Heterocycle Synthesis via Direct C-H/N-H Coupling

Enrico T. Nadres and Olafs Daugulis*

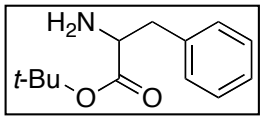
Department of Chemistry, University of Houston, Houston, TX 77204-5003

Supporting Information

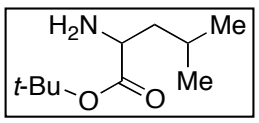
General considerations: Flash chromatography was performed on 60Å silica gel. Preparative TLC was performed on TLC plates, 20 x 20 cm, 2000 μm thick, with fluorescent indicator. Residual solvent peak was used as a reference in ^{1}H NMR and ^{13}C NMR spectra. Melting points are uncorrected.

Materials: The following starting materials were obtained from commercial sources and were used without further purification: phenylalanine, *tert*-butyl acetate, concentrated $HClO_4$, concentrated HCl, K_2CO_3, $MgSO_4$, silica, hexanes, ethyl acetate, leucine, picolinic acid, triethylamine, dichloromethane, ethyl chloroformate, phenethylamine, 2-(2-chlorophenyl)ethylamine, 2,2-diphenylethylamine, 3,4-dimethoxyphenethylamine, *tert*-octylamine, 4-methyl-2-pentanamine, (2,6-dimethylphenyl)methanamine, *tert*-butyl 2-amino-4-methylpentanoate, 3,3-dimethylbutan-1-amine, 1-(4-bromophenylethanamine, 2-methoxybenzylamine, *N*-benzylpicolinamide, $CuBr_2$, iodomethane, dodecane, iodobenzene diacetate, toluene and acetonitrile.

Synthesis of starting materials



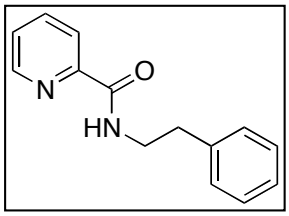
***tert*-Butyl 2-amino-3-phenylpropanoate** (S1). The procedure of Chen was used.[1] Phenylalanine (35 mmol, 5.78 g) was dissolved in *tert*-butyl acetate (85 mL). The solution was cooled to 0 °C and concentrated $HClO_4$ (55 mmol, 4.80 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 24 hours. After that, reaction mixture was extracted with water (200 mL). Then, the organic layer was extracted with 5 % HCl (100 mL). The aqueous layers were combined and solid K_2CO_3 was added with stirring until no more gas evolution was observed. The mixture was extracted with diethyl ether (2 X 200 mL). The ether layers were combined, dried with $MgSO_4$, concentrated, and loaded on silica column. After chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained (3.96 g, 51 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30). This compound is known.[1] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28–7.25 (m, 2H), 7.21–7.17 (m, 3H), 3.60–3.56 (m, 1H), 3.00 (dd, *J*=13.7, 5.5 Hz, 1H), 2.83 (dd, *J*=13.7, 6.9 Hz, 1H), 1.91 (s, 2H), 1.40 (s, 9 H).



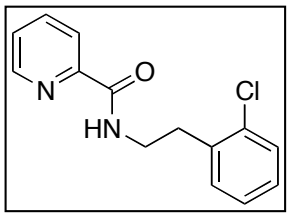
***tert*-Butyl 2-amino-4-methylpentanoate** (S2). The procedure of Chen was used.[1] Leucine (35 mmol, 4.60 g) was dissolved in *tert*-butyl acetate (85 mL). The solution was cooled to 0 °C and concentrated $HClO_4$ (55 mmol, 4.80 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 24 hours. The reaction mixture was extracted with water (200 mL). Then, the organic layer was extracted with 5 % HCl (100 mL). The aqueous layers were combined and solid K_2CO_3 was added with stirring until no more gas evolution was observed. The mixture was extracted with diethyl ether (2 X 200 mL). The ether layers were combined, dried with $MgSO_4$, concentrated, and the residue was loaded on silica column. After chromatography (hexanes/ethyl acetate 40/60), colorless oil was obtained (2.58 g, 65.5 % yield). R_f = 0.25 (hexanes/ethyl acetate 40/60). This compound is known.[2] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.87 (br s, 2H), 3.86 (m, 1H), 1.83–1.64 (m, 3H), 1.48 (s, 9H), 0.95 (d, *J*=6.9 Hz, 6H).

General procedure for the preparation of the picolinamides

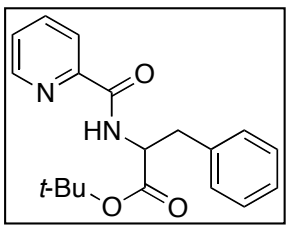
Method A: Amidation.[3] Picolinic acid (35 mmol, 4.3 g) and triethylamine (70 mmol, 9.70 mL) were dissolved in dry dichloromethane (80 mL). The solution was cooled to 0 °C followed by addition of ethyl chloroformate (35 mmol, 3.30 mL). The mixture was subsequently stirred for 30 minutes in ice bath. Amine (20 mmol) was added dropwise via a syringe and the suspension was stirred for 1 hour. The solution was warmed to room temperature and stirred for another 24 hours. Water (100 mL) was then added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent.



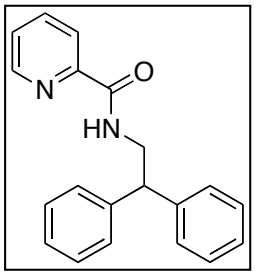
***N*-Phenethylpicolinamide** (S3). Picolinic acid (70 mmol, 8.60 g), triethylamine (140 mmol, 19.6 mL), dichloromethane (160 mL), ethyl chloroformate (70 mmol, 5.65 mL), and phenethylamine (40 mmol, 5.03 mL). After column chromatography (hexanes/ethyl acetate 70/30), yellowish crystals were obtained (9.04 g, 89 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30). This compound is known.[4] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.47 (d, *J*=4.6 Hz, 1H), 8.19 (d, *J*=7.8 Hz, 2H), 7.80–7.76 (m, 1H), 7.37–7.34 (m, 1H), 7.32–7.28 (m, 2H), 7.24–7.19 (m, 3H), 3.75–3.70 (m, 2H), 2.93 (t, *J*=7.3 Hz, 2H).



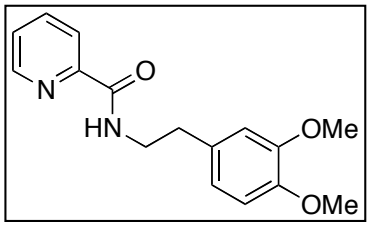
***N*-(2-Chlorophenethyl)picolinamide** (S4). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-(2-chlorophenyl)ethylamine (20 mmol, 3.1 g). After column chromatography (hexanes/ethyl acetate 60/40), colorless liquid was obtained (3.4 g, 65 % yield). R_f = 0.44 (hexanes/ethyl acetate 60/40). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.52–8.50 (m, 1H), 8.23–8.19 (m, 2H), 7.85–7.81 (m, 1H), 7.41–7.33 (m, 2H), 7.28–7.24 (m, 1H), 7.21–7.14 (m, 2H), 3.77–3.72 (m, 2H), 3.08 (t, *J*=6.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 164.5, 149.9, 148.1, 137.4, 136.6, 134.2, 131.0, 129.7, 128.1, 127.0, 126.2, 122.2, 39.2, 33.7. FT-IR (neat, cm^{-1}) υ 1673, 1524, 1475, 1434, 1288, 1053. . Anal. Calcd for $C_{14}H_{13}ClN_2O$ (260.72 g/mol): C, 64.49; H, 5.03; N, 10.74; Found: C, 64.11; H, 4.85; N, 10.53.



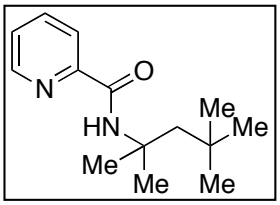
***tert*-Butyl 3-phenyl-2-(picolinamido)propanoate** (S5). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-butyl 2-amino-3-phenylpropanoate (15 mmol, 3.35 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (4.40 g, 90 % yield). R_f = 0.21 (hexanes/ethyl acetate 60/40), mp=96–97 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.52 (m, 2H), 8.16 (d, *J*=8.2 Hz, 1H), 7.84–7.80 (m, 1H), 7.42–7.39 (m, 1H), 7.28–7.21 (m, 5H), 4.97–4.92 (m, 1H), 3.20 (d, *J*=6.4 Hz, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 163.9, 149.6, 148.4, 137.3, 136.5, 129.6, 128.4, 127.0, 126.3, 122.2, 82.3, 53.9, 38.6, 28.0. FT-IR (neat, cm^{-1}) υ 3345, 1706, 1662, 1530, 1470, 1365, 1295, 1255, 1155. Anal. Calcd for $C_{19}H_{22}N_2O_3$ (326.39 g/mol): C, 69.92; H, 6.79; N, 8.58; Found: C, 69.79; H, 6.72; N, 8.54.



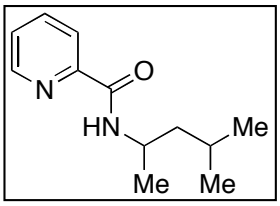
***N*-(2,2-Diphenylethyl)picolinamide** (S6). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2,2-diphenyl-ethylamine (20 mmol, 3.94 g). After column chromatography (dichloromethane), colorless oil was obtained (4.30 g, 71 % yield). R_f = 0.31 (dichloromethane), mp=152.5–153.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.41 (m, 1H), 8.18–8.15 (m, 1H), 8.1 (br s, 1H), 7.81–7.77 (m, 1H), 7.36–7.28 (m, 8H), 7.25–7.20 (m, 2H), 4.34 (t, *J*=7.8 Hz, 1H), 4.12 (dd, *J*=7.8, 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.4, 149.8, 148.2, 142.1, 137.3, 128.8, 128.2, 126.9, 126.2, 122.2, 50.9, 43.9. FT-IR (neat, cm^{-1}) υ 1665, 1522, 1440, 1250. . Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37 g/mol): C, 79.44; H, 6.00; N, 9.26; Found: C, 79.35; H, 6.11; N, 9.25.



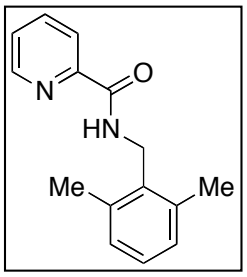
***N*-(3,4-Dimethoxyphenethyl)picolinamide** (S7). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 3,4-dimethoxyphenethylamine (20 mmol, 3.37 mL). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (5.56 g, 97 % yield). R_f = 0.30 (hexanes/ethyl acetate 60/40). This compound is known.[5] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52–8.51 (m, 1H), 8.21–8.16 (m, 2H), 7.87–7.82 (m, 1H), 7.43–7.39 (m, 1H), 6.84–6.78 (m, 3H), 3.87–3.85 (m, 6H), 3.74–3.69 (m, 2H), 2.91–2.87 (m, 2H).



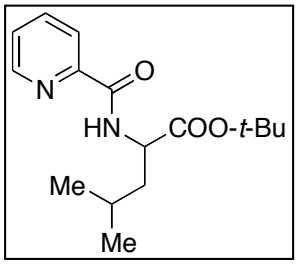
***N*-(2,4,4-Trimethylpentan-2-yl)picolinamide** (S8). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-octylamine (20 mmol, 3.20 mL). After column chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained (3.20 g, 62 % yield). R_f = 0.56 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, *J*=4.0 Hz, 1H), 8.18 (d, *J*=8.0, Hz, 1H), 8.1 (br s, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.1, 151.0, 148.9, 137.4, 125.8, 121.7, 54.7, 52.0, 31.8, 31.6, 29.2. FT-IR (neat, cm^{-1}) υ 2956, 1681, 1522, 1464, 1432, 1365, 1228. Anal. Calcd for $C_{14}H_{22}N_2O$ (234.34 g/mol): C, 71.76; H, 9.46; N, 11.95; Found: C, 71.46; H, 9.29; N, 11.86.



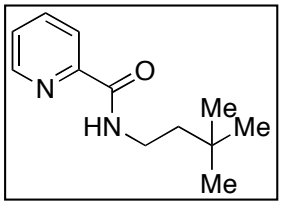
***N*-(4-Methylpentan-2-yl)picolinamide** (S9). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 4-methyl-2-pentanamine (20 mmol, 2.02 g). After column chromatography (hexanes/ethyl acetate 60/40), light orange solid was obtained (3.81 g, 93 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.22–8.20 (m, 1H), 7.88–7.81 (m, 2H), 7.42–7.39 (m, 1H), 4.30–4.26 (m, 1H), 1.71–1.66 (m, 1H), 1.56–1.50 (m, 1H), 1.39–1.33 (m, 1H), 1.25 (d, *J*=6.9 Hz, 2H), 0.94 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.5, 150.2, 148.0, 137.3, 126.0, 122.2, 46.4, 43.4, 25.1, 22.9, 22.5, 21.6. FT-IR (neat, cm^{-1}) υ 3359, 2955, 1655, 1591, 1526, 1462, 1433, 1172. Anal. Calcd for $C_{12}H_{18}N_2O$ (206.28 g/mol): C, 69.87; H, 8.80; N, 13.58; Found: C, 69.81; H, 8.59; N, 13.50.



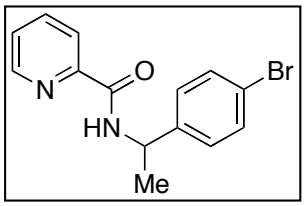
***N*-(2,6-Dimethylbenzyl)picolinamide** (S10). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and (2,6-dimethylphenyl)methanamine (12 mmol, 1.80 g). After column chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (2.75 g, 95 % yield). R_f = 0.40 (hexanes/ethyl acetate 70/30), mp=142–142.5 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.47–8.45 (m, 1H), 8.23–8.21 (m, 1H), 7.91 (br s, 1H), 7.85–7.81 (m, 2H), 7.40–7.37 (m, 1H), 7.15–7.06 (m, 2H), 4.69 (d, *J*=4.9 Hz, 2H), 2.41 9s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 164.2, 149.9, 148.1, 137.8, 137.4, 134.0, 128.5, 127.9, 126.2, 122.3, 38.3. 20.0. FT-IR (neat, cm^{-1}) υ 3387, 1671, 1521, 1463, 1434, 1241. Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30 g/mol): C, 74.97; H, 6.71; N, 11.66; Found: C, 74.98; H, 6.82; N, 11.60.



***tert*-Butyl 4-methyl-2-(picolinamido)pentanoate** (S11). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-butyl 2-amino-4-methylpentanoate (10 mmol, 1.87 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (1.64 g, 56 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.58–8.57 (m, 1H), 8.41 (d, *J*=8.2 Hz, 1H), 8.19–8.17 (m, 1H), 7.87–7.82 (m, 1H), 7.45–7.41 (m, 1H), 4.74–4.72 (m, 1H), 1.77–1.70 (m, 3H), 1.48 (s, 9H), 1.02–0.98 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 172.1, 164.0, 149.7, 148.3, 137.3, 126.3, 122.3, 81.9, 51.4, 42.1, 28.1, 25.1, 23.0, 22.1. FT-IR (neat, cm^{-1}) υ 3376, 1734, 1667, 1507, 1366, 1149, 1232, 1046. Anal. Calcd for $C_{16}H_{24}N_2O_3$ (292.37 g/mol): C, 65.73; H, 8,27; N, 9.58; Found: C, 65.84; H, 8.25; N, 9.56.

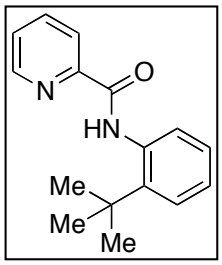


***N*-(3,3-Dimethylbutyl)picolinamide** (S12). Picolinic acid (35 mmol, 4.30 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 3,3-dimethylbutan-1-amine (12 mmol, 1.23 g). After column chromatography (hexanes/ethyl acetate 60/40), colorless oil was obtained (2.19 g, 88 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.42 (m, 1H), 8.09 (d, *J*=7.8 Hz, 1H), 7.94 (br s, 1H), 7.74–7.70 (m, 1H), 7.31–7.28 (m, 1H), 3.41–3.35 (m, 2H), 1.47–1.43 (m, 2H), 0.85 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.1, 150.1, 148.0, 137.3, 126.0, 122.1, 43.3, 36.1, 30.0, 29.4. FT-IR (neat, cm^{-1}) υ 2956, 1671, 1527, 1465, 1433, 1367, 1287. Anal. Calcd for $C_{12}H_{18}N_2O_2$ (206.28 g/mol): C, 69.87; H, 8.80; N, 13.58; Found: C, 69.09; H, 8.51; N, 13.42.



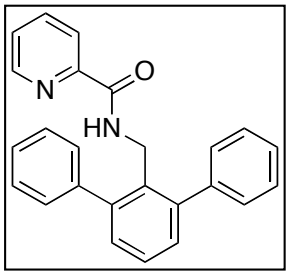
***N*-(1-(4-Bromophenyl)ethyl)picolinamide** (S13). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 1-(4-bromophenyl)ethanamine (16.5 mmol, 3.30 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (4.19 g, 83 % yield). R_f = 0.42 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.53 (m, 2H), 8.13–8.11 (m, 1H), 7.81–7.78 (m, 1H), 7.40–7.38 (m, 1H), 7.12 (s, 2H), 5.65–5.58 (m, 1H), 2.49 (s, 6H), 1.59 (d, *J*=7.45 Hz, 1H). ^{13}C

NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.8, 148.2, 138.4, 137.9 137.5, 132.1, 126.3, 122.2, 120.3, 45.5, 20.9, 19.5. FT-IR (neat, cm^{-1}) υ 3354, 1652, 1517, 1431, 1010, 997, 824, 756. Anal. Calcd for $C_{14}H_{13}BrN_2O$ (305.17 g/mol): C, 55.10; H, 4.29; N, 9.18; Found: C, 55.18; H, 4.49; N, 9.06.

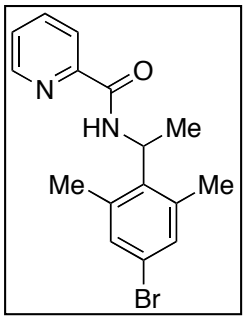


***N*-(2-(*tert*-Butyl)phenyl)picolinamide** (S14) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-*tert*-butylaniline (20 mmol, 2.58 g). After column chromatography (hexanes/ethyl acetate 80/20), yellow oil was obtained (1.12 g, 22 % yield). R_f = 0.23 (hexanes/ethyl acetate 80/20). This compound is known.[6] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.33 (br s, 1H), 8.65–8.62 (m, 1H), 8.33–8.32 (m, 1H), 8.15 (dd, *J*=9.6, 1.4 Hz, 1H), 7.92–7.87 (m, 1H), 7.49–7.43 (m, 2H), 7.32–7.28 (m, 1H), 7.18–7.14 (m, 1H), 1.51 (s, 9H).

Method B: Arylation and alkylation

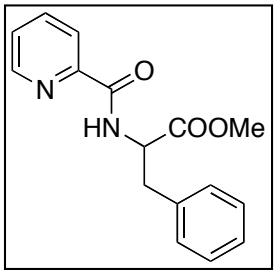


***N*-([1,1':3',1''-Terphenyl]-2'-ylmethyl)picolinamide** (S15). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1.0 mmol, 212 mg), iodobenzene (4.0 mmol, 816 mg), CsOAc (4.0 mmol, 794 mg), and *tert*- amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), white needles (360 mg, 99 % yield) were obtained. R_f = 0.34 (hexanes/ethyl acetate 70/30), mp = 119–120 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.44–8.43 (m, 1H), 7.98–7.96 (m, 1H), 7.78–7.72 (m, 2H), 7.43–7.29 (m, 14H), 4.49 (d, *J*=5.0 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.9, 149.8, 147.9, 143.9, 141.2, 137.1, 132.7, 129.8, 129.1, 128.3, 127.5, 127.4, 125.9, 122.0, 39.4. FT-IR (neat, cm^{-1}) δ 3378, 1678, 1510, 1464, 1435, 1000. Anal. Calcd for $C_{25}H_{20}N_2O$ (364.44 g/mol): C, 82.39; H, 5.53; N, 7.69; Found: C, 82.50; H, 5.45; N, 7.68.



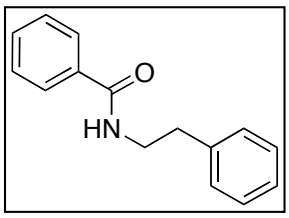
***N*-(1-(4-bromo-2,6-dimethylphenyl)ethyl)picolinamide** (S16). A 100 mL Kontes flask was charged with $Pd(OAc)_2$ (10 mol %, 224 mg), $CuBr_2$ (20 mol %, 446 mg), *N*-(1-(4-bromophenyl)ethyl)-picolinamide (10 mmol, 3.04 g), iodomethane (50 mmol, 7.10 g), K_2CO_3 (40 mmol, 552 mg), and water (3.0 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexanes/ethyl acetate 50/50), yellowish oil (175 mg, 5 % yield) was obtained. R_f = 0.41 (hexanes/ethyl acetate 50/50). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.53 (m, 2H), 8.13–8.11 (m, 1H), 7.81–7.78 (m, 1H), 7.40–7.38 (m, 1H), 7.12 9s, 2H), 5.65–5.58 (m, 1H), 2.49 (s, 6H), 1.59 (d, *J*=7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.8, 148.2, 138.4, 137.8, 137.5, 132.1, 126.3, 122.2, 120.3, 45.4, 20.9, 19.5. FT-IR (neat, cm^{-1}) υ 1676, 1572, 1512, 1464, 1433, 1245, 1144, 1040. Anal. Calcd for $C_{16}H_{17}BrN_2O$ (333.22 g/mol): C, 57.67; H, 5.14; N, 8.41; Found: C, 57.40; H, 5.24; N, 8.17.

Method C: Transesterification

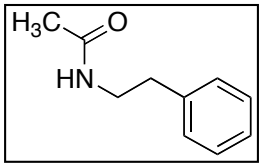


Methyl 3-phenyl-2-(picolinamido)propanoate (S17) This compound was synthesized via transesterification of the butyl ester with methanol.[7] A 6-dram vial with septum cap was charged with *tert*-butyl 1-picolinoylindoline-2-carboxylate (3.0 mmol, 978 mg) and anhydrous methanol (20 mL). The vial was cooled to 0 °C followed by dropwise addition of acetyl chloride (1.0 mL). The mixture was stirred at 50 °C. After 16 hours, the solvent was evaporated and the resulting oil was dissolved in dichloromethane and loaded in chromatography column (50/50 hexanes/ethyl acetate). The fractions containing the compound were combined and the solvent was evaporated leaving a colorless oil (792 mg, 93 % yield). R_f = 0.54 (hexanes/ethyl acetate 50/50). This compound is known.[8] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.49 (m, 2H), 8.15 (dd, *J*=7.8, 0.9 Hz, 1H), 7.84–7.80 (m, 1H), 7.43–7.39 (m, 1H), 7.30–7.17 (m, 5H), 5.09–5.05 (m, 1H), 3.72 (s. 3H), 3.16–3.27 (m, 2H).

Synthesis of other amides



***N*-Phenethylbenzamide** (S18). Procedure same as that for the synthesis of picolinamides. Benzoic acid (18 mmol, 2.19 g), triethylamine (18 mmol, 5.0 mL), dichloromethane (50 mL), ethyl chloroformate (18 mmol, 1.70 mL), phenethylamine (10 mmol, 1.21 g). After column chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (1.58 g, 70 % yield). R_f = 0.68 (hexanes/ethyl acetate 70/30). This compound is known.[9] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.74–7.25 (m, 10H), 6.29 (s, 1H), 3.74 (m, 2H), 2.56 (m, 2H).



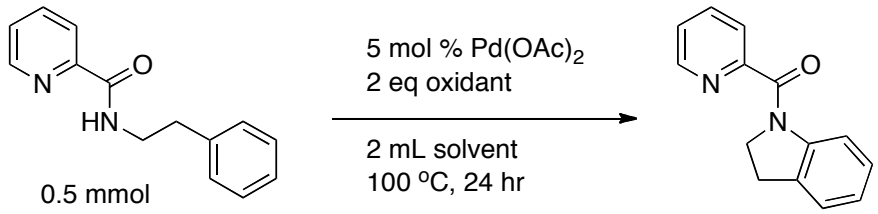
***N*-Phenethylacetamide** (S19). Acetic anhydride (12 mmol, 1.13 mL) was mixed with phenethylamine (10 mmol, 1.21 g) and the solution was stirred at room temperature. After one hour, the reaction mixture was added dropwise to saturated aqueous $NaHCO_3$ (100 mL). The mixture was then extracted with diethyl ether (2 X 100 mL). The organic extracts were combined, dried with $MgSO_4$ and the solvent was evaporated to give white powder (1.30 g, 80 % yield). This compound is known.[10] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.15-7.37 (m, 5H), 5.57 (br s, 1H), 3.51 (m, 2H), 2.81 (t, *J*= 7.1 Hz, 2H), 1.93 (s, 3H).

General procedure for the optimization of the reaction conditions for the cyclization of *N*-phenethylpicolinamide. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant and solvent were added to this mixture (Table S1). The resulting suspension was stirred in an oil bath at the specified temperature. After the designated time, the reaction mixture was cooled. A drop of sample was then diluted with about one mL ethyl acetate and the resulting mixture was passed through silica plug. The filtrate was analyzed by GC-MS.

Determination of the GC conversion using internal standard. The GC conversion for the arylation (for optimization experiments) was calculated based on an internal standard (dodecane) as described here. First, a 1:1 molar mixture of dodecane and the pure target compound was dissolved in ethyl acetate and injected into GC to determine detector response ratio $F = A_{tc}/A_{do}$ (A_{tc}: area of target compound peak, A_{do}: area of dodecane peak). Second, the investigating reaction is set up as usual on a 1 mmol scale with the addition of dodecane as internal standard (0.3 mmol). After the completion of reaction, 1 drop of reaction mixture is diluted with CH_2Cl_2 and injected into GC to determine area of dodecane (A_{dor}) and the target compound (A_{tcr}). The amount of target compound in reaction mixture can be calculated by the following equation: $n_{tcr} = 0.3.A_{tcr}/(A_{dor}*F)$ (mmol). The conversion is derived based on the amount of starting material added (n_{sm}): $C = (n_{tcr}/n_{sm})*100\%$.

Optimization of the solvent and oxidant for the cyclization of *N*-phenethylpicolinamide. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (2 equiv, 1.0 mmol) and the solvent (2.0 mL, Table 1) was added to this mixture. The resulting suspension was stirred in an oil bath at 100 °C. After 24 hours, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. The best combination is iodobenzene diacetate oxidant in toluene (Table S1, entry 2).

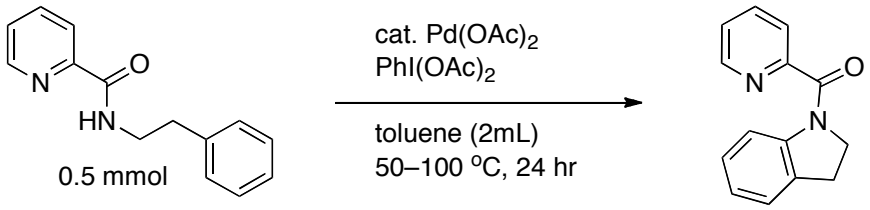
Table S1. Optimization of the solvent and oxidant combination.



Entry	Oxidant	Solvent	% Yield (GC)
1	$PhI(OAc)_2$	dichloromethane	57
2	**$PhI(OAc)_2$**	**toluene**	**73**
3	$PhI(OAc)_2$	*t*-amyl alcohol	58
4	$PhI(OAc)_2$	*m*-xylene	67
5	$PhI(OAc)_2$	CH_3COOH	44
6	$PhI(OAc)_2$	CF_3COOH	3
7	$PhI(OAc)_2$	toluene/MeCN (9/1)	65
8	1,2-dichloroethane	dichloromethane	0
9	1,2-dichloroethane	toluene	0
10	1,2-dichloroethane	*t*-amyl alcohol	0
11	1,2-dichloroethane	*m*-xylene	0
12	1,2-dichloroethane	CH_3COOH	0
13	1,2-dichloroethane	CF_3COOH	trace
14	AgOAc	dichloromethane	0
15	AgOAc	toluene	0
16	AgOAc	*t*-amyl alcohol	0
17	AgOAc	*m*-xylene	0
18	AgOAc	CH_3COOH	0
19	AgOAc	CF_3COOH	0
20	$PhI(CF_3COO)_2$	toluene	0
21	PhI(*p*-nitrobenzoate)$_2$	toluene	38

Optimization of the amount of oxidant and the temperature of the reaction: cyclization of *N*-phenethylpicolinamide. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (1.01–3.0 eq) and toluene (2.0 mL) was added to this mixture. The resulting suspension was stirred in an oil bath at 50–100 °C. After 24 hours, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. The optimum conditions involve the use of 2.0 equivalents of the iodobenzene diacetate at 80°C (Table S2, entry 10).

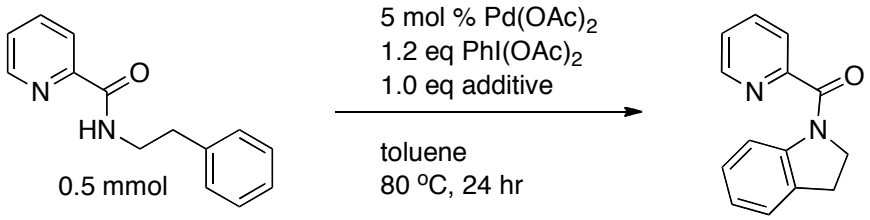
Table S2. Optimization of the amount of oxidant and the temperature of the reaction



Entry	$PhI(OAc)_2$ (eq)	Temp (°C)	% Yield (GC)
01	1.2	50	68
02	1.2	60	74
03	1.2	70	77
04	1.2	80	78
05	1.2	90	64
06	1.2	100	66
07	1.6	100	63
08	2.0	100	72
09	2.0	90	68
10	**2.0**	**80**	**82**
11	2.0	70	77
12	2.0	60	73
13	3.0	80	65
14	1.5	80	74
15	1.1	80	54

Attempted enhancement of yields using different additives. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (1.2 eq, 0.6 mmol), additive (1 eq, 0.5 mmol) and toluene (2.0 mL) was added to this mixture. The resulting suspension was stirred in an oil bath at 80 °C. After 24 hours, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. Among the additives tested, nothing was found to increase the yield of the products (Table S3).

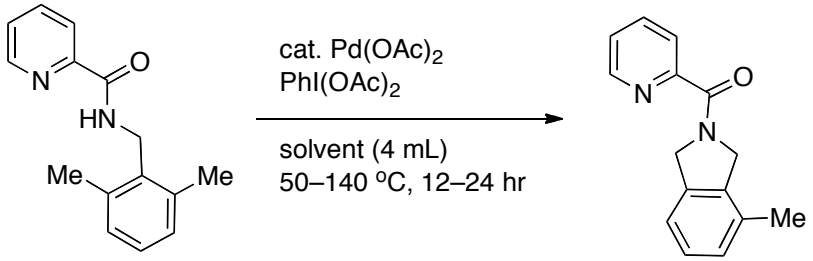
Table S3. Additives tested for the attempted enhancement of yields



Entry	Additive	% Yield (GC)
01	NaOAc	63
02	K_2CO_3	20
03	CsOAc	31
04	K_3PO_4	46
05	KPivalate	28
06	Pivalic acid	65
07	DMF	53
08	CH_3COOH	58
09	CF_3COOH	4
10	$CuBr_2$	trace
11	$Cu(OAc)_2$	4
12	LiOTf	6
13	**No additive**	**78**

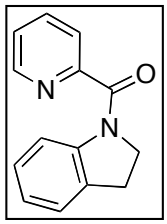
Optimization of the solvent and oxidant for the cyclization of *N*-(2,6-Dimethylbenzyl)picolinamide. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-(2,6-Dimethylbenzyl)picolinamide (1.0 mmol, 224 mg). The iodobenzene diacetate (2.0 eq, 2.0 mmol, 644 mg) and the solvent (4.0 mL, Table 2) was added to this mixture. The resulting suspension was stirred in an oil bath. After the designated reaction time, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. The best reaction condition was achieved by using 2.0 equivalent of the iodobenzene diacetate in toluene/MeCN (9:1) and stirred at 120 °C for 24 hours. (Table S4, entry 9).

Table S4. Optimization of the reaction condition for sp^3 C-H bond functionalization

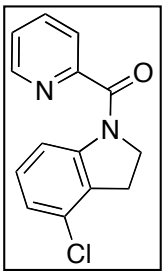


Entry	$Pd(OAc)_2$ (mol %)	$PhI(OAc)_2$ (eq)	Solvent	Temp (°C)	Time (hr)	% Yield (GC)
01	5	2.0	toluene	80	24	34
02	10	2.0	toluene	80	24	38
03	5	1.2	toluene	80	24	35
04	5	2.0	toluene	50	48	14
05	5	2.0	toluene	80	12	36
06	5	2.0	toluene	100	24	41
07	5	2.0	Toluene/MeCN (9/1)	80	24	51
08	5	2.0	Toluene/MeCN (9/1)	100	24	55
09	**5**	**2.0**	**Toluene/MeCN (9/1)**	**120**	**24**	**70**
10	5	2.0	Toluene/MeCN (9/1)	140	24	16

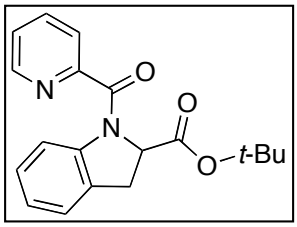
General procedure for the cyclization of picolinamides. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), picolinamide (1.0 mmol), iodobenzene diacetate (2.0 eq, 2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in an oil bath at 80–120 °C. After 24 hours, the reaction mixture was cooled and then loaded on silica chromatography column with hexanes/ethyl acetate mixture as eluent.



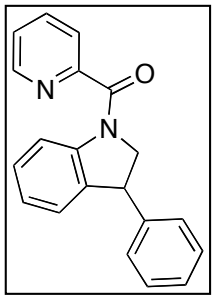
Indolin-1-yl(pyridin-2-yl)methanone (Table 1, entry 1). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-phenethylpicolinamide (1.0 mmol, 229 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 80/20), white crystals were obtained (182 mg, 80 % yield). R_f = 0.19 (hexanes/ethyl acetate 80/20), mp 103–103.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (d, *J*=5.0 Hz, 1H), 8.31 (d, *J*=7.8 Hz, 1H), 7.88–7.81 (m, 2H), 7.38–7.36 (m, 1H), 7.27–7.21 (m, 2H), 7.08–7.05 (m, 1H), 4.34 (t, *J*=8.2 Hz, 2H), 3.14 (t, *J*= 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 154.7, 148.1, 143.4, 137.1, 132.2, 127.5, 125.1, 124.7, 124.4, 124.2, 118.0, 50.6, 28.8. FT-IR (neat, cm^{-1}) υ 1632, 1592, 1482, 1436, 1397. Anal. Calcd for $C_{14}H_{12}N_2O$ (224.26 g/mol): C, 74.98; H, 5.39; N, 12.49; Found: C, 74.47; H, 5.54; N, 12.31.



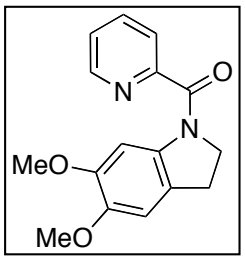
(4-Chloroindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 2). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-chlorophenethyl)picolinamide (1.0 mmol, 257 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 80/20), white crystals were obtained (204 mg, 80 % yield). R_f = 0.26 (hexanes/ethyl acetate 80/20), mp=129.5-130 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.63–8.61 (m, 1H), 8.20 (d, *J*=7.3 Hz, 1H), 7.89–7.82 (m, 2H), 7.41–7.38 (m, 1H), 7.22–7.19 (m, 1H), 7.05 (d, *J*=7.3 Hz, 1H), 4.41 (t, *J*=8.2 Hz, 2H), 3.15 (t, *J*=8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 154.2, 148.1, 144.7, 137.2, 130.7, 130.5, 129.1, 125.3, 124.4, 124.3, 116.2, 50.4, 28.2. FT-IR (neat, cm^{-1}) υ 1652, 1590, 1450, 1387, 1252. . Anal. Calcd for $C_{14}H_{11}ClN_2O$ (258.70 g/mol): C, 65.00; H, 4.29; Cl, 13.70; N, 10.83; Found: C, 64.41; H, 4.34; N, 10.67.



