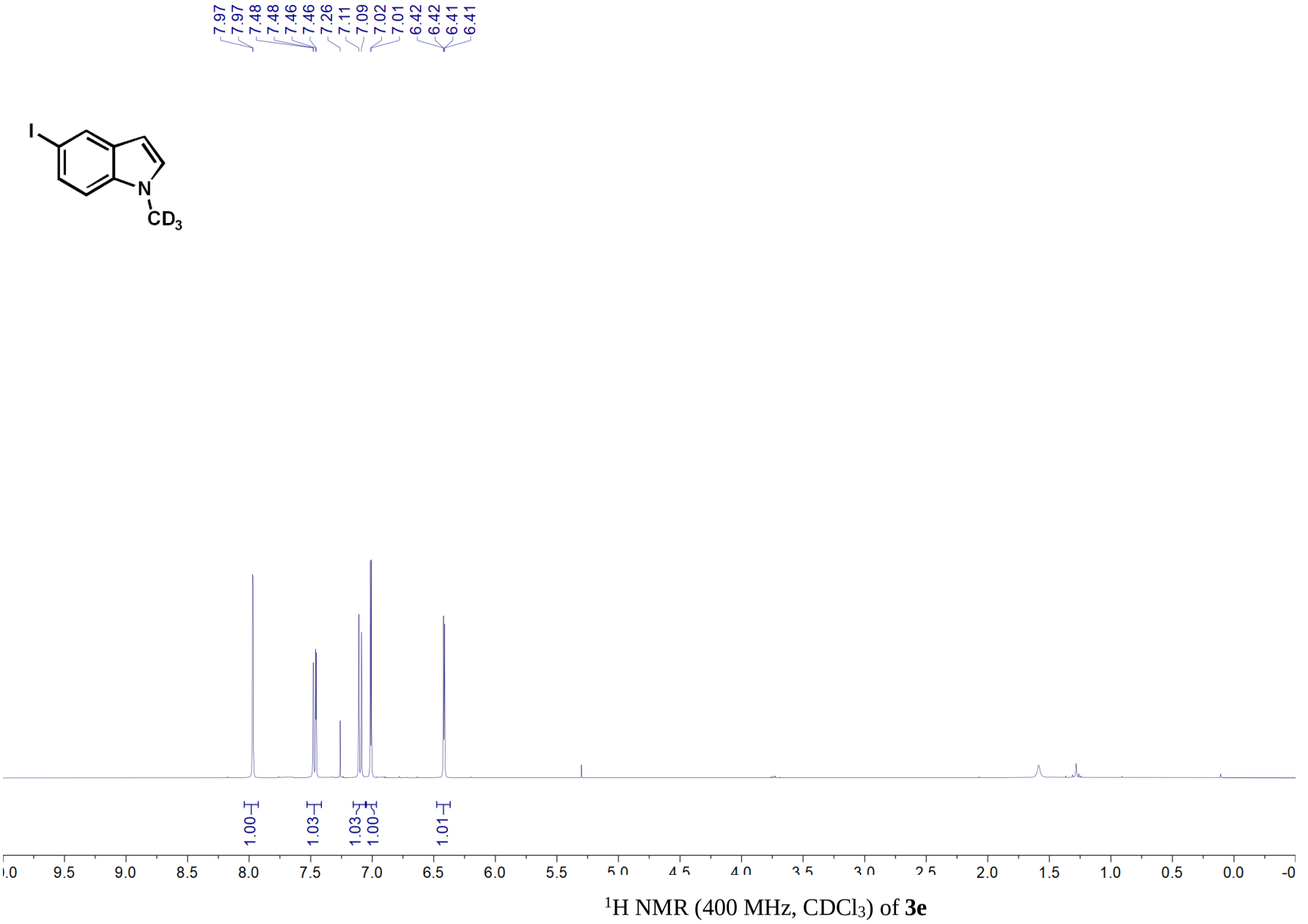
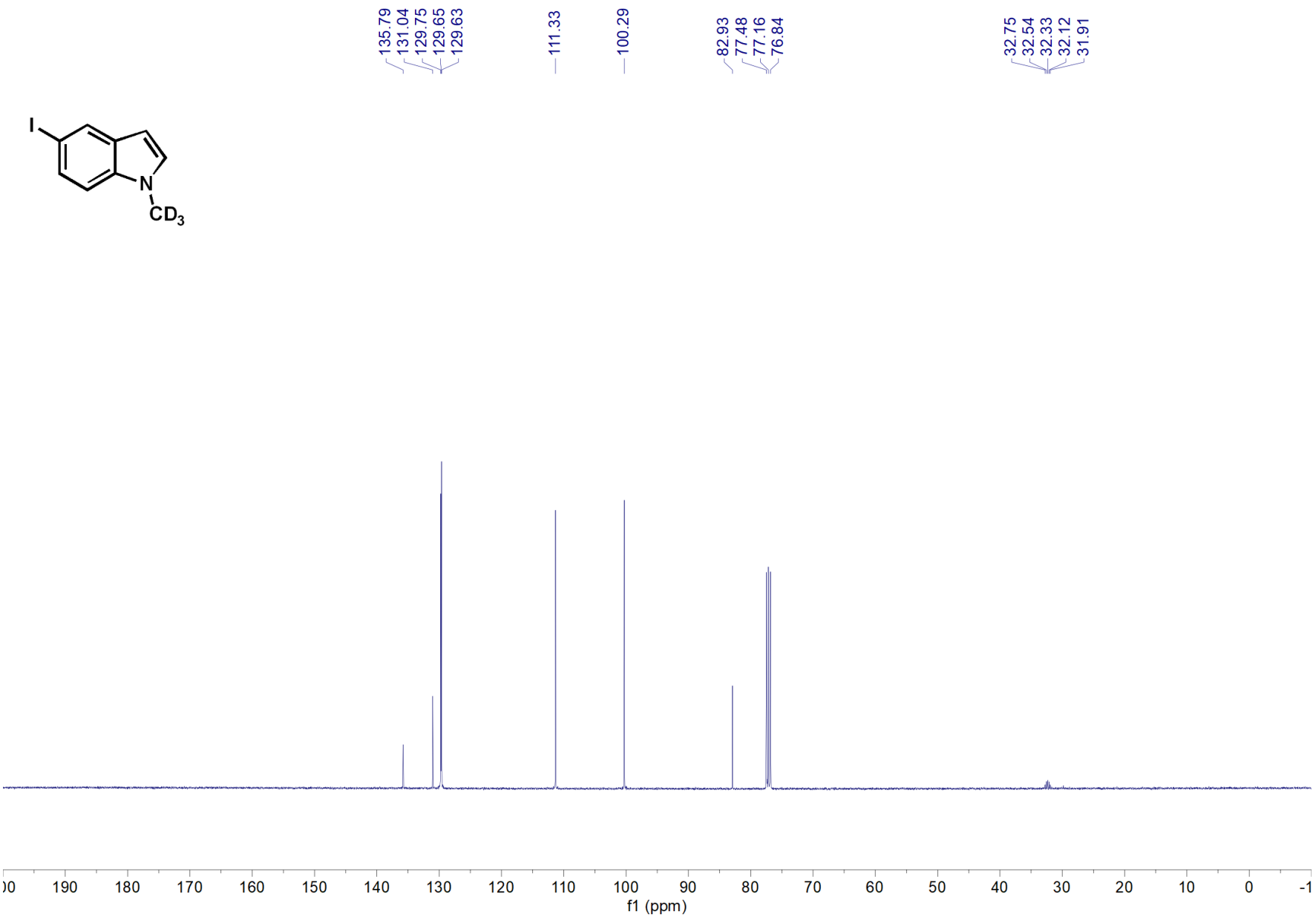
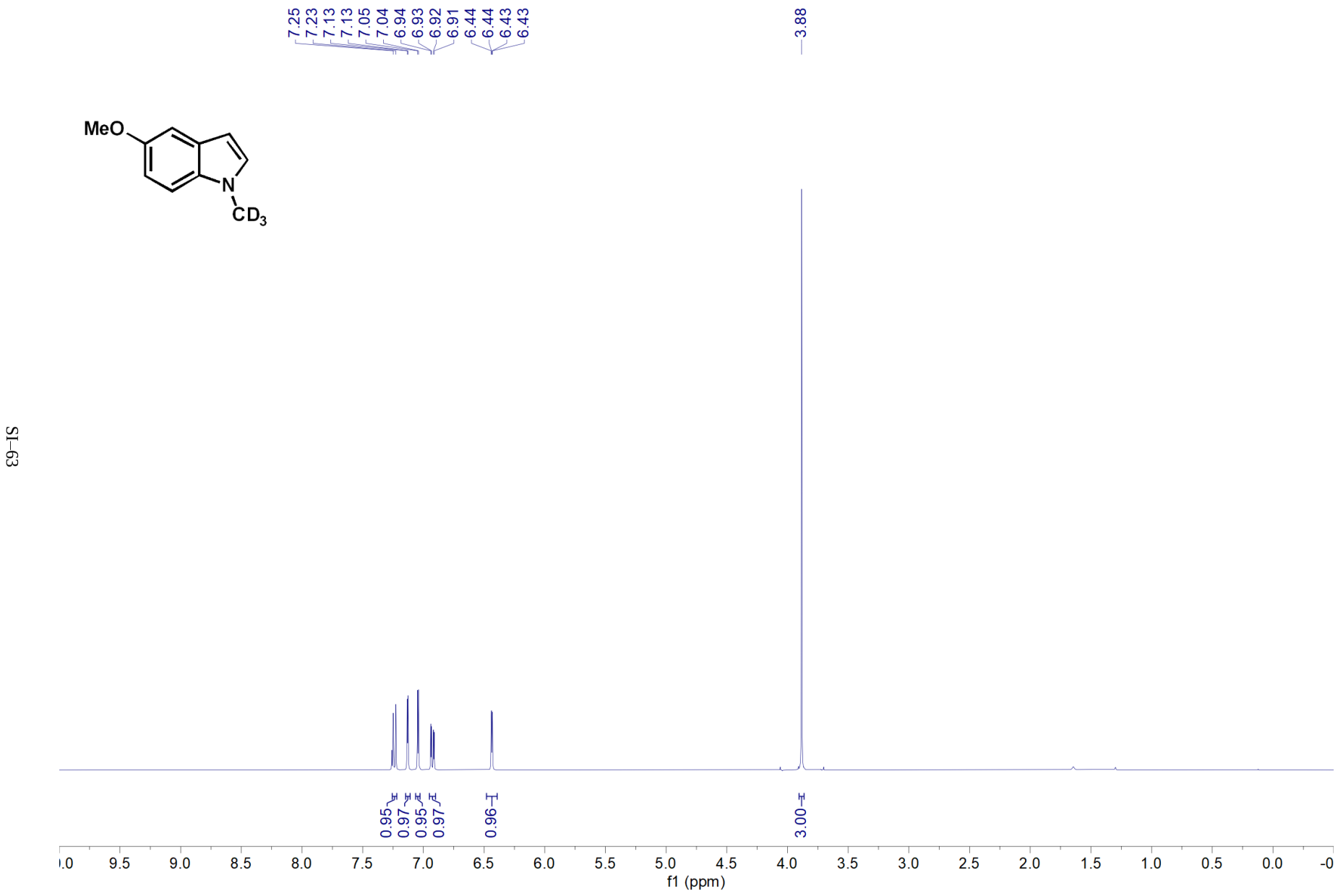


^{1}H NMR (400 MHz, $CDCl_3$) of **3e**



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



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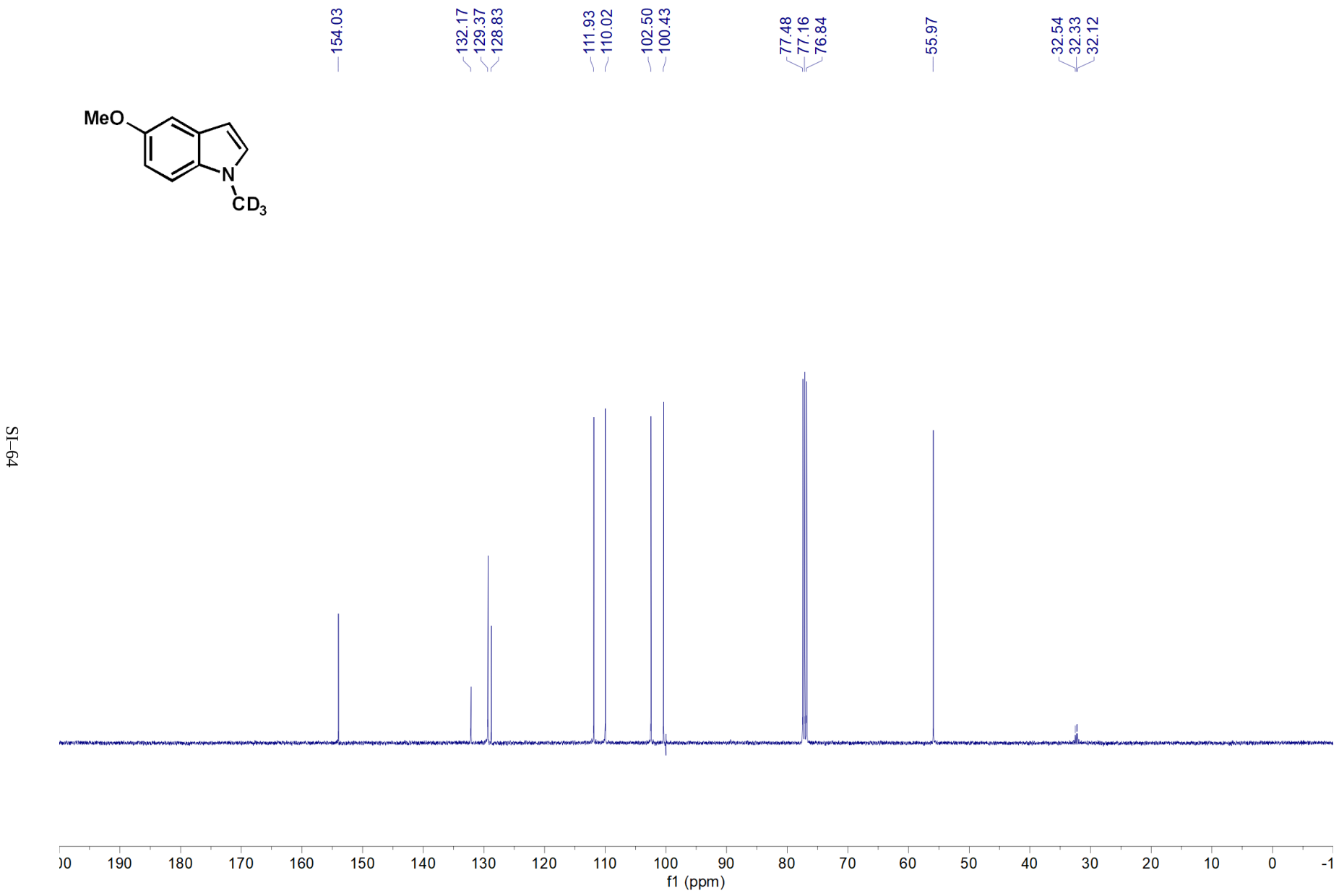

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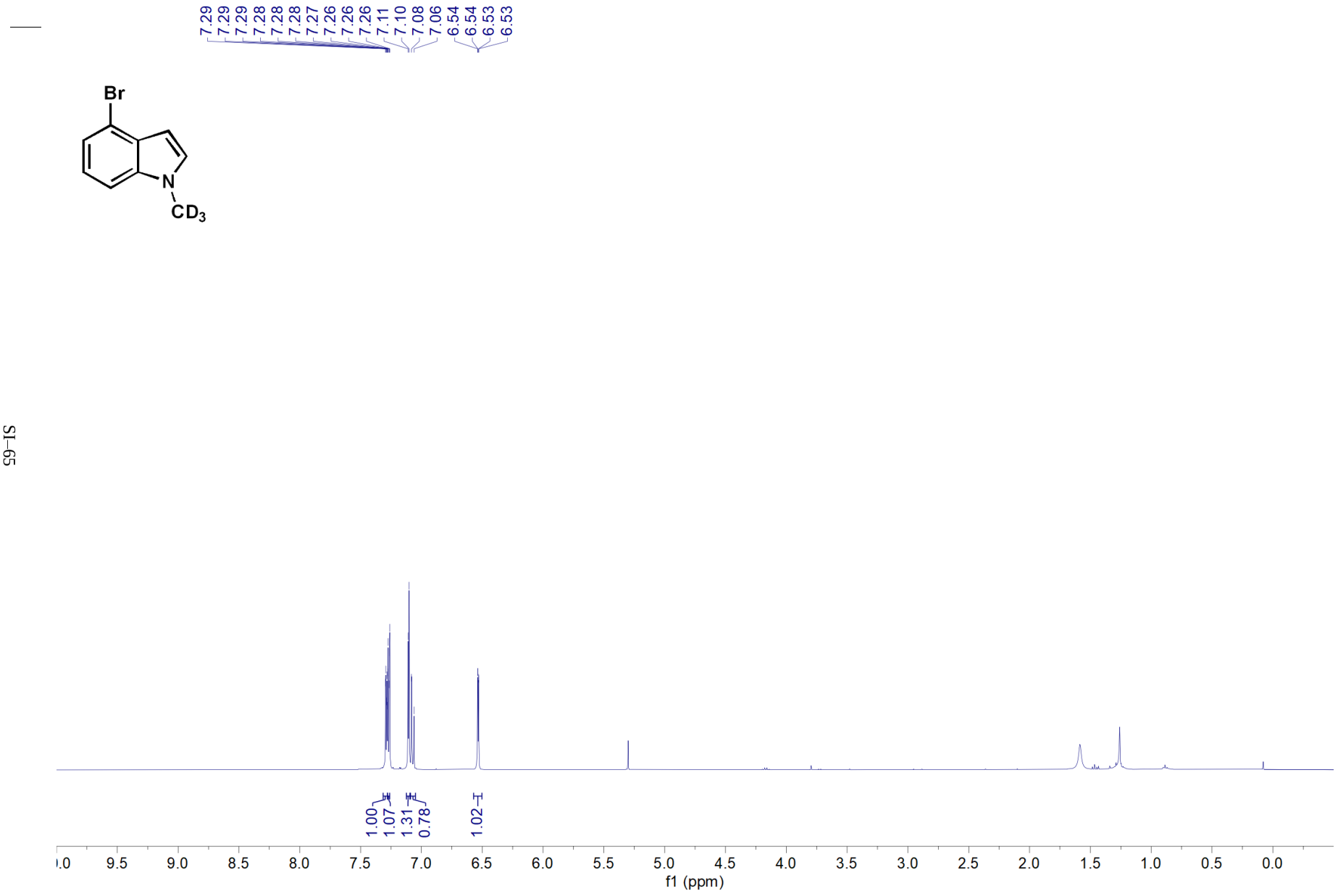
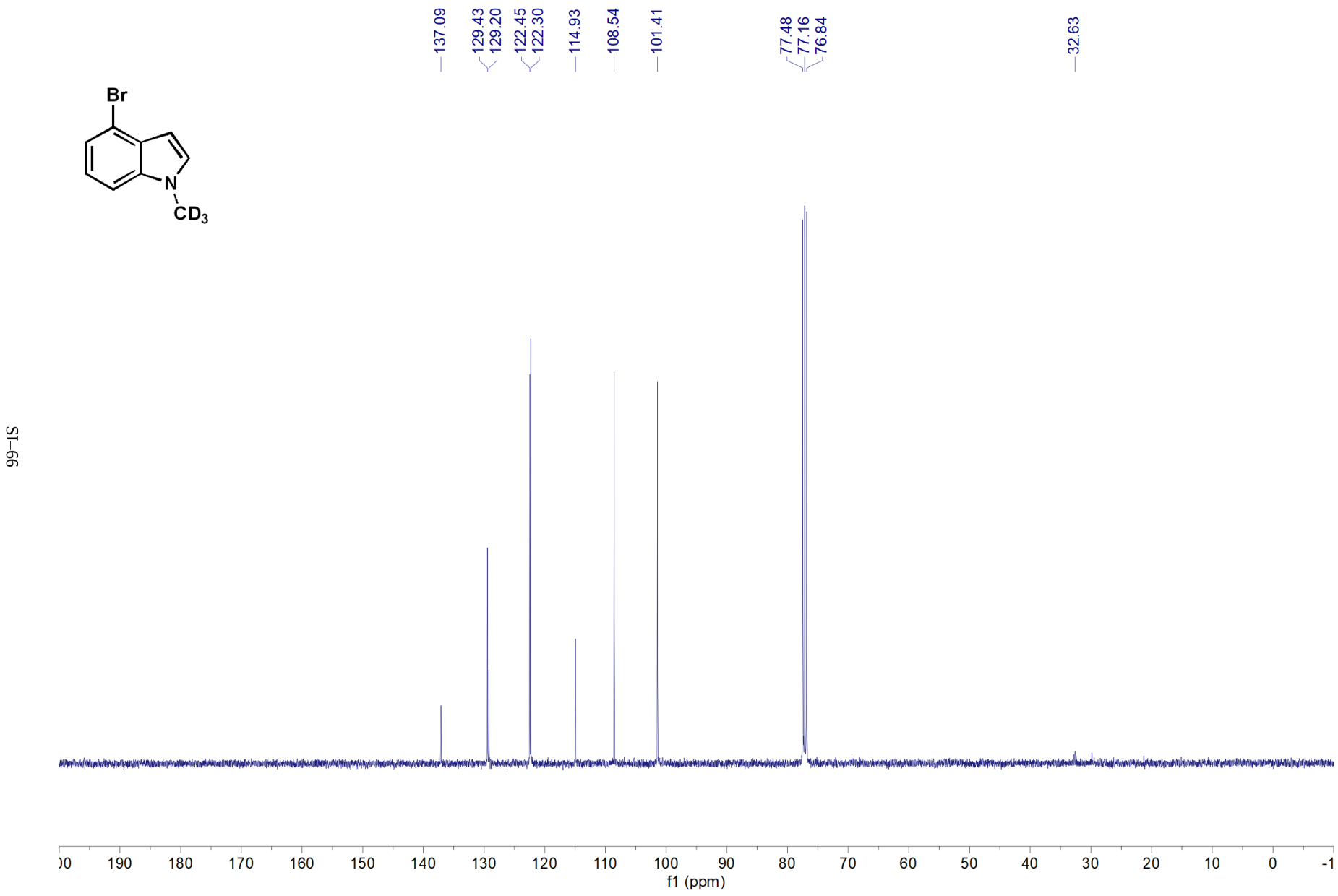
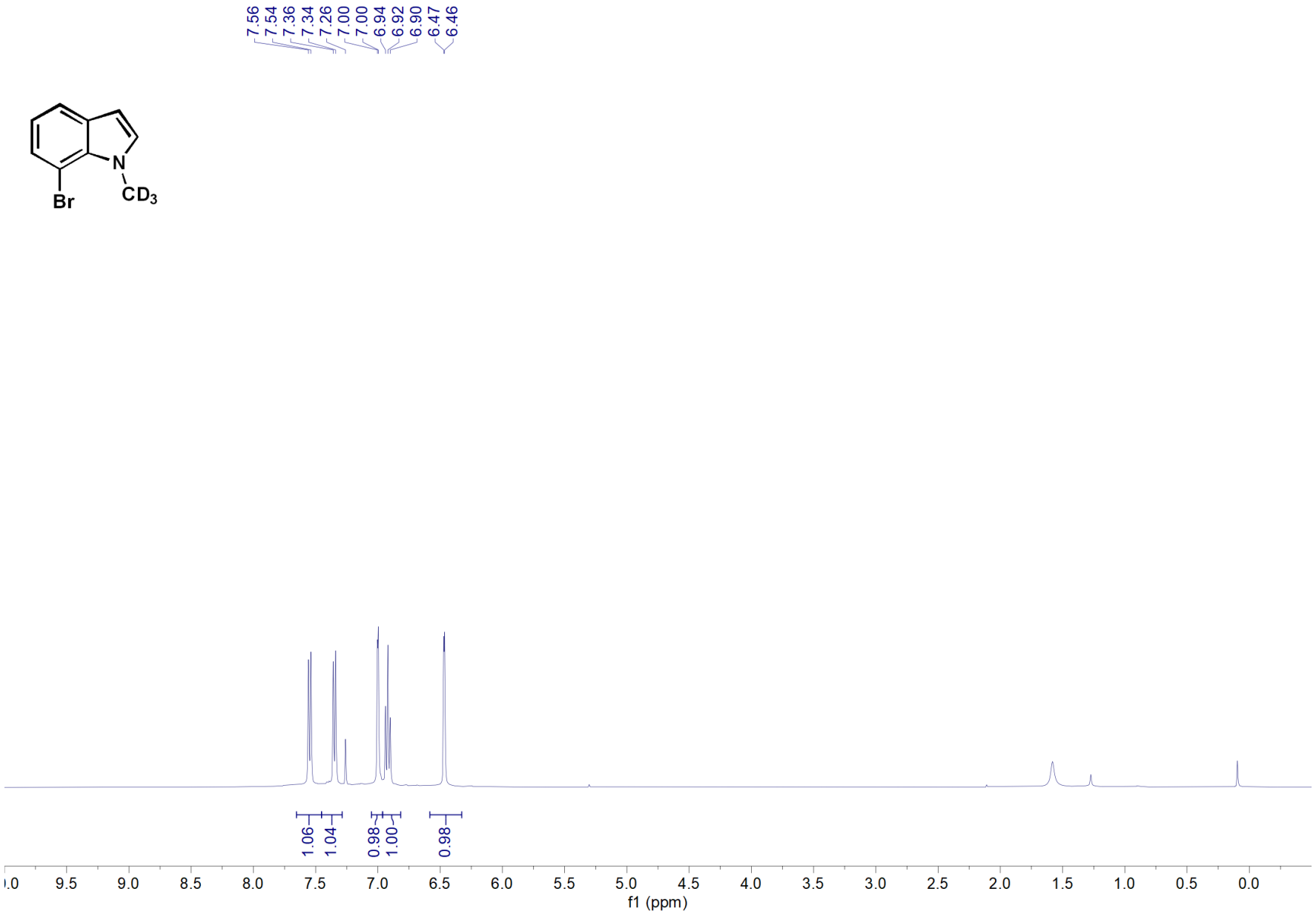


