Rediscovering aminal chemistry: Copper (II) catalysed formation under mild conditions

Supporting Information

Juliana G. Pereira,[a] João P. M. António,[a] Ricardo Mendonça,[b] Rafael F. A. Gomes*[a] and Carlos A. M. Afonso*[a]

[a] *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, University of Lisbon, Avenida Professor Gama Pinto, 1649-003, Lisbon (Portugal).*

[b] *Hovione FarmaCiencia SA, Sete Casas; 2674-506 Loures, Portugal*

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Materials and methods

All solvents were distilled prior to use. All reagents were used as received from commercial suppliers, unless otherwise stated. Furfural was distilled and stored at 4 °C.

^{1}H and ^{13}C NMR spectra were acquired on Bruker MX300 spectrometer.

HPLC analysis was performed on a Thermo Scientific Dionex Ultimate 3000 apparatus with a LPG-3400SD Pump, a UV MWD-3000(RS) detector and an autosampler ACC-3000, equipped with a 20 µL loop, using a reversed-phase EC 250/4 Nucleodur 100-5 C18ec column (250×4 mm, 5 µm) Thermo Scientific^{TM} Dionex^{TM}.

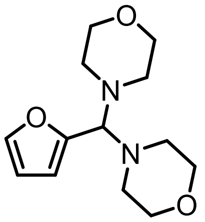
General procedure A for the preparation of aminals

To a solution of aldehyde (1.88 mmol) in water (4 M) was added the corresponding amine (2.2 eq, 4.15 mmol) or diamine/aminoethanol (1.2 eq, 2.56 mmol) and a solution of $Cu(OTf)_2$ (0.1 mol%) in water. The reaction mixture was stirred at room temperature for 2 minutes after which the product precipitates. The precipitate was filtered and washed with cold water. If the compound does not readily precipitates, concentration on a rotary evaporator was performed. All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy without further purification. The products could be further purified by recrystallization in ethyl acetate with negligible loss of yield. In some cases it is possible to observe 1-2 % hydrolysis on the NMR tube. The occurrence of hydrolysis in the NMR tube can be confirmed by adding trimethylamine to the deuterated solvent which turns to inhibit the hydrolysis (see page 62).

General procedure B for the preparation of aminals

To a solution of aldehyde (1.88 mmol) in water (4 M) was added the corresponding amine (2.2 eq, 4.15 mmol) or diamine/aminoethanol (1.2 eq, 2.56 mmol) and a solution of $Cu(OTf)_2$ (0.1 mol%) in water. The reaction mixture was stirred at room temperature for 2 minutes after which the reaction was diluted with $NaHCO_3$ (aq) (5 mL) and extracted with MTBE (5 × 5 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure, yielding the pure products.

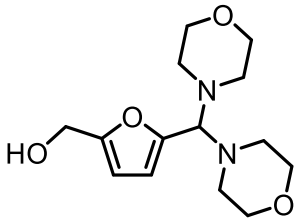
4,4'-(furan-2-ylmethylene)dimorpholine 1



The title compound was prepared according to the general procedure A using 10 g furfural. The product was isolated in 96 % yield (24.1 g) as transparent crystals. m.p 122-123 ^{o}C (reported m.p. 122-123 ^{o}C).[1] The spectral data are in agreement with the literature.[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 1.2 Hz, 1H), 6.25 (dd, J = 3.2 Hz, J = 1.8 Hz, 1H), 6.12 (dd, J = 3.2 Hz, J = 0.7 Hz, 1H), 3.63 (s, 1H), 3.58 (t, J = 4.7 Hz, 8H), 2.48-2.31 (m, 8H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 150.2, 142.1, 109.7, 109.6, 82.6, 67.0, 49.7 ppm.

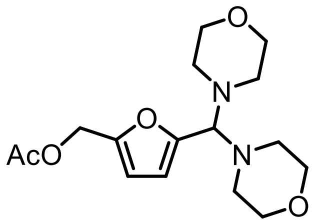
(5-(dimorpholinomethyl)furan-2-yl)methanol 2



The title compound was prepared according to the general procedure B. The product was isolated in 94 % yield (210 mg) as yellow solid. m.p. 98-100 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.16 (d, J = 2.7 Hz, 1H), 6.09 (d, J = 3.0 Hz, 1H), 4.48 (s, 2H), 3.62-3.60 (m, 9H), 2.50-2.35 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 154.6, 149.4, 110.3, 106.9, 82.5, 66.8, 56.5, 49.5 ppm. **HRMS (ESI)** m/z calcd for $C_{14}H_{22}N_2O_4$ [M + H$^+$] 283.1652, found 283.1640.

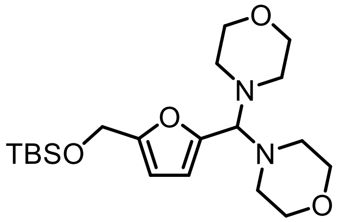
(5-(dimorpholinomethyl)furan-2-yl)methyl acetate 3



The title compound was prepared according to the general procedure A using 5 equiv of amine. The product was isolated in quantitative yield (193 mg) as a low melting point orange solid.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.24 (d, J = 3.2 Hz, 1H), 6.06 (d, J = 3.2 Hz, 1H), 4.89 (s, 2H), 3.59 (s, 1H), 3.55 (t, J = 4.6 Hz, 8H), 2.43-2.29 (m, 8H), 1.94 (s, 3H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 170.3, 150.9, 149.0, 110.7, 110.5, 82.5, 66.9, 57.9, 49.5, 20.7 ppm. **HRMS (ESI)** *m/z* calcd for $C_{16}H_{25}N_2O_5$ [M + H$^+$] 325.1758, found 325.1754.

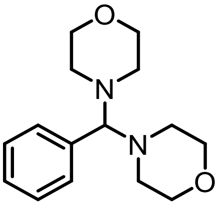
4,4'-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)dimorpholine 4



The title compound was prepared according to the general procedure B in 50 mg scale. The product was isolated in quantitative yield (82 mg) as a yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.14 (d, J = 3.1 Hz, 1H), 6.09 (d, J = 3.1 Hz, 1H), 4.57 (s, 2H), 3.65 (s, 1H) 3.63 (t, J = 4.7 Hz, 8H), 2.54-2.37 (m, 8H), 0.85 (s, 9H), 0.05 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 154.2, 149.7, 110.4, 107.3, 82.8, 67.2, 58.3, 49.8, 25.9, 18.4, -5.1 ppm. **HRMS (ESI)** *m/z* calcd for $C_{20}H_{37}N_2O_4Si$ [M + H$^+$] 397.2517, found 397.2509; *m/z* calcd for $C_{20}H_{36}N_2NaO_4Si$ [M + Na$^+$] 419.2337, found 419.2337.

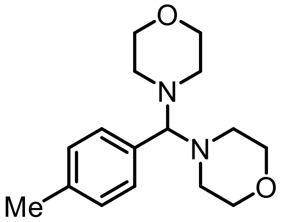
4,4'-(phenylmethylene)dimorpholine 5



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (493 mg) as a white solid. m.p. 100-101 °C. (reported m.p. 100-102 °C).[2] The spectral data are in agreement with the literature.[2]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.36-7.26 (m, 3H), 7.20-7.17 (m, 2H), 3.65 (t, J = 4.7 Hz, 8H), 3.63 (s, 1H), 2.47-2.36 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 134.0, 128.8, 127.8, 127.8, 89.1, 67.2, 49.5 ppm.

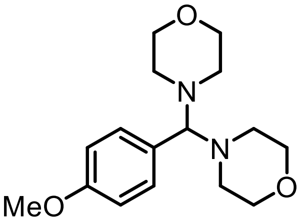
4,4'-(p-tolylmethylene)dimorpholine 6



The title compound was prepared according to the general procedure A. The product was isolated in 98 % yield (421 mg) as a white solid. m.p. 89-90 °C. (reported m.p. 89-92 °C).[3] The spectral data are in agreement with the literature.[3,4]

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.98 (d, J = 8.0 Hz, 2H), 6.92 (d, J = 8.0 Hz, 2H), 3.48 (t, J = 4.1 Hz, 8H), 3.44 (s, 1H), 2.31-2.16 (m, 8H), 2.16 (s, 3H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 136.5, 130.5, 128.2, 127.9, 88.3, 66.5, 49.0, 20.5 ppm.

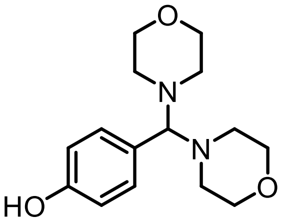
4,4'-((4-methoxyphenyl)methylene)dimorpholine 7



The title compound was prepared according to the general procedure A using 4 equiv of morpholine. The product was isolated in 95 % yield (408 mg) as a white solid. m.p. 110-113 °C. (reported m.p. 110-112 °C).[3] The spectral data are in agreement with the literature.[3]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 3.70 (s, 3H), 3.57 (t, J = 4.6 Hz, 8H), 3.51 (s, 1H), 2.40-2.29 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 159.0, 129.6, 126.1, 112.9, 88.3, 66.9, 54.9, 49.4 ppm.

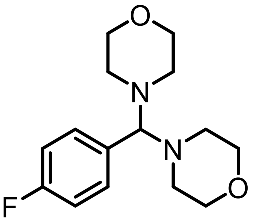
4-(dimorpholinomethyl)phenol 8



The title compound was prepared according to the general procedure B using 4 equiv of morpholine. The product was isolated in 96 % yield (492 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.87 (d, J = 8.2 Hz, 2H), 6.58 (d, J = 8.2 Hz, 2H), 3.50 (t, J = 4.6 Hz, 8H), 3.41 (s, 1H), 2.32-2.22 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 156.7, 129.8, 124.6, 114.6, 88.3, 66.9, 49.3 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{15}H_{22}N_2KO_3$ [M+K$^+$] 317.1262, found 317.1261.

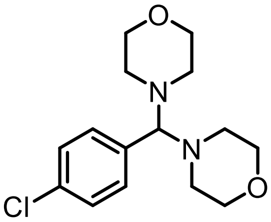
4,4'-((4-fluorophenyl)methylene)dimorpholine 9



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (450 mg) as a yellow solid. m.p. 110-112 ^{o}C. (reported m.p. 111-111.5 ^{o}C).[5] The spectral data are in agreement with the literature.[6]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.13 (dd, J = 8.7 Hz, J = 5.62 Hz, 2H), 6.99 (t, J = 8.7 Hz, 2H), 3.62 (t, J = 4.7 Hz, 8H), 3.59 (s, 1H), 2.38-2.30 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 163.9, 160.6, 130.2, 130.1, 129.9, 129.8, 114.8, 114.5, 88.2, 67.1, 49.4 ppm.

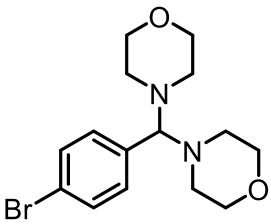
4,4'-((4-chlorophenyl)methylene)dimorpholine 10



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (422 mg) as a white solid. m.p. 132-133 ^{o}C. (reported m.p. 133-137 ^{o}C).[3] The spectral data are in agreement with the literature.[3]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.18 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 3.52 (t, J = 4.6 Hz, 8H), 3.49 (s, 1H), 2.32-2.20 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 133.3, 132.5, 129.9, 127.9, 88.2, 67.0, 49.4 ppm.

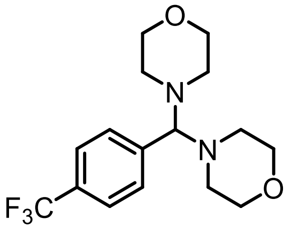
4,4'-((4-bromophenyl)methylene)dimorpholine 11



The title compound was prepared according to the general procedure A. The product was isolated in 98 % (629 mg) as a white solid. m.p. 139-140 °C. (reported m.p. 138.6-140 °C).[7] The spectral data are in agreement with the literature.[8]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.47 (d, J = 8.4, 2H), 7.07 (d, J = 8.4 Hz, 2H), 3.65 (t, J = 4.7 Hz, 8H), 3.61 (s, 1H), 2.45-2.33 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 133.2, 131.1, 130.5, 121.8, 88.5, 67.2, 49.6 ppm.

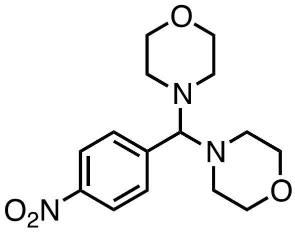
4,4'-((4-(trifluoromethyl)phenyl)methylene)dimorpholine 12



The title compound was prepared according to the general procedure B. The product was isolated in 94 % yield (356 mg) as a white solid. m.p. 188-190 °C. (reported m.p. 188-189 °C).[3] The spectral data are in agreement with the literature.[3]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.59 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 3.70 (s, 1H) 3.65 (t, J = 4.7 Hz, 8H), 2.47-2.33 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 138.2, 130.1 (q, $^2J_{CF}$ = 32.3 Hz), 129.0, 124.8 (q, $^3J_{CF}$ = 3.8 Hz), 124.2 (q, $^1J_{CF}$ = 272.0 Hz), 88.5, 67.1, 49.5 ppm.

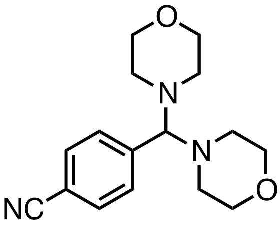
4,4'-((4-nitrophenyl)methylene)dimorpholine 13



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (407 mg) as a yellow solid. m.p. 180-182 °C. (reported m.p. 180-182 °C).[4] The spectral data are in agreement with the literature.[3,4]

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.18 (d, J = 8.7 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 3.74 (s, 1H), 3.63 (t, J = 4.6 Hz, 8H), 2.45-2.31 (m, 8H) ppm.**^{13}C NMR (75 MHz, CDCl$_3$)** δ 147.6, 141.6, 129.3, 123.1, 88.1, 67.0, 49.4 ppm.

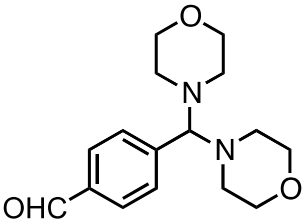
4-(dimorpholinomethyl)benzonitrile 14



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (439 mg) as a faint yellow solid. m.p. 170-171 ^{o}C. (reported m.p. 173-175 ^{o}C).[3] The spectral data are in agreement with the literature.[3]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.53 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.60 (s, 1H), 3.52 (t, J = 4.0 Hz, J = 2.5 Hz, 8H), 2.29-2.21 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 139.2, 131.3, 129.0, 118.4, 111.2, 87.8, 66.6, 49.0 ppm.

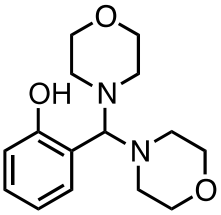
4-(dimorpholinomethyl)benzaldehyde 15



The title compound was prepared according to the general procedure A. The product was isolated as a mixture of the monoaminal and diaminal product in a ratio of 1:0.1 (404 mg) as a yellowish solid.

^{1}H NMR (300 MHz, CDCl$_3$) δ 9.95 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 3.68 (s, 1H), 3.61 (t, J = 4.7 Hz, 8H), 2.42-2.32 (m, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 191.7, 141.1, 136.0, 129.2, 128.1, 88.5, 67.0, 49.4 ppm. **HRMS (ESI):** m/z calculated for $C_{16}H_{23}N_2O_3$ [M+H$^+$] 291.1703, found 291.1684; m/z calculated for $C_{16}H_{22}N_2NaO_3$ [M+Na$^+$] 313.1523, found 313.1609.

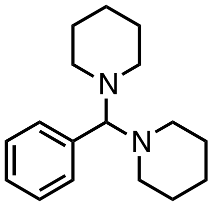
2-(dimorpholinomethyl)phenol 16



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (512 mg) as a white solid. m.p. 122-125 ^{o}C. (reported m.p. 123-124 ^{o}C).[9] The spectral data are in agreement with the literature.[10]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.16-7.10 (m, 1H), 6.78-6.73 (m, 3H), 3.70 (s, 1H), 3.65-3.62 (m, 8H), 2.50 (t, J = 4.9 Hz, J = 3.8 Hz, 8H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 157.0, 130.0, 129.3, 118.8, 117.0, 116.2, 89.4, 66.7, 49.4 ppm.

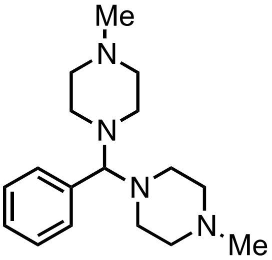
1,1'-(phenylmethylene)dipiperidine 17



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (486 mg) as a white solid. m.p. 80-82 °C. (reported m.p. 82.5-84 °C).[11] The spectral data are in agreement with the literature.[12]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.26-7.14 (m, 5H), 3.55 (s, 1H), 2.34-2.31 (m, 8H), 1.52-1.45 (m, 8H), 1.35-1.28 (m, 4H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 135.9, 128.4, 127.1, 126.8, 89.6, 50.0, 26.1, 25.2 ppm.

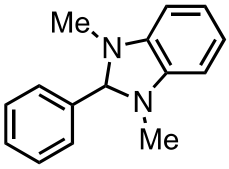
4,4'-(phenylmethylene)bis(1-methylpiperazine) 18



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (544 mg) as a yellow solid. m.p 66-68 °C.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.19-7.05 (m, 5H), 3.55 (s, 1H), 2.34 (m, 16H), 2.13 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 134.5, 128.5, 127.4, 127.3, 88.3, 55.3, 48.5, 45.9 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{17}H_{29}N_4$ [M+H$^+$] 289.23867, found 289.23591.

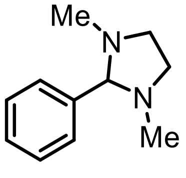
1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole 19



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (422 mg) as a dark brown solid. m.p. 90-92 °C (reported m.p. 82.5-84 °C).[13] The spectral data are in agreement with the literature.[14,15]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50-7.46 (m, 2H), 7.32-7.30 (m, 3H), 6.64-6.61 (m, 2H), 6.36-6.33 (m, 2H), 4.77 (s, 1H), 2.46 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 142.2, 139.1, 129.4, 128.9, 128.6, 119.4, 105.8, 94.1, 33.3 ppm.

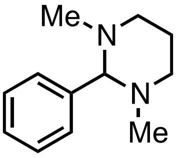
1,3-dimethyl-2-phenylimidazolidine 20



The title compound was prepared according to the general procedure B. The product was isolated in 90% yield (150 mg) as a transparent oil. The spectral data are in agreement with the literature.[3]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.23-7.09 (m, 5H), 3.19-3.17 (m, 2H), 3.05 (s, 1H), 2.35 – 2.31 (m, 2H), 1.97 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 139.7, 128.8, 128.5, 128.2, 92.4, 53.3, 39.4 ppm.

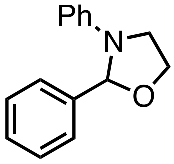
1,3-dimethyl-2-phenylhexahydropyrimidine 21



The title compound was prepared according to the general procedure B. The product was isolated in 98% yield (350 mg) as a transparent oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40-7.30 (m, 5H), 3.08-3.03 (m, 2H), 2.89 (s, 1H), 2.17-2.15 (m, 3H), 1.88 (s, 6H), 1.66-1.59 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 141.1, 128.9, 128.4, 128.3, 92.5, 55.9, 43.2, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{13}H_{23}N_2O$ [M+CH$_3$OH+H$^+$] 223.18049, found 223.17528.

2,3-diphenyloxazolidine 22

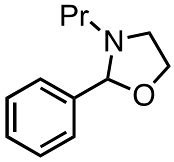


The title compound was prepared according to the general procedure B. The product was further purified by recrystallization in 94 % yield (423 mg) as white crystals. m.p. 85-86 ^{o}C. (reported m.p. 84-85 ^{o}C). [16]

The spectral data are in agreement with the literature.[17]

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.27 (dd, J = 7.6 Hz, J = 1.7 Hz, 2H), 7.16-7.09 (m, 3H), 6.97 (t, J = 8.0 Hz, J = 7.3 Hz, 2H), 6.56 (t, J = 7.3 Hz, 1H), 6.31 (d, J = 8.0 Hz, 2H), 5.70 (s, 1H), 3.80 (dd, J = 7.5 Hz, J = 5.0 Hz, 2H), 3.44-3.38 (m, 1H), 3.21 (q, J = 7.6 Hz, 1H) ppm**.** **^{13}C NMR (75 MHz, CDCl$_3$)** δ 145.8, 139.9, 129.2, 128.9, 128.7, 127.1, 117.7, 113.1, 91.8, 65.1, 48.1 ppm.

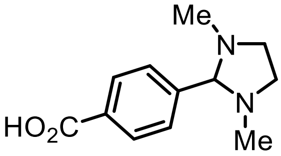
2-phenyl-3-propyloxazolidine 23



The title compound was prepared according to the general procedure B. The product was isolated in quantitative yield (360 mg) as a clear blue liquid. The spectral data are in agreement with the literature.[18]

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.92 (dd, J = 7.7 Hz, J = 1.7 Hz, 2H), 6.79 - 6.69 (m, 3H), 4.26 (s, 1H), 3.49-3.37 (m, 2H), 2.76-2.70 (m, 1H), 2.07-1.86 (m, 2H), 1.72-1.64 (m, 1H), 0.98-0.85 (m, 2H), 0.30 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 139.7, 128.4, 127.9, 127.5, 97.0, 65.0, 53.8, 51.7, 21.9, 11.6 ppm.

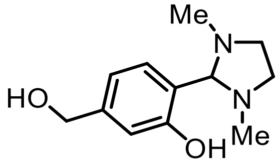
4-(1,3-dimethylimidazolidin-2-yl)benzoic acid 24



The title compound was prepared according to the general procedure A. The product was isolated in quantitative yield (413 mg) as brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.04 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.7 Hz, 2H), 3.47 – 3.42 (m, 3H), 2.68 – 2.62 (m, 2H), 2.20 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 172.0, 140.5, 129.6, 128.8 (2C), 90.7, 52.8, 39.0 ppm. **HRMS (ESI)** *m/z* calcd for $C_{12}H_{17}N_2O_2$ [M + H$^+$] 221.12845, found 221.12732.

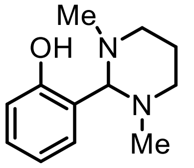
2-(1,3-dimethylimidazolidin-2-yl)-5-(hydroxymethyl)phenol 25



The title compound was prepared according to the general procedure B. The product was isolated in 94% yield (68 mg) as brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.17 (d, J = 8.2 Hz, 1H), 6.96 (s, 1H), 6.79 (d, J = 8.2 Hz, 1H), 4.54 – 4.40 (m, 2H), 3.42 – 3.37 (m, 3H), 2.58 – 2.53 (m, 2H), 2.25 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 157.9, 131.0, 129.9, 129.2, 120.3, 116.9, 91.7, 64.9, 52.2, 39.1 ppm. **HRMS (ESI)** *m/z* calcd for $C_{12}H_{19}N_2O_2$ [M + H$^+$] 223.14410, found 223.14336.

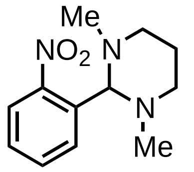
2-(1,3-dimethylhexahydropyrimidin-2-yl)phenol 26



The title compound was prepared according to the general procedure B. The product was isolated in quantitative yield (387 mg) as a transparent oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20 – 7.15 (m, 1H), 6.96 (dd, J = 7.4, 1.6 Hz, 1H), 6.85 – 6.72 (m, 1H), 6.76 – 6.71 (m, 1H), 3.13 (s, 1H), 3.07 – 3.02 (m, 2H), 2.21 – 2.12 (m, 3H), 2.05 (s, 6H), 1.65 – 1.60 (m, 1H). **^{13}C NMR (75 MHz, CDCl$_3$)** δ 156.9, 130.5, 129.6, 123.8, 118.3, 116.7, 90.9, 55.0, 43.00, 25.0 ppm. **HRMS (ESI-MS)** *m/z* calcd for compound $C_{13}H_{23}N_2O_2$ [M+CH$_3$OH+H$^+$] 239.17540, found 239.17494.

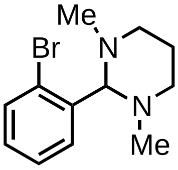
1,3-dimethyl-2-(2-nitrophenyl)hexahydropyrimidine 27



The title compound was prepared according to the general procedure B. The product was isolated in 96% (150 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.97 (dd, J = 8.3 Hz, J = 1.0 Hz, 1H), 7.61-7.56 (m, 2H), 7.44-7.38 (m, 1H), 3.50 (s, 1H), 3.04-2.99 (m, 2H), 2.22-2.04 (m, 3H), 1.91 (s, 6H), 1.64-1.59 (m, 1H) ppm.**^{13}C NMR (75 MHz, CDCl$_3$)** δ 151.8, 135.2, 132.7, 130.7, 128.9, 122.2, 84.0, 55.4, 42.6, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{12}H_{17}N_3NaO_2$ [M+Na$^+$] 258.1213, found 258.1221.

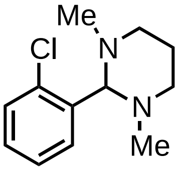
2-(2-bromophenyl)-1,3-dimethylhexahydropyrimidine 28



The title compound was prepared according to the general procedure B. The product was isolated in 89% yield (129 mg) as a brownish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.71 (dd, J = 7.8 Hz, J =1.8 Hz, 1H), 7.50 (dd, J = 8.0 Hz, 1H), 7.35-7.30 (m, 1H), 7.13 (ddd, J = 8.0 Hz, J = 7.2 Hz, J = 1.9 Hz, 1H), 3.69 (s, 1H), 3.07-3.01 (m, 2H), 2.28-2.19 (m, 2H), 2.16-2.03 (m, 1H), 1.94 (s, 6H), 1.66-1.59 (s, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 140.1, 132.1, 131.0, 129.5, 128.2, 125.7, 88.0, 55.7, 42.1, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{12}H_{18}BrN_2$ [M+H$^+$] 269.0648, found 269.0641.

2-(2-chlorophenyl)-1,3-dimethylhexahydropyrimidine 29

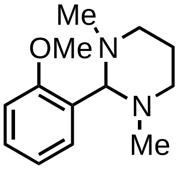


The title compound was prepared according to the general procedure B. The product was isolated in 87% yield (138 mg) as a brownish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.73 (dd, J = 7.6 Hz, J = 1.34 Hz, 1H), 7.30-7.25 (m, 2H), 7.21-7.16 (m, 1H), 3.70 (s, 1H), 3.06-3.01 (m, 2H), 2.25-2.17 (m, 2H), 2.15-2.06 (m, 1H), 1.92 (s, 6H), 1.65-1.58 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 138.7, 135.1, 130.5, 129.0, 128.8, 127.6, 85.5, 55.7, 42.1, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{12}H_{18}ClN_2$ [M+H$^+$] 225.1153, found 225.1147.

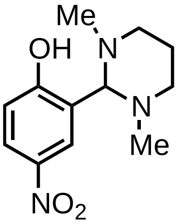
2-(2-methoxyphenyl)-1,3-dimethylhexahydropyrimidine 30

The title compound was prepared according to the general procedure B. The product was isolated in 90% yield (142 mg) as a white solid. m.p. 62-63 °C.



^{1}H NMR (300 MHz, CDCl$_3$) δ 7.62 (dd, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.24-7.17 (m, 1H), 6.98-6.93 (m, 1H), 6.83-6.80 (m, 1H), 3.78 (s, 3H), 3.64 (s, 1H), 3.05-2.99 (m, 2H), 2.26-2.05 (m, 3H), 1.90 (s, 6H), 1.60-1.53 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 158.4, 129.3, 129.2, 128.7, 121.4, 110.3, 81.8, 56.0, 55.6, 42.2, 25.2 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{13}H_{21}N_2O$ [M+H$^+$] 221.1648, found 221.1645.

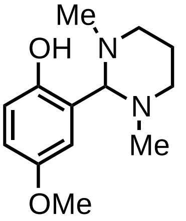
2-(1,3-dimethylhexahydropyrimidin-2-yl)-4-nitrophenol 31



The title compound was prepared according to the general procedure B. The product was isolated in 86% yield (130 mg) as a yellow solid. m.p 92-95ºC.

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.13 (dd, J = 9.0 Hz, J = 2.8 Hz, 1H), 7.96 (d, J = 2.8 Hz, 1H), 6.90 (d, J = 9.0 Hz, 1H), 3.31 (s, 1H), 3.12-3.07 (m, 2H), 2.28-2.19 (m, 2H), 2.10 (s, 6H), 2.06-1.96 (m, 1H), 1.72-1.66 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 163.7, 126.5, 126.2, 124.0, 117.2, 89.7, 54.5, 42.9, 24.7 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{12}H_{18}N_3O_3$ [M+H$^+$] 252.1343, found 252.1346.

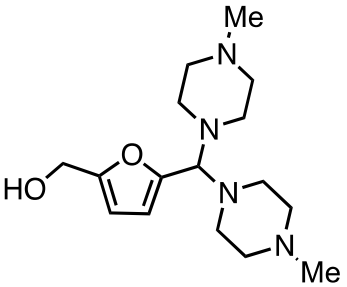
2-(1,3-dimethylhexahydropyrimidin-2-yl)-4-methoxyphenol 32



The title compound was prepared according to the general procedure B. The product was isolated in 92% (147 mg) as a yellow oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.76 (d, J = 2.4 Hz, 2H), 6.56 (dd, J = 2.2 Hz, J = 1.0 Hz, 1H), 3.73 (s, 3H), 3.06-3.02 (m, 3H), 2.19 - 2.02 (m, 9H), 1.64-1.58 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 151.9, 150.8, 124.4, 117.0, 116.5, 114.3, 91.0, 55.8, 55.0, 43.0, 25.0 ppm. **HRMS (ESI-MS)** *m/z* calculated for compound $C_{13}H_{21}N_2O_2$ [M+H$^+$] 237.1598, found 237.1583.

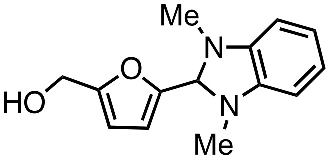
(5-(bis(4-methylpiperazin-1-yl)methyl)furan-2-yl)methanol 33



The title compound was prepared according to the general procedure A in 50 mg scale using 5 equiv of 1-methylpiperazine. The product was isolated in quantitative yield (122 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.95 (d, J = 3.1 Hz, 1H), 5.91 (d, J = 3.1 Hz, 1H), 4.22 (s, 2H), 3.53 (s, 1H), 2.22 (s, 16H), 2.04 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 154.7, 150.0, 109.8, 106.7, 81.9, 56.3, 54.9, 48.6, 45.6 ppm. **HRMS (ESI)** *m/z* calculated for $C_{11}H_{19}N_2O_2$ [M-$C_5H_{11}N_2$+H$^+$] 211.14410, found 211.14351.

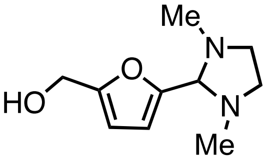
(5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol 34



The title compound was prepared according to the general procedure B. The product was isolated in quantitative yield (211 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.74 (dd, J = 5.5 Hz, J = 3.2 Hz, 2H), 6.52 (d, J = 3.2 Hz, 1H), 6.48 (dd, J = 5.5 Hz, J = 3.20 Hz, 2H), 6.30 (d, J = 3.2 Hz, 1H), 4.93 (s, 1H), 4.59 (s, 2H), 2.66 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 155.7, 150.9, 141.6, 138.3, 119.8, 119.1, 112.1, 110.5, 108.2, 106.6, 86.9, 57.4, 33.9, 31.1 ppm. **HRMS (ESI)** *m/z* calculated for $C_{14}H_{17}N_2O_2$ [M + H$^+$] 245.12845, found 245.13411.

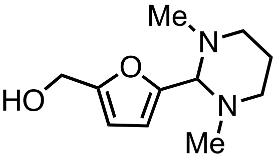
(5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol 35



The title compound was prepared according to the general procedure B. The product was isolated in 98 % yield (361 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.25 (d, J = 3.1 Hz, 1H), 6.12 (d, J = 3.1 Hz, 1H), 4.47 (s, 2H), 3.48 (s, 1H), 3.21 (q, J = 5.0 Hz, 2H), 2.48 (q, J = 5.0 Hz, 2H), 2.16 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 155.5, 151.4, 110.7, 107.4, 84.7, 57.2, 53.0, 39.8 ppm. **HRMS (ESI)** *m/z* calculated for $C_{10}H_{17}N_2O_2$ [M + H$^+$] 197.1285, found 197.1277.

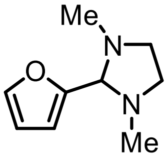
(5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol 36



The title compound was prepared according to the general procedure B in 400 mg scale. The product was isolated in quantitative yield (666 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.17 (d, J = 3.1 Hz, 1H), 6.10 (d, J = 3.1 Hz, 1H), 4.49 (s, 2H), 3.10 (s, 1H), 2.92-2.87 (m, 2H), 2.10-1.93 (m, 3H), 1.89 (s, 6H), 1.49-1.42 (m, 1H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 155.0, 151.4, 110.5, 107.0, 83.7, 56.9, 54.7, 42.5, 24.2 ppm. **HRMS (ESI)** *m/z* calculated for $C_{11}H_{19}N_2O_2$ [M + H$^+$] 211.1441, found 211.1436.

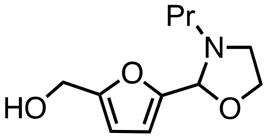
2-(furan-2-yl)-1,3-dimethylimidazolidine 37



The title compound was prepared according to the general procedure B. The product was isolated in quantitative yield (312 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29 (t, J = 0.9 Hz, J = 0.2 Hz, 1H), 6.25 (dd, J = 1.0 Hz, 1H), 6.19 (dd, J = 3.2 Hz, J = 1.8 Hz, 1H), 3.48 (s, 1H), 3.22-3.17 (m, 2H), 2.49-2.43 (m, 2H), 2.14 (s, 6H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 152.5, 142.7, 109.7, 109.4, 84.4, 53.0, 39.6 ppm.

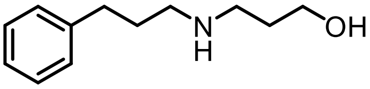
(5-(3-propyloxazolidin-2-yl)furan-2-yl)methanol 38



The title compound was prepared according to the general procedure B. The product was isolated in 95% yield (377 mg) as a brown oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 6.28 (d, J = 3.2 Hz, 1H), 6.15 (d, J = 6.2 Hz, 1H), 4.95 (s, 1H), 4.48 (s, 2H), 3.98-3.87 (m, 2H), 3.30-3.23 (m, 1H), 2.68-2.48 (m, 2H), 2.34-2.25 (m, 1H), 1.52-1.40 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H) ppm. **^{13}C NMR (75 MHz, CDCl$_3$)** δ 155.0, 152.3, 109.5, 107.9, 90.7, 65.0, 57.2, 55.1, 51.9, 22.0, 11.7 ppm. **HRMS (ESI)** *m/z* calcd for $C_{11}H_{18}NO_3$ [M+H$^+$] 212.1281, found 212.1273; *m/z* calcd for $C_{16}H_{17}NNaO_3$ [M+Na$^+$] 234.1101, found 234.1101.

Synthesis of 3-((3-phenylpropyl)amino)propan-1-ol 44



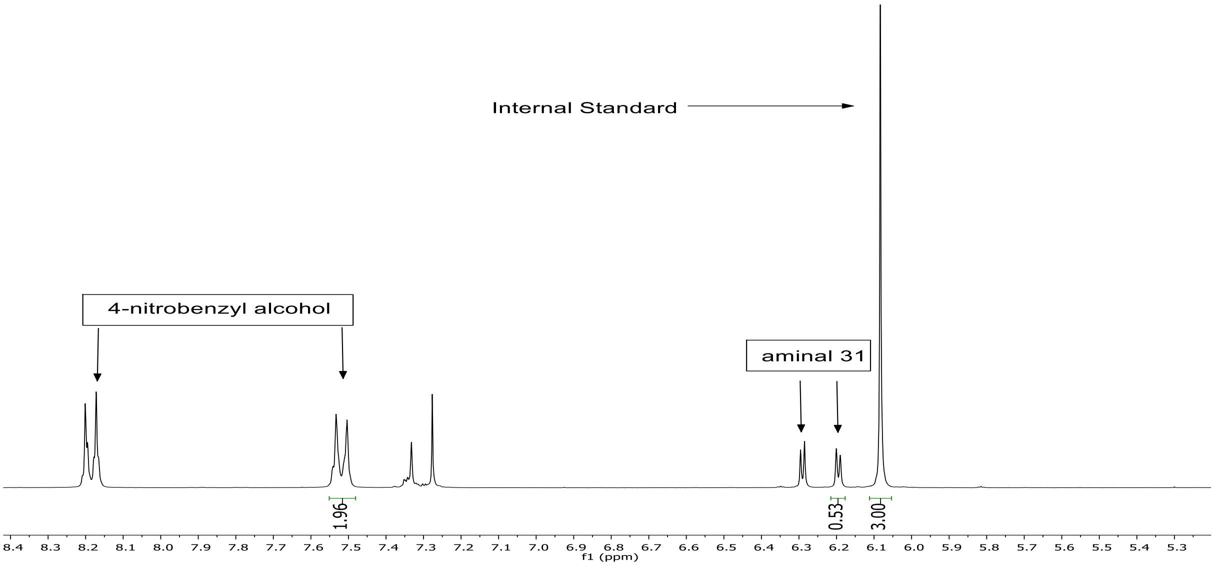
To a solution of 3-phenylpropanal (198 µL, 1.49 mmol) in methanol (1.49 mL, 1M) was added 3-aminopropan-1-ol (136 µL, 1.79 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour followed by the dropwise addition of NaBH$_4$ (68 mg, 1.79 mmol), stirred for 30 minutes followed by dropwise addition of water. Then, the mixture was extracted with dichloromethane (2x 20 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated under reduced pressure. The 3-((3-phenylpropyl)amino)propan-1-ol was obtained with 94% yield as a transparent yellowish oil.

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31-7.26 (m, 2H), 7.19 (t, *J* = 6.1 Hz, 3H), 3.81 (t, *J* = 5.3 Hz, 2H), 2.86 (t, *J* = 5.0 Hz, 2H), 2.68-2.62 (m, 4H), 1.86-1.76 (m, 2H), 1.72-1.65 (m, 2H) ppm.

^{13}C NMR (75 MHz, CDCl$_3$) δ 142.0, 128.5, 126.0, 100.1, 64.6, 50.2, 49.4, 33.7, 31.7, 30.8 ppm.

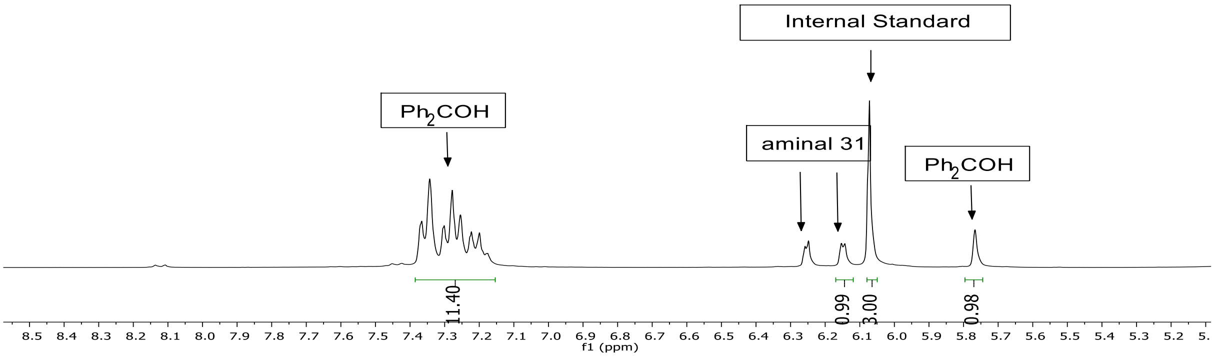
Procedure for the reduction of nitrobenzaldehyde in the presence of aminal 36

To a solution of 4-nitrobenzaldehyde (0.33 mmol, 50 mg) in methanol (0.1 M) was added aminal **36** (0.5 equiv, 0.165 mmol, 35 mg) followed by the dropwise addition of $NaBH_4$ (1 equiv, 0.33 mmol, 13 mg) was added at 0 ^{o}C The reaction was stirred for 1h after which was quenched with NH_4Cl and extracted with DCM. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in $CDCl_3$. Internal standard, 1,3,5-trimethoxybenzene (1 equiv, 0.33 mmol, 56 mg), was added and the crude was analyzed by ^{1}H NMR spectroscopy.



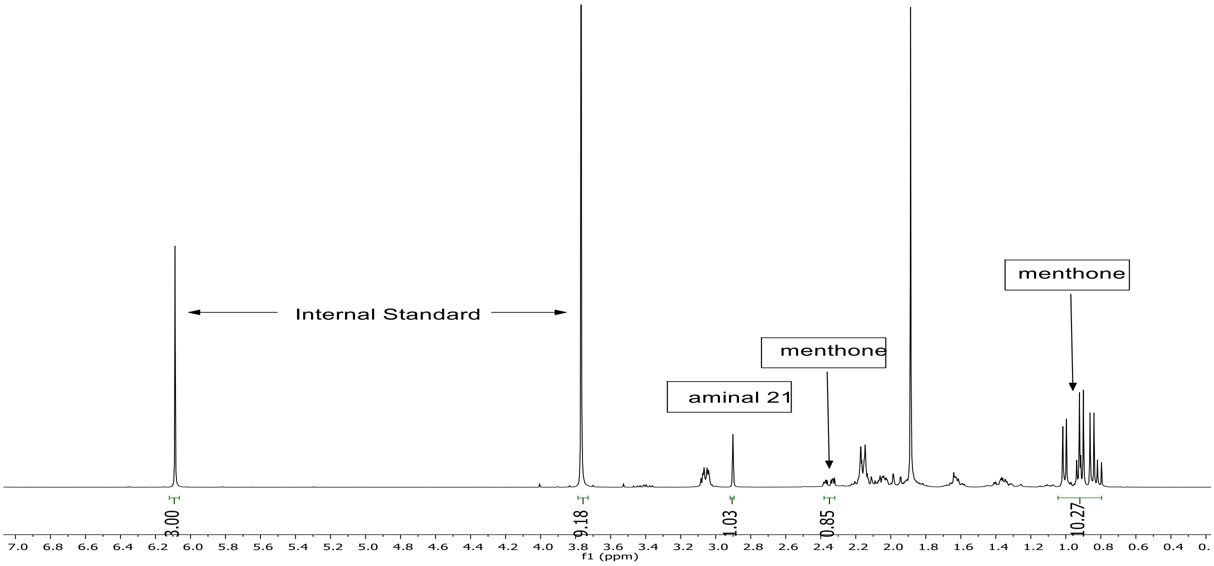
Procedure for the Grignard addition of PhMgBr to benzaldehyde in the presence of aminal 36

To a solution of benzaldehyde (0.47 mmol, 50 mg, 48 µL) in dry THF (0.1 M) was added aminal **36** (1 equiv, 0.47 mmol, 99 mg). Then, PhMgBr (3 equiv, 1.41 mmol, 1.41 mL of 1 M solution in THF) was added at 0 ^{o}C dropwise. The reaction was stirred for 12 h after which it was quenched with NH_4Cl and extracted with DCM. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in $CDCl_3$. Internal standard, 1,3,5-trimethoxybenzene (1 equiv, 0.47 mmol, 79 mg), was added and the crude was analysed by ^{1}H NMR spectroscopy.



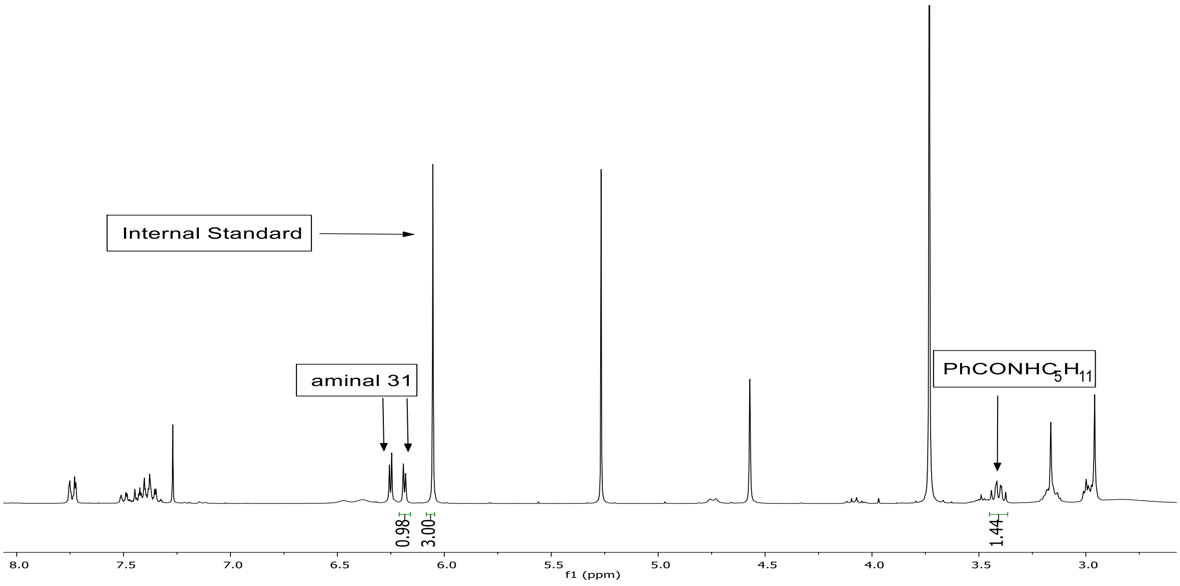
Procedure for the oxidation of menthol in the presence of aminal 21

To a solution of (-)-menthol (0.13 mmol, 20 mg) in dry DCM (0.1 M) was added aminal **21** (1 equiv, 0.13 mmol, 25 mg). Then, PCC (1.5 equiv, 0.19 mmol, 41 mg) was added at room temperature. The reaction was stirred for 4h after which the crude mixture was filtered through celite. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in $CDCl_3$. Internal standard, 1,3,5-trimethoxybenzene (1 equiv, 0.13 mmol, 21 mg), was added and the crude was analyzed by ^1H NMR spectroscopy.



