

# Synthesis of Unsymmetrical Diaryl Ureas via Pd-Catalyzed C–N Cross-Coupling Reactions

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## *Supporting Information*

### ***General Reagent Information***

All reactions were carried out under an argon atmosphere. THF and toluene were purchased from J.T. Baker in CYCLE-TAINER<sup>®</sup> solvent-delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina. DME, *t*-BuOH, and 1,4-dioxane were purchased from Aldrich Chemical Co. in Sureseal<sup>®</sup> bottles and used as received. Aryl halides, benzylurea and phenylurea were purchased from Aldrich Chemical Co., Alfa Aesar, Acros Organics or TCI America and were used as received without further purification. *p*-Methoxybenzylurea<sup>1</sup> and 2,4-dimethoxybenzylurea<sup>2</sup> were prepared according to literature procedures. Deionized water was degassed by brief (1 min) sonification under vacuum and then evacuated and backfilled with argon (this procedure was repeated a total of three times). Anhydrous cesium carbonate was purchased from Aldrich Chemical Co. The base was stored in a nitrogen-filled glovebox, ground in a coffee grinder and was taken out in small quantities and stored on the bench (in a desiccator) for up to two weeks. **L1**<sup>3</sup> was synthesized using literature procedures and **L2**, **L3**, **L4** and **L5** were purchased from Strem. Flash chromatography was performed using the Biotage SP4 or a Biotage Isolera Four instrument with prepacked silica cartridges or by the use of silica gel (SiliaFlash F60) from SiliCycle. DCM (NH<sub>3</sub> sat'd) was prepared by placing a 2:1 mixture of DCM: NH<sub>4</sub>OH (25 %) in a separatory funnel, carefully shaking the mixture for 1-2 min and then collecting the organic layer. It was stored in glass bottles for up to one week.

### ***General Analytical Information***

All compounds were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR spectroscopy as well as elemental analysis. Copies of the  $^1\text{H}$  and  $^{13}\text{C}$  spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument and a Varian 300 MHz instrument. All  $^1\text{H}$  NMR experiments are reported in  $\delta$  units, parts per million (ppm), and were measured relative to the signals for residual DMSO (2.50 ppm) in the deuterated solvent, unless otherwise stated. All  $^{13}\text{C}$  NMR spectra are reported in ppm relative to DMSO- $d^6$  (39.52 ppm), unless otherwise stated, and were obtained with  $^1\text{H}$  decoupling. All  $^{19}\text{F}$  NMR spectra are reported in ppm relative to  $\text{CFCl}_3$  (0.00 ppm). All IR spectra were taken 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.

### ***Experimental Procedures for Examples Described in Table 1***

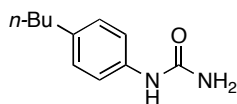
**General Procedure for Table 1:** An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with  $\text{Pd}(\text{OAc})_2$  (1 mol %) and *t*-BuBrettPhos (3 mol %). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and the solvent (2.0 mL/mmol) and degassed  $\text{H}_2\text{O}$  (4 mol %) were added via syringe. After addition of the water, the solution was heated to 110 °C for 4 min.

A second oven-dried test tube, equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with the aryl urea (1.2 mmol) and base (1.4 mmol) (aryl halides 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 three times), the aryl chloride (1.0 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula under a positive argon pressure. The solution was heated to 85 °C for 2 h. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, and washed with water. A known amount of dodecane was added to the solution as an internal standard and then the reaction mixture was analyzed via GC.

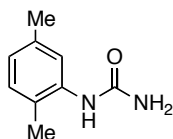
### ***Experimental Procedures for Examples Described in Table 2***

**General Procedure A:** An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with Pd(OAc)<sub>2</sub> (1 mol %) and *t*-BuBrettPhos (3 mol %). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and THF (2.0 mL/mmol) and degassed H<sub>2</sub>O (4 mol %) were added via syringe. After addition of the water, the solution was heated to 110 °C for 4 min.

A second oven-dried test tube, equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with benzylurea (1.2 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.4 mmol) (aryl halides 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 three times), the aryl chloride (1.0 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula under a positive argon pressure. The solution was heated to 85 °C until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature and MeOH (6 mL/mmol), conc. HCl and Pd/C were added. The reaction vessel was put under a H<sub>2</sub>-atmosphere and the black suspension was stirred at room temperature for 20 h. The reaction mixture was quenched with 2M NaOH and filtered through a small plug of celite. The filtrate was diluted with ethyl acetate, washed with 2M NaOH. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was adsorbed on silica gel and purified by flash chromatography on silica gel unless otherwise stated.

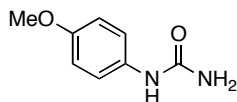


**4-*n*-Butylphenylurea.**<sup>4</sup> Following general procedure A, a mixture of 1-*n*butyl-4-chlorobenzene (168.7  $\mu$ L, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (3-7% MeOH/DCM) to provide the title compound as a white solid (173 mg, 91%), mp = 126 – 127 °C (lit. 126 – 126.5 °C).<sup>4</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 8.39 (s, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 5.78 (s, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 1.49 (m, 2H), 1.37 (sextet, *J* = 7.4 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 156.1, 138.2, 134.9, 128.3, 117.9, 34.2, 33.4, 21.7, 13.8 ppm. IR (neat, cm<sup>-1</sup>): 3336, 2856, 1657, 1639, 1600, 1588, 1541, 1514, 1356. Anal. Calcd. for C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O: C, 68.72; H, 8.39. Found: C, 68.69; H, 8.39.

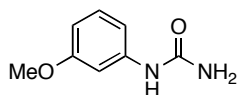


**2,5-Dimethylphenylurea.** Following general procedure A, a mixture of 2-chloro-*p*-xylene (134.0  $\mu$ L, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (3 mol %), *t*-BuBrettPhos (9 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (3 mL) was heated to 85 °C for 3 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (3-7% MeOH/DCM) to provide the title compound as a white solid (120 mg, 74%), mp = 206 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 7.63 (s, 1H), 7.60 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 2H), 6.68 (d, *J* = 7.5 Hz, 2H), 6.00 (s, 2H), 2.21 (s, 3H), 2.12 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 156.2, 138.0, 134.9, 129.8, 123.9, 122.7, 121.4, 21.0, 17.5 ppm. IR (neat, cm<sup>-1</sup>): 3431, 3302, 2901,

1662, 1615, 1582, 1541, 800. Anal. Calcd. for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O: C, 65.83; H, 7.37. Found: C, 65.95; H, 7.42.

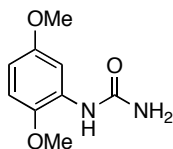


**4-Methoxyphenylurea.**<sup>4</sup> Following general procedure A, a mixture of 4-chloroanisole (122.5  $\mu$ L, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as a white solid (157 mg, 95%), mp = 165 – 166 °C (lit. 168 – 169 °C).<sup>4</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 8.31 (s, 1H), 7.28 (d, *J* = 6.8 Hz, 2H), 6.80 (d, *J* = 6.8 Hz, 2H), 5.73 (s, 2H), 3.68 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 156.3, 153.9, 133.7, 119.53, 113.9, 55.2 ppm. IR (neat, cm<sup>-1</sup>): 3468, 3299, 1644, 1590, 1546, 1511, 1248, 1038, 822. Anal. Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C, 57.82; H, 6.07. Found: C, 57.57; H, 6.18.

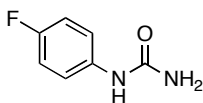


**3-Methoxyphenylurea.**<sup>5</sup> Following general procedure A, a mixture of 3-chloroanisole (121.7  $\mu$ L, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as a white solid (155 mg, 93%), mp = 130 – 131 °C (lit. 132 – 133 °C).<sup>5</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 8.53 (s, 1H), 7.14 (t, *J* = 2.1 Hz, 1H), 7.10 (t, *J* = 8.2 Hz, 1H), 6.88 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.47 (dd, *J* = 8.1, 2.3 Hz, 1H), 5.86 (s, 2H), 3.69 (s,

3H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 159.7, 156.1, 141.8, 129.4, 110.2, 106.5, 103.7, 54.88 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3446, 3306, 1660, 1589, 1551, 1492, 1346, 1200, 1026, 854, 782. Anal. Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ : C, 57.82; H, 6.07. Found: C, 57.81; H, 6.08.

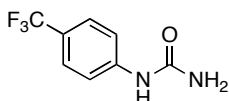


**2,5-Dimethoxyphenylurea.** Following general procedure A, a mixture of 2-chloro-1,4-dimethoxybenzene (142.7  $\mu\text{L}$ , 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85  $^\circ\text{C}$  for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of  $\text{H}_2$  for 20 h. The crude product was purified via flash chromatography (3-7% MeOH/DCM) to provide the title compound as a white solid (155 mg, 93%), mp = 155 – 156  $^\circ\text{C}$ .  $^1\text{H}$  NMR (400 MHz, DMSO- $d^6$ )  $\delta$ : 7.99 (s, 1H), 7.84 (d,  $J$  = 3.0 Hz, 1H), 6.83 (d,  $J$  = 8.9 Hz, 1H), 6.40 (dd,  $J$  = 8.8, 3.1 Hz, 1H), 6.27 (s, 2H), 3.76 (s, 3H), 3.65 (s, 3H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 156.1, 153.4, 141.7, 130.5, 111.2, 105.2, 104.5, 56.2, 55.2 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3443, 3304, 1668, 1594, 1534, 1487, 1217, 1045, 718. Anal. Calcd. for  $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ : C, 55.09; H, 6.16. Found: C, 55.10; H, 6.27.

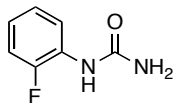


**4-Fluorophenylurea.**<sup>4</sup> Following general procedure A, a mixture of 1-chloro-4-fluorobenzene (106.5  $\mu\text{L}$ , 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85  $^\circ\text{C}$  for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of  $\text{H}_2$  for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as a white solid (137 mg, 90%), mp = 181 – 183  $^\circ\text{C}$  (lit. 190 – 191

°C).<sup>4</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.54 (s, 1H), 7.39 (dd, *J* = 9.1, 5.0 Hz, 2H), 7.04 (t, *J* = 8.9 Hz, 2H), 5.83 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.9 (d, *J* = 237.0 Hz), 156.0 (s), 136.9 (d, *J* = 2.1 Hz), 119.3 (d, *J* = 7.6 Hz), 115.0 (d, *J* = 22.0 Hz) ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sup>6</sup>) δ: -127.39 ppm. IR (neat, cm<sup>-1</sup>): 3425, 3315, 1655, 1595, 1554, 1510, 1230, 829, 549. Anal. Calcd. for C<sub>7</sub>H<sub>7</sub>FN<sub>2</sub>O: C, 54.54; H, 4.58. Found: C, 54.26; H, 4.65.

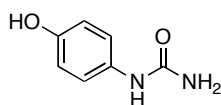


**4-Trifluoromethylphenylurea.** Following general procedure A, a mixture of 4-chlorobenzotrifluoride (133.7 μL, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as an off-white solid (167 mg, 82%), mp = 158 – 160 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.96 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 6.05 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.8, 144.4, 125.9 (q, *J* = 3.8 Hz), 124.7 (q, *J* = 270.9 Hz), 121.1 (q, *J* = 31.9 Hz), 117.4 ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sup>6</sup>) δ: -64.61 ppm. IR (neat, cm<sup>-1</sup>): 3433, 3316, 1658, 1599, 1552, 1332, 1127, 1072, 834. Anal. Calcd. for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O: C, 47.07; H, 3.46. Found: C, 47.29; H, 3.42.

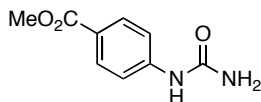


**2-Fluorophenylurea.** Following general procedure A, a mixture of 1-chloro-2-fluorobenzene (104.9 μL, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (3 mol %), *t*-BuBrettPhos (9 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 100 °C for 3 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting

reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (3-7% MeOH/DCM) to provide the title compound as a white solid (138 mg, 89%), mp = 182 – 183 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.34 (s, 1H), 8.14 (td, *J* = 8.3, 1.3 Hz, 1H), 7.16 (m, 1H), 7.06 (t, *J* = 7.7 Hz, 1H), 6.91 (m, 1H), 6.19 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.8, 151.7 (d, *J* = 240.5 Hz), 128.4 (d, *J* = 10.2 Hz), 124.4 (d, *J* = 3.4 Hz), 121.6 (d, *J* = 7.4 Hz), 120.4 (d, *J* = 1.8 Hz), 114.8 (d, *J* = 19.1 Hz) ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sup>6</sup>) δ: -135.52 ppm. IR (neat, cm<sup>-1</sup>): 3425, 3320, 1656, 1600, 1556, 1495, 1258, 754. Anal. Calcd. for C<sub>7</sub>H<sub>7</sub>FN<sub>2</sub>O: C, 54.54; H, 4.58. Found: C, 54.67; H, 4.61.

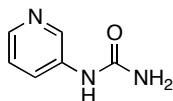


**4-Hydroxyphenylurea.**<sup>6</sup> Following general procedure A, a mixture of 4-chlorophenol (128.5 mg, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (3 mol %), *t*-BuBrettPhos (9 mol %), Cs<sub>2</sub>CO<sub>3</sub> (782.0 mg, 2.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 100 °C for 3 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.2 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (7-12% MeOH/DCM) to provide the title compound as a violet solid (111 mg, 73%), mp = 164 – 166 °C (lit. 168 – 170 °C).<sup>6</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.96 (s, 1H), 8.20 (s, 1H), 7.15 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.5 Hz, 2H), 5.70 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.6, 152.2, 132.1, 120.2, 115.2 ppm. IR (neat, cm<sup>-1</sup>): 3427, 3247, 1634, 1541, 1385, 1216, 826, 804, 547. Anal. Calcd. for C<sub>7</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>: C, 55.26; H, 5.30. Found: C, 55.13; H, 5.46.

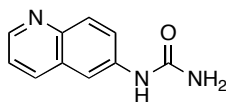




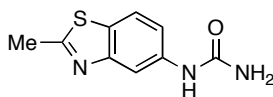
**Methyl-4-ureidobenzoate.**<sup>7</sup> Following general procedure A, a mixture of methyl-4-chlorobenzoate (170.6 mg, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (9 mol %), concentrated HCl (1.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (2-7% MeOH/DCM) to provide the title compound as a white solid (165 mg, 85%), mp = 191 – 192 °C (lit. 188 – 190 °C).<sup>7</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.96 (s, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 6.07 (s, 2H), 3.79 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 166.1, 155.7, 145.3, 130.4, 121.8, 116.9, 51.7 ppm. IR (neat, cm<sup>-1</sup>): 3326, 1700, 1670, 1589, 1537, 1290, 1176, 1115, 850, 769. Anal. Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>: C, 55.67; H, 5.19. Found: C, 55.67; H, 5.28.



**Pyridin-3-ylurea.**<sup>8</sup> Following general procedure A, a mixture of 3-chloropyridine (95.4 μL, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (20 mol %), concentrated HCl (2.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as a white solid (109 mg, 79%), mp = 185 – 187 °C (lit. 178 °C).<sup>8</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.73 (s, 1H), 8.53 (d, *J* = 2.4 Hz, 1H), 8.11 (dd, *J* = 4.6, 1.2 Hz, 1H), 7.90 (ddd, *J* = 8.3, 2.4, 1.5 Hz, 1H), 7.23 (dd, *J* = 8.3, 4.7 Hz, 1H), 6.03 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.1, 142.2, 139.7, 137.3, 124.7, 123.5 ppm. IR (neat, cm<sup>-1</sup>): 3199, 1675, 1598, 1558, 1473, 1355, 854, 806. Anal. Calcd. for C<sub>6</sub>H<sub>7</sub>N<sub>3</sub>O: C, 52.55; H, 5.14. Found: C, 52.21; H, 5.27.



**Quinolin-6-ylurea.** Following general procedure A, a mixture of 6-chloroquinoline (163.5, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (20 mol %), concentrated HCl (2.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as an off-white solid (99 mg, 53%), mp = 223 – 226 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.90 (s, 1H), 8.69 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.89 (d, *J* = 9.1 Hz, 1H), 7.65 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.03 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.0, 148.0, 143.9, 138.6, 135.0, 129.3, 128.7, 122.8, 121.6, 112.2 ppm. IR (neat, cm<sup>-1</sup>): 3297, 1663, 1559, 1338, 876, 834, 792, 612, 563. Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O: C, 64.16; H, 4.85. Found: C, 63.91; H, 4.86.



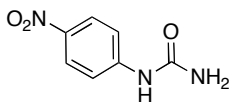
**2-Methylbenzothiaz-5-ylurea** Following general procedure A, a mixture of 5-chloro-2-methylbenzothiazole (183.5 mg, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (40 mol %), concentrated HCl (2.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. Due to incomplete conversion additional Pd/C (20 mol %) and HCl (2.0 mL) were added and stirring was continued for a total of 2 d. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as an off-white solid (123 mg, 59%), mp = 207 – 209 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.72 (s, 1H), 8.09 (d, *J* = 1.9 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.7, 2.0 Hz, 1H), 5.91 (s, 2H), 2.74 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 167.4, 156.1,

153.8, 139.2, 127.4, 121.5, 116.3, 110.4, 19.8 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3393, 3282, 1653, 1559, 1507, 1458, 1168, 897, 805. Anal. Calcd. for  $\text{C}_9\text{H}_9\text{N}_3\text{OS}$ : C, 52.16; H, 4.38. Found: C, 52.16; H, 4.33.

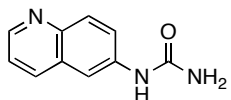
### ***Experimental Procedures for Examples Described in Table 3***

**General Procedure B:** 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 *t*-BuBrettPhos (3 mol %). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and THF (2.0 mL/mmol) and degassed  $\text{H}_2\text{O}$  (4 mol %) were added via syringe. After addition of the water, the solution was heated to 110 °C for 4 min.

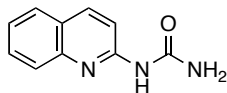
A second oven-dried test tube, equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with *p*-methoxybenzylurea (1.2 mmol) and  $\text{Cs}_2\text{CO}_3$  (1.4 mmol) (aryl halides that were solids at room temperature were added with the base). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times), the aryl chloride (1.0 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula under a positive argon pressure. The solution was heated to 85 °C until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature and TFA (8 mL/mmol) was added slowly. The resulting dark red solution was stirred at 60 °C until deprotection was complete as judged by TLC analysis. The reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator with a water bath at 40 °C. The residue was taken up with ethyl acetate and washed three times with 2M NaOH. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was adsorbed on silica gel and purified by flash chromatography on silica gel unless otherwise stated.



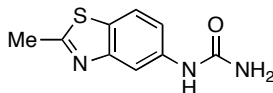
**4-Nitrophenylurea.**<sup>4</sup> Following general procedure B, a mixture of 4-chloronitrobenzene (157.8 mg, 1.0 mmol), *p*-methoxybenzylurea (216.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, TFA (8 mL) was added and the resulting reaction mixture stirred at 60 °C for 4 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as a yellow crystalline solid (130 mg, 72%), mp = 216 – 217 °C (lit. 227.5 – 228 °C).<sup>4</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.30 (s, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 7.62 (d, *J* = 9.3 Hz, 2H), 6.22 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.4, 147.3, 140.5, 125.1, 117.0 ppm. IR (neat, cm<sup>-1</sup>): 3358, 1708, 1597, 1551, 1496, 1316, 1265, 1113, 848, 751. Anal. Calcd. for C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>O<sub>3</sub>: C, 46.41; H, 3.89. Found: C, 46.23; H, 3.87.



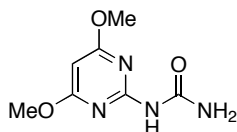
**Quinolin-6-ylurea.** Following general procedure B, a mixture of 6-chloroquinoline (163.4, 1.0 mmol), *p*-methoxybenzylurea (216.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, TFA (8 mL) was added and the resulting reaction mixture stirred at 60 °C for 6 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as an off-white solid (164 mg, 87%), mp = 224 – 227 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.91 (s, 1H), 8.69 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.65 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.04 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.1, 148.0, 143.9, 138.6, 135.0, 129.4, 128.7, 122.9, 121.6, 112.2 ppm. IR (neat, cm<sup>-1</sup>): 3370, 3315, 1668, 1609, 1568, 1385, 877, 835, 793. Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O: C, 64.16; H, 4.85. Found: C, 64.14; H, 4.71.



**Quinolin-2-ylurea.** Following general procedure B, a mixture of 2-chloroquinoline (163.5, 1.0 mmol), *p*-methoxybenzylurea (216.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, TFA (8 mL) was added and the resulting reaction mixture stirred at 60 °C for 20 h. The crude product was purified via flash chromatography (2-12% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as an off-white solid (138 mg, 74%), mp = 225 – 227 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.61 (s, 1H), 8.61 (br, 1H), 8.19 (d, *J* = 8.9 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.63 (m, 1H), 7.39 (m, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.05 (br, 1H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.5, 152.7, 145.4, 138.2, 129.9, 127.7, 126.4, 124.2, 124.1, 113.6 ppm. IR (neat, cm<sup>-1</sup>): 3319, 3146, 1762, 1690, 1592, 1425, 818, 739, 524. Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O: C, 64.16; H, 4.85. Found: C, 63.82; H, 4.72.



**2-Methylbenzothiaz-5-ylurea** Following general procedure B, a mixture of 5-chloro-2-methylbenzothiazole (183.9 mg, 1.0 mmol), *p*-methoxybenzylurea (216.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, TFA (8 mL) was added and the resulting reaction mixture stirred at 60 °C for 6 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as an off-white solid (183 mg, 88%), mp = 206 – 208 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.72 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.34 (dd, *J* = 8.7, 2.1 Hz, 1H), 5.91 (s, 2H), 2.74 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 167.4, 156.1, 153.8, 139.2, 127.4, 121.5, 116.3, 110.4, 19.8 ppm. IR (neat, cm<sup>-1</sup>): 3413, 3303, 1655, 1566, 1539, 1520, 1352, 1170, 806. Anal. Calcd. for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>OS: C, 52.16; H, 4.38. Found: C, 52.30; H, 4.39.



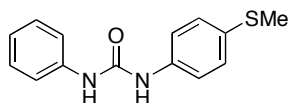
**4,6-Dimethoxypyrimidin-2-ylurea** Following general procedure B, a mixture of 2-chloro-4,6-dimethoxypyrimidine (174.5 mg, 1.0 mmol), *p*-methoxybenzylurea (216.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, TFA (8 mL) was added and the resulting reaction mixture stirred at 60 °C for 20 h. The crude product was purified via flash chromatography (2-3% MeOH/DCM (*NH<sub>3</sub> sat'd*)) to provide the title compound as a white solid (170 mg, 86%), mp = 189 – 199 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.38 (s, 1H), 8.23 (br, 1H), 7.13 (br, 1H), 5.78 (s, 1H), 3.83 (s, 6H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 171.3, 157.4, 154.7, 82.0, 54.1 ppm. IR (neat, cm<sup>-1</sup>): 3351, 1700, 1603, 1369, 1340, 1197, 771. Anal. Calcd. for C<sub>7</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>: C, 42.42; H, 5.09. Found: C, 42.64; H, 5.11.

#### *Experimental Procedures for Examples Described in Table 4*

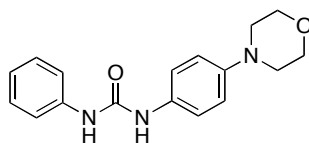
**General Procedure C:** An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with Pd(OAc)<sub>2</sub> (1 mol %) and *t*-BuBrettPhos (3 mol %). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and THF (2.0 mL/mmol) and degassed H<sub>2</sub>O (4 mol %) were added via syringe. After addition of the water, the solution was heated to 110 °C for 4 min.

A second oven-dried test tube, equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with the aryl urea (1.2 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.4 mmol) (aryl halides 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 three times), the aryl chloride (1.0 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula under a positive argon pressure. The solution was heated to 85 °C until the aryl halide had been

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 aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude product was adsorbed on silica gel and purified by flash chromatography on silica gel unless otherwise stated.

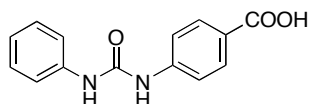


***N*-(4-(Methylthio)phenyl)-*N'*-phenylurea.**<sup>9</sup> Following general procedure C, a mixture of 4-chlorothioanisole (130  $\mu\text{L}$ , 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85  $^\circ\text{C}$  for 5 h. The crude product was purified via flash chromatography (1.25-2% MeOH/DCM) to provide the title compound as a white solid (253 mg, 98%), mp = 179 – 180  $^\circ\text{C}$  (lit. 184  $^\circ\text{C}$ ).<sup>9</sup>  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 8.71 (s, 1H), 8.62 (s, 1H), 7.52 – 7.35 (m, 4H), 7.27 (t,  $J$  = 7.8 Hz, 2H), 7.22 (d,  $J$  = 8.6 Hz, 2H), 6.96 (t,  $J$  = 7.3 Hz, 1H), 2.43 (s, 3H) ppm.  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 152.5, 139.7, 137.5, 129.9, 128.8, 127.8, 121.8, 118.9, 118.2, 16.01 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3297, 1636, 1558, 1496, 1233, 736, 692. Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{OS}$ : C, 65.09; H, 5.46. Found: C, 65.08; H, 5.28.

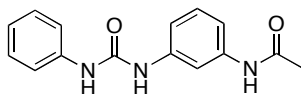


***N*-(4-Morpholinophenyl)-*N'*-phenylurea.** Following general procedure C, a mixture of 4-(4-chlorophenyl)morpholine (197.6 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85  $^\circ\text{C}$  for 7 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (50 mL) and washed with water (15 mL). The aqueous phase was extracted twice with ethyl acetate (50 mL) and the combined organic layers washed with brine and concentrated. The crude product was purified by trituration from dichloromethane, washed with a small amount of water and

dichloromethane to provide the title compound as a dark grey solid (289 mg, 97%), mp = 242 – 244 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.60 (s, 1H), 8.45 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.72 (s, 4H), 3.01 (s, 4H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 152.7, 146.5, 140.0, 132.1, 128.8, 121.6, 119.6, 118.0, 115.9, 66.2, 49.3 ppm. IR (neat, cm<sup>-1</sup>): 3296, 2961, 2851, 1647, 1555, 1448, 1239, 1124, 927.



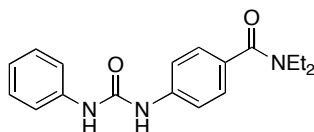
**4-(*N*-Phenylureid-*N'*-o)-benzoic acid.**<sup>10</sup> Following general procedure C, a mixture of 4-chlorobenzoic acid (156.4 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (782.0 mg, 2.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C. The reaction mixture became an unstirrable solid after 5 min and additional THF (1 mL) was added. It was then stirred at 85 °C for 5 h. The crude product was triturated from dichloromethane to provide the title compound as an off-white solid (229 mg, 89%), mp = > 400 °C (lit. 300 °C).<sup>10</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 12.61 (s, 1H), 9.06 (s, 1H), 8.79 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 167.1, 152.3, 144.1, 139.4, 130.6, 128.9, 123.7, 122.2, 118.4, 117.2 ppm. IR (neat, cm<sup>-1</sup>): 3312, 3061, 2554, 1650, 1595, 1547, 1314, 1233. Anal. Calcd. for C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: C, 65.62; H, 4.72. Found: C, 65.32; H, 4.60.



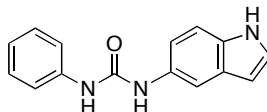
**3-(*N*-Phenylureid-*N'*-o)-acetanilide.** Following general procedure C, a mixture of 3-chloroacetanilide (169.9 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (782.0 mg, 2.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 5 h. The crude product was triturated from dichloromethane to provide the title compound as an off-white solid (243 mg, 90%), mp = 213 – 214 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.97 (s, 1H), 8.75 (s, 1H), 8.62 (s,



1H), 7.82 (s, 1H), 7.50 (d,  $J = 7.8$  Hz, 2H), 7.32 (t,  $J = 7.8$  Hz, 2H), 7.23 (s, 3H), 7.01 (s, 1H), 2.09 (s, 3H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 168.3, 152.4, 140.0, 139.8, 139.7, 128.9, 128.8, 121.8, 118.1, 112.8, 112.6, 108.8, 24.1 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3299, 1648, 1599, 1555, 1492, 1215, 692. Anal. Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$ : C, 66.90; H, 5.61. Found: C, 66.80; H, 5.46.

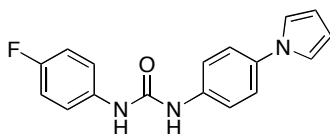


***N,N*-Diethyl 4-(3-phenylureido)benzamide.** Following general procedure C, a mixture of *N,N*-diethyl 4-bromobenzamide (256.3 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 7 h. The crude product was purified via the Biotage Isolera Four (silica-packed 50 g snap column; 50–100% EtOAc/hexanes) to provide the title compound as a white solid (291 mg, 93%), mp = 202 – 203 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d^6$ )  $\delta$ : 8.84 (s, 1H), 8.72 (s, 1H), 7.52 – 7.44 (m, 4H), 7.32 – 7.25 (m, 4H), 6.98 (t,  $J = 7.3$  Hz, 1H), 3.31 (br, 4H), 1.10 (t,  $J = 6.5$  Hz, 6H) ppm.  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$ : 172.2, 153.4, 140.9, 139.1, 129.6, 128.9, 126.9, 122.6, 119.1, 119.0, 43.9, 39.9, 14.1, 12.8 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3343, 1714, 1597, 1539, 1311, 1233, 1197. Anal. Calcd. for  $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_2$ : C, 69.43; H, 6.80. Found: C, 69.64; H, 6.82.

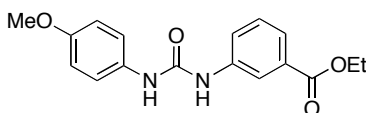


***N*-(Indol-5-yl)-*N'*-phenylurea.** Following general procedure C, a mixture of 5-chloroindole (151.8 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (782.0 mg, 2.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 7 h. The crude product was purified via flash chromatography (1–3% MeOH/DCM ( $\text{NH}_3$  sat'd)) to provide the title compound as an off-white solid (193 mg, 77%), mp = decomposition above 218 °C.  $^1\text{H}$  NMR (400 MHz,

DMSO- $d^6$ )  $\delta$ : 10.95 (s, 1H), 8.57 (s, 1H), 8.40 (s, 1H), 7.70 (d,  $J$  = 1.2 Hz, 1H), 7.47 (d,  $J$  = 8.1 Hz, 2H), 7.34 – 7.23 (m, 4H), 7.09 (dd,  $J$  = 8.6, 1.7 Hz, 1H), 6.94 (t,  $J$  = 7.2 Hz, 1H), 6.36 (s, 1H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 153.0, 140.2, 132.3, 131.4, 128.8, 127.7, 125.8, 121.4, 118.0, 114.8, 111.3, 110.0, 100.9 ppm. IR (neat,  $\text{cm}^{-1}$ ): 3312, 1636, 1597, 1552, 1321, 1223, 725. Anal. Calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ : C, 71.70; H, 5.21. Found: C, 71.70; H, 5.28.

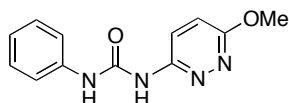


***N*-(4-Fluorophenyl)-*N'*-(4'-(1*H*-pyrrol-1-yl)phenyl)urea.** Following general procedure C, a mixture of 1-(4-chlorophenyl)-1*H*-pyrrole (177.8 mg, 1.0 mmol), 4-fluorophenylurea (184.9 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C. The reaction mixture became an unstirrable solid after 5 min and additional THF (2 mL) was added. It was then stirred at 85 °C for 5 h. The crude product was triturated from warm methanol to provide the title compound as an off-white solid (287 mg, 97%, 1.5% 4-fluorophenylurea), mp = 247 – 250 °C.  $^1\text{H}$  NMR (400 MHz, DMSO- $d^6$ )  $\delta$ : 8.76 (s, 1H), 8.73 (s, 1H), 7.57 – 7.44 (m, 6H), 7.27 (t,  $J$  = 2.0 Hz, 2H), 7.13 (t,  $J$  = 8.9 Hz, 2H), 6.23 (t,  $J$  = 2.0 Hz, 2H) ppm.  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 157.4 (d,  $J$  = 238.2 Hz), 152.7, 137.2, 136.0 (d,  $J$  = 2.2 Hz), 134.5, 120.1, 119.99, 119.3, 118.9, 115.3 (d,  $J$  = 22.2 Hz), 110.0 ppm (observed complexity is due to C–F splitting).  $^{19}\text{F}$  NMR (376 MHz, DMSO- $d^6$ )  $\delta$ : -121.66. IR (neat,  $\text{cm}^{-1}$ ): 3286, 3137, 1636, 1605, 1567, 1519, 1216, 1073, 830, 728, 529.

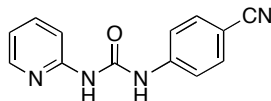


**Ethyl 3-(*N*-(4'-methoxyphenyl)ureid)-*N'*-o)benzoate.** Following general procedure C, a mixture of ethyl-3-chlorobenzoate (155.0  $\mu\text{L}$ , 1.0 mmol), 4-methoxyphenylurea (198.9 mg, 1.2 mmol),  $\text{Pd}(\text{OAc})_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $\text{Cs}_2\text{CO}_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 5 h. The

crude product was purified via flash chromatography (1-1.6% MeOH/DCM ( $NH_3$  sat'd)) to provide the title compound as a white solid (267 mg, 85%), mp = 179 – 180 °C.  $^1H$  NMR (400 MHz, DMSO)  $\delta$ : 8.86 (s, 1H), 8.48 (s, 1H), 8.14 (s, 1H), 7.65 (dd,  $J$  = 8.2, 0.8 Hz, 1H), 7.55 (d,  $J$  = 7.7 Hz, 1H), 7.41 (t,  $J$  = 7.9 Hz, 1H), 7.37 (d,  $J$  = 8.9 Hz, 2H), 6.87 (d,  $J$  = 9.0 Hz, 2H), 4.31 (q,  $J$  = 7.1 Hz, 2H), 3.72 (s, 3H), 1.32 (t,  $J$  = 7.1 Hz, 3H) ppm.  $^{13}C$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 165.7, 154.6, 152.7, 140.4, 132.5, 130.4, 129.1, 122.6, 122.2, 120.3, 118.5, 114.0, 60.7, 55.2, 14.2 ppm. IR (neat,  $cm^{-1}$ ): 3289, 1726, 1639, 1559, 1510, 1299, 1247, 1031. Anal. Calcd. for  $C_{17}H_{18}N_2O_4$ : C, 64.96; H, 5.77. Found: C, 64.71; H, 5.69.

