



Supporting Information

for

Multicomponent synthesis of α -branched amines using organozinc reagents generated from alkyl bromides

Baptiste Leroux, Alexis Beaufils, Federico Banchini, Olivier Jackowski, Alejandro Perez-Luna, Fabrice Chemla, Marc Presset and Erwan Le Gall

Beilstein J. Org. Chem. **2024**, *20*, 2834–2839. doi:10.3762/bjoc.20.239

Experimental procedures, compound characterization data, and NMR spectra for all compounds

Table of contents

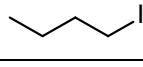
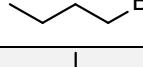
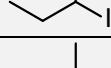
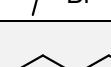
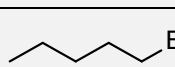
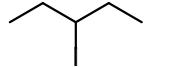
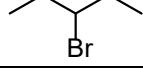
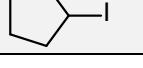
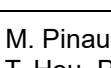
1. General information.....	S2
2. Prices/availability of aliphatic iodides vs bromides	S2
3. Formation and reactivity of organozinc reagents generated in THF or MeCN.....	S3
4. Organozinc reagents	S4
5. Mannich reactions	S5
6. Copies of NMR spectra	S10

1. General information

- All commercially available reagents, including solvents (tetrahydrofuran THF, 2-methyltetrahydrofuran = 2-MeTHF, cyclohexane = Cy, ethyl acetate = EA), were used as received.
- Room temperature means 18 – 25 °C.
- Analytical thin layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Visualization was effected using ultraviolet light ($\lambda = 254$ nm) and/or a aqueous solution of KMnO₄. Flash chromatography (FC) was performed on 40–63 μm silica gel with mixtures of solvents.
- High-resolution mass spectra were obtained at the ICOA of the Université of Orléans by electrospray ionization using a Q-TOF analyzer.
- NMR spectra were recorded on a 400 MHz spectrometer. ¹H NMR chemical shifts were referenced to the residual solvent signal; ¹³C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. Data are presented as follows: chemical shift δ (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant J (Hz), integration.
- dr was determined by NMR analysis of the crude reaction mixture.
- Compounds **5aaa**,¹ **5aba**,¹ **5fba**,² **5haa**,¹ **5hda**,¹ **5hag**,¹ **5hah**,¹ **5iaa**¹ and **5kaa**¹ have been previously described.

2. Prices/availability of aliphatic iodides vs bromides

Prices (France) for common aliphatic iodides and bromides, reported from the Sigma-Aldrich web site (<https://www.sigmaaldrich.com/FR/fr>).

Compound	Amount	Price	Quality	Stabilization
	100 g	51.00 €	99%	Copper
	100 g	28.00 €	99%	
	100 mL	76.30 €	For synthesis	
	100 mL	27.10 €	For synthesis	
	100 g	343.00 €	98%+	Copper
	100 g	38.40 €	98%	
	100 g	356.00 €	95%	Copper
	100 g	86.10 €	98%	
	100 g	71.30 €	98%	
	100 g	28.00 €	98%	
	Not available	-	-	
	25 g	183.00 €	95%	
	25 mL (~42 g)	444.00 €	97%	

¹ M. Pinaud, E. Le Gall, M. Presset, *J. Org. Chem.* **2022**, *87*, 4961–4964.

² T. Hou, P. Lu, P. Li, *Tetrahedron Lett.* **2016**, *57*, 2273–2276.

	25 mL	37.00 €	98%+	
	100 g	75.00 €	98%+	
	100 g	23.10 €	98%	
	100 g	249.00 €	98%	
	100 g	31.20 €	98%	
	50 g	52.80 €	98%	
	100 g	53.40 €	99%	
	Not available	-	-	
	25 g	92.80 €	97%	

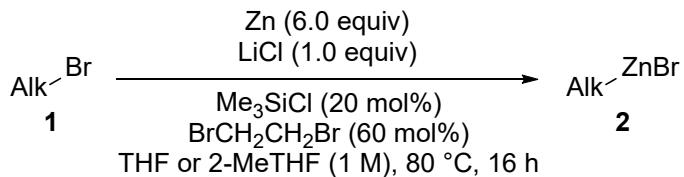
3. Formation and reactivity of organozinc reagents generated in THF or MeCN

Comparison of the preparation and reactivity in the Mannich reaction of organozinc compounds originating from primary alkyl bromides (reaction in THF described herein) and alkyl iodides (reaction in MeCN as described in JOC 2022).

Entry	Alkyl halide	Organozinc (iodolysis) yield	Mannich adduct	Yield
1		19%		NR
2		-		NR
3		62%		NR
4		99%		NR
5		60%		NR

6	<chem>CC(Cc1ccccc1)Br</chem>	68%	<chem>CC(Cc1ccccc1)C(Cc2ccccc2)N3CCOC3</chem>	56%
7	<chem>CC(Cc1ccccc1)Br</chem>	68%	<chem>CC(Cc1ccccc1)C(Cc2ccccc2O)N3CCOC3</chem>	68%
8	<chem>CC(COC)c(Cc1ccccc1)Br</chem>	76%	<chem>CC(COC)C(Cc2ccccc2)N3CCOC3</chem>	56%
9	<chem>CC(F)C(Cc1ccccc1)Br</chem>	61%	<chem>CC(F)C(Cc2ccccc2)N3CCOC3</chem>	41%
10	<chem>CC(=O)OC(Cc1ccccc1)Br</chem>	66%	<chem>CC(=O)OC(Cc2ccccc2O)N3CCOC3</chem>	59%

4. Organozinc reagents

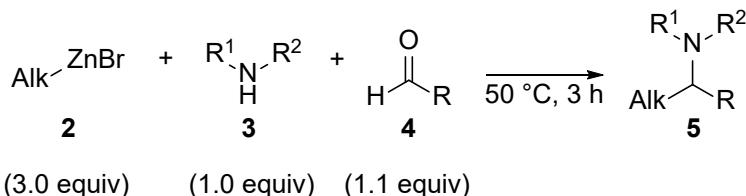


In air, a 30 mL reaction tube equipped with a stir bar was charged with zinc dust (3.92 g, 60 mmol, 6.0 equiv) and LiCl (0.42 g, 10 mmol, 1.0 equiv) and purged with Ar. THF or 2-MeTHF (10 mL, C = 0.5 M) was added and the resulting suspension was treated with chlorotrimethylsilane (0.25 mL, 2 mmol, 20 mol %) and stirred at room temperature for 2 min. 1,2-dibromoethane (0.52 mL, 6 mmol, 60 mol %) was added dropwise and the resulting suspension was at room temperature for 5 min. The alkyl bromide 1 (10 mmol, 1.0 equiv) was added and the reaction was stirred at 80 °C for 16 h. After cooling to room temperature, the solution was centrifuged at 3500 rpm for 15 min. The concentration of the solution of organozinc reagent was determined by iodometric titration of the resulting supernatant.

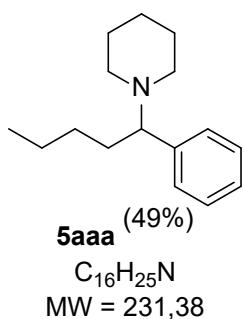
Organozinc reagent	<chem>CCCCZnBr</chem>	<chem>CC(Cc1ccccc1)C(Cc2ccccc2)ZnBr</chem>	<chem>CC(COC)C(Cc2ccccc2)ZnBr</chem>	<chem>CC(C#N)C(Cc2ccccc2)ZnBr</chem>
Yield in THF (%)	71	-	76	63
Yield in 2-MeTHF (%)	66	68	-	77
Organozinc reagent	<chem>CC(F)C(Cc1ccccc1)ZnBr</chem>	<chem>CC(=O)OC(Cc1ccccc1)ZnBr</chem>	<chem>CC(=O)OC(Cc2ccccc2)ZnBr</chem>	
Yield in THF (%)	-	-	-	
Yield in 2-MeTHF (%)	61	37	66	

Organozinc reagent				
Yield in THF (%)	55	69	-	14
Yield in 2-MeTHF (%)	-		56	-

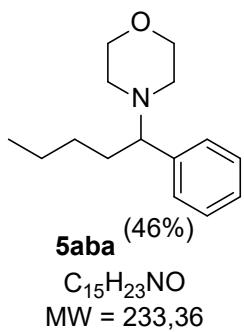
5. Mannich reactions



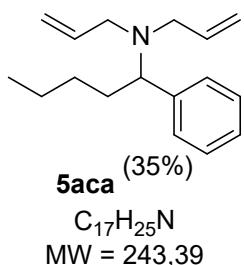
General procedure (GP): A 30 mL reaction tube equipped with a stir bar and filled with an Ar atmosphere was charged with aldehyde (1.1 equiv) and amine (1.0 equiv). A solution of the organozinc reagent (3.0 equiv) was added and the reaction was stirred at 50 °C for 3 h. Then, the reaction mixture was cooled down to room temperature and poured into sat aq NH₄Cl. The resulting solution was extracted twice with EtOAc and the combined organic layers were washed brine, dried over anhydrous Na₂SO₄ and evaporated. The crude product was purified by FC to afford the desired product.



Compound **5aaa**:¹ Following the **GP** performed with piperidine (73 µL, 0.73 mmol, 1.0 equiv), benzaldehyde (82 µL, 0.81 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (3.5 mL, 0.63 M, 2.20 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/1 (100 mL), 8/2 (150 mL)] as a pale yellow oil (83 mg, 49%).



Compound **5aba**:¹ Following the **GP** performed with morpholine (67 µL, 0.77 mmol, 1.0 equiv), benzaldehyde (86 µL, 0.85 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.66 M, 2.31 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/1 (150 mL), 8/2 (100 mL)] as a colorless oil (82 mg, 46%).



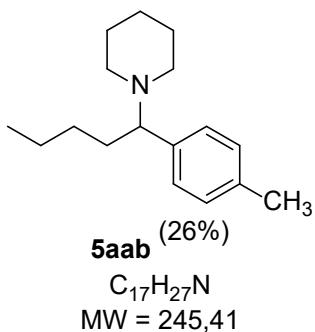
Compound **5aca**: Following the **GP** performed with diallylamine (75 µL, 0.61 mmol, 1.0 equiv), benzaldehyde (68 µL, 0.67 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (3 mL, 0.61 M, 1.82 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (150 mL), 9/1 (100 mL)] as a colorless oil (52 mg, 35%).

R_f(SiO₂, Cy/EA : 9/1): 0.63.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₇H₂₆N: 244.2060. Found: 244.2063.

¹H NMR (400 MHz, CDCl₃): δ 7.41 – 7.37 (m, 2H), 7.33 – 7.29 (m, 3H), 5.95 – 5.85 (m, 2H), 5.25 – 5.17 (m, 4H), 3.78 (dd, *J* = 8.6, 6.1 Hz, 1H), 3.35 (dd, *J* = 14.4, 4.9 Hz, 2H), 2.85 (dd, *J* = 14.4, 7.5 Hz, 2H), 2.01 – 1.93 (m, 1H), 1.86 – 1.78 (m, 1H), 1.40 – 1.30 (m, 3H), 1.24 – 1.16 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 140.5 (C), 137.2 (2 CH), 128.9 (2 CH), 128.0 (2 CH), 126.9 (CH), 116.8 (2 CH₂), 63.5 (CH), 52.8 (2 CH₂), 32.1 (CH₂), 29.1 (CH₂), 22.9 (CH₂), 14.2 (CH₃).



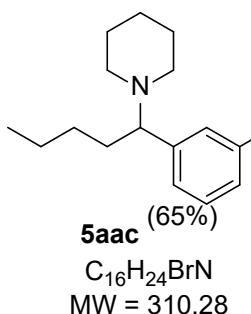
Compound 5aab: Following the **GP** performed with piperidine (60 μL, 0.61 mmol, 1.0 equiv), *p*-tolualdehyde (79 μL, 0.67 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (3 mL, 0.61 M, 1.82 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/1 (150 mL), 8/2 (100 mL)] as a colorless oil (39 mg, 26%).

R_f (SiO₂, Cy/EA : 9/1): 0.08.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₇H₂₈N: 246.2216. Found: 246.2220.

¹H NMR (400 MHz, CDCl₃): δ 7.13 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.29 (dd, *J* = 9.5, 5.0 Hz, 1H), 2.35 (br s, 7H), 1.91 – 1.75 (m, 2H), 1.60 – 1.48 (m, 4H), 1.39 – 1.22 (m, 4H), 1.15 – 1.00 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 134.0 (C), 136.3 (C), 128.96 (2 CH), 128.6 (2 CH), 70.4 (CH), 51.3 (2 CH₂), 32.6 (CH₂), 29.1 (CH₂), 26.5 (2 CH₂), 24.8 (CH₂), 23.0 (CH₂), 21.2 (CH₃), 14.2 (CH₃).



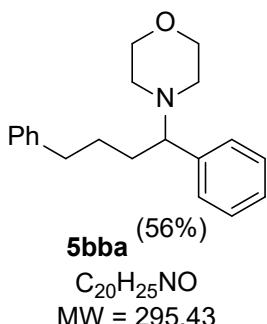
Compound 5aac: Following the **GP** performed with piperidine (73 μL, 0.73 mmol, 1.0 equiv), 3-bromobenzaldehyde (94 μL, 0.81 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (3.5 mL, 0.63 M, 2.20 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/1 (150 mL), 8/2 (100 mL)] as a yellow oil (149 mg, 65%).

R_f (SiO₂, Cy/EA : 8/2): 0.51.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₆H₂₅BrN: 310.1165. Found: 310.1163.

¹H NMR (400 MHz, CDCl₃): δ 7.42 – 7.40 (m, 2H), 7.23 – 7.16 (m, 2H), 3.29 (dd, *J* = 9.4, 4.9 Hz, 1H), 2.36 (br s, 4H), 1.92 – 1.85 (m, 1H), 1.82 – 1.74 (m, 1H), 1.59 – 1.55 (m, 4H), 1.41 – 1.28 (m, 4H), 1.21 – 1.05 (m, 2H), 0.87 (t, *J* = 7.3 Hz, 3H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 143.1 (C), 131.6 (CH), 129.9 (CH), 129.4 (CH), 127.4 (CH), 122.2 (C), 70.2 (CH), 51.2 (2 CH₂), 35.3 (CH₂), 28.8 (CH₂), 26.4 (2 CH₂), 24.7 (CH₂), 22.9 (CH₂), 14.1 (CH₃).



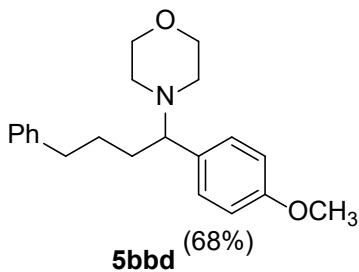
Compound 5bba: Following the **GP** performed with morpholine (69 μL, 0.79 mmol, 1.0 equiv), benzaldehyde (89 μL, 0.87 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.68 M, 2.38 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/1 (100 mL), 8/2 (150 mL)] as a colorless oil (132 mg, 56%).

R_f (SiO₂, Cy/EA : 8/2): 0.31.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₂₀H₂₆NO: 296.2009. Found: 296.2005.