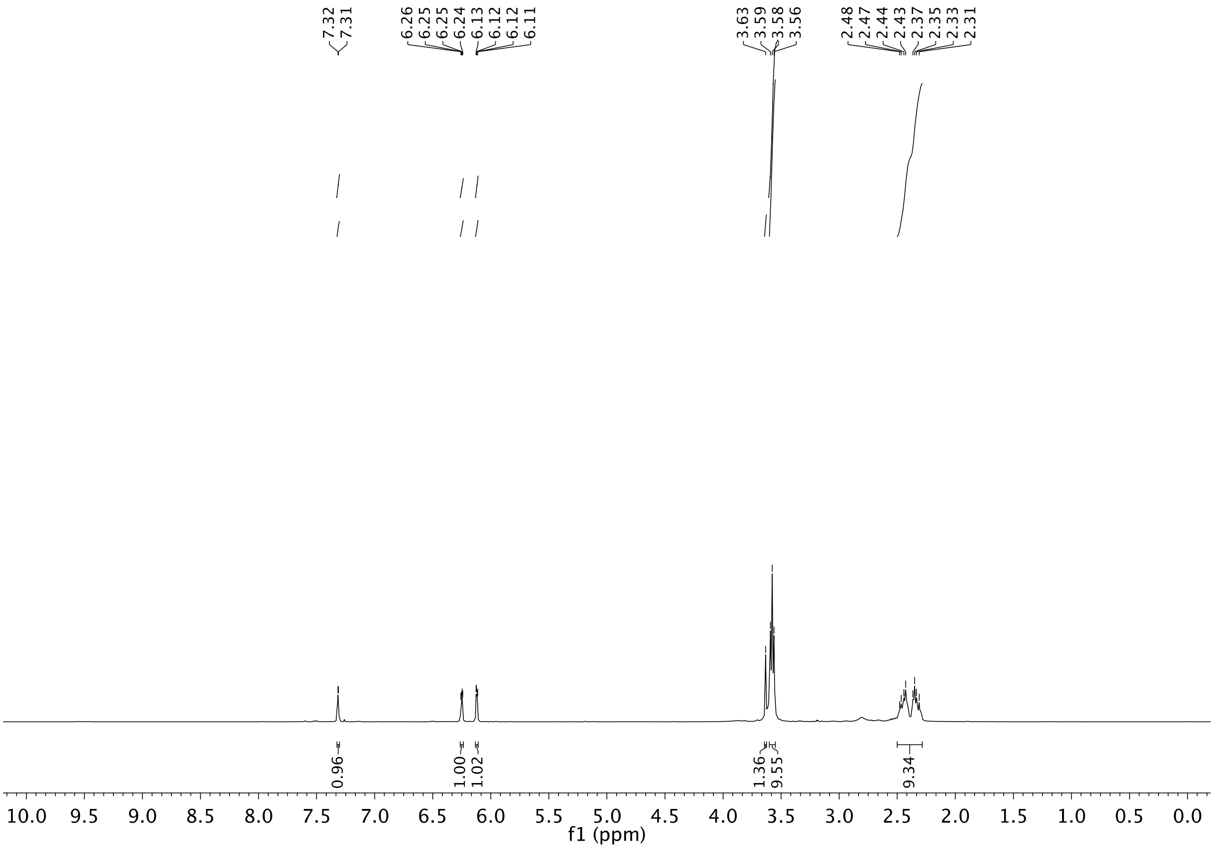
Procedure for the Steglich coupling of benzoic acid with pentylamine in the presence of aminal 36

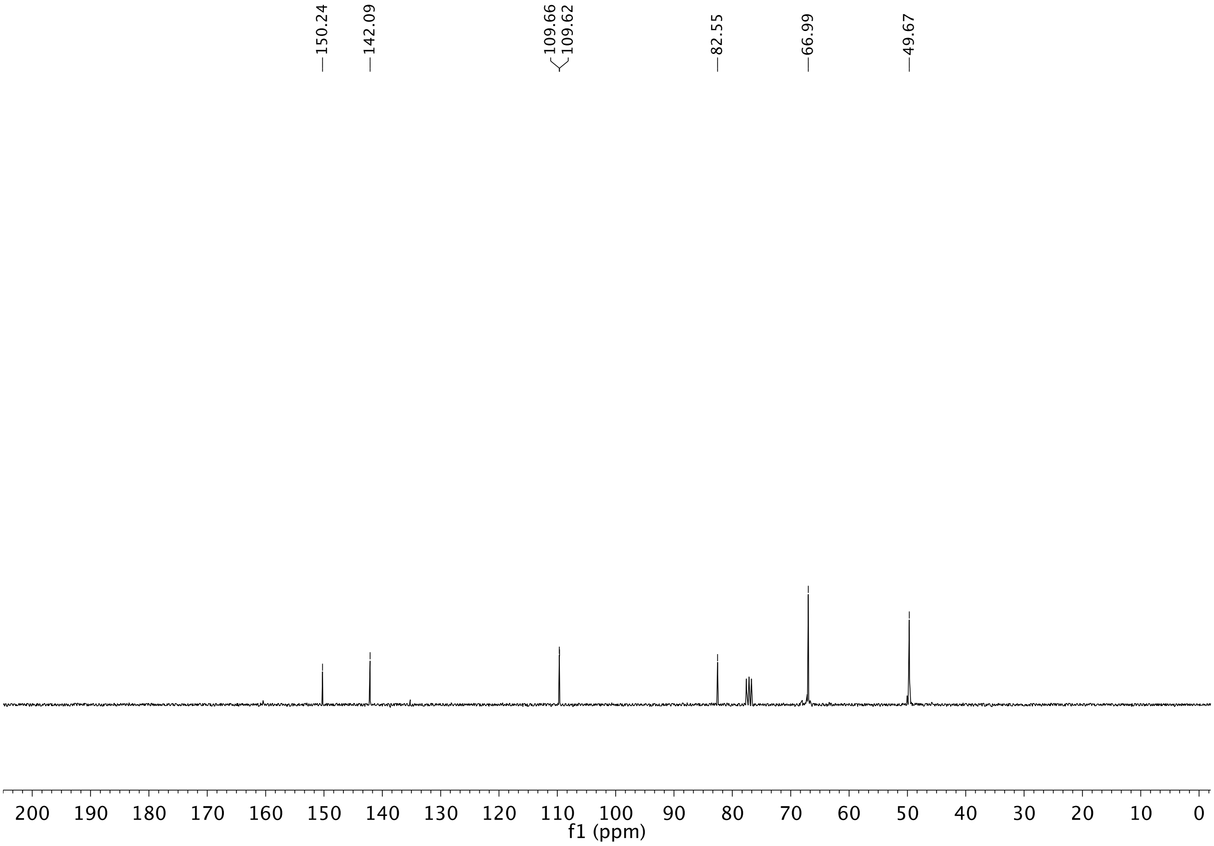
To a solution of benzoic acid (0.41 mmol, 50 mg) in dry DCM (0.1 M) was added aminal **36** (1 equiv, 0.41 mmol, 85 mg). Then, DCC (1.0 equiv, 0.41 mmol, 86 mg), DMAP (0.1 equiv, 0.04 mmol, 5 mg) and pentylamine (1 equiv, 0.41 mmol, 36 mg, 48 µL) were added at room temperature. The reaction was stirred for 12h followed by addition of water. The mixture was extracted with DCM. The solvent was evaporated under reduced pressure and the crude mixture was dissolved in $CDCl_3$. Internal standard, 1,3,5-trimethoxybenzene (1 equiv, 0.41 mmol, 69 mg), was added and the crude was analysed by ^1H NMR spectroscopy.



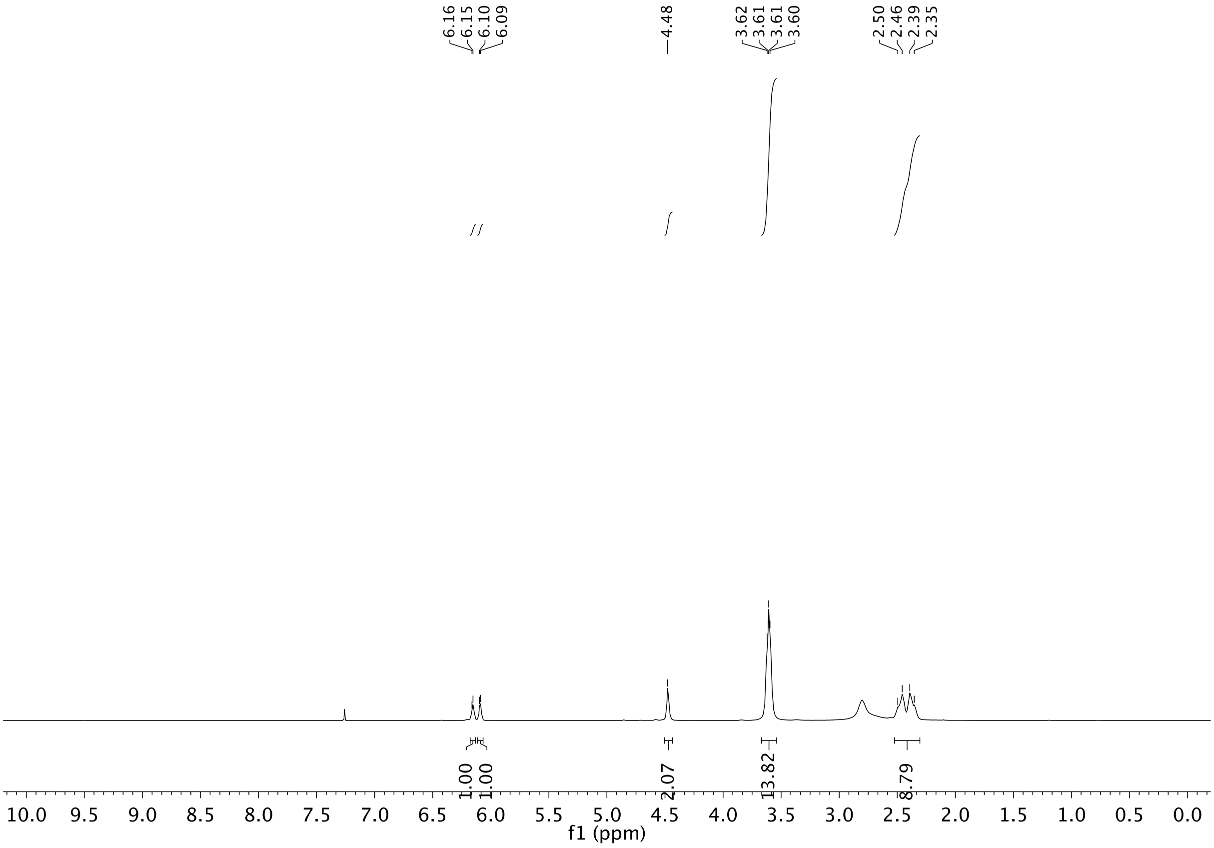
Copies of NMR spectra

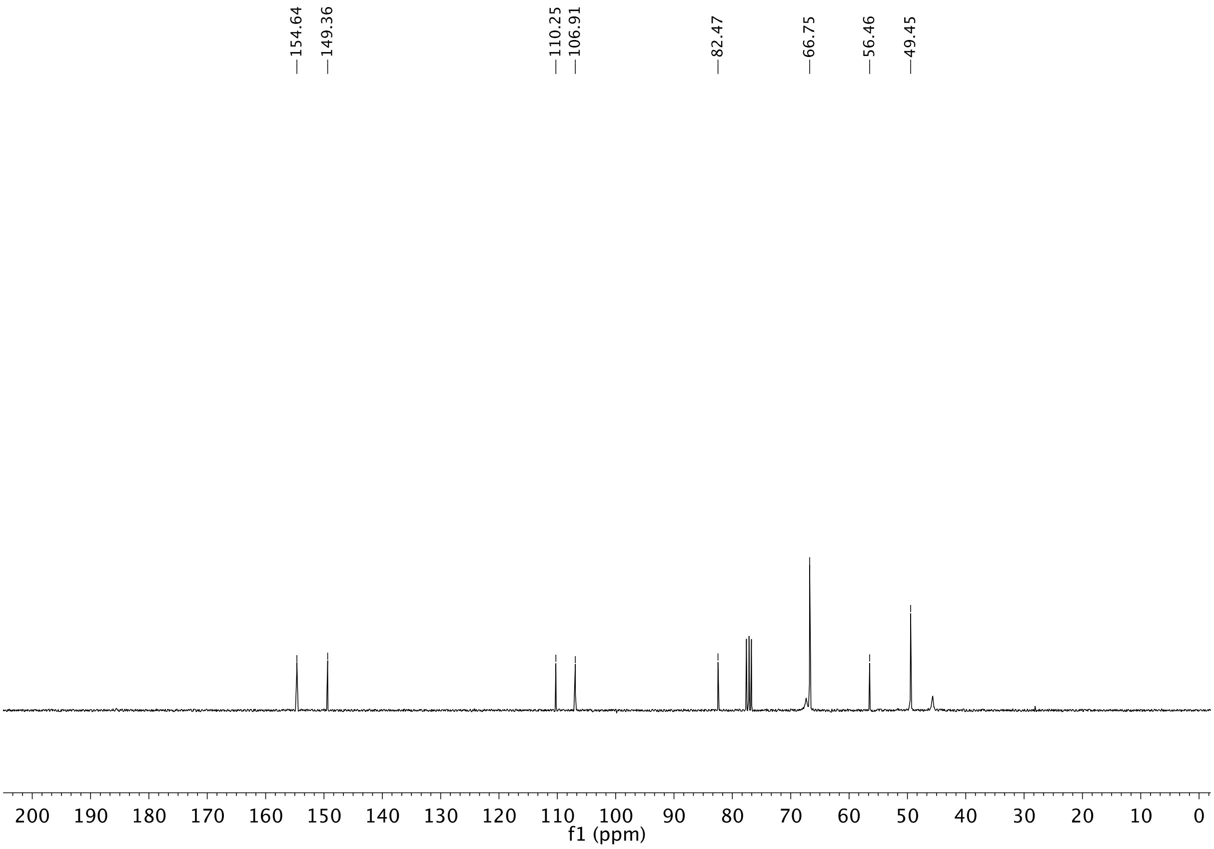
4,4'-(furan-2-ylmethylene)dimorpholine 1



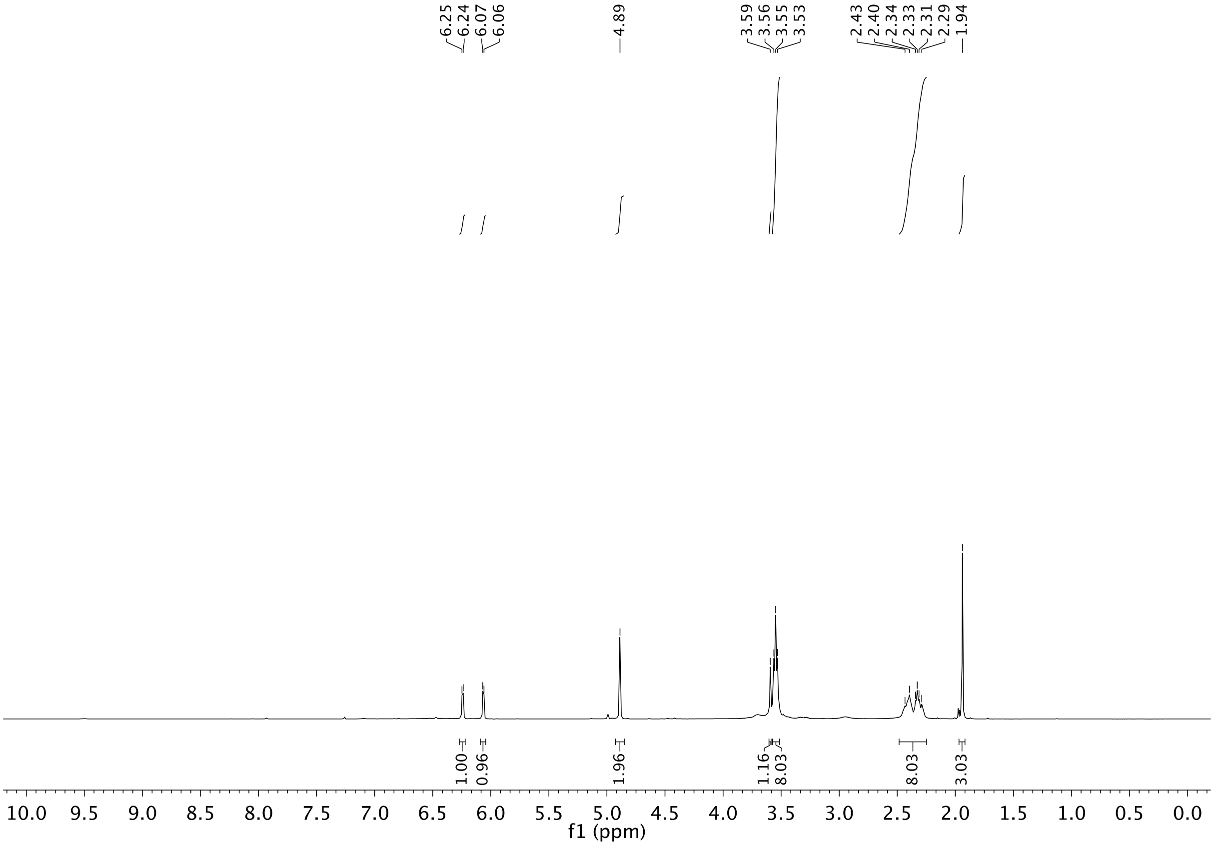


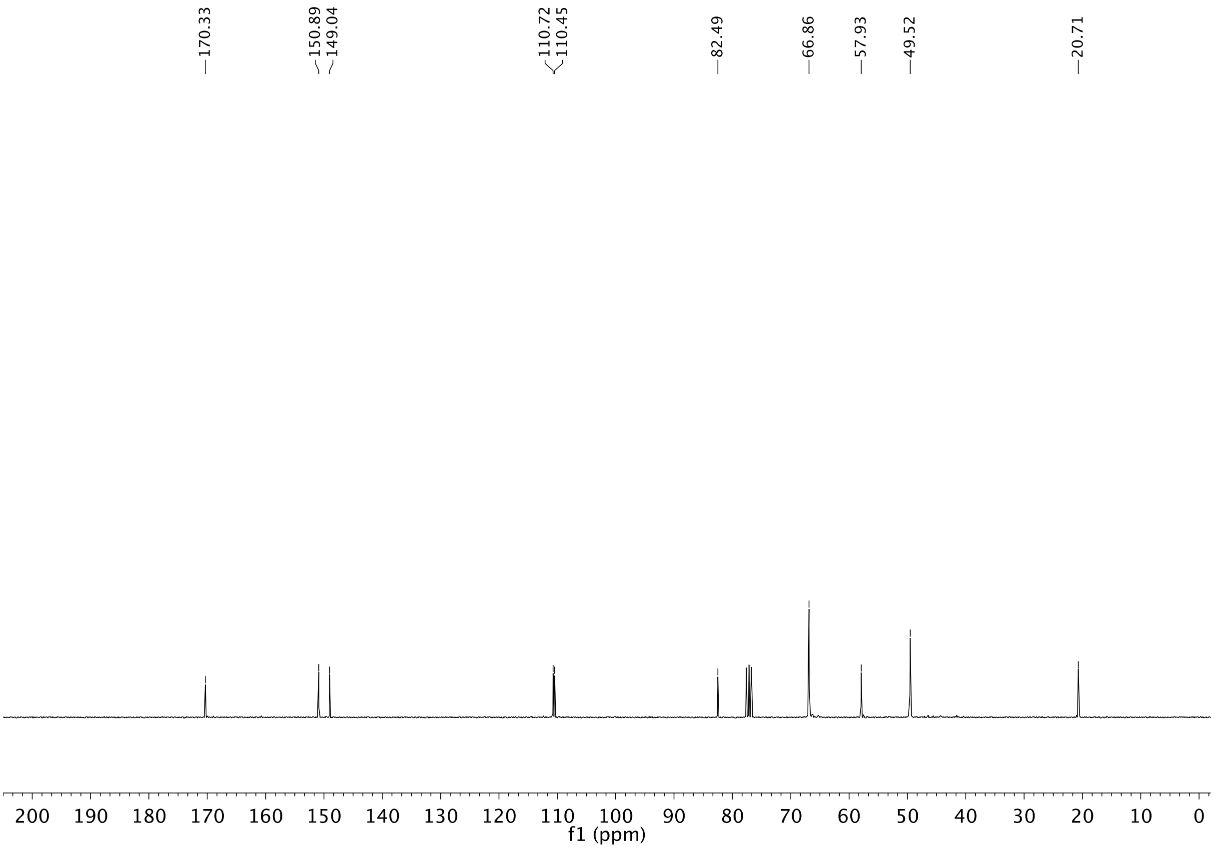
(5-(dimorpholinomethyl)furan-2-yl)methanol 2



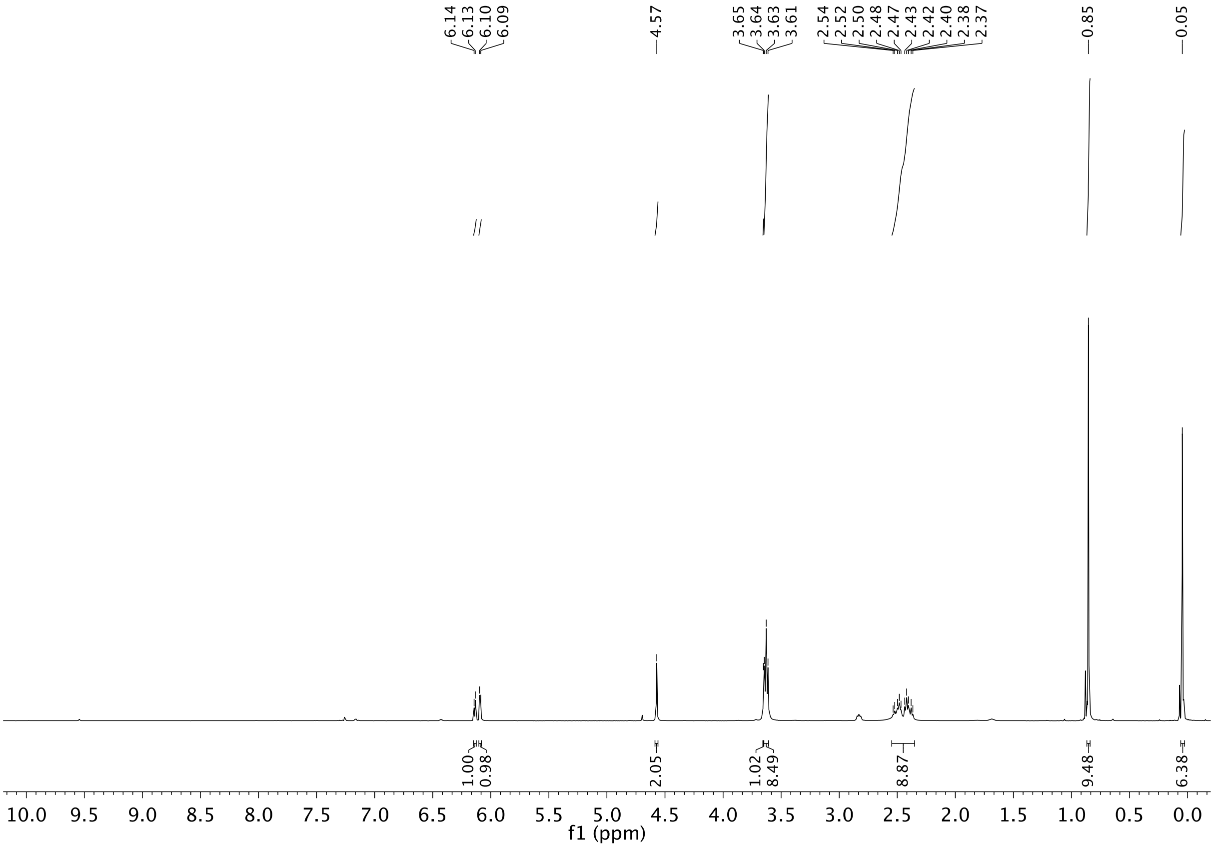


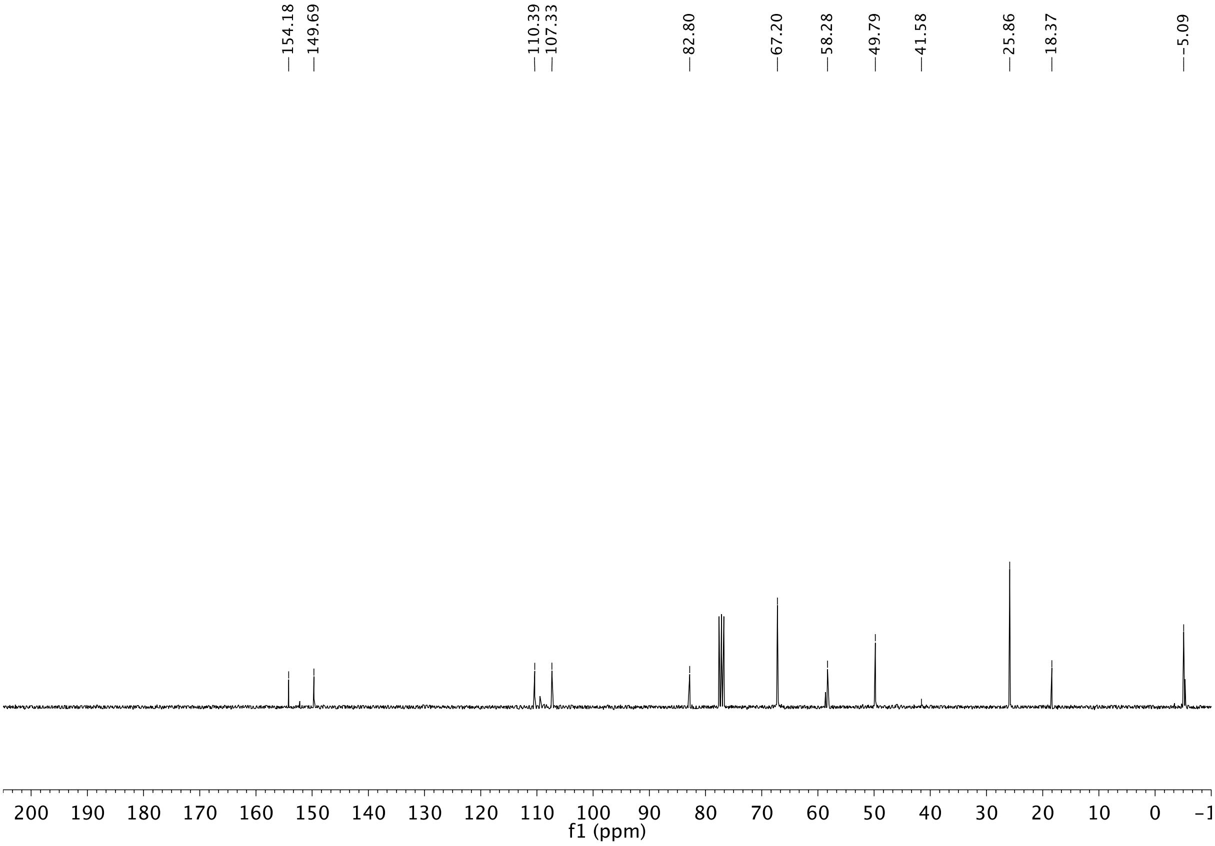
(5-(dimorpholinomethyl)furan-2-yl)methyl acetate 3



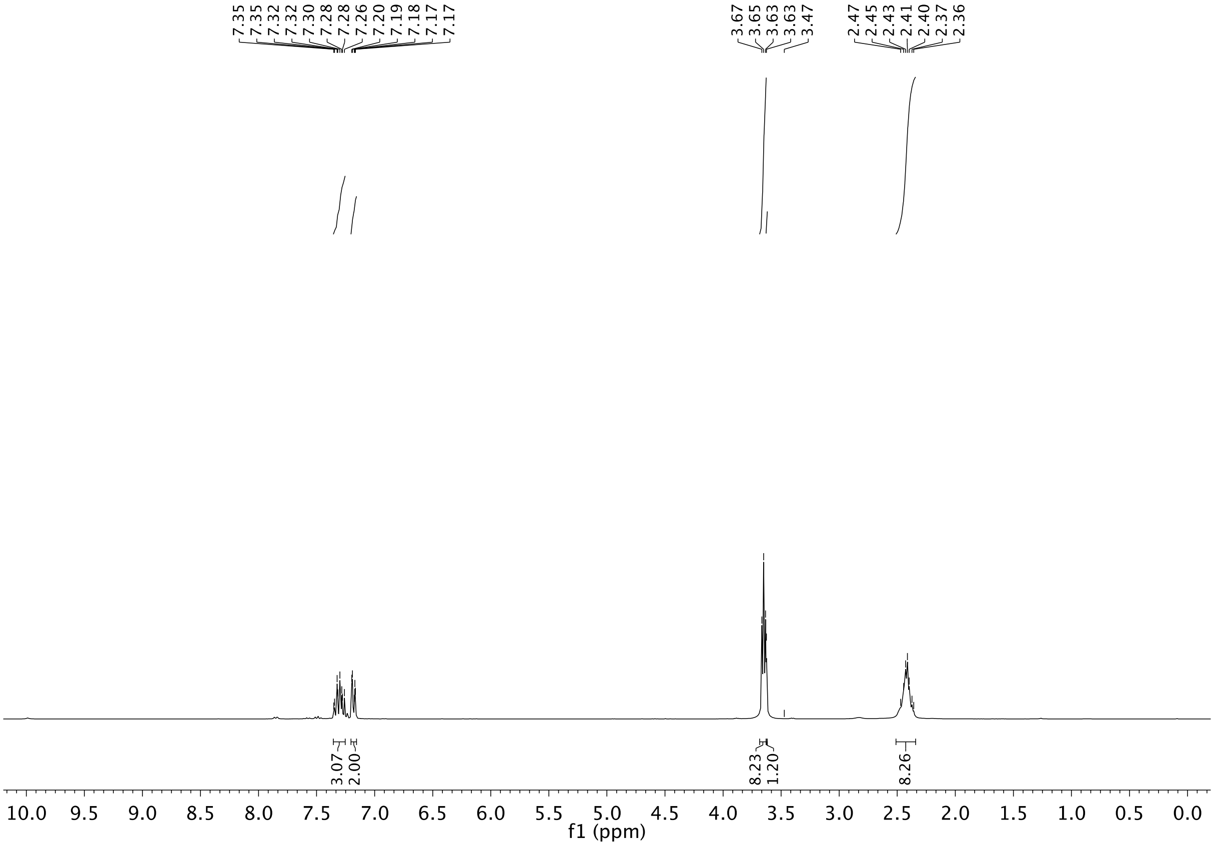


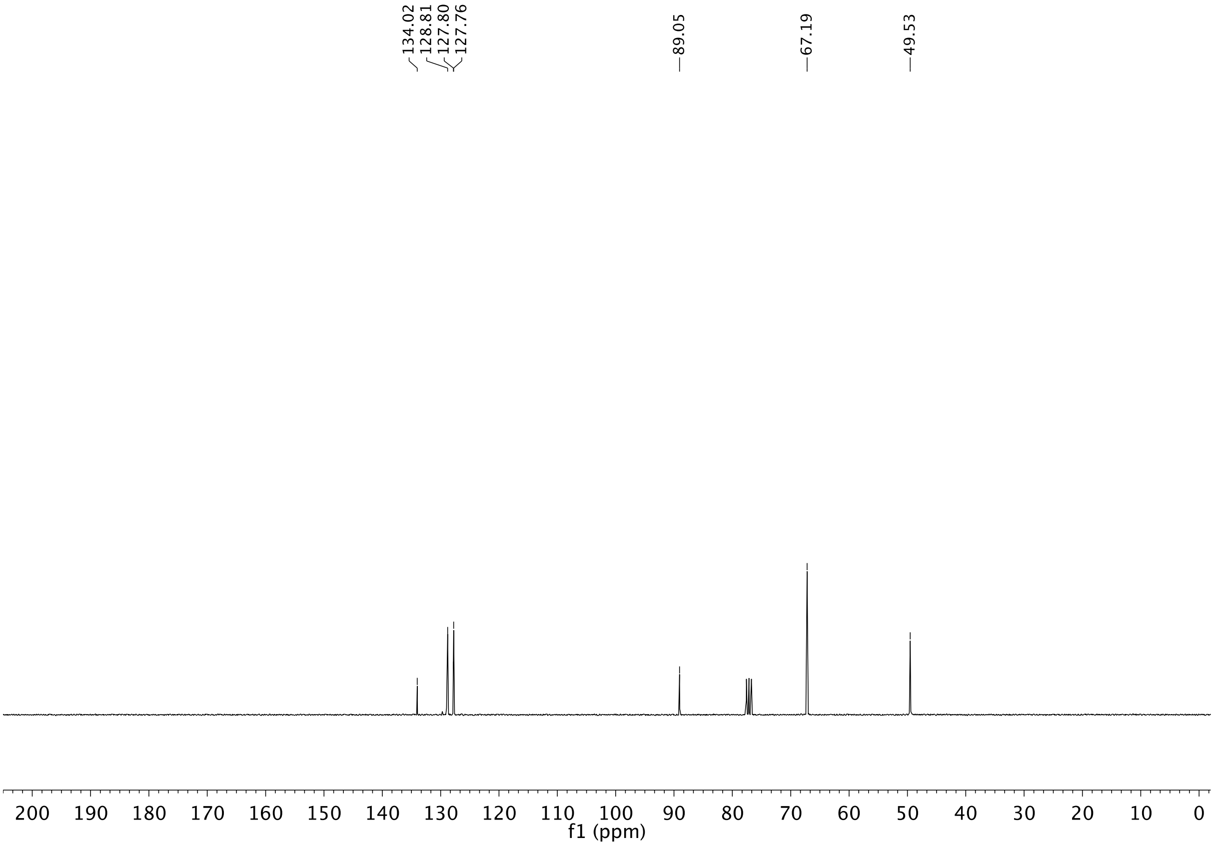
4,4'-((5-(((tert-butyldimethylsilyl)oxy)methyl)furan-2-yl)methylene)dimorpholine 4



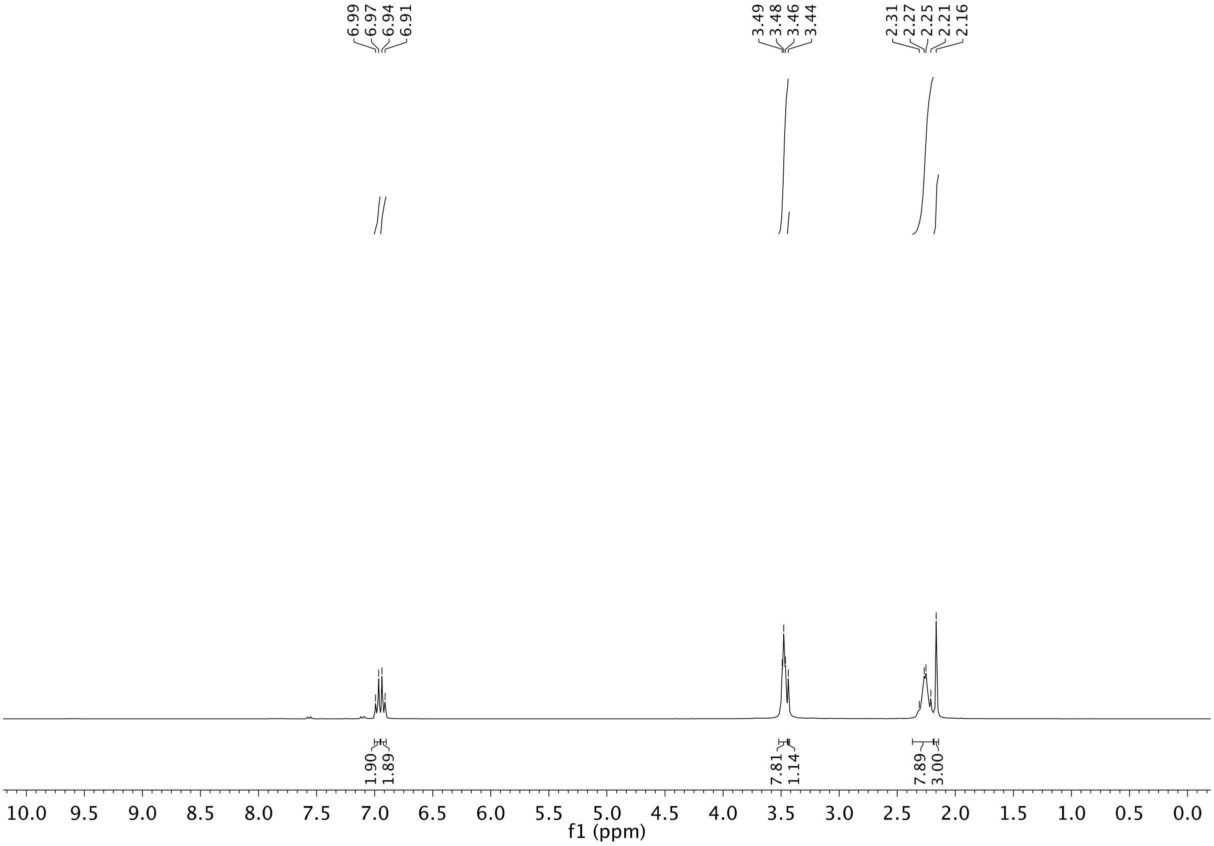


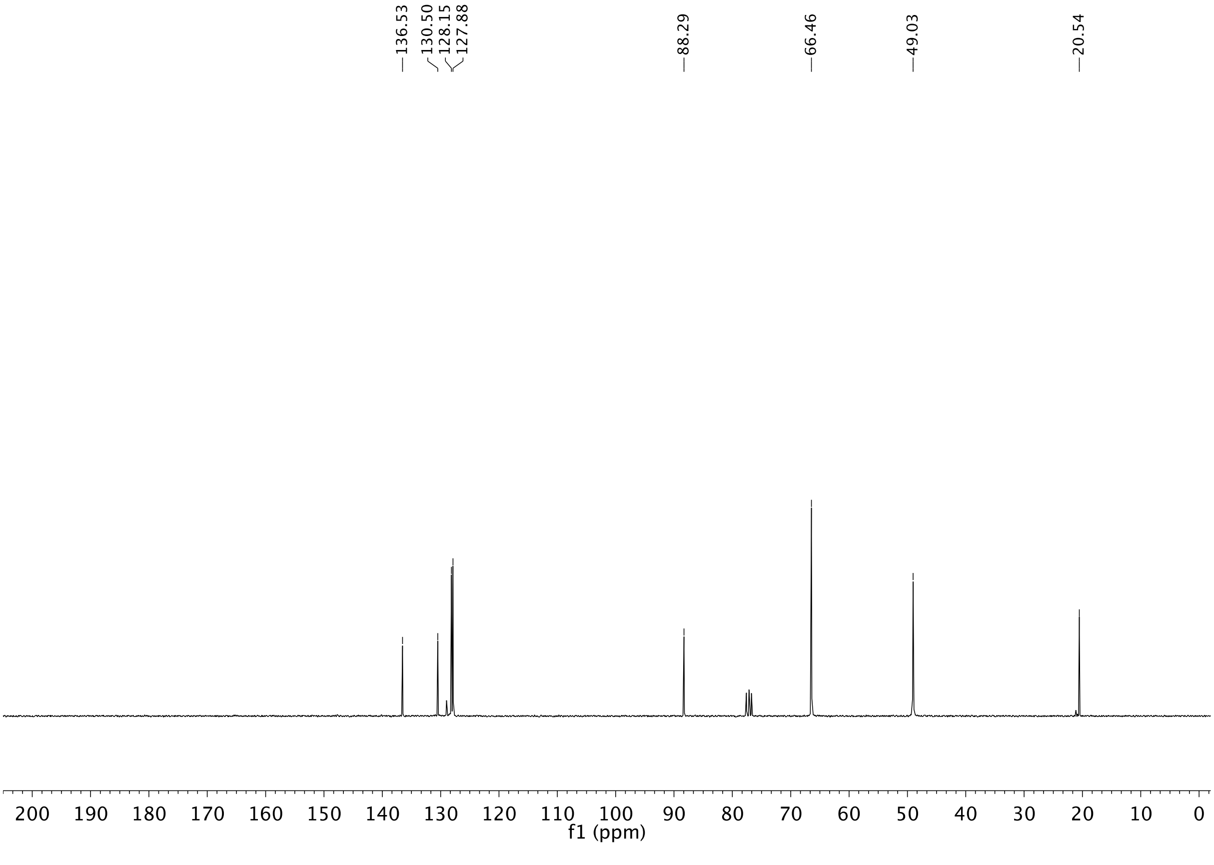
4,4'-(phenylmethylene)dimorpholine 5



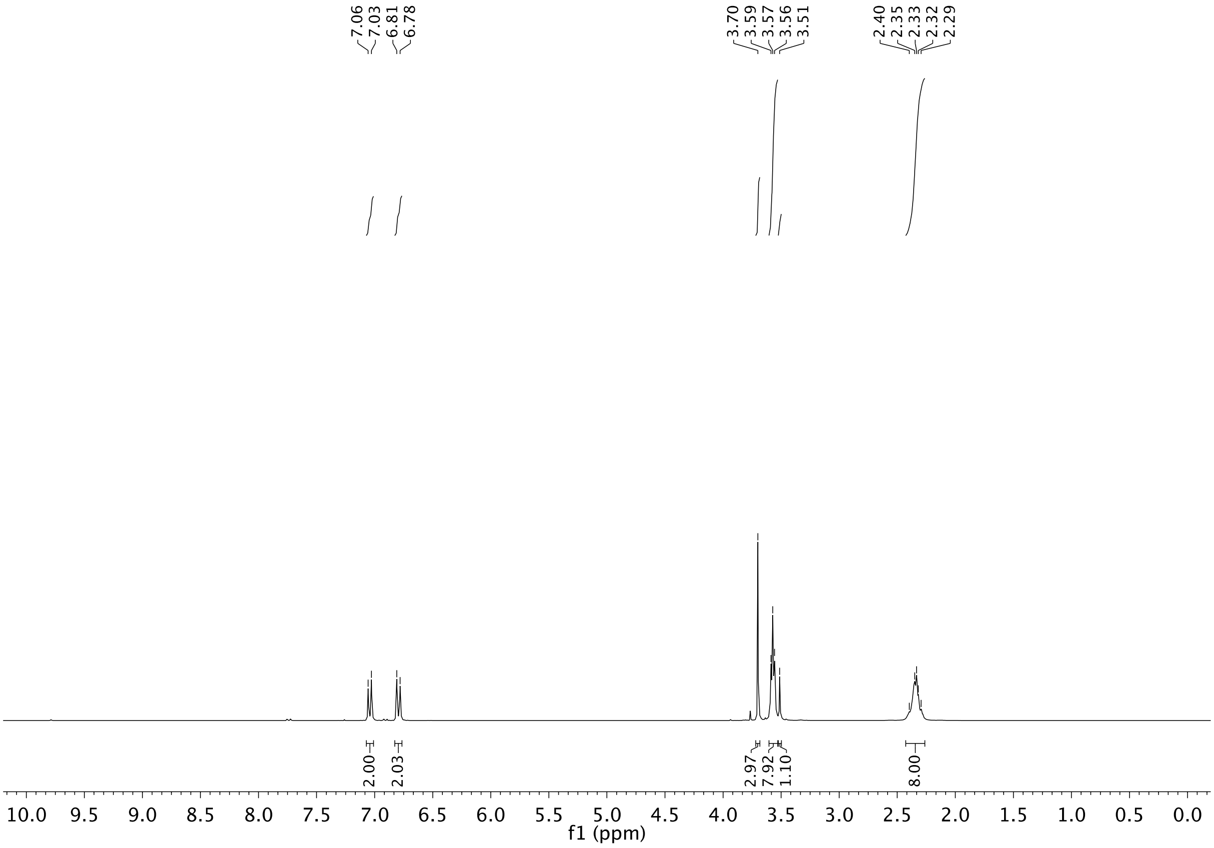


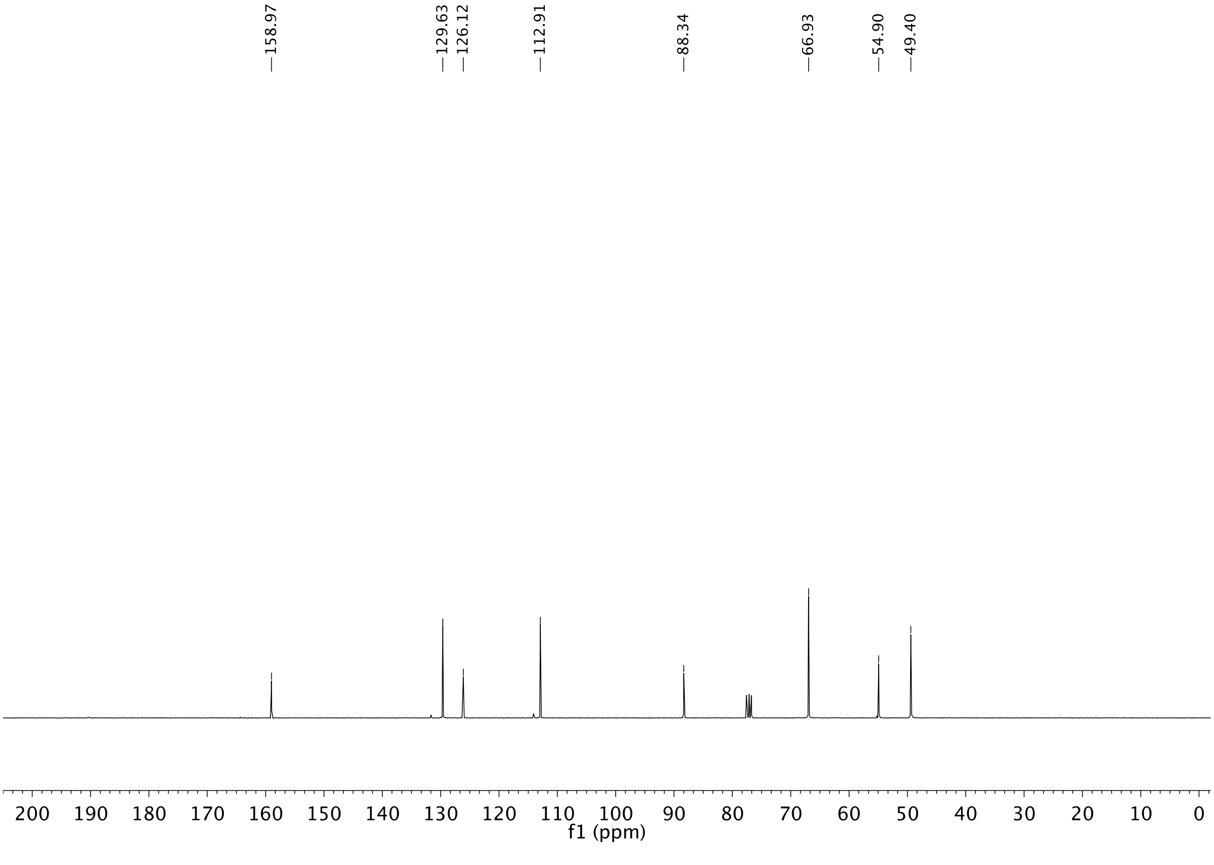
4,4'-(p-tolylmethylene)dimorpholine 6



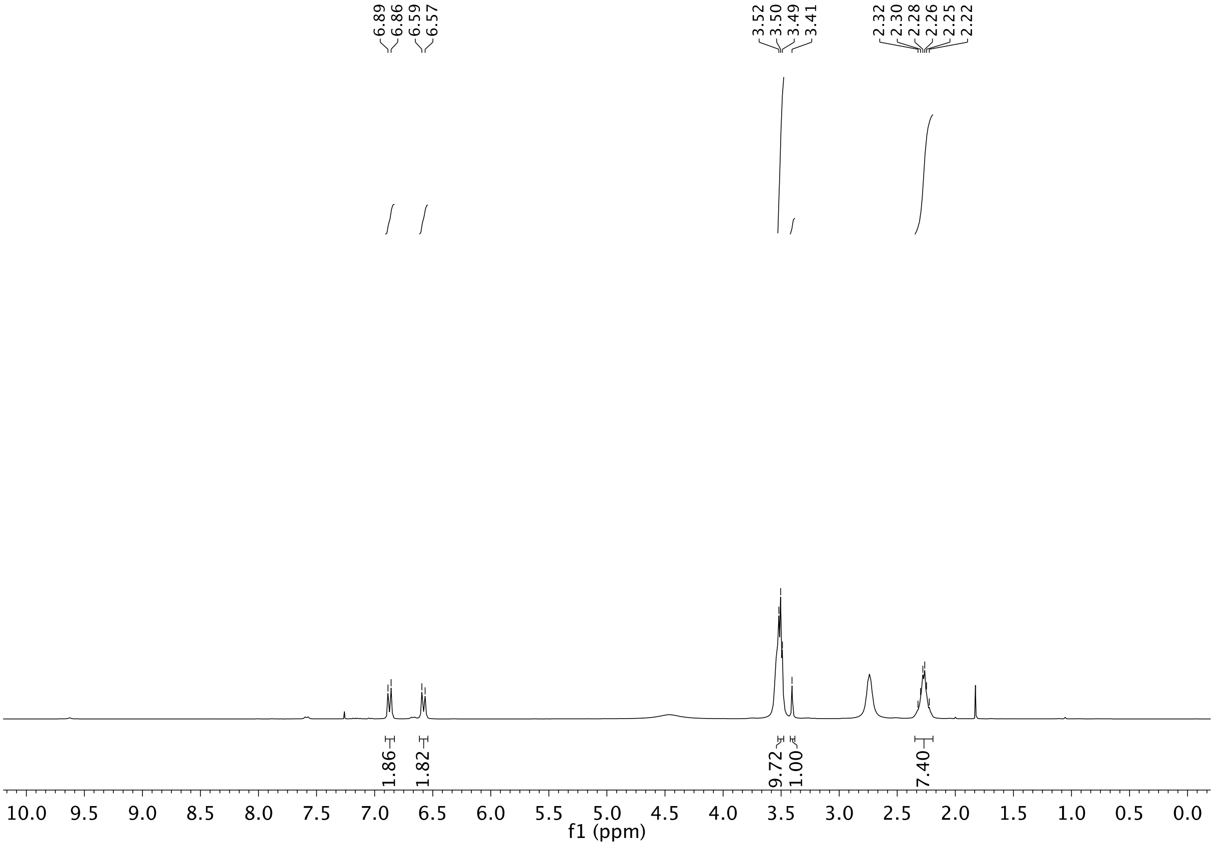


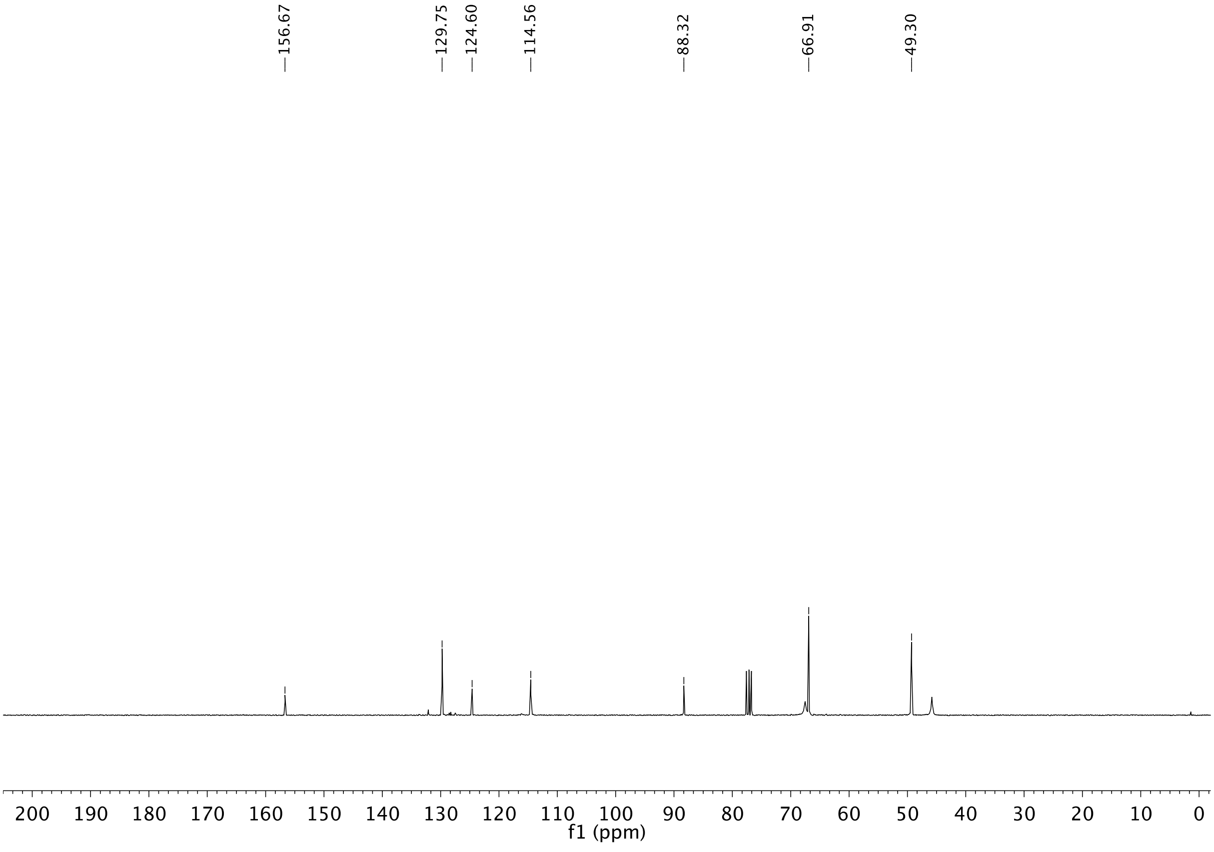
4,4'-((4-methoxyphenyl)methylene)dimorpholine 7



