

Supporting Information for:

Catalytic Reductive *N*-Alkylation of Amines using Carboxylic Acids

Keith G. Andrews, Declan M. Summers, Liam J. Donnelly and Ross M. Denton*¹

¹School of Chemistry, University Park, University of Nottingham, Nottingham NG7 2RD, United Kingdom

ross.denton@nottingham.ac.uk

Contents

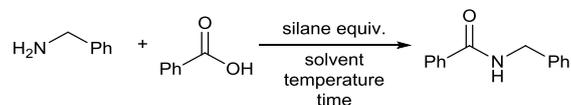
1. General Information	2
2. Amidation.....	3
2.1 Optimisation details.....	3
2.2 Amide formation as a function of time.....	4
2.3 General procedure for secondary amine amidation test reactions.....	5
3. Reductive alkylation of secondary amines with carboxylic acids	6
3.1 Optimisation details.....	6
3.2 General procedure for catalytic reductive amination reaction	7
3.3 Scale-up reaction protocol: Gram scale synthesis of 3e	8
3.4 Additional functional group tolerance experiments.....	9
3.5 Data and specific experimental details for tertiary amines 3a-n.....	10
4. Reductive alkylation of primary amines with carboxylic acids	15
4.1 Optimisation details.....	15
4.2 General procedure for the reductive alkylation of primary amines with carboxylic acids.....	16
4.2.2 Reductive alkylation under non-inert conditions	17
4.3 Data and specific experimental details for secondary amines 5a-l	17
5.0 Spectra for all compounds	24
5.1 Secondary amines	24
5.2 Tertiary amines	48
6.0 References	79

1. General Information

Glassware was dried in an oven overnight before use. All reactions were carried out under an argon balloon atmosphere unless stated otherwise. All reagents were used as supplied unless otherwise stated. Toluene and THF were obtained from stills and stored over sodium wire and under argon until use. Liquid reagents were manipulated using a microsyringe of appropriate volume. Thin layer chromatography was carried out on Polgram SIL G/UV254 silica-aluminium plates and plates were visualized using ultra-violet light (254 nm) or KMnO_4 solution. For flash column chromatography, fluorochem silica gel 60, 35–70 mesh was used. NMR data was collected (unless stated otherwise) at 400 MHz for ^1H ; 101 MHz for ^{13}C ; 377 MHz for ^{19}F . Data was manipulated directly from the spectrometer or via a networked PC with appropriate software. Reference values for residual solvent were taken as $\delta=7.26$ (CDCl_3) for ^1H NMR; $\delta=77.00$ (CDCl_3) for ^{13}C NMR; $\delta=3.31$ (MeOD) for ^1H NMR; $\delta=49.00$ (MeOD) for ^{13}C NMR. ^{19}F -NMR shifts were referenced to CFCl_3 at 0.0 ppm. NMR-yields were calculated relative to one or a half equivalent of 1,1,2,2-tetrachloroethane as an internal standard that was added to the concentrated reaction before obtaining a solution in chloroform; ^1H NMR (400 MHz, CDCl_3) δ 5.95 (s, 2H). Multiplicities for coupled signals are designated using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, quin=quintet, sex=sextet, br=broad signal. The coupling constants are reported in Hertz. Where appropriate, COSY, HMQC and HMBC experiments were performed to aid assignment. High-resolution mass spectrometry data were quoted to four decimal places (0.1 mDa) with error limits for acceptance of ± 5.0 ppm (defined as $\text{calcd}/\text{found mass } 10^{-6}$). Mass spectra were acquired on a VG micromass 70E, VG autospec or micromass LCTOF. Infrared spectra were recorded on a Perkin–Elmer 1600 FTIR instrument as dilute chloroform solutions. Melting points were recorded on a Stuart manual melting point apparatus.

2. Amidation

2.1 Optimisation details



Entry	Time h	Solvent (temp)	Amine equiv.	Acid equiv.	Silane (equiv.)	Yield (%)
1	15	toluene (reflux)	1.0	1.0	PhSiH ₃ (1.0)	75
2	15	toluene (reflux)	1.0	1.0	PhSiH ₃ (1.5)	78
3	15	toluene (reflux)	1.2	1.0	PhSiH ₃ (1.0)	83
4	13	toluene (reflux)	1.0	1.5	PhSiH ₃ (1.5)	100
5	13	toluene (reflux)	1.2	1.0	–	2
6	13	toluene (reflux)	1.0	1.2	PhSiH ₃ (1.2)	93
7	13	toluene (20 °C)	1.0	1.2	PhSiH ₃ (1.2)	0
8	13	acetonitrile (reflux)	1.0	1.2	PhSiH ₃ (1.2)	66
9	13	toluene (reflux)	1.0	1.2	PhSiH ₃ (0.66)	94
10	13	toluene (reflux)	1.0	1.2	PhSiH ₃ (0.33)	52
11	4	toluene (85 °C)	1.0	1.2	PhSiH ₃ (1.2)	63
12	13	toluene (reflux)	1.0	1.2	Ph ₂ SiH ₂ (2.0)	52
13 ^b	13	toluene (reflux)	1.0	1.2	PhSiH ₃ (1.2)	87

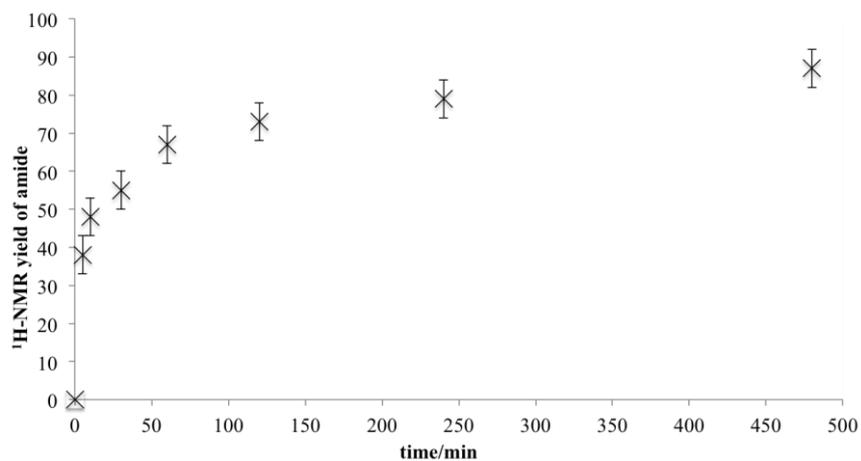
^aYields were calculated *via* ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard after concentration of the reaction. Reactions performed on a 0.16 mmol scale in 0.5 mL solvent, with the equivalents outlined in the table. In all cases, the amine was added last to a stirring solution of the acid and silane at the indicated temperature. ^bReaction performed in Winchester grade toluene in undried glassware under air atmosphere.

Diphenylsilane (entry 12) is a viable but less effective amidation agent.

2.2 Amide formation as a function of time

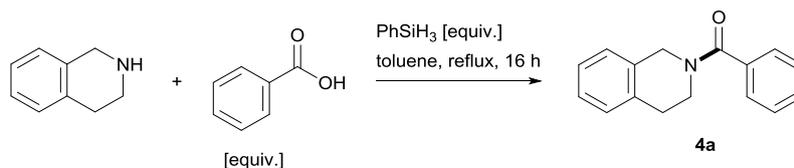
Benzoic acid (19.5 mg, 0.190 mmol) was dissolved in toluene (0.5 mL) and the reaction heated to reflux (oil bath at 116 °C). Added was benzylamine (17.5 μ L, 0.160 mmol) and phenylsilane (23.7 μ L, 0.190 mmol) and the reaction stirred for the allotted time before quenching with ethanol (2 mL) and cooling rapidly to room temperature. The reaction was concentrated and the conversion to amide deduced by integration by comparison to 1,1,2,2-tetrachloroethane as an internal standard in chloroform.

Entry	Time (min)	Amide NMR yield (%)
1	5	38
2	10	48
3	30	55
4	60	67
5	120	73
6	240	79
7	480	87



2.3 General procedure for secondary amine amidation test reactions

Benzoic acid (various equiv.) was suspended in toluene (0.2 mL) and the solution was heated to reflux (110 °C) before phenylsilane (various equiv.) and 1,2,3,4-tetrahydroisoquinoline (0.16 mmol) were added; upon the addition of amine, gas evolved rigorously from the reaction mixture. The reaction was stirred at reflux for 15 h. After this time the reaction was cooled to room temperature and the solvent removed *in vacuo*. 1,1,2,2-tetrachloroethane (0.08 mmol) was then added to the reaction and the conversion of starting material to amide was deduced by integrating the product to the 1,1,2,2-tetrachloroethane internal standard peak in the ¹H-NMR spectrum, which characteristically appears as a singlet at 5.95 ppm in CDCl₃.



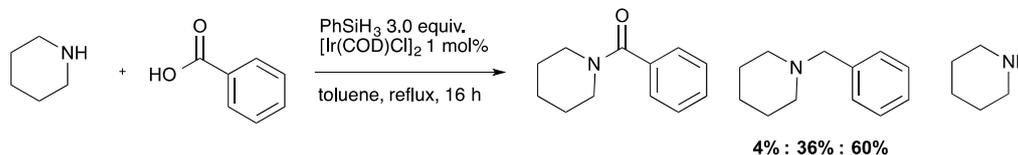
Entry	Acid Eq.	PhSiH ₃	Amide %
1	1.0	0.7	79
2	1.2	0.7	78
3	1.5	0.7	87
4	1.0	1.0	87
5	1.2	1.0	88
6	1.5	1.0	95

^aall reactions were carried out on a 0.16 mmol scale in 0.2 mL of toluene as reaction solvent. After 16 h, the reaction was concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 0.08 mmol of 1,1,2,2-tetrachloroethane as an internal standard.

3. Reductive alkylation of secondary amines with carboxylic acids

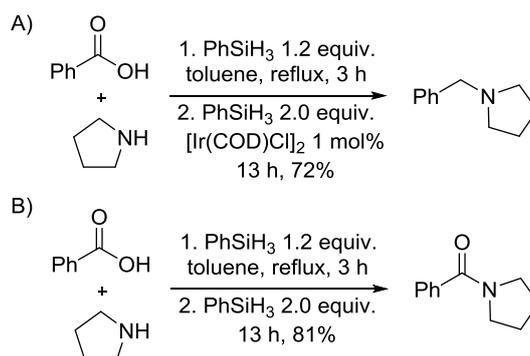
3.1 Optimisation details

One-pot procedure experiment



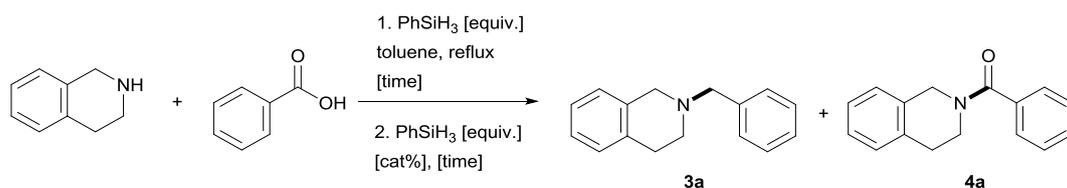
Benzoic acid (23.4 mg, 0.19 mmol) was suspended in toluene (0.2 mL) and the solution was heated to reflux (110 °C) before phenylsilane (59 μ L, 0.48 mmol) and piperidine (15.8 μ L, 0.16 mmol, 1 equiv.) were added; upon the addition of amine, gas evolved rigorously from the reaction mixture. After 2 min, [Ir(COD)Cl]₂ (1 mg, 5 μ mol, 1 mol%) was added. The reaction was stirred at reflux for 16 h before concentration and ¹H-NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. Piperidine was the major amine containing product indicating that a one pot procedure was unlikely to be viable as the amidation pathway was being shut down.

Proof of concept and requirement for the catalyst



These reactions were performed in the same way, with the exception that the iridium was omitted from the start of the reaction and the loading of phenylsilane was 1.2 equivs. For reaction A, the [Ir(COD)Cl]₂ was added after 3 h at reflux, followed by phenylsilane (0.32 mmol), whilst after the initial 3 h, to reaction B was added just the phenylsilane (0.32 mmol). Reactions A and B were then stirred at reflux for 13 h before being concentrated and processed as above. The result demonstrates that the iridium is required for reduction under these conditions.

Selected optimisation results for the alkylation of secondary amines.



Entry	amidation phase			reduction phase			Amide 6 (%)	Amine 7 (%)
	Acid Eq.	PhSiH ₃ Eq.	time/h	cat %	PhSiH ₃ Eq.	time/h		
1	1.0	0.7	15	1%	1.0	3	50	50
2	1.5	1.0	15	1%	1.5	4	35	52
3	1.5	1.2	3	1%	2.0	3	0	76
4	1.5	1.0	15	1%	2.0	3	0	80

^aEach reaction carried out with 1 equiv. amine (0.16 mmol) in toluene (0.35 mL) at reflux. The reaction was concentrated and the product ratio was determined by ¹H-NMR relative to 1,1,2,2-tetrachloroethane as internal standard.

Again note that shorter amidation times (3 h) are possible.

3.2 General procedure for catalytic reductive amination reaction

An oven-dried 10 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (0.75 mmol). Anhydrous toluene (0.6 mL) and phenylsilane (0.50 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid (if required/possible). On a small scale, the amine (0.50 mmol) was then added carefully by temporary removal of the condenser, generally accompanied by the vigorous release of hydrogen gas. *Note that at smaller scales, the amine can be added to the (almost) refluxing solution; for larger scale reactions a large volume of hydrogen is released, and it is preferable to remove the reaction from the heat and add the amine portionwise at a lower temperature.* After 15 h at reflux, [Ir(COD)Cl]₂ (5.0 μmol, 1 mol%) and then further phenylsilane (1.00 mmol) were added by temporary removal of the condenser, and the reaction mixture was stirred at reflux for 3 h.

After this time toluene was removed *in vacuo* and the residue was dissolved in ethyl acetate (7.5 mL). The organic layer was extracted with 3 M aq. hydrochloric acid (3 x 5.0 mL) and the combined acid washings were basified (pH ~ 9) with 6 M aq. sodium hydroxide with ice-bath cooling. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic layer dried over magnesium sulfate and concentrated *in vacuo* to give the crude product. (If the product contains sensitive or acidic or basic groups, the reaction should be worked-up omitting the acid/base washes as necessary.)

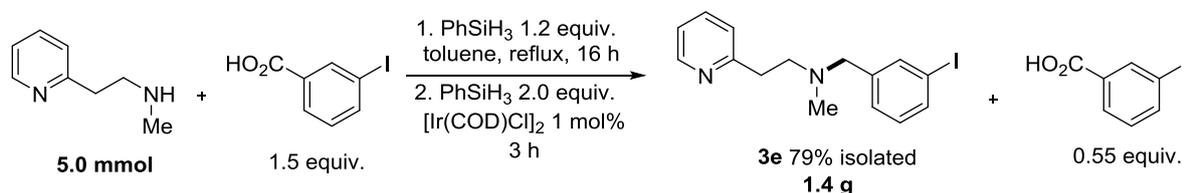
Purification 1: The crude product was dry loaded onto silica and purified by flash column chromatography (pentane/ethyl acetate) to give the product. **Purification 2:** Excess amine was removed *in vacuo* and no further purification was required. **Purification 3:** For amines with poor

aqueous solubility (i.e. poor extraction efficiency into aqueous acid), the general work-up was modified as follows: The concentrated reaction mixture was dissolved in ethyl acetate (7.5 mL). The solution was washed with 1 M aq NaOH (2 x 10 mL). The organic layer was retained and purified by flash column chromatography after drying over MgSO₄.

Reaction Notes: The reaction is best performed from the free base. The amine and acid can be combined first if desired, before adding the silane last to initiate the reaction. The room temperature combination of acid and amine in toluene sometimes this leads to a salting out of the ammonium carboxylate which may hinder the initial reaction efficiency, however successful reactions have been performed in this way. In an amidation test reaction (0.16 mmol), the conversion to product dropped from 93% to 87% when the reaction was performed under an air atmosphere (open condenser), in undried glassware and in Winchester-grade toluene (see section 2.2 in this document). In these cases it may be helpful to increase the silane loading by ~0.1 equivalents to consume the excess moisture. Hindered amides can benefit from increasing the reduction time to 4 h.

Chromatography notes: (Basic) amines may streak during chromatography. Two mitigating strategies used here are: a) running the column with 0.1-1% Et₃N in all eluent, and: b) pretreating the silica (column and/or dry-loading) with triethylamine prior to chromatography. For the latter, the following protocol was used: Silica was slurried in ethyl acetate and added was ~2 mL triethylamine/8 g silica and the slurry stirred for 15 min. The silica was filtered and washed with ethyl acetate and then petrol or pentane. The silica was then slurried as per normal in the column solvent.

3.3 Scale-up reaction protocol: Gram scale synthesis of 3e



An oven-dried 25 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (1.86 g, 7.50 mmol). Anhydrous toluene (6.0 mL) and phenylsilane (620 μ L, 5.00 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid, which appeared to be only partially soluble. The reaction was removed from the heat and allowed to cool partially. **CAUTION:** To the reaction was added portionwise (to maintain a manageable level of hydrogen gas evolution) *via* microsyringe by temporary partial removal of the condenser the amine (692 μ L, 5.00 mmol). Adding the amine caused the undissolved acid to dissolve as well as copious vigorous hydrogen gas evolution. Upon completion of addition, the reaction was returned to the heat and visually monitored for 5 minutes; the subsequent hydrogen evolution remained steady and controlled. After 15 h at reflux, the reaction was removed from the heat temporarily and [Ir(COD)Cl]₂ (50 μ mol, 1.0 mol%) and then further phenylsilane (1.24 mL, 10.0 mmol) added by temporary removal of the condenser. The reaction mixture was stirred at reflux for 3 h further. The reaction was then cooled and quenched with 1 M NaOH, leading to further hydrogen evolution. The reaction was diluted with dichloromethane and the organic layer separated. The aqueous layer was acidified and re-extracted into dichloromethane to recover the unreacted carboxylic acid. (In this case, some

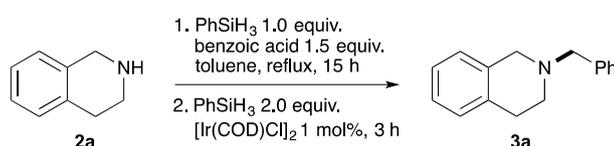
silanol/siloxane was present in the mixture. Dissolving this mixture in ethyl acetate and extracting the carboxylic acid with sodium carbonate instead of hydroxide before acidification and re-extraction with dichloromethane yielded pure carboxylic acid, as judged by $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ (0.55 equivalents, 0.68 g).

To obtain the amine, the initial organic layer was extracted with 3 x 1 M HCl solution, the combined aqueous layers basified to \sim pH 10 cautiously with 6 M NaOH with cooling in an ice bath and the desired amine extracted into dichloromethane (x3), washed with brine, dried over magnesium sulfate and concentrated. The crude mixture was purified further by chromatography (see example **3e** below) to remove a bright yellow impurity and yield the amine as a pale yellow oil (1.4 g, 79%).

3.4 Additional functional group tolerance experiments

All reactions performed as per the general reaction, and analysed by $^1\text{H-NMR}$ with 1,1,2,2-tetrachloroethane as internal standard.

Screening some external additives under the tertiary amine synthesis protocol



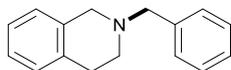
Entry	Additive	Conversion to 3a	Additive result
1		After step 1, only 39% amide	Reduction to silyl alcohols, 41% ketone remaining
2		After step 1, no conversion of benzoic acid	Conversion of aldehyde to 3a in 76% yield
3		After work-up, 44% 3a , 33% remains as amide	High conversion of decanol to silyl ethers (no ester)
4		40% conversion to 3a	90% of secondary amide remains unreacted at the end of the reaction

^aall reactions performed as for Table 1 in the main article.

3.5 Data and specific experimental details for tertiary amines 3a-p

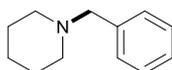
All compounds synthesized using the general procedure for tertiary amine production (above) unless stated otherwise.

2-benzyl-1,2,3,4-tetrahydroisoquinoline (**3a**)¹



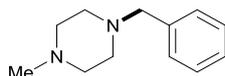
Purification 1. Product was isolated as a pale yellow oil (87 mg, 78% yield). ¹H NMR (400 MHz, CDCl₃): 7.42 – 7.38 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.15 – 7.07 (m, 3H), 7.01 – 6.96 (m, 1H), 3.70 (s, 2H), 3.64 (s, 2H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.76 (t, *J* = 5.9 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃): 137.1, 134.3, 129.1, 128.6, 128.7, 128.3, 127.2, 126.6, 126.1, 125.6, 62.7, 56.0, 50.5, 29.0; HRMS (ESI+): Exact mass calculated for C₁₆H₁₇N [M+H] 224.1395. Found; 224.1398.

1-benzylpiperidine (**3b**)²



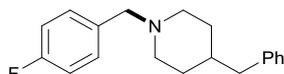
Purification 1. Product was isolated as a pale yellow oil (70 mg, 80%). ¹H NMR (270 MHz, CDCl₃): 7.40-7.10 (m, 5H), 3.48 (s, 2H), 2.37 (m, 4H), 1.68 – 1.49 (m, 4H), 1.68 – 1.49 (m, 2H); ¹³C NMR (68 MHz, CDCl₃): 138.4, 129.3, 128.1, 126.8, 63.9, 54.4, 25.9, 24.3; HRMS (ESI+): Exact mass calculated for C₁₂H₁₇N [M+H] 176.1395. Found: 176.1474.

1-benzyl-4-methylpiperazine (**3c**)³



Purification 1. Product was isolated as a pale yellow oil (54 mg, 56%). ¹H NMR (270 MHz, CDCl₃): 7.36 – 7.21 (m, 5H), 3.50 (s, 2H), 2.48 (br. s, 8H), 2.29 (s, 3H).; ¹³C NMR (68 MHz, CDCl₃): 138.0, 129.2, 128.2, 127.0, 62.9, 54.9, 52.8, 45.8; HRMS (ESI+): Exact mass calculated for C₁₂H₁₈N₂ [M+H] 191.1504. Found 191.1517.

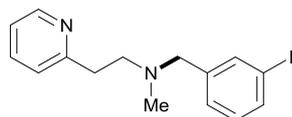
4-benzyl-1-(4-fluorobenzyl)piperidine (**3d**)⁴



Purification 3: Product isolated as an off-white waxy solid (108 mg, 76%). ¹H NMR (400 MHz, CDCl₃) δ 7.26 (s, 4H), 7.23 – 7.17 (m, 1H), 7.17 – 7.13 (m, 2H), 7.04 – 6.96 (m, 2H), 3.45 (s, 2H), 2.87 – 2.83 (m, 2H), 2.55 (d, *J* = 7.0 Hz, 2H), 1.90 (td, *J* = 11.7, 2.5 Hz, 2H), 1.68 – 1.57 (m, 2H), 1.40 – 1.24 (m, 2H);

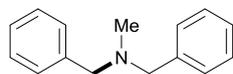
^{13}C NMR (101 MHz, CDCl_3) δ 161.9 (d, $J = 244.6$ Hz), 140.7, 134.3 (d, $J = 3.2$ Hz), 130.5 (d, $J = 7.7$ Hz), 129.1, 128.1, 125.7, 114.8 (d, $J = 20.9$ Hz), 62.6, 53.7, 43.2, 37.9, 32.2; ^{19}F NMR (377 MHz, CDCl_3) δ -116.2 – -116.3 (m); HRMS (ESI+): Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{FN}$ [M+H], 284.1809. Found 284.1819, $\sigma = 0.0019$.

N-(3-iodobenzyl)-*N*-methyl-2-(pyridin-2-yl)ethan-1-amine (**3e**)



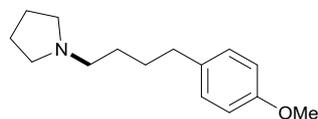
Purification 1; flash column chromatography with pentane/EtOAc/ Et_3N (0-70% gradient EtOAc, with 0.5 mol% Et_3N throughout on Et_3N pre-treated silica). Product isolated as a pale yellow oil (139 mg, 79%). ^1H NMR (400 MHz, CDCl_3) δ 8.54 – 8.50 (m, 1H), 7.64 – 7.57 (m, 2H), 7.57 – 7.53 (m, 1H), 7.23 – 7.18 (m, 1H), 7.17 – 7.14 (m, 1H), 7.14 – 7.09 (m, 1H), 7.00 (t, $J = 7.7$ Hz, 1H), 3.48 (s, 2H), 3.04 – 2.94 (m, 2H), 2.84 – 2.76 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, CDCl_3) 160.4, 149.2, 141.8, 137.7, 136.2, 136.0, 129.9, 128.0, 123.2, 121.2, 94.3, 61.5, 57.2, 42.1, 36.2; AT-IR (neat) ν (cm^{-1}): 3053, 3007, 2943, 2790, 1590, 1565, 1472, 1434, 1048, 994; HRMS (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{IN}_2$ [M+H], 353.0509. Found 353.0516, $\sigma = 0.0001$.

N-benzyl-*N*-methyl-1-phenylmethanamine (**3f**)⁵



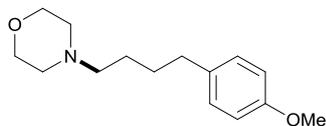
Purification 2: Product isolated as light yellow oil (71 mg, 67%). ^1H NMR (300 MHz, CDCl_3) δ 7.48 – 7.19 (m, 10H), 3.54 (s, 4H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 139.3, 128.9, 128.2, 126.9, 61.8, 42.2; HRMS (ESI+): Exact mass calcd for $\text{C}_{15}\text{H}_{18}\text{N}$ [M+H], 212.1434. Found 212.1454, $\sigma = 0.0322$.

1-(4-(4-methoxyphenyl)butyl)pyrrolidine (**3g**)



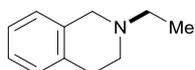
Purification 2: Product was isolated as a yellow oil (89 mg, 83%). ^1H NMR (270 MHz, CDCl_3): 7.15 - 6.99 (m, 2 H), 6.88 - 6.74 (m, 2 H), 3.78 (s, 3 H), 2.55 (t, $J = 7.2$ Hz, 2 H), 2.51 - 2.40 (m, 6 H), 1.77 (m, 4 H), 1.68 - 1.49 (m, 4 H); ^{13}C NMR (68 MHz, CDCl_3): 157.6, 134.6, 129.2, 113.6, 56.5, 55.2, 54.2, 34.9, 29.8, 28.7, 23.4; IR (CDCl_3) ν (cm^{-1}): 3011, 2937, 2801, 2424, 1612, 1513, 1465, 1300, 1246, 1178, 1121, 1036; HRMS (ESI+): Exact mass calculated for $\text{C}_{15}\text{H}_{23}\text{NO}$ [M+H] 234.1813. Found: 234.1814.

4-(4-(4-methoxyphenyl)butyl)morpholine (**3h**)



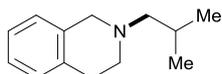
Purification 2: Product was isolated as a yellow oil (81 mg, 71%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.14 - 7.01 (m, 2H), 6.90 - 6.74 (m, 2 H), 3.78 (s, 3H), 3.69 (m, 4H), 2.55 (t, $J = 7.4$ Hz, 2H), 2.47 - 2.37 (m, 4H), 2.38 - 2.30 (m 2H) 1.69 - 1.44 (m, 4 H); $^{13}\text{C NMR}$ (68 MHz, CDCl_3): 157.7, 134.5, 129.2, 113.7, 67.0, 59.0, 55.2, 53.8, 34.9, 29.5, 26.1; **IR** (CDCl_3) ν (cm^{-1}): 3010, 2938, 1612, 1513, 1466, 1245, 1178, 1116, 1036; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{15}\text{H}_{23}\text{NO}_2$ [M+H] 250.1762. Found: 250.1824.

2-ethyl-1,2,3,4-tetrahydroisoquinoline (**3i**)⁶



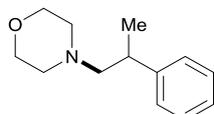
Purification 2: Product was isolated as a pale yellow oil (46 mg, 56%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.21 - 6.93 (m, 4 H), 3.65 (s, 2 H), 2.93 (t, $J = 5.9$ Hz, 2 H), 2.76 (t, $J = 5.9$ Hz, 2 H), 2.61 (q, $J = 7.2$ Hz, 2 H), 1.20 (t, $J = 7.2$ Hz, 3 H); $^{13}\text{C NMR}$ (68MHz, CDCl_3): 134.5, 134.2, 128.6, 126.6, 126.1, 125.6, 55.6, 52.1, 50.6, 29.0, 12.3; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{11}\text{H}_{15}\text{N}$ [M+H] 162.1237. Found 162.1249.

2-isobutyl-1,2,3,4-tetrahydroisoquinoline (**3j**)⁷



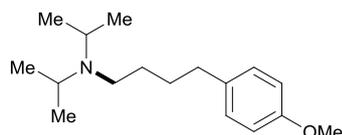
Purification 2: Product was isolated as a pale yellow oil (83 mg, 89%). $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.16 - 7.07 (m, 3H), 7.05 - 6.99 (m, 1H), 3.59 (s, 2H), 2.90 (t, $J = 5.9$ Hz, 2H), 2.69 (t, $J = 5.9$ Hz, 2H), 2.26 (d, $J = 7.4$ Hz, 2H), 1.92 (dh, $J = 7.4, 6.7$ Hz, 1H), 0.95 (d, $J = 6.7$ Hz, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): 135.3, 134.6, 128.6, 126.6, 125.9, 125.5, 66.8, 56.7, 51.1, 29.2, 25.7, 21.0; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{13}\text{H}_{19}\text{N}$ [M+H] 190.1590. Found 190.1595; $\sigma = 0.0036$.

4-(2-phenylpropyl)morpholine (**3k**)⁸



Purification 1: Product was isolated as a pale yellow oil (80 mg, 78%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.39 - 7.09 (m, 5 H), 3.80 - 3.52 (m, 4 H), 3.03 - 2.82 (m, 1 H), 2.55 - 2.24 (m, 6 H), 1.26 (d, $J = 6.9$ Hz, 3 H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): 134.2, 128.4, 127.2, 126.2, 67.0, 66.5, 54.0, 37.0, 20.0; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{13}\text{H}_{19}\text{NO}$ [M+H] 206.1500. Found: 206.1537.

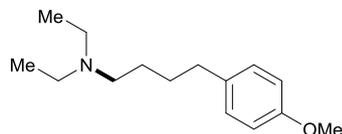
N,N-diisopropyl-4-(4-methoxyphenyl)butan-1-amine (**3l**)



Note, stopping the reaction after the amidation phase indicated 15% amide; the low yield is thus due to hindrance in the amidation step as opposed to reduction.

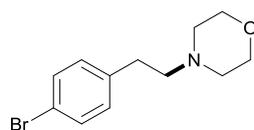
Purification 2: Product was isolated as a yellow oil (20 mg, 15%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.15 - 7.00 (m, 2 H), 6.90 - 6.76 (m, 2 H), 3.78 (s, 3 H), 3.03 (br. s., 2 H), 2.56 (t, $J = 7.5$ Hz, 2 H), 2.42 (t, $J = 6.5$ Hz, 2 H), 1.68 - 1.36 (m, 4 H), 1.02 (d, $J = 6.3$ Hz, 12 H); $^{13}\text{C NMR}$ (68 MHz, CDCl_3): 157.6, 134.9, 129.2, 113.6, 55.2, 48.7, 45.3, 34.9, 30.7, 29.5, 20.4; **IR** (CDCl_3) ν (cm^{-1}): 2937, 2801, 1612, 1513, 1465, 1245, 1178, 1121, 1036, 829; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{17}\text{H}_{29}\text{NO}$ [M+H] 264.2383. Found 264.2332.

N,N-diethyl-4-(4-methoxyphenyl)butan-1-amine (**3m**)



Purification 2: Product was isolated as a pale yellow oil. (32 mg, 27%). $^1\text{H NMR}$ (270 MHz, CDCl_3): 7.18 - 7.02 (m, 2 H), 6.90 - 6.67 (m, 2 H), 3.78 (s, 3 H), 2.70 - 2.32 (m, 8 H), 1.73 - 1.39 (m, 4 H), 1.01 (t, $J = 7.2$ Hz, 6 H); $^{13}\text{C NMR}$ (68 MHz, CDCl_3): 157.6, 134.6, 129.2, 113.6, 55.2, 52.7, 46.8, 34.9, 30.9, 26.4, 11.5; **IR** (CDCl_3) ν (cm^{-1}): 3011, 2937, 1612, 1512, 1466, 1384, 1300, 1245, 1178, 1036; **HRMS** (ESI+): Exact mass calculated for $\text{C}_{15}\text{H}_{25}\text{NO}$ [M+H] 236.1970. Found: 236.2046.

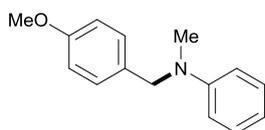
4-(4-bromophenethyl)morpholine (**3n**)⁹



Amidation: Between 2-(4-bromophenyl)acetic acid and morpholine. 16 h, 1.50 equiv. phenylsilane instead of 1.0 equiv. Purification: The crude reaction solution was quenched with HCl in methanol (0.5 mL) and 1 M aq. HCl (0.5 mL), and stirred for 1 h to break-up the enamine by-product. The

solution was diluted in ethyl acetate (7.5 mL) and subjected to the general work up. The crude product was then distilled *in vacuo* at 50 °C for 2 h to remove the final traces of morpholine. Product isolated as yellow oil (80 mg, 60%). **¹H NMR** (300 MHz, CDCl₃) δ 7.48 – 7.32 (m, 2H), 7.15 – 7.04 (m, 2H), 3.75 – 3.70 (m, 4H), 2.80 – 2.70 (m, 2H), 2.61 – 2.46 (m, 6H); **¹³C NMR** (75 MHz, CDCl₃) δ 139.1, 131.4, 130.4, 119.8, 66.9, 60.4, 53.6, 32.7; **HRMS** (ESI+): Exact mass calcd for C₁₂H₁₇BrNO [M+H], 270.0488. Found 270.0474, σ = 0.0518.

