Supporting Information

Fast Continuous Alcohol Amination Employing a Hydrogen Borrowing Protocol

Ricardo Labes,[a] Carlos Mateos,[b] Claudio Battilocchio,[a,c] Yiding Chen,[a] Paul Dingwall,[a,d] Graham R. Cumming,[b] Juan A. Rincón,[b] Maria José Nieves-Remacha,[b] Steven V. Ley.[a]**

[a]*Innovative Technology Centre, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK.*

[b]*Centro de Investigación Lilly S.A., Avda. de la Industria 30, Alcobendas-Madrid 28108, Spain.*

[c]*Current address: Syngenta Crop Protection, Process Research, Schaffhauserstrasse 101, Stein, CH-4332, Switzerland.*

[d]*Current address: Queen's University Belfast, University Rd, Belfast, BT7 1NN, UK.*

**c.mateos@lilly.com, *svl1000@cam.ac.uk*

General experimental section

General methods: Reagents were obtained from commercial sources and used without purification. Dimethylamine was purchased and used as a 2 mol/L solution in THF from Sigma-Aldrich. The removal of solvent under reduced pressure was carried out on a standard rotary evaporator.

Solvents: Toluene and dichloromethane was distilled prior to use. Tetrahydrofuran, methanol, cyclopentyl methyl ether (CPME) and trifluorotoluene were purchased from commercial sources and used without purification.

Chromatography: Analytical thin-layer chromatography (TLC) was carried out on pre-coated glass plates (silica gel 60 F_{254}) from Merck. Compound spots were visualised under ultraviolet (UV) light (254 nm), and using ninhydrin or $KMnO_4$ stain solutions. Purification of the products were performed on SiliCycle SiliaSep™ 40–63mm 60 Å flash cartridges using an automated Biotage™ flash chromatography coupled with UV detector at 254 nm.

NMR spectroscopy: ^{1}H-NMR spectra were recorded on a 400 MHz Avance III HD spectrometer or Bruker Avance DPX-600 spectrometer with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm, d_6-DMSO = 2.50 ppm, CD_3OD = 3.31 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C-NMR spectra were recorded on 400 MHz Avance III HD spectrometer with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm, d_6- DMSO = 39.52 ppm, CD_3OD = 49.00 ppm). All ^{13}C resonances are reported to the nearest 0.1 ppm. The multiplicity of ^{1}H signals are indicated as: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, t = triplet, q = quadruplet, quint = quintet, sext = sextet, m = multiplet, br = broad, or combinations of thereof. Coupling constants (*J*) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant.

High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass LCT Premier™ spectrometer using time of flight (TOF) mass detection and positive ESI ionization method. Unless otherwise stated, reported mass correspond to the parent molecular ion associated with a proton $[M+H]^+$ or a sodium cation $[M+Na]^+$ (^{23}Na isotope). All *m/z* values are reported to four decimal places.

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) analyses were conducted by Mr Alan Dickerson (Department of Chemistry, University of Cambridge) using a Thermo Scientific iCAP 7400 ICP OES.

Flow equipment

The system used was composed by a Teledyne pump (Series III), a ThalesNano Phoenix[1] reactor and Equilibar U3L Series precision[2] as back pressure regulator. The Uniqsis Flow-UV[3] was used to monitor steady state of the plug flow, for that, it was placed after the back pressure regulator using PFA tubing.

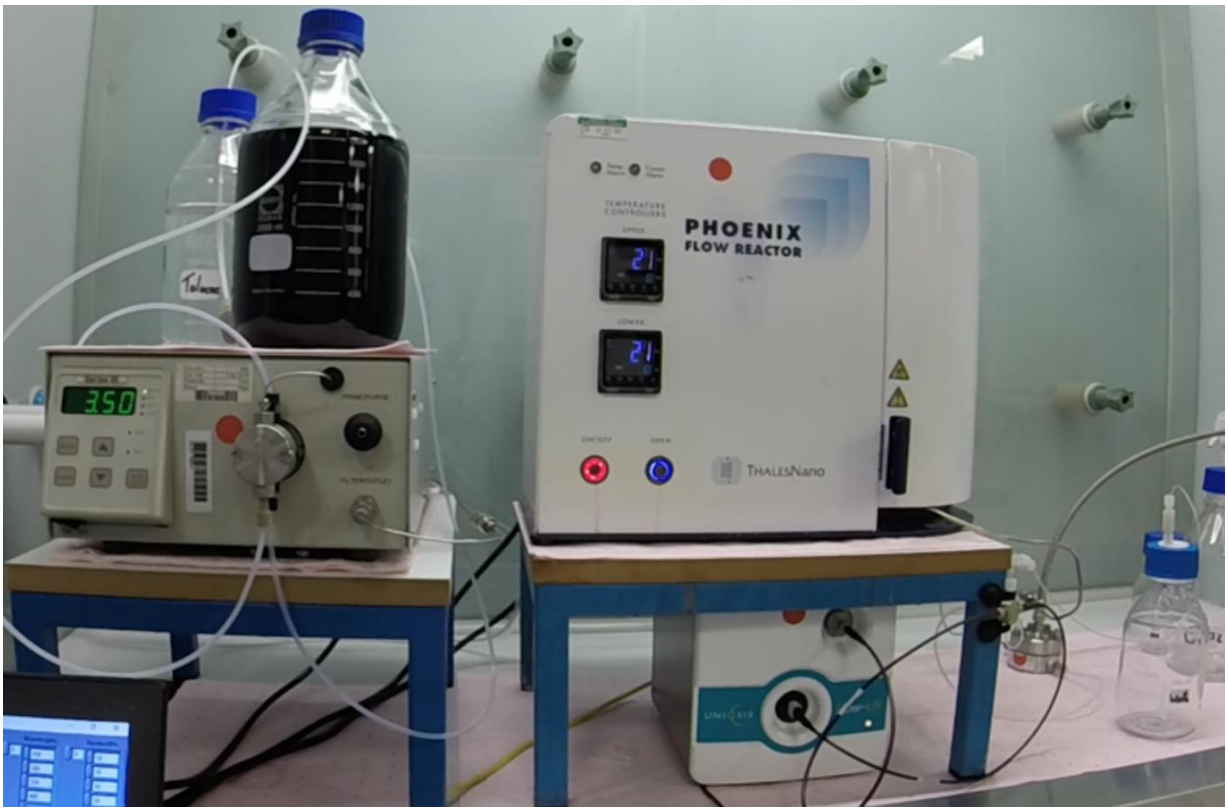
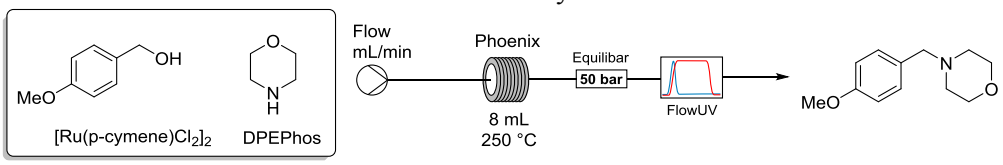


Figure S1: System composed by Series III HPLC pump, Phoenix reaction, Equilibar back pressure regulator and FlowUV.

Initial evaluation of equivalents of alcohol and different phosphines

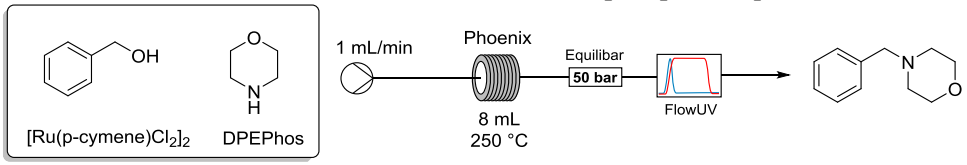
Table S1: Initial evaluation of catalyst load and concentration



Toluene Conc. (mol/L)

Entry	Residence time	Conc. (M)	Alcohol (Eq.)	Catalyst (mol%)	DPEPhos (mol %)	Conversion %	NMR Yield %
1	8	0.5	1.6	2.5	5	100	99
2	8	1	1.3	1	2	100	99
3	8	2	1.3	0.5	1	100	99
4	2	2	1.3	0.5	1	91	89

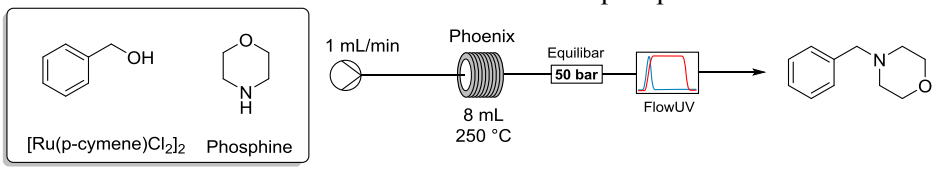
Table S2: Initial evaluation of alcohol and phosphine equivalents



Toluene 2 M

Residence time (min)	Alcohol (Eq.)	Catalyst (mol%)	DPEPhos (mol %)	Conversion %
8	1	0.5	1	87
8	1.1	0.5	1	97
8	1.1	0.5	1.25	97
8	1.3	0.5	1	99

Table S3: Evaluation of different phosphines



Toluene 2 M

Entry	Additve (1 mol %)	NMR Yield %
1	-	17
2	NEt_3 (2 Equiv.)	4
3	DPEPhos	97
4	DPPF	81
5	Triphenilphosphine (2 mol%)	74
6	Tri-*o*-tolylphosphine (2 mol%)	12

Design of Experiment (DoE)

The Design of Experiment was performed using R Commander Plugin for (industrial) Design of Experiments, available at https://CRAN.R-project.org/package=RcmdrPlugin.DoE. The plugin was developed by Prof. Dr Ulrike Grömping (http://prof.beuth-hochschule.de/groemping/software/doe/?L=1).

Four parameters were evaluated using a full factorial design with 3 centre points: Temperature (-1 = 150°C, 0 = 200, +1 = 250 °C), Residence Time (-1 = 1 min, 0 = 15.5 min, +1 = 30 min), Cat. Load (-1 = 0.1 mol%, 0 = 1.3 mol%, +1 = 2.5 mol%) and Concentration (-1 = 0.5 mol/L, 0 = 1.75 mol/L, +1 = 3 mol/L).

DoE results:

run.no	Temperature	Residence Time	Cat. Load	Concentration	Response[a]
1	200	15.5	1.3	1.75	92
2	150	30	0.1	0.5	6
3	250	30	0.1	0.5	31
4	250	1	0.1	0.5	9
5	150	1	2.5	3	1
6	250	30	2.5	3	99
7	150	1	0.1	0.5	0
8	150	30	2.5	0.5	42
9	250	30	0.1	3	30
10	200	15.5	1.3	1.75	92
11	250	1	2.5	0.5	16
12	150	30	0.1	3	0
13	150	1	0.1	3	0
14	150	1	2.5	0.5	0
15	250	1	2.5	3	93
16	250	1	0.1	3	0
17	250	30	2.5	0.5	99
18	150	30	2.5	3	74
19	200	15.5	1.3	1.75	86

[a]Response determined by NMR Yield using trimethoxybenzene as internal standard.

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	90.0000	2.000	45.00	0.000493
Temperature (x1)	15.8750	0.866	18.331	0.002963
Residence Time (x2)	16.3750	0.866	18.908	0.002785
Cat. Load (x3)	21.750	0.866	25.115	0.001582
Concentration (x4)	5.8750	0.866	6.784	0.021046

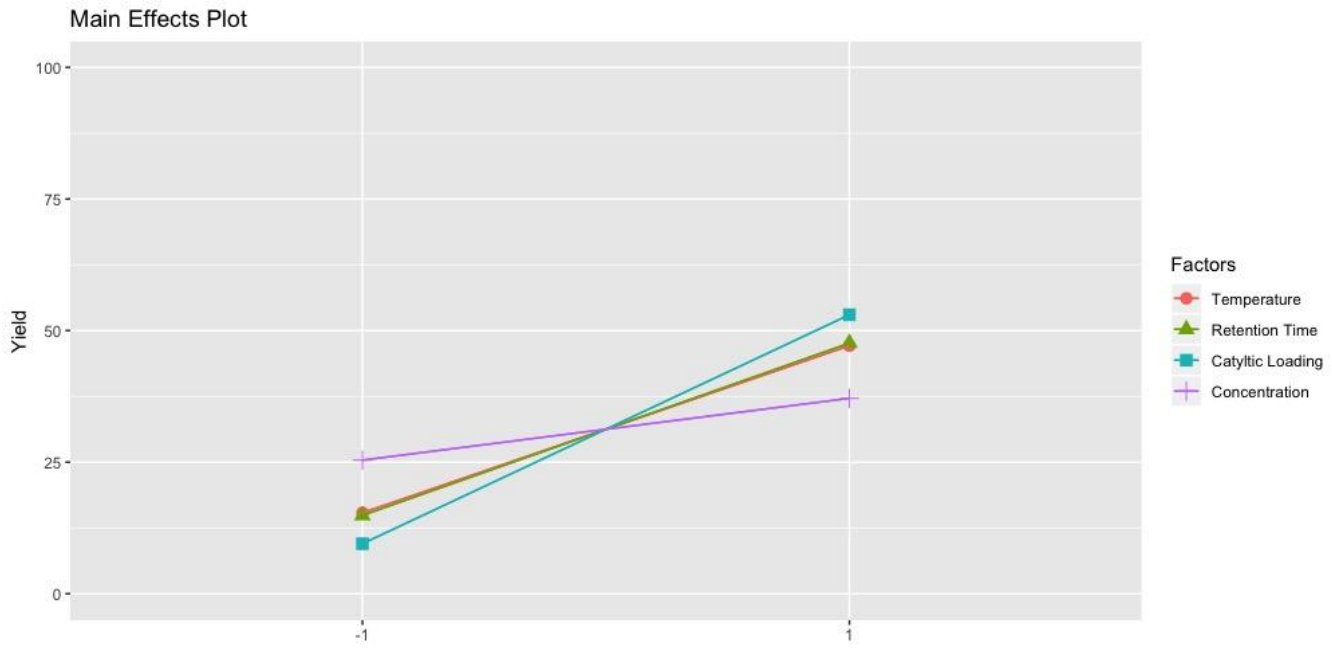


Figure S2: Main effects plot.

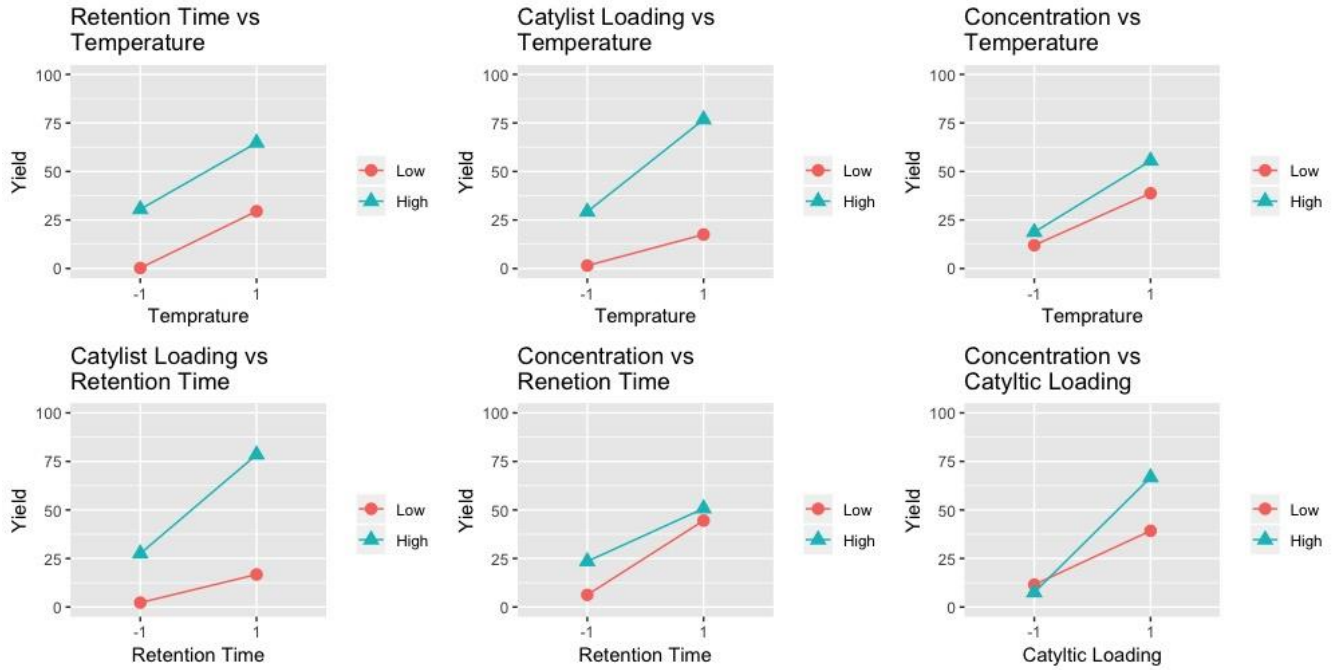
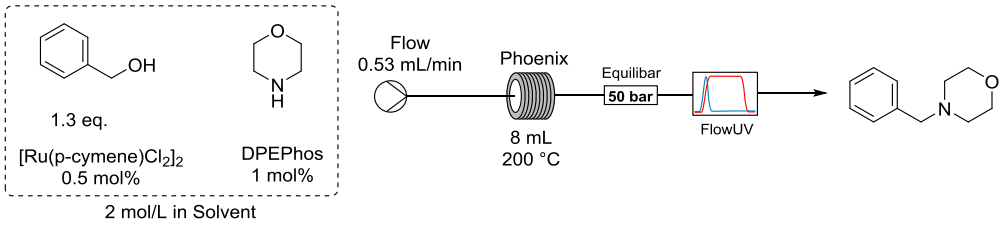


Figure S3: Interaction plots.

Evaluation of different solvents

Table S4: Evaluation of different solvents



Solvent	Conversion
Toluene	66
Trifluorotoluene	70
CPME	69
THF	67
MeOH (No BnOH)	0

Differential scanning calorimetry (DSC)

Two samples were submitted to DSC analysis in batch mode to evaluate the safety of running our method at 250 °C using tetrahydrofuran as a solvent.

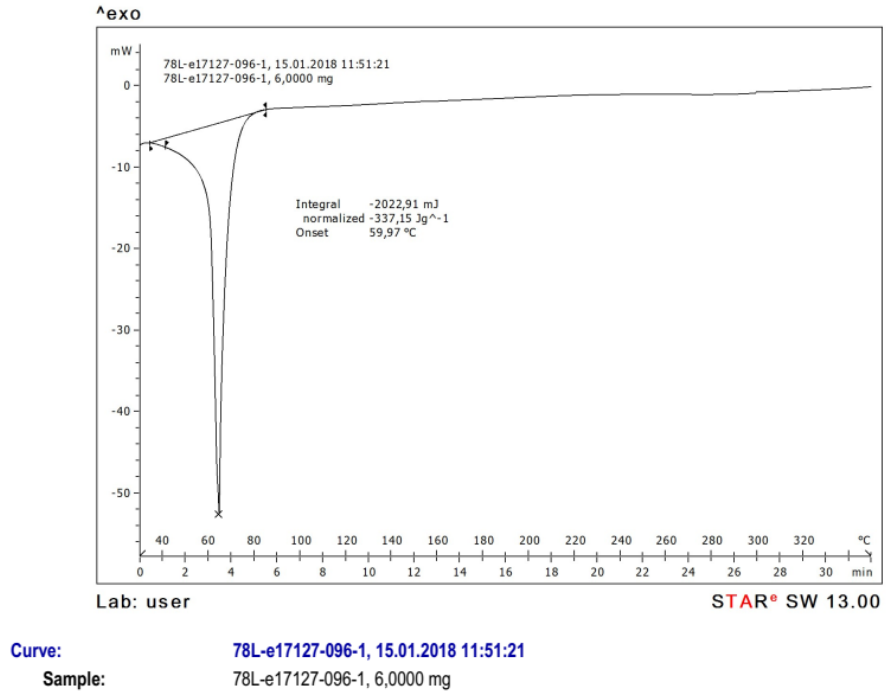


Figure S4: DSC analysis of a commercial solution of dimethylamine in THF 2 M.

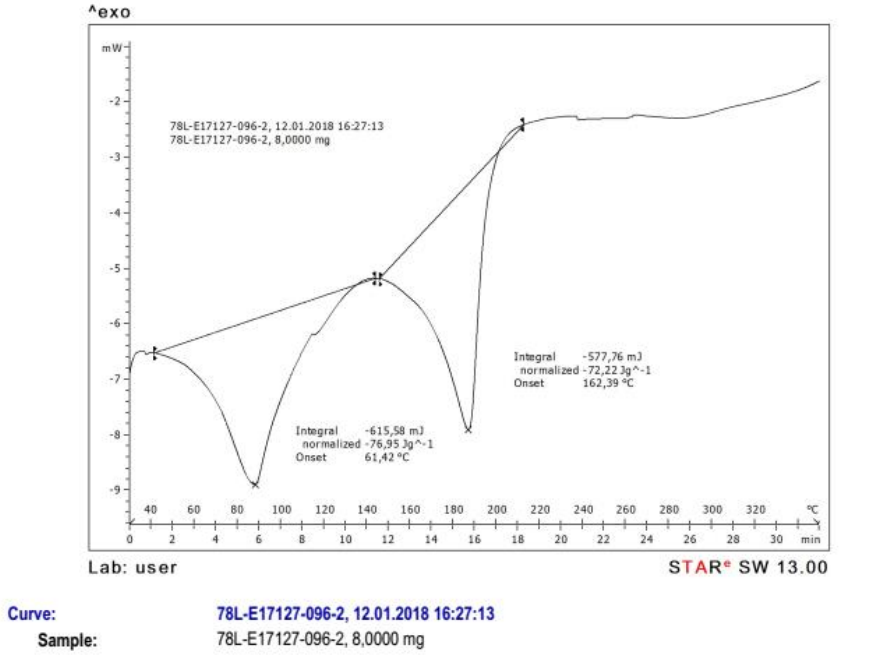


Figure S5: DSC analysis of a commercial solution containing dimethylamine in THF 2 M, benzyl alcohol 2 M, $[Ru(p\text{-cymene})Cl_2]_2$ (0.5 mol% and DPEPhos (1 mol%).

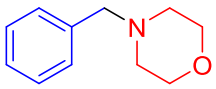
General methods for the continuous alcohol amination

The flow system was flushed with solvent, the back-pressure regulator was set to 50 bar, and the coil reactor heated to 250 °C. Then a solution (10 mL overall volume) containing the amine (20 mmol), alcohol (26 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (0.1 mmol) and bis[(2-diphenylphosphino)phenyl] ether (DPEPhos, 0.2 mmol) was pumped at 0.8 ml/min through a heated coil (8 mL, Phoenix reactor). The output solution obtained in steady state (monitored using the FlowUV) was concentrated in vacuo and the residue analyzed either by ^{1}H NMR using trimethoxybenzene as internal standard or purified using flash chromatography.

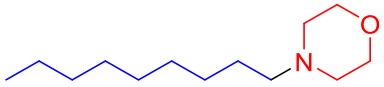
Note 1: If necessary the solution was sonicated until no visible solids were present.

Note 2: In between reactions the reactor was flushed with methanol.

