Supplementary Materials for:

A Practical Catalytic Reductive Amination of Carboxylic Acids

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1 General Experimental

1.1 Reagents and Solvents

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried according to published methods[1] and distilled before use; except for toluene which was pre-dried over sodium wire and obtained from a solvent tower, where degassed solvent was passed through two columns of activated alumina and 7-micron filter under a 4-bar pressure. Petrol refers to the fraction of petroleum ether boiling between 40–60 °C. All water was deionised before use, and unless specified, all experiments were carried out in oven dried glassware with an argon balloon atmosphere.

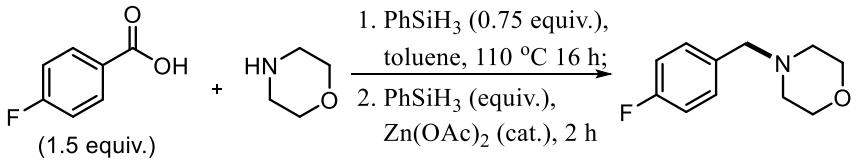
1.2 Analysis and Characterisation

Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F_{254} plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate or ninhydrin. Column chromatography was carried out using Fluorochem silica gel 60 Å (40-63 mesh). Melting points were calculated using a Stuart SMP3 and Fourier Transform Infrared Spectrometry (IR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry (HRMS) were measured on a Bruker microTOF II with Electron Spray Ionisation (ESI). Specific rotations ([α]D) were measured using an Anton Paar MCP 100 Modular Circular Polarimeter.

^{1}H NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$ or DMSO. ^{1}H NMR chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz), with residual protic solvent as the internal reference ($CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50 ppm). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons). Abbreviations used include s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, br – broad, app. – apparent. ^{13}C NMR were recorded on a 400 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to the ^{13}C signals in the solvent (central peak of $CDCl_3$ δ = 77.16 ppm, DMSO δ = 39.52) and coupling constants (*J*) are given in Hertz (Hz). All ^{13}C NMR are reported as proton decoupled spectra. ^{19}F NMR were recorded on a 376 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to $CFCl_3$ at 0.00 ppm and are reported as proton decoupled spectra.

2 Reaction Optimisation

2.1 Tertiary Amines



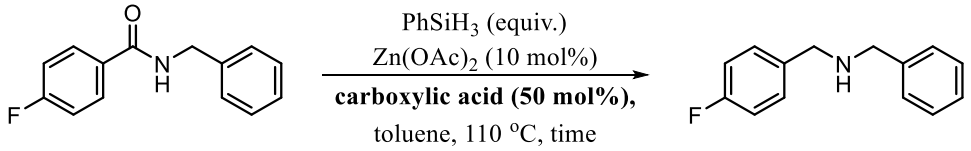
Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Yield / %[a]
1	1	10	54
2	2	10	63
3	3	10	67
4	2	5	25

a - Yield determined by ^{19}F NMR using trifluorotoluene as an internal standard.

To a refluxing solution of 4-fluorobenzoic acid (210 mg, 1.50 mmol) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by morpholine (87.5 µL, 1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (mol% as table) and phenylsilane (equiv. as table) were added. The reaction mixture was heated at reflux for a further 2 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

2.2 Secondary Amines

2.2.1 Secondary Amide Reduction

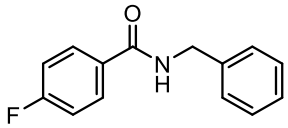


Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Carboxylic acid	Time / h	Yield / %[a]
1	1	10	-	6	1
2	2	10	-	6	20
3	3	10	-	6	22
4	2	10	-	24	27
5	3	10	$C_6H_5CO_2H$	6	65
6	3	10	$FC_6H_4CO_2H$	6	60
7	3	0	$C_6H_5CO_2H$	6	0

a -Yield determined by ^{19}F NMR using trifluorotoluene as an internal standard

To a refluxing solution of *N*-benzyl-4-fluorobenzamide (**SI-1**) (229 mg, 1.00 mmol) and carboxylic acid (as table) in toluene (1.20 mL) was added zinc acetate (mol% as table), followed by phenylsilane (equiv. as table). The reaction mixture was then heated for the specified length of time (as table), after which the heating was removed and acetic acid (1 mL of a 3 M aqueous solution) was added dropwise. The reaction mixture was cooled and diluted with EtOAc (10 mL), before the product was extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

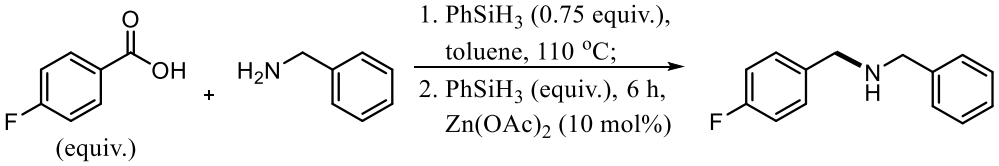
***N*-benzyl-4-fluorobenzamide (SI-1)**



To a refluxing solution of 4-fluorobenzoic acid (3.15 g, 22.5 mmol) in toluene (18.0 mL) was added phenylsilane (1.40 mL, 11.3 mmol), followed by benzylamine (1.64 mL, 15.0 mmol) dropwise. The reaction mixture was then heated for 16 h after which time the reaction mixture was cooled and diluted with EtOAc (10 mL) and washed with HCl (15 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc / petrol 1:4, to EtOAc /

petrol 1:1) to give the product as a colourless solid (2.77 g, 12.1 mmol, 81%), m.p. 138-140 °C. **IR** (ATR) νmax/cm^{-1} 3319, 3067, 3031, 1680, 1639, 1592, 1548, 1450, 1420; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.39 – 7.27 (m, 5H), 7.14 – 7.05 (m, 2H), 6.42 (s, 1H), 4.63 (d, *J* = 5.6 Hz, 2H); **^{13}C NMR**{^{19}F} (101 MHz, $CDCl_3$) δ 166.3, 166.0, 138.0, 130.5, 129.4, 128.9, 128.0, 127.7, 115.8, 44.2; **^{19}F NMR** (376 MHz, CDCl3) δ -108.09; **HRMS** [ESI (M + H^{+})] m/z calculated for $C_{14}H_{13}FNO$ 230.0976, found 230.0977.

2.2.2 One Pot Secondary Amine Synthesis Reaction Optimisation

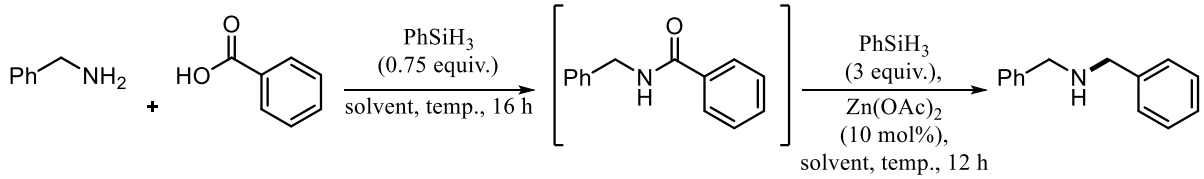


Entry	Acid / equiv.	$PhSiH_3$ / equiv.	Yield / %[a]
1	1.0	3	24
2	1.5	3	75
3	1.5	2	36

a - Yield determined by ^{19}F NMR using trifluorotoluene as an internal standard

To a refluxing solution 4-fluorobenzoic acid (equiv. as table) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by benzylamine (109 µL, 1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (mol% as table) and further phenylsilane (equiv. as table) were added. The reaction mixture was heated at reflux for a further 6 h before being cooled to room temperature and quenched with acetic acid (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the product extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

2.3 Solvent Screen



Entry	Solvent	Temperature / °C	Amide Yield / %[a]	Amine Yield / %[a]
1	toluene	110	86	93
2	chlorobenzene	132	87	96
3	methanol	65	0	-
4	*iso*-propanol	82	0	-
5	*tert*-butanol	82	0	-
6	acetone	56	0	-
7	methyl ethyl ketone	80	0	-
8	ethyl acetate	77	60	19
9	*tert*-butyl acetate	97	71	17
10	propylene carbonate	150	78	2
11	anisole	150	-[b]	90
12	dimethyl formamide	100	28	12
13	tetrahydrofuran	65	76	25
14	acetonitrile	82	76	25
15	dichloroethane	84	81	39

a – Yield determined by quantitative LCMS analysis using biphenyl as an internal standard; b – Anisole co-elutes with amide intermediate

To a solution of benzoic acid (183 mg, 1.50 mmol) in solvent (1.2 mL, as table) under a nitrogen atmosphere was added phenylsilane (92.5 µL, 0.750 eq.) and benzylamine (109 µL, 1.00 mmol) dropwise. The reaction was heated to the specified temperature (as table) for 16 h. The reaction mixture was cooled to room temperature and analysed by LC-MS. Zinc acetate (18.3 mg, 0.10 mmol) and phenylsilane (350 µL, 3.00 mmol) were added to the reaction mixture and it was heated to the specified temperature (as table) and analysed by LC-MS after 12h.

The following equation was used to calculate the weight of the desired compound in solution and the theoretical yield calculation then carried out:

$$Wt_x = k_x \times Wt_{is} \times \frac{\%_x}{\%_{is}}$$

Wt_x = weight of reaction component x in the reaction

k_x = absorption co-efficient for component x calculated above

Wt_{is} = known weight of internal standard in the reaction

$\%_x$, $\%_{is}$ = area % of component x and internal standard

3 Experimental Procedures and Characterisation of Compounds

3.1.1 General Procedure 1 – Secondary Amine Synthesis

To a refluxing solution of carboxylic acid (1.50 mmol) in anhydrous toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by amine (1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (18.3 mg, 10 mol%) and further phenylsilane (370 µL, 3.00 mmol) were added. The reaction mixture was heated at reflux for a further 4 h before being cooled to room temperature and quenched with acetic acid (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* (if the product contains sensitive, acidic or basic functional groups an alternative work-up procedure should be employed – see FAQ (Section 3.2.5)). If necessary, the products were purified by column chromatography.

3.1.2 General Procedure 2 – Tertiary Amine Synthesis

To a refluxing solution of carboxylic acid (1.50 mmol) in anhydrous toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by amine (1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (18.3 mg, 10 mol%) and further phenylsilane (247 µL, 2.00 mmol) were added. The reaction mixture was heated at reflux for a further 2 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* (if the product contains sensitive or acidic or basic groups an alternative work-up procedure should be employed – see FAQ (Section 3.2.5)). If necessary, the products were purified by column chromatography.

3.2 Graphical Guide for the Reductive Amination Reaction

3.2.1 Amidation phase of the reaction:

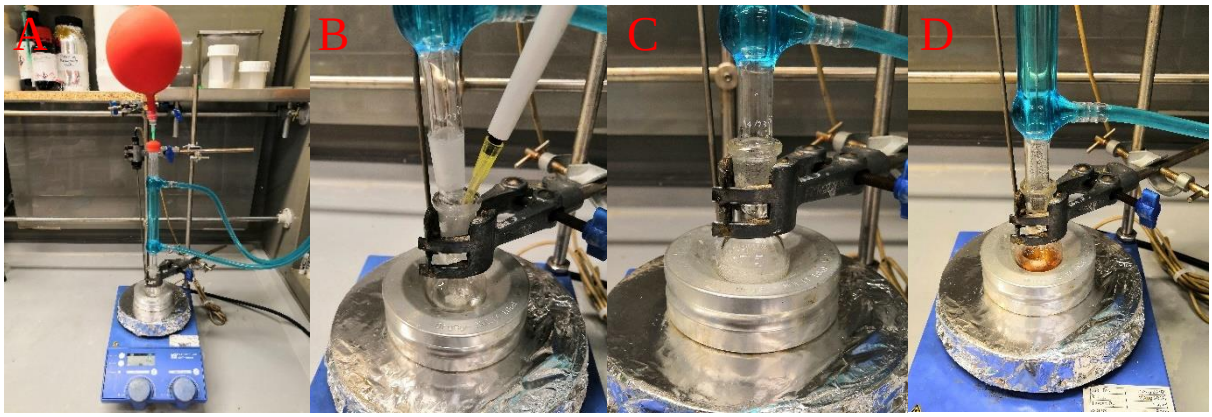


Figure S1. a) A typical reductive amination reaction set up using standard laboratory glassware and an argon balloon. b) Addition of phenylsilane to the solution of carboxylic acid in toluene by temporary removal of condenser. c) H_2 evolution after the dropwise addition of amine to the reaction mixture. d) Amidation phase of the reaction after stirring at reflux for 16 h.

3.2.2 Reduction phase of the reaction:

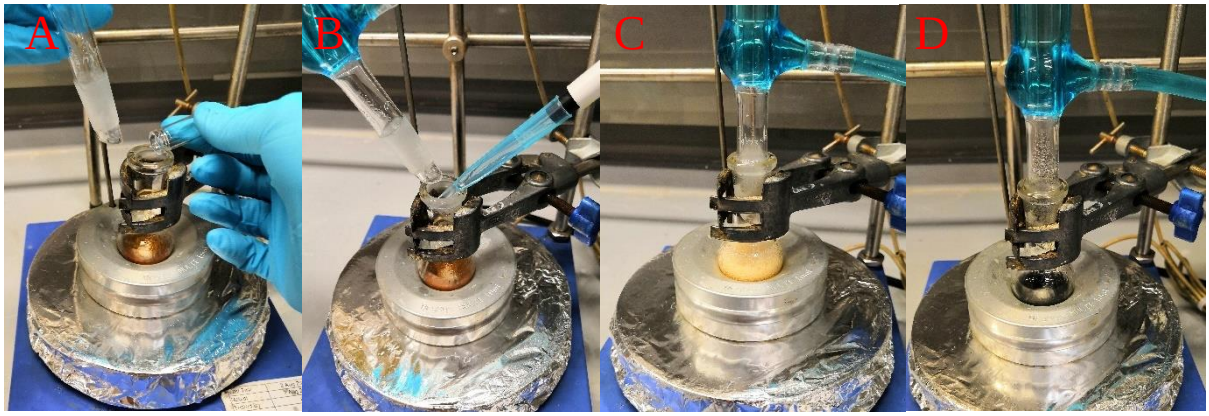


Figure S2. a) Addition of zinc acetate to the reaction mixture by temporary removal of the condenser. b) Addition of further phenylsilane to the reaction mixture. c) Resulting H_2 evolution after addition of zinc acetate and phenylsilane. d) Characteristic colour change to black signalling the end-point of the reaction after 2 h / 6 h stirring at reflux.

3.2.3 Reaction work-up:

Figure S3. a) Reaction mixture after the addition of HCl / acetic acid (1 mL of a 3 M aqueous solution) to quench the reaction. b) Extraction of the product with HCl / acetic acid (3 M aqueous solution). c) Addition of NaOH (6 M aqueous solution) to the combined aqueous layers until pH12 was reached. d) Re-extraction of the product using CH_2Cl_2. The discarded organic layer can be seen on the right hand side.

3.2.4 Reaction Analysis:

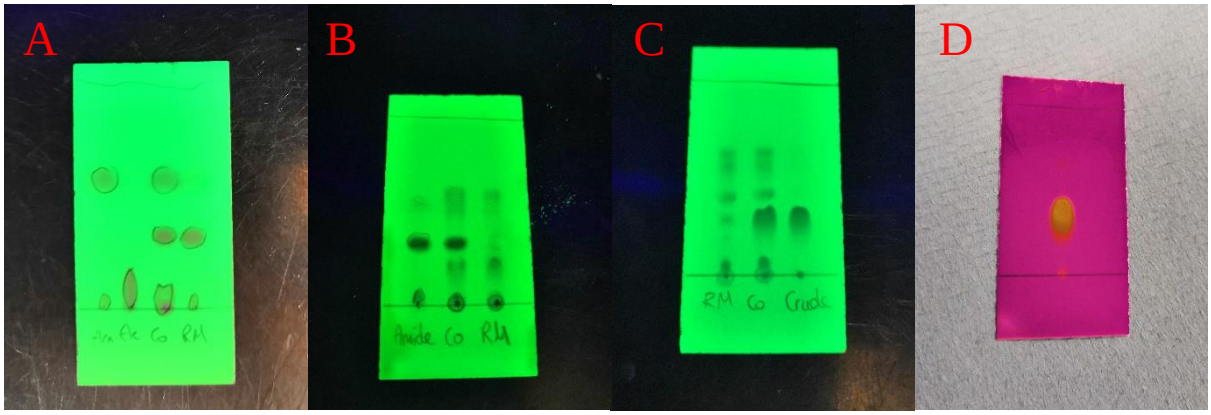


Figure S4. a) TLC of reaction mixture after complete amidation phase under UV light (left to right – amine starting material, acid starting material, Co-spot and reaction mixture). b) TLC of reaction mixture after completion of reduction phase (before work-up) under UV light (left to right – amide intermediate, co-spot, reaction mixture). c) TLC of crude product under UV light (left to right – reduction phase reaction mixture, co-spot, crude product). d) TLC of crude product stained with potassium permanganate.

3.2.5 Troubleshooting: Frequently Asked Questions

Does the reaction have to be run under strict anhydrous and inert conditions?

The reported reactions have been run using oven-dried glassware and dry solvents, under an argon atmosphere to avoid any consumption of the phenylsilane *via* reaction with water. However, it is possible to run the reactions *under the standard general conditions* in air with glassware and Winchester grade solvent, which results in a reduction in the yield of the reaction of approximately 10%.

Is the order of addition of reagents important?

The order of addition of the reagents has been designed to optimise the efficacy of the reaction. For the amidation phase of the reaction, phenylsilane was added to a solution of the carboxylic acid in toluene, at reflux. Following this, the amine was cautiously added dropwise - **Note rapid and copious evolution of H_2** (typically most of the H_2 evolution occurs at the start of the amine addition, which should be done with caution. Once the gas evolution has subsided, the remainder of the amine can be added dropwise at a faster rate). Addition of the amine as the final reagent avoids the formation of insoluble ammonium carboxylate salts. For the reduction phase of the reaction, the zinc acetate is typically added before the additional phenylsilane, as this means that the evolution of further H_2 can be more easily controlled.

Can the reaction be performed in a sealed tube?

Due to the formation of hydrogen gas during the reaction, it is not advisable to perform the reaction in a sealed tube, such as a microwave vial.

Can you stop after the amidation phase and isolate the amide product?

Yes. Use the work-up procedure detailed in the synthesis of **SI-1**. Full details of the amidation procedure and mechanism will be reported elsewhere.

Why is acetic acid used for the extraction of secondary amines, whereas HCl is used for the extraction of tertiary amines?

Due to the differences in solubility between secondary ammonium carboxylates and tertiary ammonium carboxylates. Acetic acid is used for the extraction of secondary amines as the ammonium acetates are generally more soluble than the ammonium carboxylates. It is also possible to isolate the products as HCl salts by the addition of concentrated HCl (see large scale synthesis of dibenzylamine (**26**) Section 3.5).

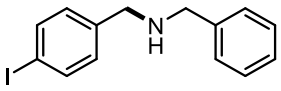
What is the alternative work-up if there are acid or base-sensitive groups present?

If there are acid or base sensitive groups, or if an acid-based extractive work-up is not possible, an alternative work-up can be employed. The reaction can be quenched with silica gel, which can be added directly to the reaction mixture and stirred for 30 mins. After removal of the solvent *in vacuo*, the silica

can be dry-loaded directly onto a column for purification (eluting with EtOAc / petrol mixture as appropriate).

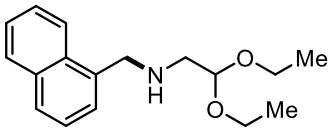
3.3 Synthesis of Secondary Amines

N-Benzyl-1-(4-iodophenyl)methanamine (1)



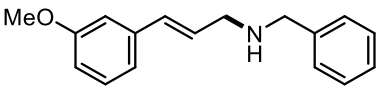
Prepared according to general procedure 1, using 4-iodobenzoic acid (372 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title compound as colourless oil (264 mg, 0.820 mmol, 82%). **IR** (ATR) νmax/cm^{-1} 3061, 2822, 1482.1452, 1006; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.24 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 1H), 3.81 (s, 2H), 3.77 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.7, 138.6, 137.5, 130.4, 128.5, 128.4, 127.4, 92.7, 52.4, 51.8; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{15}IN$ 324.0244, found 324.0251. The data matches that found in the literature.[2]

2,2-Diethoxy-*N*-(naphthalen-1-ylmethyl)ethan-1-amine (2)



Prepared according to general procedure 1, using 1-napthoic acid (258 mg, 1.50 mmol) and amino acetaldehyde diethyl acetal (145 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 3:7) to afford the title compound as a colourless oil (131 mg, 0.480 mmol, 48%). **IR** (ATR) νmax/cm^{-1} 3043, 2872, 1443, 1372, 1121, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 1H), 7.93 – 7.83 (m, 1H), 7.81 – 7.74 (m, 1H), 7.57 – 7.38 (m, 4H), 4.65 (t, *J* = 5.6 Hz, 1H), 4.27 (s, 2H), 3.68 (dq, *J* = 9.4, 7.0 Hz, 2H), 3.52 (dq, *J* = 9.4, 7.0 Hz, 2H), 2.88 (d, *J* = 5.6 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 133.8, 131.7, 128.6, 127.7, 126.0, 126.0, 125.6, 125.3, 123.6, 102.1, 62.3, 51.9, 51.4, 15.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{17}H_{23}NO_2$ 274.1802, found 274.1802. The data matches that found in the literature.[3]

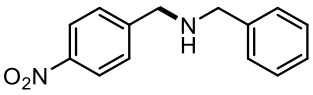
(*E*)-*N*-Benzyl-3-(3-methoxyphenyl)prop-2-en-1-amine (3)



Prepared according to general procedure 1, using 3-(3-methoxyphenyl)acrylic acid (267 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a colourless oil (151 mg, 0.590 mmol, 59%). **IR** (ATR) νmax/cm^{-1} 3315, 2920, 2833, 1598, 1489, 1453, 1261, 1154, 907; **^{1}H NMR**

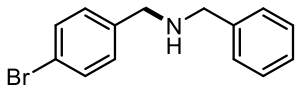
(400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.25 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.99 (ddd, *J* = 7.7, 1.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 2.6, 1.2 Hz, 1H), 6.81 (ddd, *J* = 7.7, 2.6, 1.2 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.8, 6.2 Hz, 1H), 3.89 (s, 2H), 3.83 (s, 3H), 3.48 (d, *J* = 6.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 139.9, 138.5, 131.6, 129.5, 128.5, 128.4, 128.3, 127.1, 119.0, 113.1, 111.5, 55.2, 53.2, 51.0; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{17}H_{20}NO$ 254.1539, found 254.1531.

N-Benzyl-1-(4-nitrophenyl)methanamine (4)



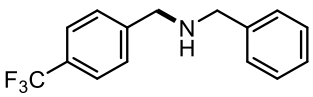
Prepared according to general procedure 1, using 4-nitrobenzoic acid (251 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title compound as yellow oil (197 mg, 0.810 mmol, 81%). **IR** (ATR) νmax/cm^{-1} 3027, 2837, 1514, 1383.; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.1 (d, *J* = 8.7 Hz, 2H), 7.5 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.17 (m, 5H), 3.83 (s, 2H), 3.74 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 147.1, 139.8, 128.8, 128.6, 128.2, 127.3, 123.7, 53.3, 52.4. **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}N_2O_2$ 243.1128, found 243.1128. The data matches that found in the literature.[4]

N-Benzyl-1-(4-bromophenyl)methanamine (5)



Prepared according to general procedure 1, using 4-bromobenzoic acid (302mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title compound as colourless oil (243 mg, 0.880 mmol, 88%). **IR** (ATR) νmax/cm^{-1} 3025, 2923, 2349, 1485, 1452; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 2H), 3.77 (s, 2H), 2.97 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.6, 138.9, 131.4, 129.9, 128.4, 128.2, 127.1, 120.7, 52.8, 52.1; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}BrN$ 276.0382, found 276.0392. The data matches that found in the literature.[5]

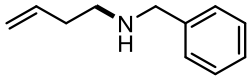
N-Benzyl-1-(4-(trifluoromethyl)phenyl)methanamine (6)



Prepared according to general procedure 1, using 4-(trifluoromethyl)benzoic acid (285 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title compound as a colourless oil (205 mg, 0.770 mmol, 77%). **IR** (ATR) νmax/cm^{-1} 3028, 2836, 1618, 1494, 1362, 1159; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.36 (m, 4H), 7.32 – 7.27 (m, 1H), 3.88 (s, 2H), 3.82 (s, 2H), 1.78 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 140.1, 129.4 (q, *J* = 32.3 Hz), 128.6,

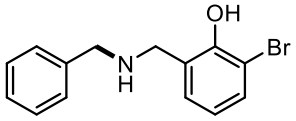
128.4, 128.3, 127.2, 125.4 (q, *J* = 4.0 Hz), 125.2 (q, *J* = 271.7 Hz), 53.3, 52.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{15}H_{15}F_3N$ 266.1151, found 266.1161. The data matches that found in the literature.[6]

N-Benzylbut-3-en-1-amine (7)



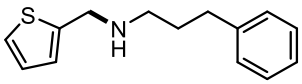
Prepared according to general procedure 1, using 3-butenoic acid (127 µL, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a pale yellow oil (119 mg, 0.740 mmol, 74%). **IR** (ATR) νmax/cm^{-1} 2917, 2813, 1639, 1453, 1116; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.21 (m, 5H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.15 – 5.08 (m, 1H), 5.08 – 5.03 (m, 1H), 3.83 (s, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.37 – 2.26 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.2, 136.3, 128.3, 128.0, 126.8, 116.3, 53.8, 48.2, 34.2; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{16}N$ 162.1277, found 162.1279. The data matches that found in the literature.[7]

2-((Benzylamino)methyl)-6-bromophenol (8)



Prepared according to general procedure 1, using 3-bromo-2-hydroxybenzoic acid (326 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol). The product was purified by column chromatography (EtOAc / petrol 2:3, R_f = 0.36) to give the product as a colourless oil (192 mg, 0.710 mmol, 71%). **IR** (ATR) νmax/cm^{-1} 3293, 2846, 2359, 1452, 1405, 1260; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 – 7.27 (m, 5H), 6.96 – 6.89 (m, 1H), 6.66 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.97 (s, 2H), 3.79 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0, 137.8, 132.1, 128.8, 128.5, 127.8, 127.6, 123.5, 120.0, 110.5, 52.5, 51.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}BrNO$ 292.0332, found 292.0333.

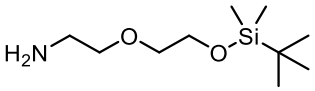
3-Phenyl-*N*-(thiophen-2-ylmethyl)propan-1-amine (9)



Prepared according to general procedure 1, using 2-thiophenecarboxylic acid (192 mg, 1.50 mmol) and 3-propylamine (142 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 2:3, R_f = 0.12) to afford the title compound as a colourless oil (149 mg, 0.640 mmol, 64%). **IR** (ATR) νmax/cm^{-1} 3025, 2926, 2855, 2814, 1602, 1452, 1329, 1109, 1031.; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.30 – 7.23 (m, 4H), 7.02 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.99 (d, *J* = 3.4 Hz, 1H), 4.04 (s, 2H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.74 (t, *J* = 8.1 Hz, 2H), 2.00 – 1.83 (m, 2H); **^{13}C**

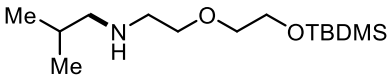
NMR (101 MHz, $CDCl_3$) δ 144.1, 142.0, 128.3, 128.3, 126.6, 125.7, 124.8, 124.2, 48.5, 48.3, 33.5, 31.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{18}NS$ 232.1154, found 232.1164.

2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (SI-2)



To 2-(2-aminoethoxy)ethanol (502 µL, 5.00 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added imidazole (1.02 g, 15.0 mmol), DMAP (61.1 mg, 0.500 mmol) and *tert*-butyldimethylsilyl chloride (829 mg, 5.50 mmol). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a colourless oil (790 mg, 3.60 mmol, 72%). **IR** (ATR) νmax/cm^{-1} 3335, 2928, 2856, 1561, 1098; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 (t, *J* = 5.3 Hz, 2H), 3.56 – 3.49 (m, 4H), 2.85 (t, *J* = 5.3 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 73.5, 72.6, 62.9, 42.1, 26.1, 18.5, -5.10; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{10}H_{25}NO_2Si$ 220.1727, found 220.1742. The data matches that found in the literature.[8]

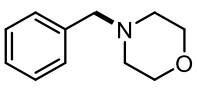
N-(2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (10)



Prepared according to general procedure 1, using isobutyric acid (139 µL, 1.50 mmol) and 2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (**SI-2**) (219 mg, 1.00 mmol), omitting the acidic and basic washes. The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a yellow oil (256 mg, 0.930 mmol, 93%). **IR** (ATR) νmax/cm^{-1} 2954, 2857, 1463, 1253, 1131; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.46 (t, *J* = 5.2 Hz, 2H), 2.69 (t, *J* = 5.2 Hz, 2H), 2.35 (d, *J* = 6.9 Hz, 2H), 1.81 – 1.69 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 6H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 72.3, 70.1, 62.5, 57.6, 49.2, 27.9, 25.8, 20.5, 18.2, -5.4; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{34}NO_2Si$ 276.2353, found 276.2348. The data matches that found in the literature.[3]

3.4 Synthesis of Tertiary Amines

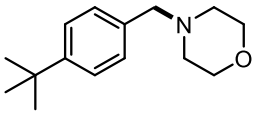
4-Benzylmorpholine (11)



Prepared according to general procedure 2, using benzoic acid (183 mg, 1.50 mmol) and morpholine (87.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (140 mg, 0.790 mmol, 79%). **IR** (ATR) νmax/cm^{-1} 2804, 2763, 1453, 1350, 1115, 1070, 1007, 913; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40

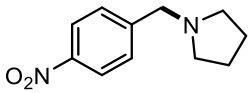
– 7.19 (m, 5H), 3.71 (t, *J* = 4.6 Hz, 4H), 3.50 (s, 2H), 2.45 (t, *J* = 4.6 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 129.2, 128.2, 127.1, 67.0, 63.4, 53.6; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{16}ON^+$ 178.1232, found 178.1229. The data matches that found in the literature.[9]

4-(4-(*tert*-butyl)benzyl)morpholine (12)



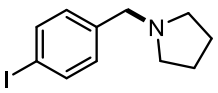
Prepared according to general procedure 1, using 4-*tert*-butylbenzoic acid (267 mg, 1.50 mmol) and morpholine (87.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (182 mg, 0.780 mmol, 78%). **IR** (ATR) νmax/cm^{-1} 2958, 2854, 2805, 1513, 1393, 1315, 1265, 1115, 1006; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.71 (t, *J* = 4.7 Hz, 4H), 3.47 (s, 2H), 2.44 (t, *J* = 4.7 Hz, 4H), 1.32 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.1, 134.6, 129.0, 125.2, 67.1, 63.2, 53.7, 34.5, 31.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{15}H_{24}NO$ 234.1852, found 234.1862.

1-(4-Nitrobenzyl)pyrrolidine (13)



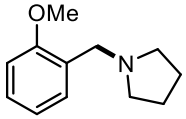
Prepared according to general procedure 2, using 4-nitrobenzoic acid (251 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (187 mg, 0.900 mmol, 90%). **IR** (ATR) νmax/cm^{-1} 2961, 2786, 1515, 1342; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 2H), 2.52 – 2.45 (m, 4H), 1.83 – 1.70 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5, 147.0, 129.3, 123.5, 59.9, 54.3, 23.6; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}N_2O_2^+$ 207.1128, found 207.1144. The data matches that found in the literature.[10]

1-(4-Iodobenzyl)pyrrolidine (14)



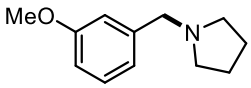
Prepared according to general procedure 2, using 4-iodobenzoic acid (372 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (250 mg, 0.900 mmol, 90%). **IR** (ATR) νmax/cm^{-1} 2960, 2784, 1491, 1371, 1240; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.52 (s, 2H), 2.62 – 2.25 (m, 4H), 1.87 – 1.61 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3, 137.2, 130.8, 92.3, 59.9, 54.0, 23.4; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}IN+$ 288.0244, found 288.0251. The data matches that found in the literature.[11]

1-(2-Methoxybenzyl)pyrrolidine (15)



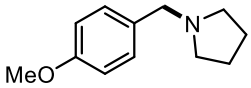
Prepared according to general procedure 2, using 2-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (174 mg, 0.910 mmol, 91%). **IR** (ATR) νmax/cm^{-1} 2953, 2780, 1654, 1510, 1247; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.23 (ddd, *J* = 8.0, 8.0, 1.3 Hz, 1H), 6.94 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 2H), 2.67 – 2.48 (m, 4H), 1.91 – 1.70 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 130.4, 127.9, 127.2, 120.2, 110.3, 55.3, 54.1, 53.7, 23.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1390.

1-(3-Methoxybenzyl)pyrrolidine (16)



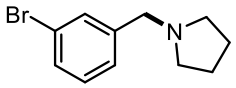
Prepared according to general procedure 2, using 3-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (160 mg, 0.840 mmol, 84%). **IR** (ATR) νmax/cm^{-1} 2957, 2781, 1597, 1262; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.79 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 2H), 2.55 – 2.42 (m, 4H), 1.82 – 1.71 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 139.1, 129.4, 121.5, 114.6, 113.3, 60.3, 55.4, 53.9, 23.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1404. The data matches that found in the literature.[12]

1-(4-Methoxybenzyl)pyrrolidine (17)



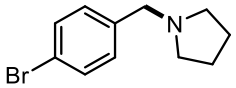
Prepared according to general procedure 2, using 4-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (162 mg, 0.850 mmol, 85%). **IR** (ATR) νmax/cm^{-1} 2955, 2778, 1654, 1511, 1242; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 2H), 2.58 – 2.40 (m, 4H), 1.82 – 1.61 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 131.3, 130.1, 113.6, 60.0, 55.2, 54.0, 23.4; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1387. The data matches that found in the literature.[13]

1-(3-Bromobenzyl)pyrrolidine (18)



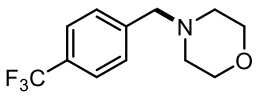
Prepared according to general procedure 2, using 3-bromobenzoic acid (302 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (172 mg, 0.720 mmol, 72%). **IR** (ATR) νmax/cm^{-1} 2960, 2780, 1568; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.14 (dd, J = 7.8, 7.8 Hz, 1H), 3.55 (s, 2H), 2.59 – 2.40 (m, 4H), 1.83 – 1.68 (m, 4H);**^{13}C** NMR (101 MHz, $CDCl_3$) δ 141.8, 131.7, 123.0, 129.8, 127.4, 122.4, 60.0, 54.1, 23.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{15}BrN^+$ 240.0382, found 240.0388. The data matches that found in the literature.[14]

1-(4-Bromobenzyl)pyrrolidine (19)



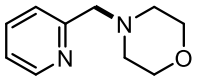
Prepared according to general procedure 2, using 4-bromobenzoic acid (302 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (203 mg, 0.850 mmol, 85%). **IR** (ATR) νmax/cm^{-1} 2960, 2783, 1487; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.62 (s, 2H), 2.71 – 2.46 (m, 4H), 1.88 – 1.68 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5, 131.3, 130.6, 120.9, 59.6, 53.9, 23.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{15}BrN^+$ 240.0382, found 240.0387. The data matches that found in the literature.[15]

4-(4-(Trifluoromethyl)benzyl)morpholine (20)



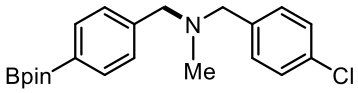
Prepared according to general procedure 2, using 4-(trifluoromethyl)benzoic acid (285 mg, 1.50 mmol) and morpholine (87.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (205 mg, 0.840 mmol, 84%). **IR** (ATR) νmax/cm^{-1} 2918, 2856, 2809, 1418; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 3.73 – 3.65 (m, 4H), 3.52 (s, 2H), 2.46 – 2.36 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 129.5 (q, *J* = 31.6 Hz), 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 267 Hz), 67.0, 62.8, 53.7; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{12}H_{15}F_3NO^+$ 246.1100, found 246.1102. The data matches that found in the literature.[16]

4-(Pyridin-2-ylmethyl)morpholine (21)



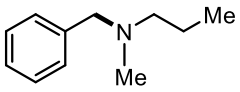
Prepared according to general procedure 2, using 2-picolinic acid (185 mg, 1.50 mmol) and morpholine (87.5 µL, 1.00 mmol) to afford the title compound as an orange oil (166 mg, 0.930 mmol, 93%). **IR** (ATR) νmax/cm^{-1} 3384, 2959, 2815, 1650, 1593, 1069; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.6 Hz, 1H), 7.49 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.00 (ddd, *J* = 7.7, 4.6, 1.2 Hz, 1H), 3.56 (t, *J* = 4.6 Hz, 4H), 3.49 (s, 2H), 2.34 (t, *J* = 4.6 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.1, 149.3, 136.4, 123.3, 122.1, 66.9, 65.0, 53.8; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{10}H_{15}ON_2^+$ 179.1184, found 179.1185. The data matches that found in the literature.[17]

***N*-(4-chlorobenzyl)-*N*-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (22)**



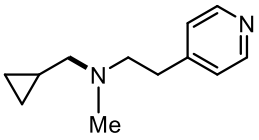
Prepared according to general procedure 2, using 4-carboxylphenylboronic acid pinacol ester (372 mg, 1.50 mmol) and 1-(4-chlorophenyl)-*N*-methanamine (145 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:9, R_f = 0.32) to afford the title compound as a colourless oil (284 mg, 0.760 mmol, 76%). **IR** (ATR) νmax/cm^{-1} 2977, 2788, 1670, 1513, 1356, 1142, 1086, 981; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.27 (m, 4H), 3.55 (s, 2H), 3.47 (s, 2H), 2.18 (s, 3H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 137.6, 134.9, 132.7, 130.5, 130.4, 128.5, 128.5, 83.9, 61.9, 61.0, 42.2, 25.0; **HRMS** [ESI (M + Na^+)] m/z calculated for $C_{21}H_{27}BClNNaO_2$ 394.1716, found 394.1711.

***N*-benzyl-*N*-methylpropan-1-amine (23)**



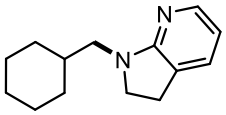
Prepared according to general procedure 2, using propionic acid (112 µL, 1.50 mmol) and *N*-benzylmethylamine (129 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:9 to EtOAc / petrol 2:3, R_f = 0.14) to afford the title compound as a colourless oil (121 mg, 0.740 mmol, 74%). **IR** (ATR) νmax/cm^{-1} 2957, 2787, 1494, 1452, 1364, 1132, 1108, 1043; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H), 3.50 (s, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.20 (s, 3H), 1.61 – 1.51 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.4, 129.2, 128.3, 127.0, 62.5, 59.7, 42.4, 20.7, 12.0; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{18}N$ 164.1434, found 164.1439.

N-(cyclopropylmethyl)-*N*-methyl-2-(pyridin-3-yl)ethan-1-amine (24)



Prepared according to general procedure 2, using cyclopropane carboxylic acid (119 µL, 1.50 mmol) and *N*-methyl-*N*-(2-pyridin-4-ylethyl)amine (136 mg, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 19:1, R_f = 0.12) to afford the title compound as a yellow oil (170 mg, 0.890 mmol, 89%). **IR** (ATR) νmax/cm^{-1} 2929, 1632, 1603, 1453, 1416, 1224, 1069, 908; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 – 8.38 (m, 2H), 7.14 – 7.03 (m, 2H), 2.80 – 2.71 (m, 2H), 2.71 – 2.62 (m, 2H), 2.35 (s, 3H), 2.29 (d, *J* = 6.5 Hz, 2H), 0.94 – 0.74 (m, 1H), 0.55 – 0.41 (m, 2H), 0.18 – 0.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 149.4, 124.2, 62.4, 57.9, 42.1, 32.9, 8.6, 4.0; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{12}H_{19}N_2$ 191.1543, found 191.1545.

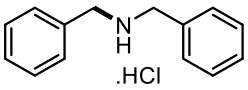
1-(Cyclohexylmethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (25)



Prepared according to general procedure 2, using cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (120 mg, 1.00 mmol) to afford the title compound as a colourless oil (163 mg, 0.750 mmol, 75%). **IR** (ATR) νmax/cm^{-1} 2923, 2850, 2795, 1612, 1505, 1447, 1287; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.12 (ddd, *J* = 6.9, 2.9, 1.4 Hz, 1H), 6.36 (dd, *J* = 6.9, 5.3 Hz, 1H), 3.48 (t, *J* = 8.4 Hz, 2H), 3.16 (d, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 8.4 Hz, 2H), 1.82-1.61 (m, 6H), 1.30-1.12 (m, 3H), 1.05-0.93 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 145.8, 130.6, 122.9, 111.6, 52.3, 50.3, 36.7, 31.2, 26.7, 26.1, 26.0; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{21}N_2^+$ 217.1705, found 217.1702.

3.5 Large-Scale Reductive Amination

Dibenzylamine hydrochloride (26)



Benzoic acid (55.8 g, 457 mmol) and benzylamine (33.3 mL, 305 mmol) were added to toluene (360 mL) under nitrogen and heated to reflux. Phenylsilane (28.2 mL, 228 mmol) was added slowly (~2 mL/min) by syringe pump, the reaction was maintained at 110 °C for 24 h then cooled at 0.5 °C/min to 50 °C and maintained until the reduction. The reaction jacket was heated to 110 °C and zinc acetate (5.59 g, 30.5 mmol) was added, followed by the slow addition of phenylsilane (75.0 mL, 609 mmol) and the reaction was stirred for 20 h then cooled to 25 °C. The reaction solution was decanted from

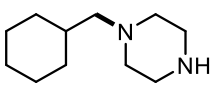
controllable lab reactor and the vessel was washed with toluene (50 mL) which was added to the reaction solution. The zinc precipitate was removed by filtration through Celite and the pad was washed with ethyl acetate (75 mL). The solution remained grey and cloudy so activated charcoal was added and the solution was filtered through Celite and washed with ethyl acetate (75 mL) to afford ~700 mL yellow clear solution. HCl (457 mmol, 1.5 equiv. of a 12 M aqueous solution) was added slowly and the precipitate was collected by filtration, the wet cake was stirred in ethyl acetate for 0.5 minutes and filtered, followed by washing with methyl tert-butyl ether. The solid was dried to afford the product HCl salt (70.9 g, 92%) as a colourless solid. HPLC purity = 93%, KF titration showed the product is a monohydrate. **IR** (ATR) νmax/cm^{-1} 3025, 2920, 2850, 1494, 1452, 1115, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.16 (m, 10H), 3.82 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2, 128.7, 128.6, 127.5, 52.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{16}N^+$ 198.1283, found 198.1291. The data matches that found in the literature.[3]

3.5.1 Graphical Guide for the Large Scale Reductive Amination Reaction

Figure S5. a) Reaction set-up using jacketed reaction vessel. Hydrogen effervescence visible from the slow addition of silane (2 mL/min) during the amidation phase of the reaction. b) After zinc acetate and further silane addition for the reduction phase of the reaction. c) Filtration of the hydrochloride salt. d) Product after filtration and drying.

3.6 Selective Reductive Amination

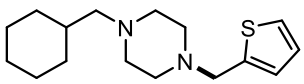
1-(cyclohexylmethyl)piperazine (28)



To a refluxing solution of cyclohexanoic acid (192 mg, 1.50 mmol) and 2-oxopiperazine (100 mg, 1.00 mmol) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol) dropwise. The reaction

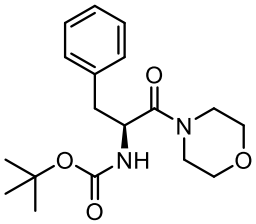
mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (45.9 mg, 0.25 mmol) and further phenylsilane (370 µL, 3.00 mmol) were added. The reaction mixture was heated at reflux for a further 6 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a pale yellow oil (99 mg, 0.540 mmol, 54%). **IR** (ATR) νmax/cm^{-1} 2919, 2848, 2804, 1658, 1448, 1123, 1004; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.86 (t, J = 4.9 Hz, 4H), 2.46 – 2.22 (m, 4H), 2.07 (d, J = 7.1 Hz, 2H), 2.03 (s, 1H), 1.82 – 1.57 (m, 4H), 1.47 (ttt, J = 10.8, 7.1, 3.5 Hz, 1H), 1.30 – 1.04 (m, 4H), 0.93 – 0.75 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 66.5, 55.2, 46.2, 34.9, 32.1, 26.9, 26.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{23}N_2$ 183.1856, found 183.1853.