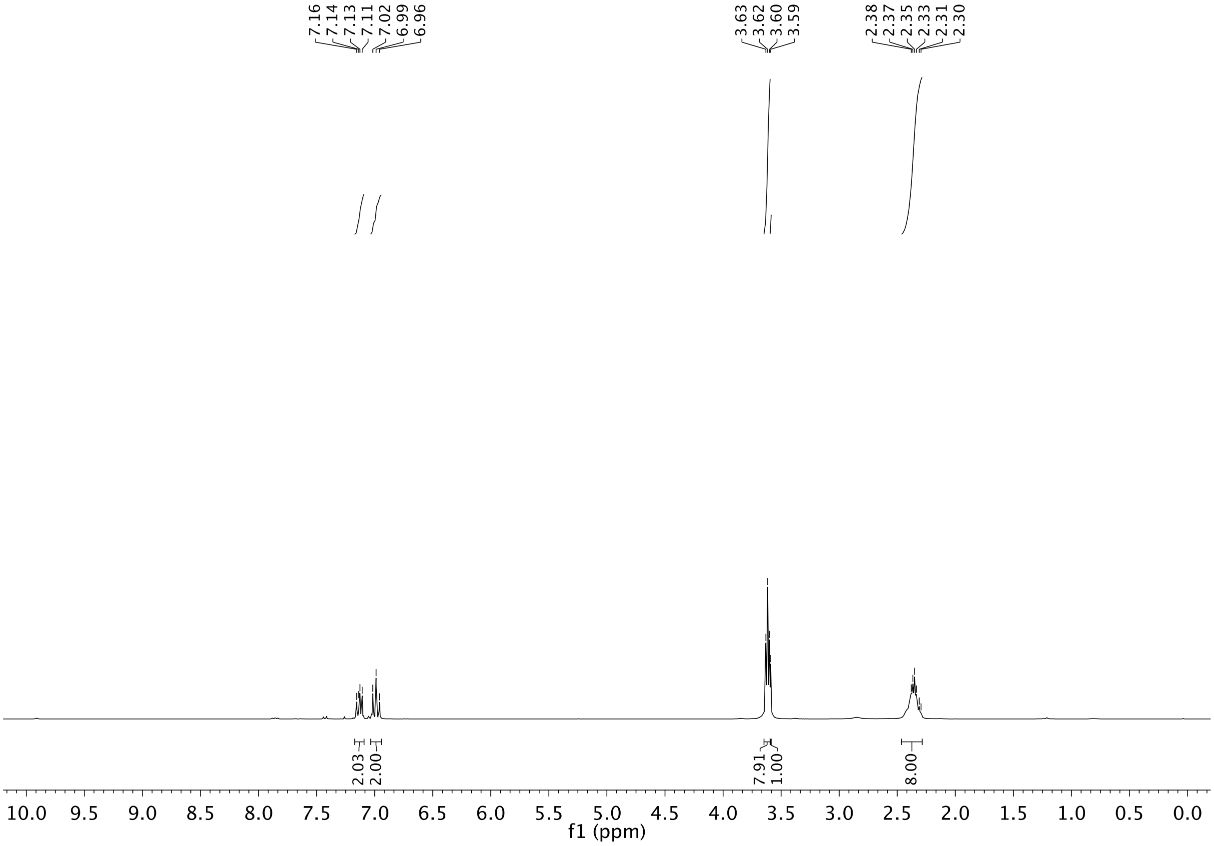


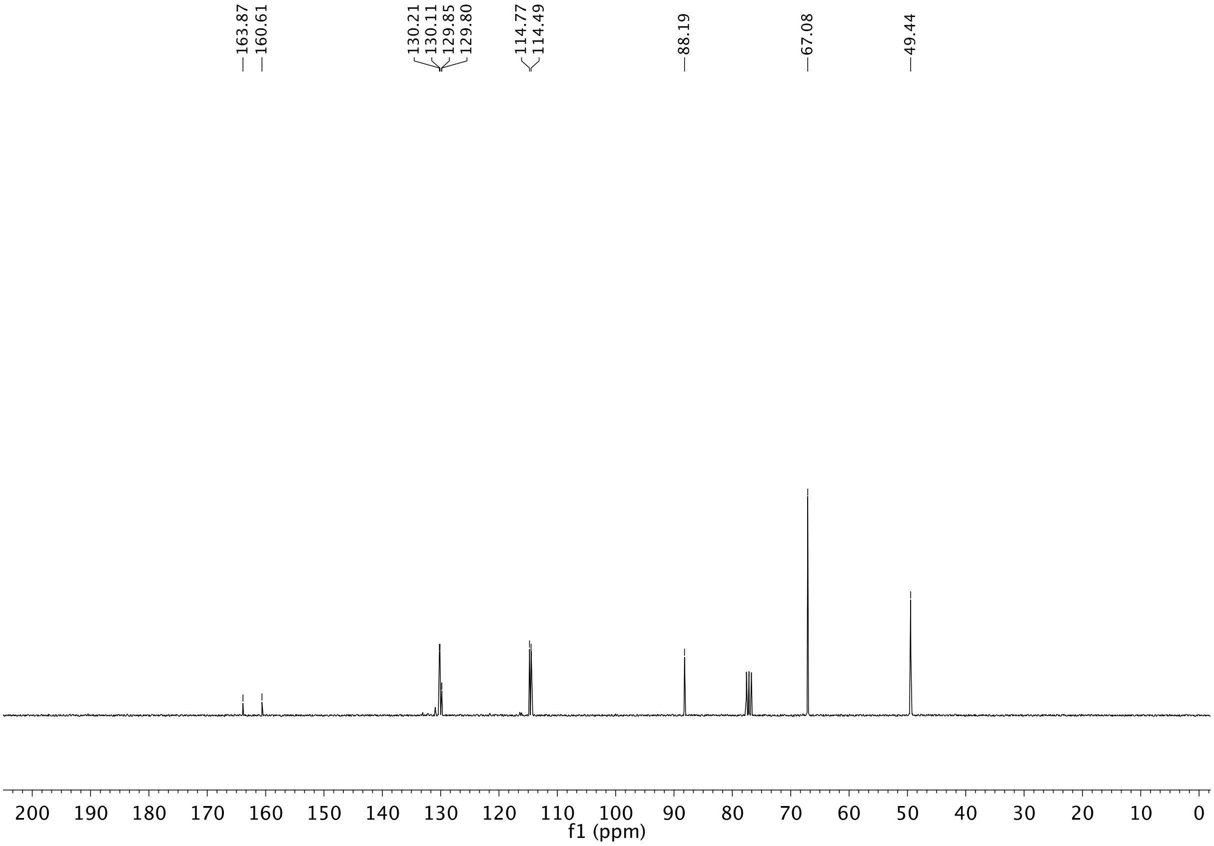
4- (dimorpholinomethyl)phenol 8



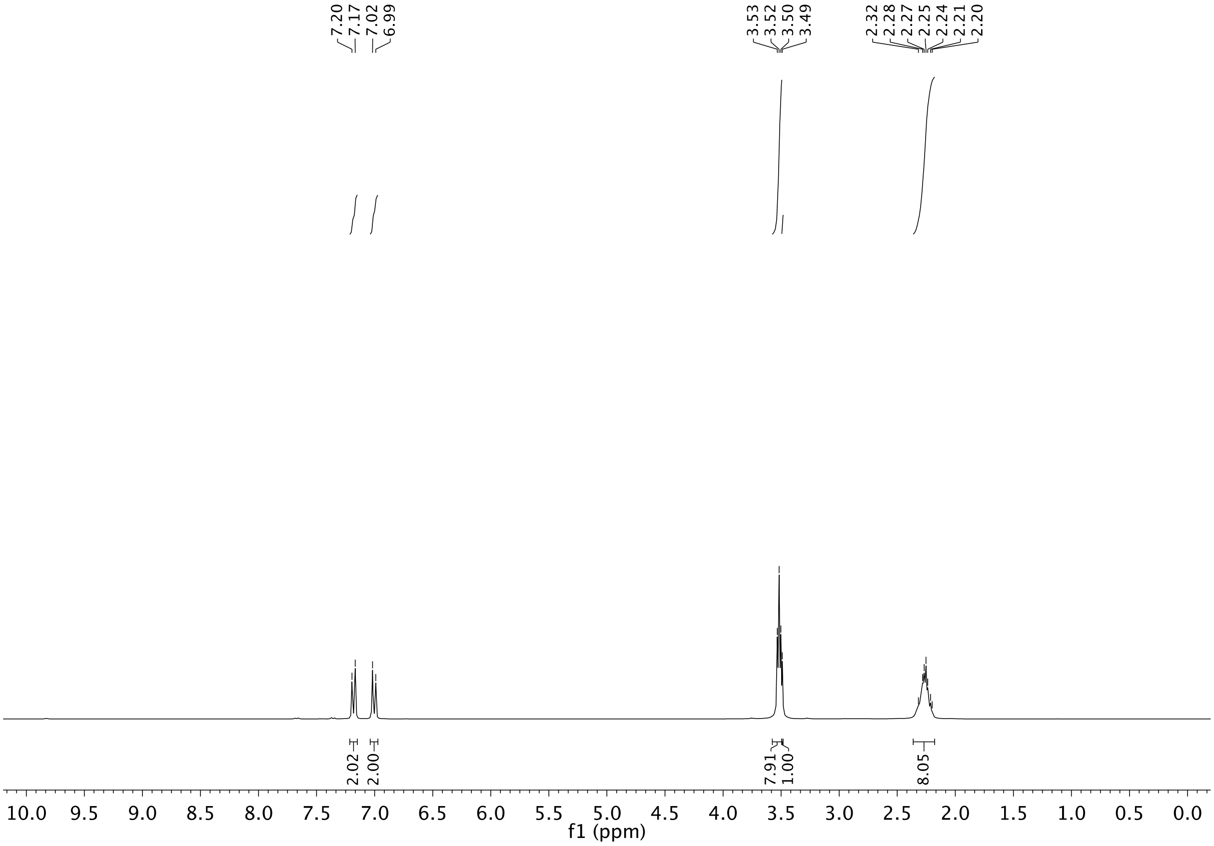


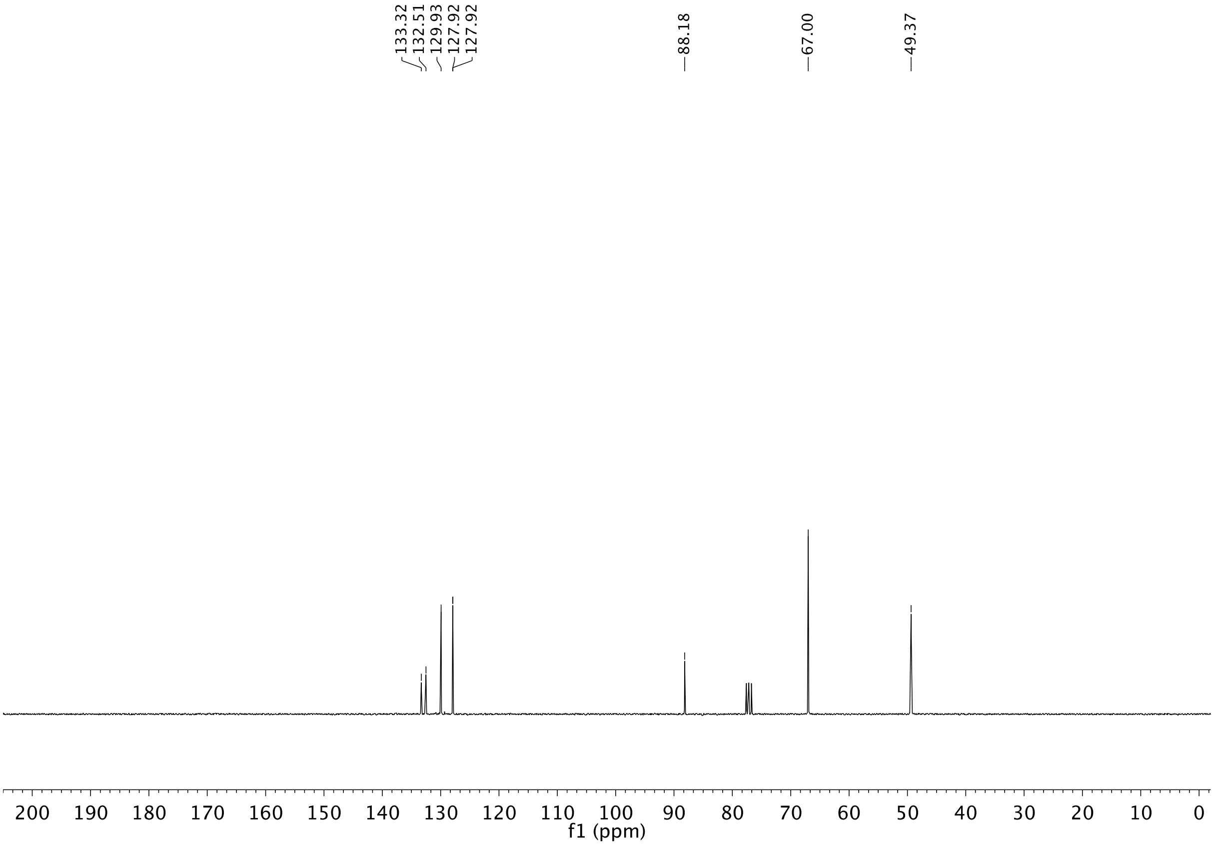
4,4'-((4-fluorophenyl)methylene)dimorpholine 9



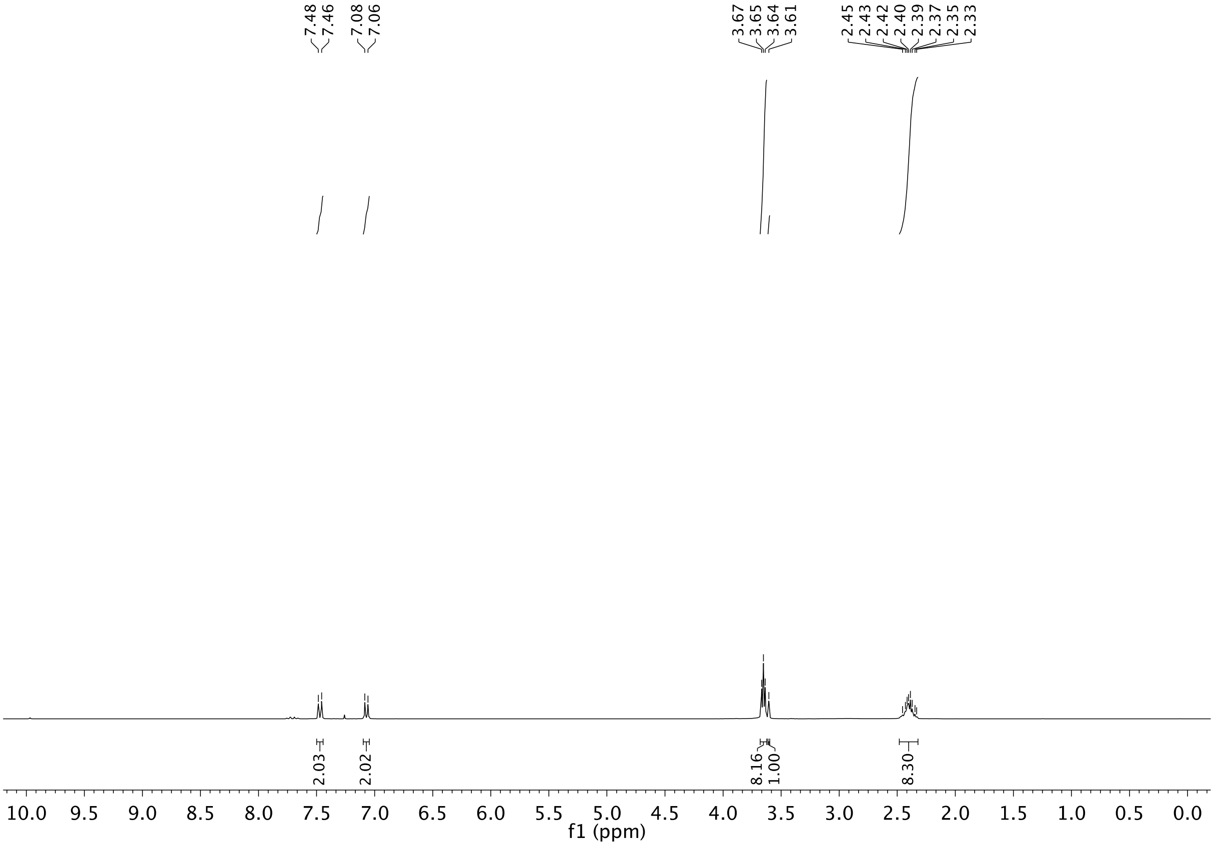


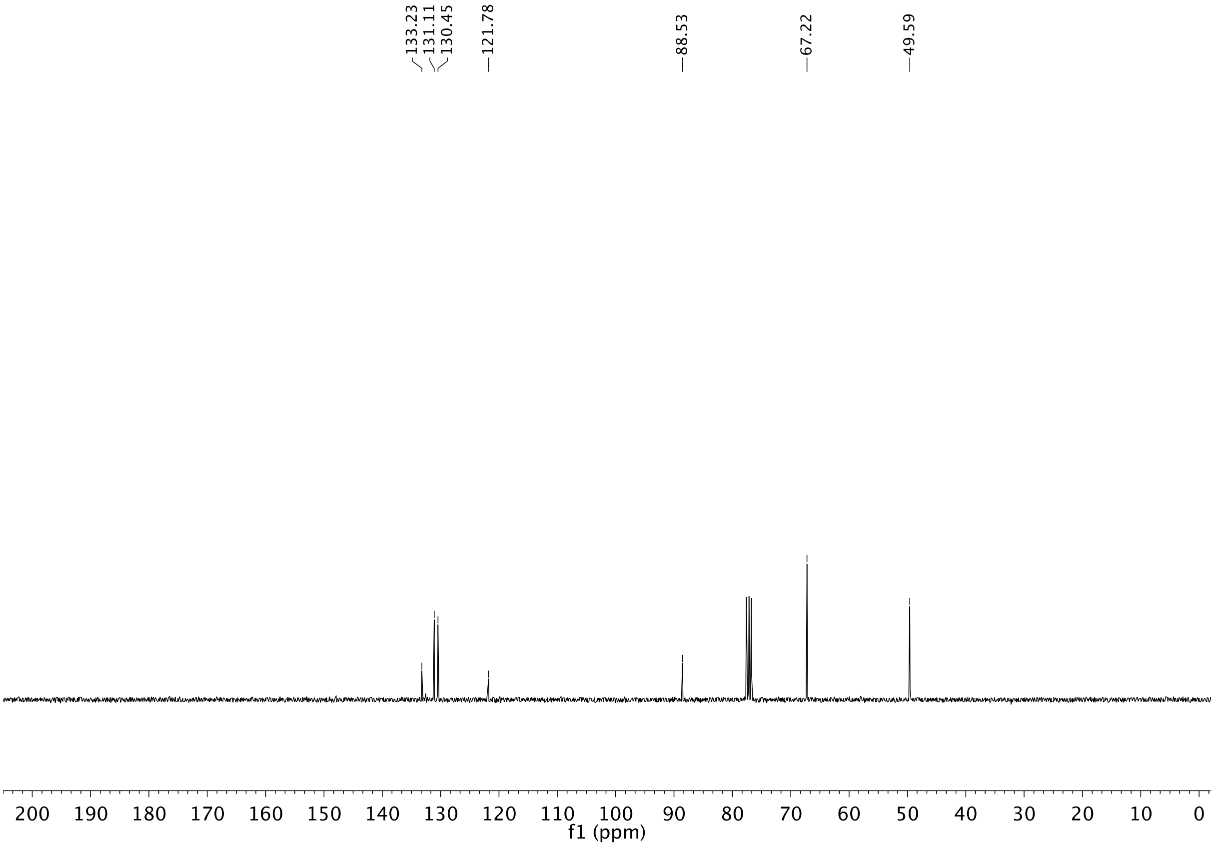
4,4'-((4-chlorophenyl)methylene)dimorpholine 10



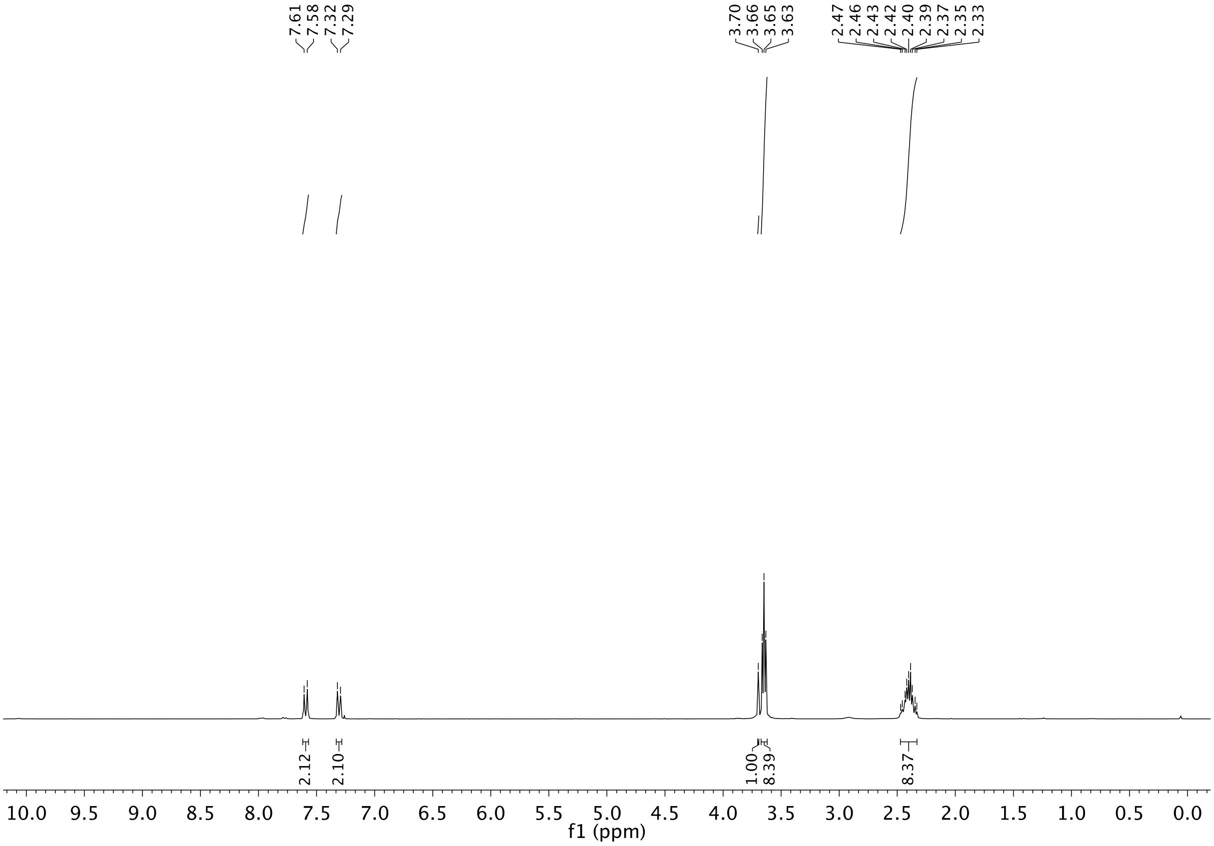


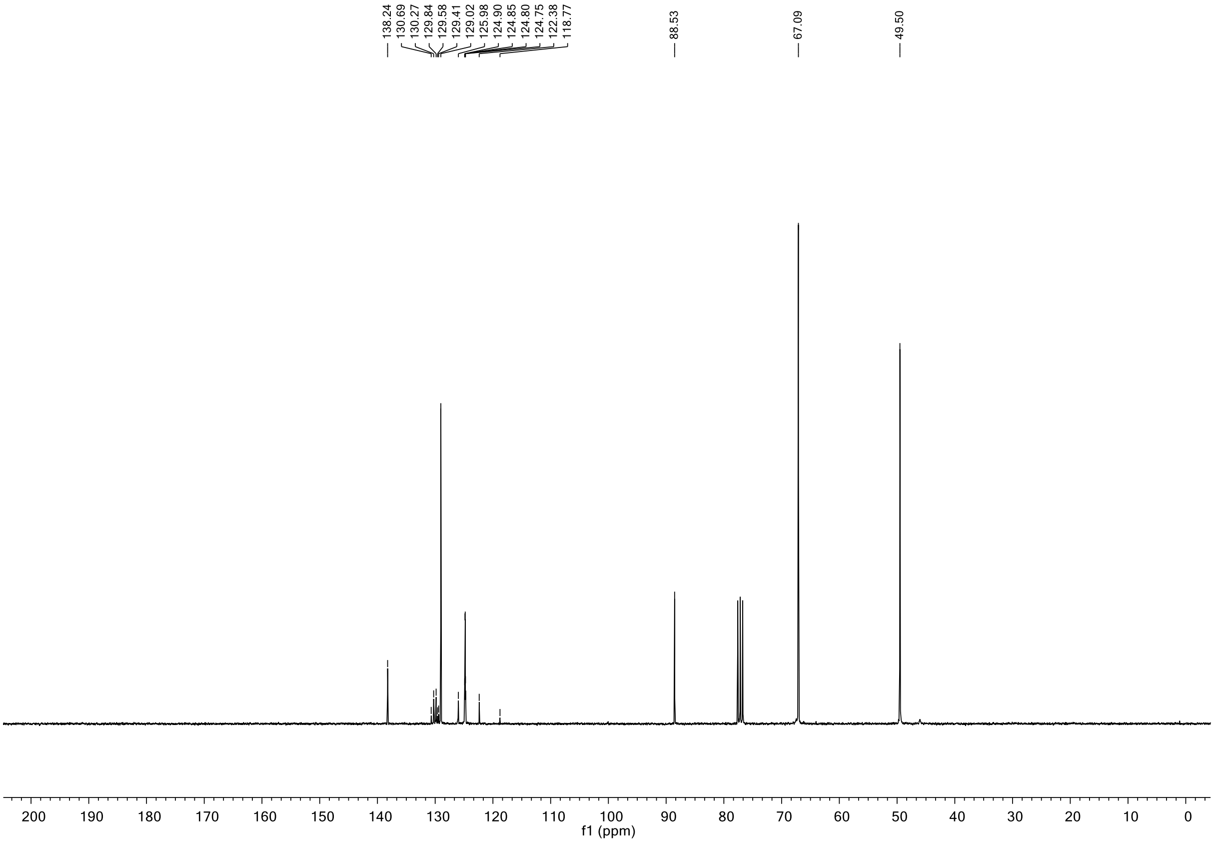
4,4'-((4-bromophenyl)methylene)dimorpholine 11



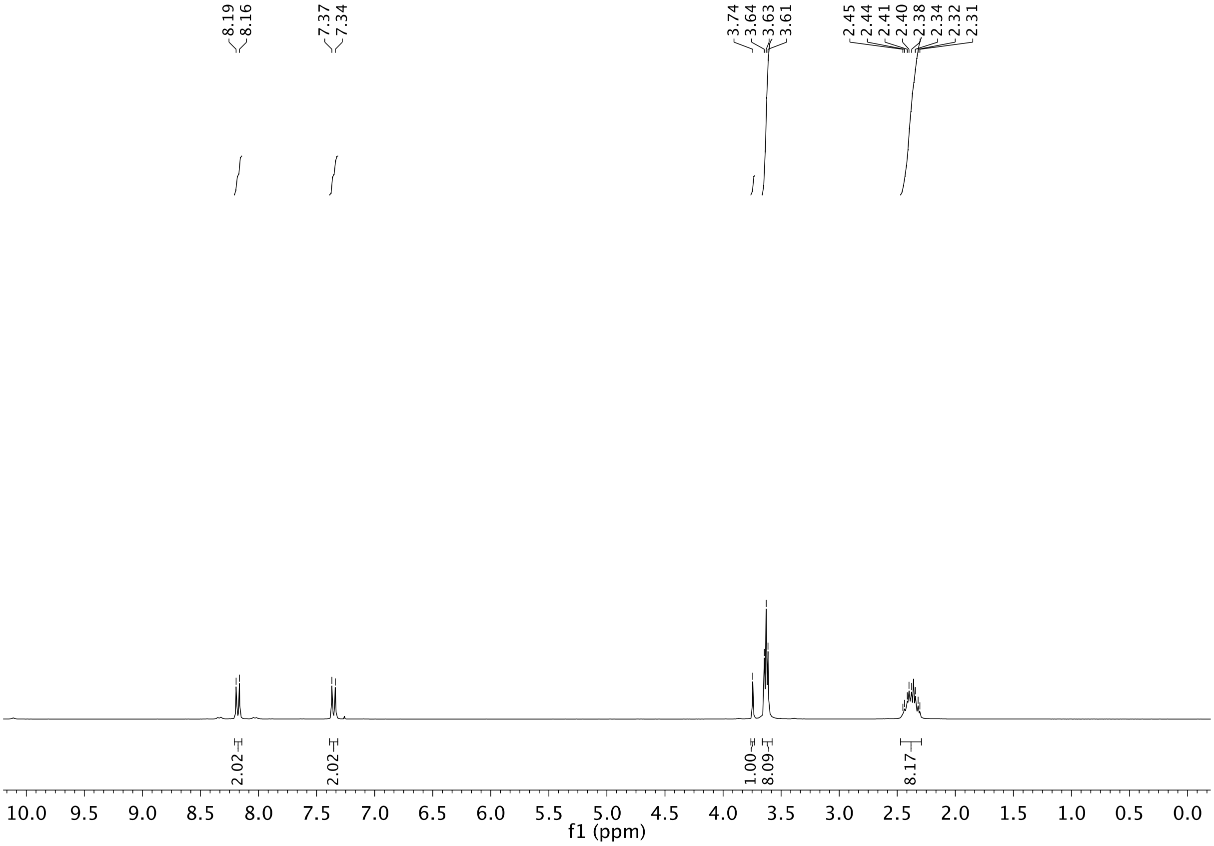


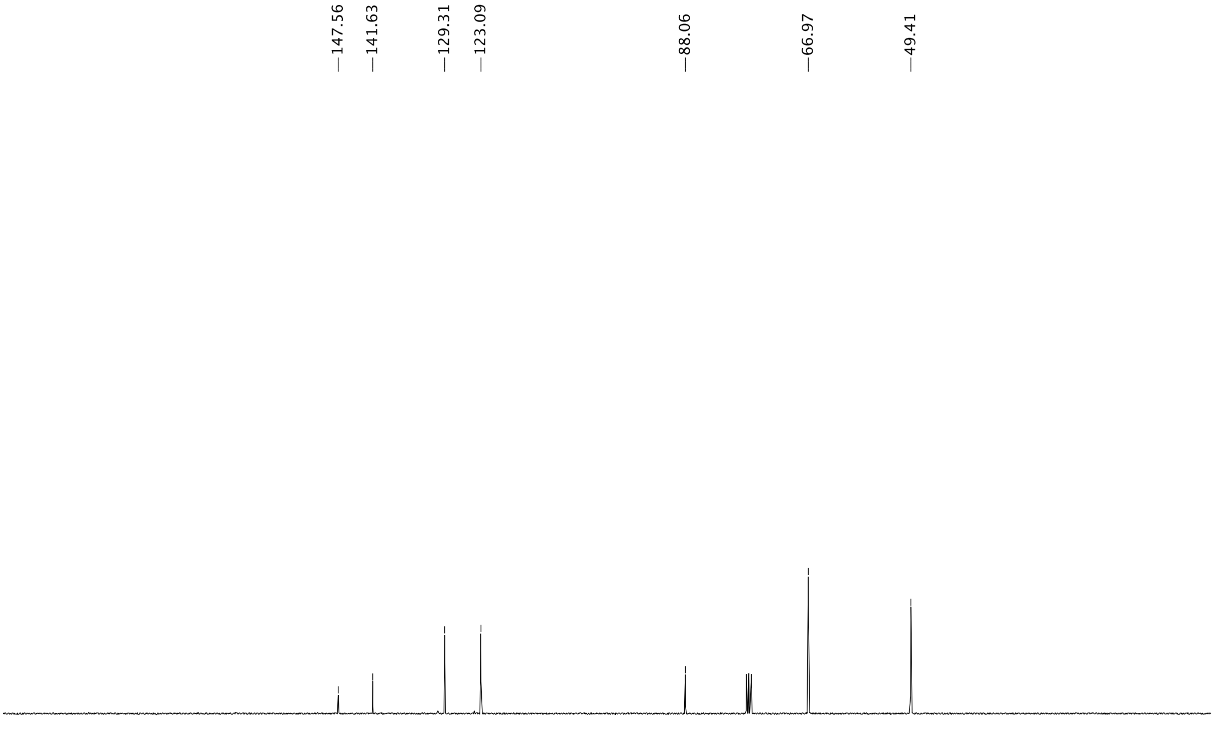
4,4'-((4-(trifluoromethyl)phenyl)methylene)dimorpholine 12



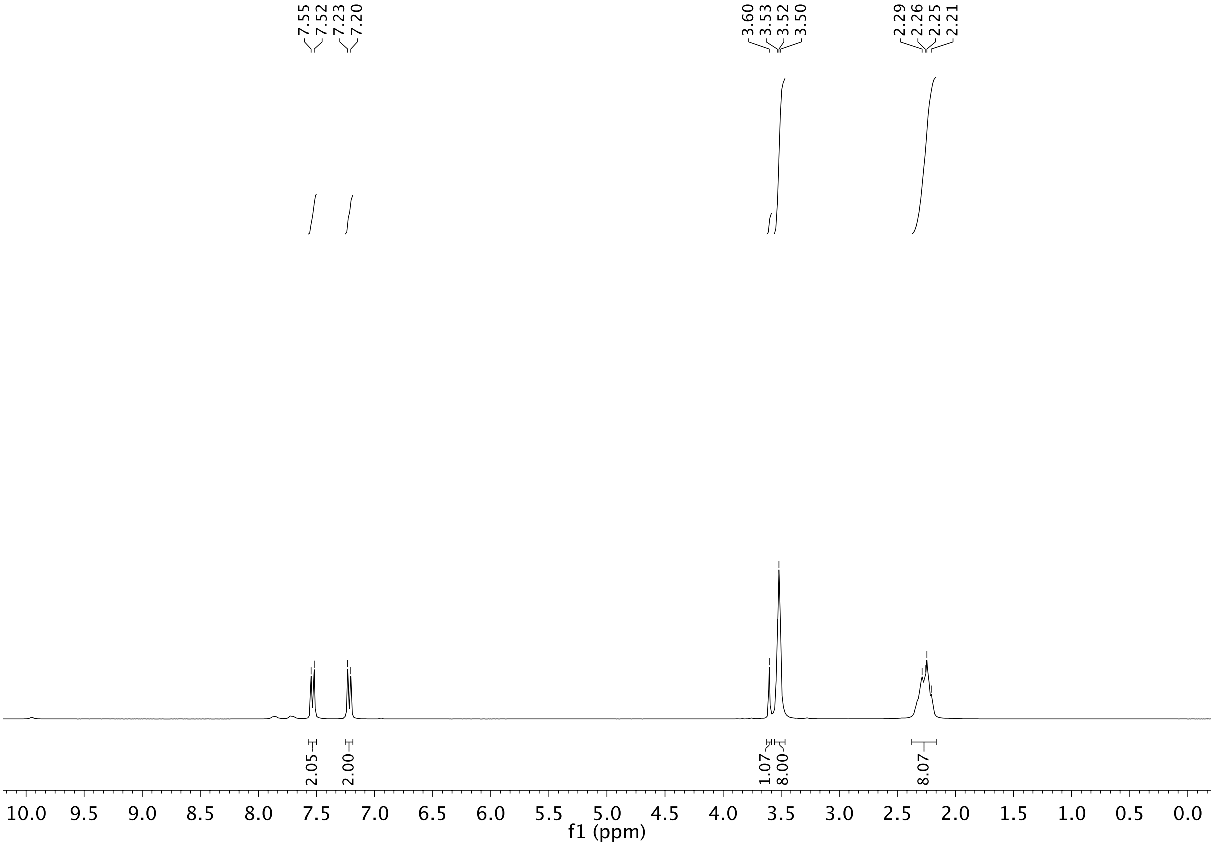


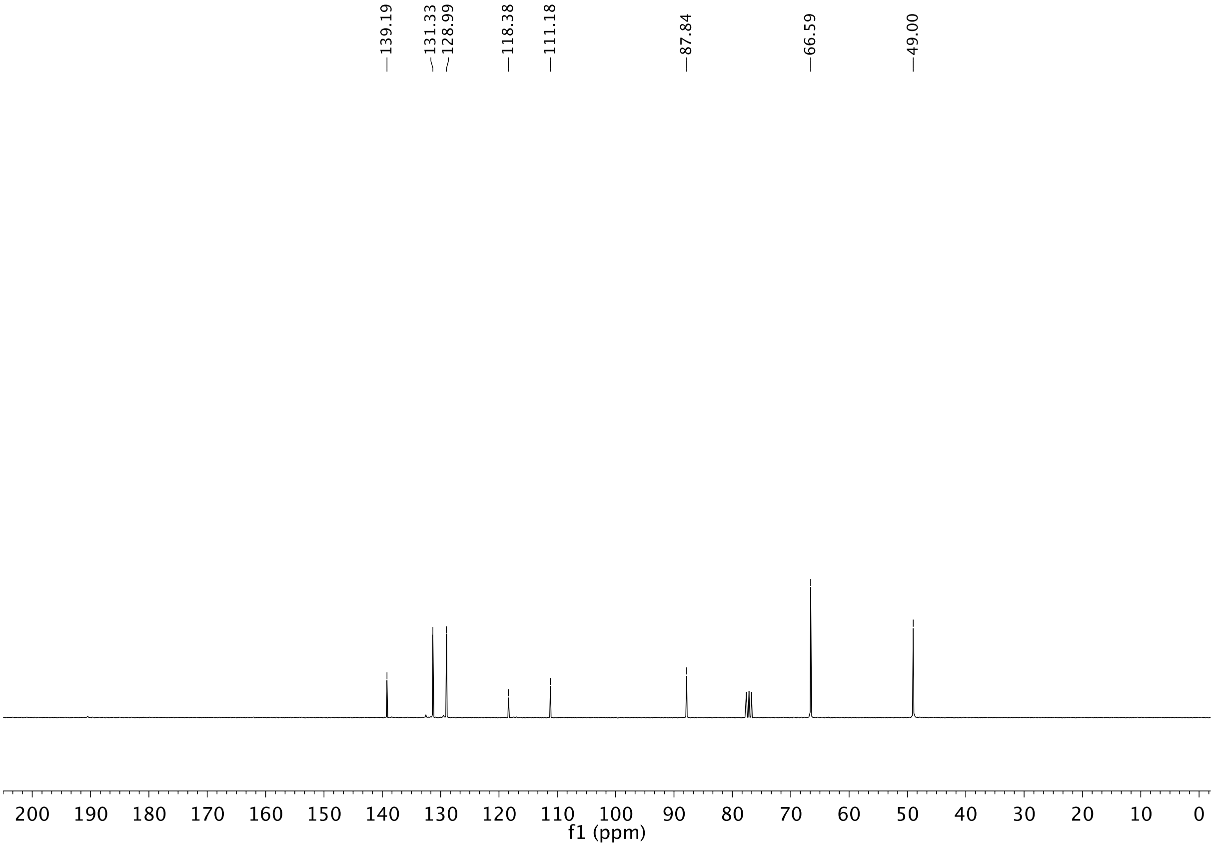
4,4'-((4-nitrophenyl)methylene)dimorpholine 13



