Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting information

Copper-Catalysed C–H Functionalisation gives access to 2-aminobenzimidazoles

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Contents

HPLC solvent gradient for reaction monitoring

The solvents utilised were:

A: Water + 0.05% v/v trifluoroacetic acid

B: Acetonitrile + 0.05% v/v trifluoroacetic acid

The gradient employed was:

Time (min)	**Flow Rate (mL min^{-1})**	**%A**	**%B**
0.00	1	97	3
3.7	1	5	95
4.0	1	5	95
4.1	1	97	3
5.5	1	97	3

LCMS High pH solvent gradient for reaction monitoring

The solvents employed were:

A = 10 mM ammonium bicarbonate in water adjusted to pH 10 with ammonia solution.

B = Acetonitrile.

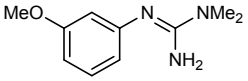
The gradient employed was:

Time (min)	**Flow Rate (mL min^{-1})**	**%A**	**%B**
0.00	1	97	3
0.05	1	97	3
1.50	1	5	95
1.90	1	5	95
2.00	1	97	3

High Resolution Mass Spectrometry solvent gradient (HRMS)

Time (min)	%A	%B
0.00	95	5
0.05	95	5
6.00	0	100
8.50	0	100
9.50	95	5
12.00	95	5

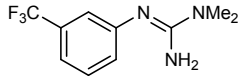
2-(3-Methoxyphenyl)-1,1-dimethylguanidine (**4**)



Using general procedure 1 with 3-methoxyaniline (6.61 g, 53.7 mmol, 1 equiv), sodium hydride (2.53 g, 63.4 mmol, 1.2 equiv) and dimethylcyanamide (4.44 g, 63.4 mmol, 1.2 equiv). 2-(3-methoxyphenyl)-1,1-dimethylguanidine (**4**) (5.42 g, 28.0 mmol, 52%) was isolated as a pale-orange crystalline solid after 3.5 hours by crystallisation from heptane/ethyl acetate and rinsing with cold tBME (10 mL).

Melting point: 134–136 °C. FTIR v_{max}/cm^{-1} 3409, 3131 (br), 1653, 1544, 1485, 1396. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.99 (6 H, s), 3.78 (3 H, s), 6.48 – 6.50 (1 H, m), 6.52 (1 H, dd, *J*=2.2, 0.9 Hz), 6.59 (1 H, ddd, *J*=8.1, 2.2, 0.9 Hz), 7.19 (1 H, *app*.t, *J*=8.1 Hz)) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.1 55.6, 109.0, 110.9, 117.6, 130.9, 152.6, 157.1, 162.2 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{10}H_{16}N_3O$ 194.1288, found [M + H]$^+$ 194.1280.

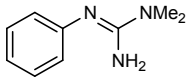
1,1-Dimethyl-2-(3-(trifluoromethyl)phenyl)guanidine (7).



Using general procedure 1 with 3-(trifluoromethyl)aniline (3.00 g, 31.0 mmol, 1 equiv), sodium hydride (1.49 g, 37.2 mmol, 1.2 equiv) and dimethylcyanamide (2.61 g, 37.2 mmol, 1.2 equiv), after a 45 minute reaction time, a precipitate formed on addition of water, which was filtered, the liquors extracted and combined with the filtered solid, yielding 1,1-dimethyl-2-(3-(trifluoromethyl)phenyl) guanidine (**7**) (4.658 g, 20.2 mmol, 65 %) as an off-white crystalline solid after crystallisation from boiling heptane and rinsing with cold tBME (5 mL).

Melting point: 102–104 °C FTIR v_{max}/cm^{-1} 3450, 3122 (br), 1637, 1566, 1334. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.98 (6 H, s), 7.09 – 7.14 (2 H, m), 7.18 – 7.22 (1 H, m) 7.40 (1 H, *app.* t, *J*=7.9 Hz) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.0, 119.1 (q, *J*=3.8 Hz), 121.7 (q, *J*=3.8 Hz), 125.9 (q, *J*=271.4 Hz), 128.8, 131.0, 132.6 (q, *J*=31.7 Hz), 152.8, 157.3. ^{19}F NMR (377 MHz, *METHANOL-d*$_4$) δ ppm -64.14 (1 F, s) HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{10}H_{13}F_3N_3$ [M + H]$^+$ 232.1056, found [M + H]$^+$ 232.1047

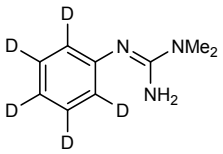
1,1-Dimethyl-2-phenylguanidine (27).



Using general procedure 1 with aniline (1.00 g, 10.7 mmol, 1 equiv), sodium hydride (0.52 g, 12.9 mmol, 1.2 equiv) and dimethylcyanamide (0.90 g, 12.9 mmol, 1.20 equiv) was reacted for 5 hours before addition of a further portion of dimethylcyanamide (0.26 g, 3.7 mmol, 0.35 equiv) and the reaction stirred at room temperature overnight. After the standard work up, the product was purified by chromatography (Biotage KP-NH silica, EtOAc) and the fractions containing product were recrystallised from EtOAc to yield 1,1-dimethyl-2-phenylguanidine (**27**) as a white crystalline solid (943 mg, 5.8 mmol, 54%)

Melting point: 91–93 °C FTIR v_{max}/cm^{-1} 3429, 3144 (br), 1635, 1561, 1484. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.99 (6 H, s), 6.90 – 6.94 (2 H, m), 7.00 (1 H, dt, *J*=14.8, 1.2 Hz), 7.26 – 7.32 (2 H, m), ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.1, 123.3, 125.3, 130.3, 151.3, 157.1. HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_9H_{14}N_3$ [M + H]$^+$ 164.1188, found [M + H]$^+$ 164.1183 *The data is in agreement with those previously reported*[1]

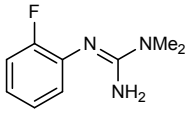
1-Dimethyl-2-phenyl(D$_5$)guanidine (28).



Using general procedure 1 with aniline-D$_5$ (1.09 g, 11.1 mmol, 1 equiv), sodium hydride (0.51 g, 12.7 mmol, 1.15 equiv) and dimethylcyanamide (0.91 g, 13.0 mmol, 1.2 equiv) was reacted for 5 hours before addition of a further portion of dimethylcyanamide (0.17 g, 0.22 equiv) and the reaction stirred at room temperature overnight. After the standard work up, the product was purified by chromatography (Biotage KP-NH silica, EtOAc) and the fractions containing product were recrystallised from EtOAc to yield 1,1-dimethyl-2-(phenyl-D$_5$)guanidine (**28**) as a white crystalline solid (461 mg, 2.7 mmol, 25%)

^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.96 (6 H, s), ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.1, 122.8 (t, *J*=23.8 Hz), 124.9 (t, *J*=24.0 Hz), 129.8 (t, *J*=25.0 Hz), 151.1, 157.1. ^{2}H NMR (92 MHz, *DMSO-d*$_6$) δ ppm 7.4 (2 D, s), 7.1 (1 D, s), 7.1 (2 D, s)

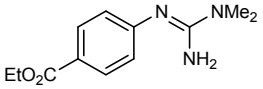
2-(2-Fluorophenyl)-1,1-dimethylguanidine (51).



Using general procedure 1 with 2-fluoroaniline (2.00 g, 18.0 mmol, 1 equiv), sodium hydride (0.87 g, 21.9 mmol, 1.21 equiv) and dimethylcyanamide (1.51 g, 21.6 mmol, 1.2 equiv), 2-(2-fluorophenyl)-1,1-dimethylguanidine (**51**) (2.02 g, 11.2 mmol, 62 %) was isolated as an off-white solid after 15 hours by column chromatography (5% MeOH / CH_2Cl_2 with 2% triethylamine in the CH_2Cl_2 portion).

Melting point: 86–88 °C FTIR ν_{max}/cm^{-1} 3458, 3134 (br), 1636, 1566, 1481. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 3.02 (6 H, s), 6.95 – 7.03 (2 H, m), 7.03 – 7.11 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.1, 116.9 (d, *J*=20.8 Hz), 124.4 (d, *J*=7.4 Hz), 125.7 (d, *J*=3.6 Hz), 128.1 (d, *J*=2.5 Hz), 139.0 (d, *J*=12.8 Hz), 157.6 (d, *J*=242.4 Hz), 157.4. ^{19}F NMR (377 MHz, *METHANOL-d*$_4$) δ ppm -126.93 (s) HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_9H_{13}FN_3$ [M + H]$^+$ 182.1088, found [M + H]$^+$ 182.1079

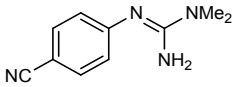
Ethyl 4-((amino(dimethylamino)methylene)amino) benzoate (52)



Using general procedure 1 with ethyl 4-aminobenzoate (1.00 g, 6.1 mmol, 1 equiv), sodium hydride (0.32 g, 8.0 mmol, 1.3 equiv) and dimethylcyanamide (0.51 g, 7.3 mmol, 1.2 equiv), after 2 hours, ethyl 4-((amino(dimethyl- amino)methylene) amino)benzoate (**52**) was isolated as a white solid by chromatography (Biotage KP-NH silica 0–10% MeOH/CH_2Cl_2) (136 mg, 0.6 mmol, 10%)

Melting point: 89–92 °C FTIR ν_{max}/cm^{-1} 3455, 3124 (br), 1703, 1624, 1551, 1493, 1401. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 1.39 (3 H, t, *J*=7.1 Hz), 3.01 (6 H, s), 4.33 (2 H, q, *J*=7.1 Hz), 6.93 – 7.01 (2 H, m), 7.87 – 7.96 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 14.8, 38.1, 61.7, 124.0, 124.3, 132.1, 157.1, 157.4, 168.5. HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{12}H_{18}N_3O_2$ [M + H]$^+$ 236.1394, found [M + H]$^+$ 236.1384

2-(4-Cyanophenyl)-1,1-dimethylguanidine (53).

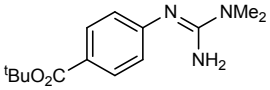


Using general procedure 1 with 4-aminobenzonitrile (3.00 g, 25.4 mmol, 1 equiv), sodium hydride (1.32 g, 33.0 mmol, 1.3 equiv) and dimethylcyanamide (2.14 g, 30.5 mmol, 1.2 equiv), after 16 hours 2-(4-cyanophenyl)-1,1-dimethylguanidine (**53**) was isolated as a white crystalline solid after recrystallisation from EtOAc (1.412 g, 7.5 mmol, 30%).

Melting point: 125–127 °C FTIR ν_{max}/cm^{-1} 3482, 3370, 2216, 1631, 1514, 1404. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 3.02 (6 H, s), 6.98 – 7.04 (2 H, m), 7.53 – 7.60 (2 H, m). ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.0, 103.9, 121.0, 125.3, 134.4, 157.4, 157.6.

HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{10}H_{13}N_3$ [M + H]$^+$ 189.1135, found [M + H]$^+$ 189.1136

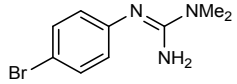
Tert-butyl 3-((amino(dimethylamino)methylene) amino)benzoate (54).



Using general procedure 1 with *tert*-butyl 4-aminobenzoate (2.52 g, 13.1 mmol, 1 equiv), sodium hydride (0.77 g, 19.3 mmol, 1.5 equiv) and dimethylcyanamide (1.13 g, 16.1 mmol, 1.2 equiv), after 16 hours and the standard work-up, the resultant crude solid was washed with heptane (15 mL) and recrystallised from heptane/EtOAc to afford *tert*-butyl 3-((amino(dimethylamino)methylene) amino)benzoate (**54**) as a white crystalline solid (2.61 g, 9.9 mmol 76%)

Melting point: 104–107 °C FTIR ν_{max}/cm^{-1} 3446, 2982 (br), 1701, 1563, 1368, 1289. ^{1}H NMR (400 MHz, METHANOL-*d*$_4$) δ ppm 1.60 (9 H, s), 3.01 (6 H, s), 6.95 (2 H, d, *J*=8.4 Hz), 7.86 (2 H, d, *J*=8.4 Hz), ^{13}C{^{1}H} NMR (101 MHz, METHANOL-*d*$_4$) δ ppm 27.1, 36.6, 80.2, 123.0, 124.4, 130.4, 155.2, 155.7, 166.5. HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{13}H_{22}N_3O_2$ [M + H]$^+$ 264.1707, found [M + H]$^+$ 264.2698

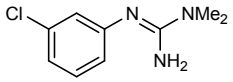
2-(4-Bromophenyl)-1,1-dimethylguanidine (55).



Using general procedure 1 with 4-bromoaniline (4.00 g, 23.3 mmol, 1 equiv), sodium hydride (1.21 g, 30.3 mmol, 1.3 equiv) and dimethylcyanamide (1.91 g, 27.2 mmol, 1.20 equiv), after 16 hours, following the standard work-up the resultant yellow solid was purified by recrystallisation from hot EtOAc and washing the resultant crystals with cold heptane to yield 2-(4-bromophenyl)-1,1-dimethylguanidine (**55**) as a yellow crystalline solid (2.19 g, 9.1 mmol, 39%)

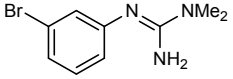
Melting point: 92–94 °C FTIR ν_{max}/cm^{-1} 3540, 3190 (br), 1693, 1633, 1593, 1556. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.99 (6 H, s), 6.81 – 6.85 (2 H, m), 7.37 – 7.42 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.0, 115.5, 127.1, 133.2, 151.0 157.1 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_9H_{13}{}^{79}BrN_3$ [M + H]$^+$ 242.0297, found [M + H]$^+$ 242.0280

3-(3-Chlorophenyl)-1,1-dimethylguanidine (56).



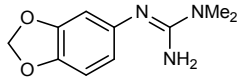
Using general procedure 1 with 3-chloroaniline (1.51 g, 11.8 mmol, 1 equiv), sodium hydride (0.58 g, 14.5 mmol, 1.2 equiv) and dimethylcyanamide (1.00 g, 14.2 mmol, 1.2 equiv), after 2.5 hours, 3-(3-chlorophenyl)-1,1-dimethylguanidine (**56**) was isolated as a white solid after chromatography (0–10% MeOH/CH_2Cl_2) (1.06 g, 5.4 mmol, 46%).
Melting point: 89–91 °C FTIR v_{max}/cm^{-1} 3437, 3122 (br), 1637, 1553, 1398, 1302. ^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 2.89 (6 H, s), 5.81 (2 H, br. s), 6.68 – 6.72 (1 H, m), 6.76 (1 H, t, *J*=2.0 Hz), 6.83 – 6.87 (1 H, m), 7.19 (1 H, t, *J*=7.9 Hz) ^{13}C{^{1}H} NMR (101 MHz, *DMSO-d*$_6$) δ ppm 37.4, 119.9, 121.7, 122.6, 130.3, 133.1, 152.0 153.4. HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_9H_{13}{}^{35}ClN_3$ [M + H]$^+$ 198.0793, found [M + H]$^+$ 198.0785

3-(3-Bromophenyl)-1,1-dimethylguanidine (57).



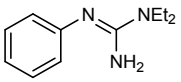
Using general procedure 1 with 3-bromoaniline (3.00 g, 17.4 mmol, 1 equiv), sodium hydride (0.84 g, 20.9 mmol, 1.2 equiv) and dimethylcyanamide (1.47 g, 20.9 mmol, 1.2 equiv), after 16 hours and the standard work-up procedure the crude product was purified by reverse-phase chromatography (kP-C_{18}-HS cartridge 15-55% water/acetonitrile with 0.1% NH_4HCO_3 buffer). The fractions containing product were evaporated to remove the acetonitrile and the aqueous pH increased to ~10 with NH_4OH, which was then extracted with tBME (3 × 50 mL). The organic portion was then washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford 3-(3-bromophenyl)-1,1-dimethylguanidine (**57**) as an off-white solid (883 mg, 3.7 mmol, 21%)
Melting point: 104–106 °C FTIR v_{max}/cm^{-1} 3437, 3128 (br), 1637, 1598, 1551, 1465, 1398. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.96 (6 H, s), 6.84 (1 H, ddd, *J*=7.8, 2.0, 1.2 Hz), 7.04 (1 H, t, *J*=2.0 Hz), 7.09 (1 H, ddd, *J*=7.8, 2.0, 1.2 Hz), 7.15 (1 H, t, *J*=7.8 Hz) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.0, 123.7, 124.1, 125.8, 128.2, 131.7, 153.7, 157.2 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_9H_{13}{}^{79}BrN_3$ [M + H]$^+$ 242.0287, found [M + H]$^+$ 242.0275

2-(Benzo[d][1,3]dioxol-5-yl)-1,1-dimethylguanidine (58).



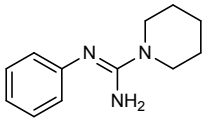
Using general procedure 1 with benzo[d][1,3]dioxol-5-amine (2.49 g, 29.5 mmol, 1 equiv), sodium hydride (1.58 g, 39.6 mmol, 1.3 equiv) and dimethylcyanamide (2.49 g, 35.5 mmol, 1.2 equiv), after 16 hours and the standard work-up, the resultant solid was washed with cold heptane and then EtOAc, and purified by chromatography (0–6% MeOH/CH_2Cl_2, Biotage KP-NH cartridge) to afford 2-(benzo[d][1,3]dioxol-5-yl)-1,1-dimethylguanidine (**58**) as a fluffy grey solid (2.63 g, 12.7 mmol, 43%)
Melting point: 137–138 °C FTIR v_{max}/cm^{-1} 3435, 3192 (br), 2898, 1634, 1574, 1437. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 2.97 (6 H, s), 5.91 (2 H, s), 6.36 (1 H, dd, *J*=8.2, 2.1 Hz), 6.43 (1 H, d, *J*=2.1 Hz), 6.75 (1 H, d, *J*=8.2 Hz) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 38.1, 102.2, 106.7, 109.4, 117.4, 144.5, 145.4, 149.7, 157.4 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{10}H_{14}N_3O_2$ [M + H]$^+$ 208.1081, found [M + H]$^+$ 208.1070

1,1-Diethyl-2-phenylguanidine (59).



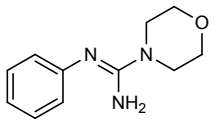
Using general procedure 1 with aniline (1.50 g, 16.1 mmol, 1 equiv), sodium hydride (0.869 g, 21.7 mmol, 1.4 equiv) and diethylcyanamide (1.74 g, 17.7 mmol, 1.1 equiv), after 24 hours using the standard work-up and purification by chromatography (0–10% MeOH/CH_2Cl_2) yielded 1,1-diethyl-2-phenylguanidine (**59**) as a white solid (1.09 g, 5.7 mmol, 35%).
Melting point: 59–61 °C FTIR v_{max}/cm^{-1} 3441, 3074 (br), 2976, 1637, 1543. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 1.22 (6 H, t, *J*=7.1 Hz), 3.41 (4 H, q, *J*=7.1 Hz), 6.89 – 6.95 (2 H, m), 7.00 (1 H, tt, *J*=7.4, 1.2 Hz), 7.25 – 7.33 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 12.5, 41.6, 121.8, 124.0, 128.9, 150.2, 153.8 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{11}H_{18}N_3$ [M + H]$^+$ 192.1495, found [M + H]$^+$ 192.1488

N-phenylpiperidine-1-carboximidamide (60).



Using general procedure 1 with aniline (1.23 g, 13.2 mmol, 1 equiv), sodium hydride (0.643 g, 16.1 mmol, 1.2 equiv) and piperidine-1-carbonitrile (1.41 g, 12.8 mmol, 1.0 equiv) after 16 hours and the standard work-up was isolated *N*-phenylpiperidine-1-carboximidamide (**60**) by chromatography (1% triethylamine in EtOAc) (555 mg, 2.7 mmol, 21% *based on piperidine-1-carbonitrile*).
Melting point: 74–76 °C FTIR v_{max}/cm^{-1} 3435, 2857, 1637. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 1.57 – 1.76 (6 H, m), 3.37 – 3.45 (4 H, m), 6.87 – 6.94 (2 H, m), 7.00 (1 H, tt, *J*=7.4, 1.2 Hz), 7.25 – 7.33 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 24.4, 25.5, 46.4, 121.9, 123.5, 128.9, 149.7, 155.6 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{12}H_{18}N_3$ [M + H]$^+$ 204.1495, found [M + H]$^+$ 204.1486

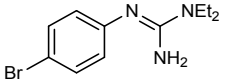
N-phenylmorpholine-4-carboximidamide (61).



Using general procedure 1 with aniline (1.00 g, 10.7 mmol, 1 equiv), sodium hydride (0.589 g, 14.7 mmol, 1.4 equiv) and morpholine-4-carbonitrile (1.26 g, 11.3 mmol, 1.1 equiv) after 24 hours and the standard work-up was isolated *N*-phenylmorpholine-4-carboximidamide (**61**) as a white solid by chromatography (80% EtOAc/heptane → EtOAc w/ 2% triethylamine in EtOAc portions). (752 mg, 3.6 mmol, 34%)

Melting point: 131–133 °C FTIR v_{max}/cm^{-1} 3453, 3354, 2848. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 3.37 – 3.41 (4 H, m), 3.72 – 3.78 (4 H, m), 6.88 – 6.94 (2 H, m), 7.02 (1 H, tt, *J*=7.6, 1.2 Hz), 7.31 (2 H, tt, *J*=7.6, 1.2 Hz) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 45.9, 66.4, 122.2, 123.4, 129.0, 149.4, 155.7 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{11}H_{16}N_3O$ [M + H]$^+$ 206.1288, found [M + H]$^+$ 206.1278

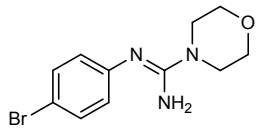
2-(4-bromophenyl)-1,1-diethylguanidine (62).



Using general procedure 1 with 4-bromoaniline (2.44 g, 14.2 mmol, 1 equiv), sodium hydride (0.732 g, 18.3 mmol, 1.3 equiv) and diethylcyanamide (1.61 g, 16.4 mmol, 1.2 equiv) after 24 hours at room temperature was added further diethylcyanamide (0.42 g, 4.3 mmol, 0.3 equiv). After a further 5 hours using the standard work-up was isolated 2-(4-bromophenyl)-1,1-diethylguanidine (**62**) as a white crystalline solid by chromatography (1% MeOH/EtOAc w/ 1% triethylamine in EtOAc portions) and subsequent recrystallisation (heptane/EtOAc) (700 mg, 2.6 mmol, 18%)

Melting point: 53–54 °C FTIR v_{max}/cm^{-1} 3453, 3139, 2976. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 1.17 (6 H, t, *J*=7.1 Hz), 3.37 (4 H, q, *J*=7.1 Hz), 6.70 – 6.88 (2 H, m), 7.28 – 7.44 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 12.4, 41.6, 114.0, 125.8, 131.8, 149.7, 153.8 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{11}H_{17}{}^{79}BrN_3$ [M + H]$^+$ 270.0600, found [M + H]$^+$ 270.0599

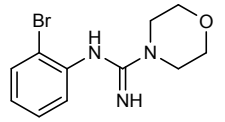
N-(4-bromophenyl)morpholine-4-carboximidamide (63).



Using general procedure 1 with 4-bromoaniline (2.46 g, 14.3 mmol, 1 equiv), sodium hydride (0.78 g, 19.6 mmol, 1.4 equiv) and morpholine 4-carbonitrile (1.76 g, 15.7 mmol, 1.1 equiv) after 16 hours and chromatography (1–3% MeOH in EtOAc w/ 1% triethylamine in EtOAc portion) was isolated *N*-phenylmorpholine-4-carboximidamide (**63**) as an off-white solid (2.84 g, 10.0 mmol, 70%)

Melting point: 110–112 °C FTIR v_{max}/cm^{-1} 3447, 3069 (br), 2852, 1635, 1589, 1560, 1433. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 3.38 (4 H, t, J=4.8 Hz), 3.74 (4 H, t, J= 4.8 Hz), 6.79 – 6.86 (2 H, m), 7.38 – 7.44 (2 H, m) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 45.8, 66.3, 114.4, 125.3, 131.9, 149.1, 155.6 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{11}H_{15}{}^{79}BrN_3O$ [M + H]$^+$ 284.0393, found [M + H]$^+$ 284.0384

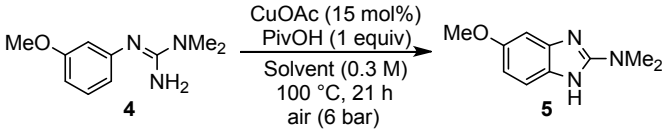
N-(2-bromophenyl)morpholine-4-carboximidamide (64).



Using general procedure 1 with 2-bromoaniline (2.00 g, 11.6 mmol, 1 equiv), sodium hydride (0.61 g, 15.1 mmol, 1.3 equiv) and morpholine 4-carbonitrile (1.44 g, 12.9 mmol, 1.1 equiv) after 16 hours and chromatography (EtOAc:heptane, 1:1, w/ 2% triethylamine in EtOAc portion) was isolated a white solid. The solid was then recrystalised from TBME to yield *N*-(2-bromophenyl)morpholine-4-carboximidamide (**64**) as a white crystaline solid (1.48 g, 5.2 mmol, 45%)

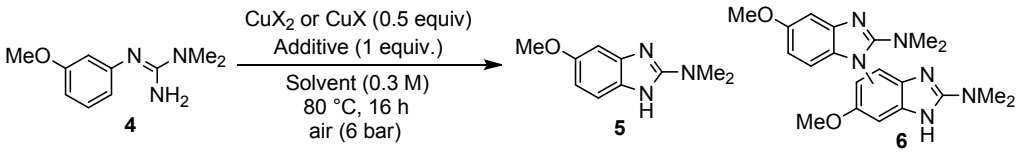
Melting point: 98–100 °C FTIR v_{max}/cm^{-1} 3458, 3150 (br), 2974, 1630, 1546, 1426, 1275. ^{1}H NMR (400 MHz, *METHANOL-d*$_4$) δ ppm 3.41 – 3.47 (4 H, m), 3.74 – 3.79 (4 H, m), 6.94 (1 H, td, *J*=7.6, 1.6 Hz), 6.98 (1 H, dd, *J*=8.0, 1.6 Hz), 7.29 (1 H, td, *J*=7.6, 1.4 Hz), 7.59 (1 H, dd, *J*=8.0, 1.4 Hz) ^{13}C{^{1}H} NMR (101 MHz, *METHANOL-d*$_4$) δ ppm 46.0, 66.4, 118.9, 123.7, 125.3, 128.1, 132.8, 148.2, 155.1 HRMS (ESI Orbitrap) m/z: [M + H]$^+$ Calcd for $C_{11}H_{15}{}^{79}BrN_3O$ [M + H]$^+$ 284.0393, found [M + H]$^+$ 284.0384

Solvent screen



Solvent	Flash point	Product (**5**, HPLC Area %)	Starting material (**4**, HPLC area %)	Comments
Ethylene carbonate	150 °C	-	-	*Decomposition*
Ethylene glycol	111 °C	0%	> 90%	*Poor conversion*
NMP	91 °C	36%	16%	
Octanoic acid	130 °C	0%	>90%	*Poor conversion*

Screen of copper sources, additives and solvent for the cyclisation of 4.



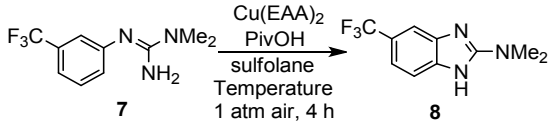
Catalyst / Solvent / Additive	[Cu] / mg	Additive / mg	**4** / HPLC %	**5** / HPLC %	**6** / HPLC %
CuOAc / Sulfolane / PivOH	7.91	*s.s*	30	45	5
CuOAc / Sulfolane / AcOH	8.06	*s.s*	33	42	6
CuOAc / Sulfolane / NaOPiv	8.02	16.02	79	9	1
CuOAc / Sulfolane / NaOAc	7.89	10.57	72	15	1
CuOAc / DMSO / PivOH	7.95	*s.s*	45	19	6
CuOAc / DMSO / AcOH	7.89	*s.s*	42	16	7
CuOAc / DMSO / NaOPiv	7.92	15.96	78	3	0.4
CuOAc / DMSO / NaOAc	7.92	10.57	80	5	0.8
CuOAc / NMP / PivOH	7.91	*s.s*	25	33	13
CuOAc / NMP / AcOH	7.92	*s.s*	27	32	12
CuOAc / NMP / NaOPiv	7.93	16.83	74	8	2
CuOAc / NMP / NaOAc	7.95	10.72	66	14	3
CuTC / Sulfolane / PivOH	11.95	*s.s*	34	27	7
CuTC / Sulfolane / AcOH	12.59	*s.s*	38	44	3
CuTC / Sulfolane / NaOPiv	12.09	15.79	82	8	0.3
CuTC / Sulfolane / NaOAc	11.81	10.58	51	19	7
CuTC / DMSO / PivOH	12.58	*s.s*	66	17	2.4
CuTC / DMSO / AcOH	11.72	*s.s*	67	17	2
CuTC / DMSO / NaOPiv	11.85	15.88	71	9	1.6
CuTC / DMSO / NaOAc	15.70	10.60	75	5	1.4
CuTC / NMP / PivOH	12.82	*s.s*	37	30	7.5
CuTC / NMP / AcOH	12.29	*s.s*	34	25	10
CuTC / NMP / NaOPiv	11.66	16.07	70	11	2
CuTC / NMP / NaOAc	15.72	10.60	57	18	4
$CuEH_2$ / Sulfolane / PivOH	23.00	*s.s*	63	30	0.5
$CuEH_2$ / Sulfolane / AcOH	23.07	*s.s*	53	35	1.5
$CuEH_2$ / Sulfolane / NaOPiv	23.24	15.86	60	27	2.5

$CuEH_2$ / Sulfolane / NaOAc	23.30	10.61	39	33	8
$CuEH_2$ / DMSO / PivOH	23.08	*s.s*	68	17	2
$CuEH_2$ / DMSO / AcOH	23.17	*s.s*	69	16	2
$CuEH_2$ / DMSO / NaOPiv	23.52	15.88	72	9	2
$CuEH_2$ / DMSO / NaOAc	23.09	10.70	75	6	1
$CuEH_2$ / NMP / PivOH	23.55	*s.s*	47	35	4
$CuEH_2$ / NMP / AcOH	23.22	*s.s*	46	30	5
$CuEH_2$ / NMP / NaOPiv	23.04	15.90	66	14	5
$CuEH_2$ / NMP / NaOAc	22.60	10.58	59	17	6
Cu 3-MeSal / Sulfolane / PivOH	13.93	*s.s*	55	29	0.8
Cu 3-MeSal / Sulfolane / AcOH	13.99	*s.s*	71	19	0
Cu 3-MeSal / Sulfolane / NaOPiv	14.01	15.93	91	2.5	0
Cu 3-MeSal / Sulfolane / NaOAc	13.97	10.67	55	10	4
Cu 3-MeSal / DMSO / PivOH	13.99	*s.s*	76	13	0
Cu 3-MeSal / DMSO / AcOH	14.00	*s.s*	62	11	2.5
Cu 3-MeSal / DMSO / NaOPiv	14.00	15.95	70	7	2
Cu 3-MeSal / DMSO / NaOAc	14.01	10.60	75	5	1
Cu 3-MeSal / NMP / PivOH	14.00	*s.s*	54	20	3.5
Cu 3-MeSal / NMP / AcOH	14.34	*s.s*	54	20	4
Cu 3-MeSal / NMP / NaOPiv	13.89	15.96	62	13	4
Cu 3-MeSal / NMP / NaOAc	13.94	10.70	67	10	3
$Cu(II)(acacF_6)_2$ / Sulfolane / PivOH	30.94	*s.s*	68	17	0.5
$Cu(II)(acacF_6)_2$ / Sulfolane / AcOH	30.96	*s.s*	78	14	0
$Cu(II)(acacF_6)_2$ / Sulfolane / NaOPiv	30.98	16.00	70	20	0.5
$Cu(II)(acacF_6)_2$ / Sulfolane / NaOAc	31.24	10.61	74	9	0.5
$Cu(II)(acacF_6)_2$ / DMSO / PivOH	31.65	*s.s*	94	1	0
$Cu(II)(acacF_6)_2$ / DMSO / NaOPiv	32.02	15.99	57	12	2.4
$Cu(II)(acacF_6)_2$ / DMSO / NaOAc	30.96	10.92	54	11	4
$Cu(II)(acacF_6)_2$ / NMP / PivOH	31.55	*s.s*	82	7	0
$Cu(II)(acacF_6)_2$ / NMP / AcOH	30.83	*s.s*	84	7	0
$Cu(II)(acacF_6)_2$ / NMP / NaOPiv	30.87	16.00	45	25	4
$Cu(II)(acacF_6)_2$ / NMP / NaOAc	32.10	10.79	53	19	4
$Cu(II)(EAA)_2$ / Sulfolane / PivOH	20.95	*s.s*	25	54	2
$Cu(II)(EAA)_2$ / Sulfolane / AcOH	20.98	*s.s*	31	49	2
$Cu(II)(EAA)_2$ / Sulfolane / NaOPiv	21.02	15.98	80	9	0
$Cu(II)(EAA)_2$ / Sulfolane / NaOAc	21.11	10.45	71	9	0
$Cu(II)(EAA)_2$ / DMSO / PivOH	21.02	*s.s*	41	32	0
$Cu(II)(EAA)_2$ / DMSO / NaOPiv	21.04	16.00	44	13	0.5
$Cu(II)(EAA)_2$ / DMSO / NaOAc	21.07	10.825	81	2	0
$Cu(II)(EAA)_2$ / NMP / PivOH	21.04	*s.s*	10	43	0.4
$Cu(II)(EAA)_2$ / NMP / AcOH	21.05	*s.s*	15	43	1
$Cu(II)(EAA)_2$c / NMP / NaOPiv	21.18	16.00	56	19	0.5
$Cu(II)(EAA)_2$ / NMP / NaOAc	21.13	10.48	46	22	0
$Cu(NCMe)_4.PF_6$ / Sulfolane / PivOH	24.00	*s.s*	52	24	5

$Cu(NCMe)_4.PF_6$ / Sulfolane / AcOH	24.01	*s.s*	60	20	4
$Cu(NCMe)_4.PF_6$ / Sulfolane / NaOPiv	24.02	16.00	78	7	0
$Cu(NCMe)_4.PF_6$ / Sulfolane / NaOAc	24.02	10.71	61	11	0.8
$Cu(NCMe)_4.PF_6$ / DMSO / PivOH	24.02	*s.s*	83	9	0
$Cu(NCMe)_4.PF_6$ / DMSO / AcOH	24.02	*s.s*	70	3	1
$Cu(NCMe)_4.PF_6$ / DMSO / NaOPiv	24.02	15.99	55	12	4
$Cu(NCMe)_4.PF_6$ / DMSO / NaOAc	24.01	10.46	53	11	4
$Cu(NCMe)_4.PF_6$ / NMP / PivOH	24.03	*s.s*	58	9	2
$Cu(NCMe)_4.PF_6$ / NMP / AcOH	24.01	*s.s*	64	7	3
$Cu(NCMe)_4.PF_6$ / NMP / NaOPiv	24.03	16.00	43	19	8
$Cu(NCMe)_4.PF_6$ NMP / NaOAc	24.04	10.52	54	16	2.5

s.s = dispensed in stock solution of solvent. Mass accuracy given to 2.d.p as weighings were performed on a 4.d.p mg balance. EH = 2-ethylhexanoate, TC = thiophene 2-carboxylate, 3-MeSal = 3-methyl salicylic acid, EAA = ethyl acetoacetate

Design of Experiments Optimisation procedure



Reaction number	**7** / mg	$Cu(EAA)_2$ / mg	$Cu(EAA)_2$/mol%	Temperature / °C	PivOH / mg	PivOH / eq
1	23.06	1.56	4.9	100	10.53	1.03
2	23.28	8.01	24.7	130	10.82	1.05
3	23.07	1.67	5.2	130	20.39	2.00
4	93.44	32.15	24.7	130	83.19	2.02
5	24.09	24.09	24.1	100	21.44	2.02
6	57.92	12.14	15.1	115	28.49	1.50
7	93.66	6.43	4.9	100	82.89	2.00
8	92.45	32.21	25.0	100	40.82	1.00
9	58.34	12.07	14.9	115	38.63	1.50
10	92.53	6.44	5.0	130	40.63	0.99

Table 1: masses used for DoE experimentation. Mass accuracy given to 2.d.p as weighings were performed on a 4.d.p mg balance.

