Supplementary material (ESI) for Organic & Biomolecular Chemistry

Rational Design of Central Selective Acetylcholinesterase Inhibitors by Means of a "Bio-oxidable Prodrug" Strategy.

Pierre Bohn,[a,b] Nicolas Le Fur,[a] Guillaume Hagues,[b] Jean Costentin,[b] Nicolas Torquet,[b] Cyril Papamicaël,[a] Francis Marsais[a] and Vincent Levacher*[a]

[a] Laboratoire de Chimie Organique Fine et Hétérocyclique
Institut de Recherche en Chimie Organique Fine (IRCOF) (UMR-6014).
INSA-Université de Rouen
Rue Tesnières, Mont-Saint-Aignan 76130-F (France)

[b]Laboratoire de Neuropharmacologie Expérimentale
associé au CNRS (FRE-2735).
Faculté de Médecine et de pharmacie, Université de Rouen 76000-F (France)

Supporting Information

Table of contents

1.1. Carbamylated quinolines **11a-g**

Ethyl 7-(*N*,*N*-dimethylcarbamate)quinoline-3-carboxylate (11a)

According to procedure A from compound **10a** (300 mg, 1.38 mmol), NaH (72 mg, 1.5 mmol, 50% dispersion in mineral oil) and dimethylcarbamoyl chloride (140 µL, 1.5 mmol). Flash chromatography of the residue (Eluent: CH_2Cl_2) provided pure **11a** (360 mg, 90%) as a pale yellow powder. mp 98°C. ^{1}H NMR($CDCl_3$) δ 9.42 (d, *J* = 2 Hz, 1H), 8.80 (d, *J* = 2 Hz, 1H), 7.90 (d, *J* = 9 Hz, 1H), 7.85 (d, *J* = 2 Hz, 1H), 7.45 (dd, *J* = 9 and 2 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.15 (s, 3H), 3.04 (s, 3H), 1.44 (t, *J* = 7.1 Hz, 3H). Found: C, 62.4; H, 5.6; N, 9.6. Calc. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72.

Ethyl 5-(*N*,*N*-dimethylcarbamate)quinoline-3-carboxylate (11b)

According to procedure A from compound **10b** (0.4 g, 1.84 mmol), NaH (96 mg, 2 mmol, 50% dispersion in mineral oil) and *N*,*N*-dimethylcarbamoyl chloride (203 µL, 2.21 mmol). Flash chromatography on silica gel of the residue (Eluent: diethyl ether) provided pure **11b** (415 mg, 78%) as a pale yellow powder. mp: 99°C. ^{1}H NMR ($CDCl_3$) δ 9.40 (d, *J* = 2 Hz, 1H), 8.89 (d, *J* = 2 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.76 (dd, *J* = 7.5 and 8.5 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 4.43 (q, *J* = 7.0 Hz, 2H), 3.24 (s, 3H), 3.04 (s, 3H), 1.41, (t, *J* = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 165.2 (C), 154.3 (C), 150.2 (CH), 147.8 (C), 133.0 (CH), 131.4 (CH), 126.6 (CH), 123.3 (C), 121.6 (C), 119.5 (CH), 61.6 (CH_2), 37.0 (CH_3), 36.7 (CH_3), 14.3 (CH_3). IR ν_{max}/cm^{-1} (KBr): 1754, 1720, 1281, 1157. Found: C, 62.6; H, 5.45; N, 9.8. Calc. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72.

Methyl 5-(*N*,*N*-dimethylcarbamate)-quinoline-3-carboxylate (11c)

According to procedure A from compound **10c** (0.7 g, 3.45 mmol), NaH (0.33 g, 6.90 mmol, 50% dispersion in mineral oil) and *N*,*N*-dimethylcarbamoyl chloride (635 µL, 6.90 mmol). Flash chromatography of the residue on silica gel (Eluent: Cyclohexane/EtOAc 1:1) provided pure **11c** (757 mg, 85%) as a pale yellow powder. mp 112°C. ^{1}H NMR ($CDCl_3$) δ 9.45 (d, *J* = 2 Hz, 1H), 8.95 (d, *J* = 2 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 7.5 and 8.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 4.03 (s, 3H), 3.29 (s, 3H), 3.10 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 165.8 (C), 154.3 (C), 150.3 (C),

150.3 (CH), 147.8 (C), 133.2 (CH), 131.5 (CH), 126.7 (CH), 123.1 (C), 121.7 (C), 119.6 (C), 52.7 (CH_3), 37.1 (CH_3), 36.8 (CH_3). IR ν_{max}/cm^{-1} (KBr): 1759, 1729, 1286, 1176, 1160. Found: C, 61.2; H, 5.2; N, 10.1. Calc. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21.

5-(*N*,*N*-Dimethylcarbamate)-3-(*N*-methylcarboxamido) quinoline (11d)

According to procedure A from compound **10d** (150 mg 0.74 mmol), NaH (48 mg, 1 mmol) and *N*,*N*-dimethylcarbamoyl chloride (82 µL, 0.89 mmol). Flash chromatography on silica gel of the residue (Eluent: CH_2Cl_2 then CH_2Cl_2/*i*-PrOH 9:1) provided pure **11d** (132 mg, 65%) as a pale yellow powder. ^{1}H NMR ($CDCl_3$) δ 9.18 (d, *J* = 2.3 Hz, 1H), 8.71 (d, *J* = 1.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.78 (dd, *J* = 7.7 and 8.5 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 6.45 (br, 1H), 3.27 (br, 3H), 3.07 (m, 6H). ^{13}C NMR δ 166.5 (C), 154.9 (C), 149.8 (C), 148.6 (CH), 147.9 (C), 130.9 (CH), 130.6 (CH), 127.7 (C), 126.9 (CH), 122.1 (C), 120.0 (CH), 37.4 (CH_3), 37.1 (CH_3), 27.3 (CH_3). Found: C, 61.45; H, 5.6; N, 15.4. Calc. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38.

5-(*N*,*N*-Dimethylcarbamate)-3-(*N*,*N*-dimethylcarboxamido) quinoline (11e)

According to procedure A from compound **10e** (0.1 g, 0.46 mmol), NaH (33 mg, 0.69 mmol, 50% dispersion in mineral oil) and *N*,*N*-dimethylcarbamoyl chloride (64 µL, 0.69 mmol). Flash chromatography on neutral alumina gel (Eluent: CH_2Cl_2/EtOAc 1:1) provided pure **11e** (72 mg, 55%) as a pale brown powder. ^{1}H NMR ($CDCl_3$) δ 8.95 (d, *J* = 2 Hz, 1H), 8.38 (d, *J* = 2 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.75 (dd, *J* = 7.9 and 8.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 3.24 (s, 3H), 3.18 (s, 3H), 3.06 (s, 6H). ^{13}C NMR δ 169.1 (C), 154.4 (C), 148.9 (CH), 148.6 (C), 147.3 (C), 130.3 (CH), 130.0 (CH), 129.3 (C), 126.8 (CH), 122.0 (C), 119.6 (CH), 39.9 (CH_3), 37.1 (CH_3), 36.8 (CH_3), 35.7 (CH_3). Found: C, 62.7; H, 5.9; N, 14.6. Calc. for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63.

4-[5-(*N*,*N*-Dimethylcarbamate)quinolin-3-yl-carbonyl]-morpholine (11f)

According to procedure A from compound **10f** (444 mg, 1.72 mmol), NaH (166 mg, 3.45 mmol, 50% dispersion in mineral oil) and *N*,*N*-dimethylcarbamoyl chloride (320 µL, 3.45 mmol). Flash chromatography on silica gel (Eluent: CH_2Cl_2 then CH_2Cl_2/*i*-PrOH 49:1) provided pure **11f** (102 mg, 18%) as a pale yellow powder. mp 130°C. ^{1}H NMR ($CDCl_3$) δ 8.91 (d, *J* = 2.3 Hz, 1H), 8.35 (d, *J* = 2.1 Hz, 1H), 7.98 (d, *J* = 8.5 Hz,

1H), 7.74 (dd, *J* = 8.5 and 7.9 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 3.30-3.90 (m, 8H), 3.23 (s, 3H), 3.04 (s, 3H). ^{13}C NMR ($CDCl_3$) 168.3 (C), 154.7 (C), 149.3 (C), 148.8 (CH), 147.5 (C), 130.8 (CH), 130.7 (CH), 128.4 (C), 127.1 (CH), 122.2 (C), 120.1 (CH), 67.2 (CH_2), 37.4 (CH_3), 37.1 (CH_3). Found: C, 62.25; H, 5.9; N, 12.0. Calc. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. IR ν_{max} /cm^{-1} (KBr): 1725, 1628, 1168, 1111.

Methyl 5-(*N*-ethylcarbamate)-quinoline-3-carboxylate (11g)

According to procedure A from compound **10c** (321 mg, 1.58 mmol), NaH (0.10 g, 1.90 mmol, 50% dispersion in mineral oil) and ethyl isocyanate (130 µL, 1.64 mmol). Flash chromatography on silica gel (Eluent: petroleum ether/*i*-PrOH 3:1) provided pure **11g** (408 mg, 94%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 9.43 (d, *J* = 1.5 Hz, 1H), 8.98 (d, *J* = 1.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.80 (t, *J* = 8 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 5.39 (t, *J* = 7.5 Hz, 1H), 4.03 (s, 3H), 3.36 (quint, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H). MS EI (70 eV) Calc. for $C_{14}H_{14}N_2O_4$ m/z = 274, Found: (MH^+) m/z = 275.

1.2. Quinolinium salts **2a-g**

Ethyl 1-methyl-7-(*N*,*N*-dimethylcarbamate)quinolinium-3-carboxylate triflate (2a)

According to procedure B from compound **11a** (300 mg, 1.0 mmol) and methyl trifluoromethanesulfonate (130 µL, 1.1 mmol). After evaporation of volatiles addition of Et_2O (10 mL) furnished a white precipitate (450 mg, 100%) which was filtered to give the desired quinolinium salt **2a** as a white powder. mp 193°C. ^{1}H NMR ($CDCl_3$) δ 9.78 (s, 1H), 9.44 (s, 1H), 8.35 (d, *J* = 9 Hz, 1H), 8.28 (s, 1H), 7.87 (d, *J* = 9 Hz, 1H), 4.74 (s, 3H), 4.54 (q, *J* = 7.1 Hz, 2H,), 3.19 (s, 3H), 3.07 (s, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (DMSO) δ 162.1 (C), 158.1 (C), 152.7 (C), 150.6 (CH), 147.2 (CH), 140.8 (C), 133.4 (CH), 126.7 (CH), 126.1 (C), 123.1 (C), 111.1 (CH), 62.6 (CH_2), 45.6 (CH_3), 36.6 (CH_3), 36.4 (CH_3), 14.2 (CH_3). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{16}H_{19}N_2O_4^+$: *m/z* 303.1339. Found: 303.1351.

Ethyl 1-methyl-5-(*N*,*N*-dimethylcarbamate)quinolinium-3-carboxylate triflate (2b)

According to procedure B from compound **11b** (300 mg, 1.0 mmol) and methyl trifluoromethanesulfonate (130 µL, 1.1 mmol). After evaporation of volatiles, addition of Et_2O (10 mL) furnished a white precipitate which was filtered to give the desired quinolinium salt **2b** (450 mg, 100 %) as a white solid. mp 170°C. ^{1}H NMR ($CDCl_3$) δ 9.89 (s, 1H), 9.58 (s, 1H), 8.25-8.35 (m, 2H), 7.87 (dd, *J* = 2.5 and 6.2 Hz, 1H), 4.83 (s, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 3.30 (s, 3H), 3.10 (s, 3H), 1.48 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 161.4 (C), 152.9 (C), 150.9 (CH), 149.8 (C), 142.5 (CH), 140.1 (C), 138.6 (CH), 124.6 (C), 124.0 (C), 123.2 (CH), 115.8 (CH), 63.8 (CH_2), 47.4 (CH_3), 37.4 (CH_3), 37.1 (CH_3), 14.2 (CH_3). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{16}H_{19}N_2O_4^+$: *m/z* 303.1339. Found: 303.1347.

Methyl 1-methyl-5-(*N*,*N*-dimethylcarbamate)quinolinium-3-carboxylate triflate (2c)

According to procedure B from compound **11c** (565 mg, 2.06 mmol) and methyl trifluoromethanesulfonate (256 µL, 2.27 mmol). After evaporation of volatiles, compound **2c** (903 mg, 100%) was obtained as a pale yellow powder. mp: 170°C ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 1H), 9.52 (s, 1H), 8.20-8.32 (m, 2H), 7.82 (dd, *J* = 6.9 and 1.6 Hz, 1H), 4.73 (s, 3H), 4.05 (s, 3H), 3.27 (s, 3H), 3.06 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 162.1 (C), 153.0 (C), 150.9 (CH), 149.6 (C), 142.4 (CH), 140.1 (C), 138.6 (CH), 124.2 (C), 123.9 (C), 123.3 (CH), 116.0 (CH), 54.0 (CH_3), 47.2 (CH_3), 37.3 (CH_3), 37.0 (CH_3). ^{19}F NMR ($CDCl_3$) δ -79.0. Found: C, 43.55; H, 3.9; N, 6.5; S, 7.2. Calc. for $C_{16}H_{17}F_3N_2O_7S$: C, 43.84; H, 3.91; N, 6.39; S, 7.31. IR ν_{max}/cm^{-1} (KBr): 1736, 1268, 1159, 1029.

1-Methyl-5-(*N*,*N*-dimethylcarbamate)-3-(*N*-methylcarboxamido)quinolinium triflate (2d)

According to procedure B from compound **11d** (146 mg, 0.53 mmol) and methyl trifluoromethanesulfonate (68 µL, 0.60 mmol). After evaporation of the volatiles compound **2d** (216 mg, 100%) was obtained as a pale brown powder. ^{1}H NMR ($CDCl_3$) δ 9.86 (s, 1H), 9.69 (s, 1H), 8.58 (br, 1H), 8.25 (dd, *J* = 8.9 and 7.9 Hz, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 4.75 (s, 3H), 3.30 (s, 3H), 3.09 (s,

3H), 3.05 (d, *J* = 4.5 Hz, 3H). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{15}H_{18}N_3O_3^+$: *m/z* 288.1343. Found: 288.1352.

1-Methyl-5-(*N*,*N*-dimethylcarbamate)-3-(*N*,*N*-dimethylcarboxamido)quinolinium triflate (2e)

According to procedure B from compound **11e** (25 mg, 0.09 mmol) and methyl trifluoromethanesulfonate (12 µL, 0.11 mmol). After evaporation of volatiles, compound **2e** (40 mg, 100%) was obtained as a brown powder. ^1H NMR ($CDCl_3$) δ 9.44 (s, 1H), 9.07 (s, 1H), 8.10-8.25 (m, 2H), 7.77 (dd, *J*= 6.5 and 1.5 Hz, 1H), 4.69 (s, 3H), 3.25 (s, 3H), 3.13 (s, 6H), 3.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 162.3 (C), 153.1 (C), 149.5 (CH), 149.0 (C), 139.7 (CH), 139.0 (C), 137.1 (CH), 130.0 (C), 124.1 (C), 123.0 (CH), 115.6 (CH), 46.9 (CH_3), 39.9 (CH_3), 37.3 (CH_3), 37.0 (CH_3), 36.0 (CH_3). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{16}H_{20}N_3O_3^+$: *m/z* 302.1499. Found: 302.1512.

1-Methyl-5-(*N*,*N*-dimethylcarbamate)-3-(morpholinocarboxy)quinolinium triflate (2f)

According to procedure B from compound **11f** (102 mg, 0.31 mmol) and methyl trifluoromethanesulfonate (35 µL, 0.31 mmol). After evaporation of volatiles, compound **2f** (152 mg, 100%) was obtained as a brown powder. mp 92°C (degrad.) ^1H NMR ($CDCl_3$) δ 9.37 (d, *J* = 1.0 Hz, 1H), 8.98 (d, *J* = 1.0 Hz, 1H), 8.10-8.25 (m, 2H), 7.76 (dd, *J* = 6.6 and 2.1 Hz, 1H), 4.65 (s, 3H), 3.50-8.85 (m, 8H), 3.24 (s, 3H), 3.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 163.2 (C), 153.0 (C), 149.7 (CH), 149.0 (C), 139.6 (CH), 139.1 (C), 137.1 (CH), 129.3 (C), 124.0 (C), 122.9 (CH), 115.6 (CH), 66.5 (CH_2), 47.0 (CH_3), 37.3 (CH_3), 37.0 (CH_3). ^{19}F NMR ($CDCl_3$) δ -79.0. IR ν_{max} (KBr): 1731, 1638, 1260, 1155, 1031 cm^{-1}. HRMS (DCI^+, isobutene): calc. for (M^+) $C_{18}H_{22}N_3O_4^+$: *m/z* 344.1605. Found: 344.1625.

Methyl 5-(*N*-ethylcarbamate)-1-methylquinolinium-3-carboxylate triflate (2g)

According to procedure B from compound **11g** (80 mg, 0.27 mmol) and methyl trifluoromethanesulfonate (36 µL, 0.32 mmol). After evaporation of volatiles, compound **2g** (125 mg, 100%) was obtained as a white powder. ^1H NMR (DMSO-d_6) δ 10.07 (s, 1H), 9.49 (s, 1H), 8.48 (t, *J* = 5.8 Hz, 1H), 8.42 (m, 2H), 8.04 (dd, *J* = 3.2 Hz and 5.3 Hz, 1H), 4.73 (s, 3H), 4.05 (s, 3H), 3.18 (q, *J* = 7.2 Hz, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 162.7, 153.0, 151.2, 149.0, 141.2, 140.1, 138.3,

123.9, 123.2, 122.7, 116.2, 53.9, 46.3, 36.0, 15.0. HRMS (DCI^+, isobutene): calc. for (M^+) $C_{15}H_{17}N_2O_4^+$: *m/z* 289.1183. Found: 289.1195.

1.3. 1,4-Dihydroquinolines **1a-g**

Ethyl 1-methyl-7-(*N*,*N*-dimethylcarbamate)-1,4-dihydroquinoline-3-carboxylate (1a)

According to procedure C from compound **2a** (100 mg, 0.22 mmol). The crude product **1a** (31 mg, 47%) was obtained as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.19 (s, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 6.67 (dd, *J* = 9Hz and 3 Hz, 1H), 6.49 (d, *J* = 3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 2H), 3.18 (s, 3H), 3.08 (s, 3H), 3.00 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.8 (C), 155.0 (C), 150.7 (C), 142.7 (CH), 139.9 (C), 130.1 (CH), 120.0 (C), 116.1 (CH), 106.7 (CH), 97.9 (C), 59.7 (CH_2), 39.0 (CH_3), 36.8 (CH_3), 36.5 (CH_3), 25.9 (CH_2), 14.7 (CH_3). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{16}H_{20}N_2O_4^+$: *m/z* 304.1423. Found: 304.1433.

Ethyl 1-methyl-5-(*N*,*N*-dimethylcarbamate)-1,4-dihydroquinoline-3-carboxylate (1b)

According to procedure C from compound **2b** (100 mg, 0.22 mmol). The crude product **1b** (31 mg, 46%) was obtained as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.19 (s, 1H), 7.12 (t, *J* = 8.5 Hz, 1H), 6.75 (dd, *J* = 8 Hz and 1 Hz, 1H), 6.56 (dd, *J* = 8 Hz and 1 Hz, 1H), 4.17 (q, *J* = 7 Hz, 2H), 3.63 (s, 2H), 3.20 (s, 3H,), 3.11 (s, 3H), 3.00 (s, 3H), 1.29 (t, *J* = 7 Hz, 3H). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{16}H_{20}N_2O_4^+$: *m/z* 304.1423. Found: 304.1428.

Methyl 1-methyl-5-(*N*,*N*-dimethylcarbamate)-1,4-dihydroquinoline-3-carboxylate (1c)

According to procedure C from compound **2c** (100 mg, 0.23 mmol). The crude product **1c** (31 mg, 47%) was a yellow powder, but yields are not reproducible. Alternatively, compound **2c** could be reduced with *N*-benzyl-1,4-dihydronicotinamide (BNAH) by following the below procedure. A solution of **2c** (0.1 g, 0.23 mmol) and *N*-benzyl-1,4-dihydronicotinamide (BNAH) (54 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature (1h). The reaction mixture was then washed with water

(3 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure at room temperature to afford **1c** (45 mg, 67%) as a pale yellow powder. mp 130°C (degrad.) ^{1}H NMR ($CDCl_3$) δ 7.18 (s, 1H), 7.11 (dd, *J* = 8.1 and 8.3 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.55 (d, *J* = 8.1 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 2H), 3.17 (s, 3H), 3.10 (s, 3H), 2.99 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 168.3 (C), 154.4 (C), 150.3 (C), 142.9 (CH), 140.1 (C), 127.4 (CH), 117.2 (CH), 116.8 (C), 109.7 (CH), 96.8 (CH), 51.2 (CH_3), 39.5 (CH_3), 36.9 (CH_3), 36.6 (CH_3), 21.3 (CH_2). IR ν_{max}/cm^{-1} (KBr): 1725, 1679, 1390, 1270, 1168, 1146. HRMS (DCI$^+$, isobutene): calc. for (M^+) $C_{15}H_{18}N_2O_4^+$: *m/z* 290.1267. Found: 290.1272.

1-Methyl-5-(*N*,*N*-dimethylcarbamate)-3-(*N*-methylcarboxamido)-1,4-dihydroquinoline (1d)

According to procedure C from compound **2d** (70 mg, 0.17 mmol). The work-up was somewhat different from the procedure C. The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 5 mL) giving after evaporation of the solvent some impure product. The pH of the aqueous layer was adjusted to 5.0 with an aqueous solution of HCl 1M. An additional extraction of the resulting aqueous phase with CH_2Cl_2 (3 x 5 mL), drying ($MgSO_4$), followed by filtration and evaporation of the solvent under reduced pressure at room temperature gave compound **1d** (26 mg, 53%) as a pale brown powder. ^{1}H NMR ($CDCl_3$) δ 7.05-7.20 (m, 2H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 5.36 (br, 1H), 3.61 (s, 2H), 3.17 (s, 3H), 3.12 (s, 3H), 3.02 (s, 3H), 2.88 (d, *J* = 4.9 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 168.6 (C), 154.8 (C), 150.5 (C), 140.9 (C), 139.8 (CH), 128.0 (CH), 116.3 (CH), 115.7 (C), 109.8 (CH), 99.3 (C), 39.5 (CH_3), 37.2 (CH_3), 37.0 (CH_3), 26.9 (CH_3), 21.9 (CH_2). HRMS (DCI$^+$, isobutene): calc. for (M^+) $C_{15}H_{19}N_3O_3^+$: *m/z* 289.1426. Found: 289.1433.

4-[1-Methyl-5-(*N*,*N*-dimethylcarbamate)-1,4-dihydroquinolin-3-yl-carbonyl] morpholine (1f)

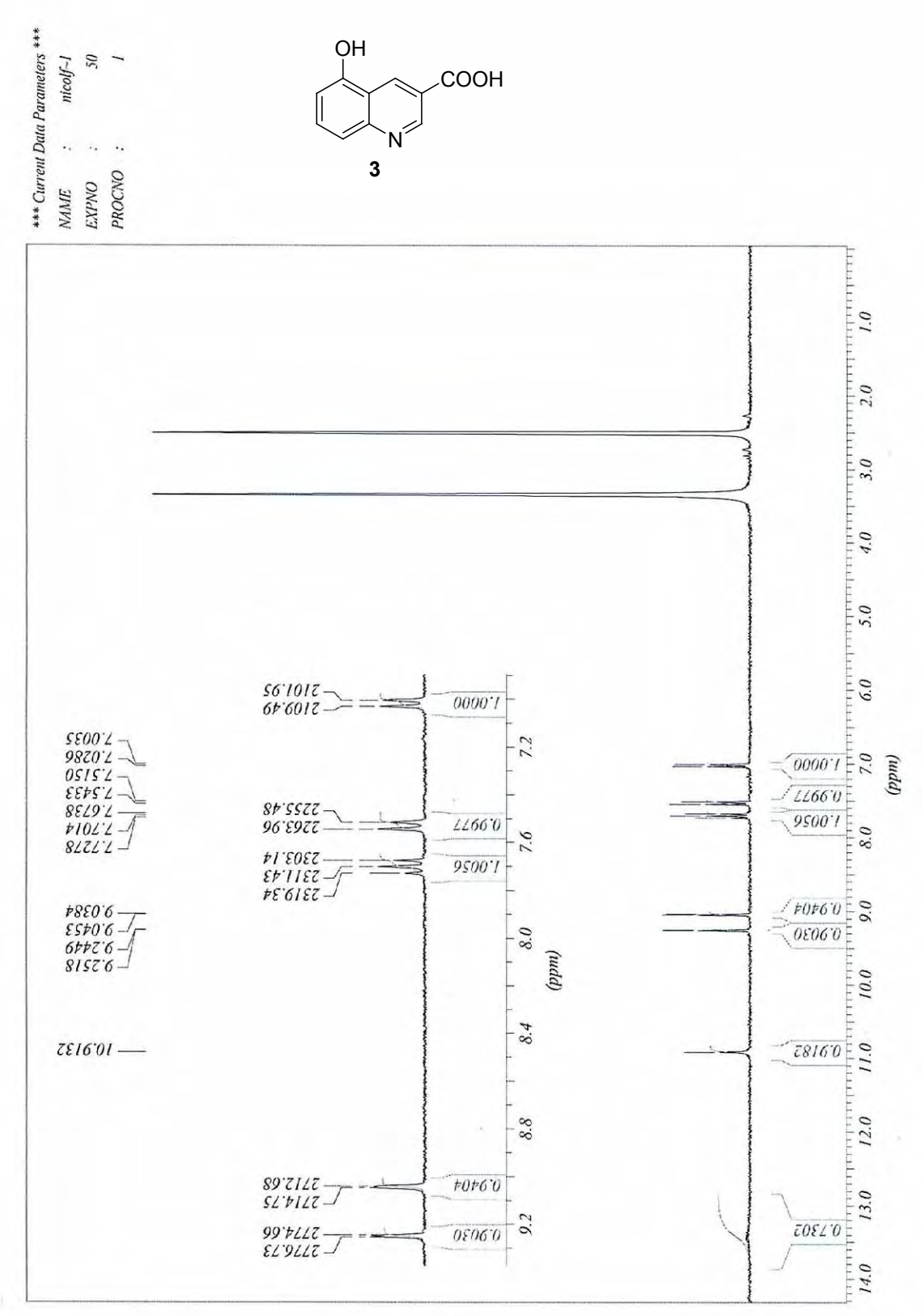
According to procedure C from compound **2f** (50 mg, 0.10 mmol). The crude product **1f** (16 mg, 46%) was obtained as a pale brown powder. ^{1}H NMR ($CDCl_3$) δ 7.12 (dd, *J* = 8.3 and 8.1 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.3 Hz, 1H), 6.40 (s, 1H), 3.50-3.75 (m, 10H), 3.15 (s, 3H), 3.09 (s, 3H), 3.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 171.5 (C), 157.2 (C), 149.9 (C), 141.2 (C), 138.2 (CH), 127.4 (CH), 116.3 (CH), 115.5 (C), 109.1 (CH), 100.2 (C), 67.2 (CH_2), 46.1 (CH_2), 39.1 (CH_3), 36.9 (CH_3), 36.7

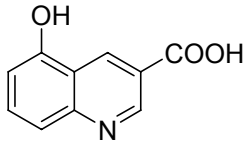
(CH_3), 23.1 (CH_2). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{18}H_{23}N_3O_4^+$: *m/z* 345.1687. Found: 345.1680.