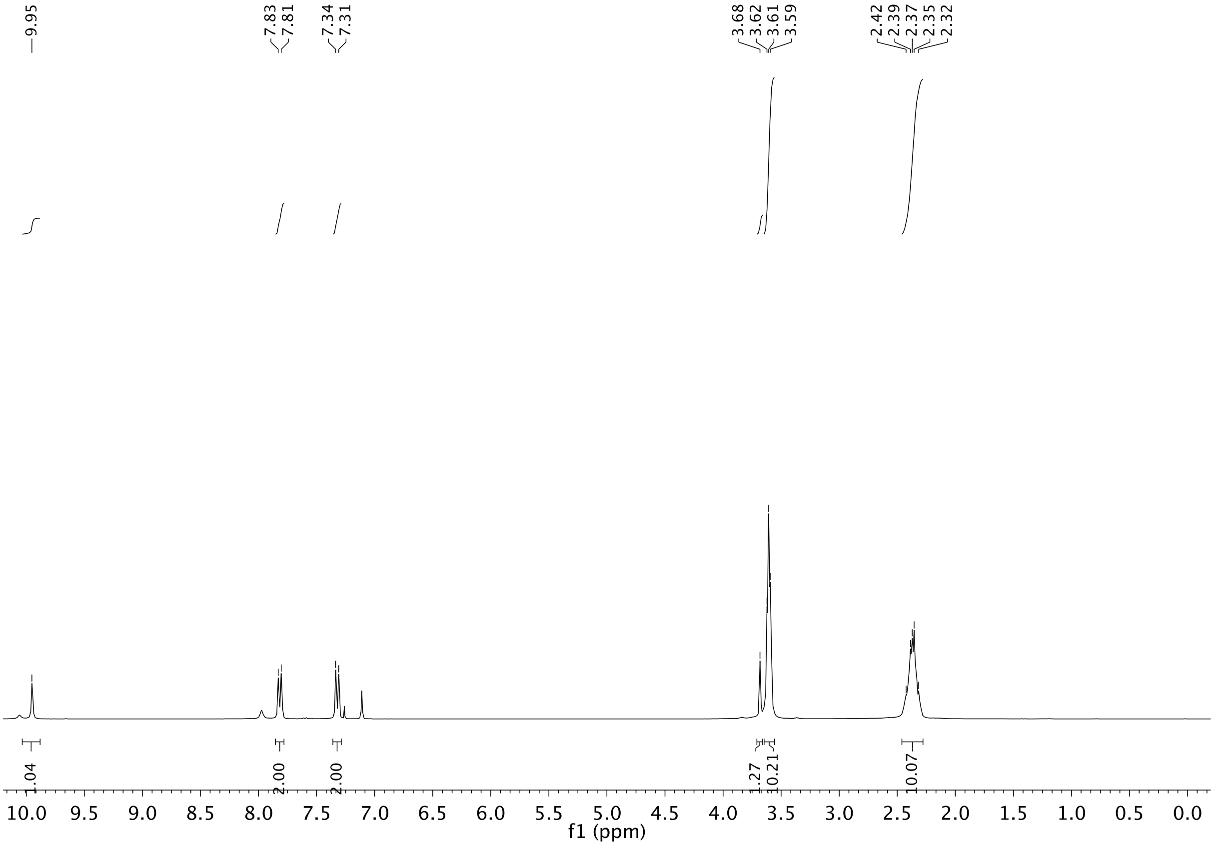


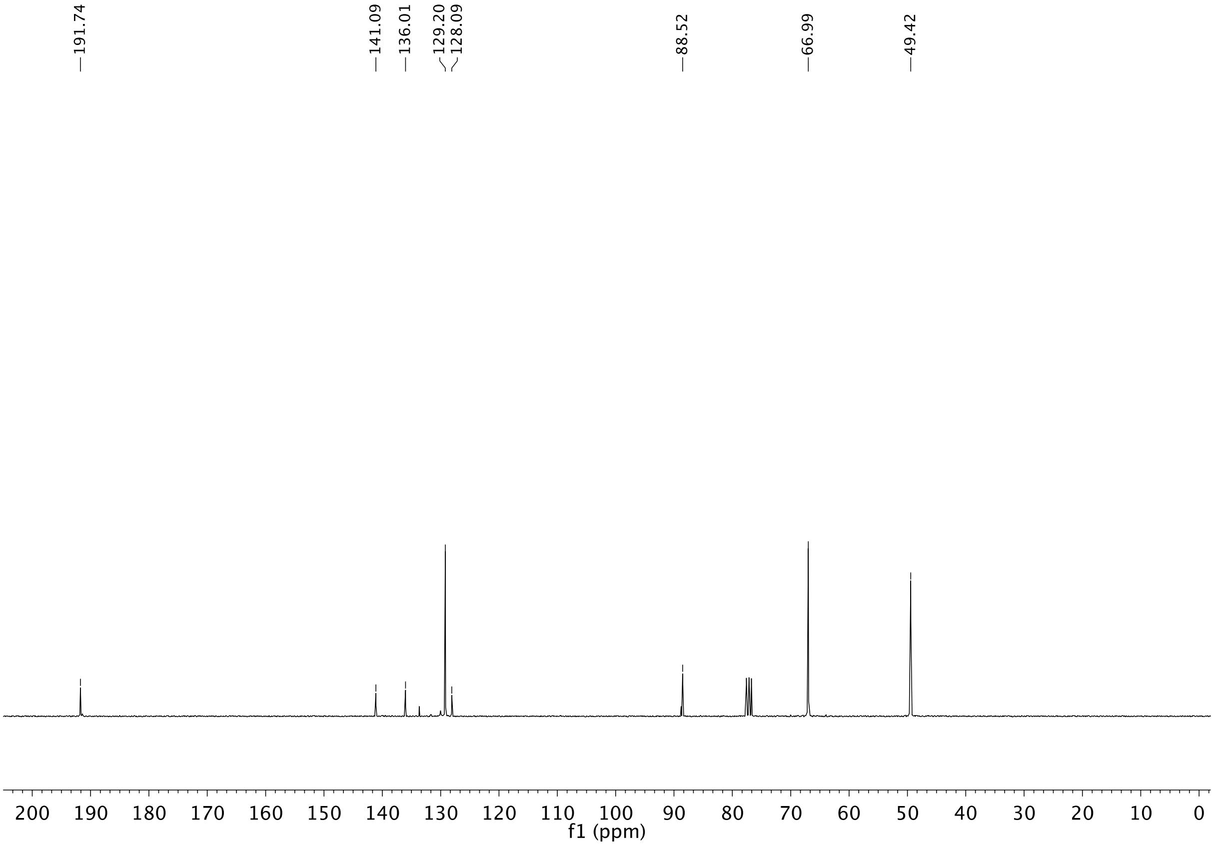
4-(dimorpholinomethyl)benzonitrile 14



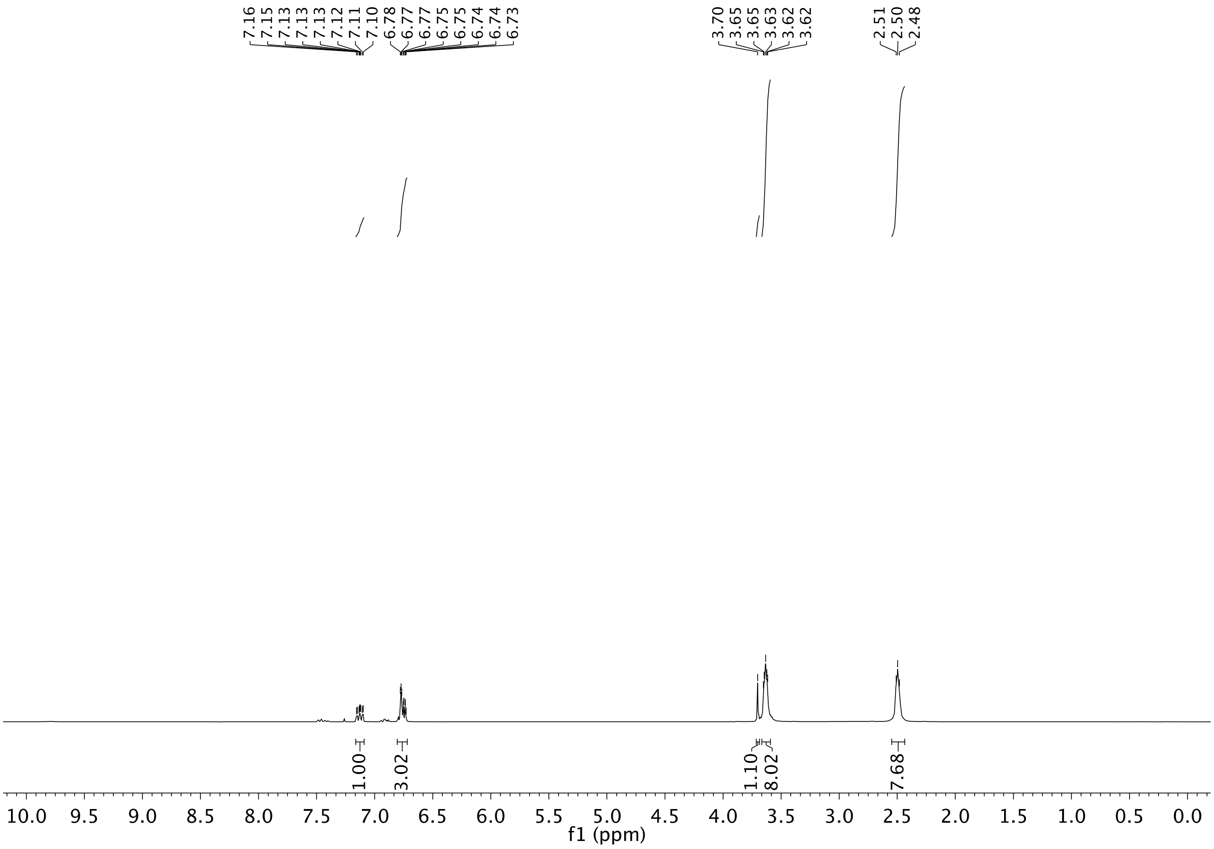


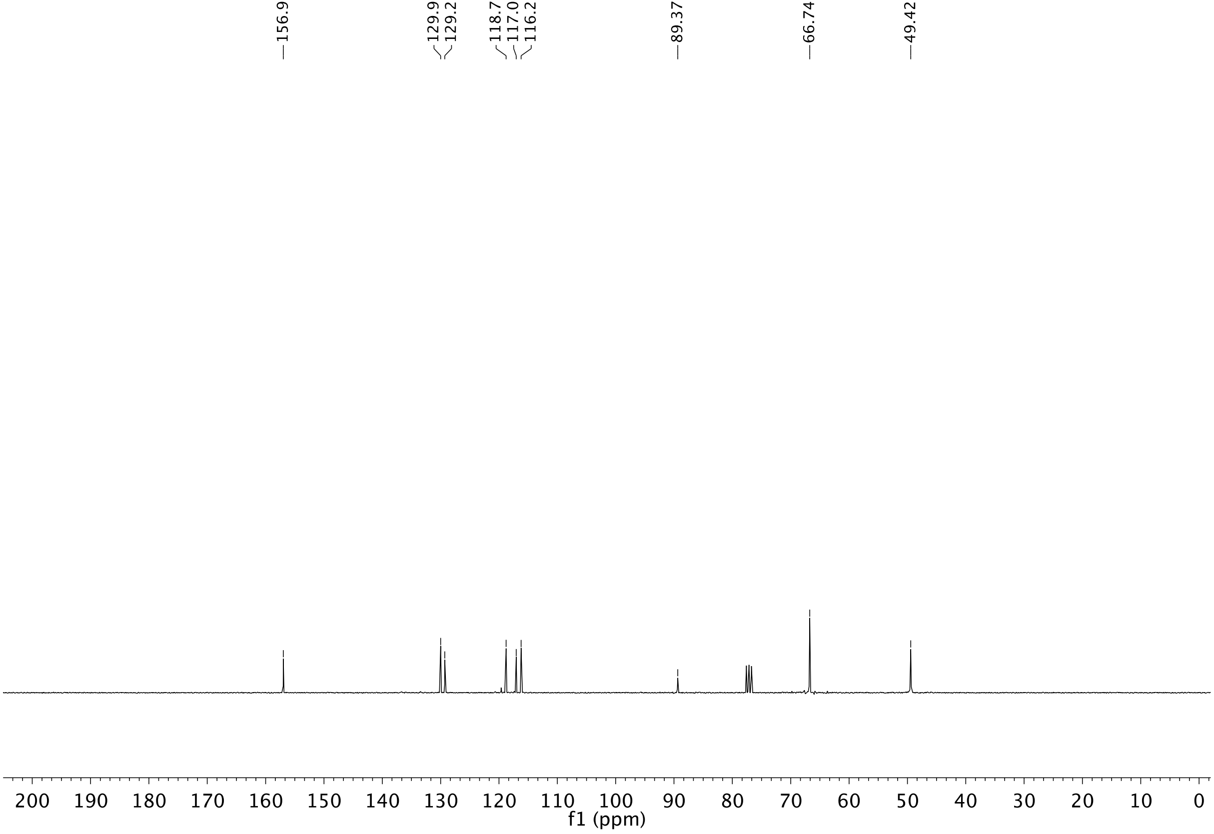
4-(dimorpholinomethyl)benzaldehyde 15



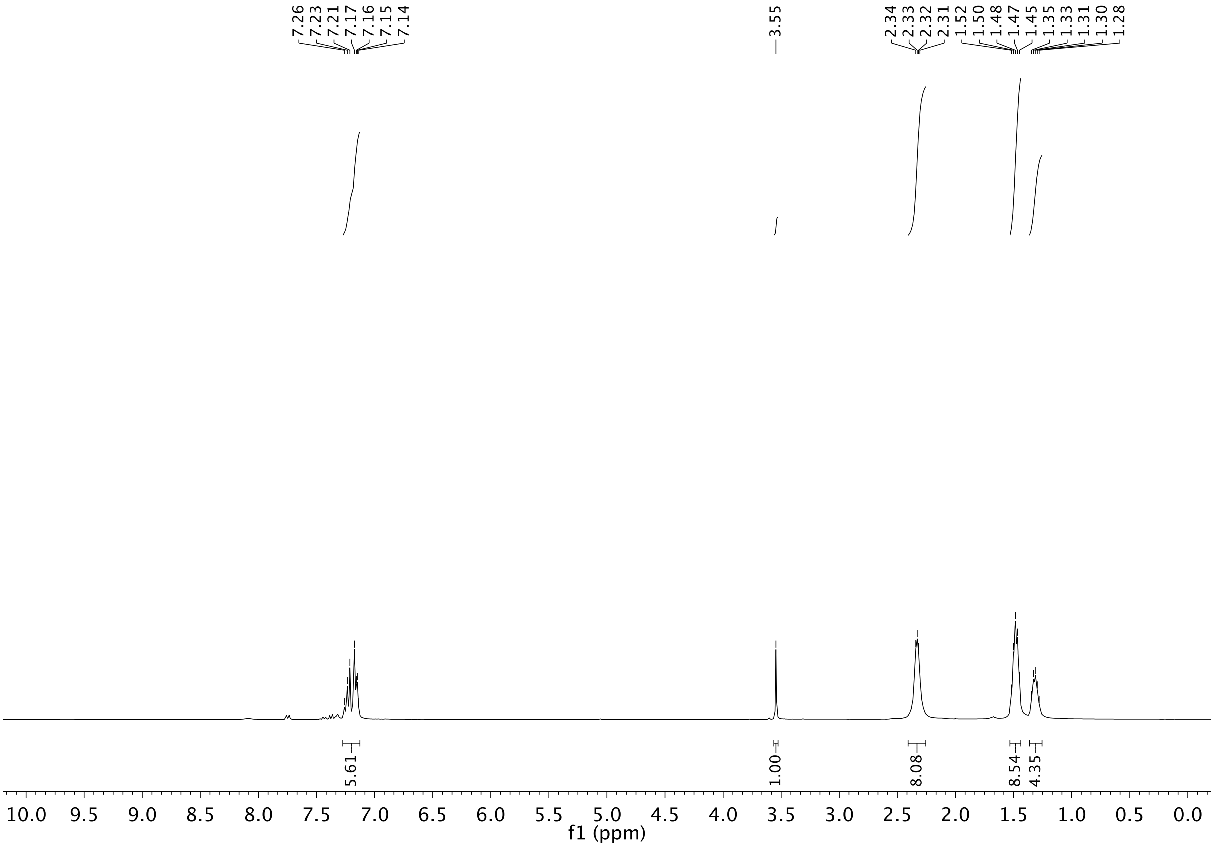


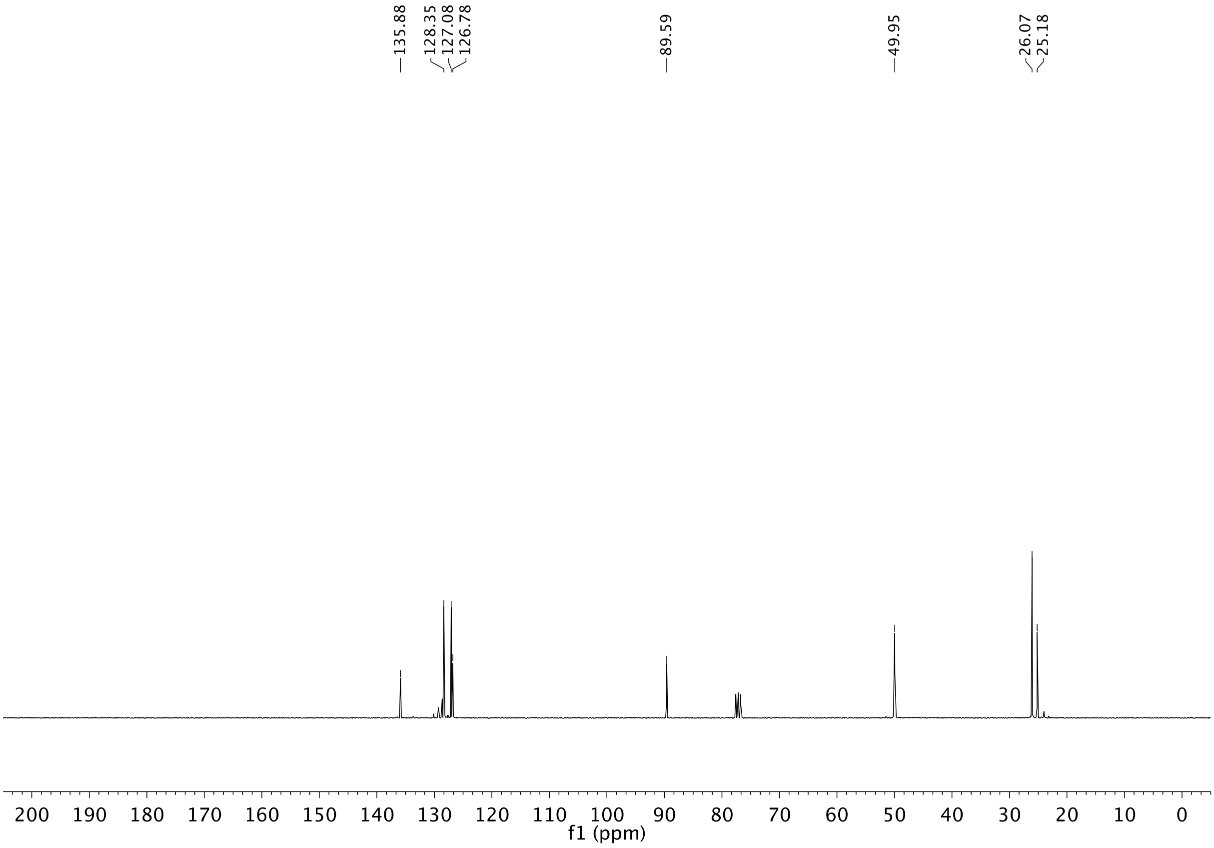
2-(dimorpholinomethyl)phenol 16



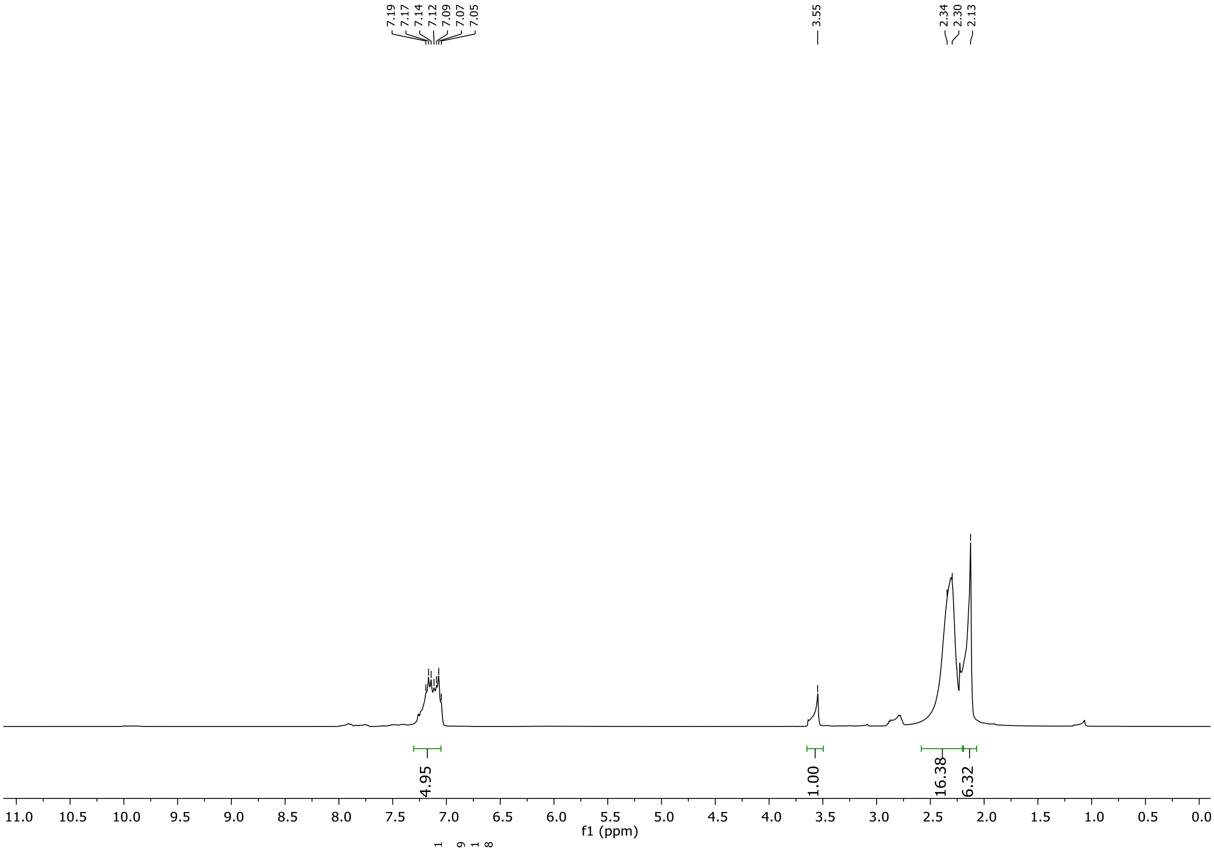


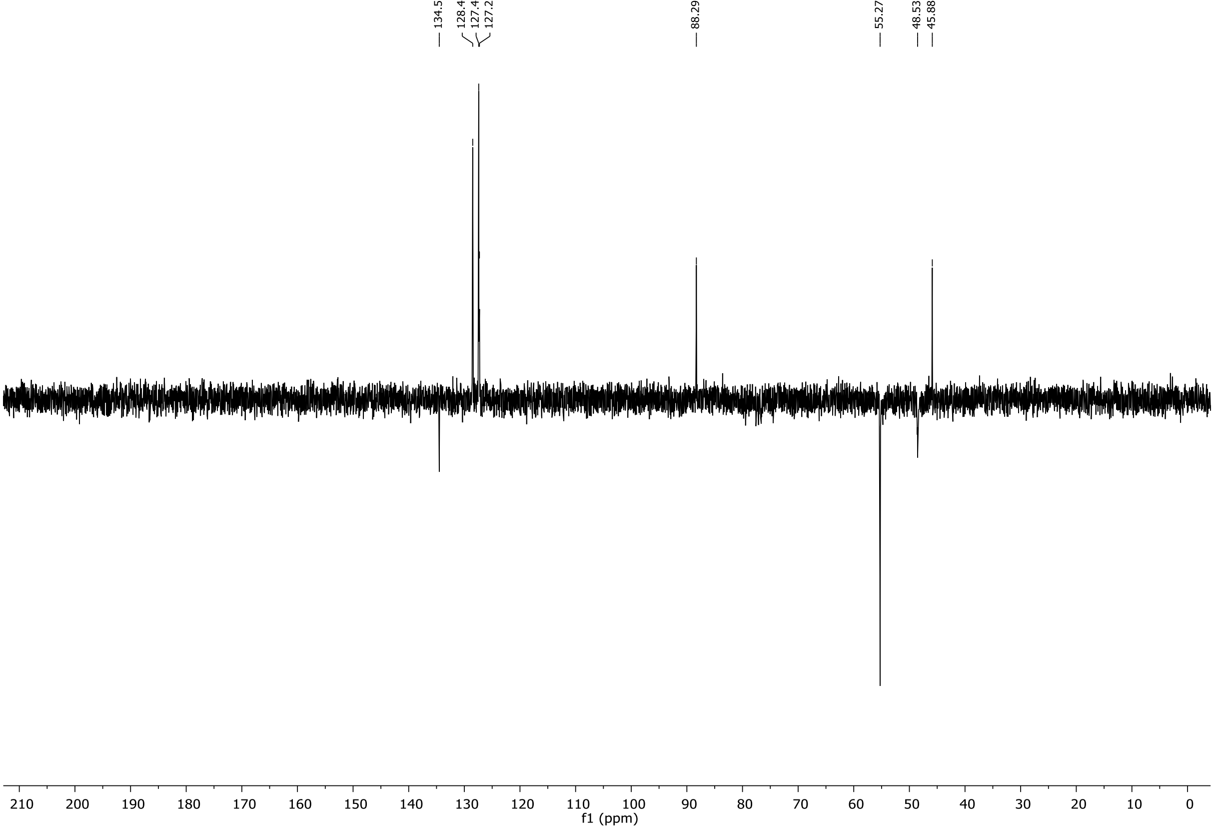
1,1'-(phenylmethylene)dipiperidine 17



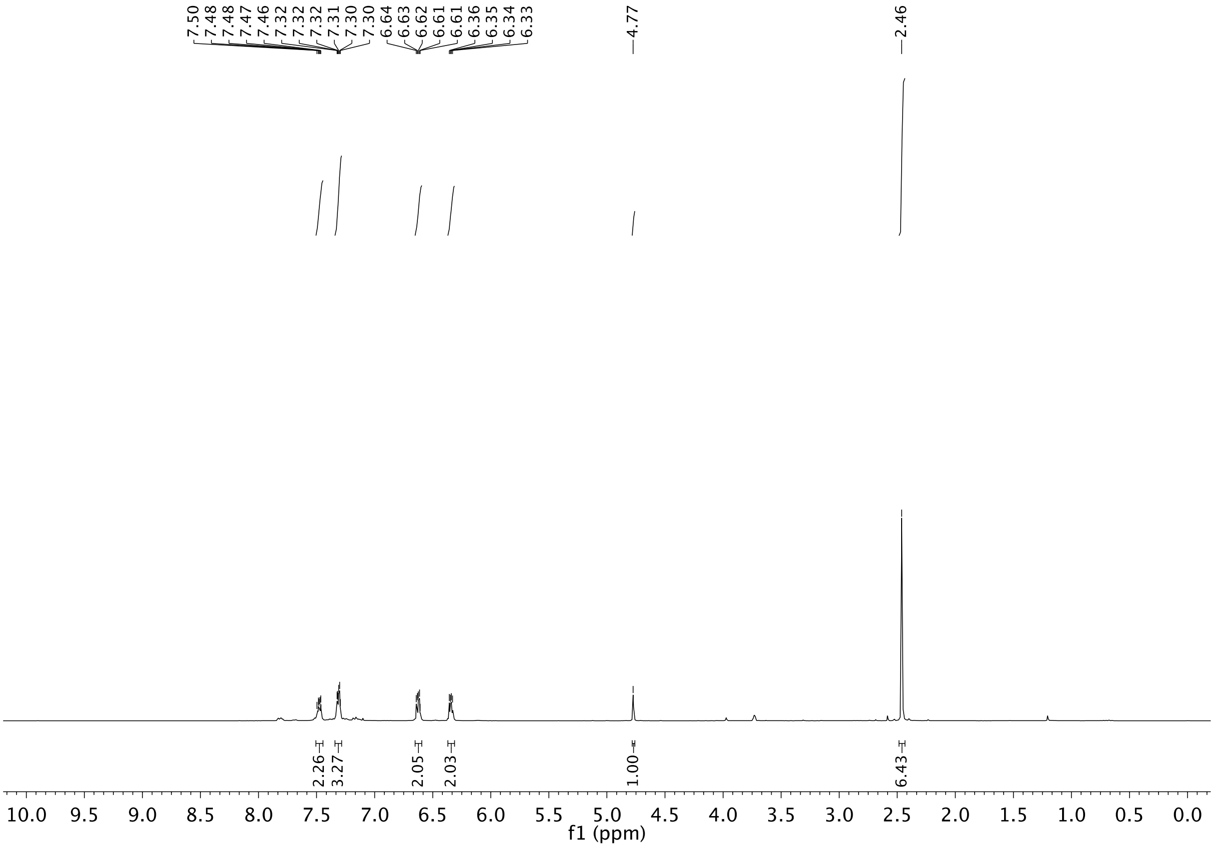


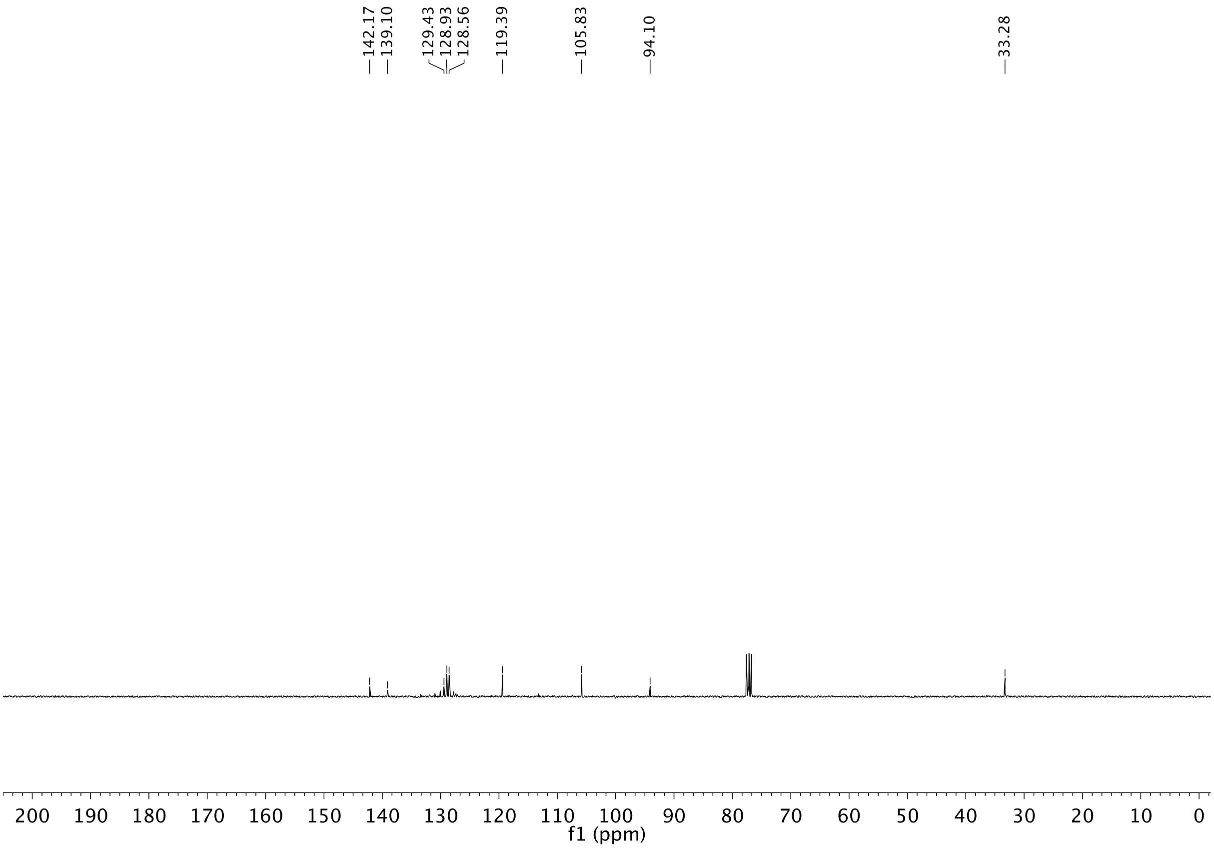
4,4'-(phenylmethylene)bis(1-methylpiperazine) 18



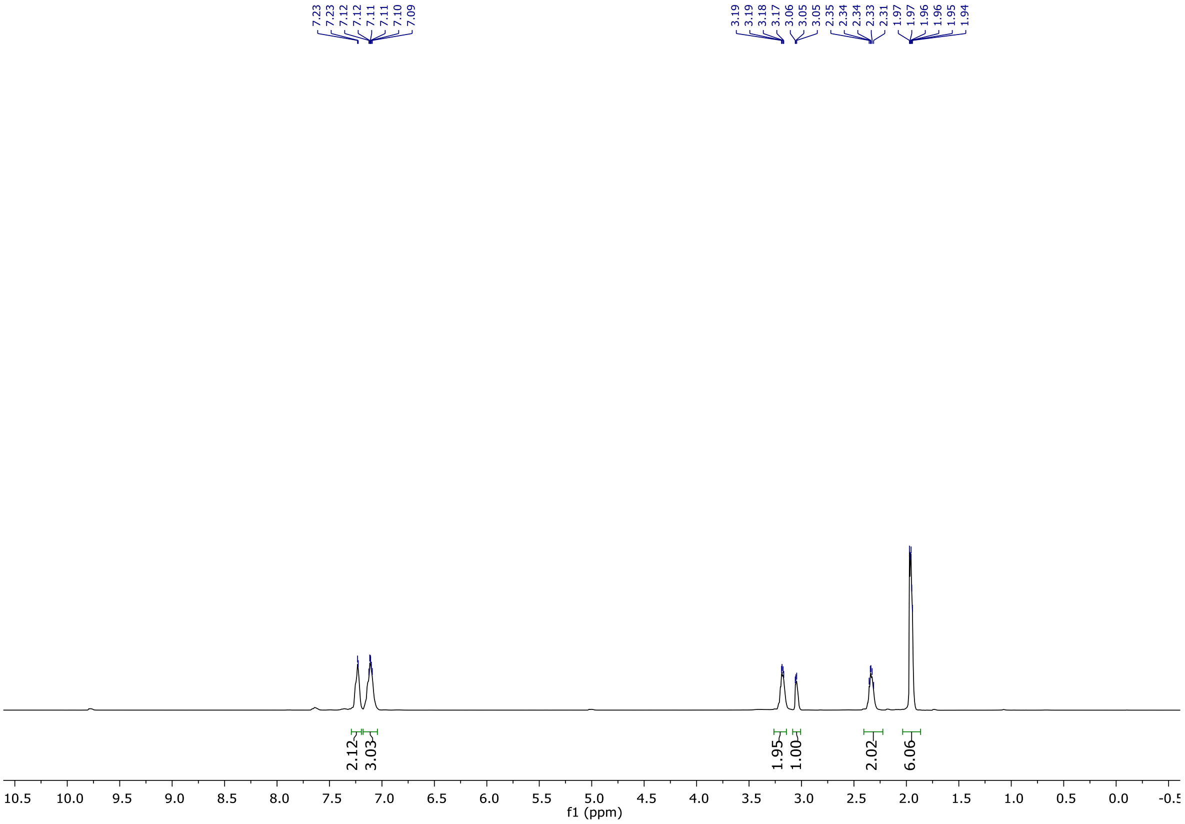


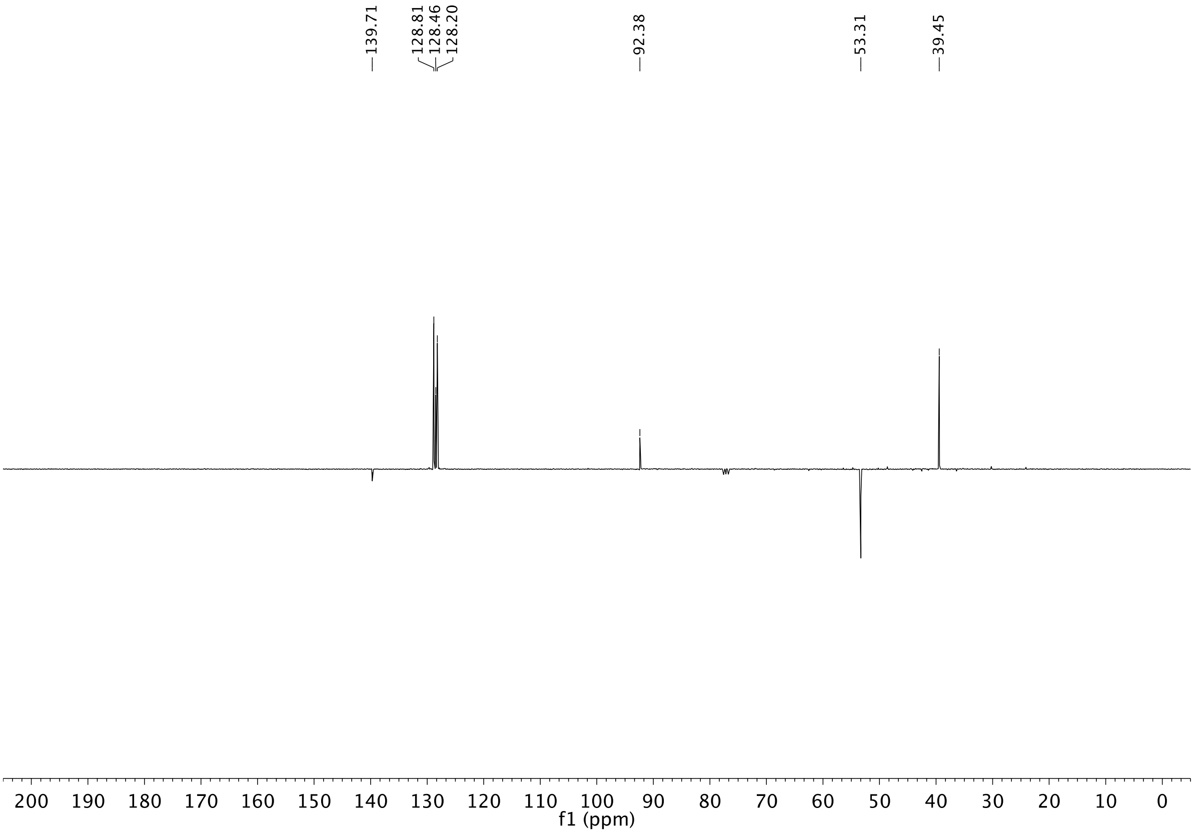
1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole 19



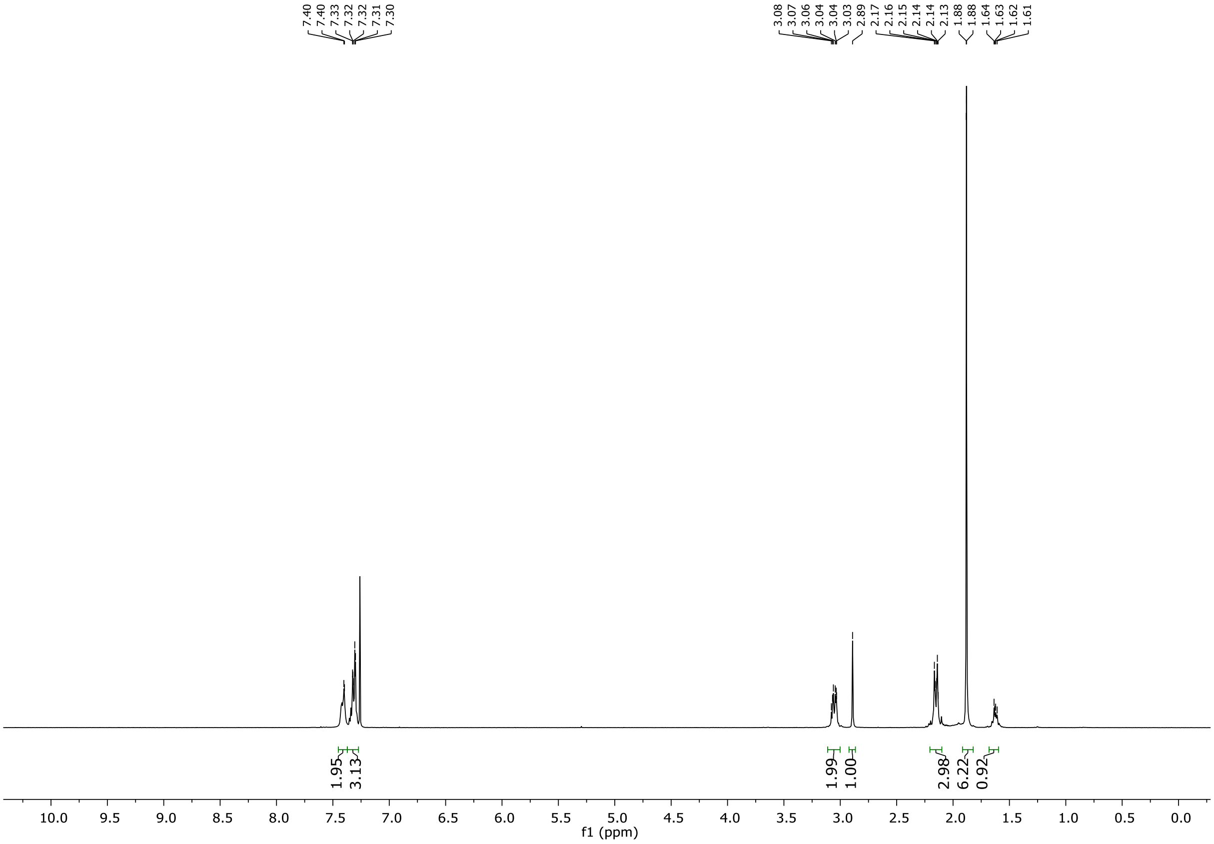


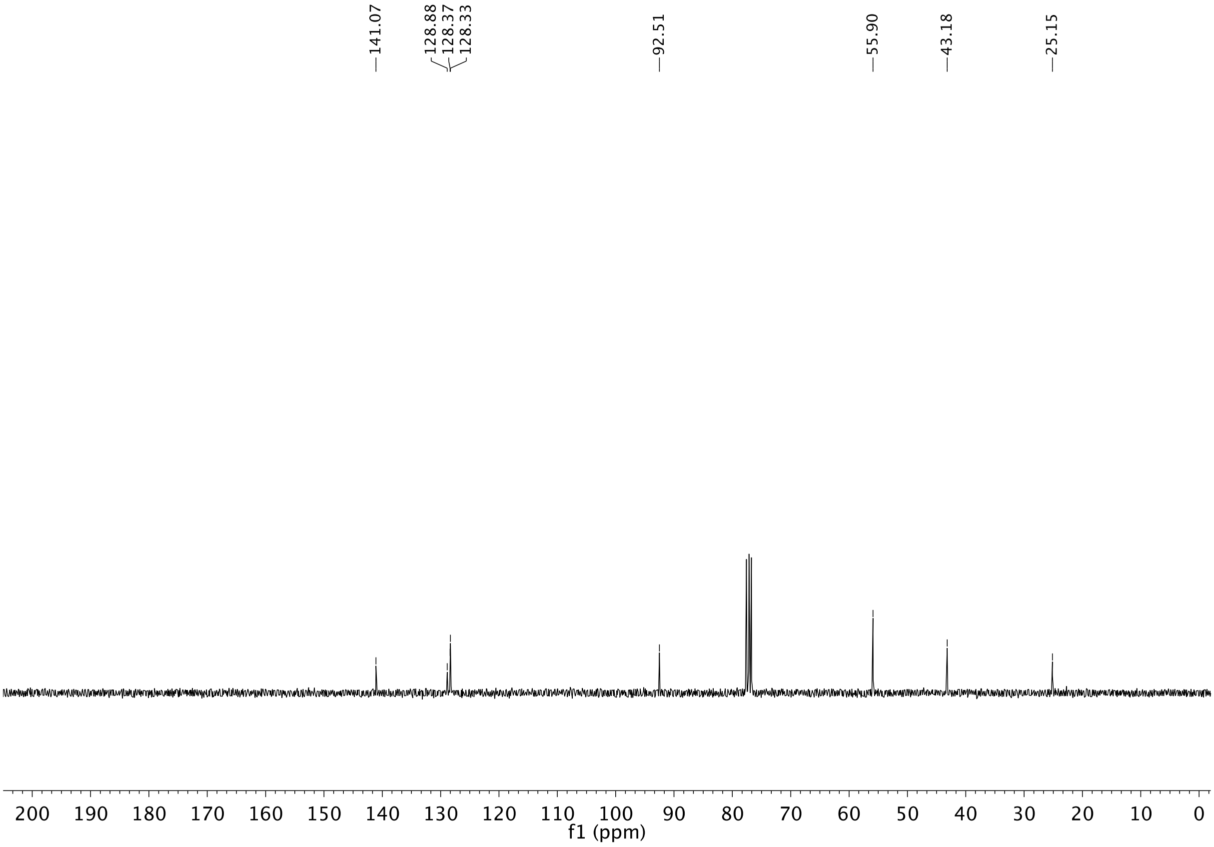
1,3-dimethyl-2-phenylimidazolidine 20



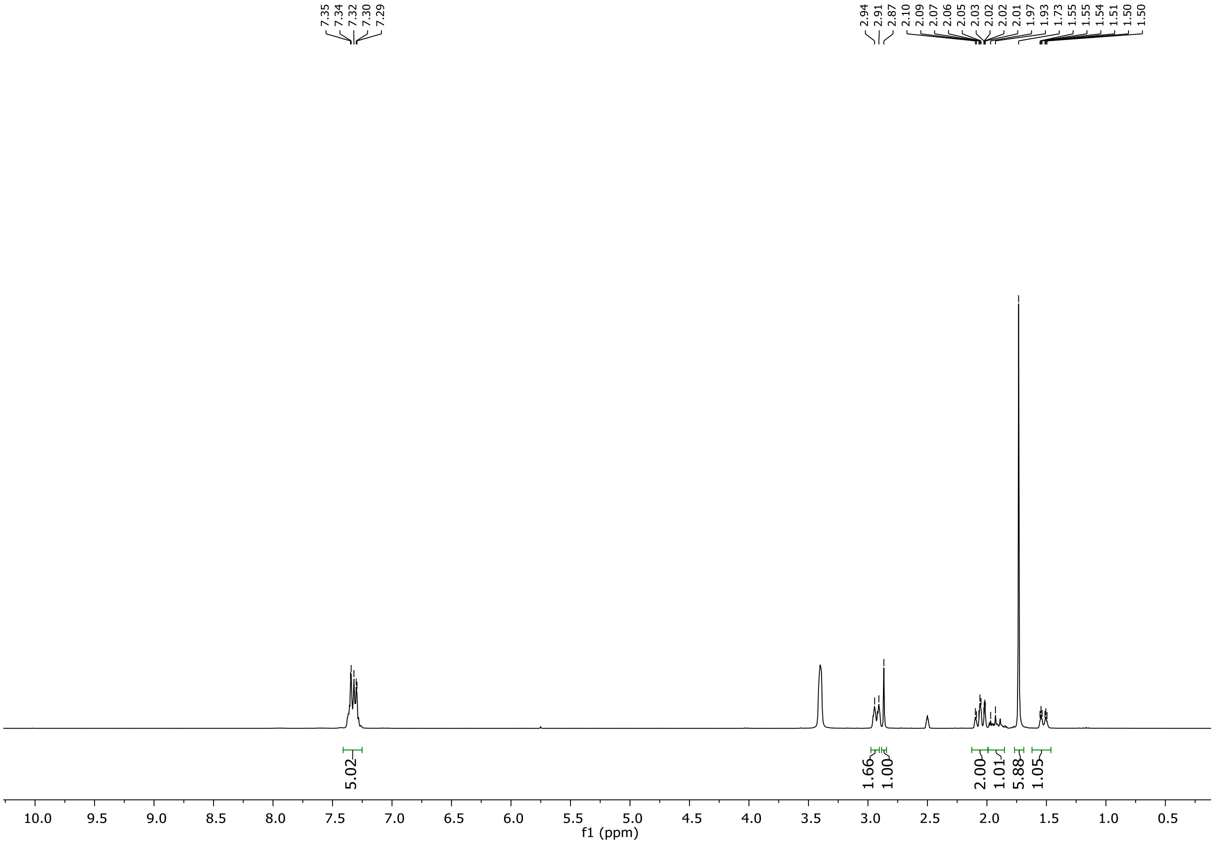


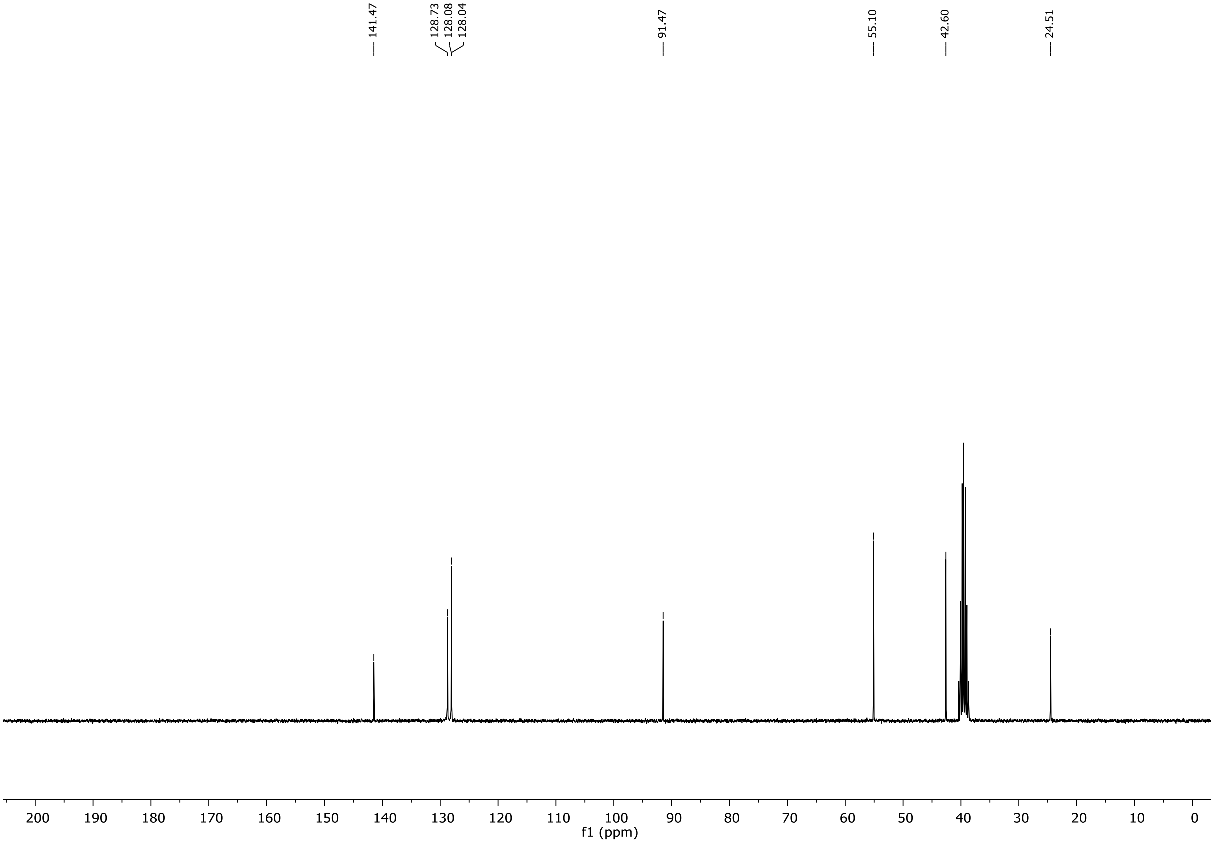
1,3-dimethyl-2-phenylhexahydropyrimidine 21



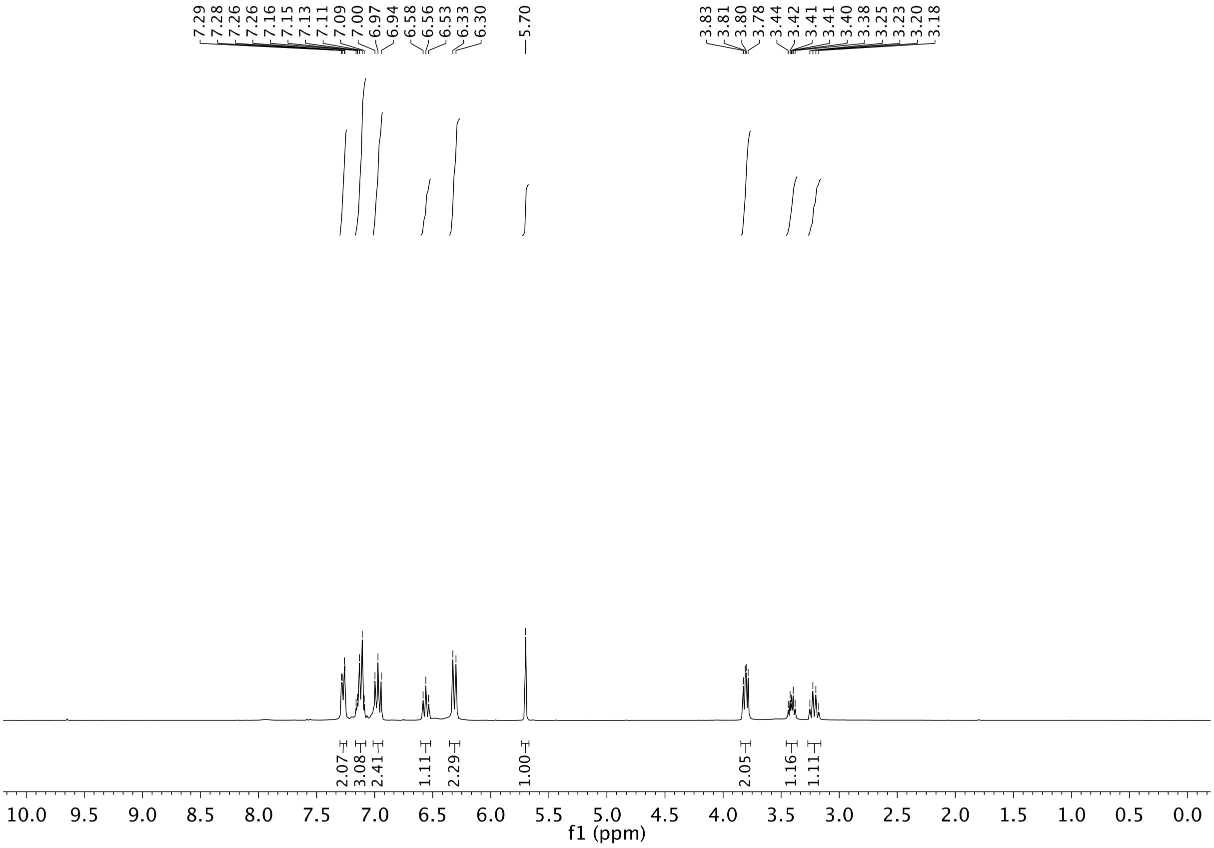


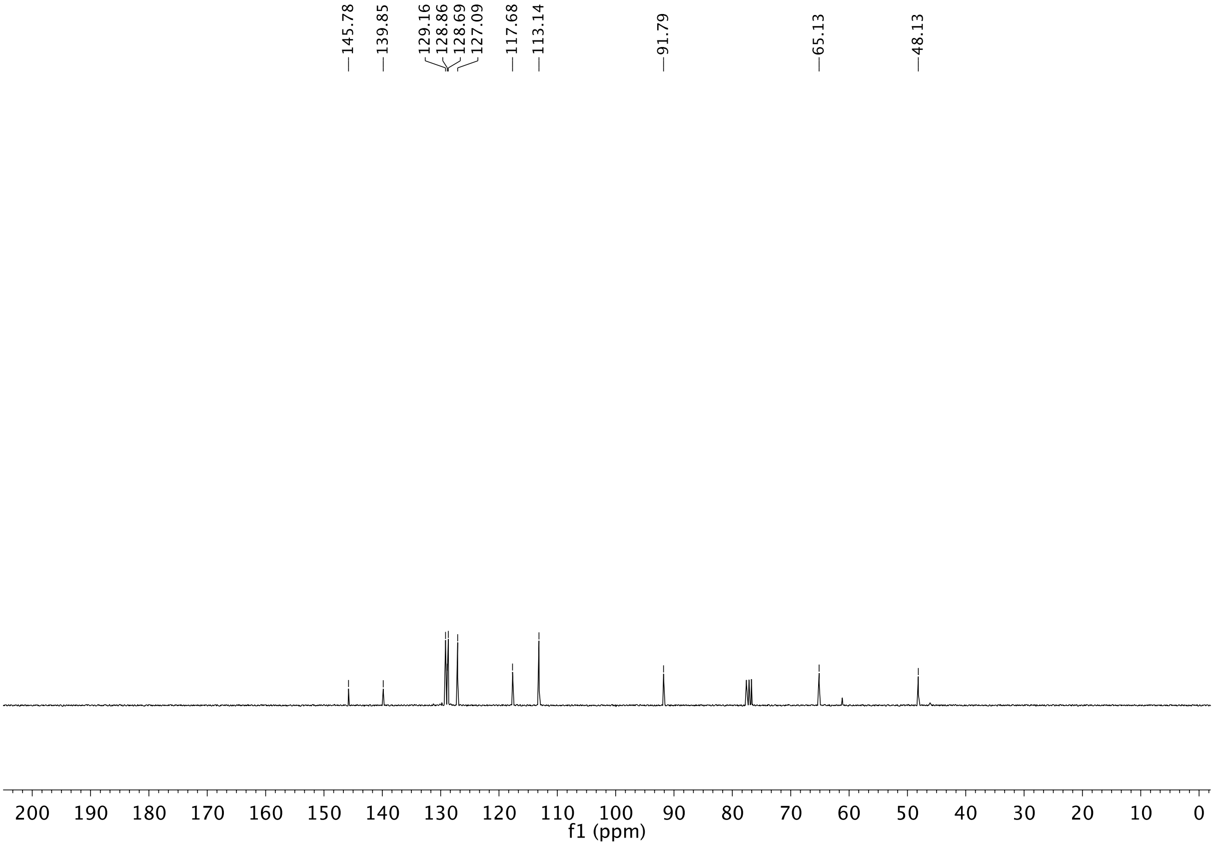
1,3-dimethyl-2-phenylhexahydropyrimidine 21 spectra in DMSO-d_6