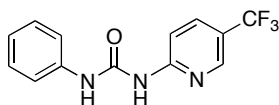


**N-(6-Methoxypyridazin-3-yl)-N'-phenylurea.** Following general procedure C, a mixture of 3-chloro-6-methoxypyridazine (144.7 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol),  $Pd(OAc)_2$  (1 mol %), *t*-BuBrettPhos (3 mol %),  $Cs_2CO_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 5 h. The crude product was purified via flash chromatography (1-2% MeOH/DCM ( $NH_3$  sat'd)) to provide the title compound as a white solid (186 mg, 76%), mp = 213 °C.  $^1H$  NMR (400 MHz, DMSO- $d^6$ )  $\delta$ : 9.85 (s, 1H), 9.59 (s, 1H), 7.92 (d,  $J$  = 9.5 Hz, 1H), 7.49 (d,  $J$  = 7.9 Hz, 2H), 7.31 (t,  $J$  = 7.8 Hz, 2H), 7.23 (d,  $J$  = 9.5 Hz, 1H), 7.02 (t,  $J$  = 7.3 Hz, 1H), 3.96 (s, 3H) ppm.  $^{13}C$  NMR (101 MHz, DMSO- $d^6$ )  $\delta$ : 161.6, 152.5, 152.1, 138.9, 128.9, 122.6, 122.1, 119.7, 118.8, 54.2 ppm. IR (neat,  $cm^{-1}$ ): 3327, 2950, 1705, 1599, 1558, 1427, 1293, 1028, 831, 749. Anal. Calcd. for  $C_{12}H_{12}N_4O_2$ : C, 59.01; H, 4.95. Found: C, 58.74; H, 4.88.

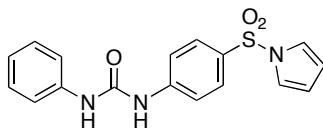


**4-(N-Pyridin-2-ylureid-N'-o)benzonitrile.** Following general procedure C, a mixture of 4-chlorobenzonitrile (137.5 mg, 1.0 mmol), pyridin-2-ylurea (164.5 mg, 1.2 mmol),  $Pd(OAc)_2$  (3 mol %), *t*-BuBrettPhos (9 mol %),  $Cs_2CO_3$  (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 6 h. The crude product was

purified via flash chromatography (20-66% EtOAc/hexanes) to provide the title compound as a white solid (163 mg, 68%), mp = 205 – 206 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 10.88 (s, 1H), 9.60 (s, 1H), 8.29 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.80 – 7.68 (m, 5H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 6.7, 5.3 Hz, 1H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 152.4, 151.9, 147.0, 143.5, 138.7, 133.4, 119.2, 118.7, 118.0, 112.1, 104.0 ppm. IR (neat, cm<sup>-1</sup>): 2979, 2222, 1713, 1583, 1549, 1326, 1247, 1177, 1156, 773. Anal. Calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>4</sub>O: C, 65.54; H, 4.23. Found: C, 65.28; H, 4.25.

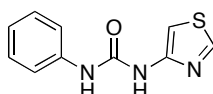


***N*-Phenyl-*N'*-(5-trifluoromethylpyridin-2-yl)urea.** Following general procedure C, a mixture of 2-chloro-5-trifluoromethylpyridine (181.6 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (3 mol %), *t*-BuBrettPhos (9 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 5 h. The crude product was purified via flash chromatography (1-1.6% MeOH/DCM) to provide the title compound as an off-white solid (244 mg, 87%), mp = 202 – 203 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.98 (s, 1H), 9.80 (s, 1H), 8.63 (s, 1H), 8.08 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 1H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.7, 151.7, 144.9 (q, *J* = 4.3 Hz), 138.7, 135.7 (q, *J* = 3.0 Hz), 128.9, 124.1 (q, *J* = 271.1 Hz), 122.8, 118.9, 118.7 (q, *J* = 32.2 Hz), 111.6 ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sup>6</sup>) δ: -60.98. IR (neat, cm<sup>-1</sup>): 3060, 1712, 1601, 1565, 1316, 1122, 845, 754. Anal. Calcd. for C<sub>13</sub>H<sub>10</sub>F<sub>3</sub>N<sub>3</sub>O: C, 55.52; H, 3.58. Found: C, 55.35; H, 3.49.



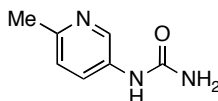
***N*-(4-((1*H*-Pyrrol-1-yl)sulfonyl)phenyl)-*N'*-phenylurea.** Following general procedure C, a mixture of 1-(4-chlorophenyl)sulfonyl-1*H*-pyrrole (241.3 mg, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 5 h.

The crude product was purified via flash chromatography (25-50% EtOAc/hexanes) to provide the title compound as an off-white solid (198 mg, 58%), mp = 170 – 171 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.28 (s, 1H), 8.87 (s, 1H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 2H), 7.33 – 7.26 (m, 4H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.33 (t, *J* = 2.2 Hz, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 152.0, 145.4, 139.1, 129.8, 128.9, 128.4, 122.4, 120.8, 118.6, 117.9, 113.6 ppm. IR (neat, cm<sup>-1</sup>): 3343, 1656, 1590, 1547, 1370, 1193, 1164, 1055, 625. Anal. Calcd. for C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S: C, 59.81; H, 4.43. Found: C, 59.69; H, 4.68.



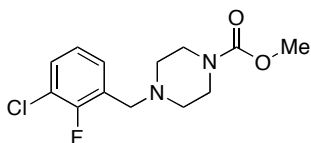
**N-Phenyl-N'-thiazol-4-ylurea.** Following general procedure C, a mixture of 4-bromothiazole (90 μL, 1.0 mmol), phenylurea (163.4 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (6 mol %), *t*-BuBrettPhos (18 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 75 °C for 8 h. The crude product was purified via flash chromatography (10-20% acetone/diethyl ether). To remove traces of ligand the product was flashed through a short silica column (2% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to give the product as a white solid (190 mg, 86%), mp = 142 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.48 (s, 1H), 8.93 (s, 1H), 8.82 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.35 (s, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 6.98 (t, *J* = 7.1 Hz, 1H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 151.9, 151.8, 149.4, 139.4, 128.9, 122.1, 118.1, 96.9 ppm. IR (neat, cm<sup>-1</sup>): 3325, 1655, 1549, 1445, 1209, 1056, 877, 755, 696. Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>OS: C, 54.78; H, 4.14. Found: C, 54.57; H, 4.08.

### *Experimental Procedures for Examples Described in Scheme 2*

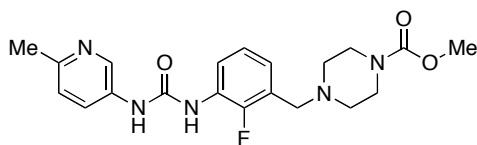


**(2-Methylpyridin-5-yl)urea.** Following general procedure A, a mixture of 5-bromo-2-picoline (172.1 mg, 1.0 mmol), benzylurea (180.2 mg, 1.2 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and

THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, Pd/C (20 mol %), concentrated HCl (2.0 mL) and MeOH (6 mL) were added and the resulting reaction mixture stirred at room temperature under one atmosphere of H<sub>2</sub> for 20 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM (*NH*<sub>3</sub> sat'd)) to provide the title compound as a white solid (117 mg, 77%), mp = decomposition above 204 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.58 (s, 1H), 8.38 (d, *J* = 2.6 Hz, 1H), 7.77 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 5.94 (s, 2H), 2.36 (s, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 156.1, 150.1, 138.9, 134.7, 125.5, 122.6, 23.2 ppm. IR (neat, cm<sup>-1</sup>): 3307, 1683, 1577, 1506, 1472, 843, 821, 786, 725, 561. Anal. Calcd. for C<sub>7</sub>H<sub>9</sub>N<sub>3</sub>O: C, 55.62; H, 6.00. Found: C, 55.72; H, 6.06.



**Methyl 4-(3-chloro-2-fluorobenzyl)piperazine-1-carboxylate.** An oven-dried 50 mL flask equipped with a stirring bar under argon was charged with 3-chloro-2-fluorobenzyl bromide (2.06 g, 9.2 mmol) which was then dissolved in anhydrous DMF (15 mL). Methyl piperazine-1-carboxylate (1.45 g, 10.2 mmol) and *N,N*-diisopropylethylamine (1.63 mL, 9.9 mmol) were added and the resulting solution stirred at room temperature for 75 min. The reaction mixture was concentrated *in vacuo*, the residue taken up in DCM, washed with brine and the aqueous phase extracted with DCM and EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude mixture was purified via the Biotage Isolera Four (silica-packed 50 g snap column; 20-100% EtOAc/hexanes) to provide the title compound as a yellow oil (1.71 mg, 65%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 7.48 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 3.57 (s, 5H), 3.34 (t, *J* = 4.9 Hz, 4H), 2.34 (t, *J* = 4.7 Hz, 4H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.8 (d, *J* = 247.2 Hz), 155.0, 130.2 (d, *J* = 4.0 Hz), 129.4, 126.4 (d, *J* = 14.4 Hz), 125.04 (d, *J* = 4.4 Hz), 119.60 (d, *J* = 18.1 Hz), 54.5, 52.2, 52.0, 43.33 ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sup>6</sup>) δ: -120.75. IR (neat, cm<sup>-1</sup>): 2952, 2816, 1705, 1458, 1244, 1127, 1004, 770. Anal. Calcd. for C<sub>13</sub>H<sub>16</sub>ClFN<sub>2</sub>O<sub>2</sub>: C, 54.46; H, 5.62. Found: C, 54.20; H, 5.68.

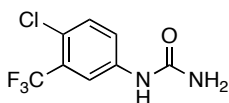


**Methyl 4-(2-fluoro-3-(3-(6-methylpyridin-3-yl)ureido)benzyl)piperazine-1-carboxylate (Omeamtiv Mecarbil).**<sup>11</sup> Following general procedure C, a mixture of methyl 4-(3-chloro-2-fluorobenzyl)piperazine-1-carboxylate (143.1 mg, 0.5 mmol), (2-Methylpyridin-5-yl)urea (90.6 mg, 0.6 mmol), Pd(OAc)<sub>2</sub> (5 mol %), *t*-BuBrettPhos (15 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 0.7 mmol), degassed water (4 mol %) and THF (1 mL) was heated to 65 °C for 6 h. The crude product was purified via flash chromatography (5-10% MeOH/DCM) to provide the title compound as a slightly brownish solid (164 mg, 82%), mp = 180 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.13 (s, 1H), 8.59 (d, *J* = 1.5 Hz, 1H), 8.47 (d, *J* = 2.3 Hz, 1H), 8.05 (t, *J* = 7.6 Hz, 1H), 7.83 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 7.00 (t, *J* = 6.7 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 2H), 3.35 (br, 4H), 2.40 (s, 3H), 2.36 (br, 4H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 155.0, 152.3, 151.1, 150.7 (d, *J* = 242.5 Hz), 139.2, 133.6, 127.3 (d, *J* = 10.9 Hz), 125.8, 124.1 (d, *J* = 13.3 Hz), 124.0 (d, *J* = 4.0 Hz), 123.8 (d, *J* = 3.8 Hz), 122.8, 119.5, 54.6, 52.2, 52.1, 43.4, 23.2 ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sup>6</sup>) δ: -135.09. IR (neat, cm<sup>-1</sup>): 3297, 2920, 2823, 1705, 1638, 1557, 1476, 1450, 1233, 1189, 1129, 779, 765. Anal. Calcd. for C<sub>20</sub>H<sub>24</sub>FN<sub>5</sub>O<sub>3</sub>: C, 59.84; H, 6.03. Found: C, 59.64; H, 5.92.

**General Procedure D:** An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with Pd(OAc)<sub>2</sub> (1 mol %) and *t*-BuBrettPhos (3 mol %). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and THF (2.0 mL) and degassed H<sub>2</sub>O (4 mol %) were added via syringe. After addition of the water, the solution was heated to 110 °C for 4 minutes.

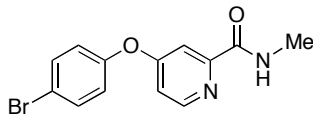
A second oven-dried test tube, equipped with a magnetic stir bar and fitted with a Teflon screwcap septum, was charged with 2,4-dimethoxybenzylurea (1.0 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (1.4 mmol). The vessel was evacuated and backfilled with argon (this process

was repeated a total of three times), the aryl bromide (1.0 mmol) was added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula under a positive argon pressure. The solution was heated to 85 °C until the aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature and concentrated HCl (2 mL) was added slowly. The reaction mixture was stirred at 40 °C for one hour before it was quenched with 2M NaOH, diluted with ethyl acetate and washed three times with 2M NaOH. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude product was adsorbed on silica gel and purified by flash chromatography on silica gel.

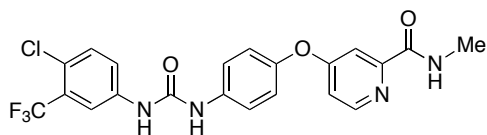


**4-Chloro-3-trifluoromethylphenylurea** Following general procedure D, a mixture of 5-bromo-2-chlorobenzotrifluoride (148.7  $\mu$ L, 1.0 mmol), 2,4-dimethoxybenzylurea (210.2 mg, 1.0 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos (3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (456.2 mg, 1.4 mmol), degassed water (4 mol %) and THF (2 mL) was heated to 85 °C for 2 h. After cooling to room temperature, concentrated HCl (2 mL) was added and the resulting reaction mixture stirred at 40 °C for 1 h. The crude product was purified via flash chromatography (4-7% MeOH/DCM) to provide the title compound as a brown amorphous solid (189 mg, 78%), mp = 94 - 97 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 9.04 (s, 1H), 8.04 (d, *J* = 2.5 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 6.09 (s, 2H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : 155.8, 140.3, 131.8, 126.7 (q, *J* = 30.4 Hz), 122.9 (q, *J* = 272.9 Hz), 122.4, 121.5 (q, *J* = 1.8 Hz), 116.3 (q, *J* = 5.7 Hz) ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (282 MHz, DMSO-*d*<sup>6</sup>)  $\delta$ : -61.94 ppm. IR (neat, cm<sup>-1</sup>): 3335, 1671, 1548, 1484, 1422, 1345, 1133, 1033, 829. Anal. Calcd. for C<sub>8</sub>H<sub>6</sub>ClF<sub>3</sub>N<sub>2</sub>O: C, 40.27; H, 2.53. Found: C, 40.53; H, 2.56.





**[4-(4-Bromophenoxy)(2-pyridyl)]-N-methylcarboxamide.** An oven-dried 3-necked 50 mL flask equipped with a reflux condenser and a stirring bar under argon was charged with 4-bromophenol (2.03 g, 11.7 mmol) and potassium *tert*-butoxide (1.32 g, 11.7 mmol). Anhydrous DMF (17 mL) was added and the resulting pale green solution stirred at room temperature for 2 h. 4-Chloropyridin-2-yl-*N*-methylcarboxamide (1.25 g, 7.3 mmol) in anhydrous DMF (3 mL) and potassium carbonate (0.81 g, 5.9 mmol) were then added and the resulting dark green suspension was heated to 80 °C for 11 h. The resulting purple suspension was cooled to room temperature and poured into EtOAc/brine (1:1), the phases separated and the aqueous layer extracted with EtOAc. The combined organic layers were subsequently washed four times with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. When the crude was treated with a mixture of hexanes and EtOAc (3:1), a white solid precipitated. It was filtered off, washed with the abovementioned mixture and dried to afford analytically pure product (1.12 g). The filtrate was concentrated and subjected to flash chromatography (30-50% EtOAc/hexanes) to give additional product as white crystals (total 2.04 g, overall yield 90%), mp = 129 – 130 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 8.79 (d, *J* = 4.6 Hz, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 5.6, 2.6 Hz, 1H), 2.79 (d, *J* = 4.8 Hz, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 158.1, 156.7, 145.7, 145.6, 143.6, 126.4, 116.2, 111.0, 107.4, 102.2, 19.0 ppm. IR (neat, cm<sup>-1</sup>): 3351, 1663, 1604, 1565, 1533, 1293, 1235, 1202. Anal. Calcd. for C<sub>13</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 50.84; H, 3.61. Found: C, 50.80; H, 3.56.

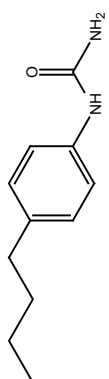


***N*-[4-Chloro-3-(trifluoromethyl)phenyl]-({4-[2-(*N*-methyl-carbamoyl)(4-pyridyloxy)]phenyl}amino)-carboxamide (Sorafenib).**<sup>12</sup> Following general procedure C, a mixture of [4-(4-Bromophenoxy)(2-pyridyl)]-*N*-methylcarboxamide (153.6 mg, 0.5 mmol), 4-chloro-3-trifluoromethylphenylurea (143.2 mg, 0.6 mmol), Pd(OAc)<sub>2</sub> (1 mol %), *t*-BuBrettPhos

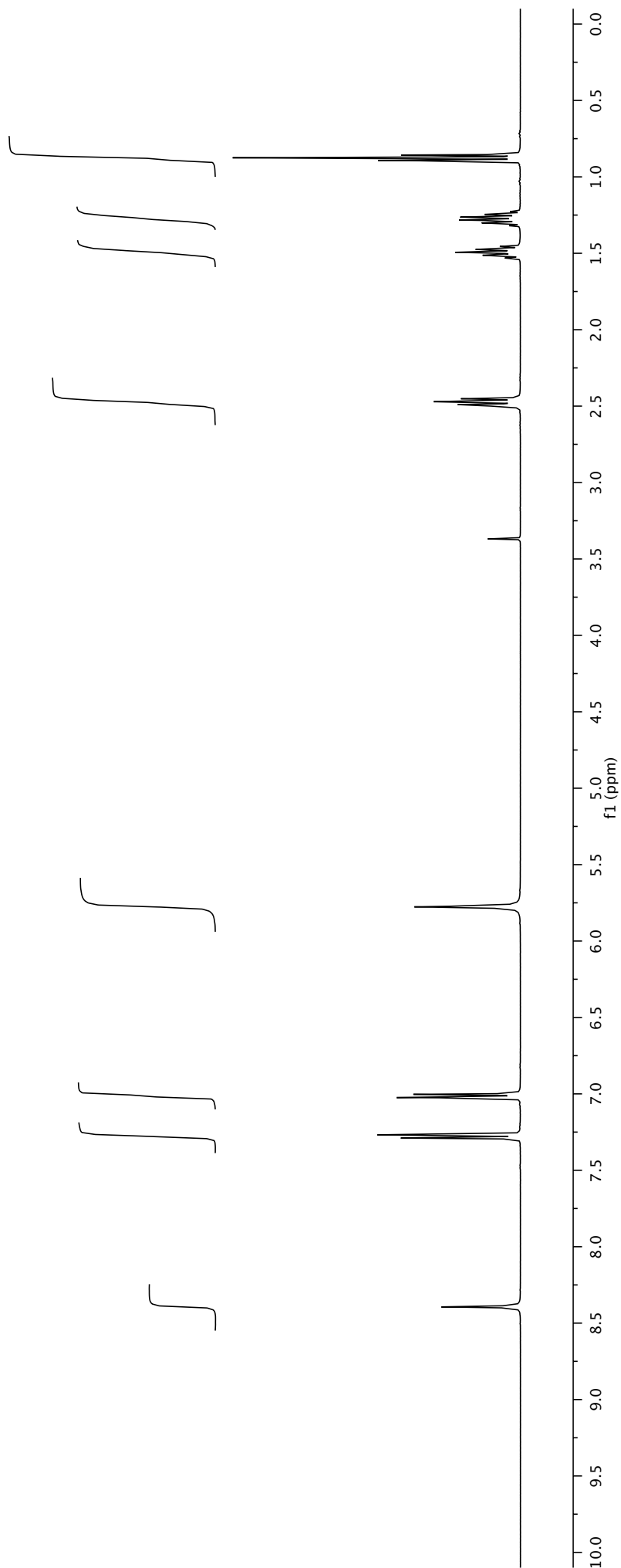
(3 mol %), Cs<sub>2</sub>CO<sub>3</sub> (391.0 mg, 1.2 mmol), degassed water (4 mol %) and THF (1 mL) was heated to 75 °C for 5 h. The crude product was purified via flash chromatography (2.5-4% MeOH/DCM) to provide the title compound as an off-white solid (206 mg, 89%), mp = 202 – 203 °C (lit. 210 – 212 °C).<sup>12</sup> <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sup>6</sup>) δ: 9.21 (s, 1H), 8.99 (s, 1H), 8.77 (d, *J* = 4.9 Hz, 1H), 8.49 (d, *J* = 5.6 Hz, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.61 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 2H), 7.13 (dd, *J* = 5.6, 2.6 Hz, 1H), 2.79 (d, *J* = 4.8 Hz, 3H) ppm. <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sup>6</sup>) δ: 166.6, 164.4, 153.1 (q, *J* = 2.4 Hz), 150.9, 148.5, 139.9, 137.7, 132.6, 127.4 (q, *J* = 20.6 Hz), 125.5, 123.7, 123.4 (q, *J* = 273.4 Hz), 123.0 (q, *J* = 1.6 Hz), 122.1, 121.1, 117.4 (q, *J* = 5.6 Hz), 114.6, 109.3, 26.6 ppm (observed complexity is due to C–F splitting). <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sup>6</sup>) δ: -61.76. IR (neat, cm<sup>-1</sup>): 3301, 1658, 1546, 1506, 1418, 1300, 1199, 1133, 924, 835. Anal. Calcd. for C<sub>21</sub>H<sub>16</sub>ClF<sub>3</sub>N<sub>4</sub>O<sub>3</sub>: C, 54.26; H, 3.47. Found: C, 54.12; H, 3.57.

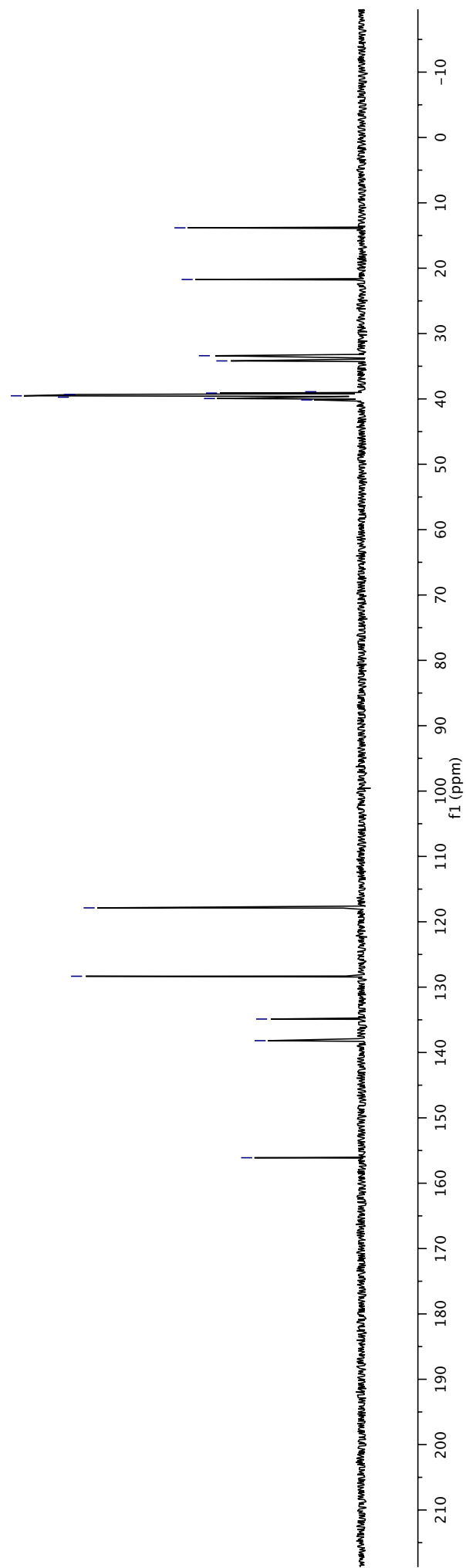
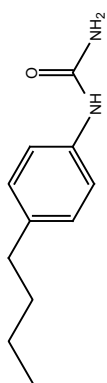
## References

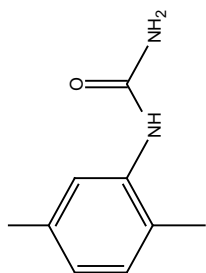
- <sup>1</sup> Moschel, R. C.; Hudgins, W. R.; Dipple, A. *J. Org. Chem.* **1986**, *51*, 4180.
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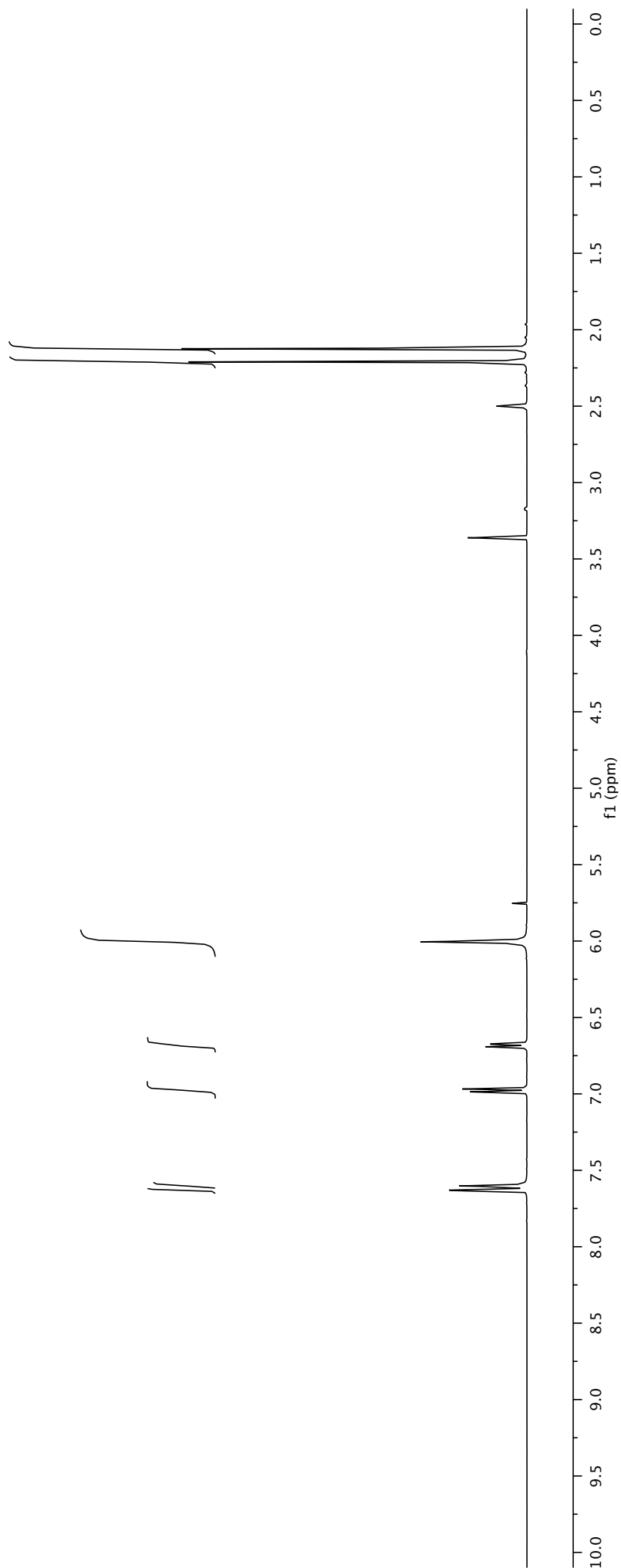
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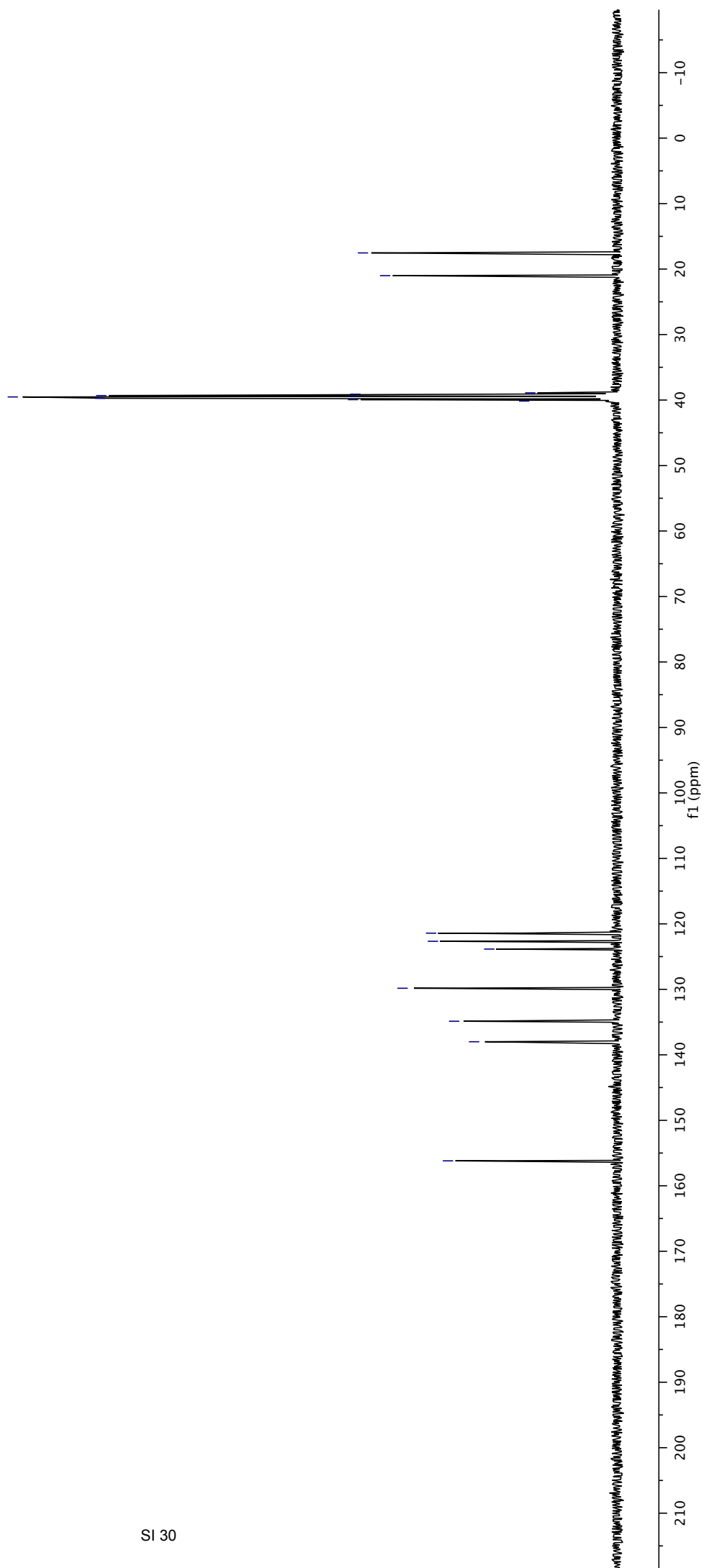