N-(4-methoxybenzyl)-*N*-methylaniline¹⁰ (**3p**)



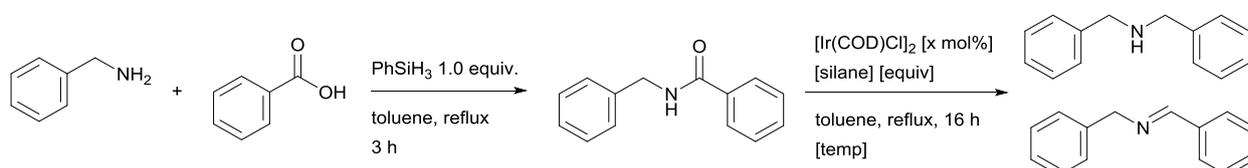
Amidation stage performed with two or three equivalents of carboxylic acid (which increases the conversion of the amidation step for lower reactivity amines such as anilines). Purification 3: (5% EtOAc/pentane) to give a pale yellow oil (62 mg, 54% for 3 equivalents carboxylic acid: 45 mg, 40% for 2 equivalents of carboxylic acid.) **¹H NMR** (400 MHz, CDCl₃) δ 7.25 – 7.19 (m, 2H), 7.18 – 7.13 (m, 2H), 6.88 – 6.83 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 4.47 (s, 2H), 3.79 (s, 3H), 2.99 (s, 3H); **¹³C NMR** (101 MHz, CDCl₃) δ 158.6, 149.8, 130.9, 129.1, 127.9, 116.5, 113.9, 112.5, 56.0, 55.3, 38.3; **HRMS** (ESI+): Exact mass calcd for C₁₅H₁₈NO [M+H], 228.1383. Found 228.1381, σ = 0.0108.

4. Reductive alkylation of primary amines with carboxylic acids

4.1 Optimisation details

Procedure: A flask fitted with a water condenser and an argon balloon was charged with acid (0.16 mmol = 1 equiv.). Toluene (0.35 mL) was added and the solution heated to reflux with stirring before adding phenylsilane (various equiv.) and finally the amine (0.16 mmol) – hydrogen gas evolution was observed. After the stated time, $[\text{Ir}(\text{COD})\text{Cl}]_2$ (various mol%) was added along with phenylsilane (various equiv.) by temporary removal of the condenser and addition, and the reaction refluxed again for the stated time. After this time, the reaction was quenched with methanol, cooled, concentrated and the conversion calculated by comparison to an added internal standard (1,1,2,2-tetrachloroethane) by $^1\text{H-NMR}$ in chloroform.

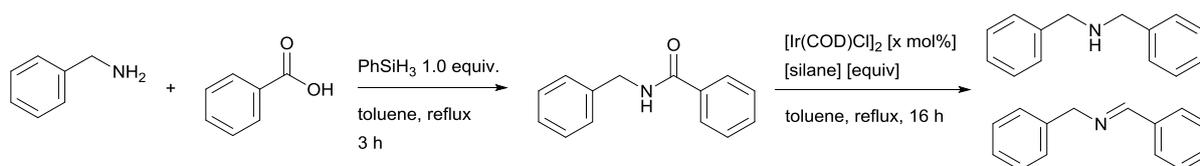
Initial optimisation



Entry	Cat mol%	Reductive Silane	Eq.	Temp °C	Result
1	1	Et_2SiH_2	4	RT	12:59:30 imine:amide:amine
2	1	Et_2SiH_2	4	80	5:4 amine:imine
3	1	PhSiH_3	2	80	major is amide
4	2	Et_2SiH_2	4	80	no amide. >4:1 amine:imine
5	2	PhSiH_3	2	80	3.5:1 amide:amine (imine minor)
6	4	PhSiH_3	2	110-80	15:5:1 amide:amine:imine
7	1	$\text{Et}_2\text{SiH}_2(2)$ $\text{PhSiH}_3(2)$		110	amine:imine (1:2), no amide.

^aAll reactions were carried out on a 0.16 mmol scale with respect to amine with 0.35 mL of toluene as reaction solvent. After the required time, the reaction was quenched with methanol, concentrated and conversion to the amide was measured by $^1\text{H-NMR}$ spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

Secondary optimisation



Entry	amid. time/h	cat. mol %	Et_2SiH_2 eq.	red. time/h	temp °C	Result
1	3	2.0	4.0	16	110	3:1 amine:imine, no amide
2	3	3.0	5.0	16	80	trace imine
3	3	2.5	5.0	16	80	~9:1 amine:imine
4	3	3.0	4.0	1	110	~9:1 amine:imine
5	3	3.0	4.0	3	110	trace imine, no amide
6	2	3.0	3.0	2	110	trace imine
7 ^b	2	3.0	3.0	2	110	77% isolated

^aAll reactions were carried out on a 0.16 mmol scale with respect to amine with 0.35 mL of toluene as reaction solvent. After the required time, the reaction was quenched with methanol, concentrated and conversion to the amide was measured by ¹H-NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. ^b0.75 equiv. PhSiH_3 used in amidation step.

A wide range of conditions are generally effective. The temperature can often be dropped to 80 °C without serious loss of conversion for the reduction step. Amidation benefits from higher temperature (see section 2). The diethylsilane loading can be increased to 4 equivalents to aid difficult reductions if required. Typical side-products include unreduced amide, imine, and starting amine, which may be liberated from its imine on work-up. Note that silylated amines are often observed as the initial product (see Brookhart procedure referenced in the main article), which are hydrolysed upon work-up.

4.2 General procedure for the reductive alkylation of primary amines with carboxylic acids

An oven-dried 10 mL round-bottom flask fitted with a water condenser and an argon balloon was charged with carboxylic acid (0.50 mmol). Anhydrous toluene (0.6 mL) and phenylsilane (0.38 or 0.50 mmol) were added and the flask incubated in an oil bath at 111-115 °C to dissolve the acid (if required/possible). On a small scale, the amine (0.5 mmol) was then added carefully by microsyringe by temporary removal of the condenser, generally accompanied by the vigorous release of hydrogen gas. *Note that at smaller scales, the amine can be added to the (almost) refluxing solution; for larger scale reactions a large volume of hydrogen is released, and it is preferable to remove the reaction from the heat and add the amine portionwise at a lower temperature.* After 2 or 13-15 h, the reaction was removed from the heat and allowed to cool slightly. Then $[\text{Ir}(\text{COD})\text{Cl}]_2$ (15 μmol , 3.0 mol%) was added along with diethylsilane (1.5 mmol) (volatile, cool reaction before adding). After 5

min, the reaction was returned to the heat and the reaction refluxed over 2-3 h. After this time, the reaction was purified in one of the following ways.

Purification 1: Reaction quenched with methanol and stirred to give a precipitate (silicon based), which was filtered off before further purification.

Purification 2: The residue was dissolved in a minimum of diethyl ether and added dropwise to a solution of HCl (1.0 M) in diethyl ether to give a precipitate, the HCl salt of the amine. Amine-HCl salt filtered. The solid was partitioned between 3 M NaOH and dichloromethane and the organics separated. The aqueous was extracted two further times, the organics combined, dried over magnesium sulfate, filtered and concentrated to give the amine.

Purification 3: The residue was dry loaded onto silica and purified by flash column chromatography.

Purification 4: The hot reaction was quenched with silica and gas evolution allowed to complete before being concentrated (i.e. an instant dry load) and purified directly by flash column chromatography.

Purification 5: The reaction was cooled, concentrated and taken up in ethyl acetate. The organics were extracted with 3 x HCl (1M aqueous solution) and the combined aqueous fractions basified to > pH10 by careful addition of sodium hydroxide (6 M, aqueous) with ice-bath cooling. The aqueous layer was extracted with dichloromethane (four portions), the combined organics dried (MgSO₄) and concentrated *in vacuo*.

Notes: The reaction is best performed from the free base. The amine and acid can be combined first, before adding the silane last to initiate the reaction. The room temperature combination of acid and amine in toluene sometimes this leads to a salting out of the ammonium carboxylate which may hinder the reaction efficiency, however successful reactions have been performed in this way.

4.2.2 Reductive alkylation under non-inert conditions

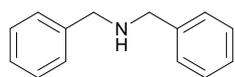
The full reduction reaction with dibenzylamine (**5a**) has been performed in *undried glassware*, *Winchester-grade toluene* and *open to air* (no argon balloon). On a 0.16 mmol scale, the reaction (1.0 PhSiH₃, amidation 15 h, reduction 2 h) gave a conversion to the desired amine of 60%. At 0.50 mmol scale (1.0 PhSiH₃, amidation 15 h, reduction 3 h), the conversion was 82%. These conversions compare well with the isolated yield under controlled conditions (2 h amidation, 2 h reduction) of 77%.

In non-controlled cases it may be helpful to increase the silane loading by ~0.1 equivalents to consume the excess moisture. Additionally, it is recommended that such reactions are performed over the longer reaction times (particularly the amidation step).

4.3 Data and specific experimental details for secondary amines 5a-l

Amines prepared according to the general method above. Reaction times, varying equivalents and purification details shown below if required.

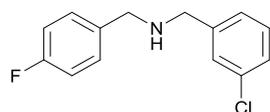
Dibenzylamine (**5a**)¹¹



Amidation: Between benzoic acid and benzylamine. 2 h, 0.75 equiv. phenylsilane. Purification: 4, eluting with 10% EtOAc in petrol. Product isolated as pale yellow oil (76 mg, 77%).

¹H NMR (400 MHz, CDCl₃) δ 7.45 - 7.23 (m, 10 H), 3.86 (s, 4 H), 1.93 (br. s., 1 H); **¹³C NMR** (101 MHz, CDCl₃) δ 140.3, 128.3, 128.1, 126.9, 53.1; **HRMS** (ESI+): Exact mass calcd for C₁₄H₁₆N [M+H], 198.1277. Found 198.1286, σ = 0.0059.

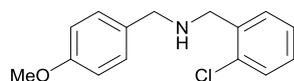
N-(3-chlorobenzyl)-1-(4-fluorophenyl)methanamine (**5b**)



Amidation: Between 4-fluorobenzoic acid and (3-chlorophenyl)methanamine. 13 h, 0.75 equiv. phenylsilane. Purification steps: 1, 2 and 3 (dry-loaded onto silica pretreated with triethylamine. Eluted with 5-20% EtOAc in pentane). Product isolated as pale yellow oil (98 mg, 79%).

¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.19 (m, 6H), 7.10 - 6.95 (m, 2H), 3.78 (s, 2H), 3.77 (s, 2H), 1.60 (s, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 161.9 (d, J = 244.7 Hz), 142.3, 135.8 (d, J = 3.1 Hz), 134.2, 129.6, 129.6 (d, J = 7.8 Hz), 128.1, 127.1, 126.2, 115.1 (d, J = 20.8 Hz), 52.5, 52.3; **AT-IR** (neat) ν (cm⁻¹): 3306, 3064, 2827, 1600, 1574, 1508, 1219, 773; **HRMS** (ESI+): Exact mass calcd for C₁₄H₁₄ClFN [M+H], 250.0793. Found 250.0805, σ = 0.0375.

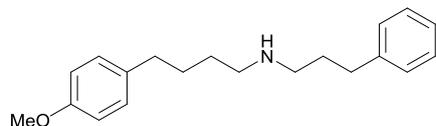
N-(2-chlorobenzyl)-1-(4-methoxyphenyl)methanamine (**5c**)¹²



Amidation: Between 4-methoxybenzoic acid and (2-chlorophenyl)methanamine. 13 h, 1.00 equiv. phenylsilane. Purification: 5 and then 3, eluting with 2-12% EtOAc in pentane, using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (87 mg, 66%).

¹H NMR (400 MHz, CDCl₃) δ 7.44 - 7.34 (m, 2H), 7.31 - 7.14 (m, 4H), 6.91 - 6.86 (m, 2H), 3.90 (s, 2H), 3.81 (s, 3H), 3.76 (s, 2H), 1.82 (s, 1H); **¹³C NMR** (101 MHz, CDCl₃) δ 158.6, 137.6, 133.7, 132.2, 130.2, 129.5, 129.3, 128.2, 126.7, 113.7, 55.2, 52.5, 50.6; **HRMS** (ESI+): Exact mass calcd for C₁₅H₁₆ClNNaO [M+Na], 284.0813. Found 284.0801, σ = 0.0330.

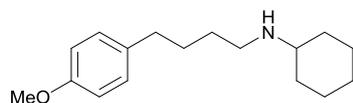
4-(4-methoxyphenyl)-N-(3-phenylpropyl)butan-1-amine (**5d**)



Amidation: Between 4-(4-methoxyphenyl)butanoic acid and 3-phenylpropan-1-amine 13 h, 0.75 equiv. phenylsilane. Purification: Petrol/EtOAc 0-100%, then flush with 20% MeOH in EtOAc. Product eluted partially as a (silicate?) salt, which was removed by dissolving in EtOAc and washing with sodium bicarbonate. (Column would benefit from inclusion of triethylamine.) Product isolated as pale yellow oil (115 mg, 77%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33 – 7.25 (m, 2H), 7.22 – 7.15 (m, 3H), 7.12 – 7.07 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 2.69 – 2.60 (m, 6H), 2.57 (t, $J = 7.5$ Hz, 2H), 1.89 – 1.77 (m, 2H), 1.66 – 1.47 (m, 4H), 1.27 (s, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) 157.6, 142.0, 134.5, 129.2, 128.3, 128.3, 125.7, 113.6, 55.2, 49.7, 49.4, 34.8, 33.6, 31.5, 29.5, 29.4; **AT-IR** (neat) ν (cm^{-1}): 3026, 3002, 2930, 1611, 1510, 1454, 1243, 1177, 1031, 819; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{20}\text{H}_{28}\text{NO}$ [M+H], 298.2165. Found 298.2163, $\sigma = 0.0173$.

N-(4-(4-methoxyphenyl)butyl)cyclohexanamine (**5e**)¹³

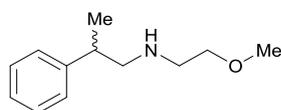


Amidation: Between 4-(4-methoxyphenyl)butanoic acid and cyclohexanamine. 13 h, 0.75 equiv. phenylsilane. Purification: 1, concentrated filtrate, dry loaded onto silica, loaded onto an equally short silica bed, washed with pentane (50 mL), then 4:96 EtOAc:pentane, and then finally the product was eluted cleanly with EtOAc/2% Et_3N and concentrated to give the amine.

Product isolated as pale yellow oil (106 mg, 81%).

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.13 – 7.01 (m, 2H), 6.85 – 6.75 (m, 2H), 3.76 (s, 3H), 2.65 – 2.58 (m, 2H), 2.55 (t, $J = 7.5$ Hz, 2H), 2.37 (tt, $J = 10.5, 3.7$ Hz, 1H), 1.93 – 1.79 (m, 2H), 1.76 – 1.66 (m, 2H), 1.66 – 1.54 (m, 3H), 1.54 – 1.43 (m, 2H), 1.32 – 0.94 (m, 5H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) 157.6, 134.5, 129.1, 113.6, 56.8, 55.1, 46.8, 34.8, 33.6, 30.0, 29.5, 26.1, 25.0; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{17}\text{H}_{27}\text{NO}$ [M+H], 262.2165. Found 262.2170, $\sigma = 0.0005$.

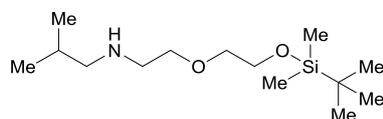
N-(2-methoxyethyl)-2-phenylpropan-1-amine (**5f**)



Amidation: Between 2-phenylpropanoic acid (1.20 equivalents) and 2-methoxyethan-1-amine. 13 h, 1.00 equiv. phenylsilane. Purification: 5, then 3 with 0-100% EtOAc in pentane, before eluting with 10% MeOH in EtOAc (+2 % Et₃N) using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (57 mg, 60%).

¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 3.43 (t, *J* = 5.3 Hz, 2H), 3.30 (s, 3H), 2.94 (ddq, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz, 1H), 2.85 – 2.68 (m, 4H), 1.54 (s, 1H), 1.26 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 145.3, 128.4, 127.1, 126.2, 71.8, 58.6, 57.1, 49.1, 39.9, 19.9; **AT-IR** (neat) ν (cm⁻¹): 3330, 3028, 2928, 2877, 2821, 1666, 1452, 1115, 910; **HRMS** (ESI⁺): Exact mass calcd for C₁₂H₂₀NO [M+H], 194.1539. Found 194.1561, σ = 0.0042.

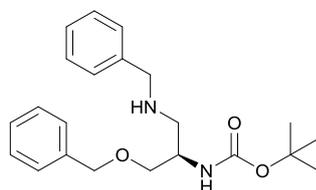
N-(2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (**5g**)



Amidation: Between isobutyric acid and 2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine. 16 h, 1.00 equiv. phenylsilane. Purification: Reaction quenched with methanol, concentrated, dissolved in dichloromethane, washed with saturated sodium bicarbonate solution, dried over MgSO₄ and concentrated. The crude residue was then purified by flash column chromatography with pentane/EtOAc/MeOH (0-100% gradient EtOAc, then 5% MeOH in EtOAc). Product isolated as a pale yellow oil (119 mg, 86%).

¹H NMR (400 MHz, CDCl₃) δ 3.75 (t, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 5.3 Hz, 2H), 2.78 (t, *J* = 5.3 Hz, 2H), 2.44 (d, *J* = 6.9 Hz, 2H), 2.14 (br. s, 1H), 1.76 (dh, *J* = 6.9, 6.7 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 6H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) 72.5, 70.5, 62.7, 58.0, 49.5, 28.3, 25.9, 20.7, 18.4, -5.3; **AT-IR** (neat) ν (cm⁻¹): 2954, 2929, 2857, 1674, 1463, 1252, 1102, 832; **HRMS** (ESI⁺): Exact mass calcd for C₁₄H₃₄NO₂Si [M+H], 276.2353. Found 276.2352, σ = 0.0062.

tert-butyl (*R*)-(1-(benzylamino)-3-(benzyloxy)propan-2-yl)carbamate (**5h**)

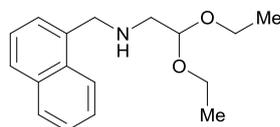


Amidation: Between *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-L-serine and benzylamine. 13 h, 0.75 equiv. phenylsilane. Purification: 1, concentration, and then 3, eluting with 2-20% EtOAc in petrol, using triethylamine treated silica for the dry load and column. Product isolated as pale yellow oil (114 mg, 62%).

¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.00 (m, 10H), 5.11 (s, 1H), 4.58 – 4.43 (m, 3H), 3.87 (s, 1H), 3.84 – 3.73 (m, 2H), 3.67 – 3.45 (m, 2H), 2.93 – 2.71 (m, 2H), 1.45 (s, 9H); ¹³C NMR (101 MHz, CDCl₃) 155.7,

140.2, 138.0, 128.4, 128.3, 128.0, 127.6, 127.6, 126.9, 79.6, 73.2, 70.6, 53.7, 50.1, 49.7, 28.4; **AT-IR** (neat) ν (cm^{-1}): 3313, 3030, 2974, 2930, 2867, 1696 (C=O), 1495, 1454, 1365, 1165, 734; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_3$ [M+H], 371.2329. Found 371.2327, $\sigma = 0.0015$.

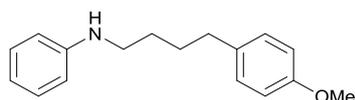
2,2-diethoxy-*N*-(naphthalen-1-ylmethyl)ethan-1-amine (**5i**)¹⁴



Amidation: Between 1-naphthoic acid and 2,2-diethoxyethan-1-amine. 16 h, 1.00 equiv. phenylsilane. Purification: Reaction quenched with methanol, concentrated, dissolved in dichloromethane, washed with 1.0 M sodium hydroxide solution, dried over MgSO_4 and concentrated. The residue was dry loaded onto silica, and purified by flash column chromatography with pentane/EtOAc (0-100% gradient, with 0.5 mol% Et_3N throughout on Et_3N pre-treated treated silica). Product isolated as a yellow oil (90 mg, 66%).

^1H NMR (400 MHz, CDCl_3) δ 8.17 – 8.09 (m, 1H), 7.91 – 7.82 (m, 1H), 7.81 – 7.73 (m, 1H), 7.58 – 7.37 (m, 4H), 4.65 (t, $J = 5.6$ Hz, 1H), 4.27 (s, 2H), 3.74 – 3.63 (m, 2H), 3.57 – 3.45 (m, 2H), 2.87 (d, $J = 5.6$ Hz, 2H), 1.70 (s, 1H), 1.19 (t, $J = 7.1$ Hz, 6H); **^{13}C NMR** ((101 MHz, CDCl_3) δ 135.8, 133.9, 131.8, 128.7, 127.7, 126.0, 126.0, 125.6, 125.4, 123.6, 102.1, 62.3, 52.0, 51.5, 15.4 **HRMS** (ESI+): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{NO}_2$ [M+H], 274.1802. Found 274.1807, $\sigma = 0.0009$.

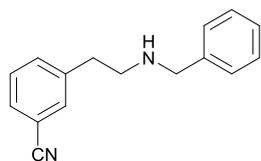
N-(4-(4-methoxyphenyl)butyl)aniline (**5j**)¹⁵



Amidation: Between 4-(4-methoxyphenyl)butanoic acid (2.00 equiv.) and aniline. 16 h, 1.00 equiv. phenylsilane. Purification: Purified by method 2 and then by flash column chromatography with pentane/EtOAc (0-40% gradient). Product isolated as a very pale yellow oil (81 mg, 63%).

^1H NMR (400 MHz, CDCl_3) δ 7.22 – 7.15 (m, 2H), 7.15 – 7.07 (m, 2H), 6.89 – 6.82 (m, 2H), 6.74 – 6.68 (m, 1H), 6.64 – 6.58 (m, 2H), 3.81 (d, $J = 1.1$ Hz, 4H), 3.14 (t, $J = 7.0$ Hz, 2H), 2.62 (t, $J = 7.2$ Hz, 2H), 1.80 – 1.57 (m, 4H). **^{13}C NMR** (101 MHz, CDCl_3) 157.7, 148.3, 134.2, 129.2, 129.2, 117.2, 113.7, 112.7, 55.2, 43.9, 34.7, 29.1, 29.0; **HRMS** (ESI+): Exact mass calcd for $\text{C}_{17}\text{H}_{22}\text{NO}$ [M+H], 256.1696. Found 256.1683, $\sigma = 0.0041$.

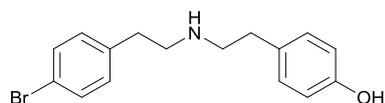
3-(2-(benzylamino)ethyl)benzonitrile (**5k**)



Amidation: Between 2-(3-cyanophenyl)acetic acid and benzylamine. 16 h, 1.00 equiv. phenylsilane. Purification: Purified by method 5 and then by flash column chromatography with pentane/EtOAc/Et₃N (0-30% gradient EtOAc, with 0.5 mol% Et₃N throughout). Product isolated as a very pale yellow oil (39 mg, 35%).

¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.47 (m, 2H), 7.46 – 7.42 (m, 1H), 7.41 – 7.22 (m, 6H), 3.81 (s, 2H), 2.94 – 2.88 (m, 2H), 2.88 – 2.82 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) 141.5, 139.8, 133.3, 132.2, 129.9, 129.2, 128.5, 128.1, 127.1, 118.9, 112.4, 53.7, 49.8, 35.9; **AT-IR** (neat) ν (cm⁻¹): 3062, 3029, 2926, 2228 (-CN), 1643, 1451, 735; **HRMS** (ESI+): Exact mass calcd for C₁₆H₁₇N₂ [M+H], 237.1386. Found 237.1389, σ = 0.0269;

4-(2-((4-bromophenethyl)amino)ethyl)phenol (**5l**)

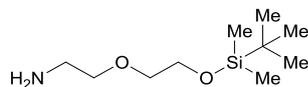


Amidation: Between 2-(4-bromophenyl)acetic acid and 4-(2-aminoethyl)phenol (tyramine). 16 h, 1.50 equiv. phenylsilane. Purification: Quenched with HCl in methanol, stirred for 1 h, concentrated, HCl precipitated by adding a solution of the crude residue slowly to HCl (1.0 M in ether). The salt was partitioned between sodium bicarbonate solution/water (just enough to neutralise the salt) and dichloromethane, and the organic layer dried and concentrated. The residue was dry loaded onto silica, and purified by flash column chromatography with pentane/EtOAc (0-100% gradient). Product isolated as an off-white solid (77 mg, 48%).

¹H NMR (400 MHz, Methanol-*d*₄) δ 7.41 – 7.37 (m, 2H), 7.09 – 7.05 (m, 2H), 6.99 – 6.94 (m, 2H), 6.71 – 6.67 (m, 2H), 2.85 – 2.65 (m, 8H); ¹³C NMR ((101 MHz, Methanol-*d*₄) δ 157.0, 140.1, 132.6, 131.6, 131.4, 130.6, 121.0, 116.3, 51.9, 51.5, 35.8, 35.6; **AT-IR** (neat) ν (cm⁻¹): 3273, 2918, 2850, 1513, 1448, 1271, 1256, 1105, 815, 733; **HRMS** (ESI+): Exact mass calcd for C₁₆H₁₉BrNO [M+H], 320.0645. Found 320.0630, σ = 0.0832.

Substrates synthesised:

2-(2-((tert-butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (**2g**)¹⁶



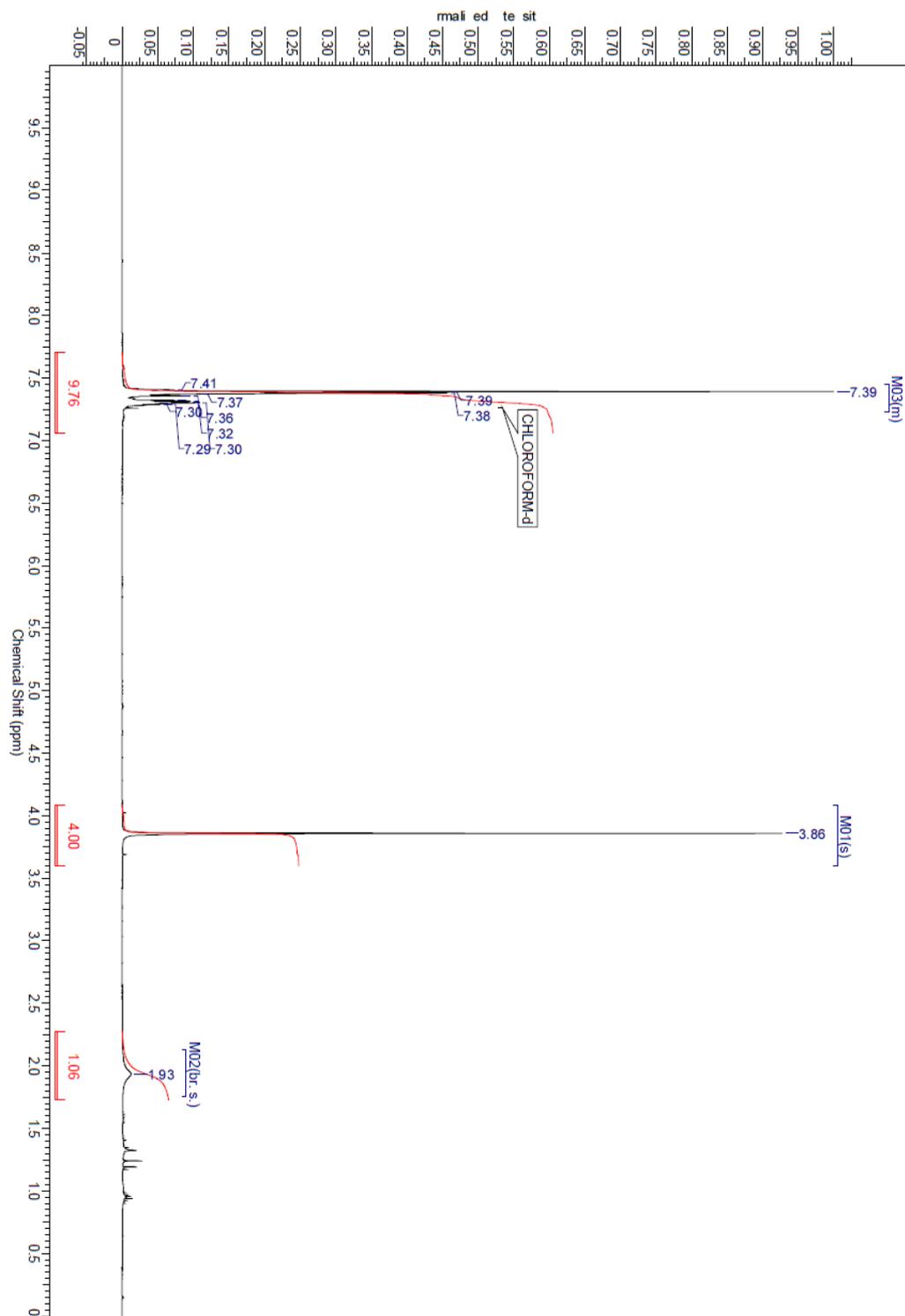
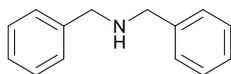
2-(2-aminoethoxy)ethan-1-ol (5.30 mmol, 557 mg) was dissolved in dichloromethane (10 mL) with imidazole (1.08 g, 15.9 mmol) at room temperature before adding tert-butylchlorodimethylsilane (10.6 mmol, 1.61 g) and stirring for 20 h. The reaction was quenched with water, solid sodium chloride was added and the organic layer separated and washed with brine, dried and concentrated. The crude was purified by flash column chromatography (pentane/ether) to give the desired as a clear oil (1.13 g, 97%).

¹H NMR (400 MHz, CDCl₃) δ 3.80 – 3.69 (m, 2H), 3.57 – 3.43 (m, 4H), 2.86 – 2.81 (m, 2H), 1.60 (s, 2H), 0.90 – 0.86 (m, 9H), 0.07 – 0.03 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ 73.4, 72.4, 62.7, 41.9, 25.9, 18.3, -5.3; HRMS (ESI+): Exact mass calcd for C₁₀H₂₆NO₂Si [M+H], 220.1727. Found 220.1737, σ = 0.0050.