The calculated statistical model fitted to the data is described below and imported directly from the DX10 Design of Experiments software.

Response 2 Product %

Center Points Detected: The ANOVA is presented in two ways:
Adjusted model: The factorial model includes a curvature term, which separates the curvature from the lack-of-fit sum of squares. The adjusted model provides the factorial model coefficients you'd get if there were no center points and is used for diagnostics (by default).
Unadjusted model: The model coefficients are fit using all the data (including the center points) without a curvature term. The unadjusted model is used to create the model graphs and for optimization predictions.

ANOVA Summary

	Adjusted	**Model**		**Unadjusted**	**Model**

	F-value	p-value		F-value	p-value	
Model	110.16	< 0.0001	significant	10.80	0.0073	significant
Curvature	65.43	0.0002	significant			
Lack of Fit	94.11	0.0781		935.36	0.0250	Curvature appears significant. Augment to RSM if you want to explain what is causing the curvature or if curvature is in a desirable direction for your goal. **Model Summary**
	Adjusted	**Model**		**Unadjusted**	**Model**	
	Coefficient			**Coefficient**		
Factor	**Estimate**	**p-value**		**Estimate**	**p-value**	
Intercept	44.66			50.68		
C-Catalyst	24.23	< 0.0001		24.23	0.0026	
D-Temp	4.64	0.0316		4.64	0.4113	
Ctr Pt 1	30.06	0.0002				

The following ANOVA is for a model that does not adjust for curvature.

ANOVA for selected factorial model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	4869.88	2	2434.94	10.80	0.0073	significant
C-Catalyst	*4697.76*	*1*	*4697.76*	*20.83*	*0.0026*	
D-Temp	*172.12*	*1*	*172.12*	*0.76*	*0.4113*	
Residual	1578.71	7	225.53			
Lack of Fit	*1578.43*	*6*	*263.07*	*935.36*	*0.0250*	*significant*
Pure Error	*0.28*	*1*	*0.28*			
Cor Total	6448.59	9				

The following ANOVA is for a model that adjusts for curvature.
This is the default model used for the diagnostic plots.
This model is also used for prediction and model plots.

ANOVA for selected factorial model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	4869.88	2	2434.94	110.16	< 0.0001	significant
C-Catalyst	*4697.76*	*1*	*4697.76*	*212.54*	*< 0.0001*	
D-Temp	*172.12*	*1*	*172.12*	*7.79*	*0.0316*	
Curvature	1446.09	1	1446.09	65.43	0.0002	
Residual	132.62	6	22.10			
Lack of Fit	*132.34*	*5*	*26.47*	*94.11*	*0.0781*	*not significant*
Pure Error	*0.28*	*1*	*0.28*			
Cor Total	6448.59	9				

The Model F-value of 110.16 implies the model is significant. There is only
a 0.01% chance that an F-value this large could occur due to noise.
Values of "Prob > F" less than 0.0500 indicate model terms are significant.
In this case C, D are significant model terms.
Values greater than 0.1000 indicate the model terms are not significant.
If there are many insignificant model terms (not counting those required to support hierarchy),
model reduction may improve your model.
The "Curvature F-value" of 65.43 implies there is significant curvature (as measured by
difference between the average of the center points and the average of the factorial points) in
the design space. There is only a 0.02% chance that a "Curvature F-value" this large
could occur due to noise.

The "Lack of Fit F-value" of 94.11 implies there is a 7.81% chance that a "Lack of Fit F-value" this large could occur due to noise. Lack of fit is bad -- we want the model to fit. This relatively low probability (<10%) is troubling.

Std. Dev.	4.70	R-Squared	0.9735
Mean	50.68	Adj R-Squared	0.9647
C.V. %	9.28	Pred R-Squared	0.9321
PRESS	339.91	Adeq Precision	19.820
-2 Log Likelihood	54.23	BIC	61.14
		AICc	64.23

The "Pred R-Squared" of 0.9321 is in reasonable agreement with the "Adj R-Squared" of 0.9647; i.e. the difference is less than 0.2.
"Adeq Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Your ratio of 19.820 indicates an adequate signal. This model can be used to navigate the design space.

	Coefficient		**Standard**	**95% CI**	**95% CI**	
Factor	**Estimate**	**df**	**Error**	**Low**	**High**	**VIF**
Intercept	44.66	1	1.66	40.60	48.73	
C-Catalyst	24.23	1	1.66	20.17	28.30	1.00
D-Temp	4.64	1	1.66	0.57	8.71	1.00
Ctr Pt 1	30.06	1	3.72			

Final Equation in Terms of Coded Factors:	
Product %	=
+44.66	
+24.23	* C
+4.64	* D

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels of the factors are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

Final Equation in Terms of Actual Factors:	
Product %	=
-21.23251	
+2.42326	* Catalyst
+0.30923	* Temp

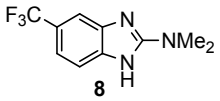
The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.
Proceed to Diagnostic Plots (the next icon in progression). Be sure to look at the:
1) Normal probability plot of the studentized residuals to check for normality of residuals.
2) Studentized residuals versus predicted values to check for constant error.
3) Externally Studentized Residuals to look for outliers, i.e., influential values.
4) Box-Cox plot for power transformations.
If all the model statistics and diagnostic plots are OK, finish up with the Model Graphs icon.

Internal standard calculations for 7 and 8

$$K_x = \frac{\%_{Int.Std.} / \%_{x.}}{Wt_{Int.Std.} / Wt_{x.}}$$

Equation 1: K_x value calculation from stock solutions of known amount of 4,4'-di-tertbutyl-1,1'-biphenyl *and* ***X*** *where X =* ***7*** *or* ***8***

5-Trifluoromethyl-*N,N*-dimethyl-1*H*-benzo[d]imidazol-2-amine (**8**) and 4,4'-di-tertbutyl-1,1'-biphenyl (internal standard) were made up to a 25 mL solution in acetonitrile in a volumetric flask. Kx calculations were performed using equation 1 with HPLC peak area response % (PAR%). Masses were recorded on a 5-figure balance.

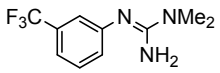


8

Int. Std. / mg	**8** / mg	Acetonitrile / mL	**8** PAR%	Int. Std. PAR%	*Kx*	
28.5	26.7	25	79.368	20.632	0.243	
28.5	26.7	25	79.241	20.759	0.245	
27.6	26.7	25	79.761	20.339	0.244	
27.6	25.7	25	79.700	20.300	0.244	
				Kx average:		**0.244**

Table 2: ***8*** *Kx calculations. Masses were recorded on a 5-figure balance.*

1,1-Dimethyl-2-(3-(trifluoromethyl)phenyl)guanidine (**7**) and 4,4'-di-tertbutyl-1,1'-biphenyl (internal standard) were made up to a 25 mL solution in acetonitrile in a volumetric flask. Kx calculations were performed using equation 1 with HPLC peak area response % (PAR%). Masses were recorded on a 5-figure balance.



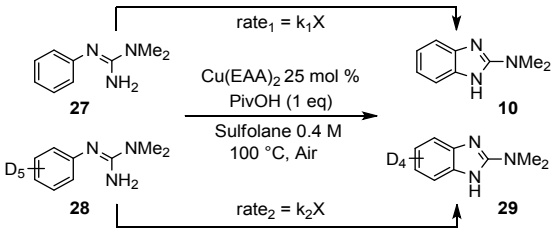
7

Int. Std. / mg	**7** / mg	Acetonitrile / mL	**7** PAR%	Int. Std. PAR%	Kx	
8.9	18.9	25	66.913	33.087	1.050	
8.9	18.9	25	66.892	33.108	1.051	
8.6	27	25	74.791	25.209	1.058	
8.6	27	25	74.865	25.135	1.054	
8.5	23.4	25	72.59	27.41	1.040	
8.5	23.4	25	72.561	27.439	1.041	
8.2	22.8	25	72.398	27.602	1.060	
8.2	22.8	25	72.48	27.52	1.056	
				Kx average*:*		**1.051**

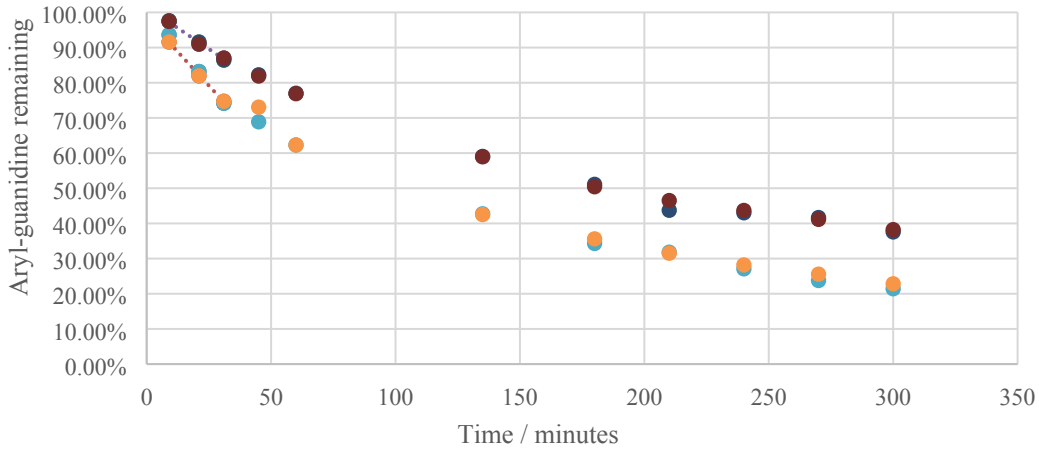
Table 3: ***7*** *Kx calculations. Masses were recorded on a 5-figure balance.*

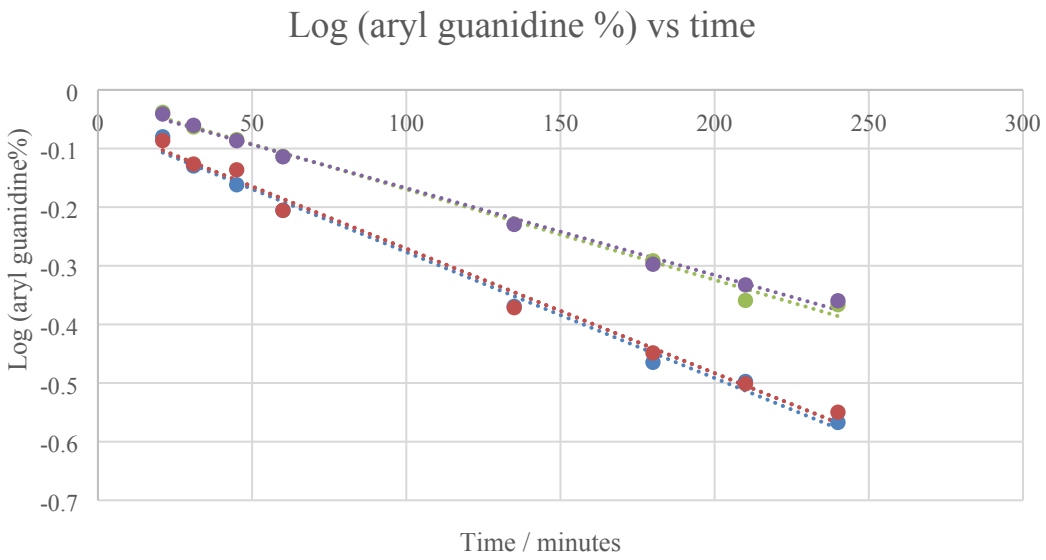
Kinetic isotope effect

Kx calculations were performed with substrates **27** and **28** as described previously. Through use of an internal standard (4,4'-di-*tert*-butylbiphenyl) the rate of consumption of aryl-guanidine was monitored by HPLC analysis. Taking a log-plot of aryl-guanidine *vs.* time and taking a ratio of the gradients from the resultant straight line plot the K.I.E was calculated. 0.0021 / 0.0015 = 1.4. This result comes from an n = 2.



Plot in

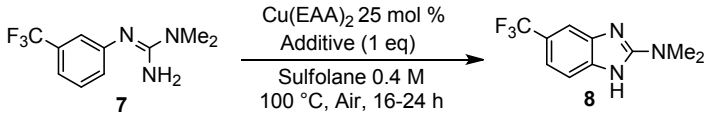




orange/baby blue is consumption of **27**, plot in red/dark blue is consumption of **28**

Different additives experimental procedure

The table below summarises the solution yield of **8** using the internal standard 4,4'-di-tertbutyl-1,1'-biphenyl. Reactions at short time points remained unchanged after 16 hours/960 mins.

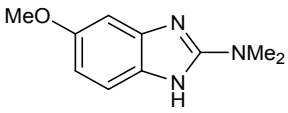


Additive	Time / minutes	Product (**8**) / %	Additive	Time / minutes	Product (**8**) / %
Pivalic acid	1440	54	Acetic acid	960	41
Adamantane carboxylic acid	1440	45	Trifluoroacetic acid	960	< 1
Benzoic acid	960	21	Methane sulfonic acid	960	0[a]
Trimethylbenzoic acid	960	37	p-Toluenesulfonic acid	960	0[a]
2,4,6-triethylbenzoic acid	960	44	Phenylphosphonic acid	960	*
2,4,6-tri-*tert*-butylbenzoic acid	960	53	Oxalic acid	240	0
p-methoxybenzoic acid	960	41	Oxamic acid	240	*
p-nitrobenzoic acid	960	23	Citric acid	240	0
3,4,5-trifluorobenzoic acid	960	16	2-hydroxypropanoic acid	960	9
3,4,5-trimethoxybenzoic acid	960	42	Ethyl acetoacetate	240	3
Triphenylacetic acid	240	3	Cyanamide	960	< 1
Alanine	150	0	Phenol	960	6
2-aminoisobutyric acid	150	0	2-hydroxypyridine	960	14

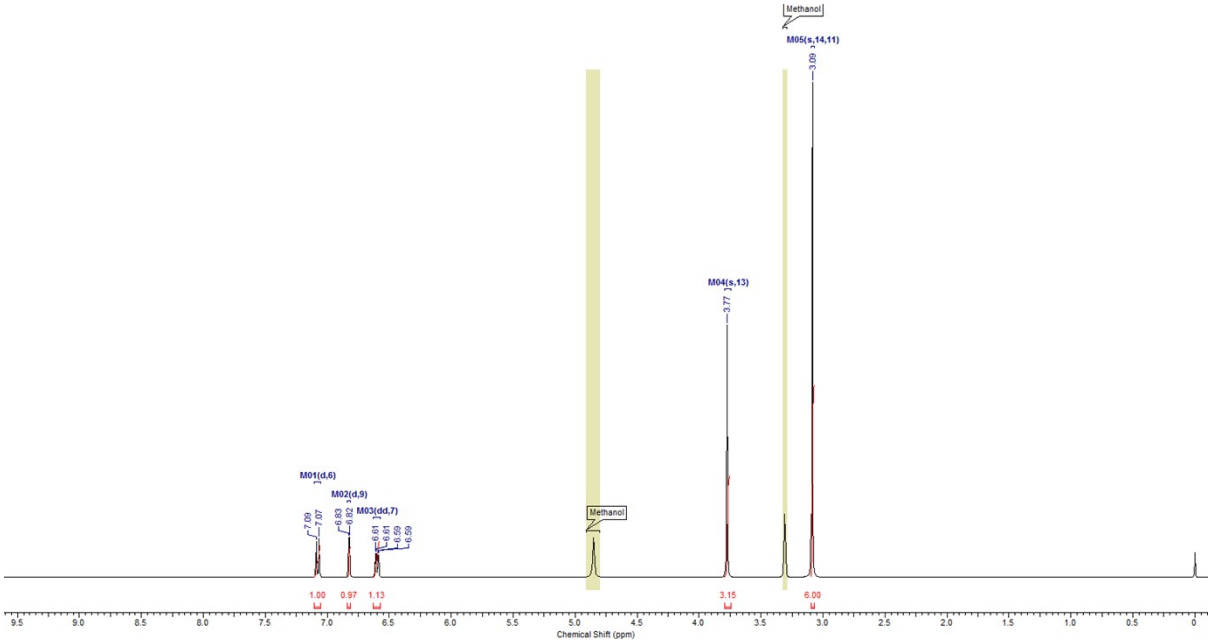
2-phenylbenzoic acid	960	40	Benzamidine	960	12
2-hydroxybenzoic acid	960	4	Benzamidine.HCl	960	1
3-hydroxypyridine	960	0			

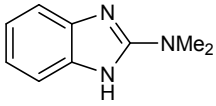
*[a]no conversion of starting material. *reaction heterogenous and sampling not accurate.*

1H NMR spectra of known compounds

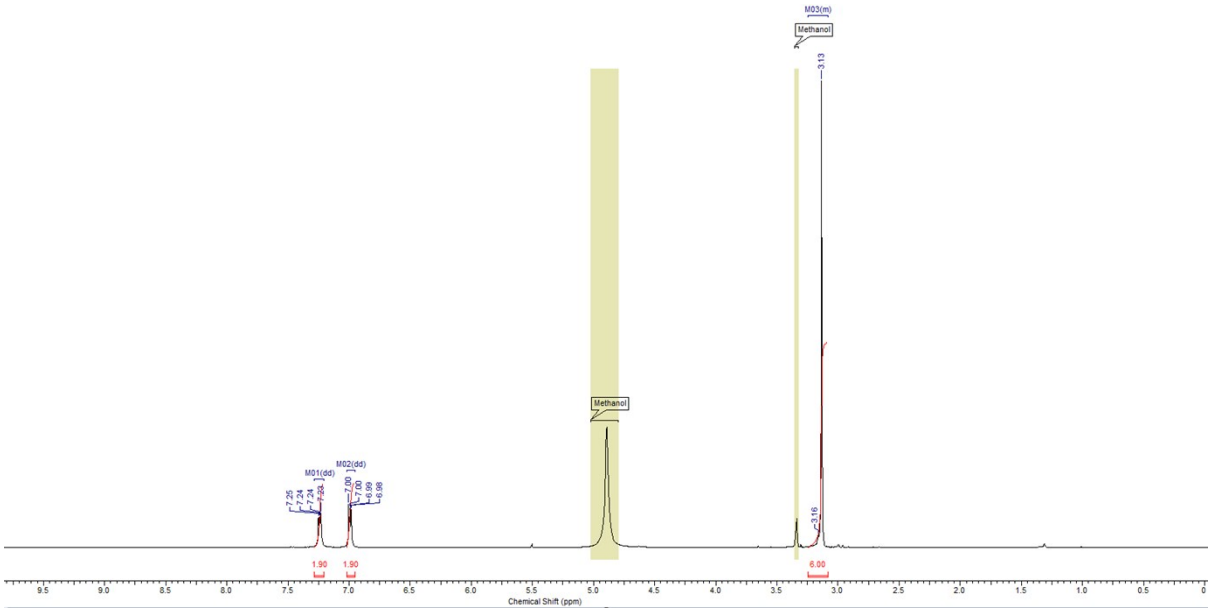


*5-Methoxy-N,N-dimethyl-1H-benzo[d]imidazol-2-amine (**5**)*

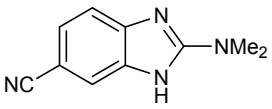


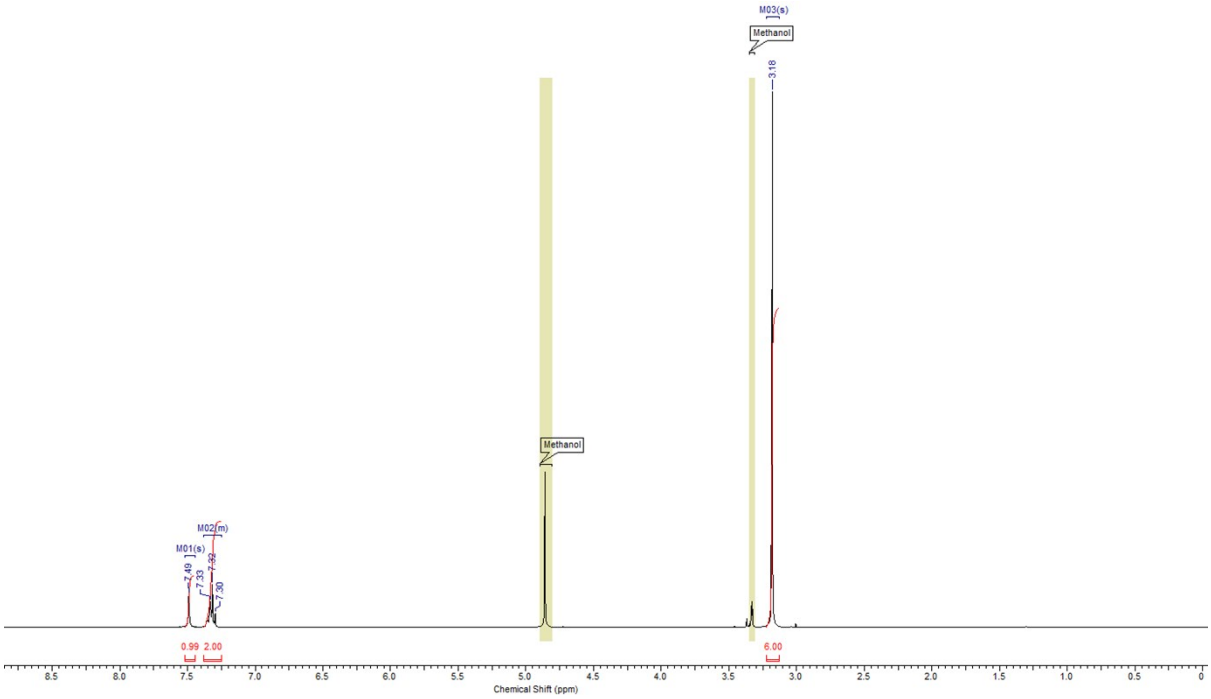


*N,N-dimethyl-1H-benzo[d]imidazol-2-amine(**10**)*

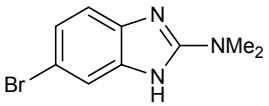


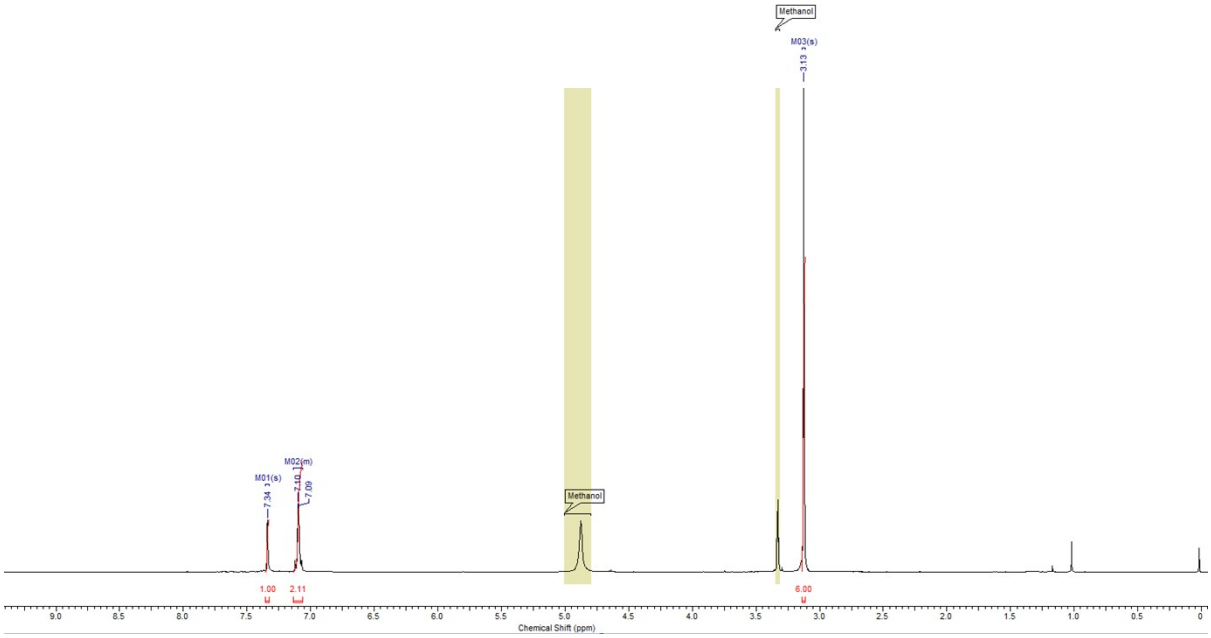
*2-(Dimethylamino)-1H-benzo[d]imidazole-6-carbonitrile (**13**)*



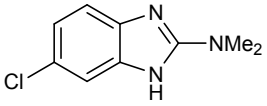


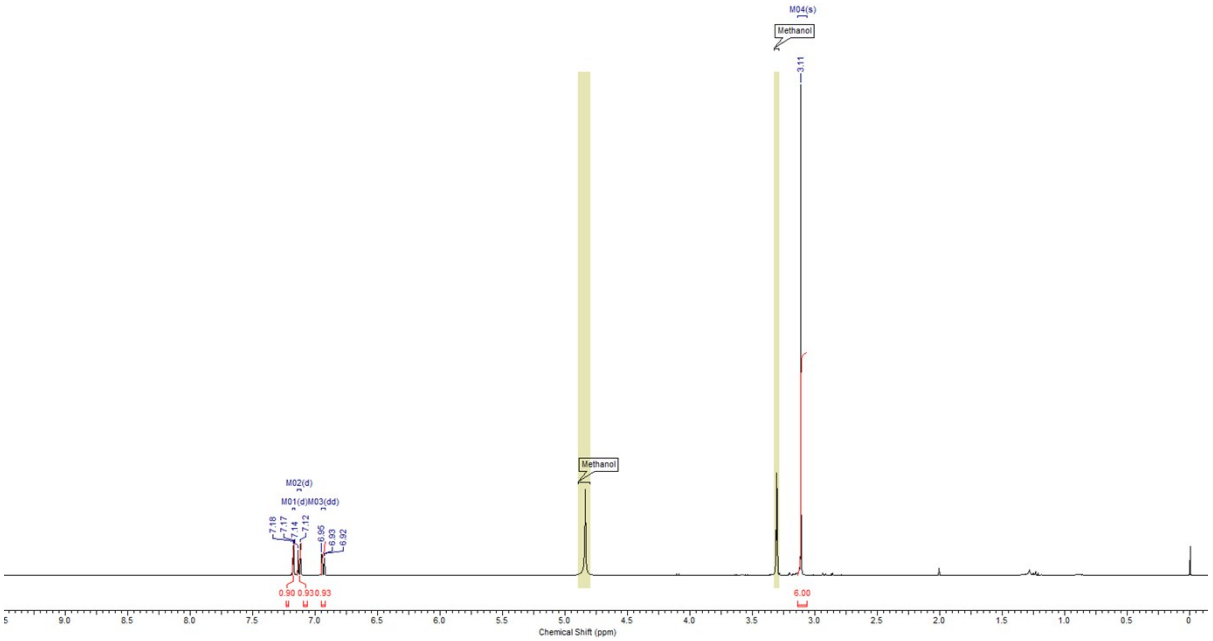
*5-Bromo-N,N-dimethyl-1H-benzo[d]imidazol-2-amine (**14**)*