¹H NMR (400 MHz, CDCl₃): δ 7.44 – 7.40 (m, 2H), 7.37 – 7.24 (m, 6H), 7.20 (d, *J* = 8.0 Hz, 2H), 3.77 (t, *J* = 4.6 Hz, 4H), 3.34 (dd, *J* = 9.2, 4.9 Hz, 1H), 2.66 (dt, *J* = 14.6, 7.3 Hz, 2H), 2.54 – 2.43 (m, 4H), 2.10 – 1.97 (m, 1H), 1.89 – 1.80 (m, 1H), 1.67 – 1.47 (m, 2H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 142.3 (C), 140.4 (C), 128.6 (3 CH), 128.4 (2 CH), 128.3 (CH), 128.1 (2 CH), 127.2 (CH), 125.78 (CH), 70.5 (CH), 67.3 (2 CH₂), 51.1 (2 CH₂), 35.9 (CH₂), 32.0 (CH₂), 27.9 (CH₂).



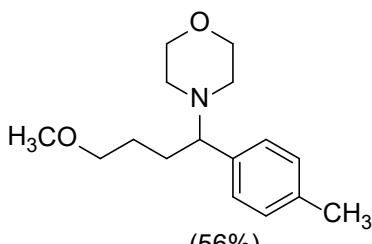
C₂₁H₂₇NO₂
MW = 325,45

R_f (SiO₂, Cy/EA : 8/2): 0.15.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₂₁H₂₈NO₂: 326.2115. Found: 326.2117.

¹H NMR (400 MHz, CDCl₃): δ 7.40 – 7.25 (m, 4H), 7.24 – 7.19 (m, 3H), 6.96 (d, J = 8.6 Hz, 2H), 3.88 (s, 3H), 3.77 – 3.71 (m, 4H), 3.29 (dd, J = 9.4, 4.7 Hz, 1H), 2.82 – 2.78 (m, 1H), 2.62 – 2.60 (m, 2H), 2.52 – 2.41 (m, 3H), 2.08 – 1.94 (m, 2H), 1.87 – 1.77 (m, 1H), 1.65 – 1.46 (m, 1H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 158.6 (C), 146.3 (C), 132.2 (C), 129.5 (2 CH), 128.3 (2 CH), 128.2 (2 CH), 125.6 (CH), 113.4 (2 CH), 69.7 (CH), 67.1 (2 CH₂), 55.1 (CH₃), 51.0 (2 CH₂), 35.8 (CH₂), 31.9 (CH₂), 18.0 (CH₂).



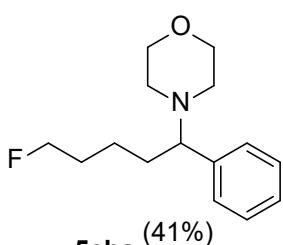
C₁₆H₂₅NO₂
MW = 263,38

R_f (SiO₂, Cy/EA : 6/4): 0.24.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₆H₂₆NO₂: 264.1958. Found: 264.1957.

¹H NMR (400 MHz, CDCl₃): δ 7.15 (br s, 4H), 3.70 (t, J = 4.5 Hz, 4H), 3.33 (t, J = 6.5 Hz, 2H), 3.30 (s, 3H), 3.24 (dd, J = 9.2, 4.9 Hz, 1H), 2.50 – 2.40 (m, 4H), 2.36 (s, 3H), 2.07 – 1.96 (m, 1H), 1.81 – 1.71 (m, 1H), 1.52 – 1.34 (m, 2H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 137.1 (C), 136.6 (C), 128.8 (2 CH), 128.5 (2 CH), 77.7 (CH₂), 70.0 (CH), 67.2 (2 CH₂), 58.4 (CH₃), 51.0 (2 CH₂), 29.0 (CH₂), 26.4 (CH₂), 21.0 (CH₃).



C₁₅H₂₂FNO
MW = 251,35

Compound 5eba: Following the **GP** performed with morpholine (62 µL, 0.71 mmol, 1.0 equiv), benzaldehyde (80 µL, 0.78 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.61 M, 2.13 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 8/2 (150 mL), 6/4 (100 mL)] as a pale yellow oil (74 mg, 41%).

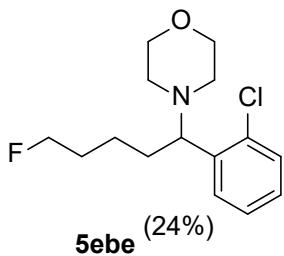
R_f (SiO₂, Cy/EA : 8/2): 0.20.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₅H₂₃FNO: 252.1758. Found: 252.1761.

¹H NMR (400 MHz, CDCl₃): δ 7.39 – 7.35 (m, 2H), 7.32 – 7.27 (m, 3H), 4.46 (t, J = 6.2 Hz, 1H), 4.35 (t, J = 6.2 Hz, 1H), 3.73 (t, J = 4.7 Hz, 4H), 3.29 (dd, J = 9.2, 4.7 Hz, 1H), 2.52 – 2.40 (m, 4H), 2.04 – 1.96 (m, 1H), 1.85 – 1.63 (m, 3H), 1.38 – 1.17 (m, 2H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 140.2 (C), 128.7 (2 CH), 128.2 (2 CH), 127.3 (CH), 84.0 (d, ¹J_{C-F} = 164.2 Hz, CH₂), 70.5 (CH), 67.2 (2 CH₂), 51.1 (2 CH₂), 32.1 (CH₂), 30.5 (d, ²J_{C-F} = 18.6 Hz, CH₂), 22.0 (d, ³J_{C-F} = 4.8 Hz, CH₂).

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ –112.1 (F).



C₁₅H₂₁ClFNO
MW = 285,79

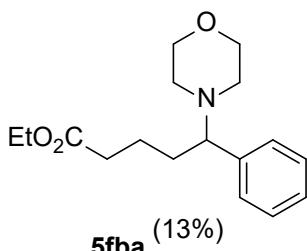
R_f (SiO₂, Cy/EA : 8/2): 0.15.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₅H₂₂ClFNO: 286.1368. Found: 286.1369.

¹H NMR (400 MHz, CDCl₃): δ 7.43 (dd, J = 7.9, 1.8 Hz, 1H), 7.35 (dd, J = 7.9, 1.4 Hz, 1H), 7.25 (td, J = 7.6, 1.4 Hz, 1H), 7.16 (td, J = 7.6, 1.8 Hz, 1H), 4.41 (t, J = 6.1 Hz, 1H), 4.30 (t, J = 6.1 Hz, 1H), 3.95 (dd, J = 8.9, 4.6 Hz, 1H), 3.66 (t, J = 4.6 Hz, 4H), 2.55 – 2.52 (m, 2H), 2.37 (dt, J = 11.0, 4.7 Hz, 2H), 1.97 – 1.88 (m, 1H), 1.76 – 1.56 (m, 3H), 1.33 – 1.14 (m, 2H).

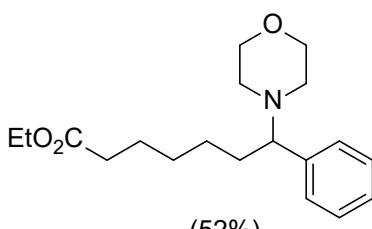
¹³C{¹H} NMR (100 MHz, CDCl₃): δ 138.6 (C), 135.0 (C), 129.6 (CH), 129.2 (CH), 128.1 (CH), 126.8 (CH), 84.0 (d, ¹J_{C-F} = 164.3 Hz, CH₂), 67.3 (2 CH₂), 64.5 (CH), 51.1 (2 CH₂), 31.8 (CH₂), 30.6 (d, ²J_{C-F} = 19.8 Hz, CH₂), 21.1 (d, ³J_{C-F} = 4.8 Hz, CH₂).

¹⁹F{¹H} NMR (376 MHz, CDCl₃): δ –112.1 (F).



C₁₇H₂₅NO₃
MW = 291,39

Compound **5fba**:² Following the **GP** performed with morpholine (76 µL, 0.86 mmol, 1.0 equiv), benzaldehyde (97 µL, 0.95 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (7.0 mL, 0.37 M, 2.59 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 8/2 (100 mL), 6/4 (150 mL)] as a pale yellow oil (33 mg, 13%).



C₁₉H₂₉NO₃
MW = 319,45

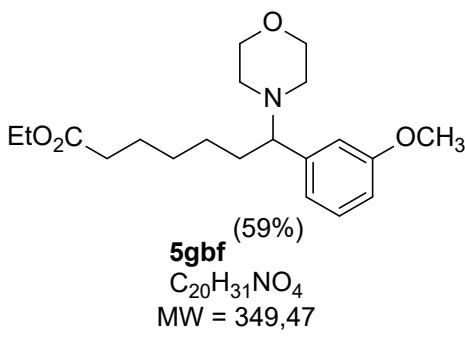
Compound **5gba**: Following the **GP** performed with morpholine (67 µL, 0.77 mmol, 1.0 equiv), benzaldehyde (86 µL, 0.85 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.66 M, 2.31 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 8/2 (100 mL), 6/4 (150 mL)] as a pale yellow oil (128 mg, 52%).

R_f (SiO₂, Cy/EA : 6/4): 0.40.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₉H₃₀NO₃: 320.2220. Found: 320.2223.

¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.32 (m, 2H), 7.30 – 7.24 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 3.71 (t, J = 4.6 Hz, 4H), 3.26 (dd, J = 9.5, 4.6 Hz, 1H), 2.51 – 2.38 (m, 4H), 2.24 (t, J = 7.5 Hz, 2H), 1.98 – 1.89 (m, 1H), 1.79 – 1.67 (m, 1H), 1.61 – 1.53 (m, 2H), 1.44 – 1.08 (m, 7H).

¹³C{¹H} NMR (100 MHz, CDCl₃): δ 173.8 (C), 140.2 (C), 128.7 (2 CH), 128.2 (2 CH), 127.2 (CH), 70.6 (CH), 67.1 (2 CH₂), 60.2 (CH₂), 51.1 (2 CH₂), 34.3 (CH₂), 32.1 (CH₂), 29.2 (CH₂), 25.9 (CH₂), 24.8 (CH₂), 14.3 (CH₃).



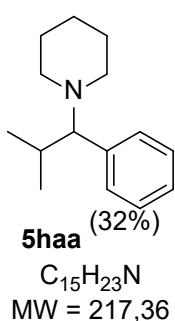
Compound 5gbf: Following the **GP** performed with morpholine (67 μ L, 0.77 mmol, 1.0 equiv), 3-anisaldehyde (103 μ L, 0.85 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.66 M, 2.31 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 8/2 (150 mL), 6/4 (100 mL)] as a pale yellow oil (158 mg, 59%).

R_f (SiO₂, Cy/EA : 6/4): 0.32.

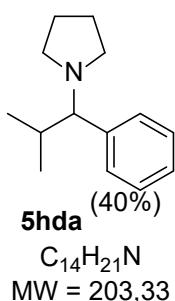
HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₂₀H₃₂NO₄: 350.2326. Found: 350.2328.

¹H NMR (400 MHz, CDCl₃): δ 7.20 – 7.16 (m, 1H), 6.78 – 6.75 (m, 3H), 4.06 (q, J = 7.1 Hz, 2H), 3.77 (s, 3H), 3.63 (t, J = 4.5 Hz, 4H), 3.13 (dd, J = 9.4, 4.6 Hz, 1H), 2.46 – 2.31 (m, 4H), 2.18 (t, J = 7.5 Hz, 2H), 1.88 – 1.80 (m, 1H), 1.68 – 1.60 (m, 1H), 1.54 – 1.47 (m, 2H), 1.38 – 1.02 (m, 7H).

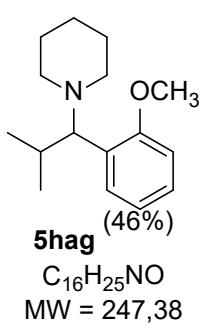
¹³C{¹H} NMR (100 MHz, CDCl₃): δ 173.7 (C), 159.5 (C), 142.2 (C), 129.0 (CH), 121.1 (CH), 114.4 (CH), 112.1 (CH), 70.6 (CH), 67.2 (2 CH₂), 60.2 (CH₂), 55.2 (CH₃), 51.2 (2 CH₂), 34.3 (CH₂), 32.2 (CH₂), 29.2 (CH₂), 25.9 (CH₂), 24.8 (CH₂), 14.3 (CH₃).



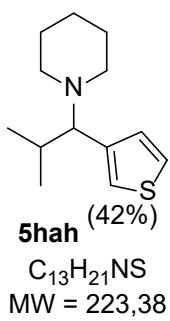
Compound 5haa:¹ Following the **GP** performed with piperidine (48 μ L, 0.48 mmol, 1.0 equiv), benzaldehyde (54 μ L, 0.53 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (2.5 mL, 0.58 M, 1.45 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (150 mL), 9/1 (100 mL)] as a pale yellow oil (33 mg, 32%).



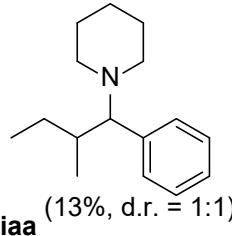
Compound 5hda:¹ Following the **GP** performed with pyrrolidine (51 μ L, 0.61 mmol, 1.0 equiv), benzaldehyde (68 μ L, 0.67 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (3.5 mL, 0.52 M, 1.82 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (100 mL), 9/1 (150 mL)] as a colorless oil (50 mg, 40%).



Compound 5hag:¹ Following the **GP** performed with piperidine (48 μ L, 0.48 mmol, 1.0 equiv), 2-anisaldehyde (64 μ L, 0.53 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (2.5 mL, 0.58 M, 1.45 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (100 mL), 9/1 (150 mL)] as a colorless oil (57 mg, 46%).

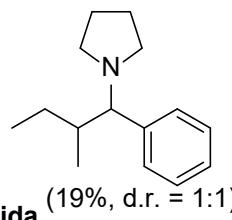


Compound 5hah:¹ Following the **GP** performed with piperidine (48 μ L, 0.48 mmol, 1.0 equiv), 3-thiophenecarboxaldehyde (47 μ L, 0.53 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (2.5 mL, 0.58 M, 1.45 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (150 mL), 9/1 (100 mL)] as a colorless oil (55 mg, 42%).



C₁₆H₂₅N
MW = 231,38

Compound **5iaa**:¹ Following the **GP** performed with piperidine (46 µL, 0.46 mmol, 1.0 equiv), benzaldehyde (52 µL, 0.51 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (2.0 mL, 0.69 M, 1.38 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (150 mL), 9/1 (100 mL)] as a colorless oil (14 mg, 13%, d.r. = 1:1).

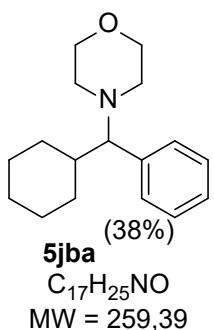


C₁₅H₂₃N
MW = 217,36

Compound **5ida**: Following the **GP** performed with pyrrolidine (39 µL, 0.46 mmol, 1.0 equiv), benzaldehyde (52 µL, 0.51 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (2.0 mL, 0.69 M, 1.38 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (150 mL), 9/1 (100 mL)] as a colorless oil (19 mg, 19%, d.r. = 1:1).

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₅H₂₄N: 218.1903. Found: 218.1904.