Methyl 5-(*N*-ethylcarbamate)-1-methyl-1,4-dihydroquinoline-3-carboxylate (1g)

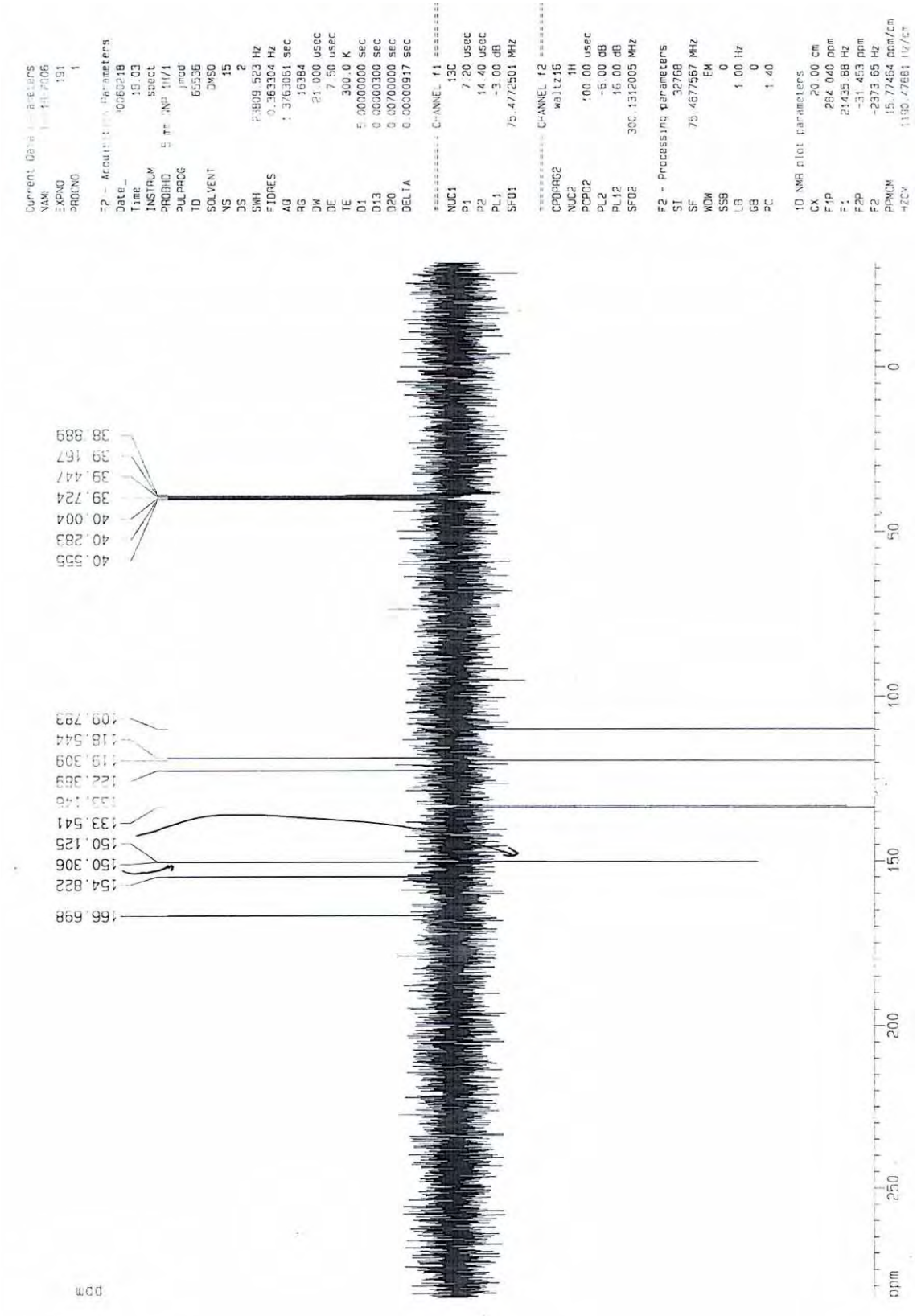
According to procedure C from compound **2g** (50 mg, 0.11 mmol). The crude product **1g** (20 mg, 62%) was obtained as a yellow powder. ^1H NMR ($CDCl_3$) δ 7.19 (s, 1H), 7.11 (t, *J* = 8.1 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.14 (s, 1H), 3.71 (s, 3H), 3.62 (s, 2H), 3.28 (q, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 168.6 (C), 154.3 (C), 150.0 (C), 143.2 (CH), 140.4 (C), 127.7(CH), 117.3 (CH), 117.1 (C), 110.0 (CH), 97.1 (C), 51.4 (CH_3), 39.7 (CH_3), 36.6 (CH_2), 21.6 (CH_2), 15.5 (CH_3). HRMS (DCI^+, isobutene): calc. for (M^+) $C_{15}H_{18}N_2O_4^+$: *m/z* 290.1267. Found: 290.1275.

