

**Supporting information**  
**For**

**The “Left-hand strategy” for design, synthesis and discovery  
of novel triazole-mercaptobenzothiazole hybrid compounds  
as potent quorum sensing inhibitors and anti-biofilm  
formation of *Pseudomonas aeruginosa*.**

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## 1. Materials and methods

### 1.1. Chemistry

Solvent, reagents were purchased from Sigma-Aldrich, TCI and were used as is. The reported NMR-spectra ( $^1\text{H-NMR}$ ) were recorded with 400/500 MHz Bruker Avance and the samples ran at 300K.  $^{13}\text{C-NMR}$  were analysed at 151 MHz or 101 MHz (as indicated). Chemical shifts ( $\delta$ ) are reported in ppm which calibrated to the internal standard (the peak of NMR solvent).  $J$  values are reported in Hertz. Silica gel 60 F<sub>254</sub> plates (pre-coated) were used for TLC and visualized under UV light. All synthesized compounds possess at least 95% purity before biological studies. Purities were analyzed on a Waters 2795 system equipped with a Waters 996 PDA detector and a Waters Symmetry C18 Column (2.1 x 50 mm, 3.5  $\mu\text{m}$ ), flow rate 0.2 mL/min. HRMS data were recorded on an electrospray (ESI) mass spectrometer

### 1.2. Biological screening of the library compounds

#### 1.2.1. Quorum sensing assay

Using the previously described methodology with a slight modification [1] *P. aeruginosa* quorum sensing reporter strains *lasB-gfp* was used for screening [2] the inhibition of QS system. The *Las* reporter strain was cultured, and grown for 20 h at 37 °C (180 rpm). Then the overnight cultures were diluted to a final OD<sub>450</sub> of 0.1. The 96-well microtiter dishes were used for the assay (Black Isoplate, Waltham MA, USA). Library compounds, **4-NPO**, growth media and reporter strains OHHL [*N*-(3-oxohexanoyl)-L-homoserine lactone] were added to the microtiter dishes. Victor X4 multilabel plate reader was used for monitoring the growth, green fluorescent protein (GFP) expression

(Waltham MA, USA). The assays were maintained at 34 °C, and the data was read every 15 min (over 20 h). GFP expression was recorded as fluorescence at 485 nm, 535 nm.

### **1.2.2. Anti-biofilm biomass.**

The *P. aeruginosa* PA14 was used for the assay using the method previously described [3,4] with slight modification. Compounds was test with the concentration of 100 µM unless otherwise noted. DMSO was used as negative control. **4-NPO** was used as positive control. Briefly, the bacterial cultures were diluted to an OD600 of 0.02 in a fresh M63 minimal medium. 200 µL bacterial culture was transferred to each well of a 24- well imaging plate. After the compounds were added, plates were incubated at 30 °C for 48 h. Bacteria grew to the same density as the DMSO control under each condition tested. [4]. The measurements of biofilm biomass were performed by crystal violet (CV) staining method [9,10]. In three wells of the 96-well biofilm microplate were added 190 µL of 0.01% CV (Sigma-Aldrich). The resulting was incubated 30 min at room temperature. After that, the CV solution was removed. The resulting was washed with sterile water (3xtimes) and dry at 50 °C. Then 96% ethanol was added dropwise to each well for detaching biofilm. Absorbance measurement values at 570 nm. If a negative value for optical density (OD) was obtained, it was presented as zero. The experiment was performed with three replicates. Statistical significance was calculated using the students *t* test

### **1.2.3. Anti-violacein formation of *CviR* receptor.**

The *C. violaceum* 31532 was used and grown at 30 °C for 24 h. The compounds were added to evaluate the production of violacein and analyzed by violacein extraction and quantification as described [5]. The overnight culture was incubated with or without peptides (100 µM) at 30 °C for 24 h. Then collect the bacterial cells. Re-dissolved in 1 mL

DMSO, remove cell debris and the absorbance of soluble violacein was read at 585nm using a microplate reader.

#### **1.2.4. The protease assays.**

The assay was performed using the previously described method [6]. Briefly, dilute the logarithmic growth phase of *P. aeruginosa* to OD600 = 0.1 PTSB medium. They then incubated at 37 °C for 8 h. In a 96 well plate, the bacterial culture and **4g, 4h, 4m** were added at a concentration of 50 µM. Then cultured for 24h at 37 °C. The absorbance was recorded using Spectramax M4 (Molecular Devices, USA) at 440 nm. Data was calculated subtracting OD440 recorded with the final OD600 values.

#### **1.2.5. Cytotoxicity Assay.**

Using the previously described methodology with a slight modification [7]. Firstly, the stock solution of the active compounds **4g, 4h, 4m** was prepared in DMSO as 200 µM. The testing concentrations were prepared from stock solution by diluting in growth medium (90% high glucose medium supplemented with 10% fetal bovine serum). The HeLa cells were grown as monolayers in the growth medium at 37°C (atmosphere containing 5% CO<sub>2</sub>). When cells reached 70% confluence were detached from the culture flask with 5% trypsin-EDTA and resuspended in fresh culture media at a density of 5 x 10<sup>4</sup> cells/mL. By use of a Falcon 24-well, flat bottom plate, 500 µL of the cell suspension was added to each of the wells, and the cells were incubated for 24h at 37°C. Then the active compounds (with concentrations of 0, 1, 5, 10, 15, 20, 25, 30, 40, 50, 70, 100 µM) were added to each cell in triplicates and incubated for 24 h. The cytotoxicity was performed using the in vitro toxicology assay kit, MTT based (Sigma). Absorbance values were measured at 570 nm and 690 nm. The absorbance values measured at 690 nm

were subtracted from the values measured at 570 nm when the data was analyzed. Data were normalized by subtracting the absorbance values of the growth medium treated equally than the rest of the samples.

## 2. Characterization of compounds

### Compounds 3a-p:

Intermediate **2** alkyne (1 equiv), corresponding alkyne (1.1 equiv), CuI (10 mol%) were added to microwave vial in DMSO. The mixture was irradiated under microwave condition at 120 °C for 10 minutes (high absorption mode) using in Biotage microwave system.

The reaction mixture was then diluted in 20 mL H<sub>2</sub>O and extracted with 20 mL of ethyl acetate (x3 times). Organic solvent was removed under vacuum and purified using flash column chromatography to afford **3a-p**.

**2-chloro-4-(4-phenyl-1H-1,2,3-triazol-1-yl)aniline (3a)**. 90% from **2**; mp 167- 1169 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 9.08 (s, 1H, CH-triazole), 7.94 – 7.88 (m, 2H, CH-phenyl), 7.63 (dd, *J*<sub>1</sub> = 12.1, *J*<sub>2</sub> = 2.4, 1H, CH-phenyl), 7.48 (dd, *J*<sub>1</sub> = 8.6, *J*<sub>2</sub> = 6.8, 3H, CH-phenyl), 7.37 (td, *J*<sub>1</sub> = 7.1, *J*<sub>2</sub> = 1.5, 1H, CH-phenyl), 6.94 (t, *J* = 9.1, 1H, CH-phenyl), 5.57 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(4-(*p*-tolyl)-1H-1,2,3-triazol-1-yl)aniline (3b)**. 94% from **2**; mp 175- 176 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 9.02 (s, 1H, CH-triazole), 7.83 – 7.76 (m, 2H, CH-phenyl), 7.62 (dd, *J*<sub>1</sub> = 12.1, *J*<sub>2</sub> = 2.4, 1H, CH-phenyl), 7.50 – 7.43 (m, 1H, CH-phenyl), 7.29 (d, *J* = 7.9, 2H, CH-phenyl), 6.93 (dd, *J*<sub>1</sub> = 9.6, *J*<sub>2</sub> = 8.6, 1H, CH-phenyl), 5.56 (s, 2H, NH<sub>2</sub>), 2.34 (s, 3H, CH<sub>3</sub>).

**2-chloro-4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)aniline (3c)**. 89% from **2**; mp 170- 172 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 9.24 (d, *J* = 1.8, 1H, CH-triazole), 8.12 (t, *J* = 1.8,

1H, CH-phenyl), 7.96 (dd,  $J_1 = 7.8$ ,  $J_2 = 1.4$ , 1H, CH-phenyl), 7.81 (d,  $J = 2.5$ , 1H, CH-phenyl), 7.61 (ddd,  $J_1 = 15.0$ ,  $J_2 = 7.1$ ,  $J_3 = 2.8$ , 2H, CH-phenyl), 7.48 (td,  $J_1 = 7.9$ ,  $J_2 = 2.7$ , 1H, CH-phenyl), 6.99 (d,  $J = 8.7$ , 1H, CH-phenyl), 5.83 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)aniline (3d).** 76% from **2**; mp 206-208 °C; <sup>1</sup>H NMR (600 MHz, DMSO)  $\delta = 9.19$  (s, 1H, CH-triazole), 7.98 – 7.93 (m, 2H, CH-phenyl), 7.81 (d,  $J = 2.5$ , 1H, CH-phenyl), 7.62 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.5$ , 1H, CH-phenyl), 7.62 – 7.56 (m, 2H, CH-phenyl), 6.99 (d,  $J = 8.7$ , 1H, CH-phenyl), 5.83 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)aniline (3e).** 87% from **2**; mp 157-160 °C; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 9.08$  (s, 1H, CH-triazole), 8.10 (dd,  $J_1 = 7.7$ ,  $J_2 = 1.8$ , 1H, CH-phenyl), 7.89 (d,  $J = 2.5$ , 1H, CH-phenyl), 7.73 – 7.41 (m, 5H, CH-phenyl), 6.99 (d,  $J = 8.8$ , 1H, CH-phenyl), 5.82 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-benzyl-1H-1,2,3-triazol-1-yl)aniline (3f).** 81% from **2**; mp 112- 113 °C; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 8.41$  (s, 1H, CH-triazole), 7.71 (d,  $J = 2.4$ , 1H, CH-phenyl), 7.52 (dd,  $J_1 = 8.8$ ,  $J_2 = 2.5$ , 1H, CH-phenyl), 7.30 (d,  $J = 5.3$ , 4H, CH-phenyl), 7.21 (tt,  $J_1 = 5.1$ ,  $J_2 = 3.2$ , 1H, CH-phenyl), 6.91 (d,  $J = 8.8$ , 1H, CH-phenyl), 5.71 (s, 2H, NH<sub>2</sub>), 4.04 (s, 2H, CH<sub>2</sub>).

**2-chloro-4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)aniline (3g).** 89% from **2**; yellow oil; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 9.19$  (s, 1H, CH-triazole), 7.79 (dt,  $J_1 = 7.7$ ,  $J_2 = 1.2$ , 1H, CH-phenyl), 7.73 (ddd,  $J_1 = 10.3$ ,  $J_2 = 2.6$ ,  $J_3 = 1.5$ , 1H, CH-phenyl), 7.68 – 7.52 (m, 2H, CH-phenyl), 7.52 – 7.45 (m, 1H, CH-phenyl), 7.28 – 7.18 (m, 1H, CH-phenyl), 6.97 (dd,  $J_1 = 9.5$ ,  $J_2 = 8.6$ , 1H, CH-phenyl), 5.63 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)aniline (3h)** was synthesized previously [8].

**2-chloro-4-(2,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)aniline (3i).** 80% from **2**; mp 164-165 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 8.90 (d, *J* = 3.2, 1H, CH-triazole), 8.17 (td, *J*<sub>1</sub> = 8.7, *J*<sub>2</sub> = 6.5, 1H, CH-phenyl), 7.85 (d, *J* = 2.5, 1H, CH-phenyl), 7.64 (dd, *J*<sub>1</sub> = 8.7, *J*<sub>2</sub> = 2.5, 1H, CH-phenyl), 7.44 (ddd, *J*<sub>1</sub> = 11.5, *J*<sub>2</sub> = 9.3, *J*<sub>3</sub> = 2.6, 1H, CH-phenyl), 7.33 – 7.16 (m, 1H, CH-phenyl), 6.95 (d, *J* = 8.7, 1H, CH-phenyl), 5.79 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(2-trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)aniline (3j).** 82% from **2**; mp 112- 114 °C; <sup>1</sup>H NMR (600 MHz, DMSO) δ = 8.84 (s, 1H, CH-triazole), 7.92 (d, *J* = 7.9, 1H, CH-phenyl), 7.85 (d, *J* = 2.5, 1H, CH-phenyl), 7.84 – 7.79 (m, 2H, CH-phenyl), 7.74 – 7.68 (m, 1H, CH-phenyl), 7.66 (dd, *J*<sub>1</sub> = 8.7, *J*<sub>2</sub> = 2.5, 1H, CH-phenyl), 6.99 (d, *J* = 8.7, 1H, CH-phenyl), 5.83 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(3-trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)aniline (3k).** 86% from **2**; mp 161- 162 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 9.34 (s, 1H, CH-triazole), 8.25 (d, *J* = 4.3, 2H, CH-phenyl), 7.83 (d, *J* = 2.5, 1H, CH-phenyl), 7.82 – 7.72 (m, 2H, CH-phenyl), 7.64 (dd, *J*<sub>1</sub> = 8.8, *J*<sub>2</sub> = 2.5, 1H, CH-phenyl), 7.00 (d, *J* = 8.7, 1H, CH-phenyl), 5.84 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(4-trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)aniline (3l).** 85% from **2**; mp 215-217 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 9.32 (s, 1H, CH-triazole), 8.15 (d, *J* = 8.1, 2H, CH-phenyl), 7.89 (d, *J* = 8.1, 2H, CH-phenyl), 7.83 (d, *J* = 2.5, 1H, CH-phenyl), 7.64 (dd, *J*<sub>1</sub> = 8.7, *J*<sub>2</sub> = 2.5, 1H, CH-phenyl), 7.00 (d, *J* = 8.7, 1H, CH-phenyl), 5.84 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)aniline (3m).** 94% from **2**; light yellow oil; <sup>1</sup>H NMR (600 MHz, DMSO) δ = 9.11 (s, 1H, CH-triazole), 7.62 (dd, *J*<sub>1</sub> = 12.0,

$J_2 = 2.4$ , 1H, CH-phenyl), 7.54 – 7.44 (m, 3H, CH-phenyl), 7.39 (t,  $J = 7.9$ , 1H, CH-phenyl), 6.96 – 6.90 (m, 2H, CH-phenyl), 5.58 (s, 2H, NH<sub>2</sub>), 3.83 (s, 3H, OCH<sub>3</sub>).

**2-chloro-4-(thiophen-3-yl)phenyl)-1H-1,2,3-triazol-1-yl)aniline (3n).** 93% from **2**; mp 188-189 °C; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 9.00$  (s, 1H, CH-triazole), 7.92 (dd,  $J_1 = 2.9$ ,  $J_2 = 1.3$ , 1H, CH-thiophen), 7.79 (d,  $J = 2.5$ , 1H, CH-phenyl), 7.71 (dd,  $J_1 = 5.0$ ,  $J_2 = 2.9$ , 1H, CH-thiophen), 7.65 – 7.55 (m, 2H, CH-phenyl & CH-thiophen), 6.99 (d,  $J = 8.8$ , 1H, CH-phenyl), 5.80 (s, 2H, NH<sub>2</sub>).

**2-chloro-4-(4-ethylphenyl)-1H-1,2,3-triazol-1-yl)aniline (3o).** 98% from **2**; mp 120-122 °C; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 9.08$  (s, 1H, CH-triazole), 7.88 – 7.79 (m, 3H, CH-phenyl), 7.63 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.5$ , 1H, CH-phenyl), 7.35 (d,  $J = 8.1$ , 2H, CH-phenyl), 6.99 (d,  $J = 8.8$ , 1H, CH-phenyl), 5.80 (s, 2H, NH<sub>2</sub>), 2.67 (q,  $J = 7.6$ , 2H, CH<sub>2</sub>), 1.24 (t,  $J = 7.6$ , 3H, CH<sub>3</sub>).

**2-chloro-4-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)aniline (3p).** 89% from **2**; mp 170.1-172.1 °C; <sup>1</sup>H NMR (400 MHz, DMSO)  $\delta = 9.15$  (s, 1H, CH-triazole), 8.67 (dt,  $J_1 = 4.7$ ,  $J_2 = 1.4$ , 1H, CH-pyridine), 8.15 – 8.08 (m, 1H, CH-phenyl), 7.95 (td,  $J_1 = 7.7$ ,  $J_2 = 1.8$ , 1H, CH-pyridine), 7.90 (d,  $J = 2.5$ , 1H, CH-pyridine), 7.69 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.6$ , 1H, CH-phenyl), 7.41 (ddd,  $J_1 = 7.6$ ,  $J_2 = 4.9$ , 1.2, 1H, CH-pyridine), 6.98 (d,  $J = 8.7$ , 1H, CH-phenyl), 5.81 (s, 2H, NH<sub>2</sub>).

### **Compounds 4a-p**

Compounds **3a-n** (100 mg) was dissolved in 10 mL DMAC followed by *O*-isopropylxanthic acid potassium salt (1.5 equiv). The mixture was irradiated under microwave condition (150 °C, 5 min). The reaction mixture was then diluted in 50 mL H<sub>2</sub>O and kept at room



temperature for 1h. The precipitated product was filtered and washed several times with H<sub>2</sub>O, cold acetone, cold ethanol to afforded the products **4a-p**.

**6-(4-phenyl-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4a):** Purity 98.2% by HPLC; Yield 88%; mp 266- 267 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 14.03 (s, 1H, SH), 9.28 (s, 1H, CH-triazole), 8.36 (d, *J* = 2.2, 1H, CH-benzothiazole), 8.02 – 7.92 (m, 3H, CH-phenyl & benzothiazole), 7.56 – 7.47 (m, 3H, CH-phenyl & benzothiazole), 7.45 – 7.36 (m, 1H). <sup>13</sup>C NMR (101 MHz, DMSO) δ 190.56, 147.35, 141.26, 133.11, 130.76, 130.13, 129.01, 128.28, 125.31, 119.83, 119.67, 113.85, 113.12. HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>11</sub>N<sub>4</sub>S<sub>2</sub><sup>+</sup> 311.0425, found 311.0425.

**6-(4-(p-tolyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4b):** Purity 100% by HPLC; Yield 70%; mp 282-283 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 14.03 (s, 1H, SH), 9.22 (s, 1H, CH-triazole), 8.35 (d, *J* = 2.2, 1H, CH-benzothiazole), 7.97 (dd, *J*<sub>1</sub> = 8.7, *J*<sub>2</sub> = 2.2, 1H, CH-benzothiazole), 7.88 – 7.81 (m, 2H, CH-phenyl), 7.51 (d, *J* = 8.7, 1H, CH-benzothiazole), 7.33 (d, *J* = 7.9, 2H, CH-phenyl), 2.38 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (101 MHz, DMSO) δ 190.52, 147.41, 141.23, 137.66, 133.13, 130.75, 129.54, 127.34, 125.23, 119.59, 119.35, 113.75, 113.10, 20.85. HRMS (ESI) *m/z* [M+H]<sup>+</sup> calcd for C<sub>16</sub>H<sub>13</sub>N<sub>4</sub>S<sub>2</sub><sup>+</sup> 325.0582, found 325.0580.

**6-(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4c):** Purity 98.8% by HPLC; Yield 89%; mp 216-217 °C; <sup>1</sup>H NMR (400 MHz, DMSO) δ = 14.06 (s, 1H, SH), 9.40 (s, 1H, CH-triazole), 8.35 (d, *J* = 2.2, 1H, CH-benzothiazole), 8.14 (t, *J* = 1.8, 1H, CH-phenyl), 7.97 (ddd, *J*<sub>1</sub> = 8.8, *J*<sub>2</sub> = 6.0, *J*<sub>3</sub> = 1.8, 2H, CH-phenyl), 7.60 (dt, *J*<sub>1</sub> = 8.3, *J*<sub>2</sub> = 1.2, 1H, CH-benzothiazole), 7.55 – 7.45 (m, 2H, CH-benzothiazole & phenyl). <sup>13</sup>C NMR (101 MHz, DMSO) δ 190.59, 145.86, 141.38, 132.97, 132.46, 131.26, 130.95,

130.80, 127.79, 124.14, 122.35, 120.64, 119.63, 113.86, 113.17. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{10}BrN_4S_2^+$  388.9530, found 388.9532.

**6-(4-(2-chlorophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4d):** Purity 100% by HPLC; Yield 80%; mp 268-269 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta$  = 14.02 (s, 1H, SH), 9.22 (s, 1H, CH-triazole), 8.42 (d,  $J$  = 2.2, 1H, CH-benzothiazole), 8.13 (dd,  $J_1$  = 7.7,  $J_2$  = 1.8, 1H, CH-phenyl), 8.05 (dd,  $J_1$  = 8.7,  $J_2$  = 2.2, 1H, CH-benzothiazole), 7.64 (dd,  $J_1$  = 7.8,  $J_2$  = 1.5, 1H, CH-phenyl), 7.50 (dq,  $J_1$  = 14.7,  $J_2$  = 7.5,  $J_3$  = 1.6, 3H, CH-benzothiazole & phenyl).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  190.59, 143.86, 141.34, 132.90, 130.68, 130.28, 129.90, 129.85, 128.66, 127.59, 122.34, 119.97, 114.15, 113.04. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{10}ClN_4S_2^+$  345.0035, found 345.0035.

**6-(4-(4-chlorophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4e):** Purity 99.9% by HPLC; Yield 90%; mp 278-280 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta$  = 14.03 (s, 1H, SH), 9.33 (dd,  $J$  = 4.3, 1.6, 1H, CH-triazole), 8.35 (q,  $J$  = 2.4, 1H, CH-benzothiazole), 7.97 (ddt,  $J_1$  = 8.4,  $J_2$  = 4.6,  $J_3$  = 1.9, 2H, CH-phenyl), 7.60 (dt,  $J_1$  = 8.6,  $J_2$  = 2.1, 2H, CH-phenyl), 7.51 (dd,  $J_1$  = 8.7,  $J_2$  = 2.4, 1H, CH-benzothiazole), 7.43 – 7.30 (m, 1H, CH-benzothiazole).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  190.58, 146.25, 141.33, 133.00, 132.73, 130.77, 129.09, 129.04, 126.97, 120.20, 119.68, 113.87, 113.12. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{10}ClN_4S_2^+$  345.0035, found 345.0035.

**6-(4-benzyl-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4f):** Purity 96.6% by HPLC; Yield 77%; mp 238- 239 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta$  = 13.97 (s, 1H, SH), 8.54 (s, 1H, CH-triazole), 8.28 (s, 1H, CH-benzothiazole), 7.91 (dd,  $J_1$  = 8.7,  $J_2$  = 2.2, 1H, CH-benzothiazole), 7.45 (d,  $J$  = 8.8, 1H, CH-benzothiazole), 7.33 (d,  $J$  = 4.4, 4H, CH-phenyl), 7.25 (m, 1H, CH-phenyl), 4.11 (s, 2H,  $CH_2$ ).  $^{13}C$  NMR (151 MHz, DMSO)  $\delta$  147.94,

139.79, 133.80, 129.18, 129.09, 126.90, 121.55, 120.10, 114.26, 31.83. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{16}H_{13}N_4S_2^+$  325.0582, found 325.0581.

**6-(4-(3-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4g):** Purity 99.7% by HPLC, Yield 90%; mp 266-267 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta$  = 14.04 (s, 1H, SH), 9.36 (s, 1H, CH-triazole), 8.35 (d,  $J$  = 2.2, 1H, CH-benzothiazole), 7.96 (dd,  $J_1$  = 8.7,  $J_2$  = 2.2, 1H, CH-benzothiazole), 7.81 (dt,  $J_1$  = 7.7,  $J_2$  = 1.2, 1H, CH-phenyl), 7.75 (ddd,  $J_1$  = 10.2,  $J_2$  = 2.6,  $J_3$  = 1.4, 1H, CH-phenyl), 7.64 – 7.47 (m, 2H, CH-phenyl), 7.25 (td,  $J_1$  = 8.5,  $J_2$  = 2.4, 1H, CH-benzothiazole).  $^{13}C$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  190.61, 163.79 (d,  $J$  = 243.4 Hz), 146.24 (d,  $J$  = 2.8 Hz), 141.36, 132.97, 132.53 (d,  $J$  = 8.5 Hz), 131.14 (d,  $J$  = 8.6 Hz), 130.79, 121.34 (d,  $J$  = 2.9 Hz), 120.59, 119.69, 115.09 (d,  $J$  = 21.1 Hz), 113.91, 113.14, 112.00 (d,  $J$  = 23.0 Hz). HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{10}FN_4S_2^+$  329.0331, found 329.0330.

**6-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4h):** Purity 100% by HPLC; Yield 71%; mp 270-273 °C;  $^1H$  NMR (600 MHz, DMSO)  $\delta$  = 14.06 (s, 1H, SH), 9.29 (s, 1H, CH-triazole), 8.35 (d,  $J$  = 2.3, 1H, CH-benzothiazole), 7.99 (tdd,  $J_1$  = 14.6,  $J_2$  = 7.8,  $J_3$  = 3.1, 3H, CH-benzothiazole & phenyl), 7.52 (d,  $J$  = 8.6, 1H, CH-benzothiazole), 7.38 (t,  $J$  = 8.8, 2H, CH-phenyl).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  191.06, 163.30 (d,  $J$  = 245.0 Hz), 146.96, 141.79, 133.55, 131.26, 127.87 (d,  $J$  = 8.5 Hz), 127.74 (d,  $J$  = 3.7 Hz), 120.27, 120.15, 116.56 (d,  $J$  = 22.2 Hz), 114.34, 113.62. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{10}FN_4S_2^+$  329.0331, found 329.0333.

**6-(4-(2,4-difluorophenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4i):** Purity 98.3% by HPLC; Yield 88%; mp 230-232 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta$  = 14.00 (s,

1H, SH), 9.03 (d,  $J = 3.1$ , 1H, CH-triazole), 8.39 (d,  $J = 2.3$ , 1H, CH-benzothiazole), 8.21 (td,  $J_1 = 8.7$ ,  $J_2 = 6.5$ , 1H, CH-phenyl), 8.03 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.3$ , 1H, CH-benzothiazole), 7.47 (td,  $J_1 = 9.8$ ,  $J_2 = 3.3$ , 2H, CH-benzothiazole & phenyl), 7.28 (td,  $J_1 = 8.5$ ,  $J_2 = 2.6$ , 1H, CH-phenyl).  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  191.18, 162.50 (dd,  $J = 247.9$ , 12.5 Hz), 159.13 (dd,  $J = 251.8$ , 13.5 Hz), 141.92, 140.89 (d,  $J = 4.4$  Hz), 133.46, 131.24, 129.42 (dd,  $J = 10.6$ , 5.5 Hz), 122.00 (d,  $J = 11.3$  Hz), 119.01, 114.65 (dd,  $J = 14.0$ , 4.5 Hz), 114.54, 113.49, 112.85 (dd,  $J = 21.9$ , 4.3 Hz), 105.18 (t,  $J = 26.2$  Hz). HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_8\text{F}_2\text{N}_4\text{S}_2^+$  347.0237, found 347.0236.

**6-(4-(2-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4j):**

Purity 98.8% by HPLC; Yield 73%; mp 266-267  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta = 14.06$  (s, 1H, SH), 8.98 (s, 1H, CH-triazole), 8.40 (d,  $J = 2.2$ , 1H, CH-benzothiazole), 8.03 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.2$ , 1H, CH-benzothiazole), 7.95 (d,  $J = 7.9$ , 1H, CH-phenyl), 7.88 – 7.80 (m, 2H, CH-phenyl), 7.73 (td,  $J_1 = 6.6$ ,  $J_2 = 3.0$ , 1H, CH-phenyl), 7.52 (d,  $J = 8.7$ , 1H, CH-benzothiazole).  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  191.10, 145.20, 142.12, 133.37, 133.23, 132.68, 131.32, 129.79, 129.38 (d,  $J = 2.3$  Hz), 127.25 (q,  $J = 30.1$  Hz), 126.95 (q,  $J = 5.5$  Hz), 124.52 (q,  $J = 273.5$  Hz), 122.82 (q,  $J = 3.2$  Hz), 120.44, 114.62, 113.72. HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{10}\text{F}_3\text{N}_4\text{S}_2^+$  379.0299, found 379.0299.

**6-(4-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4k):**

Purity 99.1 % by HPLC; Yield 78%; mp 268-272  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta = 14.08$  (s, 1H, SH), 9.50 (s, 1H, CH-triazole), 8.37 (s, 1H, CH-benzothiazole), 8.28 (d,  $J = 2.7$ , 2H, CH-phenyl), 7.98 (dd,  $J_1 = 8.5$ , 2.3, 1H, CH-benzothiazole), 7.78 (dd,  $J_1 = 4.8$ ,  $J_1 = 1.9$ , 2H, CH-phenyl), 7.54 (d,  $J = 8.7$ , 1H, CH-benzothiazole).  $^{13}\text{C}$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  191.04, 146.41, 142.01, 133.43, 131.71, 131.39, 130.78, 130.46 (q,  $J = 32.8$ , 31.8

Hz), 129.51, 125.24 (d,  $J = 4.1$  Hz), 124.52 (q,  $J = 273.7$  Hz), 122.22 (d,  $J = 4.6$  Hz), 121.36, 120.08, 114.33, 113.69. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{16}H_{10}F_3N_4S_2^+$  379.0299, found 379.0299.

**6-(4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4l):**

Purity 99.0% by HPLC; Yield 72%; mp 260-263 °C;  $^1H$  NMR (600 MHz, DMSO)  $\delta = 14.05$  (s, 1H, SH), 9.47 (s, 1H, CH-triazole), 8.37 (s, 1H, CH-benzothiazole), 8.18 (d,  $J = 8.0$ , 2H, CH-phenyl), 7.99 (d,  $J = 9.6$ , 1H, CH-benzothiazole), 7.91 (d,  $J = 8.0$ , 2H, CH-phenyl), 7.52 (d,  $J = 8.7$ , 1H, CH-benzothiazole).  $^{13}C$  NMR (151 MHz, DMSO- $d_6$ )  $\delta$  191.30, 146.62, 142.10, 134.77, 133.61, 131.45, 129.10 (q,  $J = 31.8$  Hz), 127.52 (q,  $J = 3.9$  Hz), 126.30, 124.67 (q,  $J = 271.8$  Hz), 121.64, 120.23, 114.45, 113.62. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{16}H_{10}F_3N_4S_2^+$  379.0299, found 379.0299.