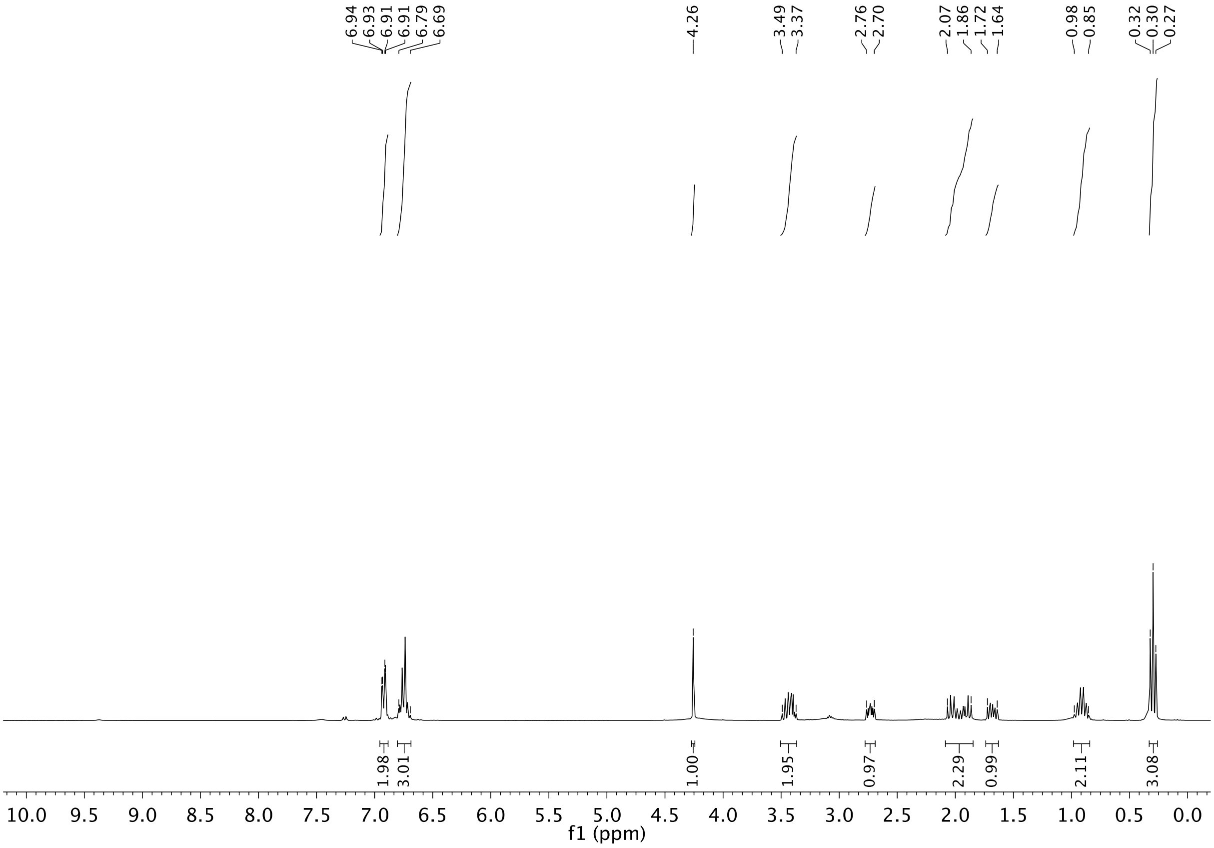


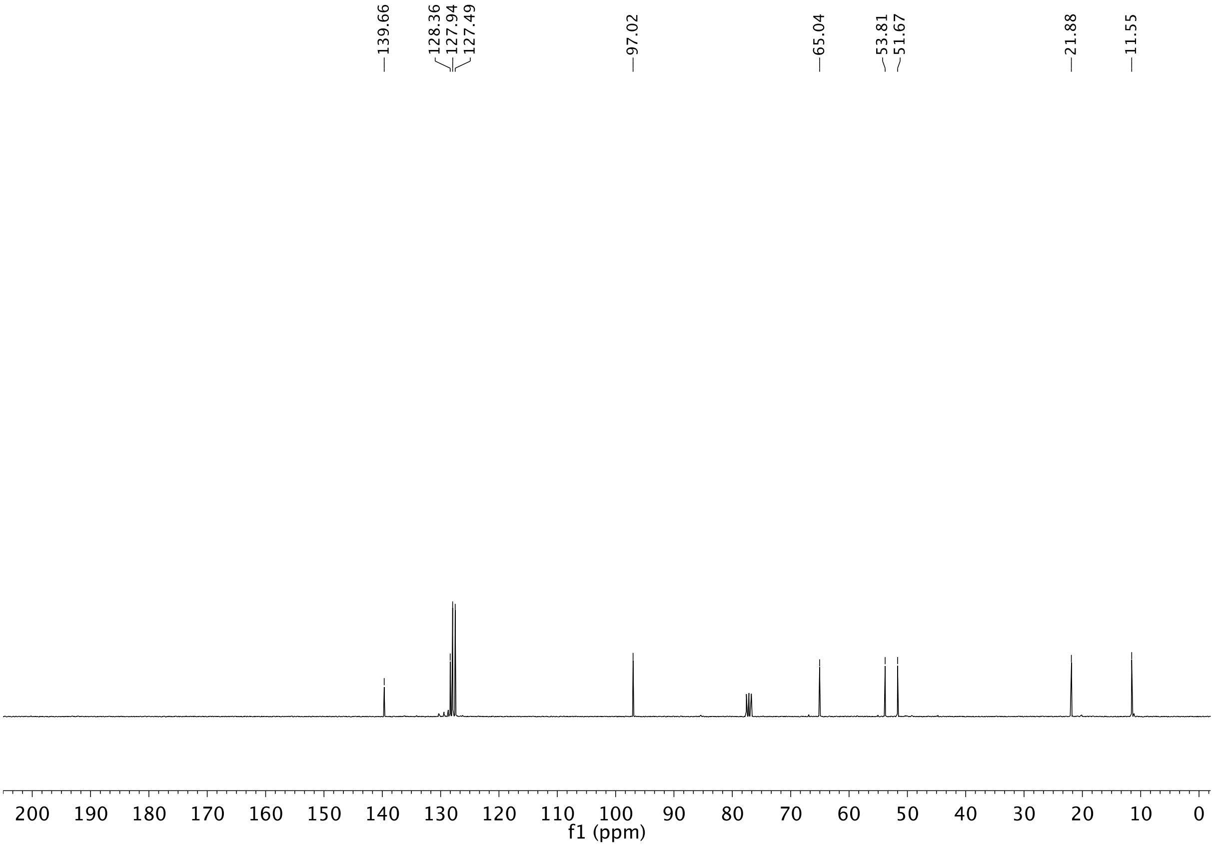
2,3-diphenyloxazolidine 22



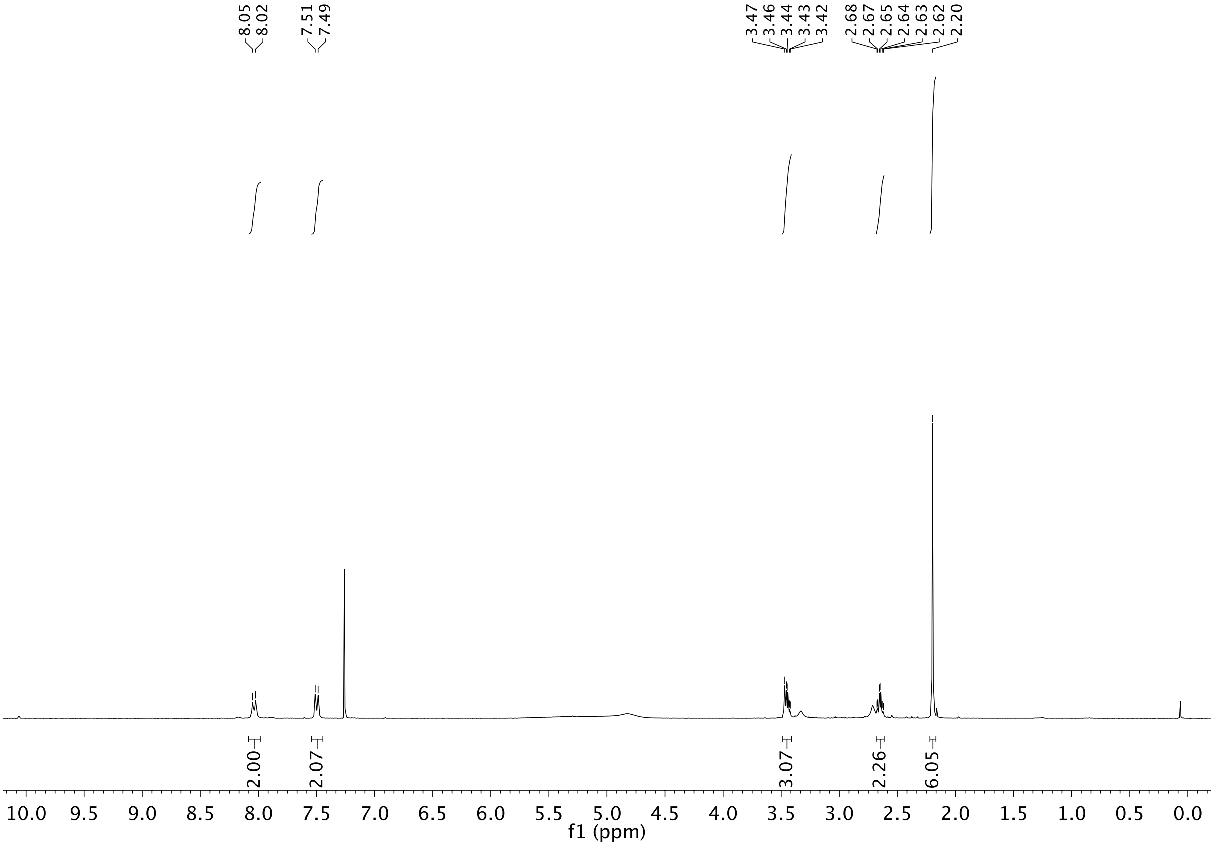


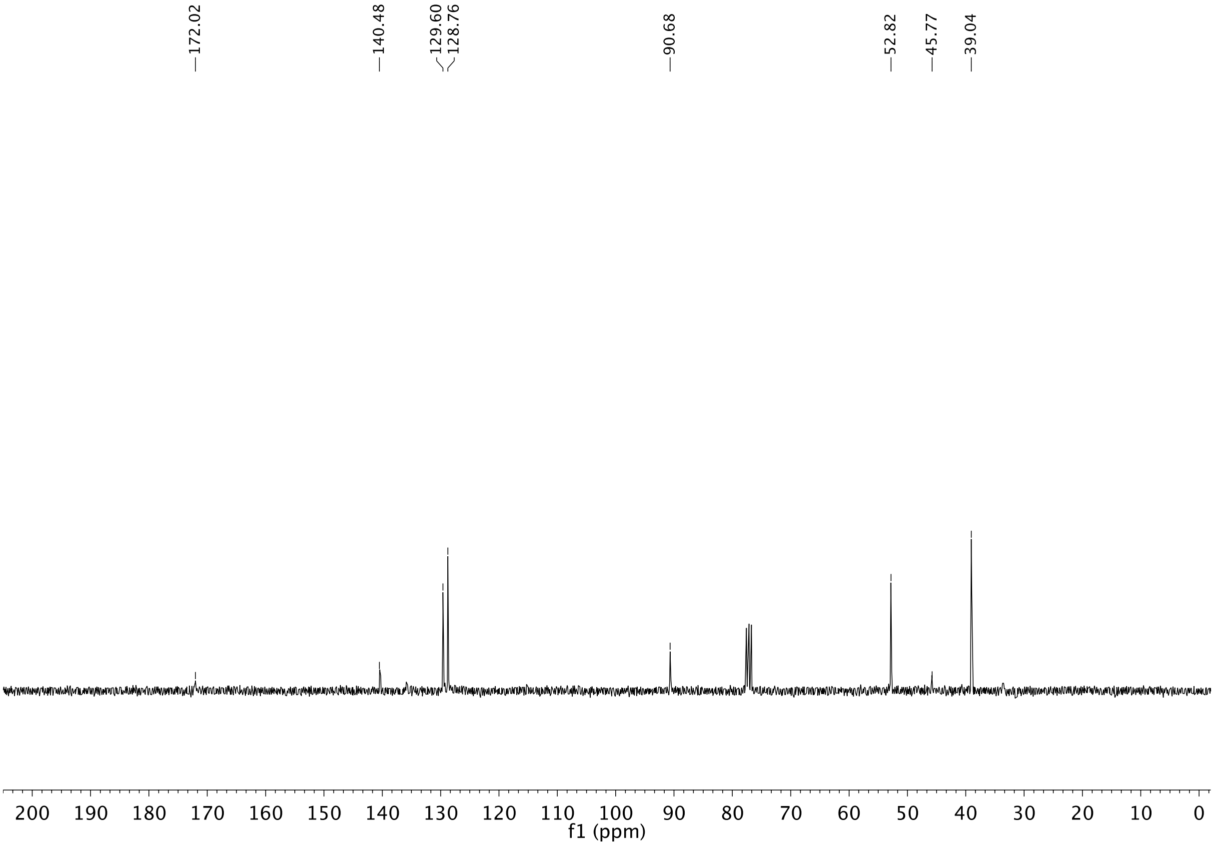
2-phenyl-3-propyloxazolidine 23



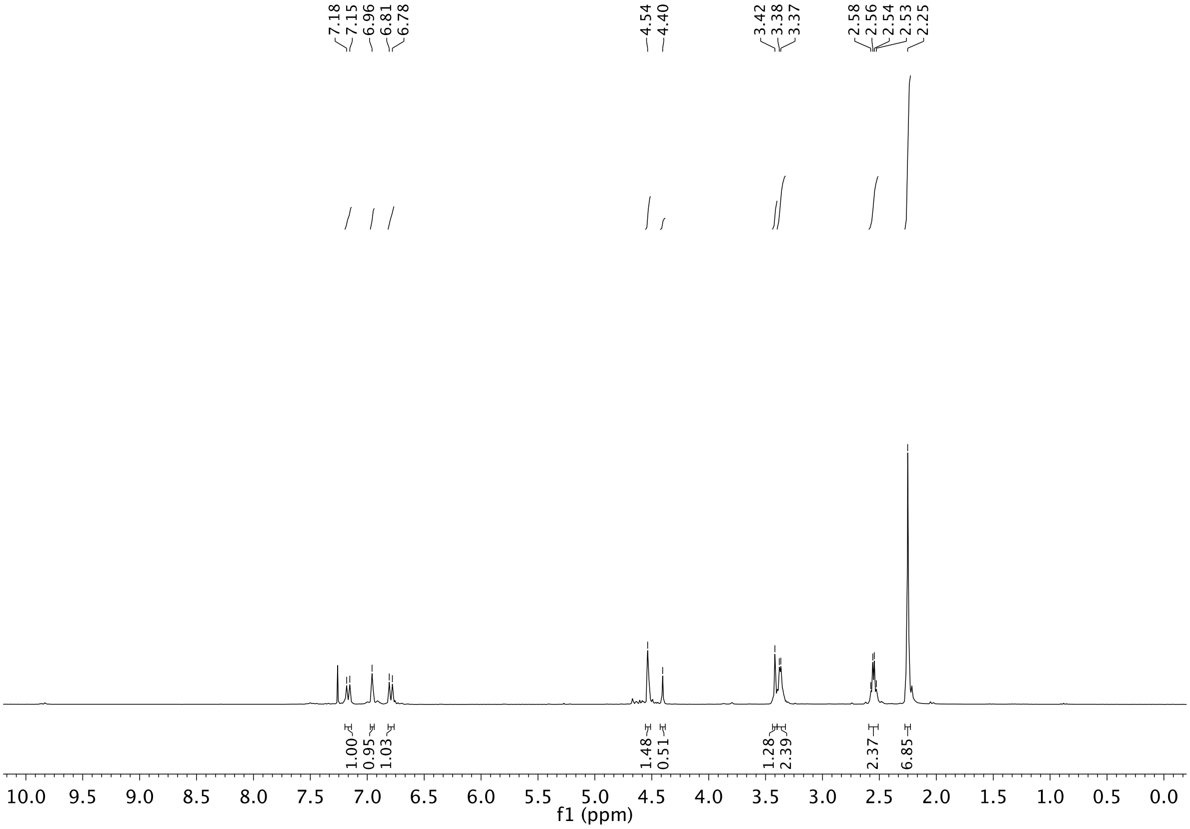


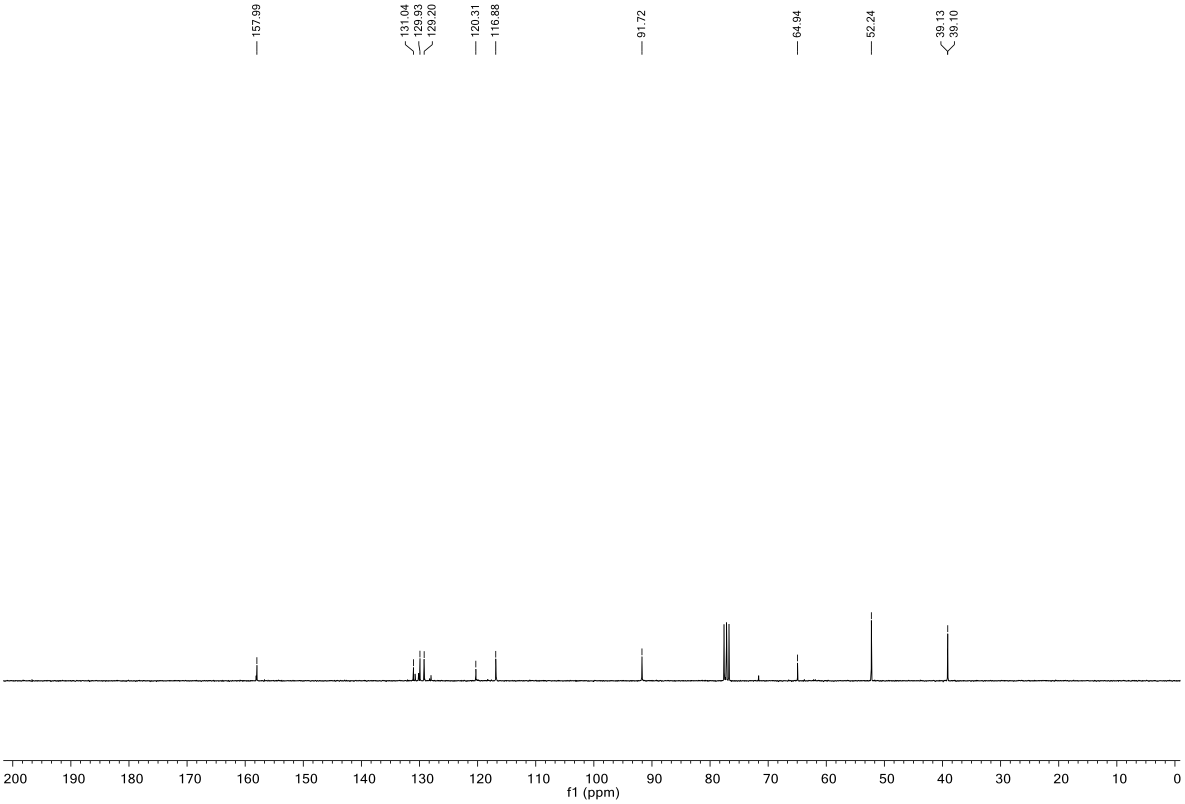
4-(1,3-dimethylimidazolidin-2-yl)benzoic acid 24



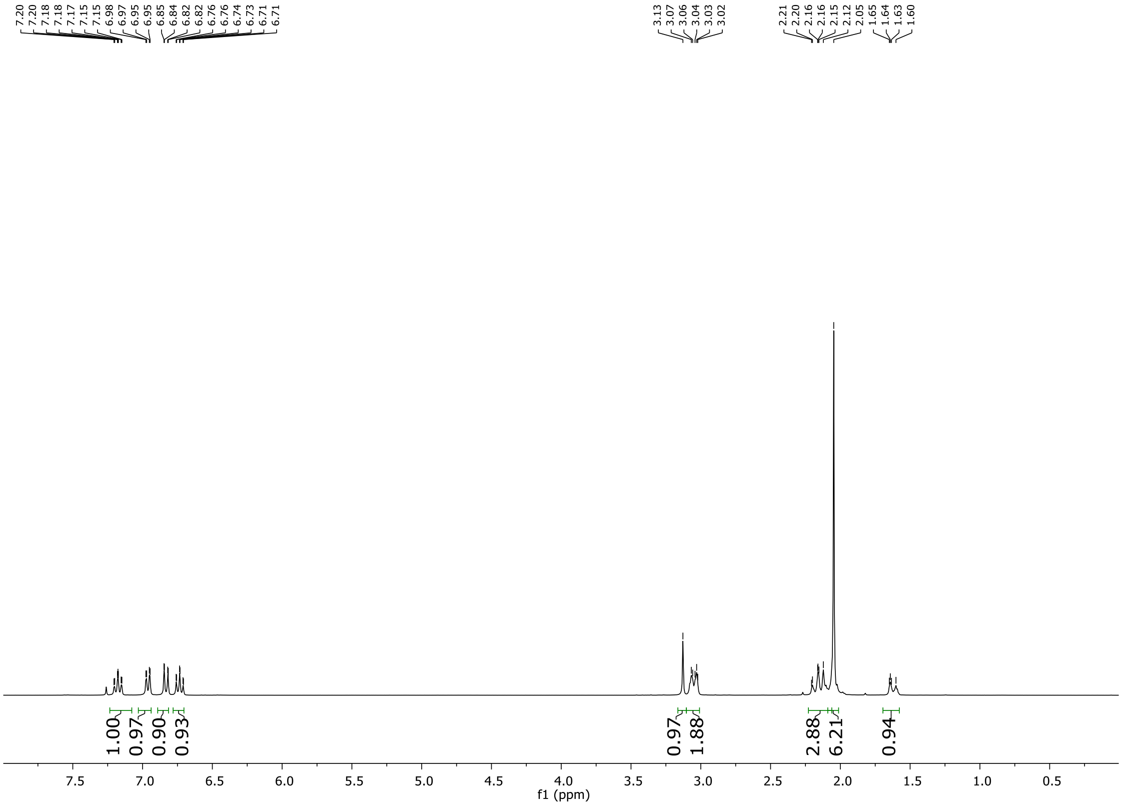


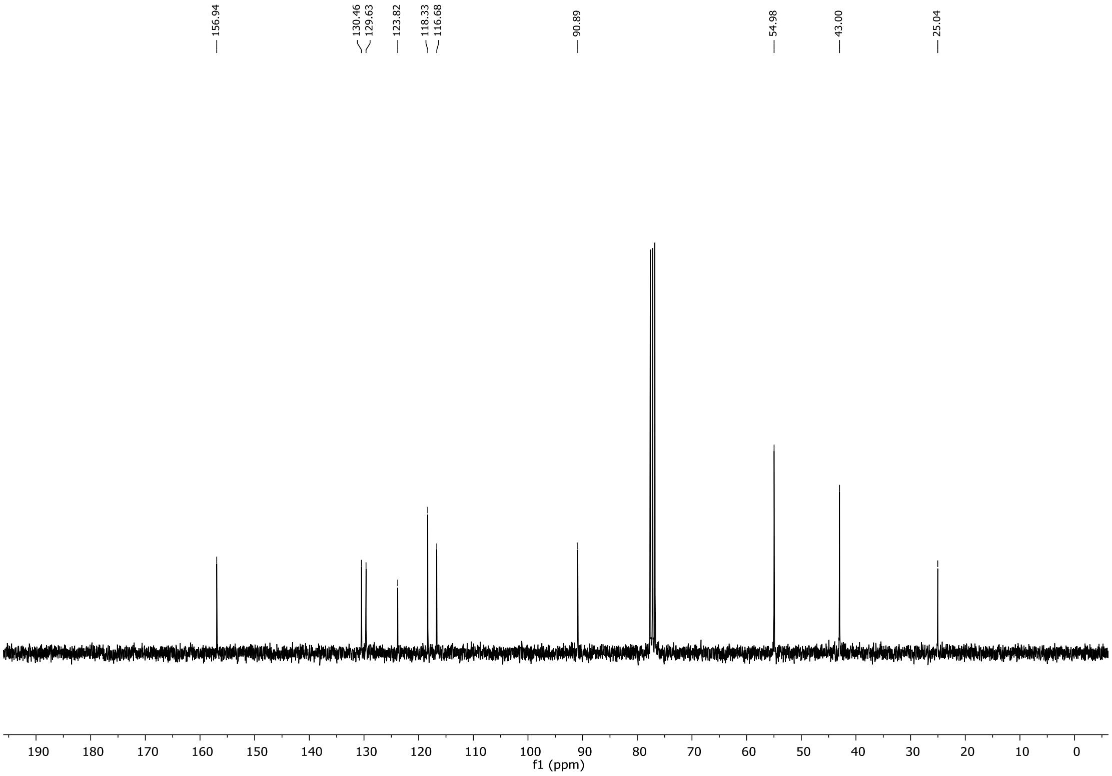
2-(1,3-dimethylimidazolidin-2-yl)-5-(hydroxymethyl)phenol 25



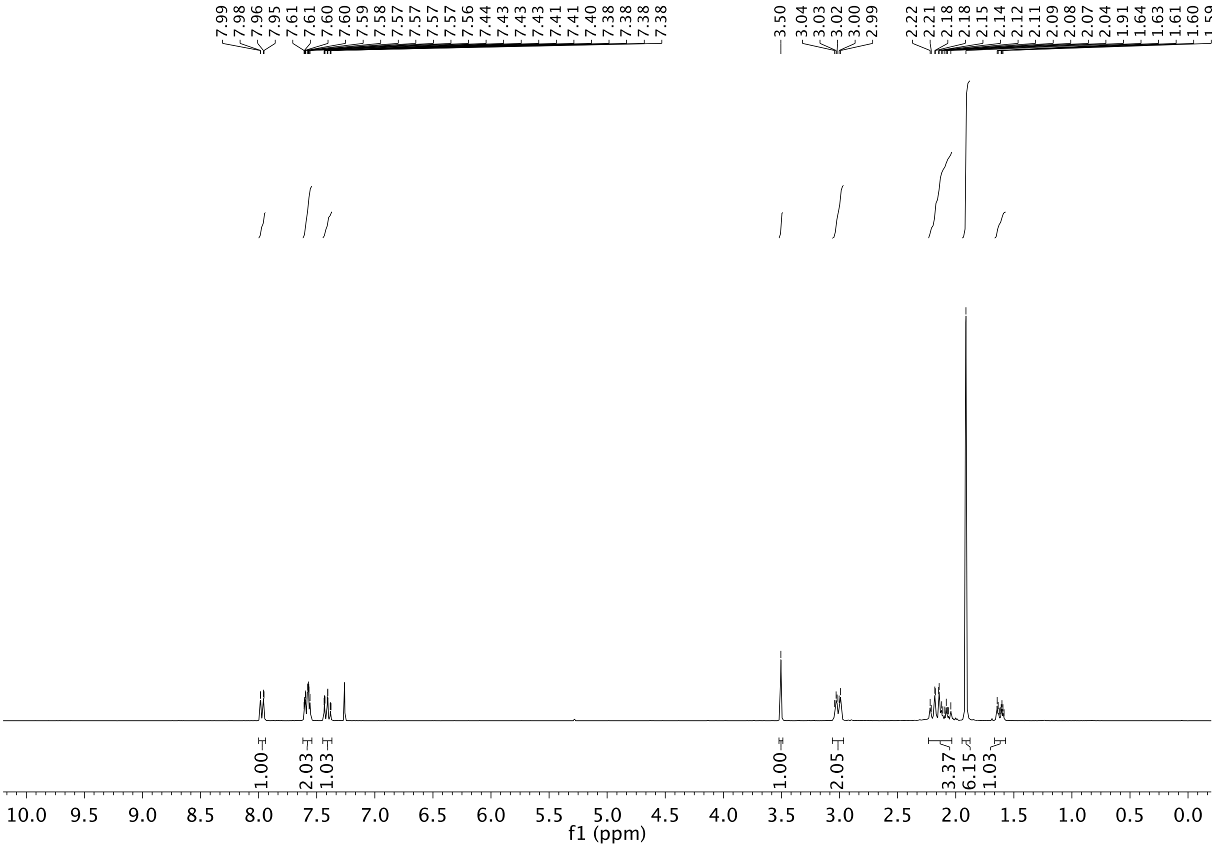


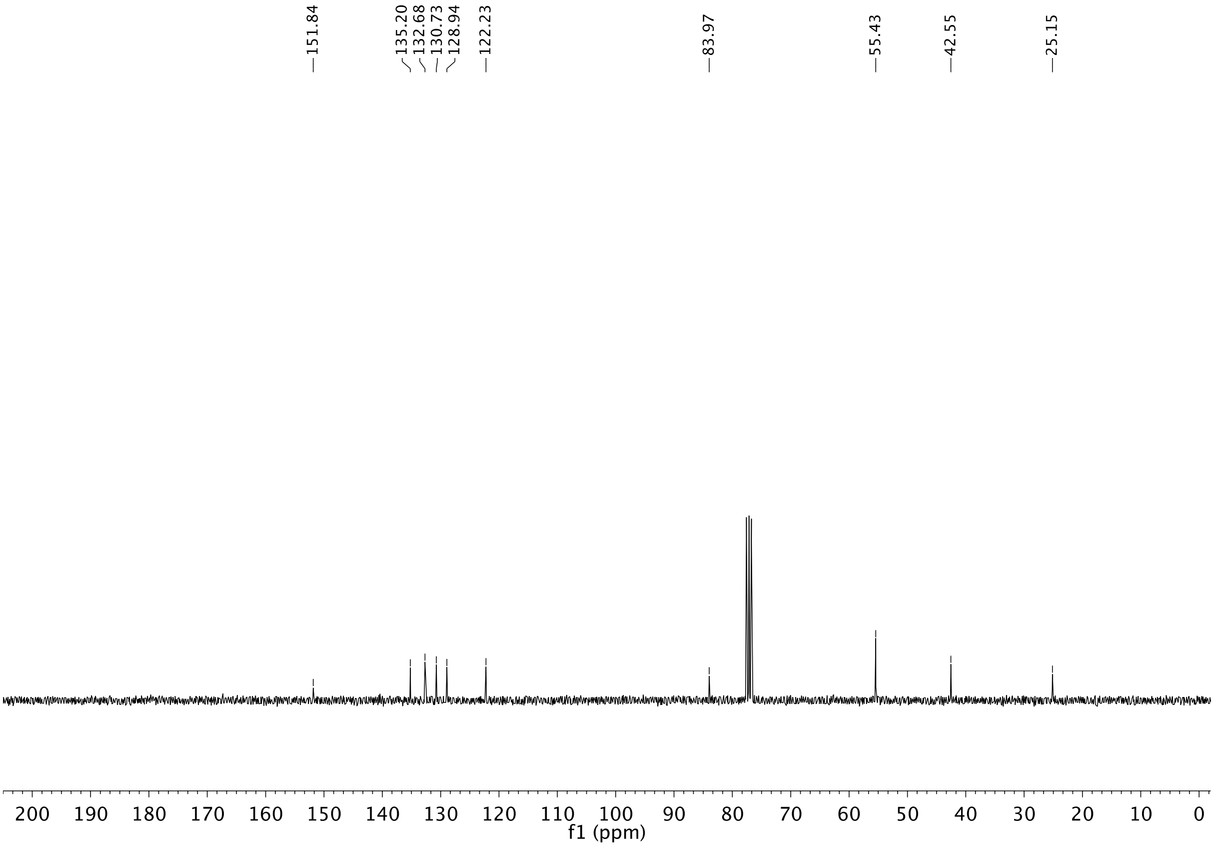
2-(1,3-dimethylhexahydropyrimidin-2-yl)phenol 26



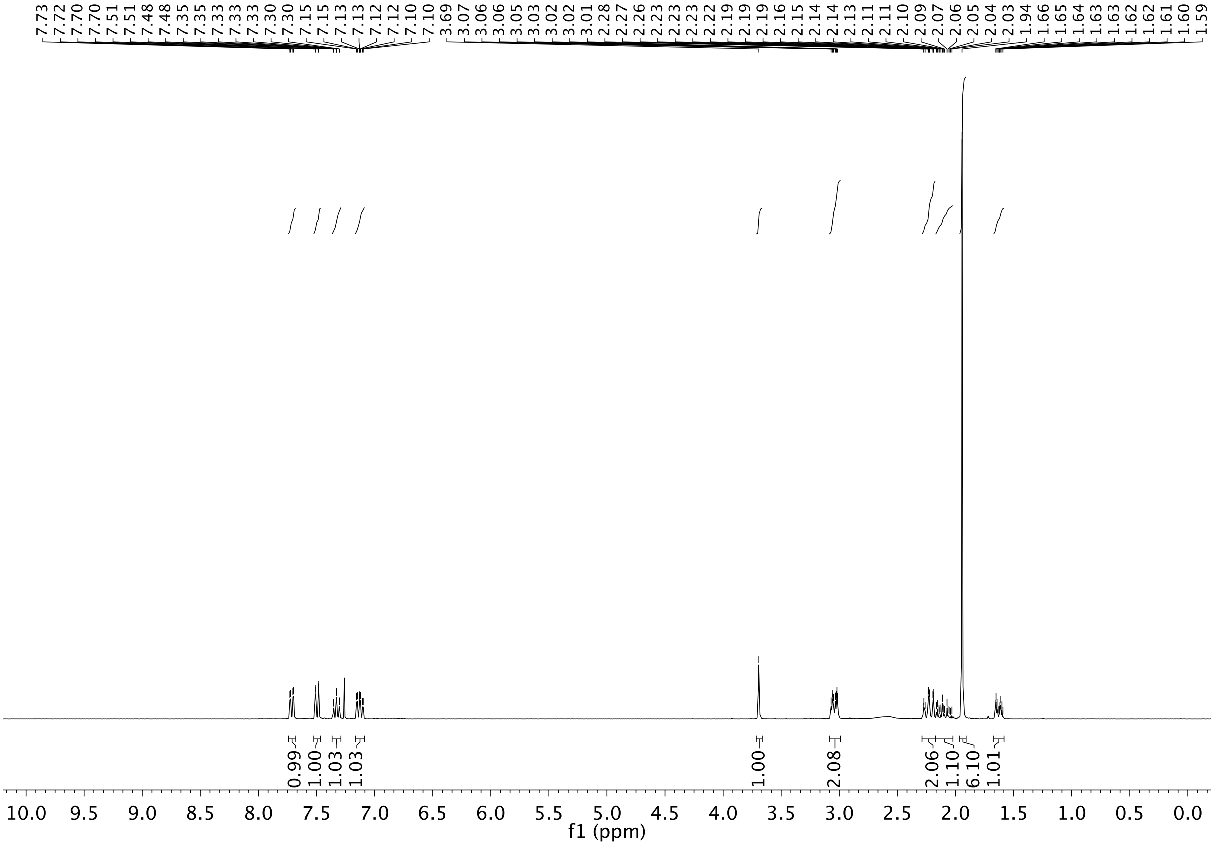


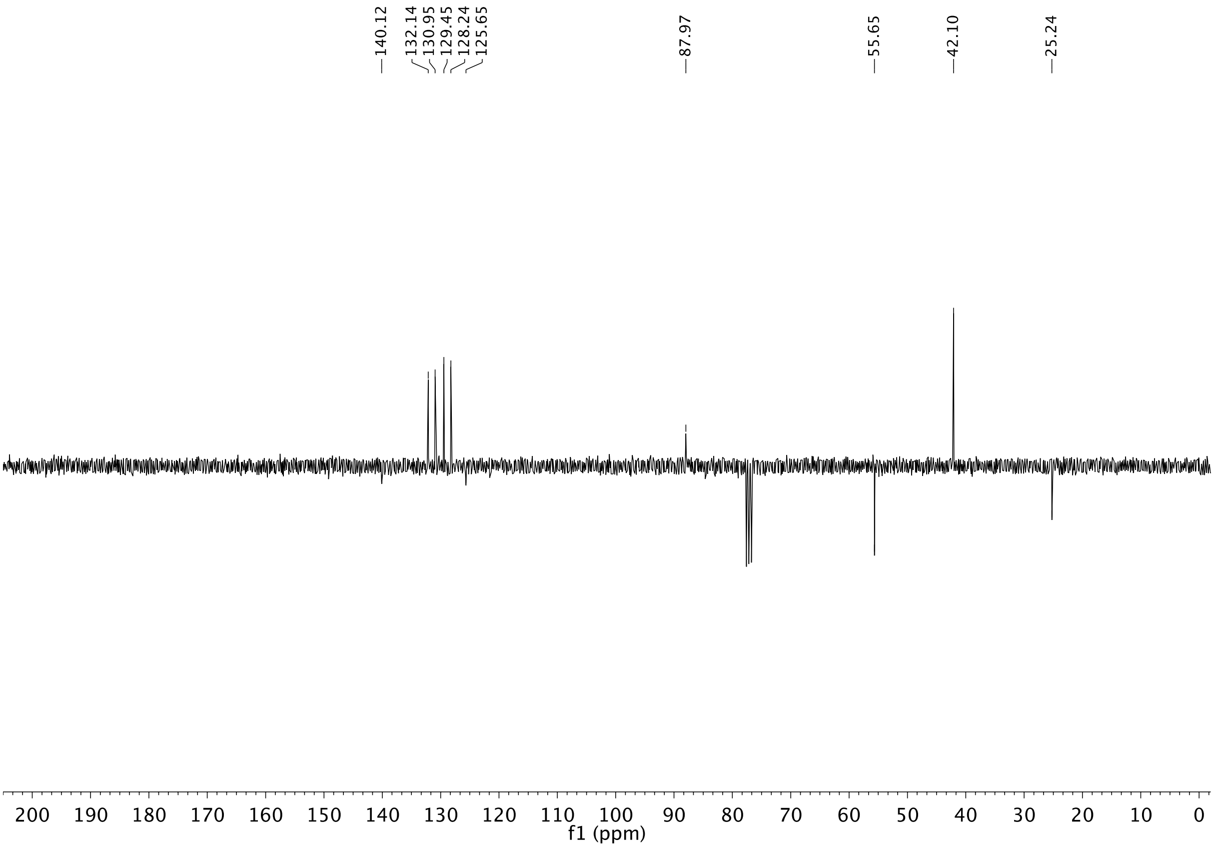
1,3-dimethyl-2-(2-nitrophenyl)hexahydropyrimidine 27



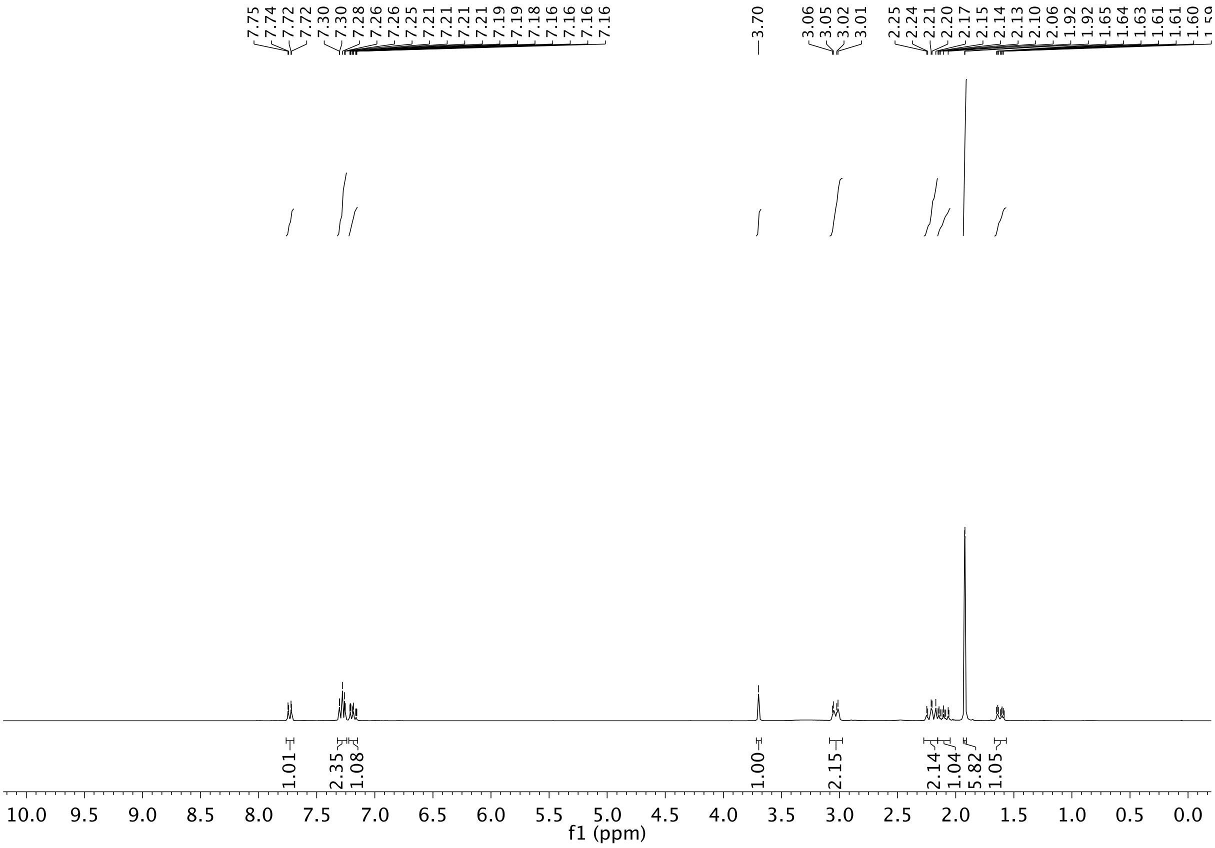


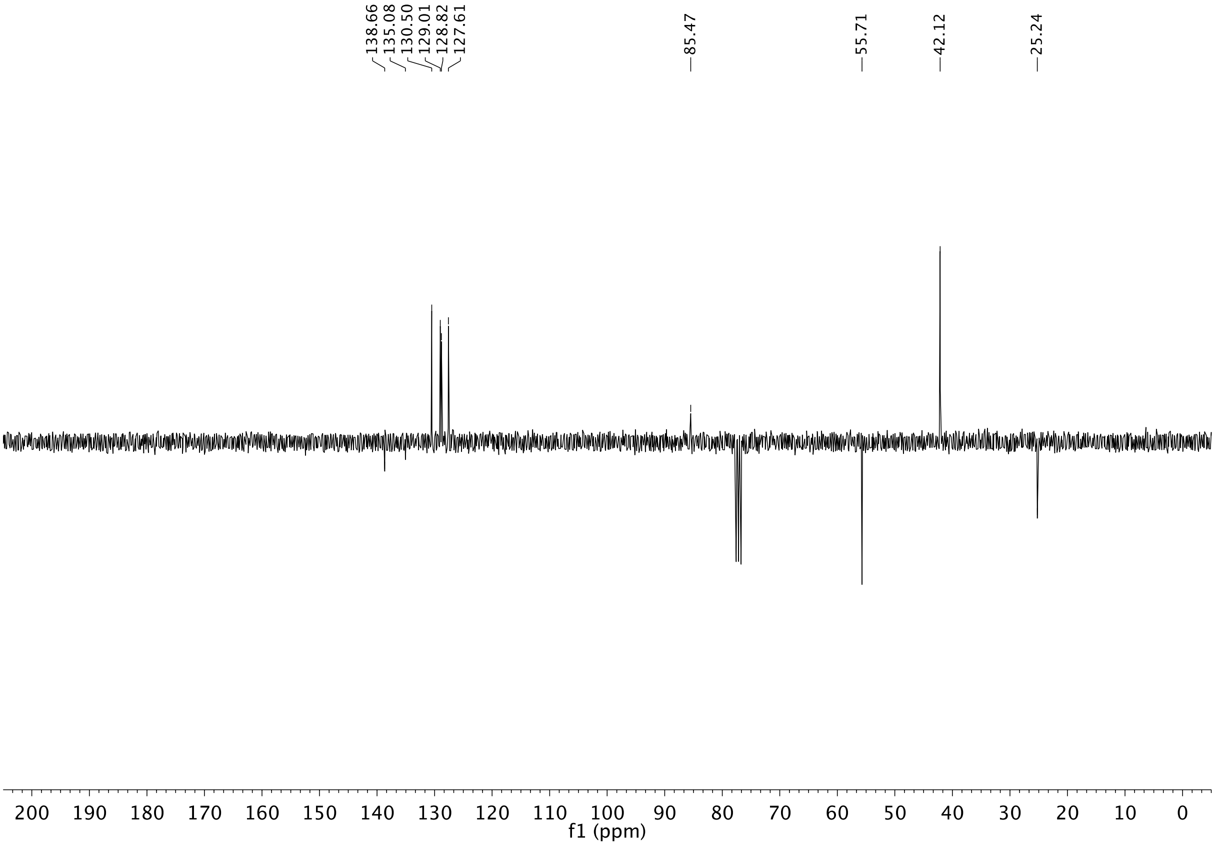
2-(2-bromophenyl)-1,3-dimethylhexahydropyrimidine 28



