

Pd-Catalyzed Cross-Coupling Reactions of Amides and Aryl Mesylates

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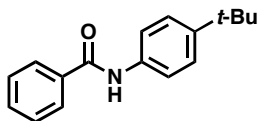
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General Reagent Information. All reactions were set up in the air and carried out under an atmosphere of argon. Flash chromatography was performed using a) silica gel from American International Chemical or b) a Biotage SP4 instrument with prepacked silica cartridges. The *tert*-butanol, toluene, 1,4-dioxane, DMF, and DME were purchased from Aldrich Chemical Co. in Sure-Seal bottles and used as received. Pd(OAc)₂ was a gift from BASF. Amides were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics, or TCI America and were used as purchased without further purification. Aryl mesylates were synthesized using literature procedures.¹ Deionized water was degassed by brief (30 sec) sonication under vacuum and then evacuated and backfilled with argon (this procedure was repeated three times). Anhydrous cesium carbonate was a gift from Chemetall and the anhydrous tribasic potassium phosphate, as well as the potassium carbonate were purchased from Fluka Chemical Co. The bases were stored in a nitrogen-filled glovebox and removed in small quantities and stored on the bench for up to two weeks. Ligands **1**² and **2**³ were synthesized using literature procedures and ligands **3**, **4**, and **5** were purchased from Strem Chemicals Inc.

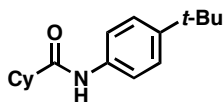
General Analytical Information. Yields refer to isolated yields of compounds greater than 95% purity as determined by gas chromatography (GC) and ¹H NMR. All yields reported are for an average of two experiments. All compounds were characterized by ¹H NMR, ¹³C NMR, IR spectroscopy, melting point, and in most cases, elemental analysis. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument. All ¹H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the solvent residual peak. All ¹³C NMR spectra are reported in ppm

relative to solvent residual peak and were obtained with ^1H decoupling. All IR spectra were made on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

General procedure. An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon screwcap septum, was charged with $\text{Pd}(\text{OAc})_2$ (1 mol%) and **1** (2.2 mol%). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and *t*-BuOH (2.0 mL) and degassed H_2O (8 mol%) were added via syringe. After addition of the water, the solution was heated to 110 °C for 2 min. A second oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with the amide (1.2 mmol) and Cs_2CO_3 (1.4 mmol) (aryl mesylates that were solids at room temperature were added with the base). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl mesylate (0.50 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second *via* cannula. The solution was heated to 110 °C until the aryl mesylate was completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate and washed with water. The layers were separated and the organic layer was dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel.

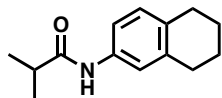


***N*-(4-*tert*-Butylphenyl)benzamide**⁴ (Table 2, entry 1) Following the general procedure, a mixture of 4-*tert*-butylphenyl methanesulfonate (114 mg, 0.50 mmol), benzamide (73 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 1 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25+M; 5-50% EtOAc/hexanes) to provide the title compound as a white solid (116 mg, 91%). Mp = 144 – 146 °C (lit. 140 – 142 °C)⁴. ¹H NMR (300 MHz, CDCl₃) δ: 7.97 (br s, 1H), 7.85 (dt, *J* = 6.9, 1.5 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.53-7.50 (m, 1H), 7.46 (d, *J* = 7.5 Hz, 2H), 7.38 (dt, *J* = 8.7, 2.1 Hz, 2H), 1.33 (9H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 165.9, 147.7, 135.4, 135.2, 131.9, 128.9, 127.1, 126.0, 120.2, 34.5, 31.5 ppm. IR (neat, cm⁻¹): 3279, 3058, 2962, 2867, 1648, 1602, 1520, 1324, 831, 708. Anal. Calcd. for C₁₇H₁₉NO: C, 80.60; H, 7.56. Found: C, 80.59; H, 7.62.

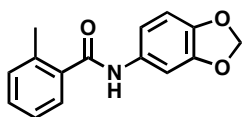


***N*-(4-*tert*-Butylphenyl)cyclohexanecarboxamide** (Table 2, entry 2) Following the general procedure, a mixture of 4-*tert*-butylphenyl methanesulfonate (114 mg, 0.50 mmol), cyclohexanecarboxamide (76 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 1 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 + M, 15-50% EtOAc in hexanes) to provide the title compound as a white solid (123 mg, 95%). Mp = 188 – 190 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.47 (m, 3H), 7.31 (d, *J* = 8.7 Hz, 2H), 2.23 (tt, *J* = 11.7, 3.6 Hz, 1H), 1.93 (d, *J* = 12.6 Hz, 2H), 1.83-1.79 (m, 2H), 1.70-1.67 (m, 1H), 1.53 (quarternary d, *J* = 12.3, 2.7 Hz, 2H), 1.29 (s, 9H), 1.26-1.23 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 174.6, 147.0, 135.7, 125.8, 119.7, 46.5, 34.4, 31.4, 29.8, 25.8 ppm. IR (neat, cm⁻¹): 3301, 2929,

2856, 1661, 1603, 1537, 1518, 1407, 836, 554. Anal. Calcd. for C₁₇H₂₅NO: C, 78.72; H, 9.71. Found: C, 78.57; H, 9.80.

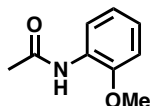


N-(5,6,7,8-Tetrahydronaphthalen-2-yl)isobutyramide (Table 2, entry 3) Following the general procedure, a mixture of 5,6,7,8-tetrahydronaphthalen-2-yl methanesulfonate (113 mg, 0.50 mmol), isobutyramide (52 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol) and *t*-BuOH (2.0 mL) was heated to 110 °C for 2 h. The crude product was purified *via* flash chromatography on silica gel (20% EtOAc in hexanes) to provide the title compound as a white solid (105 mg, 97%). Mp = 101 – 103 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.32 – 7.27 (m, 2H), 7.18 (d, *J* = 8.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 2.72 – 2.71 (m, 4H), 2.49 (septet, *J* = 6.9 Hz, 1H), 1.78 – 1.76 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 6H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 175.3, 137.8, 135.5, 133.2, 129.5, 120.5, 117.5, 36.7, 29.6, 29.0, 23.3, 23.2, 19.8 ppm. IR (neat, cm⁻¹): 3296, 2967, 2930, 1660, 1596, 1540, 1504, 1418, 1214, 828. Anal. Calcd. for C₁₄H₁₉NO: C, 77.38; H, 8.81. Found: C, 77.26; H, 8.91.

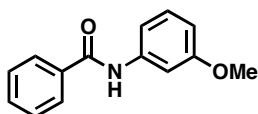


N-(Benzo[d][1,3]dioxol-5-yl)-2-methylbenzamide (Table 2, entry 4) Following the general procedure, a mixture of benzo[d][1,3]dioxol-5-yl methanesulfonate (108 mg, 0.50 mmol), *o*-toluamide (81 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 2 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 g, 20-60% EtOAc in hexanes) to provide the title compound as a white solid (119 mg, 93%). Mp = 146 – 148 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.55 (br s, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.25 – 7.19 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 5.96 (s, 2H), 2.47 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 168.1, 148.0, 144.5, 136.5, 136.4, 132.3, 131.3, 130.3, 126.7, 126.0, 113.2, 108.2, 102.9,

101.4, 19.9 ppm. IR (neat, cm^{-1}): 3286, 2889, 1650, 1540, 1502, 1448, 1345, 1245, 1193, 1039, 938, 803. Anal. Calcd. for $\text{C}_{15}\text{H}_{13}\text{NO}_3$: C, 70.58; H, 5.13. Found: C, 70.37; H, 5.11.

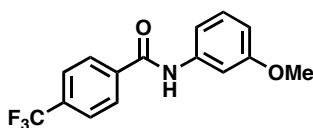


***N*-(2-Methoxyphenyl)acetamide⁵** (Table 2, entry 5) Following the general procedure, a mixture of 2-methoxyphenyl methanesulfonate (101 mg, 0.50 mmol), acetamide (35 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 4 h. The crude product was purified *via* flash chromatography on silica gel (40% EtOAc in hexanes) to provide the title compound as a white solid (76 mg, 92%). Mp = 88 – 90 $^\circ\text{C}$ (lit. 87 – 88 $^\circ\text{C}$)⁵. ^1H NMR (300 MHz, CDCl_3) δ : 8.36 (d, J = 7.5 Hz, 1H), 7.77 (br s, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 8.1 Hz, 1H), 3.87 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 168.3, 147.7, 127.8, 123.7, 121.2, 119.8, 109.9, 55.7, 25.1 ppm. IR (neat, cm^{-1}): 3248, 3062, 1658, 1596, 1544, 1496, 1368, 1252, 1025, 751, 524. Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{NO}_2$: C, 65.44; H, 6.71. Found: C, 65.29; H, 6.82.

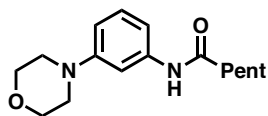


***N*-(3-Methoxyphenyl)benzamide⁶** (Table 2, entry 6) Following the general procedure, a mixture of 3-methoxyphenyl methanesulfonate (101 mg, 0.50 mmol), benzamide (73 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 20 min. The crude product was purified *via* flash chromatography on silica gel (20% EtOAc in hexanes) to provide the title compound as a white solid (113 mg, 99%). Mp = 112 – 114 $^\circ\text{C}$ (lit. 116 $^\circ\text{C}$)⁶. ^1H NMR (300 MHz, CDCl_3) δ : 8.06 (br s, 1H), 7.85 (d, J = 6.9 Hz, 2H), 7.53 (tt, J = 6.9, 1.5 Hz, 1H), 7.47-7.42 (m, 3H), 7.25 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1

Hz, 1H), 6.71 (ddd, $J = 8.4, 2.7, 1.2$ Hz, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 166.0, 160.3, 139.3, 135.0, 131.9, 129.8, 128.8, 127.1, 112.4, 110.6, 105.9, 55.4 ppm. IR (neat, cm^{-1}): 3304, 1563, 1608, 1540, 1492, 1452, 1420, 1276, 1160, 1048, 775, 690. Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77. Found: C, 73.69; H, 5.85.

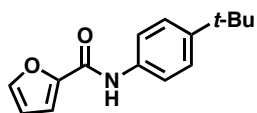


***N*-(3-Methoxyphenyl)-4-(trifluoromethyl)benzamide** (Table 2, entry 7) Following the general procedure, a mixture of 3-methoxyphenyl methanesulfonate (101 mg, 0.50 mmol), 4-trifluoromethylbenzamide (113 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 14 min. The crude product was purified *via* flash chromatography on silica gel (20% EtOAc in hexanes) to provide the title compound as a white solid (135 mg, 91%). Mp = 134 – 136 $^\circ\text{C}$. ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 10.5 (br s, 1H), 8.14 (d, $J = 8.1$ Hz, 2H), 7.91 (d, $J = 8.1$ Hz, 2H), 7.47 (t, $J = 2.1$ Hz, 1H), 7.38 (d, $J = 9.0$ Hz, 1H), 7.27 (t, $J = 8.1$ Hz, 1H), 6.71 (dd, $J = 8.1, 2.4$ Hz, 1H), 3.76 (s, 3H) ppm. ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 164.5, 159.5, 140.1, 138.8 (d, $J = 1.2$ Hz), 131.4 (quartet, $J = 31.7$ Hz), 129.5, 128.6, 125.8, 125.4 (quartet, $J = 3.8$ Hz), 122.2, 112.6, 109.5, 106.1, 55.0 ppm (complexity is due to the CF_3 -group). IR (neat, cm^{-1}): 3320, 1654, 1611, 1598, 1493, 1427, 1283, 1161, 1110, 857, 773, 680. Anal. Calcd. for $\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_2$: C, 61.02; H, 4.10. Found: C, 61.14; H, 4.12.

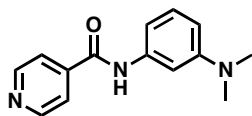


***N*-(3-Morpholinophenyl)hexanamide** (Table 2, entry 8) Following the general procedure, a mixture of 3-morpholinophenyl methanesulfonate (129 mg, 0.50 mmol), capronamide (69 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated

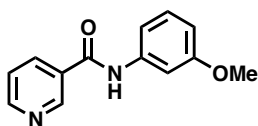
to 110 °C for 4 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 g, 30-80% EtOAc in hexanes) to provide the title compound as a white solid (120 mg, 87%). Mp = 81 – 84 °C. ¹H NMR (300 MHz, CDCl₃) δ: 7.43 – 7.41 (m, 2H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 6.6 Hz, 1H), 3.82 (t, *J* = 4.8 Hz, 4H), 3.14 (t, *J* = 4.2 Hz, 4H), 2.33 (t, *J* = 7.5 Hz, 2H), 1.71 (quintet, *J* = 7.2 Hz, 2H), 1.35 – 1.33 (m, 4H), 0.92 – 0.87 (m, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 171.8, 152.1, 139.2, 129.5, 111.4, 111.0, 107.2, 67.0, 49.2, 37.9, 31.5, 25.4, 22.6, 14.1 ppm. IR (neat, cm⁻¹): 3303, 2958, 2857, 1661, 1560, 1548, 1495, 1448, 1246, 1123, 997, 775, 690.



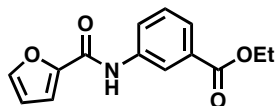
***N*-(4-*tert*-Butylphenyl)furan-2-carboxamide** (Table 3, entry 1) Following the general procedure, a mixture of 4-*tert*-butylphenyl methanesulfonate (114 mg, 0.50 mmol), 2-furamide (67 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 4 h. The crude product was purified *via* flash chromatography on silica gel (25% EtOAc in hexanes) to provide the title compound as a white solid (120 mg, 99%). Mp = 150 – 153 °C. ¹H NMR (300 MHz, CDCl₃) δ: 8.15 (br s, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.48 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 3.6 Hz, 1H), 6.53 (m, 1H), 1.32 (s, 9H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 156.2, 148.0, 147.6, 144.2, 134.8, 126.0, 119.8, 115.19, 115.15, 112.7, 112.6, 34.5, 31.4 ppm (complexity is due to the detection of rotamers). IR (neat, cm⁻¹): 3273, 2962, 1655, 1600, 1529, 1474, 1325, 831, 776, 555. Anal. Calcd. for C₁₅H₁₇NO₂: C, 74.05; H, 7.04. Found: C, 73.98; H, 7.13.