**6-(4-(3-methoxyphenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4m):** Purity

100% by HPLC; Yield 91%; mp 252-253 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta = 14.03$  (s, 1H, SH), 9.30 (s, 1H, CH-triazole), 8.35 (d,  $J = 2.1$ , 1H, CH-benzothiazole), 7.97 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.2$ , 1H, CH-benzothiazole), 7.58 – 7.48 (m, 3H, CH-benzothiazole & phenyl), 7.44 (t,  $J = 7.9$ , 1H, CH-phenyl), 6.98 (ddd,  $J_1 = 8.2$ ,  $J_2 = 2.5$ ,  $J_3 = 1.0$ , 1H, CH-phenyl), 3.86 (s, 3H,  $CH_3$ ).  $^{13}C$  NMR (101 MHz, DMSO)  $\delta$  190.57, 159.73, 147.26, 141.26, 133.08, 131.44, 130.76, 130.16, 120.04, 119.62, 117.61, 114.01, 113.80, 113.11, 110.56, 55.16. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{16}H_{13}N_4OS_2^+$  341.0531, found 341.0532.

**6-(4-(thiophen-3-yl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4n):** Purity 100%

by HPLC; Yield 75%; mp 266-269 °C;  $^1H$  NMR (400 MHz, DMSO)  $\delta = 14.05$  (s, 1H, SH), 9.18 (s, 1H, CH-triazole), 8.38 (s, 1H, CH-benzothiazole), 8.02 – 7.95 (m, 2H, CH-

benzothiazole & thiophen), 7.76 (dd,  $J_1 = 5.0$ ,  $J_1 = 2.9$ , 1H, CH-thiophen), 7.63 (dd,  $J_1 = 5.0$ ,  $J_1 = 1.3$ , 1H, CH-thiophen), 7.54 (d,  $J_1 = 8.7$ , 1H, CH-benzothiazole).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  191.06, 144.38, 141.73, 133.56, 131.86, 131.26, 127.94, 126.22, 121.98, 120.11, 120.01, 114.31, 113.60. HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_9\text{N}_4\text{S}_3^+$  316.9989, found 316.9987.

**6-(4-(4-ethylphenyl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thiol (4o).** Purity 99.7% by HPLC; Yield 84%; mp 276-279 °C;  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  = 14.03 (s, 1H, SH), 9.23 (s, 1H, CH-triazole), 8.35 (d,  $J = 2.2$ , 1H, CH-benzothiazole), 7.98 (dd,  $J_1 = 8.7$ ,  $J_2 = 2.2$ , 1H, CH-benzothiazole), 7.87 (d,  $J = 8.1$ , 2H, CH-phenyl), 7.51 (d,  $J = 8.7$ , 1H, CH-benzothiazole), 7.36 (d,  $J = 8.0$ , 2H, CH-phenyl), 2.68 (q,  $J = 7.6$ , 2H,  $\text{CH}_2$ ), 1.24 (t,  $J = 7.6$ , 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (101 MHz, DMSO)  $\delta$  190.53, 147.44, 143.98, 133.14, 130.76, 128.37, 127.60, 125.33, 119.61, 119.38, 113.77, 113.11, 27.94, 15.44. HRMS (ESI)  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{15}\text{N}_4\text{S}_2^+$  339.0738, found 339.0738.

**6-(4-(pyridin-2-yl)-1H-1,2,3-triazol-1-yl)benzo[d]thiazole-2-thio (4p):** Purity 97.4% by HPLC; Yield 59%; mp 292-296 °C;  $^1\text{H}$  NMR (600 MHz, DMSO)  $\delta$  = 14.06 (s, 1H, SH), 9.35 (s, 1H, CH-triazole), 8.72 – 8.68 (m, 1H, CH-pyridine), 8.44 (d,  $J = 2.2$ , 1H, CH-benzothiazole), 8.17 (d,  $J = 7.9$ , 1H, CH-pyridine), 8.07 (dd,  $J = 8.7$ , 2.2, 1H, CH-benzothiazole), 8.03 (td,  $J_1 = 7.7$ ,  $J_1 = 1.8$ , 1H, CH-pyridine), 7.53 – 7.45 (m, 2H, CH-benzothiazole & pyridine).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO-d}_6$ )  $\delta$  14.04 (s, 1H), 9.32 (s, 1H), 8.68 (d,  $J = 4.2$  Hz, 1H), 8.42 (d,  $J = 2.2$  Hz, 1H), 8.15 (d,  $J = 7.9$  Hz, 1H), 8.05 (dd,  $J = 8.7$ , 2.2 Hz, 1H), 8.00 (td,  $J = 7.7$ , 1.8 Hz, 1H), 7.49 (d,  $J = 8.7$  Hz, 1H), 7.45 (ddd,  $J = 7.6$ , 4.9, 1.2 Hz, 1H).  $^{13}\text{C}$  NMR (151 MHz, DMSO)  $\delta$  190.45, 149.17, 148.83, 147.64,

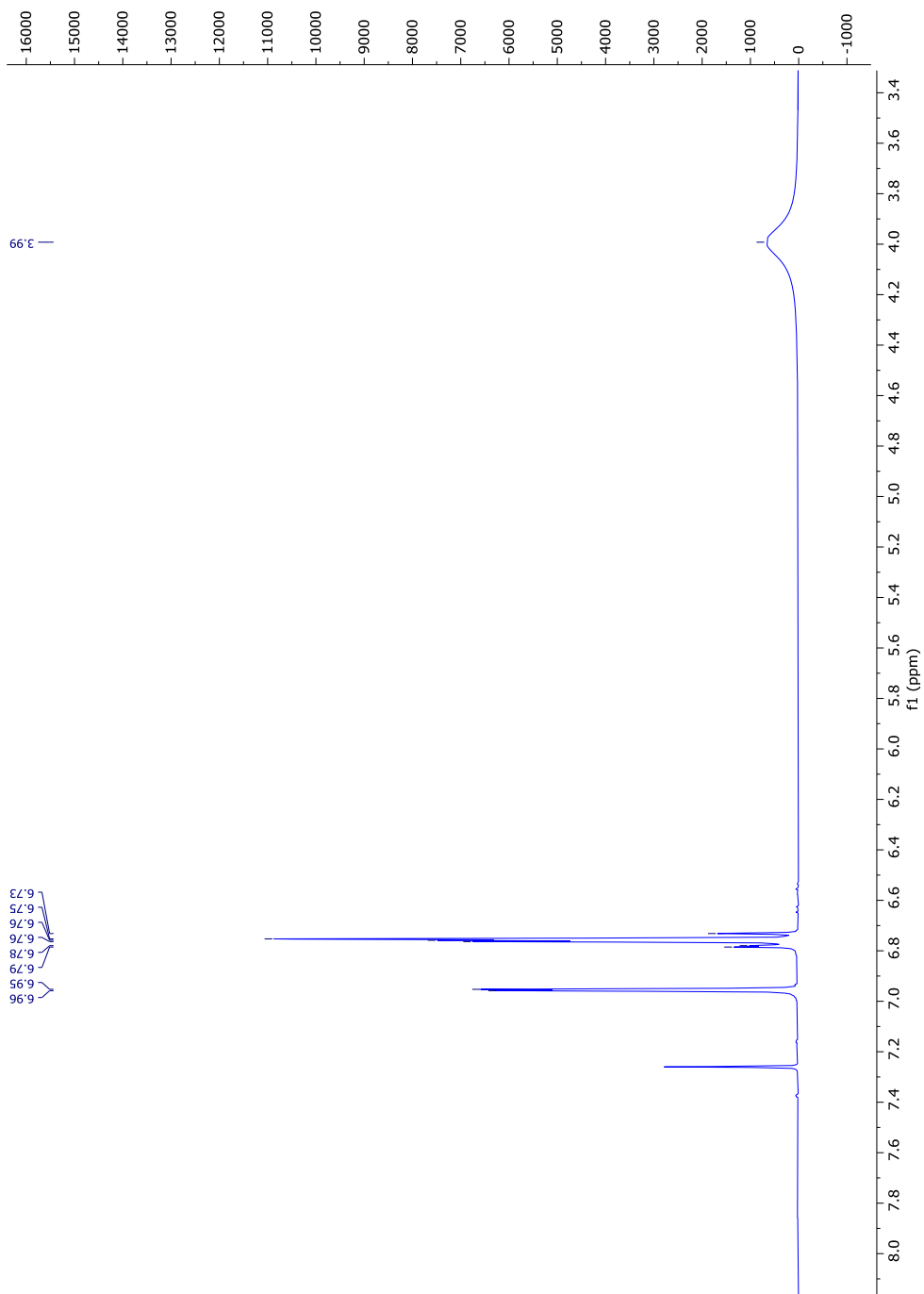
141.27, 137.79, 132.83, 130.58, 123.42, 121.52, 119.90, 119.71, 113.91, 112.97. HRMS (ESI)  $m/z$   $[M+H]^+$  calcd for  $C_{14}H_{10}N_5S_2^+$  312.0377, found 312.0376.

## References

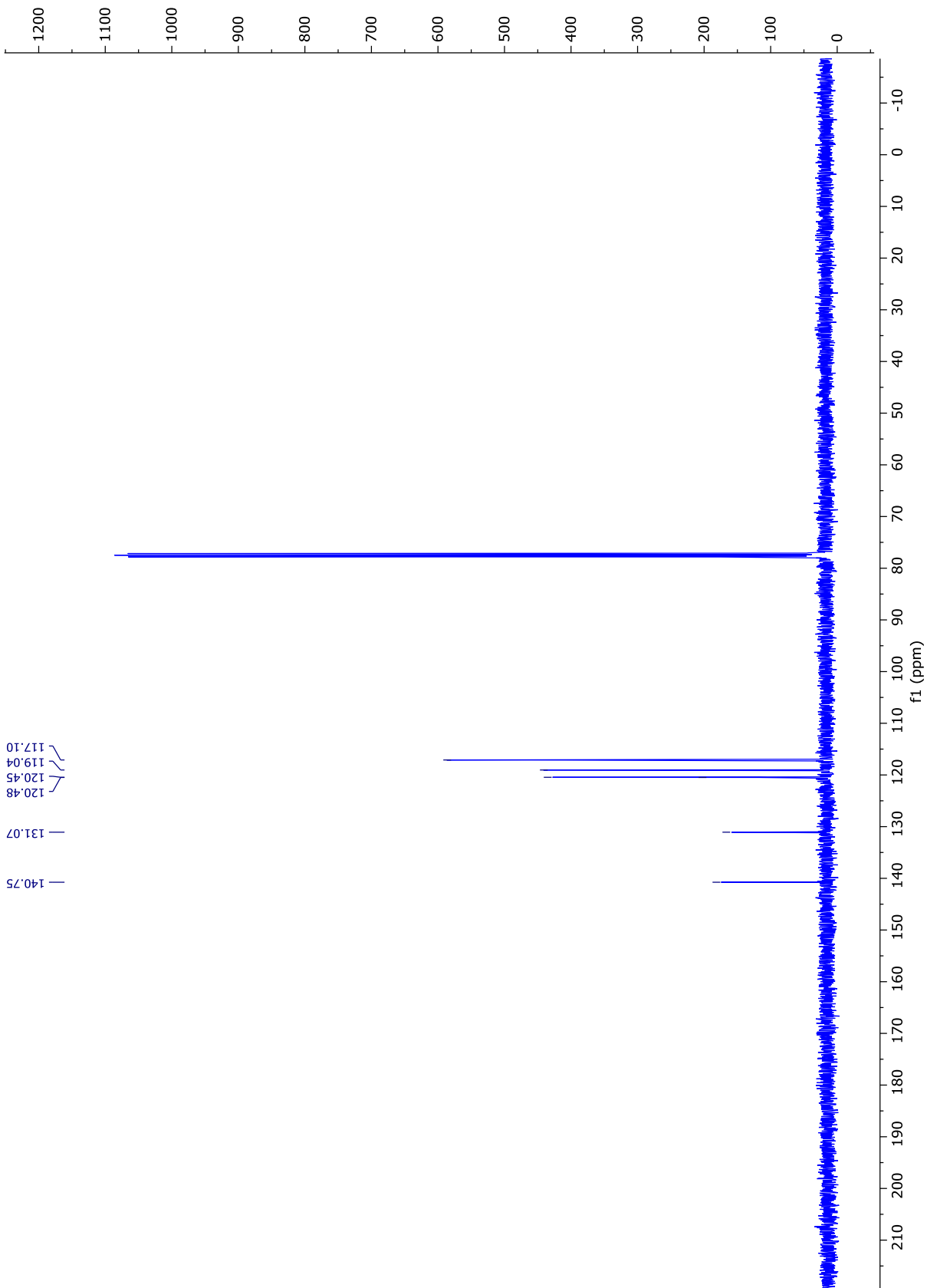
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## 6.Copy of NMR of all compounds and Chromatographic Analysis for 4a-p

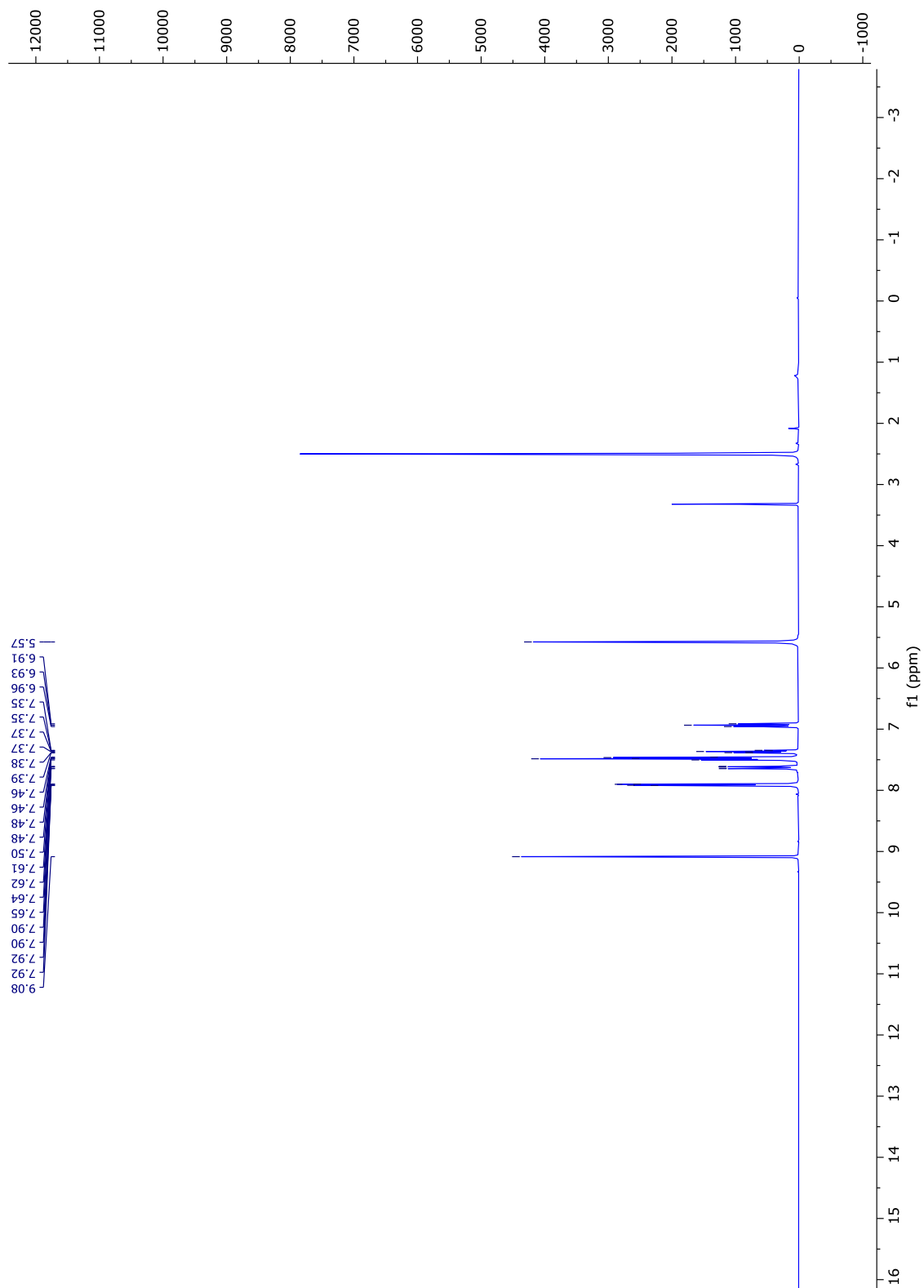
Compound 2.



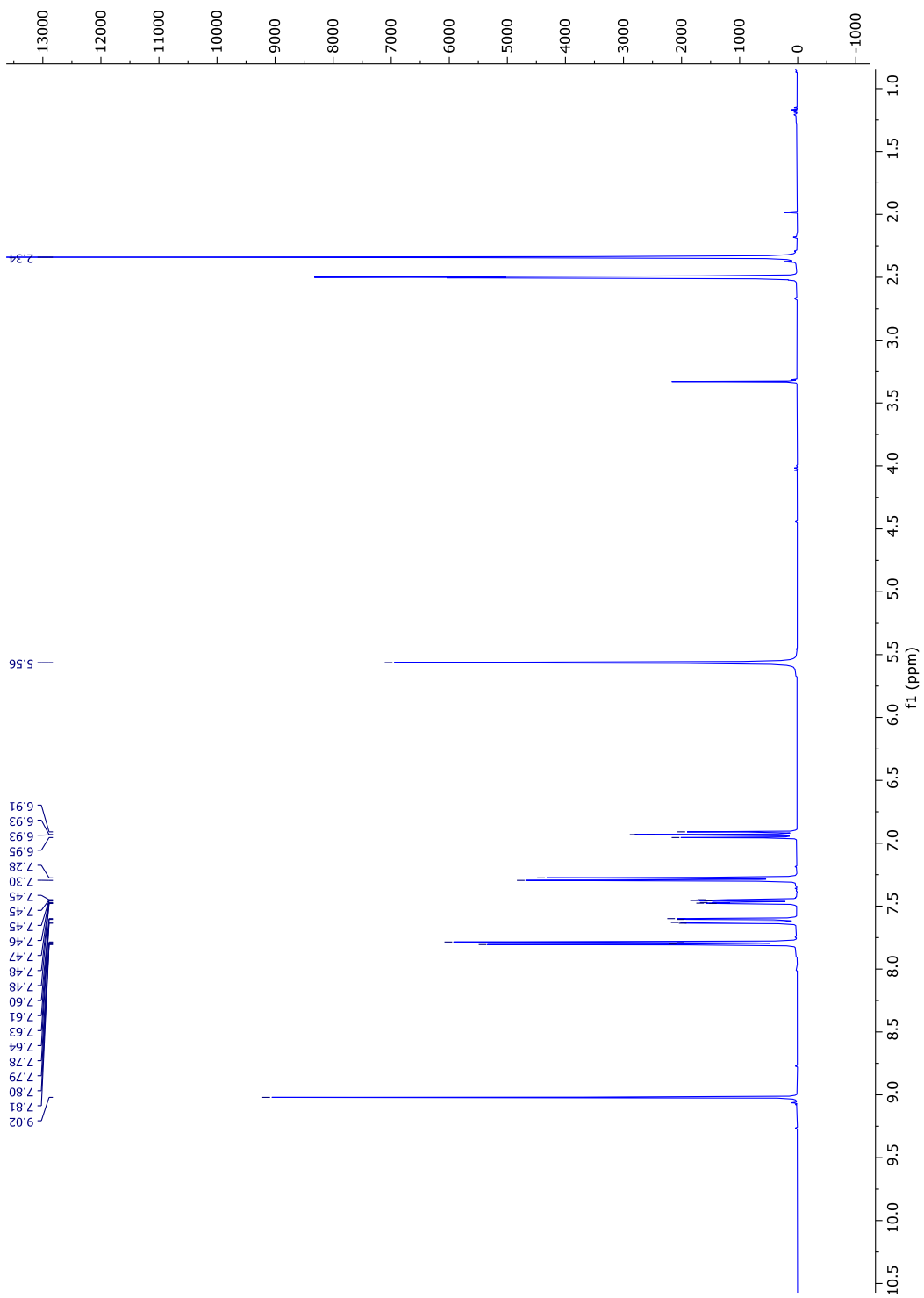




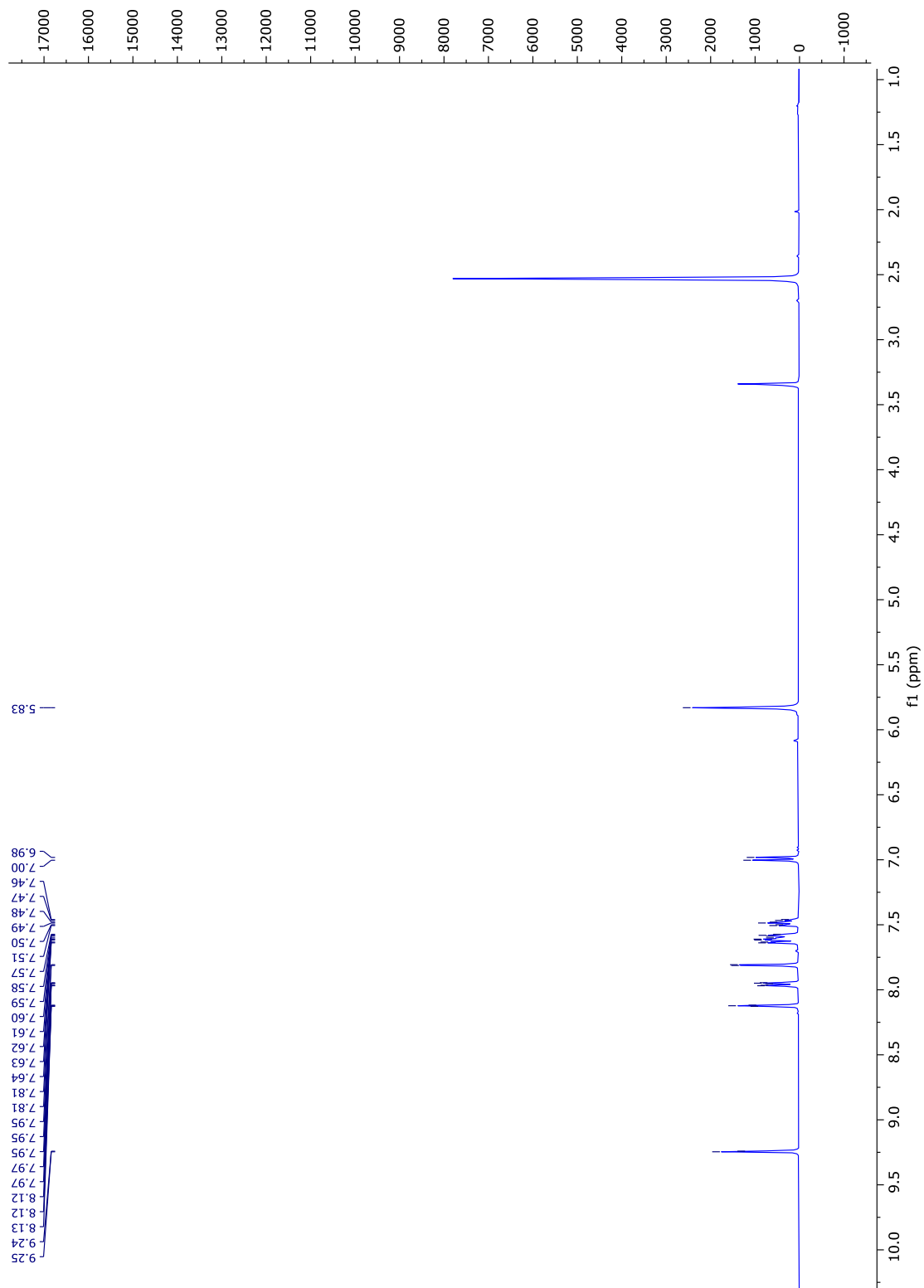
# Compound 3a



# Compound 3b

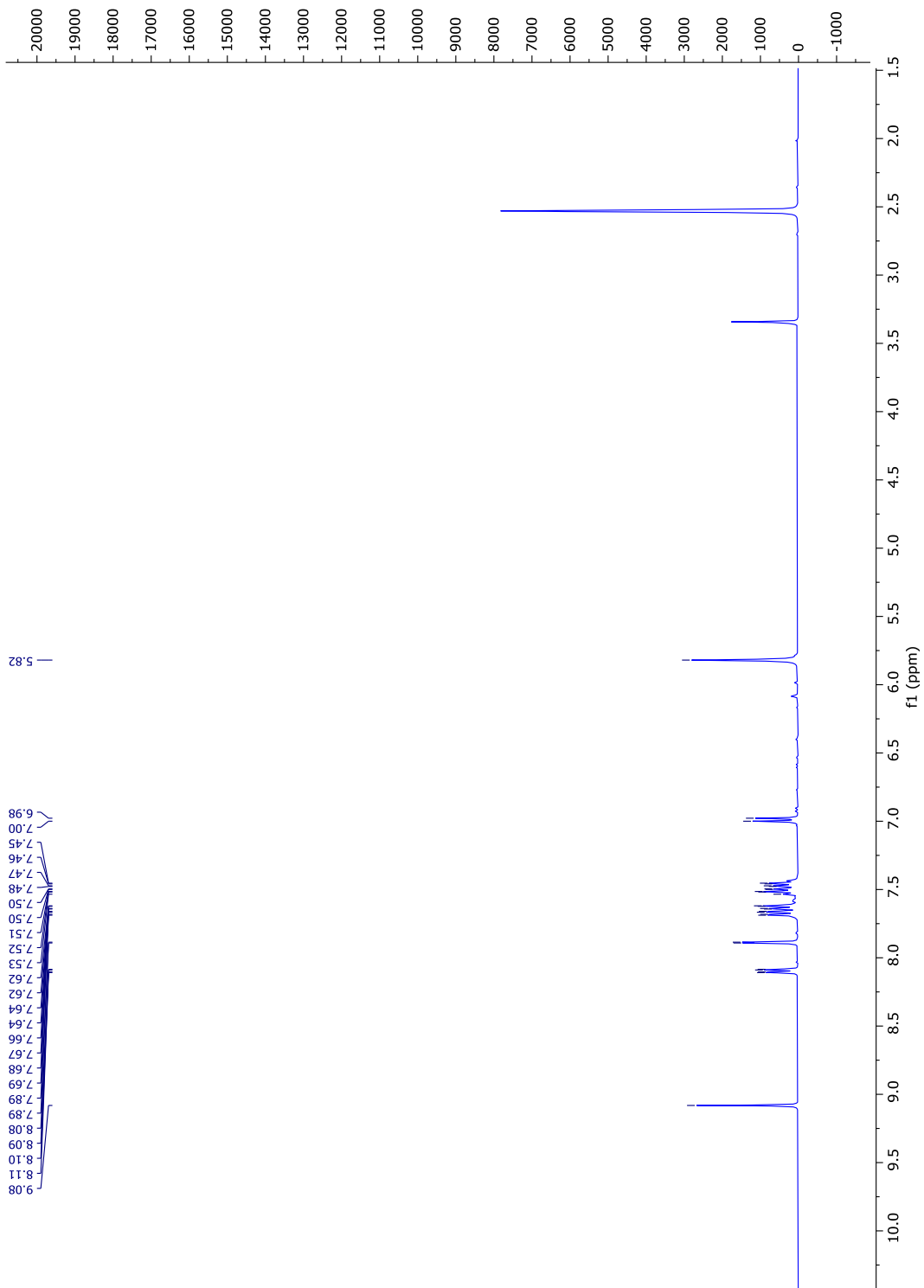


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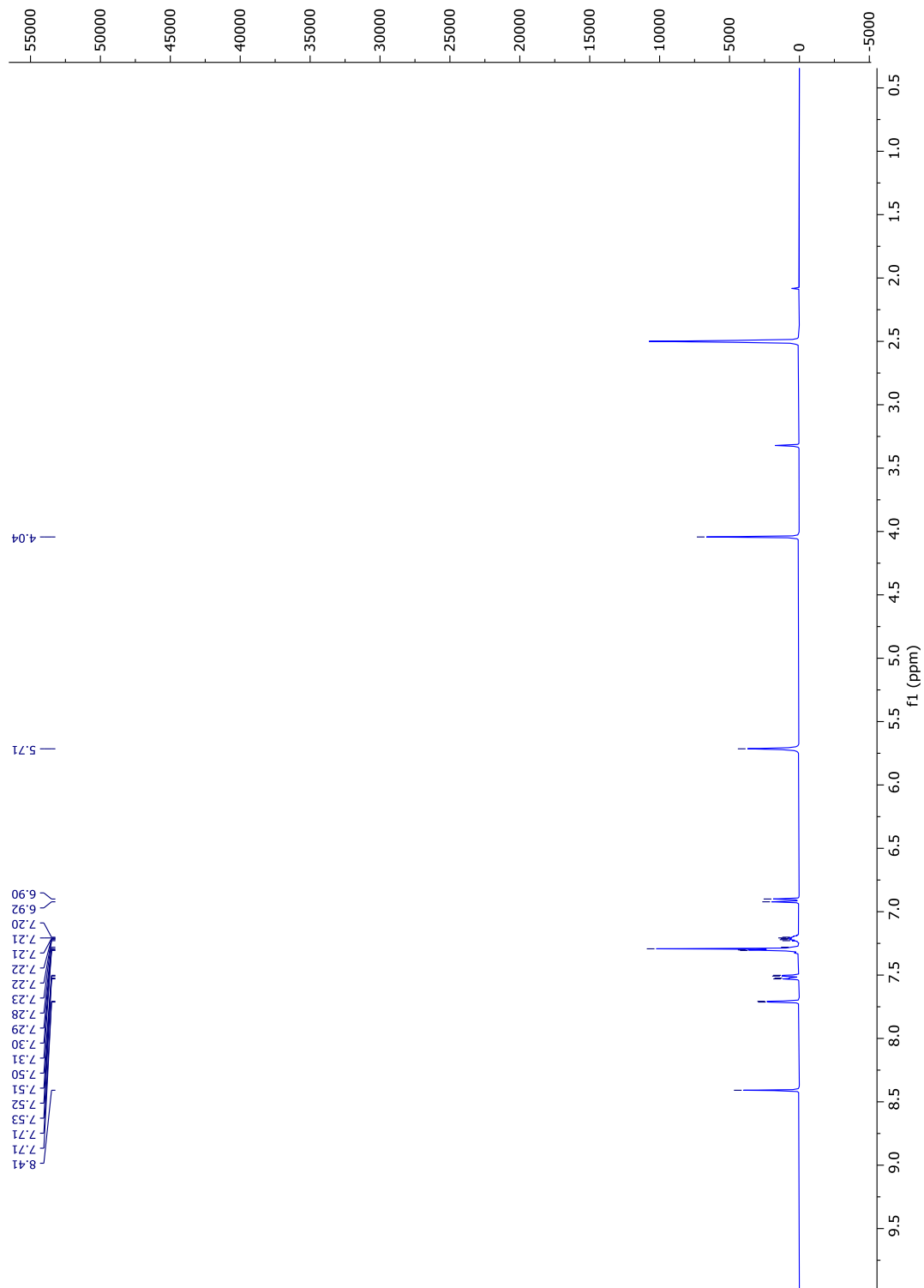