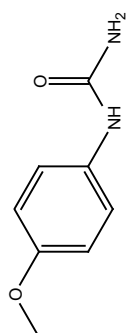
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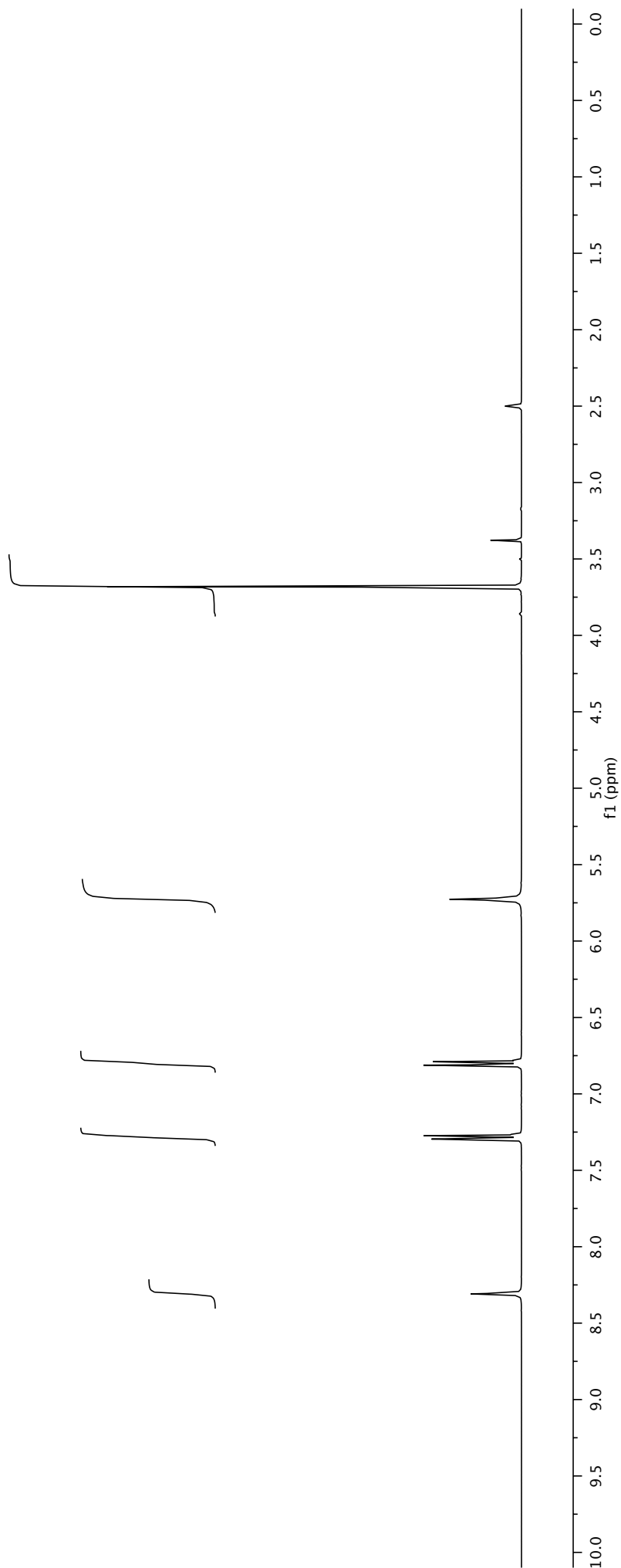
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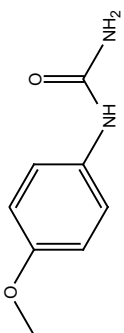
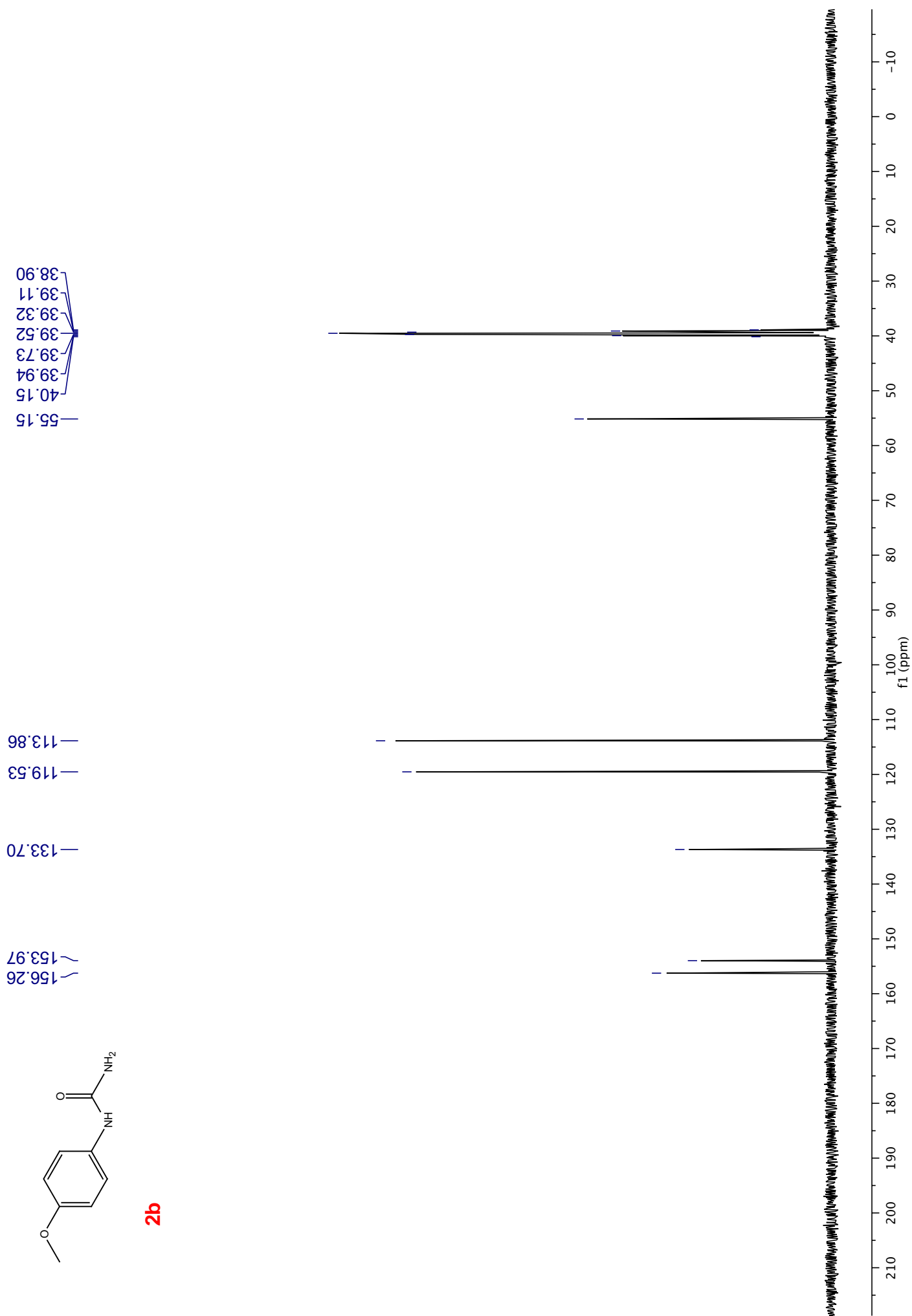




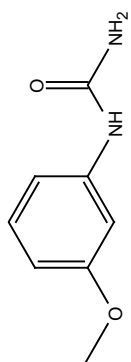


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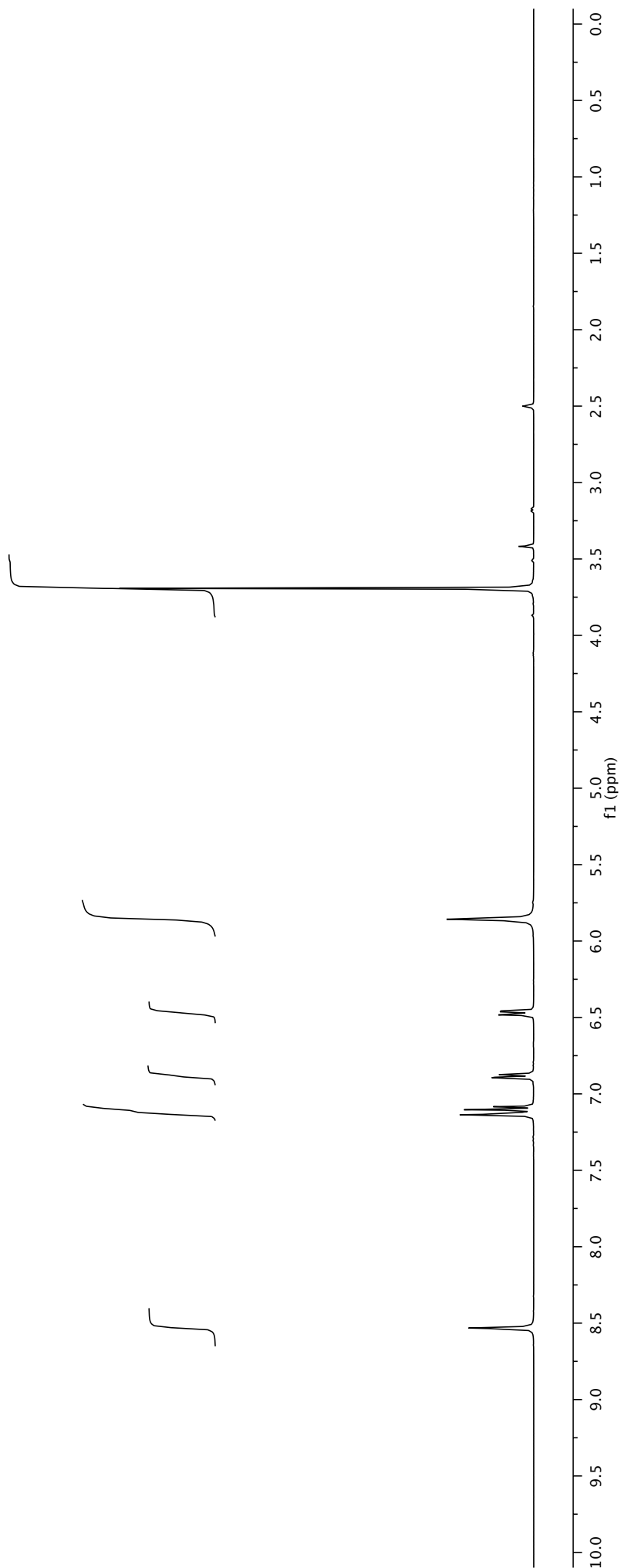


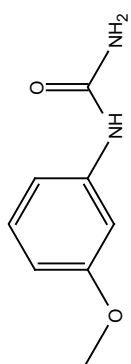
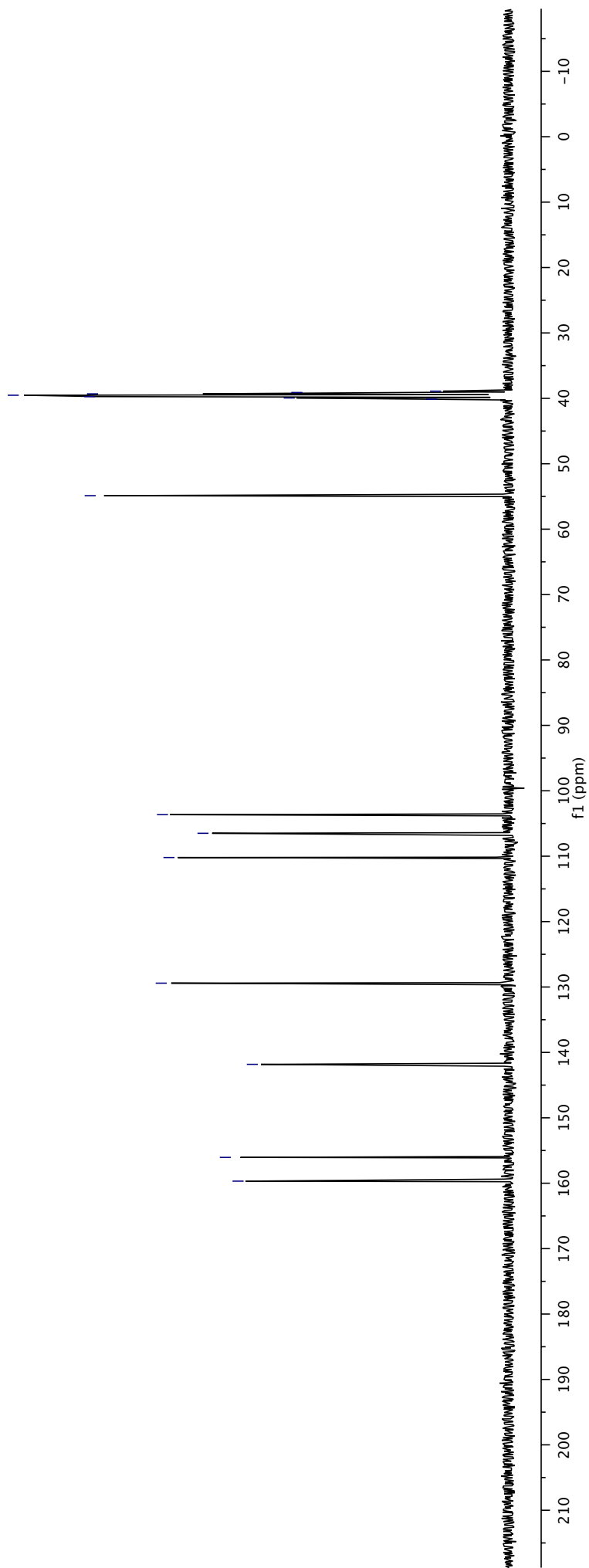
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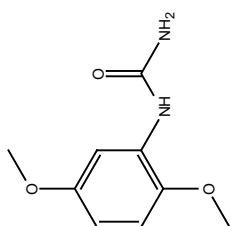




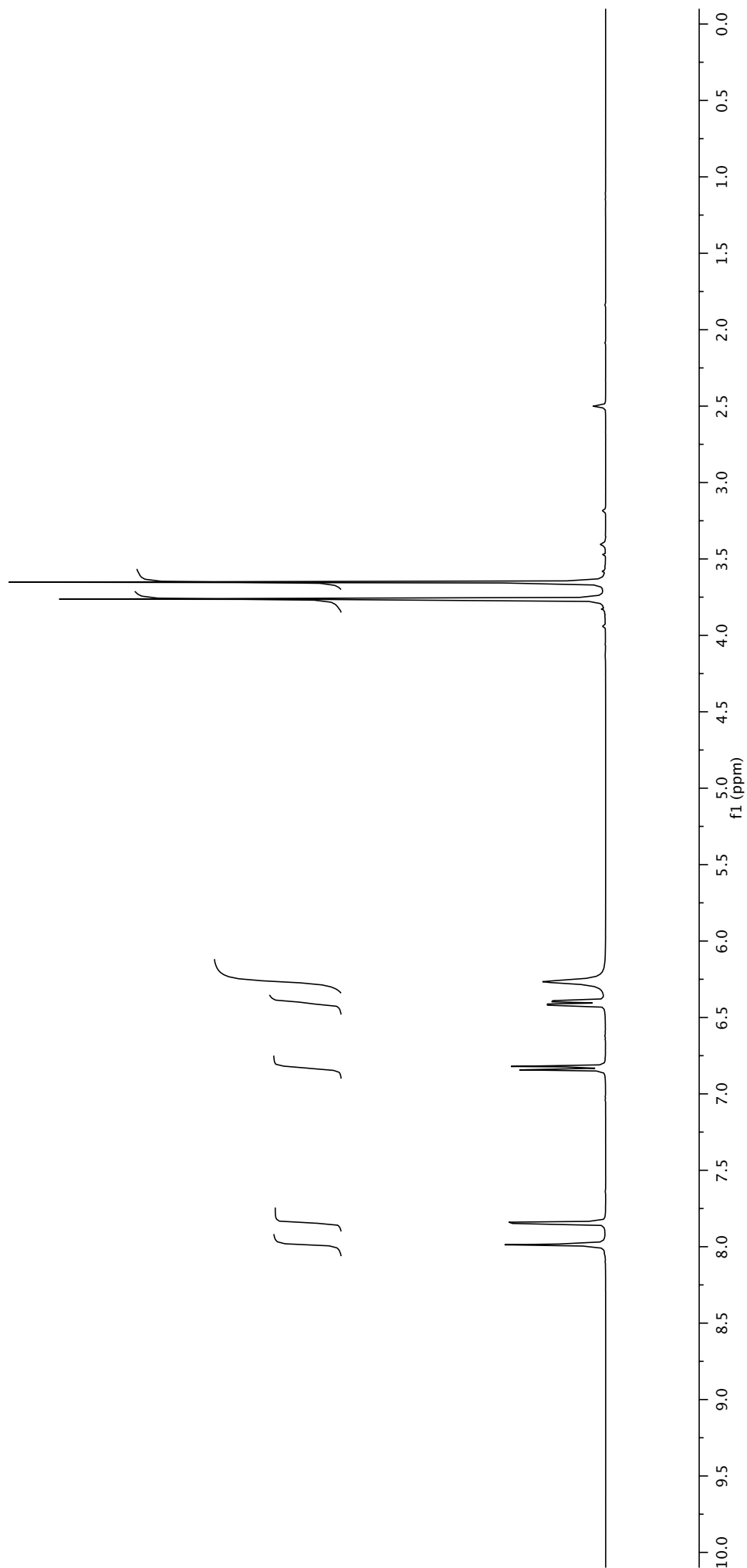
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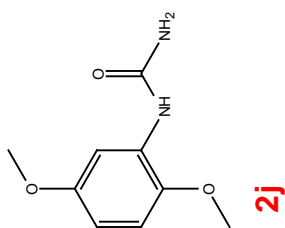
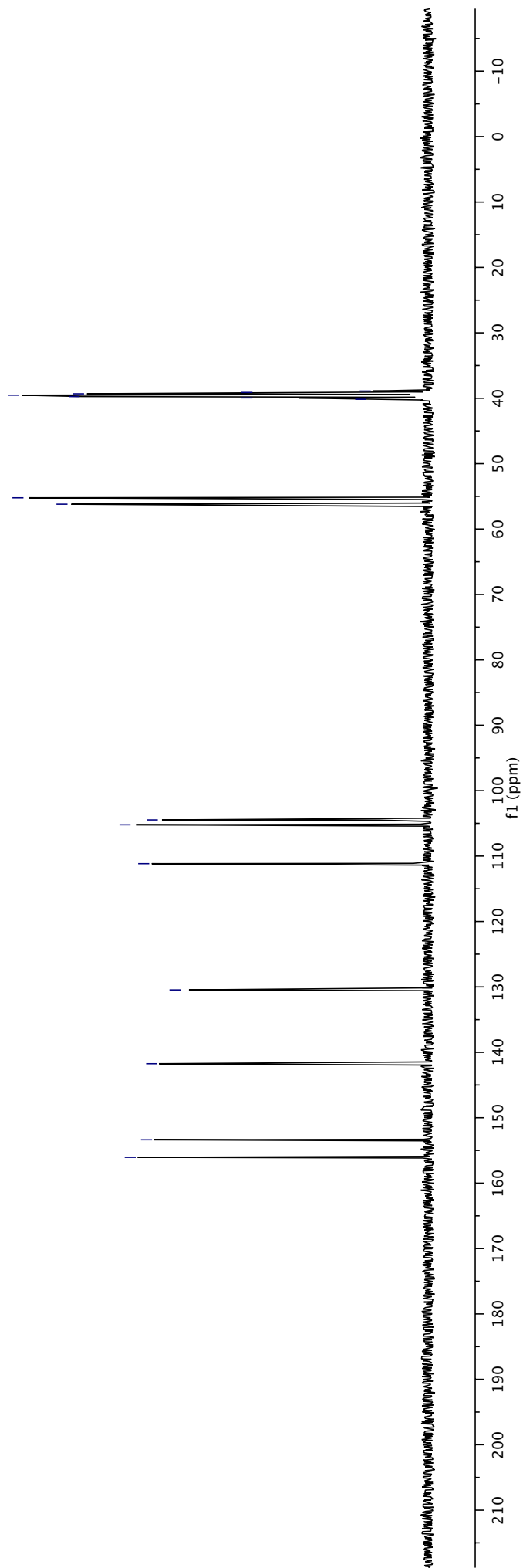


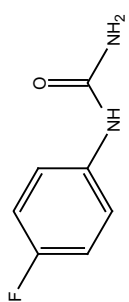
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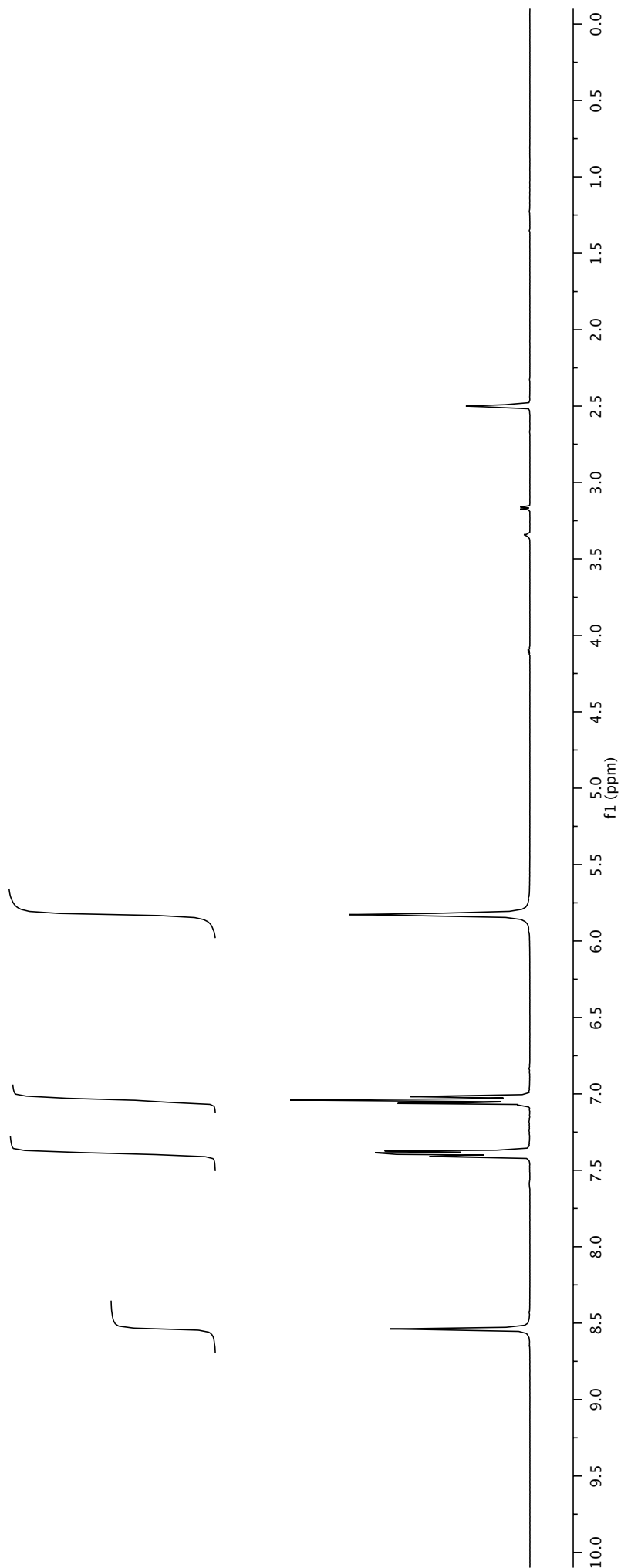
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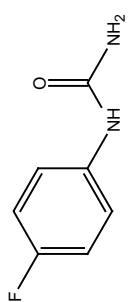
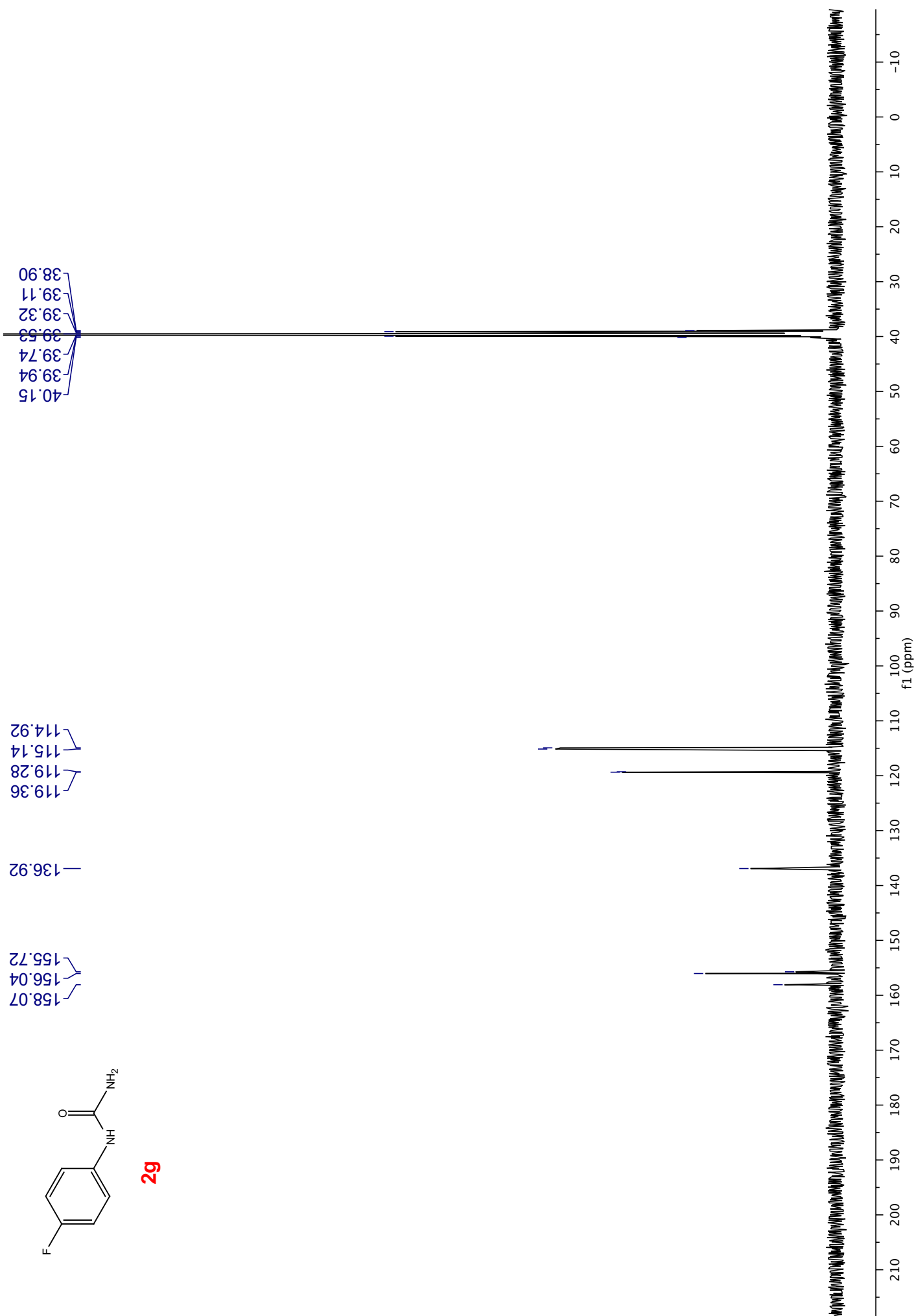


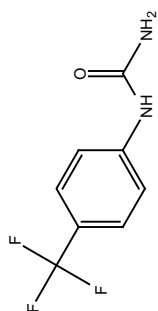




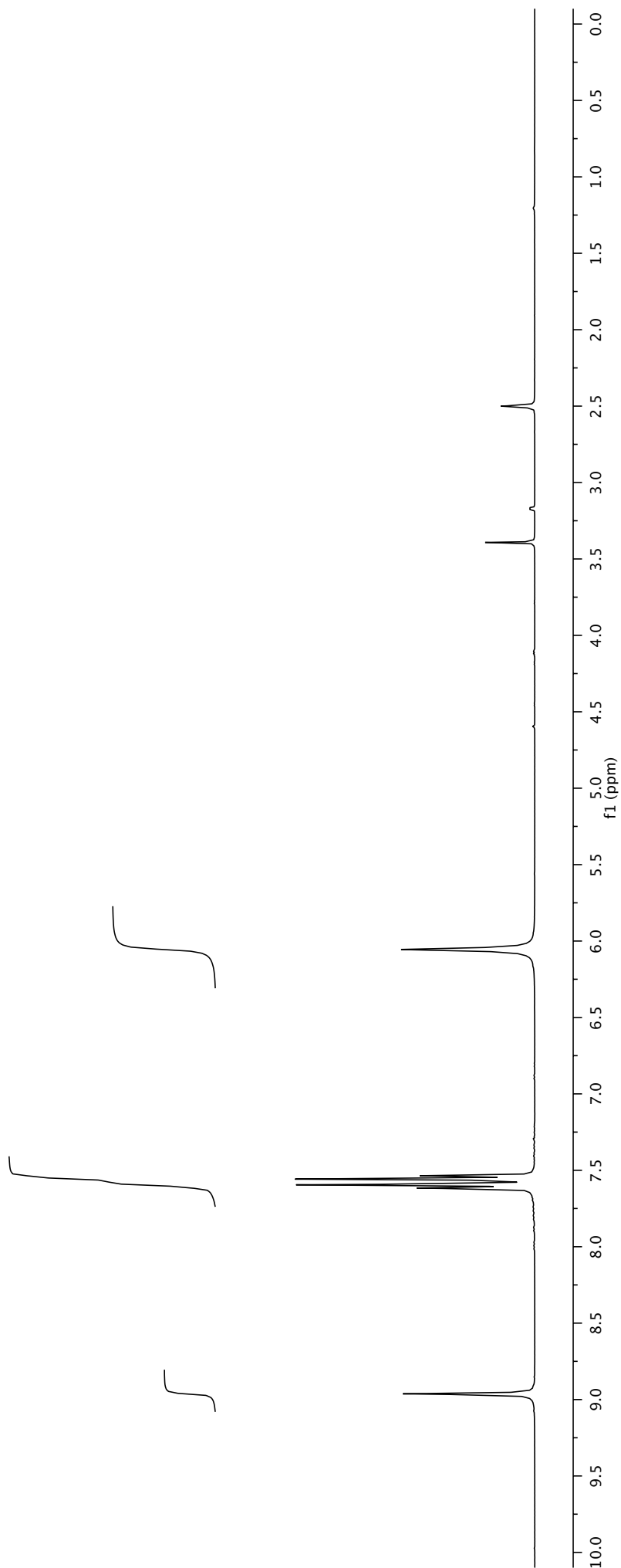
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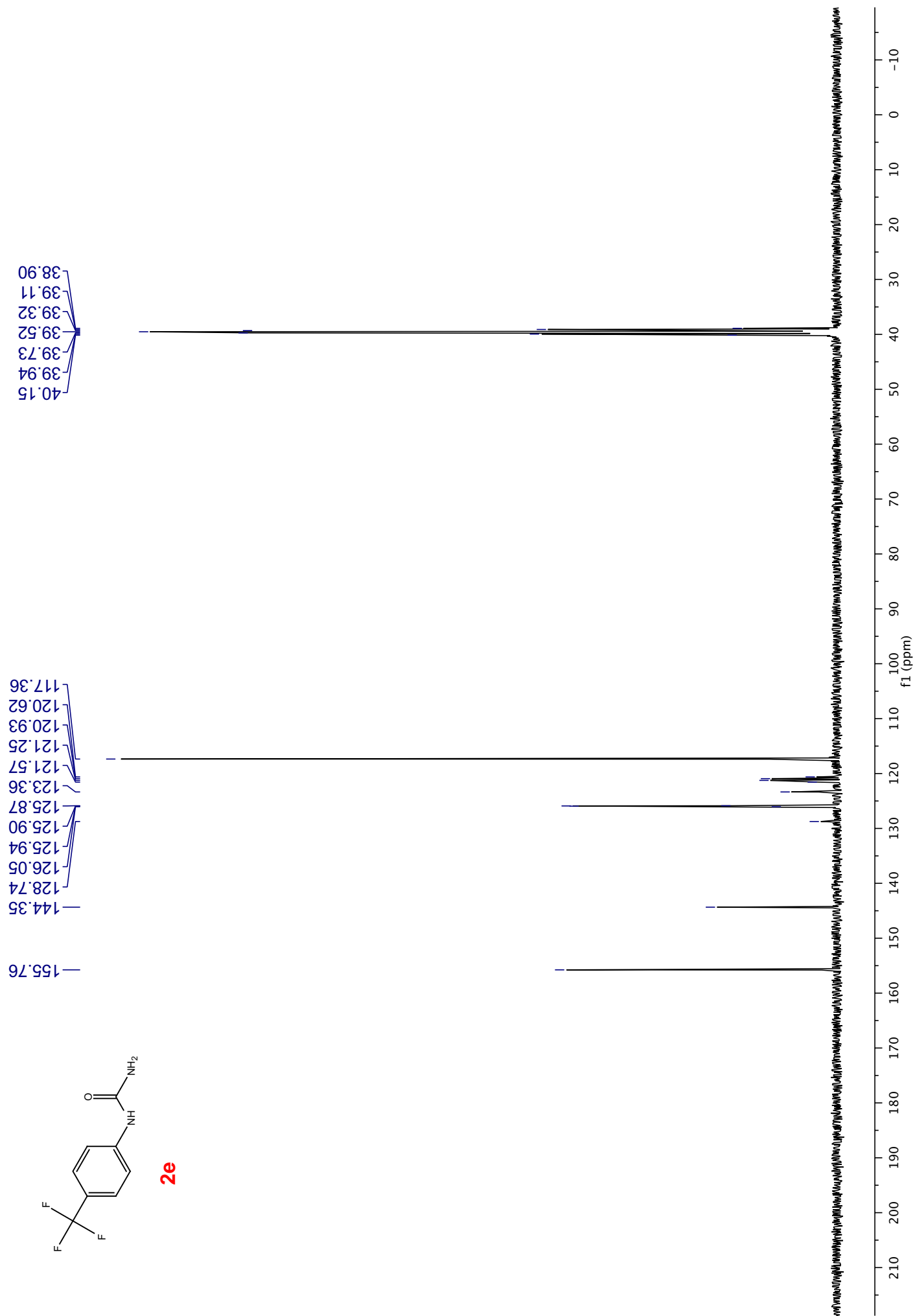


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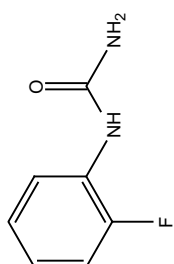


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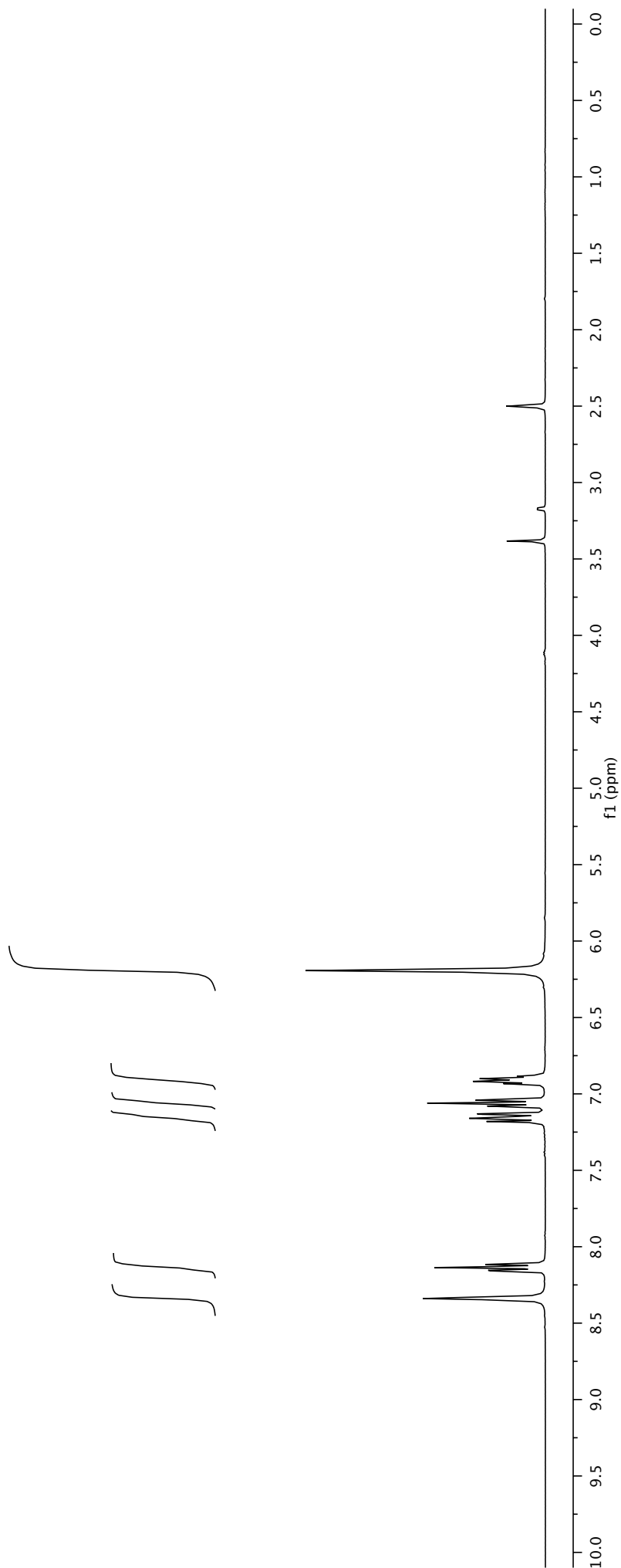