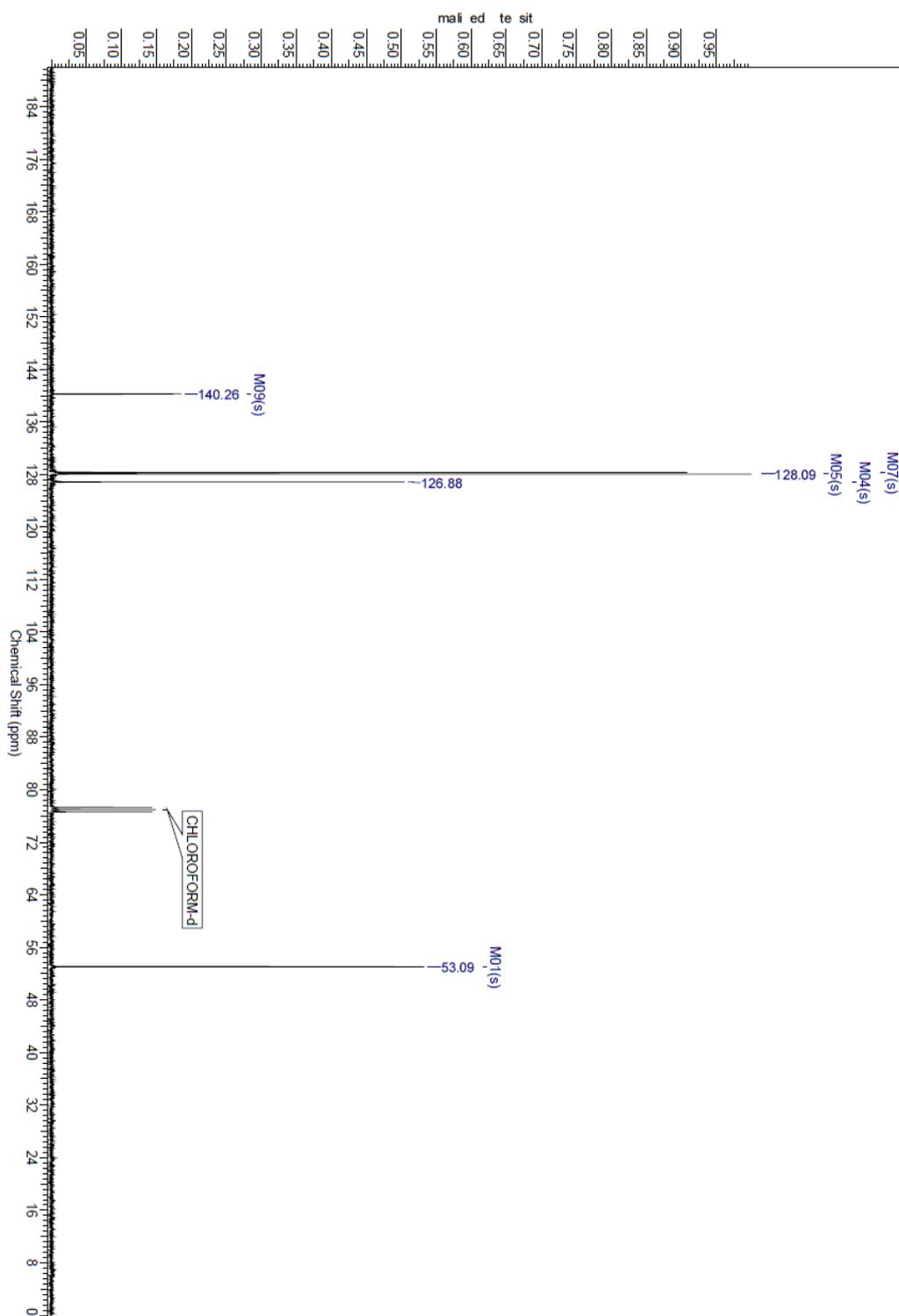
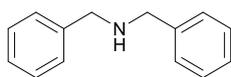
5.0 Spectra for all compounds

5.1 Secondary amines

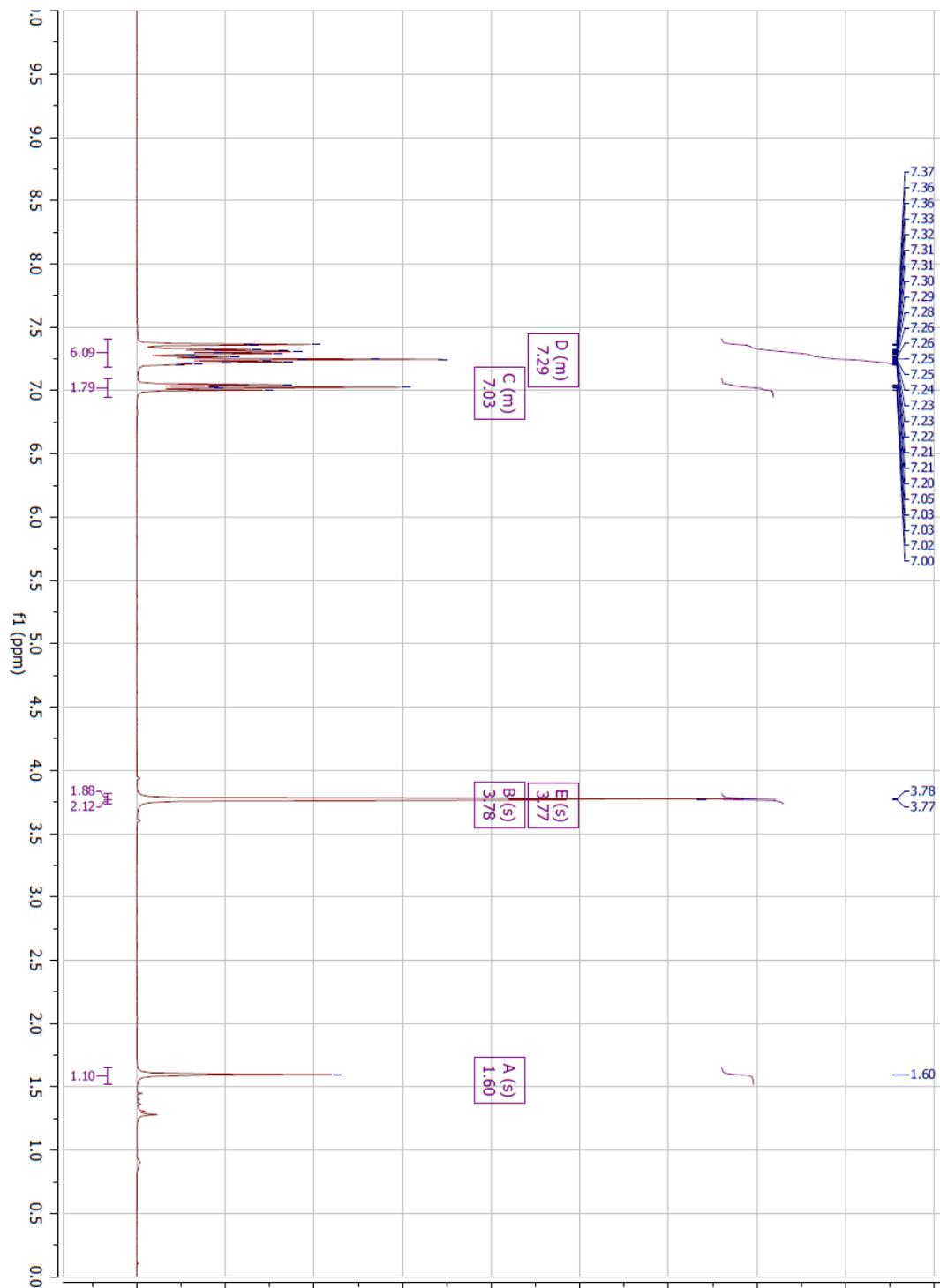
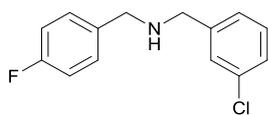
^1H NMR (400 MHz, CDCl_3): Dibenzylamine (5a)



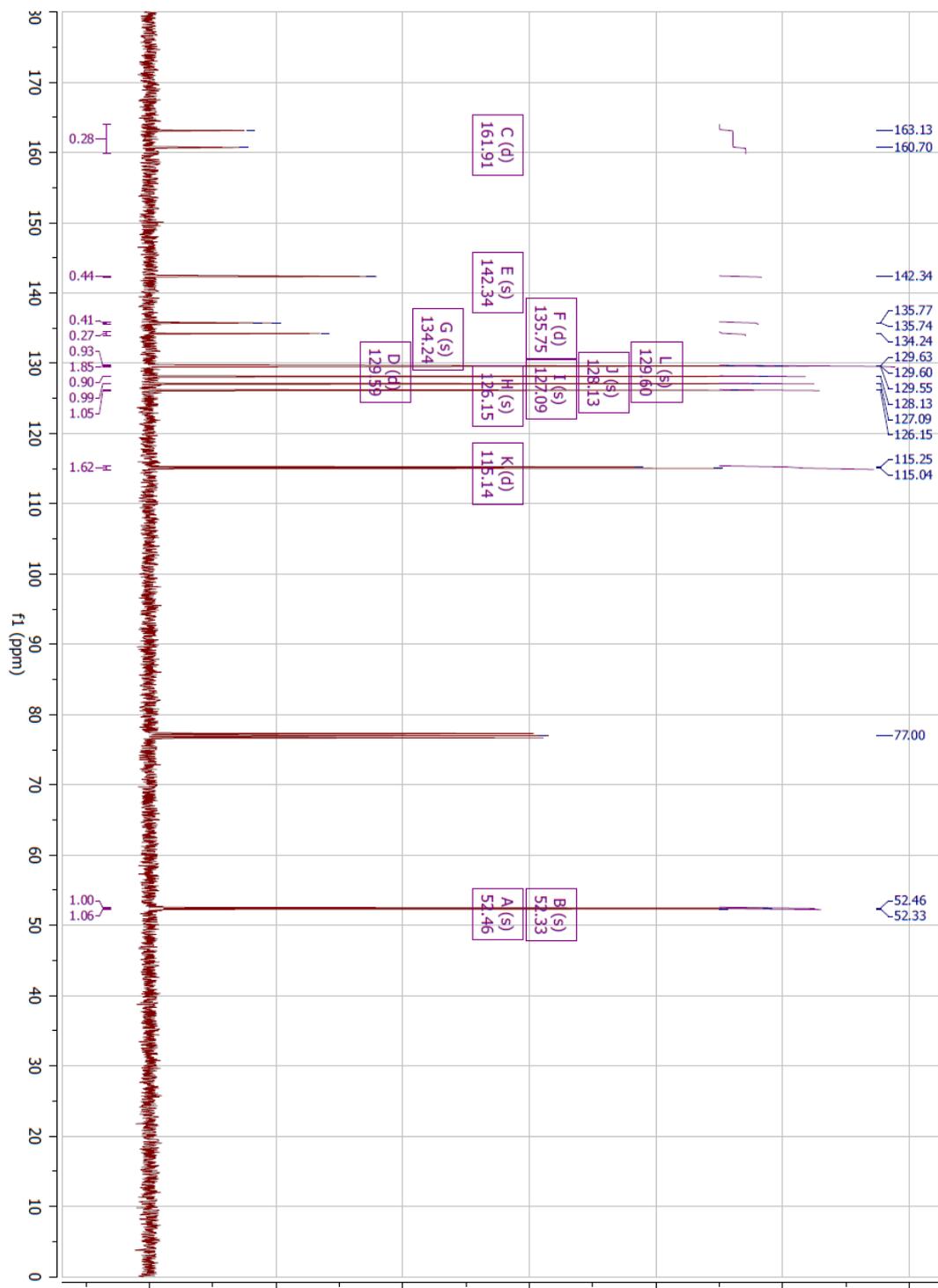
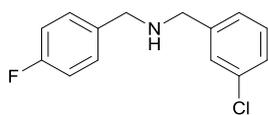
^{13}C NMR (101 MHz, CDCl_3): Dibenzylamine (**5a**)



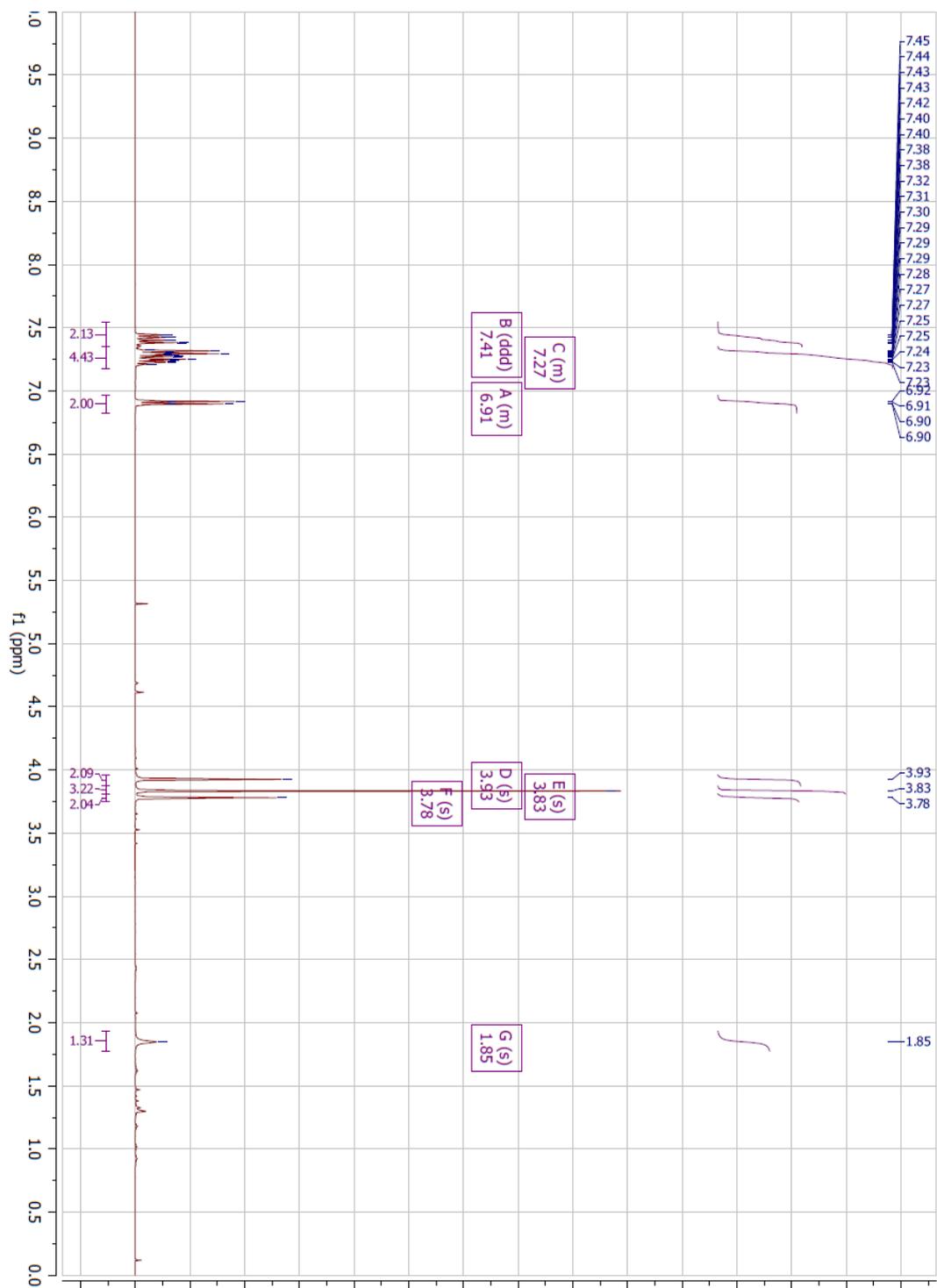
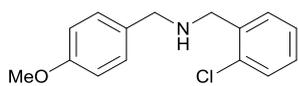
^1H NMR (400 MHz, CDCl_3): *N*-(3-chlorobenzyl)-1-(4-fluorophenyl)methanamine (**5b**)



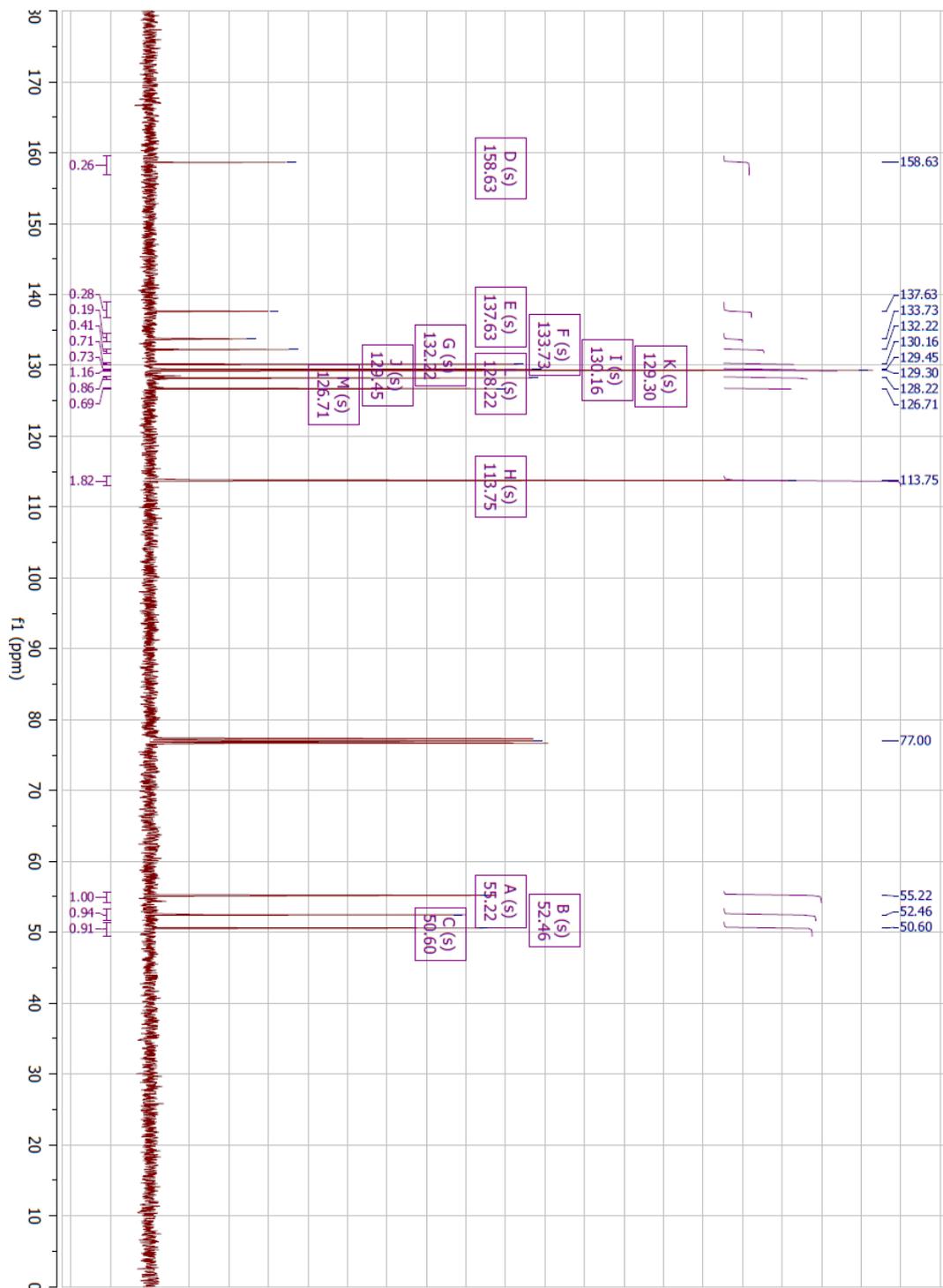
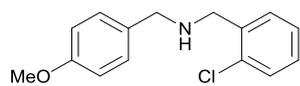
^{13}C NMR (101 MHz, CDCl_3): *N*-(3-chlorobenzyl)-1-(4-fluorophenyl)methanamine (**5b**)



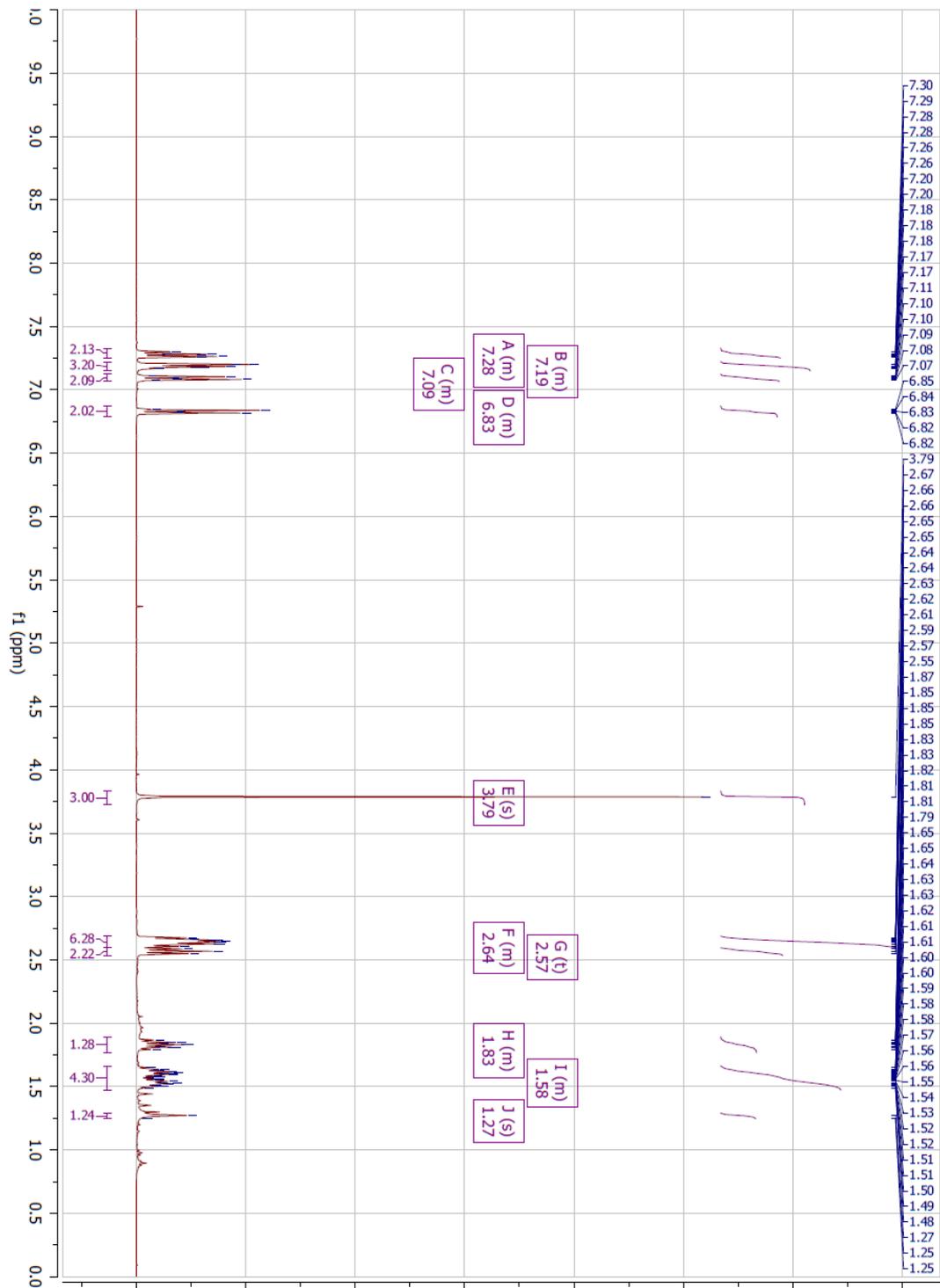
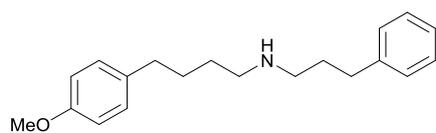
^1H NMR (400 MHz, CDCl_3): *N*-(2-chlorobenzyl)-1-(4-methoxyphenyl)methanamine (**5c**)



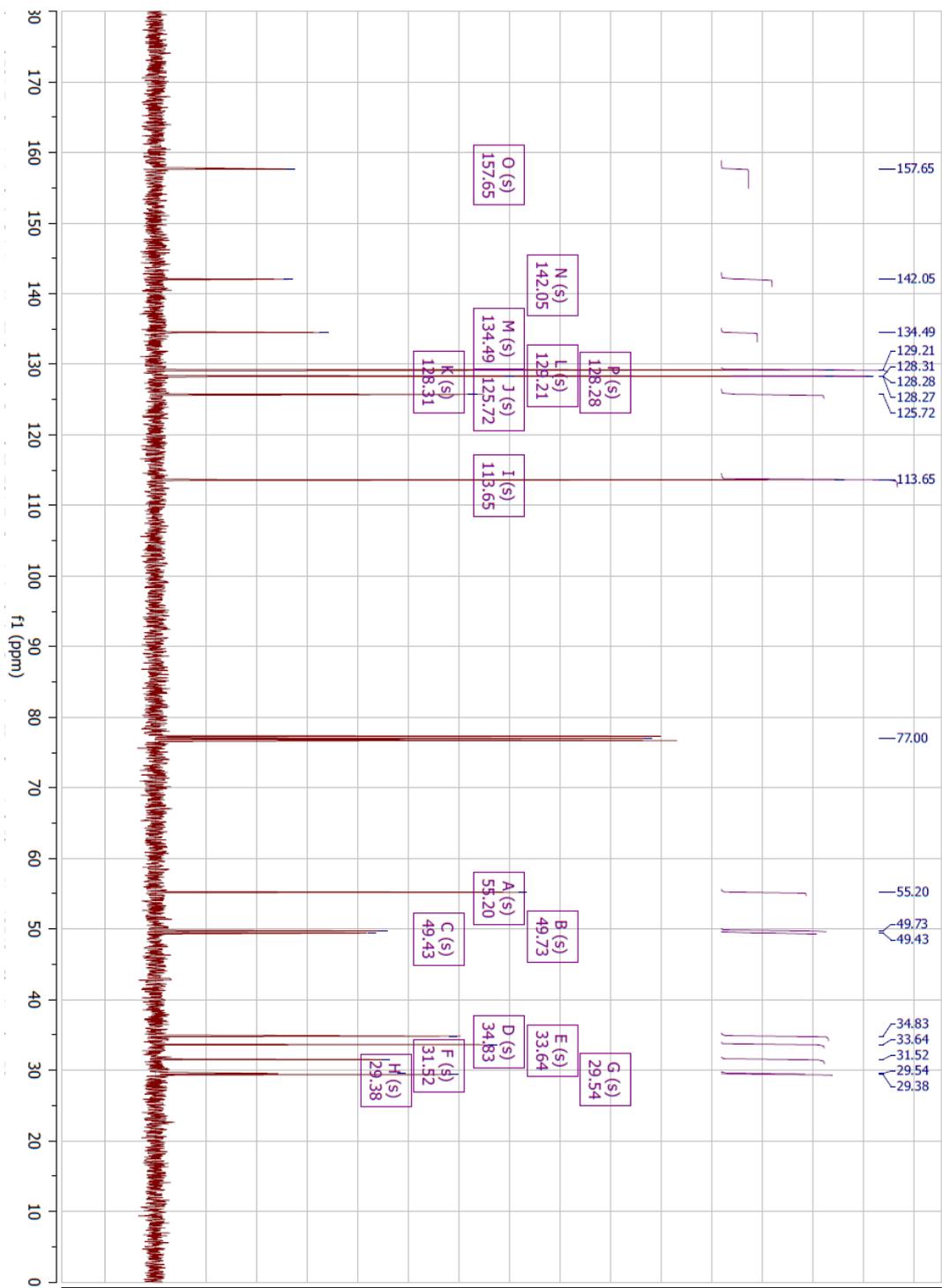
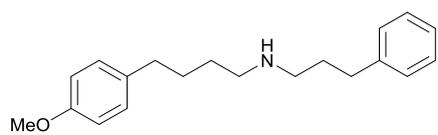
^{13}C NMR (101 MHz, CDCl_3): *N*-(2-chlorobenzyl)-1-(4-methoxyphenyl)methanamine (**5c**)



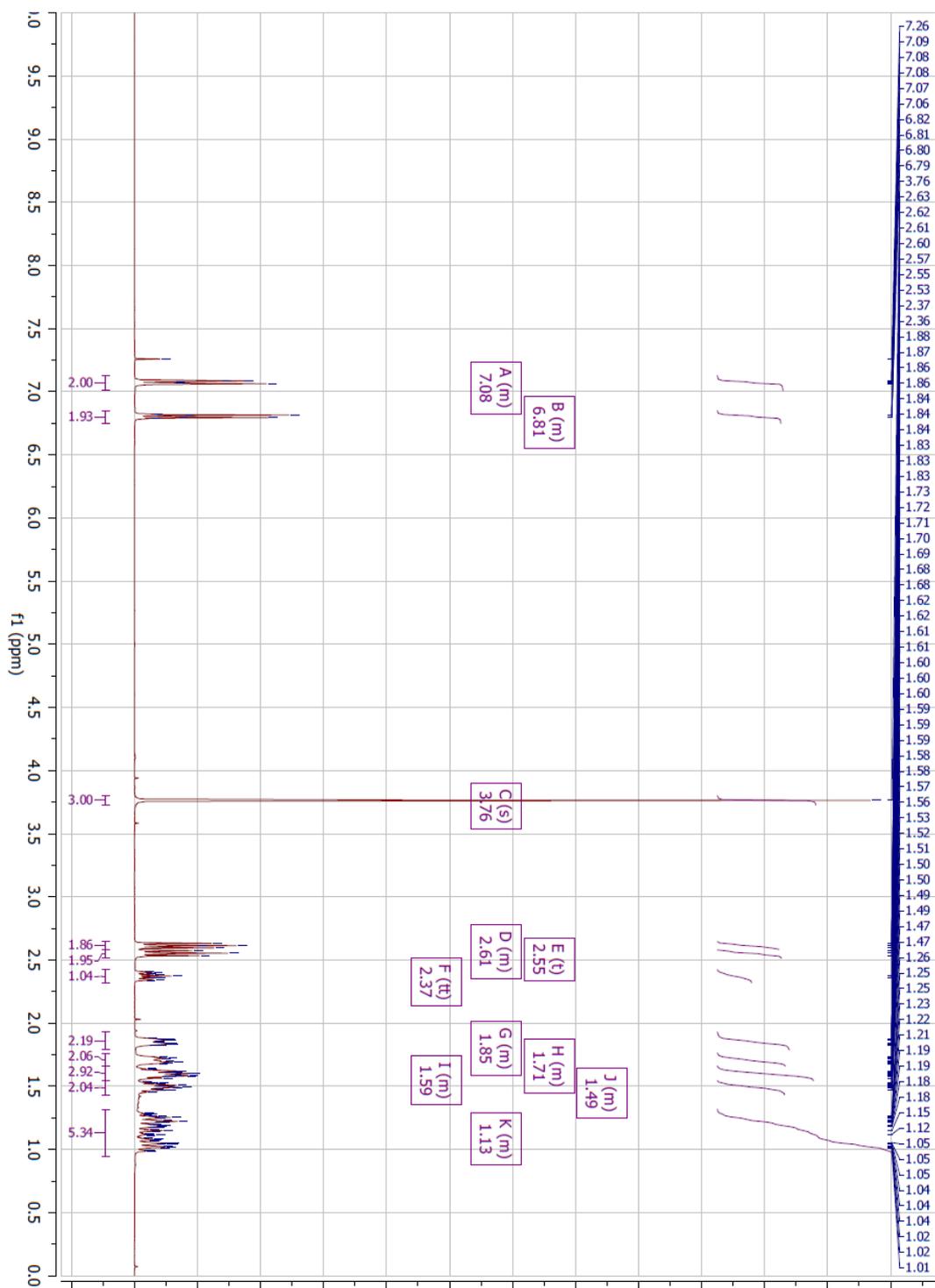
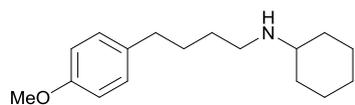
¹H NMR (400 MHz, CDCl₃): 4-(4-methoxyphenyl)-N-(3-phenylpropyl)butan-1-amine (5d)



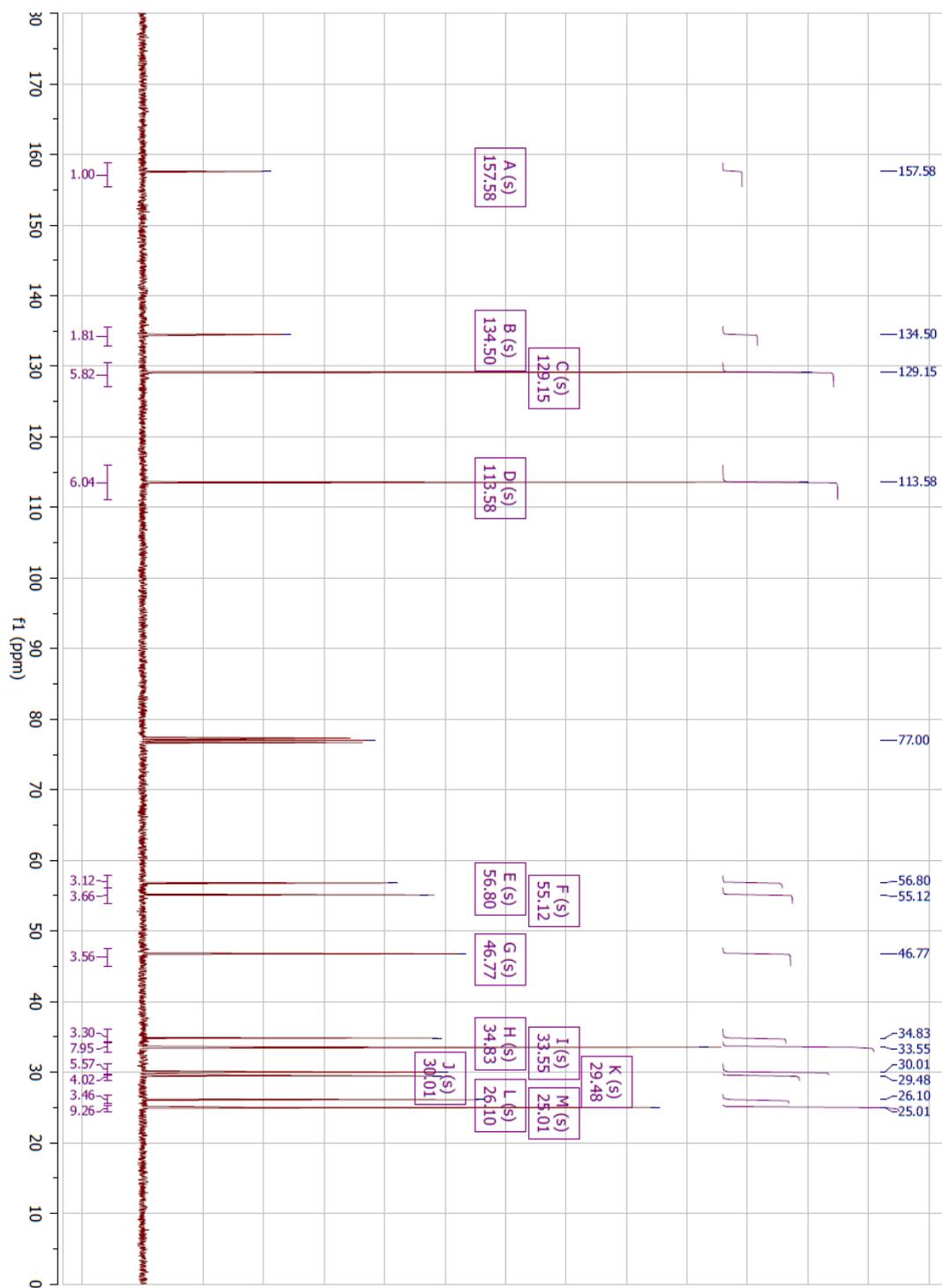
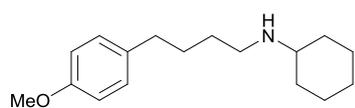
¹³C NMR (101 MHz, CDCl₃): 4-(4-methoxyphenyl)-N-(3-phenylpropyl)butan-1-amine (**5d**)