¹H NMR (400 MHz, CDCl₃): δ 7.34 – 7.28 (m, 10H), 3.20 (d, J = 4.8 Hz, 1H), 3.14 (d, J = 5.4 Hz, 1H), 2.56 – 2.48 (m, 8H), 2.03 – 1.85 (m, 4H), 1.82 – 1.76 (m, 8H), 1.43 – 1.31 (m, 2H), 0.97 – 0.84 (m, 12H).
¹³C{¹H} NMR (100 MHz, CDCl₃): δ 139.9 (2 C), 129.5 (2 CH), 129.5 (2 CH), 127.5 (4 CH), 126.8 (CH), 126.8 (CH), 75.7 (CH), 74.8 (CH), 52.6 (2 CH₂), 52.1 (2 CH₂), 37.8 (2 CH), 27.6 (CH₂), 23.3 (2 CH₂), 23.3 (2 CH₂), 23.2 (CH₂), 17.1 (CH₃), 13.5 (CH₃), 12.3 (CH₃), 12.1 (CH₃).



C₁₇H₂₅NO
MW = 259,39

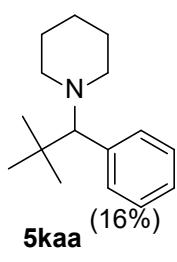
Compound **5jba**: Following the **GP** performed with morpholine (57 µL, 0.65 mmol, 1.0 equiv), benzaldehyde (73 µL, 0.72 mmol, 1.1 equiv) and a solution of alkylzinc bromide in 2-MeTHF (3.5 mL, 0.56 M, 1.96 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9/0 (150 mL), 8/2 (100 mL)] as a pale yellow oil (65 mg, 38%).

R_f (SiO₂, Cy/EA : 8/2): 0.64.

HRMS (ESI+): m/z [M+H]⁺ Calcd. for C₁₇H₂₆NO: 260.2009. Found: 260.2011.

¹H NMR (400 MHz, CDCl₃): δ 7.38 – 7.30 (m, 3H), 7.20 (d, J = 6.8 Hz, 2H), 3.73 (t, J = 5.7 Hz, 4H), 3.14 (d, J = 8.1 Hz, 1H), 2.45 – 2.37 (m, 4H), 2.03 – 1.93 (m, 2H), 1.70 (td, J = 44.7, 42.2, 13.3 Hz, 4H), 1.37 – 1.11 (m, 3H), 0.87 (dq, J = 25.6, 12.8 Hz, 2H).

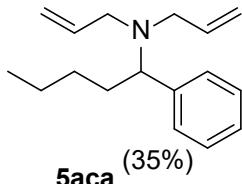
¹³C{¹H} NMR (100 MHz, CDCl₃): δ 137.9 (C), 129.4 (2 CH), 127.7 (2 CH), 126.9 (CH), 75.6 (CH), 67.5 (2 CH₂), 50.6 (2 CH₂), 37.7 (CH), 31.3 (CH₂), 29.1 (CH₂), 26.9 (CH₂), 26.6 (CH₂), 26.4 (CH₂).



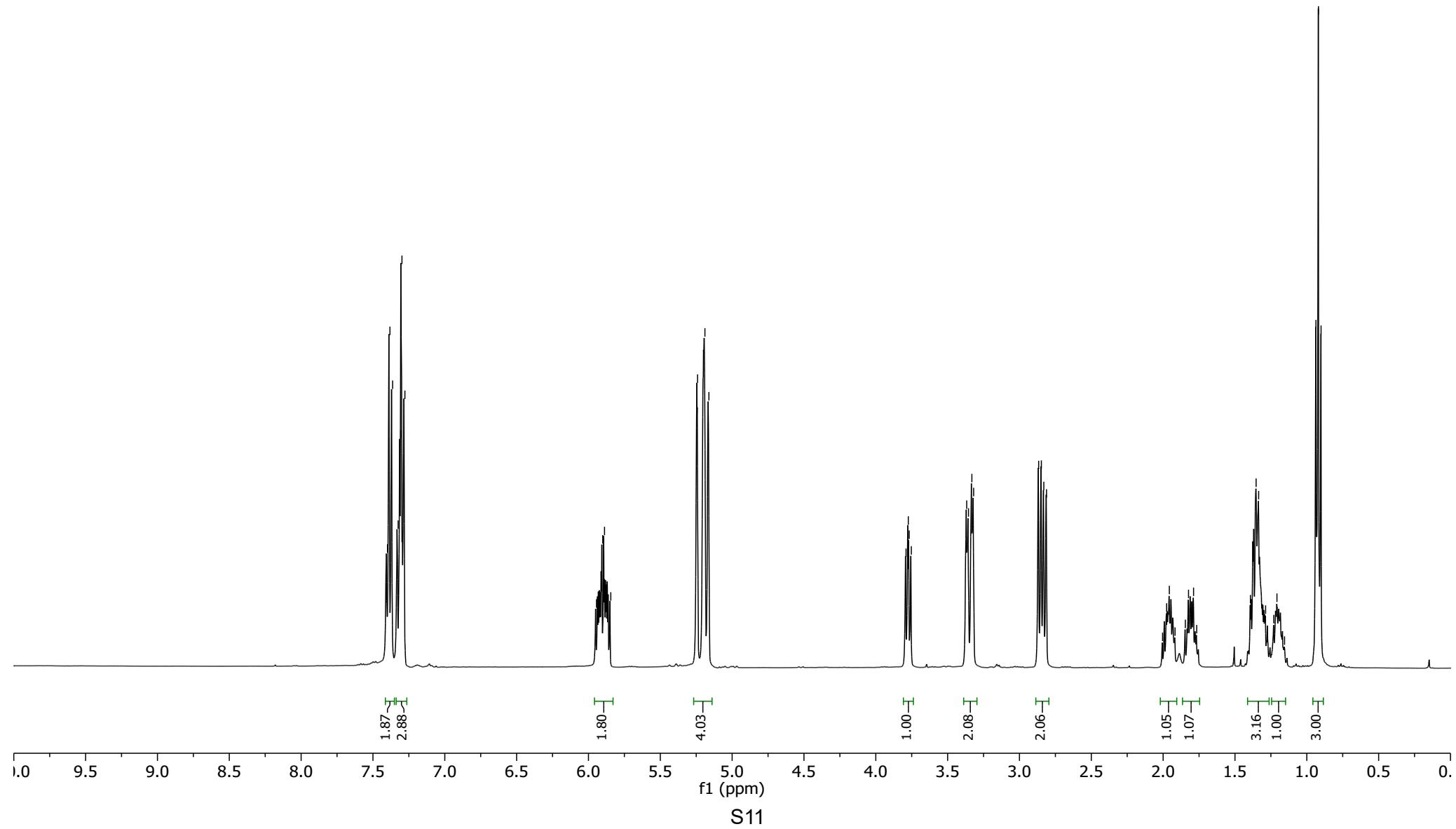
C₁₆H₂₅N
MW = 231,38

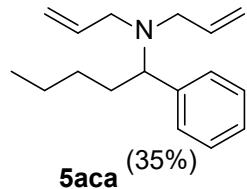
Compound **5kaa**:¹ Following the **GP** performed with piperidine (32 µL, 0.33 mmol, 1.0 equiv), benzaldehyde (37 µL, 0.36 mmol, 1.1 equiv) and a solution of alkylzinc bromide in THF (7.0 mL, 0.14 M, 0.98 mmol, 3.0 equiv), the desired product was obtained after purification by FC [V(SiO₂) = 25 mL, Cy/EA : 9.5/0.5 (100 mL), 9/1 (150 mL)] as a pale yellow oil (12 mg, 16%).

6. Copies of NMR spectra



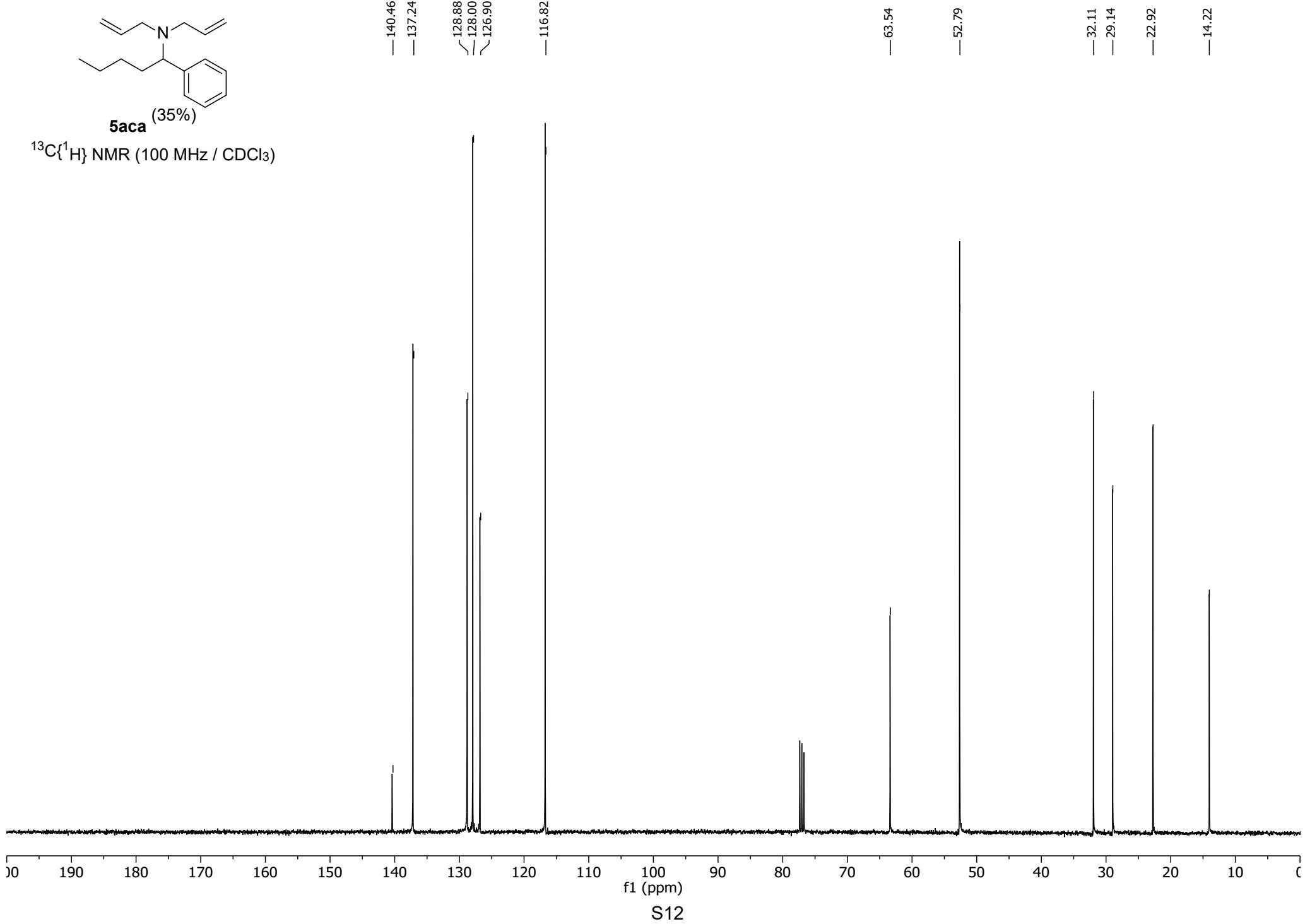
¹H NMR (400 MHz / CDCl₃)

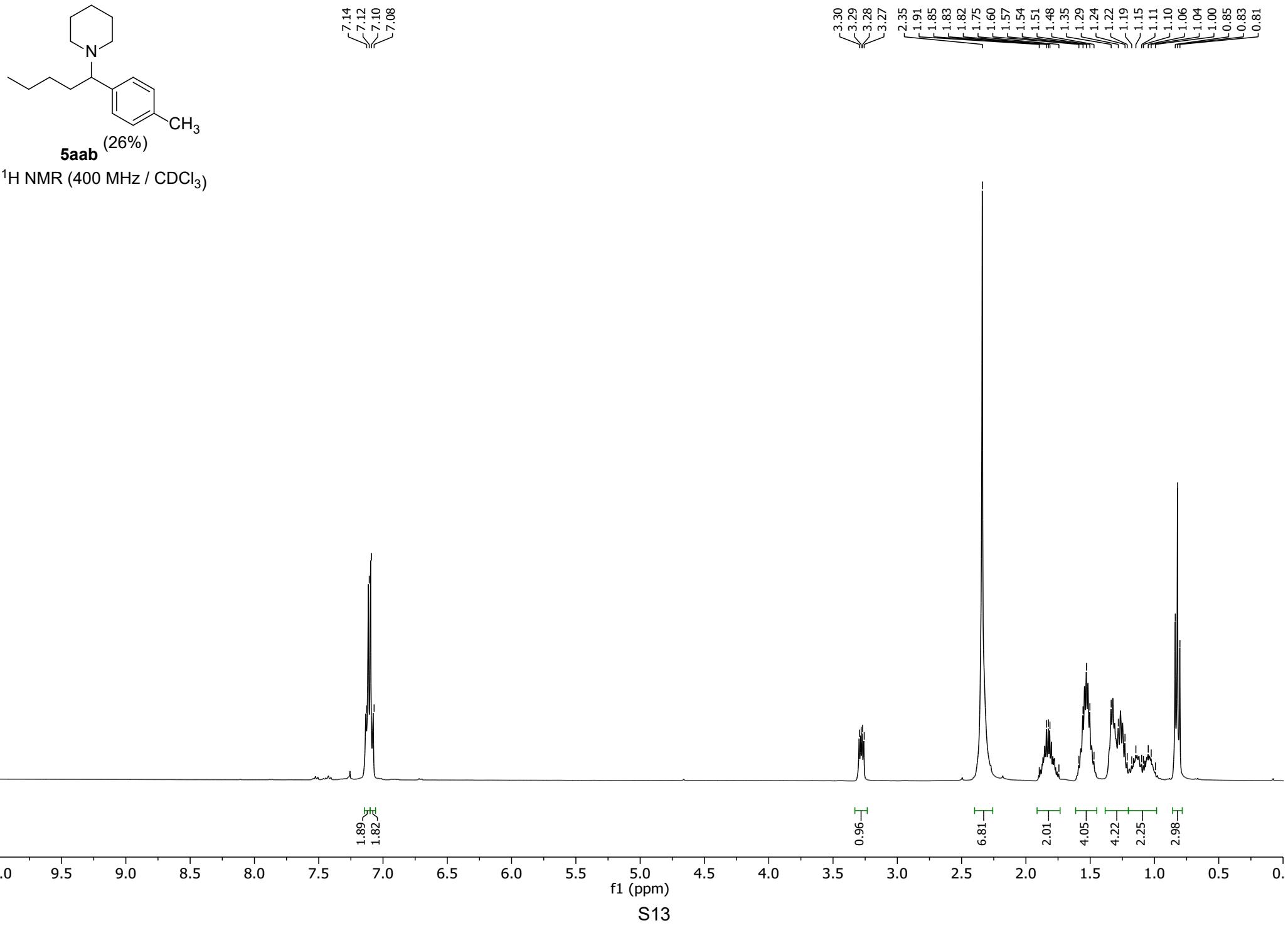


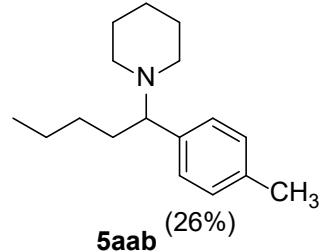


5aca (35%)

