Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

'In-water', nickel-catalyzed mild preparation of allylic amines employing alcohols: Application to 'all-water' synthesis of pharmaceuticals

Gargi Nikhil Vaidya,† Ramesh Choudhary,† Mithilesh Nagpure,† Shyam Kumar Lokhande, Pooja Rana, Dinesh Kumar*

Department of Medicinal Chemistry
National Institute of Pharmaceutical Education and Research (NIPER) – Ahmedabad
Palaj, Gandhinagar-382355, Gujarat, India

Author Contributions: †Equal first authorship

Table of Contents

1. General Method

Unless otherwise noted, all manipulations (reactions) were carried out in oven-dried glasswares in glovebox under an atmosphere of dinitrogen. Concentration of reaction mixtures were done under reduced pressure by rotary evaporation at 25–40 °C at an appropriate pressure. Purified compounds were further dried under vacuum. Yields refer to purified and spectroscopically pure compounds, unless otherwise stated.

Chemicals

All the catalysts, ligands were purchased from Sigma-Aldrich®. All the other reagents like starting materials, additives, bases were used as received from commercial suppliers, unless otherwise stated and were purchased from Alfa Aesar®, Sigma-Aldrich®.

Solvents

Ethyl acetate, Hexane, Dichloromethane, Methanol was purchased from Fisher Scientific Qualigen and used as received without further purification or distillation. All the surfactants and anhydrous 1,4-Dioxane were obtained from Sigma Aldrich. All deuterated solvents were purchased from Sigma Aldrich and used as received.

Chromatography

Thin layer chromatography (TLC) was performed using Merck TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. All the compounds were purified using column chromatography with 100-200 mesh size silica or with flash chromatography on CombiFlash®Rf+ Lumen™, Teledyne ISCO using RediSep® Rf prepacked columns (24g, CV 33 mL-35 mL/min) and eluted using either EtOAc: Hexane and DCM: Methanol as mobile phase.

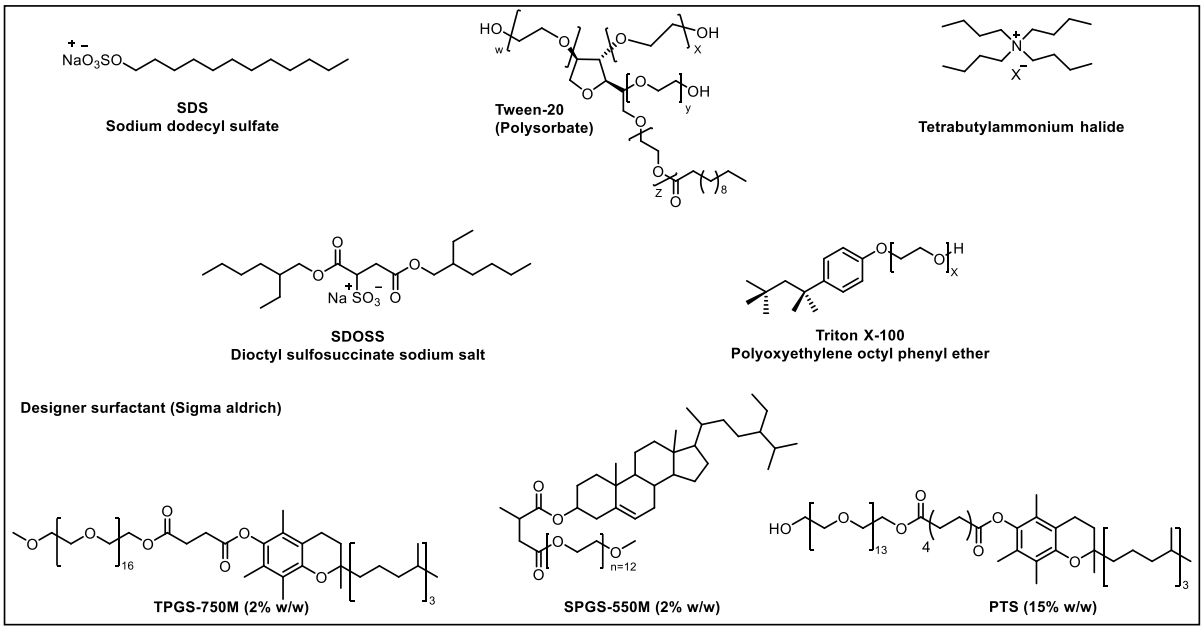
Spectroscopy and Instruments:

NMR: ^{1}H NMR and ^{13}C NMR spectra were recorded on Brukar 500 MHz and 125 MHz spectrometers respectively using tetramethylsilane (1% v/v solution in the respective solvent) as an internal standard. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0) with the solvent residual peak. For ^{1}H NMR: $CDCl_3$, δ 7.26; For ^{13}C NMR: $CDCl_3$, δ 77.16; ^{19}F NMR spectra were referenced using a unified chemical shift scale based on the ^{1}H resonance of tetramethylsilane (1% v/v solution in the respective solvent) Coupling constants (*J*) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), b (broad), d (doublet), t (triplet), q (quartet) and m (multiplet).

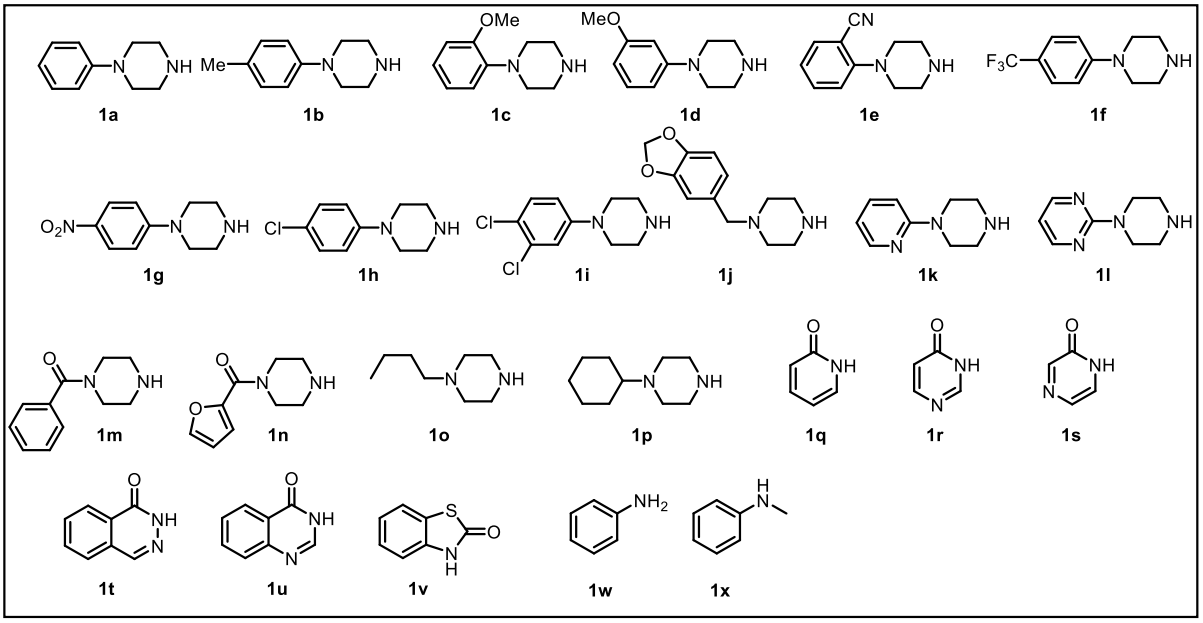
High-resolution mass spectra (HRMS): spectra of compounds were obtained at Agilent Q-TOF spectrometer in positive (ESI^+) ion mode.

2. List of chemicals/reagents

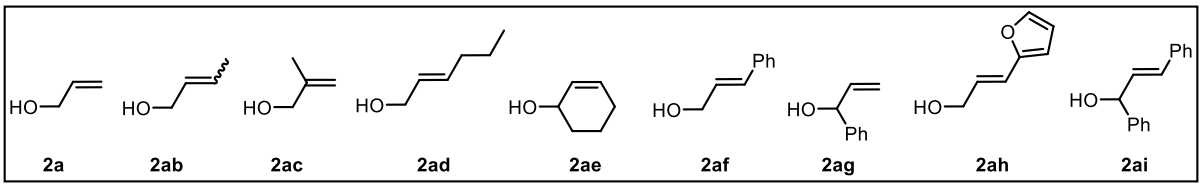
Surfactant used in the studies (Sigma Aldrich):



Amines (Sigma Aldrich):

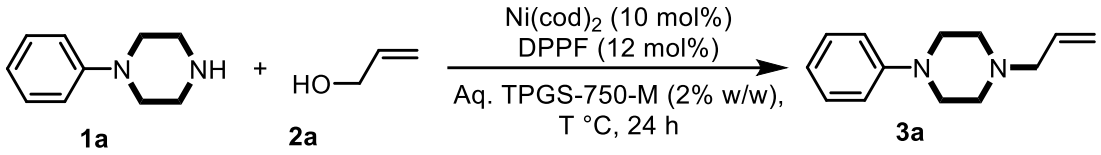


Allylic Alcohols (Sigma Aldrich; Spectrochem):



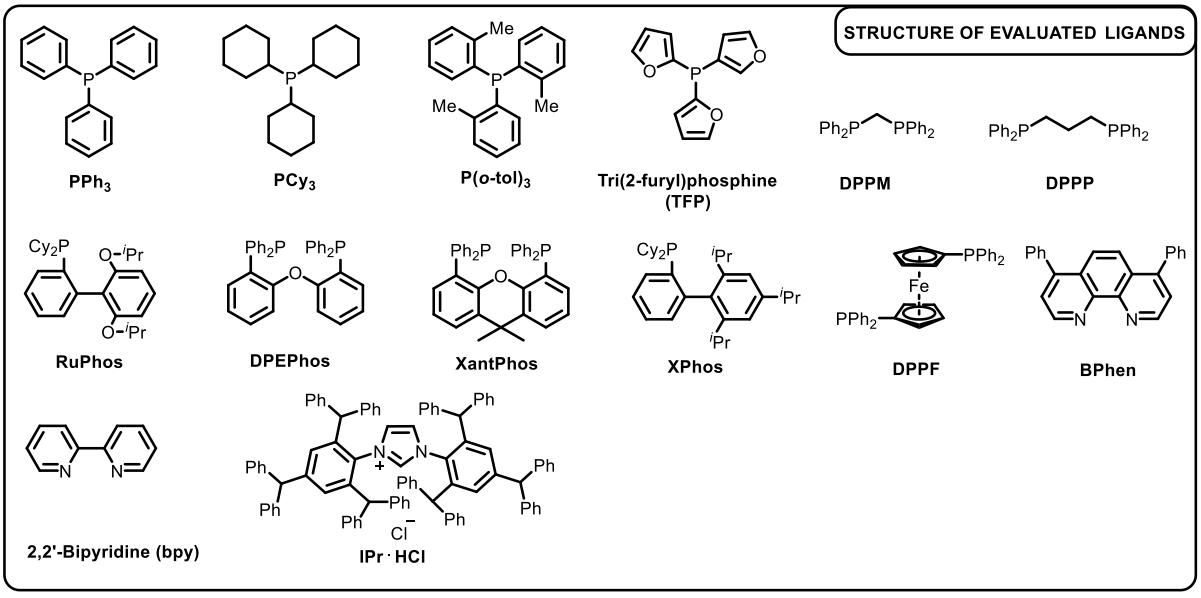
3. Preliminary ligand evaluation

Table S1. Investigation of ligand using 10 mol% $Ni(cod)_2$.[a]



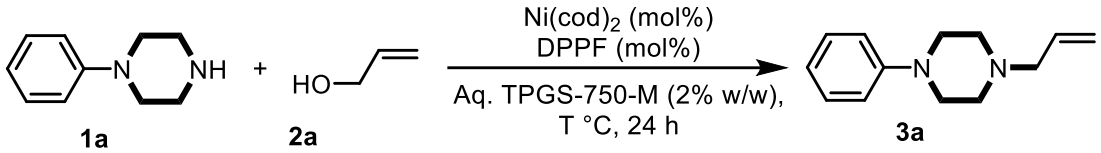
Entry	Ligand (12 mol%)	Yield (%)[b] 3a
1	Triphenylphosphine (PPh_3)	25
2	Tricyclohexylphosphine (PCy_3)	20
3	Tri(2-furyl)phosphine (TFP)	0[c]
4	Tri(*o*-tolyl)phosphine [P(*o*-tol)$_3$]	traces[c]
5	Bis(diphenylphosphino)methane (DPPM)	0[c]
6	1,3-Bis(diphenylphosphino)propane (DPPP)	0[c]
7	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl (RuPhos)	15
8	(Oxydi-2,1-phenylene)bis(diphenylphosphine) (DPEPhos)	67
9	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos)	10
10	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos)	traces[c]
11	1,1′-Ferrocenediyl-bis(diphenylphosphine) (DPPF)	85
11	Bathophenanthroline (Bphen)	traces[c]
12	2,2′-Bipyridyl (BiPy)	0[c]
13	1,3-Bis-(2,6-diisopropylphenyl)imidazolinium chloride (IPr.HCl)	0[c]

[a]**1a** (0.2 mmol) was treated with **2a** (0.3 mmol, 1.5 equiv) in TPGS-750M (0.5 mL) in presence of different ligand using 10 mol% of $Ni(cod)_2$ at room temperature for 24 h. [b]Isolated yield of **3a**. [c]Starting **1a** was found intact.



4. Optimization studies

Table S2. Optimization of reaction conditions.[a]

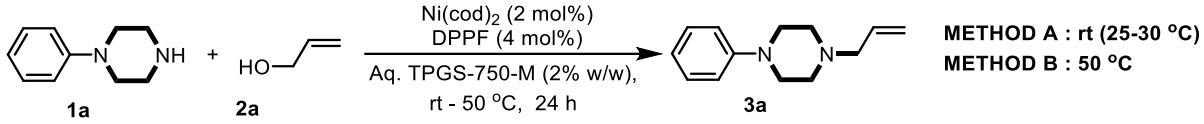


Entry	$Ni(cod)_2$ (mol%)	DPPF (mol%)	Temperature (°C)	Yield (%)[b] 3a
1	8	10	rt	88
2	6	10	rt	89
3	4	10	rt	89
4	2	10	rt	88
5	1	10	rt	77
6	2	8	rt	88
7	2	6	rt	89
8	2	4	rt	89
9	2	2	rt	71

[a]**1a** (0.2 mmol) was treated with **2a** (0.3 mmol, 1.5 equiv) in TPGS-750M (0.5 mL) in presence of $Ni(cod)_2$– DPPF system under different reaction conditions for 24 h. [b]Isolated yield of **3a**. [c]Starting **1a** was found intact.

5. Representative experimental procedure

General procedure for the *N*-allylation using allyl alcohols under aqueous micellar nickel-catalysis:



To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (1.1 mg, 0.004 mmol, 2 mol%), DPPF (4.4 mg, 0.008 mmol, 4 mol%), 1-phenylpiperazine **1a** (32.4 mg, 30.5 μL, 0.2 mmol), allyl alcohol **2a** (17.4 mg, 20.4 μL, 0.3 mmol, 1.5 equiv), and aqueous TPGS-750-M (2% w/w, 0.5 mL) were added. The resultant mixture was stirred at room temperature (Method A) and or 50 °C (Method B) for 24 h. The reaction mixture was diluted with EtOAc (2 X 0.5 mL) and vortexed the resultant mixture. The supernatant liquid containing product and other organic residue was removed carefully. The recovered organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a** (36.0 mg, 89%) as pale yellow liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (td, J = 7, 2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.85 (t, J = 7.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.23 (dq, J = 17.0, 2.0 Hz, 1H), 5.20 - 5.18 (m, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 134.8, 129.1, 119.7, 118.3, 116.08, 61.8, 53.1, 49.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{19}N_2^+$ 203.1543, Found 203.1543.

6. Spectroscopic characterization data

1-Allyl-4-(*p*-tolyl)piperazine (3b): Pale yellow liquid (39.8 mg, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.09 – 7.05 (m, 2H), 6.86 – 6.83 (m, 2H), 5.90 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.25 – 5.16 (m, 2H), 3.19 – 3.14 (m, 4H), 3.06 (dt, *J* = 6.6, 1.3 Hz, 2H), 2.64 – 2.60 (m, 4H), 2.26 (s, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.2, 134.8, 129.6, 129.2, 118.3, 116.4, 61.8, 53.1, 49.7, 20.4; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{21}N_2^+$ 217.1699 Found 217.1705.

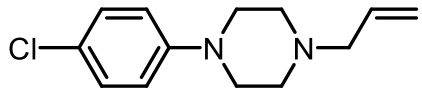
1-Allyl-4-(3-methoxyphenyl)piperazine (3c): Pale yellow liquid (39.5 mg, 85%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.18 (t, *J* = 8.2 Hz, 1H), 6.58 – 6.54 (m, 1H), 6.48 (t, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.1, 2.3 Hz, 1H), 5.91 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.26 – 5.18 (m, 2H), 3.79 (s, 3H), 3.25 – 3.19 (m, 4H), 3.07 (dt, *J* = 6.6, 1.4 Hz, 2H), 2.64 – 2.59 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.6, 152.8, 134.9, 129.8, 118.3, 108.9, 104.4, 102.5, 61.9, 55.2, 53.1, 49.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{21}N_2O^+$ 233.1648 Found 233.1649.

1-Allyl-4-(2-methoxyphenyl)piperazine (3d): Pale yellow liquid (38.6 mg, 83%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.00 (td, *J* = 7.9, 1.9 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.86 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.92 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.39 – 5.05 (m, 2H), 3.86 (s, 3H), 3.19 – 3.02 (m, 6H), 2.68 (br s, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 152.3, 141.3, 134.9, 122.9, 121.0, 118.3, 118.2, 111.2, 61.9, 55.4, 53.3, 50.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{21}N_2O^+$ 233.1648 Found 233.1650.

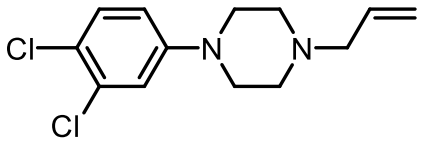
2-(4-Allylpiperazin-1-yl)benzonitrile (3e): Pale yellow liquid (37.2 mg, 91%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.47 (ddd, *J* = 8.8, 7.4, 1.7 Hz, 1H), 7.08 – 6.92 (m, 2H), 5.89 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.41 – 5.09 (m, 2H), 3.33 – 3.20 (m, 4H), 3.08 (dd, *J* = 6.7, 1.3 Hz, 2H), 2.77 – 2.62 (m, 4H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.8, 134.8, 134.5, 133.9, 121.8, 118.8, 118.6, 106.1, 61.8, 53.1, 51.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{18}N_3^+$ 228.1495 Found 228.1502.

1-Allyl-4-(4-(trifluoromethyl)phenyl)piperazine (3f): Colourless liquid (43.7 mg, 81%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.89 (td, *J* = 16.8, 6.6 Hz, 1H), 5.22 (dd, *J* = 17.2, 13.7 Hz, 2H), 3.30 (t, *J* = 5.1 Hz, 4H), 3.07 (d, *J* = 6.6 Hz, 2H), 2.61 (t, *J* = 5.1 Hz, 4H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 153.3, 134.5, 126.4 (q, *J* = 3.7 Hz), 124.8 (q, *J* = 270.6 Hz), 120.5 (q, *J* = 32.9 Hz), 118.5, 114.5, 61.7, 52.7, 47.9; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -61.36; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{18}F_3N_2$ 271.1417, Found 271.1422.

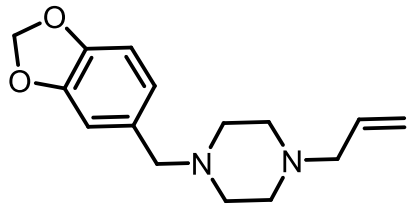
1-Allyl-4-(4-chlorophenyl)piperazine (3h): Pale yellow liquid (39.3 mg, 83%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 6.89 – 6.81 (m, 2H), 5.89 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.45 – 5.08 (m, 2H), 3.42 – 3.08 (m, 4H), 3.06 (dt, *J* = 6.6, 1.3 Hz, 2H), 2.76 – 2.39 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.9, 134.7, 128.9, 124.5, 118.4, 117.2, 61.7, 52.9, 49.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{18}ClN_2^+$ 237.1153 Found 237.1154.



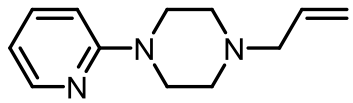
1-Allyl-4-(3,4-dichlorophenyl)piperazine (3i) Pale yellow liquid (43.4 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.26 (d, *J* = 8.5Hz, 1H), 6.95 (d, *J* = 3.0 Hz, 1H), 6.73 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.88 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H), 5.25 - 5.18 (m, 2H), 3.20 (t, *J* = 5 Hz, 4H), 3.05 (dt, *J* = 6.5, 1.0 Hz, 2H), 2.60 (t, *J* = 5 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 150.7, 134.6, 132.8, 130.4, 122.1, 118.4, 117.2, 115.3, 61.7, 52.7, 48.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{17}Cl_2N_2$ 271.0763, Found 271.0792.



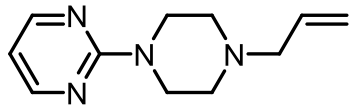
1-Allyl-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine (3j): Yellow liquid (37.4 mg, 72%); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 7.22 (s, 1H), 7.11 (d, *J* = 1.1 Hz, 2H), 6.29 (s, 2H), 6.27 – 6.20 (m, 1H), 5.57 (q, *J* = 1.6 Hz, 1H), 5.55 – 5.47 (m, 1H), 3.79 (s, 2H), 3.37 (dt, *J* = 6.7, 1.3 Hz, 2H), 2.84 (br s, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 147.6, 146.5, 135.0, 132.0, 122.2, 118.0, 109.5, 107.8, 100.8, 62.7, 61.8, 53.0, 52.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{15}H_{21}N_2O_2^+$ 261.1598 Found 261.1611.



1-allyl-4-(pyridin-2-yl)piperazine (3k): Pale yellow liquid id (35.7 mg, 88%); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.19 (ddd, *J* = 4.9, 1.9, 0.7 Hz, 1H), 7.46 (ddd, *J* = 8.9, 7.1, 2.0 Hz, 1H), 6.68 – 6.56 (m, 2H), 5.90 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.29 – 5.13 (m, 2H), 3.61 – 3.50 (m, 4H), 3.05 (dt, *J* = 6.6, 1.3 Hz, 2H), 2.61 – 2.50 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 159.5, 147.9, 137.4, 134.8, 118.3, 113.3, 107.1, 61.8, 52.9, 45.2; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{12}H_{18}N_3^+$ 204.1495 Found 204.1500.



2-(4-Allylpiperazin-1-yl)pyrimidine (3l): Pale yellow liquid (35.1 mg, 86%); **^{1}H NMR** (500 MHz, $CDCl_3$): *δ* 8.23 (d, *J* = 4.7 Hz, 2H), 6.40 (t, *J* = 4.7 Hz, 1H), 5.87 – 5.79 (m, 1H), 5.17 – 5.09 (m, 2H), 3.80 – 3.75 (m, 4H), 2.97 (dt, *J* = 6.6, 1.4 Hz, 2H), 2.47 – 2.42 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): *δ* 161.6, 157.6, 134.7, 118.3, 109.8, 61.8, 52.9, 43.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{11}H_{17}N_4^+$ 205.1448 Found 205.1447.



(4-Allylpiperazin-1-yl)(phenyl)methanone (3m): Pale yellow liquid (33.1 mg, 72%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.48 – 7.32 (m, 5H), 5.84 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.28 – 5.09 (m, 2H), 3.81 (s, 2H), 3.53 – 3.35 (m, 2H), 3.03 (dt, *J* = 6.5, 1.3 Hz, 2H), 2.46 (d, *J* = 74.4 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.3, 135.8, 134.4, 129.7, 128.5, 127.1, 118.6, 61.6, 53.3, 52.7; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{19}N_2O^+$ 231.1492 Found 231.1497.

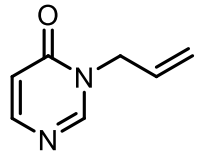
(4-Allylpiperazin-1-yl)(furan-2-yl)methanone (3n): Pale yellow liquid (33.0 mg, 75%); mp; 42 - 44 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.99 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.47 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.87 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.23 – 5.14 (m, 2H), 3.82 (br s, 4H), 3.05 – 3.01 (m, 2H), 2.51 (t, *J* = 5.1 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.1, 147.9, 143.7, 134.2, 118.8, 116.4, 111.3, 61.5, 53.0, 46.5; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{12}H_{17}N_2O_2^+$ 221.1285 Found 221.1285.

1-Allyl-4-butylpiperazine (3o): Black liquid (40.2 mg, 78%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.39 – 7.36 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.22 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.26 – 3.20 (m, 2H), 2.63 (d, *J* = 90.7 Hz, 10H), 1.58 (q, *J* = 8.1 Hz, 2H), 1.34 (h, *J* = 7.3 Hz, 2H)., 0.93 (t, *J* = 7.4 Hz, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 136.6, 134.0, 128.8, 128.6, 128.3, 127.7, 126.4, 60.6, 58.0, 52.6, 51.9, 20.6, 13.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{27}N_2^+$ 259.2169 Found 259.2180.

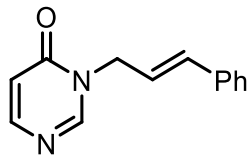
1-Cinnamyl-4-cyclohexylpiperazine (3p): Brownish liquid (45.4 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.24 (dt, *J* = 15.8, 6.9 Hz, 1H), 3.22 (d, *J* = 6.9 Hz, 2H), 2.99 – 2.65 (m, 7H), 2.62 – 2.53 (m, 1H), 2.10 – 1.99 (m, 2H), 1.85 (d, *J* = 12.1 Hz, 2H), 1.66 (d, *J* = 13.4 Hz, 1H), 1.37 – 1.23 (m, 5H), 1.17 – 1.10 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 136.6, 133.9, 128.6, 127.7, 126.4, 125.4, 64.3, 60.6, 51.8, 48.5, 28.0, 25.8, 25.5; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{19}H_{29}N_2^+$ 285.2325 Found 285.2317.

1-Cinnamylpyridin-2(1*H*)-one (4a): Pale yellow liquid (28.7 mg, 68%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 – 7.27 (m, 3H), 7.26 – 7.22 (m, 3H), 7.21 – 7.16 (m, 1H), 6.56 – 6.48 (m, 2H), 6.24 (dt, *J* = 15.9, 6.5 Hz, 1H), 6.12 (td, *J* = 6.7, 1.4 Hz, 1H), 4.64 (dd, *J* = 6.4, 1.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 162.5, 139.7, 137.2, 136.0, 134.0, 128.6, 128.1, 126.6, 123.6, 120.9, 106.4, 50.7; **HRMS** (ESI-QTOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{14}NO$ 212.1070, Found 212.1078.

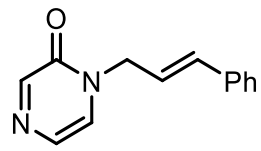
3-Allylpyrimidin-4(3*H*)-one (4b): Pale yellow liquid (20.1 mg, 74%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.89 (d, J = 6.6 Hz, 1H), 6.47 (d, J = 7.4 Hz, 1H), 5.97 (ddt, J = 16.3, 10.6, 6.0 Hz, 1H), 5.50 – 5.14 (m, 2H), 4.56 (dt, J = 5.8, 1.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.7, 153.4, 151.0, 131.3, 119.5, 116.1, 48.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_7H_9N_2O^+$ 137.0709; Found 137.0716.



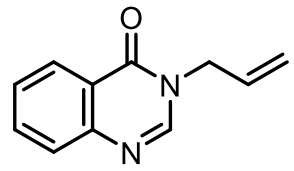
3-Cinnamylpyrimidin-4(3*H*)-one (4c): White solid (30.1 mg, 71%); mp: 138 - 141 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.90 (d, J = 6.6 Hz, 1H), 7.40 – 7.26 (m, 5H), 6.68 – 6.62 (m, 1H), 6.48 (dd, J = 6.6, 1.1 Hz, 1H), 6.30 (dt, J = 15.8, 6.6 Hz, 1H), 4.70 (dt, J = 6.5, 1.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.1, 149.7, 135.9, 135.5, 128.8, 128.6, 127.9, 126.7, 124.0, 121.6, 50.3; **HRMS** (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{13}N_2O$ 213.1022, Found 213.1037.



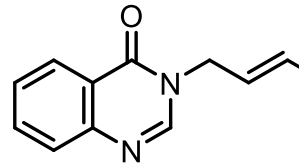
1-Cinnamylpyrazine-2(1*H*)-one (4d): White solid (32.2 mg, 76%); mp: 56-59 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.19 (d, J = 1.2 Hz, 1H), 7.42 – 7.28 (m, 6H), 7.18 (dd, J = 4.4, 1.2 Hz, 1H), 6.69 – 6.64 (m, 1H), 6.26 (dt, J = 15.8, 6.7 Hz, 1H), 4.68 (dd, J = 6.7, 1.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 156.1, 149.7, 135.9, 135.5, 128.8, 128.6, 127.9, 126.7, 124.0, 121.6, 50.3; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{12}N_2O_2$ 213.1022, Found 213.1035.



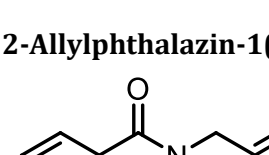
3-Allylquinazolin-4(3*H*)-one (4e): White solid (27.2 mg, 73%); mp: 66-69 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.33 (dd, J = 8.1, 1.5 Hz, 1H), 8.02 (s, 1H), 7.78 – 7.70 (m, 2H), 7.51 (ddd, J = 8.2, 7.0, 1.4 Hz, 1H), 6.00 (ddt, J = 17.2, 10.2, 5.7 Hz, 1H), 5.33 – 5.25 (m, 2H), 4.65 (dt, J = 5.7, 1.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 160.8, 148.1, 146.2, 134.3, 131.9, 127.5, 127.4, 126.8, 122.1, 118.9, 48.3; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{11}H_{11}N_2O^+$ 187.0866, Found 187.0870.



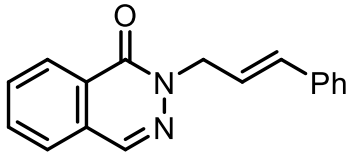
3-Cinnamylquinazolin-4(3*H*)-one (4f): White solid (36.6 mg, 70%); mp: 107-110 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.41 – 8.27 (m, 1H), 8.11 (s, 1H), 7.77 (ddd, J = 8.4, 7.0, 1.5 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.53 (ddd, J = 8.2, 7.0, 1.3 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.25 (m, 1H), 6.67 (d, J = 15.9 Hz, 1H), 6.35 (dt, J = 15.8, 6.5 Hz, 1H), 4.80 (dd, J = 6.5, 1.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.0, 148.1, 146.2, 135.8, 134.5, 134.3, 128.7, 128.3, 127.6, 127.4, 126.8, 126.6, 122.8, 122.2, 48.2; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O^+$ 263.1179 Found 263.1182.



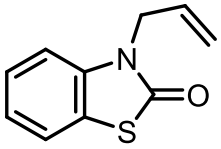
2-Allylphthalazin-1(2*H*)-one (4g): Colourless liquid (26.0 mg, 70%)K;°C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.48 – 8.41 (m, 1H), 8.19 (s, 1H), 7.91 – 7.74 (m, 2H), 7.76 – 7.67 (m, 1H), 6.06 (ddt, J = 17.3, 10.2, 5.9 Hz, 1H), 5.49 – 5.15 (m, 2H), 4.87 (dt, J = 5.9, 1.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.2, 138.1, 133.1, 132.5, 131.7, 129.7, 128.0, 126.8, 126.0, 118.0, 53.5; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{11}H_{11}N_2O^+$ 187.0866 Found 187.0874.



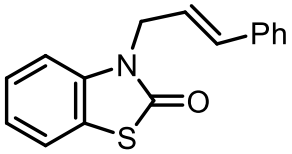
2-Cinnamylphthalazin-1(2*H*)-one (4h): White solid (35.7 mg, 68%); mp: 63-65 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.45 – 8.42 (m, 1H), 8.16 (s, 1H), 7.84 – 7.70 (m, 2H), 7.66 (dd, J = 7.8, 1.5 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.31 – 7.22 (m, 2H), 7.23 – 7.16 (m, 1H), 6.70 (d, J = 15.9 Hz, 1H), 6.45 (dt, J = 15.9, 6.6 Hz, 1H), 5.00 (dd, J = 6.6, 1.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 159.2, 138.1, 133.1, 132.5, 131.7, 129.7, 128.0, 126.8, 126.0, 118.0, 53.5; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{15}N_2O^+$ 263.1179 Found 263.1187.



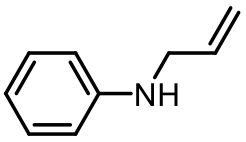
3-Allylbenzo[d]thiazol-2(3*H*)-one (4i): Colourless liquid (27.1 mg, 71%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 (dd, J = 7.8, 1.3 Hz, 1H), 7.29 (td, J = 7.8, 1.3 Hz, 1H), 7.16 (td, J = 7.7, 1.1 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 5.88 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H), 5.53 – 5.11 (m, 2H), 4.58 (dt, J = 5.4, 1.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.8, 137.0, 130.7, 126.3, 123.2, 122.6, 122.6, 118.1, 111.1, 44.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{10}H_{10}NOS^+$ 192.0478 Found 192.0480.



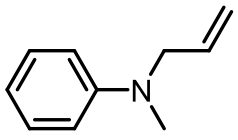
3-Cinnamylbenzo[*d*]thiazol-2(3*H*)-one (4j): Pale yellow solid (37.4 mg, 70%); mp: 45 – 48 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.8, 1.3 Hz, 1H), 7.35 – 7.27 (m, 5H), 7.25 – 7.22 (m, 1H), 7.16 (td, J = 7.7, 1.1 Hz, 1H), 7.11 (dd, J = 8.2, 1.1 Hz, 1H), 6.61 (d, J = 15.9 Hz, 1H), 6.23 (dt, J = 15.9, 6.0 Hz, 1H), 4.74 (dd, J = 6.0, 1.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.9, 137.0, 135.9, 133.5, 128.6, 128.1, 126.5, 126.4, 123.2, 122.7, 122.7, 122.1, 111.1, 44.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{16}H_{14}NOS$ 268.0791 Found 268.0802.



***N*-Allylaniline (5a):** Brownish liquid (21.5 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.24 – 7.17 (m, 2H), 6.74 (tt, J = 7.3, 1.1 Hz, 1H), 6.65 (dd, J = 8.6, 0.9 Hz, 2H), 5.98 (ddt, J = 17.2, 10.5, 5.4 Hz, 1H), 5.31 (dq, J = 17.2, 1.7 Hz, 1H), 5.19 (dq, J = 10.2, 1.5 Hz, 1H), 3.80 (dt, J = 5.4, 1.7 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 148.0, 135.4, 129.2, 117.5, 116.2, 113.0, 46.5. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_9H_{12}N^+$ 134.0964 Found 134.0963.



***N*-Allyl-*N*-methylaniline (5b):** Pale yellow liquid (27.0 mg, 92%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ ; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 7.37 – 7.21 (m, 2H), 6.82 – 6.73 (m, 3H), 5.90 (ddt, J = 17.2, 10.2, 5.0 Hz, 1H), 5.37 – 5.09 (m, 2H), 3.97 (dd, J = 3.5, 1.6 Hz, 2H), 2.99 (s, 3H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 149.5, 133.9, 129.1, 116.5, 116.2, 112.5, 55.3, 38.0; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{14}N^+$ 148.1121 Found 148.1120.



1-Allyl-4-phenylpiperazine (3a): Pale yellow liquid (36.0 mg, 89%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (td, J = 7, 2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.85 (t, J = 7.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.23 (dq, J = 17.0, 2.0 Hz, 1H), 5.20 - 5.18 (m, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 134.8, 129.1, 119.7, 118.3, 116.08, 61.8, 53.1, 49.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{19}N_2^+$ 203.1543, Found 203.1543.

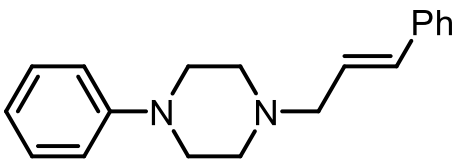
(*E*)-1-(But-2-en-1-yl)-4-phenylpiperazine (3q): Yellowish liquid (34.5 mg, 80%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.85 (t, J = 7.3 Hz, 1H), 5.70 – 5.60 (m, 1H), 5.57 – 5.51 (m, 1H), 3.25 – 3.18 (m, 4H), 2.98 (d, J = 6.7 Hz, 2H), 2.63 (d, J = 5.1 Hz, 1H), 2.60 (q, J = 5.7, 5.0 Hz, 3H), 1.71 (d, J = 6.3 Hz, 2H), 1.67 (d, J = 6.9 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 129.5, 129.1, 127.4, 119.7, 116.0, 61.0, 53.1, 49.1, 17.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{21}N_2^+$ 217.1699, Found 217.1699.

1-(2-Methylallyl)-4-phenylpiperazine (3r): Brownish liquid (35.0 mg, 81%); **^{1}H NMR** (500 MHz $CDCl_3$): δ 7.31 – 7.19 (m, 2H), 7.02 – 6.88 (m, 2H), 6.88 – 6.79 (m, 1H), 4.89 (d, J = 14.8 Hz, 2H), 3.51 – 3.06 (m, 4H), 2.92 (s, 2H), 2.71 – 2.37 (m, 4H), 1.77 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 142.6, 129.1, 119.5, 116.0, 113.1, 65.4, 53.1, 49.2, 20.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{21}N_2^+$ 217.1699, Found 217.1699.

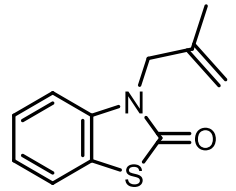
1-(Hex-2-en-1-yl)-4-phenylpiperazine (3s): Brownish liquid (38.0 mg, 78%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27 – 7.24 (m, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.3 Hz, 1H), 5.70 – 5.56 (m, 1H), 5.56 – 5.47 (m, 1H), 3.24 – 3.19 (m, 4H), 3.08 (dd, J = 6.8, 1.5 Hz, 1H), 3.00 (dd, J = 6.6, 1.1 Hz, 1H), 2.61 (dt, J = 10.2, 5.0 Hz, 4H), 2.22 – 1.94 (m, 2H), 1.58 – 1.34 (m, 2H), 0.91 (td, J = 7.4, 5.3 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 151.4, 134.9, 133.4, 129.1, 126.2, 119.6, 116.0, 61.0, 53.1, 49.1, 34.5, 29.6, 22.4, 13.7; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{16}H_{25}N_2^+$ 245.2012 Found 245.2020.

4-(Cyclohex-2-en)-1-phenylpiperazine (3t): Brownish liquid (35.8 mg, 74%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.31 – 7.21 (m, 2H), 6.99 – 6.89 (m, 2H), 6.85 (tt, J = 7.3, 1.0 Hz, 1H), 5.92 – 5.81 (m, 1H), 5.74 – 5.66 (m, 1H), 3.31 – 3.25 (m, 1H), 3.21 (dt, J = 6.1, 3.8 Hz, 4H), 2.89 – 2.65 (m, 4H), 1.99 (br s, 2H), 1.90 – 1.76 (m, 2H), 1.67 – 1.50 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.5, 130.3, 129.2, 129.1, 119.6, 116.1, 60.2, 49.7, 48.6, 25.3, 23.1, 21.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{16}H_{23}N_2^+$ 243.1856, Found 243.1856.

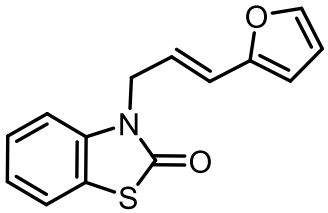
1-Cinnamyl-4-phenylpiperazine (3u): Yellowish liquid (43.3 mg, 78%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 – 7.37 (m, 2H), 7.31 (td, J = 8.4, 6.8 Hz, 2H), 7.28 – 7.20 (m, 3H), 6.95 – 6.91 (m, 2H), 6.87 – 6.82 (m, 1H), 6.55 (d, J = 15.9 Hz, 1H), 6.31 (dt, J = 15.9, 6.8 Hz, 1H), 3.28 – 3.11 (m, 6H), 2.71 – 2.58 (m, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 136.9, 133.3, 129.2, 128.7, 127.6, 126.5, 126.4, 119.8, 116.1, 61.2, 53.3, 49.2; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{19}H_{23}N_2^+$ 279.1856 Found 279.1850.



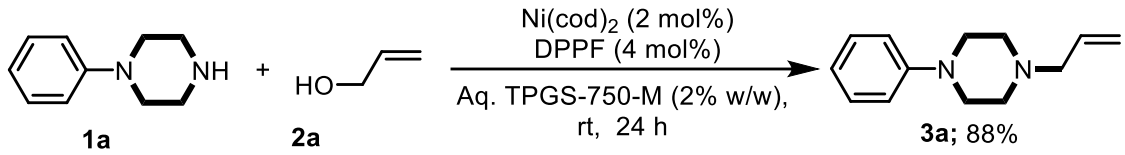
3-(2-Methylallyl)benzo[*d*]thiazol-2(3*H*)-one (4k): Pale yellow liquid (27.9 mg, 68%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 (dd, J = 7.8, 1.3 Hz, 1H), 7.28 (td, J = 7.7, 1.1 Hz, 1H), 7.15 (td, J = 7.6, 1.1 Hz, 1H), 7.01 (dd, J = 8.1, 1.1 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.84 – 4.78 (m, 1H), 4.50 (d, J = 1.5 Hz, 2H), 1.76 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 170.0, 138.5, 137.2, 126.3, 123.2, 122.5, 122.5, 112.8, 111.3, 48.2, 19.8; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{11}H_{12}NOS^+$ 206.0634 Found 206.0637.



(*E*)-3-(3-(Furan-2-yl)allyl)benzo[*d*]thiazol-2(3*H*)-one (4l): Colourless liquid (28.7 mg, 56%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44 (dd, J = 7.8, 1.3 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.16 (td, J = 7.7, 1.1 Hz, 1H), 7.07 (dd, J = 8.2, 1.1 Hz, 1H), 6.44 – 6.30 (m, 2H), 6.22 (d, J = 3.3 Hz, 1H), 6.17 (dt, J = 15.8, 5.8 Hz, 1H), 4.70 (dd, J = 5.8, 1.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 169.8, 151.6, 142.3, 136.9, 126.4, 123.2, 122.7, 122.6, 121.5, 120.5, 111.3, 111.0, 108.8, 44.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{14}H_{12}NO_2S^+$ 258.0583 Found 258.0598.

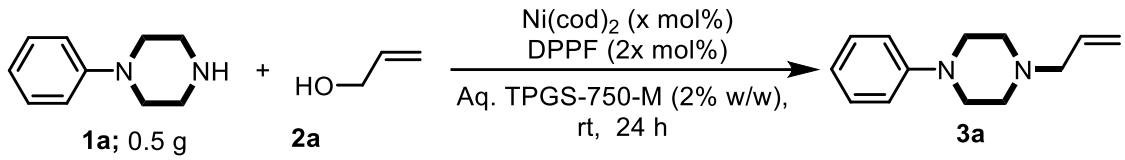


7. Scale up study



To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (30.84 mg, 0.12 mmol, 2 mol%), DPPF (136.6 mg, 0.24 mmol, 4 mol%), 1-phenylpiperazine **1a** (1.0 g, 0.97 mL, 6.1 mmol), allyl alcohol **2a** (536.6 mg, 628.3 μL, 9.2 mmol, 1.5 equiv), and aqueous TPGS-750-M (2% w/w, 5 mL) were added. The resultant mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (2 X 5 mL) and vortexed the resultant mixture. The supernatant liquid containing product and other organic residue was removed carefully. The recovered organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a** (1.1 g, 88%) as pale yellow liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (td, J = 7, 2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.85 (t, J = 7.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.23 (dq, J = 17.0, 2.0 Hz, 1H), 5.20 - 5.18 (m, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 134.8, 129.1, 119.7, 118.3, 116.08, 61.8, 53.1, 49.1; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calculated for $C_{13}H_{19}N_2^+$ 203.1543, Found 203.1543.

Scale-up reduction of catalysts loading:



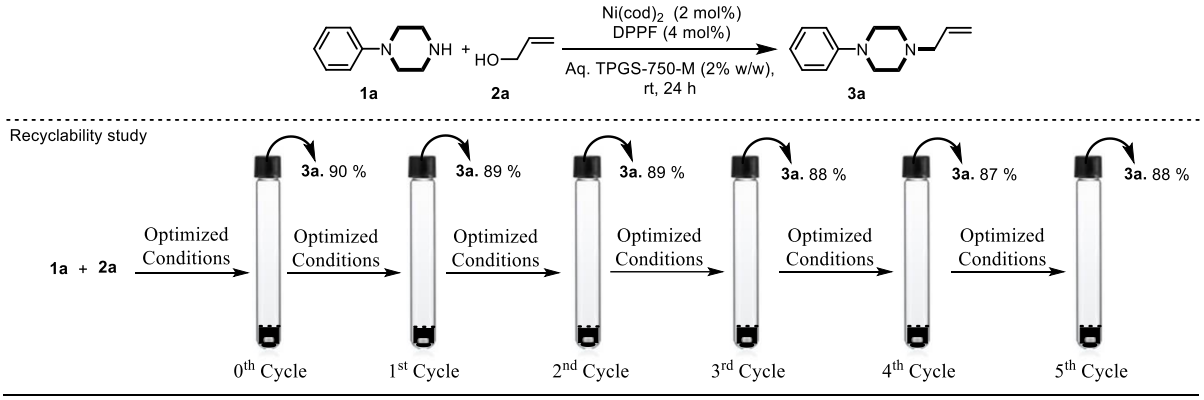
	Ni (mg)	DPPF (mg)	3a (g)	3a (%)
Ni (1 mol%)	7.71	33.26	0.53	86
Ni (0.5 mol%)	3.95	16.63	0.44	71

8. Recyclability study

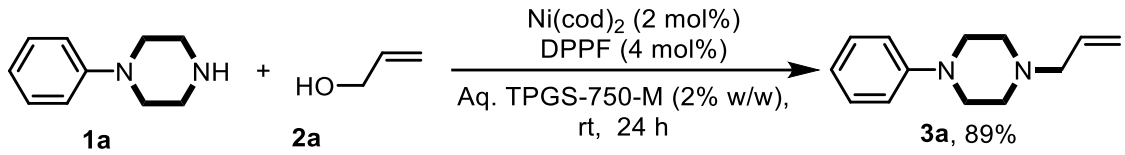
Procedure:

To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 2 mol%), DPPF (22.17 mg, 0.04 mmol, 4 mol%), 1-Phenylpiperazine **1a** (162.2 mg, 157.5 µL, 1 mmol), allyl alcohol **2a** (87.12 mg, 102.01 μL, 1.5 mmol, 1.5 equiv), and aqueous TPGS-750-M (2% w/w, 3 mL) were added. The resultant mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc (2 X 3 mL) and vortexed the resultant mixture. The supernatant liquid containing product and other organic residue was removed carefully after centrifugation. The recovered organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a** (36.5 mg, 90%) as pale yellow liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (td, J = 7, 2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.85 (t, J = 7.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.23 (dq, J = 17.0, 2.0 Hz, 1H), 5.20 - 5.18 (m, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 134.8, 129.1, 119.7, 118.3, 116.08, 61.8, 53.1, 49.1; **HRMS** (ESI-TOF) m/z: $[M + H]^+$ Calculated for $C_{13}H_{19}N_2^+$ 203.1543, Found 203.1543.

To the remaining aqueous layer same protocol as mentioned above was repeated except addition of fresh aqueous TPGS-750-M for product formation in the next consecutive cycles as summarized below.



9. E-factor determination for the developed protocol



To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (1.1 mg, 0.004 mmol, 2 mol%), DPPF (4.4 mg, 0.008 mmol, 4 mol%), 1-phenylpiperazine **1a** (32.4 mg, 30.5 μL, 0.2 mmol), allyl alcohol **2a** (17.4 mg, 20.4 μL, 0.3 mmol, 1.5 equiv), and aqueous TPGS-750-M (2% w/w, 0.5 mL) were added. The resultant mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with minimum volume of EtOAc (300 μL) and vortexed the resultant mixture. The supernatant liquid containing product and other organic residue was removed carefully. The recovered organic layer was dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and pass through the column (eluent: Hexane/EtOAc) to get analytically pure product **3a** (36.0 mg, 89%) as pale yellow liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.26 (td, J = 7, 2 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.85 (t, J = 7.0 Hz, 1H), 5.91 (ddt, J = 17.0, 10.0, 6.5 Hz, 1H), 5.23 (dq, J = 17.0, 2.0 Hz, 1H), 5.20 - 5.18 (m, 1H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (d, J = 6.5 Hz, 2H), 2.62 (t, J = 5.0 Hz, 4H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 151.4, 134.8, 129.1, 119.7, 118.3, 116.08, 61.8, 53.1, 49.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{19}N_2^+$ 203.1543, Found 203.1543.

Volume of EtOAc used = 300 μL = 0.3 mL
Density of EtOAc = 0.902 g/mL
Product yield = 36.0 mg = 0.036 g

$$\text{E Factor} = \frac{\text{organic waste (g)}}{\text{product (g)}} = \frac{\text{Waste of EtOAc used during workup (g)}}{\text{product (g)}}$$

$$= \frac{\text{Density of EtOAc (g/ mL) X EtOAc used (mL)}}{\text{Mass of product (g)}}$$

$$= \frac{0.902 \text{ X } 0.3}{0.036} = 7.5$$

Volume of TBME used = 300 μL = 0.3 mL
Density of TBME = 0.7404 g/mL
Product yield = 36.0 mg = 0.036 g

$$\text{E Factor} = \frac{\text{organic waste (g)}}{\text{product (g)}} = \frac{\text{Waste of TBME used during workup (g)}}{\text{product (g)}}$$

$$= \frac{\text{Density of TBME (g/ mL) X TBME used (mL)}}{\text{Mass of product (g)}}$$

$$= \frac{0.7404 \text{ X } 0.3}{0.036} = 6.1$$

---

10. Synthesis of Pharmaceuticals

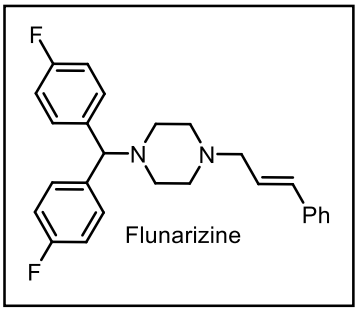
Flunarizine, sold under the brand name Sibelium among others, was discovered at Janssen Pharmaceutical (R14950) in 1968.