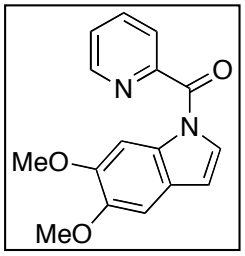
***tert*-Butyl 1-picolinoylindoline-2-carboxylate** (Table 1, entry 3). $Pd(OAc)_2$ (5 mol %, 11 mg), *tert*-butyl 3-phenyl-2-(picolinamido)propanoate (1.0 mmol, 332 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 70/30), colorless solid was obtained (254 mg, 77 % yield). R_f = 0.36 (hexanes/ethyl acetate 70/30), mp=108.6–109.1 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 (d, *J*=4.1 Hz, 1H), 8.41 (d, *J*=8.2 Hz, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 7.86–7.82 (m, 1H), 7.38–7.36 (m, 1H), 7.30–7.26 (m, 1H), 7.20 (d, *J*=7.3 Hz, 1H), 7.09–7.06 (m, 1H), 5.77 (m, 1H), 3.61 (dd, *J*=16.5, 5.0 Hz, 1H), 3.20 (dd, *J*=16.5, 2.7 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 165.7, 153.7, 147.3, 143.9, 137.2, 129.3, 127.8, 125.3, 124.4, 124.3, 118.1, 81.6, 62.9, 34.0, 27.8 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 1737, 1641, 1568, 1481, 1395, 1161, 1105. Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.37 g/mol): C, 70.35; H, 6.21; N, 8.64; Found: C, 70.14; H, 6.20; N, 8.47.



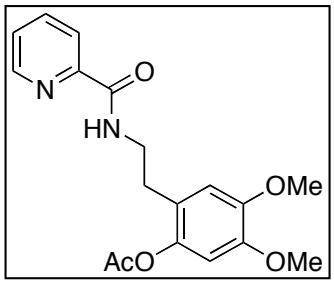
(3-Phenylindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 4). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,2-diphenylethyl)picolinamide (1.0 mmol, 308 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 hrs. After column chromatography (dichloromethane/ethyl acetate 90/10), white powder was obtained (234 mg, 76 % yield). R_f = 0.22 (dichloromethane/ethyl acetate 90/10), mp=141–142 °C (acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.57 (d, *J*=4.6 Hz, 1H), 8.38 (d, *J*=7.8 Hz, 1H), 7.92–7.77 (m, 2H), 7.42–7.19 (m, 7H), 7.09–6.94 (m, 2H), 4.77 (dd, *J*=11.4, 10.1 Hz, 1H), 4.60 (dd, *J*=10.1, 7.8 Hz, 1H), 4.29 (dd, *J*=11.4, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 154.3, 154.2, 148.1, 143.5, 142.9, 137.2, 135.6, 128.9, 128.2, 127.3, 125.2, 125.1, 124.9, 124.4, 118.0, 59.8, 47.4. FT-IR (neat, cm^{-1}) υ 1648, 1594, 1480, 1453, 1440, 1395, 1327, 1296, 1248, 1155, 1087, 1048, 1032.



(5,6-Dimethoxyindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 5). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(3,4-dimethoxyphenethyl)-picolinamide (1.0 mmol, 284 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 40/60), colorless oil was obtained (44 mg, 16 % yield). R_f = 0.41 (hexanes/ethyl acetate 40/60). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.52 (m, 1H), 8.21–8.18 (m, 2H), 7.88–7.84 (m, 1H), 7.44–7.41 (m, 1H), 7.23 (s, 1H), 6.78 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.72–3.67 (m, 2H), 3.01 (t, *J*=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 149.9, 149.4, 148.2, 148.1, 137.5, 134.0, 126.3, 122.3, 121.7, 112.8, 88.1, 56.2, 55.9, 40.2, 39.5. FT-IR (neat, cm^{-1}) υ 2929, 1671, 1569, 1591, 1525, 1505, 1463, 1436, 1254, 1217, 1162, 1377, 1254, 1218, 1031.

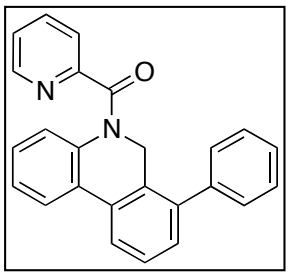


(5,6-Dimethoxy-1*H*-indol-1-yl)(pyridin-2-yl)methanone (Table 1, entry 5). In addition to the indoline above, dehydrogenation product was also isolated from the reaction mixture as yellowish crystals (53 mg, 18 % yield). R_f = 0.56 (hexanes/ethyl acetate 40/60), mp=128–129 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.74–8.73 (m, 1H), 8.20 (s, 1H), 8.07–8.06 (m, 1H), 7.94–7.90 (m, 1H), 7.84 (d, *J*=4.1 Hz, 1H), 7.52–7.48 (m, 1H), 7.04 (s, 1H), 6.54 (d, *J*=3.7 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 152.5, 148.6, 147.9, 147.3, 137.4, 130.6, 127.1, 126.1, 125.7, 123.5, 109.2, 102.4, 100.7, 56.3, 56.2. FT-IR (neat, cm^{-1}) υ 2928, 1673, 1583, 1540, 1480, 1470, 1438, 1382, 1344, 1301, 1251, 1151, 1194.

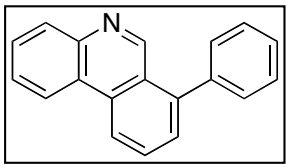


4,5-Dimethoxy-2-(2-(picolinamido)ethyl)phenyl acetate (Table 1, entry 5). In addition to indole and indoline products described above, acetoxylation product was also observed. The product was isolated as yellowish oil (206 mg, 59 % yield). R_f = 0.24 (hexanes/ethyl acetate 40/60). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.50 (m, 1H), 8.24–8.18 (m, 1H), 7.86–7.82 (m, 1H), 7.43–7.40 (m, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.83 (s, 3H), 3.81 (s, 1H), 3.68–3.63 (m, 2H), 2.80 (t, *J*=7.3 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.1, 164.5, 149.9, 148.1, 148.0, 147.0, 142.3, 137.4, 126.3, 122.2, 112.7, 106.4, 56.2, 56.1,

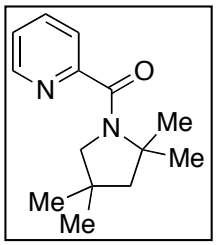
39.8, 30.2, 20.9 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 2938, 1756, 1669,1515, 1465, 1402, 1368, 1208, 1179, 1104, 1015. Anal. Calcd for $C_{18}H_{20}N_2O_5$ (344.36 g/mol): C, 62.78; H, 5.85; N, 8.13; Found: C, 62.22; H, 5.90; N, 7.94.



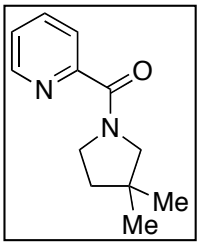
(7-Phenylphenanthridin-5(6*H*)-yl)(pyridin-2-yl)methanone (Table 1, entry 6). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-([1,1':3',1"-terphenyl]-2'-ylmethyl)picolinamide (1.0 mmol, 369 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 60/40), white solid was obtained (315 g, 86 % yield). R_f = 0.23 (hexanes/ethyl acetate 60/40), 165–166 °C (hexanes). ^{1}H NMR (400 MHz, acetonitrile-d_3, ppm, 80 °C) δ 8.27–8.25 (m, 1H), 7.93–7.89 (m, 2H), 7.22–7.68 (m, 1H), 7.50–7.47 (m, 1H), 7.42–7.37 (m, 4H), 7.32–7.23 (m, 7H), 4.82 (s, 2H). ^{13}C NMR (125 MHz, acetonitrile-d_3, ppm, 80 °C) δ 167.2, 154.1, 148.4, 139.9, 139.8, 138.1, 136.8, 132.6, 132.0, 129.4, 129.3, 129.0, 128.3, 127.9, 127.6, 127.4, 125.8, 124.9, 124.6, 124.5, 123.4, 123.0, 116.9. FT-IR (neat, cm^{-1}) υ 1648, 1594, 1480, 1453, 1440, 1395, 1327, 1296, 1248, 1155, 1087, 1048, 1032. Anal. Calcd for $C_{25}H_{18}N_2O$ (362.42 g/mol): C, 82.85; H, 5.01; N, 7.73; Found: C, 82.80; H, 4.98; N, 7.77.



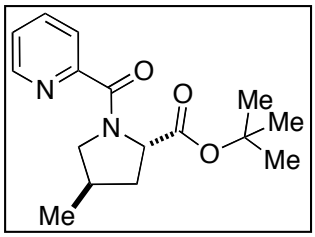
7-Phenylphenanthridine (Table 1, entry 6)**.** In addition to the major product in previous entry, phenanthridine byproduct was also isolated (19 mg, 7 % yield). R_f = 0.65 (hexanes/ethyl acetate 60/40), mp=114–114.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.36 (s, 1H), 8.66–8.63 (m, 2H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 7.89 (dd, *J*=8.7, 7.3 Hz, 1H), 7.78–7.70 (m, 2H), 7.63 (dd, *J*=7.3, 0.9 Hz, 1H), 7.55–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.0, 144.2, 142.4, 138.9, 133.1, 130.5, 130.4, 130.1, 128.9, 128.6, 128.1, 127.2, 124.1, 124.0, 122.5, 121.3 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 1600, 1451, 1032.



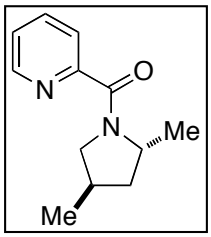
Pyridin-2-yl(2,2,4,4-tetramethylpyrrolidin-1-yl)methanone (Table 1, entry 7). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 50/50), white powder was obtained (204 g, 88 % yield). R_f = 0.38 (hexanes/ethyl acetate 50/50), mp=90–90.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56–8.55 (m, 1H), 7.78–7.74 (m, 1H), 7.62–7.60 (m, 1H), 7.31–7.28 (m, 1H), 3.39 (s, 2H), 1.79 (s, 2H), 1.68 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 156.4, 148.1, 136.9, 124.1, 122.8, 63.5, 63.0, 56.0, 36.8, 27.8, 27.6. FT-IR (neat, cm^{-1}) υ 2963, 1626, 1444, 1407, 1152, 1033. Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32 g/mol): C, 72.38; H, 8.68; N, 12.06; Found: C, 72.40; H, 8.82; N, 11.98.



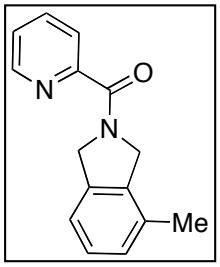
(3,3-Dimethylpyrrolidin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 8) $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(3,3-dimethylbutyl)picolinamide (1.0 mmol, 206 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.6 mL), 120 °C for 24 hours. After column chromatography (dichloromethane/ethyl acetate 30/70), yellow oil was obtained (80 mg, 40 % yield). R_f = 0.36 (dichloromethane/ethyl acetate 30/70). ^{1}H NMR (500 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.35–8.49 (m, 1H), 7.85–7.77 (m, 2H), 7.36–7.32 (m, 1H), 3.82–3.79 and 3.72–3.69 (m, 2H), 3.48 and 3.46 (s, 2H), 1.73 (t, *J*=6.9 Hz, 2H), 1.16 and 1.07 (s, 6H,). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 166.7, 166.6, 154.5, 154.4, 148.0, 136.9, 136.8, 124.8, 124.7, 124.0, 61.8, 59.5, 48.3, 46.1, 40.1, 39.1, 37.5, 36.5, 26.4, 25.9 (signal for two carbons could not be located). FT-IR (neat, cm^{-1}) υ 1625, 1586, 1476, 1446, 1414, 1144.



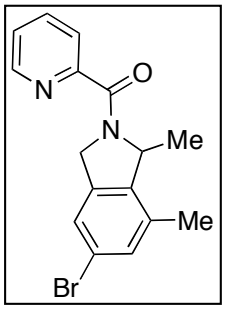
***trans tert*-Butyl 4-methyl-1-picolinoylpyrrolidine-2-carboxylate** (Table 1, entry 9) $Pd(OAc)_2$ (5 mol %, 11 mg), *tert*-butyl 2-amino-4-methylpentanoate (1.0 mmol, 292 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.60 mL), 100 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 50/50), yellow oil was obtained (105 mg, 36 % yield, 9/1 trans/cis). R_f = 0.39 (hexanes/ethyl acetate 50/50. ^{1}H NMR (500 MHz, $CDCl_3$, ppm, 1.8/1 mixture of rotamers) δ 8.60–8.59 and 8.50–8.49 (m, 1H), 8.04–8.01 and 7.89–7.87 (m, 1H), 7.81–7.76 (m, 1H), 7.36–7.30 (m, 1H), 5.11 (dd, *J*=10.9, 8.5 Hz) and 4.61 (dd, *J*=9.2 Hz, 2.9 Hz; 1H), 4.07–4.03 (m, 1H), 3.49 (dd, *J*=10.9, 8.6 Hz) and 3.31 (dd, *J*=12.0, 9.2 Hz; 1H), 2.53–2.38 (m, 1H), 2.22–1.83 (m, 2H), 1.49 (s) and 1.34 (s; 9H), 1.13 (d, *J*=6.9 Hz) and 1.05 (d, *J*= 6.3 Hz; 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of rotamers) δ 172.0, 171.4, 162.2, 165.7, 153.8, 153.1, 148.0, 147.3, 136.9, 124.9, 124.7, 124.3, 81.3, 80.9, 62.7, 61.0, 56.5, 55.1, 39.7, 36.6, 32.8, 29.7, 28.1, 27.9, 27.7, 17.6, 17.3 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 2968, 1737, 1633, 1567, 1445, 1409, 1367, 1219, 1154. Minor amounts of cis-isomer and its rotamer were also observed but are not reported. Anal. Calcd for $C_{16}H_{22}N_2O$ (290.36 g/mol): C, 66.18; H, 7.64; N, 9.65; Found: C, 65.68; H, 8.21; N, 9.52.



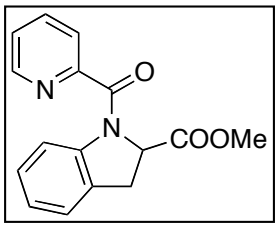
***trans*-(2,4-Dimethylpyrrolidin-1-yl)(pyridin-2-yl)methanone** (Table 1, entry 10). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(4-methylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 120 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 50/50), yellowish oil was obtained (127 mg, 59 % yield). R_f = 0.30 (dichloromethane/ethyl acetate 50/50). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, mixture of 2 amide rotamers) δ 8.59–8.57 (m, 1H), 7.81–7.73 (m, 2H), 7.40–7.29 (m, 1H), 4.78–4.74 and 4.50–4.42 (m, 1H), 4.02–3.90 (m, 1H), 3.25–3.13 (m, 1H), 2.49–2.40 (m, 1H), 1.83–1.67 (m, 1H), 1.36 (d, *J*=6.4 Hz) and 1.13 (d, *J*=6.2 Hz; 3H), 1.00 and 0.97 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 166.5, 155.1, 154.9, 148.1, 148.0, 136.9, 124.6, 124.5, 123.8, 123.7, 56.1, 54.6, 54.0, 53.8, 41.8, 39.9, 32.1, 29.4, 21.7, 19.8, 18.1, 17.8 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 1739, 1674, 1631, 1567, 1521, 1409, 1229, 1050, 1032. Anal. Calcd for $C_{12}H_{16}N_2O$ (204.27 g/mol): C, 70.56; H, 7.90; N, 13.71; Found: C, 69.93; H, 8.05; N, 13.13.



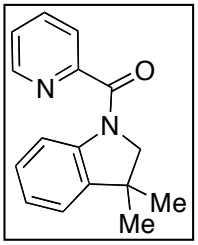
(4-Methylisoindolin-2-yl)(pyridin-2-yl)methanone (Table 1, entry 11). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,6-dimethylbenzyl)picolinamide (1.0 mmol, 238 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.6 mL), 120 °C for 24 hr. After column chromatography (dichloromethane/ethyl acetate 50/50), white powder was obtained (159 mg, 68 % yield). R_f = 0.35 (dichloromethane /ethyl acetate 50/50), mp=87–88 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.67–8.63 (m, 1H), 7.97–7.95 (m, 1H), 7.85–7.80 (m, 1H), 7.40–7.36 (m, 1H), 7.21–7.13 and 7.08–7.01 (m, 3H), 5.22 and 5.13 (s, 2H), 5.05 and 4.98 (s, 2H), 2.30 and 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) 170.5, 166.5, 153.9, 153.8, 148.1, 148.0, 147.9, 137.3, 137.1, 136.9, 136.6, 135.4, 134.8, 133.0, 132.6, 131.6, 128.3, 128.2, 127.9, 127.8 125.1, 124.4, 120.1, 119.8, 55.5, 54.3, 54.0, 53.0, 18.9, 18.1 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 2962, 1626, 1586, 1565, 1468, 1444, 1407, 1289, 1224, 1152, 1033. Anal. Calcd for $C_{15}H_{14}N_2O$ (238.28 g/mol): C, 75.61; H, 5.92; N, 11.76; Found: C, 74.70; H, 6.76; N, 11.61.



(5-Bromo-1,7-dimethylisoindolin-2-yl)(pyridin-2-yl)methanone (Table 1, entry 12) $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-(4-bromophenyl)-ethyl)picolinamide (0.5 mmol, 142 mg), iodobenzene diacetate (1.0 mmol, 322 mg), acetonitrile (0.20 mL), and toluene (1.8 mL), 120 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 50/50), yellowish oil was obtained (59 mg, 42 % yield). R_f = 0.46 (hexanes/ethyl acetate 50/50). ^{1}H NMR (500 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.62–8.61 (m, 1H), 7.91–7.84 (m, 1H), 7.83–7.78 (m, 1H), 7.37–7.35 (m, 1H), 7.26 and 7.13 (s, 1H), 7.18 (m, 1H), 6.08–6.59 and 5.46–5.59 (m, 1H), 5.27 (d, *J*=15.5 Hz) and 5.03 (d, *J*=17.2 Hz; 1H), 4.89–4.84 (m, 1H), 2.30 and 2.23 (s, 3H), 1.55 (d, *J*=6.3 Hz) and 1.18 (d, *J*=6.3 Hz; 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.2, 165.9, 153.8, 153.7, 148.2, 148.0, 140.7, 139.2, 138.9, 137.2, 137.1, 137.0, 134.5 134.0, 131.9, 125.2, 125.1, 124.5, 124.4, 123.4, 123.0, 121.3, 121.2, 59.2, 59.1, 53.8, 51.9, 21,3, 18.8, 18.6, 18.6 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) υ 1631, 1566, 1445, 1407, 1333, 1155, 1051.

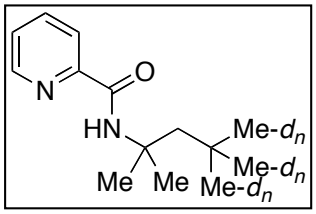


Methyl 1-picolinoylindoline-2-carboxylate (Table 1, entry 13). $Pd(OAc)_2$ (5 mol %, 11 mg), methyl 3-phenyl-2-(picolinamido)-propanoate (1.0 mmol, 289 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 hrs. After column chromatography (hexanes/ethyl acetate 60/40), colorless oil was obtained (287 mg, 67 % yield). R_f = 0.38 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, *J*=4.0 Hz, 1H), 8.41 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.85–7.83 (m, 1H), 7.38 (dd, *J*=6.9, 5.2 Hz, 1H), 7.31–7.26 (m, 1H), 7.21 (d, *J*=6.9 Hz, 1H), 7.09 (m, 1H), 5.79 (dd, *J*=10.9, 2.3 Hz, 1H), 3.65–3.60 (m, 4H), 3.26–3.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.9, 165.4, 153.2, 147.2, 143.7, 137.3, 129.3, 127.9, 125.5, 125.2, 124.7, 124.4, 118.2, 62.7, 52.5, 33.9. FT-IR (neat, cm^{-1}) υ 1747, 1650, 1585, 1481, 1389, 1279, 1203, 1099.



(3,3-Dimethylindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 14). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-(*tert*-butyl)phenyl)picolinamide (1.0 mmol, 275 mg), iodobenzene diacetate (2.0 mmol, 644 mg), toluene (3.6 mL) and dimethylformamide (0.40 mL) at 120 °C for 24 hrs. After column chromatography (dichloromethane/ethyl acetate 90/10), yellow oil was obtained (99 mg, 36 % yield). R_f = 0.46 (dichloromethane/ethyl acetate 90/10). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.63 (d, *J*=4.6 Hz, 1H), 8.28 (d, *J*=8.2 Hz, 1H), 7.91–7.80 (m, 2H), 7.41–7.38 (m, 1H), 7.29–7.26 (m, 1H), 7.19–7.10 (m, 2H), 4.09 (s, 2H), 1.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 154.5, 148.1, 142.0, 141.5, 137.2, 127.7, 125.1, 124.8, 124.4, 121.9, 118.0, 65.1, 40.7, 28.3. FT-IR (neat, cm^{-1}) υ 2925, 1645, 1596, 1481, 1397, 1289, 1095, 1022.

Deuterium Exchange Experiment



A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), cesium acetate (2.0 mmol, 392 mg), CH_3COOH-d_4 (30 mmol, 1.70 mL) and toluene (2.0 mL). The resulting suspension was stirred in an oil bath at 120 °C. After 6 hours, the reaction mixture was cooled and an aliquot was purified by preparative TLC (hexane/ethyl acetate 70/30) followed by NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, *J*=4.0 Hz, 1H), 8.18 (d, *J*=8.0, Hz, 1H), 8.1 (br s, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (m, 6H).

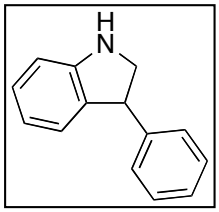
Control Experiments

Use of *N*-phenethylbenzamide. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-phenethylbenzamide (1.0 mmol, 225 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in oil bath at 80 °C. After 24 hours, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

Exclusion of palladium acetate catalyst from the reaction mixture. A 2-dram screw-cap vial was charged with *N*-phenethylpicolinamide (1.0 mmol, 227 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in oil bath at 80 °C. After 24 hours, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

A 2-dram screw-cap vial was charged with *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in an oil bath at 80 °C. After 24 hours, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

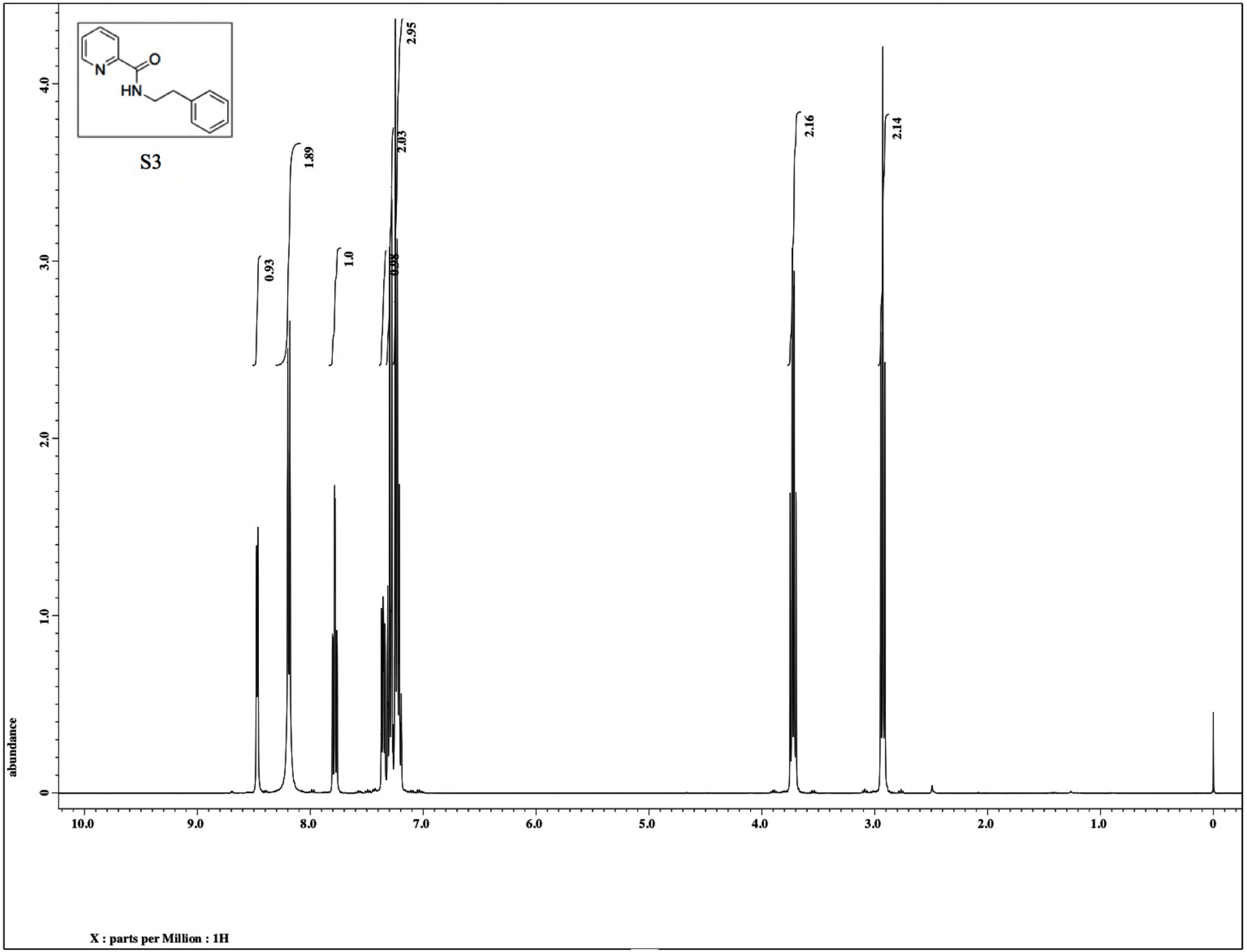
Removal of the Auxillary.

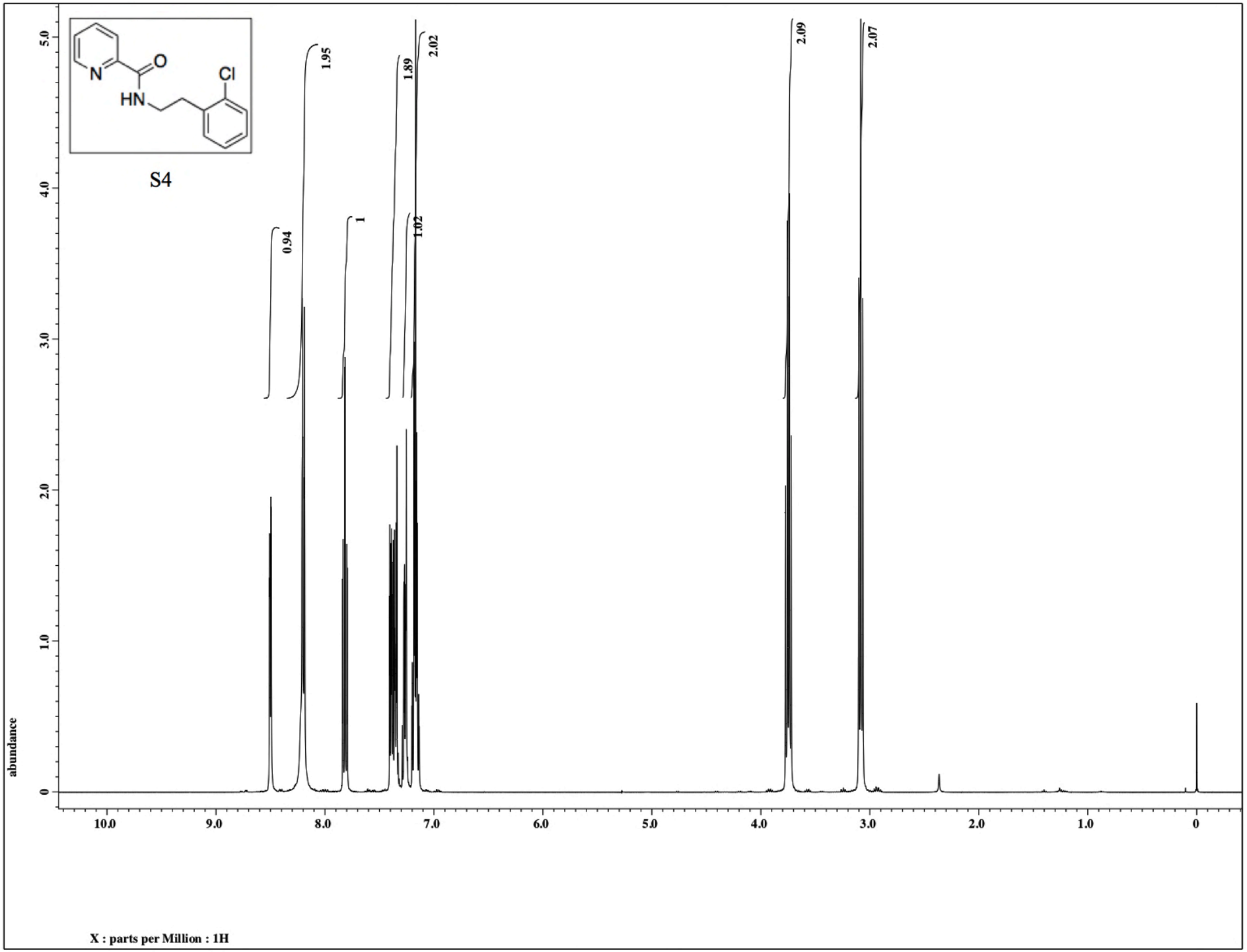


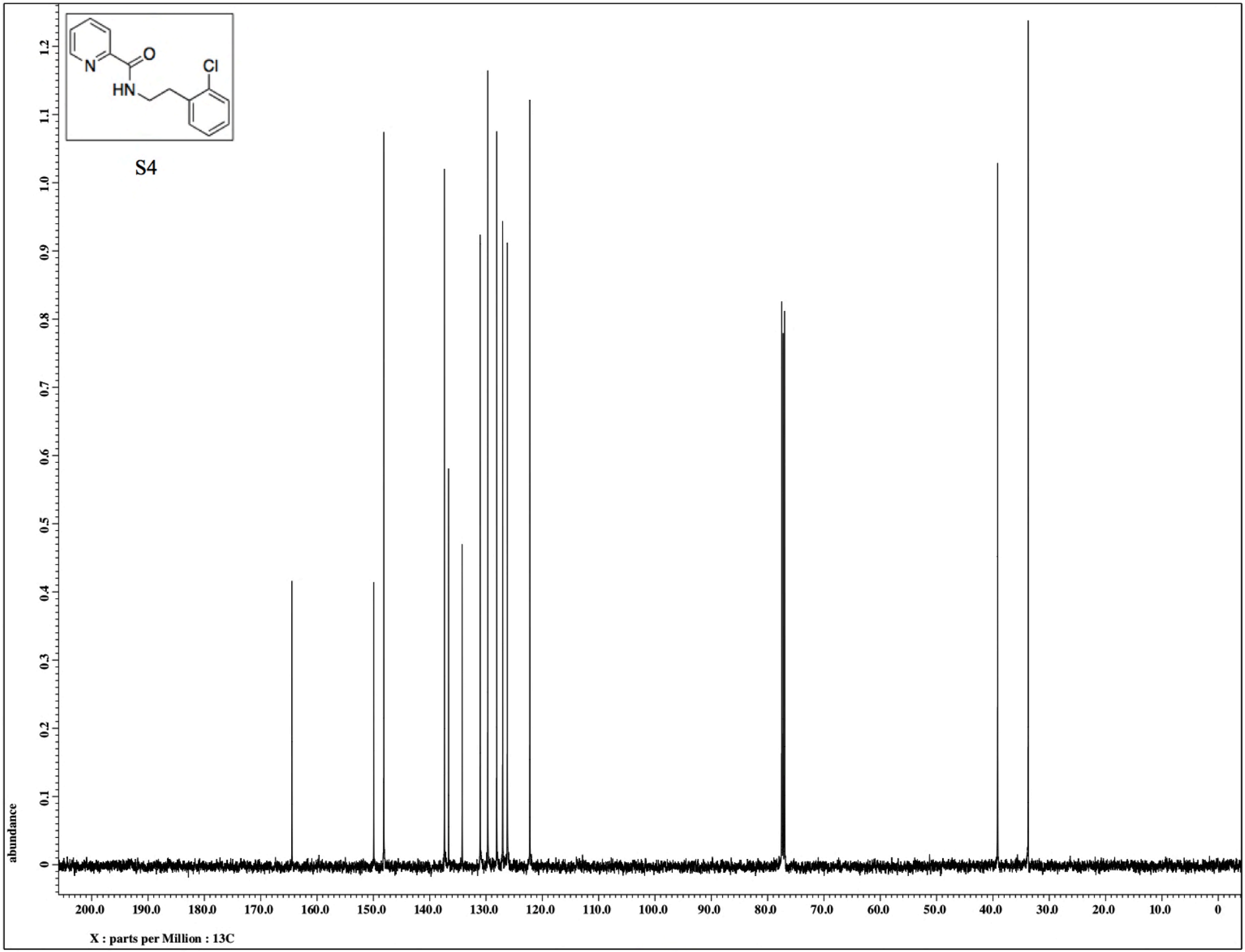
3-Phenylindoline. Method by Tanaka, et al.[11] was followed with a minor modification. In a 50 mL Schlenk flask, (3-phenylindolin-1-yl)(pyridin-2-yl)methanone (1.0 mmol, 300 mg) was dissolved in anhydrous THF (10 mL). The mixture was cooled in an ice bath and then Super-Hydride (4.0 mL, 1.0 M solution in THF) was added dropwise. The mixture was warmed to room temperature and stirred for an hour. After that, THF was evaporated. The residue was suspended in dichloromethane and loaded onto chromatography column (hexane/ethyl acetate). Evaporation of the solvent gave yellow crystals (168 mg, 86 %). R_f = 0.63 ((hexane/ethyl acetate 80/20) This compound is known.[12] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32–7.20 (m, 5H), 7.08–7.05 (m, 1H), 6.92–6.80 (m, 1H), 6.72–6.86 (m, 2H), 4.47 (dd, *J*=9.2, 8.7 Hz, 1H), 3.91 (dd, *J*=9.2, 9.2 Hz, 1H), 3.59 (br s. 1H), 3.48 (dd, *J*=9.2, 8.7 Hz, 1H).