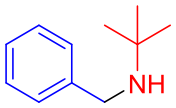
Characterization of the isolated compounds



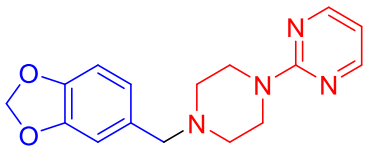
4-benzylmorpholine (1): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.16, 25% AcOEt/PE). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.37 – 7.34 (m, 4H), 7.35 – 7.24 (m, 1H), 3.78 – 3.71 (m, 4H), 3.53 (s, 2H), 3.56 – 2.40 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 137.72, 129.22, 128.27, 127.18, 67.01, 63.48, 53.64. **HRMS for $[C_{11}H_{16}NO]^+$** calculated 178.1226 found 178.1228. Data in agreement with spectra reported in the literature.[4]



4-nonylmorpholine (3): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.2, 40% AcOEt/PE). **^{1}H NMR (400 MHz, $CDCl_3$)** δ =3.73 (t, *J*=4.6, 4H), 2.44 (t, *J*=4.6, 4H), 2.38 – 2.27 (m, 2H), 1.56 – 1.41 (m, 2H), 1.38 – 1.19 (m, 12H), 0.89 (t, *J*=7.0, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 67.03, 59.27, 53.82, 31.88, 29.58, 29.54, 29.28, 27.54, 26.59, 22.67, 14.10. **HRMS for $[C_{13}H_{28}NO]^+$** calculated 214.2165 found 214.2167. Data in agreement with spectra reported in the literature.[5]

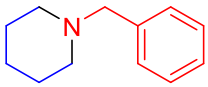


***N*-benzyl-2-methylpropan-2-amine (4)**: Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.2, 30% AcOEt/PE). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.36 – 7.30 (m, 4H), 7.26 – 7.21 (m, 1H), 3.74 (s, 2H), 1.19 (s, 9H). Data in agreement with spectra reported in the literature.[6]

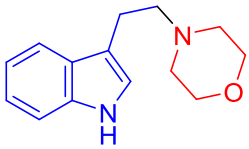


2-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (Piribedil, 5): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.16, 35% AcOEt/PE). **^{1}H NMR (400 MHz, $CDCl_3$)** δ =8.31 (d, *J*=4.7, 2H),

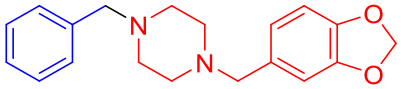
6.91 (s, 1H), 6.78 (s, 2H), 6.48 (t, *J*=4.7, 1H), 5.97 (s, 2H), 3.93 – 3.74 (m, 4H), 3.47 (s, 2H), 2.50 (t, *J*=5.1, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 161.67, 157.69, 147.67, 146.66, 131.89, 122.23, 109.71, 109.49, 107.89, 100.90, 62.89, 52.85, 43.70. **HRMS for $[C_{16}H_{19}N_4O_2]^+$** calculated 299.1503 found 299.1522. Data in agreement with spectra reported in the literature.[7]



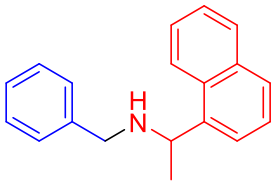
1-benzylpiperidine (6): Purification by column chromatography on silica gel (R_f = 0.2, 10 % MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ =7.38 – 7.22 (m, 5H), 3.50 (s, 2H), 2.40 (t, *J*=5.4, 4H), 1.60 (p, *J*=5.6, 4H), 1.51 – 1.40 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ =138.61, 129.24, 128.08, 126.81, 63.91, 54.51, 26.00, 24.41. **HRMS for $[C_{12}H_{18}N]^+$** calculated 176.1434 found 176.1436. Data in agreement with spectra reported in the literature.[8]



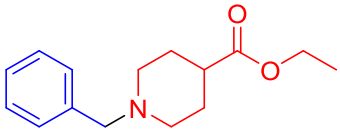
4-(2-(1*H*-indol-3-yl)ethyl)morpholine (7): Purification by column chromatography on silica gel (R_f =0.40, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.14 (s, 1H), 7.65 (d, *J*=8.0, 1H), 7.38 (d, *J*=8.0, 1H), 7.27 – 7.20 (m, 1H), 7.16 (t, *J*=7.4, 1H), 7.06 (s, 1H), 3.82 (t, *J*=4.7, 4H), 3.02 (d, *J*=8.0, 2H), 2.75 (d, *J*=8.0, 2H), 2.62 (t, *J*=4.7, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 136.25, 127.47, 122.00, 121.53, 119.25, 118.80, 114.22, 111.16, 67.06, 59.68, 53.79, 22.65. **HRMS for $[C_{14}H_{18}N_2O]^+$** calculated 231.1492 found 231.1506. Data in agreement with spectra reported in the Patent US2010009986, 2010.



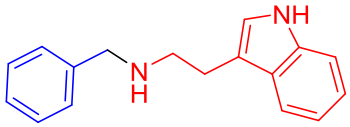
1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-benzylpiperazine (8): Purification by column chromatography on silica gel (R_f =0.3, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ =7.40 – 7.23 (m, 5H), 6.89 (s, 1H), 6.77 (s, 2H), 5.95 (s, 2H), 3.55 (s, 2H), 3.45 (s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ =147.60, 146.55, 138.20, 132.14, 129.23, 128.21, 127.01, 122.25, 109.57, 107.84, 100.86, 63.10, 62.81, 53.13, 52.99. **HRMS for $[C_{19}H_{23}N_2O_2]^+$** calculated 311.1754 found 311.1773. Data in agreement with spectra reported in the literature.[9]



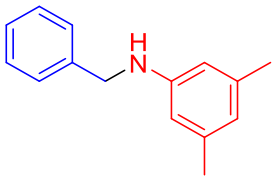
***N*-benzyl-1-(naphthalen-1-yl)ethan-1-amine (9)**: Purification by column chromatography on silica gel (R_f =0.3, 20% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.27 – 8.19 (m, 1H), 7.99 – 7.91 (m, 1H), 7.88 – 7.80 (m, 2H), 7.62 – 7.50 (m, 3H), 7.43 – 7.34 (m, 4H), 7.36 – 7.27 (m, 1H), 4.76 (q, *J*=6.6, 1H), 3.90 – 3.70 (AB dd, 2H), 1.59 (d, *J*=6.6, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ =141.07, 140.75, 134.08, 131.45, 129.01, 128.44, 128.25, 127.29, 126.95, 125.82, 125.76, 125.36, 123.09, 122.96, 53.11, 51.97, 23.75. **HRMS for $[C_{19}H_{20}N]^+$** calculated 262.1590 found 262.1595. Data in agreement with spectra reported in the literature.[10]



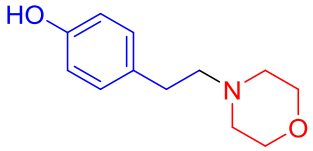
Ethyl 1-benzylpiperidine-4-carboxylate (10): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.26, 35% AcOEt/PE). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 7.34 – 7.29 (m, 4H), 7.29 – 7.22 (m, 1H), 4.13 (q, *J*=7.1, 2H), 3.50 (s, 2H), 2.85 (m, 2H), 2.28 (tt, *J*=11.2, 4.1, 1H), 2.08 – 1.97 (m, 2H), 1.91 – 1.84 (m, 2H), 1.78 (m, 2H), 1.25 (t, *J*=7.1, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 175.25, 138.44, 129.06, 128.18, 126.96, 63.27, 60.25, 52.95, 41.26, 28.33, 14.24. **HRMS for $[C_{15}H_{22}NO_2]^+$** calculated 248.1645 found 248.1660. Data in agreement with spectra reported in the literature.[11]



***N*-benzyl-2-(1*H*-indol-3-yl)ethan-1-amine (11)**: Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.26, 35% AcOEt/PE). **^{1}H NMR (400 MHz, DMSO)** δ =10.80 (s, 1H), *J*=7.50 (d, 7.8, 1H), 7.40 – 7.27 (m, 5H), 7.27 – 7.20 (m, 1H), 7.13 (d, *J*=2.2, 1H), 7.06 (t, *J*=7.5, 1H), 6.96 (t, *J*=7.5, 1H), 3.79 (s, 2H), 2.93 – 2.78 (m, 4H). **^{13}C NMR (100 MHz, DMSO)** δ =140.51, 136.69, 128.58, 127.67, 127.17, 123.05, 121.31, 118.73, 118.60, 112.72, 111.81, 53.06, 49.76, 25.53. **HRMS for $[C_{17}H_{19}N_2]^+$** calculated 251.1543 found 251.1552. Data in agreement with spectra reported in the literature.[12]



***N*-benzyl-3,5-dimethylaniline (14)**: Purification by column chromatography on silica gel ($\mathbf{R_f}$ =0.27, 5% AcOEt/PE). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.60 – 7.51 (m, 4H), 7.50 – 7.45 (m, 1H), 6.61 (s, 1H), 6.47 (s, 2H), 4.47 (s, 2H), 4.05 (s, 1H), 2.45 (s, 6H). **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 148.51, 139.88, 139.08, 128.81, 127.73, 127.36, 119.75, 110.93, 48.47, 21.79. Data in agreement with spectra reported in the literature.[13]



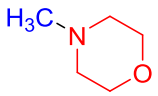
4-(2-morpholinoethyl)phenol (15): Purification by column chromatography on silica gel ($\mathbf{R_f}$ =0.2, 10% MeOH/DCM). **^{1}H NMR (400 MHz, MeOD)** δ 7.04 (d, *J*=8.4, 2H), 6.72 (d, *J*=8.4, 2H), 3.73 (t, *J*=4.7, 4H), 2.73 (dd, *J*=10.3, 6.1, 2H), 2.61 – 2.51 (m, 6H). **^{13}C NMR (100 MHz, MeOD)** δ = 155.37, 130.42, 129.15, 114.81, 66.19, 60.90, 53.32, 31.50. **HRMS for $[C_{12}H_{18}NO_2]^+$** calculated 208.1332 found 208.1344.

General methods for the continuous methylation of amines using methanol

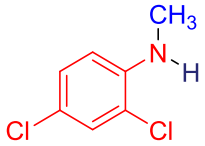
The flow system was flushed with toluene, the back-pressure regulator was set to 50 bar, and the coil reactor heated to 250 °C. Then a solution (10 mL overall volume) in toluene containing the amine (20 mmol), methanol (22 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (0.3 mmol) and bis[(2-diphenylphosphino)phenyl] ether (DPEPhos, 0.6 mmol) was pumped at 0.8 ml/min through a heated coil (8 mL, Phoenix reactor). The output solution obtained in steady state (monitored using the FlowUV) was concentrated in vacuo and the residue analyzed either by ^{1}H NMR using trimethoxybenzene as internal standard or purified using flash chromatography.

Note: Order of addition in the preparation of the solution: dichloro(*p*-cymene)ruthenium(II) dimer, bis[(2-diphenylphosphino)phenyl] ether, toluene (5 mL), amine, methanol, toluene (to complete 10 mL).

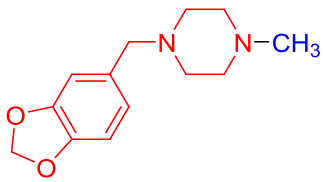
Characterization of the isolated compounds



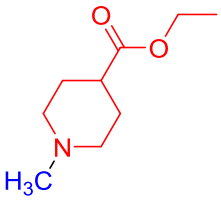
4-(2-morpholinoethyl)phenol (16): Purification by distillation under reduced pressure. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.86 – 3.57 (m, 4H), 2.45 – 2.32 (m, 4H), 2.32 – 2.19 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 66.88, 55.40, 46.41. Data in agreement with a commercial sample.



2,4-dichloro-*N*-methylaniline (17): Purification by column chromatography on silica gel (**R_f** = 0.32, 1% AcOEt/PE). **^{1}H NMR (400 MHz, $CDCl_3$)** δ =7.26 (d, *J* = 2.4 Hz, 1H), 7.13 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 4.32 (s, 1H), 2.90 (d, *J* = 5.2 Hz, 3H), 1.56 (s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 143.74, 128.55, 127.76, 120.94, 119.24, 111.11, 30.47. **HRMS for $[C_7H_7Cl_2N]^+$** calculated 176.0028 found 176.0022. Data in agreement with spectra reported in the literature.[14]



1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methylpiperazine (18): Purification by column chromatography on silica gel (**R_f** = 0.28, 10% MeOH/DCM). **^{1}H NMR (600 MHz, $CDCl_3$)** δ = 6.84 (s, 1H), 6.73 (d, *J* = 1.1 Hz, 2H), 5.92 (s, 2H), 3.41 (s, 2H), 2.78 – 2.34 (m, 8H), 2.30 (s, 3H. **^{13}C NMR (151 MHz, $CDCl_3$)** δ = 147.58, 146.54, 132.01, 122.21, 109.47, 107.81, 100.83, 62.67, 55.06, 52.78, 45.91. **HRMS for $[C_{13}H_{19}N_2O_2]^+$** calculated 235.1441 found 235.1466. Data in agreement with spectra reported in the literature.[9]

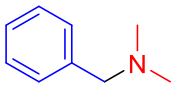


Ethyl 1-methylpiperidine-4-carboxylate (19): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.21, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 4.13 (q, *J* = 7.1 Hz, 2H), 2.90 – 2.75 (m, 2H), 2.29 (s, 3H), 2.25 (m, 1H), 2.12 – 1.99 (m, 2H), 1.99 – 1.87 (m, 2H), 1.87 – 1.70 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 174.93, 60.32, 54.88, 46.25, 28.09, 14.19. **HRMS for $[C_9H_{18}NO_2]^+$** calculated 172.1332 found 172.1329. Data in agreement with spectra reported in the literature.[15]

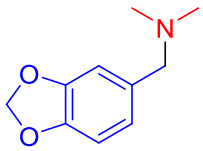
General methods for the continuous dimethylamination of alcohols

The flow system was flushed with THF, the back-pressure regulator was set to 50 bar, and the coil reactor heated to 250 °C. Then a solution containing the alcohol (18 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (0.3 mmol), bis[(2-diphenylphosphino)phenyl] ether (DPEPhos, 0.6 mmol) and dimethylamine (commercial solution in THF 2M, 20 mL) was pumped at 0.53 ml/min through a heated coil (8 mL, Phoenix reactor). The output solution obtained in steady state (monitored using the FlowUV) was concentrated in vacuo and the residue analyzed either by ^{1}H NMR using trimethoxybenzene as internal standard or purified using flash chromatography.

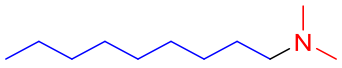
Characterization of the isolated compounds



***N,N*-dimethyl-1-phenylmethanamine (20)**: Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.23, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.47 – 7.21 (m, 5H), 3.47 (s, 2H), 2.28 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 138.54, 129.18, 128.26, 127.13, 64.32, 45.26. **HRMS for $[C_9H_{14}N]^+$** calculated 136.1121 found 136.1122. Data in agreement with spectra reported in the literature.[16]

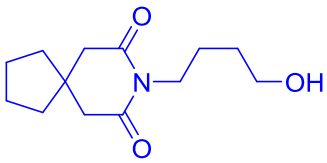


1-(benzo[*d*][1,3]dioxol-5-yl)-*N,N*-dimethylmethanamine (21): Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.23, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 6.86 (s, 1H), 6.77 (s, 2H), 5.96 (s, 2H), 3.38 (s, 2H), 2.27 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 147.65, 146.69, 132.27, 122.32, 109.56, 107.91, 100.90, 63.96, 45.03. **HRMS for $[C_{10}H_{14}NO_2]^+$** calculated 180.1019 found 180.1033. Data in agreement with spectra reported in the literature.[17]



***N,N*-dimethylnonan-1-amine (22)**: Purification by column chromatography on silica gel ($\mathbf{R_f}$ = 0.2, 10% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 2.38 – 2.31 (m, 2H), 2.29 (s, 6H), 1.49 (dt, *J* = 13.7, 6.5 Hz, 2H), 1.36 – 1.16 (m, 12H), 0.91 – 0.80 (m, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 59.61, 45.01, 45.01, 31.84, 29.51, 29.24, 27.37, 27.17, 22.63, 14.06. **HRMS for $[C_{11}H_{26}N]^+$** calculated 172.2060 found 172.2072. Data in agreement with spectra reported in the literature.[18]

Synthesis of Buspirone



8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione (23): A solution of 3,3-tetramethyleneglutaric anhydride (0.25 mol/L in THF) was combined in a tee piece with a solution of 4-amino-1-butanol (0.25 mol/L in THF) and reacted in a 20 mL reactor coil (stainless steel, 20 min residence time) heated at 250 °C. The output was concentrated in vacuo and the residue purified by column chromatography on silica gel to afford the product in 84% yield ($\mathbf{R_f}$ = 0.31, 63% DCM/AcOEt). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 3.78 (t, *J* = 7.2 Hz, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 2.58 (s, 4H), 1.77 – 1.64 (m, 4H), 1.64 – 1.53 (m, 4H), 1.53 – 1.43 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.33, 62.28, 44.87, 39.47, 39.14, 37.54, 29.81, 24.35, 24.17. **HRMS for $[C_{13}H_{22}NO_3]^+$** calculated 240.1594 found 240.1605.

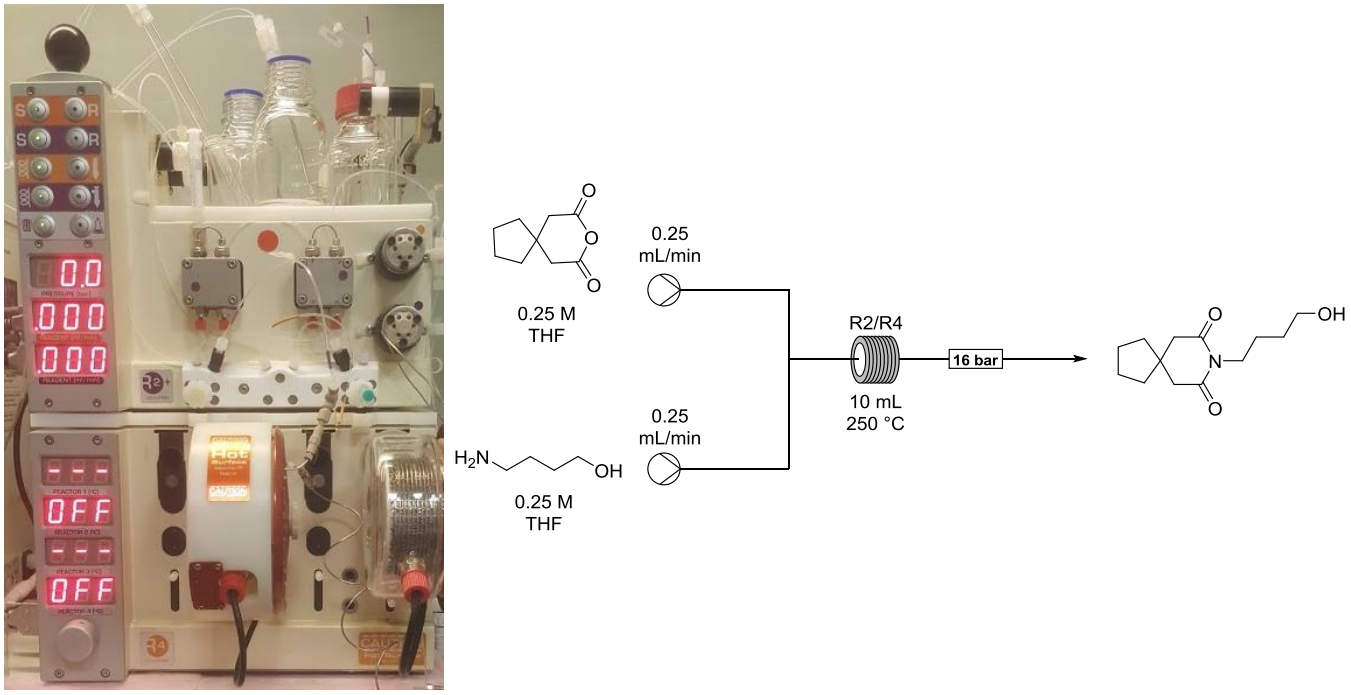
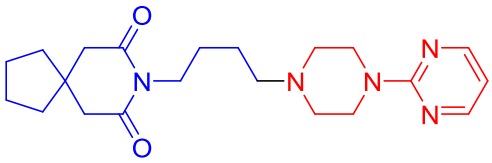


Figure S6: System used in the synthesis of 8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione (23)



8-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl)-8-azaspiro[4.5]decane-7,9-dione (Buspirone, 25): The flow system was flushed with THF, the back-pressure regulator was set to 50 bar, and the coil reactor heated to 250 °C. Then a solution (10 mL overall volume) containing 1-(2-pyrimidyl)piperazine (2 mmol), 8-(4-hydroxybutyl)-8-azaspiro[4.5]decane-7,9-dione **(23)** (2 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (0.08 mmol) and bis[(2-diphenylphosphino)phenyl] ether (DPEPhos, 0.17 mmol) was pumped at 0.8 ml/min through a heated coil (8 mL, Phoenix reactor). The output solution obtained in steady state (monitored using the FlowUV) was concentrated in vacuo and purified by column chromatography on silica gel to afford the desired product in 76% yield ($\mathbf{R_f}$ = 0.29, 5% MeOH/DCM). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 8.31 (d, *J* = 4.7 Hz, 2H), 6.48 (t, *J* = 4.7 Hz, 1H), 3.84 (t, *J* = 5.1 Hz, 4H), 3.79 (t, *J* = 6.8 Hz, 2H), 2.60 (s, 4H), 2.50 (t, *J* = 5.1 Hz, 4H), 2.40 (t, *J* = 6.8 Hz, 2H), 1.79 – 1.65 (m, 4H), 1.65 – 1.42 (m, 8H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.19, 161.63, 157.68, 109.77, 58.31, 53.06, 44.92, 43.60, 39.48, 39.35, 37.56, 26.04, 24.19, 24.19. **HRMS for $[C_{21}H_{32}N_5O_2]^+$** calculated 386.2551 found 386.2570.

Scale-up experiment

The flow system was flushed with solvent, the back-pressure regulator was set to 50 bar, and the coil reactor heated to 250 °C. Then a solution (1900 mL) containing the morpholine (7.43 mol, 650 mL), benzyl alcohol (12.14 mol, 1250 mL), dichloro(*p*-cymene)ruthenium(II) dimer (37.2 mmol, 22.7 g) and bis[(2-diphenylphosphino)phenyl] ether (DPEPhos, 74.3 mmol, 40 g) was pumped at 3.5 ml/min through a heated coil (35 mL, Phoenix reactor) during 9 hours.

Note: The tubing in the system was exchanged from 1/16" to 1/8" O.D. stainless steel.

Note 2: A 5 mL coil was added after the reactor to reduce the temperature before the system output.

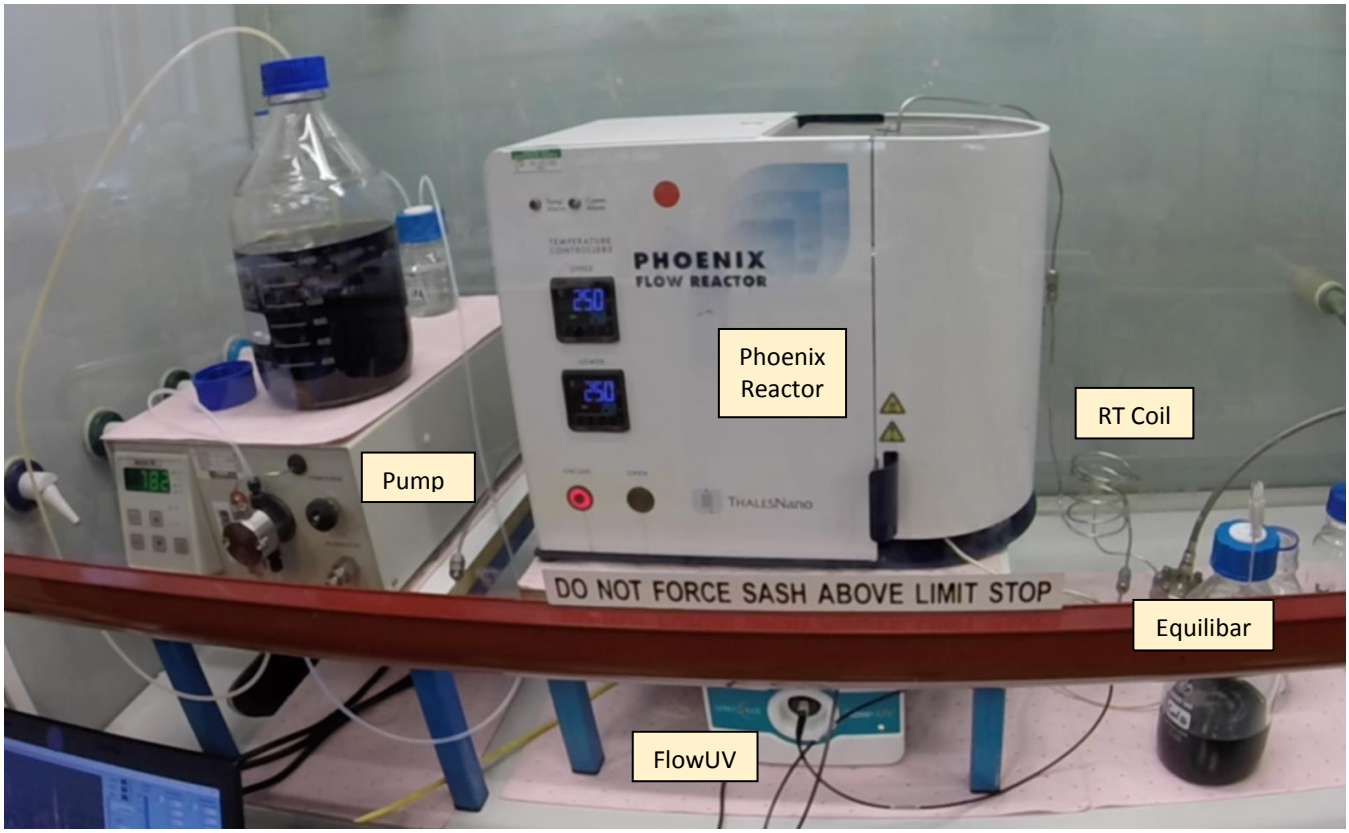


Figure S7: System used in the scale-up experiment.