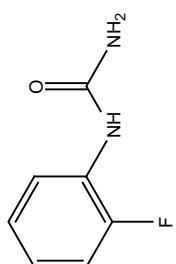






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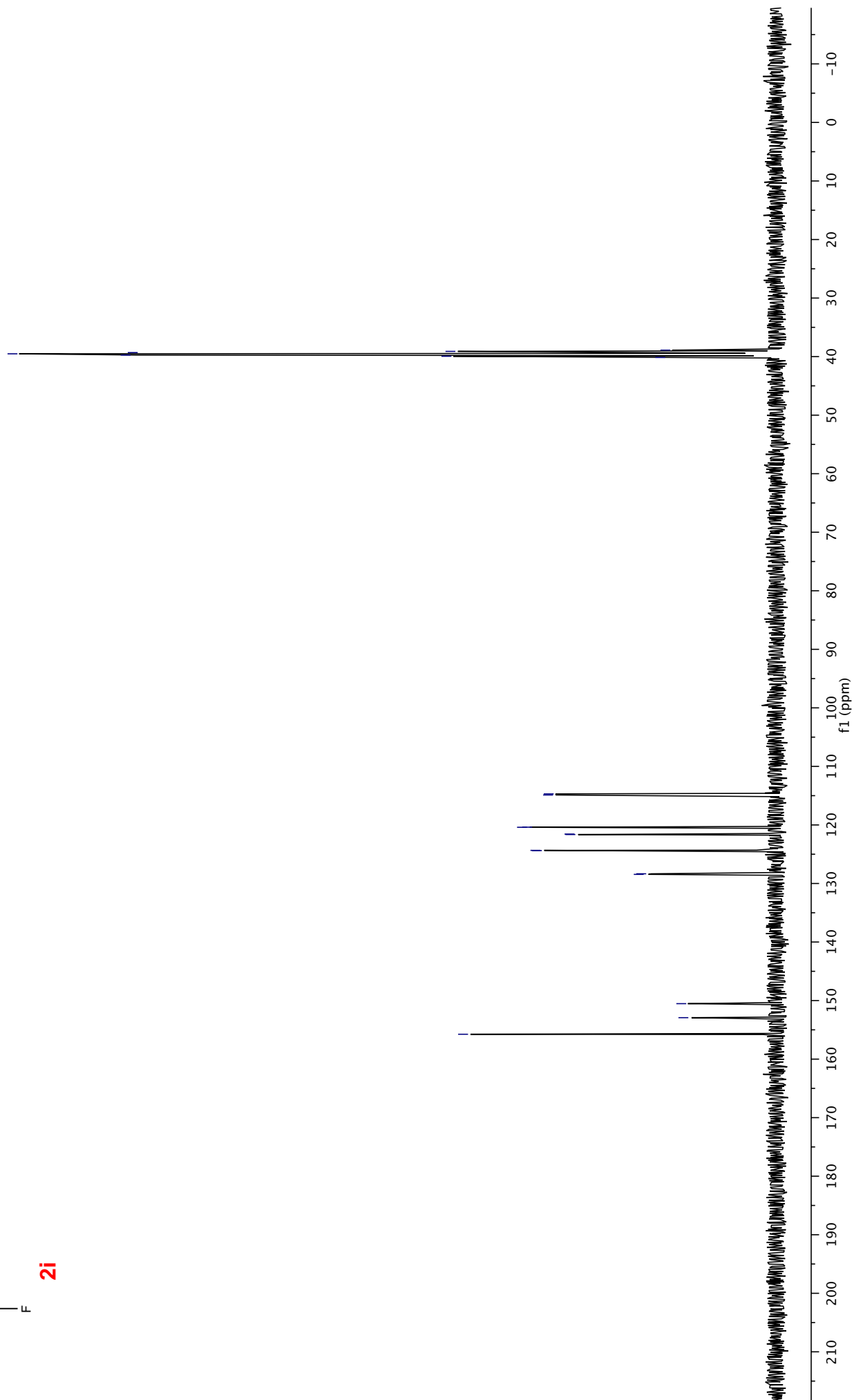


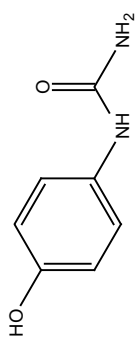
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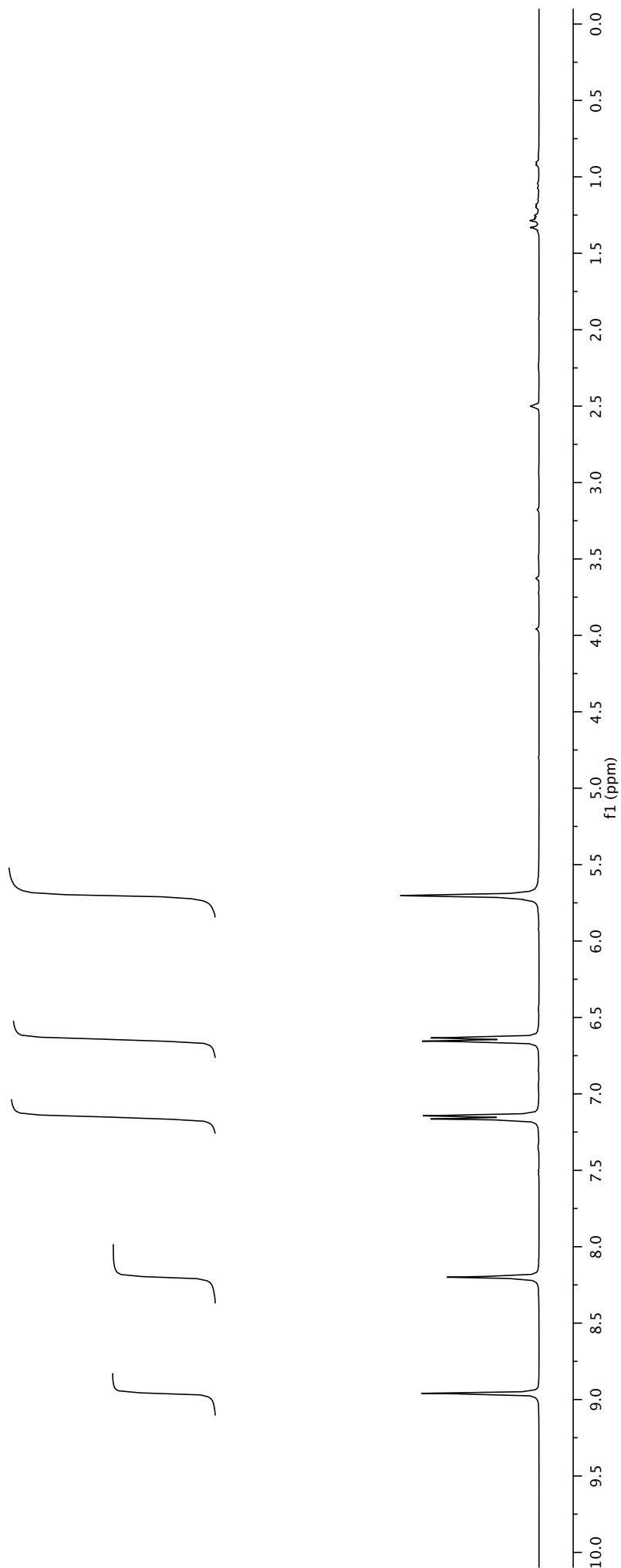
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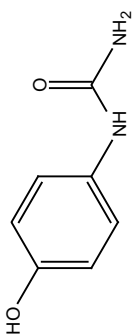
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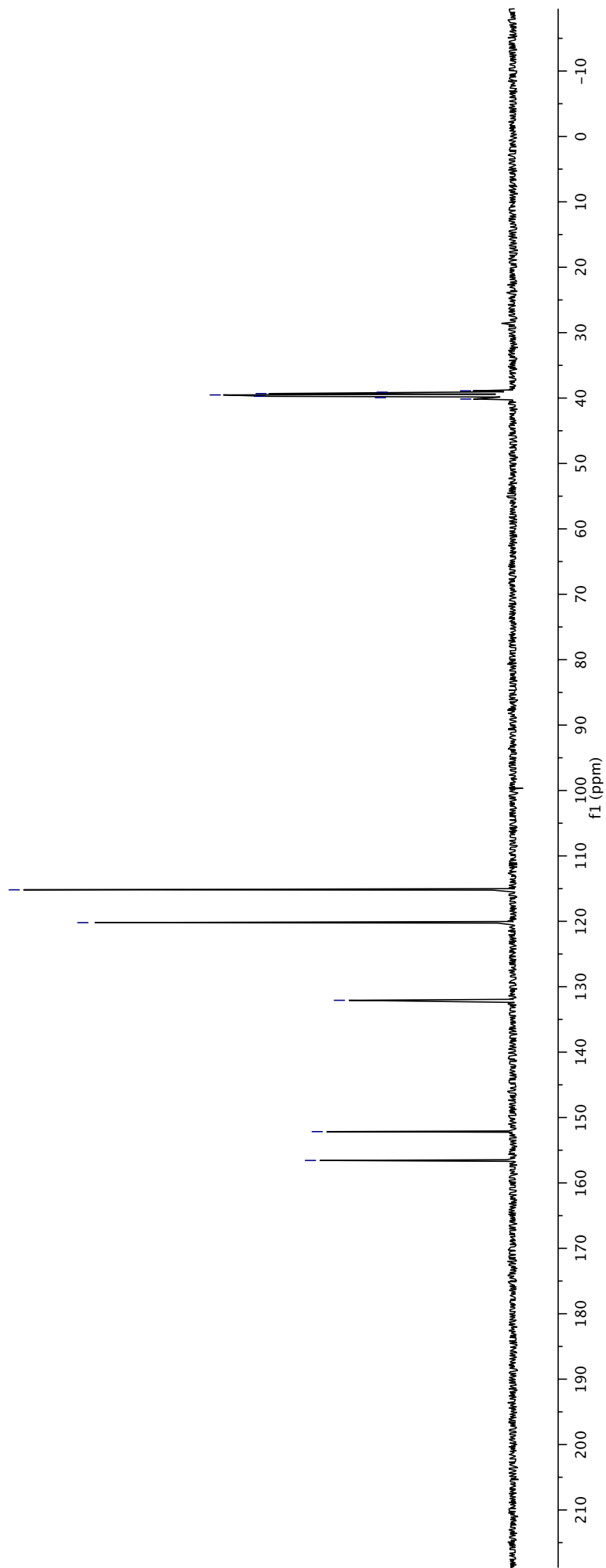
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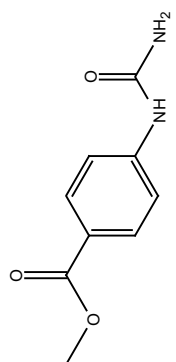


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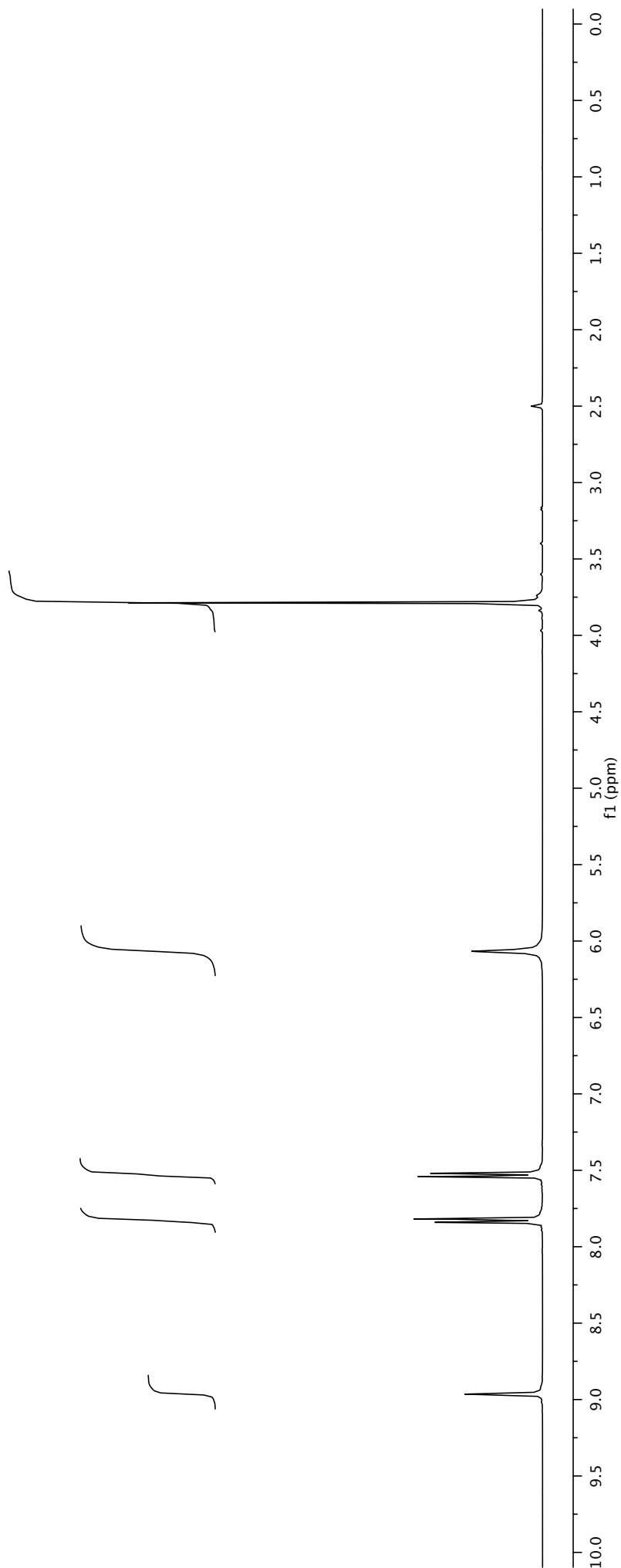
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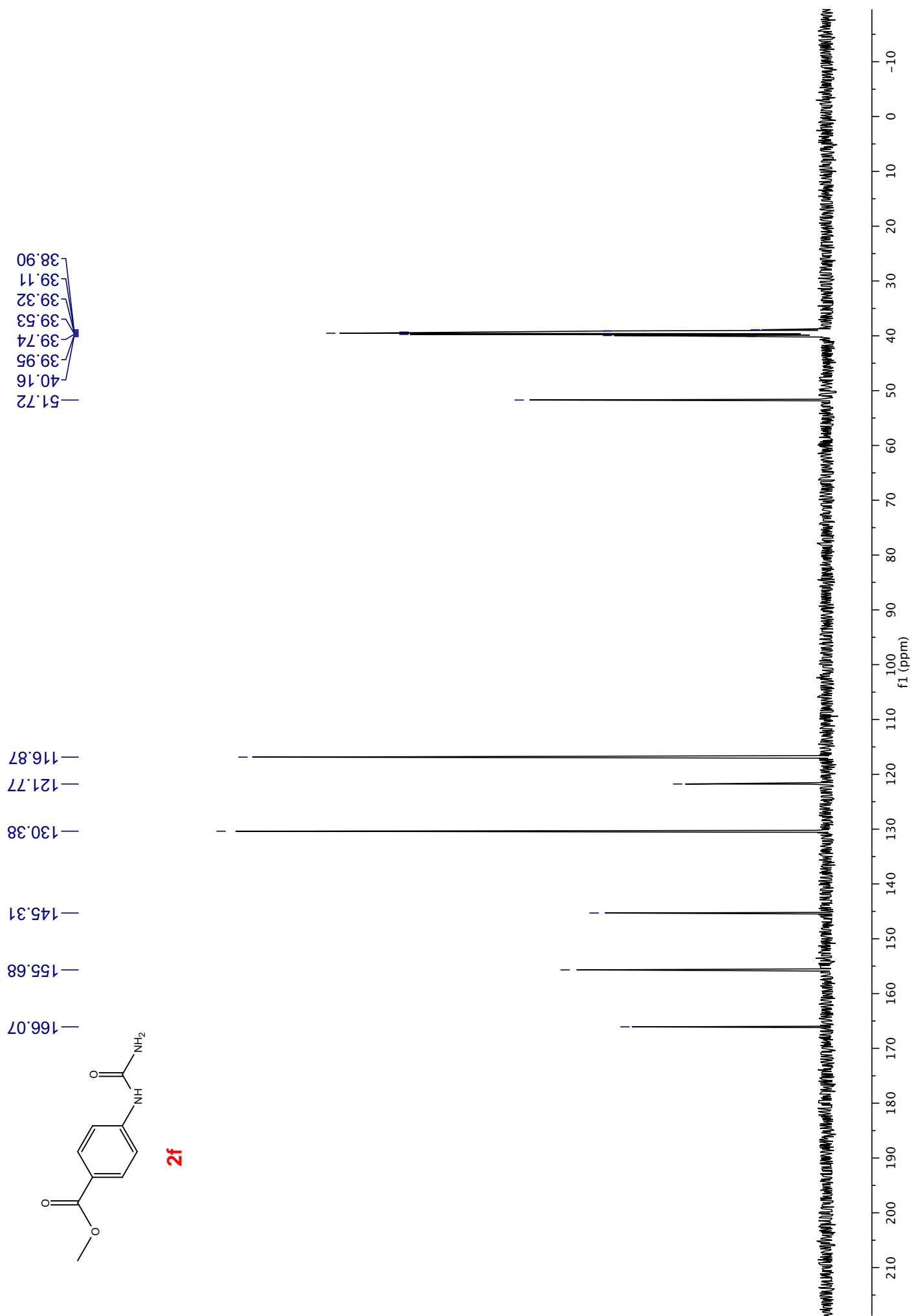
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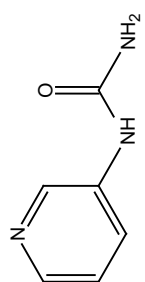




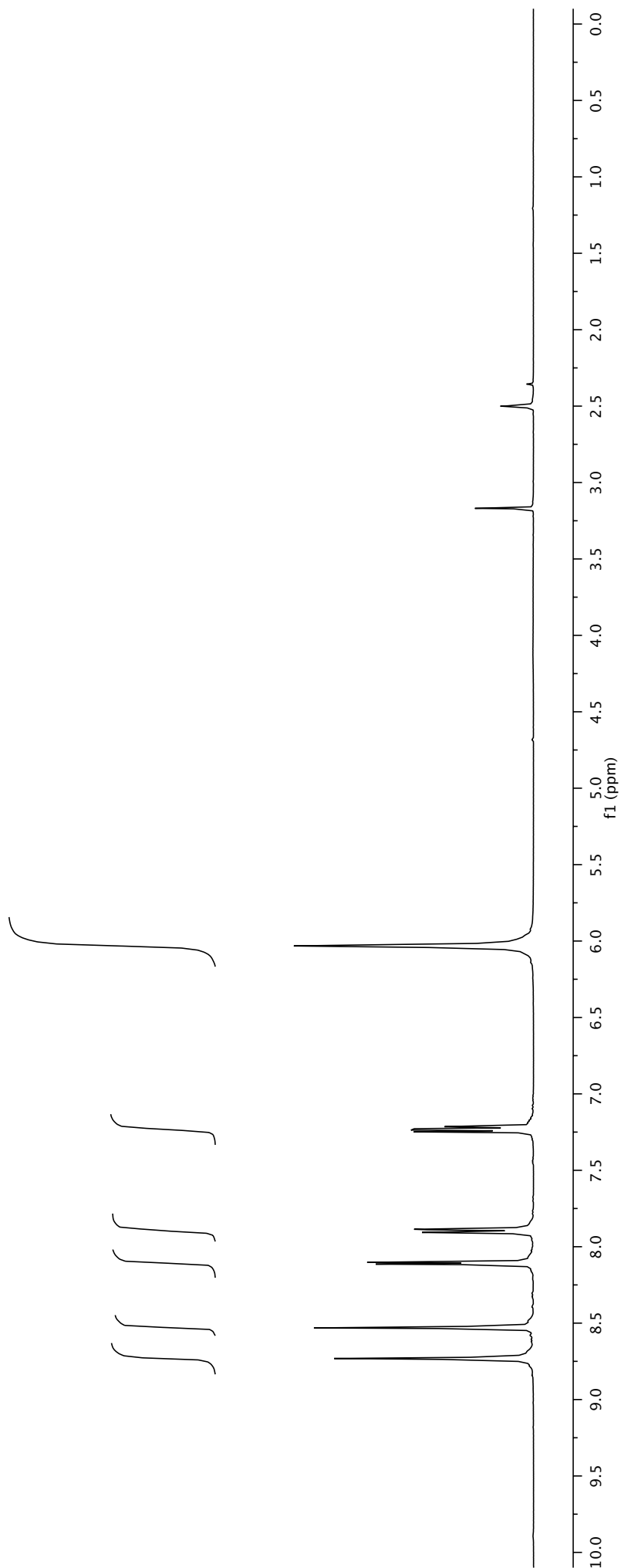
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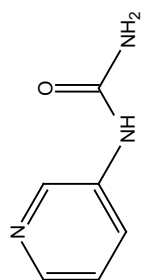






2k



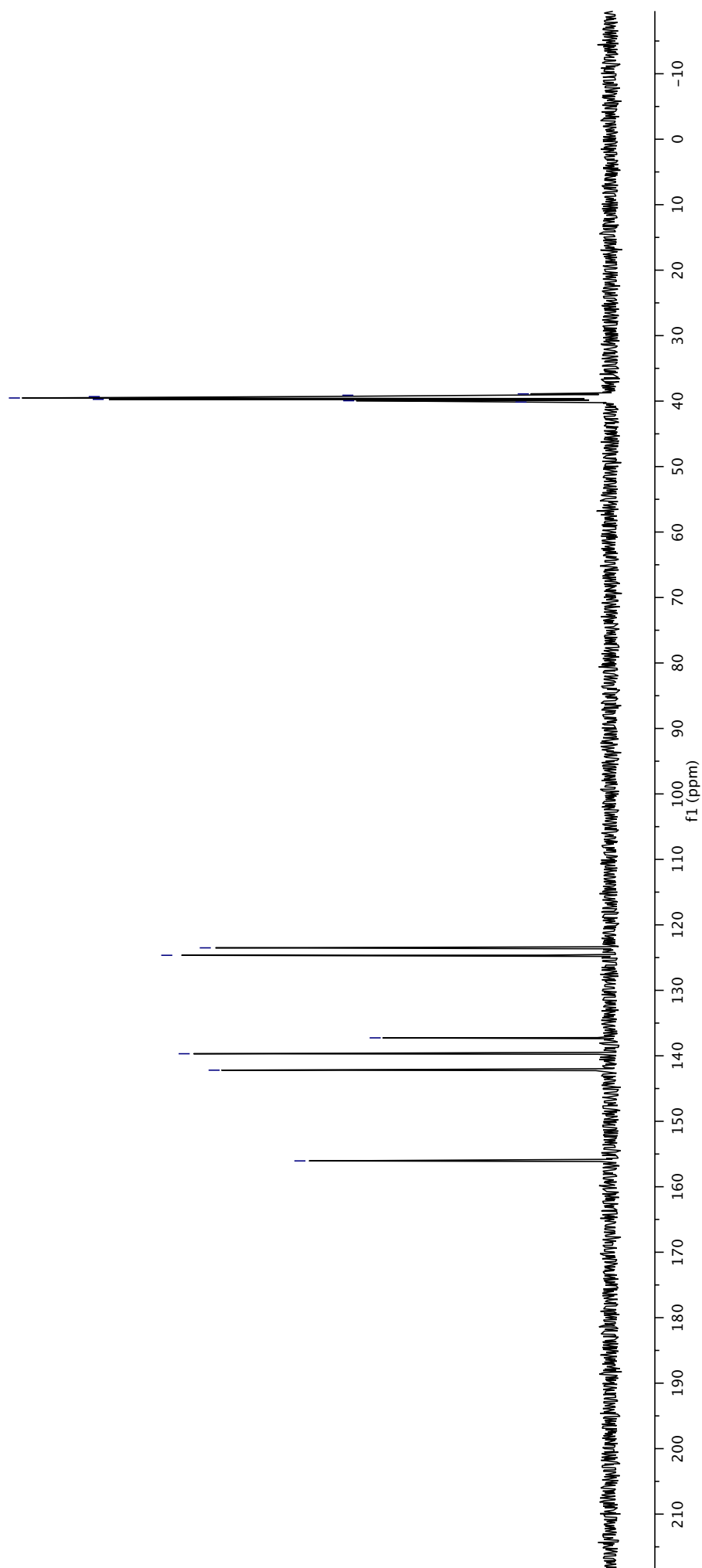


2k

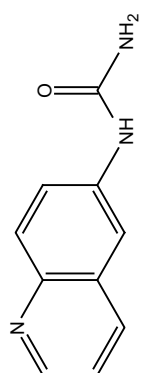
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39.94  
39.73  
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39.32  
39.11  
38.90

142.19  
139.69  
137.26  
124.65  
123.51

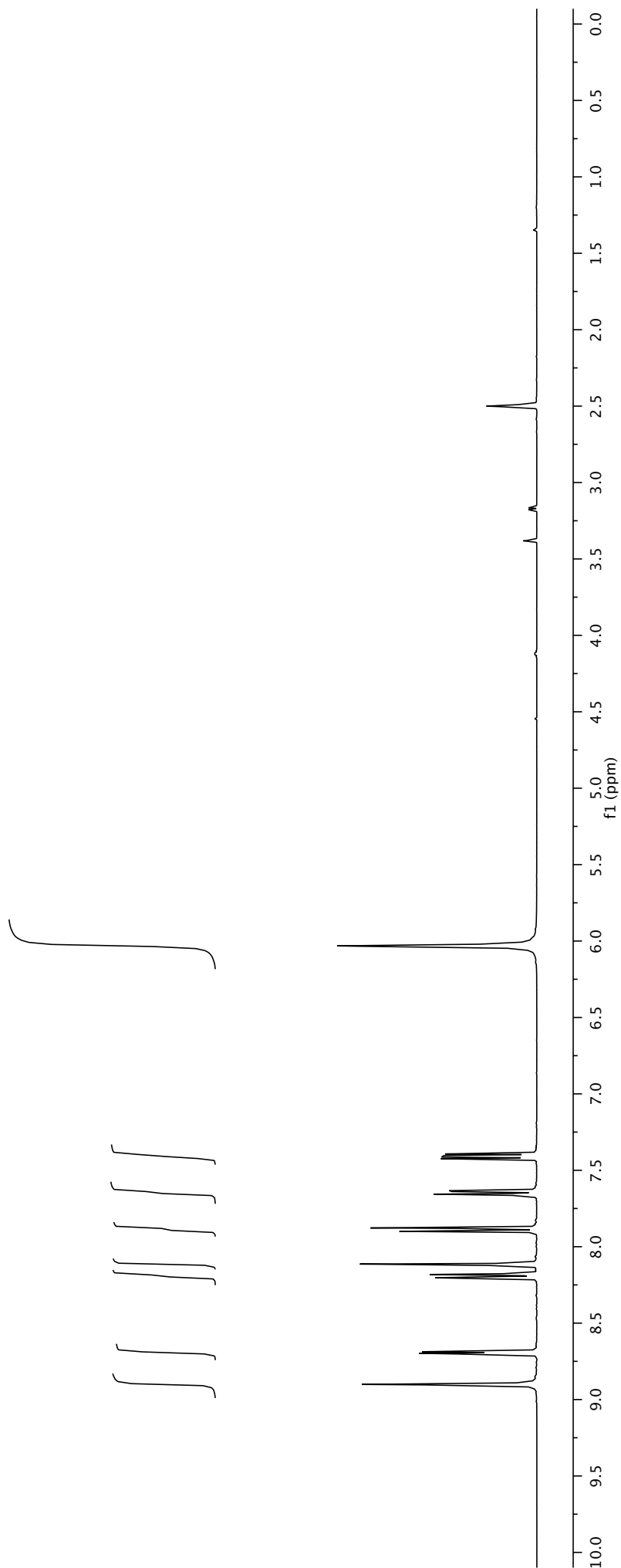
156.05

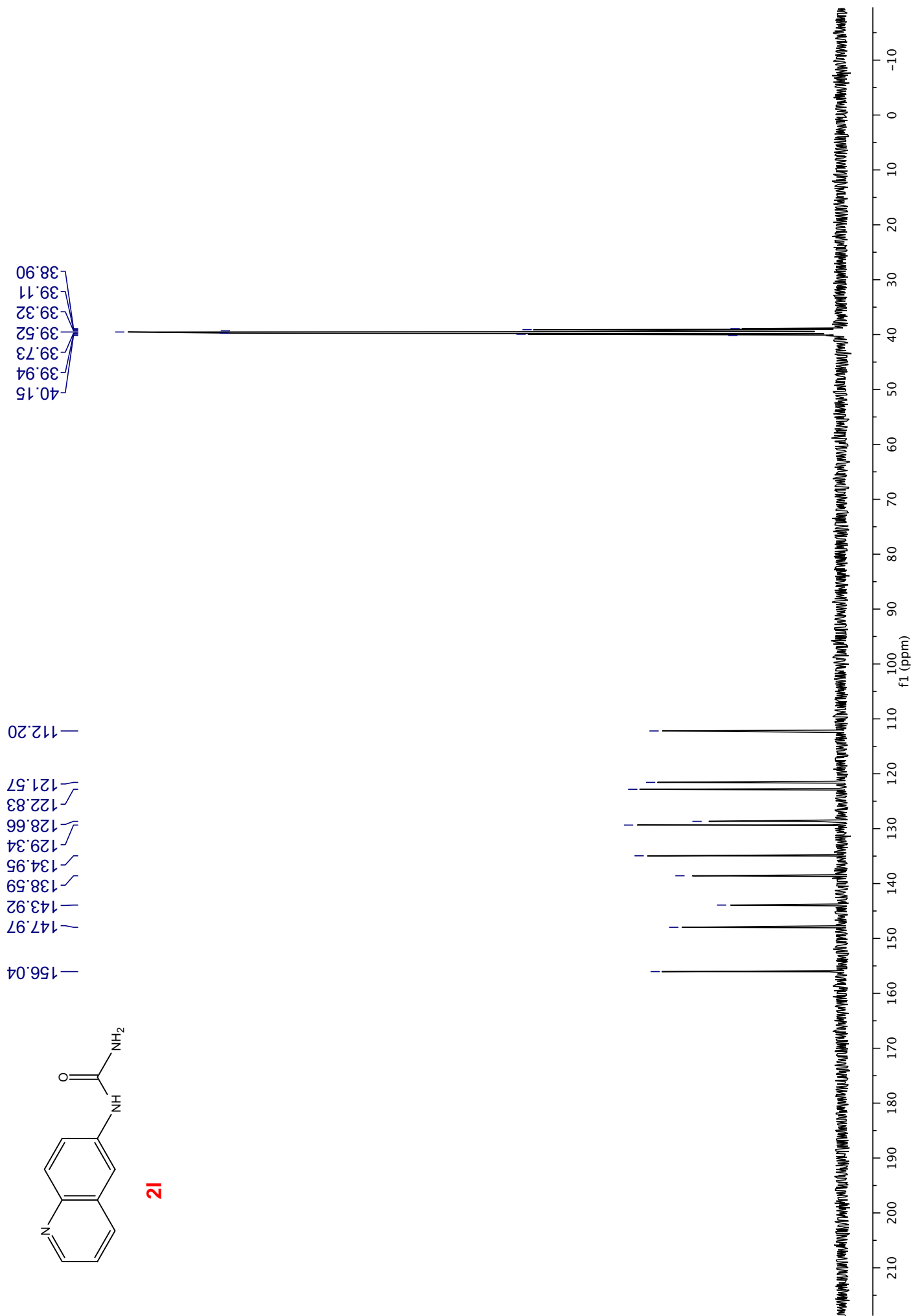


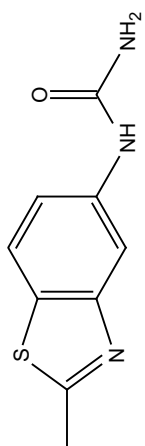




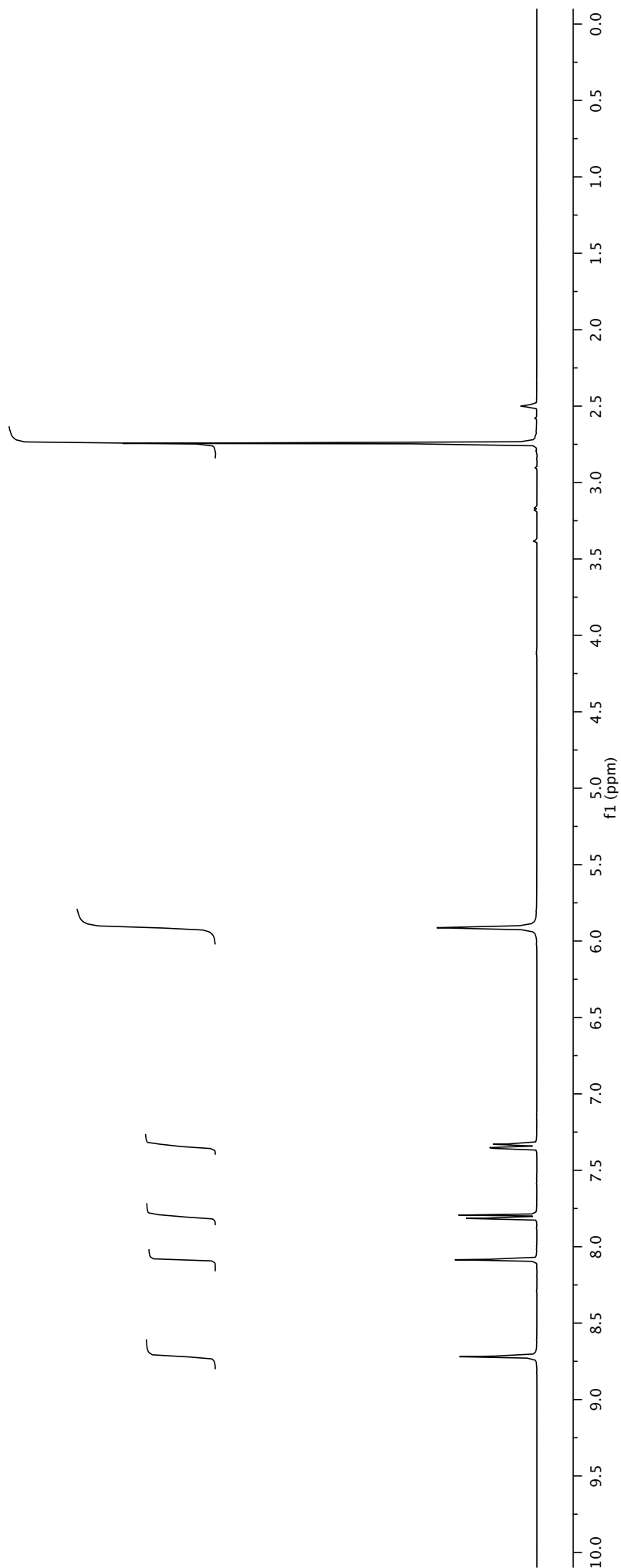
**2I**

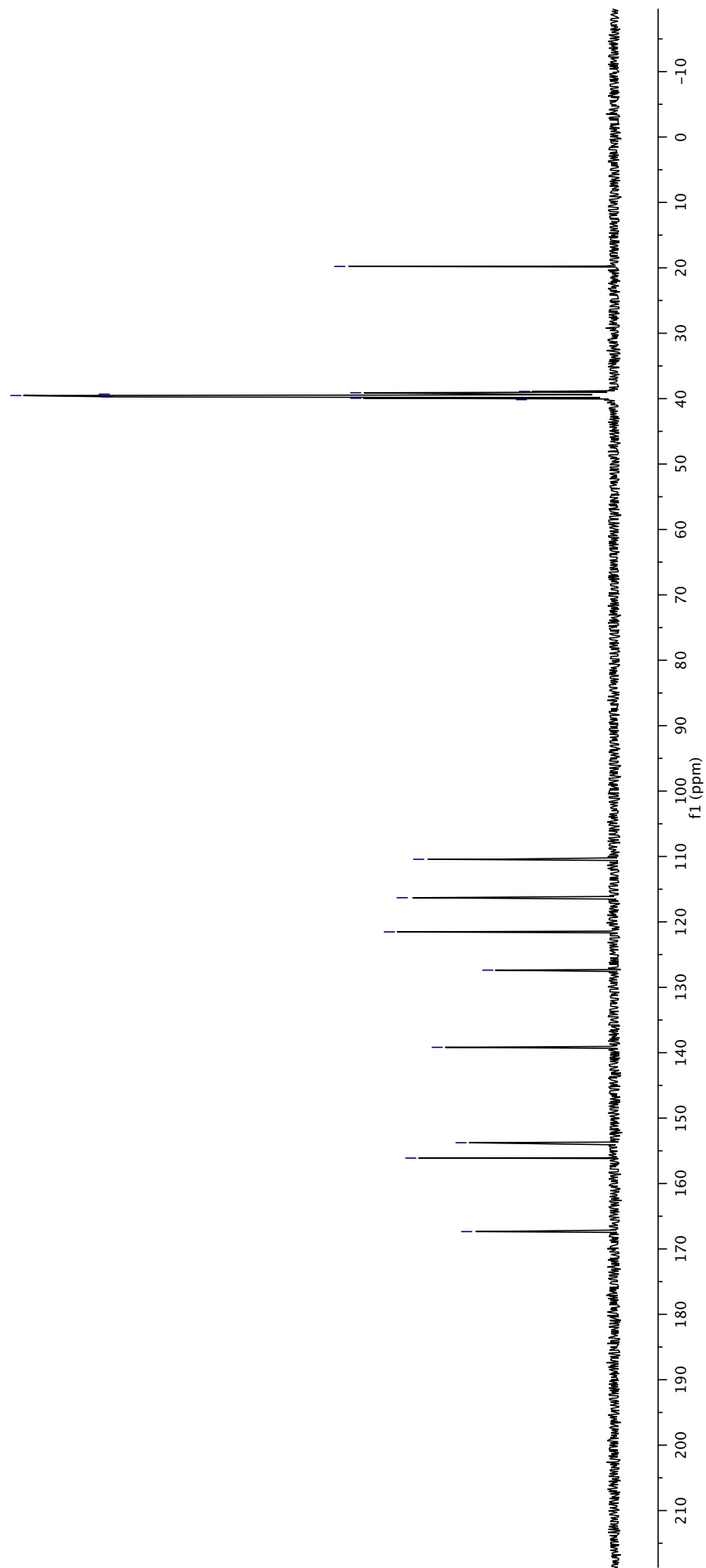
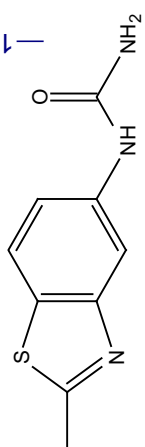