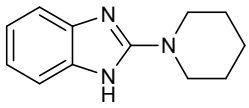


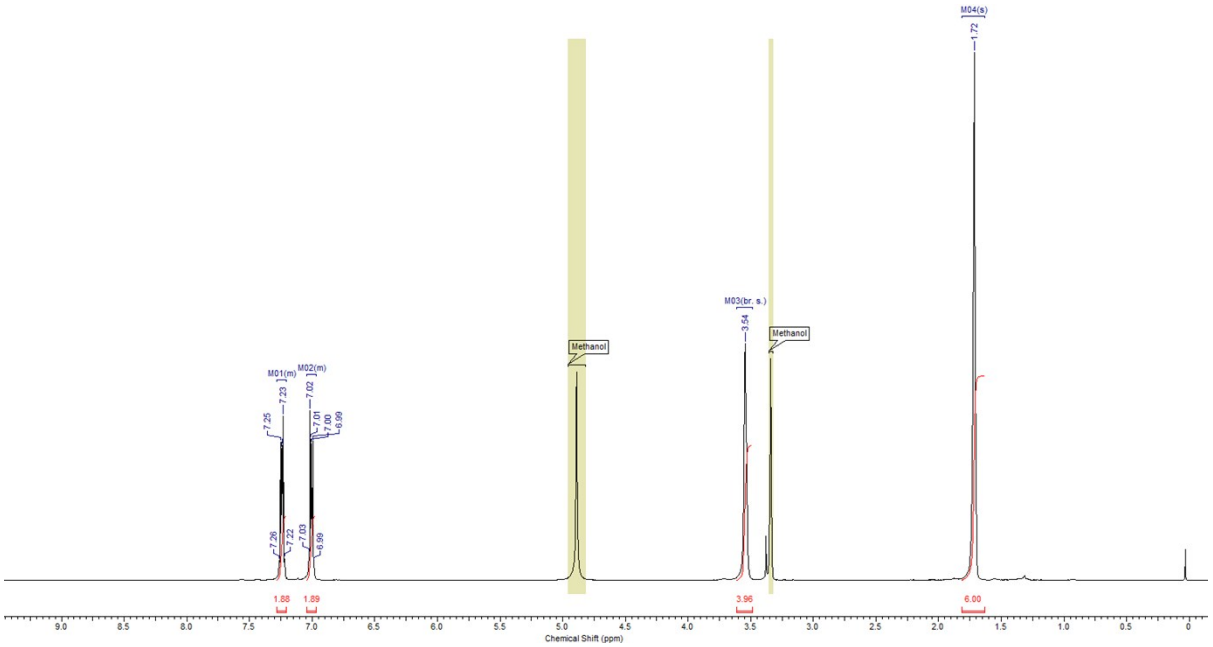
5-chloro-*N,N*-dimethyl-1*H*-benzo[*d*]imidazol-2-amine (**15**)

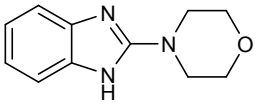




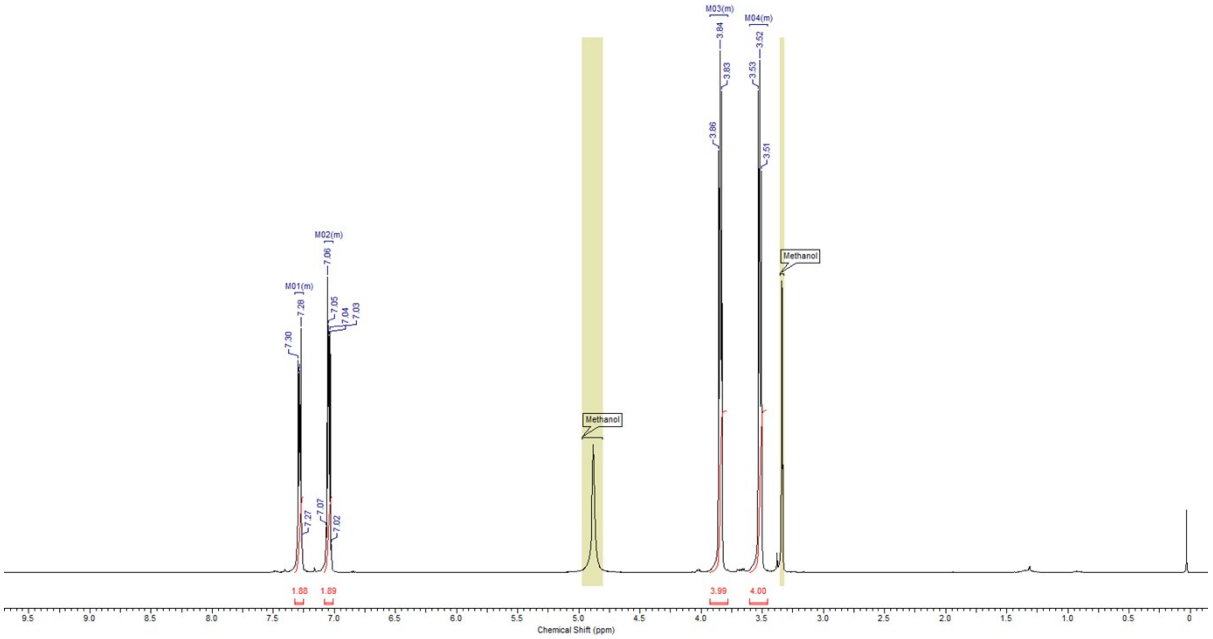
2-(Piperidin-1-yl)-1H-benzo[d]imidazole (***23***)

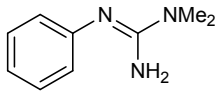




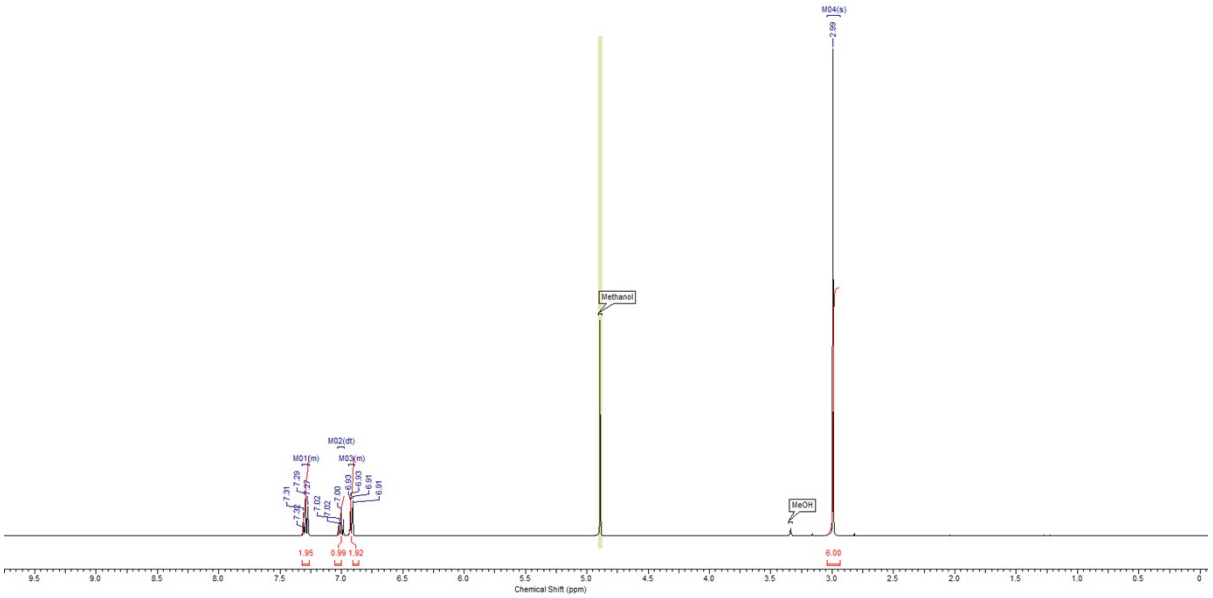


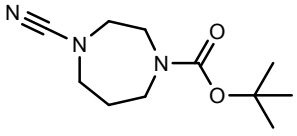
4-(1*H*-Benzo[*d*]imidazol-2-yl)morpholine (**24**)



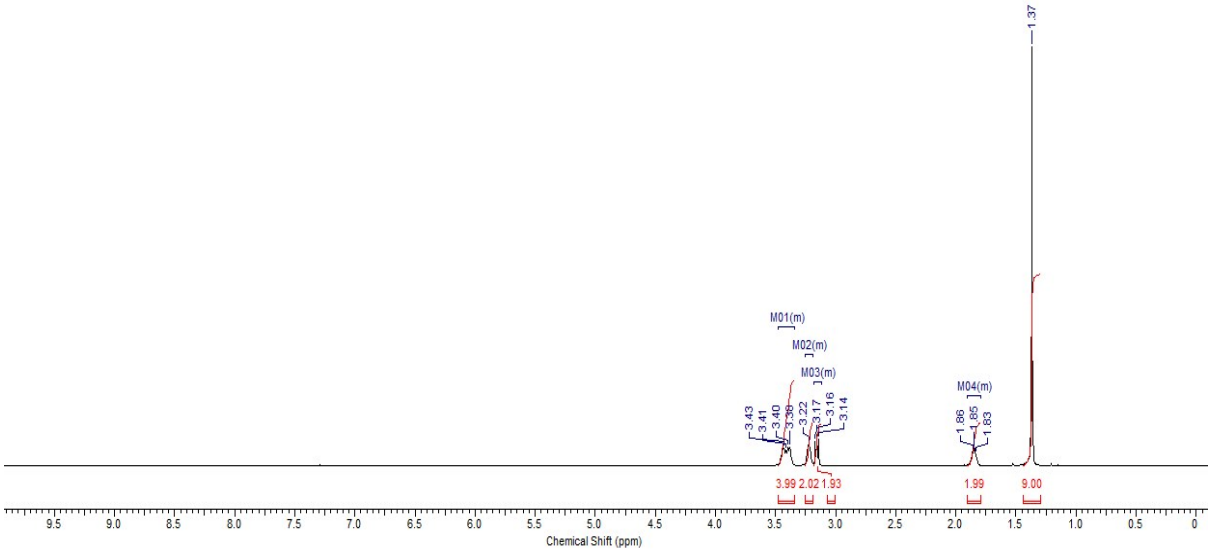


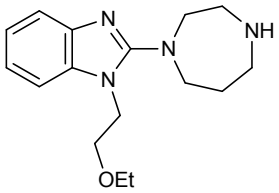
*1,1-Dimethyl-2-phenylguanidine (**27**)*



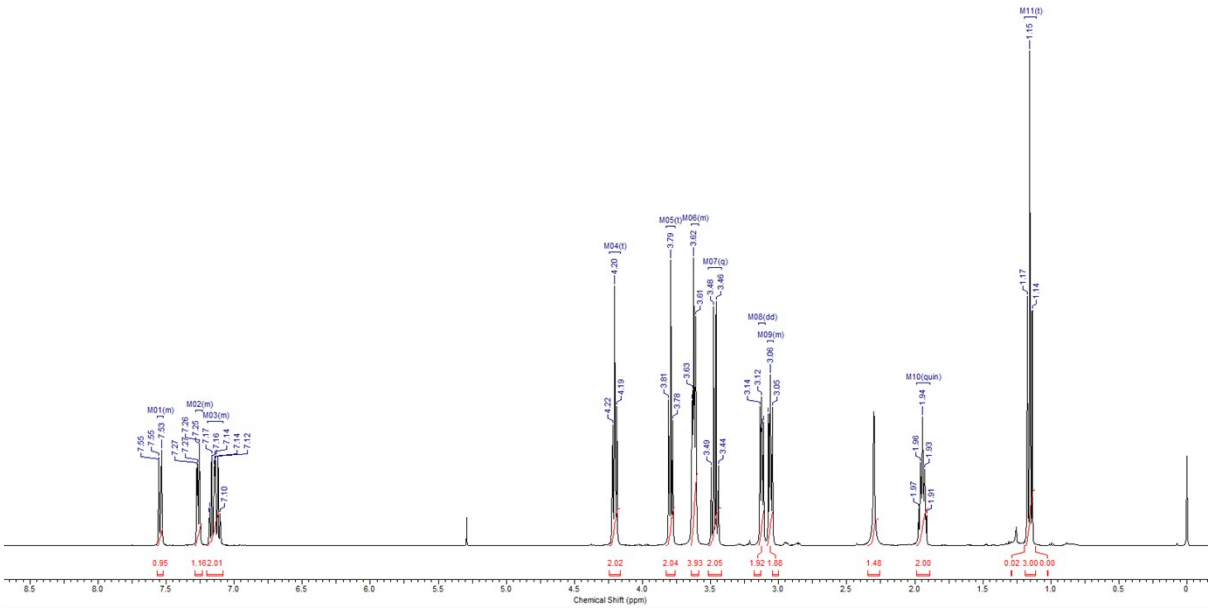


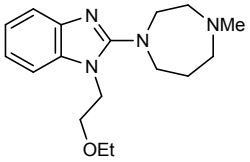
4-cyano-1,4-diazepane-1-carboxylate **(45)**



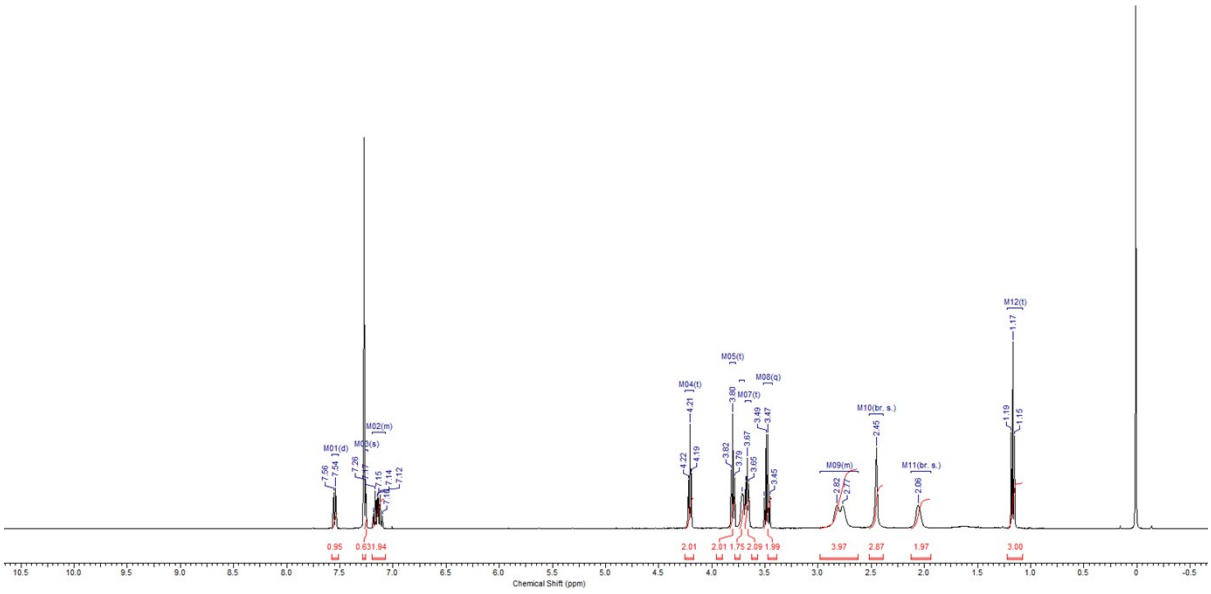


2-(1,4-Diazepan-1-yl)-1-(2-ethoxyethyl)-1H-benzo[*d*]imidazole (**50**)



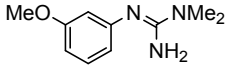


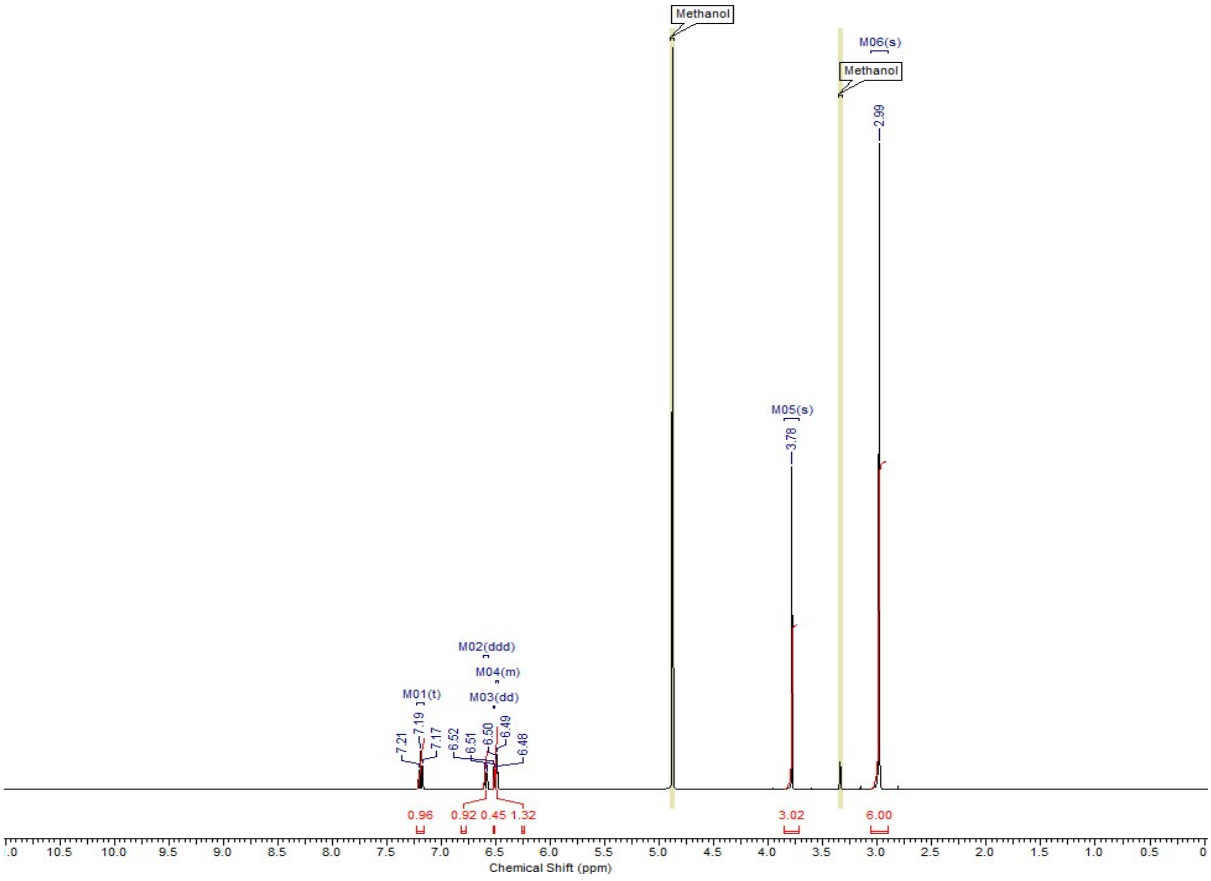
2-(4-Methyl-1,4-diazepan-1-yl)-1-(2-ethoxyethyl)-1H-benzo[d]imidazole, Emedastine (2).

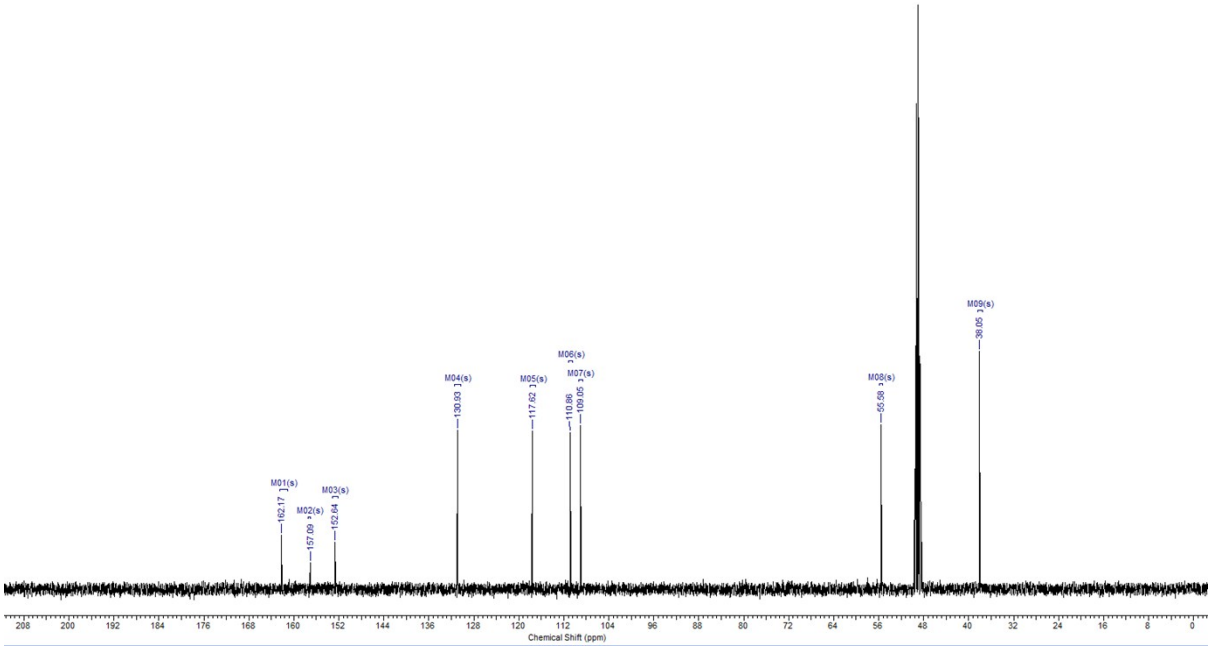


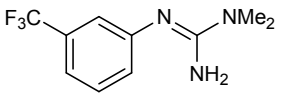
NMR Spectra of novel compounds

*2-(3-Methoxyphenyl)-1,1-dimethylguanidine (**4**).*

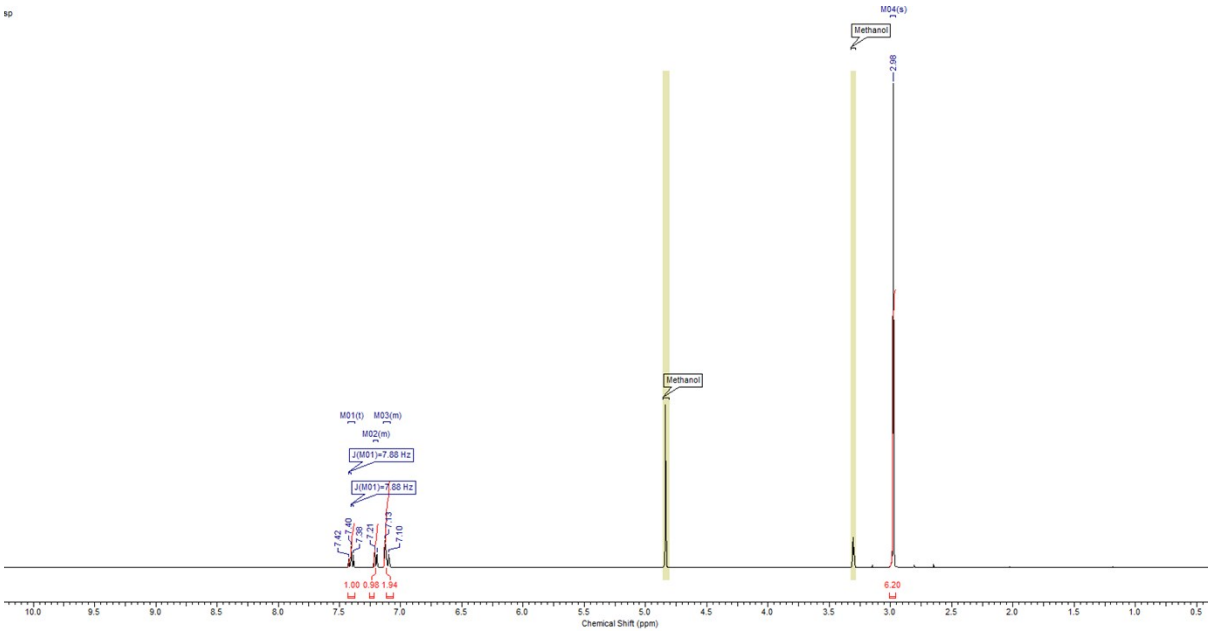


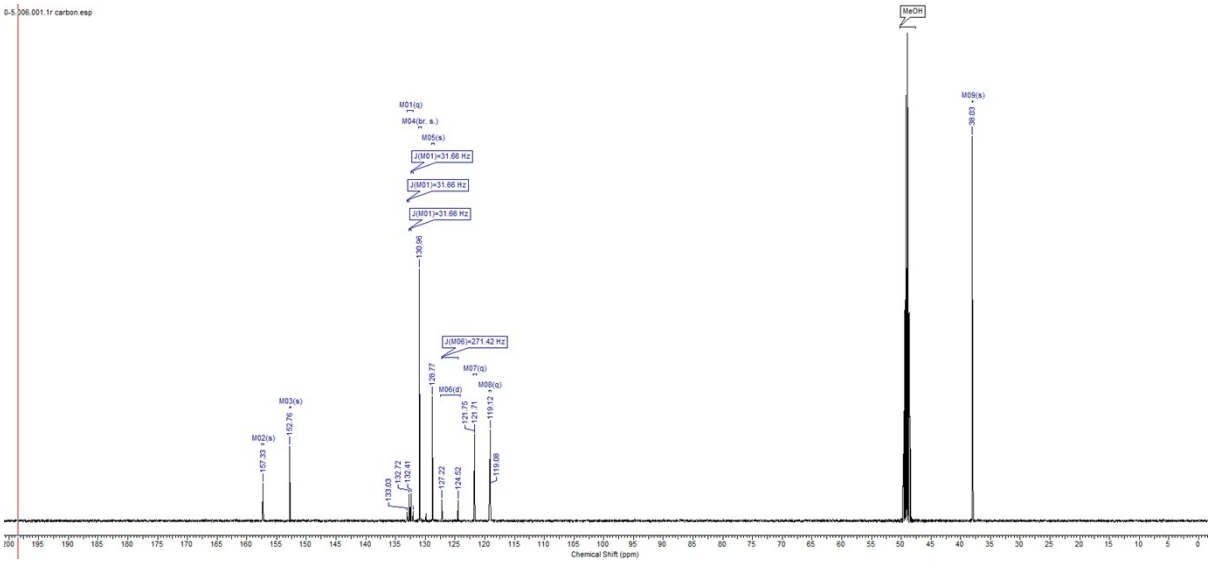


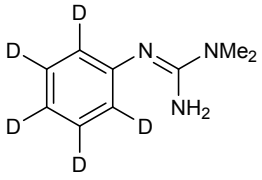




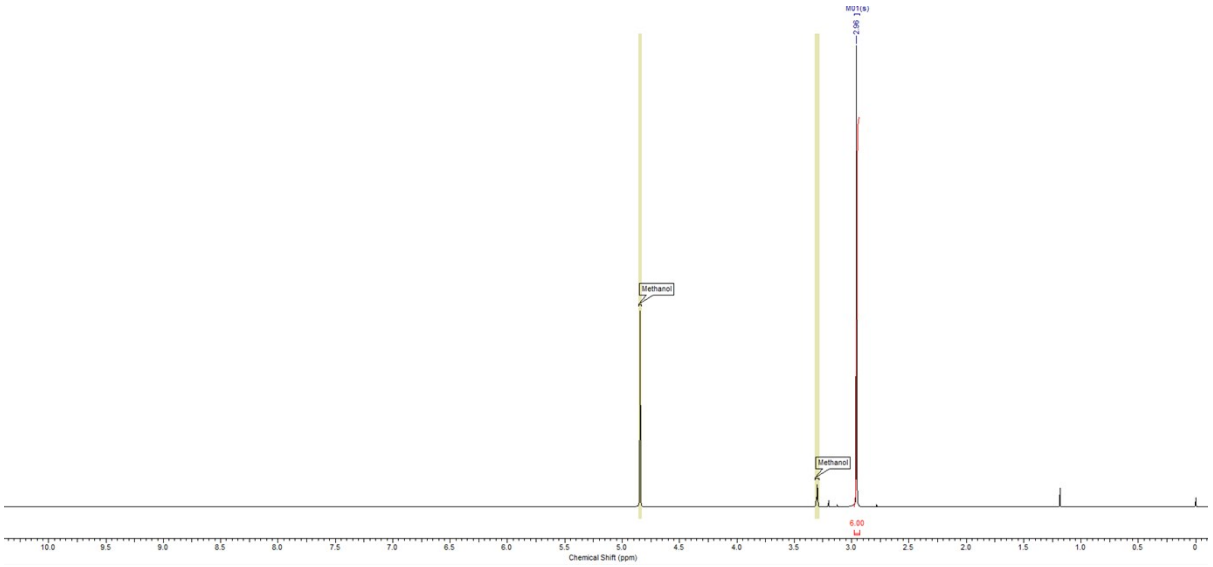
*1,1-Dimethyl-2-(3-(trifluoromethyl)phenyl)guanidine (**7**)*

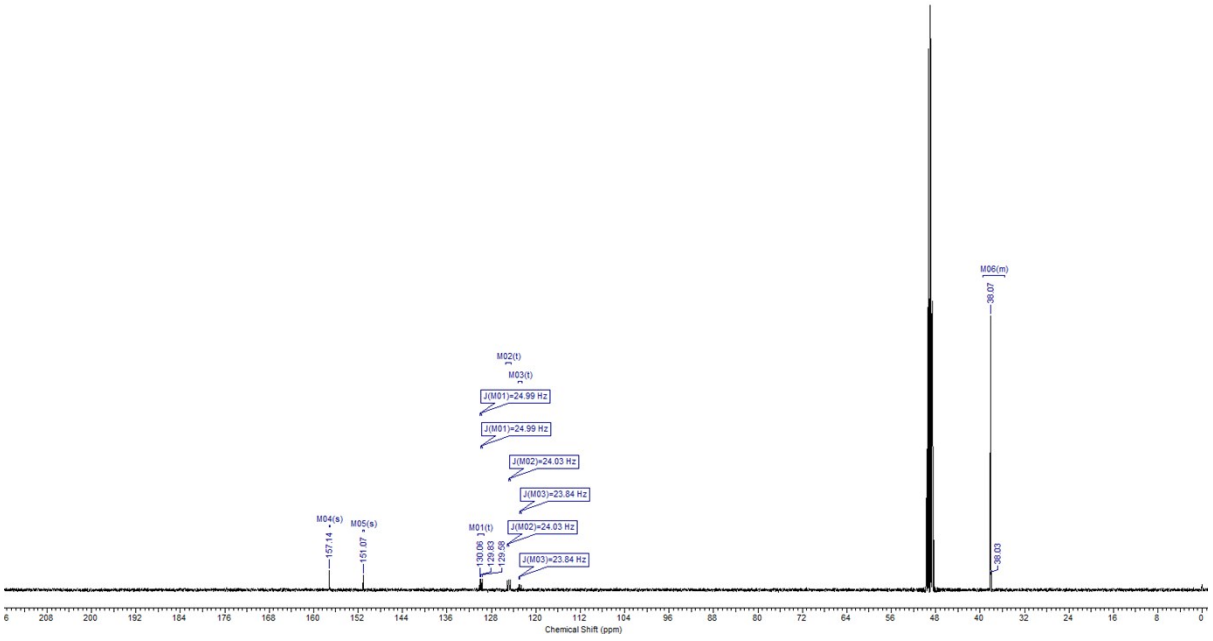

sp
M04(s)
Methanol
2.98
Methanol
M01(t) M03(m)
M02(m)
J(M01)=7.88 Hz
J(M01)=7.88 Hz
7.42
7.40
7.39
7.21
7.13
7.10
1.00 0.98 1.94
6.20
Chemical Shift (ppm)


0-5-206.001.1r carbon.esp
MeOH
M09(s)
49.83
M01(q)
M04(br. s.)
M05(s)
J(M01)=31.66 Hz
J(M01)=31.66 Hz
J(M01)=31.66 Hz
130.96
J(M06)=271.42 Hz
128.77
M07(q)
M06(d)
M08(q)
121.75
121.71
119.12
119.08
157.33
M02(s)
152.76
M03(s)
133.03
132.72
132.41
127.22
124.62
Chemical Shift (ppm)