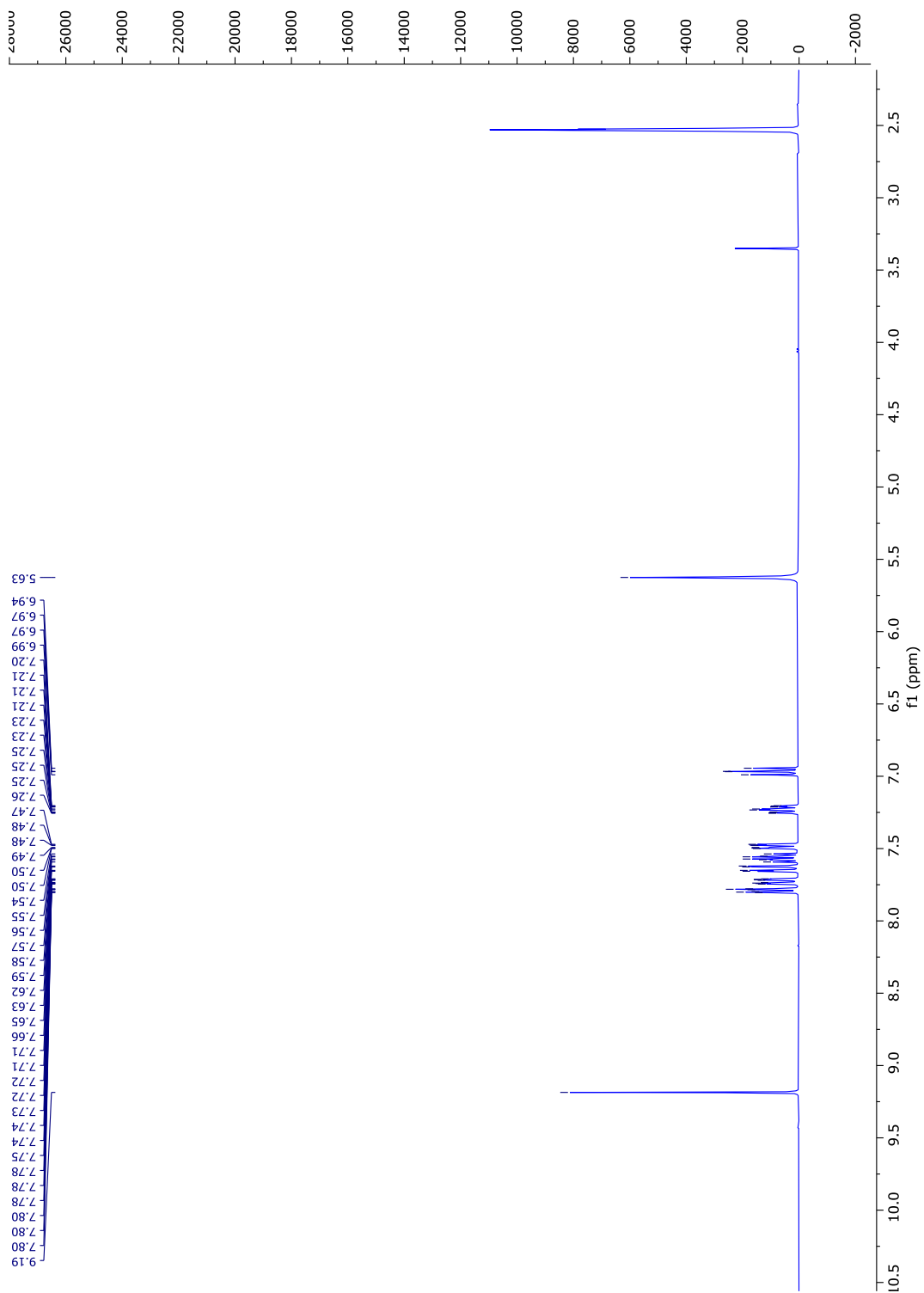
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Compound 3f

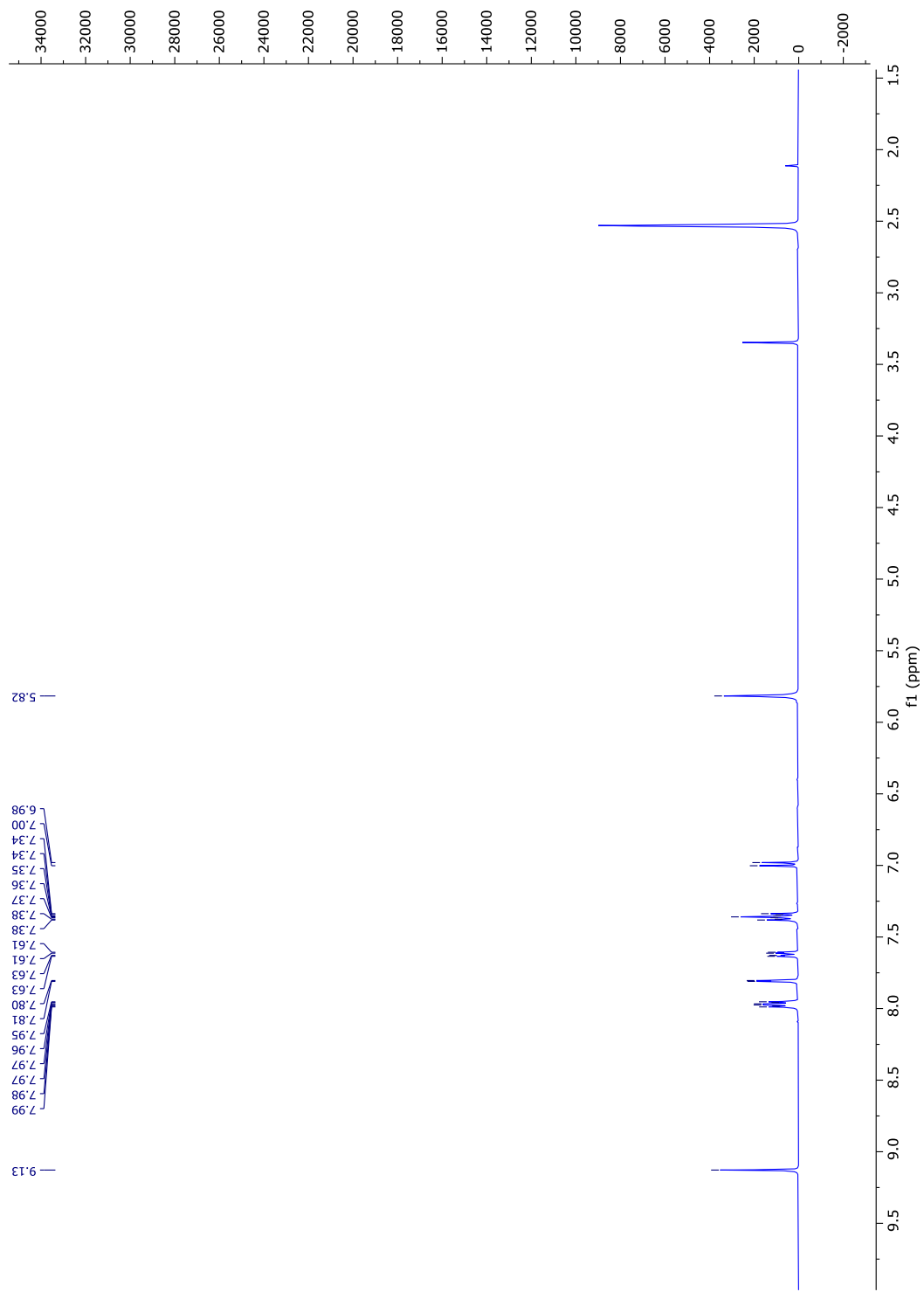


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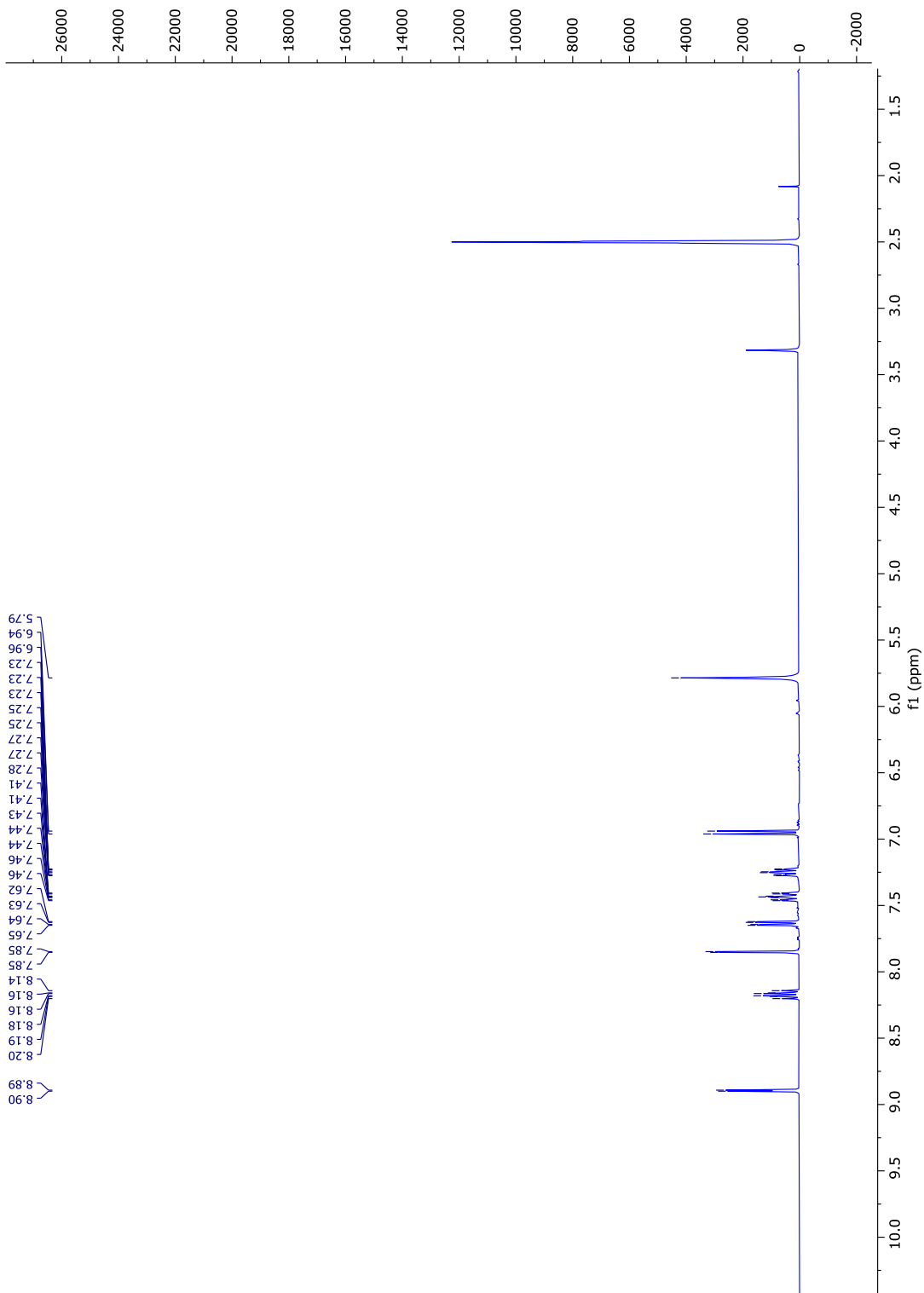




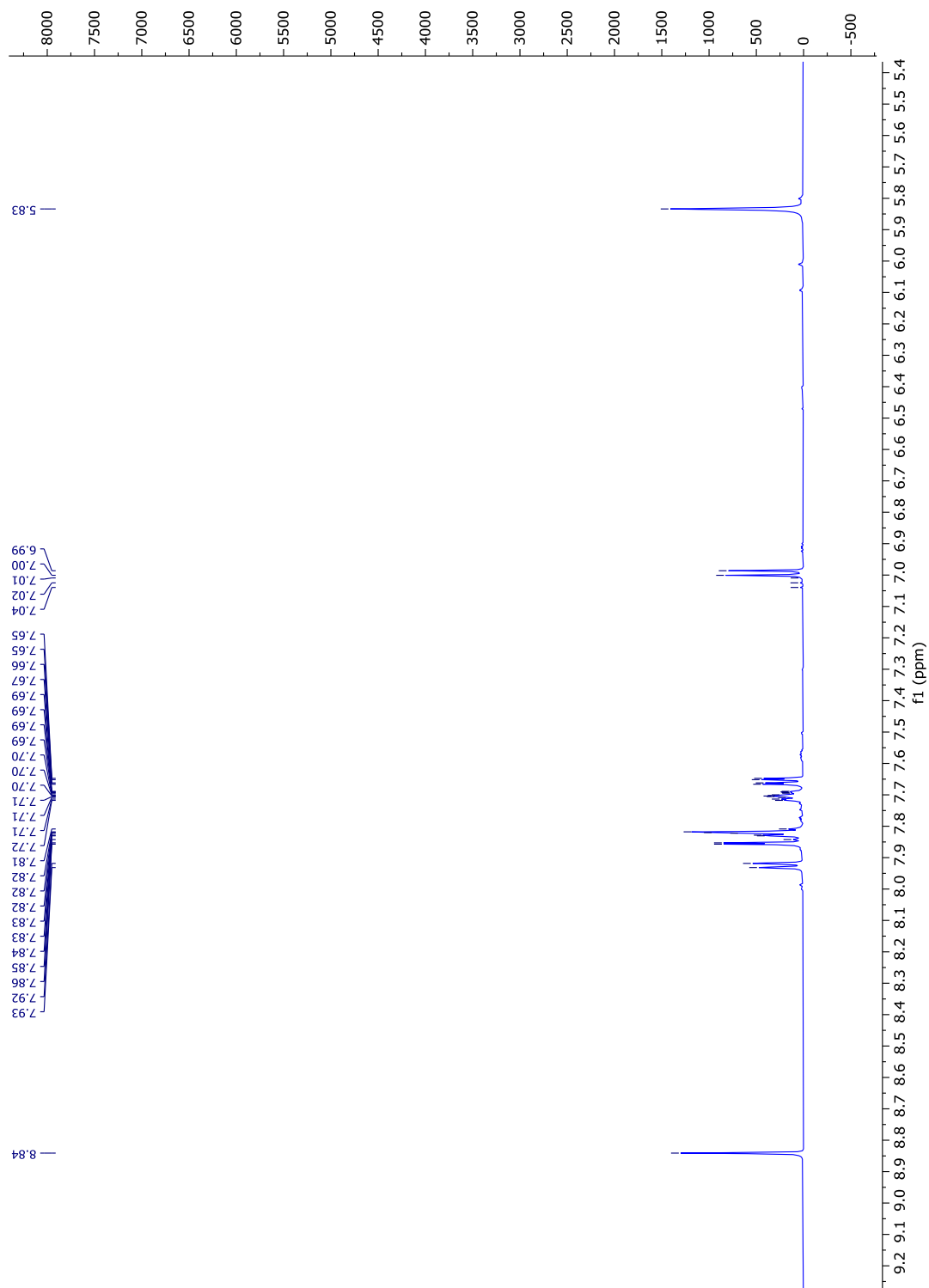
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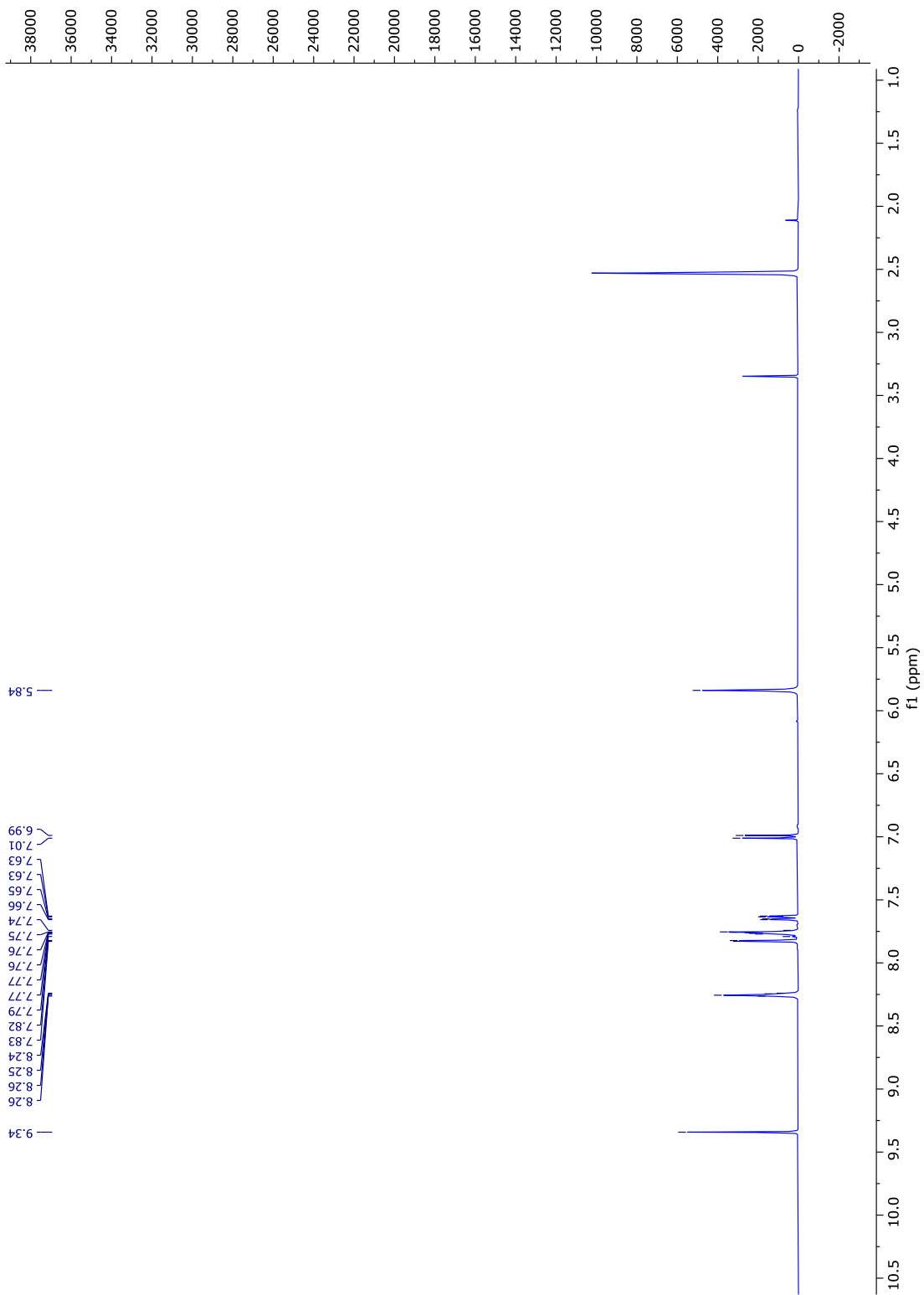
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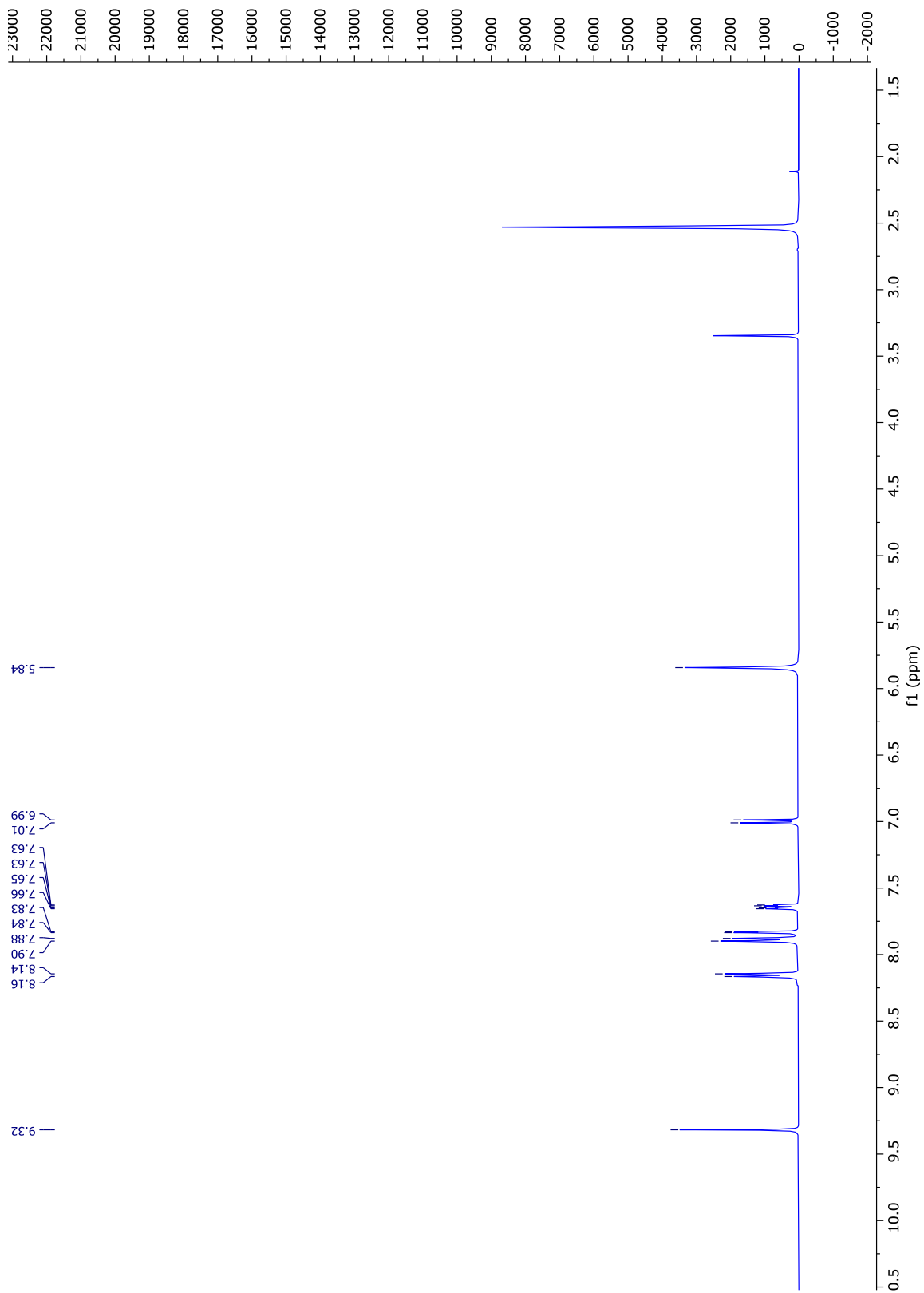
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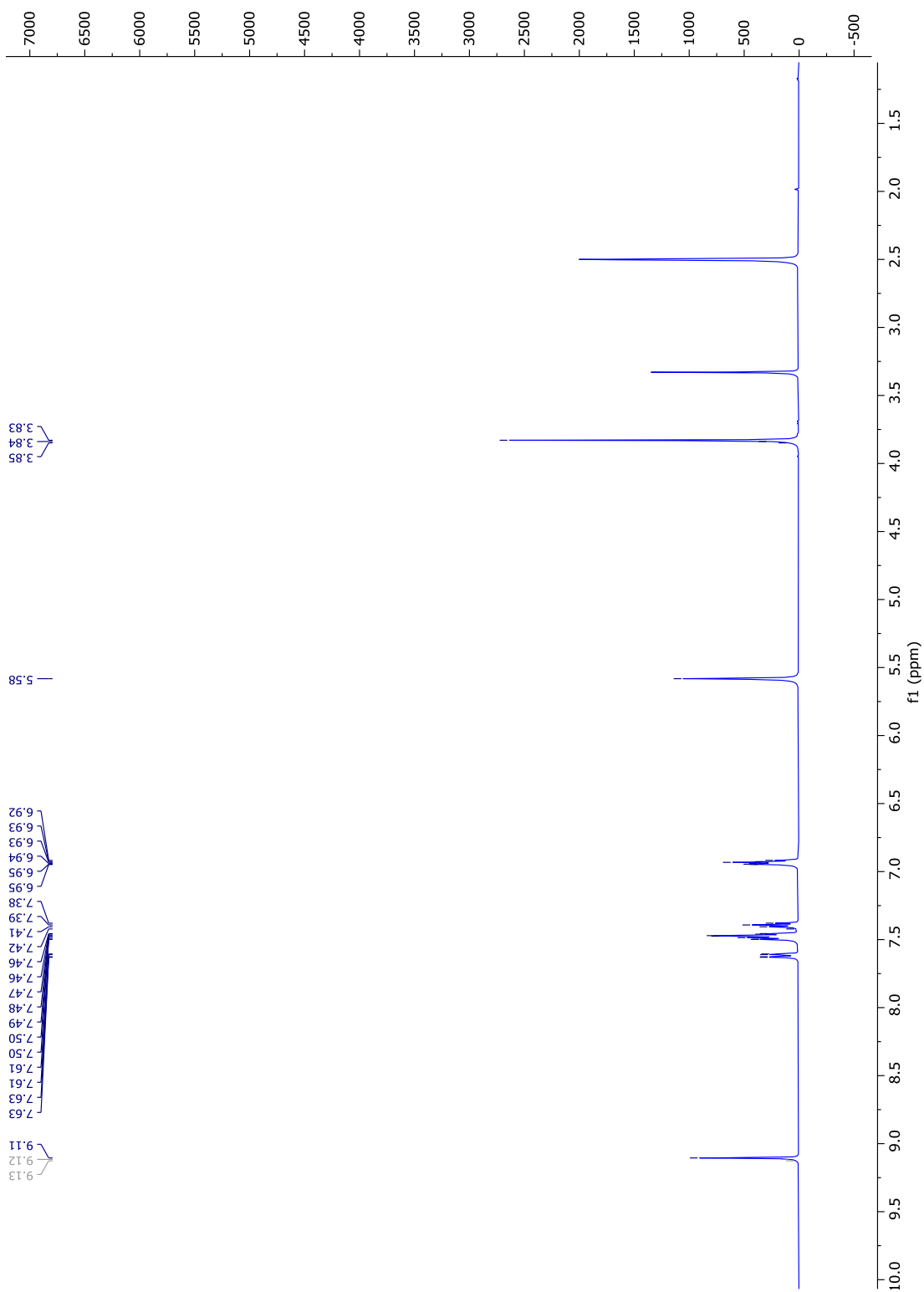
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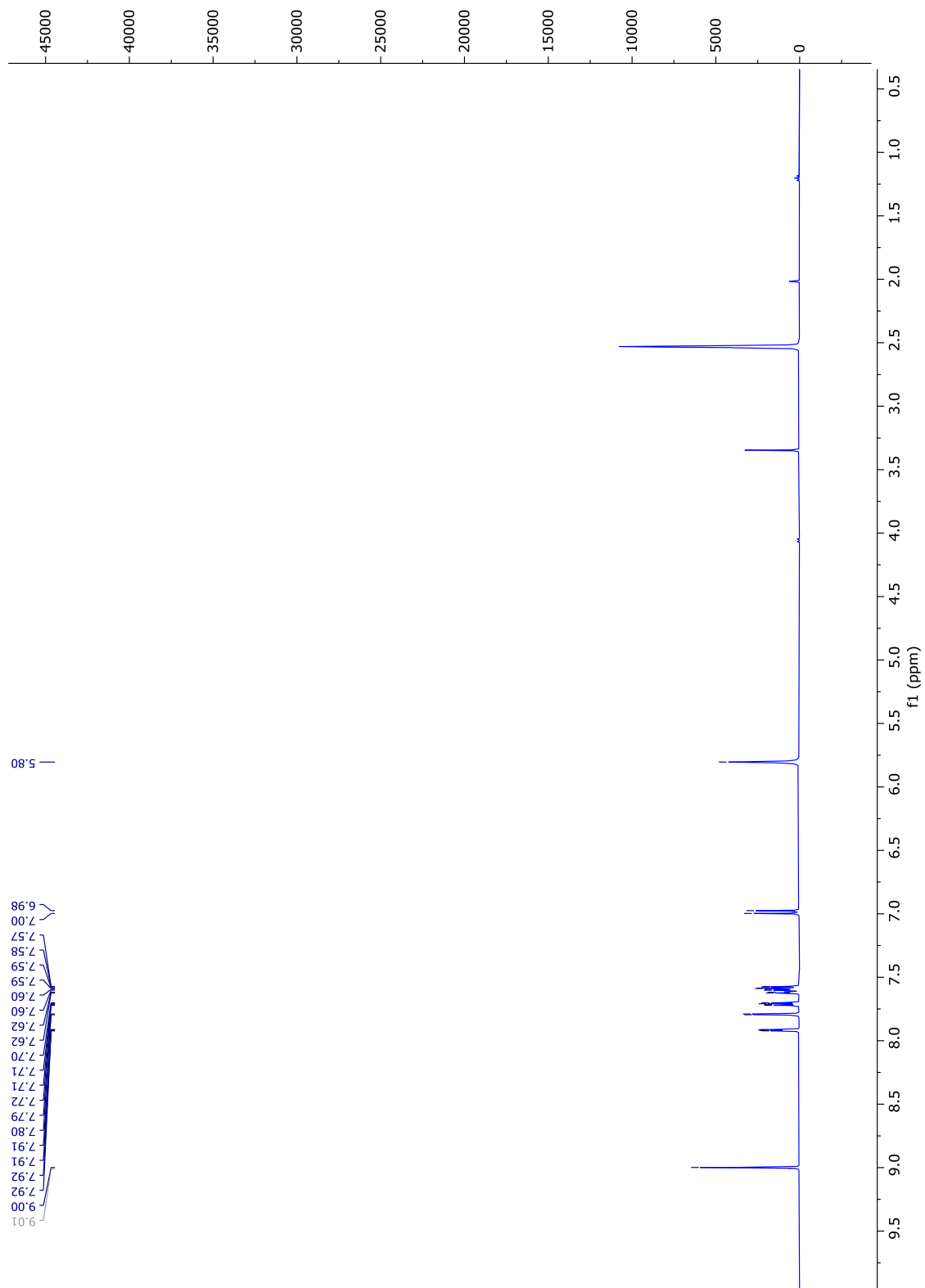
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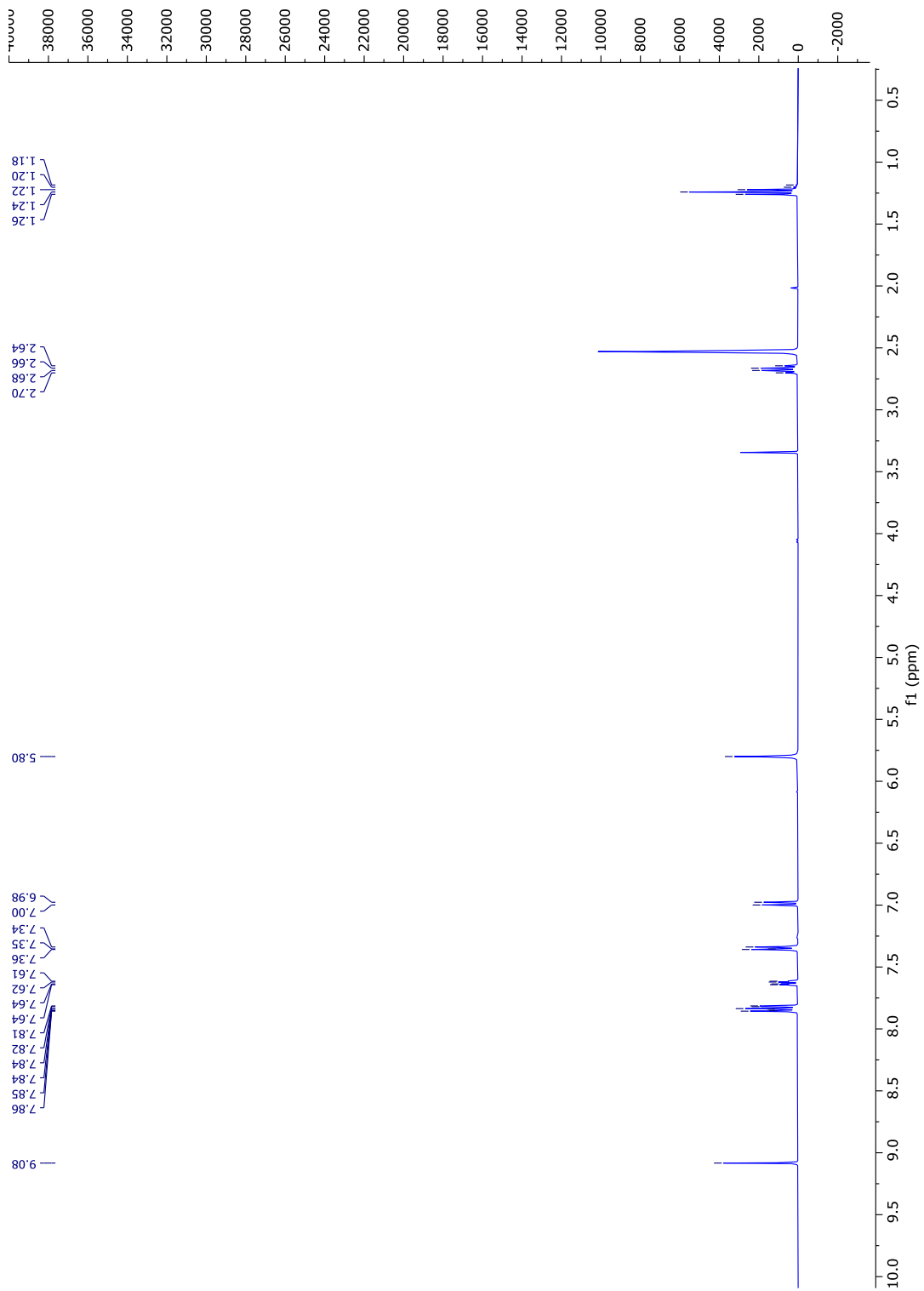
# Compound 3m