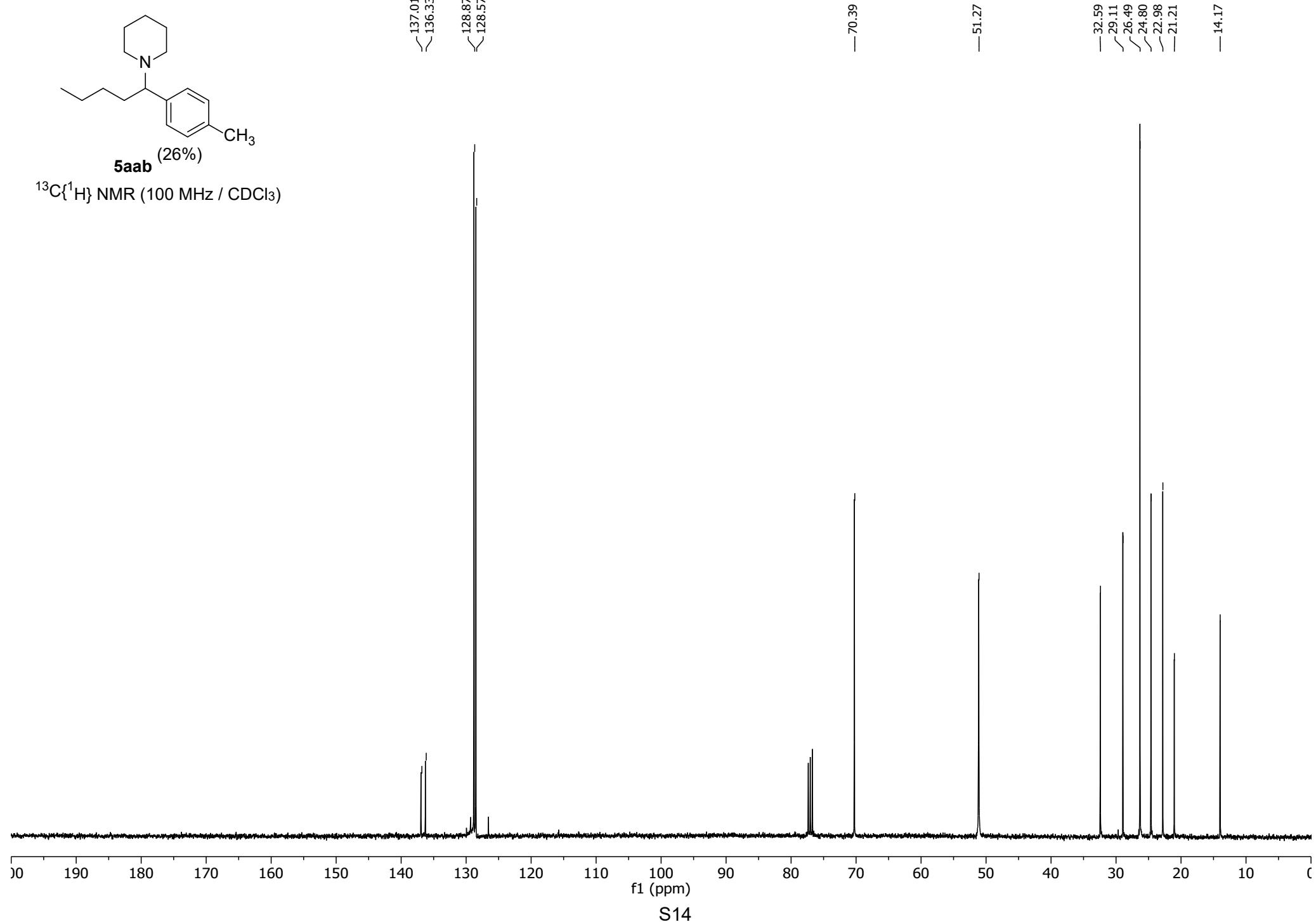
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

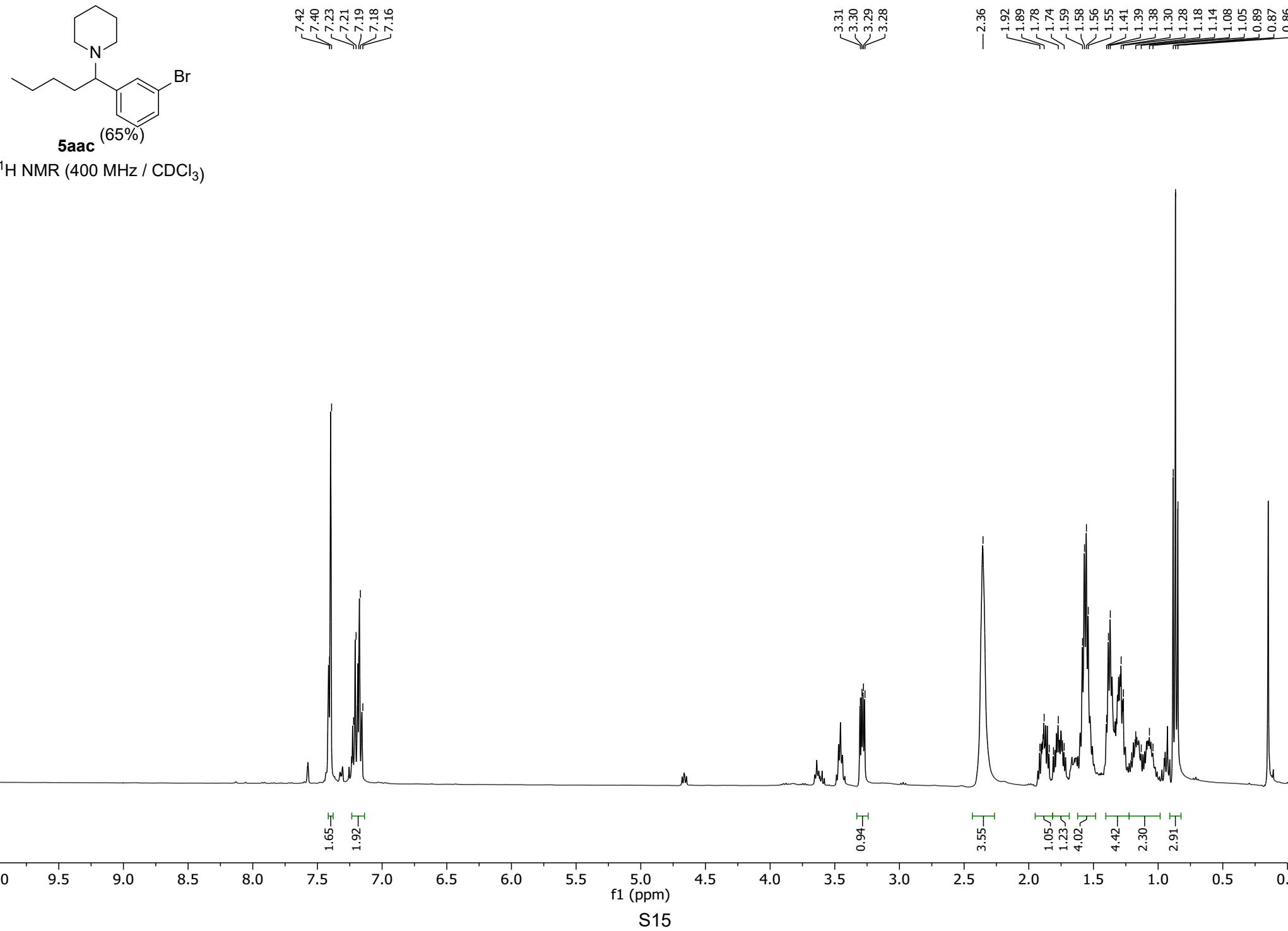


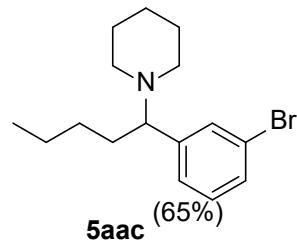




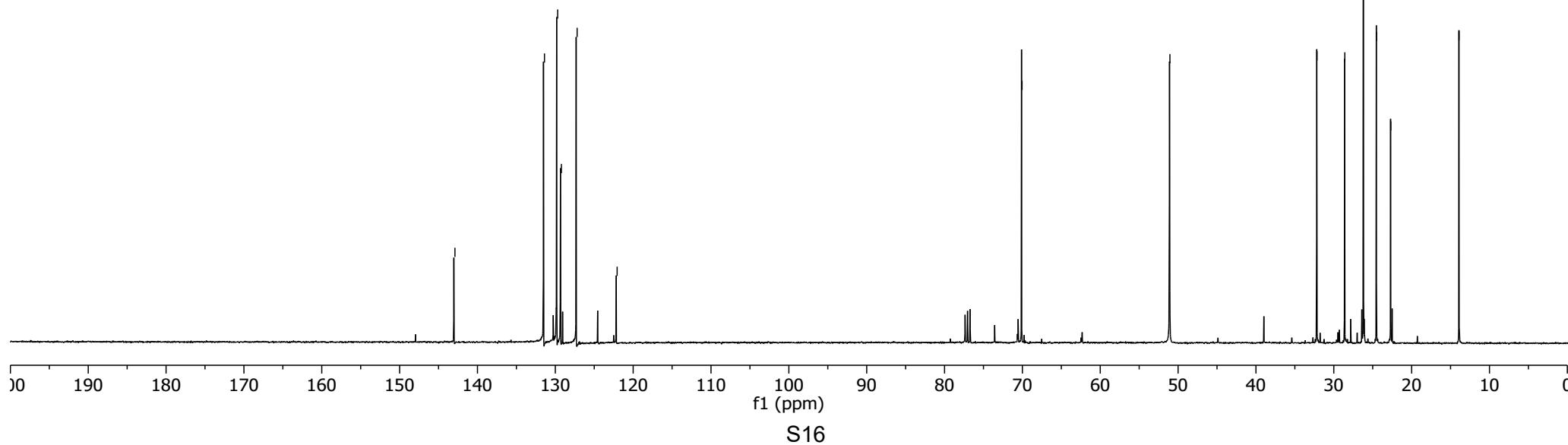
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

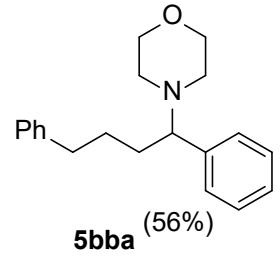




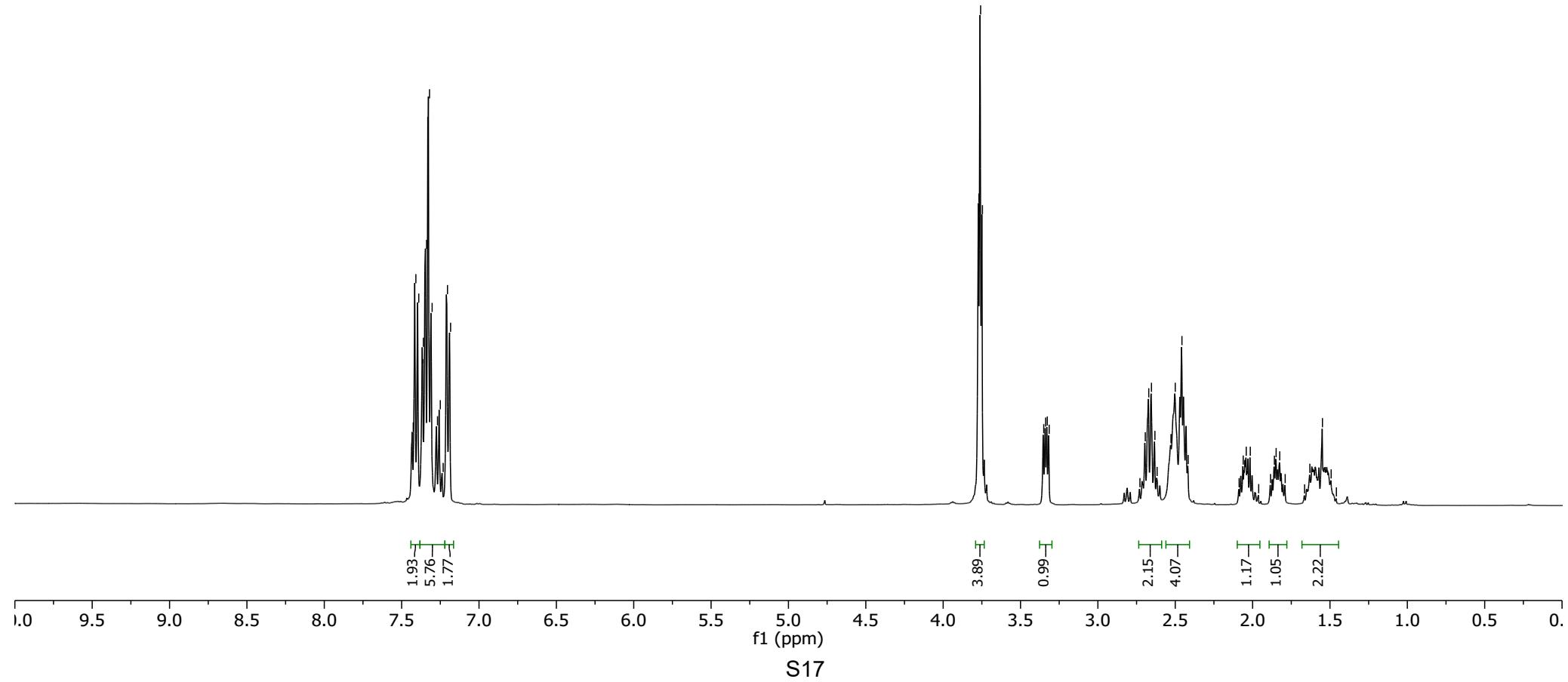


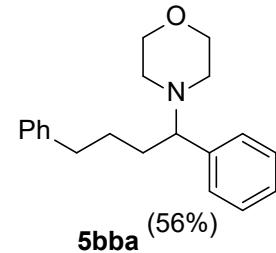
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)



