

Supporting Information for

Nickel catalyzed alkylation of N-aromatic heterocycles with Grignard reagents through direct C-H bond functionalization

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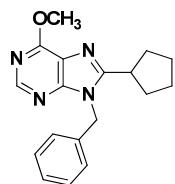
General:

Melting points were recorded with a micro melting point apparatus and uncorrected. NMR spectra were recorded with a 400 NMR spectrometer for ¹H-NMR, 100 MHz for ¹³C-NMR. Proton chemical shifts δ were given in ppm relative to tetramethylsilane (0.00 ppm) in CDCl₃ or to the residual proton signals of the deuterated solvent CD₃OD (3.31 ppm). High resolution mass spectra were taken with a 3000 mass spectrometer, using Waters Q-TofMS/MS system. For column chromatography 200-300 mesh silica gel (GF254) was used as the stationary phase. All reactions were monitored by thin layer chromatography (TLC). All reactions were set up in air (with no use of a glove box) and carried out under nitrogen atmosphere. Ni(dppp)Cl₂ was purchased from commercial source and used as received. 1,2-Dichloroethane and THF were purified using standard methods before used. All other reagents were purchased from commercial sources and used as received.

General procedure for the Ni-catalyzed direct sp² C-H bond alkylation of N-aromatic heterocycles with Grignard reagents. An oven-dried Schlenk tube containing a stirbar was charged with N-aromatic heterocycles (0.125 mmol) and Ni(dppp)Cl₂ (20 mol %). The Schlenk tube was fitted with a rubber cap, evacuated and back-filled with nitrogen (this sequence was repeated an additional two times). Then the 1,2-dichloroethane (0.03 mL, 3 equiv) was added to the tube along with THF (1 mL). The mixture was then stirred at room temperature. The Grignard reagent (8 equiv) was then added drop by drop via syringe and stirred for the corresponding reaction time at room temperature. After completion of the reaction, the mixture was then diluted with brine (3 mL) and extracted with ethyl acetate (3×3 mL). The organic layer was collected and dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (eluting with petroleum ether/ethyl acetate mixtures) to give the desired products.

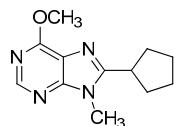
Characterization of compounds

9-benzyl-8-cyclopentyl-6-methoxy-9H-purine (3a)



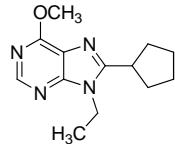
White solid. M.p. 45-47 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.51 (s, 1H), 7.30 (t, $J = 6.4$ Hz, 3H), 7.10 (d, $J = 6$ Hz, 2H), 5.47 (s, 2H), 4.19 (s, 3H), 3.20-3.12 (m, 1H), 2.03-1.96 (m, 2H), 1.94-1.81 (m, 4H), 1.62-1.58 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.0, 159.1, 151.3, 136.0, 128.9, 128.0, 126.6, 54.0, 45.8, 37.5, 32.1, 25.8. HRMS: calcd for $\text{C}_{18}\text{H}_{21}\text{N}_4\text{O} [\text{M}+\text{H}]^+$ 309.1715, found 309.1717.

8-cyclopentyl-6-methoxy-9-methyl-9H-purine (3b)



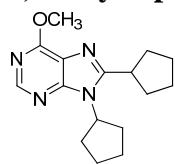
Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 8.43 (s, 1H), 4.11 (2, 3H), 3.75 (s, 3H), 2.39-3.20 (m, 1H), 2.10-1.99 (m, 4H), 1.89-1.80 (m, 2H), 1.71-1.65 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.8, 158.7, 153.6, 150.9, 120.2, 53.9, 37.3, 31.3, 28.8, 25.7. HRMS: calcd for $\text{C}_{12}\text{H}_{17}\text{N}_4\text{O} [\text{M}+\text{H}]^+$ 233.1402, found 233.1406.