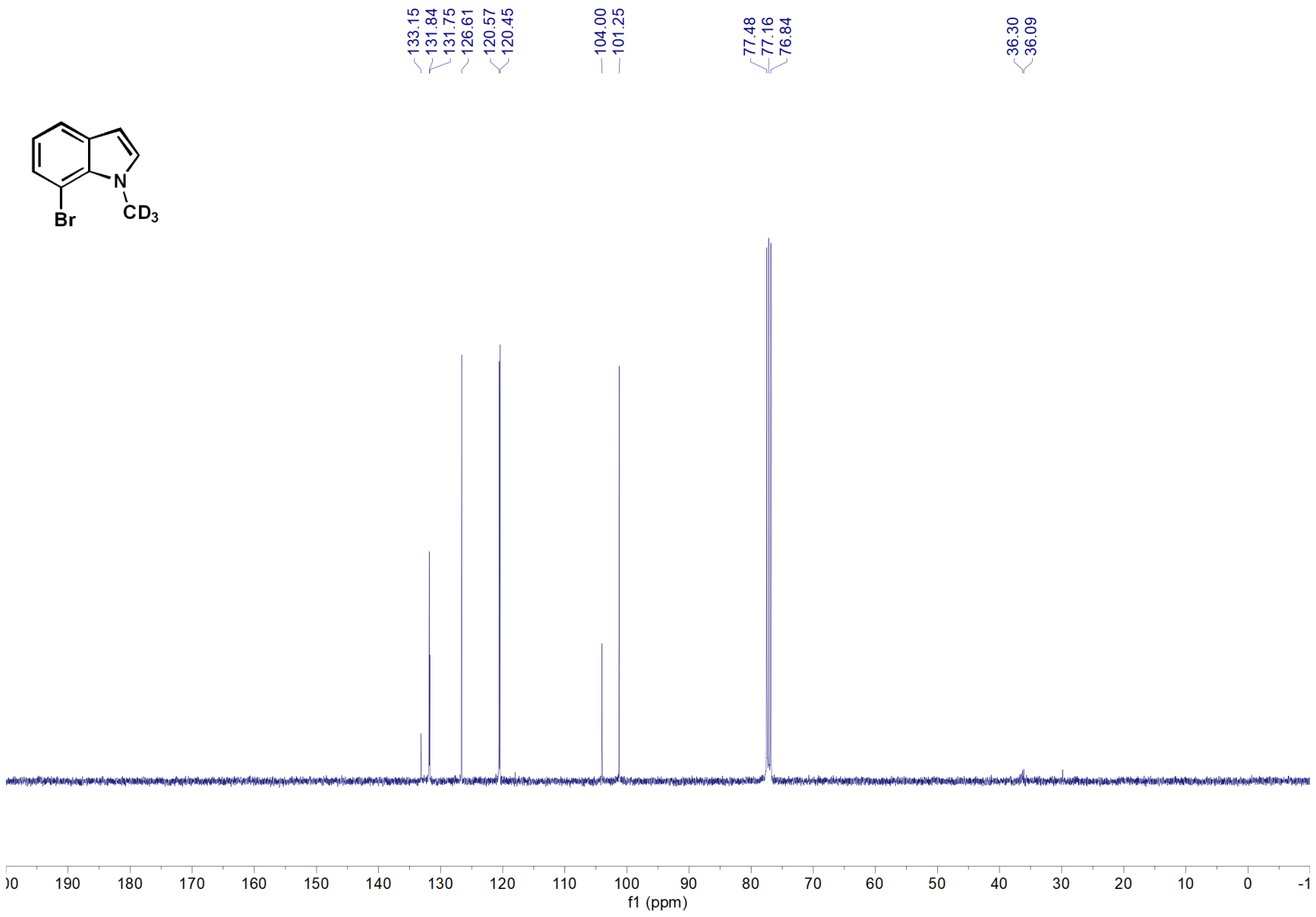
^{1}H NMR (400 MHz, $CDCl_3$) of **3g**



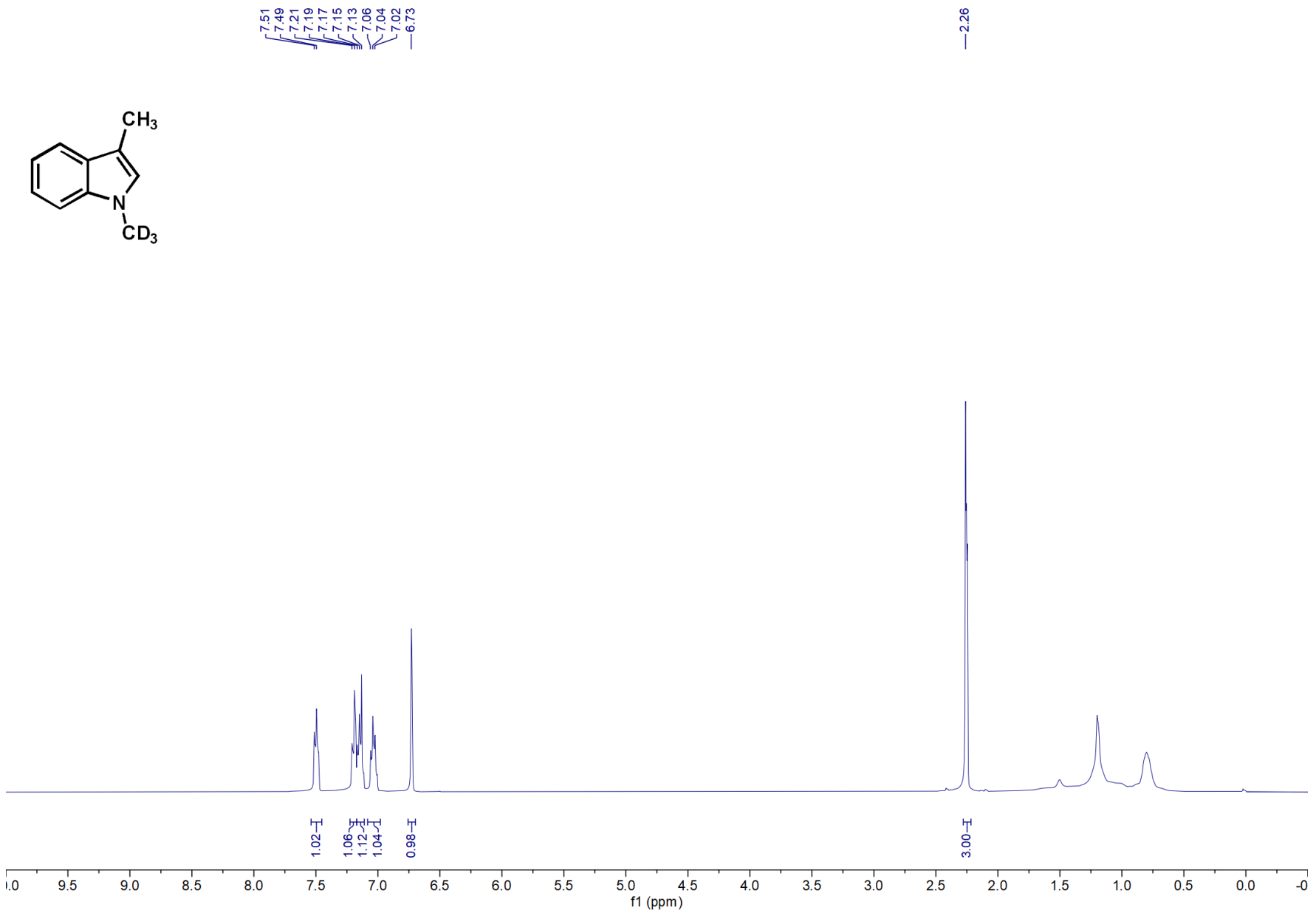
^{13}C NMR (100 MHz, $CDCl_3$) of **3g**



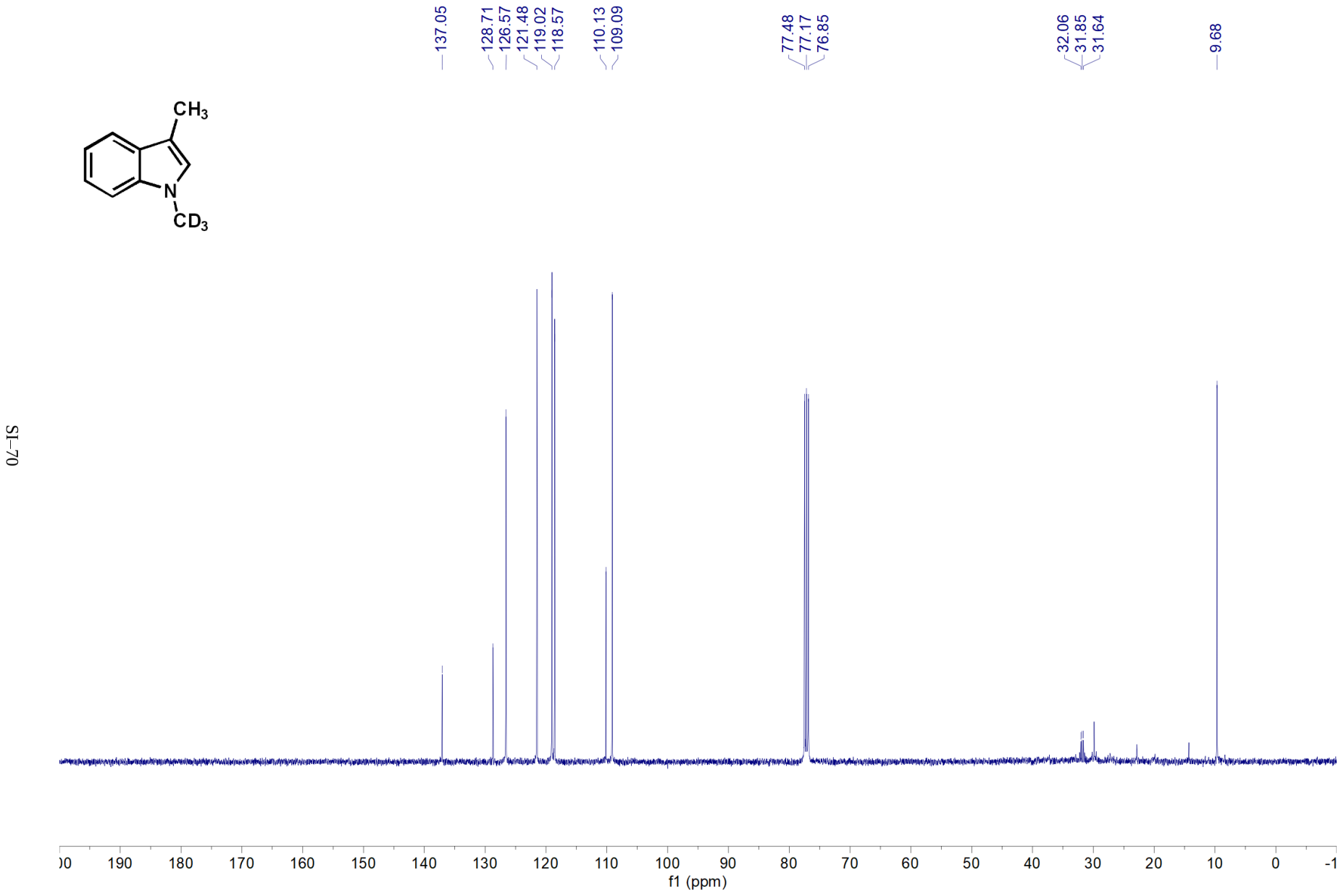
^{1}H NMR (400 MHz, $CDCl_3$) of **3h**



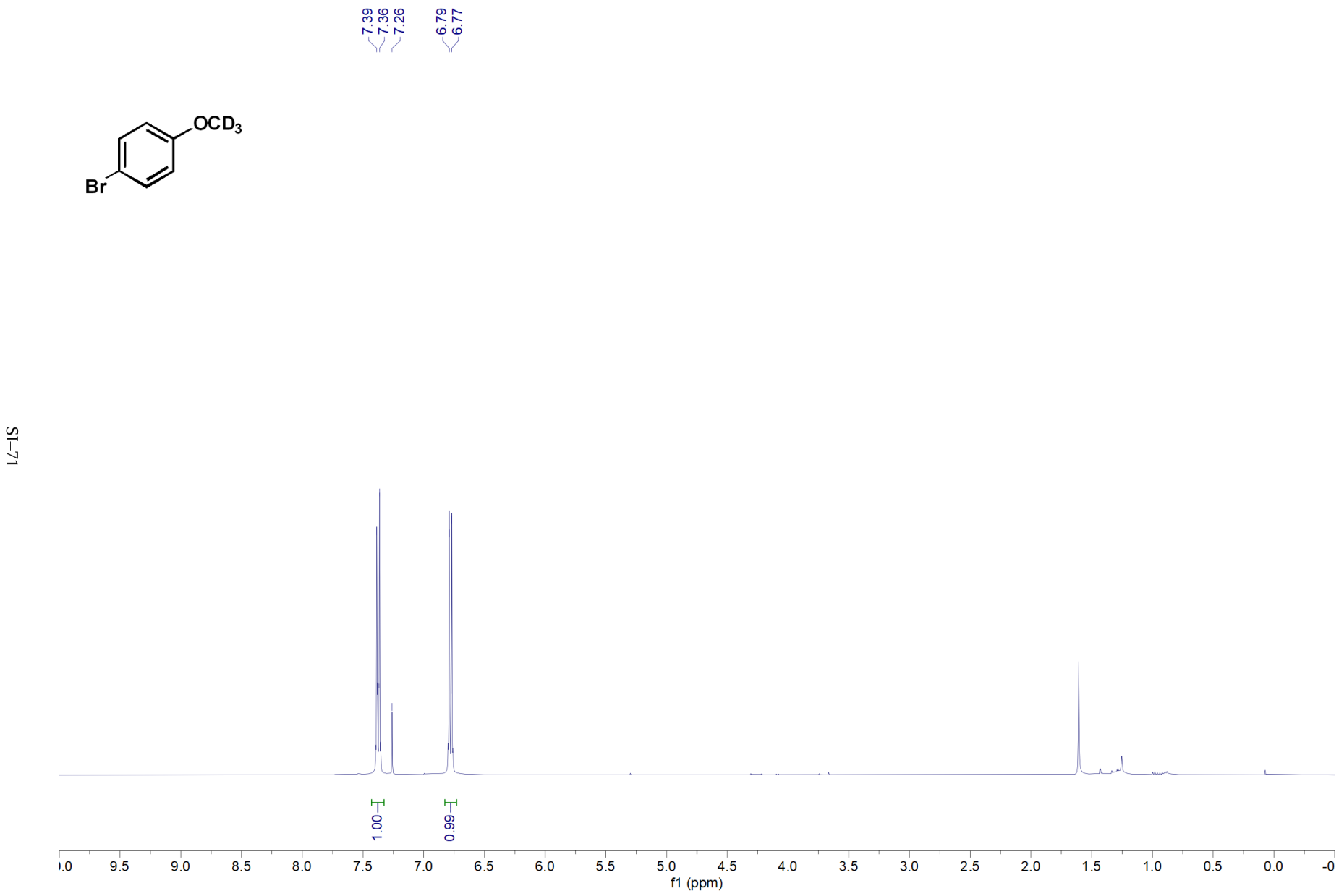
^{13}C NMR (100 MHz, $CDCl_3$) of **3h**



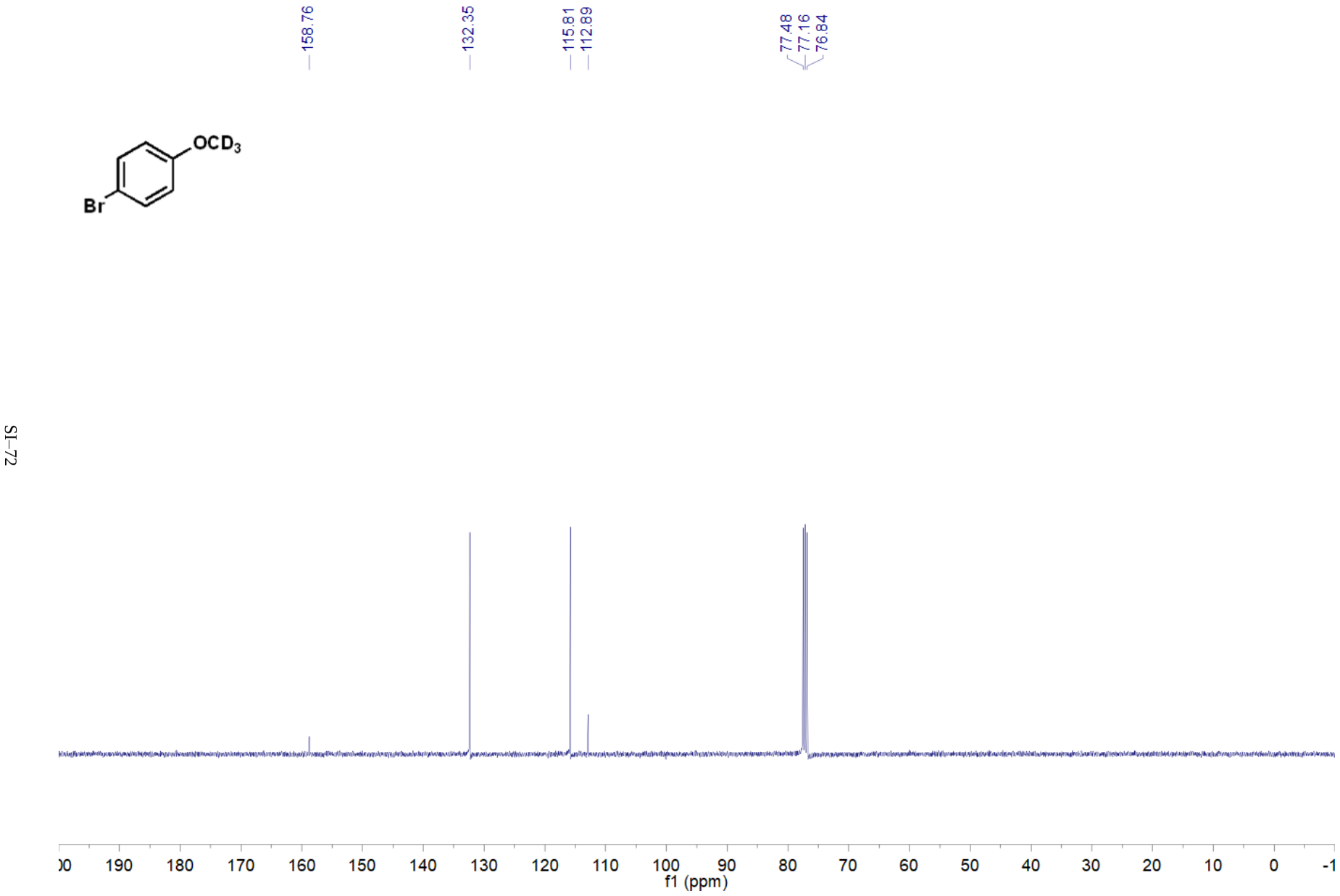
^{1}H NMR (400 MHz, $CDCl_3$) of **3i**



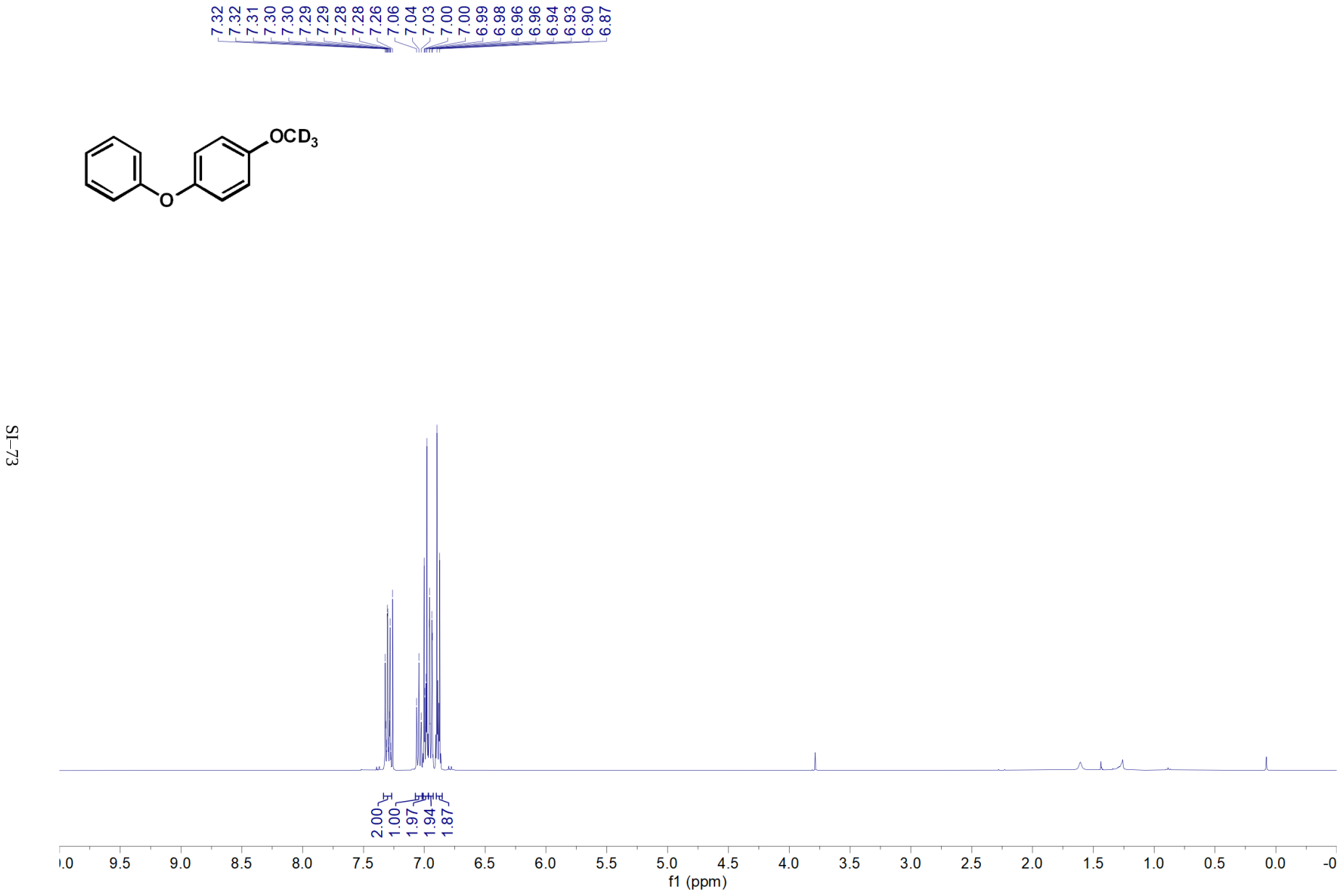
^{13}C NMR (100 MHz, $CDCl_3$) of **3i**



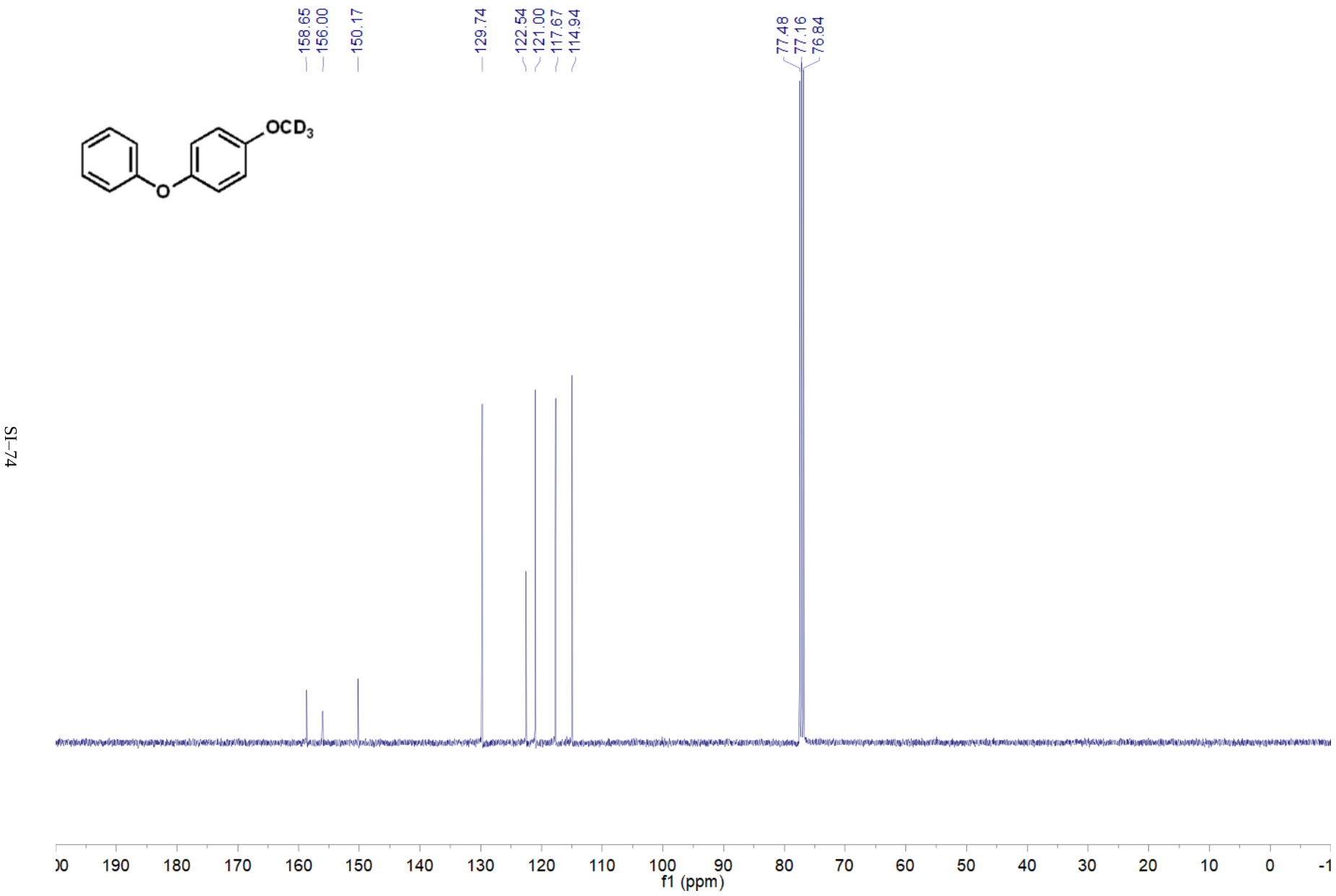
^{1}H NMR (400 MHz, $CDCl_3$) of **3j**



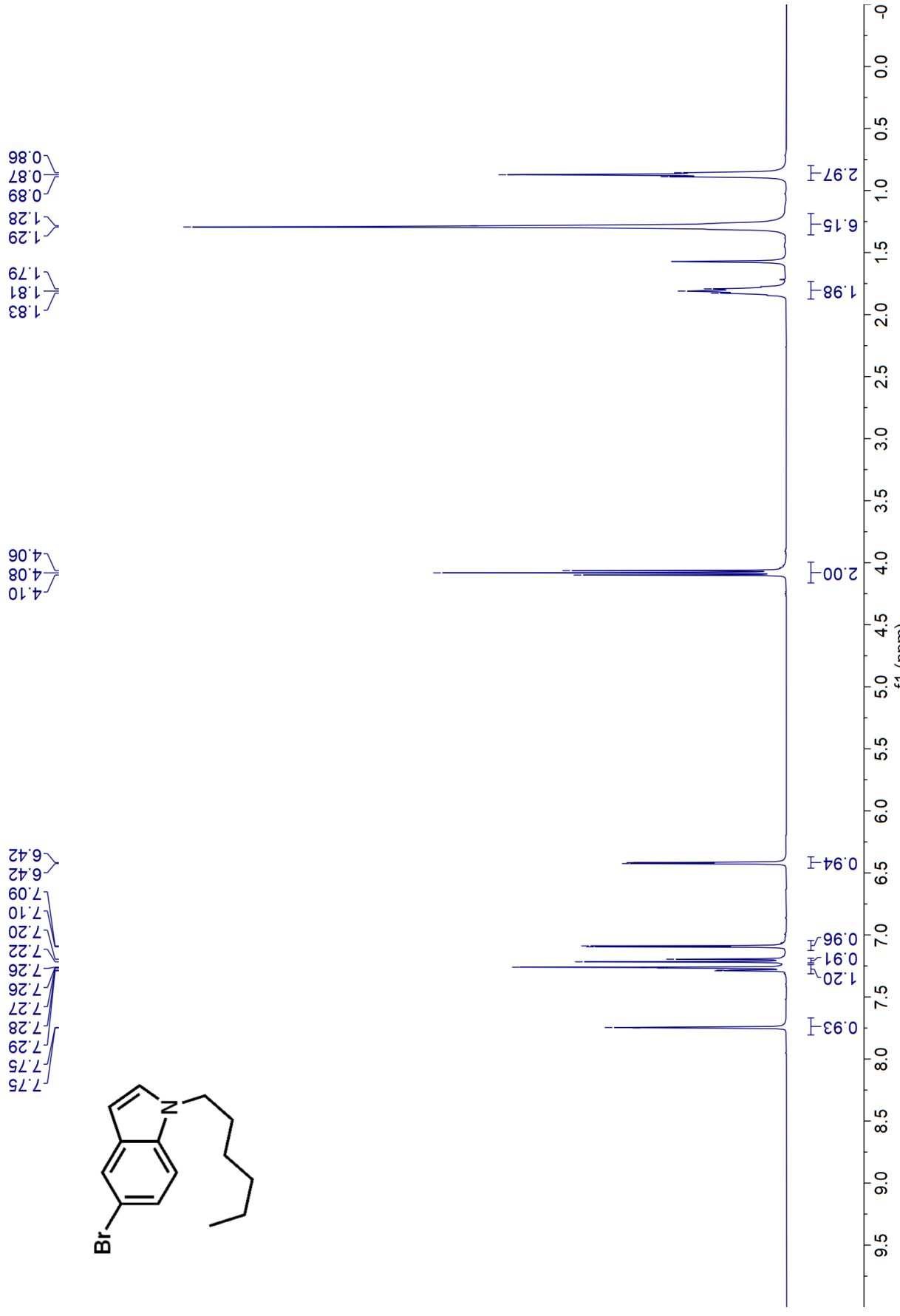
^{13}C NMR (100 MHz, $CDCl_3$) of **3j**