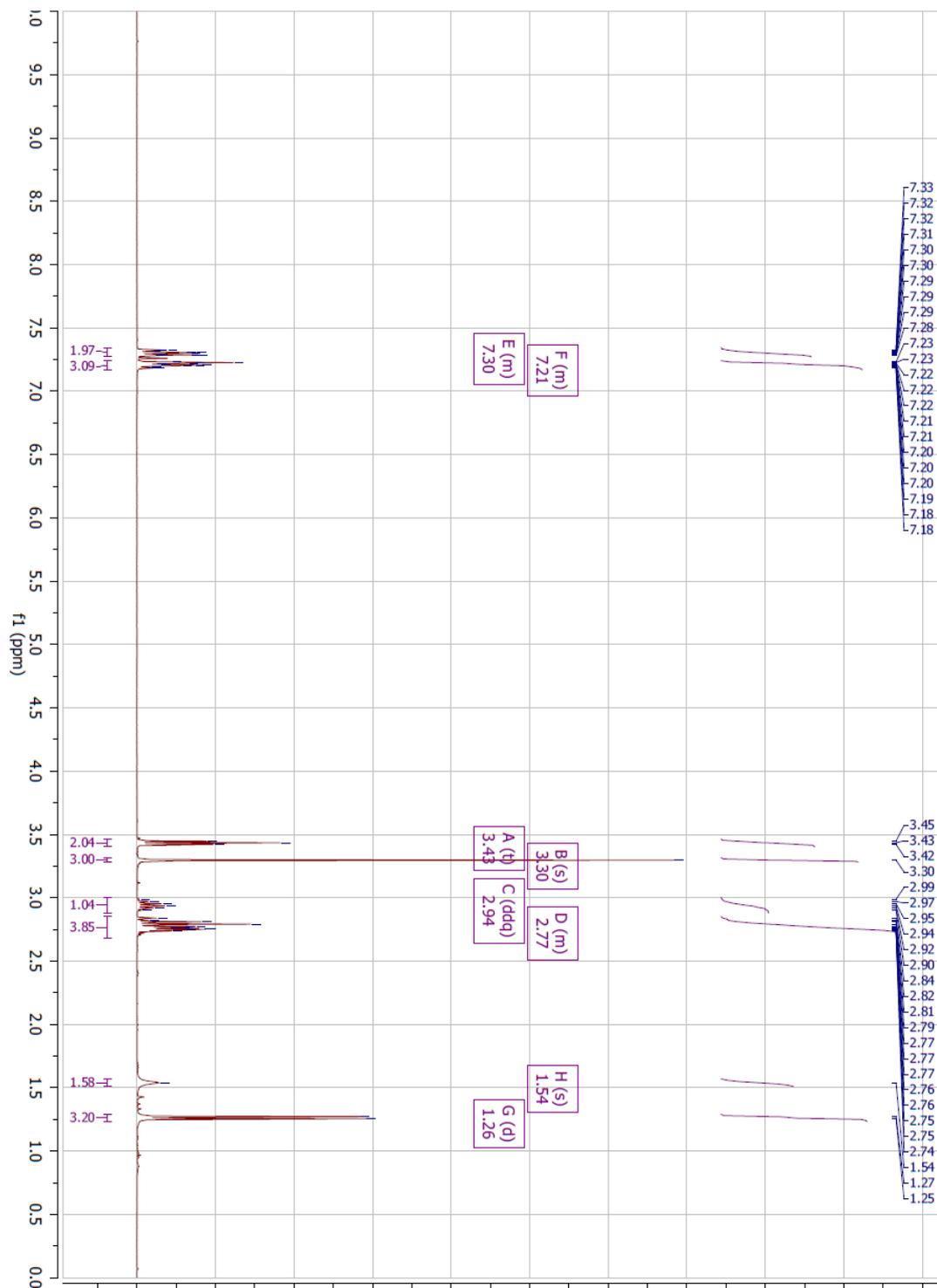
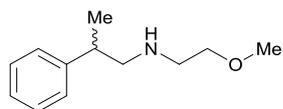
¹H NMR (400 MHz, CDCl₃): *N*-(4-(4-methoxyphenyl)butyl)cyclohexanamine (**5e**)



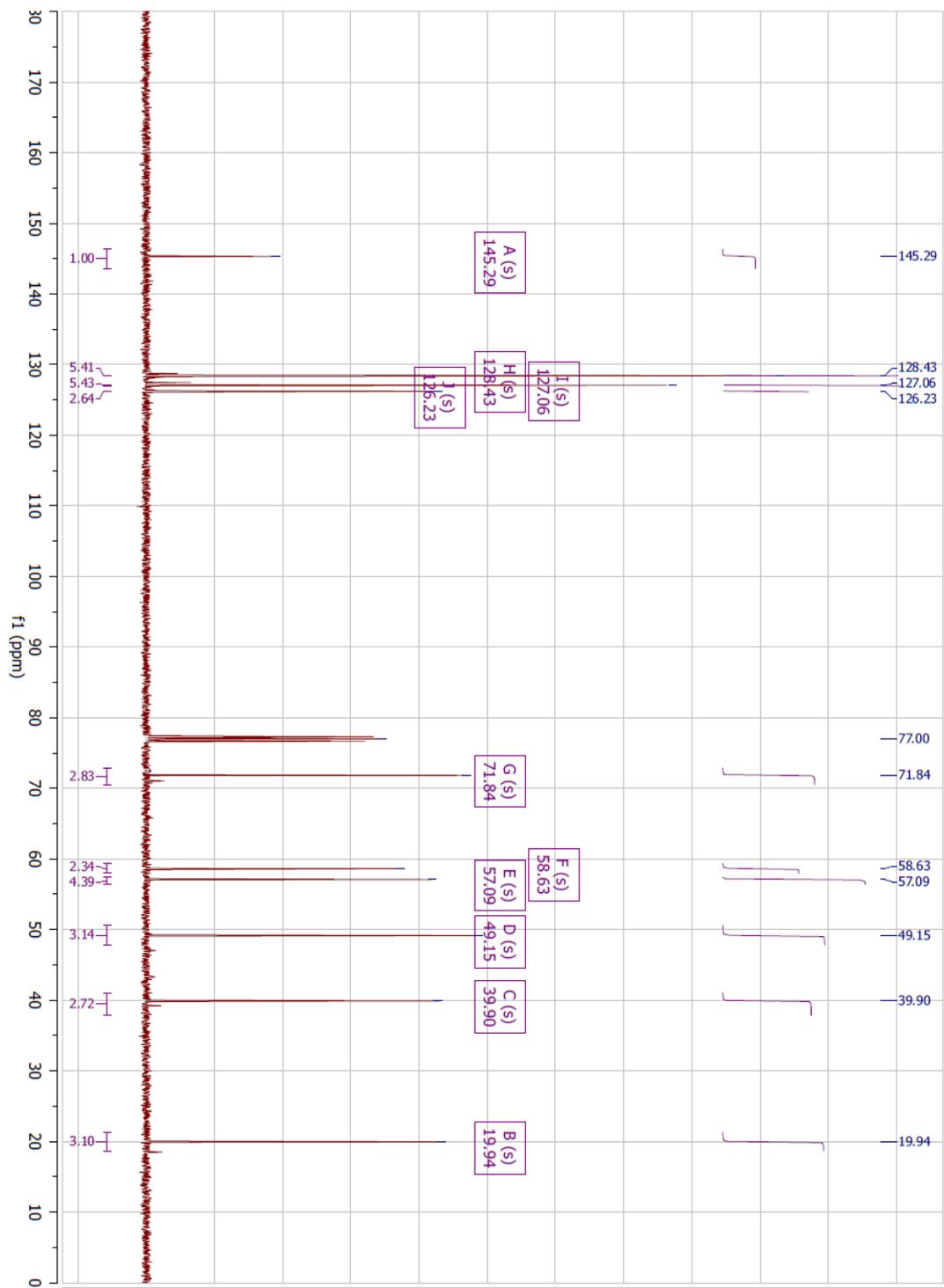
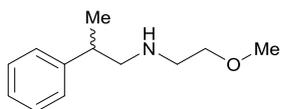
¹³C NMR (101 MHz, CDCl₃): *N*-(4-(4-methoxyphenyl)butyl)cyclohexanamine (**5e**)



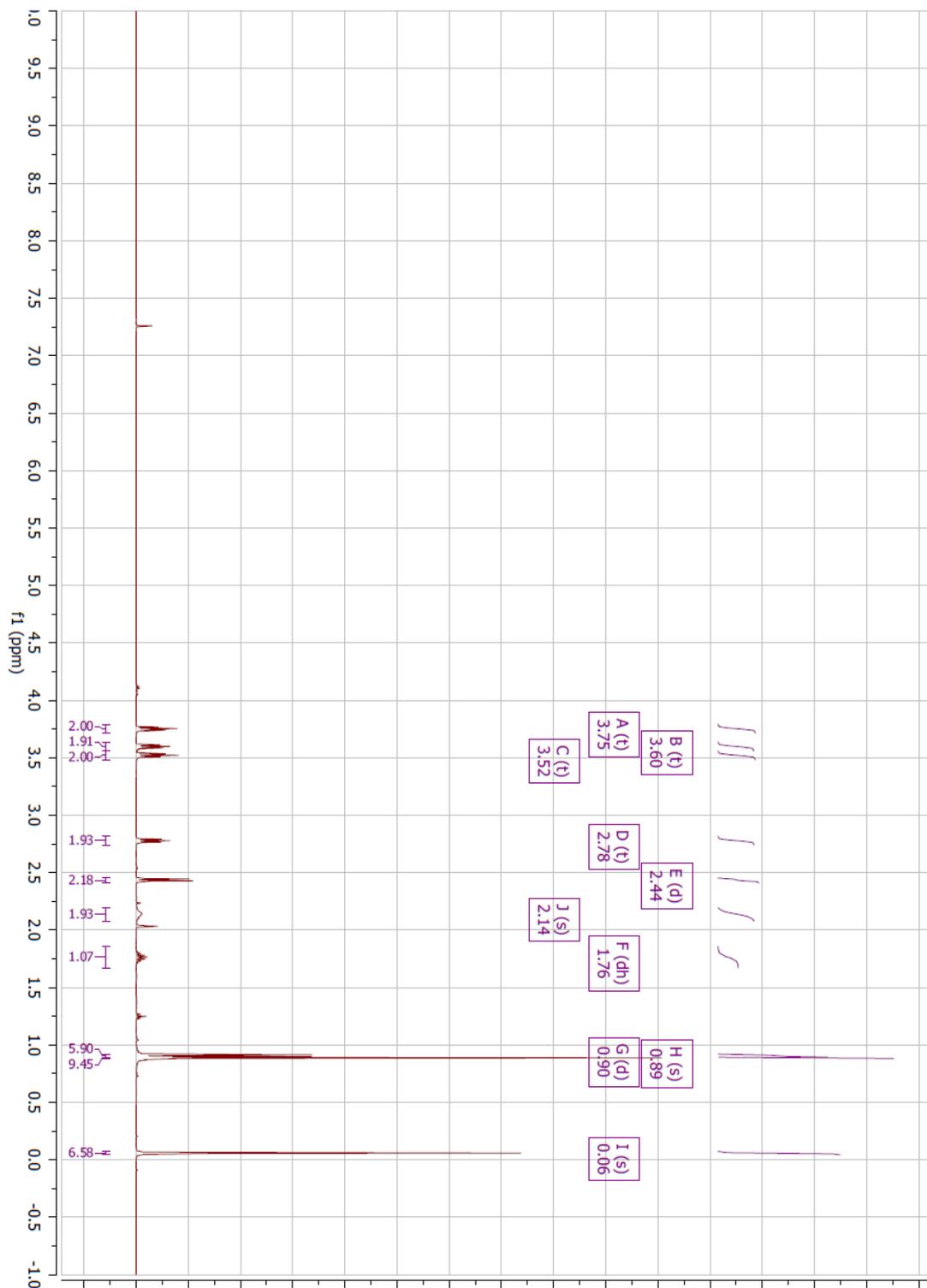
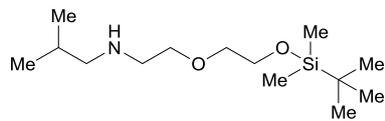
^1H NMR (400 MHz, CDCl_3): *N*-(2-methoxyethyl)-2-phenylpropan-1-amine (**5f**)



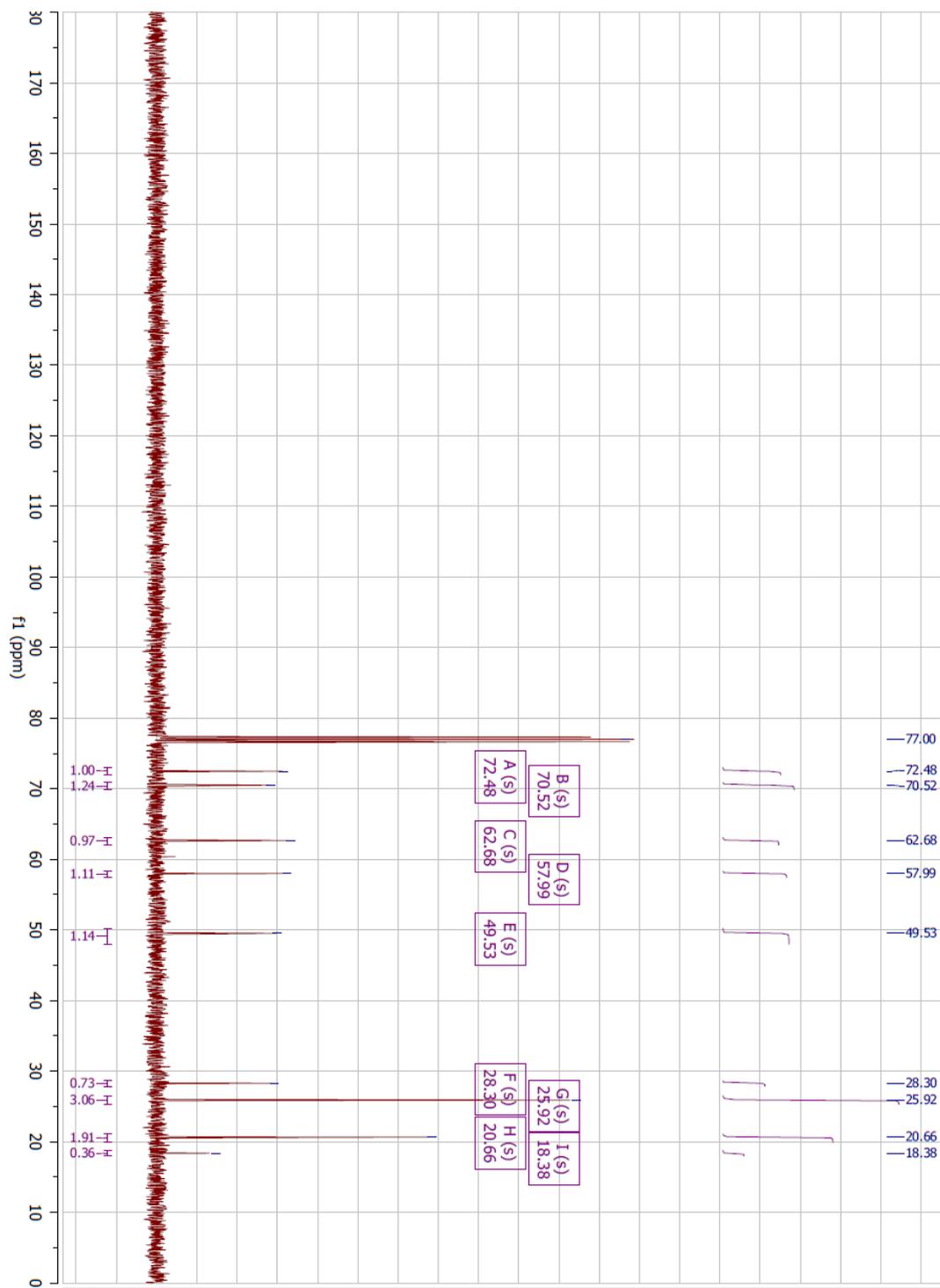
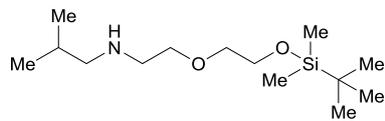
^{13}C NMR (101 MHz, CDCl_3): *N*-(2-methoxyethyl)-2-phenylpropan-1-amine (**5f**)



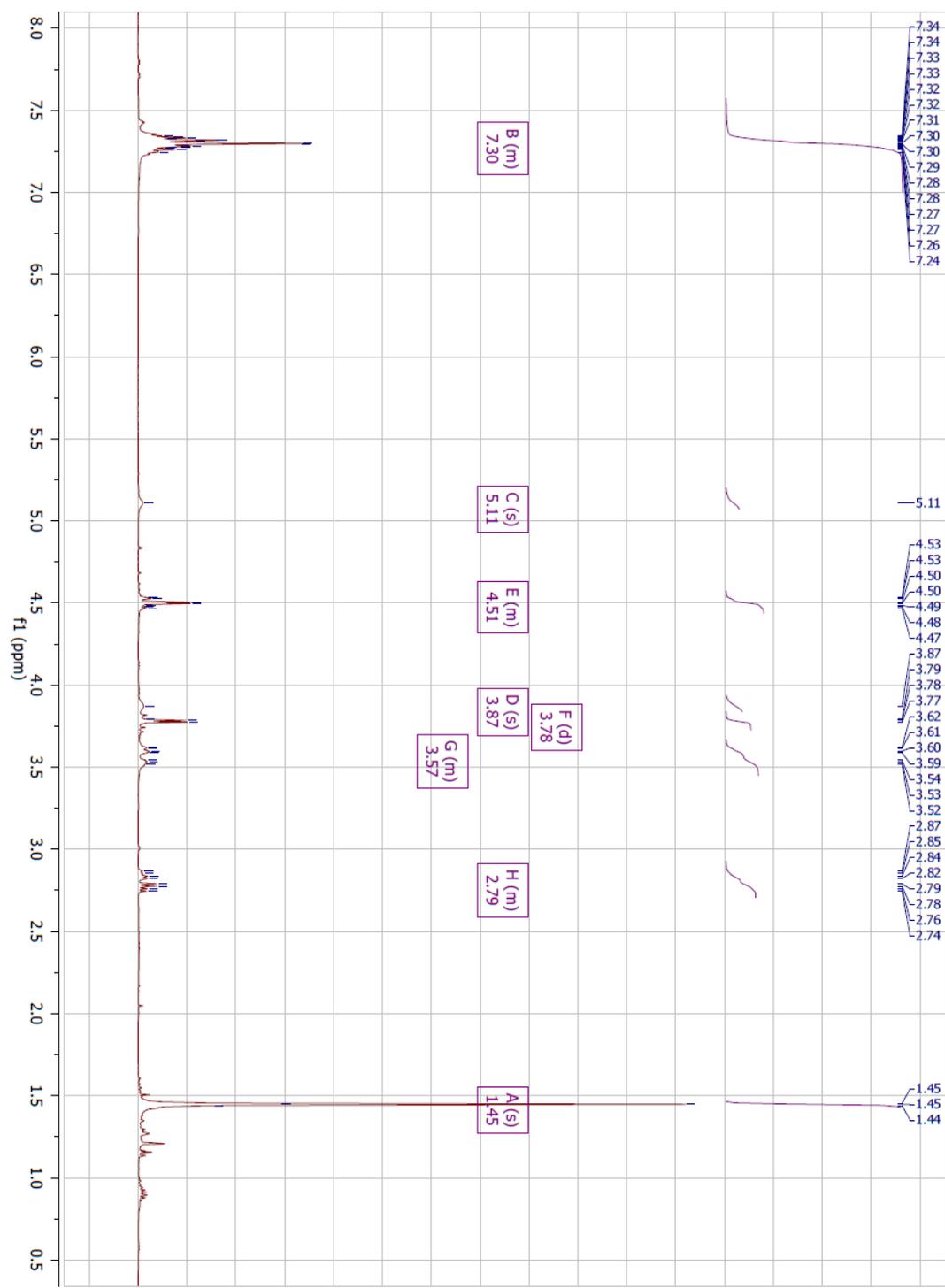
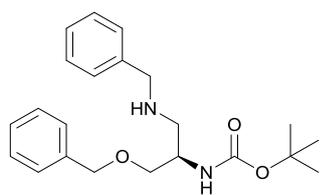
^1H NMR (400 MHz, CDCl_3): *N*-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (**5g**)



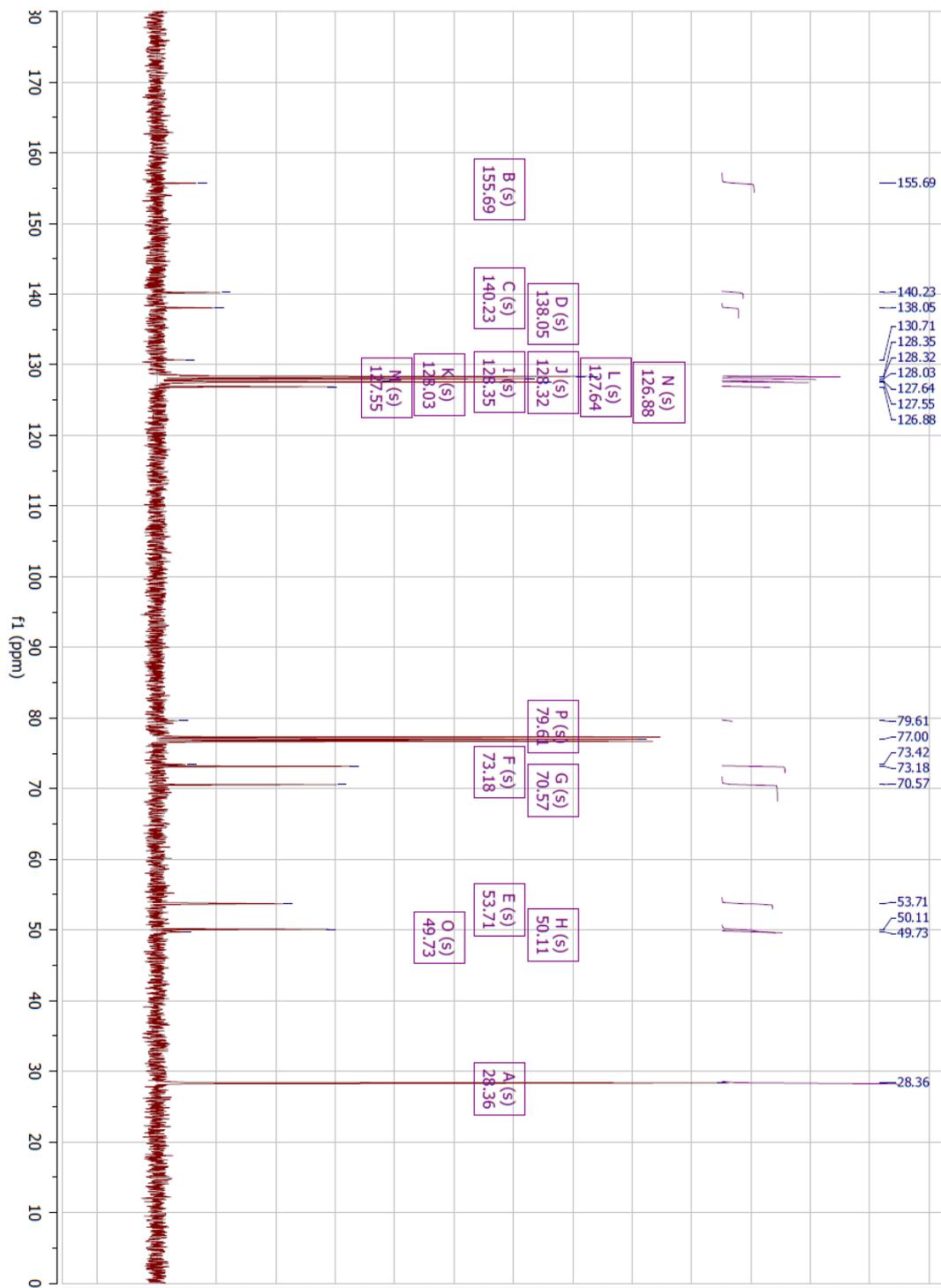
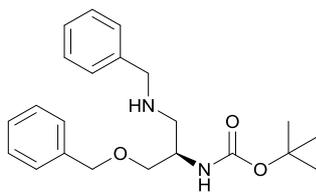
^{13}C NMR (101 MHz, CDCl_3): *N*-(2-(2-((*tert*-butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (**5g**)



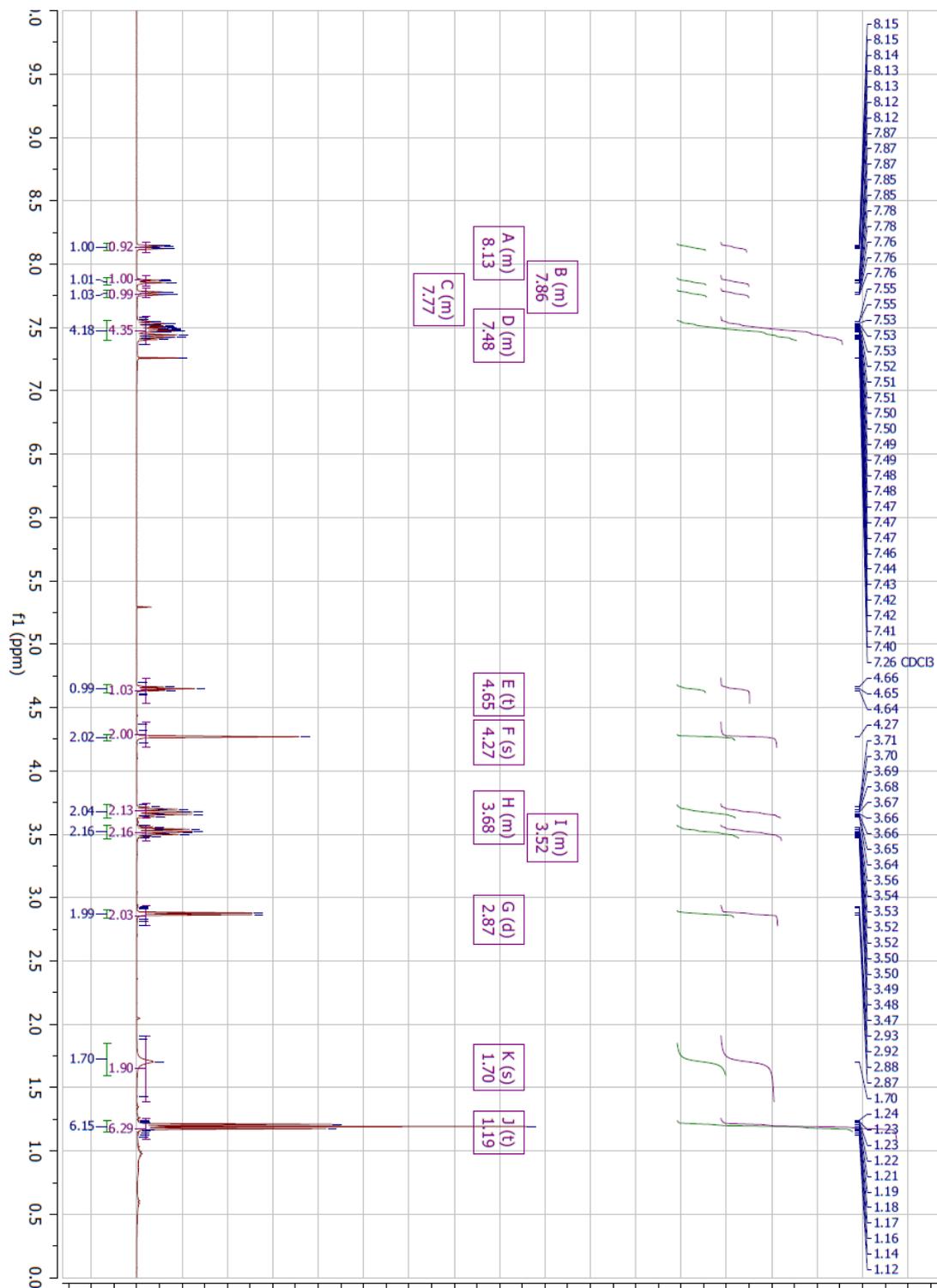
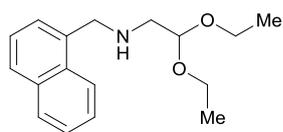
^1H NMR (400 MHz, CDCl_3): *tert*-butyl (*R*)-(1-(benzylamino)-3-(benzyloxy)propan-2-yl)carbamate (**5h**)



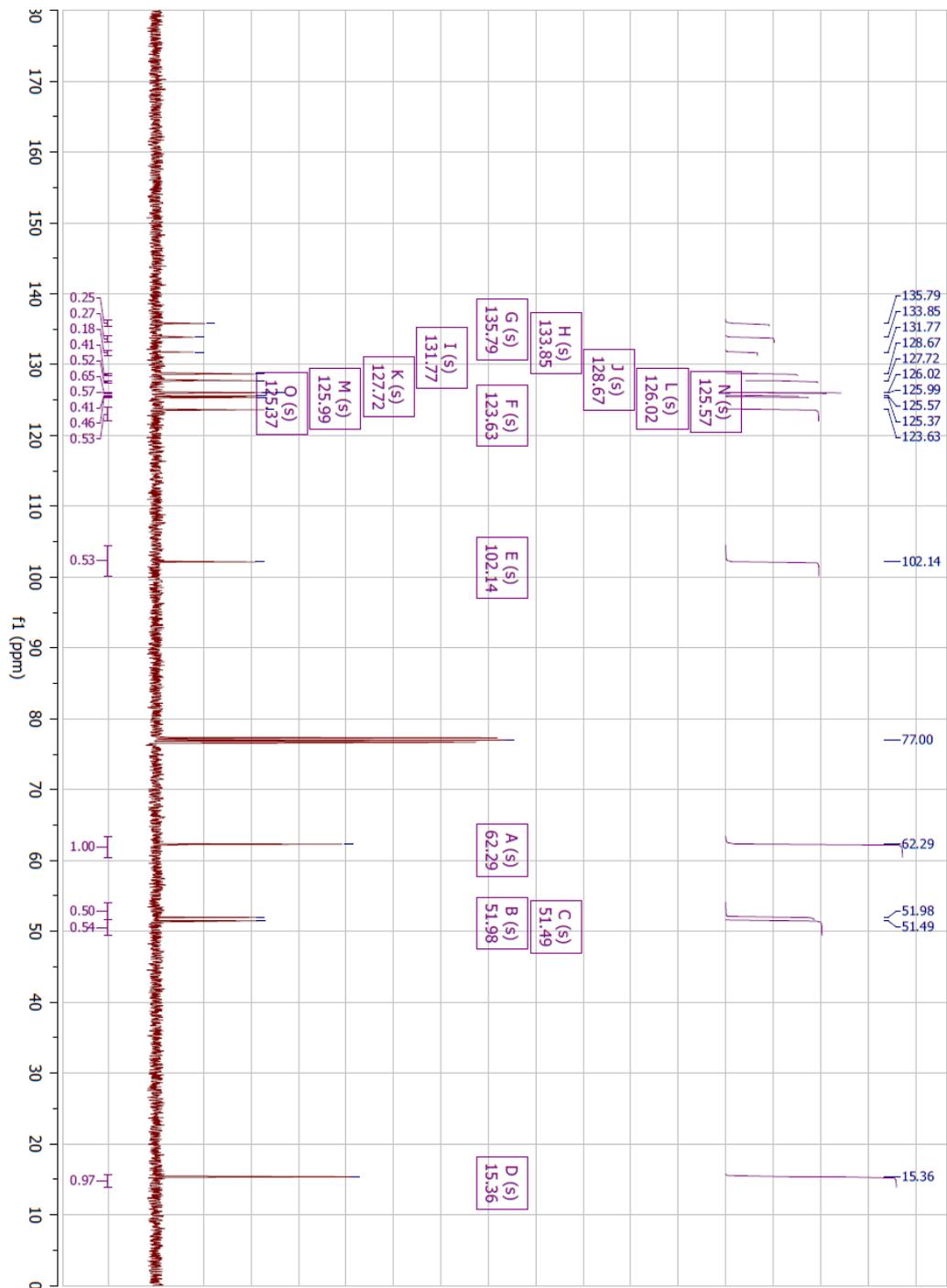
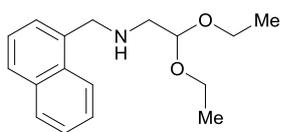
¹³C NMR (101 MHz, CDCl₃): *tert*-butyl (*R*)-(1-(benzylamino)-3-(benzyloxy)propan-2-yl)carbamate (**5h**)