8-cyclopentyl-9-ethyl-6-methoxy-9H-purine (3c)



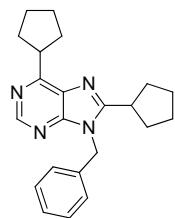
White solid. M.p. 53-55 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.44 (s, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.12 (s, 3H), 3.27-3.19 (m, 1H), 2.10-2.04 (m, 4H), 1.93-1.83 (m, 2H), 1.72-1.65 (m, 2H), 1.41 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.8, 158.3, 153.0, 150.8, 120.5, 53.9, 37.7, 37.2, 32.2, 25.8, 15.5. HRMS: calcd for $\text{C}_{13}\text{H}_{19}\text{N}_4\text{O} [\text{M}+\text{H}]^+$ 247.1559, found 247.1555.

8,9-dicyclopentyl-6-methoxy-9H-purine (3d)



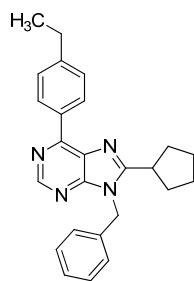
White solid. M.p. 115-116 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1H), 4.77-4.70 (m, 1H), 4.12 (s, 3H), 4.30 (s, 3H), 3.32-3.24 (m, 1H), 2.47-2.40 (m, 2H), 2.10-2.00 (m, 8H), 1.90-1.80 (m, 2H), 1.74-1.66 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.9, 158.5, 153.2, 150.2, 120.9, 56.6, 53.7, 37.8, 31.9, 30.8, 25.8, 24.7. HRMS: calcd for $\text{C}_{16}\text{H}_{23}\text{N}_4\text{O} [\text{M}+\text{H}]^+$ 287.1872, found 287.1873.

9-benzyl-6,8-dicyclopentyl-9H-purine (3e)



White solid. M.p. 61-62 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.83 (s, 1H), 7.29 (q, $J = 7.6$ Hz, 3H), 7.12 (d, $J = 6.8$ Hz, 2H), 5.45 (s, 2H), 4.13 (s, 3H), 3.94-3.85 (m, 1H), 3.21-3.13 (m, 1H), 2.16-2.13 (m, 2H), 2.06-1.83 (m, 10H), 1.77-1.784 (m, 2H), 1.70-1.61 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 164.3, 160.1, 152.3, 151.8, 136.0, 131.6, 128.9, 127.9, 126.7, 45.5, 42.0, 37.7, 32.9, 32.1, 26.4, 25.7. HRMS: calcd for $\text{C}_{22}\text{H}_{27}\text{N}_4 [\text{M}+\text{H}]^+$ 347.2236, found 347.2232.

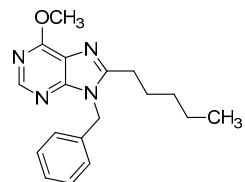
9-benzyl-8-cyclopentyl-6-(4-ethylphenyl)-9H-purine (3f)



White solid. M.p. 175-177 °C. ^1H NMR (400 MHz, CDCl_3) δ 8.95 (s, 1H), 8.82 (d, $J = 8$ Hz, 2H), 7.40 (d, $J = 8.4$ Hz, 2H), 7.32-7.27 (m, 3H), 7.13 (d, $J = 6.8$ Hz, 2H), 5.51 (s, 2H), 3.27-3.19 (m, 1H), 2.74 (q, $J = 7.6$ Hz, 2H), 2.11-2.02 (m, 2H), 1.97-1.90 (m, 4H), 1.71-1.65 (m, 2H), 1.30 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ

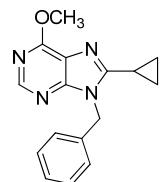
161.1, 154.2, 152.8, 151.6, 147.1, 136.0, 133.6, 130.2, 129.8, 128.9, 128.1, 128.0, 126.7, 45.5, 37.6, 32.1, 29.0, 25.9, 15.4. HRMS: calcd for $C_{25}H_{27}N_4$ [M+H]⁺ 383.2236, found 383.2232.

9-benzyl-6-methoxy-8-pentyl-9*H*-purine (3g)



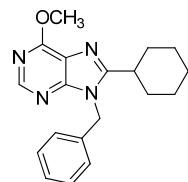
Yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 7.30-7.22 (m, 3H), 7.09 (t, *J* = 6.4 Hz, 2H), 5.40 (s, 2H), 4.15 (s, 3H), 2.72 (t, *J* = 8 Hz, 2H), 1.79-1.71 (m, 2H), 1.32-1.24 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 155.3, 153.4, 151.4, 135.7, 128.9, 128.0, 126.8, 120.4, 54.0, 45.9, 31.5, 27.9, 26.7, 22.3, 13.9. HRMS: calcd for C₁₈H₂₃N₄O [M+H]⁺ 311.1872, found 311.1871.