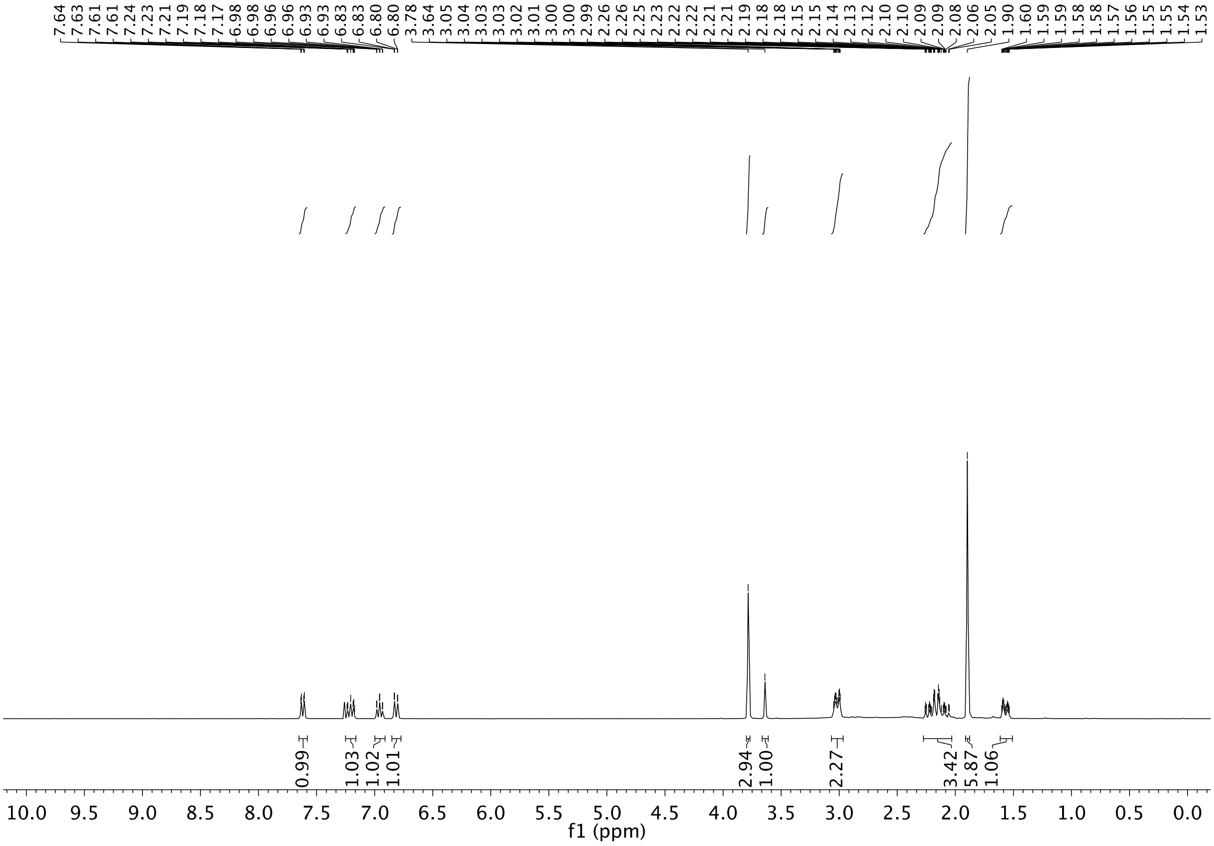


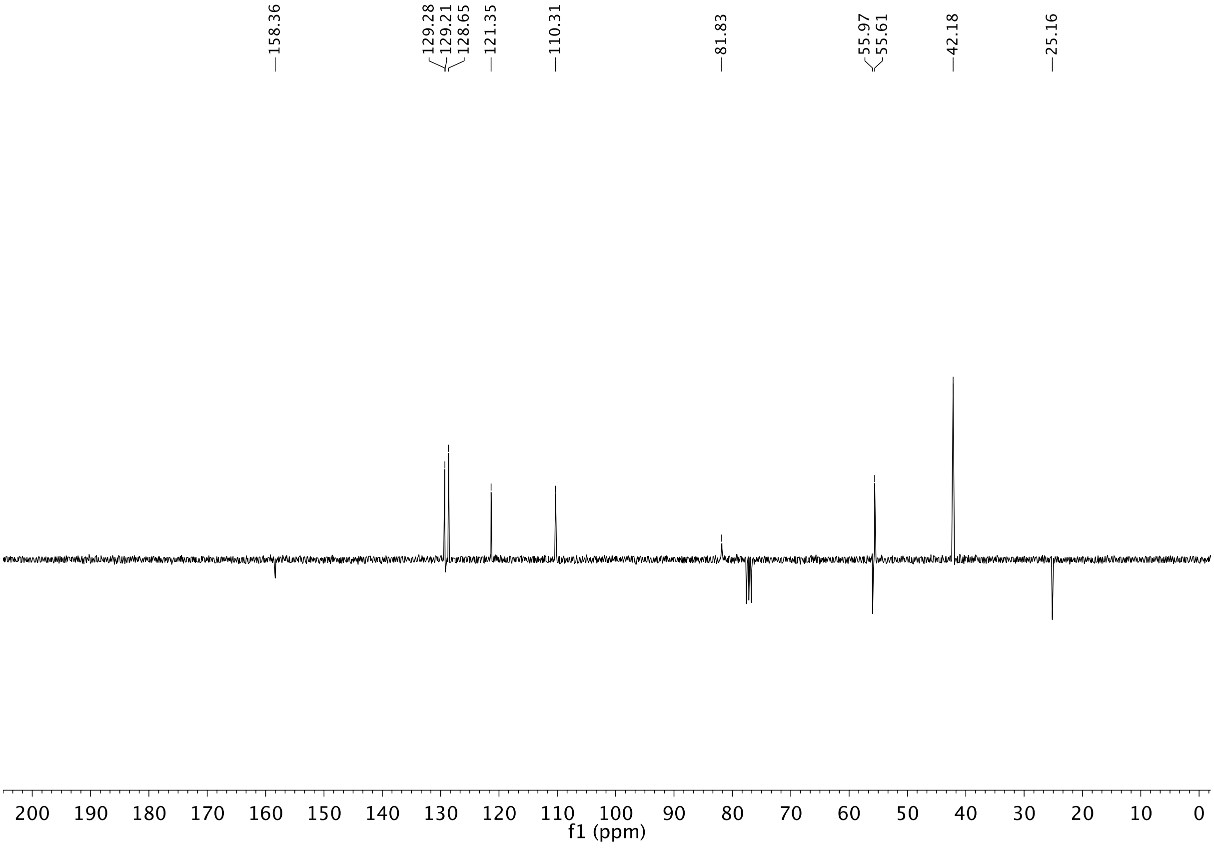
2-(2-chlorophenyl)-1,3-dimethylhexahydropyrimidine 29



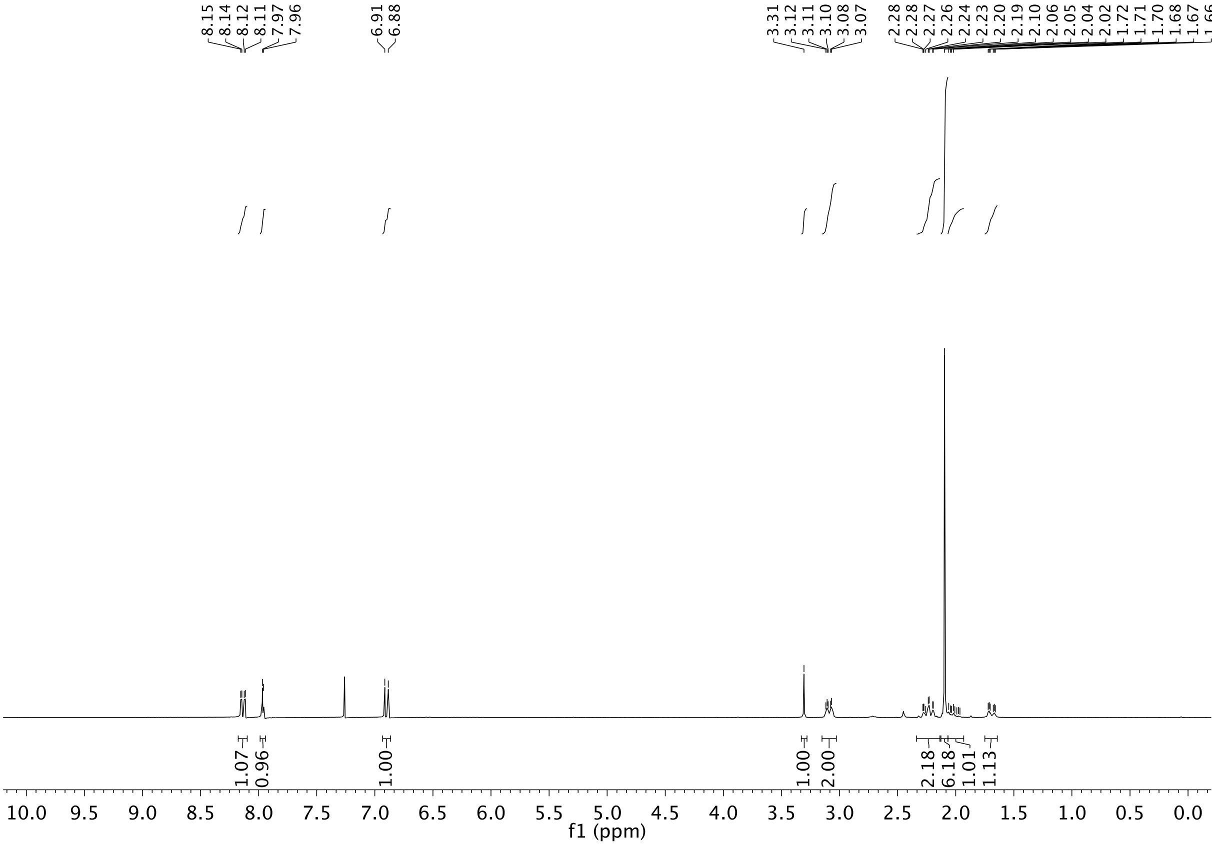


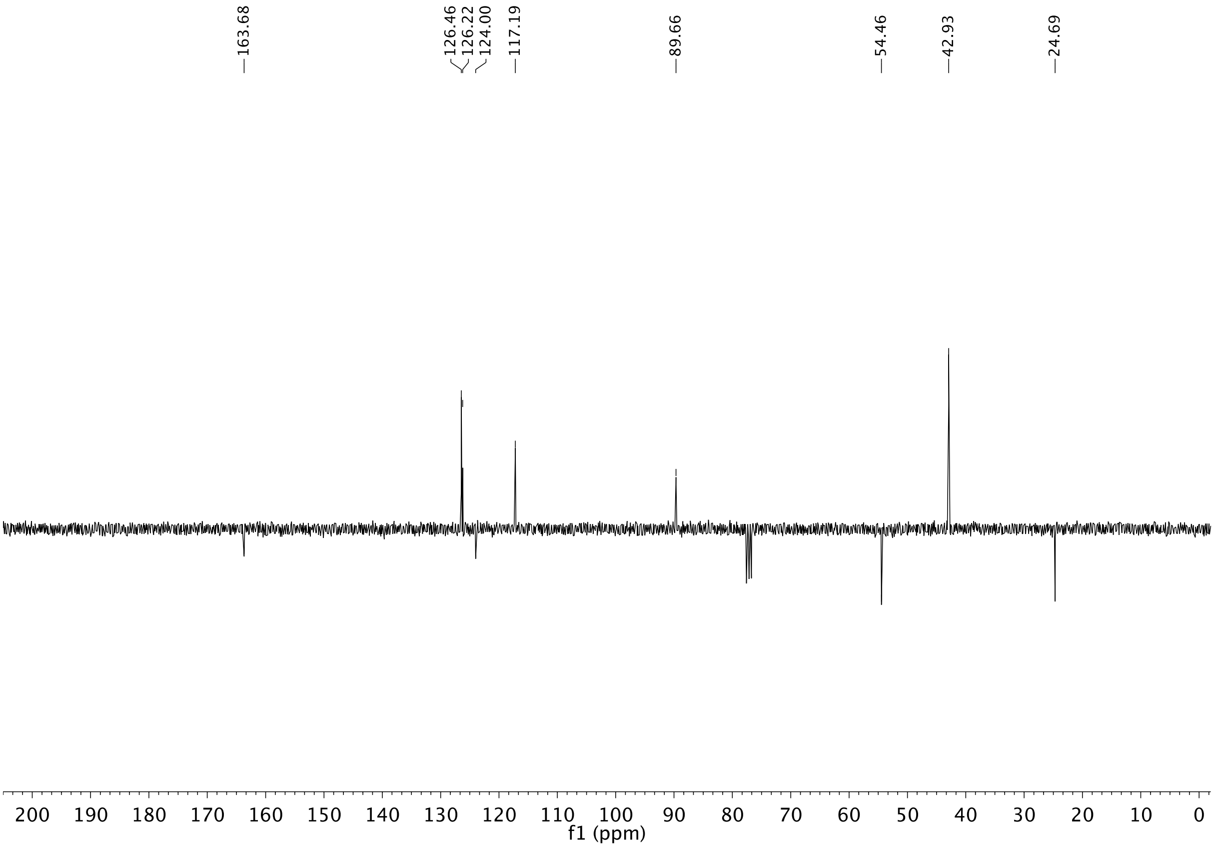
2-(2-methoxyphenyl)-1,3-dimethylhexahydropyrimidine 30



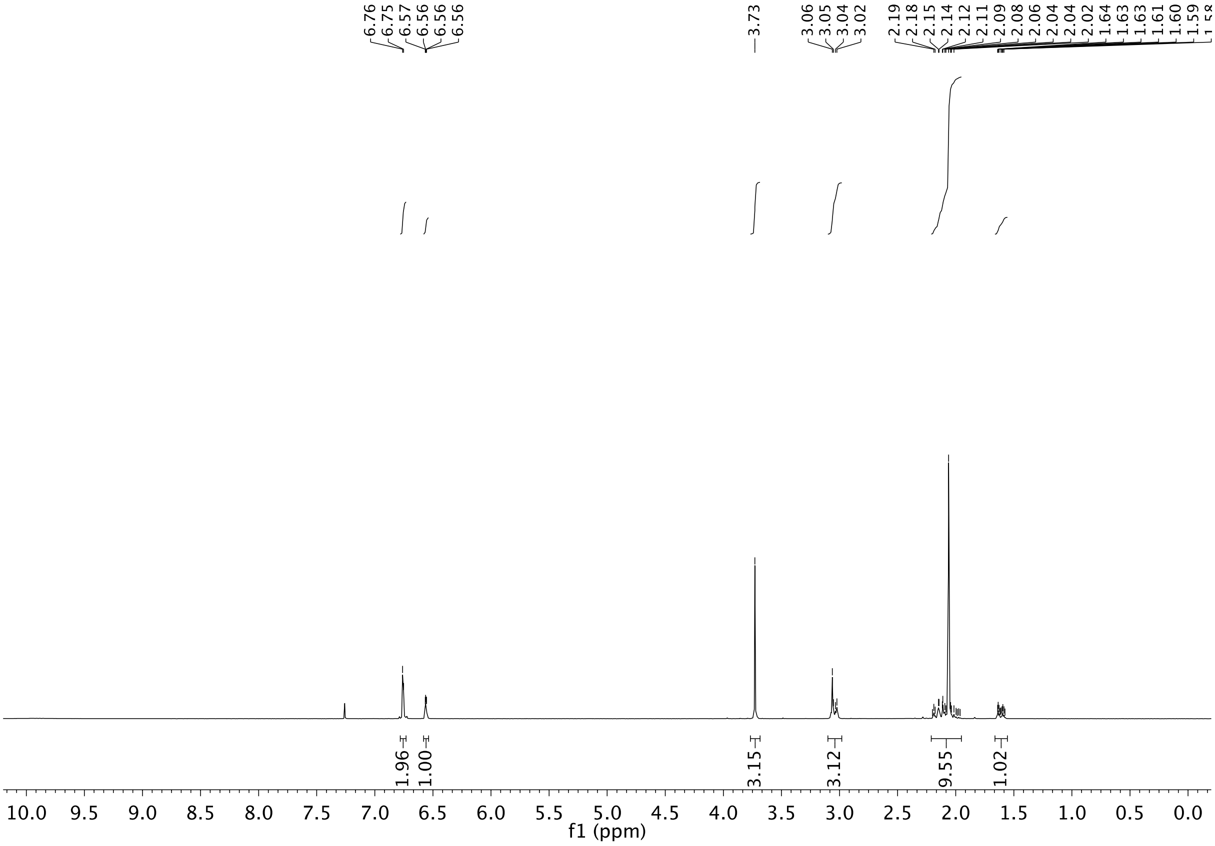


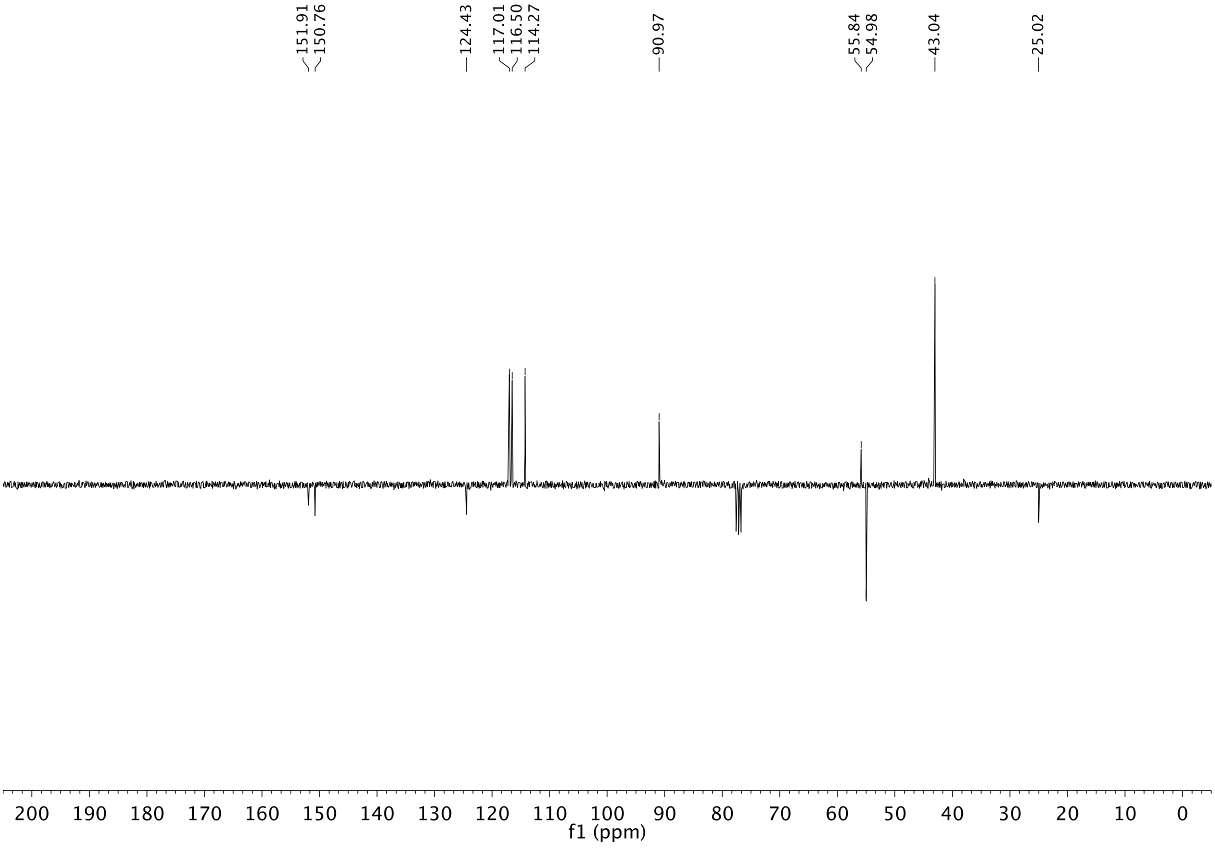
2-(1,3-dimethylhexahydropyrimidin-2-yl)-4-nitrophenol 31



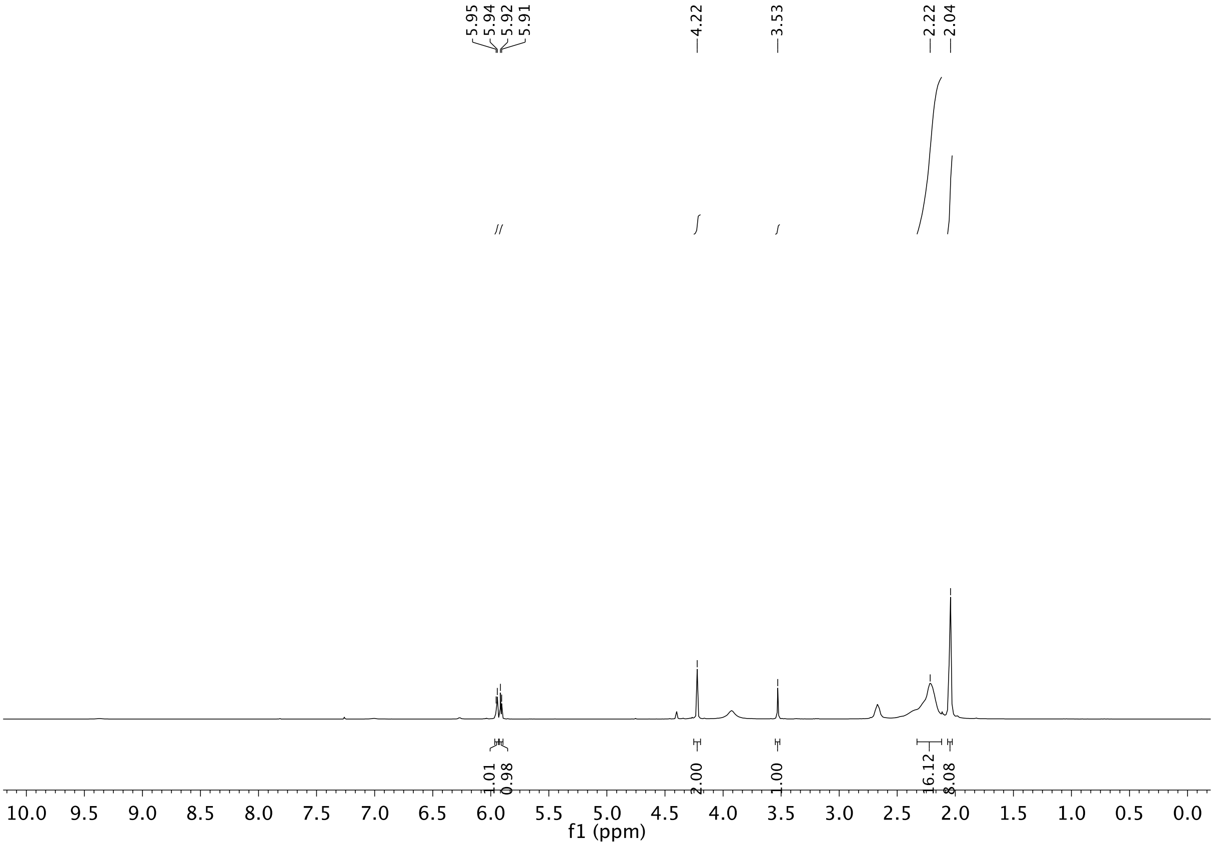


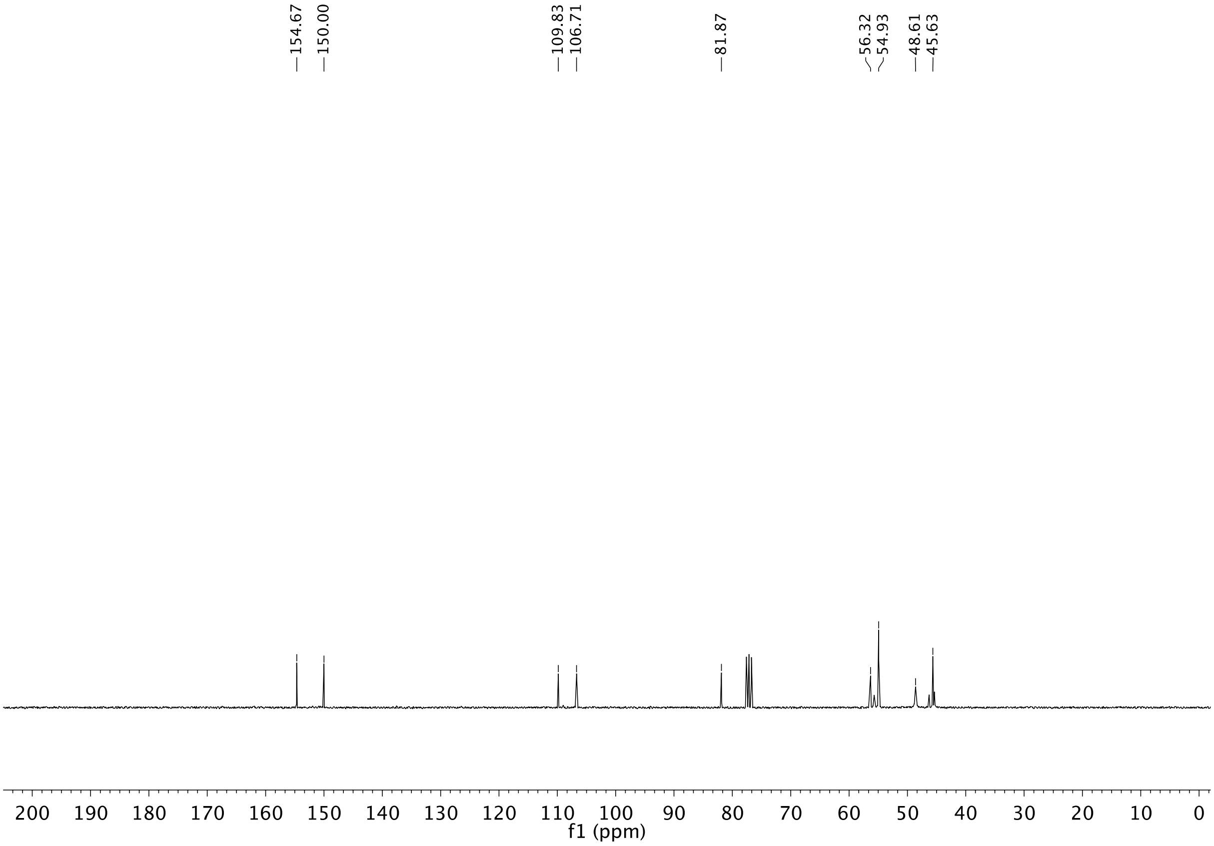
2-(1,3-dimethylhexahydropyrimidin-2-yl)-4-methoxyphenol 32



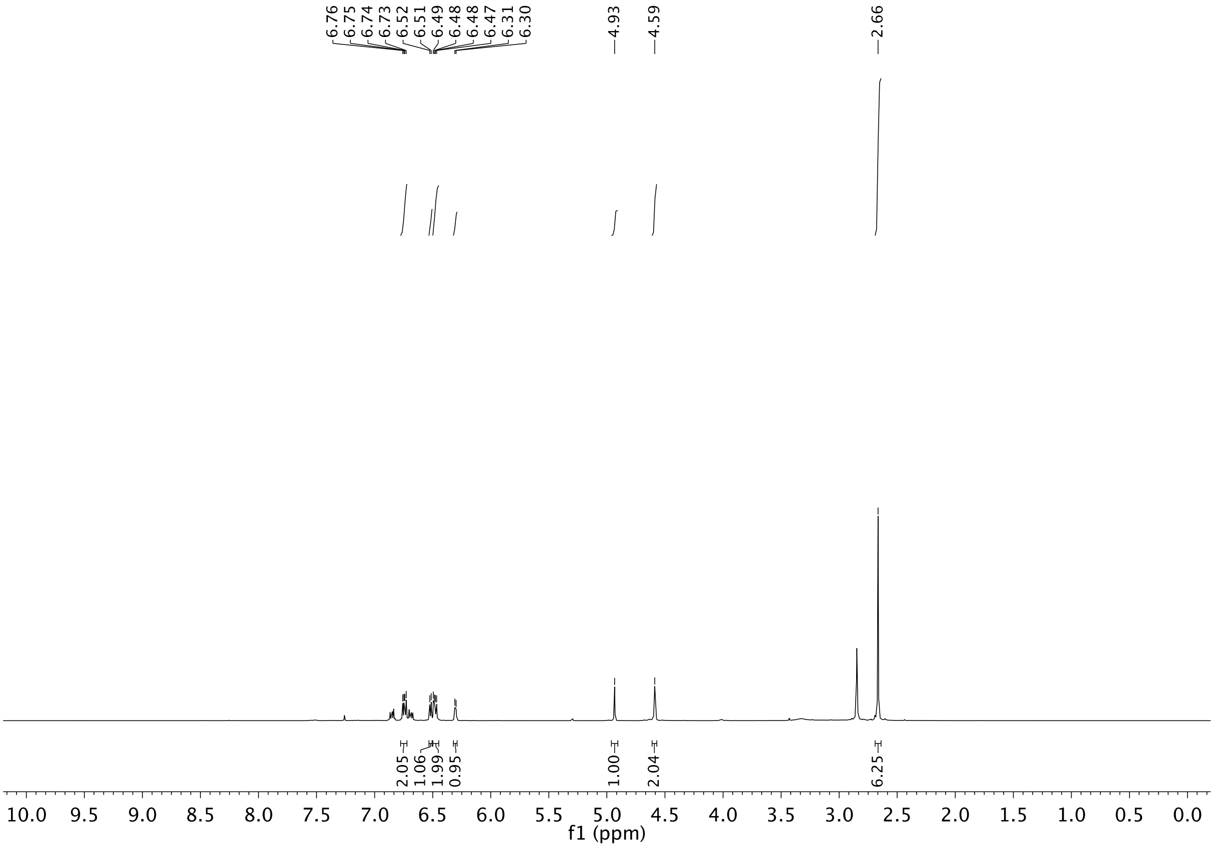


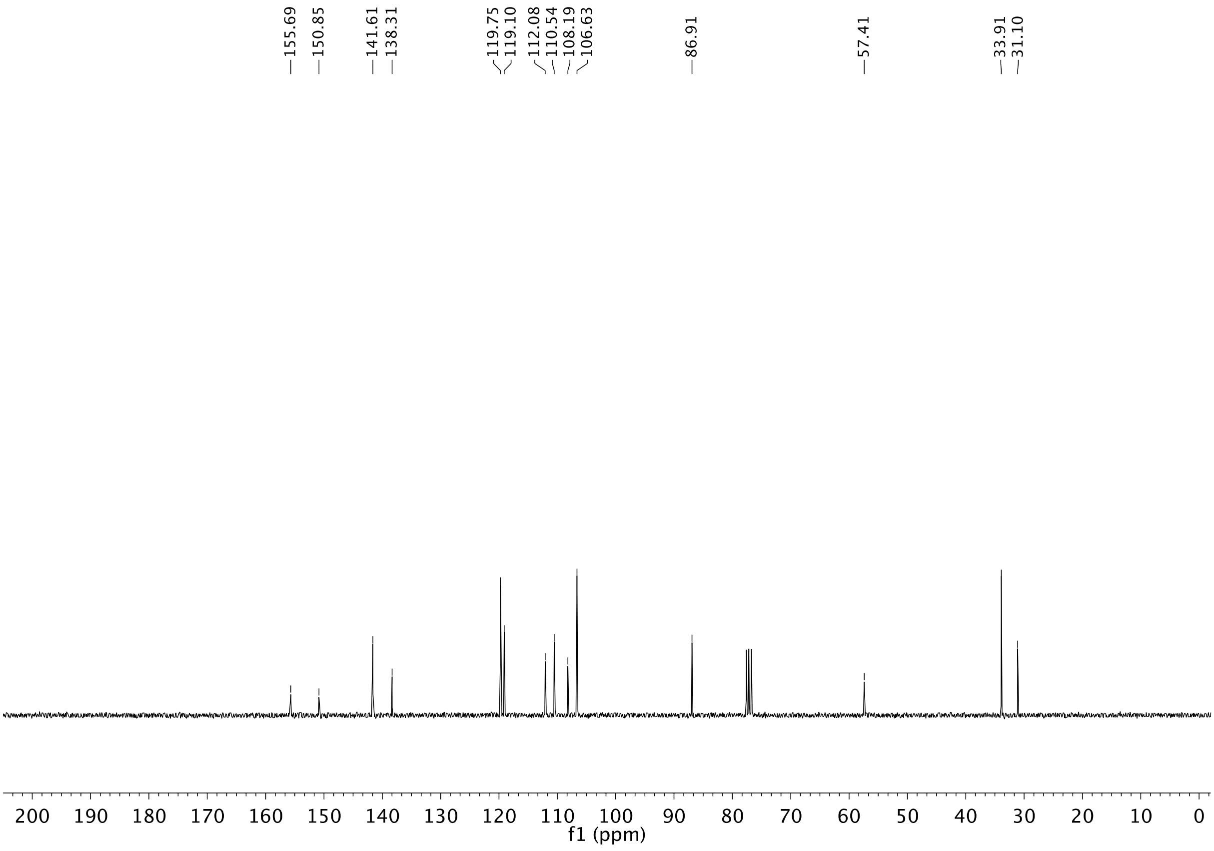
(5-(bis(4-methylpiperazin-1-yl)methyl)furan-2-yl)methanol 33



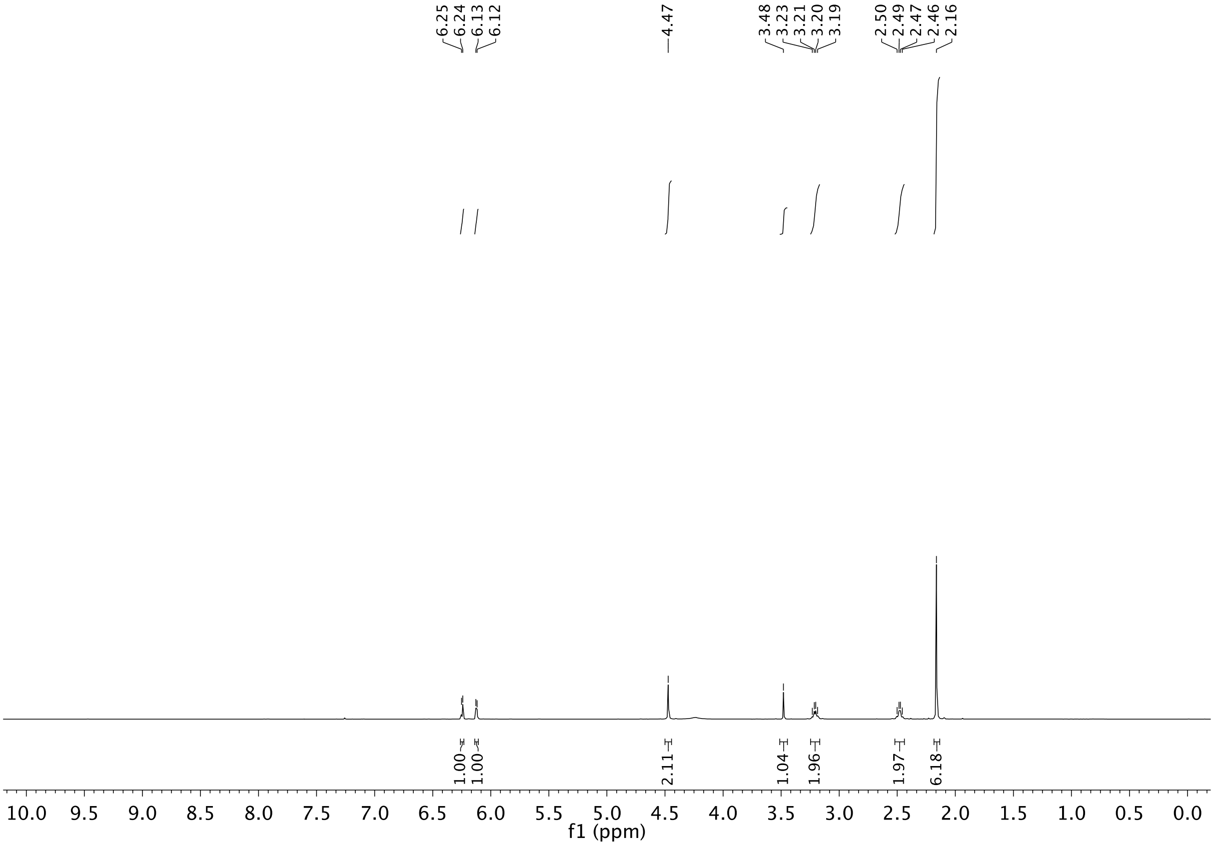


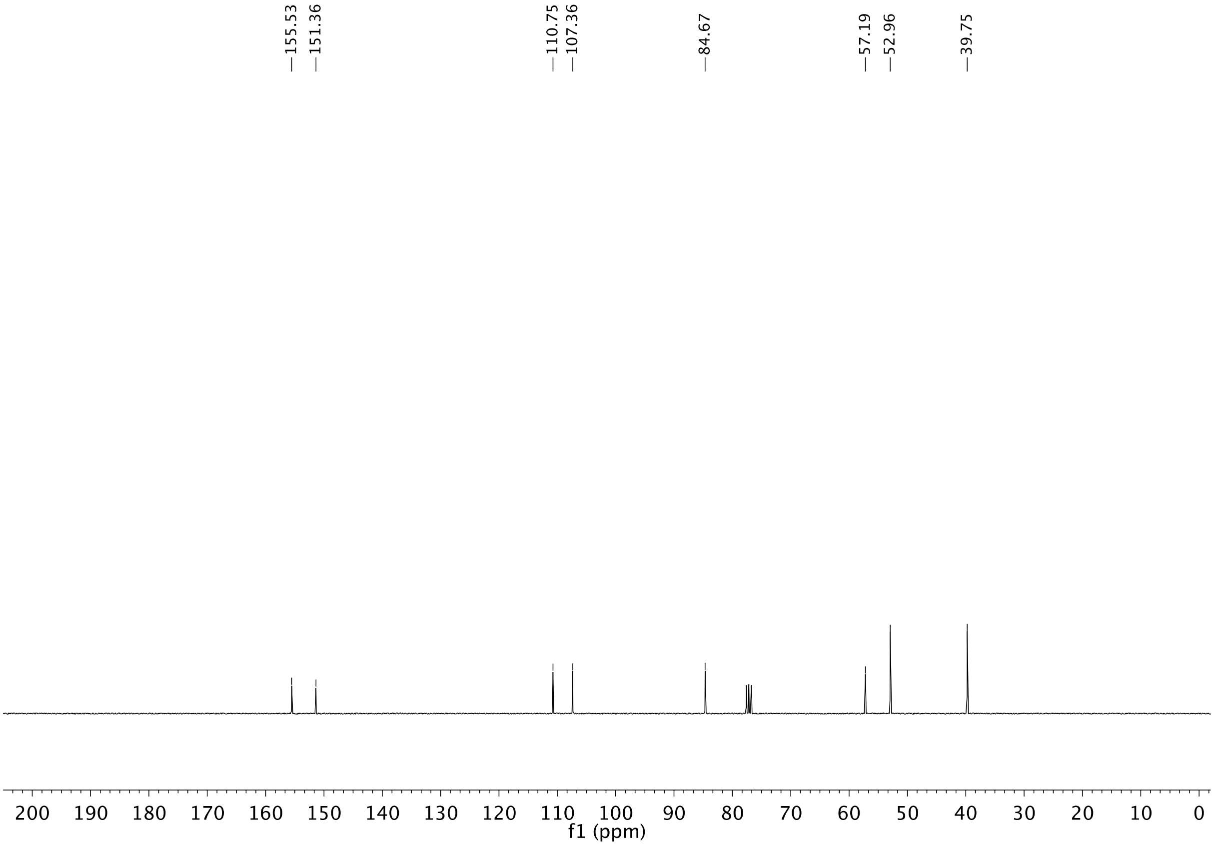
(5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol 34



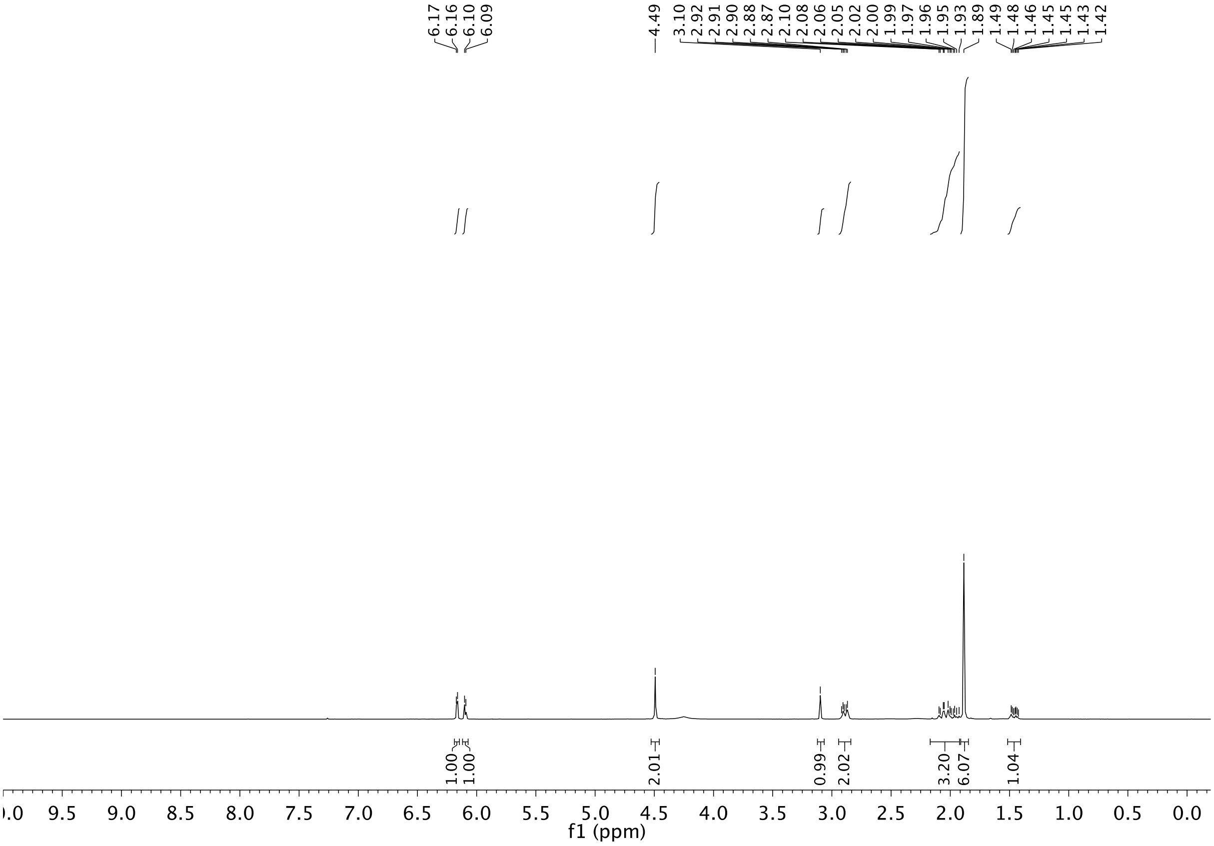


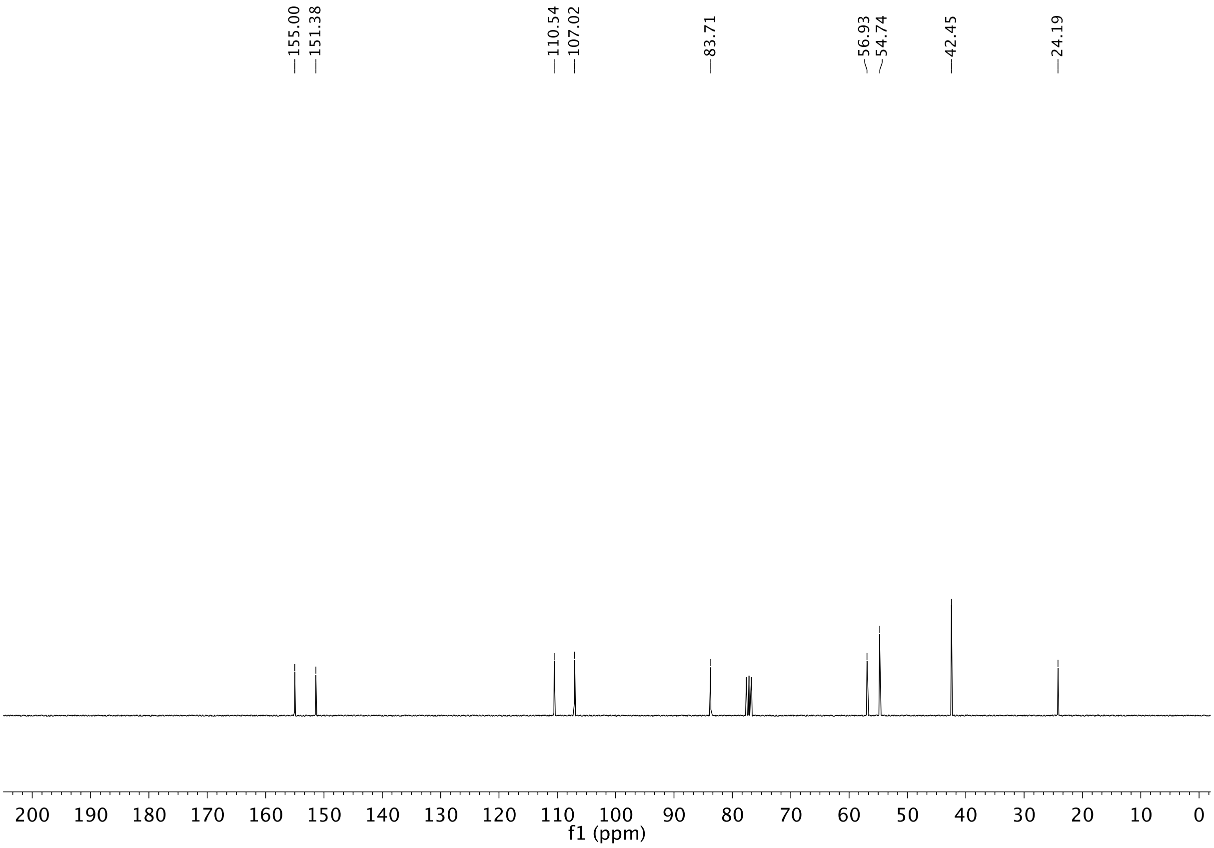
(5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol 35



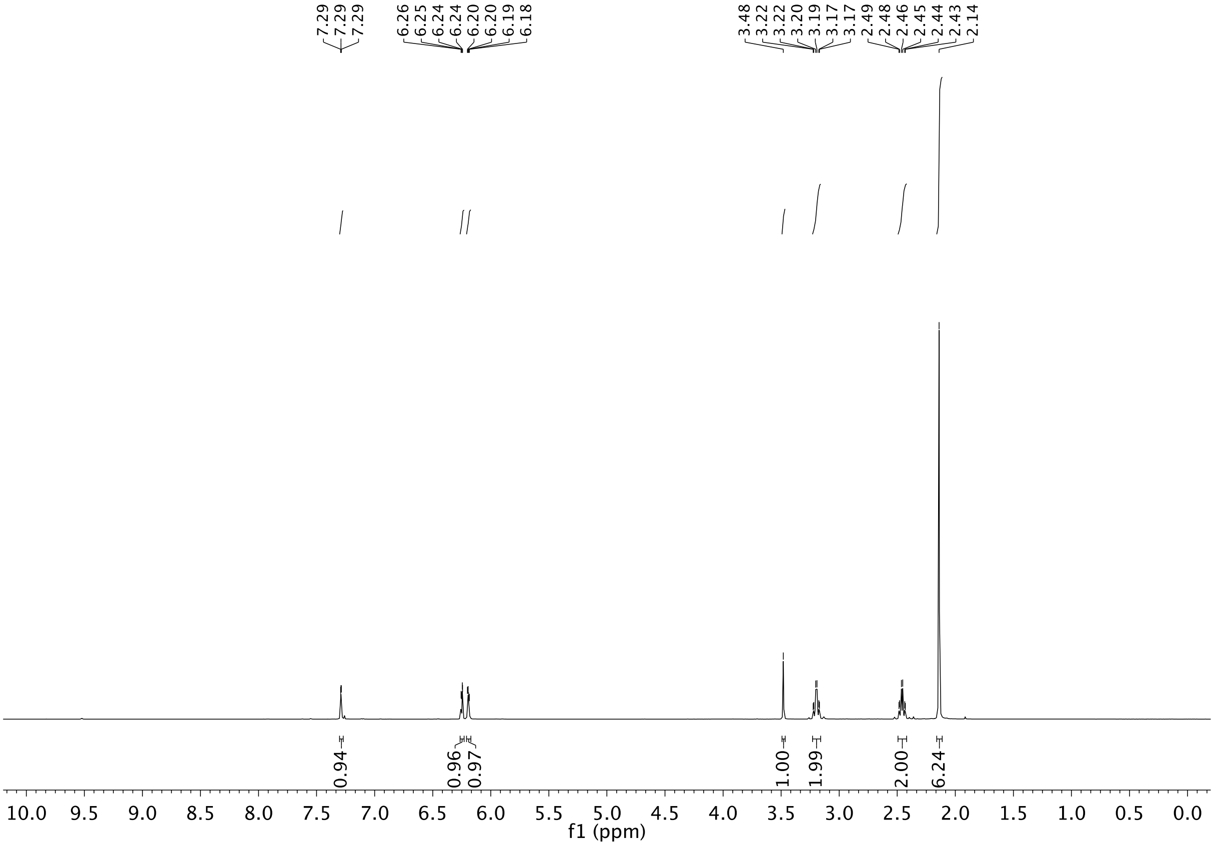


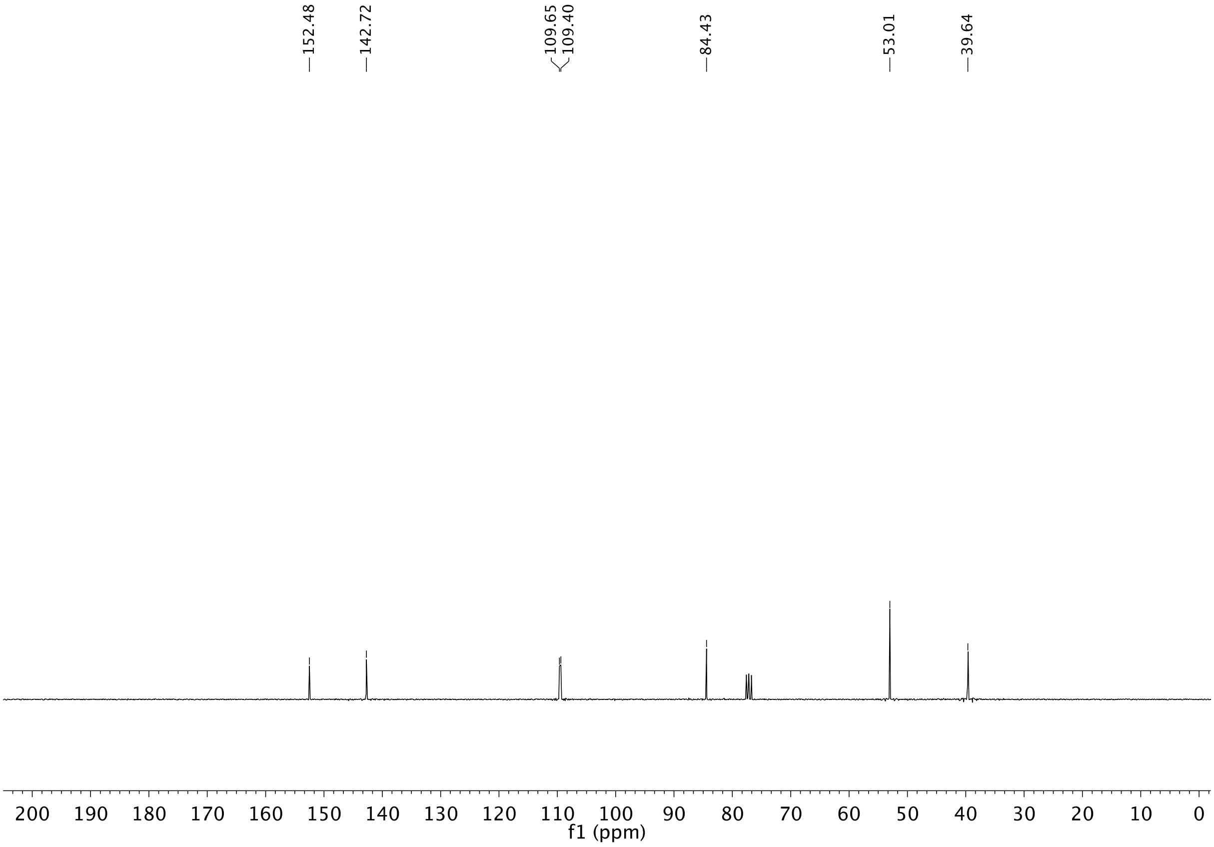
(5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol 36