From the overall collection a fraction of 0.5 L was processed as the HCl salt.

Downstream flow system: The system was composed by a piston pump (Teledyne Series III), a peristaltic pump (Vapourtec SF-10) and a reactor coil (1/8" O.D., PFA tubing on a Polar Bear Plus) was used. The tee piece used to mix the solutions had the mixing point "along" the tubing, as shown on **Figure S8**. That intended to avoid blockages at the mixing point from salt formation. The reaction was open end and no back-pressure regulator was used. The Polar Bear Plus was set to 10 °C to counter the exotherm from the reaction.

Figure S8: Tee piece used in the continuous downstream.

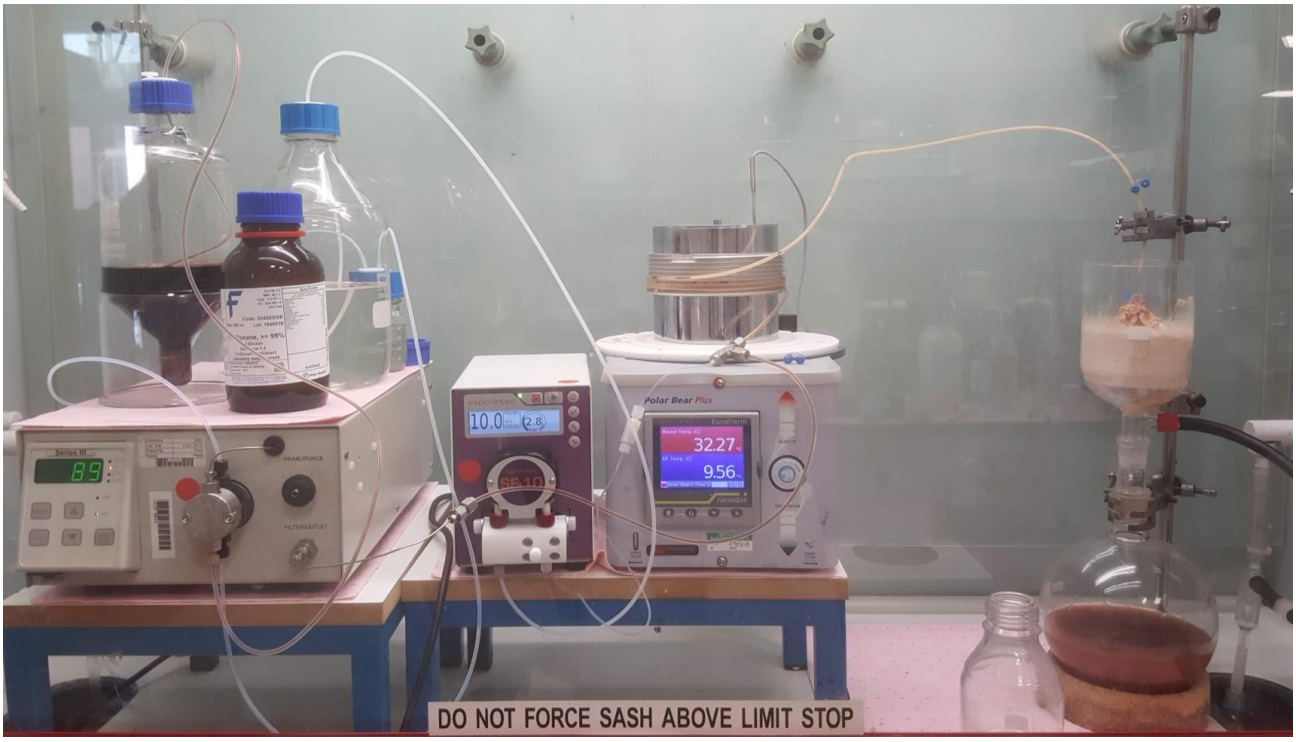
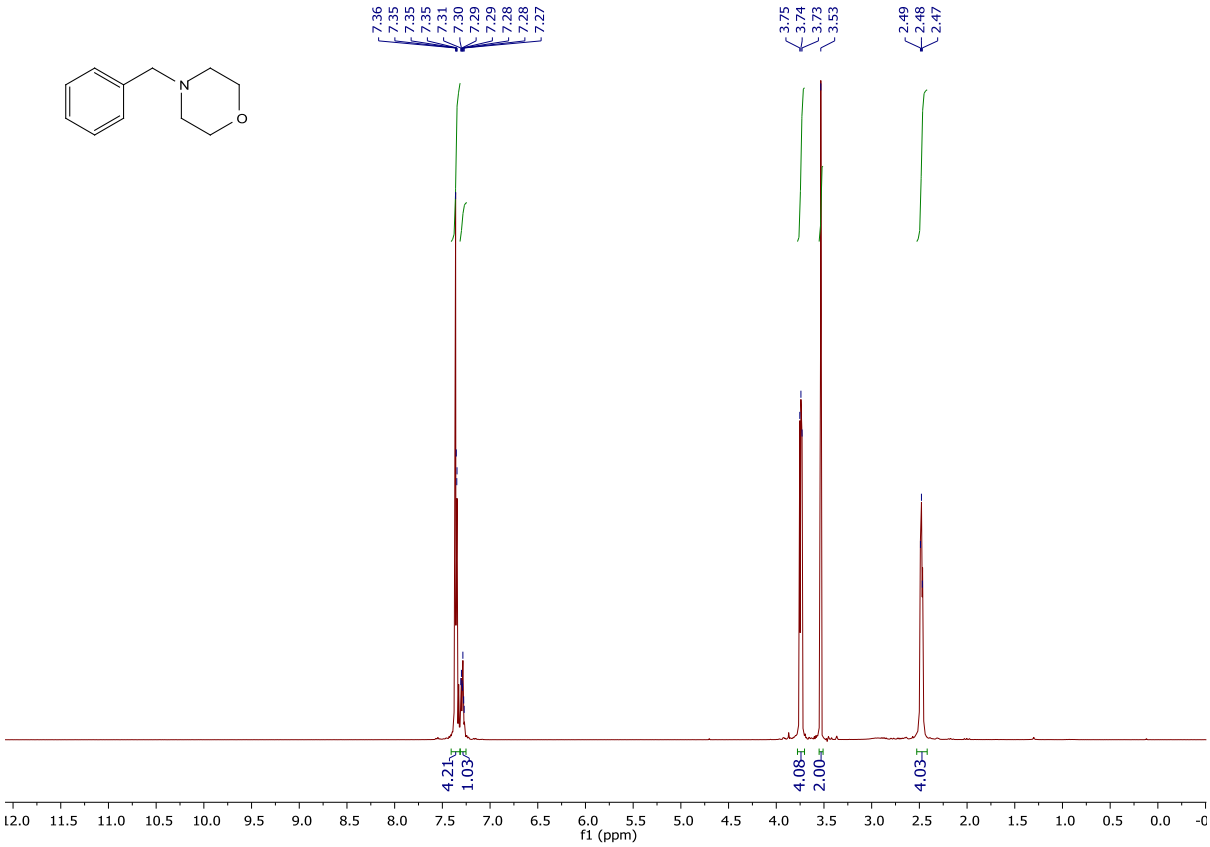
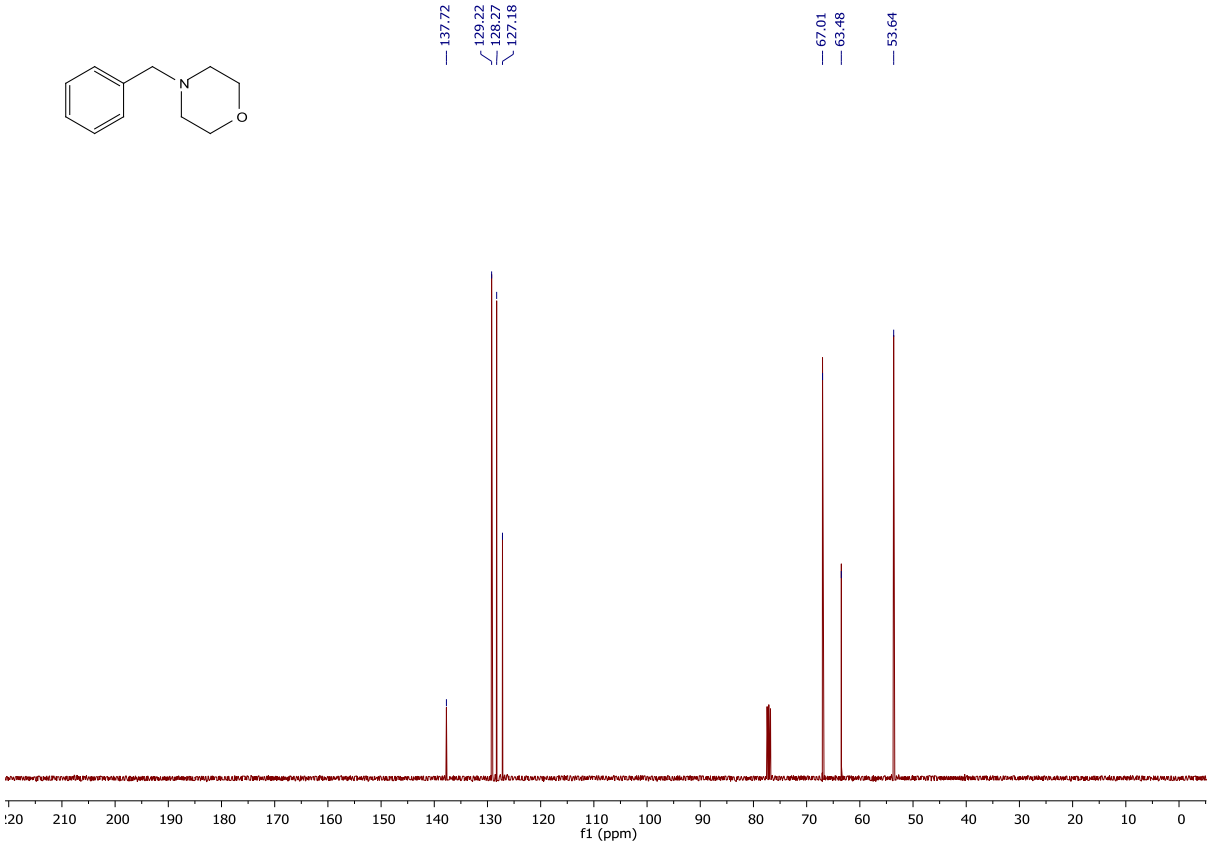


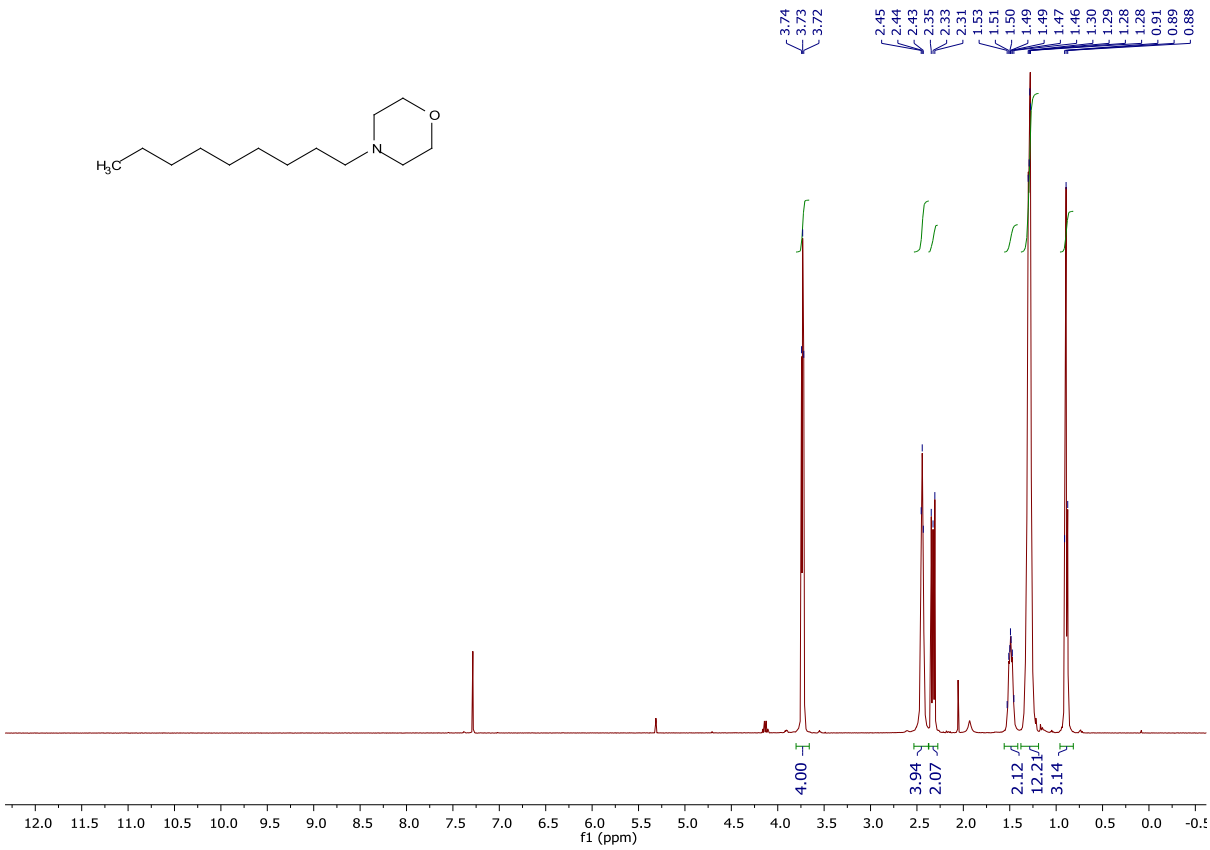
Figure S9: Continuous downstream setup.

Continuous downstream: 0.5 L of the scale-up experiment output, that was previously evaporated to eliminate any residual morpholine, was pumped at 4 mL/min and combined in a tee piece (Figure S8) with a solution HCl (2 mol/L in 1,4-dioxane, 10 mL/min) and reacted in a 15 mL reactor coil (1/8", PFA) set to 10 °C. The output was filtered and washed with diethylether and afforded the product as a white solid in 88% yield (364.92 g, 1.71 mol). Note: Free flowing of the salt was possible without blockage providing that continuous pumping was maintained together with the use of 1/8" PFA tubing and using 2 mol/L HCl solution. Higher concentrations led to blockages.