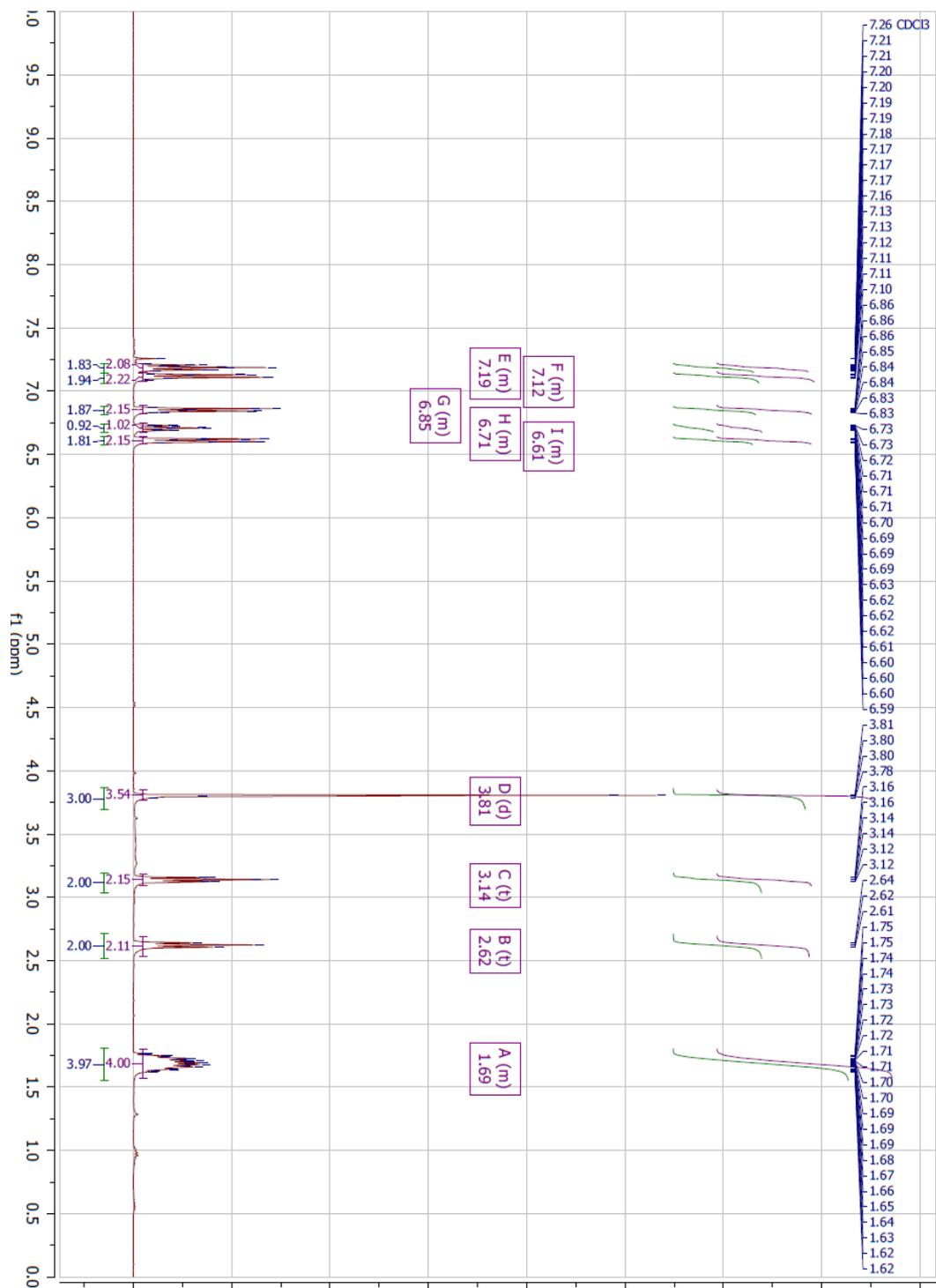
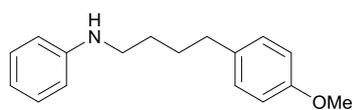
¹H NMR (400 MHz, CDCl₃): 2,2-diethoxy-N-(naphthalen-1-ylmethyl)ethan-1-amine (**5i**)



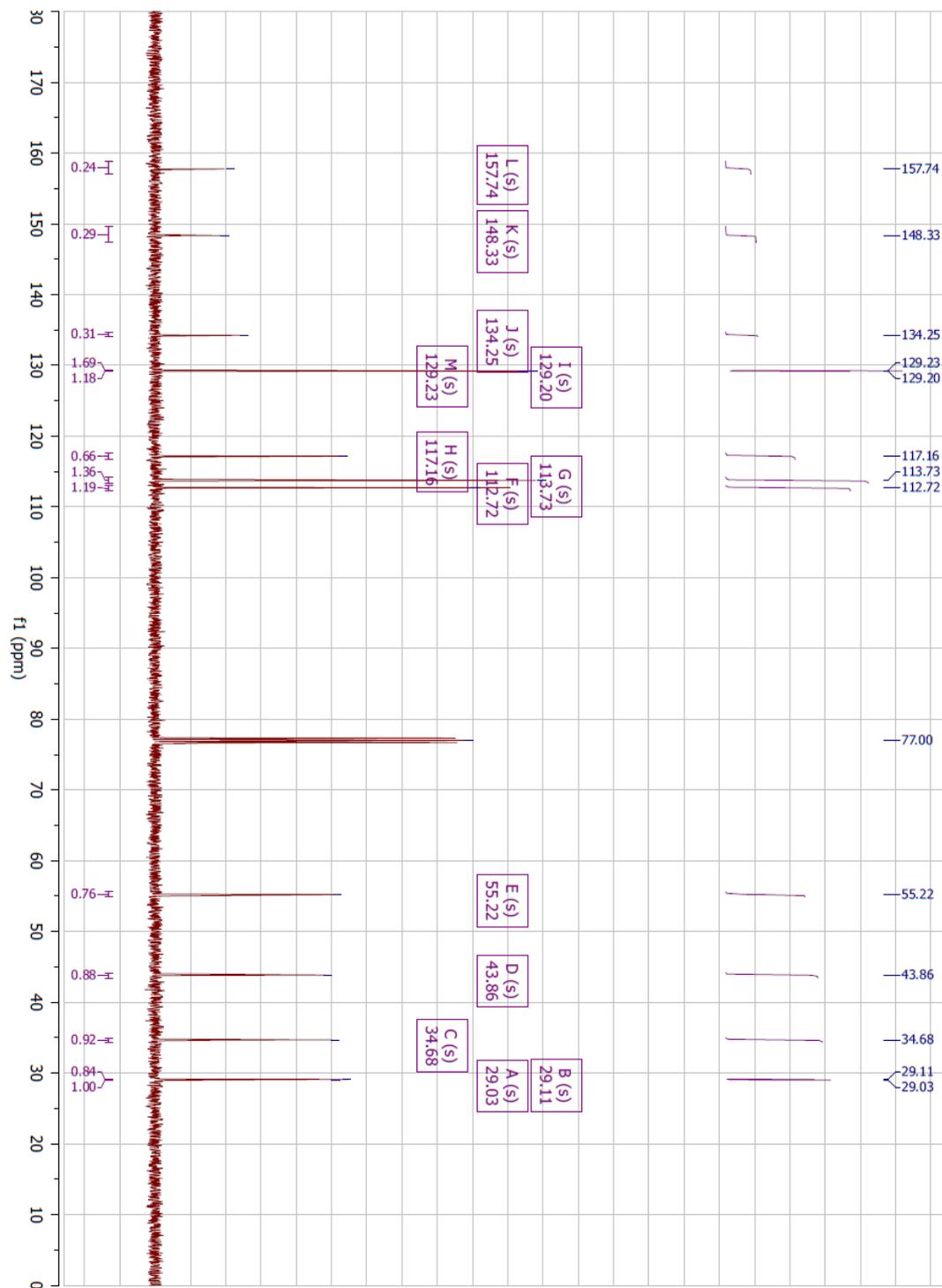
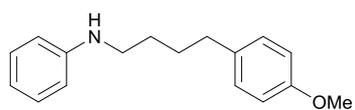
¹³C NMR (101 MHz, CDCl₃): 2,2-diethoxy-N-(naphthalen-1-ylmethyl)ethan-1-amine (5i)



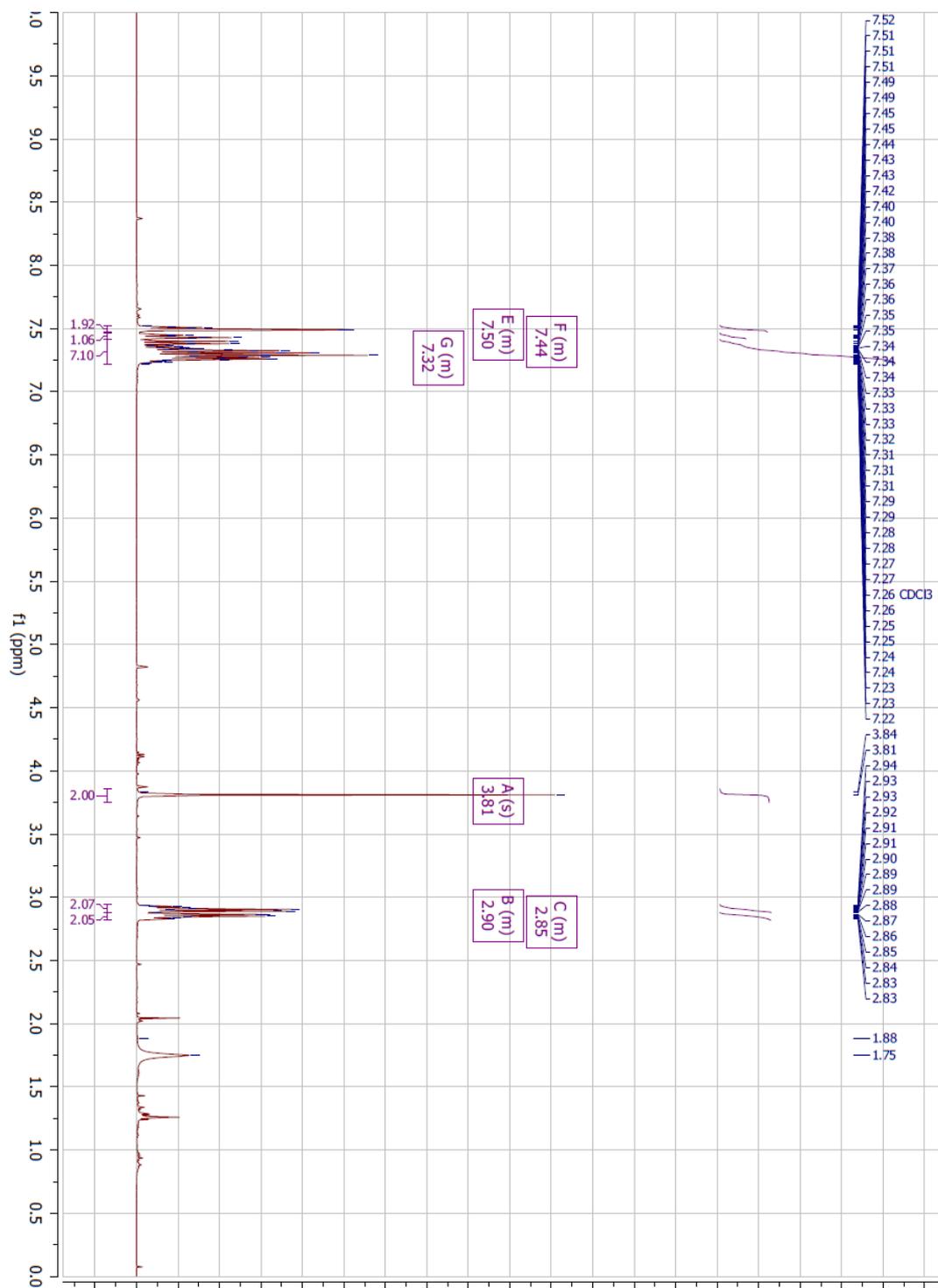
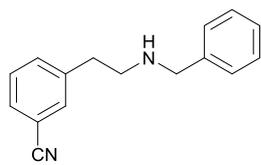
¹H NMR (400 MHz, CDCl₃): *N*-(4-(4-methoxyphenyl)butyl)aniline (**5j**)



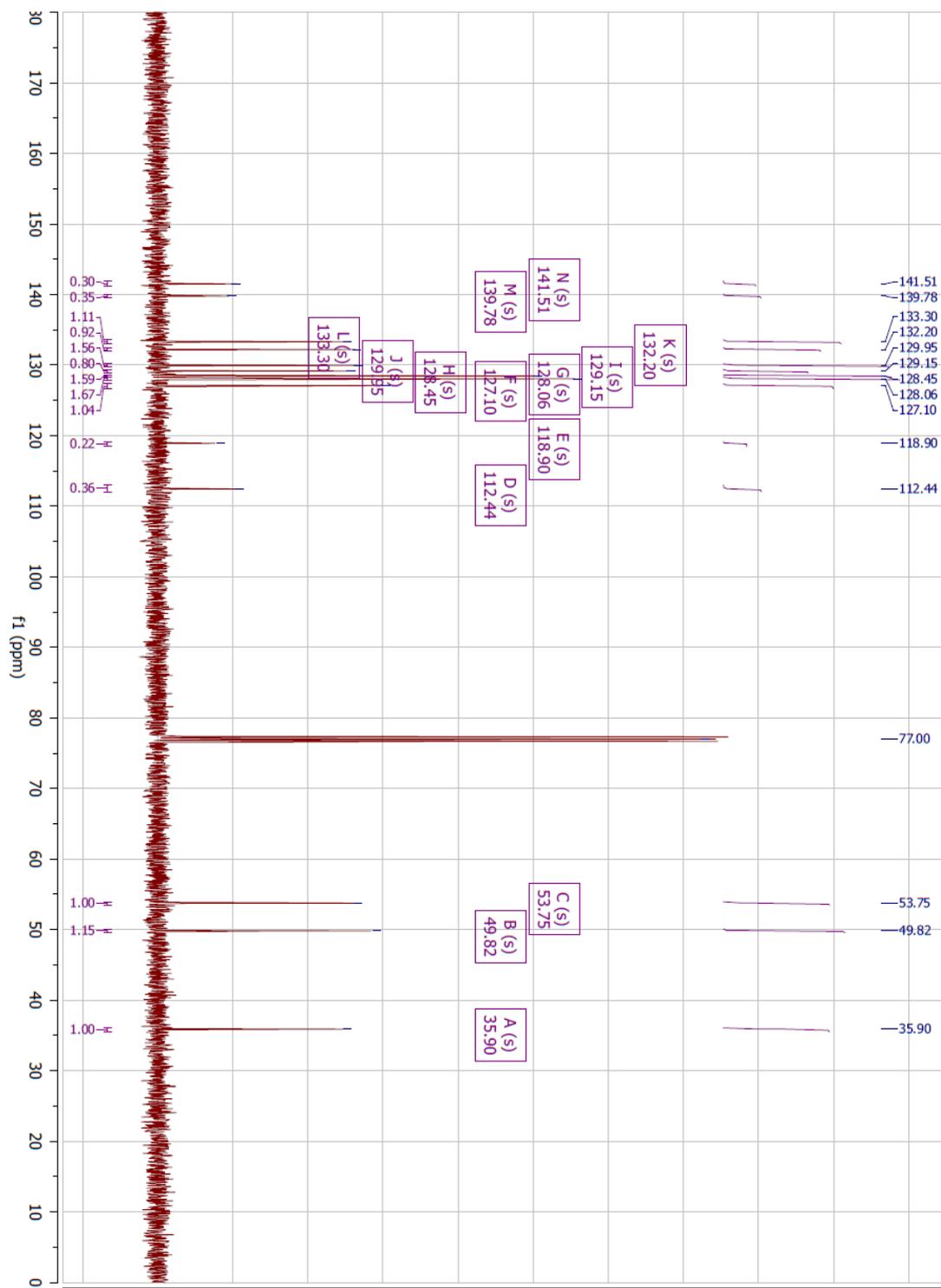
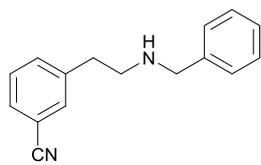
¹³C NMR (101 MHz, CDCl₃): *N*-(4-(4-methoxyphenyl)butyl)aniline (**5j**)



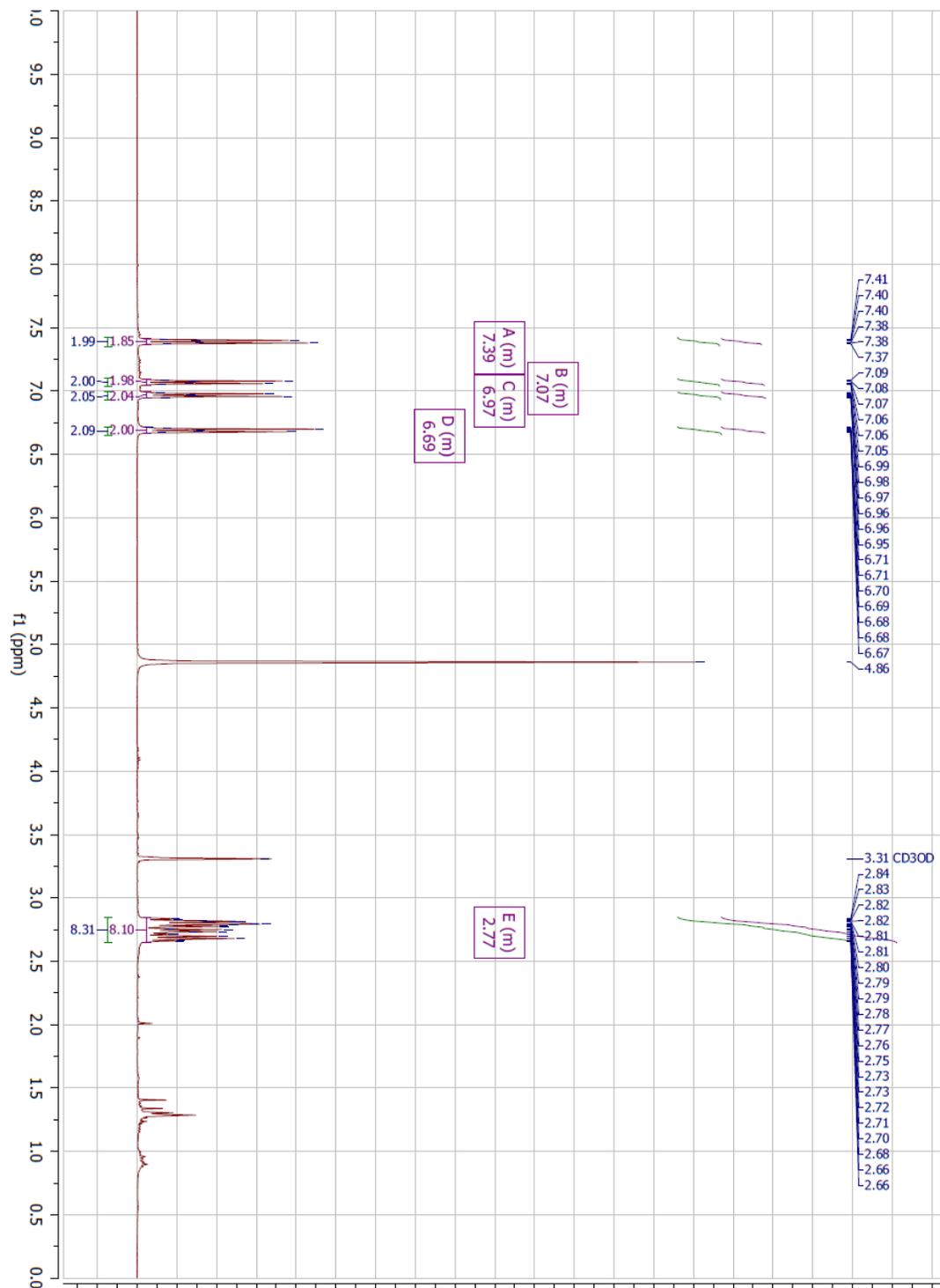
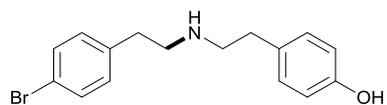
^1H NMR (400 MHz, CDCl_3): 3-(2-(benzylamino)ethyl)benzonitrile (**5k**)



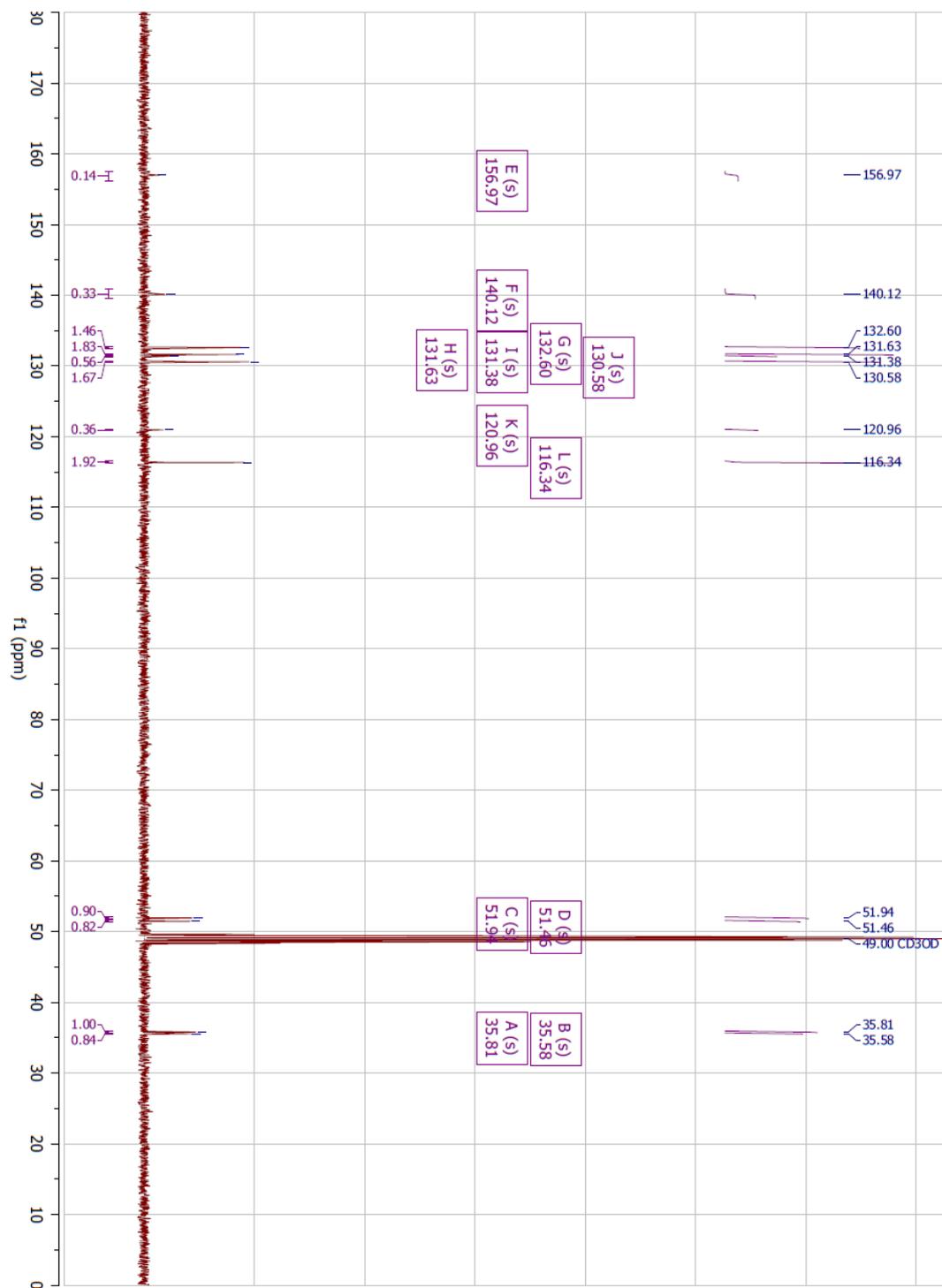
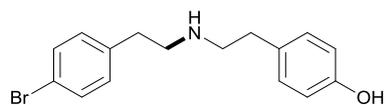
¹³C NMR (101 MHz, CDCl₃): 3-(2-(benzylamino)ethyl)benzonitrile (**5k**)



^1H NMR (400 MHz, CDCl_3): 4-(2-((4-bromophenethyl)amino)ethyl)phenol (**5I**)

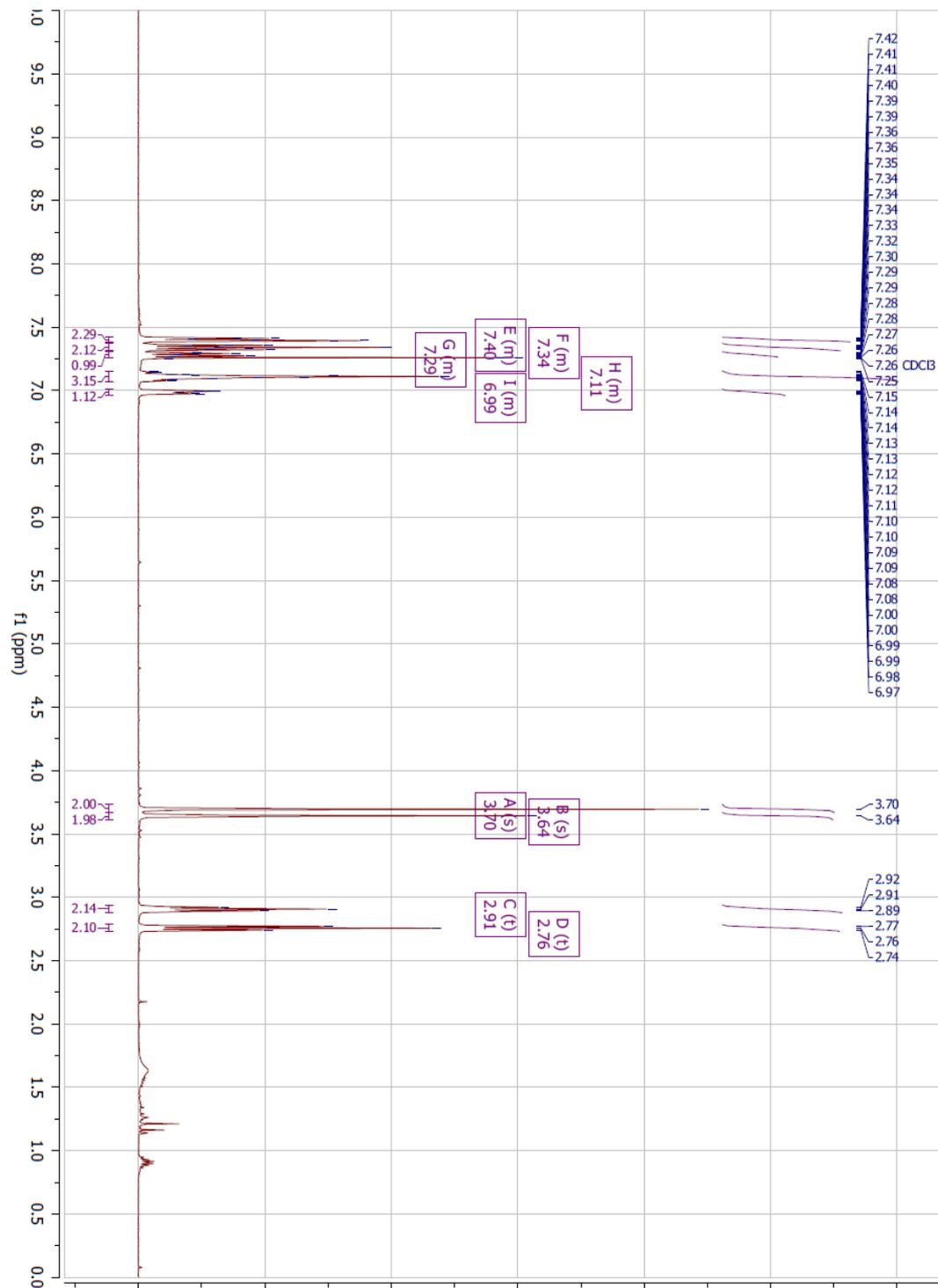
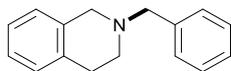


^{13}C NMR (101 MHz, CDCl_3): 4-(2-((4-bromophenethyl)amino)ethyl)phenol (**5I**)

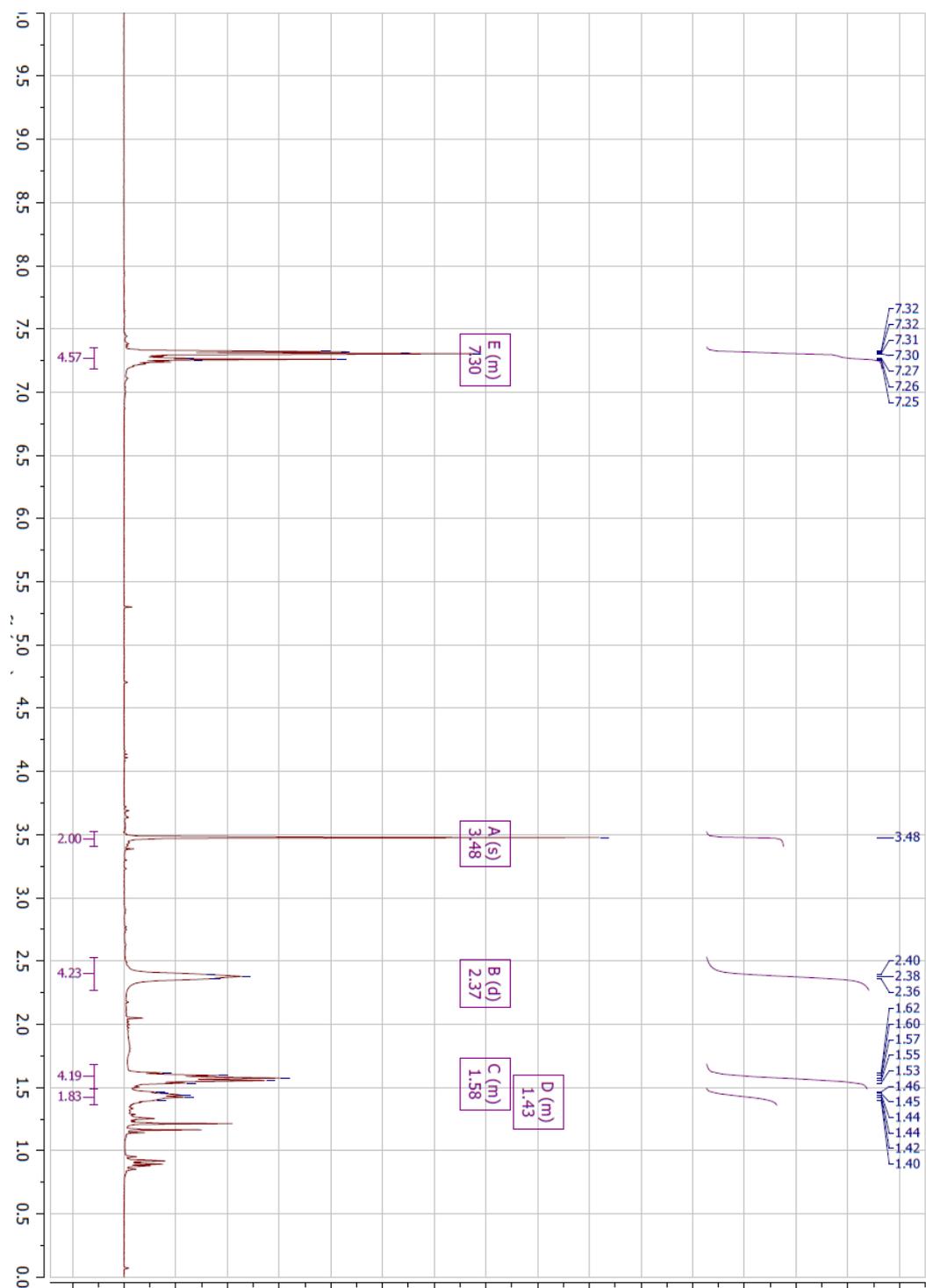
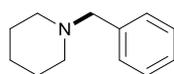


5.2 Tertiary amines

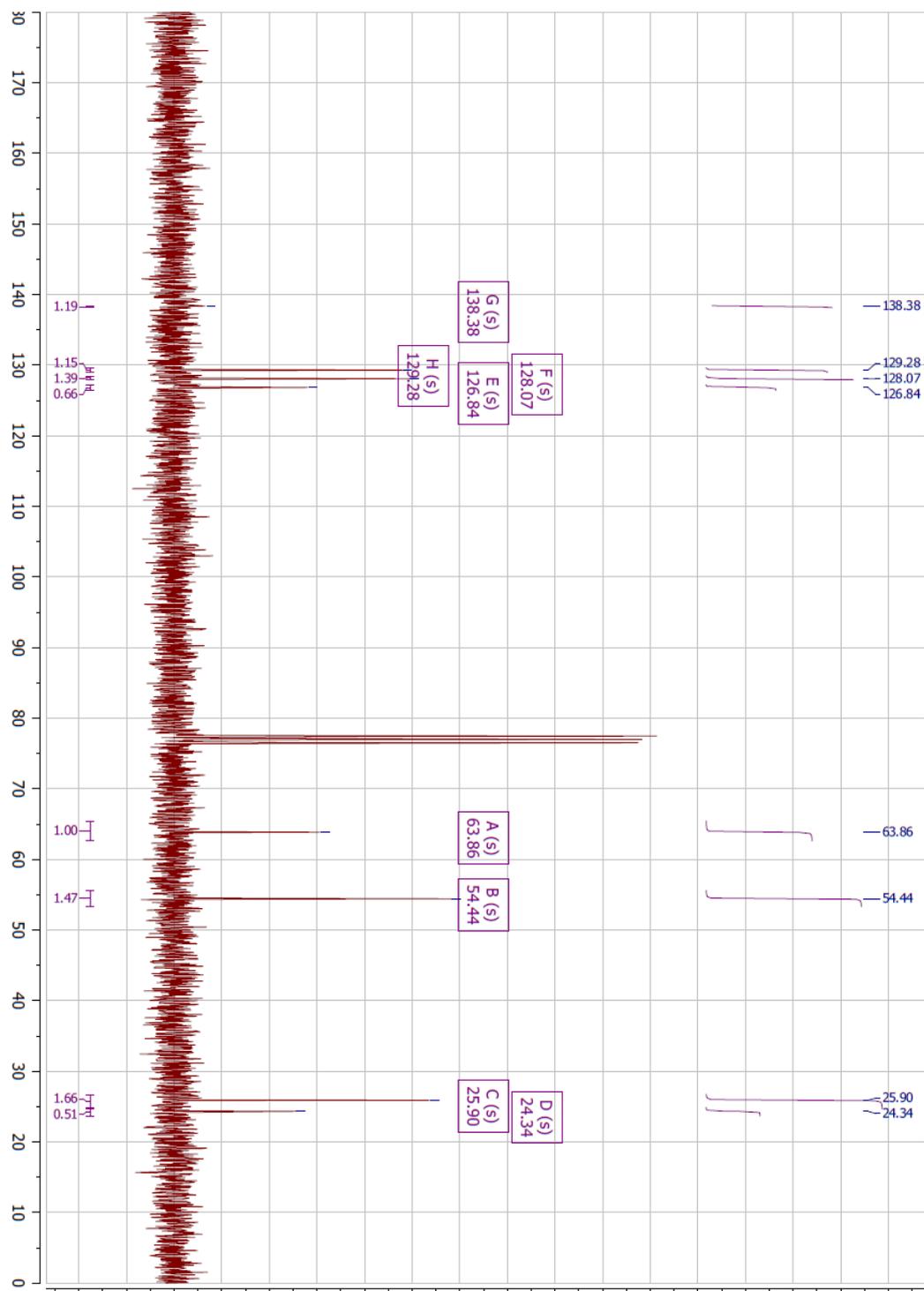
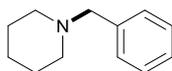
^1H NMR (400 MHz, CDCl_3): 2-benzyl-1,2,3,4-tetrahydroisoquinoline (**3a**)