References

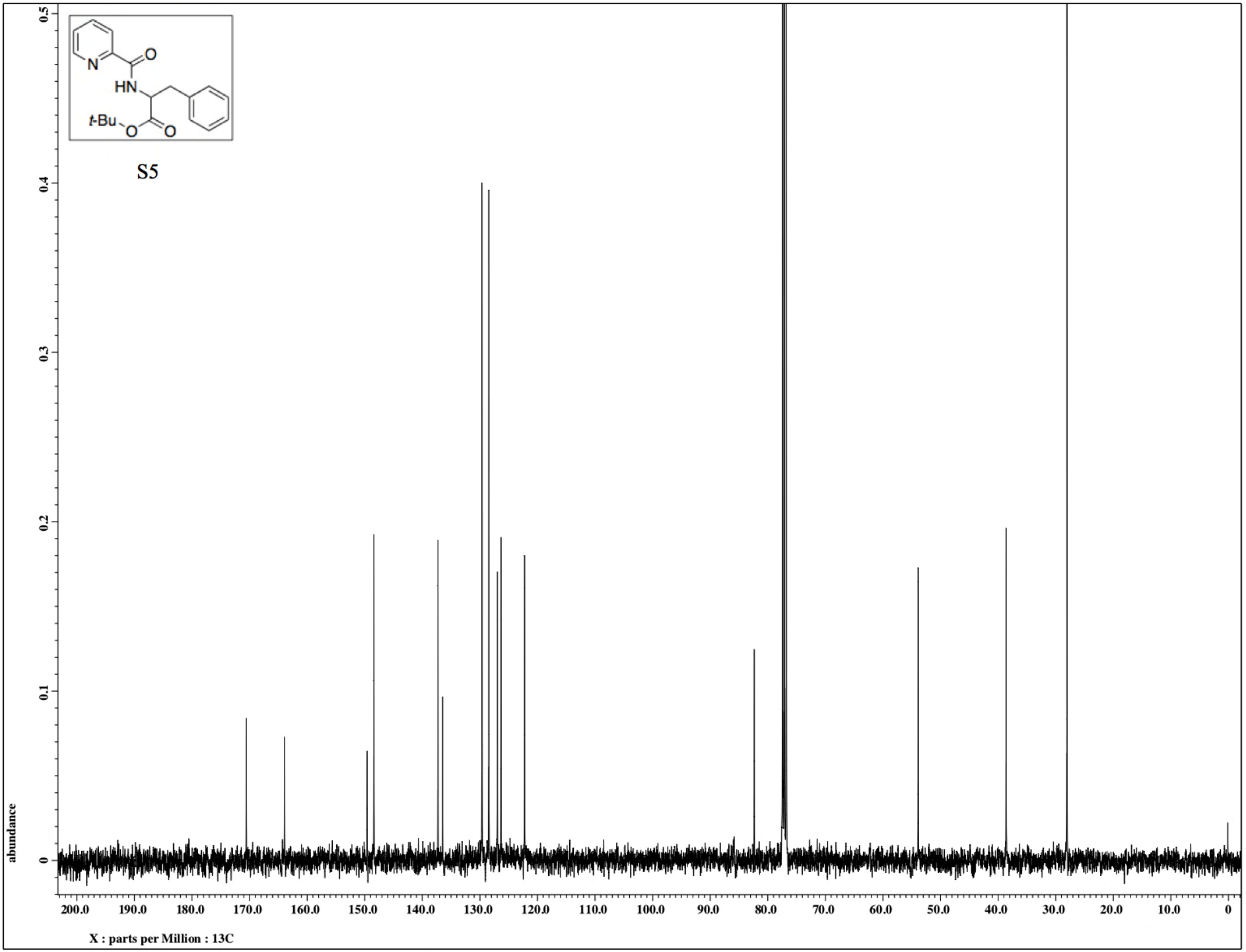
1. Chen, H.; Feng, Y.; Xu, Z. *Tetrahedron* **2005**, *61*, 11132.
2. Yang, P.-Y.; Liu, K.; Ngai, M. H.; Lear, M. J.; Wenk, M. R.; Yao, S. Q. *J. Am. Chem. Soc.* **2010**, *132*, 656-666 .
3. Shinji, C.; Maeda, S.; Imai, K.; Yoshida, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem.* **2006**, *14*, 7625.
4. Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* 2007, **46**, 1281.
5. Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
6. Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessy, E. J. (Massachusetts Institute of Technology, USA), US Patent 20021031, **2001**.
7. Lepage, G.; Roy, C. C. *J. Lipid Res.* **1986**, *27*, 114.
8. Boehner, C. M.; Marsden, D. M.; Sore, H. F.; Norton, D.; Spring, D. R. *Tetrahedron Lett.* **2010**, *51*, 5930.
9. Srinivas, P.; Likhar, P. R.; Maheswaran, H.; Sridhar, B.; Ravikumar, K.; Kantam, M. L. *Chem. Eur. J.* **2009**, *15*, 1578.
10. Hanada, S.; Yuasa, A.; Kuroiwa, H.; Motoyama, Y.; Nagashima, H. *Eur. J. Org. Chem.* **2010**, *2010*, 1021.
11. Tanaka, H.; Ogasawara, K. *Tett. Lett.* **2002**, *43*, 4417.
12. Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929.

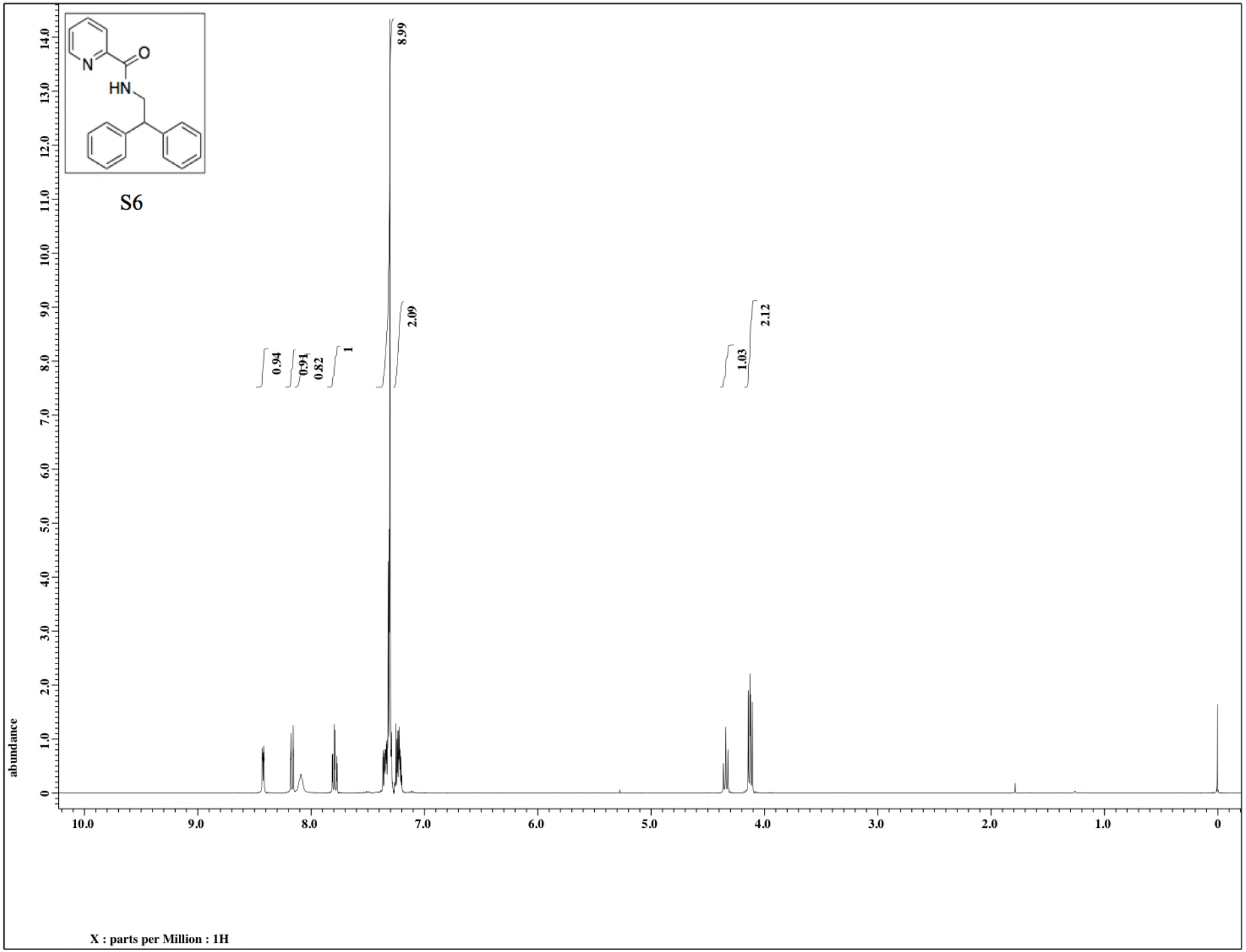

S3
0.93
1.89
1.0
0.98
2.03
2.95
2.16
2.14
abundance
X : parts per Million : 1H

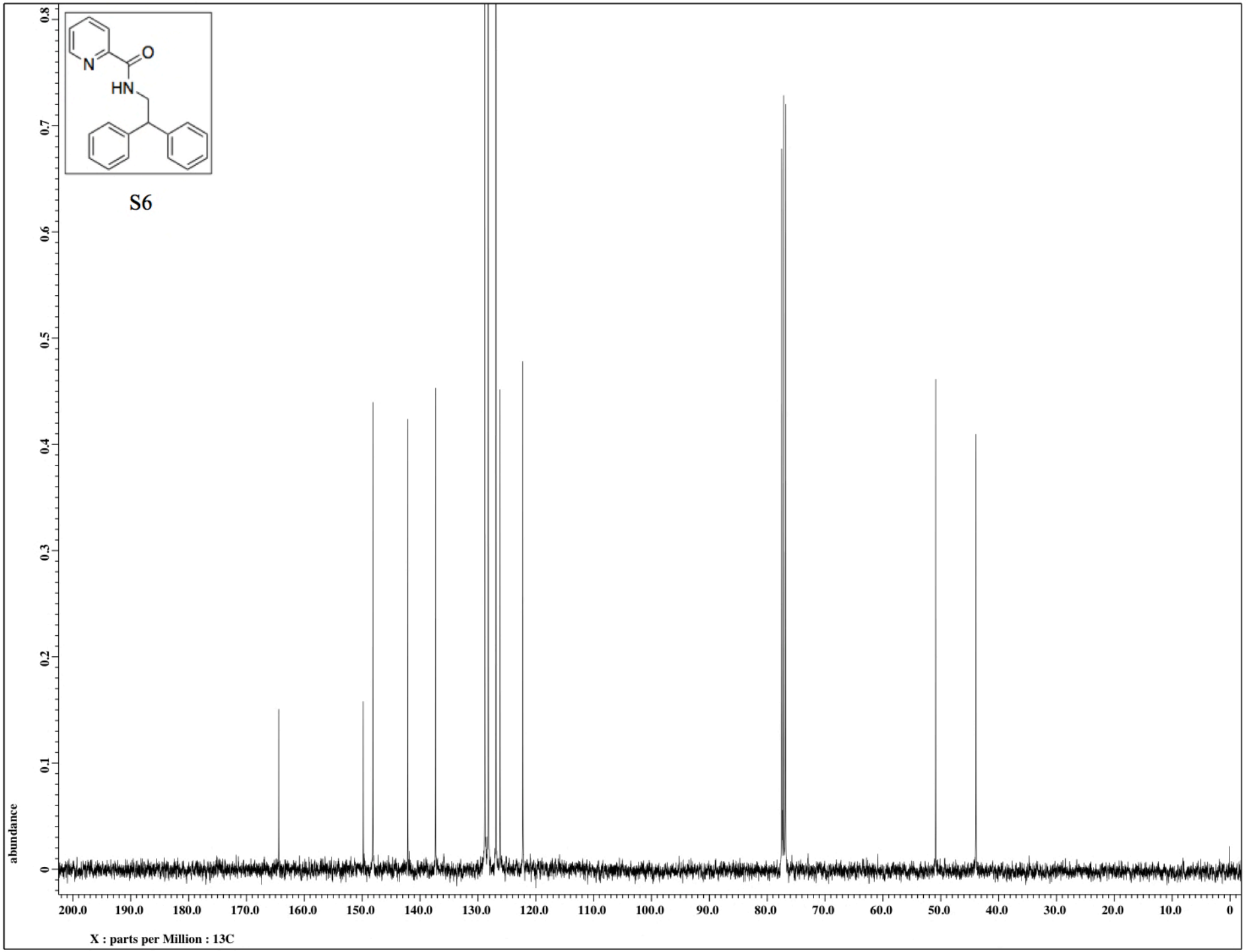

S4
N
O
HN
Cl
0.94
1.95
1
1.89
1.02
2.02
2.09
2.07
abundance
X : parts per Million : 1H

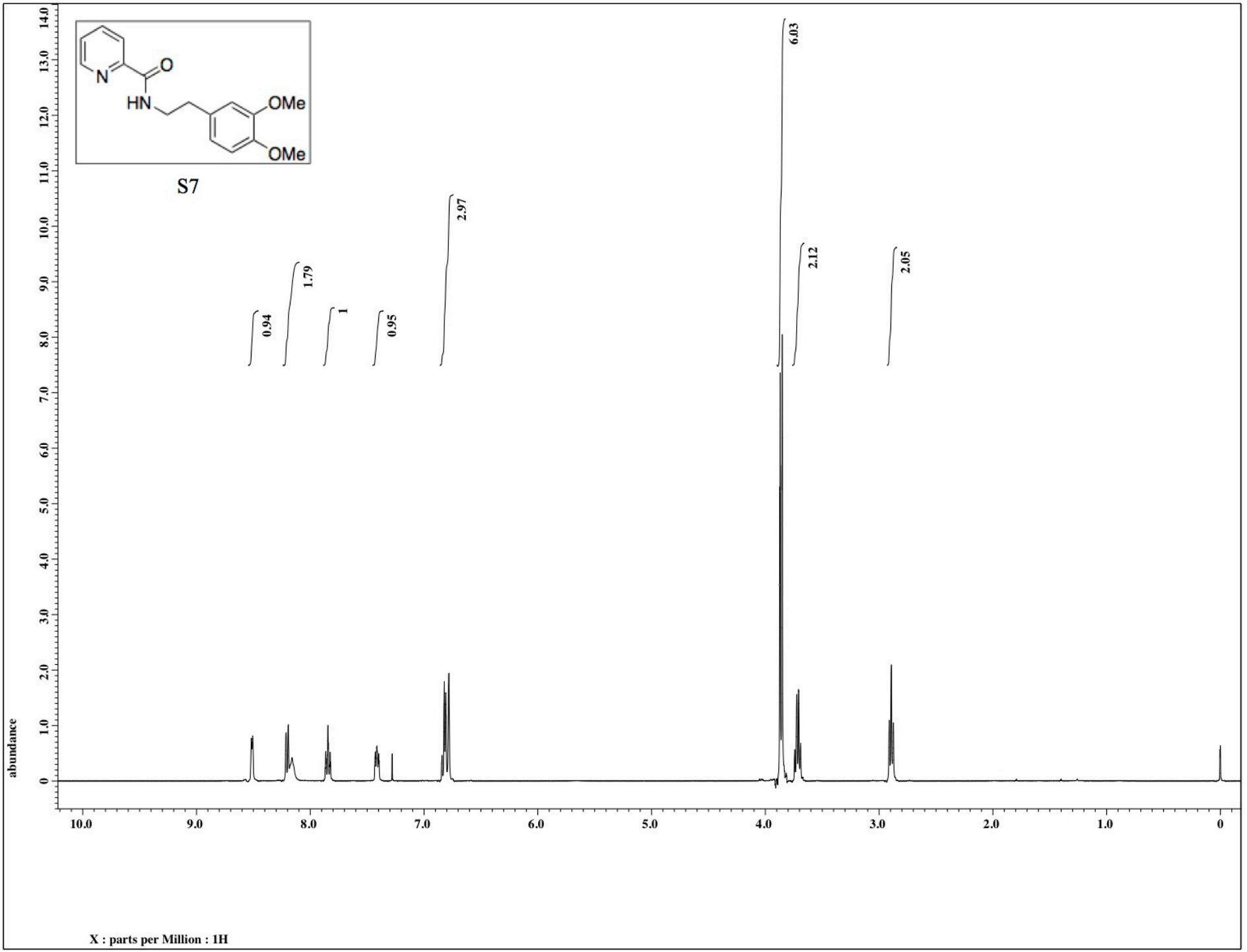

N
O
HN
Cl
S4
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

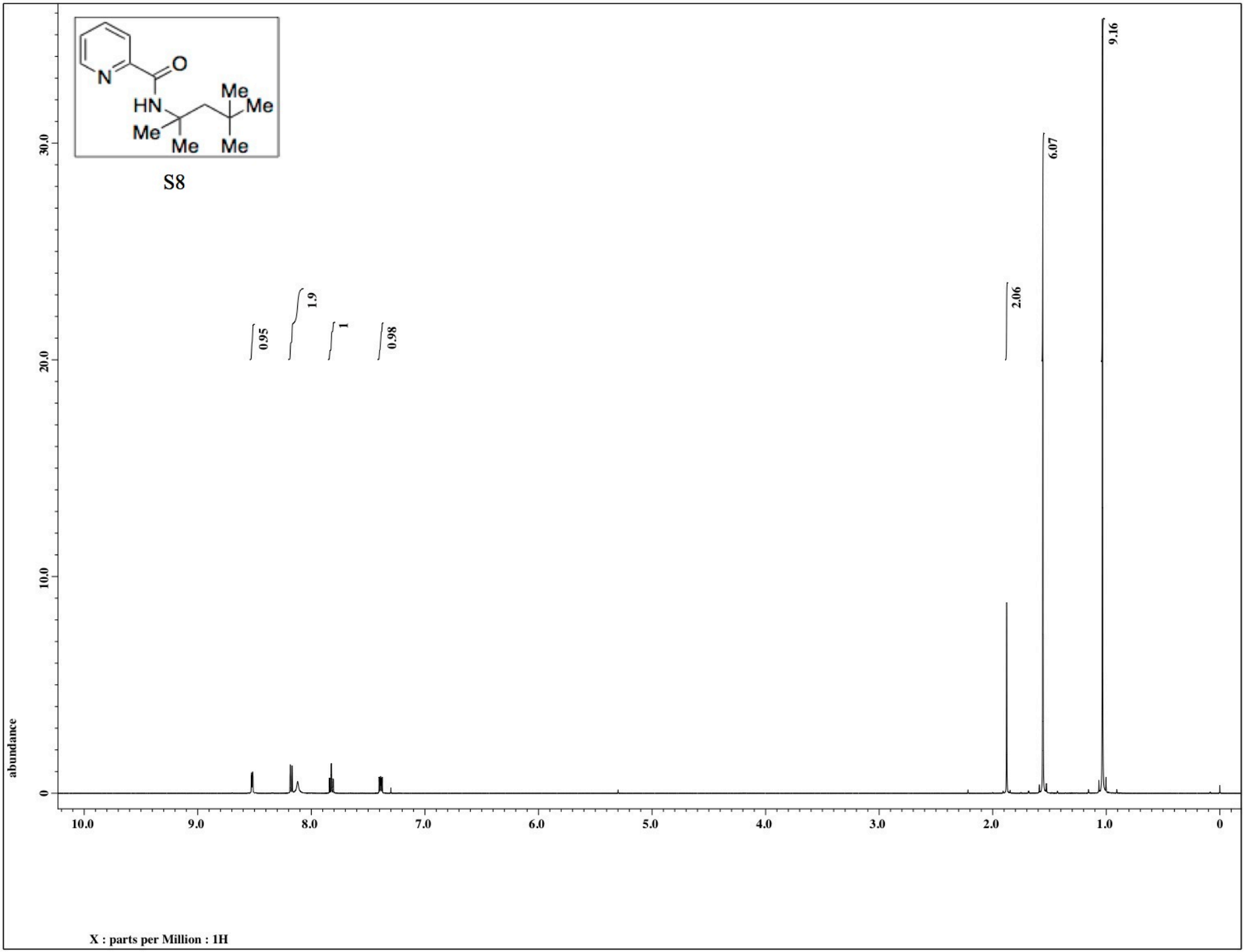

S5
1.95
0.94
0.94
5.48
1.02
2.07
9.04
abundance
X : parts per Million : 1H

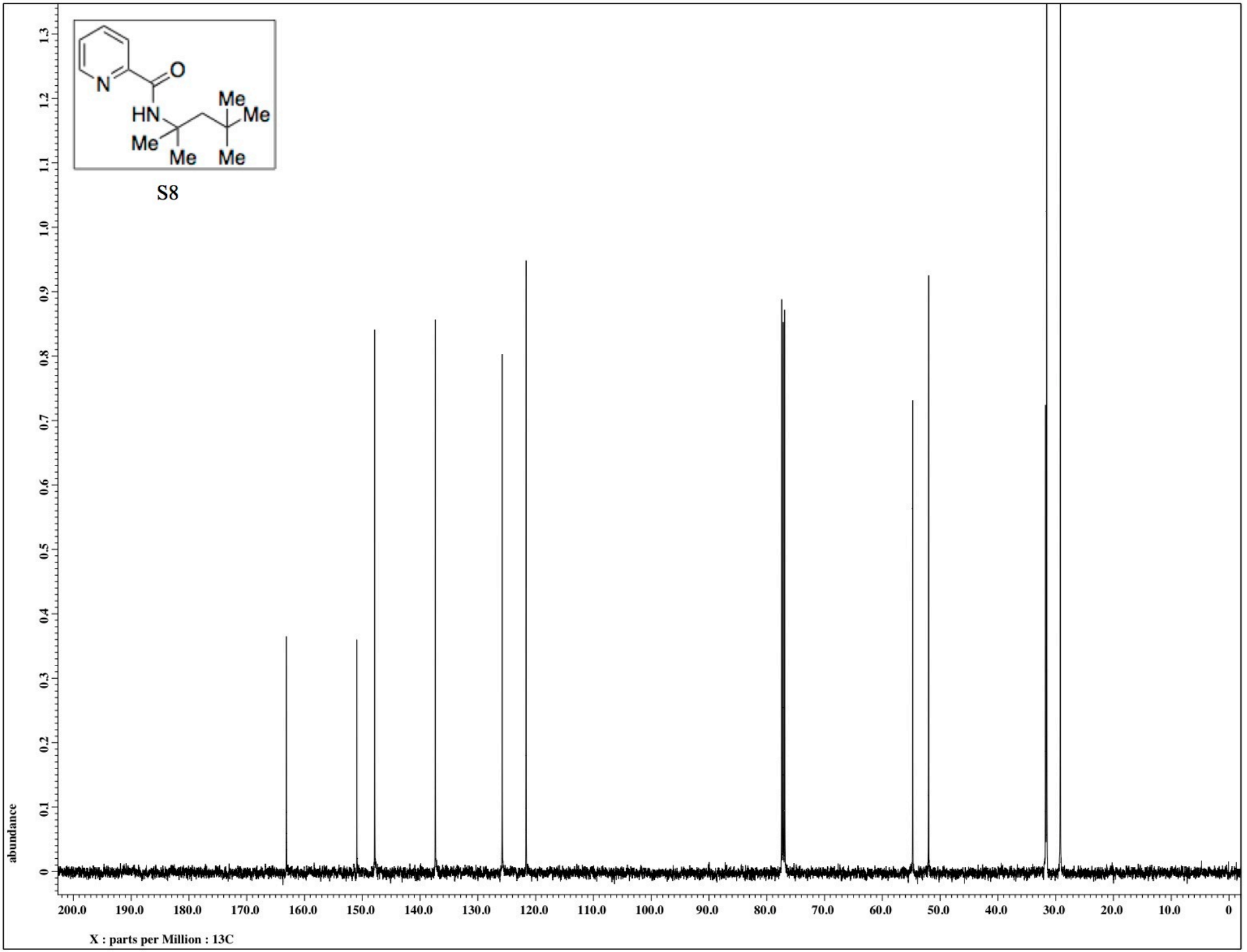

S5
abundance
X : parts per Million : 13C

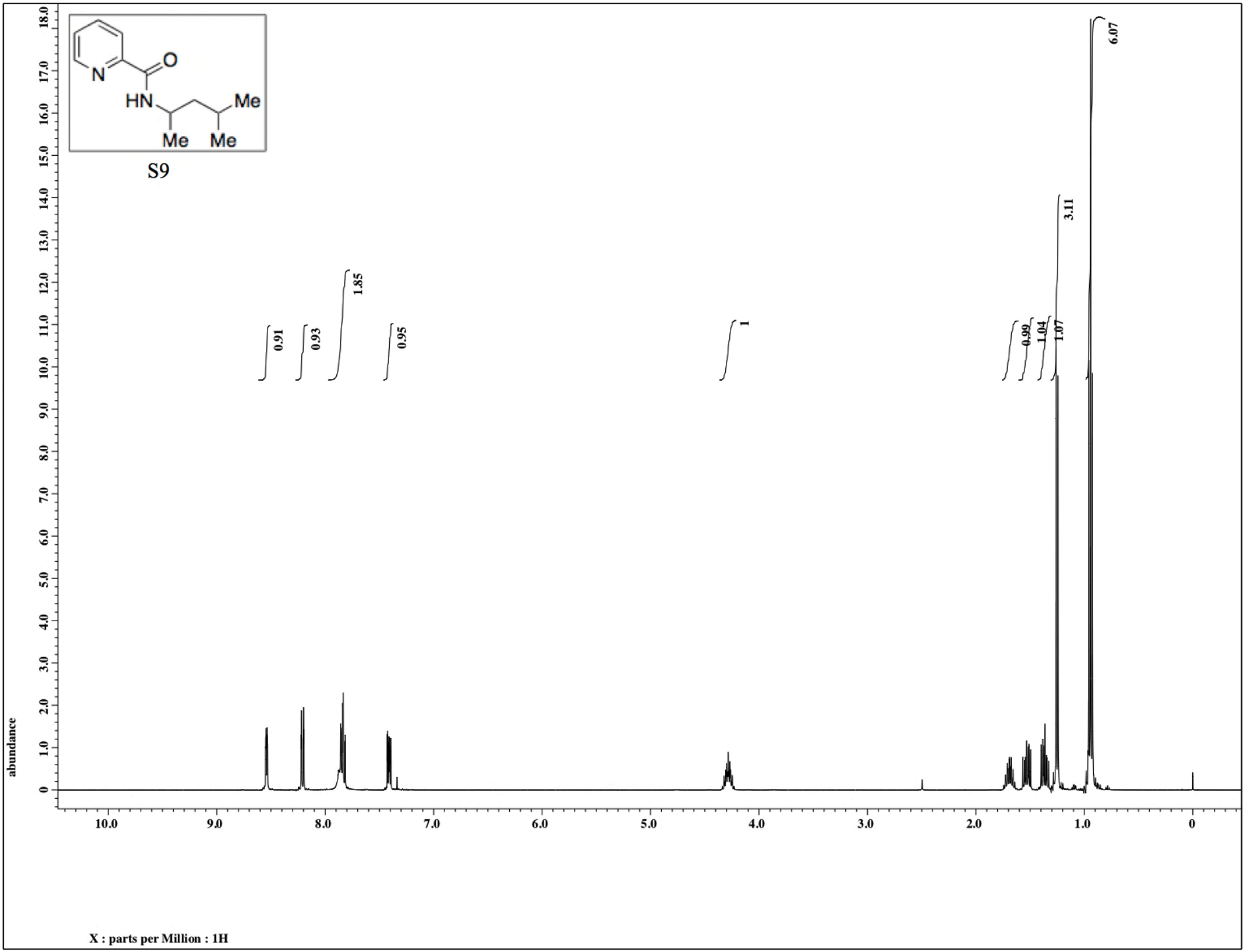

S6
N
O
HN
8.99
2.09
0.94
0.91
0.82
1
1.03
2.12
abundance
X : parts per Million : 1H

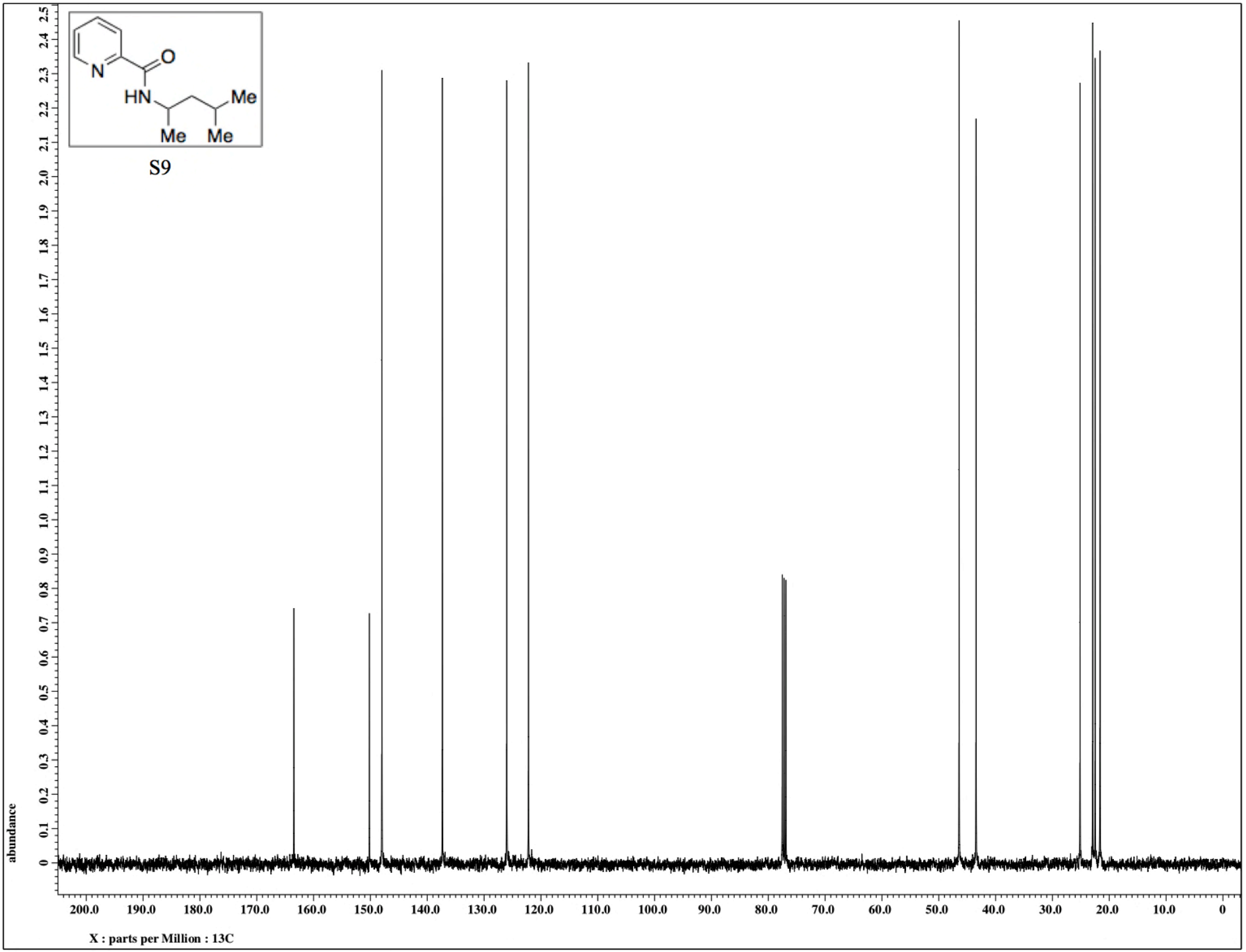

N
O
HN
S6
abundance
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
HN
OMe
OMe
S7
0.94
1.79
1
0.95
2.97
6.03
2.12
2.05
abundance
X : parts per Million : 1H

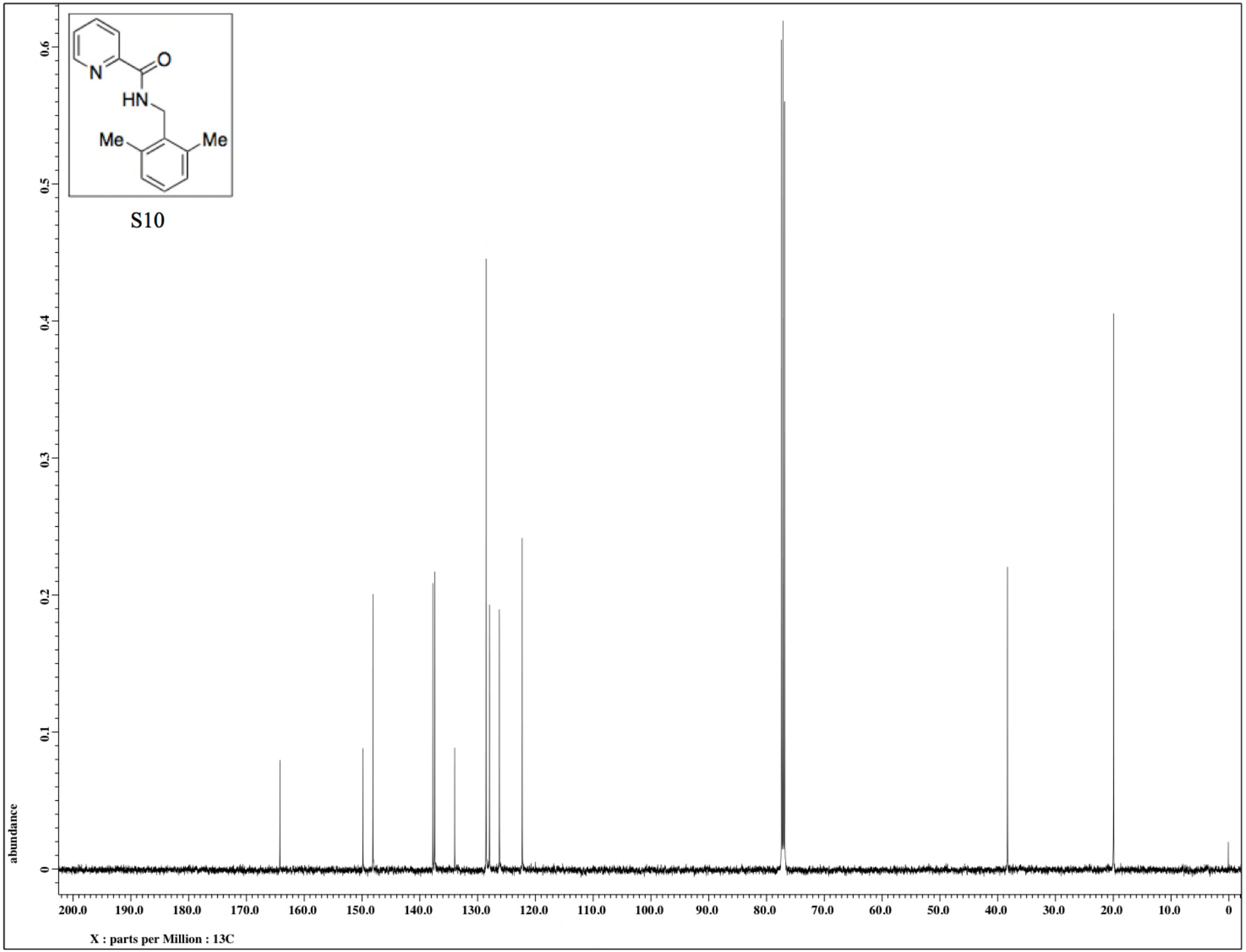

N
O
HN
Me
Me
Me
Me
Me
S8
0.95
1.9
1
0.98
2.06
6.07
9.16
abundance
30.0
20.0
10.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H