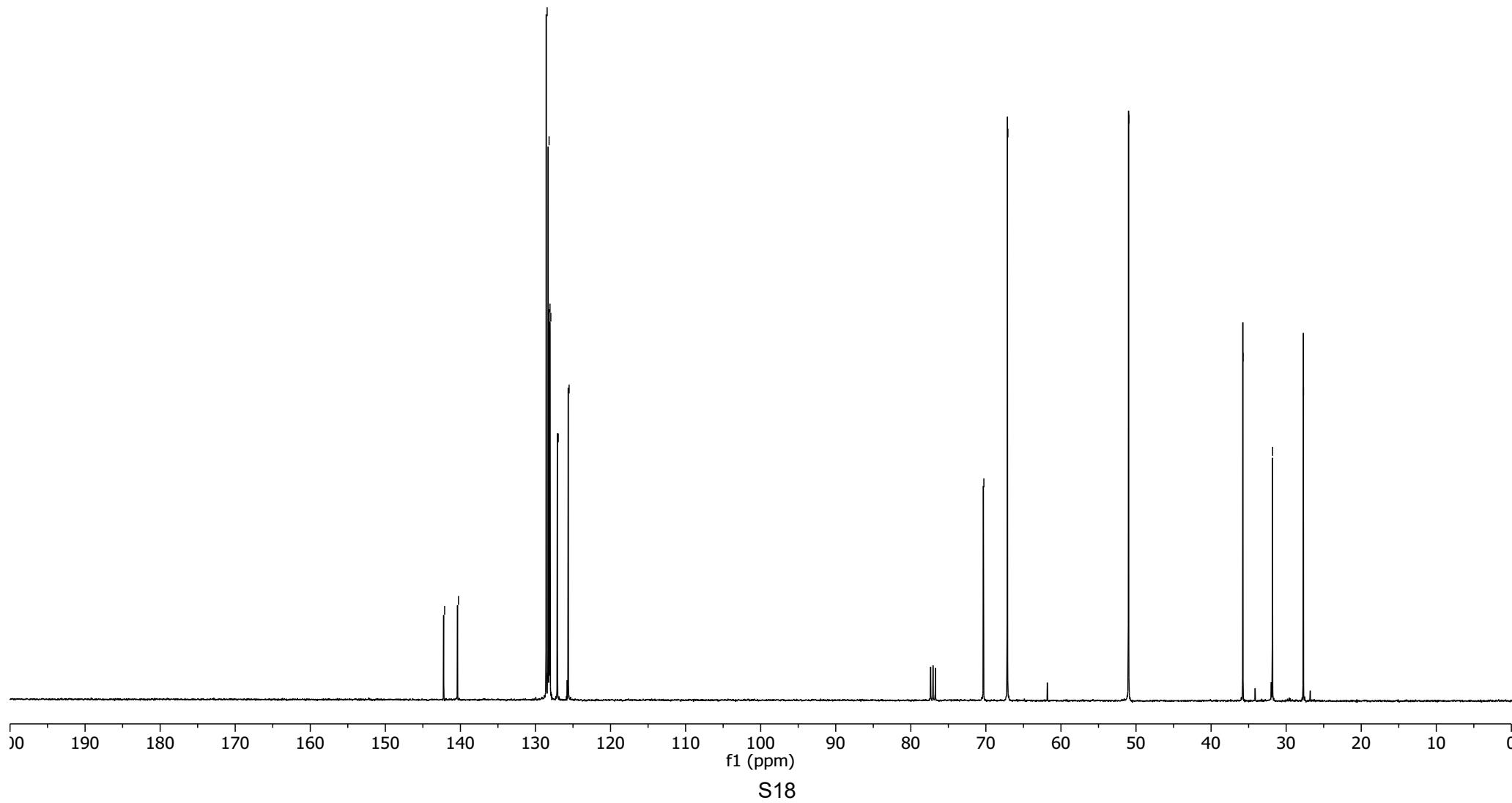


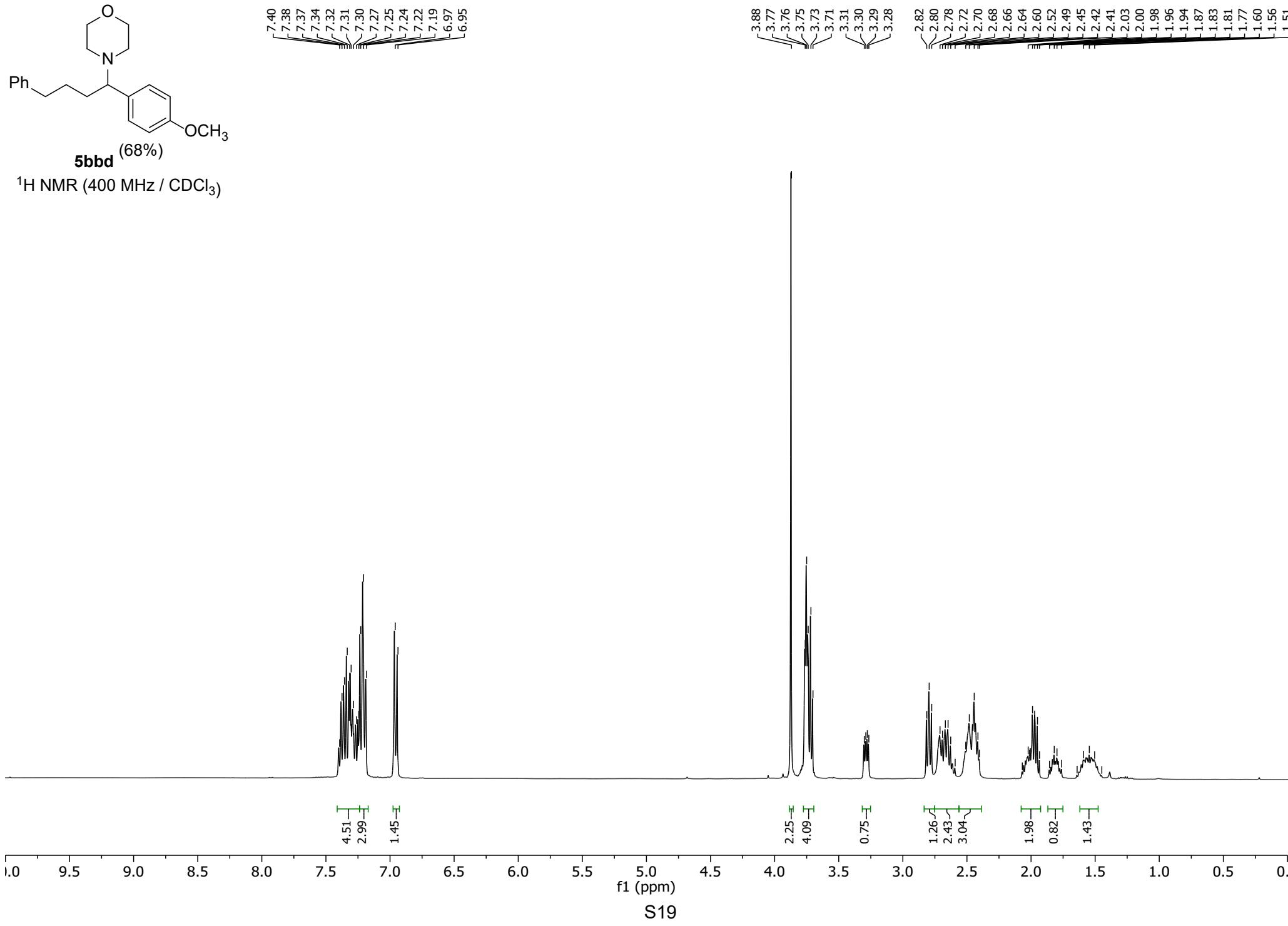
¹H NMR (400 MHz / CDCl₃)

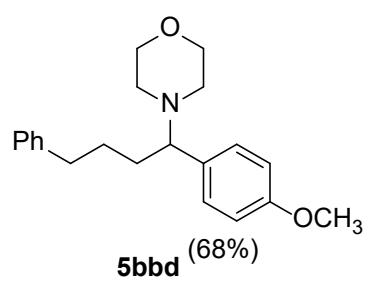




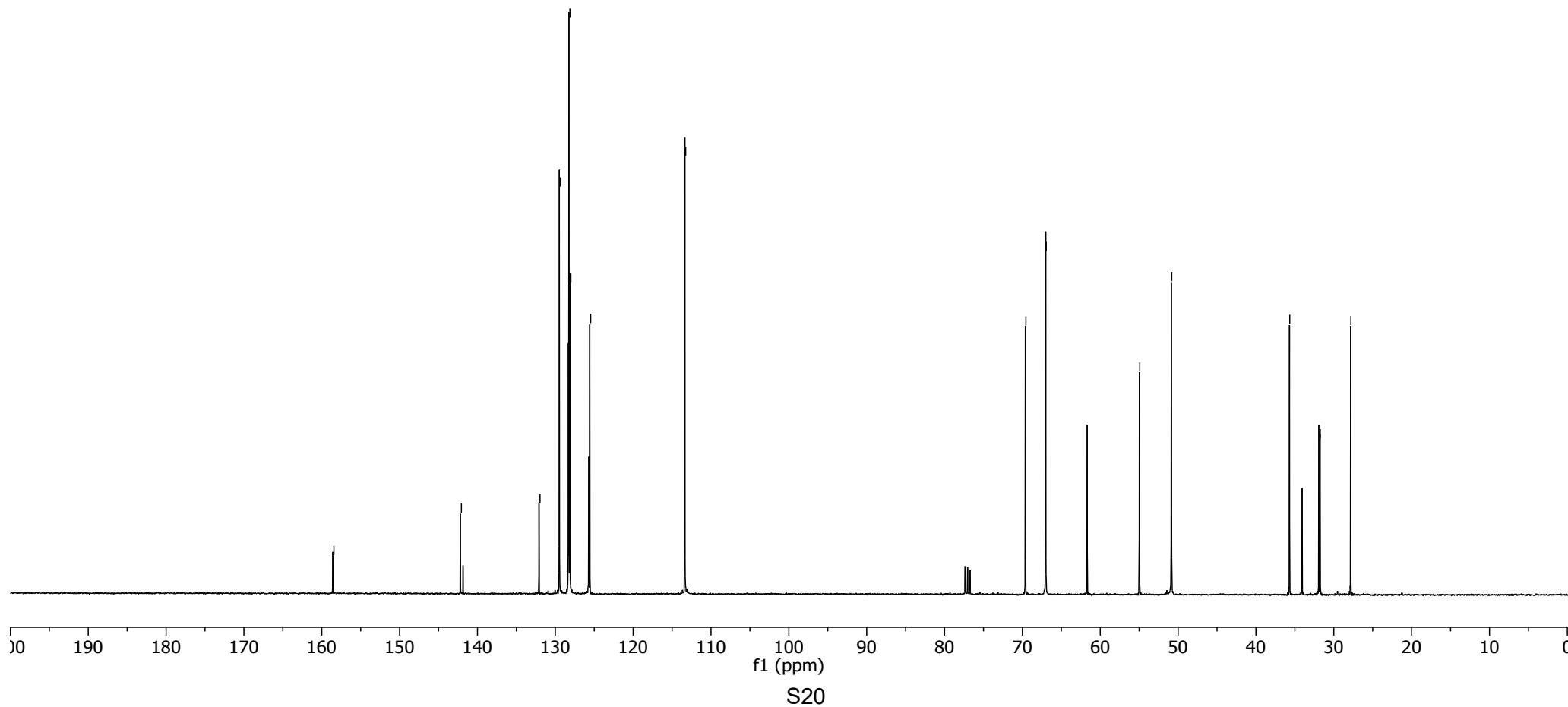
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

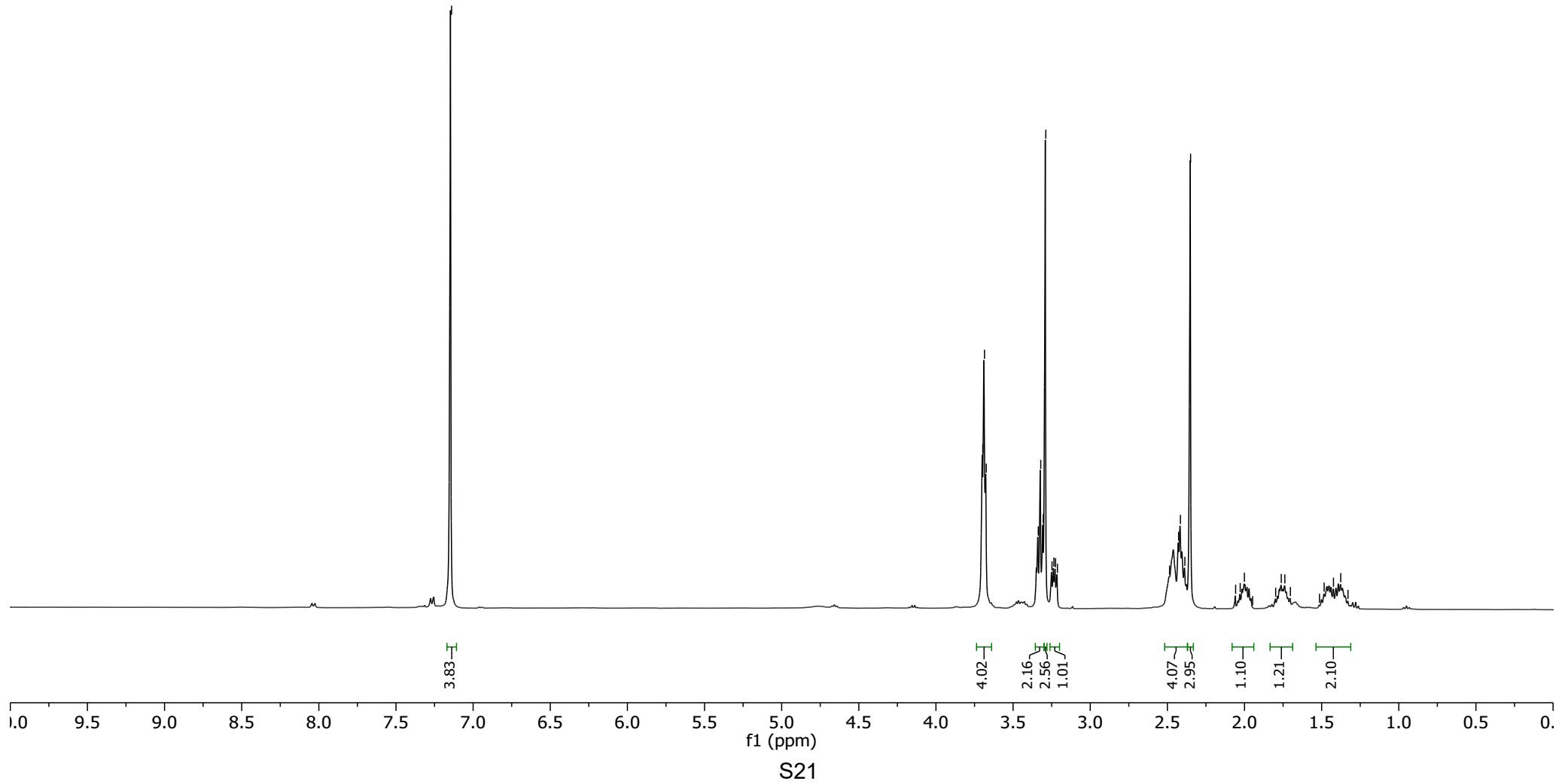
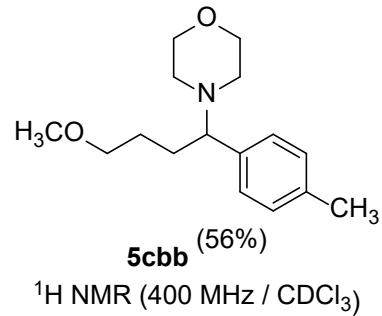


