A Novel Strategy for Alkylation via Amide Activation: Synthesis of *N*-Substituted 2-Pyridones and Tetrahydropyridines

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Supplementary information

Contents:

1. General Information

All reagents were sourced from Aladdin, Energy Chemical, Adamas-beta, and Bidepharm. All solvents were purchased from Chengdu Jinshan Chemical Reagent Co., Ltd. All solvents were distilled from appropriate drying agents prior to use. CH_2Cl_2 was distilled over calcium hydride under a nitrogen atmosphere and stored over 4Å MS. Tf_2O was distilled over phosphorous pentoxide (P_2O_5) and was stored for no more than a week before redistilling. Flash column chromatography was performed using silica gel (300-400 mesh). ^1H NMR and ^{13}C NMR (400 and 101 MHz, respectively) spectra were recorded on a Bruker 400 MHz NMR spectrometer in $CDCl_3$. ^1H NMR chemical shifts were reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, 7.26 ppm; DMSO-*d6*, 2.50 ppm). ^{13}C NMR chemical shifts were reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$, 77.16 ppm; DMSO-*d6*, 39.60 ppm). HRMS data were recorded on a SCIEX X500R QTOF HRMS apparatus.

2. Experimental procedure and characterization data

2.1 General procedure A for the synthesis of 2-pyridone derivatives

The amide substrate (2.0 mmol, 1.0 equiv.) was dissolved in anhydrous DCM (20.0 mL) under argon protection. Upon reaching -78 °C, 2-F-Py (2.4 mmol, 1.2 equiv.) was added, followed by the addition of Tf_2O (2.2 mmol, 1.1 equiv) and stirred for 30 minutes. The reaction temperature was then raised to 40 °C and maintained for 2 hours. Subsequently, the system was brought to room temperature, H_2O (10 mL) was introduced, and the reaction mixture continued stirring for an additional 2 hours. After completion of the reaction as monitored by TLC analysis (DCM: MeOH = 30: 1), the organic layer underwent extraction with DCM (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Column chromatography (starting gradient elution with DCM: MeOH = 150:1, using a mixture of elution agents 100 mL at a time until the target product is obtained) produces the final product.

2.2 General procedure B for the synthesis of 1,2,5,6-tetrahydropyridine derivatives

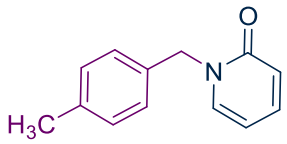
Under argon protection, the amide substrate (2.0 mmol, 1.0 equiv) is dissolved in dry dichloromethane (20 mL). Subsequently, at -78 °C, the addition of 2-F-Py (2.4 mmol, 1.2 equiv) occurs, followed by stirring for five minutes before introducing Tf_2O

(2.2 mmol, 1.1 equiv), leading to a thirty-minute stirring period at this low temperature (-78 °C). The mixture is then heated to a controlled temperature of 40 °C over a period of two hours and subsequently cooled back to room temperature. Thereupon, the addition of sodium borohydride ($NaBH_4$) (7 mmol, 3.5 equiv), followed by the addition of methanol (10 mL), initiates another 2-hour stirring process.

Throughout this procedure, monitoring is performed via thin-layer chromatography (TLC) using a solvent system consisting of dichloromethane (DCM) and methanol (MeOH) in a 30:1 ratio. The resulting organic layer is extracted three times with fresh portions of dichloromethane (10 mL each time). The combined organic phase is dried using anhydrous sodium sulfate (Na_2SO_4) and concentrated under reduced pressure to yield a crude product. This crude product is subsequently purified through column chromatography, employing a starting gradient elution composed of dichloromethane (DCM) and methanol (MeOH) in a 150: 1 ratio. Fractions are collected after passing through 100 mL of mixed eluent until the desired final compound is isolated.

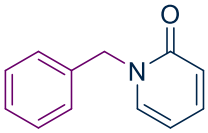
3. Characterization

1-(4-methylbenzyl) pyridin-2(1*H*)-one (**3a**)



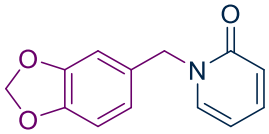
Prepared according to general procedure A; 87% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.26 (m, 1H), 7.24 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 9.1 Hz, 1H), 6.11 (td, *J* = 6.7, 1.3 Hz, 1H), 5.09 (s, 2H), 2.32 (s, 3H). **HRMS (ESI)**: calcd for $C_{13}H_{14}NO^+$(M+ H)$^+$: 200.1075, found: 200.1062.[1]

1-benzylpyridin-2(1*H*)-one (**3b**)



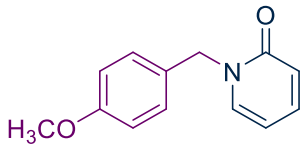
Prepared according to general procedure A; 83% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.21 (m, 6H), 6.61 (d, *J* = 9.4 Hz, 1H), 6.13 (td, *J* = 6.7, 1.4 Hz, 1H), 5.14 (s, 2H). **HRMS (ESI)**: calcd for $C_{12}H_{12}NO^+$(M+ H)$^+$: 186.0919, found: 186.0912.[1]

1-(benzo[*d*][1,3]dioxol-5-ylmethyl) pyridin-2(1*H*)-one (**3c**)



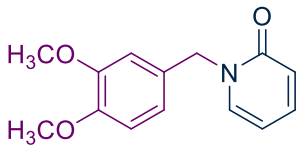
Prepared according to general procedure A; 57% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.26 (m, 2H), 6.86 – 6.75 (m, 3H), 6.67 (d, *J* = 9.0 Hz, 1H), 6.18 (t, *J* = 6.4 Hz, 1H), 5.94 (s, 2H), 5.05 (s, 2H). **HRMS (ESI)**: calcd for $C_{13}H_{12}NO_3$ $^+$(M+ H)$^+$: 230.0817, found: 230.0812.[2]

1-(4-methoxybenzyl) pyridin-2(1*H*)-one (**3d**)



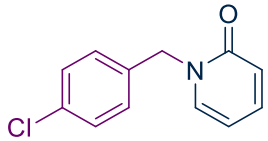
Prepared according to general procedure A; 60% yield; Pale yellow solid; m.p. 71.4 – 74.3 ℃; **^{1}H NMR (400 MHz, DMSO-*d6*)** δ 7.75 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 9.1 Hz, 1H), 6.20 (td, *J* = 6.7, 1.4 Hz, 1H), 5.01 (s, 2H), 3.72 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 161.4, 158.7, 139.9, 138.8, 129.4, 129.3, 119.8, 113.9, 105.4, 55.0, 50.4. **HRMS (ESI)**: calcd for $C_{13}H_{14}NO_2^+$(M+ H)$^+$: 216.1025, found: 216.1019.[2]

1-(3,4-dimethoxybenzyl) pyridin-2(1*H*)-one (**3e**)



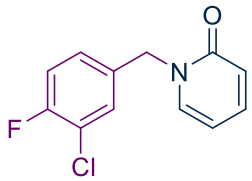
Prepared according to general procedure A; 68% yield; Yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.33 – 7.25 (m, 2H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.61 (d, *J* = 9.1 Hz, 1 H), 6.14 (td, *J* = 6.7, 1.3 Hz, 1H), 5.08 (s, 2H), 3.86 (s, 3H), 3.86 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.8, 149.5, 149.1, 139.4, 137.1, 129.0, 121.2, 120.9, 111.8, 111.4, 106.3, 56.0, 56.0, 51.7. **HRMS (ESI)**: calcd for $C_{14}H_{16}NO_3^+$(M+ H)$^+$: 246.1130, found: 246.1125.

1-(4-chlorobenzyl) pyridin-2(1*H*)-one (**3f**)



Prepared according to general procedure A; 83% yield; White solid; m.p. 61.2 – 62.8 ℃; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.32 – 7.26 (m, 3H), 7.25 – 7.20 (m, 3H), 6.58 (d, *J* = 9.2 Hz, 1H), 6.13 (td, *J* = 6.7, 1.3 Hz, 1H), 5.07 (s, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.7, 139.7, 137.2, 135.0, 134.0, 129.5, 129.1, 121.4, 106.5, 51.5. **HRMS (ESI)**: calcd for $C_{12}H_{11}ClNO^+$(M+ H)$^+$: 220.0529, found: 220.0524.[2]

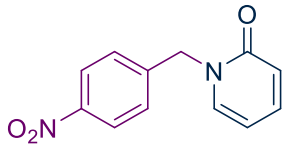
1-(3-chloro-4-fluorobenzyl) pyridin-2(1*H*)-one (**3g**)



Prepared according to general procedure A; 66% yield; Yellow oil; **^{1}H NMR (400**

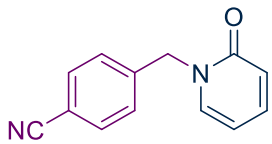
MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 2H), 7.26 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.22 – 7.17 (m, 1H), 7.10 (t, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 9.1 Hz, 1H), 6.18 (td, *J* = 6.7, 1.3 Hz, 1H), 5.07 (s, 2H). **HRMS(ESI)**: calcd for $C_{12}H_{10}ClFNO^+$(M+ H)$^+$: 238.0429, found: 238.0425.[3]

1-(4-nitrobenzyl) pyridin-2(1*H*)-one (**3h**)



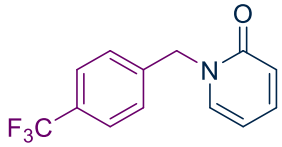
Prepared according to general procedure A; 48% yield; Pale yellow solid; m.p. 54.1 – 57.2 ℃; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.28 (dd, *J* = 6.8, 1.9 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H), 6.21 (td, *J*=6.7,1.2 Hz, 1H), 5.22 (s, 2H). **HRMS (ESI)**: calcd for $C_{12}H_{11}N_2O_3^+$ (M+ H)$^+$: 231.0770, found: 231.0764.[4]

4-((2-oxopyridin-1(2*H*)-yl) methyl) benzonitrile (**3i**)



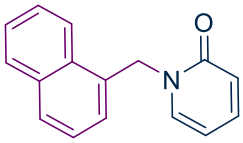
Prepared according to general procedure A; 45% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.28 – 7.26 (m, 1H), 6.63 (d, *J* = 9.2 Hz, 1H), 6.21 (td, *J* = 6.7, 1.3 Hz, 1H), 5.18 (s, 2H). **HRMS (ESI)**: calcd for $C_{13}H_{11}N_2O^+$(M+ H)$^+$: 211.0871, found: 211.0871.[1]

1-(4-(trifluoromethyl) benzyl) pyridin-2(1*H*)-one (**3j**)



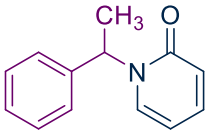
Prepared according to general procedure A; 35% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.30 – 7.23 (d, 2H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.18 (td, *J* = 6.7, 1.3 Hz, 1H), 5.18 (s, 2H). **HRMS (ESI)**: calcd for $C_{13}H_{11}F_3NO^+$(M+ H)$^+$: 254.0787, found: 254.0787.[2]

1-(naphthalen-1-ylmethyl) pyridin-2(1*H*)-one (**3k**)



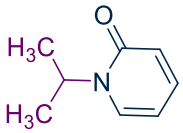
Prepared according to general procedure A; 85% yield; White solid; m.p. 140.6 – 140.7 ℃; **^{1}H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.15 (d, *J* = 7.4 Hz, 1H), 7.98 (dd, *J* = 6.9, 2.5 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.54 (m, 3H), 7.50 – 7.42 (m, 2H), 7.14 (d, *J* = 7.0 Hz, 1H), 6.51 (d, *J* = 9.2 Hz, 1H), 6.24 (td, *J* = 6.7, 1.4 Hz, 1H), 5.60 (s, 2H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 161.4, 140.1, 138.7, 133.3, 132.9, 130.5, 128.6, 128.1, 126.6, 126.1, 125.5, 125.1, 123.2, 119.9, 105.8, 48.2. **HRMS (ESI)**: calcd for $C_{16}H_{14}NO^+$ (M+ H)$^+$: 236.1070, found: 236.1066.[2]

1-(1-phenylethyl) pyridin-2(1*H*)-one (**3l**)



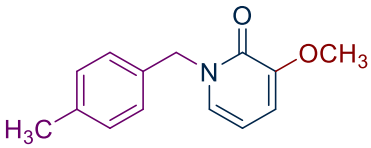
Prepared according to general procedure A; 88% yield; White solid; m.p. 68.9 – 71.2 ℃; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40 – 7.25 (m, 6H), 7.11 (dd, *J* = 7.0, 1.8 Hz, 1H), 6.61 (dd, *J* = 9.2, 0.7 Hz, 1H), 6.47 (q, *J* = 7.1 Hz, 1H), 6.11 (td, *J* = 6.8, 1.4 Hz, 1H), 1.73 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.6, 140.3, 138.9, 134.4, 128.9, 128.1, 127.6, 120.8, 106.5, 52.5, 19.1. **HRMS (ESI)**: calcd for $C_{13}H_{14}NO^+$ (M+ H)$^+$: 200.1070, found: 200.1068.[5]

1-isopropylpyridin-2(1*H*)-one (**3m**)



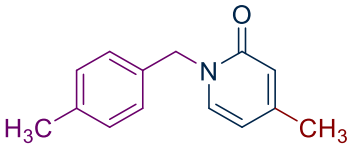
Prepared according to general procedure A; 40% yield; Yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.30 (ddt, *J* = 17.7, 6.6, 2.8 Hz, 2H), 6.56 (d, *J* = 9.1 Hz, 1H), 6.22 (t, *J* = 6.7 Hz, 1H), 5.28 (hept, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 162.36, 138.55, 132.70, 120.76, 106.33, 46.10, 21.96. **HRMS (ESI)**: calcd for $C_8H_{12}NO^+$ (M+ Na)$^+$: 160.0738, found: 160.0733.[6]

3-methoxy-1-(4-methylbenzyl) pyridin-2(1*H*)-one (**3n**)



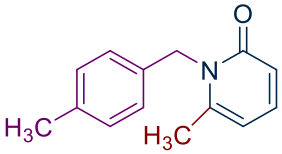
Prepared according to general procedure A; 65% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 7.9 Hz,2H), 6.86 (d, *J* = 7.0 Hz, 1H), 6.56 (d, *J* = 7.4 Hz, 1H), 6.05 (t, *J* = 7.2 Hz, 1H), 5.12 (s, 2H), 3.79 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.3, 150.3, 137.8, 133.6, 129.5, 128.4, 127.9, 112.0, 105.0, 56.0, 51.7, 21.2. **HRMS (ESI)**: calcd for $C_{14}H_{16}NO_2^+$ $(M+H)^+$: 230.1176, found: 230.1175.

4-methyl-1-(4-methylbenzyl) pyridin-2(1*H*)-one (**3o**)



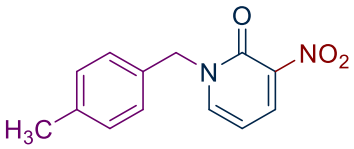
Prepared according to general procedure A; 70% yield; White solid; m.p. 67.3 – 68.5 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.20 – 7.10 (m, 5H), 6.41 (s, 1H), 5.97 (dd, *J* = 7.0, 1.9 Hz, 1H), 5.06 (s, 2H), 2.32 (s, 3H), 2.15 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 162.7, 151.0, 137.7, 136.0, 133.6, 129.5, 128.1, 119.4, 108.8, 51.1, 21.2, 21.1. **HRMS (ESI)**: calcd for $C_{14}H_{16}NO^+$ $(M+H)^+$: 214.1226, found: 214.1221.

6-methyl-1-(4-methylbenzyl) pyridin-2(1*H*)-one (**3p**)



Prepared according to general procedure A; 65% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.16 – 7.08 (m, 3H), 6.41 (s, 1H), 5.97 (dd, *J* = 7.0, 1.9 Hz, 1H), 5.06 (s, 2H), 2.32 (s, 3H), 2.15 (s, 3H). **HRMS (ESI)**: calcd for $C_{14}H_{16}NO^+$$(M+H)^+$: 214.1226, found: 214.1221.[7]

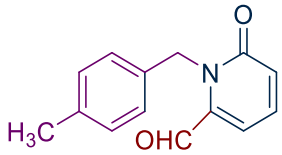
1-(4-methylbenzyl)-3-nitropyridin-2(1*H*)-one (**3q**)



Prepared according to general procedure A; 83% yield; Yellow solid; m.p. 95.7 –

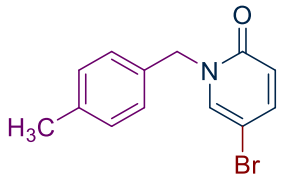
97.8 °C; **^{1}H NMR (400 MHz, DMSO-*d6*)** δ 8.40 (dd, *J* = 7.7, 2.1 Hz, 1H), 8.34 (dd, *J* = 6.6, 2.1 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.46 (dd, *J* = 7.6, 6.7 Hz, 1H), 5.18 (s, 2H), 2.27 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 153.7, 146.0, 138.9, 138.4, 137.3, 133.1, 129.2, 128.1, 103.7, 52.2, 20.7. **HRMS (ESI)**: calcd for $C_{13}H_{13}N_2O_3^+$(M+ H)$^+$: 245.0921, found: 245.0926.

1-(4-methylbenzyl)-6-oxo-1,6-dihydropyridine-2-carbaldehyde (**3r**)



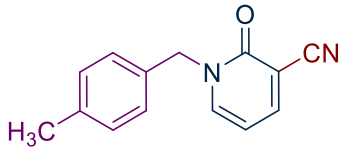
Prepared according to general procedure A; 37% yield; Yellow solid; m.p. 195.6 –198.2 °C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 10.36 (s, 1H), 8.01 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.59 (dd, *J* = 6.6, 1.5 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.29 (t, *J* = 6.9 Hz, 1H), 5.15 (s, 2H), 2.34 (s, 3H). **HRMS (ESI)**: calcd for $C_{14}H_{14}NO_2^+$(M+ H)$^+$: 228.1025, found: 228.1018.

5-bromo-1-(4-methylbenzyl) pyridin-2(1*H*)-one (**3s**)



Prepared according to general procedure A; 85% yield; Pale yellow solid; m.p. 76.5 - 80.3 °C; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.35 (d, *J* = 2.7 Hz, 1H), 7.31 (dd, *J* = 9.6, 2.7 Hz, 1H), 7.18 (q, *J* = 8.2 Hz,4H),5.05(s, 2H),2.34(s, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ 161.2, 142.5, 138.4, 137.0, 132.8, 129.8, 128.5, 122.5, 98.2, 52.0, 21.3; **HRMS (ESI)**: calcd for $C_{13}H_{13}BrNO^+$(M+ H)$^+$: 278.0175, found; 278.0175.[8]

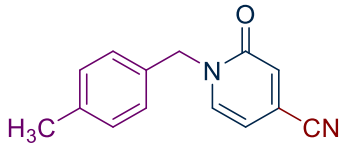
1-(4-methylbenzyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (**3t**)



Prepared according to general procedure A; 75% yield; Pink solid; m.p. 137.7 – 139.4 °C; **^{1}H NMR (400 MHz, DMSO-*d6*)** δ 8.22 (dd, *J* = 6.7, 2.1 Hz, 1H), 8.15 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.43 (t, *J* = 7.0 Hz, 1H), 5.11 (s, 2H), 2.27 (s, 3H). **^{13}C NMR (101 MHz, DMSO-*d6*)** δ 159.2, 148.5,

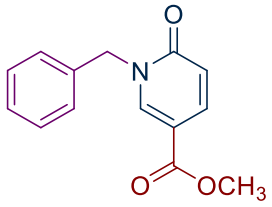
145.1, 137.3, 133.2, 129.2, 128.0, 116.3, 105.7, 103.2, 52.0, 20.7. **HRMS (ESI)**: calcd for $C_{14}H_{13}N_2O^+$(M+ H)$^+$: 225.1022, found: 225.1018.

1-(4-methylbenzyl)-2-oxo-1,2-dihydropyridine-4-carbonitrile (**3u**)



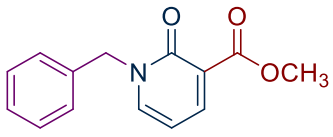
Prepared according to general procedure A; 35% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (d, *J* = 7.0 Hz, 1H), 7.18 (s, 4H), 6.92 (d, *J* = 1.2 Hz, 1H), 6.22 (dd, *J* = 7.0, 1.9 Hz, 1H), 5.08 (s, 2H), 2.34 (s, 3H). **HRMS (ESI)**: calcd for $C_{14}H_{13}N_2O^+$(M+ H)$^+$: 225.1022, found: 225.1018.

methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate (**3v**)



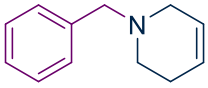
Prepared according to general procedure A; 62% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.18 (d, *J* = 2.5 Hz, 1H), 7.82 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.40 – 7.26 (m, 5H), 6.56 (d, *J* = 8.9 Hz, 1H), 5.16 (s, 2H), 3.82 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.6, 162.4, 142.7, 138.5, 135.5, 129.7, 128.4, 128.2, 120.0, 110.7, 52.7, 52.1. **HRMS (ESI)**: calcd for $C_{14}H_{14}NO_3^+$(M+ H)$^+$: 244.0968, found: 244.0970.

methyl 1-benzyl-2-oxo-1, 2-dihydropyridine-3-carboxylate (**3w**)



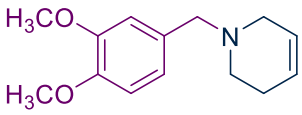
Prepared according to general procedure A; 57% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.13 (dd, J = 7.2, 2.2 Hz, 1H), 7.52 (dd, J = 6.7, 2.2 Hz, 1H), 7.38 – 7.25 (m, 5H), 6.21 (t, J = 6.9 Hz, 1H), 5.17 (s, 2H), 3.89 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.9, 159.4, 144.9, 142.1, 135.8, 129.0, 128.5, 128.3, 121.1, 104.9, 52.6, 52.4. **HRMS (ESI)**: calcd for $C_{14}H_{14}NO_3$+(M+ H)+: 244.0968, found: 244.0966.