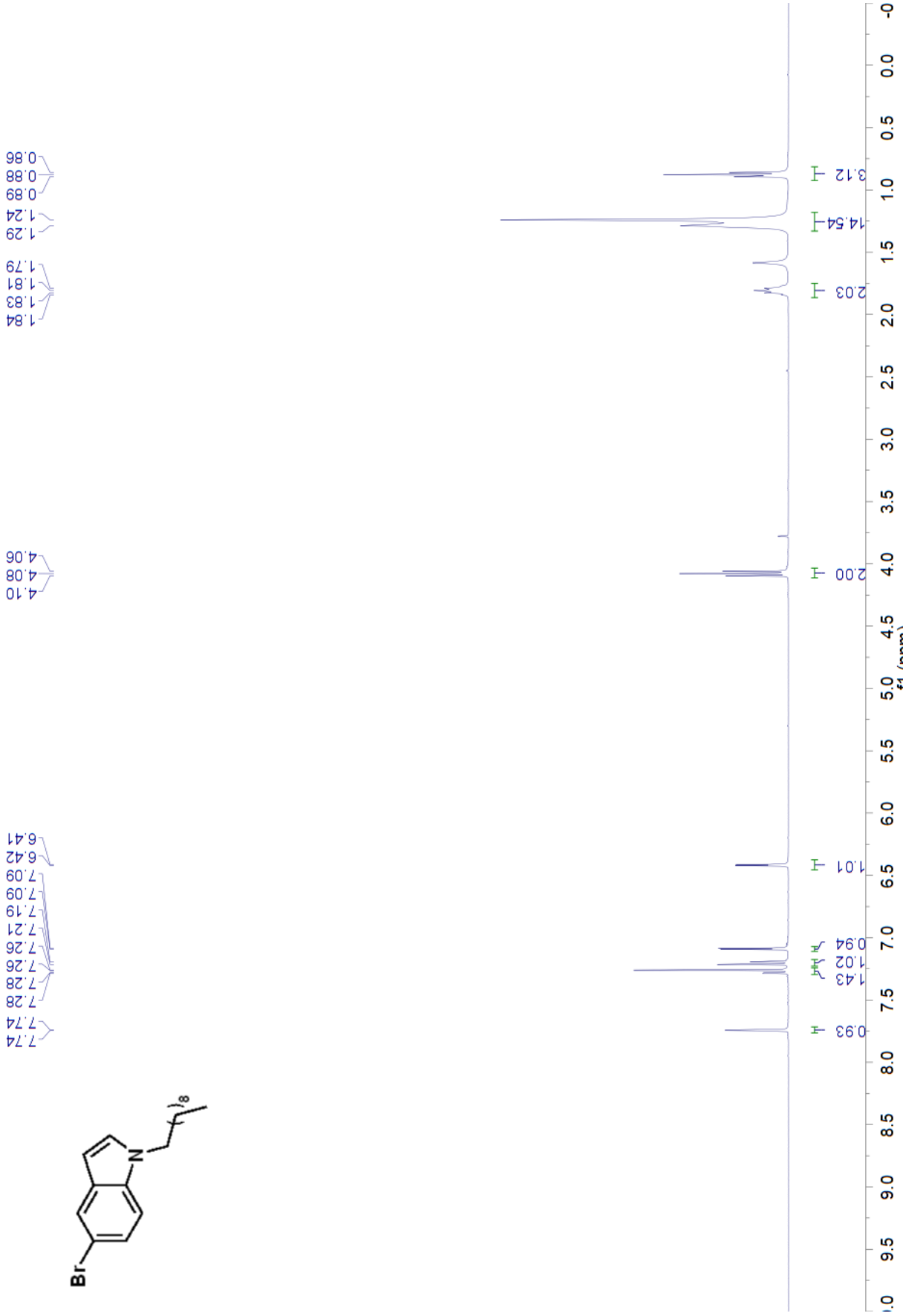
^{1}H NMR (400 MHz, $CDCl_3$) of **3k**



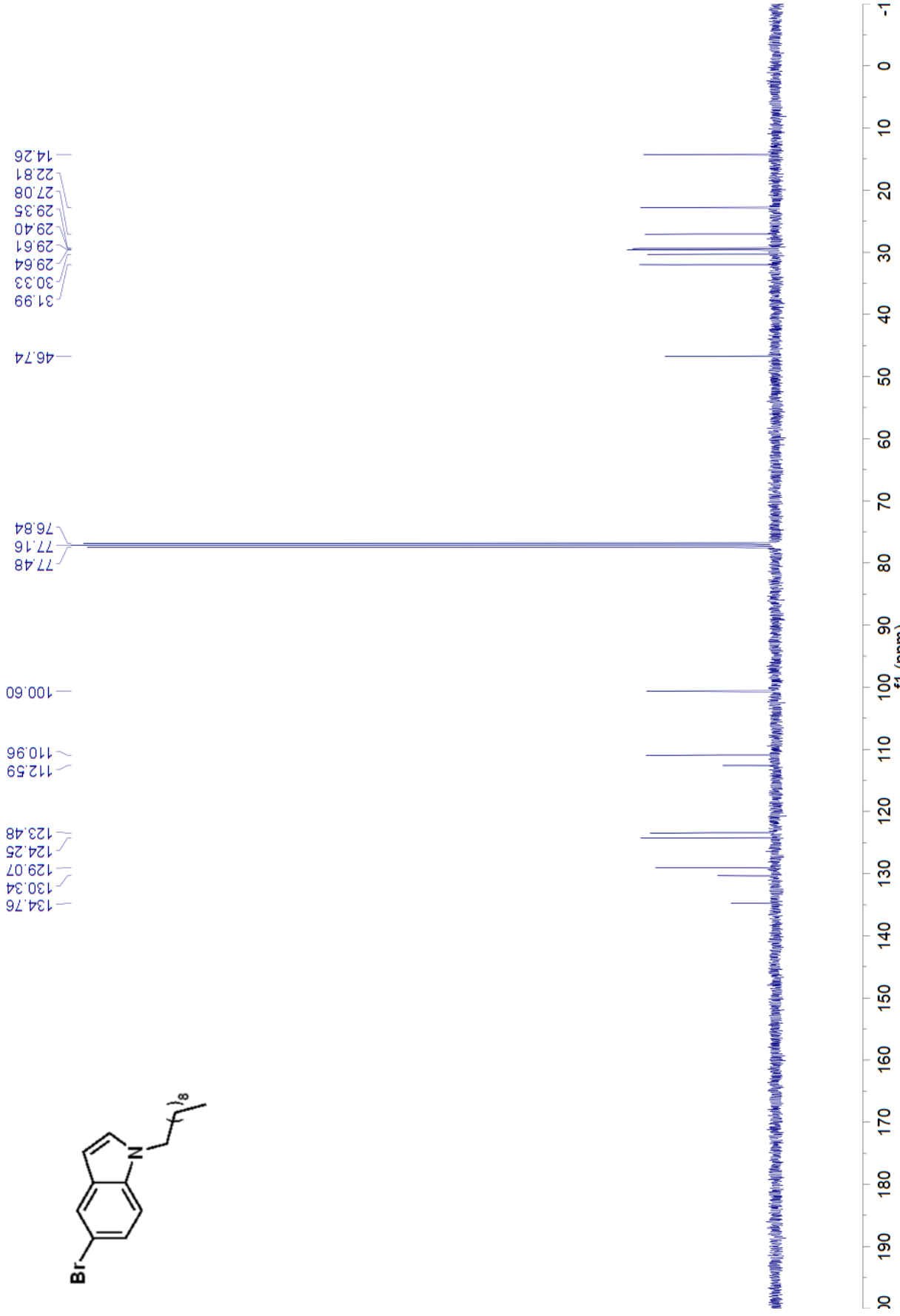
^{13}C NMR (100 MHz, $CDCl_3$) of **3k**



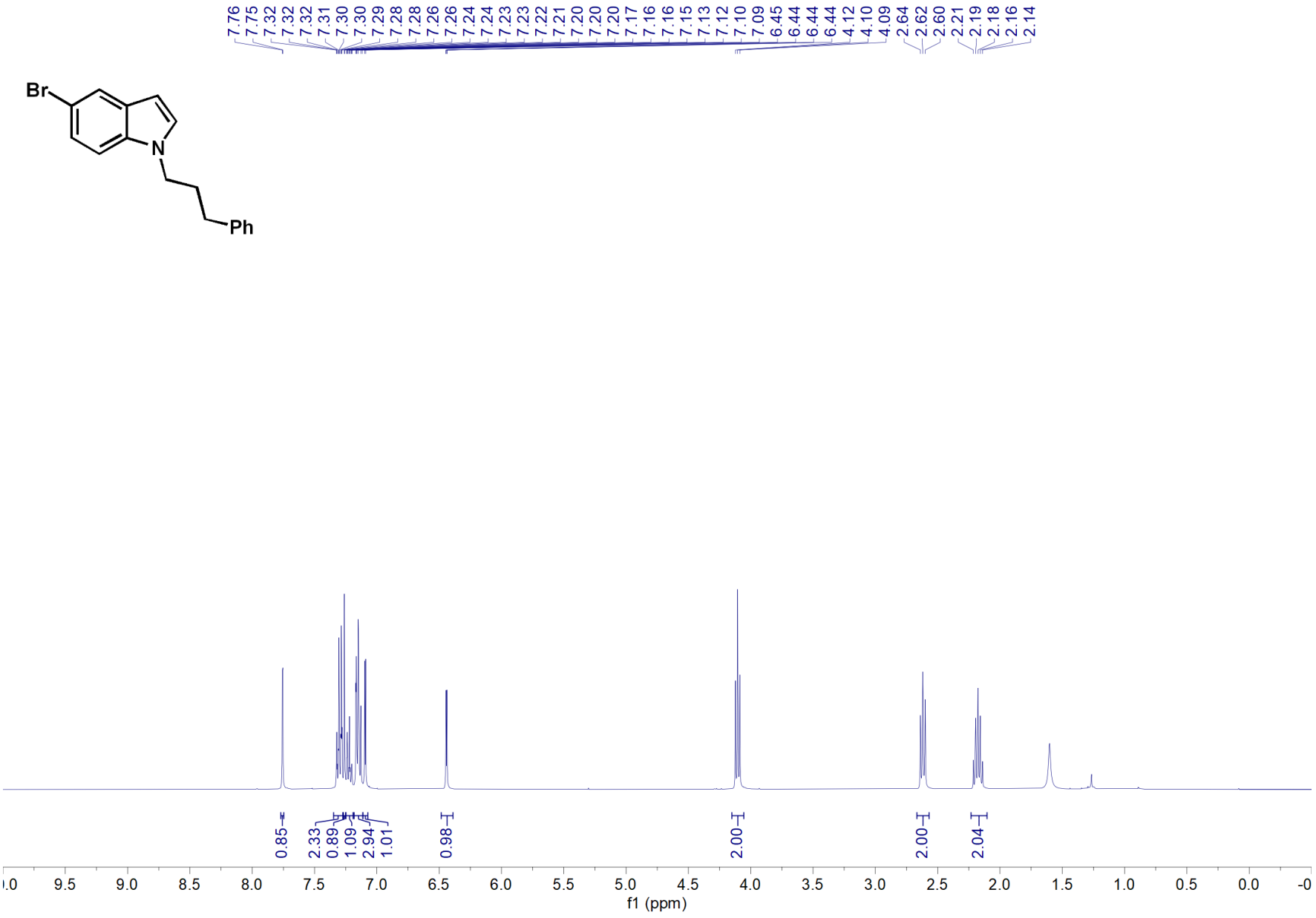
^{1}HNMR (400 MHz, $CDCl_3$) of **4a**



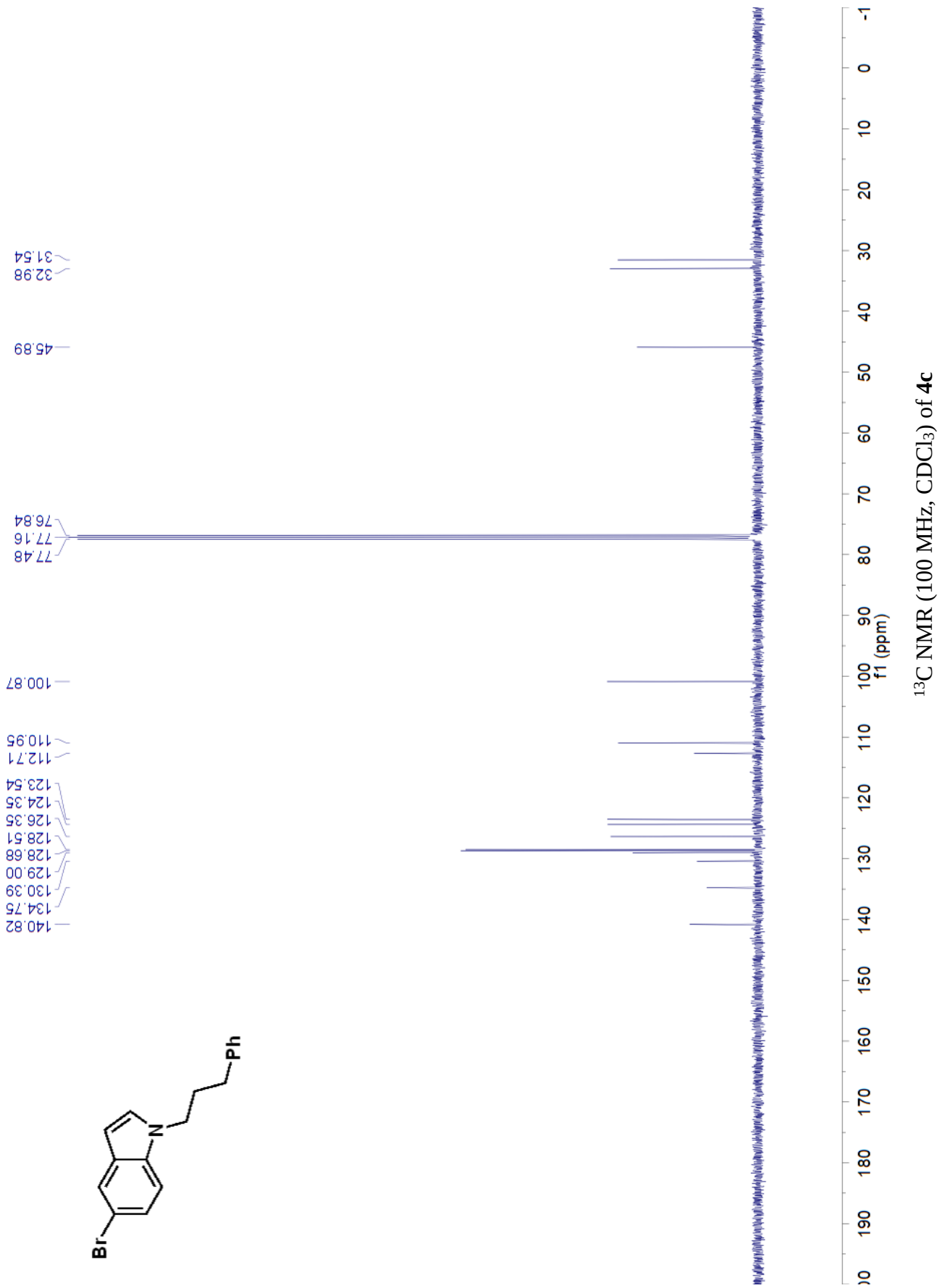
^{1}H NMR (400 MHz, $CDCl_3$) of **4b**



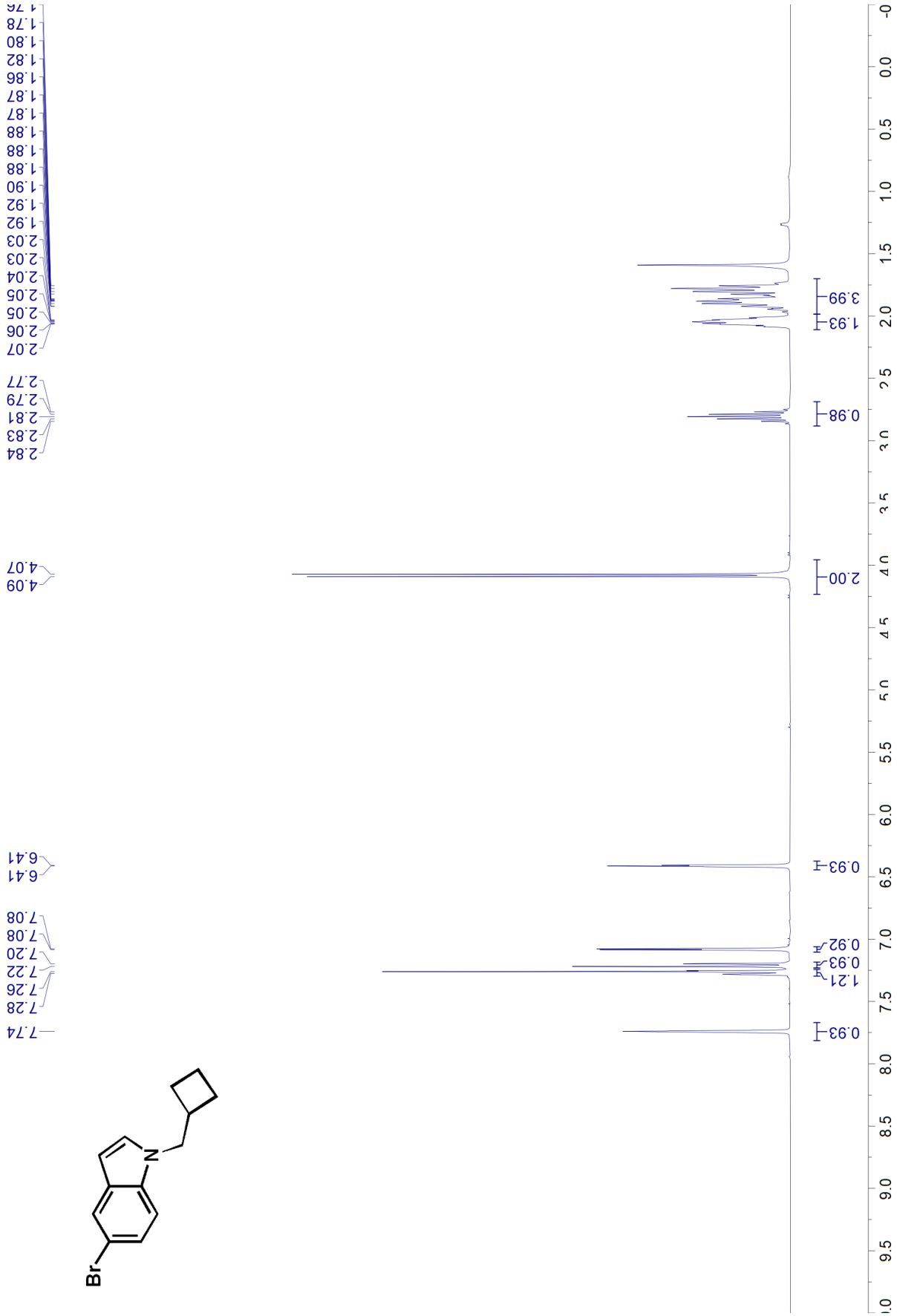
^{13}C NMR (100 MHz, $CDCl_3$) of **4b**



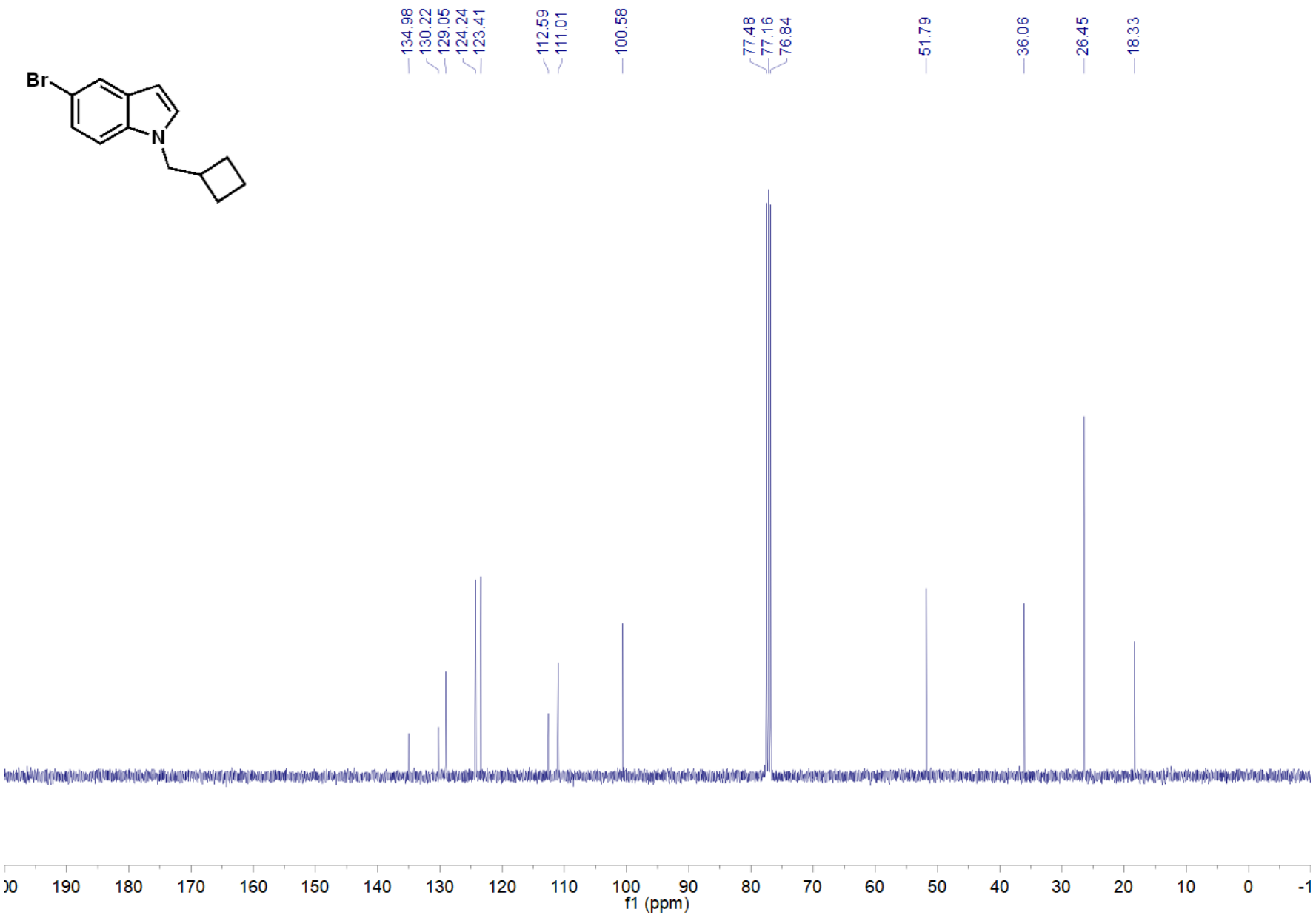
^{1}H NMR (400 MHz, $CDCl_3$) of **4c**



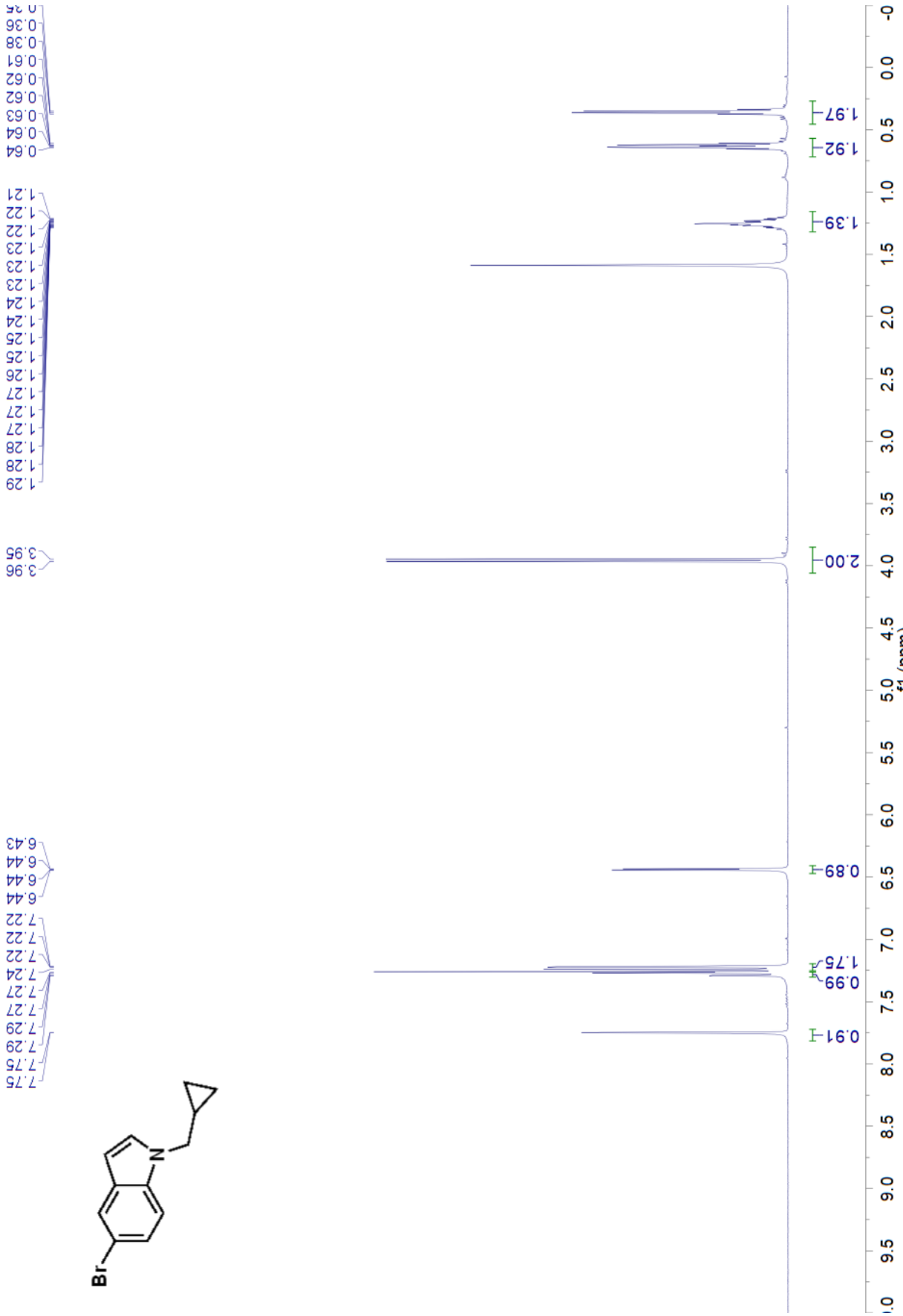
^{13}C NMR (100 MHz, $CDCl_3$) of **4c**