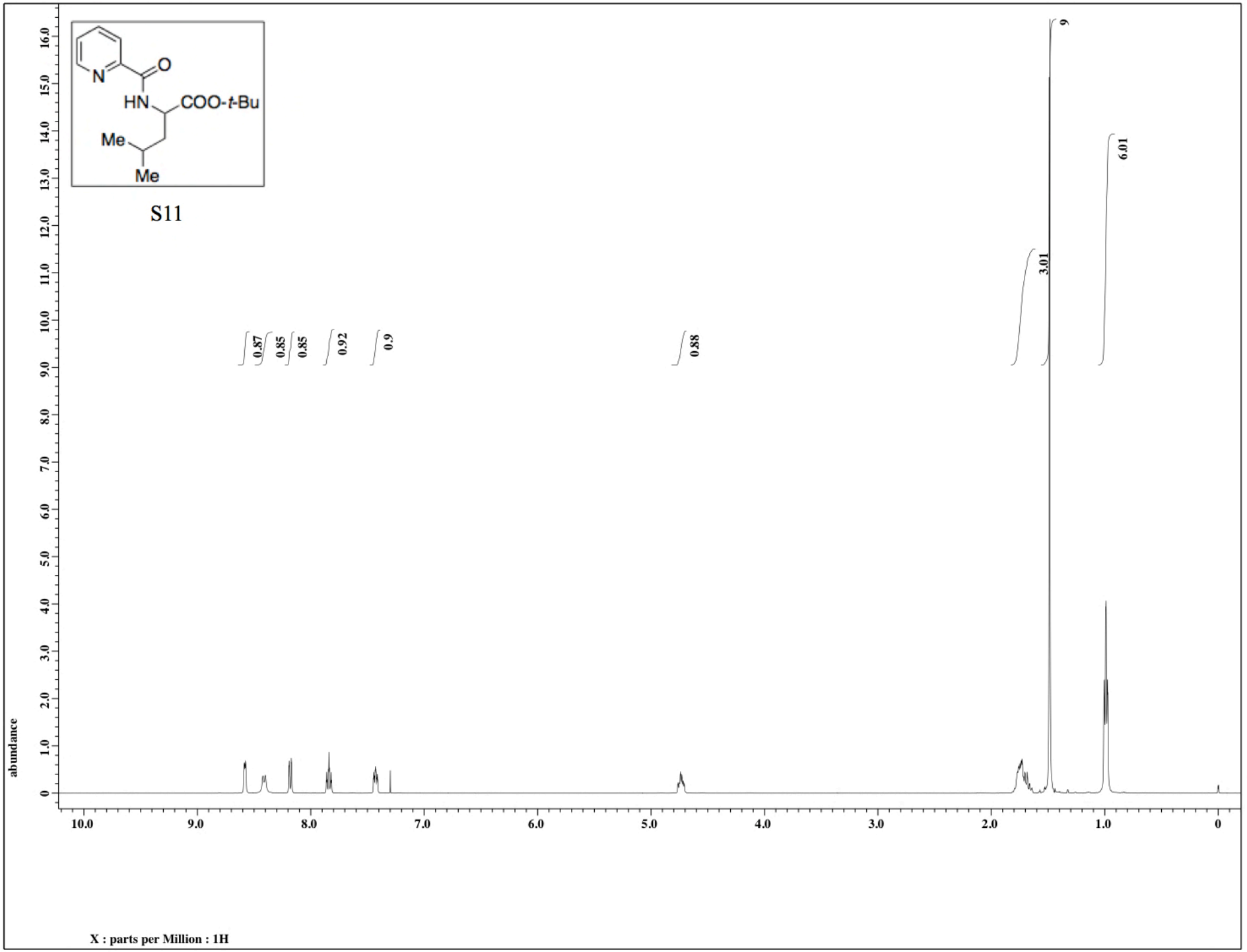

N
O
HN
Me
Me
Me
Me
Me
S8
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

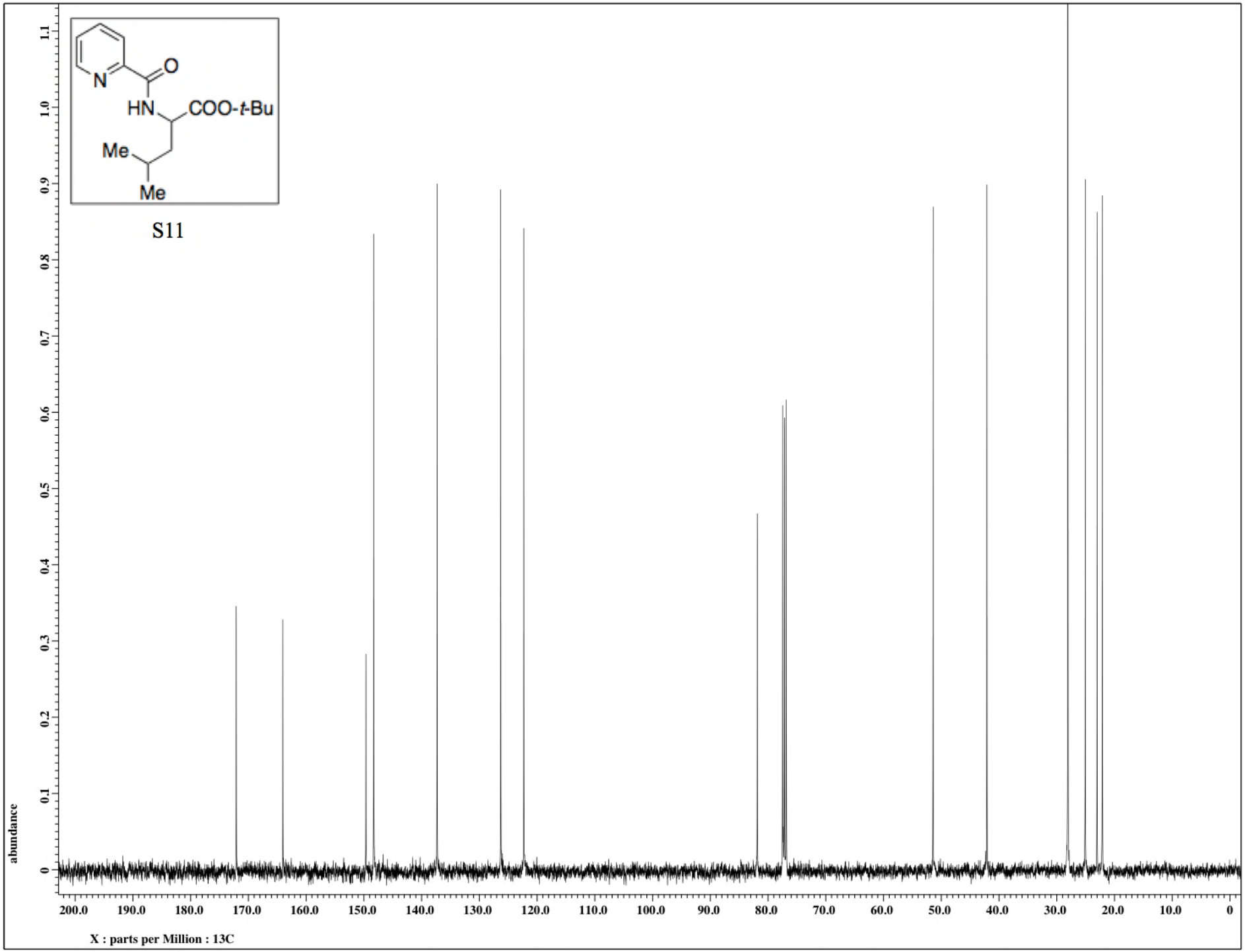

N
O
HN
Me
Me
Me
S9
0.91
0.93
1.85
0.95
1
0.99
1.04
1.07
3.11
6.07
abundance
X : parts per Million : 1H

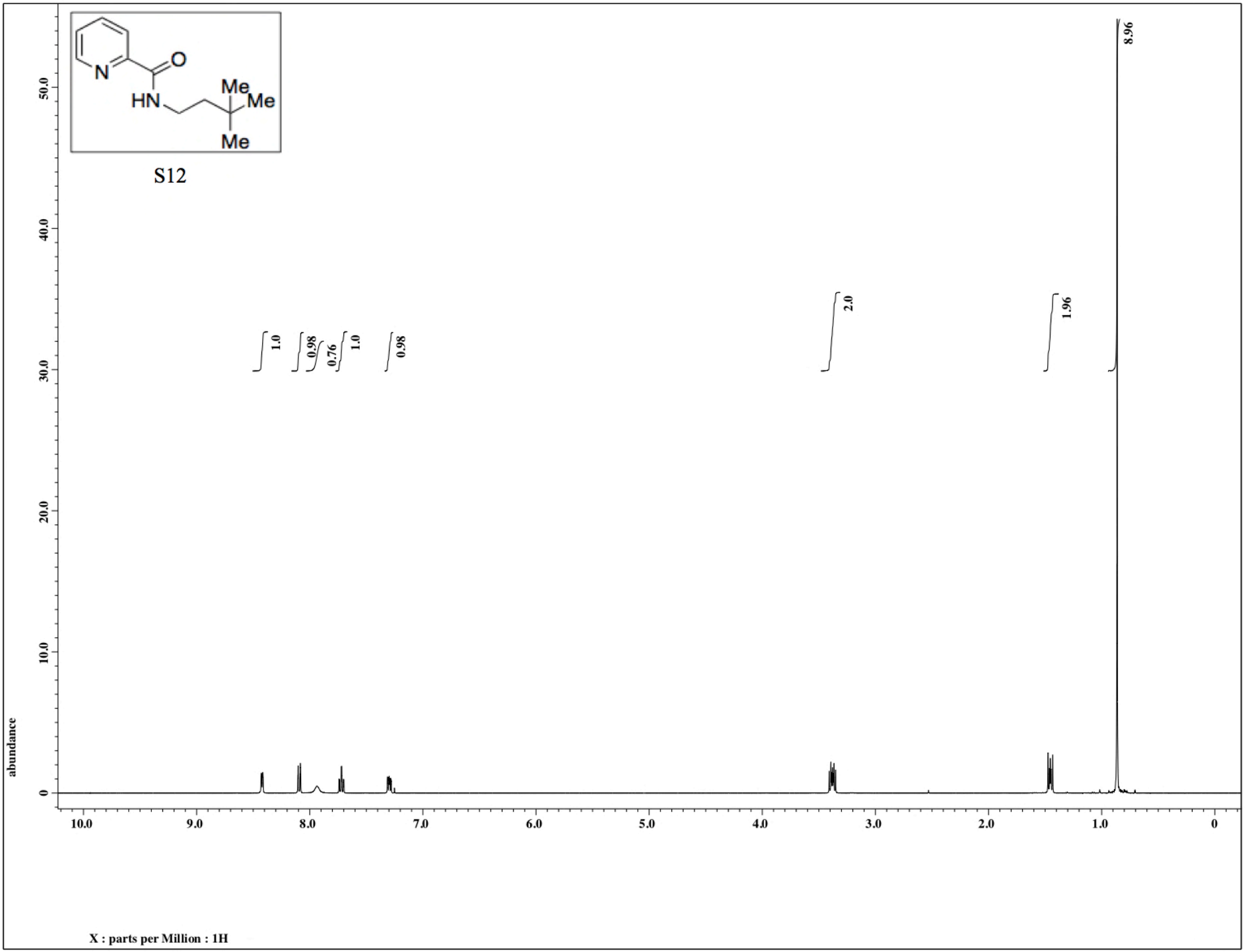

N
O
HN
Me
Me
Me
S9
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
2.2
2.3
2.4
2.5
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

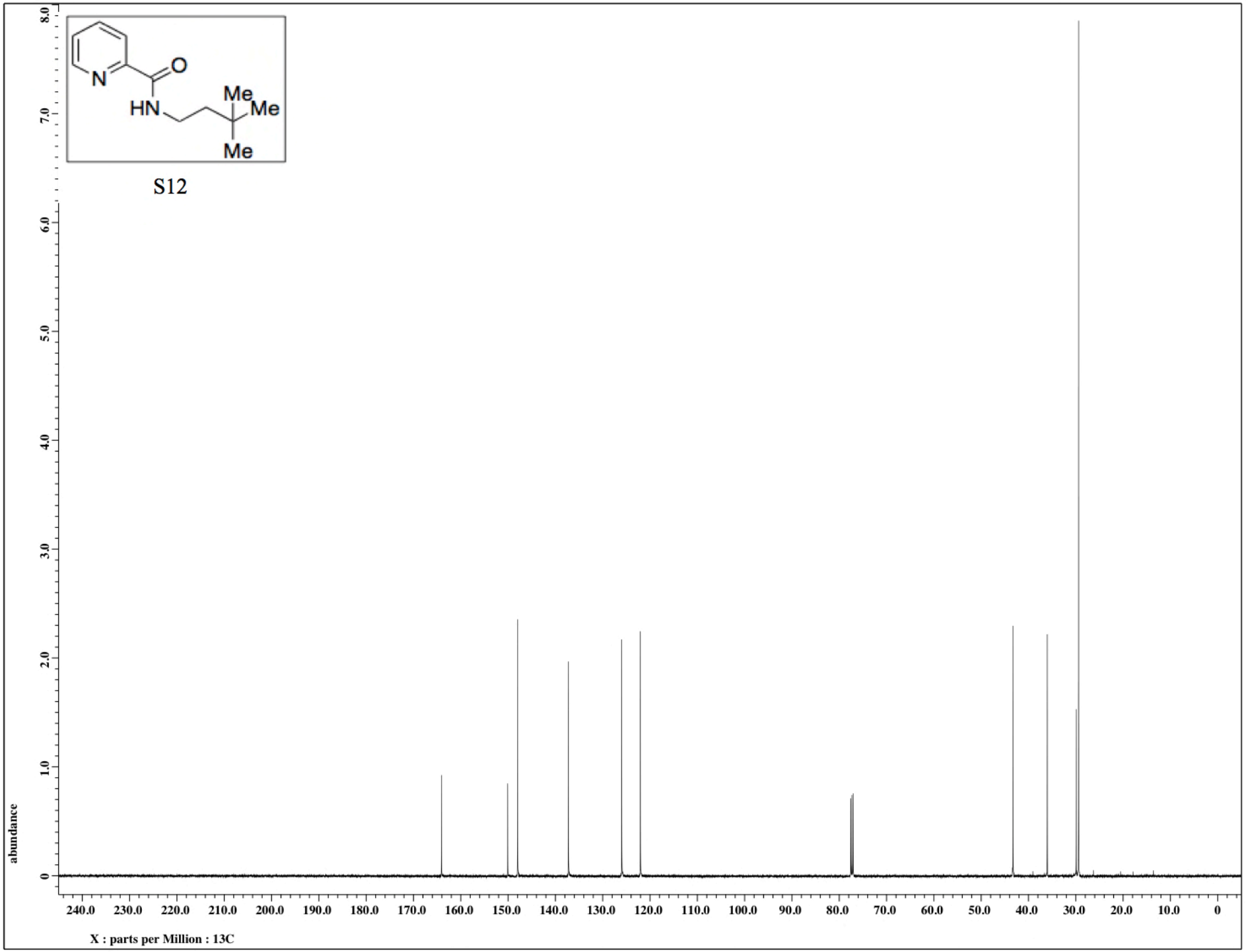

N
O
HN
Me
Me
S10
6.15
3.01
2.22
0.96
0.96
0.93
1.1
1
abundance
X : parts per Million : 1H

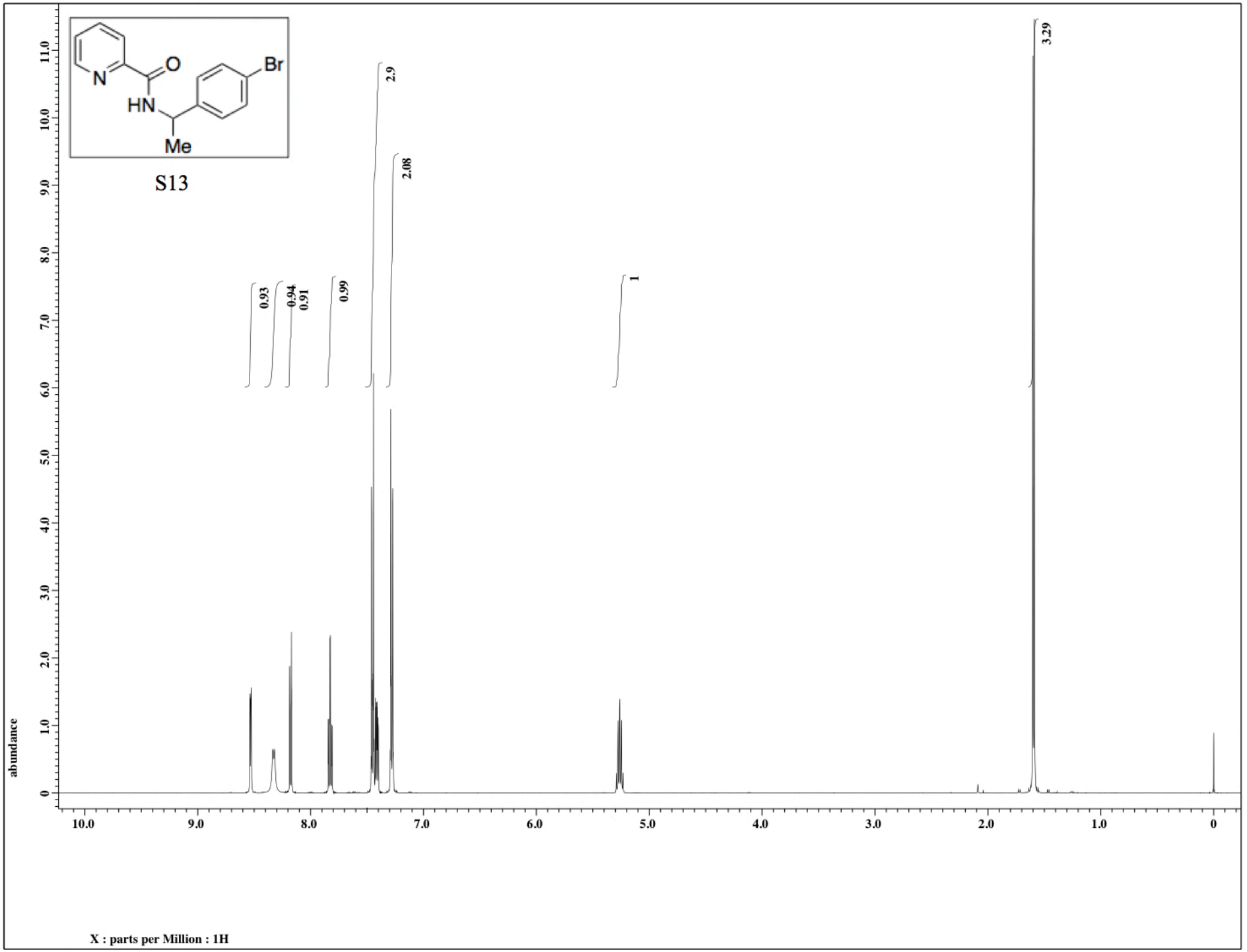

N
O
HN
Me
Me
S10
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

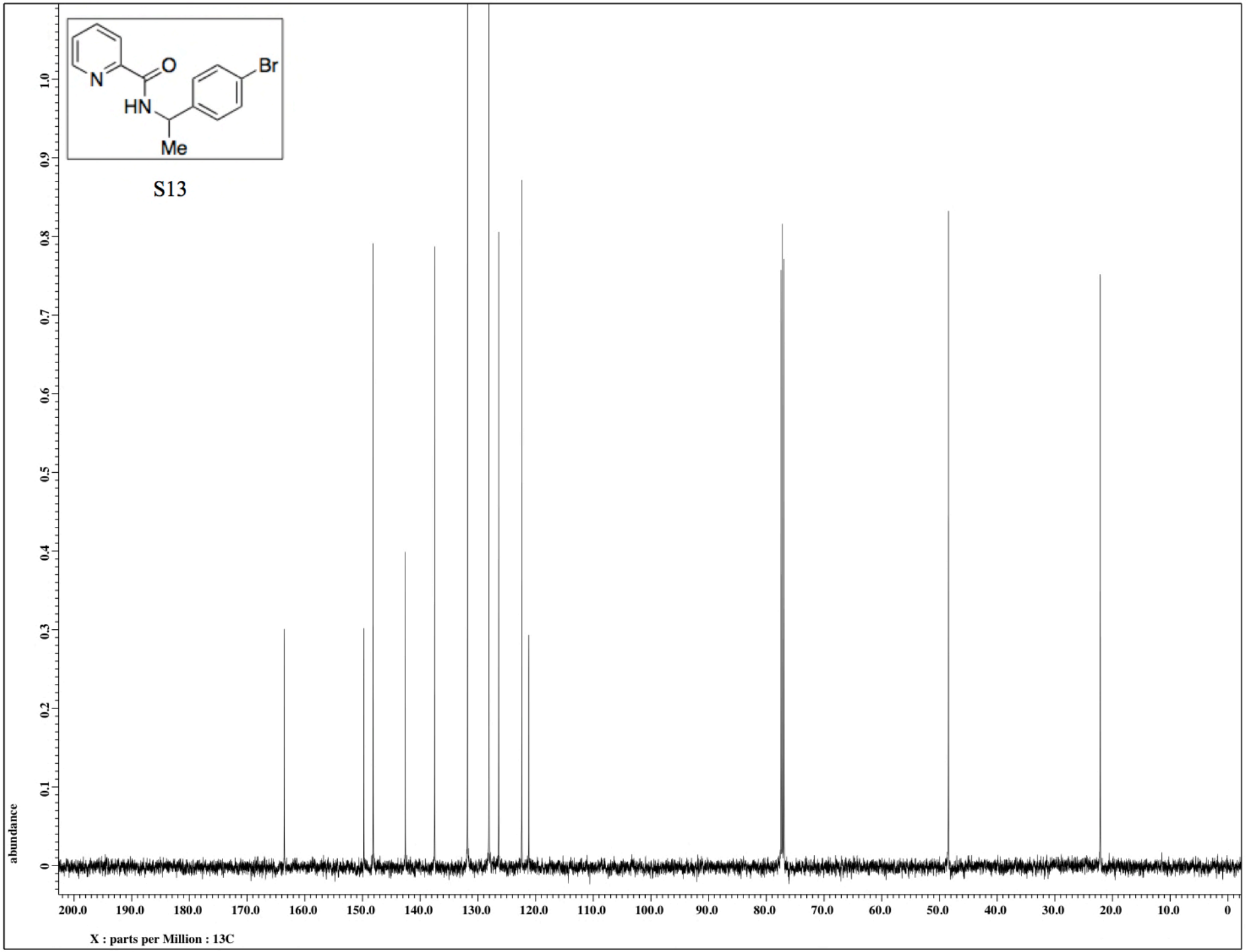

N
O
HN
COO-t-Bu
Me
Me
S11
0.87
0.85
0.85
0.92
0.9
0.88
3.01
9
6.01
abundance
X : parts per Million : 1H

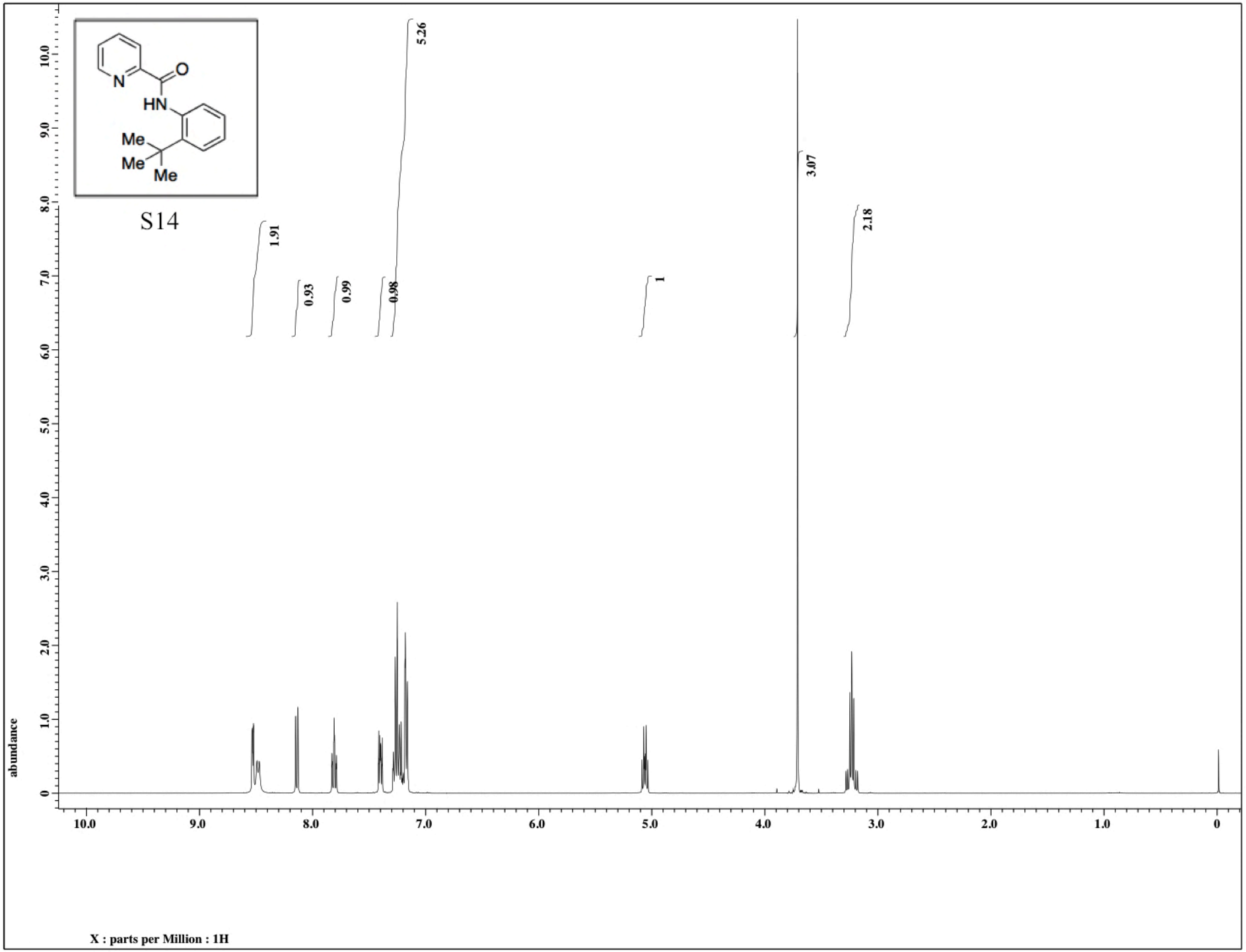

N
O
HN
COO-t-Bu
Me
Me
S11
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

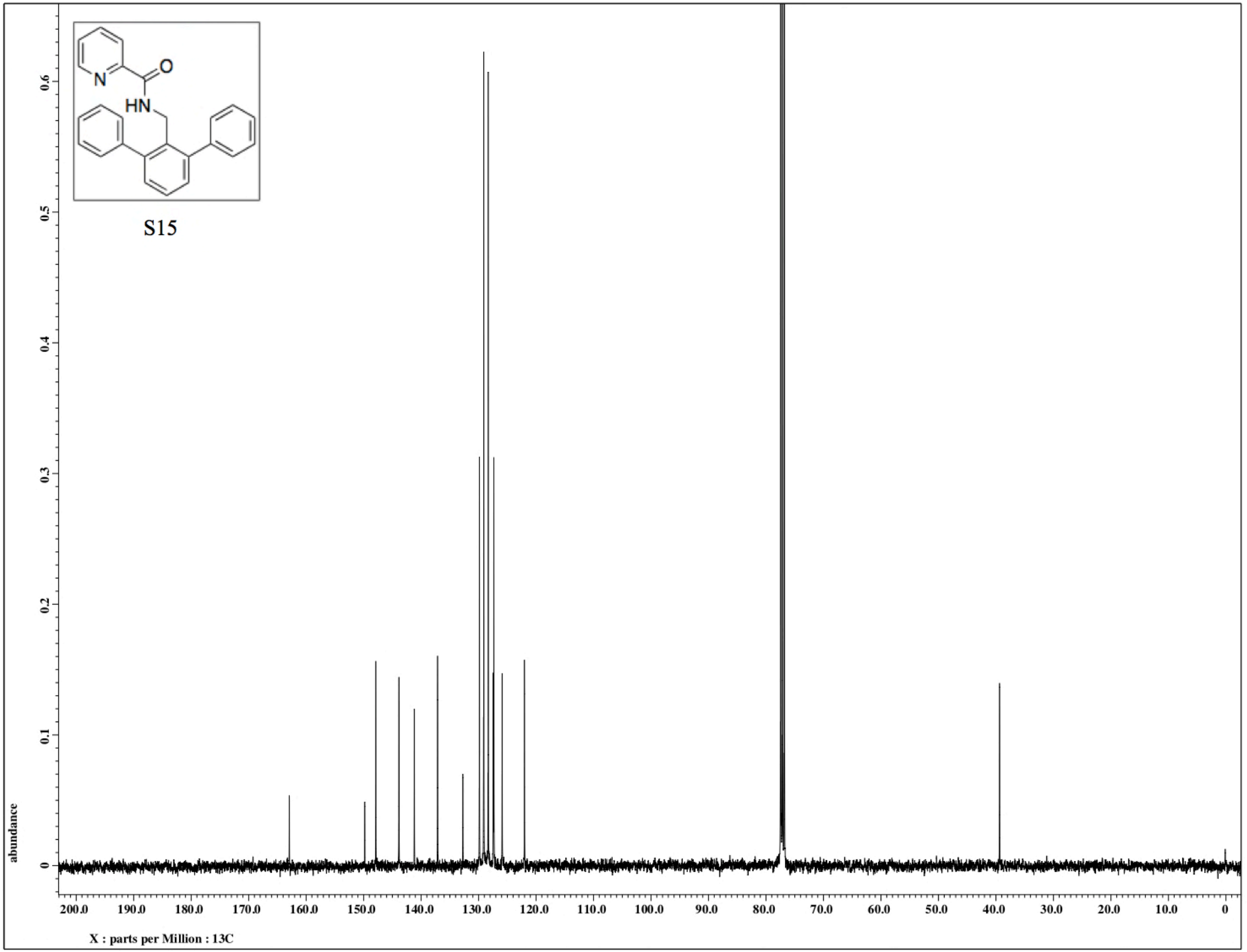

N
O
HN
Me
Me
Me
S12
8.96
2.0
1.96
1.0
0.98
0.76
1.0
0.98
abundance
50.0
40.0
30.0
20.0
10.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H

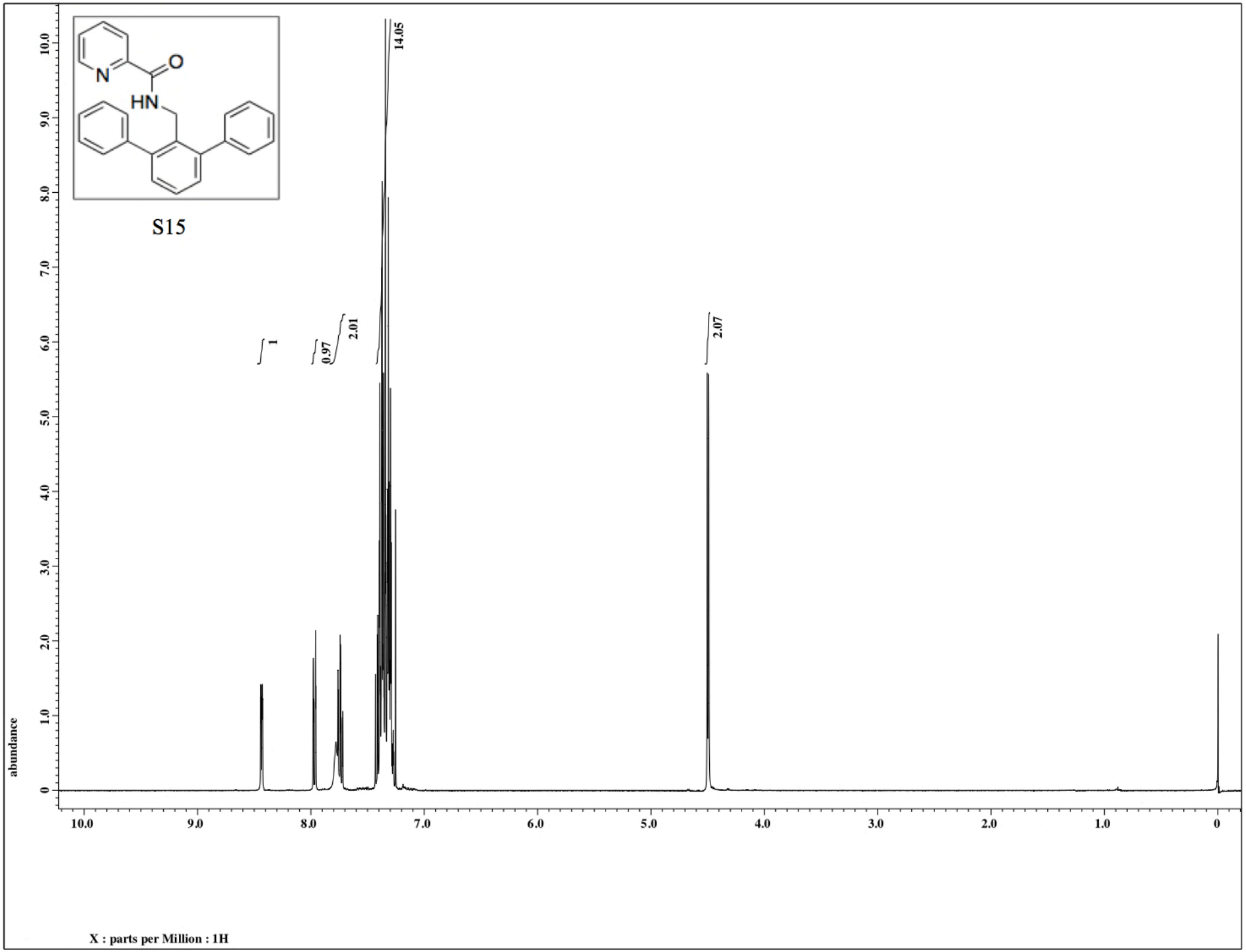

N
O
HN
Me
Me
Me
S12
abundance
X : parts per Million : 13C

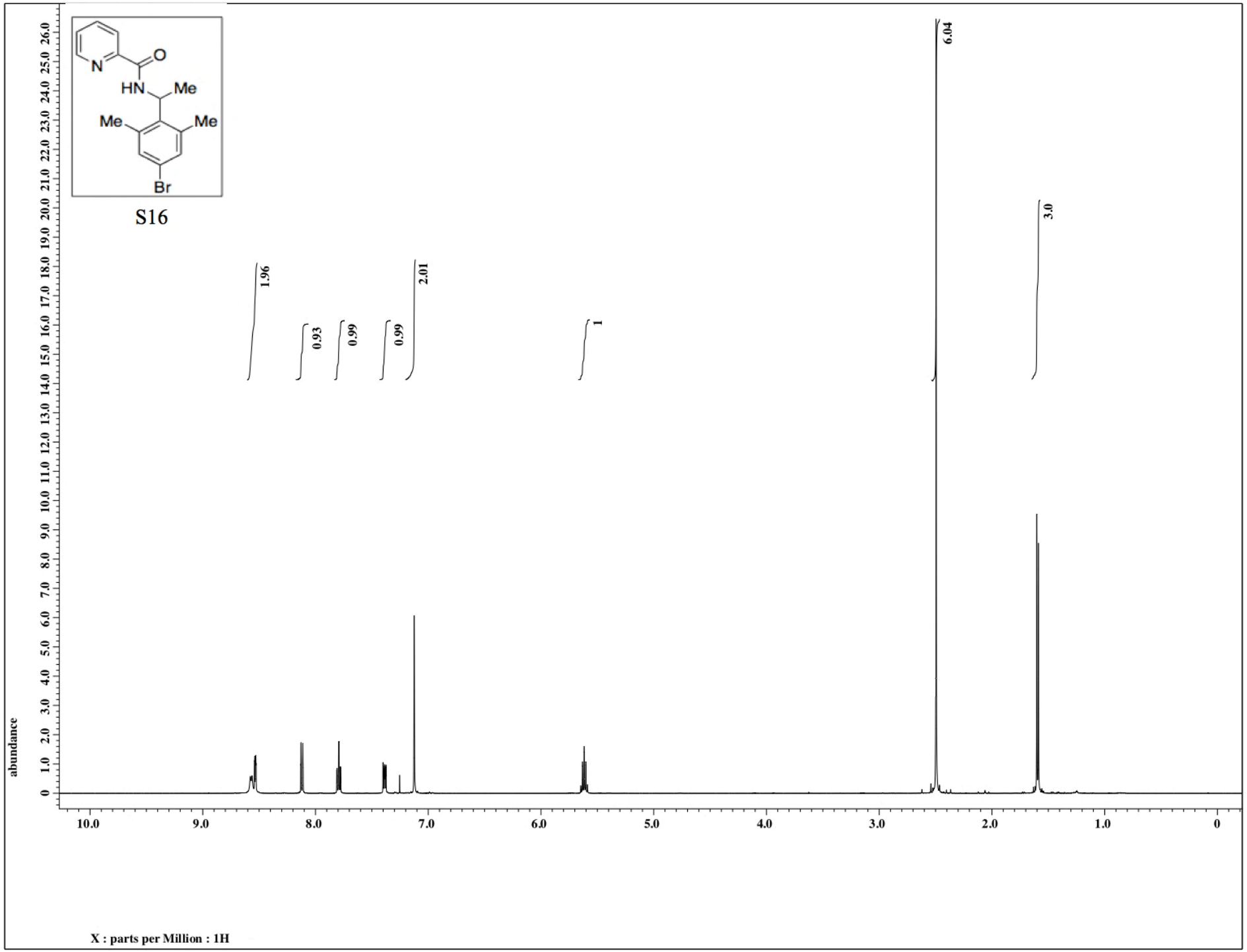

N
O
HN
Br
Me
S13
3.29
2.9
2.08
1
0.93
0.94
0.91
0.99
abundance
X : parts per Million : 1H