9-benzyl-8-cyclopropyl-6-methoxy-9*H*-purine (3h)



Light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 7.34-7.30 (m, 3H), 7.19 (d, *J* = 6.4 Hz, 2H), 5.54 (s, 2H), 4.17 (s, 2H), 1.94-1.88 (m, 1H), 1.28-1.24 (m, 2H), 1.04-0.99 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 159.8, 156.7, 151.1, 135.9, 128.9, 128.0, 126.9, 54.0, 45.8, 8.9, 8.2. HRMS: calcd for C₁₆H₁₇N₄O [M+H]⁺ 281.1402, found 281.1405.

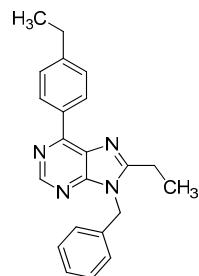
9-benzyl-8-cyclohexyl-6-methoxy-9*H*-purine (3i)



Light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.51 (s, 1H), 7.29 (d, *J* = 7.2 Hz, 3H), 7.11 (d, *J* = 6.4 Hz, 2H), 5.44 (s, 2H), 4.17 (s, 3H), 2.77-2.71 (m, 1H), 1.80-1.63 (m, 10H). ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 159.2, 153.1, 151.3, 136.01, 128.9, 128.0,

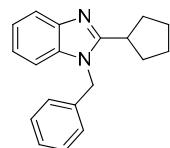
126.7, 120.5, 54.0, 45.8, 36.8, 31.5, 26.1, 25.5. HRMS: calcd for C₁₉H₂₃N₄O [M+H]⁺ 323.1872, found 323.1874.

9-benzyl-8-ethyl-6-(4-ethylphenyl)-9*H*-purine (3j)



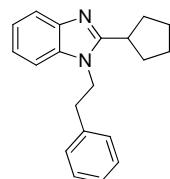
Light yellow solid. M.p. 110-112 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.96 (s, 1H), 8.76 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.36-7.30 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 2H), 5.48 (s, 3H), 2.87 (q, *J* = 7.2 Hz, 2H), 2.74 (q, *J* = 7.6 Hz, 2H), 1.40 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 158.1, 154.0, 153.1, 151.8, 147.2, 135.7, 133.4, 130.3, 129.7, 129.0, 128.2, 128.1, 126.9, 45.6, 29.0, 21.5, 15.4, 11.2. HRMS: calcd for C₂₂H₂₃N₄ [M+H]⁺ 343.1923, found 343.1920.

1-benzyl-2-cyclopentyl-1*H*-benzoimidazole (5a)



White solid. M.p. 82-84 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8 Hz, 1H), 7.30-7.28 (m, 3H), 7.24-7.21 (m, 1H), 7.18-7.17 (m, 2H), 7.03 (d, *J* = 6.4 Hz, 2H), 5.38 (s, 2H), 3.25-3.17 (m, 1H), 2.11-2.02 (m, 4H), 1.93-1.89 (m, 2H), 1.67-1.64 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 142.5, 136.3, 135.5, 128.9, 127.8, 126.0, 122.2, 121.9, 119.3, 109.4, 46.7, 37.3, 32.3, 25.8. HRMS: calcd for C₁₉H₂₁N₂ [M+H]⁺ 277.1705, found 277.1701.

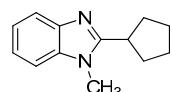
2-cyclopentyl-1-phenethyl-1*H*-benzoimidazole (5b)



Light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.75 (m, 1H), 7.33-7.31 (m, 3H),

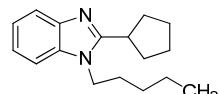
7.27-7.23 (m, 3H), 7.05 (d, $J = 6.4$ Hz, 2H), 4.36 (t, $J = 7.4$ Hz, 2H), 3.09 (t, $J = 7.4$ Hz, 2H), 2.92-2.83 (m, 1H), 1.95-1.85 (m, 6H), 1.67-1.61 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.9, 142.6, 137.8, 134.8, 128.8, 128.7, 127.0, 121.9, 121.8, 119.3, 109.1, 45.1, 36.9, 36.1, 32.3, 25.8. HRMS: calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2$ $[\text{M}+\text{H}]^+$ 291.1861, found 291.1858.