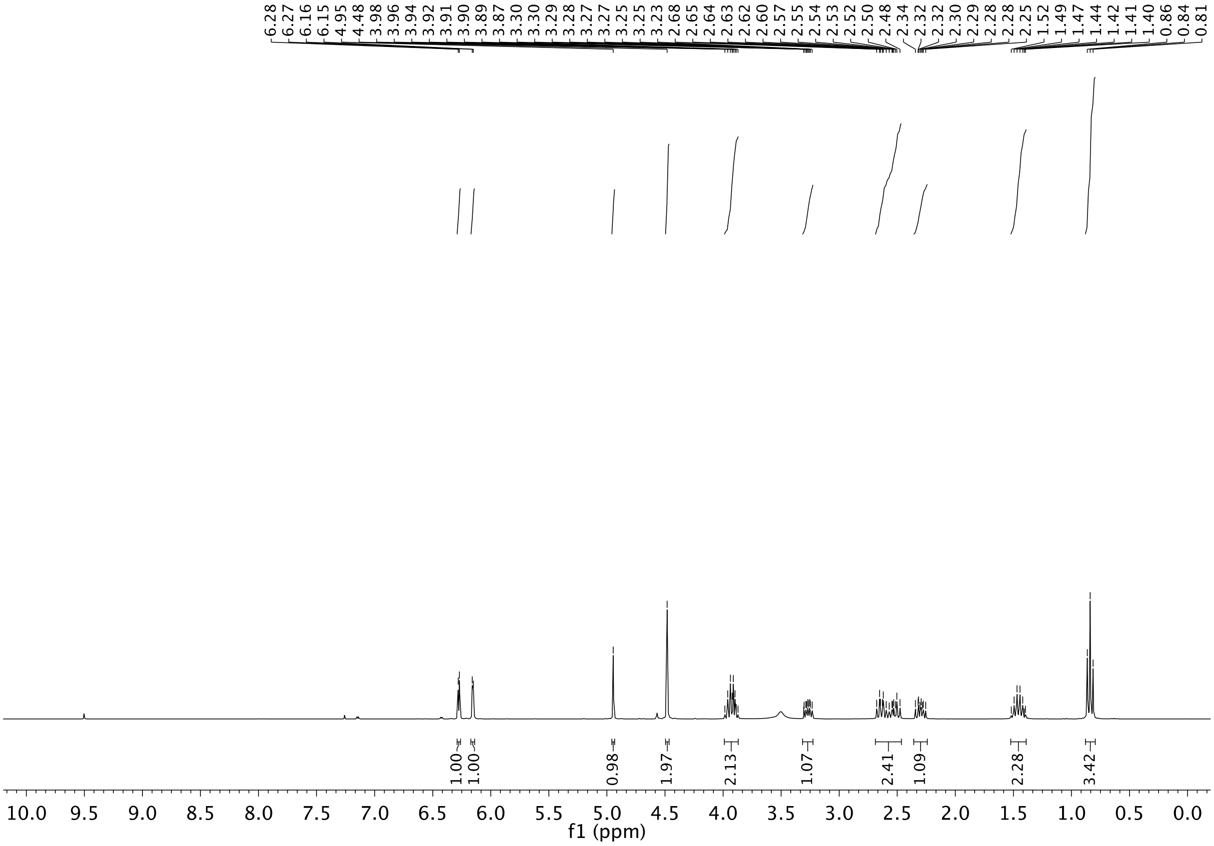


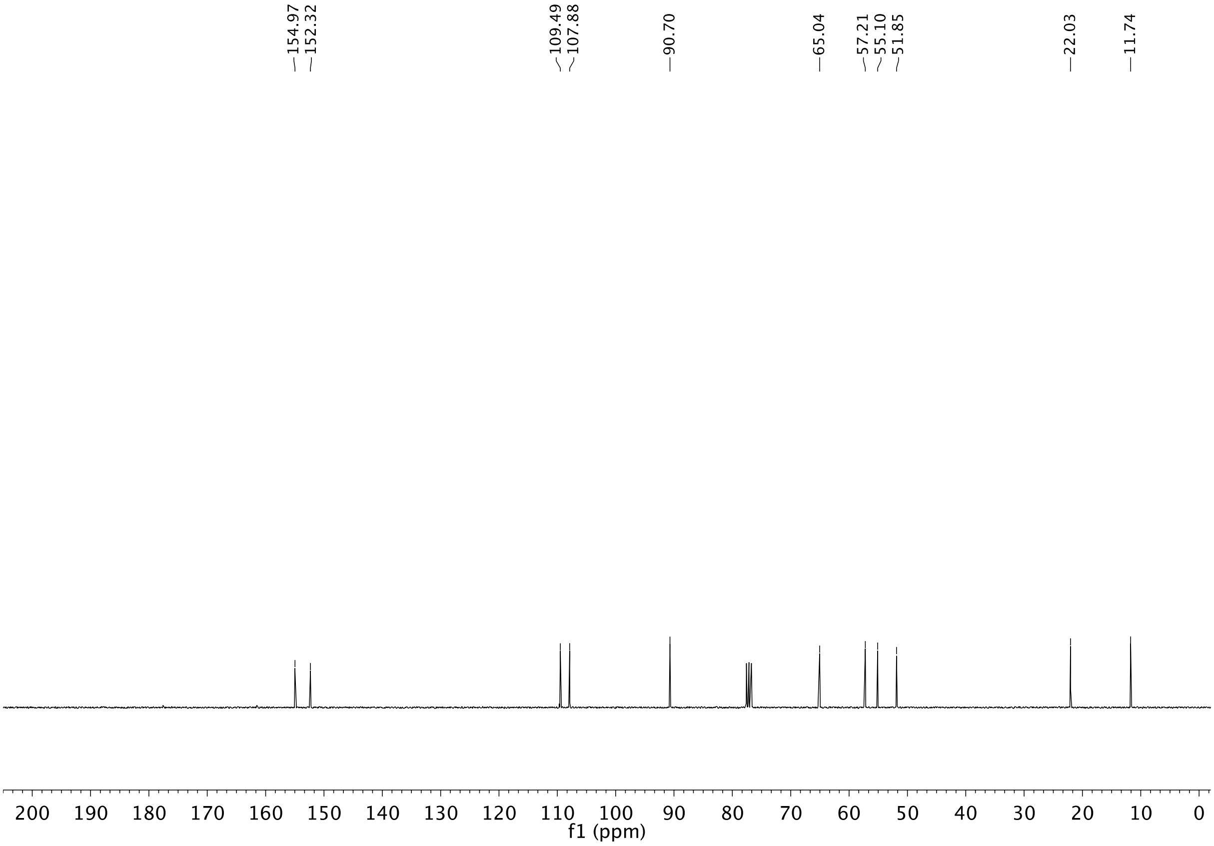
2-(furan-2-yl)-1,3-dimethylimidazolidine 37



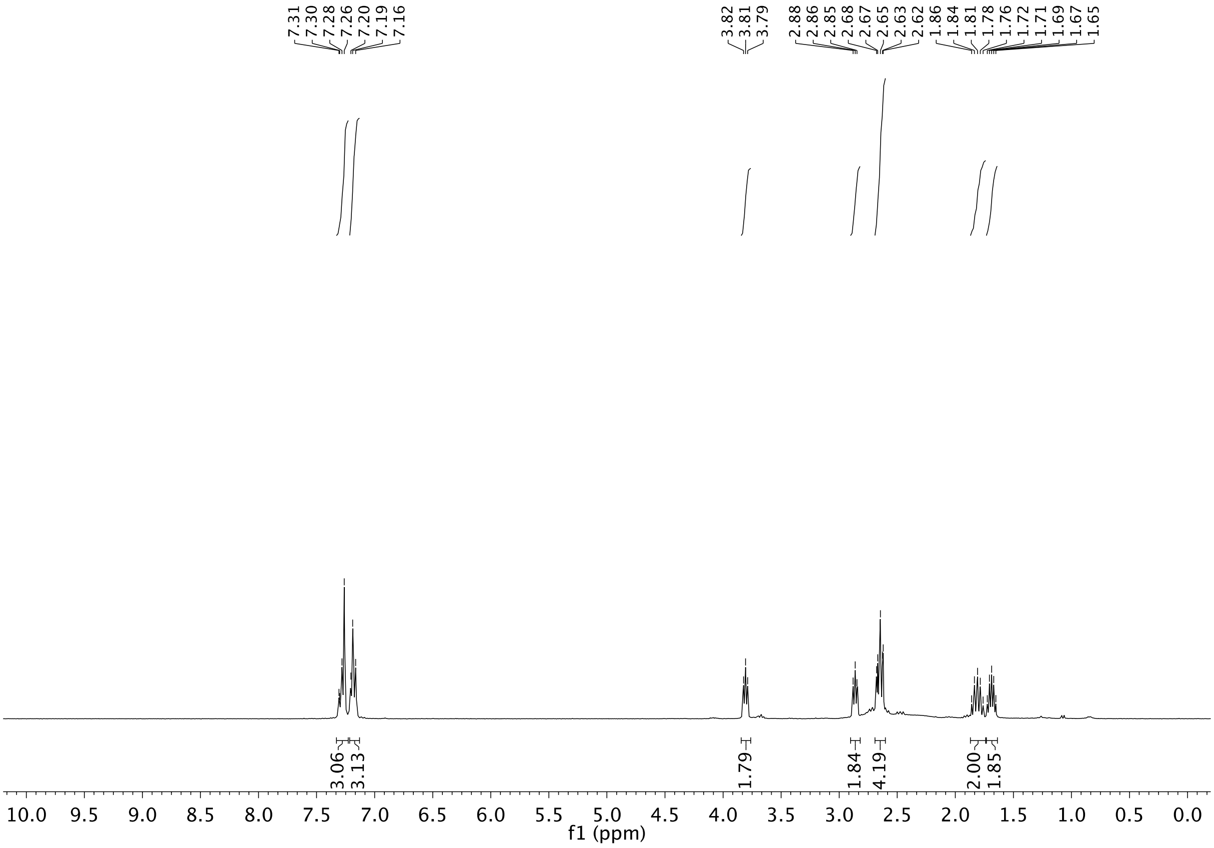


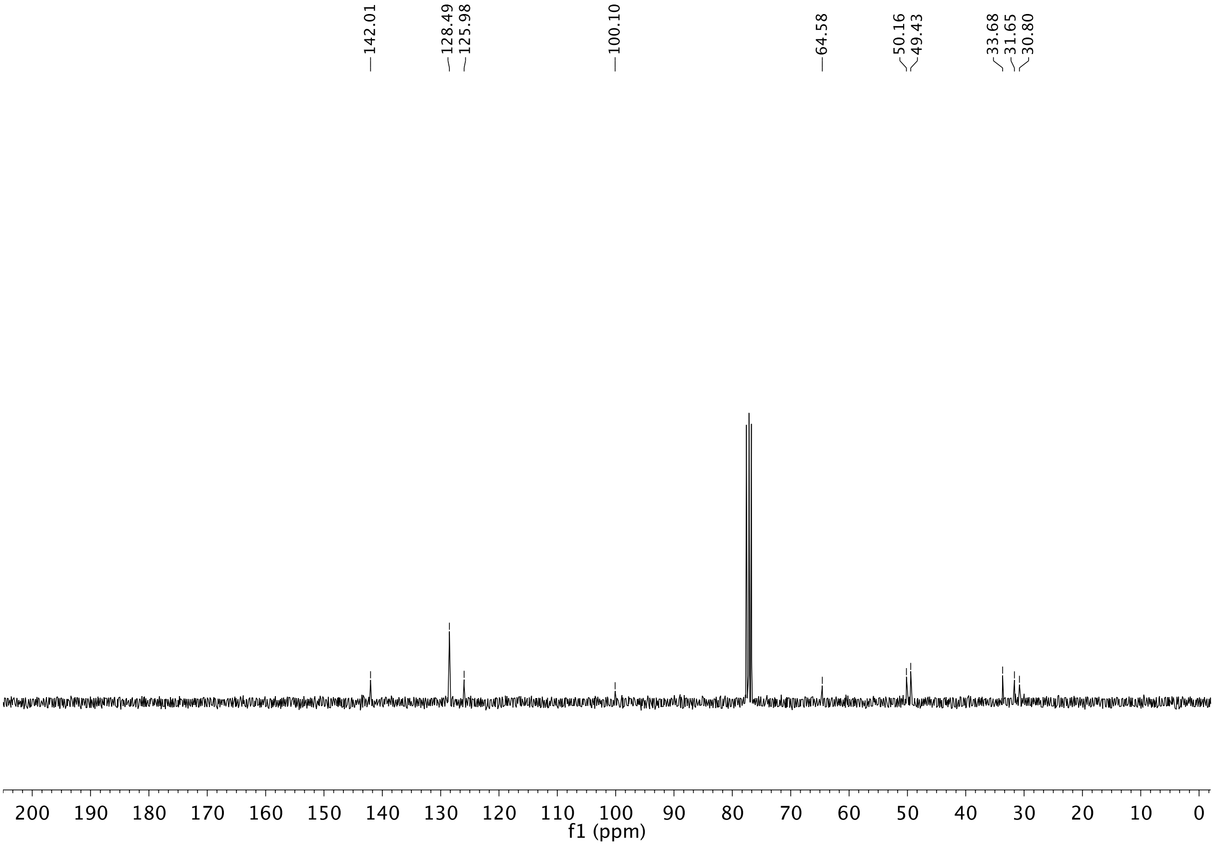
(5-(3-propyloxazolidin-2-yl)furan-2-yl)methanol 38



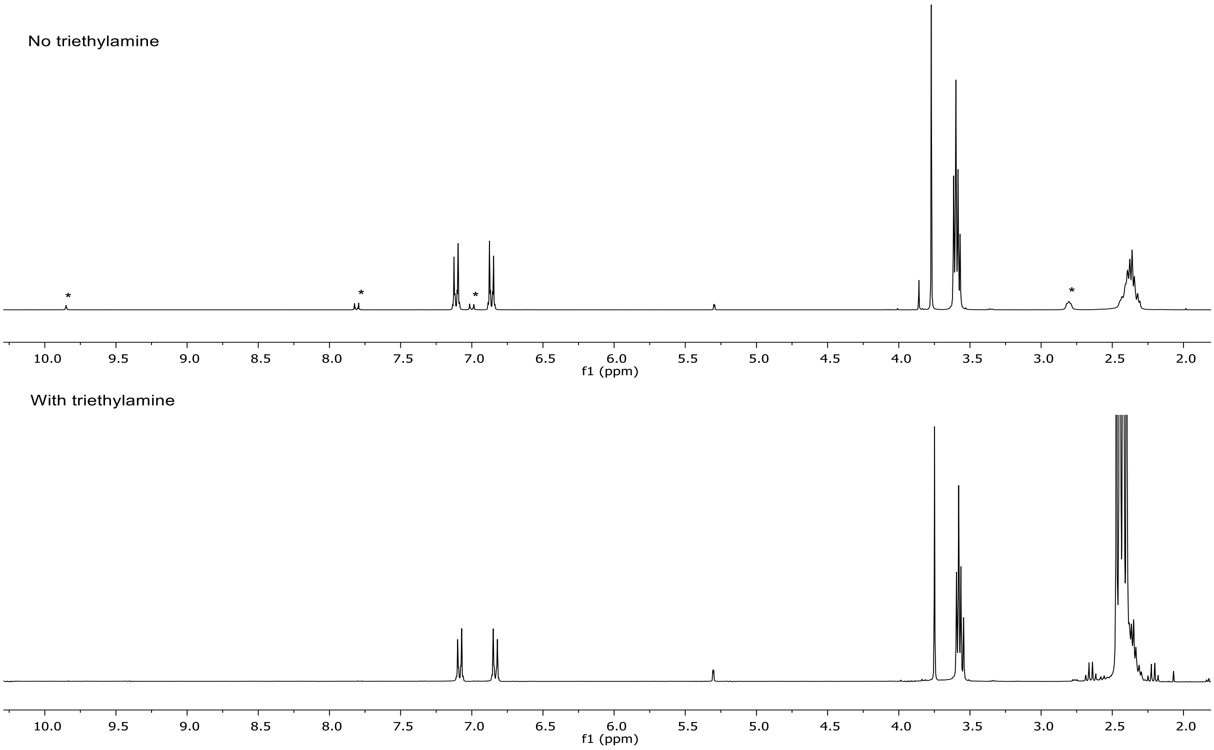


3-((3-phenylpropyl)amino)propan-1-ol 44

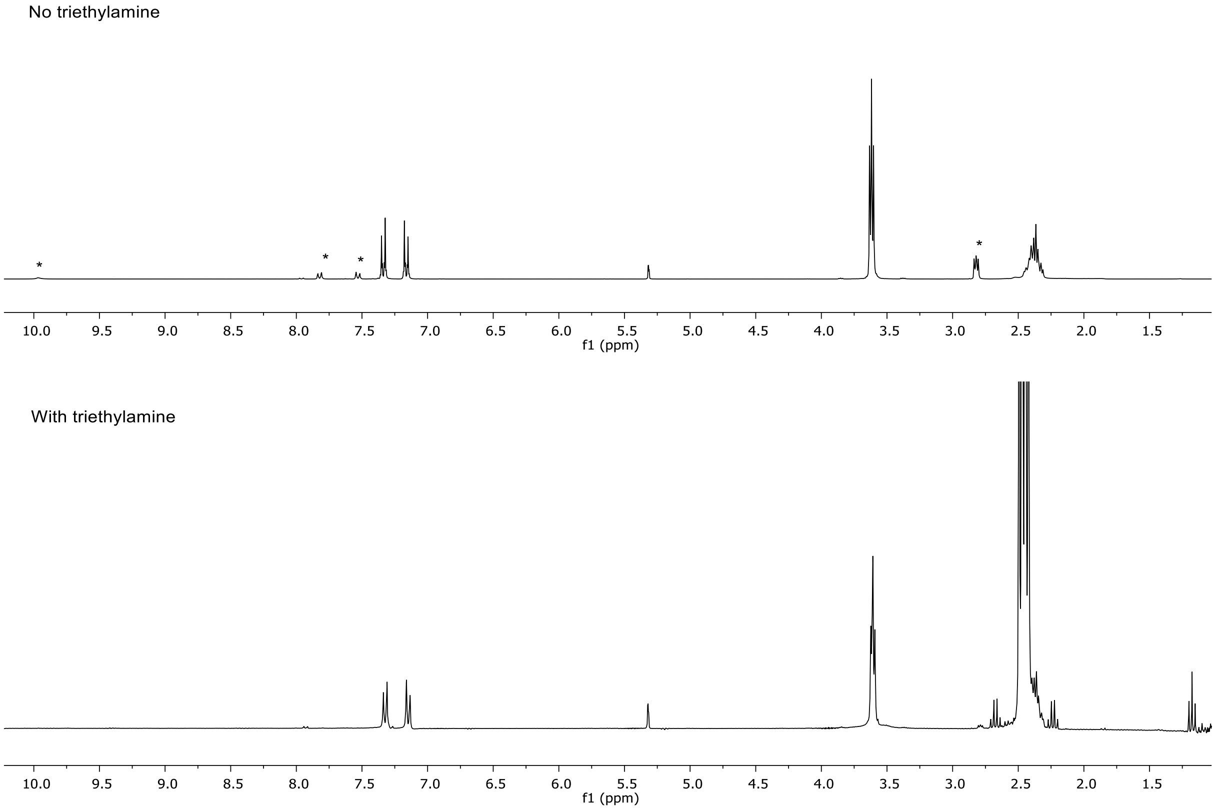




^{1}H NMR spectra of 7 in CD_2Cl_2 (top) and CD_2Cl_2:TEA (bottom). (*) corresponds to hydrolysis products

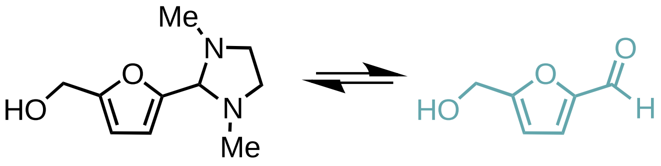


^{1}H NMR spectra of 10 in CD_2Cl_2 (top) and CD_2Cl_2:TEA (bottom). (*) corresponds to hydrolysis products



Stability studies of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol 35 and (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol 36 at different pH

To a solution of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** or (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** (30 mM) separately, in DMSO-d6 (50 µL) was added a phosphate buffer solution 0.1 M (450 µL) at different pH (7, 8, 9 and 12) into an NMR tube. The conversion of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** and (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** into hydroxymethylfurfural was measured by quantitative ^{1}H NMR experiments using 1,3,5-methoxybenzene (≈ 30 mM, in a capillary tube) as internal standard.



35 **HMF**

pH 7

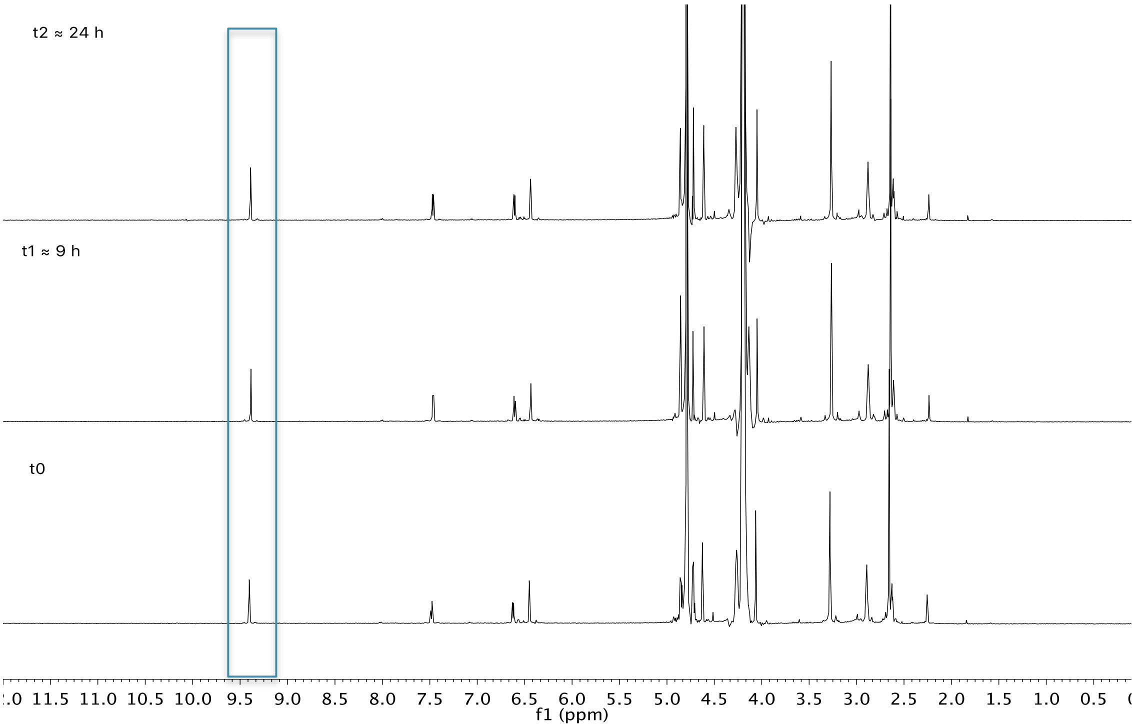


Figure S1. Stability studies of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** at pH 7 at t_0, t_1 = 9h and t_2 = 24h**.**

pH 8

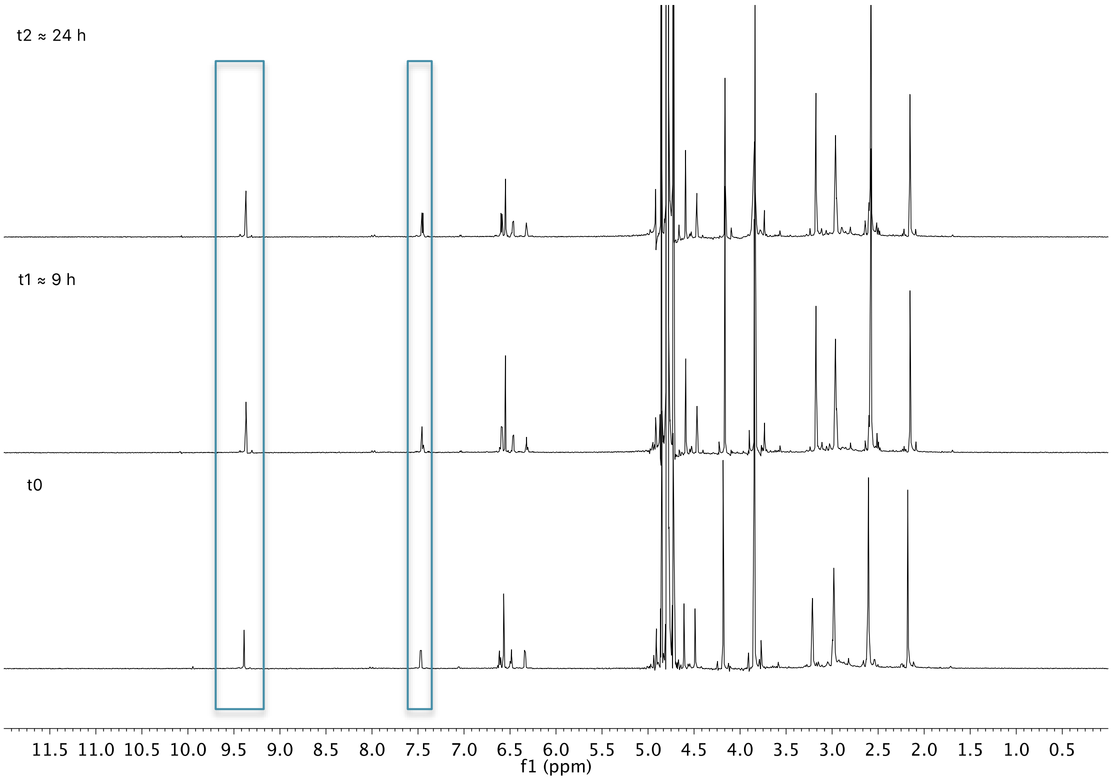


Figure S2. Stability studies of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** at pH 8 at t_0, t_1 = 9h and t_2 = 24h.

pH 9

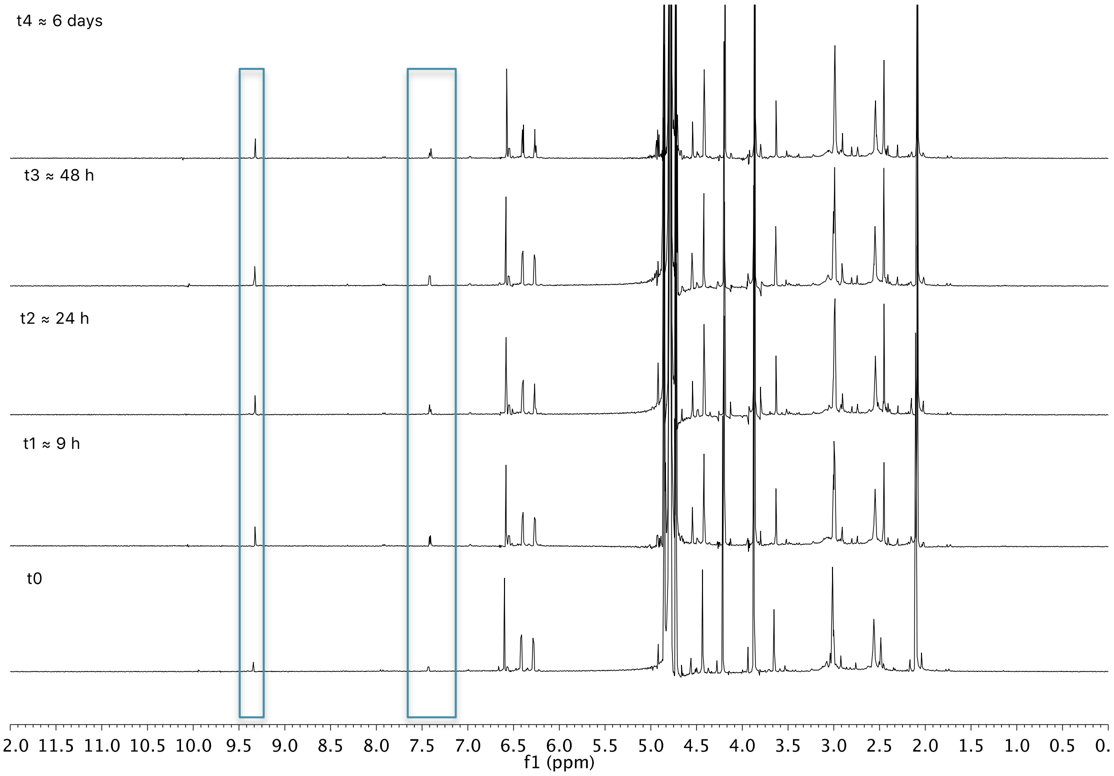


Figure S3. Stability studies of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** at pH 9 at t_0, t_1 = 9h, t_2 = 24h, t_3 = 48h and t_4 = 6 days.

pH 12

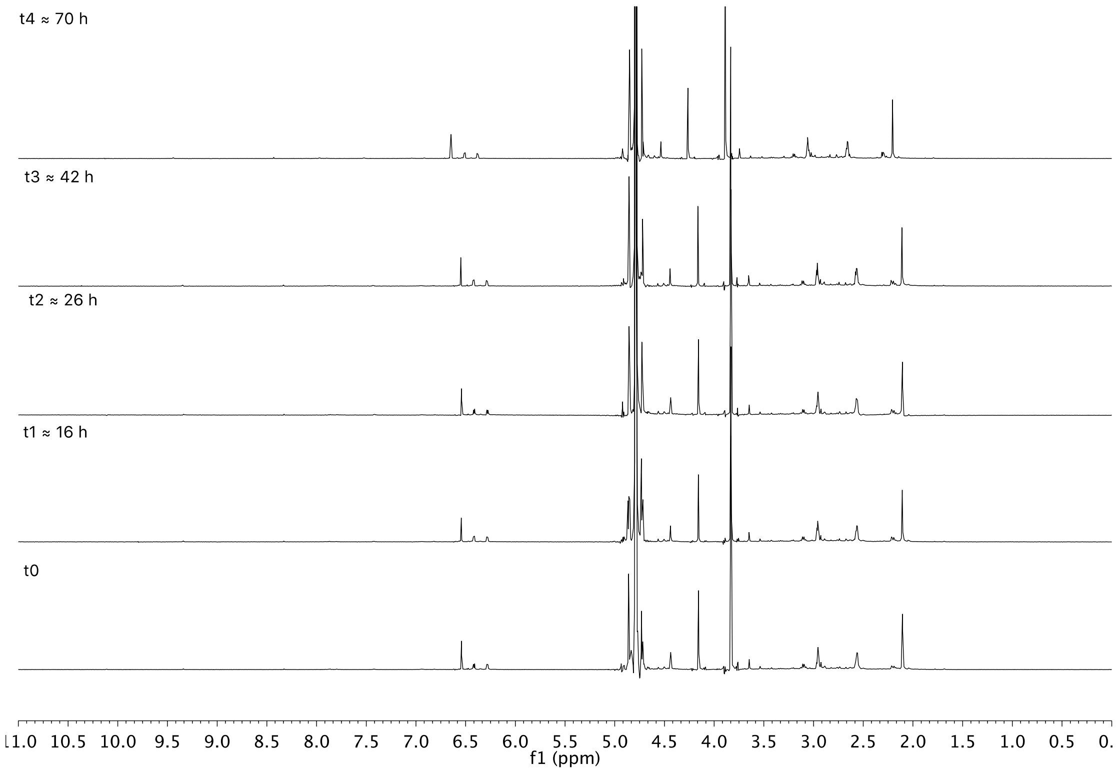
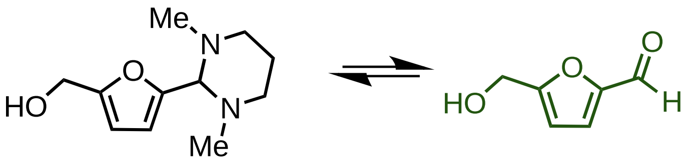


Figure S4. Stability studies of (5-(1,3-dimethylimidazolidin-2-yl)furan-2-yl)methanol **35** at pH 12 at t_0, t_1 = 16h, t_2 = 26h, t_3 = 42h and t_4 = 70h.



36 **HMF**

pH 7

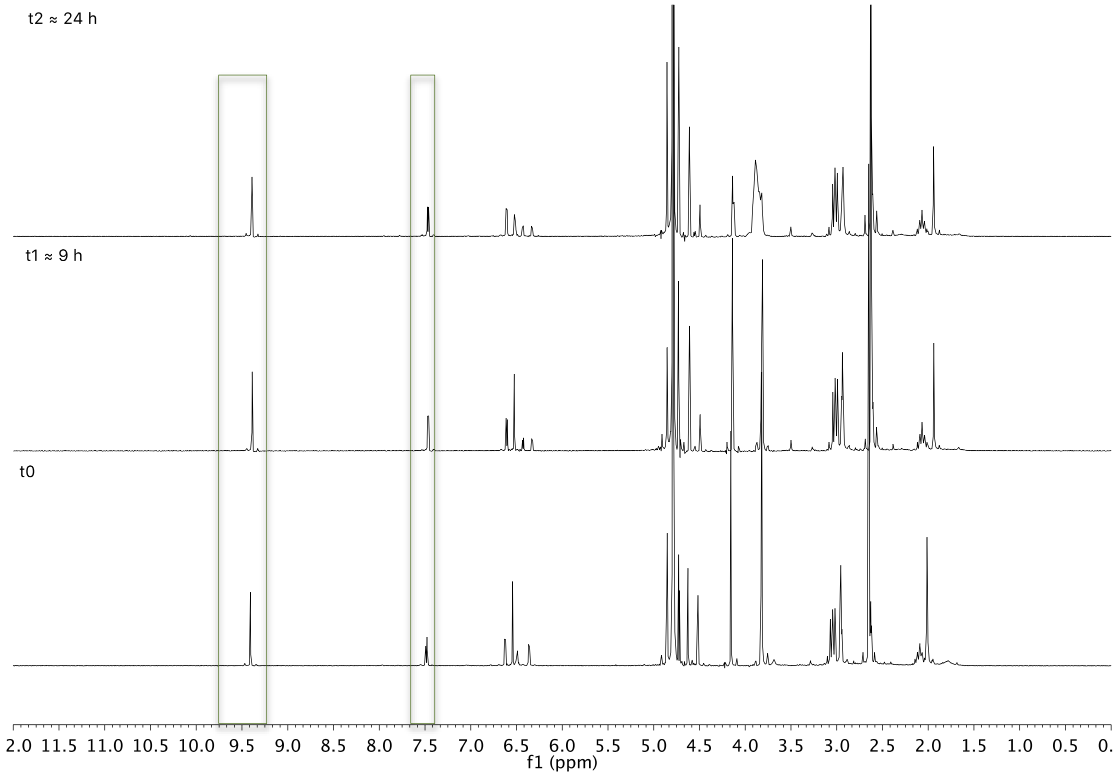


Figure S5. Stability studies of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** at pH 7 at t_0, t_1 = 9h and t_2 = 24h.

pH 8

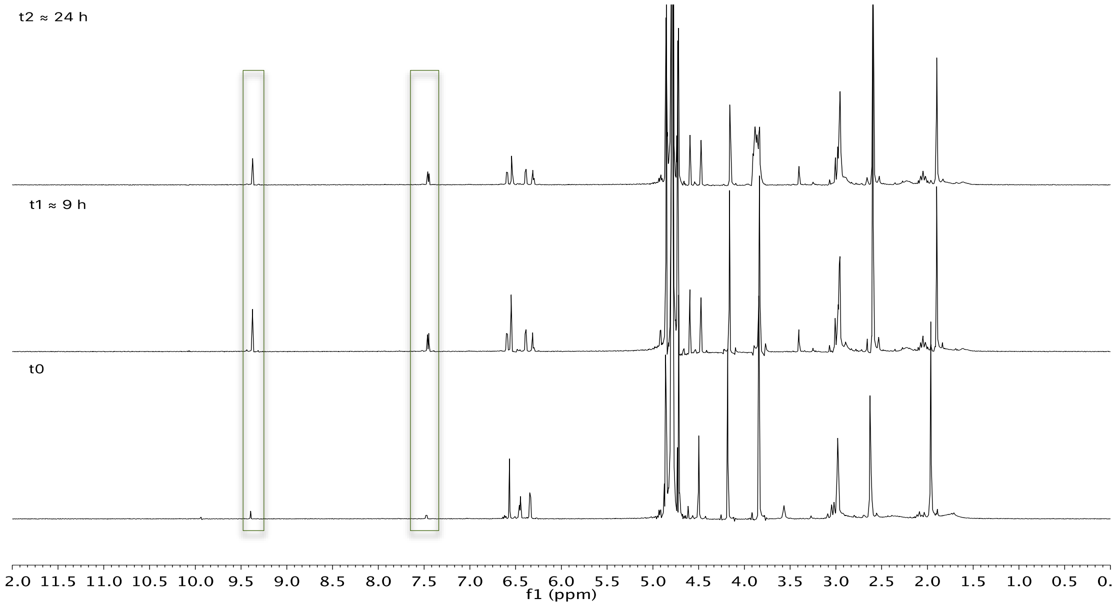


Figure S6. Stability studies of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** at pH 8 at t_0, t_1 = 9h and t_2 = 24h.

pH 9

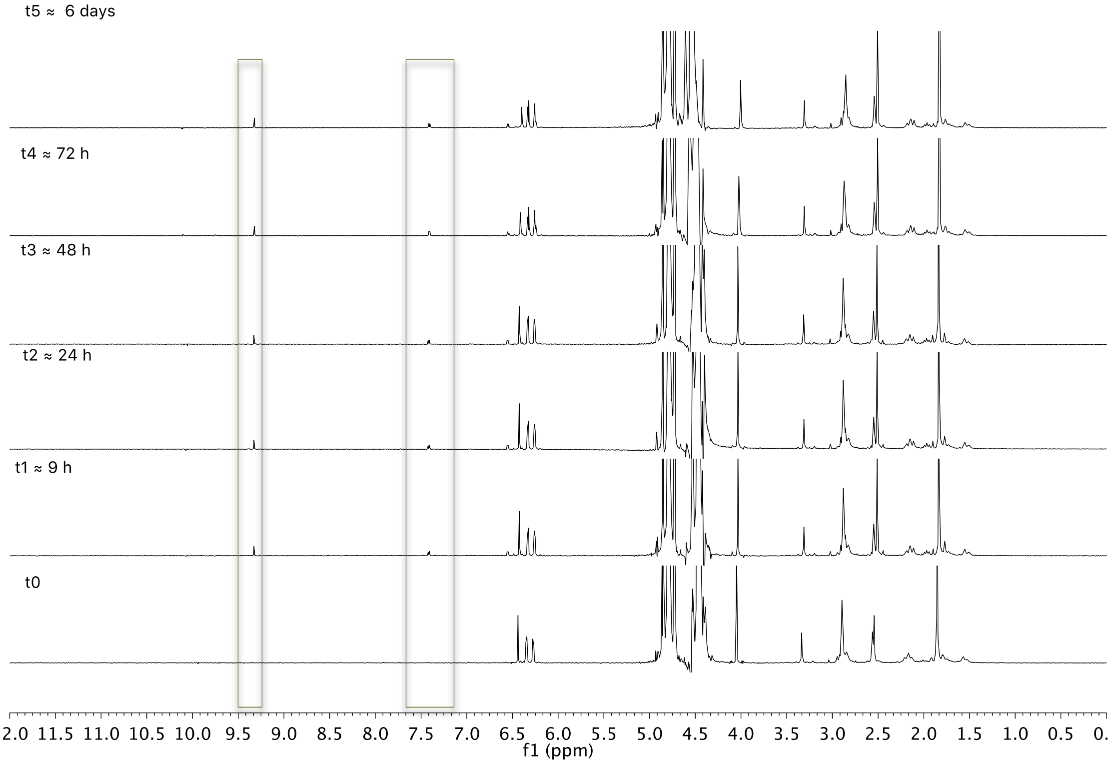


Figure S7. Stability studies of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** at pH 9 at t_0, t_1 = 9h, t_2 = 24h, t_3 = 48h, t_4 = 72h and t_5 = 6 days.

pH 12

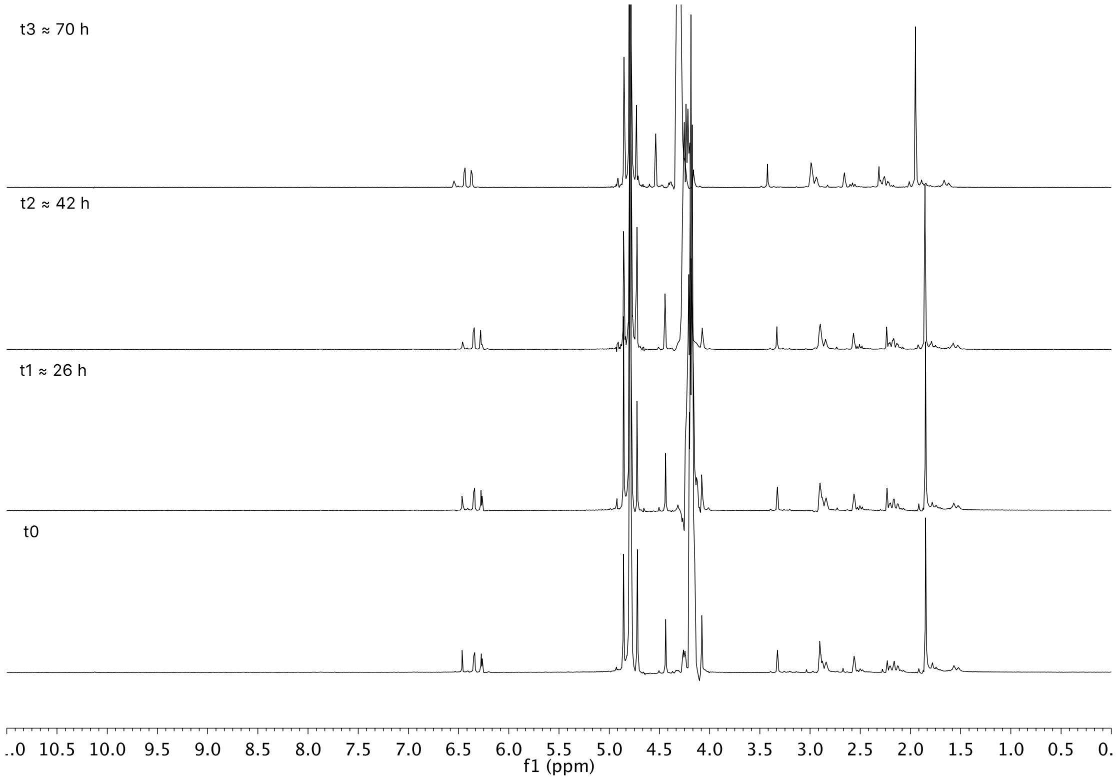
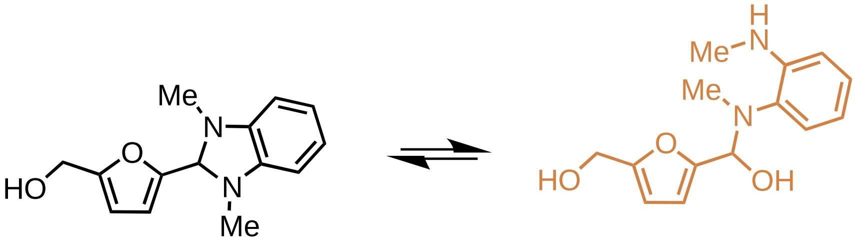


Figure S8. Stability studies of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** at pH 12 at t_0, t_1 = 26h, t_2 = 42h and t_3 = 70h.

Stability studies of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol 34 at different pH

To a solution of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** (23 mM) in DMSO-d6 (200 µL) was added a phosphate buffer solution 0.1 M (450 µL) at different pH (4.5, 8, 9 and 12) into an NMR tube. The conversion of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** into (5-(hydroxymethyl)furan-2-yl)(methyl(2-(methylamino)phenyl)amino)methanol was measured by spectroscopy ^{1}H NMR using 1,3,5-methoxybenzene (≈ 30 mM, in a capillary tube) as internal standard.