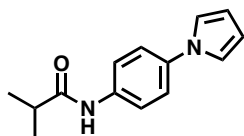
***N*-(3-(Dimethylamino)phenyl)isonicotinamide** (Table 3, entry 2) Following the general procedure, a mixture of 3-(dimethylamino)phenyl methanesulfonate (108 mg, 0.50 mmol), isonicotinamide (73 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 1 h. The crude product was purified *via* flash chromatography on silica gel (80-100% EtOAc in hexanes) to provide the title compound as a pale yellow solid (115 mg, 95%). Mp = 134 – 136 °C (lit. 136 °C)⁷. ¹H NMR (300 MHz, (CD₃)₂SO) δ: 10.3 (s, 1H), 8.78 (d, *J* = 6.0 Hz, 2H), 7.85 (d, *J* = 5.7 Hz, 2H), 7.19 (s, 1H), 7.15 (d, *J* = 5.1 Hz, 2H), 6.54 – 6.50 (m, 1H), 2.90 (s, 6H) ppm. ¹³C NMR (75 MHz, (CD₃)₂SO) δ: 163.8, 150.8, 150.3, 142.2, 139.4, 129.1, 121.6, 108.7, 108.6, 104.5, 40.1 ppm. IR (neat, cm⁻¹): 3291, 1655, 1611, 1584, 1555, 1499, 1428, 1317, 1001, 841, 769, 688.



***N*-(3-Methoxyphenyl)nicotinamide** (Table 3, entry 3) Following the general procedure, a mixture of 3-methoxyphenyl methanesulfonate (101 mg, 0.50 mmol), nicotinamide (73 mg, 0.60 mmol), Cs₂CO₃ (228 mg, 0.70 mmol), Pd(OAc)₂ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H₂O (0.7 μL, 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 4 h. The crude product was purified *via* flash chromatography on silica gel (75% EtOAc in hexanes) to provide the title compound as a white solid (101 mg, 88%). Mp = 88 – 90 °C. ¹H NMR (300 MHz, (CD₃)₂SO) δ: 10.4 (br s, 1H), 9.10 (d, *J* = 2.4 Hz, 1H), 8.76 (d, *J* = 4.8 Hz, 1H), 8.30-8.27 (m, 1H), 7.57 (dd, *J* = 8.1, 5.1 Hz, 1H), 7.47 (t, *J* = 1.8 Hz, 1H), 7.36 (d, 7.8 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 6.71 (dd, *J* = 8.1, 2.7 Hz, 1H), 3.76 (s, 3H) ppm. ¹³C NMR (75 MHz, (CD₃)₂SO) δ: 164.1, 159.5, 152.2, 148.7, 140.1, 135.5, 130.6, 129.5, 123.5, 112.5, 109.5, 106.0, 55.0 ppm. IR (neat, cm⁻¹): 3296, 1656, 1610, 1546, 1492, 1418, 1281, 1162, 1048, 705. Anal. Calcd. for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.30. Found: C, 68.32; H, 5.27.

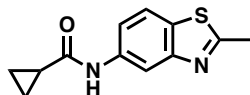


Ethyl 3-(furan-2-carboxamido)benzoate (Table 3, entry 4) Following the general procedure, a mixture of ethyl 3-(methylsulfonyloxy)benzoate (122 mg, 0.50 mmol), 2-furamide (67 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 45 min. The crude product was purified *via* flash chromatography on silica gel (EtOAc in hexanes in a gradient from 20-50%) to provide the title compound as a white-tan sticky solid (100 mg, 74%). ^1H NMR (300 MHz, CDCl_3) δ : 8.17 (br s, 1H), 8.13 (s, 1H), 8.09 – 8.06 (m, 1H), 7.84 – 7.81 (m, 1H), 7.54 – 7.53 (m, 1H), 7.45 (t, J = 8.1 Hz, 1H), 7.27 – 7.26 (m, 1H), 6.58 (ddd, J = 3.6, 1.8, 0.9 Hz, 1H), 4.39 (quartet, J = 6.9 Hz, 2H), 1.40 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 166.3, 156.3, 147.6, 144.5, 137.7, 131.4, 129.3, 125.6, 124.4, 120.8, 115.7 (d, J = 3.1 Hz), 112.8 (d, J = 3.4 Hz), 61.3, 14.4 ppm. IR (neat, cm^{-1}): 3319, 2982, 1718, 1667, 1583, 1543, 1488, 1265, 1224, 1013, 756, 594.



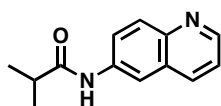
N-(4-(1H-Pyrrol-1-yl)phenyl)isobutyramide (Table 3, entry 5) Following the general procedure, a mixture of 4-(1H-pyrrol-1-yl)phenyl methanesulfonate (119 mg, 0.50 mmol), isobutyramide (52 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 °C for 4 h. The crude product was dissolved in EtOAc and evaporated on to a small amount of silica gel and purified *via* flash chromatography on silica gel (10-30% EtOAc in hexanes) to provide the title compound as a white solid (108 mg, 94%). Mp = 199 – 201 °C. ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 9.93 (br s, 1H), 7.70 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.29 (t, J = 1.8 Hz, 2H), 6.23 (t, J = 2.1 Hz, 2H), 2.60 (septet, J = 6.9 Hz, 1H), 1.11 (d, J = 6.9 Hz, 6H) ppm. ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$) δ :

175.2, 136.9, 135.2, 120.1, 119.6, 118.9, 110.2, 35.0, 19.6 ppm. IR (neat, cm^{-1}): 3265, 2968, 1653, 1605, 1525, 1333, 1262, 1101, 822, 722.



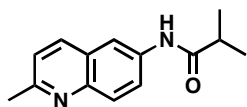
***N*-(2-Methylbenzo[*d*]thiazol-5-yl)cyclopropanecarboxamide** (Table 3, entry 6)

Following the general procedure, a mixture of 2-methylbenzo[*d*]thiazol-5-yl methanesulfonate (122 mg, 0.50 mmol), cyclopropanecarboxamide (51 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 24 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 g, 60-100% EtOAc in hexanes) to provide the title compound as a white solid (25 mg, 22%). Mp = 196 – 198 $^\circ\text{C}$. ^1H NMR (300 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 10.4 (br s, 1H), 8.28 (s, 1H), 7.90 (d, J = 8.7 Hz, 1H), 7.54 (dd, J = 8.7, 1.5 Hz, 1H), 2.76 (s, 3H), 1.82 – 1.76 (m, 1H), 0.84 – 0.77 (m, 4H) ppm. ^{13}C NMR (75 MHz, $(\text{CD}_3)_2\text{SO}$) δ : 171.8, 167.8, 153.5, 137.9, 129.2, 121.8, 116.9 (d, J = 3.7 Hz), 111.7 (d, J = 6.8 Hz), 19.8, 14.7, 7.3 ppm (complexity due to detection of rotamers). IR (neat, cm^{-1}): 3290, 1661, 1579, 1524, 1466, 1417, 1385, 1222, 955, 810.



***N*-(Quinolin-6-yl)isobutyramide** (Table 3, entry 7) Following the general procedure, a mixture of quinolin-6-yl methanesulfonate (112 mg, 0.50 mmol), isobutyramide (52 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 6 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 g, 50-100% EtOAc in hexanes) to provide the title compound as a white solid (43 mg, 40%). Mp = 156 – 158 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ : 8.79 (dd, J = 4.2, 1.5 Hz, 1H), 8.45 (d, J = 2.1 Hz, 1H), 8.38 (br s, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.58 (dd, J = 9.0, 2.4 Hz, 1H), 7.34 (dd, J = 8.4, 1.2 Hz, 1H), 2.60 (septet, J = 6.9 Hz, 1H), 1.25 (d, J =

1.25 Hz, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 176.3, 149.3, 145.4, 136.4, 136.1, 129.9, 129.0, 123.5, 121.7, 116.3, 36.7, 19.7 ppm. IR (neat, cm^{-1}): 3283, 2971, 1670, 1554, 1500, 1468, 1385, 1228, 834.



N-(2-Methylquinolin-6-yl)isobutyramide (Table 3, entry 8) Following the general procedure, a mixture of 2-methylquinolin-6-yl methanesulfonate (119 mg, 0.50 mmol), isobutyramide (52 mg, 0.60 mmol), Cs_2CO_3 (228 mg, 0.70 mmol), $\text{Pd}(\text{OAc})_2$ (1.1 mg, 5.0 μmol), **1** (5.3 mg, 11 μmol), H_2O (0.7 μL , 0.04 mmol), and *t*-BuOH (2.0 mL) was heated to 110 $^\circ\text{C}$ for 6 h. The crude product was purified *via* the Biotage SP4 (silica-packed 25 g, 50-100% EtOAc in hexanes) to provide the title compound as a white solid (71 mg, 62%). Mp = 175 – 178 $^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3) δ : 8.37 (d, J = 2.1 Hz, 1H), 7.93 (m, 3H), 7.51 (dd, J = 9.0, 2.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 2.70 (s, 3H), 2.57 (septet, J = 6.6 Hz, 1H), 1.26 (d, J = 6.9 Hz, 6H) ppm. ^{13}C NMR (75 MHz, CDCl_3) δ : 175.9, 158.1, 145.1, 136.2, 135.4, 129.2, 127.0, 123.2, 122.7, 116.3, 36.8, 25.3, 19.8 ppm. IR (neat, cm^{-1}): 3284, 2970, 1670, 1606, 1557, 1497, 1387, 1236, 834. Anal. Calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}$: C, 73.66; H, 7.06. Found: C, 73.63; H, 7.07.

¹ Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754.

² Fors, B. P.; Dooleweerd, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576.

³ Fors, B. P.; Watson, D. W.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552.

⁴ Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.

⁵ Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001.

⁶ Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P.; Semnes, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489.

⁷ Pushechnikov, A. O.; Krotko, D. G.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2001**, 860.

KD154A

Pulse Sequence: s2pu1

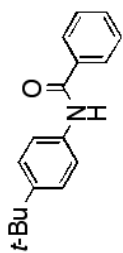
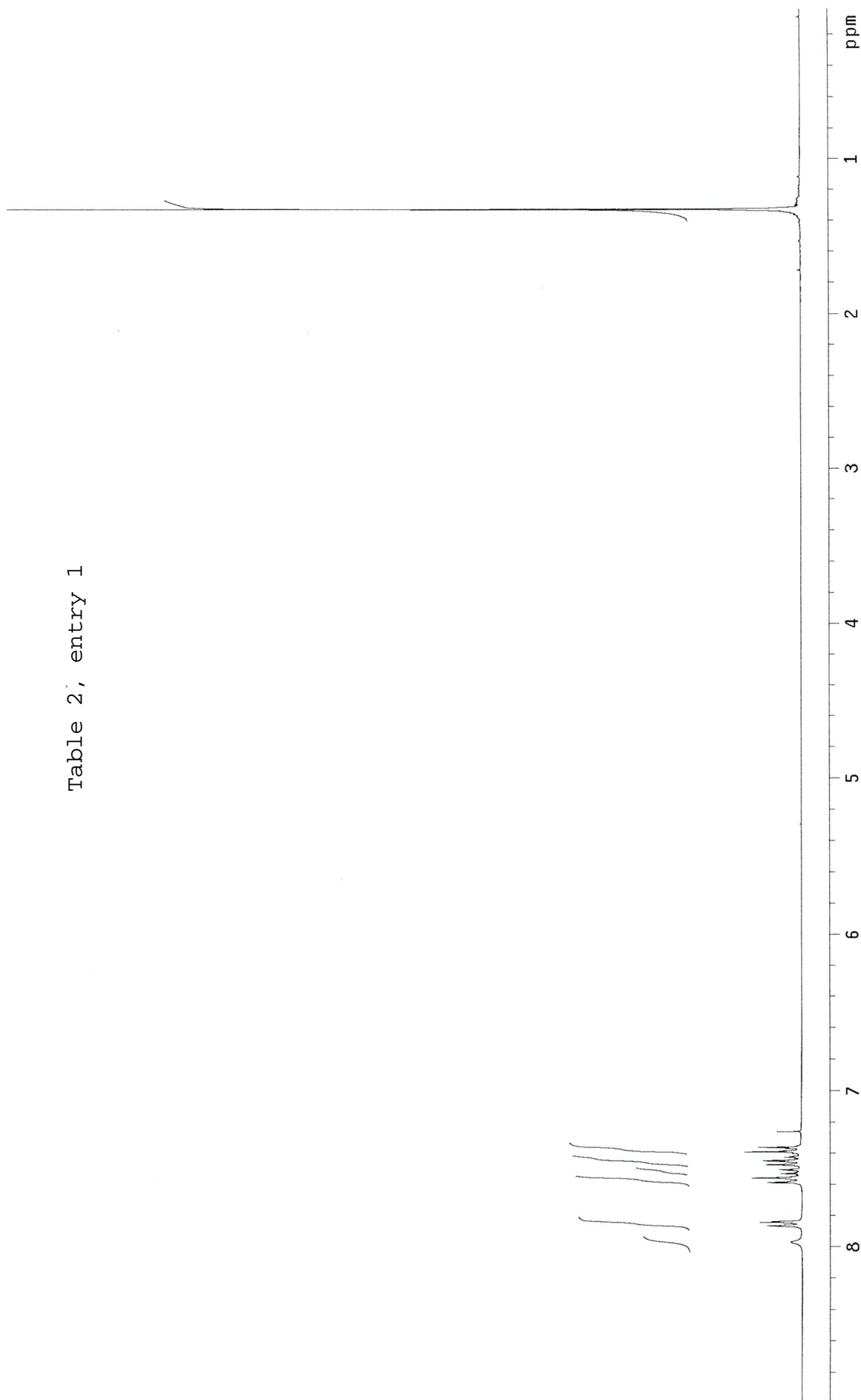