NMR Spectra for isolated compounds



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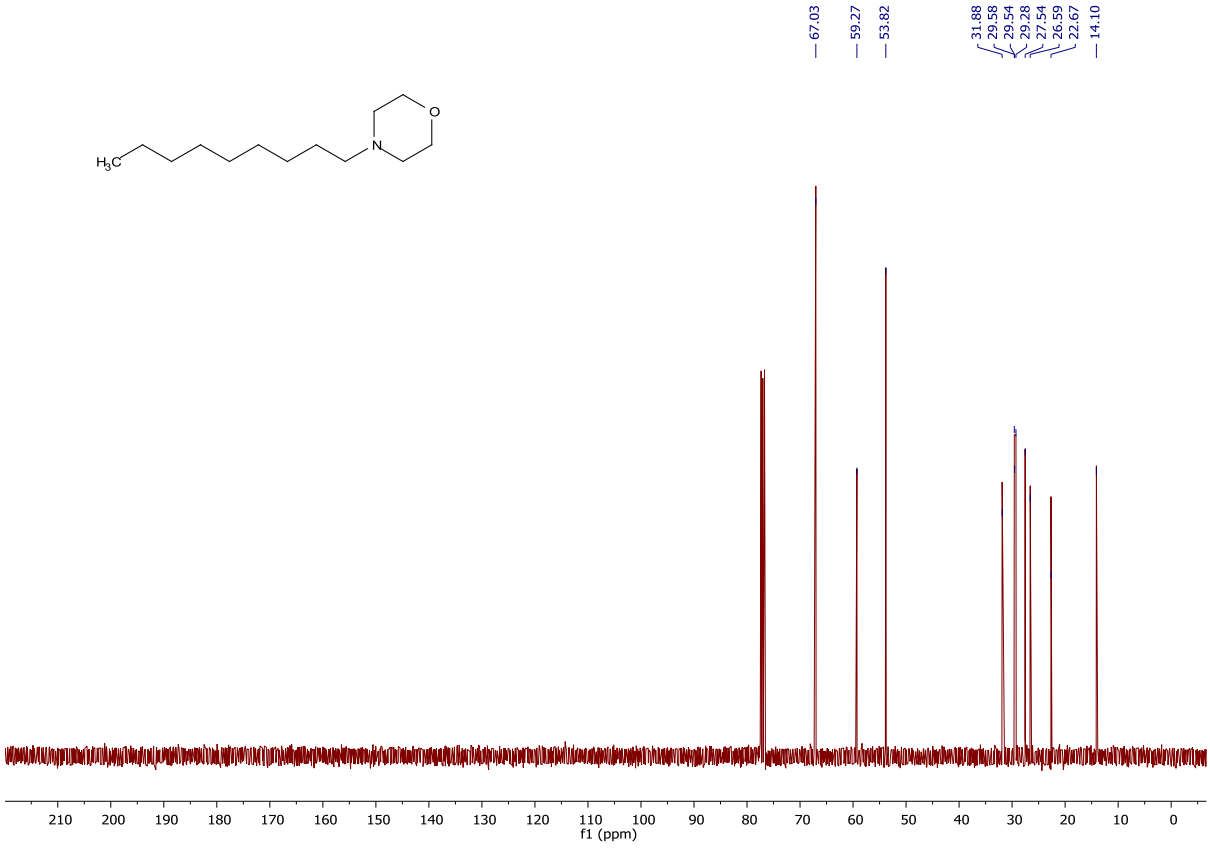
1.49
1.47
1.46
1.30
1.29
1.28
1.28
0.91
0.89
0.88
O
N
H3C
4.00
3.94
2.07
2.12
12.21
3.14
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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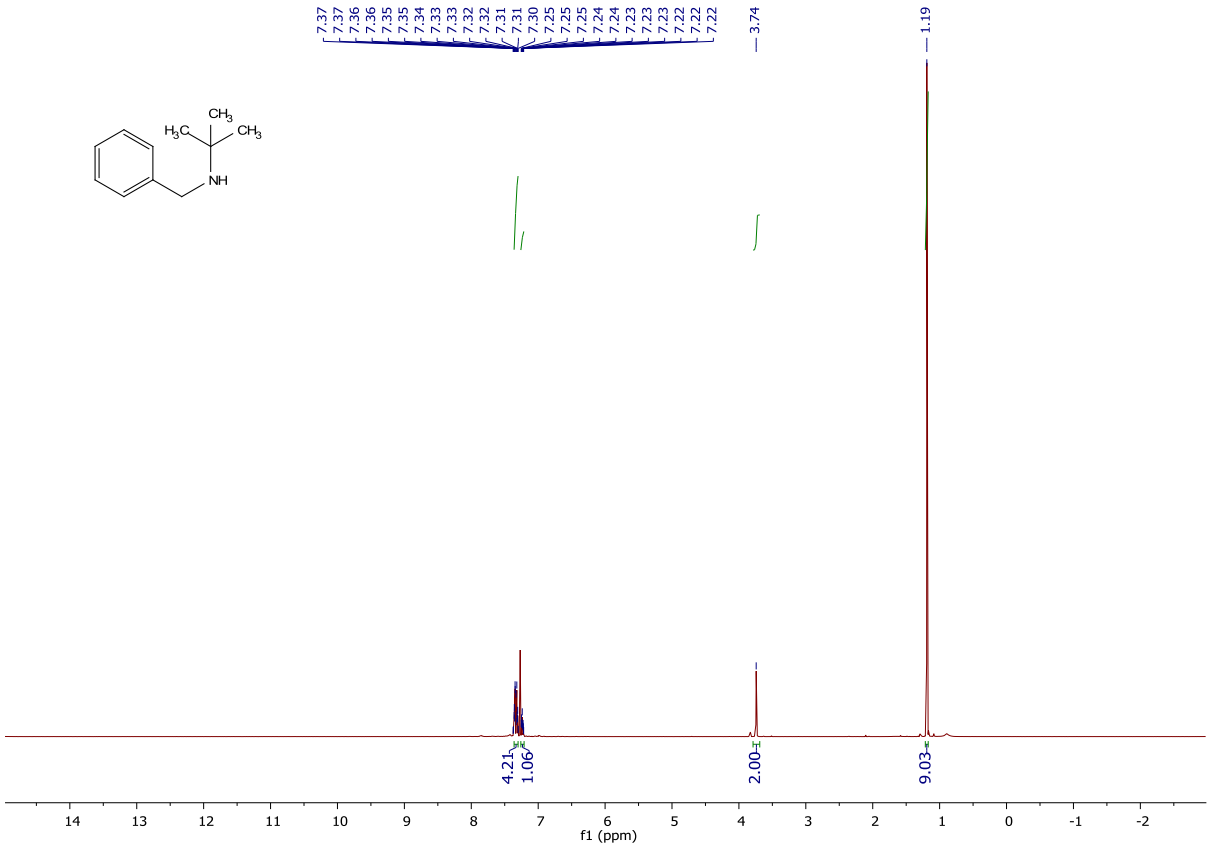
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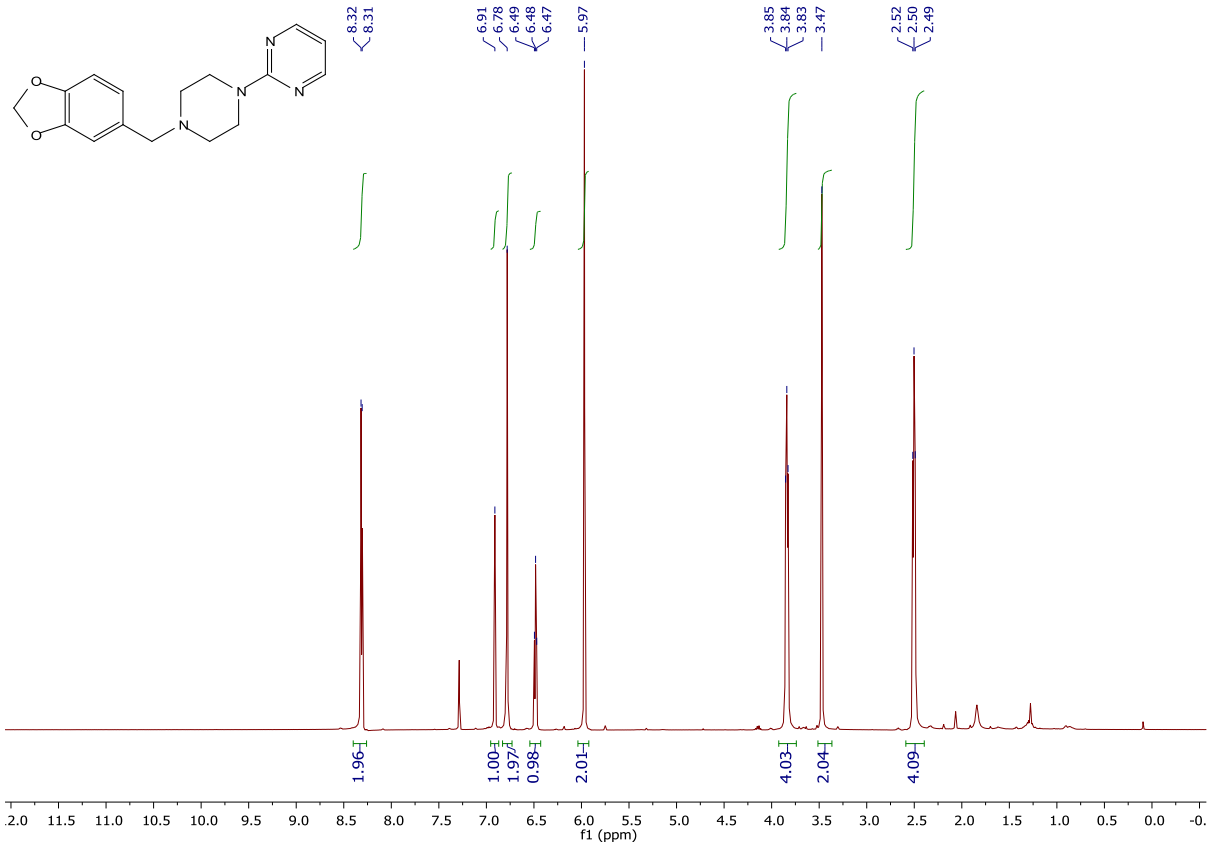
f1 (ppm)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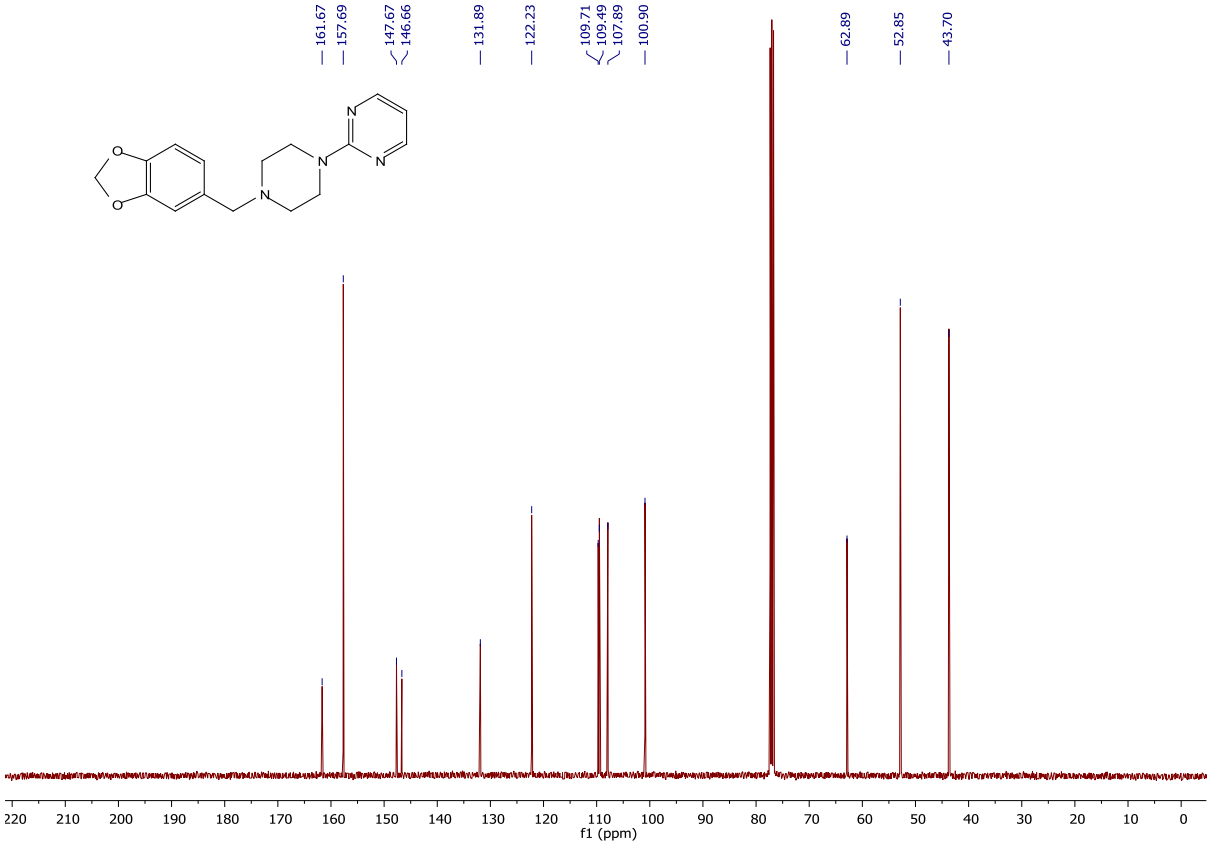
f1 (ppm)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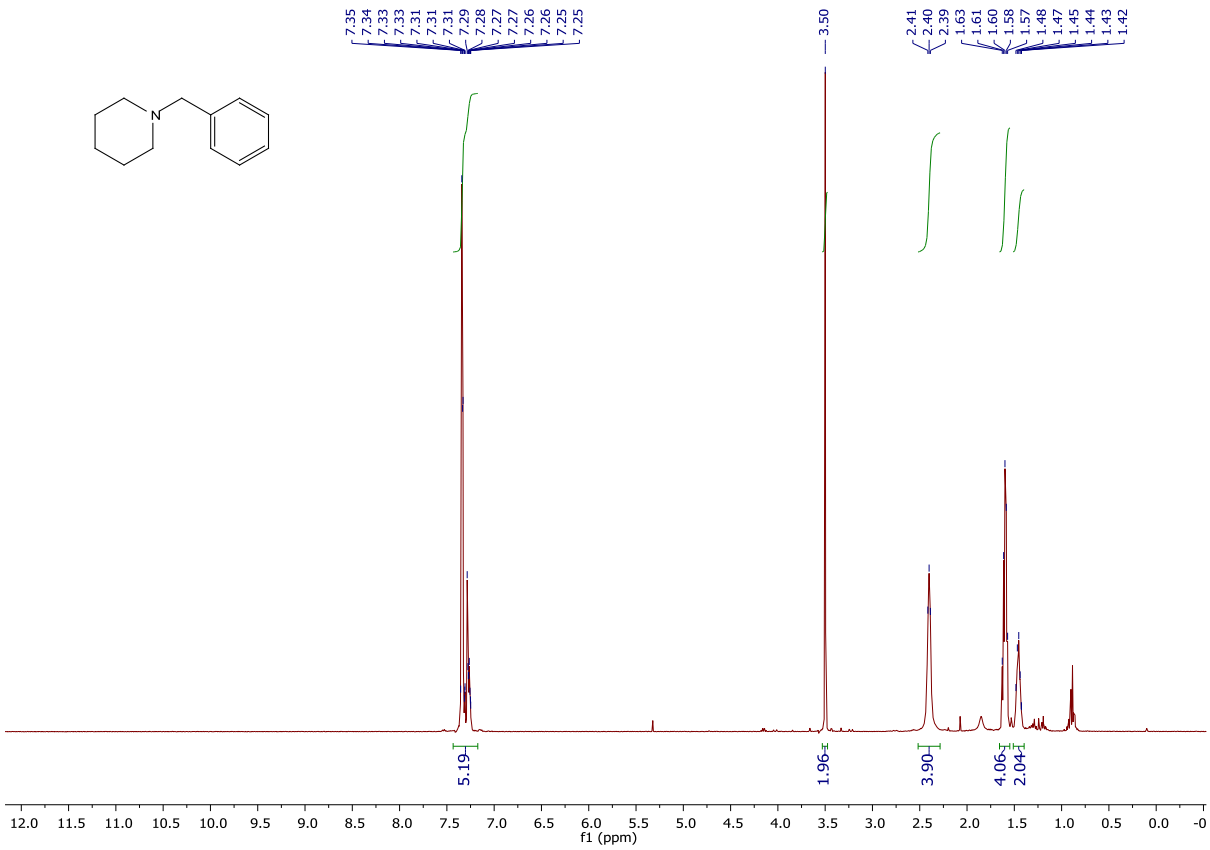
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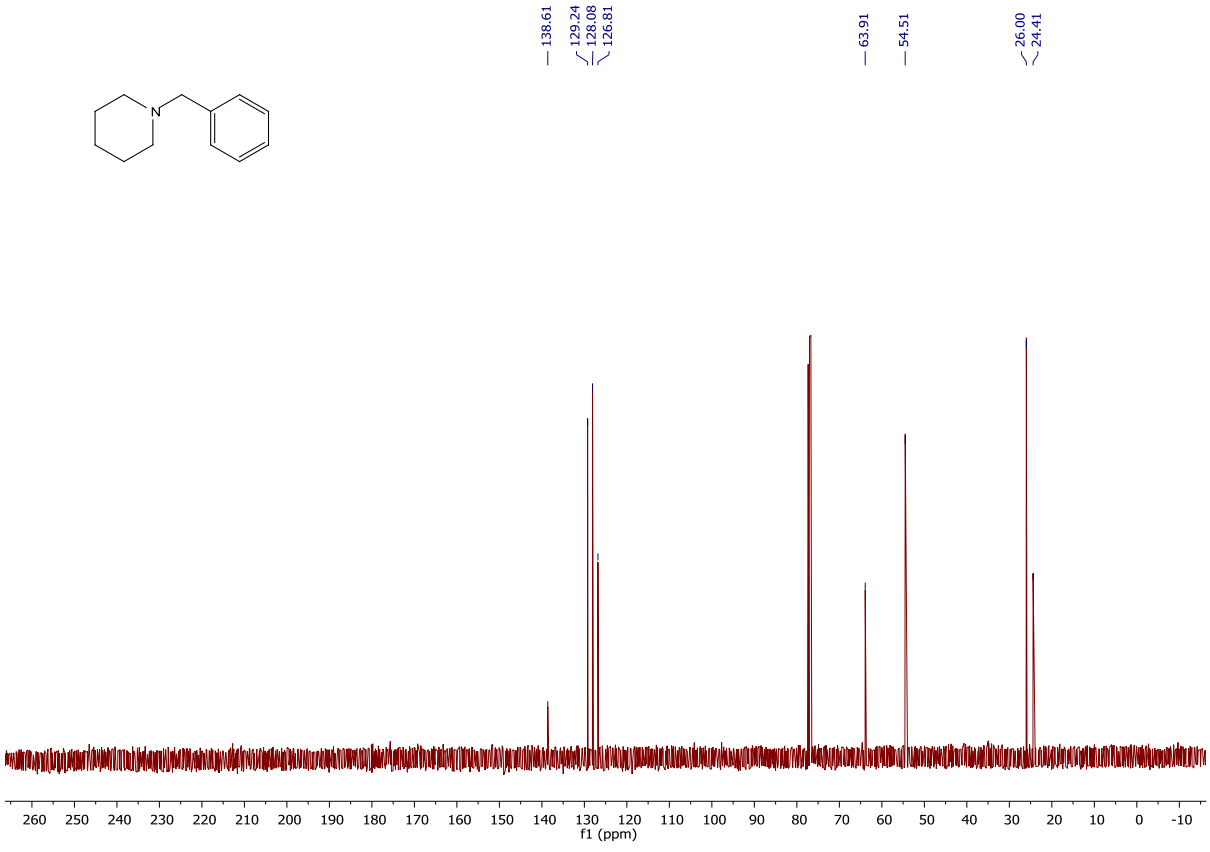
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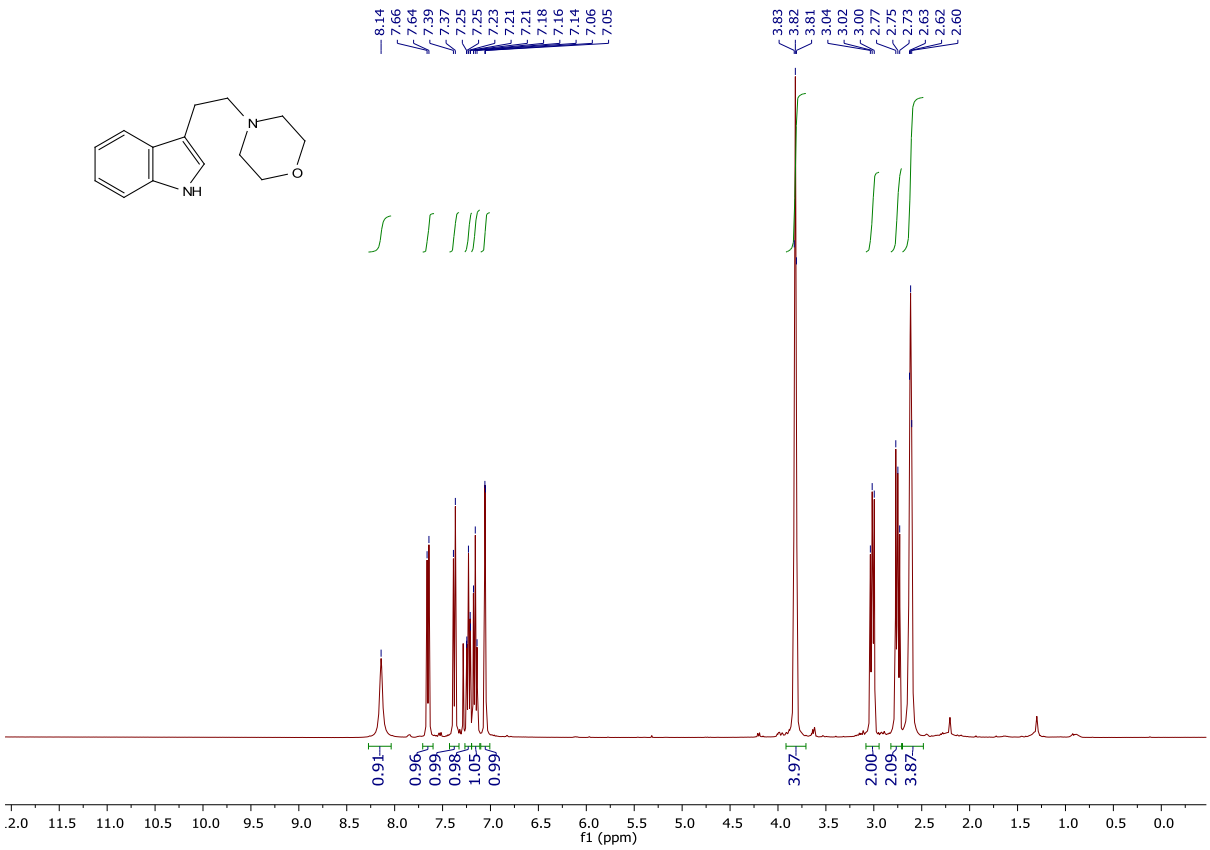
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3.82
3.81
3.04
3.02
3.00
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2.75
2.73
2.63
2.62
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0.91
0.96
0.99
0.98
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0.99
3.97
2.00
2.09
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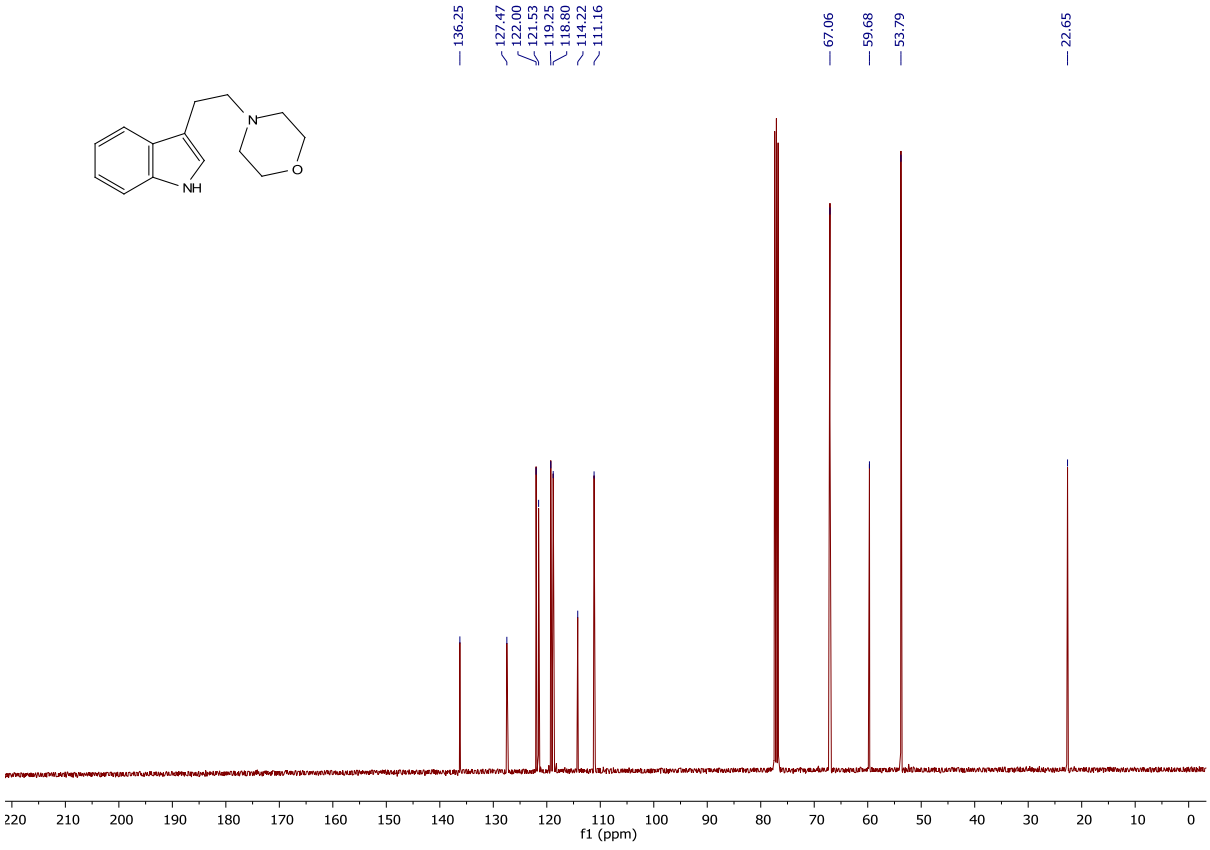
f1 (ppm)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111.16
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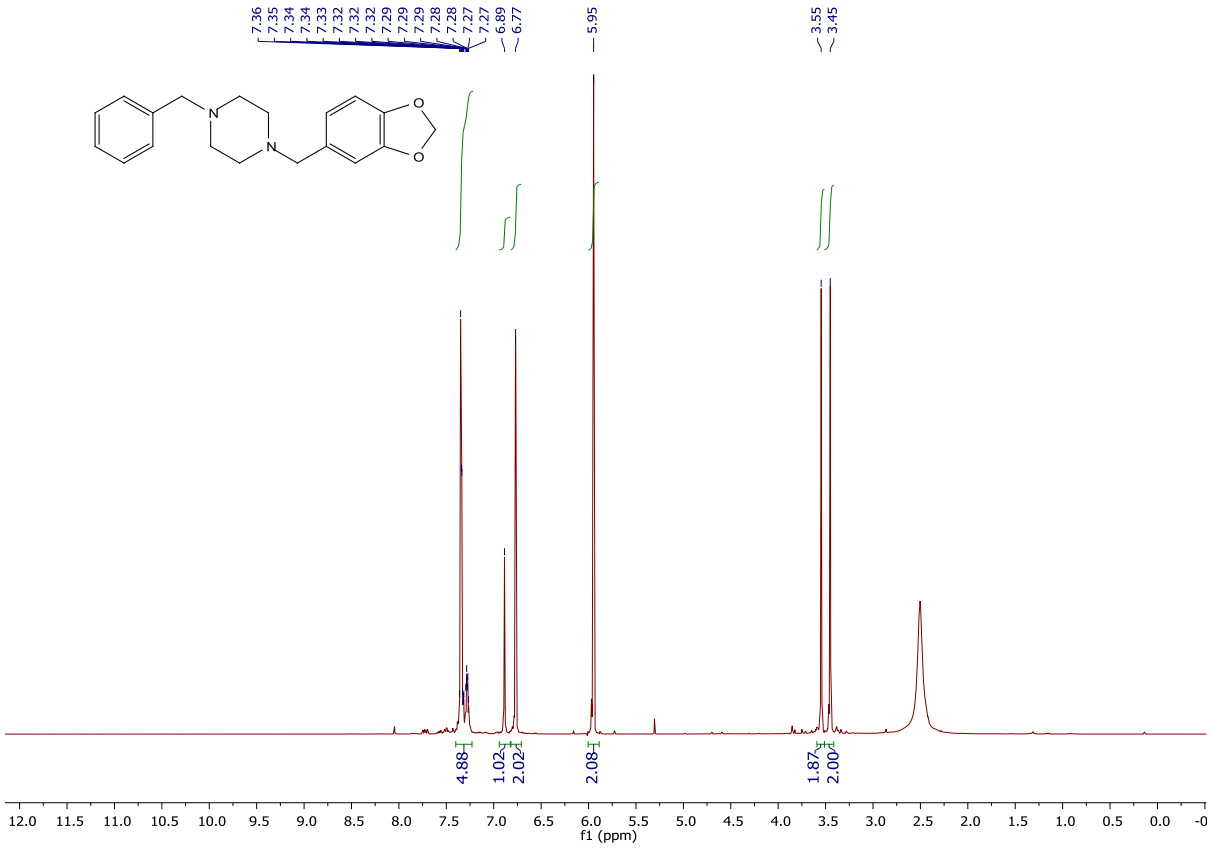
22.65
f1 (ppm)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7.35
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7.29
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7.28
7.27
7.27
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4.88
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2.08
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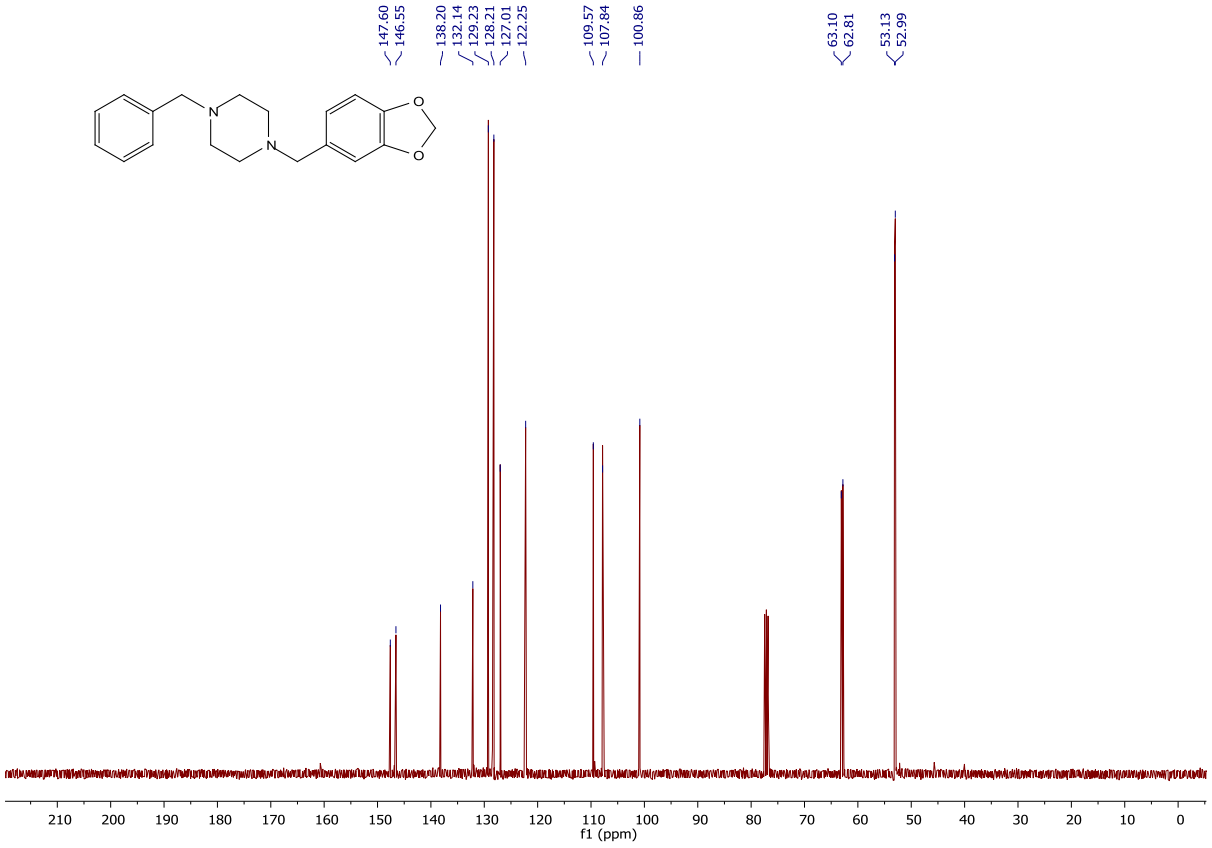
2.00
f1 (ppm)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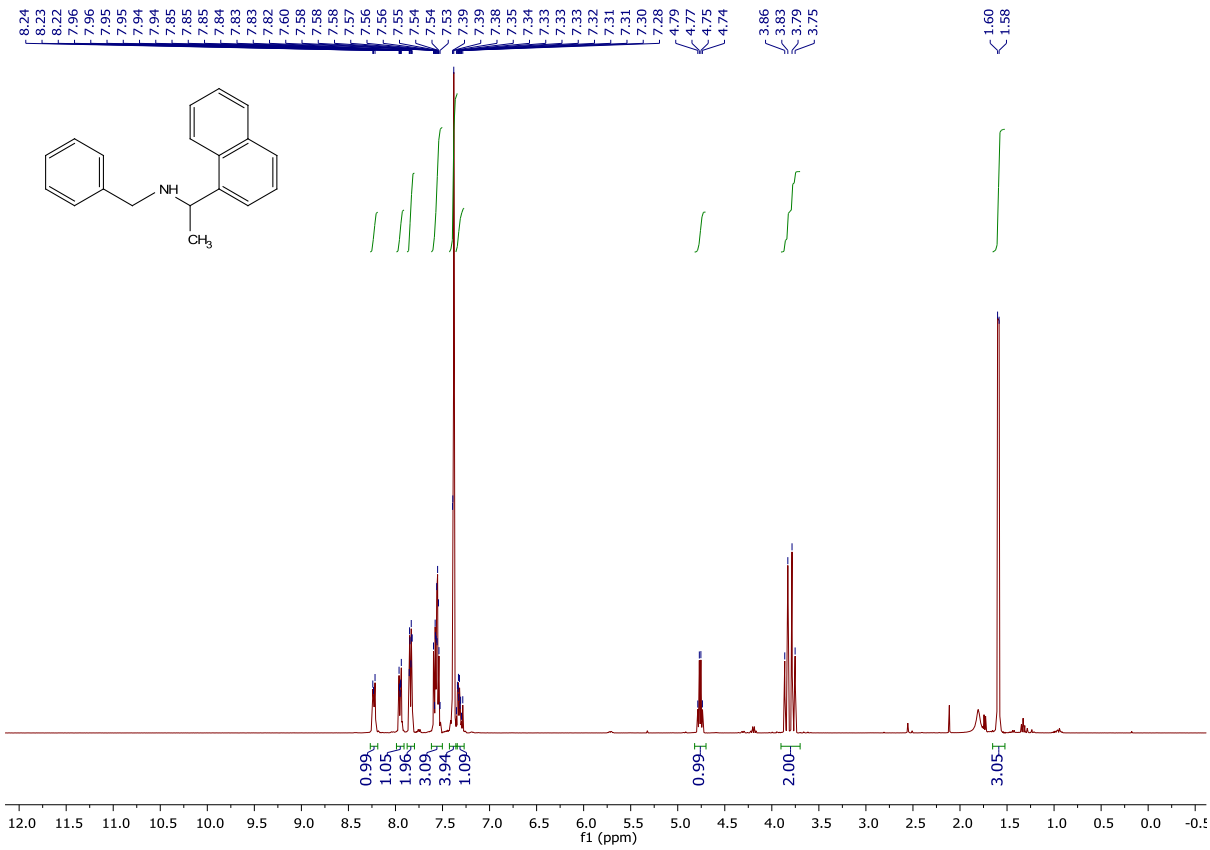
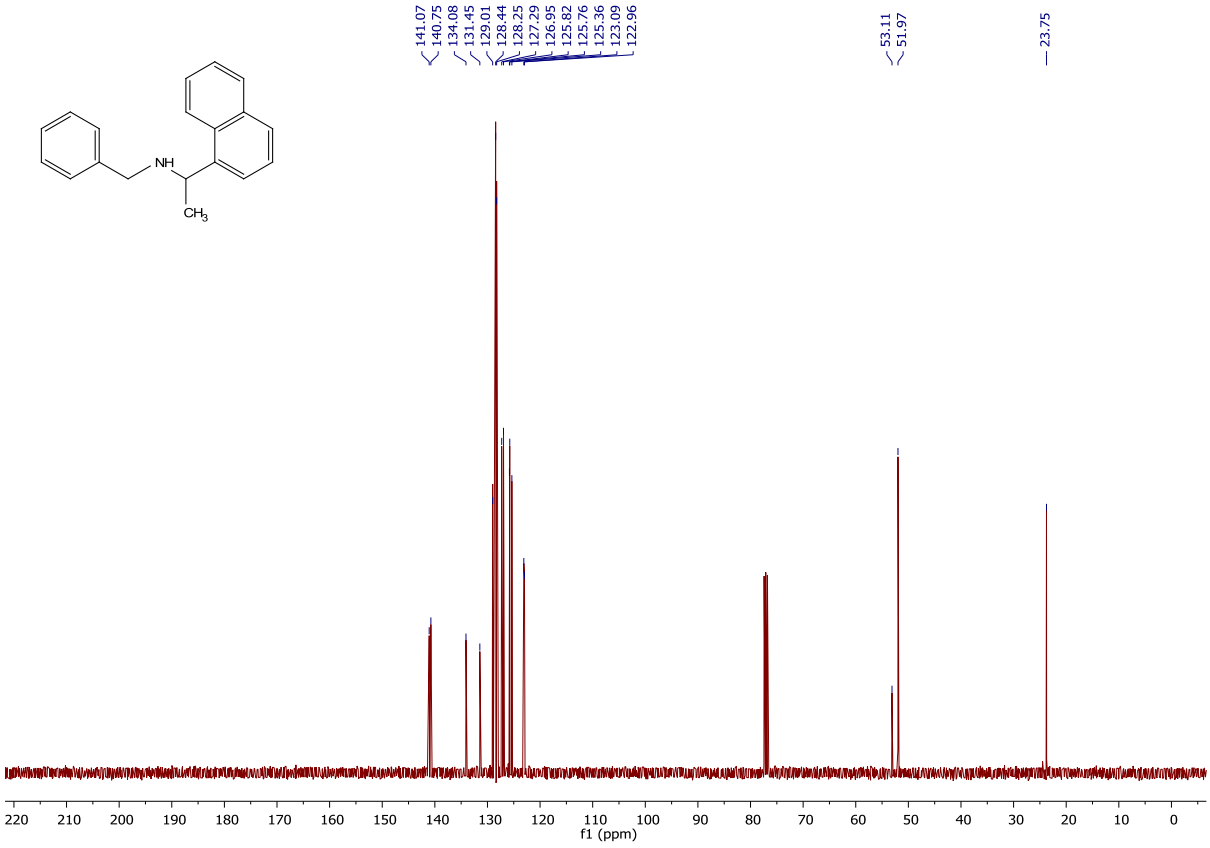
52.99
f1 (ppm)


