Supplementary Material (ESI) for Chemical Communications

Supplementary Information for

N-Formylation and Related Reactions of Amines *via* Umpolung of Cyanide Ion Promoted by Esters

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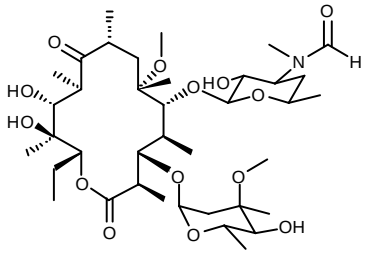
Contents:

General.

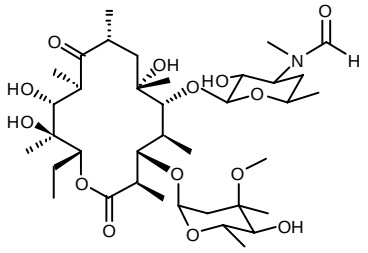
The moisture content of methanol played an important role in the reaction and affected the yield obviously. Methanol was purchased commercially and used as received (the moisture content was 0.1%). Unless otherwise noted, all the materials were obtained from commercially available sources and were used without purification. Thin-layer chromatography was performed on GF254 silica gel plates to monitor the reaction and the plates were examined under UV light or detected with a solution of phosphomolybdic acid in ethanol (5%). The purification of the products was performed using column chromatography (60 Å, 200-300 mesh, Qingdao Ocean Chemicals) or silica gel plates (0.25mm layer, Qingdao Ocean Chemicals) with the designated solvents. Melting points were measured on a hot-stage microscope (X-4, Beijing Taike Ltd.) and are uncorrected. Mass spectra were obtained on a Waters Quattro Micro API or Agilent 1100 series MSD TRAP using ESI. Elemental analyses were conducted at the Analytical Centre, Jilin University, China. ^{1}H and ^{13}C NMR were recorded at 300 or 600 MHz and 75 or 150 MHz respectively on a Bruker ARX-300 and Bruker AVANCE-600 spectrometers with TMS as the internal reference. Chemical shifts were reported in ppm (™) downfield from tetramethylsilane and proton-proton coupling constants (*J*) in Hz.

Typical experimental procedure for the *N*-Formylation and related reactions:



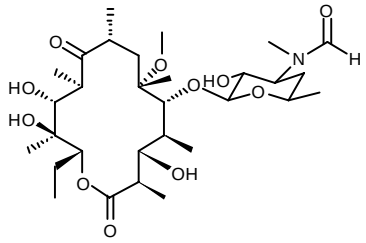
De(*N*-methyl)-*N*-formyl clarithromycin **2a** (known compound, CAS# 127140-69-6)

To a solution of De(N-methyl) erythromycin A (0.15 g, 0.20 mmol) in methanol (10 mL) was added potassuim cyanide (27mg, 0.41 mmol) and dimethyl malonate (7μL, 0.06mmol). The mixture was stirred at 45°C for 4 h and then refluxed. After 48 hours, the reaction was cooled to room temperature and concentrated. Then poured into Brine, and the aqueous phase was extracted with chloroform and dried over Na_2SO_4, evaporated to dryness. The resulting crude product was purified by column chromatography on silica gel eluting with chloroform-methanol-ammonium hydroxide solution (10:0.5:0.01 to 10:1:0.05) to give the title compound (0.12 g, 79%) as a white solid (cis/trans 0.8:1), m.p. 121-123 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12/8.11 (s, 1H), 5.07 (d, 1H, J=11.2, H-13), 4.93 (d, 1H, J=4.2, H-1″), 4.54/4.49 (d, 1H, J=7.3/6.2, H-1′), 4.41 (m, 1H, H-5″), 3.98 (d, 1H, J=13.2, H-3), 3.76/3.71 (s, 3H, 6-OCH_3), 3.34/3.32 (s, 3H, 3″-OCH_3), 2.92/2.83 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) 220.7 (C-9), 175.6/175.5 (C-1), 163.8/163.5 (N-CHO), 103.4/102.8 (C-1′), 96.3/96.1 (C-1″), 82.3 (C-5), 81.9 (C-3), 78.7/78.5 (C-4″), 78.24/78.1 (C-13), 77.8/77.7 (C-6), 74.2 (C-12), 73.0 (C-3″), 71.1 (C-2′), 70.5 (C-11), 69.1 (C-5′), 68.4/68.1 (C-3′), 66.1/66.0 (C-5″), 50.6 (6-OCH_3), 49.5 (3″-OMe), 45.1/45.0 (C-2), 39.2/38.7 (N-Me), 37.3 (C-4), 36.4 (C-7), 35.0/34.9 (C-2″), 31.9 (C-8), 29.7 (C-4′), 25.4 (C-10), 22.7 (6-Me), 21.5/21.5 (5′-Me), 21.1 (3″-Me), 19.7 (C-14), 18.6 (10-Me), 18.0 (5″-Me), 16.1 (2-Me), 15.9 (12-Me), 12.3 (8-Me), 11.0/10.6 (C-15), 9.8/9.6 (4-Me); MS (ESI, m/z) 784.8 [M+Na^+], 800.8 [M+K^+]. Anal. Calcd. for $C_{38}H_{67}NO_{14}$: C,59.90; H, 8.86; N, 1.84. Found: C, 59.76; H, 8.97; N, 1.86. Compounds **2b–2e**, **4a–4f**, were prepared by the same procedure as for **2a**.



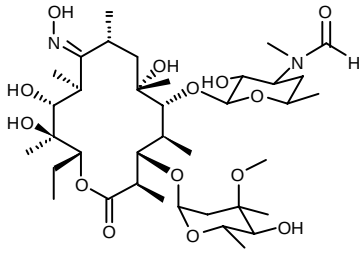
De(*N*-methyl)-*N*-formyl erythromycin A **2b** (known compound, CAS# 127955-44-6)

82% yield; white solid (*cis*/*trans* 0.7:1), m.p. 106-107 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12/8.11 (s, 1H), 5.05 (d, 1H, J=10.9, H-13), 4.88 (s, 1H, H-1″), 4.49/4.44 (d, 1H, J=7.4/6.5, H-1′), 4.22 (m, 1H, H-5″), 3.93 (d, 1H, J=9.5, H-3), 3.31/3.30 (s, 3H, 3″-OCH_3), 2.92/2.83 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) 207.0 (C-9), 175.5 (C-1), 163.8/163.5 (N-CHO), 104.0/103.5 (C-1′), 96.5 (C-1″), 85.5(C-5), 80.2 (C-3), 78.0 (C-4″), 77.8 (C-13), 74.9 (C-6), 74.60 (C-12), 72.8 (C-3″), 71.0 (C-2′), 70.3 (C-11), 69.0 (C-5′), 68.2 (C-3′), 65.8 (C-5″), 49.4 (3″-OMe), 45.0 (C-2), 38.7/38.6 (N-Me), 38.1 (C-4), 36.4 (C-7), 34.9 (C-2″), 31.9 (C-8), 29.7 (C-4′), 26.7 (6-Me), 25.4 (C-10), 23.0 (5′-Me), 21.5 (3″-Me), 21.0 (C-14), 18.5 (10-Me), 18.3 (5″-Me), 16.3 (2-Me), 16.0 (12-Me), 14.1 (8-Me), 10.7 (C-15), 9.8 (4-Me); MS (ESI, m/z) 770.9 [M+Na^+], 786.8 [M+K^+]. Anal. Calcd. for $C_{37}H_{65}NO_{14}$: C,59.42; H, 8.76; N, 1.87. Found: C, 59.35; H, 8.72; N, 1.77.



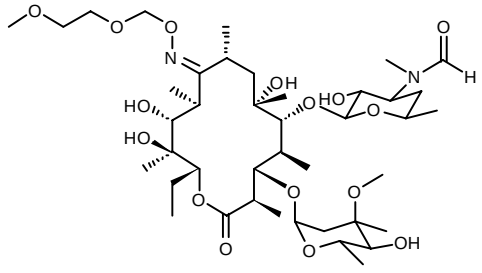
3-Decladinose de(*N*-methyl)-*N*-formyl clarithromycin **2c**

70% yield; white solid (*cis*/*trans* 0.6:1), m.p. 265-267 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.11/8.09 (s, 1H), 5.17 (dd, 1H, J=9.3,1.7, H-13), 4.54/4.50 (d, 1H, J=7.3/7.0, H-1′), 4.43 (m, 1H, H-5″), 3.83/3.75 (s, 3H, 6-OCH_3), 3.26 (s, 3H, 3″-OCH_3), 2.91/2.81 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) 220.5 (C-9), 174.7 (C-1), 164.0/163.6 (N-CHO), 104.7/104.3 (C-1′), 86.1/85.8 (C-5), 78.7 (C-3), 78.7 (C-13), 77.9 (C-6), 77.0 (C-12), 74.2 (C-2′), 70.7 (C-11), 70.0/69.8 (C-5′), 69.2/69.0 (C-3′), 53.0 (6-OCH_3), 49.7 (3″-OMe), 45.5/44.2 (C-2), 38.8/37.5 (N-Me), 36.4 (C-4), 35.6/35.0 (C-7), 30.3 (C-8), 29.7 (C-4′), 25.5 (C-10), 21.4 (6-Me), 21.1 (5′-Me), 20.9/20.9 (C-14), 19.0 (10-Me), 17.9 (2-Me), 16.2 (12-Me), 12.7 (8-Me), 10.5 (C-15), 8.4 (4-Me); MS (ESI, m/z) 626.3 [M+Na^+]. Anal. Calcd. for $C_{30}H_{53}NO_{11}$: C,59.68; H, 8.85; N, 2.32. Found: C, 59.59; H, 8.77; N, 2.37.



De(*N*-methyl)-*N*-formyl-9(E)-oxime erythromycin A **2d**

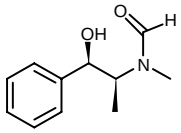
69% yield; white solid (*cis*/*trans* 0.7:1), m.p. 147-149 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12/8.11 (s, 1H), 5.05 (d, 1H, J=21.6, H-13), 4.91 (d, 1H, H-1″), 4.49/4.42 (d, 1H, J=14.5, H-1′), 4.02 (m, 1H, H-5″), 3.94 (d, 1H, J=19.5, H-3), 3.31/3.30 (s, 3H, 3″-OCH_3), 2.92/2.83 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$, 150 MHz) 175.2 (C-1), 171.2 (C-9), 163.9/163.6 (N-CHO), 104.0/103.4 (C-1′), 96.6/96.5 (C-1″), 85.7/85.4 (C-5), 80.8 (C-3), 80.6 (C-4″), 78.00 (C-13), 77.9 (C-13), 77.4/(C-6), 74.4 (C-12), 72.9 (C-3″), 71.1 (C-2′), 70.4 (C-11), 68.6/68.3 (C-5′), 65.6 (C-3′), 65.5 (C-5″), 49.5 (3″-OMe), 44.8 (C-2), 38.6 (N-Me), 37.8 (C-4), 36.4 (C-7), 35.3/35.2 (C-2″), 32.7 (C-8), 29.7 (C-4′), 26.7 (C-10), 25.5/25.4 (6-Me), 21.5 (3″-Me), 21.1 (5′-Me), 21.0 (C-14), 18.7 (10-Me), 18.5/18.5 (5″-Me), 16.4 (2-Me), 16.3 (12-Me), 14.4 (8-Me), 10.7 (C-15), 9.8/9.7 (4-Me); MS (ESI, m/z) 763.3 [M+H^+], 785.3 [M+Na^+], 1547.2 [2M+Na^+]. Anal. Calcd. for $C_{37}H_{66}N_2O_{14}$: C,58.25; H, 8.72; N, 3.67. Found: C, 58.10; H, 8.55; N, 3.53.



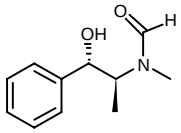
De(*N*-methyl)-*N*-formyl roxithromycin **2e**

65% yield; white solid (*cis*/*trans* 0.6:1), m.p. 99-102 °C; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12/8.10 (s, 1H), 5.19 (s, 2H, $\underline{CH_2}OCH_2CH_2OCH_3$), 5.11 (d, 1H, J=18, H-13), 4.88 (d, 1H, J=9, H-1″), 4.49/4.42 (d,

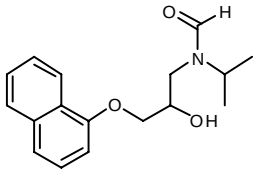
1H, J=14.9/13.3, H-1′), 4.02 (m, 1H, H-5″), 3.90 (d, 1H, J=20.0, H-3), 3.81 (t, 2H, $CH_2O\underline{CH_2}CH_2OCH_3$), 3.73 (m, 2H, $CH_2OCH_2\underline{CH_2}OCH_3$), 3.43 (s, 3H, $CH_2OCH_2CH_2O\underline{CH_3}$), 3.32/3.30 (s, 3H, 3″-$OCH_3$), 2.92/2.83 (s, 3H, N-$CH_3$); ^{13}C NMR ($CDCl_3$, 150 MHz) 175.0/174.9 (C-1), 172.4 (C-9), 163.8/163.5 (N-CHO), 103.8/103.3 (C-1′), 97.5 ($\underline{CH_2}OCH_2CH_2OCH_3$), 96.4/96.3 (C-1″), 85.7/85.6 (C-5), 80.5/80.4 (C-3), 77.9/77.8 (C-4″), 76.9 (C-13), 74.7/74.6 (C-6), 74.3 (C-12), 72.9 (C-3″), 71.9 (C-2′), 71.0 ($CH_2O\underline{C}H_2CH_2OCH_3$), 70.4 (C-11), 68.5 ($CH_2OCH_2\underline{C}H_2OCH_3$), 68.3/68.3 (C-5′), 65.6 (C-3′), 65.4 (C-5″), 59.1/59.1 ($CH_2OCH_2CH_2O\underline{C}H_3$), 49.4 (3″-OMe), 44.8 (C-2), 38.6/37.5 (N-Me), 37.4 (C-4), 36.4 (C-7), 35.2/34.9 (C-2″), 31.9 (C-8), 29.7 (C-4′), 25.4 (C-10), 22.7 (6-Me), 1.5 (3″-Me), 21.2 (5′-Me), 21.0 (C-14), 18.7 (10-Me), 18.5/18.4 (5″-Me),16.2 (2-Me), 14.8 (12-Me), 14.1 (8-Me), 10.6 (C-15), 9.8/9.6 (4-Me); MS (ESI, m/z) 851.9 [$M+H^+$], 873.9 [$M+Na^+$]. Anal. Calcd. for $C_{41}H_{74}N_2O_{16}$: C, 57.86; H, 8.76; N, 3.29. Found: C, 57.80; H, 8.68; N, 3.43.



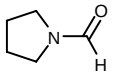
(1R, 2S)-*N*-Formylephedrine **4a** (known compound, CAS# 1630-35-9)
83% yield; pale yellow viscous liquid (*cis*/*trans* 0.6:1); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82/7.66 (s, 1H, -CHO), 7.23-7.33 (m, 5H, ArH), 4.84/4.58 (d, 1H, J=3.5/6.5, -CH(OH)-), 4.26/3.60 (m, 1H, -CH-CH_3), 4.08/3.83 (bs, 1H, -OH), 2.78/2.67 (s, 3H, -NCH_3), 1.32/1.18 (d, 3H, J=6.8/7.1, -CH-CH_3); MS (ESI, m/z) 194.2 [$M+H^+$], 216.2 [$M+Na^+$], 409.3 [$2M+Na^+$],192.2 [$M-H^+$], 228.2 [$M+Cl^-$]. Anal. Calcd. for $C_{11}H_{15}NO_2$: C,68.37; H, 7.82; N, 7.25. Found: C, 68.22; H, 7.91; N, 7.03.