1-benzyl-1,2,5,6-tetrahydropyridine (**4a**)



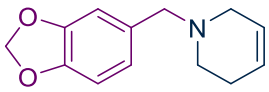
Prepared according to general procedure B; 70% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.22 (m, 5H), 5.80 – 5.72 (m, 1H), 5.70 – 5.63 (m, 1H), 3.59 (s, 2H), 3.07 – 2.87 (m, 2H), 2.57 (t, *J* = 5.7 Hz, 2H), 2.23 – 2.11 (m, 2H). **HRMS (ESI)**: calcd for $C_{12}H_{16}N^+$(M+ H)$^+$: 174.1283, found: 174.1281.[9]

1-(3,4-dimethoxybenzyl)-1,2,5,6-tetrahydropyridine (**4b**)



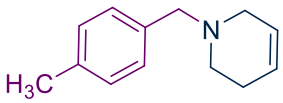
Prepared according to general procedure B; 68% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.04 (d, *J* = 1.9 Hz, 1H), 6.88 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.88 – 5.81 (m, 1H), 5.70 – 5.62 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.82 (s, 2H), 3.29 – 3.21 (m, 2H), 2.87 (t, *J* = 5.9 Hz, 2H), 2.34 – 2.27 (m, 2H). **HRMS (ESI)**: calcd for $C_{14}H_{20}NO_2^+$(M+ H)$^+$: 234.1494, found: 234.1499.

1-(benzo[*d*][1,3]dioxol-5-ylmethyl)-1,2,5,6-tetrahydropyridine (**4c**)



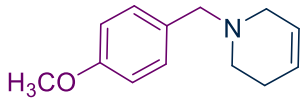
Prepared according to general procedure B; 85% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 (d, *J* = 1.4 Hz, 1H), 7.12 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.01 (s, 2H), 5.99 (s, 1H), 5.68 (d, *J* = 10.3 Hz, 1H), 4.22 (dd, *J* = 13.0, 5.1 Hz, 1H), 4.17 – 4.06 (m, 1H), 3.76 (d, *J* = 13.7 Hz, 1H), 3.54 – 3.44 (m, 1H), 3.36 (d, *J* = 16.5 Hz, 1H), 3.07 – 2.82 (m, 2H), 2.34 (d, *J* = 18.4 Hz, 1H). **^{13}C NMR (101 MHz, DMSO-*d*6)** δ 147.70, 146.59, 132.82, 126.01, 125.28, 122.27, 109.42, 108.26, 101.21, 62.11, 52.55, 49.52, 26.22. **HRMS (ESI)**: calcd for $C_{13}H_{16}NO_2^+$(M+ H)$^+$: 218.1181, found: 218.1171.

1-(4-methylbenzyl)-1,2,5,6-tetrahydropyridine (**4d**)



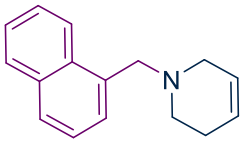
Prepared according to general procedure B; 85% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 (d, 2H), 7.13 (d, J = 6.8 Hz, 2H), 5.80 – 5.72 (m, 1H), 5.71 – 5.63 (m, 1H), 3.56 (s, 2H), 2.97 (dd, J = 5.0, 2.7 Hz, 2H), 2.56 (td, J = 5.7, 2.6 Hz, 2H), 2.35 (s, 3H), 2.20 – 2.13 (m, 2H). **HRMS (ESI)**: calcd for $C_{13}H_{18}N^+$(M+ H $)^+$: 188.1439, found: 188.1427.

1-(4-methoxybenzyl)-1,2,5,6-tetrahydropyridine (**4e**)



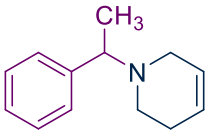
Prepared according to general procedure B; 88% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.80 – 5.71 (m, 1H), 5.69 – 5.60 (m, 1H), 3.80 (s, 3H), 3.52 (s, 2H), 2.95 (dt, *J* = 5.6, 2.9 Hz, 2H), 2.54 (t, *J* = 5.7 Hz, 2H), 2.22 – 2.10 (m, 2H). **HRMS (ESI)**: calcd for $C_{13}H_{18}NO^+$(M+ H $)^+$: 204.1383, found: 204.1385.[10]

1-(naphthalen-1-ylmethyl)-1,2,5,6-tetrahydropyridine (**4f**)



Prepared according to general procedure B; 57% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.33 (d, *J* = 8.0 Hz, 1H), 7.86 (t, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.40 (m, 4H), 5.83 – 5.63 (m, 2H), 4.00 (s, 2H), 3.11 – 3.04 (m, 2H), 2.66 (t, *J* = 5.7 Hz, 2H), 2.22 – 2.13 (m, 2H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 134.4, 134.0, 132.7, 128.5, 127.9, 127.3, 125.9, 125.7, 125.6, 125.4, 125.3, 124.8, 61.0, 53.3, 50.1, 26.4. **HRMS (ESI)**: calcd for $C_{16}H_{18}N^+$ (M+ H $)^+$: 224.1434, found: 224.1425.

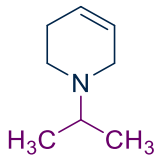
1-(1-phenylethyl)-1,2,5,6-tetrahydropyridine (**4g**)



Prepared according to general procedure B; 52% yield; Yellow oil; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.24 (m, 5H), 5.81 – 5.65 (m, 2H), 3.47 (q, *J* = 6.7 Hz, 1H), 3.20 (d, *J* = 16.2 Hz, 1H), 2.95 – 2.86 (m, 1H), 2.63 (td, *J* = 11.0, 5.6 Hz, 1H), 2.47 – 2.38 (m, 1H), 2.25 – 2.02 (m, 2H), 1.44 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR (101 MHz,**

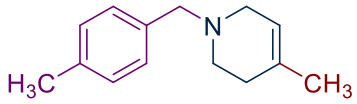
CDCl$_3$) δ 144.2, 128.4, 127.8, 127.0, 125.7, 125.4, 65.1, 50.5, 47.4, 26.6, 20.2. **HRMS (ESI)**: calcd for $C_{13}H_{18}N^+$ (M+ H)$^+$: 188.1434, found: 188.1429.

1-isopropyl-1,2,5,6-tetrahydropyridine (**4h**)



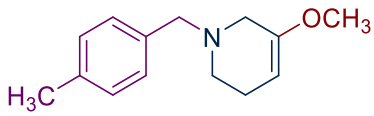
Prepared according to general procedure B; 87% yield; Yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.40 (s, 2H), 3.34 (s, 1H), 3.05 (s, 2H), 1.42 (d, *J* = 6.7 Hz, 1H), 1.37 (s, 3H), 1.37 (s, 2H), 1.35 (s, 3H), 1.35 (s, 1H). **HRMS (ESI)**: calcd for $C_8H_{16}N^+$ (M+ H)$^+$: 126.1277,found: 126.1280.[11]

4-methyl-1-(4-methylbenzyl)-1,2,5,6-tetrahydropyridine (**4i**)



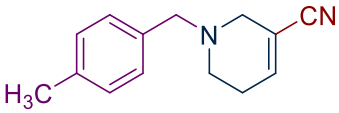
Prepared according to general procedure B; 78% yield; Yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.19 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.7 Hz, 2H), 5.31 (td, *J* = 3.4, 1.8 Hz, 1H), 3.47 (s, 2H), 2.88 (q, *J* = 2.6 Hz, 2H), 2.49 (t, *J* = 5.8 Hz, 2H), 2.29 (s, 3H), 2.01 (q, *J* = 5.6, 5.0 Hz, 2H), 1.63 (s, 3H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 136.55, 135.43, 132.68, 129.26, 128.95, 119.50, 62.66, 53.00, 49.94, 30.94, 23.03, 21.18. **HRMS (ESI)**: calcd for $C_{14}H_{20}N^+$ (M+ H)$^+$: 202.1596, found: 202.1590.

5-methoxy-1-(4-methylbenzyl)-1,2,5,6-tetrahydropyridine (**4j**)



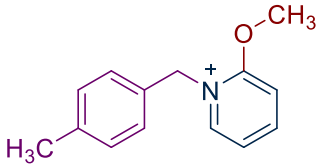
Prepared according to general procedure B; 60% yield; Yellow oil; **^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.27 (d, *J* = 7.8 Hz,2H), 7.16 (d, *J* = 7.8 Hz,2H), 4.69 (s, 1H), 3.60 (s2H), 3.54 (s,3H), 2.96 (s,2H), 2.55 (t, *J* = 5.7 Hz2H), 2.37 (s,3H), 2.21 (d, *J* = 5.3 Hz, 2H). **^{13}C NMR (101 MHz, CDCl$_3$)** δ 153.2, 136.7, 134.9, 129.2, 129.0, 91.1, 62.1, 54.1, 53.9, 50.0, 23.7, 21.1. **HRMS (ESI)**: calcd for $C_{14}H_{20}NO^+$ (M+ H)$^+$: 218.1539, found: 218.1534.

1-(4-methylbenzyl)-1,2,5,6-tetrahydropyridine-3-carbonitrile (**4k**)



Prepared according to general procedure B; 43% yield; Yellow oil; **^{1}H NMR (400 MHz, DMSO-*d6*)** δ 8.66 (s, 1H), 7.35 (t, *J* = 9.9 Hz, 2H), 7.25 (t, 2H), 4.16 – 3.94 (m, 2H), 3.75 (s, 2H), 3.07 (d, *J* = 81.4 Hz, 2H), 2.32 (s, 3H), 1.98 – 1.71 (m, 2H). **HRMS (ESI)**: calcd for $C_{14}H_{17}N_2^+$(M+ H)$^+$: 213.1386, found: 213.1376.

Intermediate Compounds **10**



^{1}H NMR (400 MHz, CDCl$_3$) δ 8.42 (dd, *J* = 6.4, 1.8 Hz, 1H), 8.31 (ddd, *J* = 9.1, 7.4, 1.9 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.46 – 7.34 (m, 1H), 7.21 – 7.17 (m, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 5.48 (s, 2H), 4.25 (s, 3H), 2.27 (s, 3H). **HRMS (ESI)**: calcd for $C_{14}H_{16}NO^+$ (M)$^+$: 214.1226, found: 214.1238.

4. References

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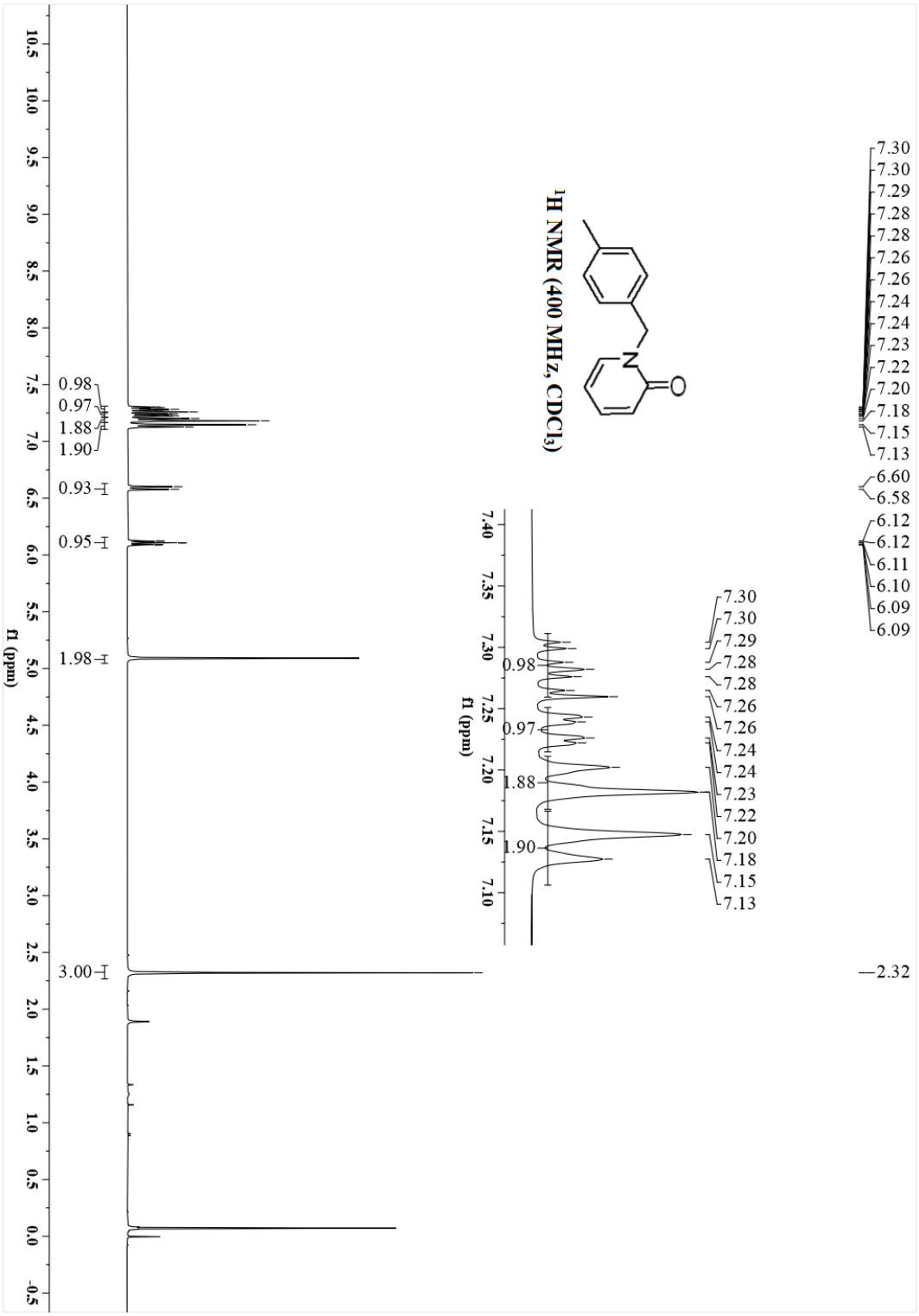
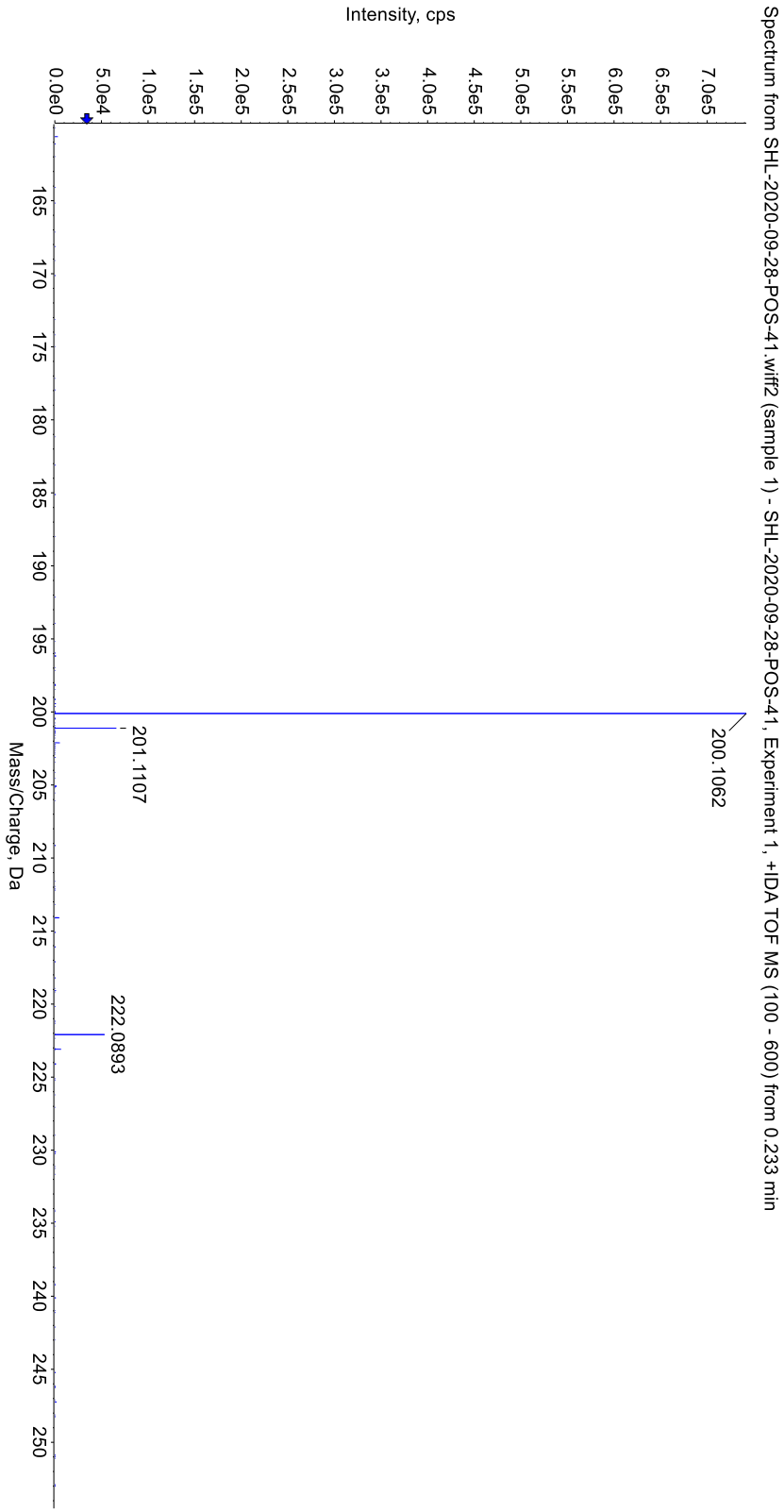
5. ^{1}H, ^{13}C NMR and HRMS spectra