2-cyclopentyl-1-methyl-1*H*-benzoimidazole (**5c**)



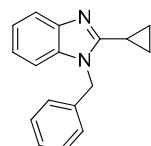
Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.75-7.73 (m, 1H), 7.30-7.28 (m, 1H), 7.24-7.20 (m, 2H), 3.75 (s, 3H), 3.34-3.25 (m, 1H), 2.14-2.04 (m, 4H), 1.95-1.88 (m, 2H), 1.76-1.71 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 158.8, 136.00, 121.9, 121.7, 119.2, 108.7, 37.2, 31.7, 29.7, 25.8. HRMS: calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2$ $[\text{M}+\text{H}]^+$ 201.1392, found 201.1390.

2-cyclopentyl-1-pentyl-1*H*-benzoimidazole (**5d**)



Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.75-7.72 (m, 1H), 7.31-7.28 (m, 1H), 7.23-7.20 (m, 2H), 4.12 (t, $J = 7.6$ Hz, 2H), 3.29-3.20 (m, 1H), 2.13-2.05 (m, 4H), 1.97-1.90 (m, 2H), 1.81 (t, $J = 7.6$ Hz, 2H), 1.74-1.71 (m, 2H), 1.38 (t, $J = 3.6$ Hz, 4H), 0.91 (t, $J = 7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 121.7, 121.6, 119.2, 109.2, 107.0, 43.6, 37.1, 32.6, 29.8, 29.1, 25.9, 22.4, 13.9. HRMS: calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2$ $[\text{M}+\text{H}]^+$ 257.2018, found 257.2016.

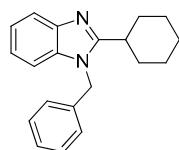
1-benzyl-2-cyclopropyl-1*H*-benzoimidazole (**5e**)



Light yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (d, $J = 8.8$ Hz, 1H), 7.33-7.27 (m,

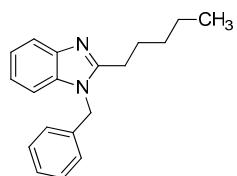
3H), 7.24-7.17 (m, 3H), 7.11 (d, $J = 6.8$ Hz, 2H), 5.45 (s, 2H), 1.96-1.90 (m, 1H), 1.26-1.22 (m, 2H), 1.07-1.02 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 156.7, 142.4, 136.2, 135.7, 128.9, 127.8, 126.3, 122.0, 119.0, 109.1, 46.8, 8.2, 7.7. HRMS: calcd for $\text{C}_{17}\text{H}_{17}\text{N}_2$ $[\text{M}+\text{H}]^+$ 249.1392, found 249.1389.

1-benzyl-2-cyclohexyl-1*H*-benzoimidazole (**5f**)



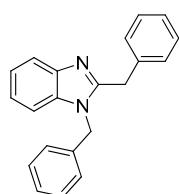
White solid. M.p. 79-81 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.79 (d, $J = 7.6$ Hz, 1H), 7.32-7.28 (m, 3H), 7.25-7.21 (m, 1H), 7.17 (d, $J = 3.6$ Hz, 2H), 7.04 (d, $J = 6.4$ Hz, 2H), 5.36 (s, 2H), 2.83-2.76 (m, 1H), 1.90-1.73 (m, 8H), 1.37-1.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.3, 142.7, 136.3, 135.0, 129.0, 127.8, 126.1, 122.2, 121.9, 119.3, 109.6, 46.7, 36.4, 31.9, 26.3, 25.7. HRMS: calcd for $\text{C}_{20}\text{H}_{23}\text{N}_2$ $[\text{M}+\text{H}]^+$ 291.1861, found 291.1865.