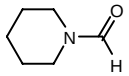
(1 S,2S)-*N*-Formylpseudoephedrine **4b** (known compound, CAS# 55123-97-2)
57% yield; white solid (*cis*/*trans* 0.6:1), m.p. 105-106 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.11/8.05 (s, 1H, -CHO), 7.27-7.36 (m, 5H, -ArH), 4.69/4.60 (d, 1H, J=7.7/8.3, -CH(OH)-), 4.32/3.68 (m, 1H, -CH-CH_3), 2.77 (bs, 1H, -OH), 2.90/2.84 (s, 3H, -NCH_3), 1.16/1.07 (d, 3H, J=4.1/2.9, -CH-CH_3); MS (ESI, m/z) 194.3 [$M+H^+$], 216.3 [$M+Na^+$], 387.3 [$2M+H^+$], 192.0 [$M-H^+$]. Anal. Calcd. for $C_{11}H_{15}NO_2$: C,68.37; H, 7.82; N, 7.25. Found: C, 68.31; H, 8.04; N, 7.33.



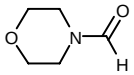
(±)-*N*-formylpropranolol **4c** (known compound, CAS# 77252-87-0)
62% yield; colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.28 (s, 1H, -CHO), 8.21 (dd, 1H, J=6.9, 2.6, -ArH8), 7.81 (dd, 1H, J=6.6, 2.6, -ArH5), 7.47-7.51 (m, 2H, -ArH6, -ArH7), 7.46 (d, 1H, J=9.0, -ArH4), 7.38 (t, 1H, J=7.6, -ArH3), 6.86 (d, 1H, J=7.5, -ArH2), 4.90 (bs, 1H, –OH), 4.28-4.29(m, 1H, -CH_2-$\underline{CH}$(OH)-CH_2-), 4.24 (dd, 1H, J=10.4, 5.4, -O-CH_2-CH(OH)-), 4.07 (dd, 1H, J=9.0, 7.4, -O-CH_2-CH(OH)-), 3.88 (m, 1H, -N-$CH(CH_3)_2$), 3.66 (d, 1H, J=7.0, -CH(OH)-CH_2-N-), 3.61 (dd, 1H, J=15.1, 5.1, -CH(OH)-CH_2-N-), 1.34 (d, 3H, J=6.7, -$CH(CH_3)_2$), 1.27 (d, 3H, J=7.1, -$CH(CH_3)_2$); MS (ESI, m/z) 322.1 [$M+Cl^-$]. Anal. Calcd. for $C_{17}H_{21}NO_3$: C,71.06; H, 7.37; N, 4.87. Found: C, 71.02; H, 7.15; N, 4.78.



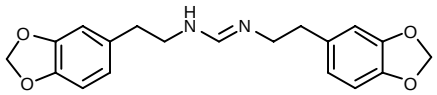
N-Formylpyrrolidine **4d** (known compound, CAS# 3760-54-1)
60% yield; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27(1 H, s, -CHO), 3.49 (t, 2H, J=8.5, -N-CH_2-), 3.43 (t, 2 H, J=6.3, -NCH_2-), 1.88-1.95 (m, 4H, -CH_2-CH_2-); MS (ESI, m/z) 100.3 [M+H^+], 122.3 [M+Na^+].



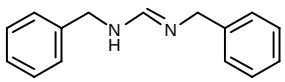
N-Formylpiperidine **4e** (known compound, CAS# 2591-86-8)
66% yield; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01(1 H, s, -CHO), 3.48 (t, 2 H, J=5.7, -NCH_2-), 3.31 (t, 2 H, J=5.4, -NCH_2-), 1.65-1.69 (m, 2H, -CH2-), 1.52-1.60 (m, 4H, -CH_2-CH_2-); MS (ESI, m/z) 114.3 [M+H^+], 136.3 [M+Na^+].



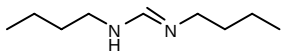
N-Formylmorpholine **4f** (known compound, CAS# 4394-85-8)
55% yield; white solid, m.p. 21-23 °C (lit.,[1] 20–21 °C); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.07 (s, 1H, -CHO), 3.69/3.67 (t, 2H, J=4.9/4.7, -CH_2-O-), 3.59/3.40 (t, 2H, J=5.0, -CH_2-N-); MS (ESI, m/z) 116.3 [M+H^+], 138.3 [M+Na^+], 154.2 [M+K^+].



(*E*)-*N*,*N*'-Bis(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)formamidine **6a**
Typical procedure: To a solution of 2-(3,4-Methylenedioxyphen)ethylamine (0.81 mL, 6.09 mmol) in methanol (50 mL), potassuim cyanide (0.79g, 12.18 mmol) and dimethyl malonate (0.21mL, 1.83mmol) were added. The mixture was stirred at 45°C for 4 h and then refluxed for 48 h. After the mixture was cooled to room temperature and concentrated to dryness, the residual solid was washed with ethyl acetate (3×25mL), and the combined extracts were dried (Na_2SO_4), filtered, and evaporated in *vacuo*. Recrystallization from methanol gave 0.58 g (56% yield) of the title compound as a white solid. m.p. 149-150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.59-6.75 (m, 6H, -ArH), 5.94/5.93 (s, 2H, -OCH_2-O-), 3.37 (t, 2H, J=6.7, -CH_2-N-), 2.76 (t, 2H, J=6.7, -CH_2-Ar); ^{13}C NMR ($CDCl_3$, 75 MHz) 161.1(-NH-CH=N-), 147.8, 147.6, 146.4, 146.1, 131.7, 131.2, 122.1, 121.6, 109.2, 109.0, 108.4, 108.2, 101.0 (-OCH_2-O-), 100.8 (-OCH_2-O-), 39.7, 39.3, 36.3, 35.2; MS (ESI, m/z) 341.3 [M+H^+], 339.1 [M-H^+], 375.0 [M+Cl^-]. Anal. Calcd. for $C_{19}H_{20}N_2O_4$: C,67.05; H, 5.92; N, 8.23. Found: C, 66.91; H, 5.94; N, 8.16. Compounds **6b–6e** were prepared by the same procedure as for **6a**.

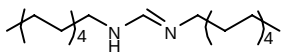


(*E*)-*N*,*N*'-Dibenzylformamidine **6b** (known compound, CAS# 4636-51-5)
70% yield; white solid, m.p. 135-137 °C (lit.,[2] 136–137 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (s, 1H, -N=CH-), 7.23-7.35 (m, 10H, -Ar), 4.43 (s, 4H, -CH_2-Ar); MS (ESI, m/z) 225.3 [M+H^+].

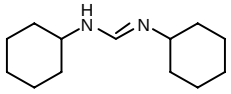


(*E*)-*N*,*N*'-Dibutylformamidine **6c** (known compound, CAS# 2303-94-8)
77% yield; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (s, 1H, -N=CH-), 3.21-3.28 (m, 4H, -CH_2-N-), 1.29-1.41, 1.45-1.55 (m, 8H, -CH_2-), 0.92 (t, 6H, J=7.2, -CH_3);

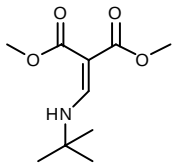
MS (ESI, m/z) 157.3 [M+H$^+$]. Anal. Calcd. for $C_9H_{20}N_2$: C,69.17; H, 12.90; N, 17.93. Found: C, 69.05; H, 12.98; N, 17.91.



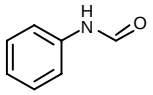
(*E*)-*N*,*N*'-Didecylformamidine **6d** (known compound, CAS# 31815-45-9)
81% yield; white solid, m.p. 48-49 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 1H, -N=CH-), 3.16 (t, 4H, J=6.8, -CH_2-N-), 1.51(t, 4H, -$\underline{CH_2}$-CH_2-N-), 1.26 (m, 28H, -CH_2-), 0.88 (t, 6H, J=6.0, -CH_3); MS (ESI, m/z) 325.5 [M+H$^+$]. Anal. Calcd. for $C_{21}H_{44}N_2$: C,77.71; H, 13.66; N, 8.63. Found: C, 77.74; H, 13.63; N, 8.62.



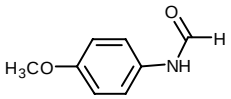
(*E*)-*N*,*N*'-Dicyclohexylformamidine **6e** (known compound, CAS# 2303-89-1)
75% yield; white solid, m.p. 99-101°C (lit.,[3] 102–104 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (s, 1H, -N=CH-), 3.02 (bs, 2H, -CH-N-), 1.17-1.80 (m, 20H, -CH_2-); MS (ESI, m/z) 209.3 [M+H$^+$]. Anal. Calcd. for $C_{13}H_{24}N_2$: C,74.94; H, 11.61; N, 13.45. Found: C, 74.97; H, 11.68; N, 13.41.



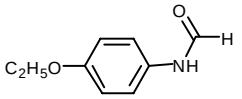
Dimethyl 2-((*tert*-butylamino)methylene)malonate **6f** (known compound, CAS# 73619-78-0)
Potassuim cyanide (78 mg, 1.2 mmol) and dimethyl malonate (21μL, 0.18mmol) were added to a solution of *t*-Butylamine (63 μL, 0.6 mmol) in methanol (10 mL) and the mixture was stirred at 45°C for 4 h and refluxed for 48 h. Then the mixture was cooled to room temperature, and concentrated to dryness. The residual solid was washed with ethyl acetate (3×20mL), and then the combined extracts were dried (Na_2SO_4), filtered, and evaporated in *vacuo*. The crude product was purified by preparative thin layer chromatography (3:1 Petroleum: EtOAc) to yield title compound as a white solid (57 mg, 44% yield). m.p. 47-50°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, 1H, J=14.7, -C=CH-N-), 3.79/3.73 (s, 6H, -OCH_3), 1.36 (s, 9H, -$C(CH_3)_3$); MS (ESI, m/z) 216.3 [M+H$^+$], 238.3 [M+Na$^+$], 254.3[M+K$^+$]. Anal. Calcd. for $C_{10}H_{17}NO_4$: C,55.80; H, 7.96; N, 6.51. Found: C, 55.72; H, 7.92; N, 6.54.



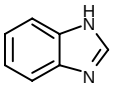
N-Phenylformamide **8a** (cis/trans 1:0.9) (known compound, CAS# 103-70-8)
Potassuim cyanide (0.78 g, 12 mmol) and dimethyl malonate (0.21mL, 1.8mmol) were added to a solution of aniline (0.55 mL, 6 mmol) in methanol (50 mL) and the mixture was stirred at 45°C for 4 h and then refluxed for 48 h. After the disappearance of aniline (monitored by TLC), H_2O (8 mL) was added and stirred 3 h at room temperature, and then the reaction was concentrated and poured into Brine, and the aqueous phase was extracted with ethyl acetate and dried over Na_2SO_4, evaporated to dryness. Purification by flash chromatography over silica gel (20:1, Petroleum: EtOAc) gave *N*-phenylformamide as a pale brownish solid (0.48 g, 66% yield), m.p. 46 °C (lit.,[4] 45–47 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.70(d, 1H, J=11.4, -CHO *cis*), 8.39 (s, 1H, -CHO, *trans*), 8.10(1H, -NH-, *cis*), 7.54 (d, 2H, J=7.8, *o*-H, *trans*), 7.31-7.39 (m, 4H, *m*-H), 7.09 (d, 2H, J=7.7, *o*-H, *cis*), 7.14-7.22 (m, 2H, *p*-H); MS (ESI, m/z) 122.3 [M+H$^+$], 144.3 [M+Na$^+$], 120.1 [M-H$^+$]. Compounds **8b–8d** were prepared by the same procedure as for **8a**.



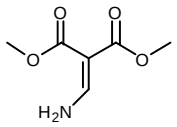
N-(4-Methoxyphenyl)formamide **8b** (cis/trans 1:0.9) (known compound, CAS# 5470-34-8)
82% yield; pale brownish solid, m.p.79-81 °C (lit.,[5] 80–81 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49(d, 1H, J=11.6, -CHO *cis*), 8.34 (s, 1H, -CHO, *trans*), 7.45 (d, 2H, J=8.9, *o*-H, *trans*), 7.03 (d, 2H, J=8.8, *o*-H, *cis*), 6.86-6.91 (m, 4H, *m*-H), 3.80/3.81 (s, 6H, -OCH_3); MS (ESI, m/z) 152.3 [M+H^+], 174.2 [M+Na^+].



N-(4-Ethoxyphenyl)formamide **8c** (cis/trans 1:0.9) (known compound, CAS# 61587-14-2)
85% yield; pale brownish solid, m.p. 56-57 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51(d, 1H, J=11.3, -CHO *cis*), 8.31 (s, 1H, -CHO, *trans*), 8.26 (bs,1H, -NH-, *cis*), 7.53 (bs,1H, -NH, *trans*), 7.43 (d, 2H, J=8.9, *o*-H, *trans*), 7.03 (d, 2H, J=8.8, *o*-H, *cis*), 6.83-6.89 (m, 4H, *m*-H), 3.97-4.05 (m, 4H, -OCH_2-), 1.37-1.44 (m, 6H, -CH_2-$\underline{CH_3}$); MS (ESI, m/z) 166.3 [M+H^+], 188.2 [M+Na^+], 164.0 [M-H^+]. Anal. Calcd. for $C_9H_{11}NO_2$: C,65.44; H, 6.71; N, 8.48. Found: C, 65.26; H, 6.66; N, 8.32.



Benzimidazole **8d** (known compound, CAS# 51-17-2)
78% yield; white solid, m.p. 172-173 °C (lit.,[6] 171 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1H, -N=CH-NH-), 7.69 (d, 1H, J=5.7), 7.68 (d, 1H, J=5.6), 7.31(dd, 2H, J=6.0, 3.0); MS (ESI, m/z) 119.3 [M+H^+], 141.2 [M+Na^+], 117.1 [M-H^+], 153.0 [M+Cl^-].



Dimethyl 2-(aminomethylene)malonate **8e** (known compound, CAS# 72179-93-2)
To a solution of dimethyl malonate (44 μL, 0.38mmol) in methanol (10 mL), potassuim cyanide (49 mg, 0.76 mmol) was added. The mixture was stirred at 45°C for 3 h and then cooled to room temperature, concentrated to dryness. The residual solid was washed with ethyl acetate (3×20mL), and then the combined extracts were dried (Na_2SO_4), filtered, and evaporated to give amide as a pale yellow oil (52 mg, 86% yield); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 (dd, 1H, J=15.6,8.4, -C=CH-NH_2), 7.23-7.35 (m, 10H, -Ar), 4.44 (s, 4H, -CH_2-Ar); MS (ESI, m/z) 182.2 [M+Na^+], 341.2 [2M+Na^+]. Anal. Calcd. for $C_6H_9NO_4$: C,45.28; H, 5.70; N, 8.80. Found: C, 45.35; H, 5.61; N, 8.56.