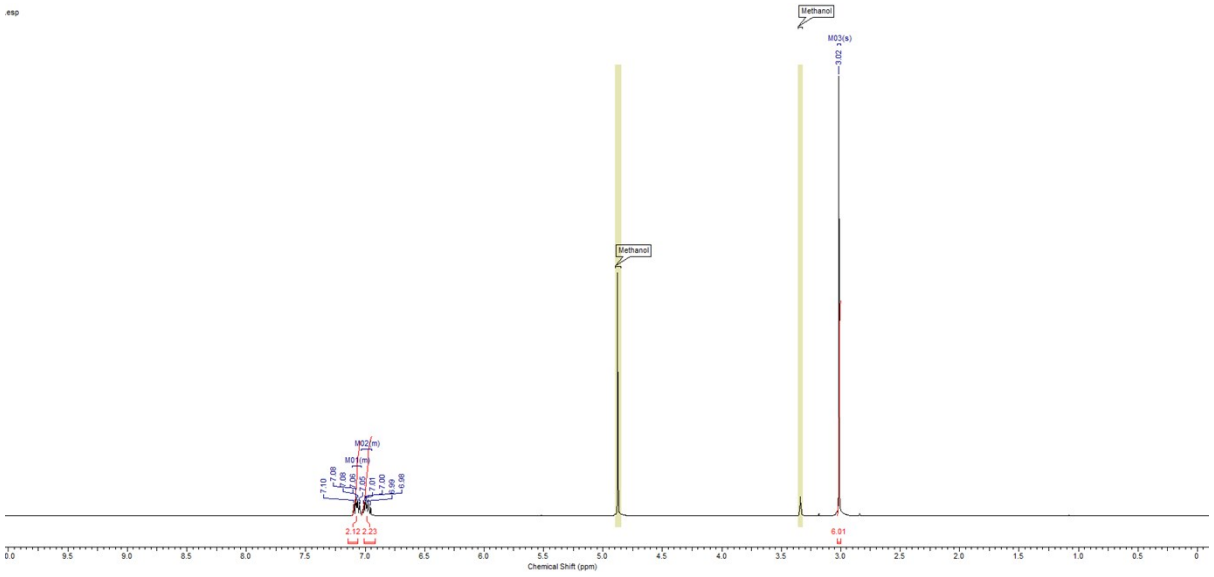


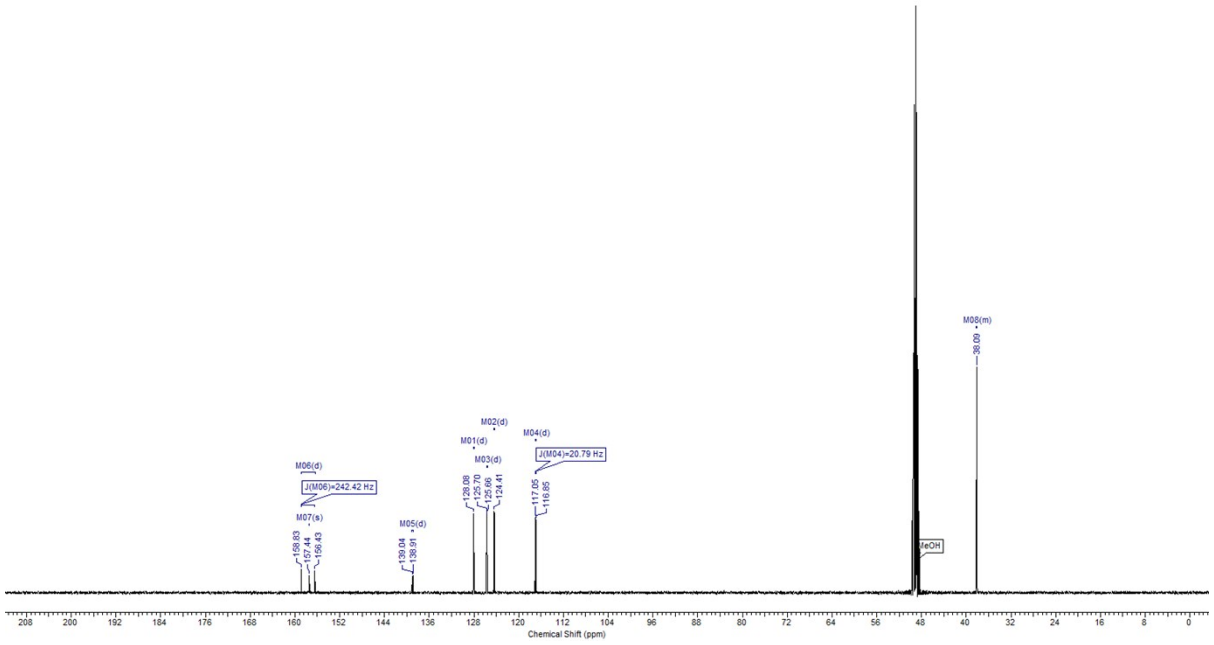
*1-Dimethyl-2-phenyl(D_5)guanidine (**28**)*



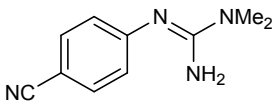


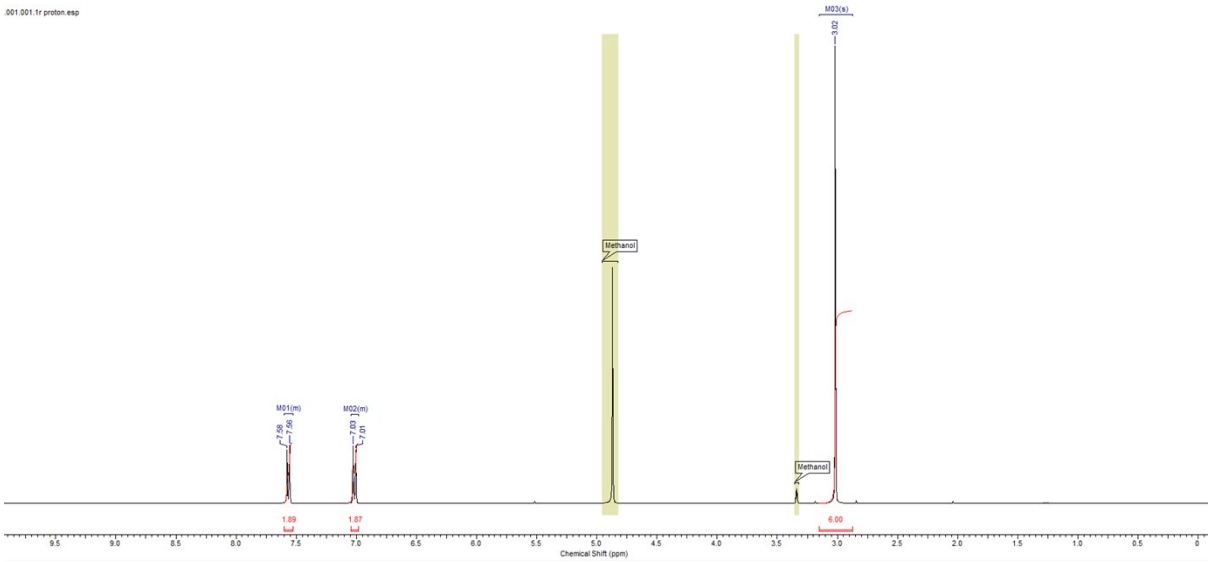
*2-(2-Fluorophenyl)-1,1-dimethylguanidine (**51**).*

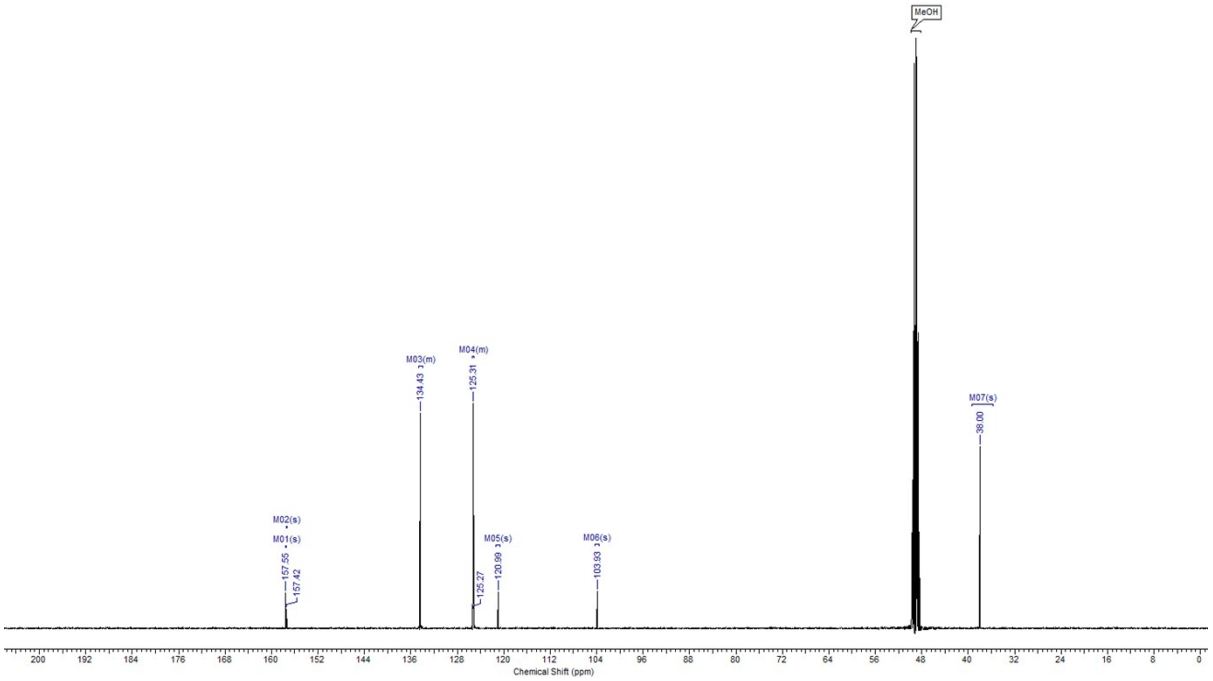


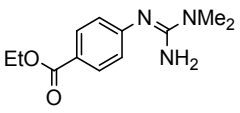


*2-(4-Cyanophenyl)-1,1-dimethylguanidine (**53**)*

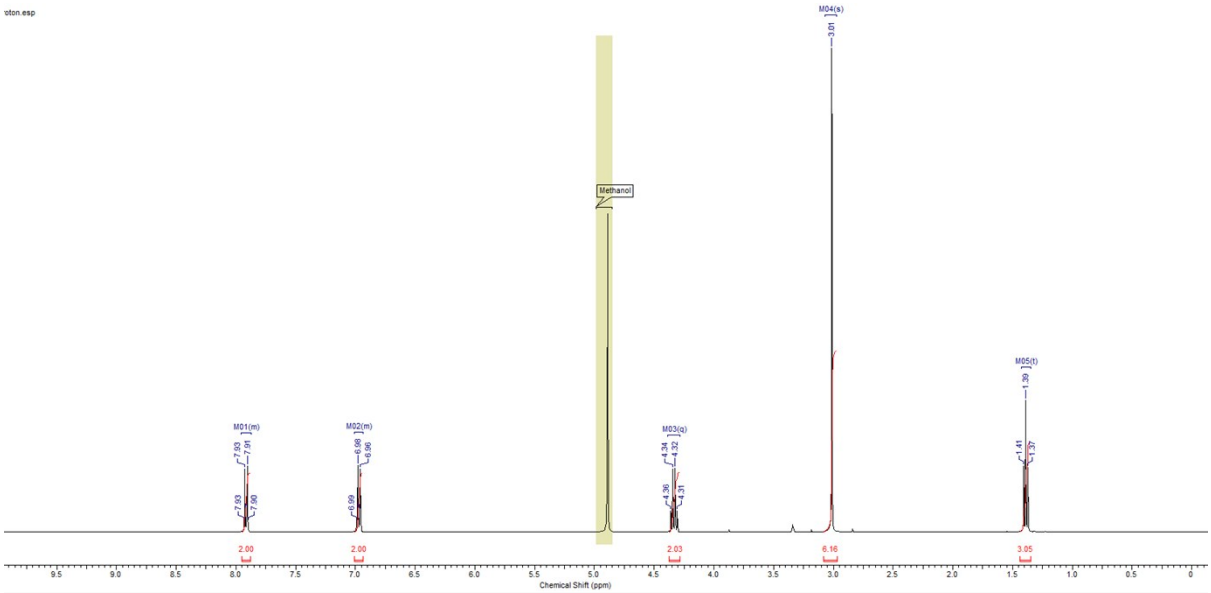


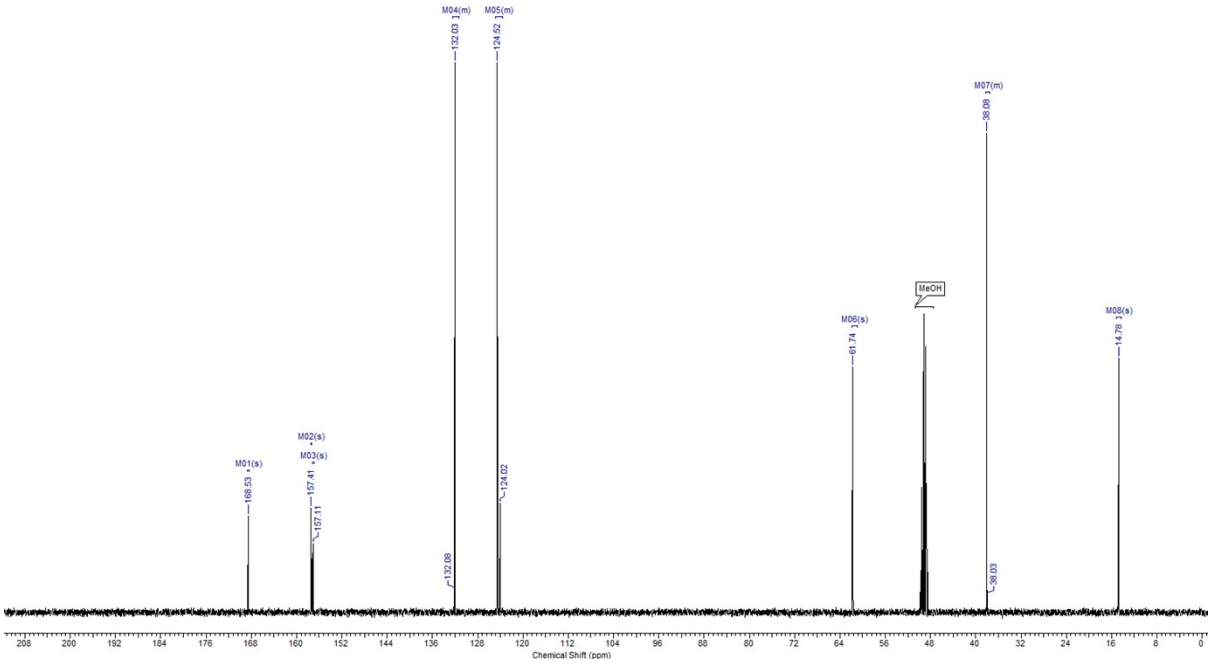


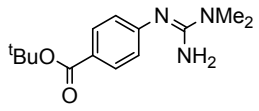




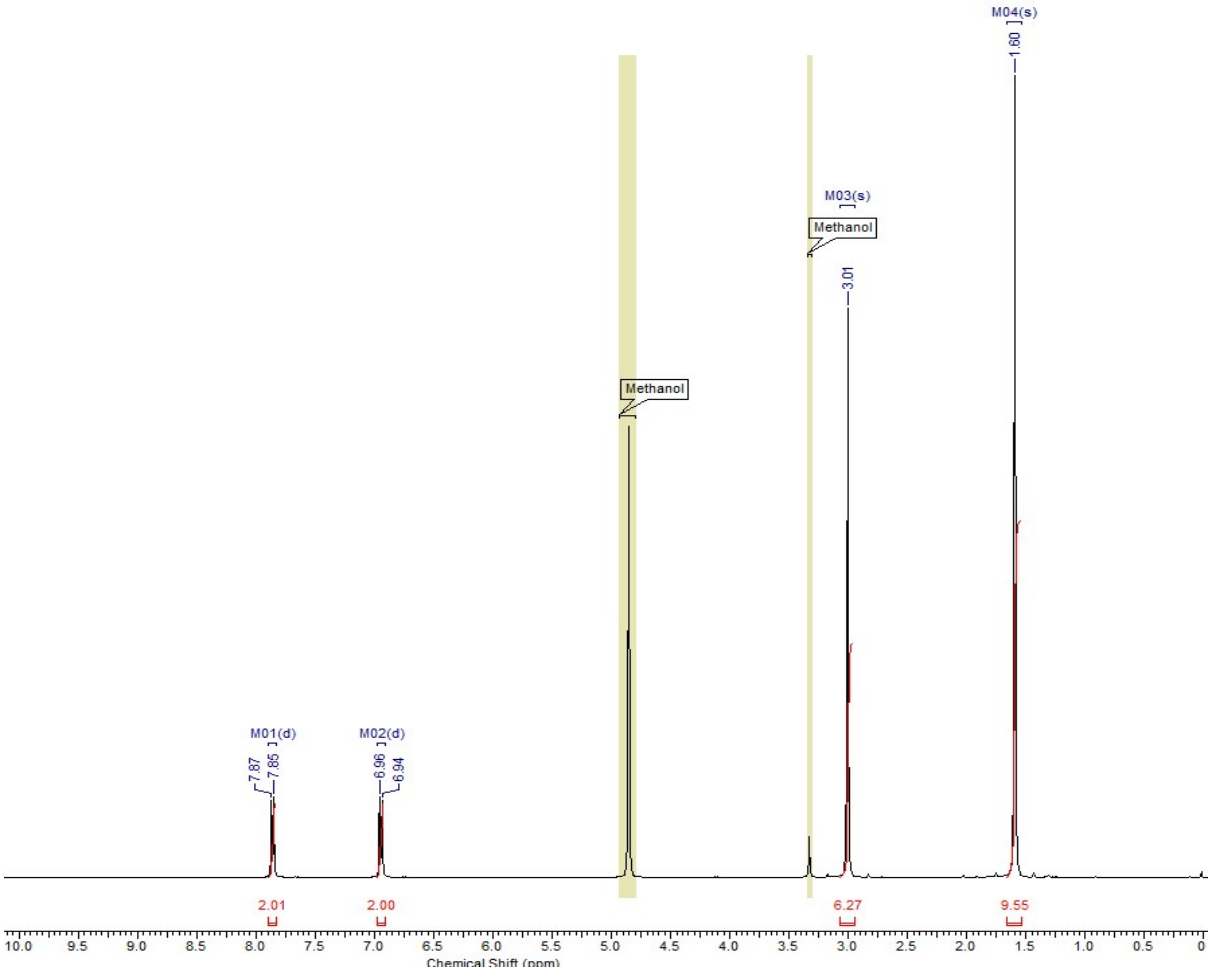
*Ethyl 4-((amino(dimethylamino)methylene)amino) benzoate (**52**)*

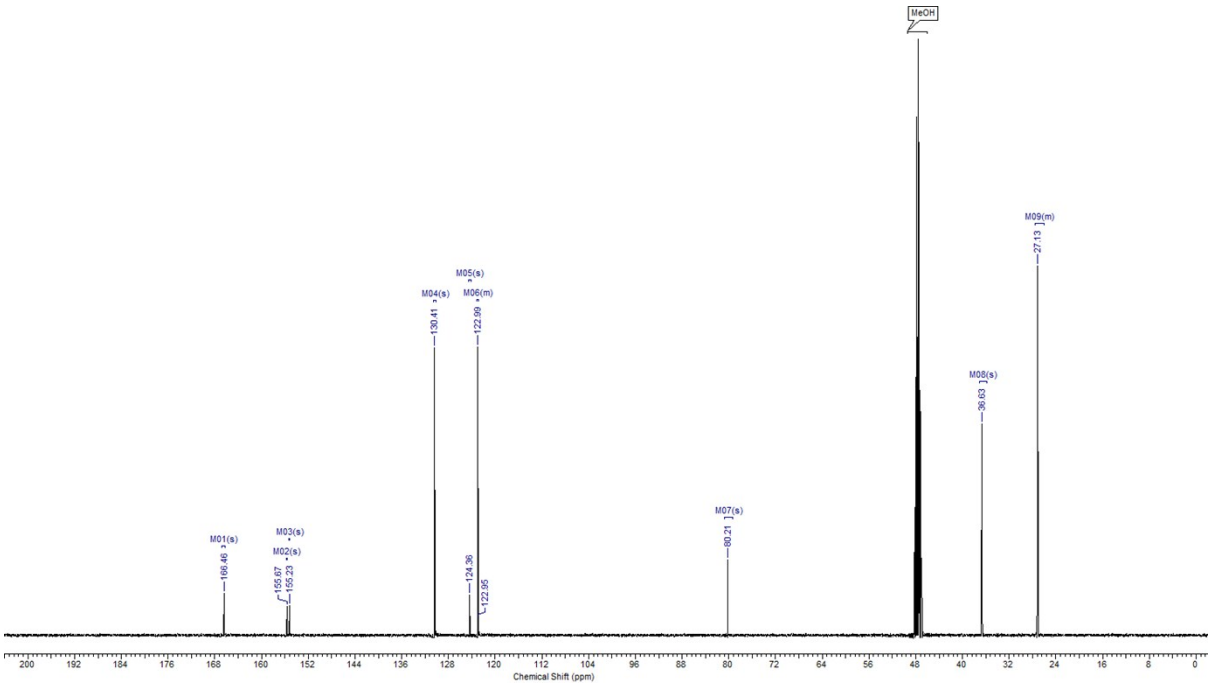




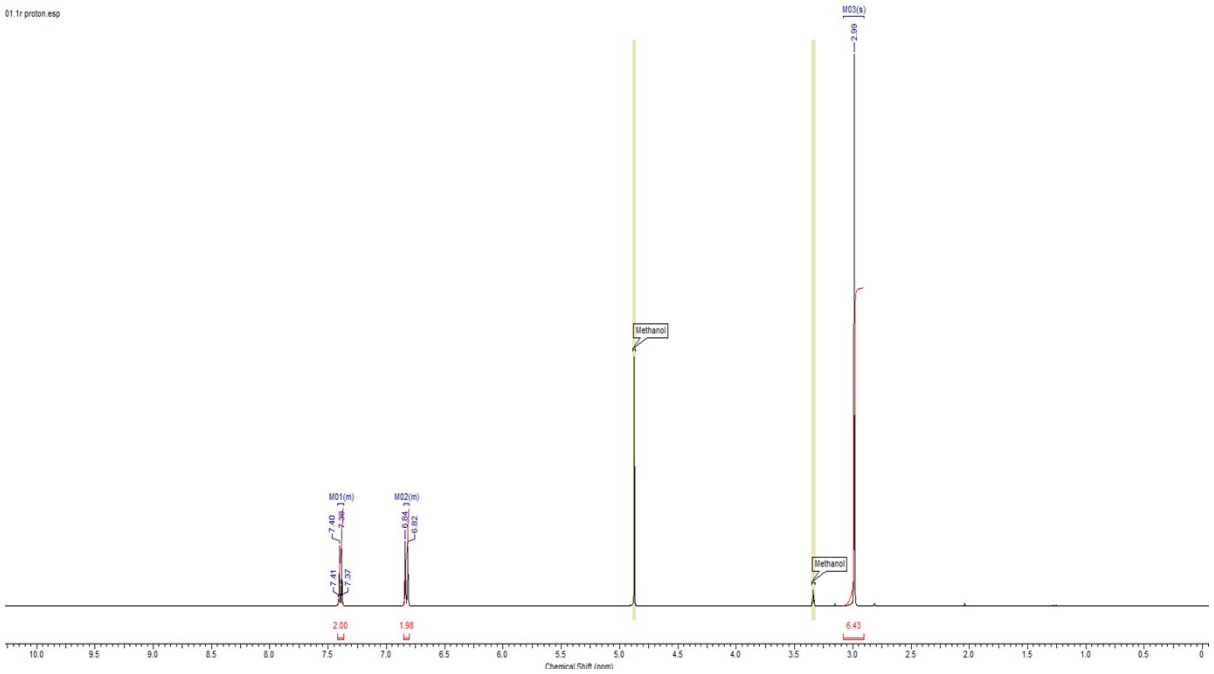


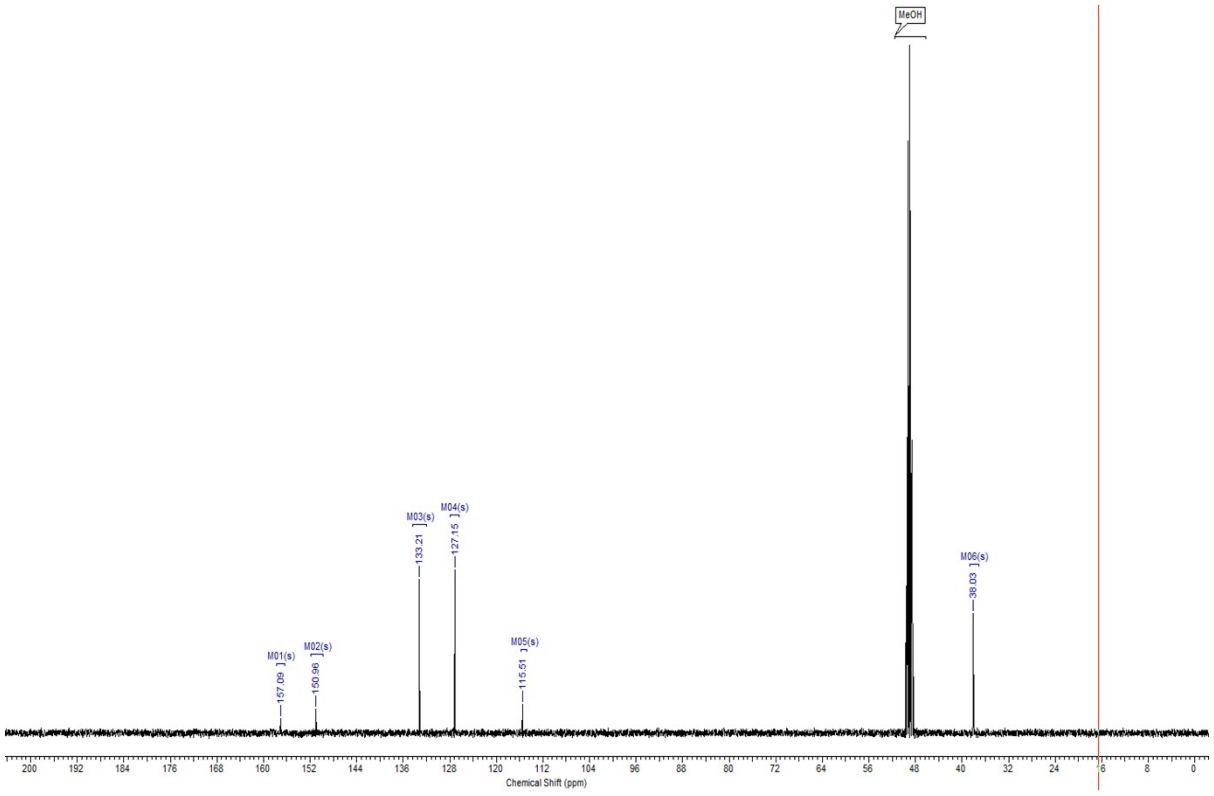
*Tert-butyl 3-((amino(dimethylamino)methylene) amino)benzoate (**54**)*

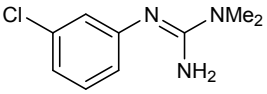




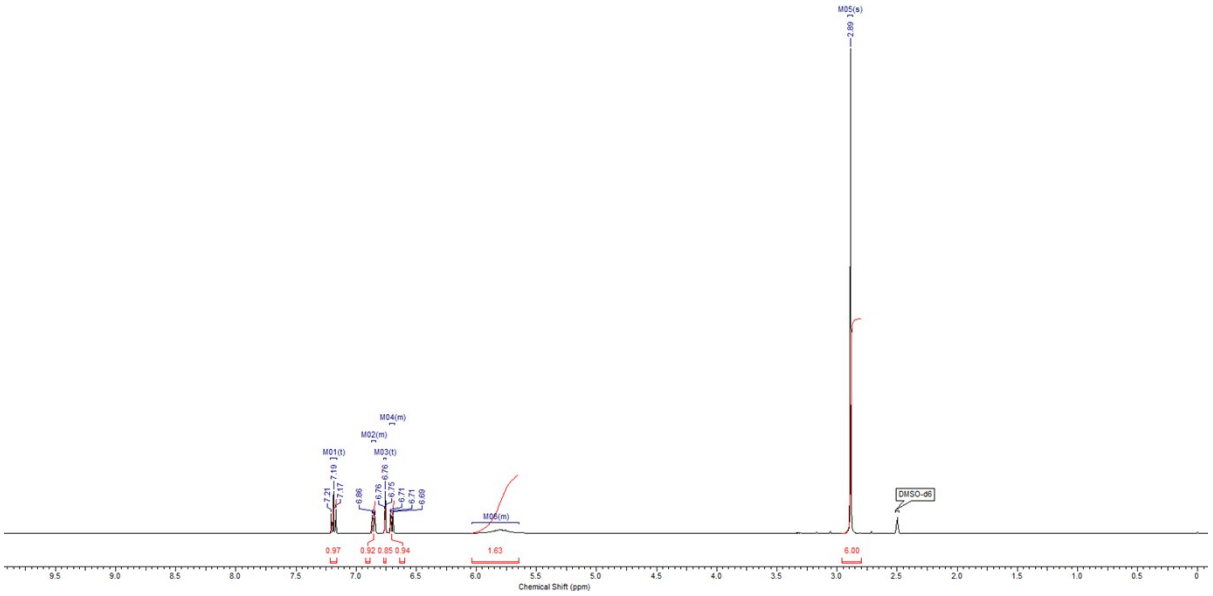
*2-(4-Bromophenyl)-1,1-dimethylguanidine (**55**)*

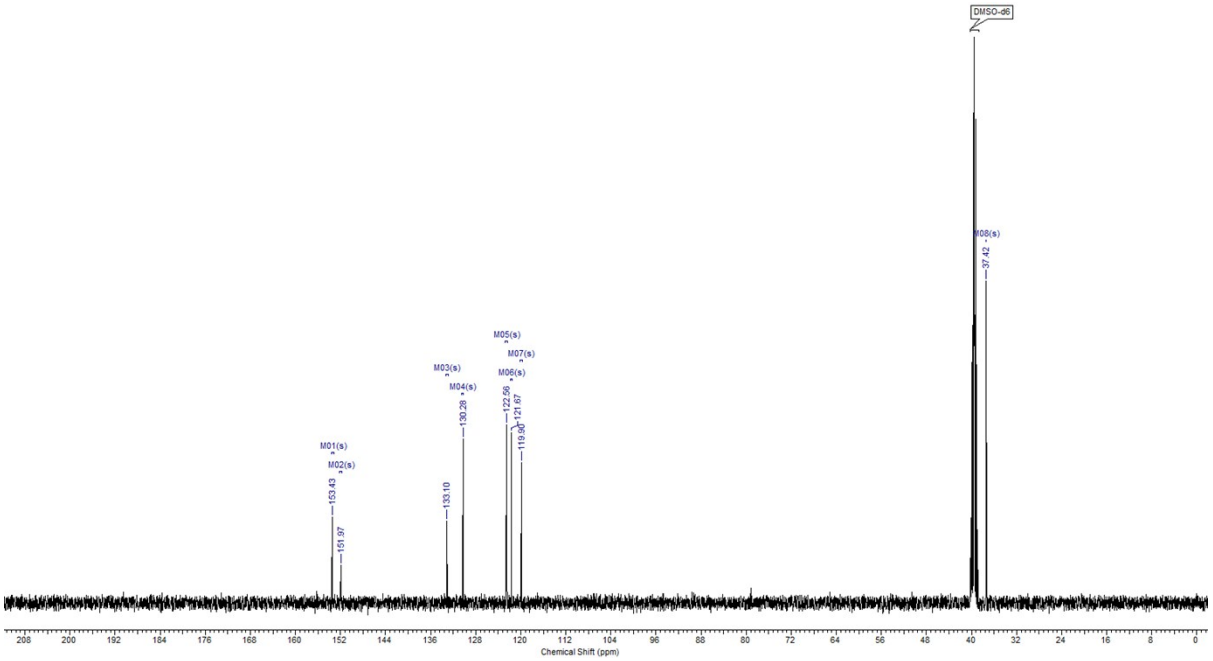


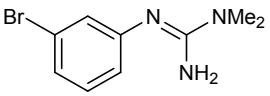




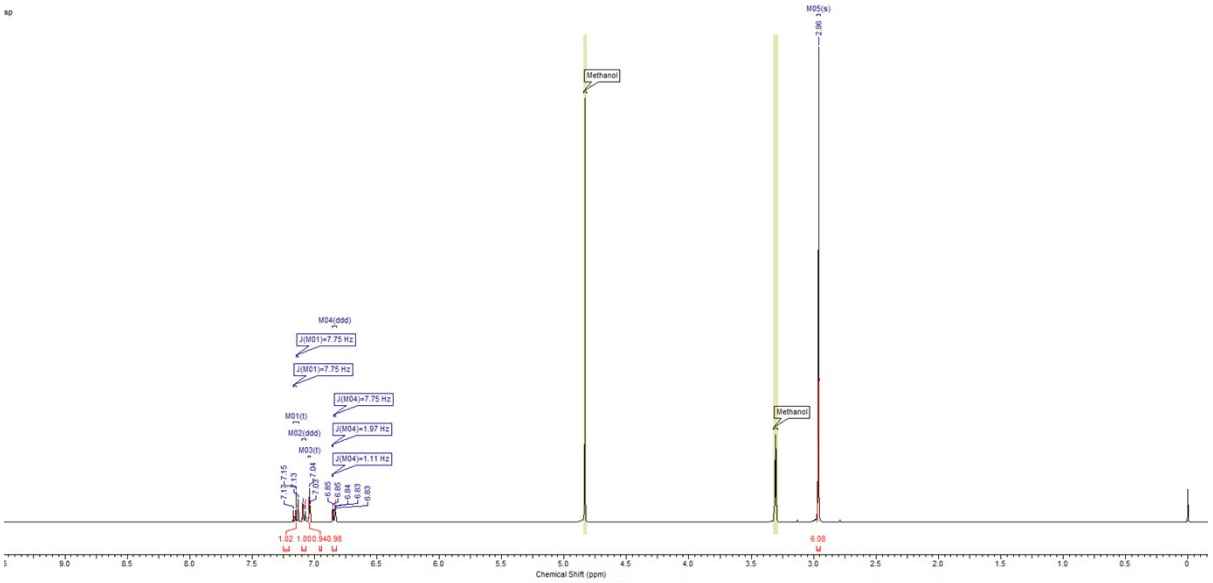
*3-(3-Chlorophenyl)-1,1-dimethylguanidine (**56**)*