1-(cyclohexylmethyl)-4-(thiophen-2-ylmethyl)piperazine (29)



Prepared according to general procedure 1, using 2-thiophene carboxylic acid (192 mg, 1.50 mmol) and 1-(cyclohexylmethyl)piperazine (**28**) (182 mg, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.27) to afford the title compound as a colourless oil (209 mg, 0.750 mmol, 75%). **IR** (ATR) νmax/cm^{-1} 2919, 2848, 2805, 2768, 1447, 1360, 1269, 1009; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.4 Hz, 1H), 6.90 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.72 (s, 2H), 2.51 (m, 4H), 2.42 (m, 4H), 2.12 (d, *J* = 7.1 Hz, 2H), 1.80 – 1.60 (m, 4H), 1.52 – 1.41 (m, 1H), 1.30 – 1.11 (m, 4H), 0.97 – 0.78 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7, 126.5, 126.2, 125.0, 65.8, 57.3, 53.8, 53.0, 35.2, 32.1, 27.0, 26.3; **HRMS** [ESI (M + Na$^+$)] m/z calculated for $C_{16}H_{26}N_2NaS$ 301.1709, found 301.1718.

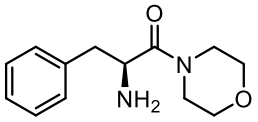
tert-Butyl (*S*)-(1-morpholino-1-oxo-3-phenylpropan-2-yl)carbamate (30)



To a refluxing solution of *N*-Boc-L-Phenylalanine (1.19 g, 4.50 mmol) in toluene (3.6 mL) was added phenylsilane (278 µL, 2.25 mmol), followed by morpholine (262 µL, 3.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time the reaction mixture was quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10

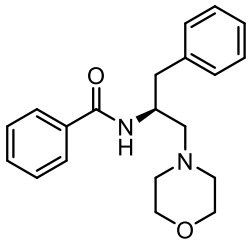
mL) and the amine product washed with HCl (10 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc / petrol 1:1 R_f = 0.23) to give a pale yellow solid (812 mg, 2.43 mmol, 81%). **$[\alpha]_D$** 76.0° (c = 1.0, CH_2Cl_2) Lit - $[\alpha]_D$ 75.7° (c = 1.0, CH_2Cl_2); **IR** (ATR) νmax/cm^{-1} 3305, 2973, 2923, 2855, 1701, 1634; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.85 – 4.73 (m, 1H), 3.65 – 3.39 (m, 5H), 3.35 – 3.25 (m, 1H), 3.11 – 2.84 (m, 4H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 155.2, 136.5, 129.7, 128.7, 127.2, 80.0, 66.6, 66.2, 50.9, 46.1, 42.4, 40.6, 28.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{18}H_{27}N_2O_4$ 335.1965, found 335.1957. The data matches that found in the literature.[18]

(*S*)-2-amino-1-morpholino-3-phenylpropan-1-one (31)



To a solution of *tert*-Butyl-(*S*)-(1-morpholino-1-oxo-3-phenylpropan-2-yl)carbamate (**30**) (800 mg, 2.40 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added HCl (3.60 mL of a 4 M solution in dioxane) dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h, after which it was diluted with CH_2Cl_2 and extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give a colourless oil (466 mg, 1.99 mmol, 83%). **IR** (ATR) νmax/cm^{-1} 3356, 2921, 2857, 1700, 1446, 1068; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.52 – 3.41 (m, 3H), 3.35 – 3.24 (m, 1H), 3.06 – 2.91 (m, 2H), 2.90 – 2.79 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ173.5, 137.5, 129.5, 128.8, 127.1, 66.7, 66.2, 52.4, 45.8, 43.3, 42.4; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{13}H_{19}N_2O_2$ 235.1441, found 235.1440. The data matches that found in the literature.[19]

(*S*)-*N*-(1-Morpholino-3-phenylpropan-2-yl)benzamide (32)

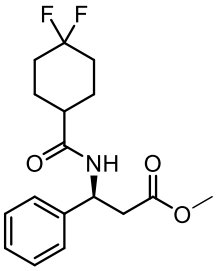


Prepared according to general procedure 2, using benzoic acid (183 mg, 1.50 mmol) and (S)-2-amino-1-morpholino-3-phenylpropan-1-one (**31**) (234 mg, 1.00 mmol) with the critical exception that the reduction phase of the reaction (tertiary amide reduction) was 1 h at reflux. The crude product was

purified by column chromatography (EtOAc / petrol 3:2, R_f = 0.17) to give the desired product as a yellow oil (204 mg, 0.630 mmol, 63%), mp = 120-122 °C. **[α]$_D$** +8.00° (c = 1.0, chloroform); **IR** (ATR) νmax/cm^{-1} 3322, 2922, 2860, 2816, 1631, 1530, 1110; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.39 (m, 2H), 7.35 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 6.36 (d, *J* = 6.7 Hz, 1H), 4.46 (app. dqd, *J* = 8.7, 6.5, 4.8 Hz, 1H), 3.66 (t, *J* = 4.8 Hz, 4H), 3.14 – 2.96 (m, 2H), 2.57 – 2.34 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 137.6, 134.9, 131.6, 129.9, 128.7, 128.5, 126.9, 126.7, 67.1, 60.5, 53.7, 47.5, 38.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{20}H_{25}N_2O_2$ 325.1911, found 325.1900. Enantiomeric excess was determined by chiral HPLC with a Chiral Pak AS-H column (*iso*-hexane / EtOH 90:10), 1.0 mL/min, 254 nm, 25 °C, t_r (minor) = 7.78 min, t_r (major) = 8.72 min, 94% *e.e.*.

3.7 Synthesis of Maraviroc

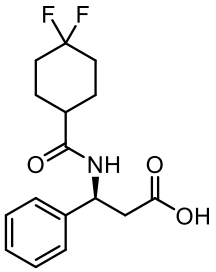
Methyl (S)-3-(4,4-difluorocyclohexane-1-carboxamido)-3-phenylpropanoate (SI-3)



To a refluxing solution of methyl (*S*)-3-amino-3-phenylpropanoate (**33**) (1.00 g, 5.58 mmol) and 4,4-difluorocyclohexane-1-carboxylic acid (1.37 g, 8.37 mmol) in toluene (7 mL) was added phenylsilane (0.52 mL, 4.18 mmol). The reaction mixture was then heated for 16 h after which time (amidation now complete) the reaction mixture was cooled and concentrated *in vacuo*. The residue was diluted with EtOAc (25 mL) and washed with water (30 mL), sodium carbonate (2 × 30 mL of a saturated aqueous solution). The organic layer was filtered through a hydrophobic frit and the solvent was removed *in vacuo* to afford the crude product (2.40 g) as a yellow solid, which was taken into the hydrolysis crude without further purification. For characterisation, the crude product was purified using column chromatography (EtOAc / petrol 3:7, R_f = 0.19), 128 - 130 °C. **[α]$_D$** -12.0° (c = 1.0, chloroform); **IR** (ATR) νmax/cm^{-1} 3270, 2950, 1735, 1646, 1558, 1370, 1234, 1107; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.28 – 7.21 (m, 3H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.41 (dt, *J* = 8.4, 5.8 Hz, 1H), 3.61 (s, 3H), 2.95 – 2.76 (m, 2H), 2.31 – 2.07 (m, 3H), 2.00 – 1.89 (m, 2H), 1.88 – 1.63 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.4, 172.0, 140.6, 128.9, 127.8, 126.2, 124.7, 122.7, 120.8, 52.0, 49.3, 42.8, 39.8, 33.1, 33.1, 32.9, 32.9, 32.9, 32.70, 32.68, 25.96, 25.89, 25.82.; **^{19}F NMR** (376 MHz, CDCl3) δ -92.96 (d, *J* = 236.5 Hz), -100.68 (d, *J* = 235.2 Hz); **HRMS** [ESI (M + H$^+$)] m/z calculated $C_{17}H_{22}F_2NO_3$ 326.1562, found 326.1566. Enantiomeric excess was determined by chiral HPLC with a Chiral Pak IC

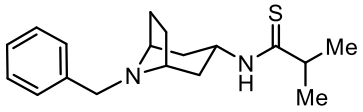
column (*iso*-hexane / *i*PrOH 90:10), 1.0 mL/min, 210 nm, 25 °C, t_r (minor) = 24.88 min, t_r (major) = 28.86 min, >99% *e.e.*.

(*S*)-3-(4,4-Difluorocyclohexanecarboxamido)-3-phenylpropanoic acid (34)



SI-3 as the crude product (5.58 mmol) was then dissolved in THF (17 mL) and slowly added to a solution of sodium hydroxide (1.12 g, 27.9 mmol) in water (17 mL) at 0 °C. After 5 minutes the reaction was allowed to warm to room temperature and stirred for 1.5 h. Water (10 mL) was added and the mixture was washed with CH_2Cl_2 (2 × 20 mL) and EtOAc (20 mL). The pH was adjusted to pH 1 using HCl (3 M aqueous solution) and the product was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were filtered through a hydrophobic frit and the solvent was removed *in vacuo*. The crude product was purified using column chromatography (CH_2Cl_2 / MeOH 9:1 R_f = 0.30 to 4:1) to afford the title compound as a colourless solid (1.32 g, 4.24 mmol, 76%), mp = 158-160 °C. **IR** (ATR) νmax/cm^{-1} 3306, 1697, 1648, 1633, 1535, 1375, 1214, 1113, 937; **^{1}H NMR** (400 MHz, d^6-DMSO) δ 8.35 (d, *J* = 8.2 Hz, 1H), 7.35-7.18 (m, 5H), 5.28 – 5.10 (m, 1H), 2.69 – 2.63 (m, 2H), 2.38 – 2.20 (m, 1H), 2.11-1.94 (m, 2H), 1.90-1.68 (m, 4H), 1.67-1.47 (m, 2H); **^{13}C NMR** (101 MHz, d^6-DMSO) δ 172.8 (d, *J* = 1.9 Hz), 171.7, 142.7, 128.3, 126.9, 126.3, 124.3 (dd, *J* = 241.7, 239.6 Hz), 49.7, 41.5, 41.3, 33.0-32.4 (m), 26.0 (dd, *J* = 22.3, 9.2 Hz); **^{19}F NMR** (376 MHz, d^6-DMSO) δ -90.28 (d, *J* = 232.9 Hz), -98.72 (d, *J* = 232.1 Hz); **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{16}H_{18}O_3F_2N^-$ 310.1255, found 310.1262.

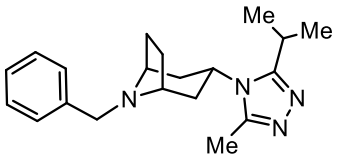
N-(8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl)-2-methylpropanethioamide (SI-4)



To a solution of *N*-((1R,3S,5S)-8-benzyl-8-azabicyclo[3.2.1]octan-3-yl)isobutyramide (1.60 g, 5.59 mmol), prepared according to a literature procedure,[20] in toluene (20 mL) was added phosphorus pentasulfide (1.86 g, 8.38 mmol) followed by 1,1,1,3,3,3-hexamethyldisiloxane (5.94 mL, 27.9 mmol) and the reaction was heated at reflux for 16 h. The reaction was cooled to room temperature and potassium carbonate (25 mL of a saturated aqueous solution) was added. After 30 mins the reaction mixture was diluted with EtOAc (30 mL) and the organic layer was washed with water (30 mL). The aqueous layer was then extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with potassium carbonate (30 mL of a saturated aqueous solution) and brine (50 mL of a saturated aqueous solution), filtered through a hydrophobic frit and concentrated *in vacuo*. The crude residue was

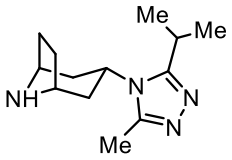
purified by column chromatography using 56 g KP-NH silica cartridge (EtOAc / heptane 1:9 to 2:8) to afford the title compound as an orange oil (1.22 g, 4.03 mmol 72%). **IR** (ATR) νmax/cm^{-1} 3181, 3028, 2948, 1532, 1424, 1300, 1060, 1003, 724, 694; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.34 - 7.28 (m, 2H), 7.27 – 7.21 (m, 1H), 7.02 – 6.82 (br. s, 1H), 4.83 (tdt, *J* = 11.6, 8.2, 5.9 Hz, 1H), 3.54 (s, 2H), 3.29 – 3.24 (m, 2H), 2.70 (sept, *J* = 6.7 Hz, 1H), 2.12 – 1.98 (m, 4H), 1.80 – 1.73 (m, 2H), 1.55 (td, *J* = 11.9, 2.2 Hz, 2H), 1.22 (d, *J* = 6.7 Hz, 6H); **^{13}C NMR** (101 MHz, CDCl3) δ 210.3, 139.9, 128.6, 128.3, 126.9, 58.8, 56.5, 47.3, 44.8, 36.9, 26.4, 22.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{18}H_{27}N_2S^+$ 303.1895, found 303.1886.

8-Benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (SI-5)



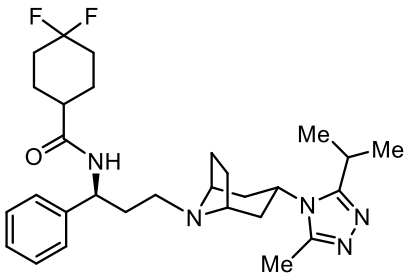
To a solution of *N*-((1R,3S,5S)-8-benzyl-8-azabicyclo[3.2.1]octan-3-yl)-2-methylpropanethioamide (**SI-4**) in *iso*propanol (4 mL) was added acetohydrazide (167 mg, 2.25 mmol) and peracetic acid (334 µL, 1.59 mmol of a 32% weight solution in acetic acid) and the reaction mixture was heated at 50 °C for three hours. After which time further peracetic acid (277 µL, 1.32 mmol of a 32% weight solution in acetic acid) was added and the reaction was heated at 50 °C for a further 16 h. The reaction was allowed to cool to room temperature, where sodium bisulfite (513 mg, 0.493 mmol of a 10% aqueous solution) and potassium carbonate (1.02 g, 3.31 mmol of a 45% w/w aqueous solution) were added to the reaction mixture and stirred for 10 mins. The reaction was diluted with water (10 mL) then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were filtered through a hydrophobic frit and concentrated *in vacuo*. The crude residue was purified by column chromatography using 28 g KP-NH silica cartridge (pure CH_2Cl_2 to CH_2Cl_2 / MeOH 19:1) to afford the title compound as a pale yellow oil (1.22 g, 3.76 mmol, 72%). **IR** (ATR) νmax/cm^{-1} 2966, 1518, 1495, 1453, 1419, 1345, 1286, 1250, 1097, 1029; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41-7.31 (m, 4H), 7.31-7.24 (m, 1H), 4.32 (tt, *J* = 12.4, 6.1 Hz, 1H), 3.59 (s, 2H), 3.40-3.33 (m, 2H), 3.04 (sept., *J* = 6.9 Hz, 1H), 2.59 (s, 3H), 2.28 (dd, *J* = 12.4, 12.4, 2.7 Hz, 2H), 2.22-2.14 (m, 2H), 1.72-1.63 (m, 4H), 1.40 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.1, 150.8, 139.6, 128.4, 128.3, 127.1, 58.9, 56.7, 47.4, 37.2, 26.5, 25.9, 21.7, 13.2; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{20}H_{29}N_4^+$ 325.2392, found 325.2392. The data matches that found in the literature.[21]

3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (35)



Palladium hydroxide on carbon (131 mg, 20% wt.) was added to a solution of 8-benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (**SI-5**) (656 mg, 2.02 mmol) under an atmosphere of nitrogen. The mixture was placed under a hydrogen atmosphere (1 bar) and stirred at room temperature for 16 h. The reaction was filtered through a pad of Celite and washed with CH_2Cl_2 (20 mL), the filtrate was concentrated *in vacuo* to afford the title compound as a colourless solid (445 mg, 1.90 mmol, 94%), m.p. 160-162 °C. **IR** (ATR) νmax/cm^{-1} 2964, 1517, 1454, 1418, 1347, 1252, 1096, 1033; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.35 (tt, *J* = 12.3, 5.9 Hz, 1H), 3.81-3.72 (m, 2H), 3.04 (sept., *J* = 6.8 Hz, 1H), 2.55 (s, 3H), 2.22 (dd, *J* = 12.6, 12.6, 2.6 Hz, 2H), 2.00-1.92 (m, 2H), 1.83-1.74 (m, 4H), 1.41 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 150.7, 54.6, 47.4, 37.9, 29.4, 25.9, 21.7, 13.2; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{13}H_{23}N_4^+$ 234.1923, found 235.1915. The data matches that found in the literature.[22]

4,4-Difluoro-*N*-((1S)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octan-8-yl)-1-phenylpropyl)cyclohexanecarboxamide (Maraviroc) (36)



To a refluxing solution of (*S*)-3-(4,4-difluorocyclohexane-1-carboxamido)-3-phenylpropanoic acid (**34**) (39.9 mg, 0.128 mmol) in toluene (0.5 mL), was added phenylsilane (7.90 µl, 0.0640 mmol), followed by 3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (**35**) (15.0 mg, 0.0640 mmol) dropwise. The reaction was sealed and heated to 170 °C for 1 h in a microwave, after which it was diluted with EtOAc (5 mL) and extracted with HCl (3 × 3 mL of a 3 M aqueous solution). 6 M NaOH was added to the combined aqueous layers until pH 12 was reached and the product was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were filtered through a hydrophobic frit and concentrated *in vacuo* to afford the crude product as an orange oil, which was dissolved in chlorobenzene (1.5 mL) and heated to reflux. Zinc acetate (7.8 mg, 0.04 mmol) and phenylsilane (0.21 mL, 1.71 mmol) were added to the reaction mixture and it was heated to 100 °C for 1 h. The reaction was then cooled to room temperature, diluted with EtOAc (5 mL) and extracted with HCl (3 M) (3 × 3 mL). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution)

and the product was re-extracted with EtOAc (3 × 5 mL). The combined organic layers were filtered through a hydrophobic frit and concentrated *in vacuo* to afford a pale yellow residue. The crude material was purified by reverse phase chromatography eluted with 5-35% MeCN using a 0.05% formic acid buffer, the pure fractions were combined and concentrated *in vacuo* to ~10 mL, then adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted with EtOAc (3 x 5 mL). The organic layers were combined, filtered through a hydrophobic frit and concentrated *in vacuo* to afford the title compound as a colourless oil (50 mg, 0.100 mmol, 57%). **IR** (ATR) νmax/cm^{-1} 3291(br), 2938, 1650, 1530, 1450, 1372, 1108, 963; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 2H), 7.30-7.24 (m, 3H), 6.89 (d, *J* = 7.5 Hz, 1H), 5.07 (dd, *J* = 14.3, 7.5 Hz, 1H), 4.33 (att, *J* = 12.3, 6.1 Hz, 1H), 3.52 (d, *J* = 12.7 Hz, 2H), 3.02 (sept., *J* = 6.9 Hz, 1H), 2.71 – 2.56 (m, 2H), 2.53 (s, 3H), 2.37 (q, *J* = 10.7 Hz, 2H), 2.28 – 2.08 (m, 6H), 2.06 – 1.61 (m, 11H), 1.39 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.8, 159.2, 150.8, 142.0, 126.5, 125.2, 122.76 (dd, J = 241.8, 240.3 Hz), 59.7, 58.3, 51.9, 48.0, 47.0, 42.9, 35.1, 34.9, 34.0, 33.06 (dd, J = 23.6, 2.4 Hz), 32.79 (dd, J = 23.2, 2.3 Hz), 26.6, 26.5, 26.06 (d, J = 9.0 Hz), 25.9, 21.8, 13.2; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{29}H_{42}OF_2N_5^+$ 514.3357, found 514.3358.

4 Mechanistic Studies

Preparation of Phenylsilylacetate (39)

Chloro(phenyl)silane (21.3 μL, 0.160 mmol) was added to a refluxing suspension/solution of sodium acetate (13.1 mg, 0.160 mmol) in C_6D_6 (0.5 mL) and heated with stirring for 30 min. After cooling the silyl ester was characterised. ^{1}H NMR (400MHz, C_6D_6) δ 7.69 - 7.64 (m, 2H), 7.20 - 7.10 (m, 3H), 5.19 (SiH_2, s, 2H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 171.7, 135.8, 131.3, 130.8, 128.4, 21.5; ^{29}Si NMR (79 MHz, C_6D_6) δ −21.2.

1,3-Diphenyldisiloxane

Chloro(phenyl)silane (0.160 mmol, 21.3 μL) was added to C_6D_6 (0.4 mL) and stirred overnight at room temperature in the presence of 2 drops (an excess) of water. The resulting solution was filtered by gravity through magnesium sulfate to remove water/HCl. ^{1}H NMR (400MHz, C_6D_6) δ 7.53 - 7.47 (m, 4H), 7.15 - 7.08 (m, 6H), 5.28 (s, 4H); ^{13}C NMR (101 MHz, C_6D_6) δ 134.4, 134.0, 130.8, 128.4; ^{29}Si NMR (79 MHz, C_6D_6) δ −25.3.

4.1 Reaction of Phenylsilane and Zinc Acetate

Zinc acetate (91.7 mg, 0.500 mmol) and phenylsilane (61.7 μL, 0.500 mmol) were suspended in d_8-toluene (0.5 mL) and heated to reflux. The cooled reaction mixture was analysed by ^{1}H NMR spectroscopy (Figure S6), which showed phenylsilane was unchanged.

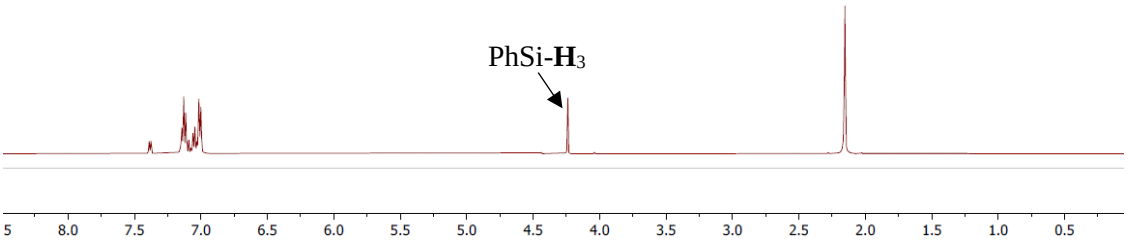


Figure S6. ^{1}H NMR spectrum of the zinc acetate and phenylsilane crude reaction mixture.

4.2 Reaction of Phenylsilyl acetate 39 with Zinc Acetate

Chlorophenylsilane (67.0 µL, 0.500 mmol) and sodium acetate (41.0 mg, 0.500 mmol) were suspended in d_8-toluene (0.5 mL) and heated for 1 h at reflux. Analysis of the cooled crude reaction mixture by ^{1}H NMR spectroscopy (Figure S7) confirmed that the desired mono silyl ester species **39** was present along with diphenyldisiloxane and further silyl ester species. After analysis zinc acetate (91.7 mg, 0.50 mmol) was added and the reaction mixture heated for a further 1 h at reflux. Further analysis of the reaction mixture by ^{1}H NMR spectroscopy (Figure S8) revealed that the silyl ester had been consumed and a new broad signal ^{1}H δ 3.55-4.30 ppm was now present. This is in the region expected for a zinc hydride species of general structure HZn(OAc)L_n as depicted in Scheme 2[23] and it is tentatively proposed to be zinc hydride species.

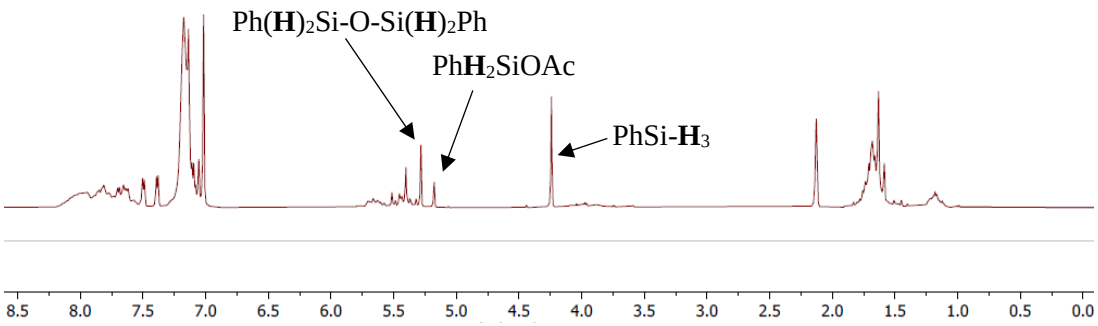


Figure S7. ^{1}H NMR spectrum crude phenylsilyl acetate **39**.

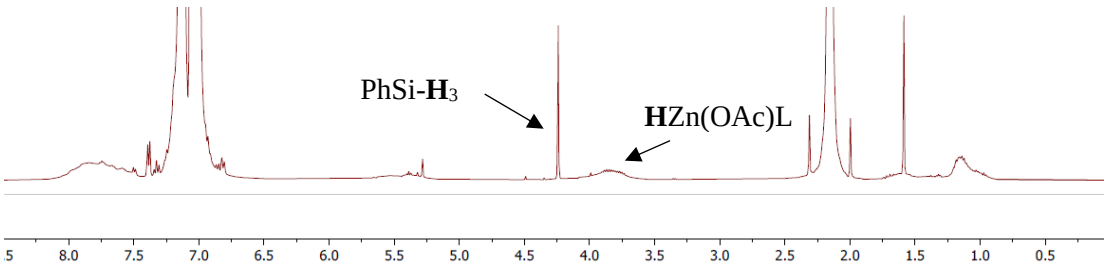


Figure S8. ^{1}H NMR spectrum of the zinc acetate and phenylsilyl acetate crude reaction mixture.

4.3 Reaction Monitoring

To a refluxing solution of 4-fluorobenzoic acid (105 mg, 0.750 mmol) in d^8-toluene (0.6 mL) was added phenylsilane (46.0 µL, 0.375 mmol), followed by benzylamine (55.0 µL, 0.500 mmol) dropwise. The reaction mixture was then heated for 16 h after which time ^{19}F NMR analysis was performed (Figure S9, trace (a)), which showed the presence of amide **37** along with residual carboxylic acid **36**.

Zinc acetate (9.20 mg, 0.050 mmol) and further phenylsilane (185 µL, 1.50 mmol) were added to the reaction mixture, the reaction was heated to 75 °C in the NMR spectrometer and ^{19}F NMR analysis was performed every 10 mins. Four representative traces are depicted (Figure S9, traces (b),(c), (d) and (e)), which show the formation and decay of silyl ester species. The broad peaks observed at circa -115 ppm in traces (d) and (e) are possibly to be silanamines derived from the dehydro coupling of silanes with the secondary amine product.[24] The reaction mixture was then subjected to the standard acid/base workup protocol after which a single species, amine **38**, was present.

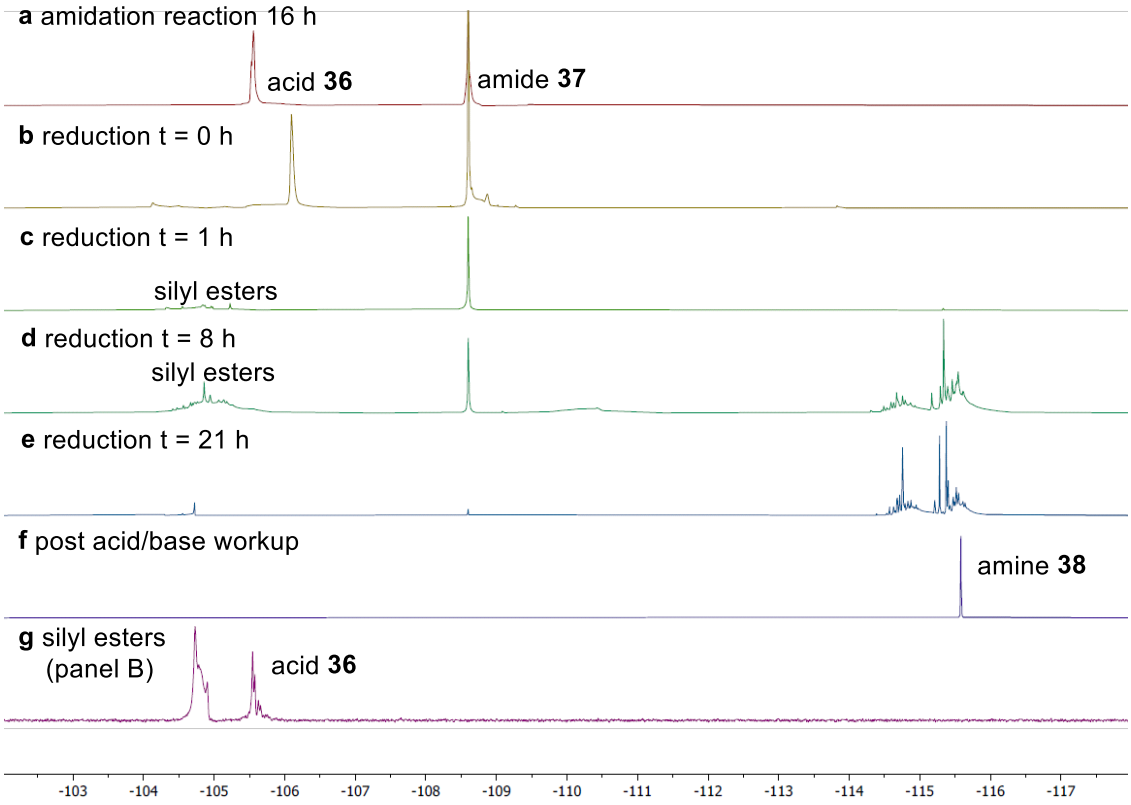
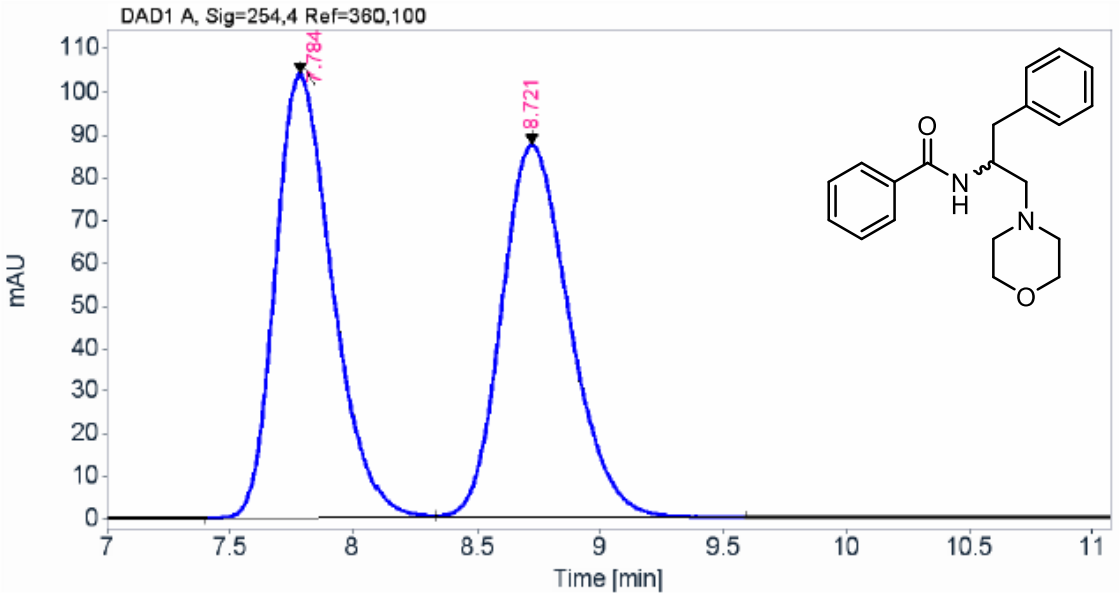


Figure S9. ^{19}F NMR spectra of the reductive amination of acid **36** and amide **37**. (a) Amidation step. (b). (c), (d) and (e) reduction step. (f) Post workup. (g) Silyl ester species obtained in Scheme 2 panel B from the treatment of acid **36** with phenylsilane in the presence of *N*-methylmorpholine.

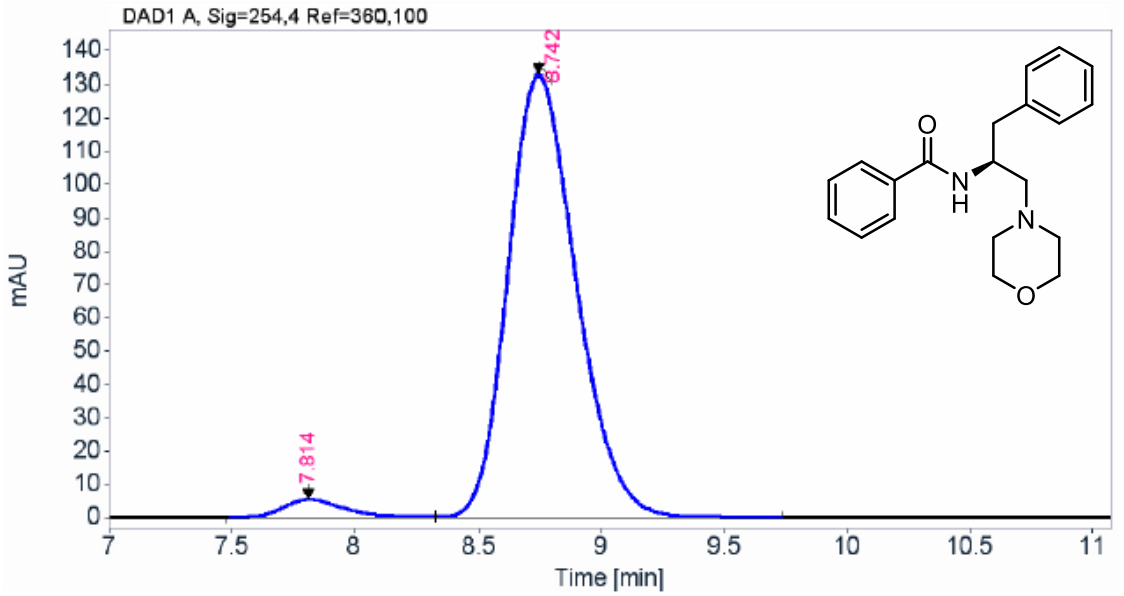
5 HPLC Traces

(*S*)-*N*-(1-Morpholino-3-phenylpropan-2-yl)benzamide (32)



Signal: DAD1 A, Sig=254,4 Ref=360,100

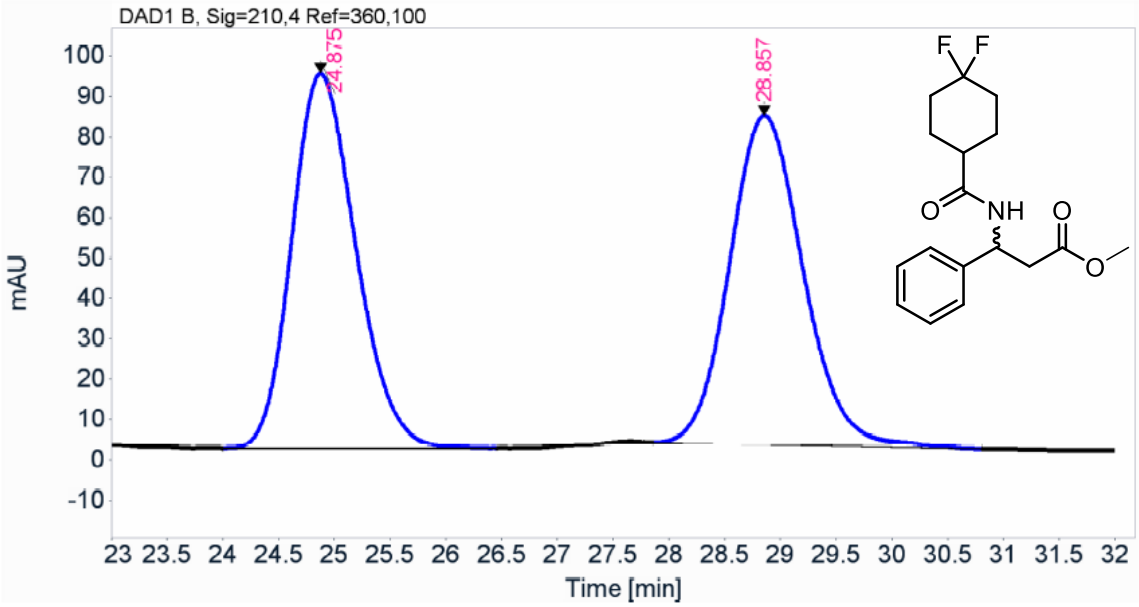
RT [min]	Type	Width [min]	Area	Height	Area%
7.784	BV	0.2477	1667.120	103.6408	49.96
8.721	VB	0.2973	1669.501	87.2298	50.04



Signal: DAD1 A, Sig=254,4 Ref=360,100

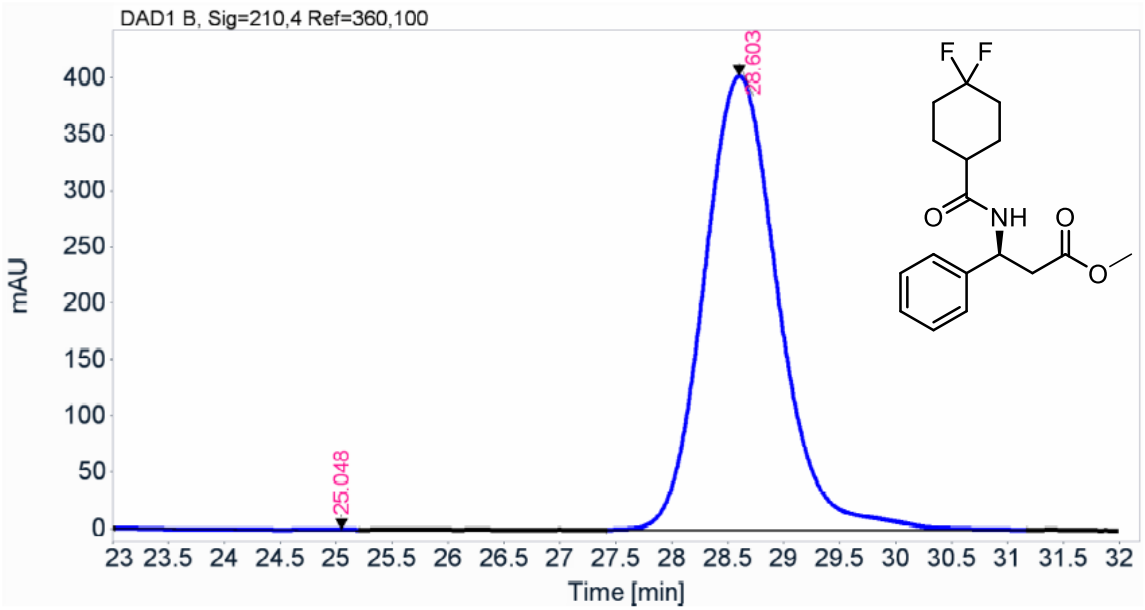
RT [min]	Type	Width [min]	Area	Height	Area%
7.814	BV	0.2567	89.890	5.3323	3.40
8.742	VB	0.2987	2557.327	132.7770	96.60

Methyl (*S*)-3-(4,4-difluorocyclohexane-1-carboxamido)-3-phenylpropanoate (SI-3)



Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
24.875	BB	0.6169	3692.250	92.6646	49.73
28.857	BB	0.7016	3732.556	81.3046	50.27



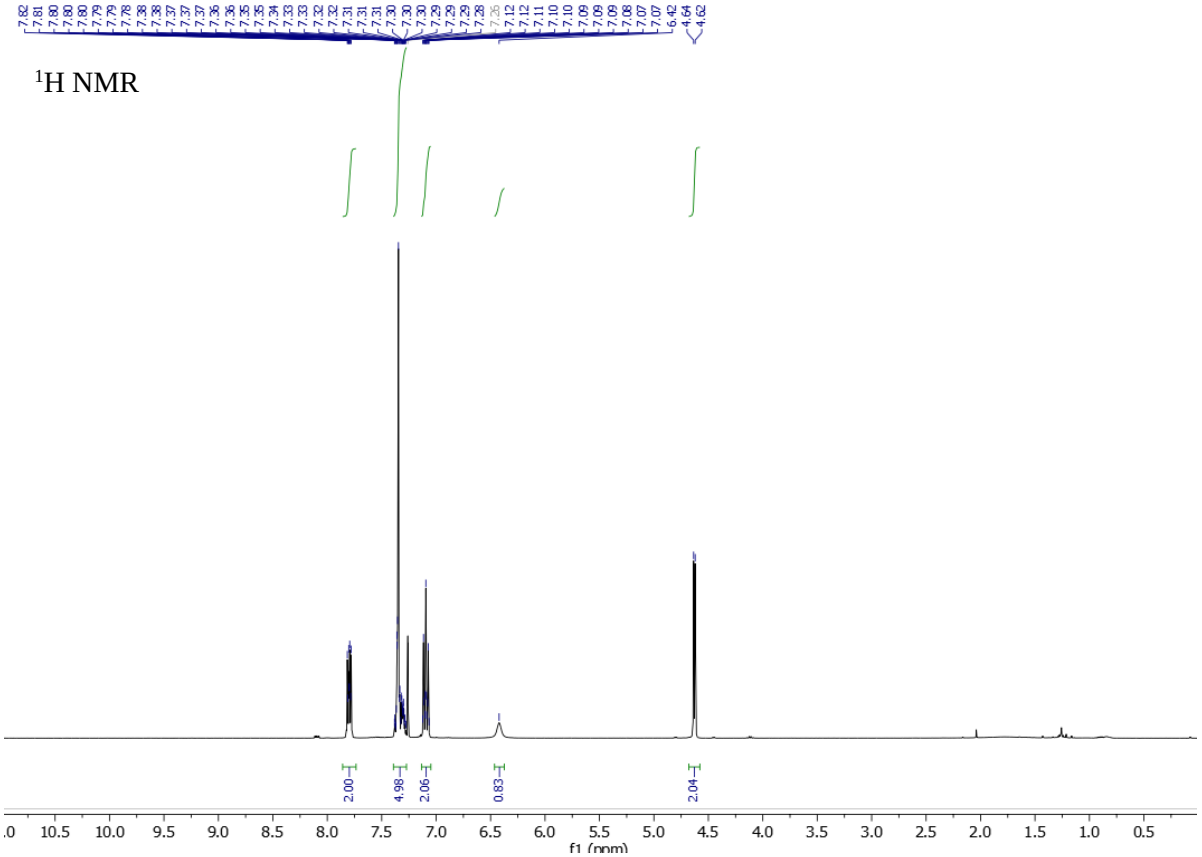
Signal: DAD1 B, Sig=210,4 Ref=360,100

RT [min]	Type	Width [min]	Area	Height	Area%
25.048	MM	0.5237	31.356	0.9980	0.17
28.603	BB	0.7111	18551.084	402.9271	99.83

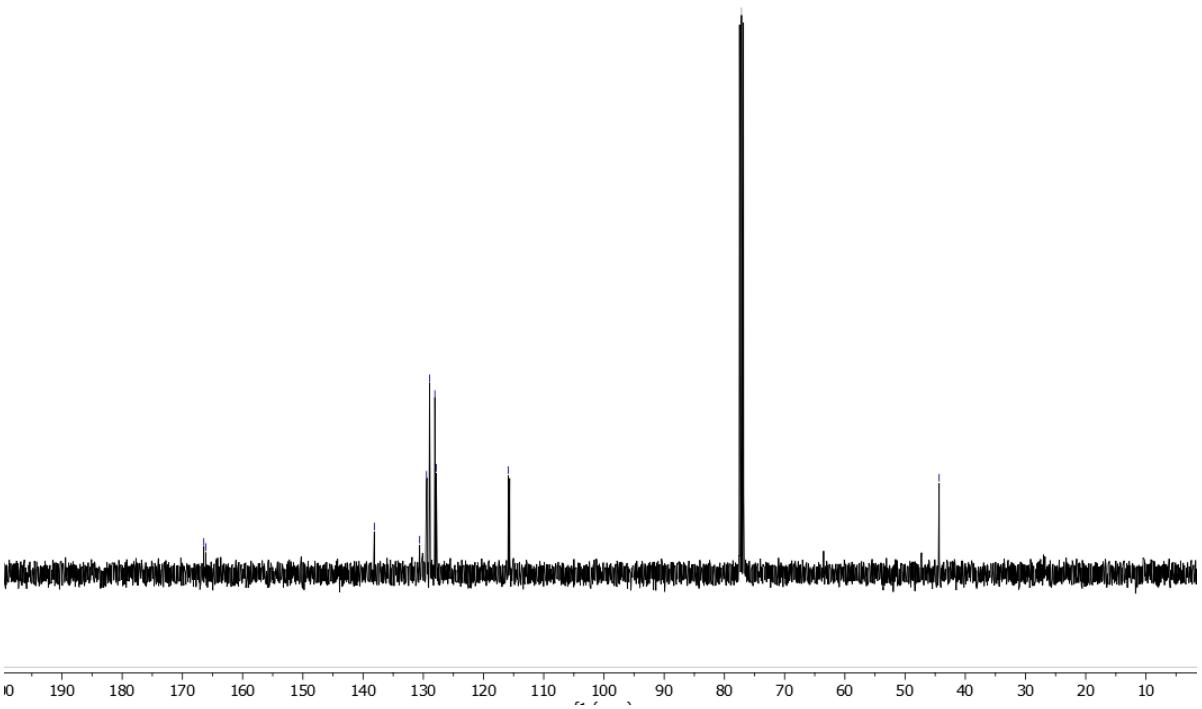
6 NMR Spectra

N-benzyl-4-fluorobenzamide (**SI-1**)