References for melting points

1) G. B. L. Smith, M. Silver and E. I. Becker, *J. Am. Chem. Soc.* **1948**, *70*, 4254-4254.
2) C. Kashima, M. Shimizu, T. Eto and Y. Omote, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3317-3319.
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5) L. D. Nunno and A. Scilimati, *Tetrahedron* **1986**, *42*, 3913-3920.
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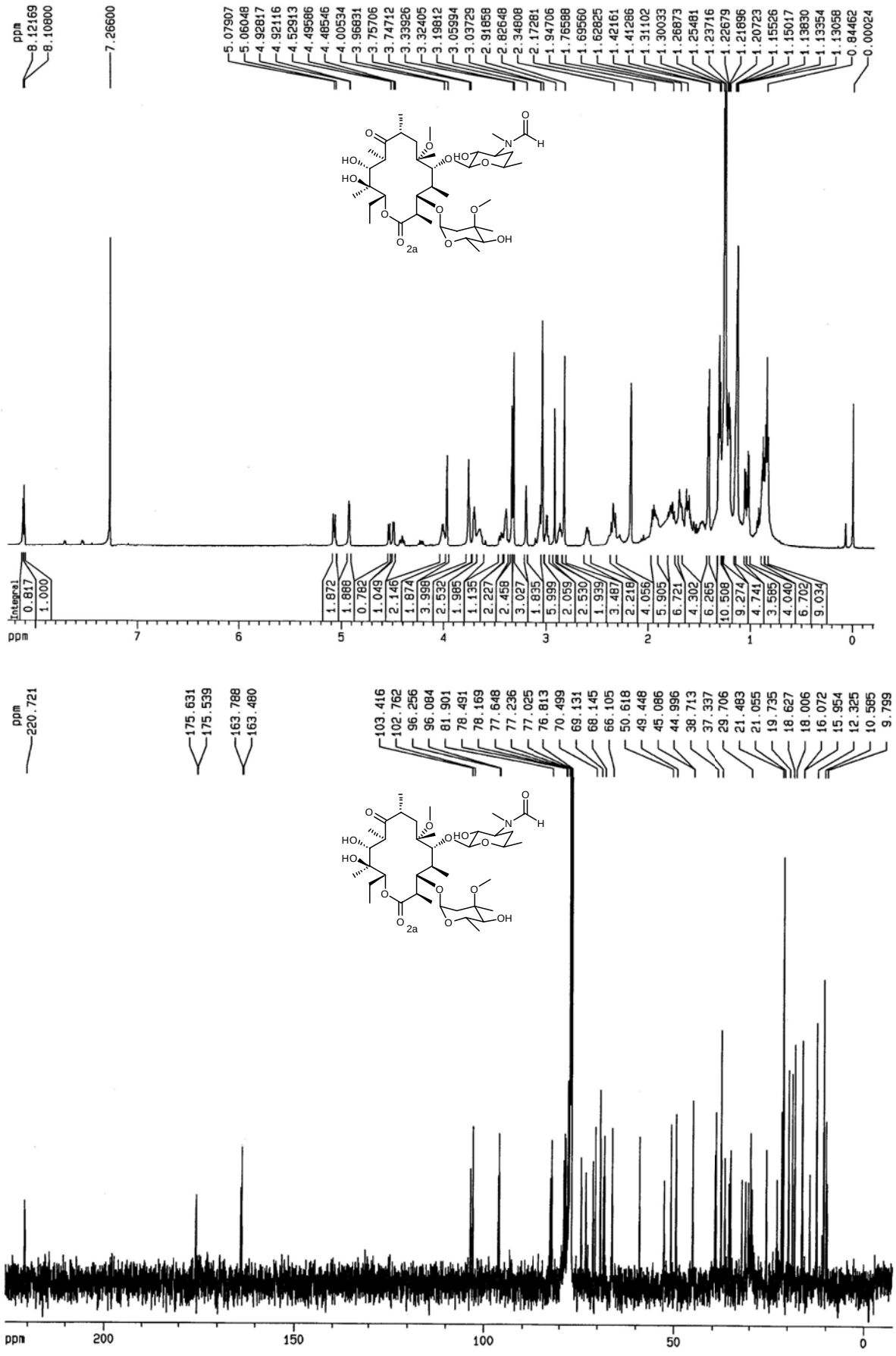
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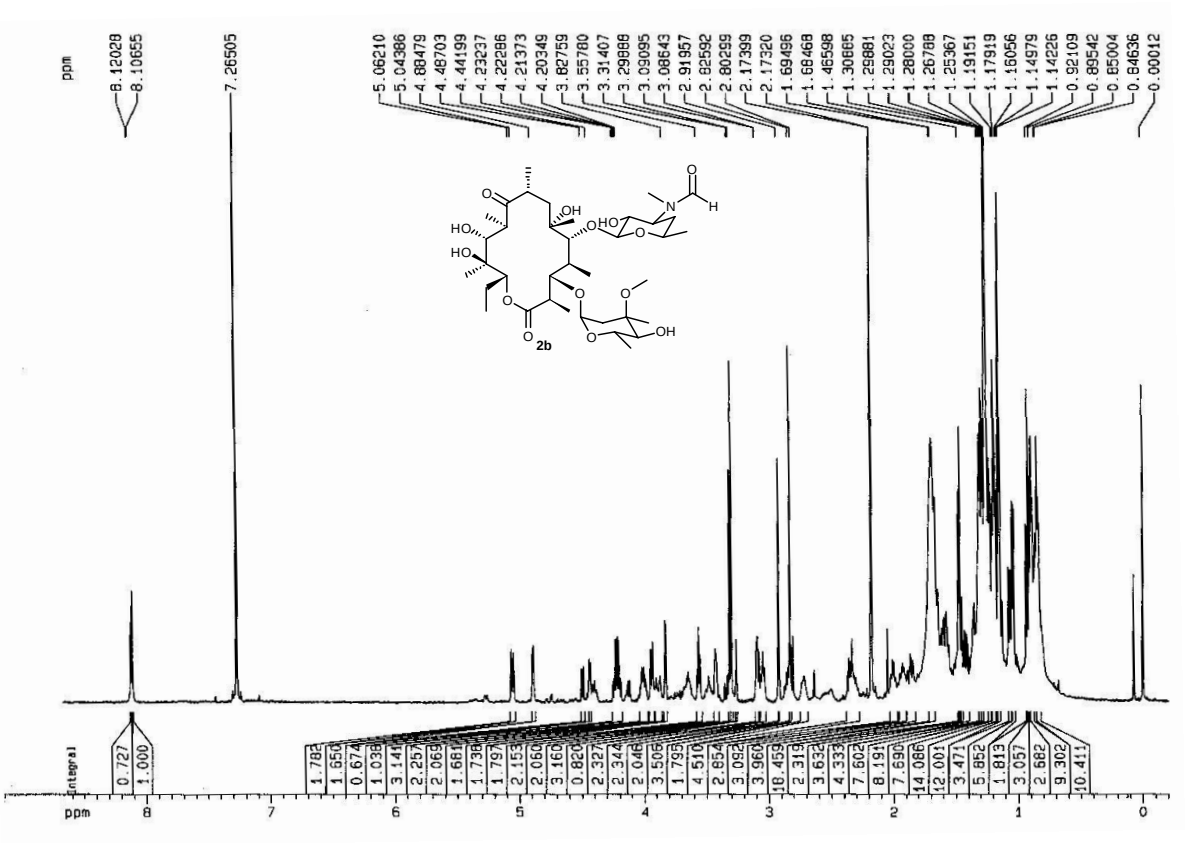
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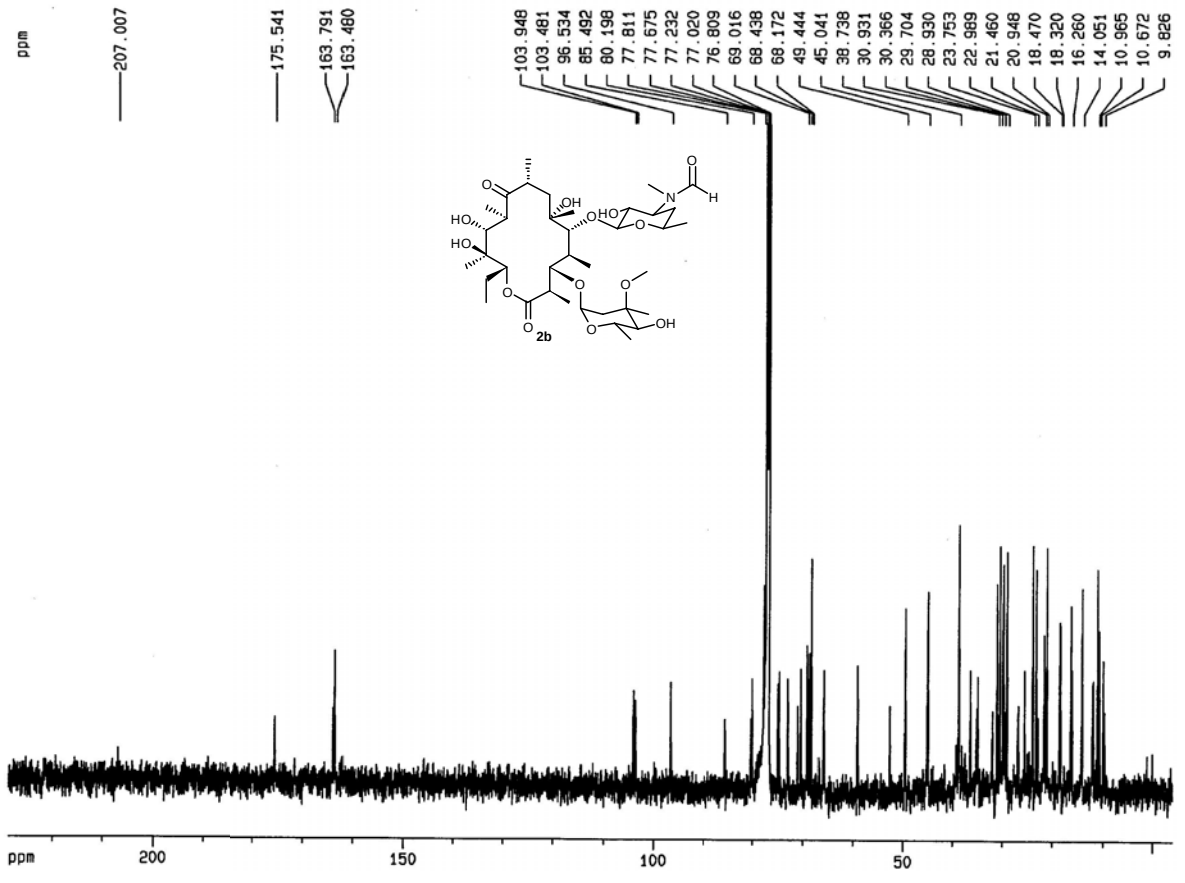
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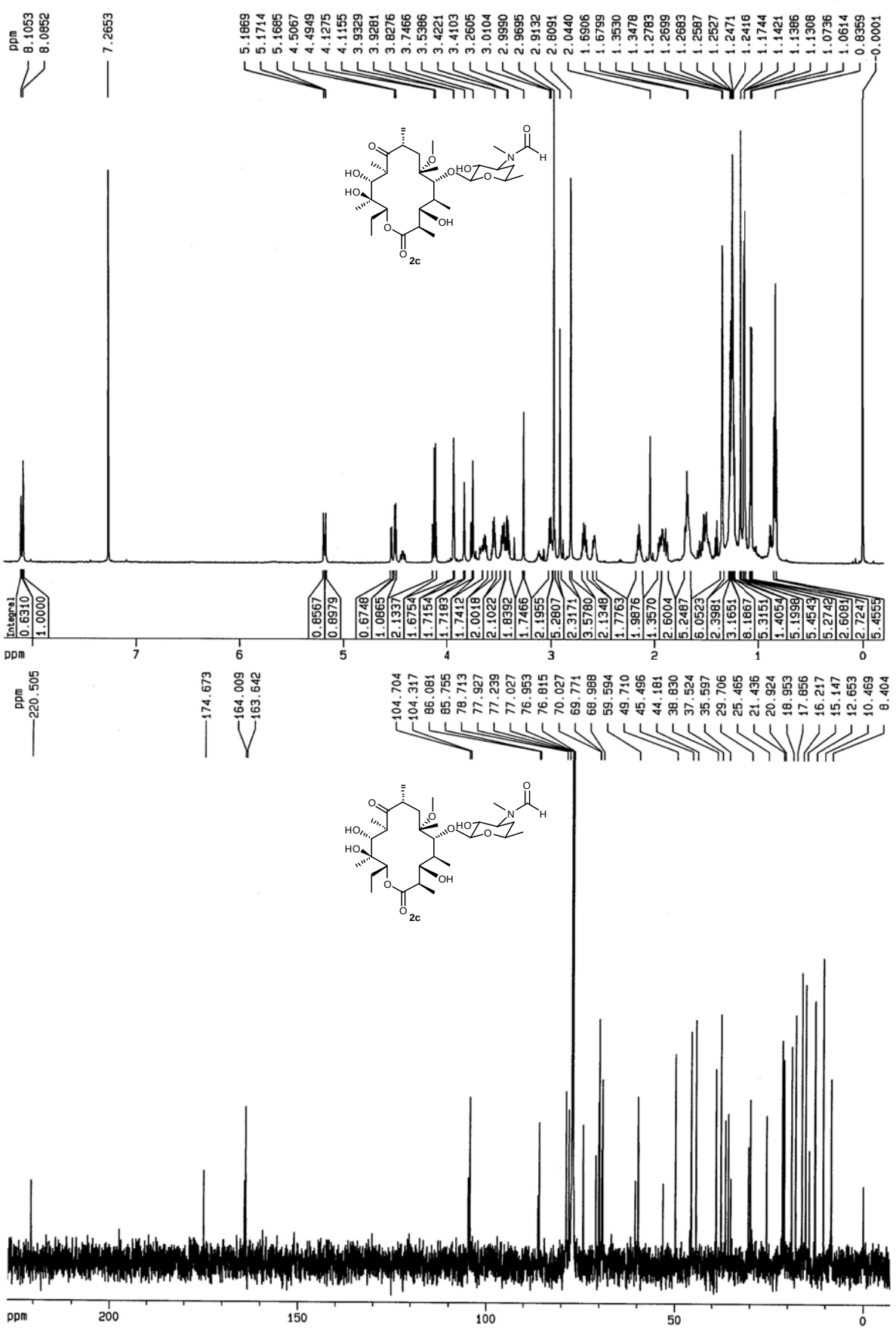