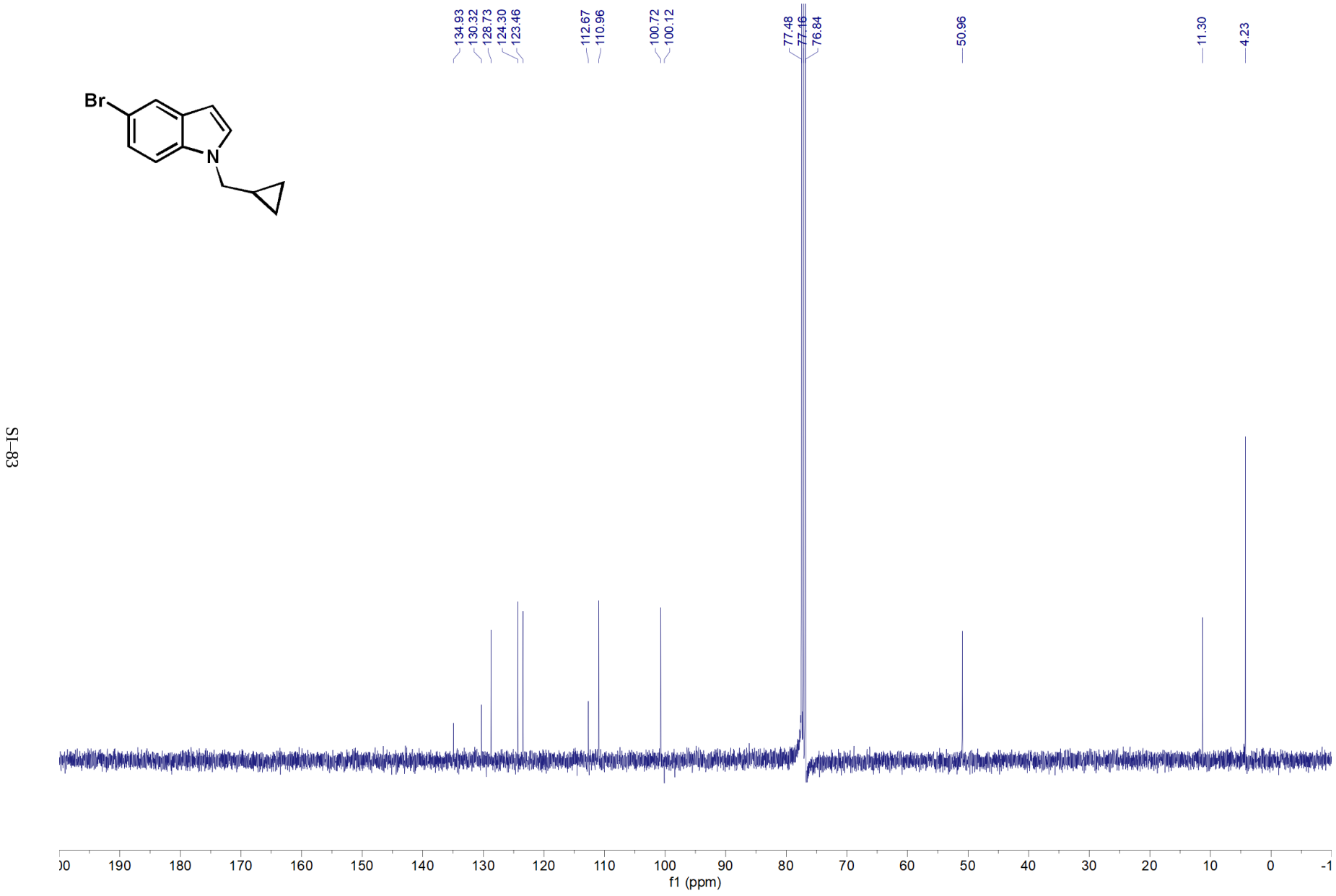
^{1}H NMR (400 MHz, $CDCl_3$) of **4d**



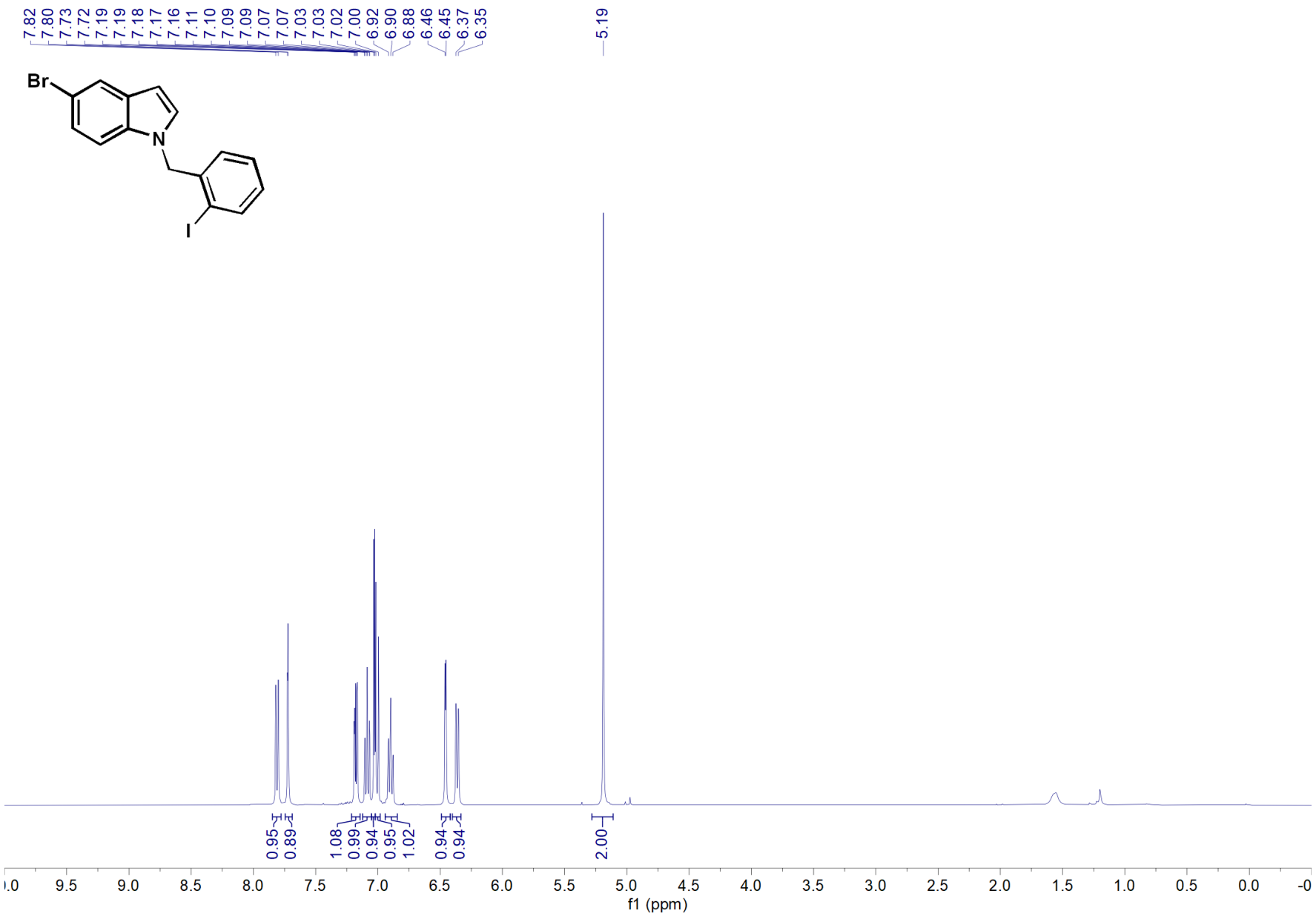
^{13}C NMR (100 MHz, $CDCl_3$) of **4d**



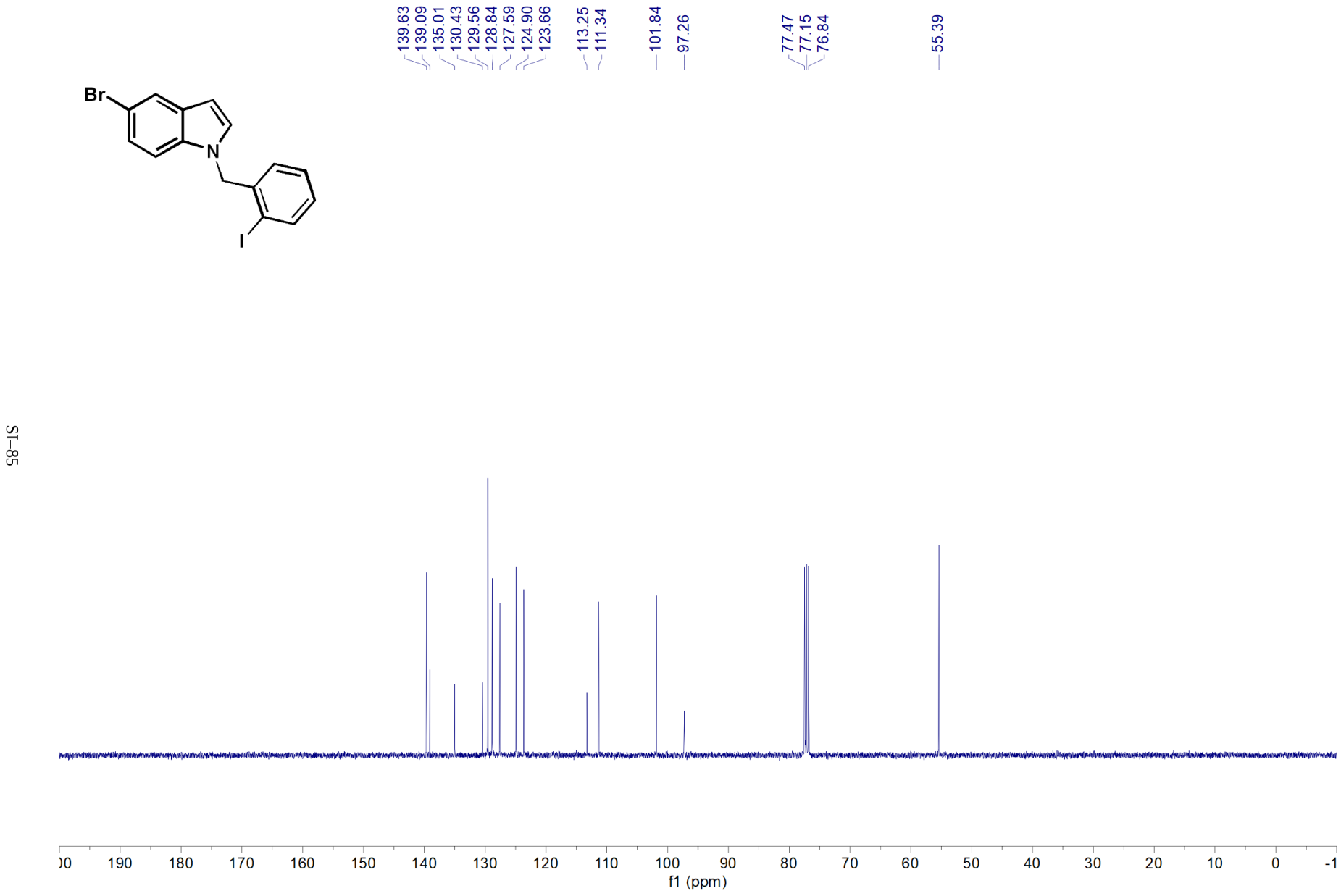
^{1}HNMR (400 MHz, $CDCl_3$) of **4e**



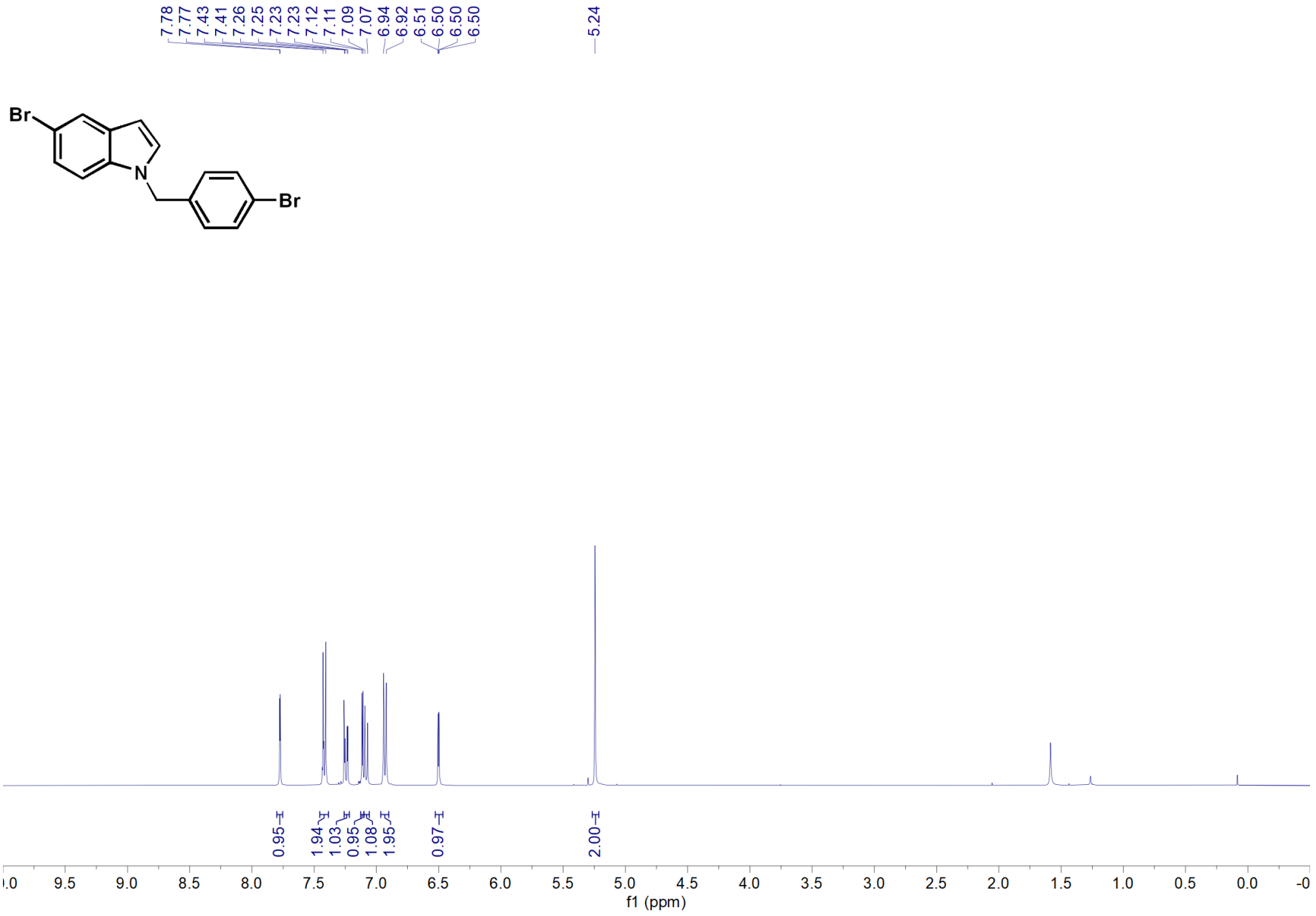
^{13}C NMR (100 MHz, $CDCl_3$) of **4e**



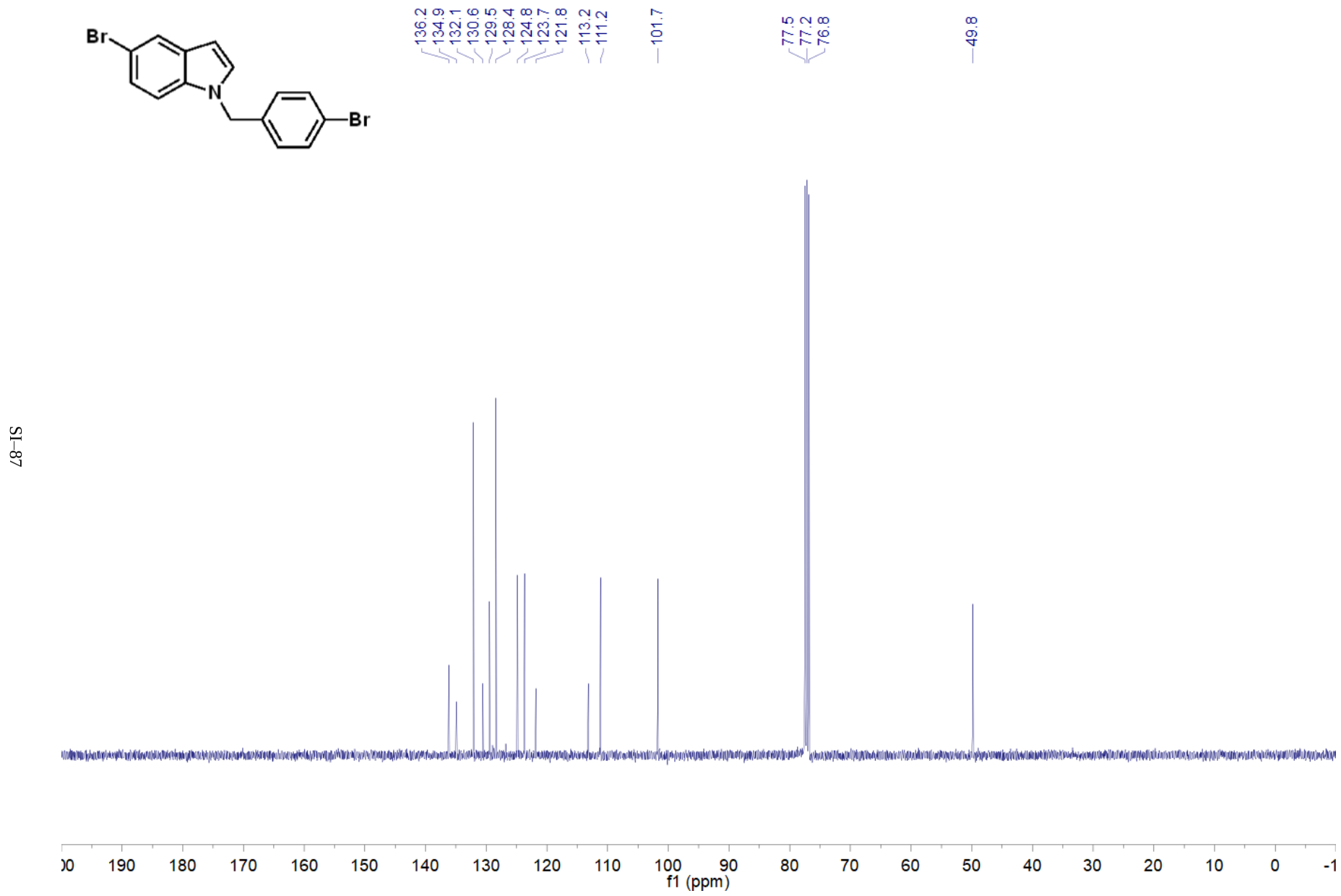
^{1}HNMR (400 MHz, $CDCl_3$) of **4f**



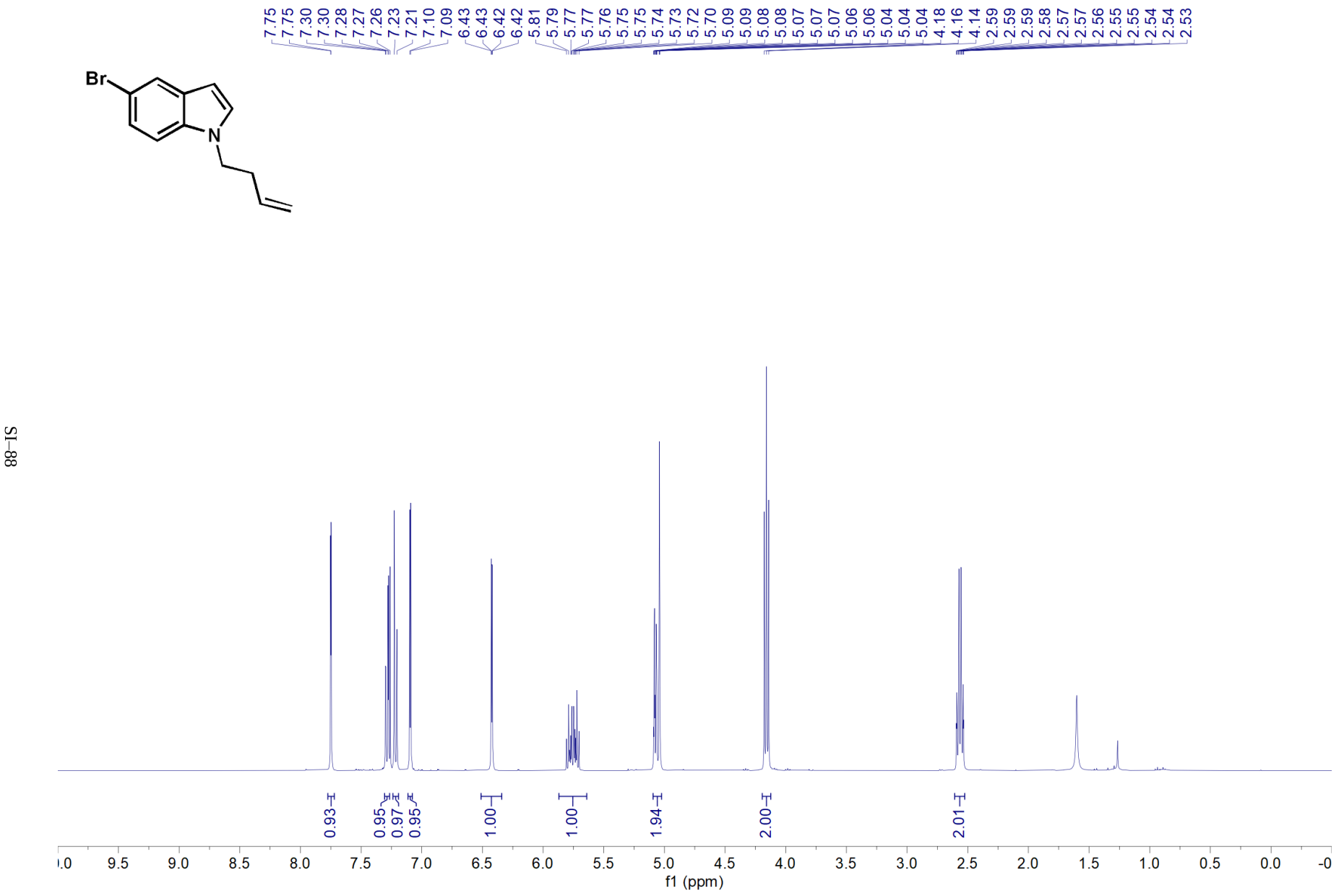
^{13}C NMR (100 MHz, $CDCl_3$) of **4f**