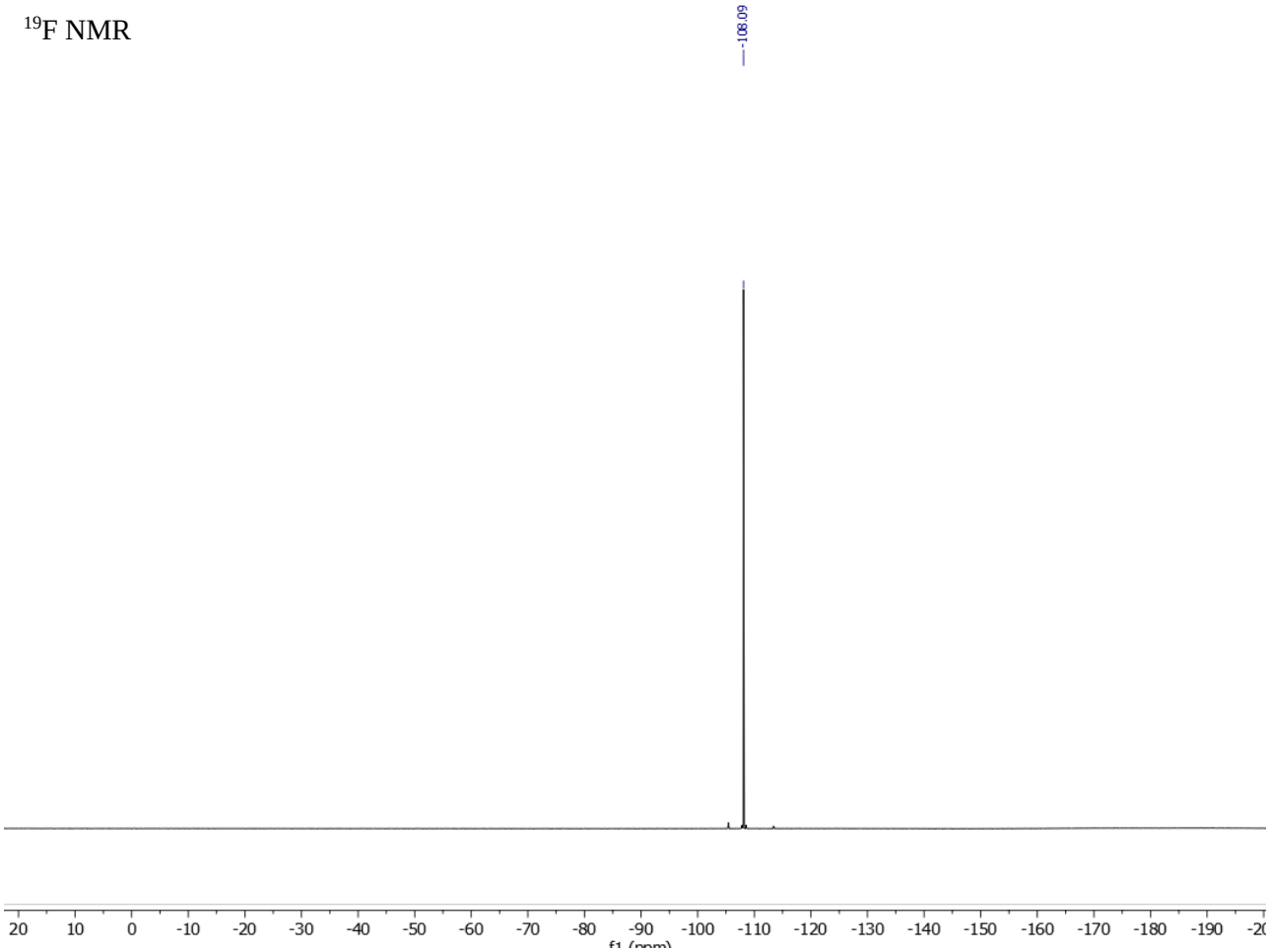
^{1}H NMR



^{13}C NMR



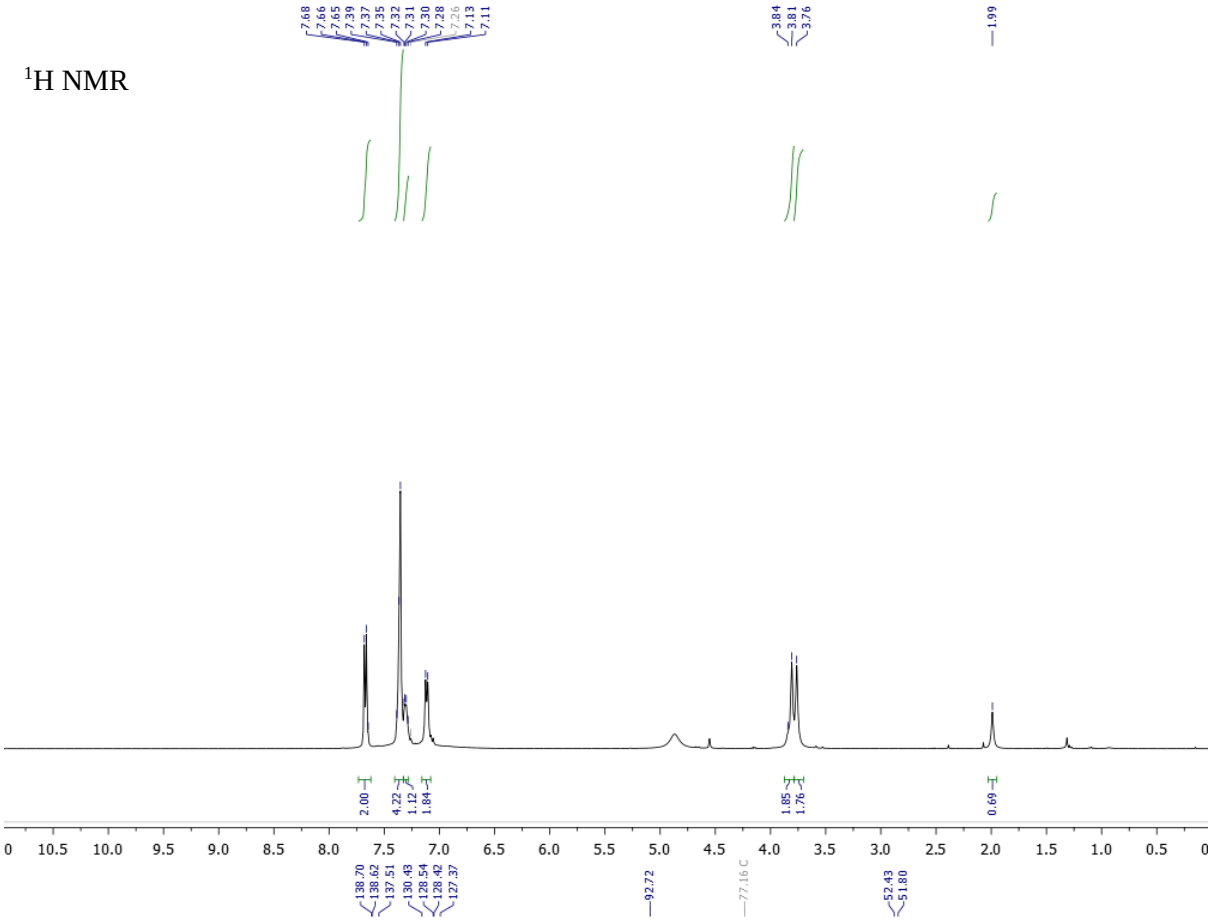
^{19}F NMR


-108.09
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

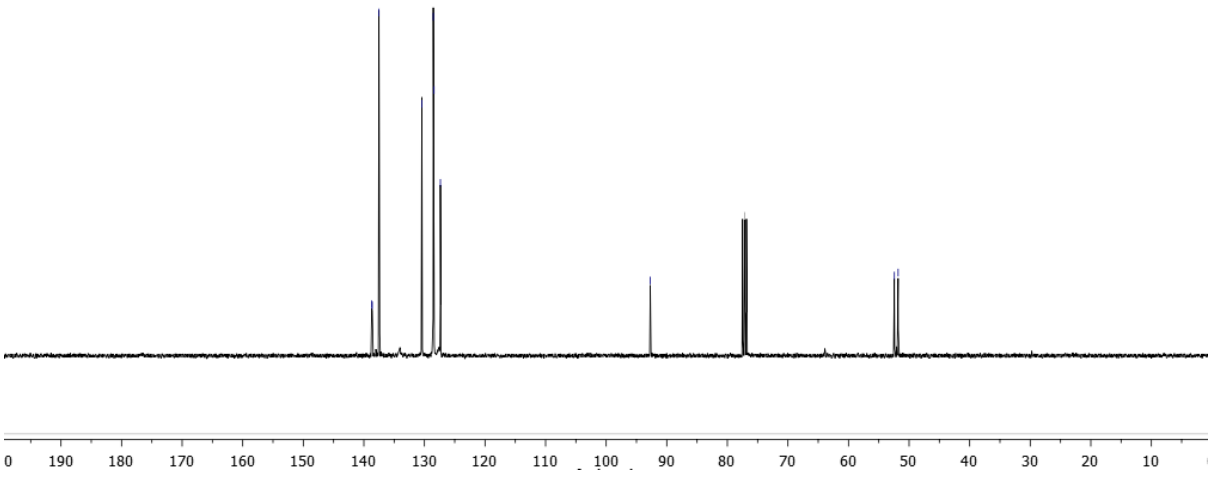
6.1 Secondary Amines

N-Benzyl-1-(4-iodophenyl)methanamine (**1**)

^{1}H NMR

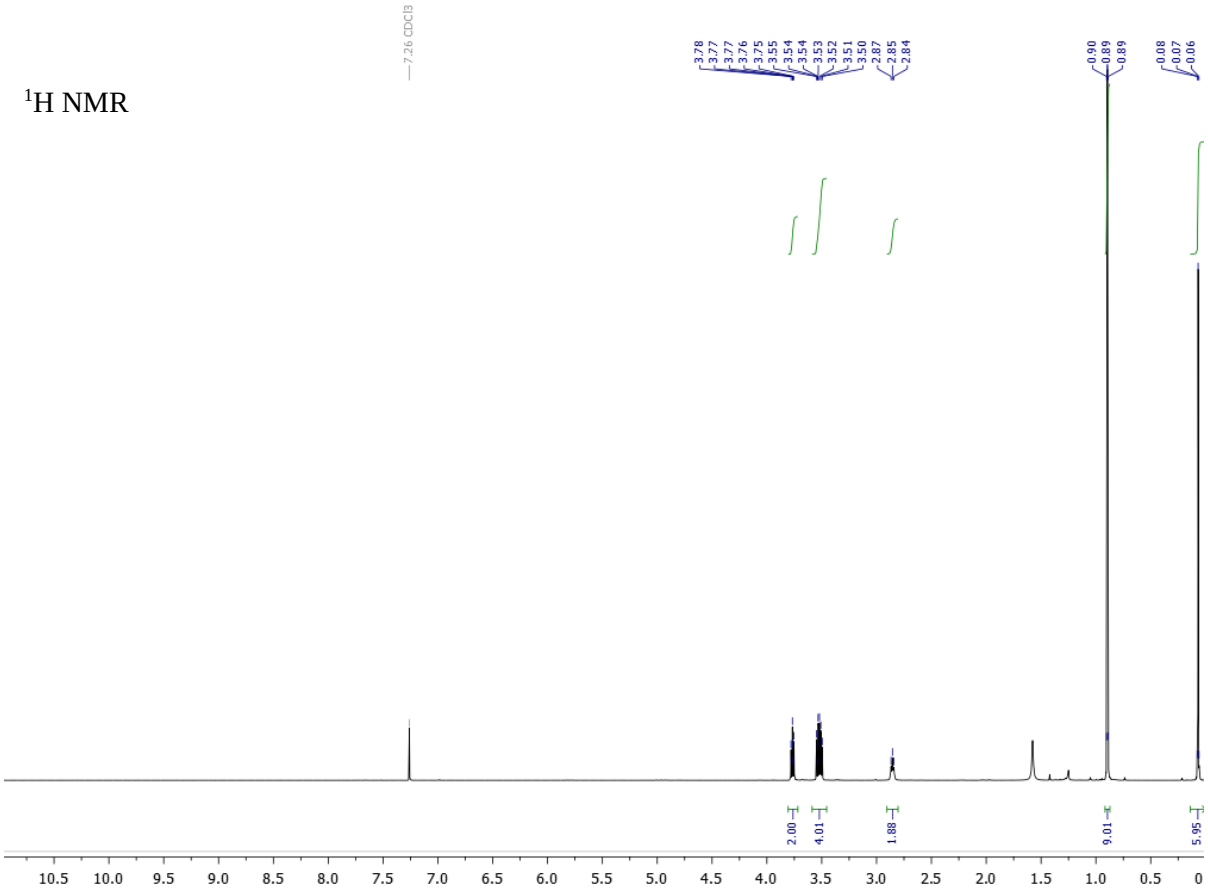


^{13}C NMR

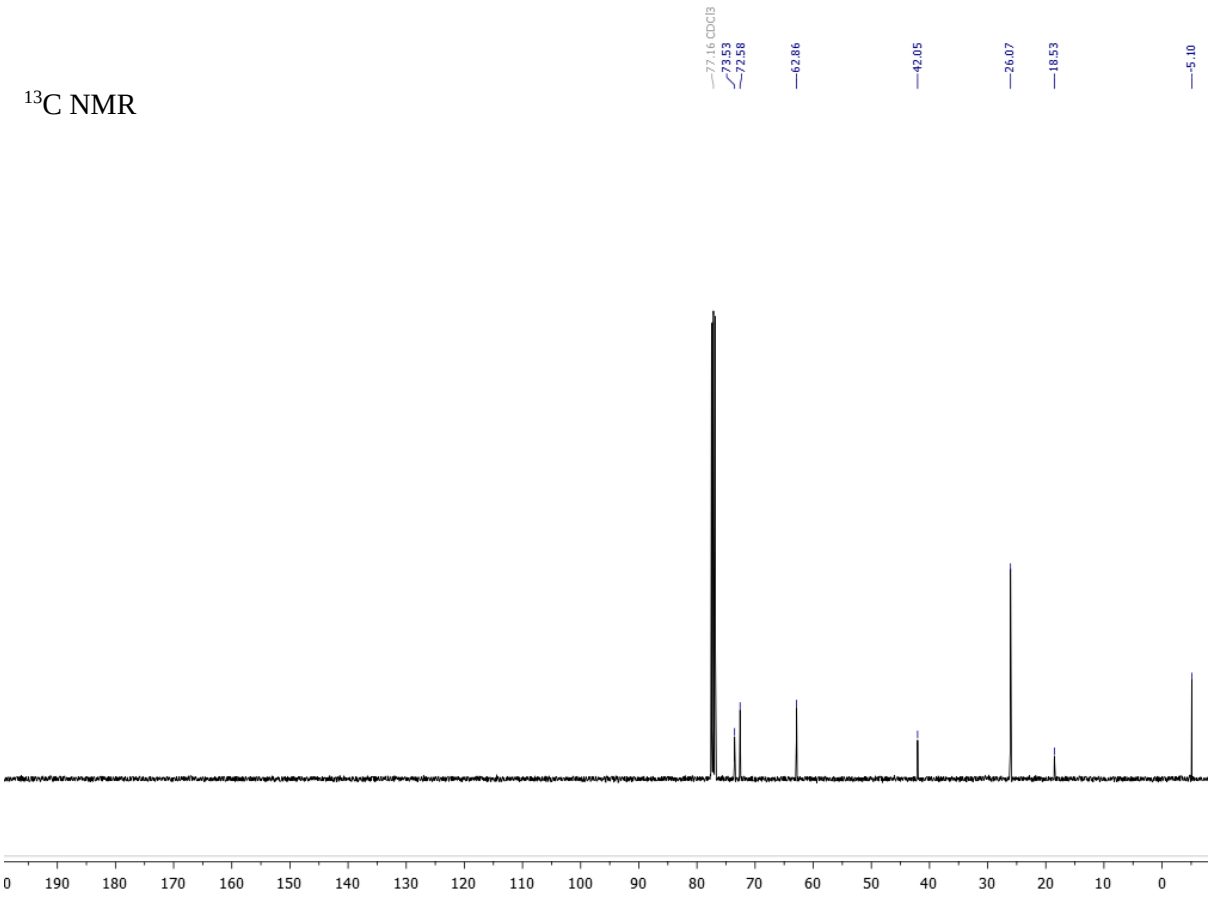


2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (**2**)

^{1}H NMR

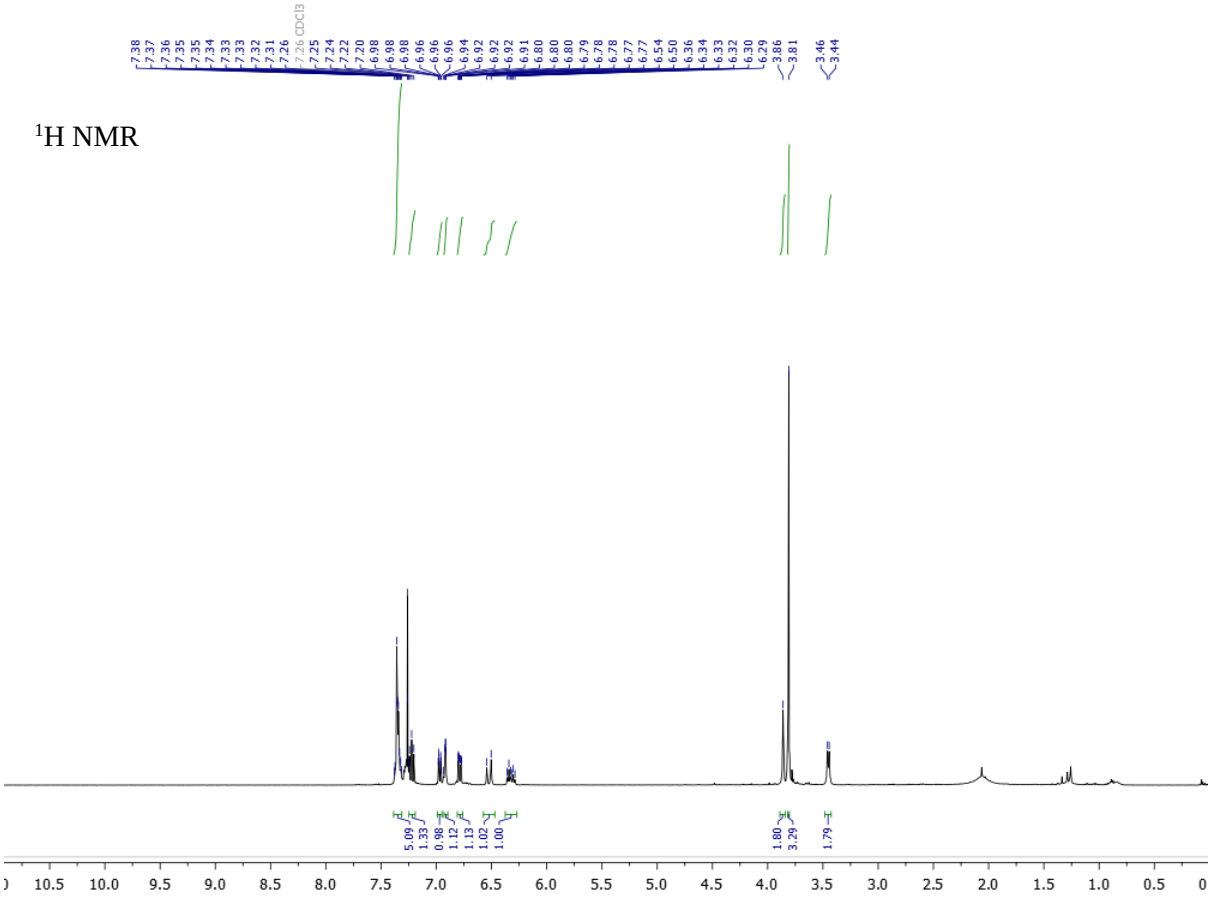


^{13}C NMR

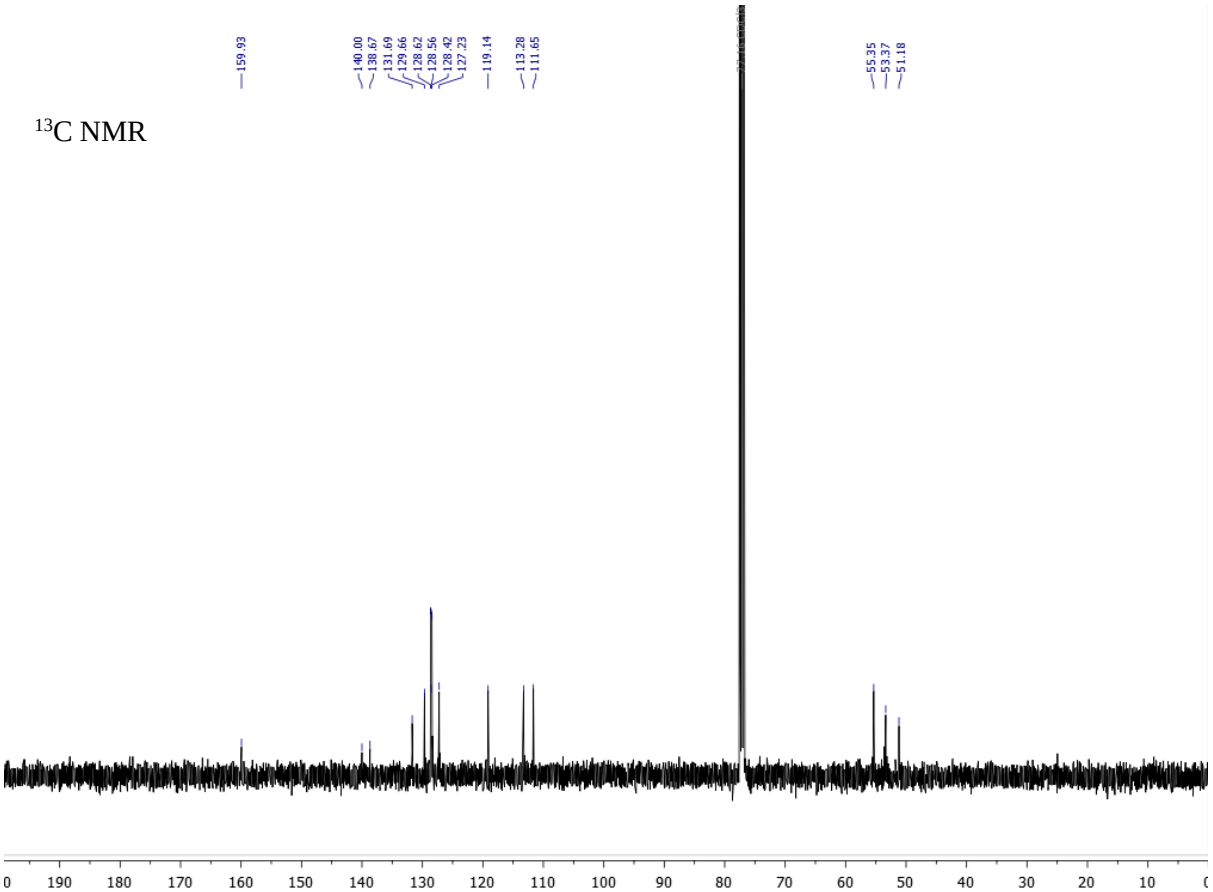


(E)-*N*-Benzyl-3-(3-methoxyphenyl)prop-2-en-1-amine (**3**)

^{1}H NMR

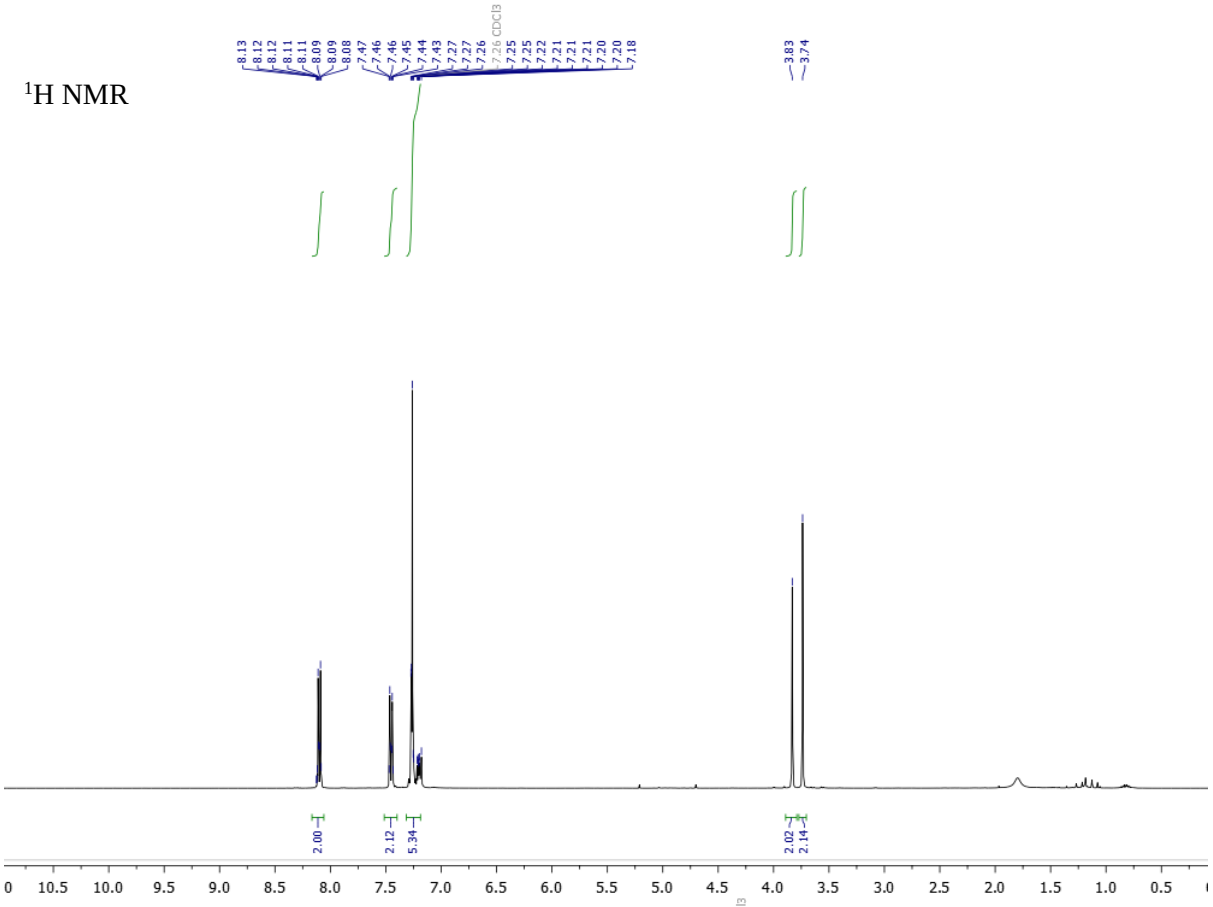


^{13}C NMR

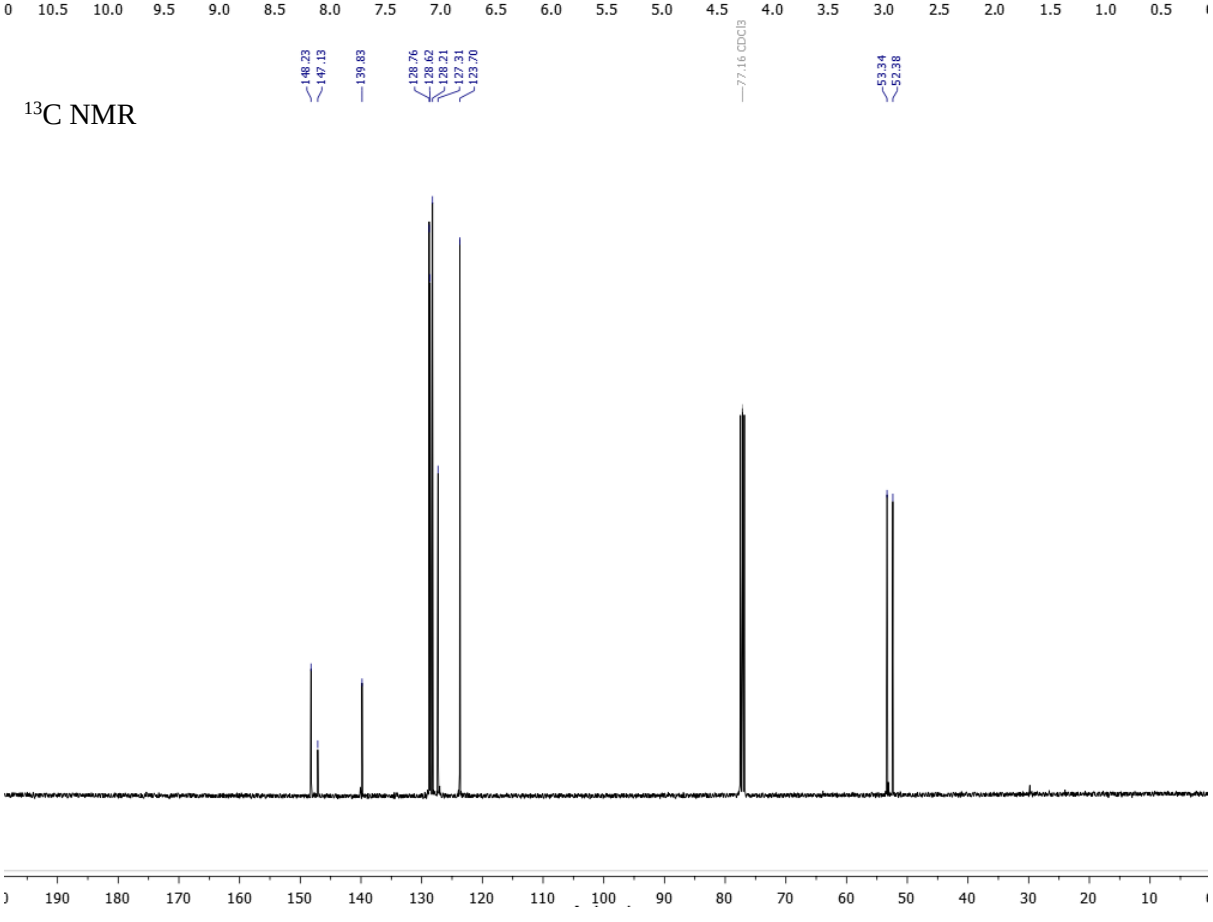


N-Benzyl-1-(4-nitrophenyl)methanamine (**4**)

^{1}H NMR

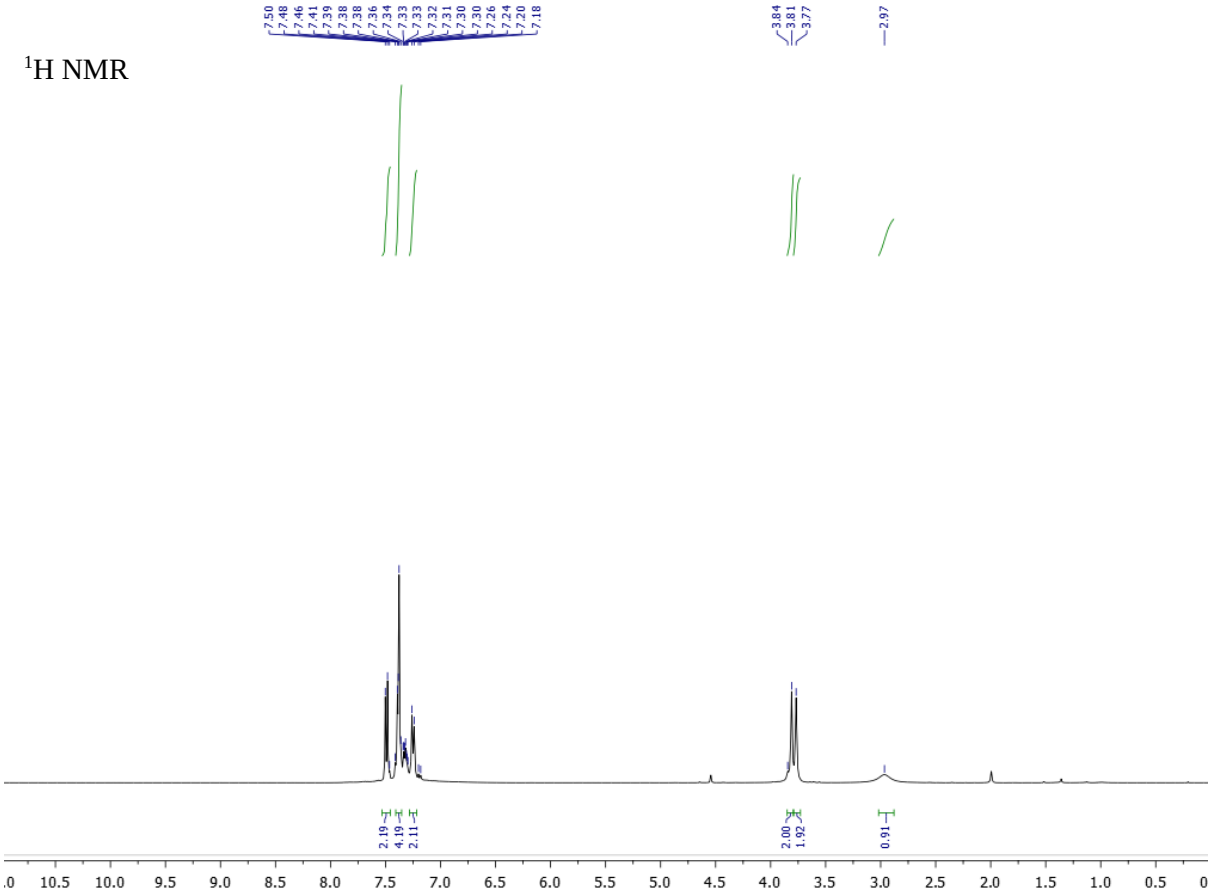


^{13}C NMR

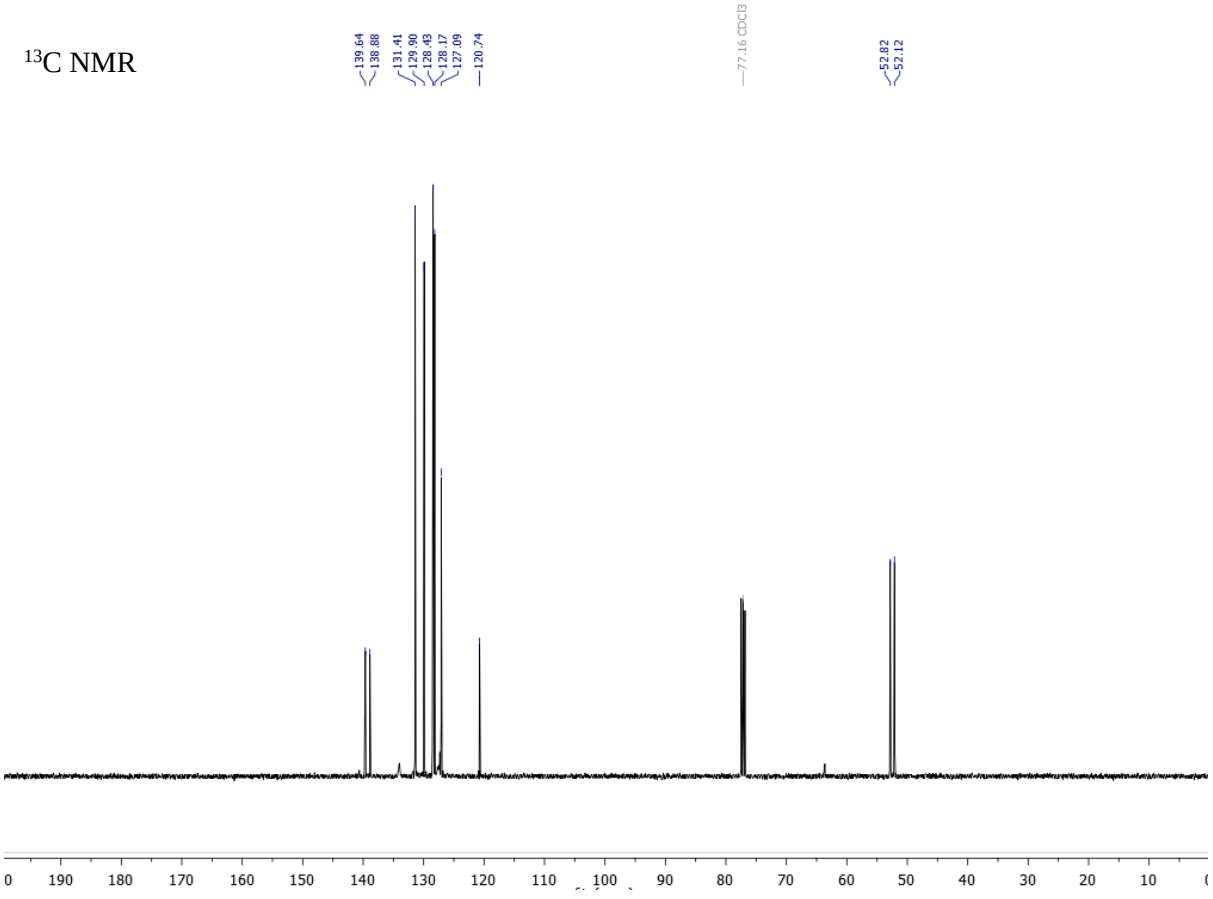


N-benzyl-1-(4-bromophenyl)methanamine (**5**)

^{1}H NMR

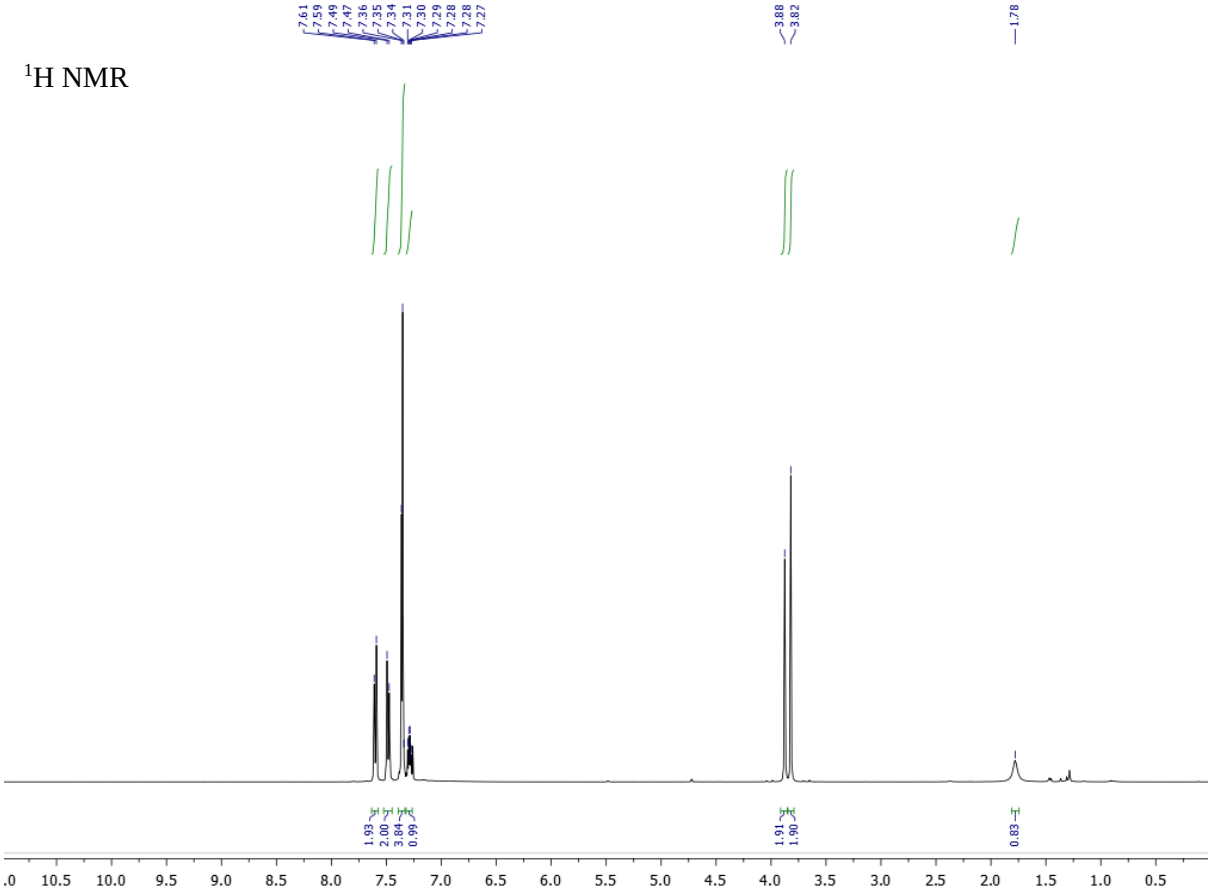


^{13}C NMR

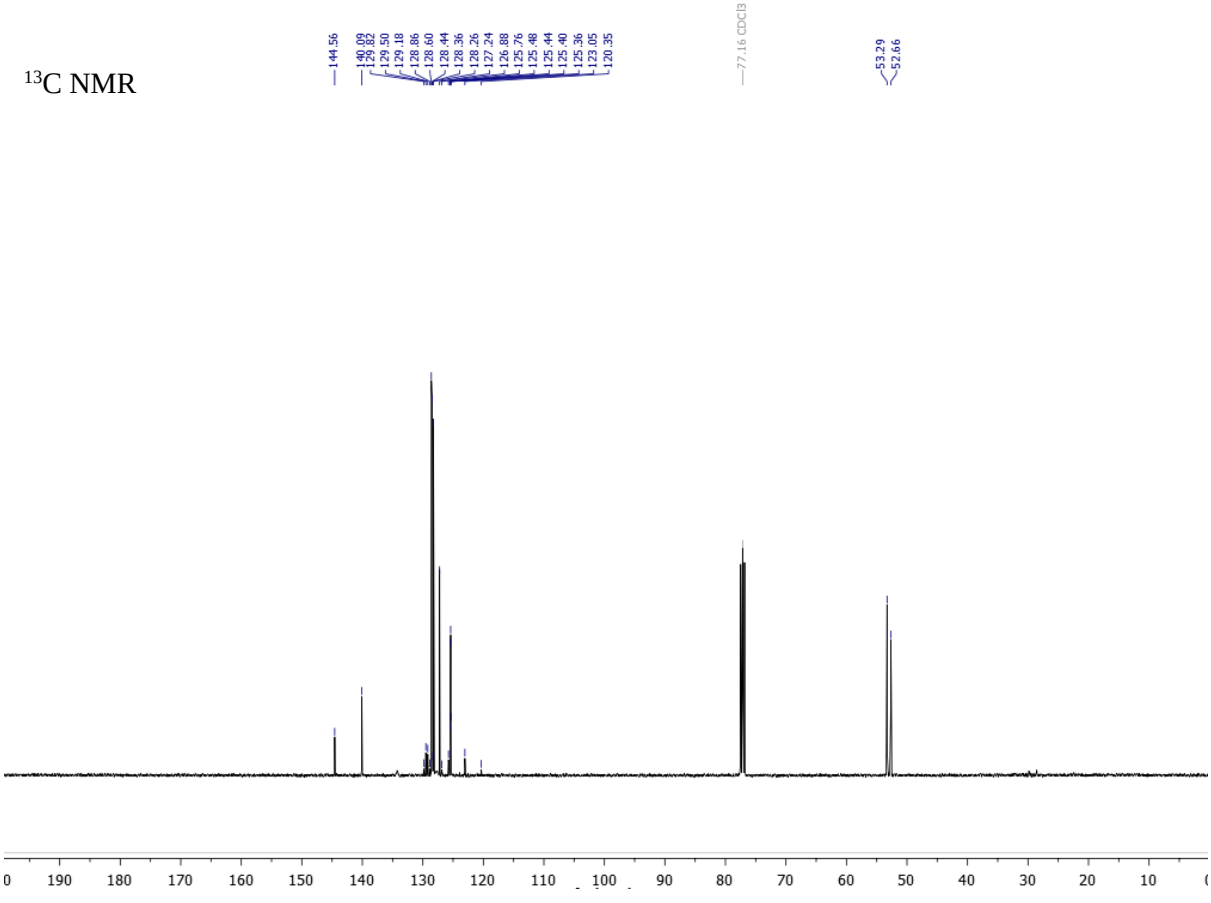


N-Benzyl-1-(4-(trifluoromethyl)phenyl)methanamine (**6**)