It is useful in the prophylaxis of migraine, treatment for vertigo of central and peripheral origin, and a worthwhile alternative as 'adjuvant' therapy in patients with epilepsy resistant to conventional drugs mainly where its effect is weak and not recommended. The available drug formulations are in form of tablets and capsules. Flunarizine is effective in the prophylaxis of occlusive peripheral vascular disease, It has been shown to significantly reduce headache frequency and severity in both adults and children.

	FLUNNARIZINE
Therapeutic Categories	• Vasodilator • Antivertigo agent • Histamine receptor antagonist (antihistaminic agent) • Calcium channel blocker (Class IV)
Key players in the global flunarizine hydrochloride market include:	• Johnson & Johnson • Cipla Limited • Torrent Pharmaceuticals Ltd. • Aa Pharma, Inc. • Karnataka Antibiotics & Pharmaceuticals Ltd. • Cadila Pharmaceuticals Ltd. • Orchid Chemicals & Pharmaceuticals Ltd. • Fdc Ltd. • Alkem Laboratories Ltd. • Intas Pharmaceuticals Ltd.
Mechanism of action	Flunarizine is a selective calcium antagonist with moderate other actions including antihistamine, serotonin receptor blocking and dopamine D2 blocking activity. Compared to other, flunarizine has low affinity to voltage-dependent calcium channels. It is theorized that it may act by an intracellular mechanism such as antagonising calmodulin, a calcium binding protein.
Available drug formulations	Tablet and capsules

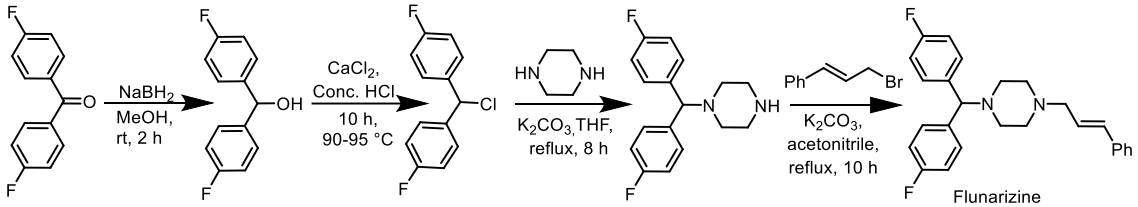
10.1 Synthesis of Flunarizine

Flunarizine, chemically known as 1-[bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine.



Reported synthetic routes for the Flunarizine

Narsaiah's Method (*Org Chem Ind J*., **2011**, *7*, 105)



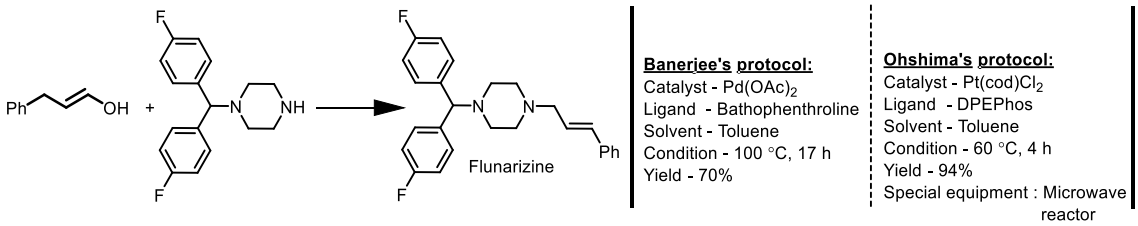
Drawbacks of Narsaiah's method:

(i) Use of highly corrosive Conc. HCl for the chlorination of corresponding alcohols. The corrosive nature of HCl causing damage to the reaction vessel as well as tissue. The concentrated fumes also cause serious irritation to the eye and respiratory tract.

(ii) Use of cinnamyl bromide led to the generation of highly corrosive acidic (HBr) waste which required separate (additional) basic treatment before its disposal.

(iii) All the steps were carried out in the volatile organic solvent (methanol, THF, acetonitrile) resulting enhanced cost and environment damage.

Banerjee's (*ChemSusChem*. **2012**, *5* 2044) and **Ohshima's** (*J. Am. Chem. Soc.*, **2009**, *131*, 14317) **Methods**



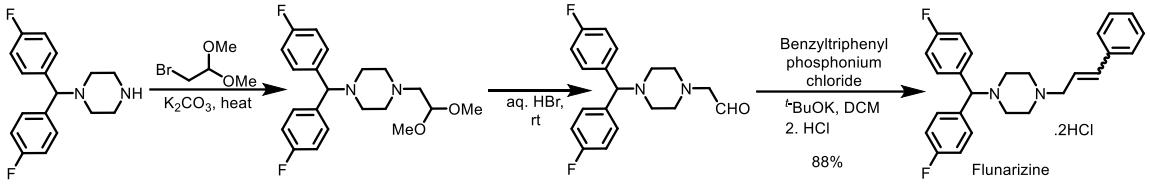
Drawback of these methods:

(i) Use of preformed key intermediates which require additional 3 – 4 steps for its preparation.

(ii) Use of precious metal-based catalytic systems (Pd – Banerjee's method; Pt – Ohshima's method)

(iii) Use of organic solvent as reaction media.

c) Shivprakash's Method (*Synth. Commun.*, **2013**, *44*, 600)



Drawbacks of Shivprakash's method:

(i) Use of preformed key starting materials which required additional 3 – 4 steps for its preparation.

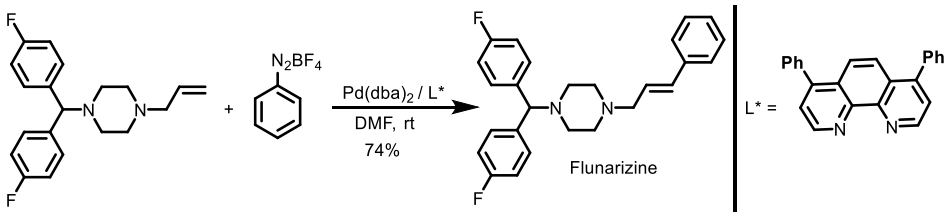
(ii) Use of additional protection/deprotection strategy thus lowering the overall atom-economy.

(ii) Use of highly corrosive acidic reagents (Aq. HBr) for the conversional of dimethyl acetal to the corresponding aldehyde.

(iv) A separate step for the preparation of benzyltriphenyl phosphonium chloride is needed.

(v) It led to the formation of stereoisomer, an undesirable outcome for drug development.

d) Ye's Method (*Org. Lett.* **2015**, *17*, 892)



Drawbacks of Ye's method:

(i) Use of preformed key intermediates. In general, it requires additional four steps to prepare it, increasing the cost of the overall process.

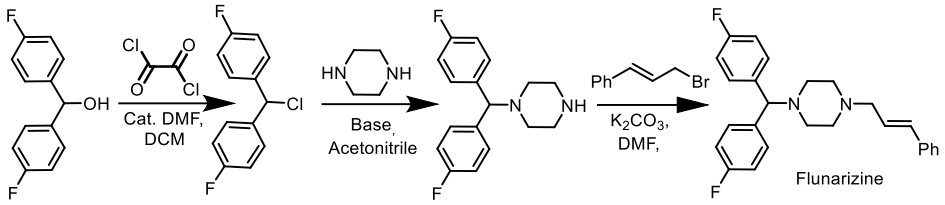
(ii) The preparation of phenyl diazonium salt requires an additional step.

(iii) Uses of expensive Pd-based metal catalysts.

(iv) Uses of *N*, *N*-dimethyl formamide (DMF; organic solvent) as reaction medium.

(v) Synthesis of 1-allyl-4-(bis(4-fluorophenyl)methyl)piperazine.

(e) Mahmoud's Method (*Mol Pharmacol.* **2015**, *87*, 197)



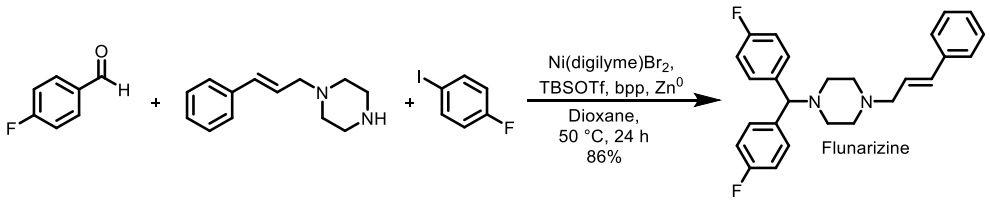
Drawback of Mahmoud's methods:

(i) Uses of highly flammable oxalyl chloride as chlorinating reagent.

(ii) Use of cinnamyl bromide led to the generation of highly corrosive acidic (HBr) waste which required separate basic treatment before its disposal.

(iii) Use of volatile organic solvents as reaction media e.g. DCM (causes ozone layer depilation), MeCN, and DMF.

(f) Heinz's Method (*J. Am. Chem. Soc.* **2018**, *140*, 2292)



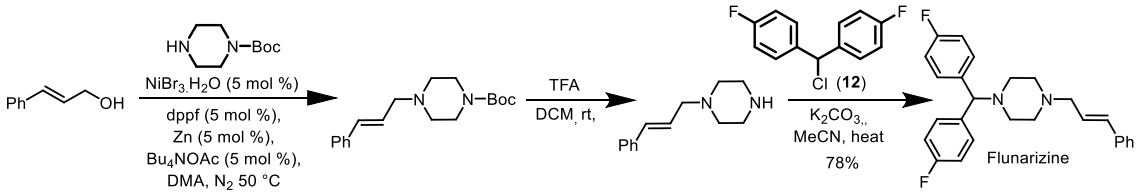
Drawback of Heinz's methods:

(i) Preparation of cinnamyl piperazine requires additional 3-steps.

(ii) Use of stoichiometric amount of TBSOTf as promoter, generate stoichiometric amount of highly acidic waste (triflic acid, TfOH) which require additional basic treatment before its disposal.

(iii) Use of 1,4-dioxane (organic solvent) as reaction medium.

Sweeney's Method (*Angew. Chem. Int. Ed.*, **2018**, *57*, 10202)



Drawbacks of Sweeney's methods:

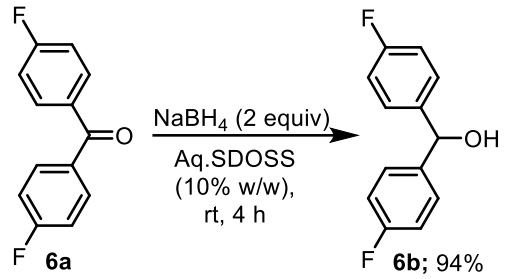
(i) Use of dimethylacetamide (DMA) as solvent for *N*-cinnamylation step. DMA is classified as Substance of Very High Concern (SVHC) because of its reproductive toxicity and teratogenicity by European Union (EU).

(ii) Use of Boc-piperazine as starting material which required additional step (protection and deprotection)

(iii) Use of dichloromethane (DCM) and acetonitrile (MeCN) as solvents.

"All-water" synthesis of Flunarizine (present study)

STEP 1: Synthesis of bis(4-fluorophenyl)methanol (6b):



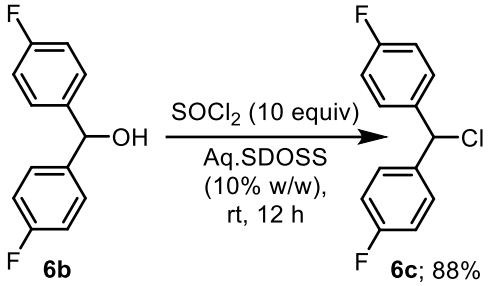
To a solution of 4,4'-difluorobenzophenone (**6a**) (436.0 mg, 2 mmol) in aqueous micellar system, $NaBH_4$ (151.0 mg, 4 mmol, 2 equiv) was added and the resultant mixture was stirred magnetically at room temperature. After completion of reaction (4 h, TLC), the precipitate was filtered off and washed with cold water and dried to get analytically pure bis-(4-fluorophenyl)methanol (**6b**, 207.0 mg , 94%); White solid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33 - 7.29 (m, 4H), 7.02 - 6.91 (m, 4H), 5.80 (d, J = 3.5 Hz 1H), 2.30 - 2.28 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.2 (d, $^1J_{C\text{-}F}$ = 244.6 Hz), 139.4, 128.2 (d, $^3J_{C\text{-}F}$ = 7.75 Hz), 115.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz), 74.9; **^{19}F NMR** (471 MHz $CDCl_3$): δ -114.7(s); **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_{11}F_2O^+$ 221.0772, Found 221.0769.

Table S3. Effect of aqueous micellar system on the reduction of 4,4'-difluorobenzophenone (**6a**) with $NaBH_4$.[a]

Entry	Aq. Surfactant (% w/w)	$NaBH_4$ (x equiv)	Time (h)	Yield (%)[b]
1.	SDS (10% w/w)	2	12	62
2.	SDOSS (10% w/w)	2	12	91
3.	Tween 20 10% w/w	2	12	42
4.	SDOSS (10% w/w)	2	4	91
5.	SDOSS (10% w/w)	0.5	4	10
6.	SDOSS (10% w/w)	1	4	16
7.	SDOSS (10% w/w)	1.5	4	56
8.	SDOSS (10% w/w)	2	4	91
9.	SDOSS (10% w/w)	3	4	91
10.	SDOSS (10% w/w)	2	2	58
11.	**SDOSS (10% w/w)**	**2**	**4**	**94**

[a]Treatment of **6a** (0.2 mmol) with sodium borohydride (x equiv) in different aqueous micellar system at room temperature under different conditions. [b]Isolated yield.

STEP 2: Synthesis of chloro-bis (4-fluorophenyl)methane (6c)



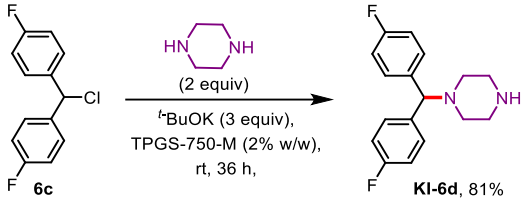
To the solution of bis(4-fluorophenyl)methanol (**6c**) (220 mg, 1 mmol) in aqueous micellar system, $SOCl_2$ (1.2 g, 1.45 mL, 10 mmol, 10 equiv) was added and the resultant mixture was stirred magnetically at room temperature. After completion of reaction (12 h, TLC), the reaction mixture was quenched by Na_2CO_3 and subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure chloro-bis (4-fluorophenyl)methane (**6c**, 210.0 mg, 92%); Pale yellow liquid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37 - 7.34 (m, 4H), 7.05 - 7.02 (m, 4H), 6.10 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.4 (d, $^1J_{C\text{-}F}$ = 246.25 Hz), 136.8, 129.6 (d, $^3J_{C\text{-}F}$ = 8.25 Hz), 115.7 (d, $^2J_{C\text{-}F}$ = 21.62 Hz), 62.8; **^{19}F NMR** (471 MHz $CDCl_3$): δ -113.6 (s); **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_9ClF_2^+$ 239.0434; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{13}H_9ClF_2$ 239.0434, Found 239.0433.

Table S4. Effect of aqueous micellar system on the chlorination of bis (4-fluorophenyl)methanol (**6b**) using $SOCl_2$.[a]

Entry	Aq. Surfactant (% w/w)	$SOCl_2$ (X equiv)	Time (h)	Yield (%)[b]
1.	SDS (10% w/w)	10	12	58
2.	SDOSS (10% w/w)	10	12	89
3.	SPGS-750-M (2% w/w)	10	12	32
4.	SDOSS (10% w/w)	5	12	67
5.	SDOSS (10% w/w)	10	2	52
6.	SDOSS (10% w/w)	10	4	88

[a]Treatment of **6b** (0.2 mmol) with $SOCl_2$ (2 mmol, 10 equiv) in different aqueous micellar system at room temperature under different conditions. [b]Isolated yield.

STEP-3: Synthesis of bis (4-fluorophenyl)methyl piperazine (KI-6d)



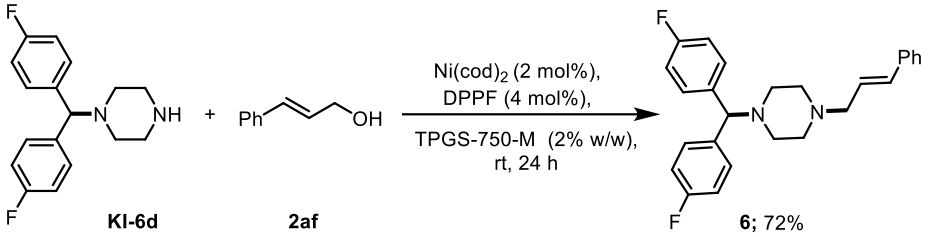
To the solution of chloro-bis(4-fluorophenyl)methane (**6c**) (119.3 mg, 0.5 mmol) in aqueous micellar system, piperazine (86.15 mg, 1 mmol, 2 equiv) and ^{t}-BuOK (168.3 mg, 1.5 mmol, 3 equiv) were added and the resultant mixture was stirred magnetically at room temperature. After completion of reaction (36 h, TLC), the reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure bis (4-fluorophenyl)methyl piperazine (**KI-6d**, 233.5 mg, 81%); White solid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35-7.32 (m, 4H), 6.98-6.94 (m, 4H), 4.20 (s, 1H), 2.89-2.86 (t, J = 5 Hz, 4H), 2.31 (s, 4H), 1.56 (br, s, 1H NH); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.8 (d, $^{1}J_{C\text{-}F}$ = 245.82 Hz), 138.2, 129.4 (d, $^{3}J_{C\text{-}F}$ = 7.81 Hz), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.42 Hz), 75.1, 53.2, 46.3; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -115.8 (s); **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{19}F_2N_2$ 289.1511, found 289.1512.

Table S5. Effect of aqueous micellar system on the amination reaction using chloro-bis (4-fluorophenyl)methane (**6c**) with piperazine.[a]

Entry	Aq. Surfactant (% w/w)	Base (X equiv)	Time (h)	Yield (%)[b]
1.	SDS (10% w/w)	K_2CO_3 (3 equiv)	12	16
2.	SDOSS (10% w/w)	K_2CO_3 (3 equiv)	12	26
3.	Tween 20 10% w/w	K_2CO_3 (3 equiv)	12	25
4.	TPGS-750-M (10% w/w)	K_2CO_3 (3 equiv)	12	45
5.	SPGS-750-M (2% w/w)	K_2CO_3 (3 equiv)	12	32
6.	TPGS-750-M (10% w/w)	K_2CO_3 (3 equiv)	24	58
7.	TPGS-750 M (2% w/w)	Na_2CO_3(3equiv)	24	46
8.	TPGS-750 M (2% w/w)	Cs_2CO_3(3 equiv)	24	56
9.	TPGS-750 M (2% w/w)	^{t}-BuOK (3 equiv)	24	69
10.	TPGS-750 M (2% w/w)	K_3PO_4 (3 equiv)	24	52
11.	TPGS-750 M (2% w/w)	^{t}-BuOK (2 equiv)	24	48
12.	TPGS-750 M (2% w/w)	^{t}-BuOK (4 equiv)	24	71
13.	TPGS-750 M (2% w/w)	^{t}-BuOK (3 equiv)	36	81[c]

[a] Treatment of **6c** (0.2 mmol) with piperazine (0.4 mmol, 2 equiv) in different aqueous micellar system at room temperature under different conditions. [b]Isolated yield. [c]Under heating condition

STEP-4: Synthesis of 1-[bis(4-fluorophenyl)methyl]-4-[(2*E*)-3-phenylprop-2-en-1-yl]piperazine (Flunarizine)



To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (1.1 mg, 0.004 mmol, 2 mol%), DPPF (4.4 mg, 0.008 mmol, 4 mol%) and bis-(4-fluorophenyl)methyl piperazine (**KI-6d**) (86.5 mg, 0.3 mmol, 1.5 equiv) were added followed by addition of aqueous TPGS-750-M (2% w/w, 0.5 mL), and cinnamyl alcohol (**2af**) (26.83 mg, 25.7 µL, 0.2 mmol, 1 equiv). The resultant mixture was stirred magnetically at room temperature for 24 h. The reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure flunarizine (**6,** 58.2 mg, 72%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.38 – 7.27 (m, 8H), 7.24 – 7.20 (m, 1H), 7.02 – 6.89 (m, 4H), 6.51 (d, J = 15.8 Hz, 1H), 6.26 (dt, J = 15.9, 6.9 Hz, 1H), 4.23 (s, 1H), 3.18 (dd, J = 6.9, 1.4 Hz, 2H), 2.48 (d, J = 65.2 Hz, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 161.8 (d, J = 245.4 Hz), 138.2 (d, J = 3.2 Hz), 136.9, 133.4, 129.3 (d, J = 7.9 Hz), 128.6, 127.5, 126.3, 115.4 (d, J = 21.4 Hz), 74.4, 60.9, 53.3, 51.6; **^{19}F NMR** (471 MHz, $CDCl_3$): δ -115.69 (s); **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{26}H_{27}F_2N_2$ 405.2137, Found 405.2137.

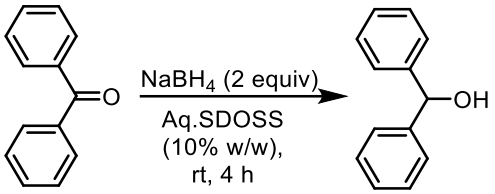
10.2. Synthesis of Cinnarizine

Cinnarizine, sold under the brand name Stugeron, Stunarone, Cinarin among others, was first synthesized as R1575 by Janssen Pharmaceutical in 1955.

	CINNARIZINE
Therapeutic Categories	Cinnarizine is predominantly used to treat nausea and vomiting associated with 1. motion sickness, 2. vertigo 3. Ménière's disease 4. Cogan's syndrome.
Key players in the global cinnarizine market include: (Alone or in combination)	• Goodwill Pharma • Allena Pharmaceuticals • East West Pharma • Hennig Arzneimittel • Johnson and Johnson • Novartis • Gedeon Richter • Nidda Healthcare • Teva • Sanofi • Eurofarma • Zambon • McNeil • Glenmark • Yuan Chou • Meda AB • Medical Need Europe AB • Balkanpharma-Razgrad. • Torrent Pharmaceuticals Ltd.
Mechanism of action	Calcium ion channel antagonist-T-type calcium channels Antihistaminic-H1 receptors Antiserotinergic-5-HT_2 receptors Antidopaminergic-D2 receptors. It acts by interfering with the signal transmission between vestibular apparatus of the inner ear and the vomiting centre of the hypothalamus by limiting the activity of the vestibular hair cells which send signals about movement
Available drug formulations	Tablet and capsules

"All-water" synthesis of Cinnarizine (present study)

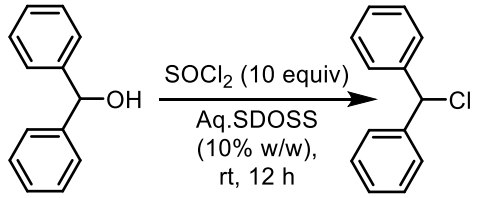
STEP 1: Synthesis of Diphenylmethanol (8c):



7a **7b;** 96%

To a solution of benzophenone (**7a**) (364.0 mg, 2 mmol) in aqueous micellar system, $NaBH_4$ (151.0 mg, 4 mmol, 2 equiv) was added and the resultant mixture was stirred magnetically at room temperature. After completion of reaction (4 h, TLC), the precipitate was filtered off and washed with cold water and dried to get analytically pure diphenylmethanol (**7b**, 353.6 mg, 96%); White solid; mp: 64 - 67 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 – 7.40 (m, 4H), 7.37 (t, J = 7.6 Hz, 4H), 7.32 – 7.28 (m, 2H), 5.88 (s, 1H), 2.28 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 143.8, 128.5, 127.6, 127.1, 126.6, 76.3.

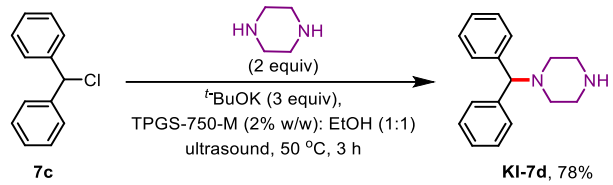
STEP 2: Synthesis of diphenylchloromethane



7b **7c**; 82%

To the solution of diphenylmethanol (**7b**) (184.0 mg, 1 mmol) in aqueous micellar system, $SOCl_2$ (1.2 g, 1.45 mL, 10 mmol, 10 equiv) was added and the resultant mixture was stirred magnetically at room temperature. After completion of reaction (12 h, TLC), the reaction mixture was quenched by Na_2CO_3 and subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure diphenylchloromethane (**7c**, 166.2 mg, 82%); **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 – 7.38 (m, 4H), 7.37 – 7.33 (m, 4H), 7.30 – 7.27 (m, 2H), 5.43 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 142.2, 128.4, 127.4, 127.3, 80.0.

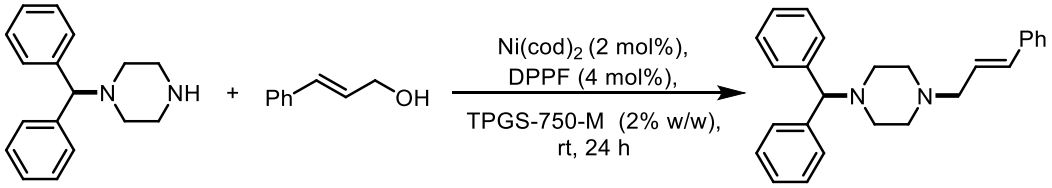
STEP-3: Synthesis of 1-benzhydrylpiperazine (8a)



7c **KI-7d**, 78%

To the solution of diphenylchloromethane (**7c**) (101.3 mg, 0.5 mmol) in aqueous micellar system, piperazine (86.15 mg, 1 mmol, 2 equiv) and ^{t}-BuOK (168.3 mg, 1.5 mmol, 3 equiv) were added and the resultant mixture was stirred magnetically in sonicator at 50 °C. After completion of reaction (3 h, TLC), the reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure 1-benzhydrylpiperazine (**KI-7d**, 196.8 mg, 78%); White solid; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41 – 7.34 (m, 4H), 7.32 – 7.23 (m, 5H), 7.18 (tt, J = 6.7, 1.1 Hz, 2H), 4.27 (s, 1H), 3.04 (t, J = 5.0 Hz, 4H), 2.53 (t, J = 4.9 Hz, 4H), 1.95 (s, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$): δ 141.8, 128.7, 127.8, 127.3, 76.0, 50.0, 44.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{17}H_{21}N_2$ 253.1699, found 253.1711.

Synthesis of 1-benzhydryl-4-cinnamylpiperazine (Cinnarizine)



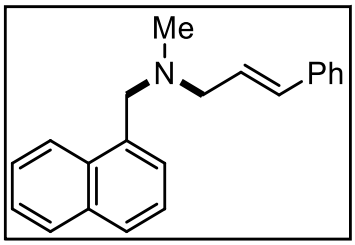
KI-6d **2af** **7**; 68%

To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (1.1 mg, 0.004 mmol, 2 mol%), DPPF (4.4 mg, 0.008 mmol, 4 mol%) and 1-benzhydrylpiperazine (**KI-6d**) (75.7 mg, 0.3 mmol, 1.5 equiv) were added followed by addition of aqueous TPGS-750-M (2% w/w, 0.5 mL), and cinnamyl alcohol (**2af**) (26.83 mg, 25.7 µL, 0.2 mmol, 1 equiv). The resultant mixture was stirred magnetically at room temperature for 24 h. The reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure cinnarizine (**7**, 50.1 mg, 68%); as buff white solid, **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 – 7.39 (m, 4H), 7.38 – 7.34 (m, 2H), 7.32 – 7.27 (m, 4H), 7.27 – 7.24 (m, 2H), 7.24 – 7.19 (m, 1H), 7.20 – 7.14 (m, 2H), 6.68 – 6.39 (m, 1H), 6.27 (dt, J = 15.8, 6.8 Hz, 2H), 4.24 (s, 1H), 3.17 (dd, J = 6.9, 1.4 Hz, 2H), 2.53 (br s, 8H).; **^{13}C NMR** (125 MHz, $CDCl_3$): δ 142.7, 136.9, 133.0, 128.5, 128.4, 127.9, 127.4, 126.9, 126.6, 126.3, 76.2, 61.0, 53.5, 51.9; **HRMS** (ESI-TOF) *m/z*: [M + H]+ Calculated for $C_{26}H_{29}N_2$ 369.2325, Found 369.2341.

10.3. Synthesis of Naftifine

Naftifine, mainly sold as Naftifine hydrochloride (naftifine), is an antifungal drug used to topically treat fungal infections /skin infections such as athlete's foot, jock itch, and ringworm infections. Naftifine topical is for use in adults and children who are at least 12 years old.

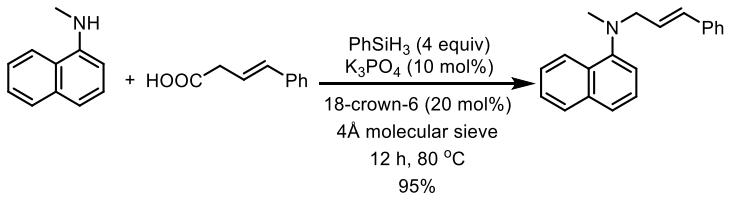
	NAFTIFINE
Therapeutic Categories	Naftifine topical is used in the treatment of: Tinea Corporis Tinea Cruris Tinea Pedis
Key players in the global Naftifine. HCl market include:	• Merz Dermatology • Parchem Fine and Specialty Chemicals • LGM Pharma • Sebela Pharmaceuticals • Erregierre • Simagchem Corporation • Taro Pharmaceutical Industrues • Renaissance Pharma • Shanghai Yisa Biotechnology • Shaanxi TOP Pharm Chemical
Mechanism of action	It has a complete anti-microbial mechanism of action comprising anti-fungal, anti-bacterial, and anti-inflammatory activity.
Available drug formulations	Topical application only: Cream, Ointment, gel



Naftifine, chemically known as (*E*)-N-methyl-N-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine

Selective reported synthetic routes for the Naftifine

a) Lin's (*Adv. Synth. Catal.* **2020,** *362,* 4151-4158.) **Methods**



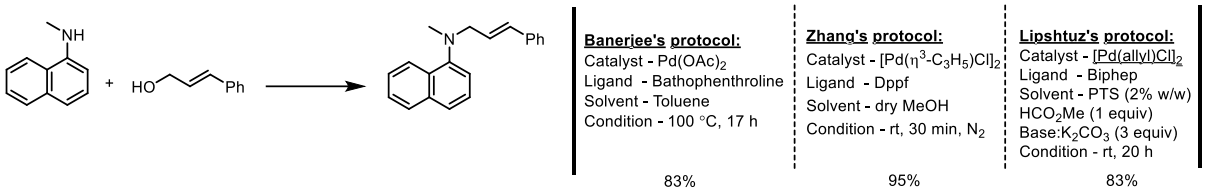
Drawback of these methods:

(i) Use of preformed key intermediates which require additional step for its preparation

(ii) Use of excessive additives

(iii) Use of acids as starting materials which needs to be synthesised from respective cinnamyl sources

b) Banerjee's (*ChemSusChem*. **2012**, *5* 2044) and **Zhang's** (*Chem. Commun.,* **2017,** *53,* 5151-5154) and **Lipshtuz's** (*Chem. Commun.* **2009**, 6472-6474) **Methods**



Drawback of these methods:

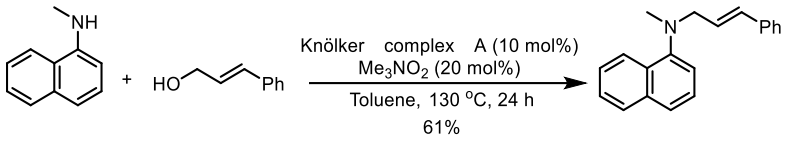
(i) Use of preformed key intermediates which require additional step for its preparation

(ii) Use of precious metal-based catalytic systems (Pd catalsyts)

(iii) Use of organic solvent as reaction media (Banerjee's protocol) and need of anhydrous conditions and inert environment (Zhang's protocol).

(iv) Use of additives like base and acid derivatives (Lipshtuz's protocol)

c) Sundararaju's Method (*Chem - A Euro. J.,* **2016,** *22,* 3952-3955)



Drawback of these methods:

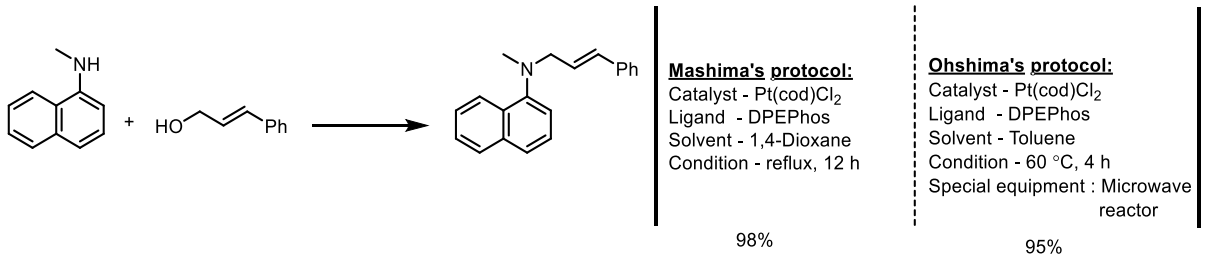
(i) Use of preformed key intermediates which require additional step for its preparation

(ii) Use of complex catalyst (Fe) which needs to be synthesized prior to use requiring additional steps

(iii) Use of organic solvent as reaction media and harsh reaction condition

(iv) Use of additives like reductants.

d) Mashima *et al*. (*Org. Lett.* **2007**, *9*, 3371–3374) **Ohshima's** (*J. Am. Chem. Soc.*, **2009**, *131*, 14317) **Methods**



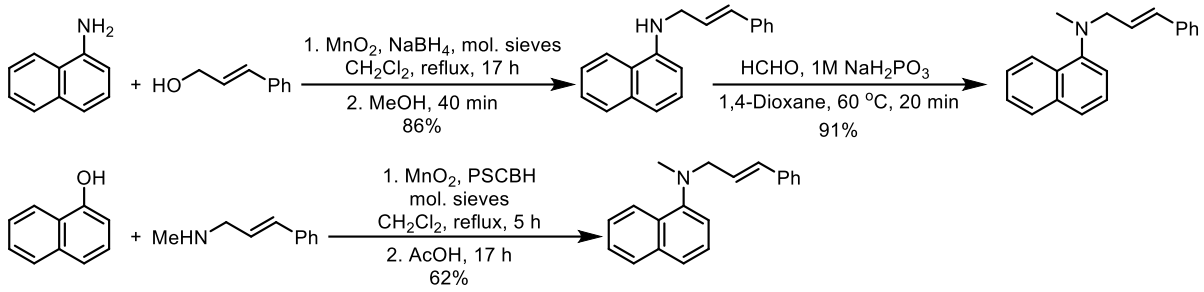
Drawbacks of Mashima's method:

(i) Use of precious metal-based catalytic systems

(ii) Use of preformed key intermediates which require additional step for its preparation

(iii) Use of organic solvent (1,4-Dioxane and Toluene) as reaction media resulting enhanced cost and environment damage.

e) Taylor *et al.* (*Tetrahedron Lett.*** **2002**, *43,* 7337-7340.) Method**



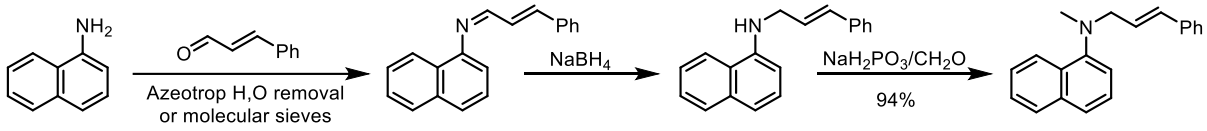
Drawbacks of Taylor's method:

(i) Use of additives like oxidants and reductants.

(ii) Cost of the resin-bound reductant and cyanohydrin derived by-products due to cyanide leaching from the resin

(iii) Use of organic halogenated solvent as reaction media resulting enhanced cost and environment damage.

f) Stuetz's Method (*J. Med. Chem.* **1986,** *29,* 112–125)



Drawback of these methods:

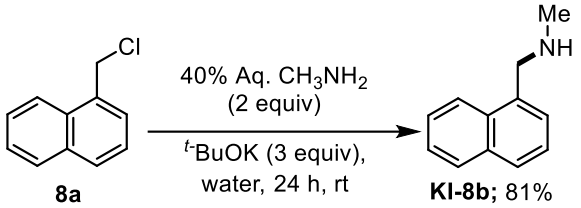
(i) Multistep reaction

(ii) Use of organic solvent as reaction media and harsh reaction condition

(iii) Use of additives like reductants.

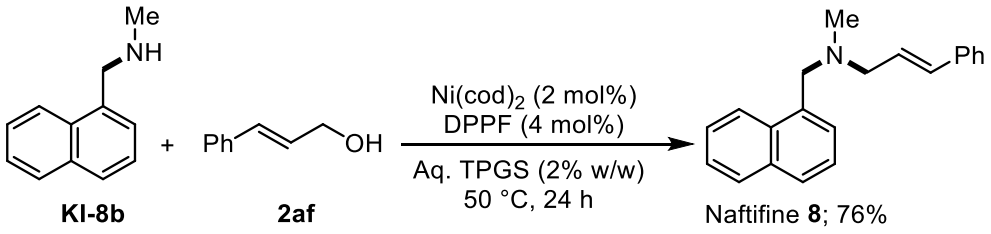
"All-water" synthesis of Naftifine (present study)

Step 1: Synthesis of *N*-methyl-1-(naphthalen-1-yl)methanamine (9a)



To the aqueous solution of 1-(chloromethyl)naphthalene (**8a**) (176.6 mg, 1 mmol) and ^{t}BuOK (336.6 mg, 3 mmol, 3 equiv) aqueous methyl amine 40% w/w solution (62.1 mg, 2 mmol, 2 equiv) was added and was stirred magnetically at room temperature till completion of reaction (24 h, TLC), the reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were was adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure *N*-methyl-1-(naphthalen-1-yl)methanamine (**KI-8b**, 138.7 mg, 81%); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.11 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.55 – 7.40 (m, 4H), 4.19 (s, 2H), 2.54 (s, 3H), 1.51 (br, s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 135.8, 133.9, 131.8, 128.7, 127.8, 126.2, 126.1, 125.6, 125.4, 123.7, 53.8, 36.6; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{12}H_{14}N$ 172.1121, Found 172.1121

Step 2: (*E*)-*N*-methyl-*N*-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine



To a well cleaned tube equipped with a stir bar, $Ni(cod)_2$ (1.0 mg, 0.004 mmol, 2 mol%), DPPF (4.4 mg, 0.008 mmol, 4 mol%) and *N*-methyl-1-(naphthalen-1-yl)methanamine **KI-8b** (51.37 mg, 0.3 mmol, 1.5 equiv) were added followed by addition of aqueous TPGS-750-M (2% w/w, 0.5 mL), and cinnamyl alcohol (**2af**) (26.83 mg, 25.7 µL, 0.2 mmol, 1 equiv). The resultant mixture was stirred magnetically at 100^{o}C for 24 h. The reaction mixture was subjected to aqueous workup using organic solvent (EtOAc). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were adsorbed on silica gel and purified by column chromatography (EtOAc : Hexane) to get analytically pure Naftifine (**8**, 43.6 mg, 76%); **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 8.30 (dd, J = 8.4, 1.2 Hz, 1H), 7.84 (dd, J = 8.2, 1.5 Hz, 1H), 7.77 (dt, J = 8.1, 1.1 Hz, 1H), 7.54 – 7.43 (m, 3H), 7.42 – 7.37 (m, 3H), 7.30 (d, J = 7.8 Hz, 2H), 7.24 – 7.20 (m, 1H), 6.57 (dt, J = 15.7, 1.4 Hz, 1H), 6.37 (dt, J = 15.9, 6.7 Hz, 1H), 3.94 (s, 2H), 3.28 (dd, J = 6.7, 1.4 Hz, 2H), 2.27 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.1, 134.8, 133.9, 132.7, 132.5, 128.5, 128.4, 127.9, 127.6, 127.4, 127.4, 126.3, 125.9, 125.6, 125.1, 124.6, 60.4, 60.1, 42.5; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calculated for $C_{21}H_{22}N$ 288.1747, Found 288.1748.

11. ICP-MS study

The ICH categorized the various elemental impurities in four different classifications to facilitate decisions during the risk assessment process. Nickel falls under Class 2a with **200 mg/L** (for oral application) and set according to the permitted daily exposure limits (PDE).

परिष्कृत वैश्लेषिक यंत्र सुविधा
भारतीय प्रौद्योगिकी संस्थान मुंबई
पवई, मुंबई-400 076, भारत
Sophisticated Analytical
Instrument Facility
Indian Institute of Technology Bombay
Powai, Mumbai-400 076, India

Tel : (+91-22) 25767691
(+91-22) 25767692
(+91-22) 25767690
Website : www.rsic.iitb.ac.in

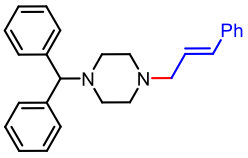
IIT Bombay

Ref: -ICP-MS-22
Date: 17/02/2021

Analytical report of the samples submitted by **Mr. Ramesh Chaudhary, NIPER, Ahmedabad-382355,** using Inductively Coupled Plasma Mass Spectroscopy (ICP-MS).

Sample	Ni (%)
MCRHC-527220	0.0012

ND MEANS LESS THAN 1 PPT

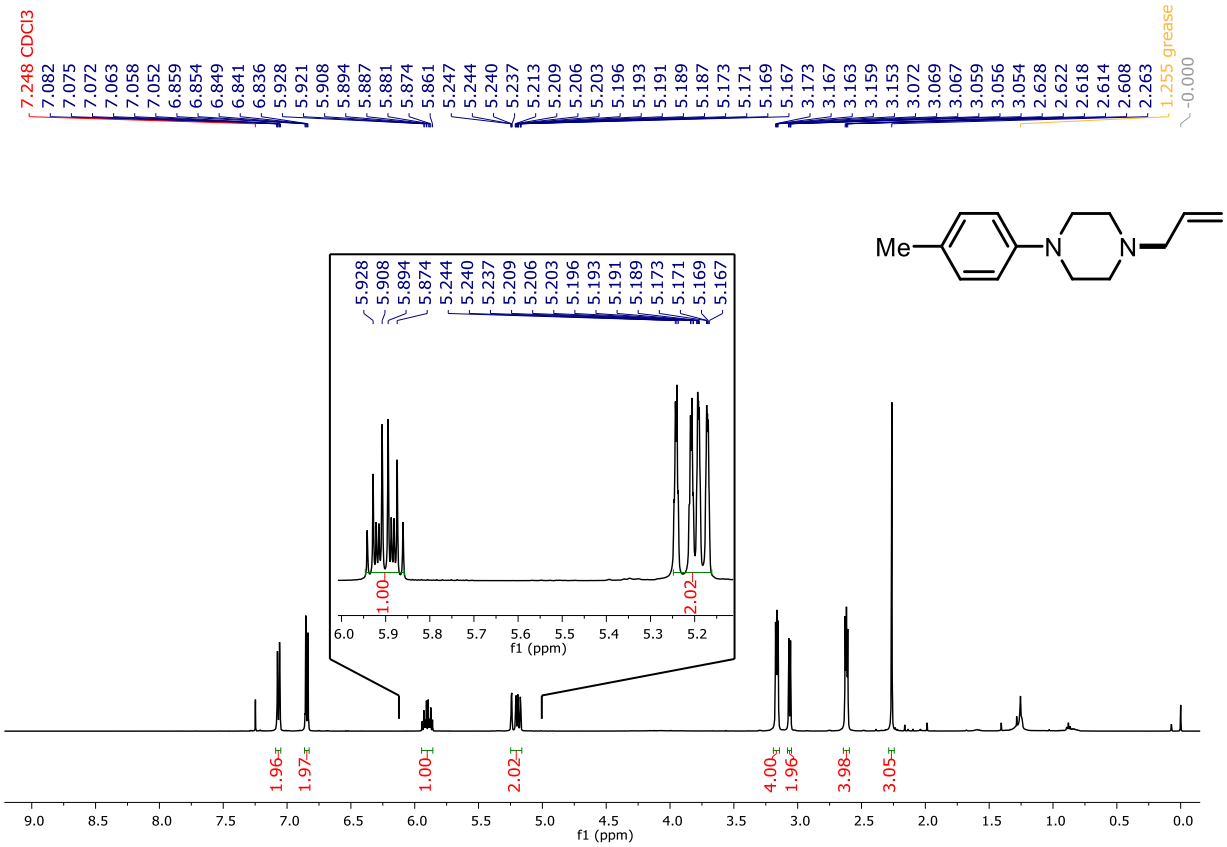


MCRHC-527220 (7)

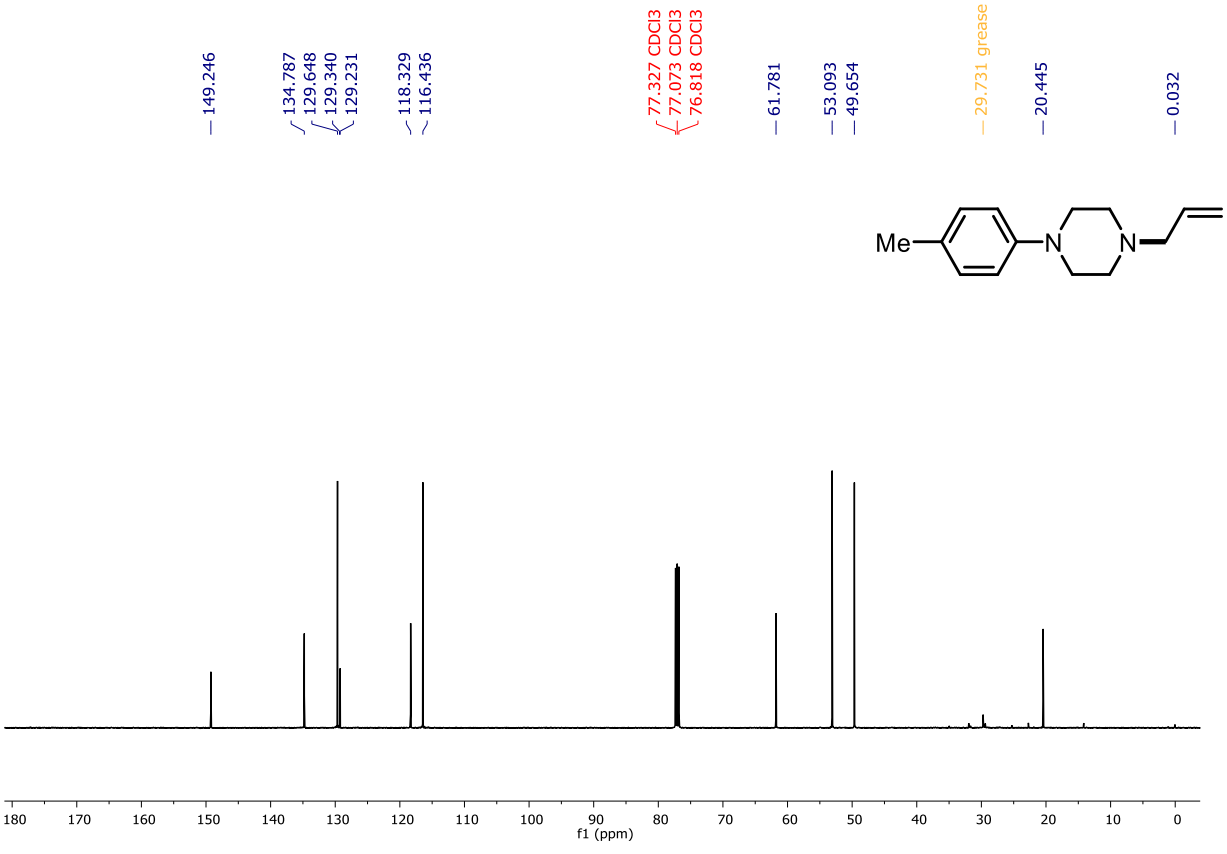
To,
Dr Dinesh Kumar,
Assistant Professor,
Dept Of Medicinal Chemistry,
NIPER,
Ahmedabad-382355