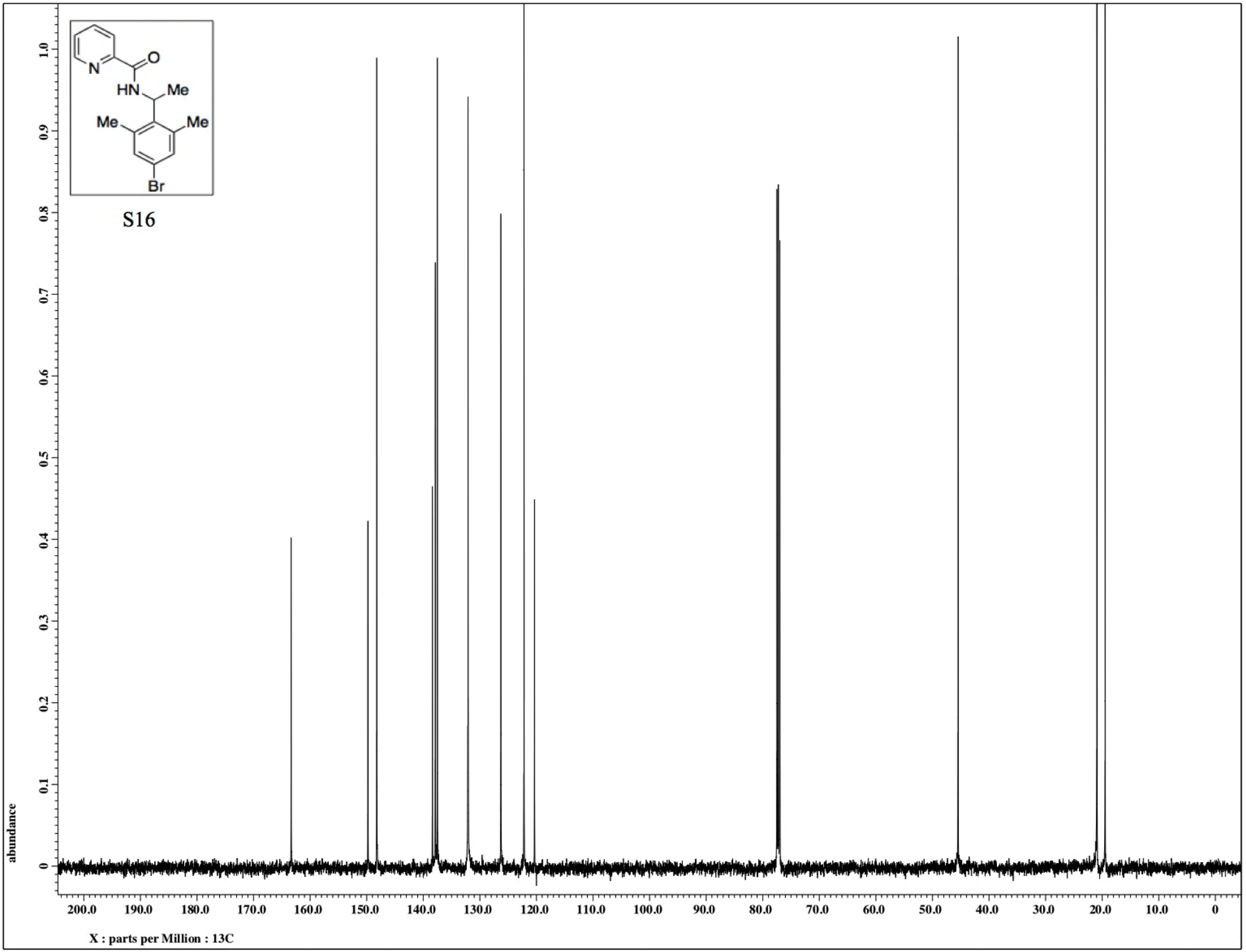

N
O
HN
Me
Br
S13
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

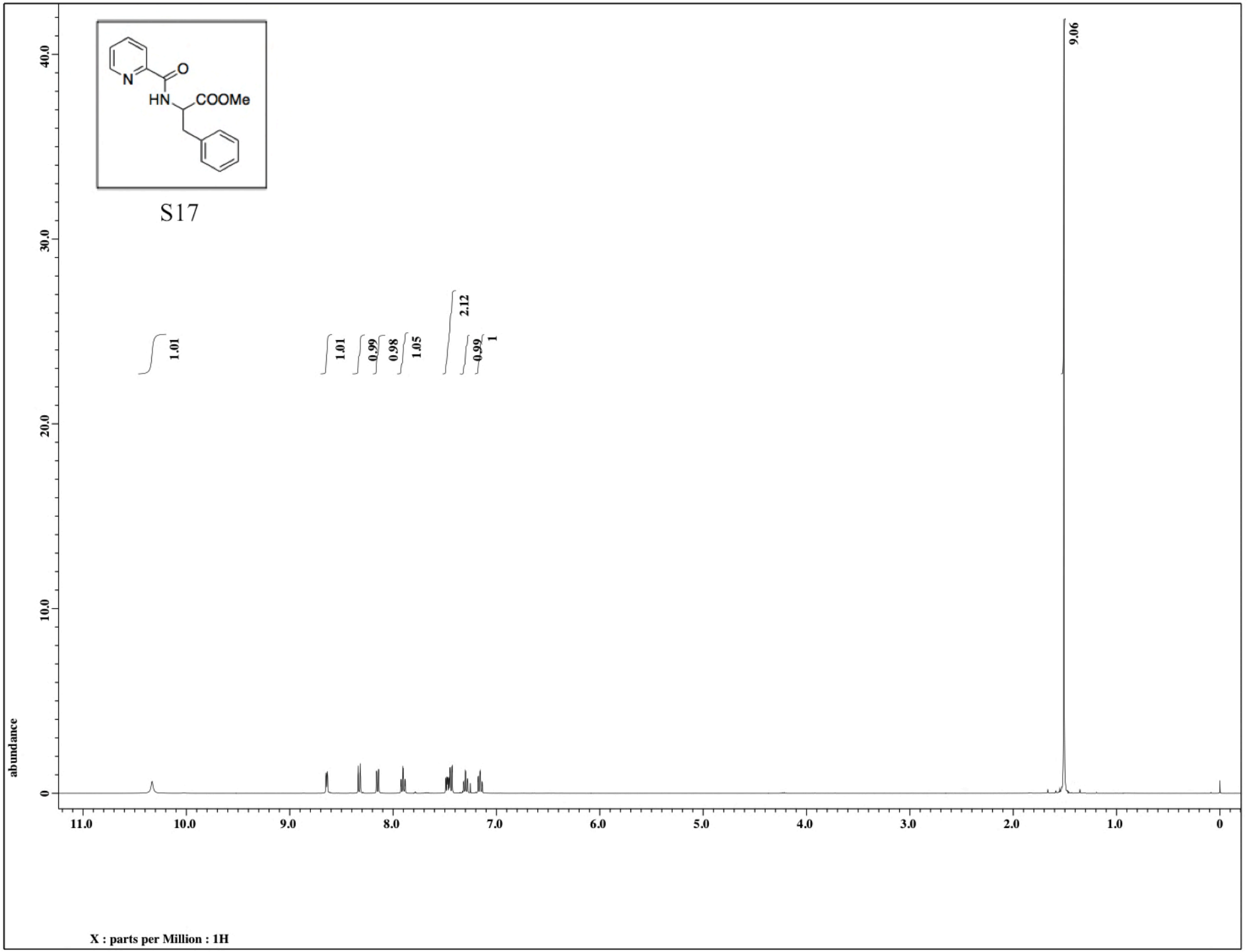

S14
1.91
0.93
0.99
0.98
5.26
1
3.07
2.18
abundance
X : parts per Million : 1H


N
O
HN
S15
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


S15
14.05
2.07
2.01
0.97
1
abundance
X : parts per Million : 1H


N
O
HN
Me
Me
Me
Br
S16
1.96
0.93
0.99
0.99
2.01
1
6.04
3.0
abundance
X : parts per Million : 1H


N
O
HN
Me
Me
Me
Br
S16
abundance
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
HN
COOMe
S17
9.06
1.01
1.01
0.99
0.98
1.05
2.12
0.99
1
40.0
30.0
20.0
10.0
0
abundance
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H

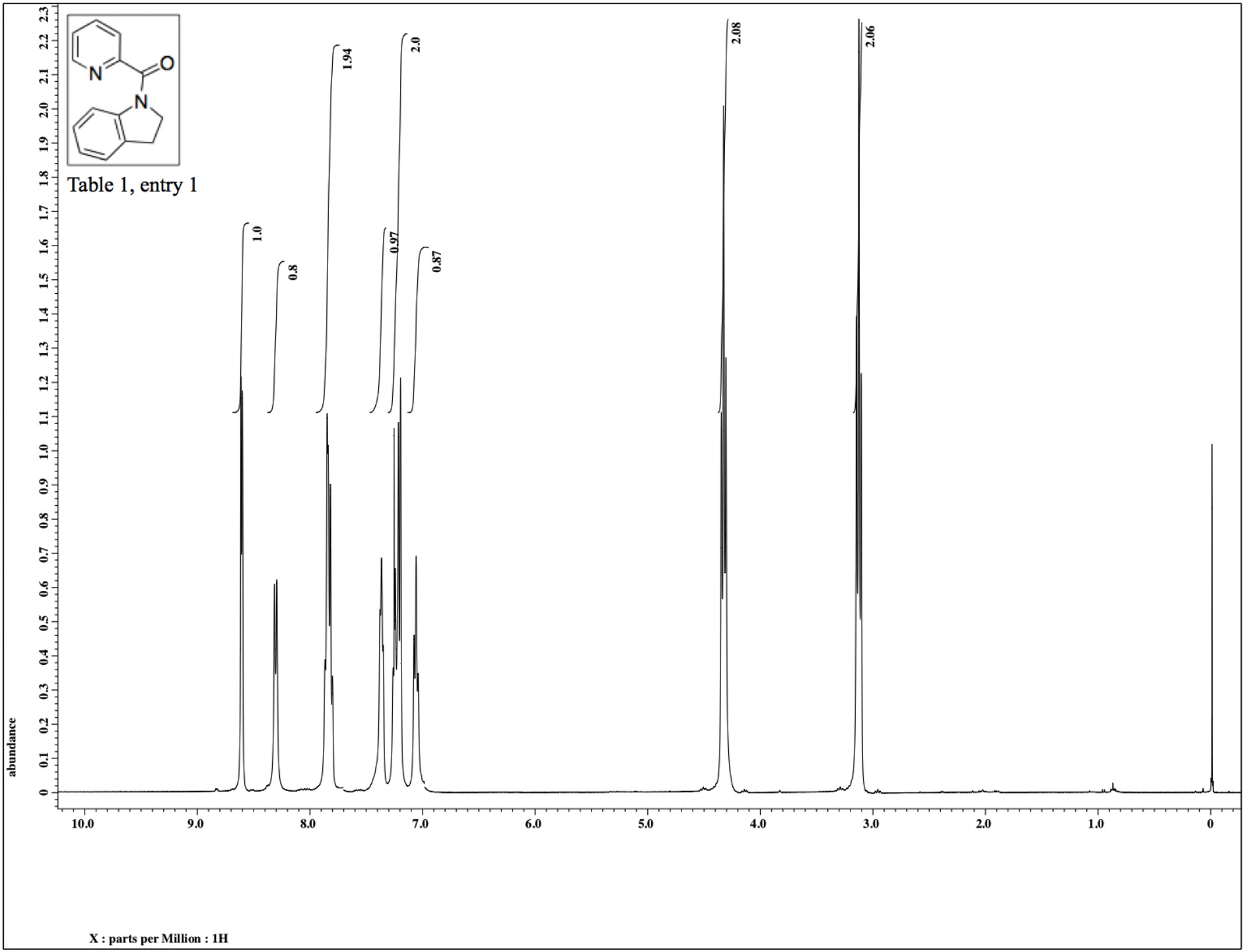


Table 1, entry 1
1.0
0.8
1.94
0.97
2.0
0.87
2.08
2.06
abundance
X : parts per Million : 1H

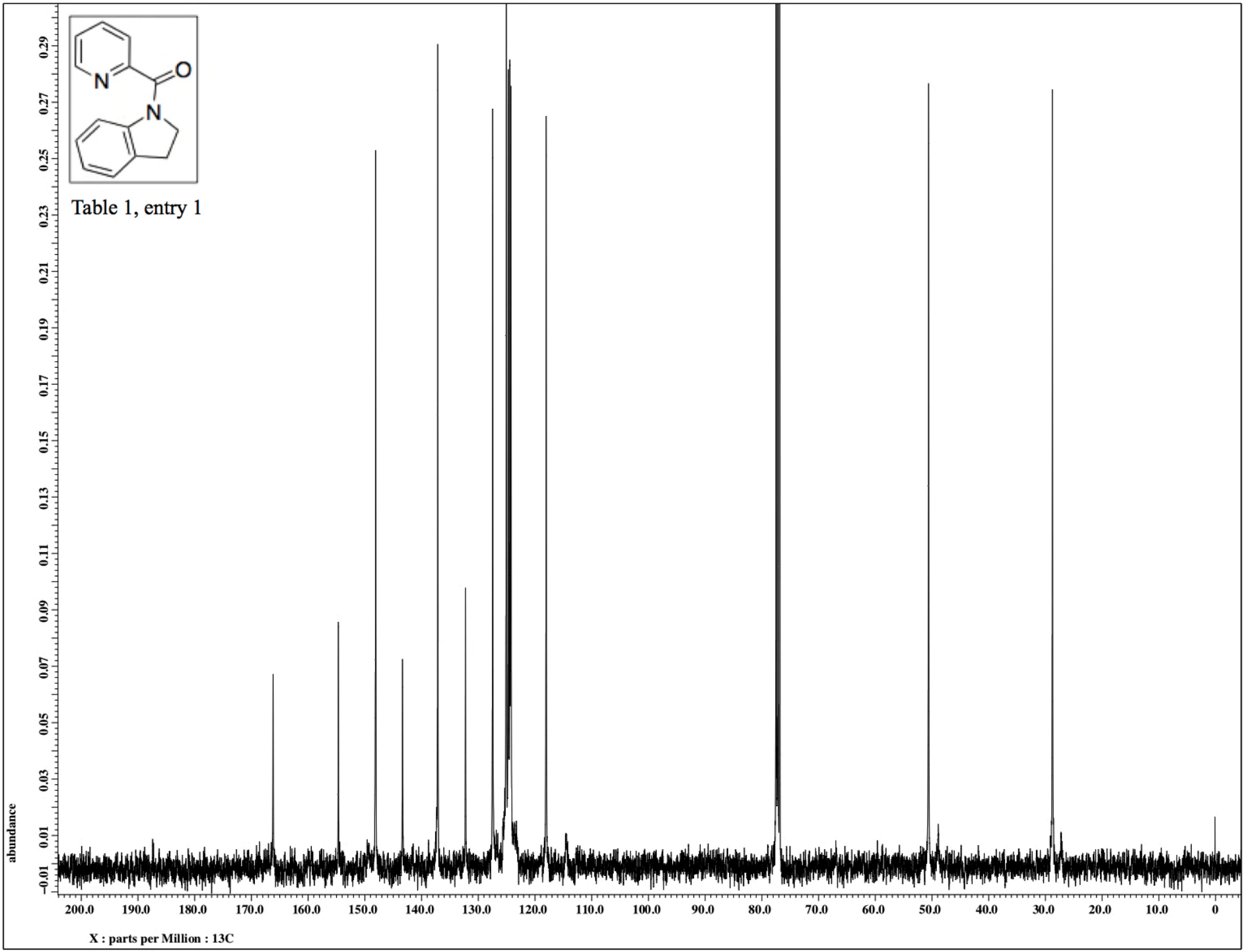


Table 1, entry 1
abundance
X : parts per Million : 13C

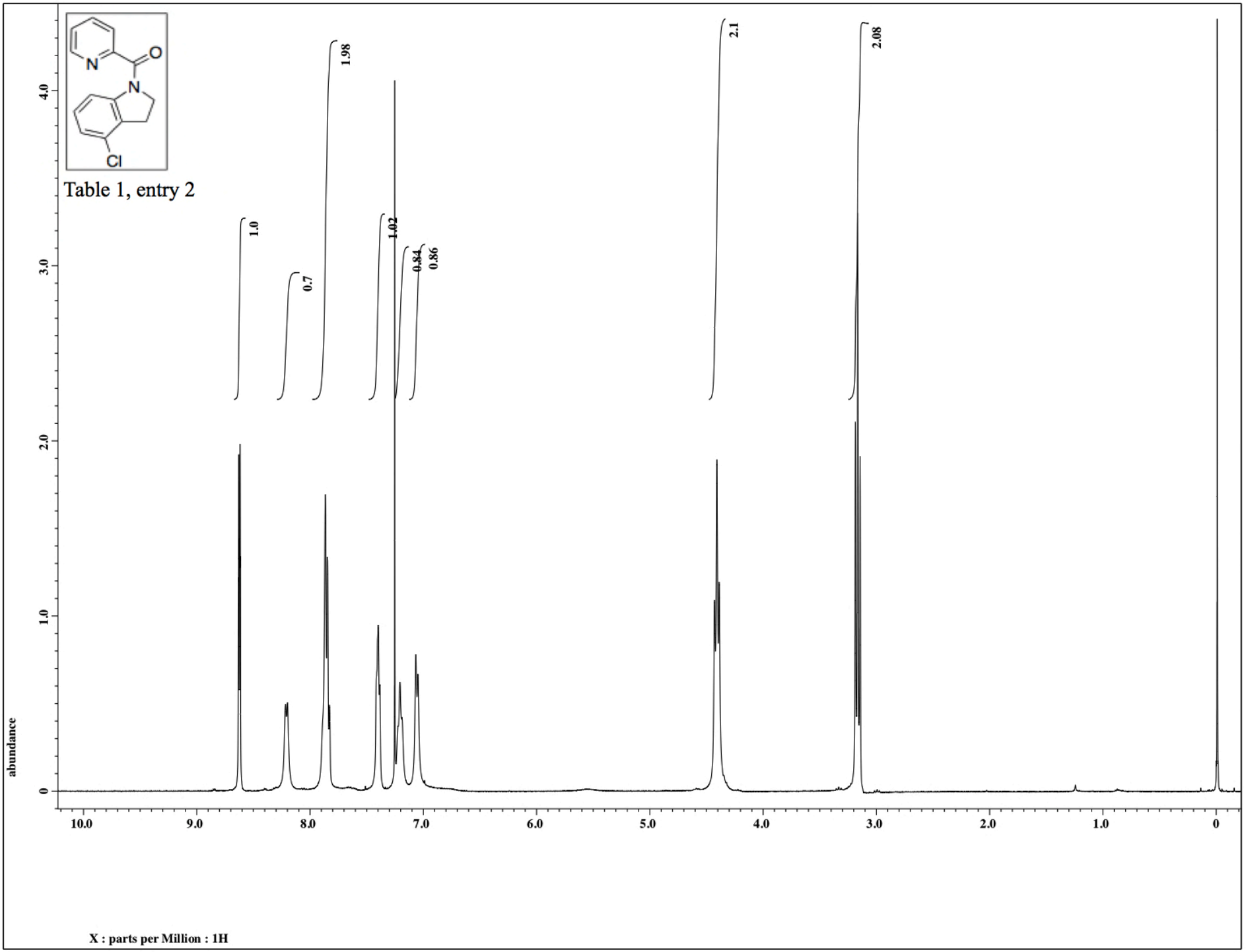
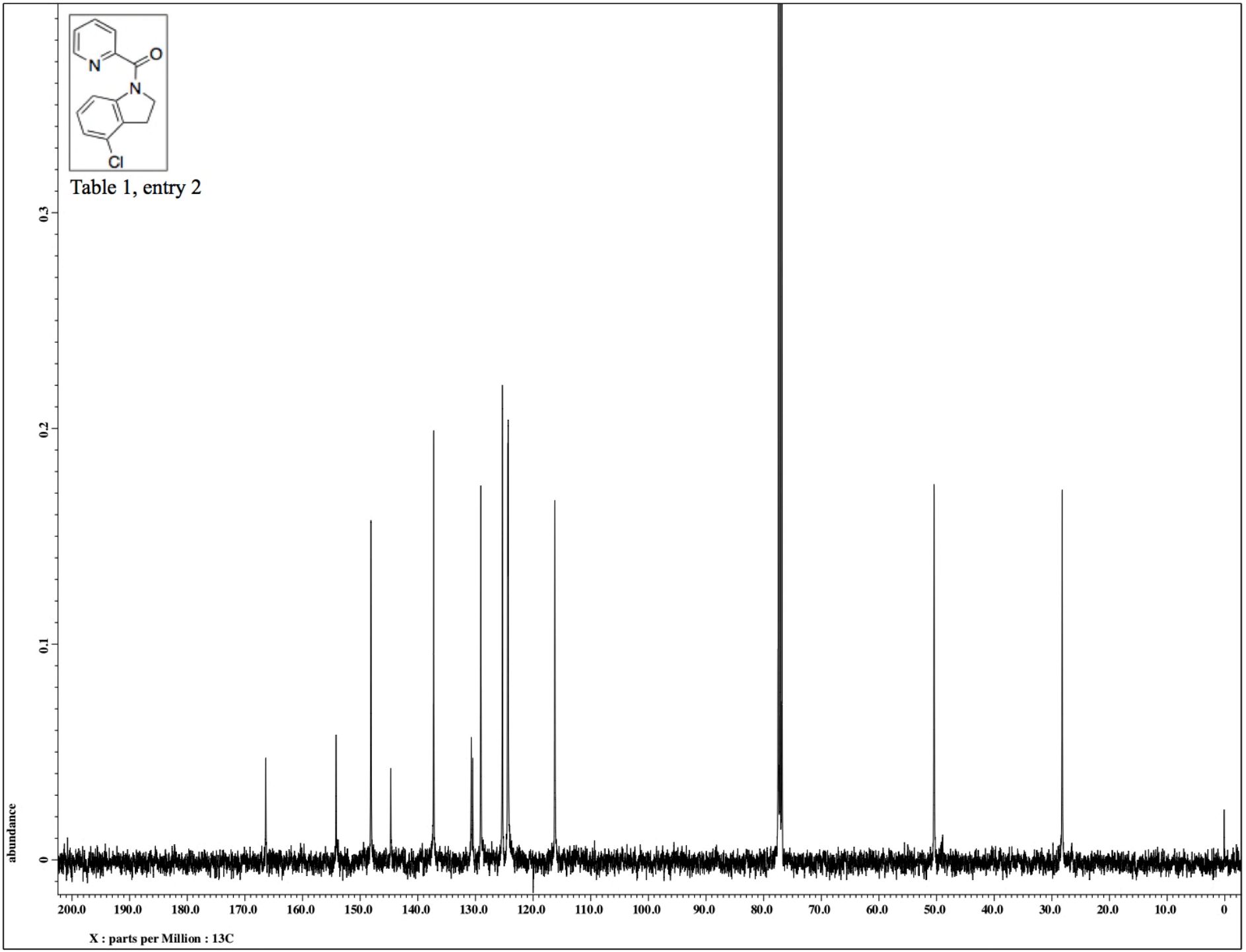


Table 1, entry 2
1.0
0.7
1.98
1.02
0.84
0.86
2.1
2.08
abundance
X : parts per Million : 1H


N
O
N
Cl
Table 1, entry 2
0.3
0.2
0.1
0
abundance
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

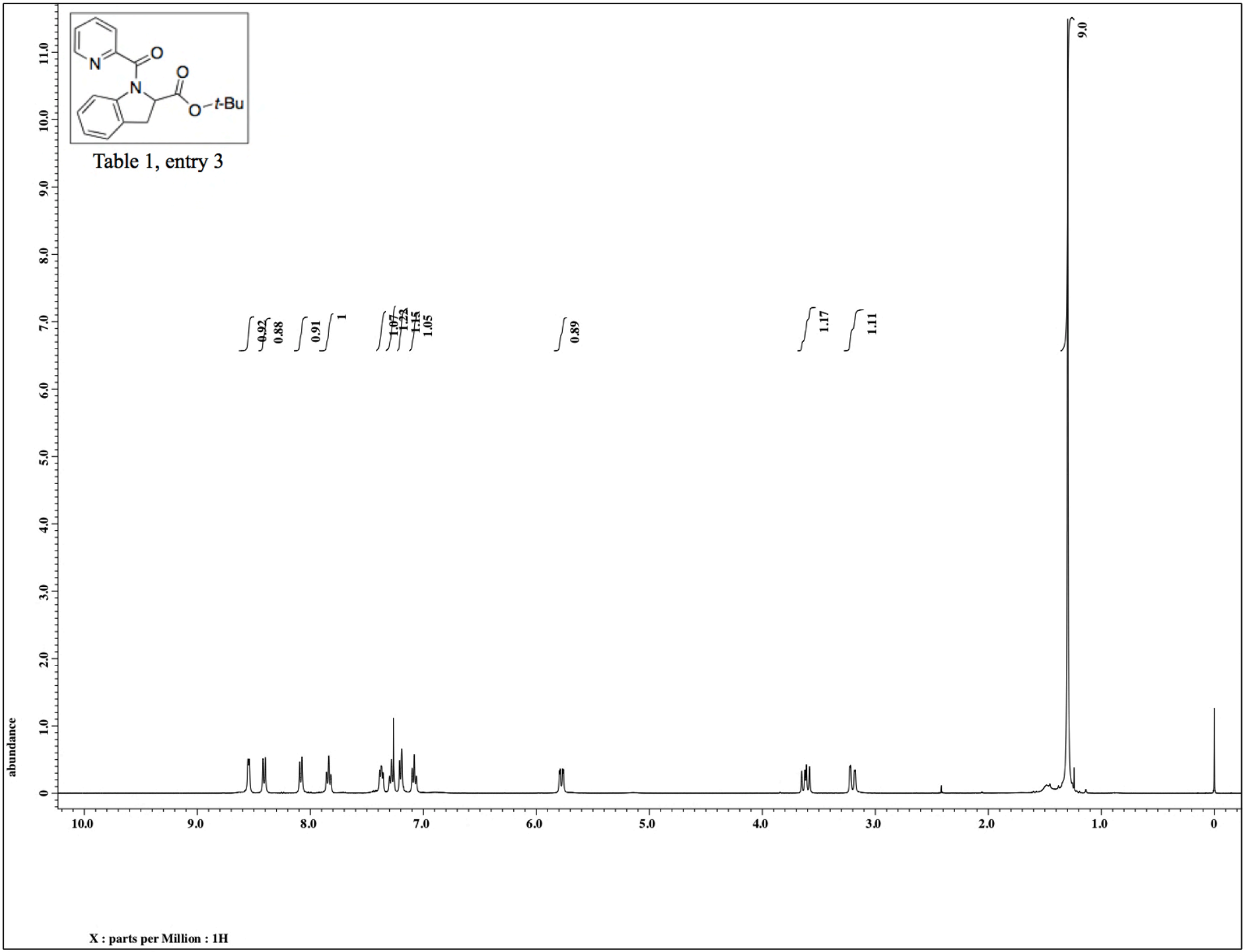


Table 1, entry 3
abundance
X : parts per Million : 1H
9.0
0.92
0.88
0.91
1
1.07
1.23
1.15
1.05
0.89
1.17
1.11

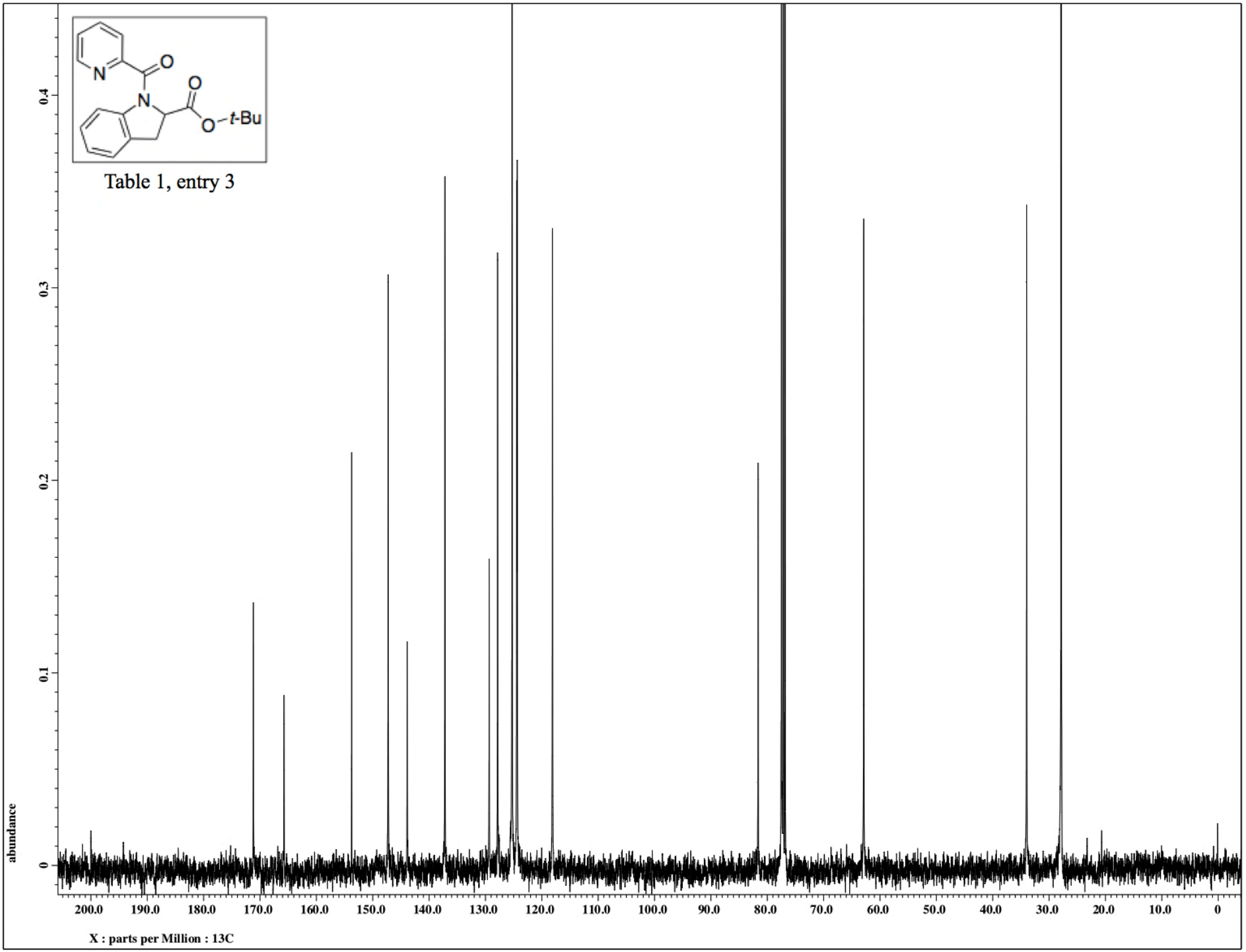


Table 1, entry 3
abundance
X : parts per Million : 13C

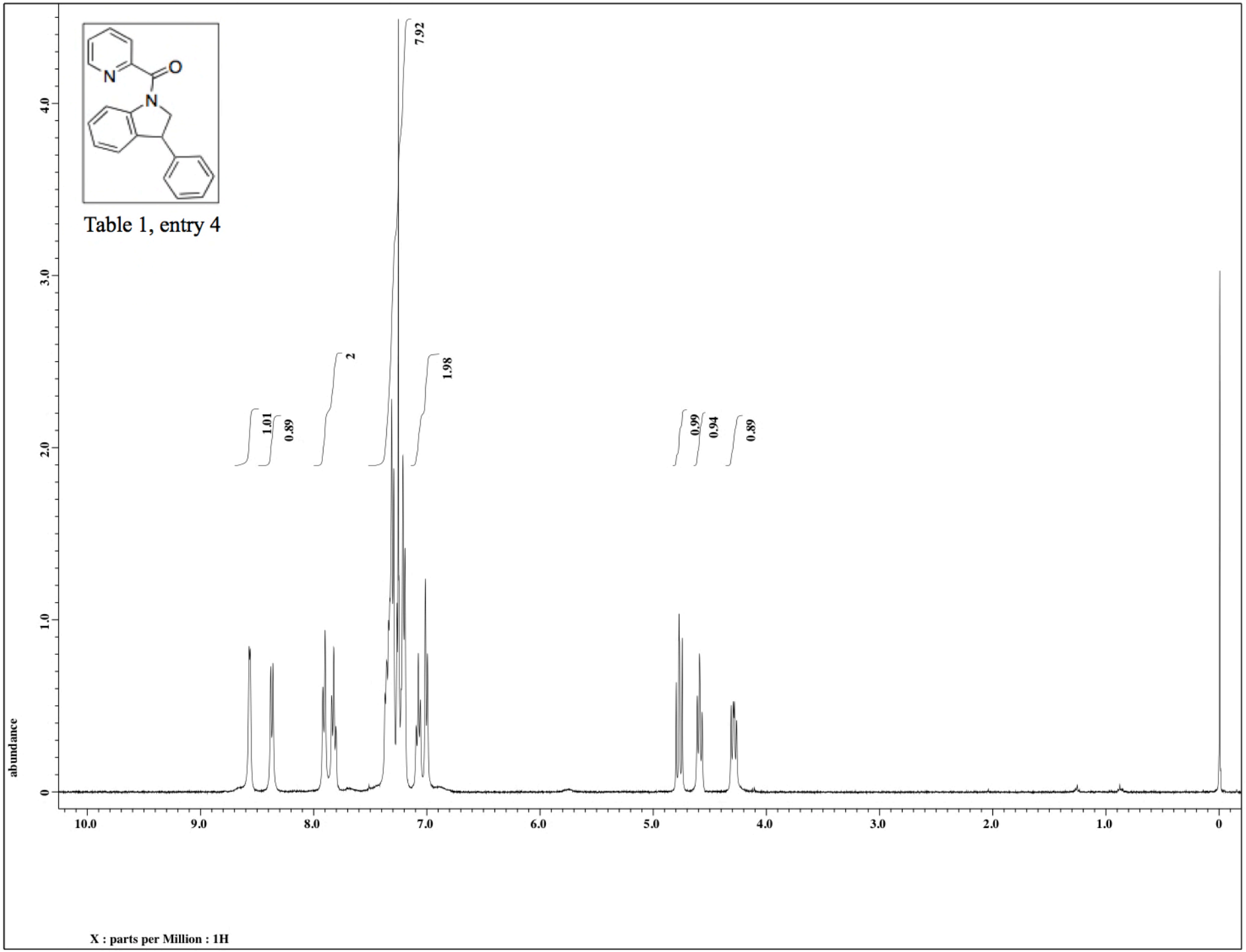


Table 1, entry 4
7.92
2
1.98
1.01
0.89
0.99
0.94
0.89
abundance
X : parts per Million : 1H