34

pH 4.5

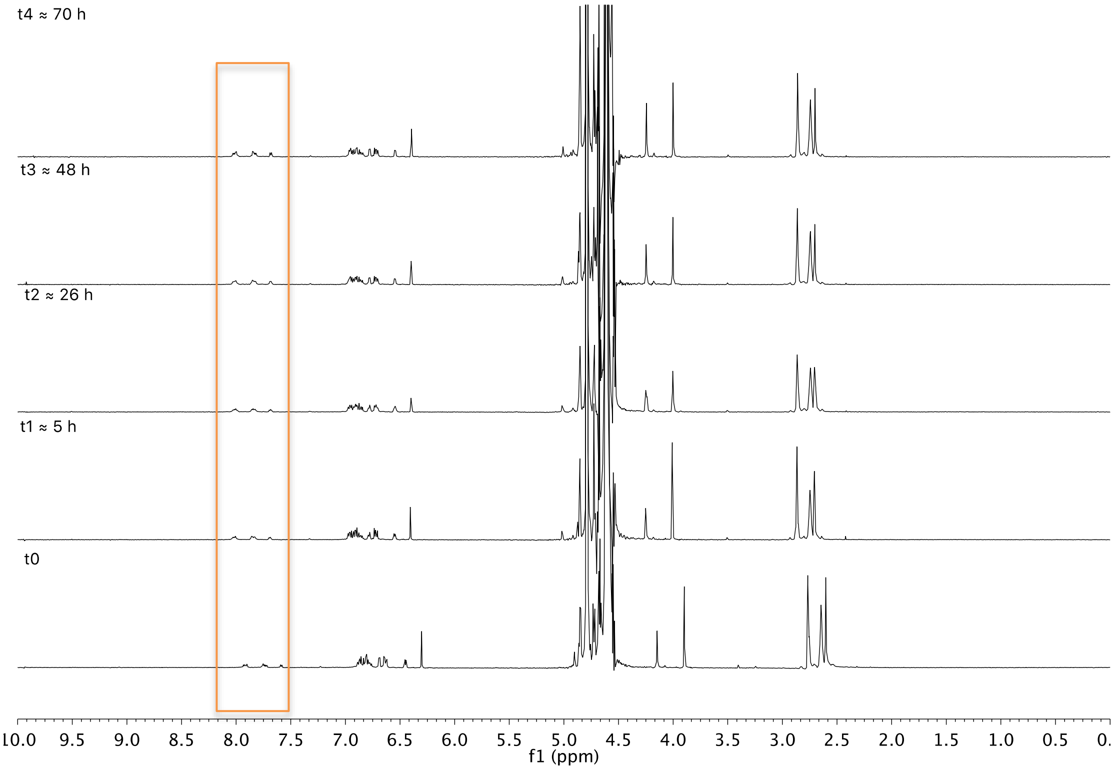


Figure S9. Stability studies of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** at pH 4.5 at t_0, t_1 = 5h, t_2 = 26h, t_3 = 48h and t_4 = 70h.

pH 8

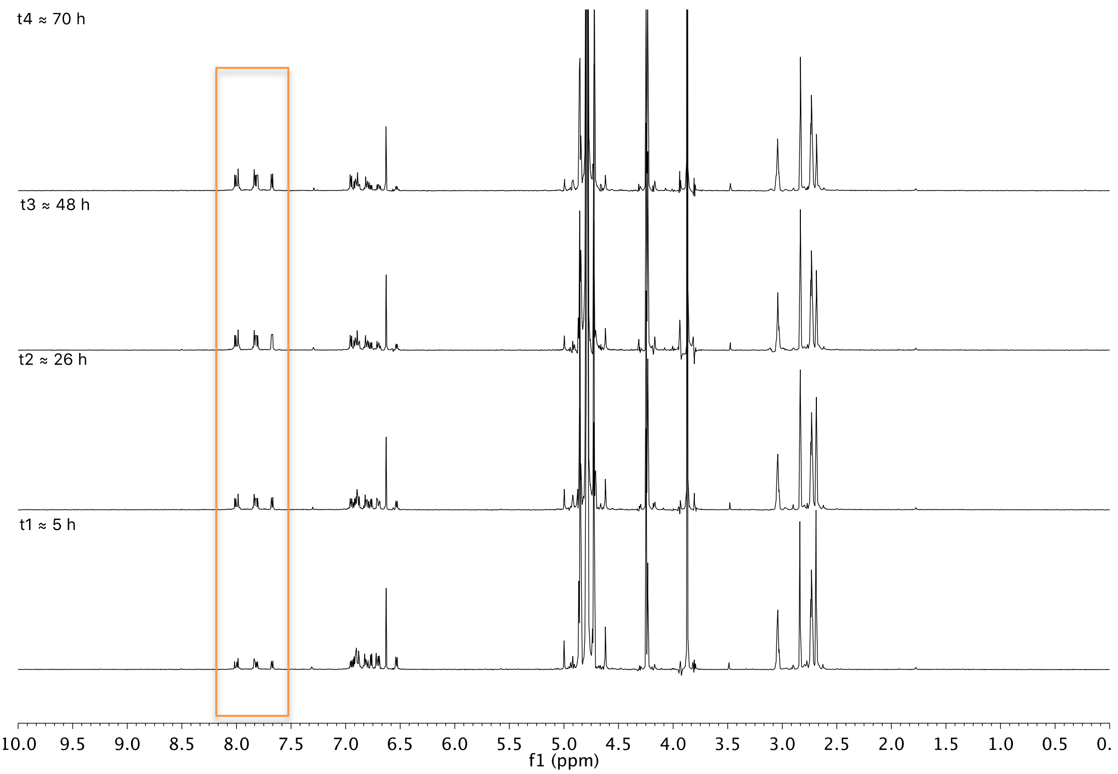


Figure S10. Stability studies of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** at pH 8 at t_1 = 5h, t_2 = 26h, t_3 = 48h and t_4 = 70h.

pH 9

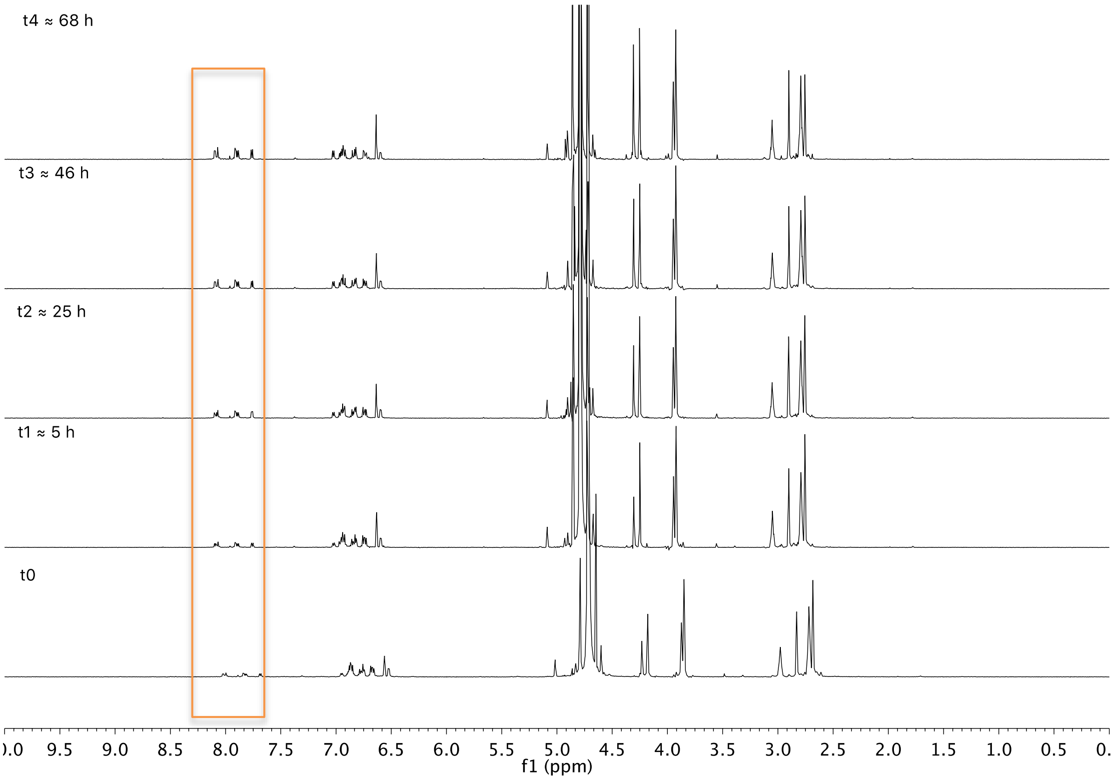


Figure S11. Stability studies of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** at pH 9 at t_0, t_1 = 5h, t_2 = 25h, t_3 = 46h and t_4 = 68h.

pH 12

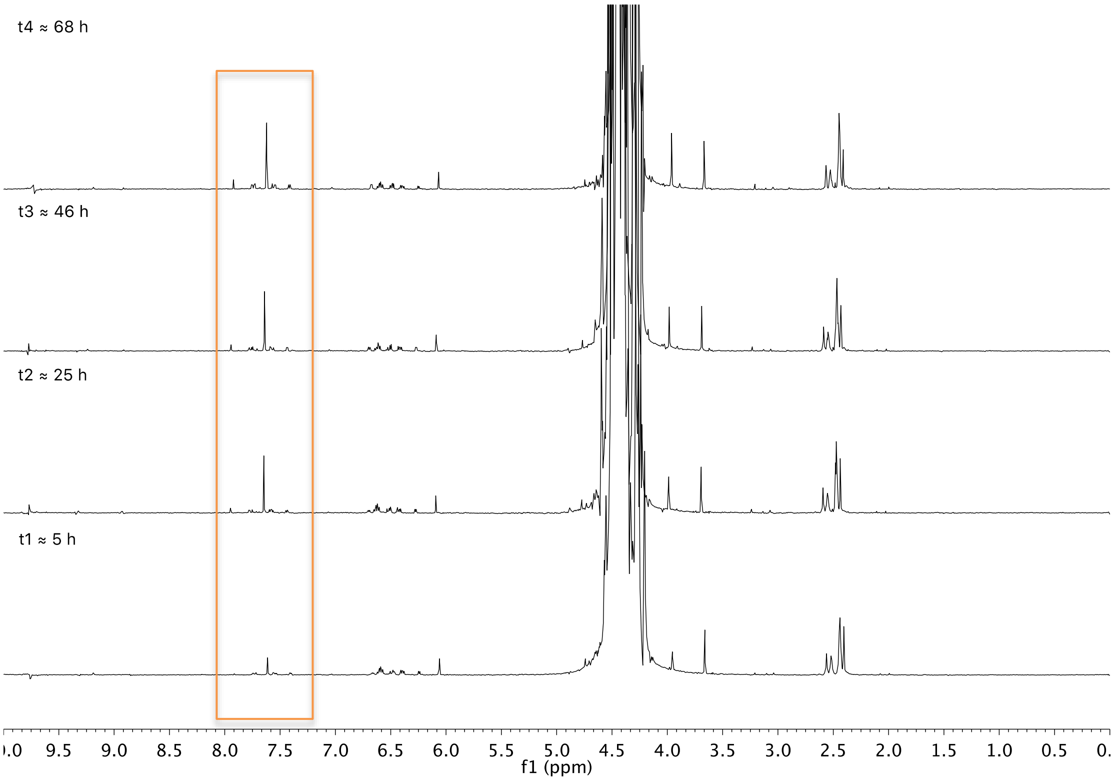
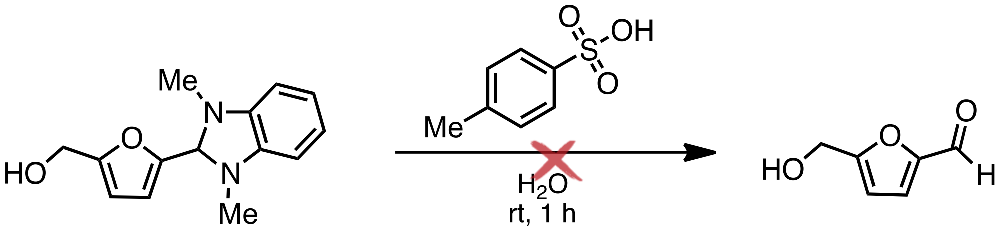


Figure S12. Stability studies of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** at pH 12 at t_1 = 5h, t_2 = 25h, t_3 = 46h and t_4 = 68h.

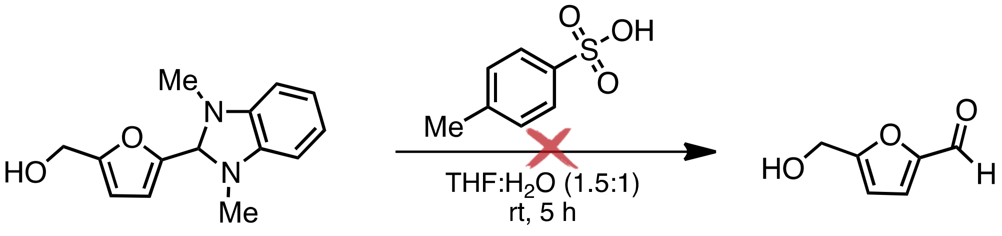
Deprotection studies of 1,3-dimethyl-2-phenyl-2,3-dihydro-1H-benzo[d]imidazole 34



34

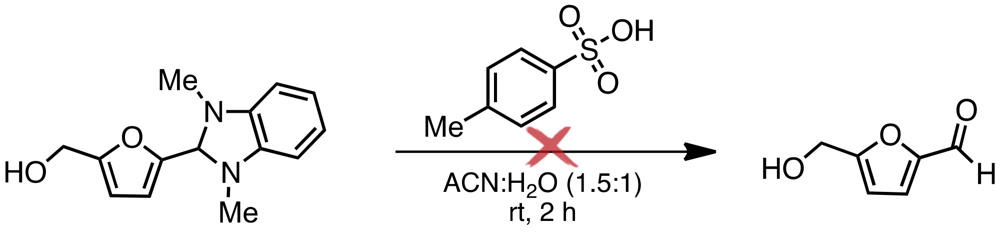
HMF

To a solution of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** (50 mg, 0.20 mmol) in water (0.205 mL, 1 M) was added *p*-toluenesulfonic acid (3.5 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 1 hour and then extracted with ethyl acetate (3x). The deprotection reaction of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** was not observed and consequently the formation of hydroxymethylfurfural did not occurred.



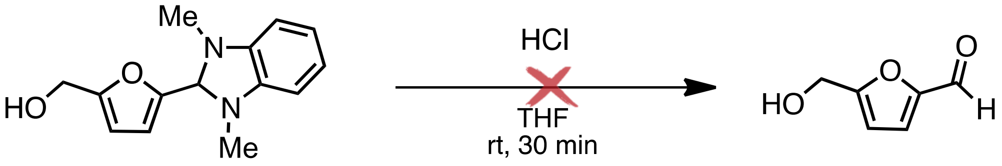
34 **HMF**

To a solution of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** (50 mg, 0.20 mmol) in a mixture of THF:H_2O (1.5:1) (0.250 mL, 0.82 M) was added *p*-toluenesulfonic acid (3.5 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 5 hours and then extracted with ethyl acetate (3x). The deprotection reaction of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** was not observed and consequently the formation of hydroxymethylfurfural did not occurred.



34 **HMF**

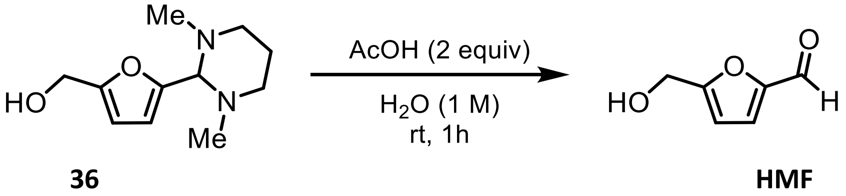
To a solution of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** (50 mg, 0.20 mmol) in a mixture of ACN:H_2O (1.5:1) (0.250 mL, 0.82 M) was added *p*-toluenesulfonic acid (35 mg, 0.20 mmol). The reaction mixture was stirred at room temperature for 2 hours and then extracted with ethyl acetate (3x). The deprotection reaction of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** was not observed and consequently the formation of hydroxymethylfurfural did not occurred.



34 **HMF**

To a solution of (5-(1,3-dimethyl-2,3-dihydro-1*H*-benzo[*d*]imidazol-2-yl)furan-2-yl)methanol **34** (40 mg, 0.16 mmol) in THF (0.100 mL, 1.6 M) was added a aqueous solution of HCl (0.200 mL, 1 M). The reaction mixture was stirred at room temperature for 30 minutes and then extracted with ethyl acetate (3x). The deprotection reaction of 1,3-dimethyl-2-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazole **34** was not observed and consequently the formation of HMF did not occurred.

Deprotection studies of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol 36



To a solution of (5-(1,3-dimethylhexahydropyrimidin-2-yl)furan-2-yl)methanol **36** (33 mg, 0.16 mmol) in water (0.159 mL, 1 M) was added acetic acid (18 µL, 0.31 mmol). The reaction mixture was stirred at room temperature for 1 hour and then extracted with ethyl acetate (3x). The hydroxymethylfurfural was obtained with 96% yield (19 mg) as a brownish oil.

General procedure for optimization of scavenging benzaldehyde

To a solution of aldehyde in a mixture of alcohol:water (0.002 - 1M) was added $Cu(OTf)_2$ (0-10 mol%) catalyst. The mixture was injected in the continuous flow reactor (Figure S13, below) containing polymer-bound ethylenediamine resin (Sigma Aldrich: 472093; 395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at the appropriate flow. The resultant solution was collected and analysed by HPLC.

Continuous Flow:

Injected Volume = 1 mL

Reactor (g) (empty HPLC column, ID= 4.6 mm, L= 50 mm, g)	62.362
Reactor + Resin (g)	62.7568
Amount of resin (g)	0.395
Reactor + Resin + CH_3OH* (g)	63.0338
Amount of methanol (g/mL)	0.277/0.348

*ρ = 0.791 g/mL

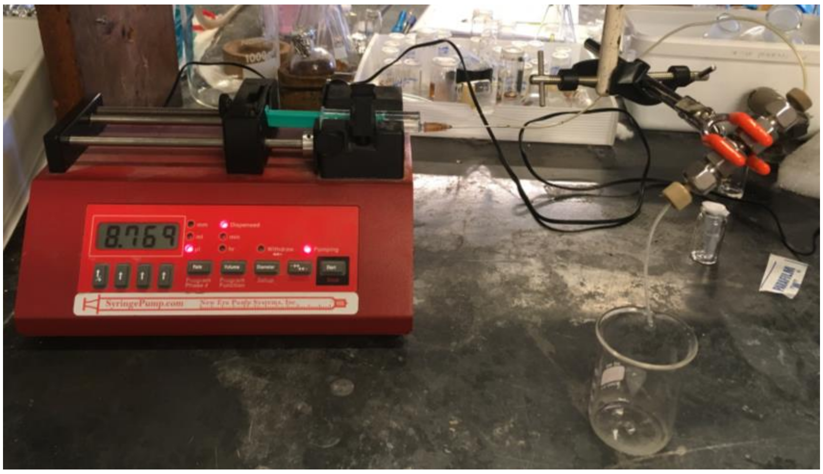


Figure S13. Continuous flow system.

Each HPLC sample was diluted to final concentration of 200 µM. The injection volume was 20 µL and the flow rate was set to 1 mL/min. The recovery of the aldehydes were analysed using a mixture of (A) H_2O and (B) ACN as a mobile phase in a multistep gradient: 5% B – 40% B (0-30 min); 40% B – 95% B (30-45 min); 95% B (45-48 min); 95% B – 5% B (48-50 min)

HPLC-UV calibration curves for the aromatic aldehydes and furfural derivatives were performed at determined concentrations 50, 100, 150, 200 and 300 µM using a mixture of (A) H_2O and (B) ACN as mobile phase in a multistep gradient: 5% B – 95% B (0-10 min); 95% B (10-13 min); 95% B – 5% B (13-15 min).

Calibration curves for HPLC analysis

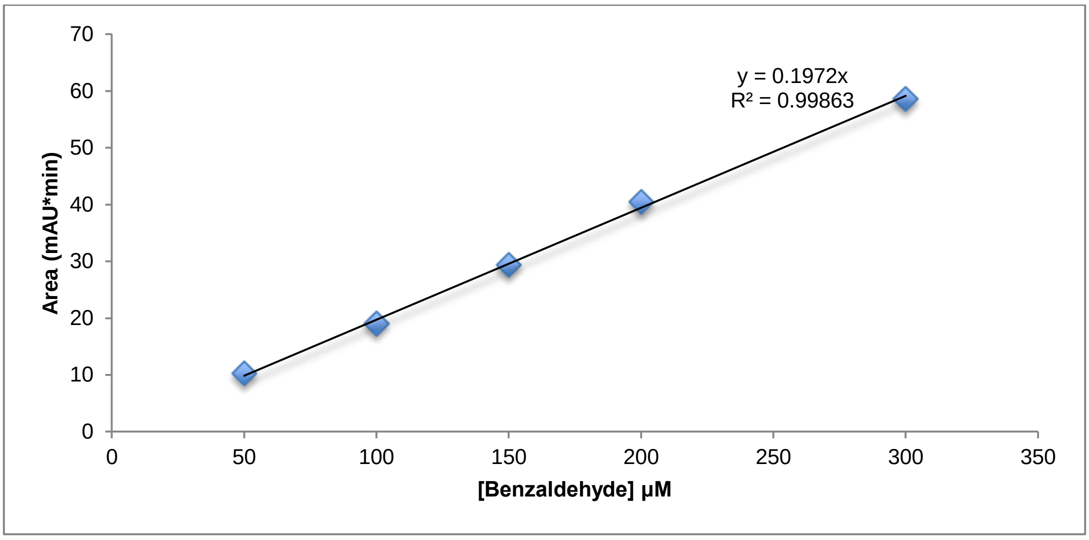


Figure S14. Calibration curve of benzaldehyde at 254 nm.

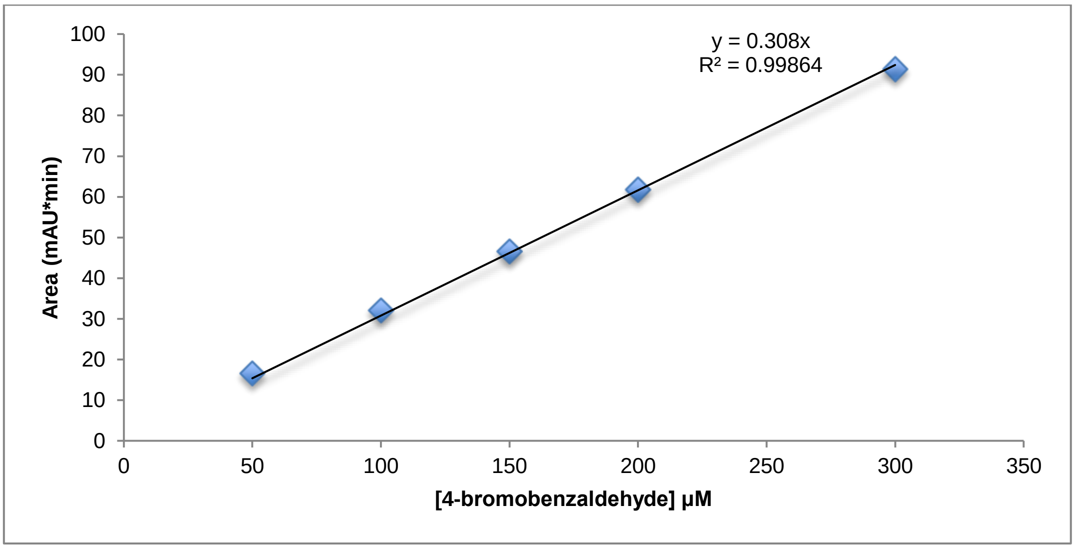


Figure S15. Calibration curve of 4-bromobenzaldehyde at 254 nm.

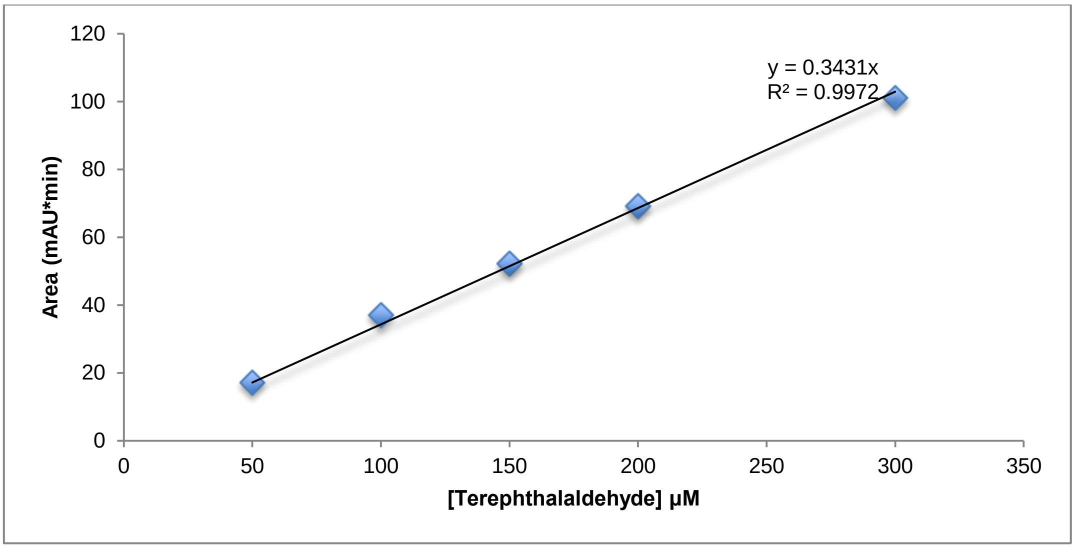


Figure S16. Calibration curve of terephthaldehyde at 254 nm.

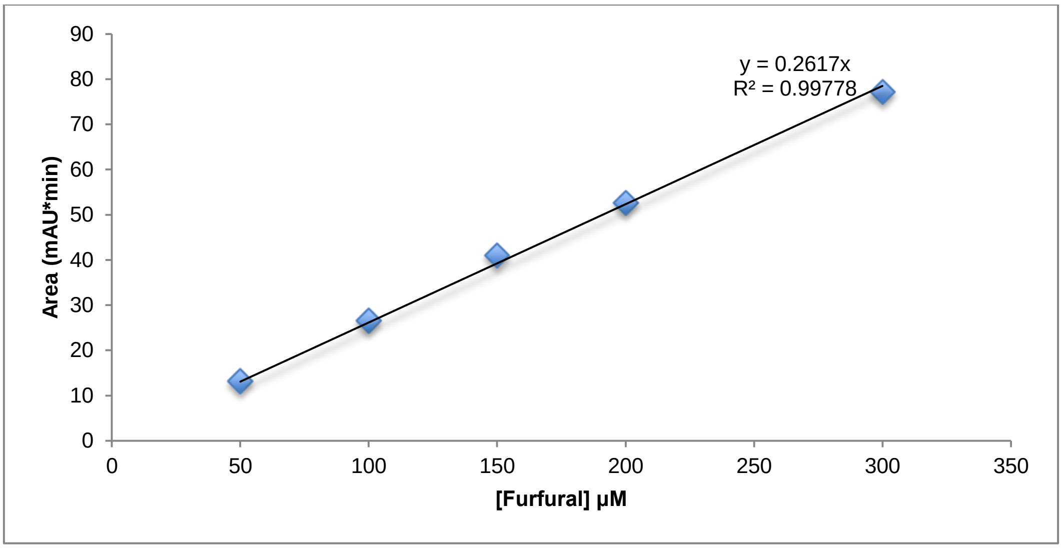


Figure S17. Calibration curve of furfural at 254 nm.

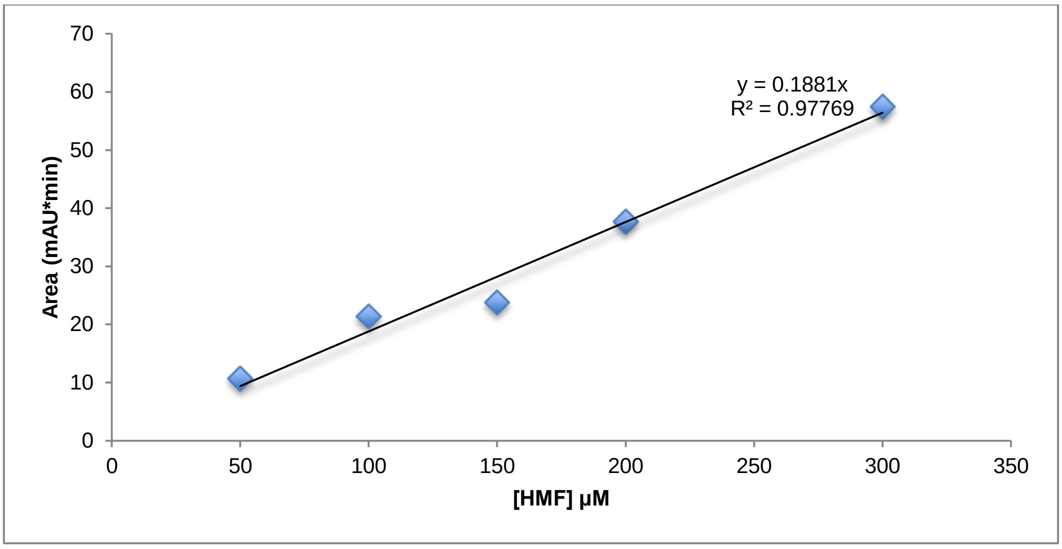


Figure S18. Calibration curve of HMF at 280 nm.

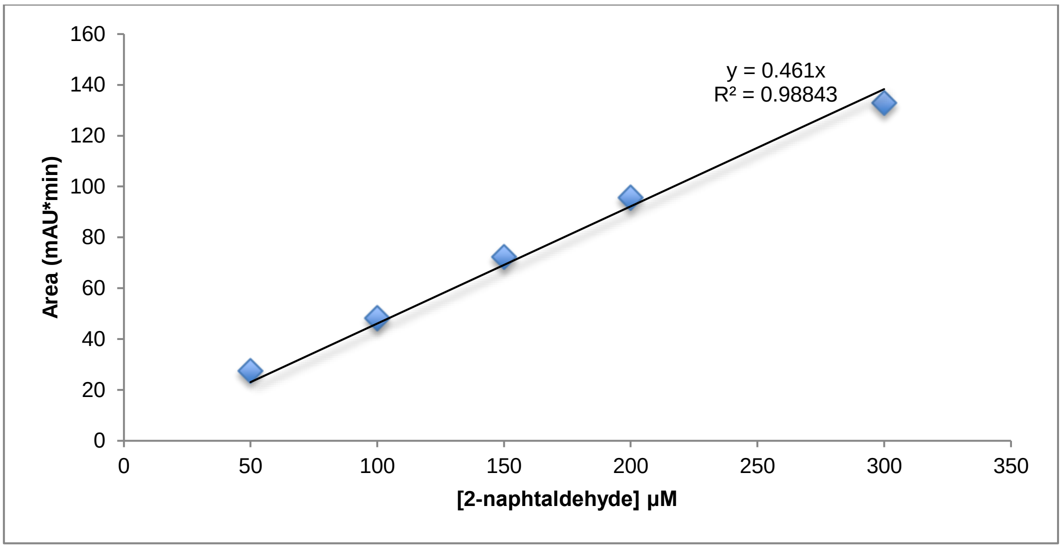


Figure S19. Calibration curve of 2-naphtaldehyde at 254 nm.

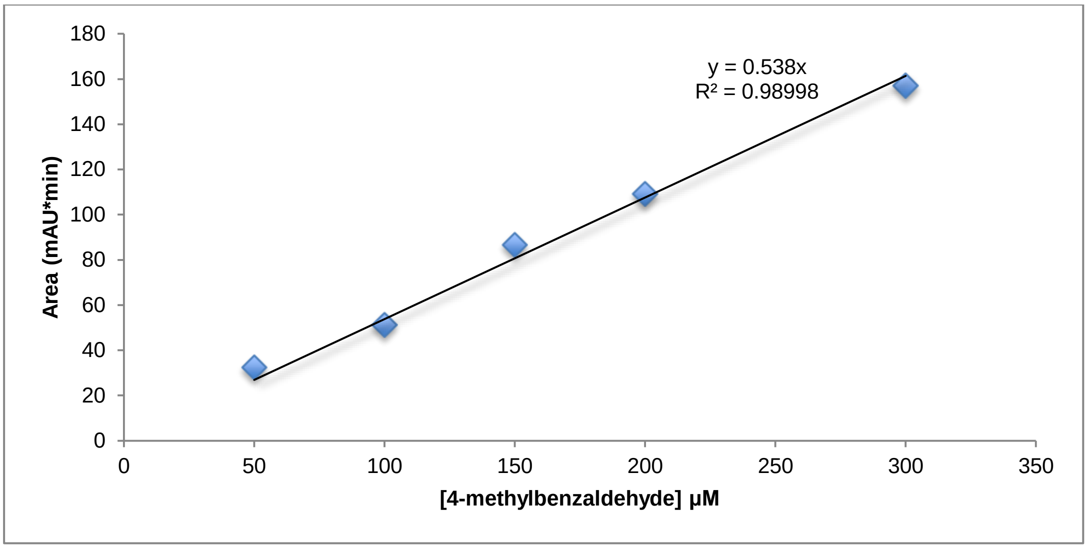


Figure S20. Calibration curve of 4-methylbenzaldehyde at 254 nm.

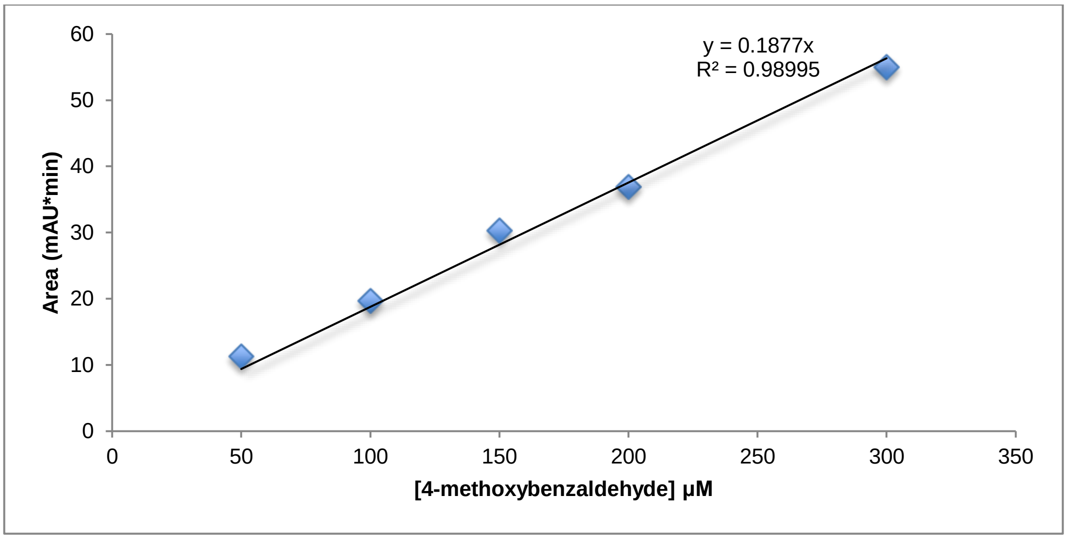


Figure S21. Calibration curve of 4-methoxybenzaldehyde at 254 nm.

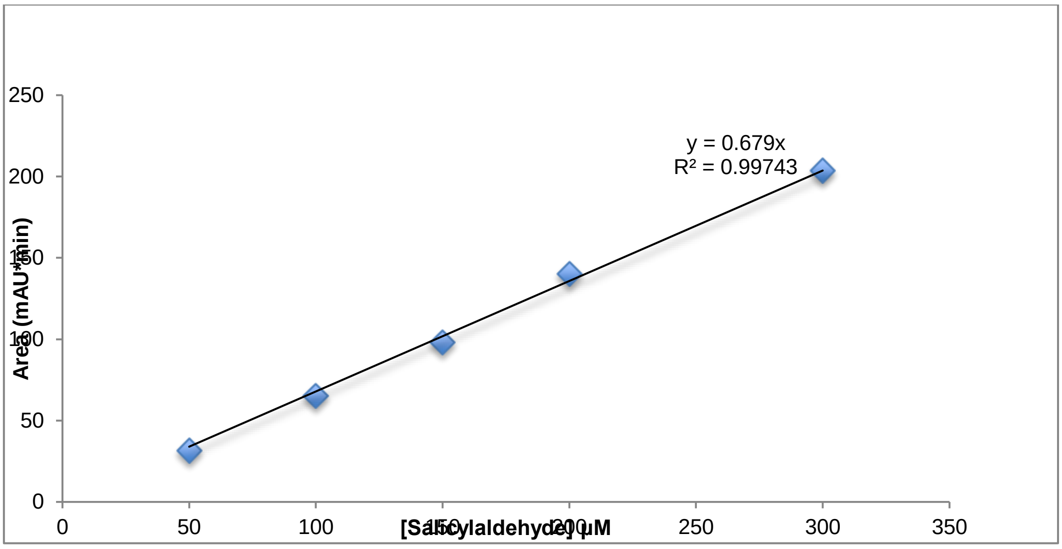
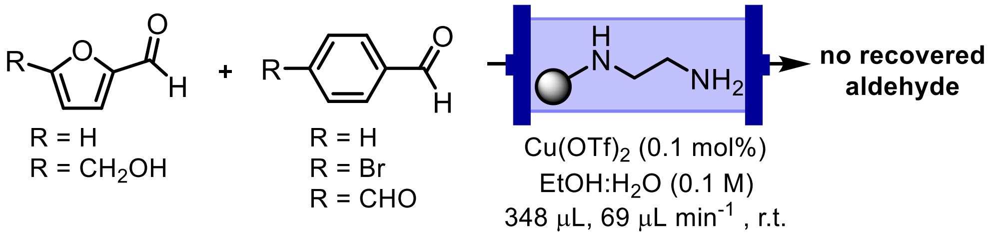


Figure S22. Calibration curve of salicylaldehyde at 210 nm.

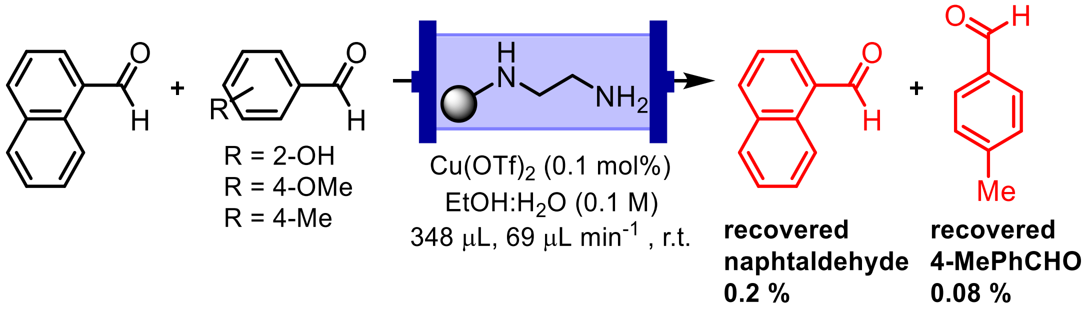
General procedure for reutilization of the scavenging resin

To a solution of benzaldehyde (0.67 mmol) in a mixture of ethanol:water (1:1) was added $Cu(OTf)_2$ (0.1 mol%) catalyst. The mixture was injected continuously with a syringe pump into an HPLC column, containing polymer-bound ethylenediamine resin (Sigma Aldrich: 472093; 266 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL.min^{-1} and the reactor volume was 348 µL. The resultant solution was collected and analysed by HPLC. The polymer-bound ethylenediamine resin was washed with an HCl solution (1 M) followed by NaOH solution (1 M). This procedure was repeated 5 times.

Scavenging of different aromatic aldehydes and furfural derivatives

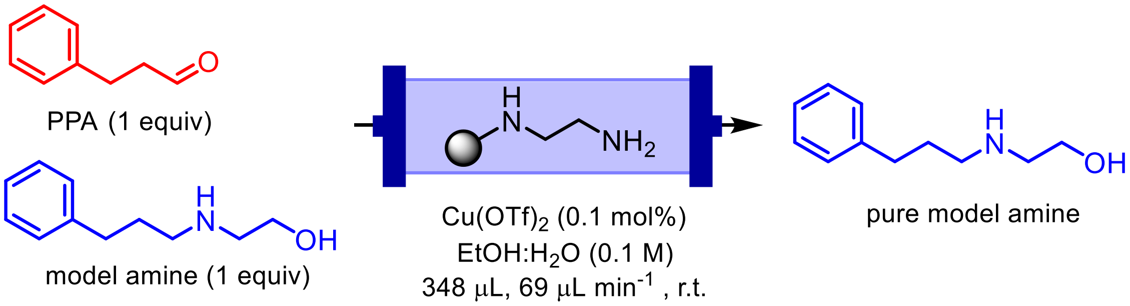


To a solution of benzaldehyde, 4-bromobenzaldehyde, terephthalaldehyde, furfural and 5-hydroxymethylfurfural in a mixture of EtOH:H_2O (1:1) (0.1 M, 0.02 M each aldehyde) was added $Cu(OTf)_2$ (0.1 mol%) catalyst. The mixture was injected in the continuous flow reactor containing polymer-bound ethylenediamine resin (Sigma Aldrich: 472093; 395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL min^{-1} and the residence time was selected for 5 minutes, respectively. The resultant solution was collected and analysed by HPLC.



To a solution of 2-naphthaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde and salicyladehyde in a mixture of EtOH:H_2O (1:1) (0.1 M, 0.025 M each aldehyde) was added $Cu(OTf)_2$ (0.1 mol%) catalyst. The mixture was injected with a syringe pump into the Agilent flow reactor, containing polymer-bound ethylenediamine resin (Sigma Aldrich: 472093; 395 mg, 4-5.7 mmol/g), at room temperature. The flow rate was set at 69.6 µL.min^{-1} and the residence time was selected for 5 minutes respectively. The resultant solution was collected and analysed by HPLC.

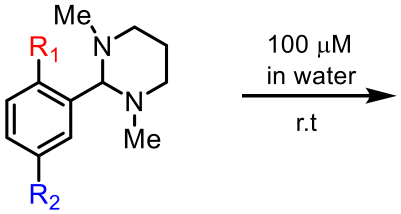
Scavenging of 3-phenylpropanal (PPA) in the presence of 3-((3-phenylpropyl)amino)propan-1-ol (44)



To a solution of 3-phenylpropanal (13 mg, 0.1 mmol) and 3-((3-phenylpropyl)amino)propan-1-ol (18 mg, 0.1 mmol) in a mixture of ethanol:water (1:1) (1 mL) was added $Cu(OTf)_2$ catalyst (0.1 mol%). The mixture was injected with a syringe pump into the Agilent flow reactor containing polymer-bound ethylenediamine resin (Sigma Aldrich: 472093; 395 mg, 4-5.7 mmol/g) at room temperature. The flow rate was set at 69 µL.min^{-1} and the residence time was selected for 5 minutes. The resultant solution was collected and evaporated to obtain 18 mg of pure **44** by ^1H NMR analysis.

General procedure for measuring stability in UV-vis spectrometer

10 mM solutions of aminals **21** and **26-32** in acetonitrile were freshly prepared and were diluted in 2 ml of MilliQ water to a final concentration of 100 µM. The quartz cuvette was swiftly mixed by inversion and analyzed by UV-Visible spectroscopy. Full-scan analysis were performed every minute until a constant absorbance value was reached. UV-Vis spectra of the correspondent aldehydes (Figure S24) were also performed in similar conditions to confirm that the reaction observed is indeed the expected hydrolysis. To compare the results obtained, we plotted the absorbance values obtained for each aminal at a particular wavelength over time. After normalization, the results can be observed in Figure S25. The apparent constant rate for each reaction was calculated by fitting the results to the following exponential decay function $y = y_0 + Ae^{-x/t}$ where kobs = 1/t. By plotting the calculated k_{obs} with the Hammett parameter σ_{para} and Taft parameter σ^* (retrieved from the literature; reference 19), it is possible to determine the Hammett and Taft equations, respectively, for our aminal series.



21	R_1= H	R_2= H
26	R_1= OH	R_2= H
27	R_1= NO_2	R_2= H
28	R_1= Br	R_2= H
29	R_1= Cl	R_2= H
30	R_1= OMe	R_2= H
31	R_1= OH	R_2= NO_2
32	R_1= OH	R_2= OMe

BzAld	R_1= H	R_2= H
OHAld	R_1= OH	R_2= H
NO2Ald	R_1= NO_2	R_2= H
BrAld	R_1= Br	R_2= H
ClAld	R_1= Cl	R_2= H
OMeAld	R_1= OMe	R_2= H
NO2-OH Ald	R_1= OH	R_2= NO_2
OMe-OH Ald	R_1= OH	R_2= OMe

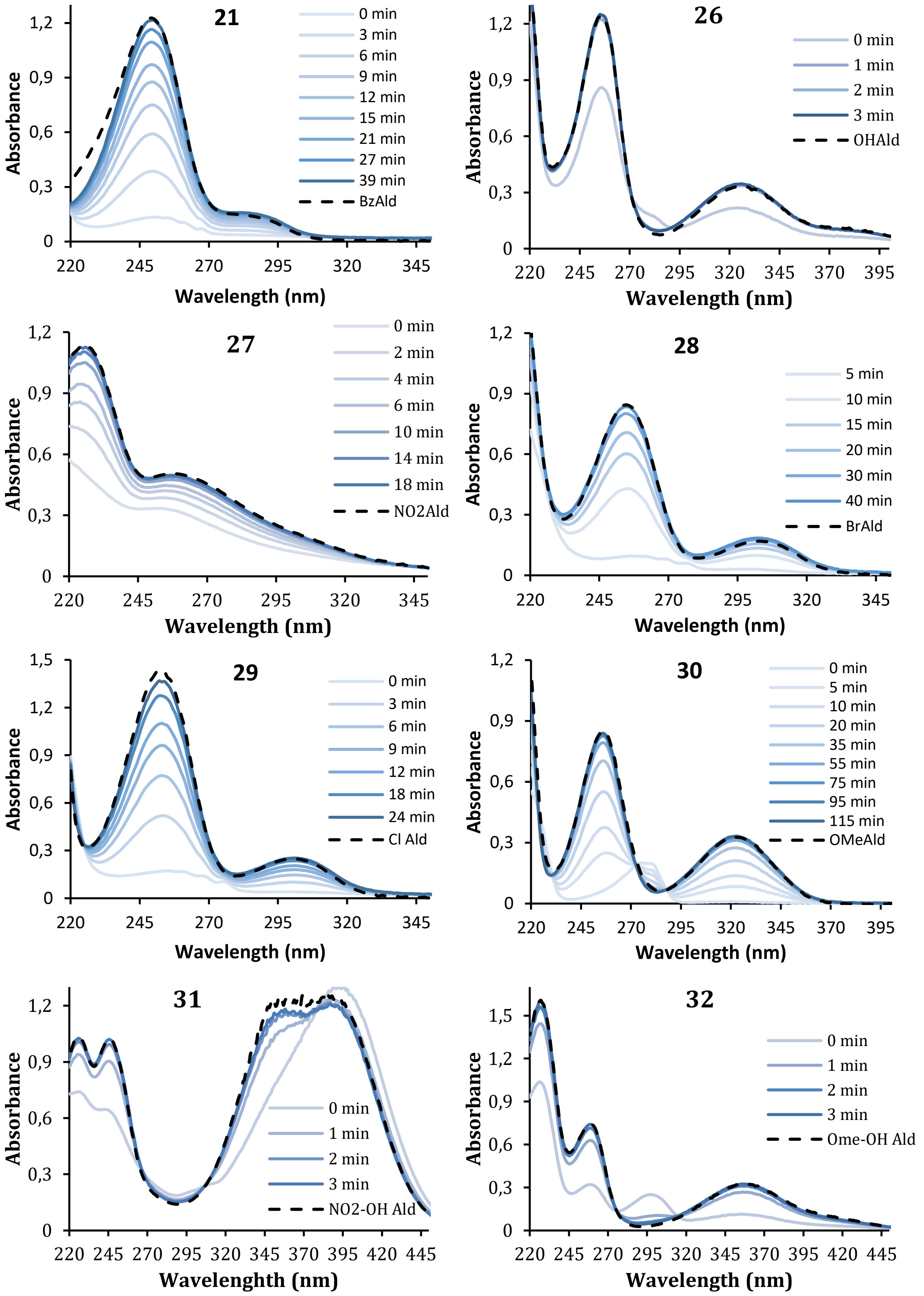


Figure S23. UV-Vis spectra of aminals **21** and **26-32** with the correspondent aldehyde spectrum highlighted.

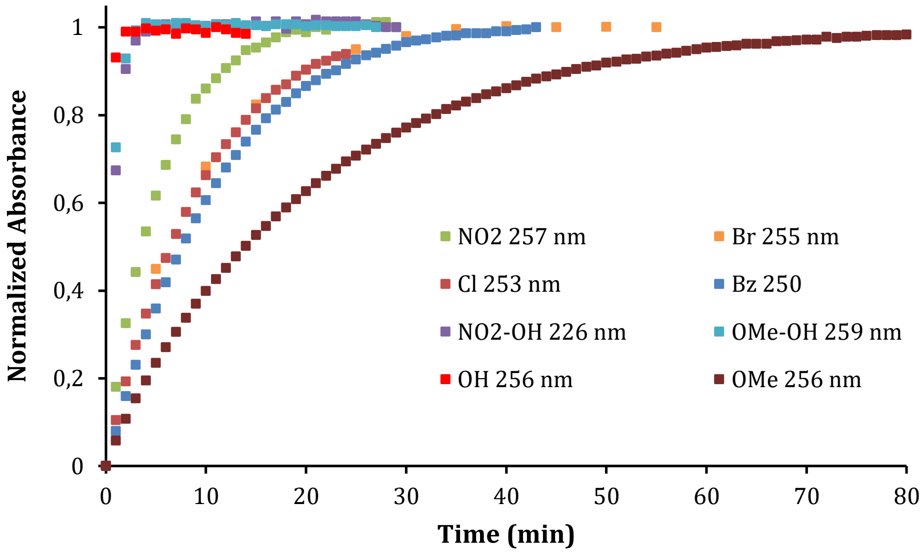
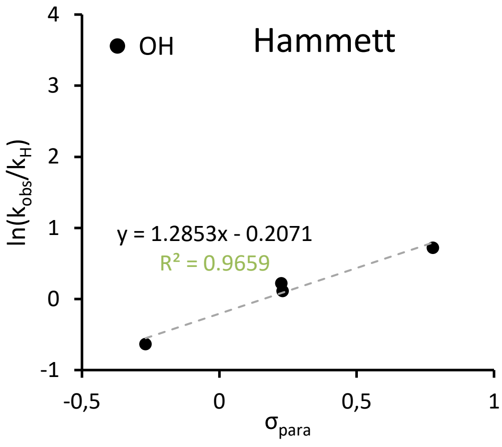
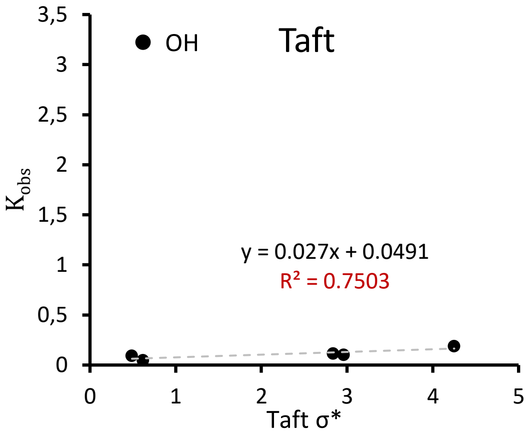


Figure S24. Normalized hydrolysis rate of aminals **21** and **26-32** at the indicated wavelengths.

Table S1. Hammett parameter σ_{para}, Taft parameter σ* and calculated k_{obs} for aminals **21** and **26-32**.

Aminal	k_{obs}	$Ln(k_{obs}/k_H)$	σ_{para}	Taft σ*
27	0,188324	2,048964	0,78	4.25
28	0,114679	1,247706	0,23	2.84
29	0,102987	1,120494	0,23	2.96
21	0,091912	1	0	0.49
30	0,04869	35,09677	-0,268	0.62
26	3,225806	0,529747	-0,37	1.34





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