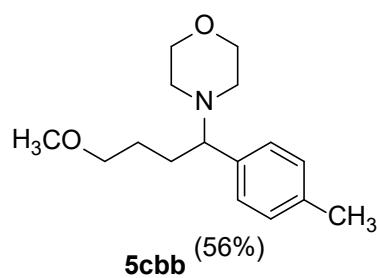




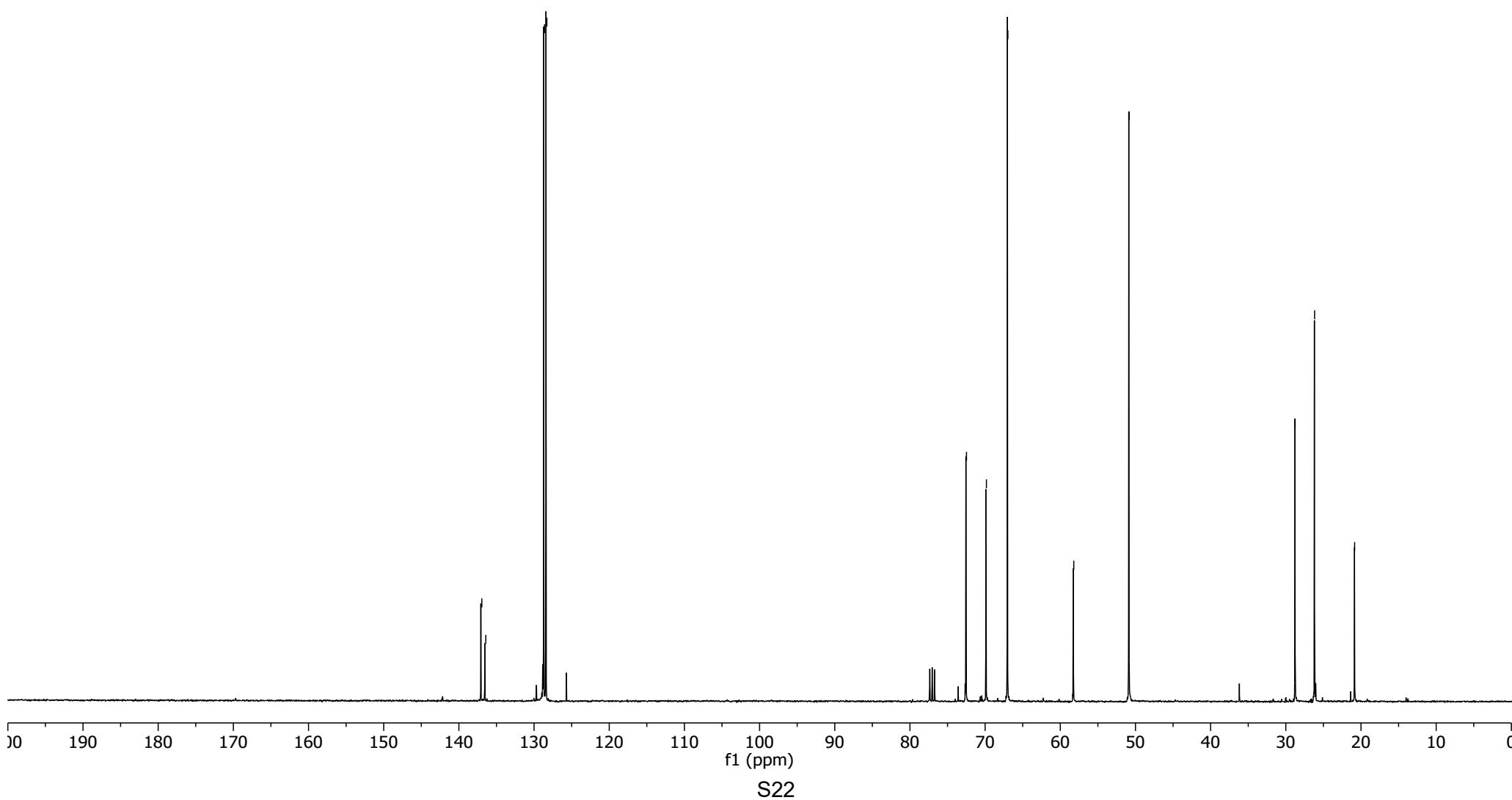
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

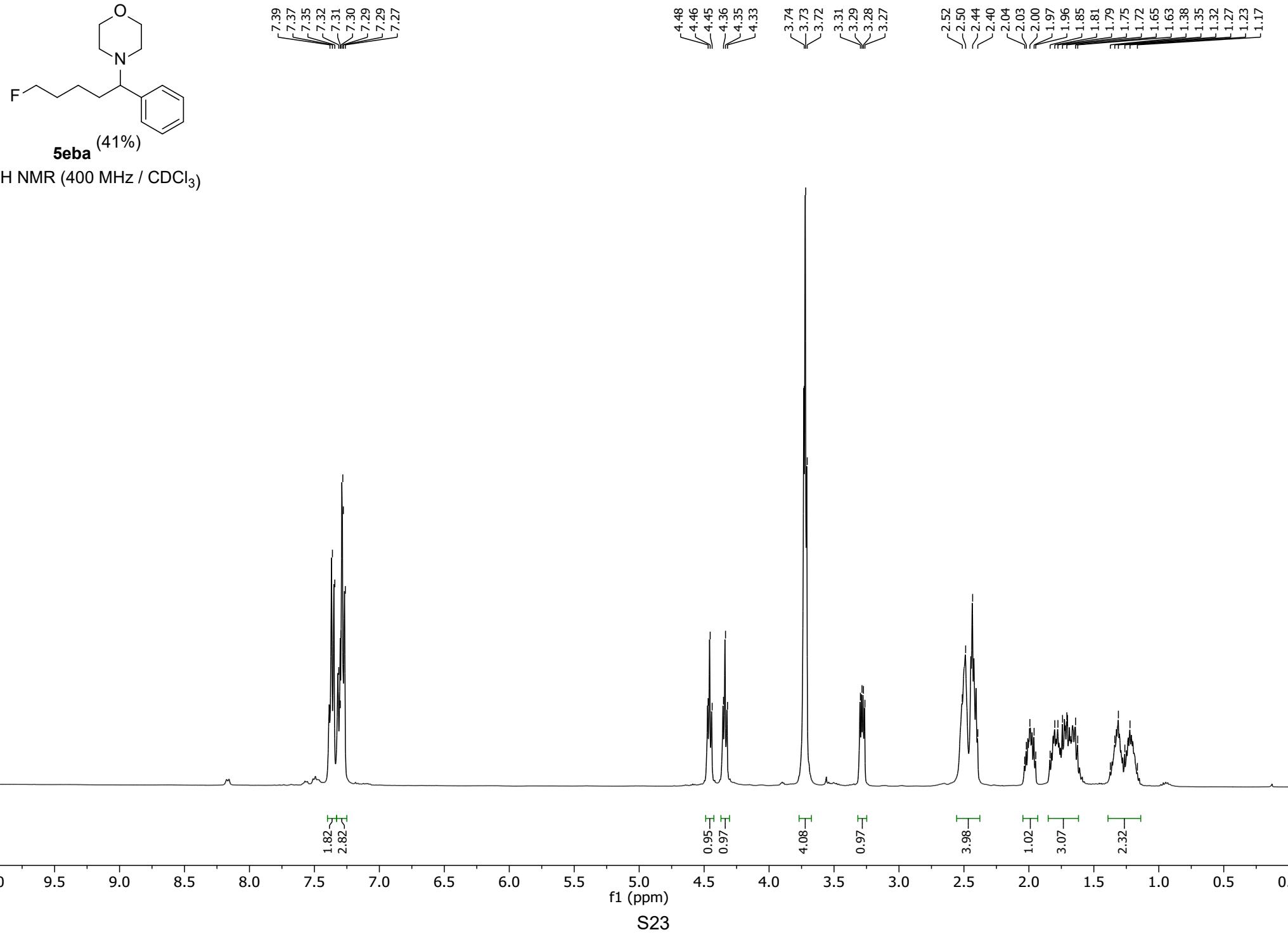


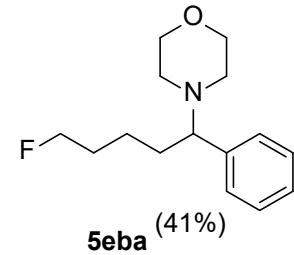




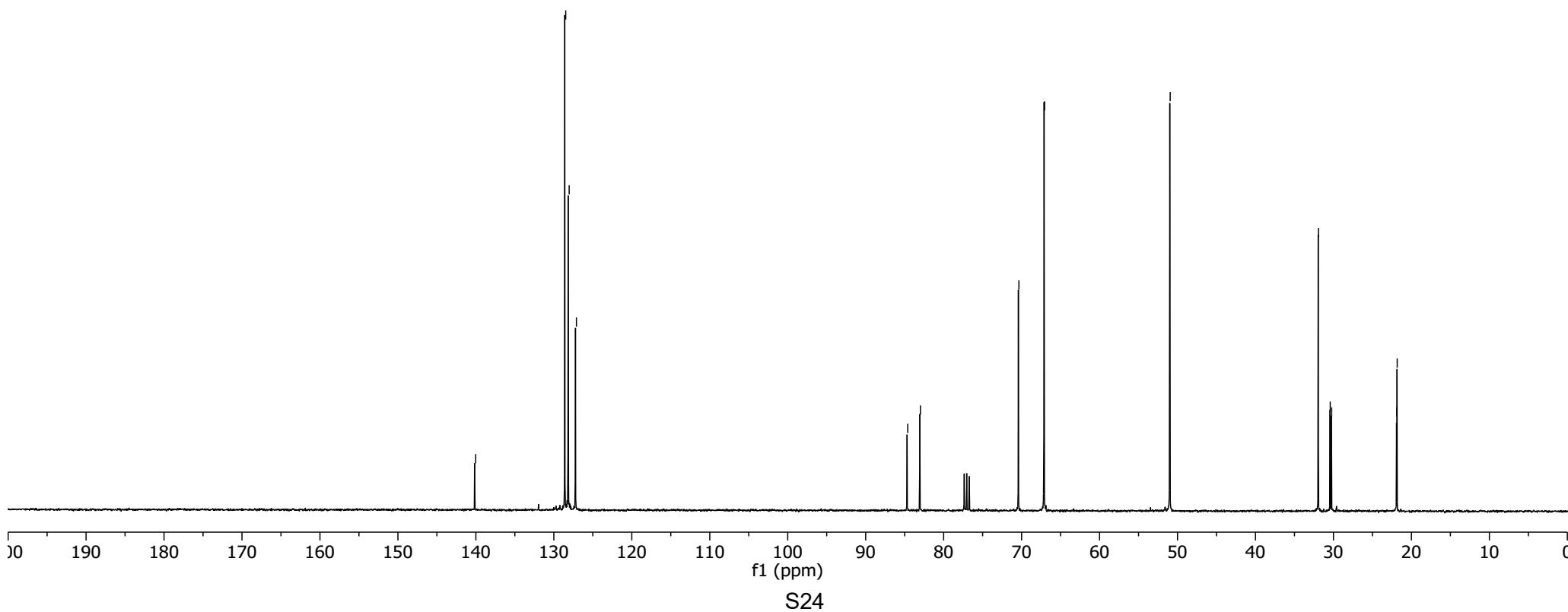
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