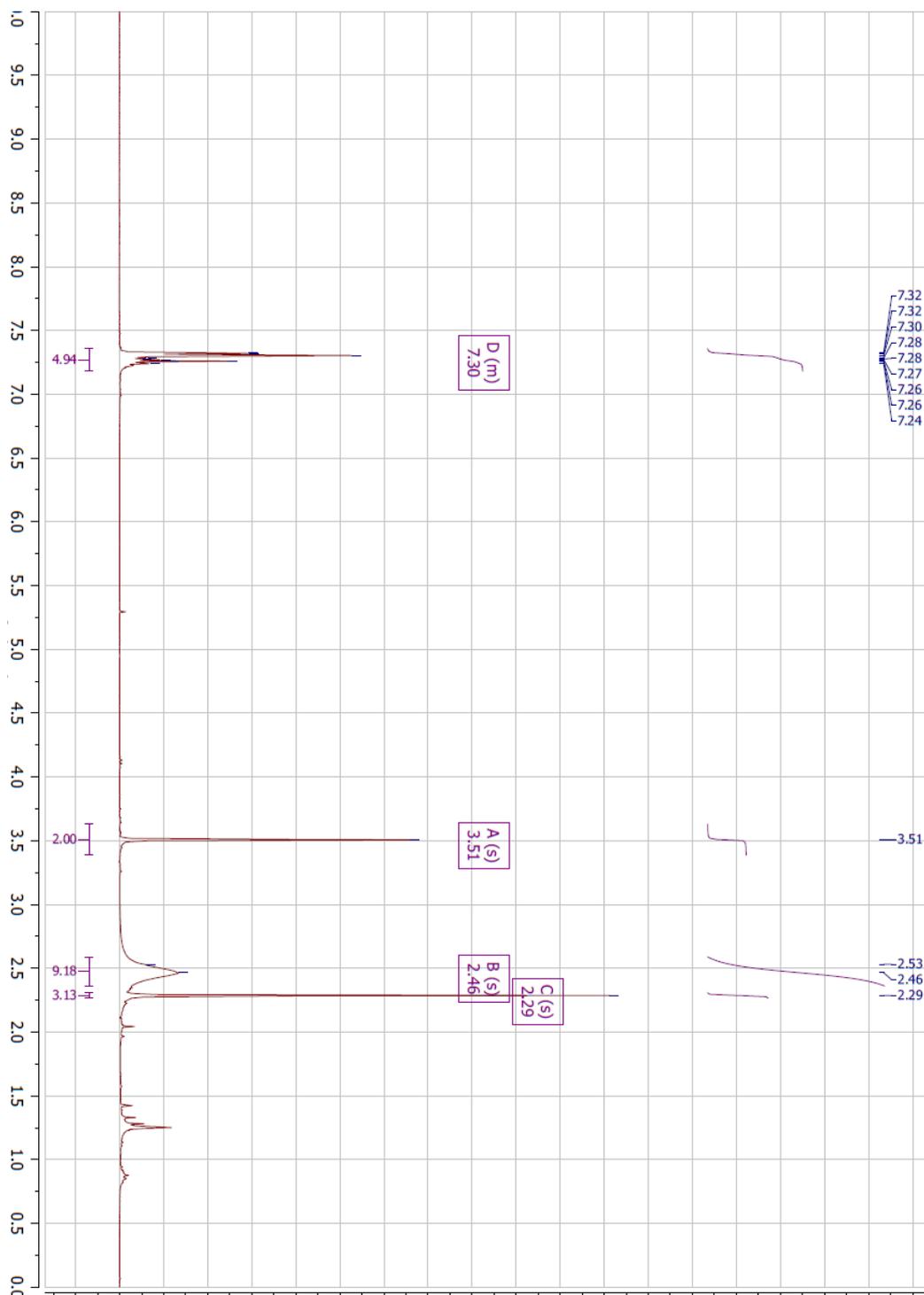
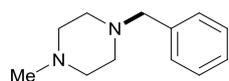
^1H NMR (270 MHz, CDCl_3): 1-benzylpiperidine (**3b**)



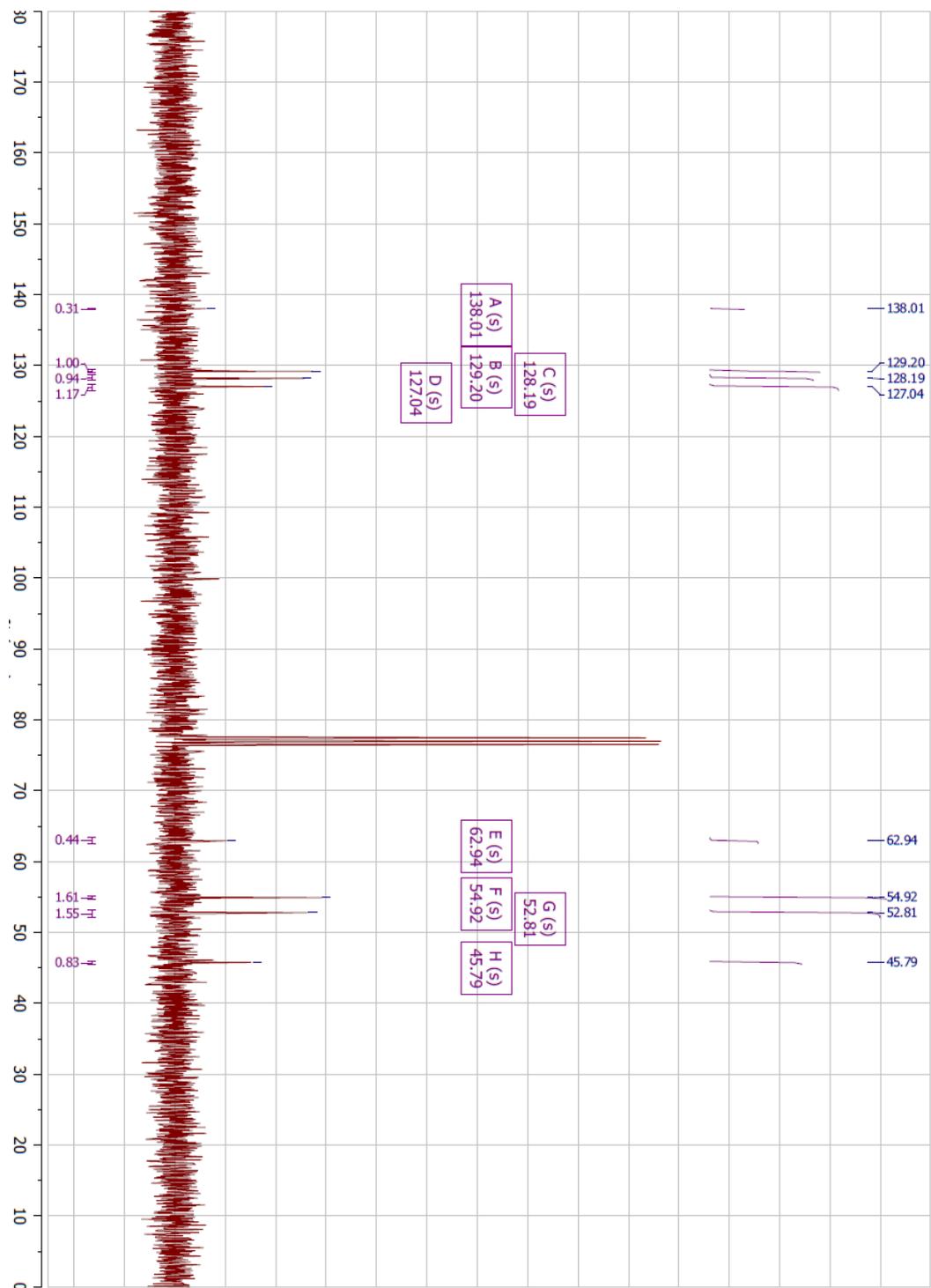
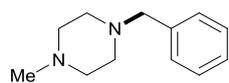
^{13}C NMR (68 MHz, CDCl_3): 1-benzylpiperidine (**3b**)



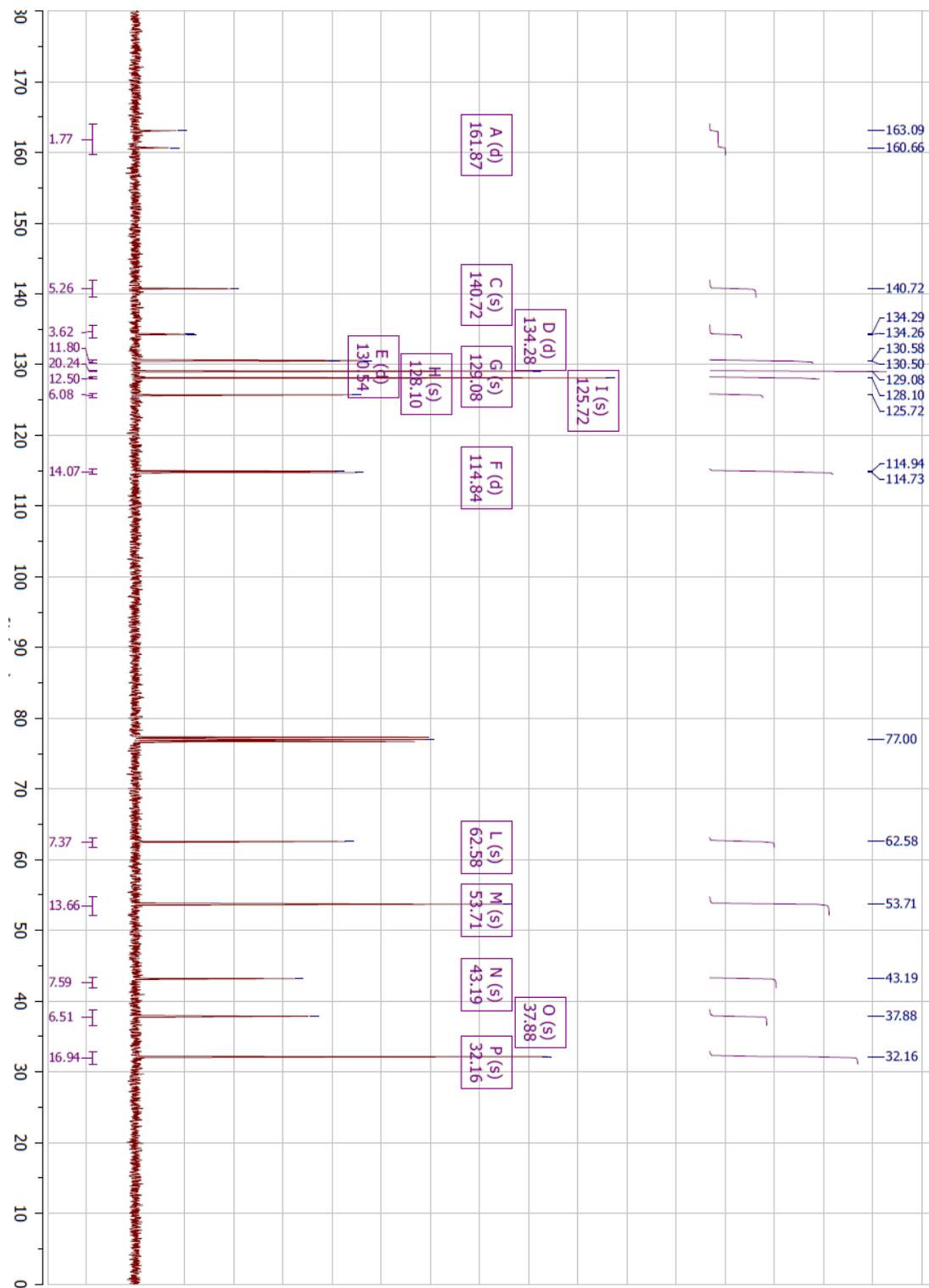
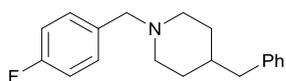
^1H NMR (270 MHz, CDCl_3): 1-benzyl-4-methylpiperazine (**3c**)



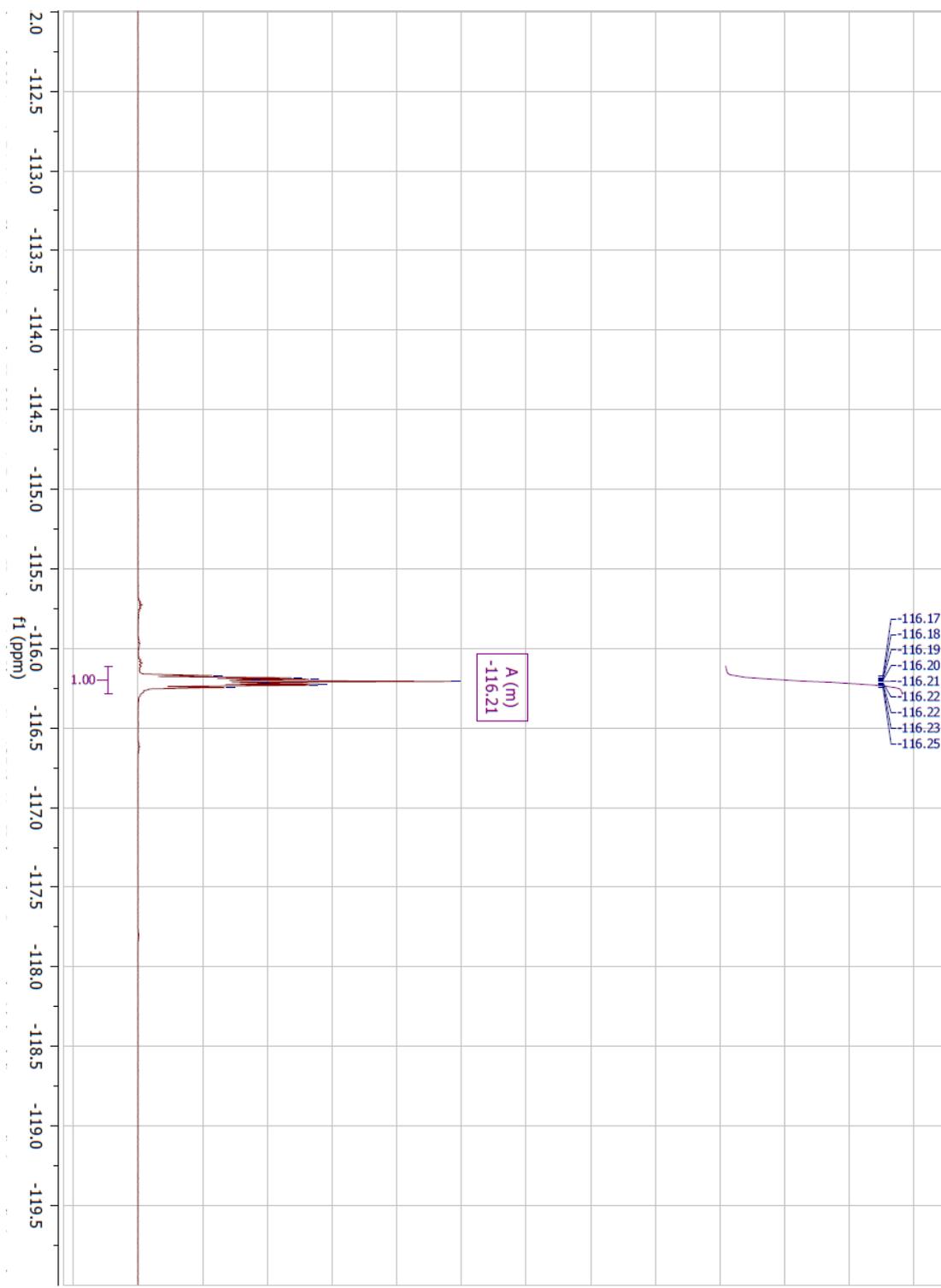
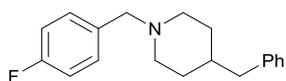
^{13}C NMR (68 MHz, CDCl_3): 1-benzyl-4-methylpiperazine (**3c**)



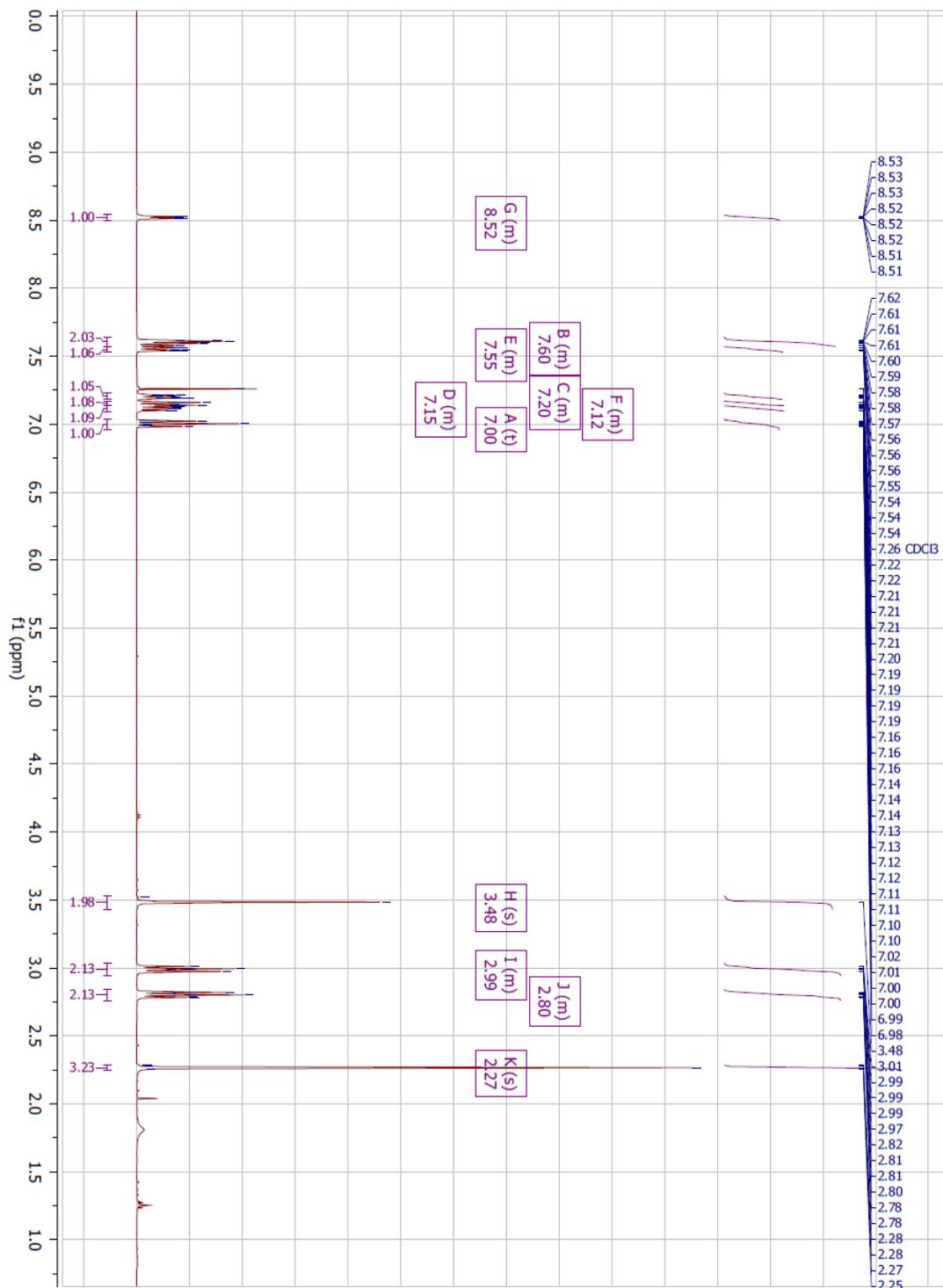
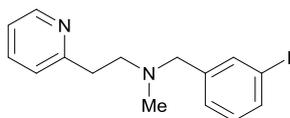
¹³C NMR (101 MHz, CDCl₃): 4-benzyl-1-(4-fluorobenzyl)piperidine (**3d**)



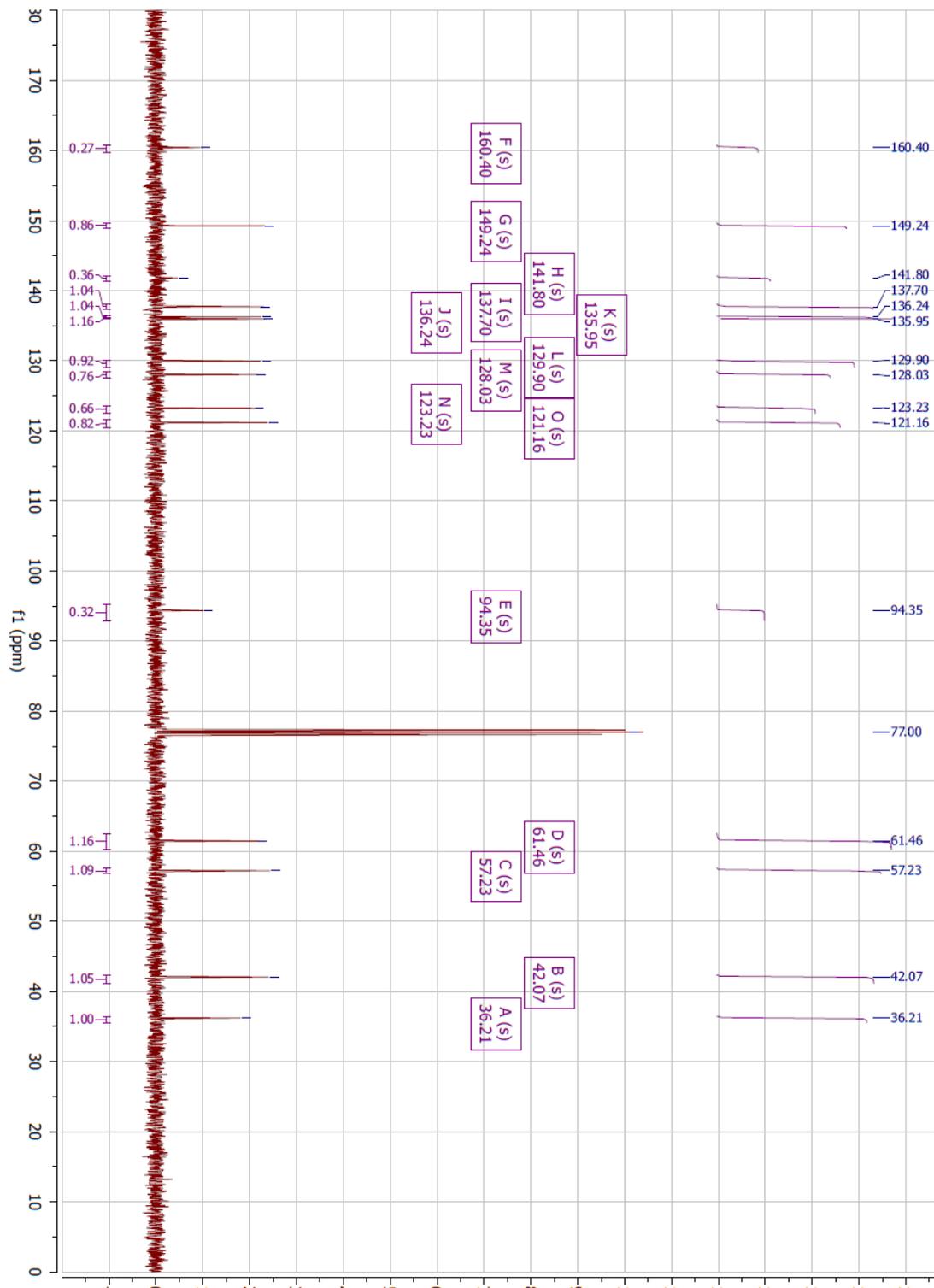
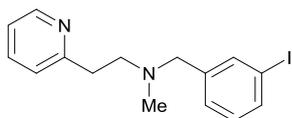
¹⁹F NMR (377 MHz, CDCl₃): 4-benzyl-1-(4-fluorobenzyl)piperidine (**3d**)



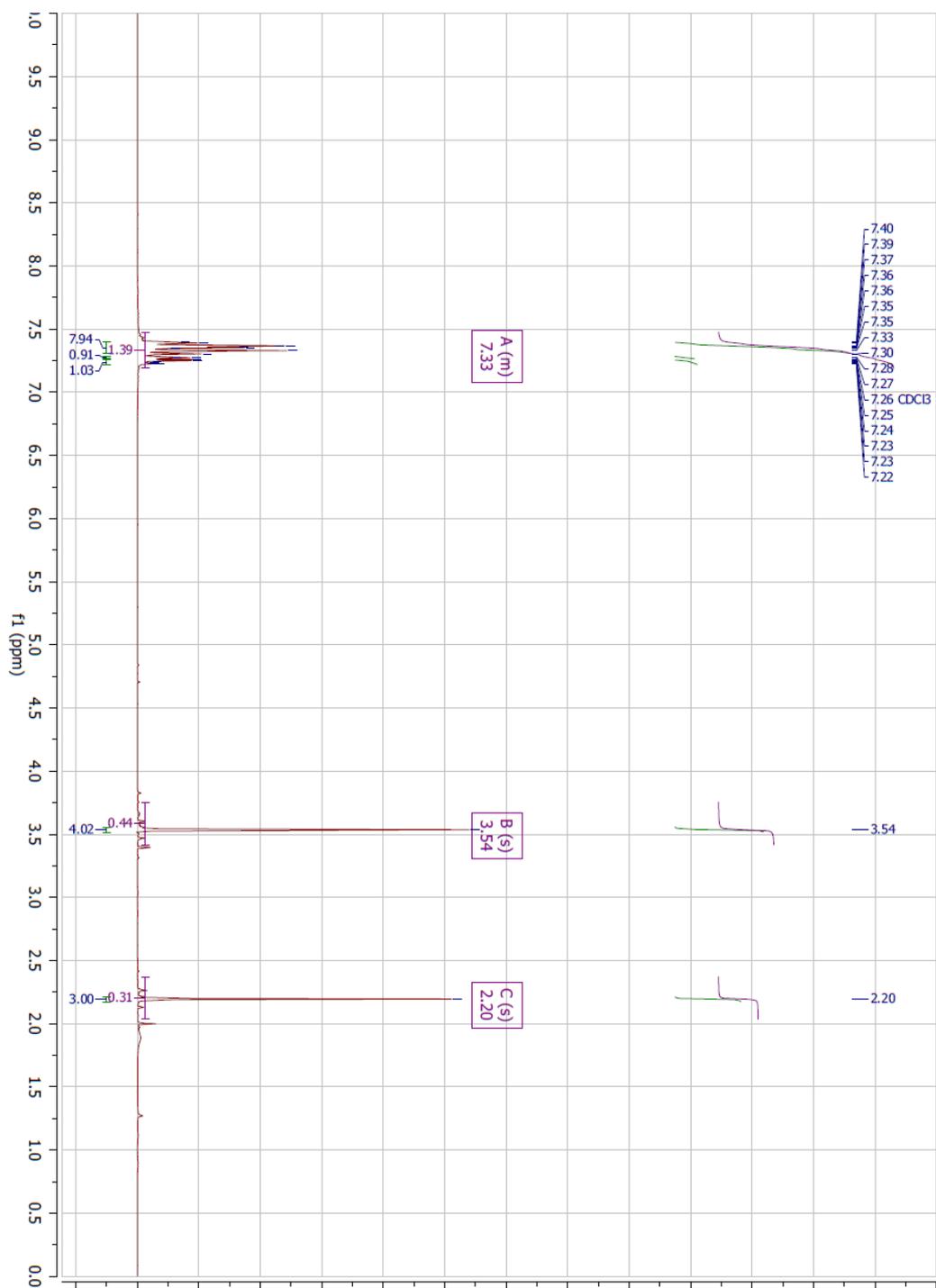
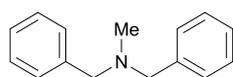
¹H NMR (400 MHz, CDCl₃): *N*-(3-iodobenzyl)-*N*-methyl-2-(pyridin-2-yl)ethan-1-amine (**3e**)



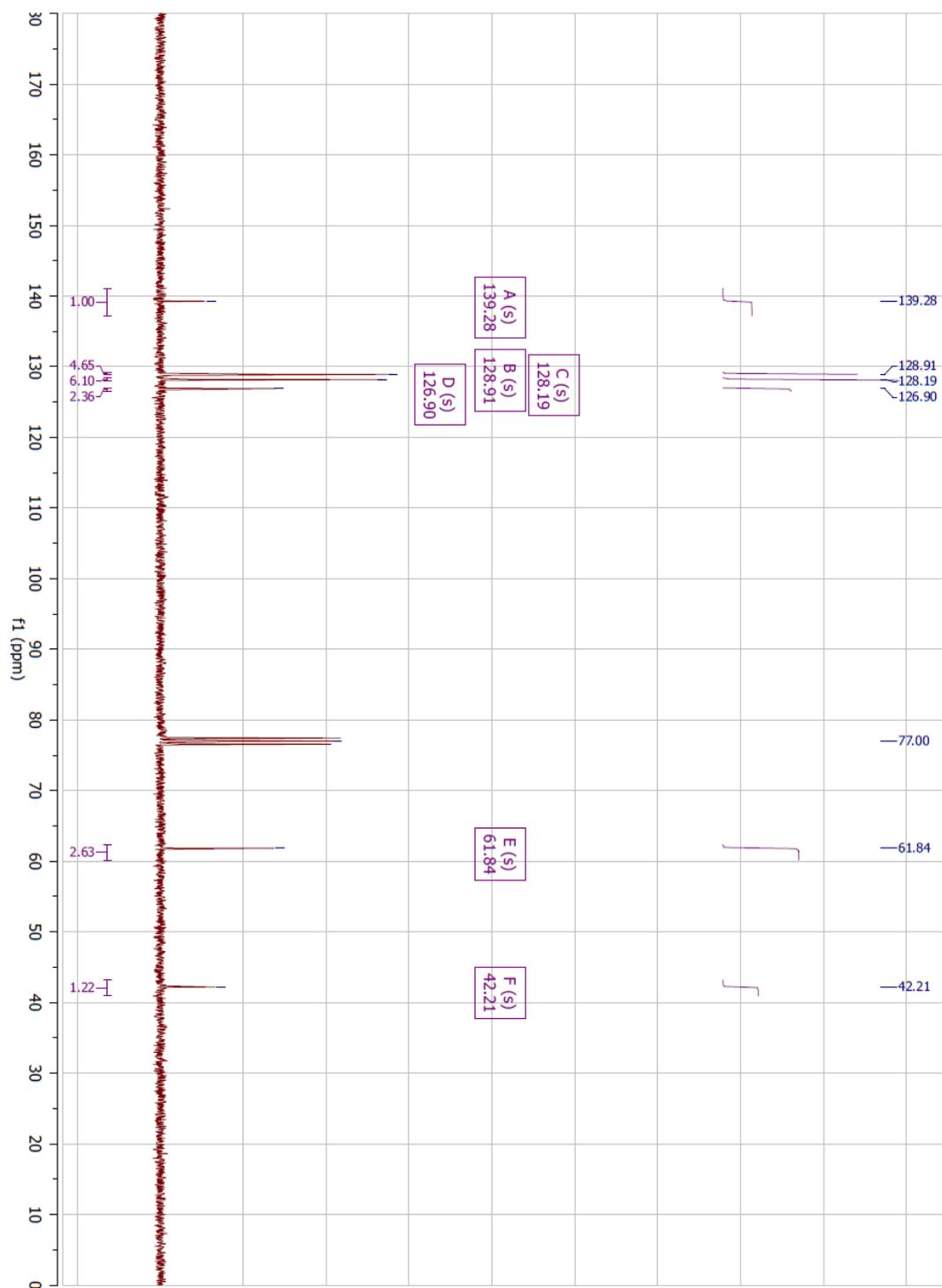
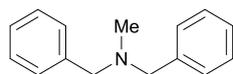
^{13}C NMR (101 MHz, CDCl_3): *N*-(3-iodobenzyl)-*N*-methyl-2-(pyridin-2-yl)ethan-1-amine (**3e**)