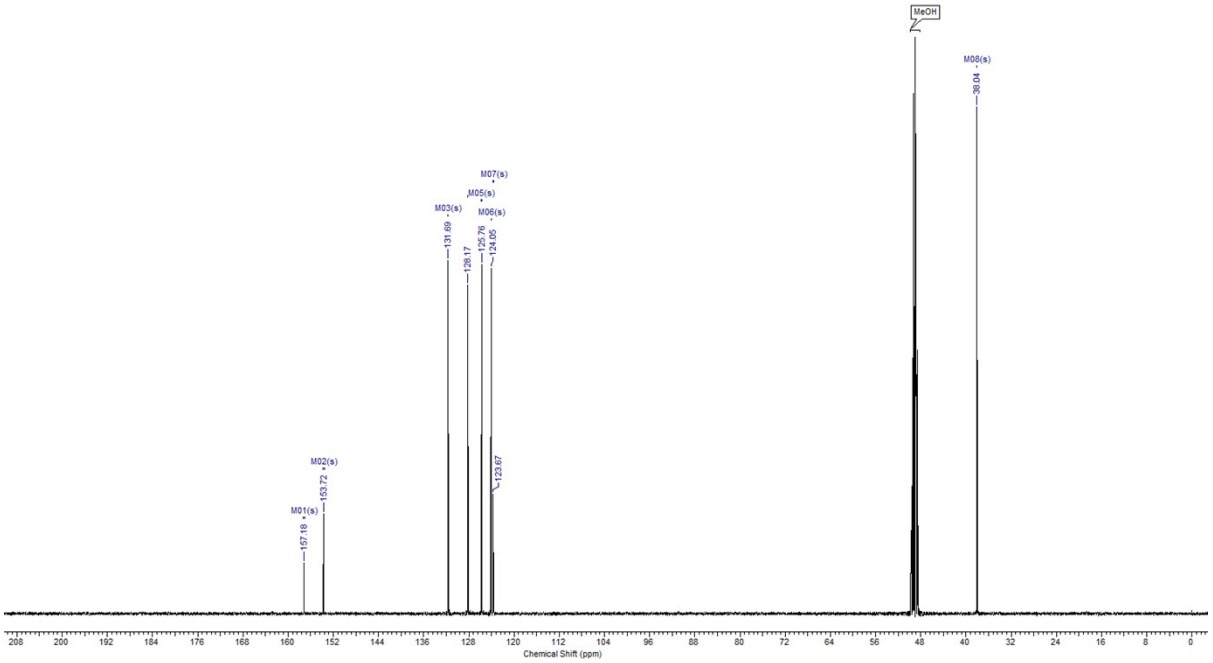




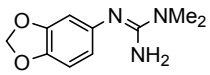


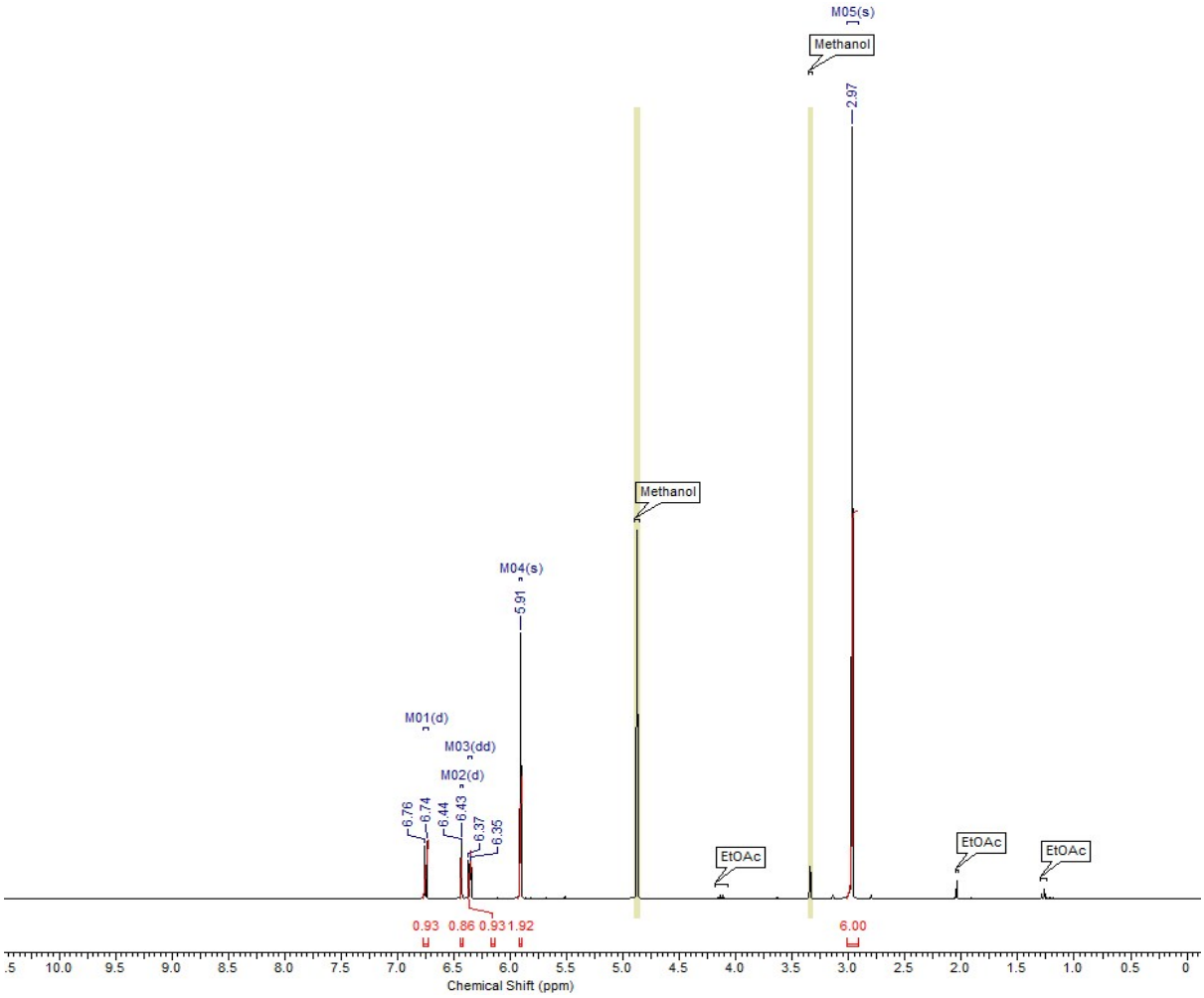
*3-(3-Bromophenyl)-1,1-dimethylguanidine (**57**)*

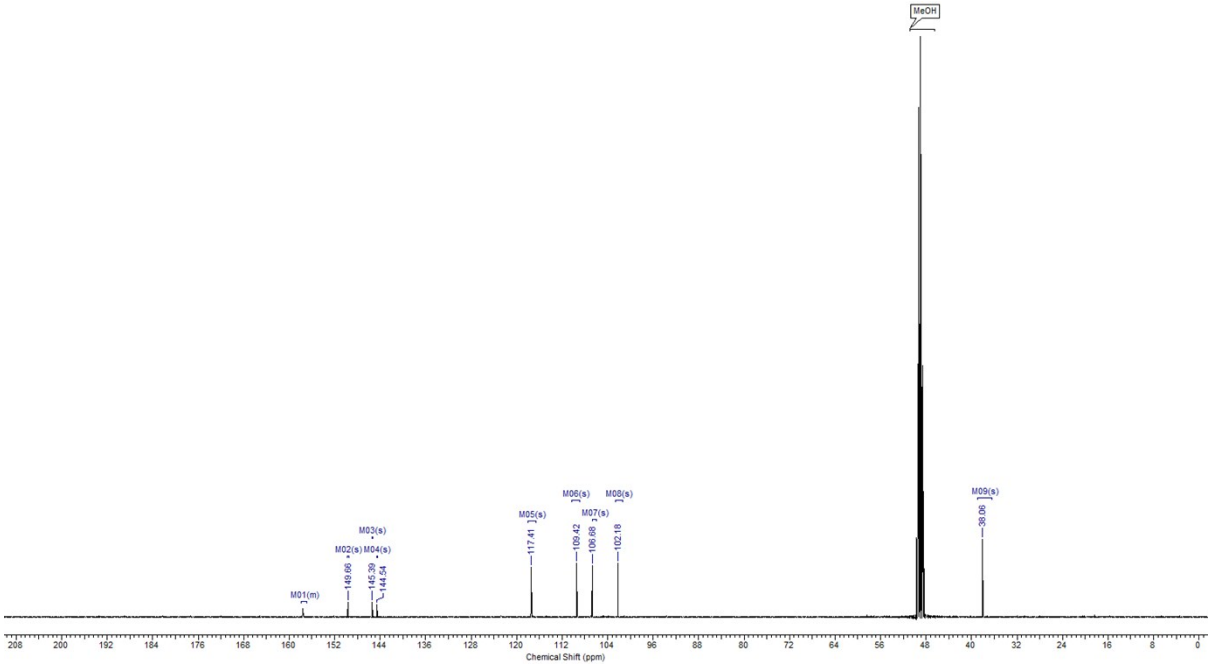




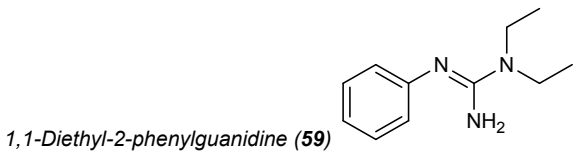
*2-(Benzo[d][1,3]dioxol-5-yl)-1,1-dimethylguanidine (**58**)*

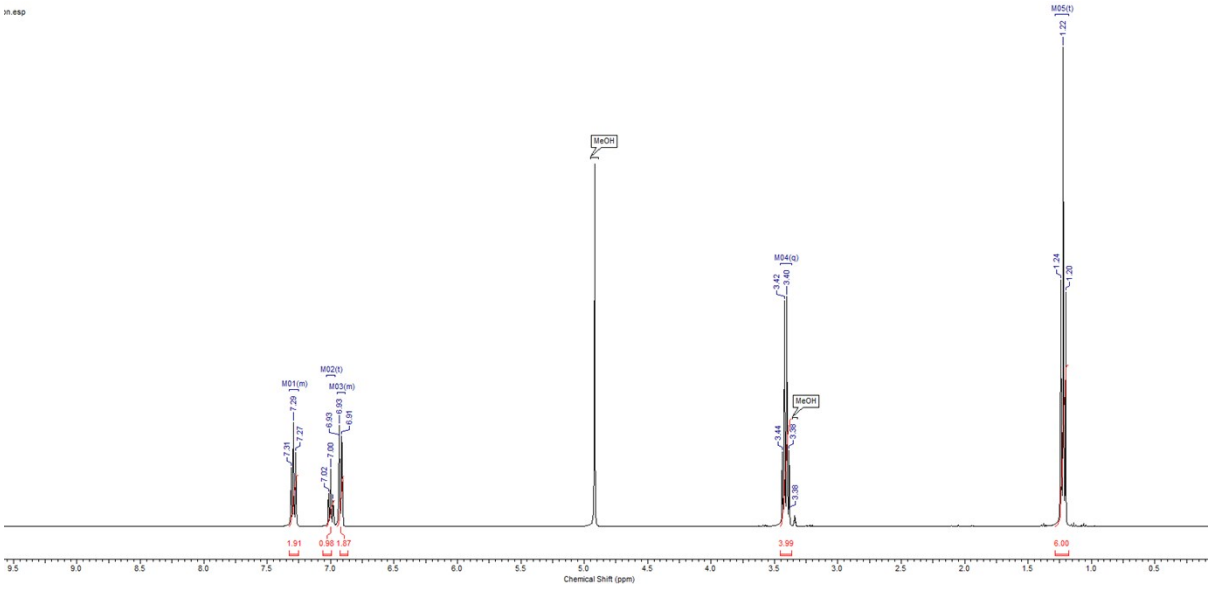


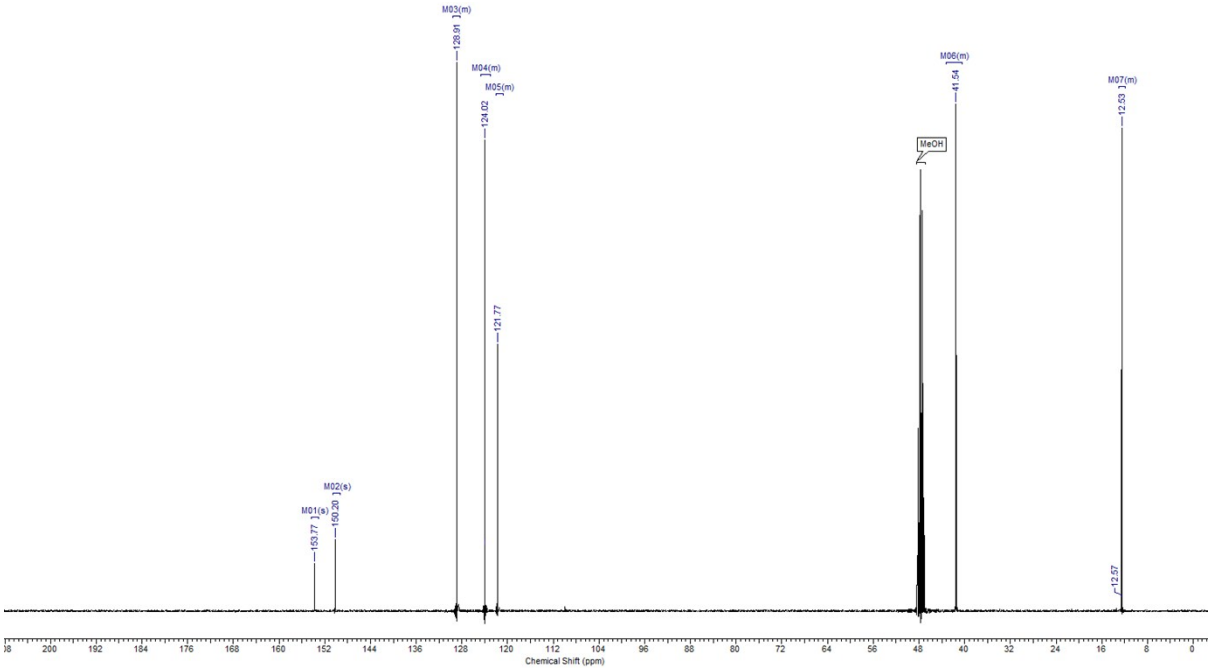




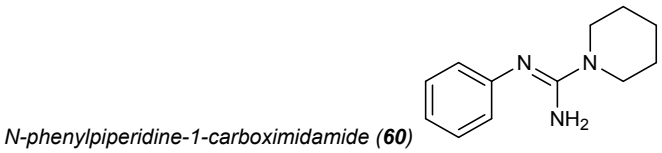
*1,1-Diethyl-2-phenylguanidine (**59**)*

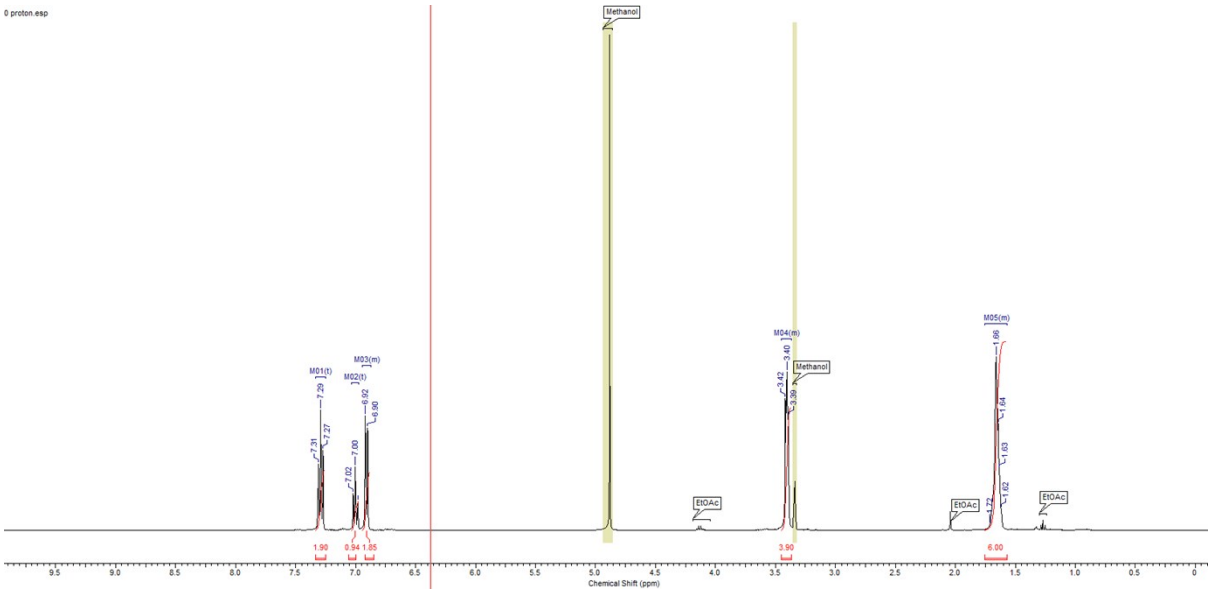


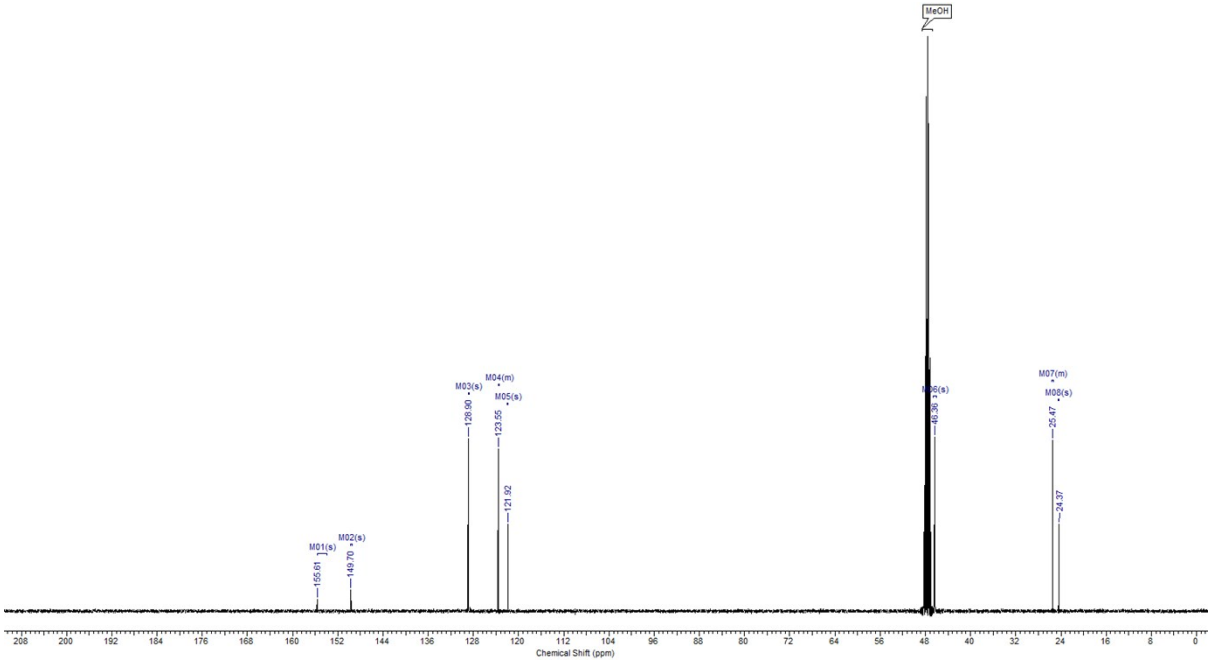


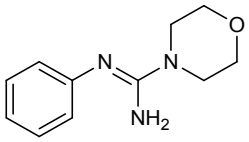


*N-phenylpiperidine-1-carboximidamide (**60**)*

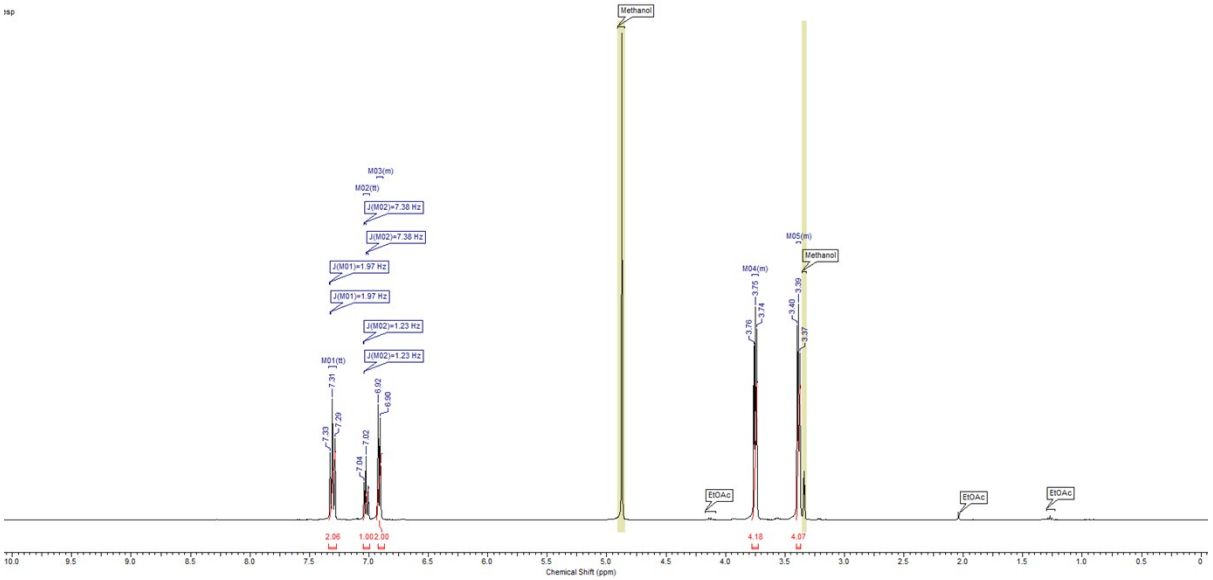


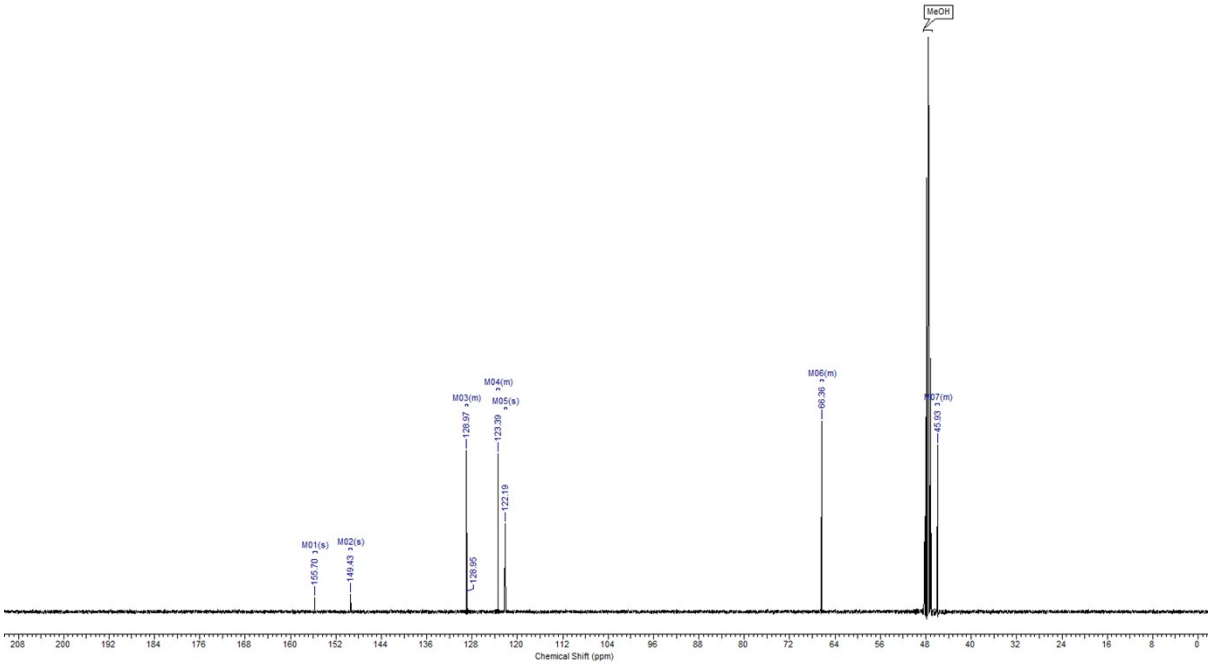




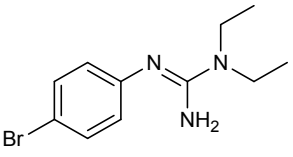


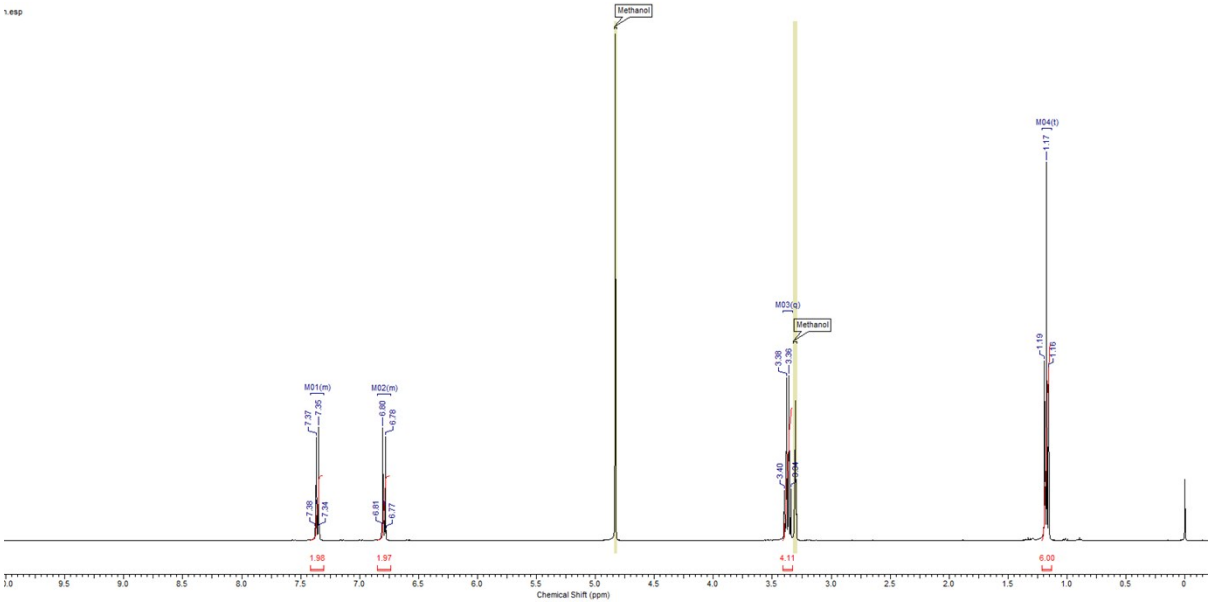
*N-phenylmorpholine-4-carboximidamide (**61**)*

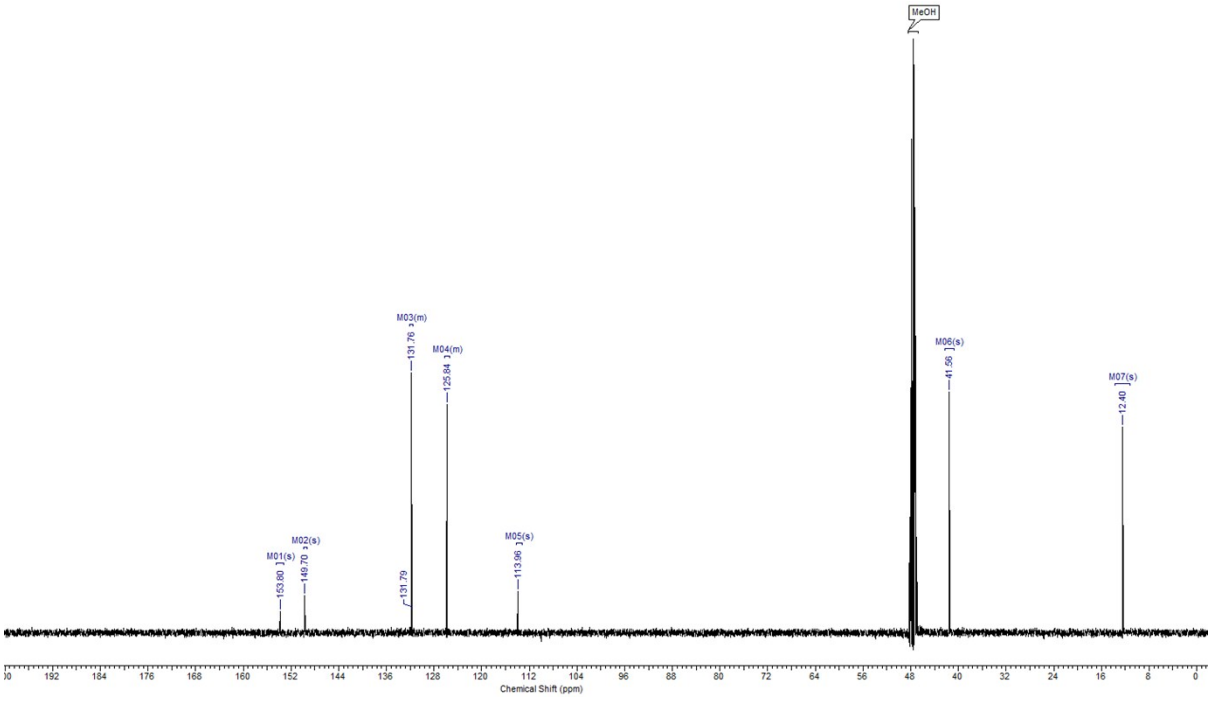




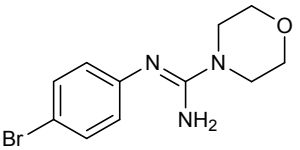
*2-(4-bromophenyl)-1,1-diethylguanidine (**62**)*