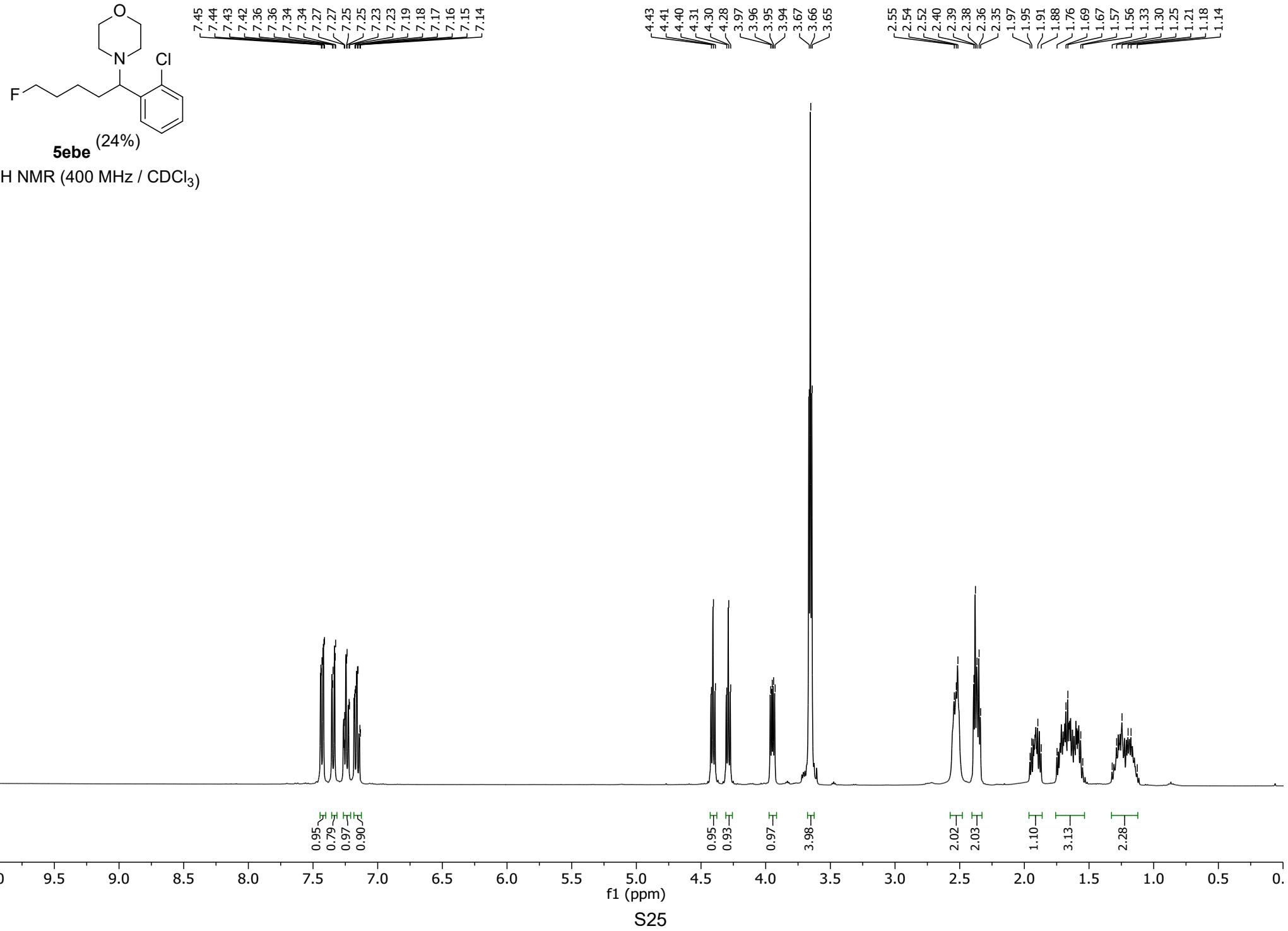


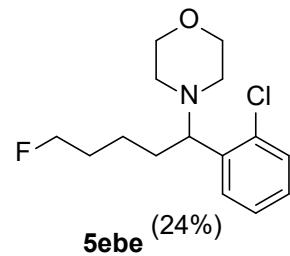




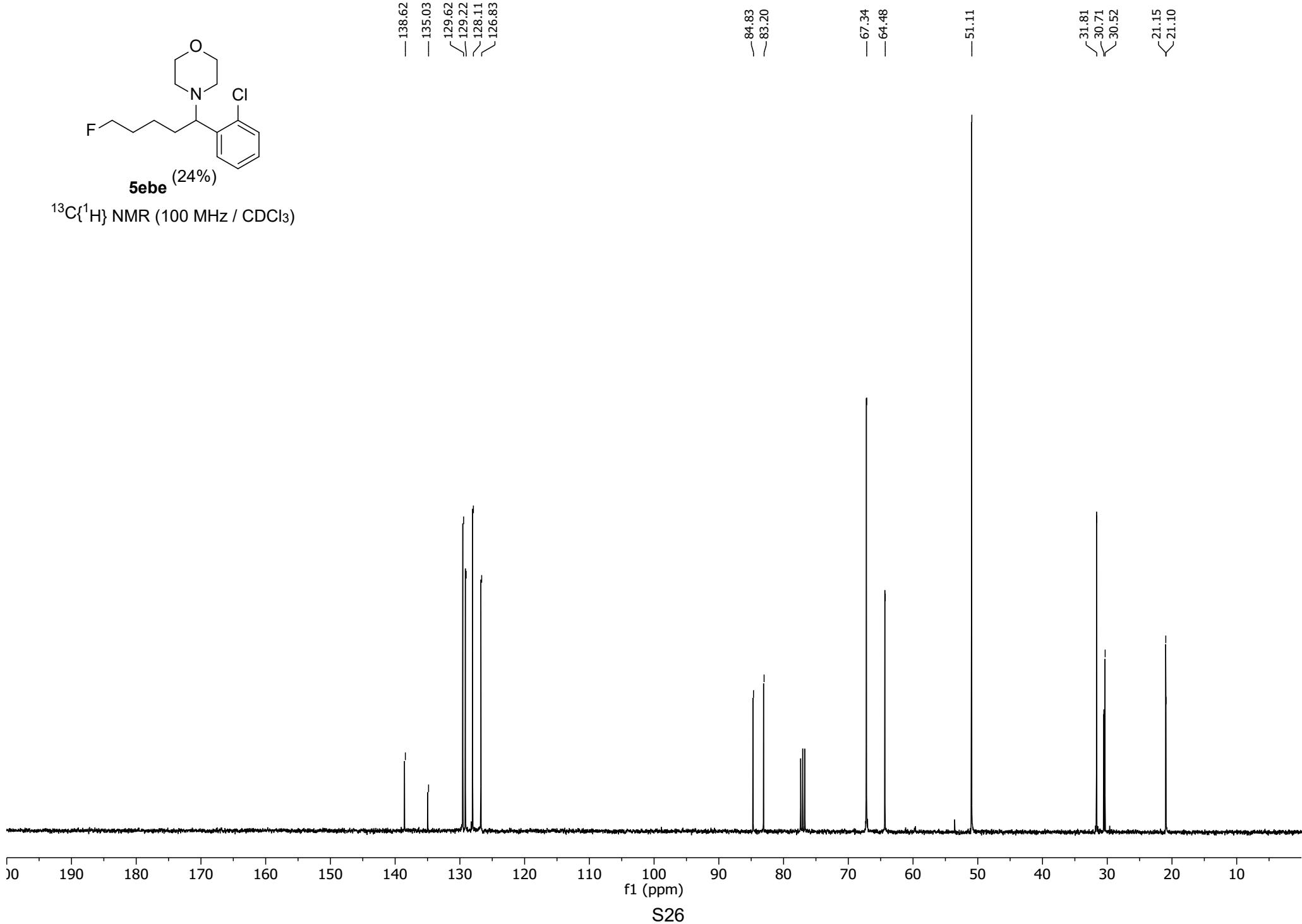
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

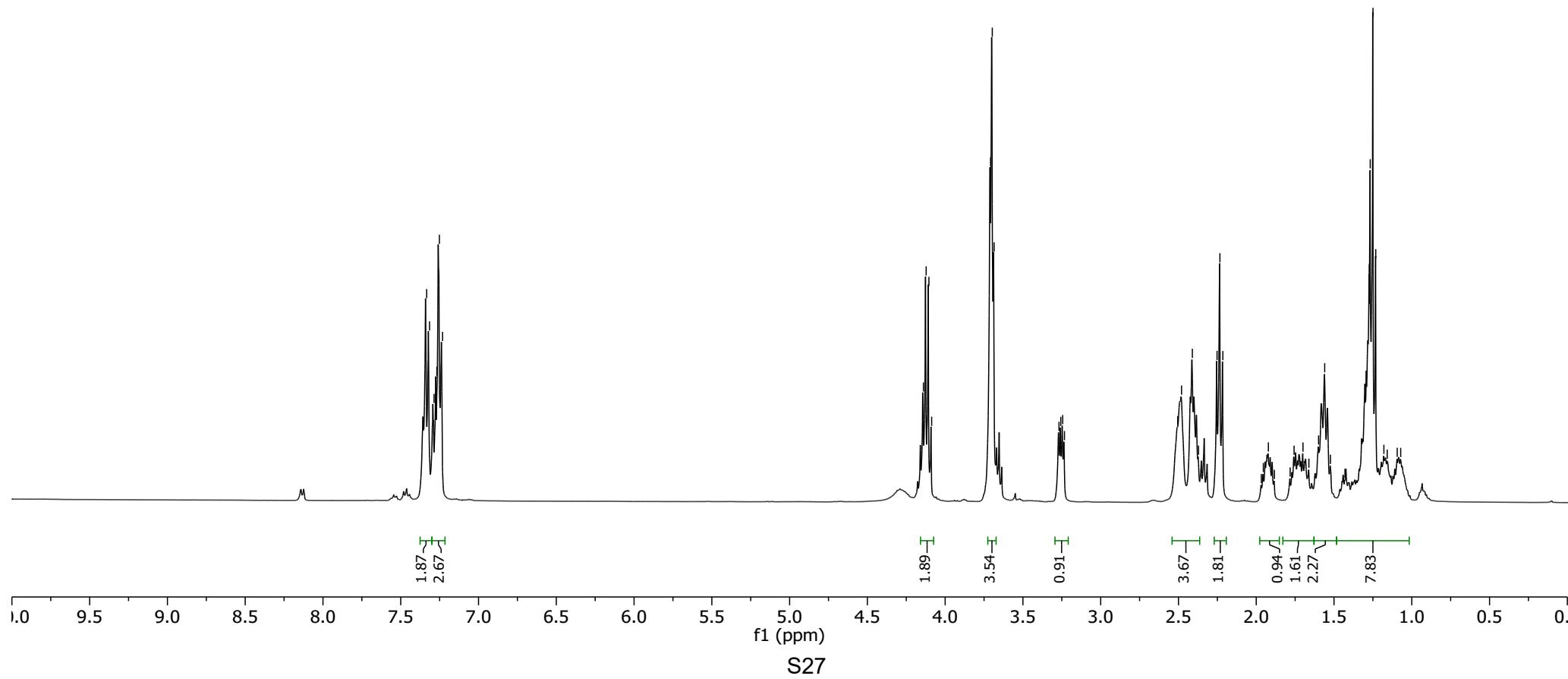


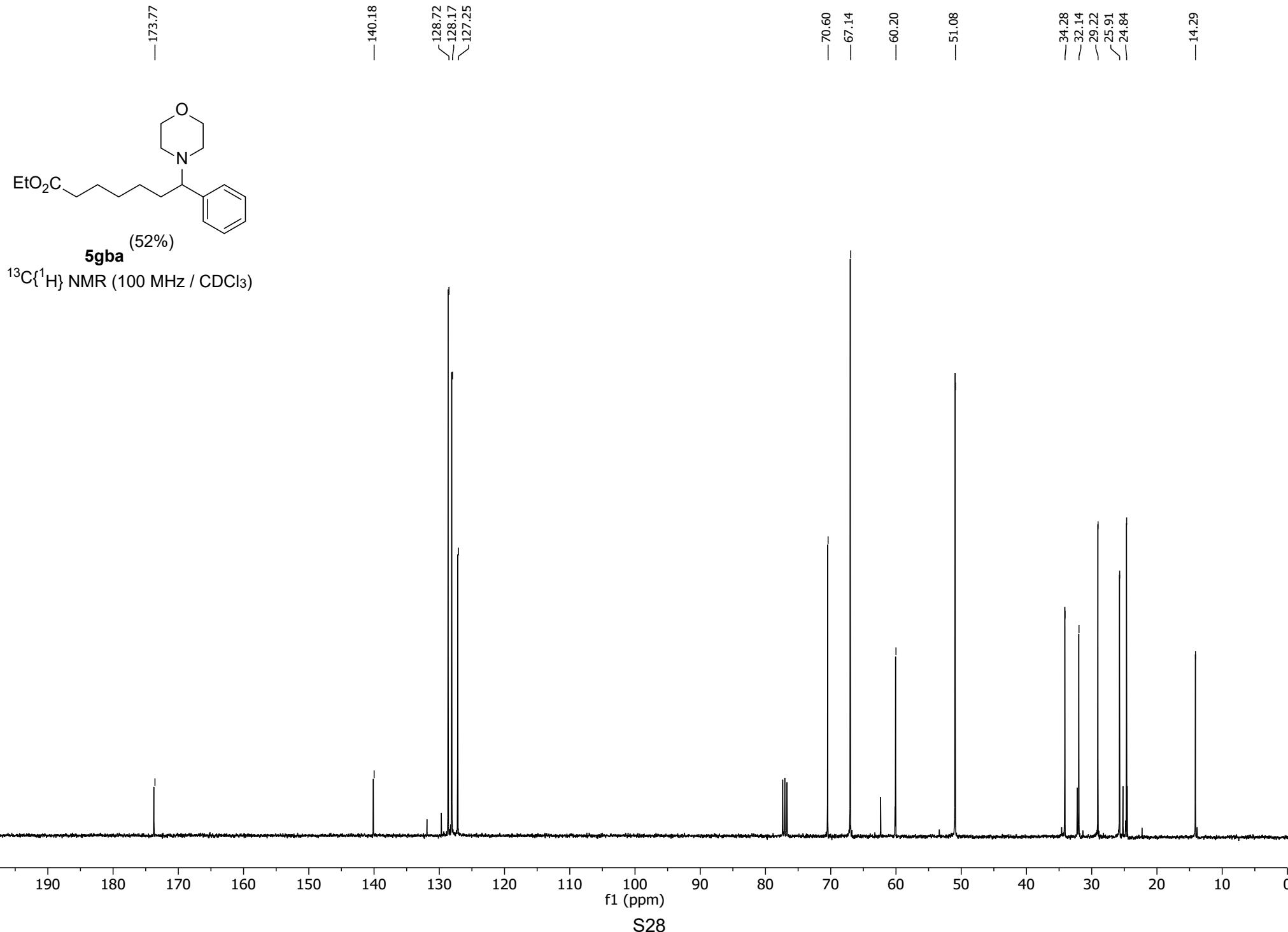


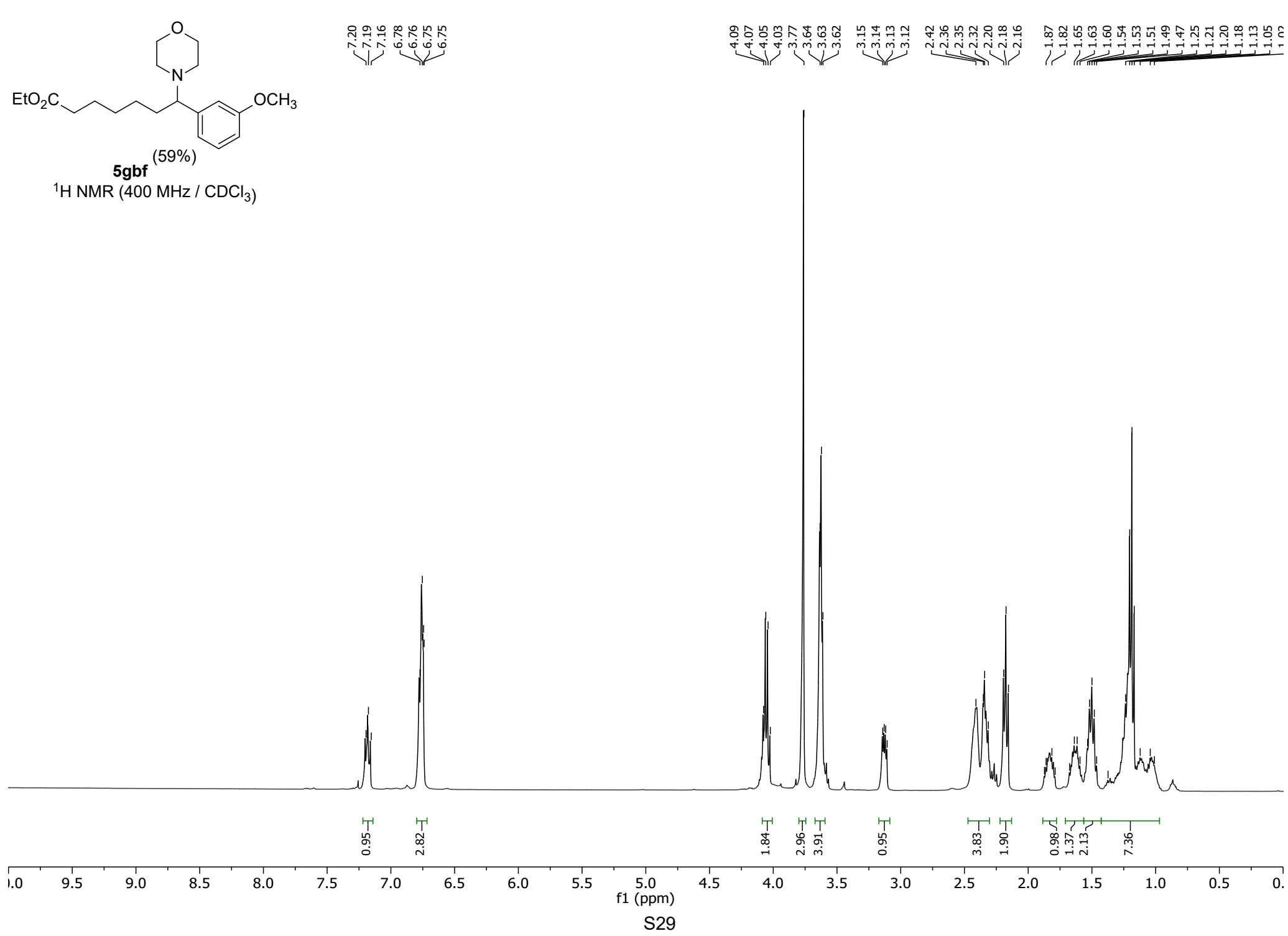
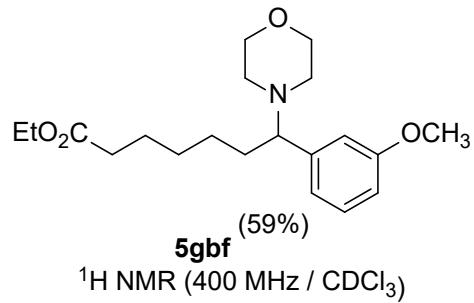