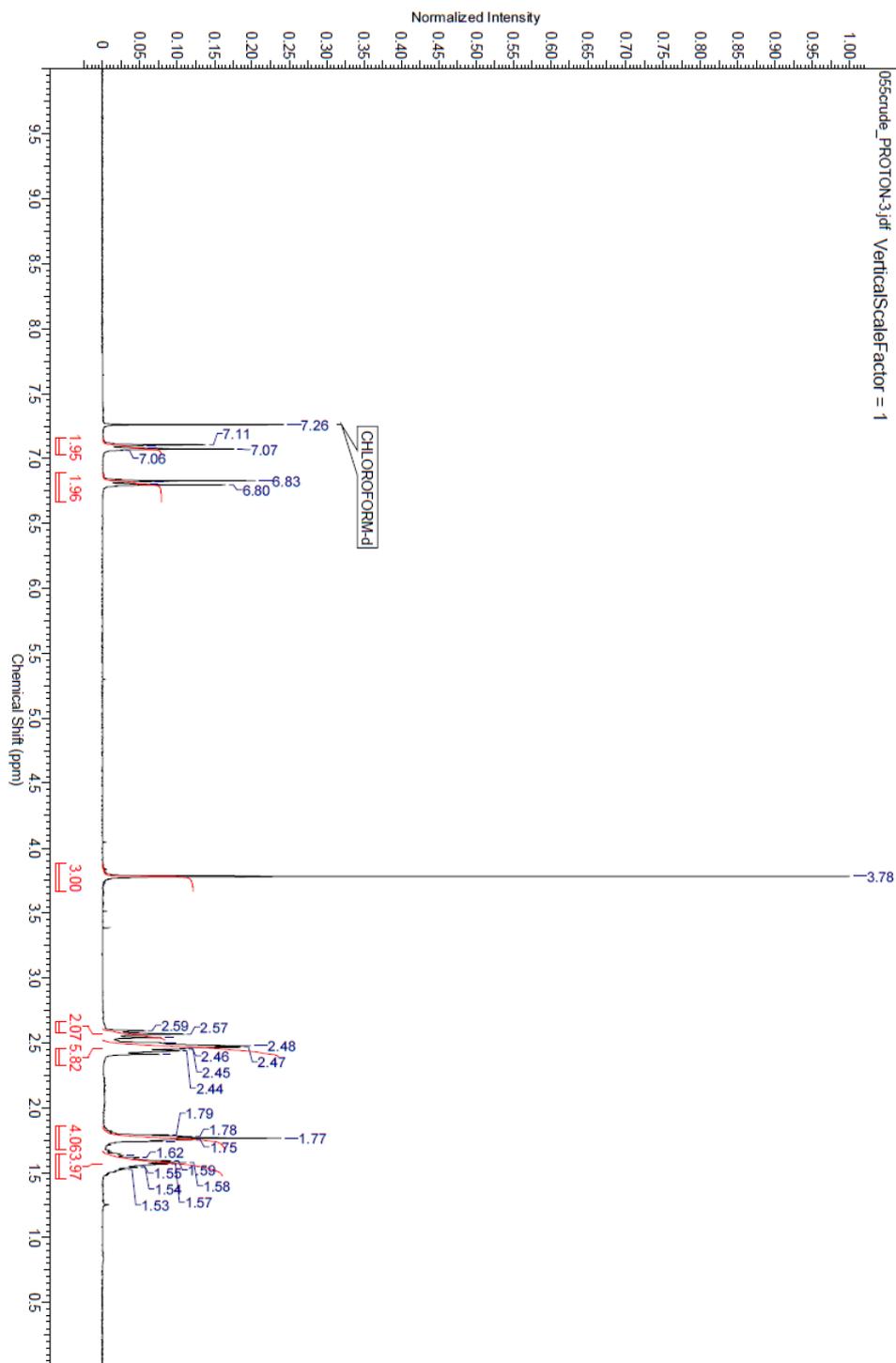
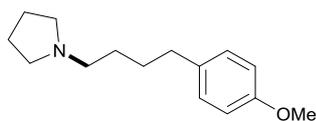
^1H NMR (300 MHz, CDCl_3): *N*-benzyl-*N*-methyl-1-phenylmethanamine (**3f**)



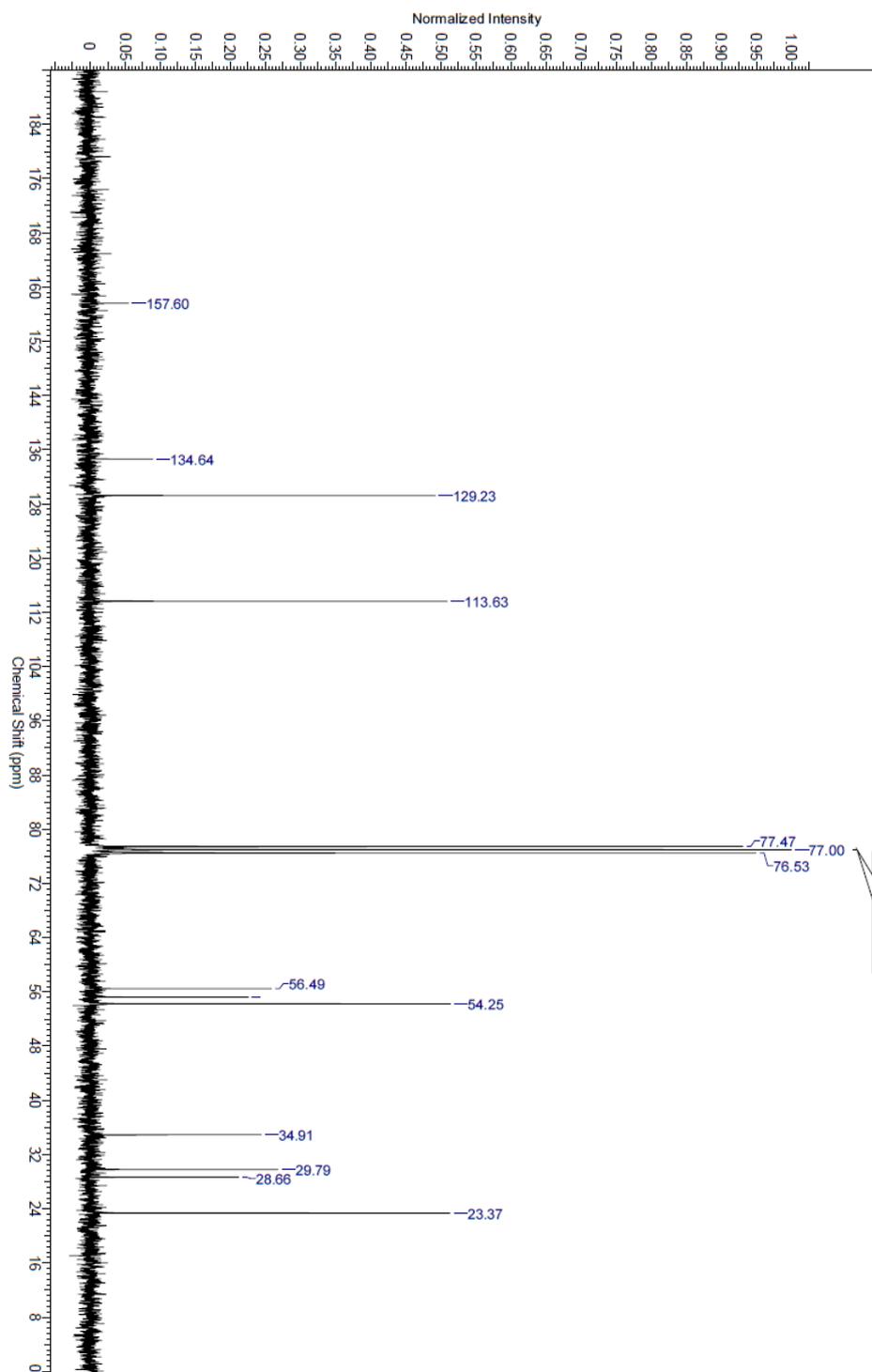
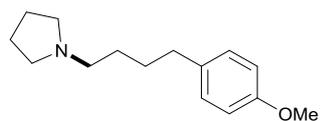
^{13}C NMR (75 MHz, CDCl_3): *N*-benzyl-*N*-methyl-1-phenylmethanamine (**3f**)



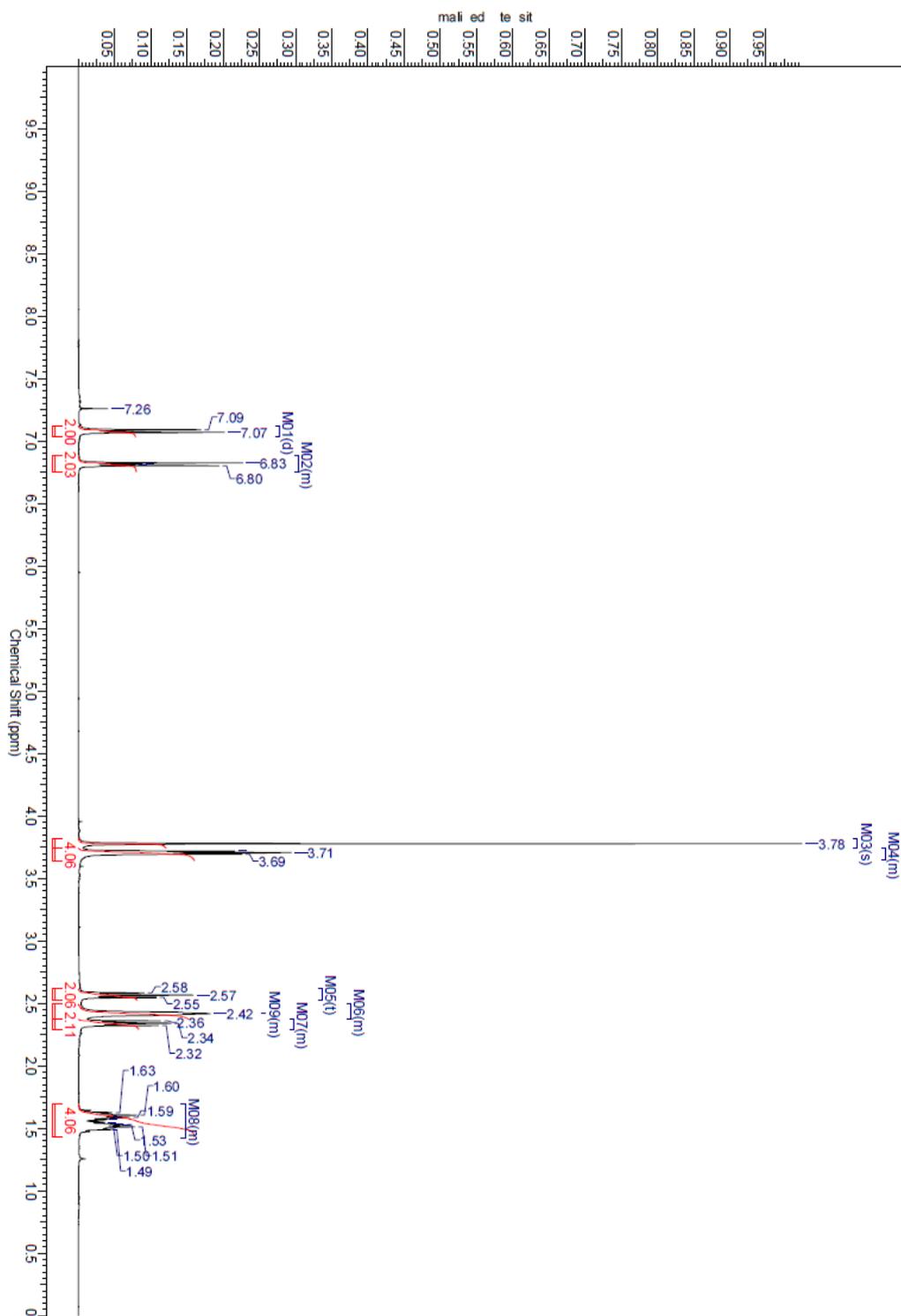
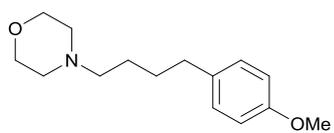
¹H NMR (270 MHz, CDCl₃): 1-(4-(4-methoxyphenyl)butyl)pyrrolidine (**3g**)



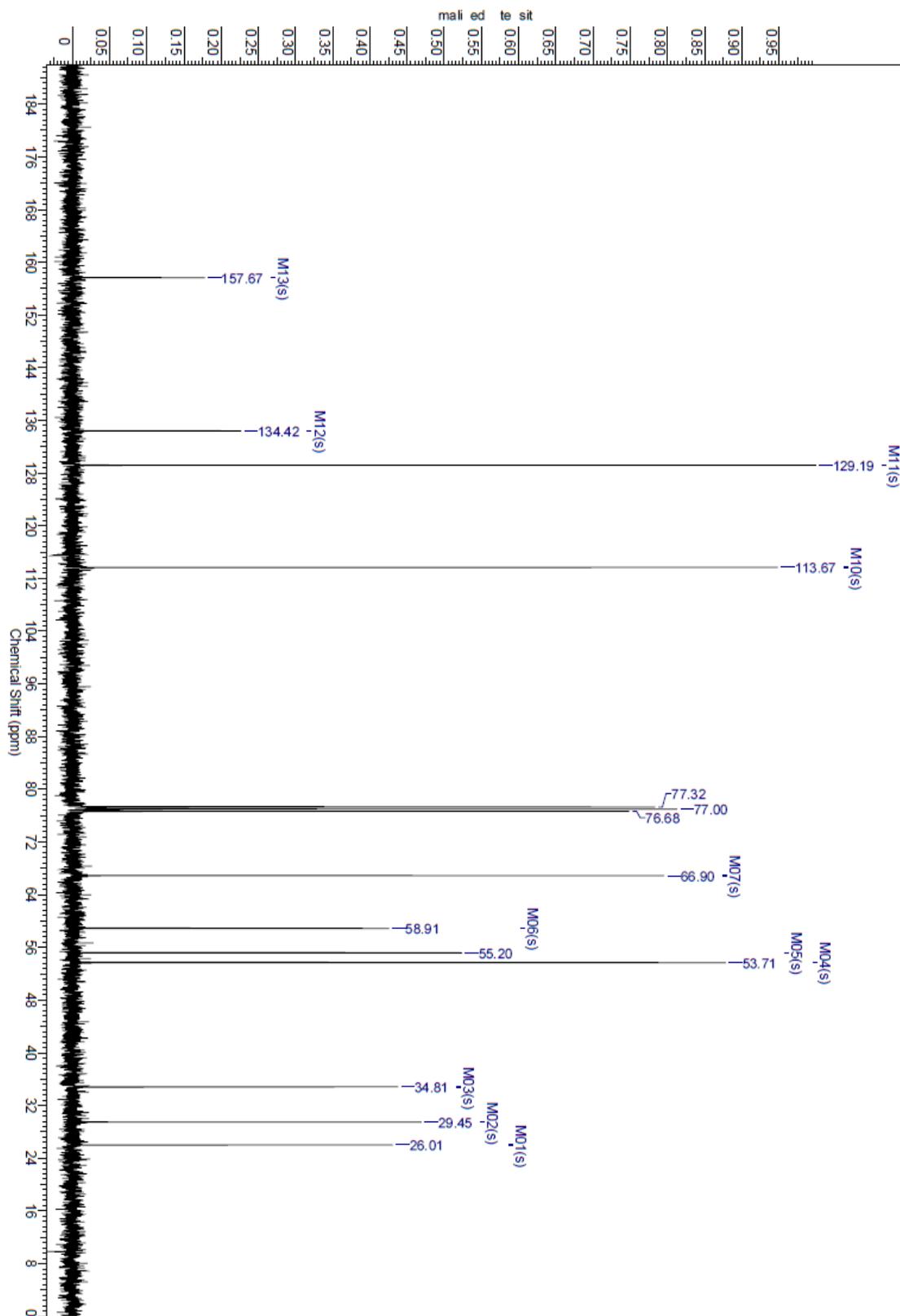
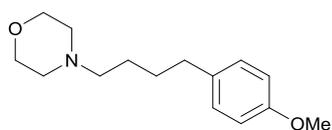
¹³C NMR (68 MHz, CDCl₃): 1-(4-(4-methoxyphenyl)butyl)pyrrolidine (**3g**)



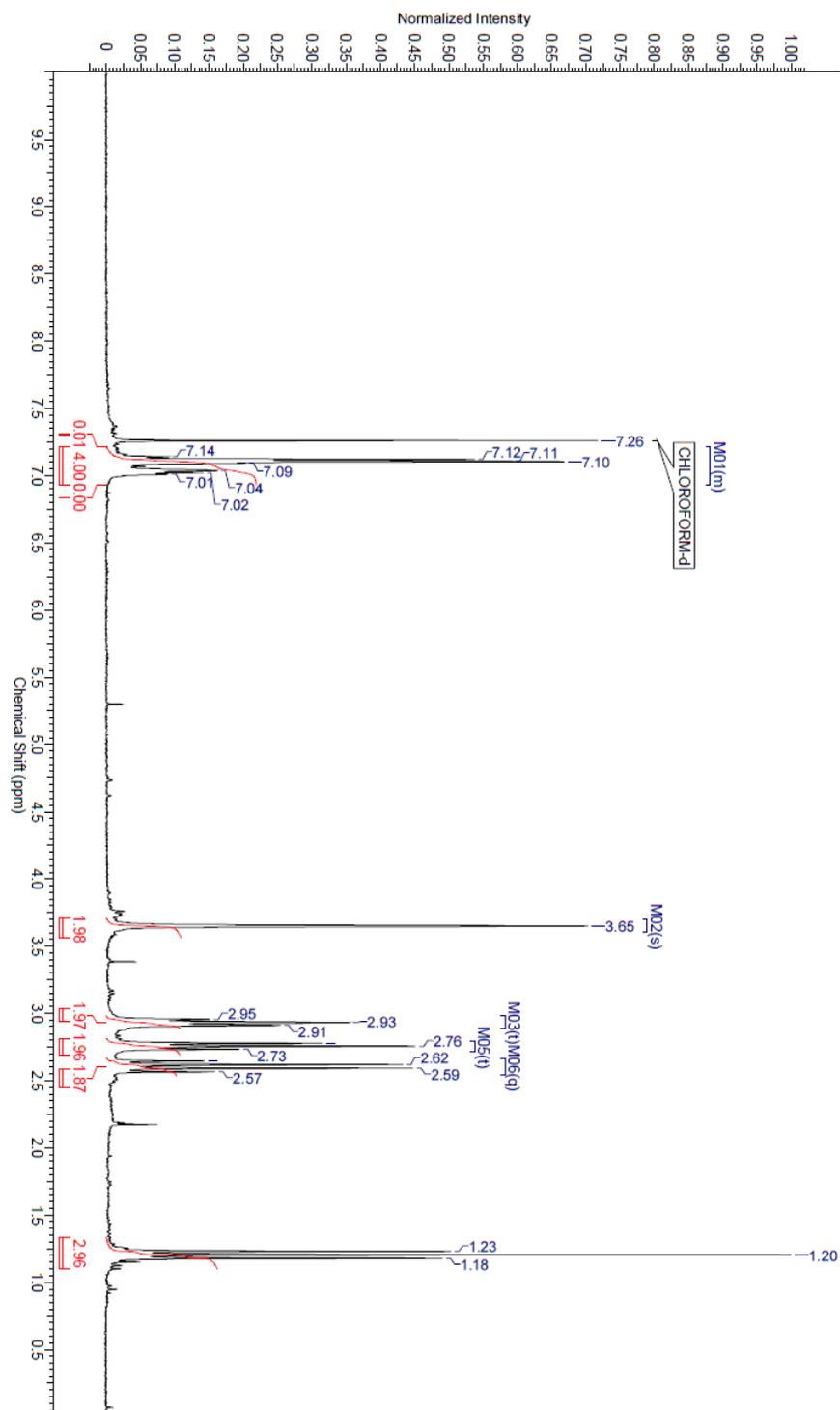
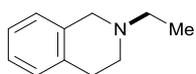
¹H NMR (400 MHz, CDCl₃): 4-(4-(4-methoxyphenyl)butyl)morpholine (**3h**)



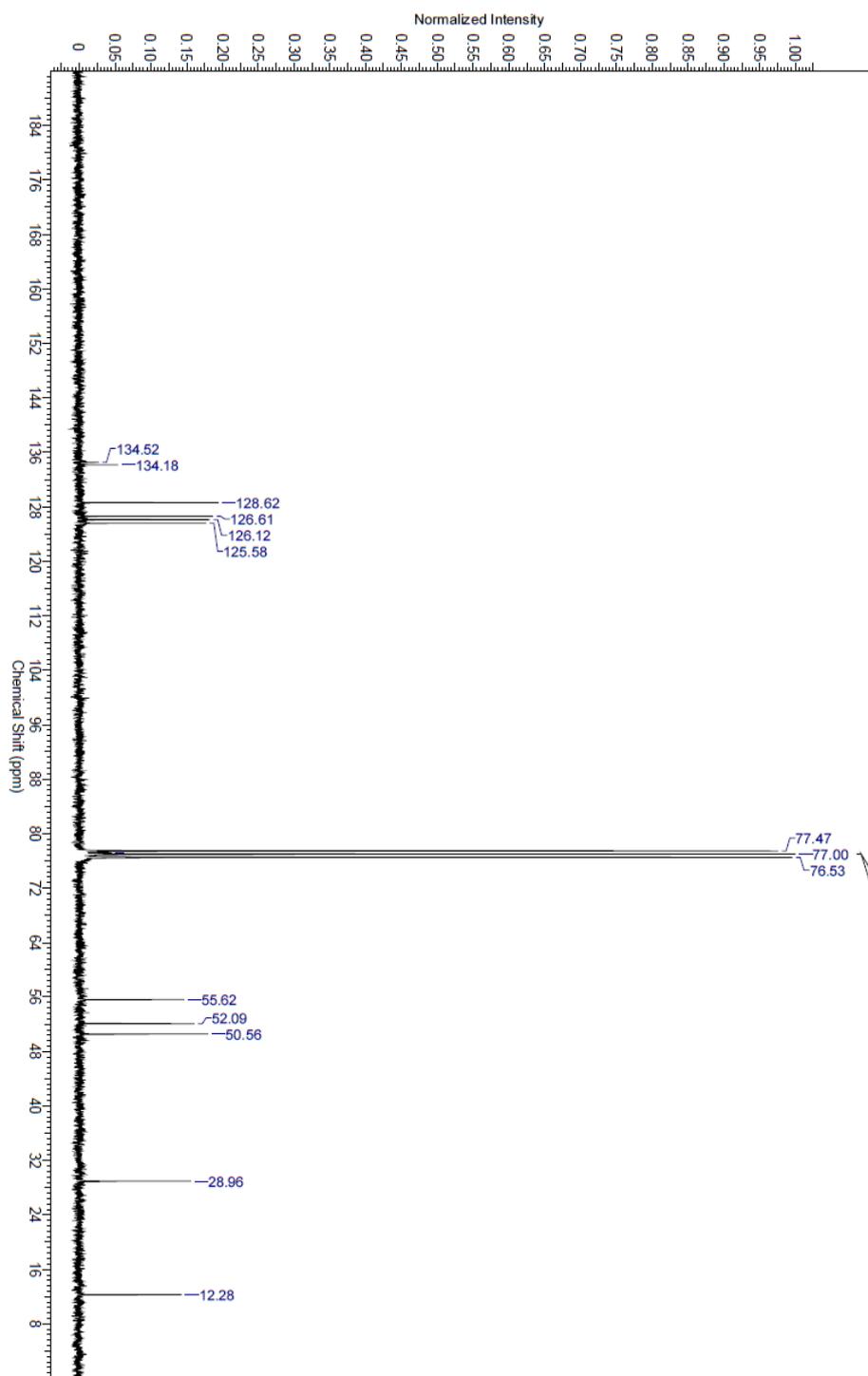
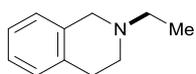
¹³C NMR (101 MHz, CDCl₃): 4-(4-(4-methoxyphenyl)butyl)morpholine (**3h**)



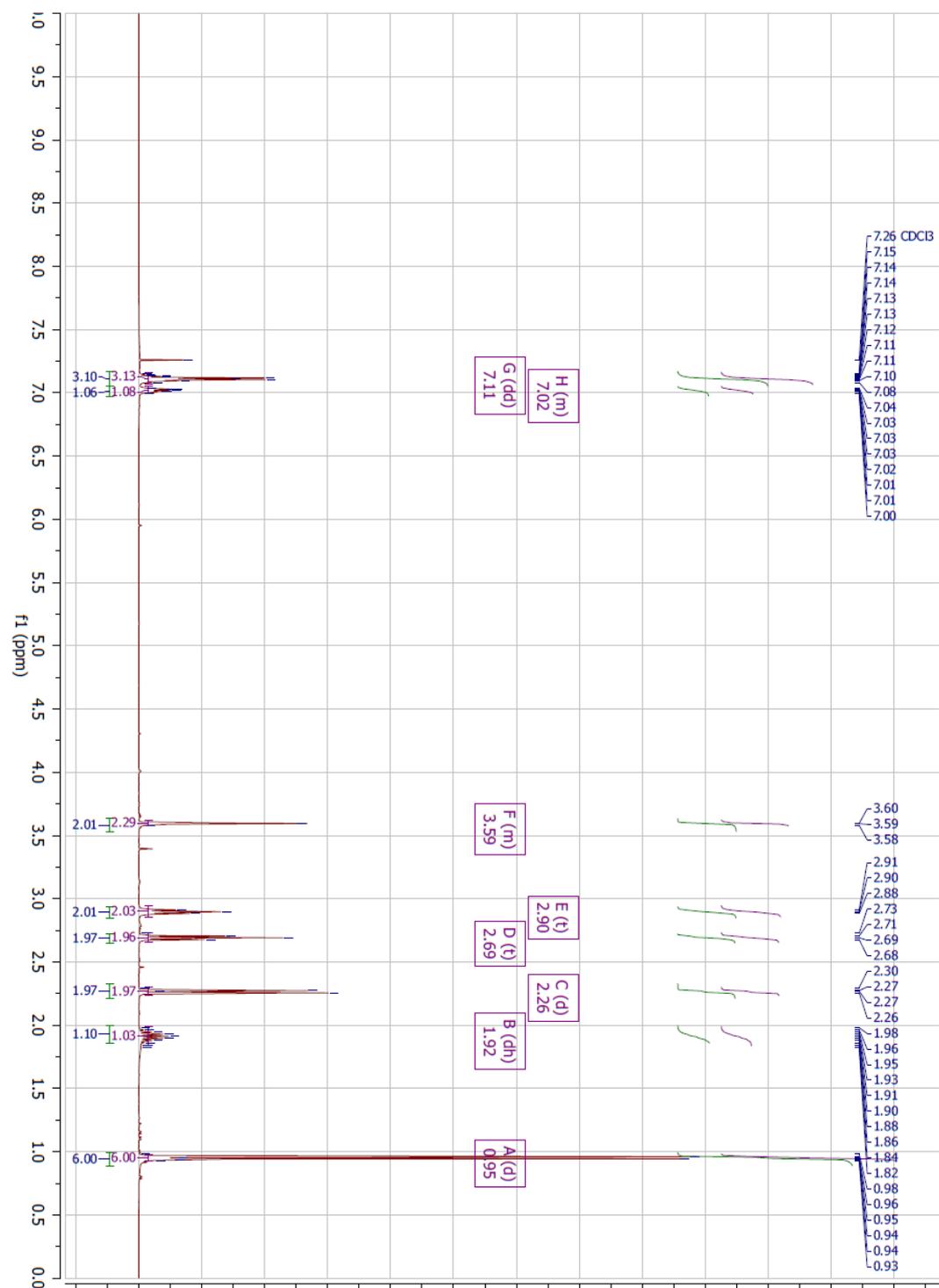
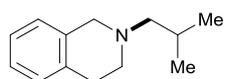
¹H NMR (270 MHz, CDCl₃): 2-ethyl-1,2,3,4-tetrahydroisoquinoline (**3i**)



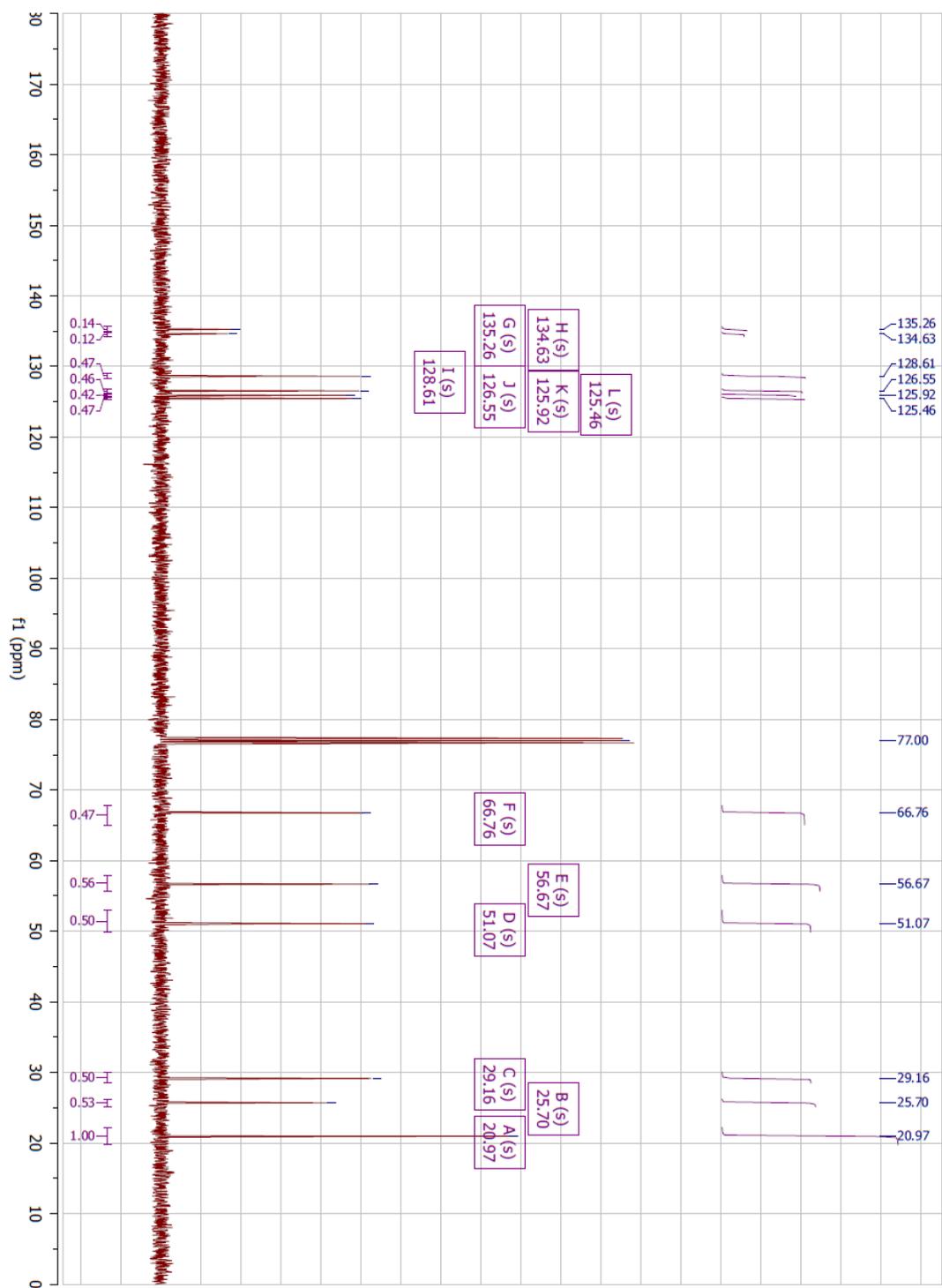
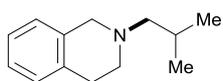
^{13}C NMR (68 MHz, CDCl_3): 2-ethyl-1,2,3,4-tetrahydroisoquinoline (**3i**)



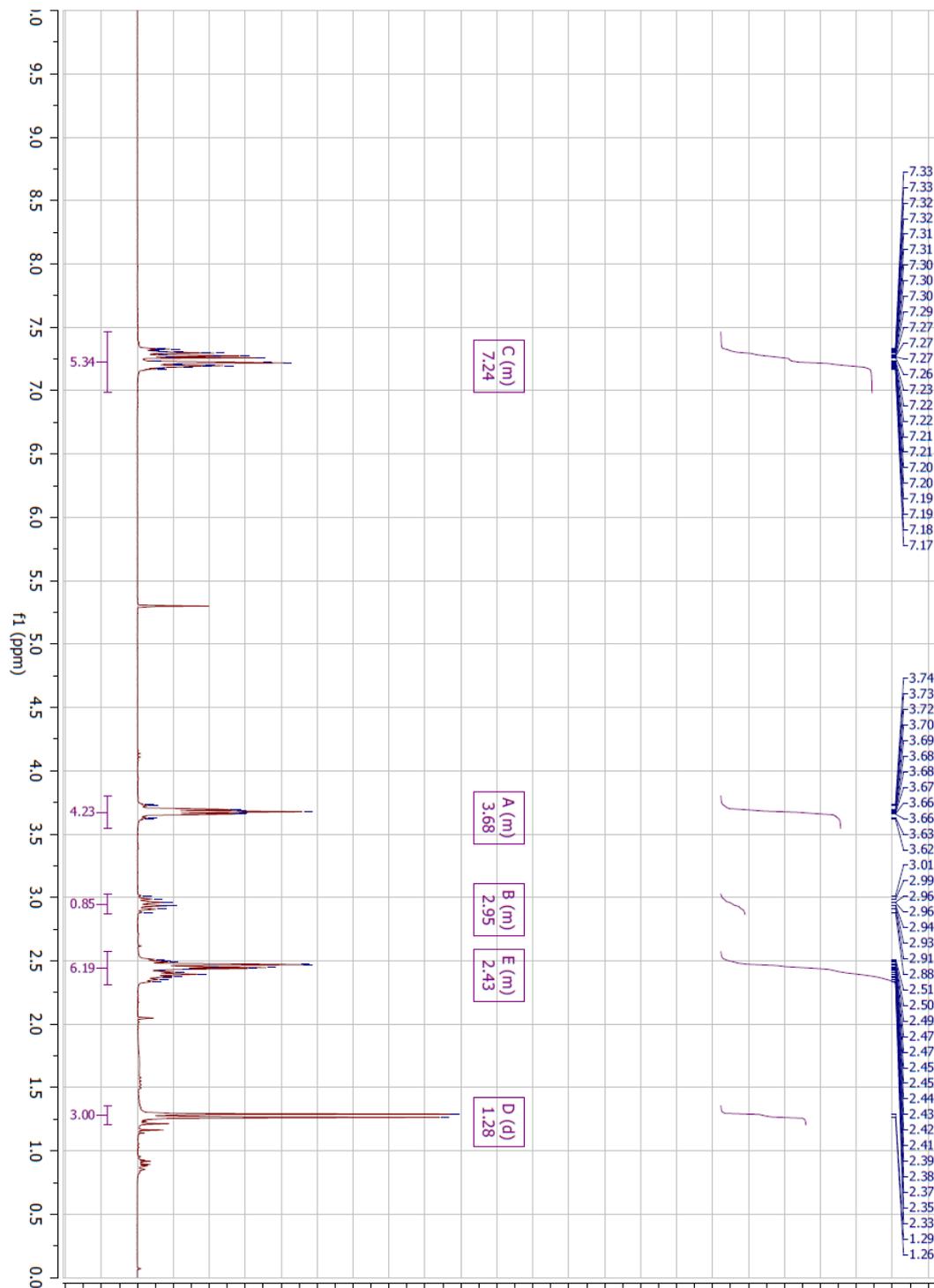
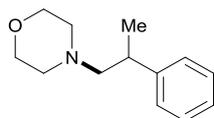
^1H NMR (400 MHz, CDCl_3): 2-isobutyl-1,2,3,4-tetrahydroisoquinoline (**3j**)