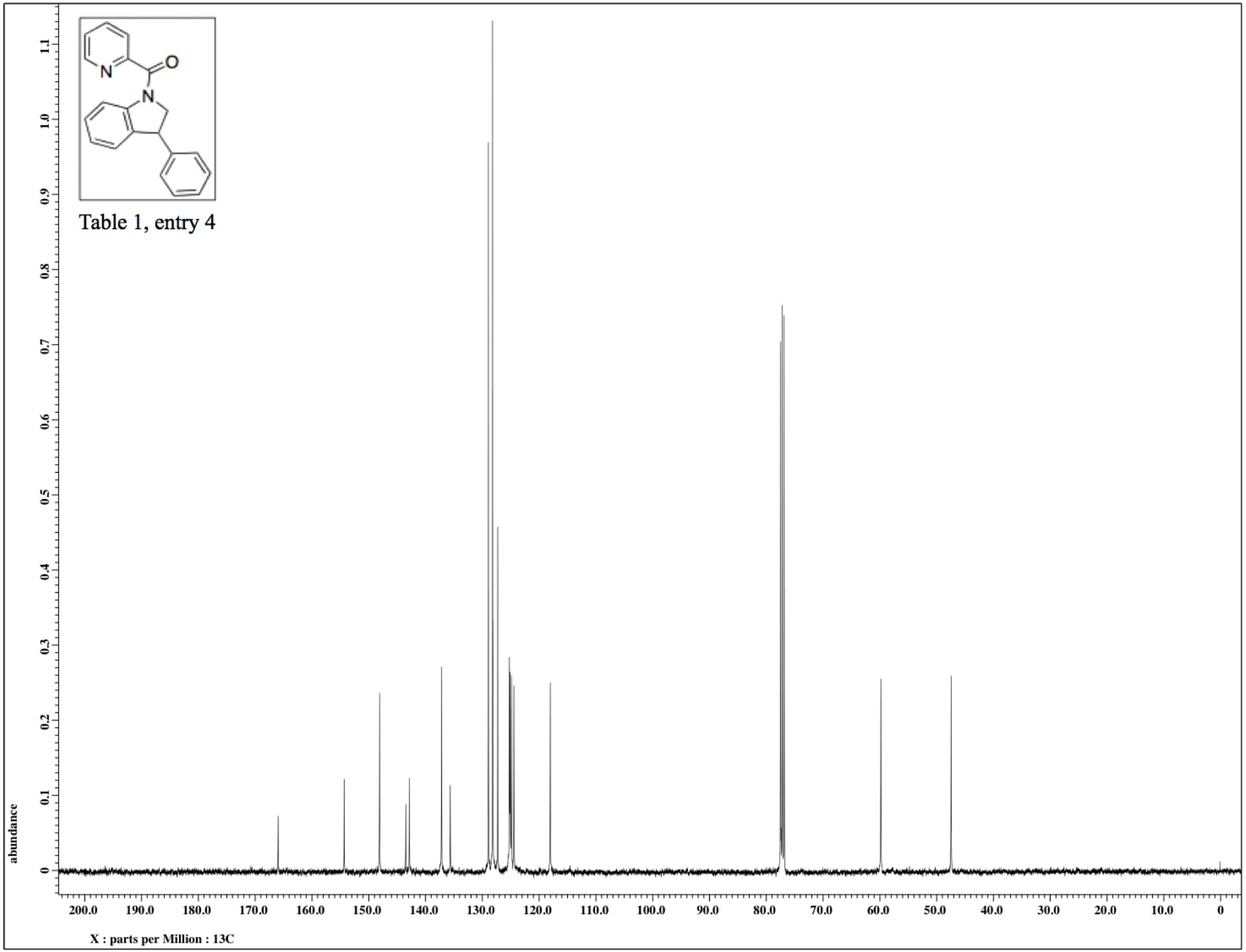
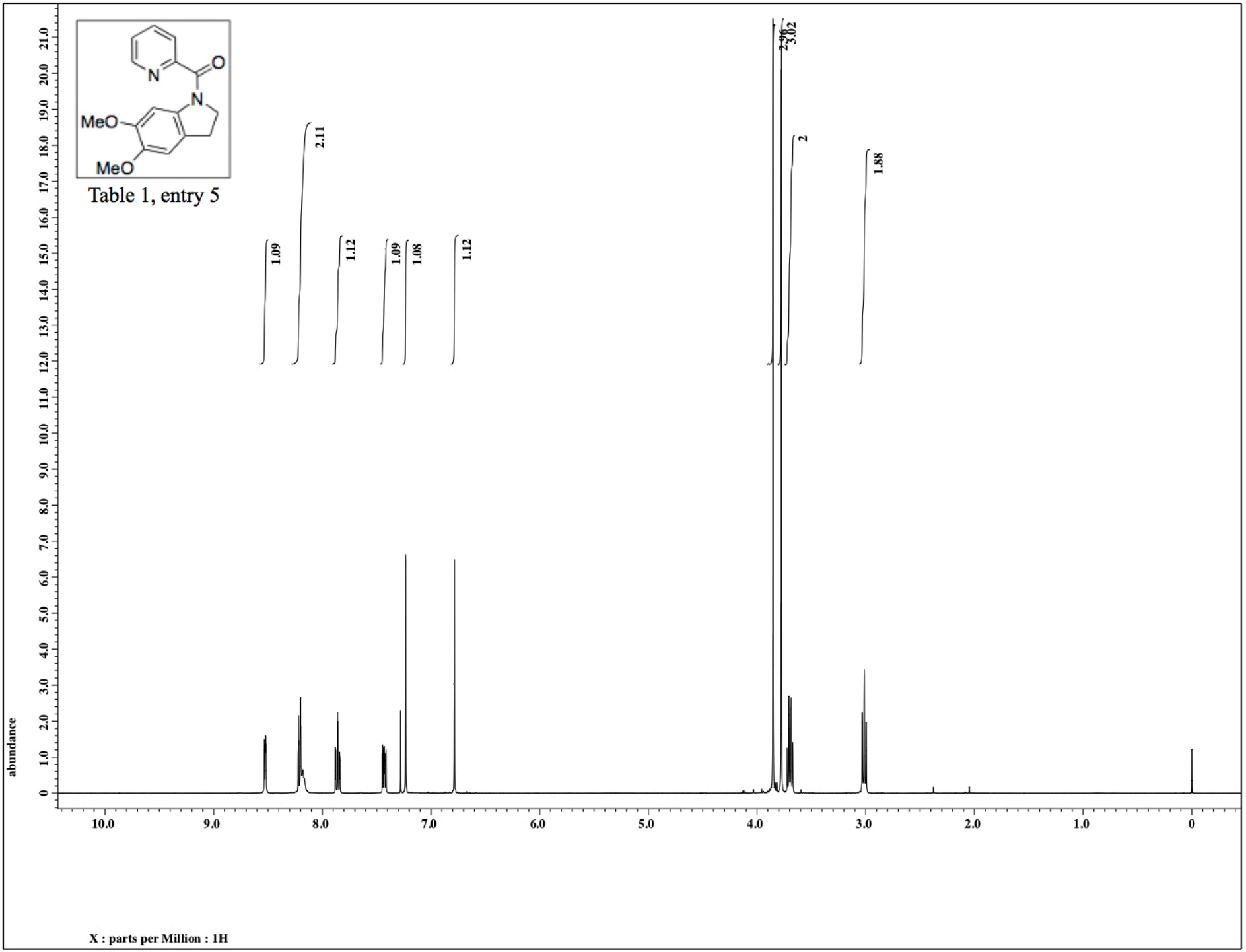
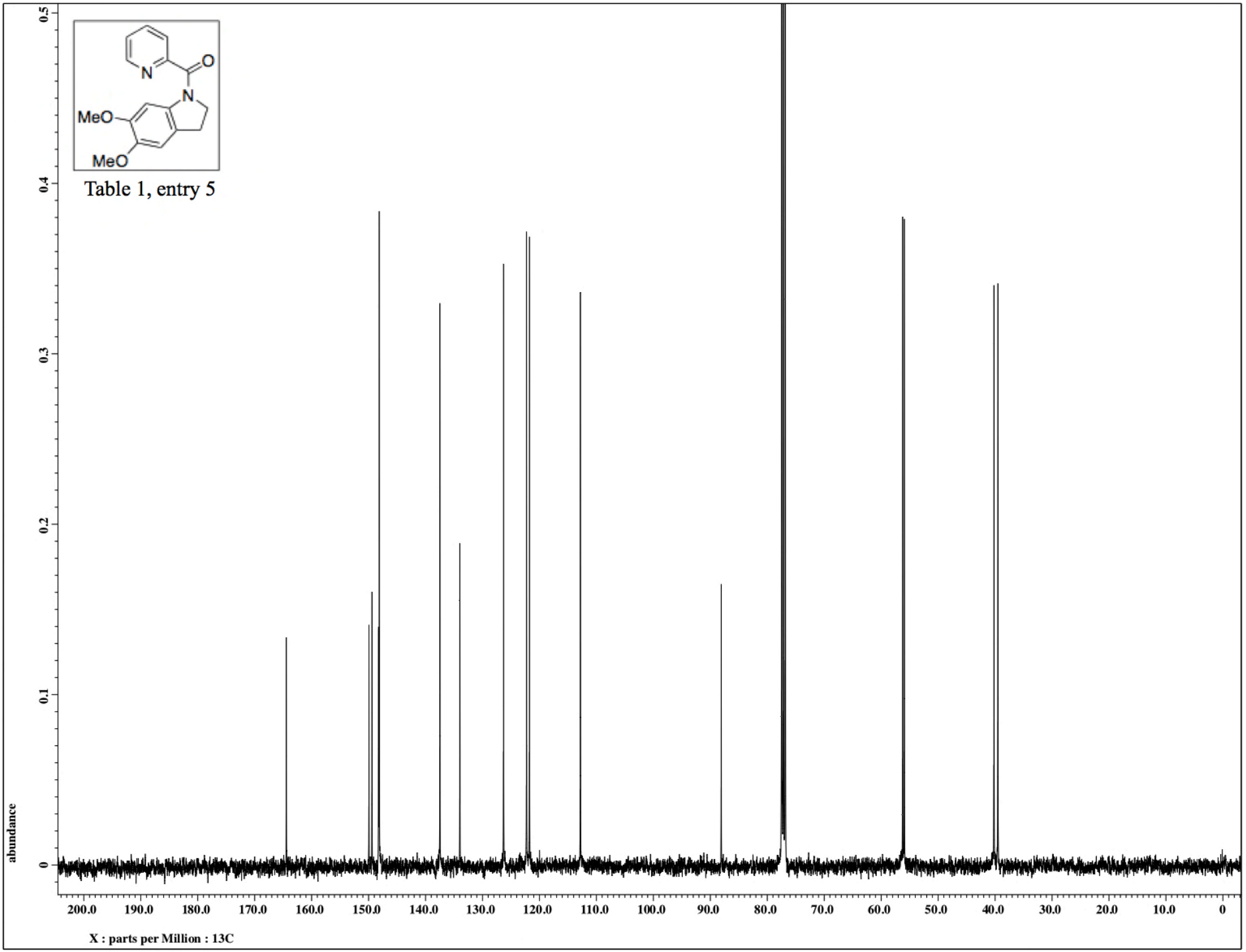
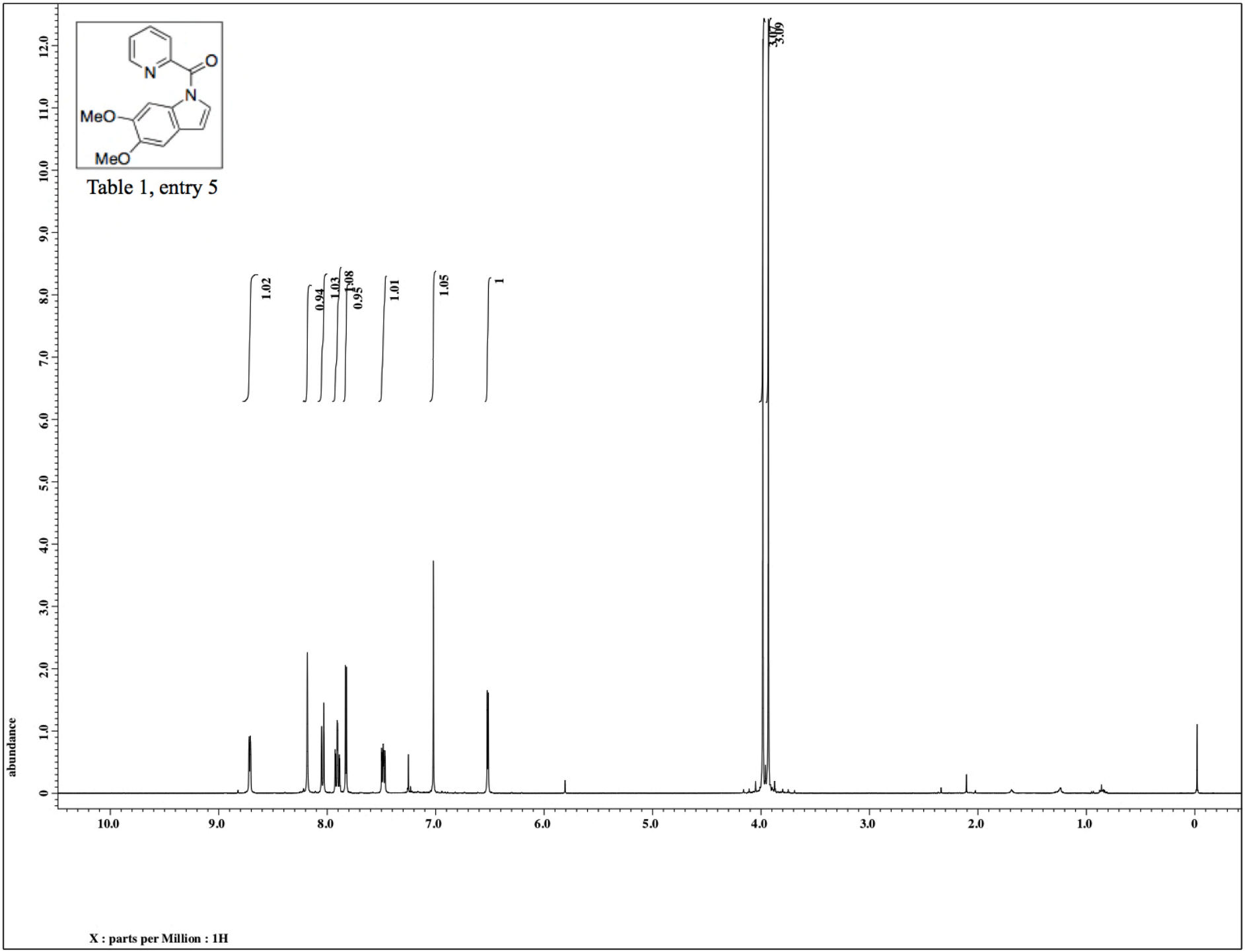
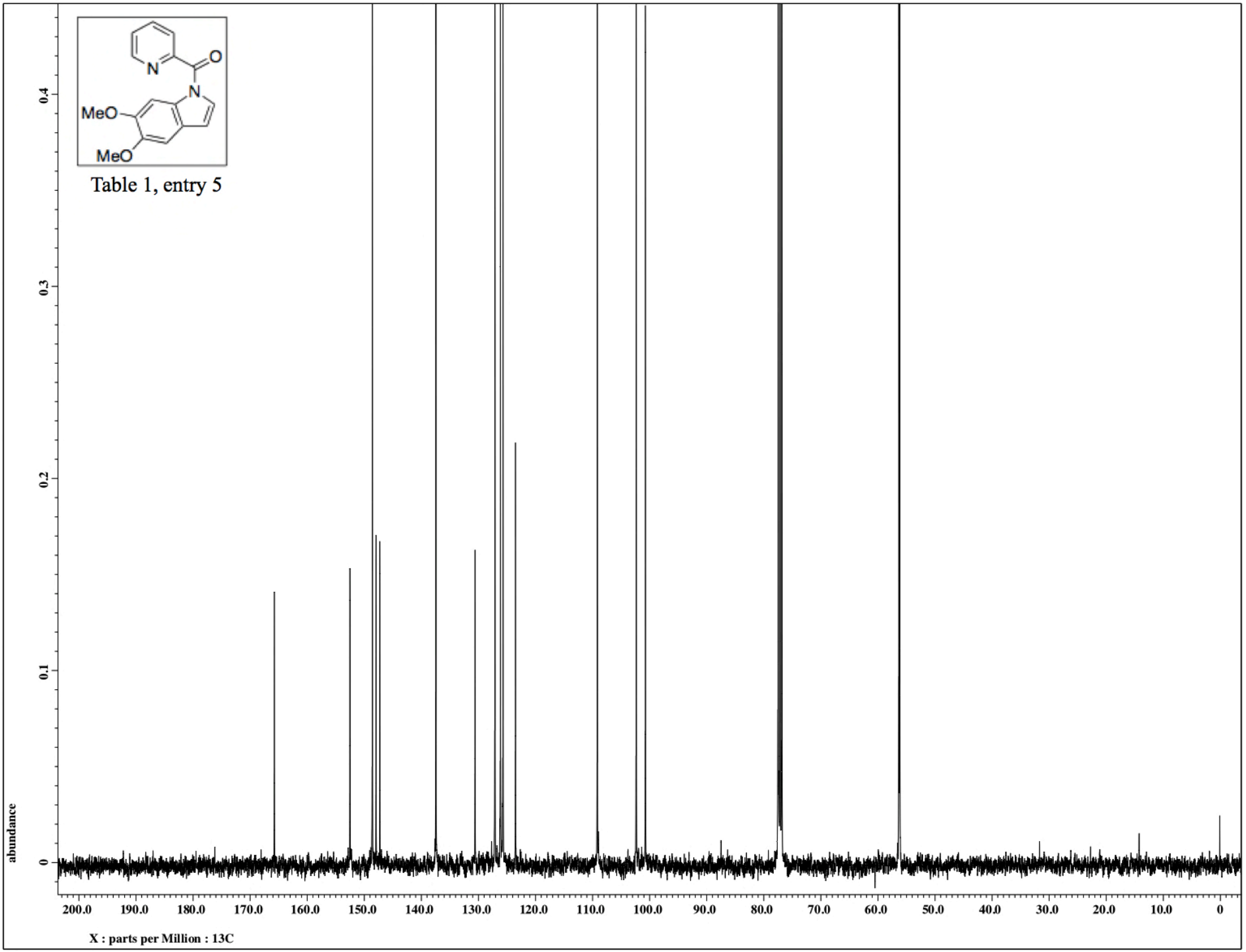


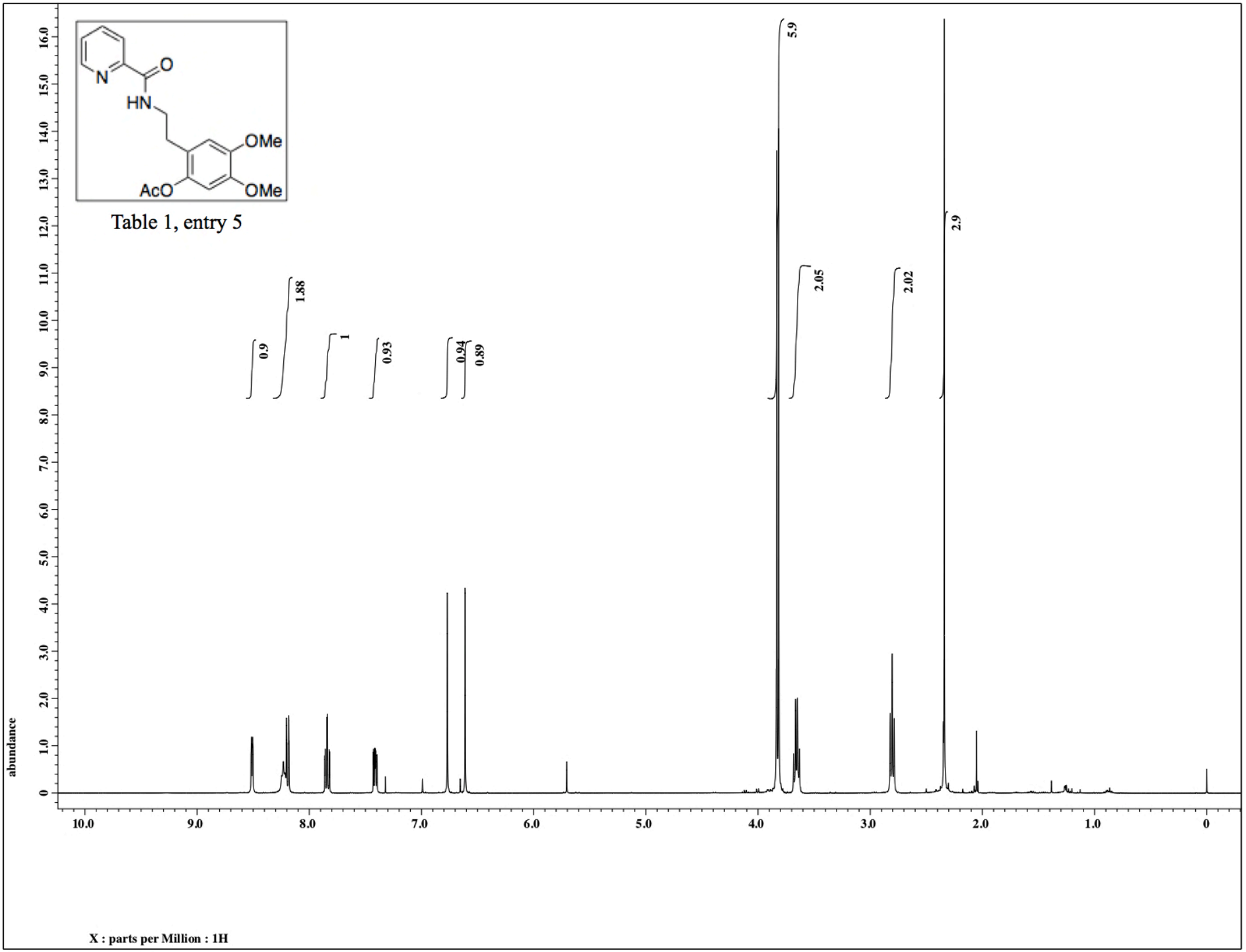
Table 1, entry 4
abundance
X : parts per Million : 13C


MeO
MeO
N
O
N
Table 1, entry 5
1.09
2.11
1.12
1.09
1.08
1.12
3.02
2
1.88
abundance
X : parts per Million : 1H


N
O
N
MeO
MeO
Table 1, entry 5
abundance
0.5
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
N
MeO
MeO
Table 1, entry 5
1.02
0.94
1.03
1.08
0.95
1.01
1.05
1
3.07
3.06
abundance
X : parts per Million : 1H


MeO
MeO
N
O
N
Table 1, entry 5
abundance
0
0.1
0.2
0.3
0.4
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
HN
OMe
AcO
OMe
Table 1, entry 5
0.9
1.88
1
0.93
0.94
0.89
5.9
2.05
2.02
2.9
abundance
X : parts per Million : 1H

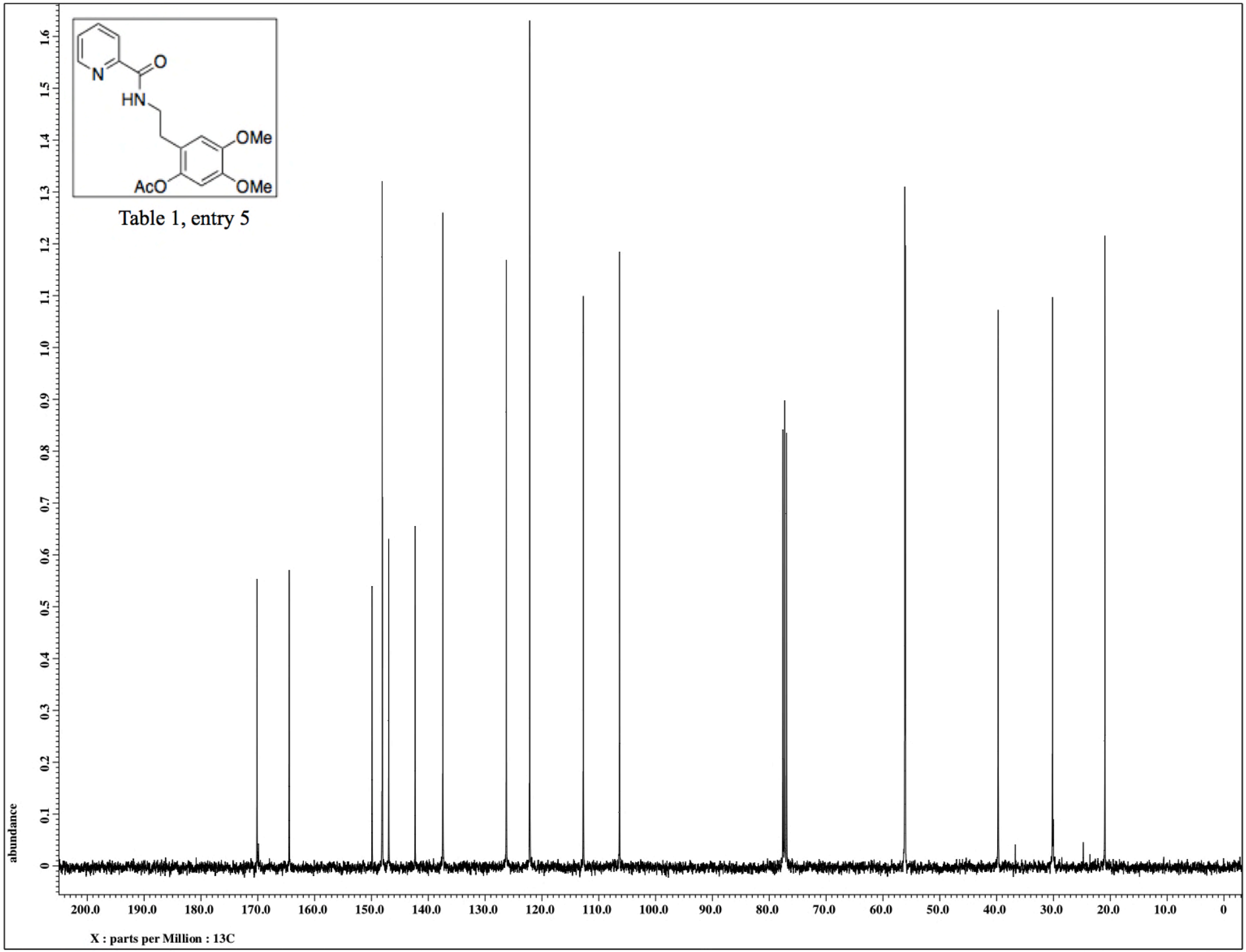


Table 1, entry 5

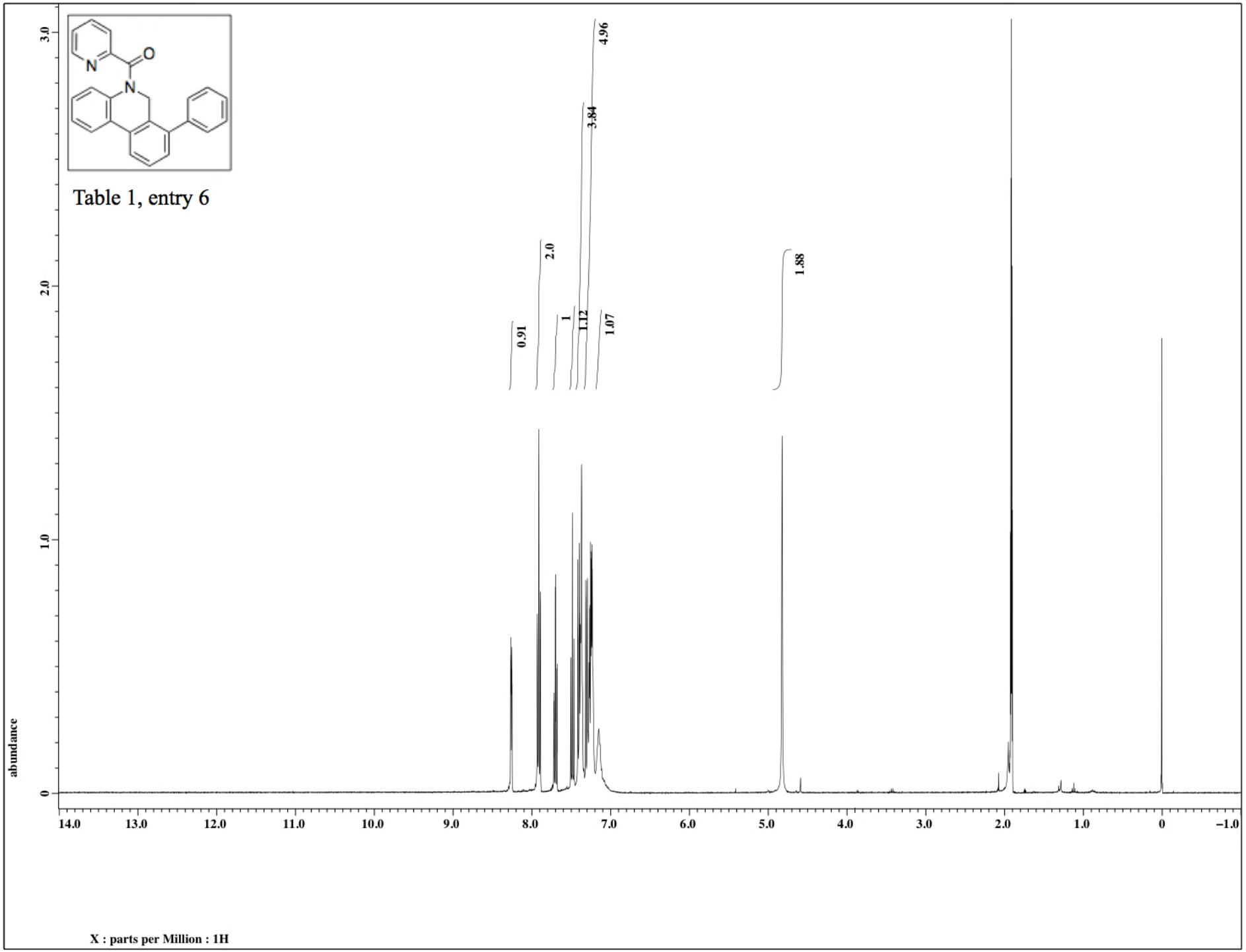


Table 1, entry 6
0.91
2.0
1
1.12
3.84
4.96
1.07
1.88
abundance
X : parts per Million : 1H

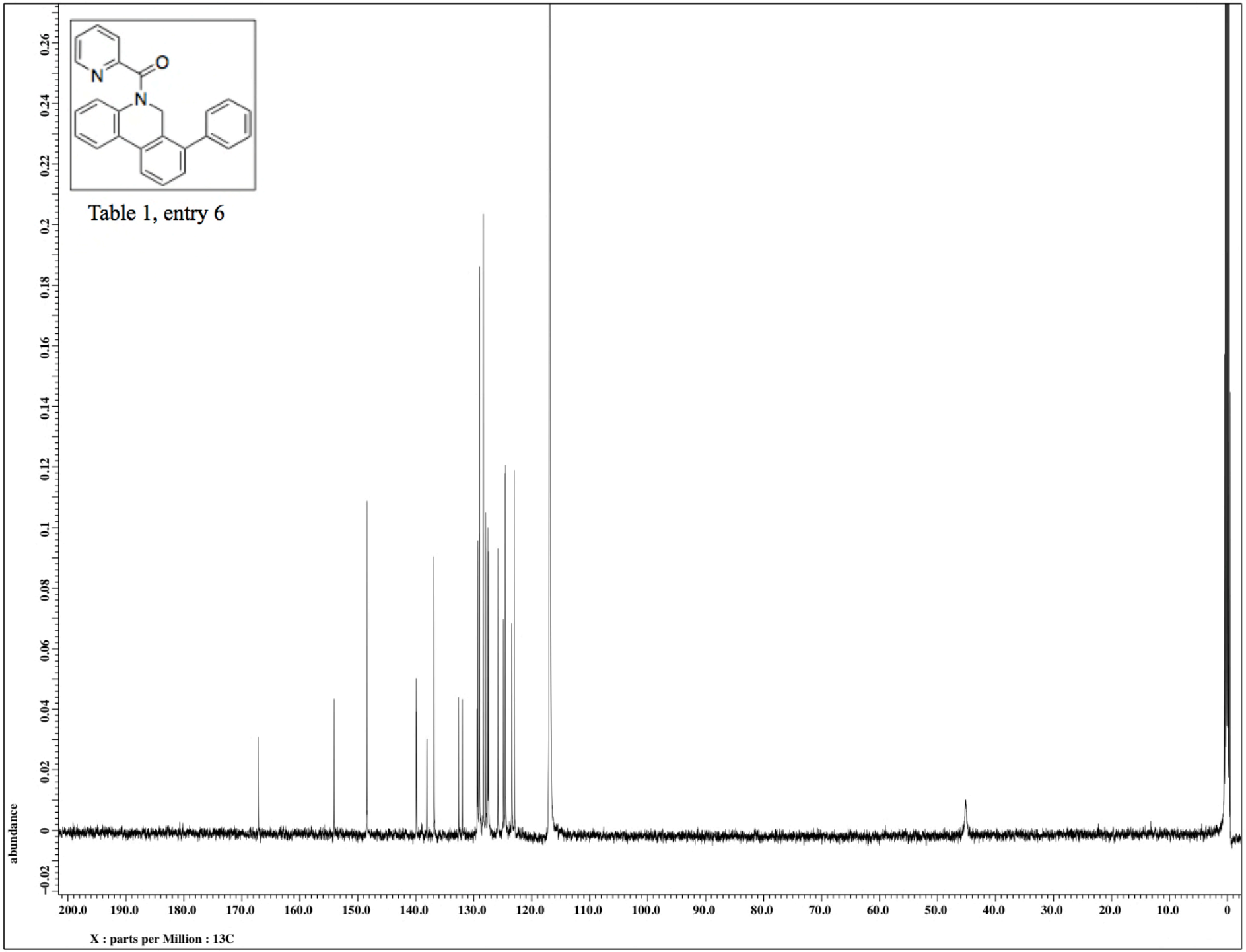


Table 1, entry 6
abundance
X : parts per Million : 13C

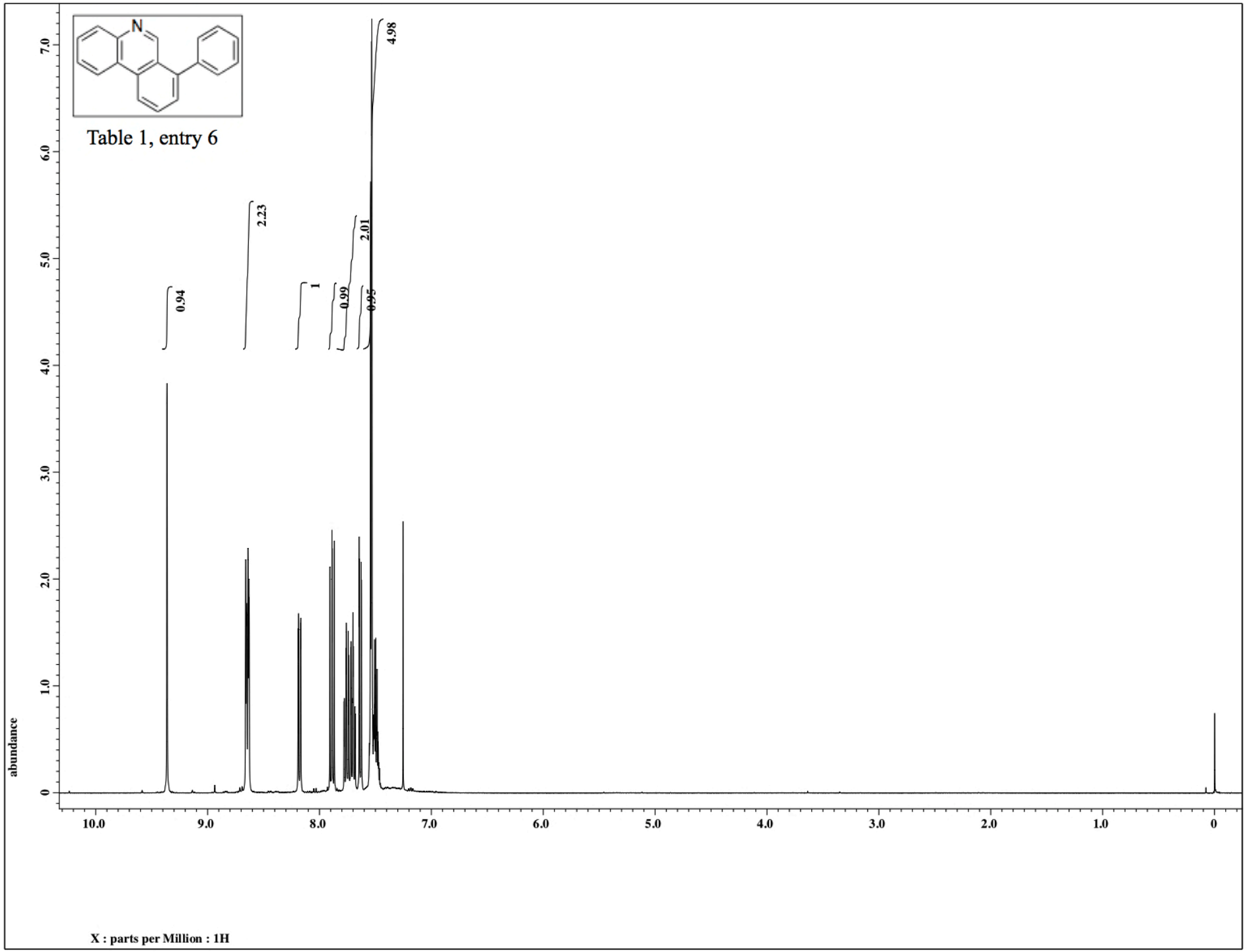


Table 1, entry 6
0.94
2.23
1
0.99
2.01
0.95
4.98
abundance
X : parts per Million : 1H