^{1}H NMR

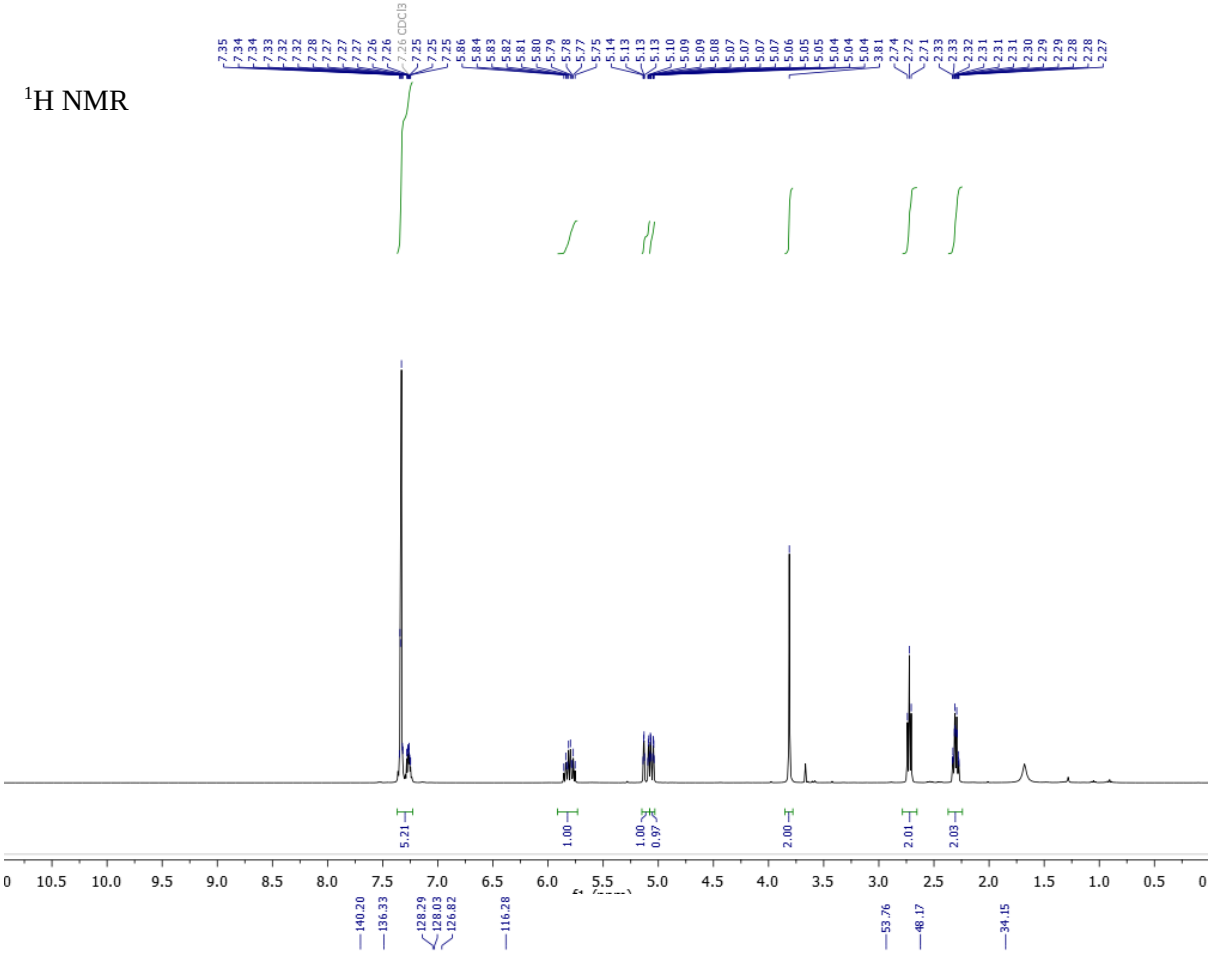


^{13}C NMR

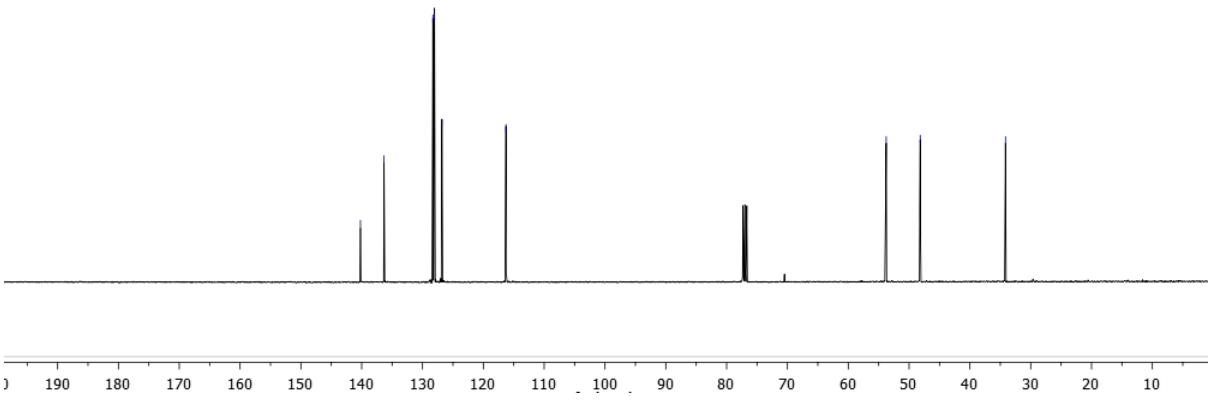


N-Benzylbut-3-en-1-amine (**7**)

^{1}H NMR

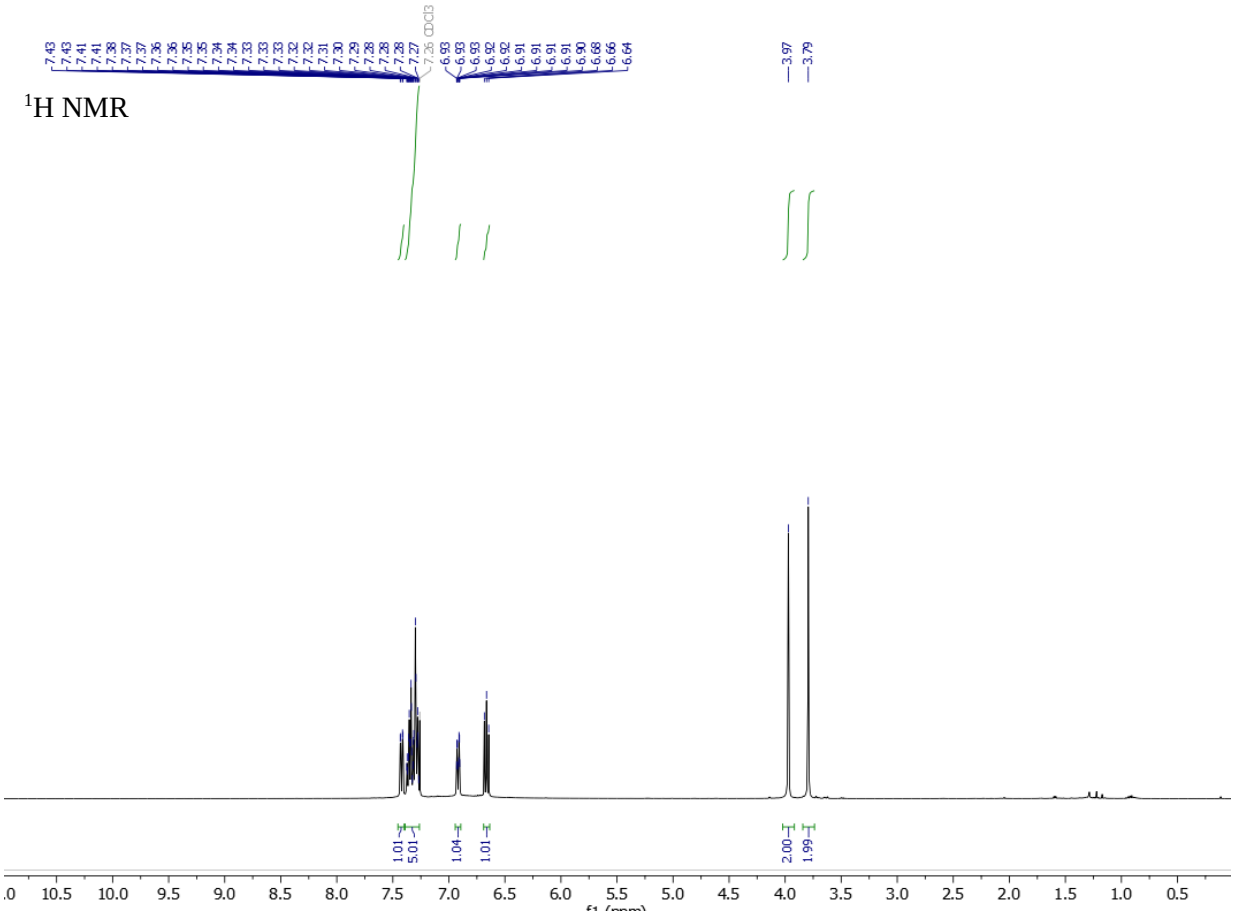


^{13}C NMR

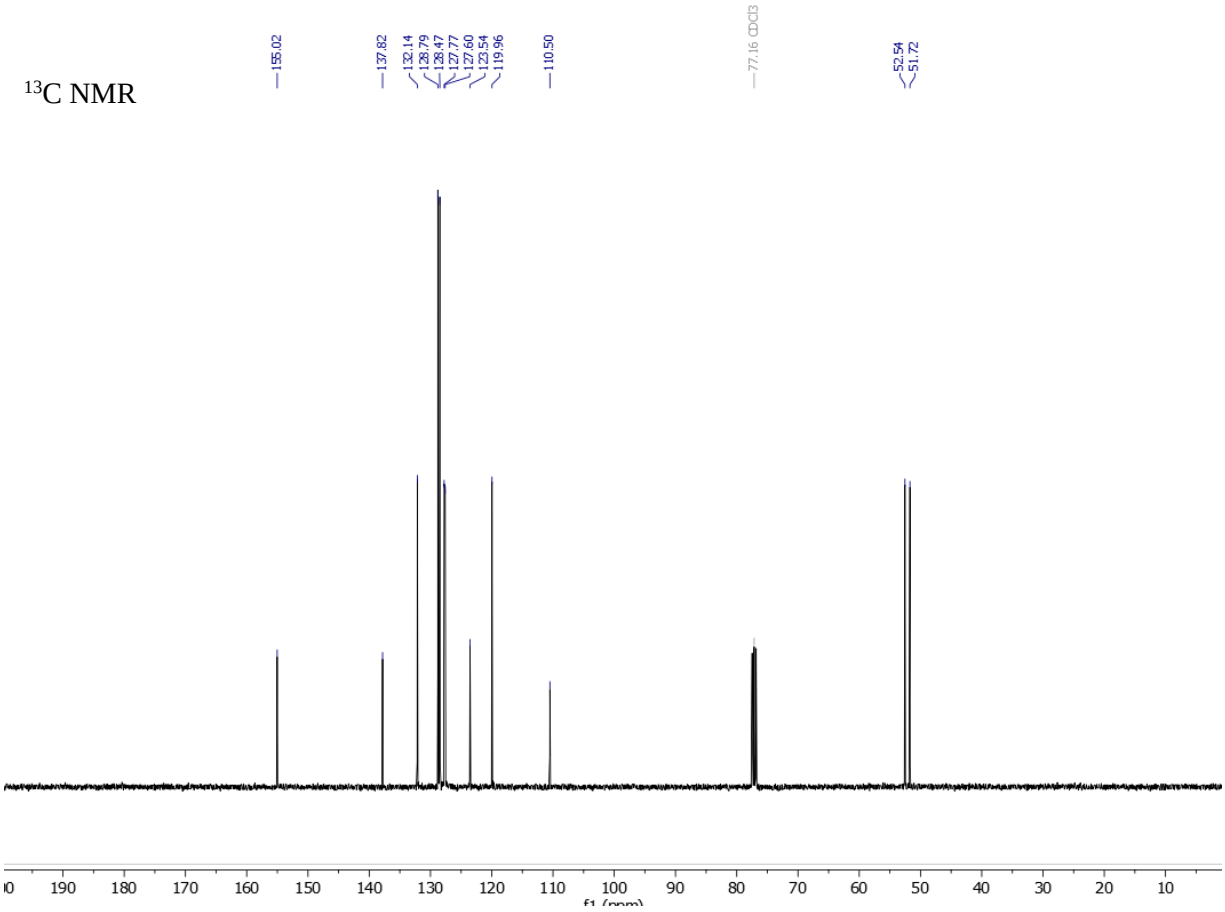


2-((Benzylamino)methyl)-6-bromophenol (**8**)

^{1}H NMR

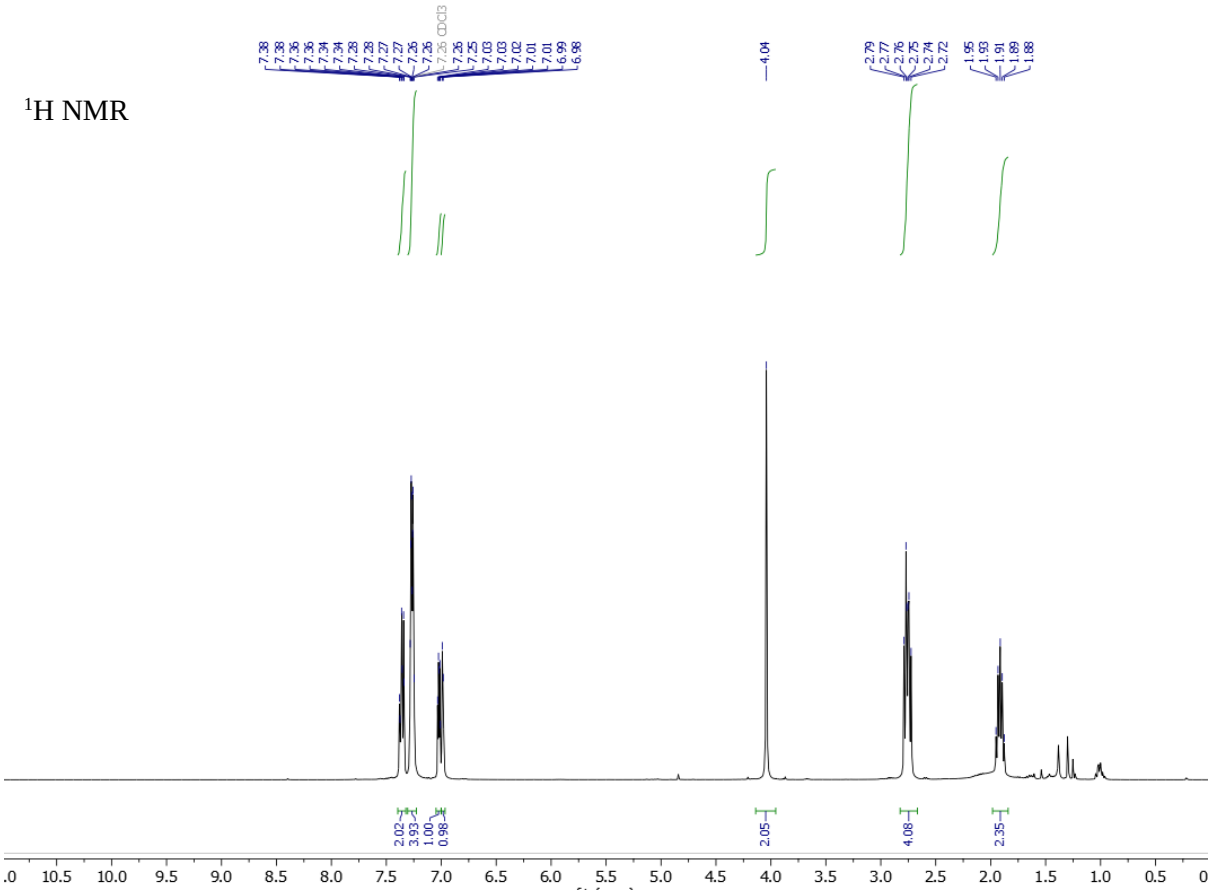


^{13}C NMR

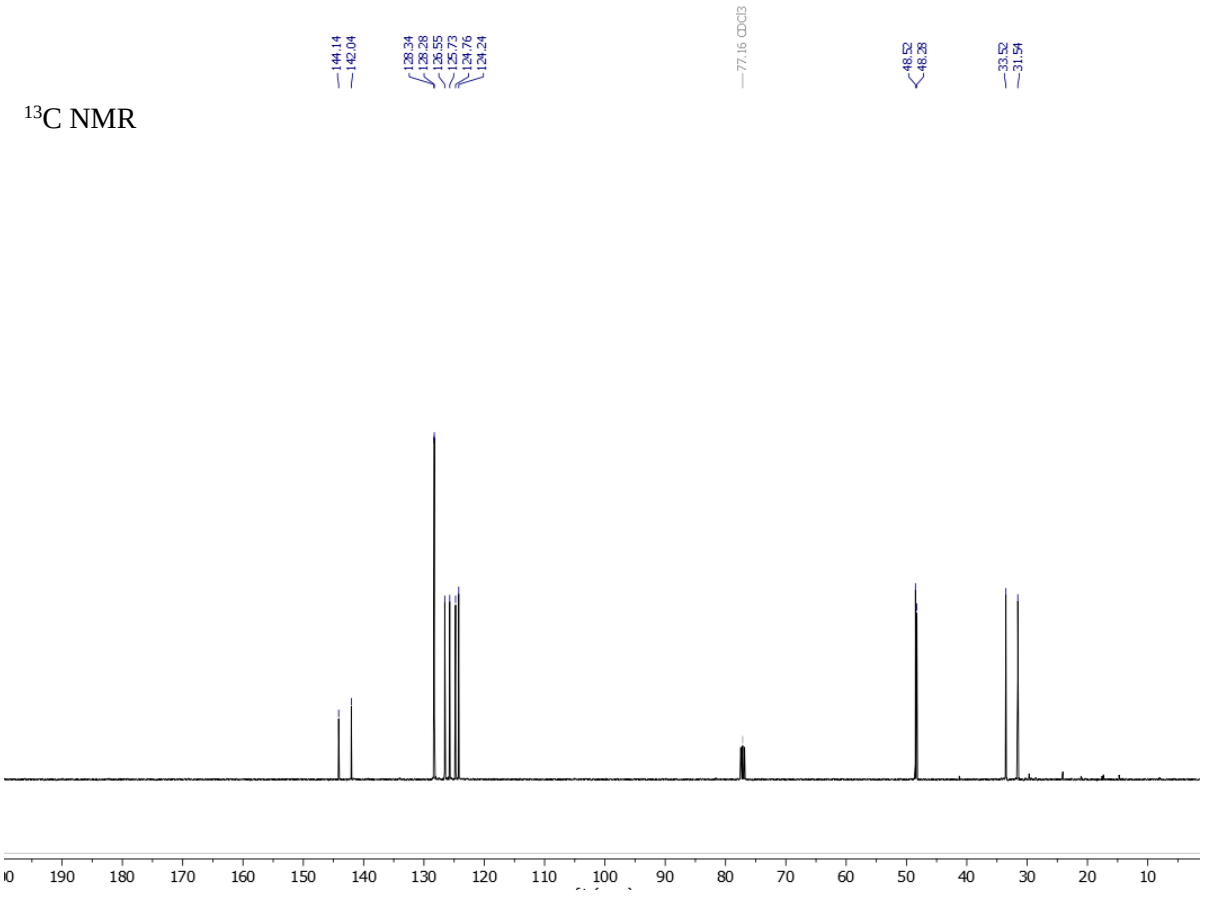


3-Phenyl-*N*-(thiophen-2-ylmethyl)propan-1-amine (**9**)

^{1}H NMR

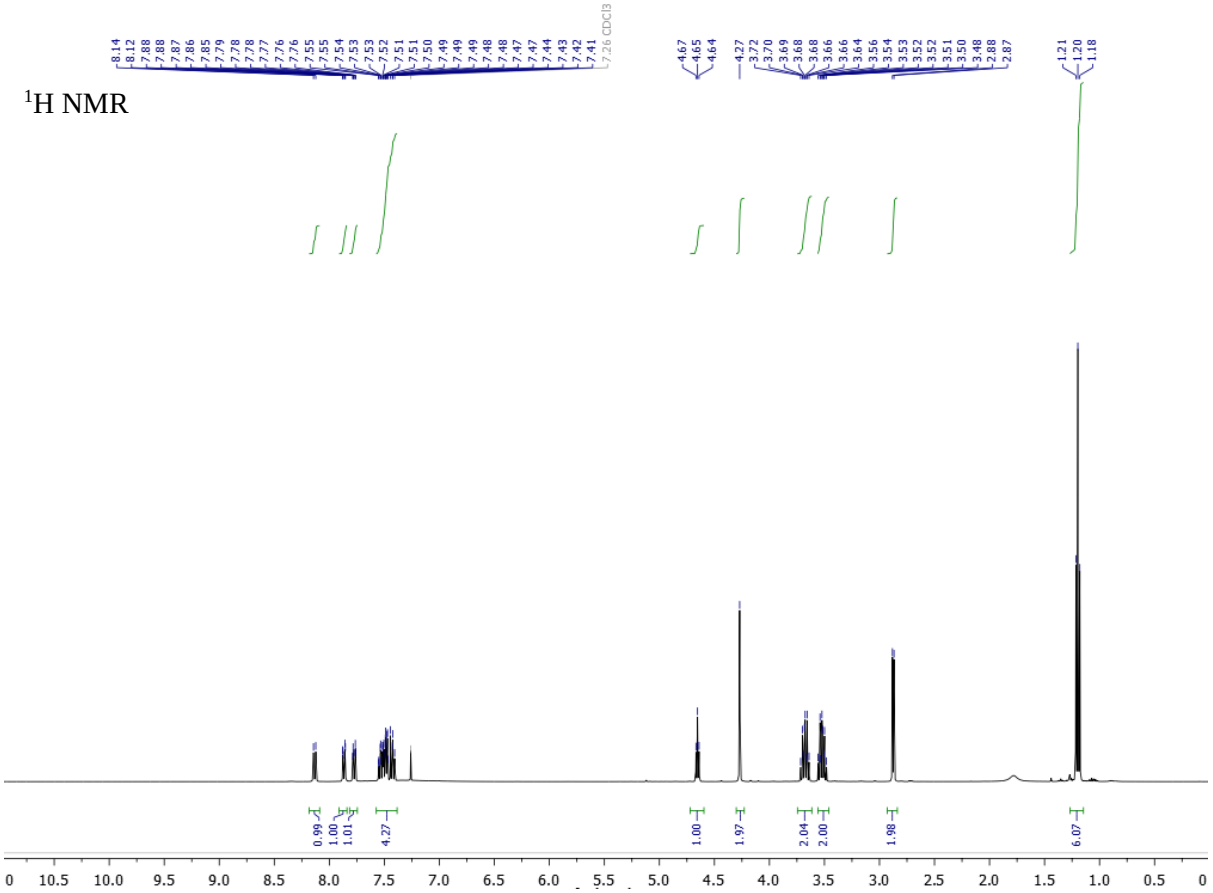


^{13}C NMR

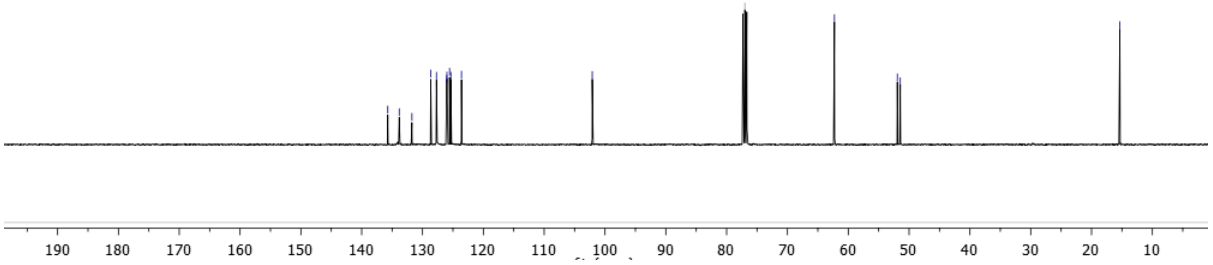


2,2-Diethoxy-*N*-(naphthalen-1-ylmethyl)ethan-1-amine (**SI-2**)

^{1}H NMR

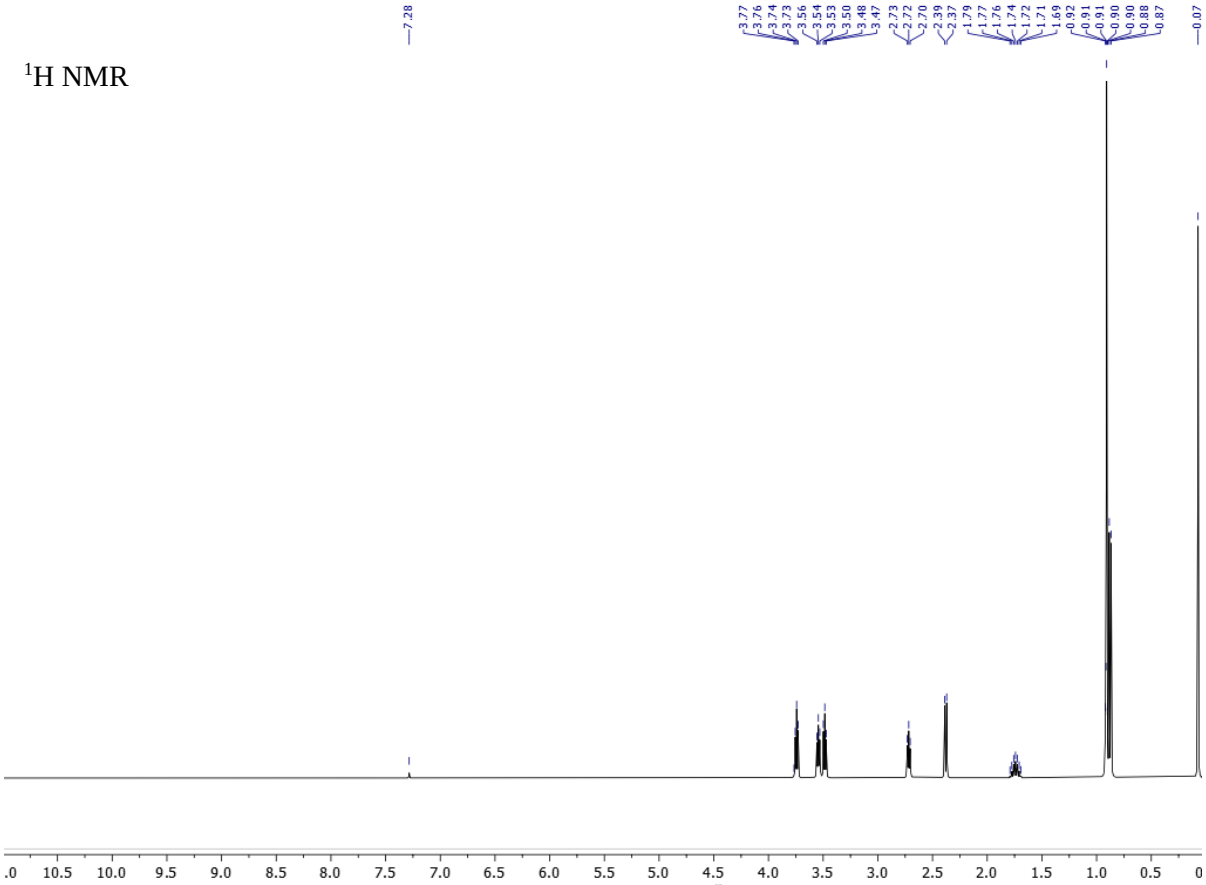


^{13}C NMR

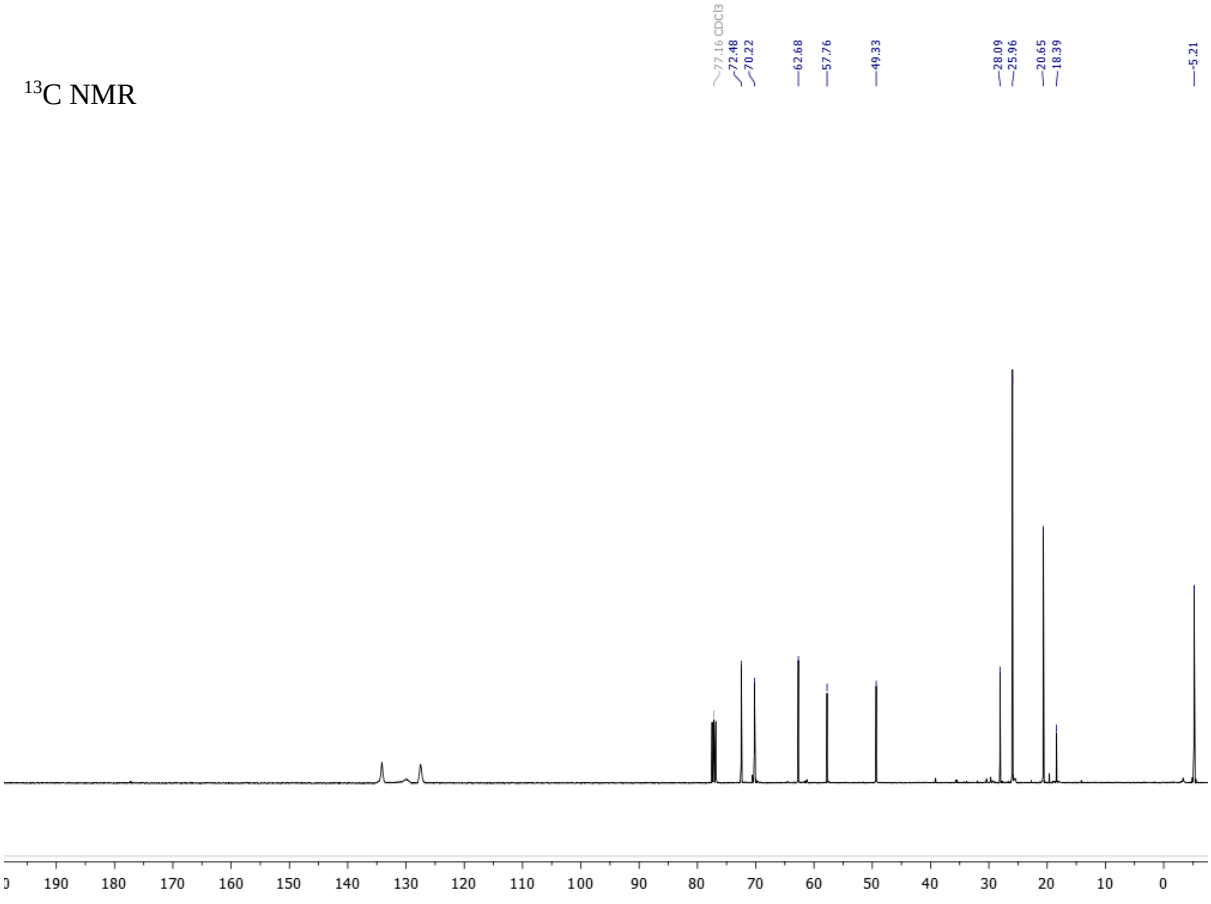


N-(2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (**10**)

^{1}H NMR



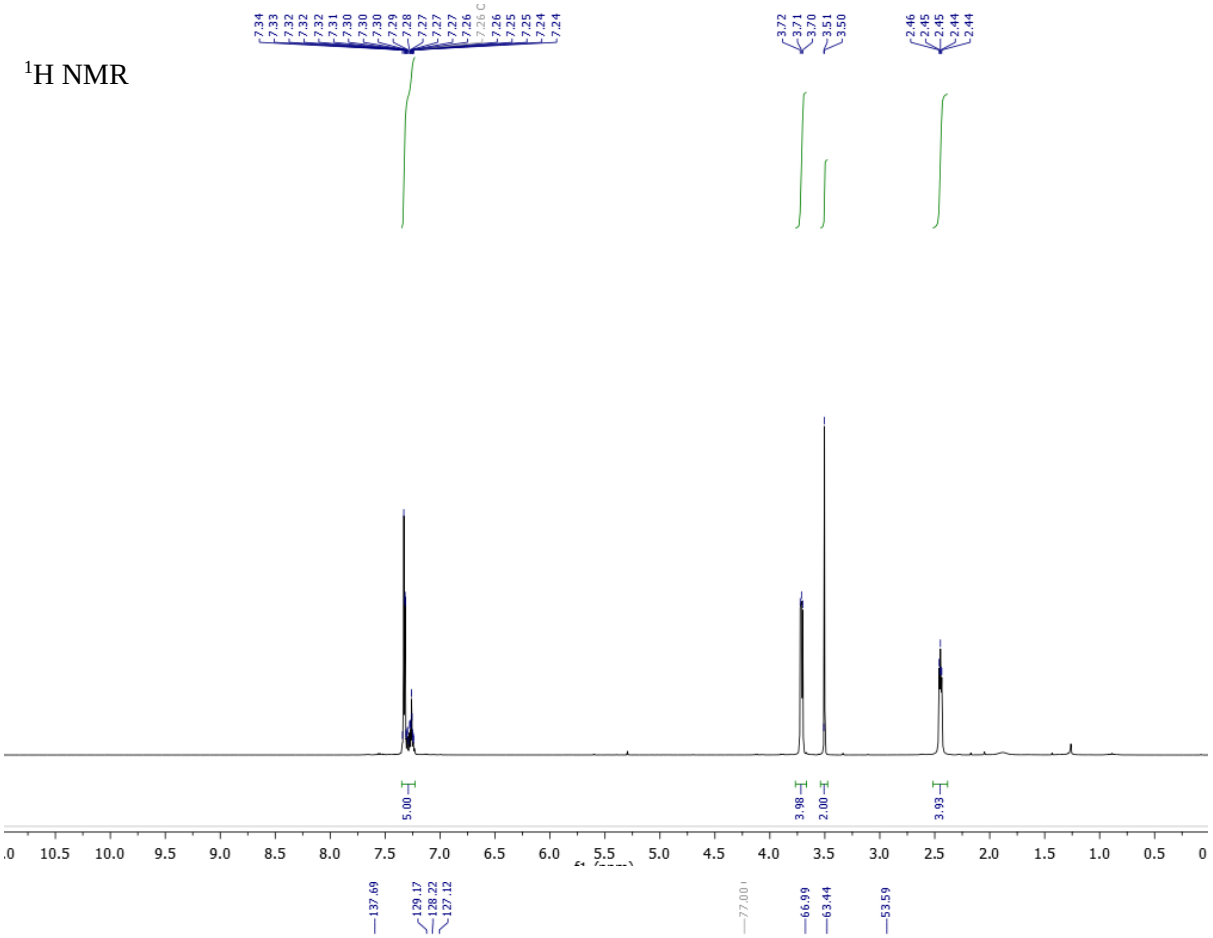
^{13}C NMR



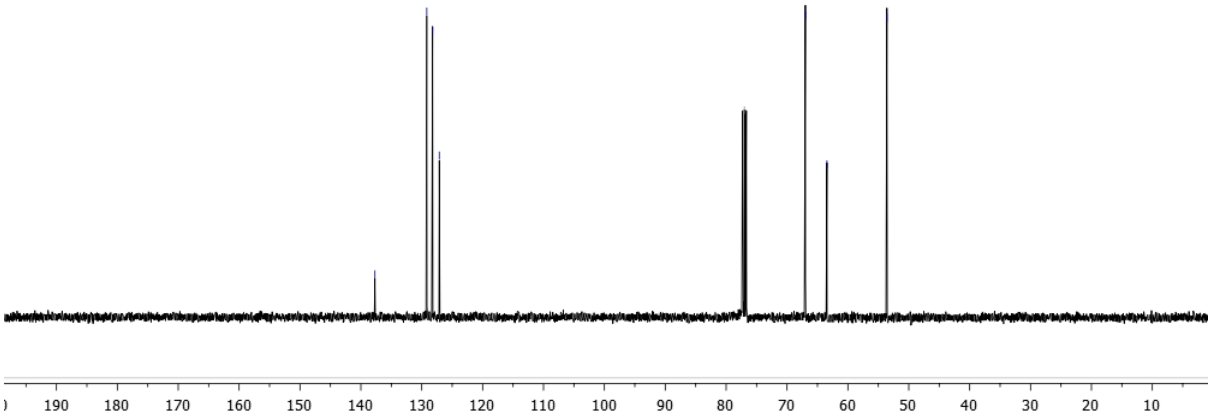
6.2 Tertiary Amines

4-Benzylmorpholine (**11**)

^{1}H NMR

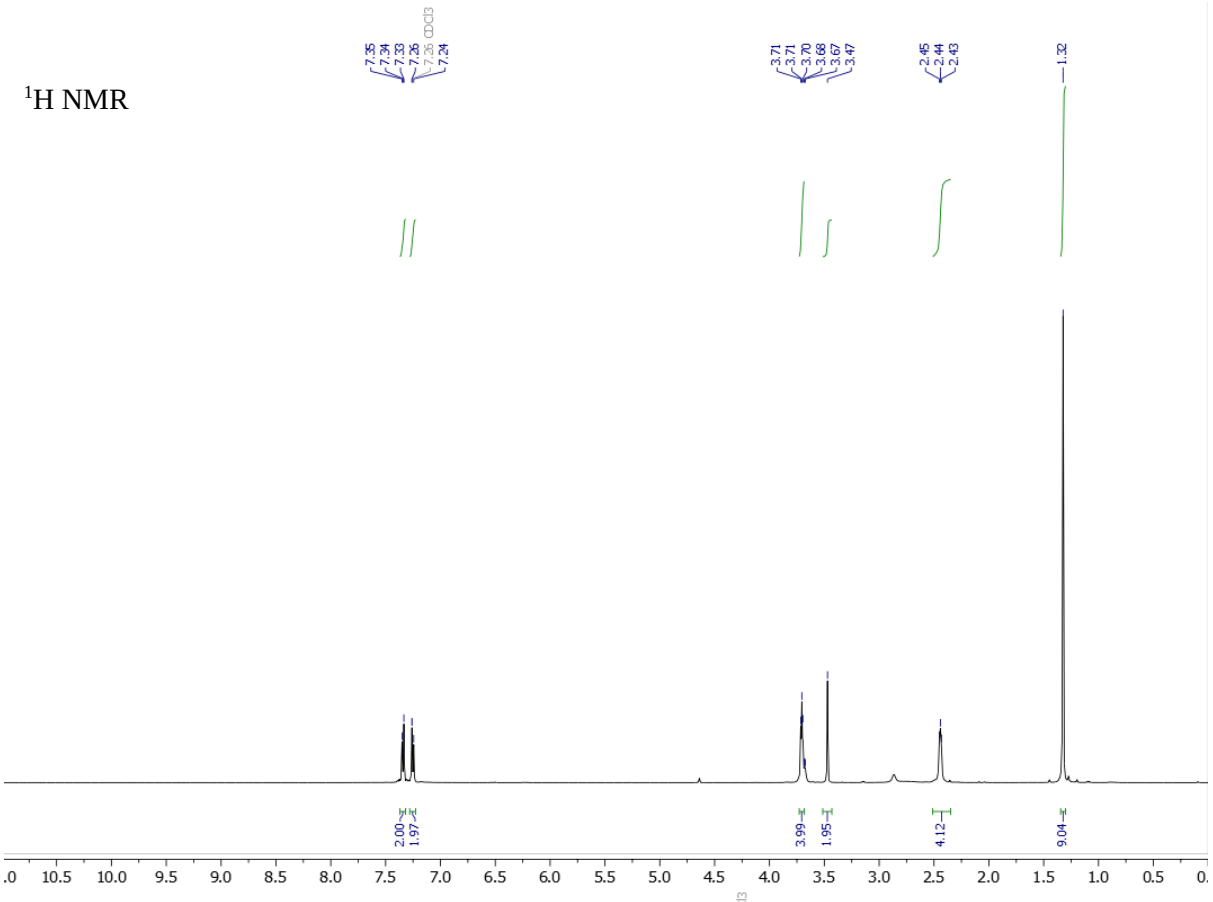


^{13}C NMR

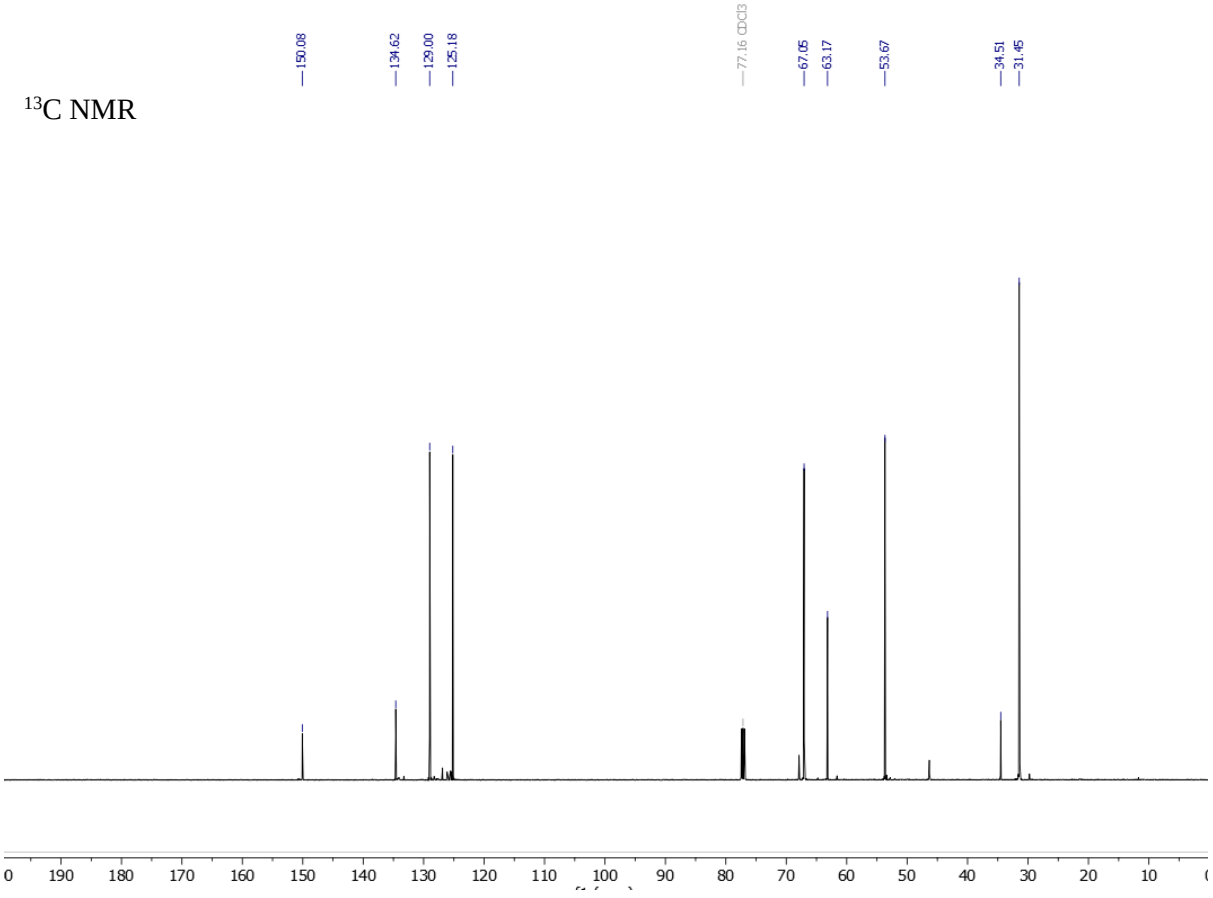


4-(4-(*tert*-butyl)benzyl)morpholine (**12**)