Table 2, entry 1



KD160C

Pulse Sequence: s2pu1

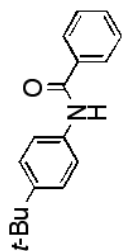
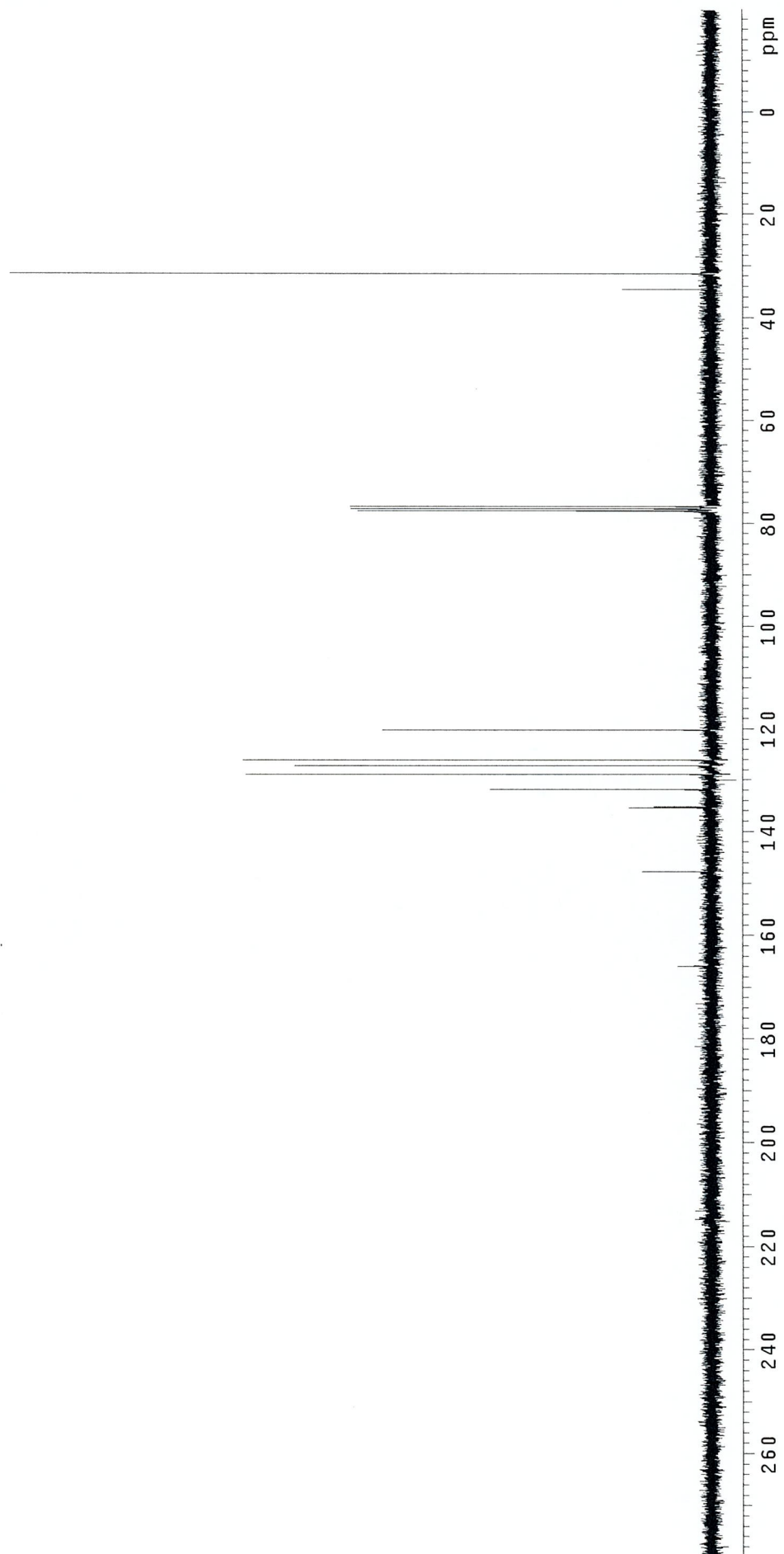


Table 2, entry 1



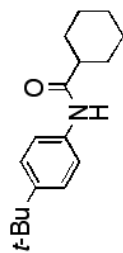
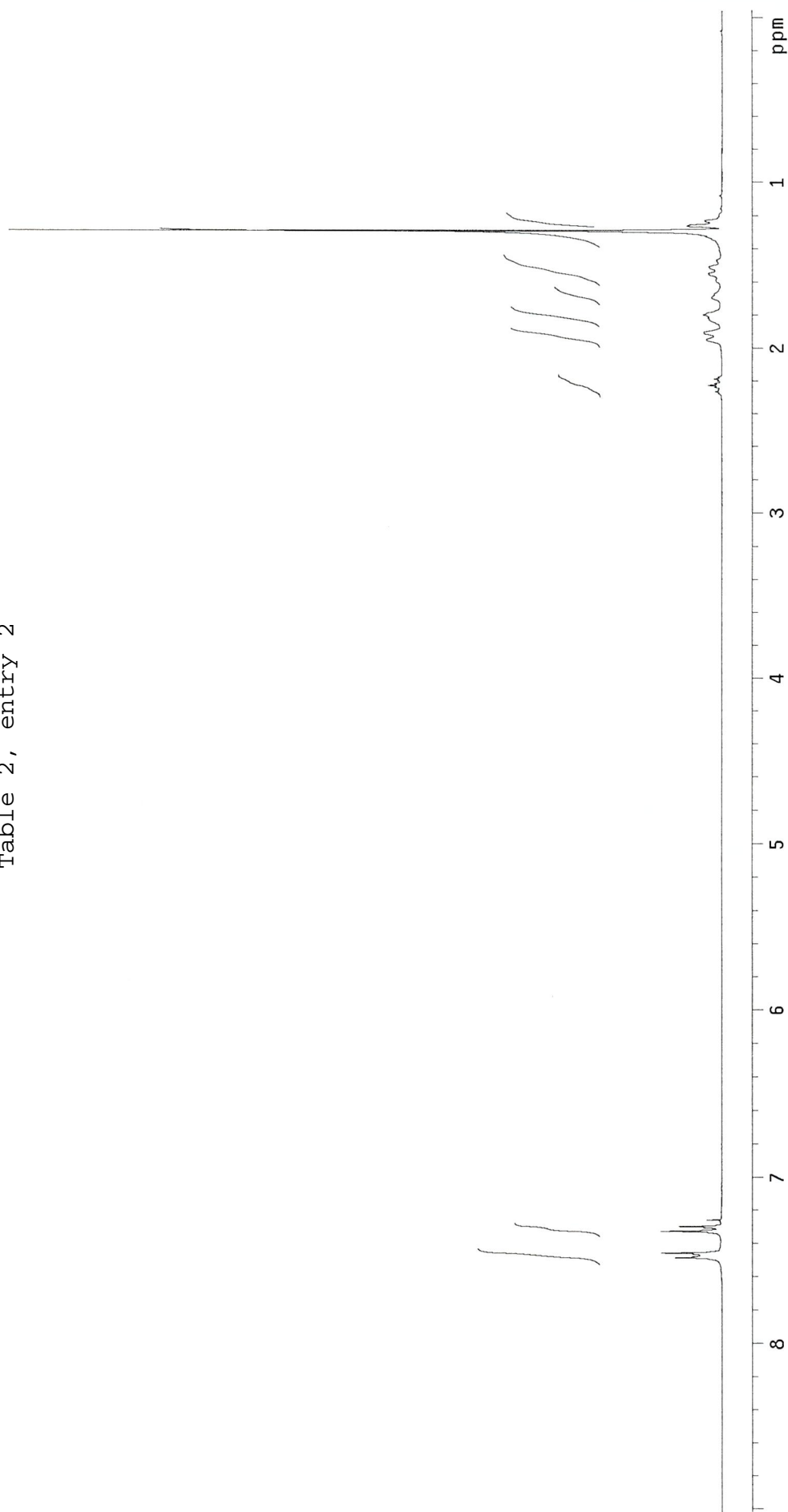


Table 2, entry 2



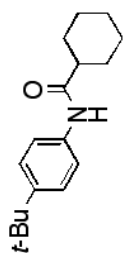
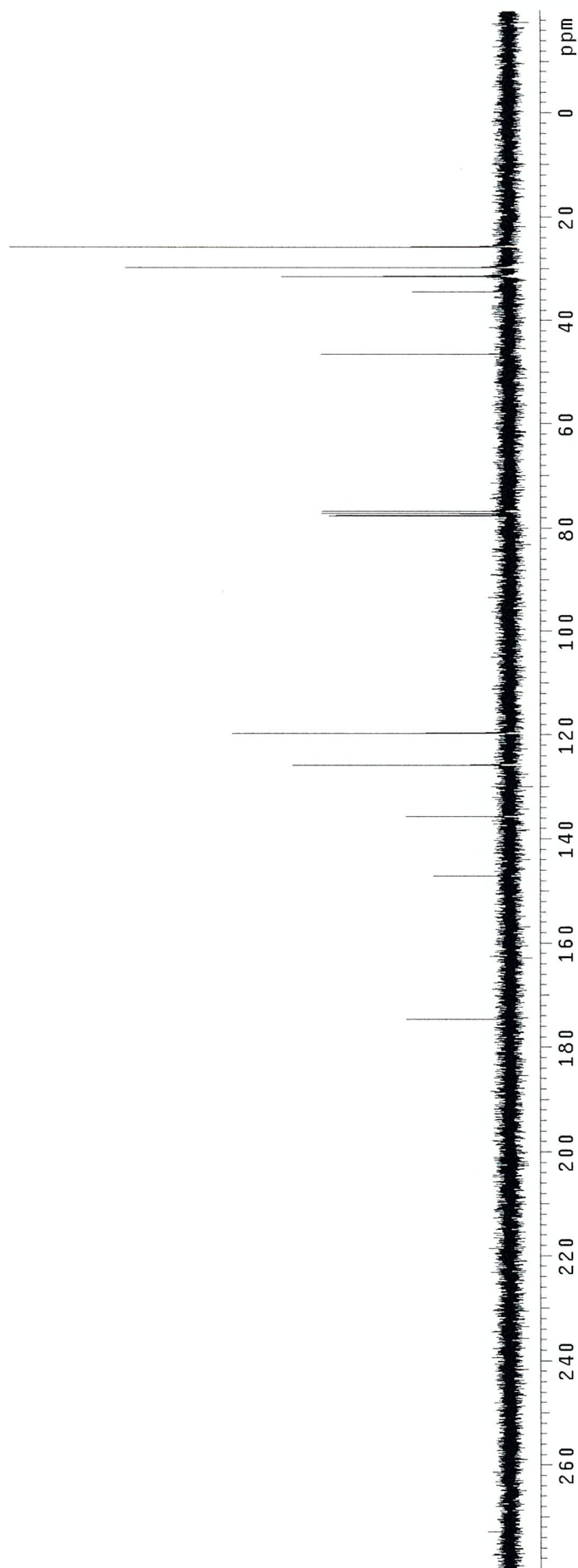


Table 2, entry 2



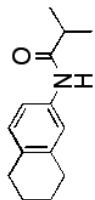
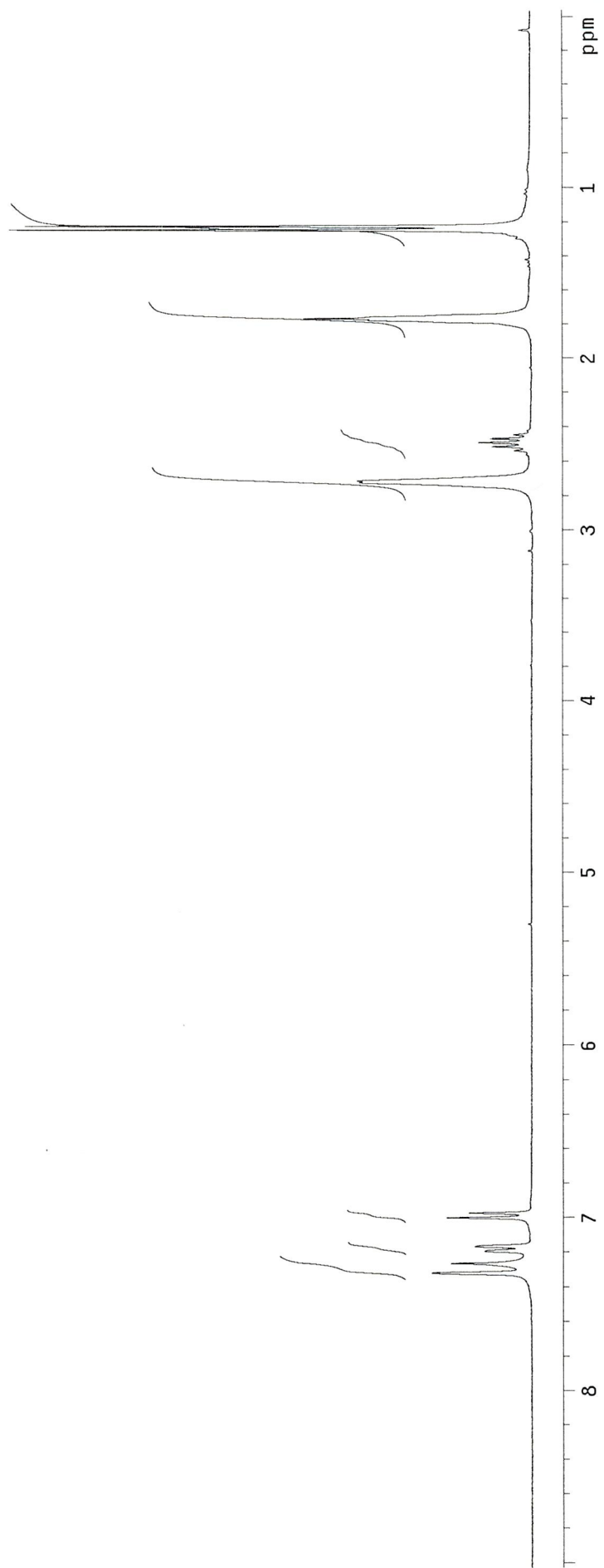


Table 2, entry 3



KD221

Pulse Sequence: s2pu1

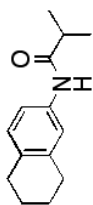
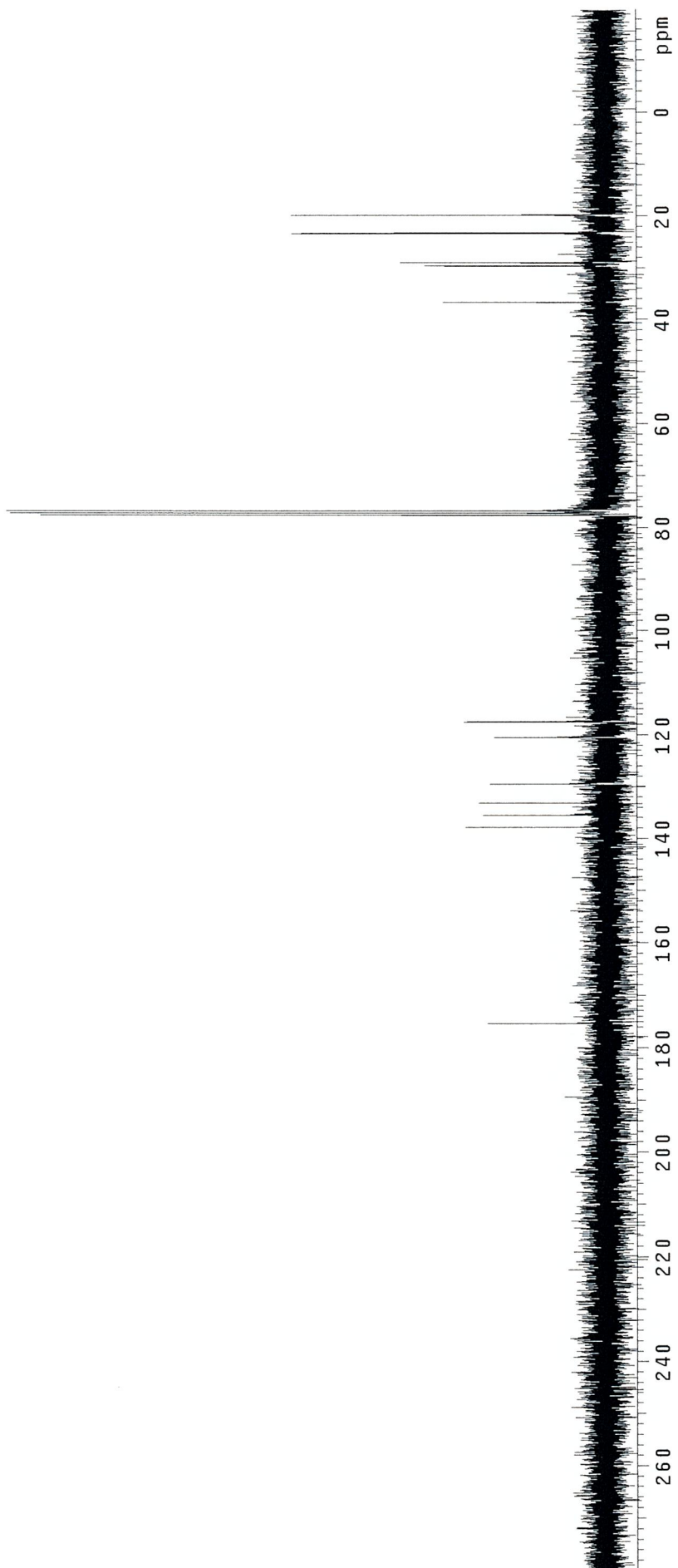