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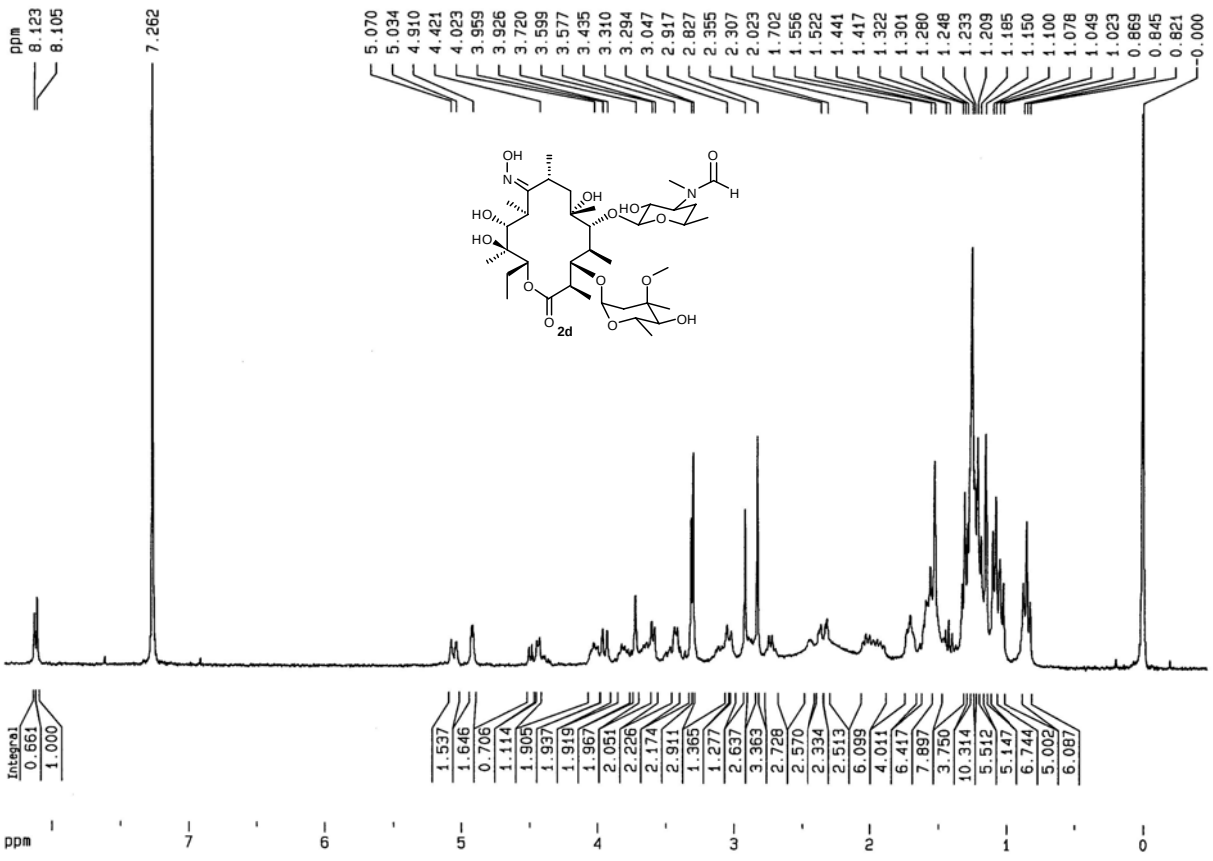
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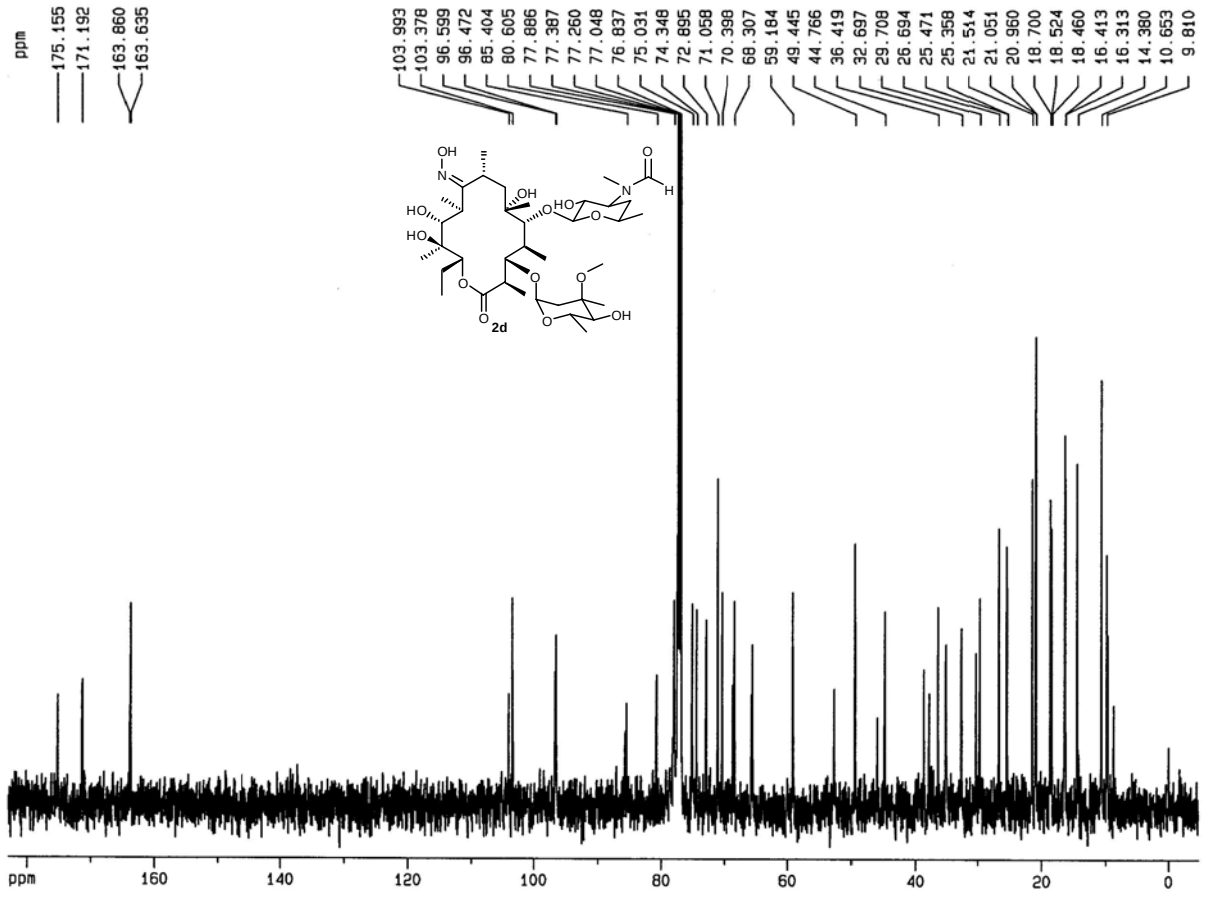
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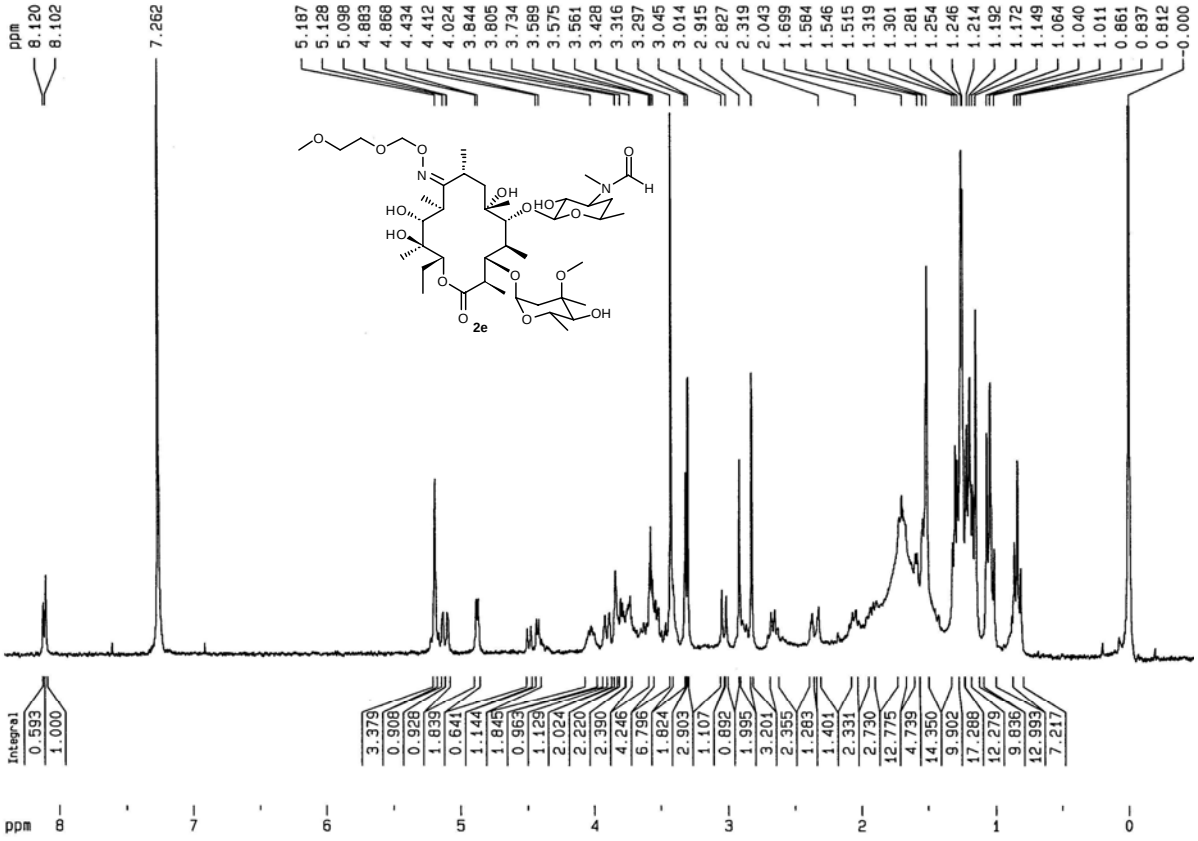
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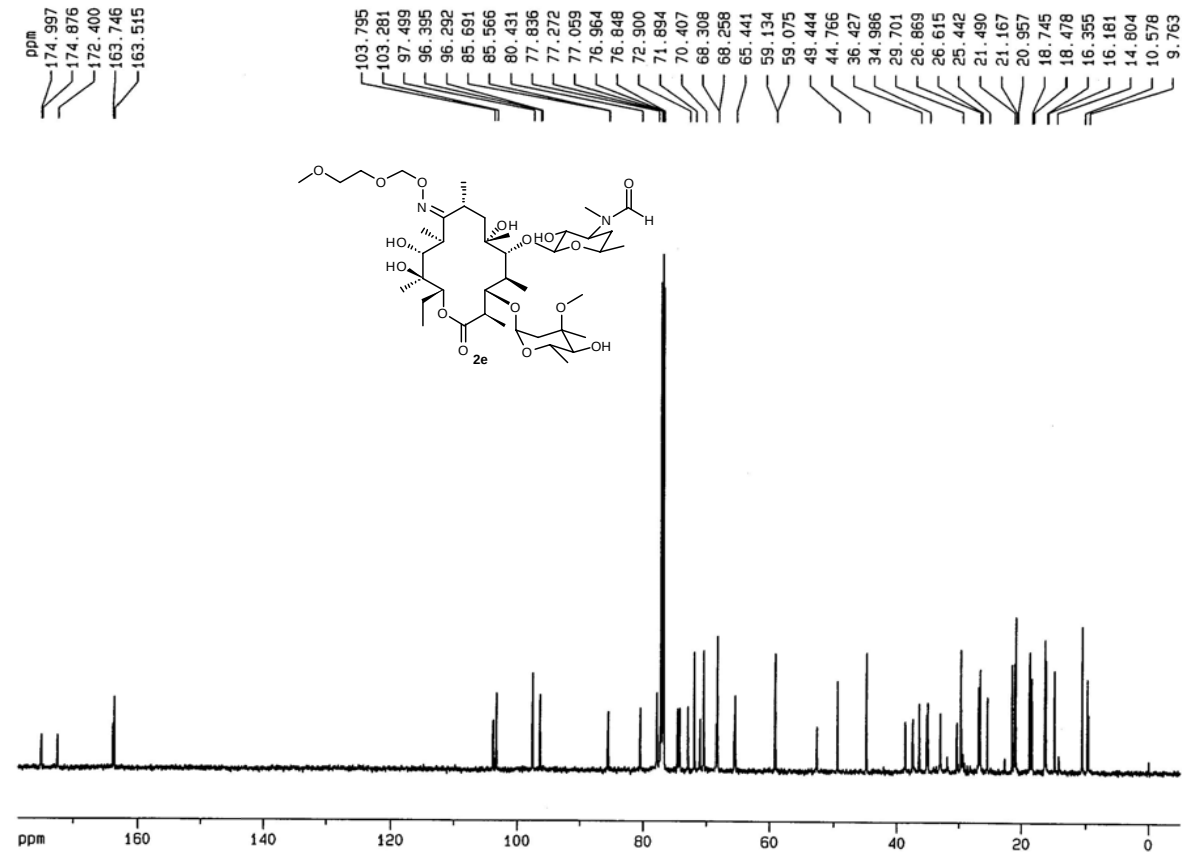
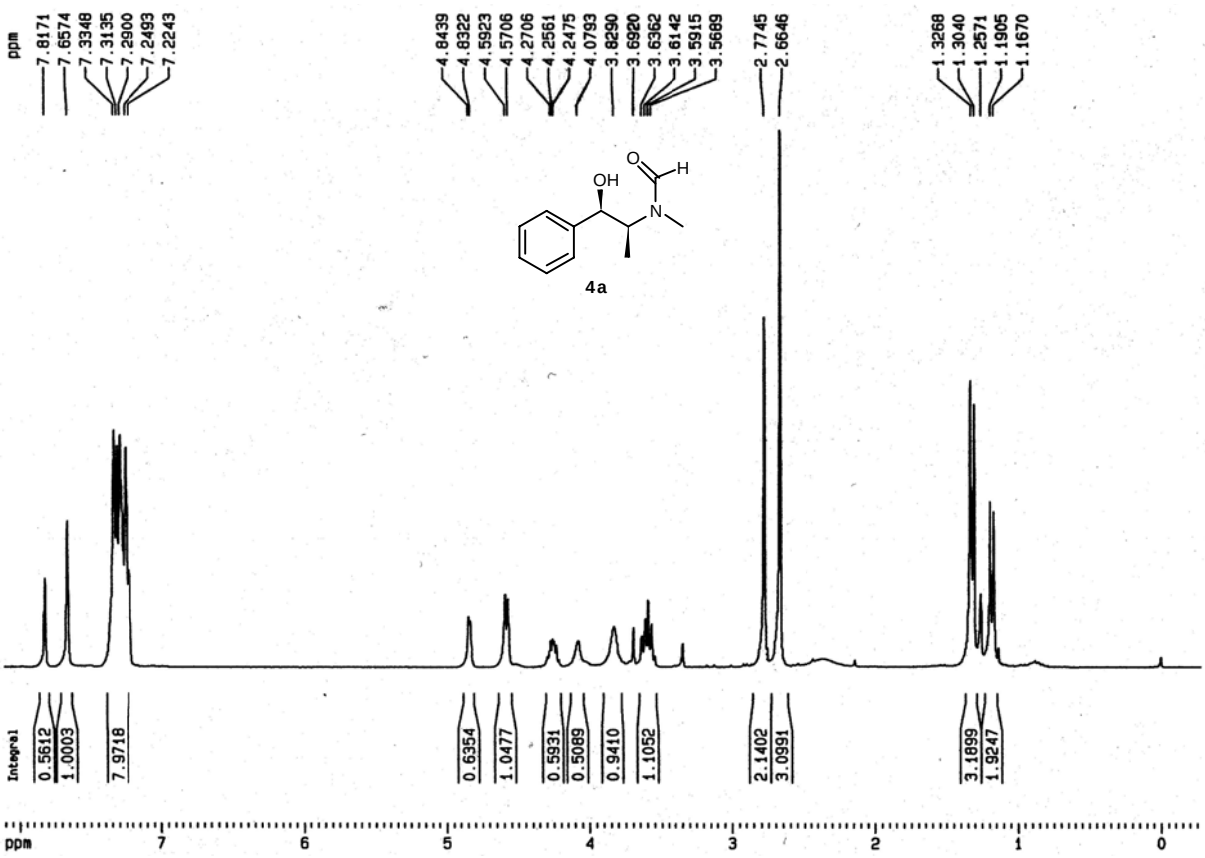
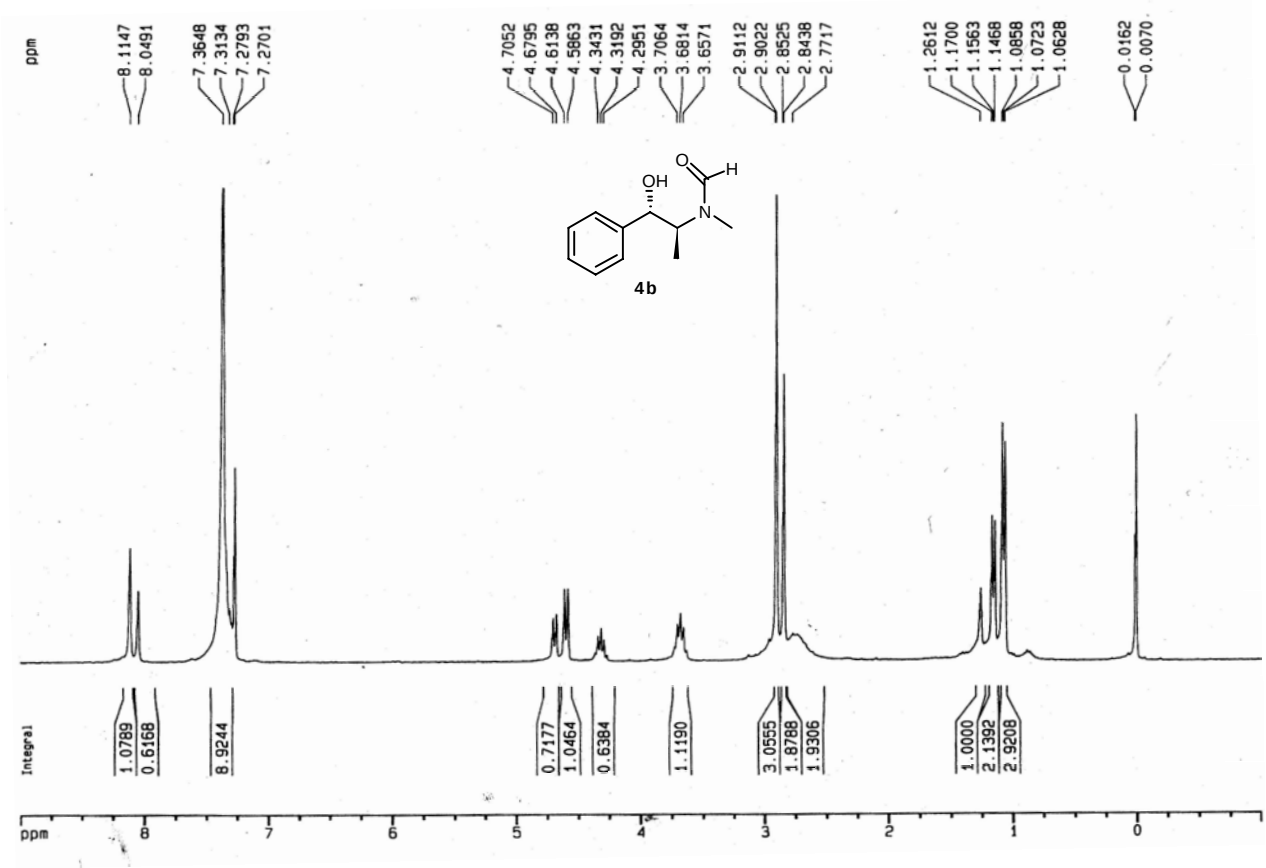
1.319
1.301
1.281
1.254
1.246
1.214
1.192
1.172
1.149
1.064
1.040
1.011
0.861
0.837
0.812
0.000
2e
Integral
0.593
1.000
3.379
0.908
0.928
1.839
0.641
1.144
1.845
0.963
1.129
2.024
2.220
2.390
4.246
6.796
1.824
2.903
1.107
0.892
1.995
3.201
2.355
1.283
1.401
2.331
2.730
12.775
4.739
14.350
9.902
17.288
12.279
9.836
12.993
7.217
ppm
8
7
6
5
4
3
2
1
0