^{1}H NMR

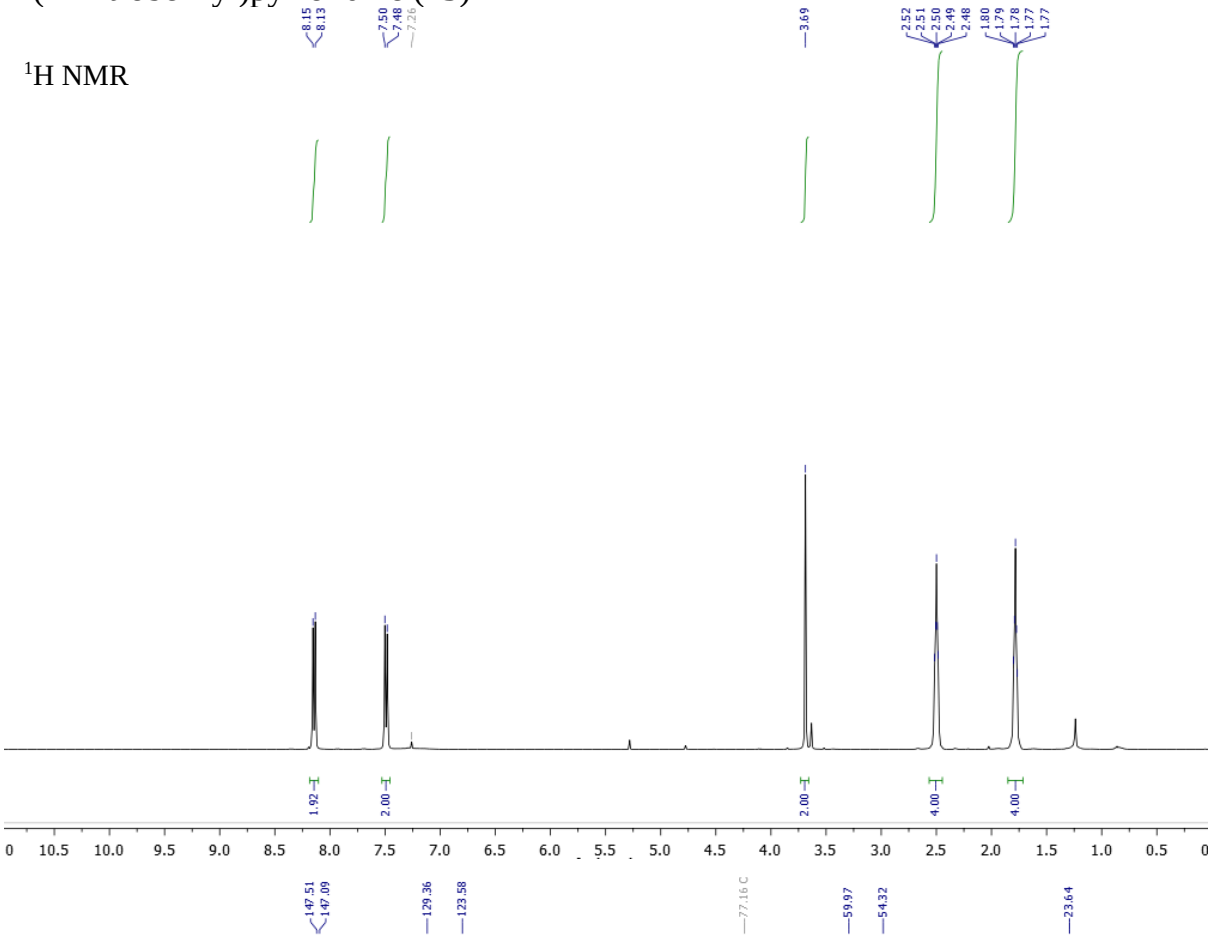


^{13}C NMR

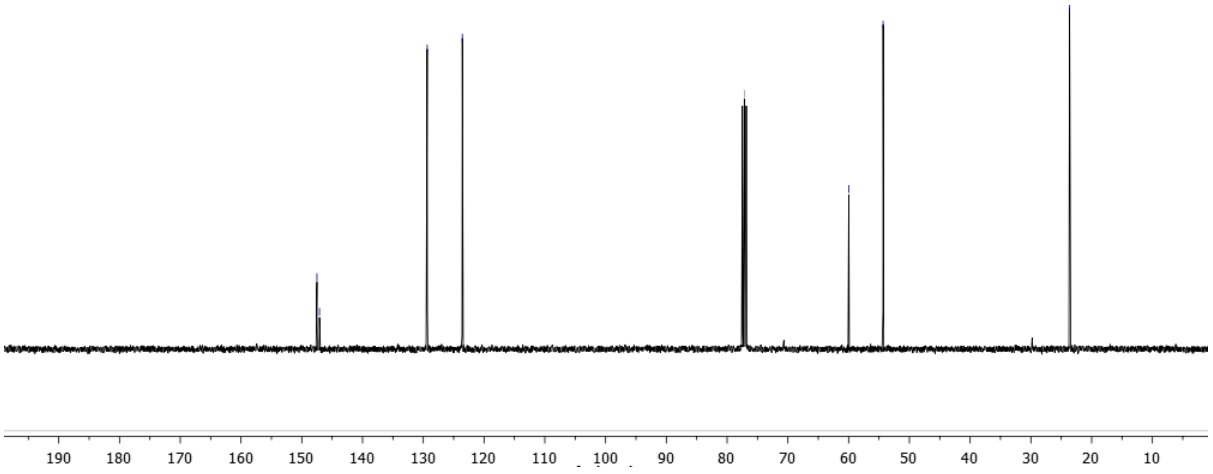


1-(4-Nitrobenzyl)pyrrolidine (**13**)

^{1}H NMR

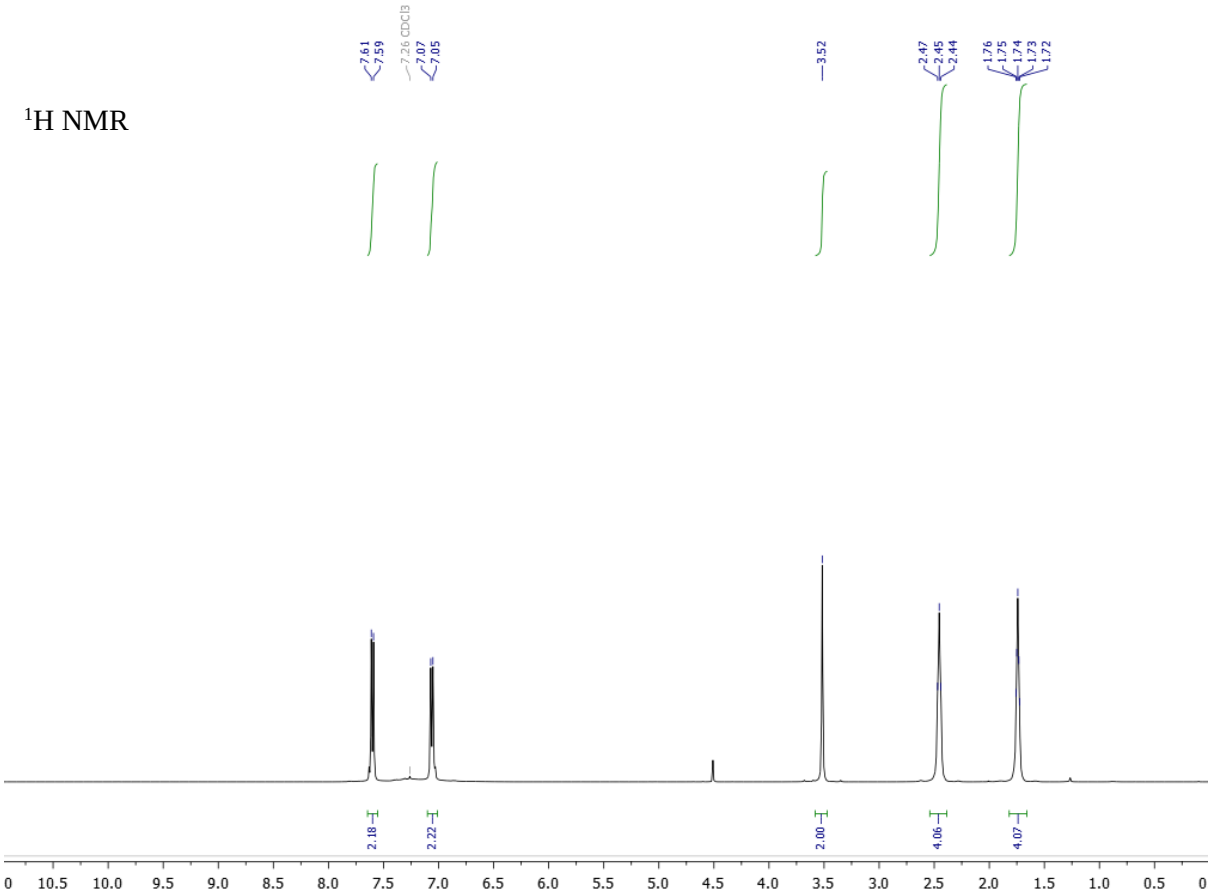


^{13}C NMR

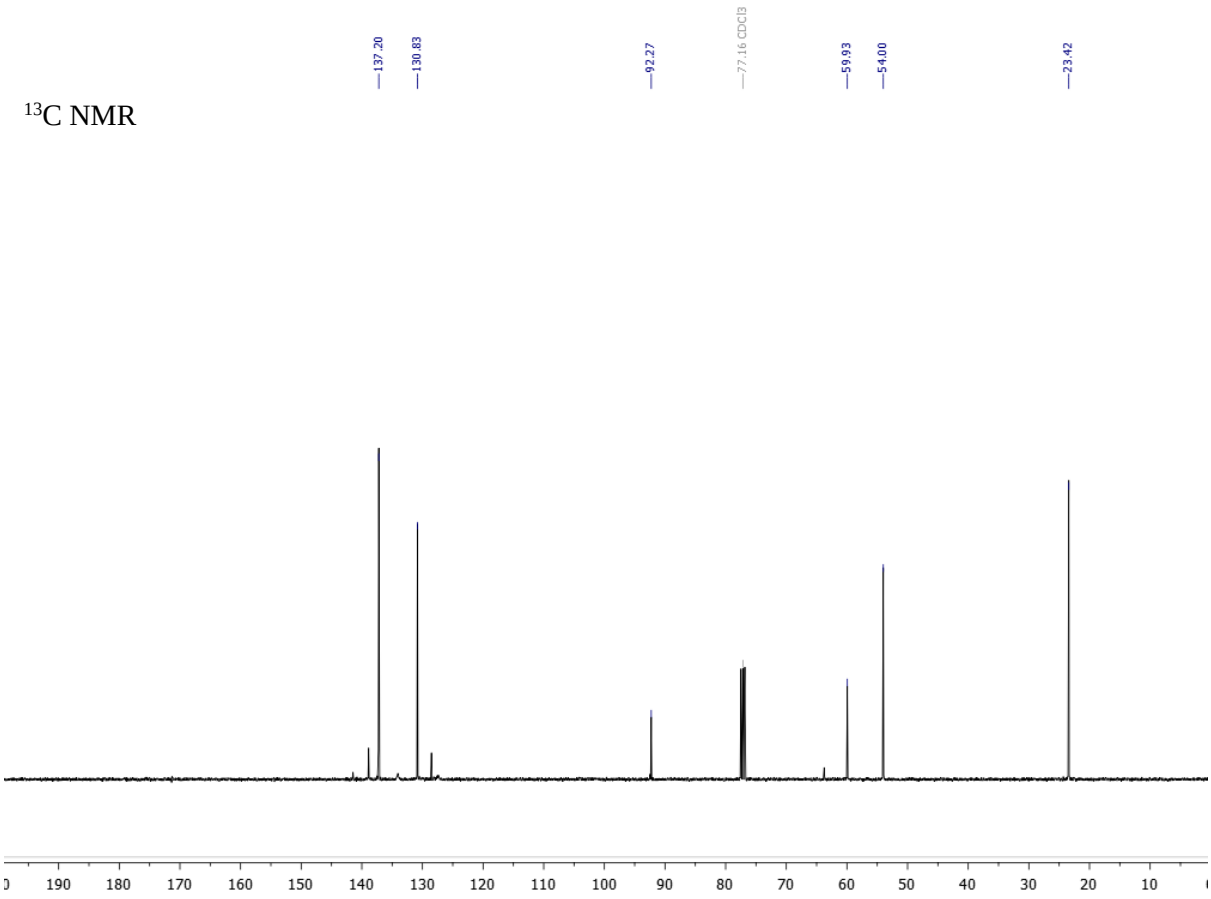


1-(4-Iodobenzyl)pyrrolidine (**14**)

^{1}H NMR

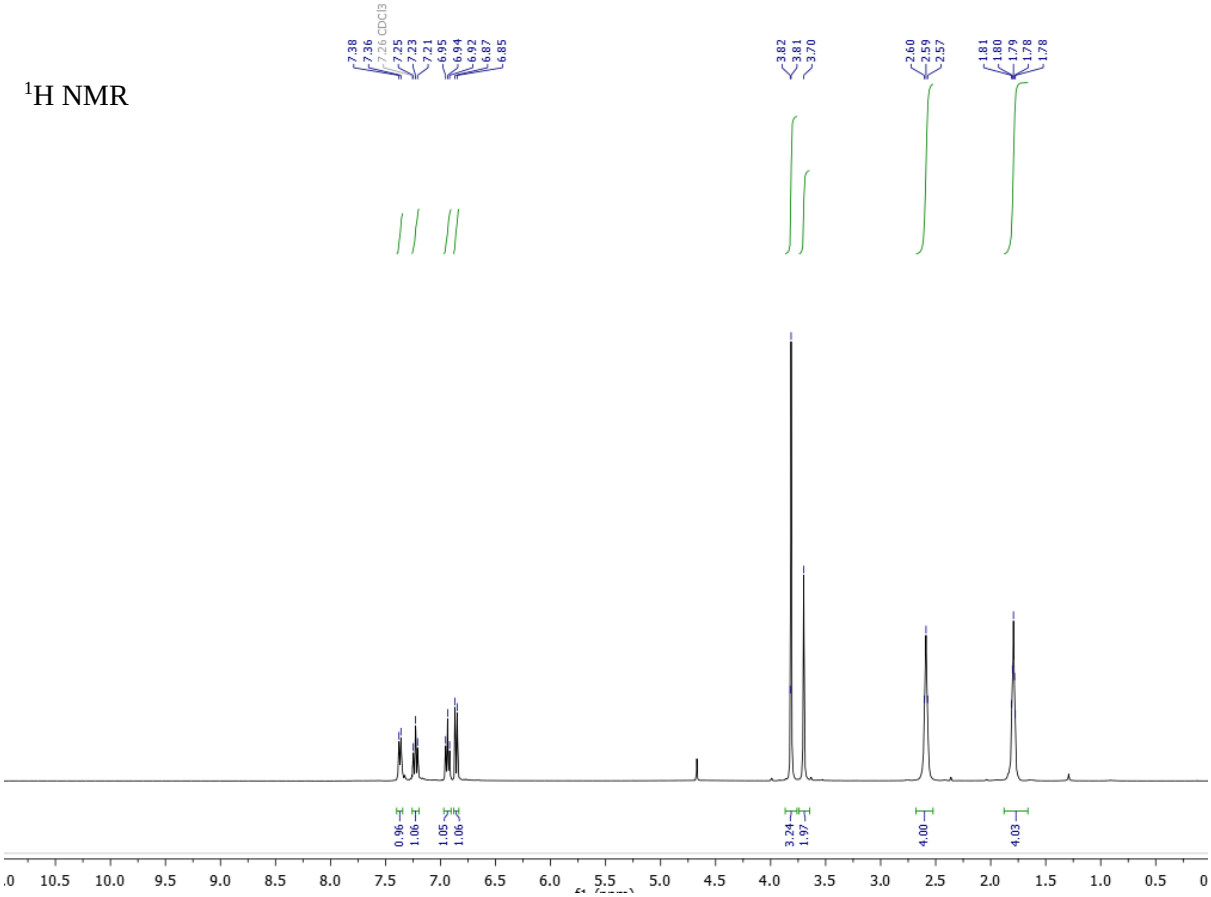


^{13}C NMR

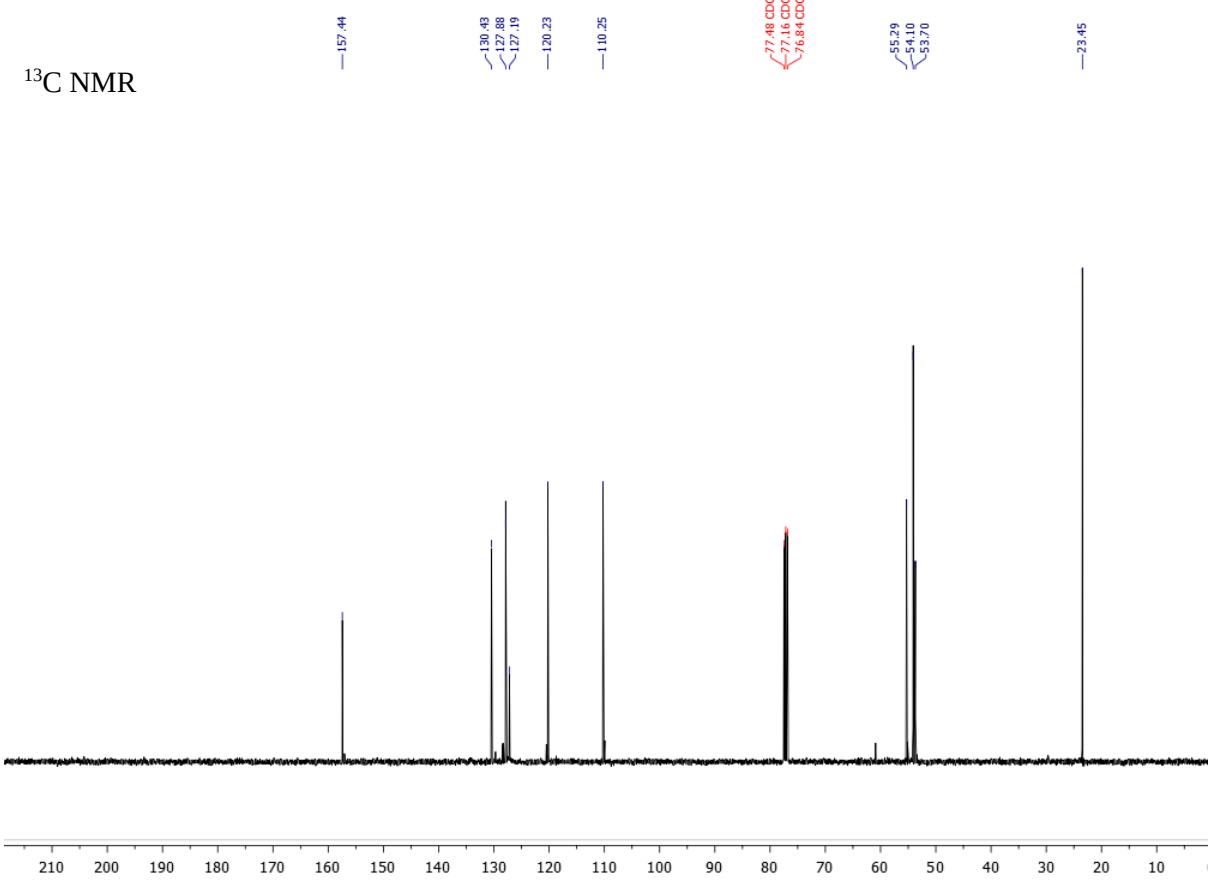


1-(2-Methoxybenzyl)pyrrolidine (**15**)

^{1}H NMR

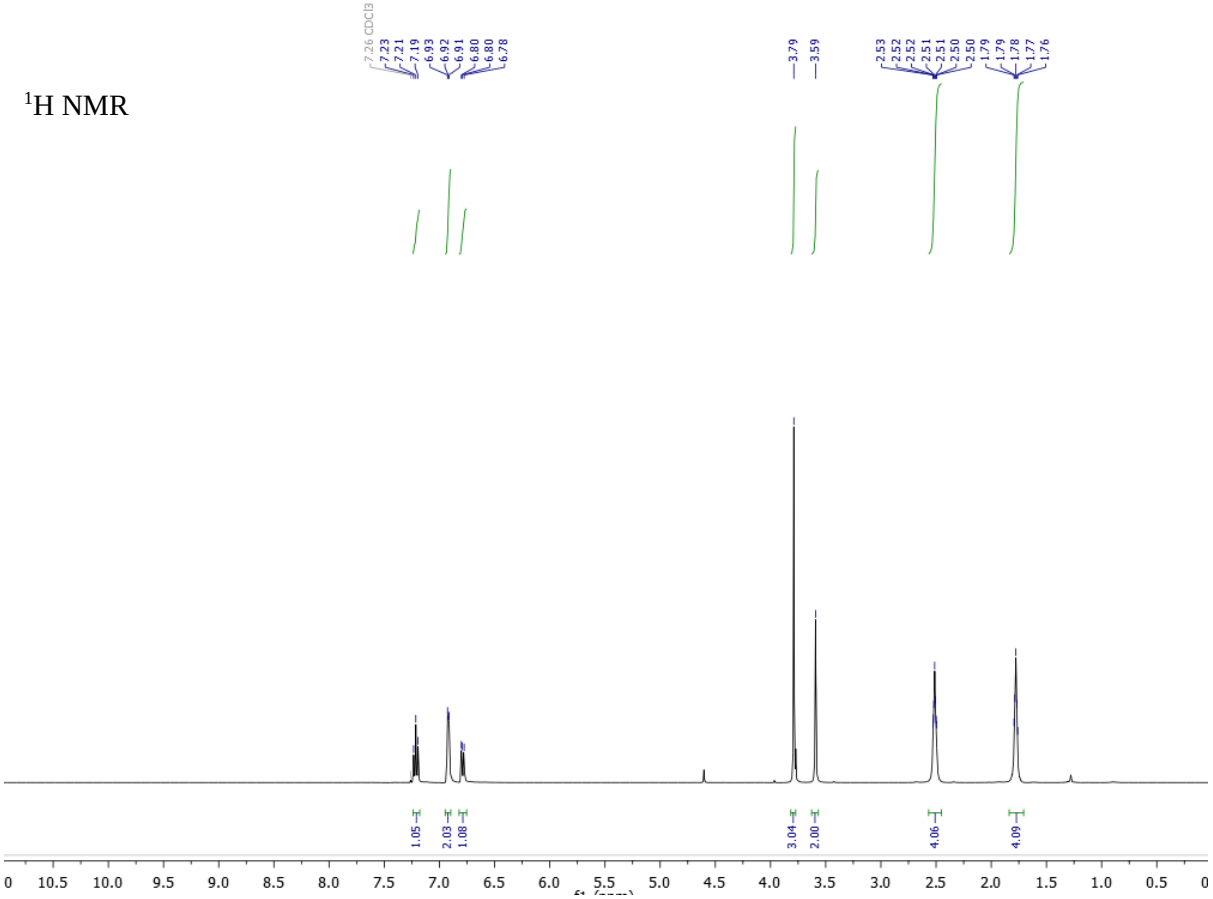


^{13}C NMR

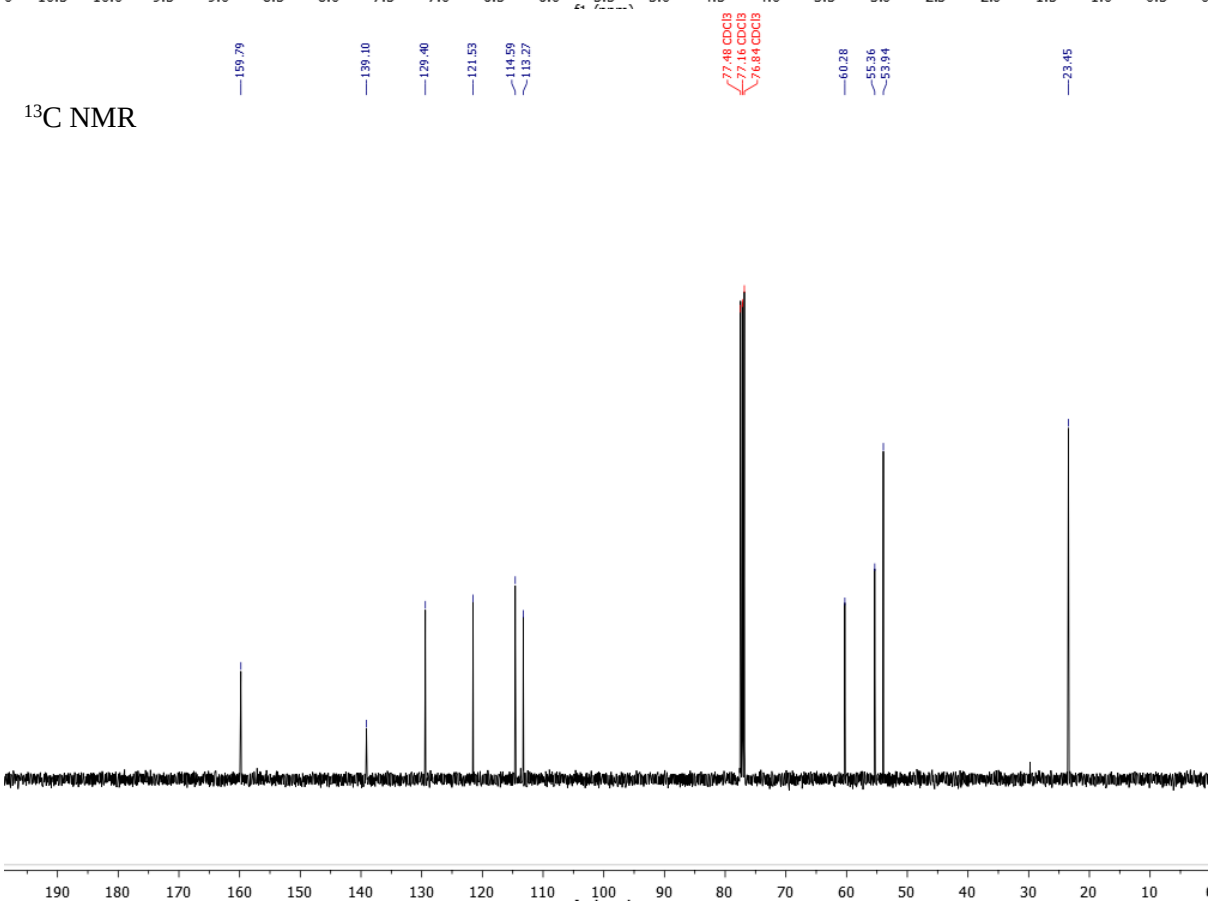


1-(3-Methoxybenzyl)pyrrolidine (**16**)

^{1}H NMR

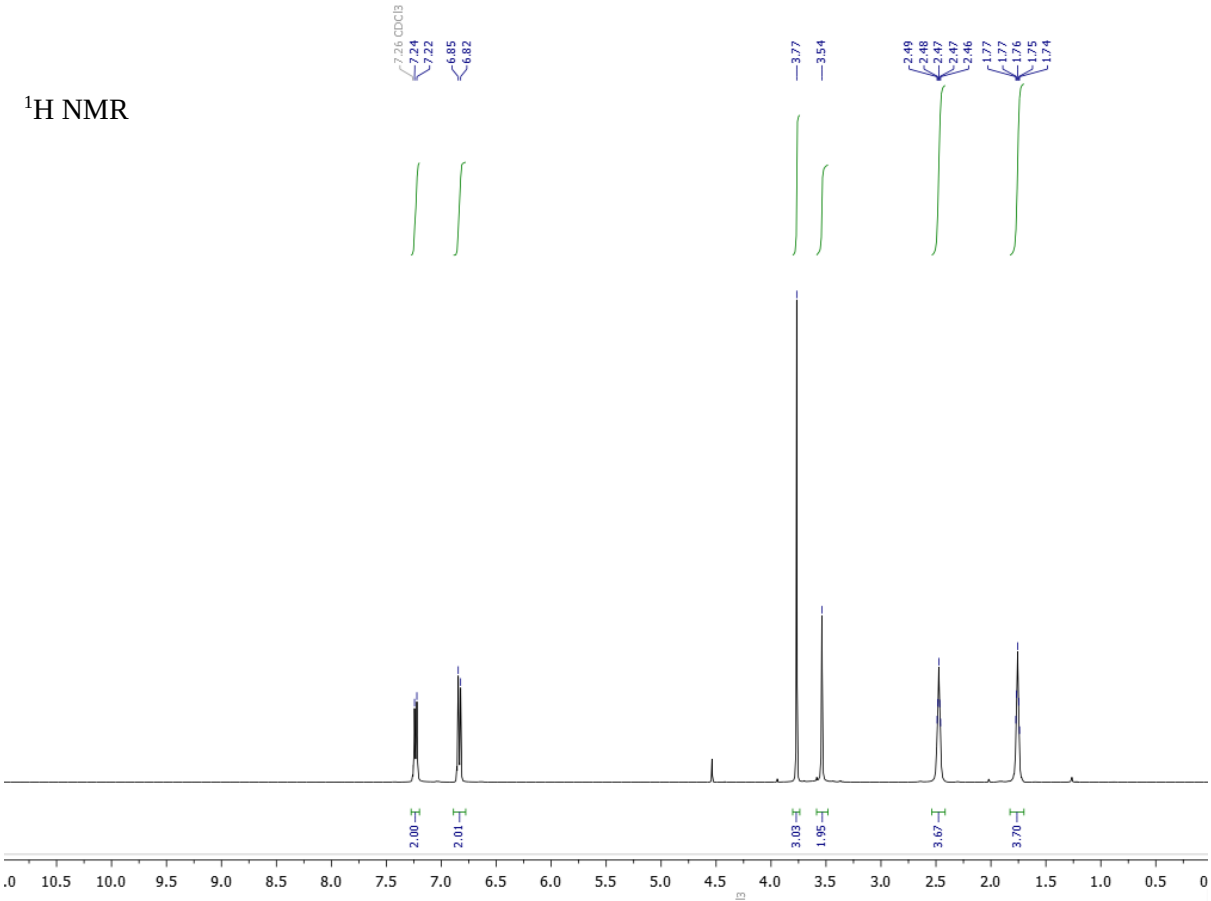


^{13}C NMR

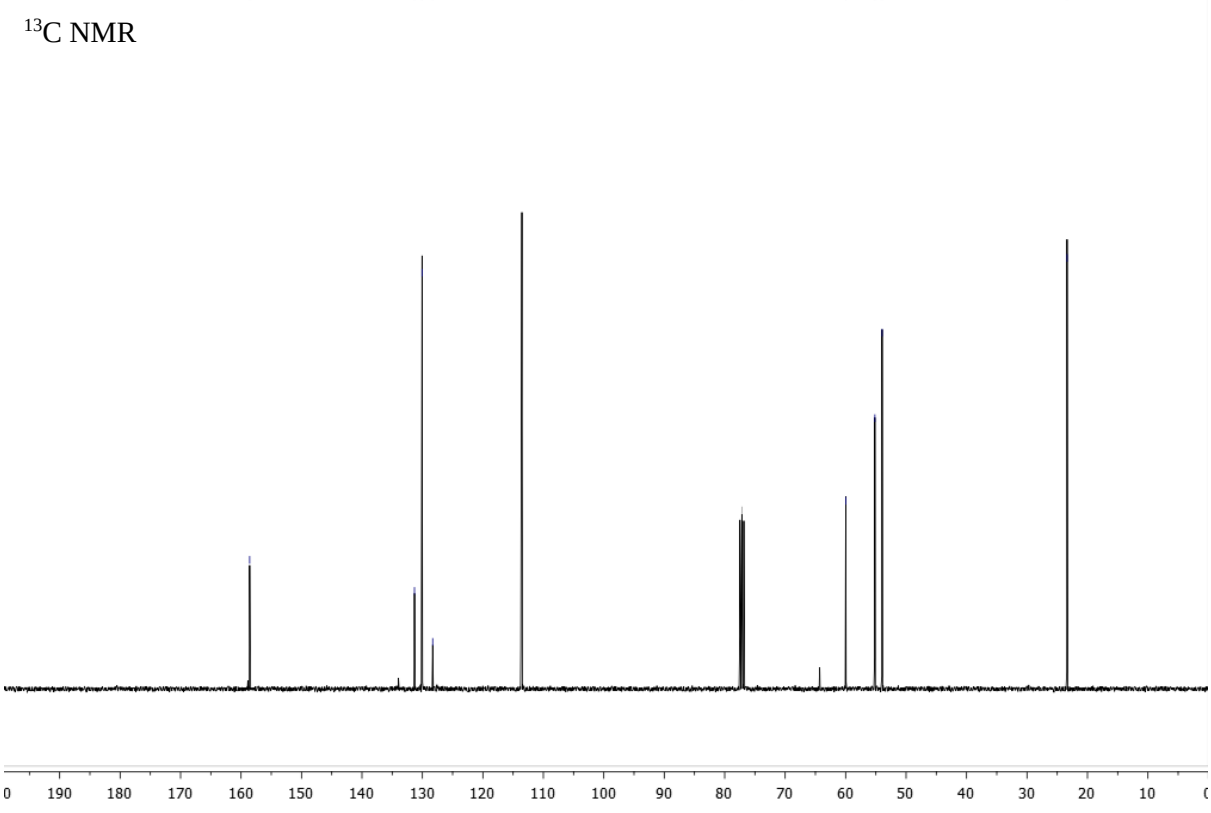


1-(4-Methoxybenzyl)pyrrolidine (**17**)

^{1}H NMR

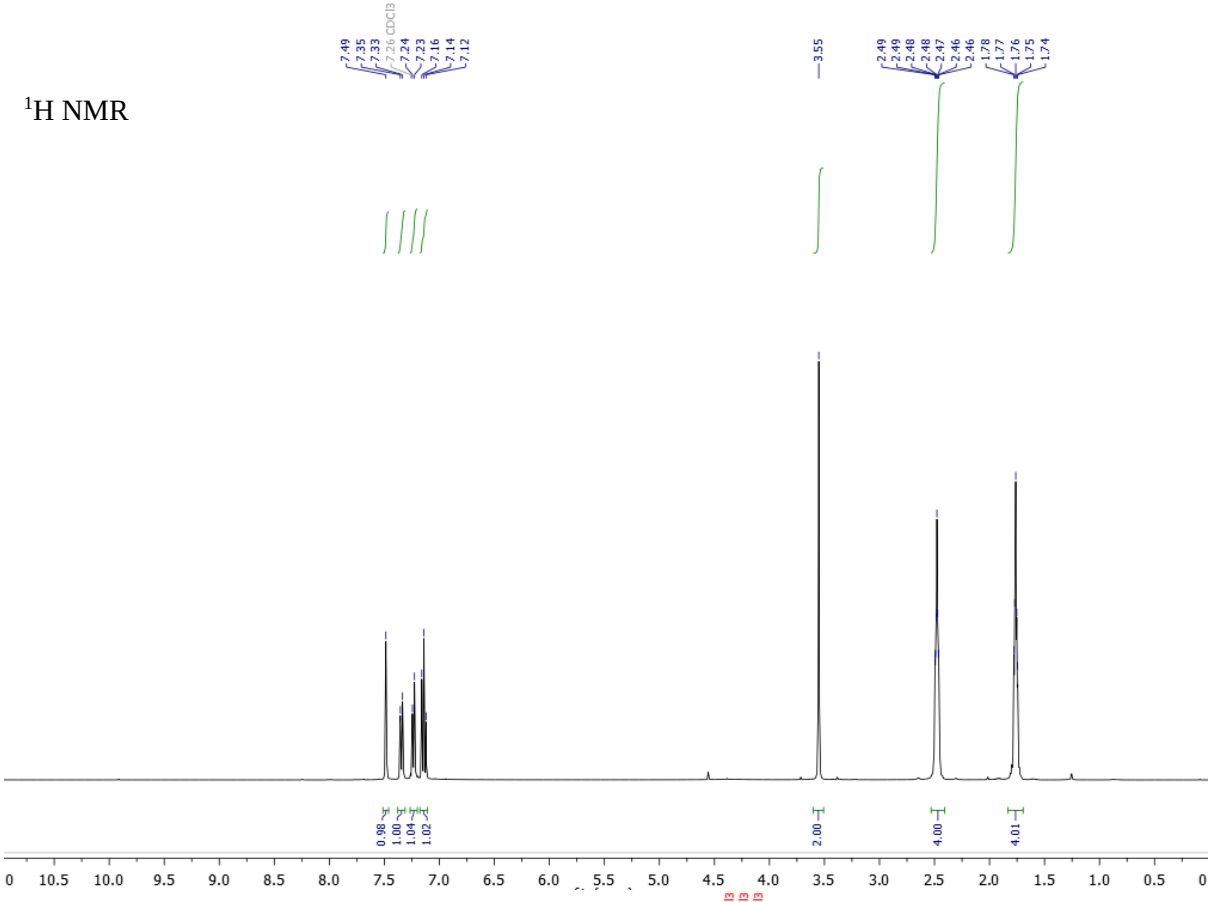


^{13}C NMR

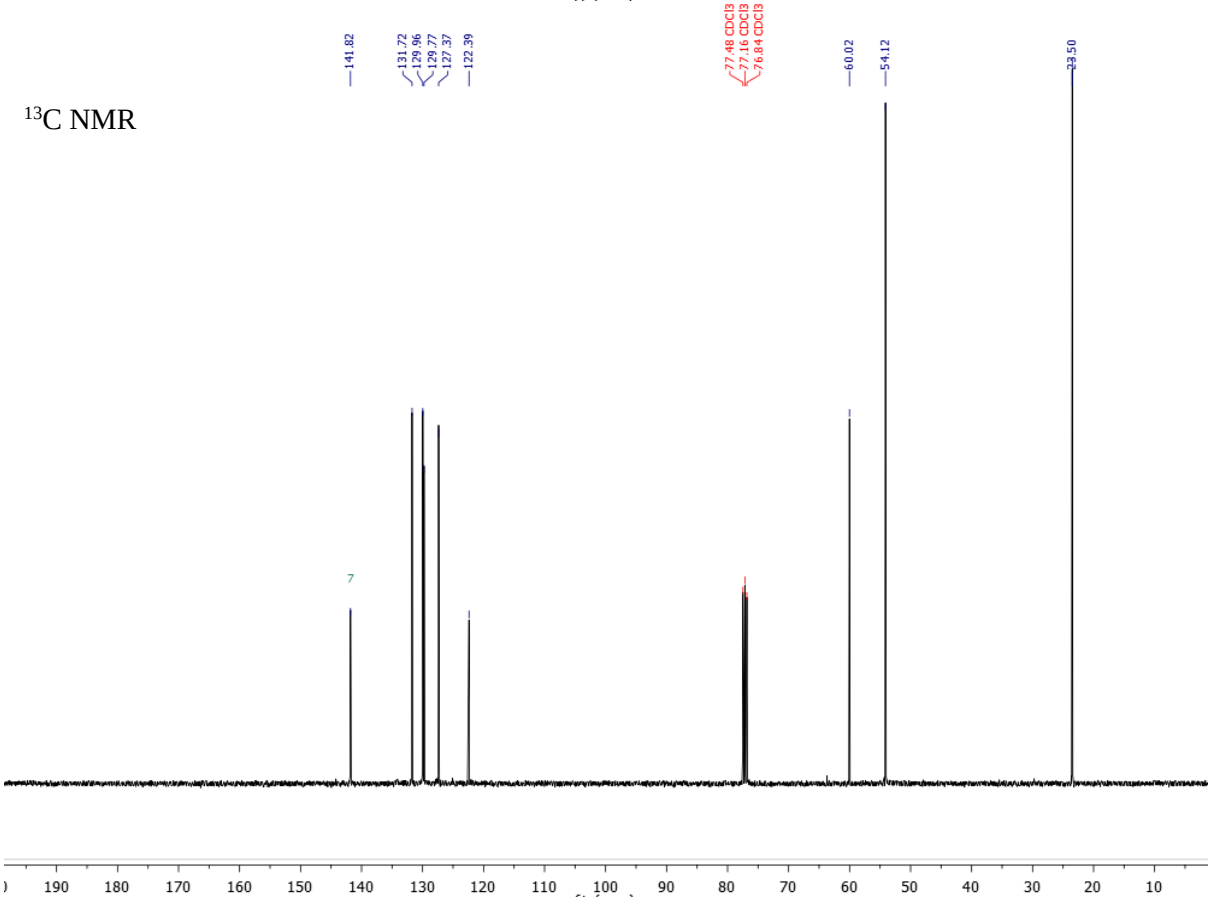


1-(3-Bromobenzyl)pyrrolidine (**18**)

^{1}H NMR

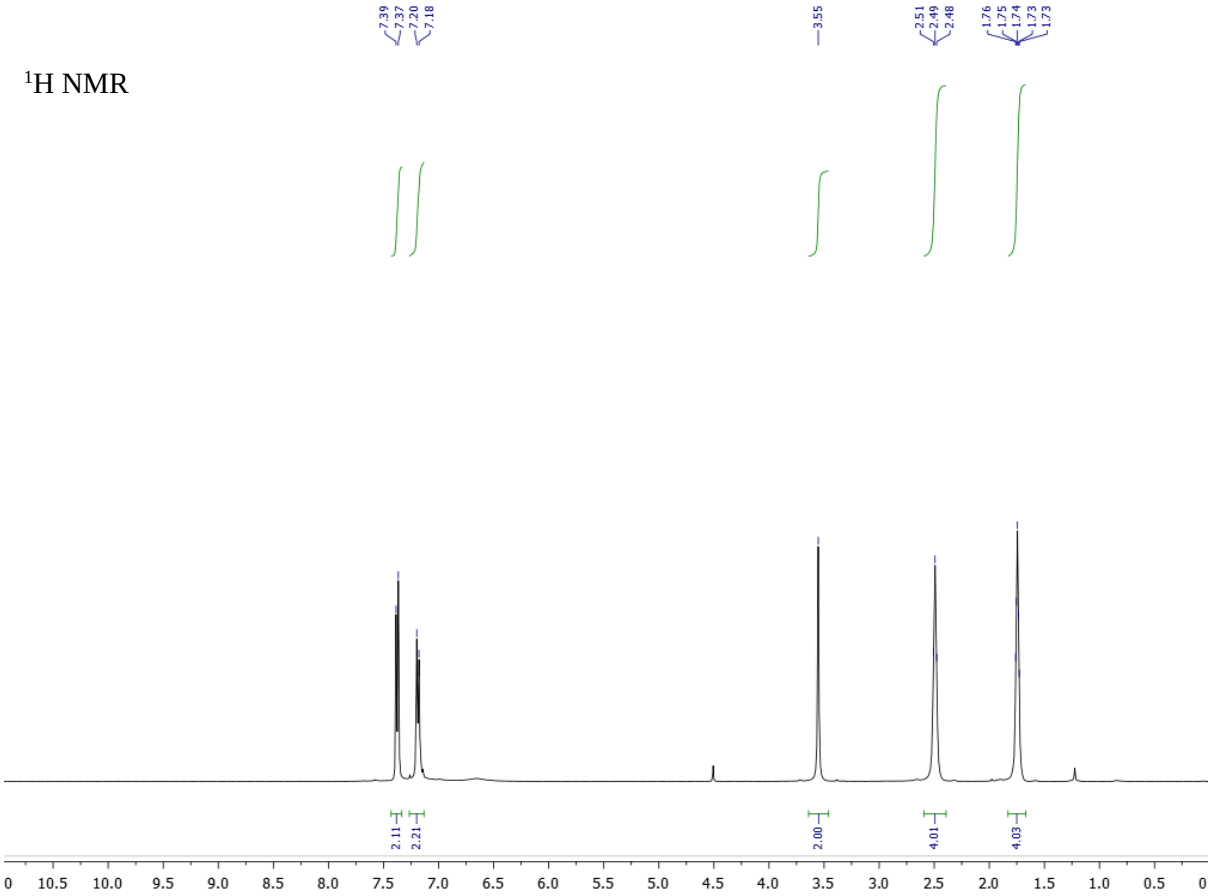


^{13}C NMR

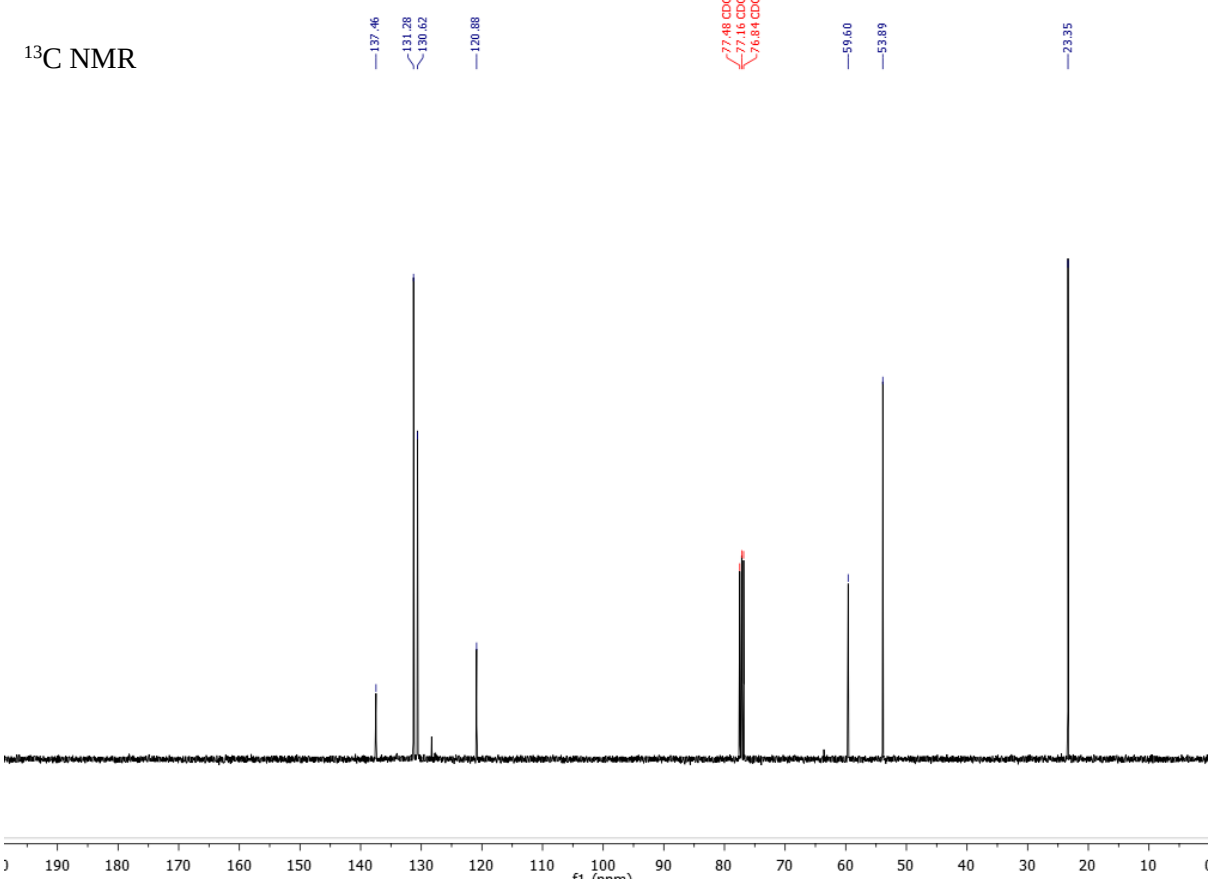


1-(4-Bromobenzyl)pyrrolidine (**19**)