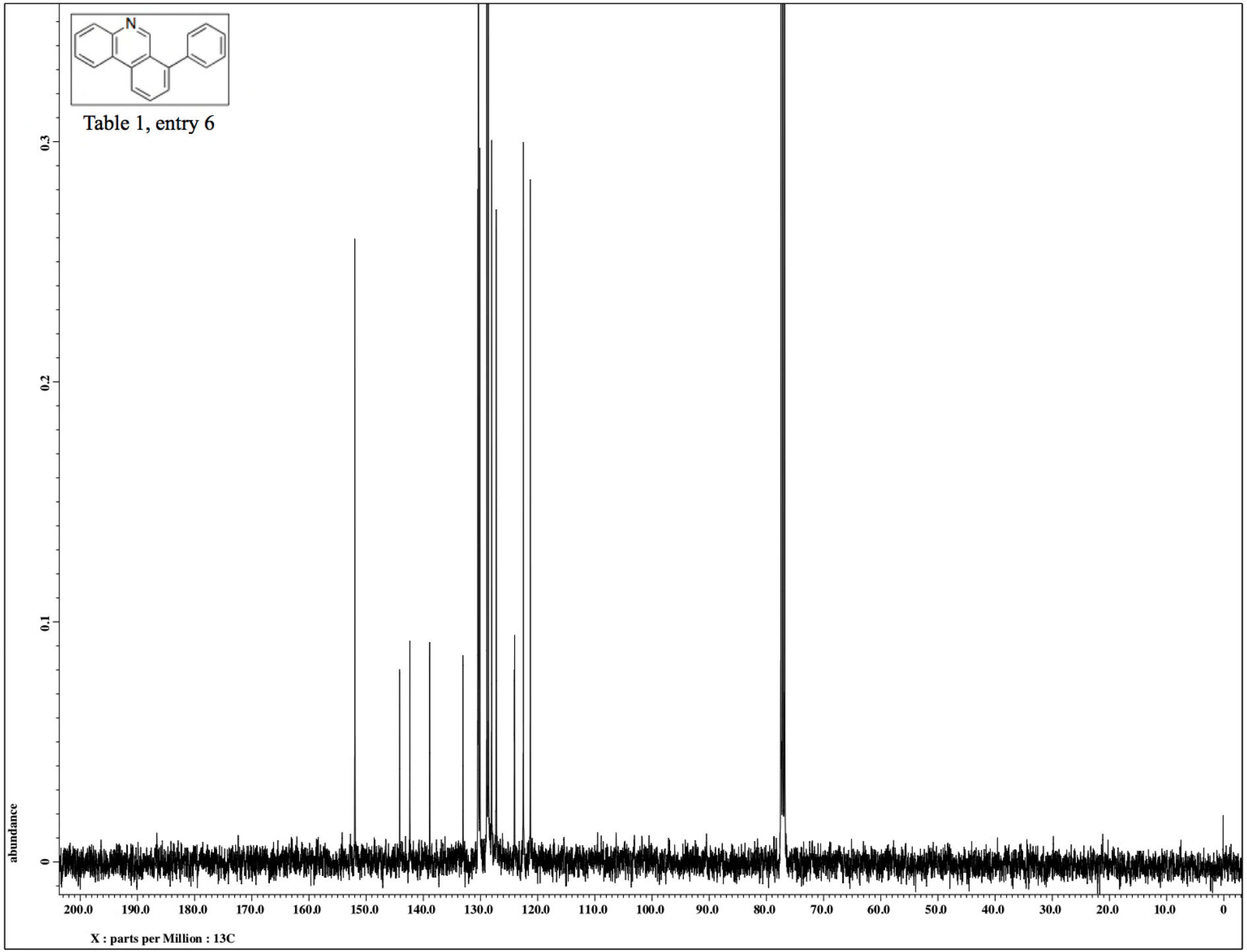


Table 1, entry 6
abundance
0
0.1
0.2
0.3
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

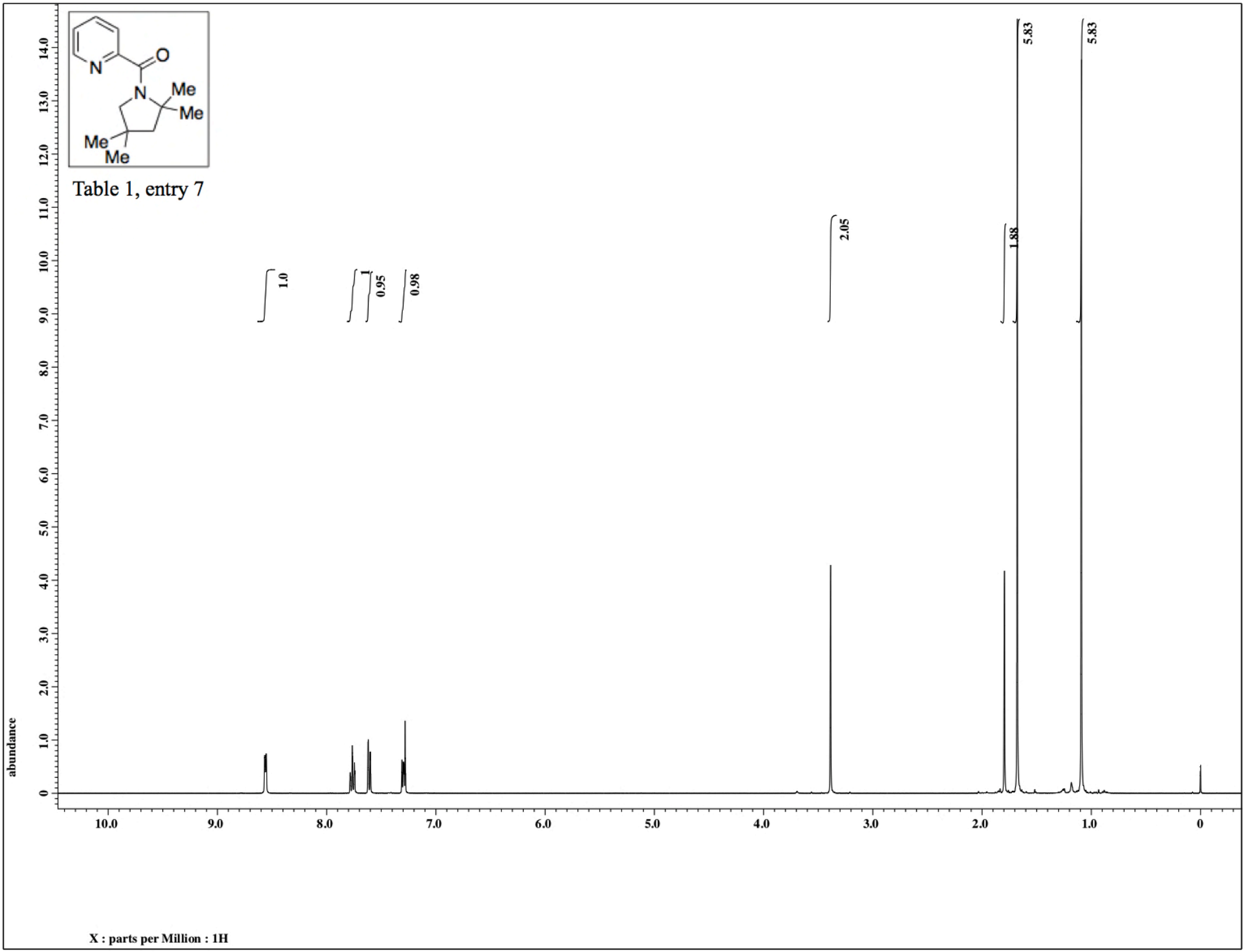
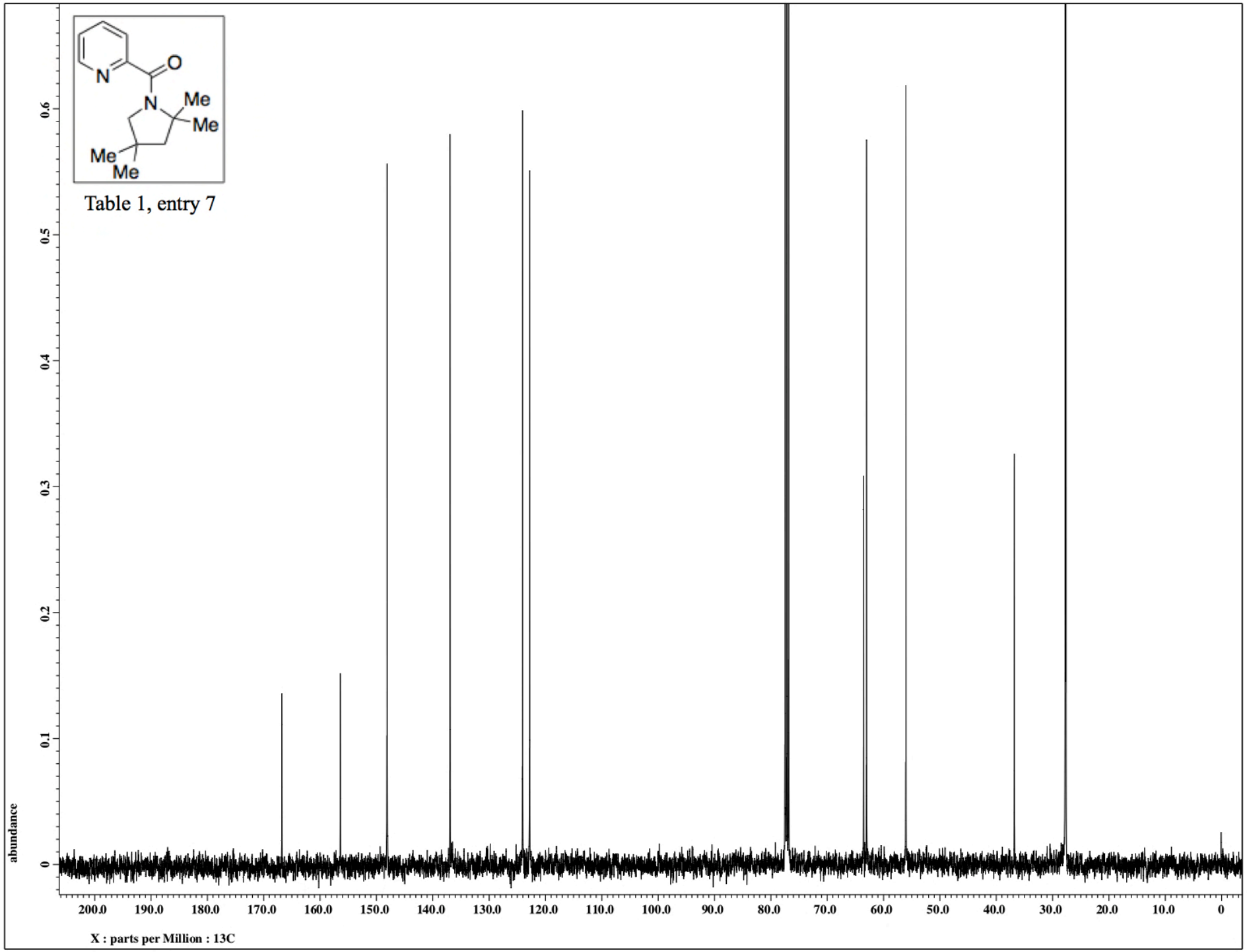


Table 1, entry 7
1.0
1
0.95
0.98
2.05
1.88
5.83
5.83
abundance
X : parts per Million : 1H


N
O
N
Me
Me
Me
Me
Table 1, entry 7
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

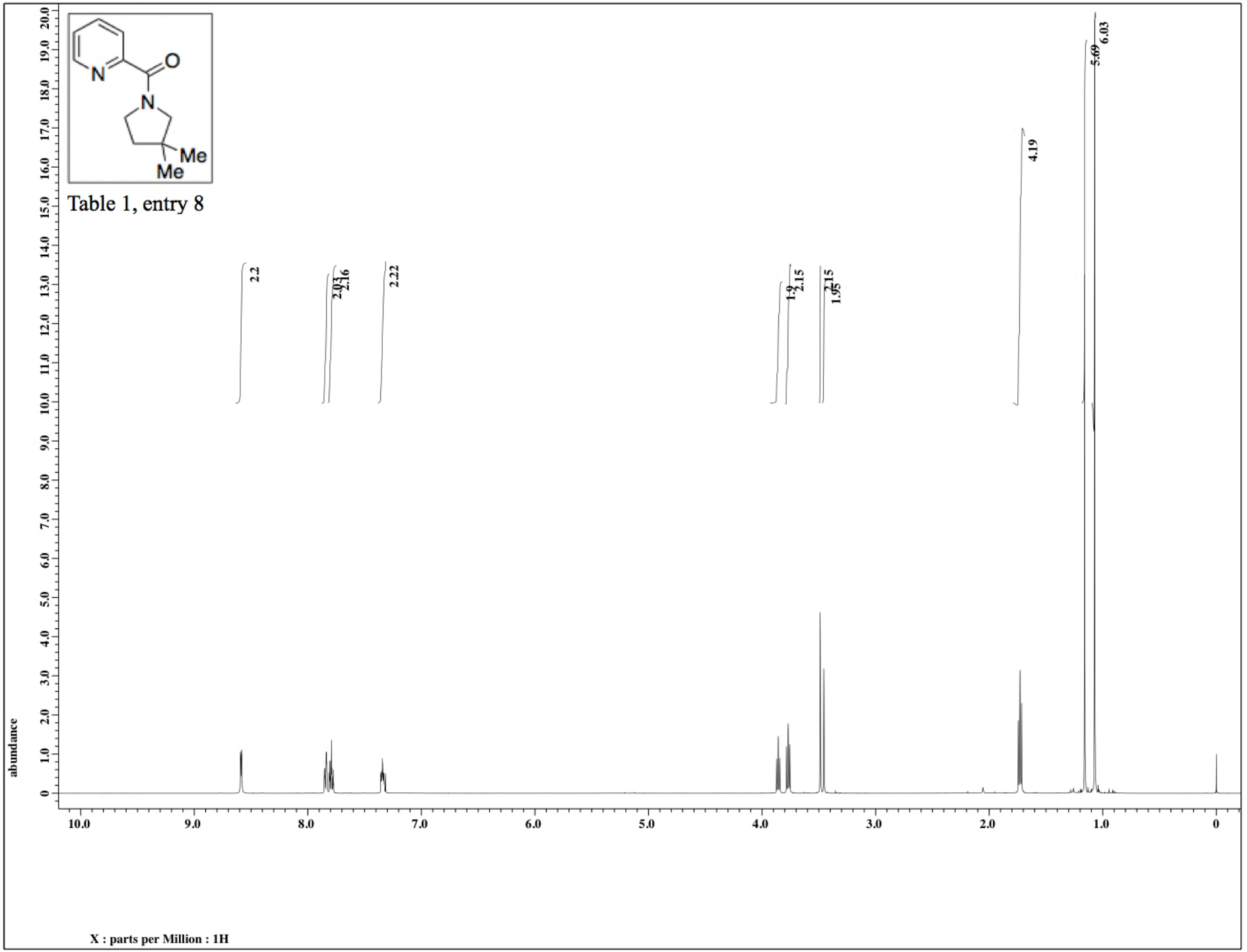
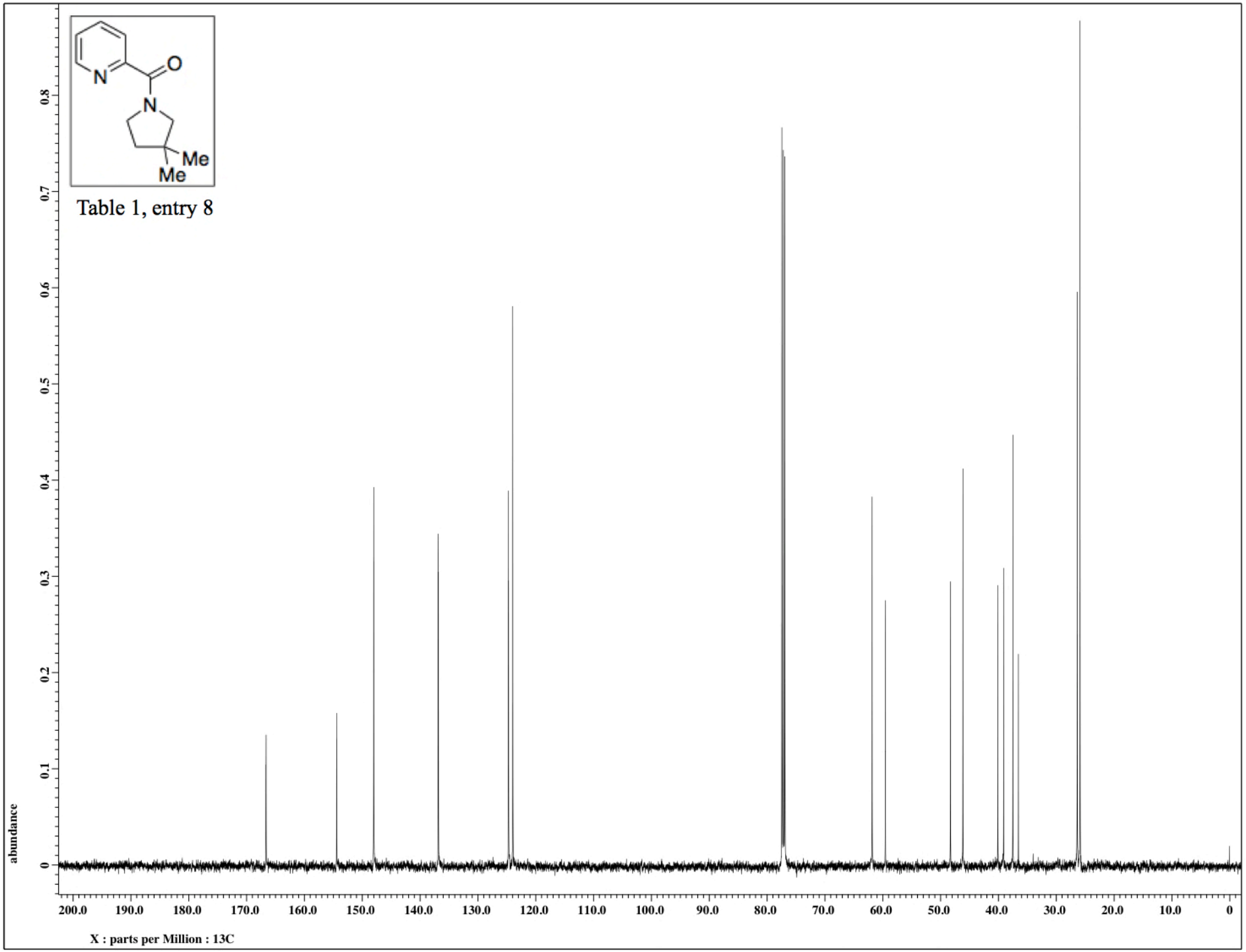


Table 1, entry 8
Me
Me
2.2
2.03
2.16
2.22
1.9
2.15
2.15
1.95
4.19
5.69
6.03
abundance
X : parts per Million : 1H


N
O
N
Me
Me
Table 1, entry 8
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

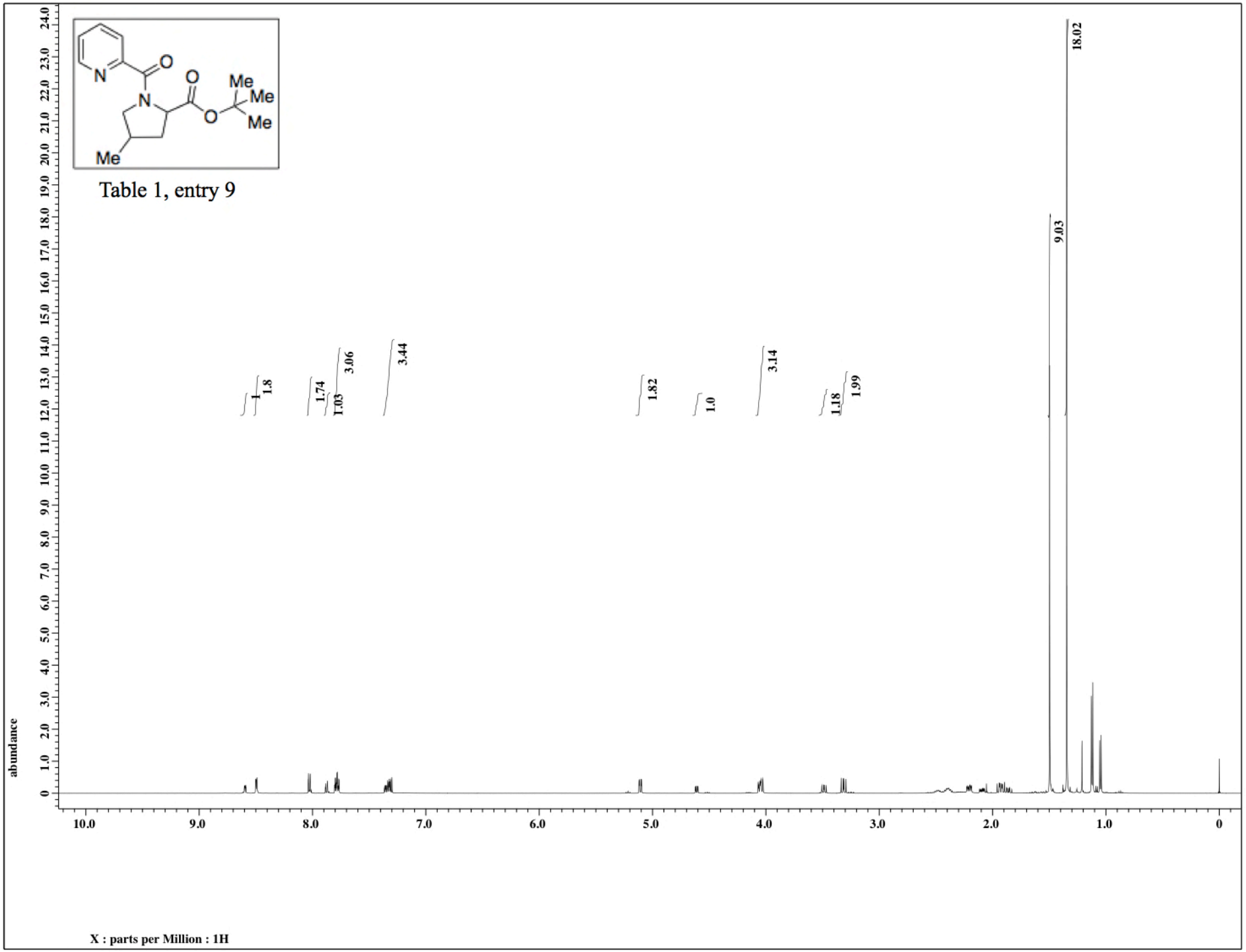
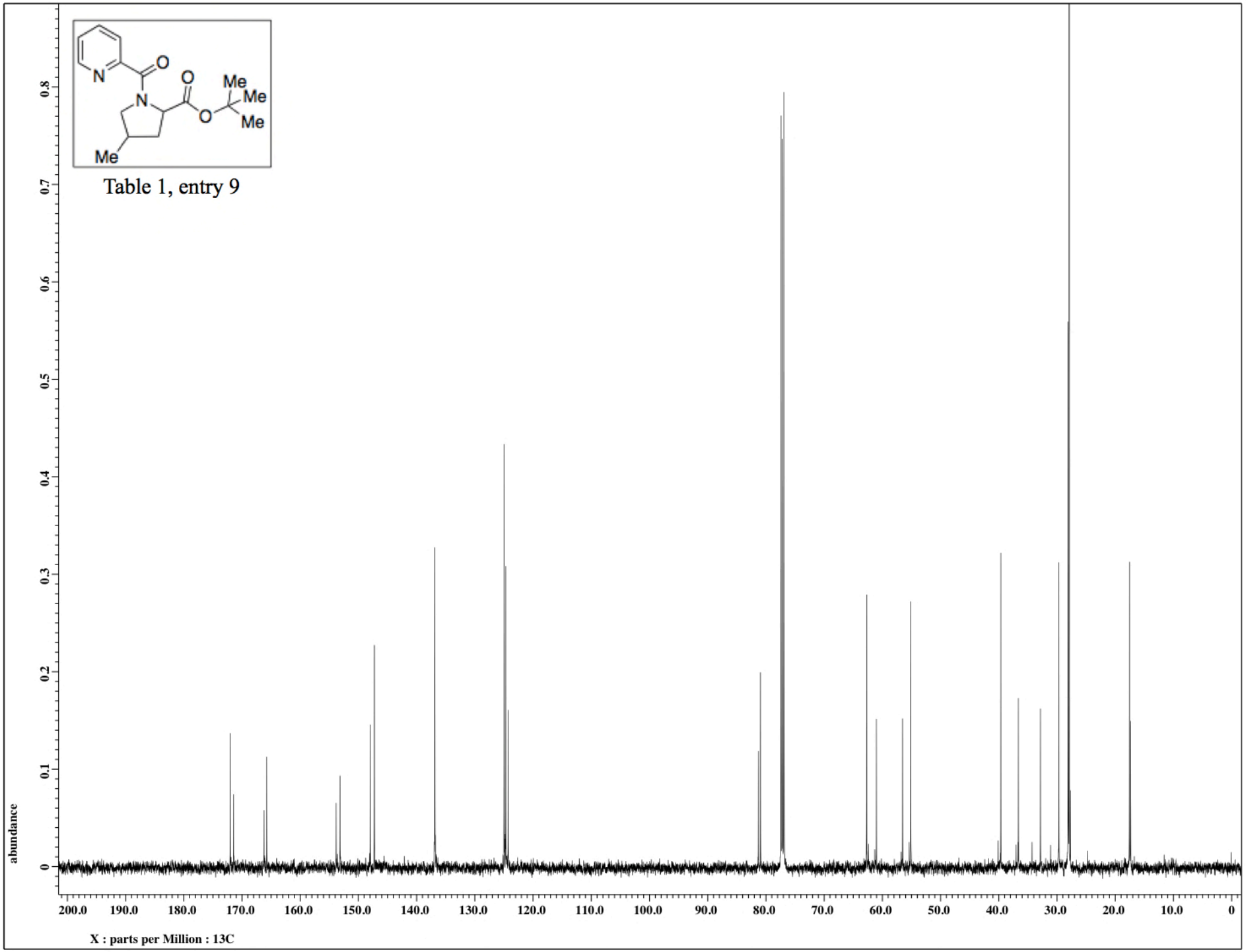


Table 1, entry 9
abundance
X : parts per Million : 1H
1.8
1.74
1.03
3.06
3.44
1.82
1.0
3.14
1.18
1.99
9.03
18.02


N
O
N
O
O
Me
Me
Me
Me
Table 1, entry 9
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

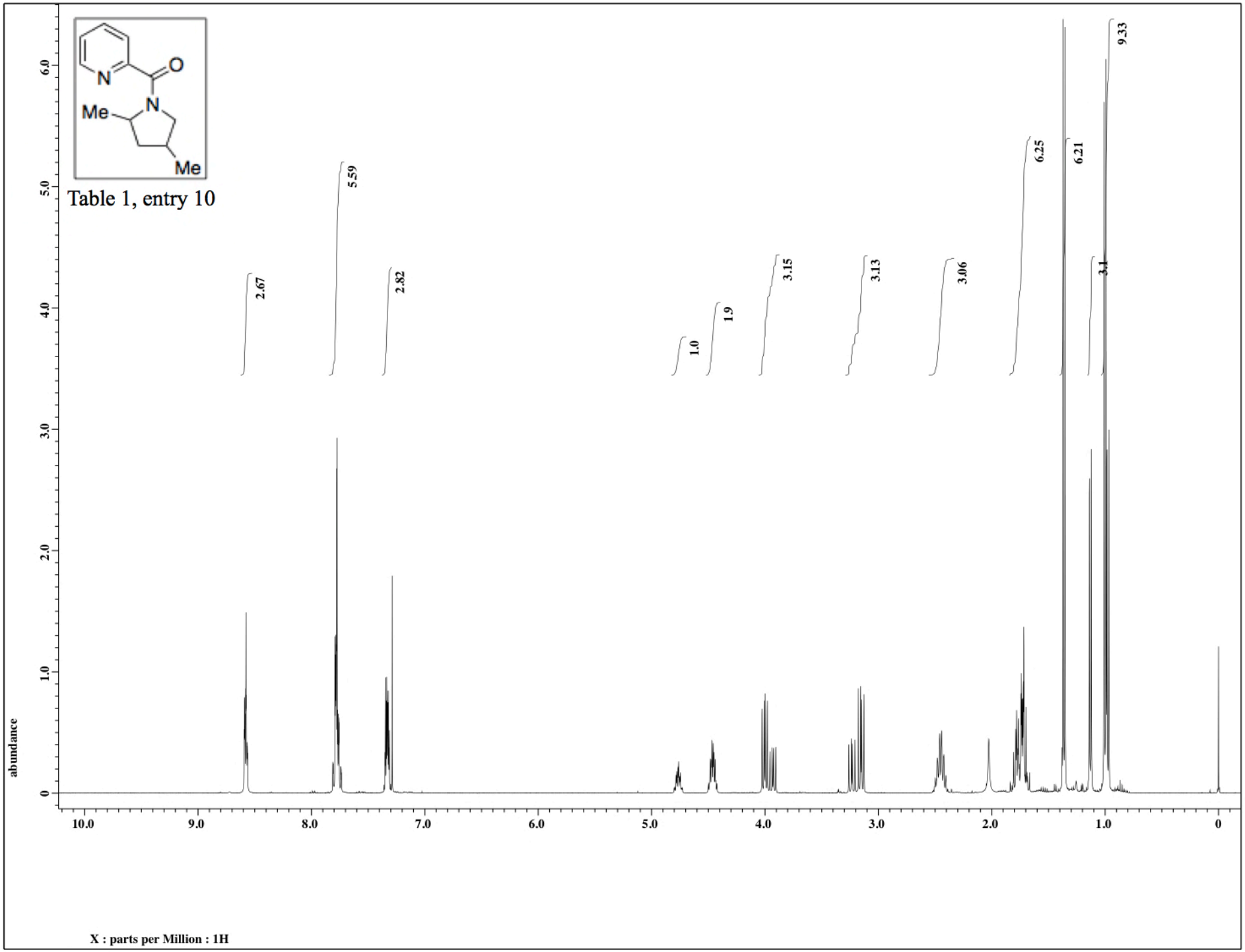
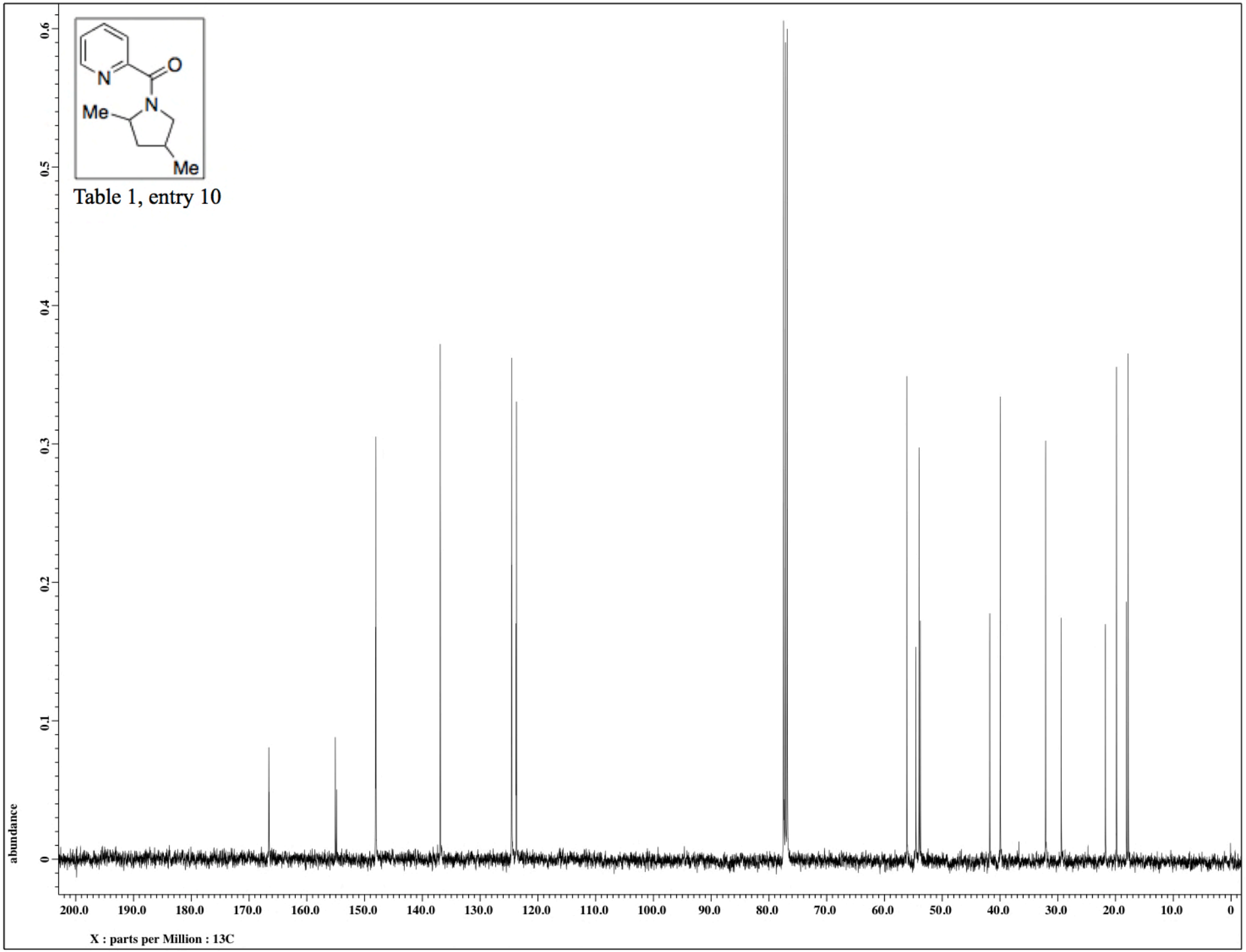