Table 2, entry 3



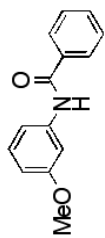
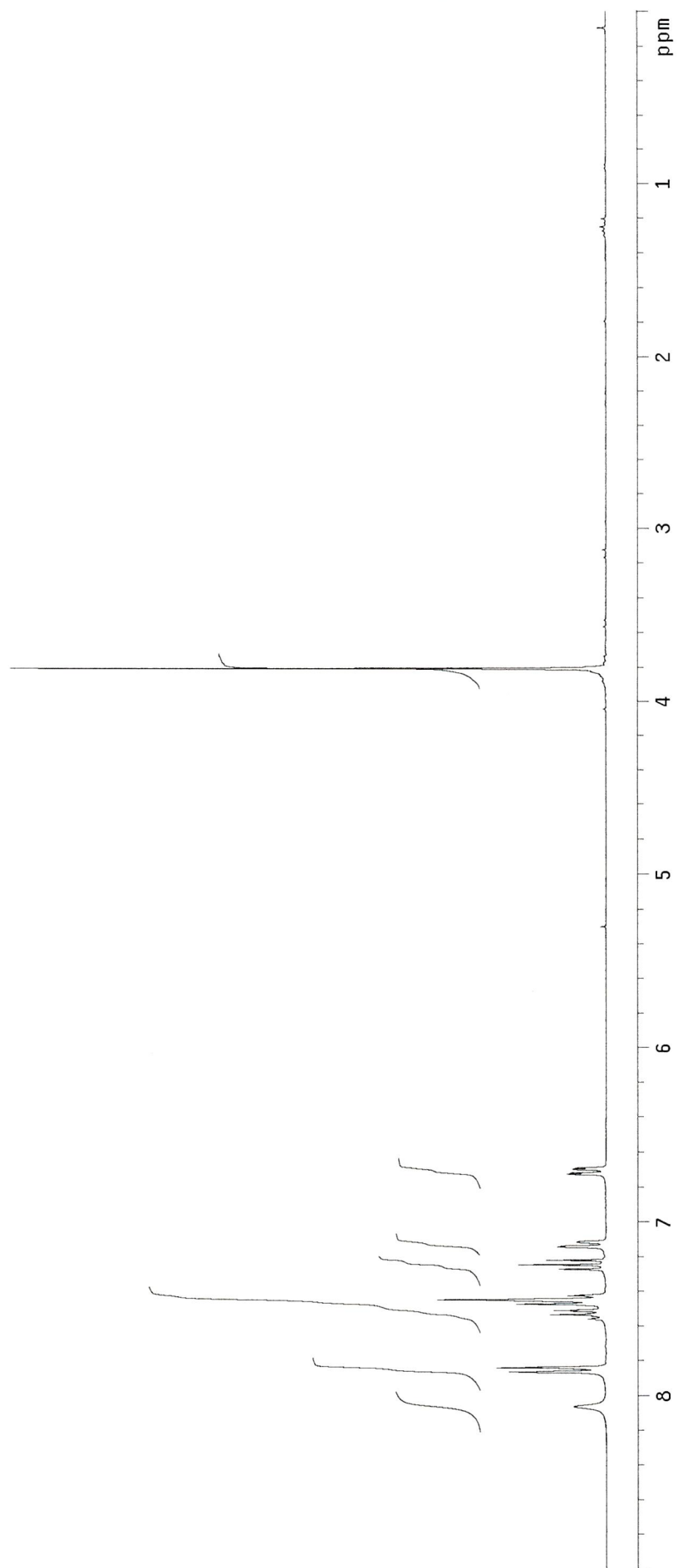


Table 2, entry 6



KD191

Pulse Sequence: s2pul

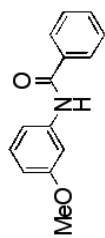
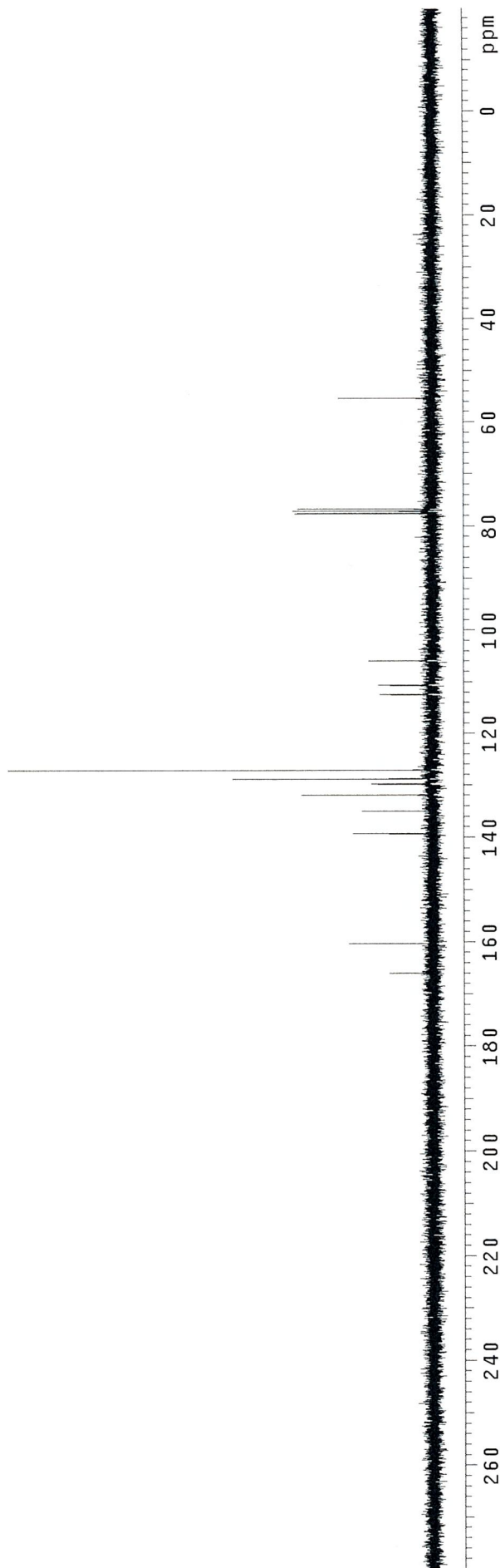


Table 2, entry 6



KD175

Pulse Sequence: s2pu1

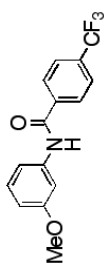
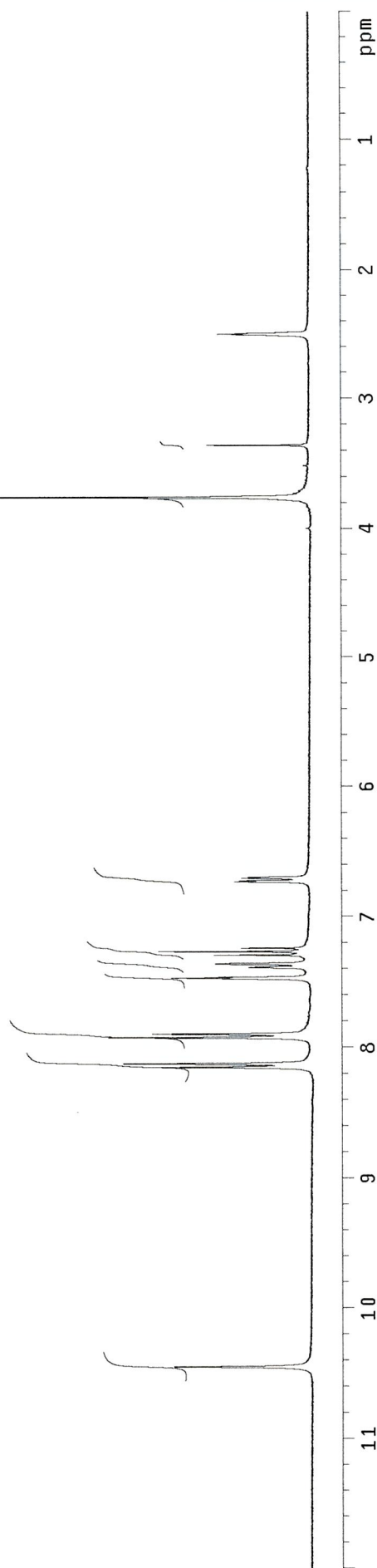


Table 2, entry 7



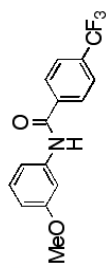
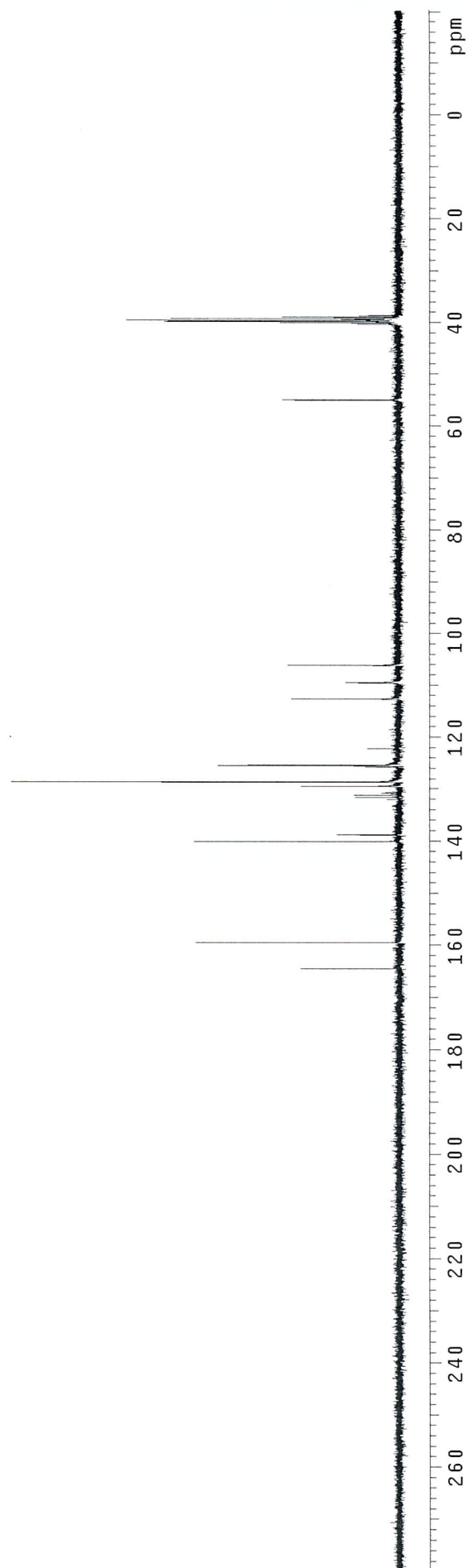


Table 2, entry 7



KD299B

Pulse Sequence: s2pu1

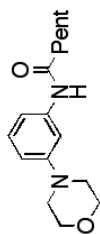
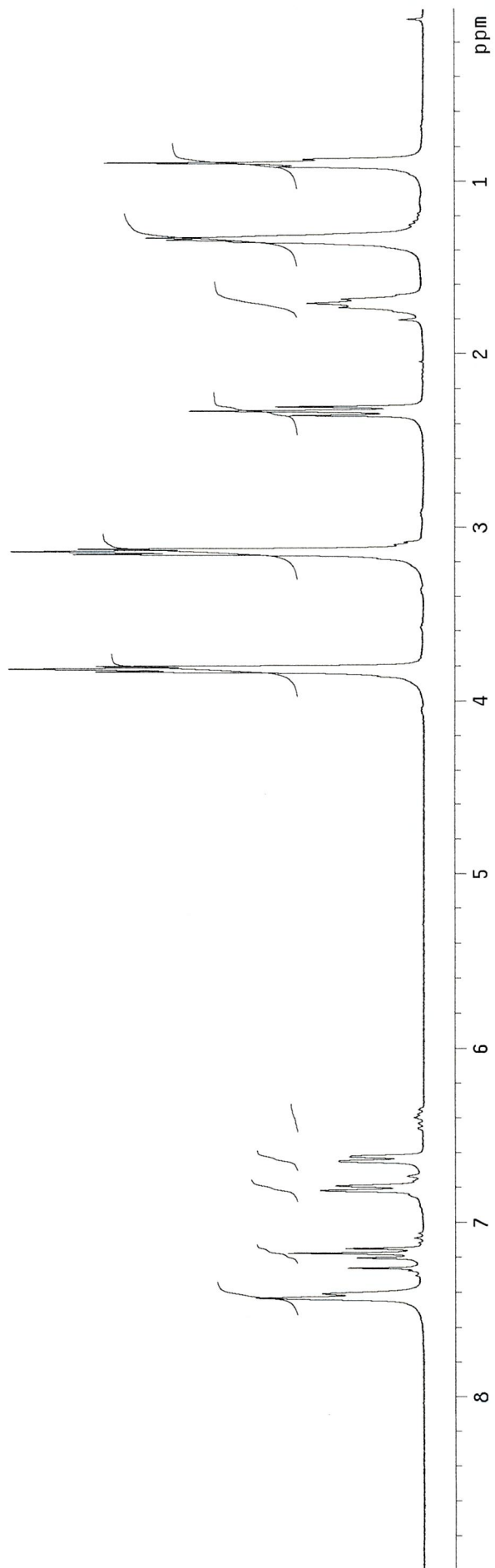