8.24 8.23 8.22 7.96 7.96 7.95 7.95 7.94 7.94 7.85 7.85 7.85 7.84 7.83 7.83 7.82 7.60 7.58 7.58 7.58 7.57 7.56 7.56 7.55 7.54 7.54 7.53 7.39 7.39 7.38 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.30 7.28 4.79 4.77 4.75 4.74 3.86 3.83 3.79 3.75 1.60 1.58
NH
CH3
0.99 1.05 1.96 3.09 3.94 1.09 0.99 2.00 3.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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53.11 51.97
23.75
NH
CH3
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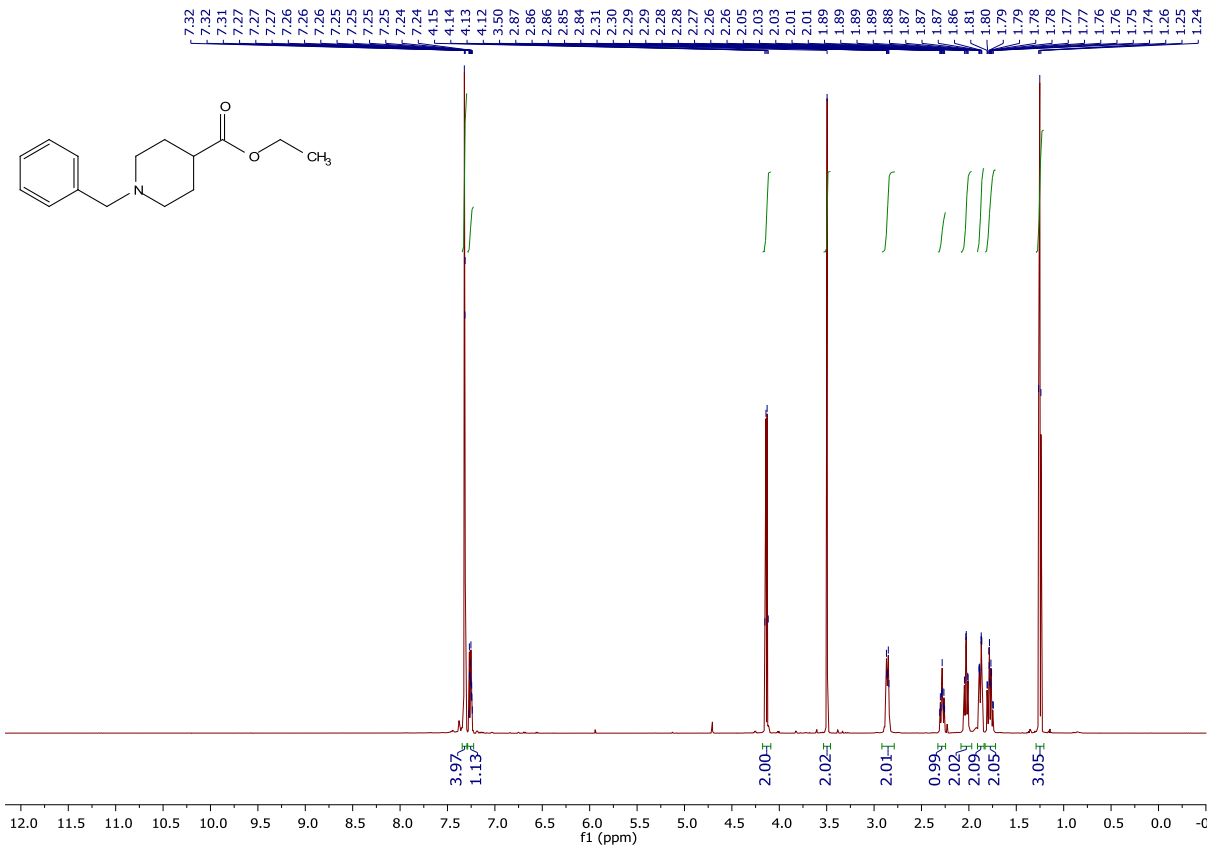
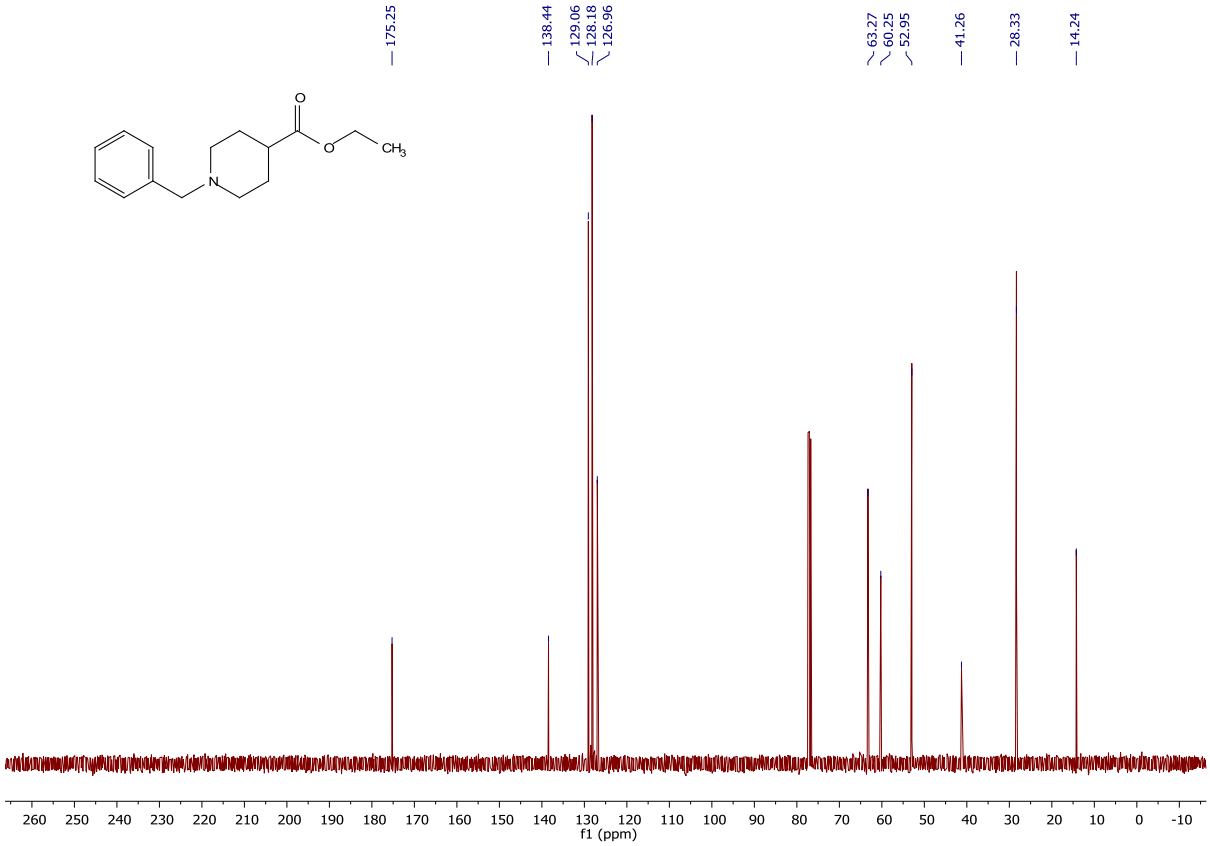
f1 (ppm)


7.32 7.32 7.31 7.27 7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.25 7.25 7.24 7.24 4.15 4.14 4.13 4.12 3.50 2.87 2.86 2.86 2.85 2.84 2.31 2.30 2.29 2.29 2.28 2.28 2.27 2.26 2.26 2.05 2.03 2.03 2.01 2.01 1.89 1.89 1.89 1.89 1.88 1.87 1.87 1.87 1.86 1.81 1.80 1.79 1.79 1.78 1.78 1.77 1.77 1.76 1.76 1.75 1.74 1.26 1.25 1.24
O
O
CH3
N
3.97
1.13
2.00
2.02
2.01
0.99
2.02
2.09
2.05
3.05
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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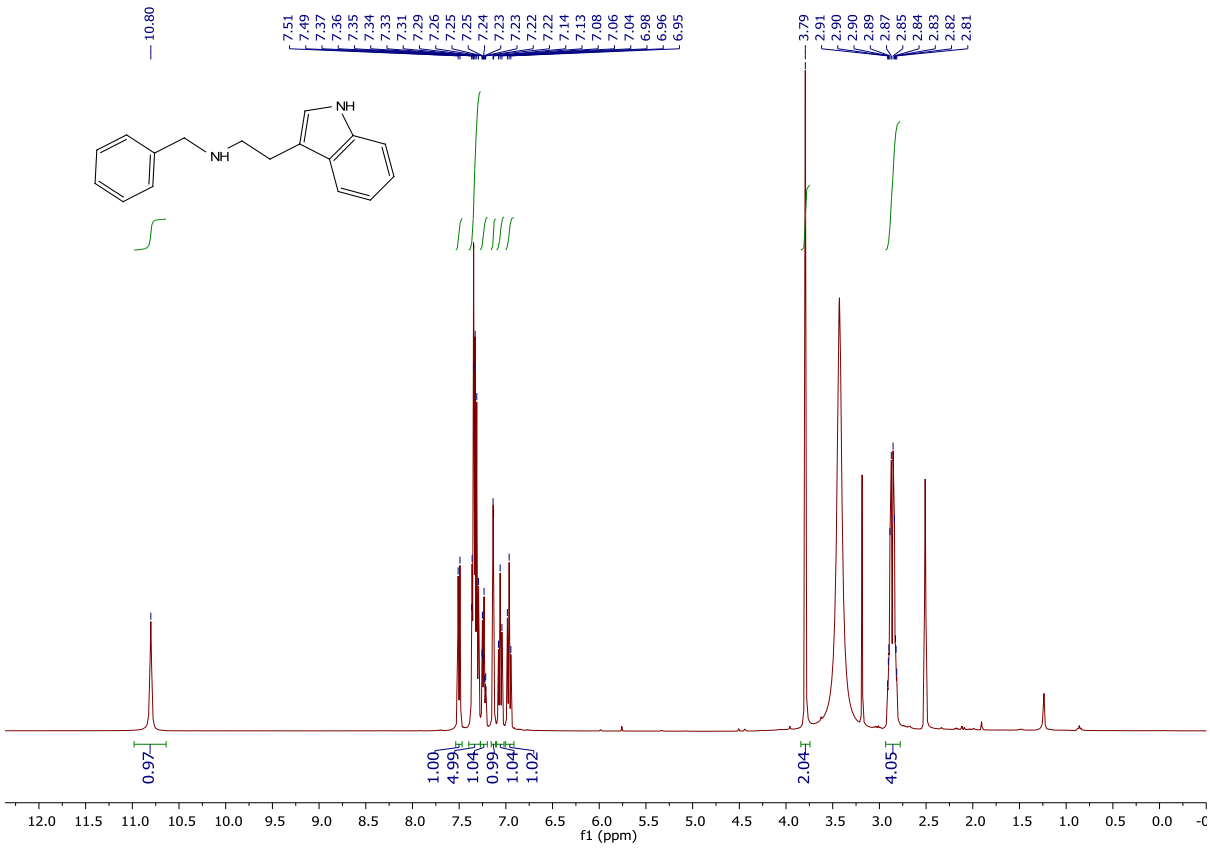
126.96
63.27
60.25
52.95
41.26
28.33
14.24
O
O
CH3
N
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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7.49
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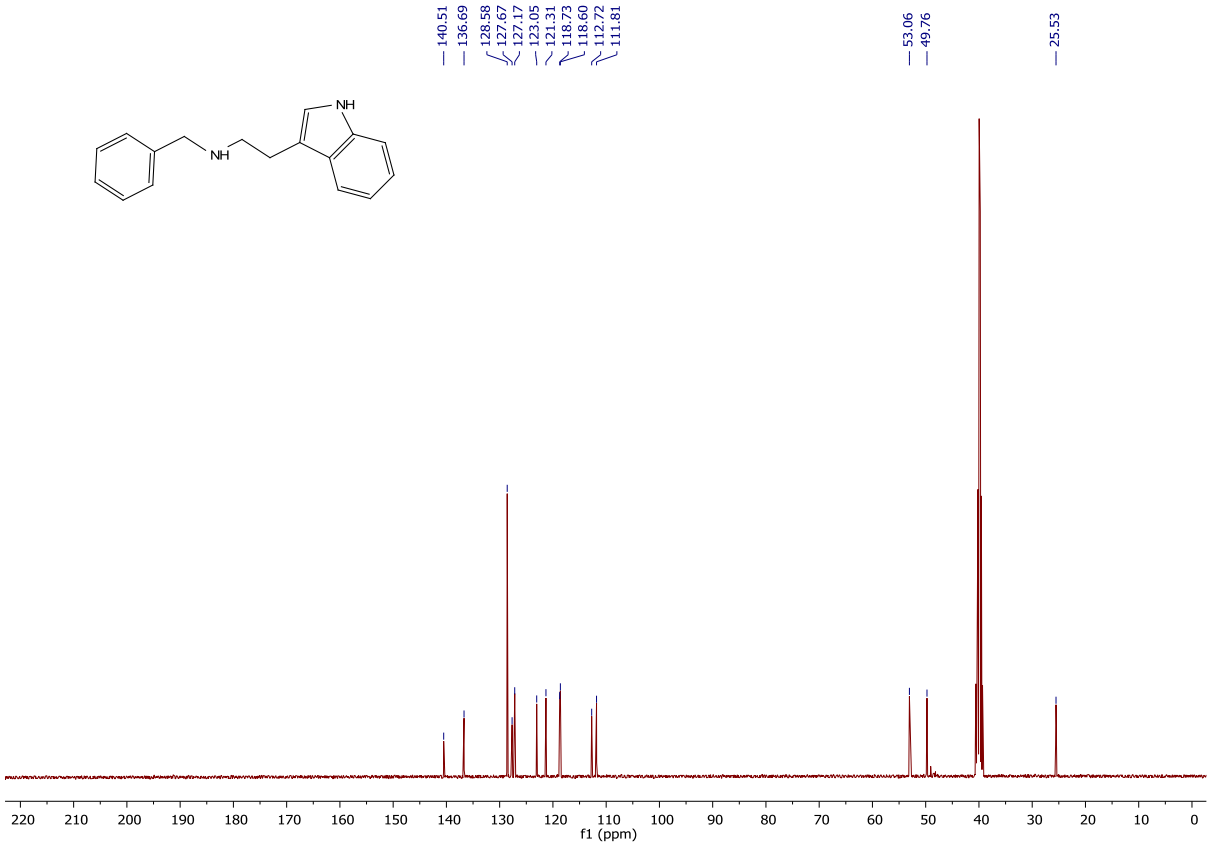
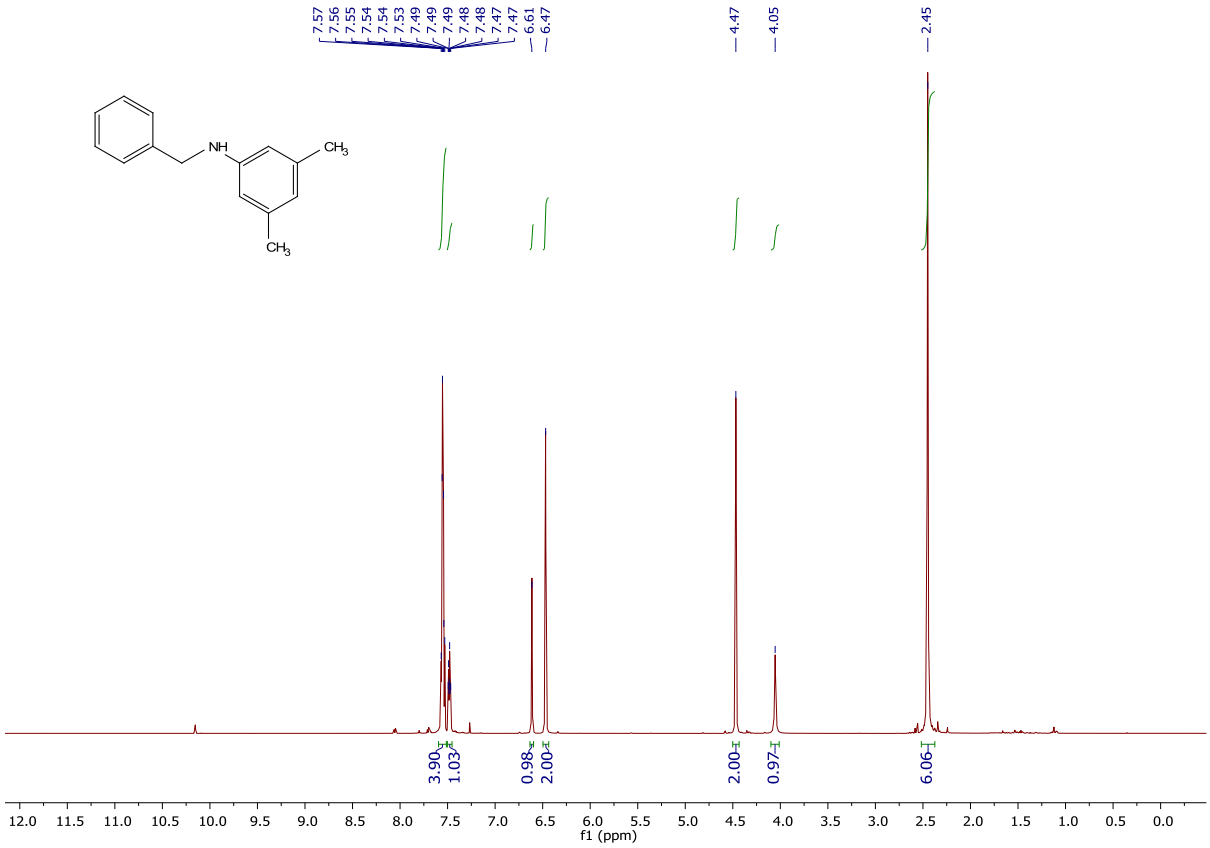
7.35
7.34
7.33
7.31
7.29
7.26
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.14
7.13
7.08
7.06
7.04
6.98
6.96
6.95
3.79
2.91
2.90
2.90
2.89
2.87
2.85
2.84
2.83
2.82
2.81
NH
NH
0.97
1.00
4.99
1.04
0.99
1.04
1.02
2.04
4.05
f1 (ppm)