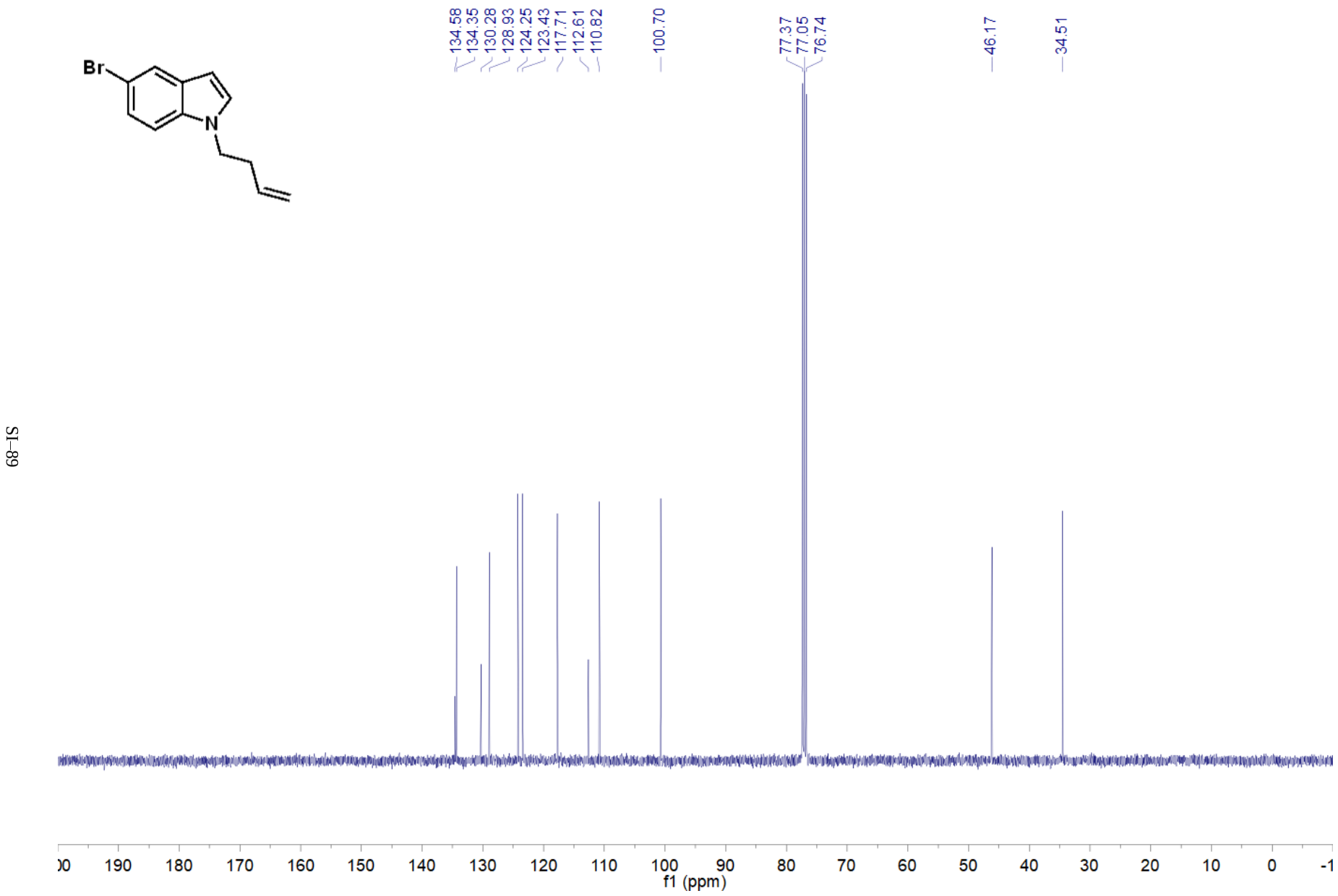
^{1}HNMR (400 MHz, $CDCl_3$) of **4g**



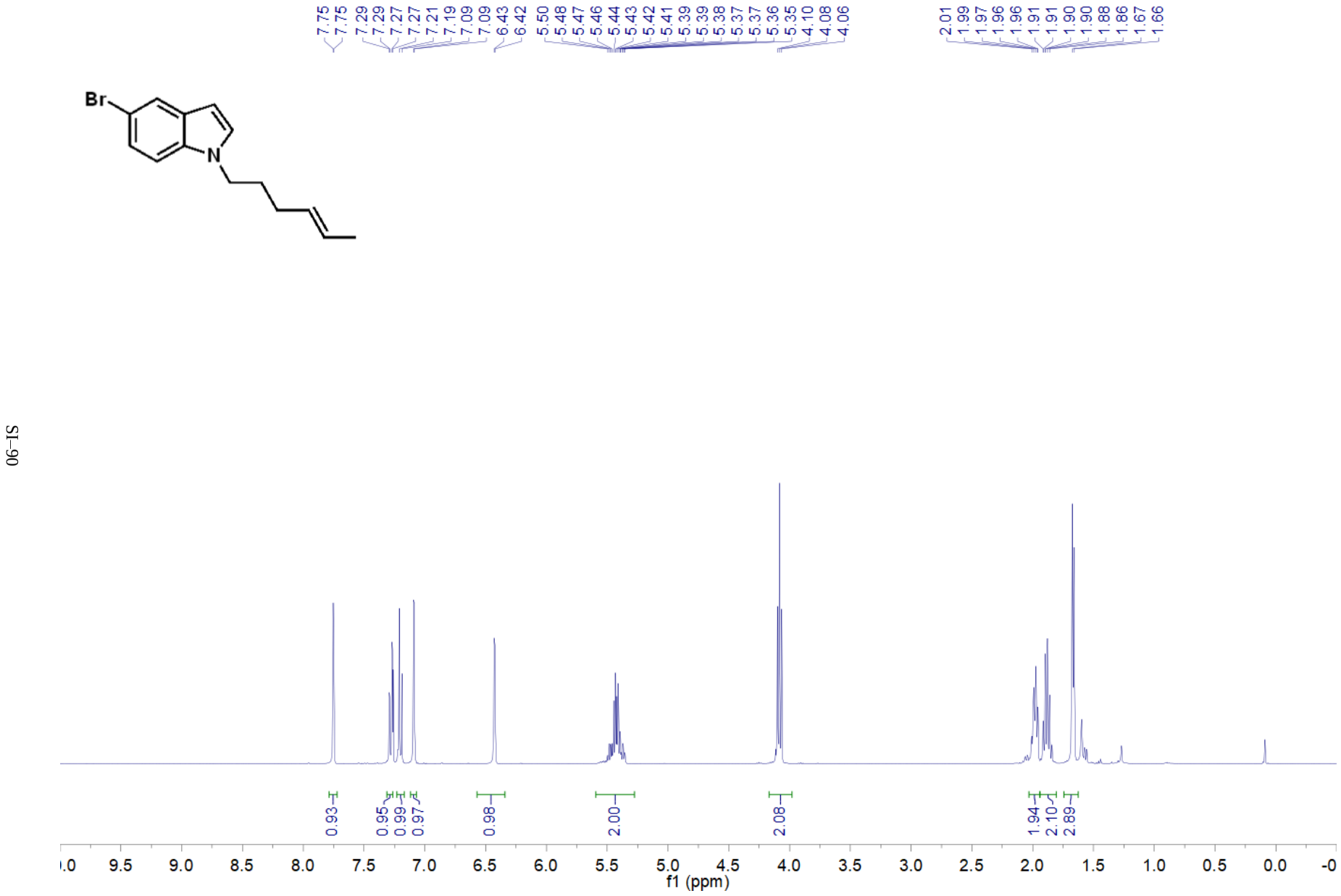
^{13}C NMR (100 MHz, $CDCl_3$) of **4g**



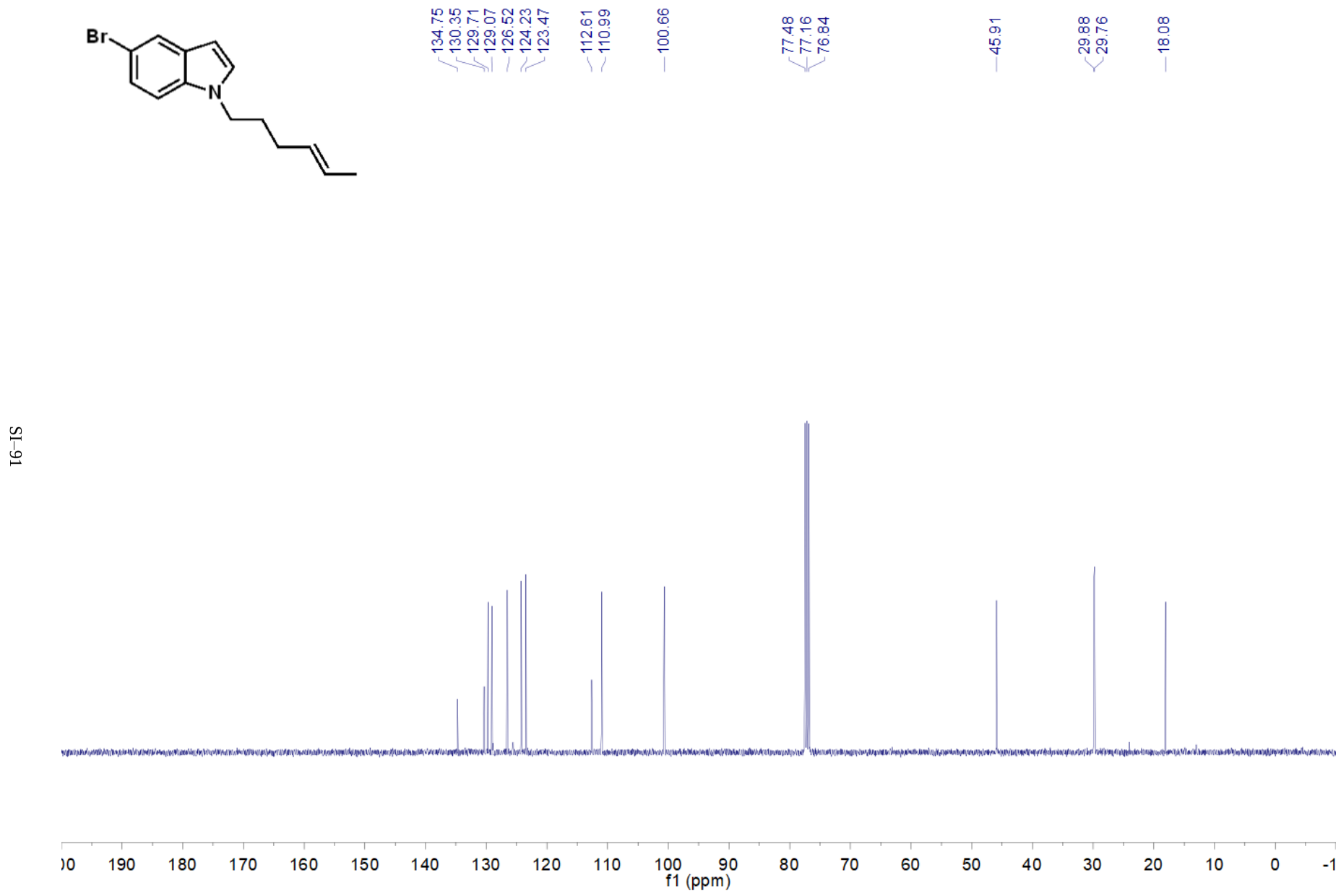
^{1}H NMR (400 MHz, $CDCl_3$) of **4h**



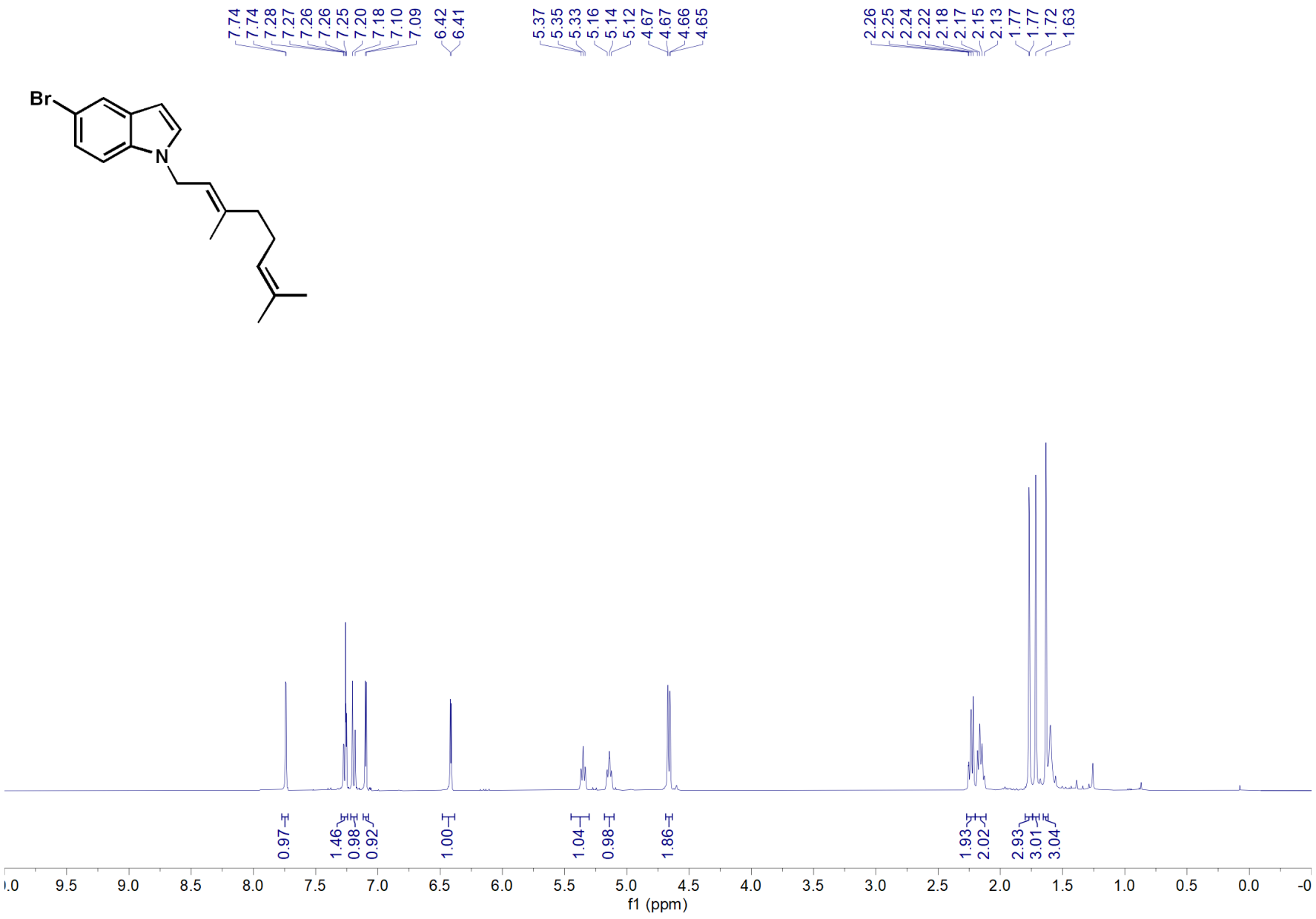
^{13}C NMR (100 MHz, $CDCl_3$) of **4h**



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



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



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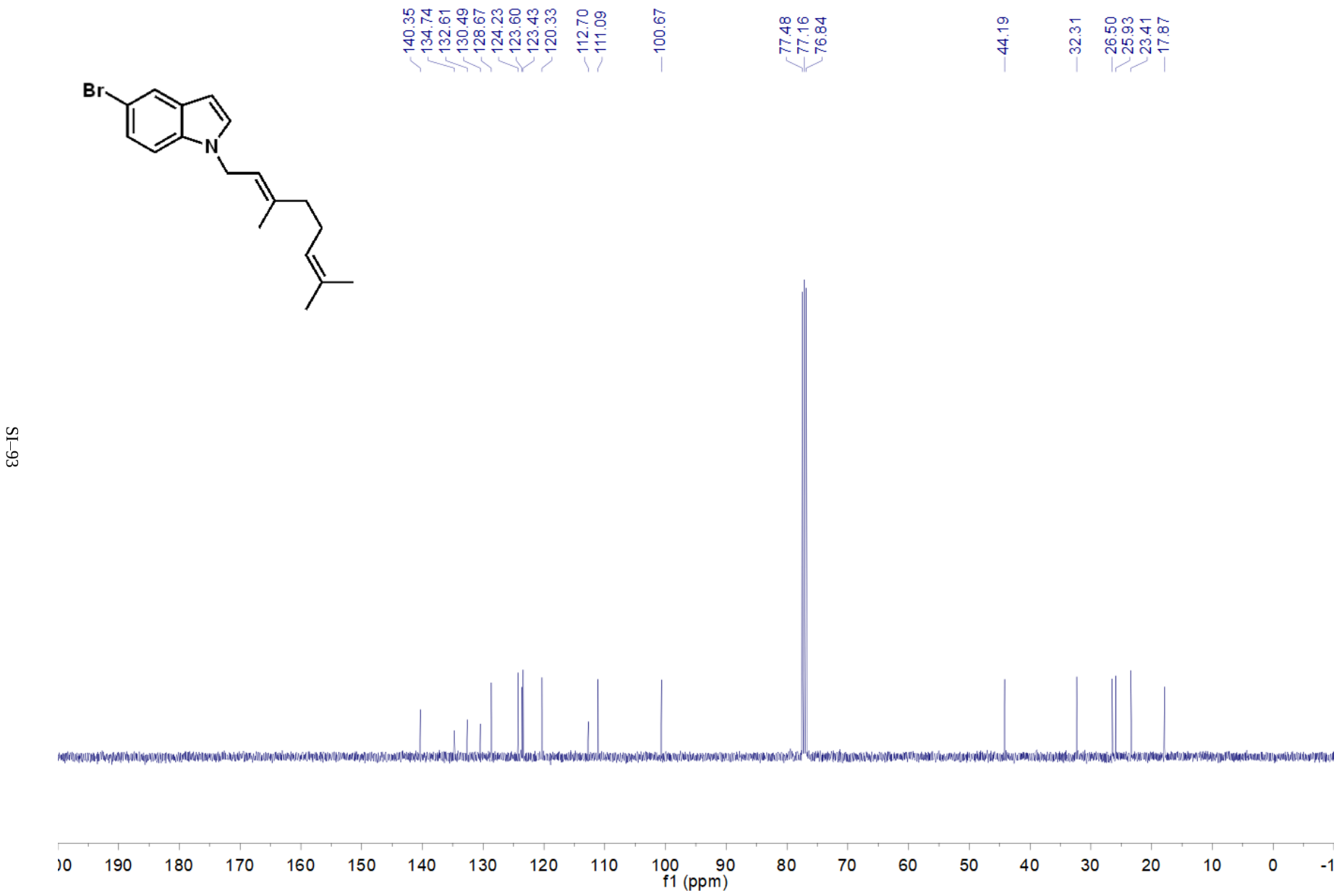
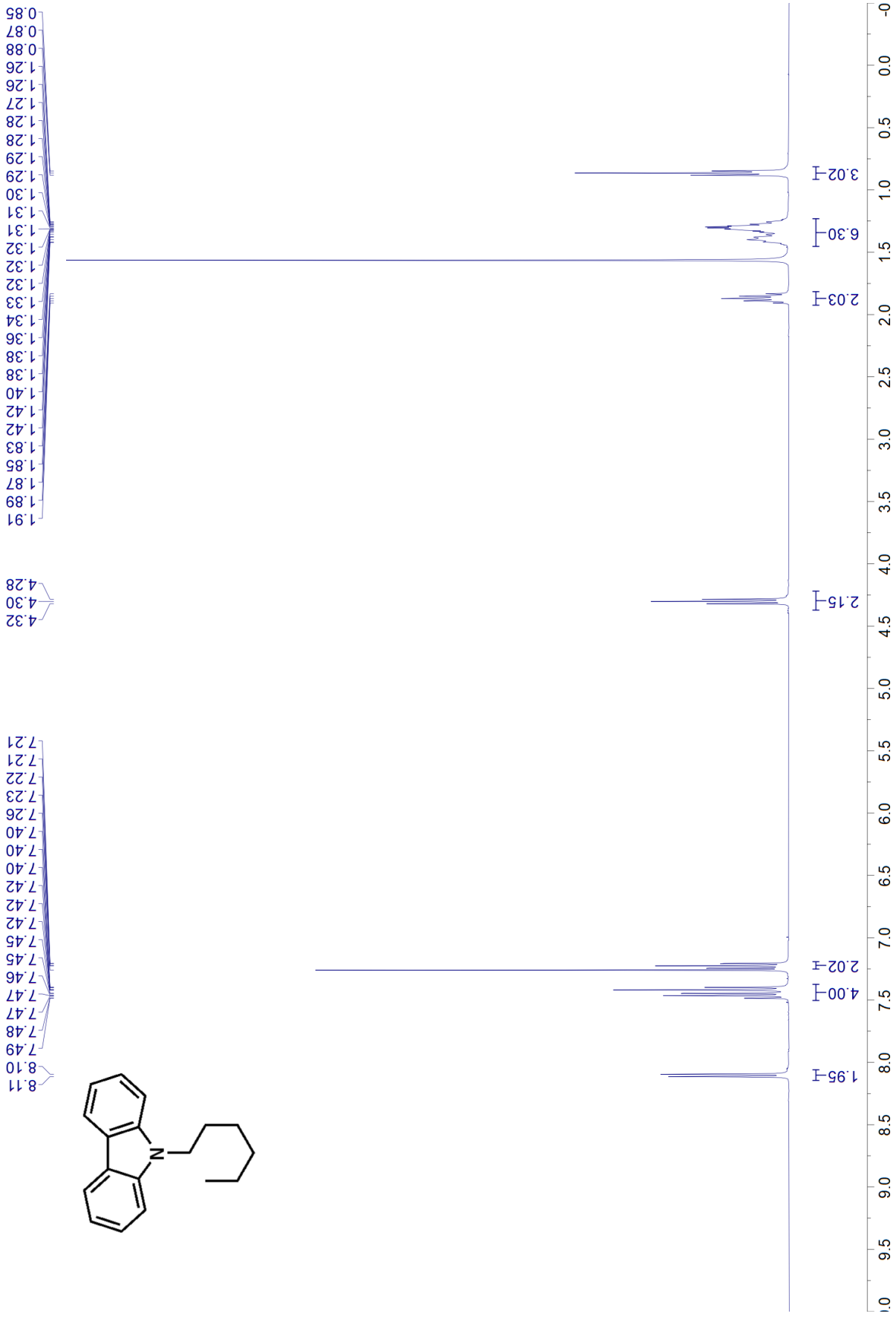
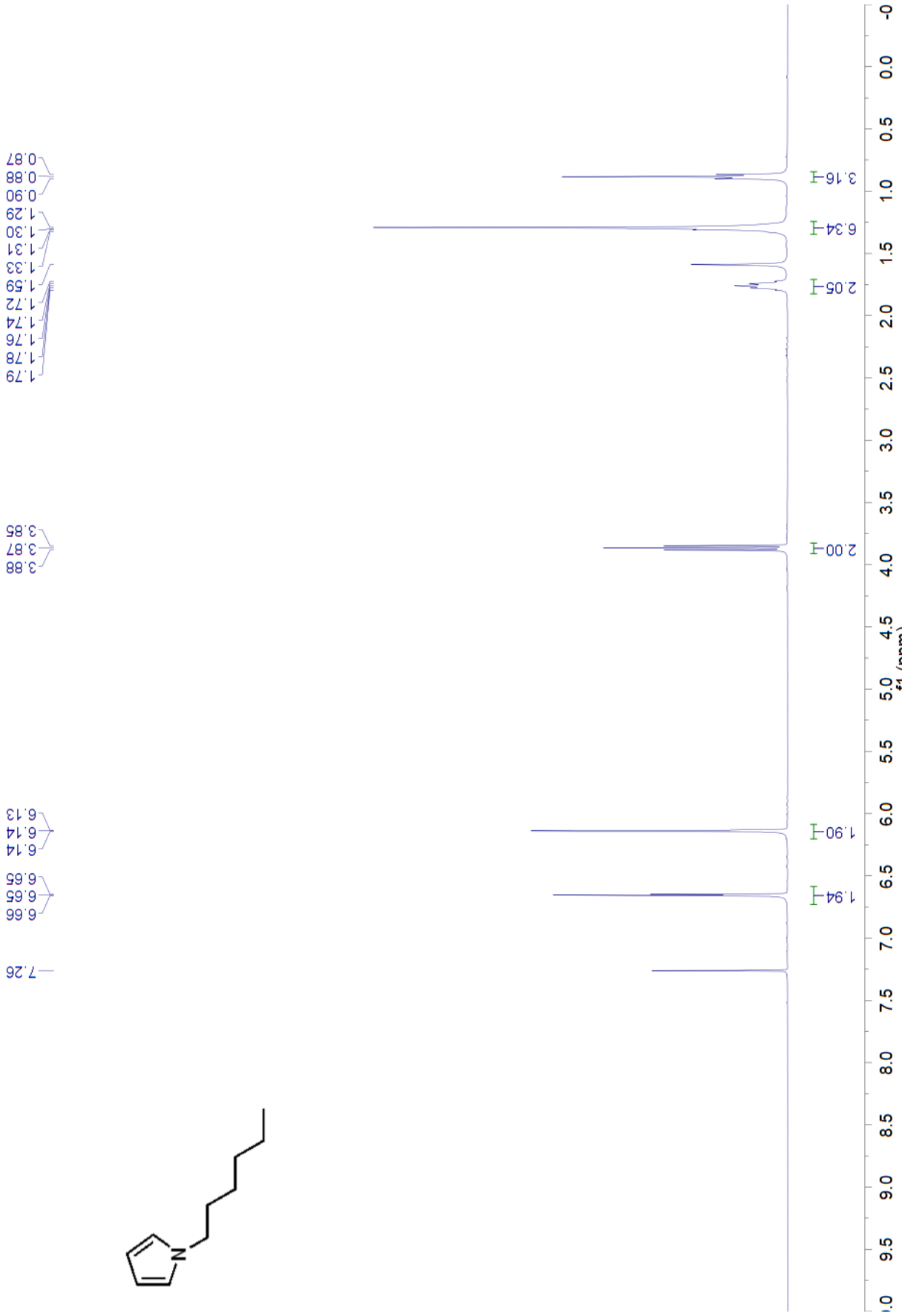


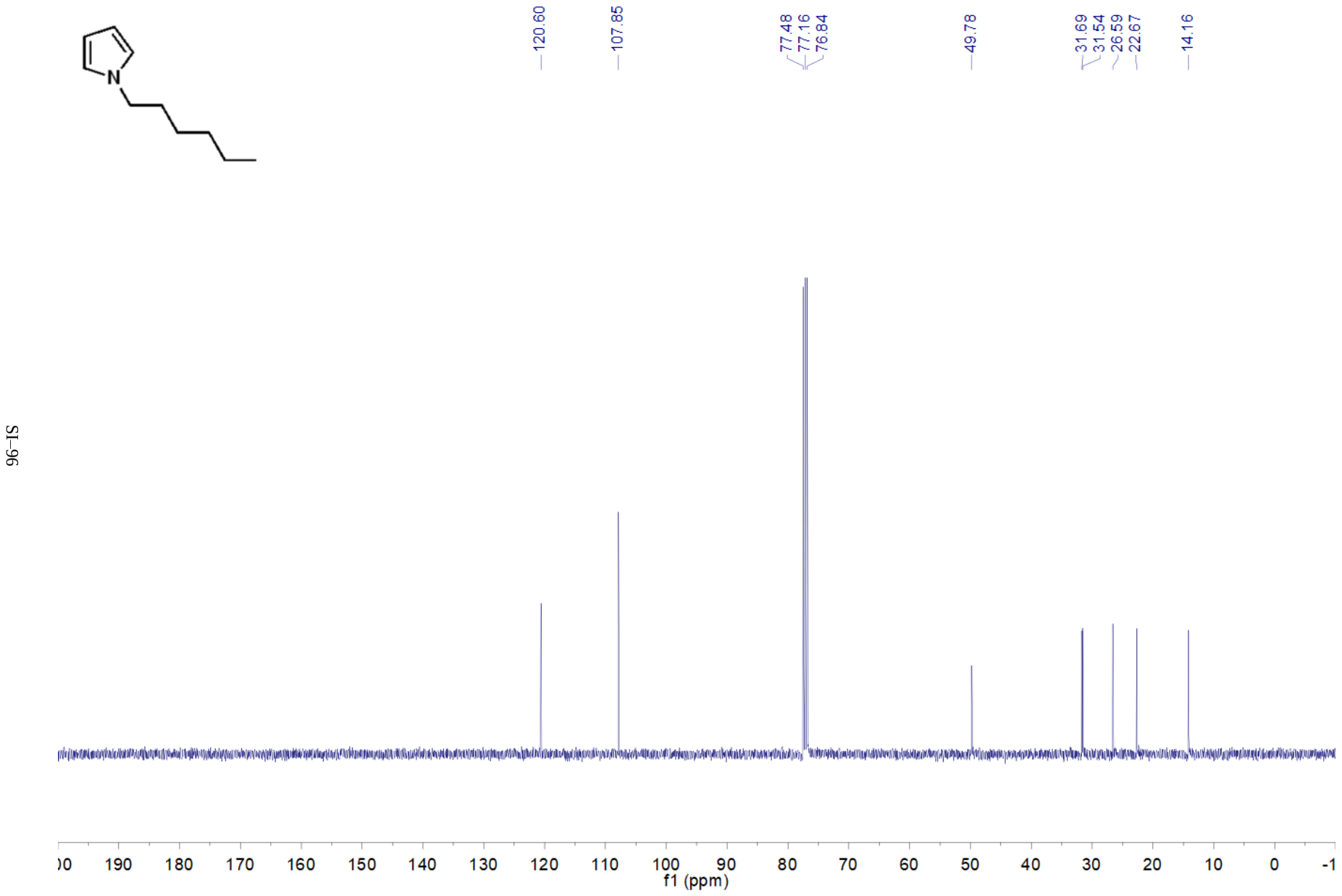
^{13}C NMR (100 MHz, $CDCl_3$) of **4j**