Table 2, entry 8



Pulse Sequence: s2pul

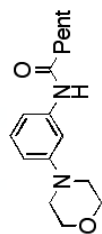
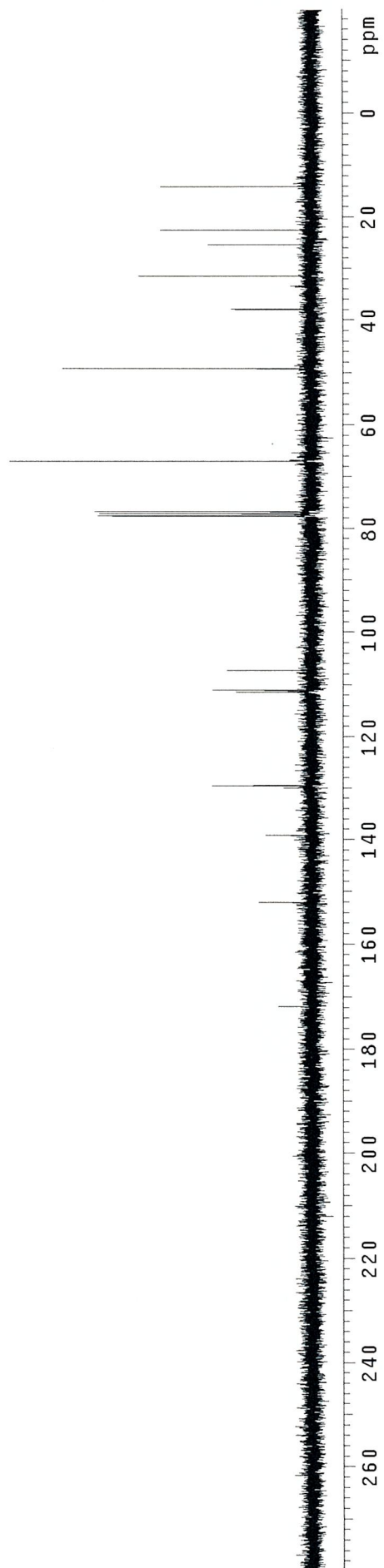


Table 2, entry 8



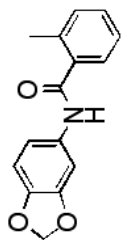
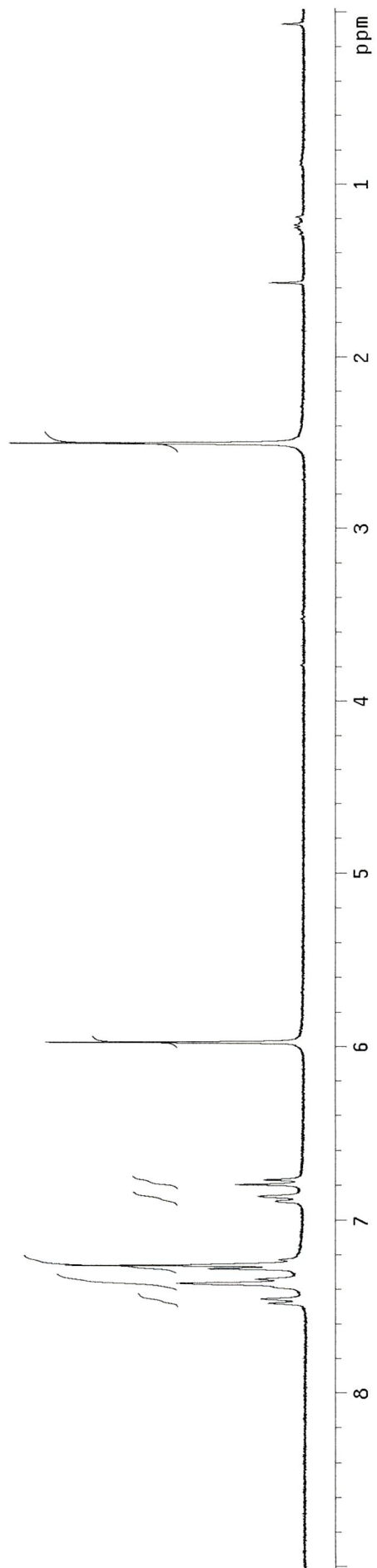


Table 2, entry 4



KD300A

Pulse Sequence: s2pu1

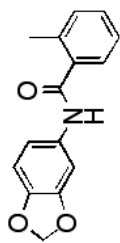
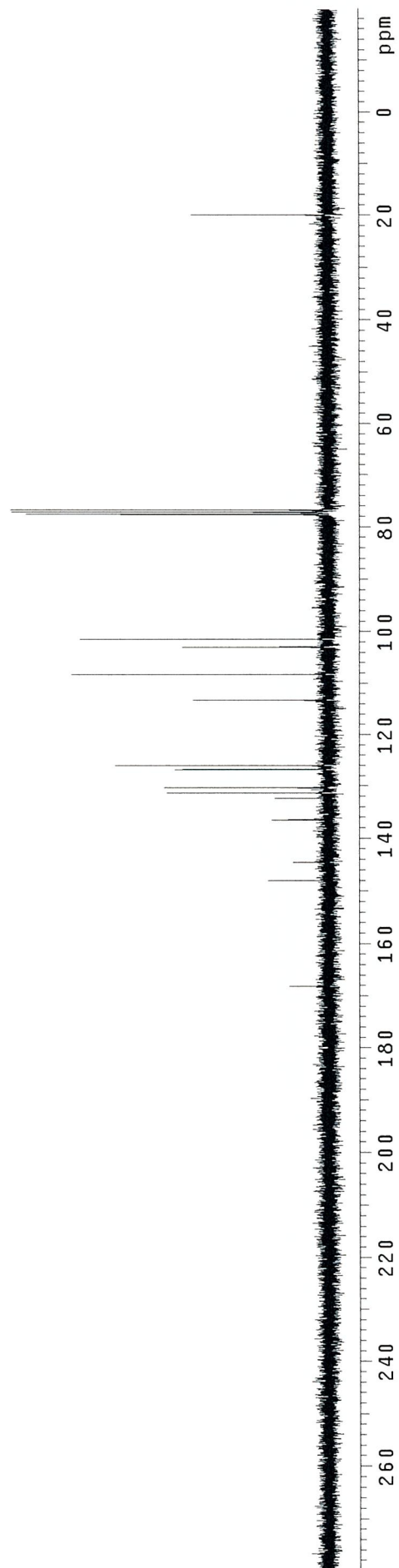


Table 2, entry 4



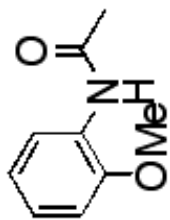
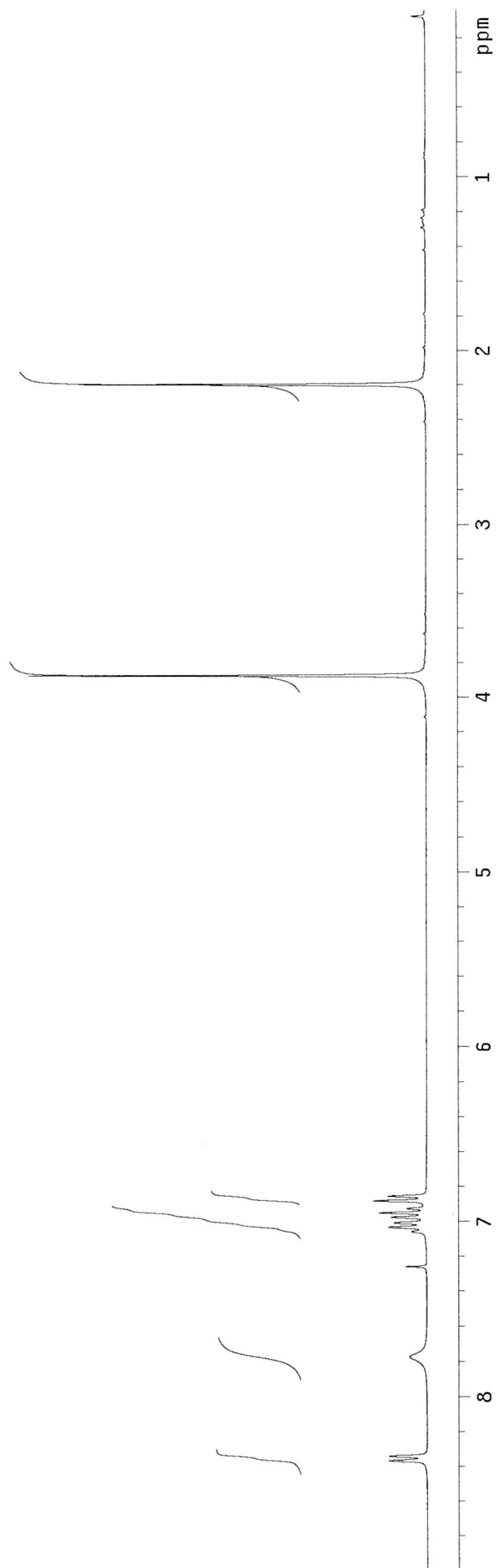


Table 2, entry 5



K0222

Pulse Sequence: s2pu1

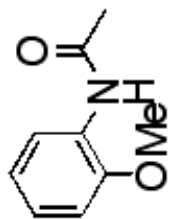
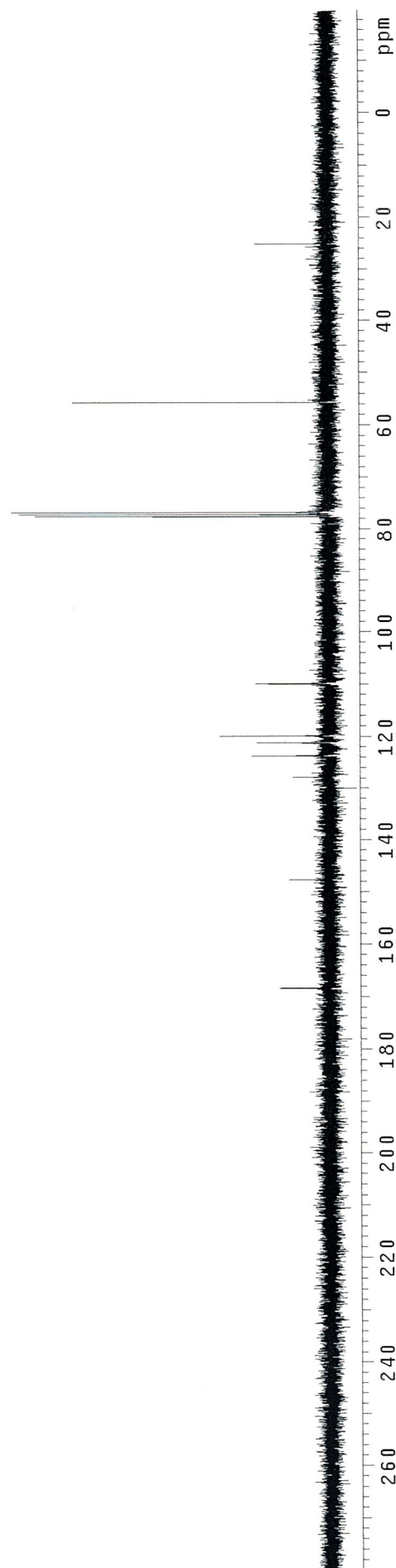


Table 2, entry 5



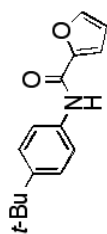
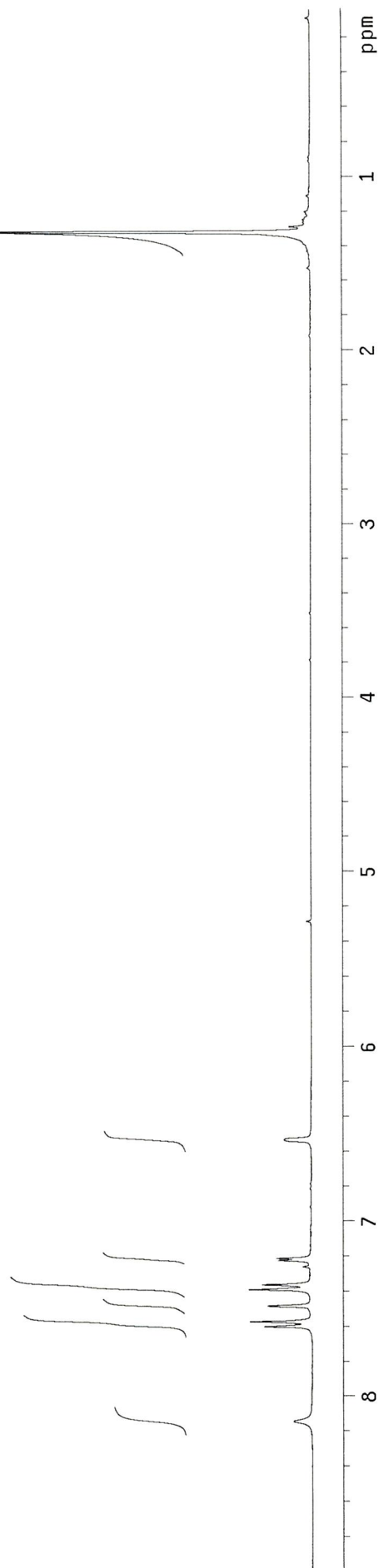