1-benzyl-2-pentyl-1*H*-benzoimidazole (**5g**)



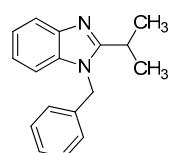
Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.6$ Hz, 1H), 7.31-7.18 (m, 6H), 7.03 (d, $J = 6.4$ Hz, 2H), 5.32 (s, 2H), 2.82 (t, $J = 8$ Hz, 2H), 1.86-1.79 (m, 2H), 1.38-1.29 (m, 4H), 0.86 (t, $J = 7$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.5, 142.6, 136.1, 135.4, 128.9, 127.8, 126.1, 122.2, 121.9, 119.2, 109.4, 46.9, 31.6, 27.6, 27.4, 22.4, 14.0. HRMS: calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2$ $[\text{M}+\text{H}]^+$ 279.1861, found 279.1859.

1,2-dibenzyl-1*H*-benzoimidazole (**5h**)



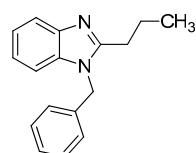
White solid. M.p. 139-141 °C. ^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, $J = 7.6$ Hz, 1H), 7.29-7.20 (m, 11H), 6.93 (d, $J = 3.6$ Hz, 2H), 5.19 (s, 2H), 4.26 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 153.4, 142.6, 136.1, 135.8, 128.9, 128.8, 128.5, 127.8, 127.0, 126.2, 122.6, 122.1, 119.6, 109.6, 47.1, 34.6. HRMS: calcd for $\text{C}_{21}\text{H}_{19}\text{N}_2$ [$\text{M}+\text{H}]^+$ 299.1548, found 299.1544.

1-benzyl-2-isopropyl-1*H*-benzoimidazole (**5i**)



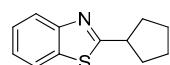
Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.80 (d, $J = 8$ Hz, 1H), 7.32-7.28 (m, 3H), 7.24-7.20 (m, 3H), 7.03 (d, $J = 6.8$ Hz, 2H), 5.38 (s, 2H), 3.19-3.13 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 160.1, 142.5, 136.2, 135.2, 129.0, 127.8, 126.0, 122.3, 122.0, 119.4, 109.5, 46.7, 26.6, 21.7. HRMS: calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2$ [$\text{M}+\text{H}]^+$ 251.1548, found 251.1552.

1-benzyl-2-propyl-1*H*-benzoimidazole (**5j**)



Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 7.6$ Hz, 1H), 7.30-7.18 (m, 6H), 7.04 (d, $J = 6.4$ Hz, 2H), 5.34 (s, 2H), 2.82 (t, $J = 7.6$ Hz, 1H), 1.91-1.82 (m, 2H), 1.01 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 155.3, 142.6, 136.0, 135.3, 129.0, 127.8, 126.1, 122.2, 122.0, 119.2, 109.5, 46.9, 29.5, 21.1, 14.0. HRMS: calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2$ [$\text{M}+\text{H}]^+$ 251.1548, found 251.1550.

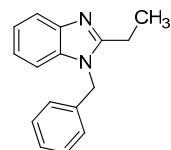
2-cyclopentylbenzothiazole (**7**)



Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ 7.96 (d, $J = 8$ Hz, 1H), 7.84 (d, $J = 8$ Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.33 (t, $J = 7.6$ Hz, 3H), 3.59-3.51 (m, 1H), 2.30-2.23 (m, 2H), 1.99-1.86 (m, 4H), 1.77-1.73 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 177.2,

153.2, 134.8, 125.8, 124.5, 122.5, 121.5, 44.8, 34.1, 25.6. HRMS: calcd for C₁₂H₁₄NS [M+H]⁺ 204.0847, found 204.0849.

1-benzyl-2-ethyl-1*H*-benzoimidazole (5k**)**



Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.32-7.18 (m, 6H), 7.04 (d, *J* = 6.8 Hz, 2H), 5.34 (s, 2H), 2.86 (q, *J* = 7.6 Hz, 2H), 1.41 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 142.4, 135.9, 135.4, 129.0, 127.9, 126.1, 122.3, 122.0, 119.2, 109.4, 46.8, 20.9, 11.7. HRMS: calcd for C₁₆H₁₇N₂ [M+H]⁺ 237.1392, found 237.1389.

Copies of ^1H and ^{13}C NMR spectra