# Compound 3n



# Compound 3o

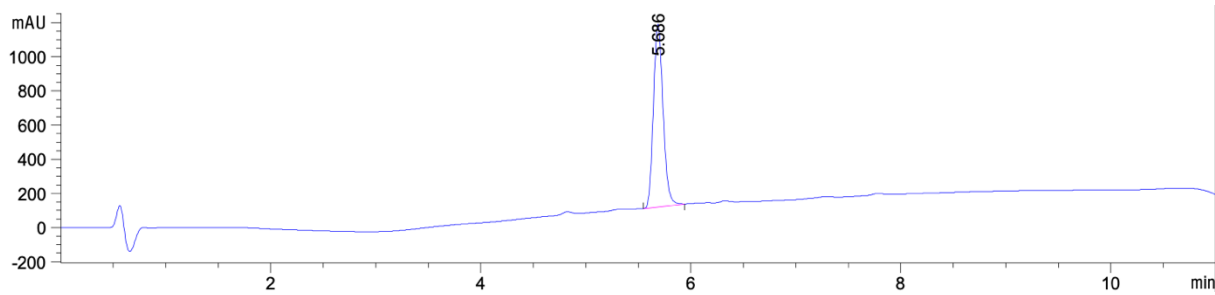




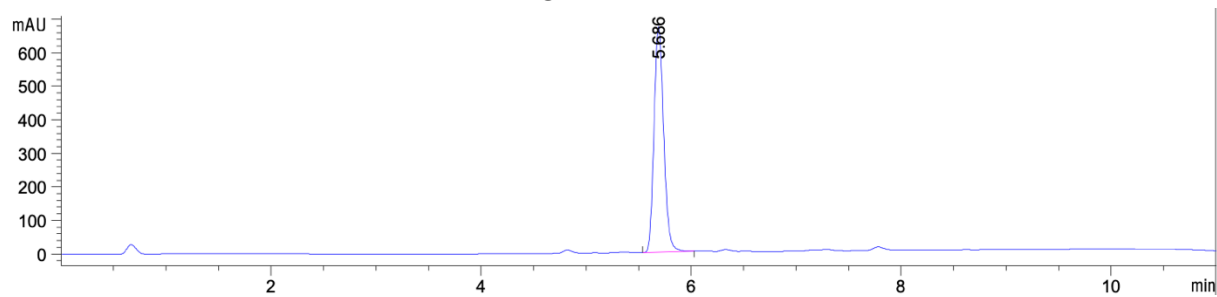


Compound 4a

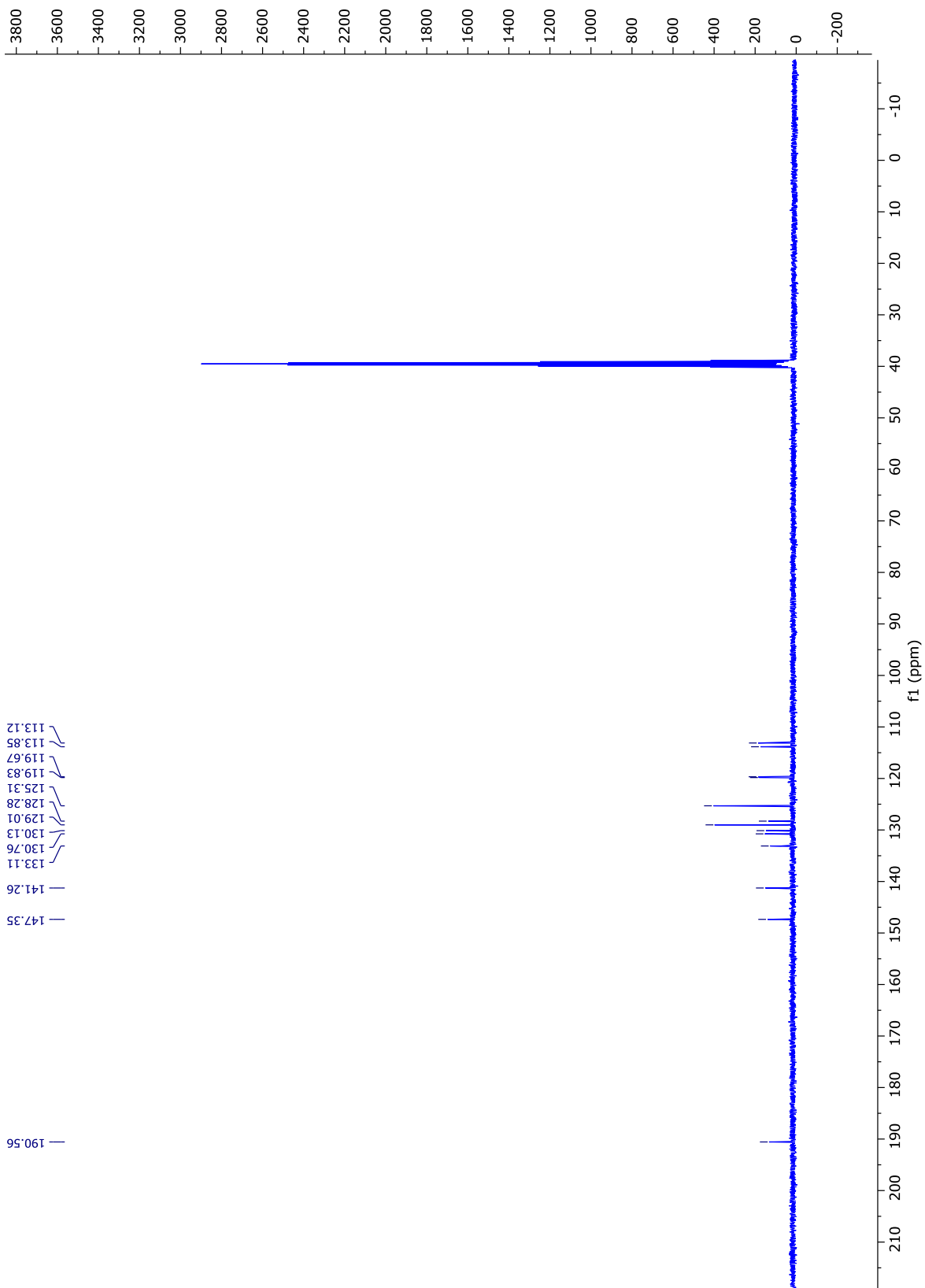
Copy of Chromatographic Analysis of 4a  
220nm



254nm

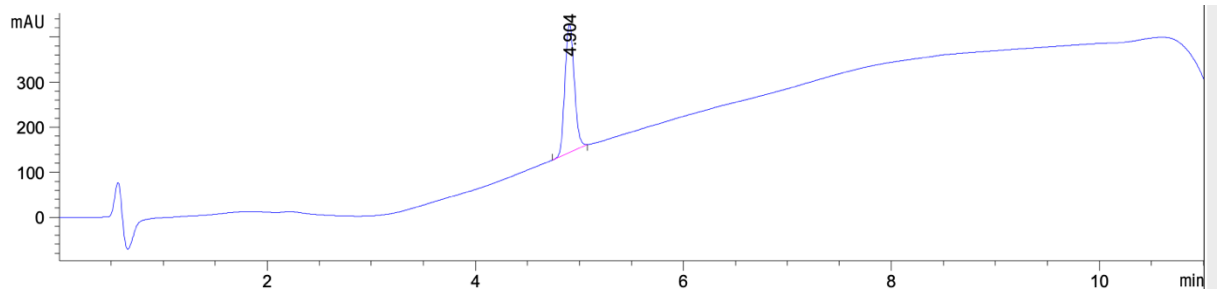




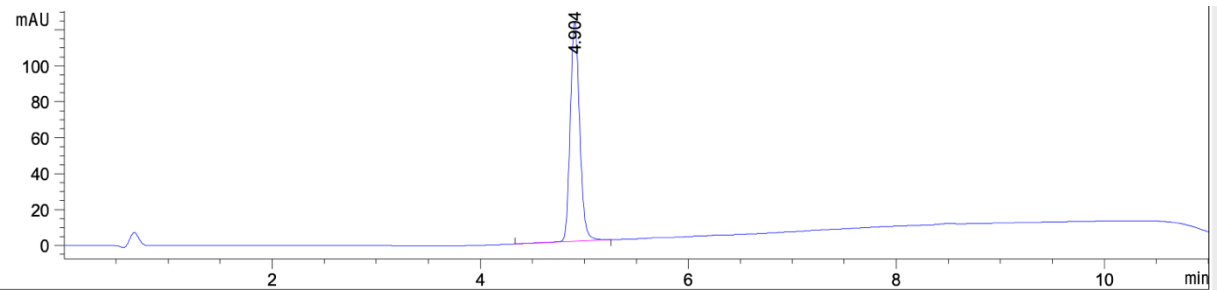


Compound **4b**

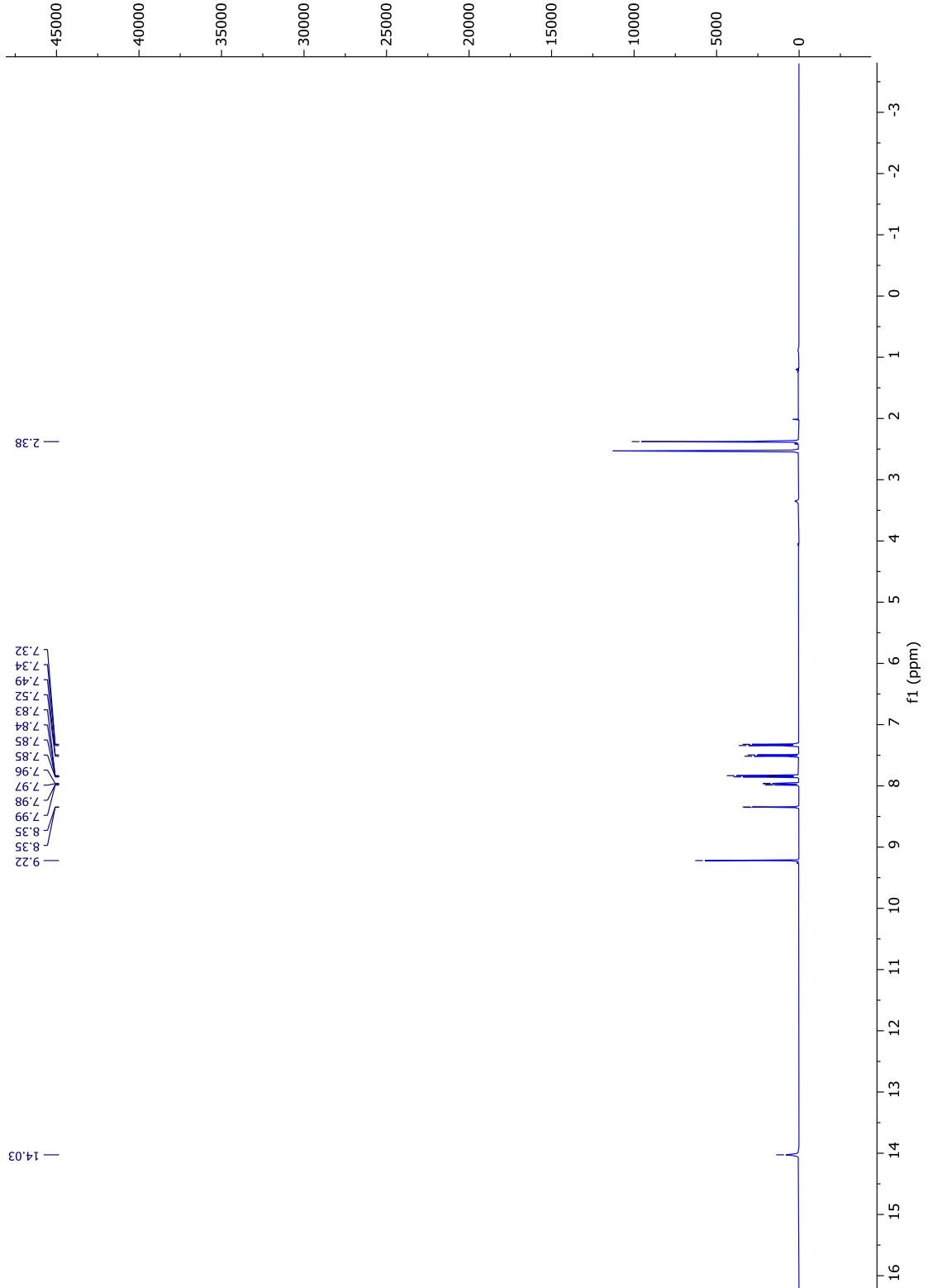
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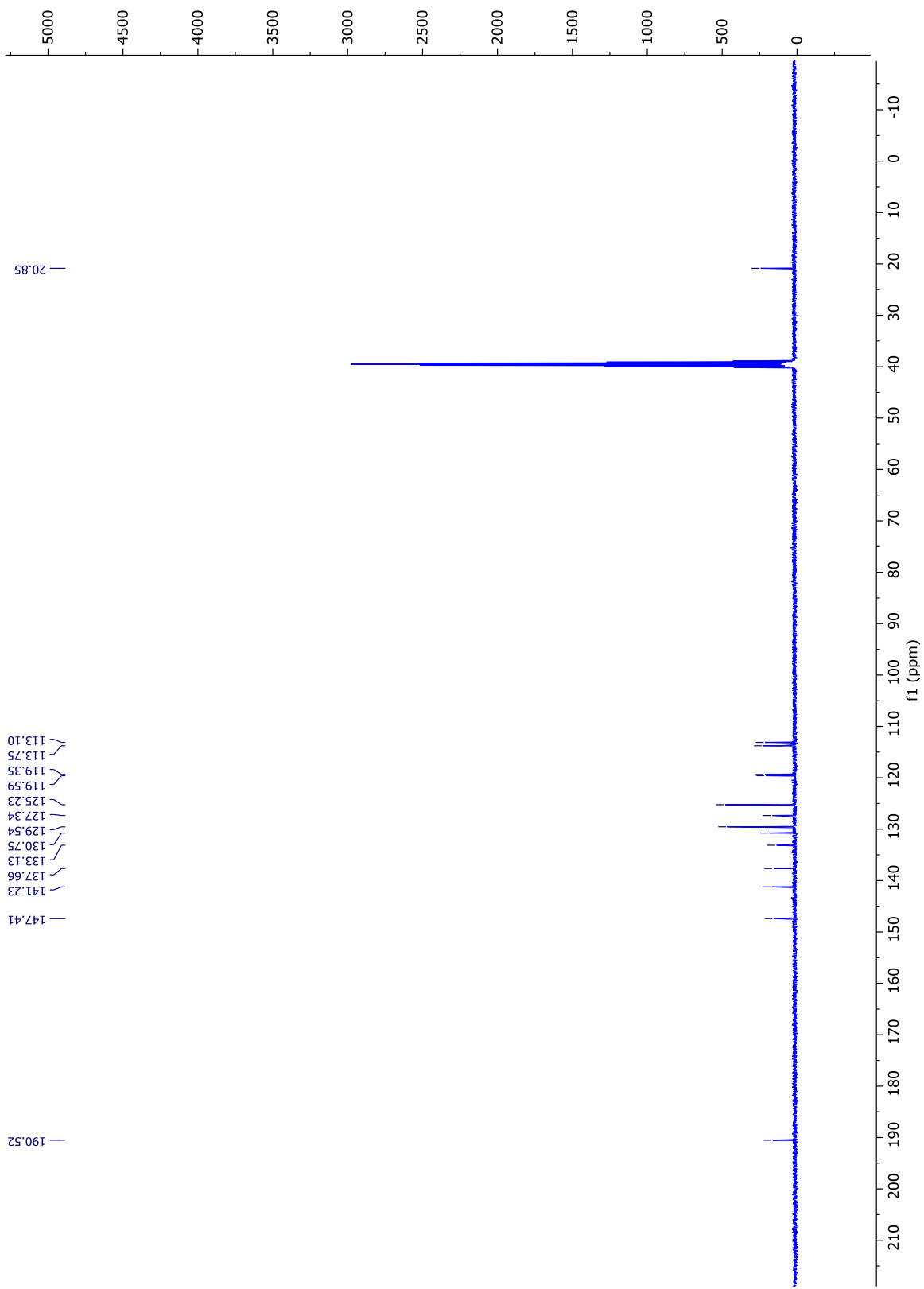


**254nm**

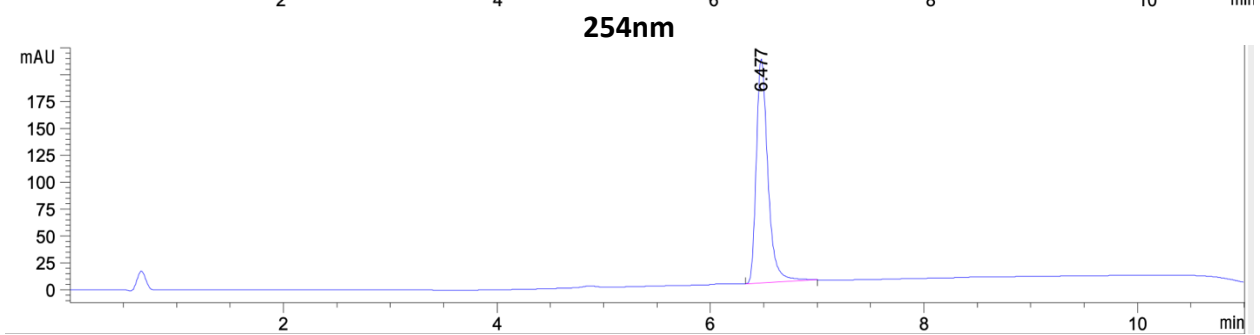
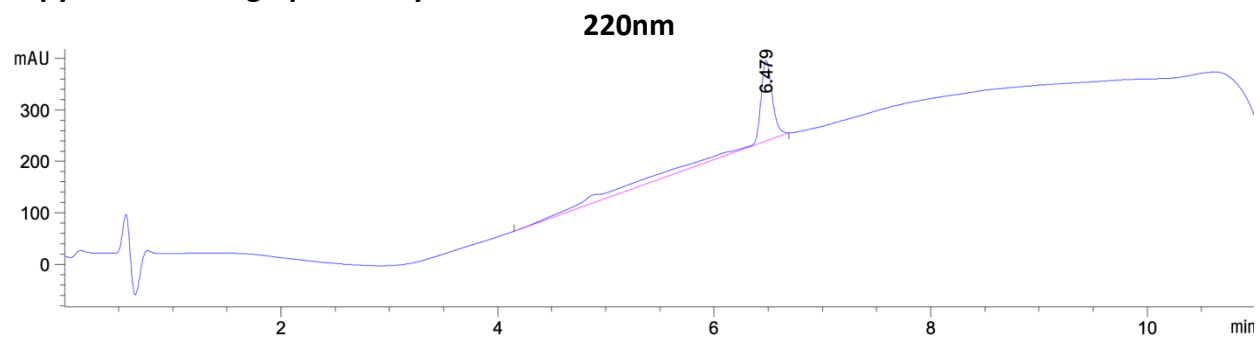


Copy of NMR of 4b



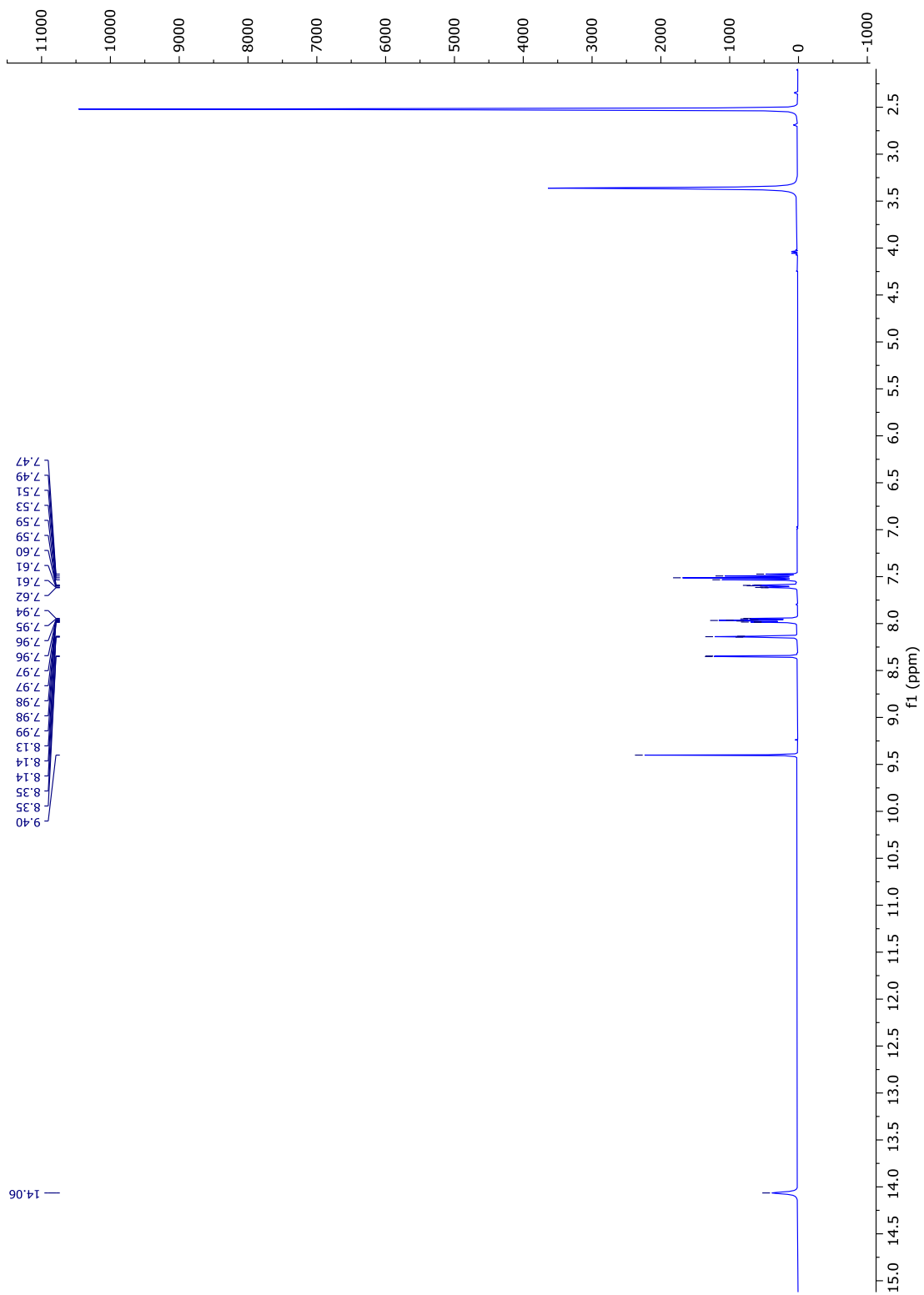


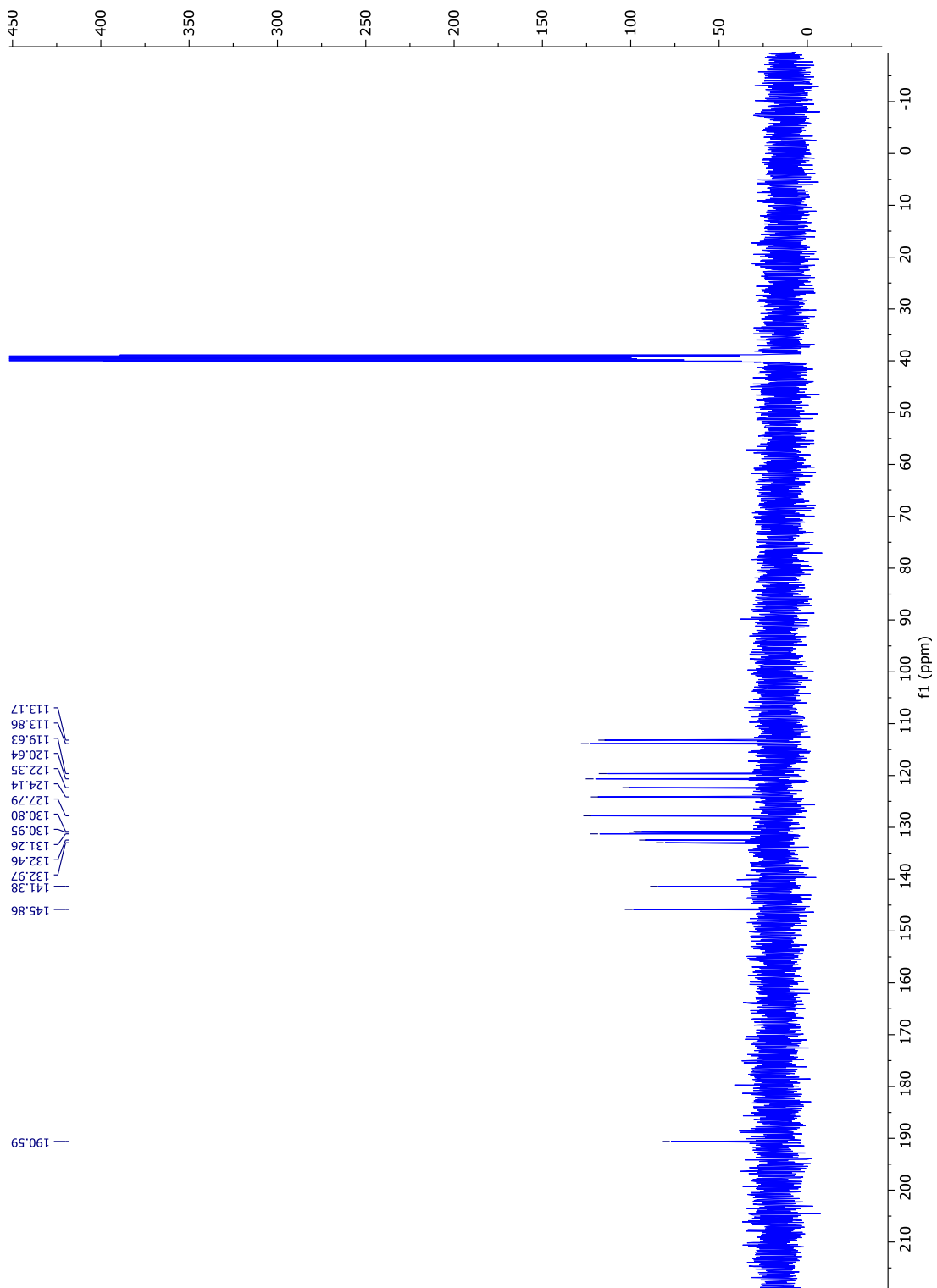
Compound 4c  
Copy of Chromatographic Analysis of 4c