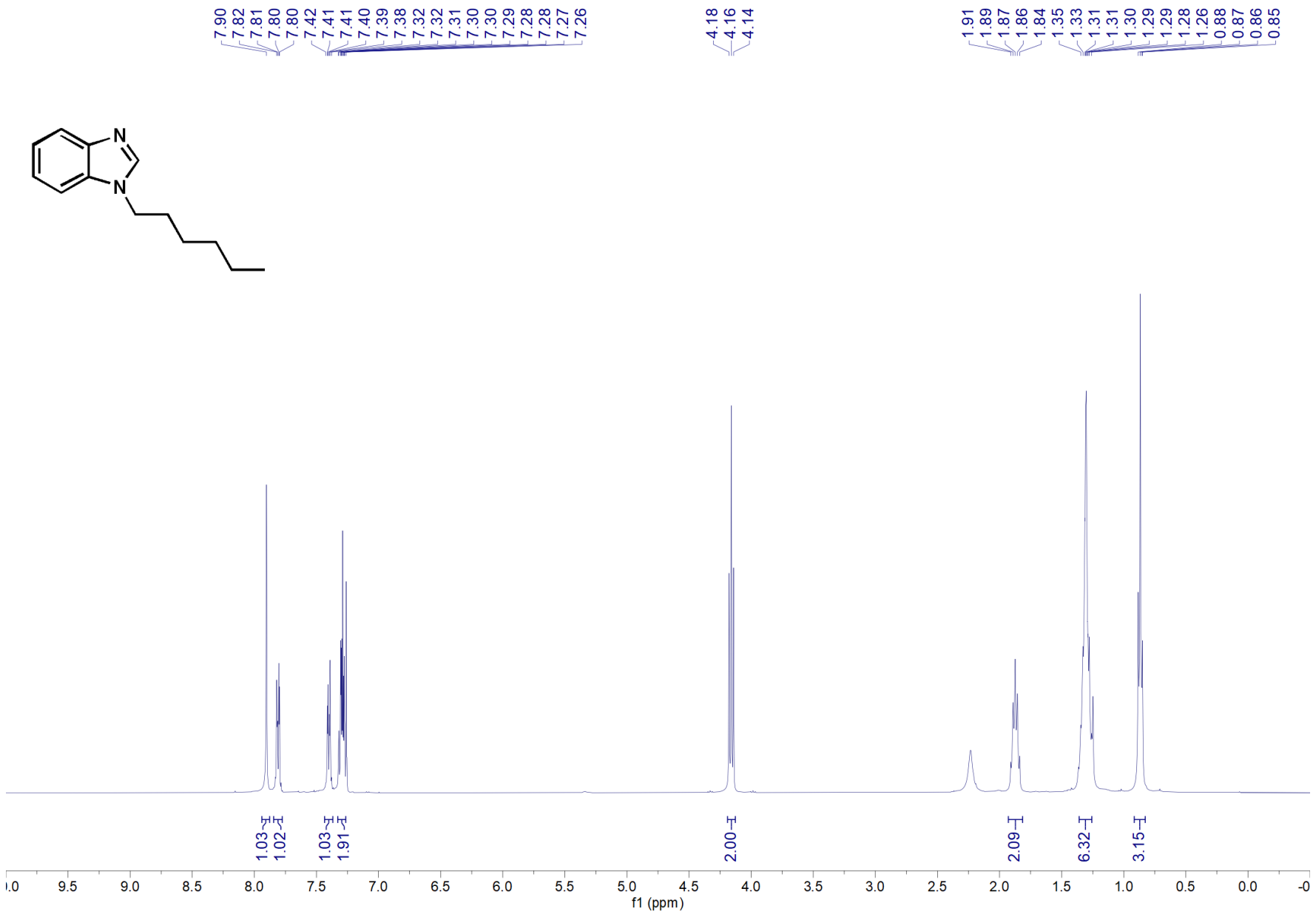
^{1}H NMR (400 MHz, $CDCl_3$) of **4k**



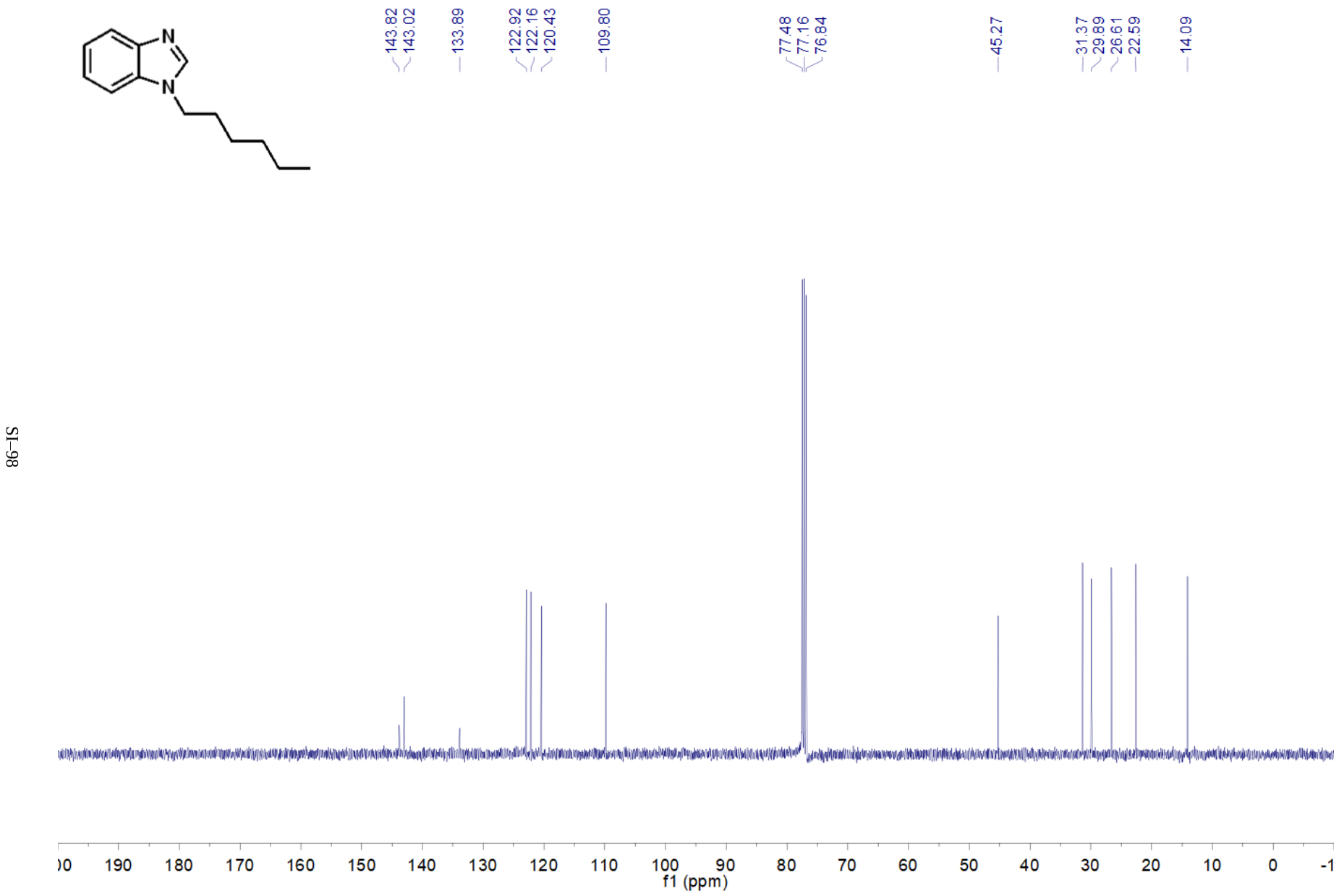
^{1}H NMR (400 MHz, $CDCl_3$) of **4l**



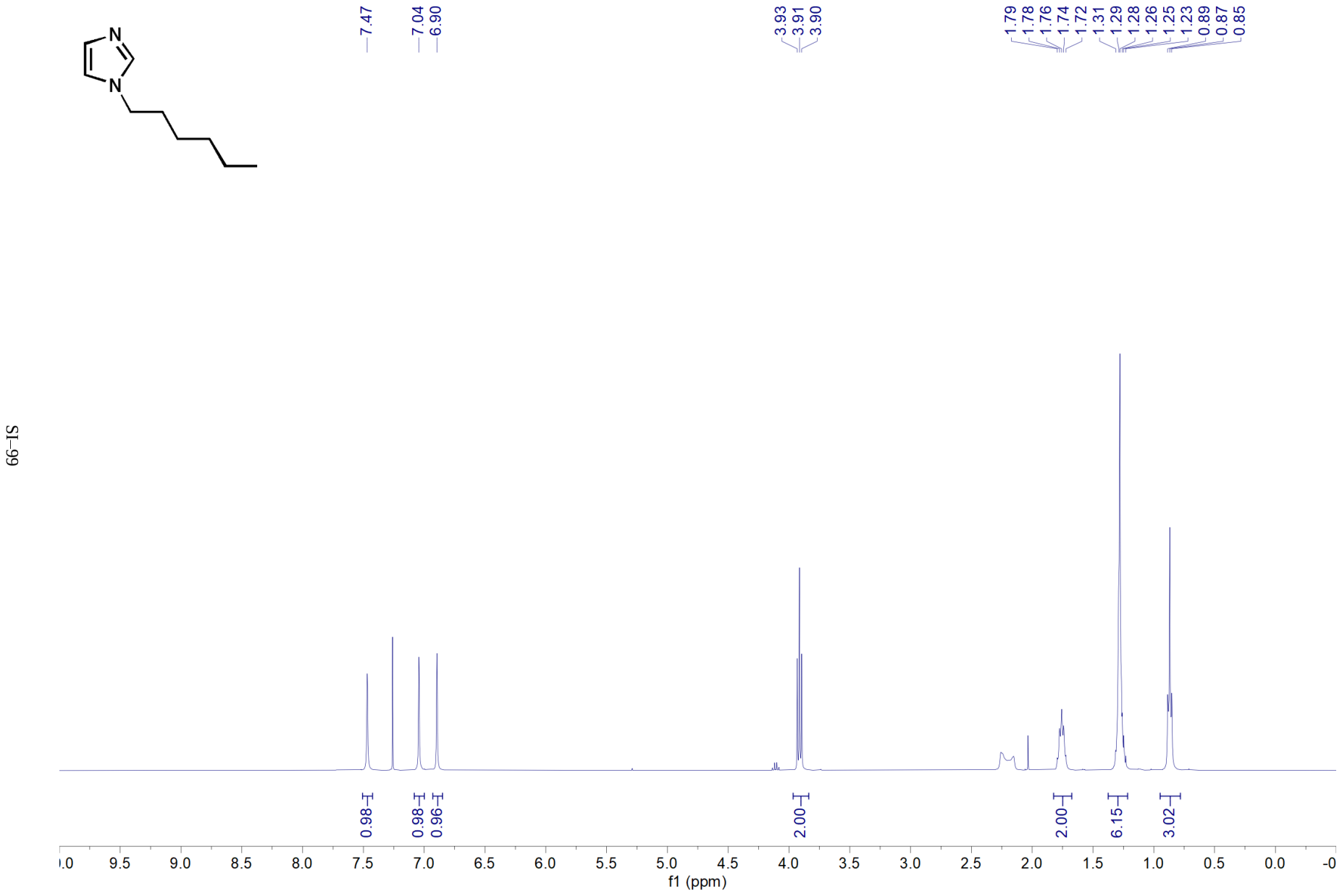
^{13}C NMR (100 MHz, $CDCl_3$) of **4l**



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



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



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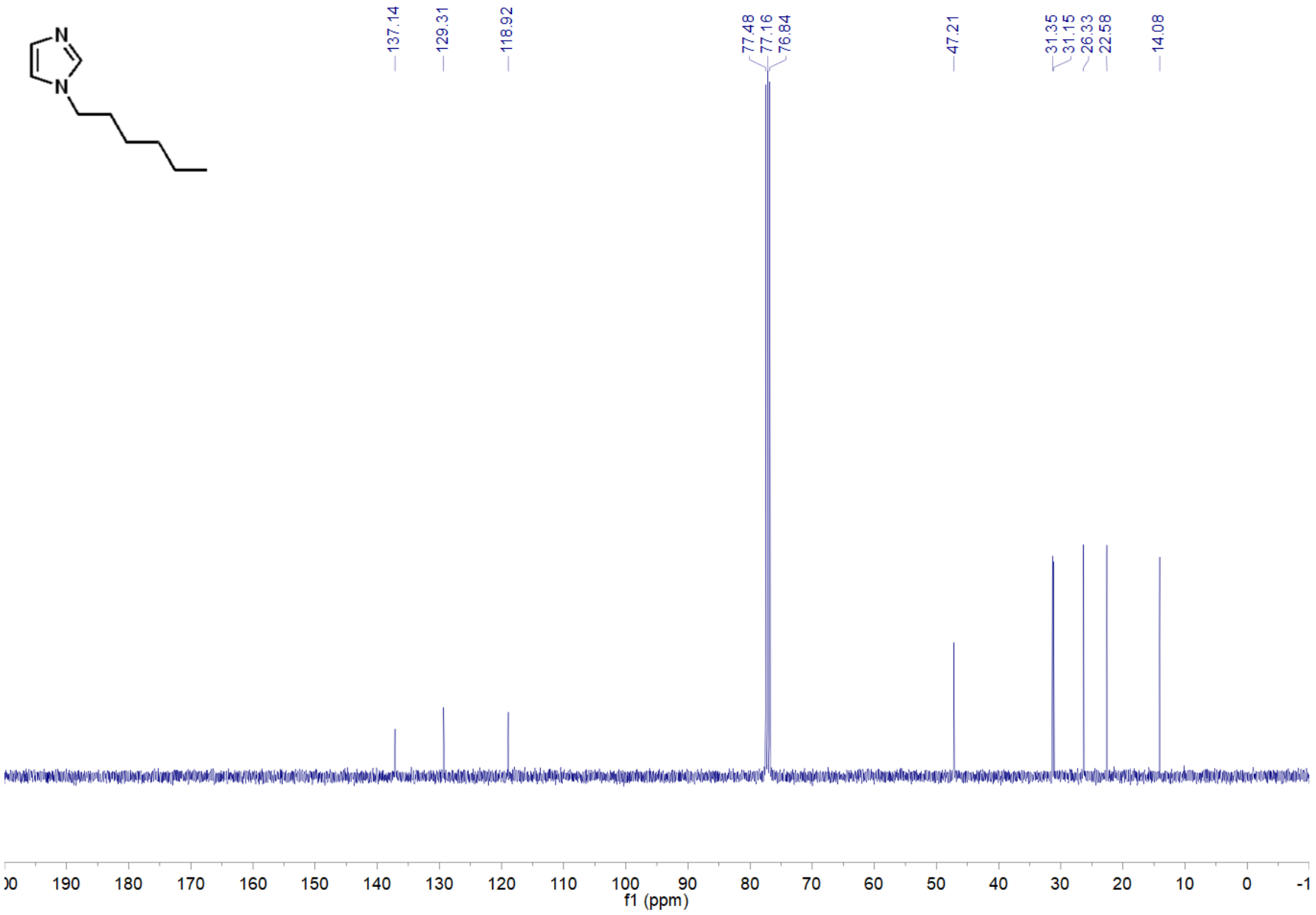
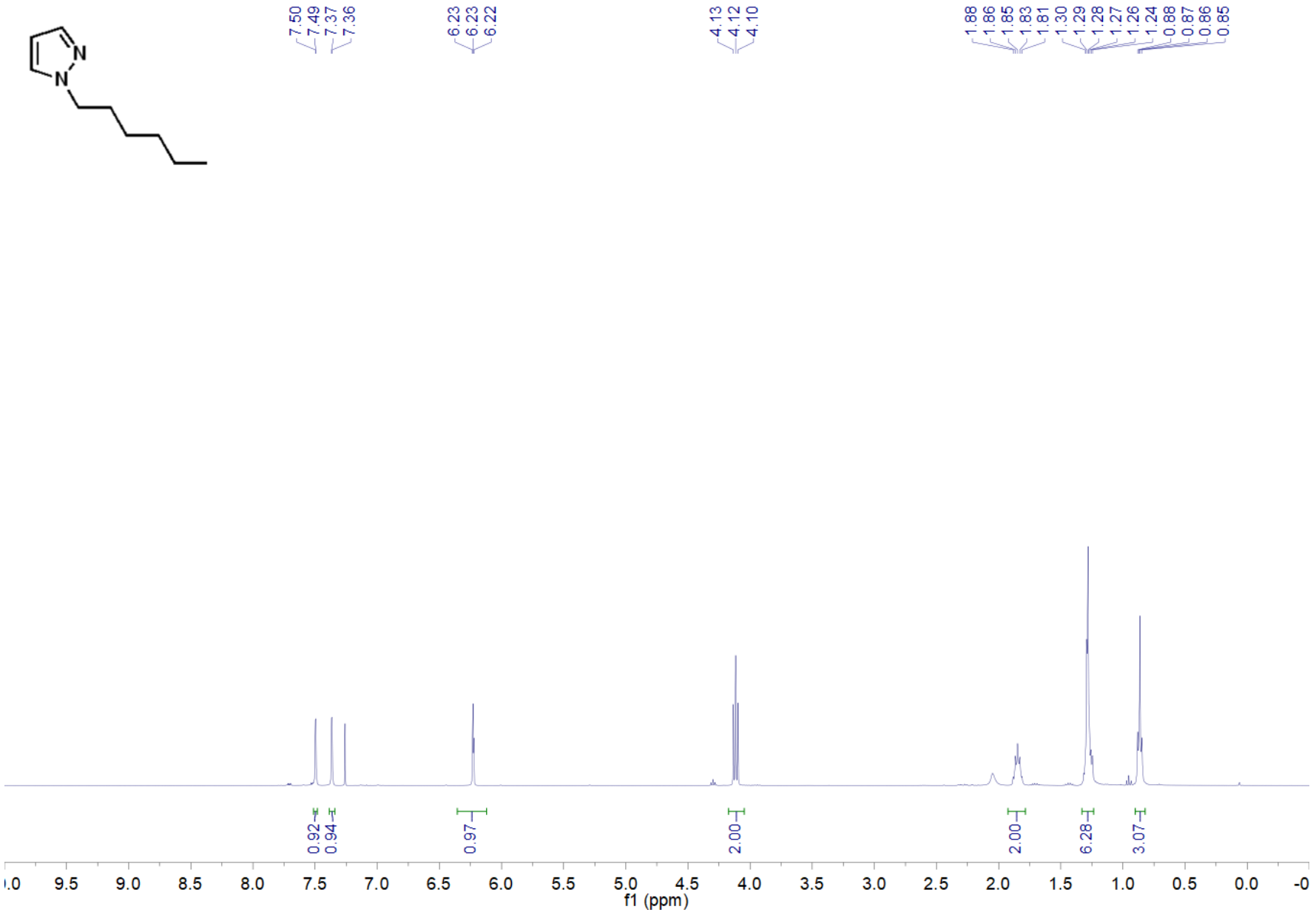
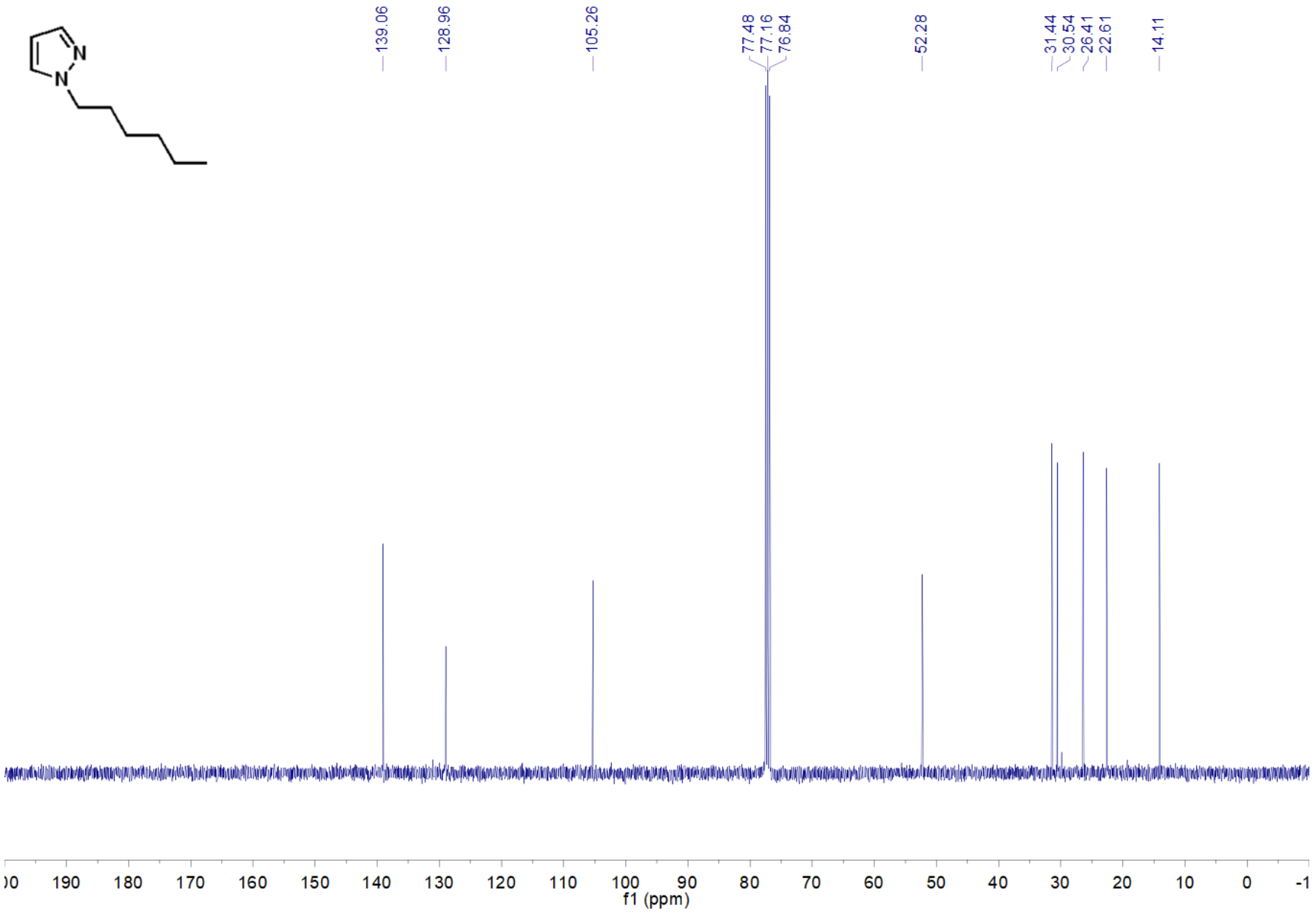
^{1}H NMR (400 MHz, $CDCl_3$) of **4n**



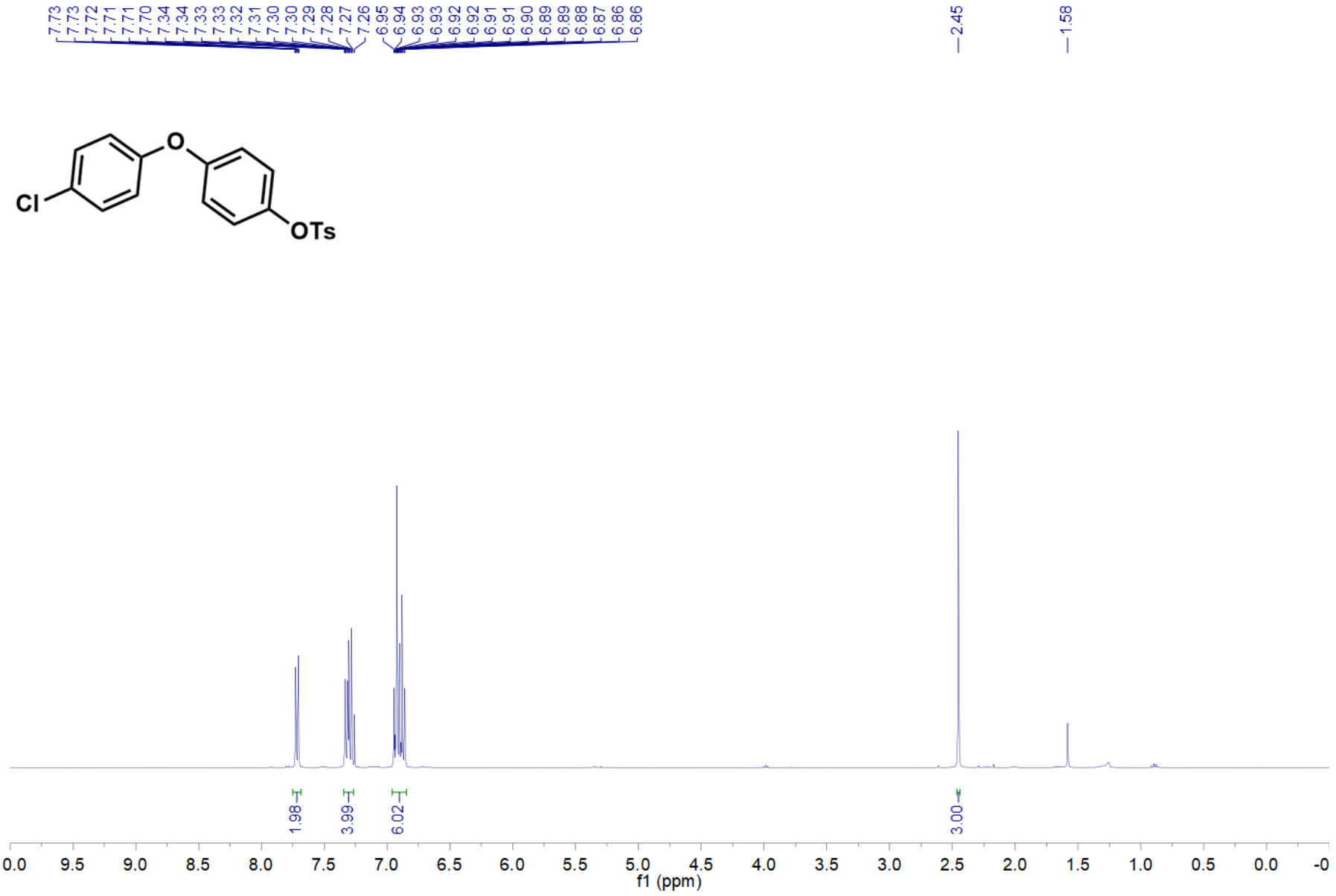
^{13}C NMR (100 MHz, $CDCl_3$) of **4n**