140.51
136.69
128.58
127.67
127.17
123.05
121.31
118.73
118.60
112.72
111.81
53.06
49.76
25.53
NH
NH
f1 (ppm)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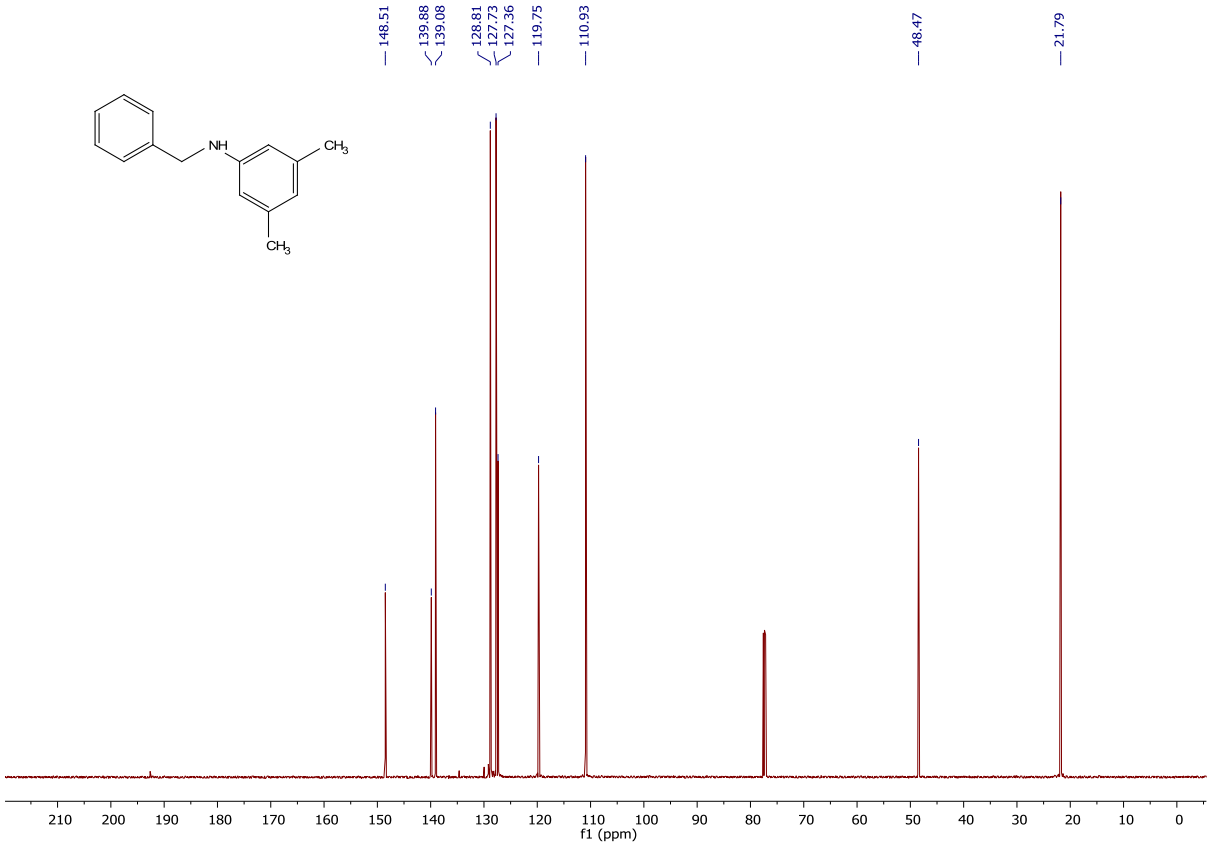
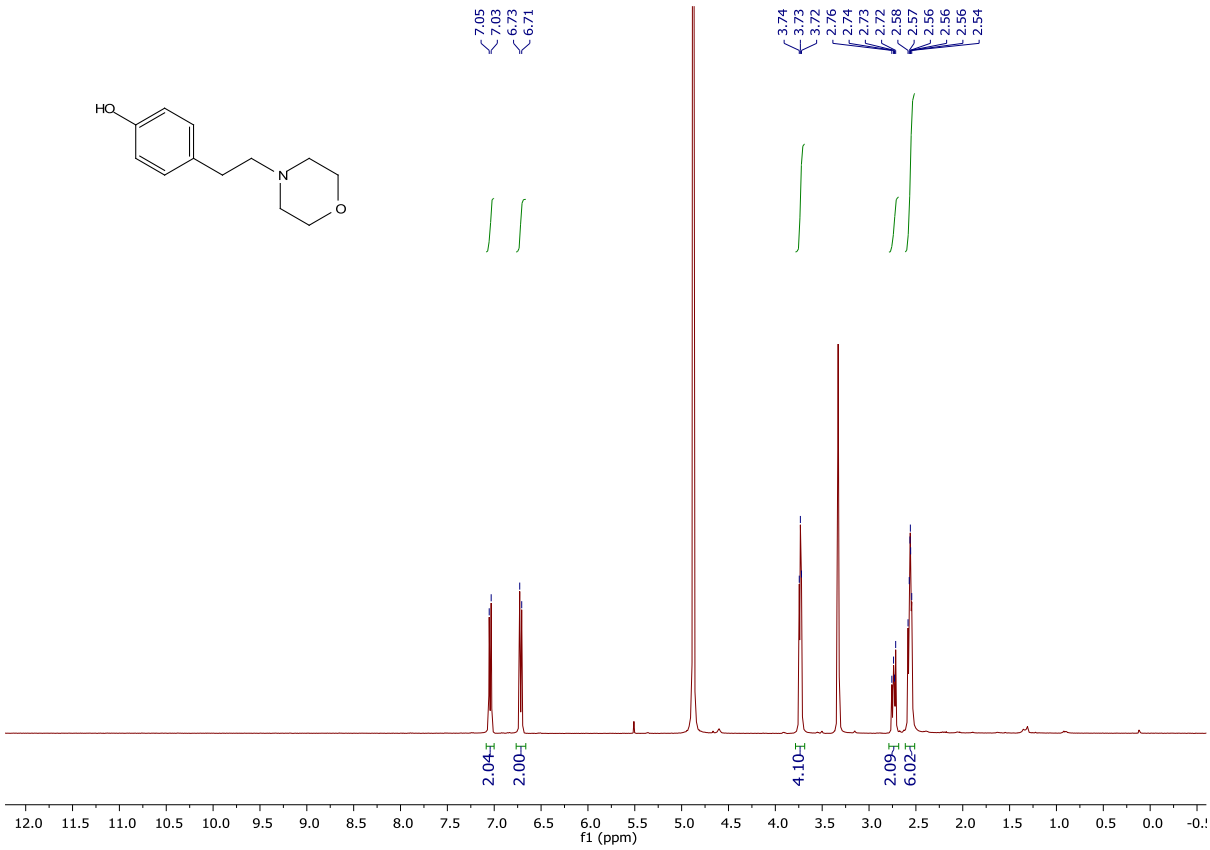
7.56
7.55
7.54
7.54
7.53
7.49
7.49
7.49
7.48
7.47
7.47
6.61
6.47
4.47
4.05
2.45
NH
CH3
CH3
3.90
1.03
0.98
2.00
2.00
0.97
6.06
f1 (ppm)


148.51
139.88
139.08
128.81
127.73
127.36
119.75
110.93
48.47
21.79
NH
CH3
CH3
f1 (ppm)


HO
N
O
7.05
7.03
6.73
6.71
3.74
3.73
3.72
2.76
2.74
2.73
2.72
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2.56
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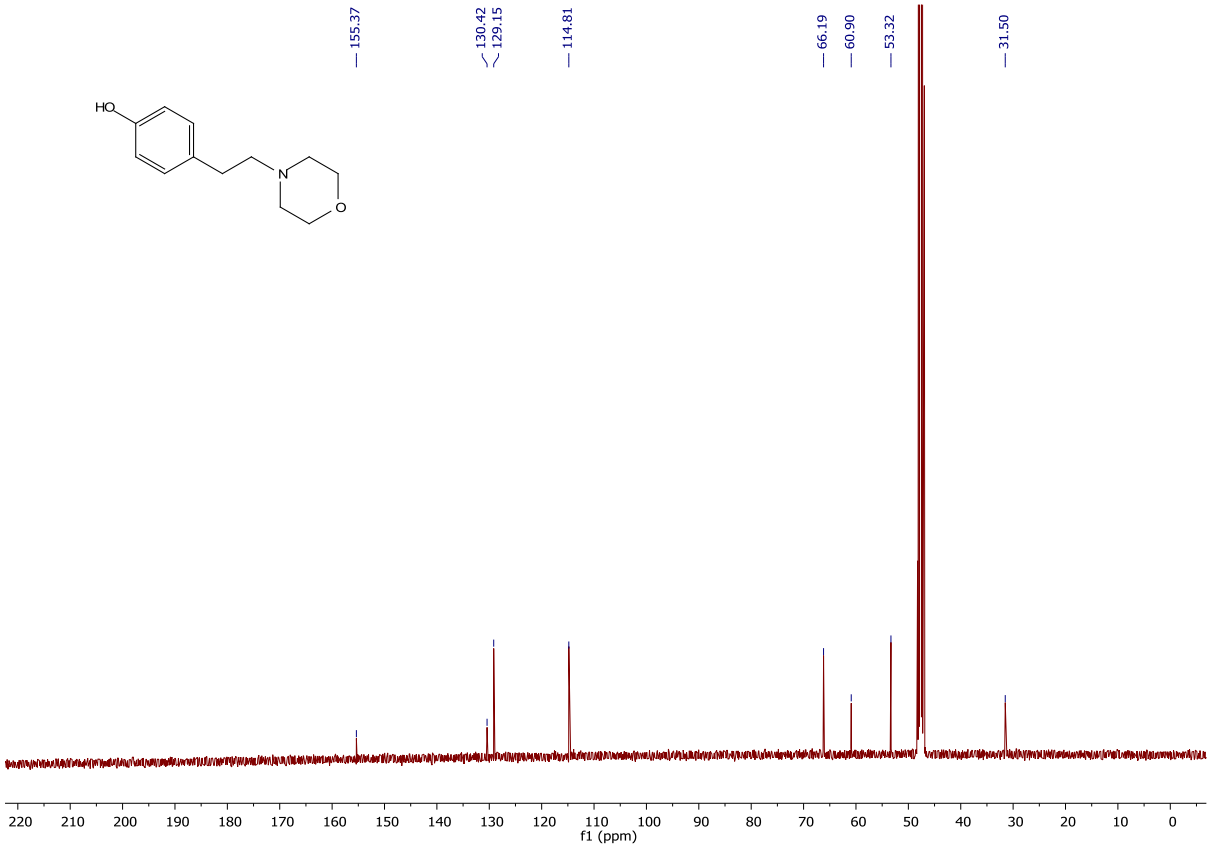
2.00
4.10
2.09
6.02
f1 (ppm)


HO
N
O
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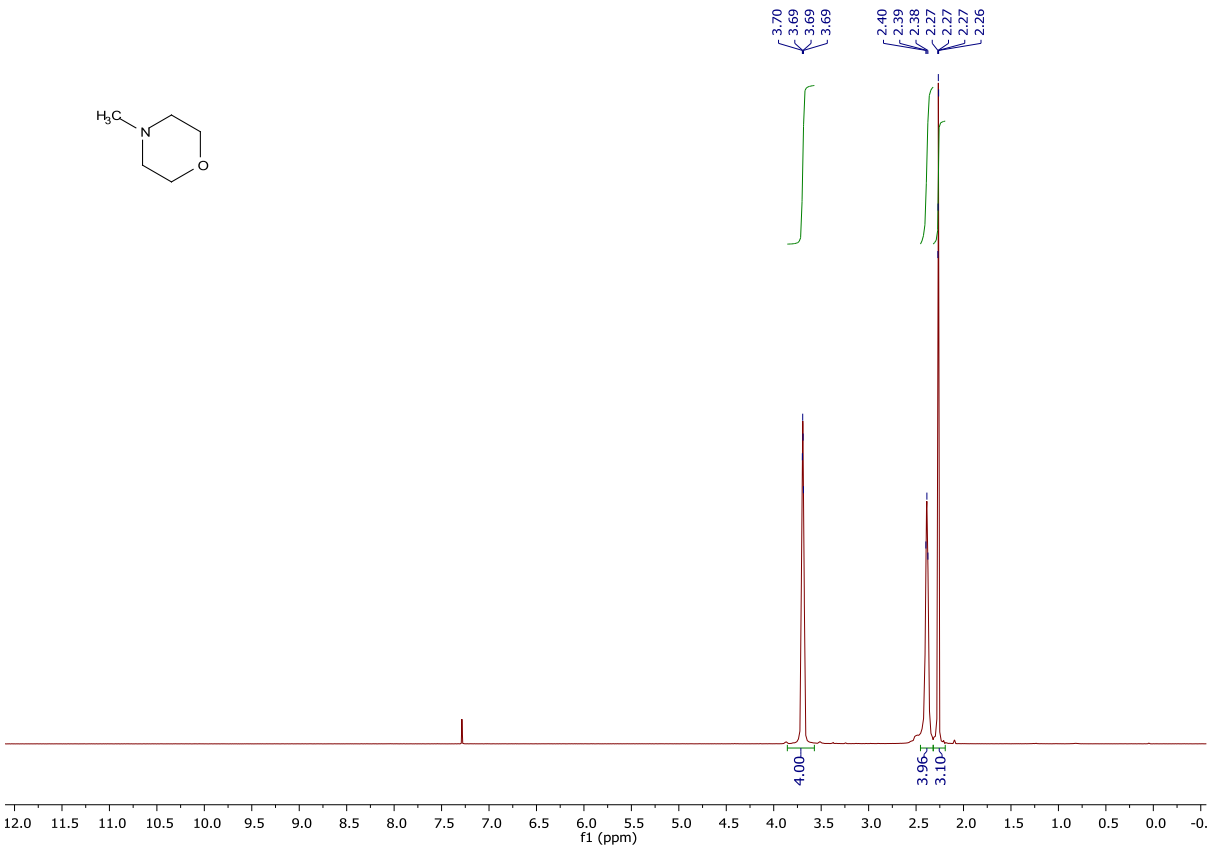
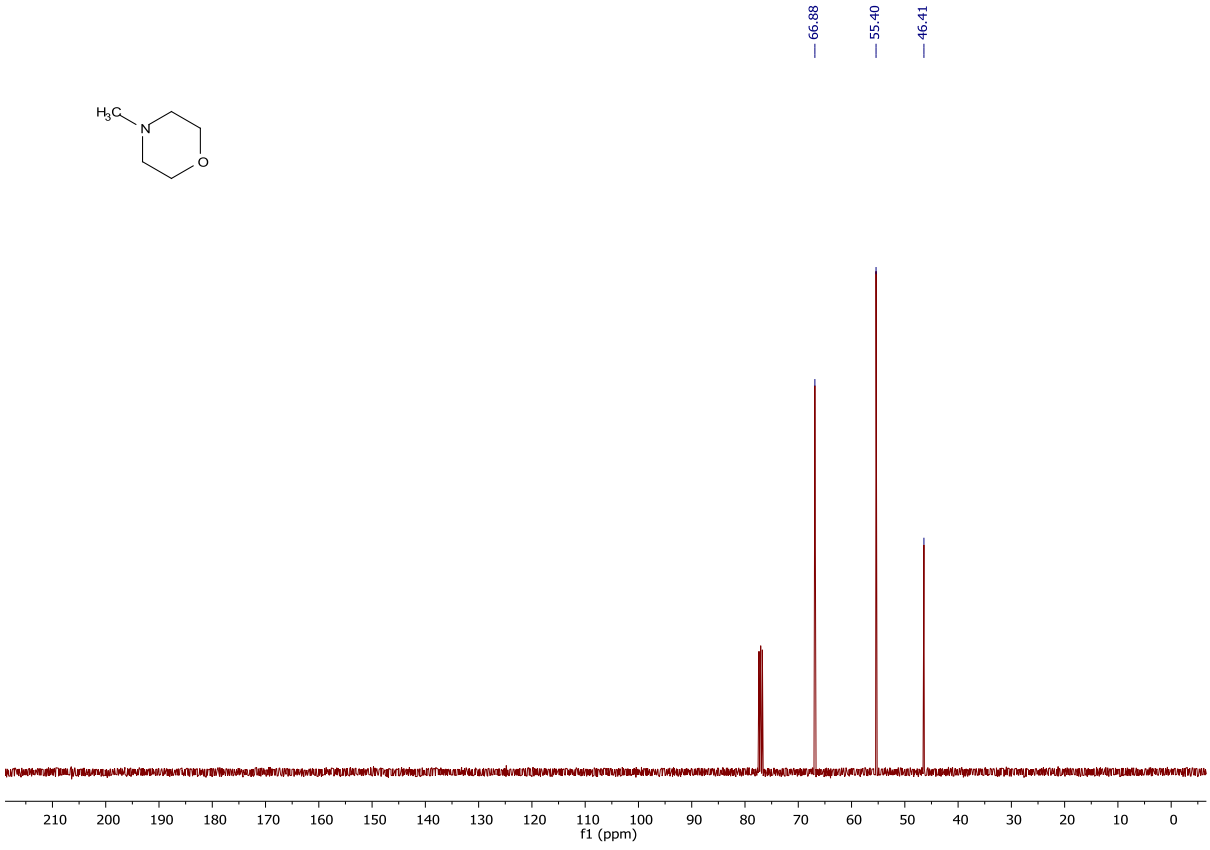
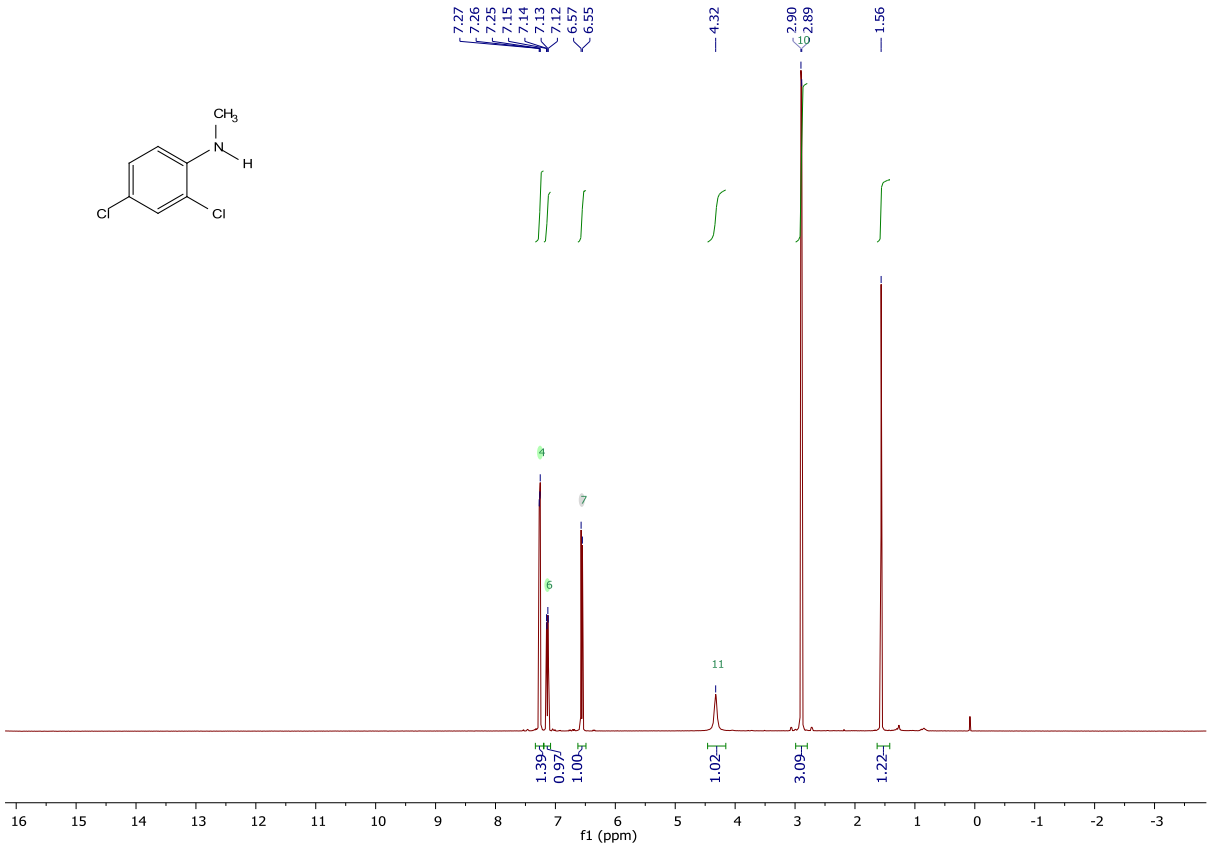
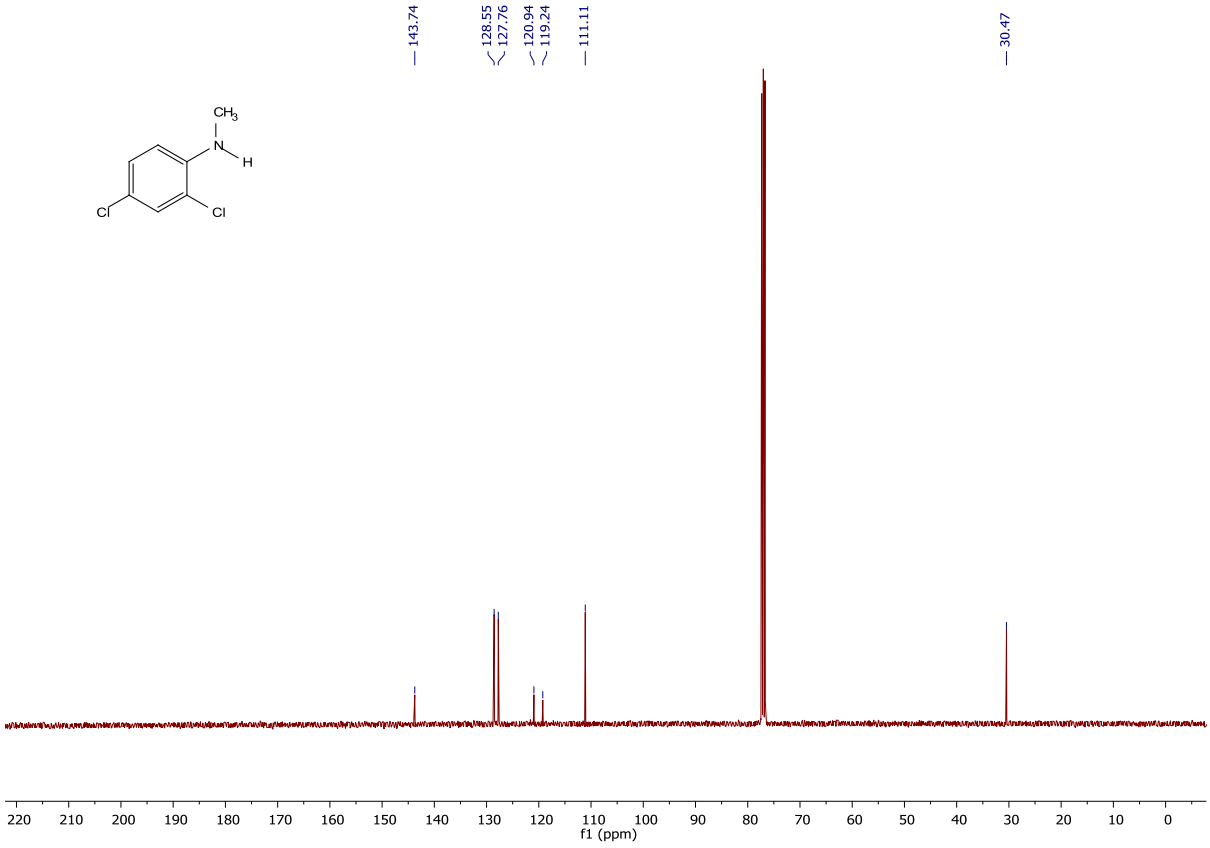
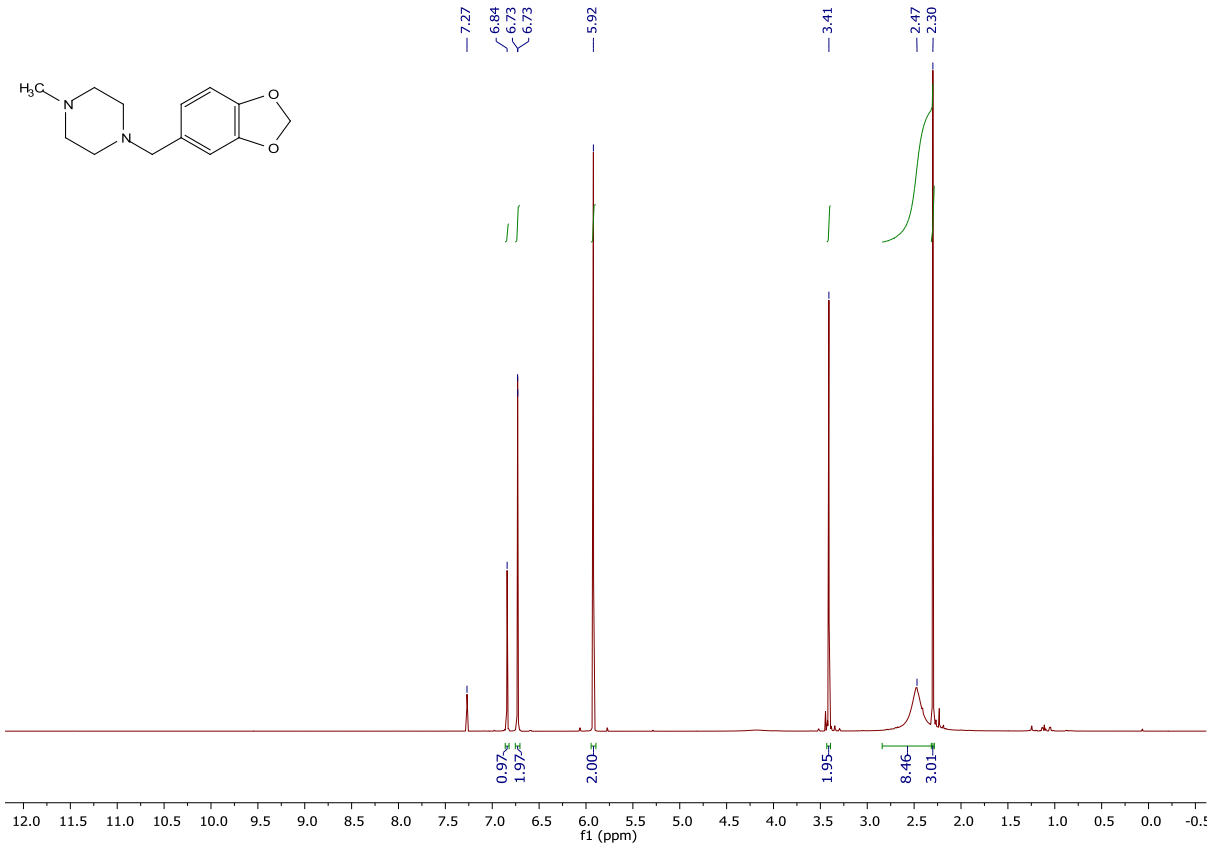
130.42
129.15
114.81
66.19
60.90
53.32
31.50
f1 (ppm)