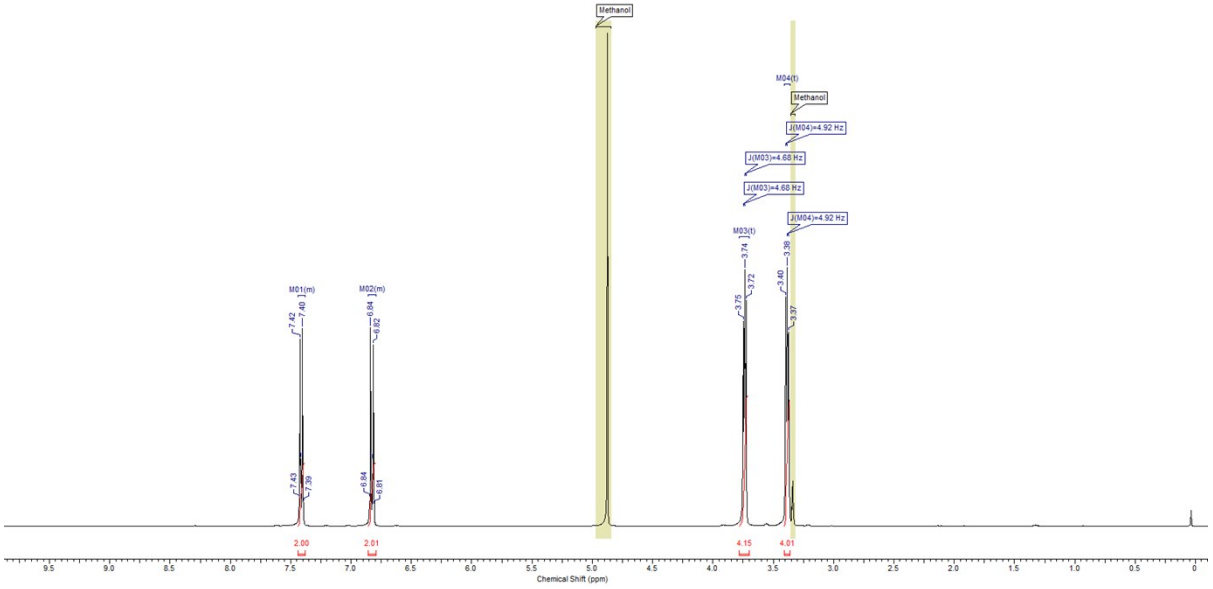


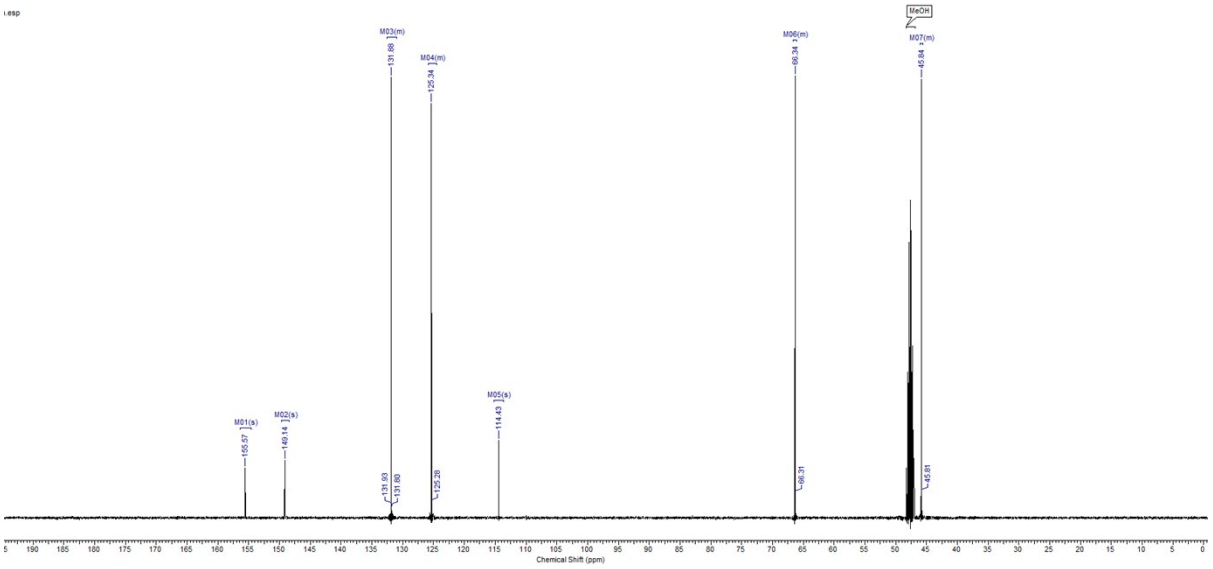




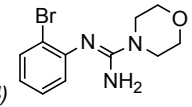
*N-(4-bromophenyl)morpholine-4-carboximidamide (**63**)*

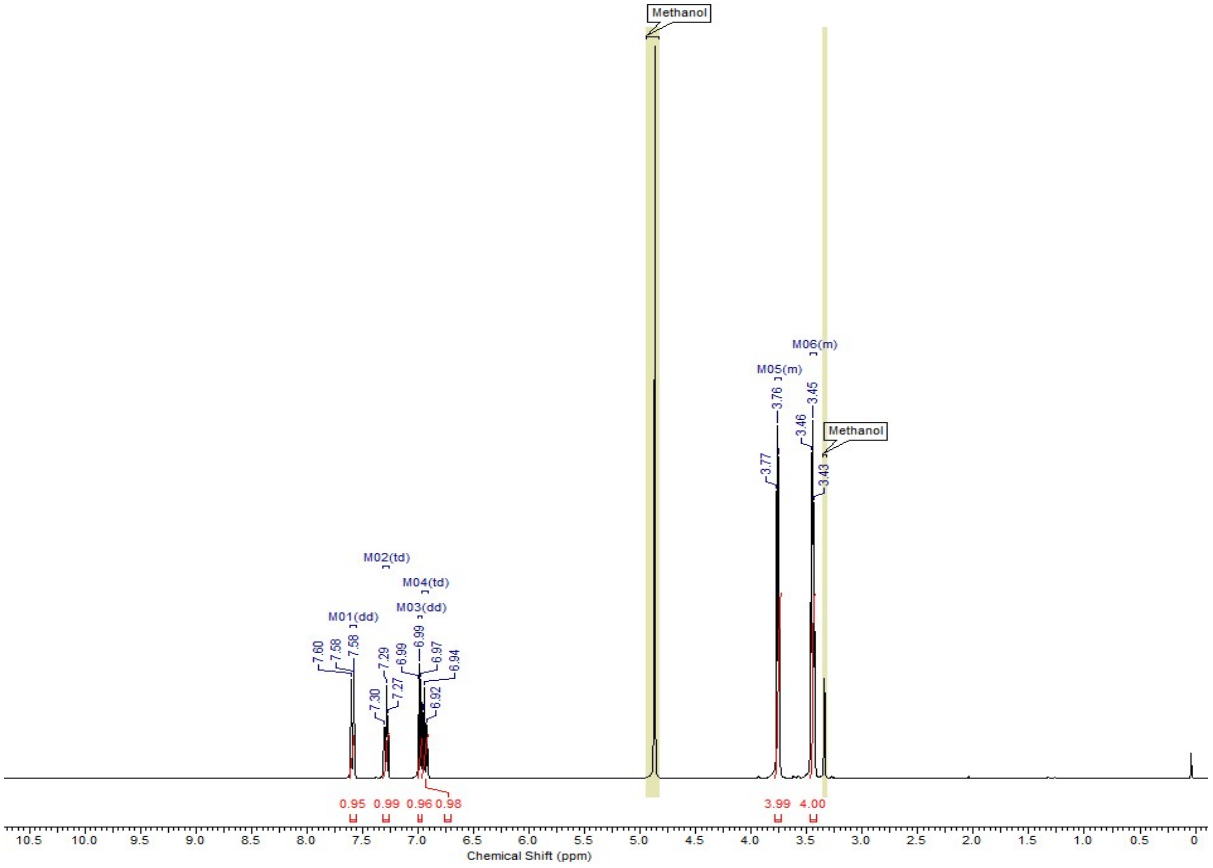


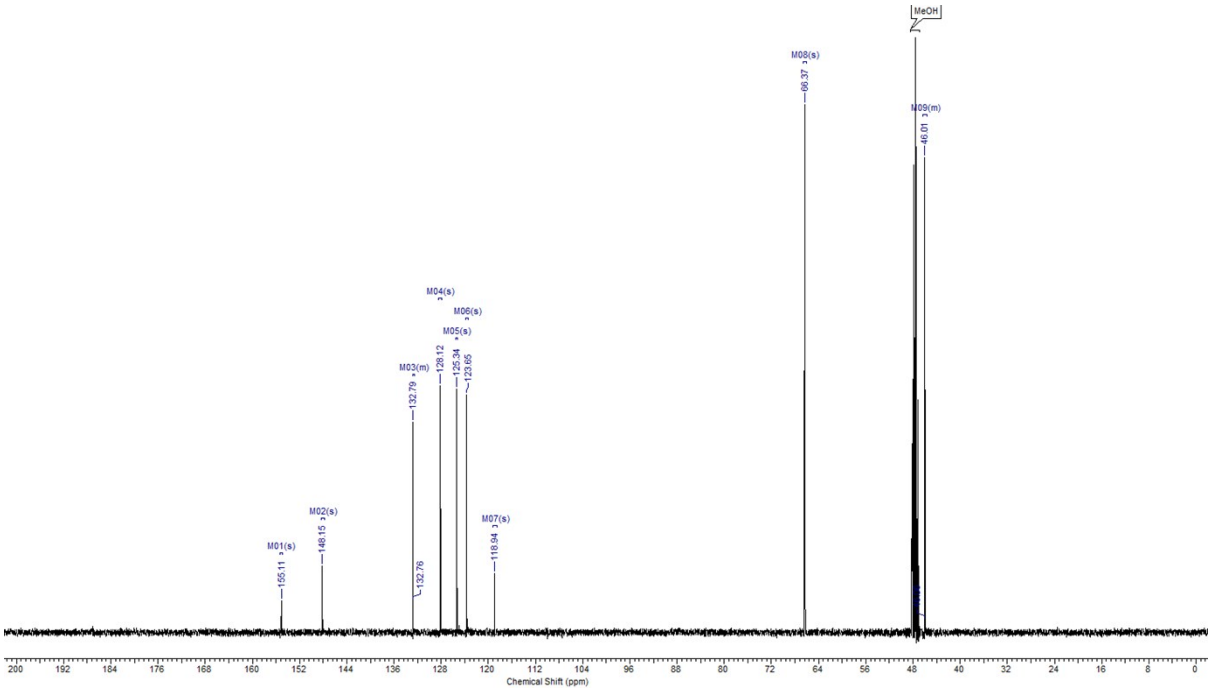


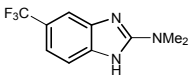


*N-(2-bromophenyl)morpholine-4-carboximidamide (**64**)*

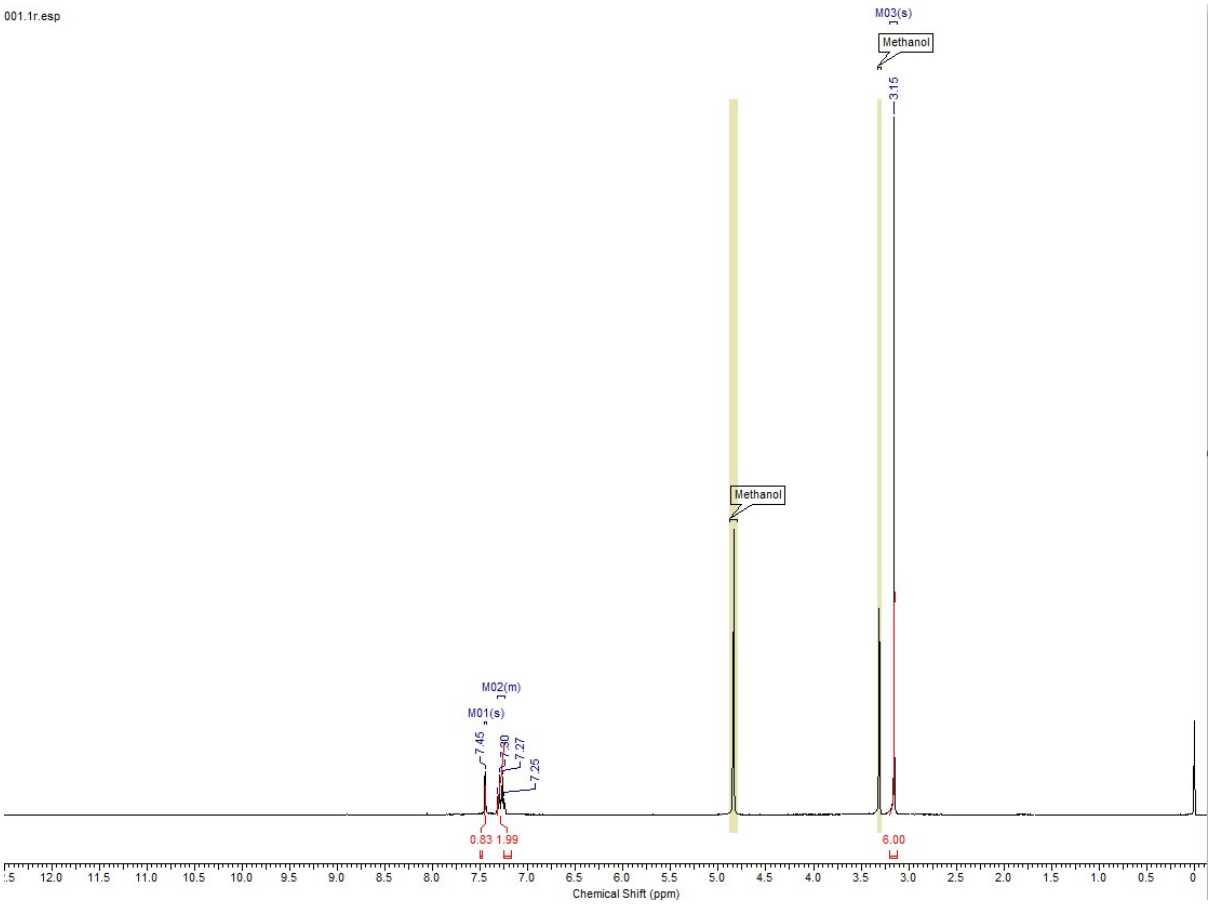


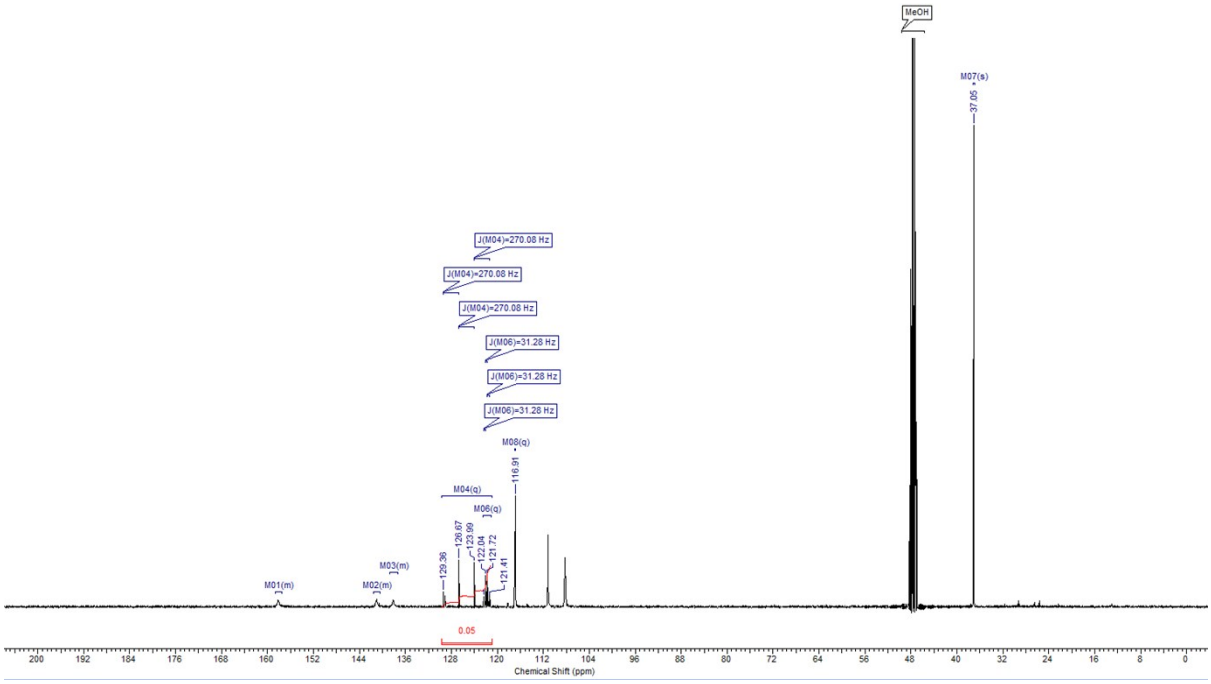




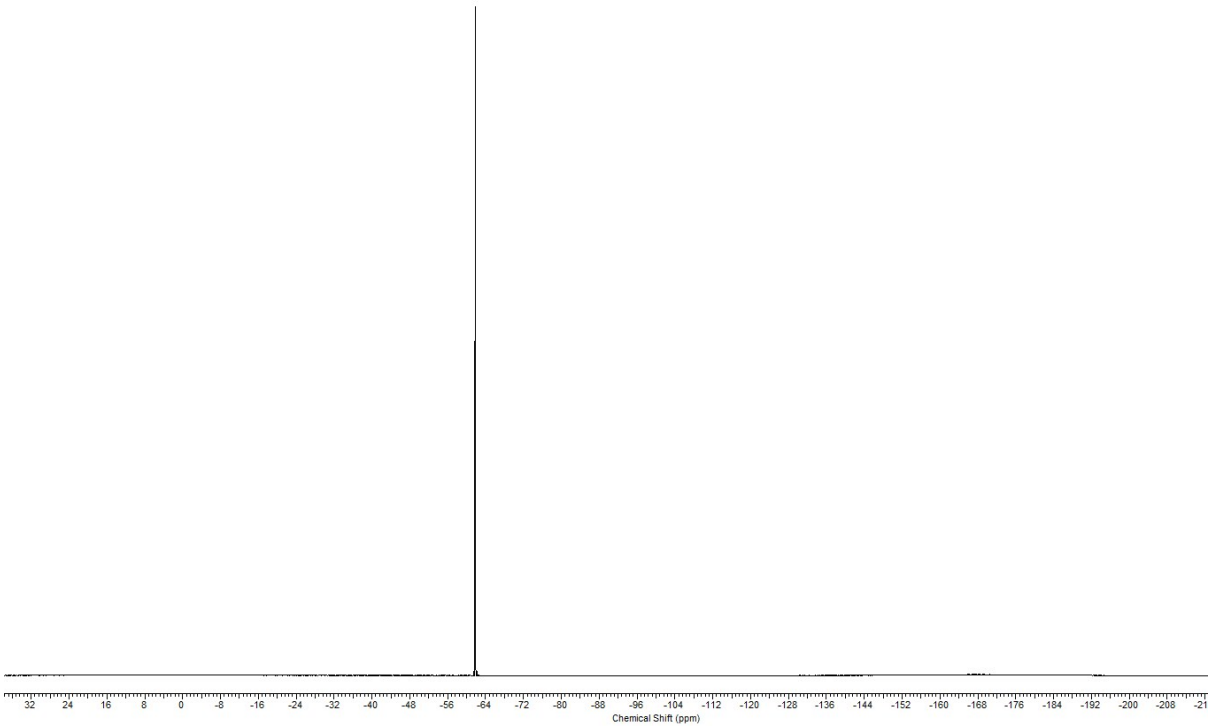


*5-Trifluoromethyl-N,N-dimethyl-1Hbenzo[d] imidazol-2-amine (**8**)*

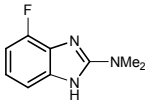


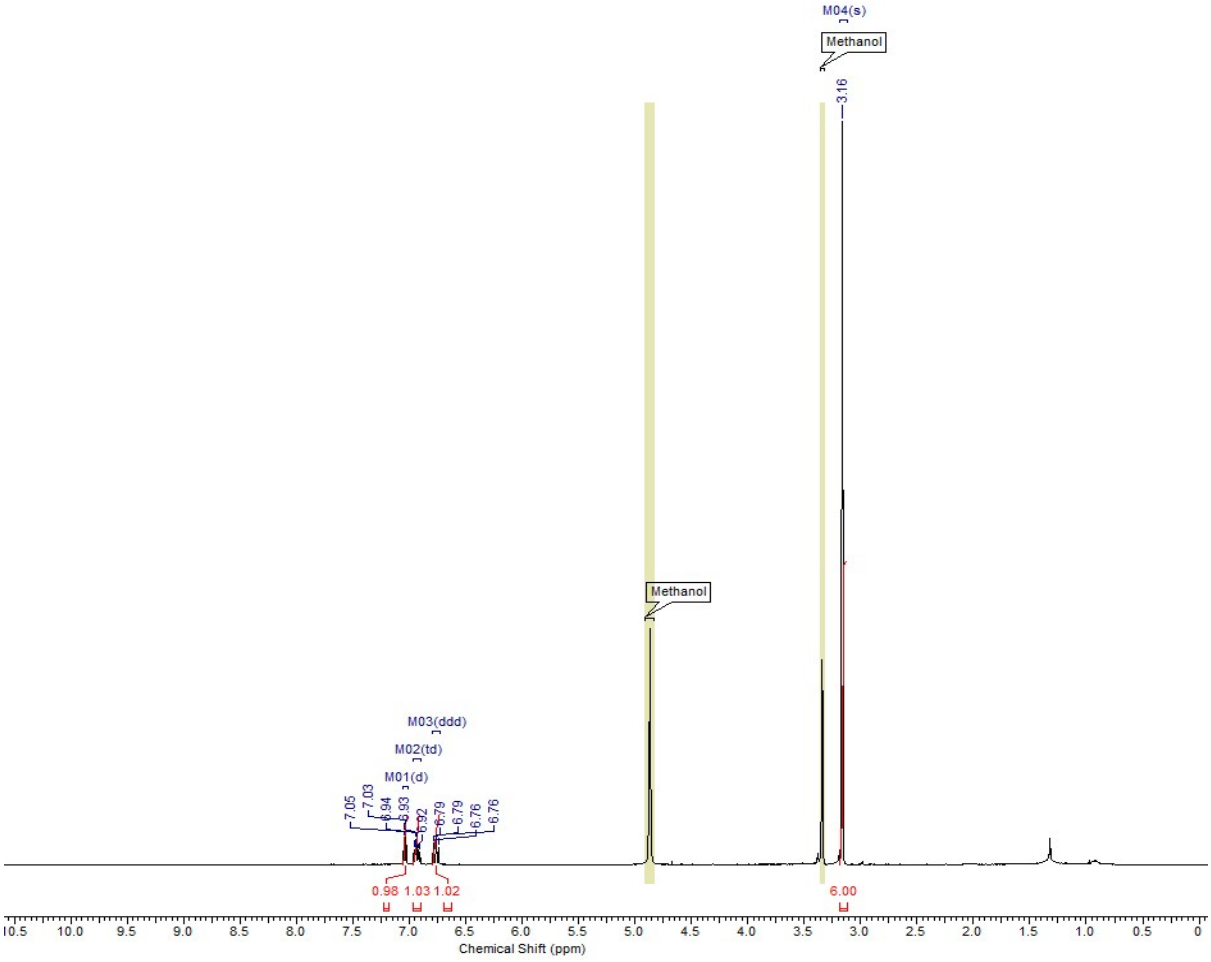


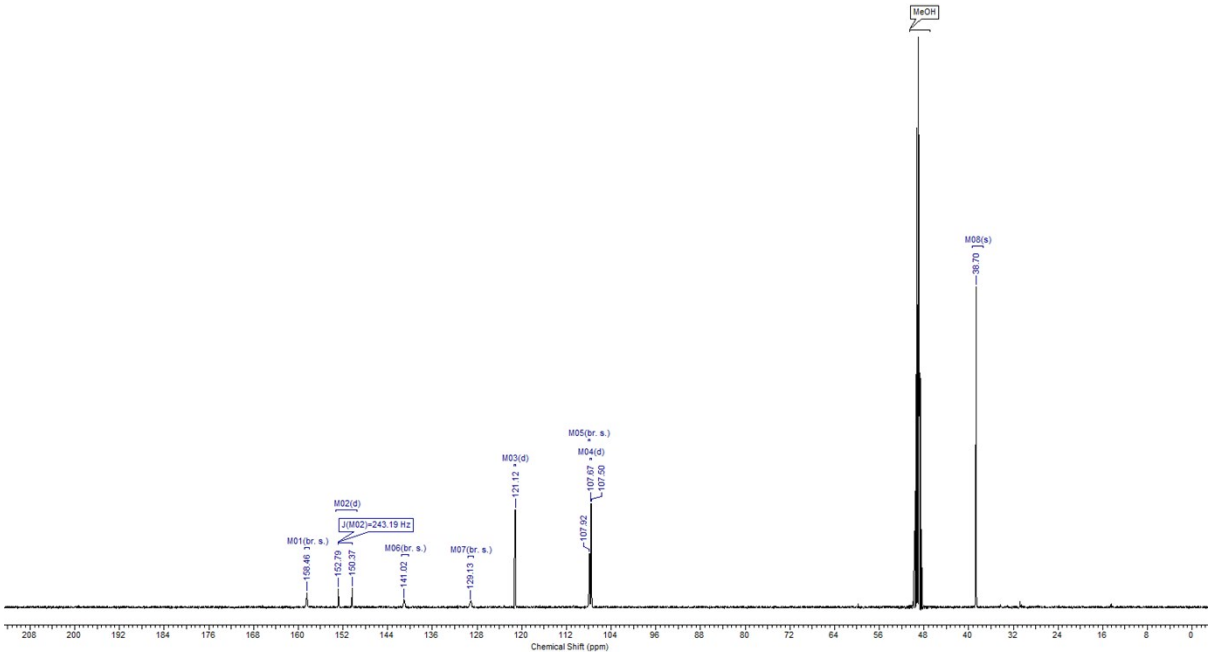
^{19}F NMR


32 24 16 8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168 -176 -184 -192 -200 -208 -21
Chemical Shift (ppm)

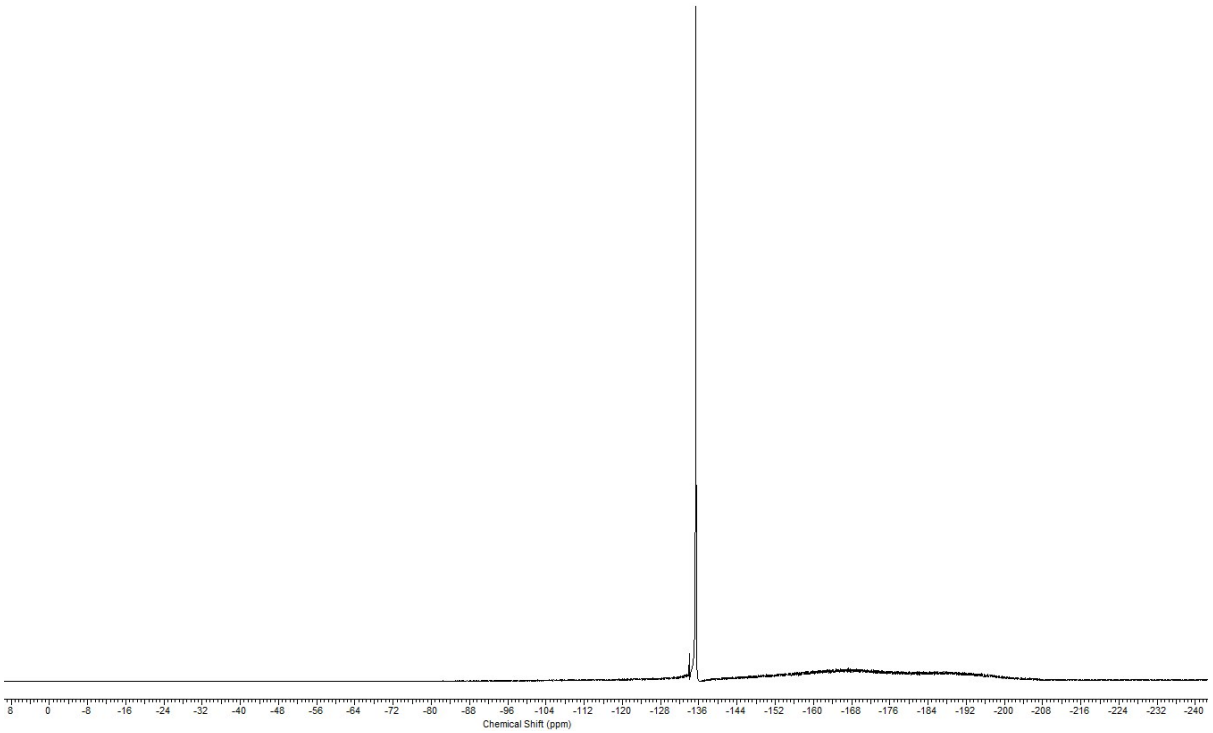
*4-fluoro-N,N-dimethyl-1H-benzo[d]imidazol-2-amine (**9**)*

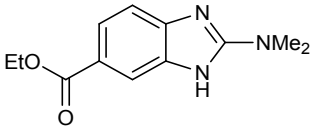




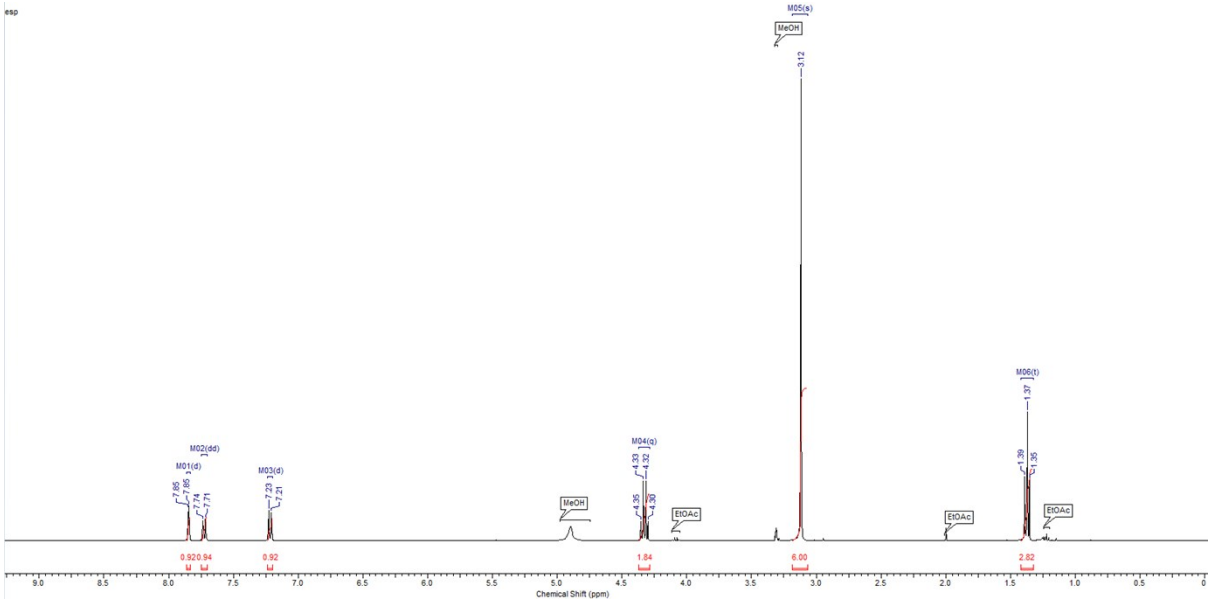


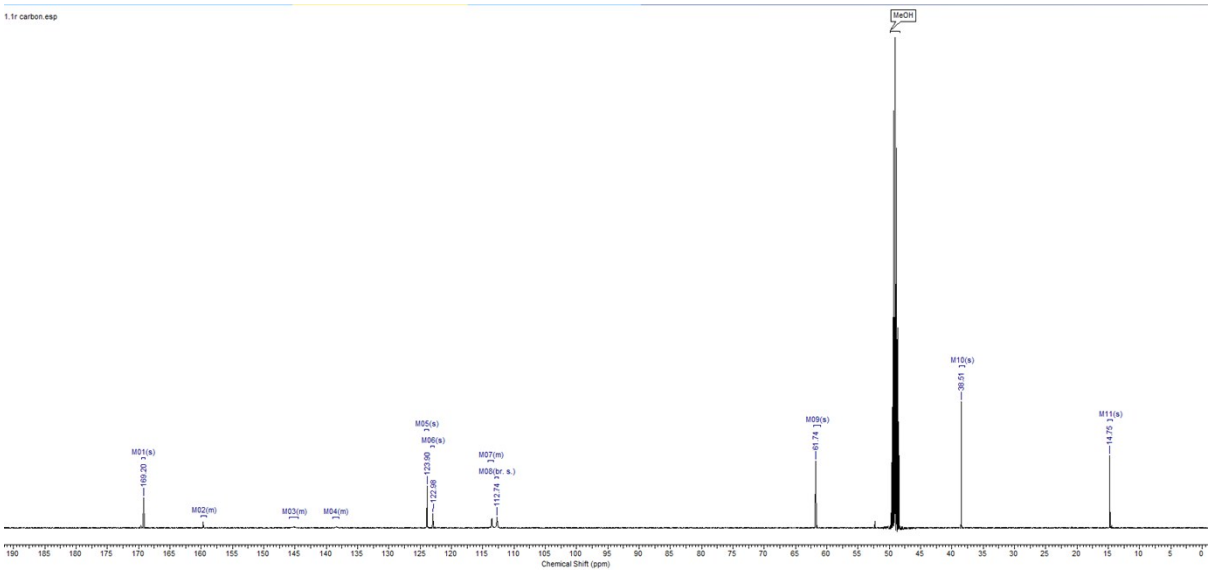
^{19}F NMR

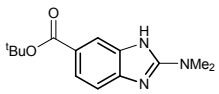

8 0 -8 -16 -24 -32 -40 -48 -56 -64 -72 -80 -88 -96 -104 -112 -120 -128 -136 -144 -152 -160 -168 -176 -184 -192 -200 -208 -216 -224 -232 -240
Chemical Shift (ppm)