Table 3, entry 1



KD229

Pulse Sequence: s2pu1

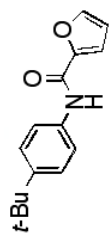
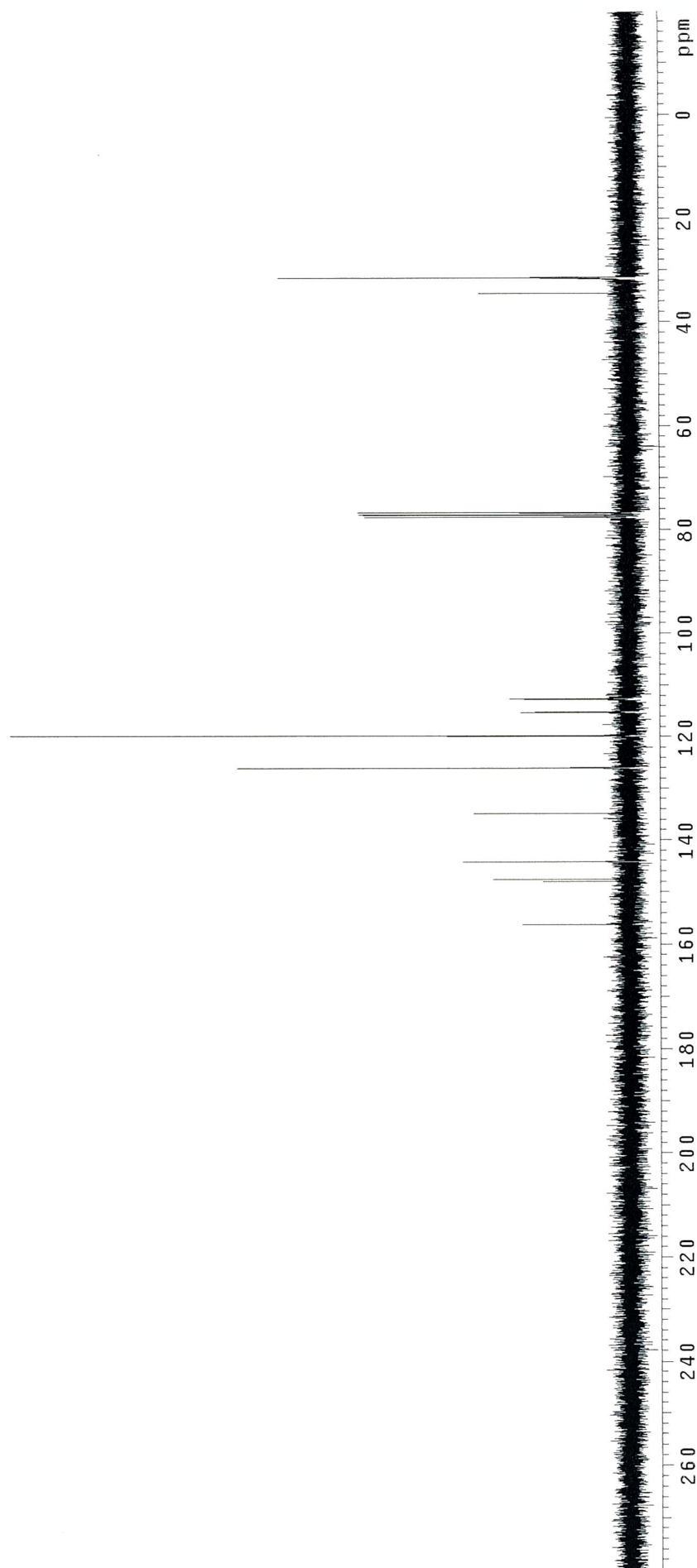


Table 3, entry 1



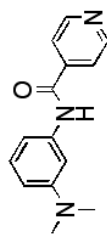
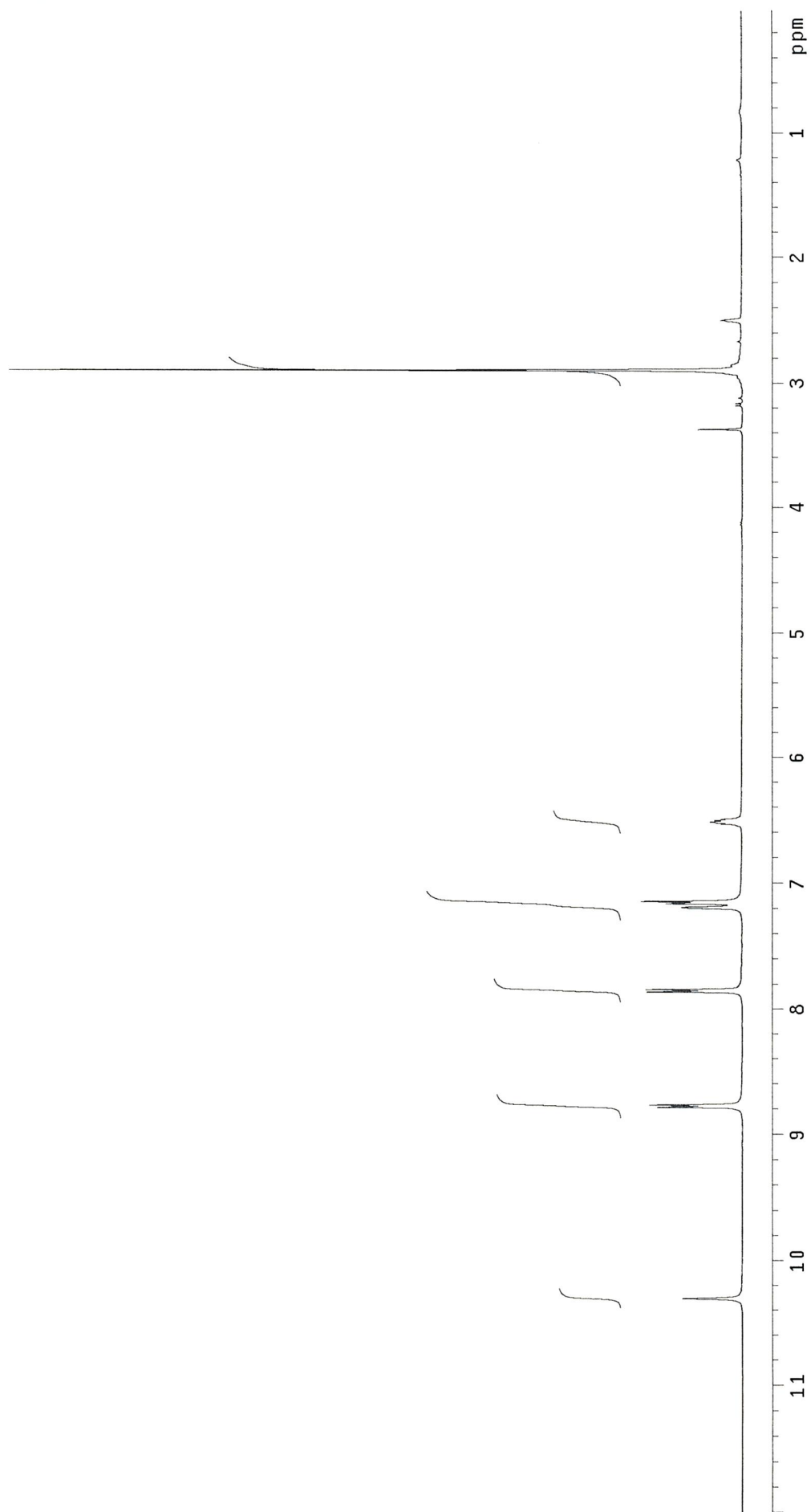


Table 3, entry 2



KD236

Pulse Sequence: s2pu1

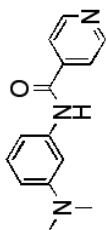
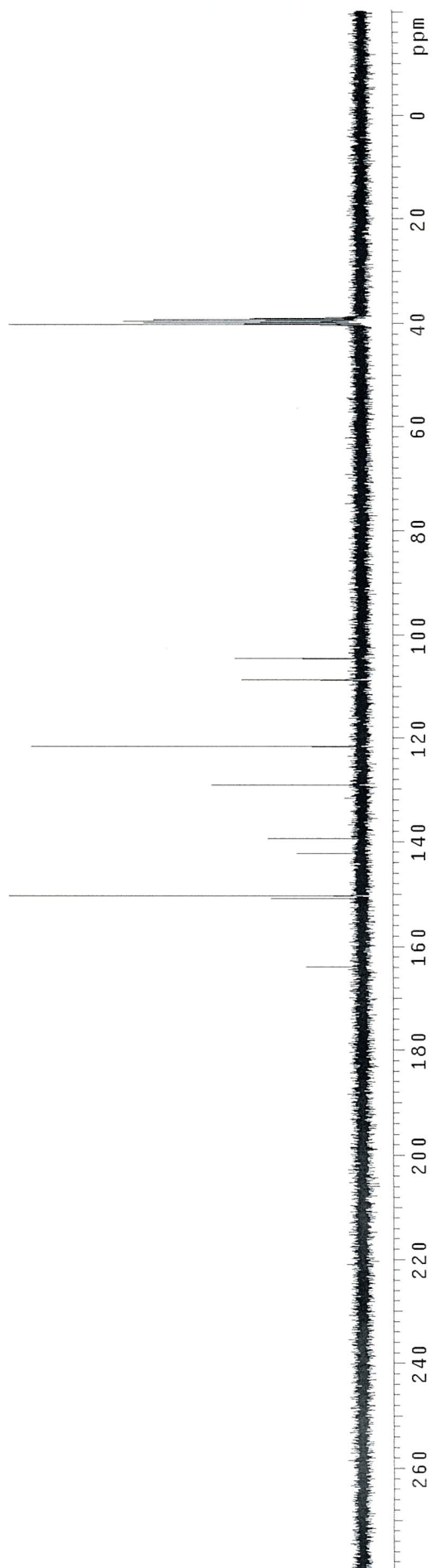


Table 3, entry 2



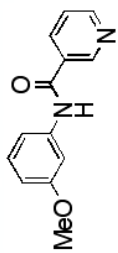
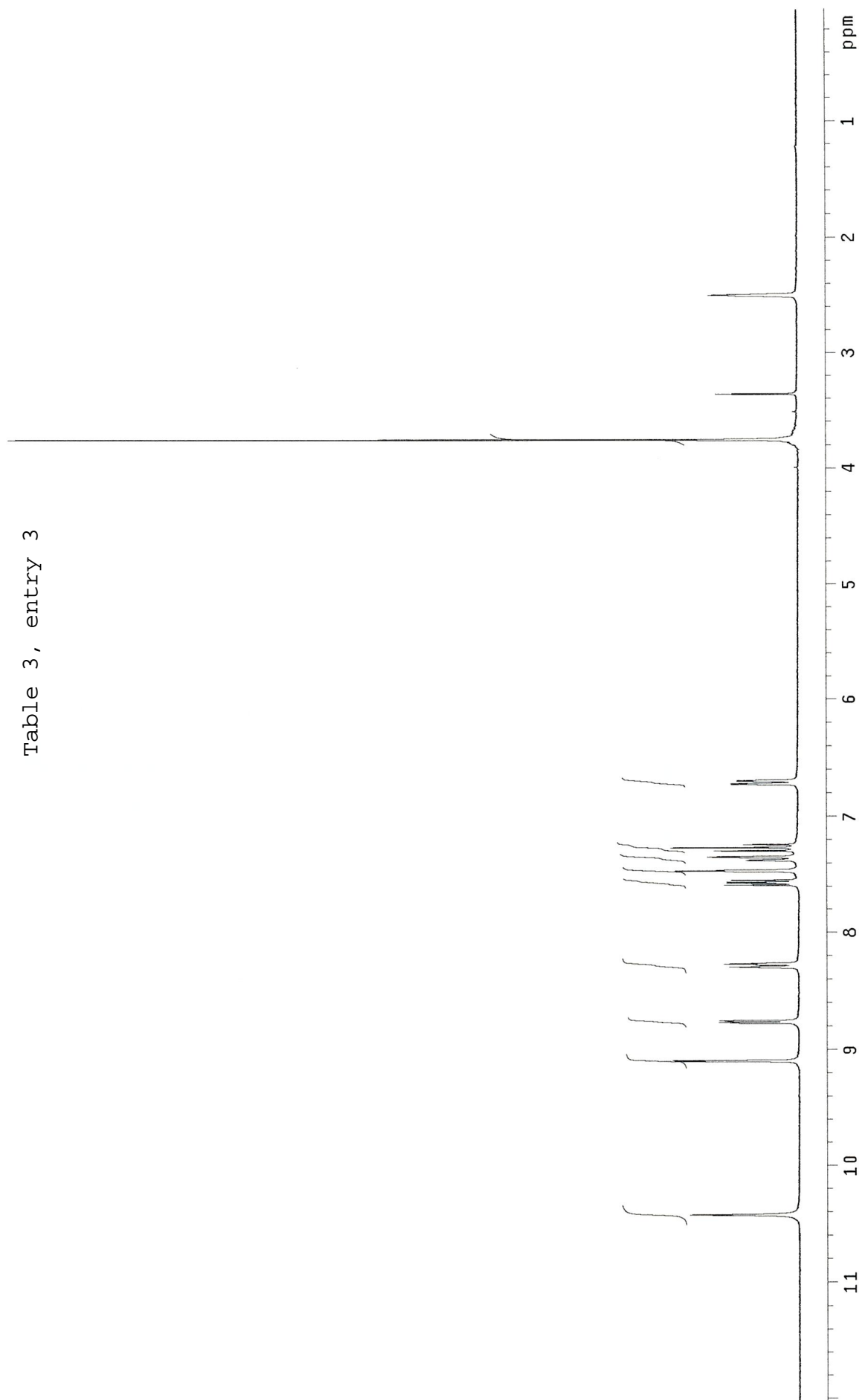


Table 3, entry 3



Pulse Sequence: s2pul

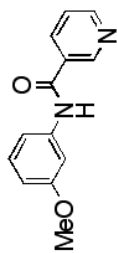
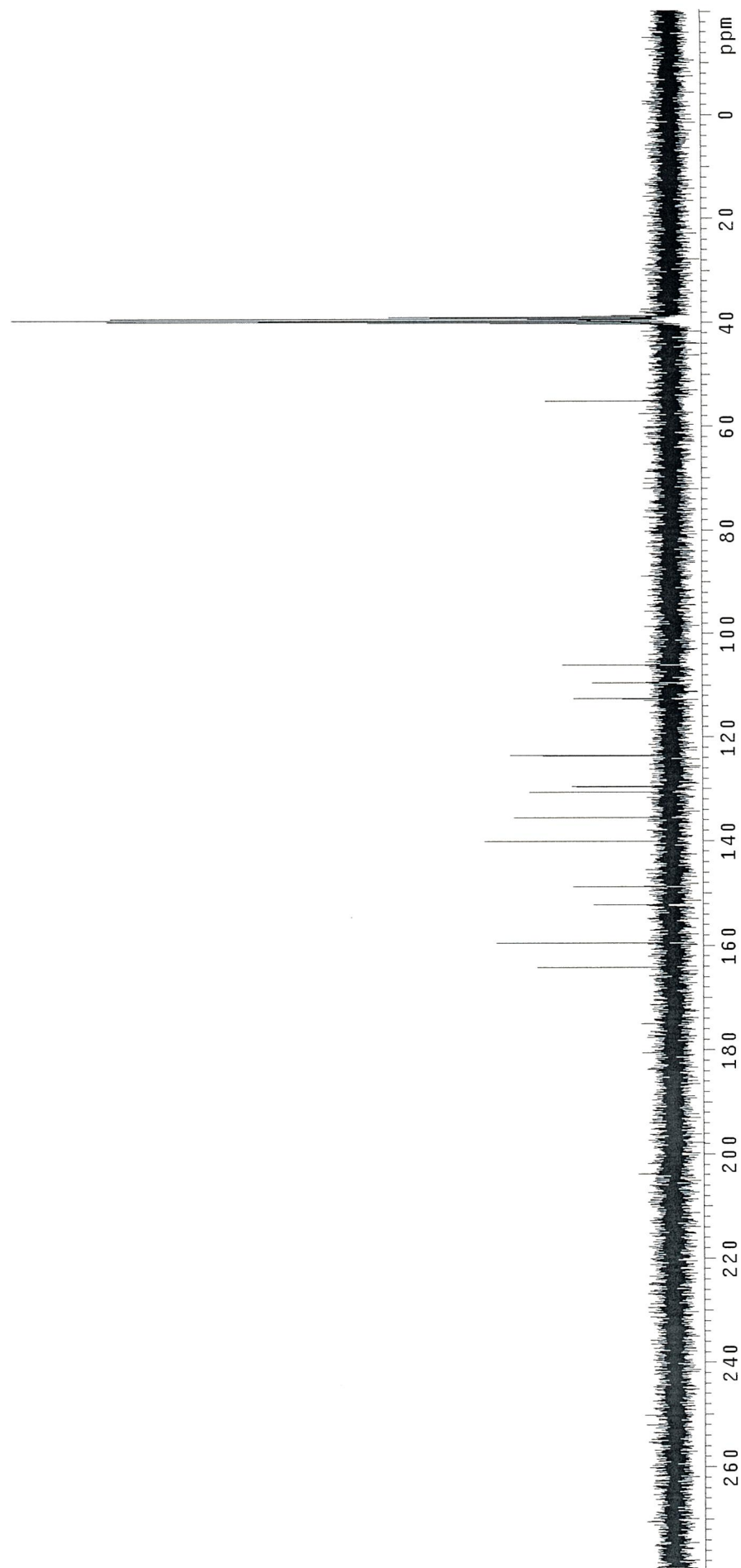