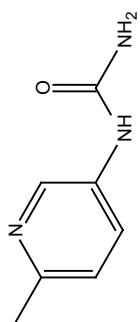




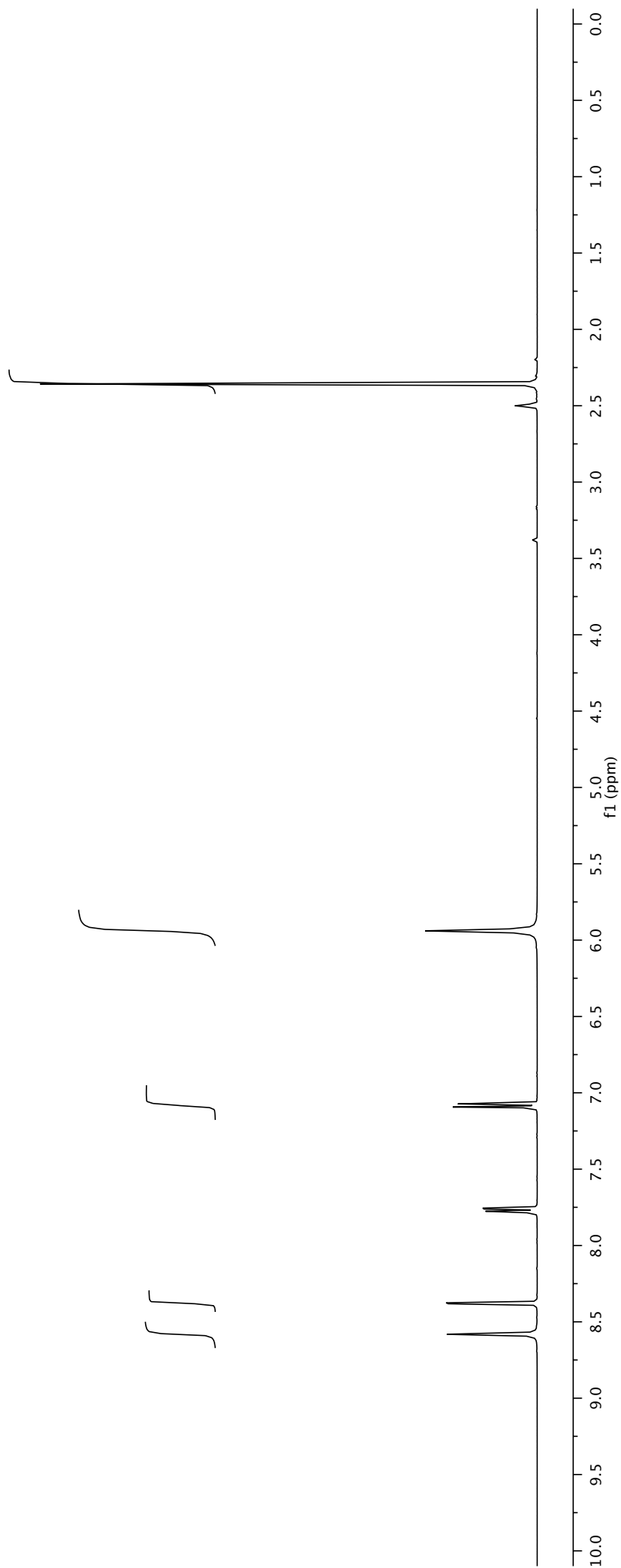
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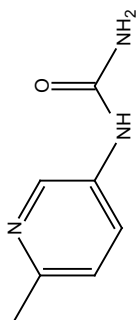
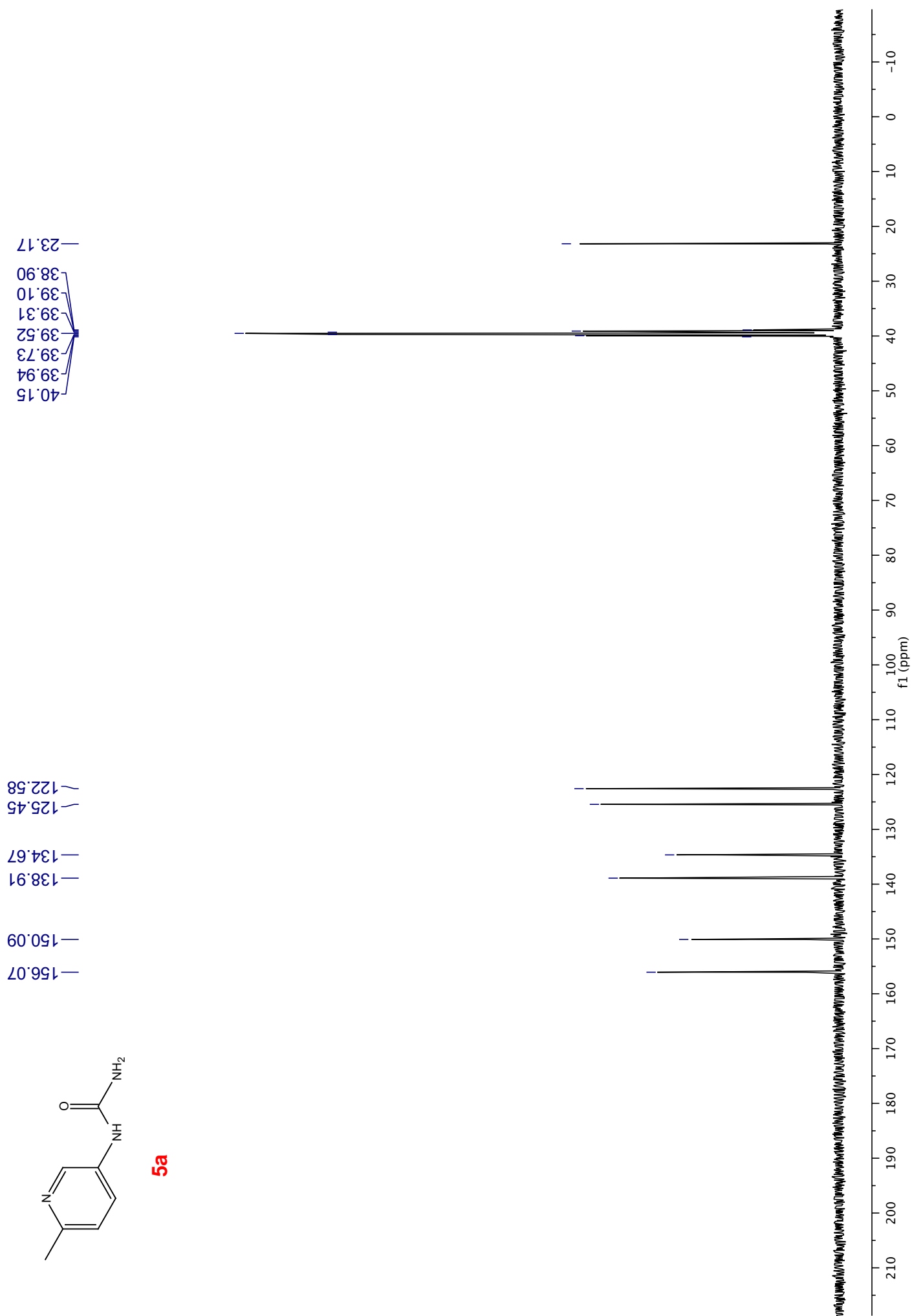


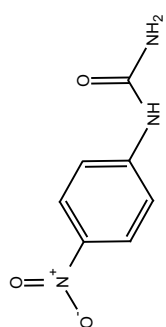
**2m**



5a

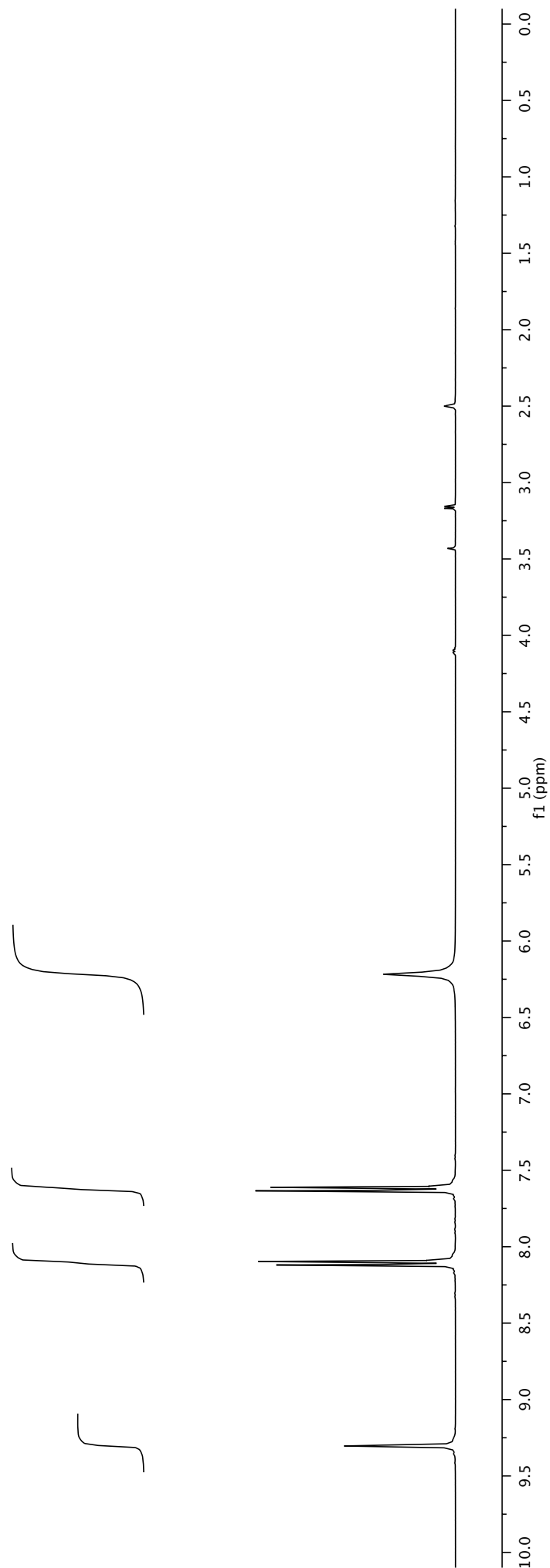


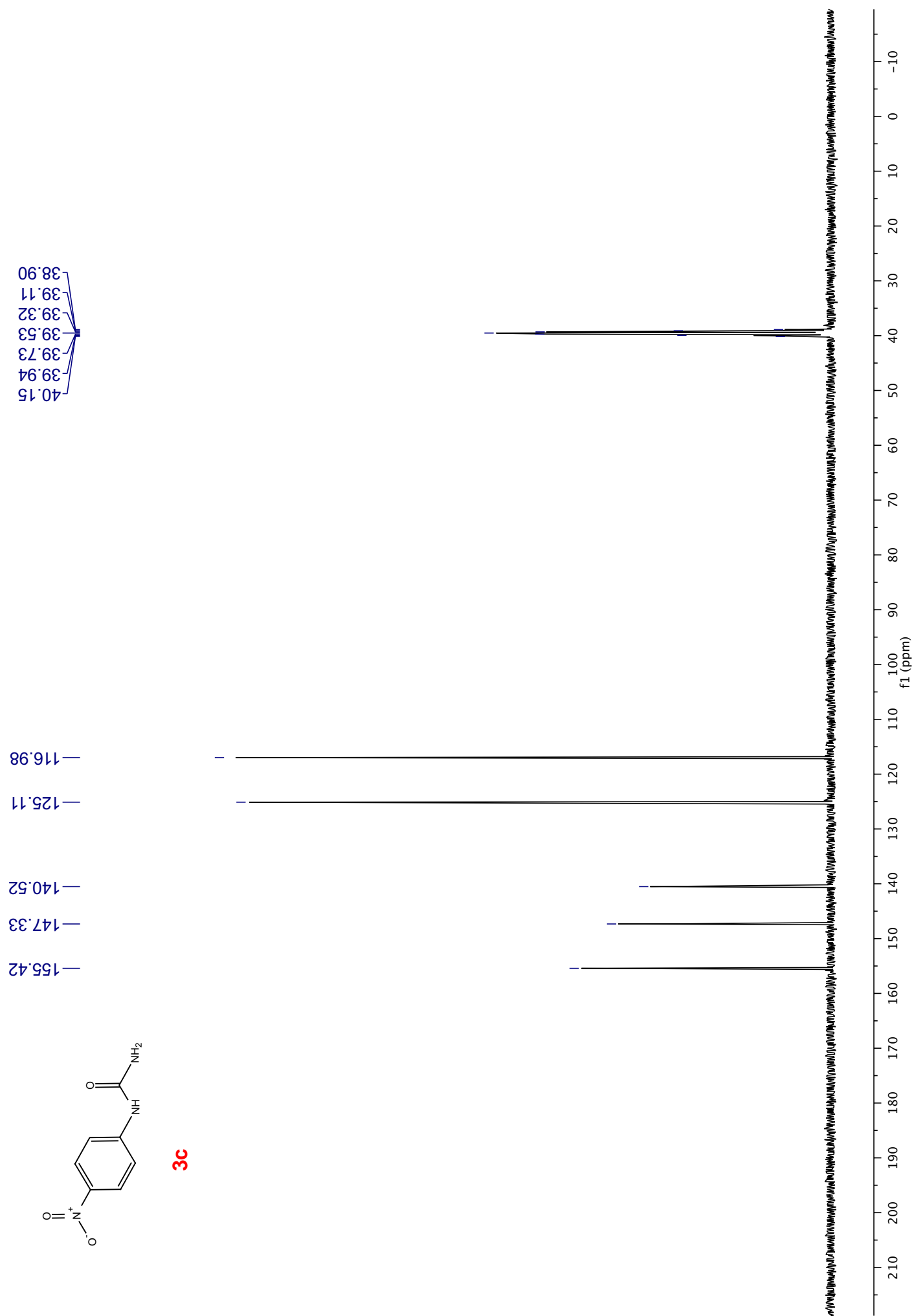
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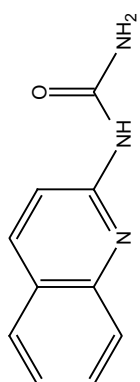
**3c**

SI 55

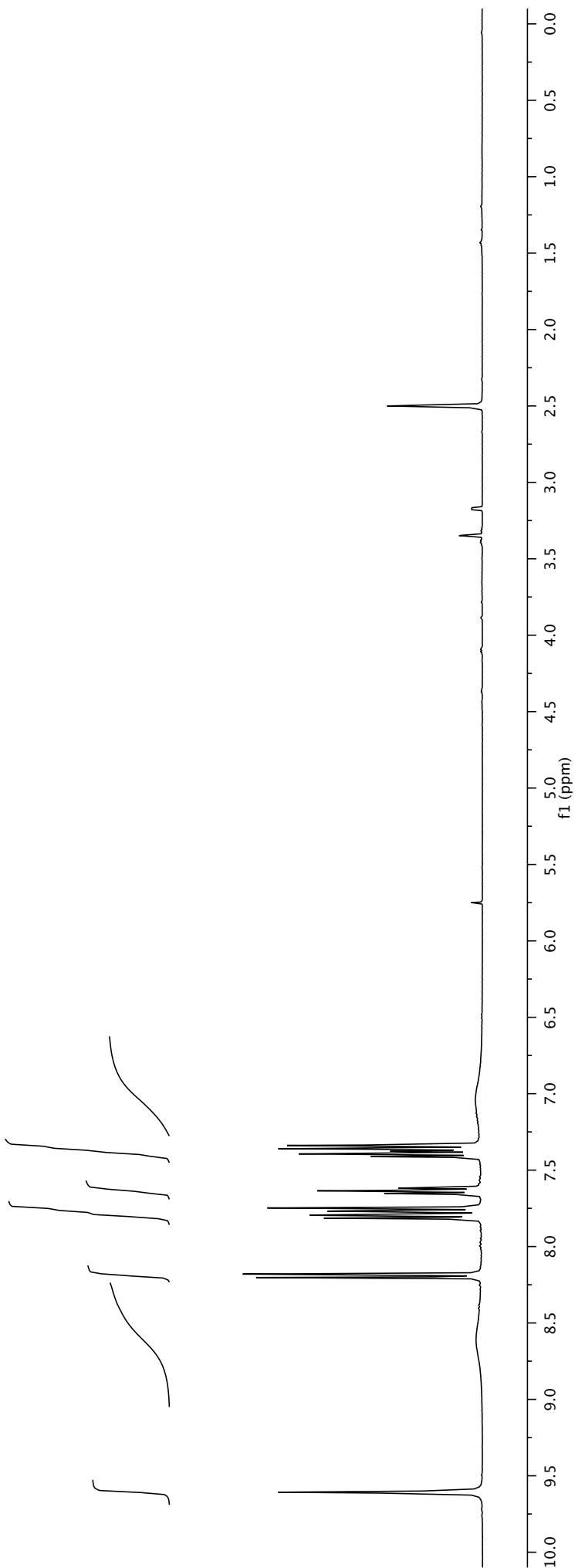


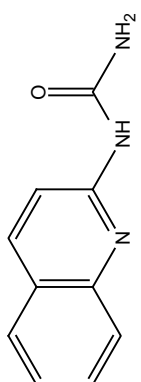






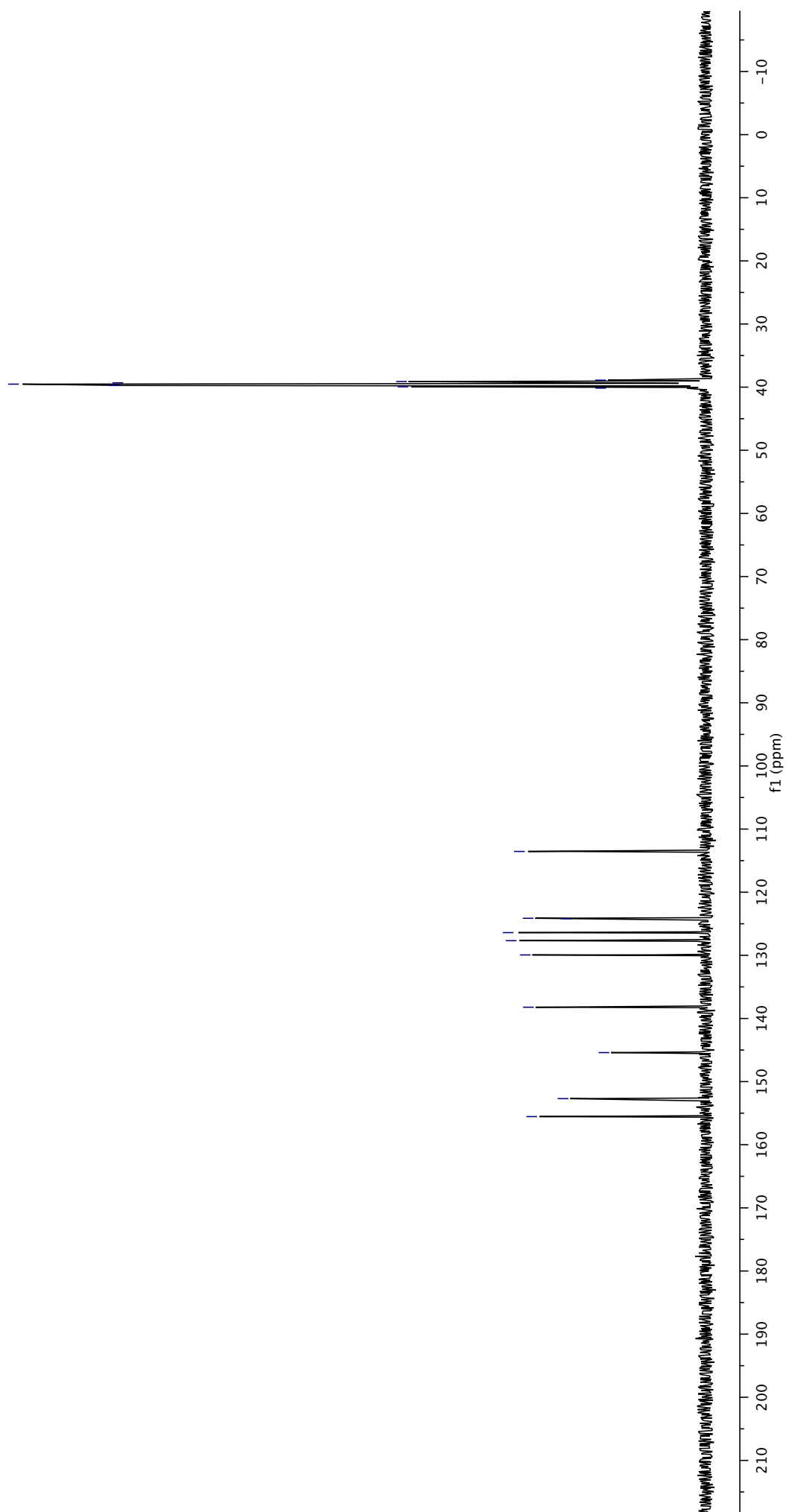
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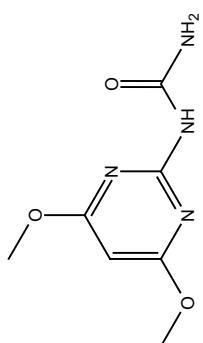


**3d**

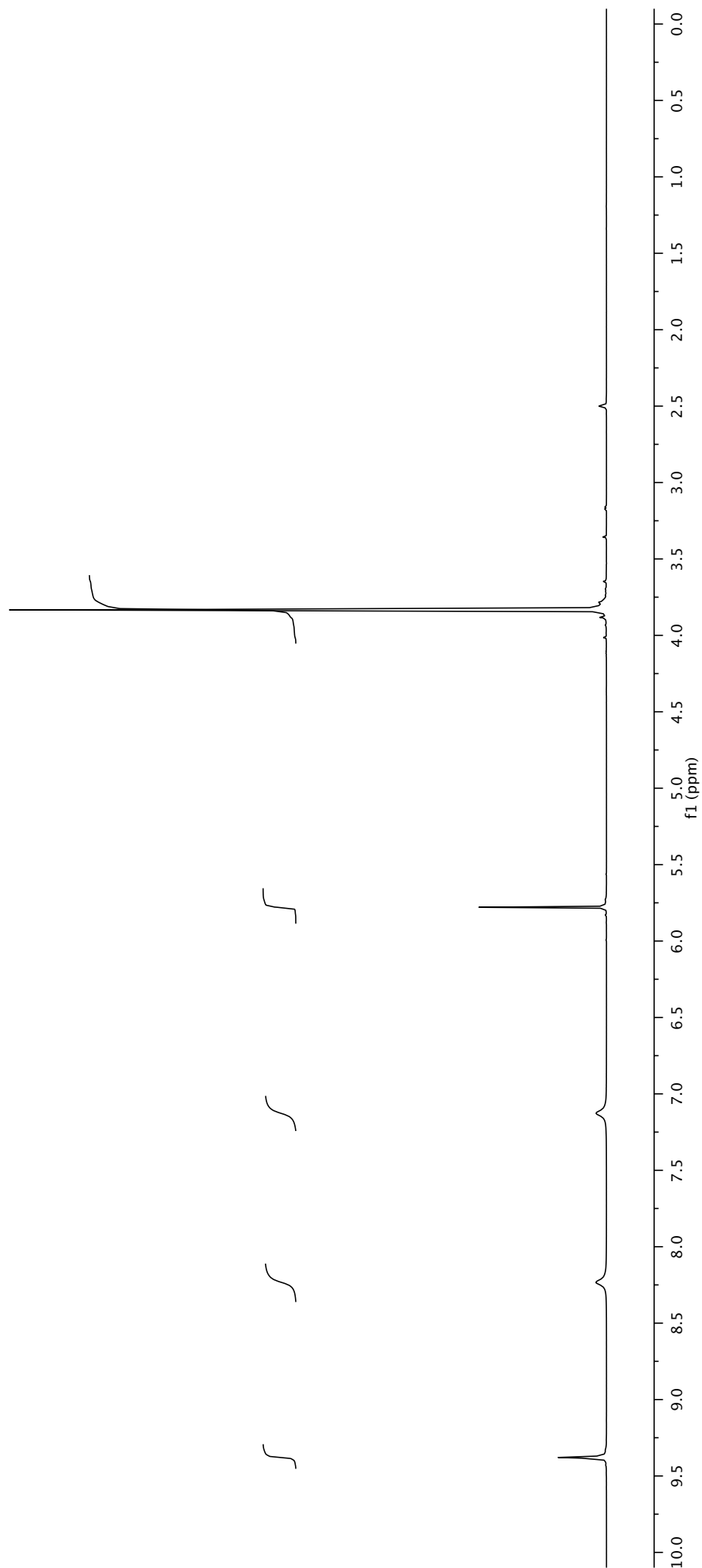
40.15  
39.94  
39.73  
39.53  
39.32  
39.11  
38.90

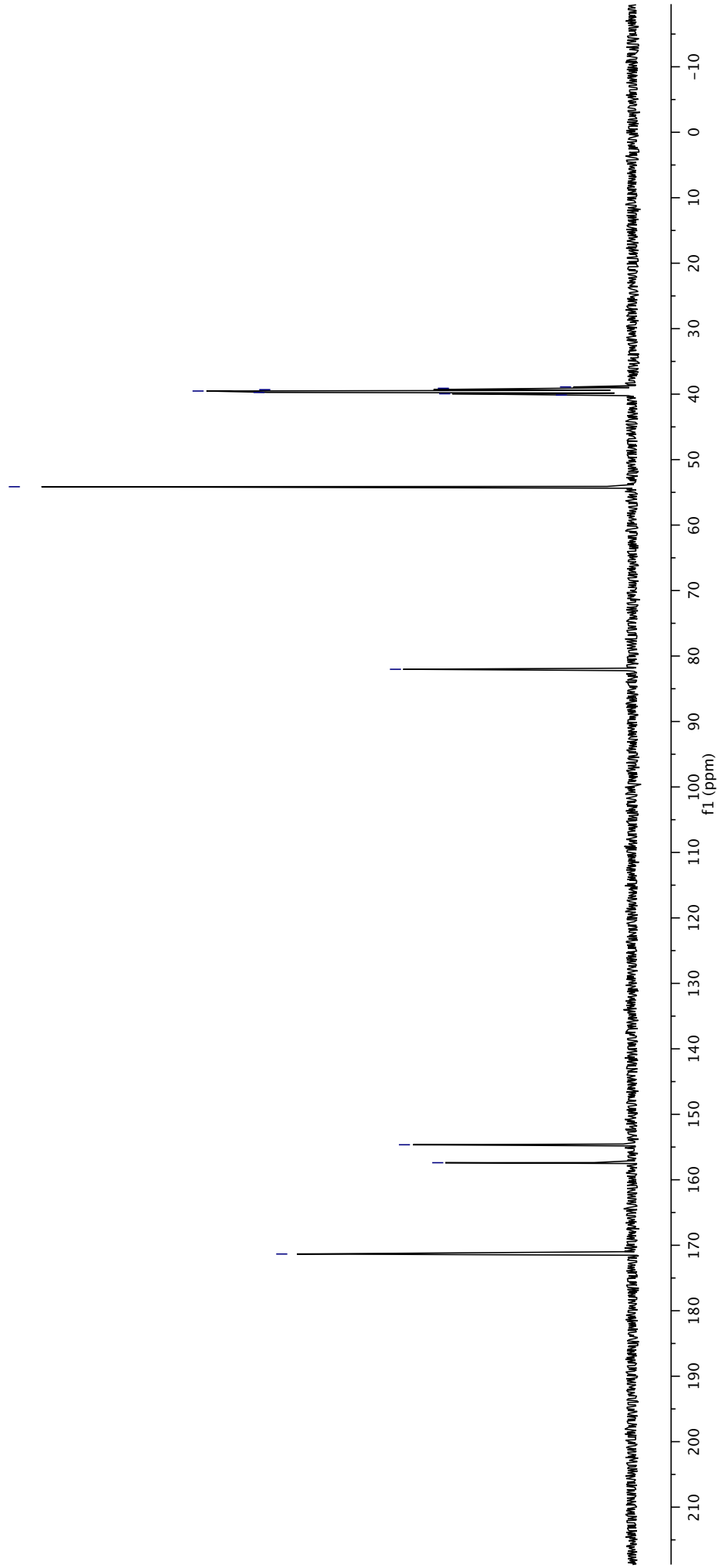
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152.70  
145.41  
138.22  
129.94  
127.68  
126.40  
124.20  
124.13  
113.55