^{1}H NMR

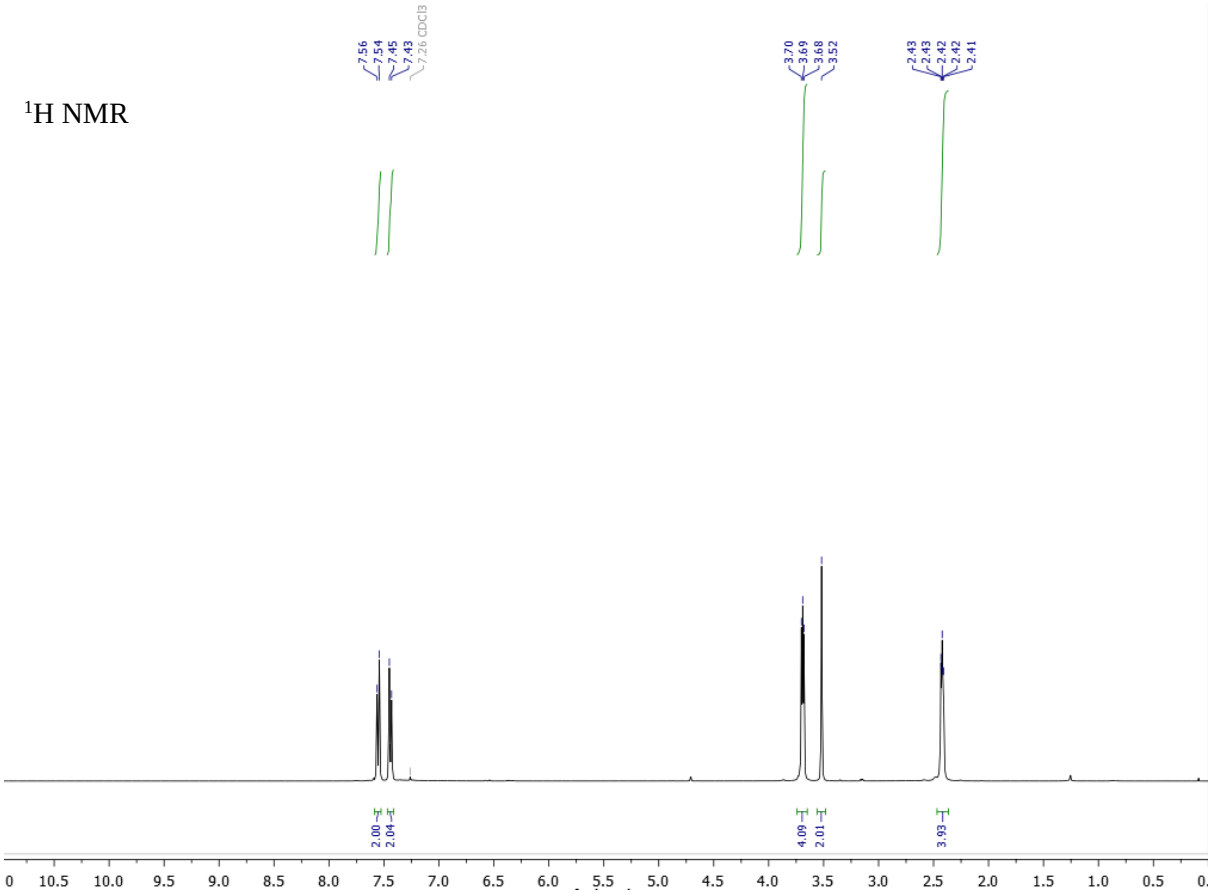


^{13}C NMR

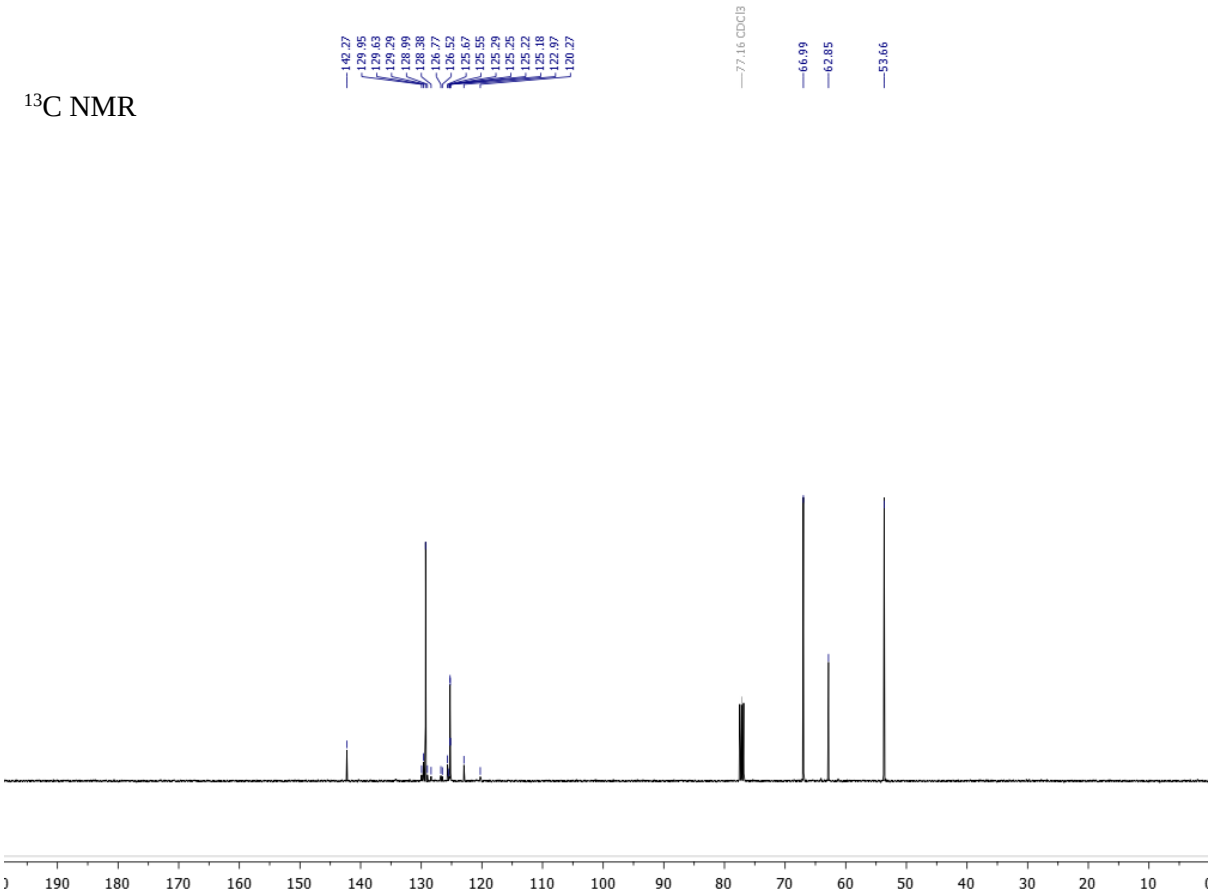


4-(4-(Trifluoromethyl)benzyl)morpholine (**20**)

^{1}H NMR

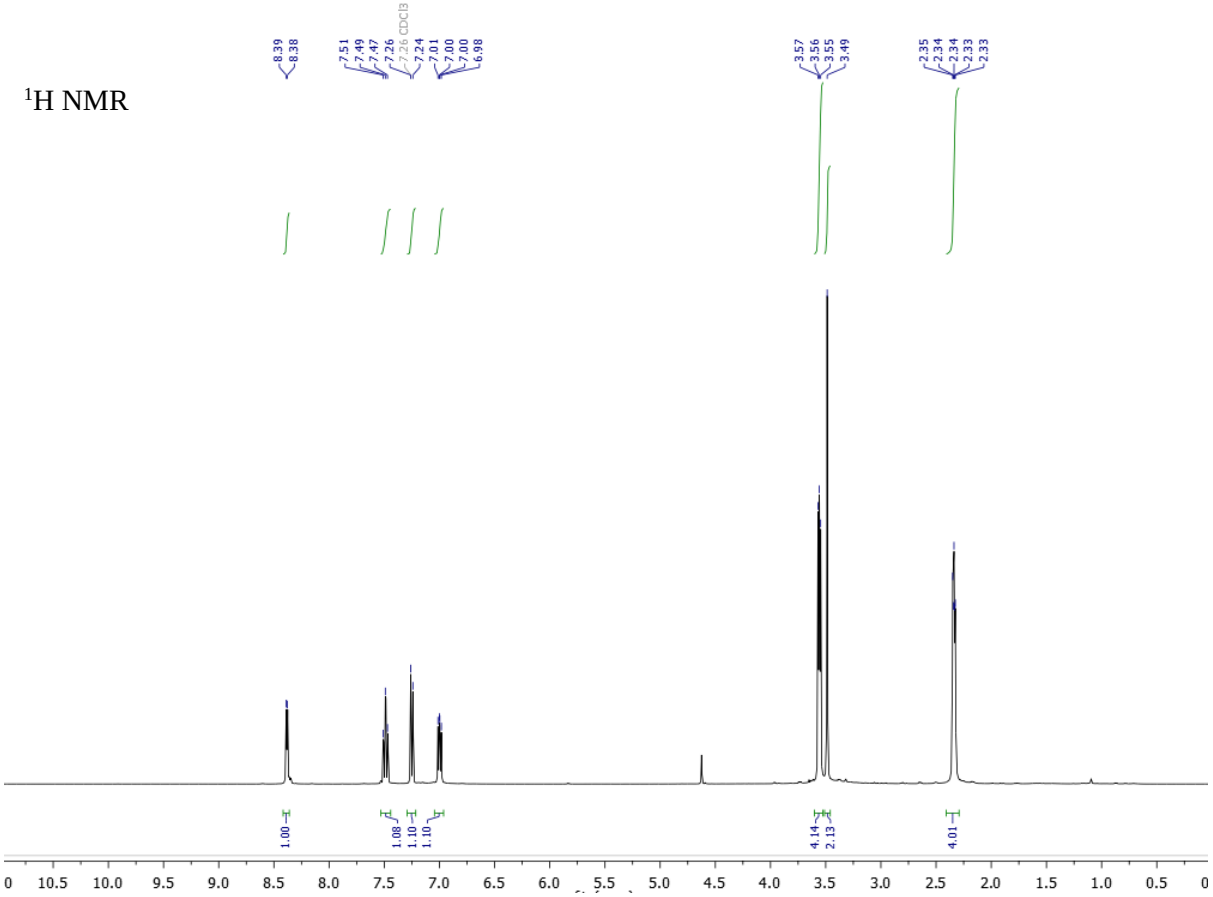


^{13}C NMR

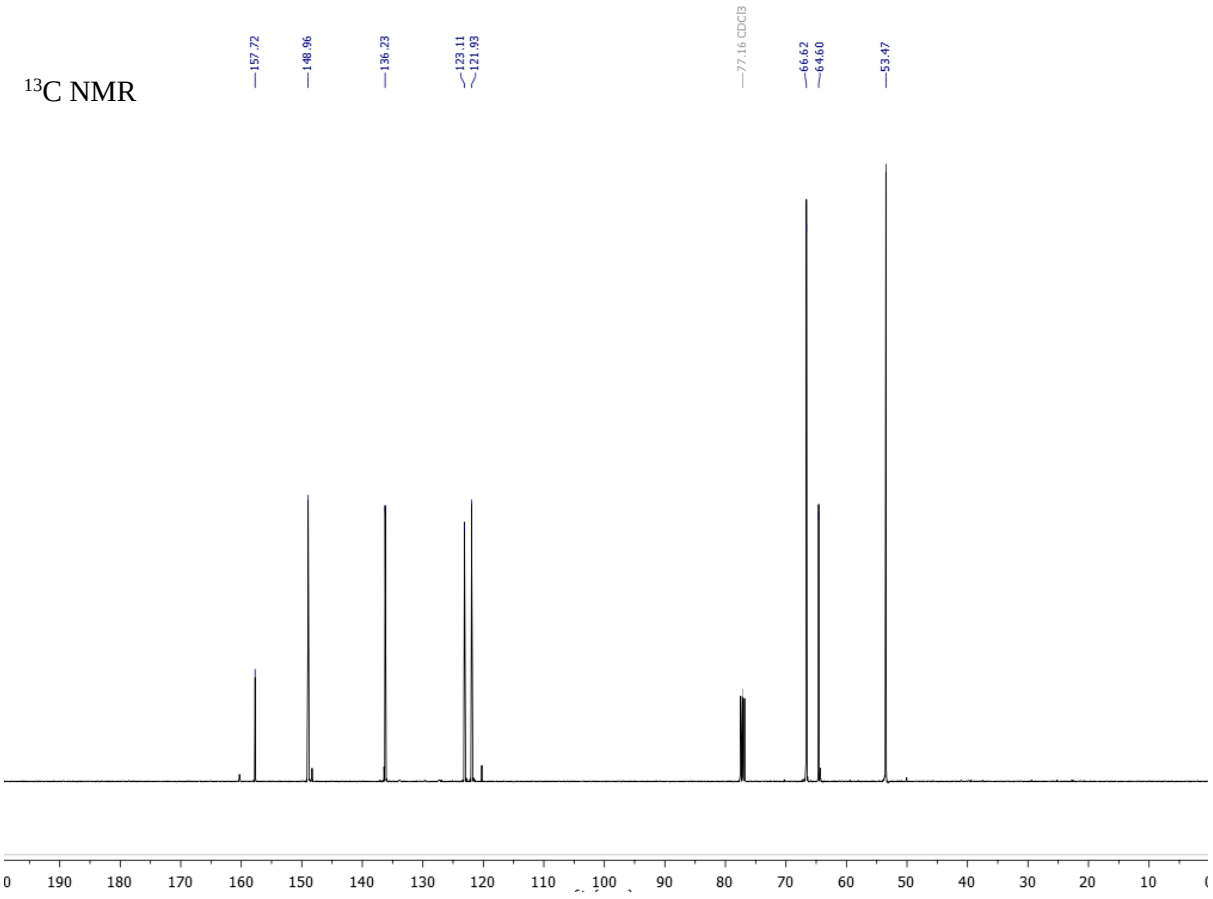


4-(Pyridin-2-ylmethyl)morpholine (**21**)

^{1}H NMR

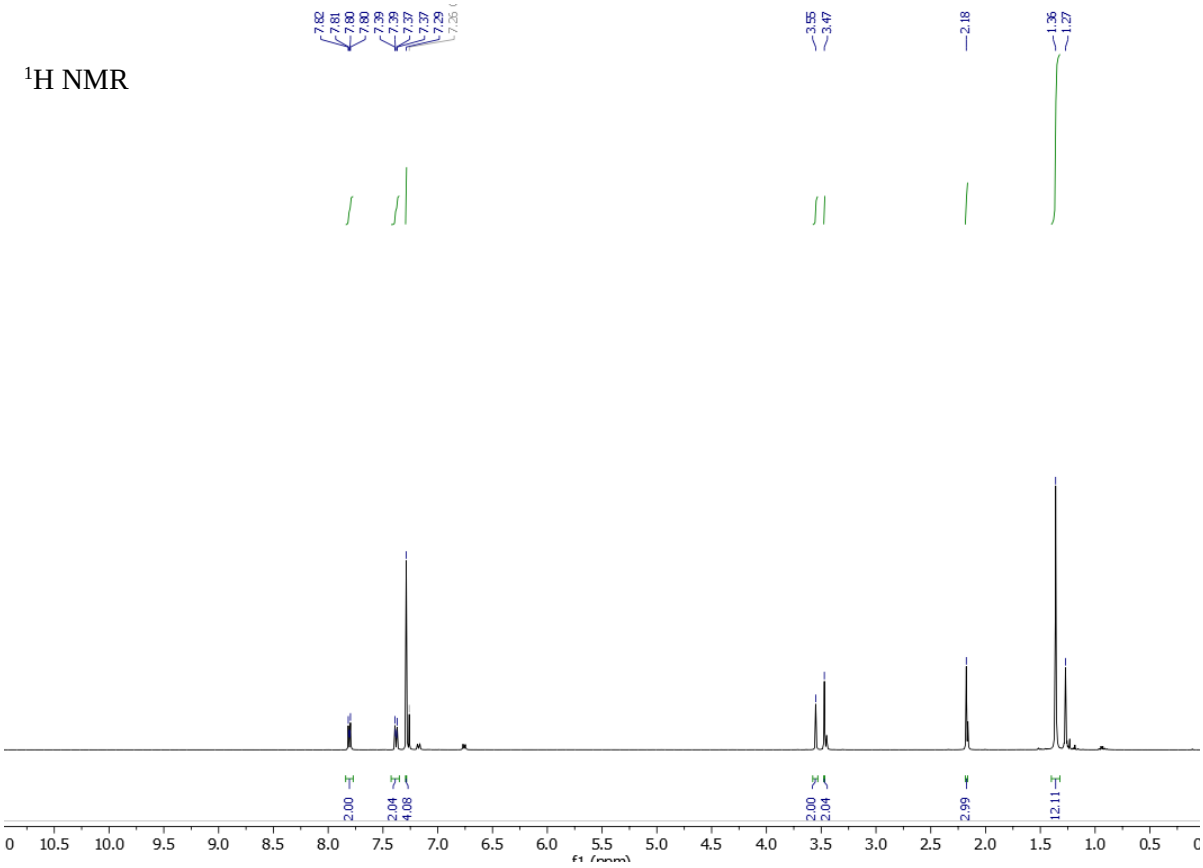


^{13}C NMR

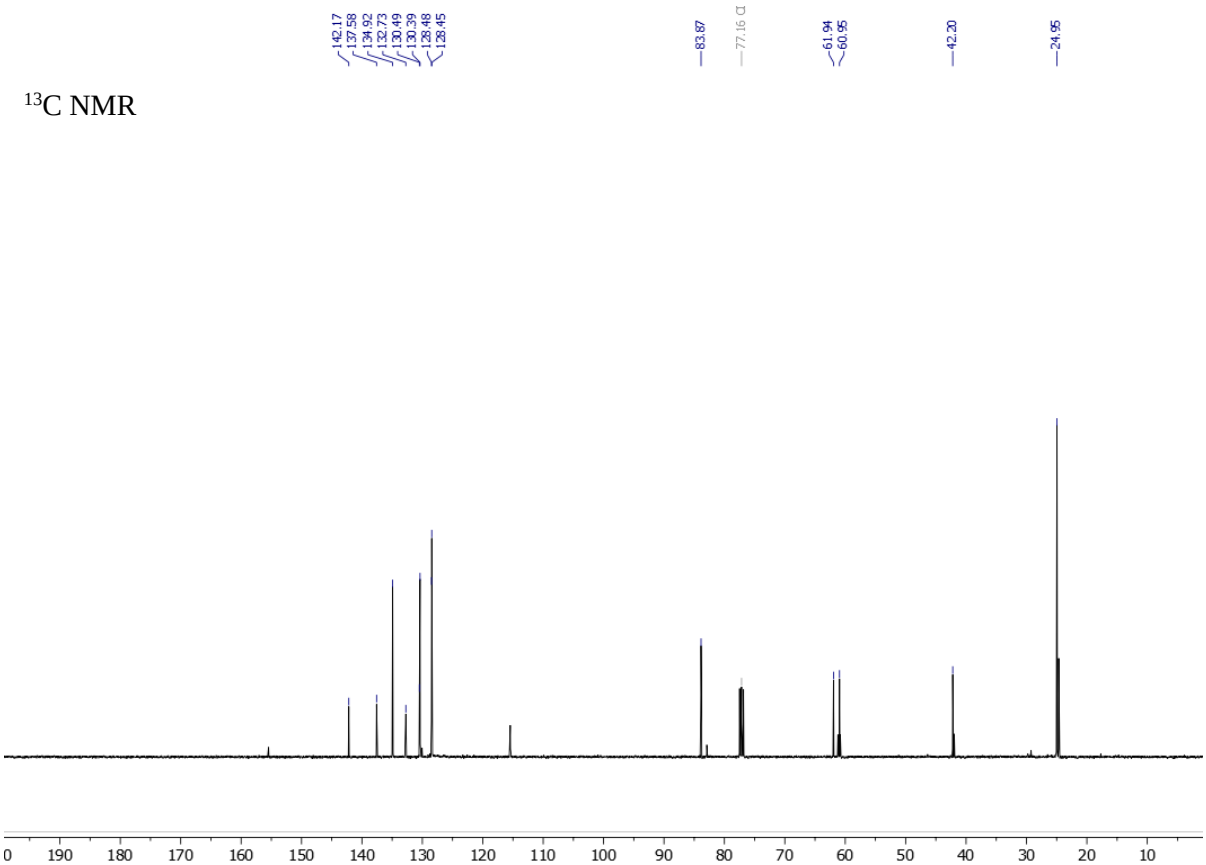


N-(4-chlorobenzyl)-*N*-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (**22**)

^{1}H NMR

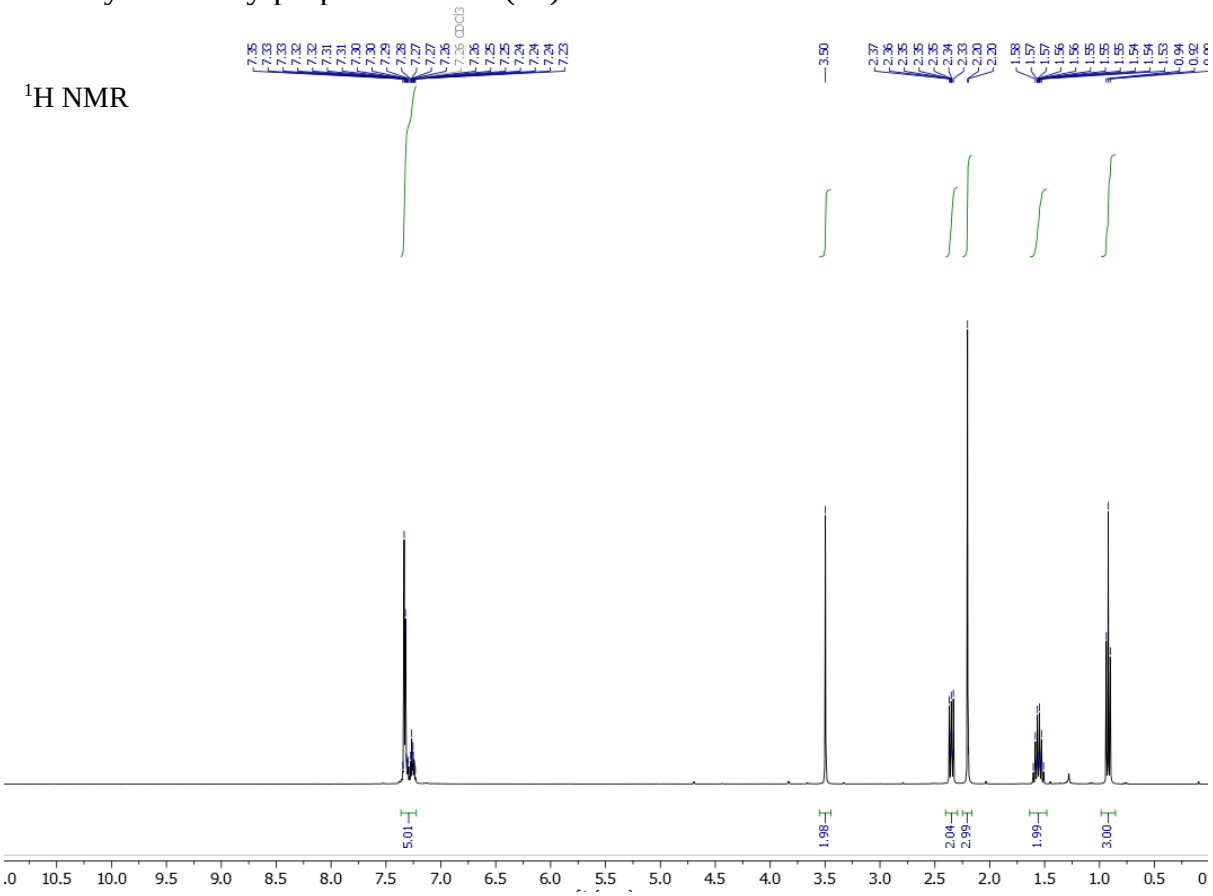


^{13}C NMR

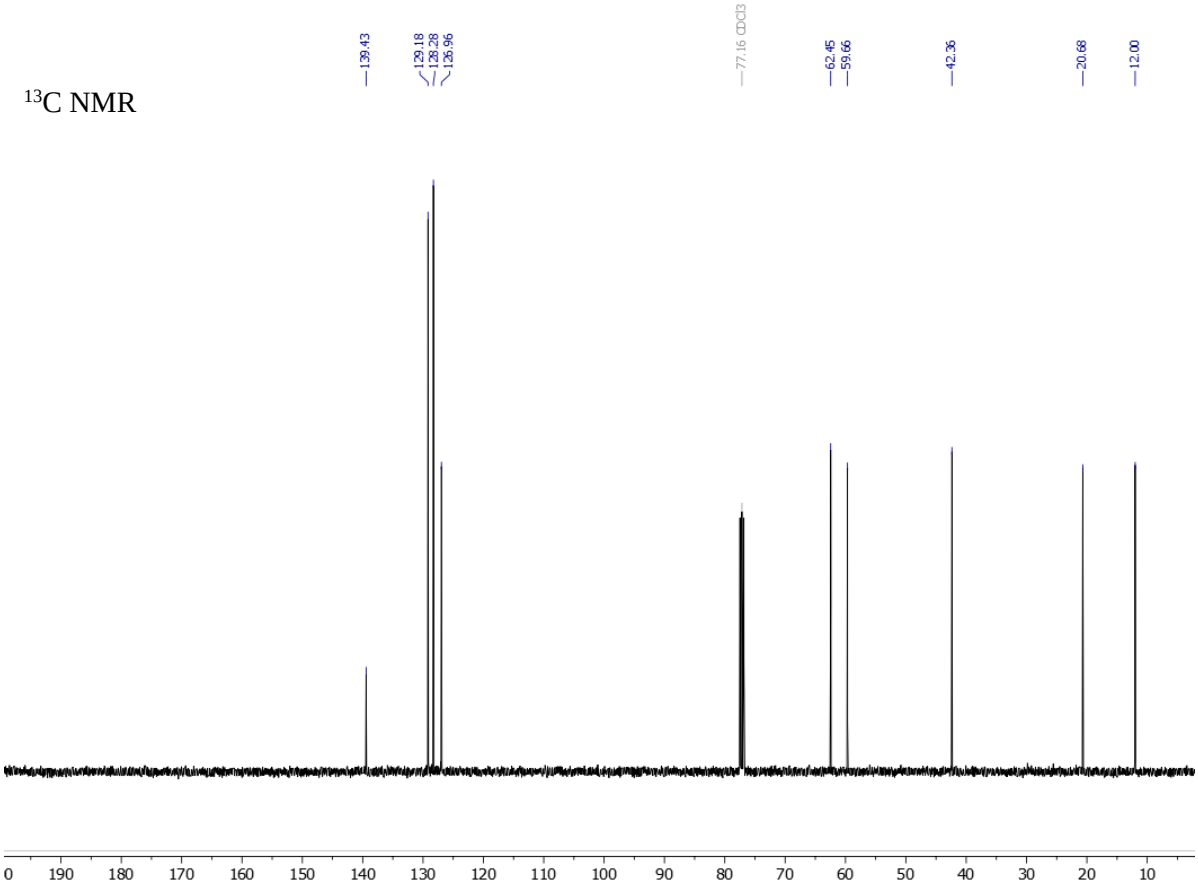


N-benzyl-*N*-methylpropan-1-amine (**23**)

^{1}H NMR

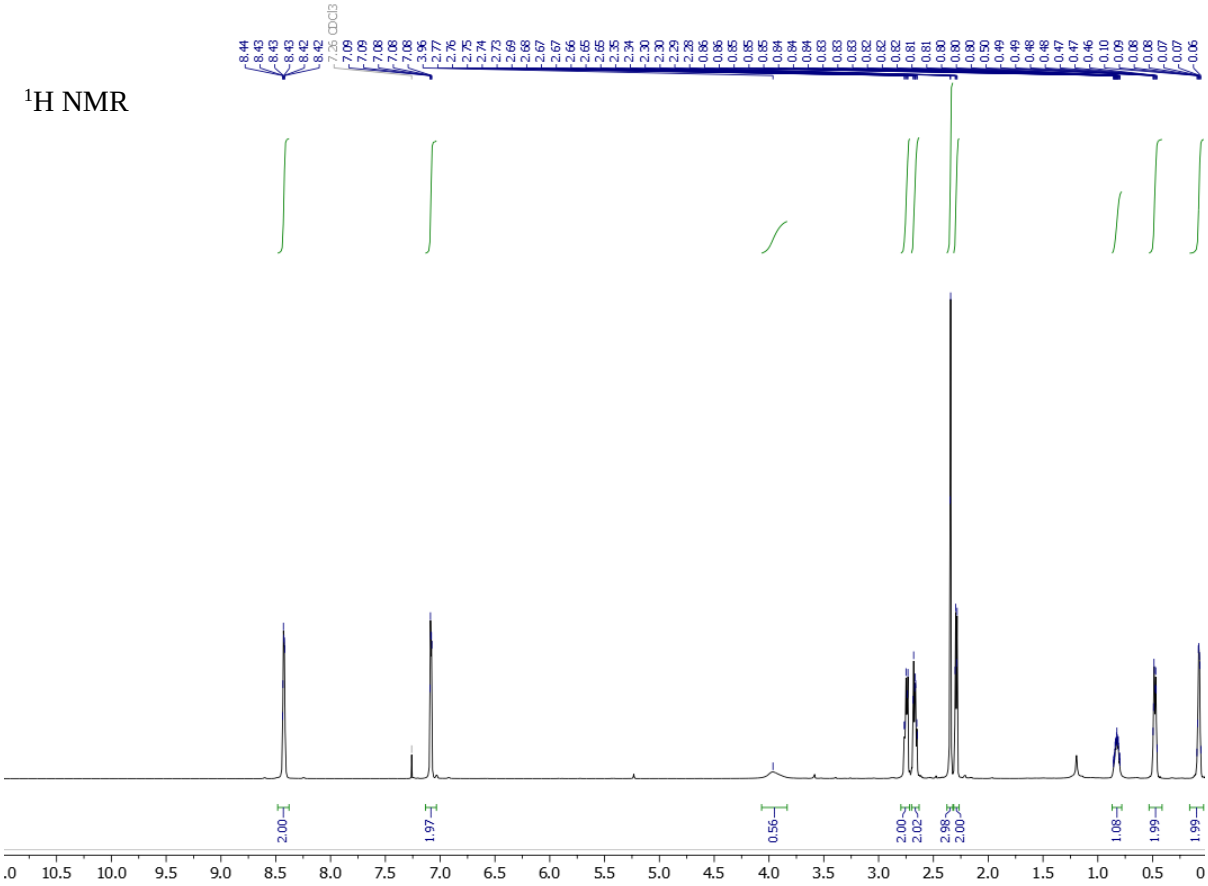


^{13}C NMR

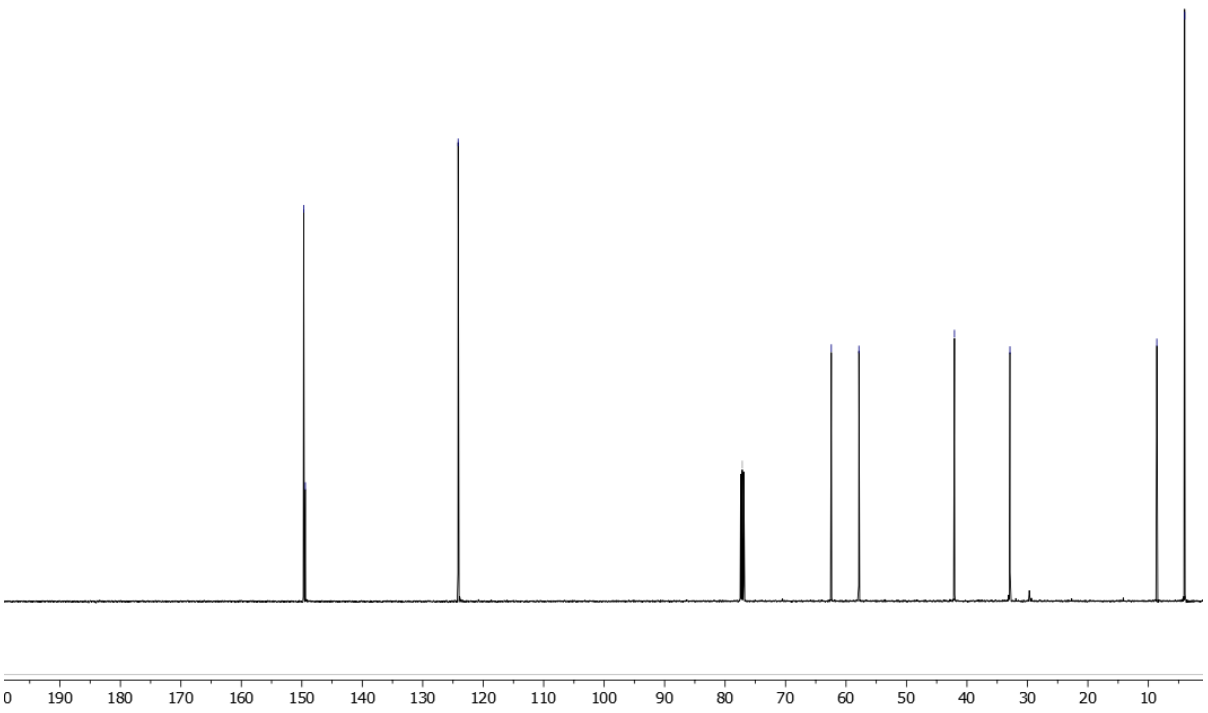


N-(cyclopropylmethyl)-*N*-methyl-2-(pyridin-3-yl)ethan-1-amine (**24**)

^{1}H NMR

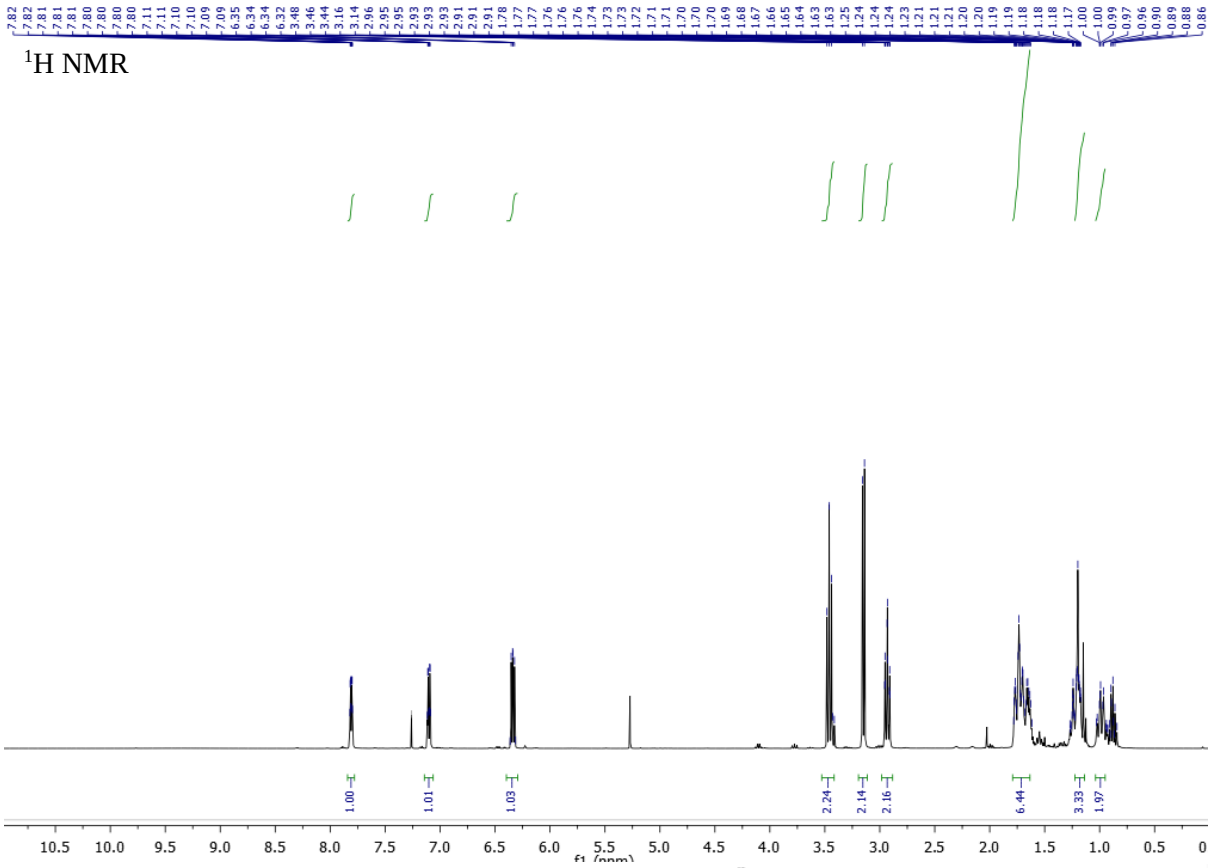


^{13}C NMR

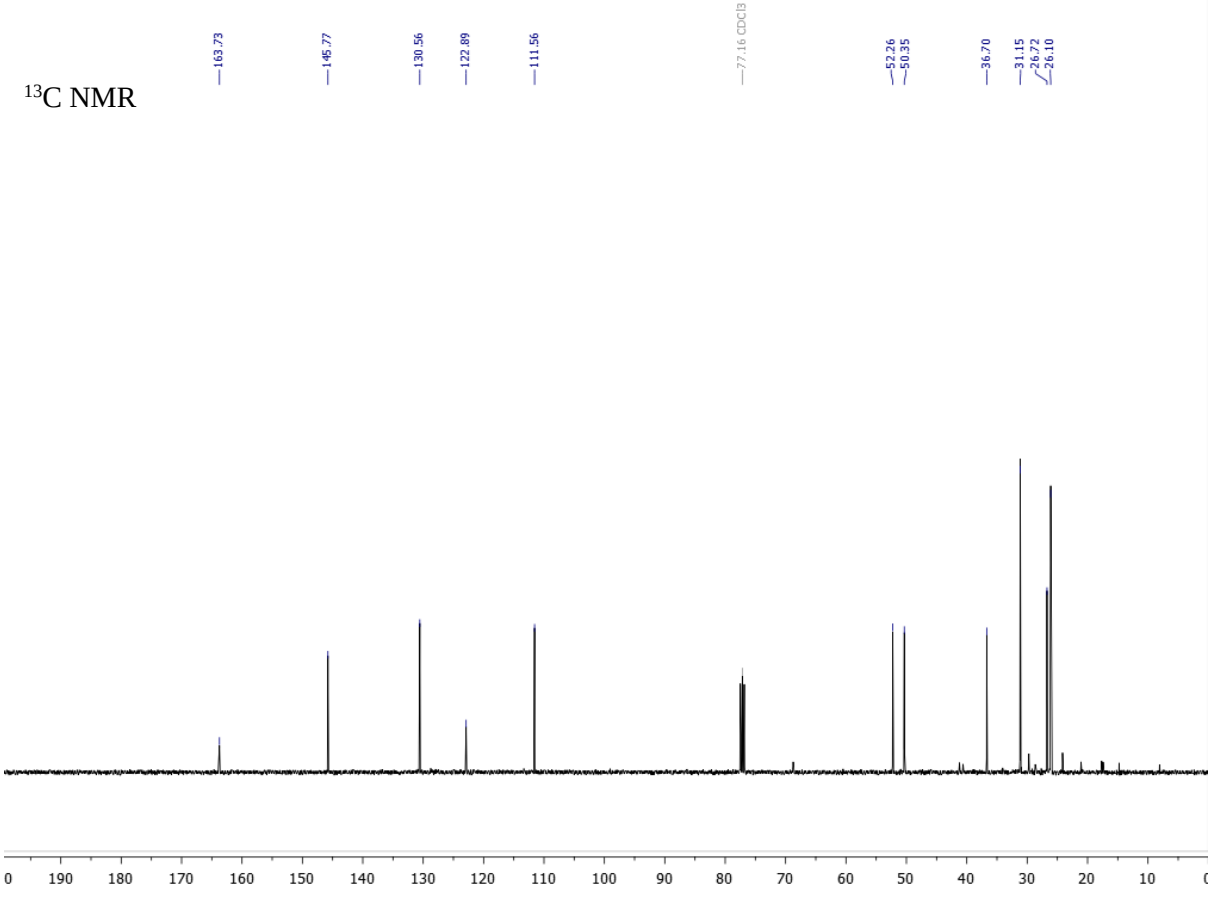


1-(Cyclohexylmethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (**25**)