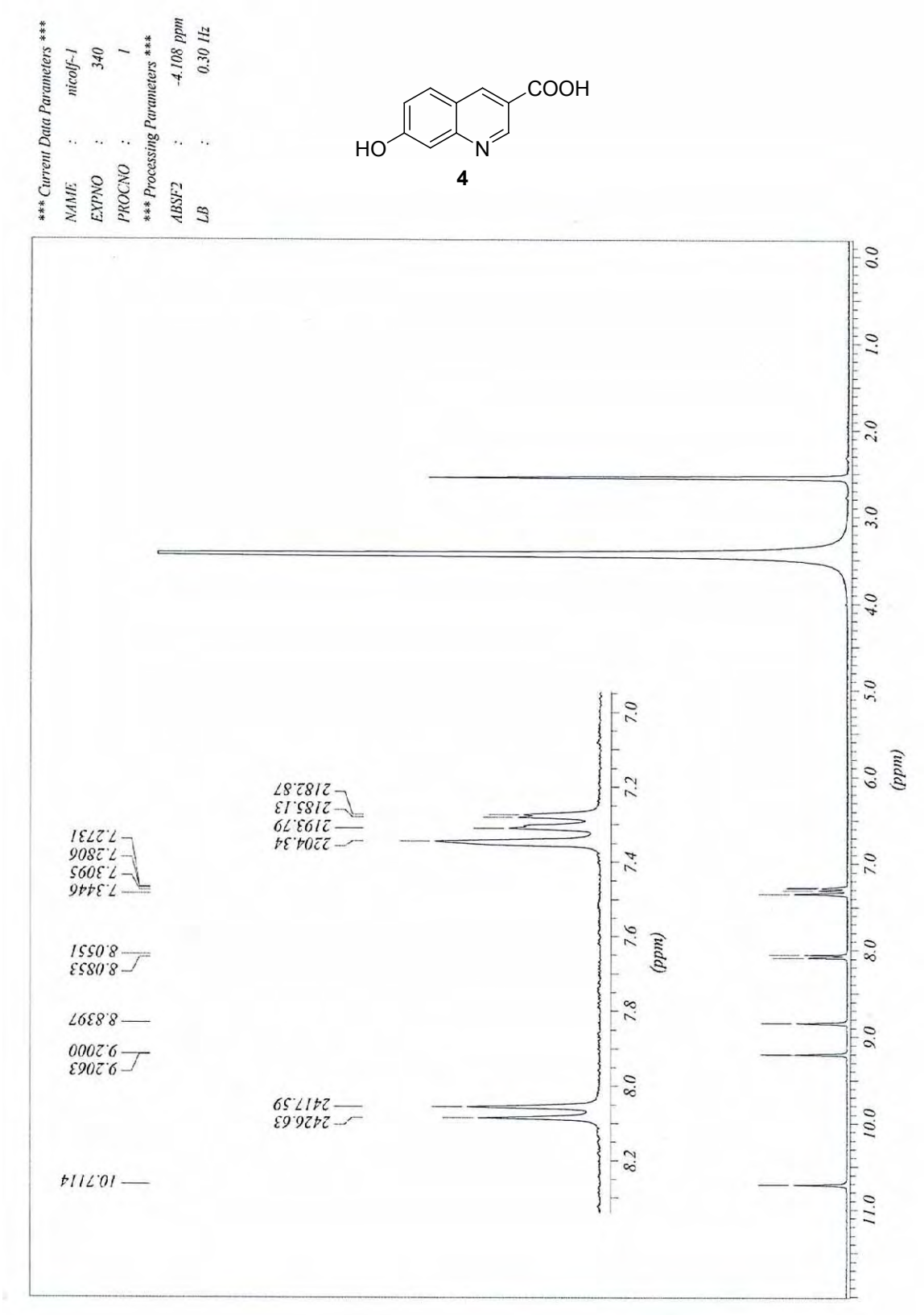
1.4. ^{1}H and ^{13}C NMR spectra

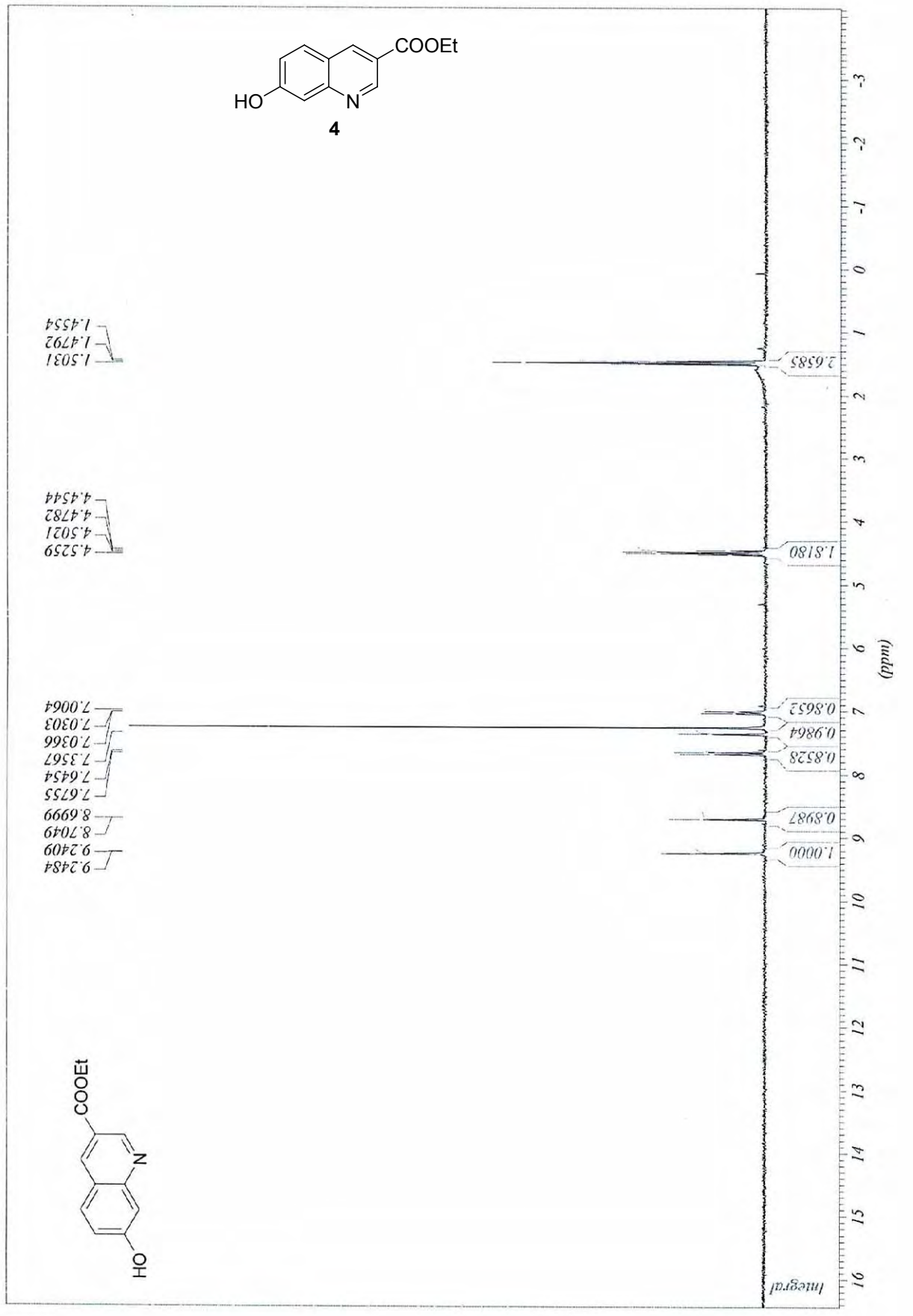


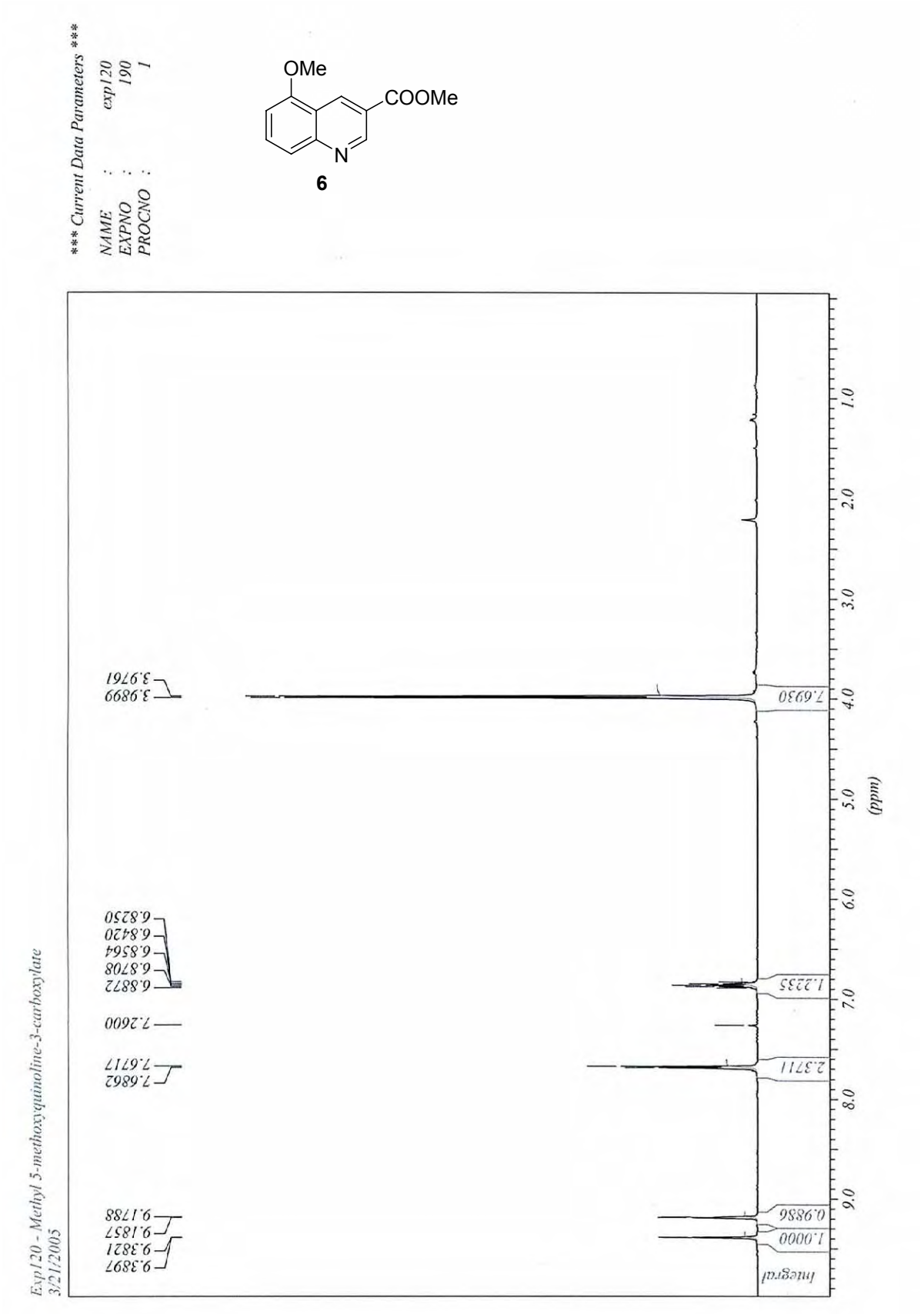


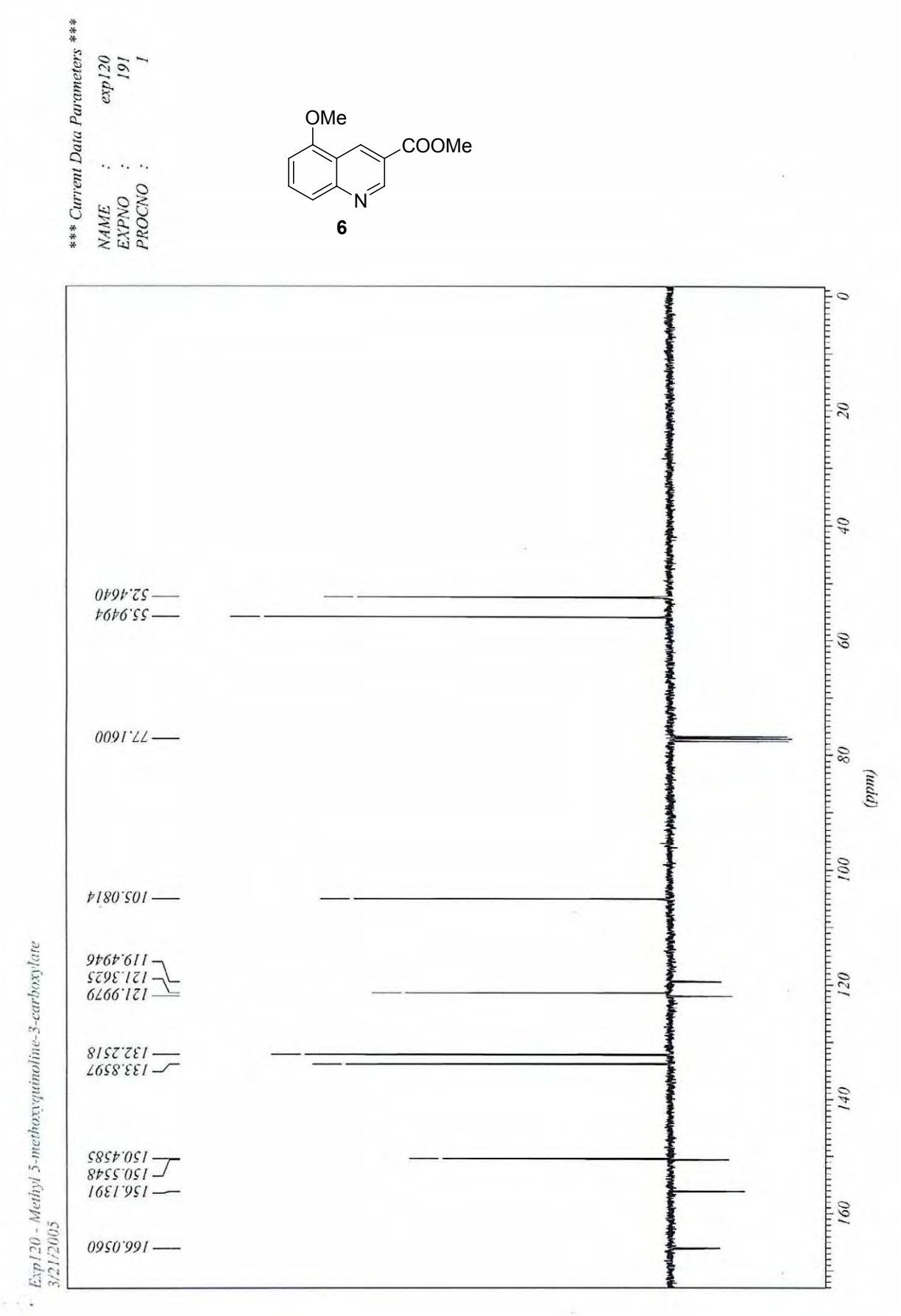
3

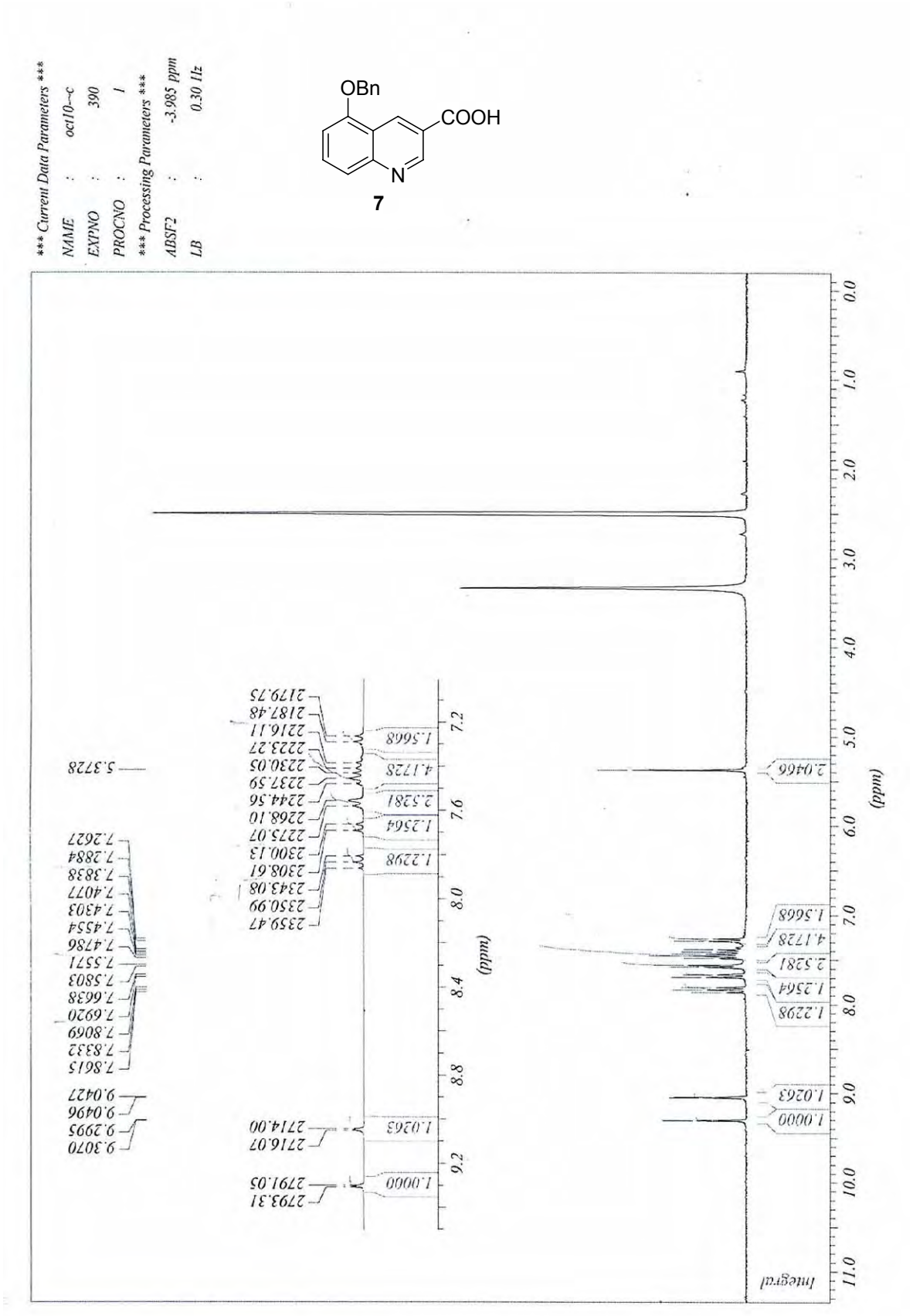


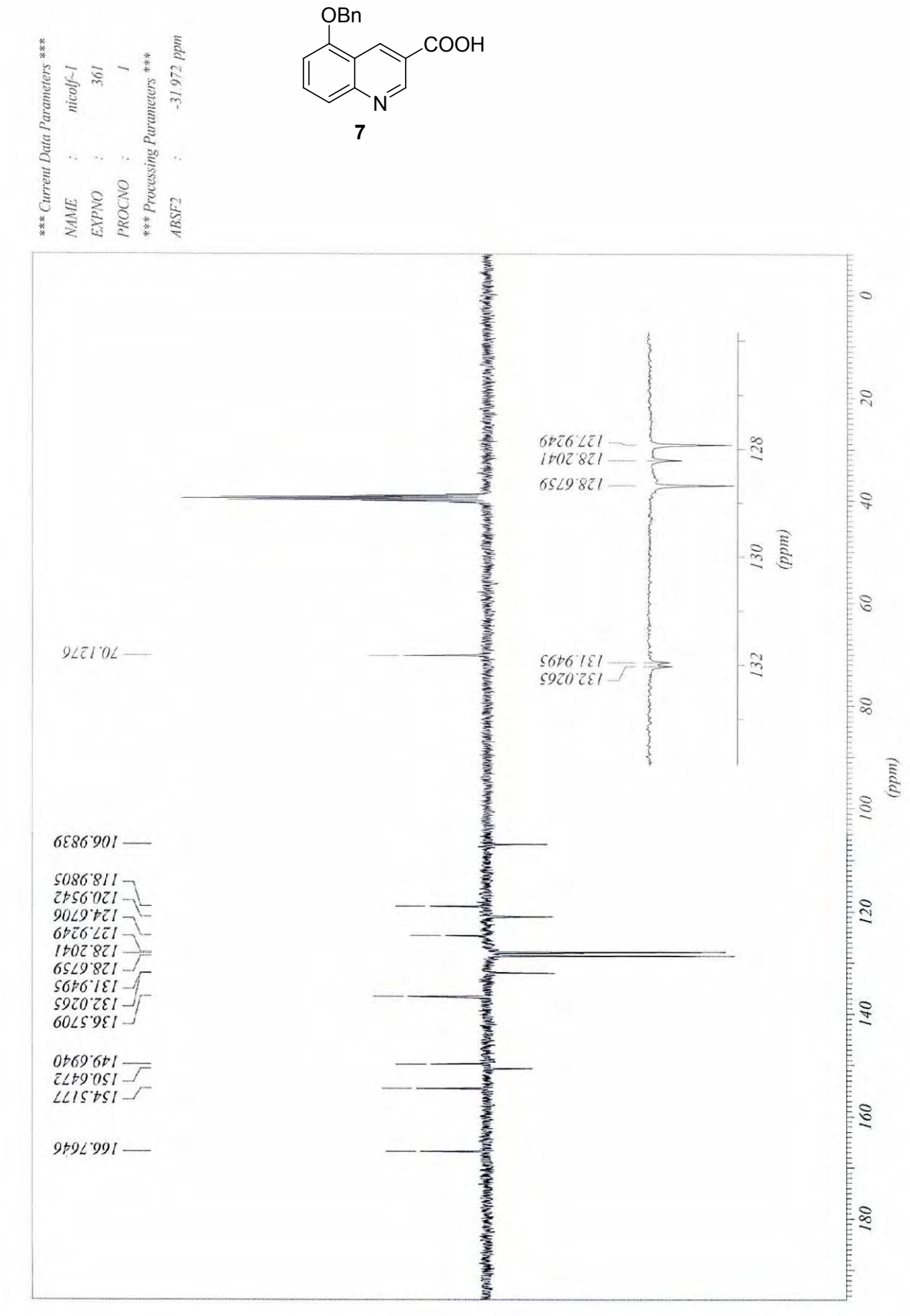


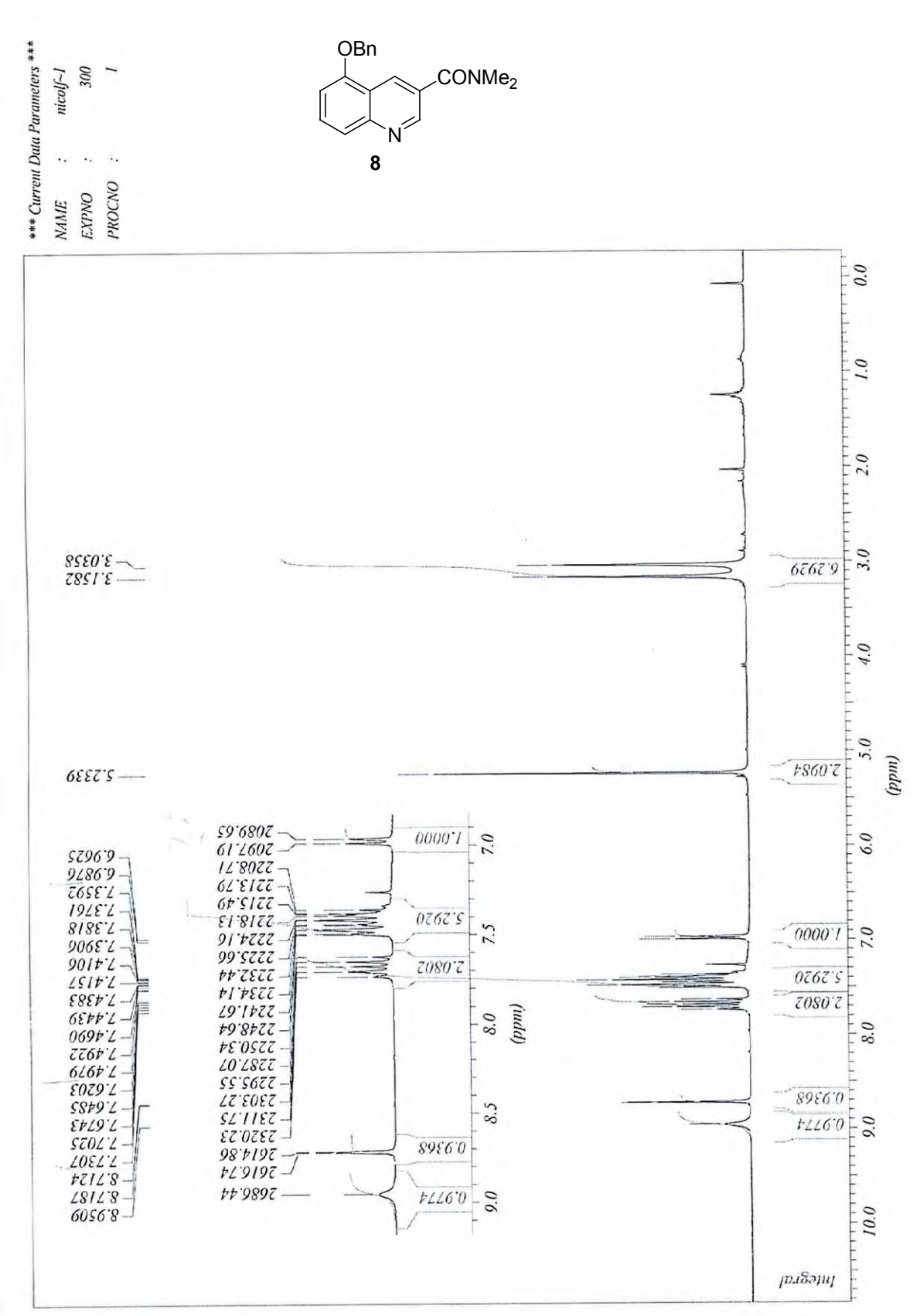


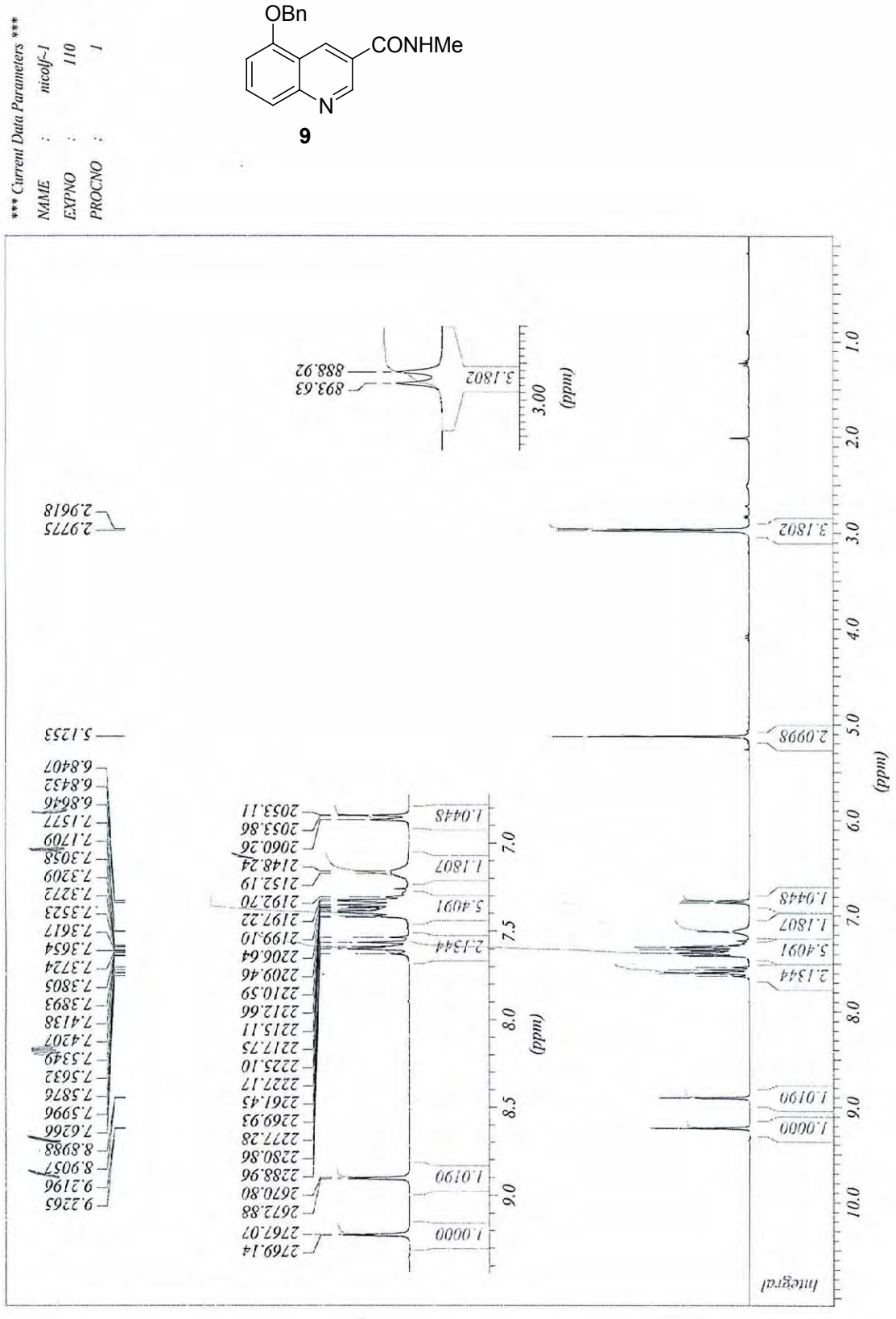


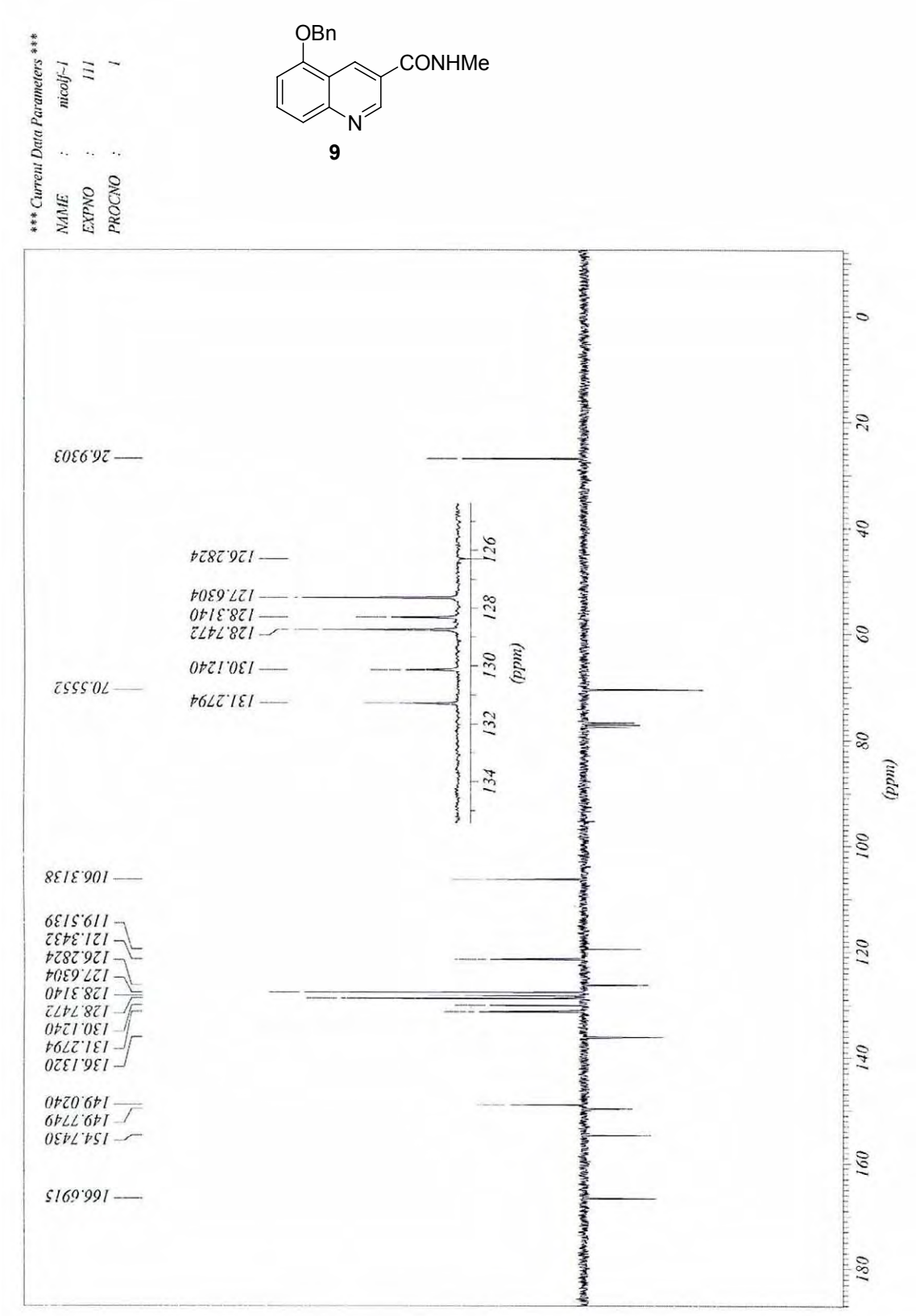

*** Current Data Parameters ***
NAME exp120
EXPNO 191
PROCNO 1
OMe
COOMe
N
6
52.4640
55.9494
77.1600
105.0814
119.4946
121.3625
121.9979
132.2518
133.8597
150.4585
150.5548
156.1391
166.0560
(ppm)
Exp120 - Methyl 5-methoxyquinoline-3-carboxylate
3/21/2005

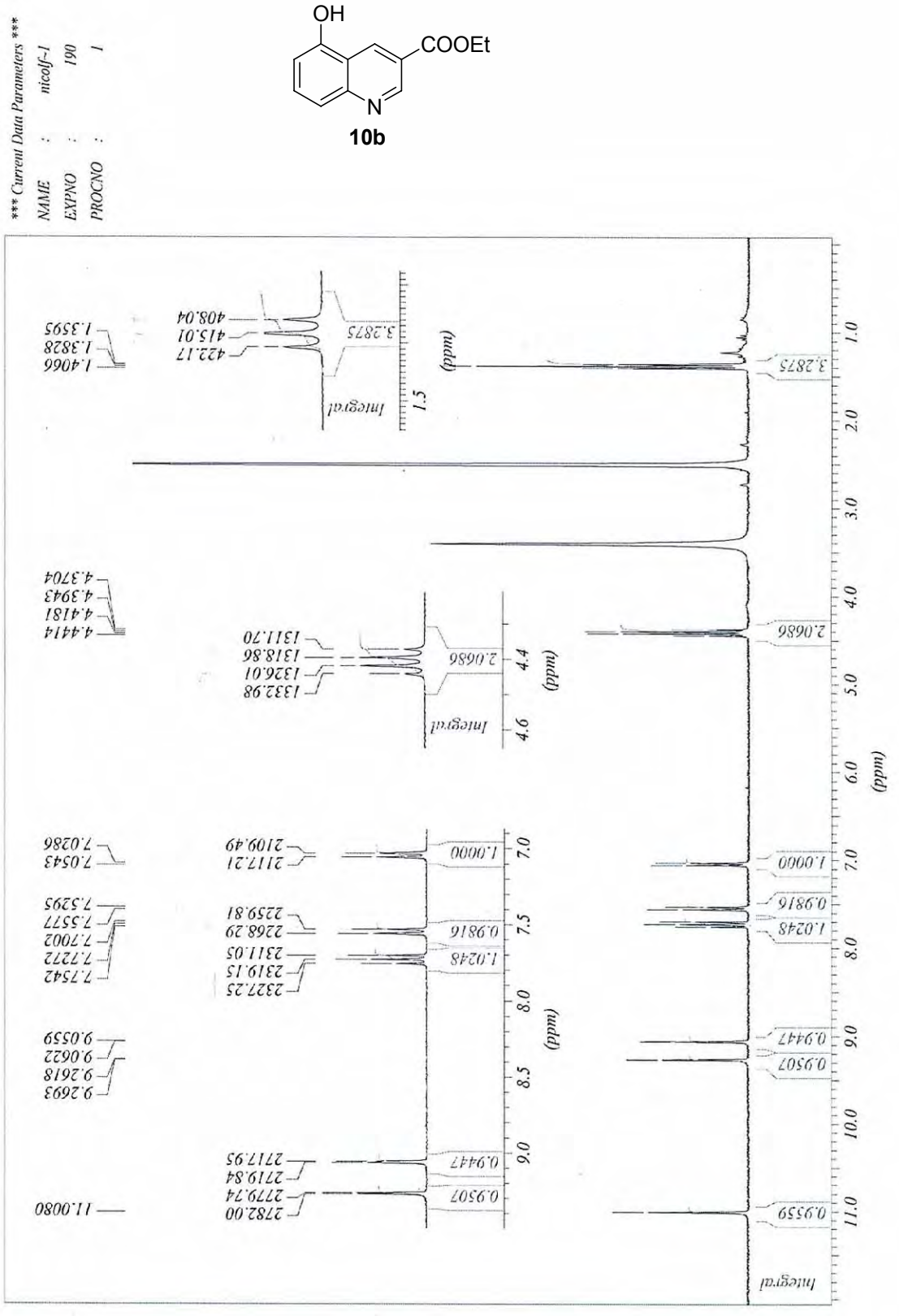


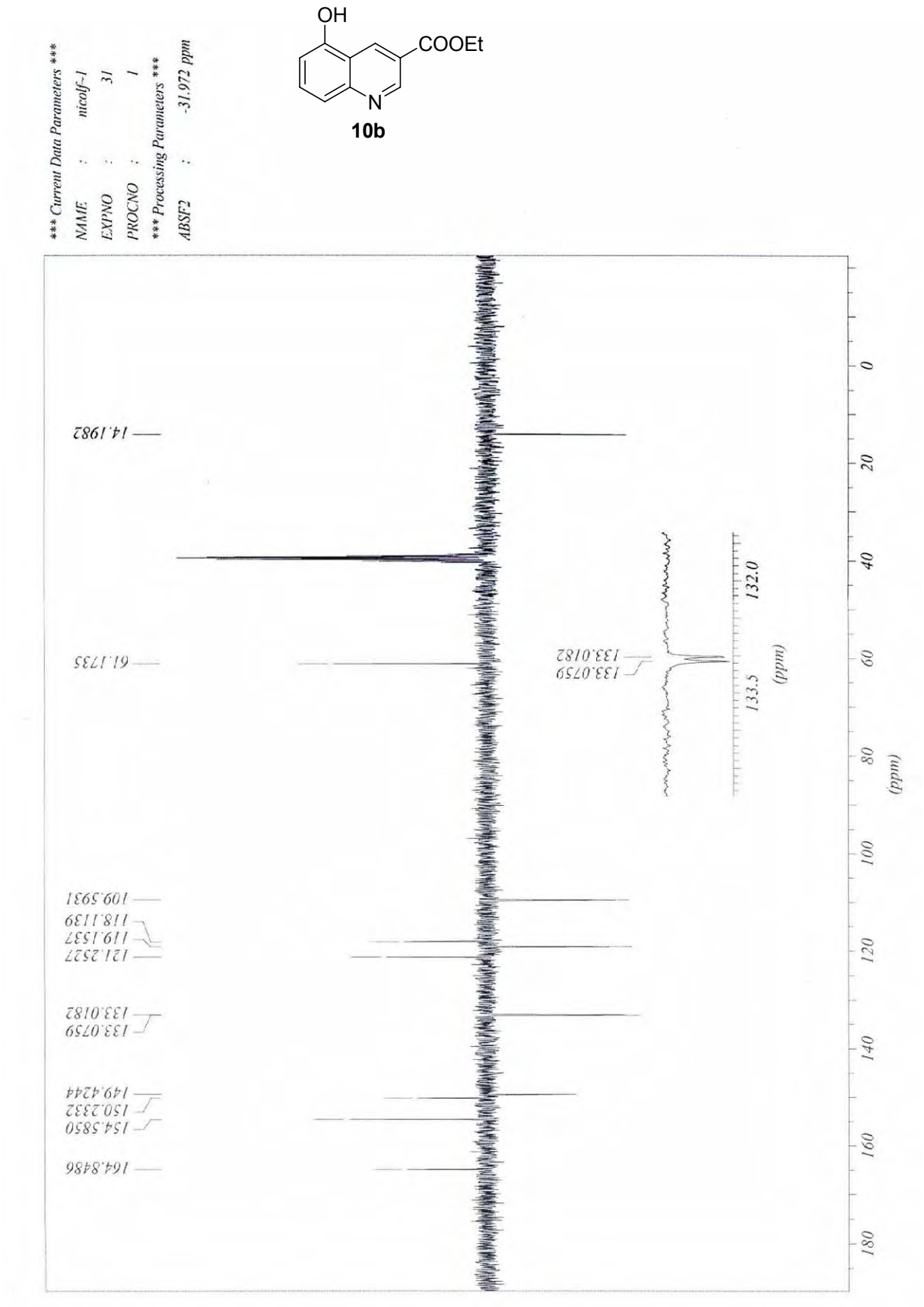


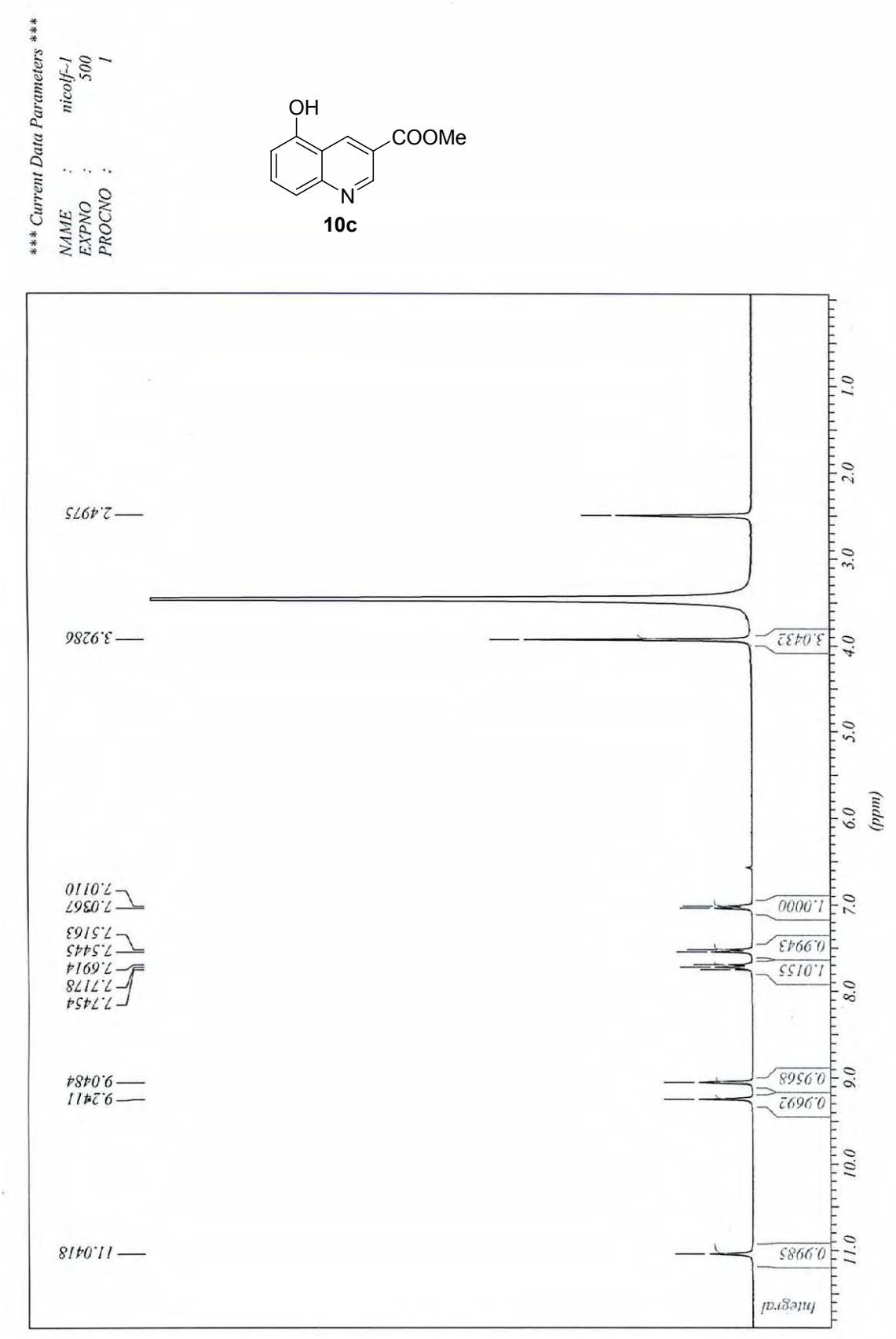

OBn
CONMe2
N
8
*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 300
PROCNO : 1
3.0358
3.1582
5.2339
8.9509
8.7187
8.7124
7.7307
7.7025
7.6743
7.6485
7.6203
7.4979
7.4922
7.4690
7.4439
7.4383
7.4157
7.4106
7.3906
7.3818
7.3761
7.3592
6.9876
6.9625
2089.65
2097.19
2208.71
2213.79
2215.49
2218.13
2224.16
2225.66
2232.44
2234.14
2241.67
2248.64
2250.34
2287.07
2295.55
2303.27
2311.75
2320.23
2614.86
2616.74
2686.44
1.0000
5.2920
2.0802
0.9368
0.9774
6.2929
2.0984
1.0000
5.2920
2.0802
0.9368
0.9774
Integral
(ppm)

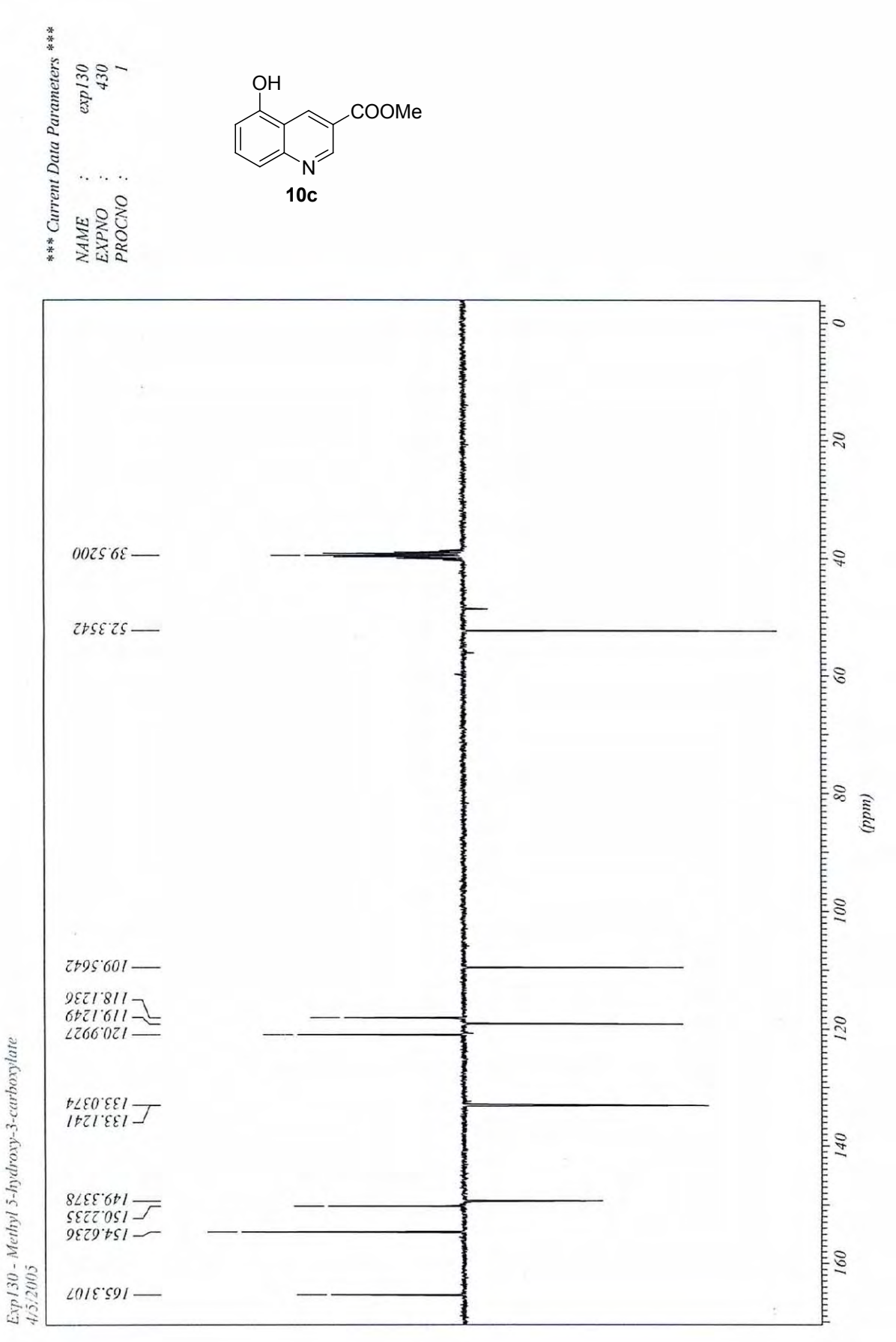


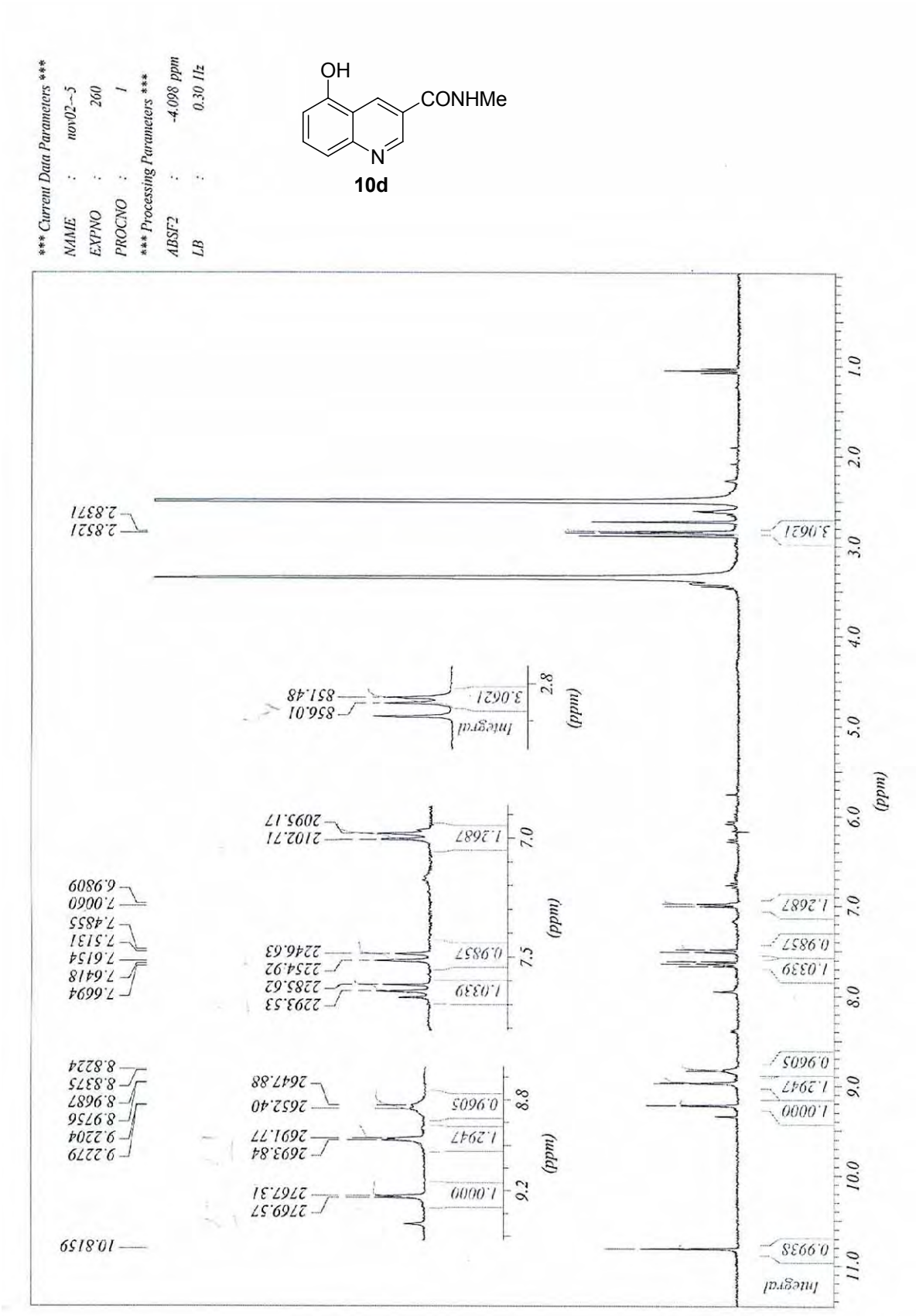


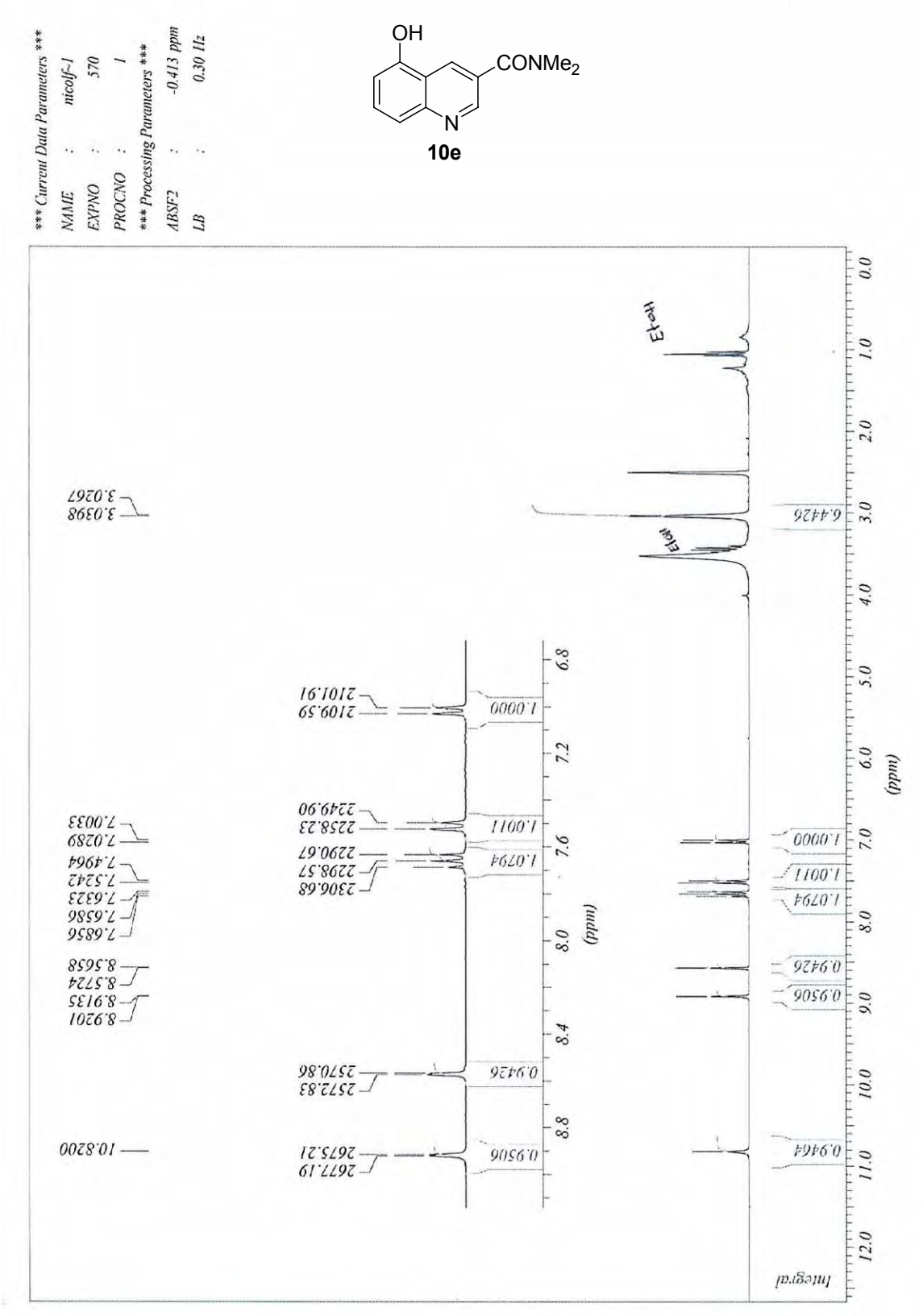

OH
COOEt
N
10b
*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 190
PROCNO : 1
(ppm)
Integral