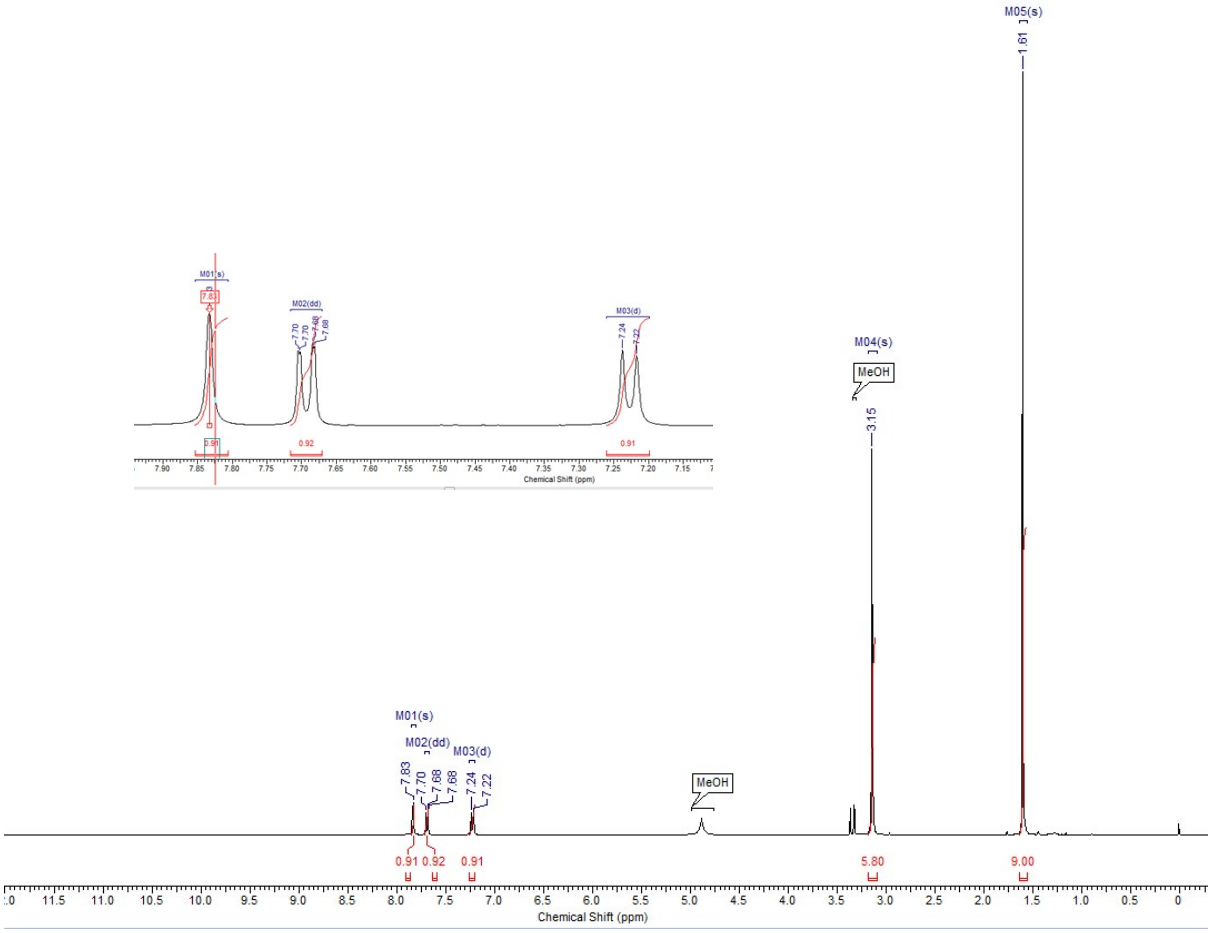
*Ethyl 2-(dimethylamino)-1H-benzo[d]imidazole-6-carboxylate (**11**)*

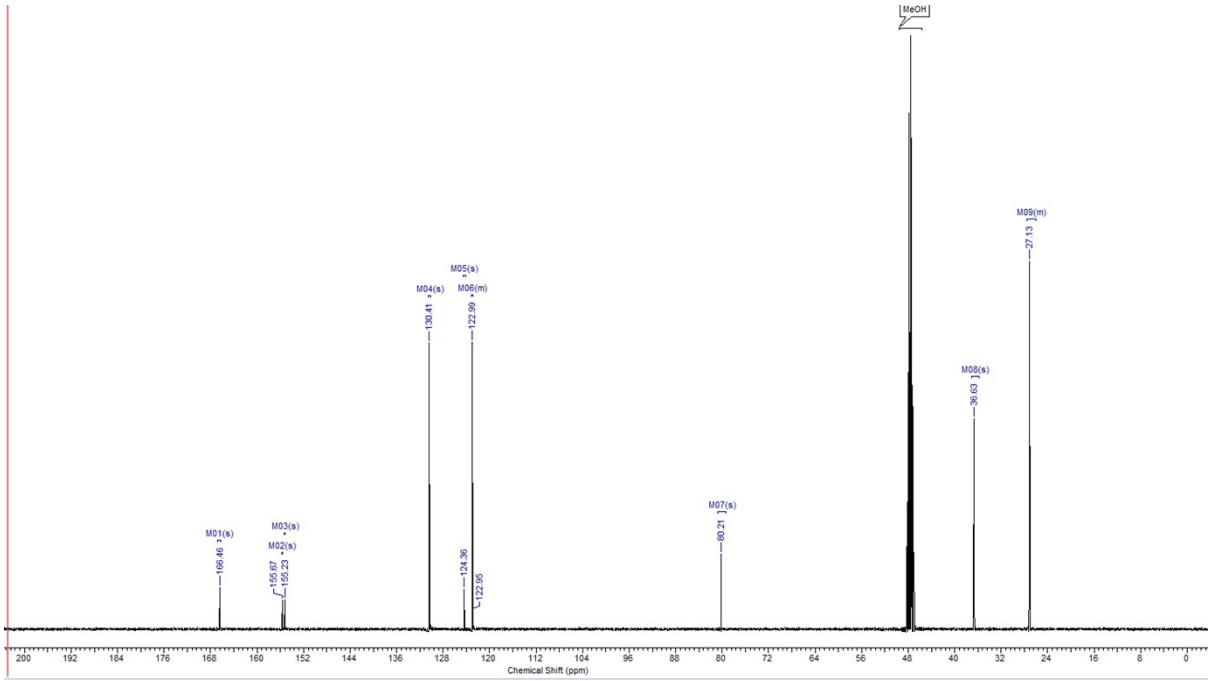




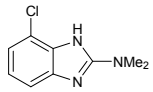


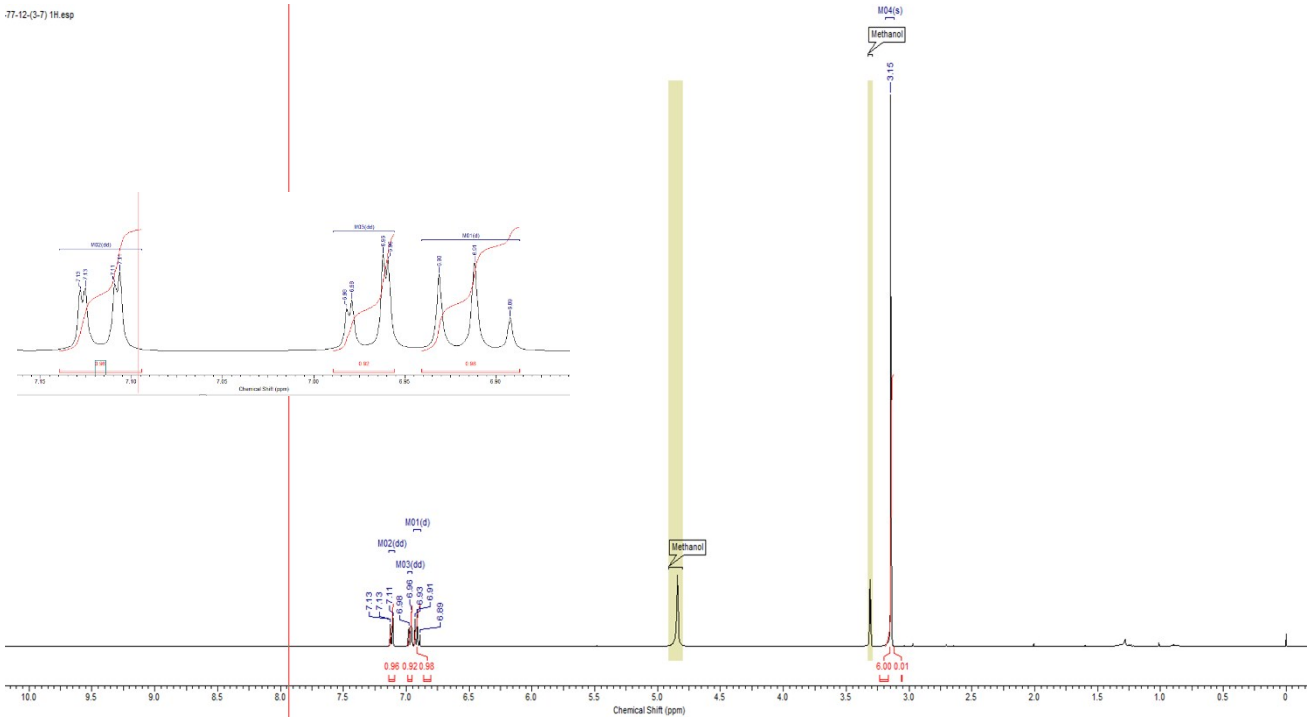
*Tert-butyl 2-(dimethylamino)-1H-benzo[d]- imidazole-5-carboxylate (**12**)*

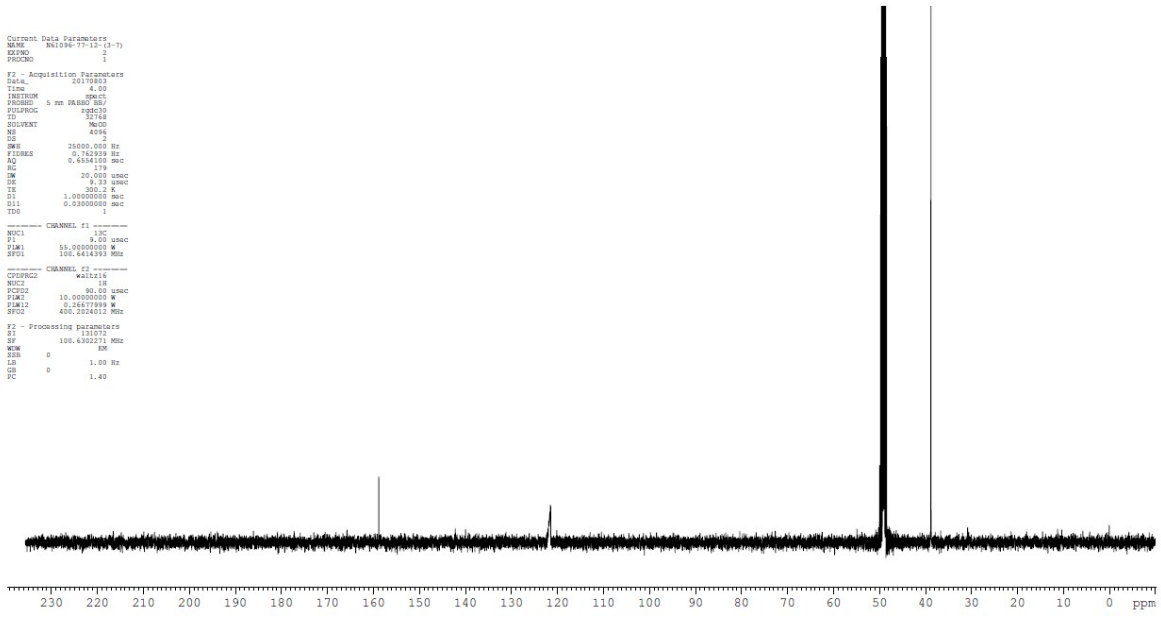


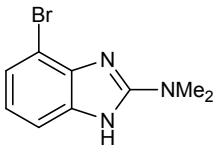


4-chloro-*N*,*N*-dimethyl-1*H*-benzo[*d*]imidazol-2-amine (**16**)

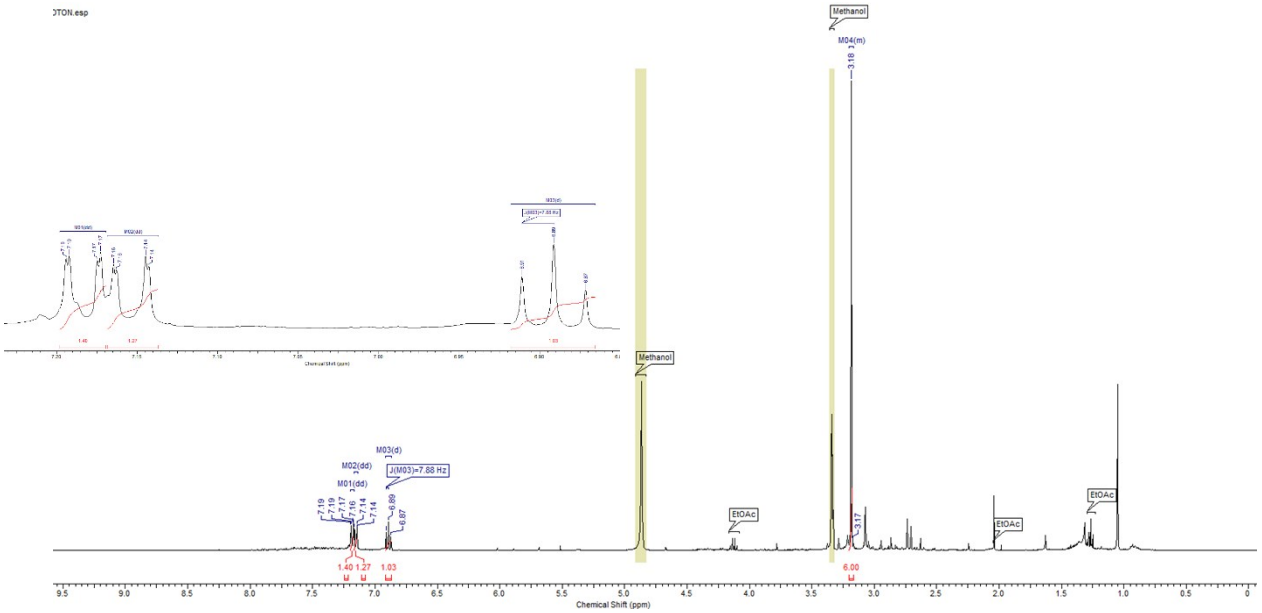


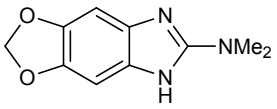




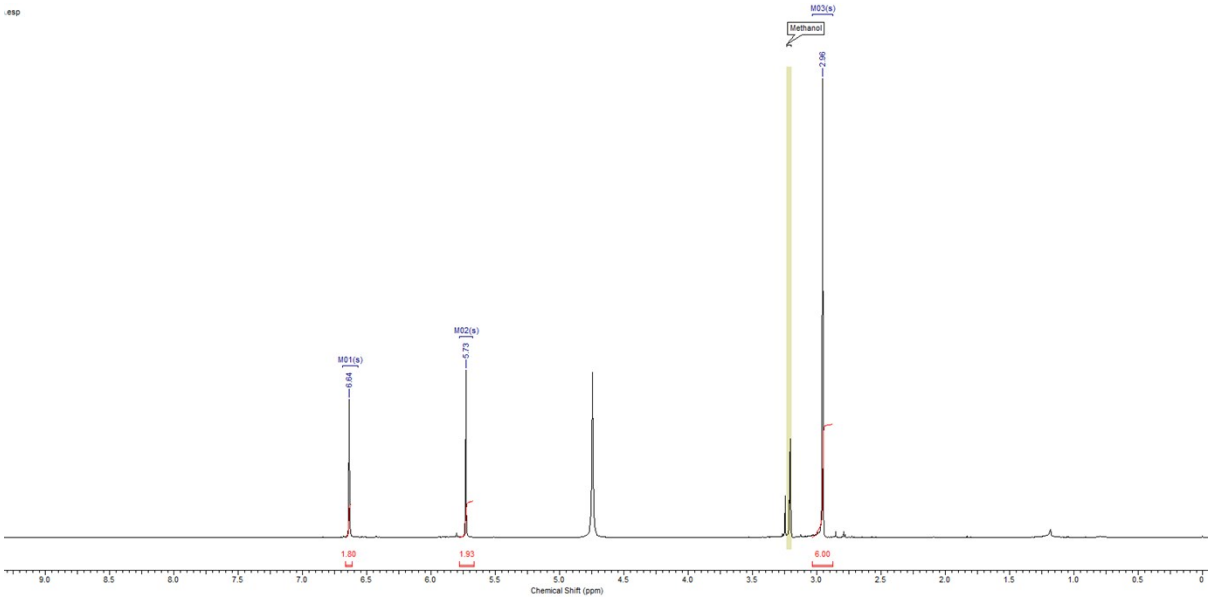


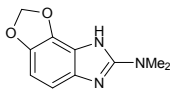
4-Bromo-*N*,*N*-dimethyl-1*H*-benzo[*d*]imidazol-2-amine (**18**)



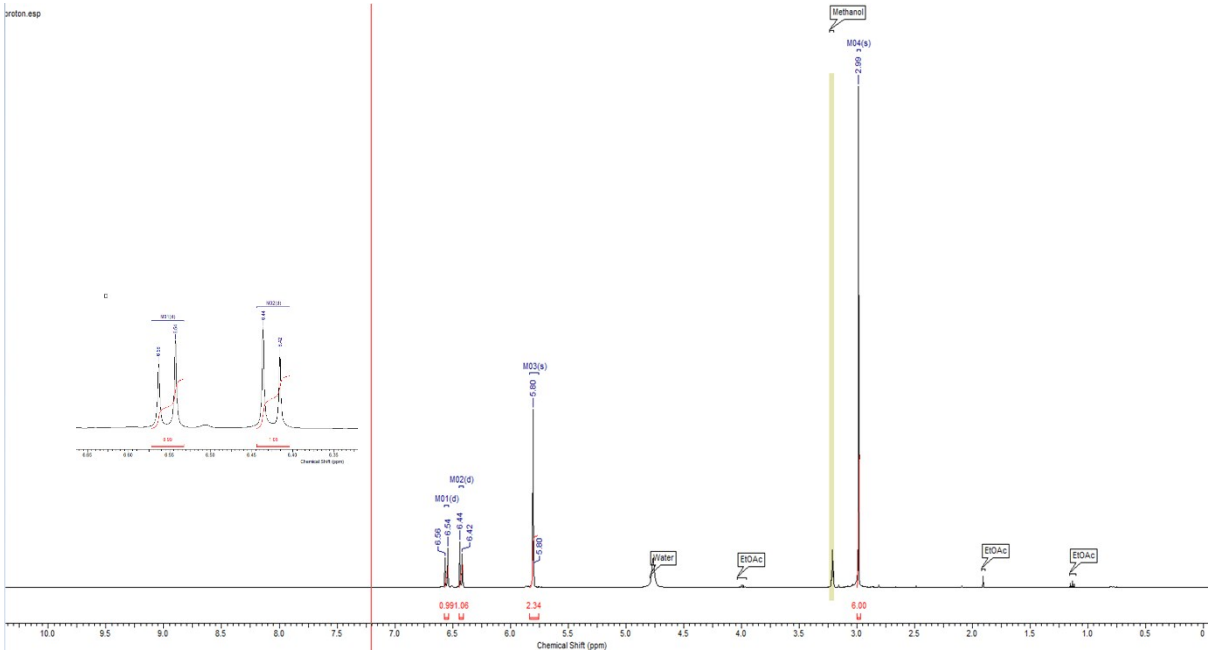


*N,N-dimethyl-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]imidazol-6-amine (**19**)*

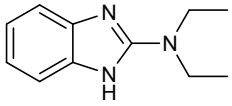


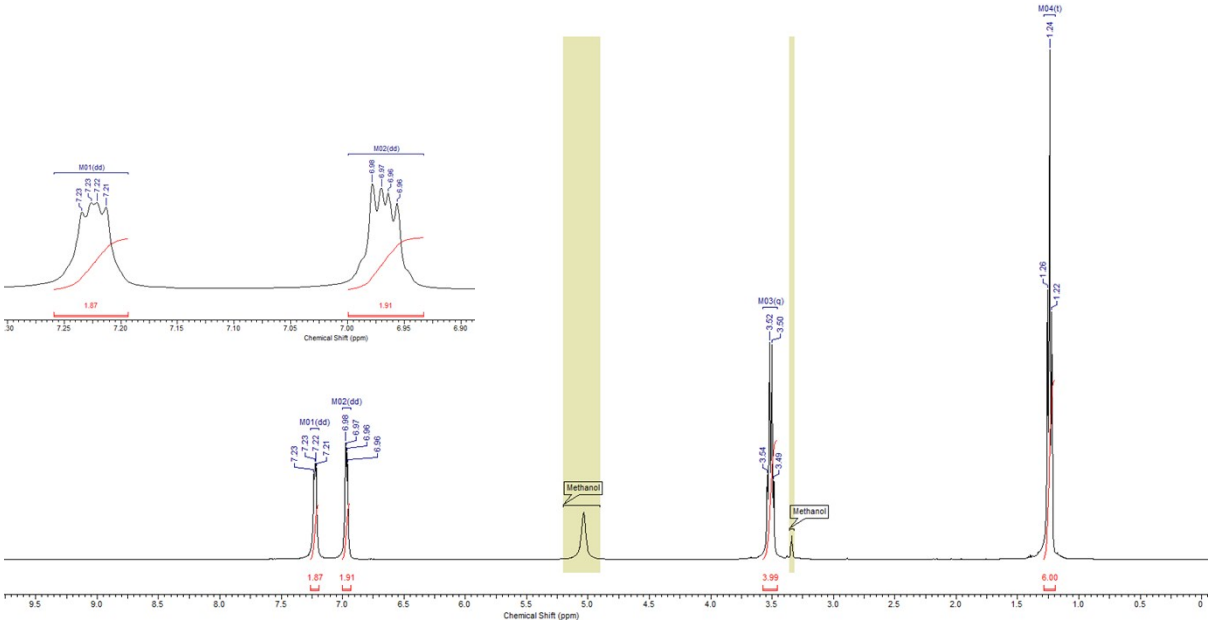


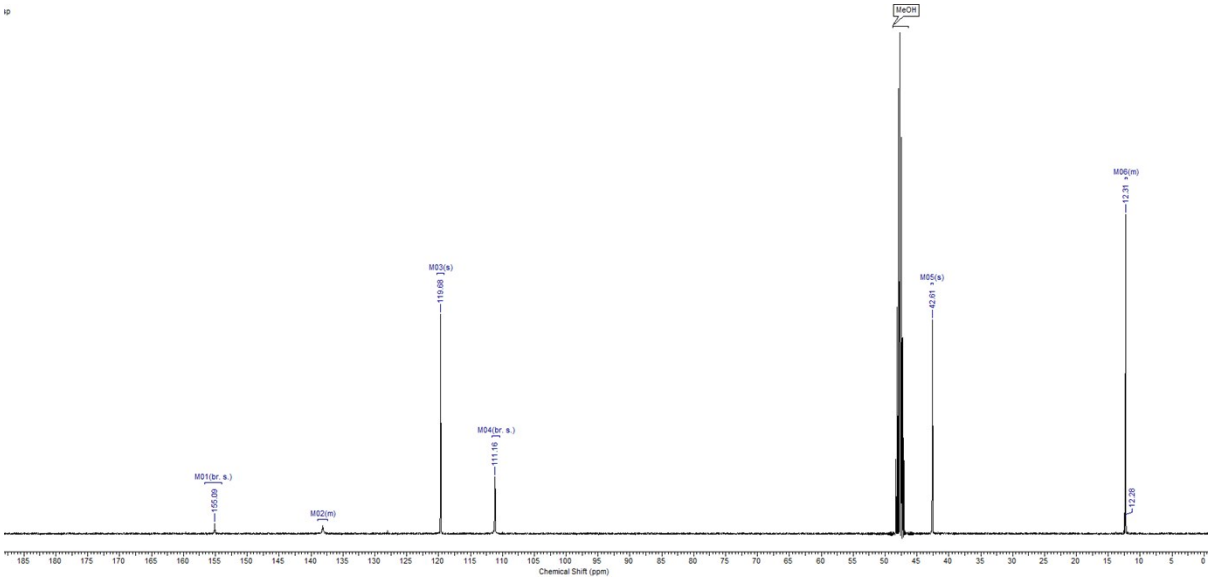
N,N-dimethyl-8*H*-[1,3]dioxolo[4',5':3,4]benzo[1,2-*d*]imidazol-7-amine (**20**)



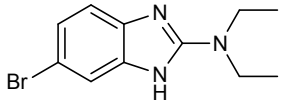
*N,N-diethyl-1H-benzo[d]imidazol-2-amine (**21**)*

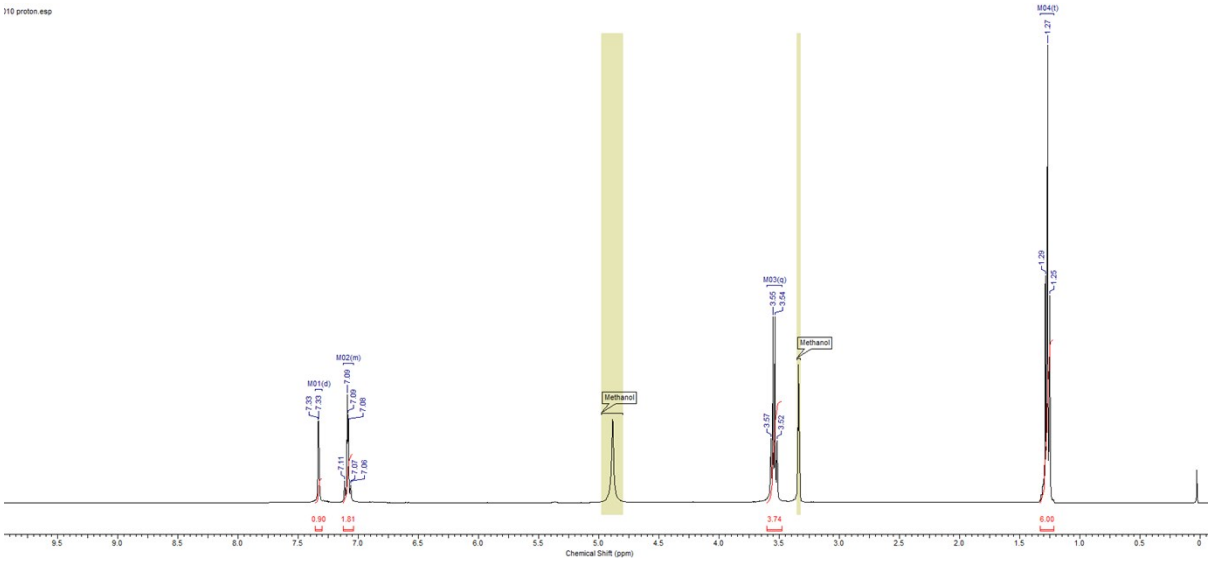




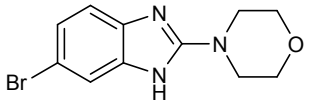


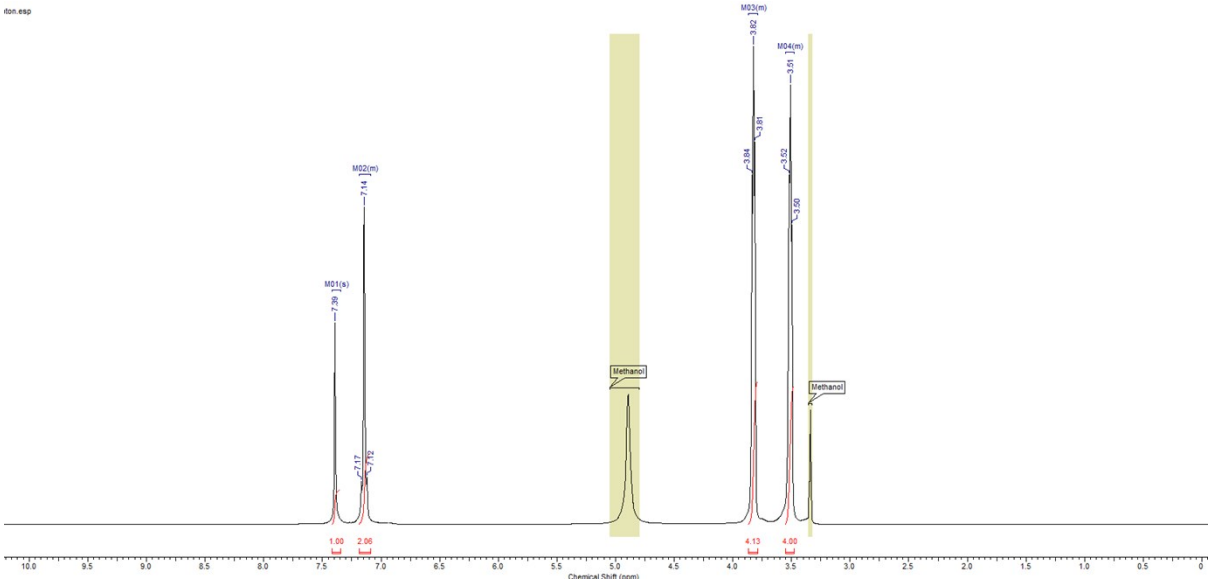
*6-Bromo-N,N-diethyl-1H-benzo[d]imidazol-2-amine (**22**)*