ppm
174.997
174.876
172.400
163.746
163.515
103.795
103.281
97.499
96.395
96.292
85.691
85.566
80.431
77.836
77.272
77.059
76.964
76.848
72.900
71.894
70.407
68.308
68.258
65.441
59.134
59.075
49.444
44.766
36.427
34.986
29.701
26.869
26.615
25.442
21.490
21.167
20.957
18.745
18.478
16.355
16.181
14.804
10.578
9.763
2e
ppm
160
140
120
100
80
60
40
20
0


ppm
7.8171
7.6574
7.3348
7.3135
7.2900
7.2493
7.2243
4.8439
4.8322
4.5923
4.5706
4.2706
4.2561
4.2475
4.0793
3.8290
3.6920
3.6362
3.6142
3.5915
3.5689
2.7745
2.6646
1.3268
1.3040
1.2571
1.1905
1.1670
OH
O
H
N
4a
Integral
0.5612
1.0003
7.9718
0.6354
1.0477
0.5931
0.5089
0.9410
1.1052
2.1402
3.0991
3.1899
1.9247
ppm
7
6
5
4
3
2
1
0


ppm
8.1147
8.0491
7.3648
7.3134
7.2793
7.2701
4.7052
4.6795
4.6138
4.5863
4.3431
4.3192
4.2951
3.7064
3.6814
3.6571
2.9112
2.9022
2.8525
2.8438
2.7717
1.2612
1.1700
1.1563
1.1468
1.0858
1.0723
1.0628
0.0162
0.0070
OH
O
H
N
4b
Integral
1.0789
0.6168
8.9244
0.7177
1.0464
0.6384
1.1190
3.0555
1.8788
1.9306
1.0000
2.1392
2.9208
ppm
8
7
6
5
4
3
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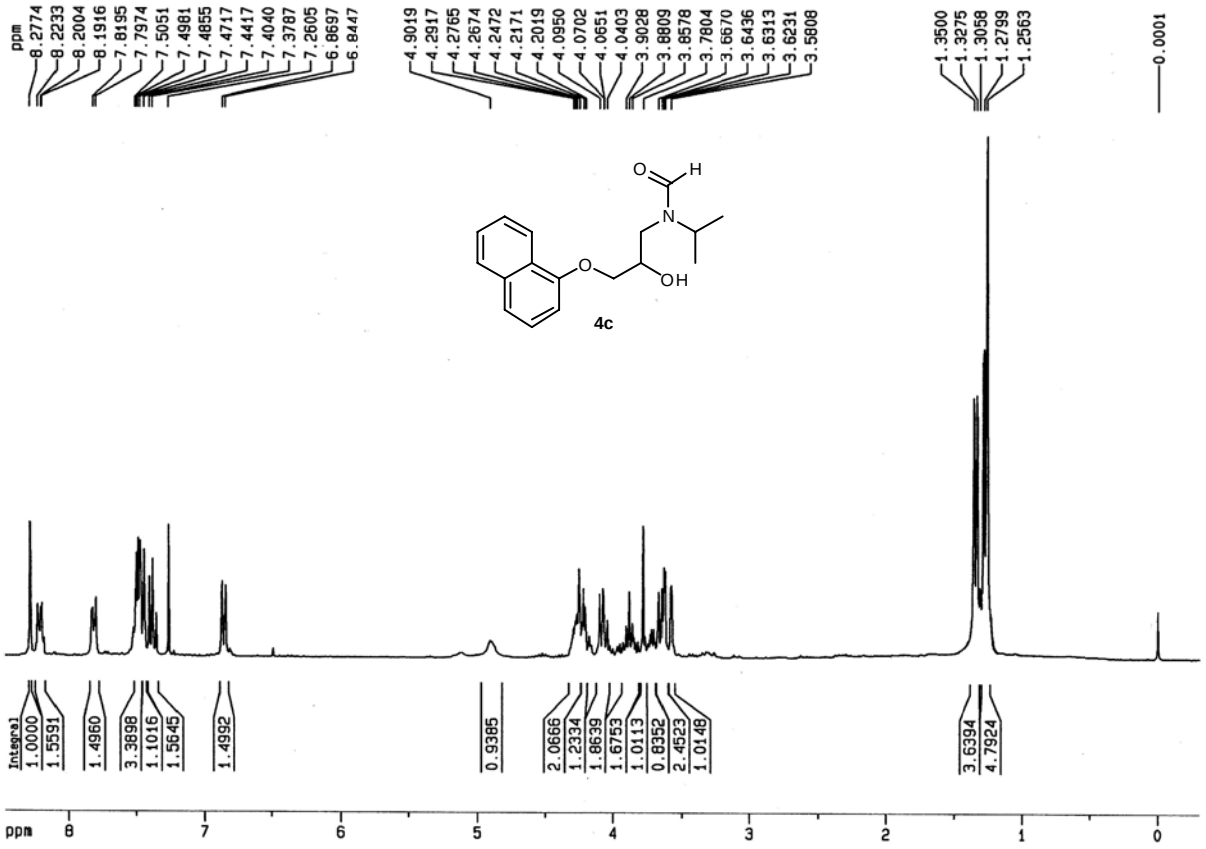
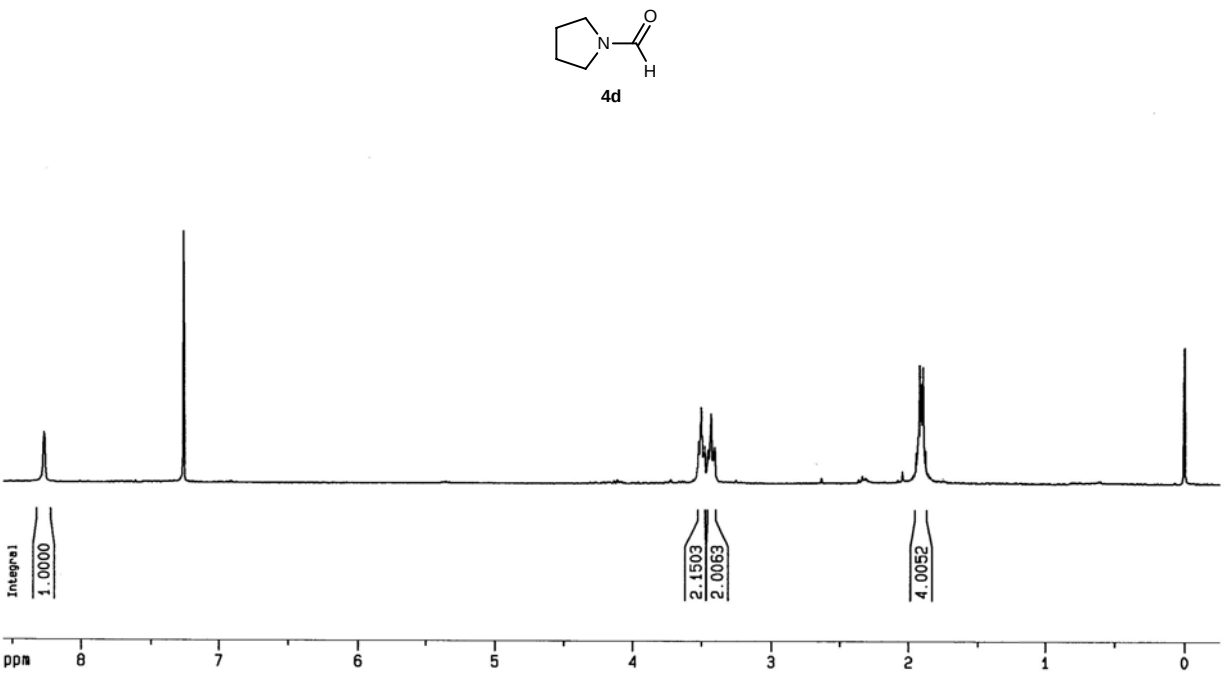
1
0

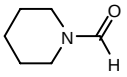

ppm
8.2774
8.2233
8.2004
8.1916
8.1695
7.7974
7.5051
7.4981
7.4855
7.4717
7.4417
7.4040
7.3787
7.2605
6.8697
6.8447
4.9019
4.2917
4.2765
4.2674
4.2472
4.2171
4.2019
4.0950
4.0702
4.0651
4.0403
3.9028
3.8809
3.8578
3.7804
3.6670
3.6436
3.6313
3.6231
3.5808
1.3500
1.3275
1.3058
1.2799
1.2563
0.0001
Integral
1.0000
1.5591
1.4960
3.3898
1.1016
1.5645
1.4992
0.9385
2.0666
1.2334
1.8639
1.6753
1.0113
0.8352
2.4523
1.0148
3.6394
4.7924
ppm

4c

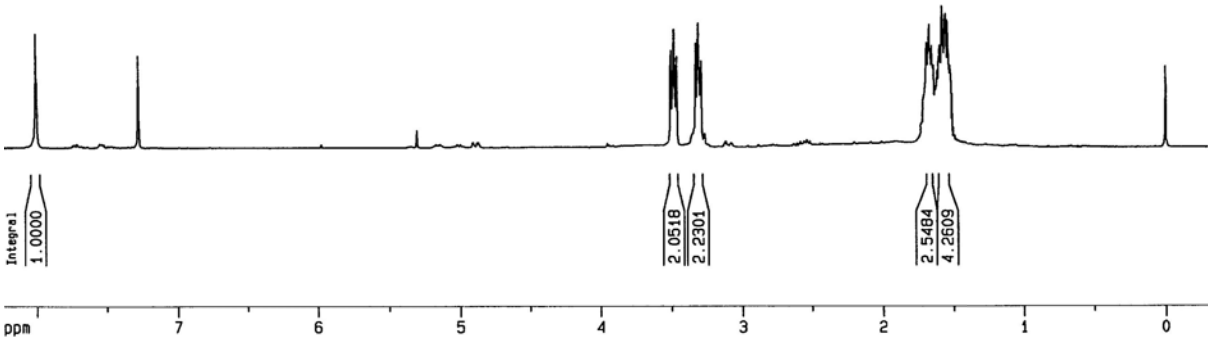

ppm
8.2690
7.2644
3.5194
3.4911
3.4764
3.4507
3.4296
3.4069
1.9472
1.9245
1.9132
1.9019
1.8805
0.0002
Integral
1.0000
2.1503
2.0063
4.0052
ppm

4d


ppm
8.005
7.281
3.503
3.484
3.465
3.326
3.308
3.290
1.692
1.672
1.656
1.647
1.620
1.599
1.581
1.560
1.542
1.523
0.000