12. NMR spectra (^{1}H, ^{13}C, ^{19}F)

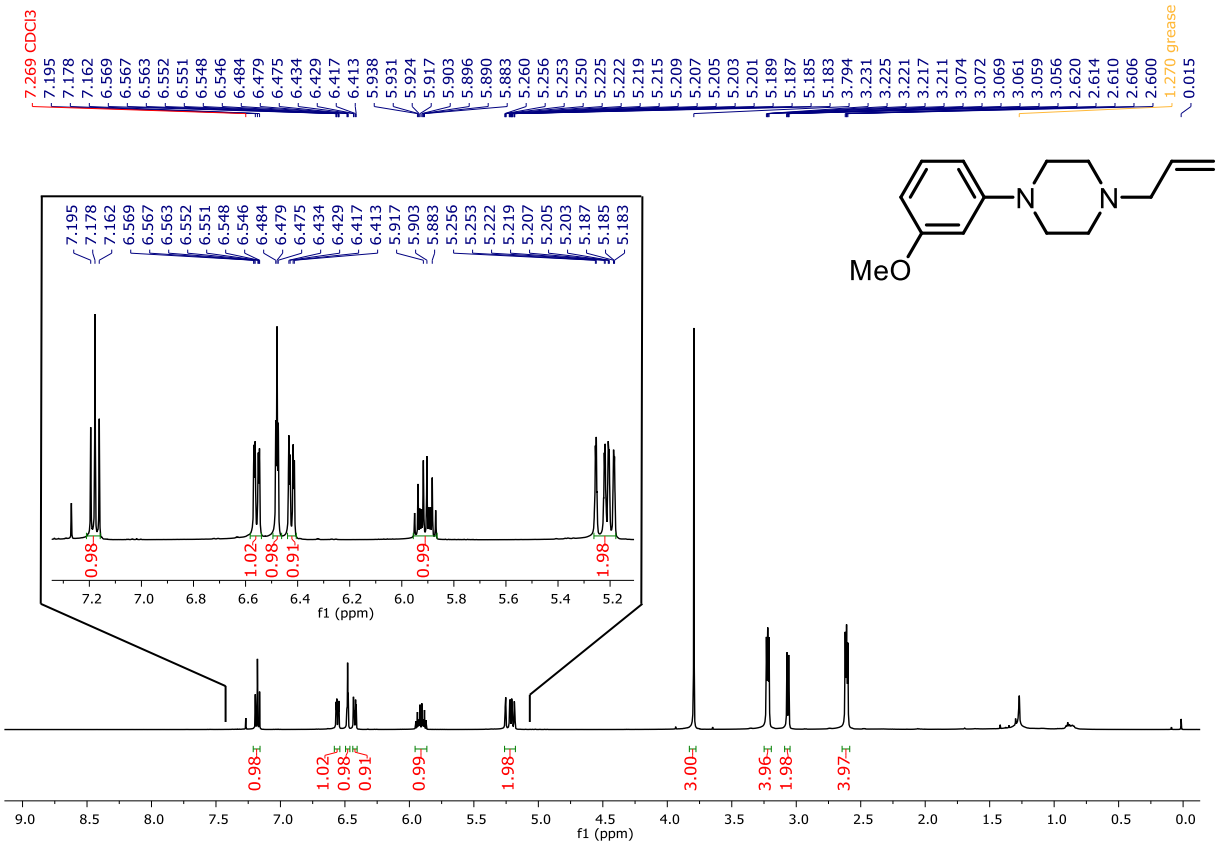
1-Allyl-4-(p-tolyl)piperazine (3b): ^{1}H NMR (500 MHz, CDCl3, 27°C, TMS)



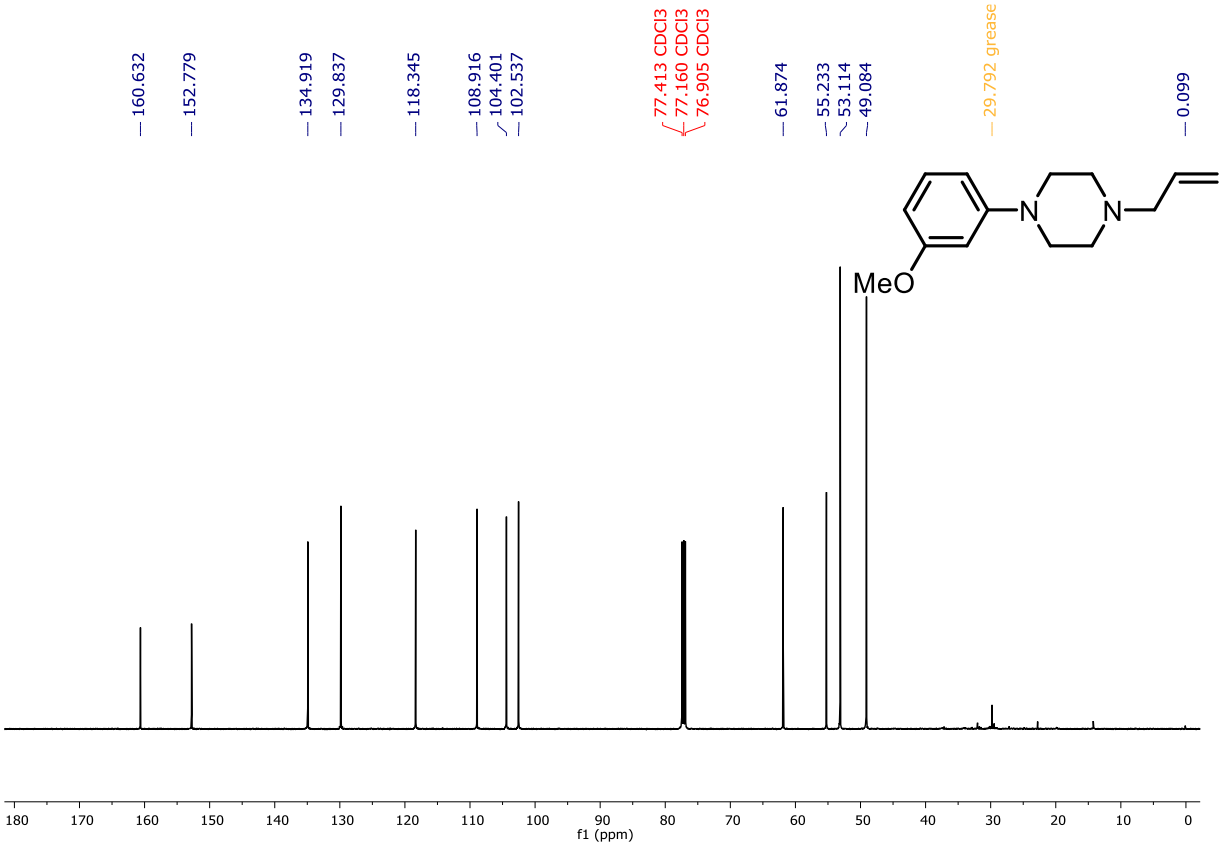
1-Allyl-4-(p-tolyl)piperazine (3b): ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS)



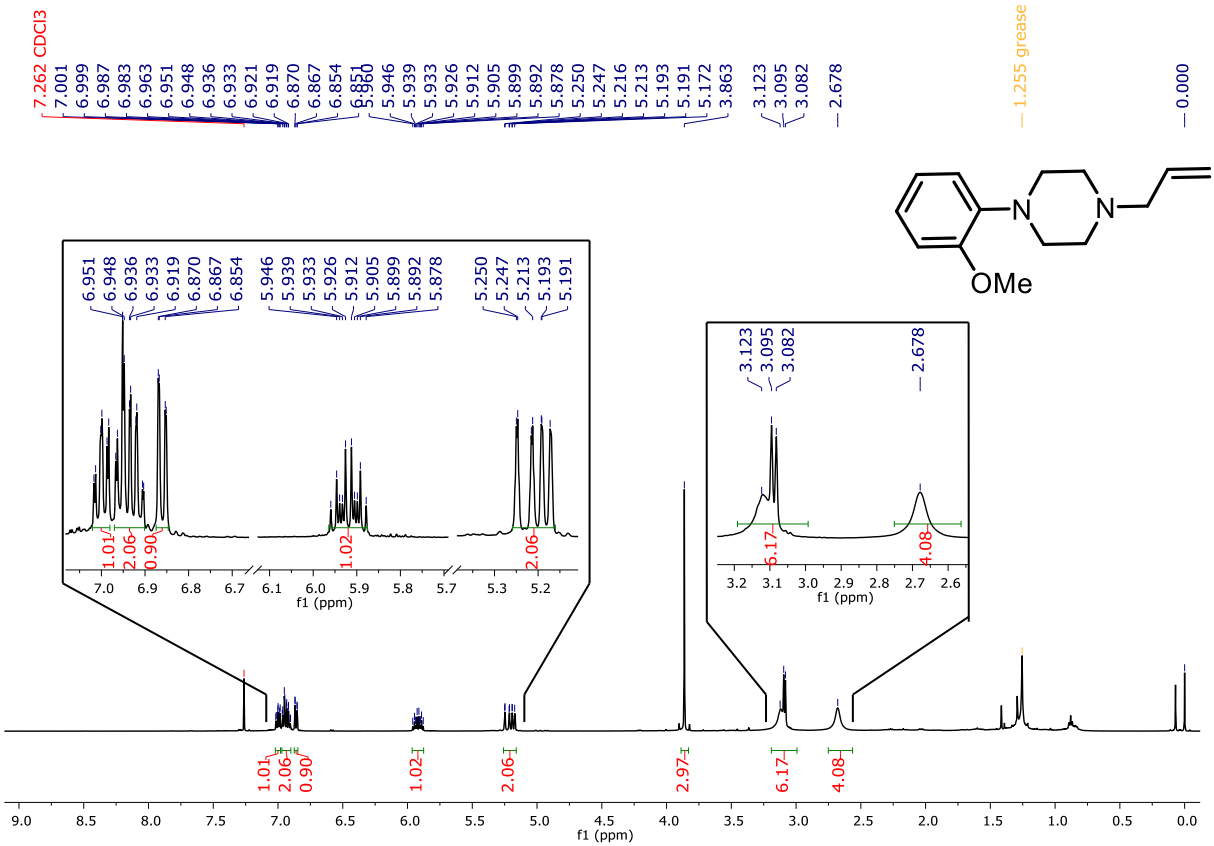
1-Allyl-4-(3-methoxyphenyl)piperazine (3c): ^{1}H NMR (500 MHz, $CDCl_3$)



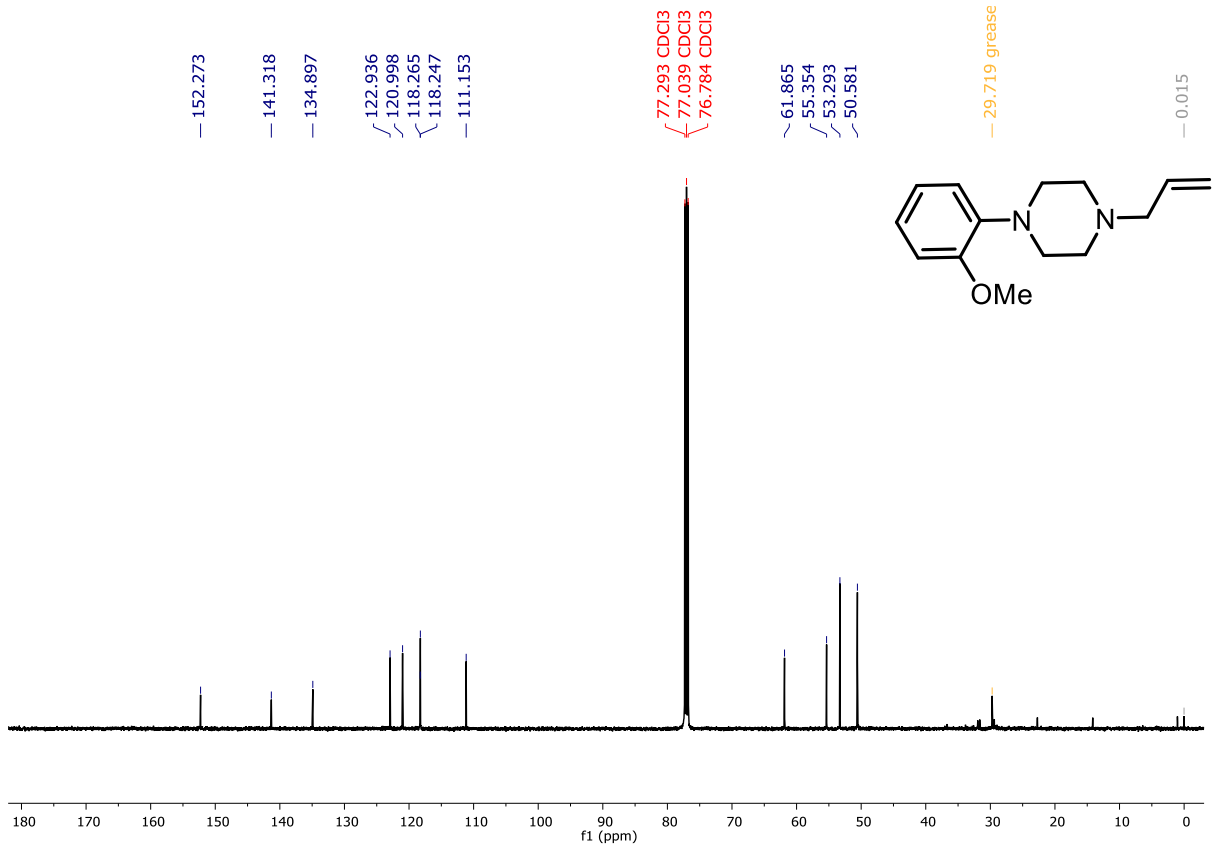
1-Allyl-4-(3-methoxyphenyl)piperazine (3c): ^{13}C NMR (125 MHz, $CDCl_3$)



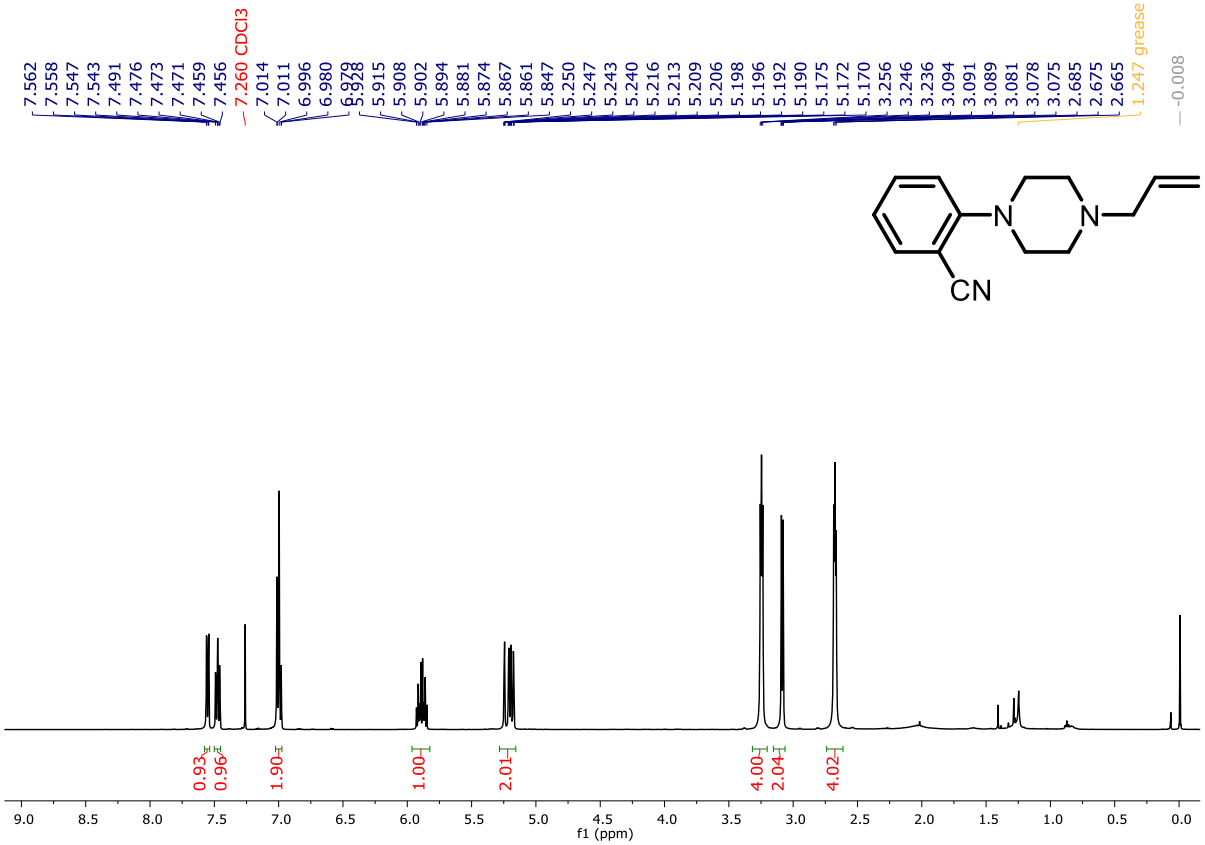
1-Allyl-4-(2-methoxyphenyl)piperazine (3d): ^{1}H NMR (500 MHz, $CDCl_3$)



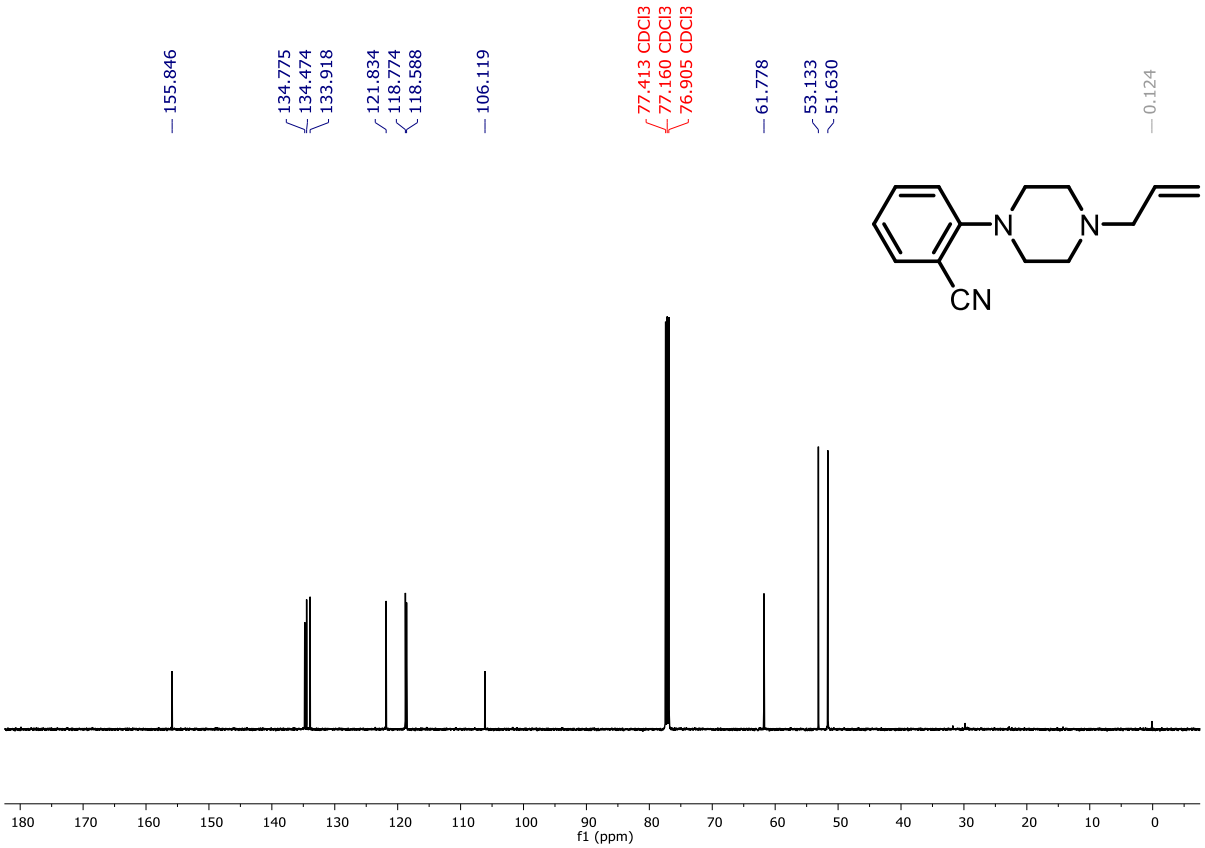
1-Allyl-4-(2-methoxyphenyl)piperazine (3d): ^{13}C NMR (125 MHz, $CDCl_3$)



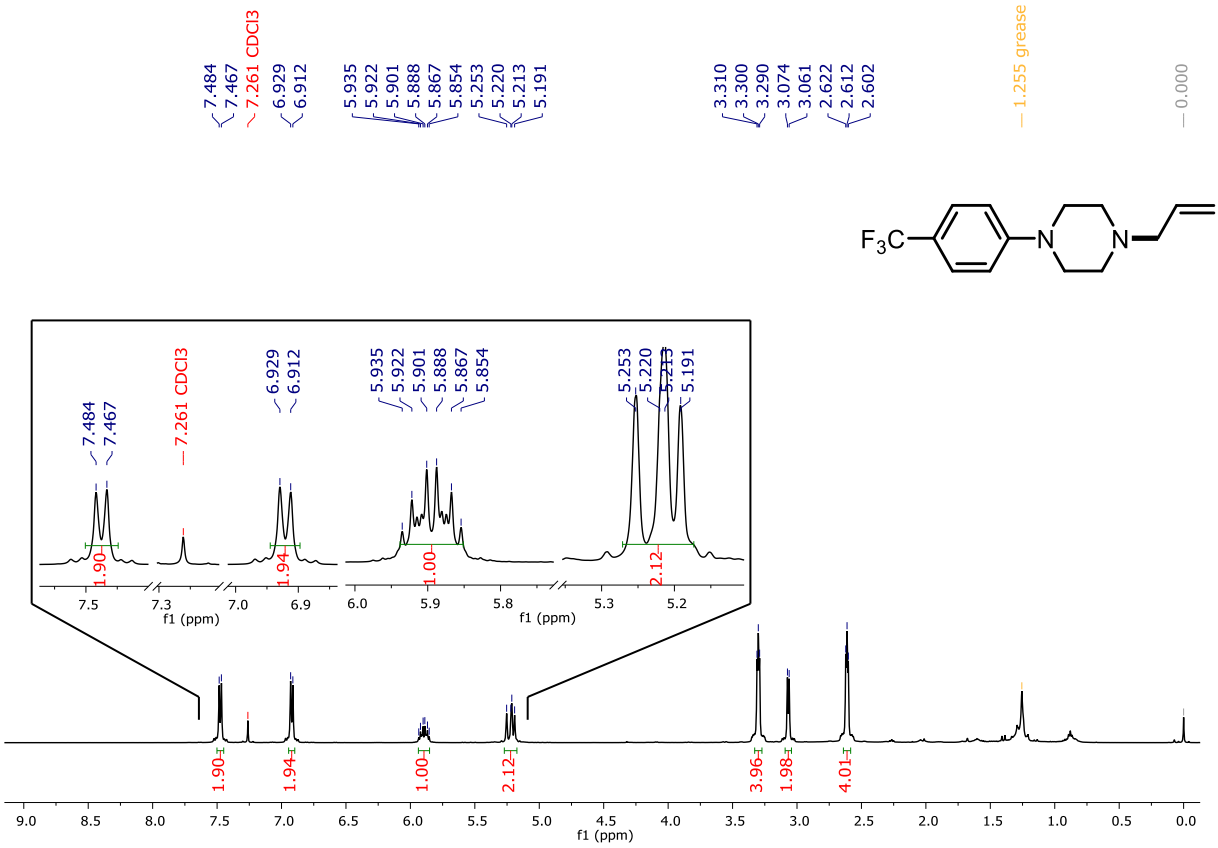
2-(4-Allylpiperazin-1-yl)benzonitrile (3e): ^{1}H NMR (500 MHz, $CDCl_3$)



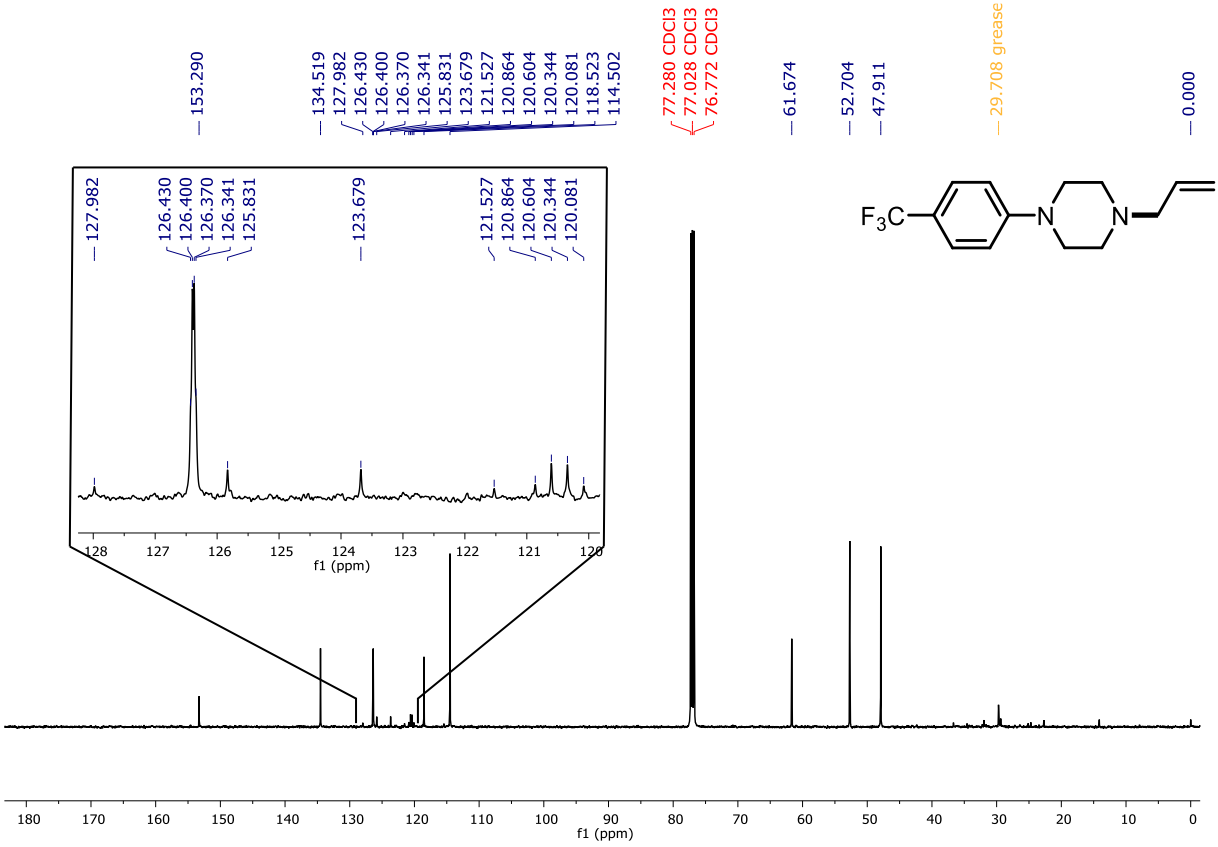
2-(4-Allylpiperazin-1-yl)benzonitrile (3e): ^{13}C NMR (125 MHz, $CDCl_3$)



1-Allyl-4-(4-(trifluoromethyl)phenyl)piperazine (3f): ^{1}H NMR (500 MHz, $CDCl_3$, 27°C, TMS)

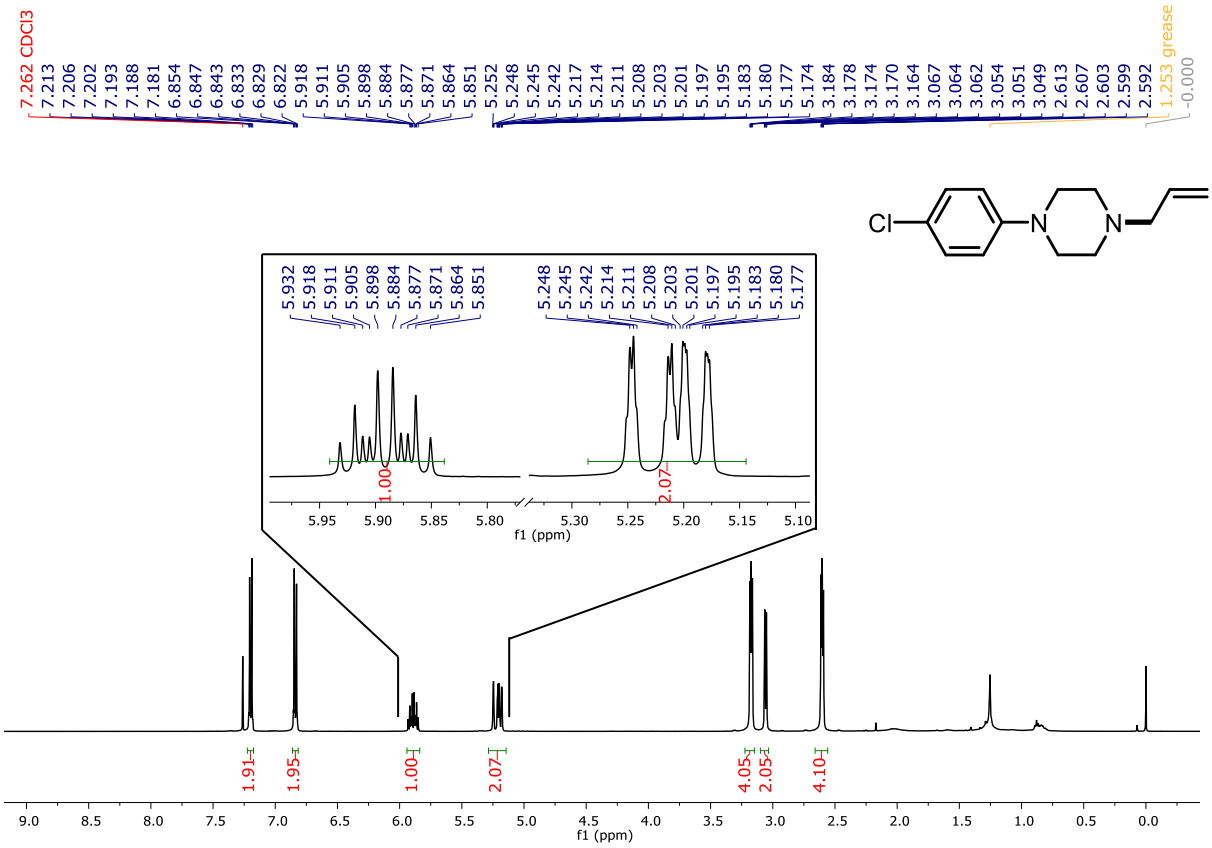


1-Allyl-4-(4-(trifluoromethyl)phenyl)piperazine (3f): ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS)

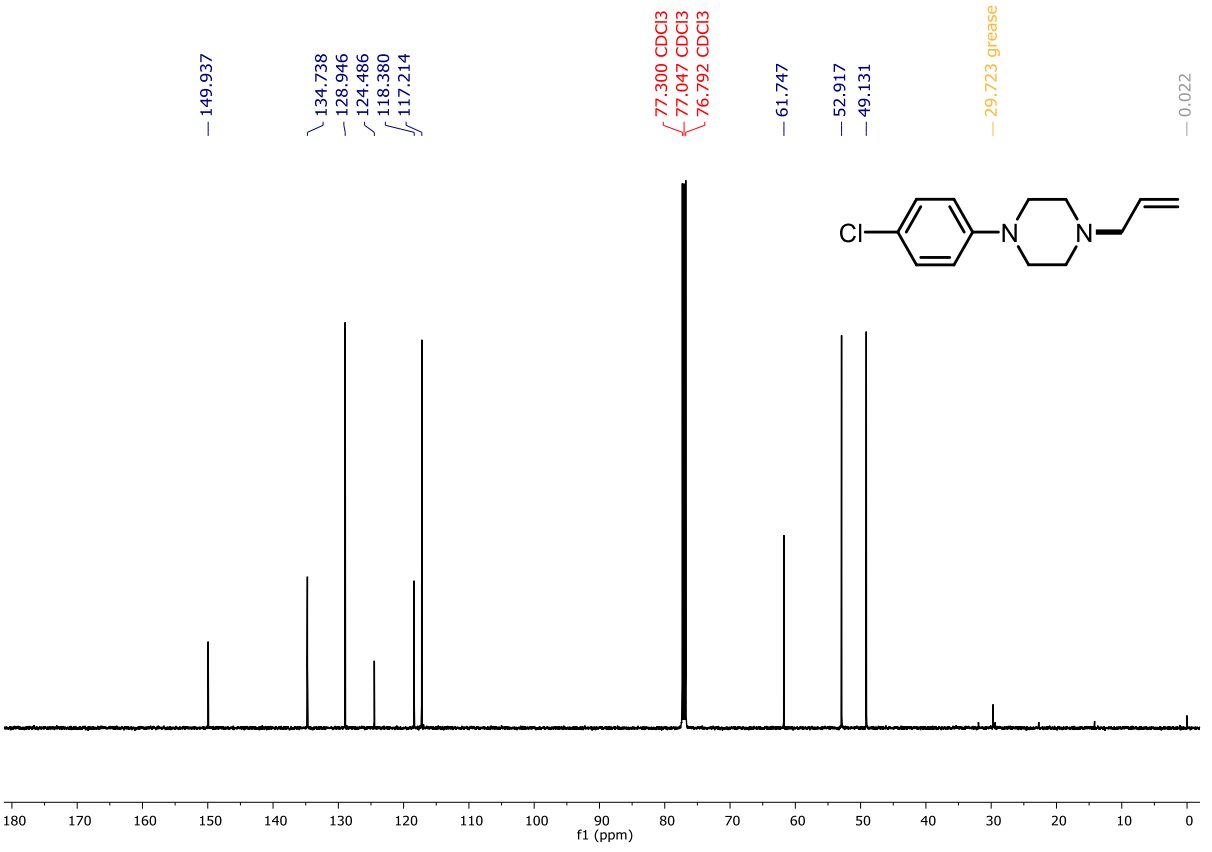


1-Allyl-4-(4-(trifluoromethyl)phenyl)piperazine (3f): ^{19}F NMR (471 MHz, $CDCl_3$):

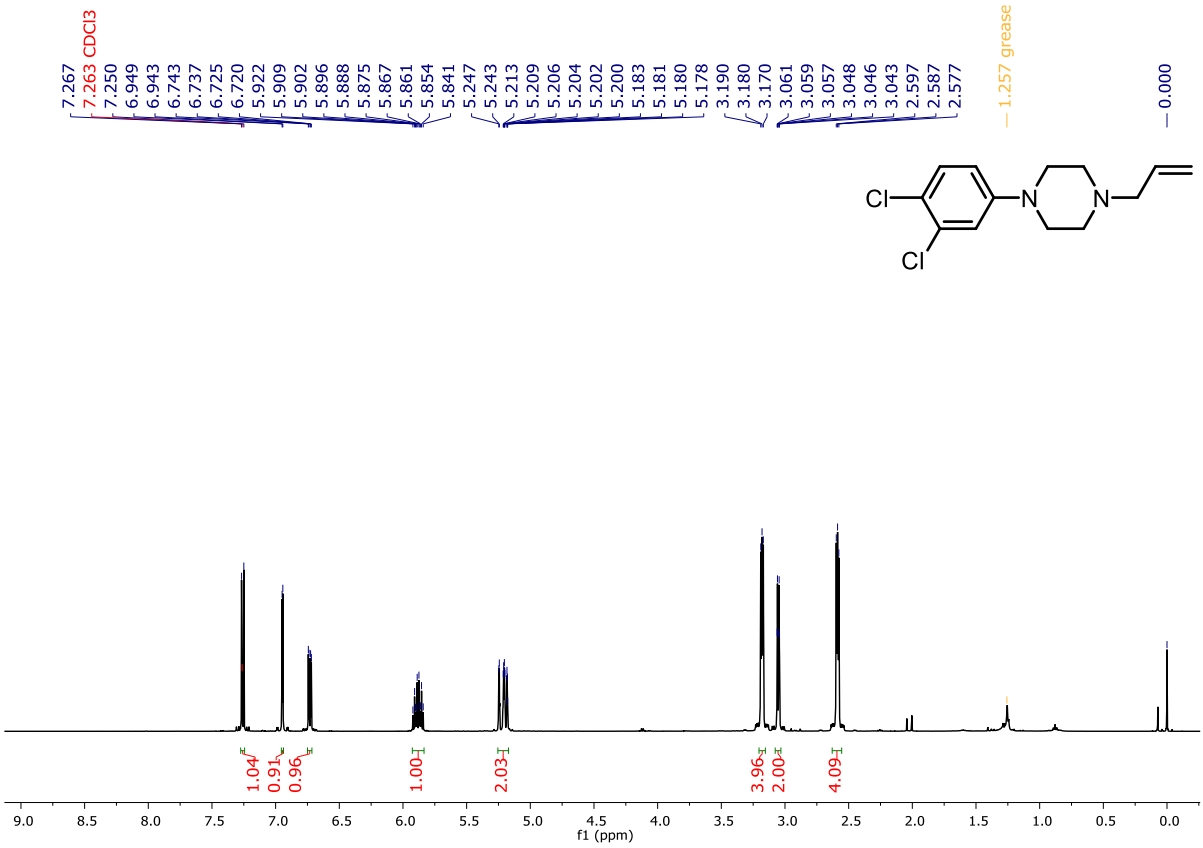
1-Allyl-4-(4-chlorophenyl)piperazine (3h): ^{1}H NMR (500 MHz, $CDCl_3$, 27°C, TMS)



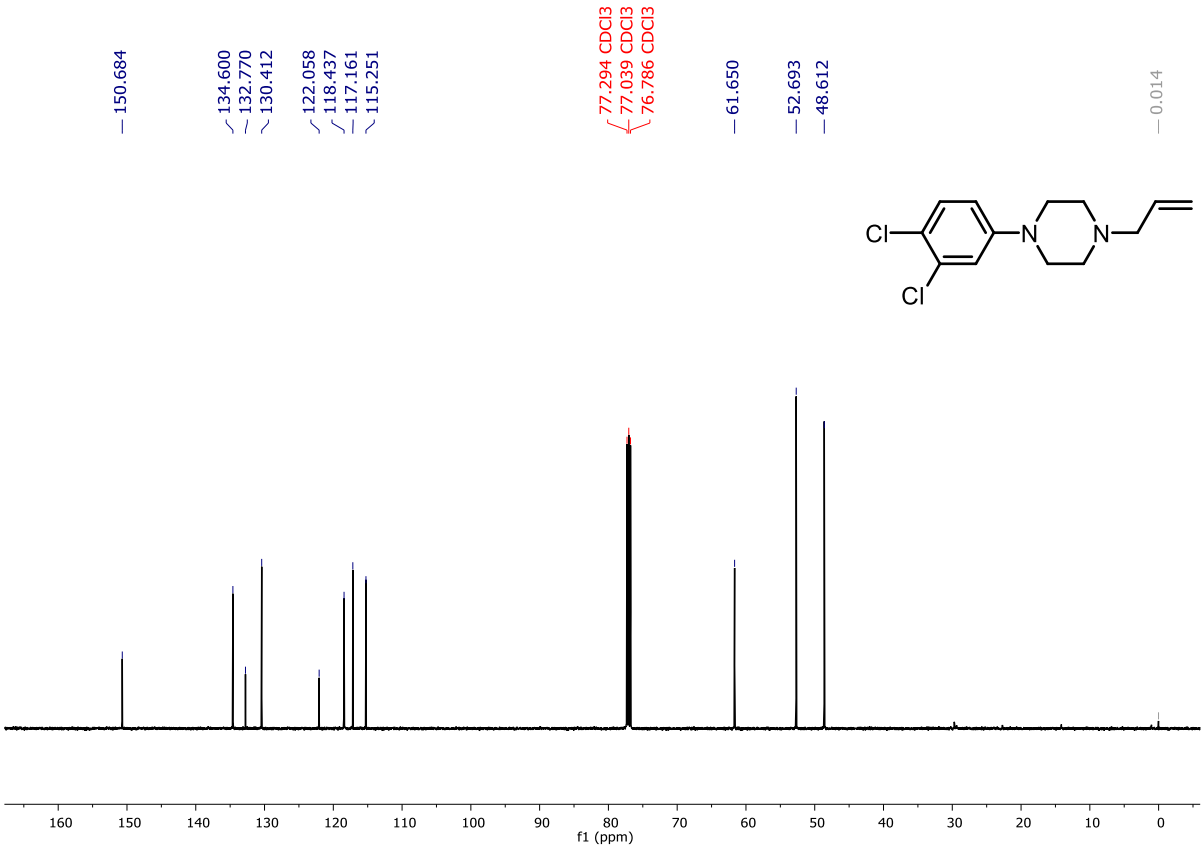
1-Allyl-4-(4-chlorophenyl)piperazine (3h): ^{13}C NMR (125 MHz, $CDCl_3$, 27°C, TMS)



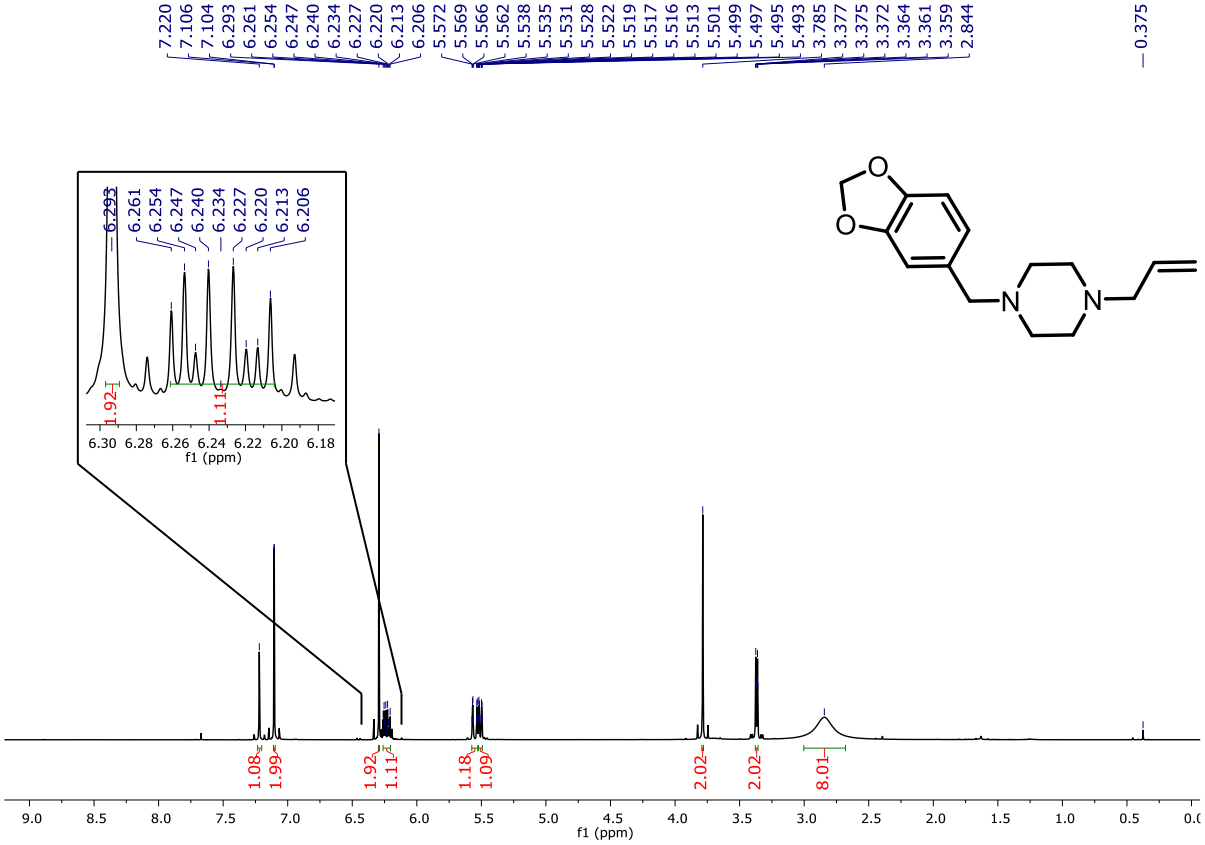
1-Allyl-4-(3,4-dichlorophenyl)piperazine (3i): ^{1}H NMR (500 MHz, $CDCl_3$)



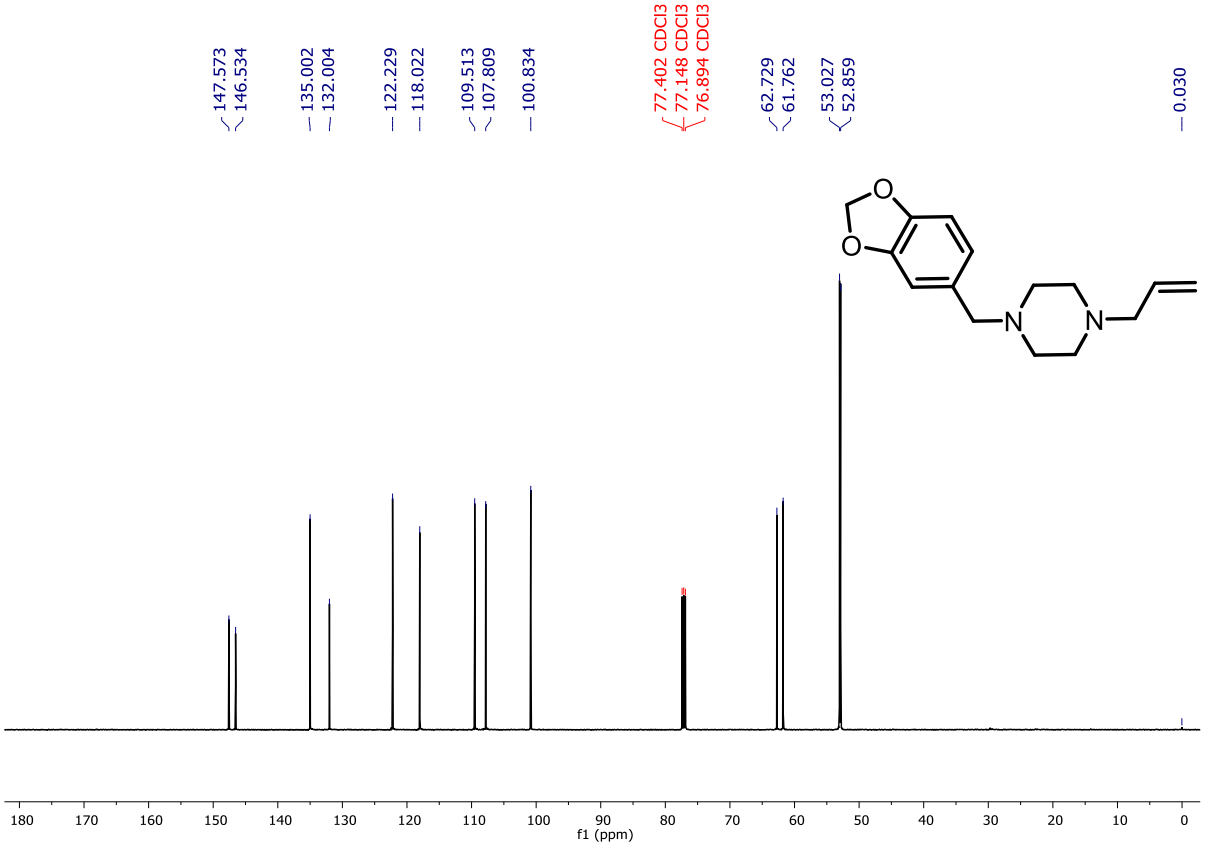
1-Allyl-4-(3,4-dichlorophenyl)piperazine (3i): ^{13}C NMR (125 MHz, $CDCl_3$)



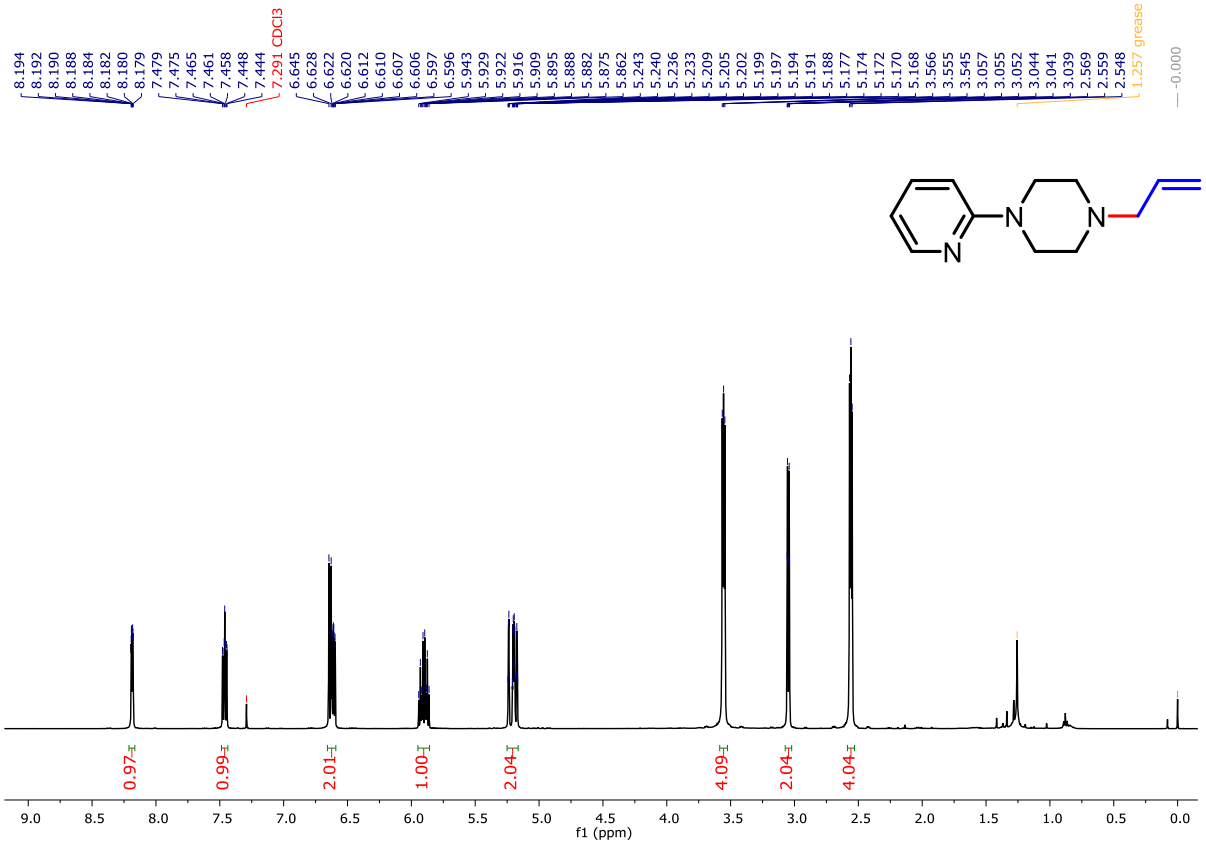
1-Allyl-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine (3j): ^{1}H NMR (500 MHz, $CDCl_3$)