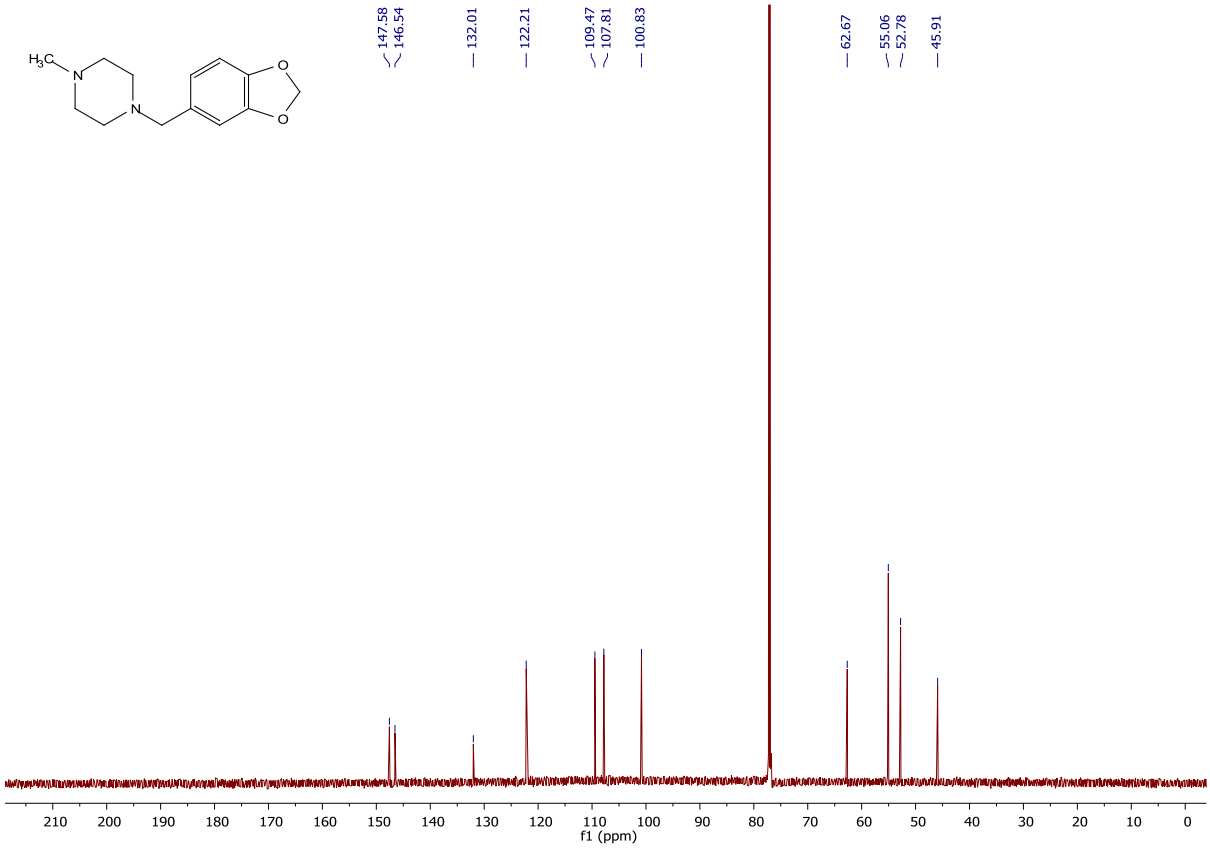

3.70
3.69
3.69
3.69
2.40
2.39
2.38
2.27
2.27
2.27
2.26
4.00
3.96
3.10
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

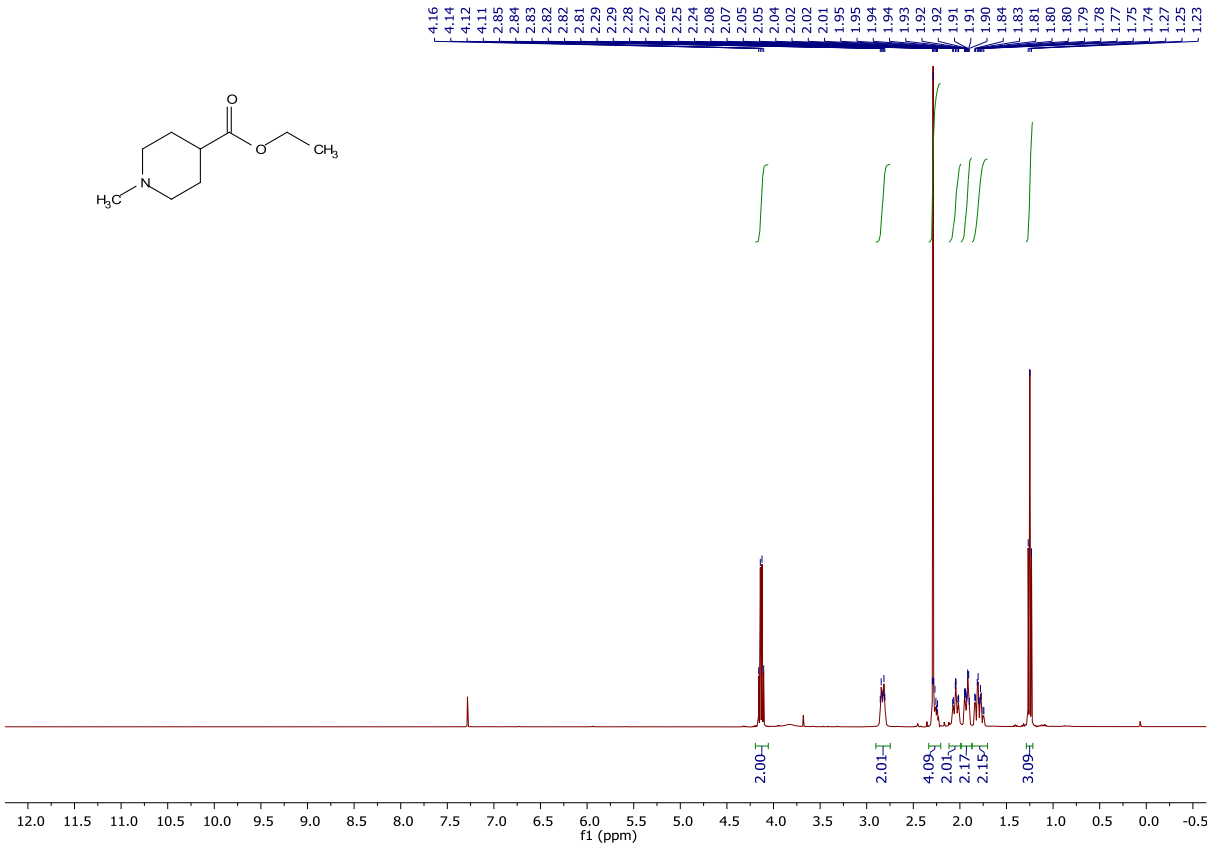

66.88
55.40
46.41
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

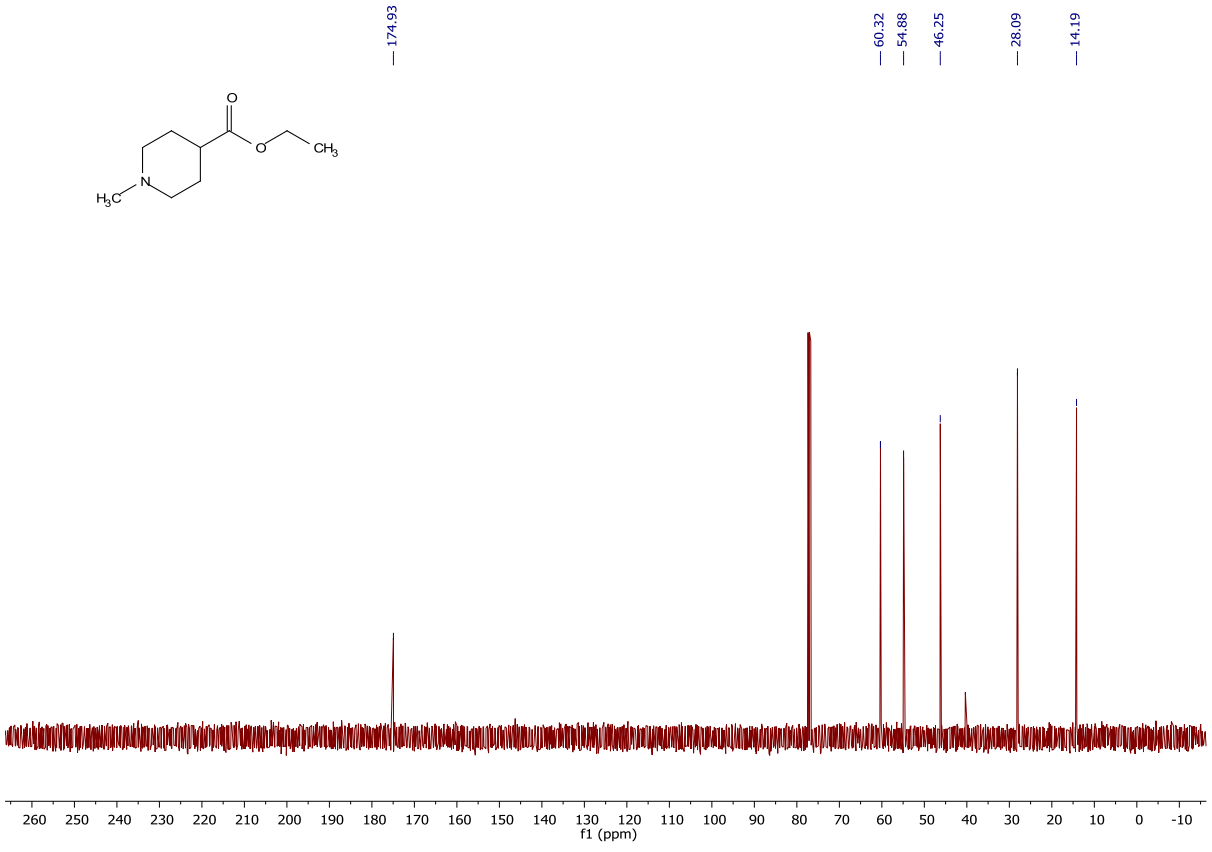

7.27
7.26
7.25
7.15
7.14
7.13
7.12
6.57
6.55
4.32
2.90
2.89
1.56
CH3
N
H
Cl
Cl
4
6
7
11
1.39
0.97
1.00
1.02
3.09
1.22
f1 (ppm)

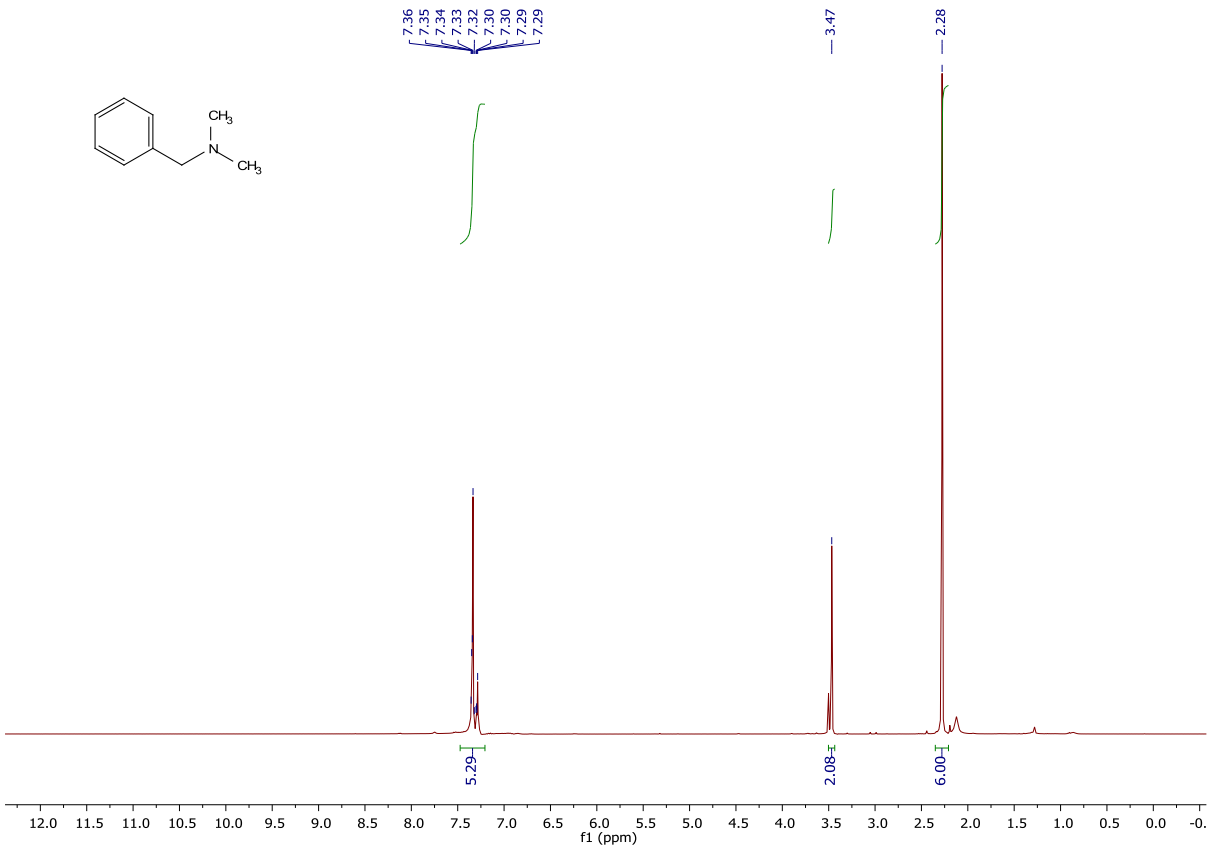

143.74
128.55
127.76
120.94
119.24
111.11
30.47
CH3
N
H
Cl
Cl
f1 (ppm)

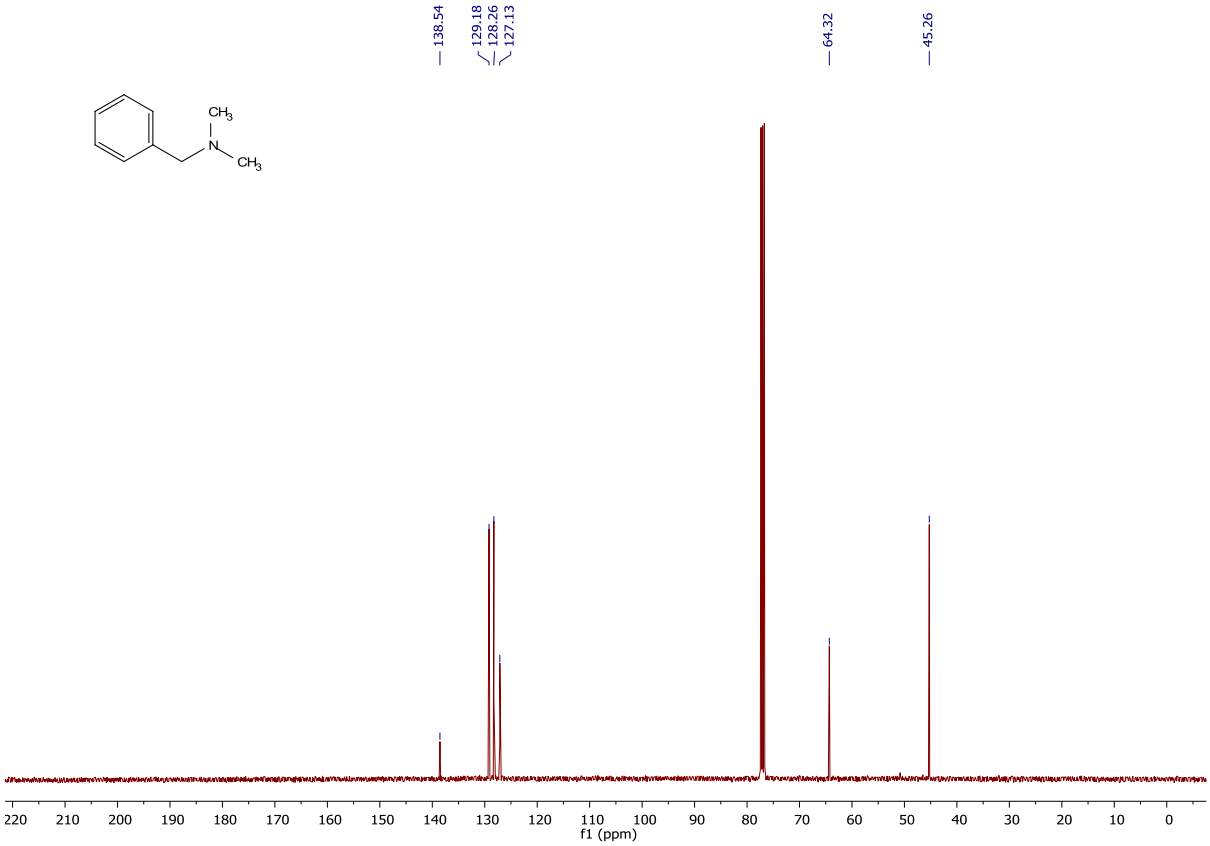

7.27
6.84
6.73
6.73
5.92
3.41
2.47
2.30
0.97
1.97
2.00
1.95
8.46
3.01
f1 (ppm)

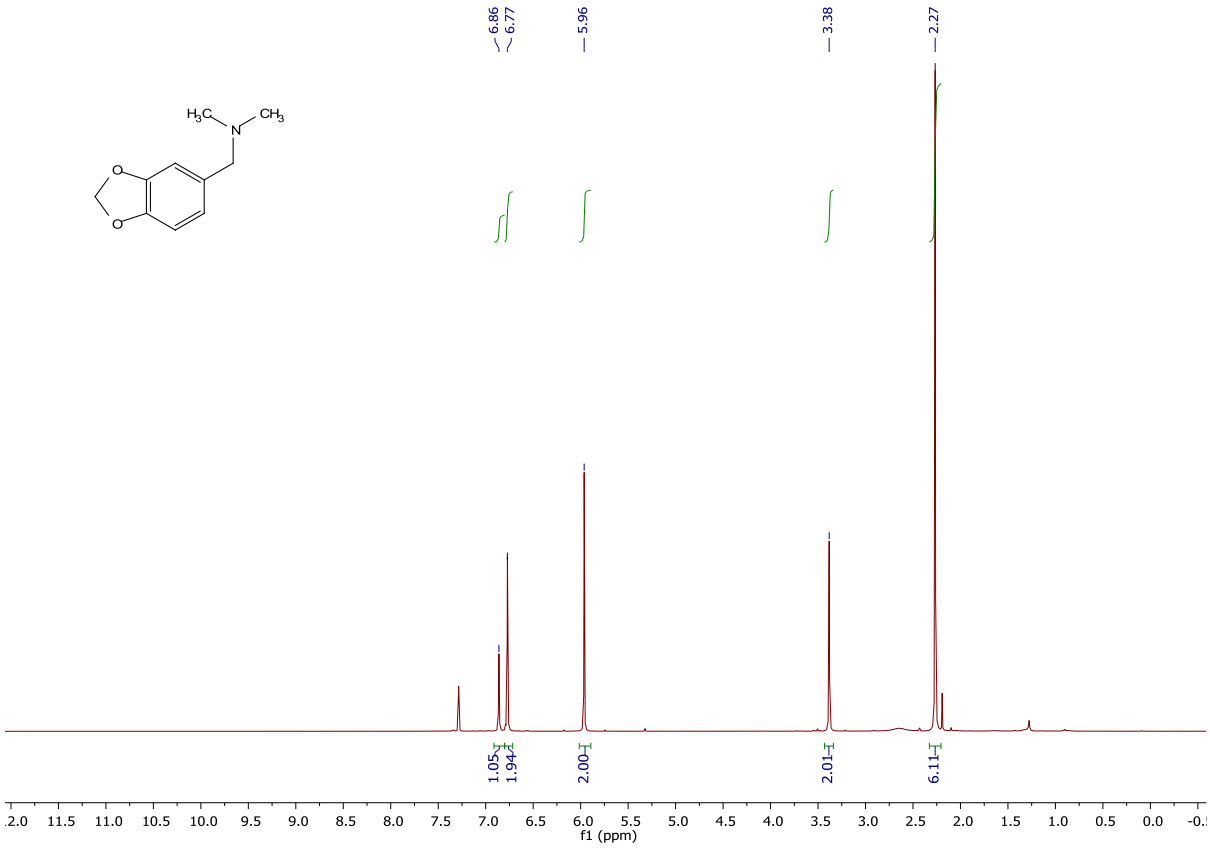

147.58
146.54
132.01
122.21
109.47
107.81
100.83
62.67
55.06
52.78
45.91
f1 (ppm)