4e


Integral
1.0000
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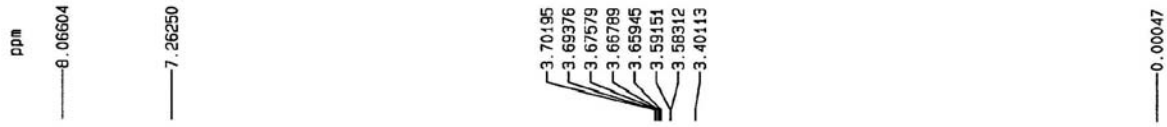
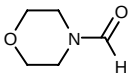
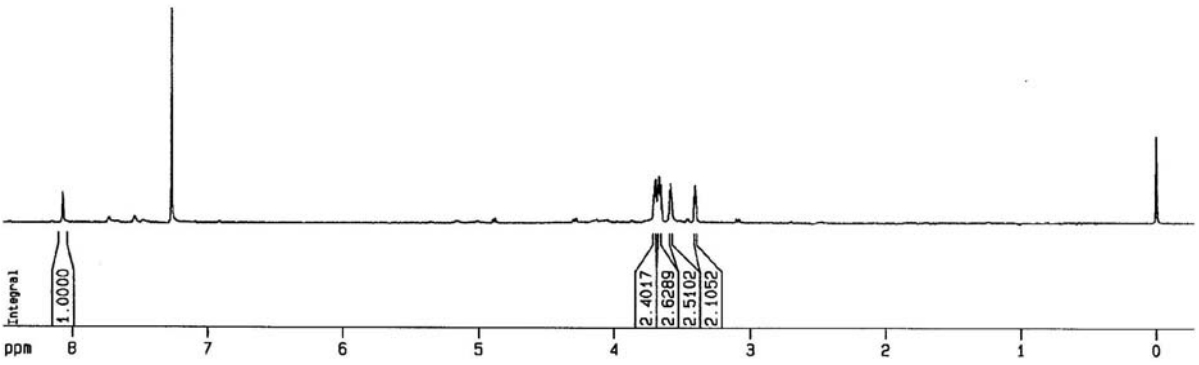
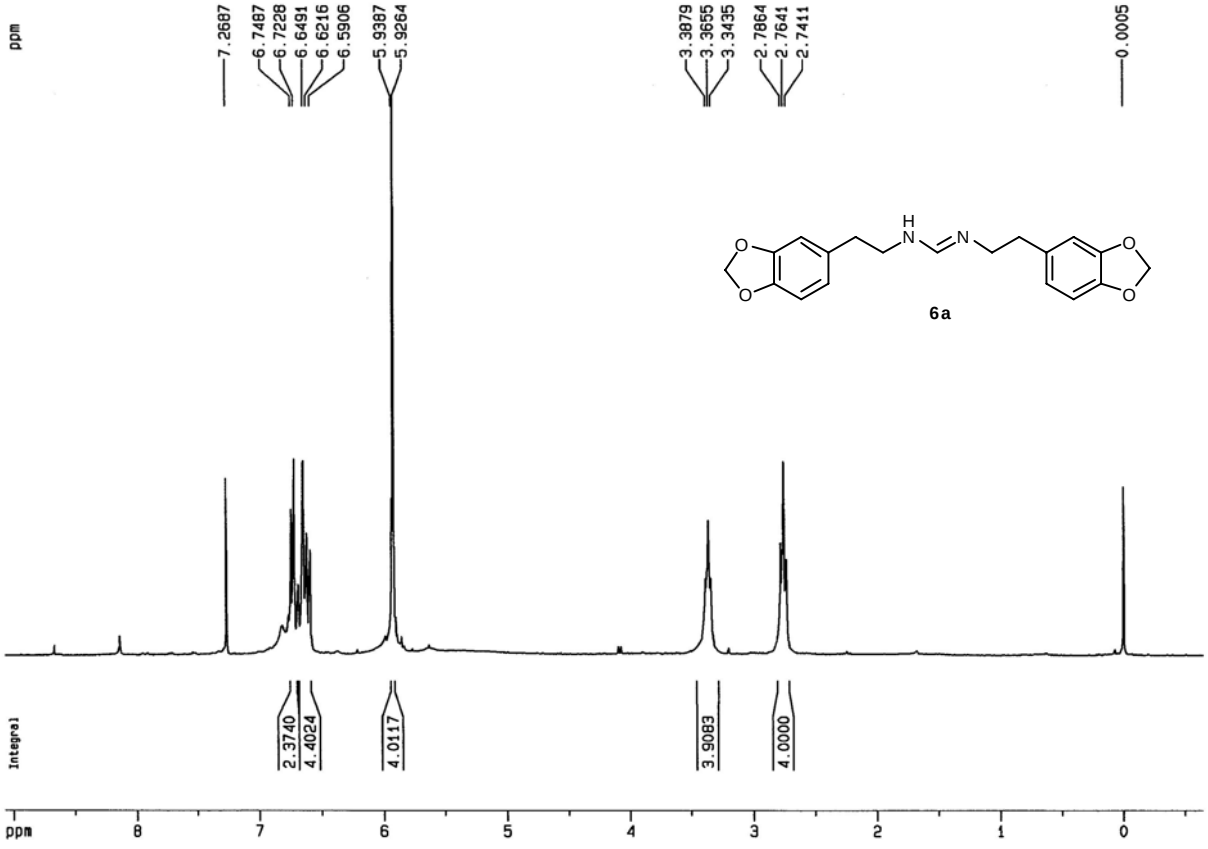
2.2301
2.5484
4.2609
ppm
7
6
5
4
3
2
1
0


ppm
8.06604
7.26250
3.70195
3.69376
3.67579
3.66789
3.65945
3.59151
3.58312
3.40113
0.00047



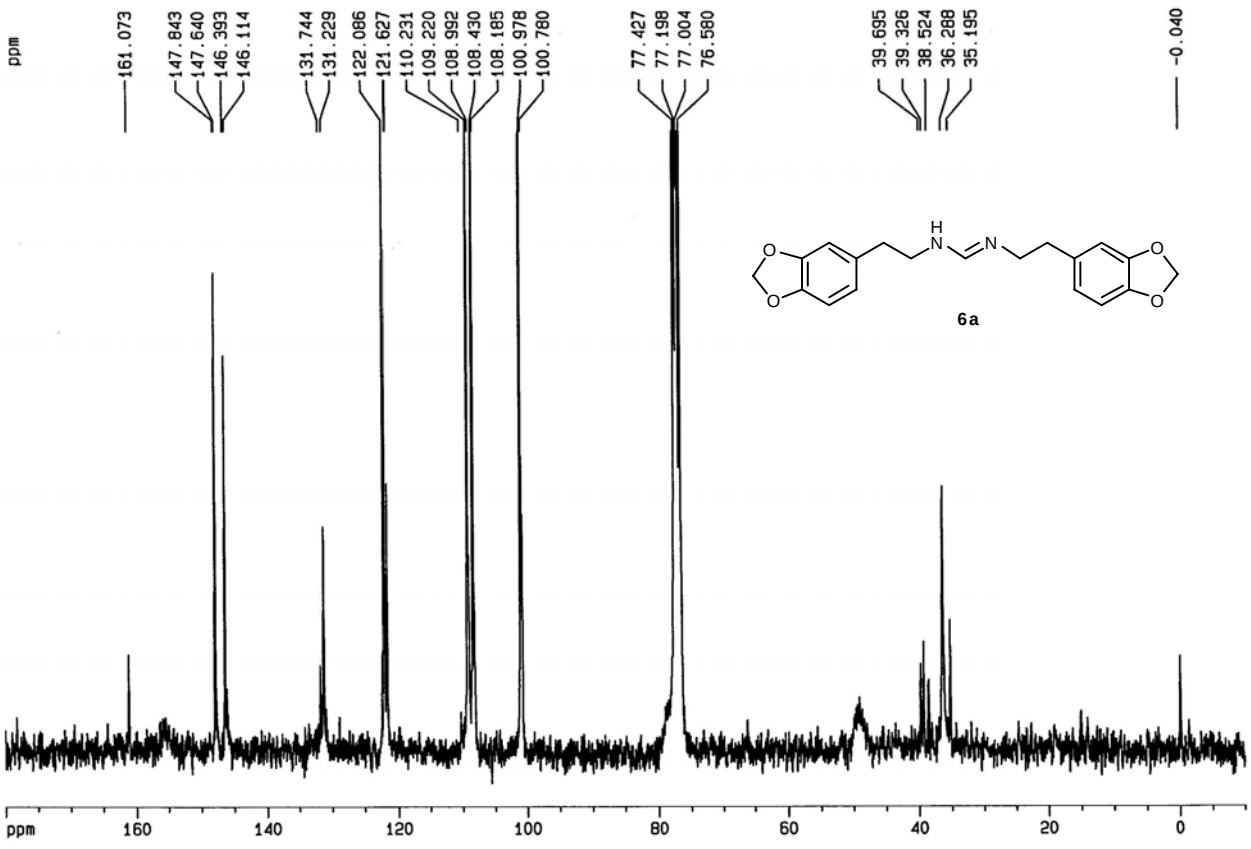
4f


Integral
1.0000
2.4017
2.6289
2.5102
2.1052
ppm
8
7
6
5
4
3
2
1
0


ppm
7.2687
6.7487
6.7228
6.6491
6.6216
6.5906
5.9387
5.9264
3.3879
3.3655
3.3435
2.7864
2.7641
2.7411
0.0005
Integral
2.3740
4.4024
4.0117
3.9083
4.0000
ppm
8
7
6
5
4
3
2
1
0

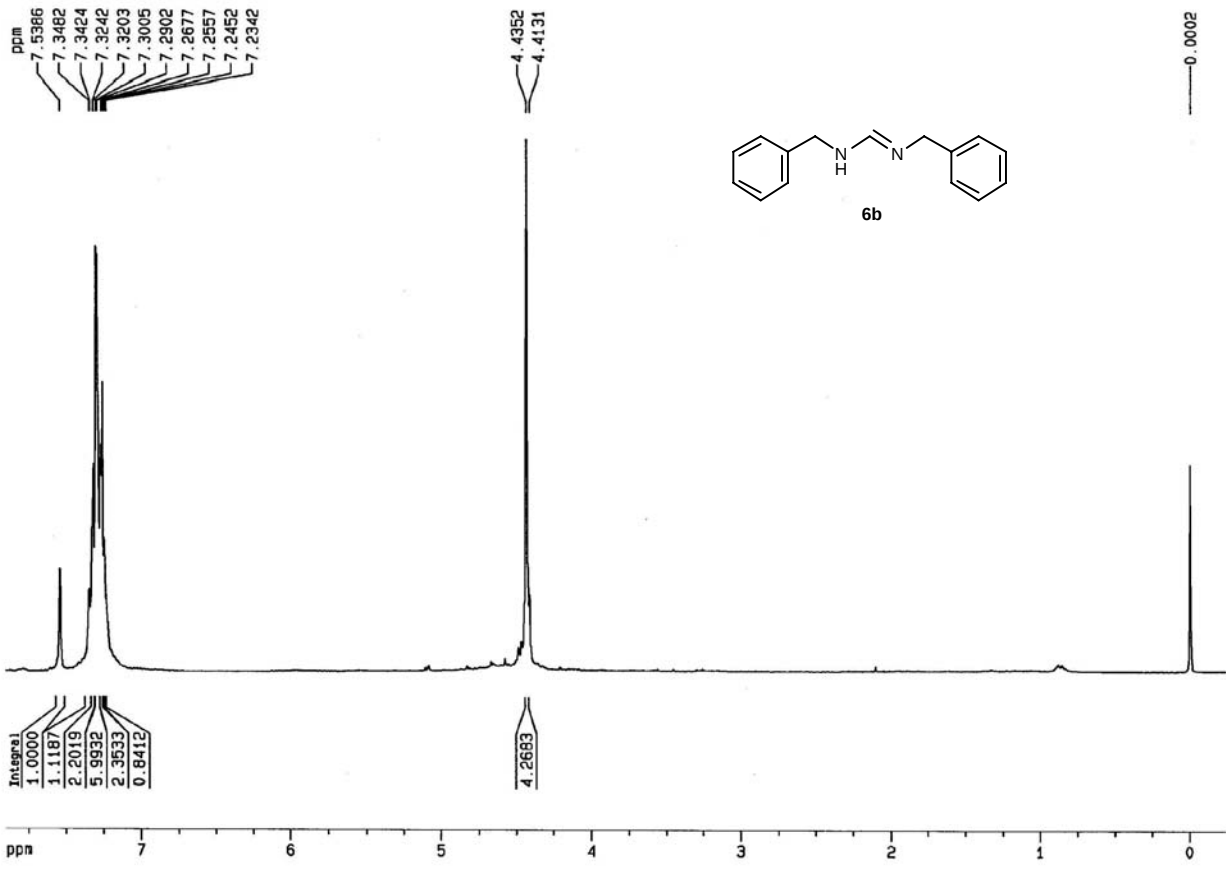
H
N
N
O
O
O
O

6a

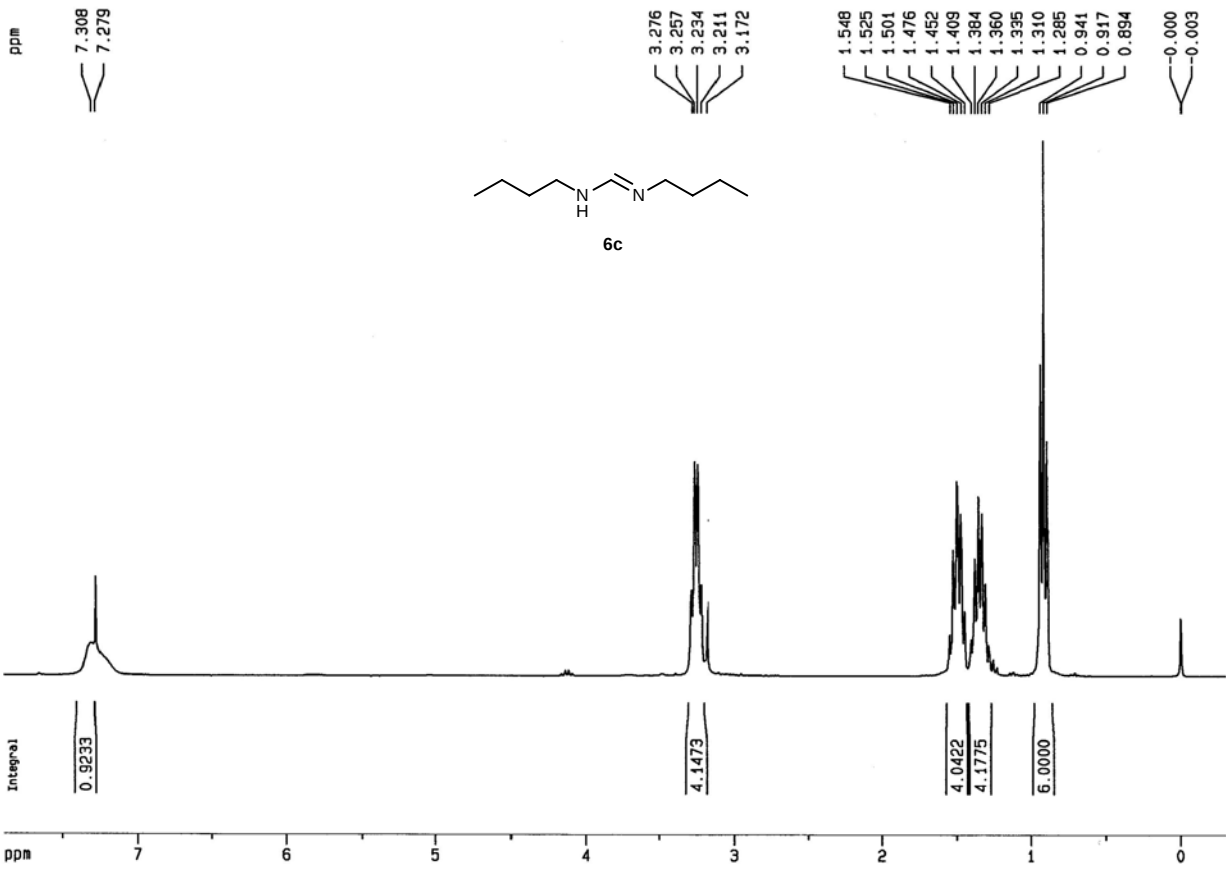

ppm
161.073
147.843
147.640
146.393
146.114
131.744
131.229
122.086
121.627
110.231
109.220
108.992
108.430
108.185
100.978
100.780
77.427
77.198
77.004
76.580
39.695
39.326
38.524
36.288
35.195
-0.040
ppm
160
140
120
100
80
60
40
20
0