^{1}H NMR



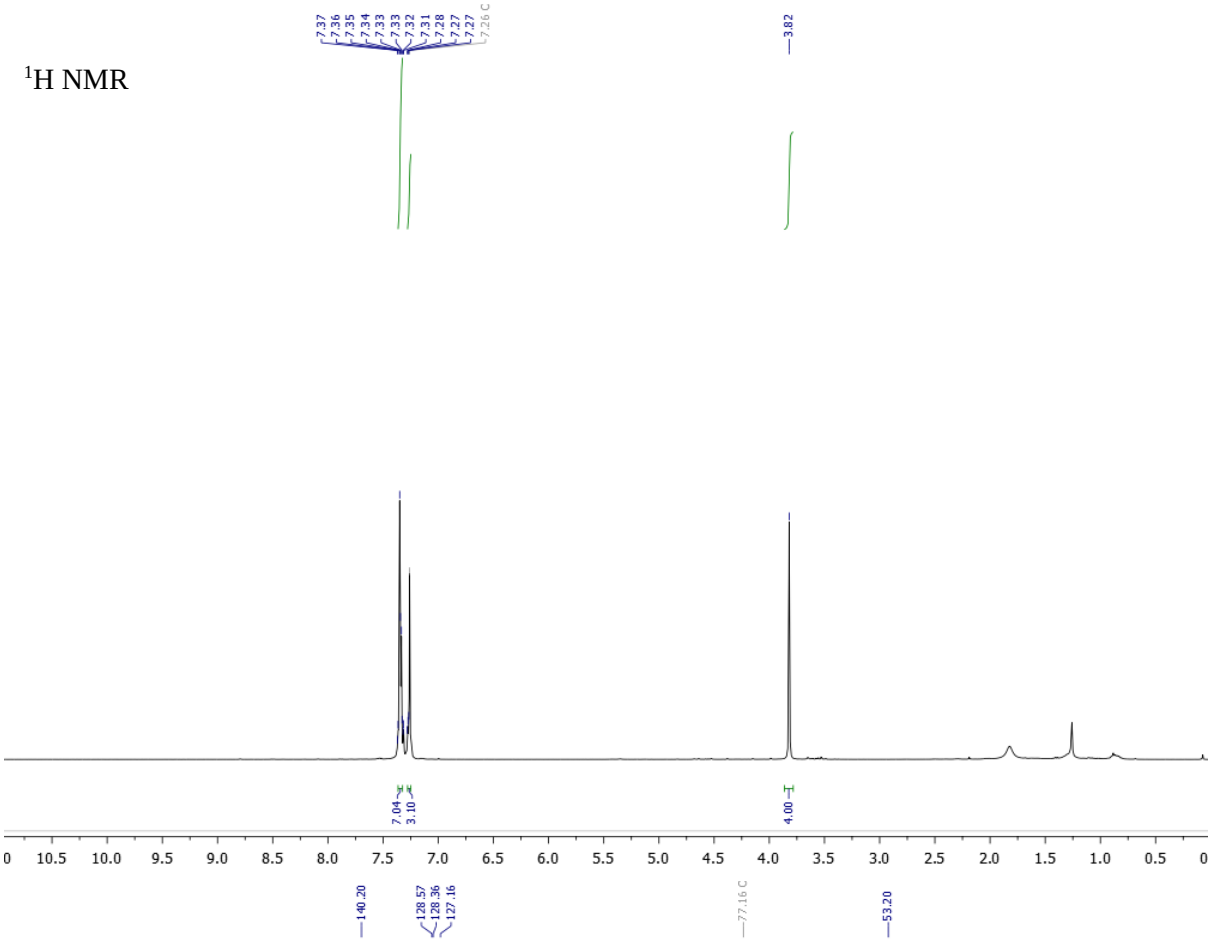
^{13}C NMR



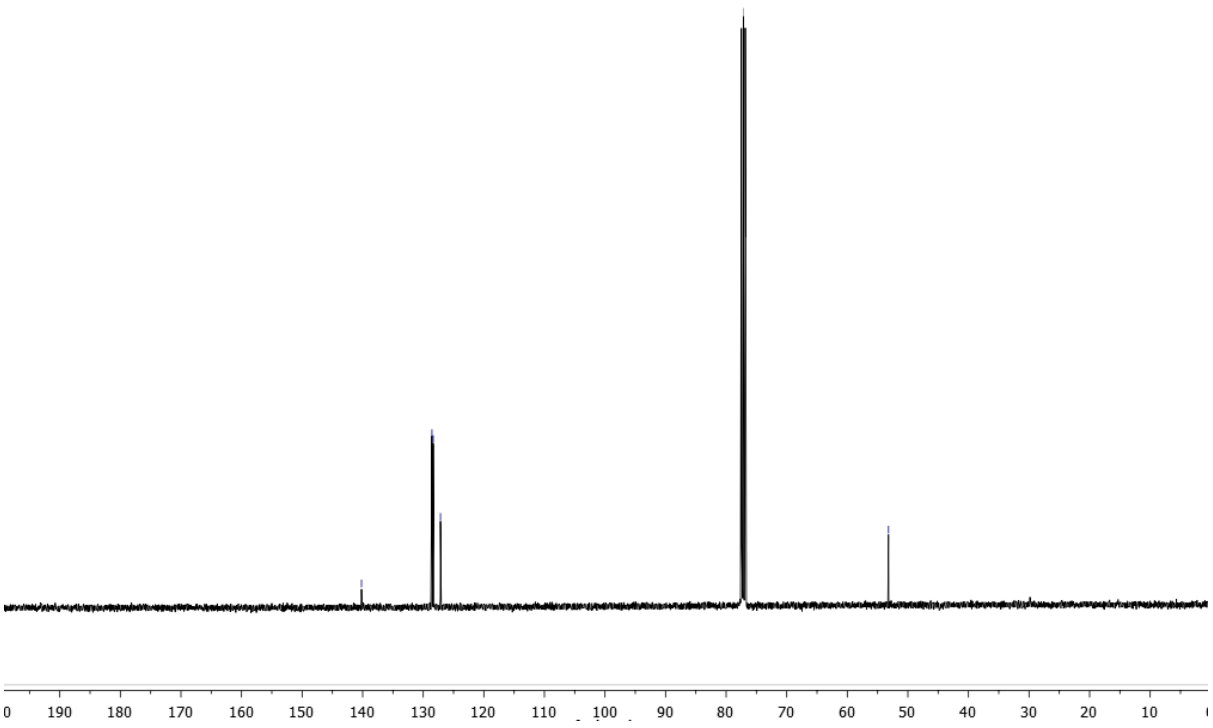
6.3 Large Scale and Selective Reductive Aminations

Dibenzylamine (**26**)

^{1}H NMR

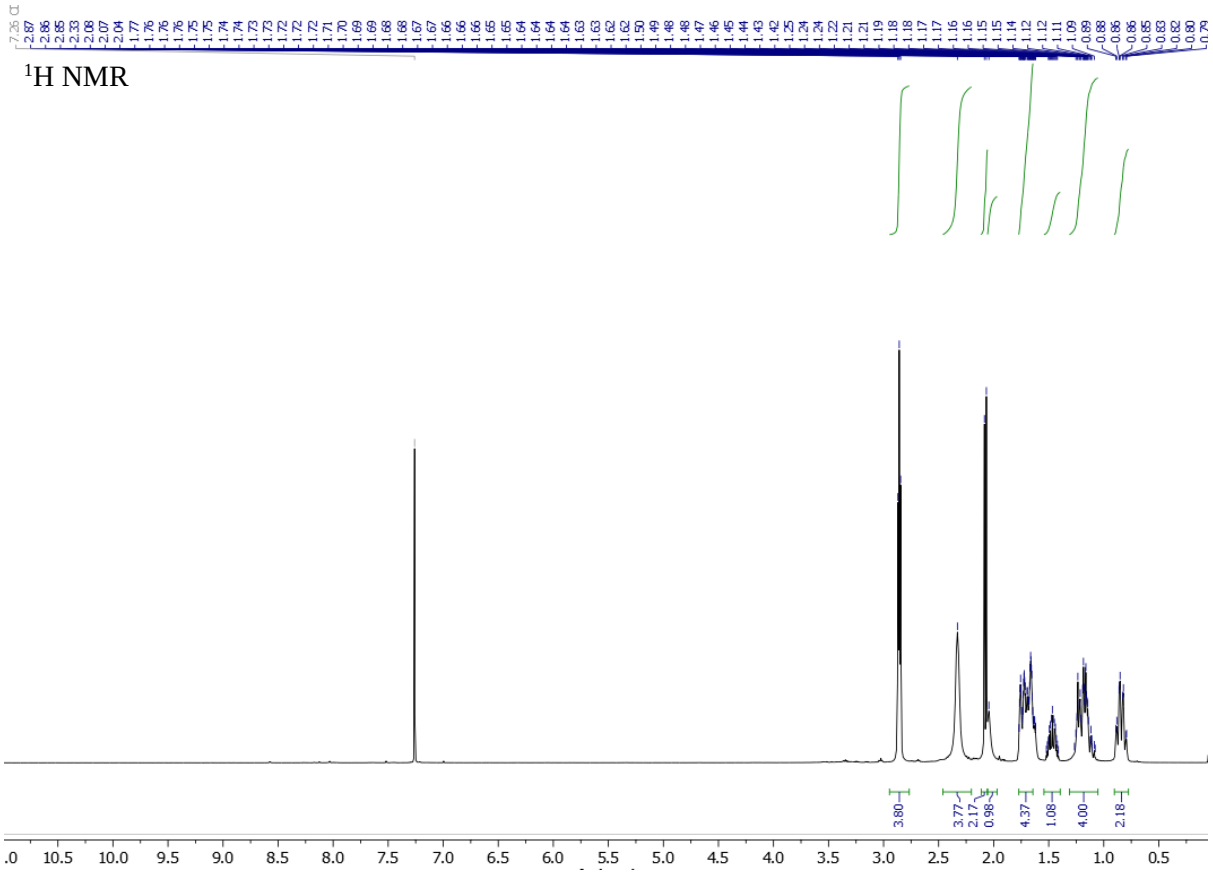


^{13}C NMR

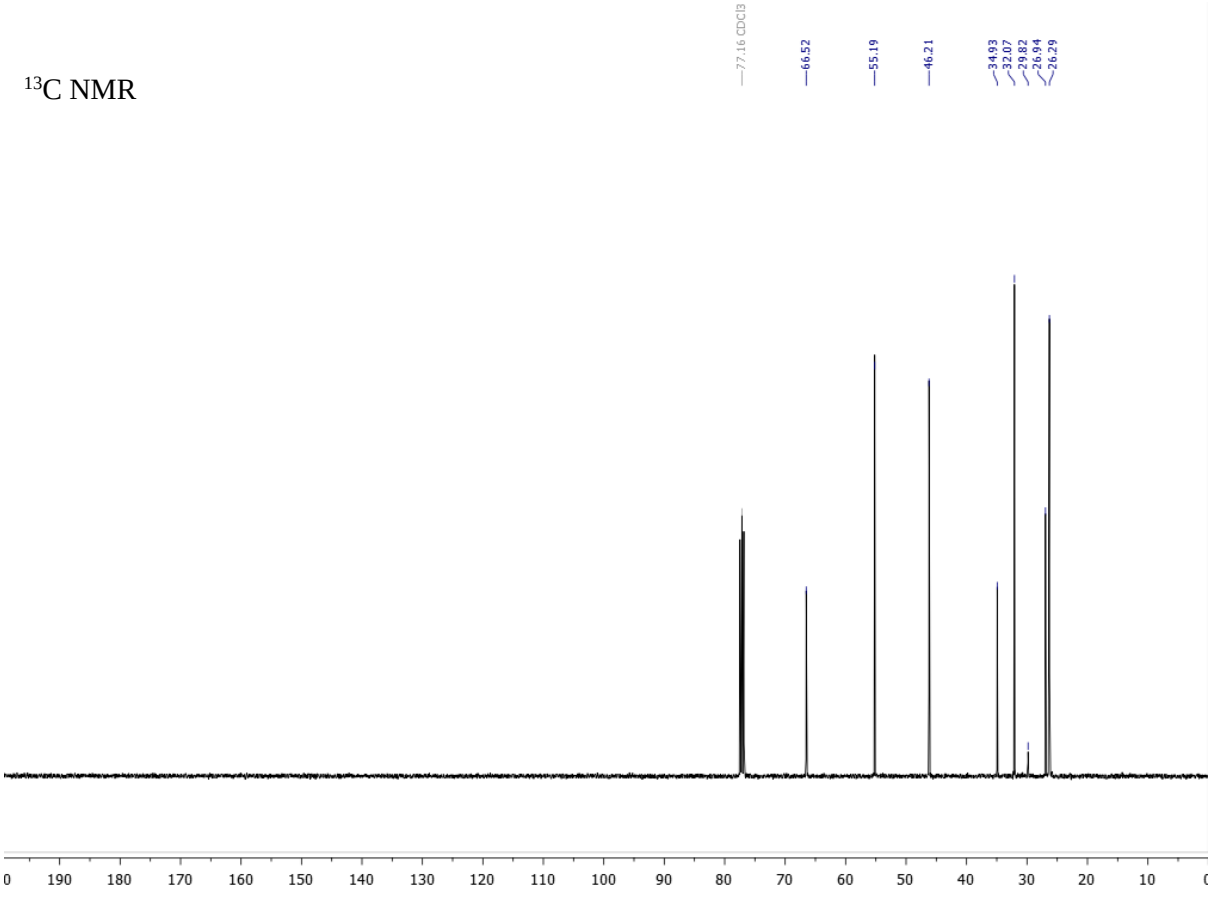


1-(Cyclohexylmethyl)piperazine (**28**)

^{1}H NMR

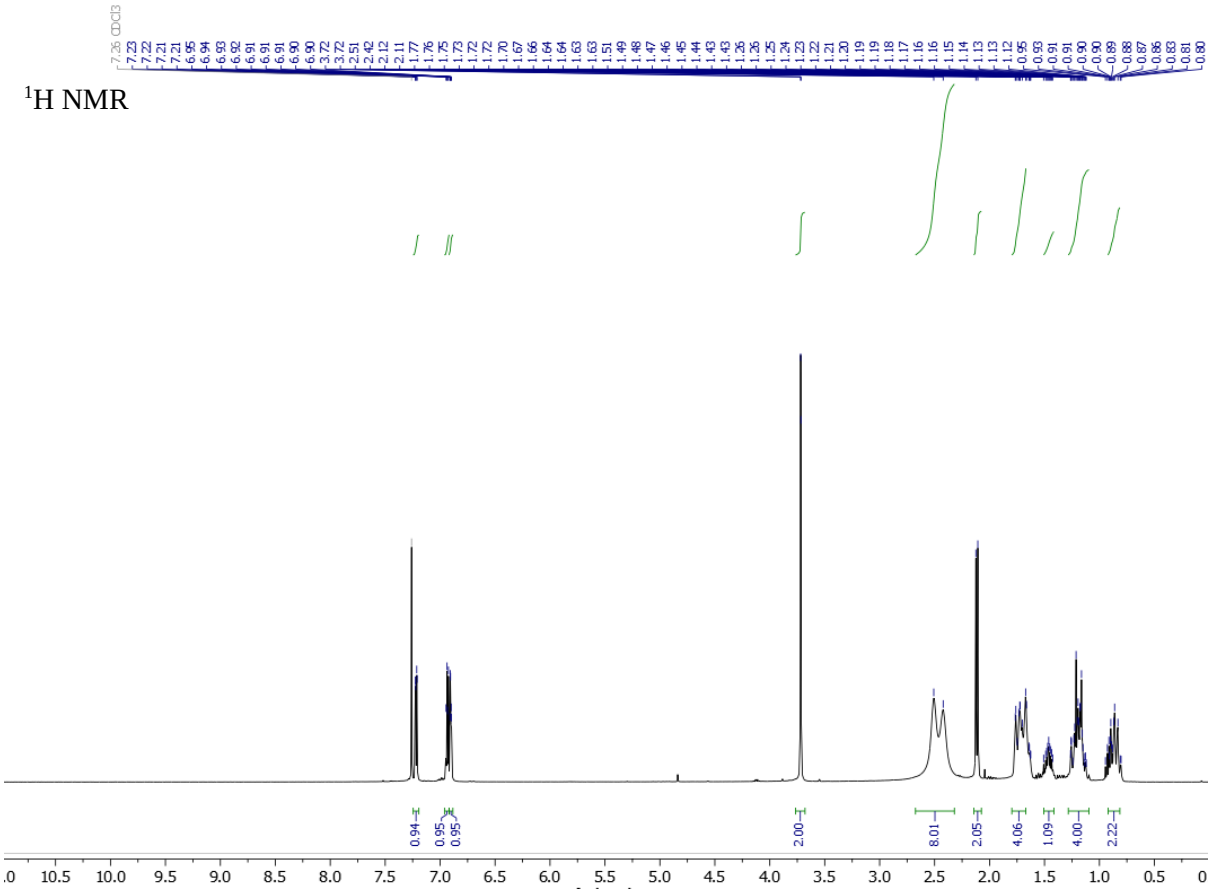


^{13}C NMR

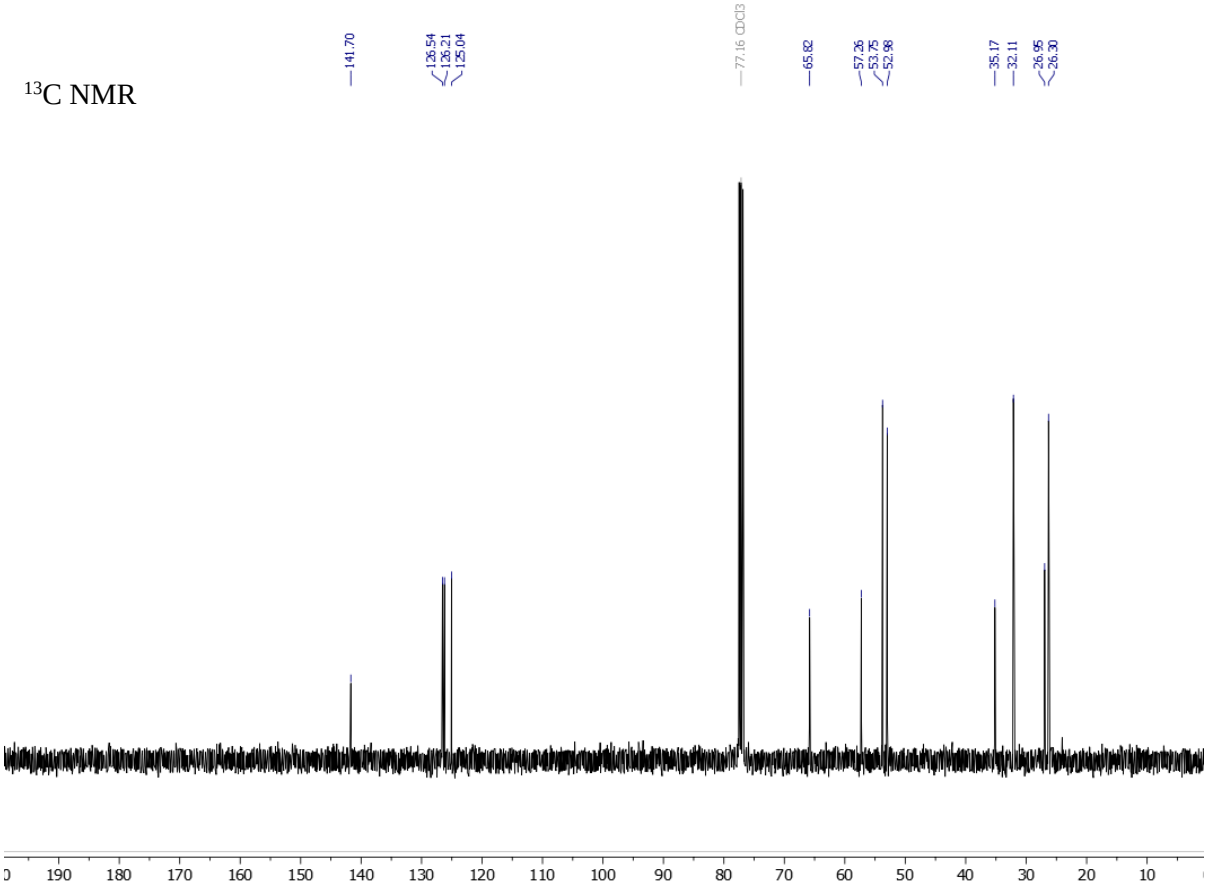


1-(cyclohexylmethyl)-4-(thiophen-2-ylmethyl)piperazine (**29**)

^{1}H NMR

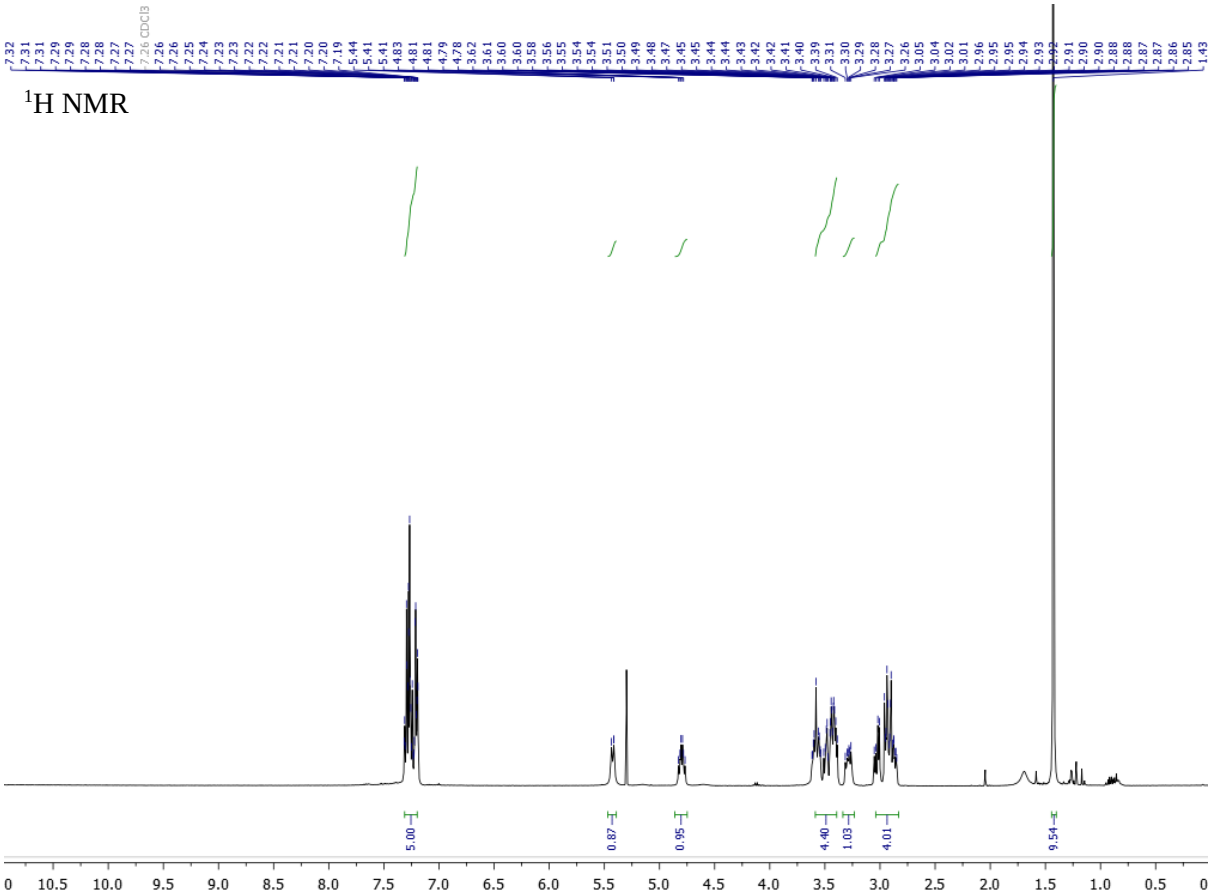


^{13}C NMR

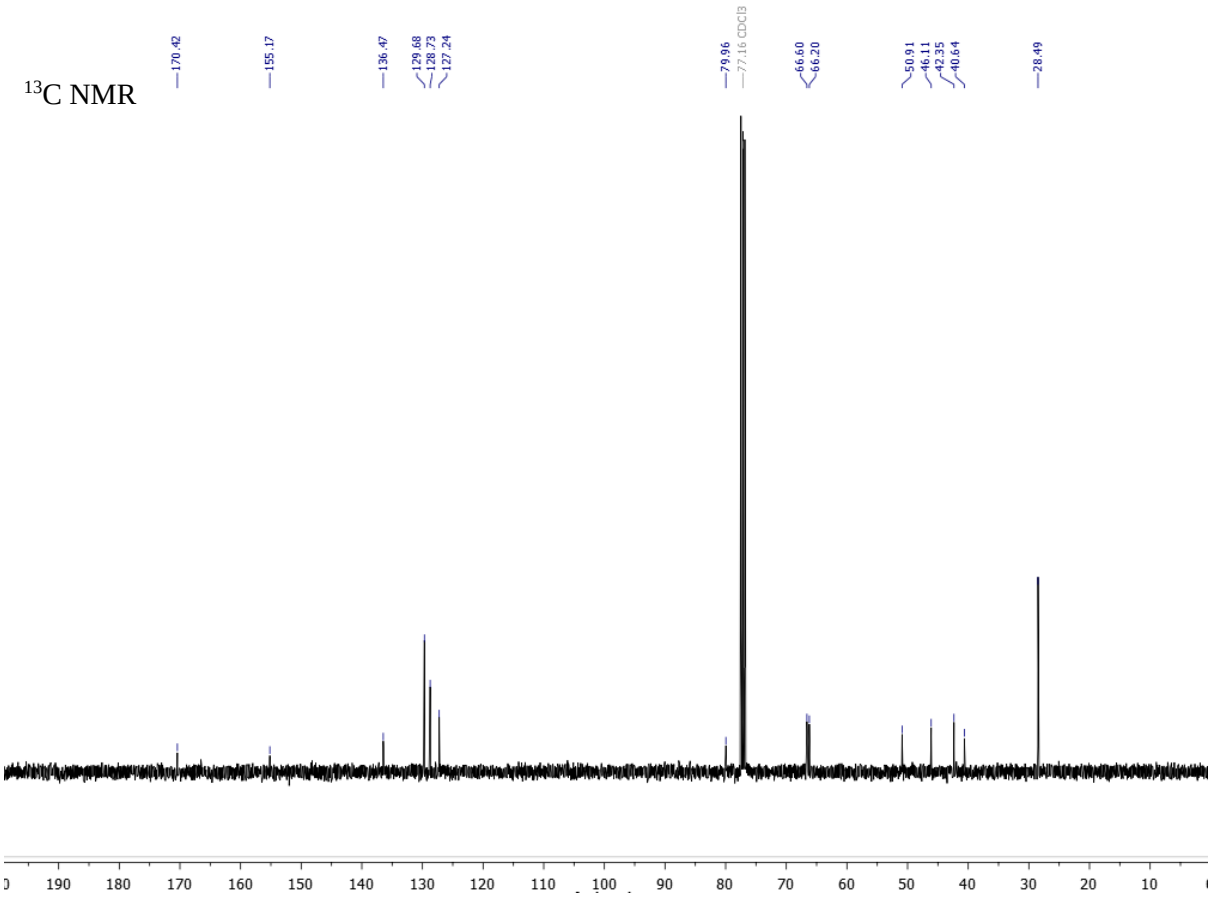


tert-Butyl (*S*)-(1-morpholino-1-oxo-3-phenylpropan-2-yl)carbamate (**30**)

^{1}H NMR

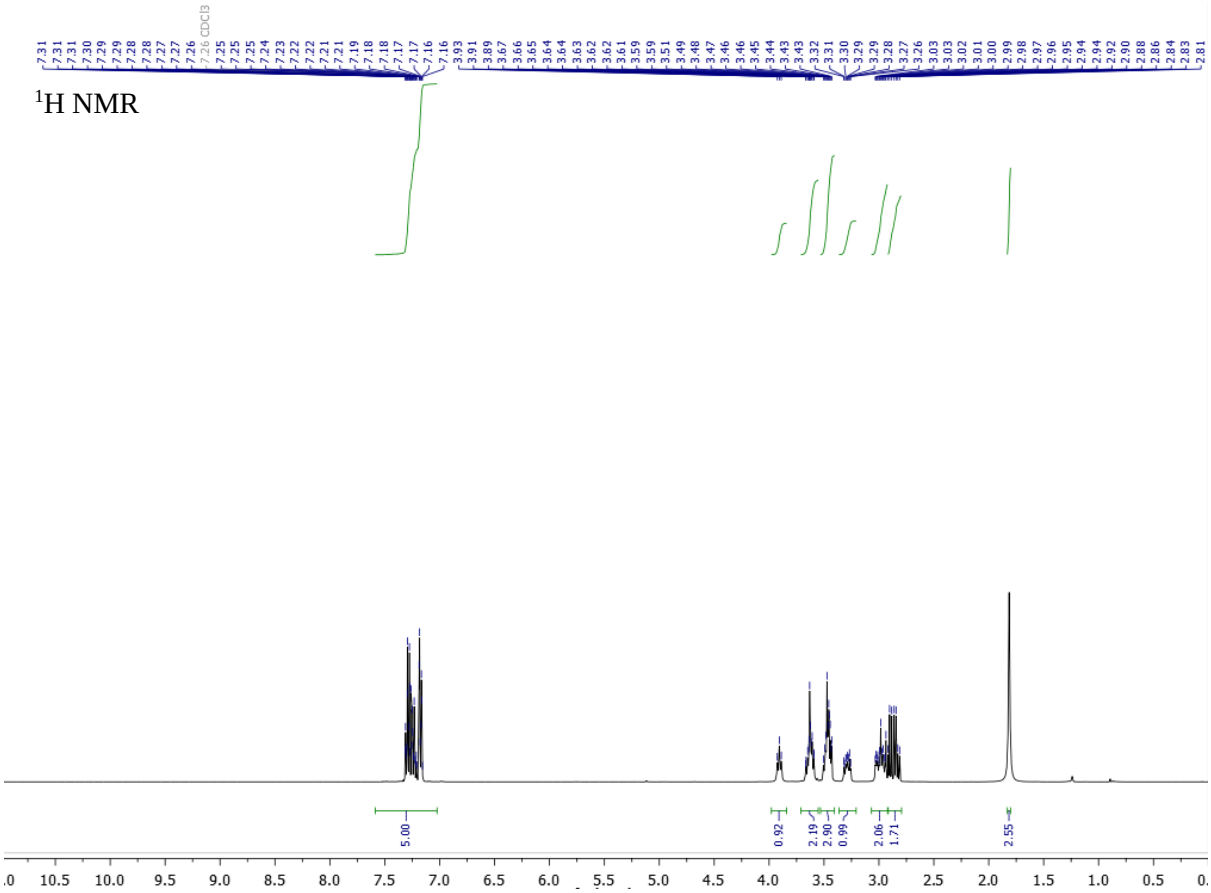


^{13}C NMR

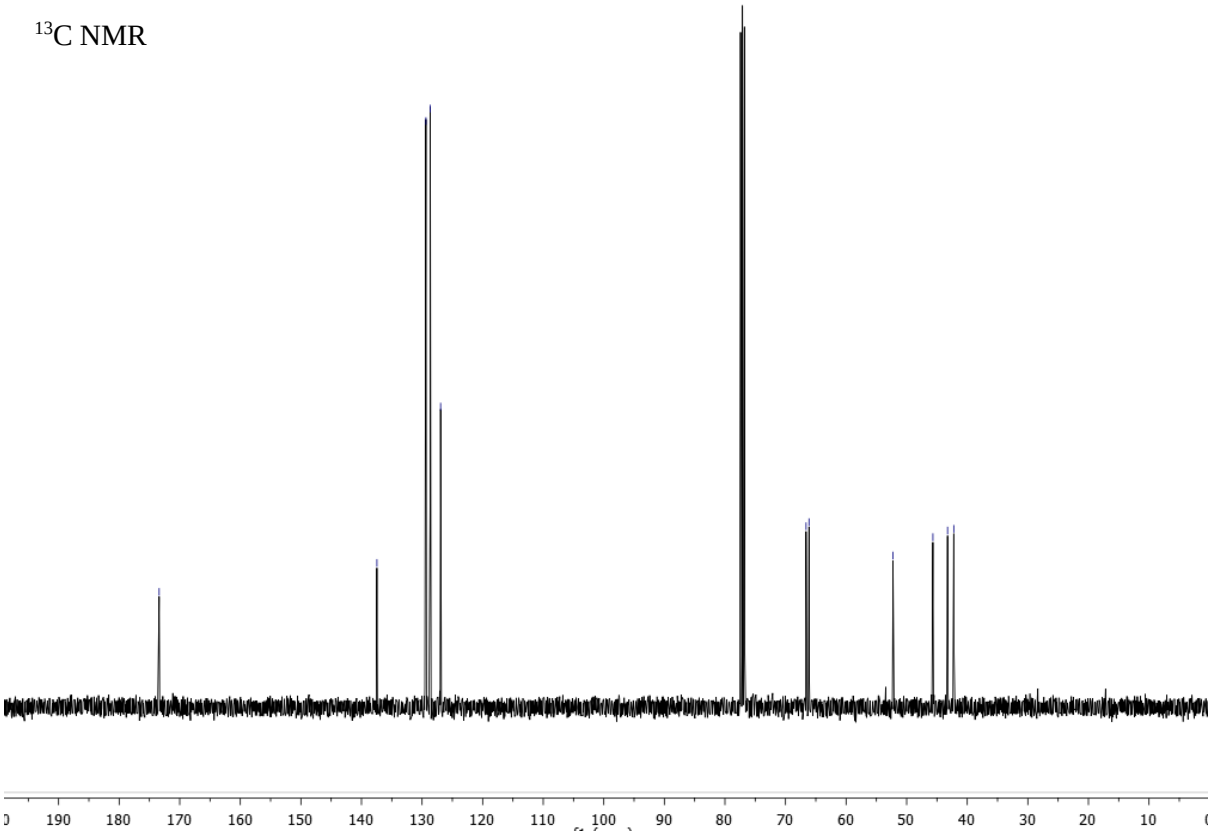


(*S*)-2-amino-1-morpholino-3-phenylpropan-1-one (**31**)

^{1}H NMR

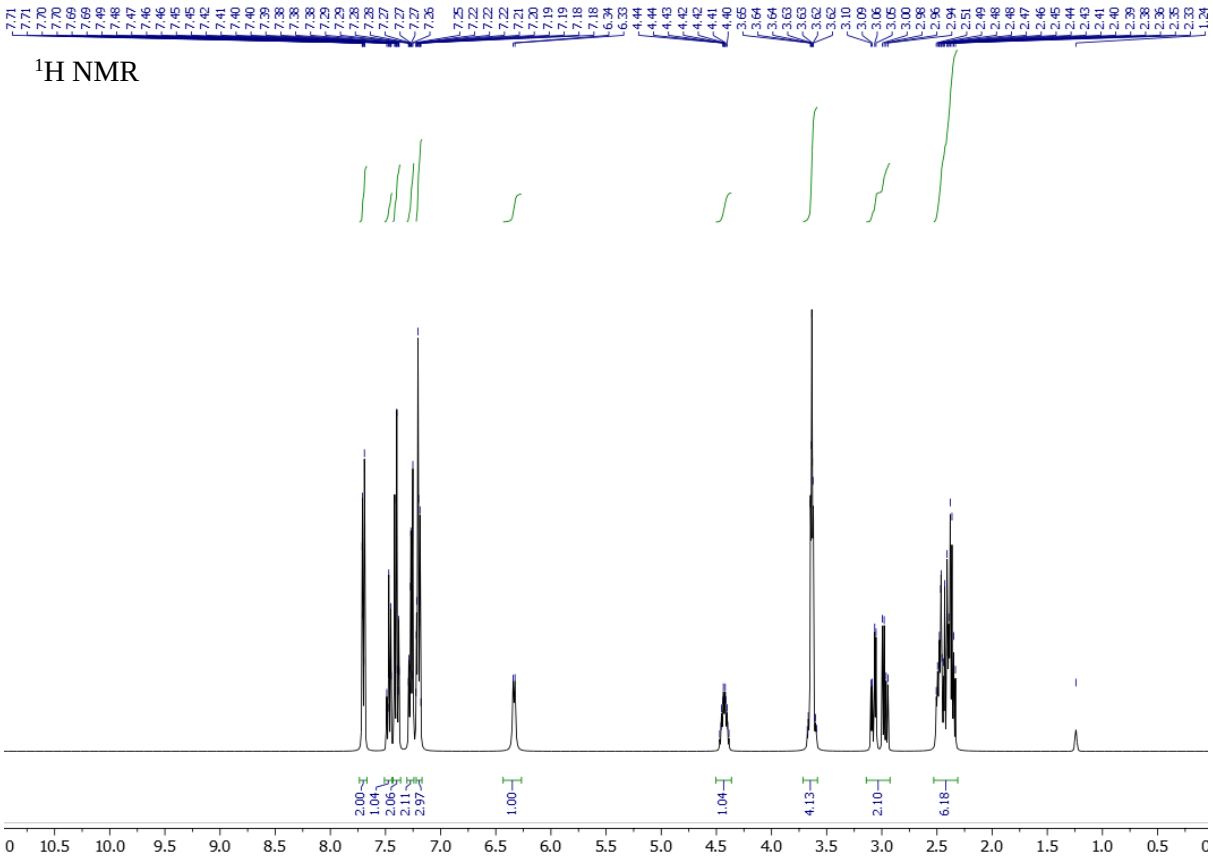


^{13}C NMR

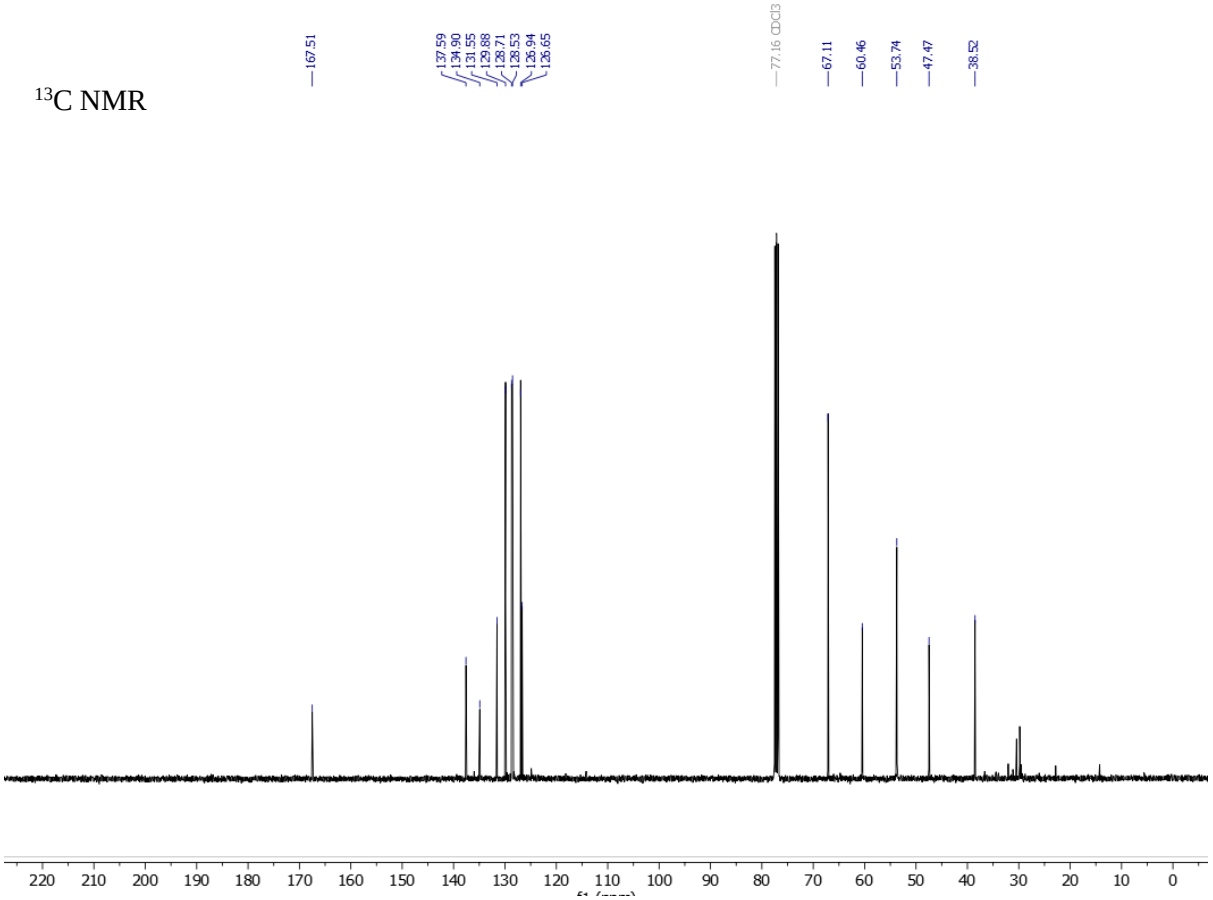


(*S*)-*N*-(1-Morpholino-3-phenylpropan-2-yl)benzamide (**32**)

^{1}H NMR



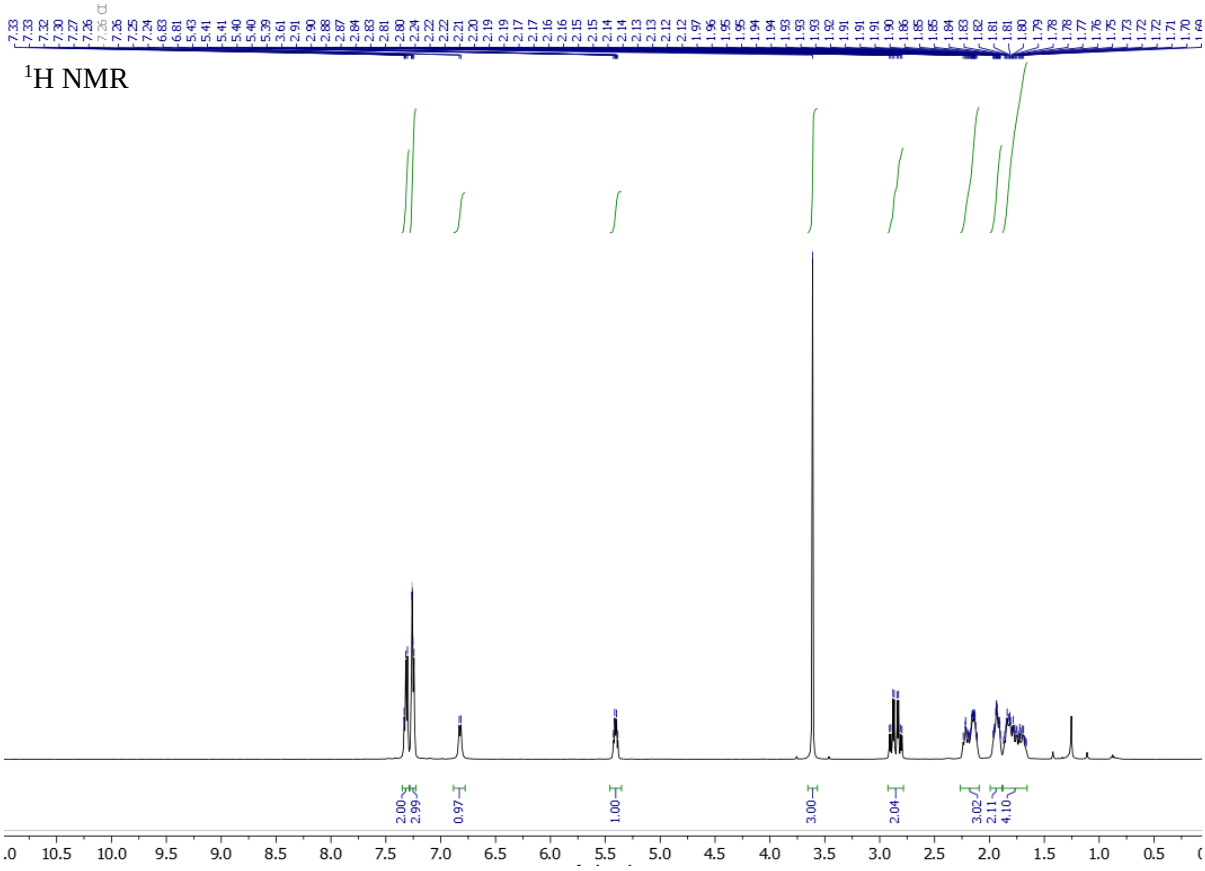
^{13}C NMR



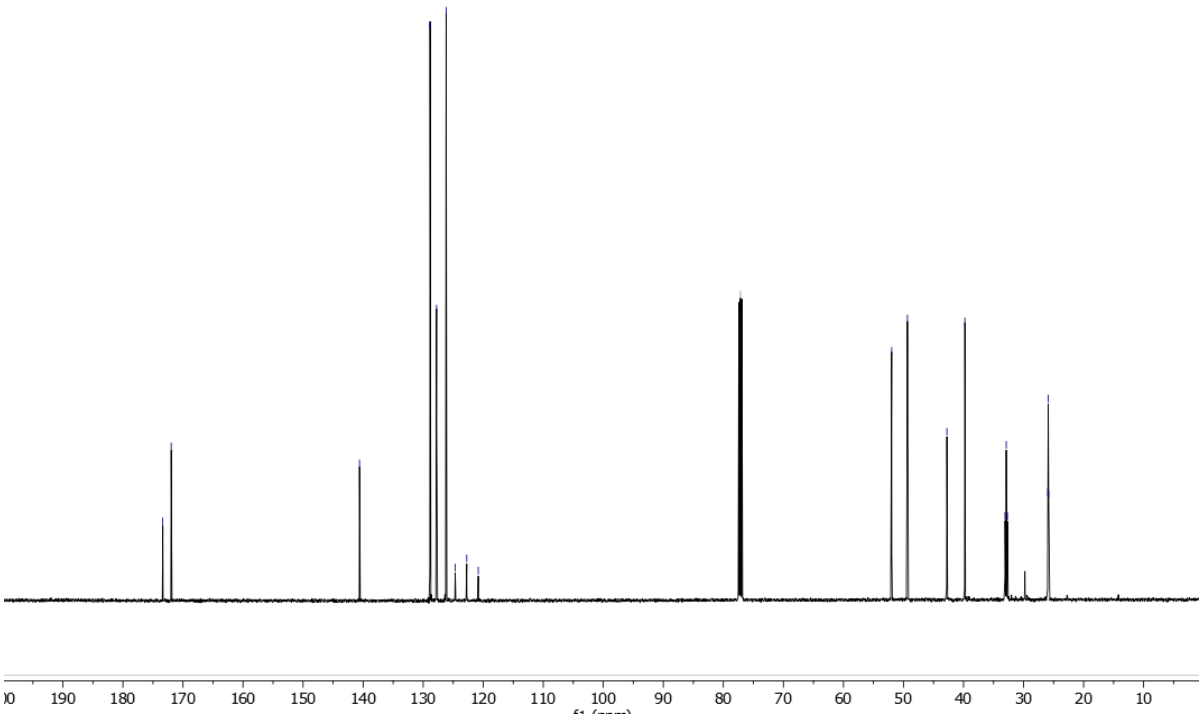
6.4 Maraviroc

Methyl (*S*)-3-(4,4-difluorocyclohexane-1-carboxamido)-3-phenylpropanoate (SI-**3**)