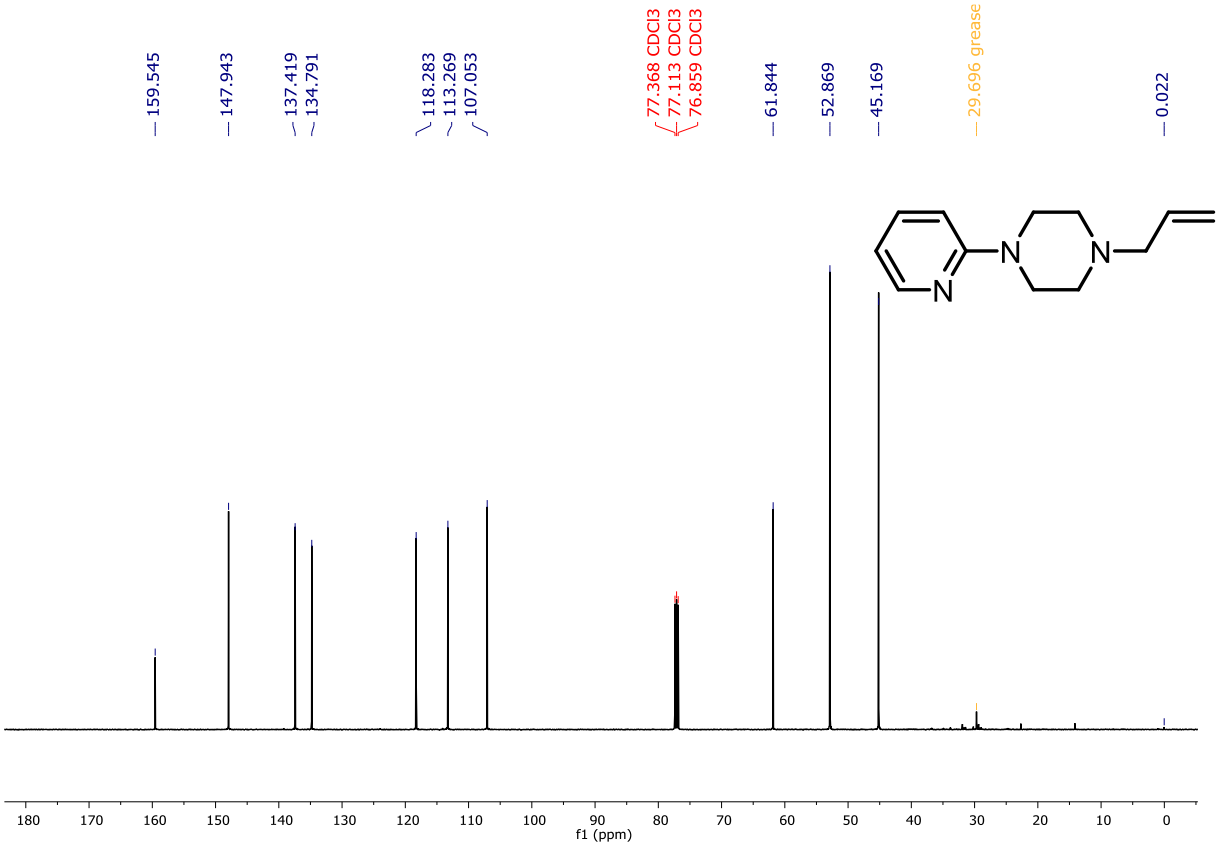
1-Allyl-4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazine (3j): ^{13}C NMR (125 MHz, $CDCl_3$)



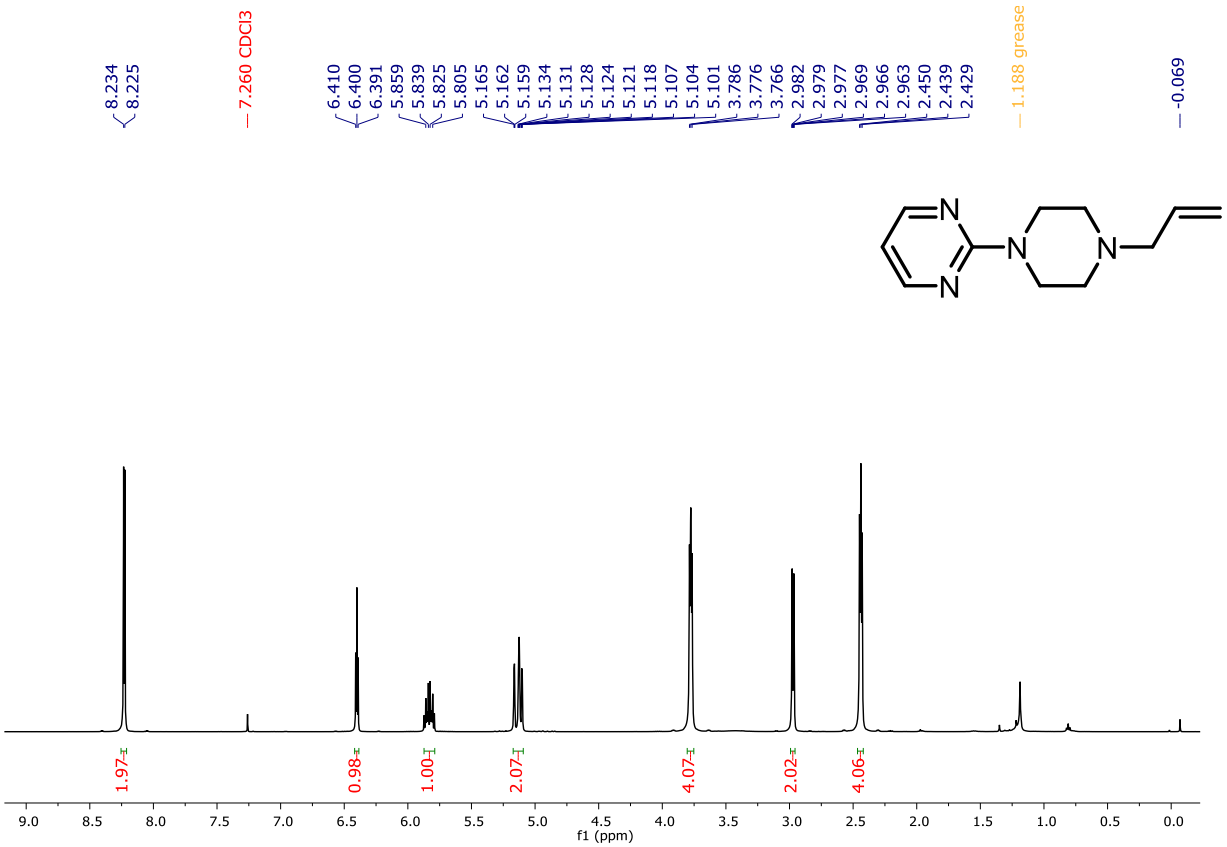
1-Allyl-4-(pyridin-2-yl)piperazine (3k): ^{1}H NMR (500 MHz, $CDCl_3$)



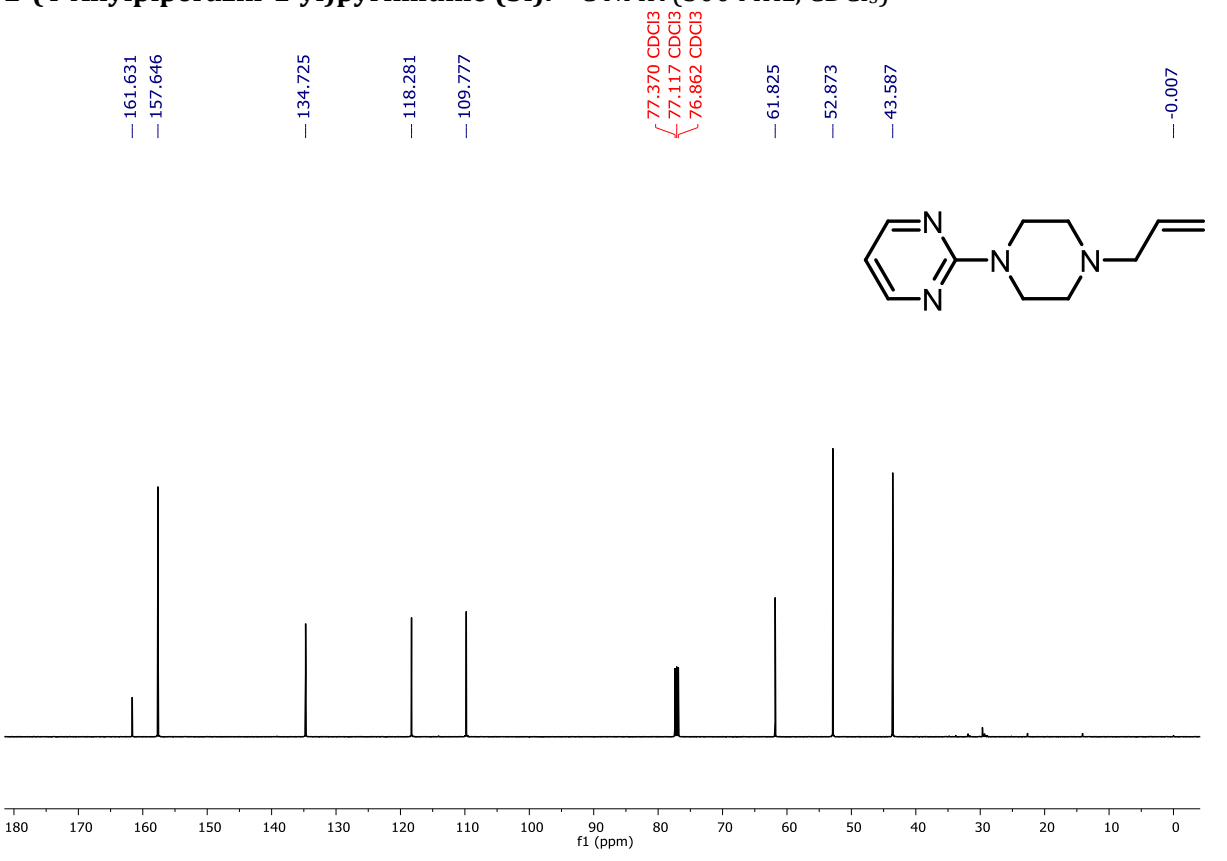
1-Allyl-4-(pyridin-2-yl)piperazine (3k): ^{13}C NMR (125 MHz, $CDCl_3$)



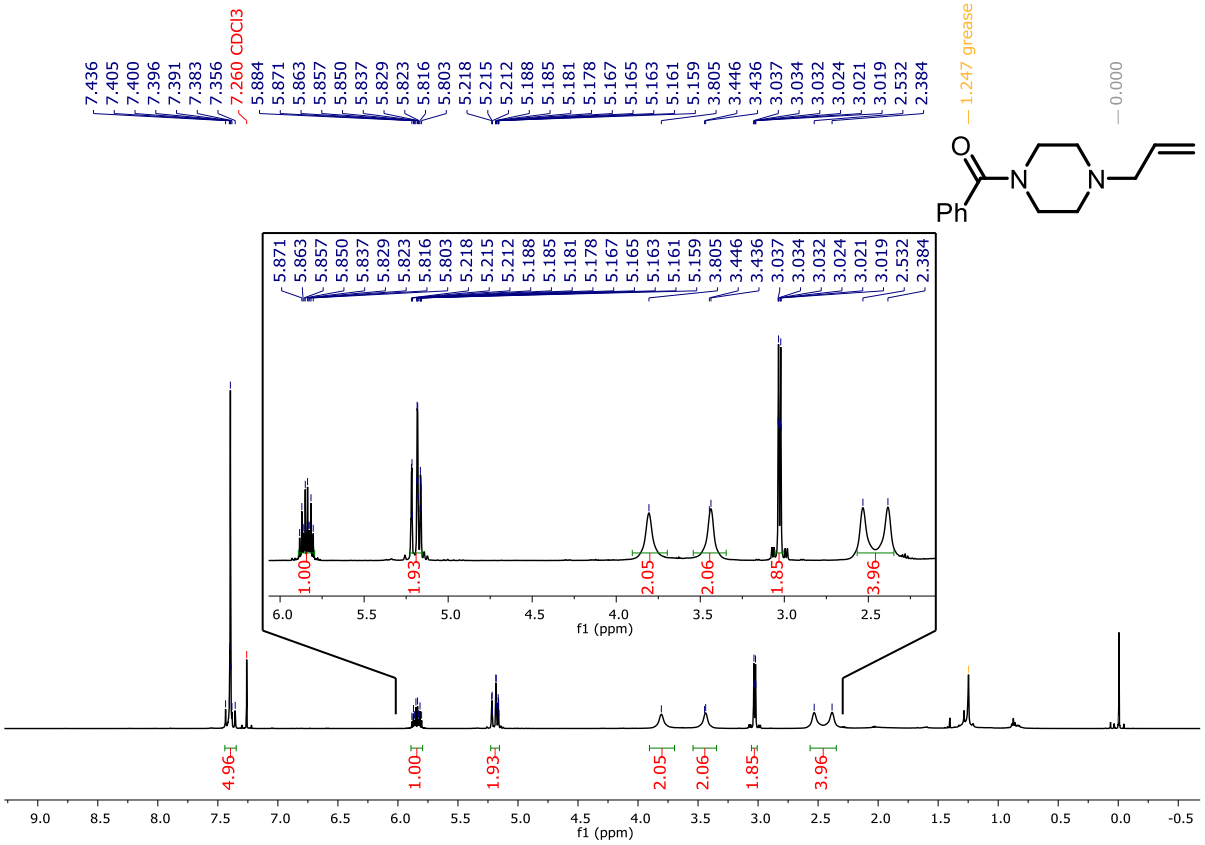
2-(4-Allylpiperazin-1-yl)pyrimidine (3l): ^{1}H NMR (500 MHz, $CDCl_3$)



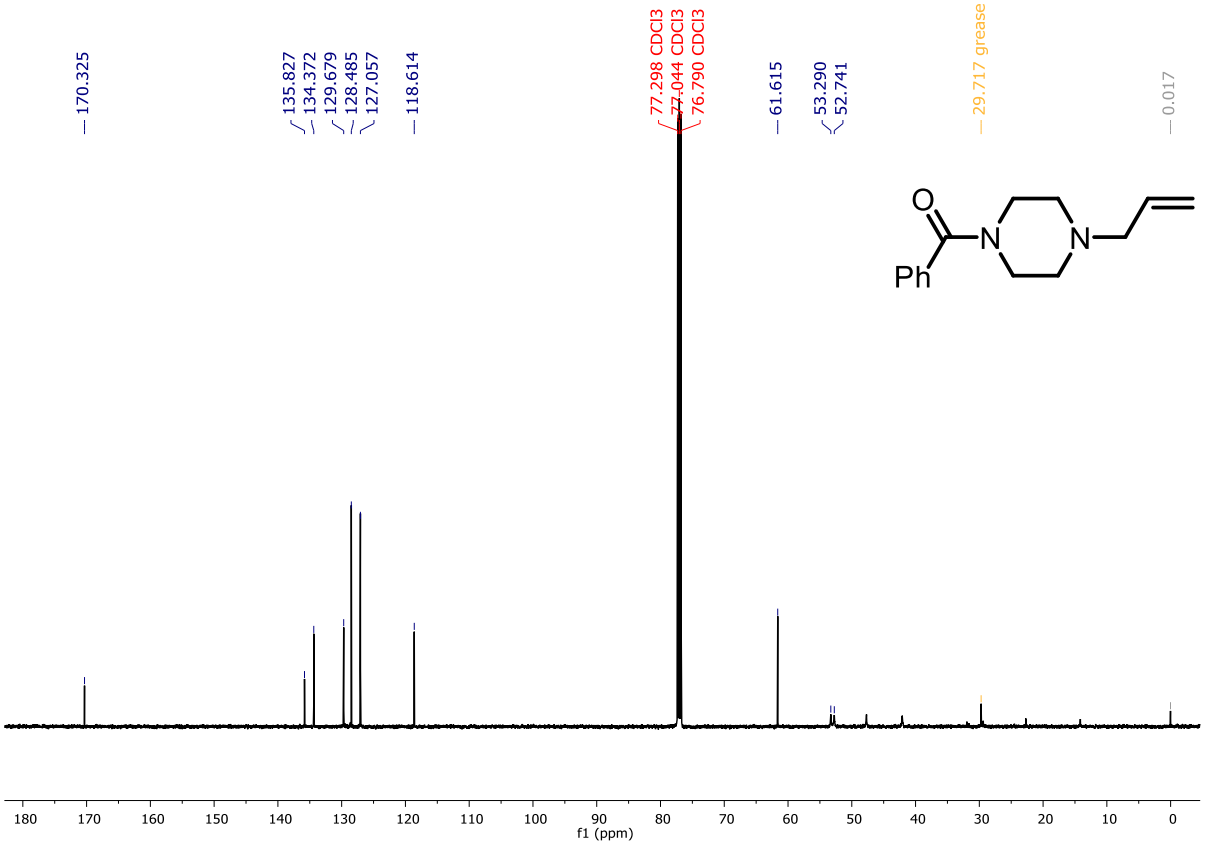
2-(4-Allylpiperazin-1-yl)pyrimidine (3l): ^{13}C NMR (500 MHz, $CDCl_3$)



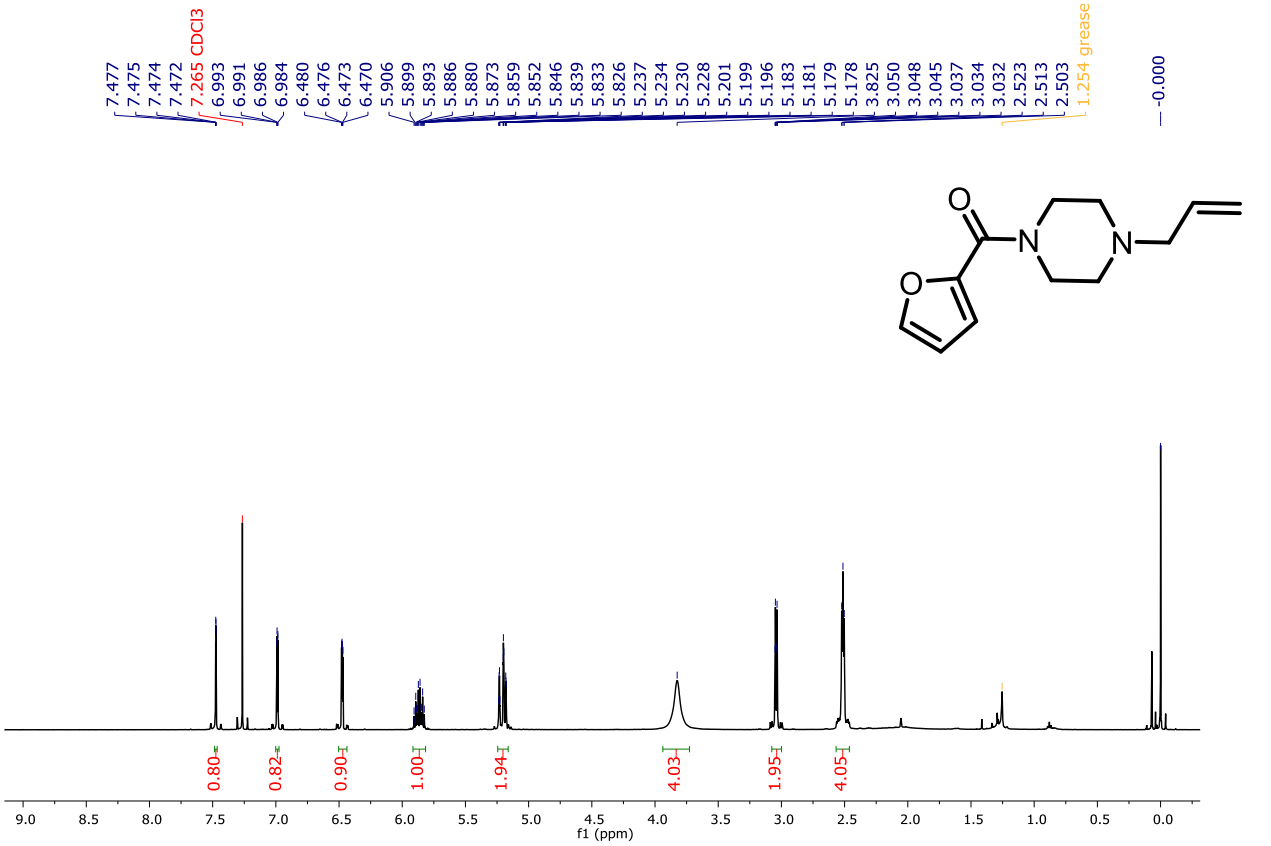
(4-Allylpiperazin-1-yl)(phenyl)methanone (3m): ^{1}H NMR (500 MHz, $CDCl_3$)



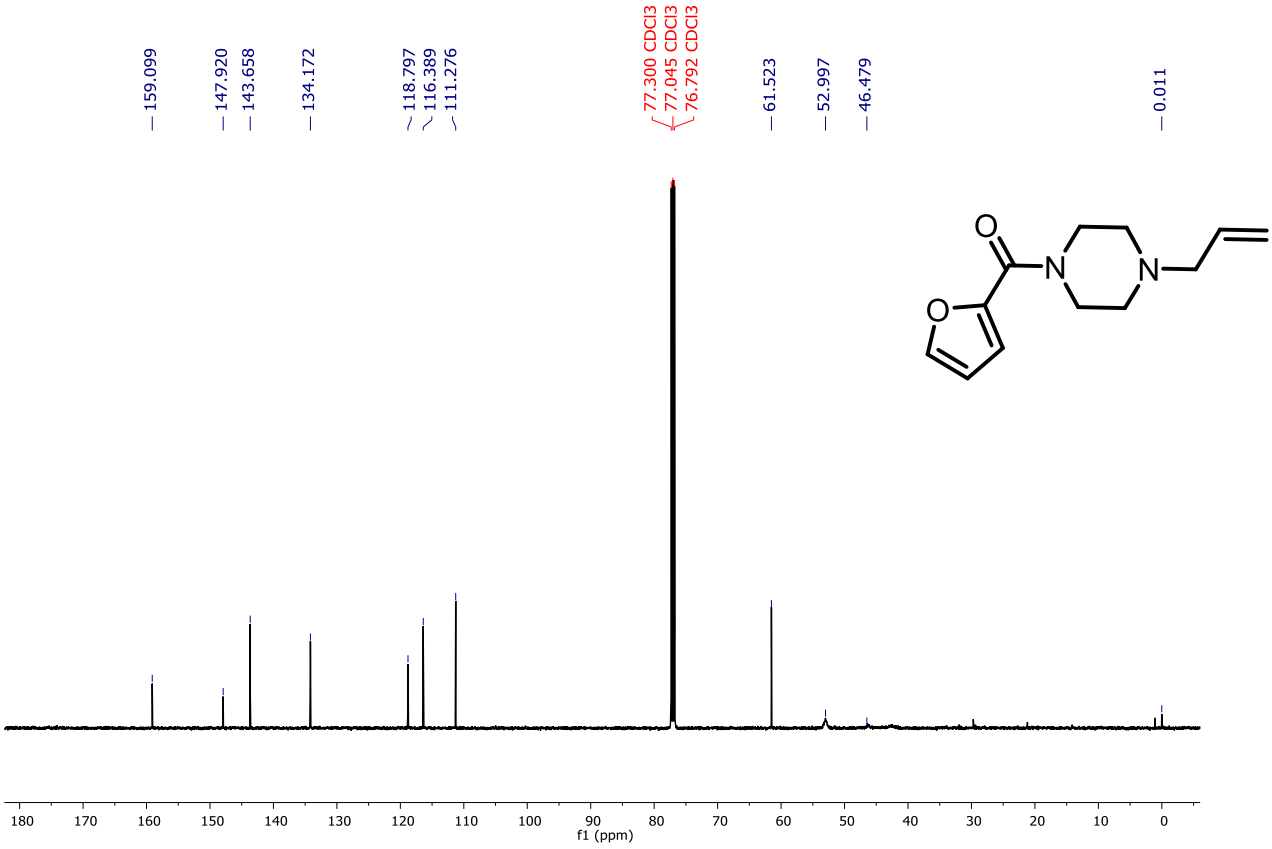
(4-Allylpiperazin-1-yl)(phenyl)methanone (3m): ^{13}C NMR (500 MHz, $CDCl_3$)



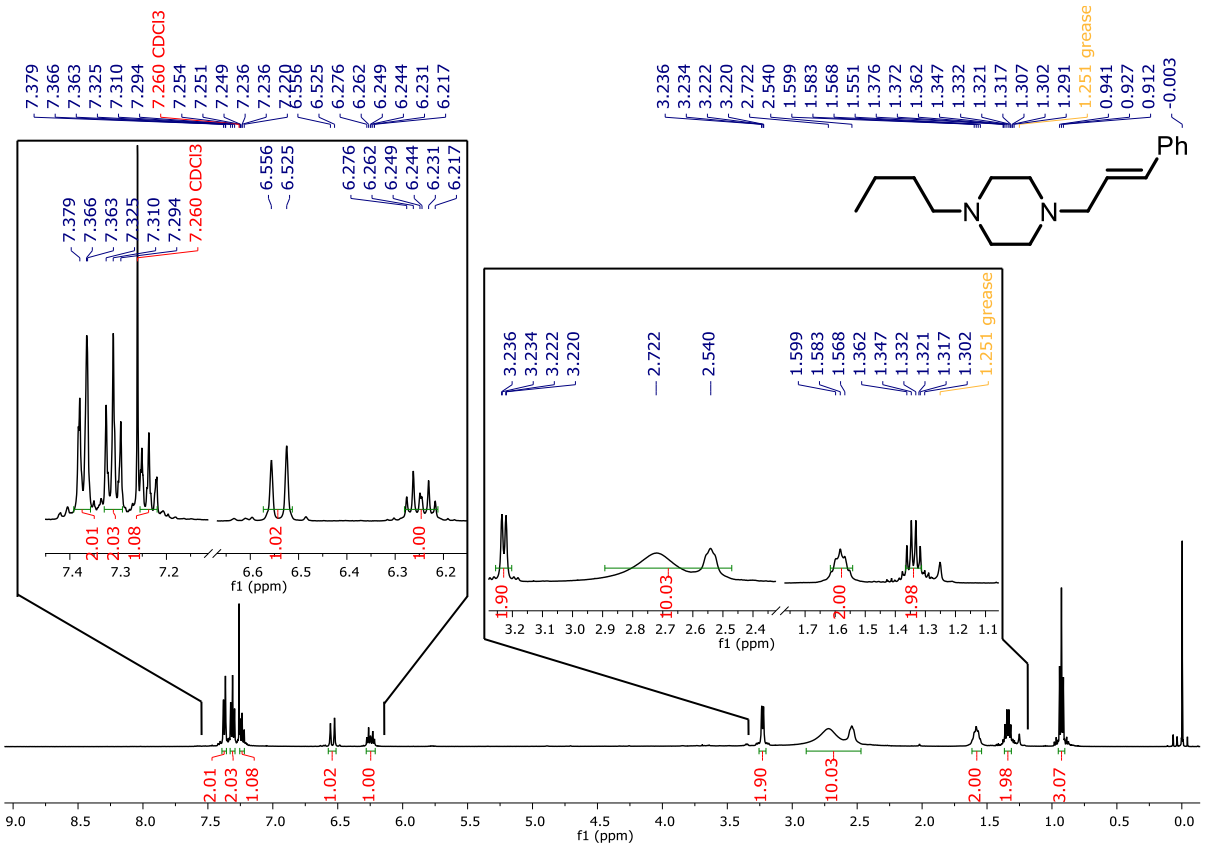
(4-Allylpiperazin-1-yl)(furan-2-yl)methanone (3n): ^{1}H NMR (500 MHz, $CDCl_3$)



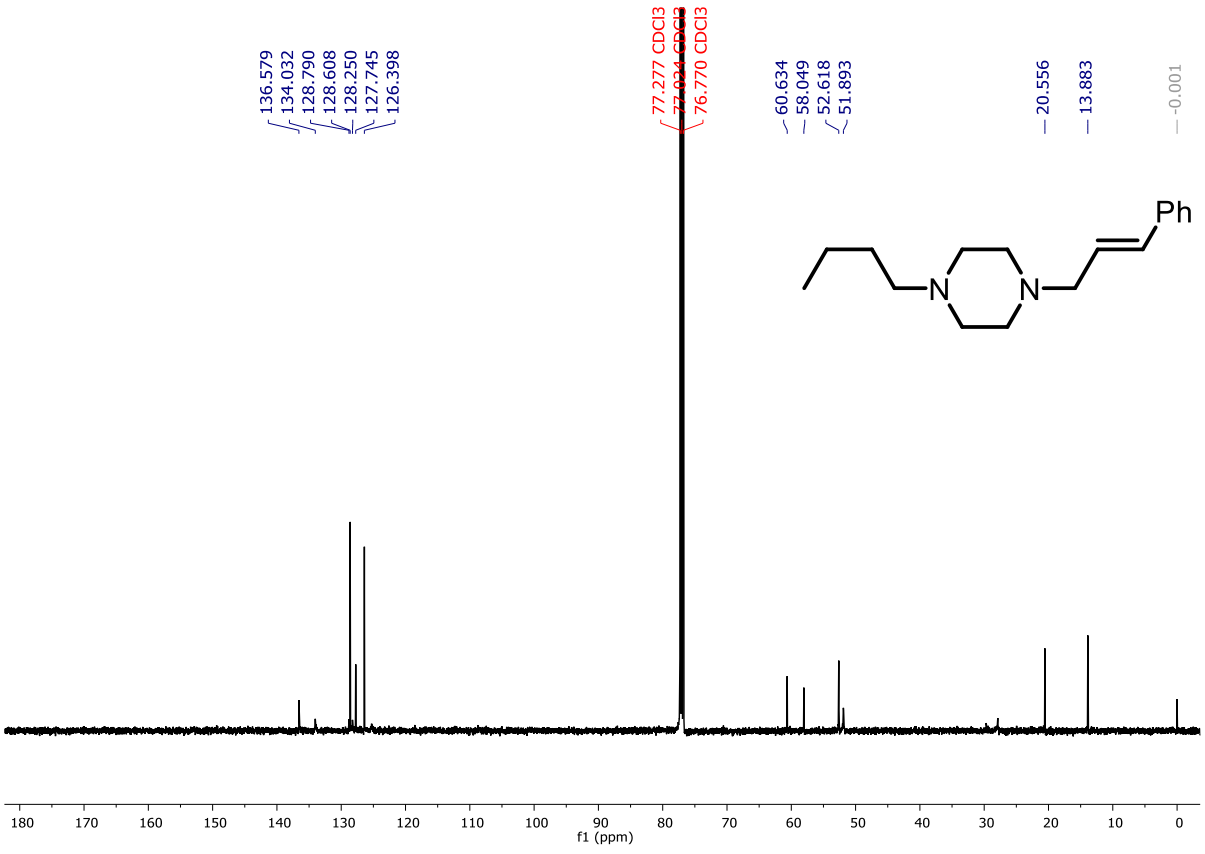
(4-Allylpiperazin-1-yl)(furan-2-yl)methanone (3n): ^{13}C NMR (500 MHz, $CDCl_3$)



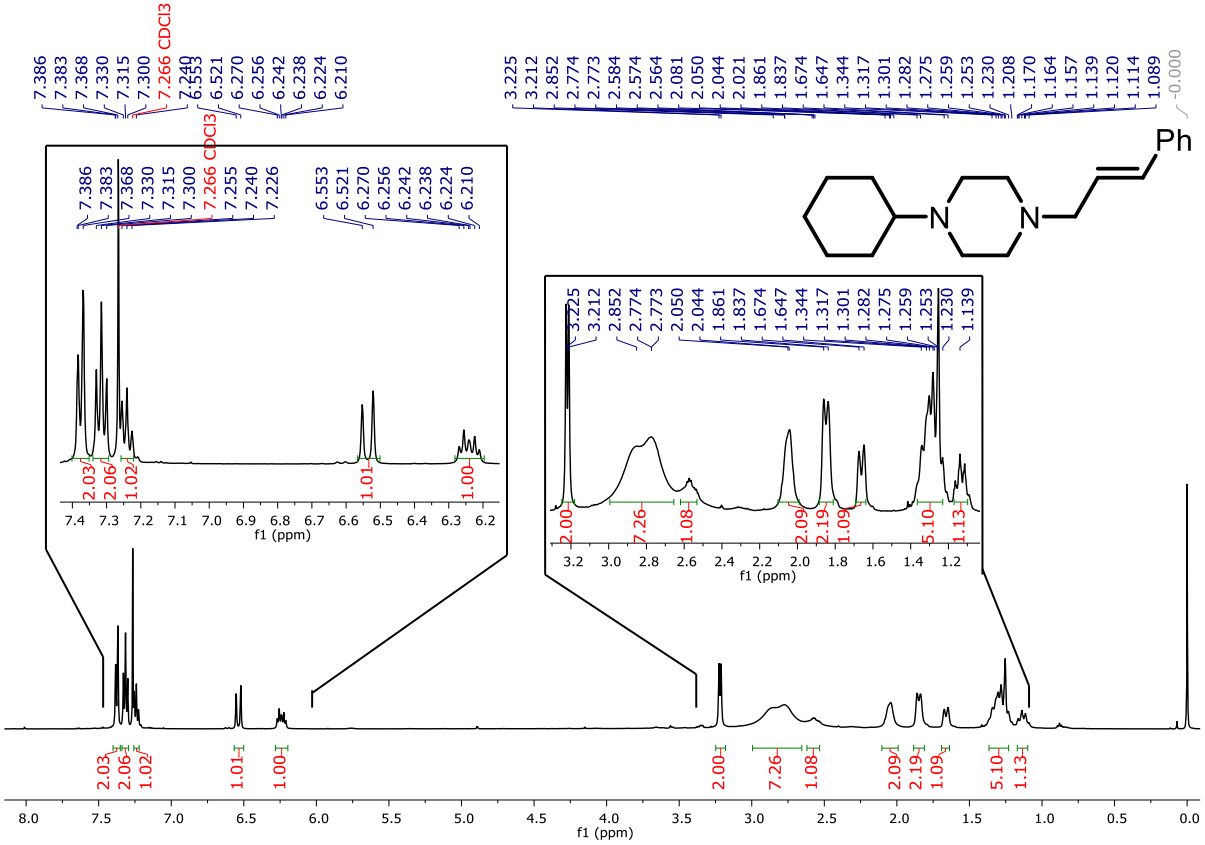
1-Butyl-4-cinnamylpiperazine (3o): ^{1}H NMR (500 MHz, $CDCl_3$)



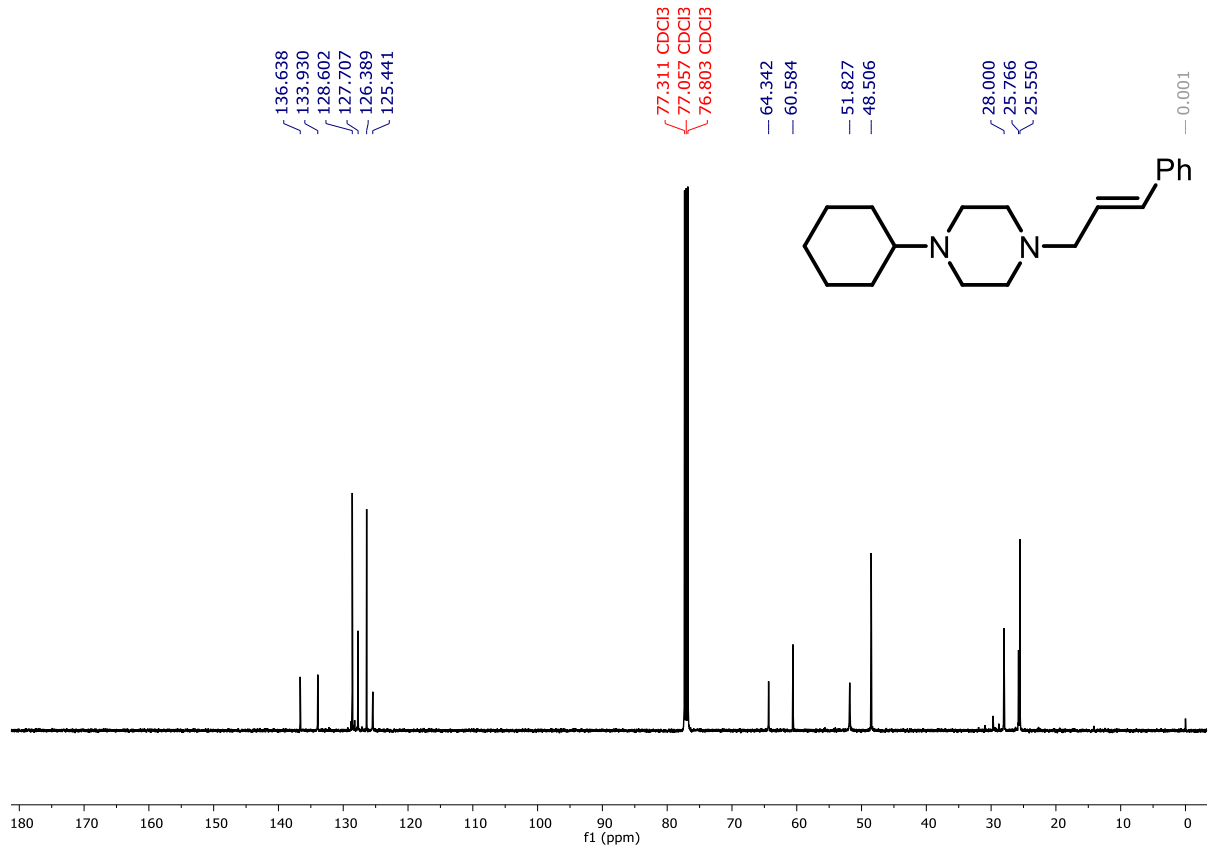
1-Butyl-4-cinnamylpiperazine (3o): ^{13}C NMR (500 MHz, $CDCl_3$)



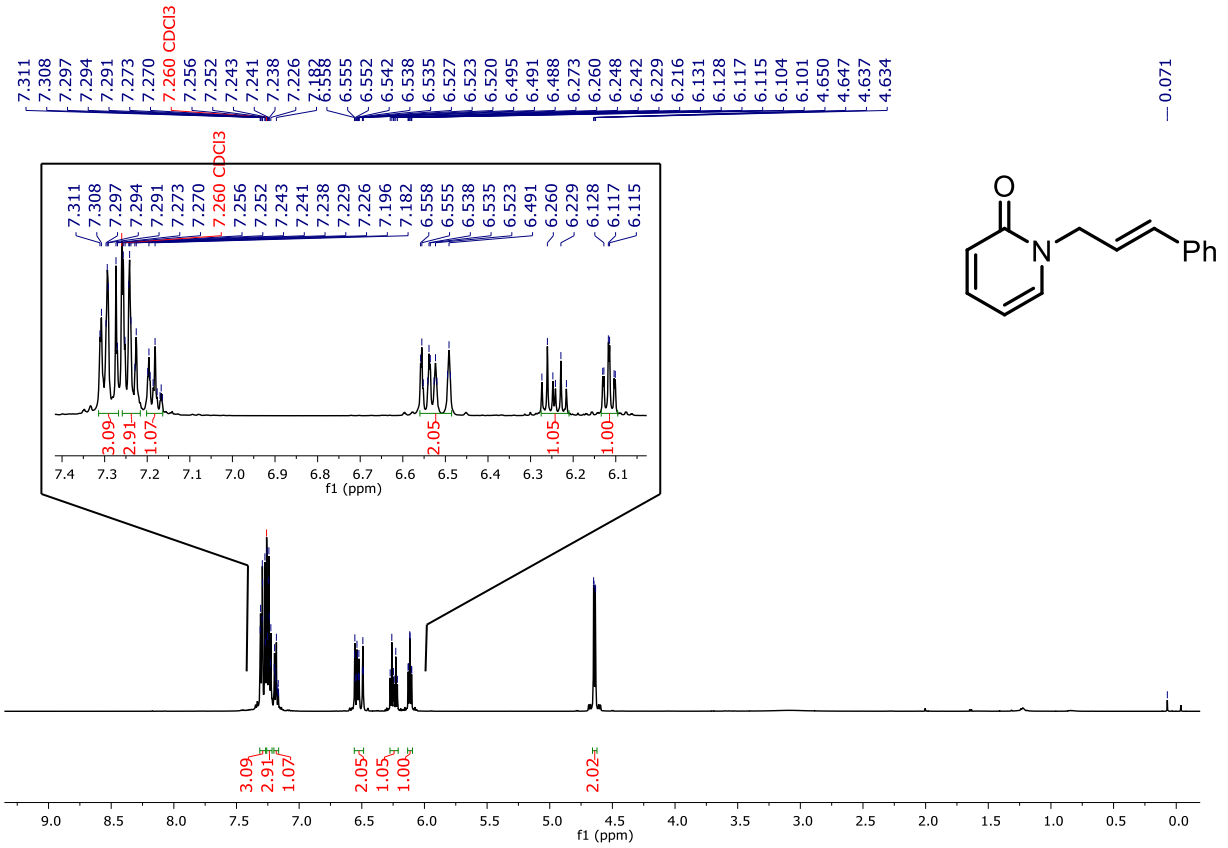
1-Cinnamyl-4-cyclohexylpiperazine (3p): ^{1}H NMR (500 MHz, $CDCl_3$)



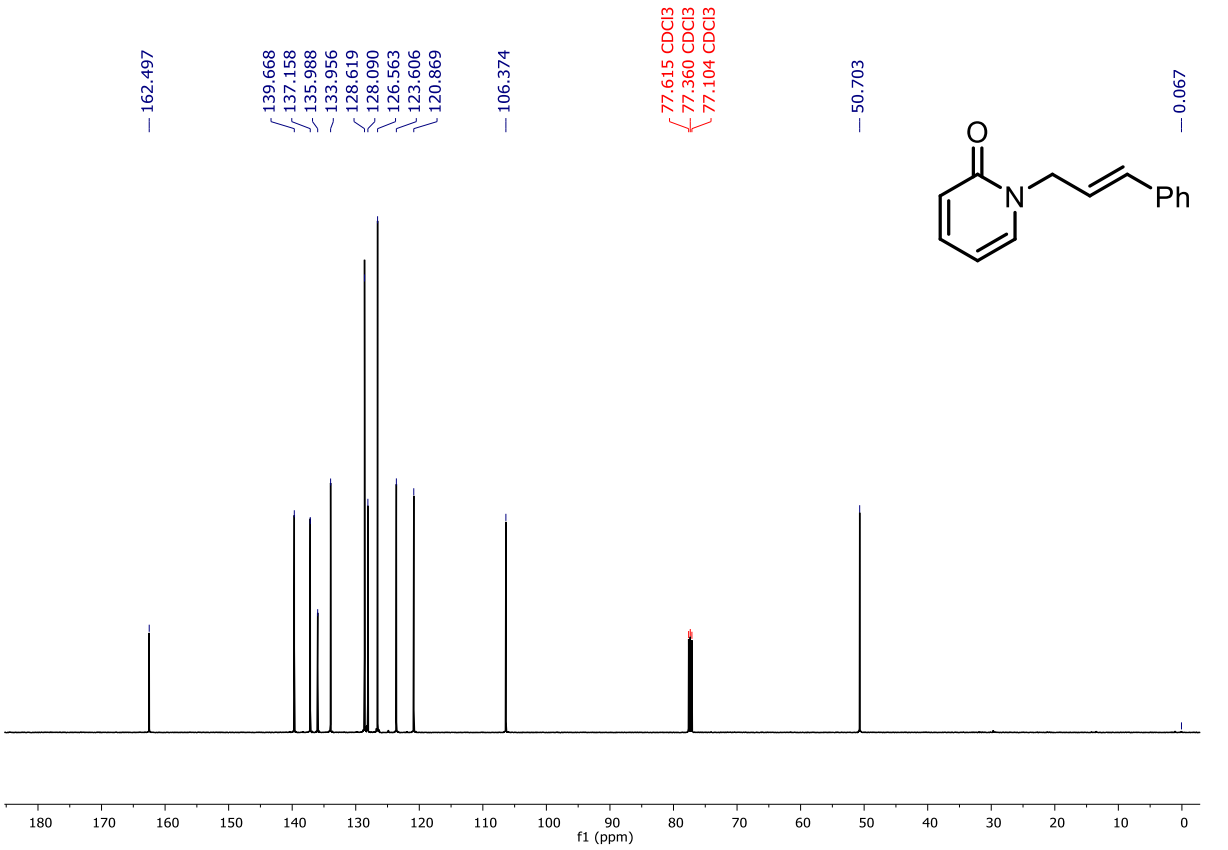
1-Cinnamyl-4-cyclohexylpiperazine (3p): ^{13}C NMR (500 MHz, $CDCl_3$)



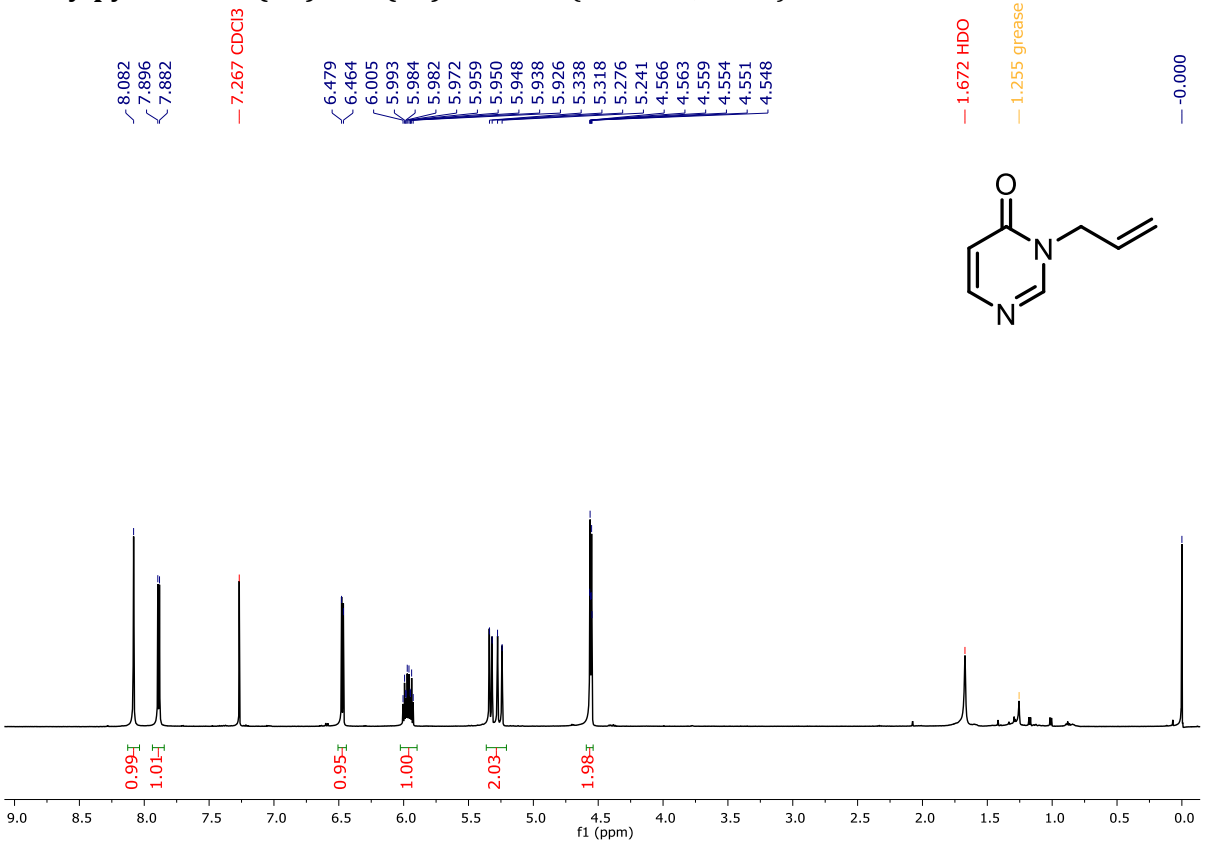
1-Cinnamylpyridin-2(1*H*)-one (4a): ^{1}H NMR (500 MHz, $CDCl_3$)