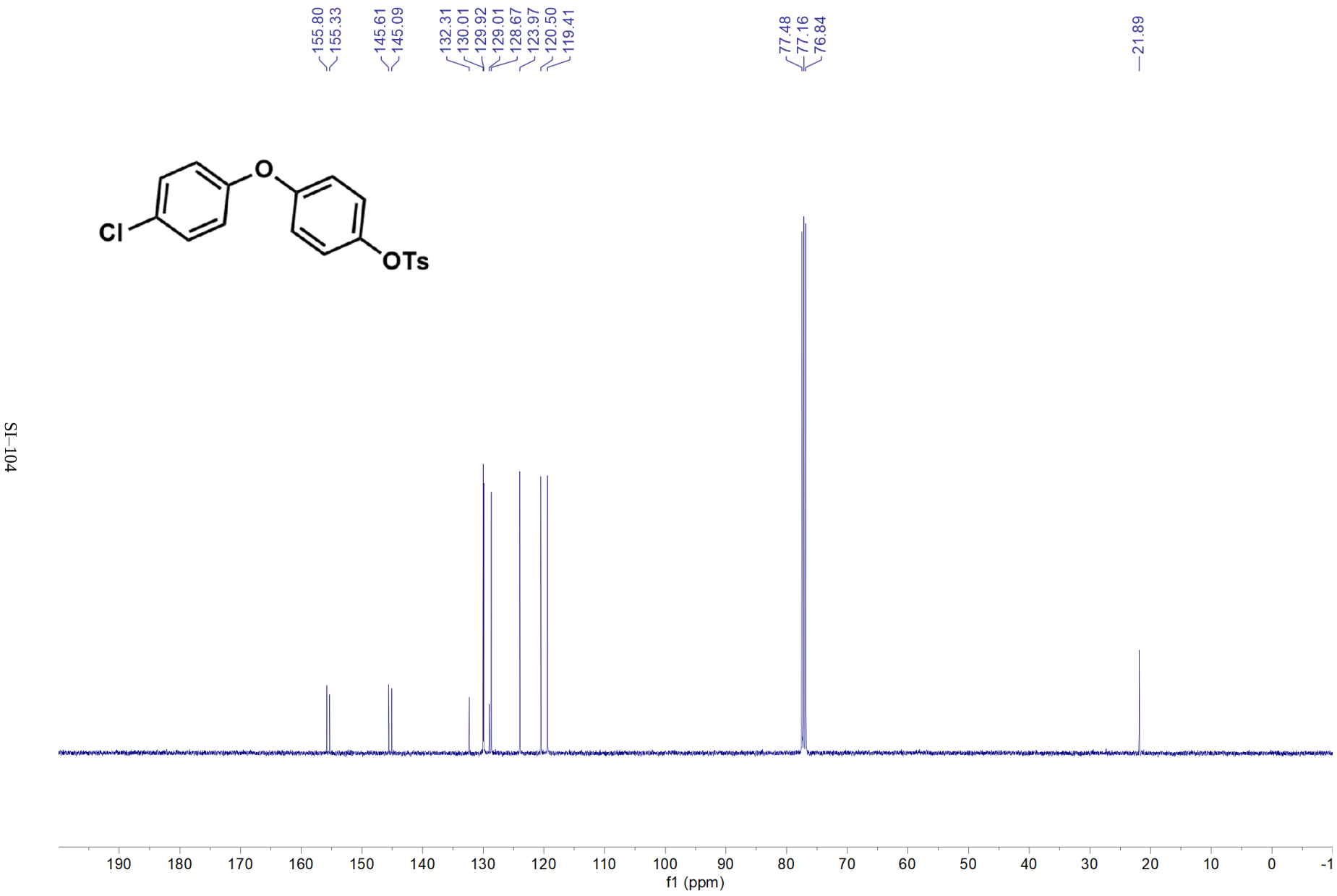
^{1}H NMR (400 MHz, $CDCl_3$) of **4o**



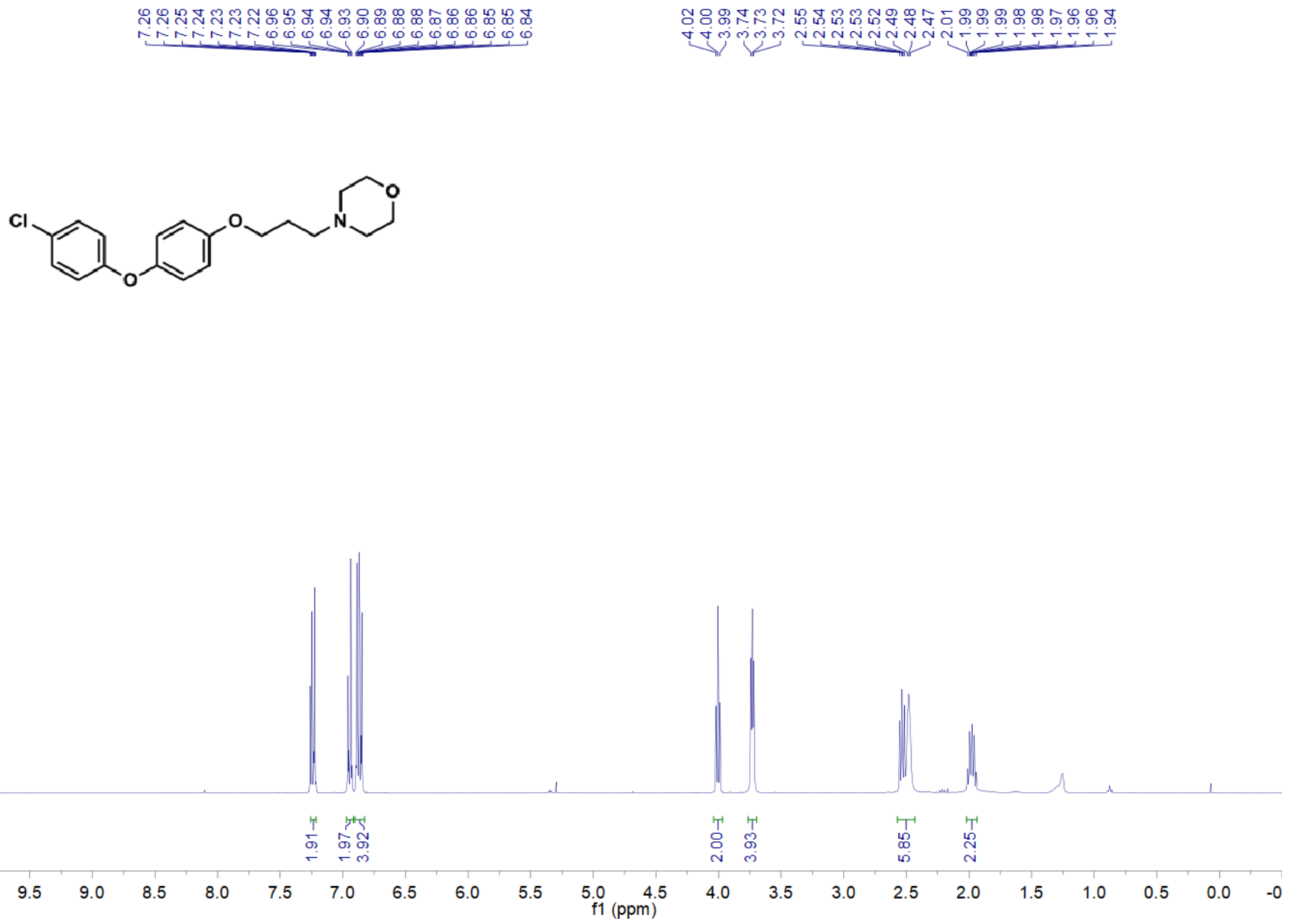
^{13}C NMR (100 MHz, $CDCl_3$) of **4o**



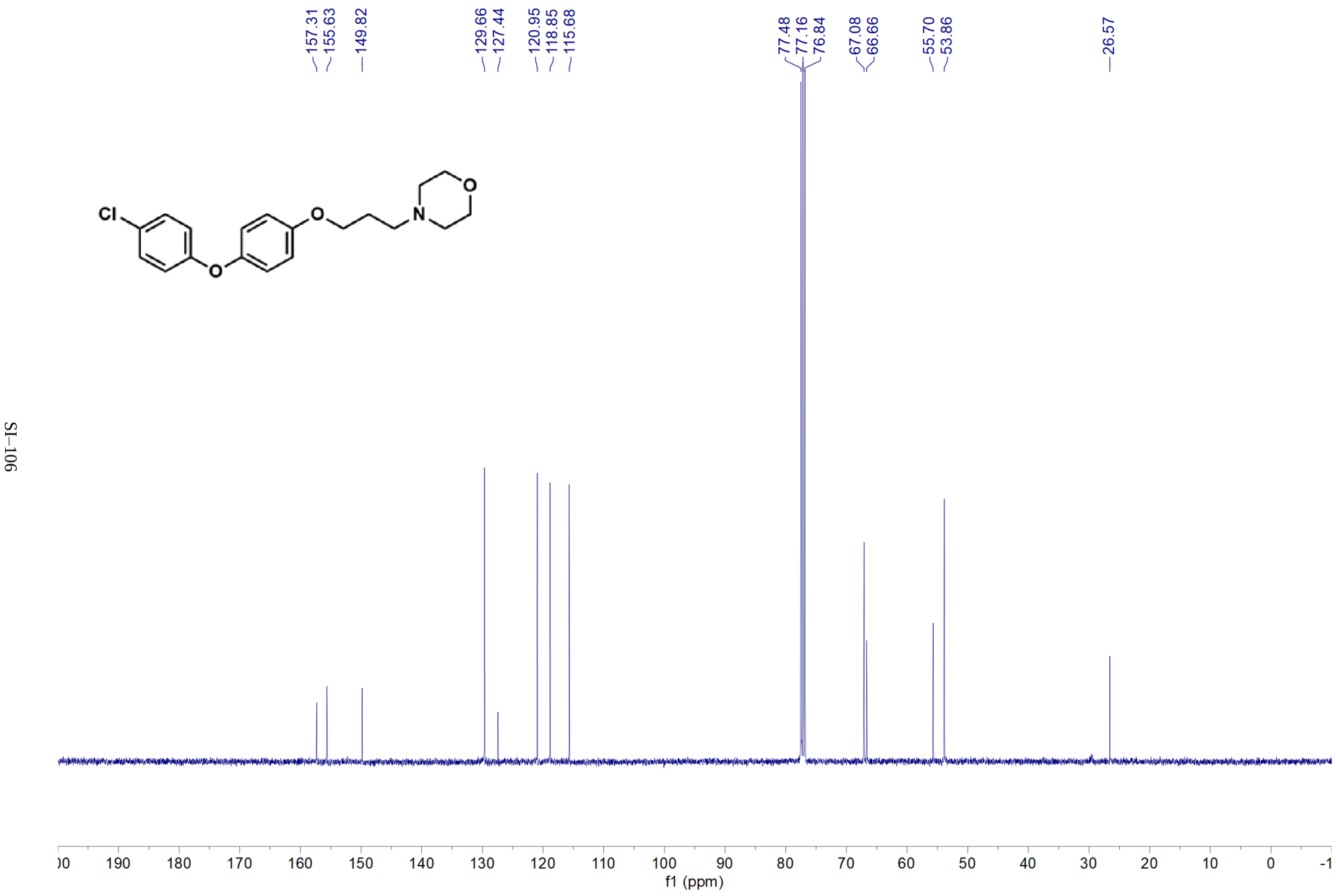
^{1}H NMR (400 MHz, $CDCl_3$) of **1ae**



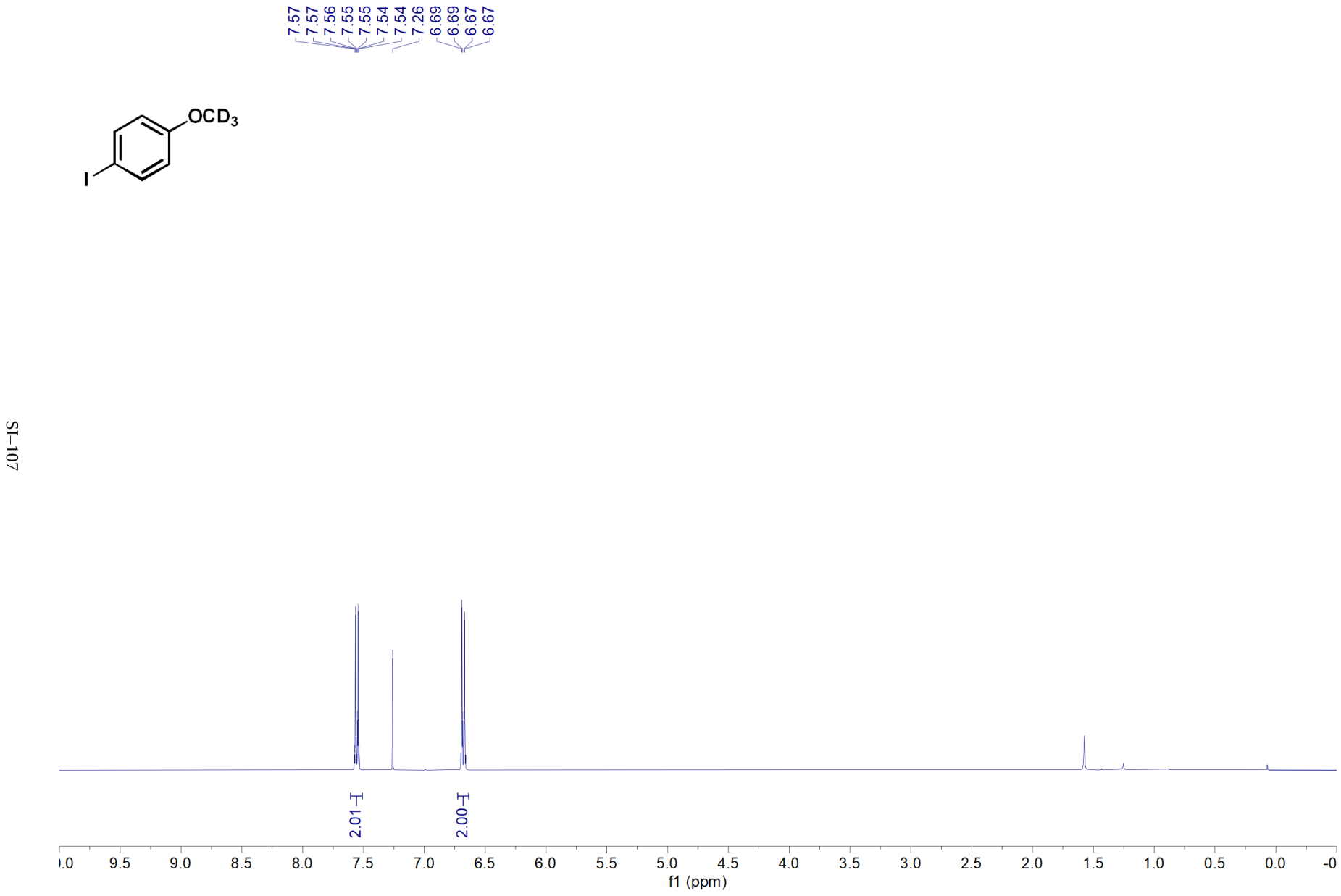
^{13}C NMR (100 MHz, $CDCl_3$) of **1ae**



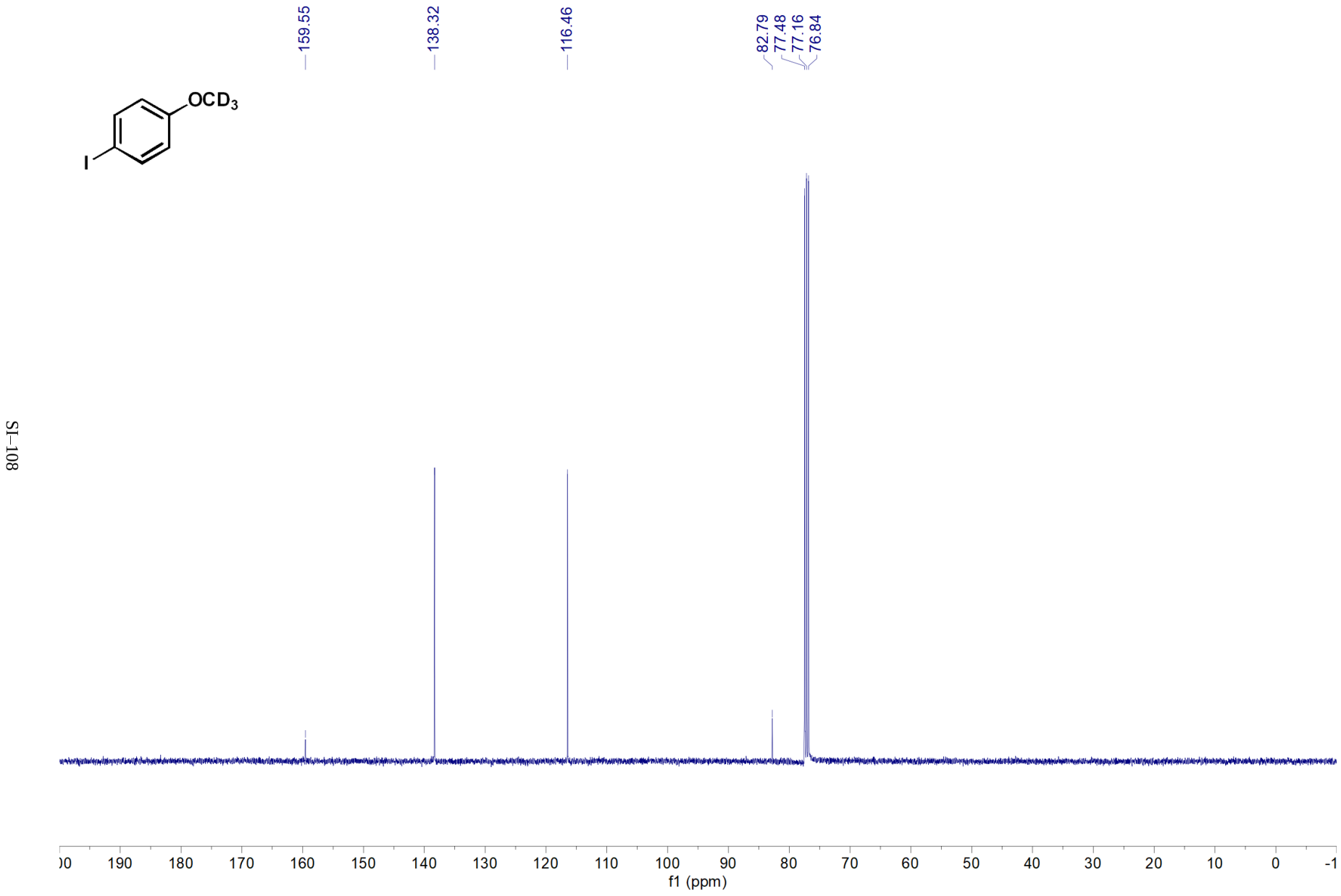
^{1}H NMR (400 MHz, $CDCl_3$) of **4p**



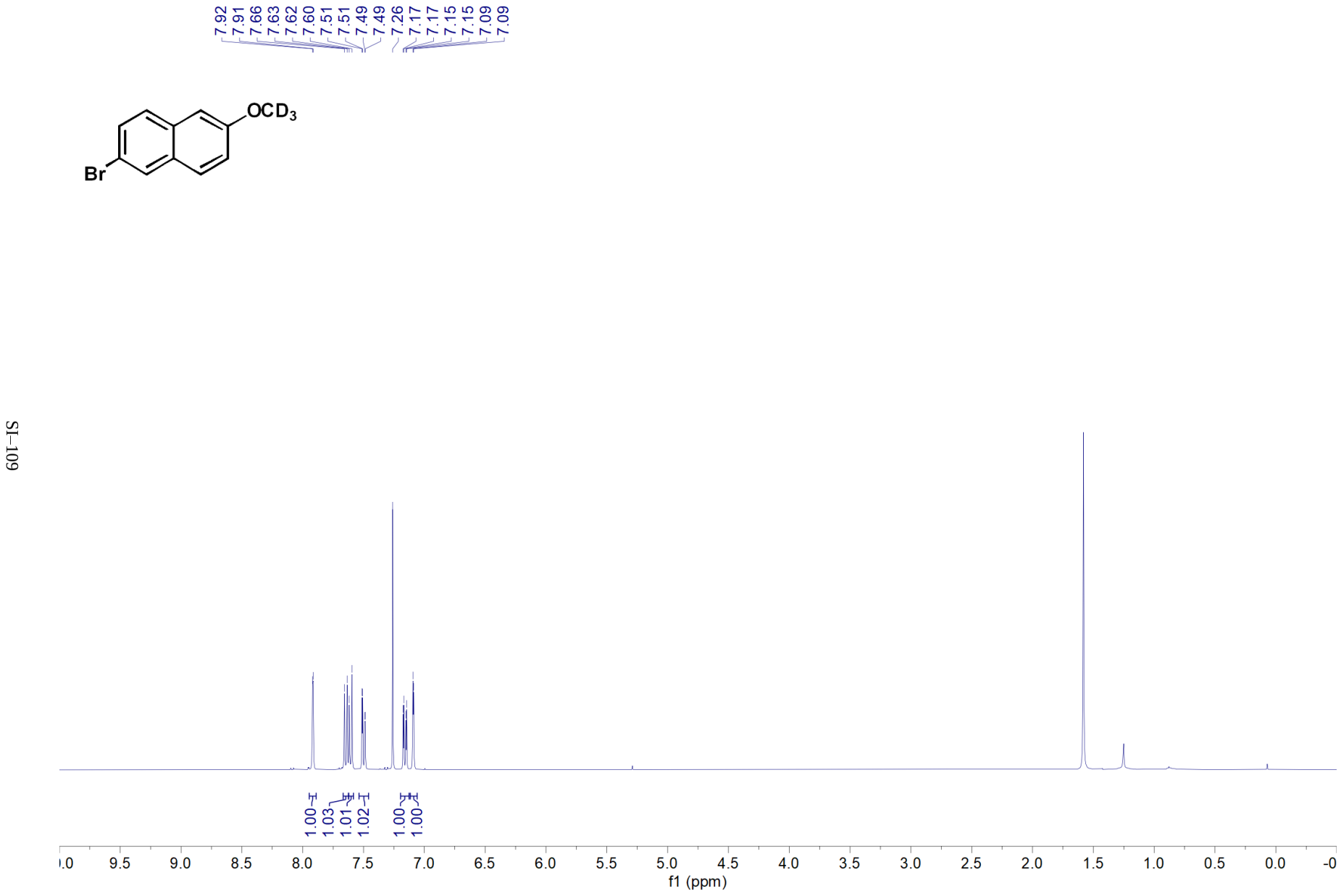
^{13}C NMR (100 MHz, $CDCl_3$) of **4p**