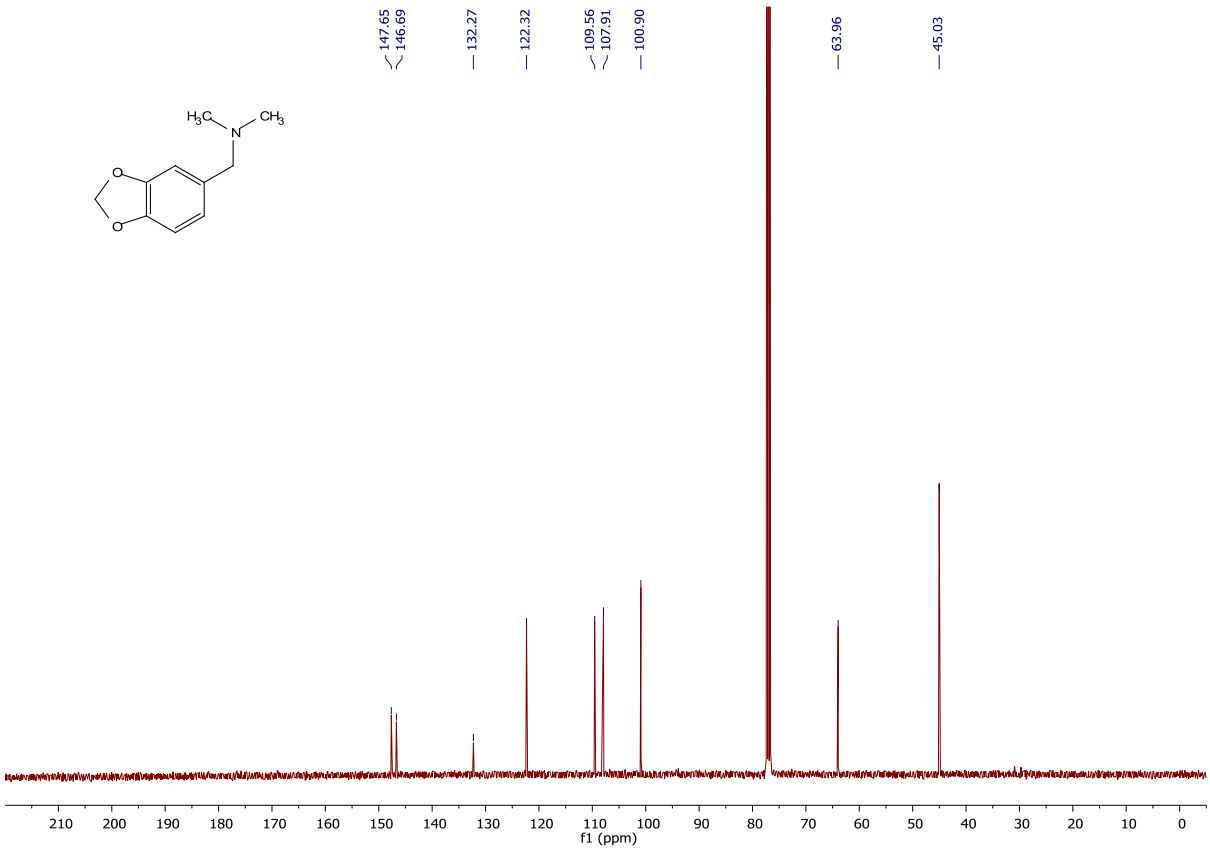

4.16 4.14 4.12 4.11 2.85 2.84 2.83 2.82 2.82 2.81 2.29 2.29 2.28 2.27 2.26 2.25 2.24 2.08 2.07 2.05 2.05 2.04 2.02 2.02 2.01 1.95 1.95 1.94 1.94 1.93 1.92 1.92 1.91 1.91 1.90 1.84 1.83 1.81 1.80 1.80 1.79 1.78 1.77 1.75 1.74 1.27 1.25 1.23
O
O
CH3
N
H3C
2.00
2.01
4.09
2.01
2.17
2.15
3.09
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

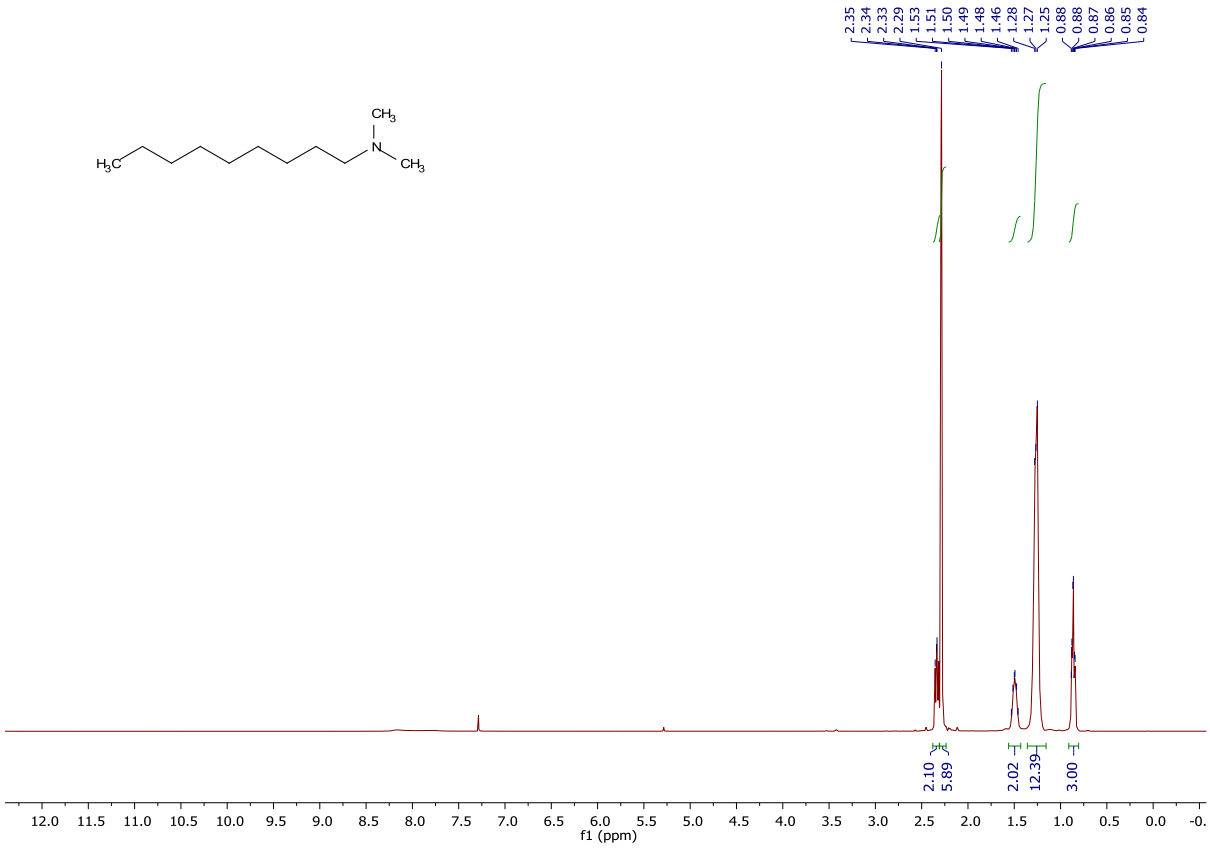

174.93
60.32
54.88
46.25
28.09
14.19
O
O
CH3
N
H3C
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

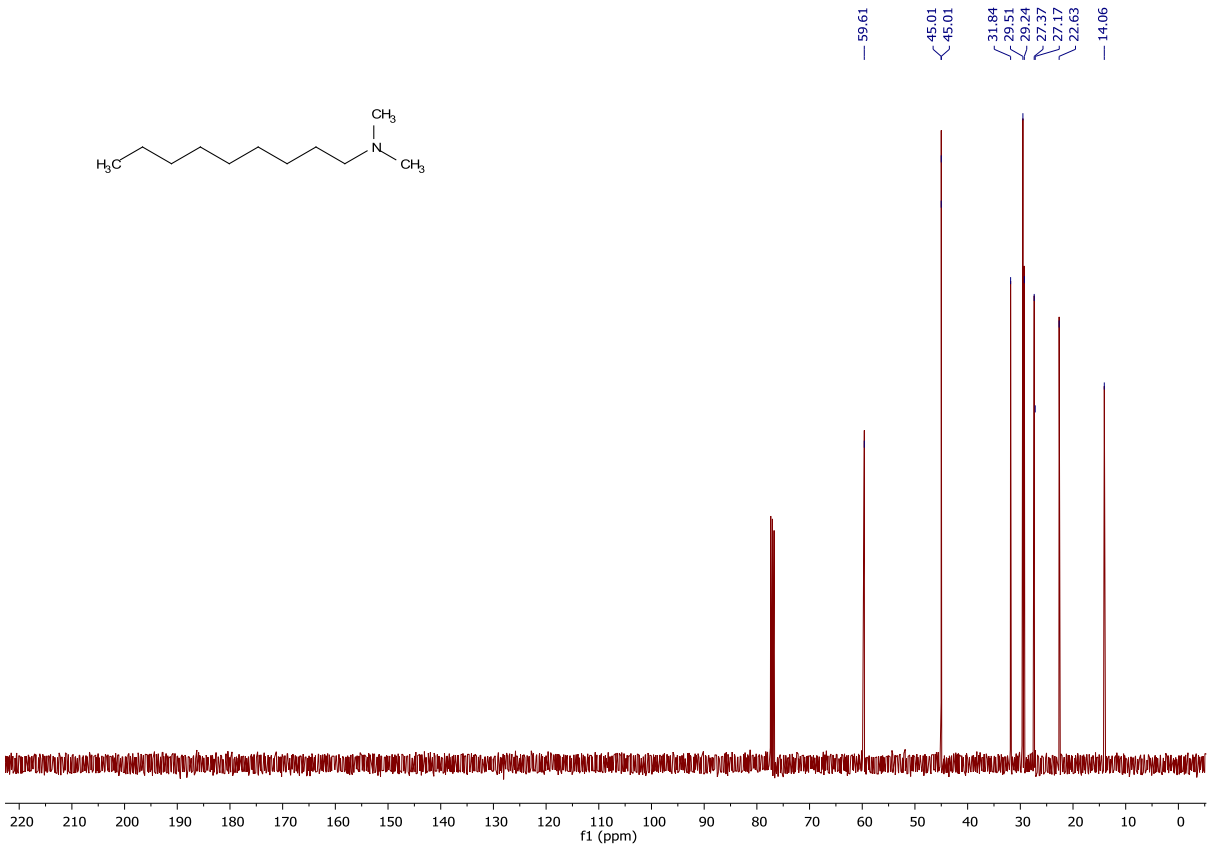

7.36
7.35
7.34
7.33
7.32
7.30
7.30
7.29
7.29
3.47
2.28
CH3
N
CH3
5.29
2.08
6.00
f1 (ppm)

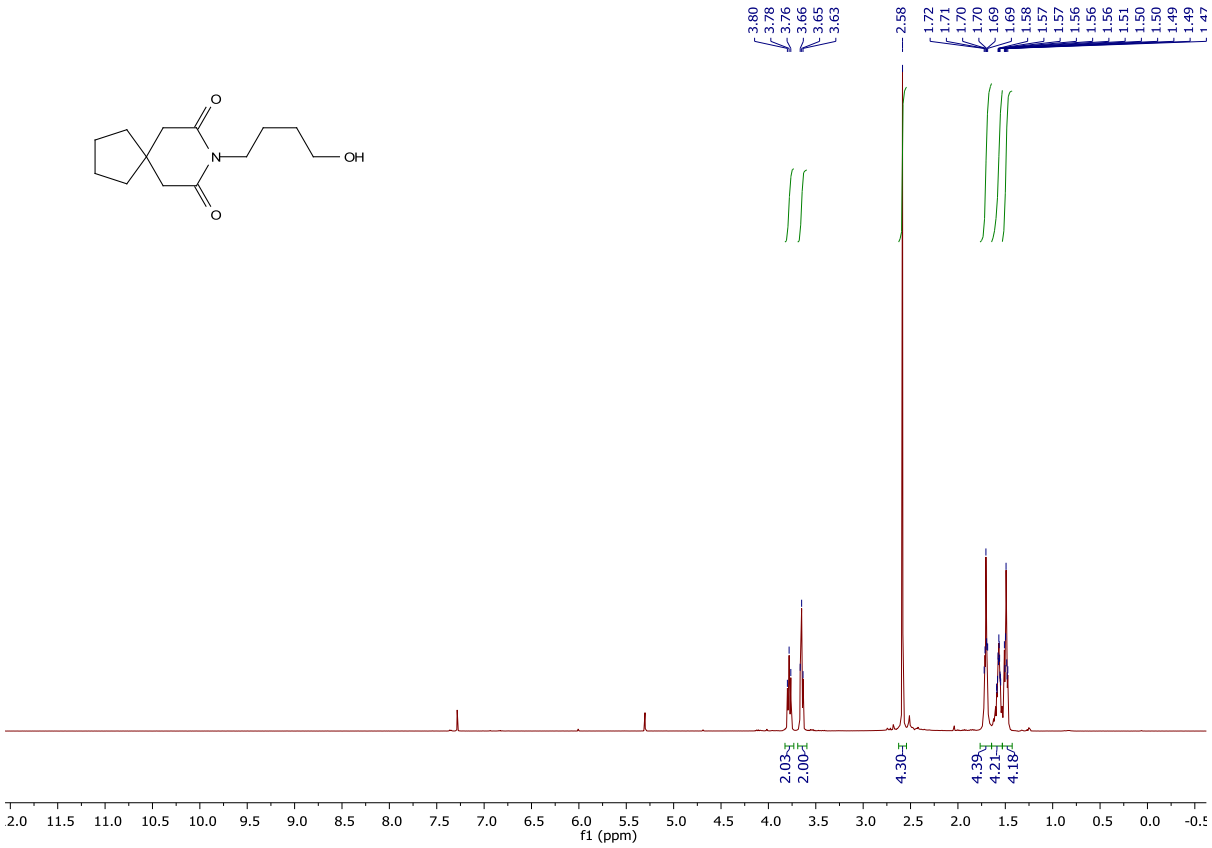

138.54
129.18
128.26
127.13
64.32
45.26
CH3
N
CH3
f1 (ppm)


6.86
6.77
5.96
3.38
2.27
1.05
1.94
2.00
2.01
6.11
f1 (ppm)


147.65
146.69
132.27
122.32
109.56
107.91
100.90
63.96
45.03
f1 (ppm)


2.35
2.34
2.33
2.29
1.53
1.51
1.50
1.49
1.48
1.46
1.28
1.27
1.25
0.88
0.88
0.87
0.86
0.85
0.84
CH3
N
CH3
H3C
2.10
5.89
2.02
12.39
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)


59.61
45.01
45.01
31.84
29.51
29.24
27.37
27.17
22.63
14.06
CH3
N
CH3
H3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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3.78
3.76
3.66
3.65
3.63
2.58
1.72
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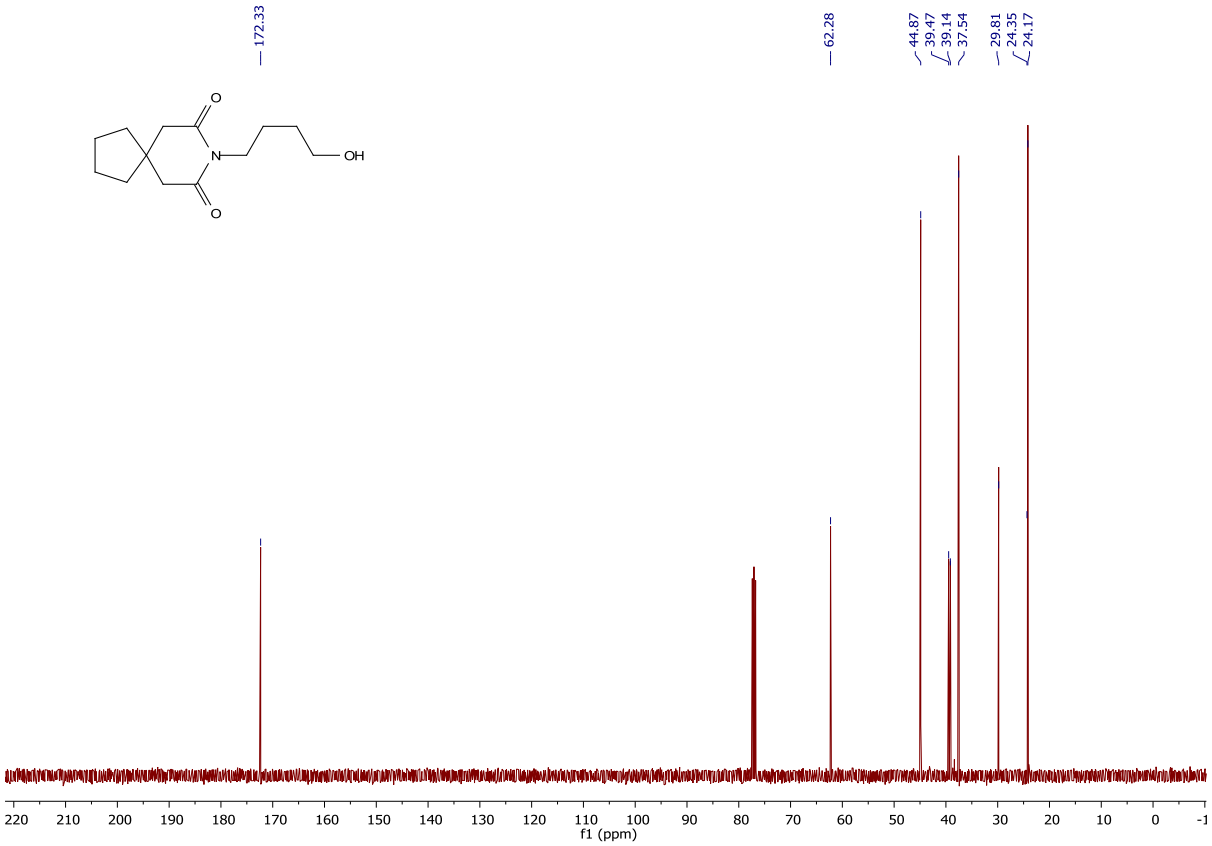
1.70
1.70
1.69
1.69
1.58
1.57
1.57
1.56
1.56
1.56
1.51
1.50
1.50
1.49
1.49
1.47
O
N
OH
O
2.03
2.00
4.30
4.39
4.21
4.18
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


172.33
62.28
44.87
39.47
39.14
37.54
29.81
24.35
24.17
O
N
OH
O
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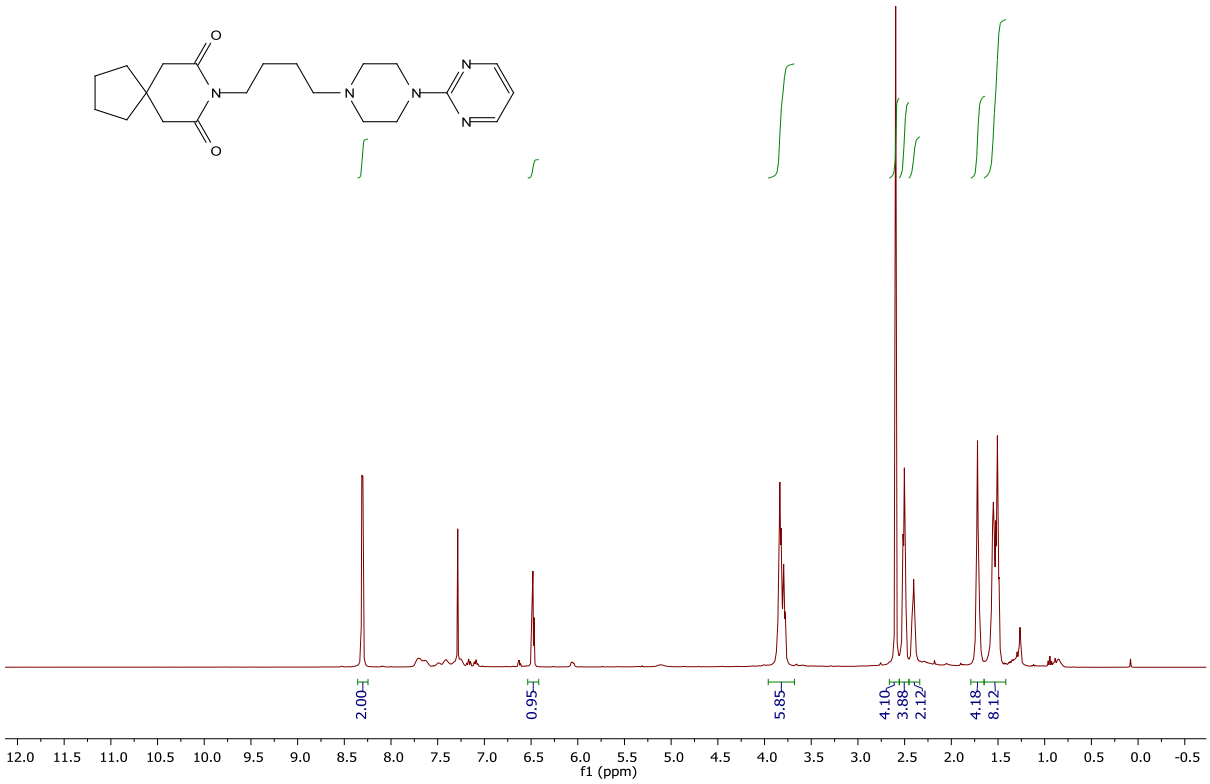
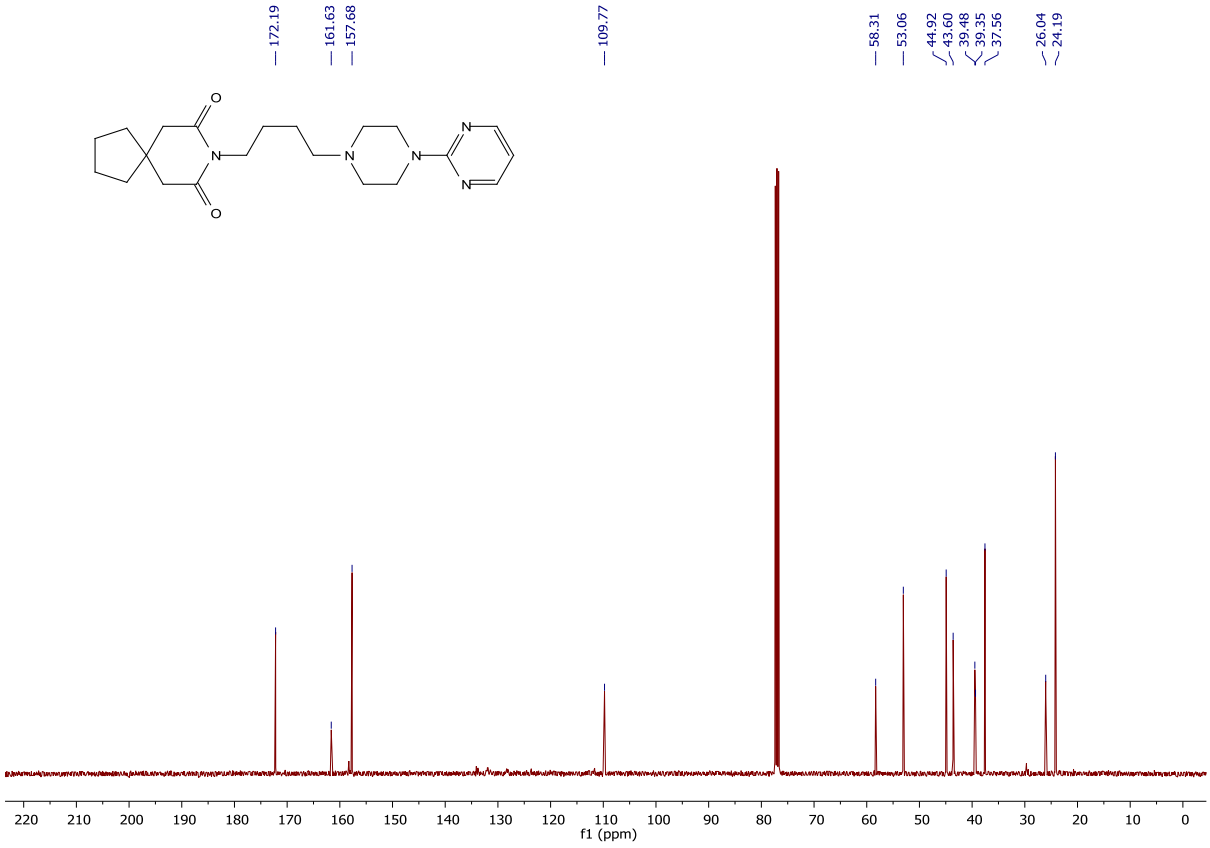
f1 (ppm)


2.00
0.95
5.85
4.10
3.88
2.12
4.18
8.12
f1 (ppm)


172.19
161.63
157.68
109.77
58.31
53.06
44.92
43.60
39.48
39.35
37.56
26.04
24.19
f1 (ppm)

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