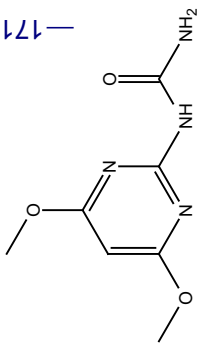


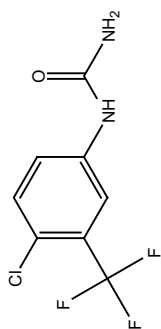
3e



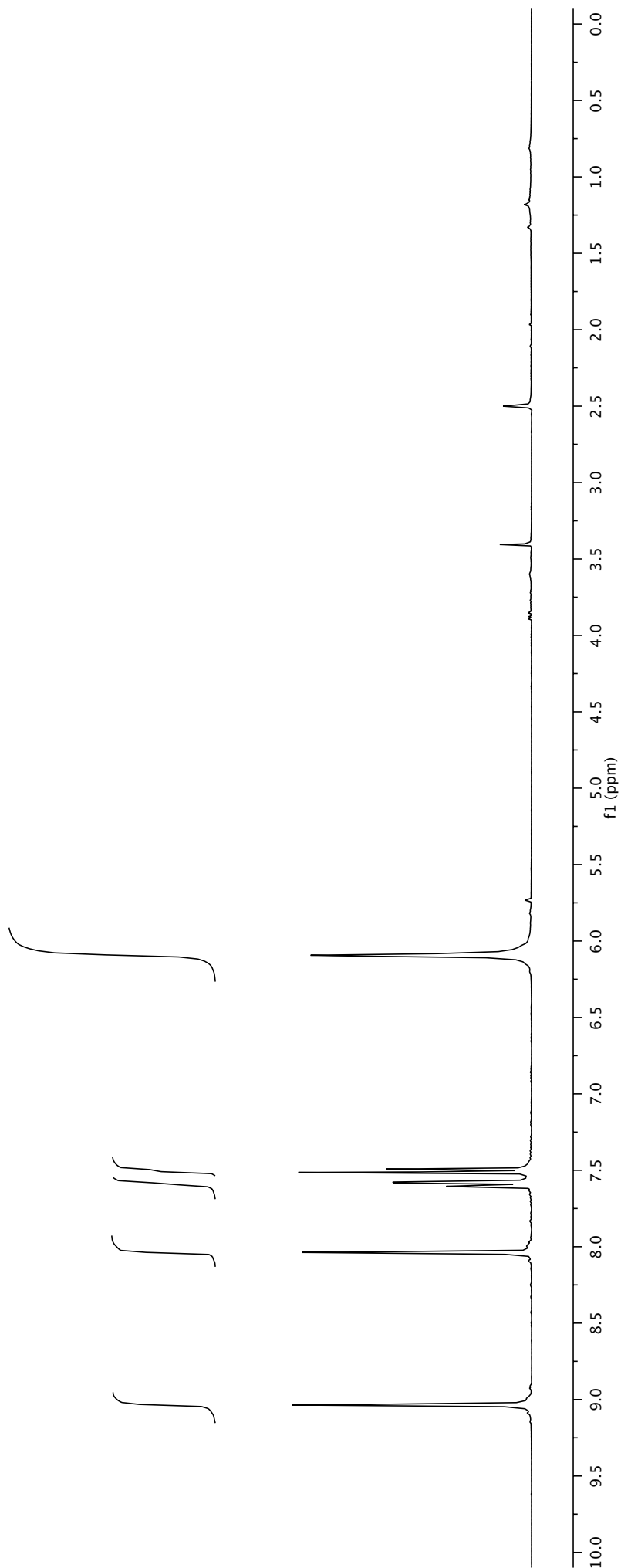


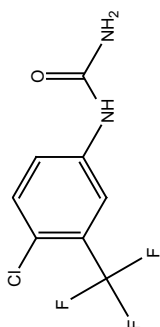
**3e**





**5c**

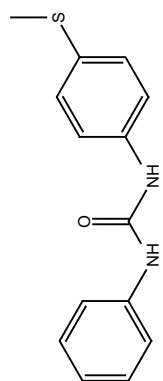


**5c**

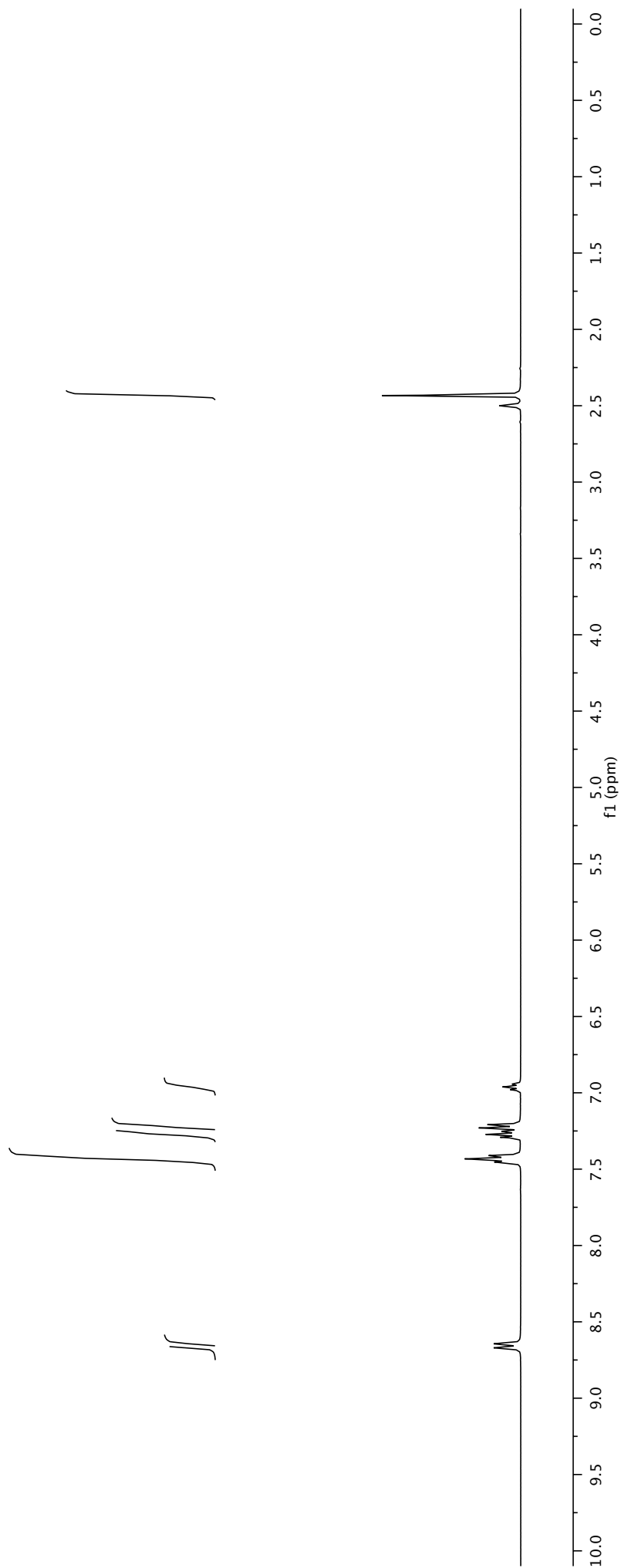
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127.00  
126.80  
126.50  
126.20  
124.29  
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121.58  
121.49  
121.48  
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116.34  
116.29  
116.23  
116.17

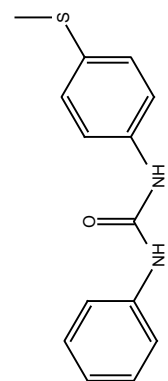
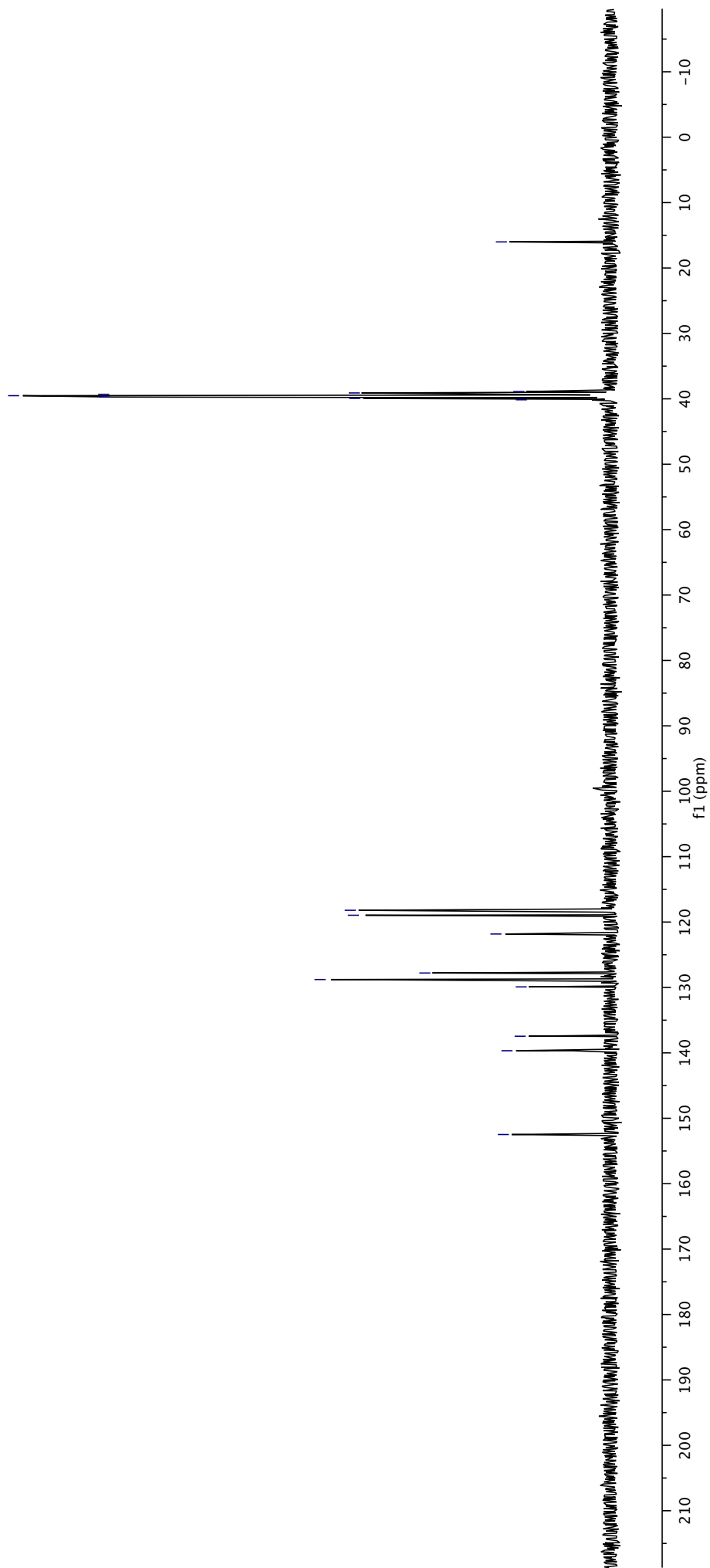
40.15  
39.94  
39.73  
39.52  
39.32  
39.11  
38.90

f1 (ppm)

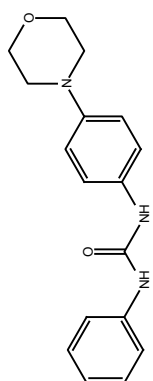


**4a**

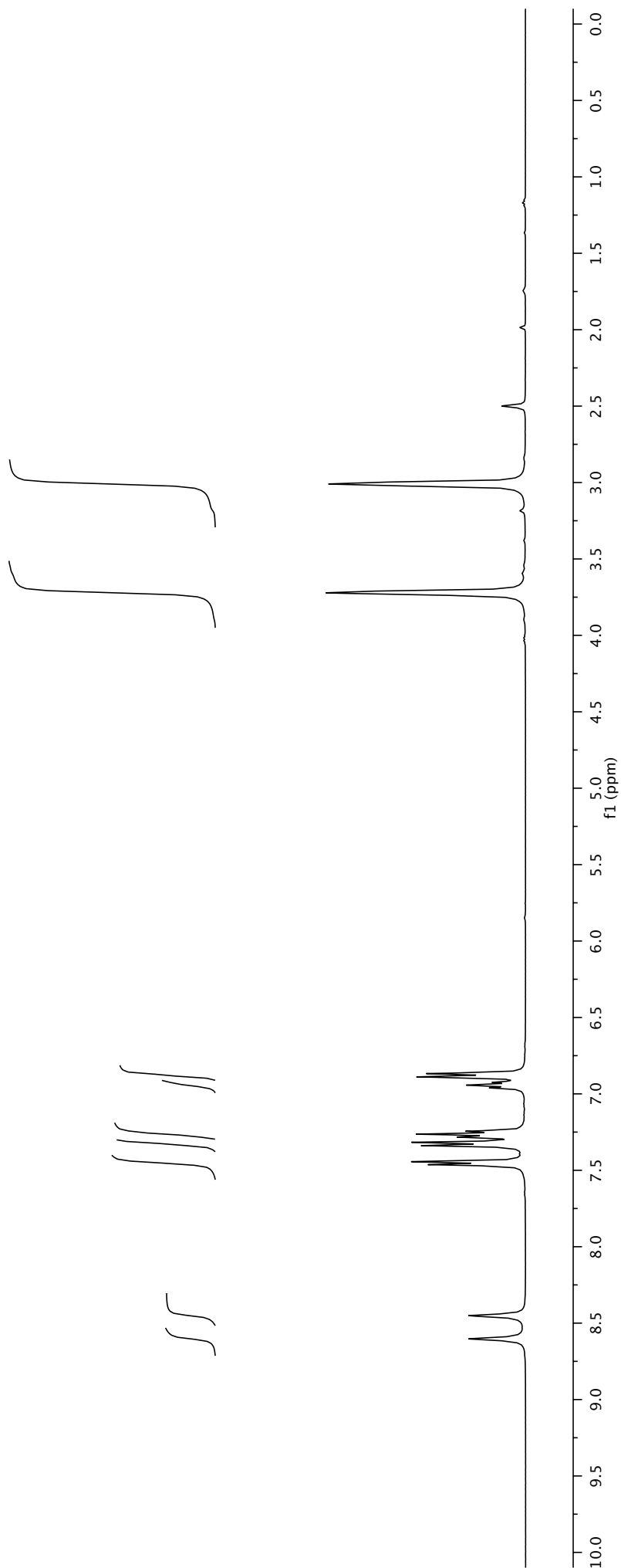


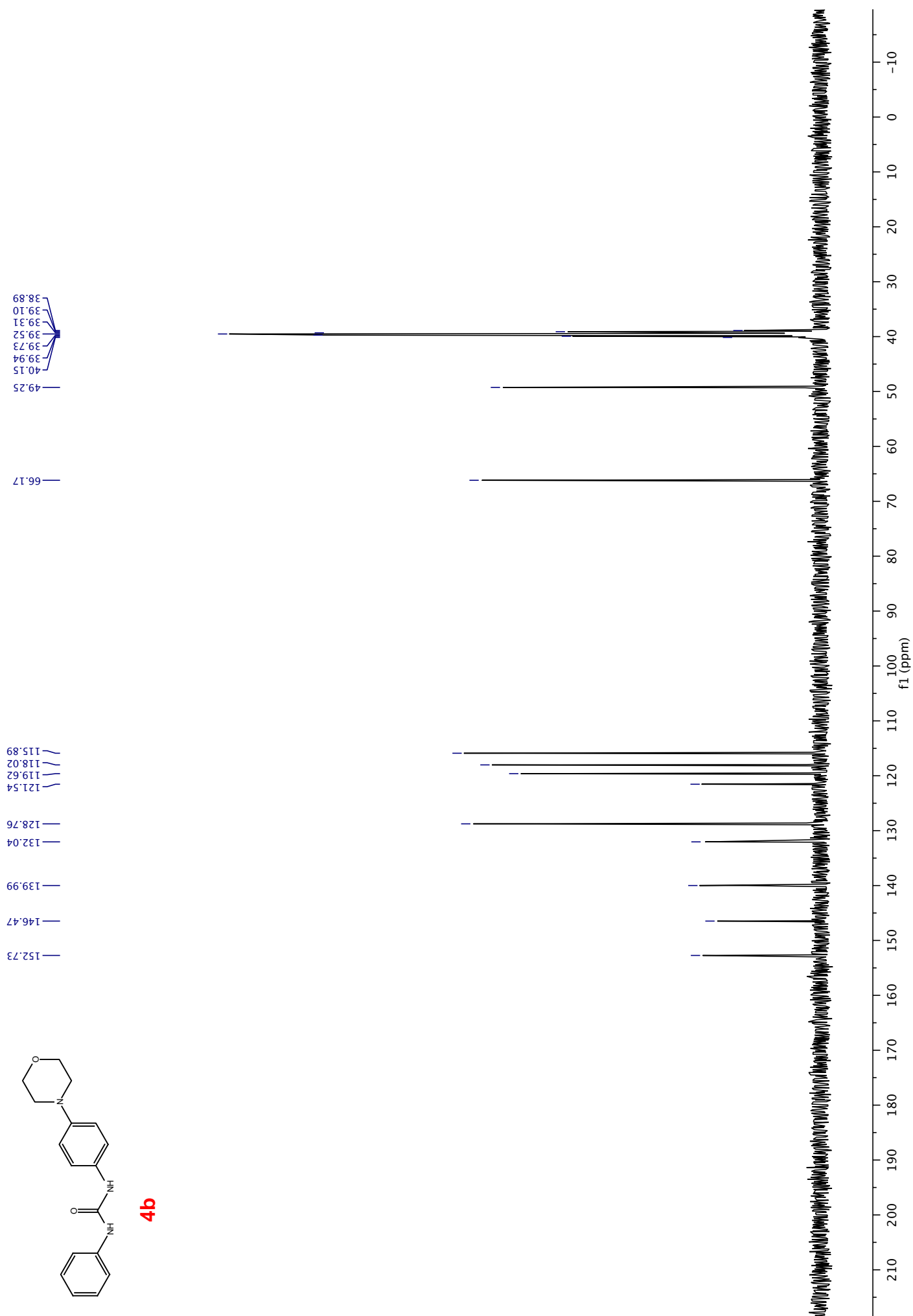
**4a**

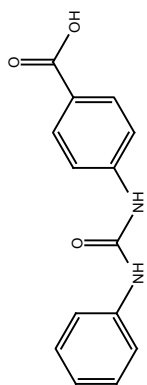




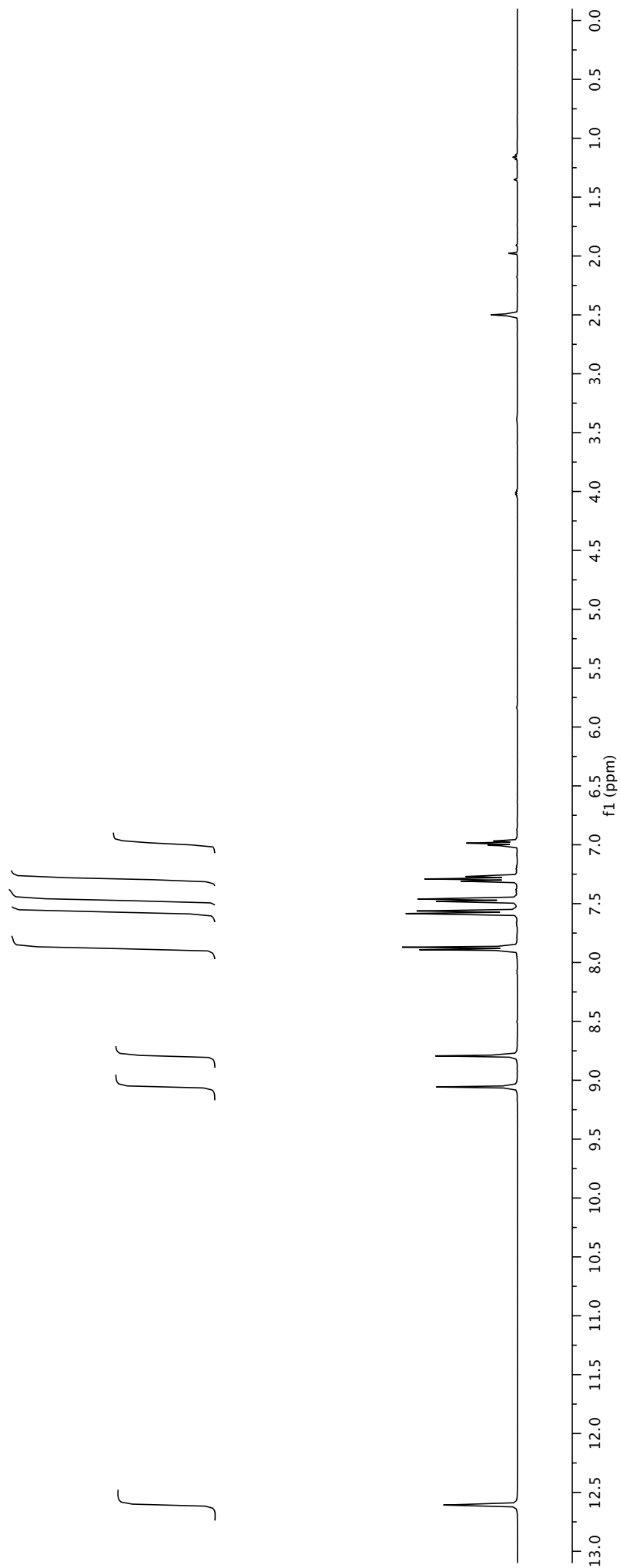
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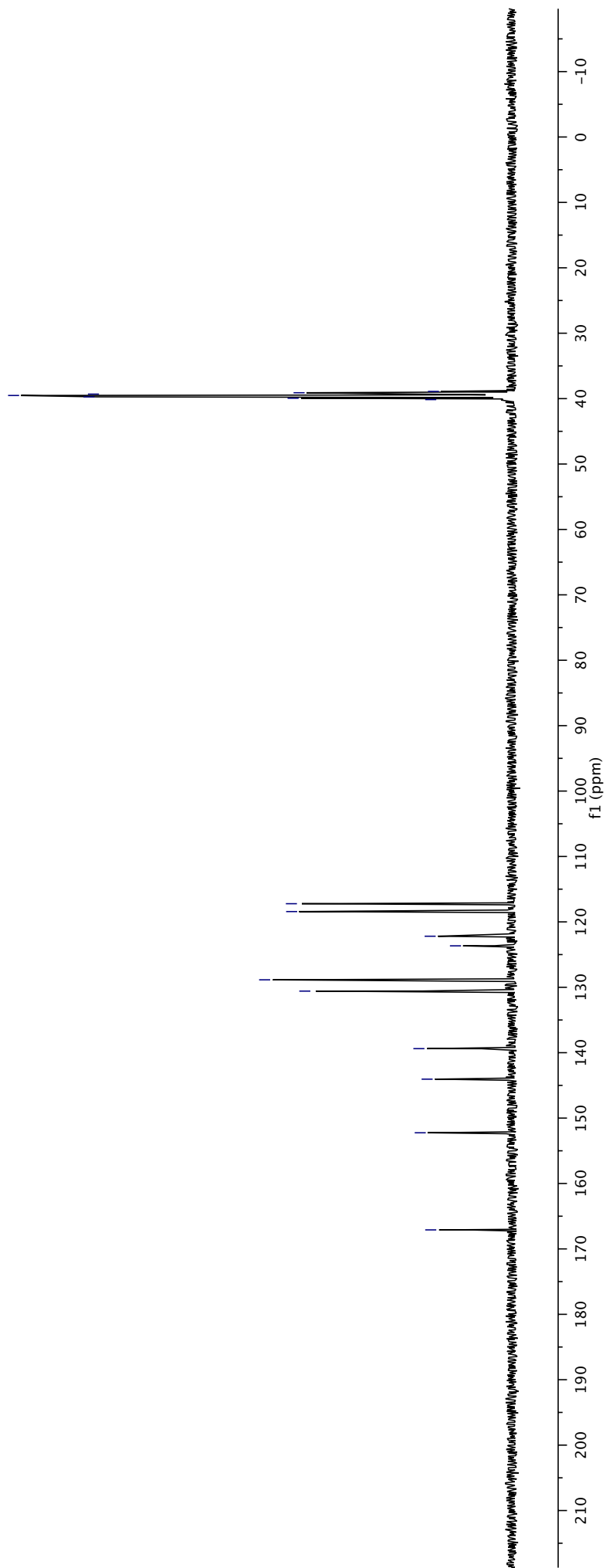
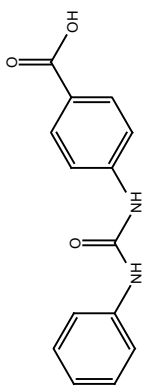






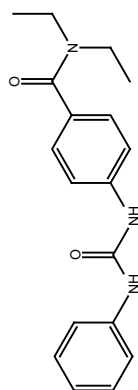
**4c**



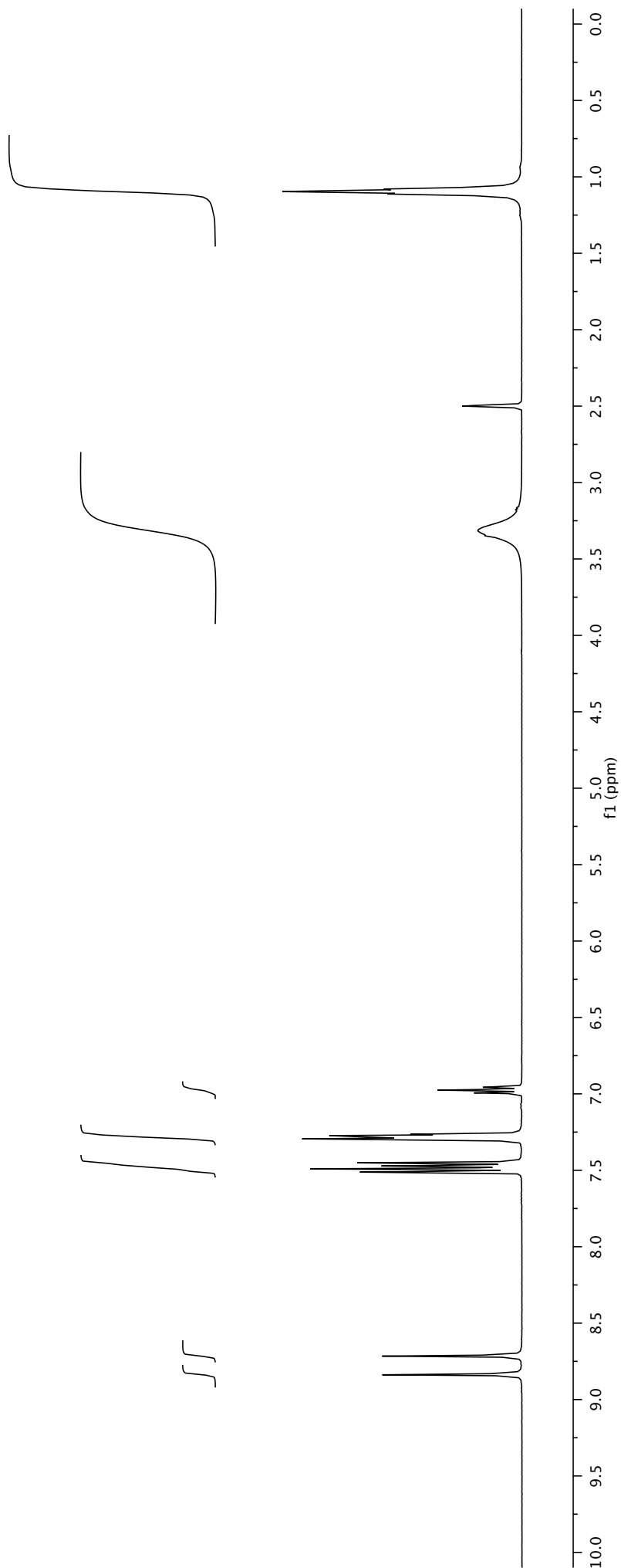
**4c**

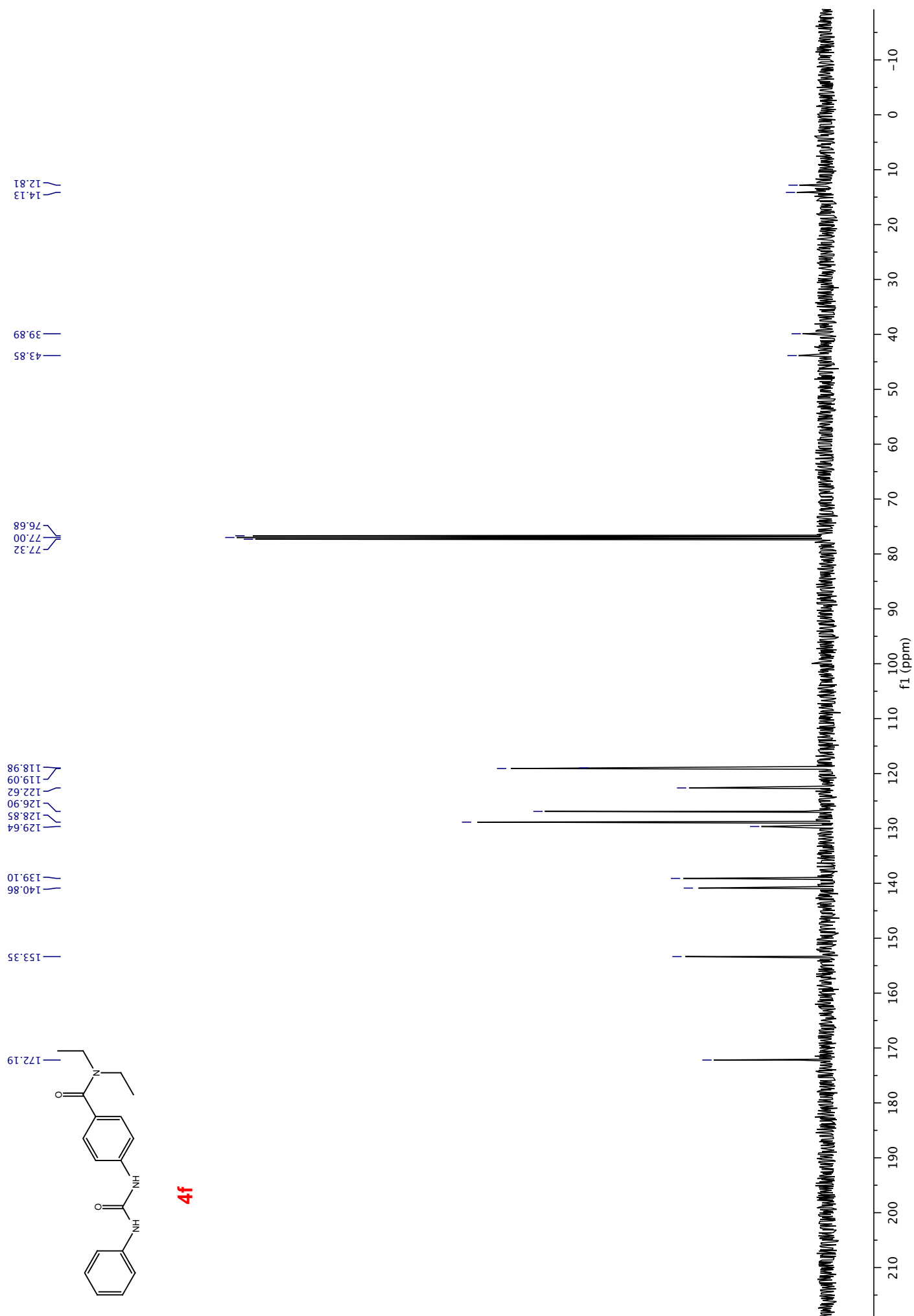
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122.20
118.43
117.22

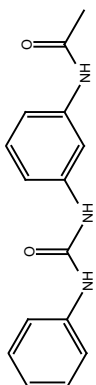
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39.73
39.52
39.31
39.10
38.90