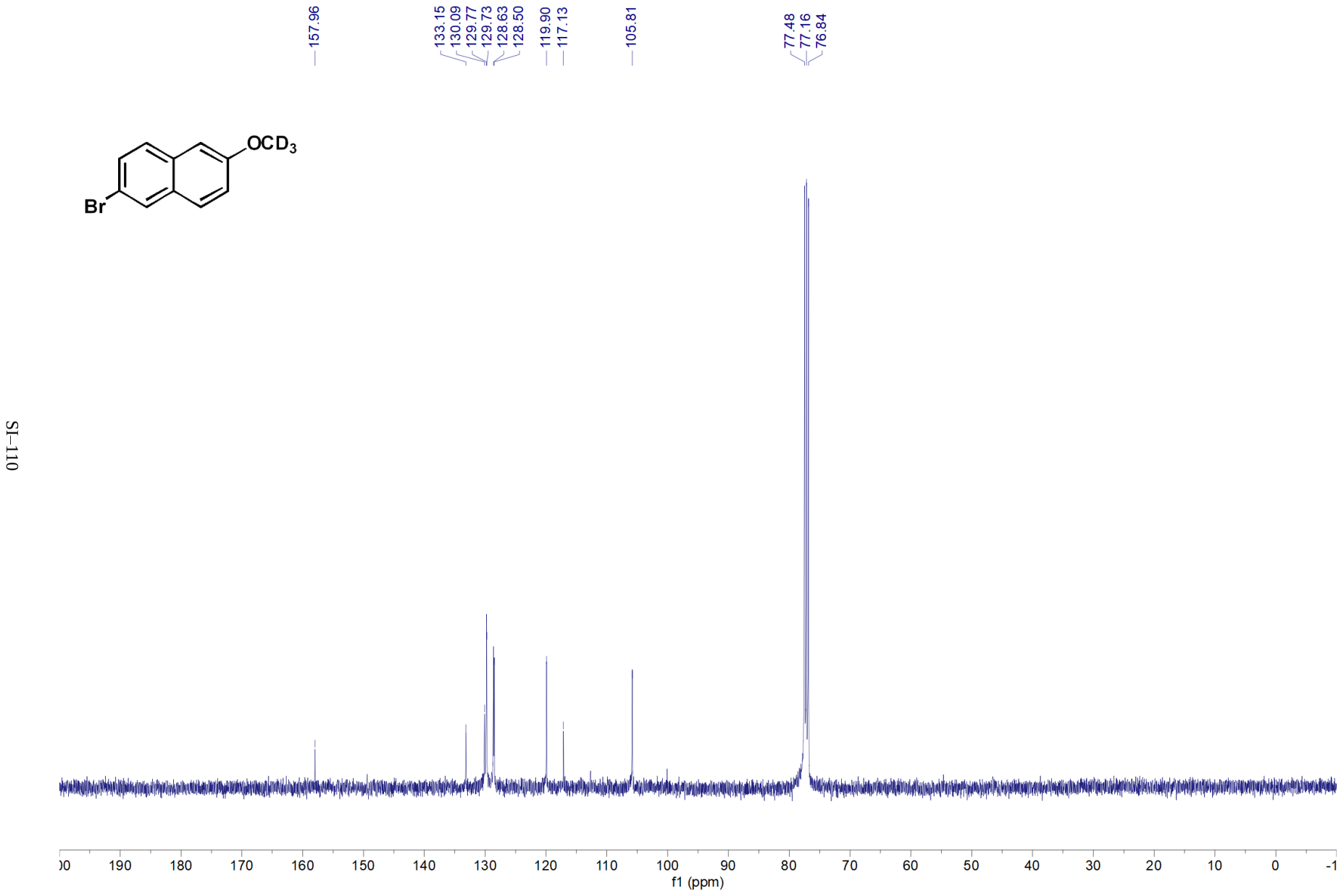
^{1}H NMR (400 MHz, $CDCl_3$) of **3l**



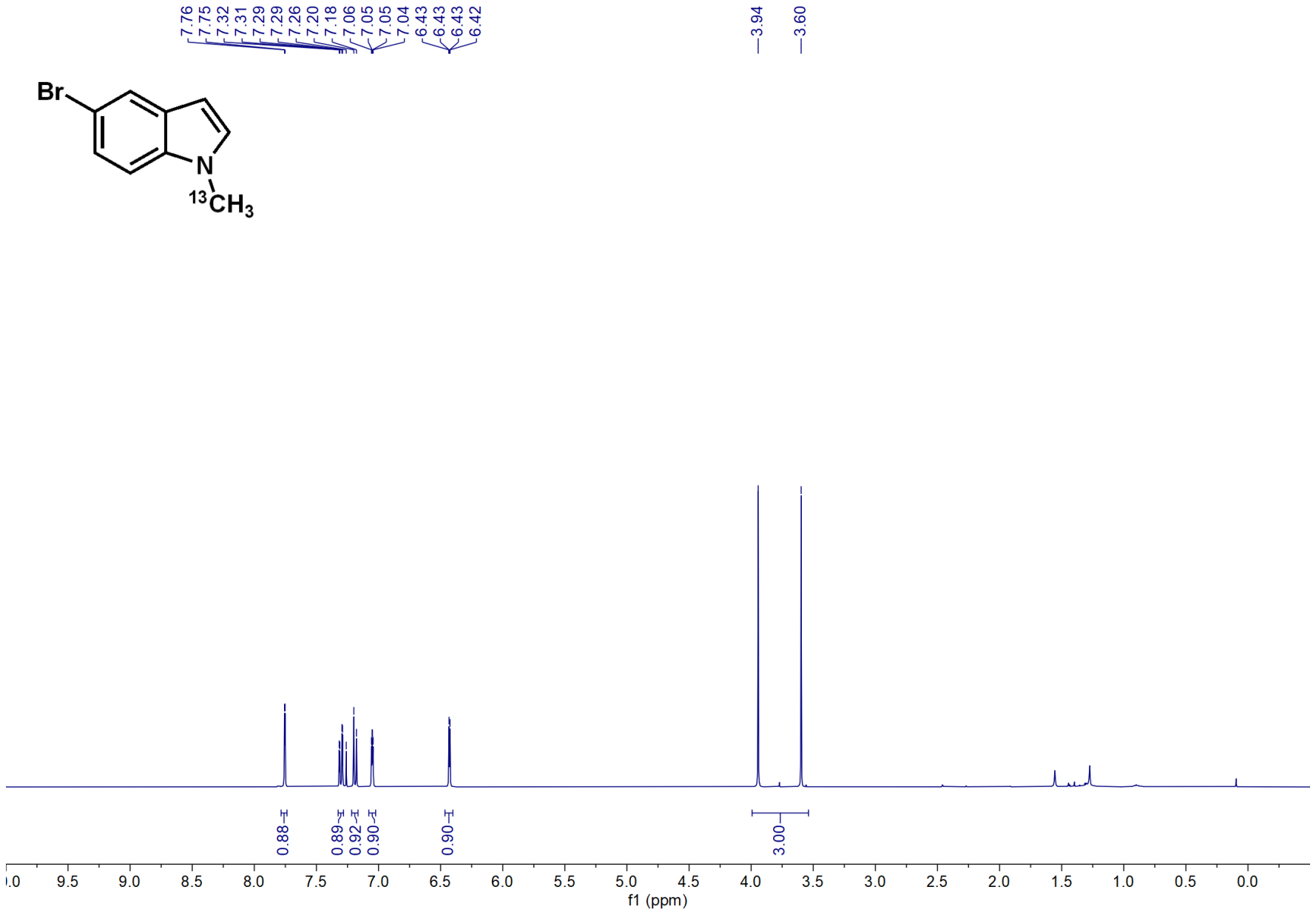
^{13}C NMR (100 MHz, $CDCl_3$) of **3l**



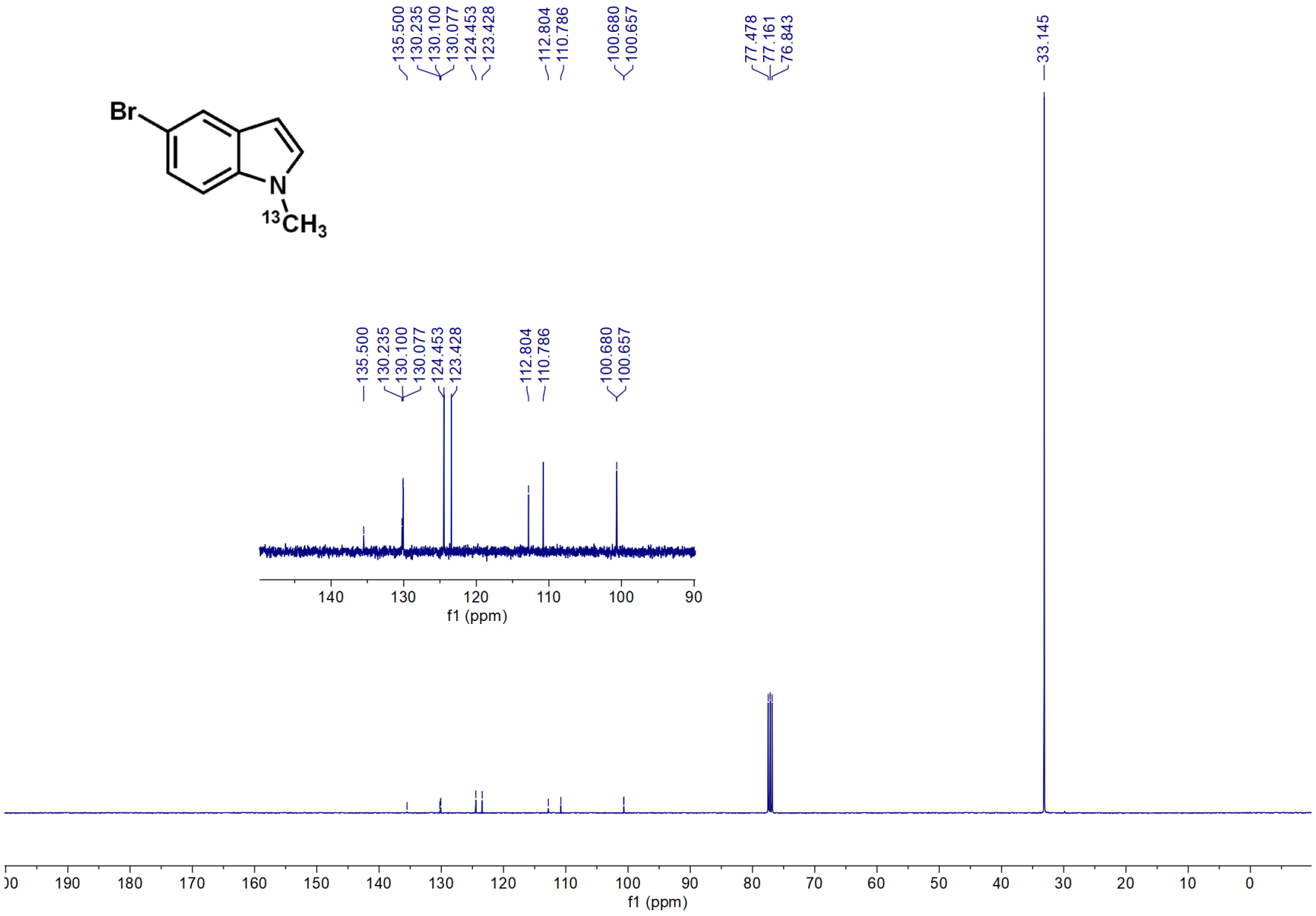
^{1}H NMR (400 MHz, $CDCl_3$) of **3m**



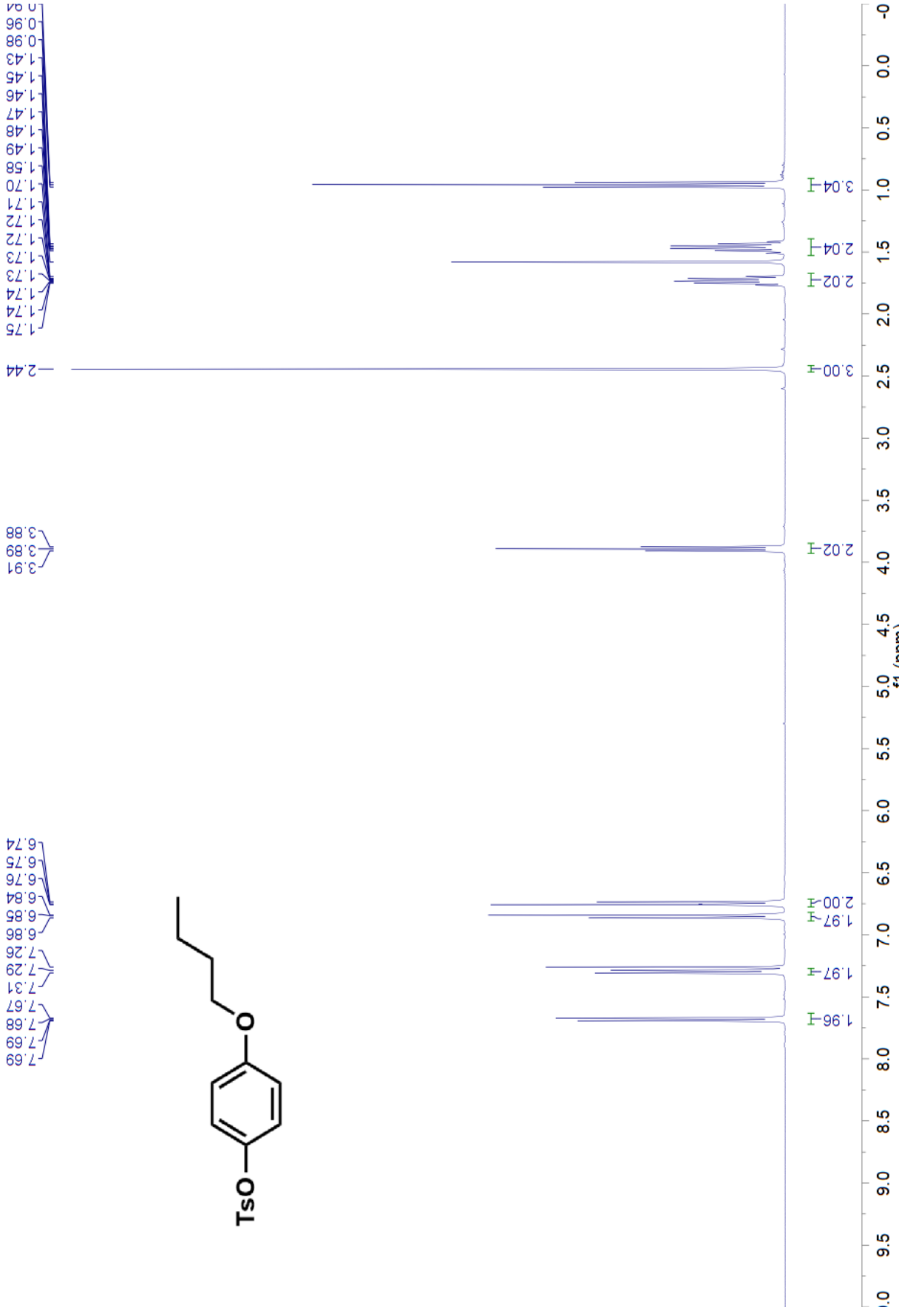
^{13}C NMR (100 MHz, $CDCl_3$) of **3m**



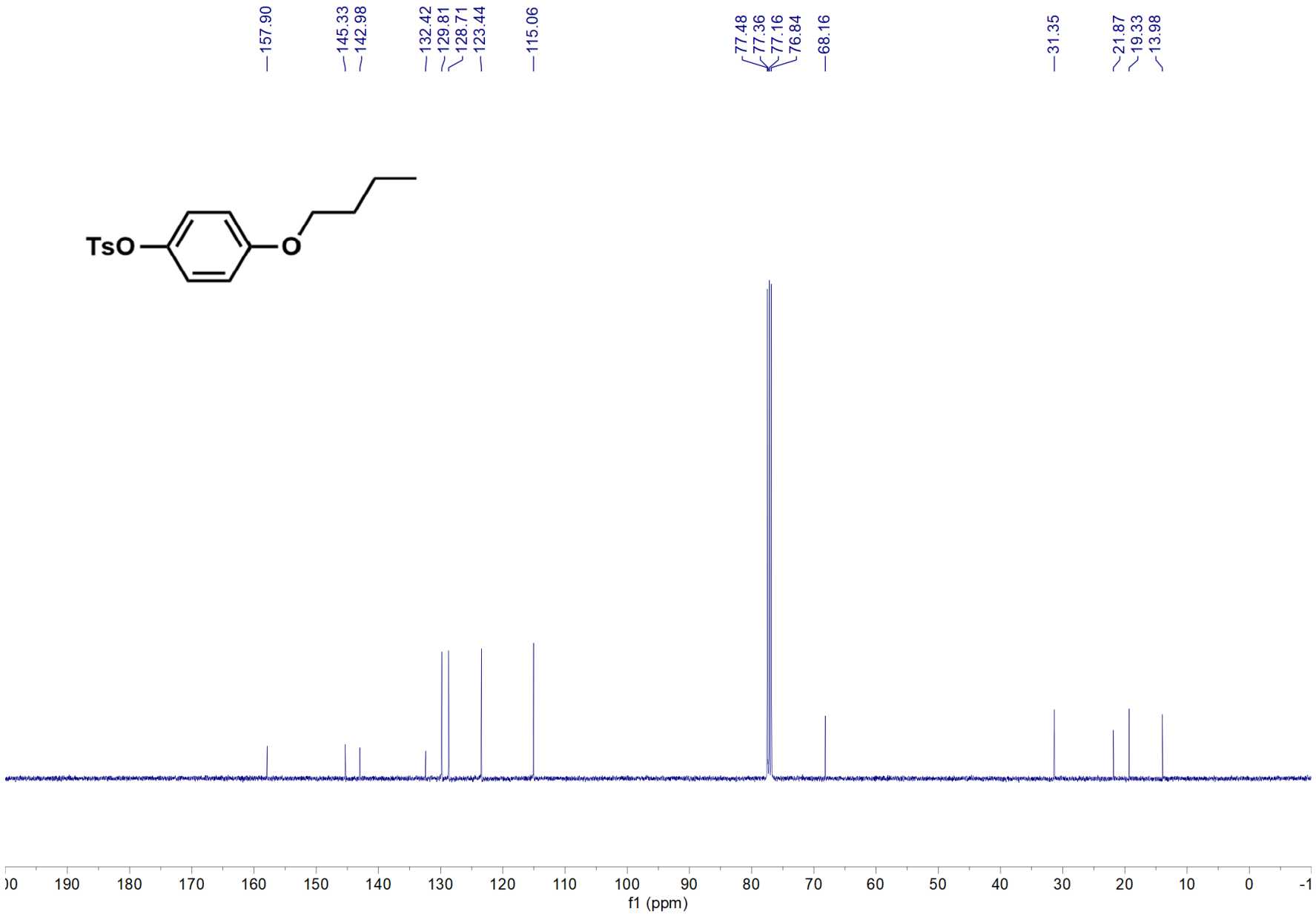
^{1}H NMR (400 MHz, $CDCl_3$) of **3 d'**



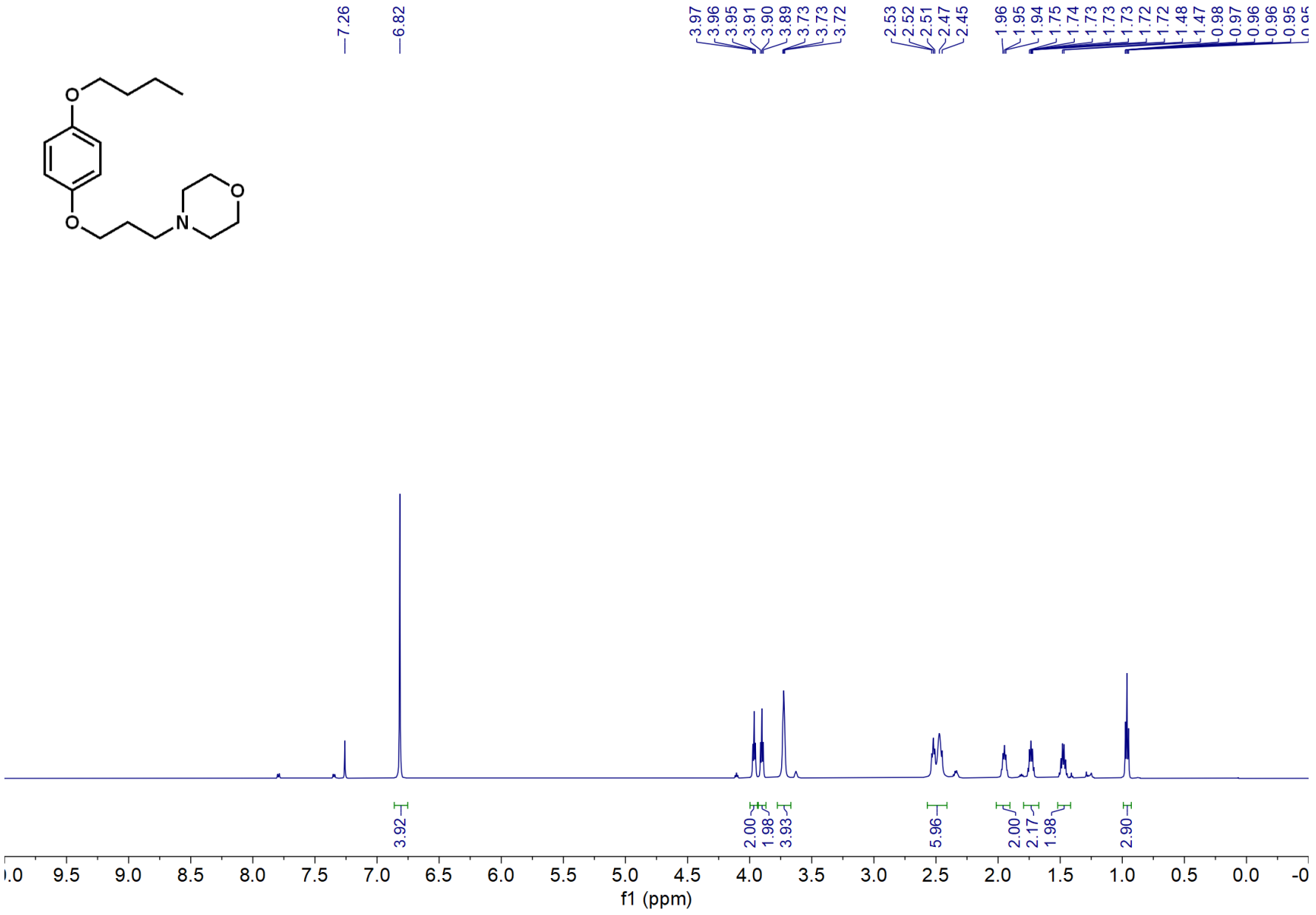
^{13}C NMR (100 MHz, $CDCl_3$) of **3 d'**



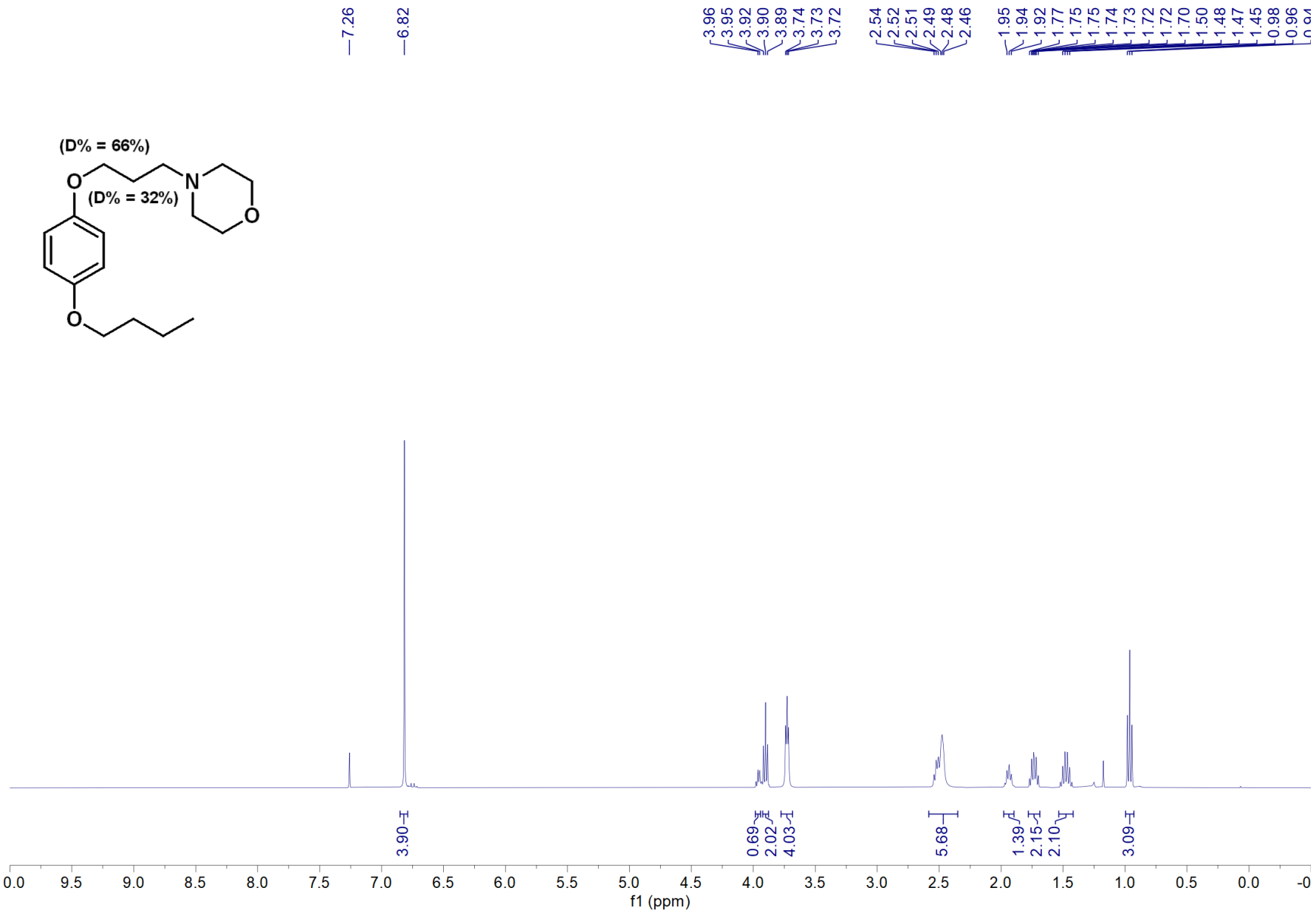
^{1}H NMR (400 MHz, $CDCl_3$) of **6**



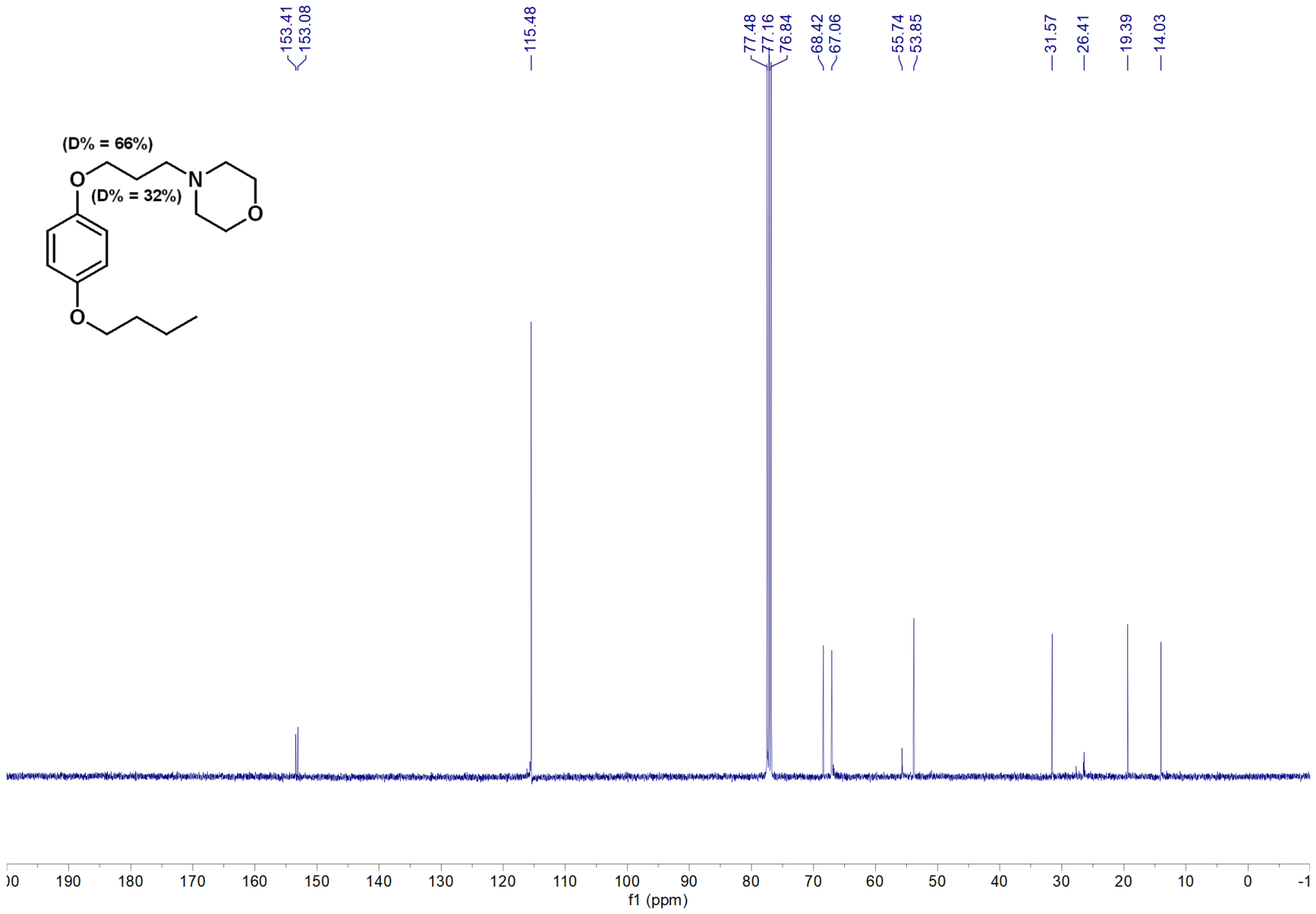
^{13}C NMR (100 MHz, $CDCl_3$) of **6**



^{1}H NMR (400 MHz, $CDCl_3$) of **8**



^{1}H NMR (400 MHz, $CDCl_3$) of **8-*d***



^{13}C NMR (100 MHz, $CDCl_3$) of **8-*d***