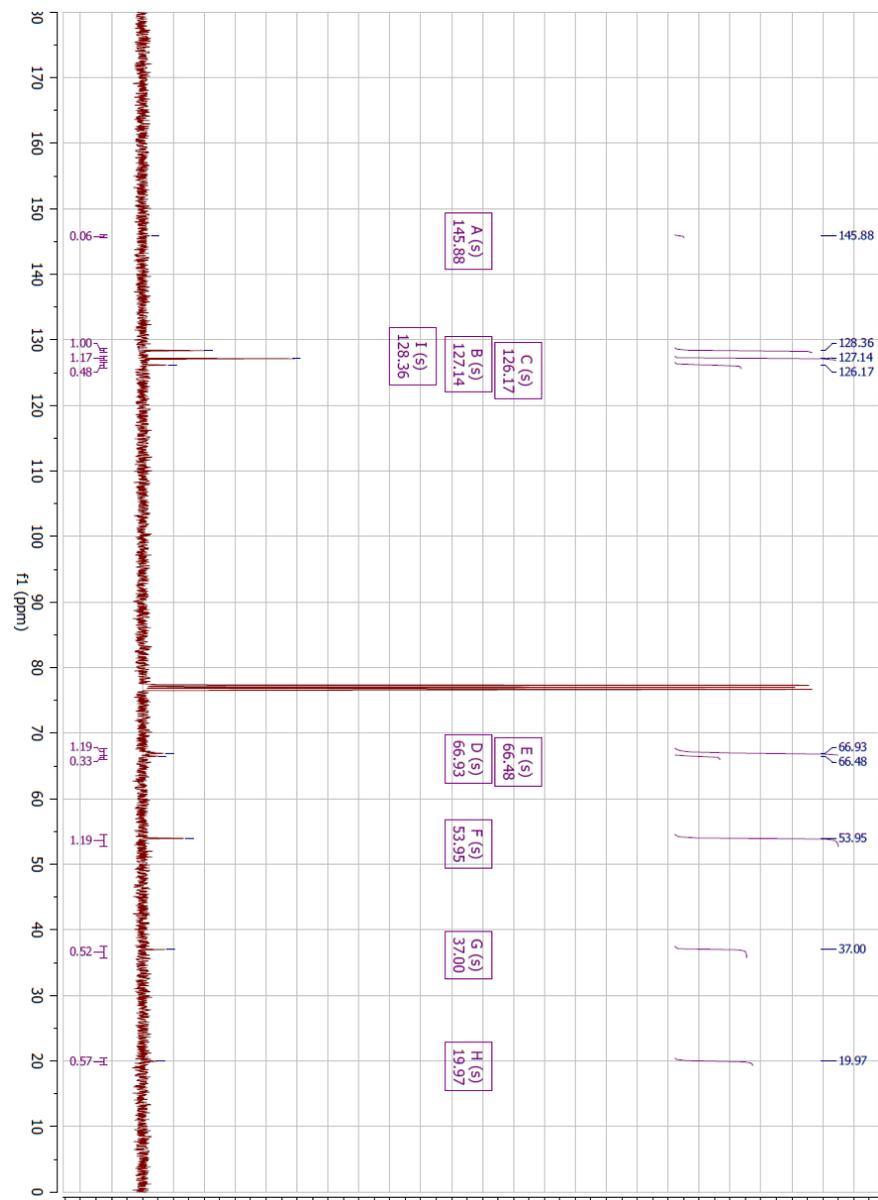
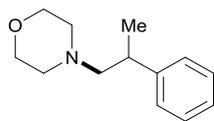
¹³C NMR (101 MHz, CDCl₃): 2-isobutyl-1,2,3,4-tetrahydroisoquinoline (**3j**)



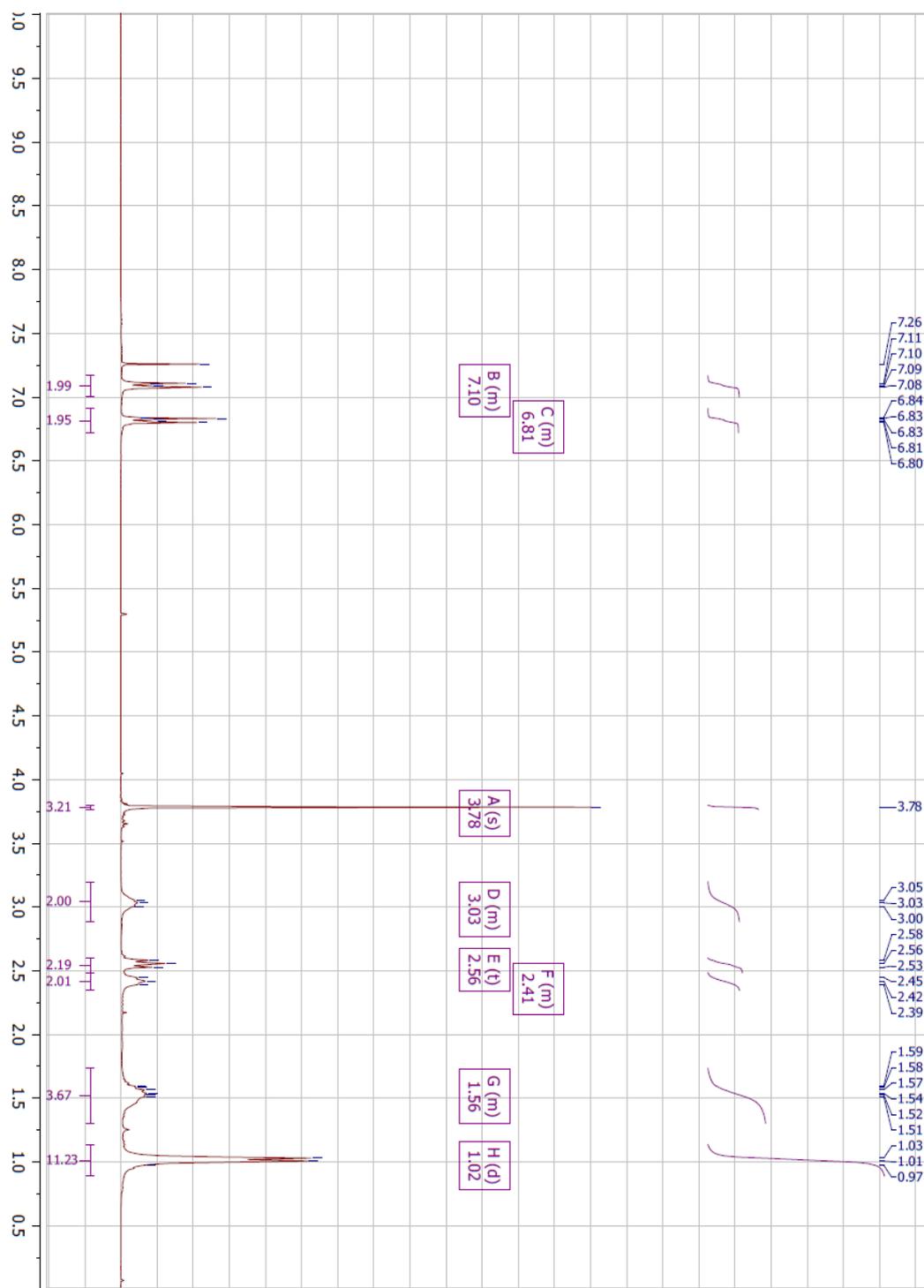
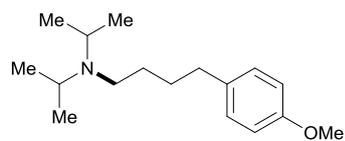
^1H NMR (270 MHz, CDCl_3): 4-(2-phenylpropyl)morpholine (**3k**)



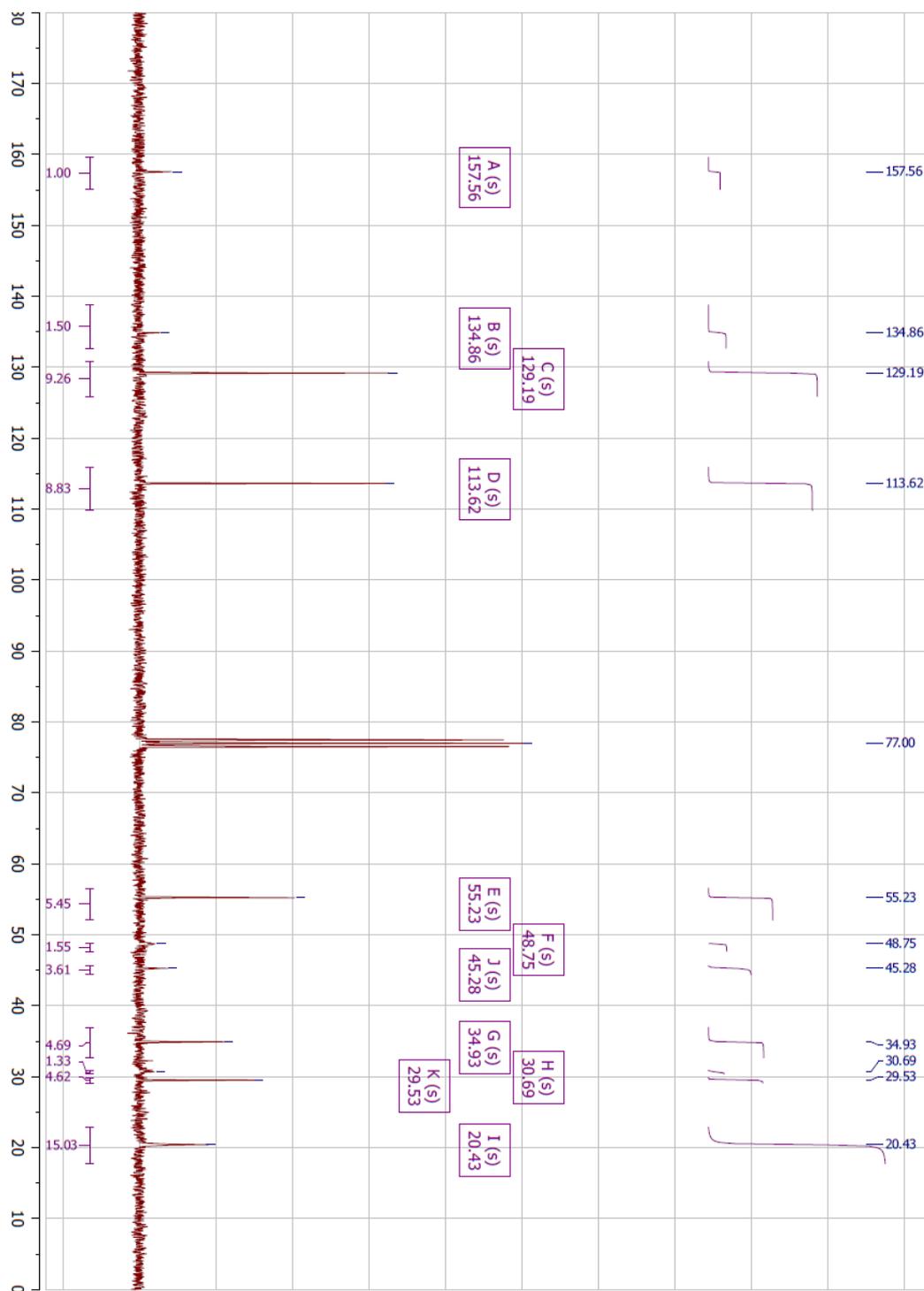
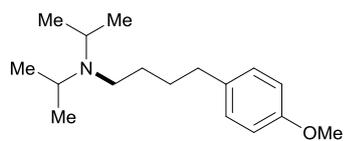
^{13}C NMR (101 MHz, CDCl_3): 4-(2-phenylpropyl)morpholine (**3k**)



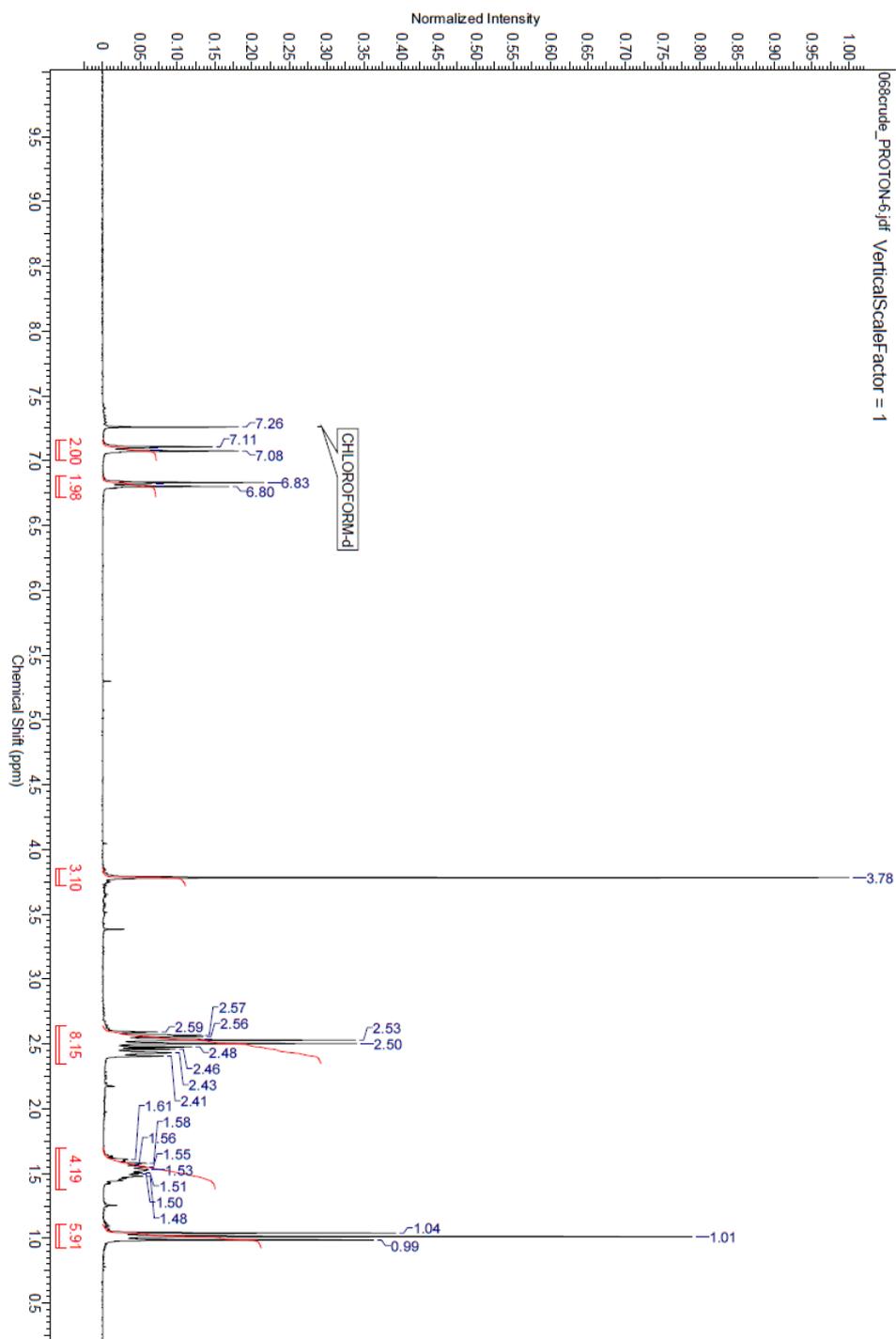
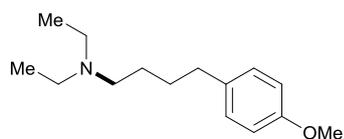
^1H NMR (270 MHz, CDCl_3): *N,N*-diisopropyl-4-(4-methoxyphenyl)butan-1-amine (**31**)



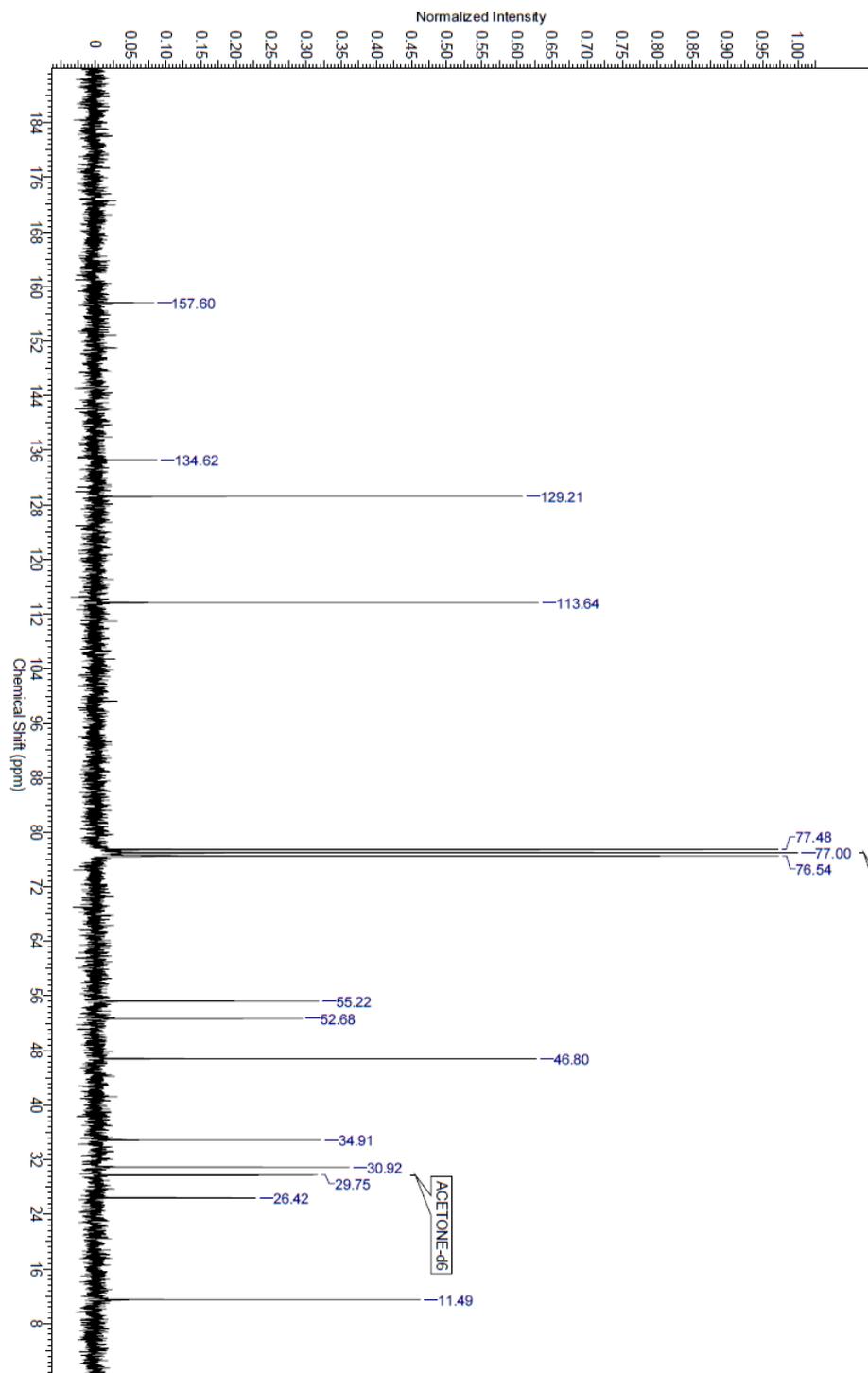
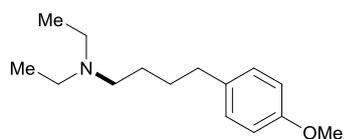
¹³C NMR (68 MHz, CDCl₃): *N,N*-diisopropyl-4-(4-methoxyphenyl)butan-1-amine (**31**)



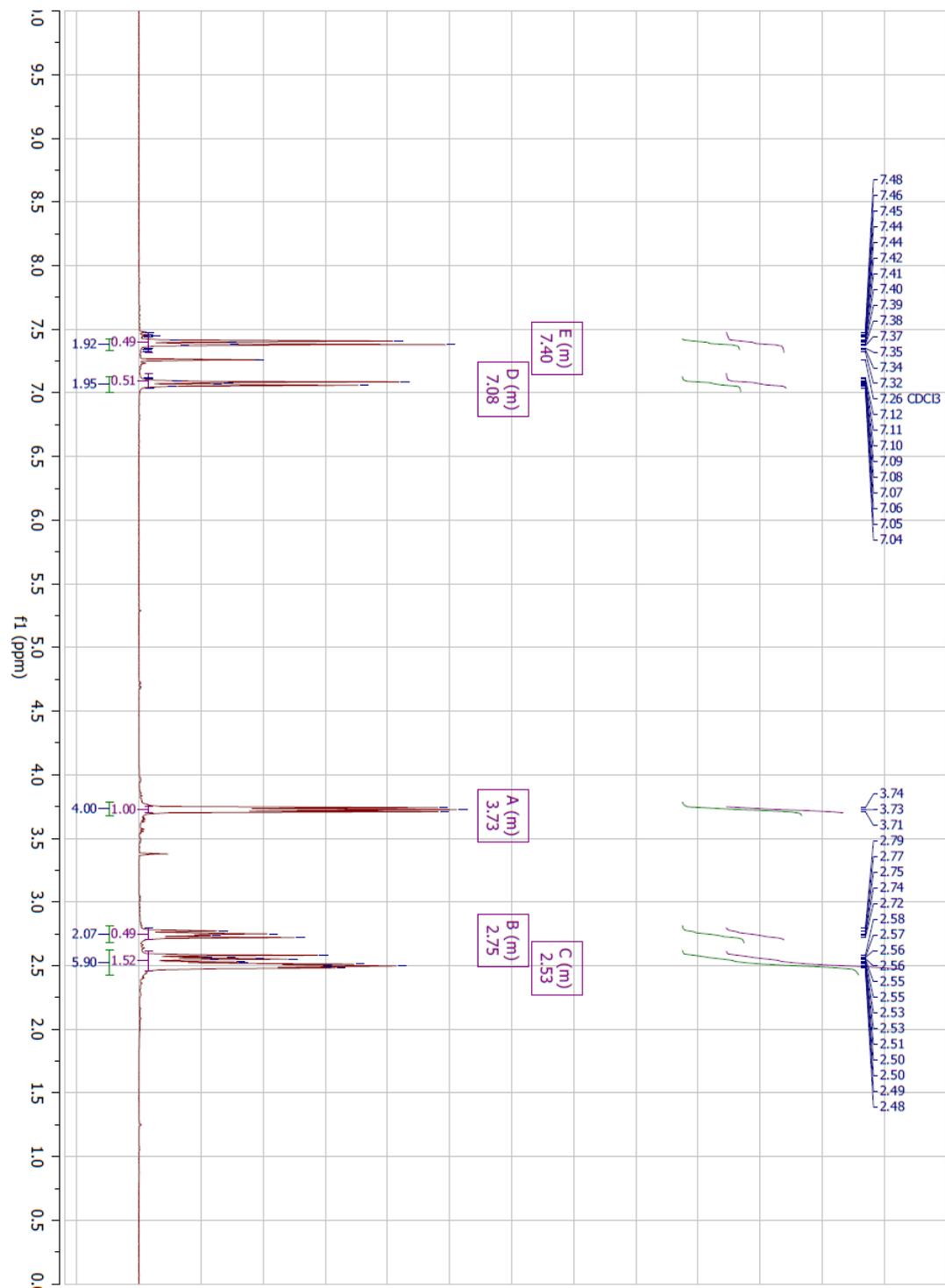
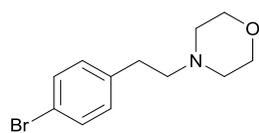
^1H NMR (270 MHz, CDCl_3): *N,N*-diethyl-4-(4-methoxyphenyl)butan-1-amine (**3m**)



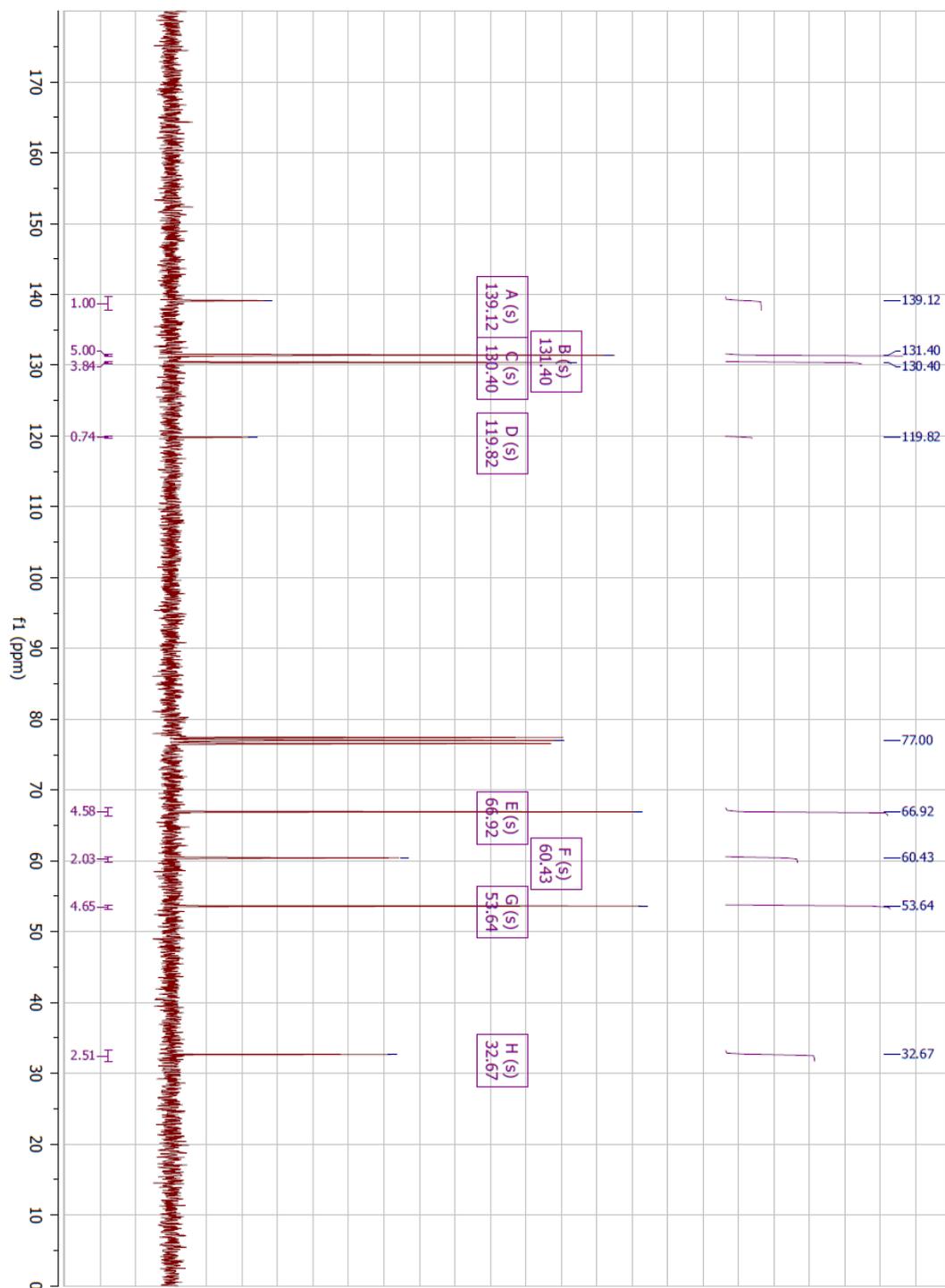
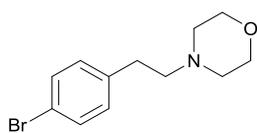
^{13}C NMR (68 MHz, CDCl_3): *N,N*-diethyl-4-(4-methoxyphenyl)butan-1-amine (**3m**)



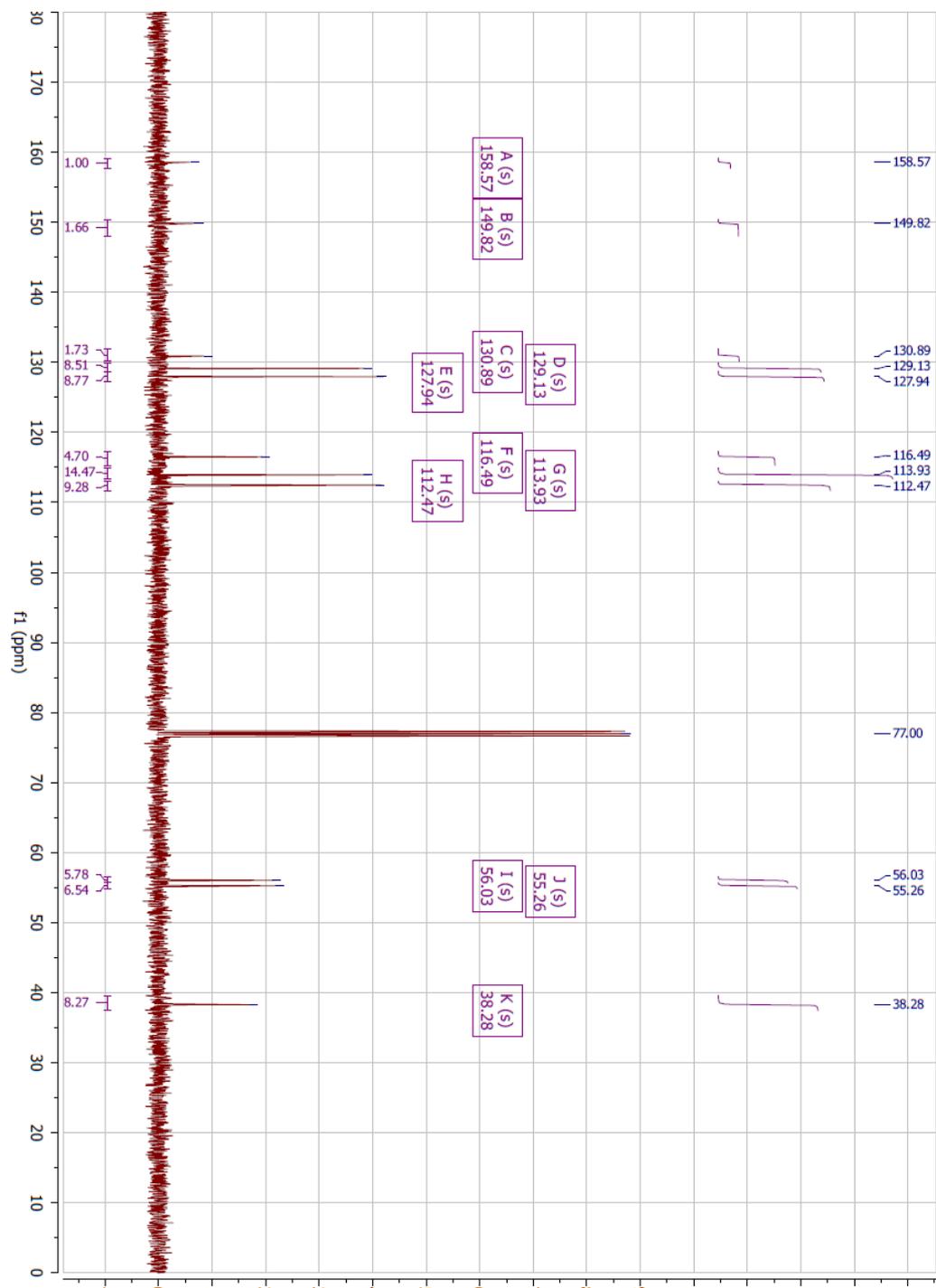
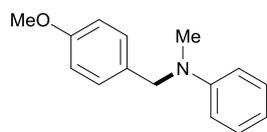
^1H NMR (300 MHz, CDCl_3): 4-(4-bromophenethyl)morpholine (**3n**)



^{13}C NMR (75 MHz, CDCl_3): 4-(4-bromophenethyl)morpholine (**3n**)



^{13}C NMR (101 MHz, CDCl_3): *N*-(4-methoxybenzyl)-*N*-methylaniline (**3p**)



6.0 References

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