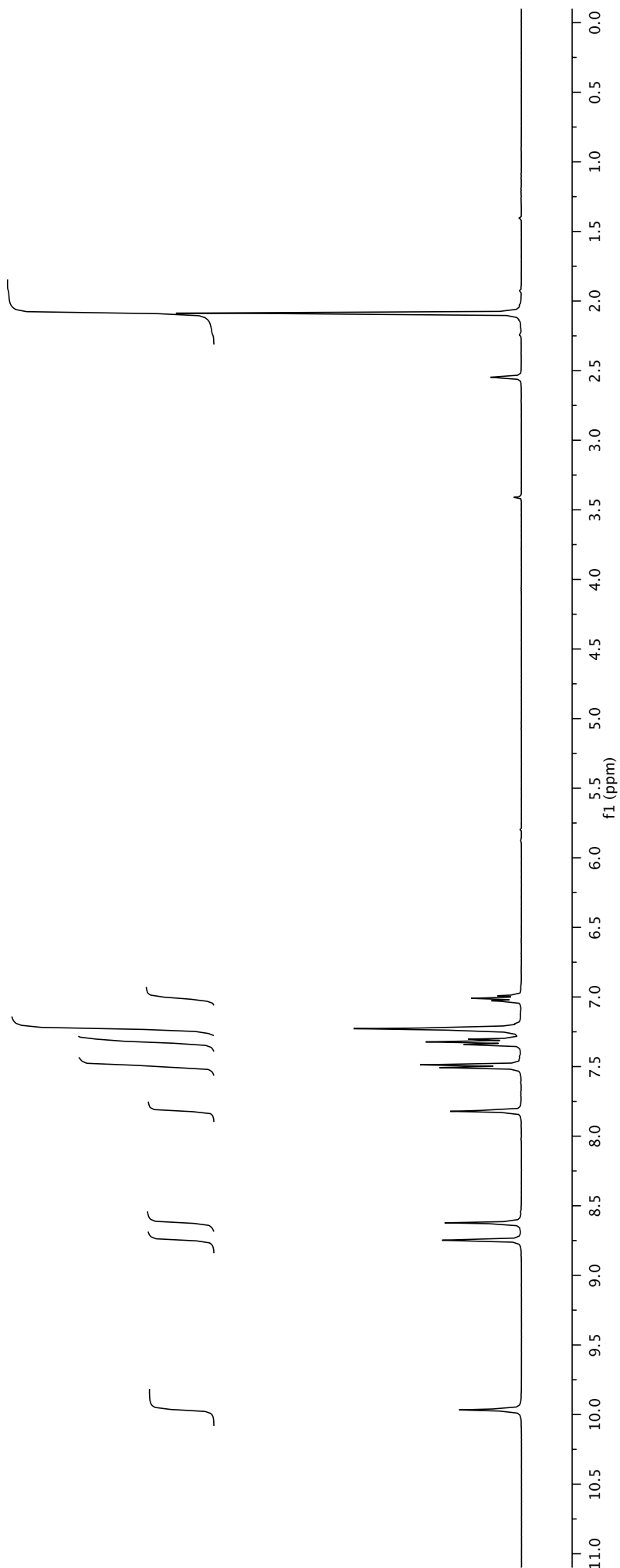
4f

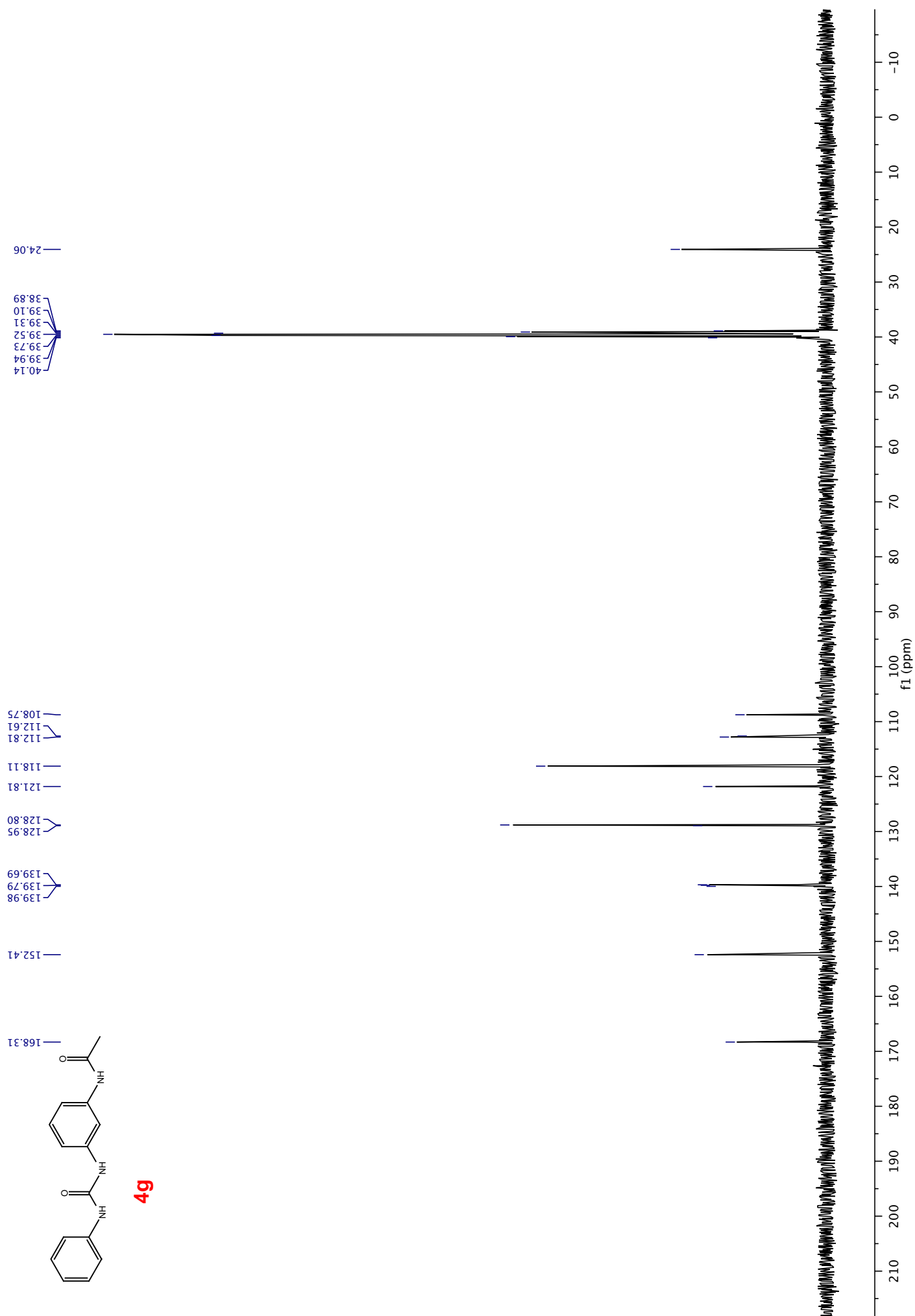




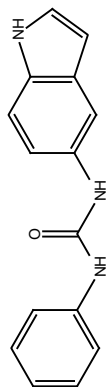


4g

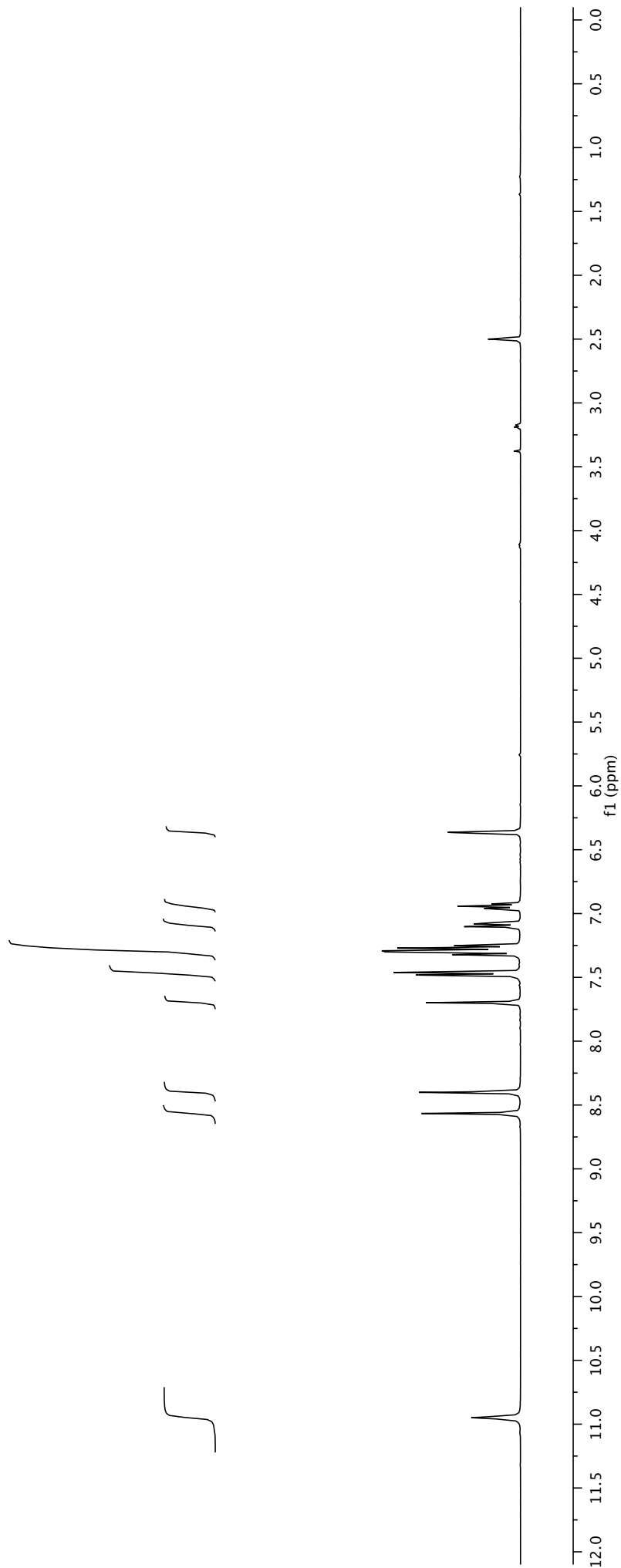


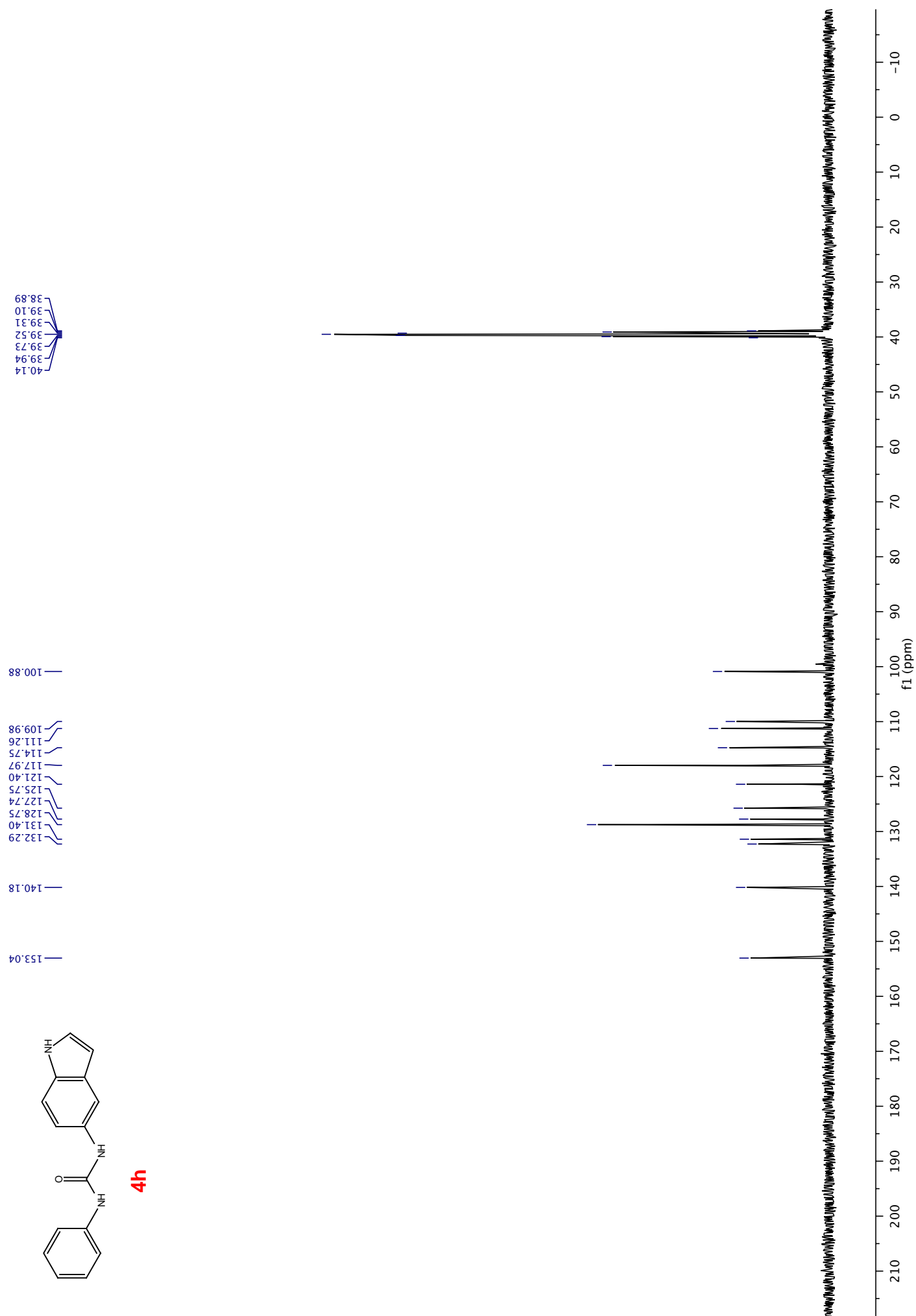


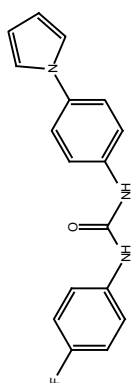




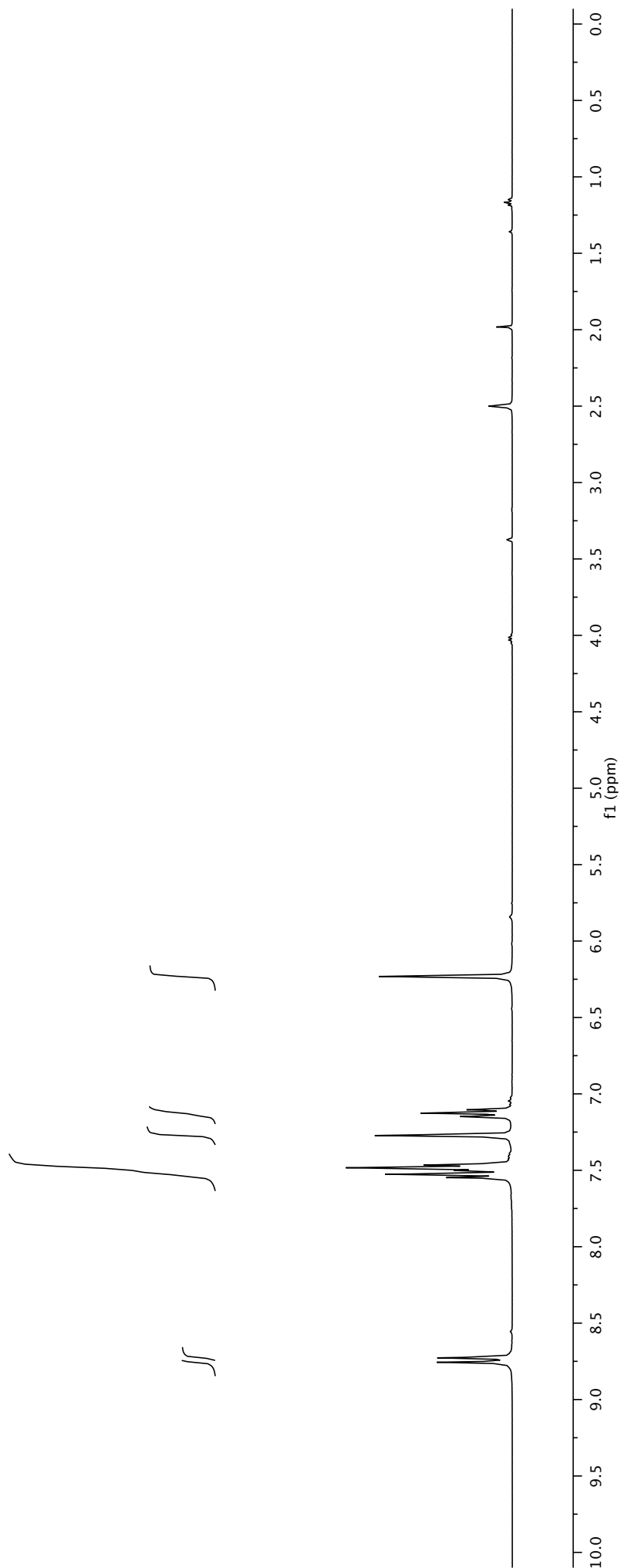
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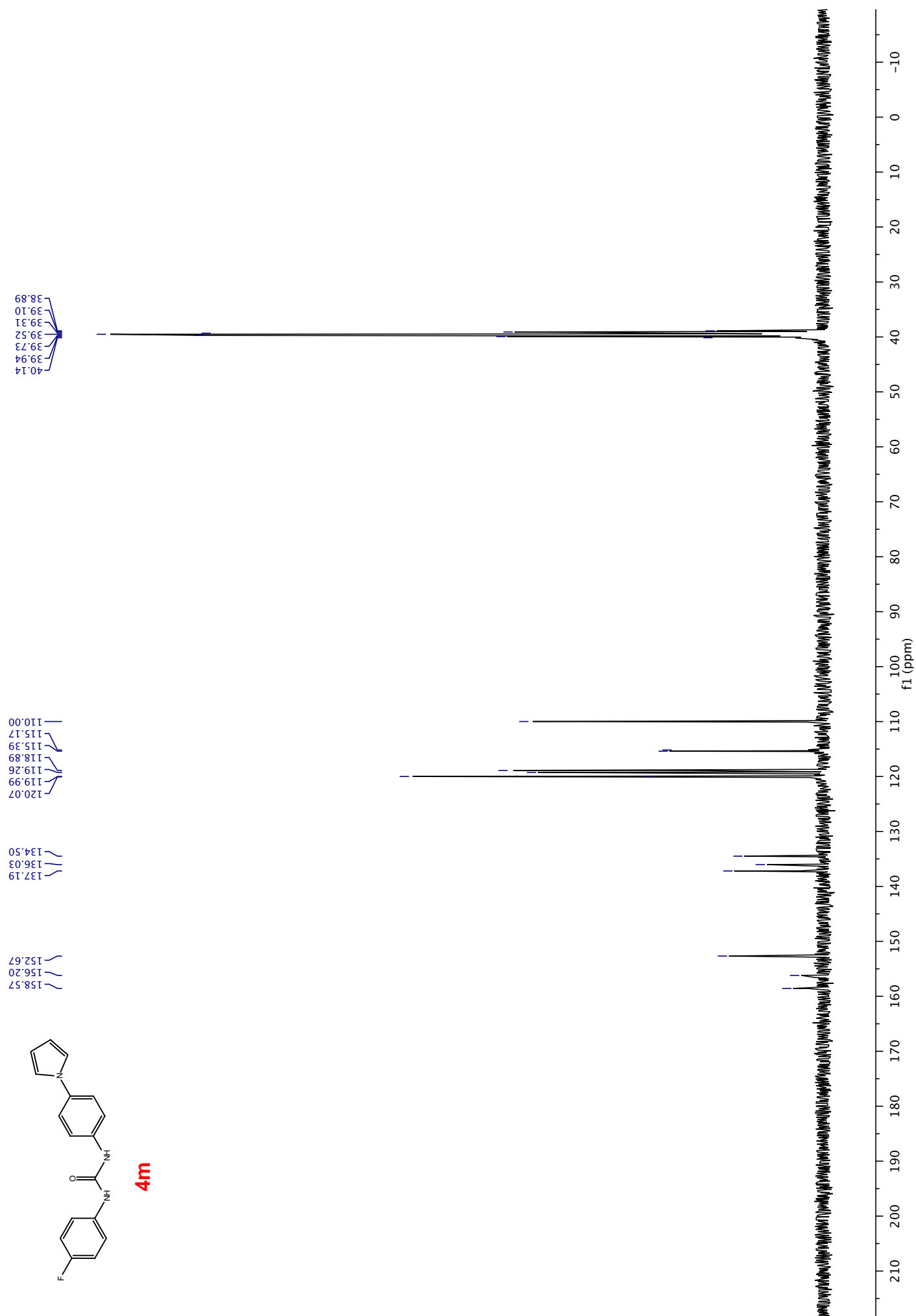


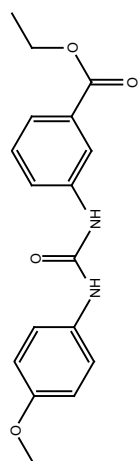




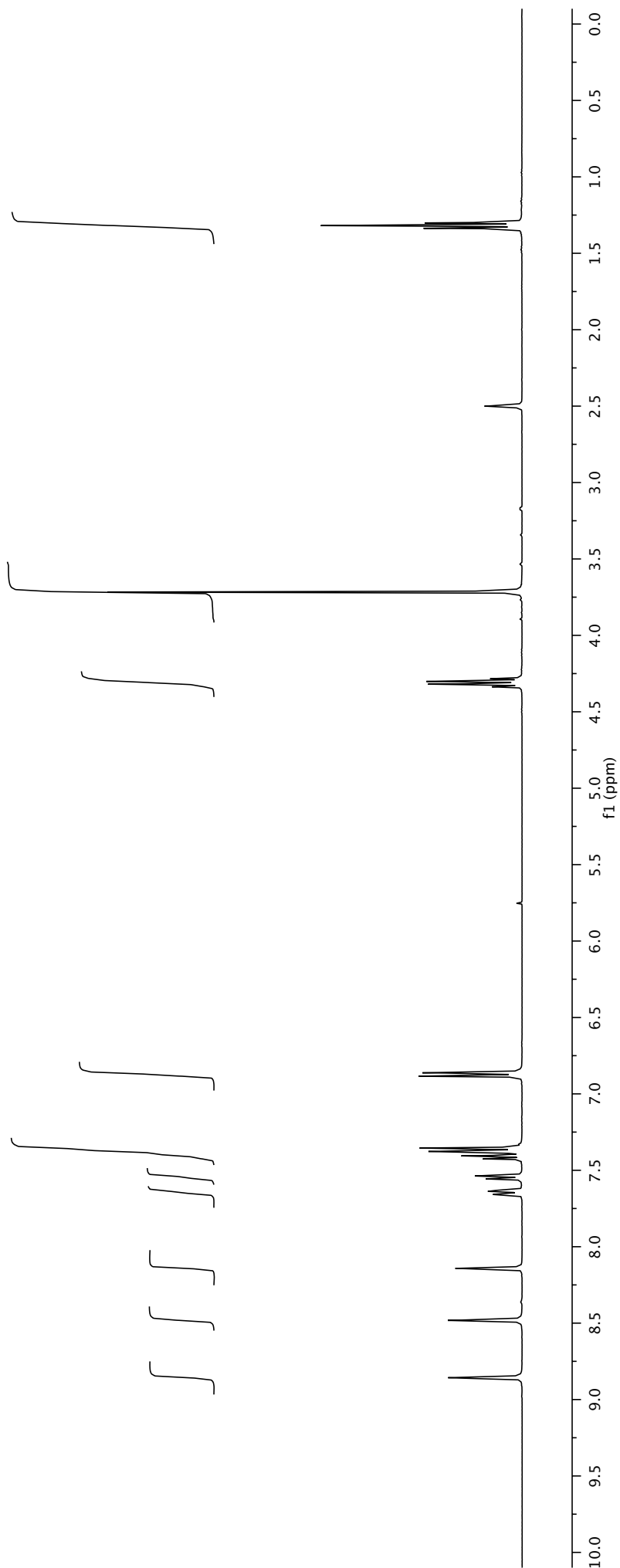
4m

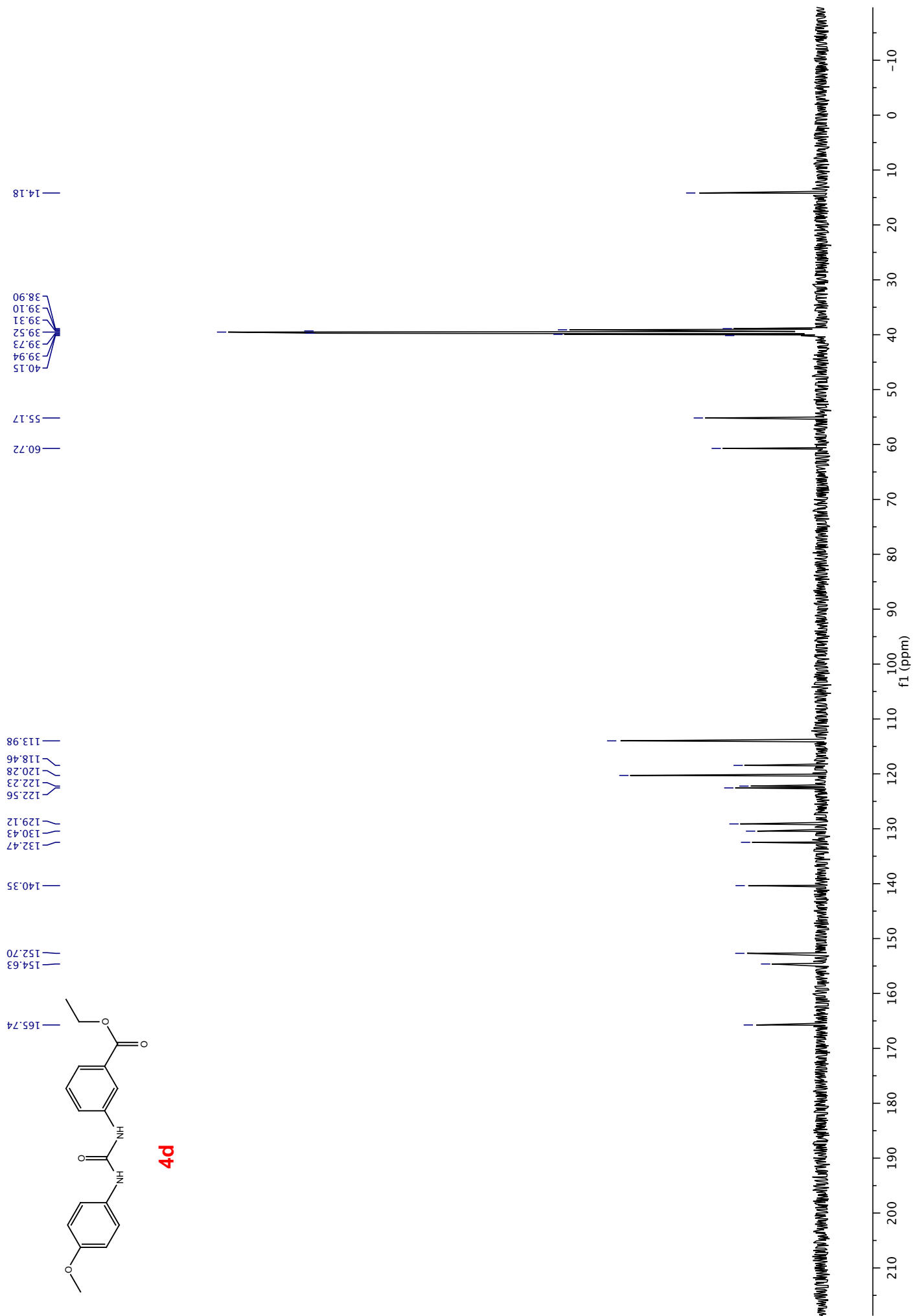


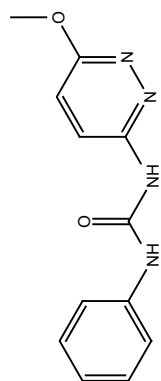




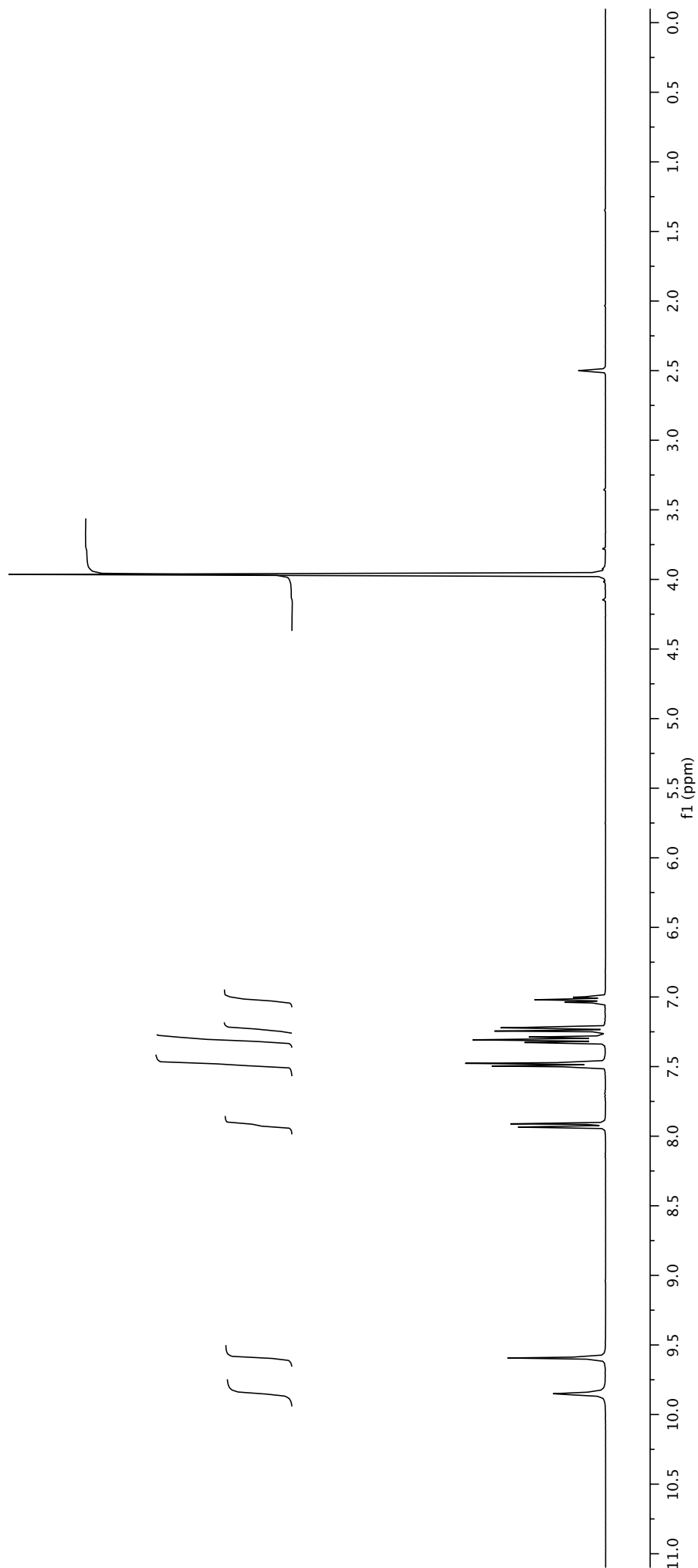
4d



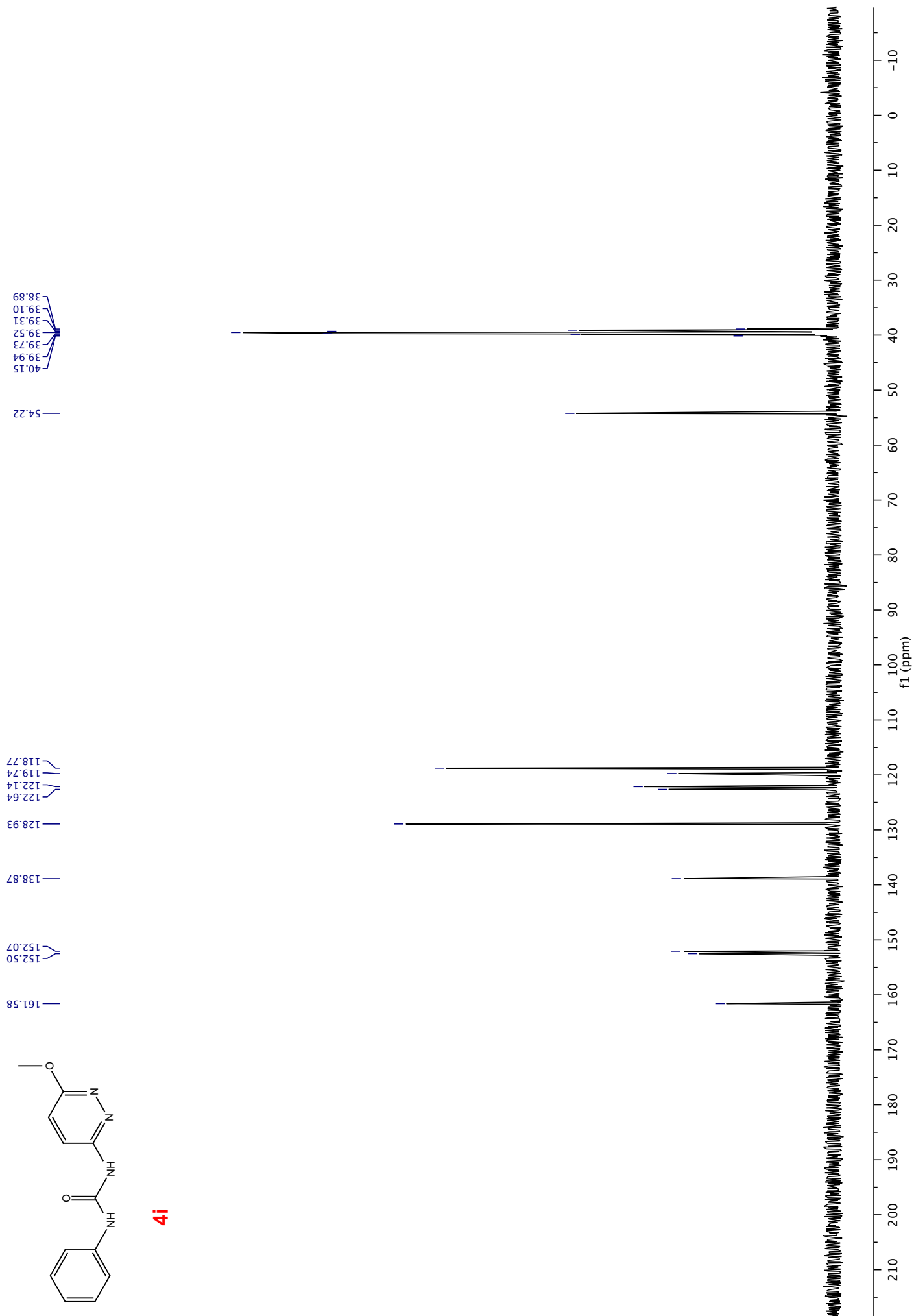
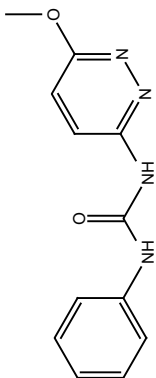