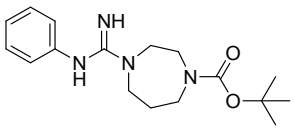




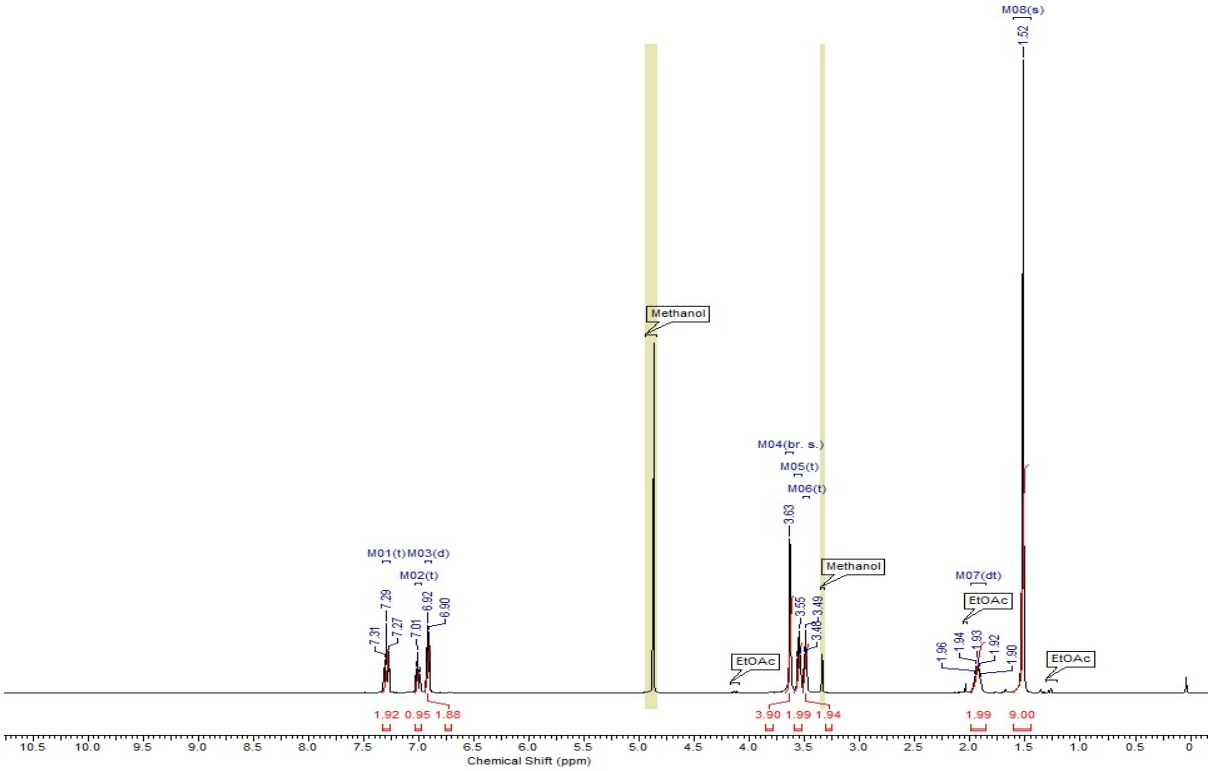
*4-(6-bromo-1H-benzo[d]imidazol-2-yl)morpholine (**25**)*

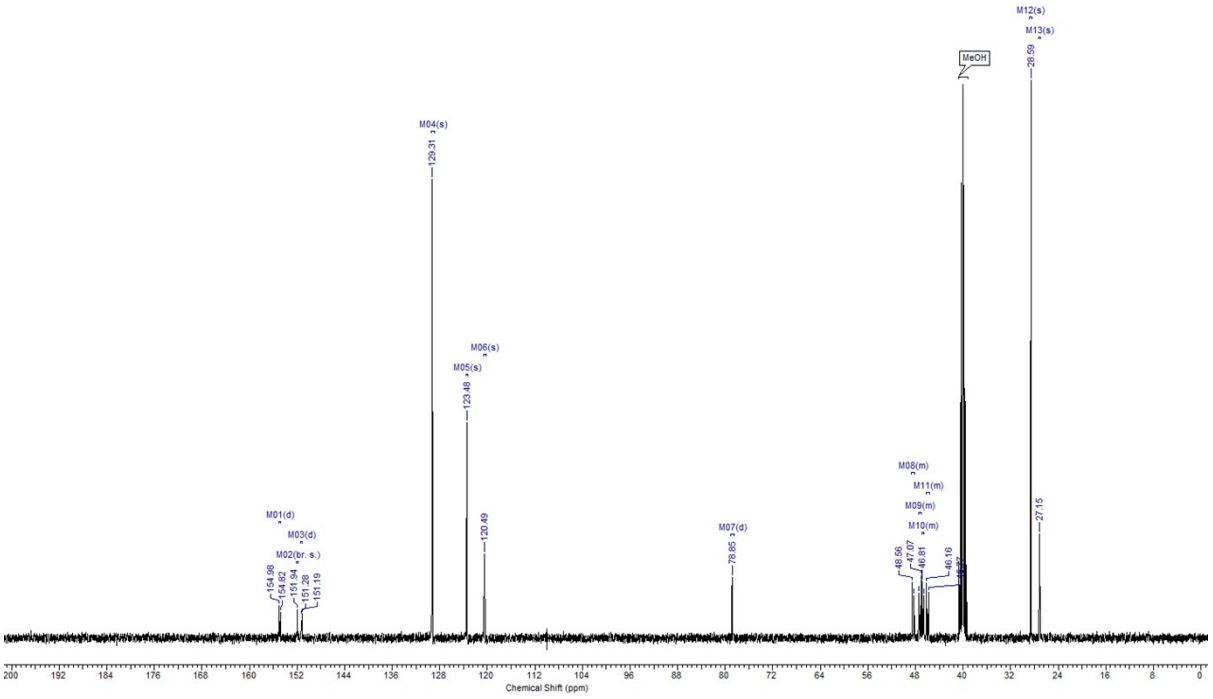




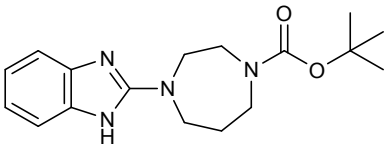


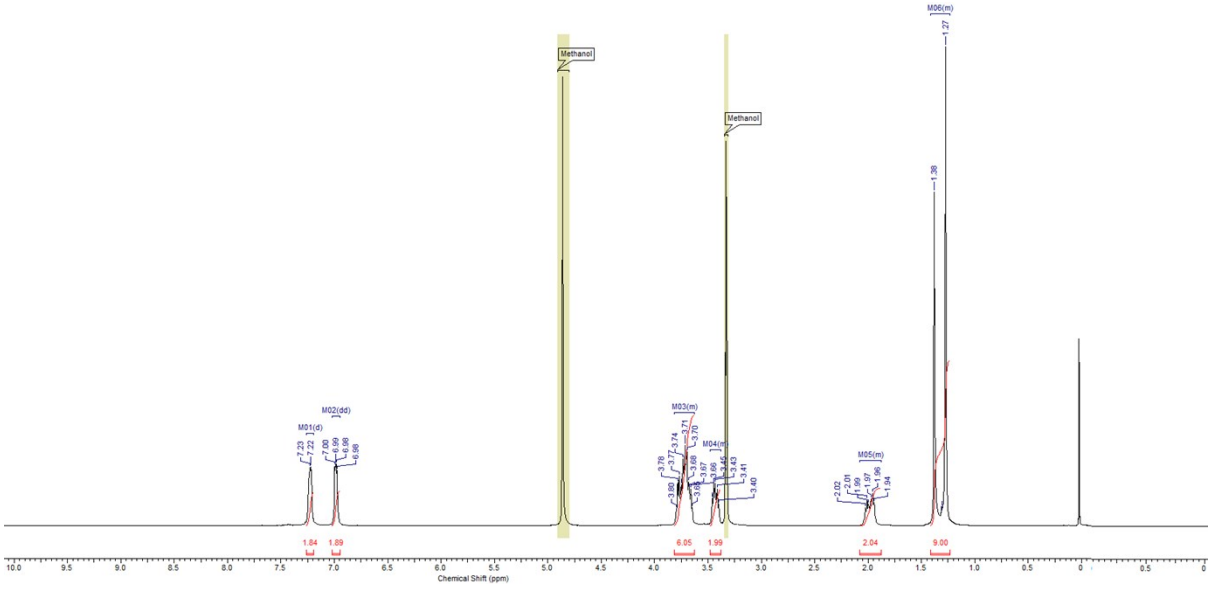
*Tert-butyl 4-(N'-phenylcarbamimidoyl)-1,4-diazepane-1-carboxylate (**46**)*

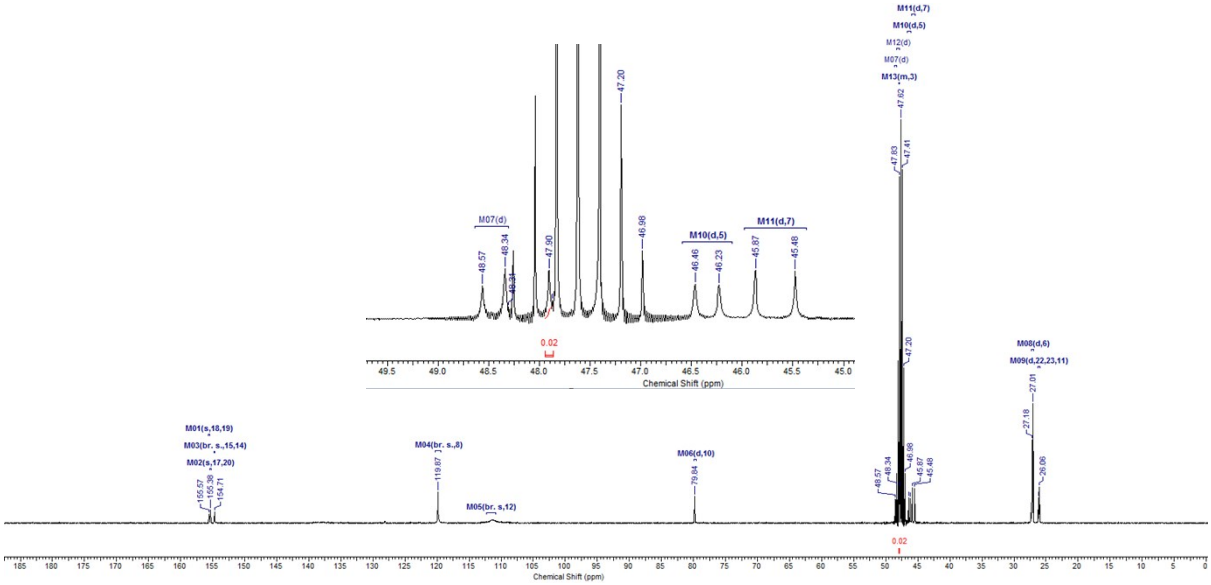


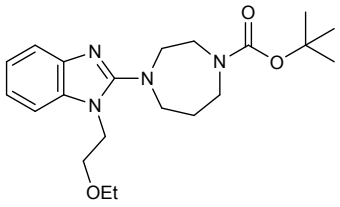


*Tert-butyl 4-(1H-benzo[d]imidazol-2-yl)-1,4-diazepane-1-carboxylate (**47**)*

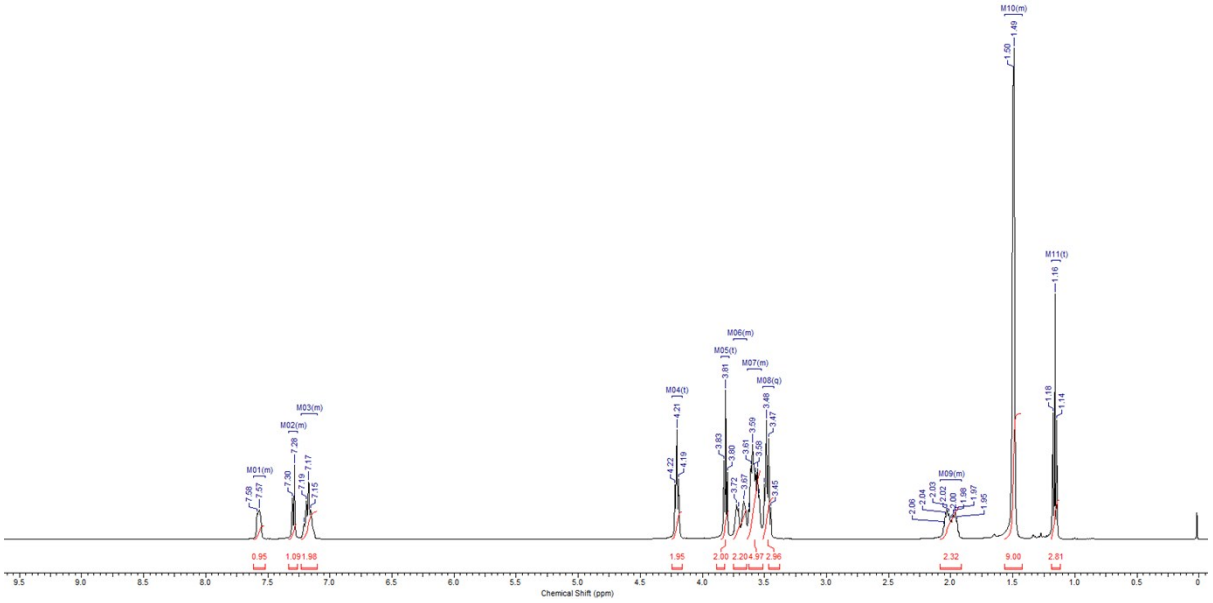


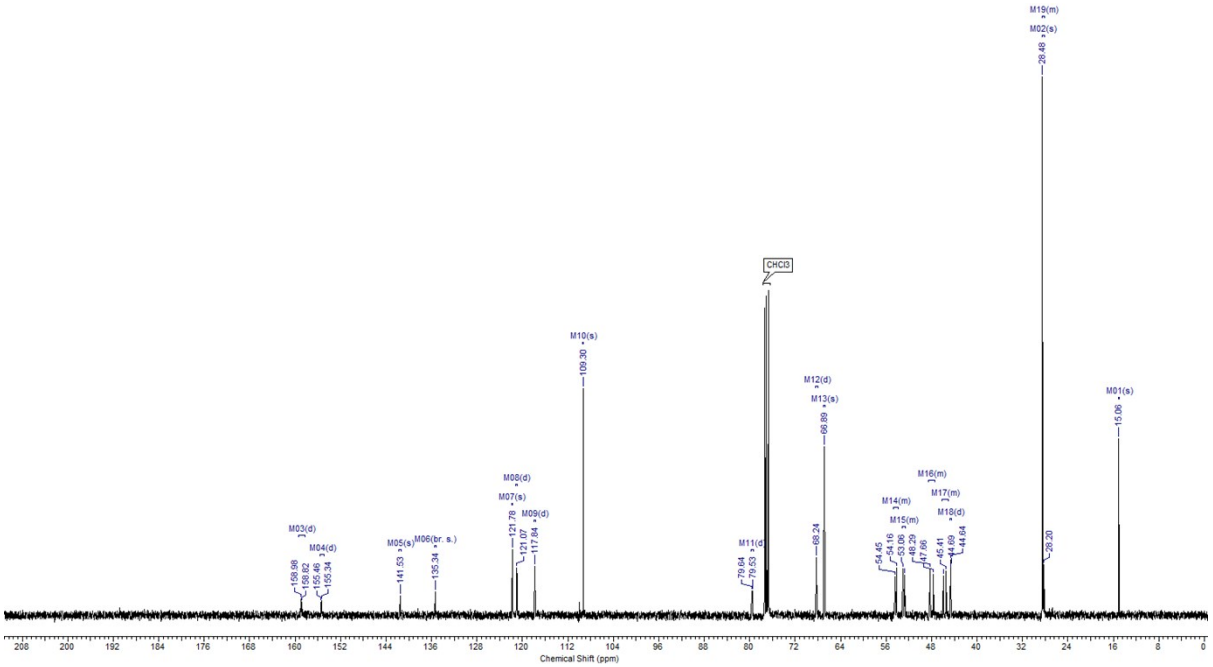




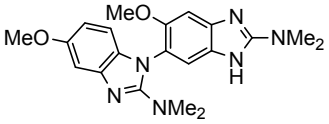


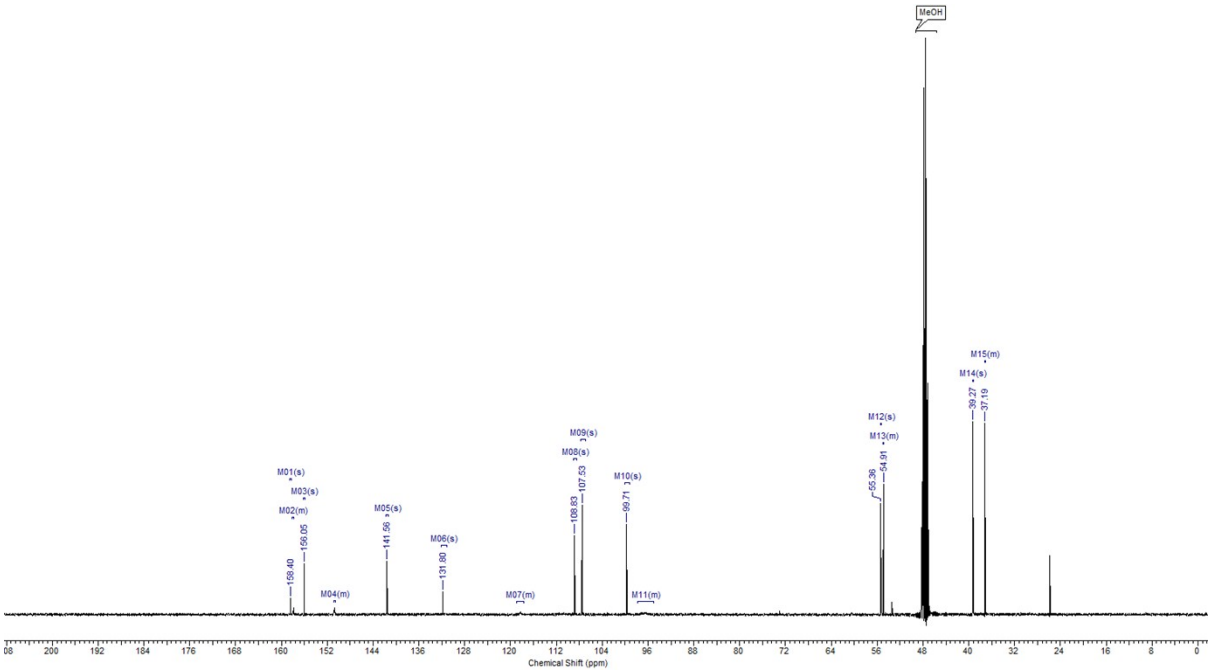
*Tert-butyl 4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol-2-yl)-1,4-diazepane-1-carboxylate (**49**)*



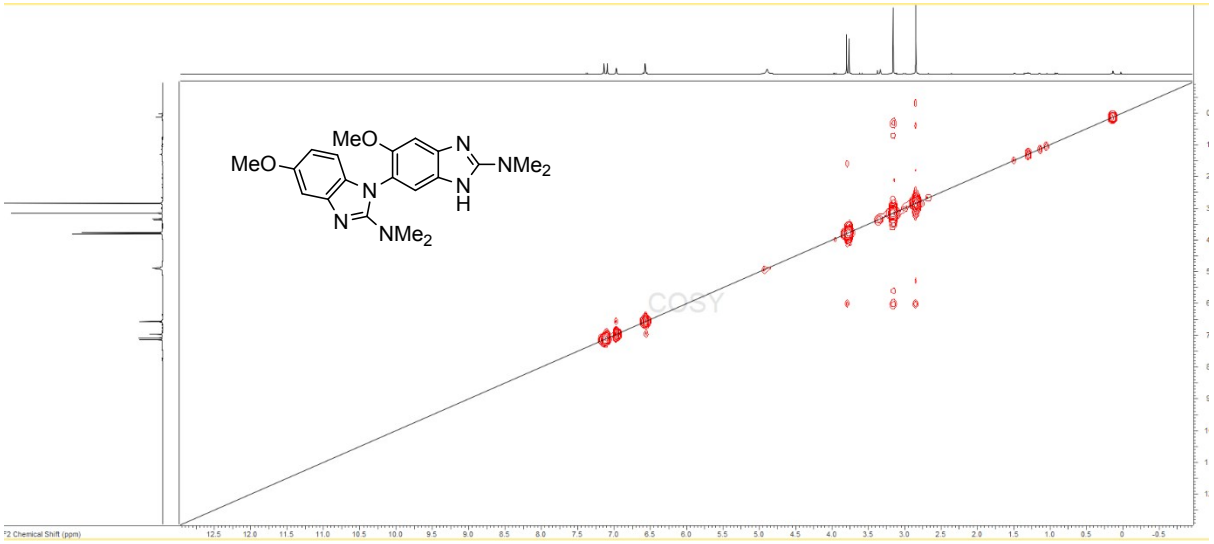


Compound 6 elucidation

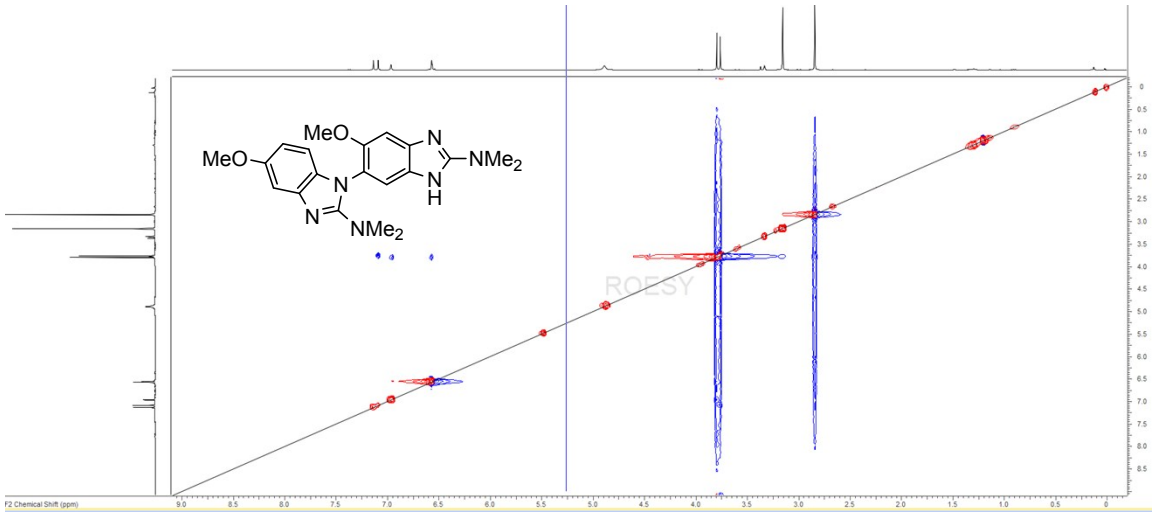




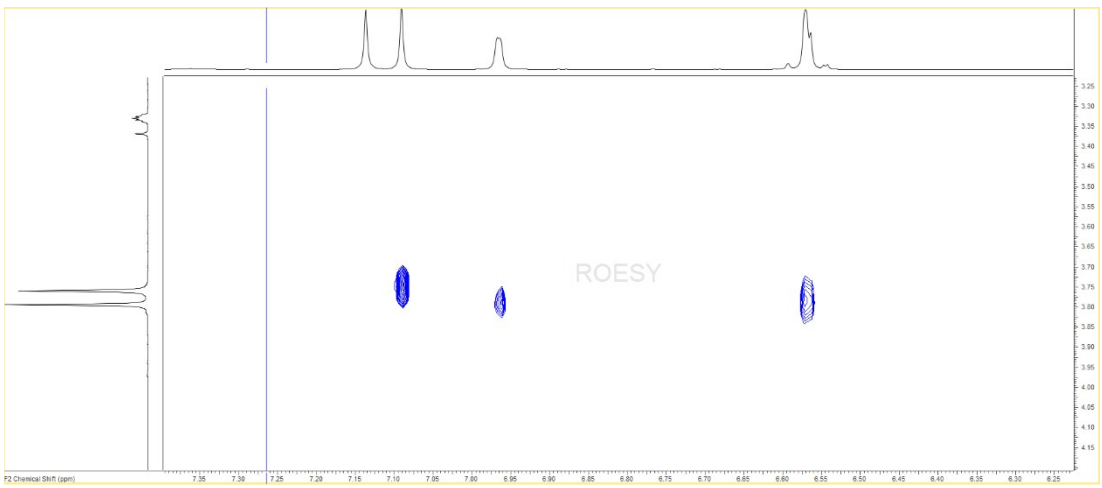
COSY NMR



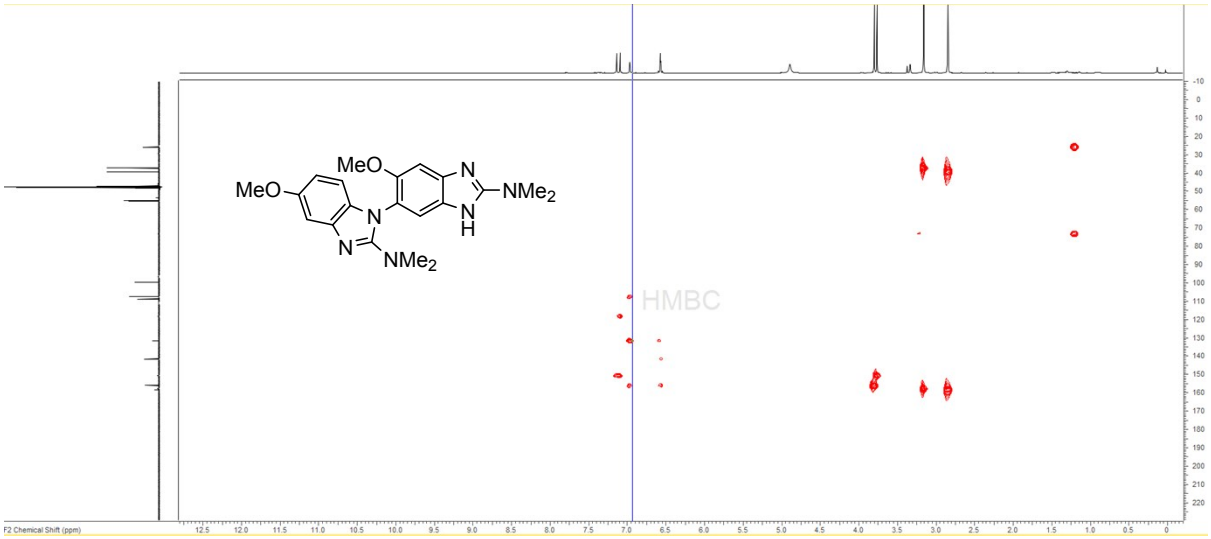
ROESY NMR



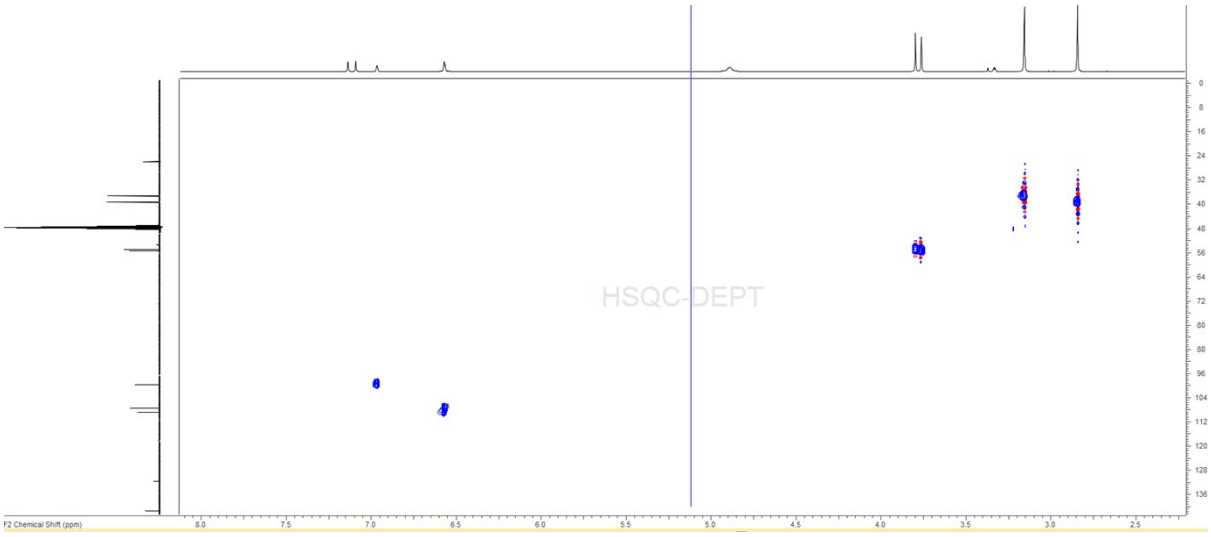
ROSEY NMR (zoomed)



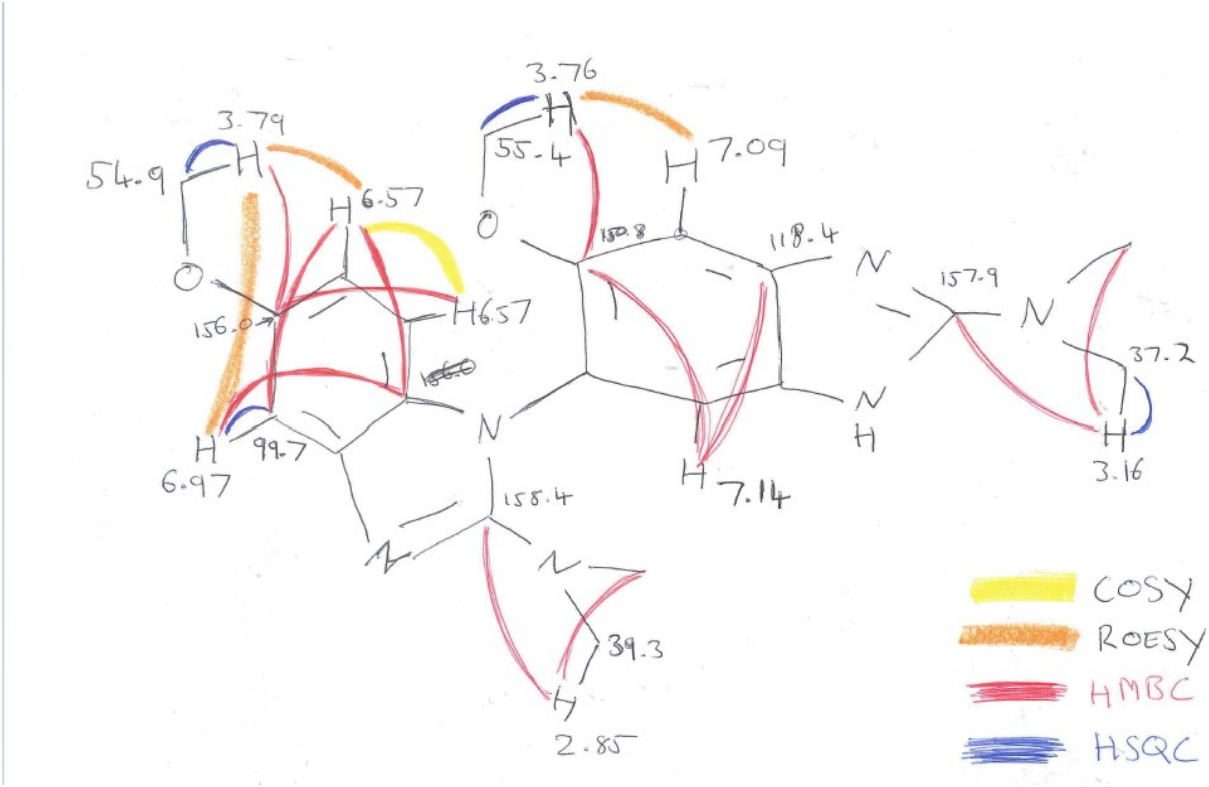
HMBC NMR



HSQC



Interpretation of NMRs



(1) Gross, M.; Held, P.; Schubert, H. *Journal für Praktische Chemie* **1974**, *316*, 434.