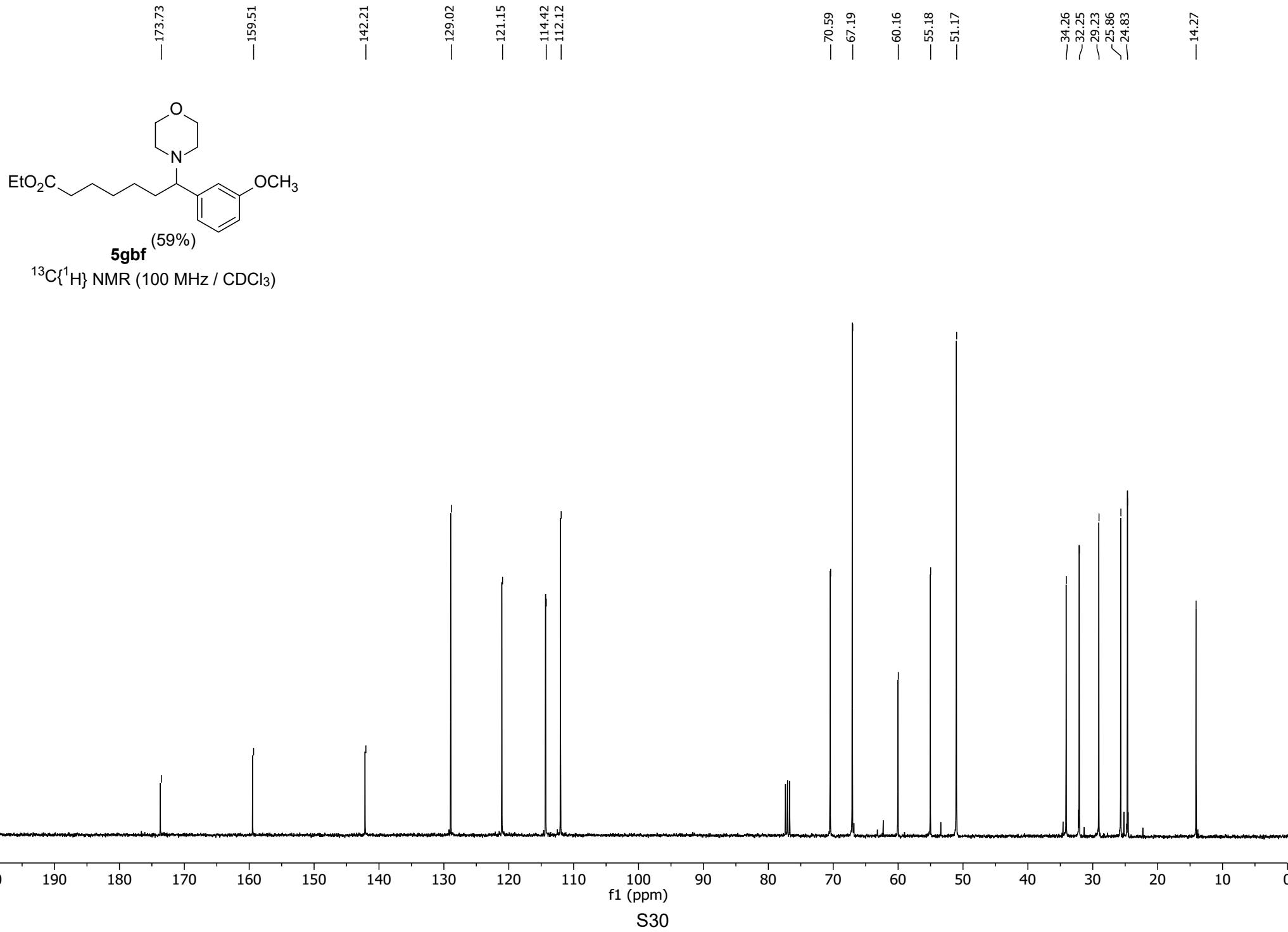
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

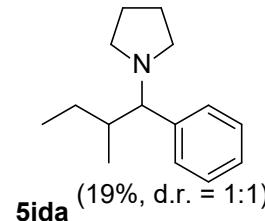




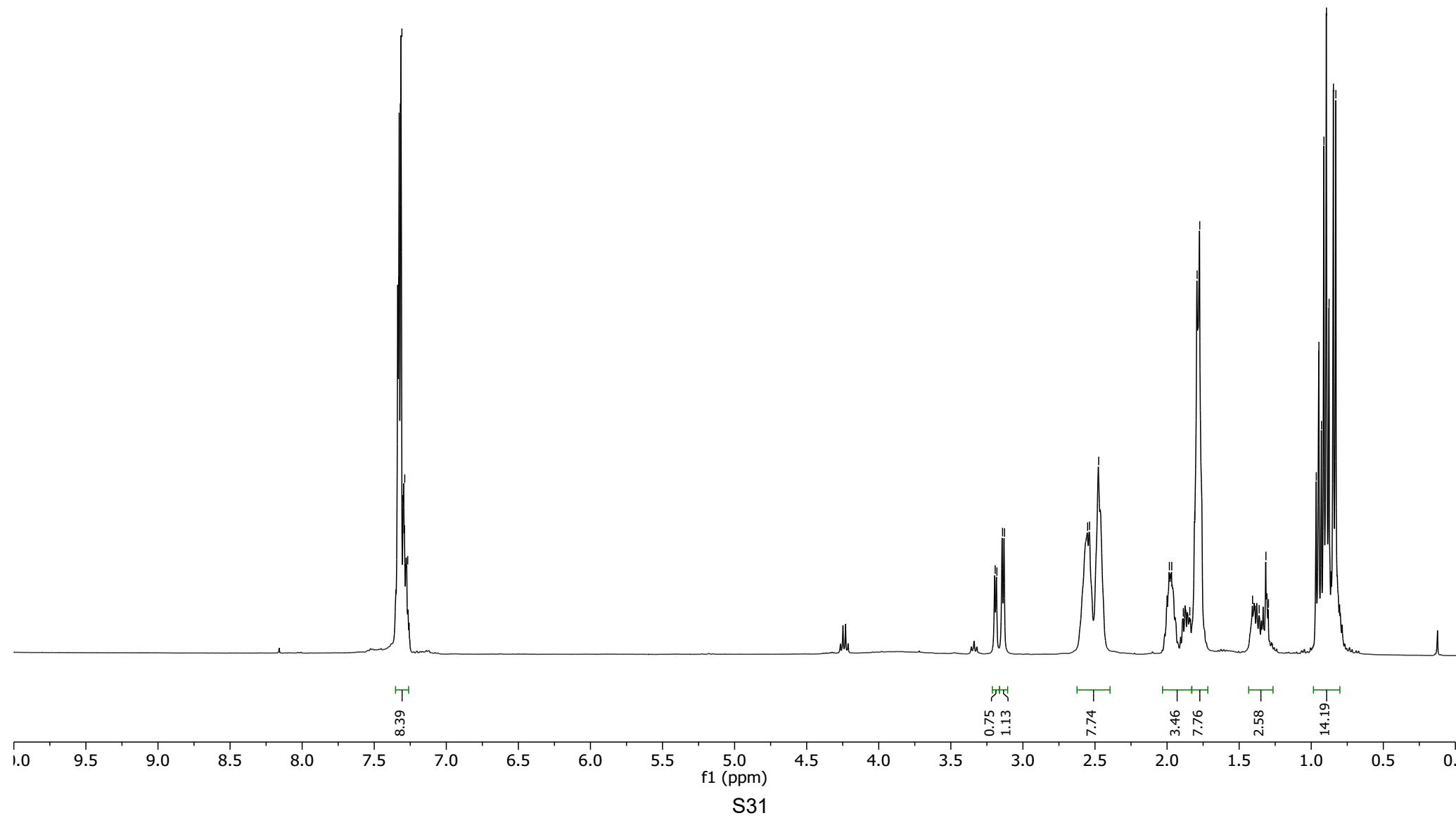


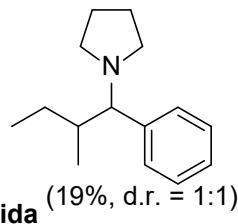




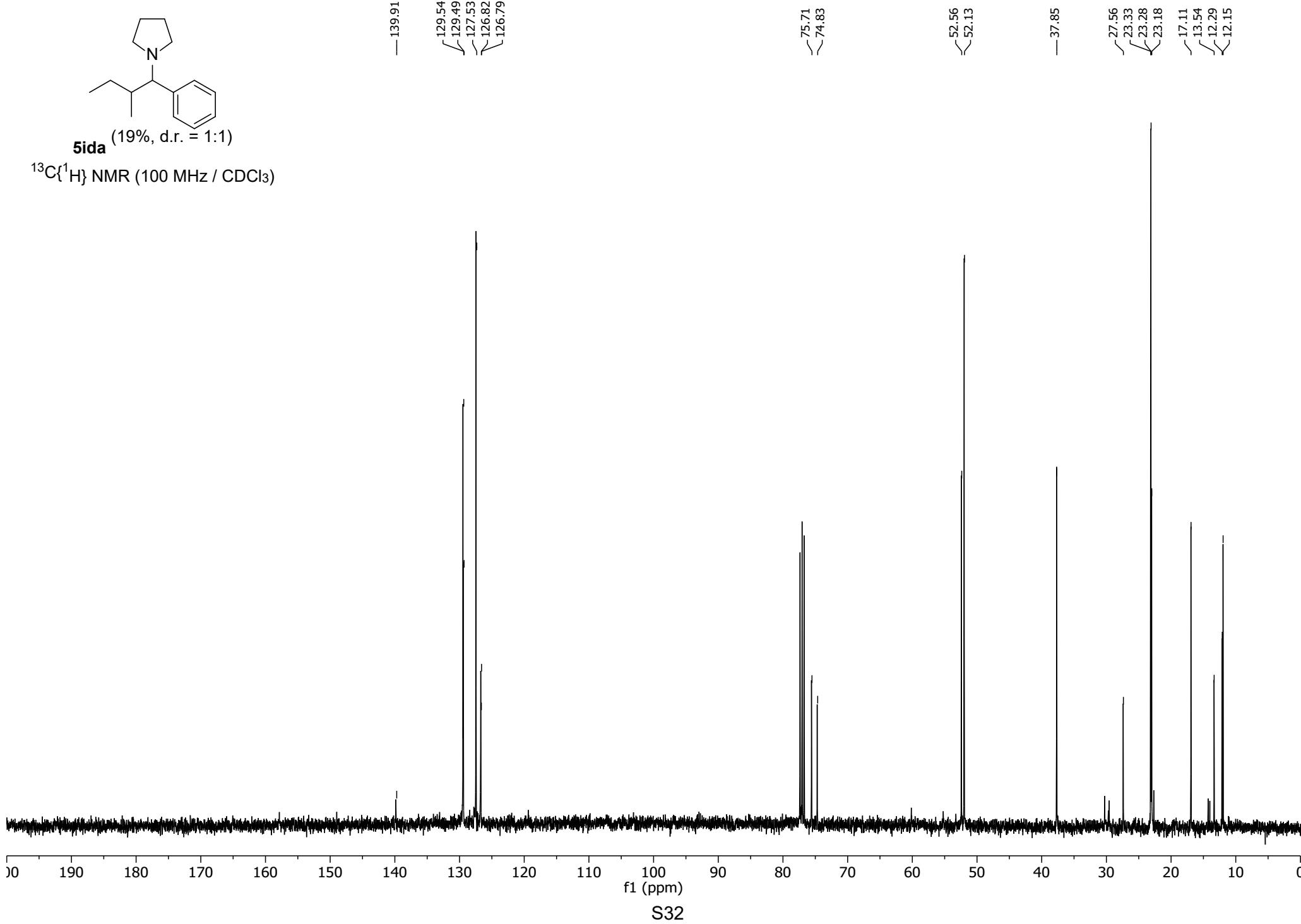


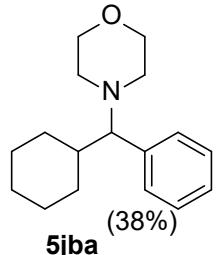
¹H NMR (400 MHz / CDCl₃)



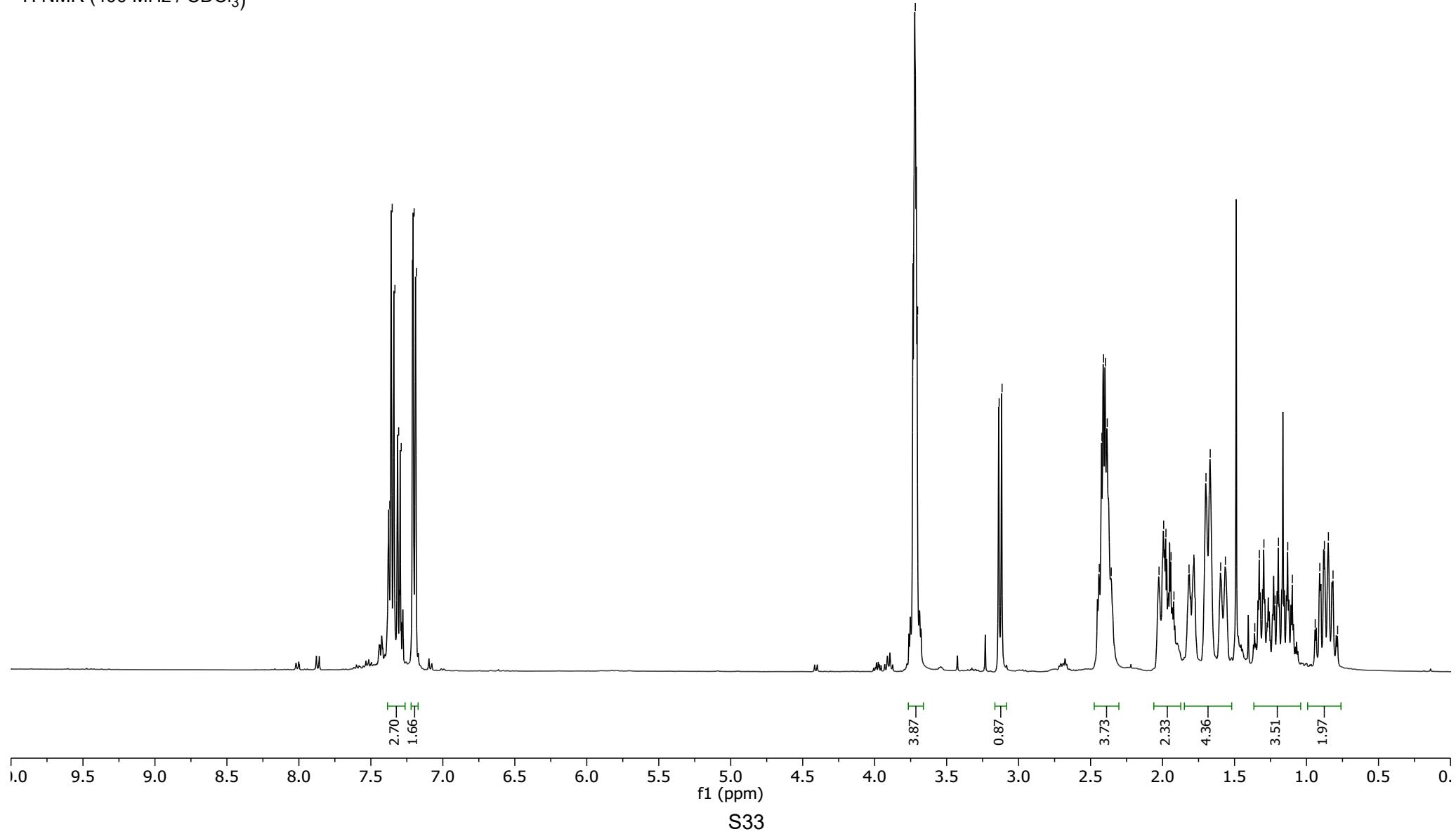


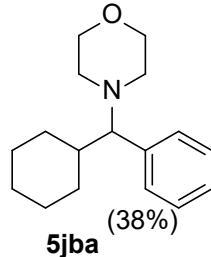
$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)





^1H NMR (400 MHz / CDCl_3)





$^{13}\text{C}\{\text{H}\}$ NMR (100 MHz / CDCl_3)