Table 3, entry 3



KD232

Pulse Sequence: s2pul

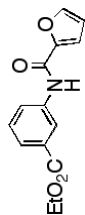
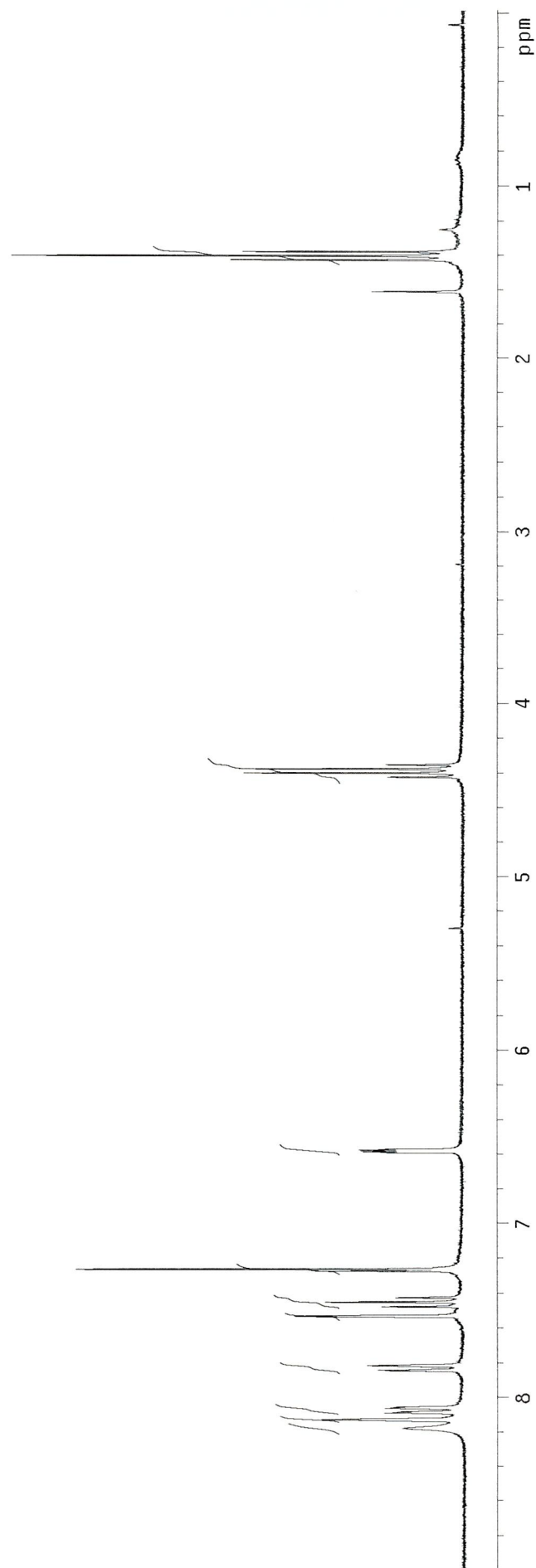


Table 3, entry 4



KD207A

Pulse Sequence: s2pu1

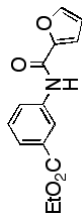
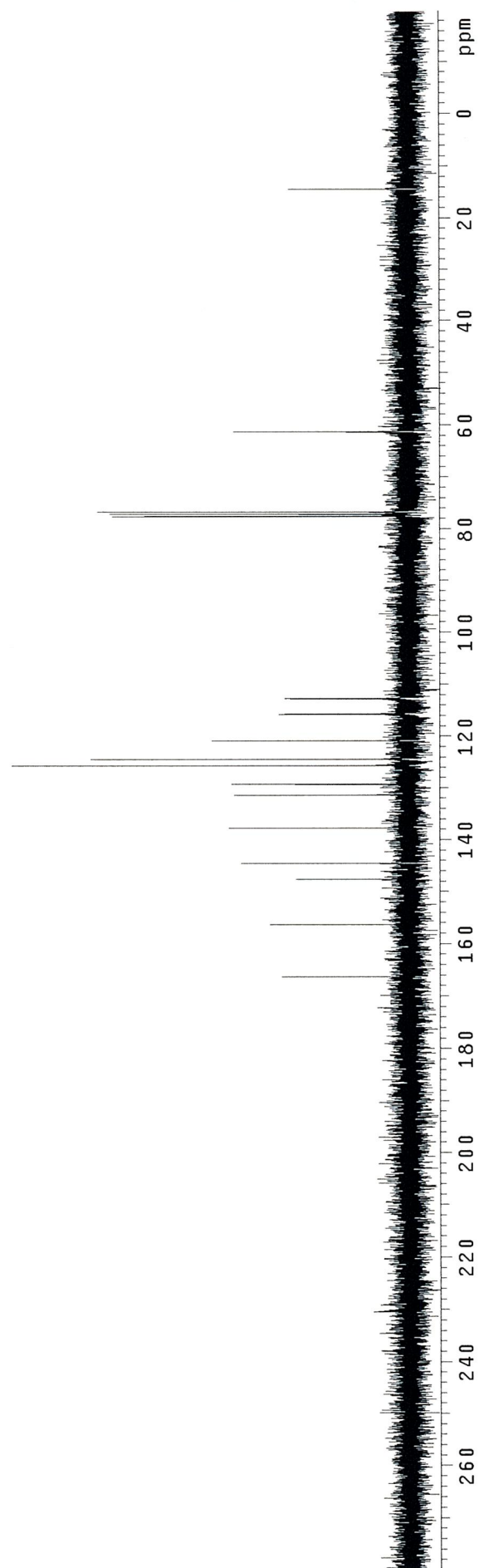


Table 3, entry 4



KD250A

Pulse Sequence: s2pu1

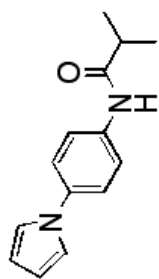
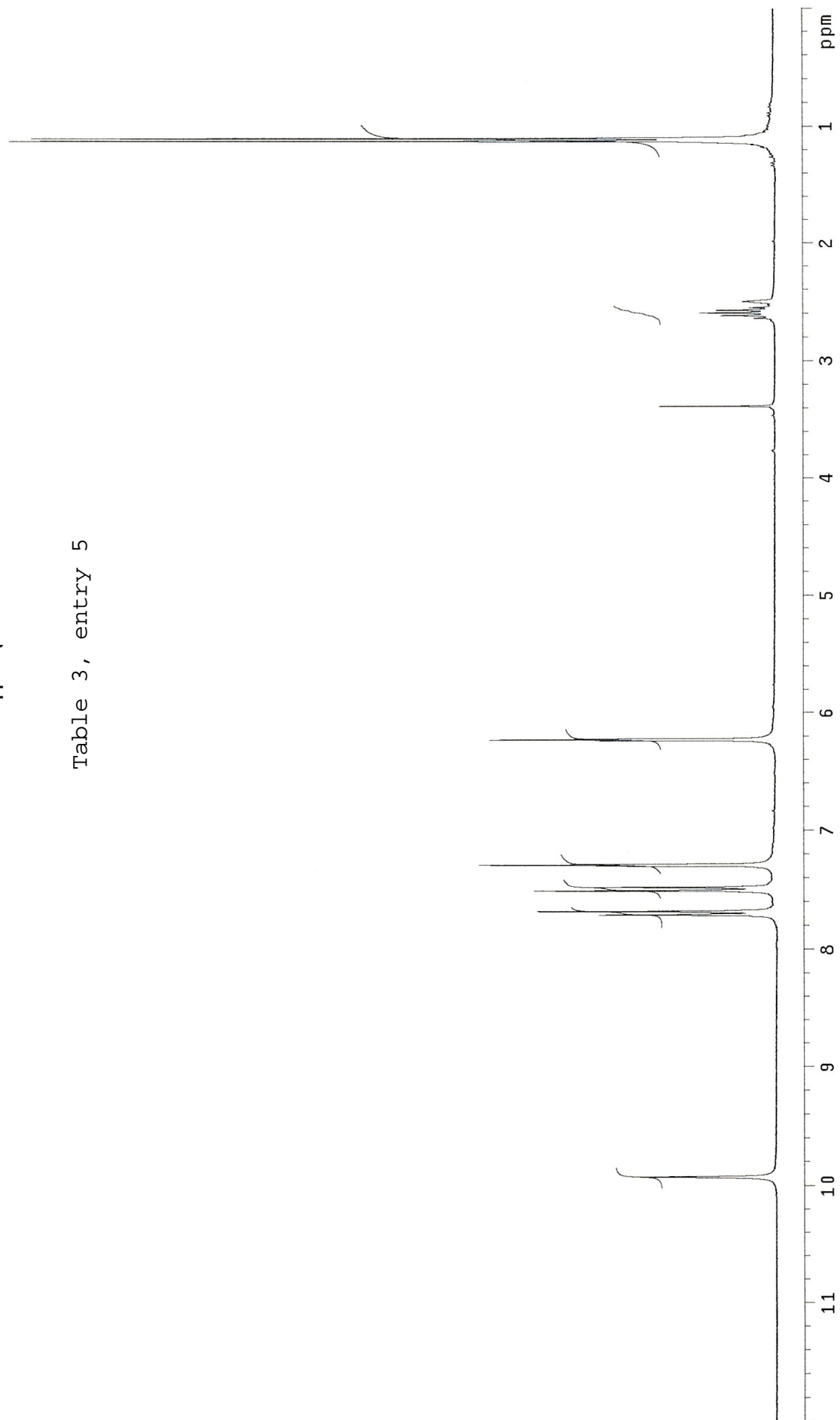


Table 3, entry 5



KD260A
Pulse Sequence: s2pul

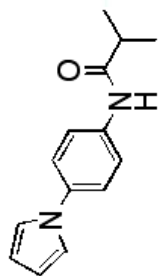
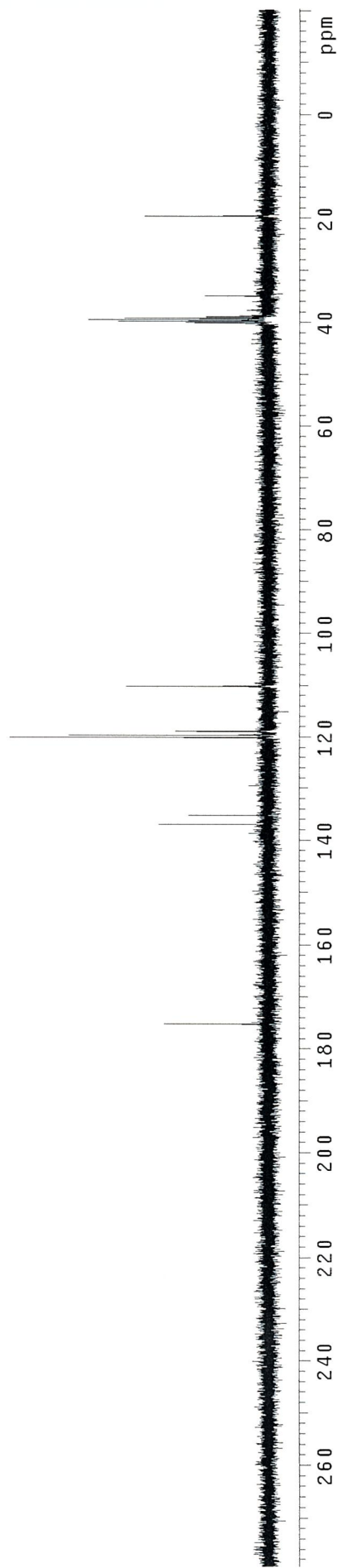


Table 3, entry 5



KD301

Pulse Sequence: s2pu1

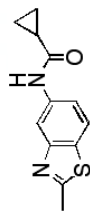
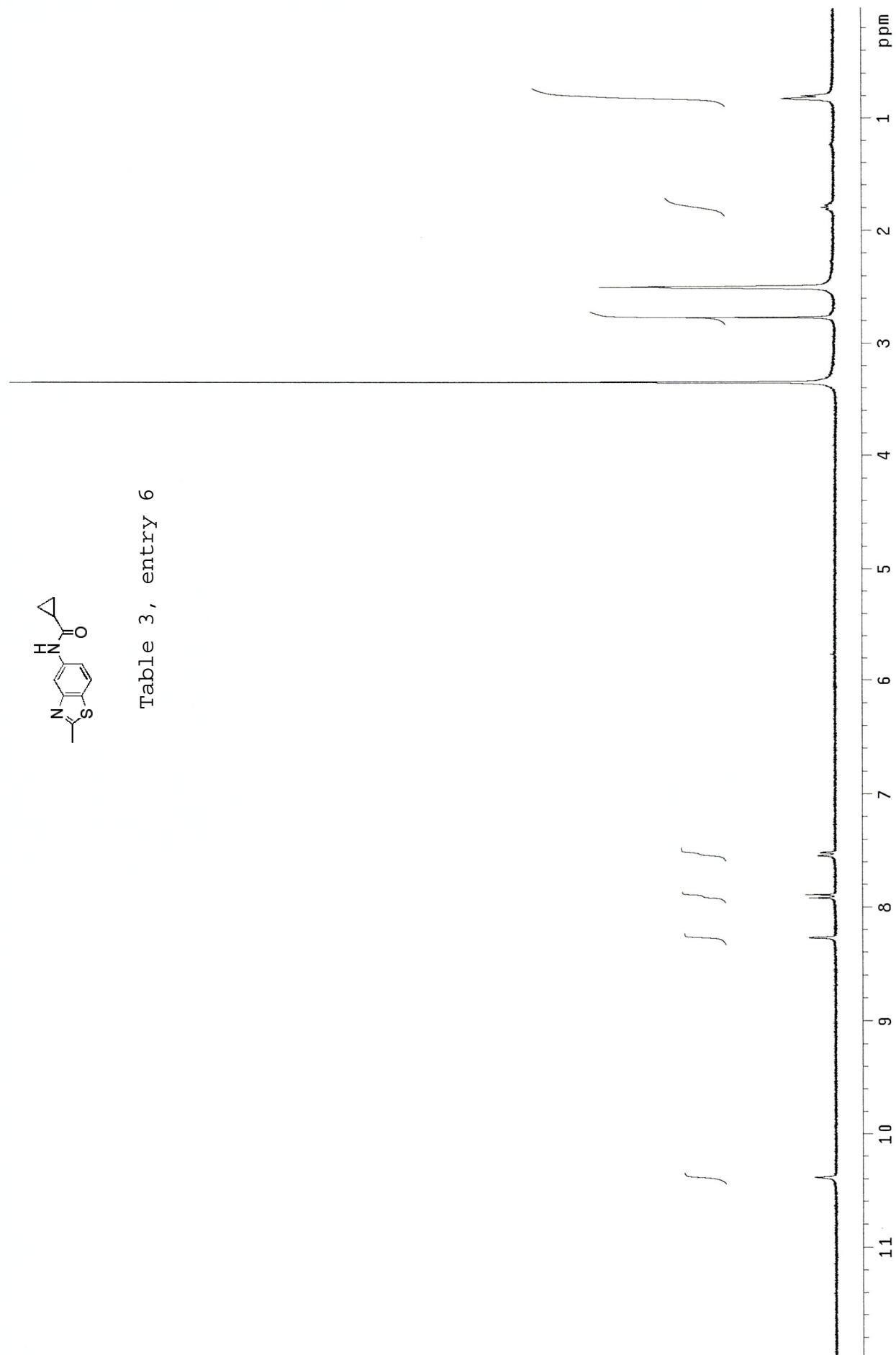