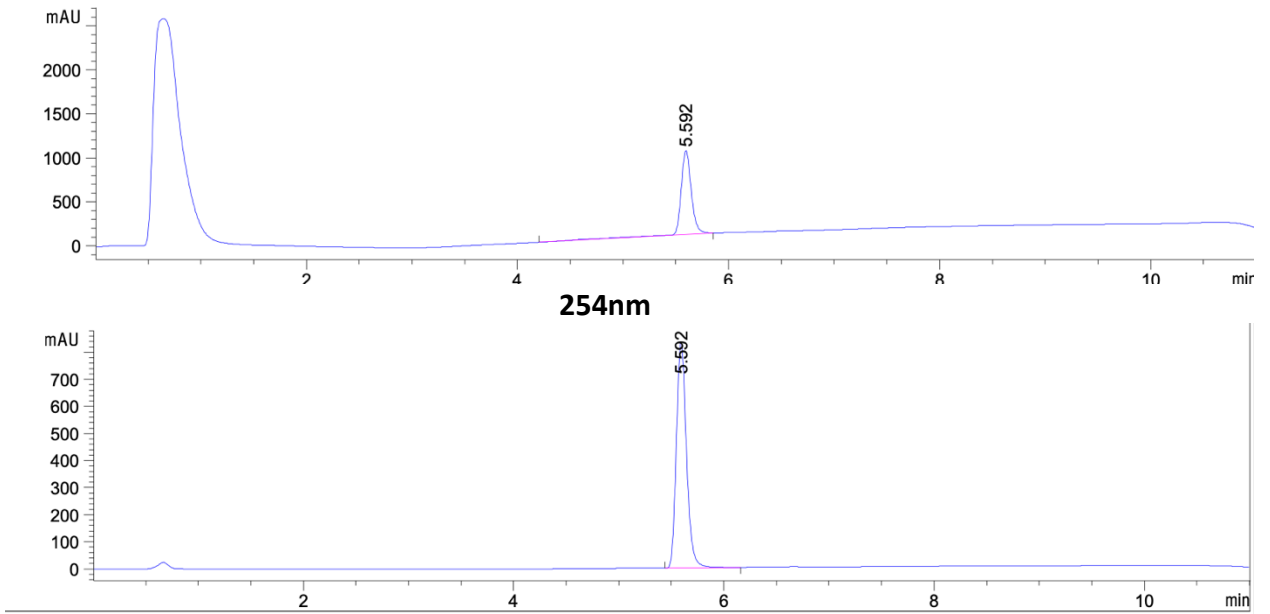
# Copy of NMR of 4c



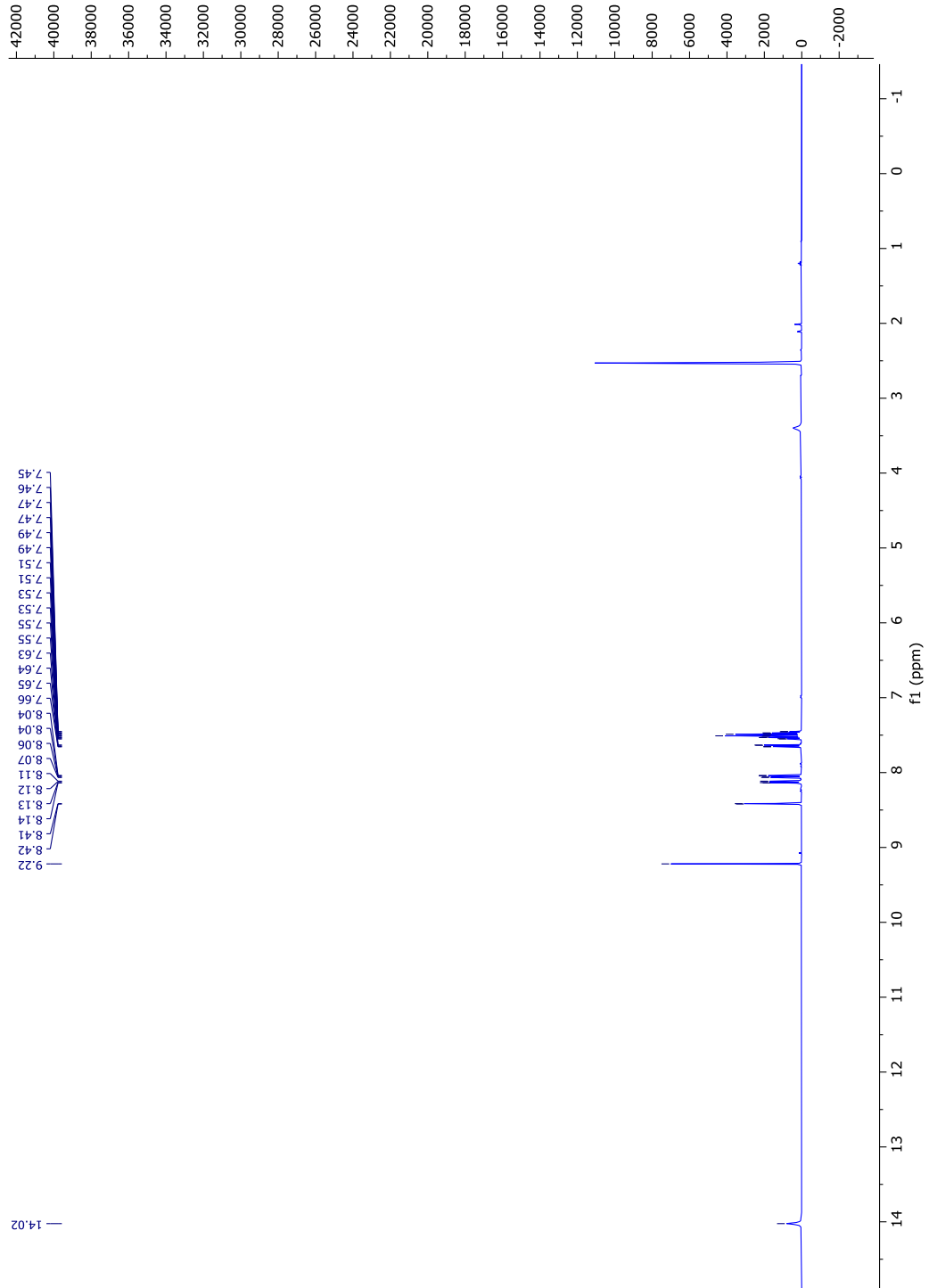


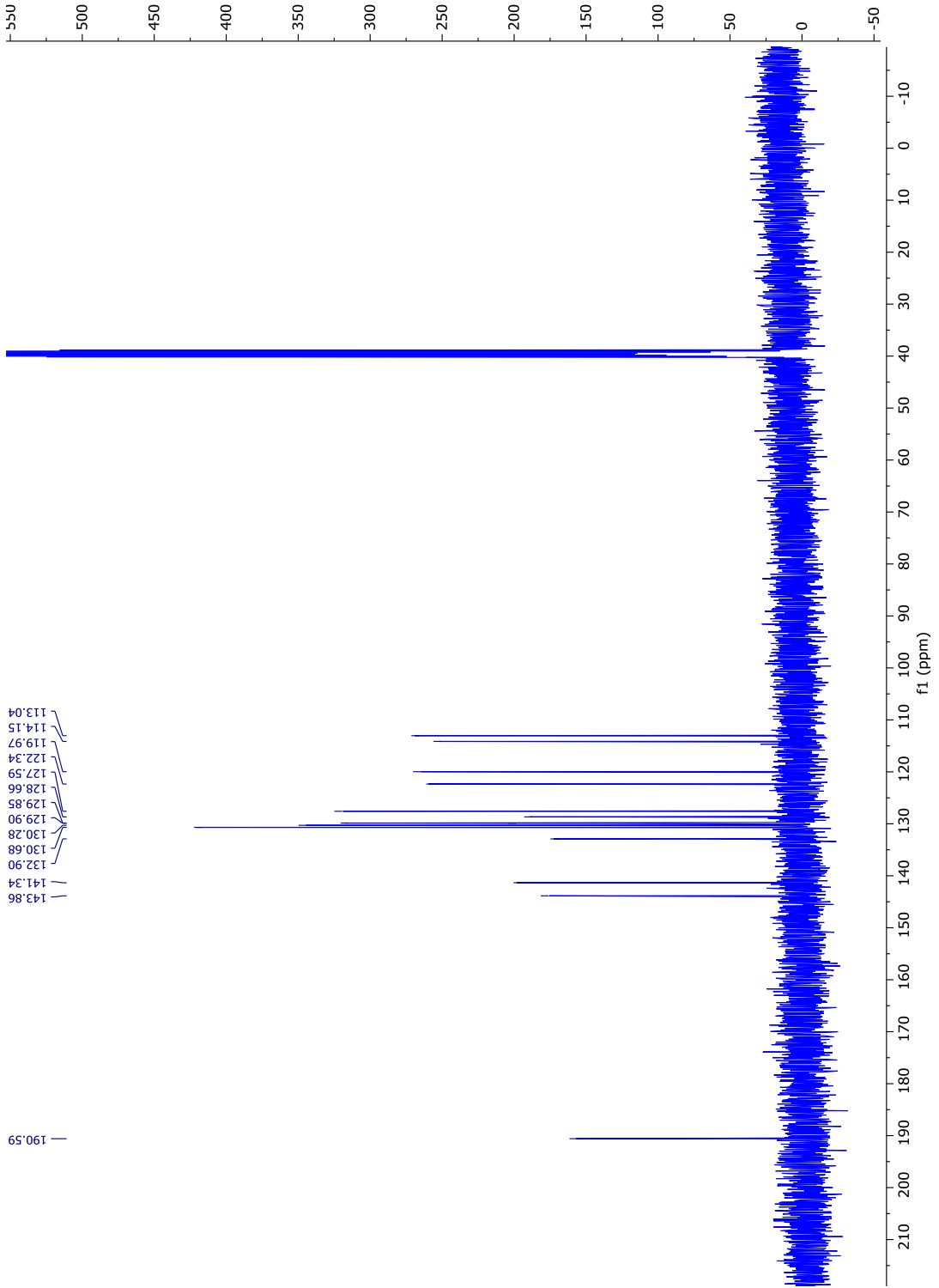
Compound **4d**

Copy of Chromatographic Analysis of **4d**  
220nM



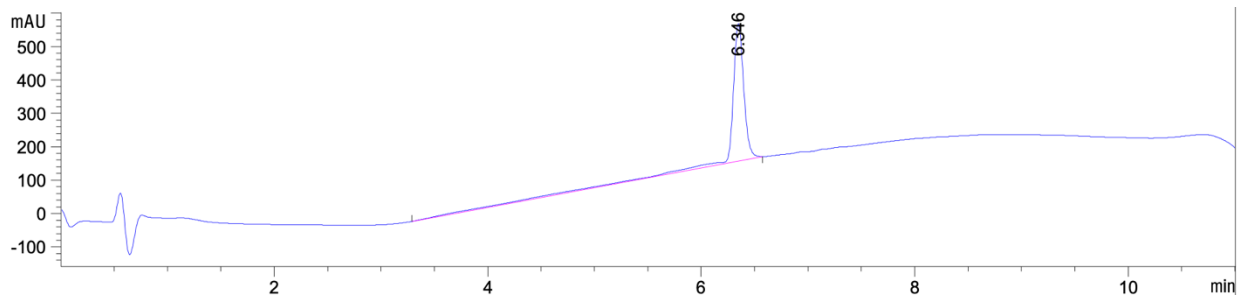
# Copy of NMR of 4d



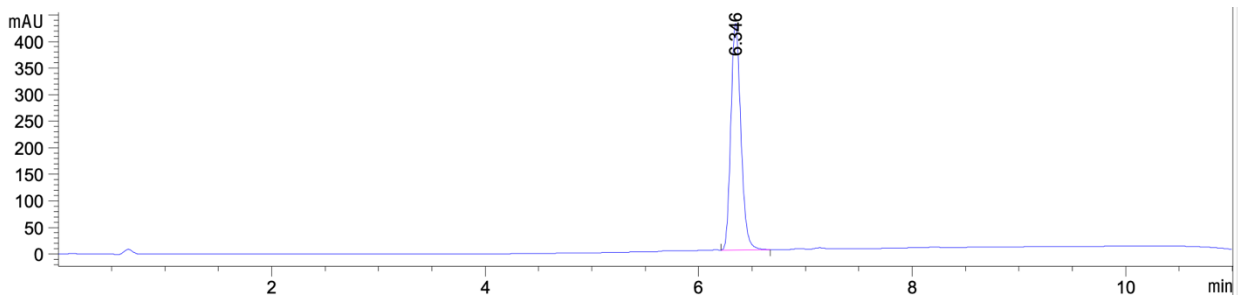


Compound 4e

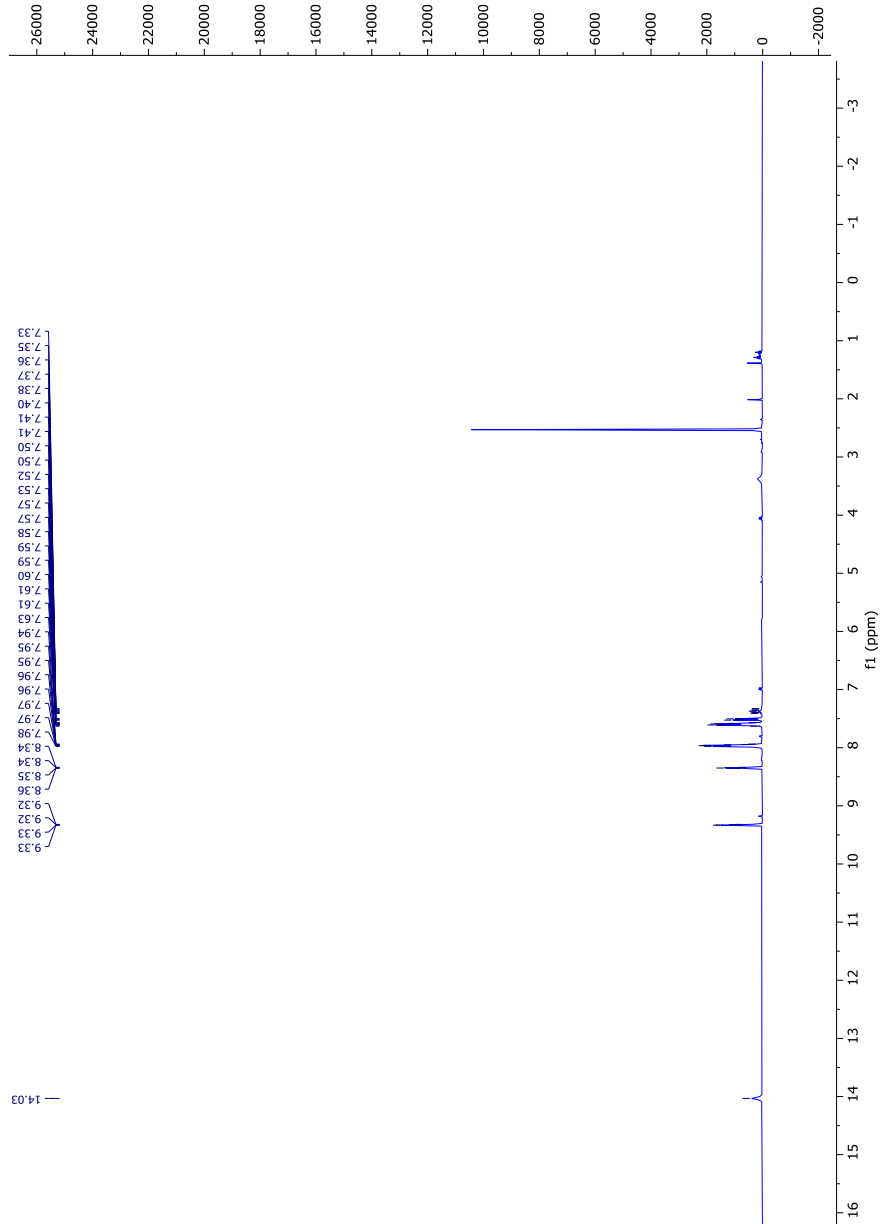
Copy of Chromatographic Analysis of 4e  
220nm