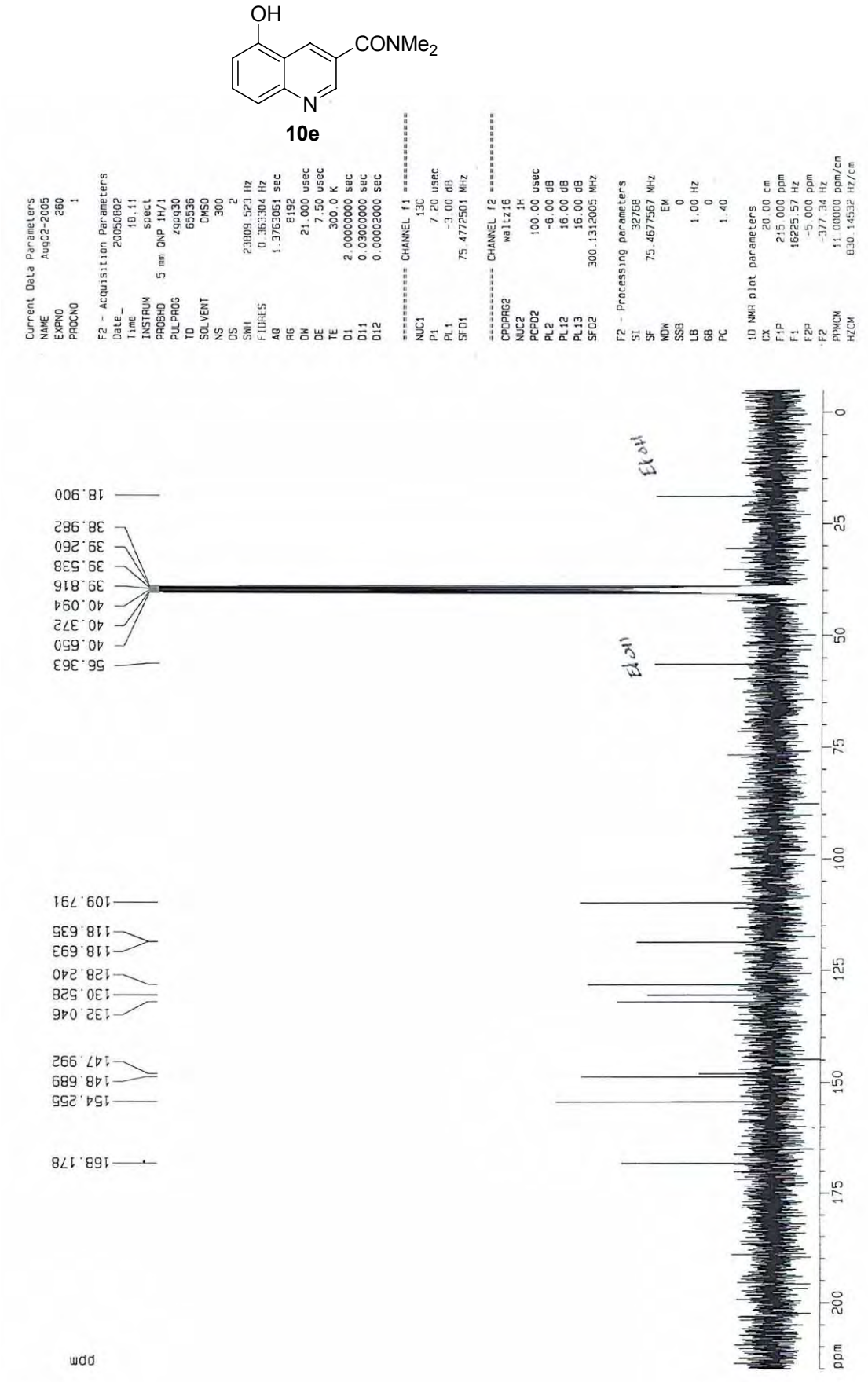


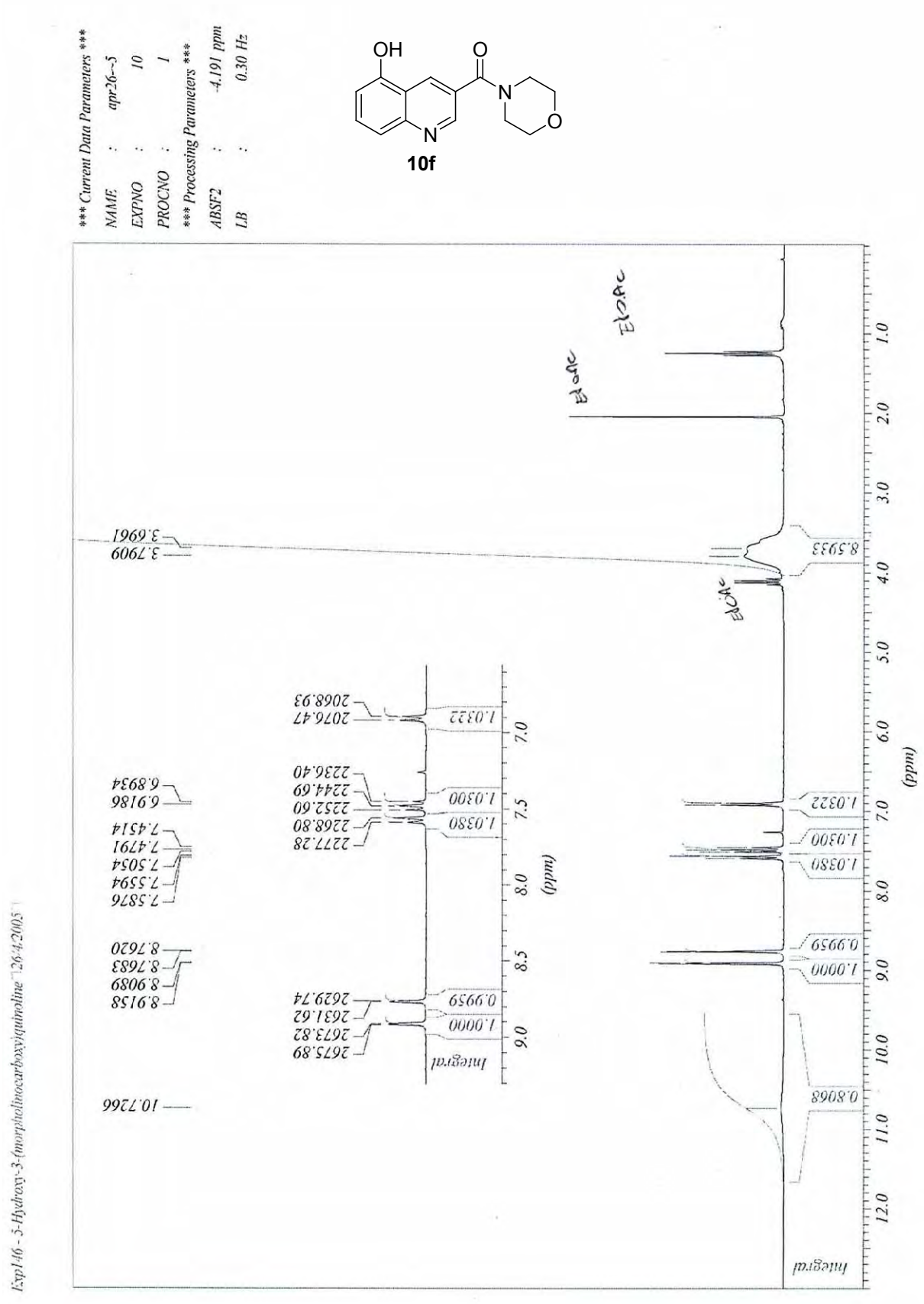


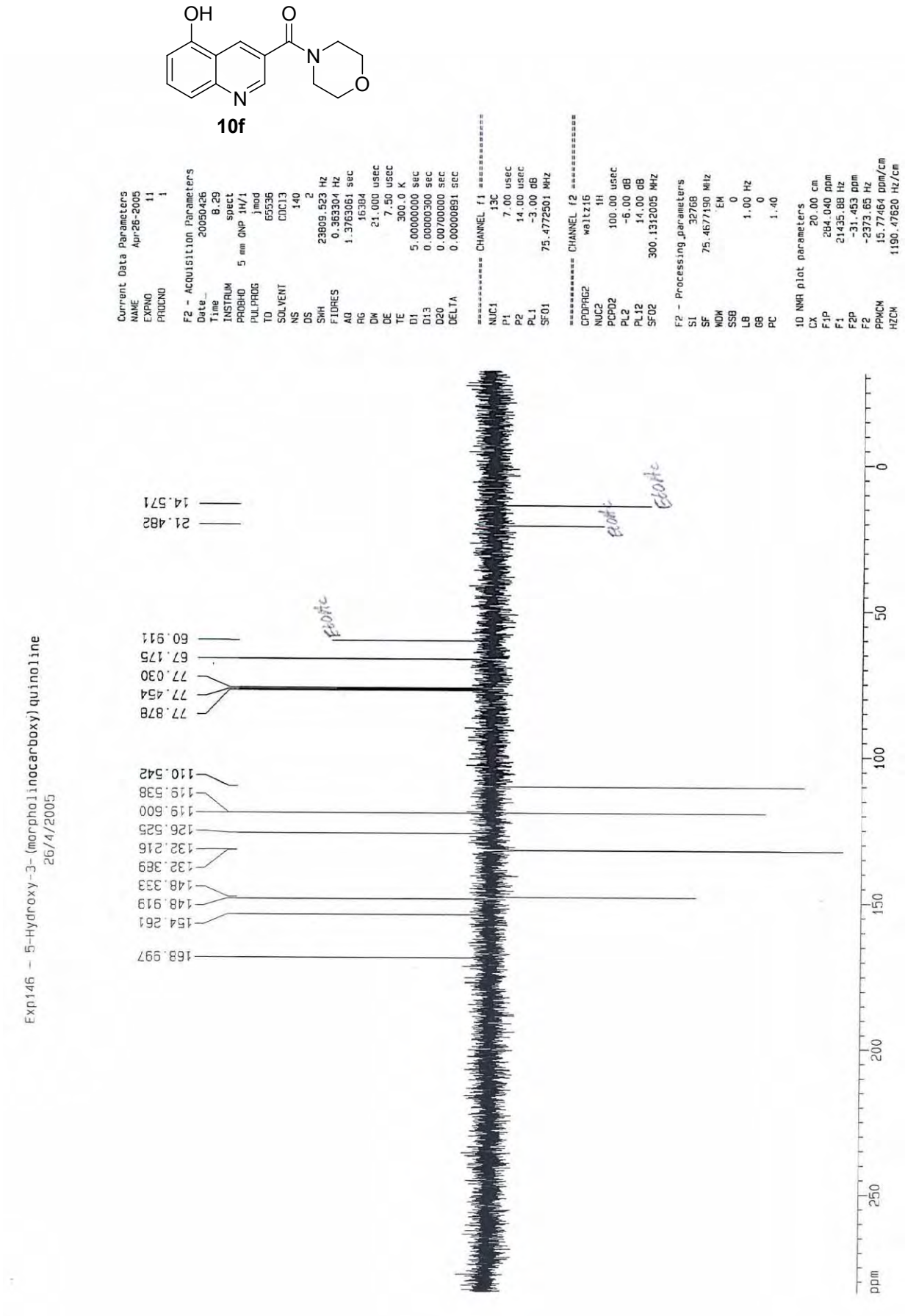


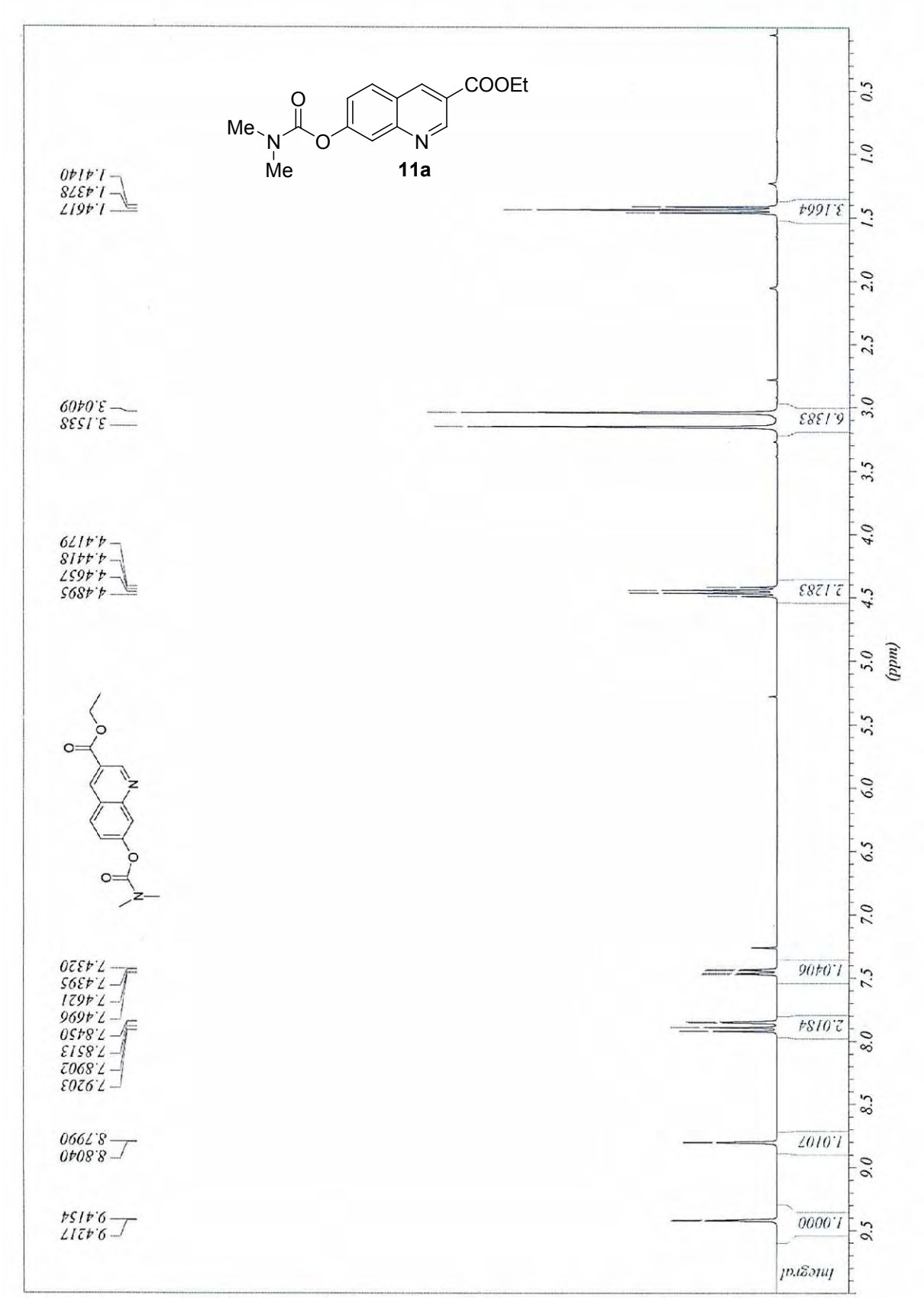


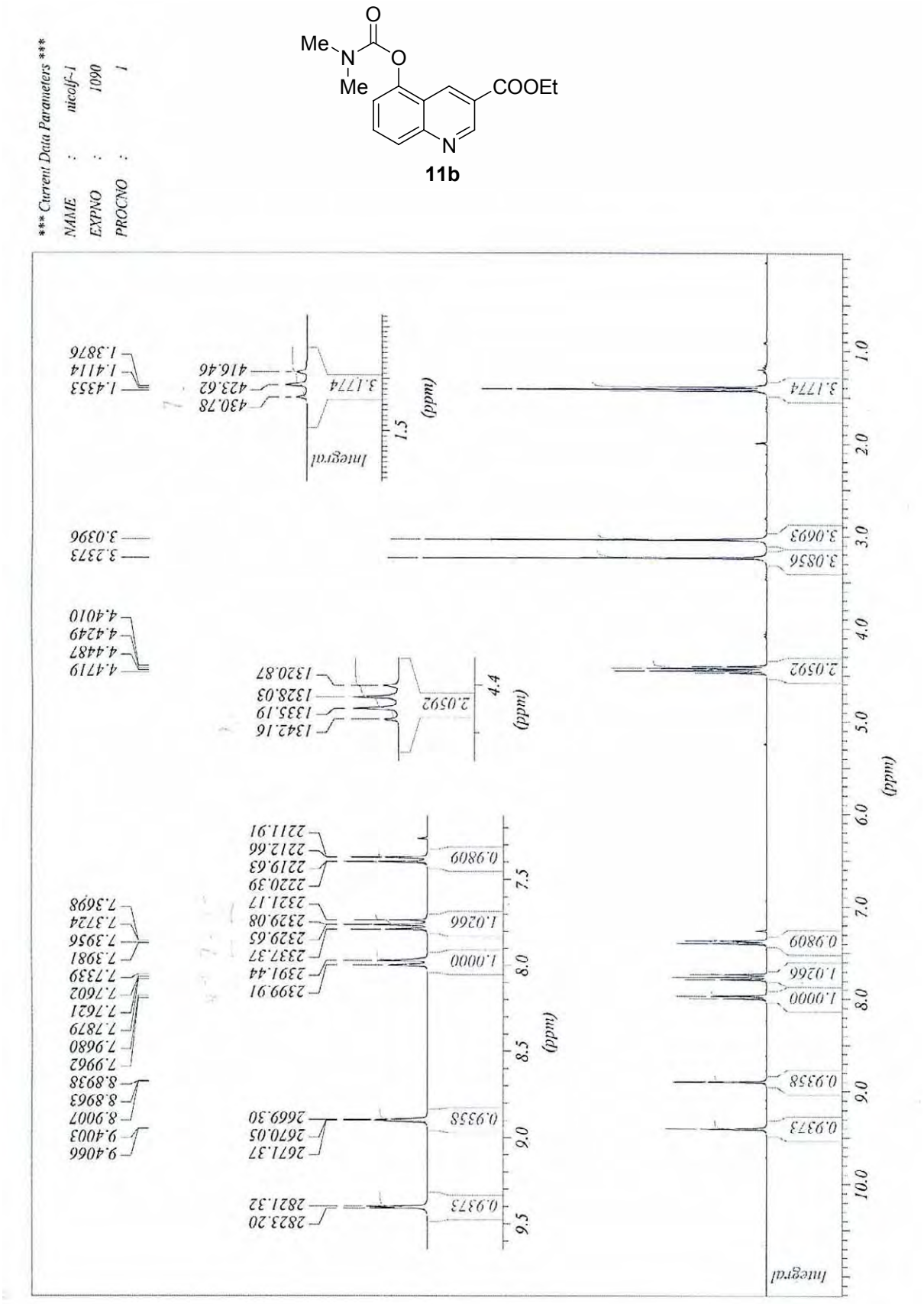


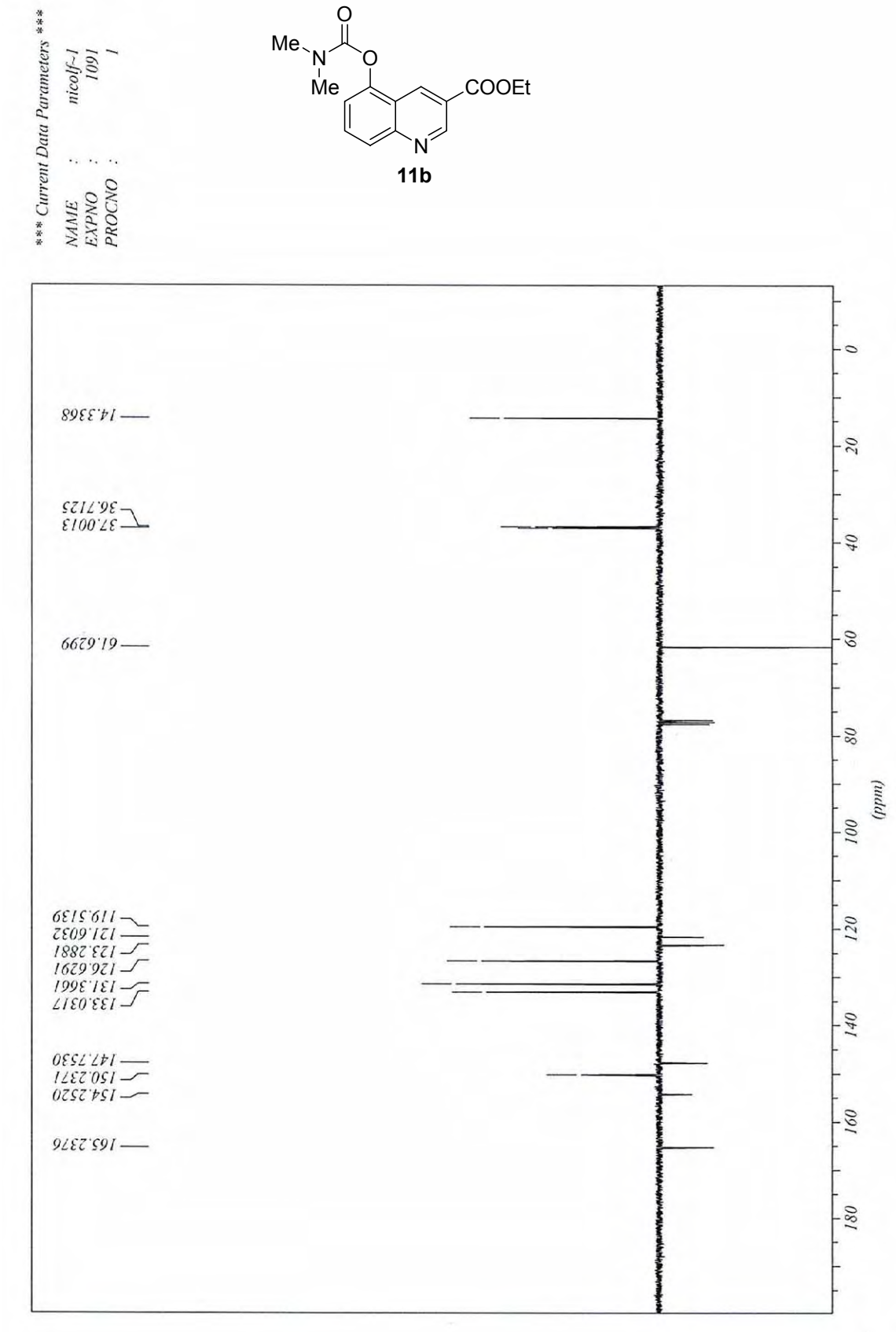

OH
CONMe2
N
10e
Current Data Parameters
NAME Aug02-2005
EXPNO 260
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050802
Time 18.11
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 300
DS 2
SWH 23809.523 Hz
FIDRES 0.363304 Hz
AQ 1.3763051 sec
RG 8192
DW 21.000 usec
DE 7.50 usec
TE 300.0 K
D1 2.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
CHANNEL f1
NUC1 13C
P1 7.20 usec
PL1 -3.00 dB
SFO1 75.4772501 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 16.00 dB
PL13 16.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677567 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 215.000 ppm
F1 16225.57 Hz
F2P -5.000 ppm
F2 -377.34 Hz
PPMCM 11.00000 ppm/cm
HZCM 830.14532 Hz/cm
18.900
38.982
39.260
39.538
39.816
40.094
40.372
40.650
56.363
109.791
118.635
118.693
128.240
130.528
132.046
147.992
148.689
154.255
168.178
ppm