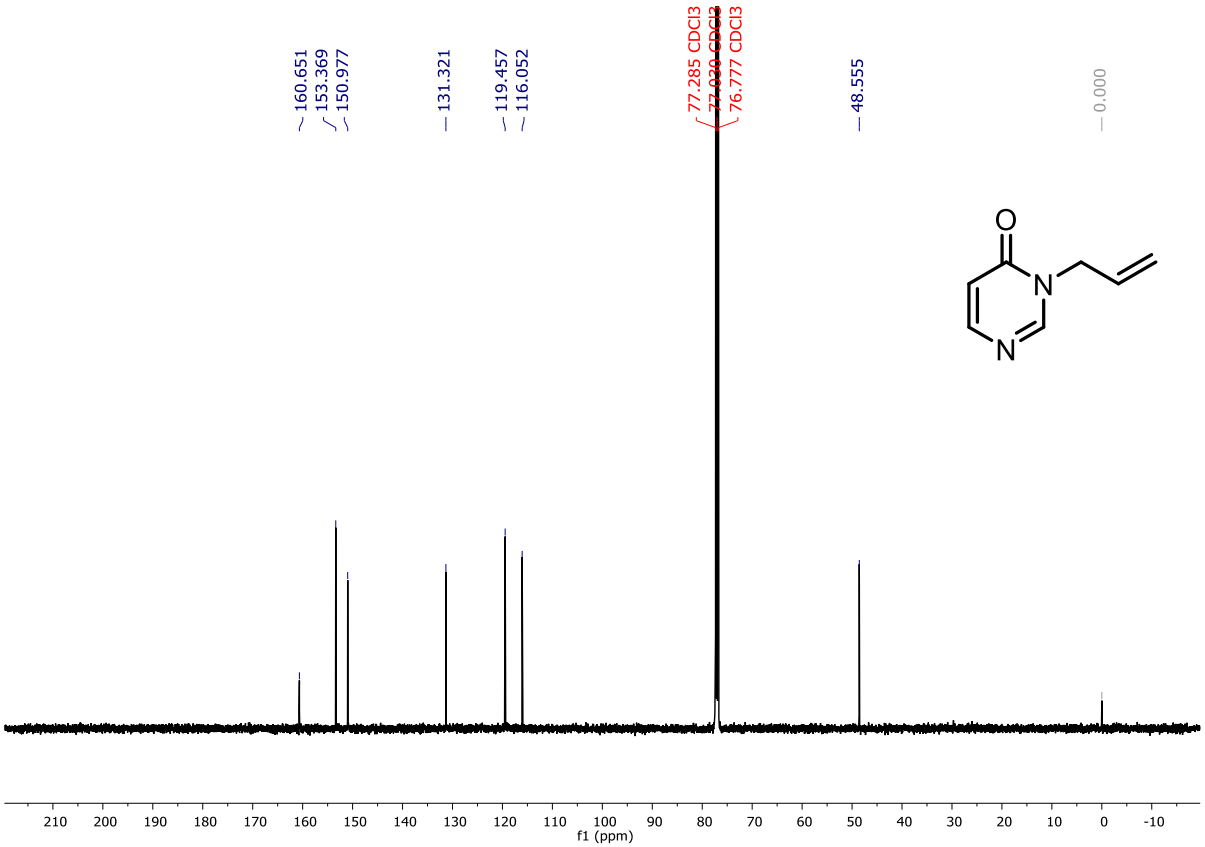
1-Cinnamylpyridin-2(1*H*)-one (4a):^{13}C NMR (500 MHz, $CDCl_3$)



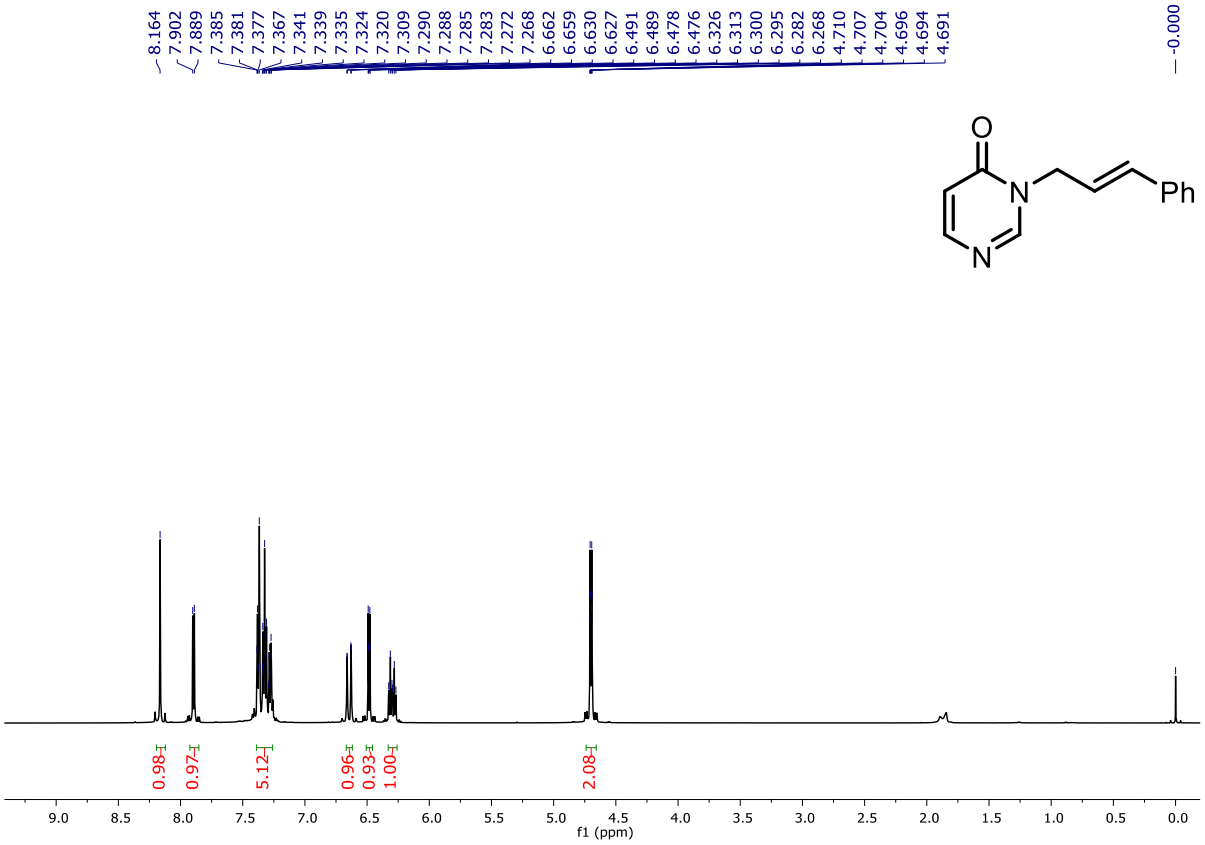
3-Allylpyrimidin-4(3*H*)-one (4b): ^{1}H NMR (500 MHz, $CDCl_3$)



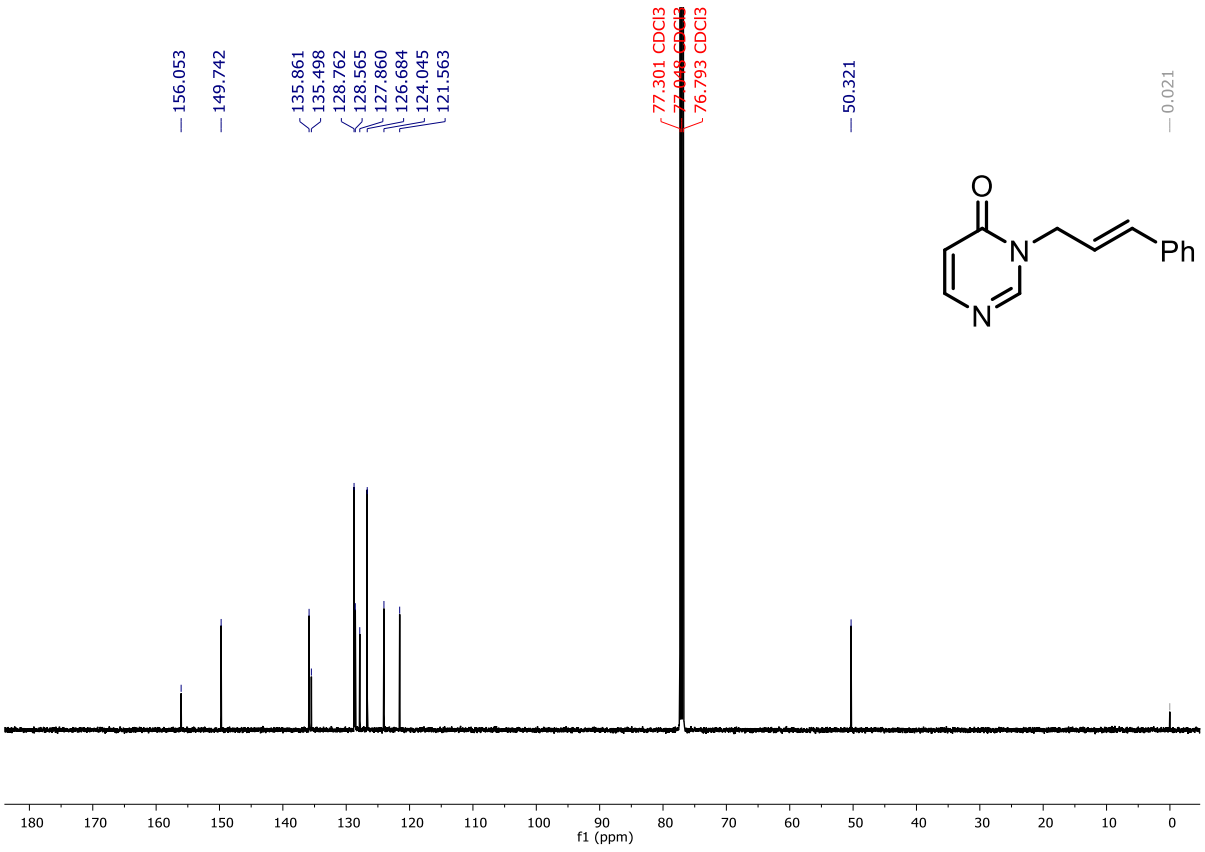
3-Allylpyrimidin-4(3*H*)-one (4b): ^{13}C NMR (500 MHz, $CDCl_3$)



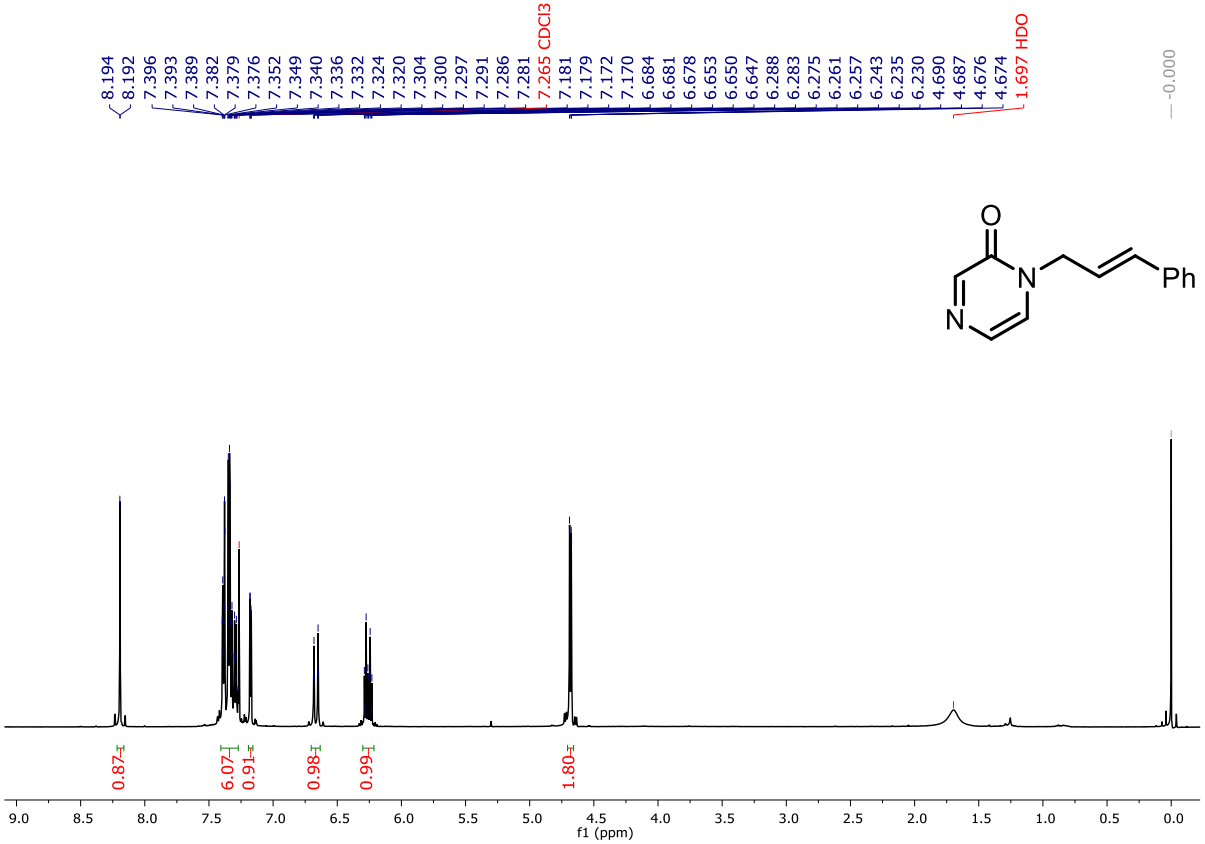
3-Cinnamylpyrimidin-4(3*H*)-one (4c): ^{1}H NMR (500 MHz, $CDCl_3$)



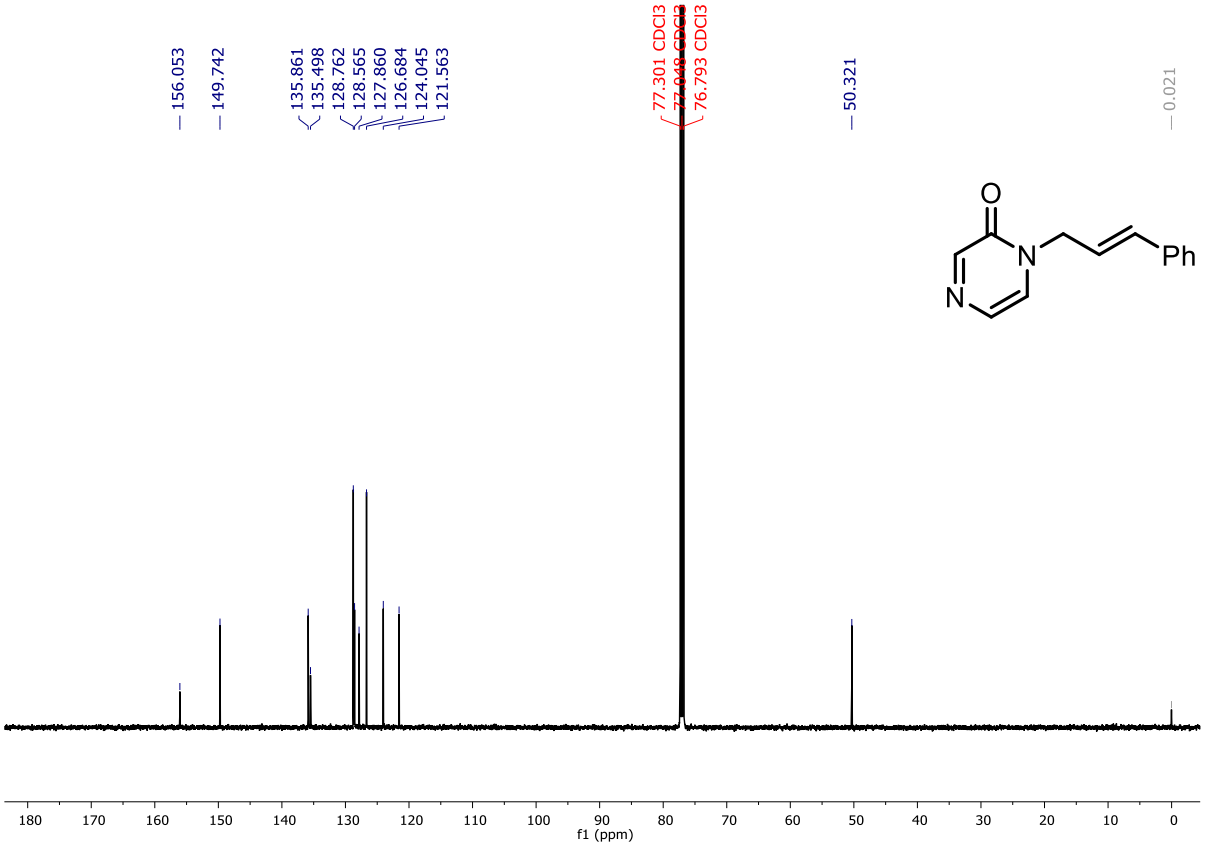
3-Cinnamylpyrimidin-4(3*H*)-one (4c): ^{13}C NMR (500 MHz, $CDCl_3$)



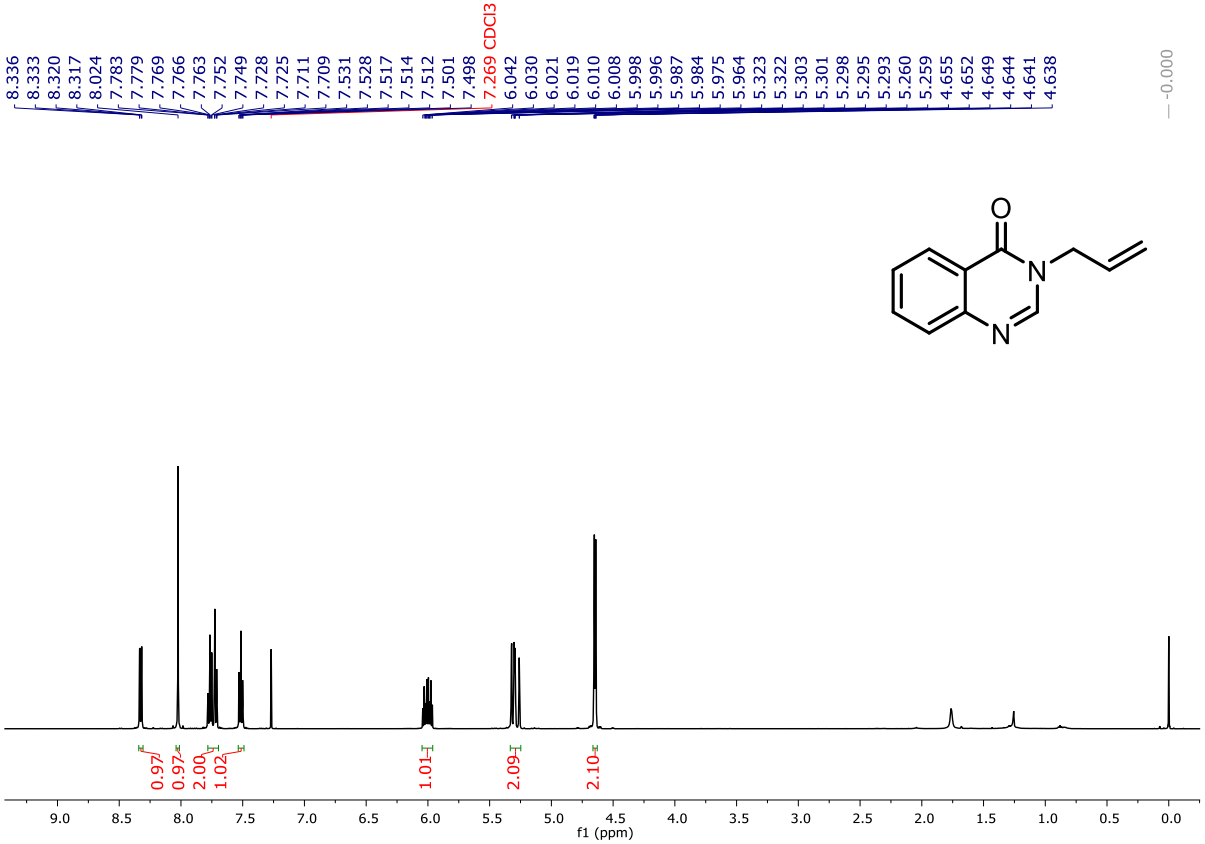
1-Cinnamylpyrazine-2(1*H*)-one (4d): ^{1}H NMR (500 MHz, $CDCl_3$)



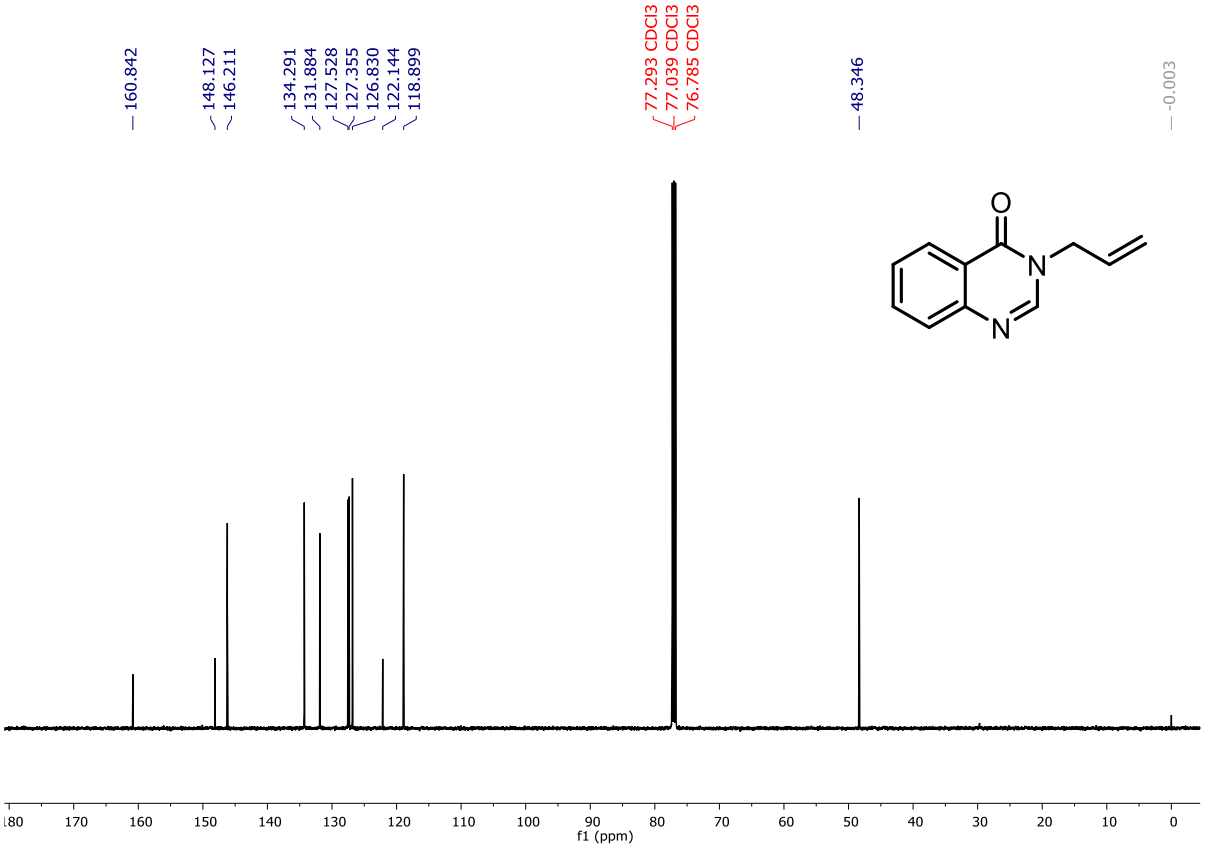
1-Cinnamylpyrazine-2(1*H*)-one (4d): ^{13}C NMR (500 MHz, $CDCl_3$)



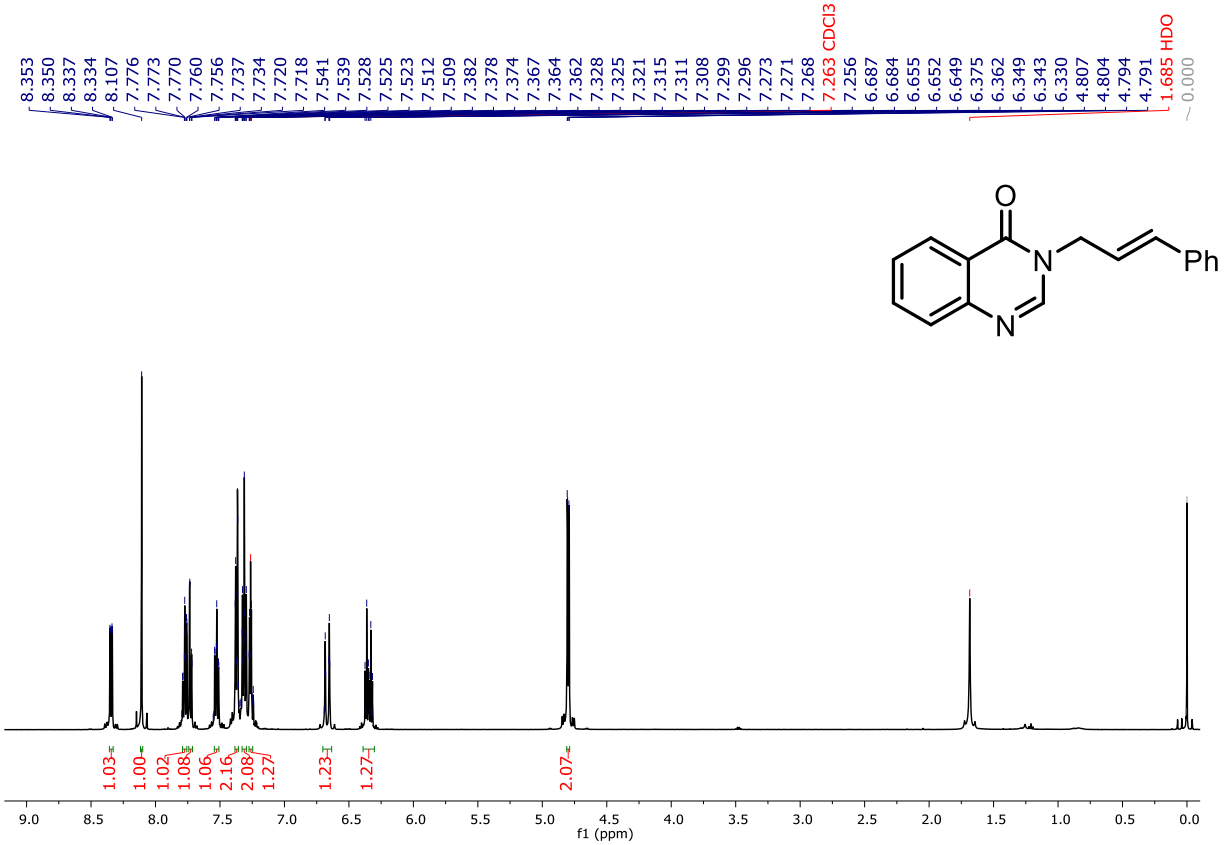
3-Allylquinazolin-4(3*H*)-one (4e): ^{1}H NMR (500 MHz, $CDCl_3$)



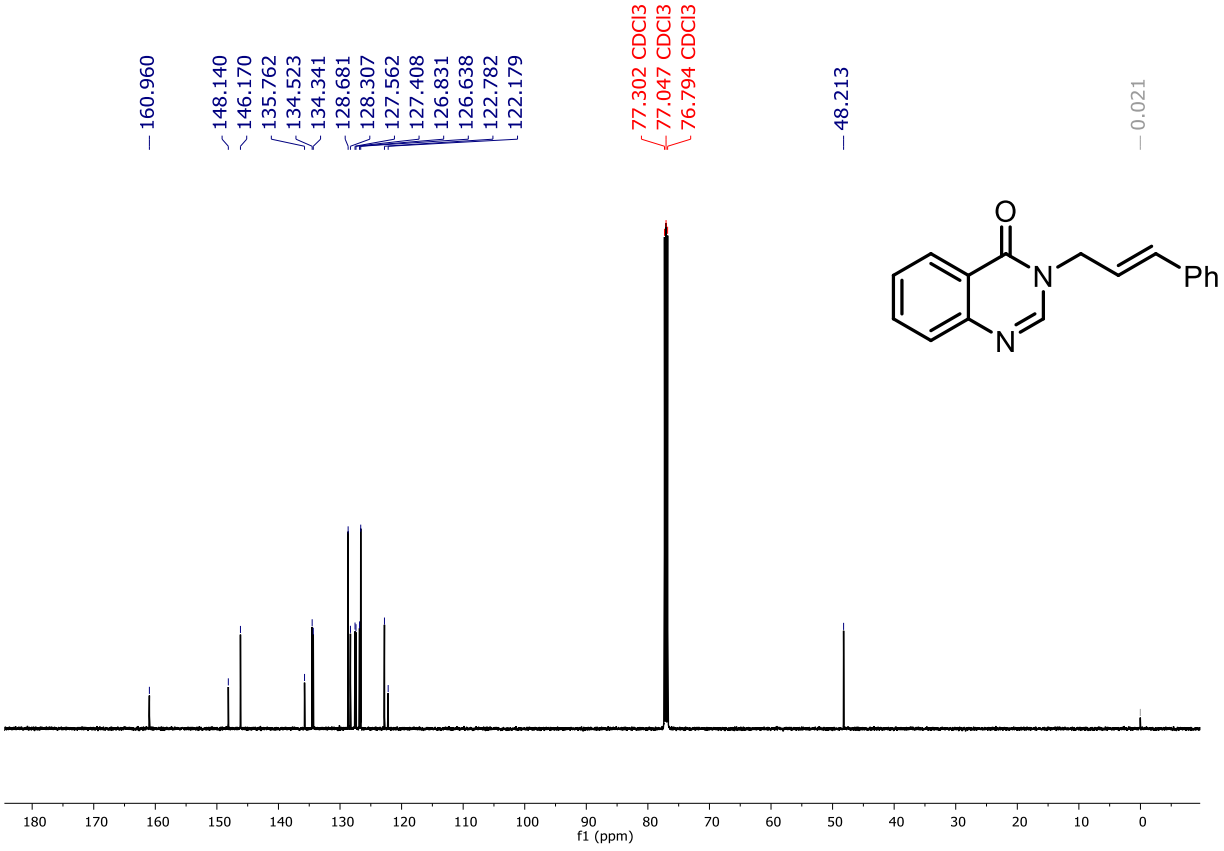
3-Allylquinazolin-4(3*H*)-one (4e): ^{13}C NMR (500 MHz, $CDCl_3$)



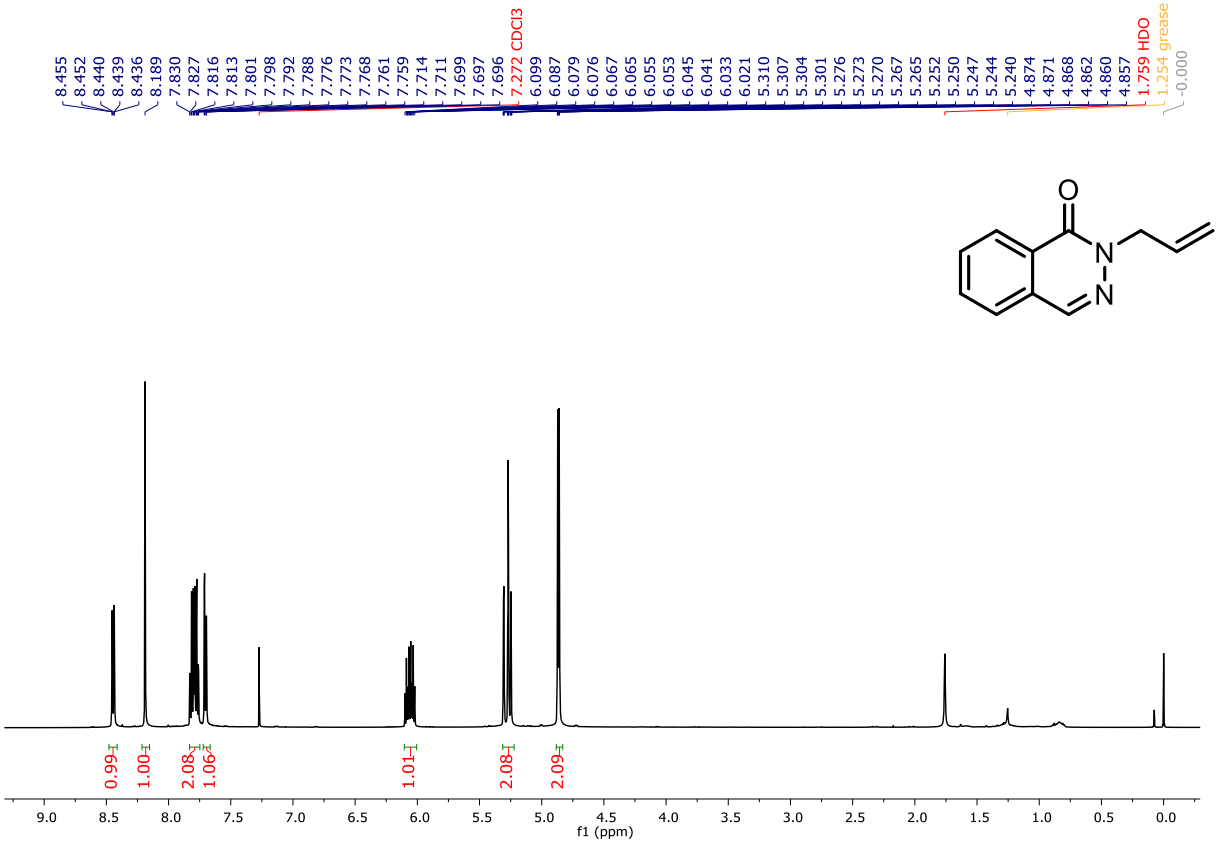
3-Cinnamylquinazolin-4(3*H*)-one (4f): ^{1}H NMR (500 MHz, $CDCl_3$)



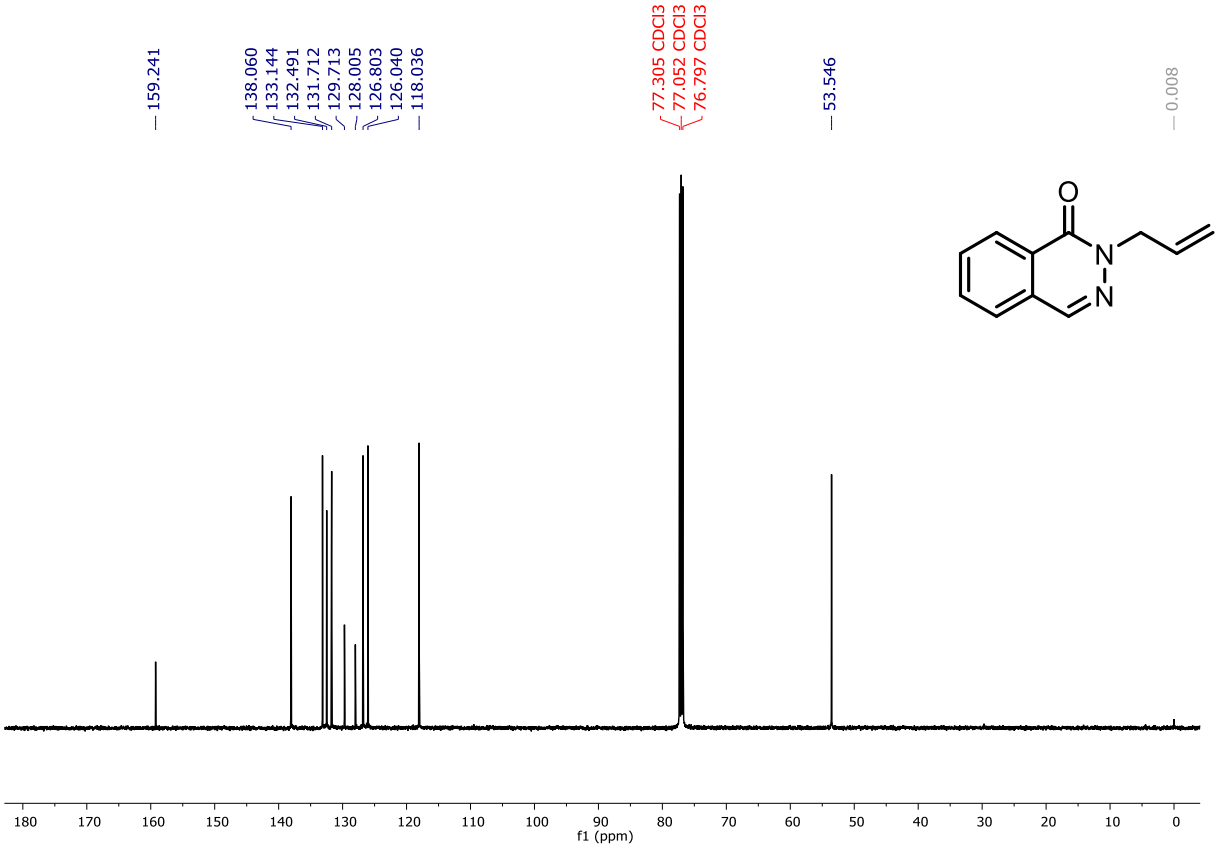
3-Cinnamylquinazolin-4(3*H*)-one (4f): ^{13}C NMR (500 MHz, $CDCl_3$)



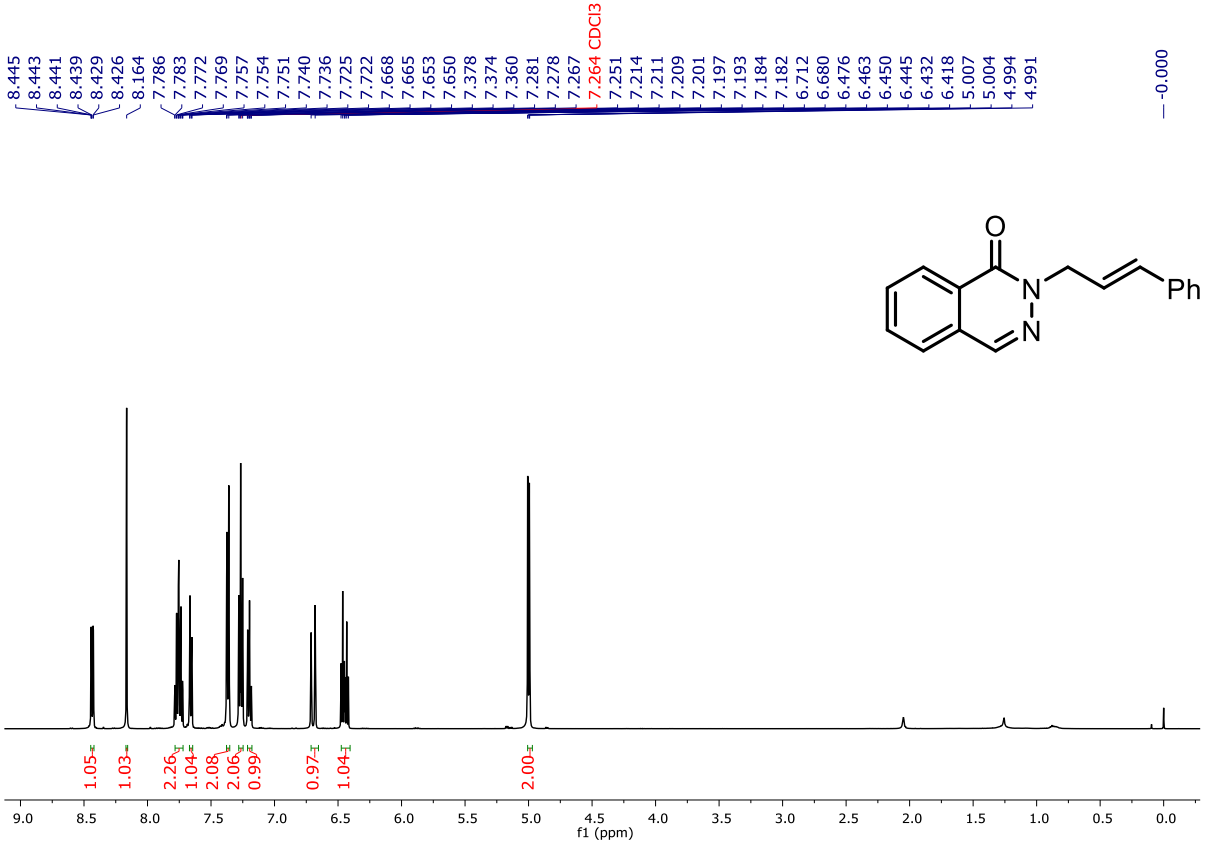
2-Allylphthalazin-1(2*H*)-one (4g): ^{1}H NMR (500 MHz, $CDCl_3$)



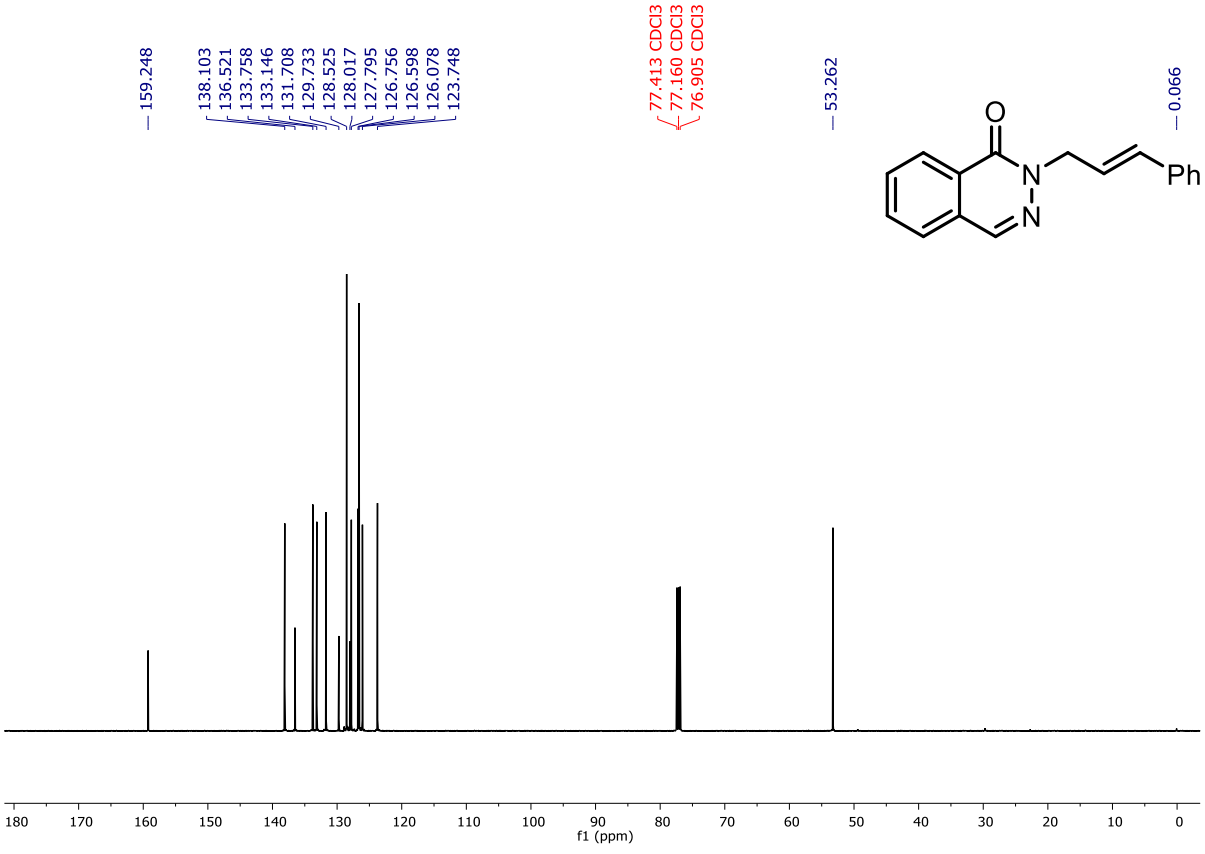
2-Allylphthalazin-1(2*H*)-one (4g): ^{13}C NMR (500 MHz, $CDCl_3$)



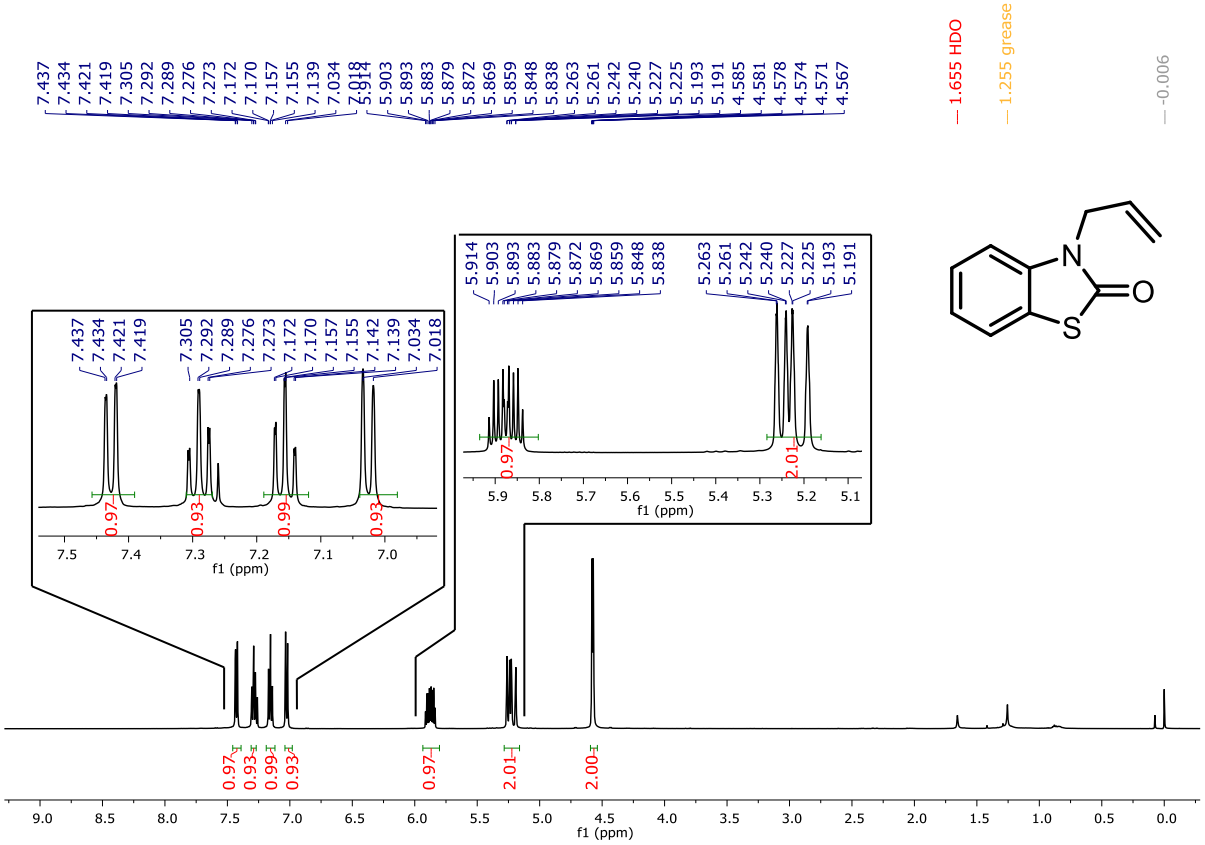
2-Cinnamylphthalazin-1(2*H*)-one (4h): ^{1}H NMR (500 MHz, $CDCl_3$)



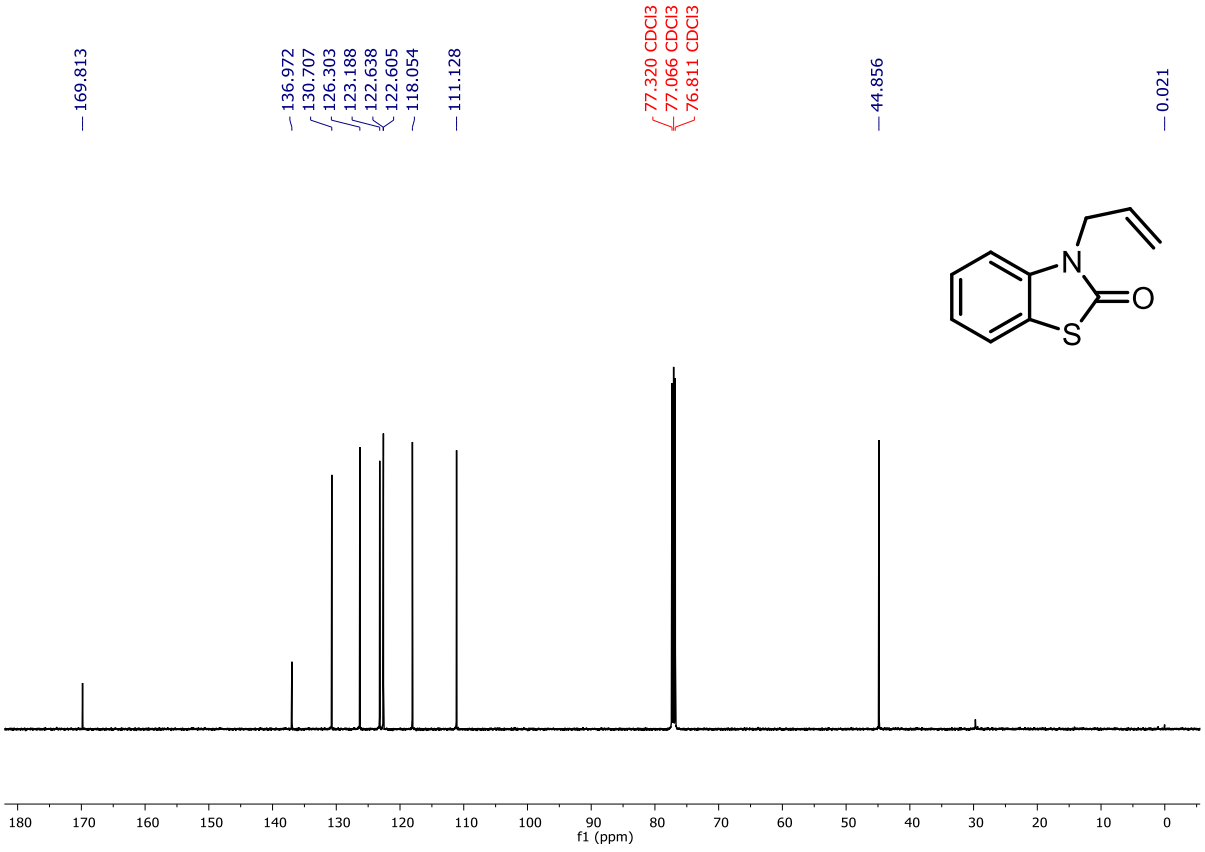
2-Cinnamylphthalazin-1(2*H*)-one (4h): ^{13}C NMR (500 MHz, $CDCl_3$)