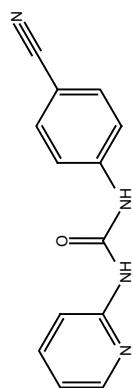
4i



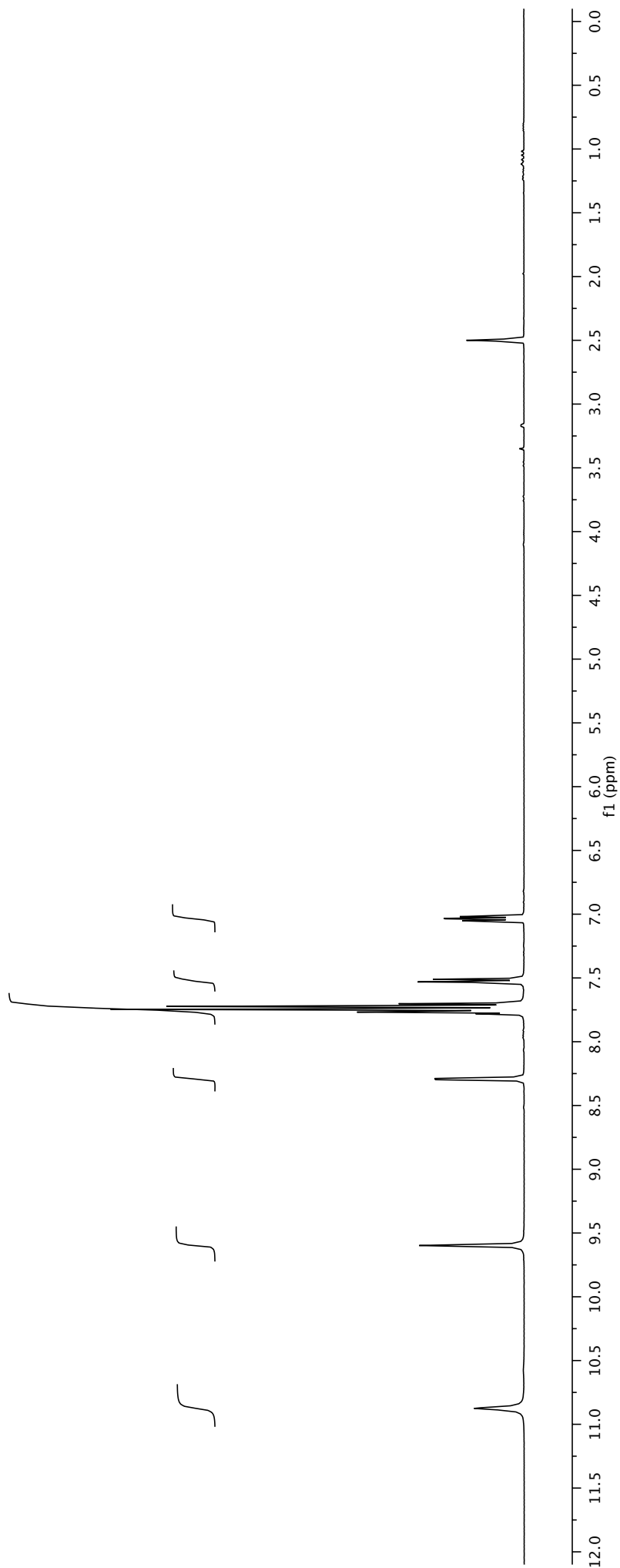
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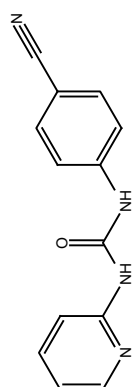
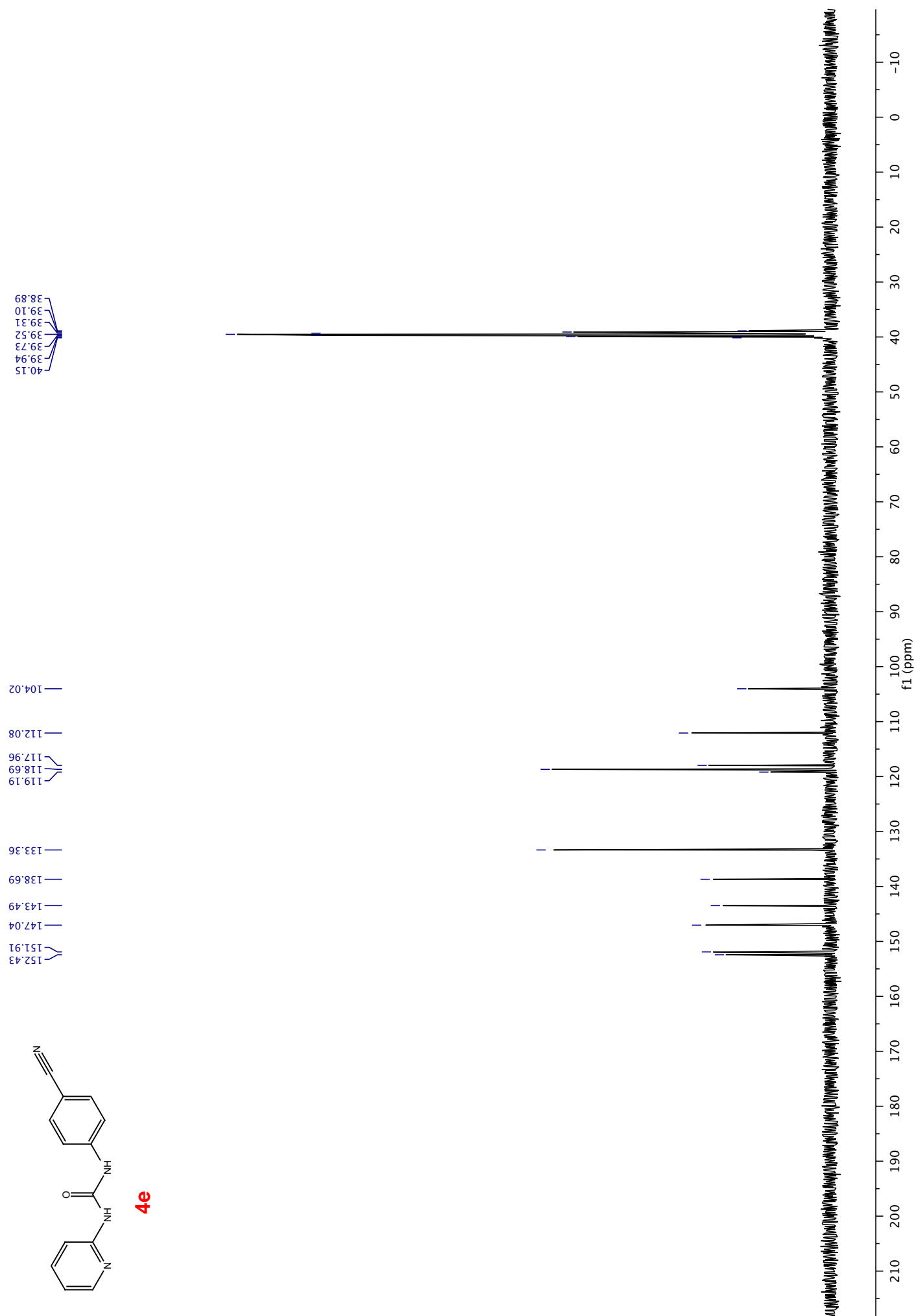


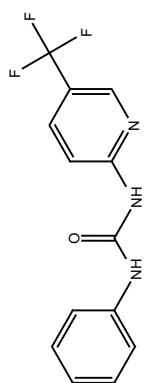




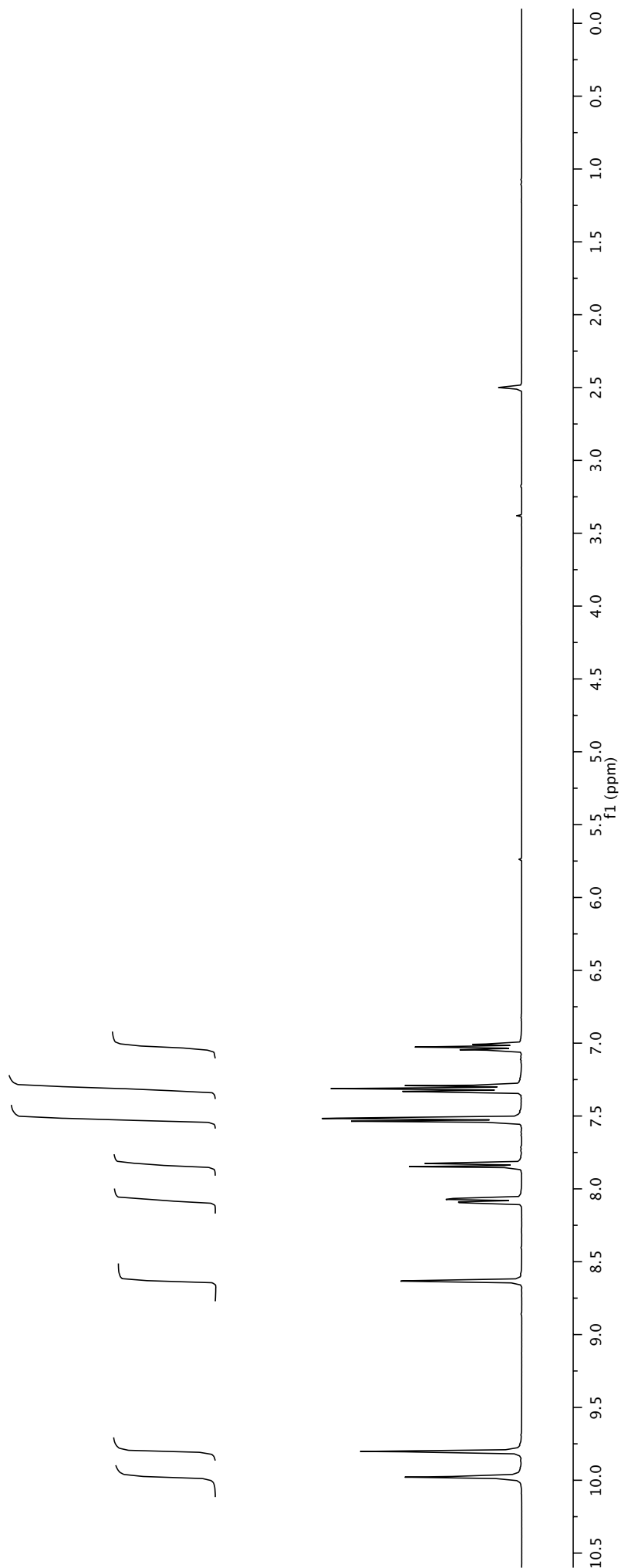
4e

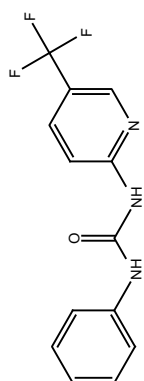
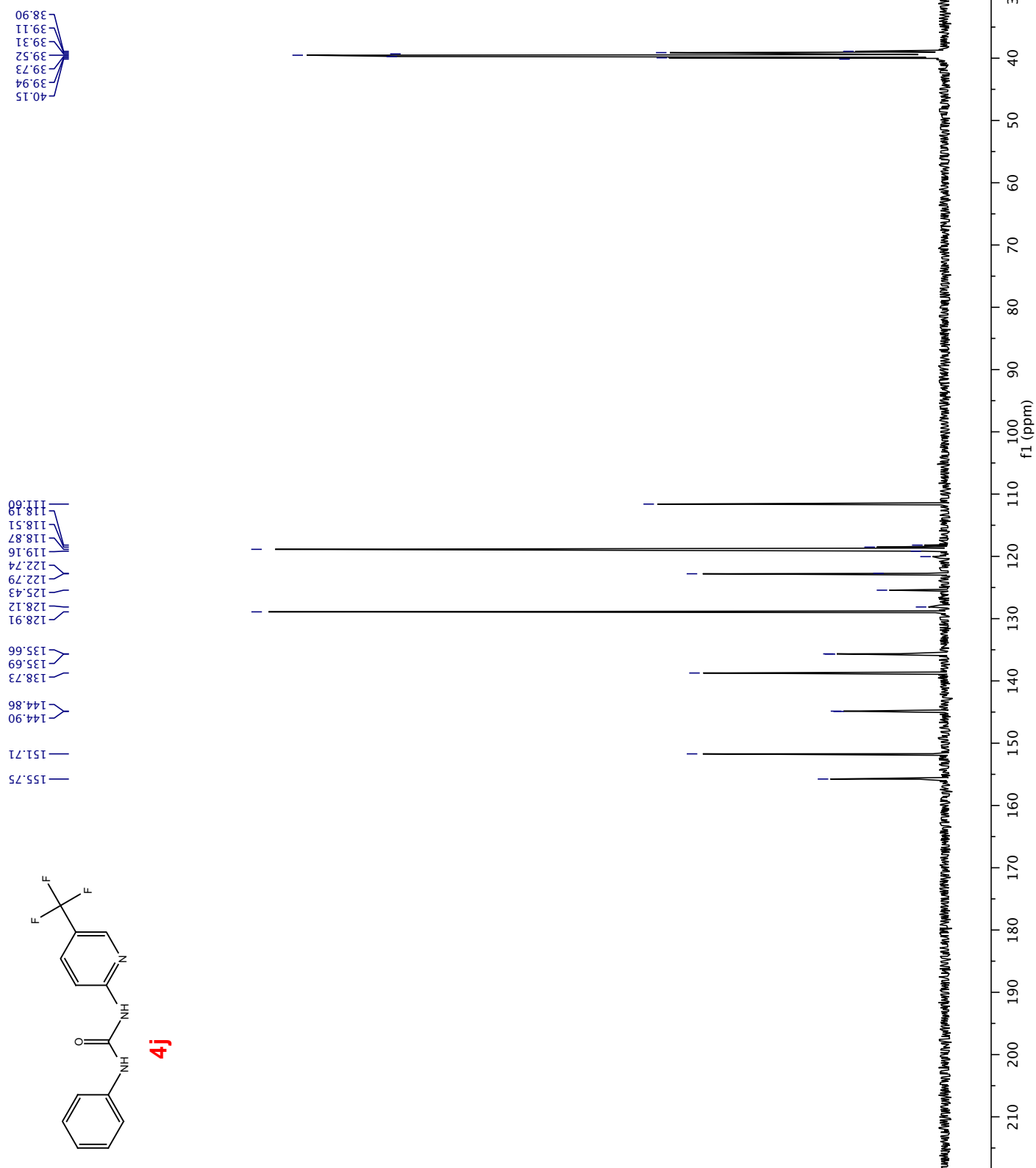


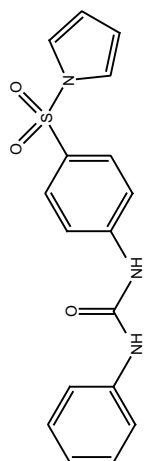
**4e**



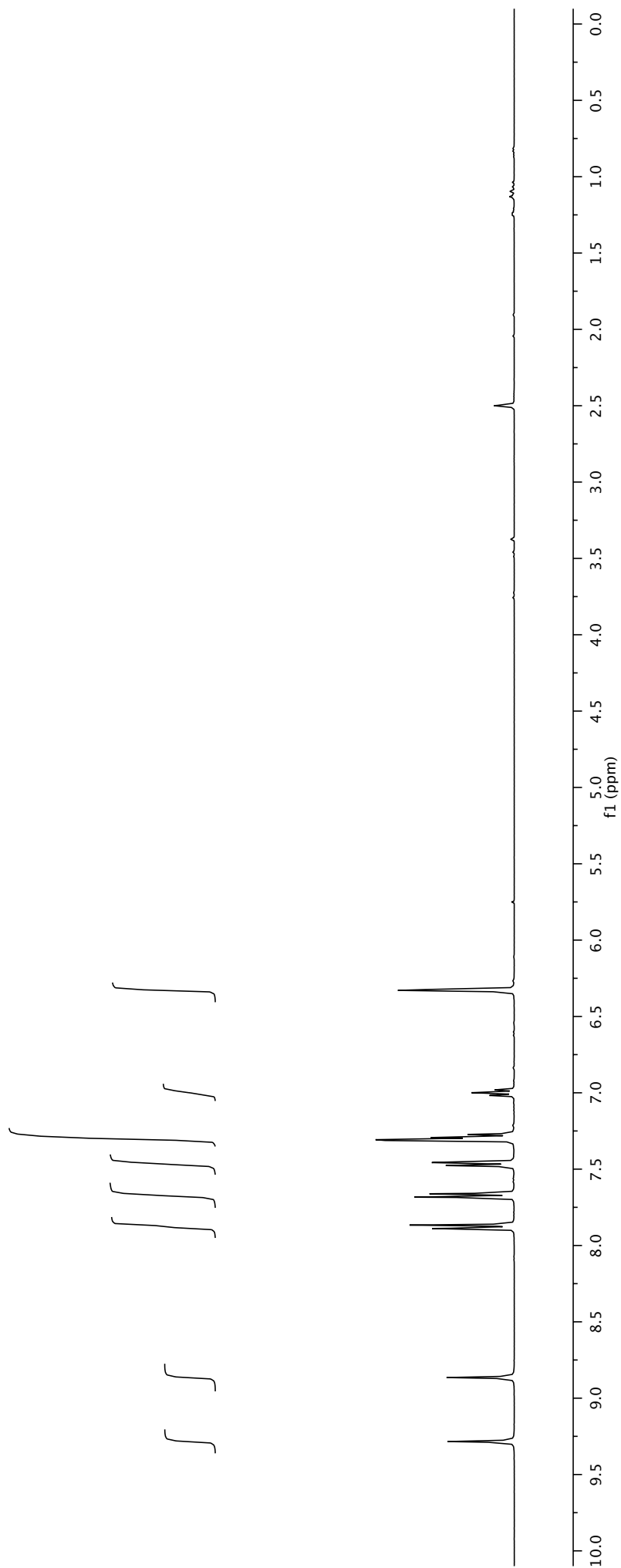
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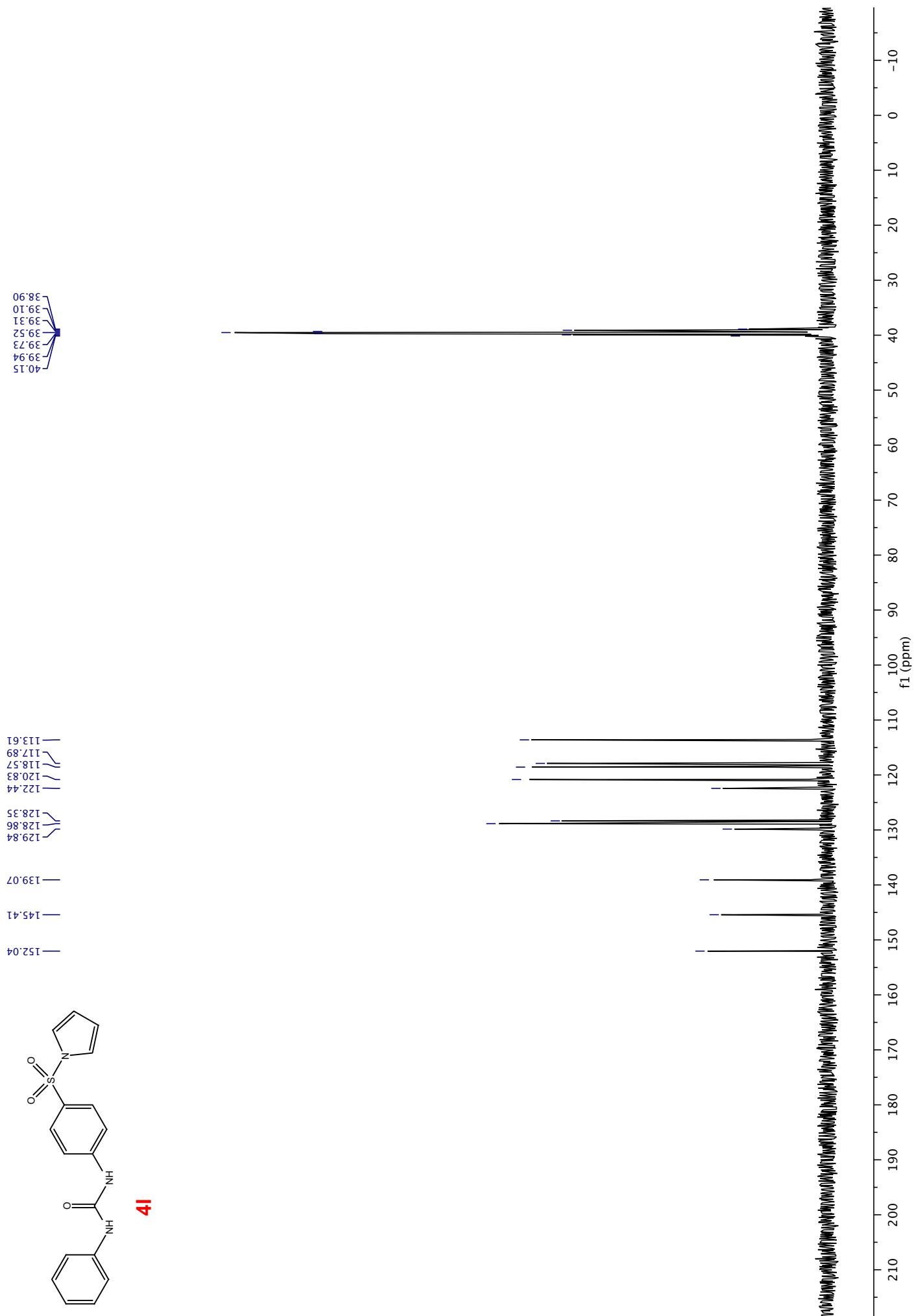


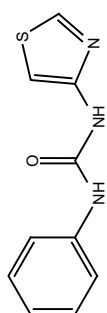
**4j**



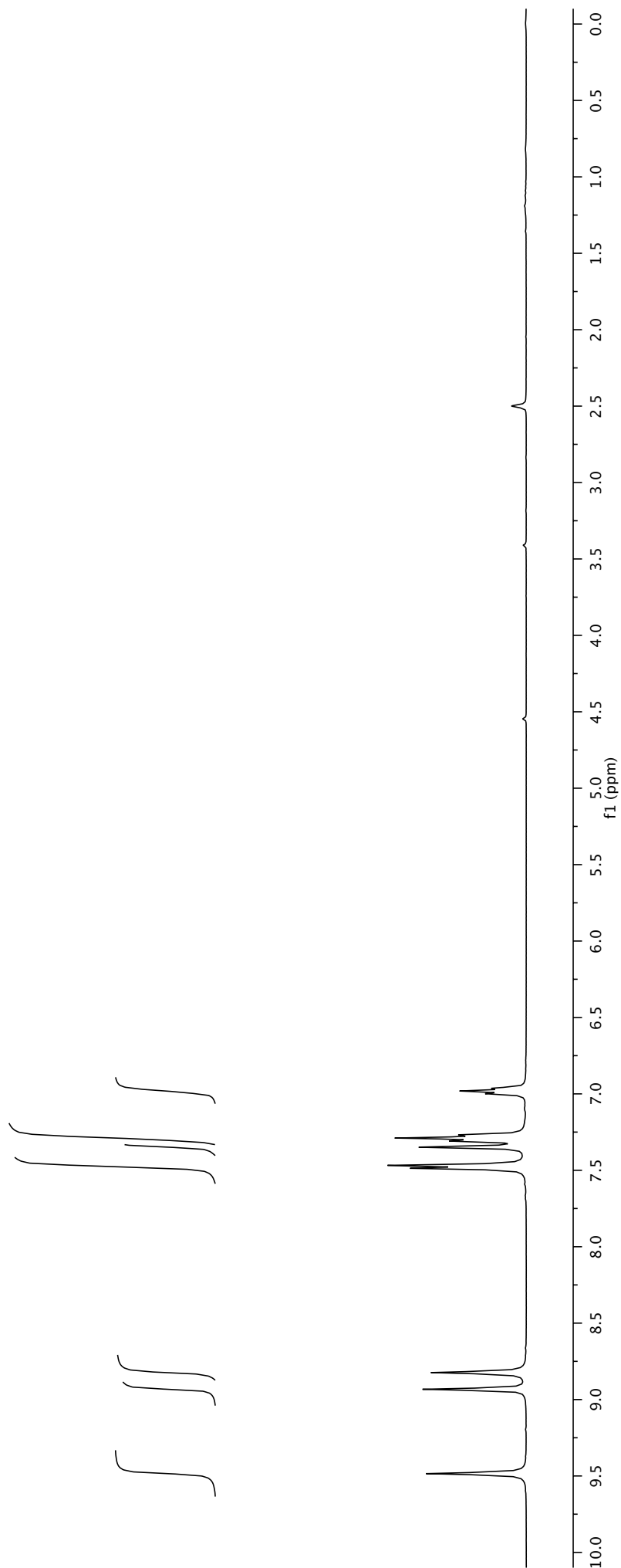
4I

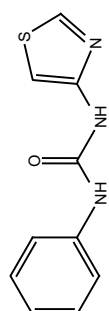




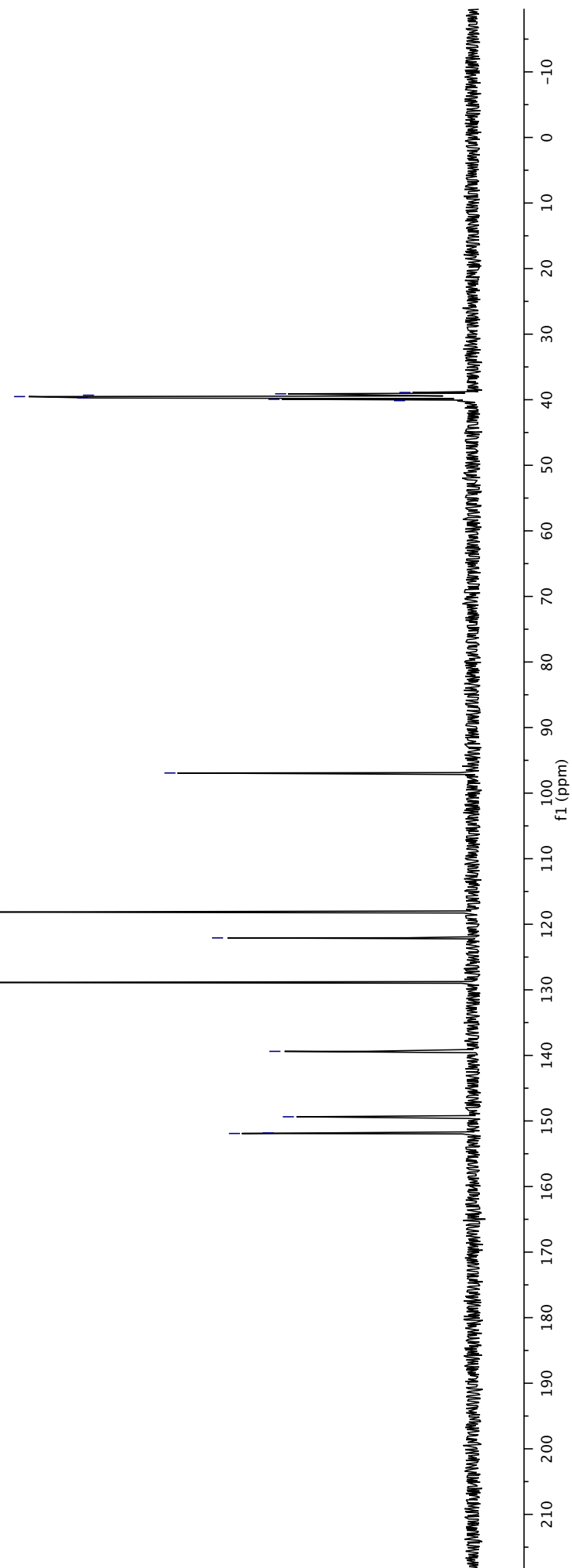


4k

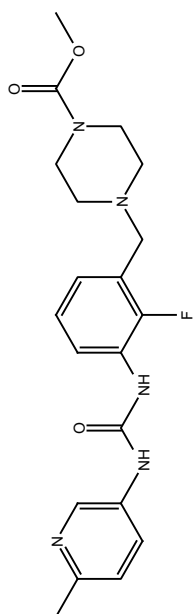




**4k**

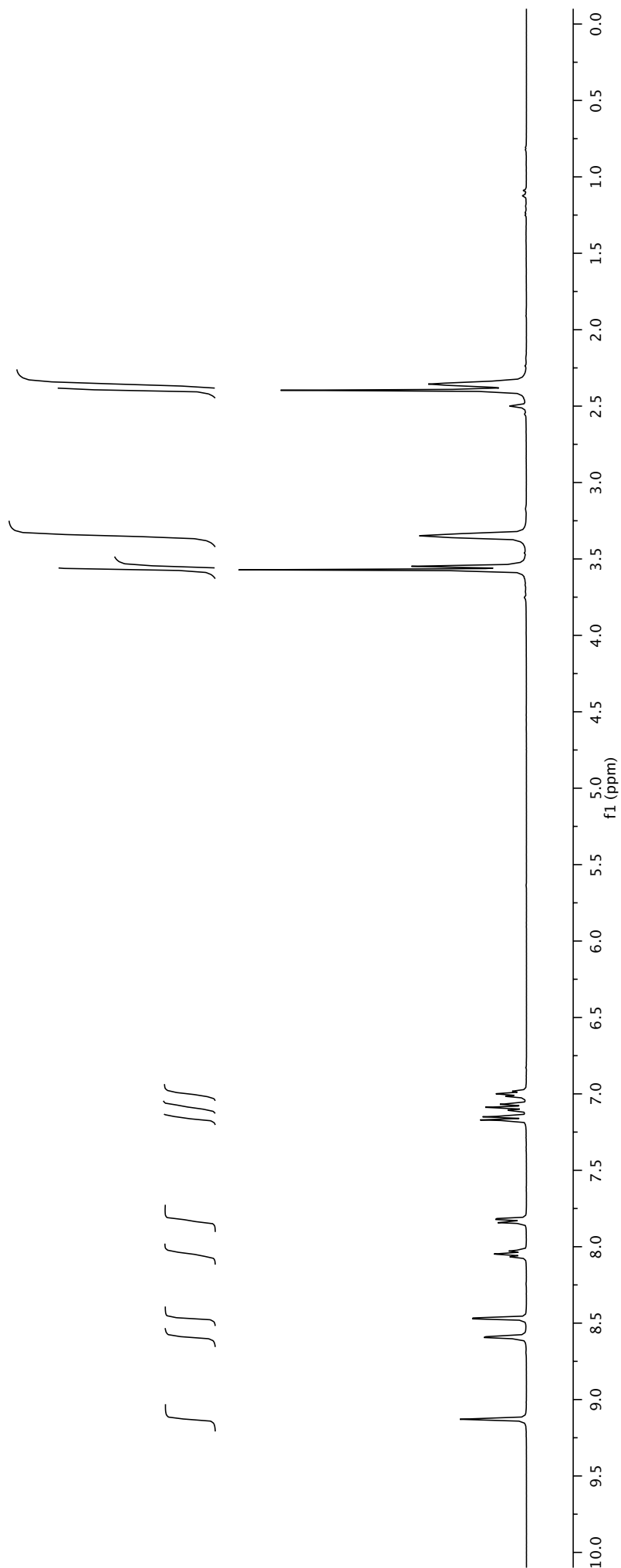


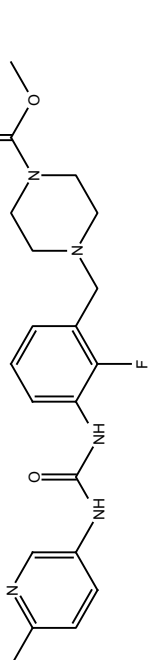




**Omecamtiv  
Mecarbil**

SI 89

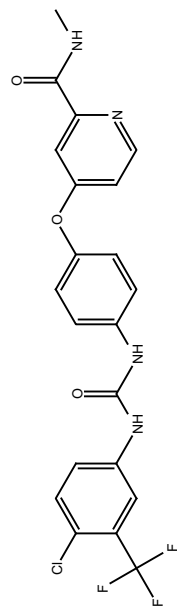


**Omecamtiv  
Mecarbil**

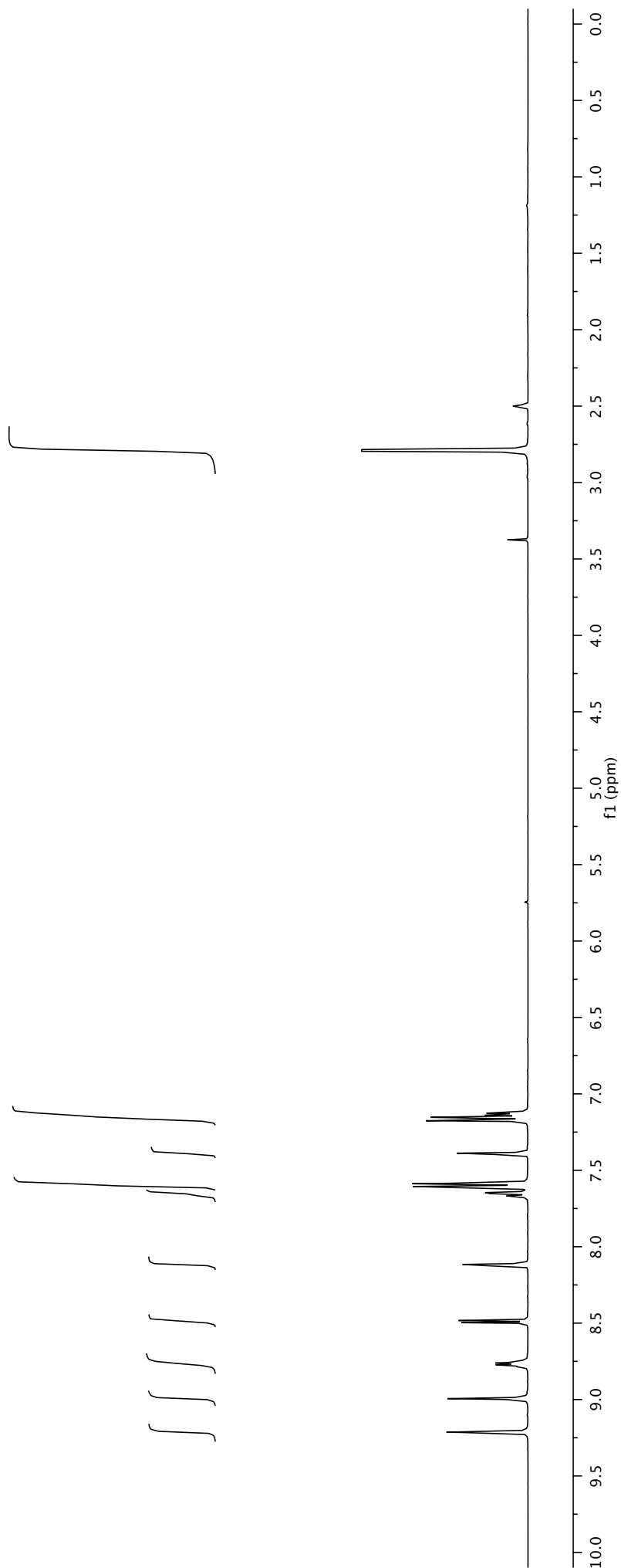
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149.53  
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133.64  
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127.27  
125.83  
124.14  
124.00  
123.98  
123.94  
123.78  
123.74  
122.78  
119.53

54.56  
52.25  
52.08  
43.39  
40.15  
39.94  
39.73  
39.52  
39.31  
39.10  
38.90  
23.22

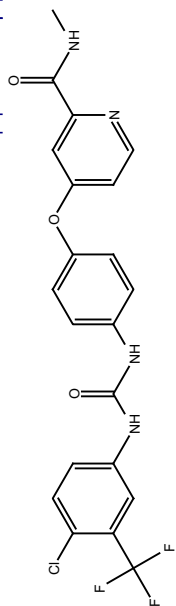
f1 (ppm)



Sorafenib



# Sorafenib



166.59  
164.42  
153.09  
153.07  
150.92  
148.45  
139.95  
137.70  
132.56  
127.52  
127.22  
123.66  
122.98  
122.05  
121.11  
117.46  
117.41  
114.59  
109.32

40.73  
40.52  
40.32  
40.11  
39.90  
39.69  
39.48  
26.60