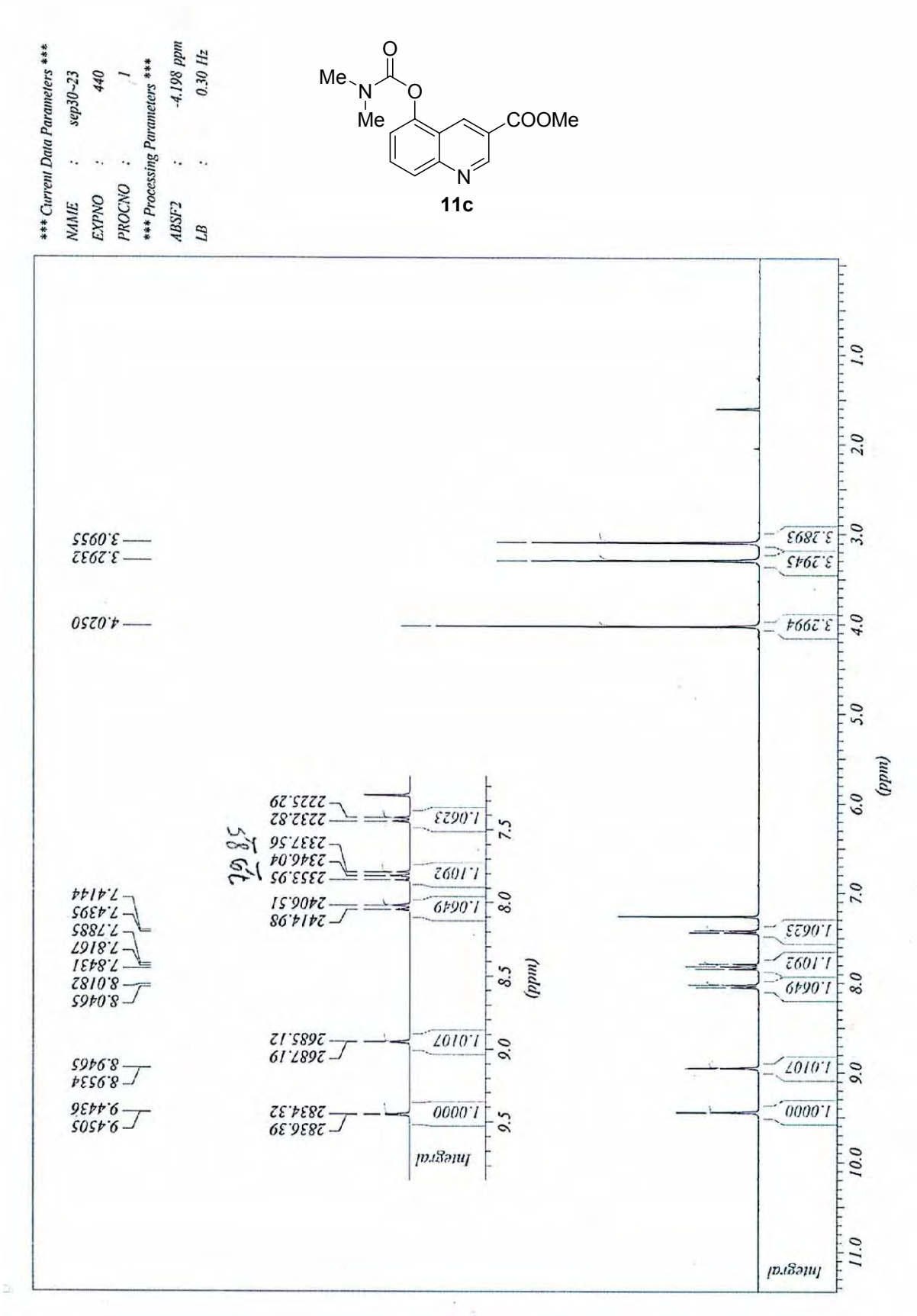

OH
O
N
N
O
10f
*** Current Data Parameters ***
NAME : apr26--5
EXPNO : 10
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.191 ppm
LB : 0.30 Hz
Exp146 - 3-Hydroxy-3-(morpholinocarboxy)quinoline 26.4.2005
(ppm)
Integral

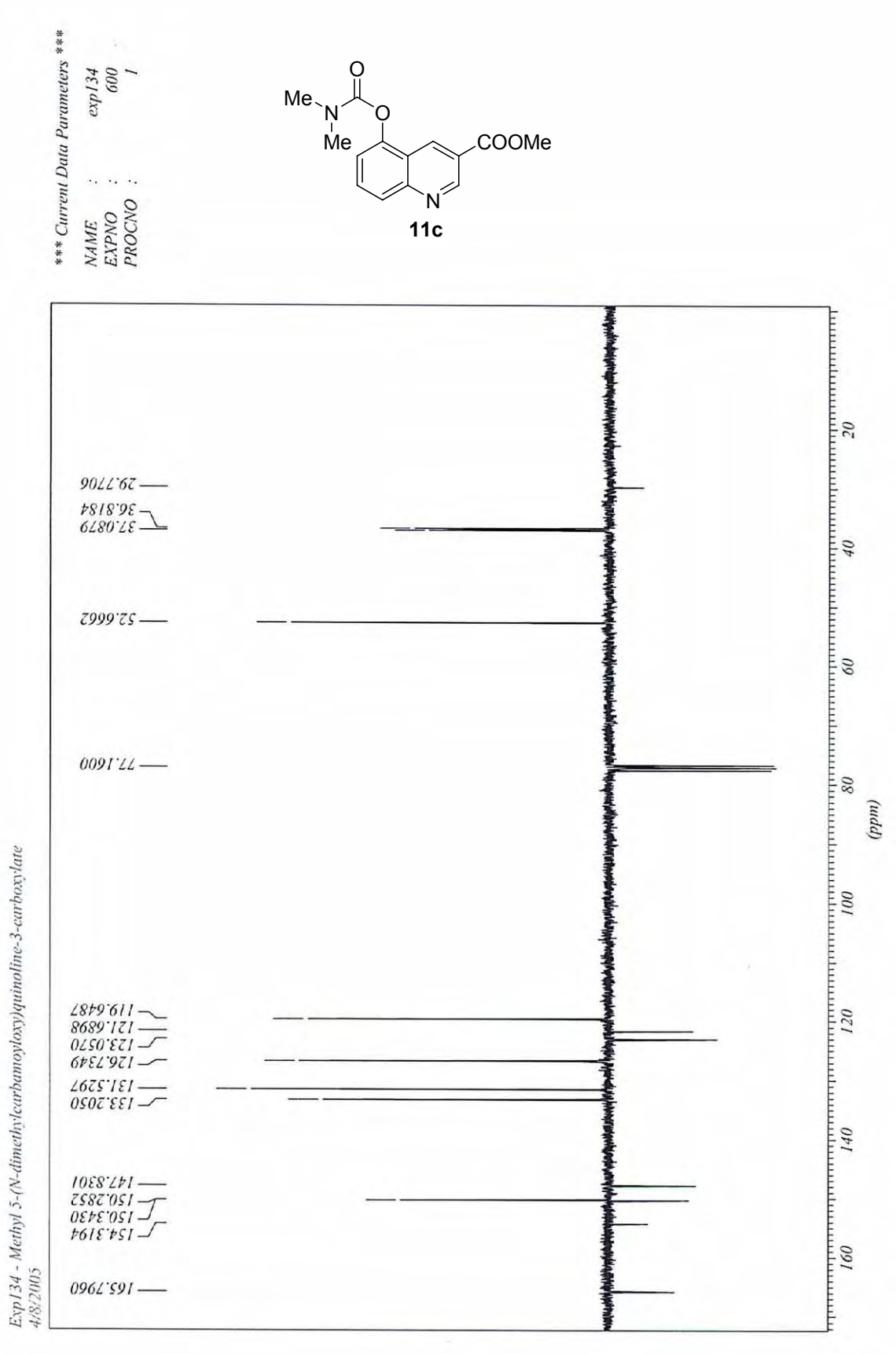

OH
O
N
N
O
10f
Current Data Parameters
NAME Apr26-2005
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050426
Time 8.29
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 140
DS 2
SWH 23809.523 Hz
FIDRES 0.363304 Hz
AQ 1.3763061 sec
RG 16384
DW 21.000 usec
DE 7.50 usec
TE 300.0 K
D1 5.00000000 sec
D13 0.00000300 sec
D20 0.00700000 sec
DELTA 0.00000891 sec
CHANNEL f1
NUC1 13C
P1 7.00 usec
P2 14.00 usec
PL1 -3.00 dB
SF01 75.4772501 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 14.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 284.040 ppm
F1 21435.88 Hz
F2P -31.453 ppm
F2 -2373.65 Hz
PPMCM 15.77464 ppm/cm
HZCM 1190.47620 Hz/cm
Exp146 - 5-Hydroxy-3-(morpholinocarboxy) quinoline
26/4/2005
14.571
21.482
60.911
67.175
77.030
77.454
77.878
110.542
119.538
119.600
126.525
132.216
132.389
148.333
148.919
154.261
168.997
Ethoxy
Ethoxy
ppm

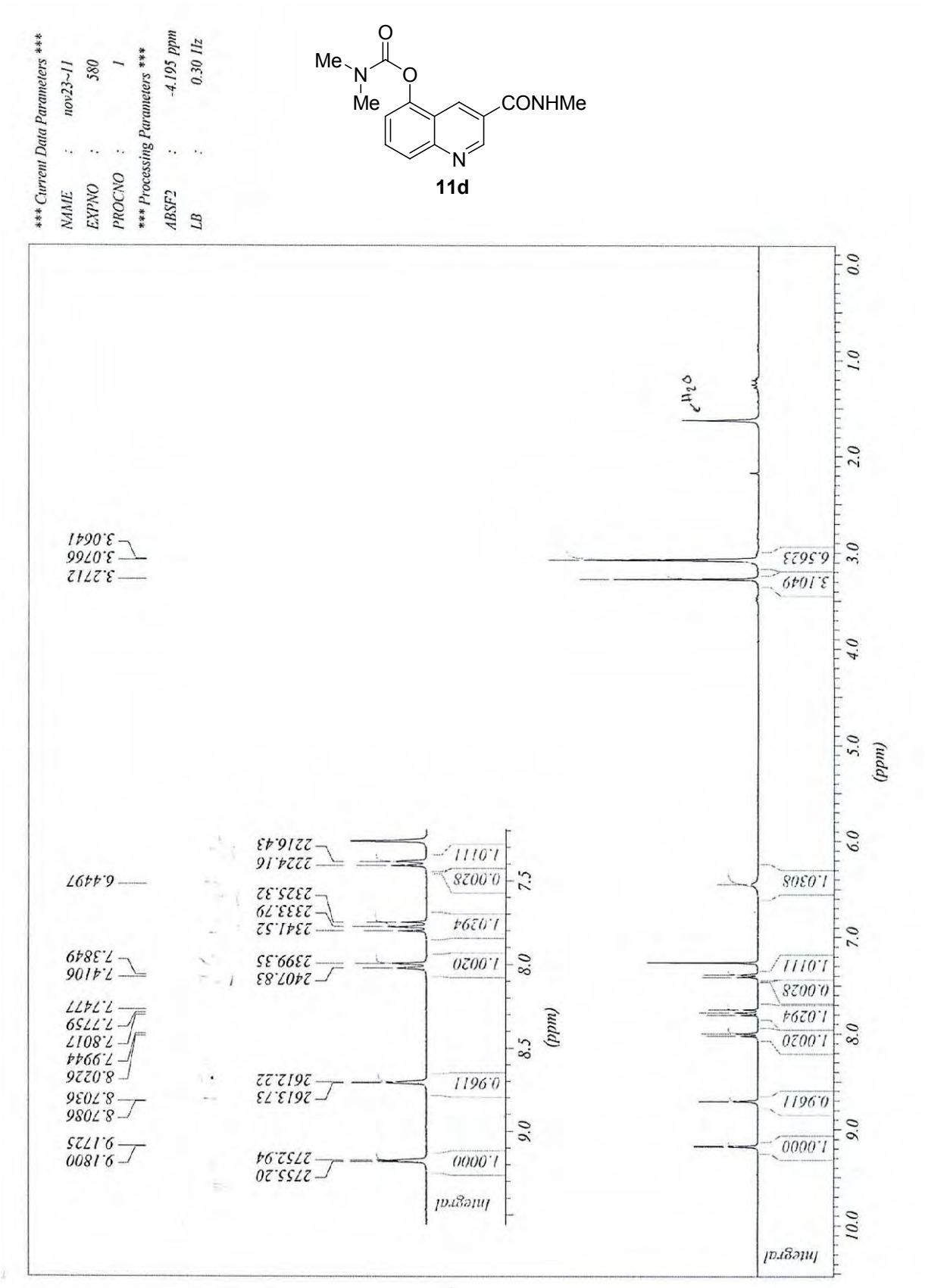


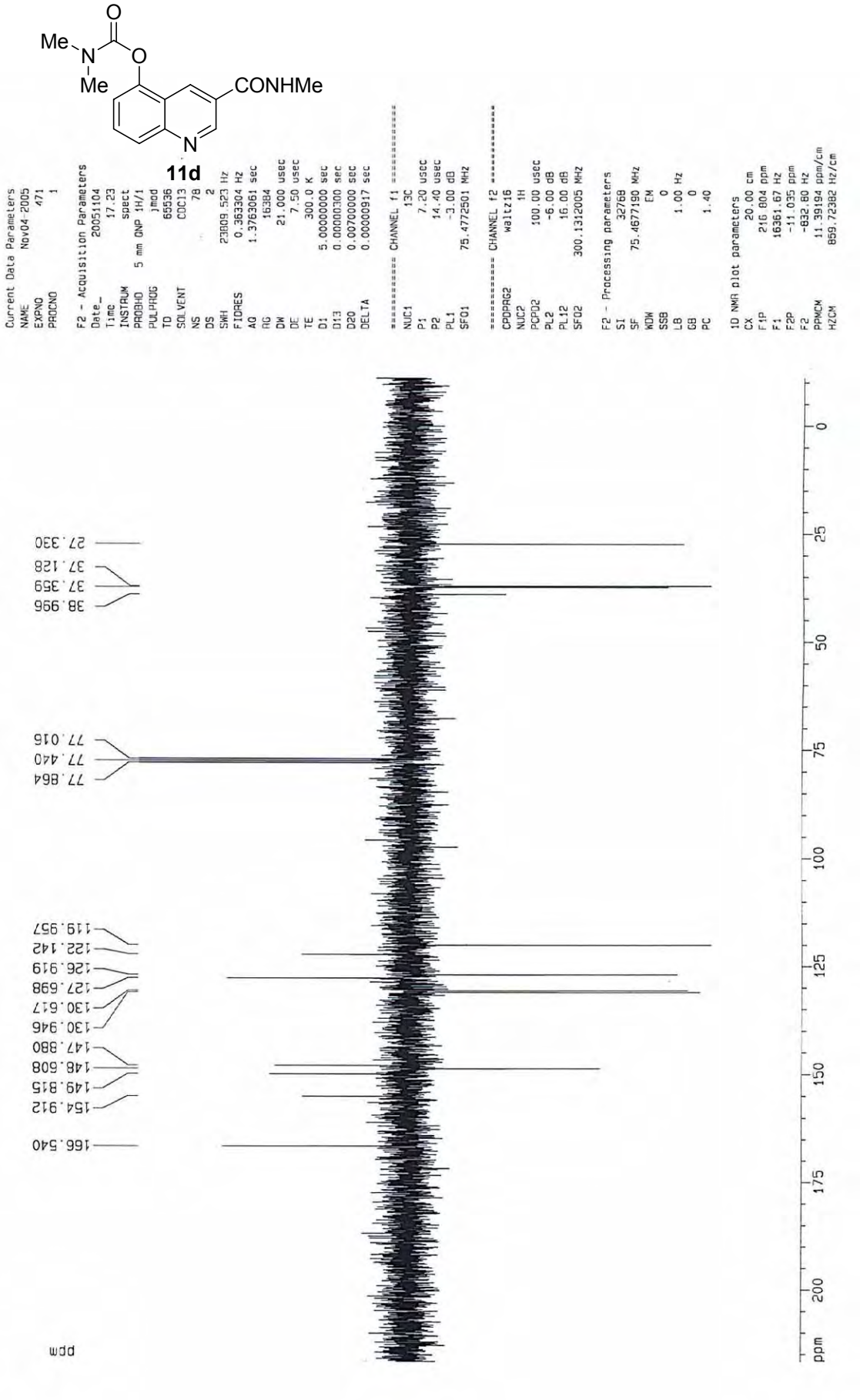

*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 1090
PROCNO : 1
Me
N
Me
O
O
COOEt
N
11b
Integral
(ppm)

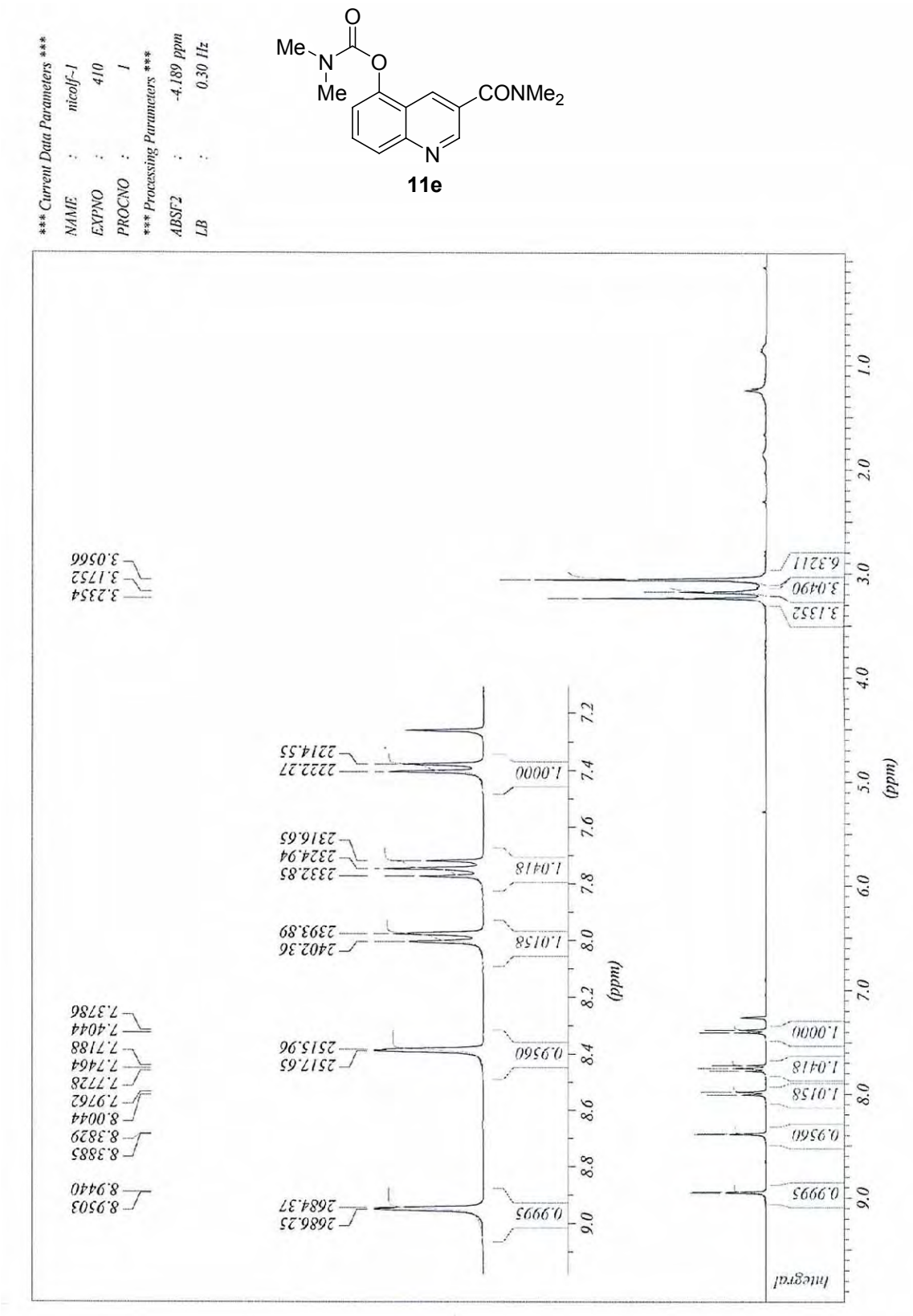

*** Current Data Parameters ***
NAME nicolf-1
EXPNO 1091
PROCNO 1
Me
N
Me
O
O
COOEt
N
11b
14.3368
36.7125
37.0013
61.6299
119.5139
121.6032
123.2881
126.6291
131.3661
133.0317
147.7530
150.2371
154.2520
165.2376
0
20
40
60
80
100
120
140
160
180
(ppm)

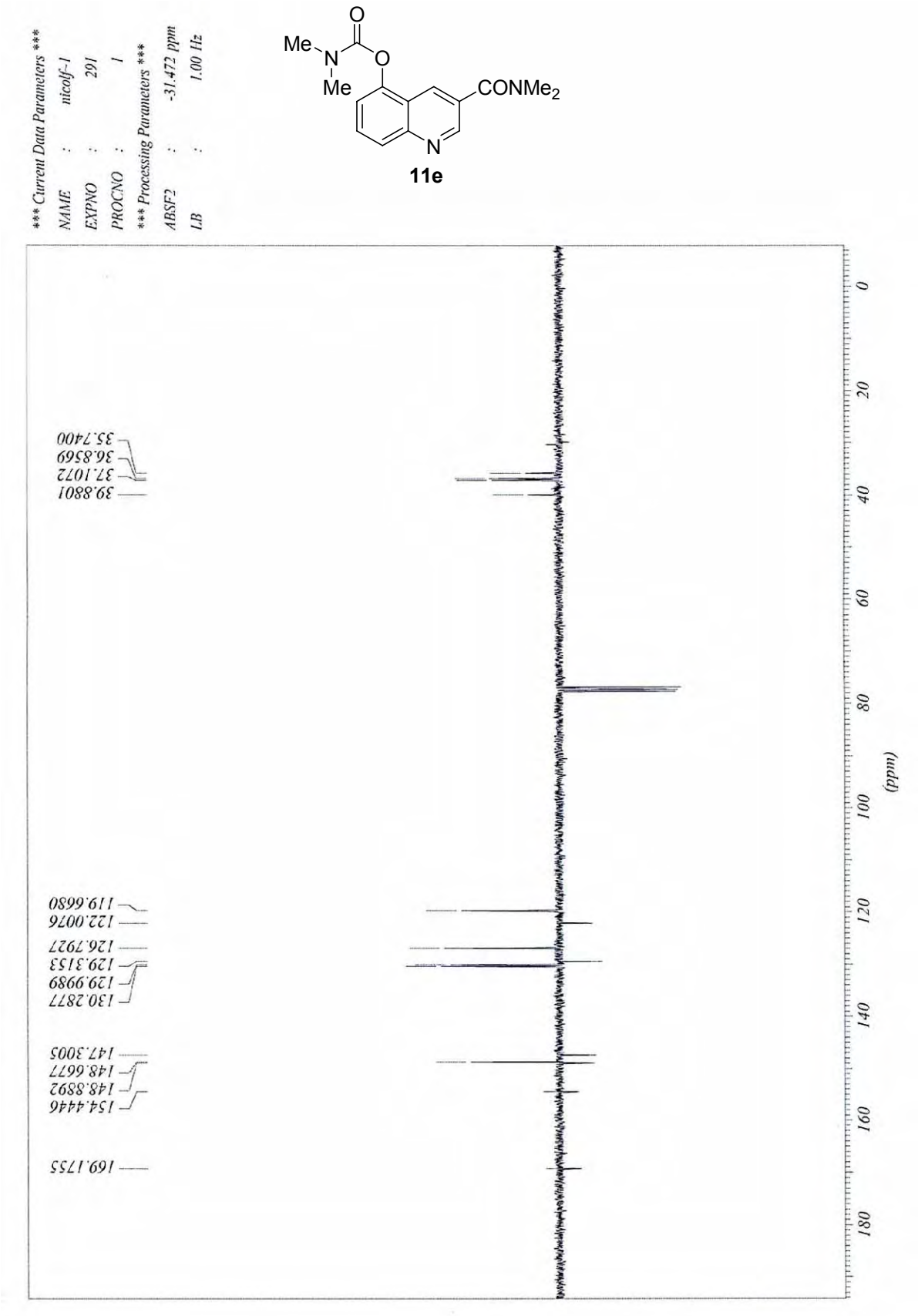


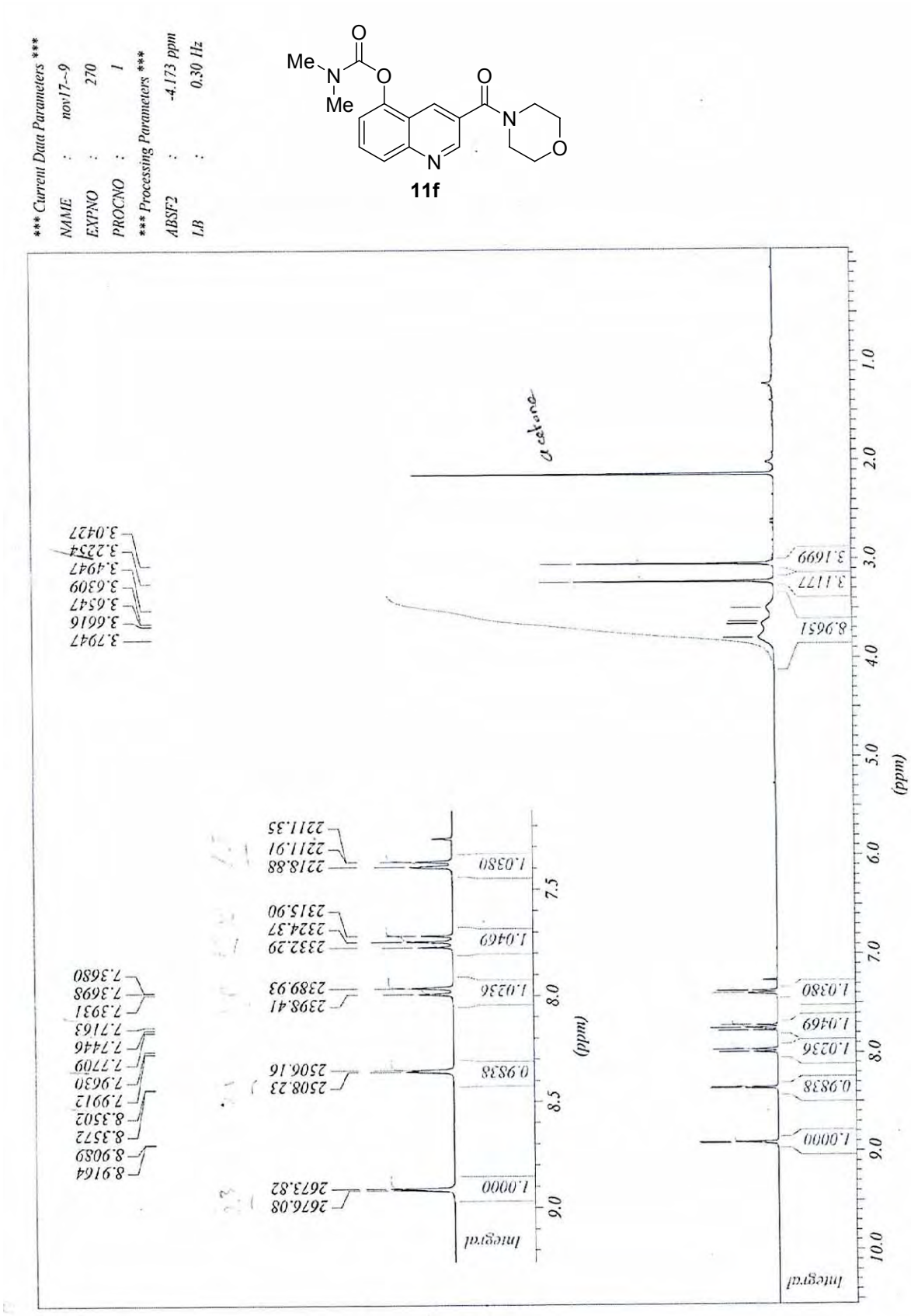

*** Current Data Parameters ***
NAME exp134
EXPNO 600
PROCNO 1
Me
N
Me
O
O
COOMe
N
11c
29.7706
36.8184
37.0879
52.6662
77.1600
119.6487
121.6898
123.0570
126.7349
131.5297
133.2050
147.8301
150.2852
150.3430
154.3194
165.7960
20
40
60
80
100
120
140
160
(ppm)
Exp134 - Methyl 5-(N-dimethylcarbamoyloxy)quinoline-3-carboxylate
4/8/2005