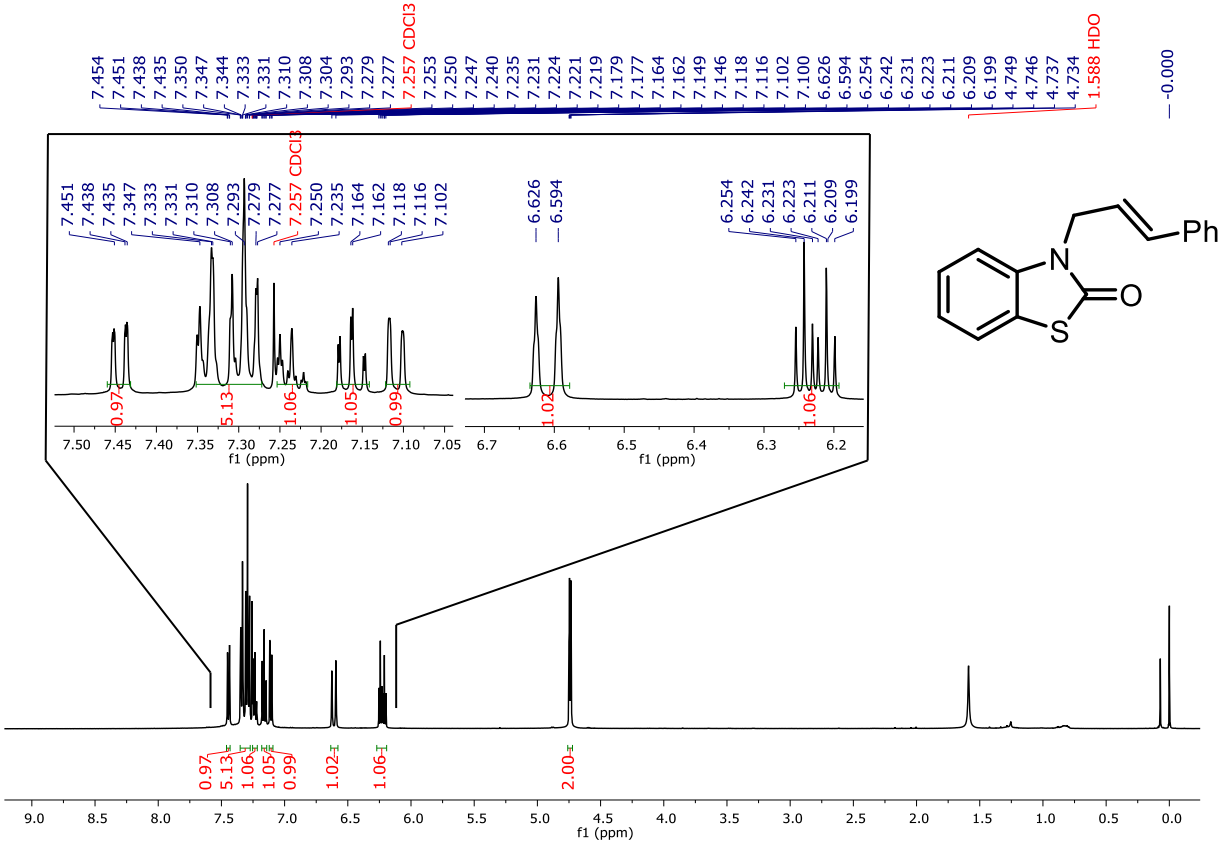
3-Allylbenzo[d]thiazol-2(3*H*)-one (4i): ^{1}H NMR (500 MHz, $CDCl_3$)



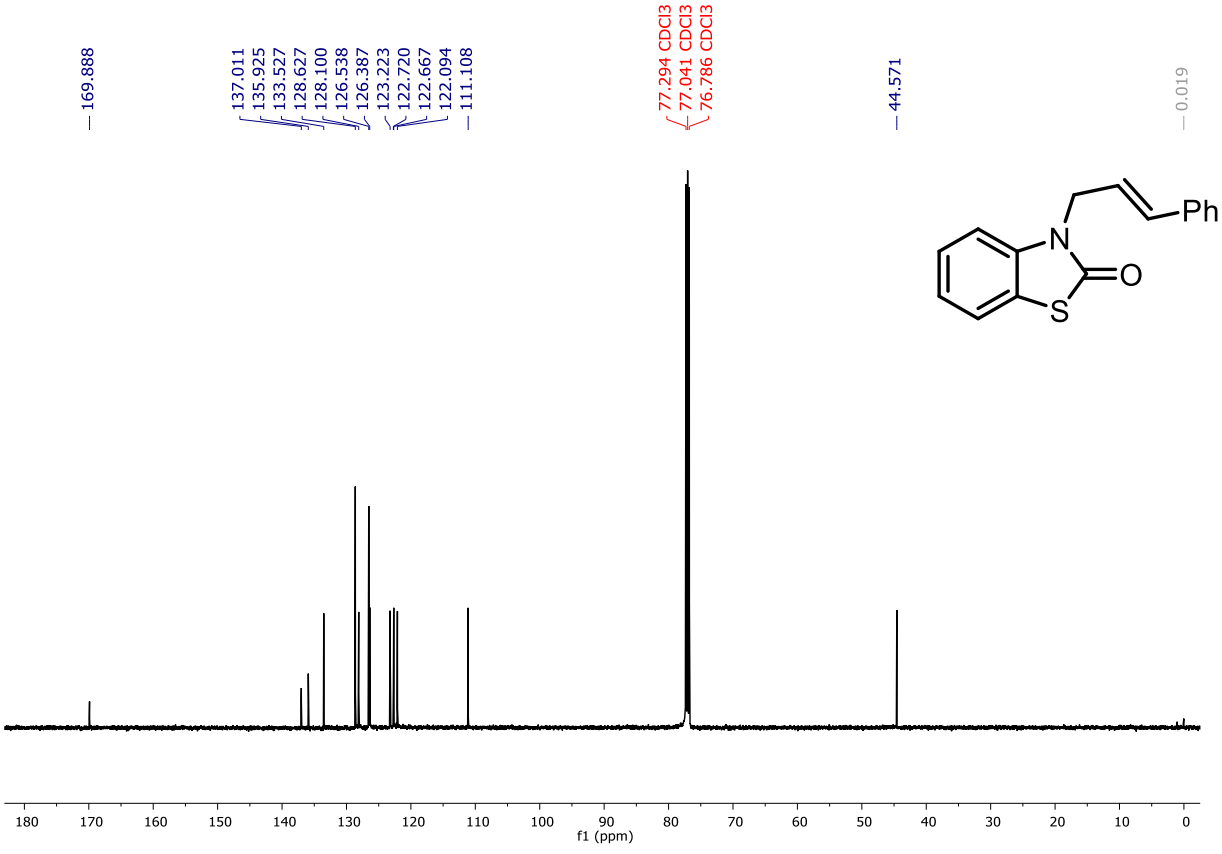
3-Allylbenzo[d]thiazol-2(3*H*)-one (4i): ^{13}C NMR (500 MHz, $CDCl_3$)



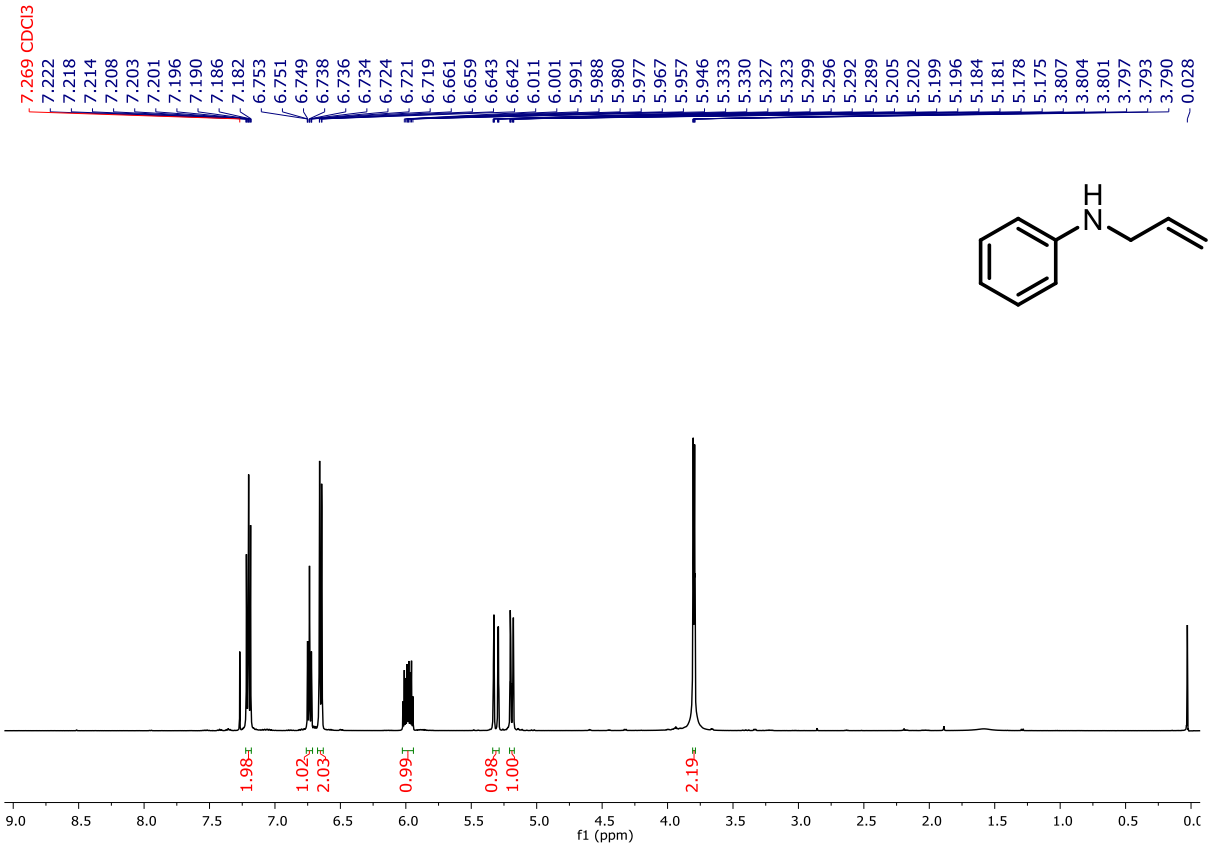
3-Cinnamylbenzo[d]thiazol-2(3*H*)-one (4j): ^{1}H NMR (500 MHz, $CDCl_3$)



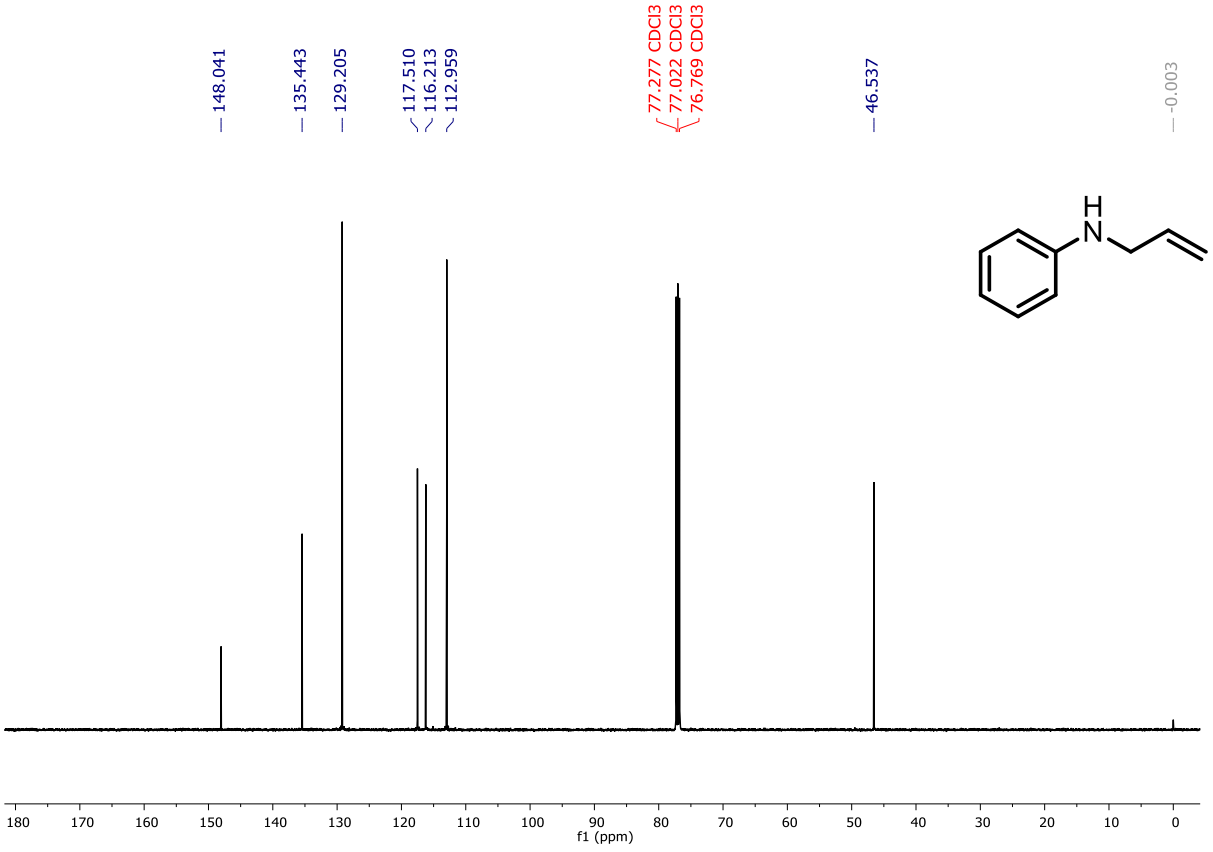
3-Cinnamylbenzo[d]thiazol-2(3*H*)-one (4j): ^{13}C NMR (500 MHz, $CDCl_3$)



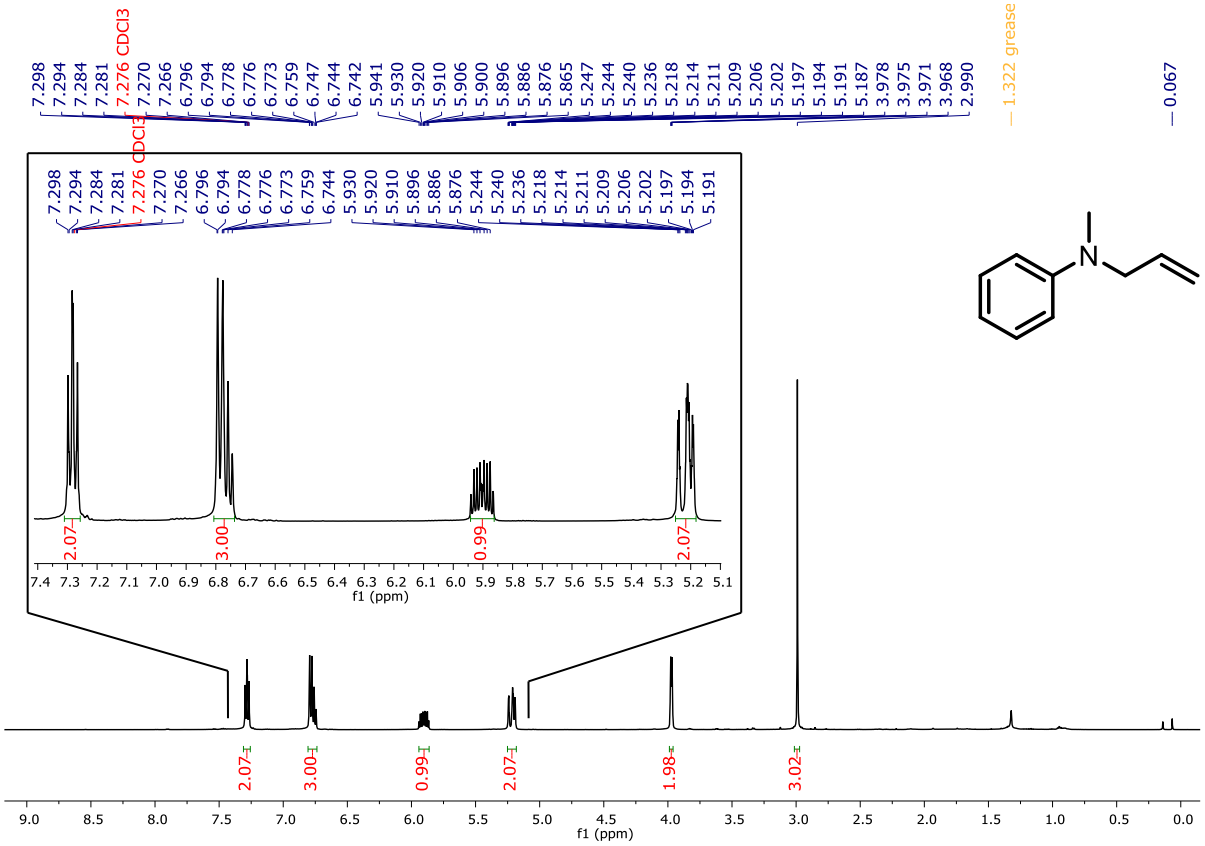
***N*-Allylaniline (5a):** ^{1}H NMR (500 MHz, $CDCl_3$)



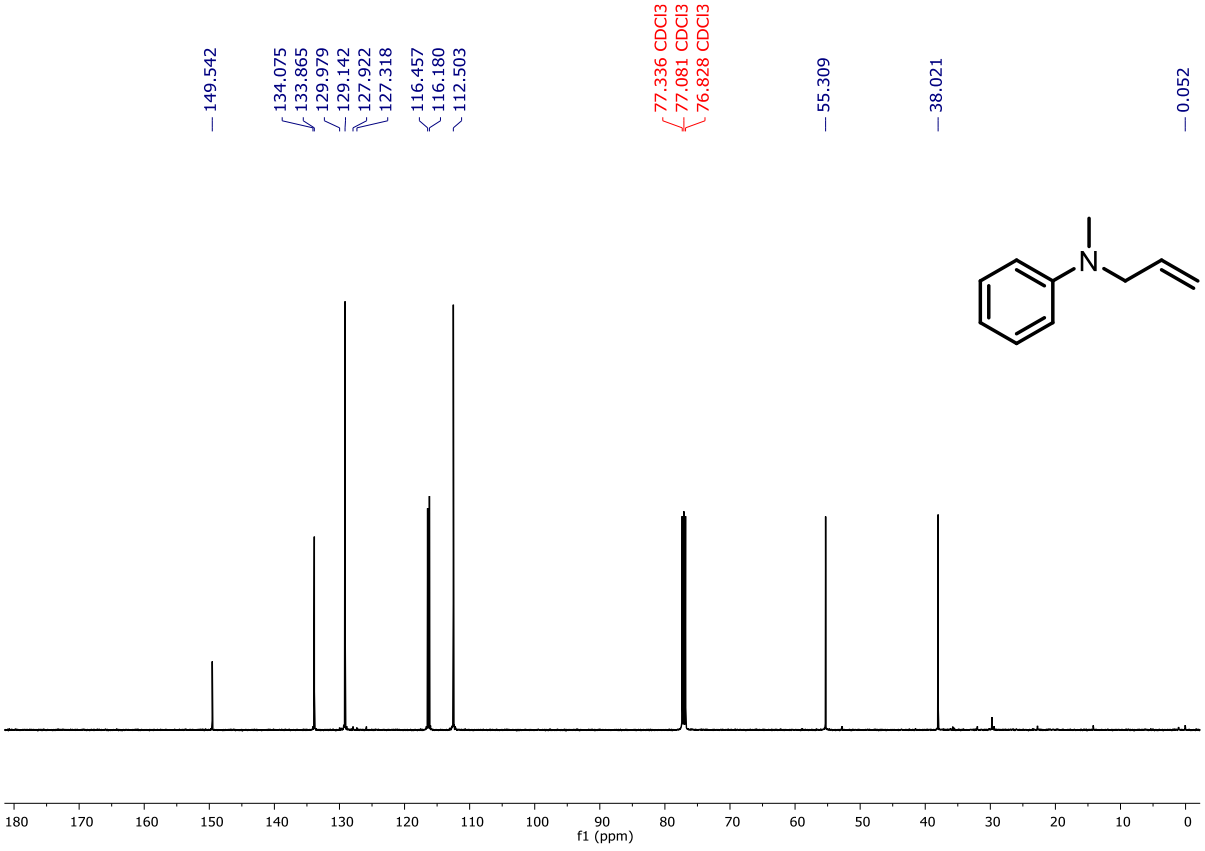
***N*-Allylaniline (5a):** ^{13}C NMR (500 MHz, $CDCl_3$)



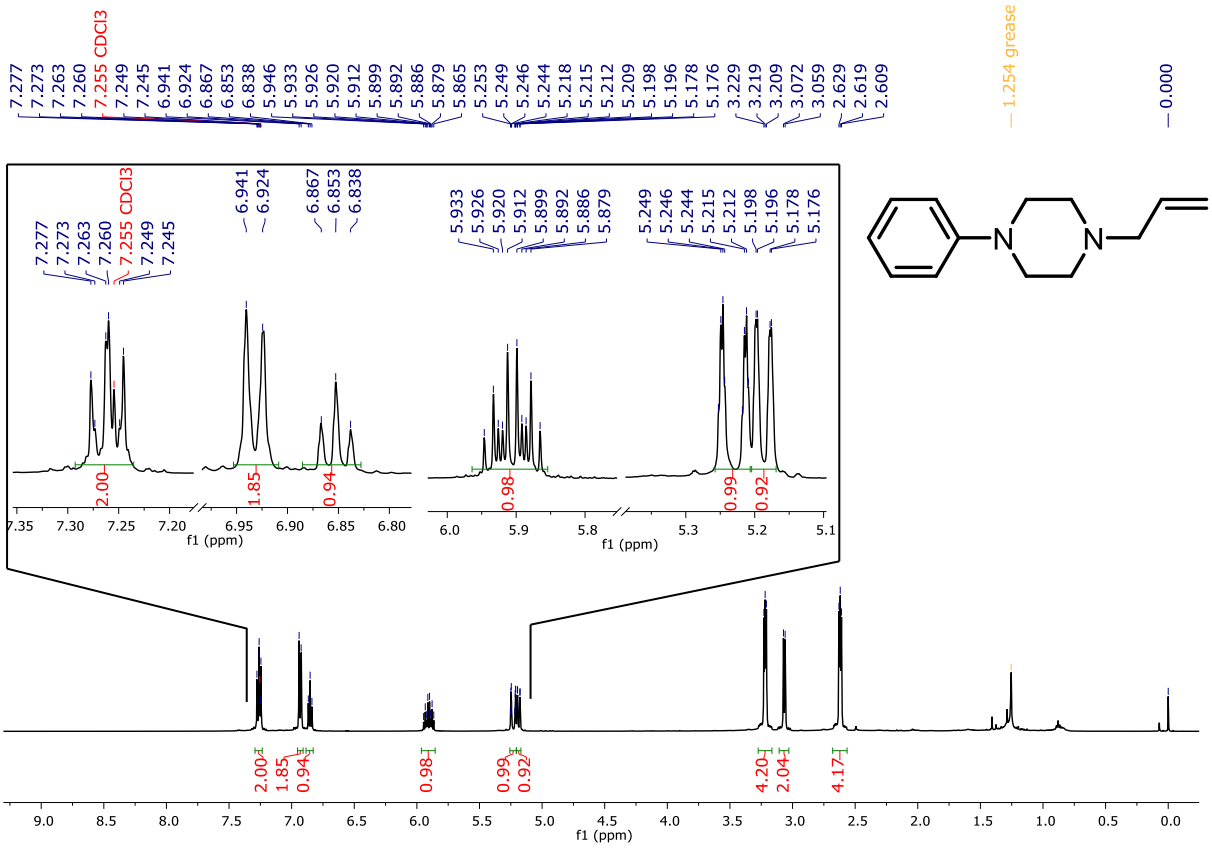
***N*-Allyl-*N*-methylaniline (5b):** ^{1}H NMR (500 MHz, $CDCl_3$)



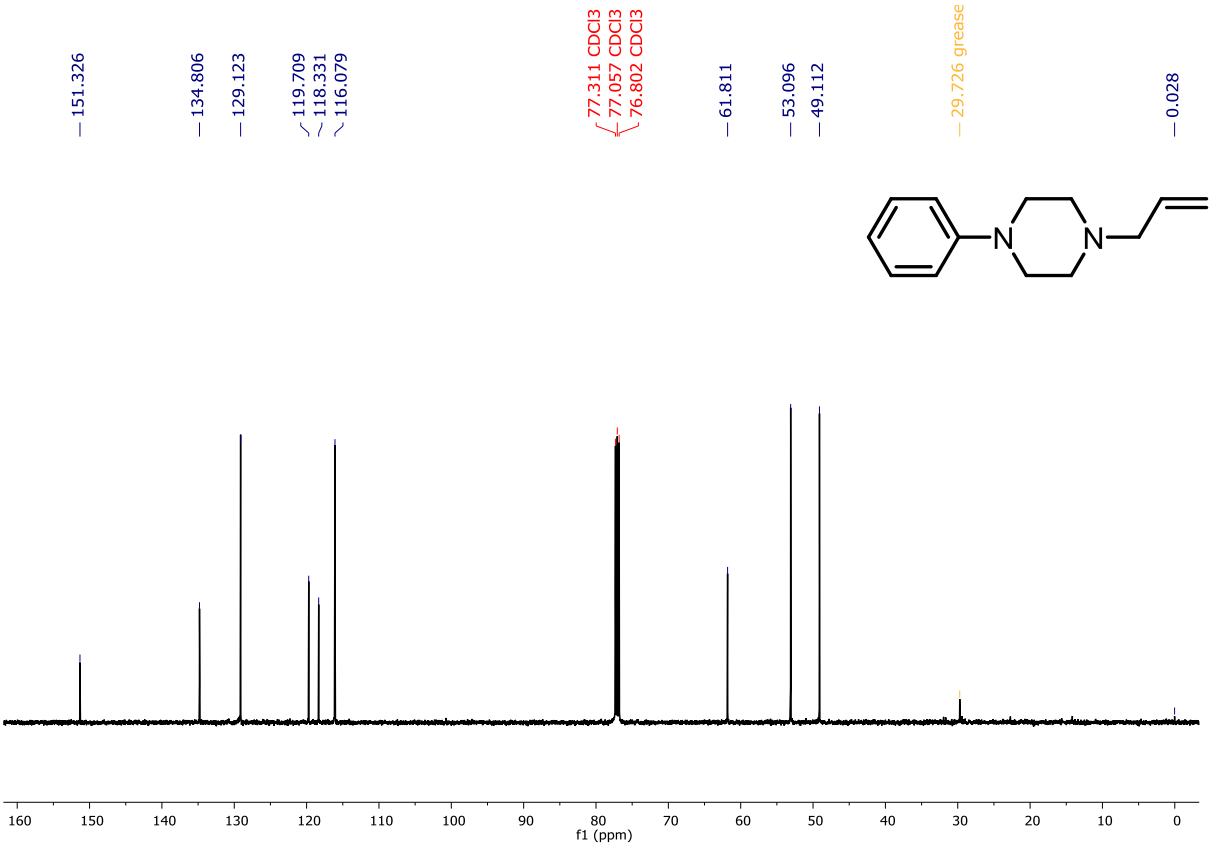
***N*-Allyl-*N*-methylaniline (5b):** ^{13}C NMR (500 MHz, $CDCl_3$)



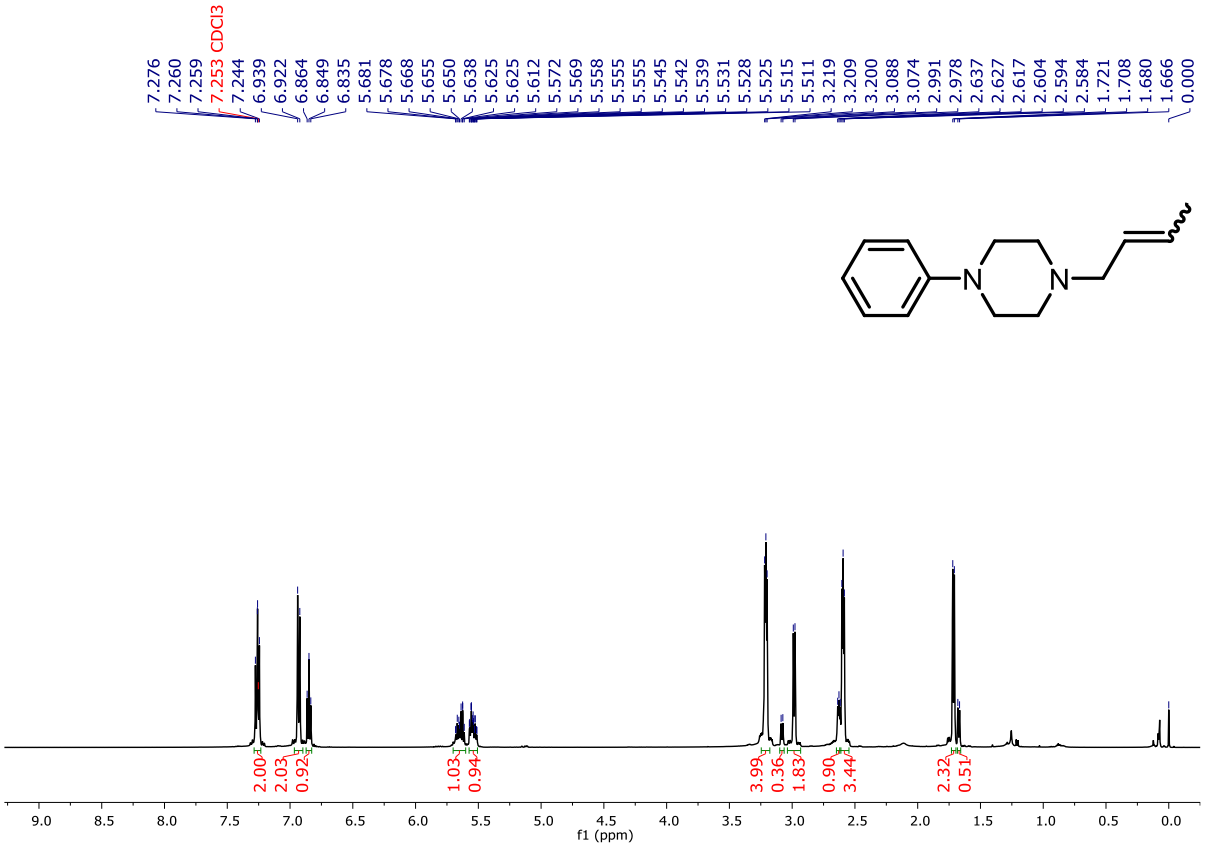
1-Allyl-4-phenylpiperazine (3a): ^{1}H NMR (500 MHz, $CDCl_3$)



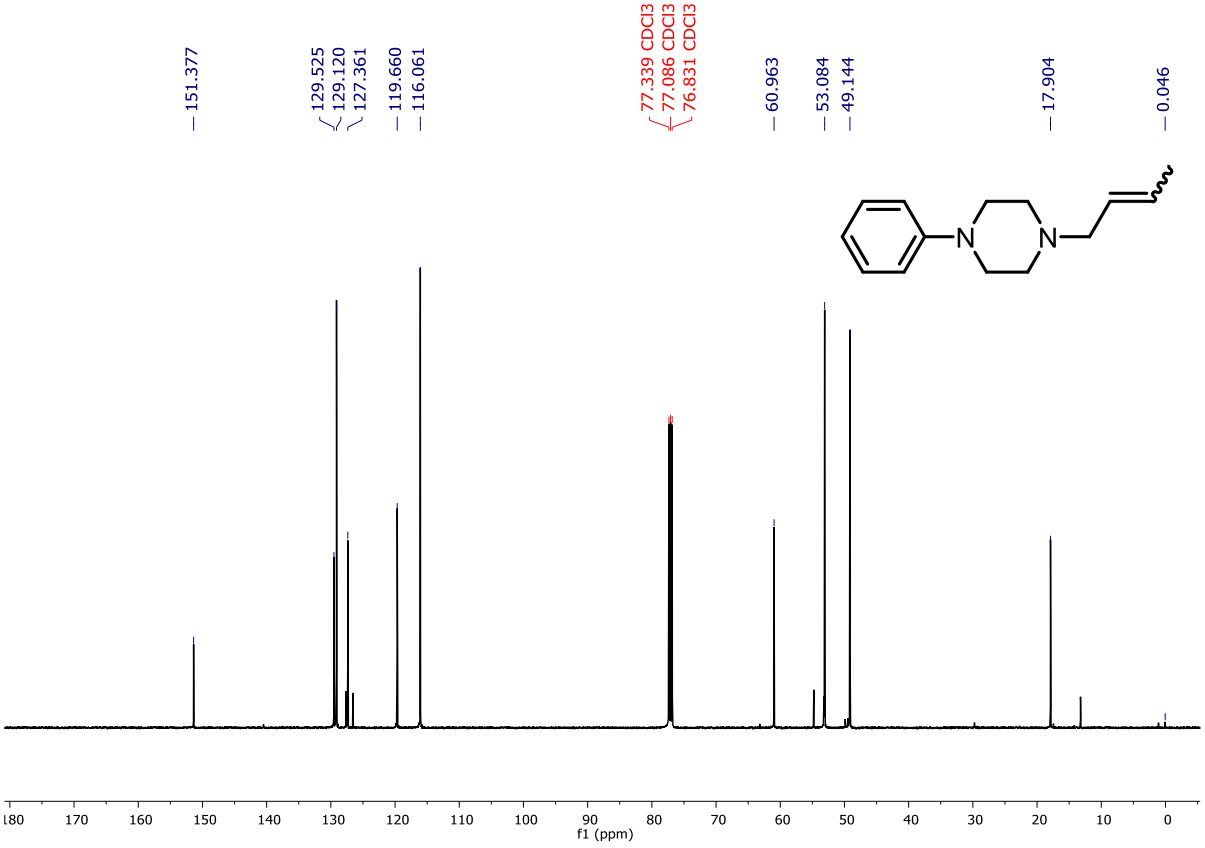
1-Allyl-4-phenylpiperazine (3a): ^{13}C NMR (125 MHz, $CDCl_3$)



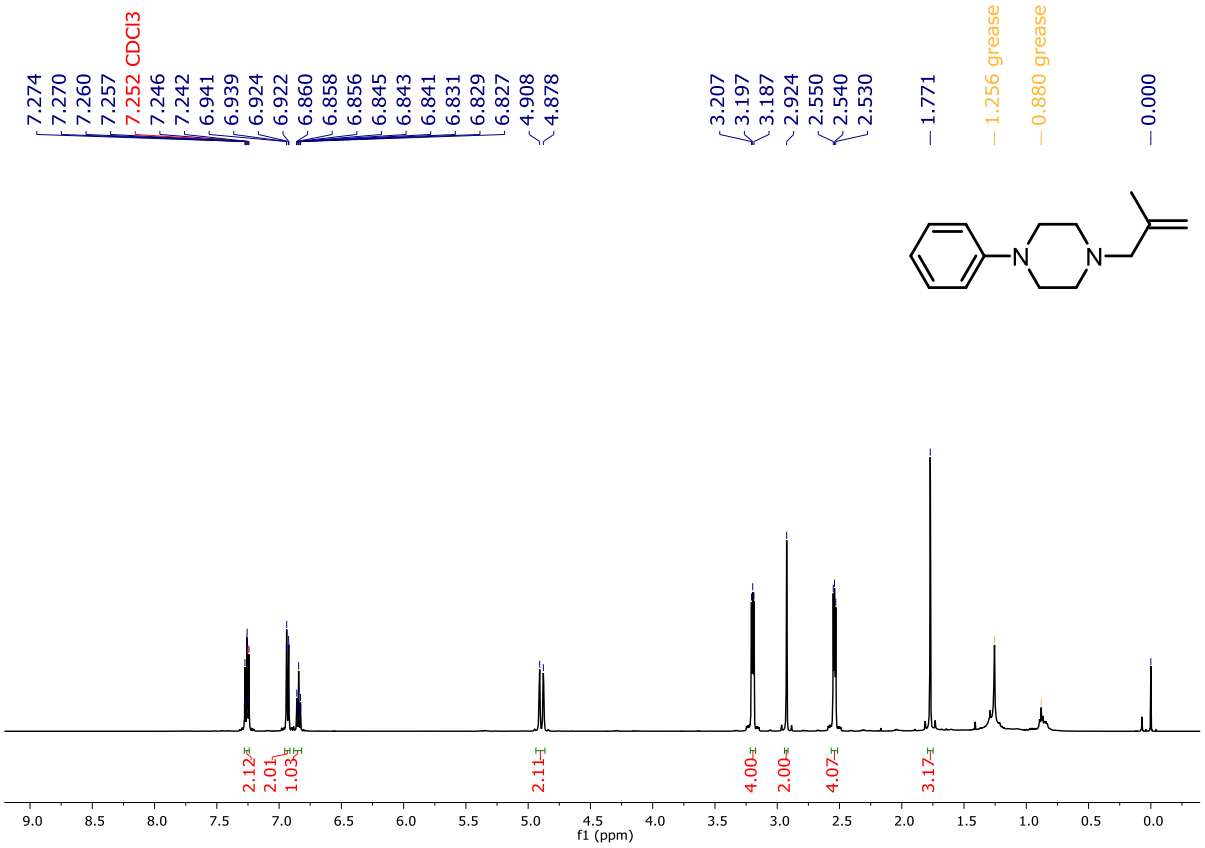
(*E*)-1-(But-2-en-1-yl)-4-phenylpiperazine (3q): ^{1}H NMR (500 MHz, $CDCl_3$)



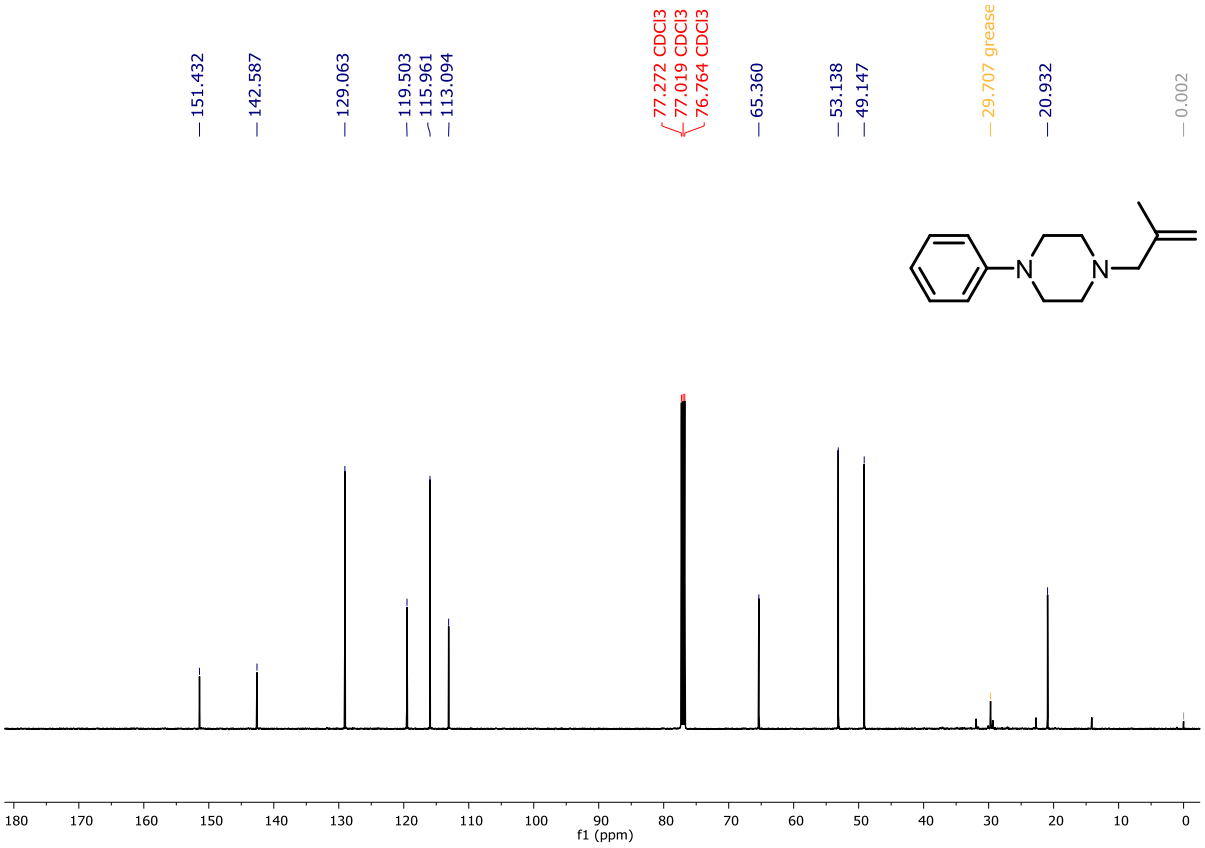
(*E*)-1-(But-2-en-1-yl)-4-phenylpiperazine (3q): ^{13}C NMR (125 MHz, $CDCl_3$)



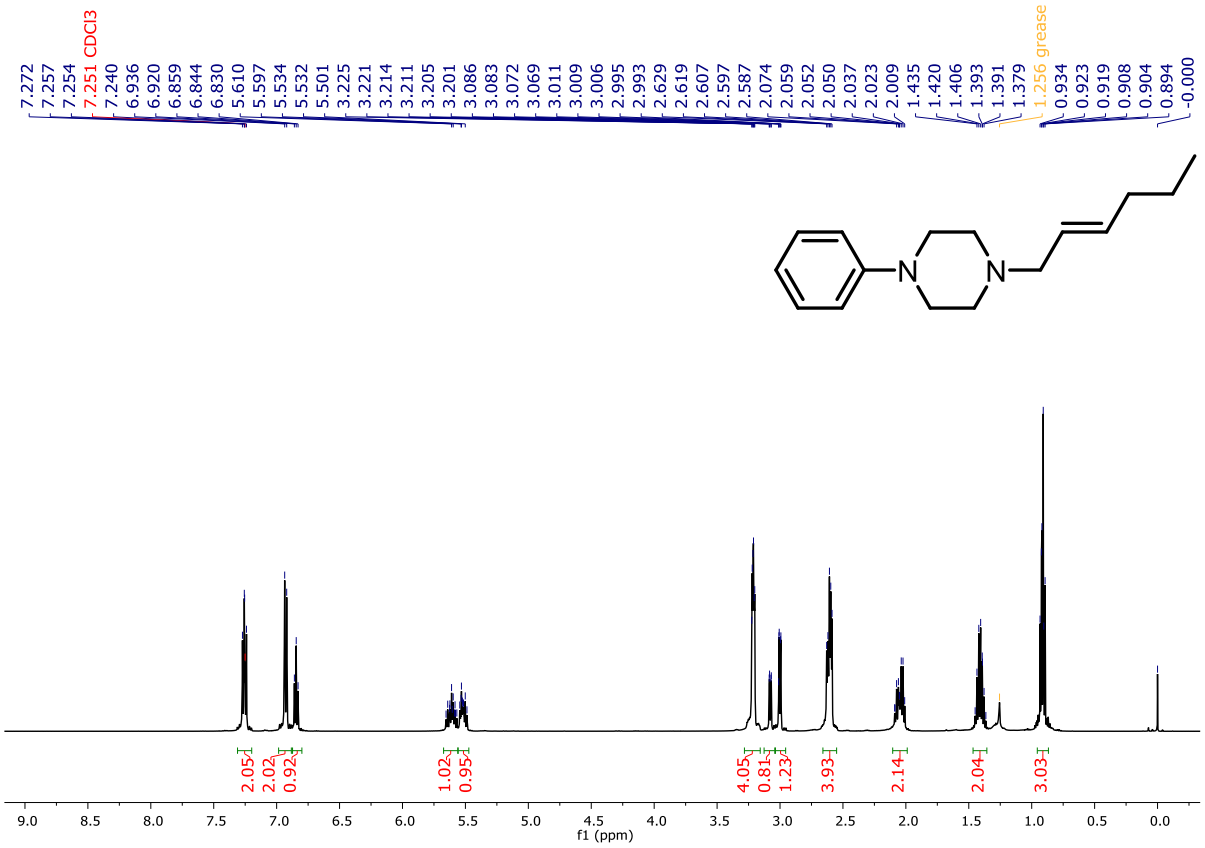
1-(2-Methylallyl)-4-phenylpiperazine (3r): ^{1}H NMR (500 MHz, $CDCl_3$)



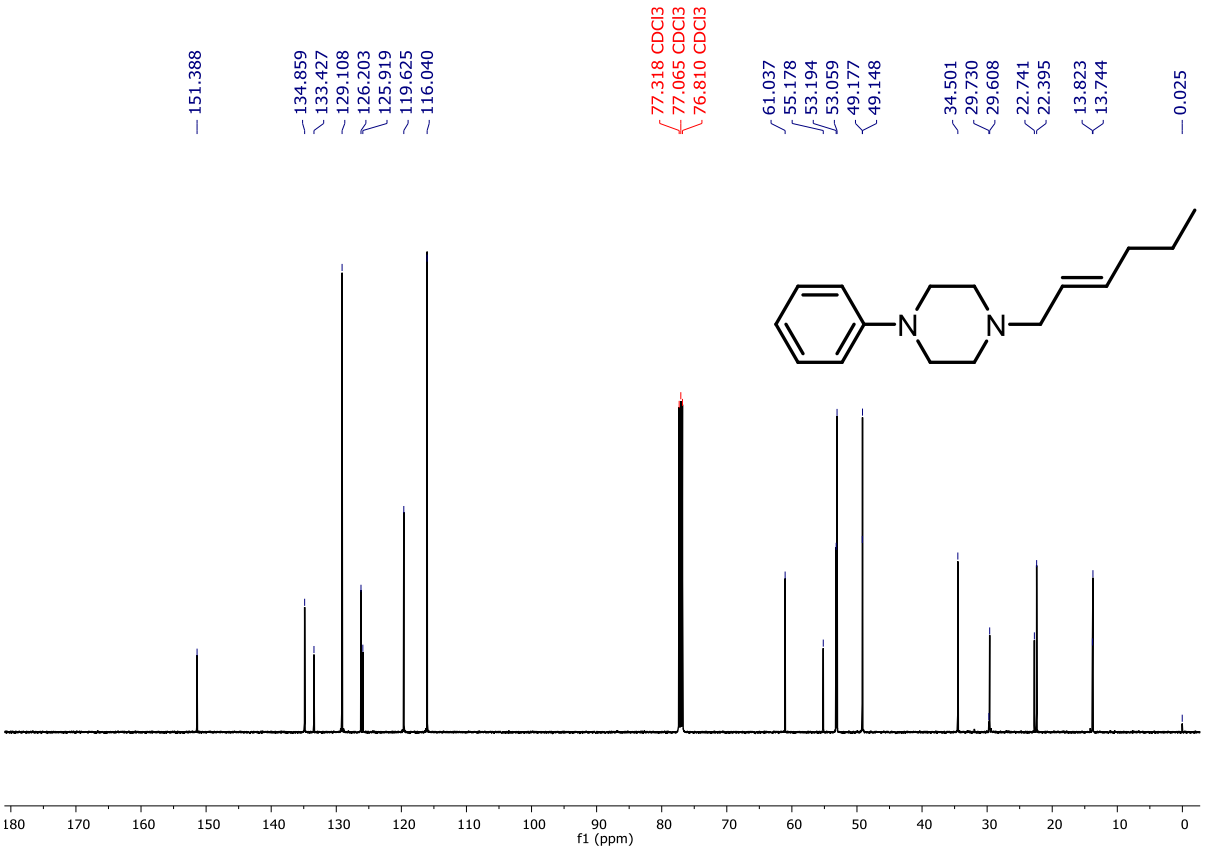
1-(2-Methylallyl)-4-phenylpiperazine (3r): ^{13}C NMR (125 MHz, $CDCl_3$)



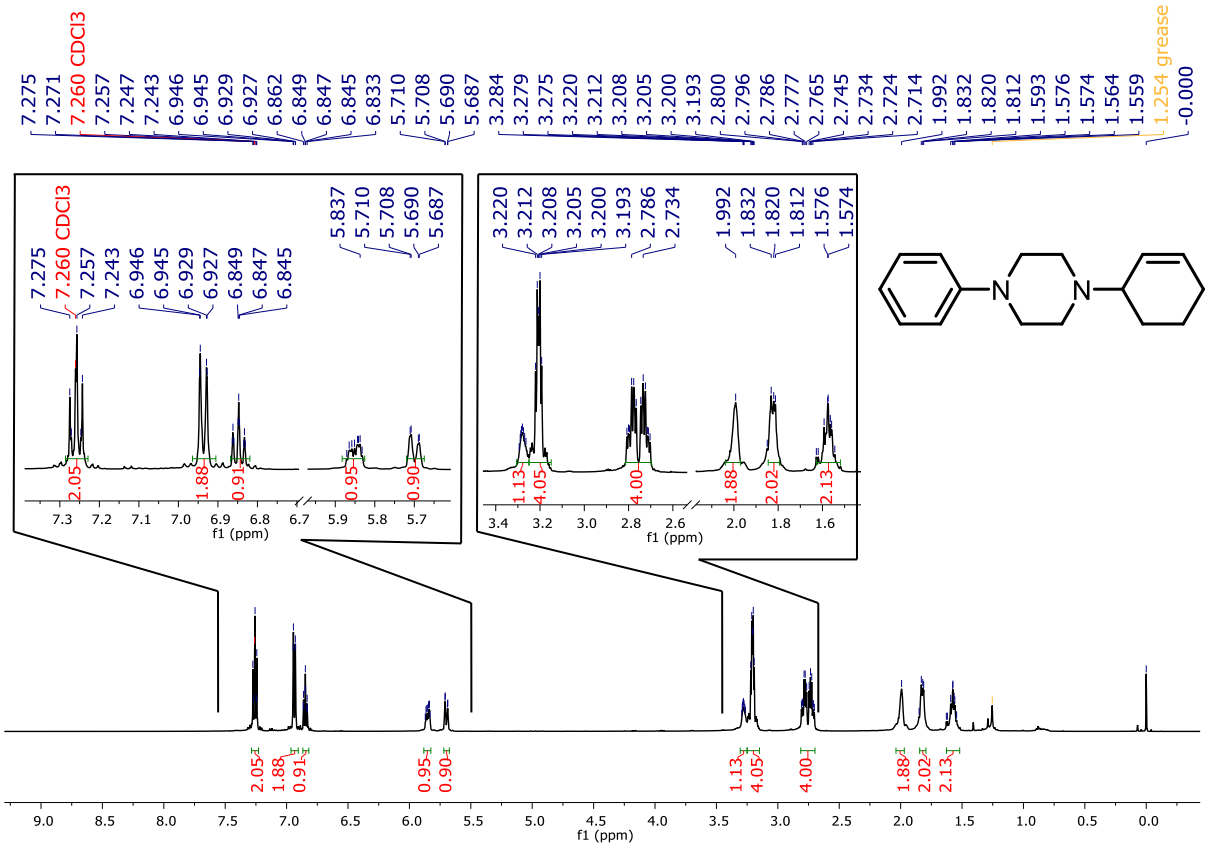
1-(Hex-2-en-1-yl)-4-phenylpiperazine (3s): ^{1}H NMR (500 MHz, $CDCl_3$)