H
N
N
O
O
O
O

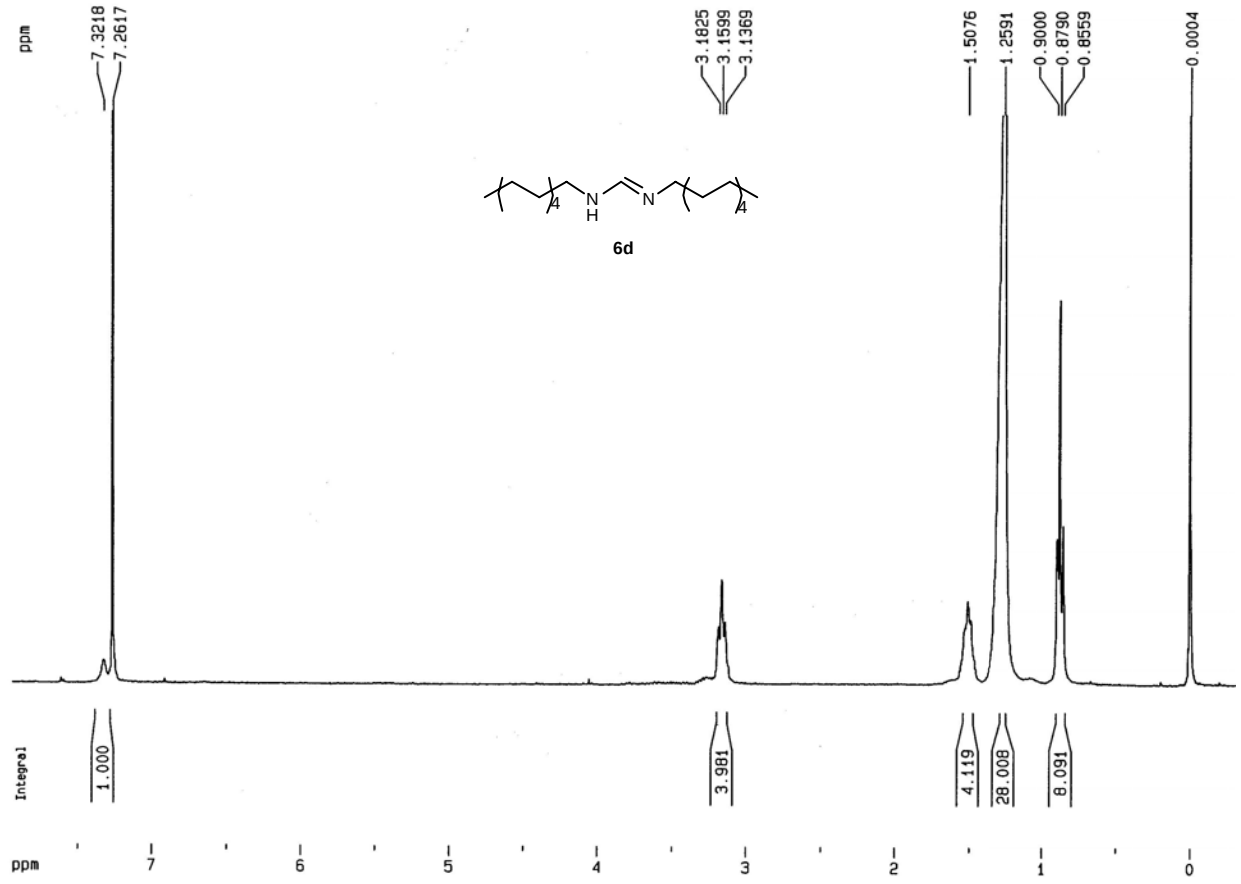
6a


ppm
7.5366
7.3482
7.3424
7.3242
7.3203
7.3005
7.2902
7.2677
7.2557
7.2452
7.2342
4.4352
4.4131
0.0002
Integral
1.0000
1.1187
2.2019
5.9932
2.3533
0.8412
4.2683
ppm

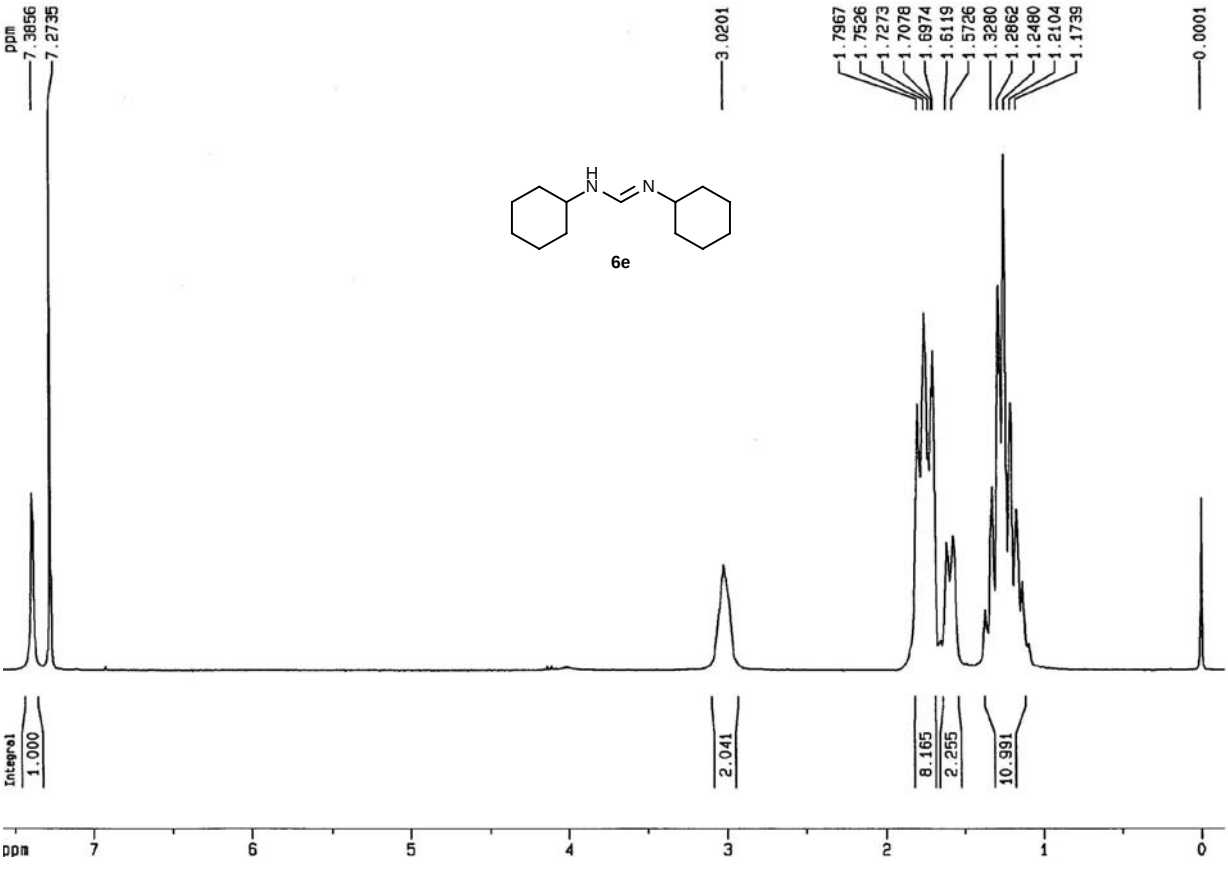
6b


ppm
7.308
7.279
3.276
3.257
3.234
3.211
3.172
1.548
1.525
1.501
1.476
1.452
1.409
1.384
1.360
1.335
1.310
1.285
0.941
0.917
0.894
-0.000
-0.003
Integral
0.9233
4.1473
4.0422
4.1775
6.0000
ppm

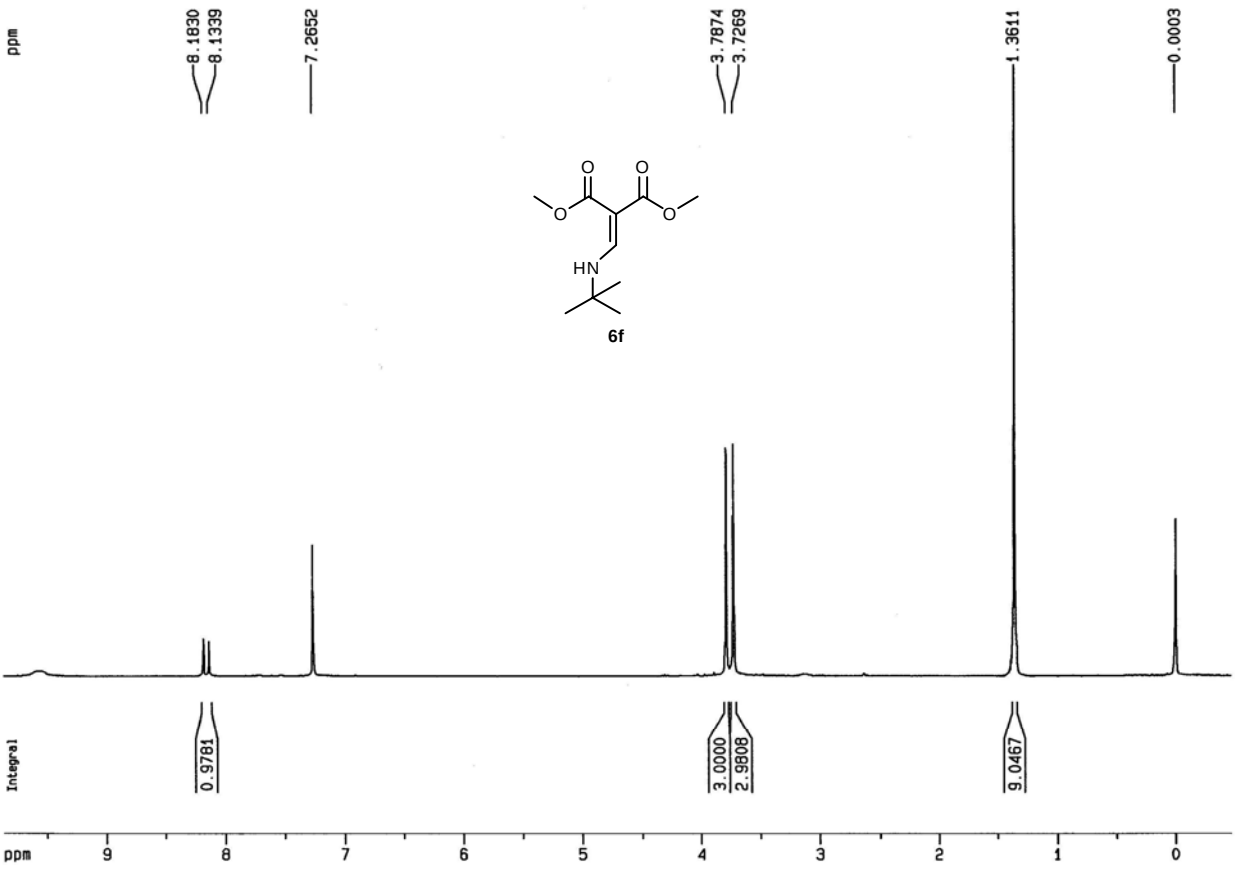
6c


ppm
7.3218
7.2617
3.1825
3.1599
3.1369
1.5076
1.2591
0.9000
0.8790
0.8559
0.0004
Integral
1.000
3.981
4.119
28.008
8.091
ppm
7
6
5
4
3
2
1
0

6d


ppm
7.3856
7.2735
3.0201
1.7967
1.7526
1.7273
1.7078
1.6974
1.6119
1.5726
1.3280
1.2862
1.2480
1.2104
1.1739
0.0001
Integral
1.000
2.041
8.165
2.255
10.991
ppm
7
6
5
4
3
2
1
0