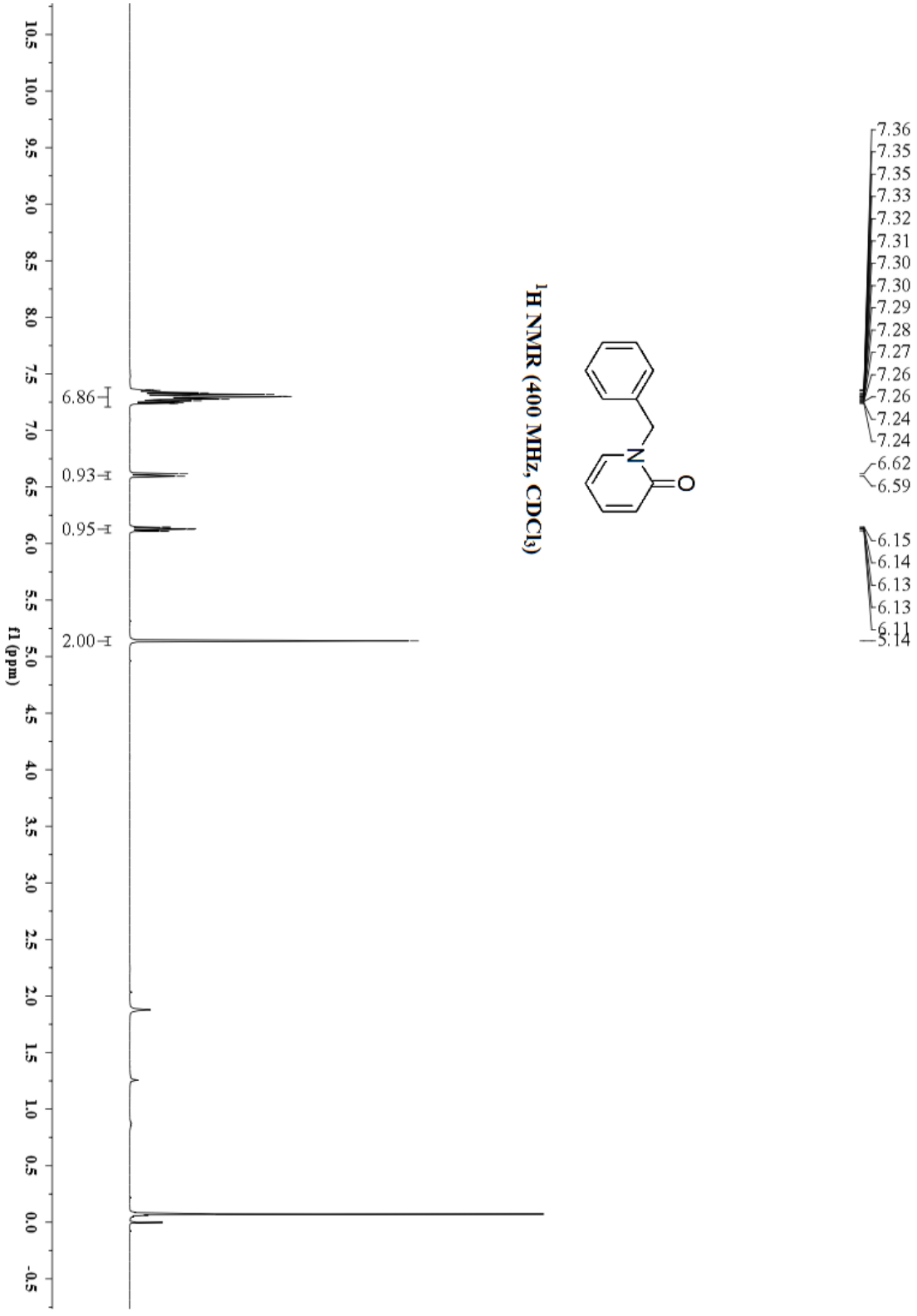
^{1}H NMR spectra of **3a**



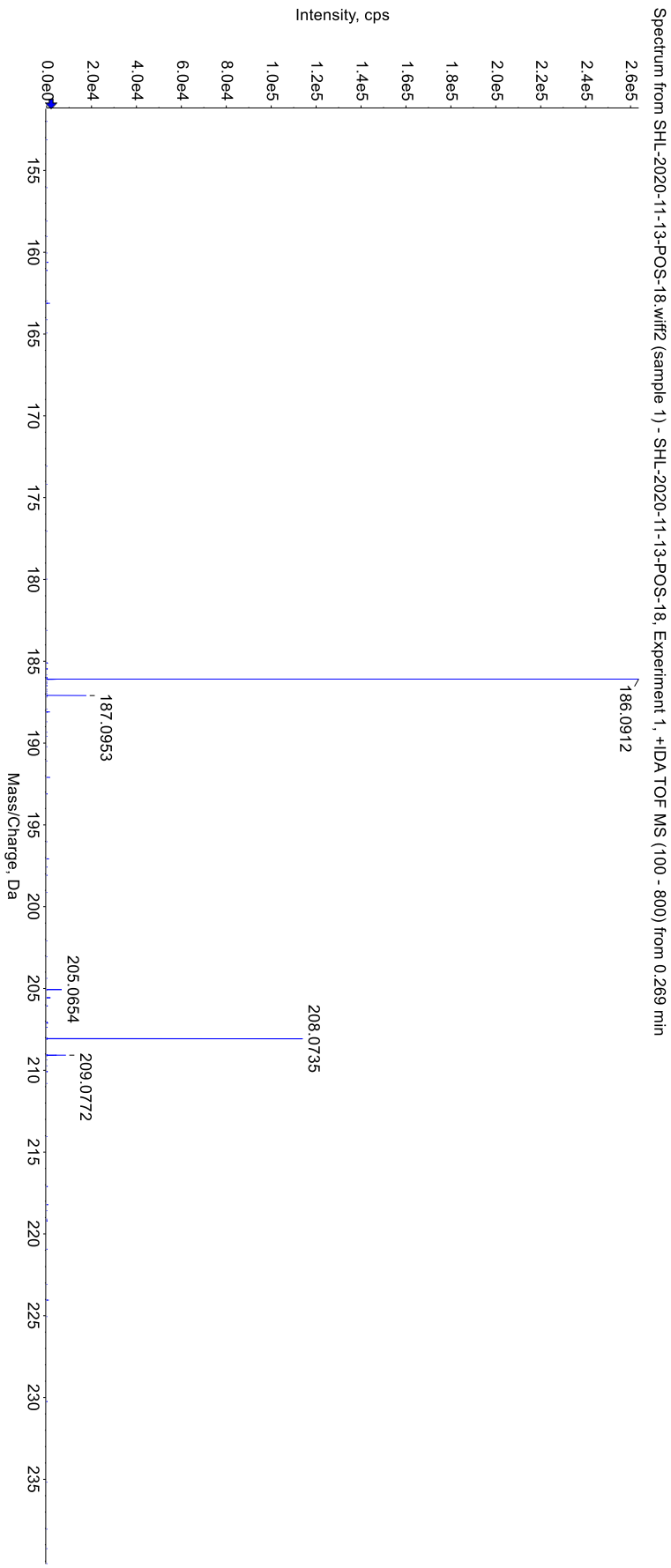
HRMS spectra of **3a**



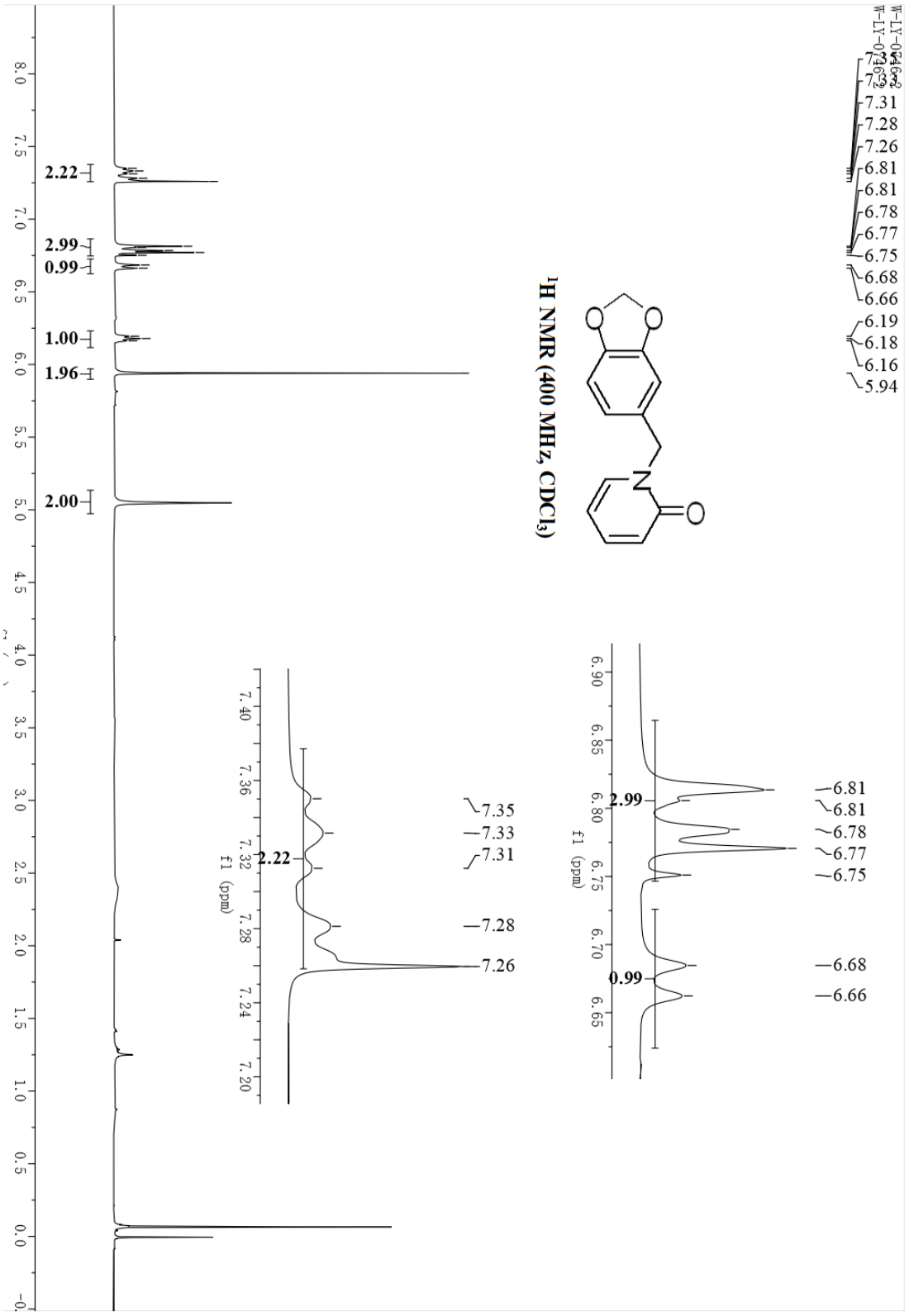
^{1}H NMR spectra of **3b**



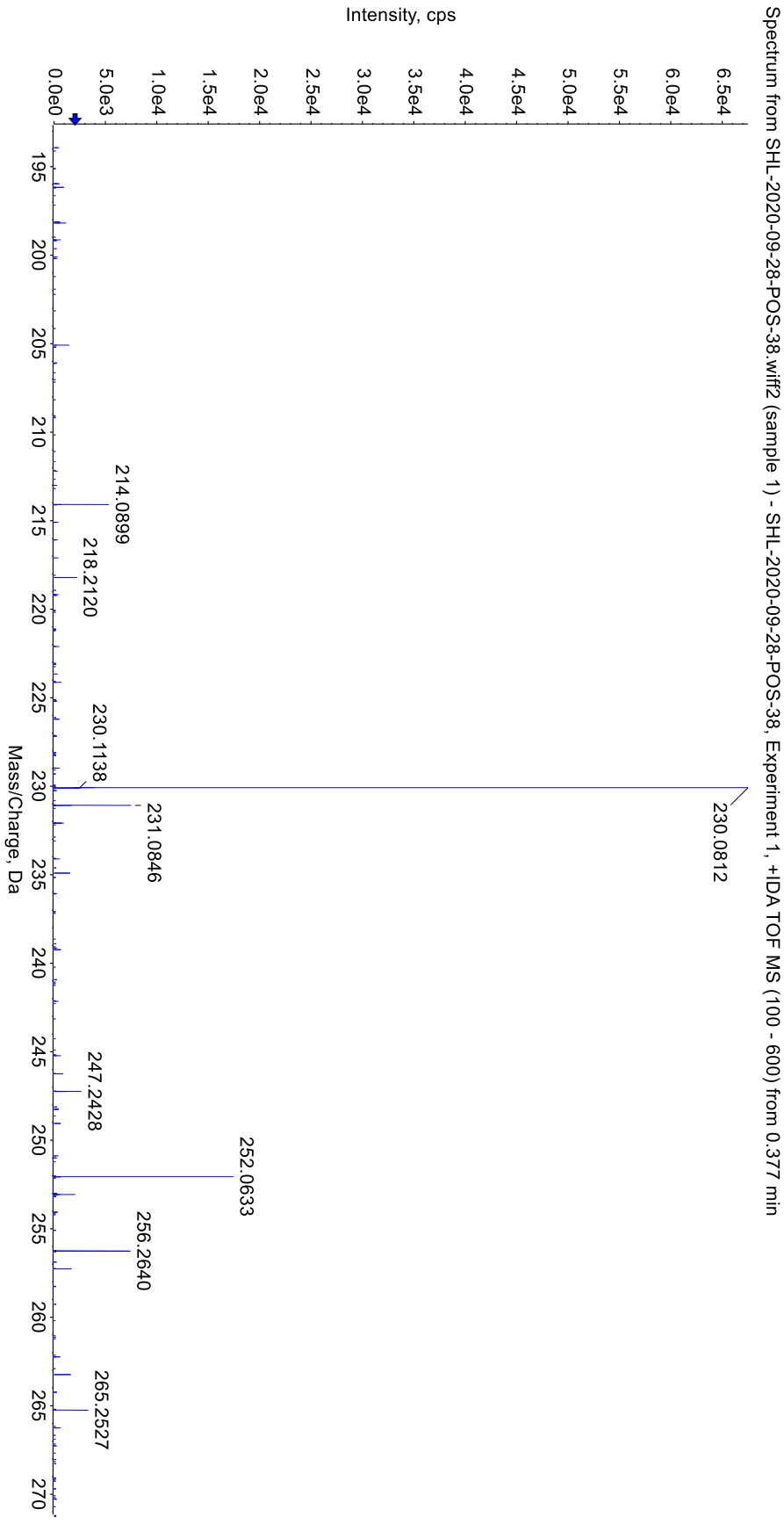
HRMS spectra of **3b**



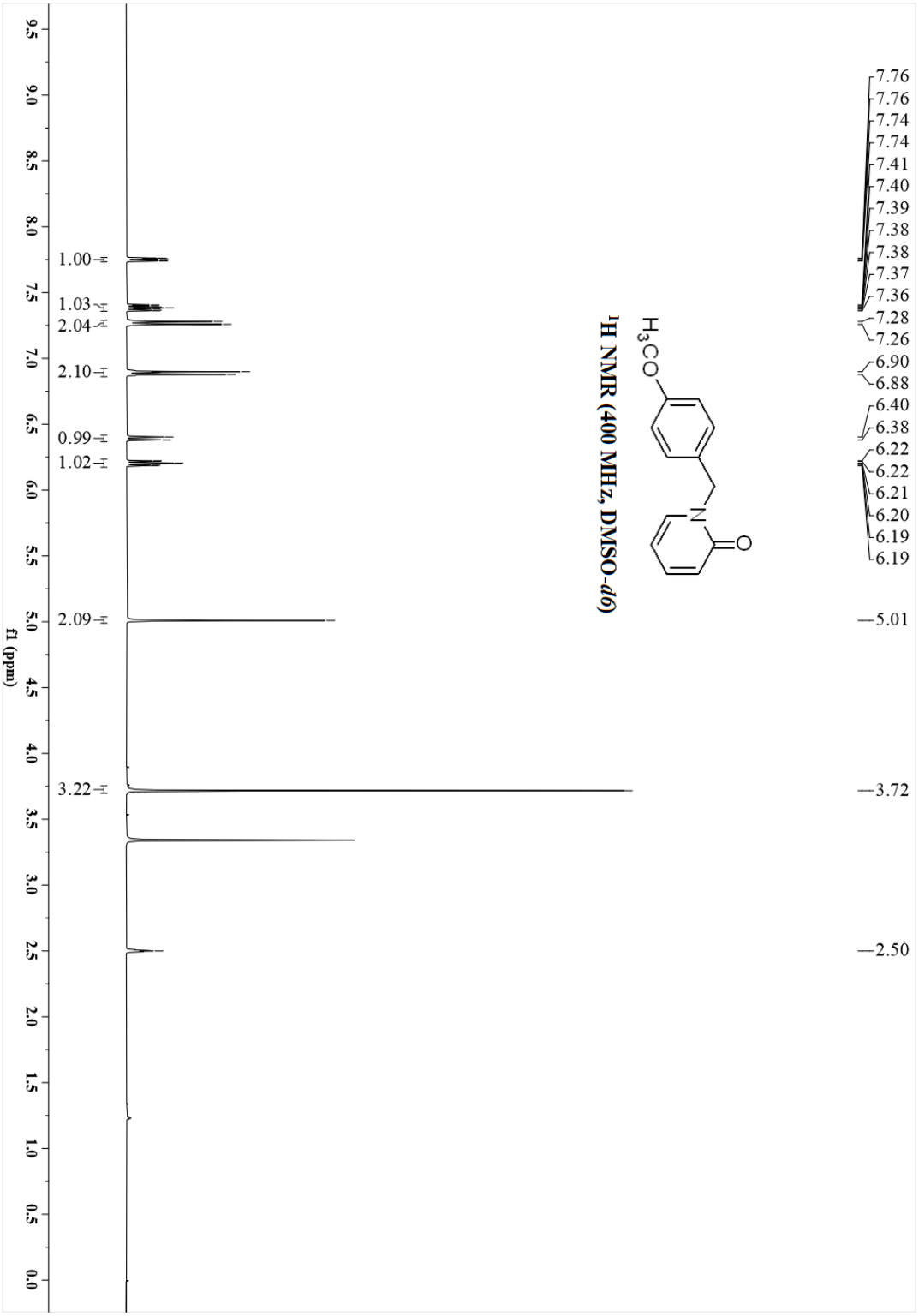
^{1}H NMR spectra of **3c**



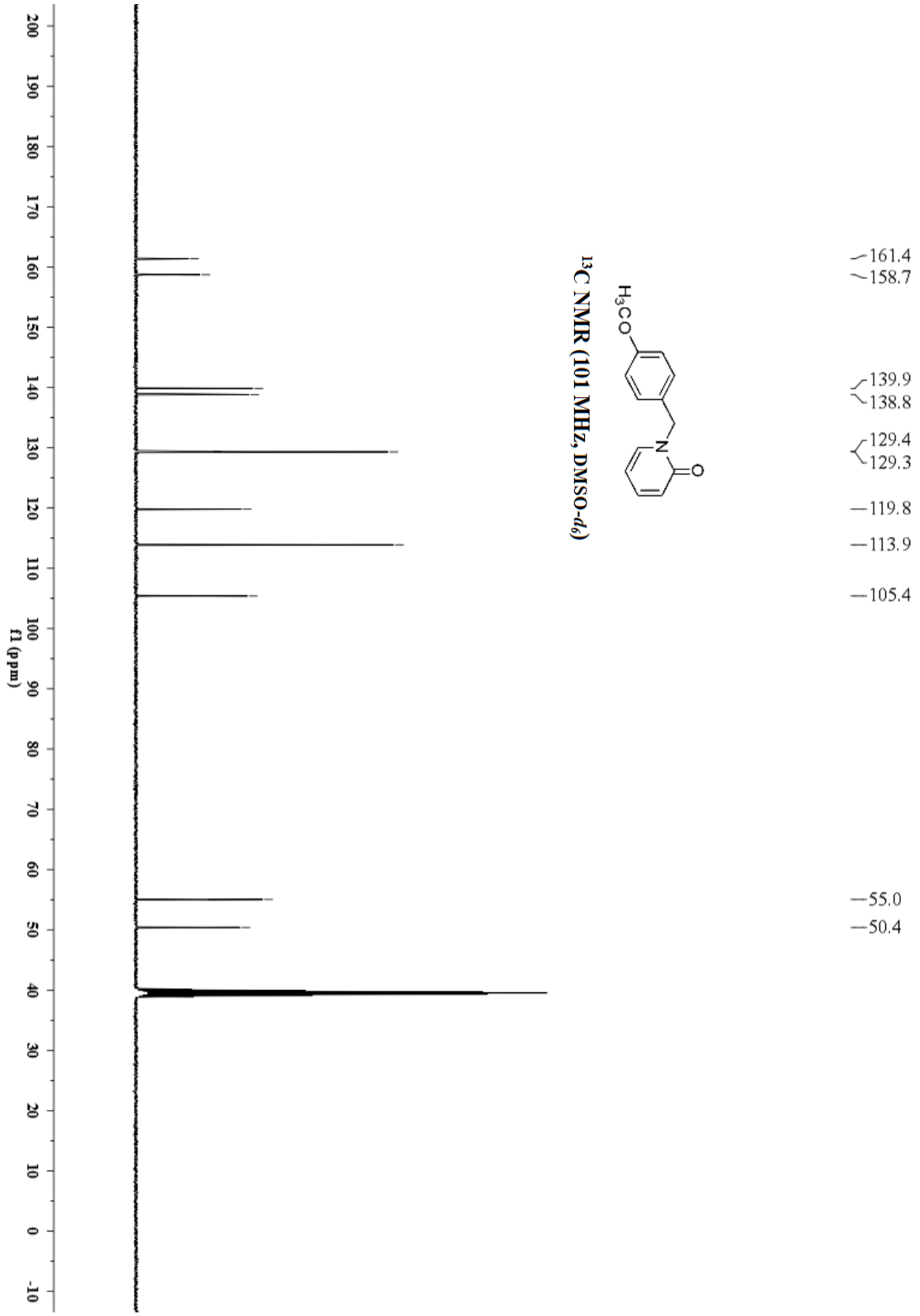
HRMS spectra of **3c**



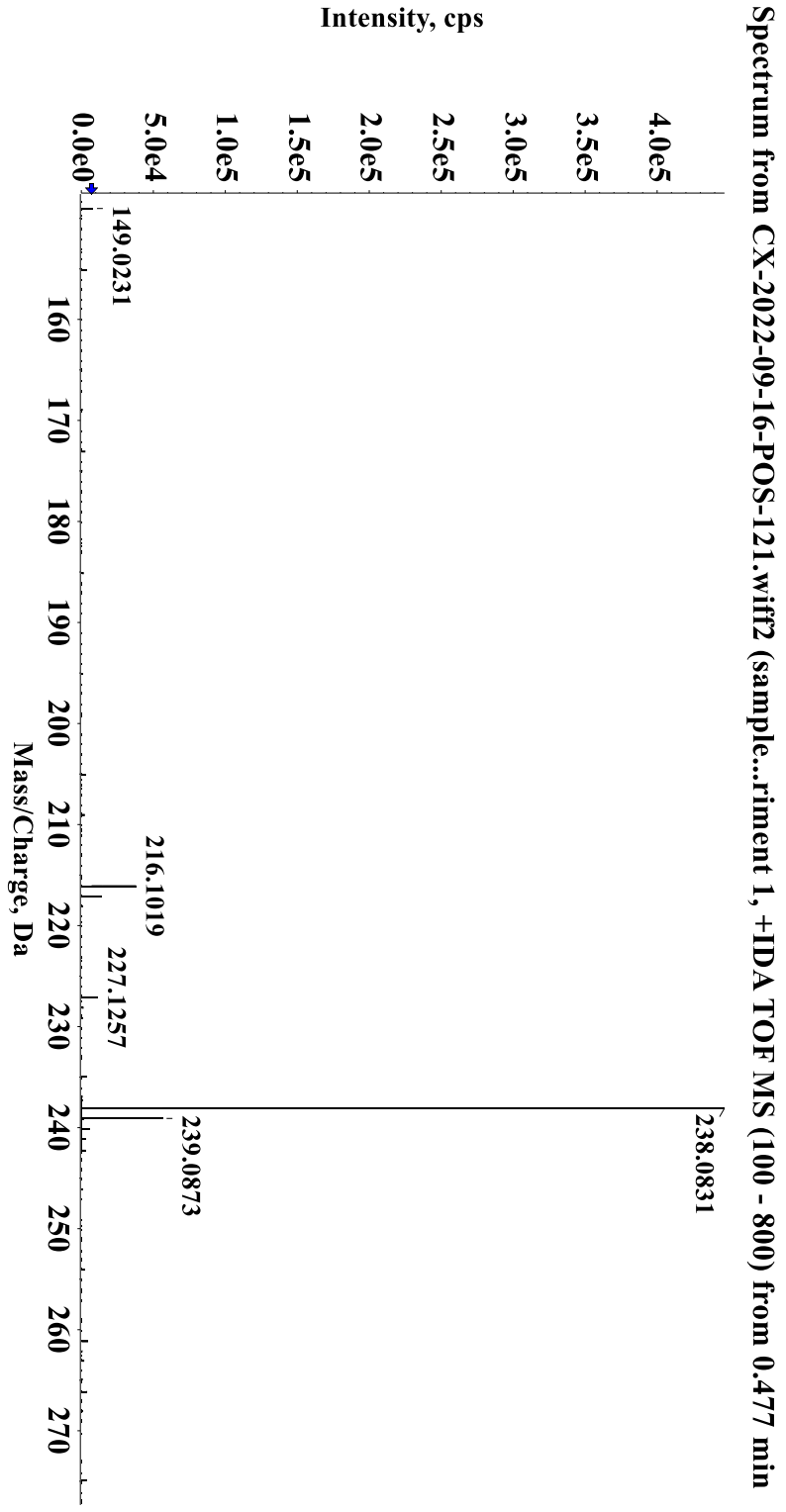
^{1}H NMR spectra of **3d**



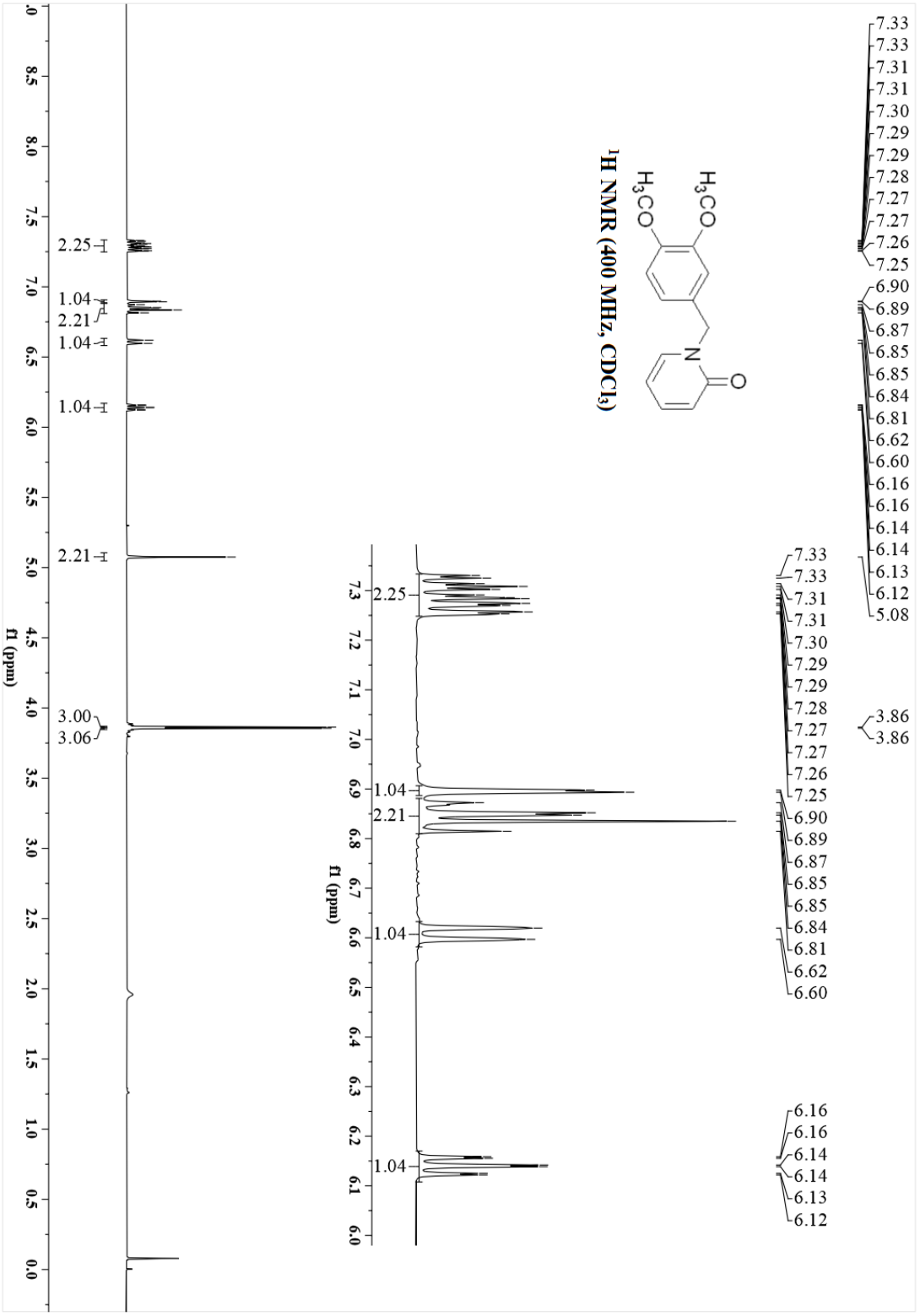