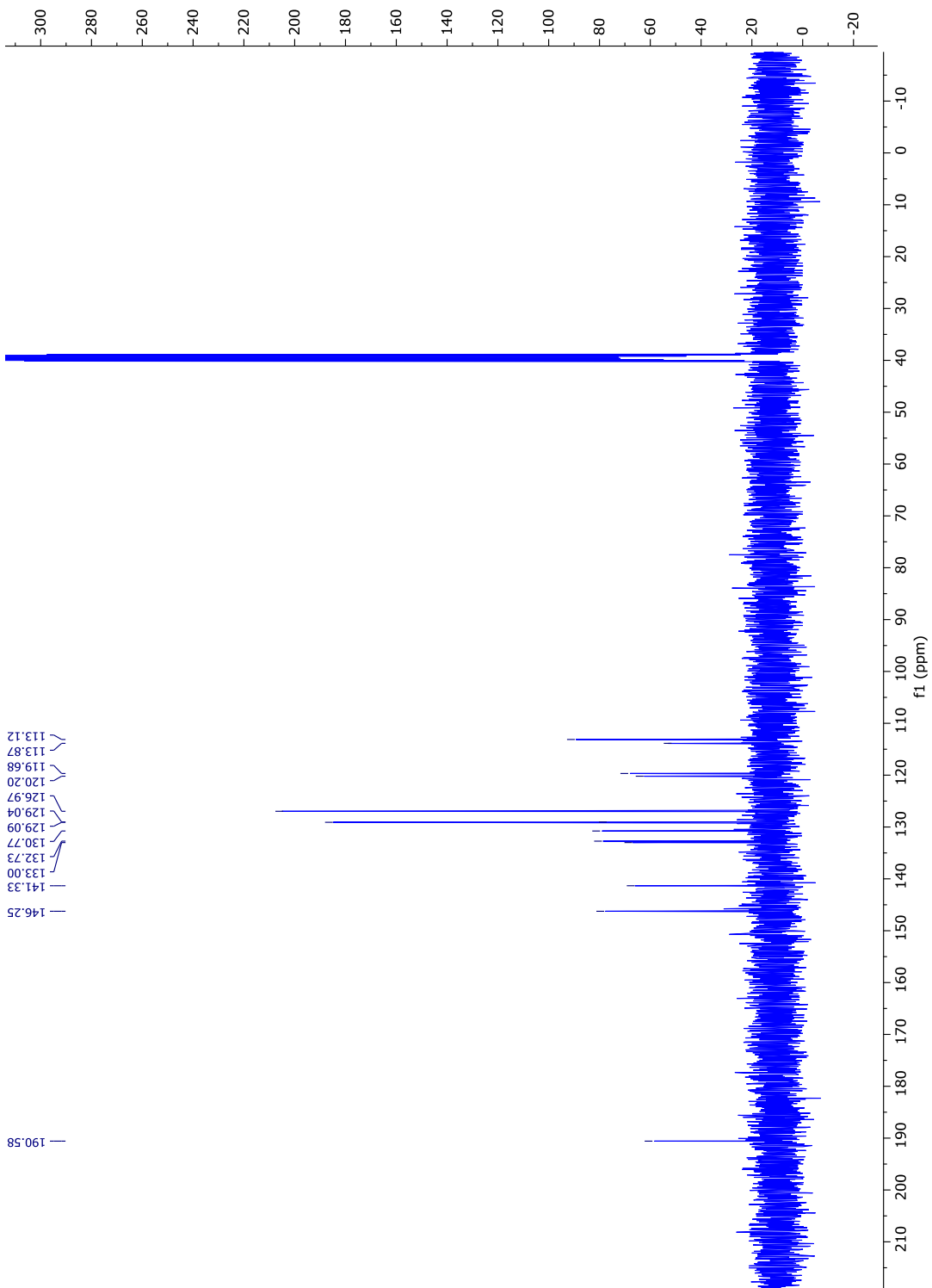


254nm



Copy of NMR of 4e

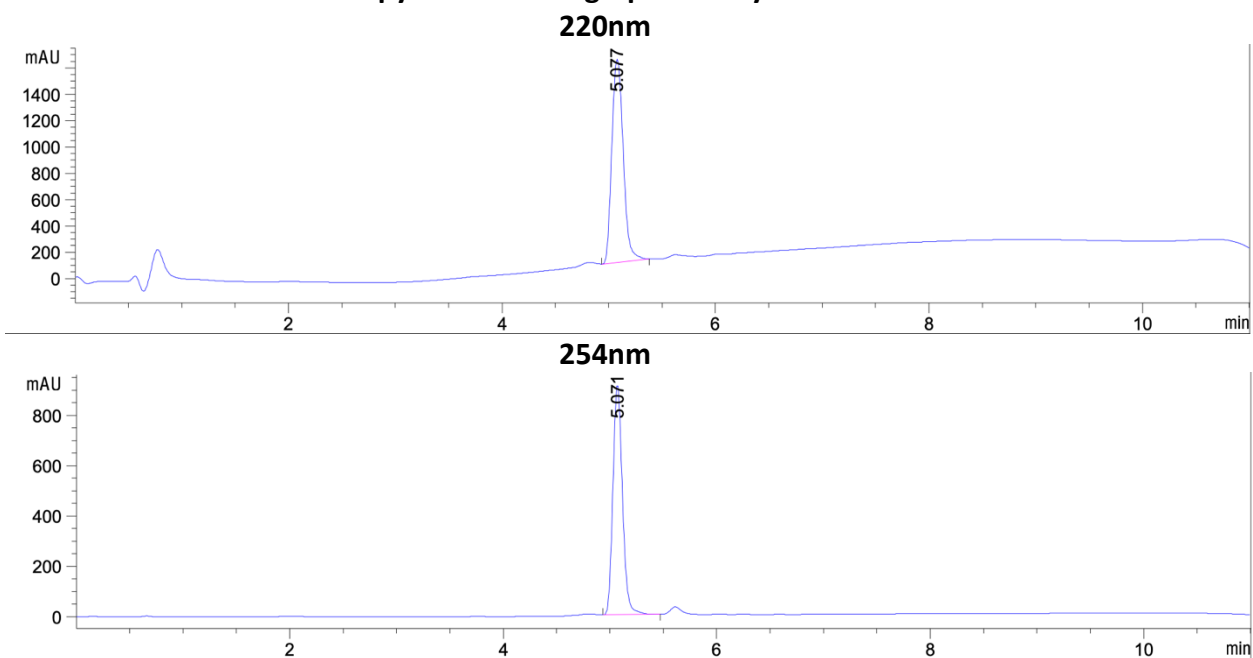




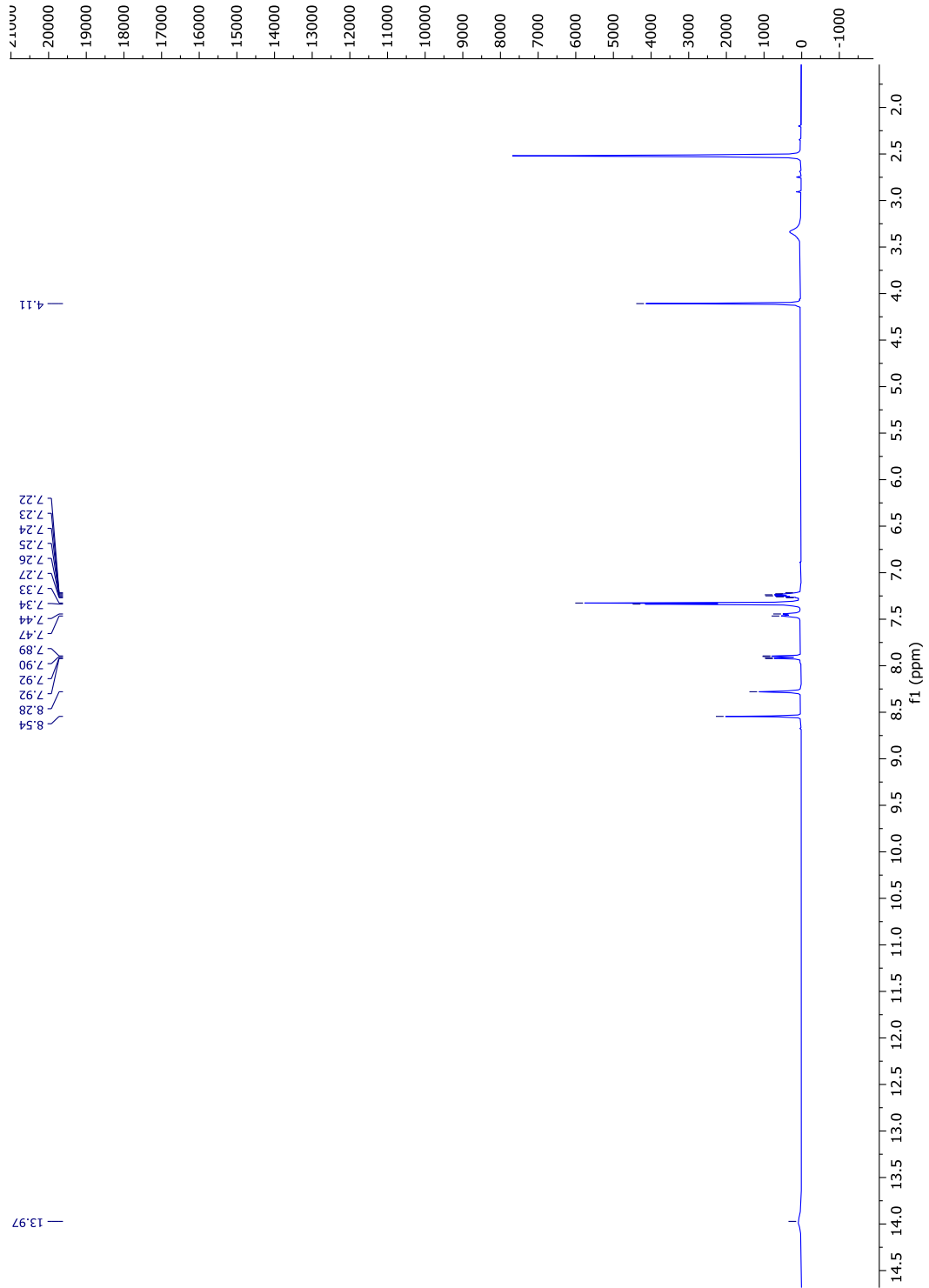


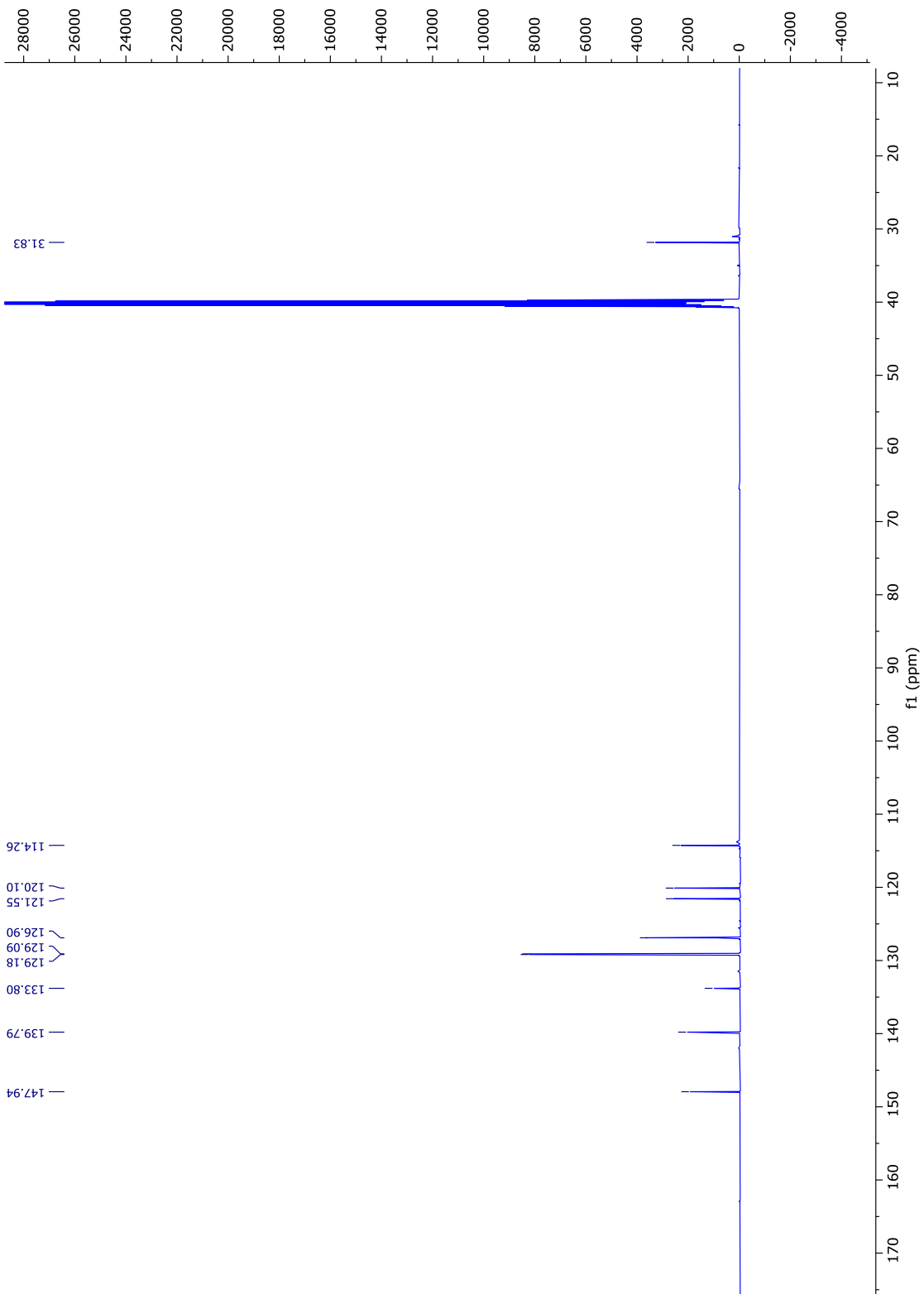
Compound **4f**

Copy of Chromatographic Analysis of **4f**



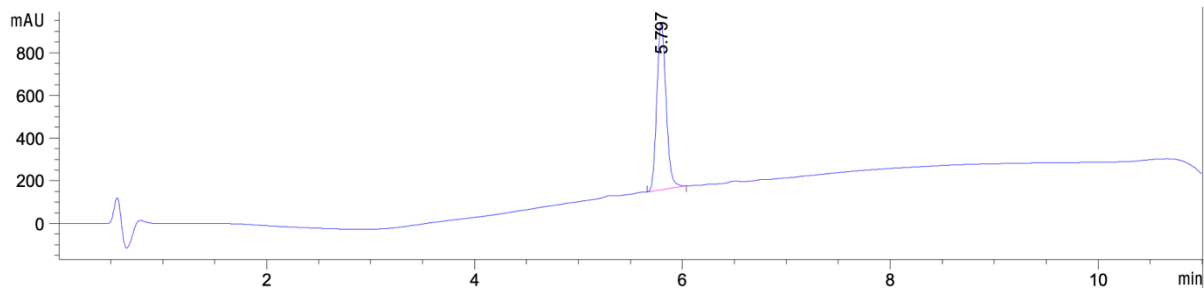
Copy of NMR of 4f



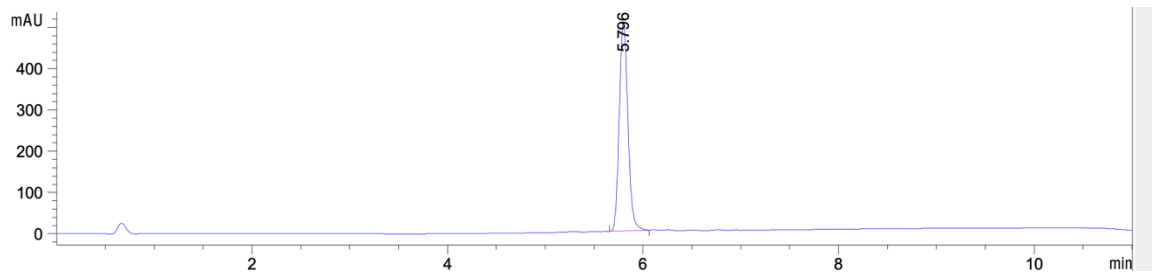


Compound 4g

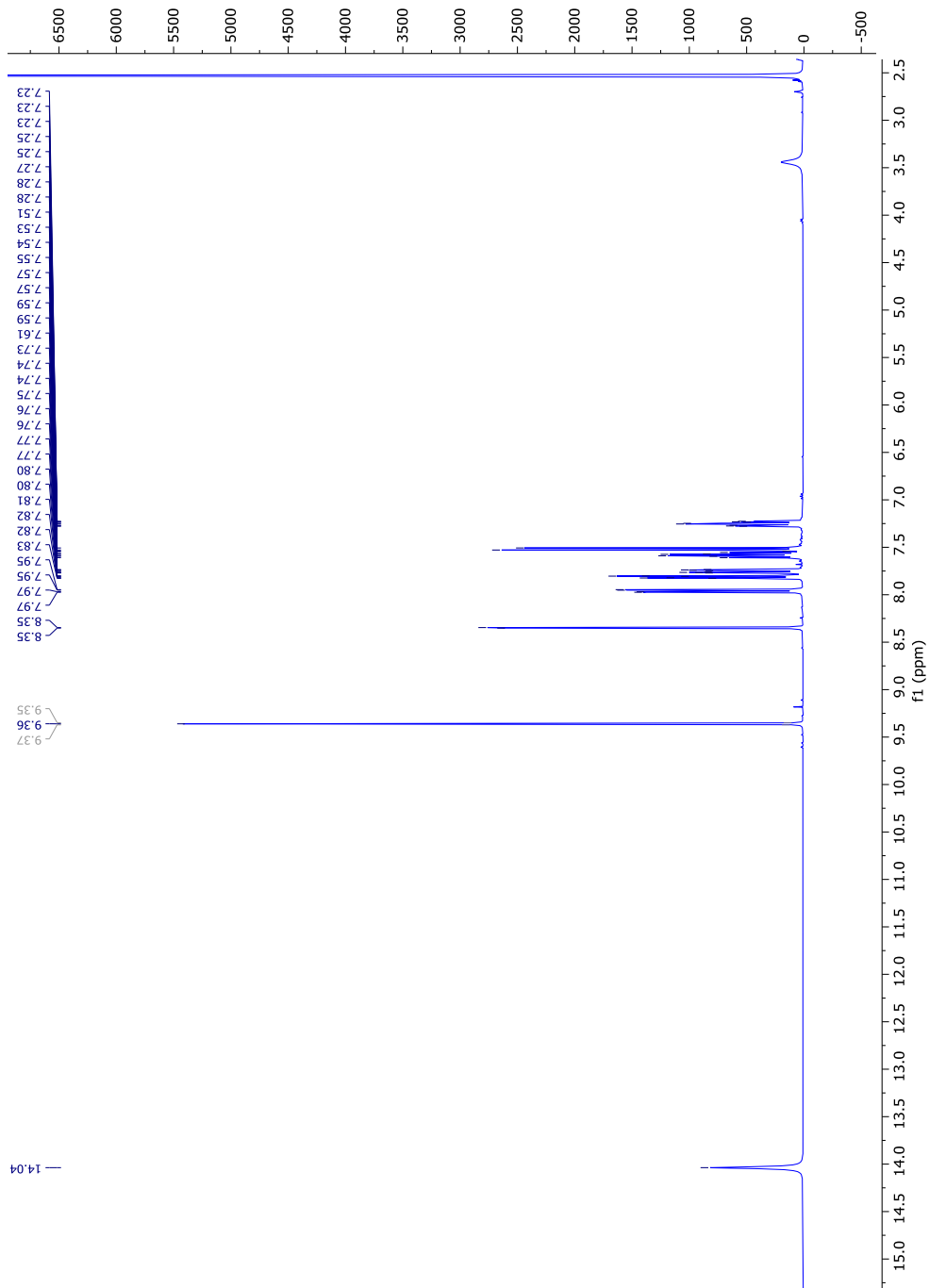
**Copy of Chromatographic Analysis of 4g**  
**220nm**

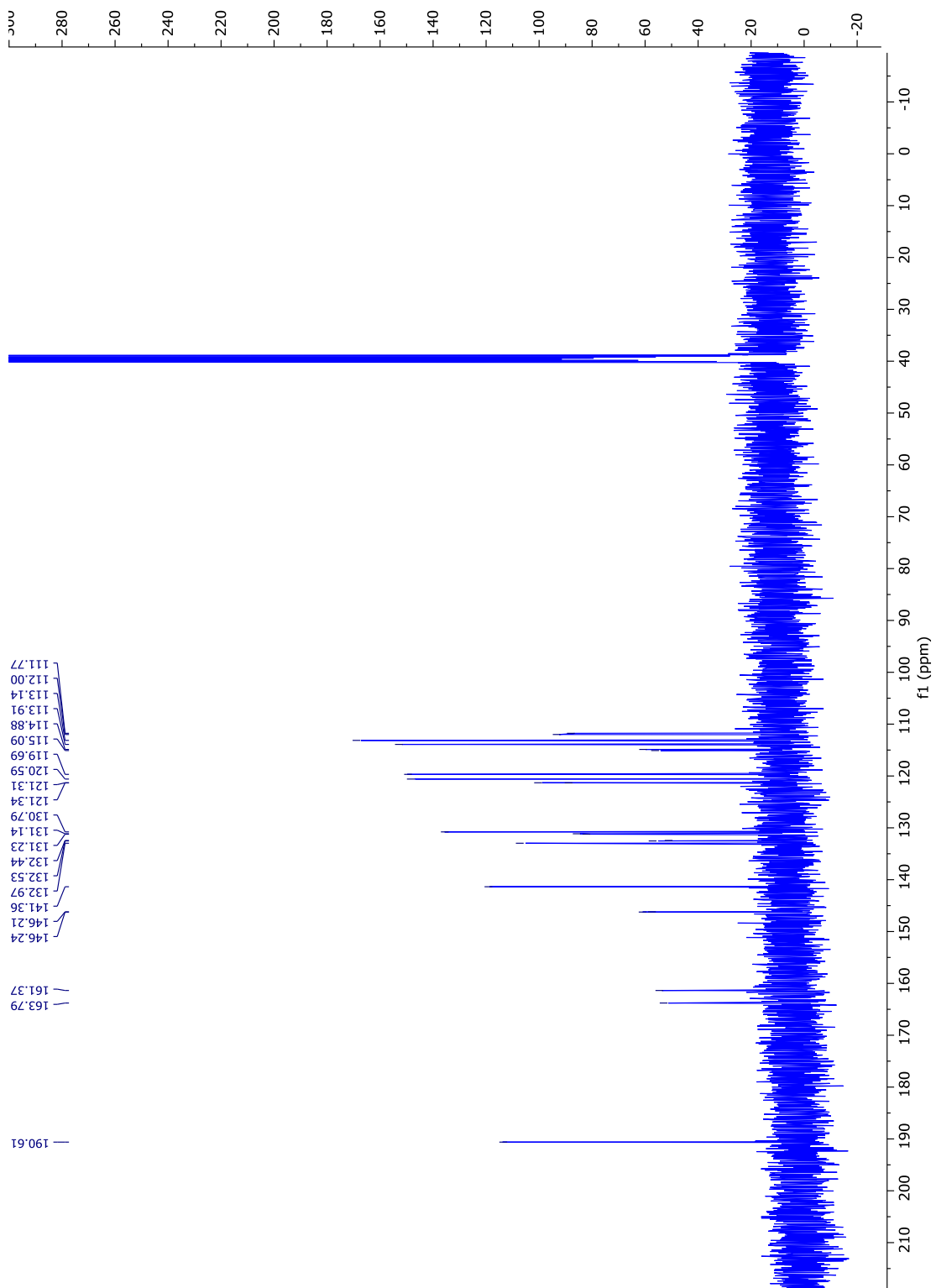


**254nm**



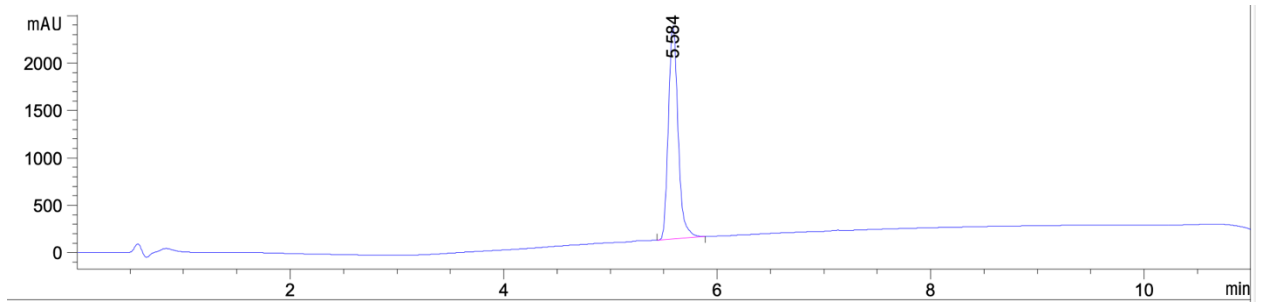
# Copy of NMR of 4g



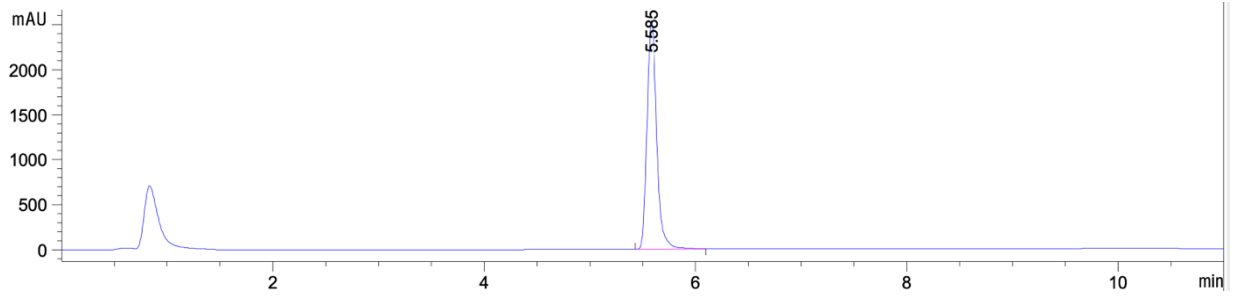


Compound 4h

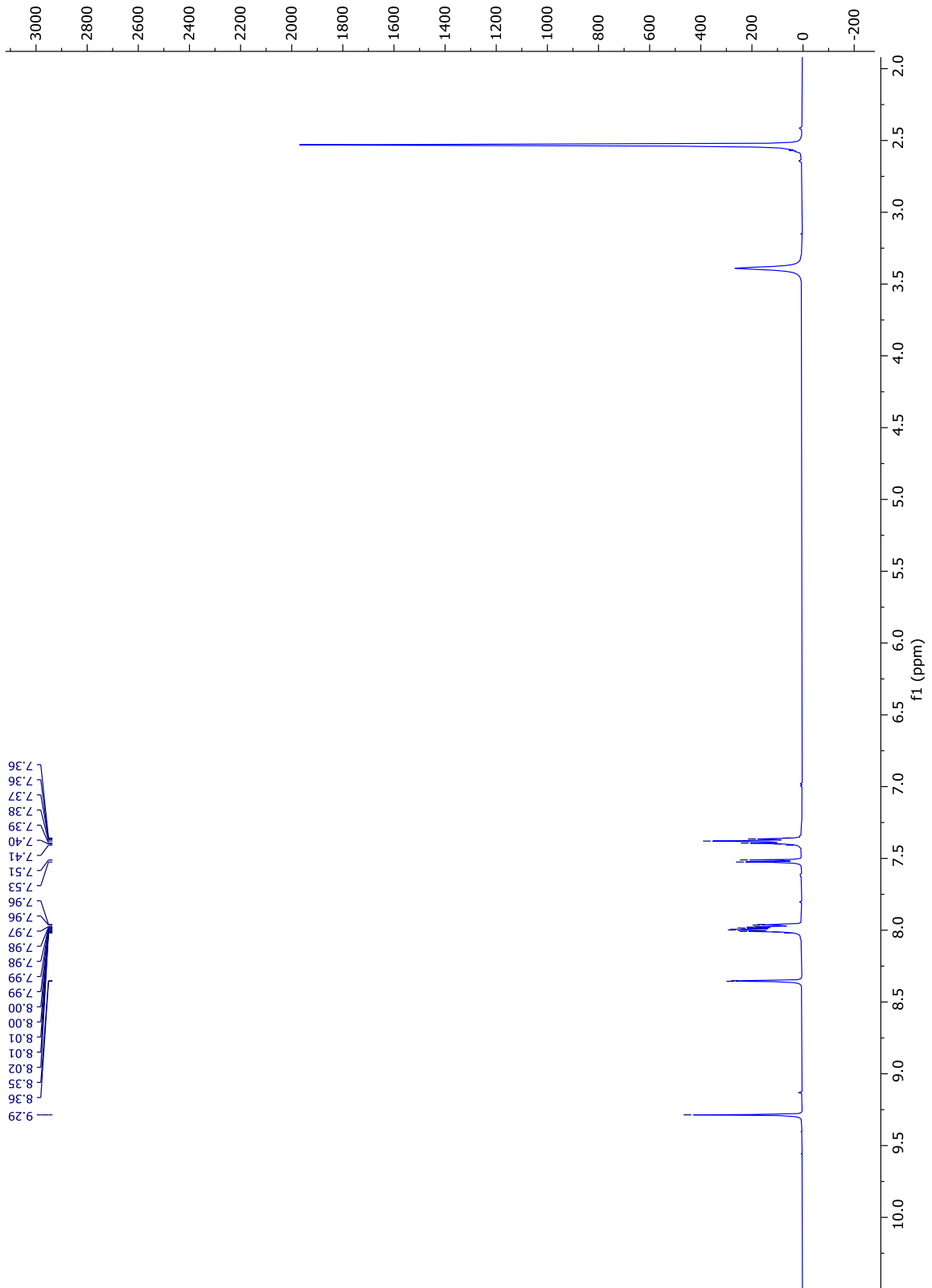
Copy of Chromatographic Analysis of 4h  
220nm



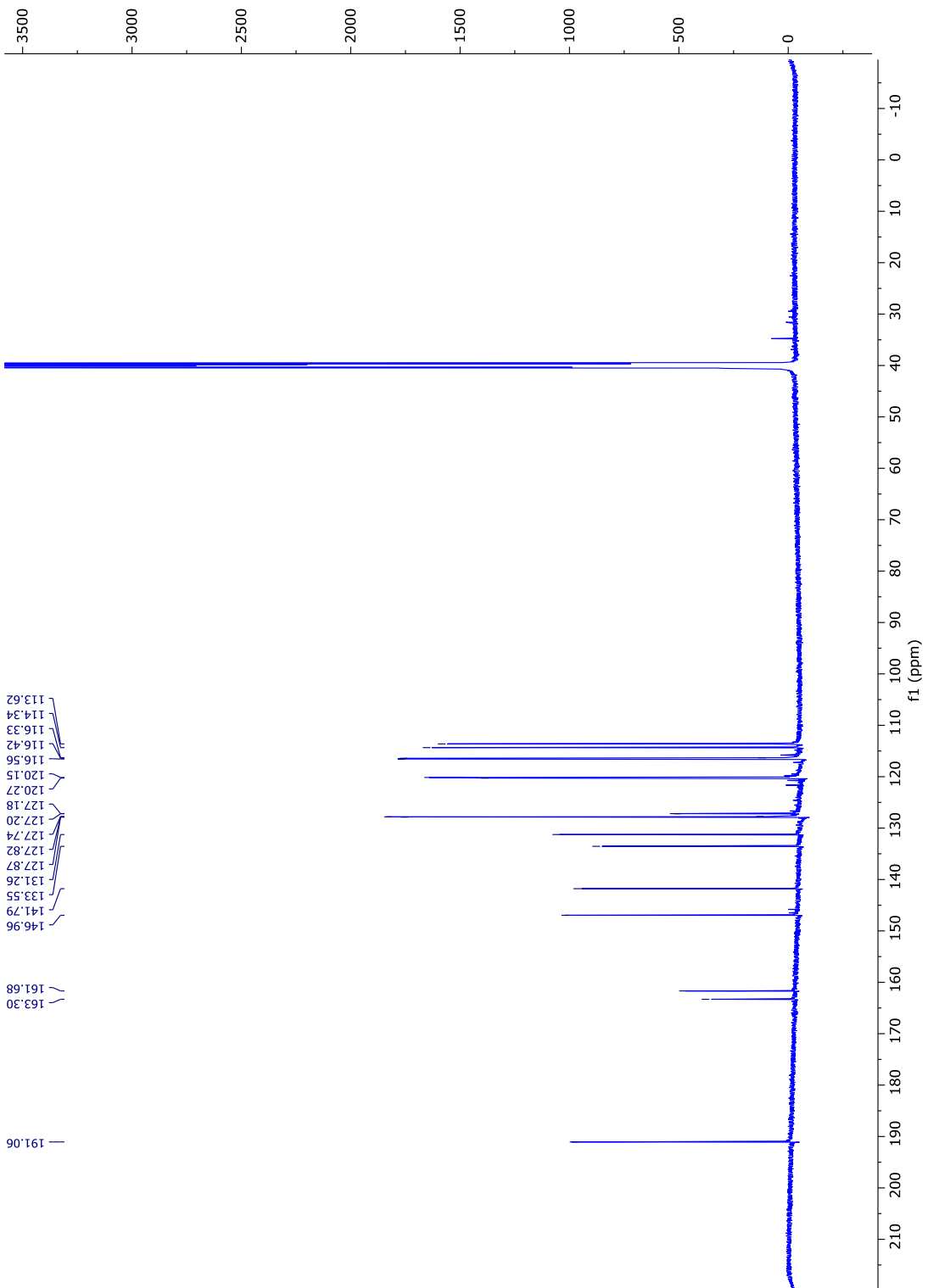
254nm



# Copy of NMR of 4h

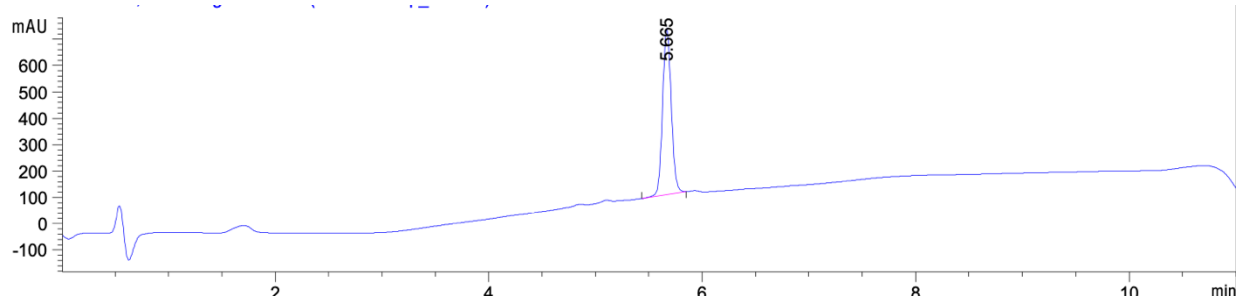




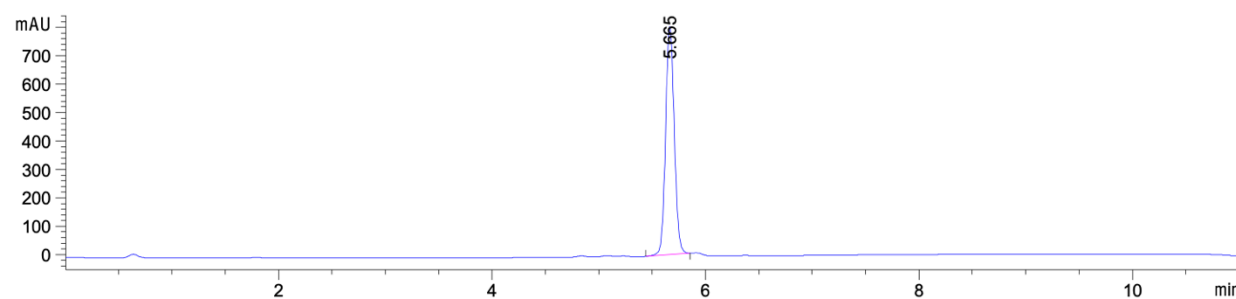


Compound **4i**

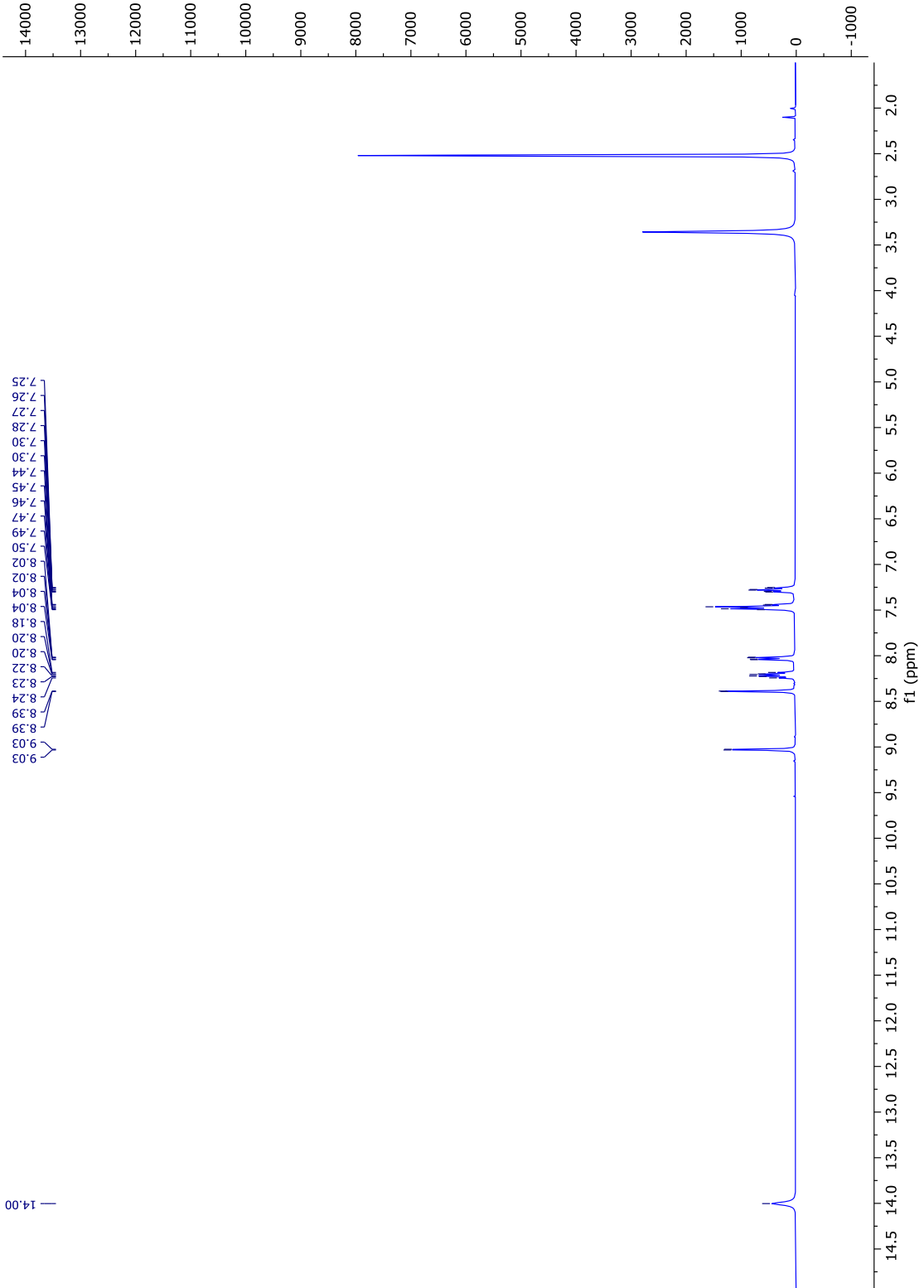
**Copy of Chromatographic Analysis of 4i**  
**220nm**

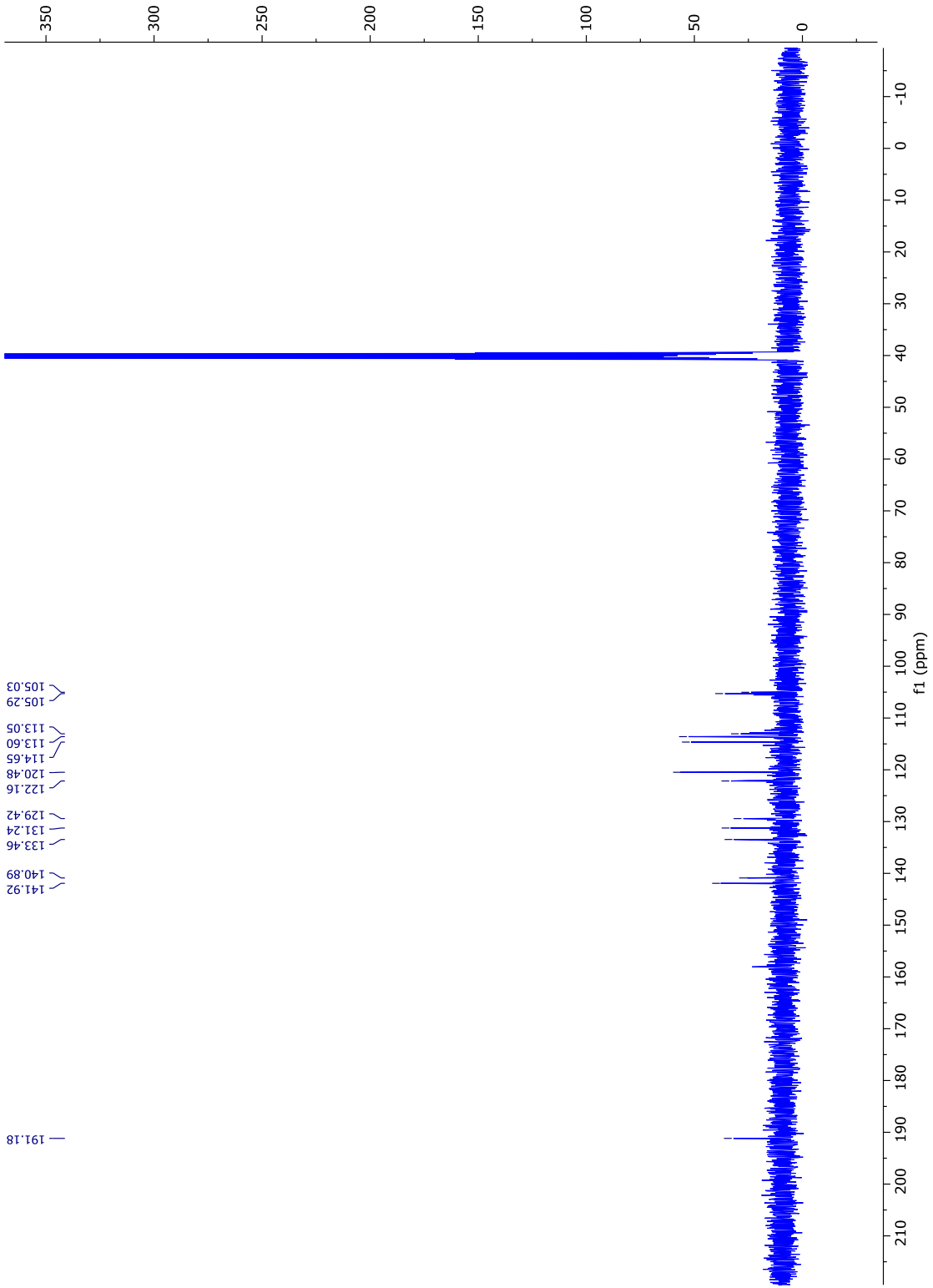


**254nm**



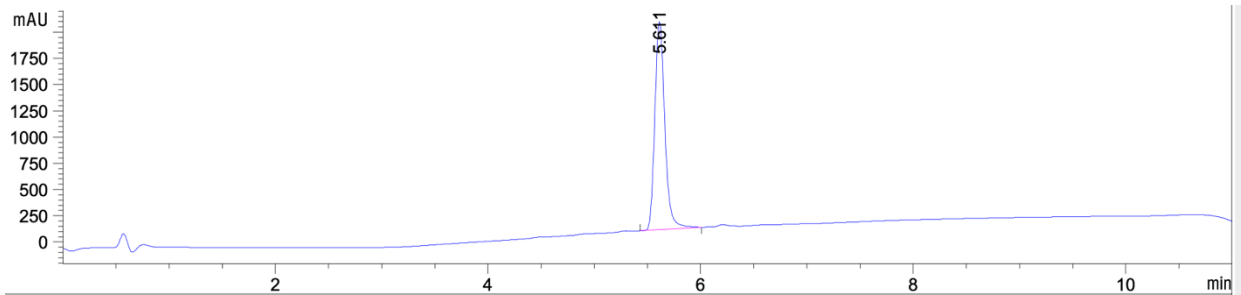
Copy of NMR of 4i



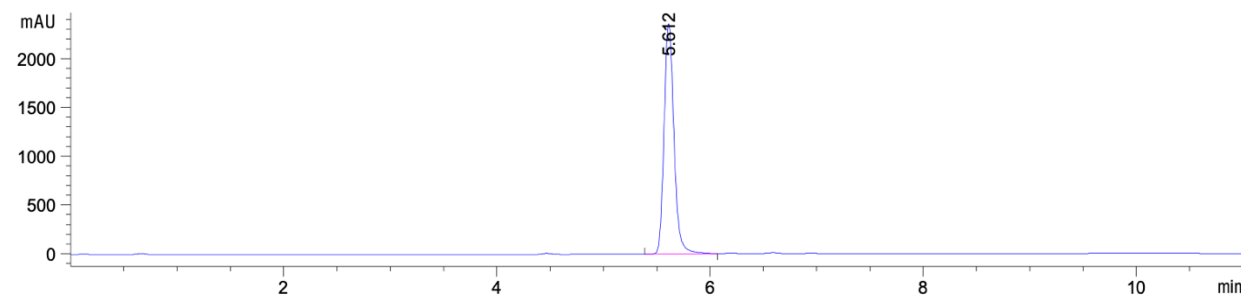


Compound 4j

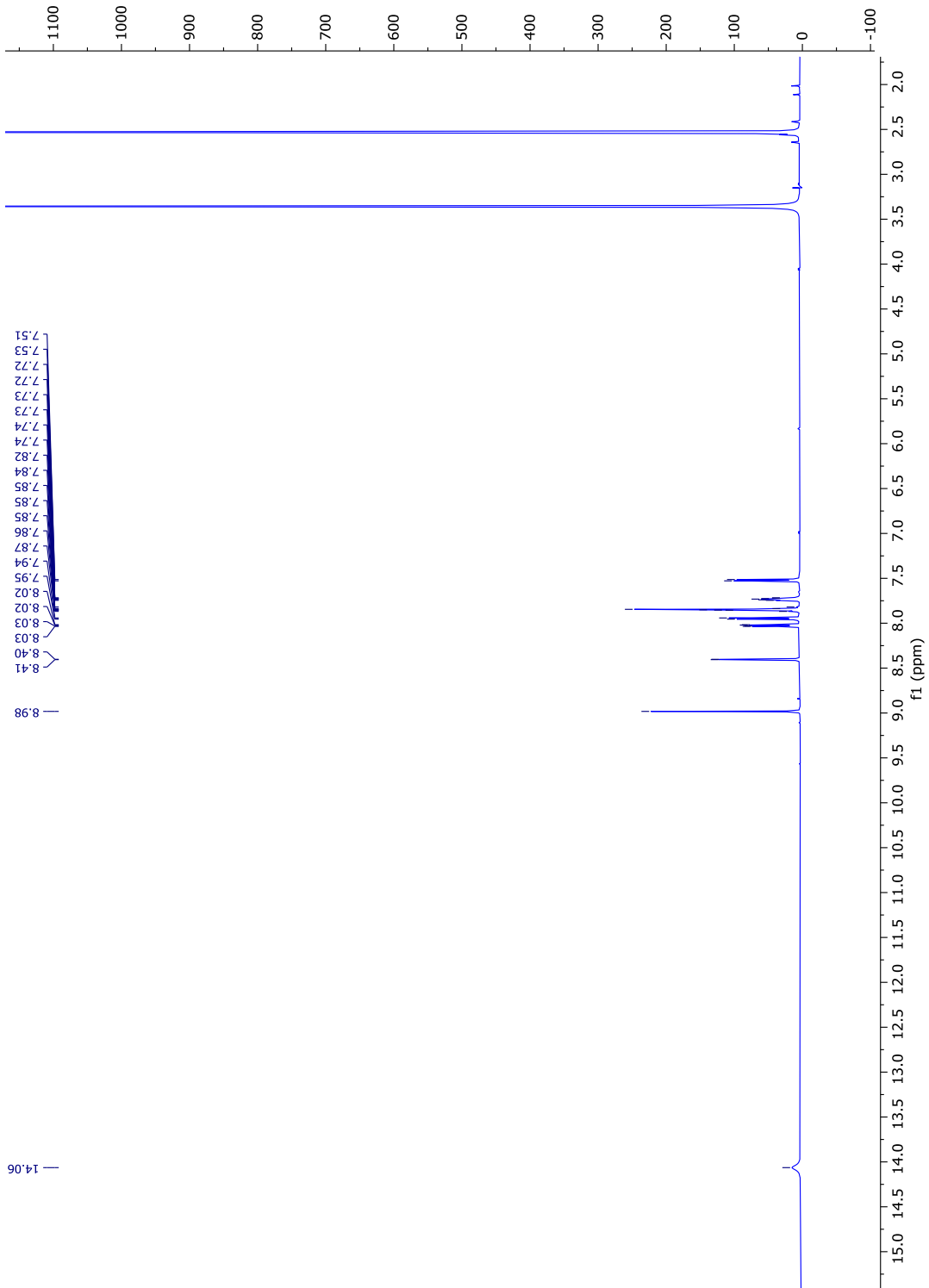
Copy of Chromatographic Analysis of 4j  
220nm