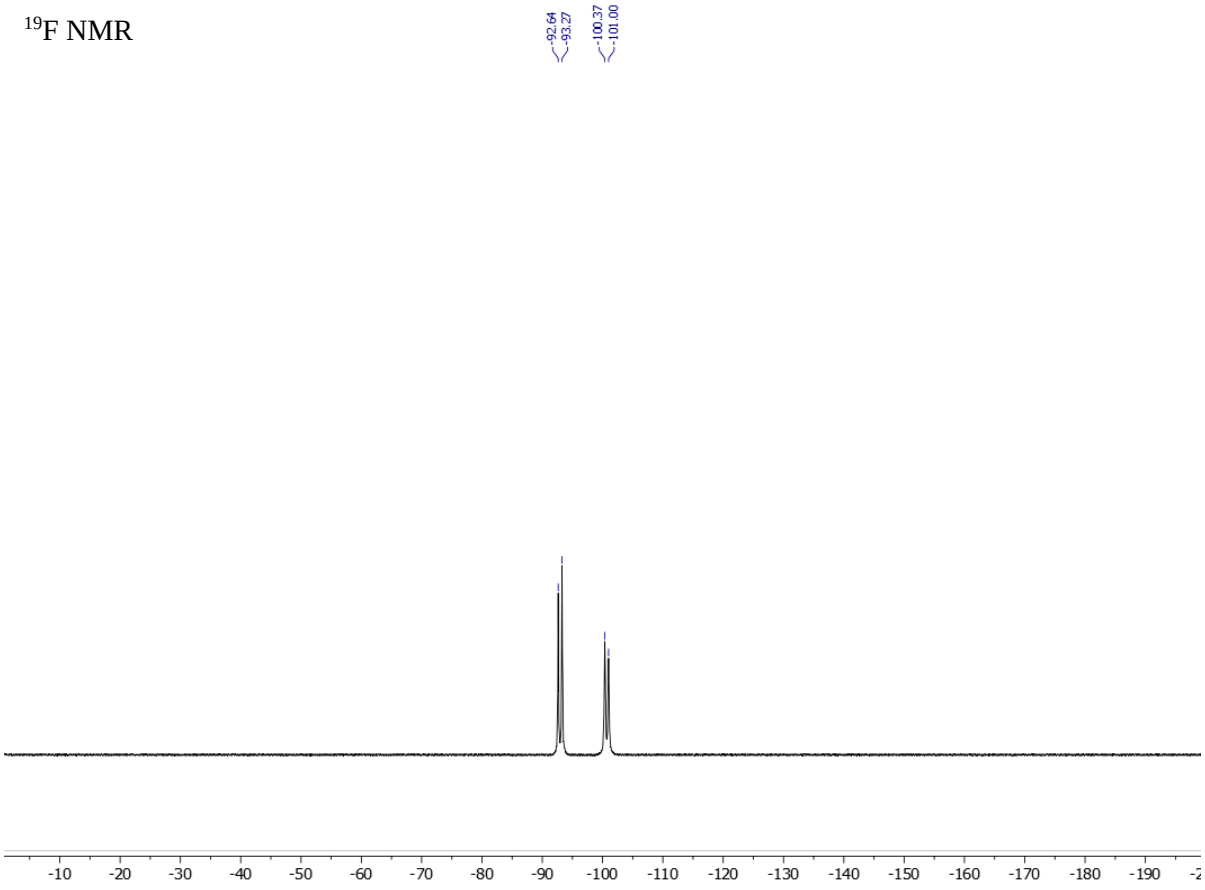
^{1}H NMR



^{13}C NMR

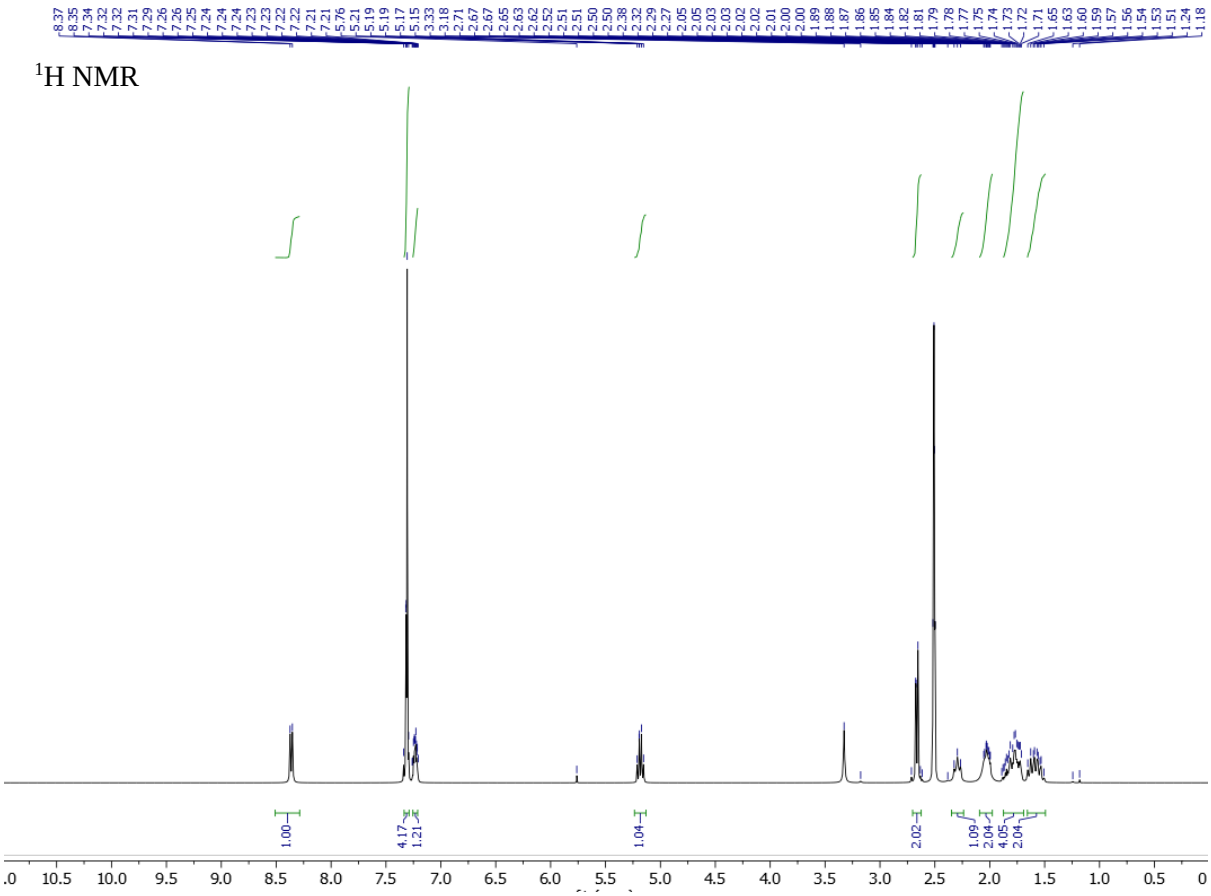


^{19}F NMR

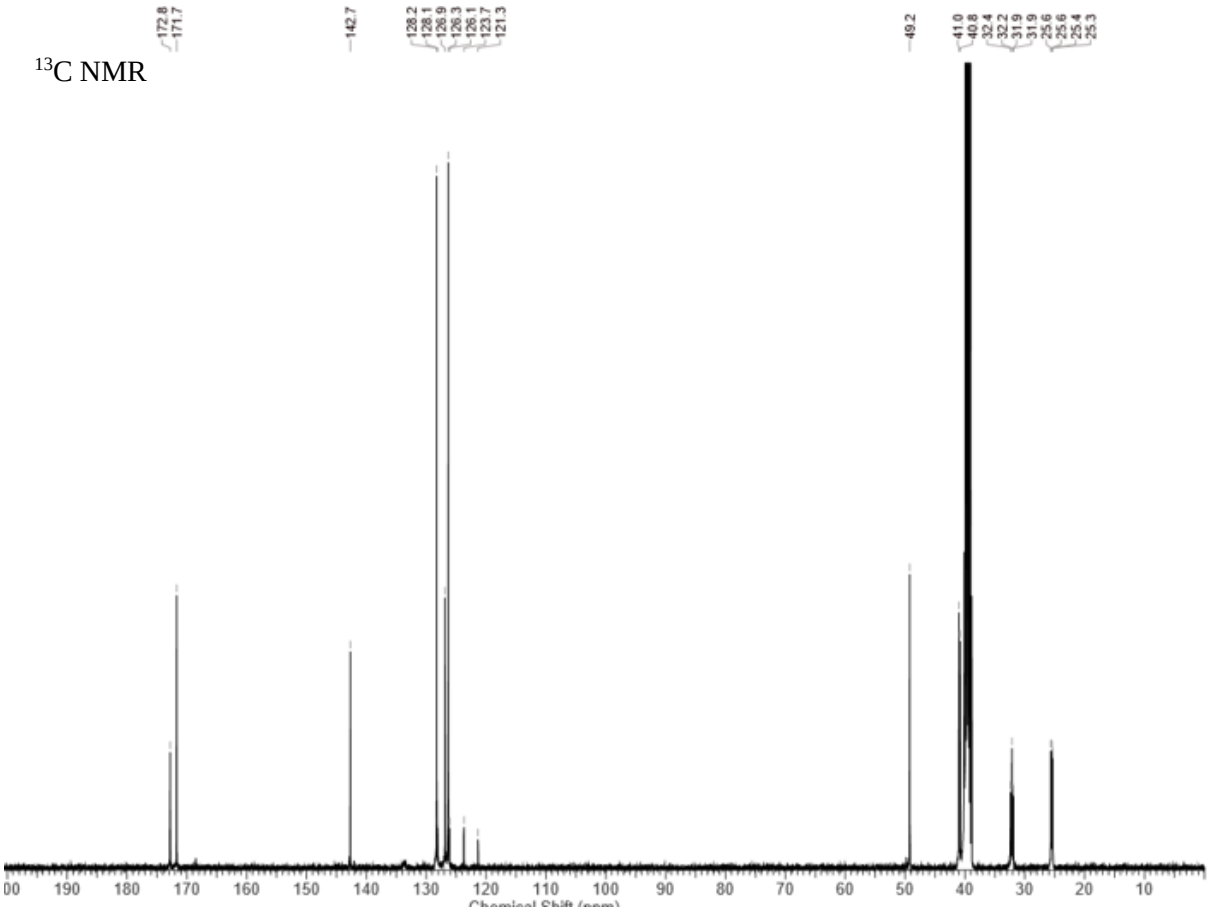

-92.64
-93.27
-100.37
-101.00
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

(*S*)-3-(4,4-Difluorocyclohexanecarboxamido)-3-phenylpropanoic acid (**34**)

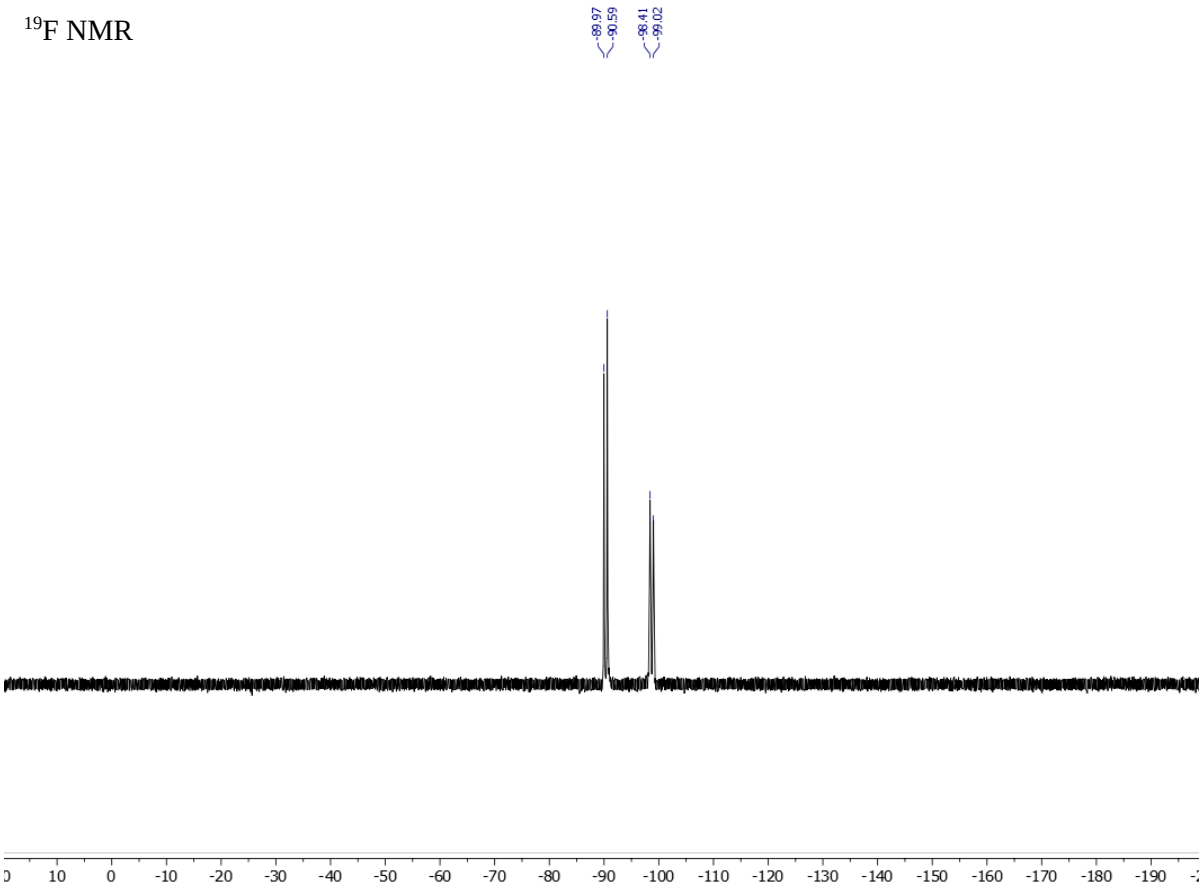
^{1}H NMR



^{13}C NMR

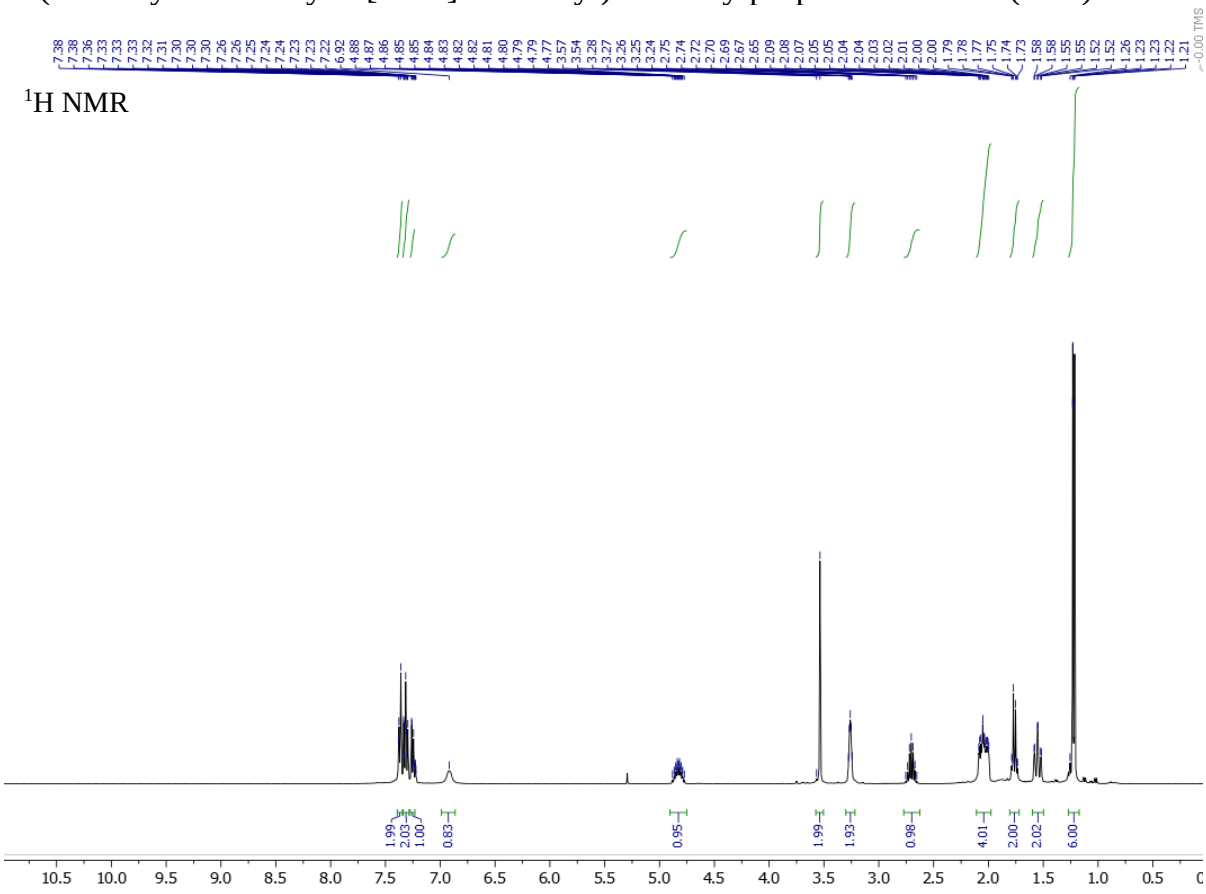


^{19}F NMR

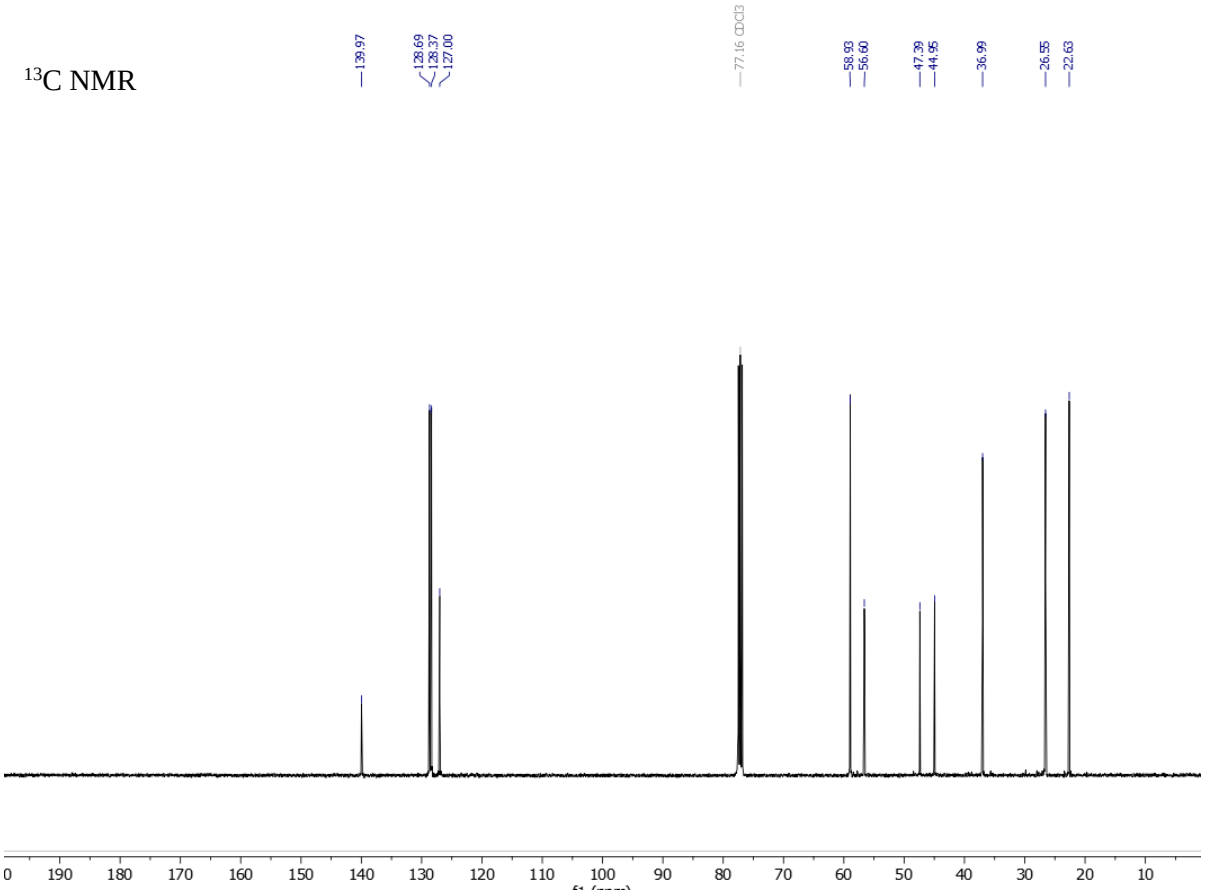

-89.97
-90.59
-98.41
-99.02
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

N-(8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl)-2-methylpropanethioamide (**SI-4**)

^{1}H NMR

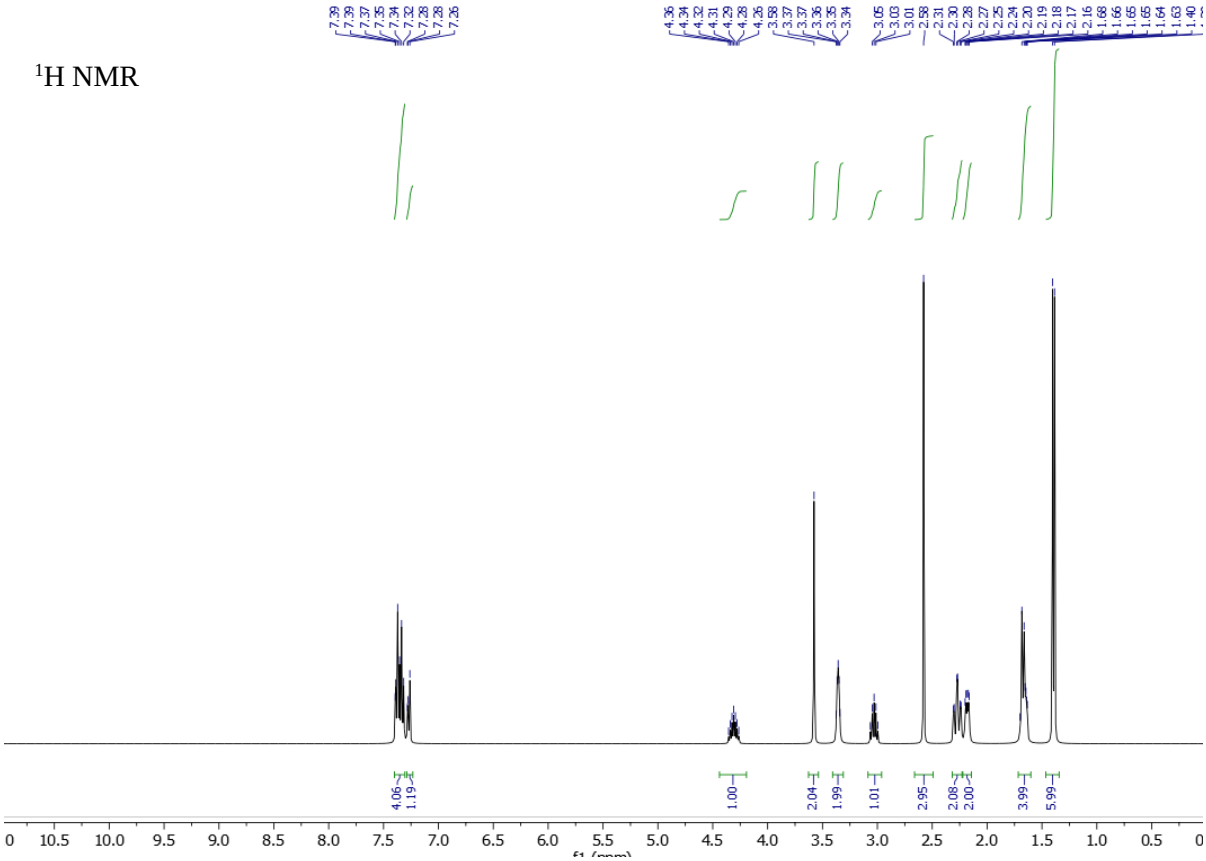


^{13}C NMR

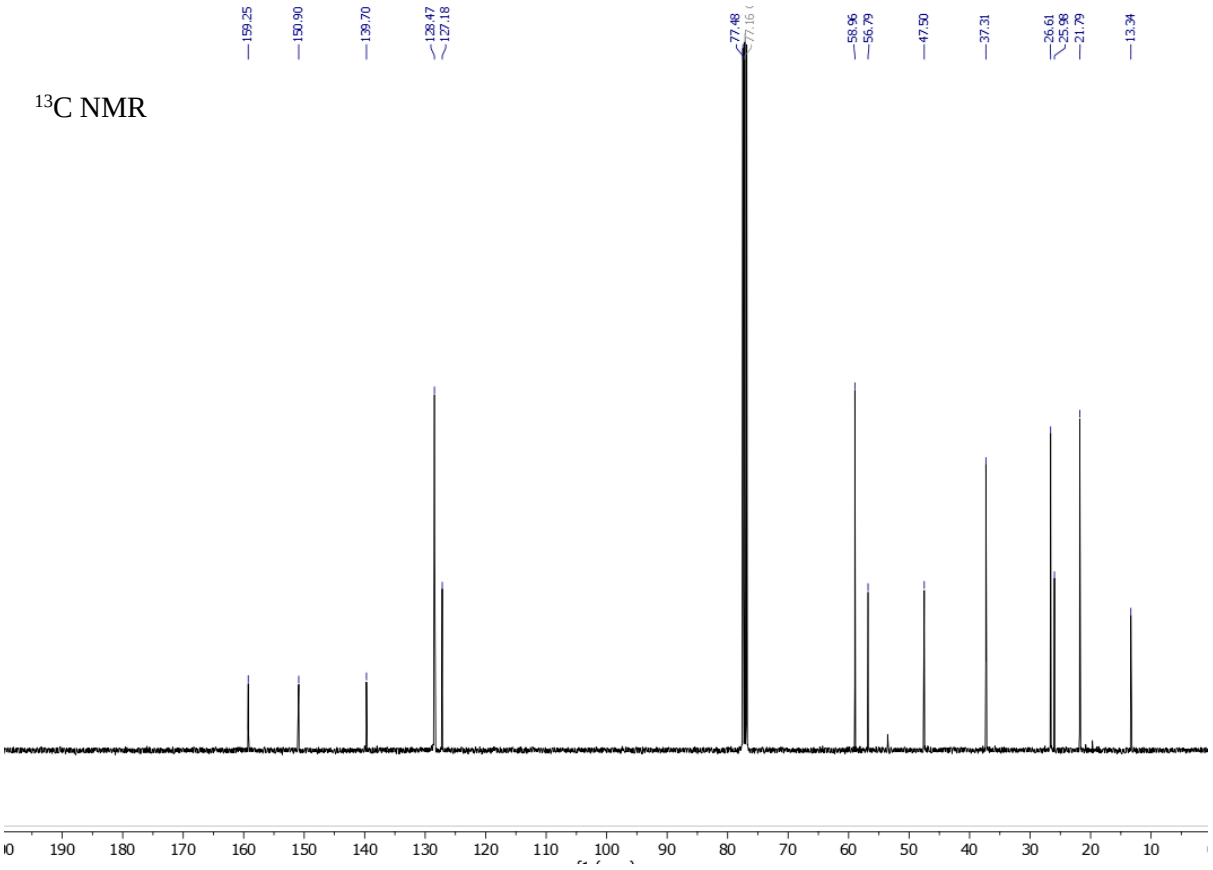


8-Benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (**SI-5**)

^{1}H NMR

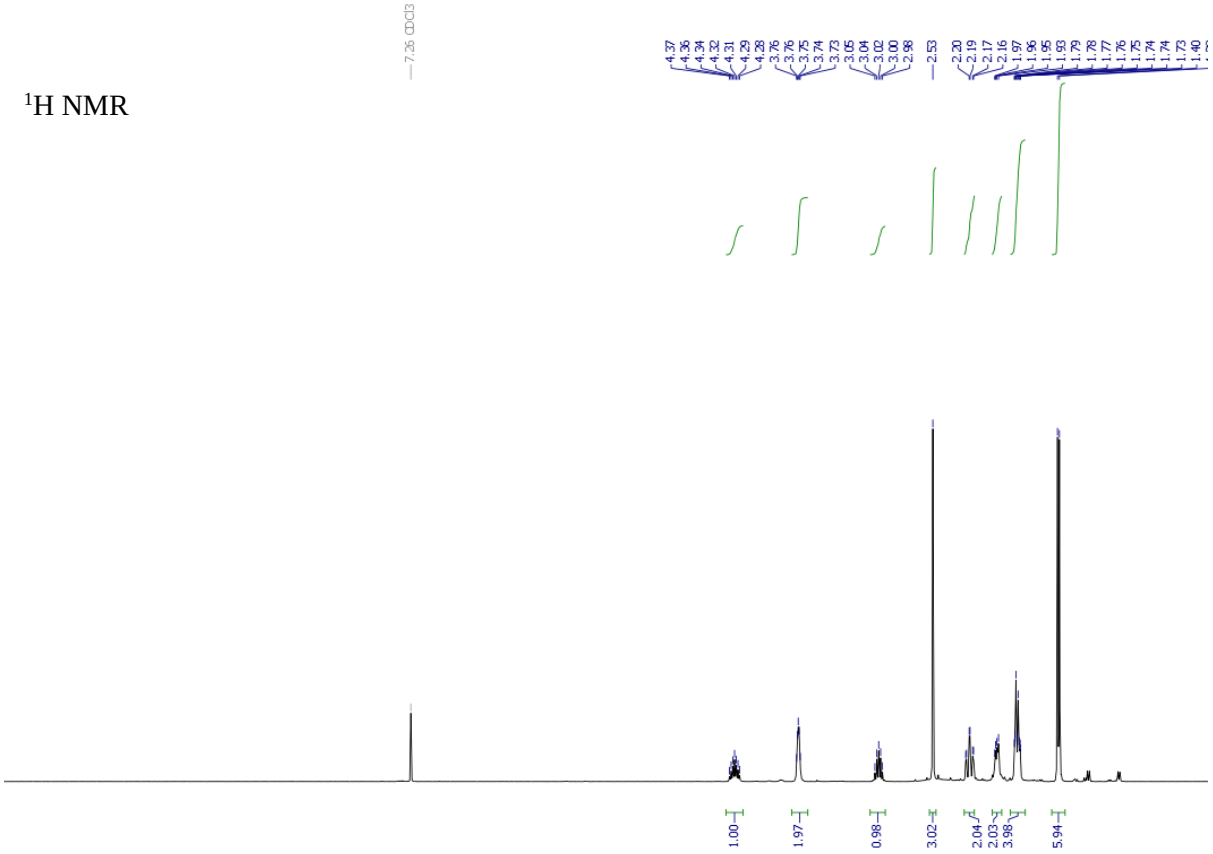


^{13}C NMR

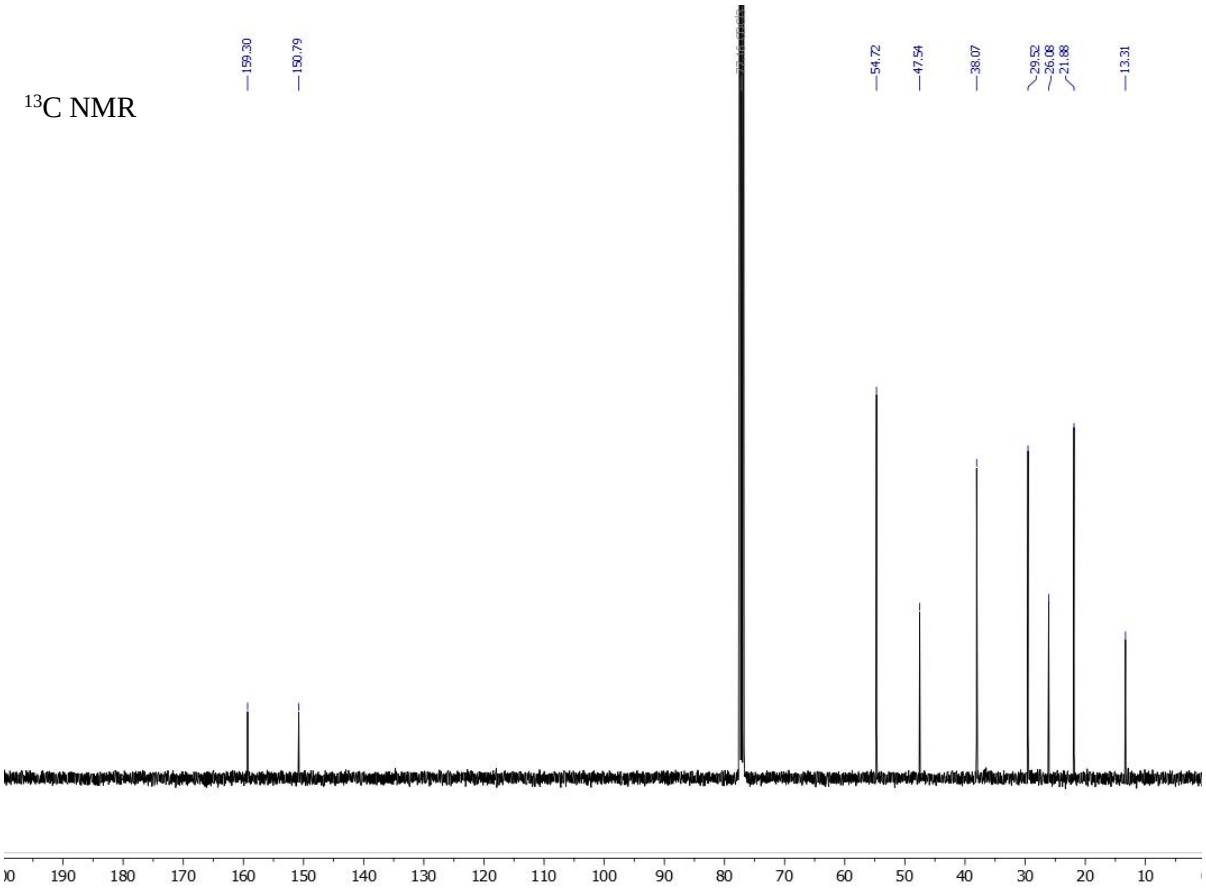


3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (**35**)

^{1}H NMR

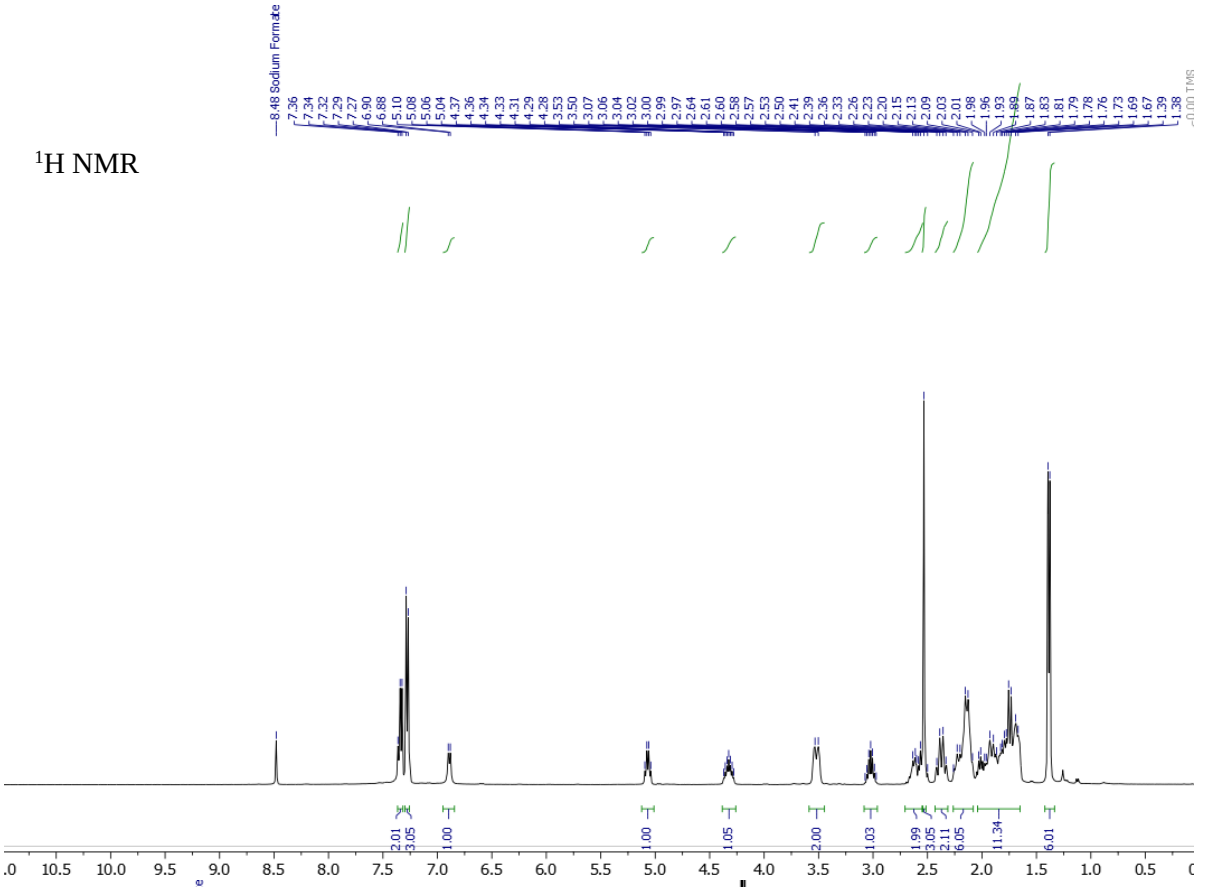


^{13}C NMR

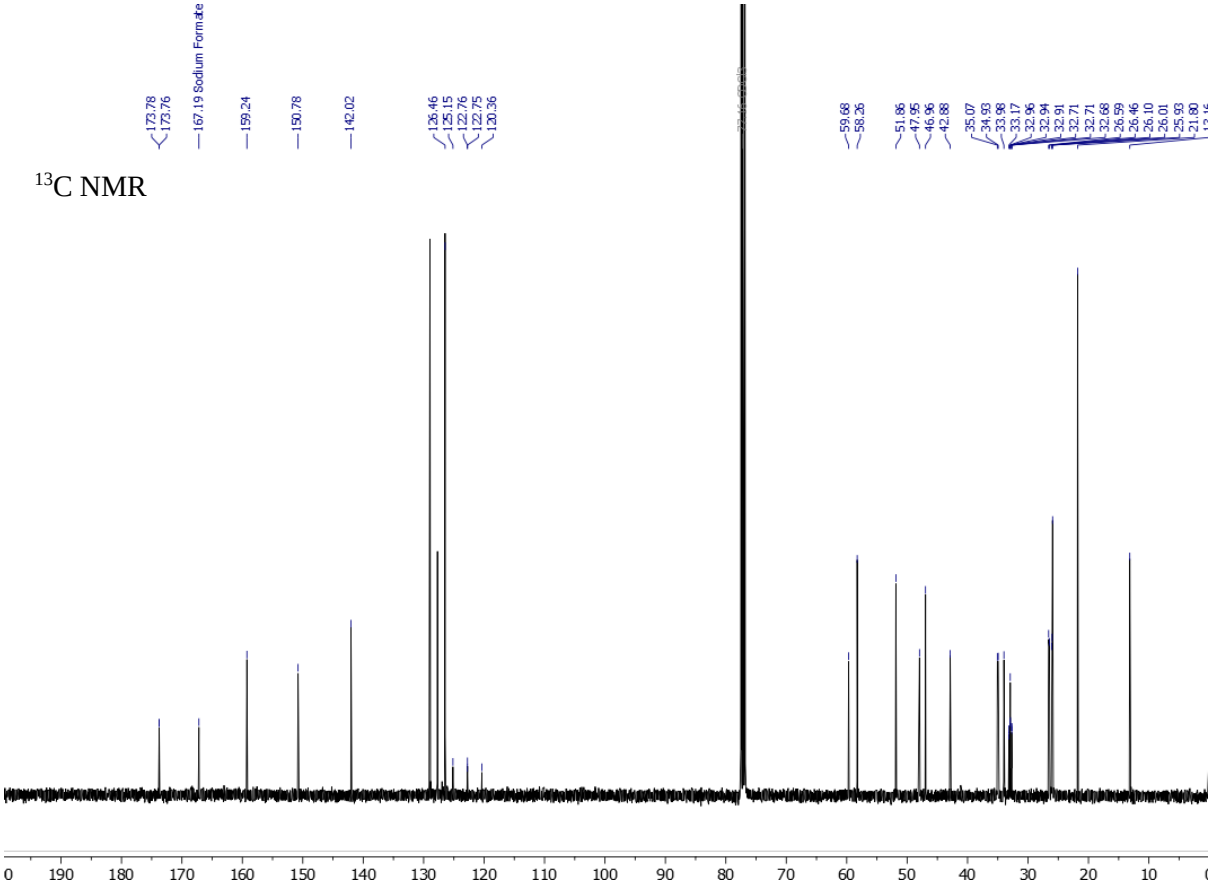


4,4-Difluoro-*N*-((1*S*)-3-(3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo-[3.2.1]octan-8-yl)-1-phenylpropyl)cyclohexanecarboxamide (Maraviroc) (**36**)

^{1}H NMR



^{13}C NMR



7 References

1 W. L. F. Armarego and C. L. L. Chai, *Purification of Organic Chemicals*, 2009.

2 B. M. Illescas, J. Santos, M. C. Díaz, N. Martín, C. M. Atienza and D. M. Guldi, *Eur. J. Org. Chem.*, 2007, 5027–5037.

3 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chem. Commun.*, 2016, **52**, 1855–8.

4 P. R. Likhar, R. Arundhathi, M. L. Kantam and P. S. Prathima, *Eur. J. Org. Chem.*, 2009, 5383–5389.

5 M. R. Saidi, R. S. Brown and A. Ziyaei-Halimjani, *J. Iran. Chem. Soc.*, 2007, **4**, 194–198.

6 S. Das, B. Join, K. Junge and M. Beller, *Chem. Commun.*, 2012, **48**, 2683.

7 J.-C. Castillo, J. Orrego-Hernández and J. Portilla, *Eur. J. Org. Chem.*, 2016, 3824–3835.

8 C. Sauvée, G. Casano, S. Abel, A. Rockenbauer, D. Akhmetzyanov, H. Karoui, D. Siri, F. Aussenac, W. Maas, R. T. Weber, T. Prisner, M. Rosay, P. Tordo and O. Ouari, *Chem. Eur. J.*, 2016, **22**, 5598–5606.

9 D. B. Bagal, R. A. Watile, M. V. Khedkar, K. P. Dhake and B. M. Bhanage, *Catal. Sci. Technol.*, 2012, **2**, 354–358.

10 S. Chandrasekhar, C. R. Reddy, R. J. Rao and J. M. Rao, *Synlett*, 2002, **2**, 0349–0351.

11 A. Chardon, T. Mohy El Dine, R. Legay, M. De Paolis, J. Rouden and J. Blanchet, *Chem. Eur. J.*, 2017, **23**, 2005–2009.

12 M. S. Cooper, R. A. Fairrurst, G. Papagfdrgiou and R. F. Wilkins, *Tetrahedron*, 1989, **45**, 1155–1166.

13 G. A. Molander, P. E. Gormisky and D. L. Sandrock, *J. Org. Chem.*, 2008, **73**, 2052–2057.

14 WO 2016/044183 A1, 2016.

15 H. J. Reich, W. S. Goldenberg and A. W. Sanders, *Arkivoc*, 2004, 97–129.

16 T. R. Long, P. K. Maity, T. B. Samarakoon and P. R. Hanson, *Org. Lett.*, 2010, **12**, 2904–2907.

17 B. S. Kim, J. Jiménez, F. Gao and P. J. Walsh, *Org. Lett.*, 2015, **17**, 5788–5791.

18 T. K. Pradhan, K. S. Krishnan, J. L. Vasse and J. Szymoniak, *Org. Lett.*, 2011, **13**, 1793–1795.

19 L. Ribeiro, N. Silva, J. Iley, J. Rautio, T. Järvinen, H. Mota-Filipe, R. Moreira and E. Mendes, *Arch. Pharm.*, 2007, **340**, 32–40.

20 S. J. Haycock-Lewandowski, A. Wilder and J. Åhman, *Org. Process Res. Dev.*, 2008, **12**, 1094–

1103.

21 G. L. Zhao, S. Lin, A. Korotvička, L. Deiana, M. Kullberg and A. Córdova, *Adv. Synth. Catal.*, 2010, **352**, 2291–2298.

22 WO 2013/106528 A1, 2013.

23 V. Bette, A. Mortreux, D. Savoia and J. F. Carpentier, *Adv. Synth. Catal.*, 2005, **347**, 289–302.

24 R. J. P. Corriu, D. Leclercq, P. H. Mutin, J. M. Planeix and A. Vioux, *J. Organomet. Chem.*, 1991, **406**, 22–25.