^{13}C NMR spectra of **3d**



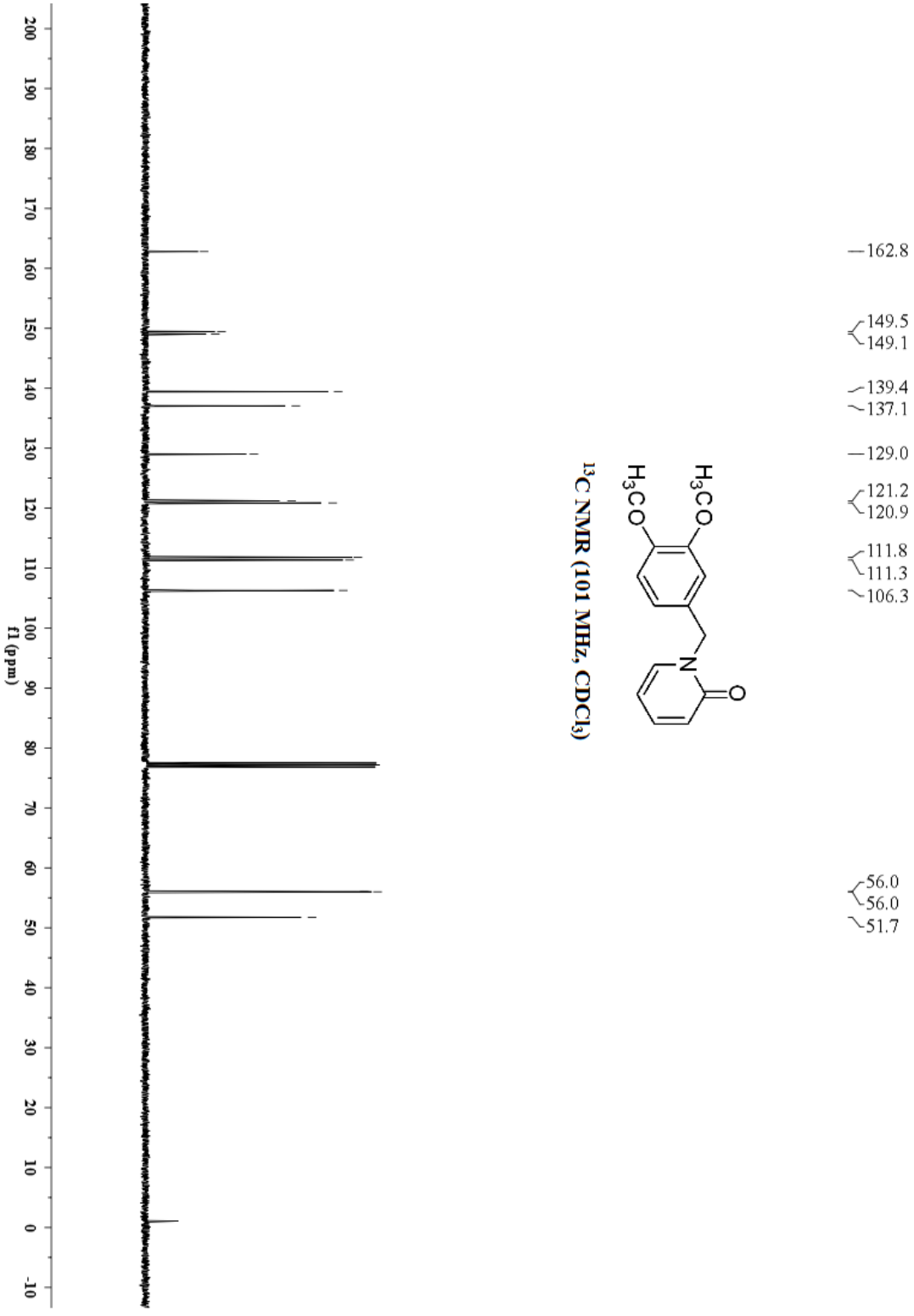
HRMS spectra of **3d**



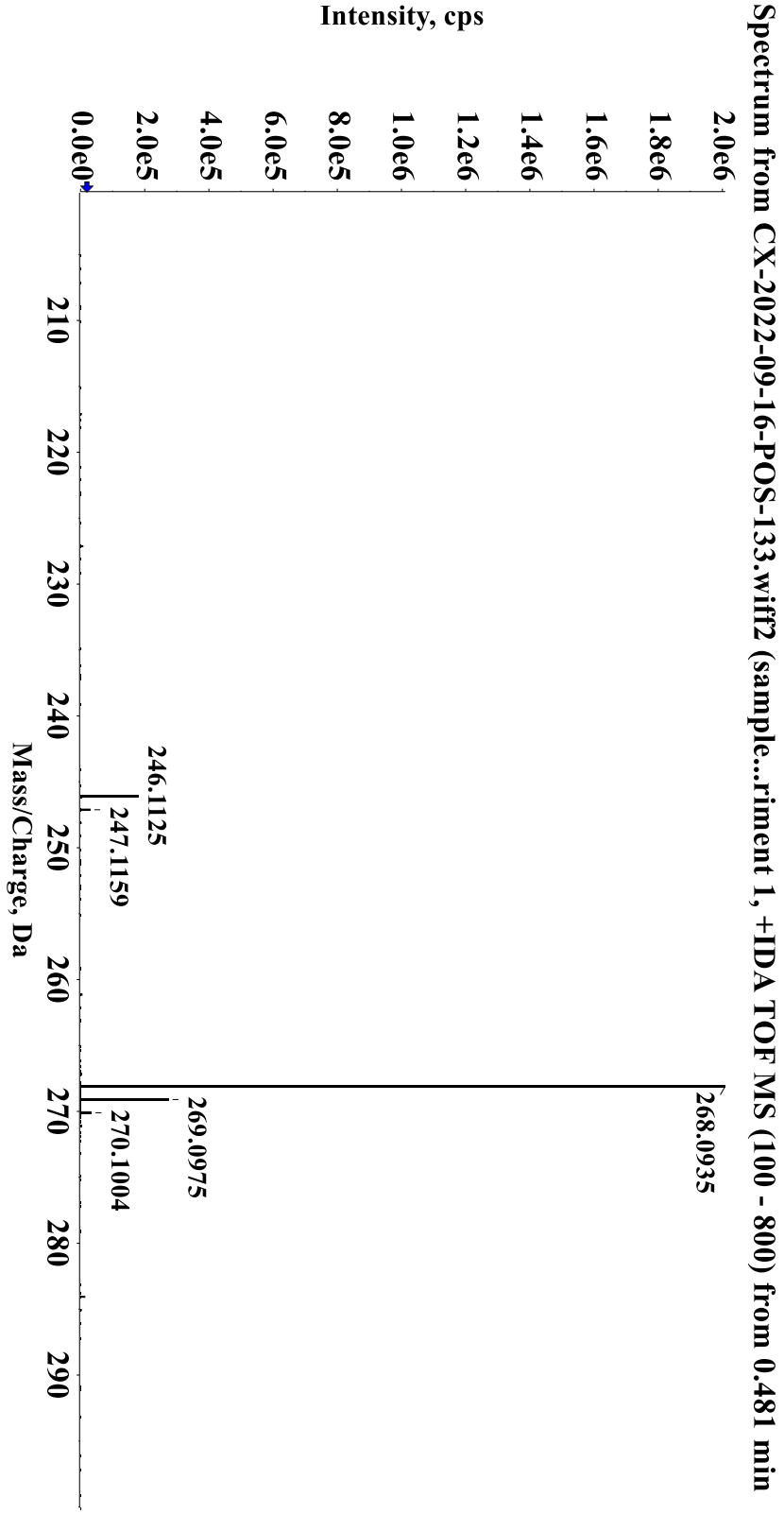
^{1}H NMR spectra of **3e**



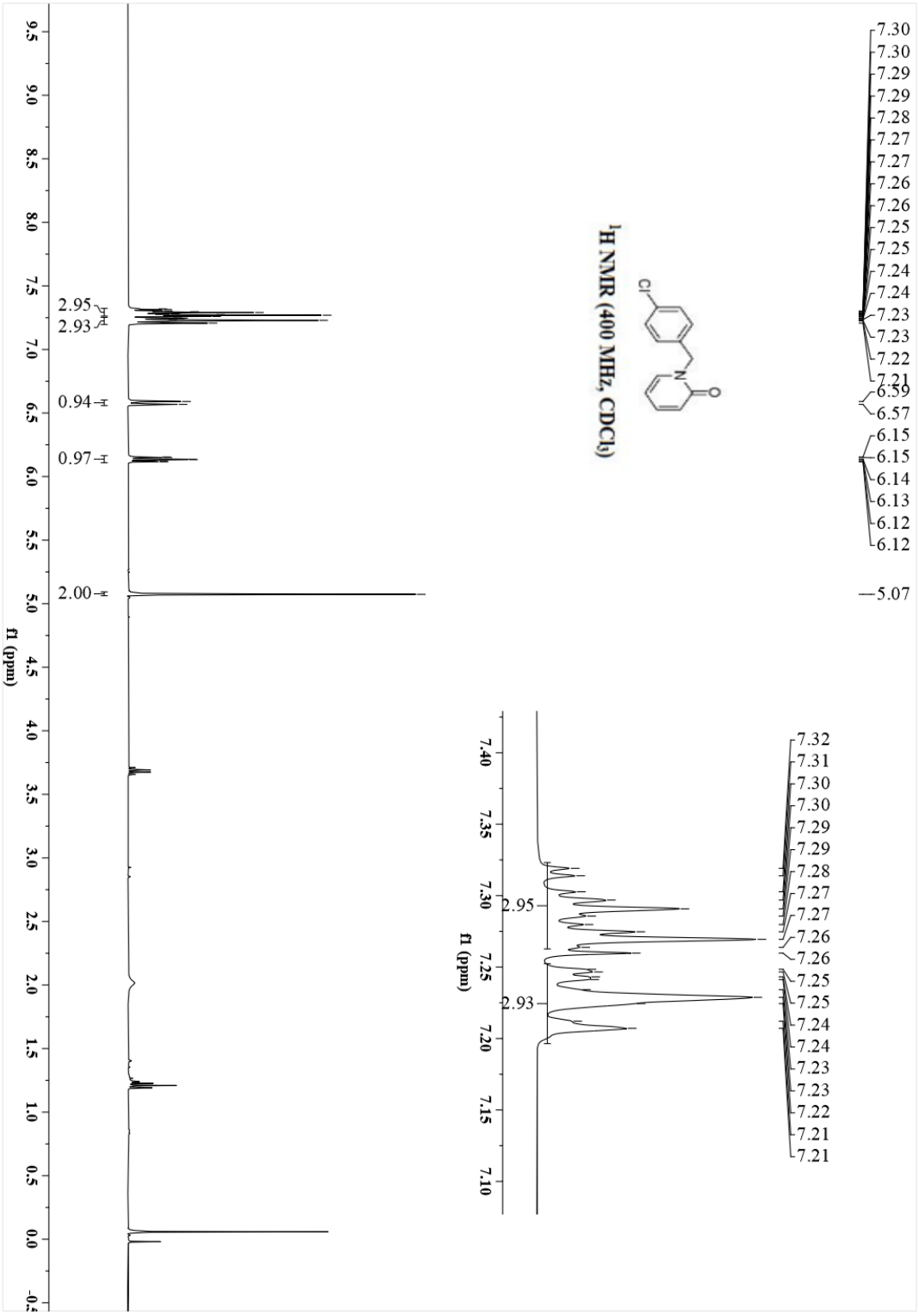
^{13}C NMR spectra of **3e**



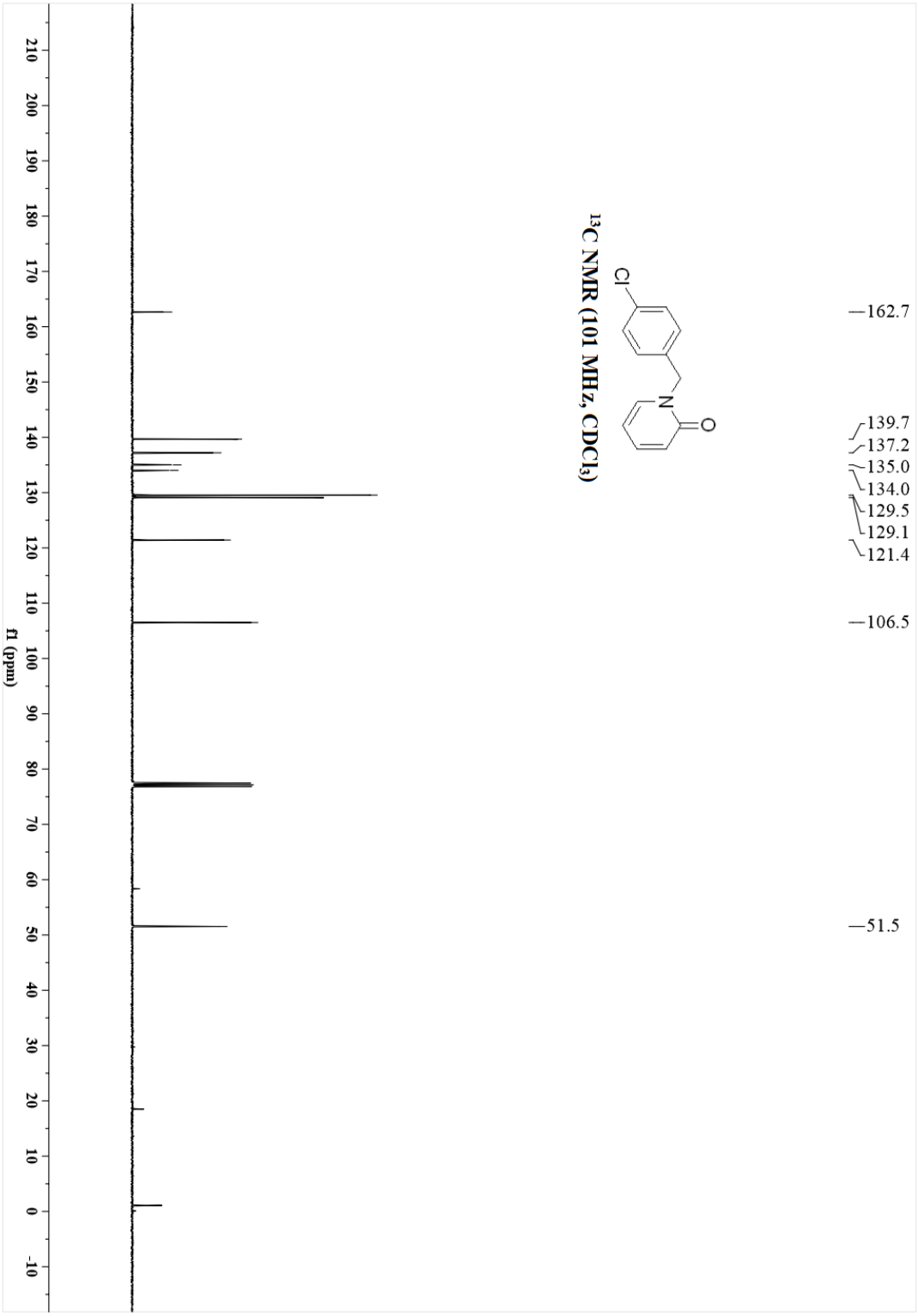
HRMS spectra of **3e**



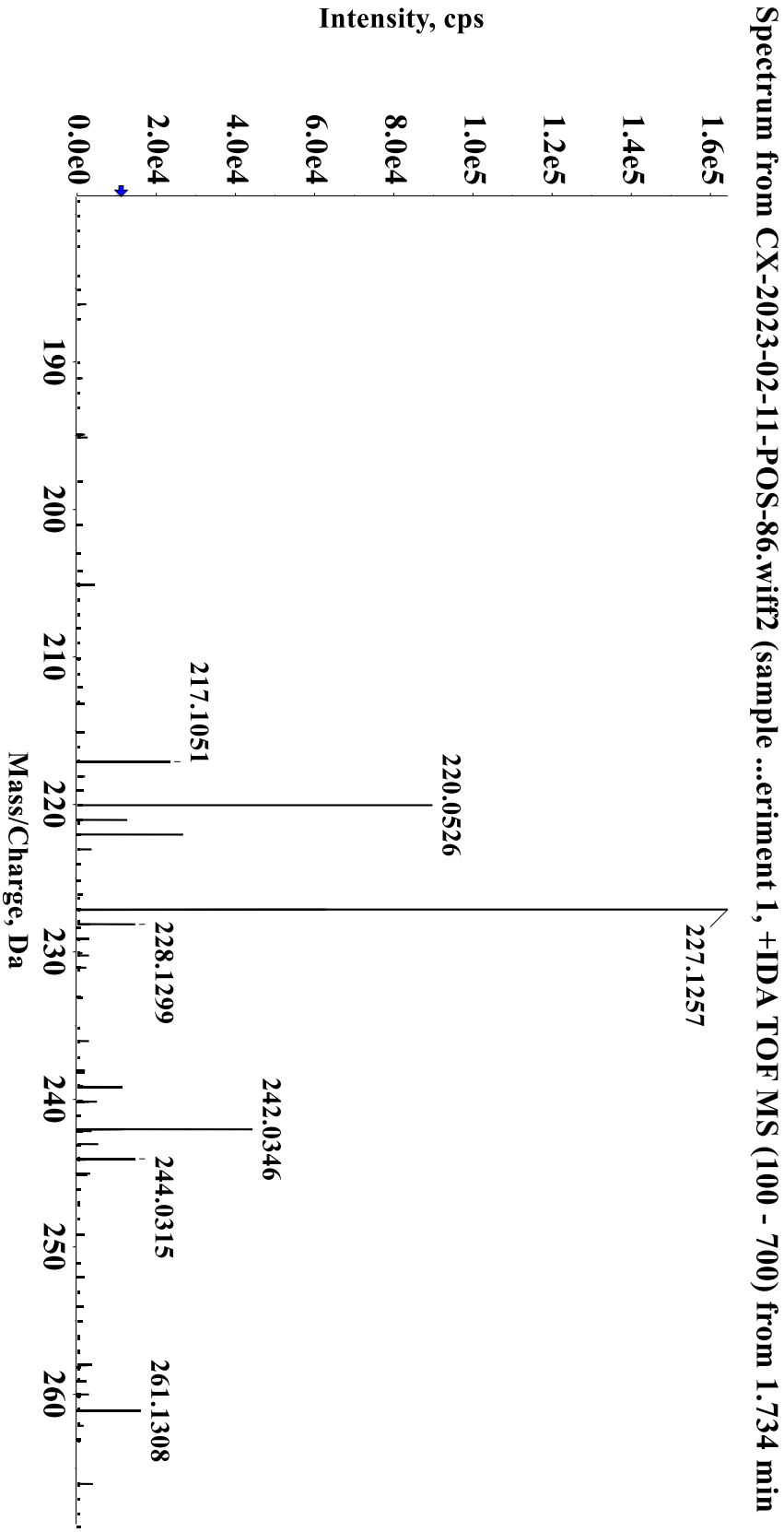
^{1}H NMR spectra of **3f**



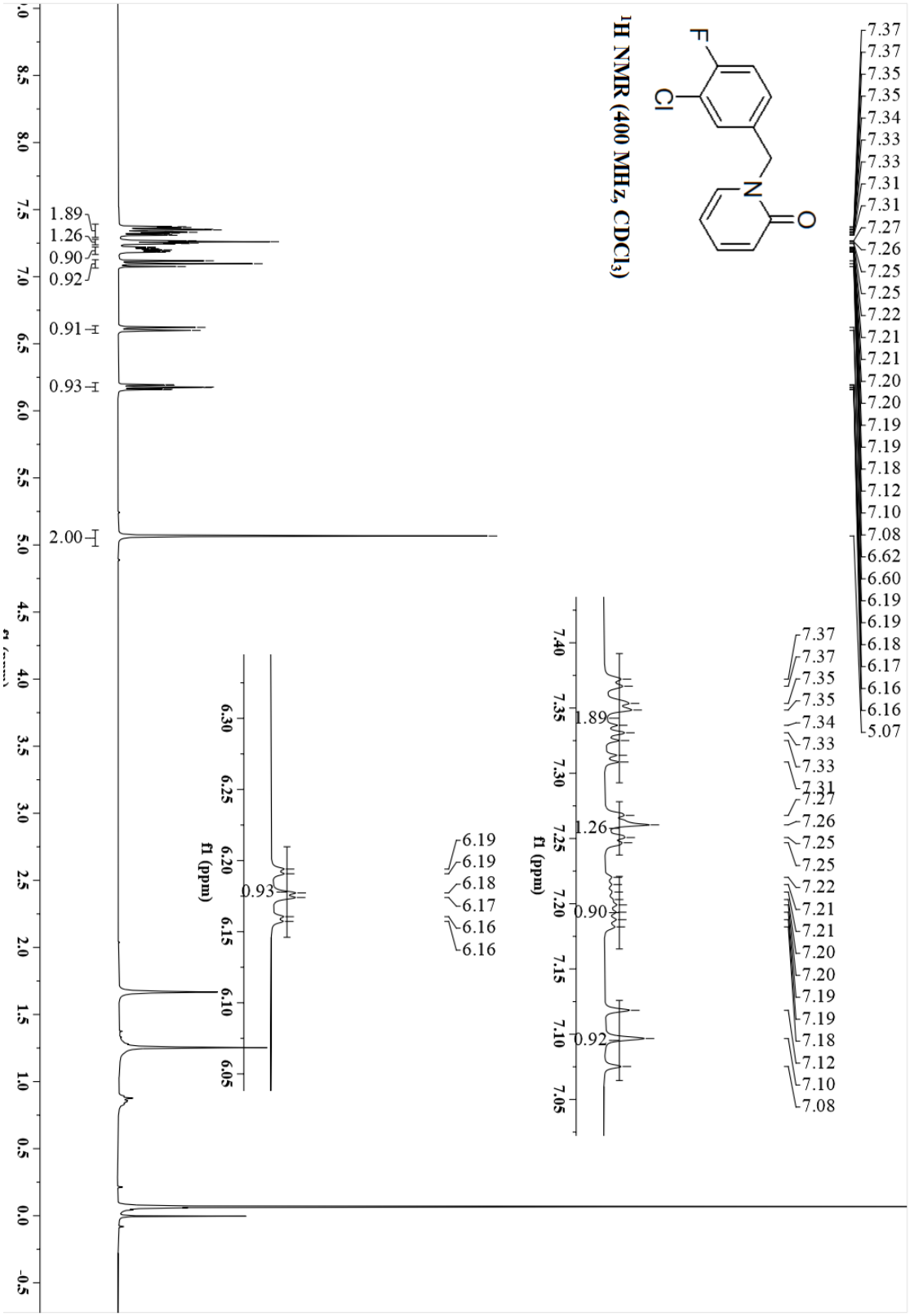
^{13}C NMR spectra of **3f**



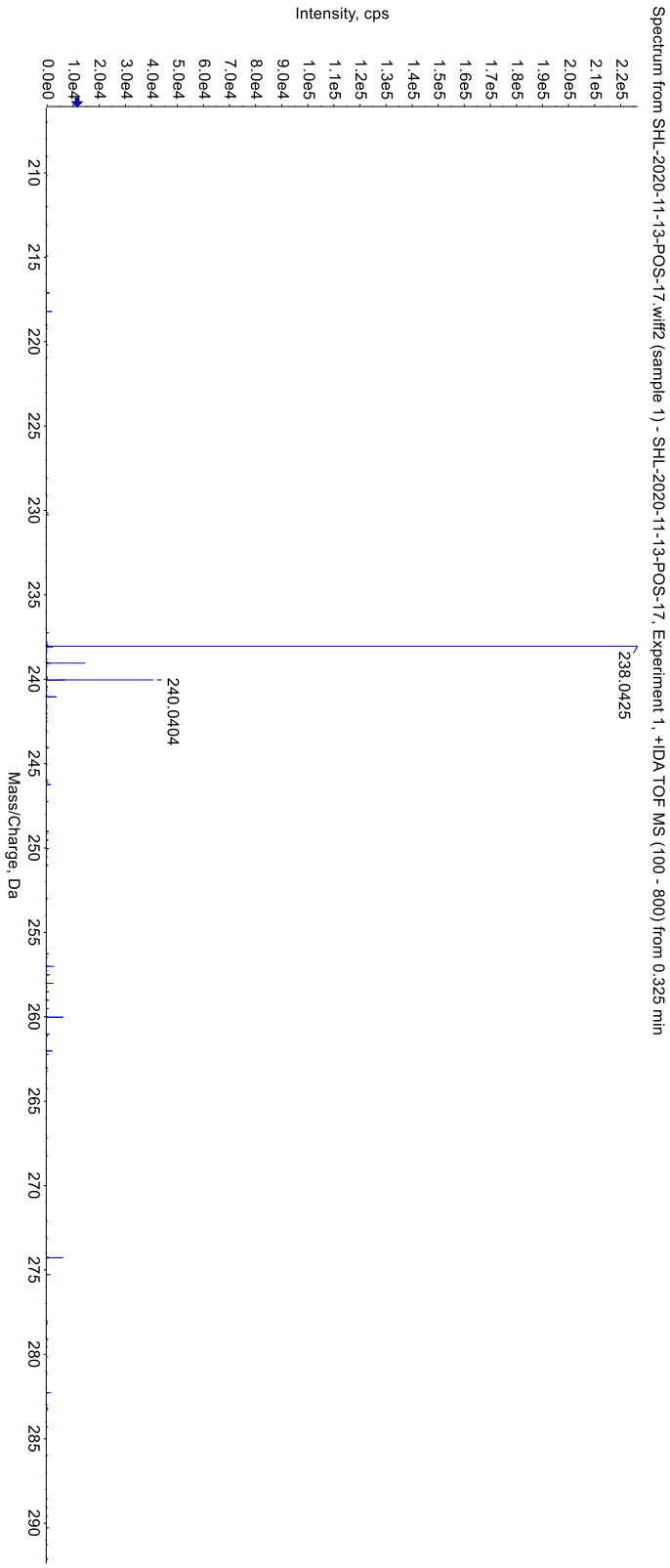
HRMS spectra of **3f**