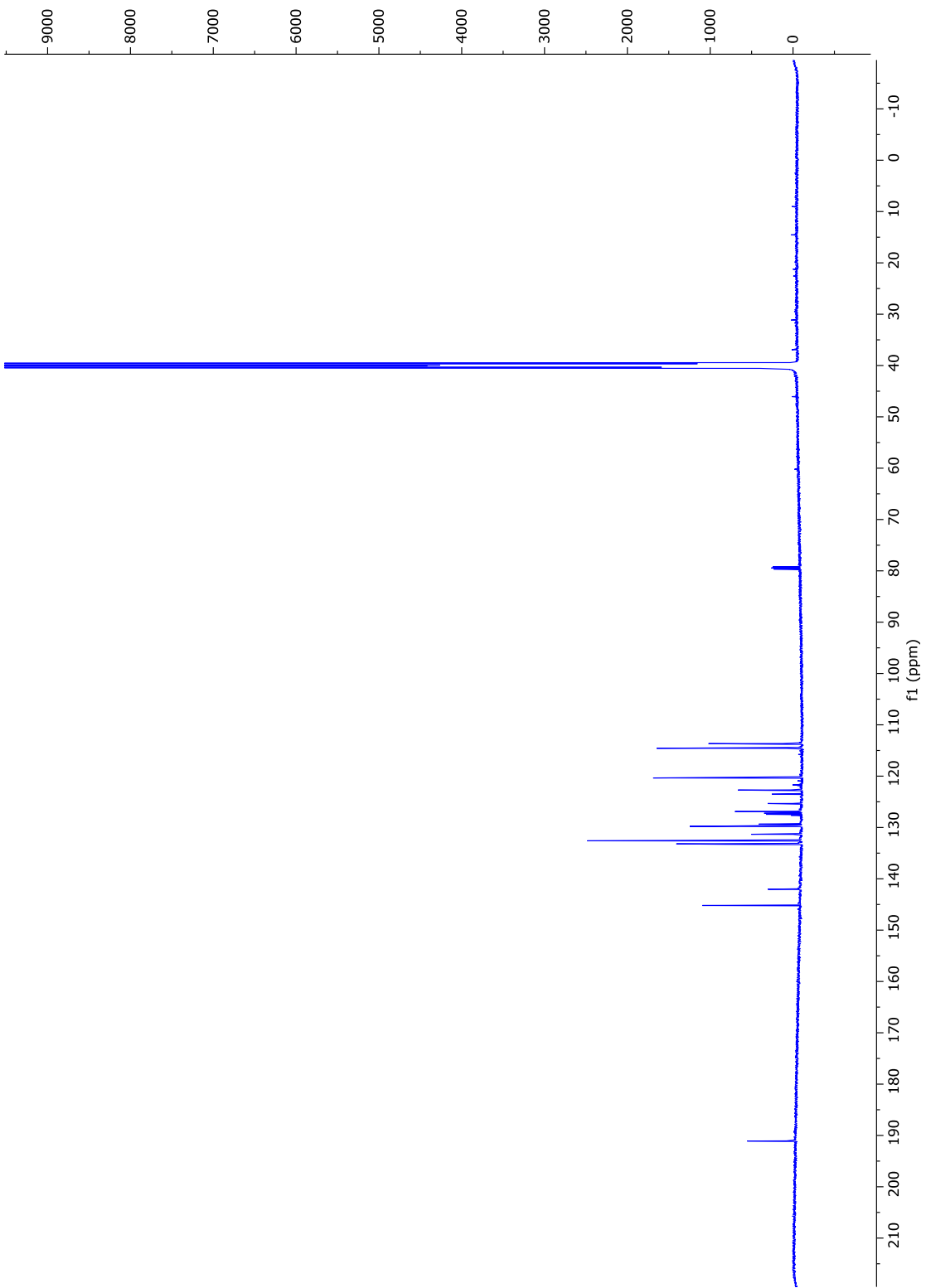


254nm



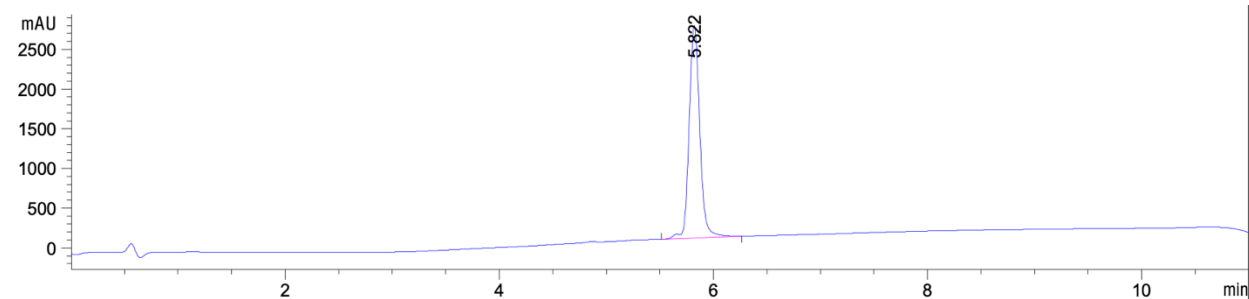
Copy of NMR of 4j



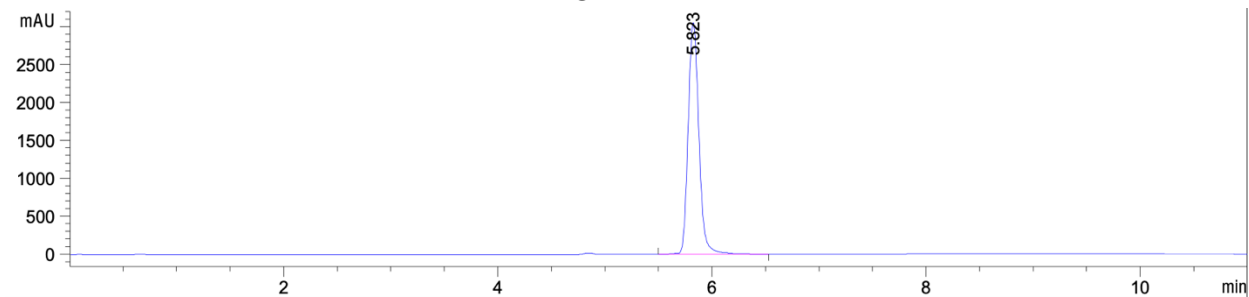


Compound **4k**

**Copy of Chromatographic Analysis of 4k**  
**220nm**

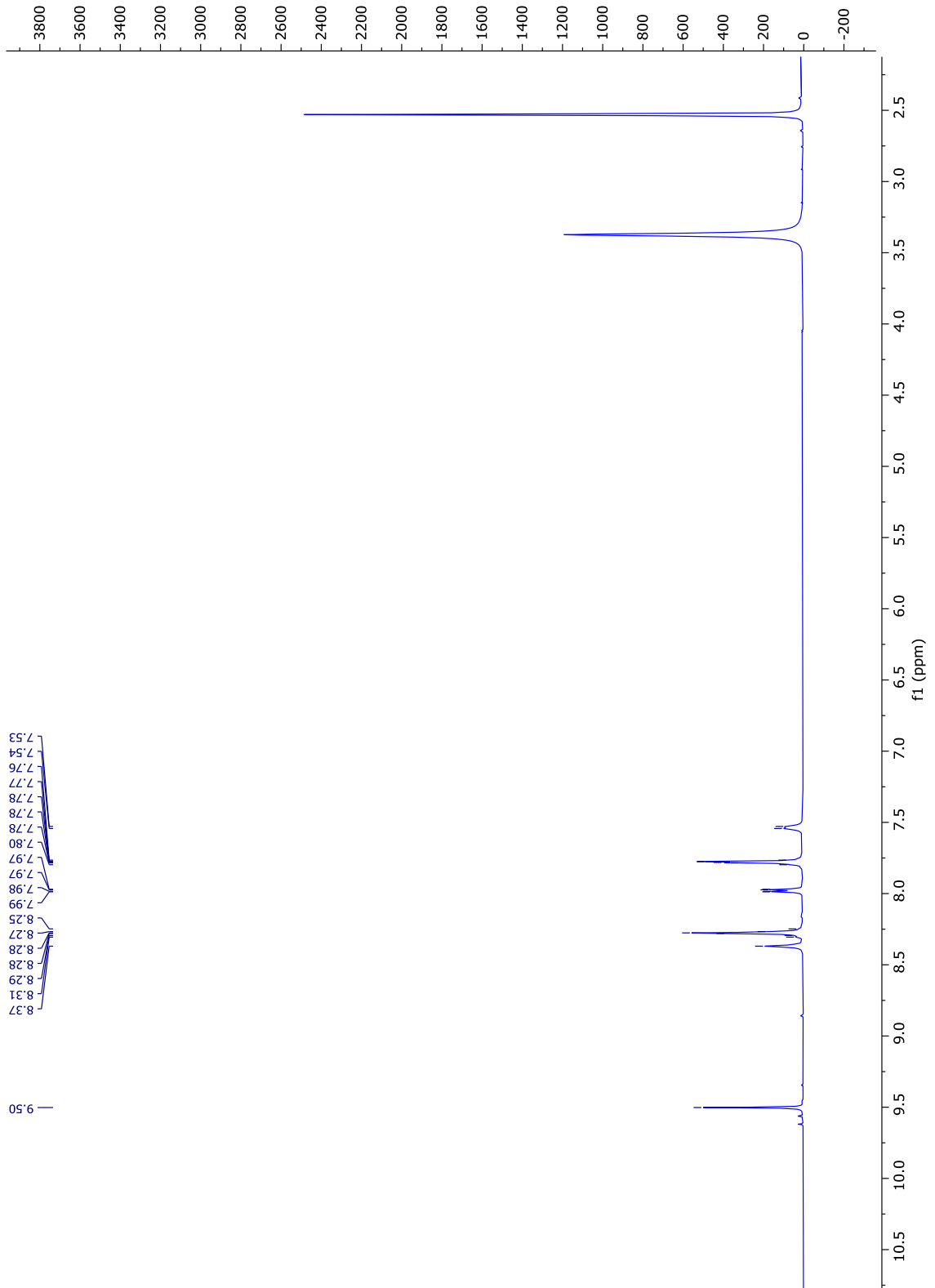


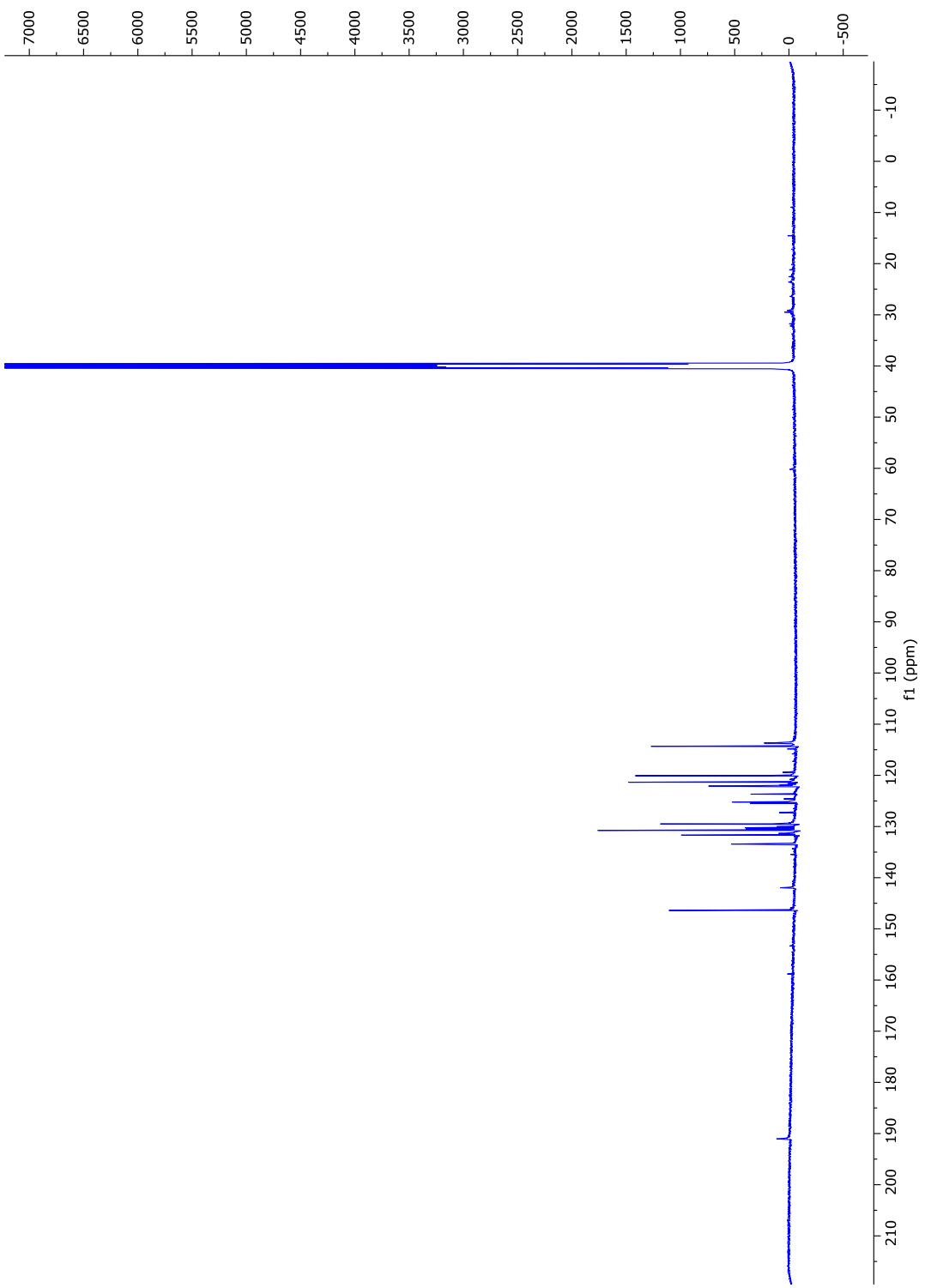
**254nm**





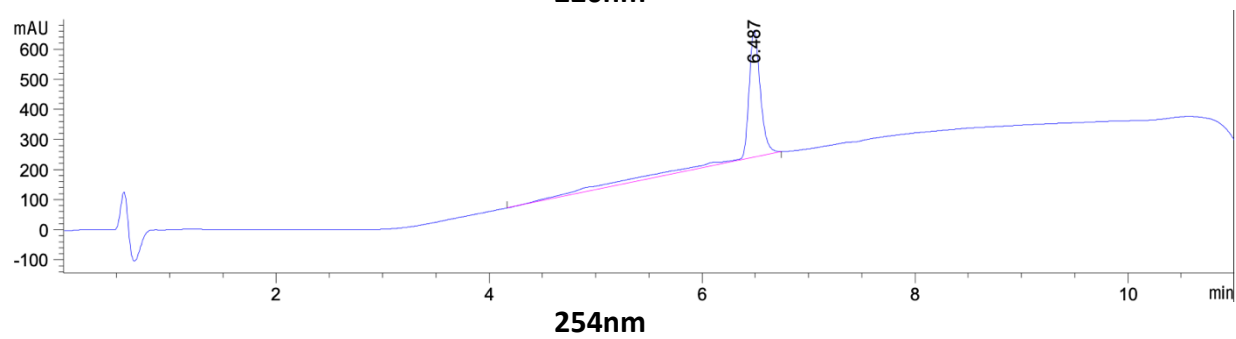
Copy of NMR of 4k



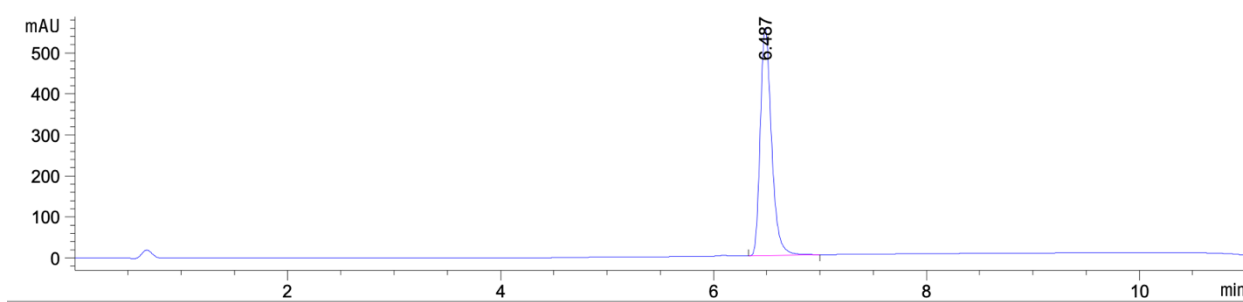


Compound 4I

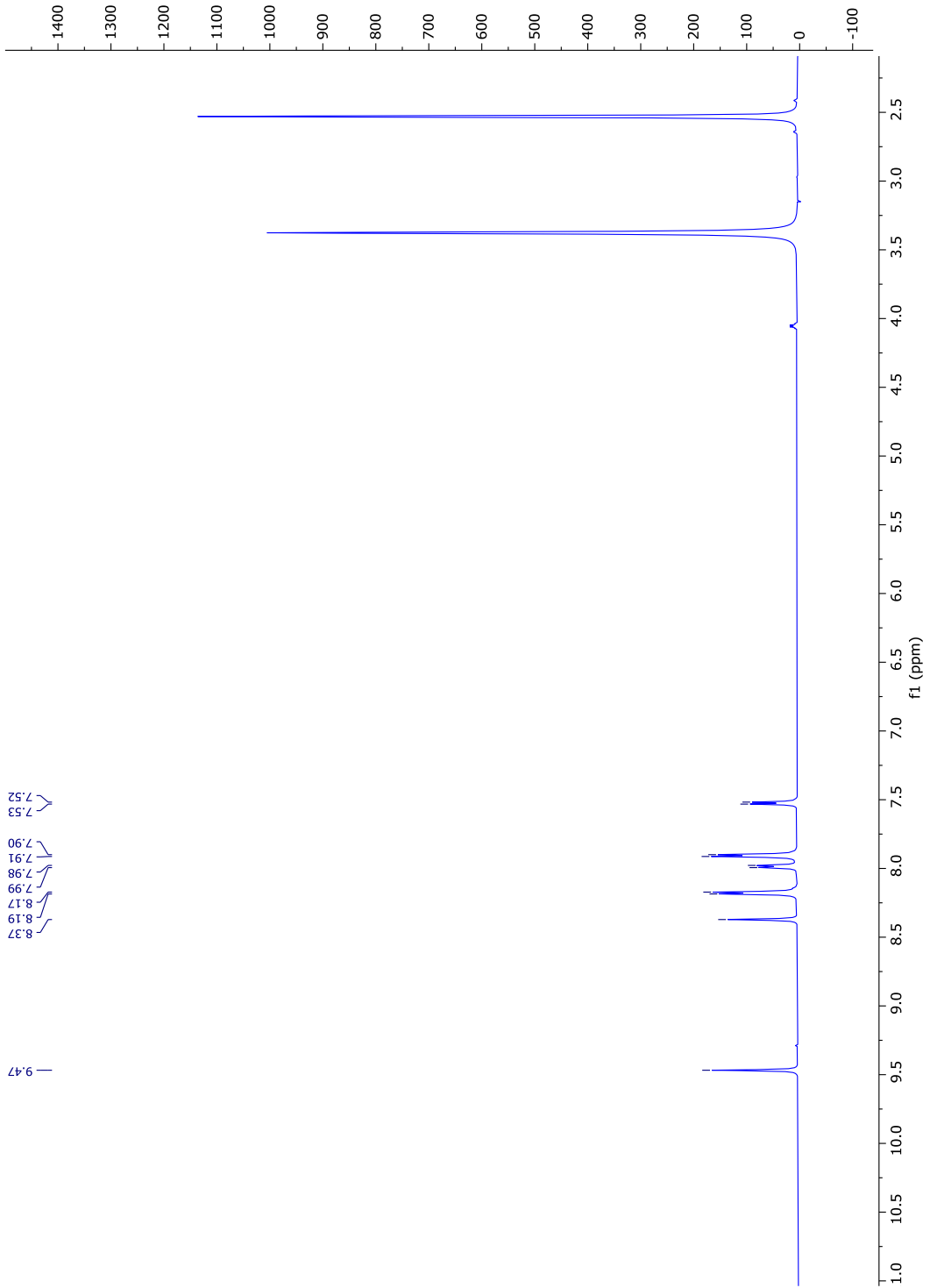
Copy of Chromatographic Analysis of 4I  
220nm