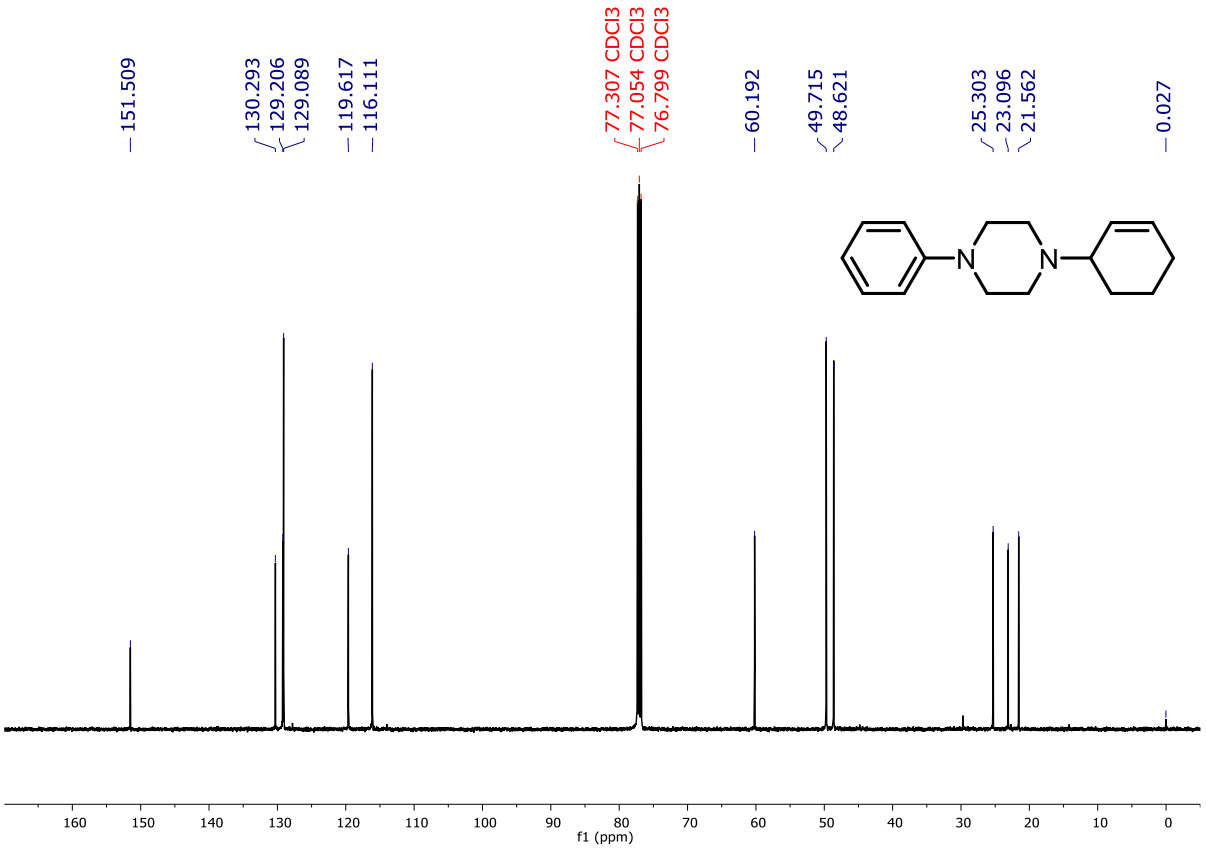
(*E*)-1-(Hex-2-en-1-yl)-4-phenylpiperazine (3s): ^{13}C NMR (125 MHz, $CDCl_3$)



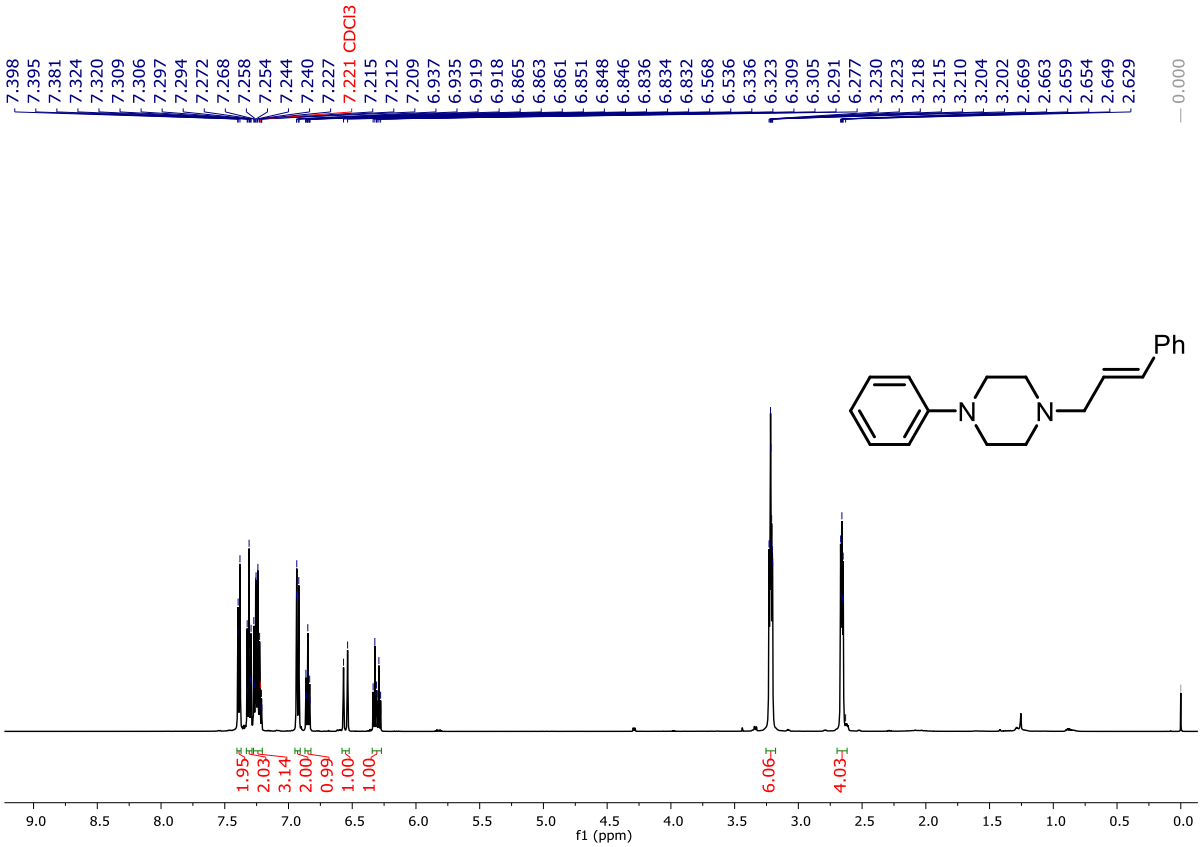
4-(Cyclohex-2-en)-1-phenylpiperazine (3t): ^{1}H NMR (500 MHz, $CDCl_3$)



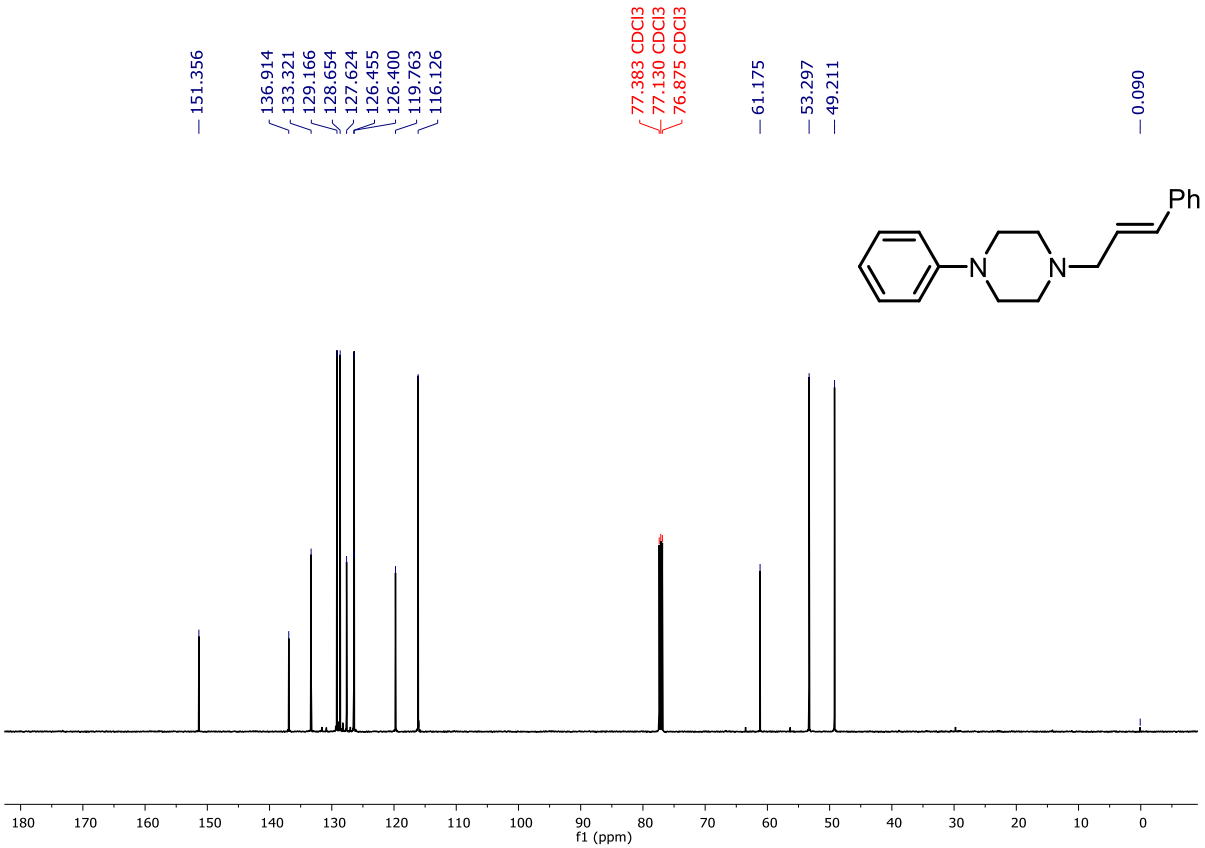
4-(Cyclohex-2-en)-1-phenylpiperazine (3t): ^{13}C NMR (125 MHz, $CDCl_3$)



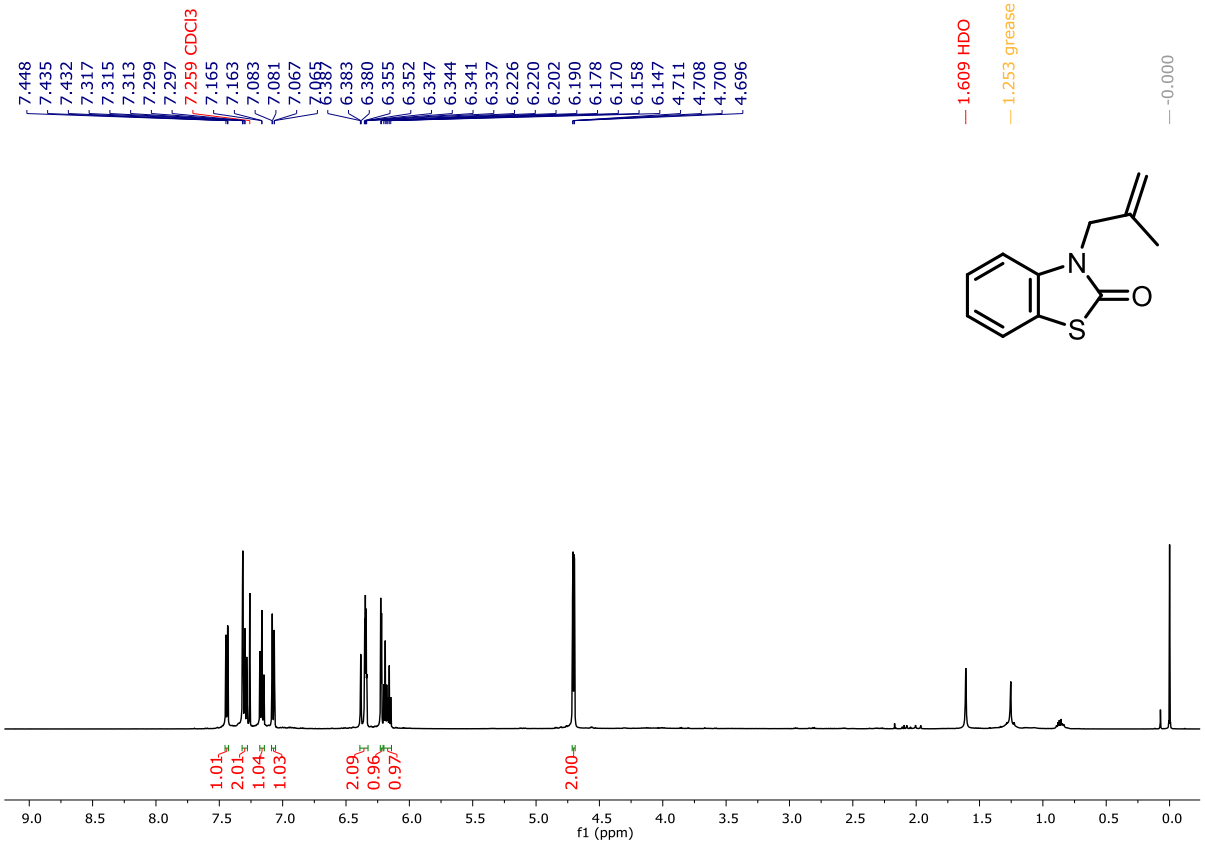
1-Cinnamyl-4-phenylpiperazine (3u): ^{1}H NMR (500 MHz, $CDCl_3$)



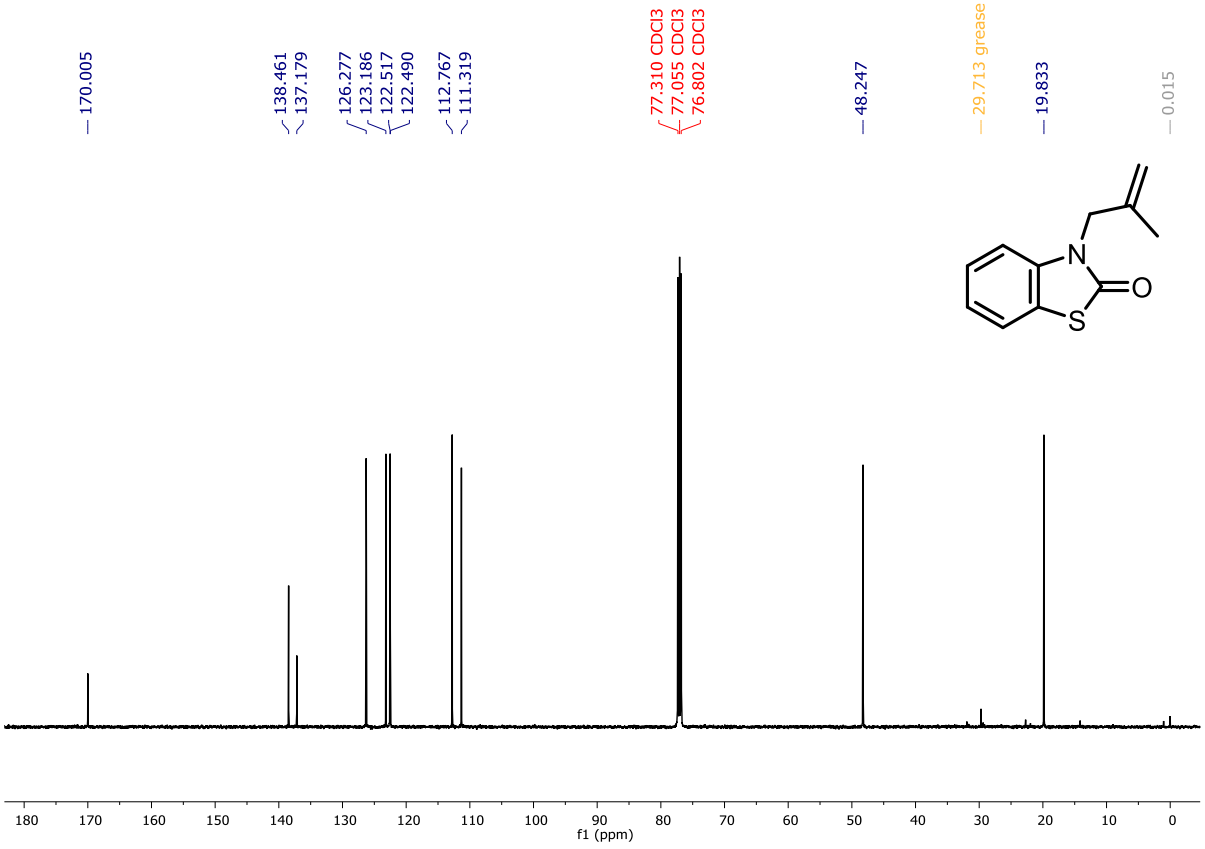
1-Cinnamyl-4-phenylpiperazine (3u): ^{13}C NMR (125 MHz, $CDCl_3$)



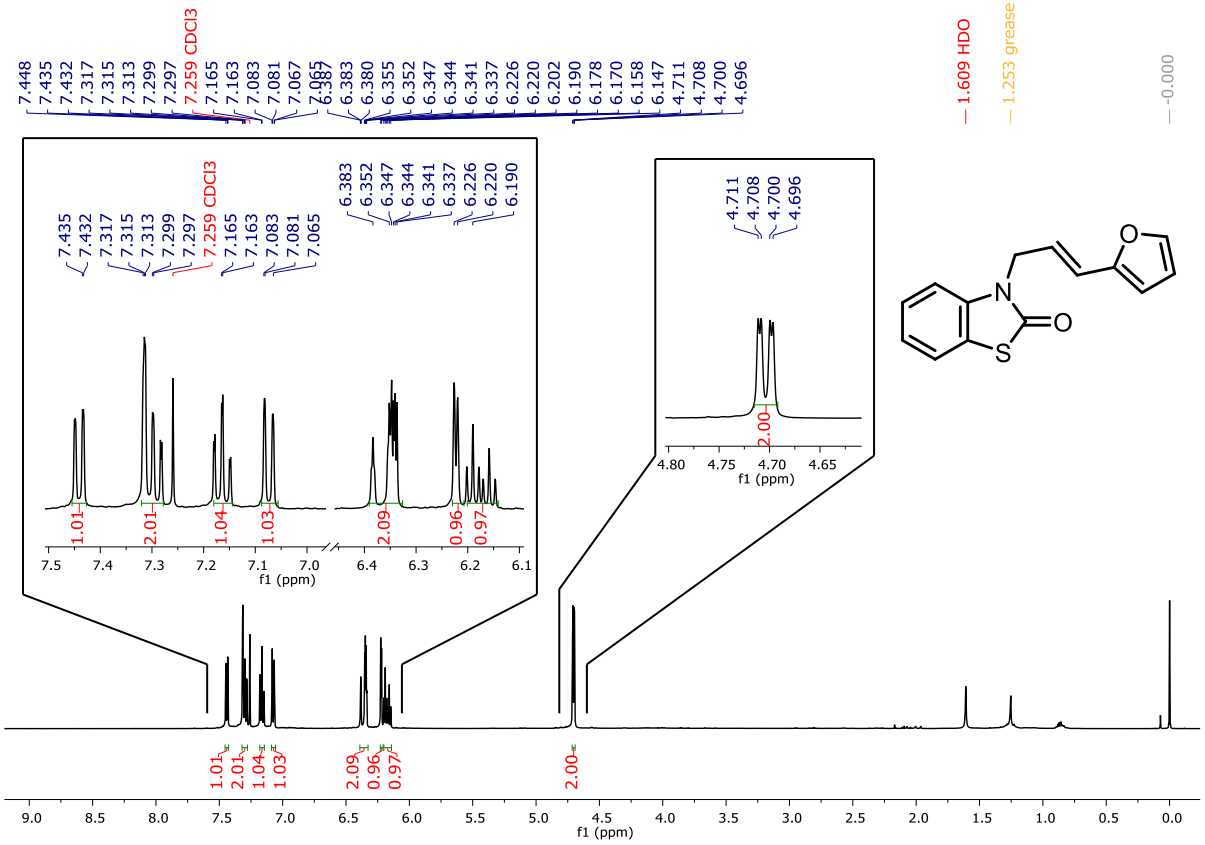
3-(2-Methylallyl)benzo[*d*]thiazol-2(3*H*)-one (4k): ^{1}H NMR (500 MHz, $CDCl_3$)



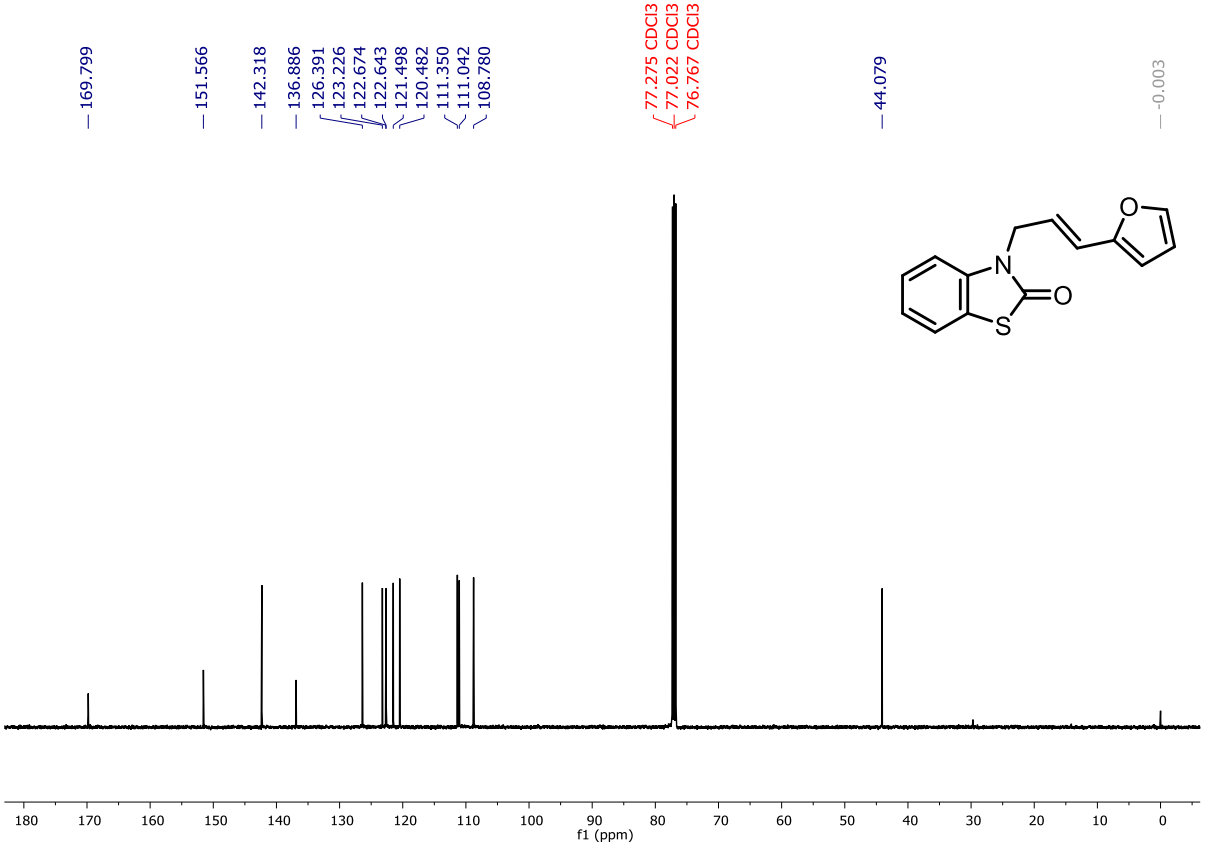
3-(2-Methylallyl)benzo[*d*]thiazol-2(3*H*)-one (4k): ^{13}C NMR (500 MHz, $CDCl_3$)



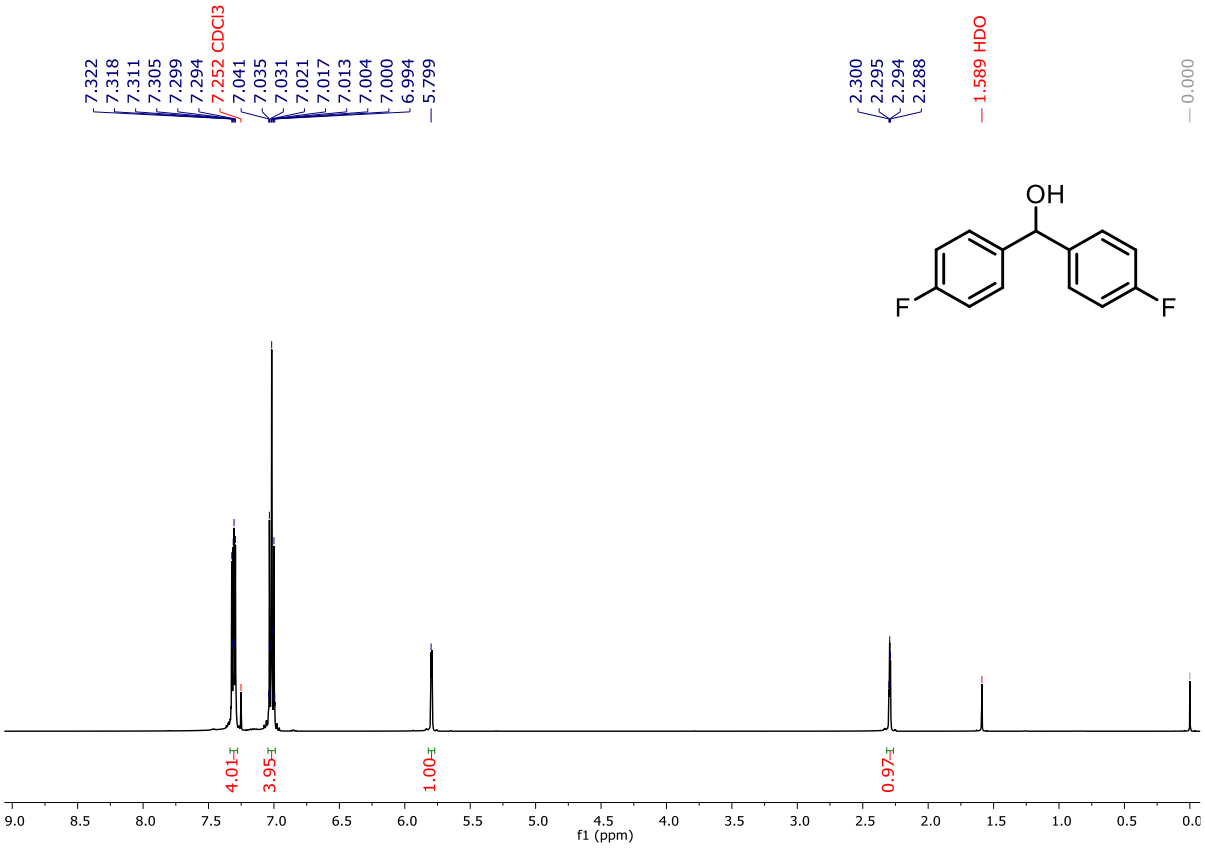
(*E*)-3-(3-(Furan-2-yl)allyl)benzo[*d*]thiazol-2(3*H*)-one (4l): ^{1}H NMR (500 MHz, $CDCl_3$)



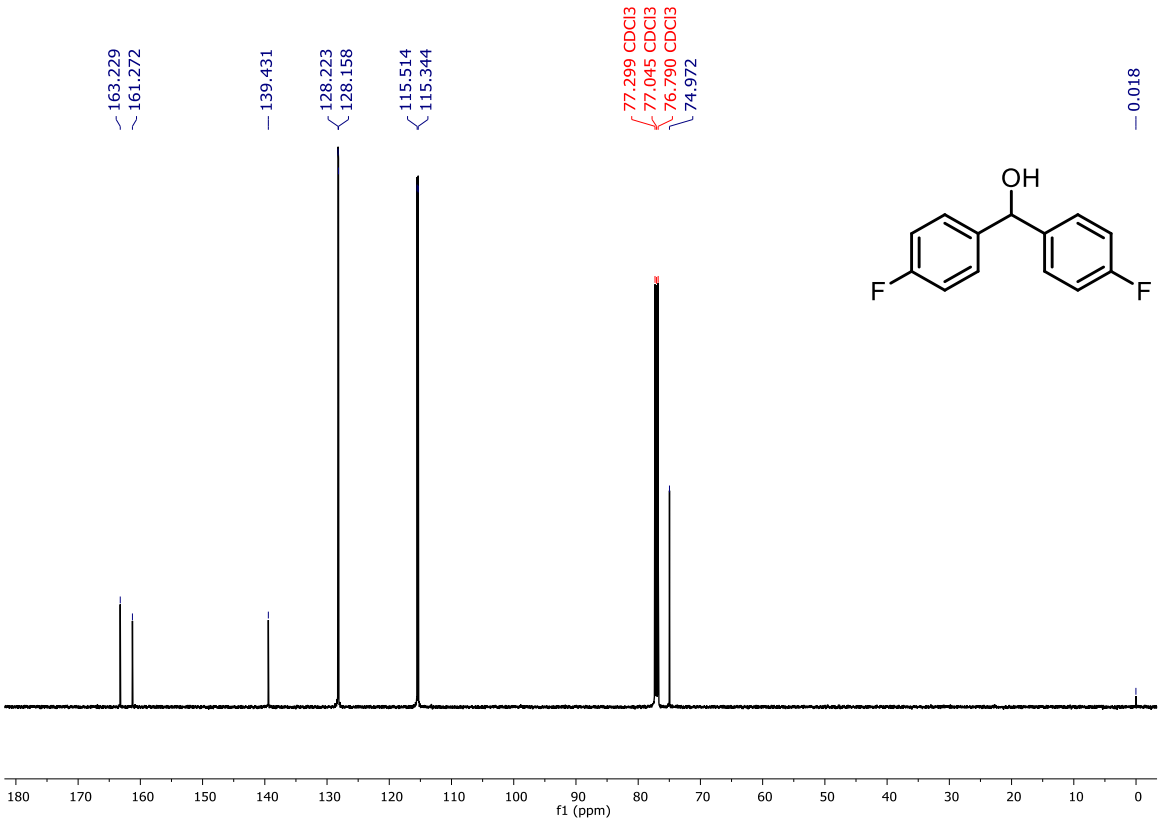
(*E*)-3-(3-(Furan-2-yl)allyl)benzo[*d*]thiazol-2(3*H*)-one (4l): ^{13}C NMR (500 MHz, $CDCl_3$)



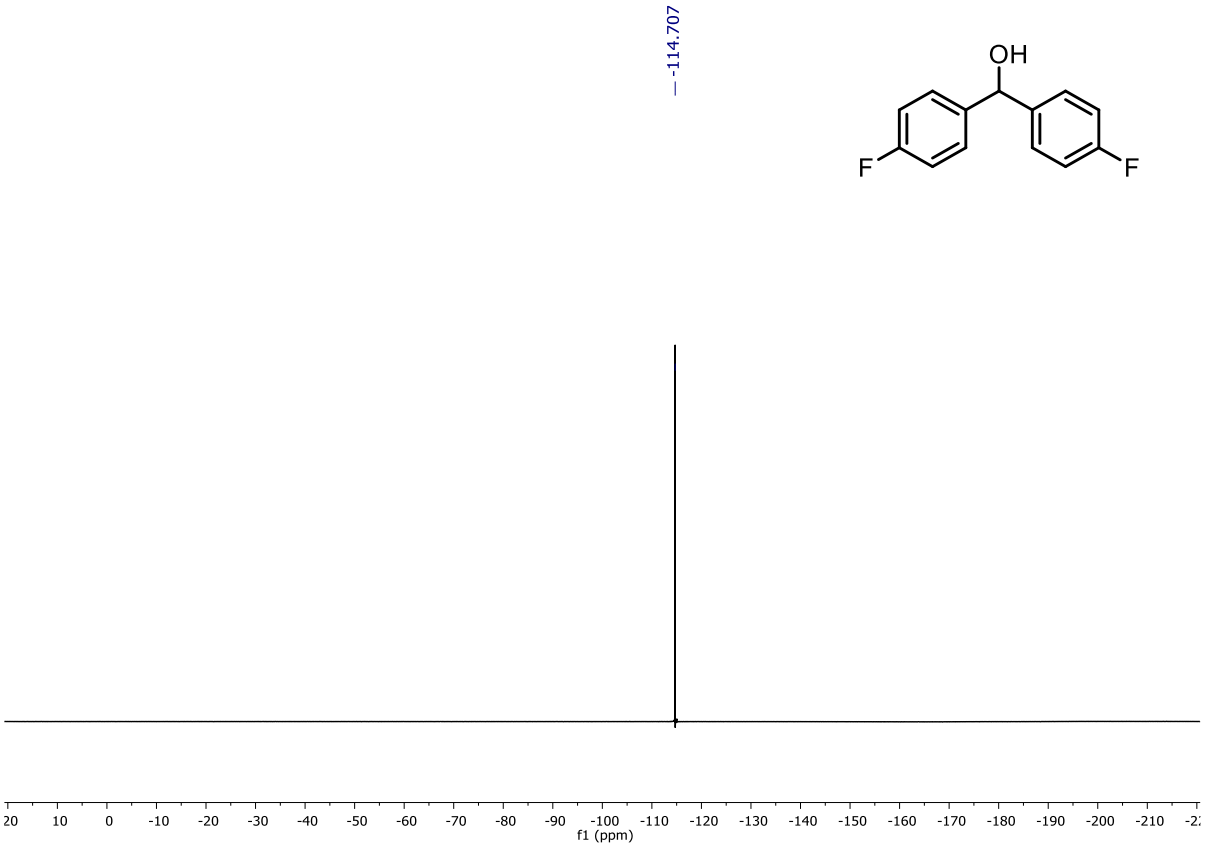
Bis(4-fluorophenyl)methanol (6b): ^{1}H NMR (500 MHz, $CDCl_3$)



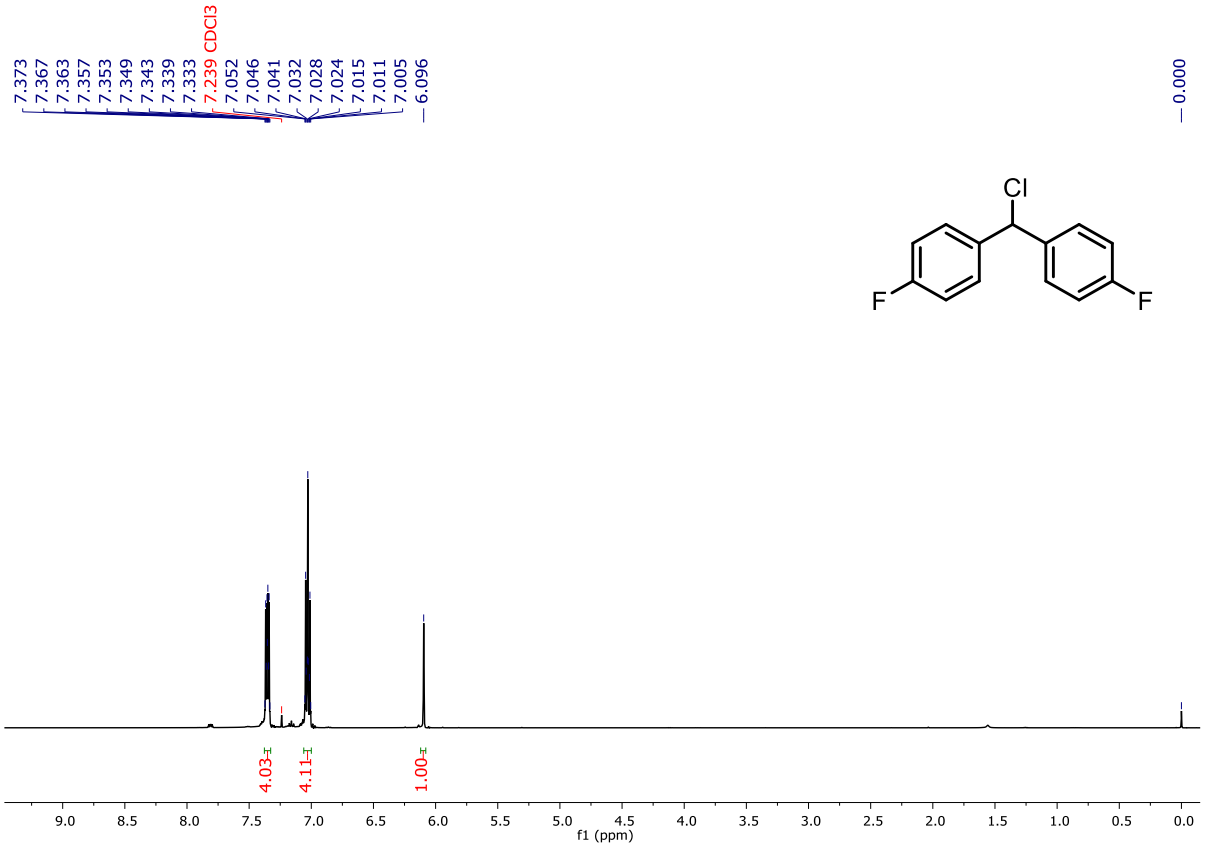
Bis(4-fluorophenyl)methanol (6b): ^{13}C NMR (125 MHz, $CDCl_3$)



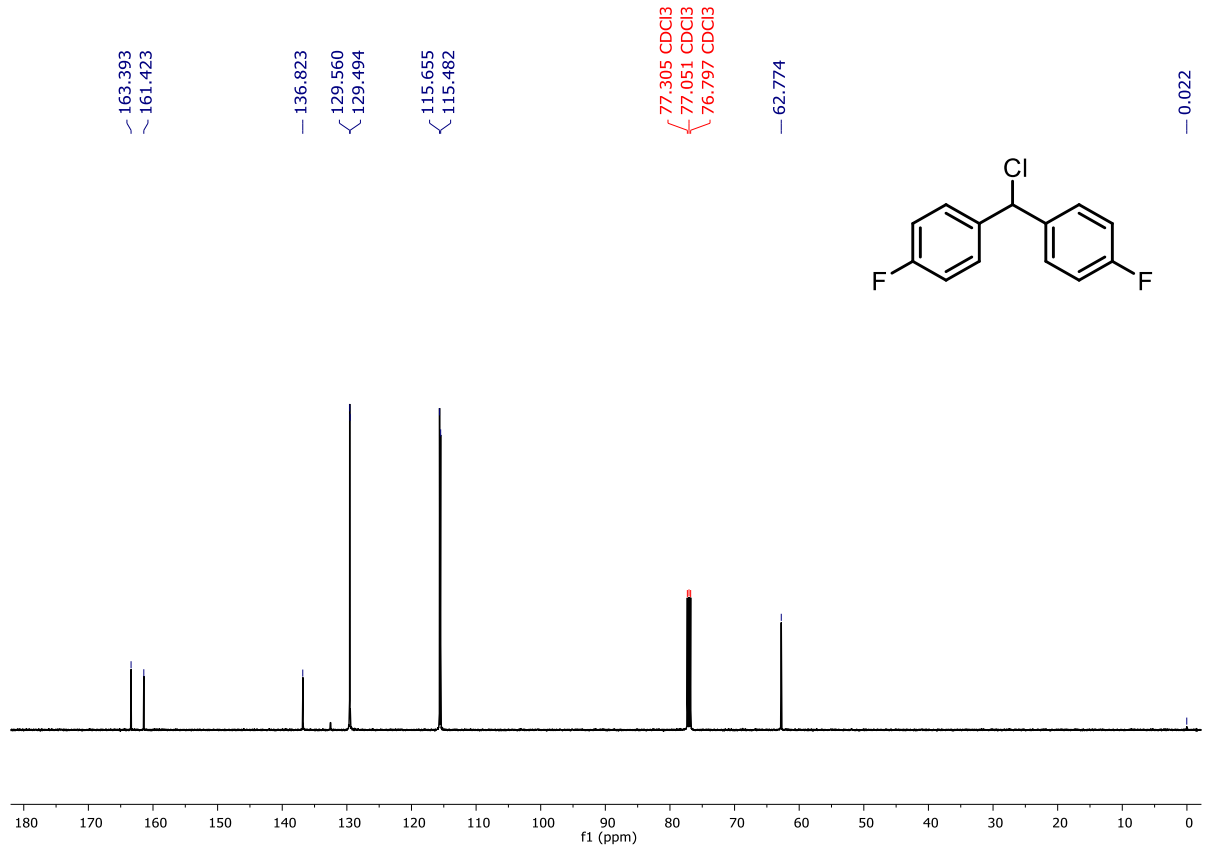
Bis(4-fluorophenyl)methanol (6b): ^{19}F NMR (471 MHz, $CDCl_3$)



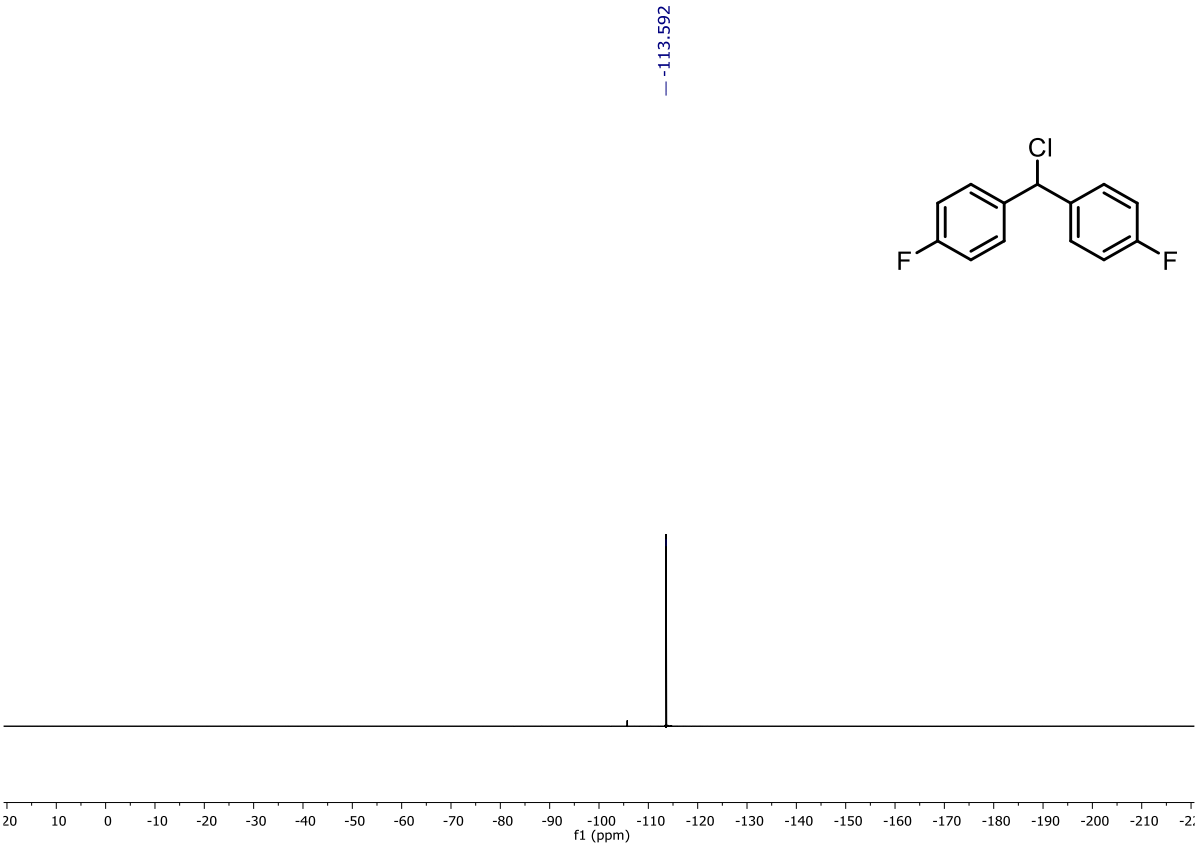
Chloro-bis(4-fluorophenyl)methane (6c): ^{1}H NMR (500 MHz, $CDCl_3$)



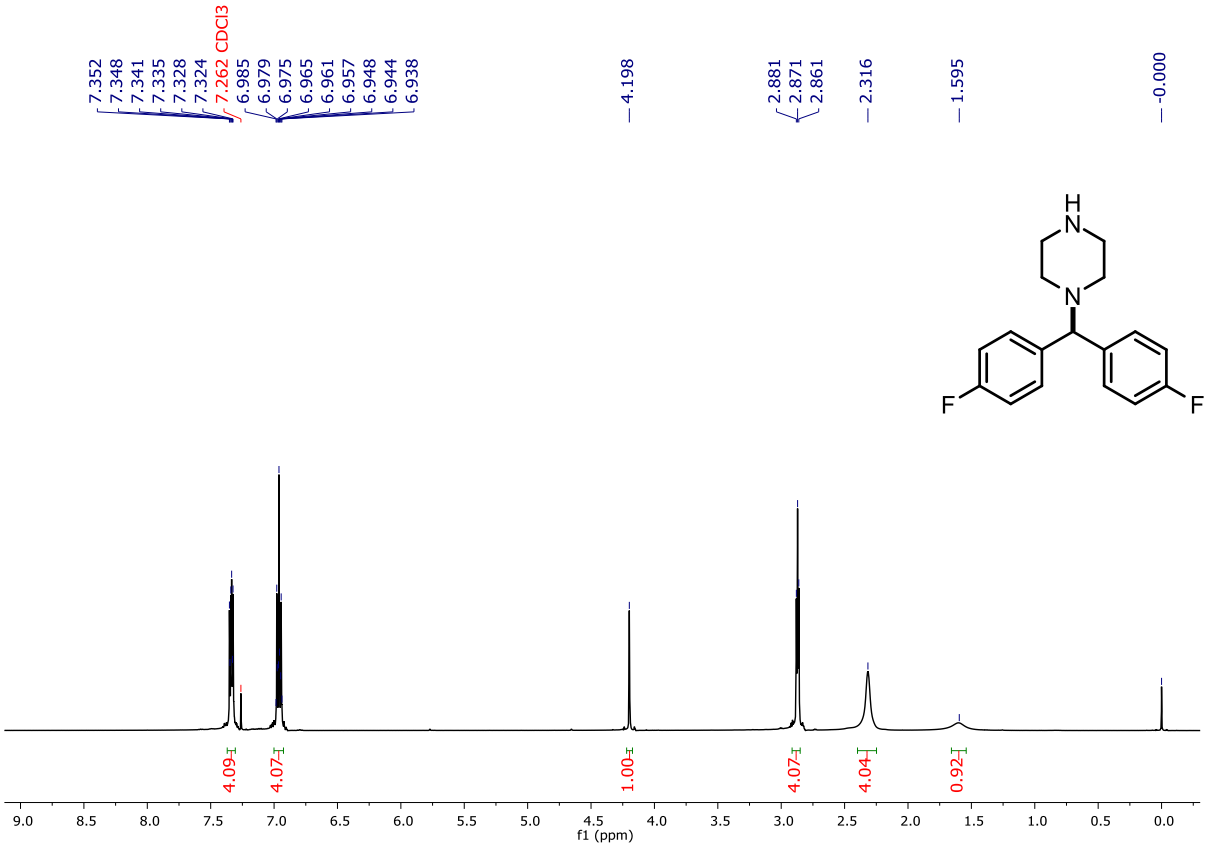
Chloro-bis(4-fluorophenyl)methane (6c): ^{13}C NMR (125 MHz, $CDCl_3$)