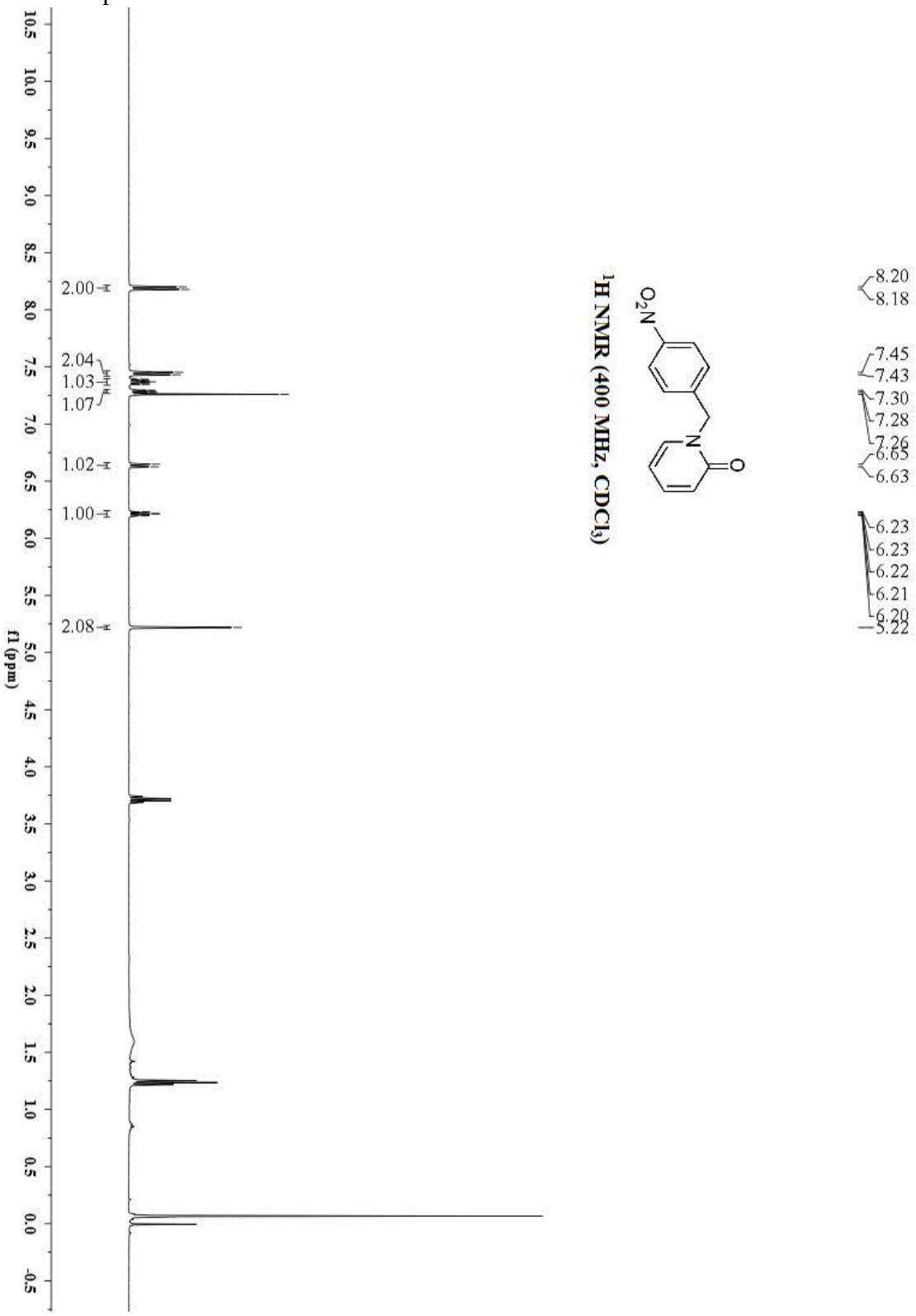
^{1}H NMR spectra of **3g**



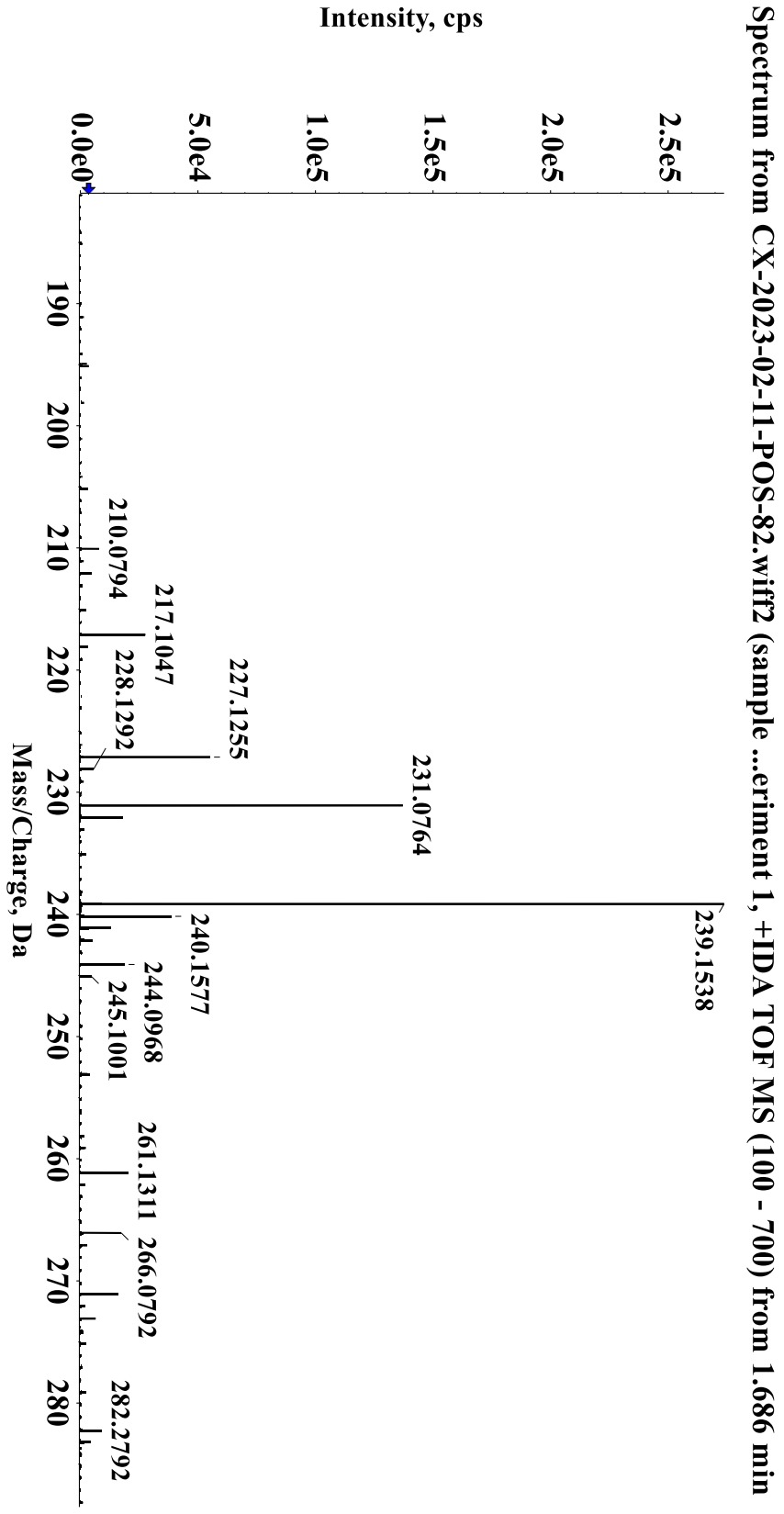
HRMS spectra of **3g**



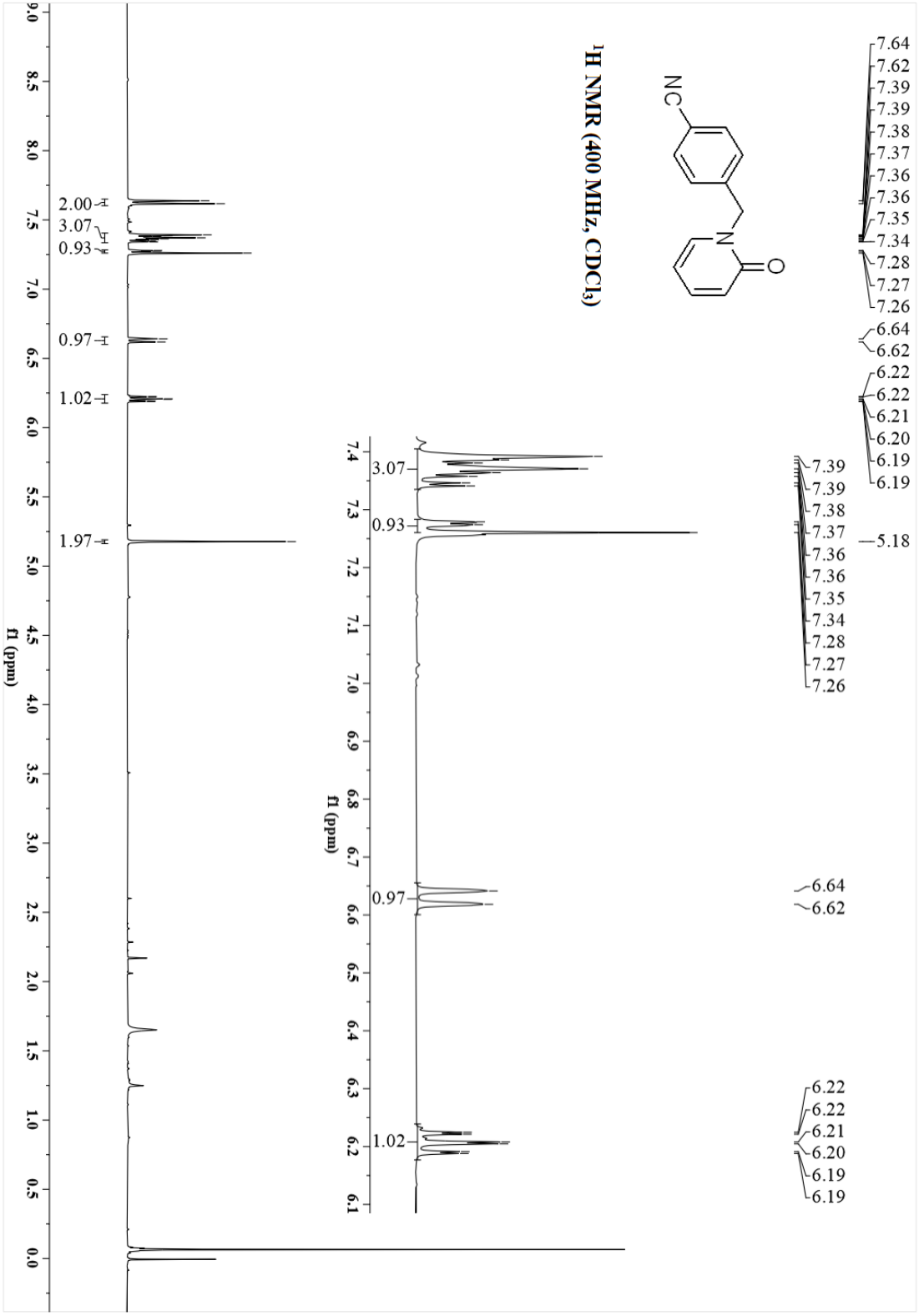
[1]HRMS spectra of **3h**



HRMS spectra of **3h**



^{1}H NMR spectra of **3i**



Elemental Composition Report

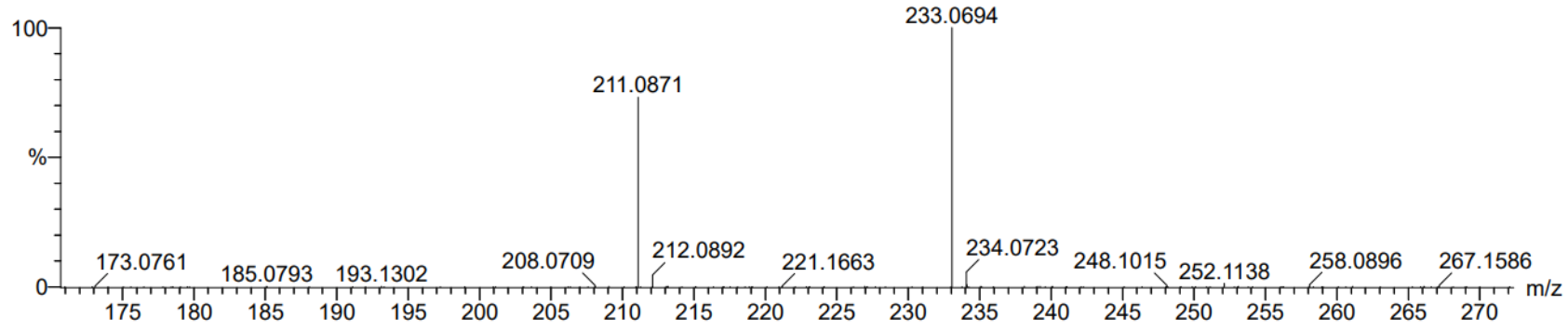
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
225 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 13-13 H: 10-10 N: 0-100 O: 0-100 Na: 0-1

30
240401-1-WS-CN 10 (0.072)