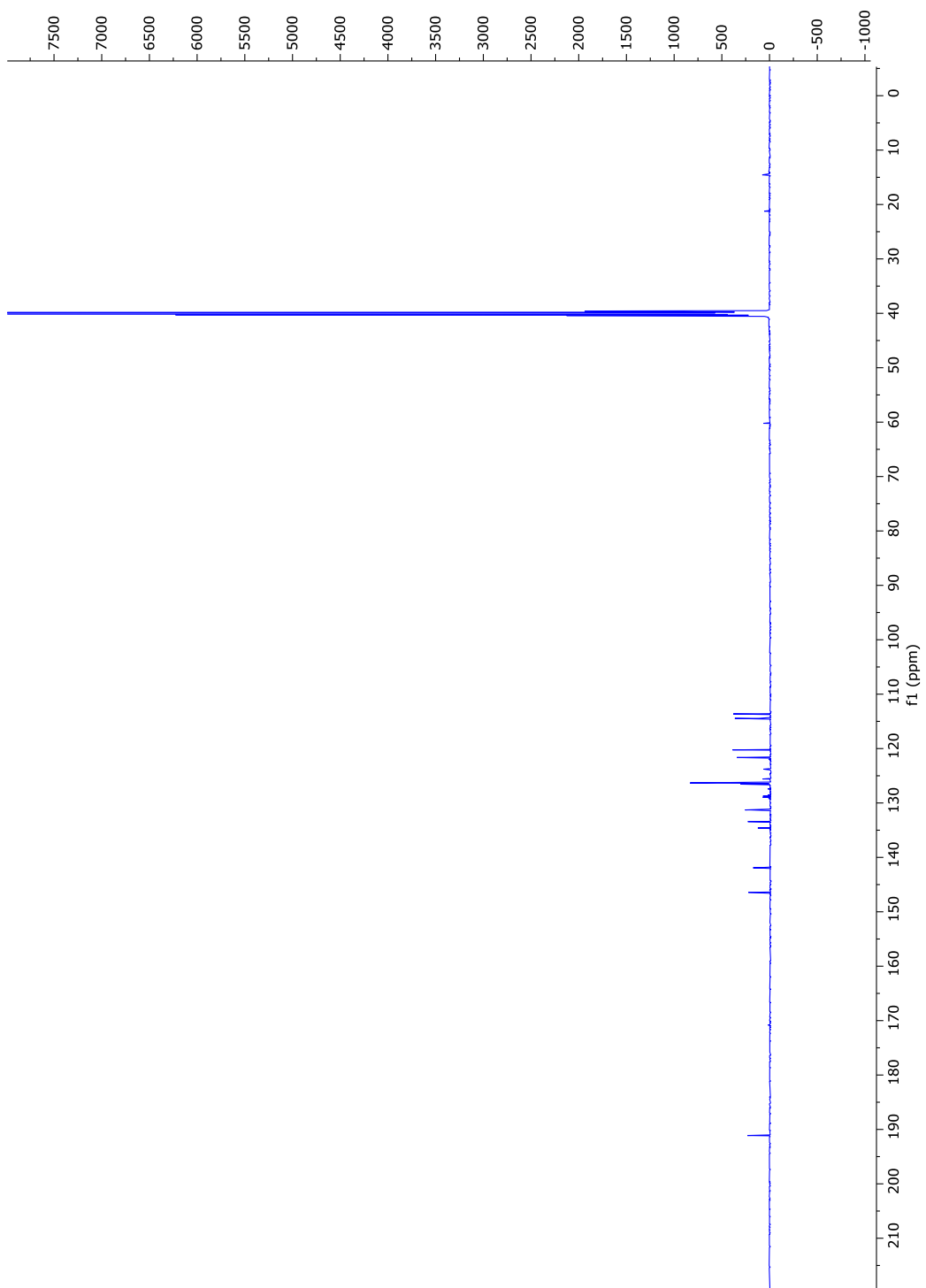


254nm



Copy of NMR of 4l

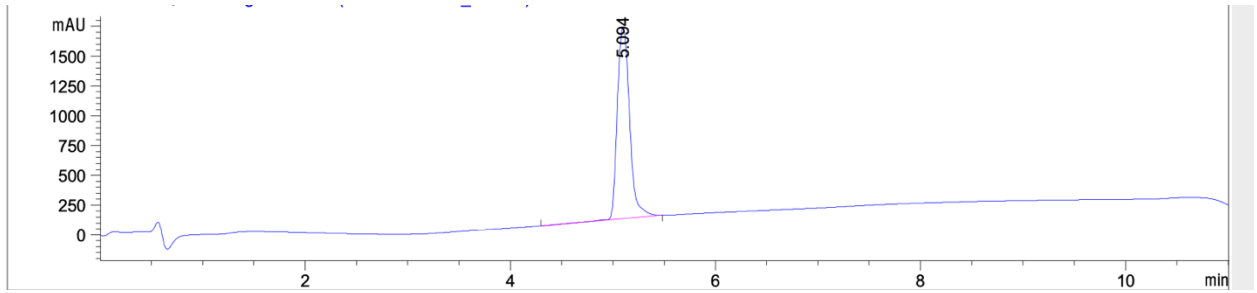




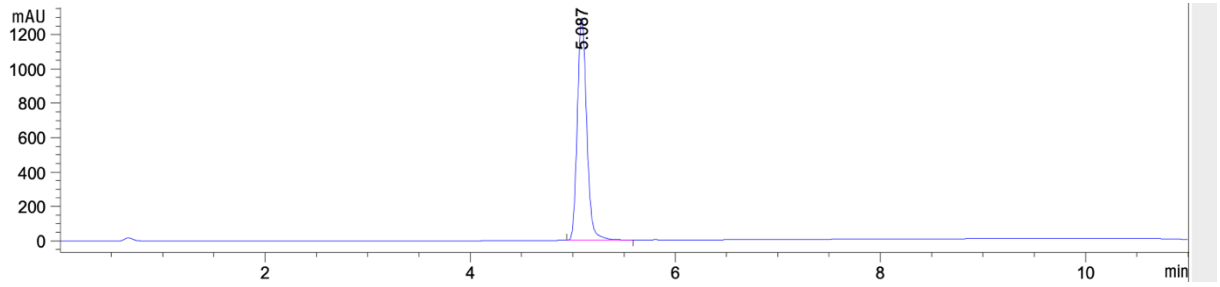
Compound 4m

Copy of Chromatographic Analysis of 4m

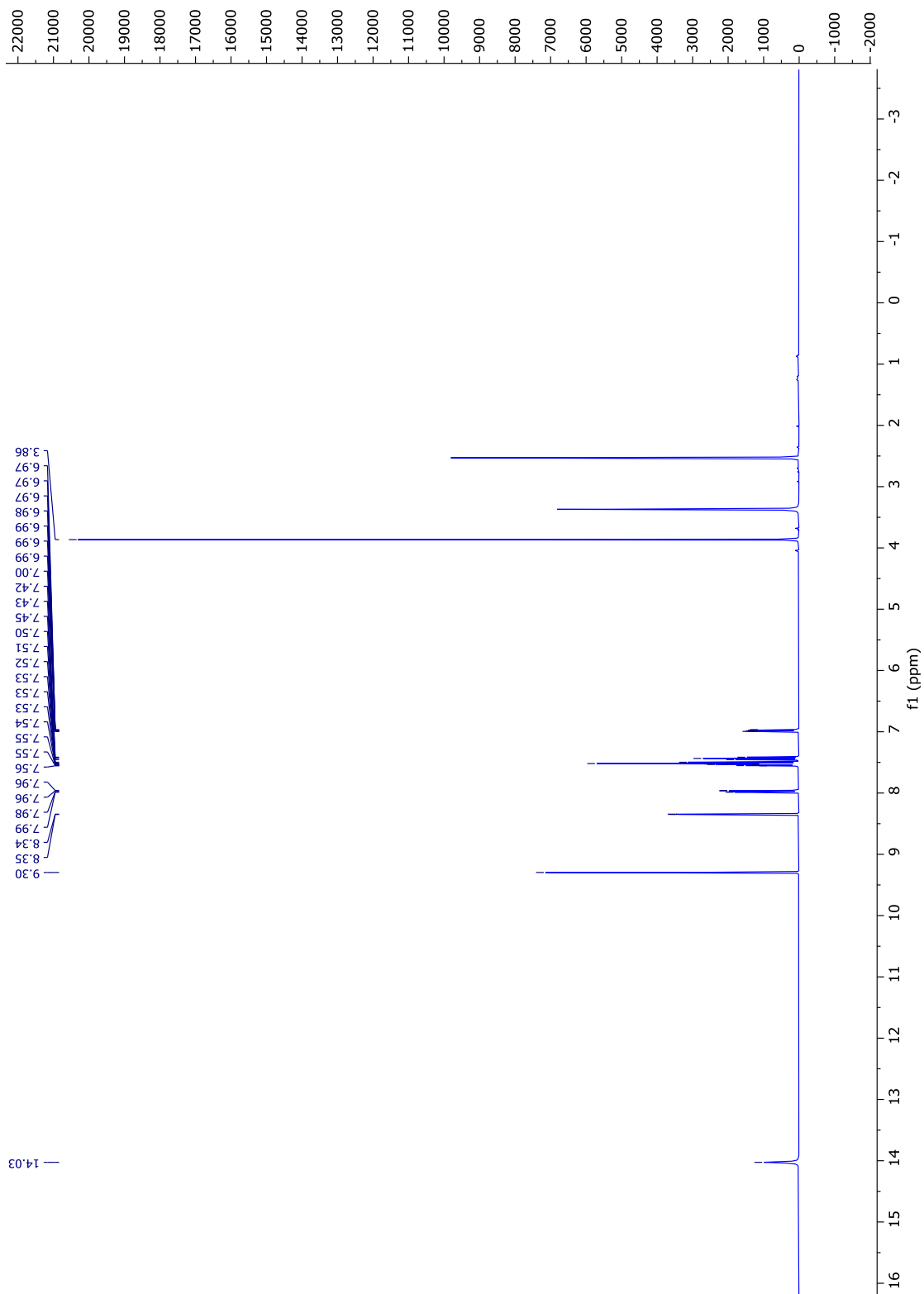
220nm

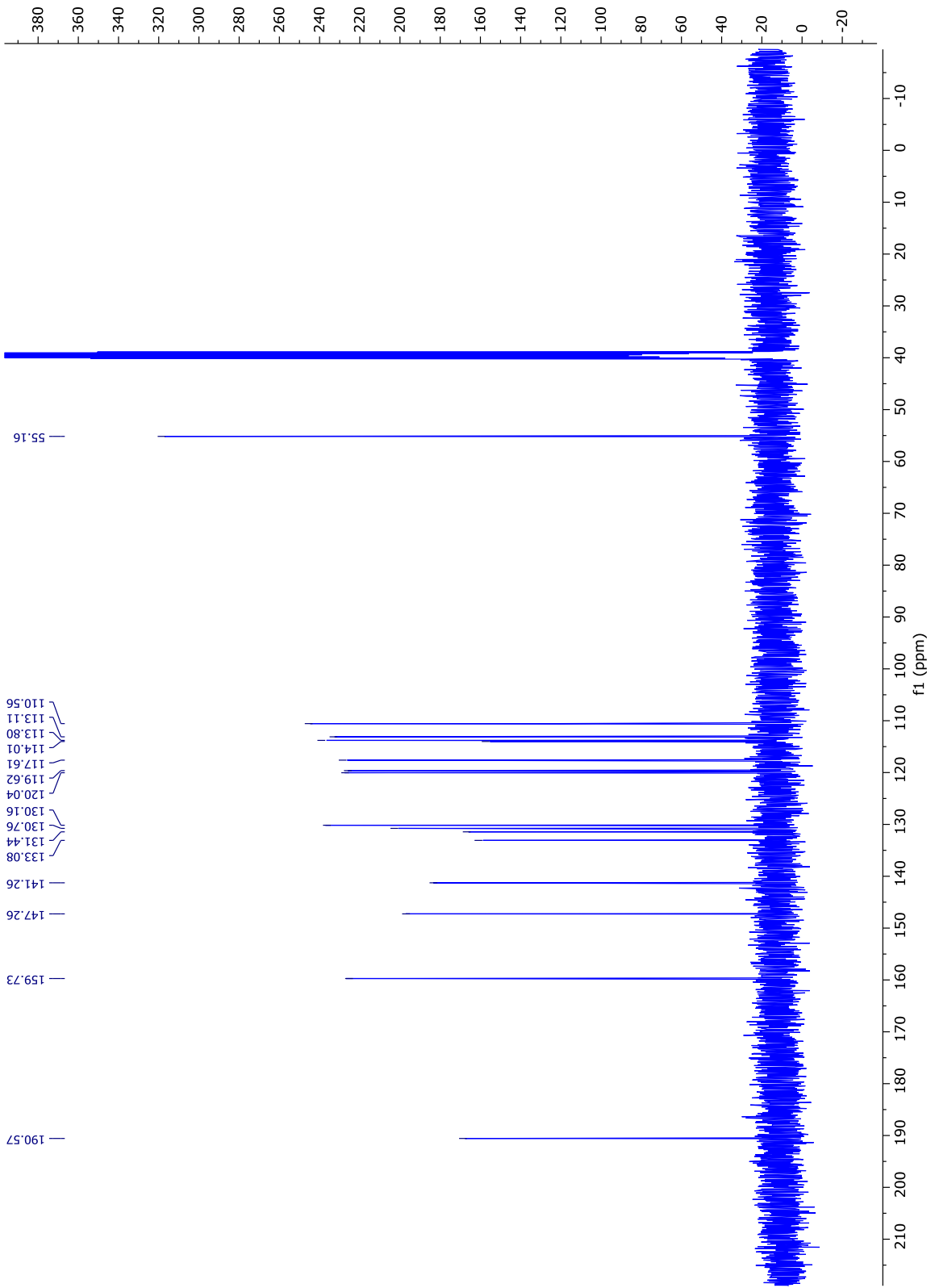


254nm



# Copy of NMR of 4m

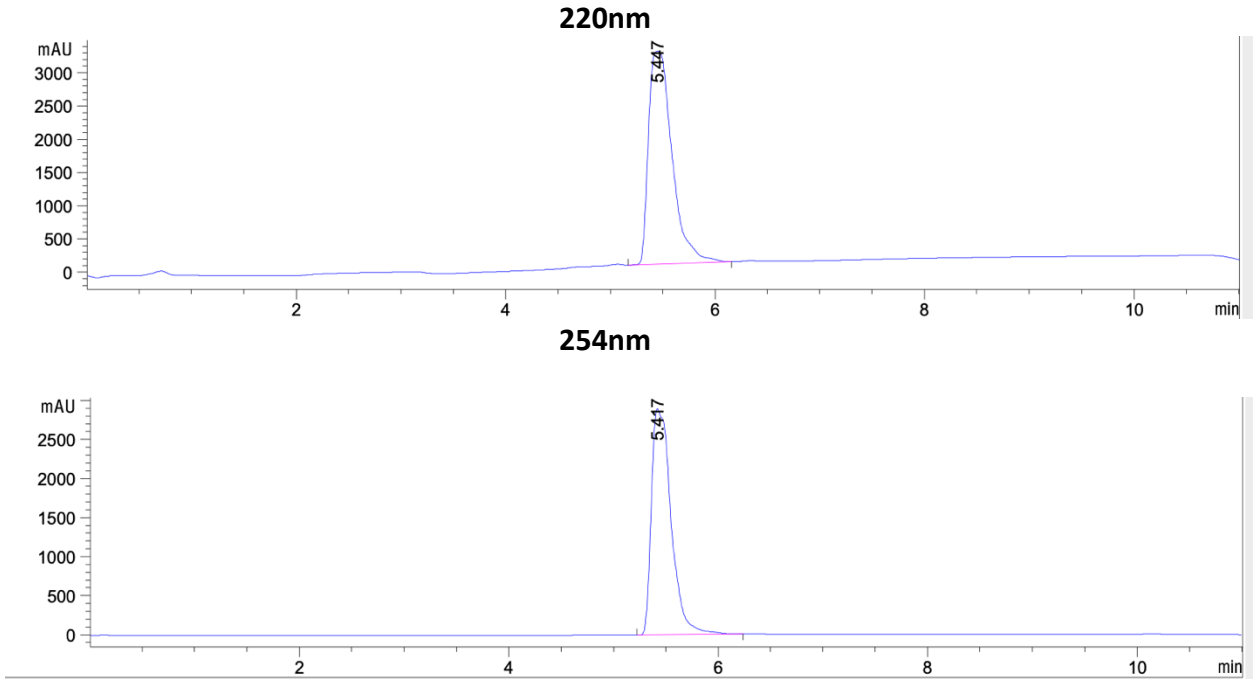




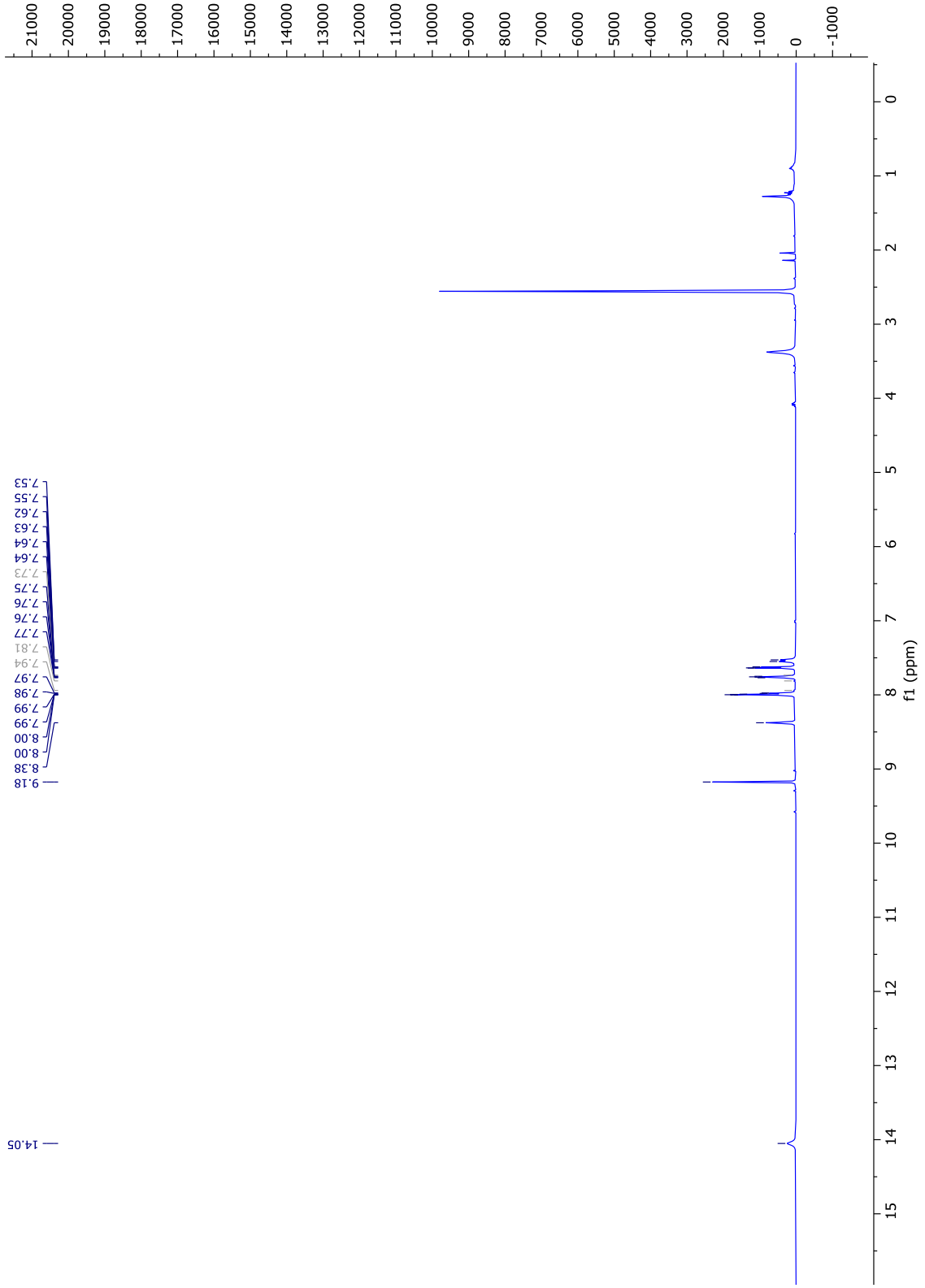


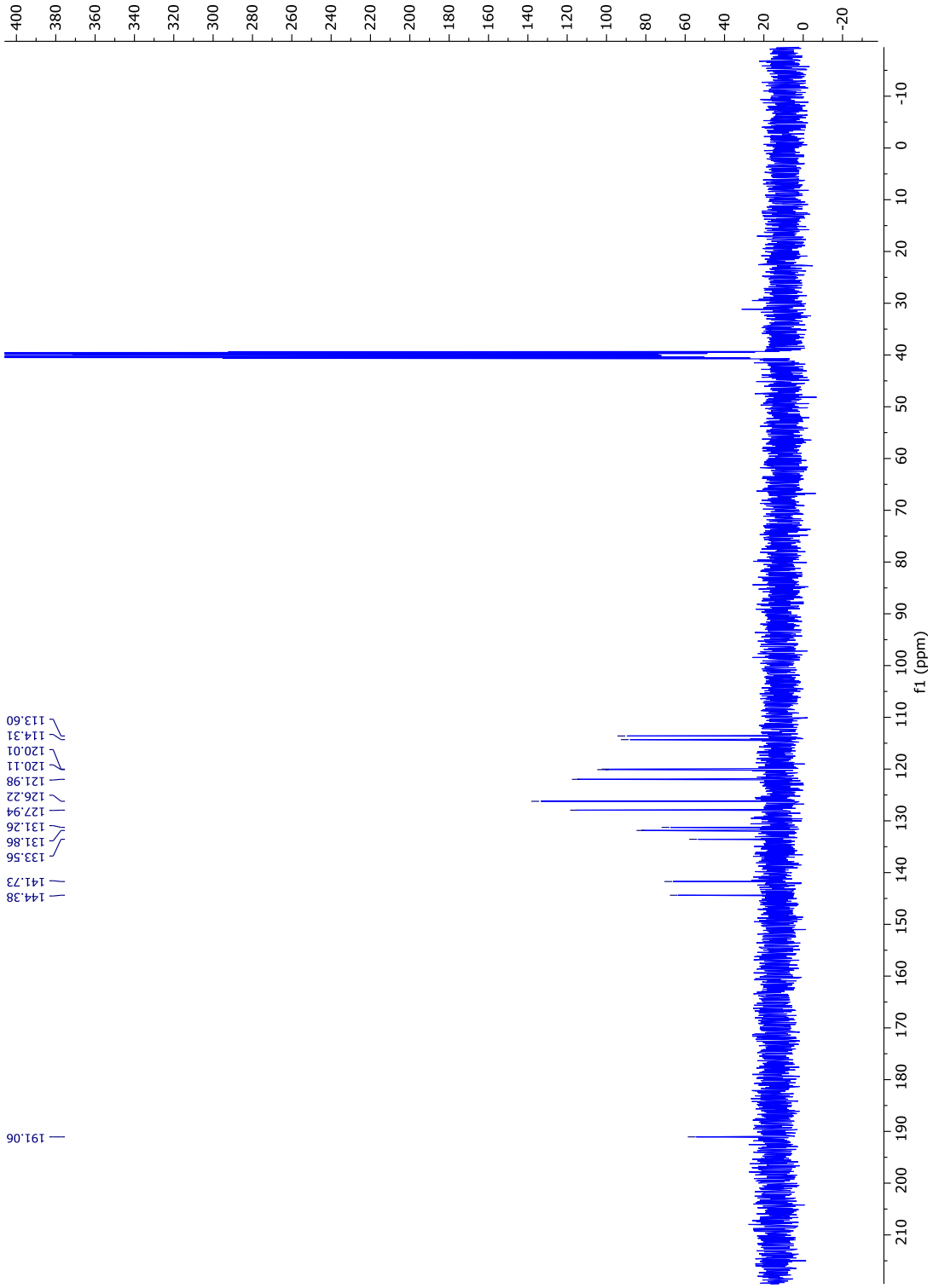
Compound 4n

Copy of Chromatographic Analysis of 4n



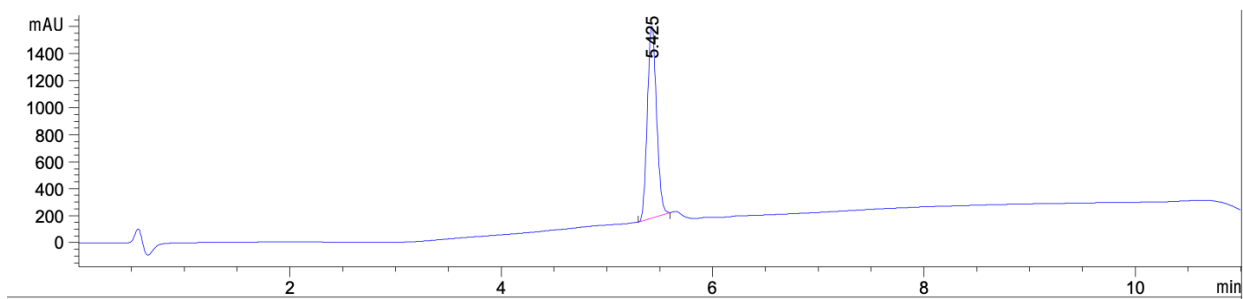
Copy of NMR of 4n



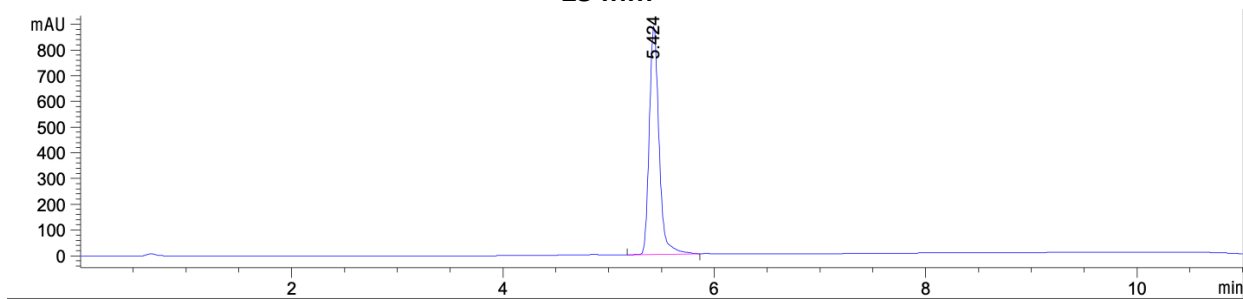


Compound 4o

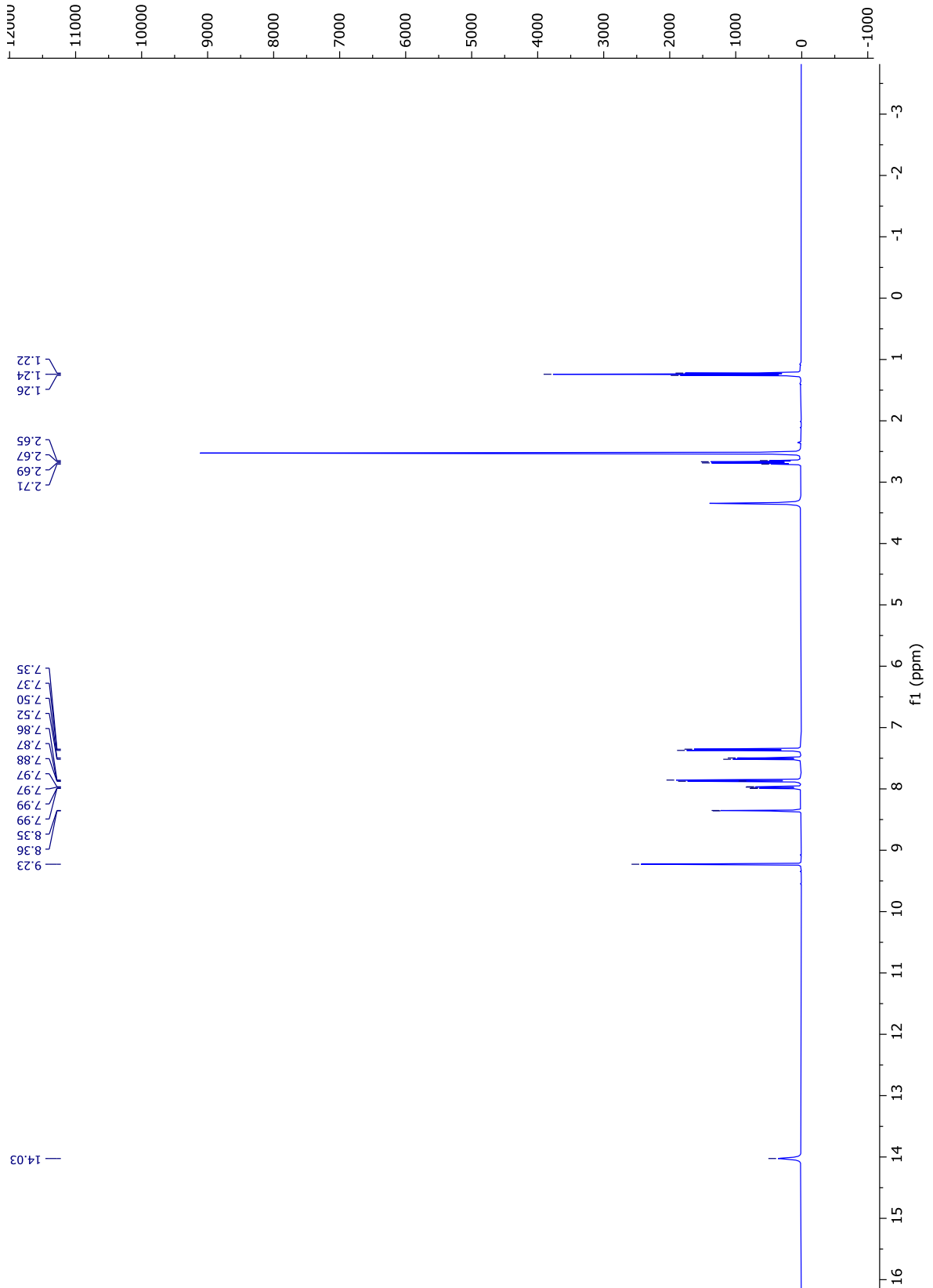
**Copy of Chromatographic Analysis of 4o  
220nm**

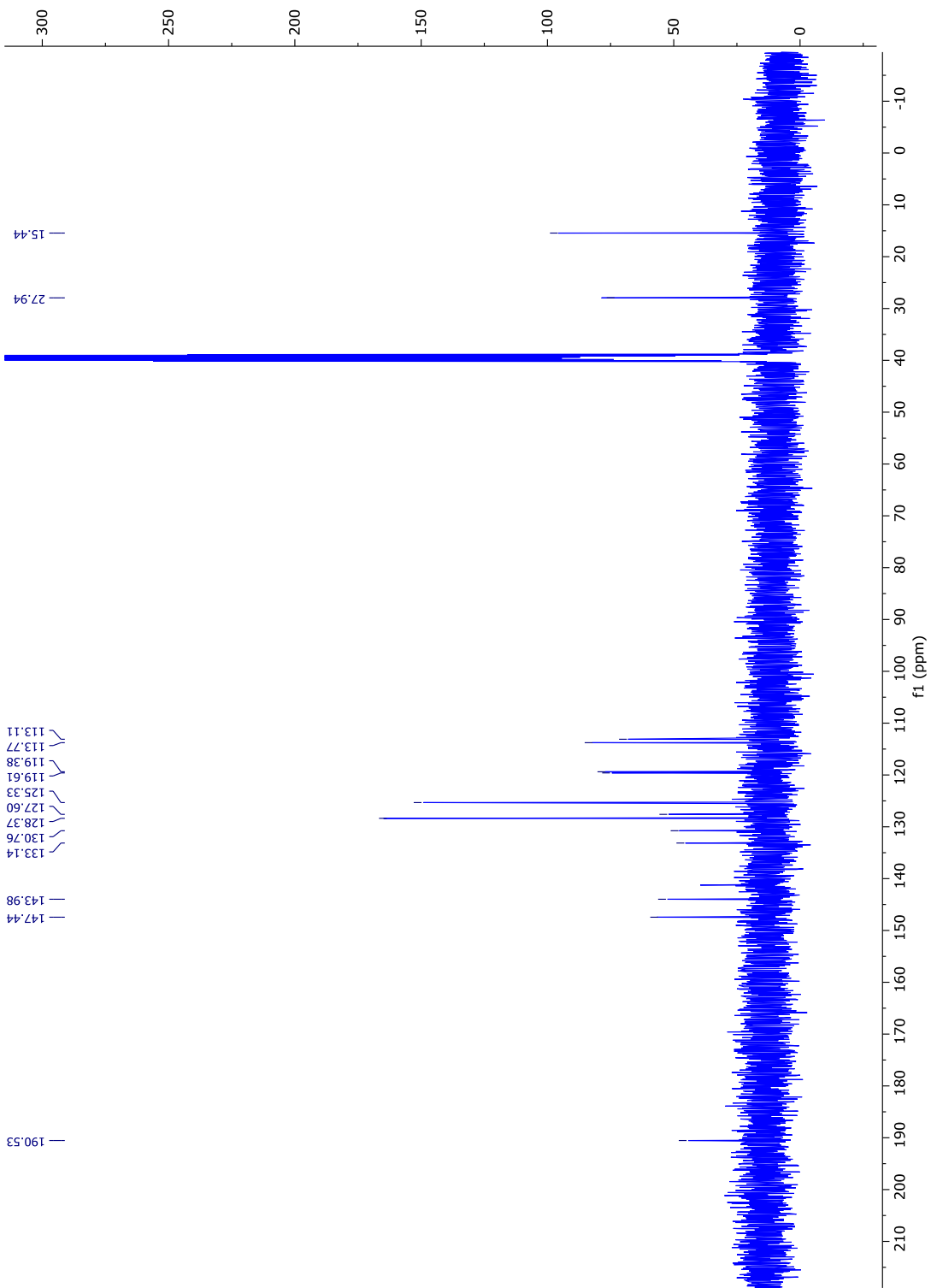


**254nm**



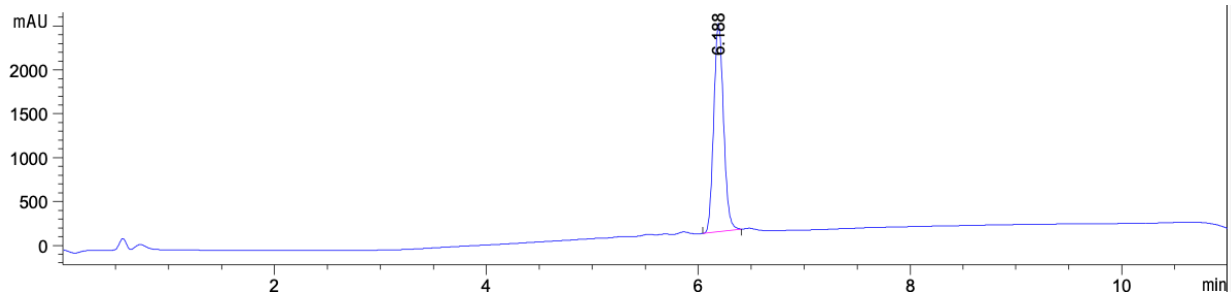
Copy of NMR of 4o



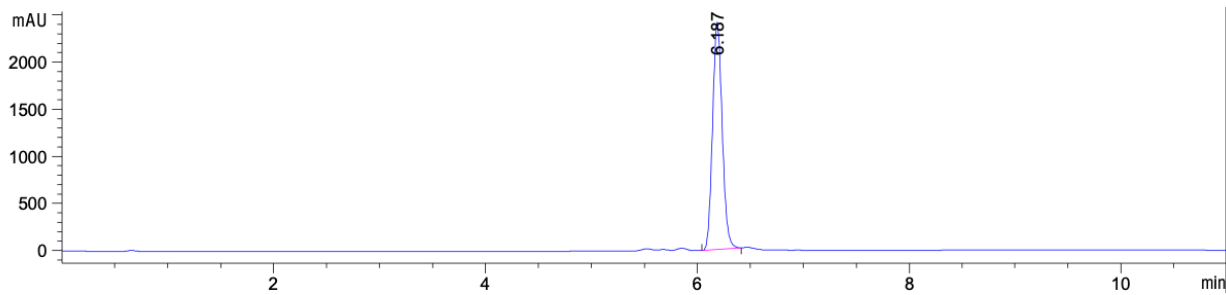


Compound **4p**

Copy of Chromatographic Analysis of **4p**  
220nm



254nm



# Copy of NMR of 4p