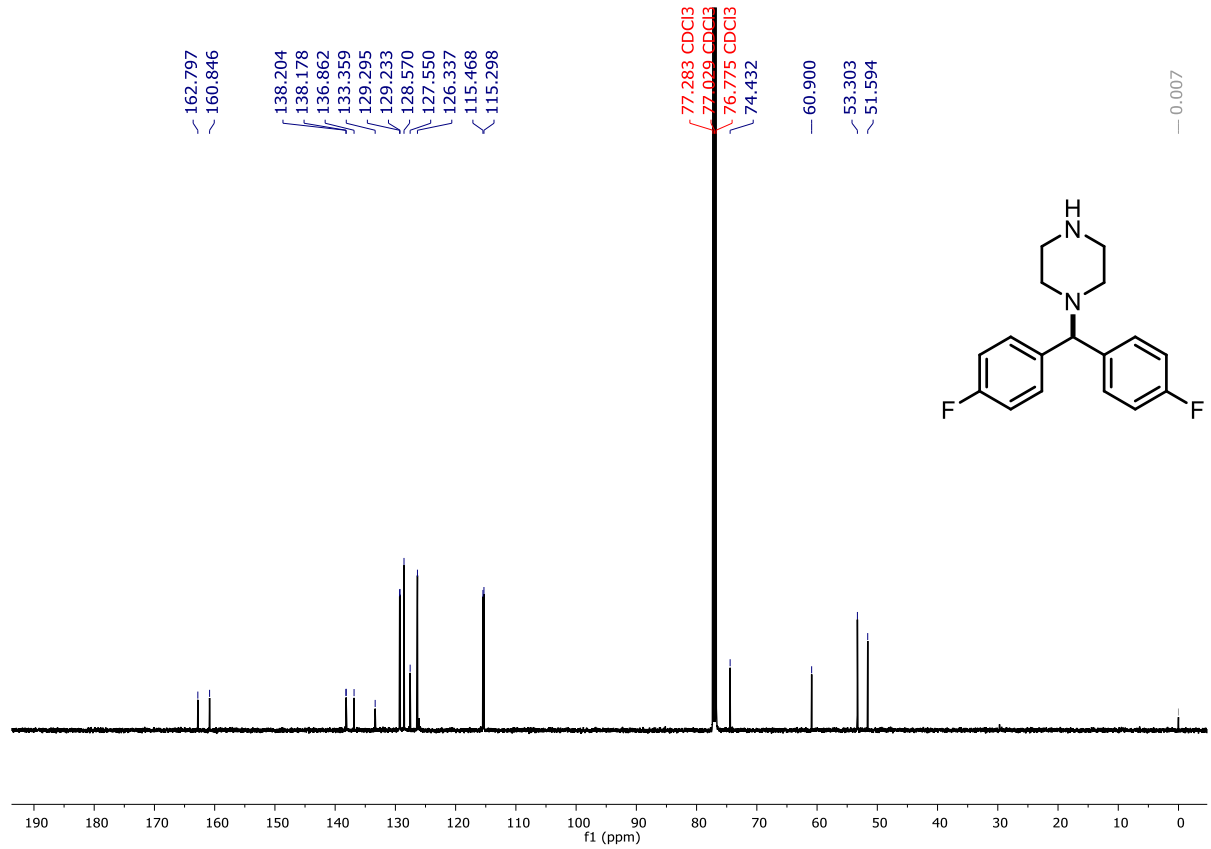
Chloro-bis(4-fluorophenyl)methane (6c): ^{19}F NMR (471 MHz, $CDCl_3$)



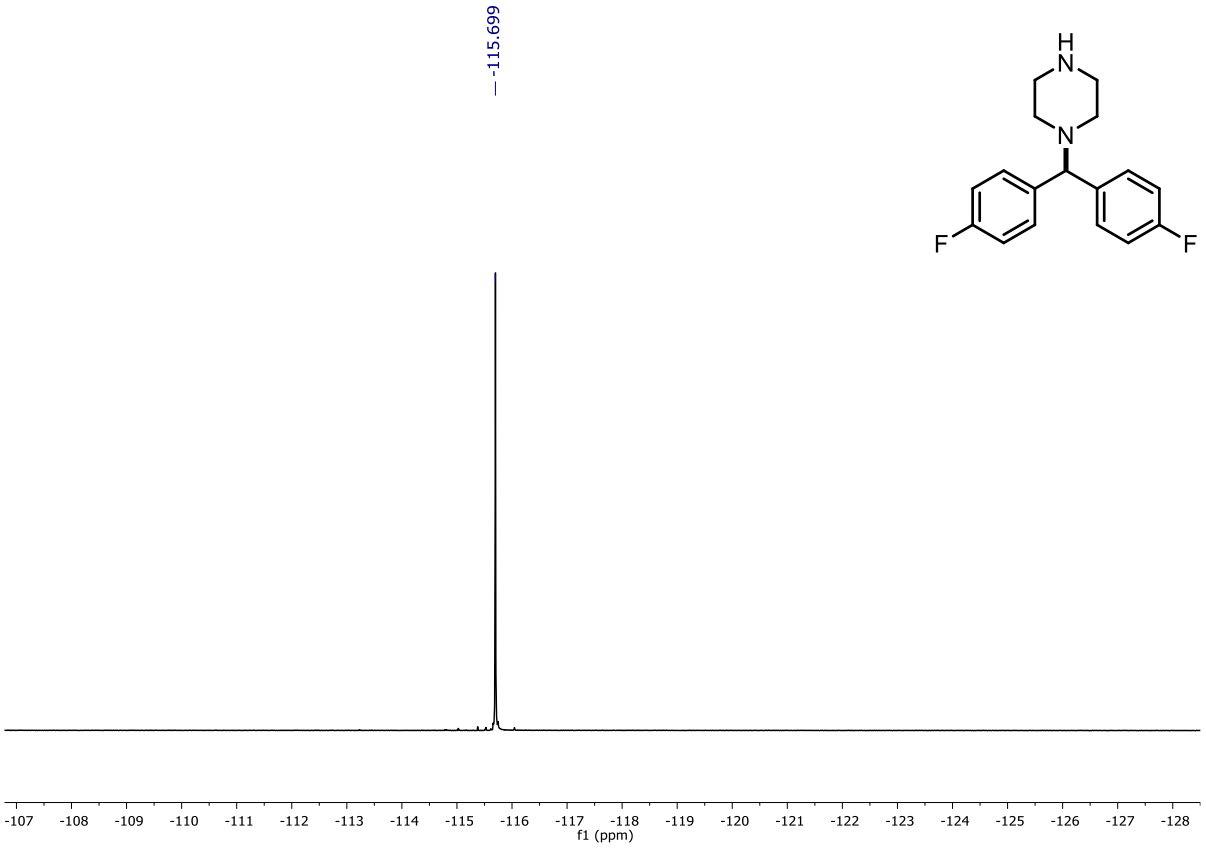
Bis(4-fluorophenyl)methyl piperazine (KI-6d): ^{1}H NMR (500 MHz, $CDCl_3$)



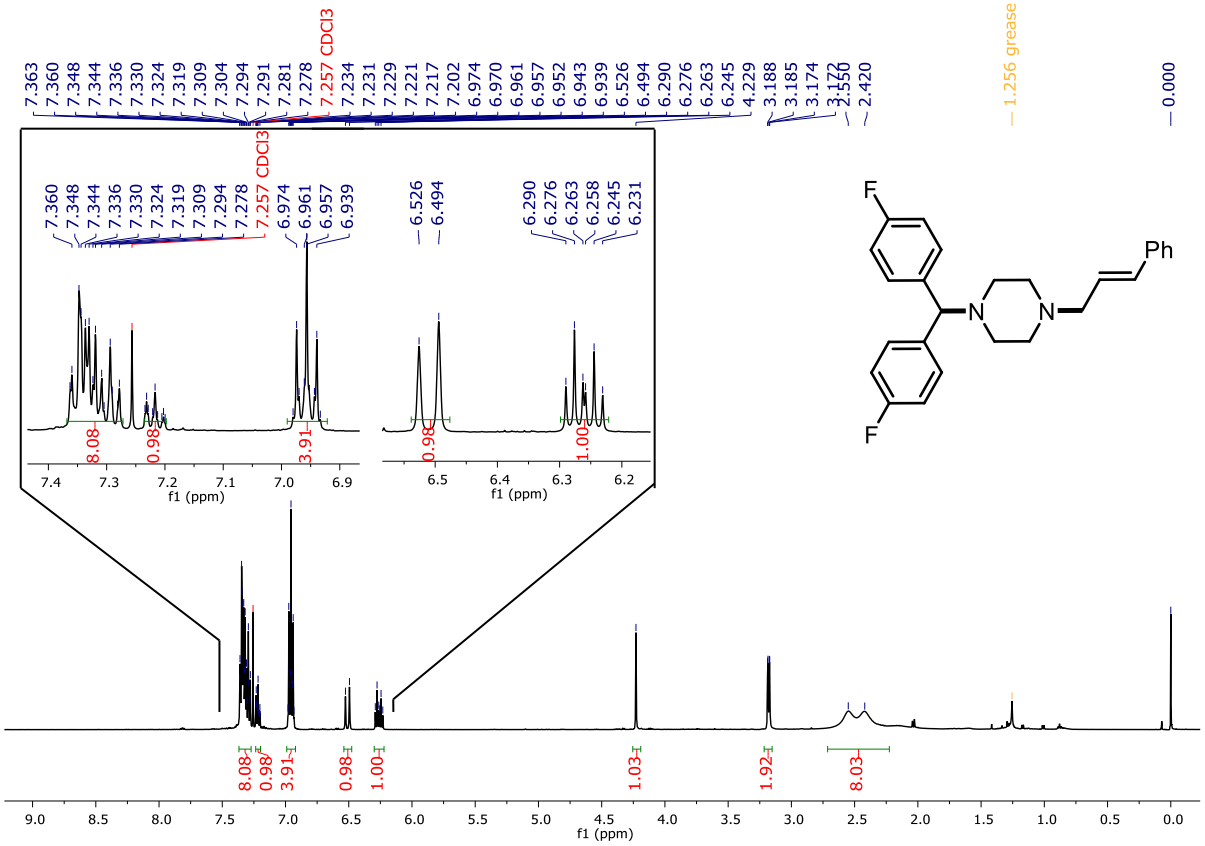
Bis(4-fluorophenyl)methyl piperazine (KI-6d): ^{13}C NMR (125 MHz, $CDCl_3$)



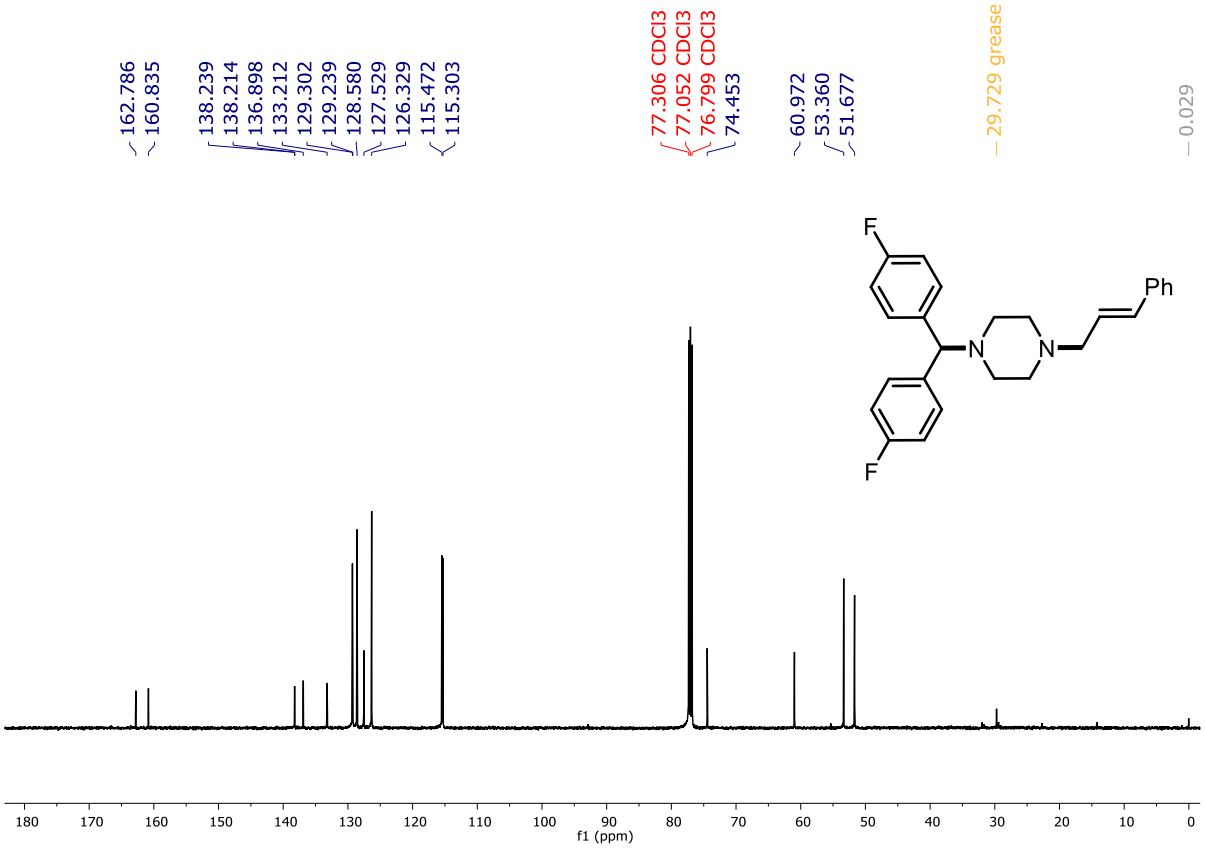
Bis(4-fluorophenyl)methyl piperazine (KI-6d): ^{19}F NMR (471 MHz, $CDCl_3$)



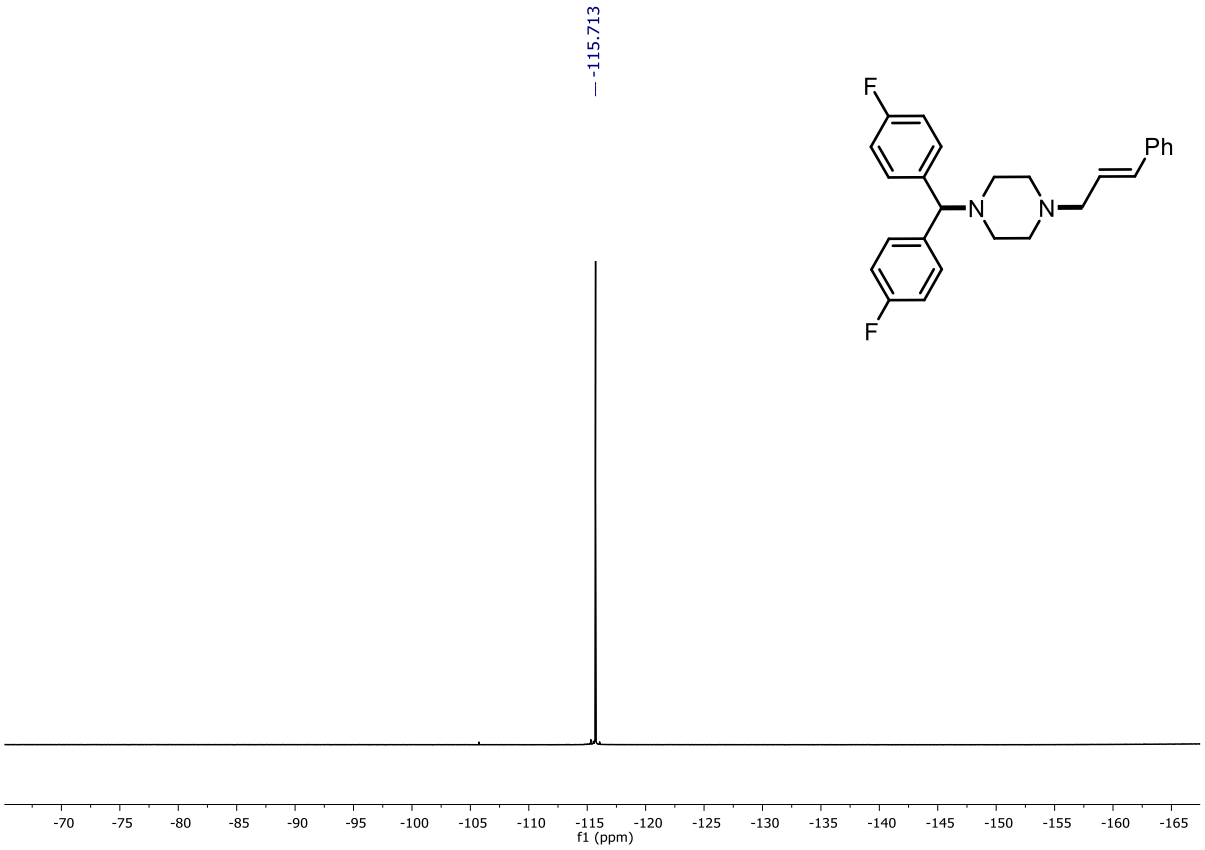
Flunarizine (6): ^{1}H NMR (500 MHz, $CDCl_3$)



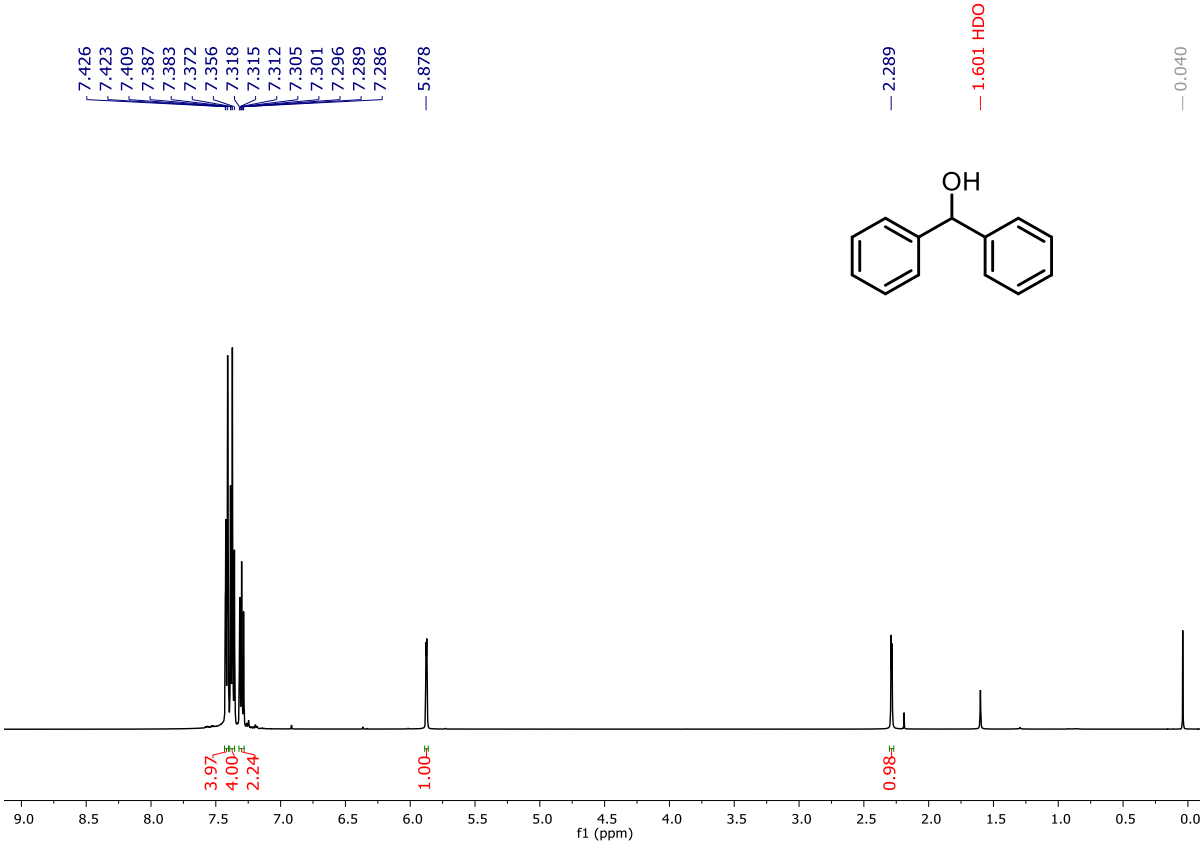
Flunarizine (6): ^{13}C NMR (125 MHz, $CDCl_3$)



Flunarizine (6): ^{19}F NMR (471 MHz, $CDCl_3$)

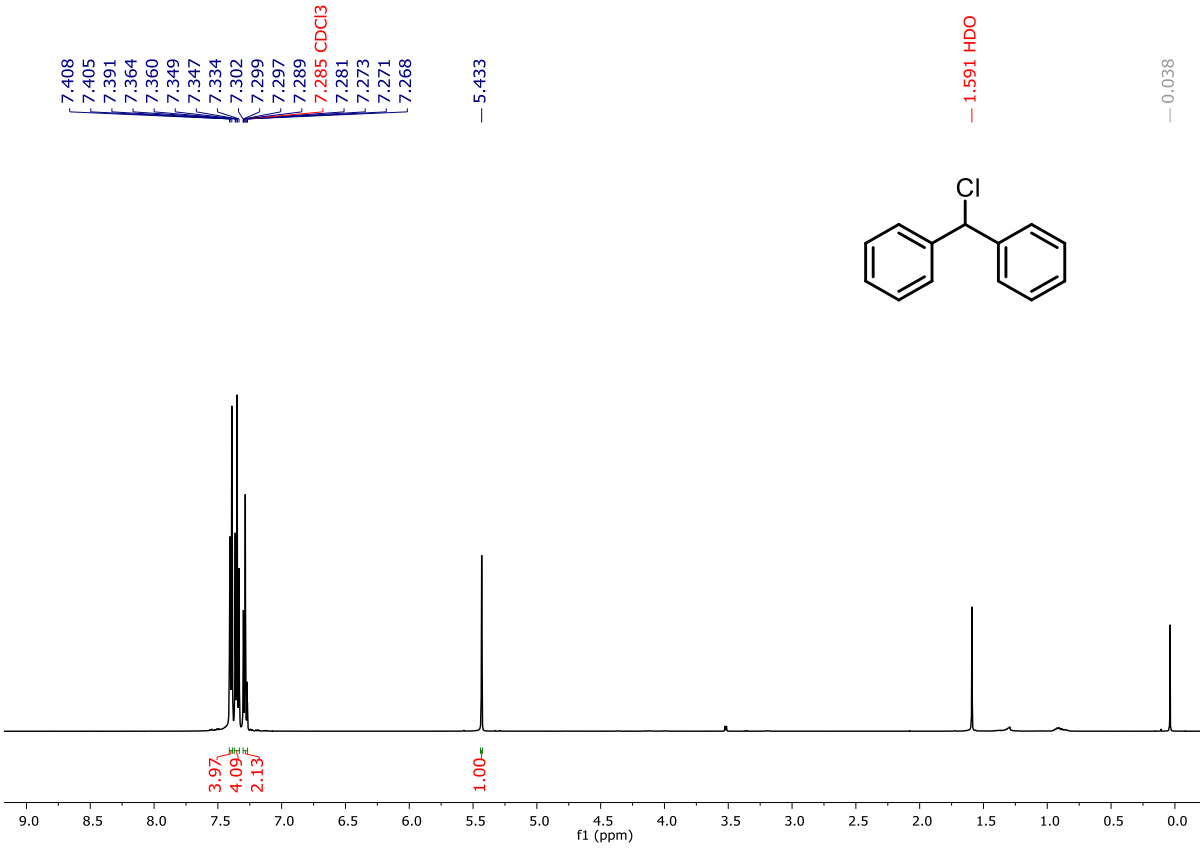


Diphenylmethanol (7b): ^{1}H NMR (500 MHz, $CDCl_3$)

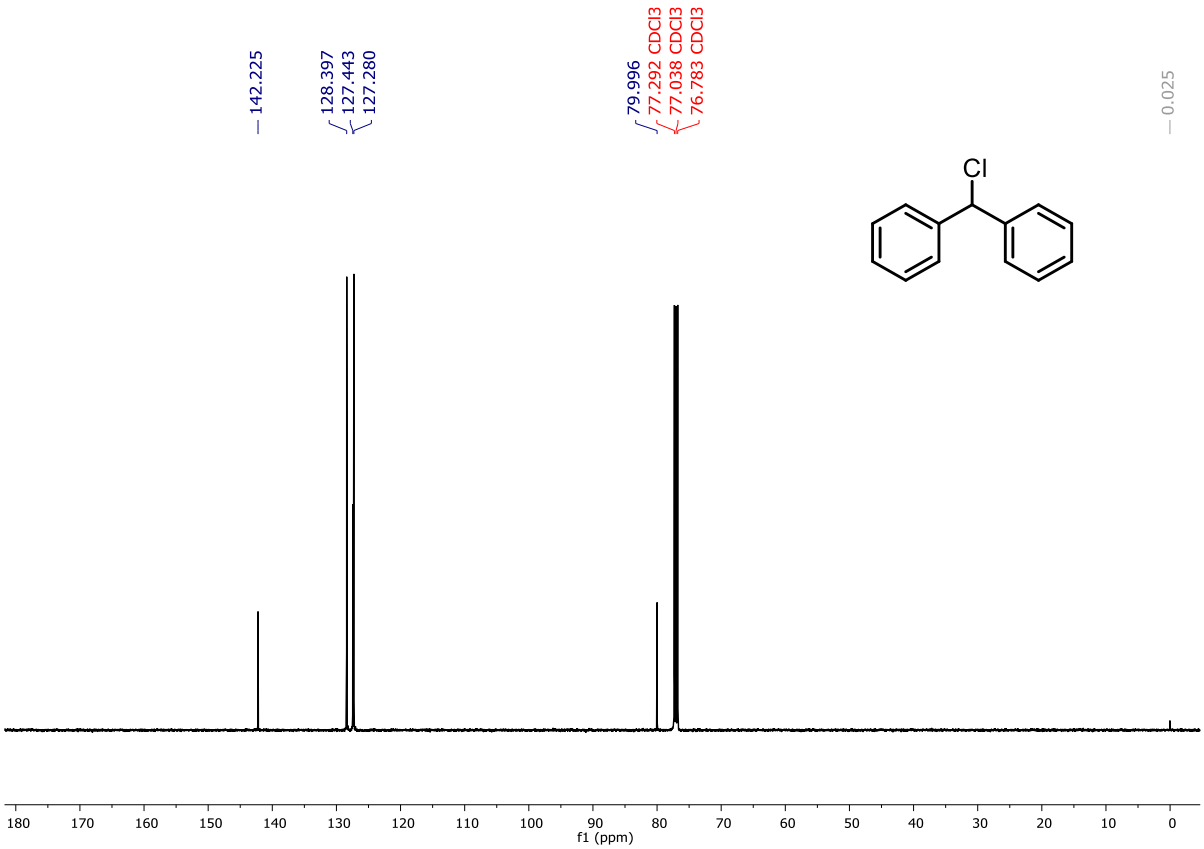


Diphenylmethanol (7b): ^{13}C NMR (125 MHz, $CDCl_3$)

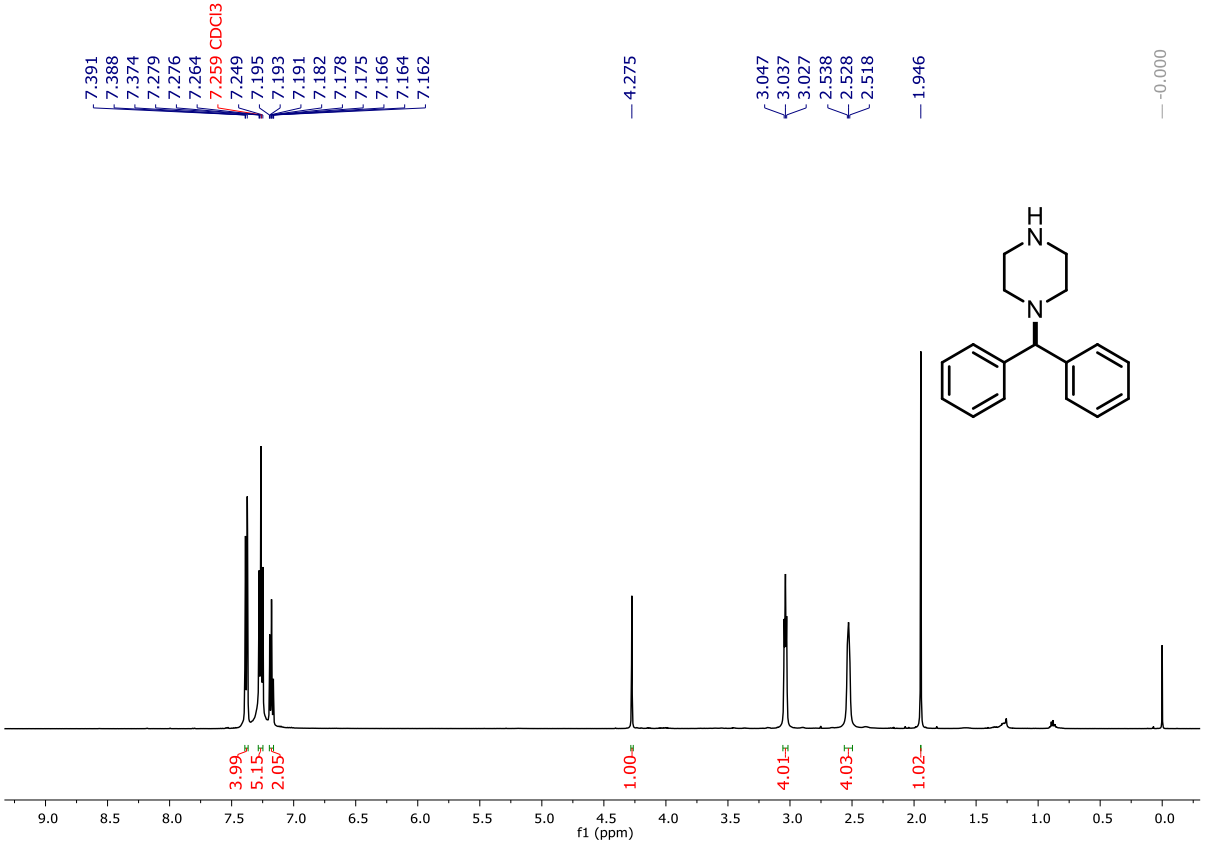
Diphenylchloromethane (7c): ^{1}H NMR (500 MHz, $CDCl_3$)



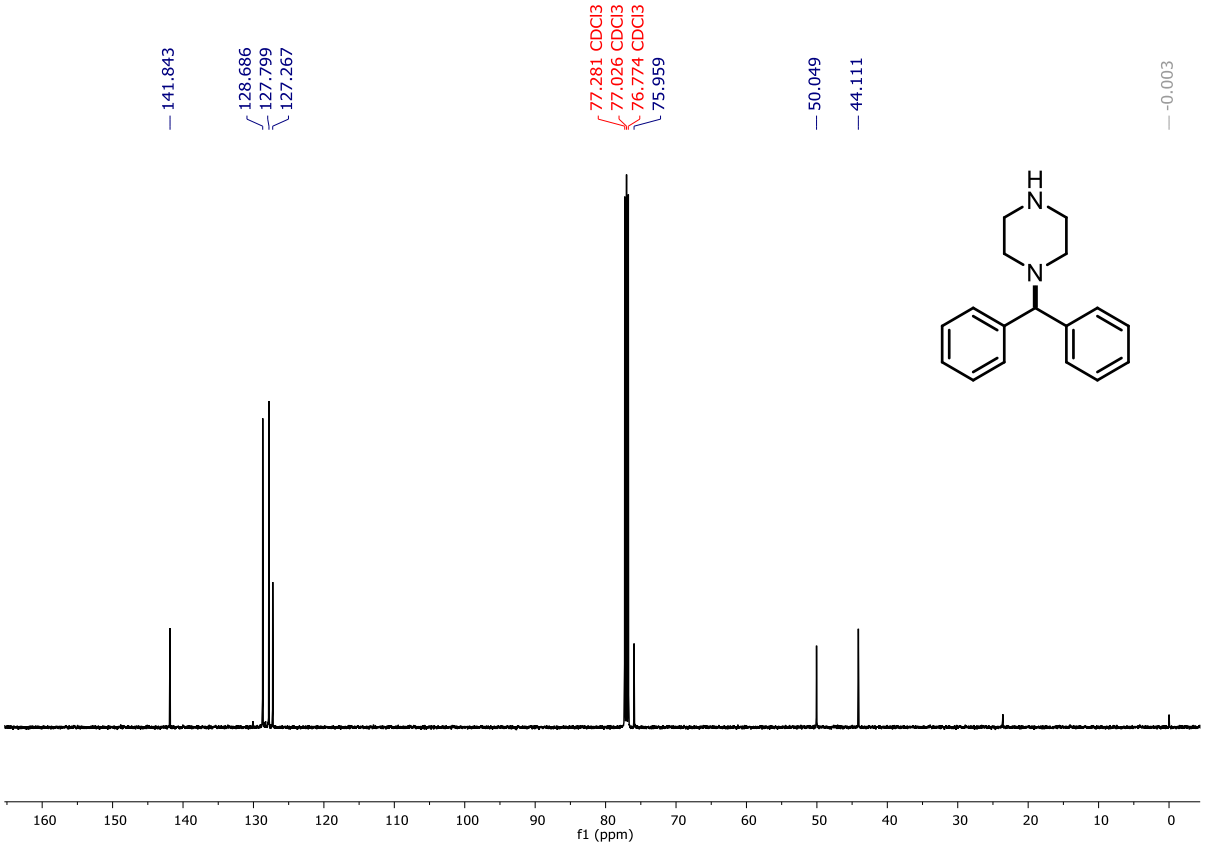
Diphenylchloromethane (7c): ^{13}C NMR (125 MHz, $CDCl_3$)



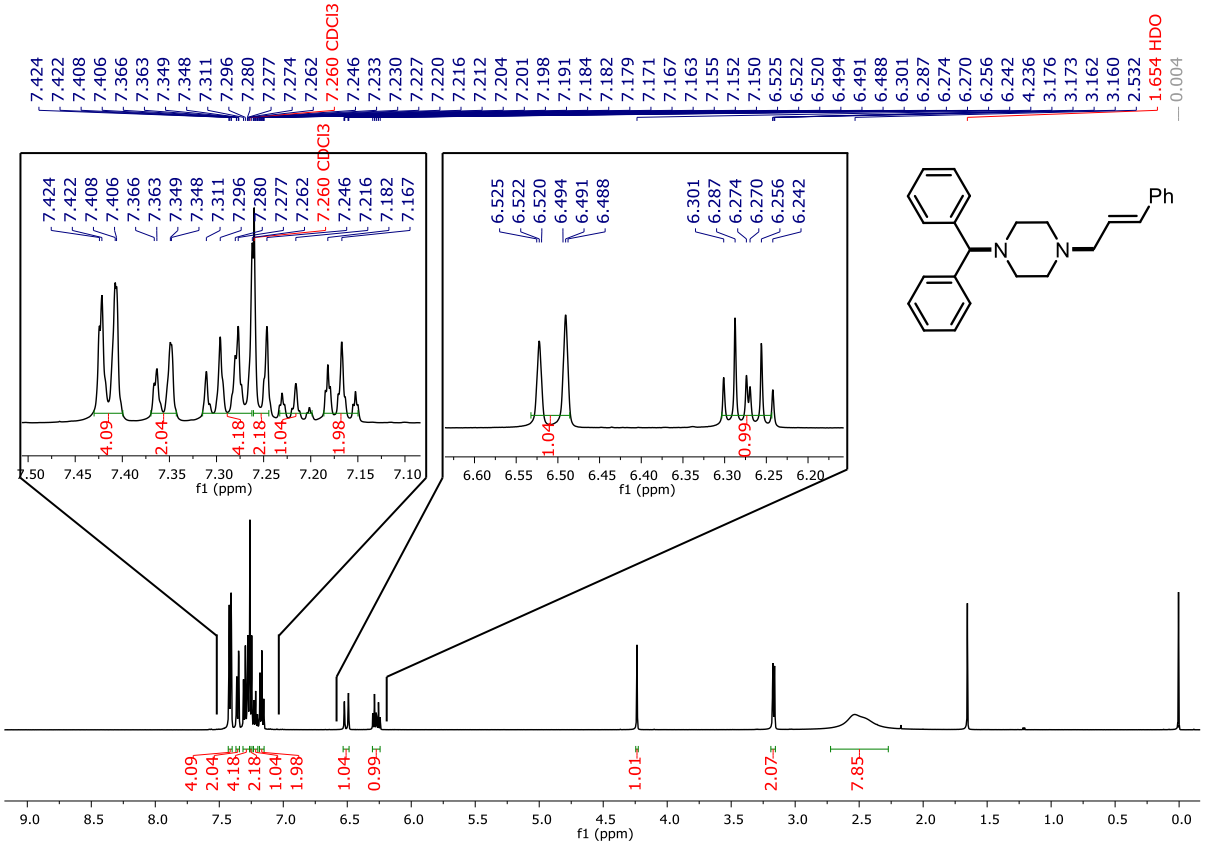
1-Benzhydrylpiperazine (KI-7d): ^{1}H NMR (500 MHz, $CDCl_3$)



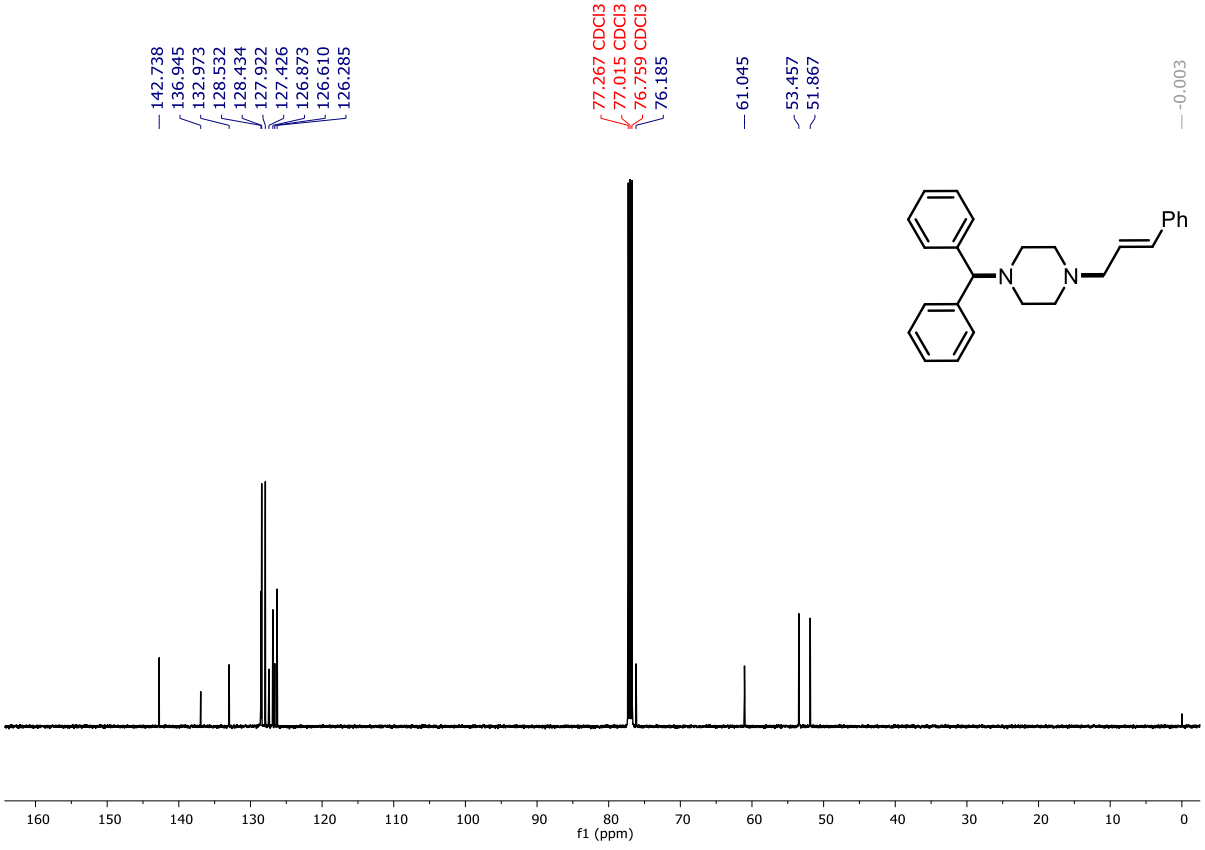
1-Benzhydrylpiperazine (KI-7d): ^{13}C NMR (125 MHz, $CDCl_3$)



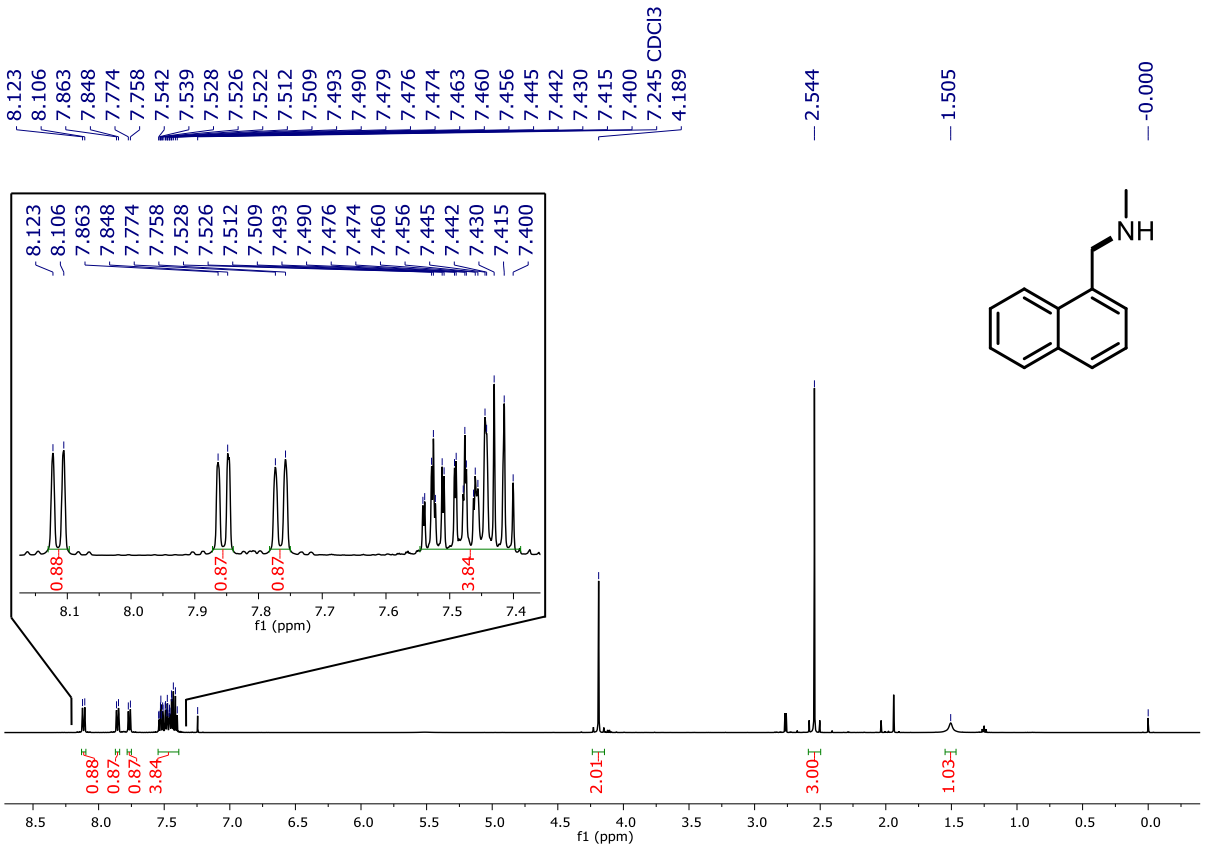
1-Benzhydryl-4-cinnamylpiperazine (Cinnarizine) (7): ^{1}H NMR (500 MHz, $CDCl_3$)



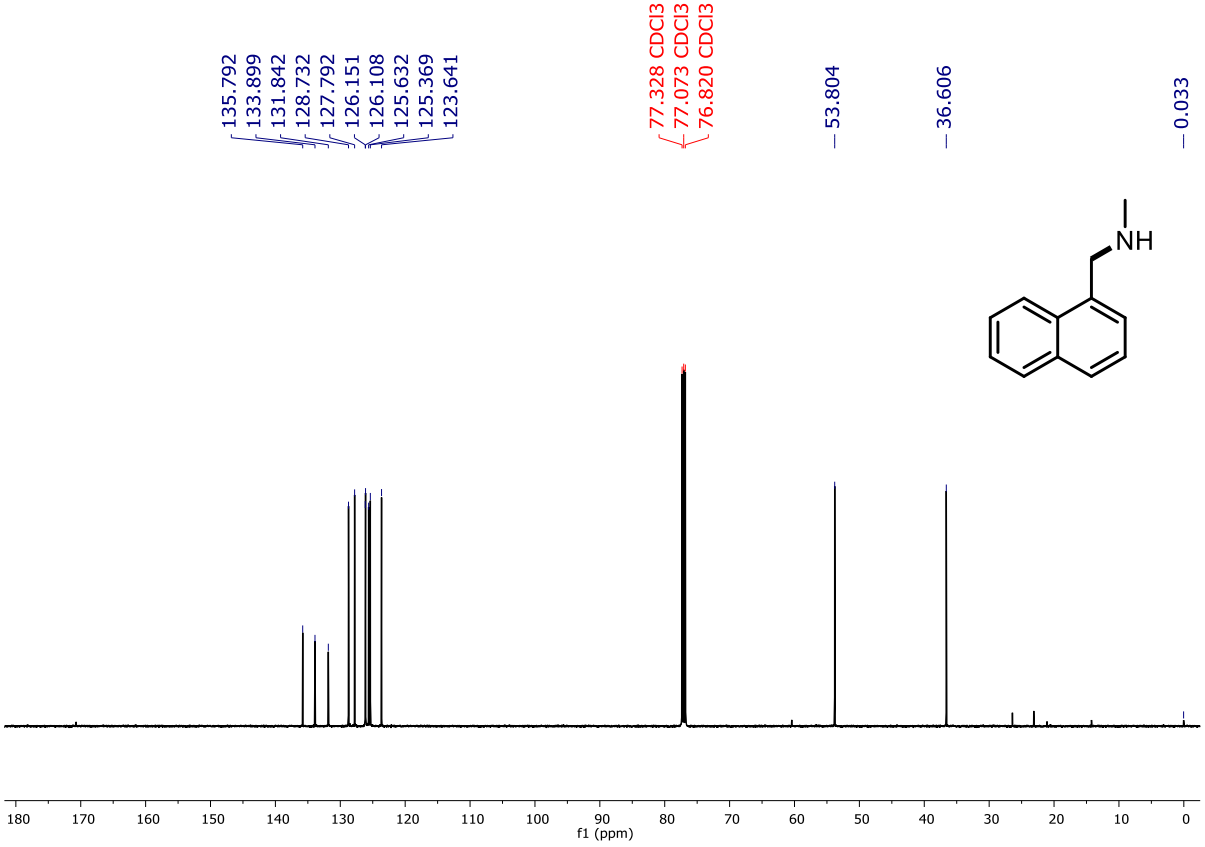
1-Benzhydryl-4-cinnamylpiperazine (Cinnarizine) (7): ^{13}C NMR (125 MHz, $CDCl_3$)



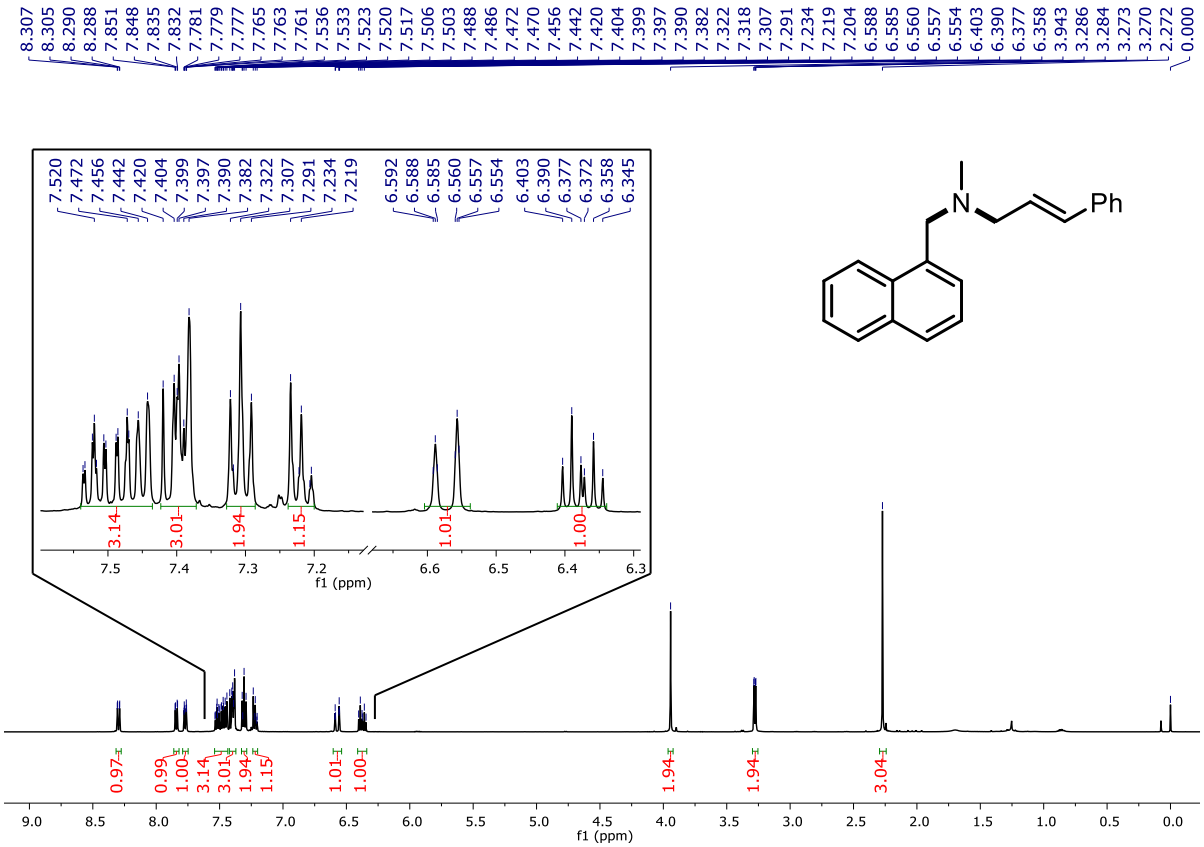
_N_-Methyl-1-(naphthalen-1-yl)methanamine (KI-8b): ^{1}H NMR (500 MHz, $CDCl_3$)



_N_-Methyl-1-(naphthalen-1-yl)methanamine (KI-8b): ^{13}C NMR (125 MHz, $CDCl_3$)



Naftifine (8): ^{1}H NMR (500 MHz, $CDCl_3$)



Naftifine (8): ^{13}C NMR (125 MHz, $CDCl_3$)