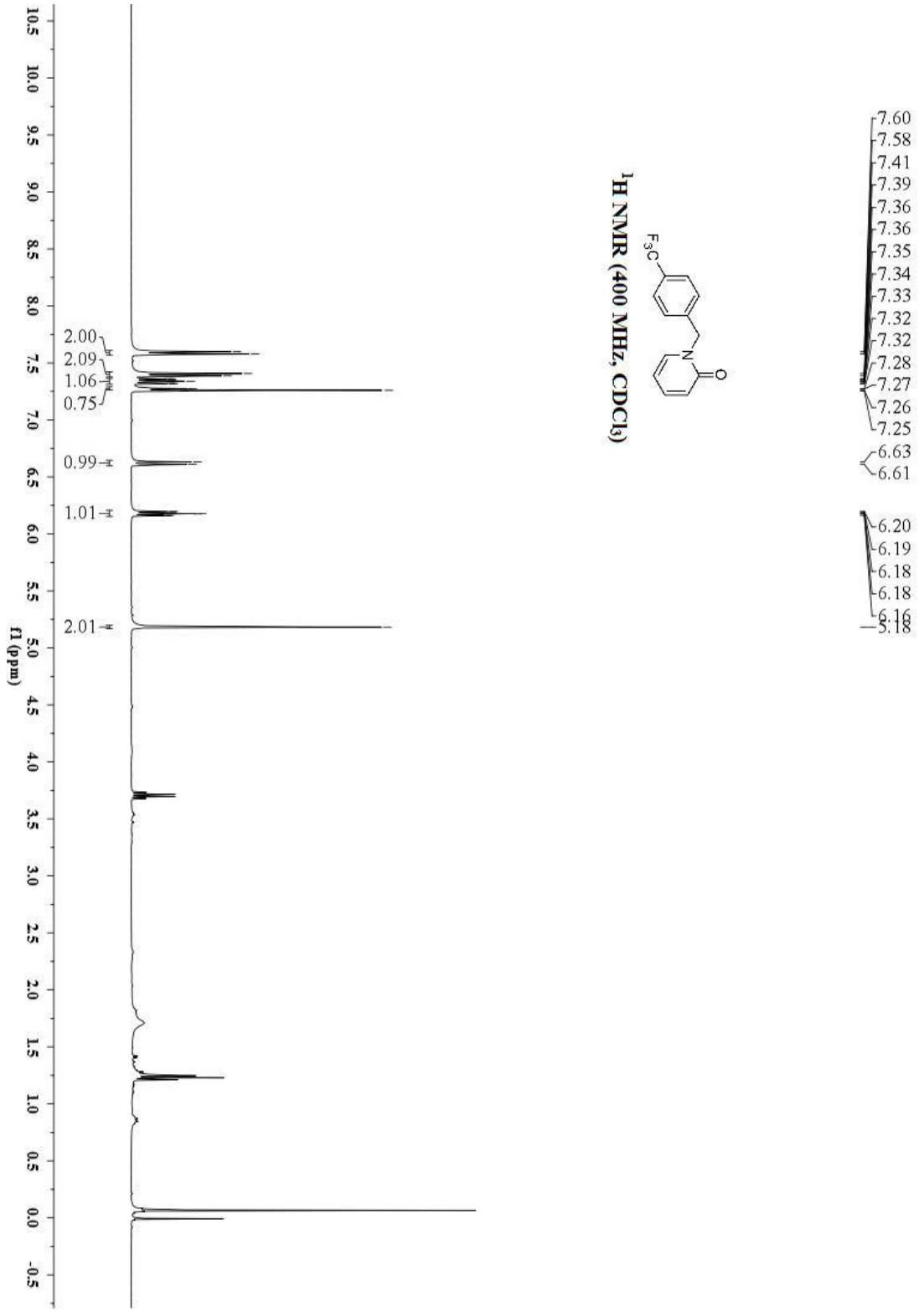
1: TOF MS ES+
4.87e+004



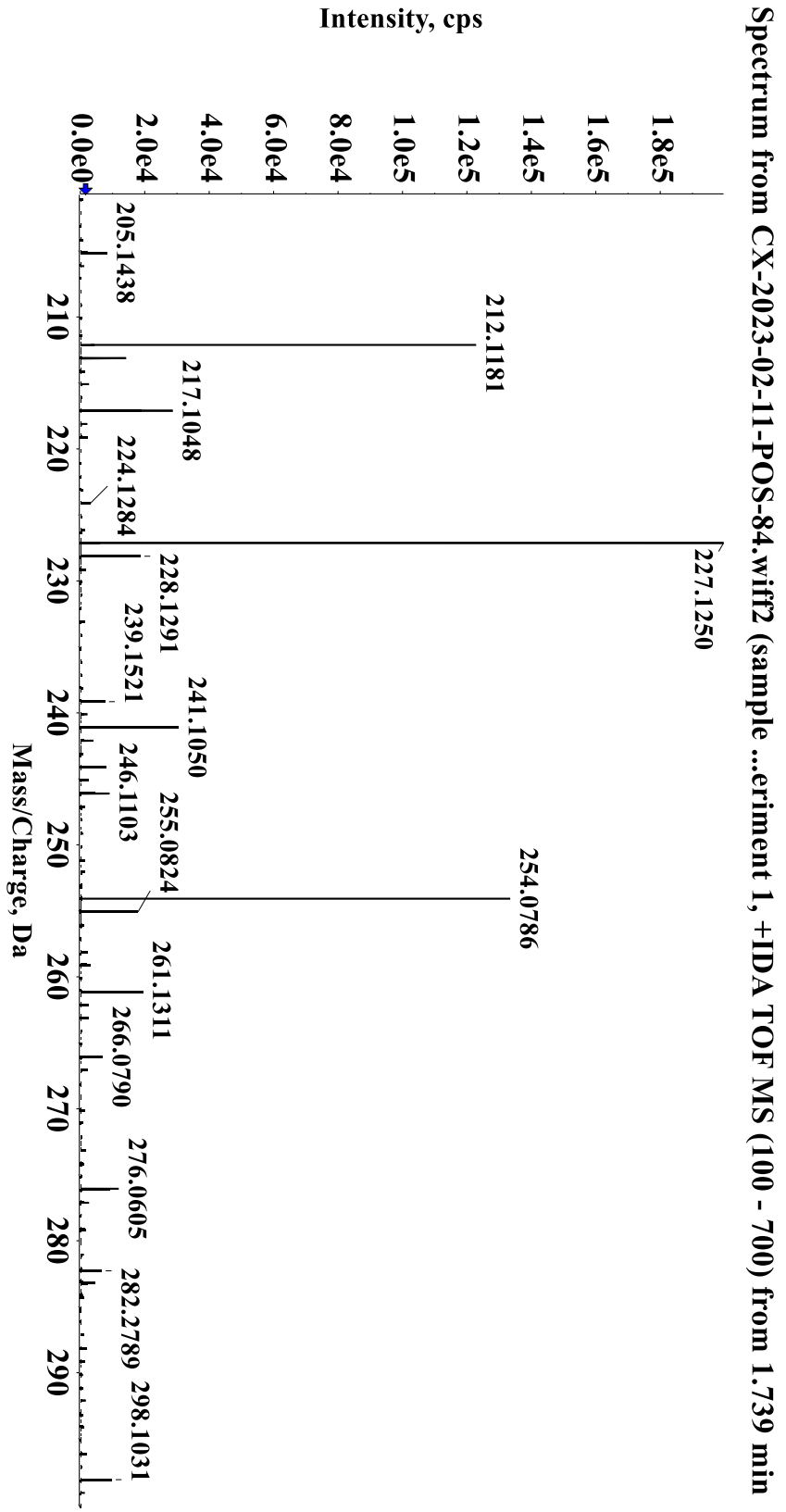
Minimum:				-1.5				
Maximum:		5.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
233.0694	233.0691	0.3	1.3	9.5	67.6	n/a	n/a	C13 H10 N2 O Na