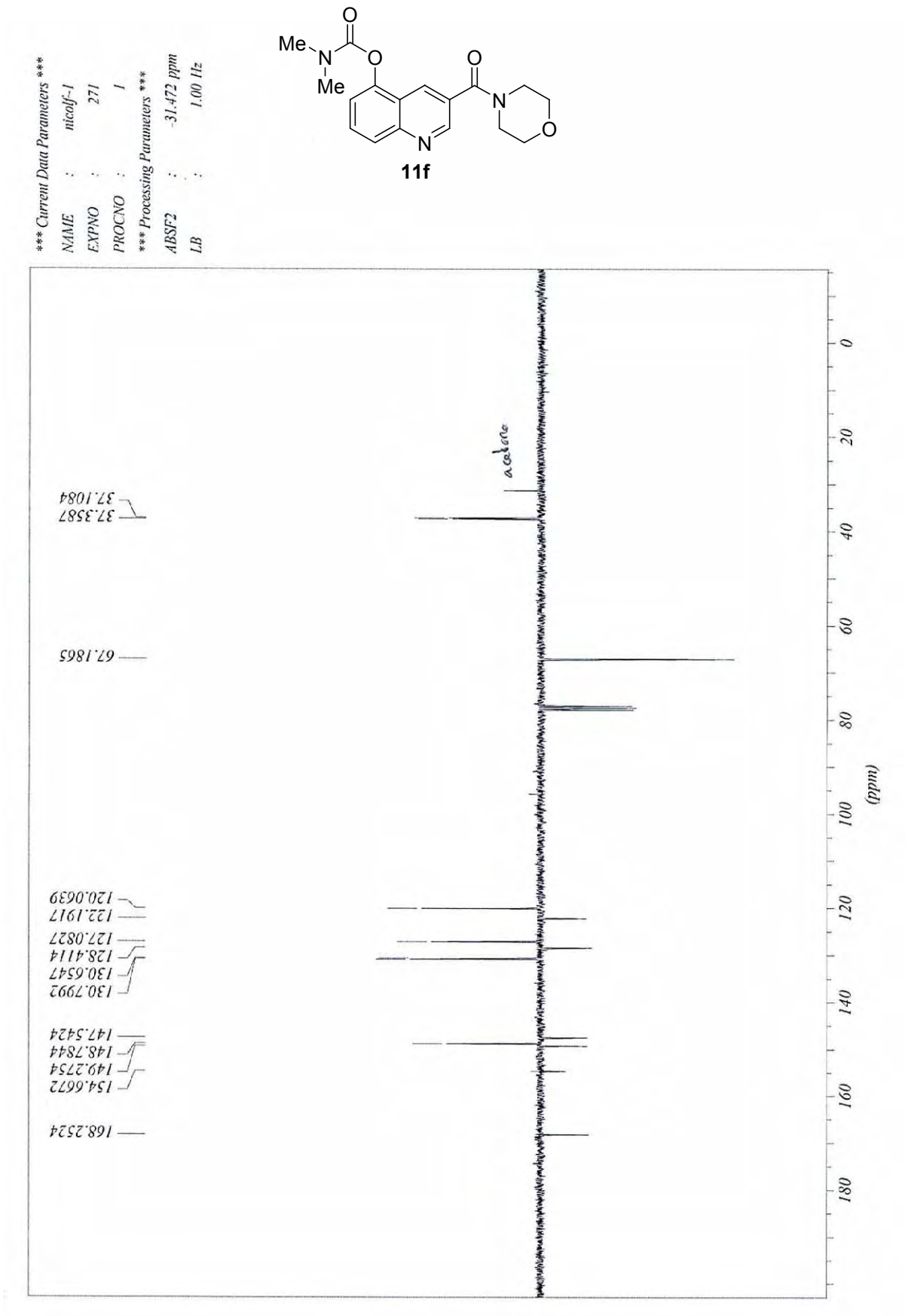

*** Current Data Parameters ***
NAME : nov23-11
EXPNO : 580
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.195 ppm
LB : 0.30 Hz
Me
N
Me
O
O
CONHMe
N
11d
integral
(ppm)

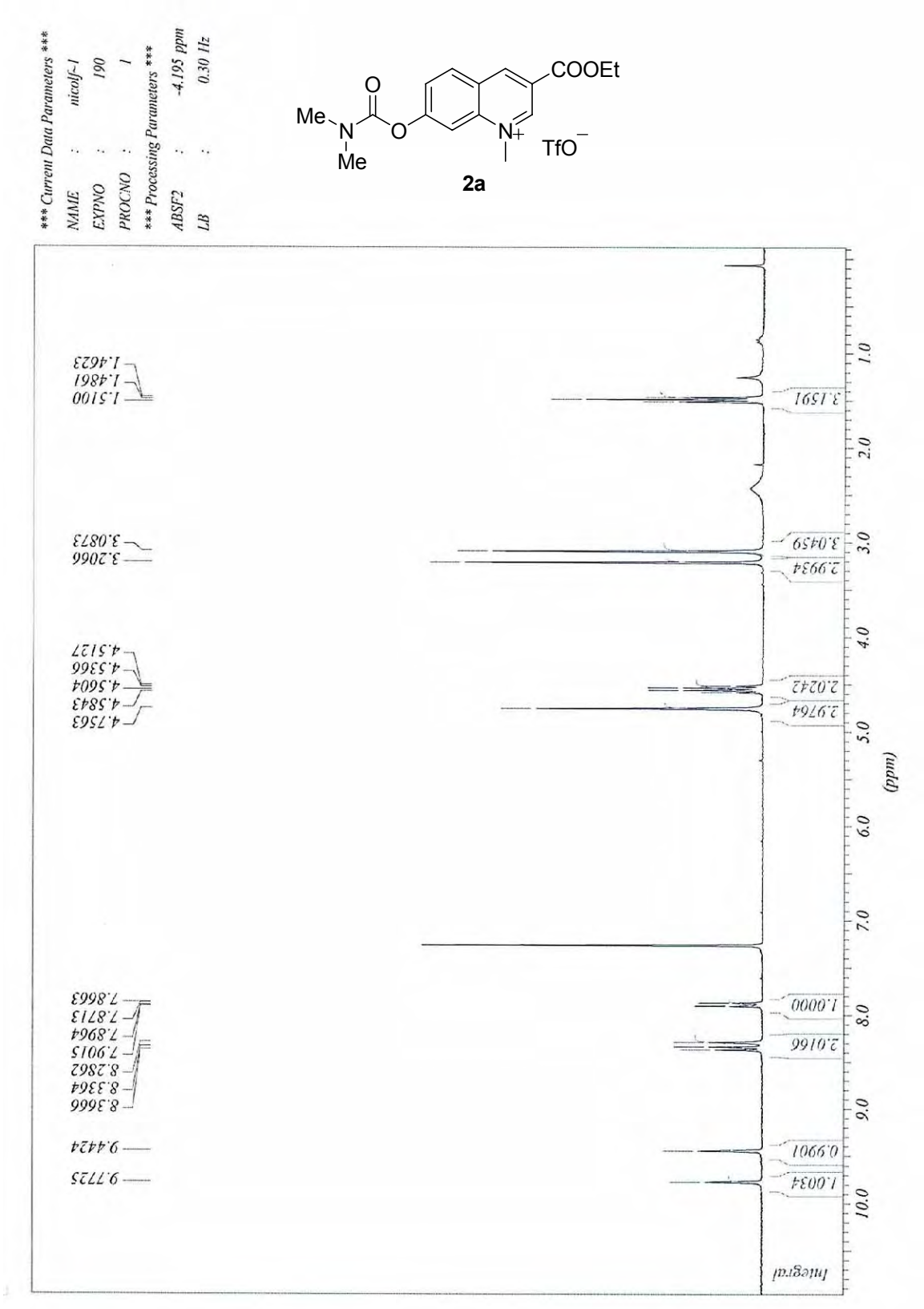

Me
N
Me
O
O
CONHMe
N
11d
Current Data Parameters
NAME Nov04-2005
EXPNO 471
PROCNO 1
F2 - Acquisition Parameters
Date_ 20051104
Time_ 17.23
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG jmod
TD 65536
SOLVENT CDCl3
NS 78
DS 2
SWH 23809.523 Hz
FIDRES 0.363304 Hz
AQ 1.3763061 sec
RG 16384
DW 21.000 usec
DE 7.50 usec
TE 300.0 K
D1 5.00000000 sec
D13 0.00000300 sec
D20 0.00700000 sec
DELTA 0.00000917 sec
======== CHANNEL f1 ========
NUC1 13C
P1 7.20 usec
P2 14.40 usec
PL1 -3.00 dB
SFO1 75.4772501 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -6.00 dB
PL12 16.00 dB
SFO2 300.1312005 MHz
F2 - Processing parameters
SI 32768
SF 75.4677190 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 216.804 ppm
F1 16361.67 Hz
F2P -11.035 ppm
F2 -832.80 Hz
PPMCM 11.39194 ppm/cm
HZCM 869.72382 Hz/cm
27.330
37.128
37.359
38.996
77.016
77.440
77.864
119.957
122.142
126.819
127.698
130.617
130.946
147.880
148.508
149.815
154.912
166.540
ppm
0
25
50
75
100
125
150
175
200
ppm

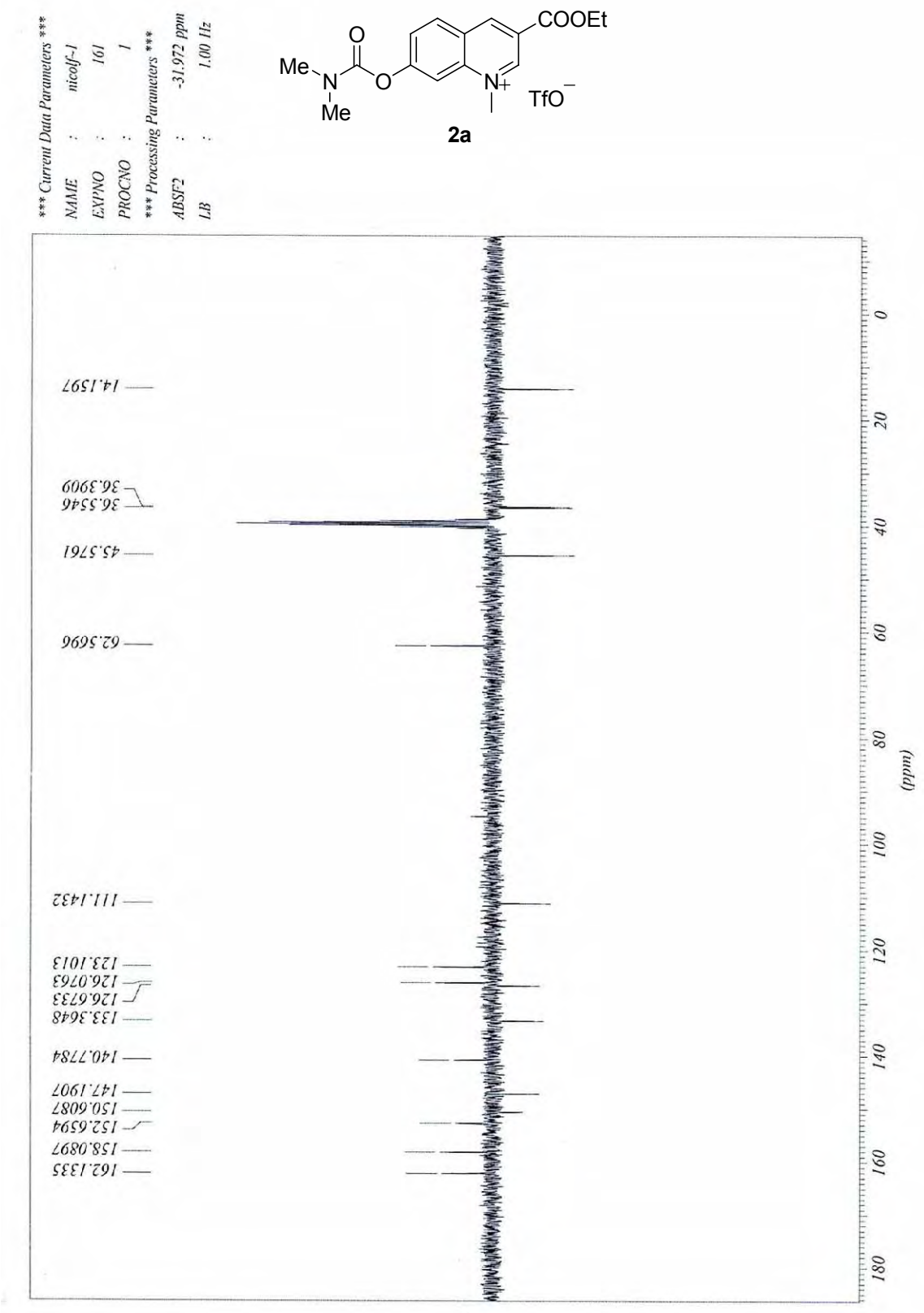

*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 410
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.189 ppm
LB : 0.30 Hz
Me
N
Me
O
O
CONMe2
N
11e
integral
(ppm)
6.3211
3.0490
3.1352
1.0000
1.0418
1.0158
0.9560
0.9995
3.0566
3.1752
3.2354
2214.55
2222.27
2316.65
2324.94
2332.85
2393.89
2402.36
2515.96
2517.65
2684.37
2686.25
8.9503
8.9440
8.3885
8.3829
8.0044
7.9762
7.7728
7.7464
7.7188
7.4044
7.3786

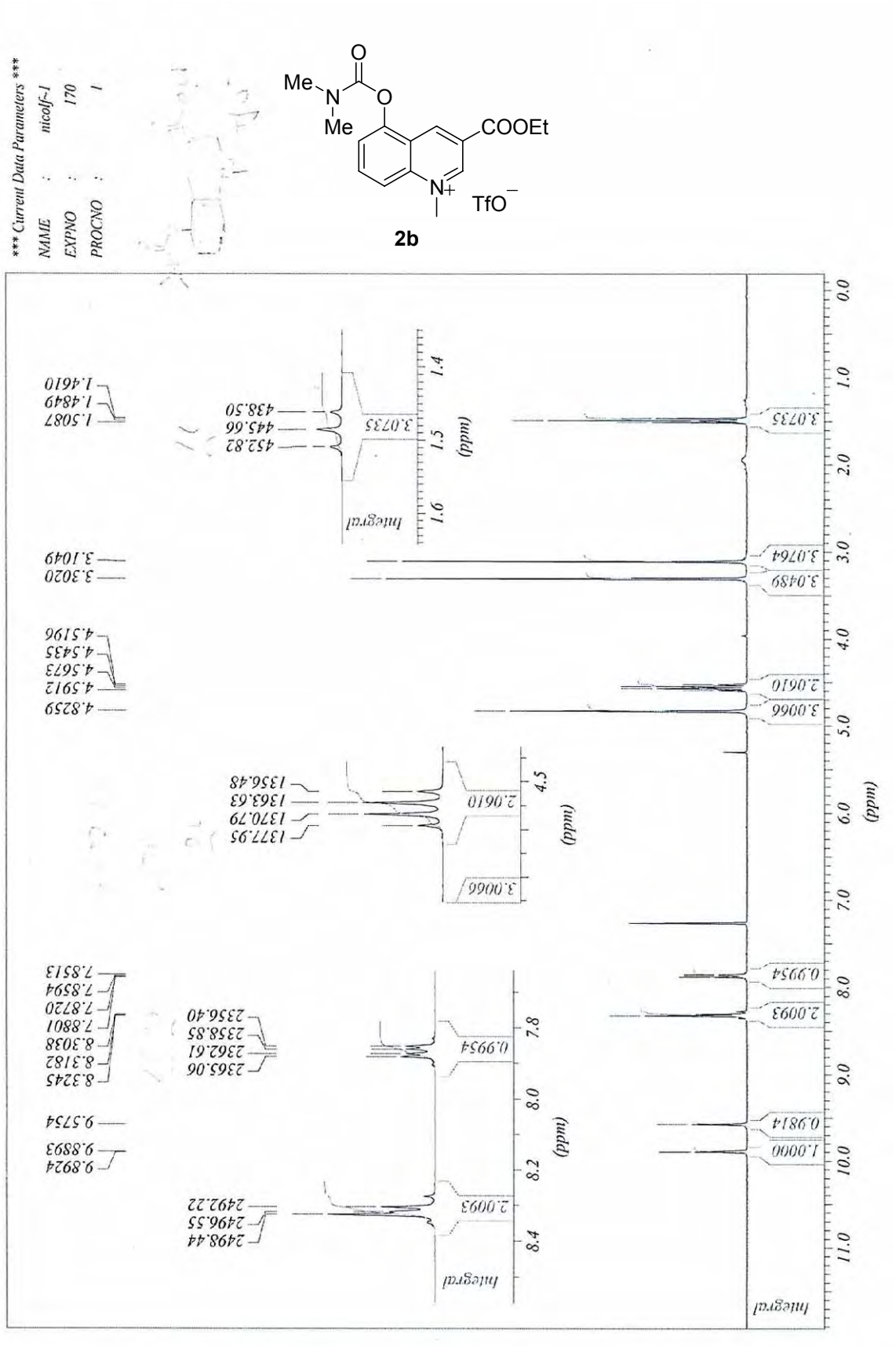


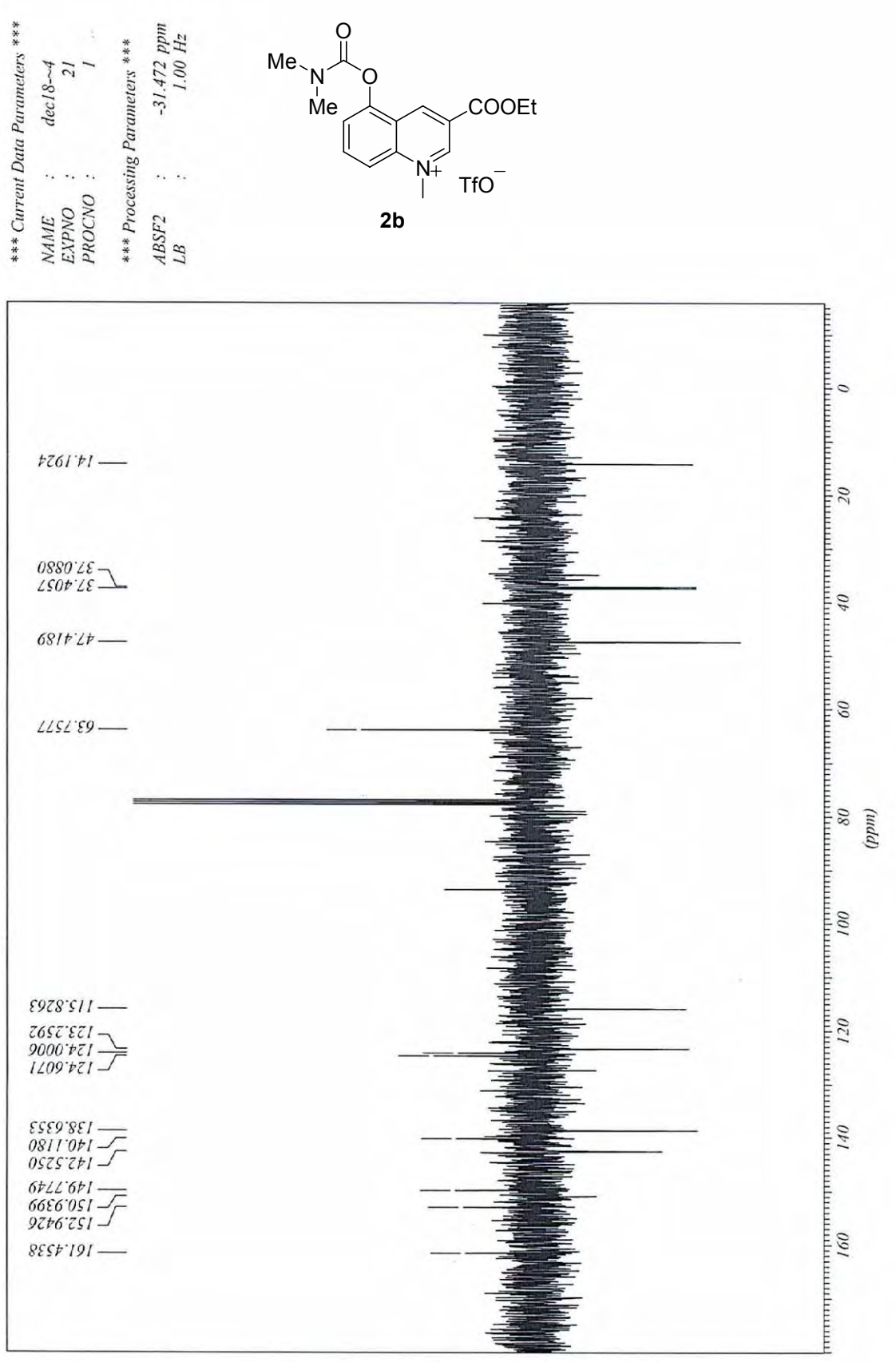


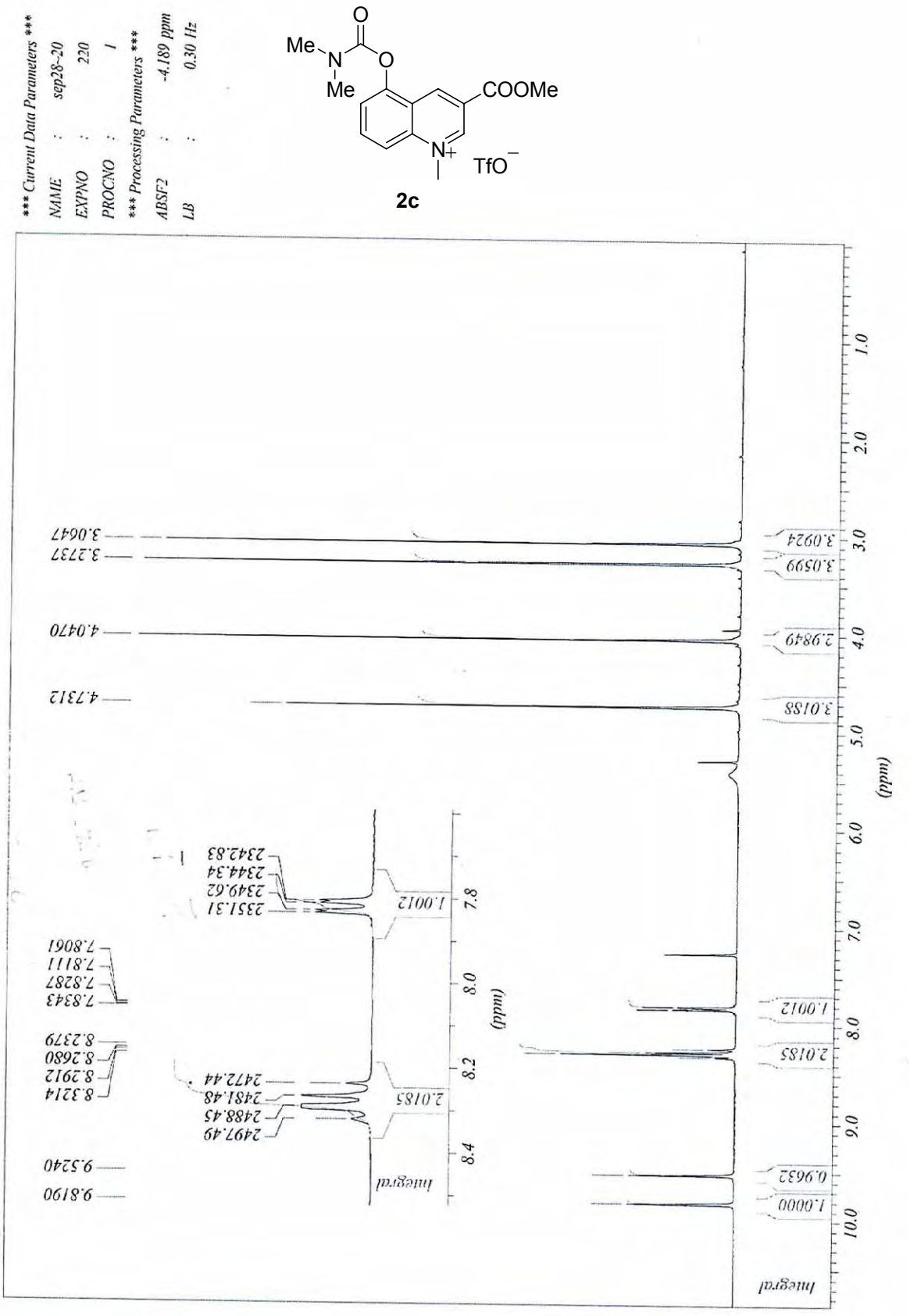


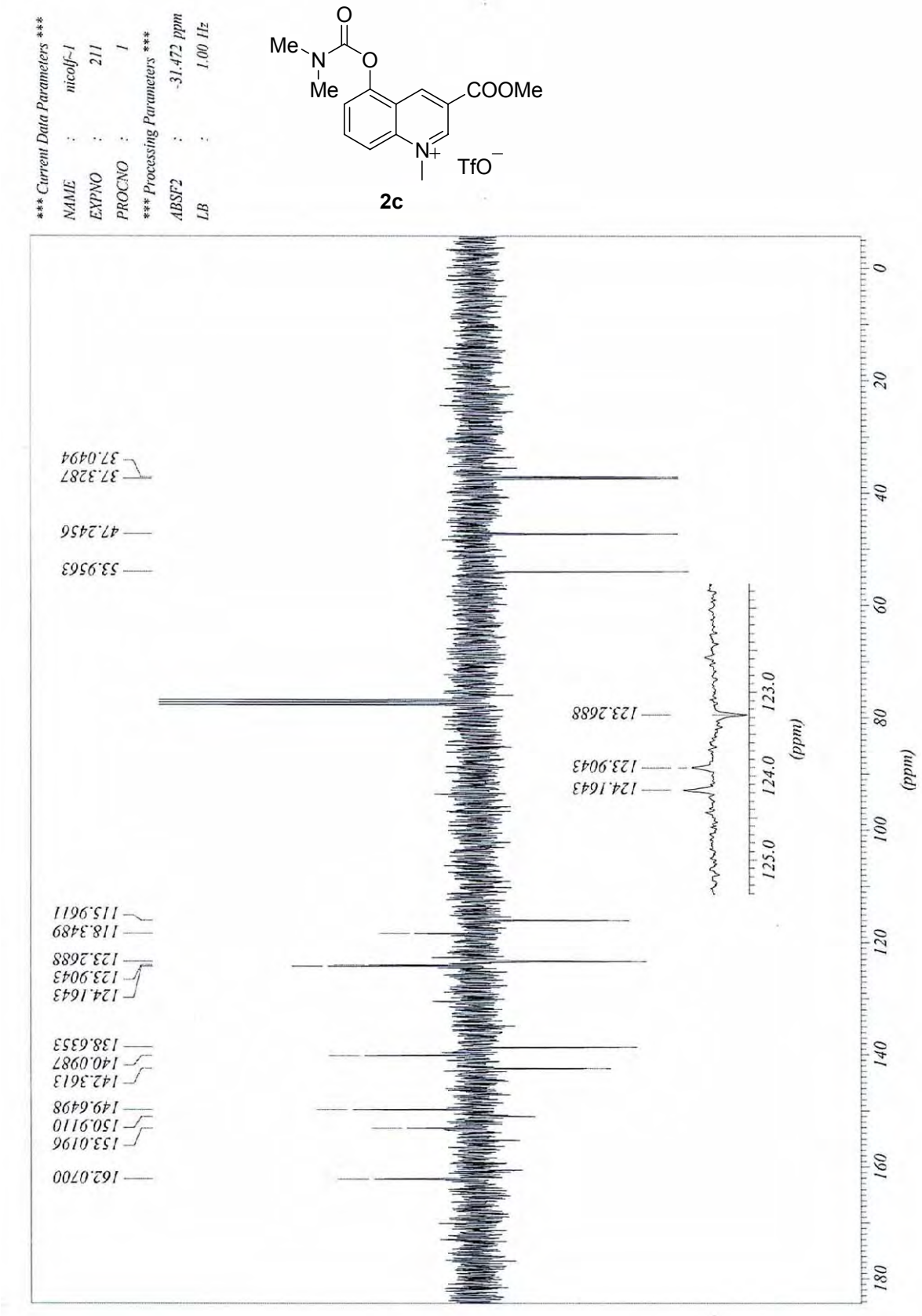

*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 190
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.195 ppm
LB : 0.30 Hz
Me
N
Me
O
O
COOEt
N+
TfO−
2a
1.4623
1.4861
1.5100
3.0873
3.2066
4.5127
4.5366
4.5604
4.5843
4.7563
7.8663
7.8713
7.8964
7.9015
8.2862
8.3364
8.3666
9.4424
9.7725
3.1591
3.0459
2.9934
2.0242
2.9764
1.0000
2.0166
0.9901
1.0034
integral
(ppm)