Table 1, entry 10
N
O
N
Me
Me
2.67
5.59
2.82
1.0
1.9
3.15
3.13
3.06
6.25
6.21
3.1
9.33
abundance
X : parts per Million : 1H


Me
Me
Table 1, entry 10
abundance
0.6
0.5
0.4
0.3
0.2
0.1
0
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

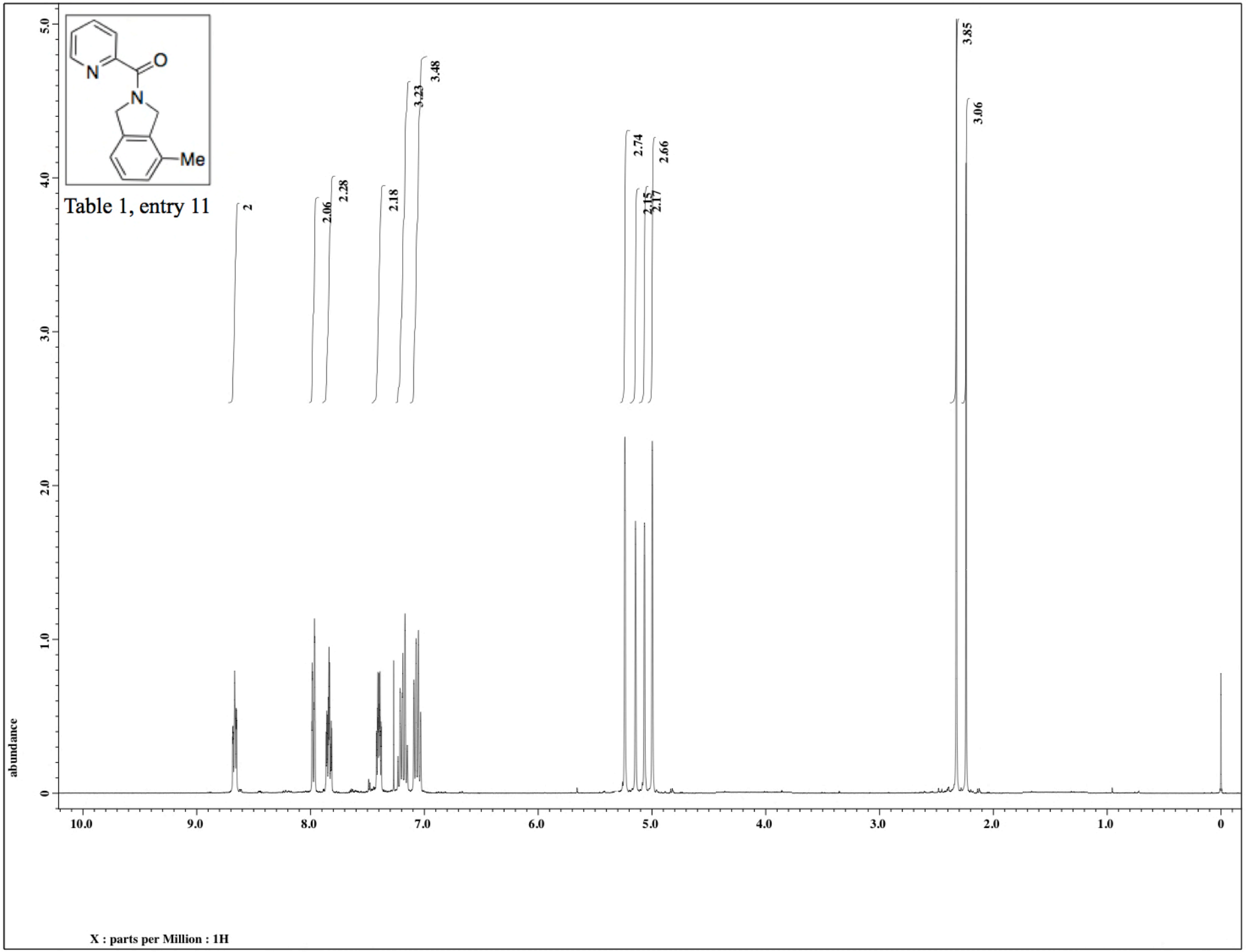
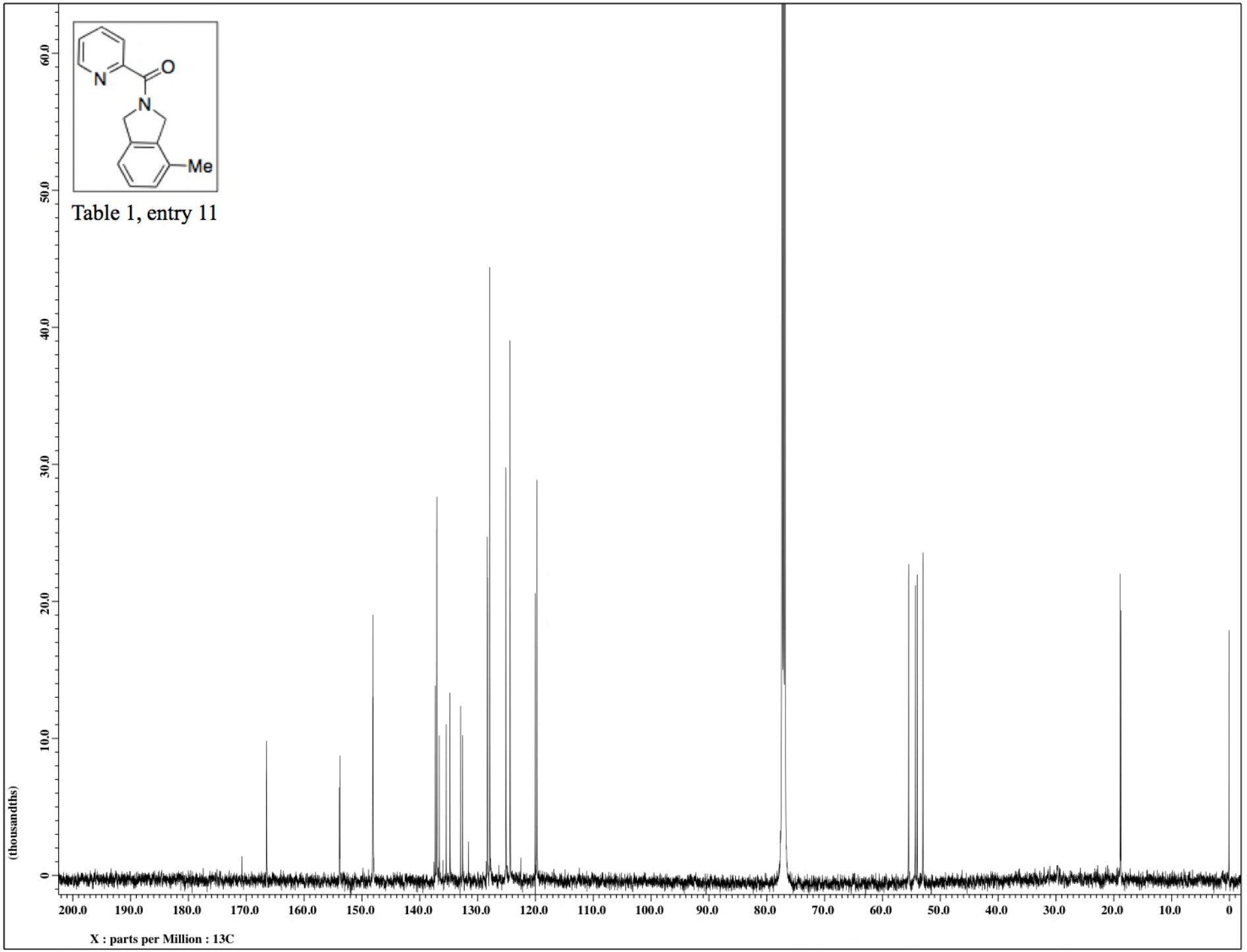


Table 1, entry 11
N
O
N
Me
2
2.06
2.28
2.18
3.23
3.48
2.74
2.15
2.17
2.66
3.85
3.06
abundance
5.0
4.0
3.0
2.0
1.0
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H


N
O
N
Me
Table 1, entry 11
60.0
50.0
40.0
30.0
20.0
10.0
0
(thousandths)
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

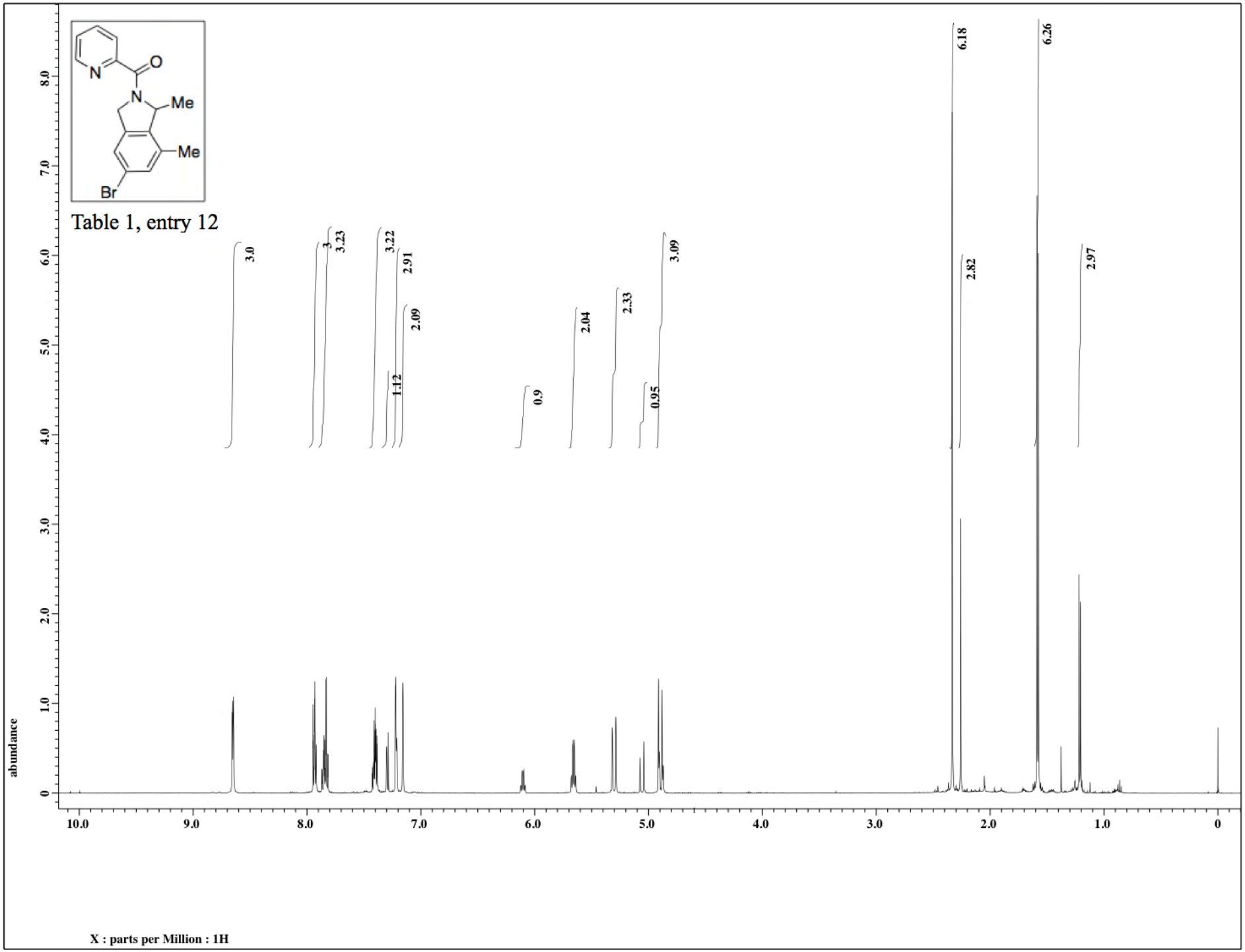
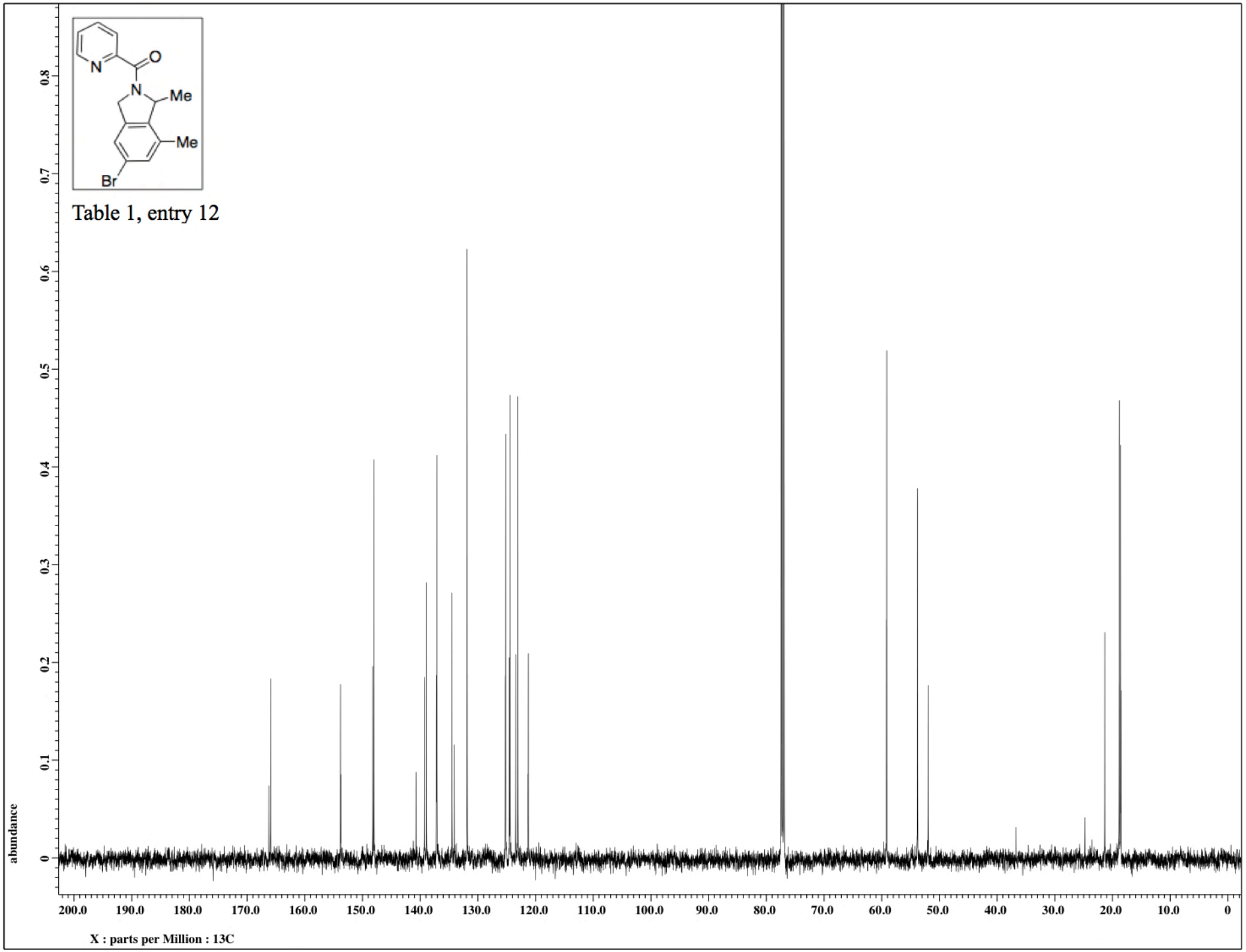


Table 1, entry 12
Br
Me
Me
N
O
N
3.0
3
3.23
3.22
2.91
2.09
1.12
0.9
2.04
2.33
0.95
3.09
6.18
2.82
6.26
2.97
abundance
X : parts per Million : 1H


N
O
N
Me
Me
Br
Table 1, entry 12
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C

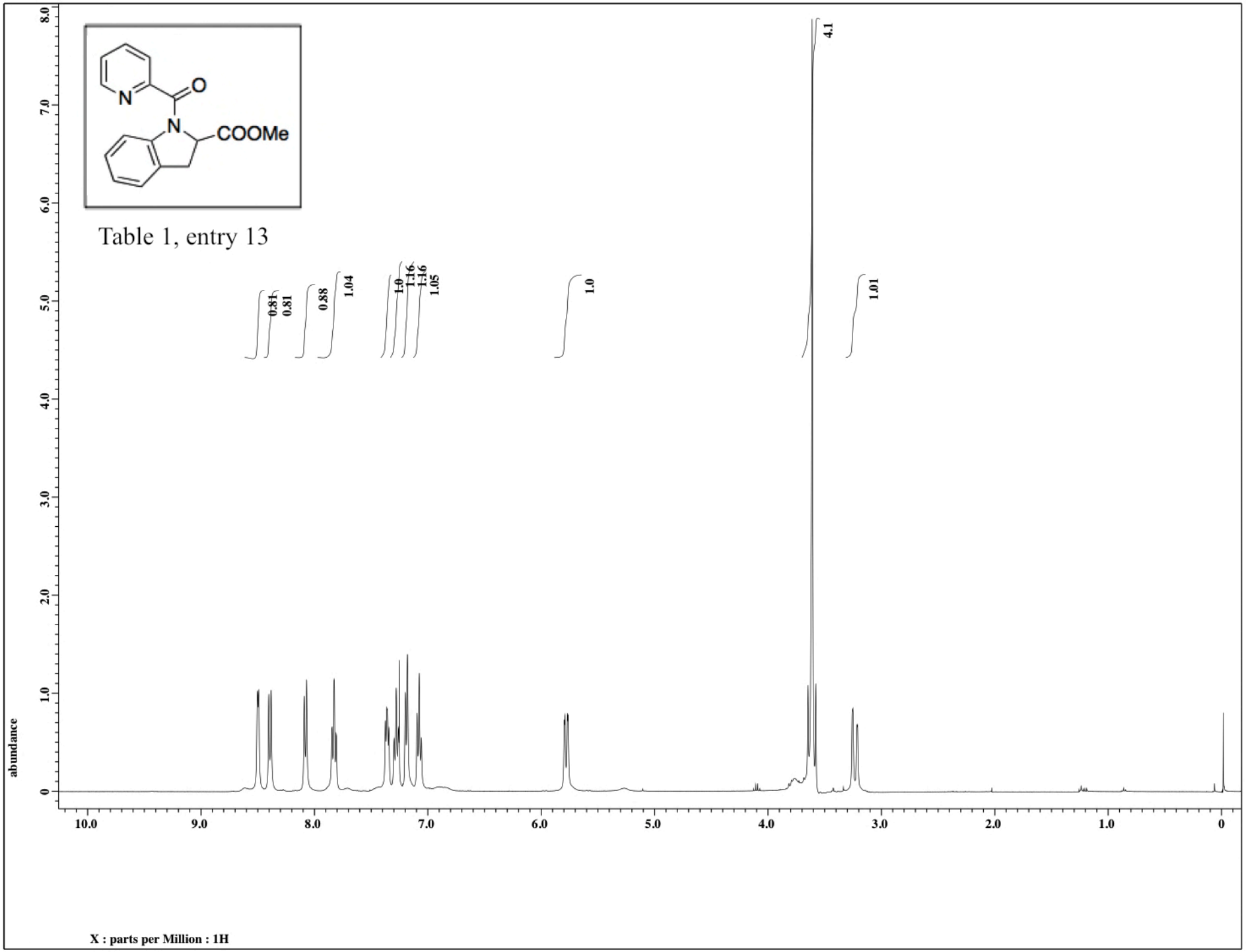
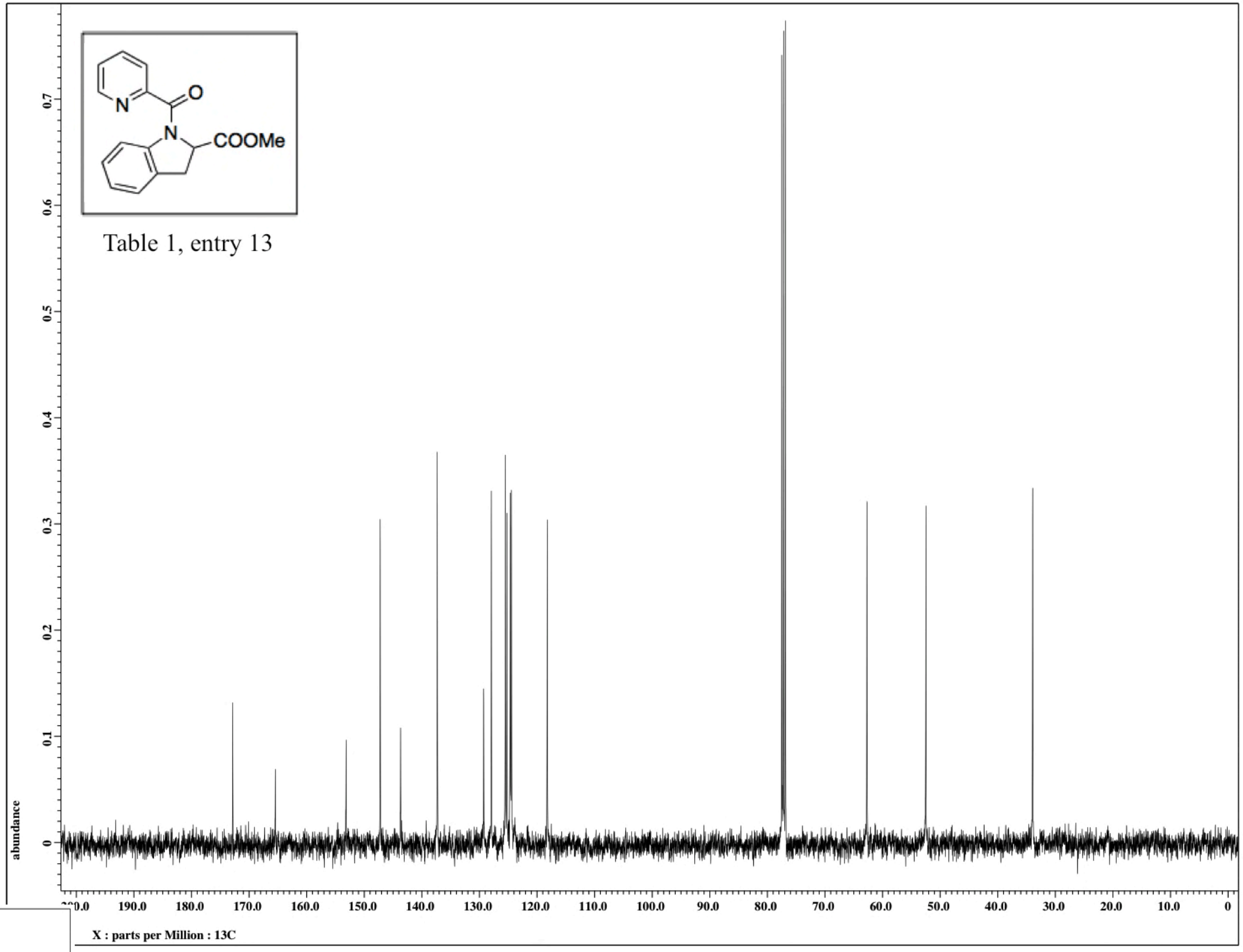
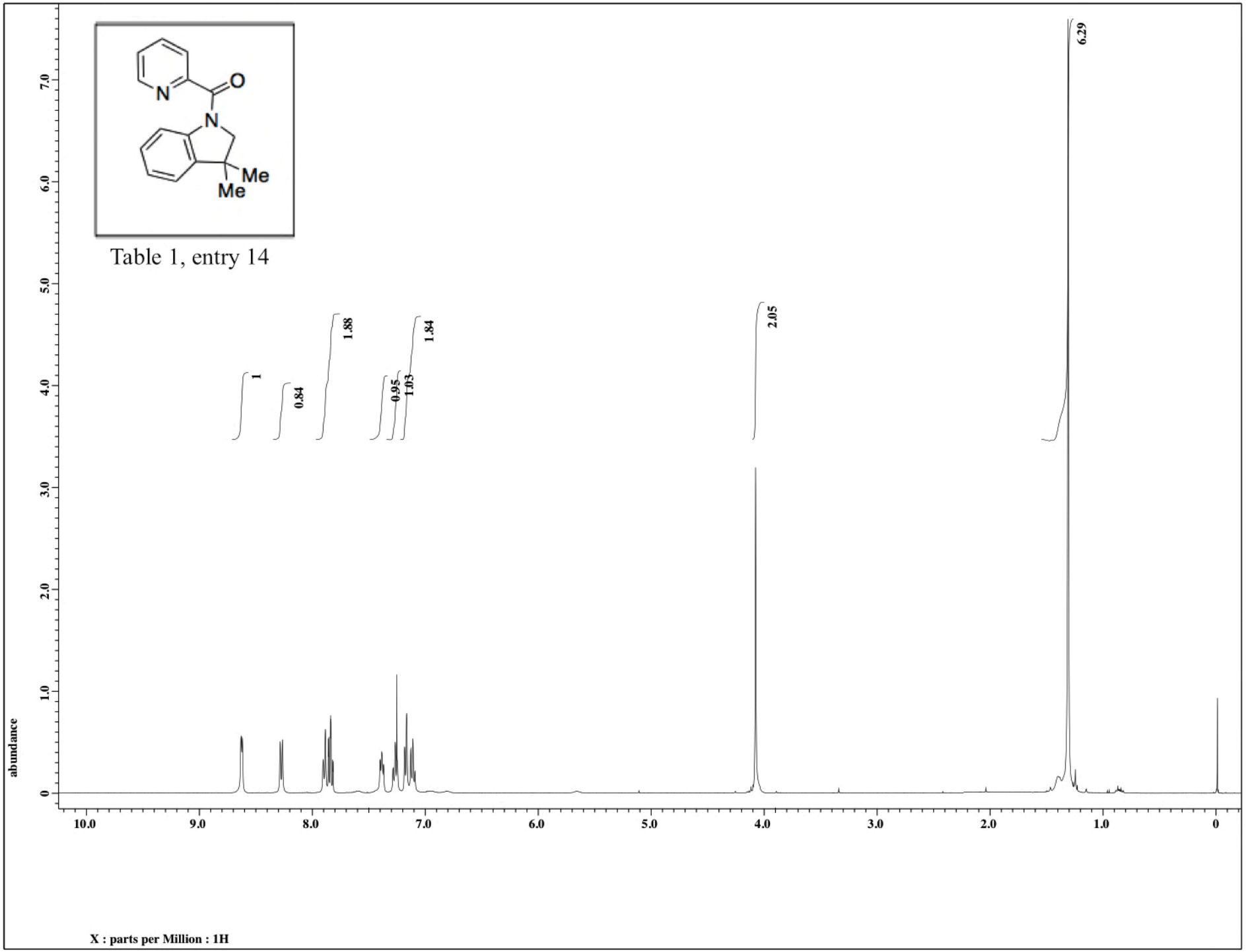
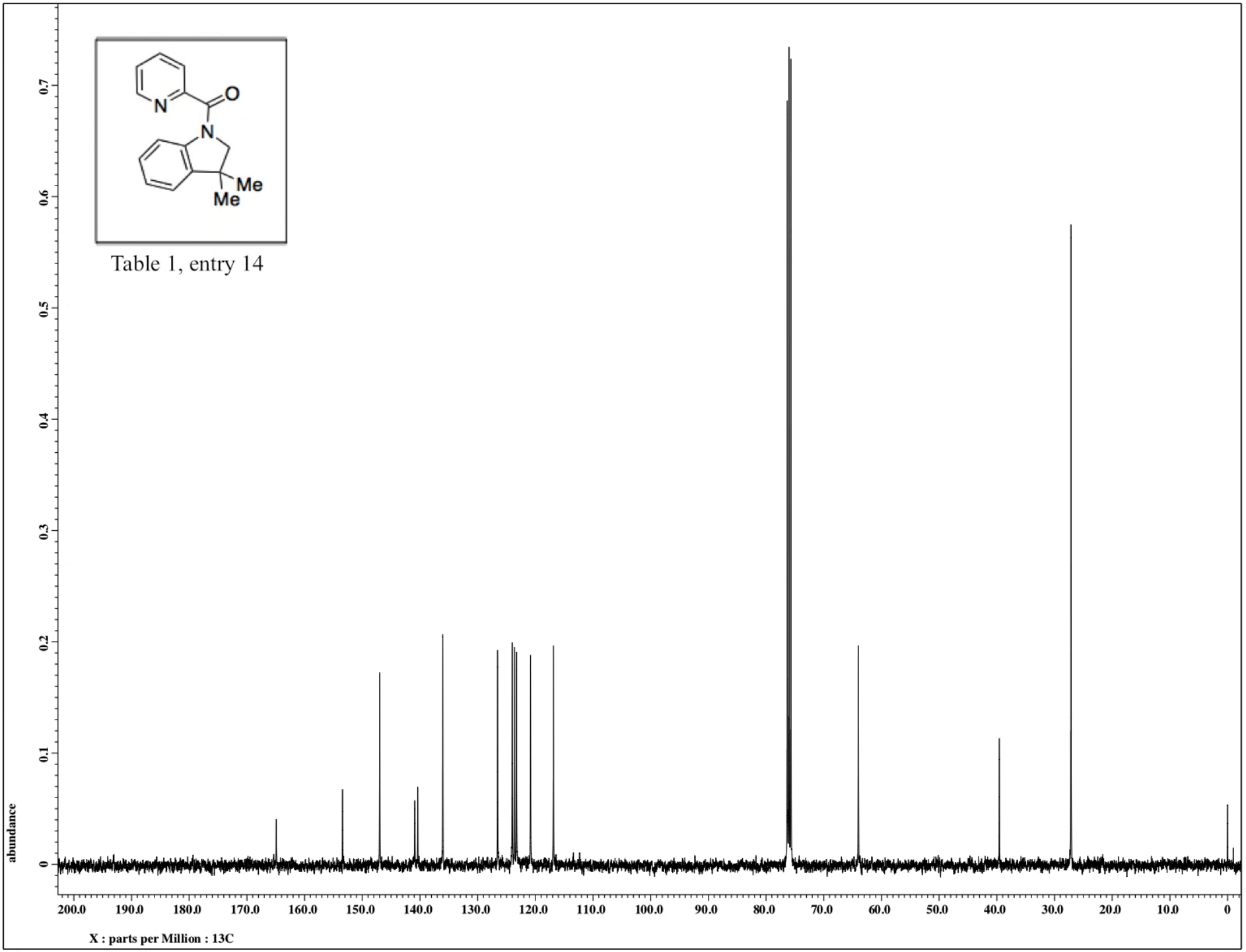
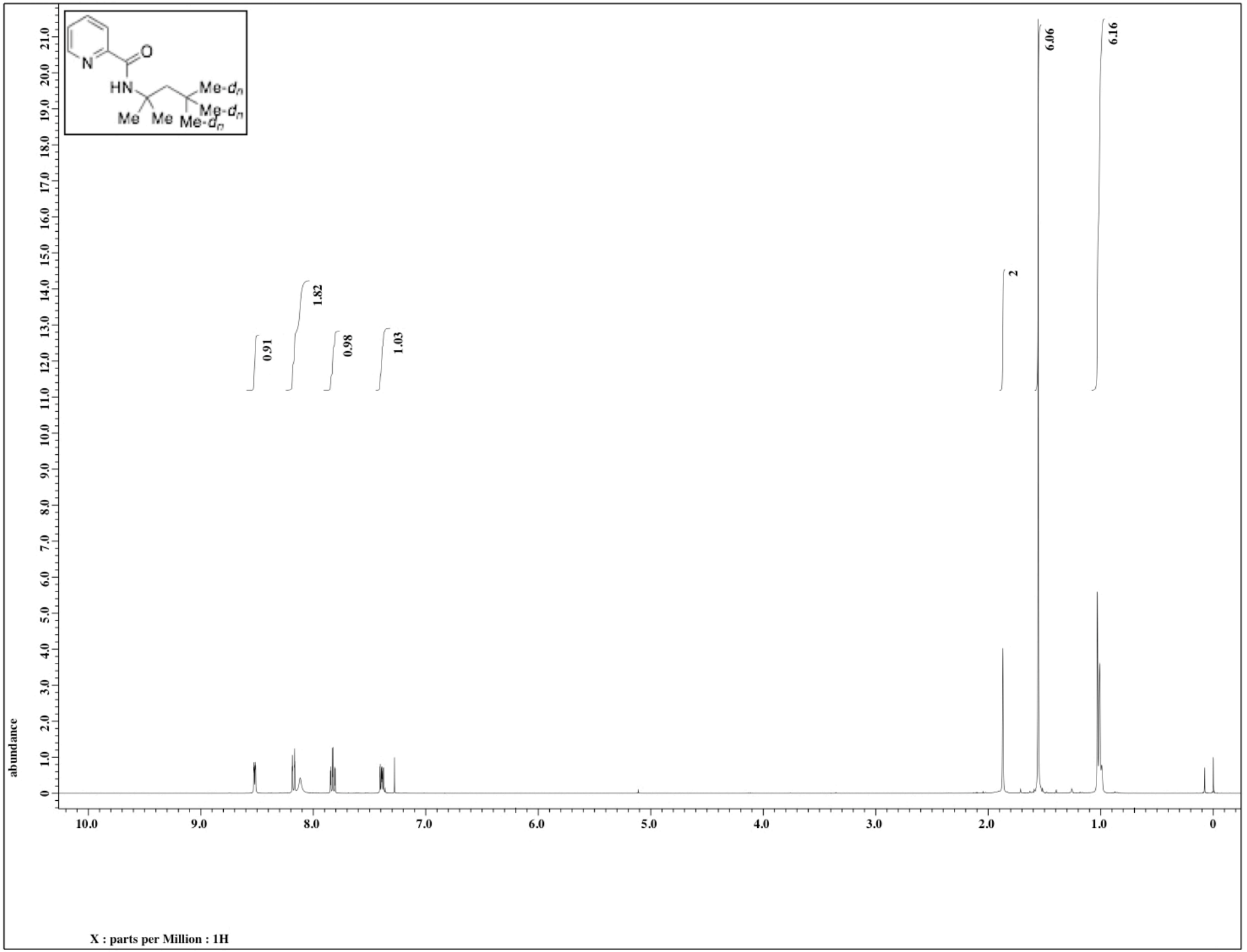


Table 1, entry 13
0.81
0.81
0.88
1.04
1.0
1.16
1.16
1.05
1.0
4.1
1.01
abundance
X : parts per Million : 1H


N
O
N
COOMe
Table 1, entry 13
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
N
Me
Me
Table 1, entry 14
1
0.84
1.88
0.95
1.03
1.84
2.05
6.29
abundance
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
X : parts per Million : 1H


N
O
N
Me
Me
Table 1, entry 14
abundance
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
X : parts per Million : 13C


N
O
HN
Me
Me
Me-d_n
Me-d_n
Me-d_n
0.91
1.82
0.98
1.03
2
6.06
6.16
abundance
X : parts per Million : 1H