HRMS spectra of **3i**

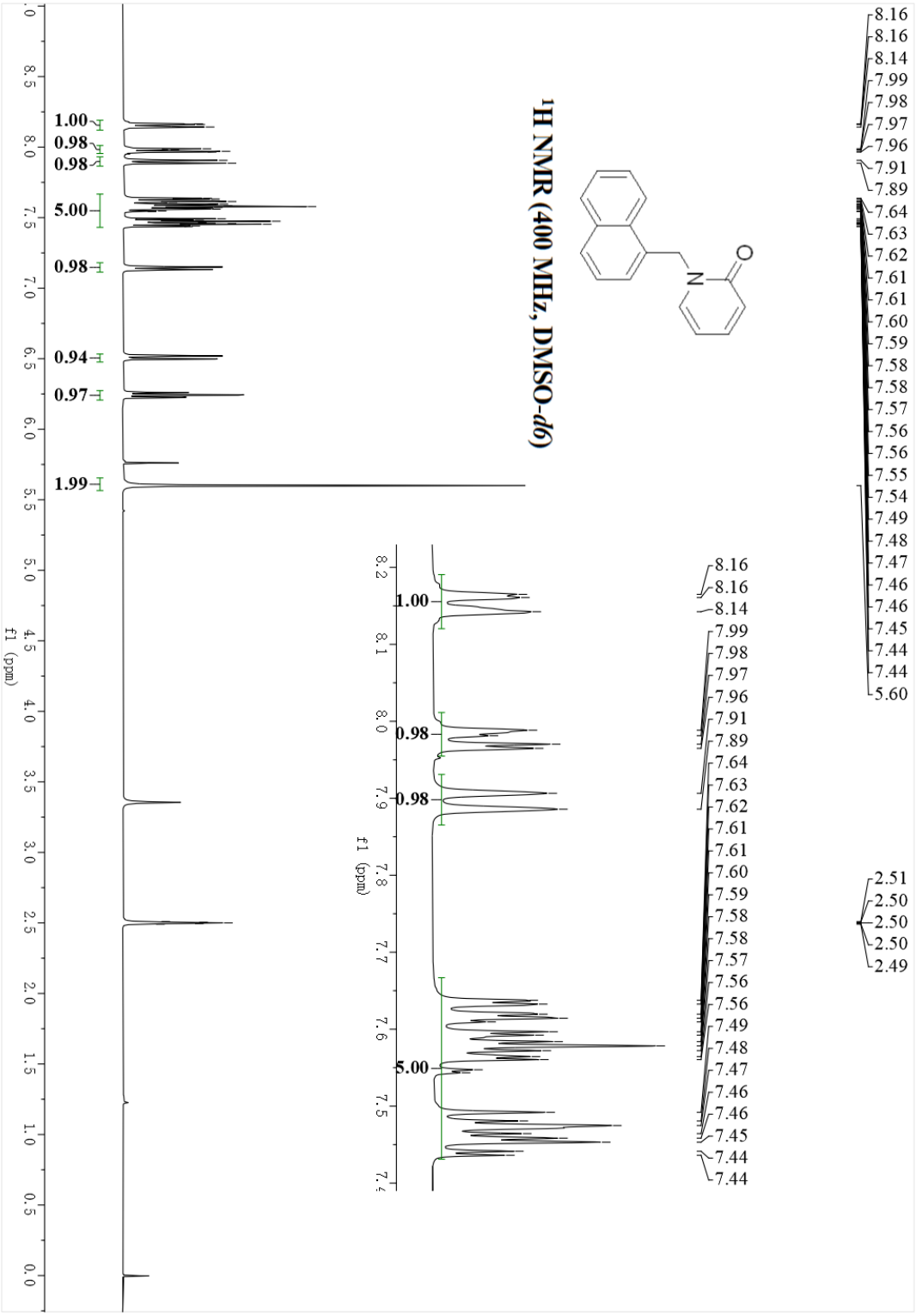
^{1}H NMR spectra of **3j**



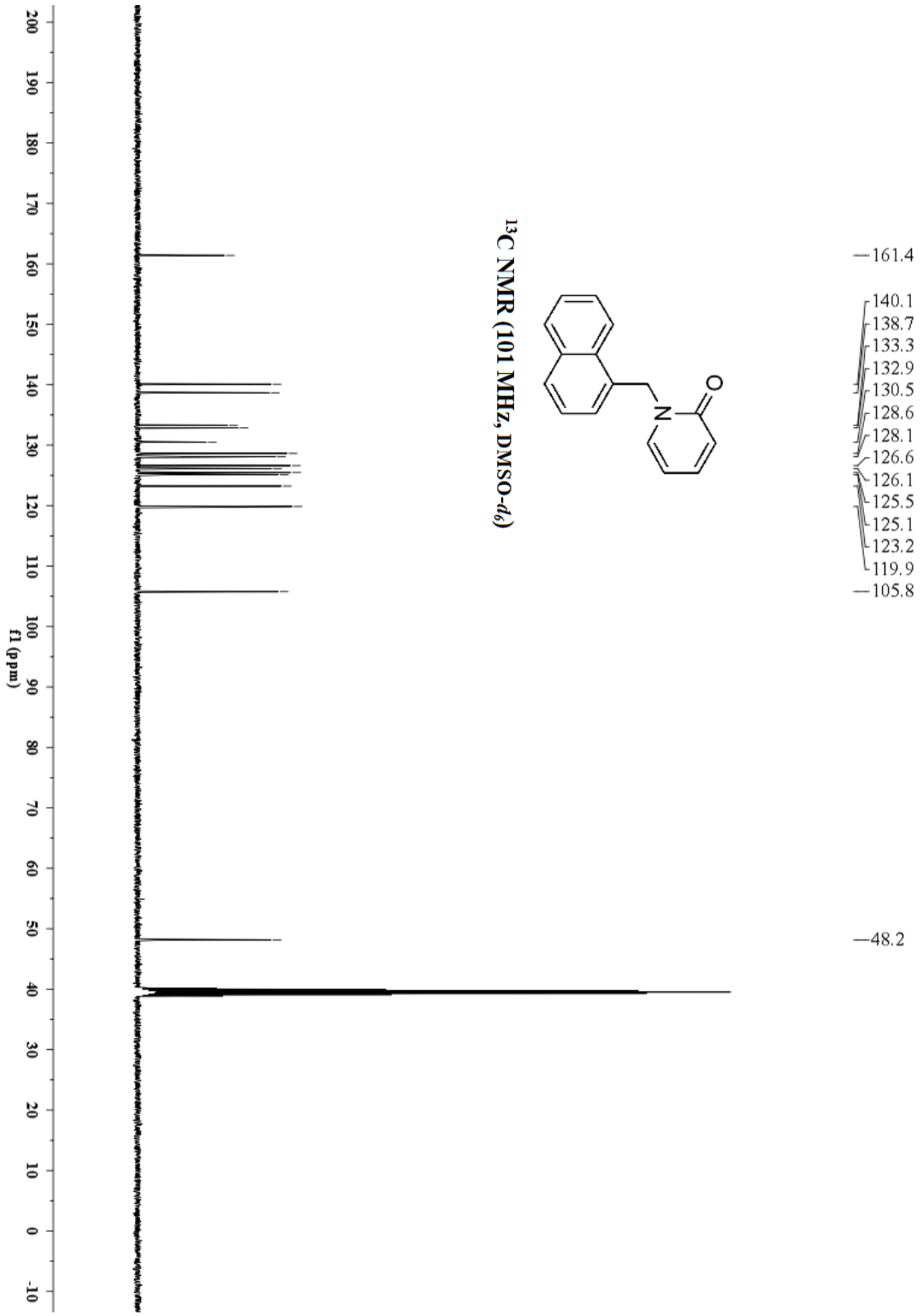
HRMS spectra of **3j**



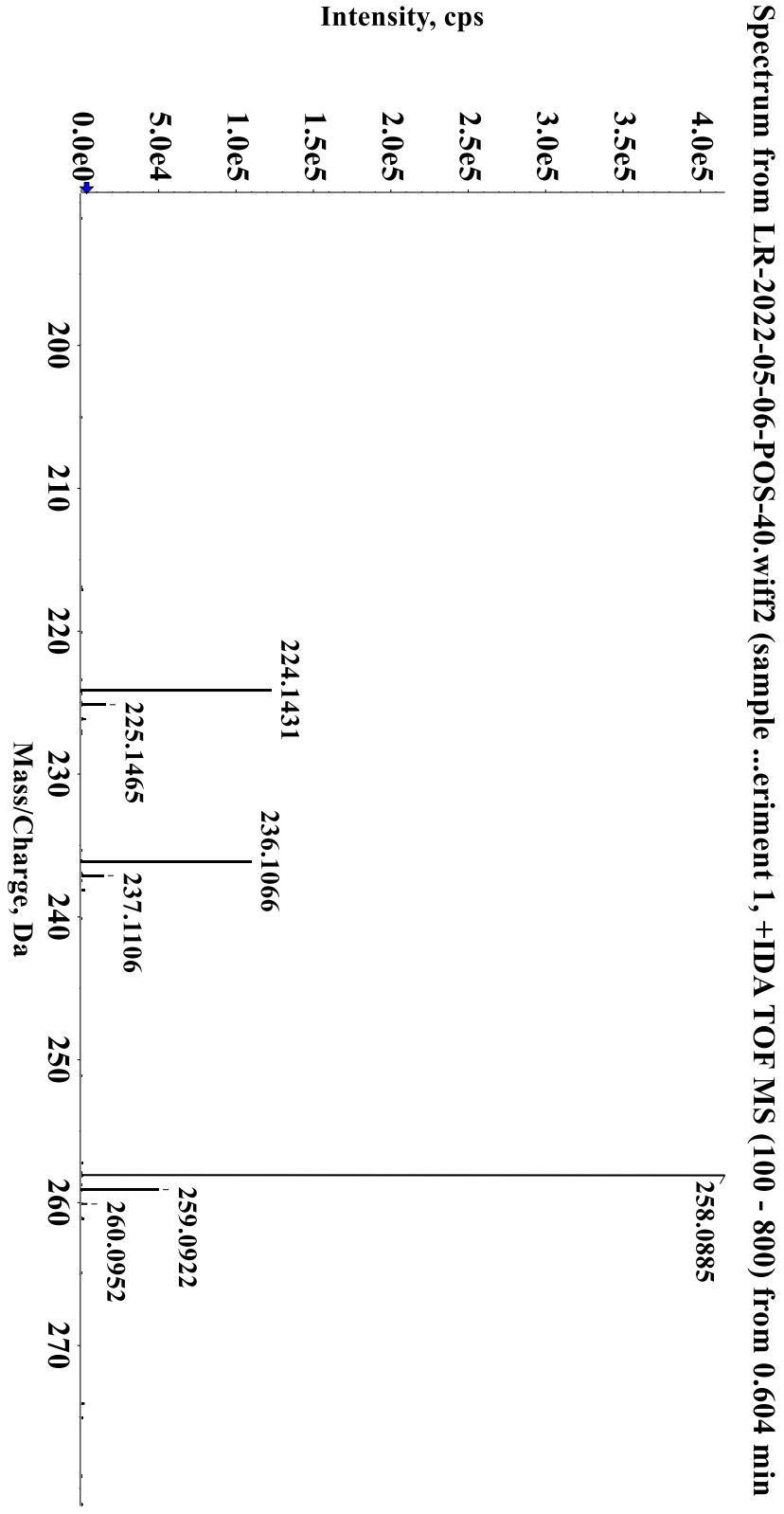
^{1}H NMR spectra of **3k**



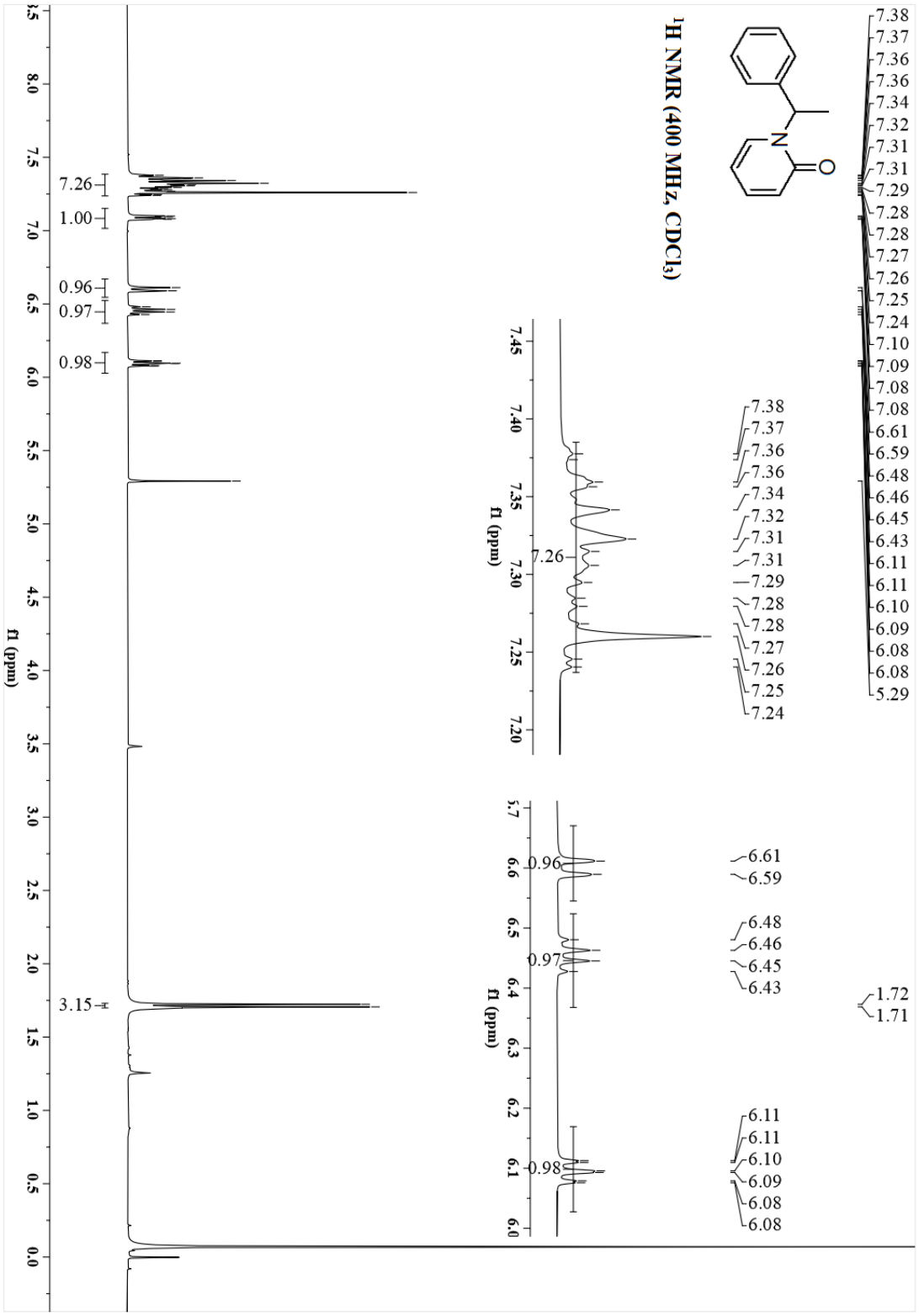
^{13}C NMR spectra of **3k**



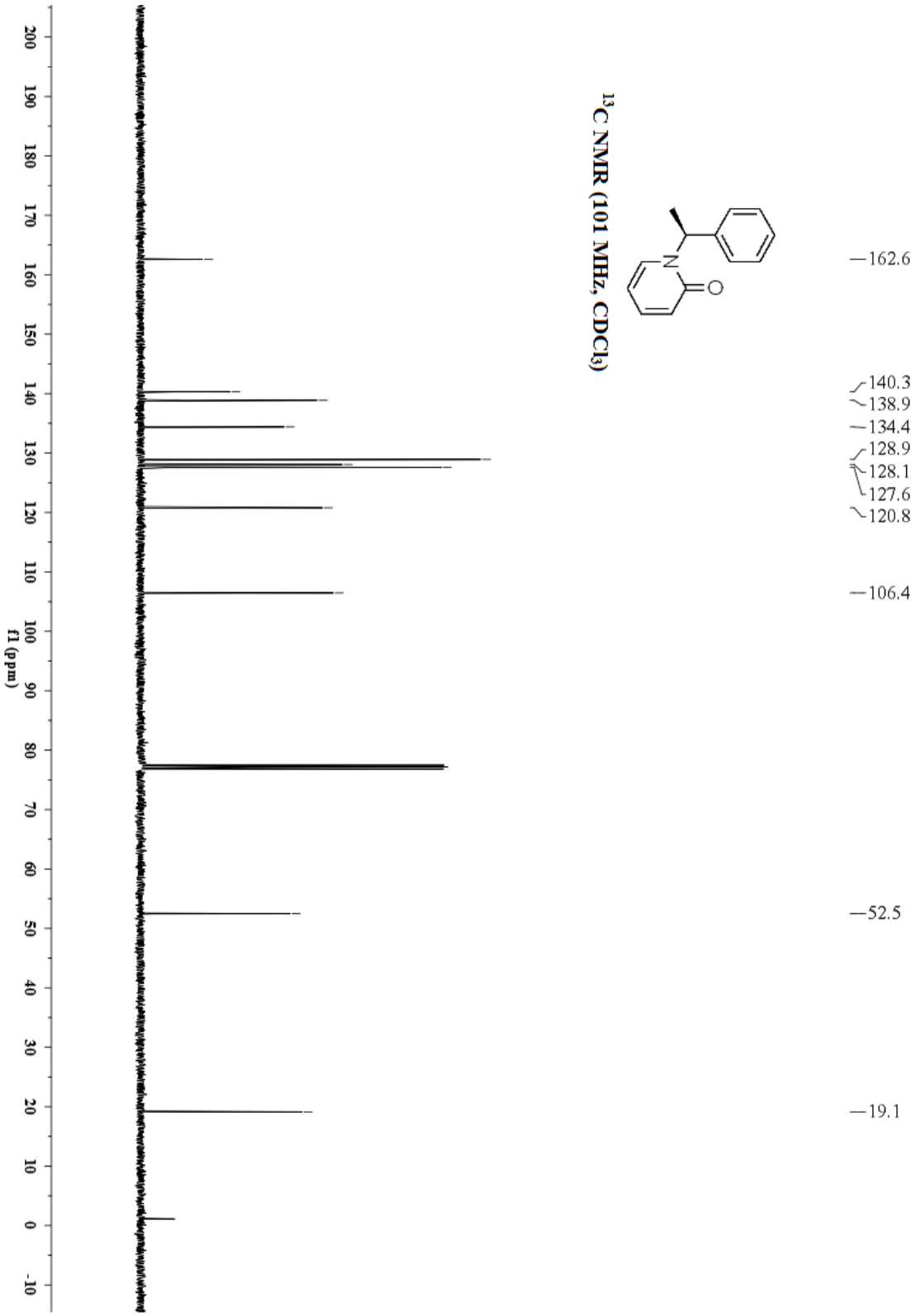
HRMS spectra of **3k**



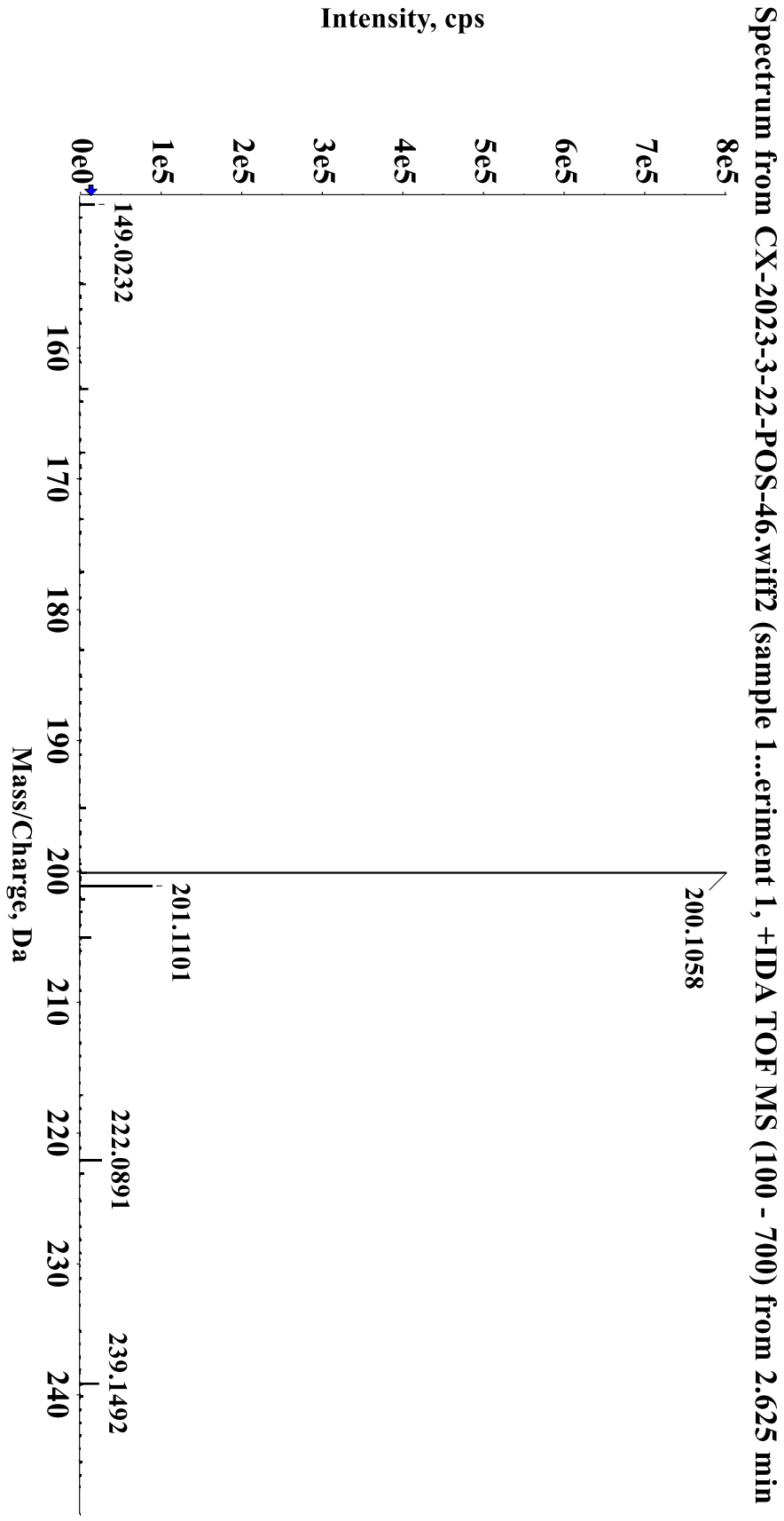
^{1}H NMR spectra of **3l**



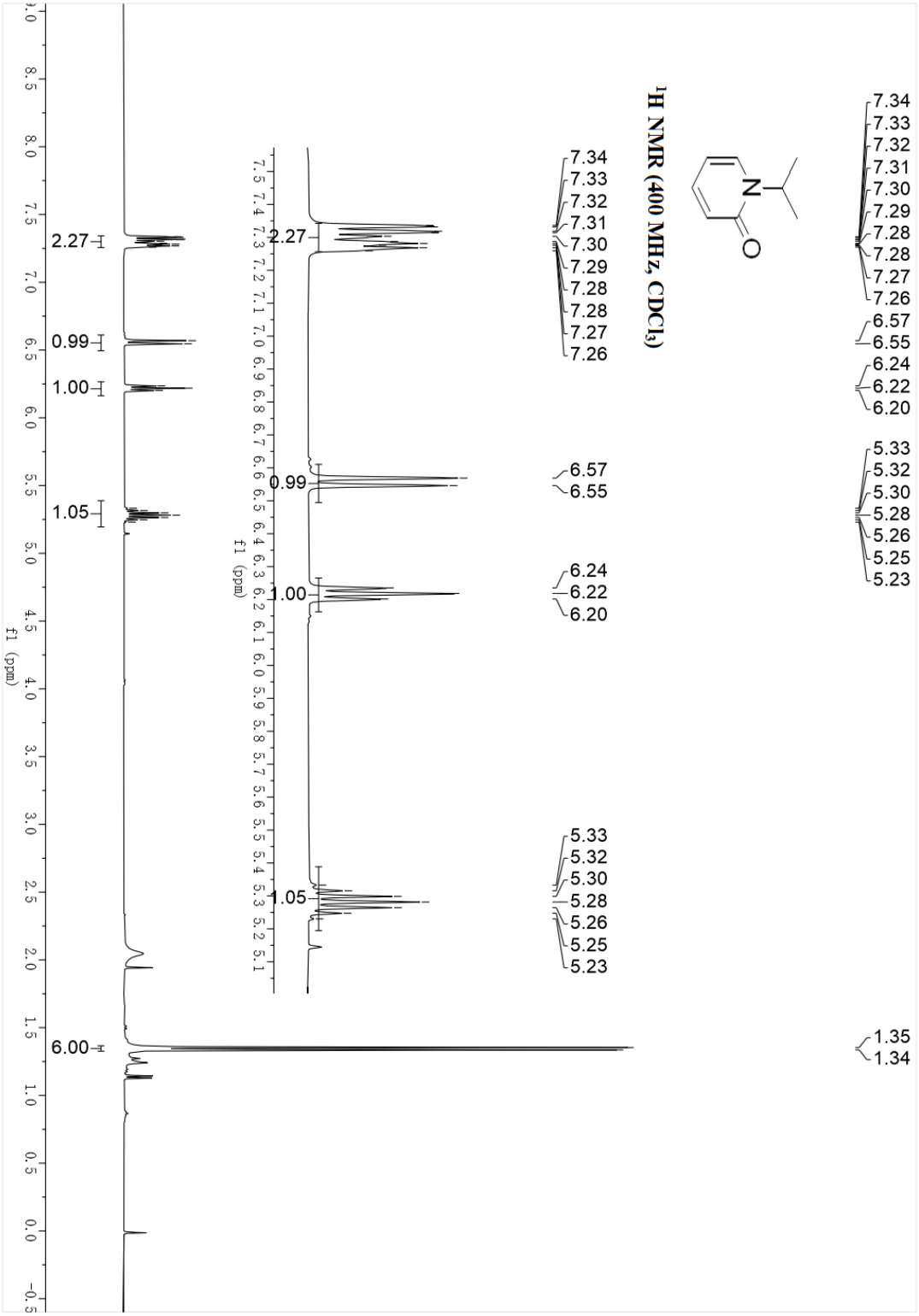
^{13}C NMR spectra of **3l**



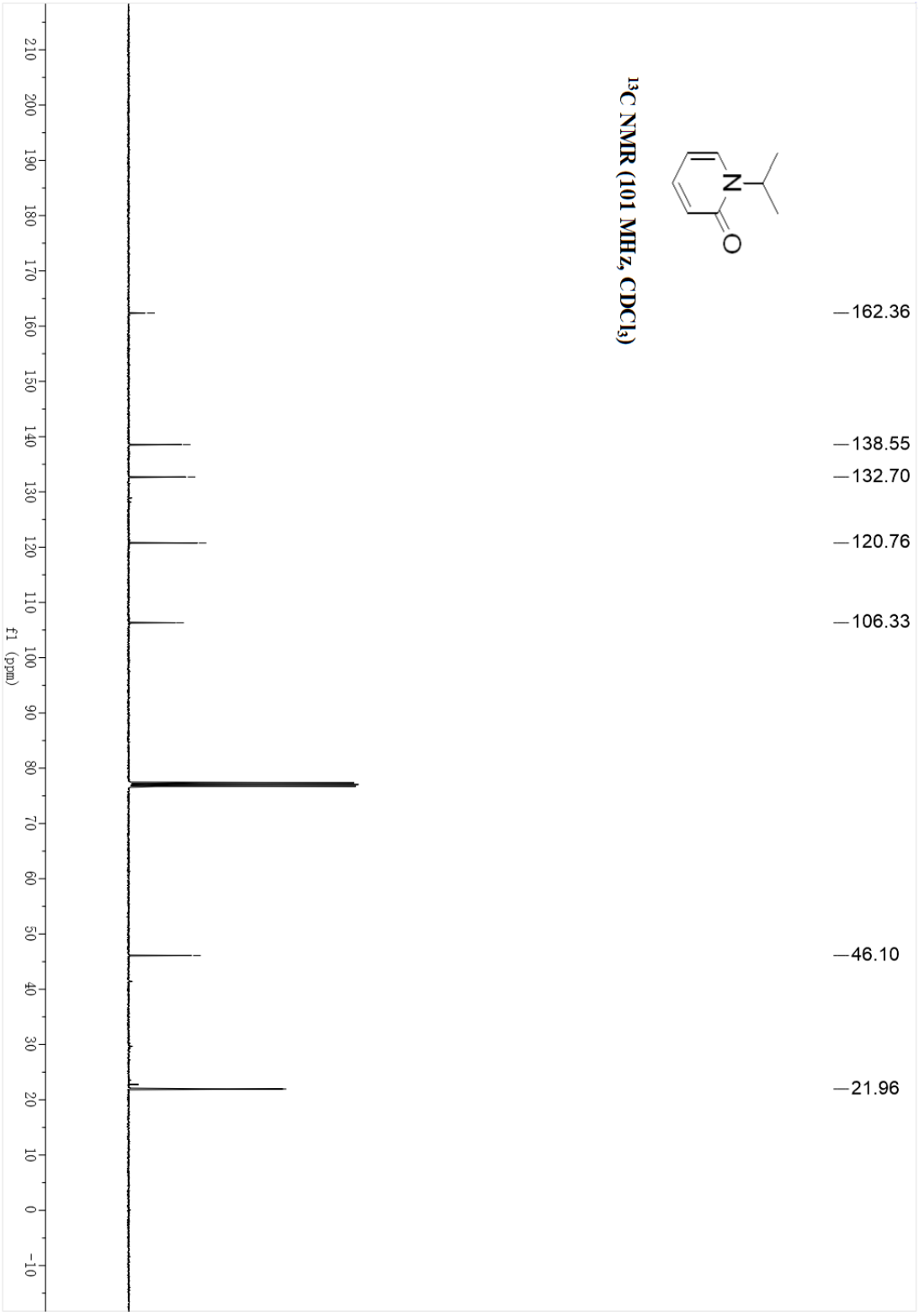
HRMS spectra of **3l**



^{1}H NMR spectra of **3m**



^{13}C NMR spectra of **3m**



Elemental Composition Report

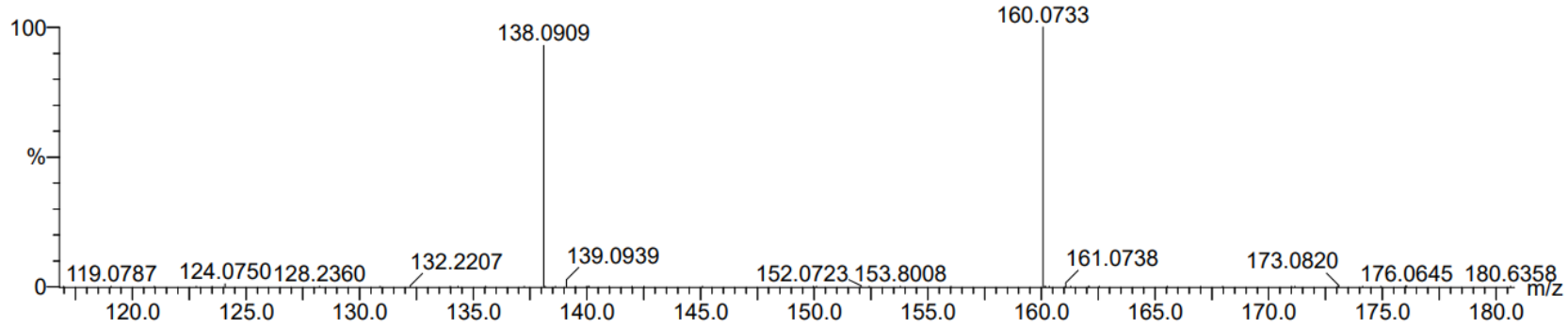
Single Mass Analysis

Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
102 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 8-8 H: 11-11 N: 0-100 O: 0-100 Na: 0-1

30
240401-1-WS-31-1 13 (0.083)

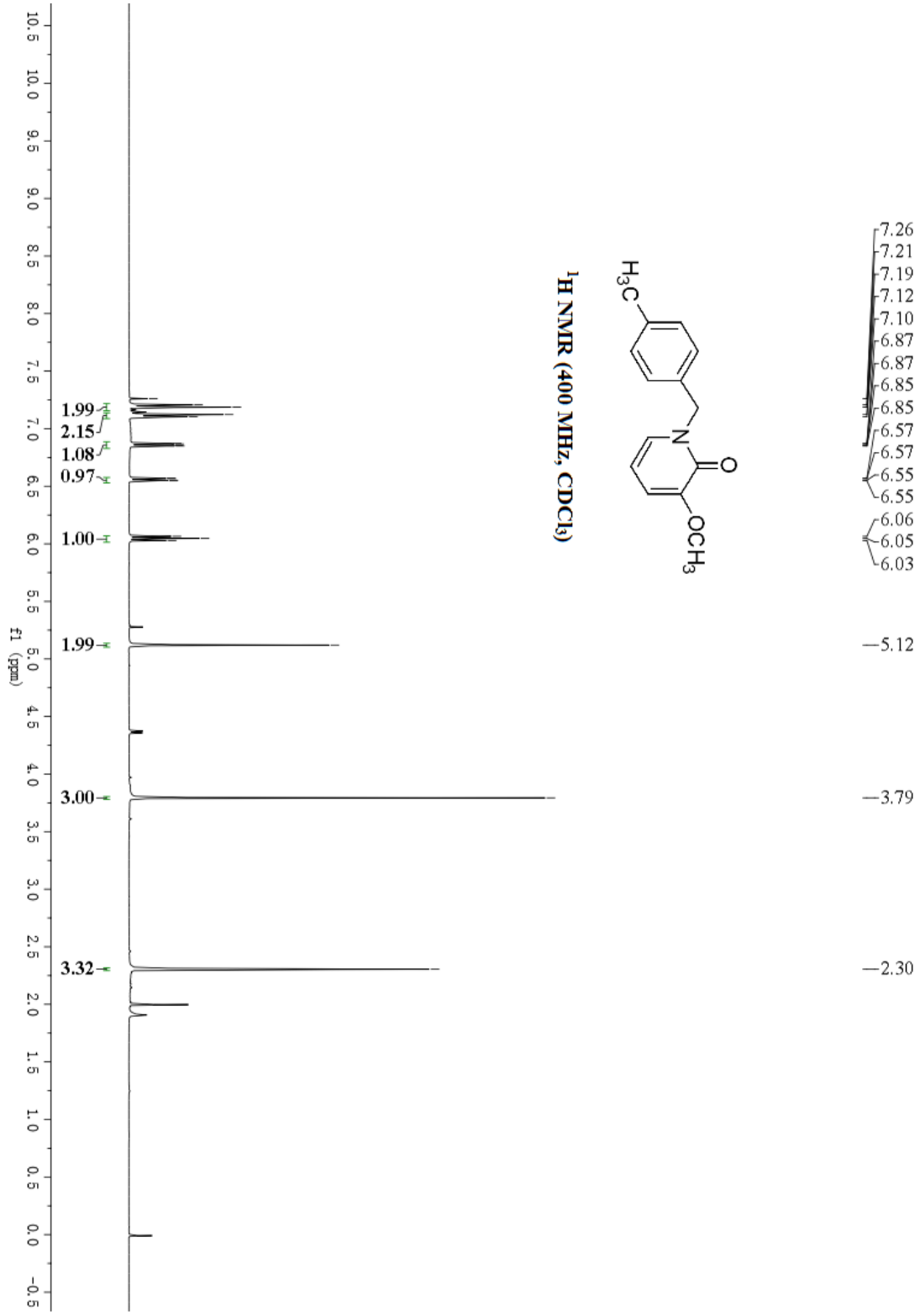
1: TOF MS ES+
1.81e+004



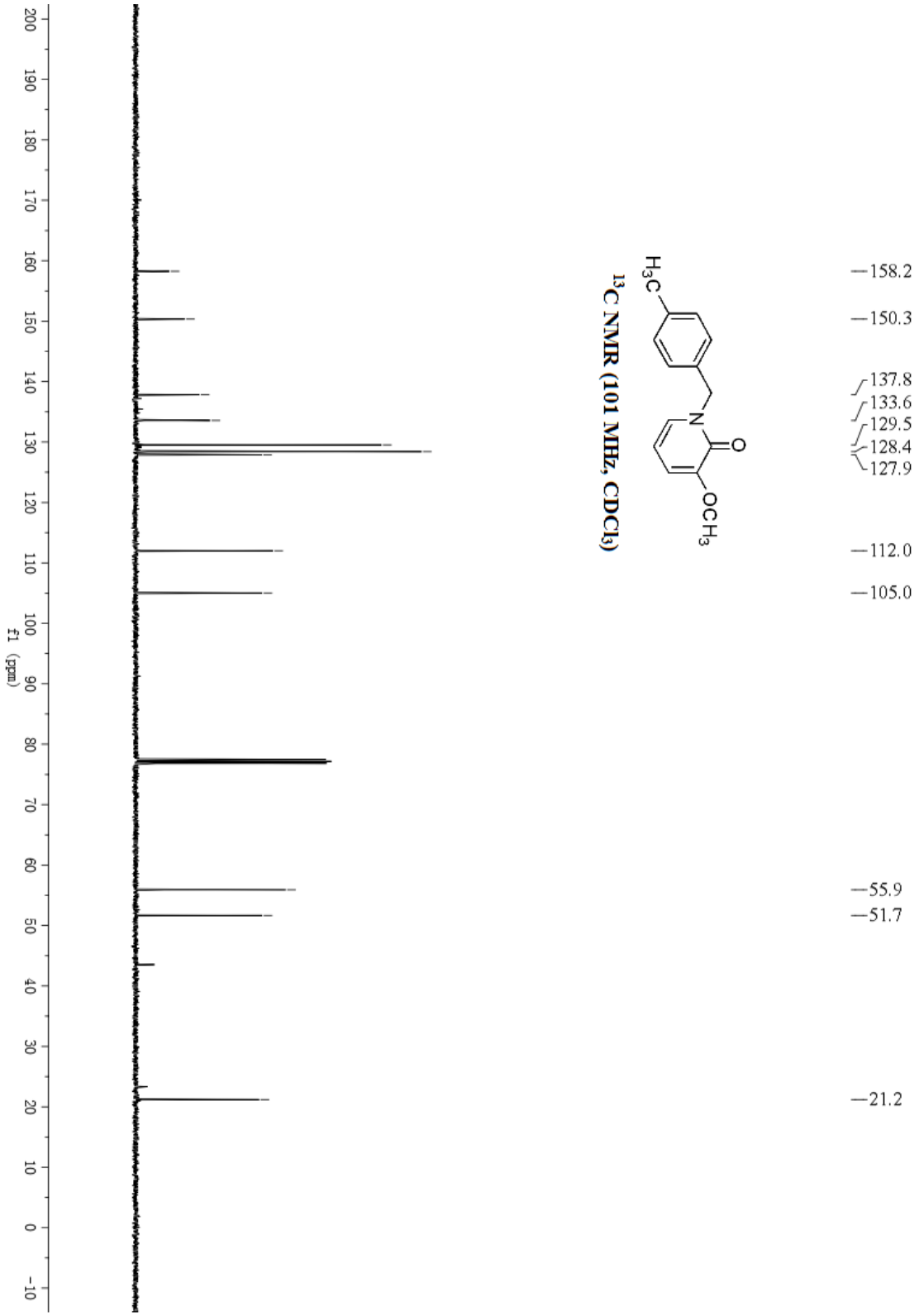
Minimum:				-1.5				
Maximum:		5.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
160.0733	160.0738	-0.5	-3.1	3.5	65.8	n/a	n/a	C8 H11 N 0 Na