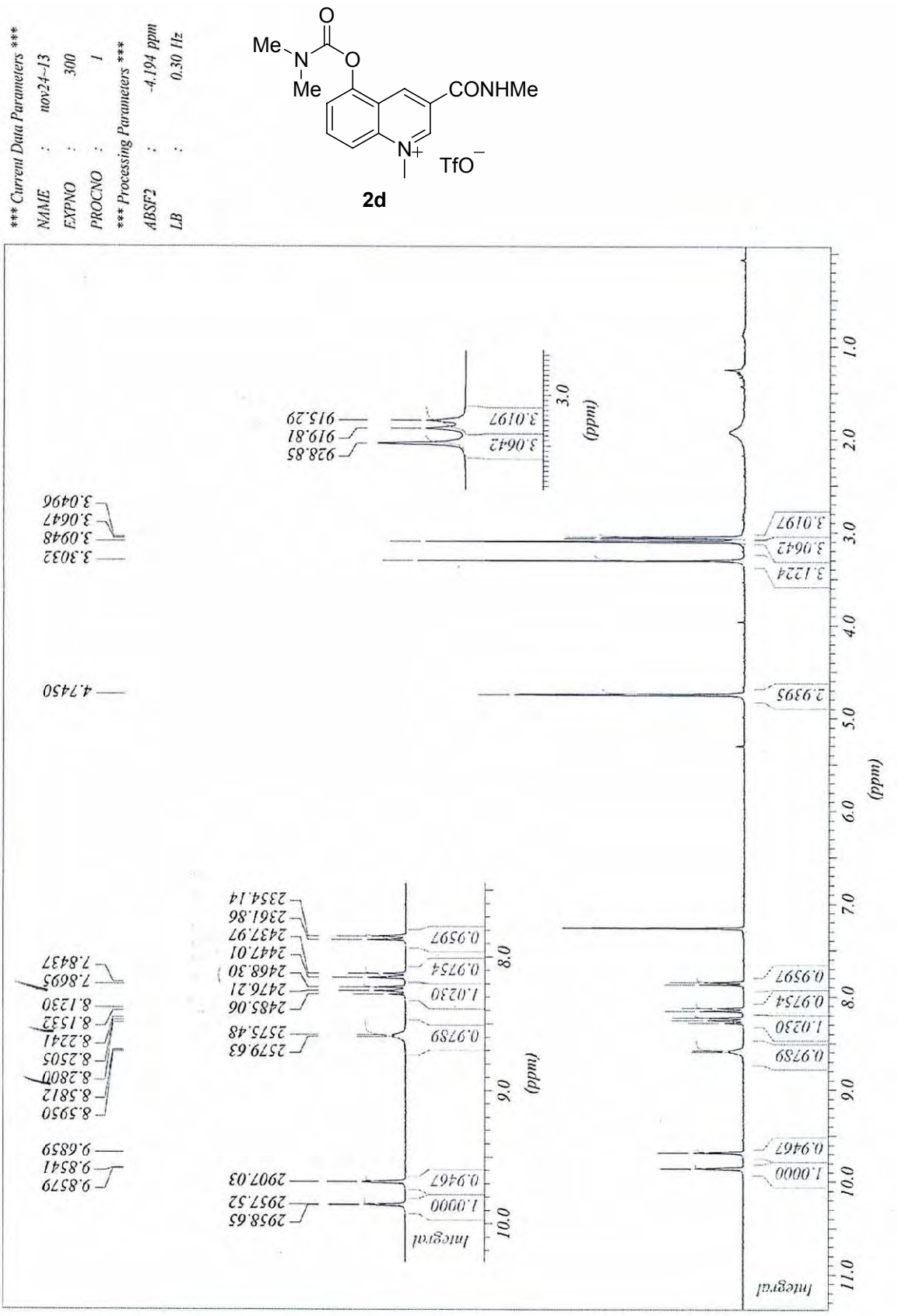


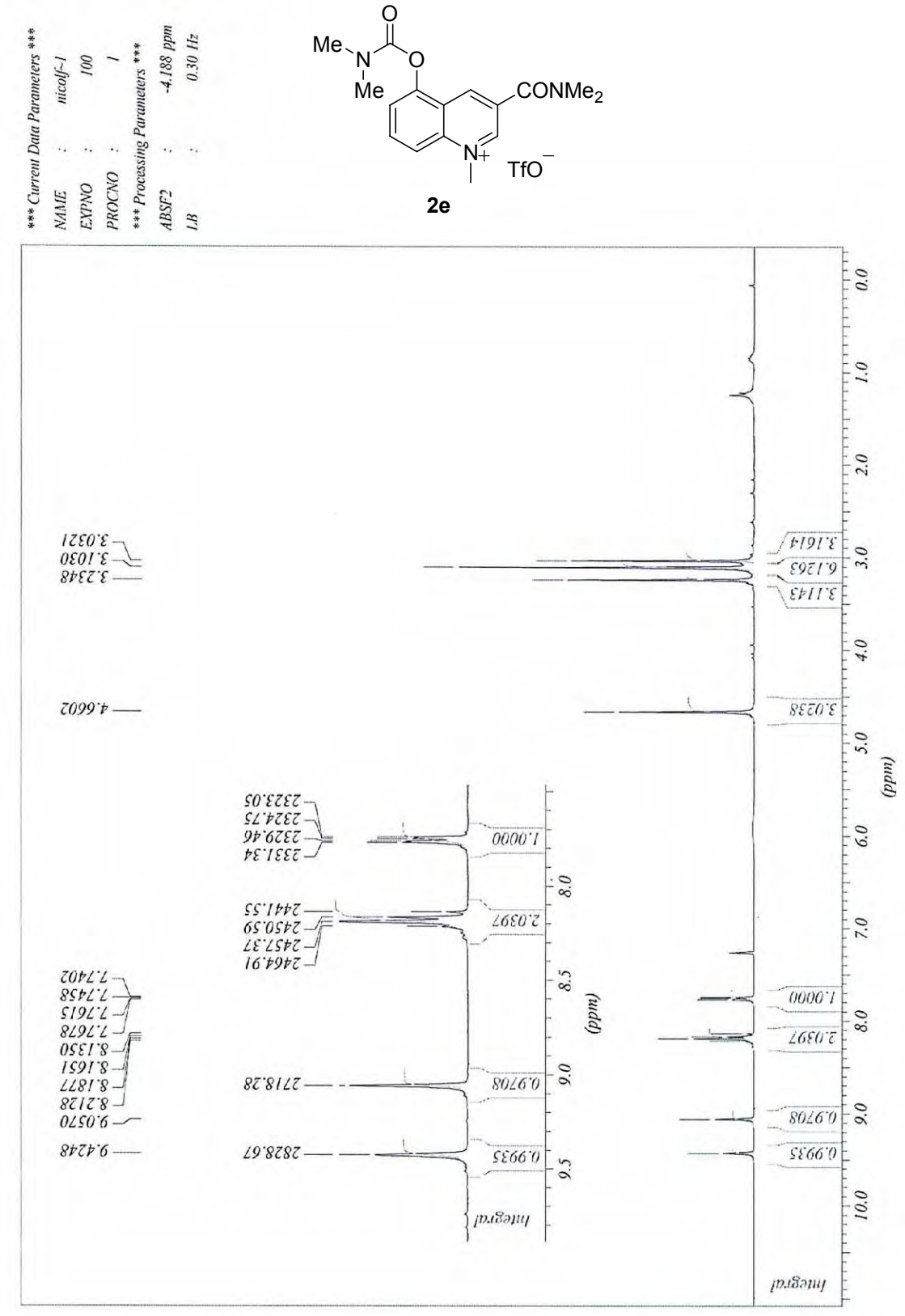


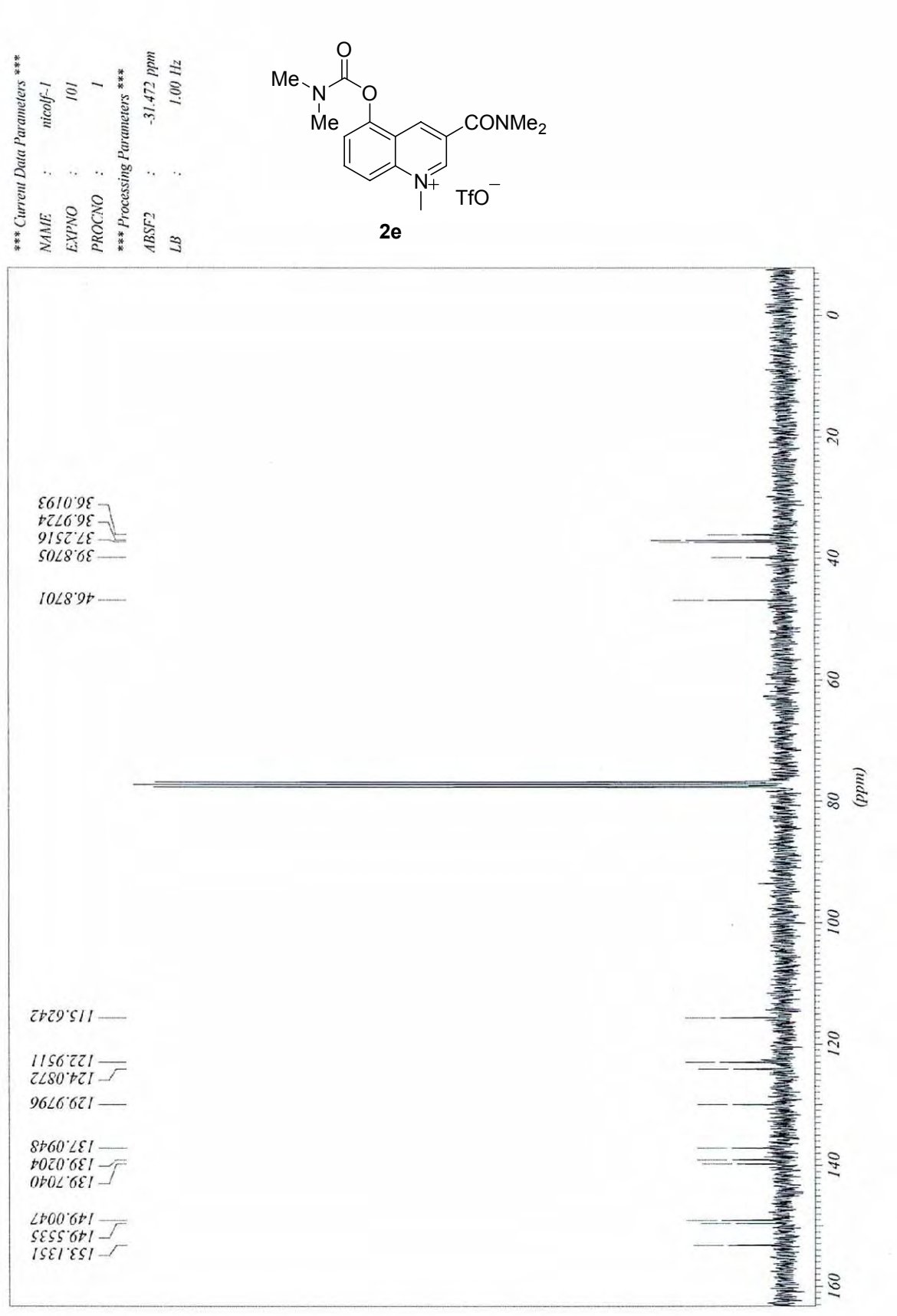


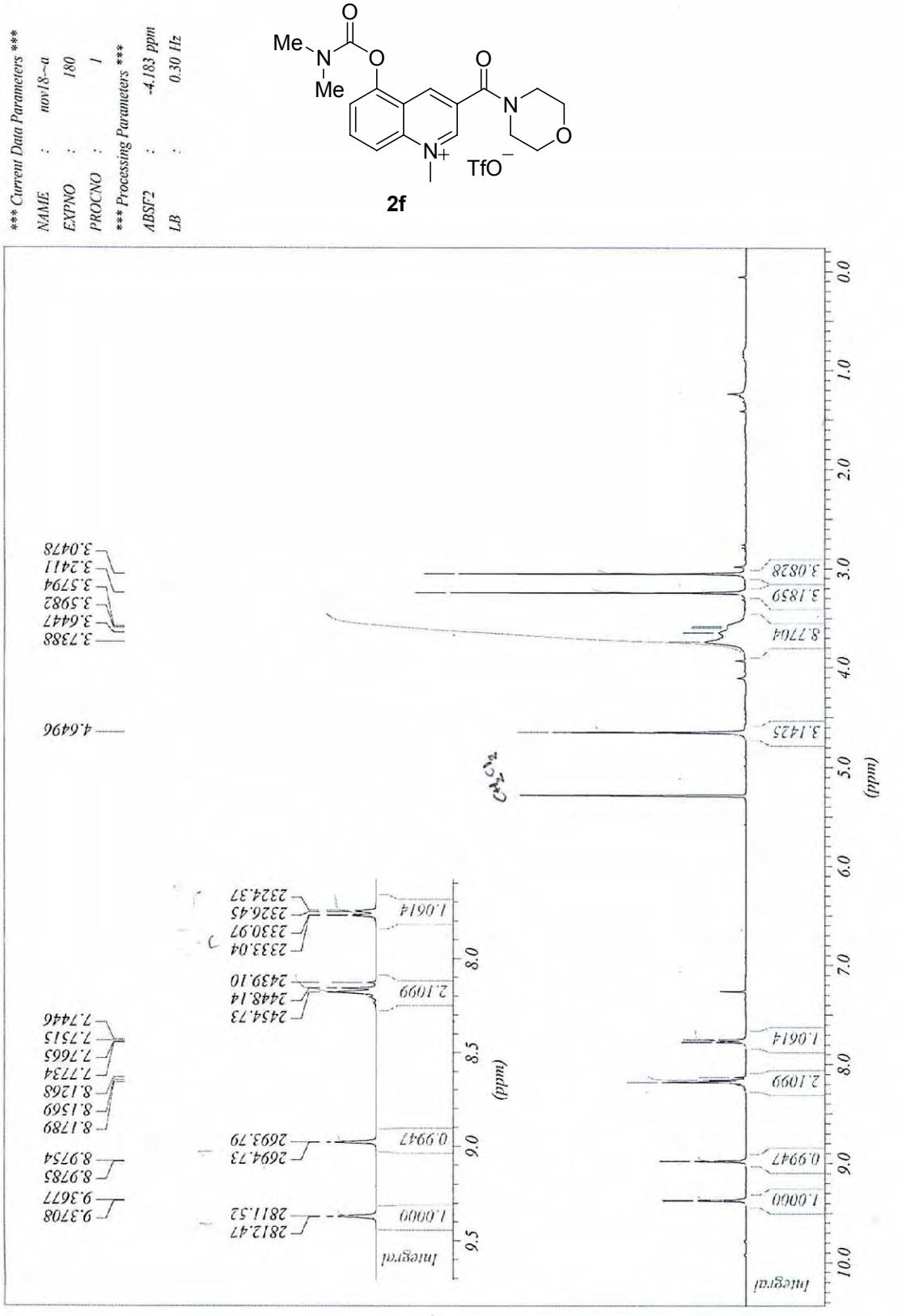


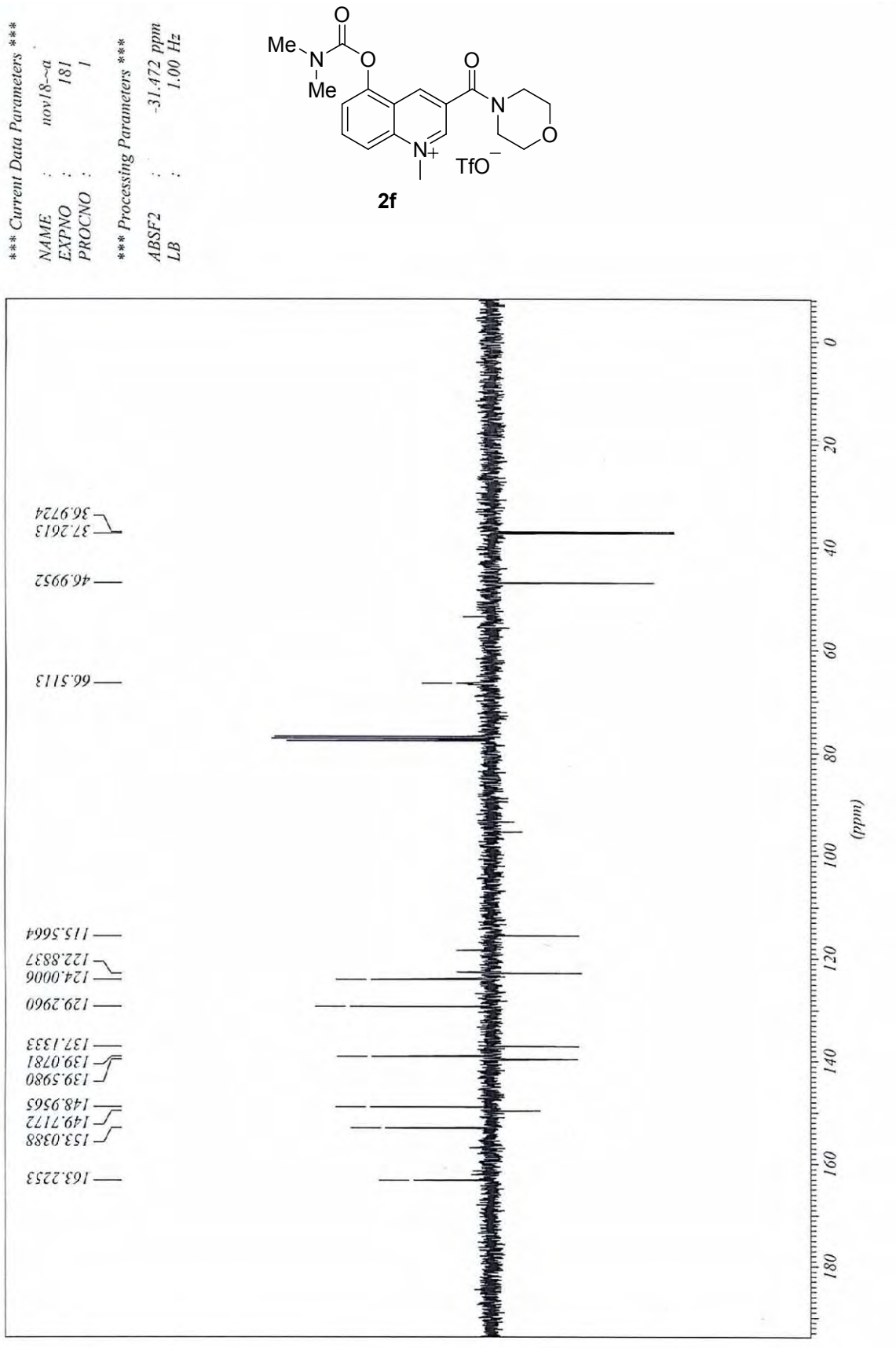


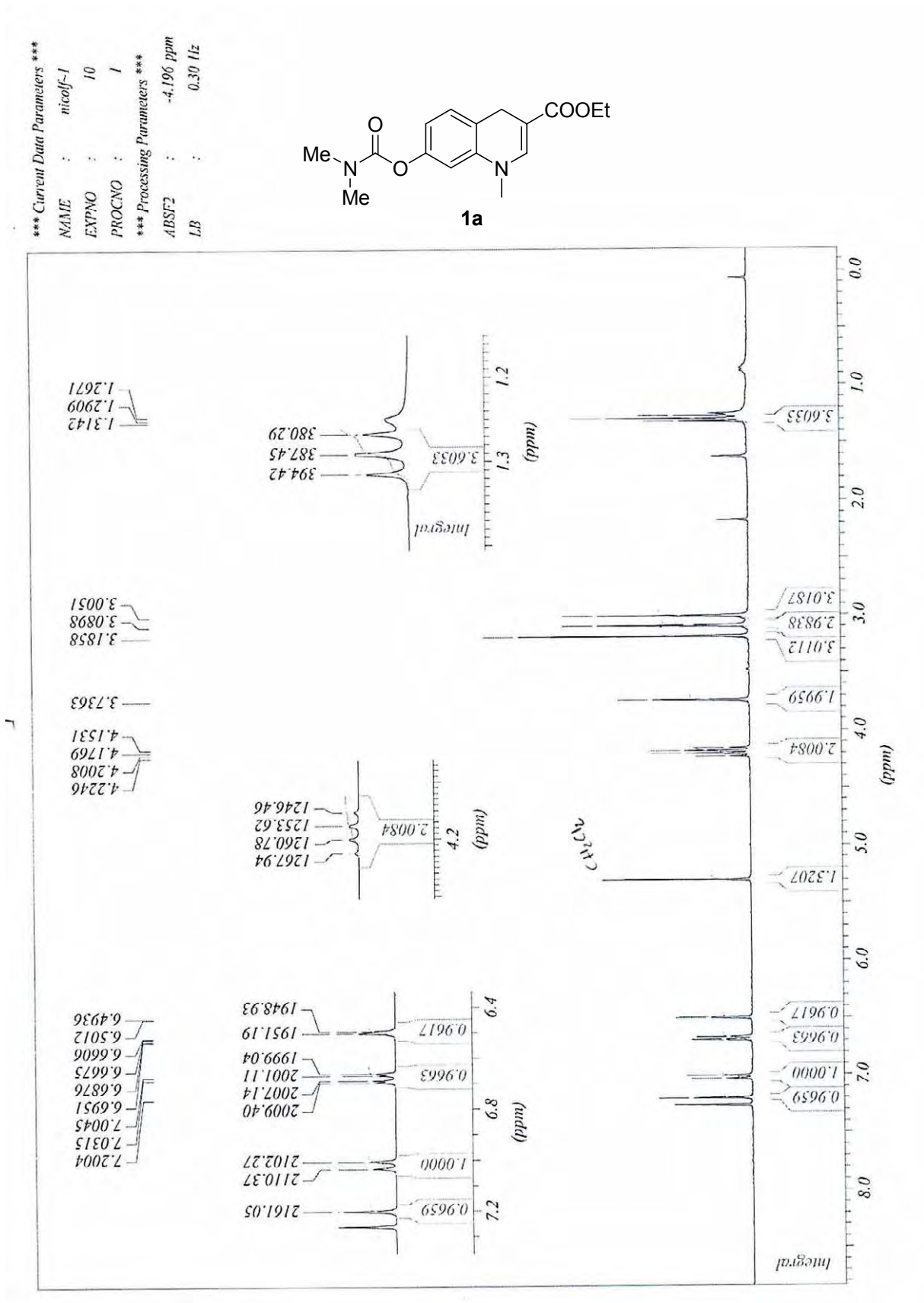

*** Current Data Parameters ***
NAME : nov24-13
EXPNO : 300
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.194 ppm
LB : 0.30 Hz
Me
N
Me
O
O
CONHMe
N+
TfO−
2d
(ppm)
Integral