6e


ppm
8.1830
8.1339
7.2652
3.7874
3.7269
1.3611
0.0003
O
O
O
O
HN
6f
Integral
0.9781
3.0000
2.9808
9.0467
ppm
9
8
7
6
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4
3
2
1
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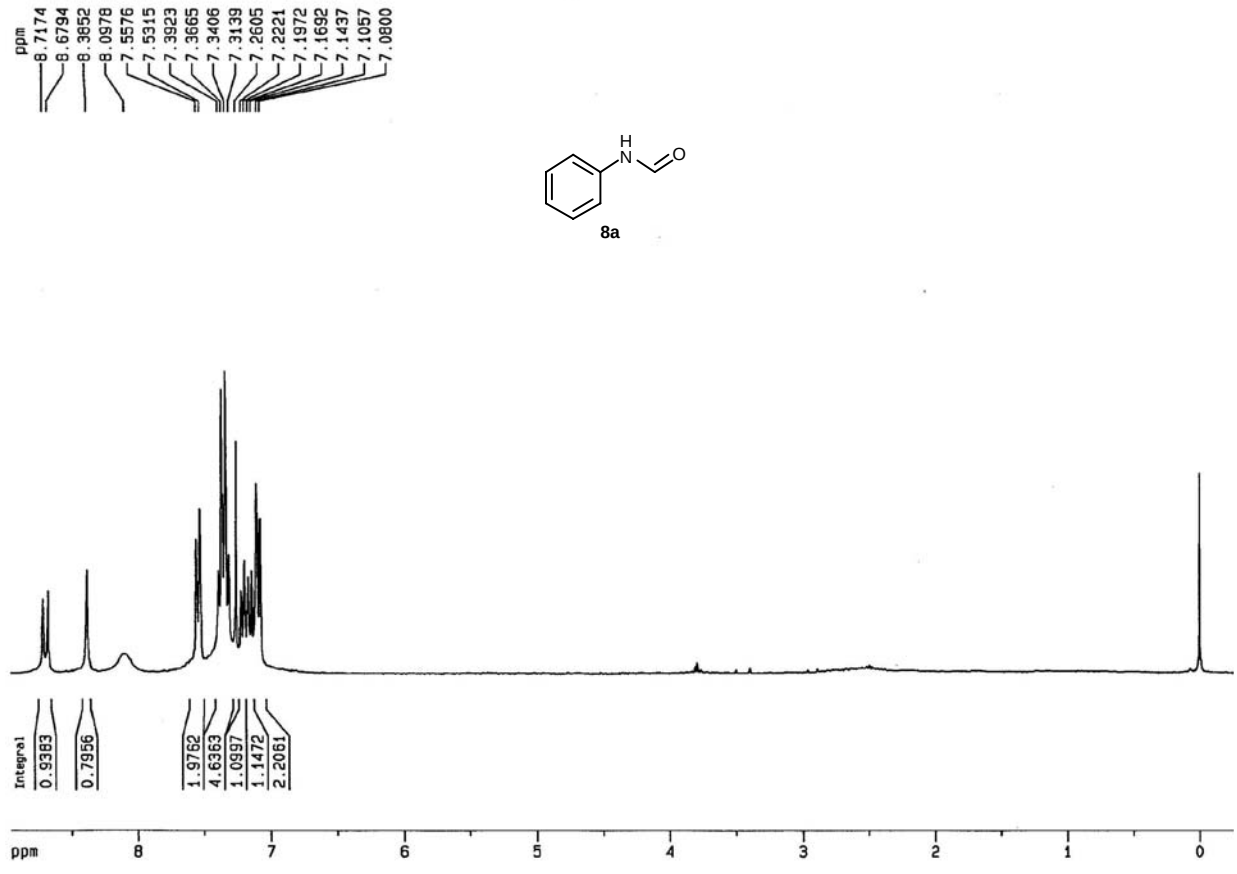
ppm
8.7174
8.6794
8.3852
8.0978
7.5576
7.5315
7.3923
7.3665
7.3406
7.3139
7.2605
7.2221
7.1972
7.1692
7.1437
7.1057
7.0800
H
N
O
8a
Integral
0.9383
0.7956
1.9762
4.6363
1.0997
1.1472
2.2061
ppm
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7
6
5
4
3
2
1
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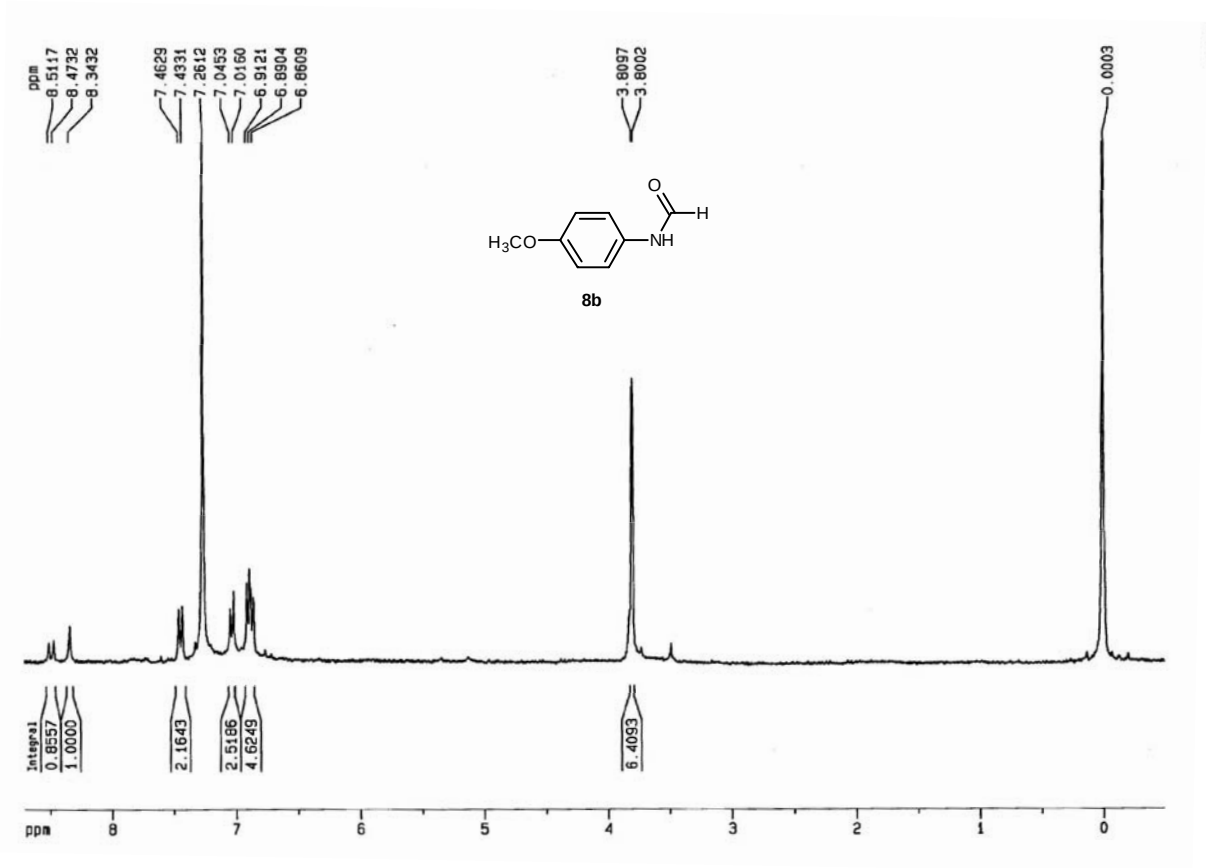
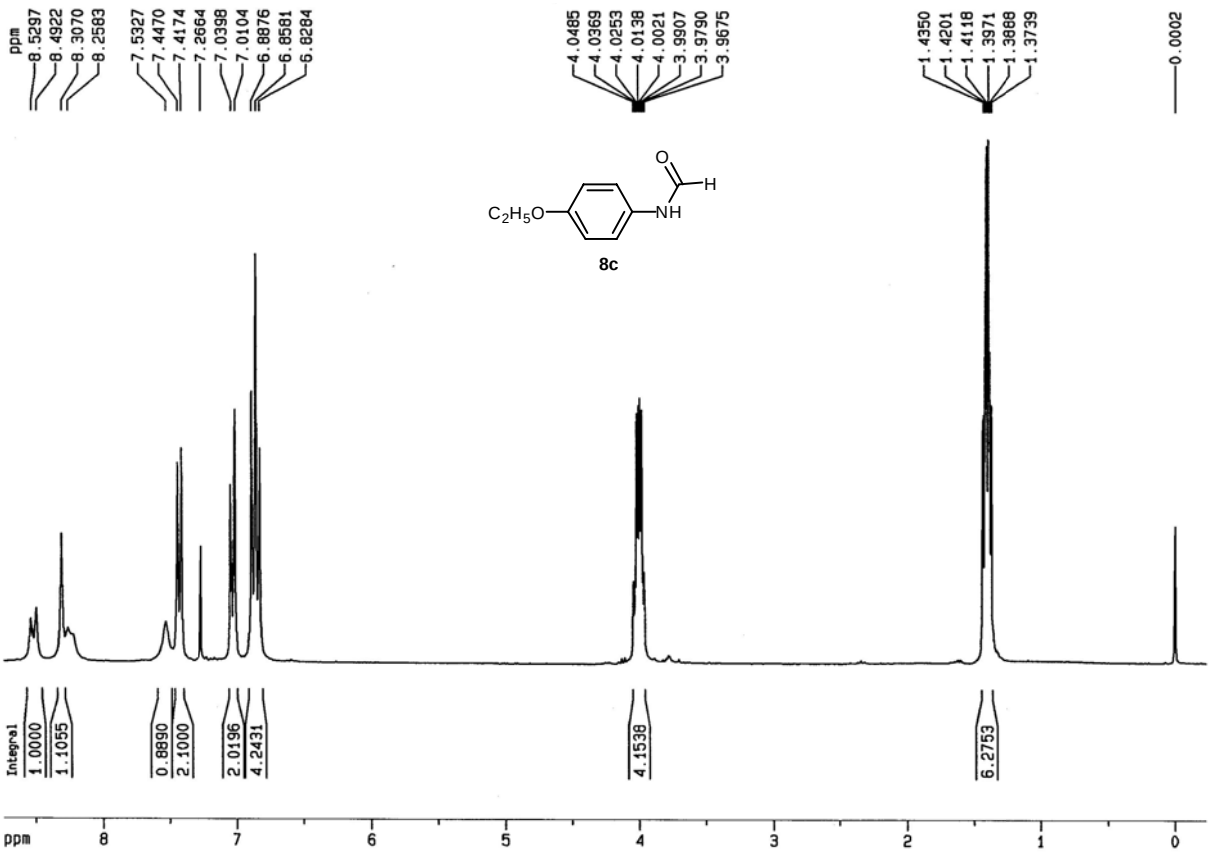

ppm
8.5117
8.4732
8.3432
7.4629
7.4331
7.2612
7.0453
7.0160
6.9121
6.8804
6.8609
3.8097
3.8002
0.0003
O
H
NH
H3CO
8b
Integral
0.8557
1.0000
2.1643
2.5186
4.6249
6.4093
ppm
8
7
6
5
4
3
2
1
0


ppm
8.5297
8.4922
8.3070
8.2583
7.5327
7.4470
7.4174
7.2664
7.0398
7.0104
6.8876
6.8581
6.8284
4.0485
4.0369
4.0253
4.0138
4.0021
3.9907
3.9790
3.9675
1.4350
1.4201
1.4118
1.3971
1.3688
1.3739
0.0002
O
H
NH
C2H5O
8c
Integral
1.0000
1.1055
0.8890
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2.0196
4.2431
4.1538
6.2753
ppm
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7
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5
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1
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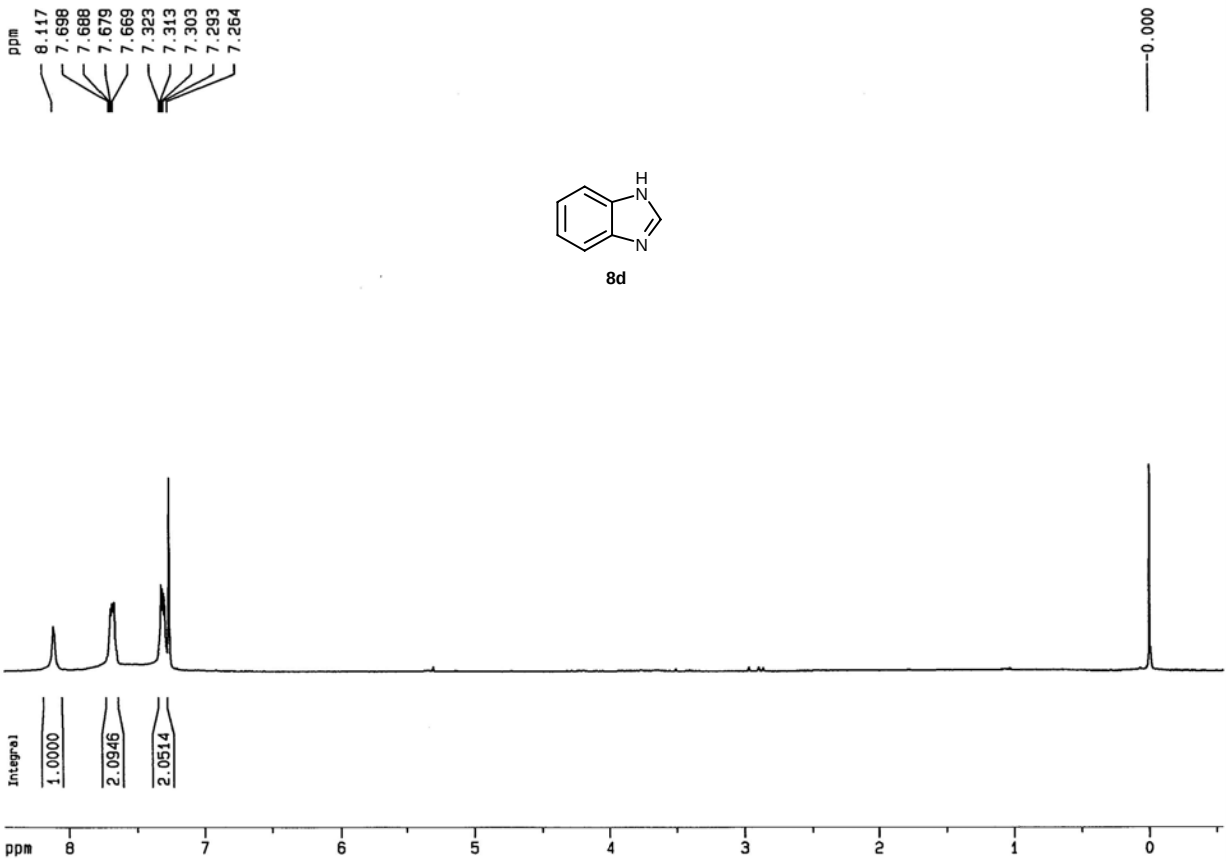
ppm
8.117
7.698
7.688
7.679
7.669
7.323
7.313
7.303
7.293
7.264
0.000
H
N
N
Integral
1.0000
2.0946
2.0514
ppm
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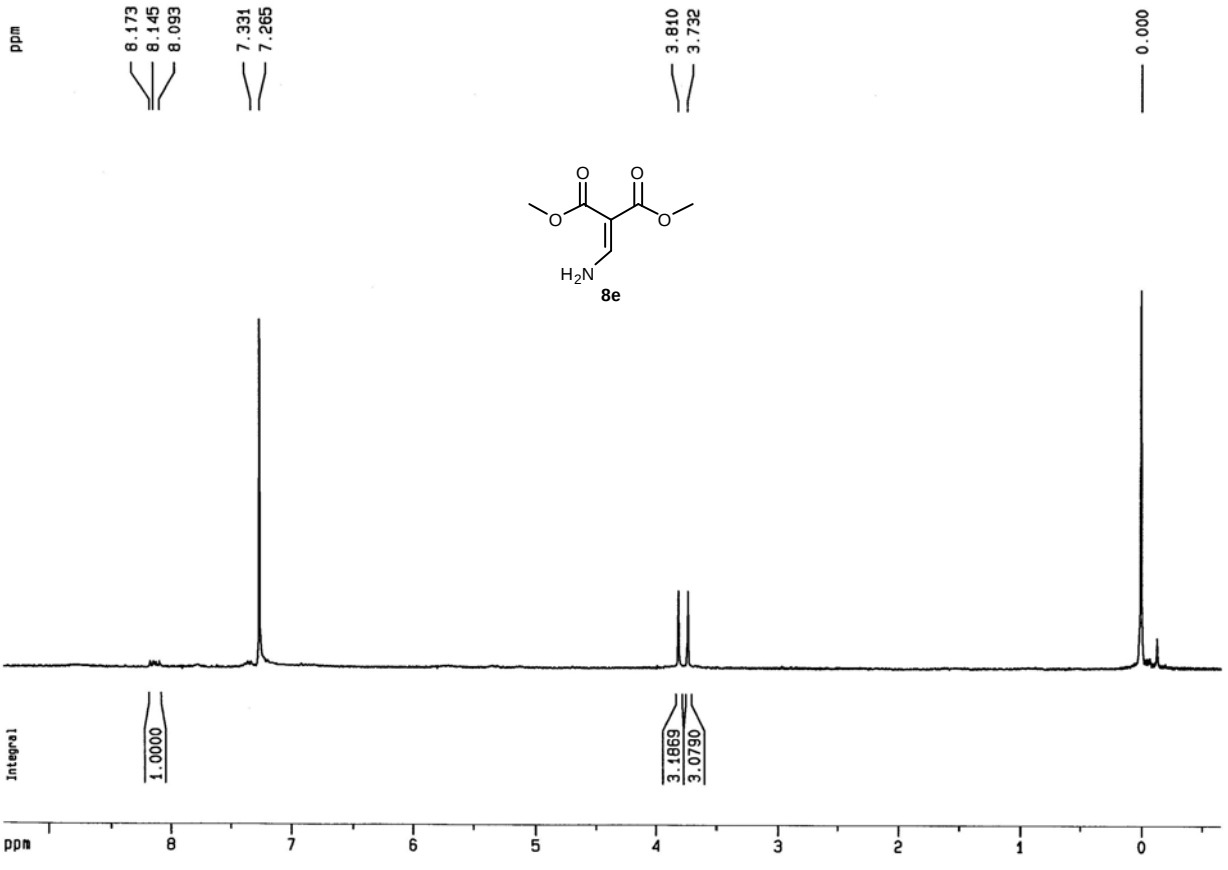
6
5
4
3
2
1
0

8d


ppm
8.173
8.145
8.093
7.331
7.265
3.810
3.732
0.000
O
O
O
O
H_2N
Integral
1.0000
3.1869
3.0790
ppm
8
7
6
5
4
3
2
1
0

8e