Table 3, entry 6



KD294

Pulse Sequence: s2pul

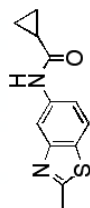
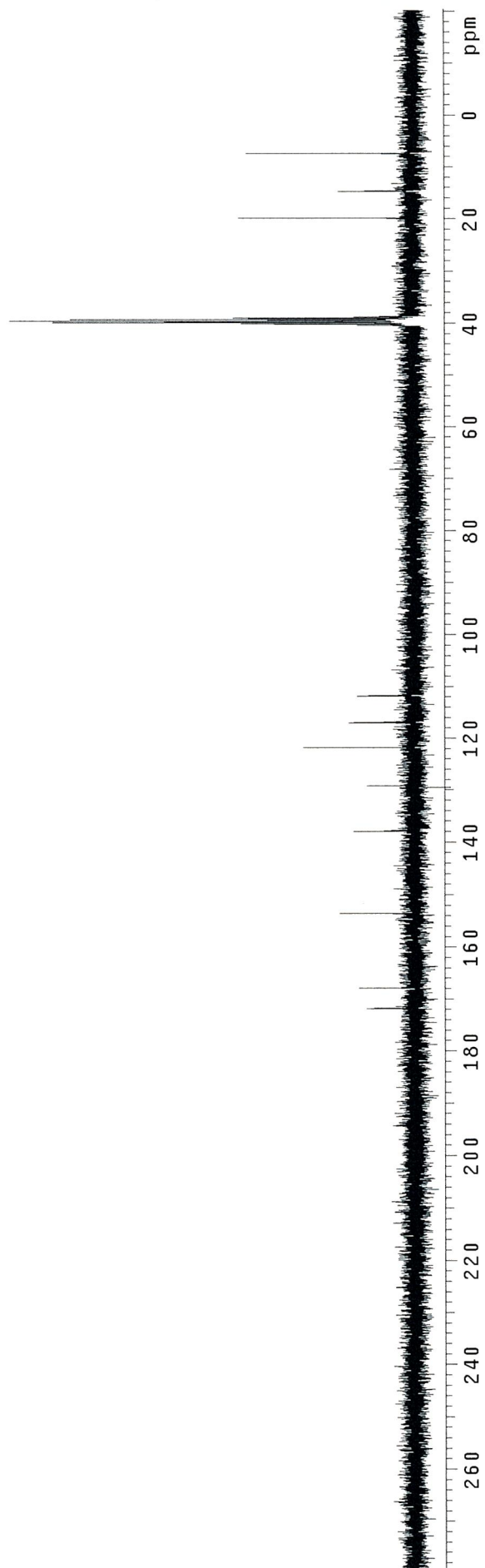


Table 3, entry 6



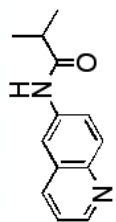
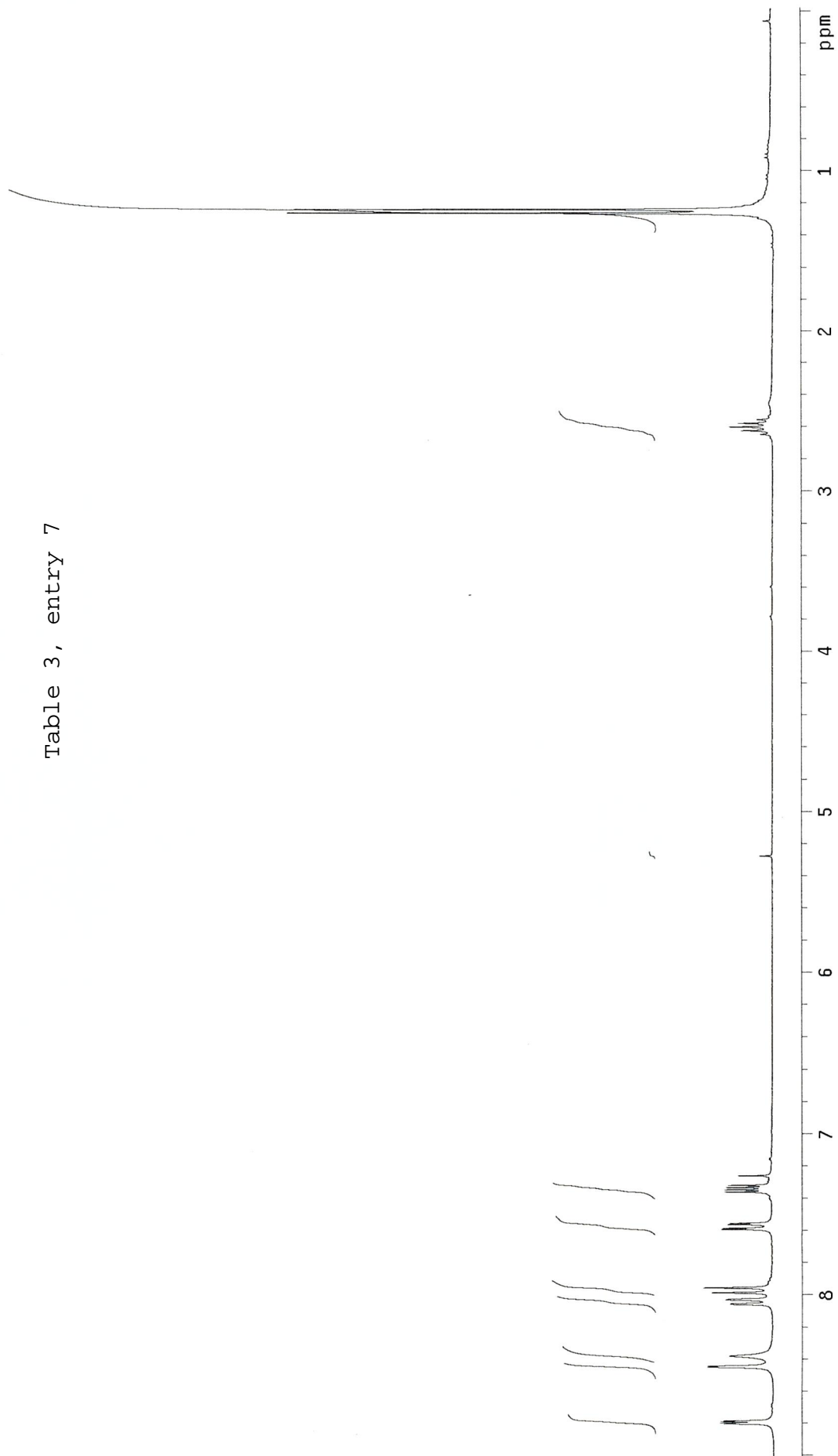


Table 3, entry 7



KD290

Pulse Sequence: s2pul1

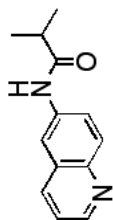
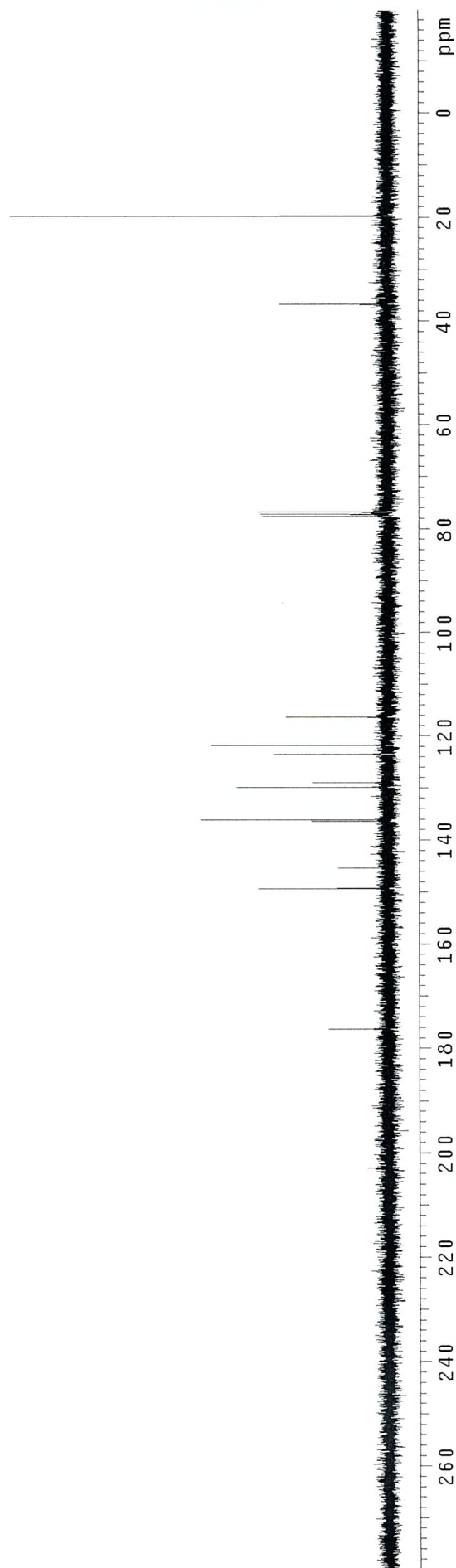


Table 3, entry 7



KD305B

Pulse Sequence: s2pu1

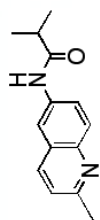
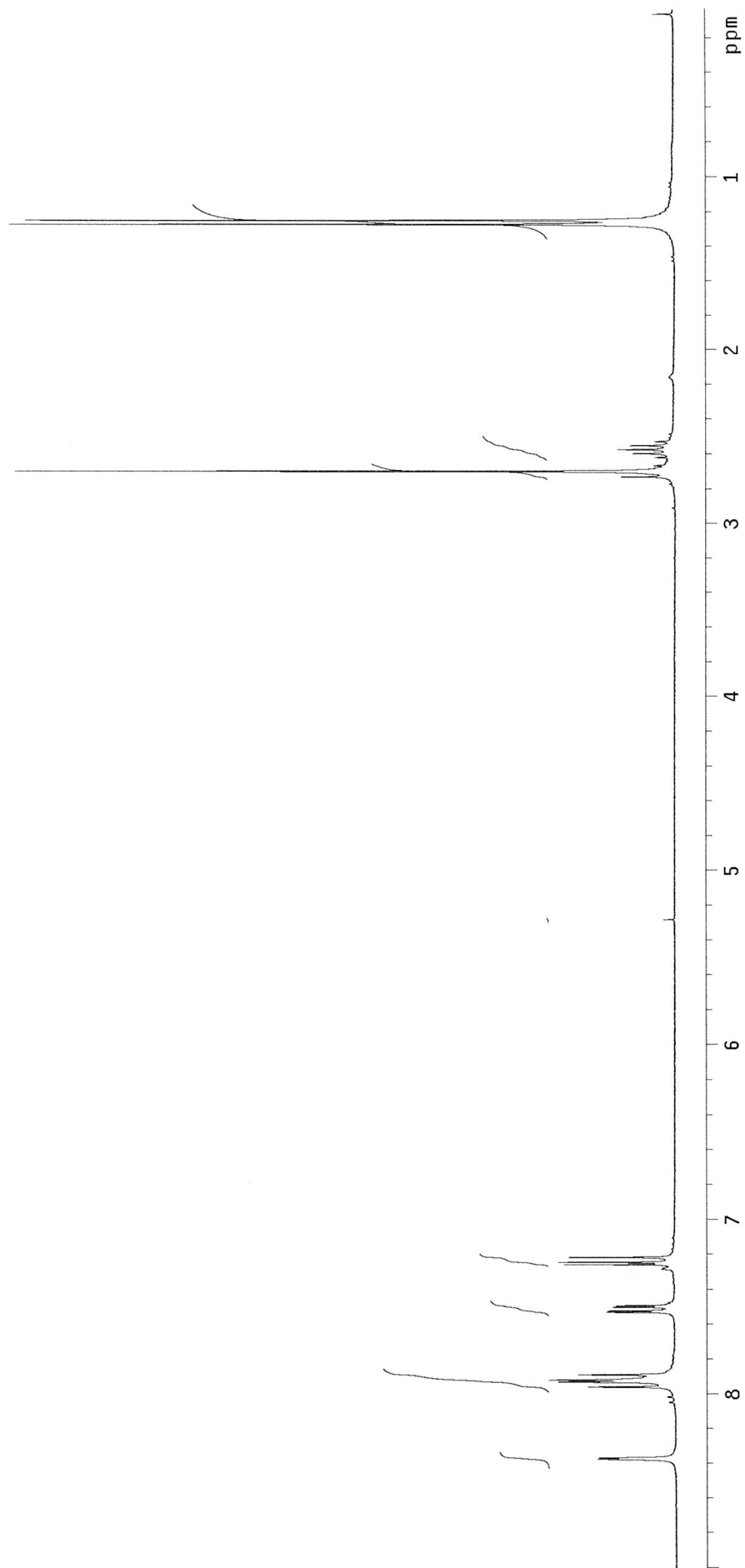


Table 3, entry 8



KD305B

Pulse Sequence: s2pu1

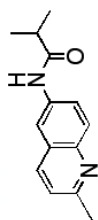


Table 3, entry 8