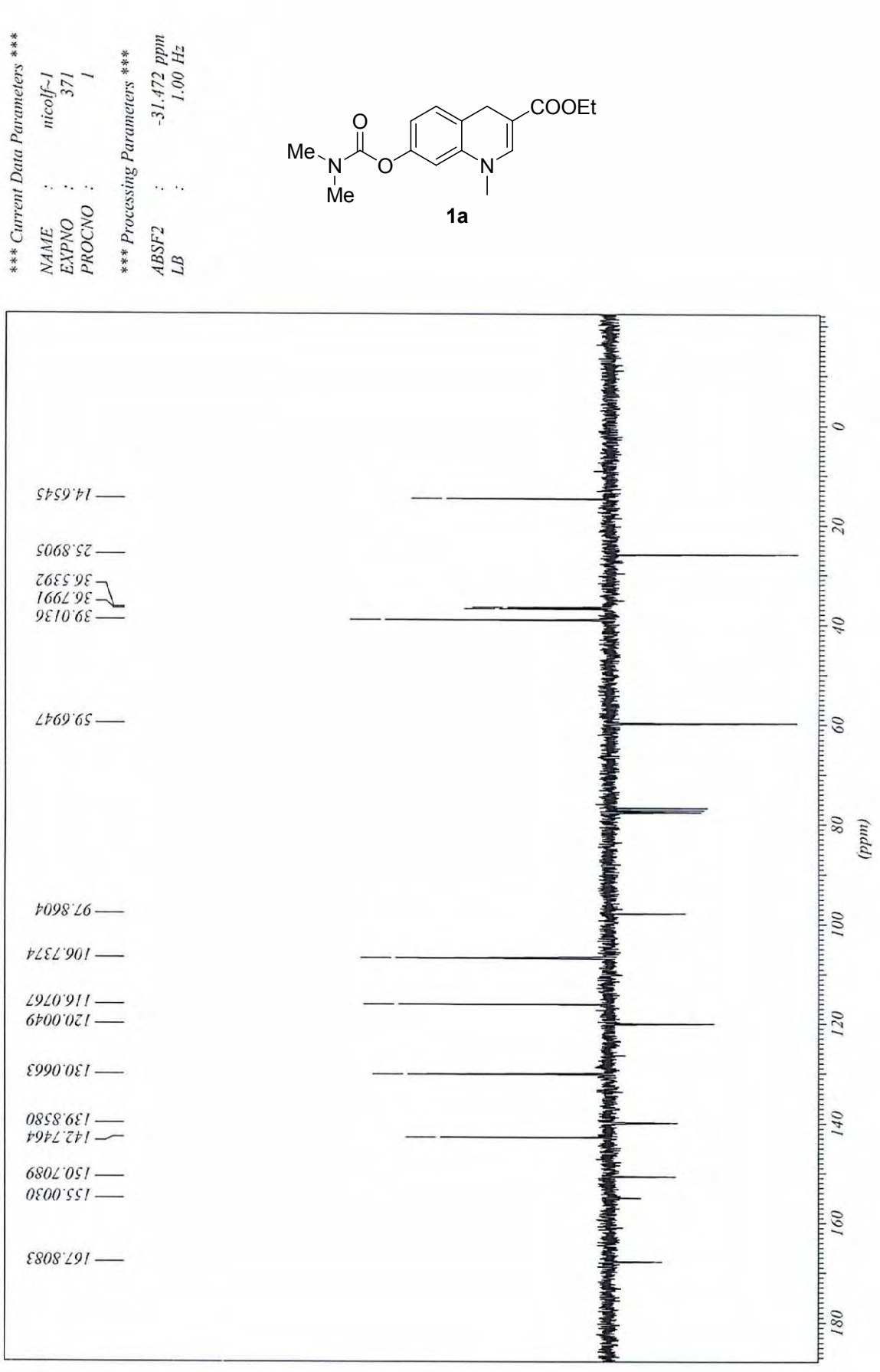


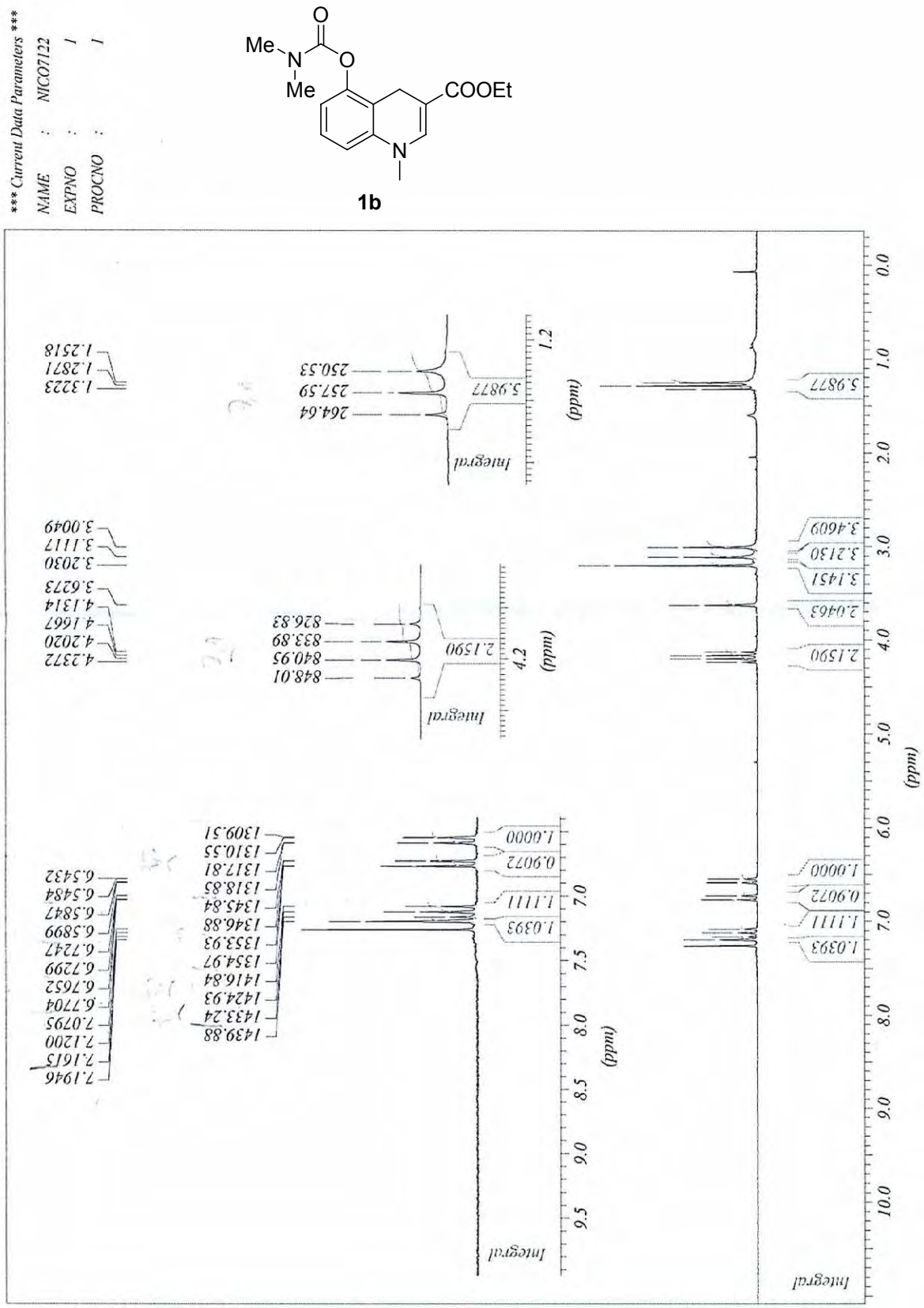


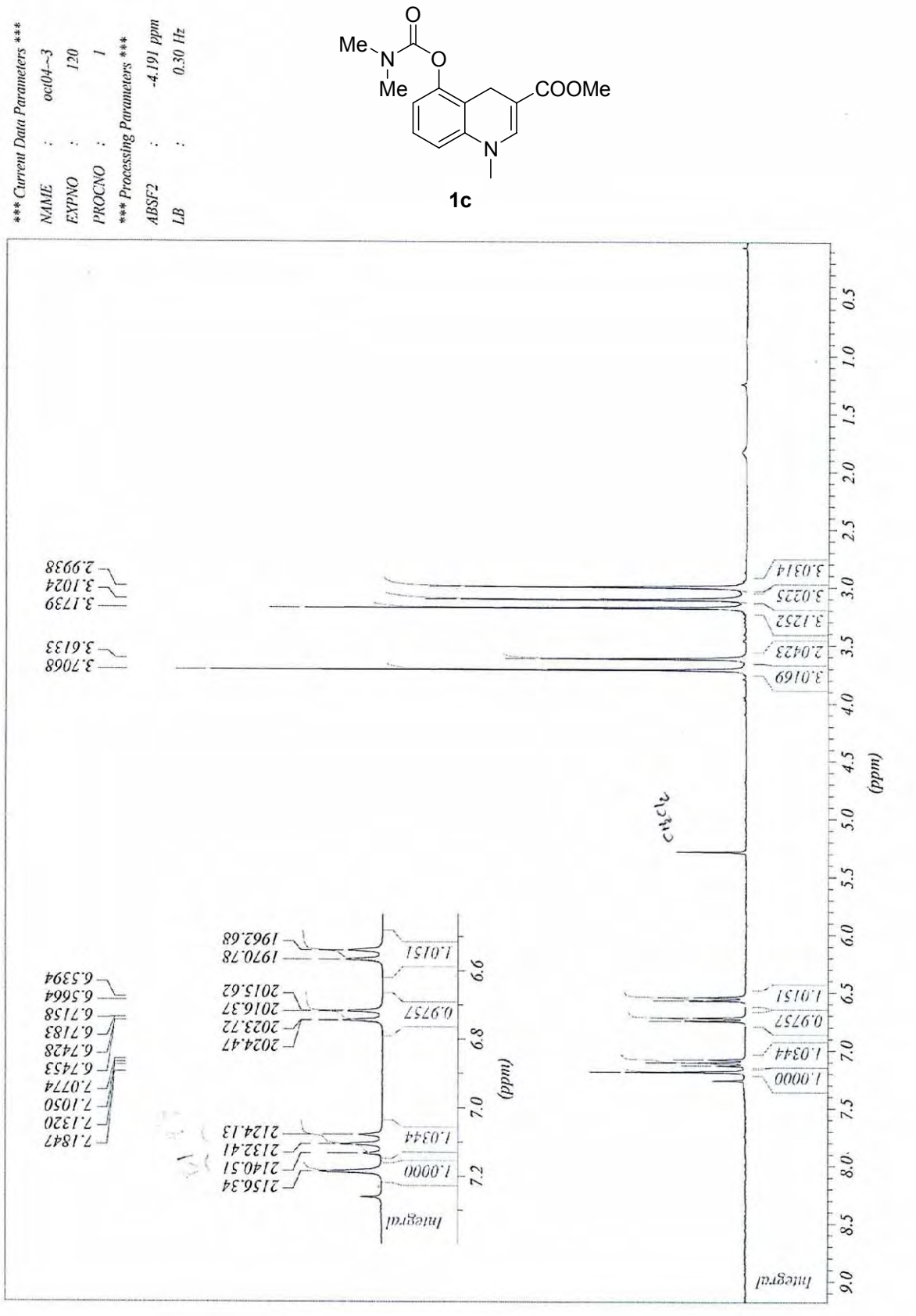

*** Current Data Parameters ***
NAME : nov18~a
EXPNO : 180
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.183 ppm
LB : 0.30 Hz
Me
N
Me
O
O
O
N
O
N+
TfO−
2f
3.0478
3.2411
3.5794
3.5982
3.6447
3.7388
4.6496
7.7446
7.7515
7.7665
7.7734
8.1268
8.1569
8.1789
8.9754
8.9785
9.3677
9.3708
3.0828
3.1859
8.7704
3.1425
1.0614
2.1099
0.9947
1.0000
integral
2324.37
2326.45
2330.97
2333.04
2439.10
2448.14
2454.73
2693.79
2694.73
2811.52
2812.47
1.0614
2.1099
0.9947
1.0000
integral
(ppm)

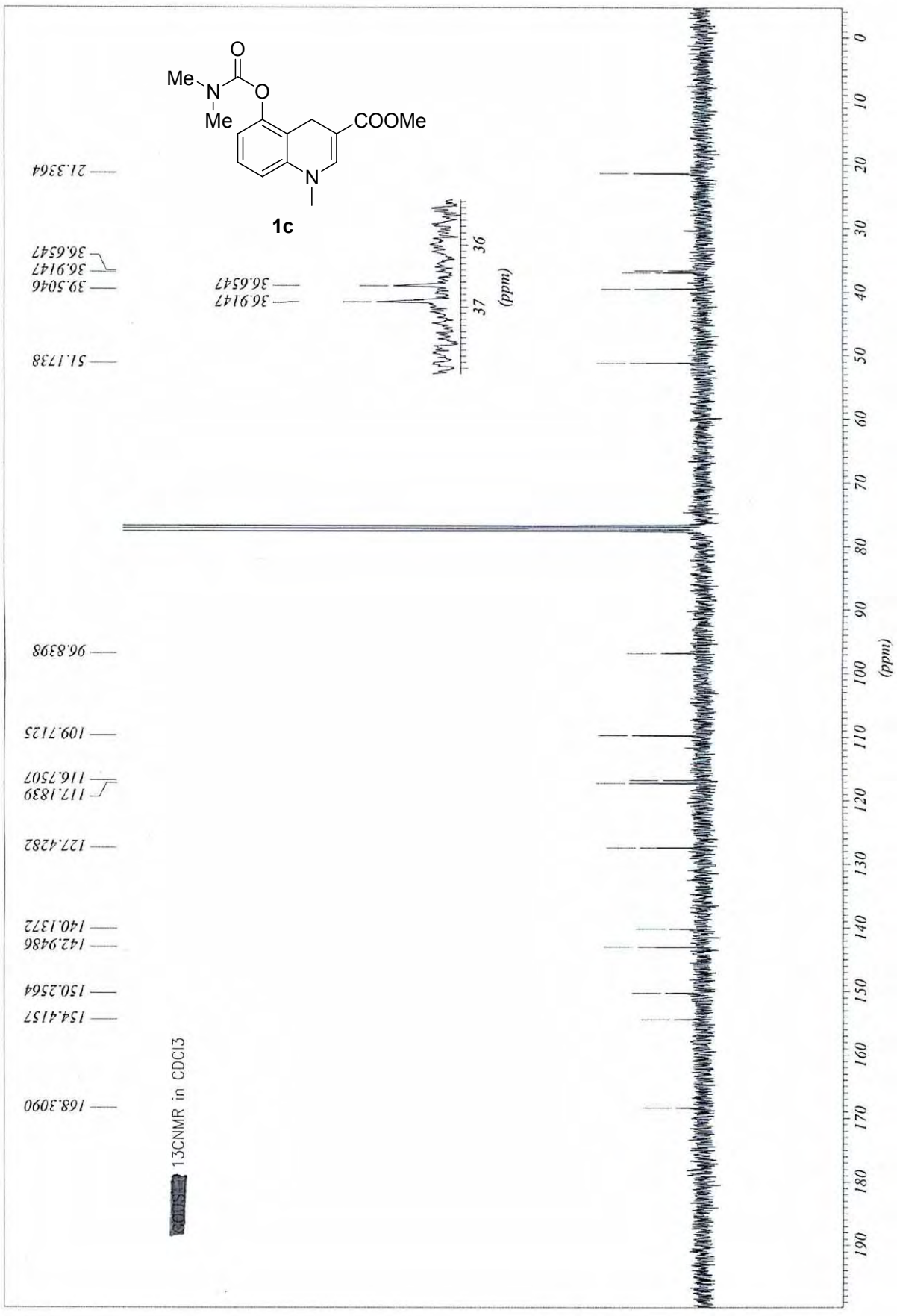


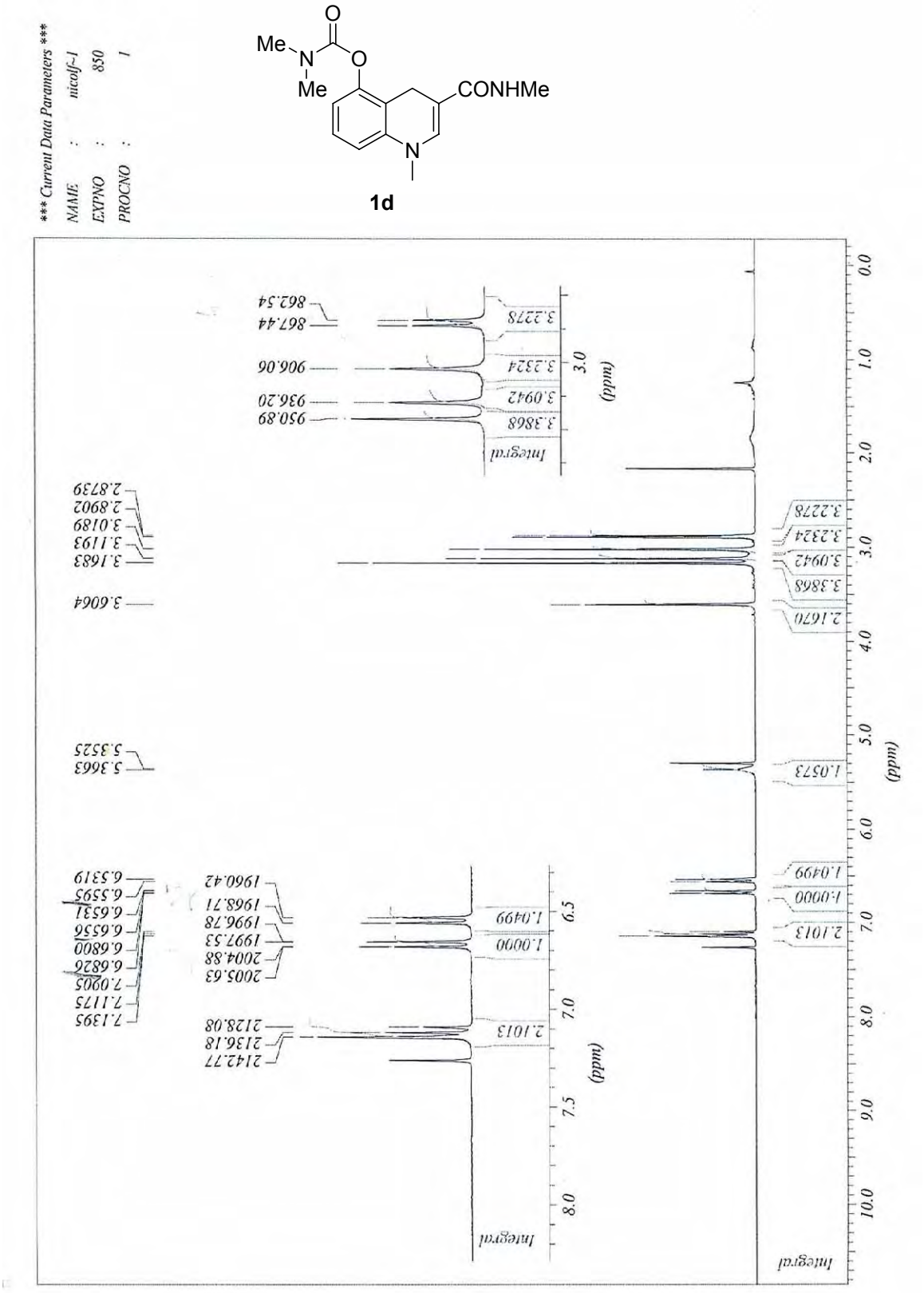


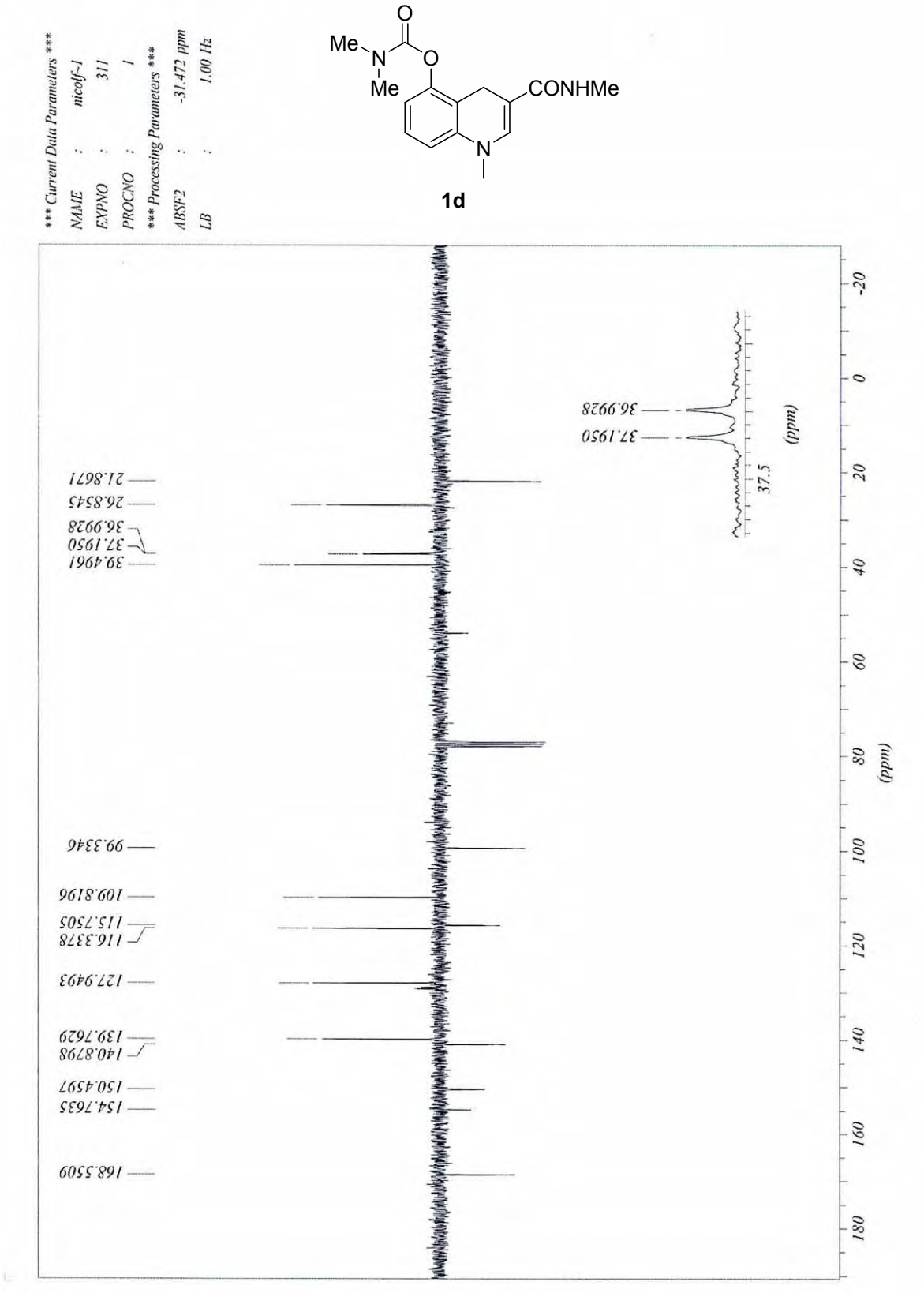


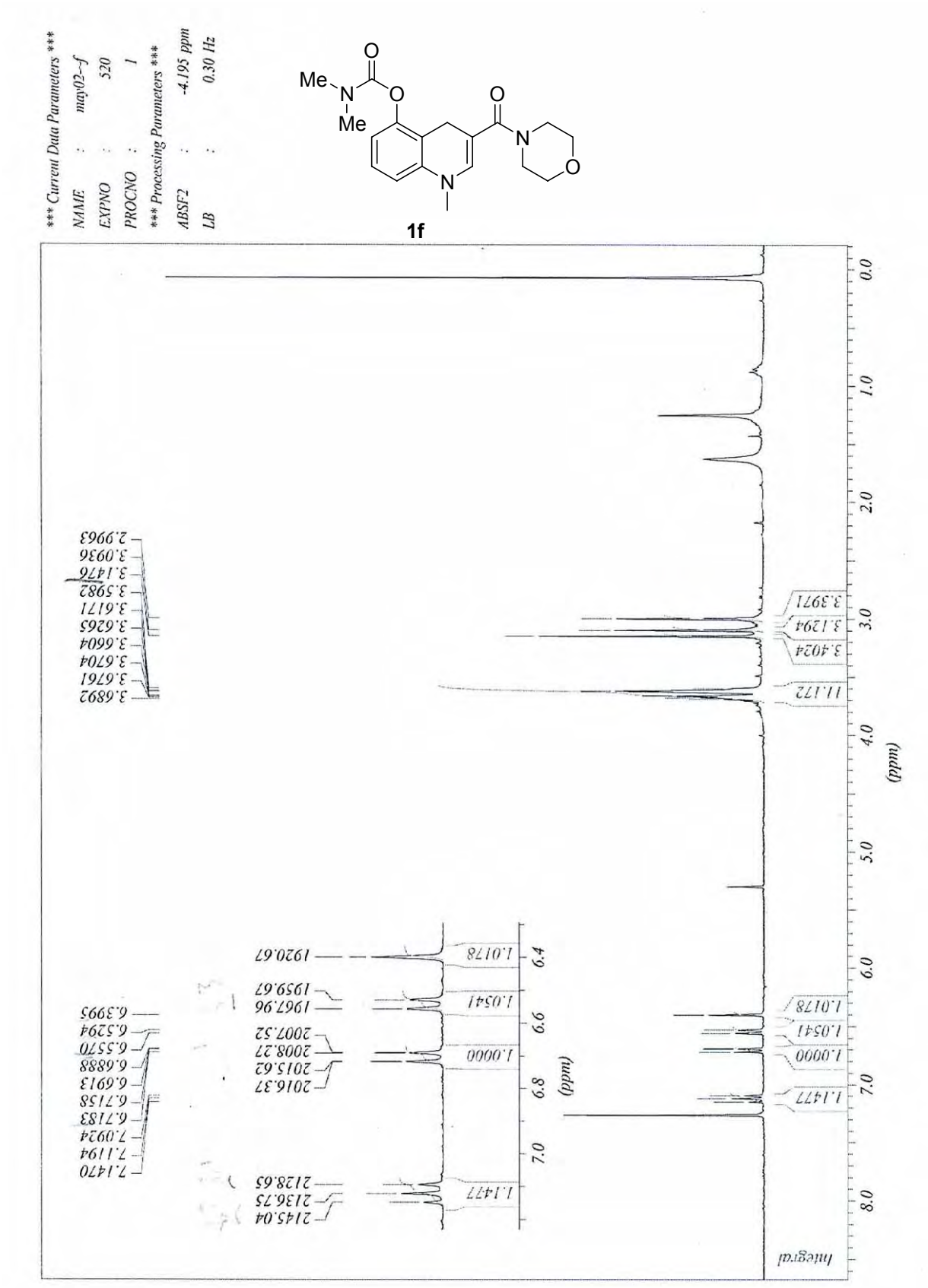

*** Current Data Parameters ***
NAME : NICO7122
EXPNO : 1
PROCNO : 1
Me
N
Me
O
O
COOEt
N
1b
integral
(ppm)

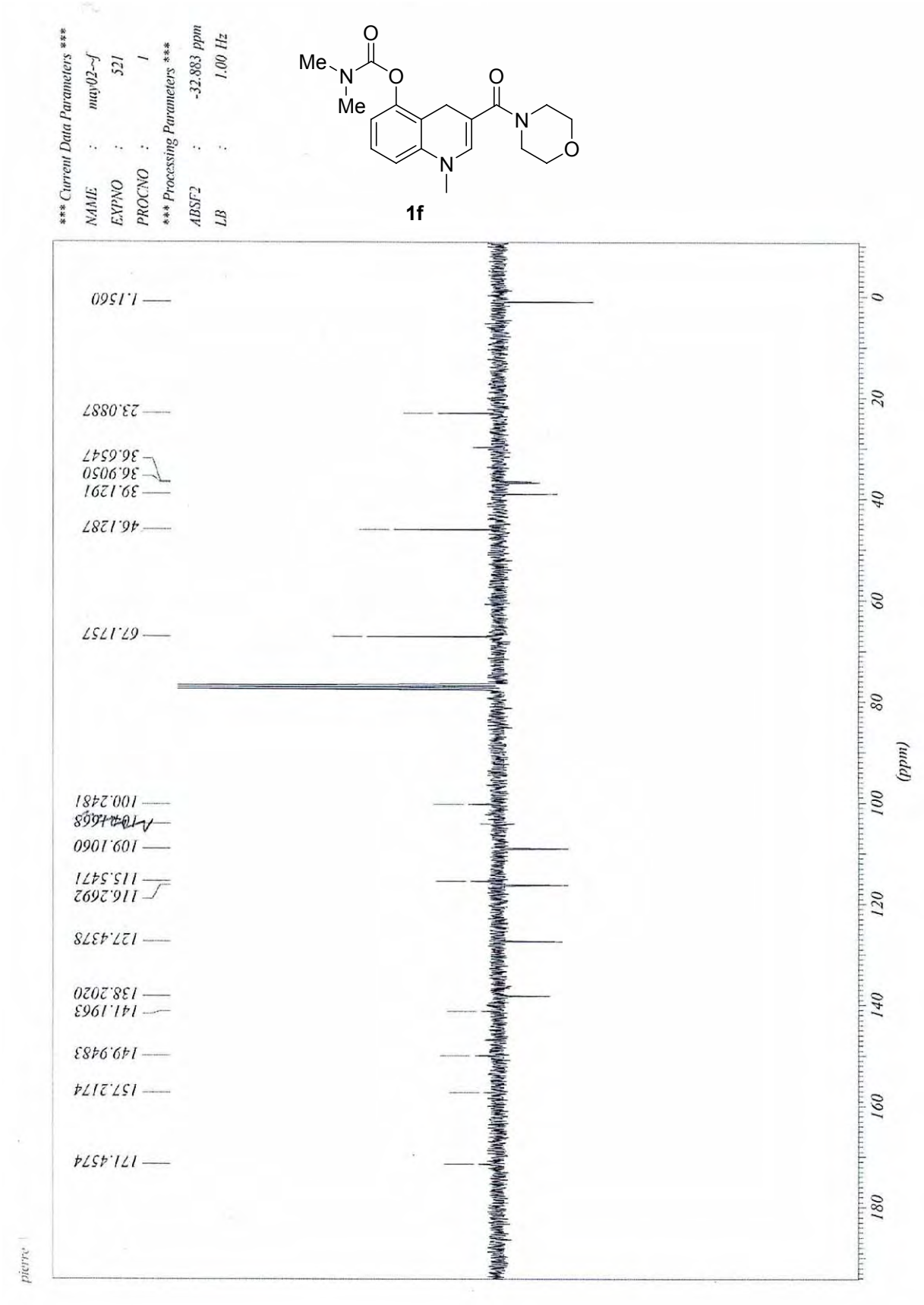





*** Current Data Parameters ***
NAME : nicolf-1
EXPNO : 850
PROCNO : 1
Me
N
Me
O
O
CONHMe
N
1d
Integral
(ppm)




*** Current Data Parameters ***
NAME : may02-f
EXPNO : 520
PROCNO : 1
*** Processing Parameters ***
ABSF2 : -4.195 ppm
LB : 0.30 Hz
Me
N
Me
O
O
O
N
O
N
1f
integral
(ppm)
1.4477
1.0000
1.0541
1.0178
11.172
3.4024
3.1294
3.3971
1.4477
1.0000
1.0541
1.0178
2128.65
2136.75
2145.04
2008.27
2015.62
2016.37
2007.52
1959.67
1967.96
1920.67
7.1470
7.1194
7.0924
6.7183
6.7158
6.6913
6.6888
6.5570
6.5294
6.3995
3.6892
3.6761
3.6704
3.6604
3.6265
3.6171
3.5982
3.1476
3.0936
2.9963



2. *In vitro* AChE inhibition assay

2.1. Preparation of enzyme: human acetylcholinesterase : Blood was collected from various patients hospitalized at the Rouen University Hospital. These patients have no blood disease and no anticholinesterasic treatment. After centrifugation at 3000 rotation per minutes for ten minutes, the plasma was removed. The globular pellet was washed twice by aqueous NaCl (9 $g.L^{-1}$), and pooled. The washed cells were haemolysed by dilution with 3 or 4 volumes of distilled water. After centrifugation at 20000g for 20 minutes, the cell membranes were washed twice by NaCl (9 $g.L^{-1}$). Additional centrifugation at 20000g furnished erythrocyte membranes with high cholinesterase activity. These sedimented membranes were mixed with 0.2 volumes of 5% Triton X-100 in NaCl 9 $g.L^{-1}$. The AChE inhibitory activity was measured by a modified Ellmann assay[1] and must be set between 500 and 800 IU (1 unit is the amount of enzyme which hydrolyze 1 µmol of acetylthiocholine per minute at 25°C).

2.2. Preparation of the solution

a) Phosphate buffer (pH = 7.4)

for 1L of buffer:
NaH_2PO_4 (3.1 g)
$Na_2HPO_4 \cdot 12H_2O$ (10.4 g)
5,5'-dithio-bis(2-nitrobenzoic) acid (0.1 g)

b) Substrate (acetylthiocholine 0.156M)

135 mg of acetylthiocholine iodide in 3 mL water

2.3. Measurement of inhibitory activity of compounds 1a-g and 2a-g

The enzymatic solution (20 µL) was added to phosphate buffer (2.9 mL) mixed with various concentrations of compound **1** or **2**. After 10 minutes of incubation, substrate was added (100 µL) and enzymatic hydrolysis kinetic was measured by a Schimadzu

[1] (a) Ellmann G.L., Courtney K.D., Andres V. Jr. and Featherstone R.M. *"A new and rapid colorimetric determination of acetylcholinesterase activity."* Bioch. Pharmacol. **1961**, *7*, 88-95 (b) Rosenberry T.L., Richardson J.M. Biochemistry. **1977**, *16*, 3550-8.

spectrophotometer. This experiment was conducted without inhibitor or without enzyme to determine maximal enzymatic kinetic and chemical hydrolysis of substrate in the buffer respectively.

	Total	Blank	Measure points[2]
Phosphate buffer	2.9 mL	2.9 mL	2.6 mL
Human acetylcholinesterase solution	20 µL	0 µL	20 µL
Solutions of unknown compound (**1** or **2**)[2]	0 µL	0 µL	300 µL
Acetylthiocholine 0.156M	100 µL	100 µL	100 µL

Table 1 – Assay method used to determine AChE inhibitory activity

A dose-effect curve was obtained, and IC_{50} was determined.

Example: determination of the experimental IC_{50} for 2a

The experimental IC_{50} for **2a** is determined at 0.53 µM on this test (Figure 1).

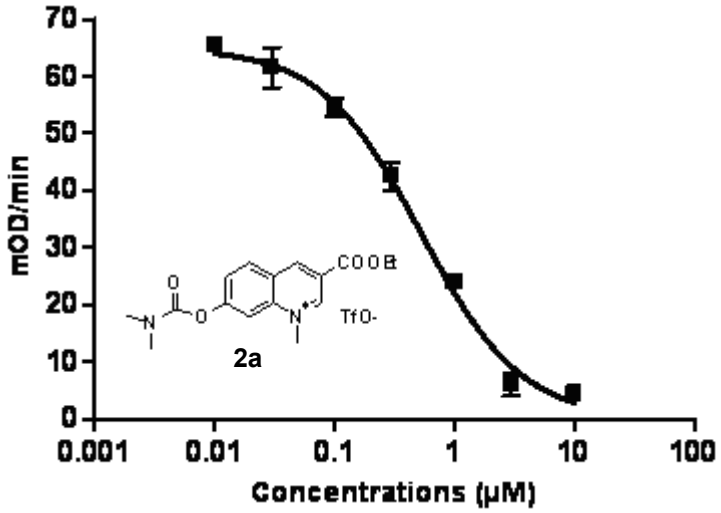


Figure 1 – Cholinesterase inhibition by **2a**

[2] Final concentrations ranging: 10^{-5}M to 10^{-8}M, or less if necessary