HRMS spectra of **3m**

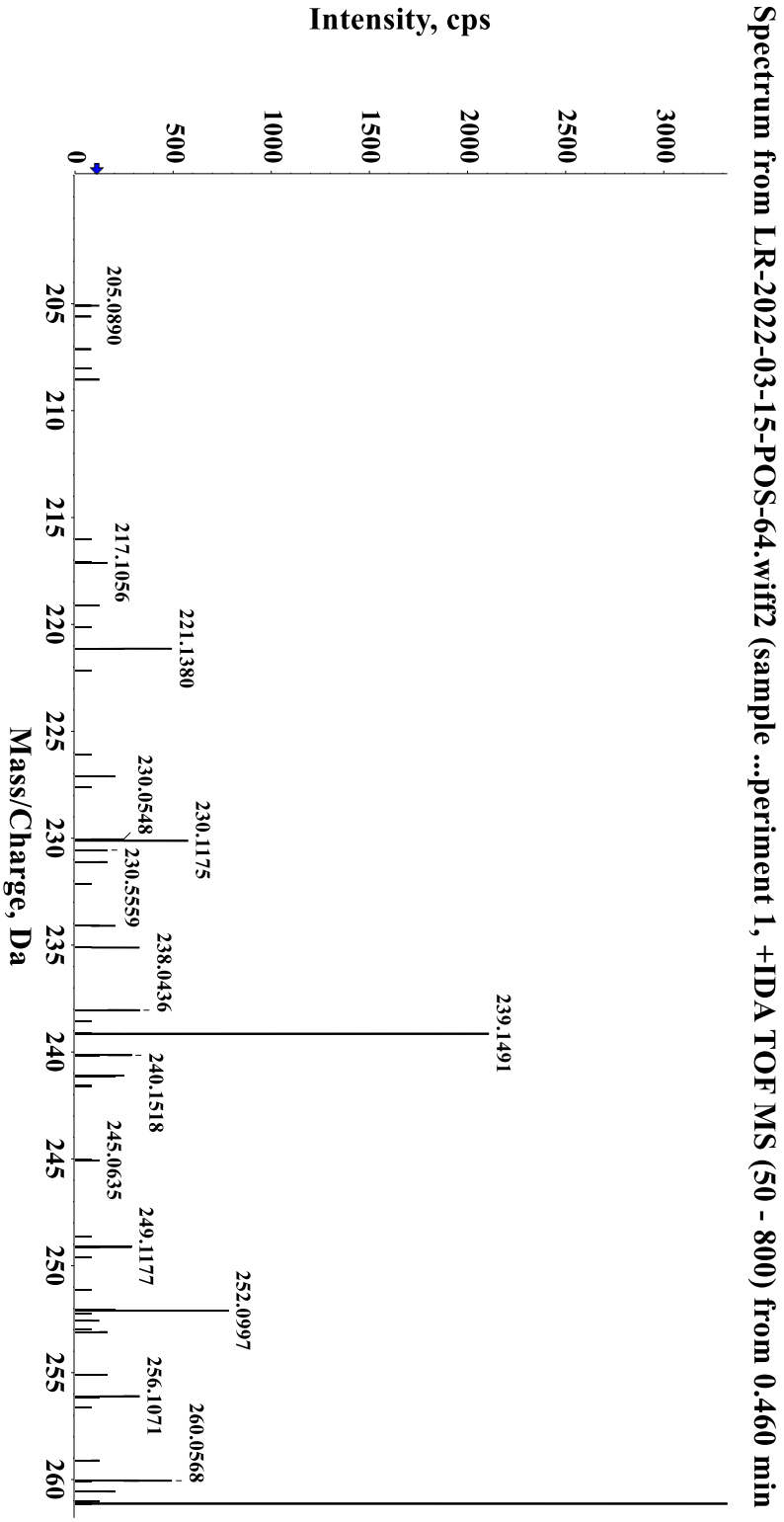
^{1}H NMR spectra of **3n**



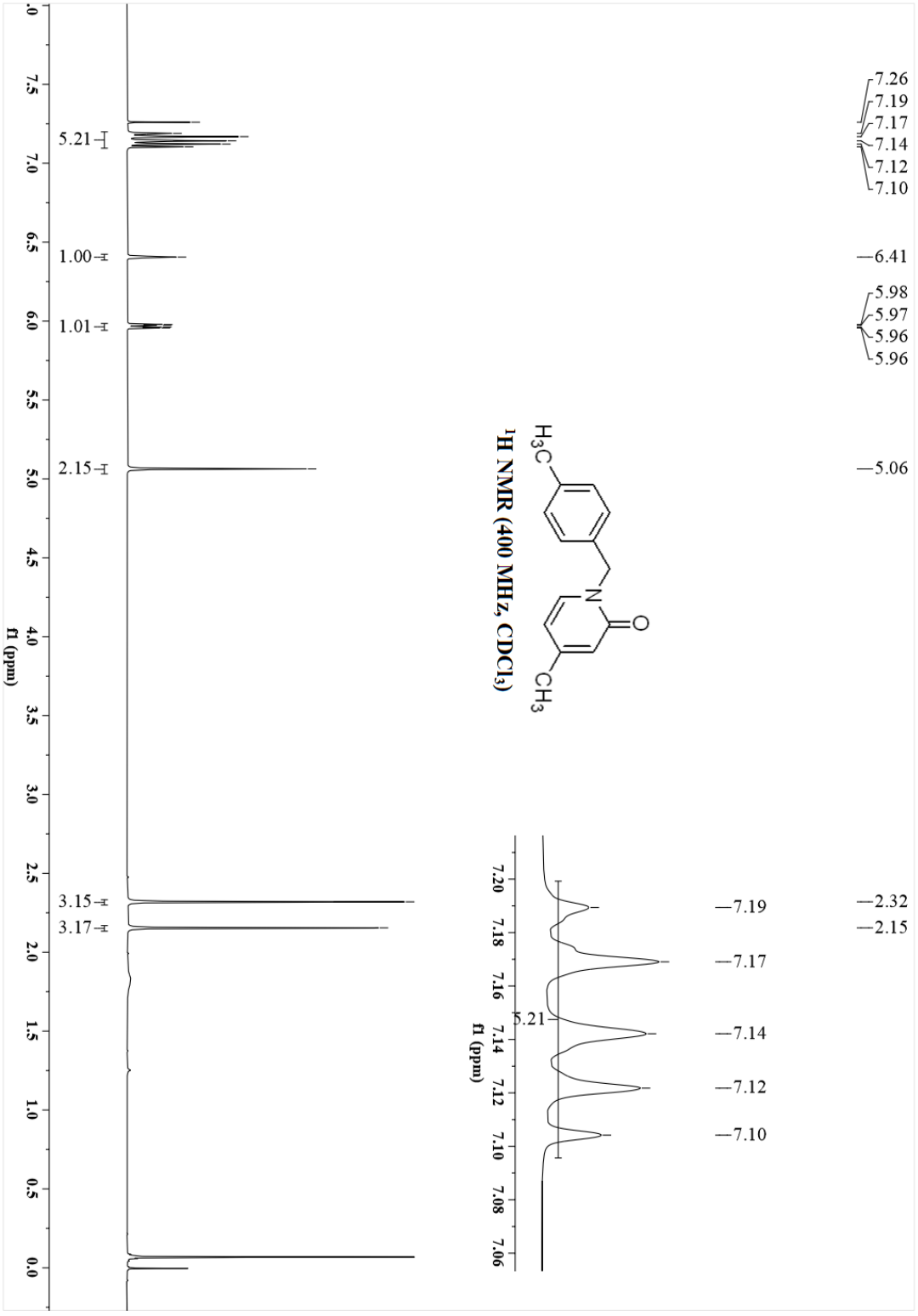
^{13}C NMR spectra of **3n**



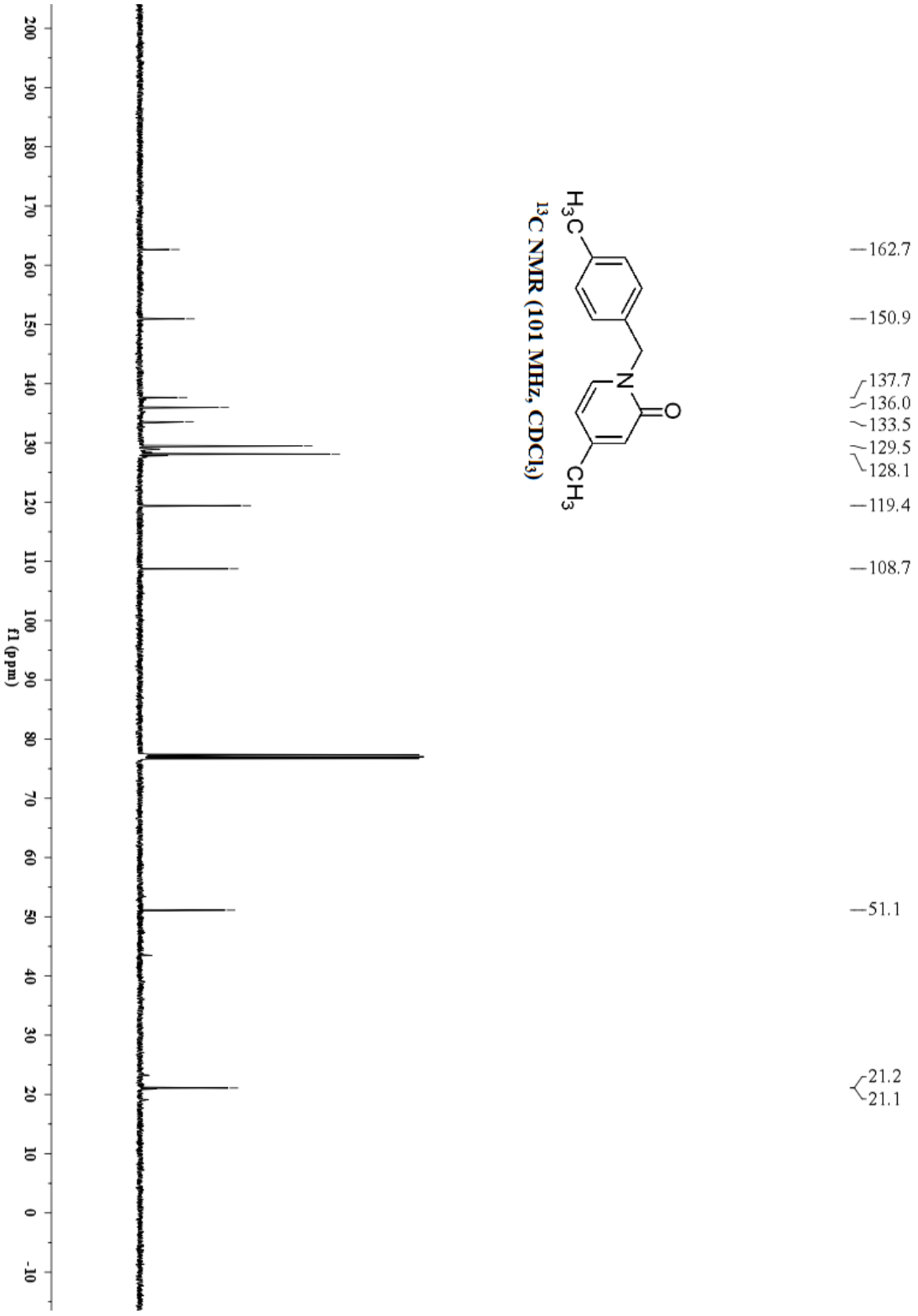
HRMS spectra of **3n**



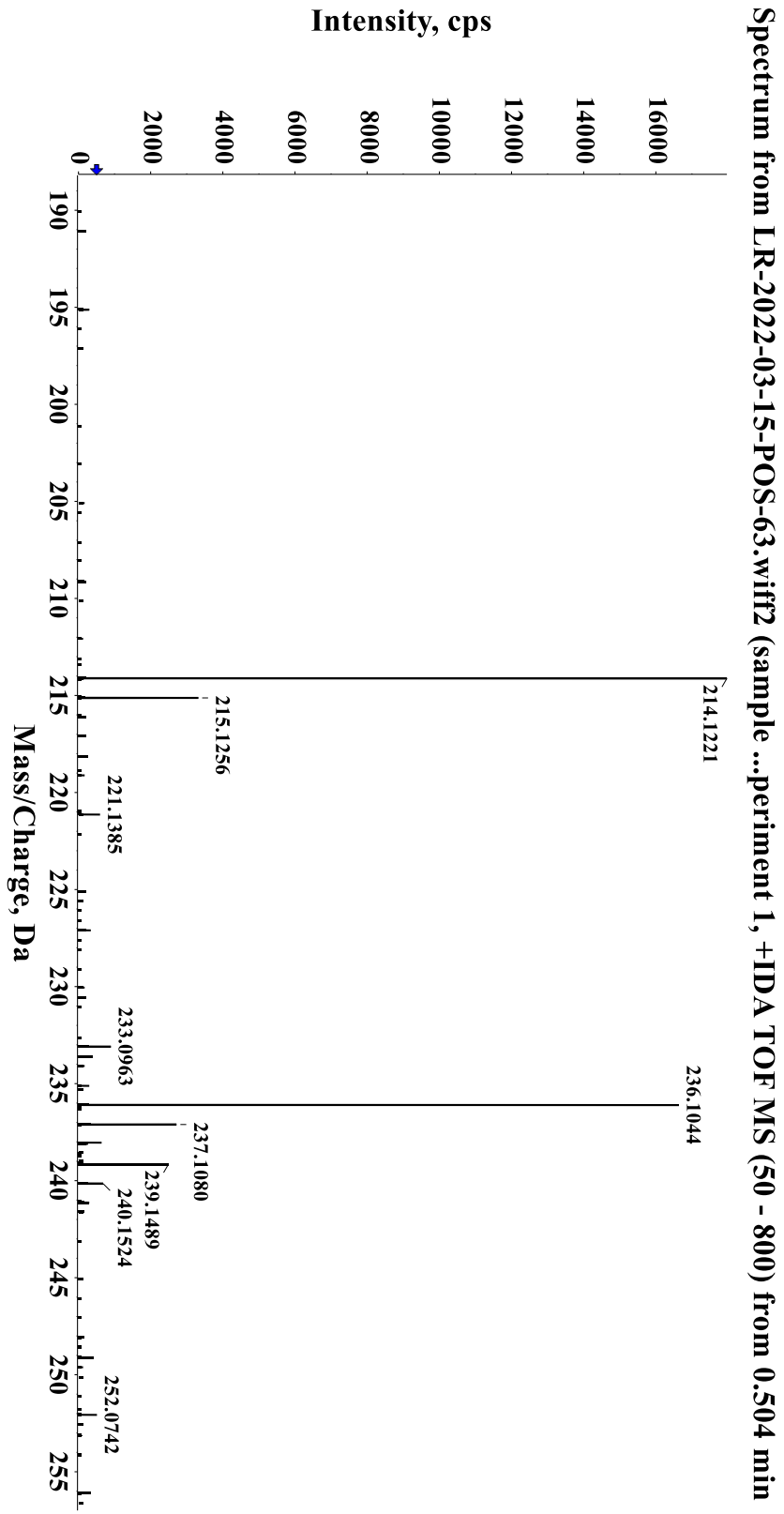
^{1}H NMR spectra of **3o**



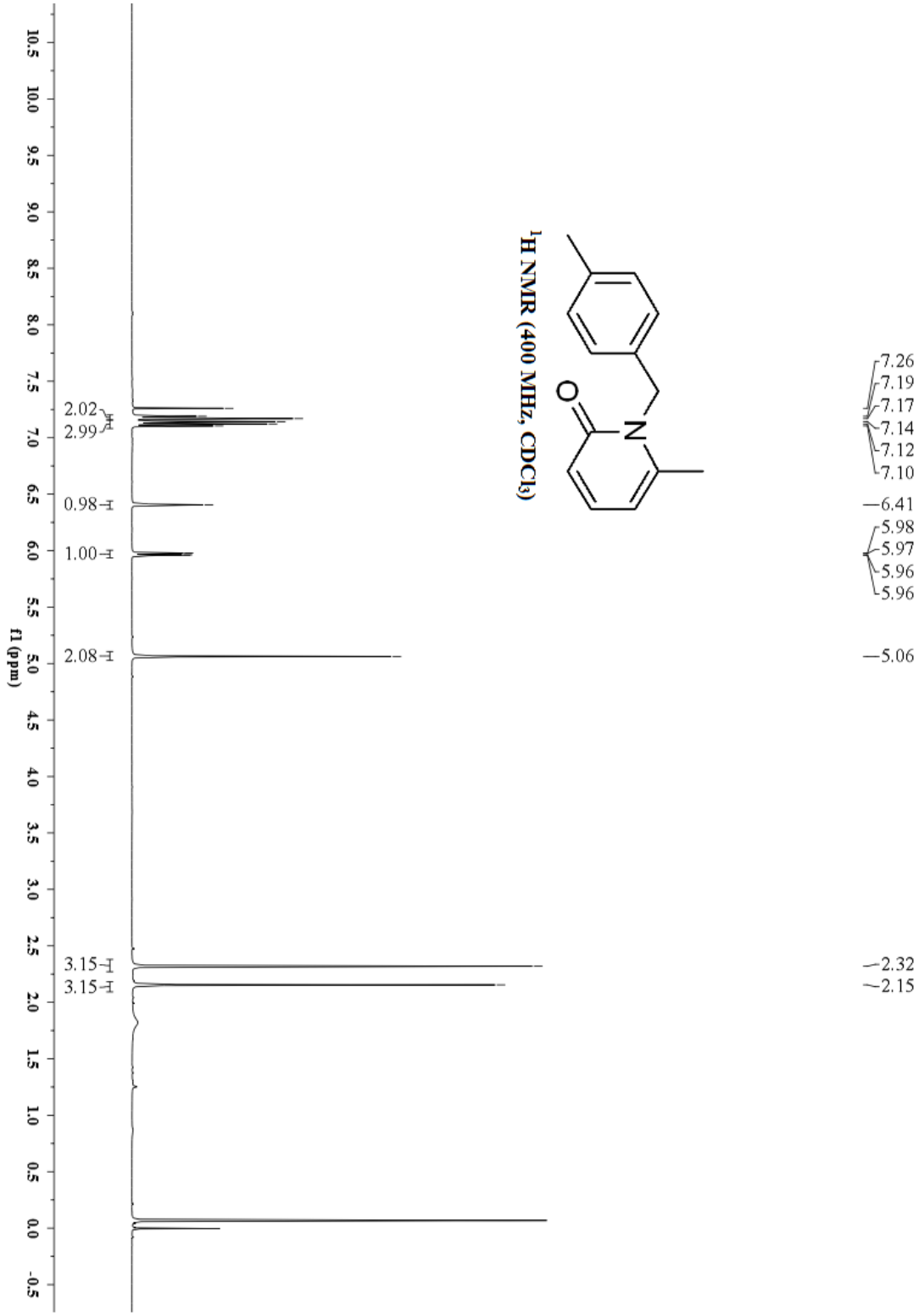
^{13}C NMR spectra of **3o**



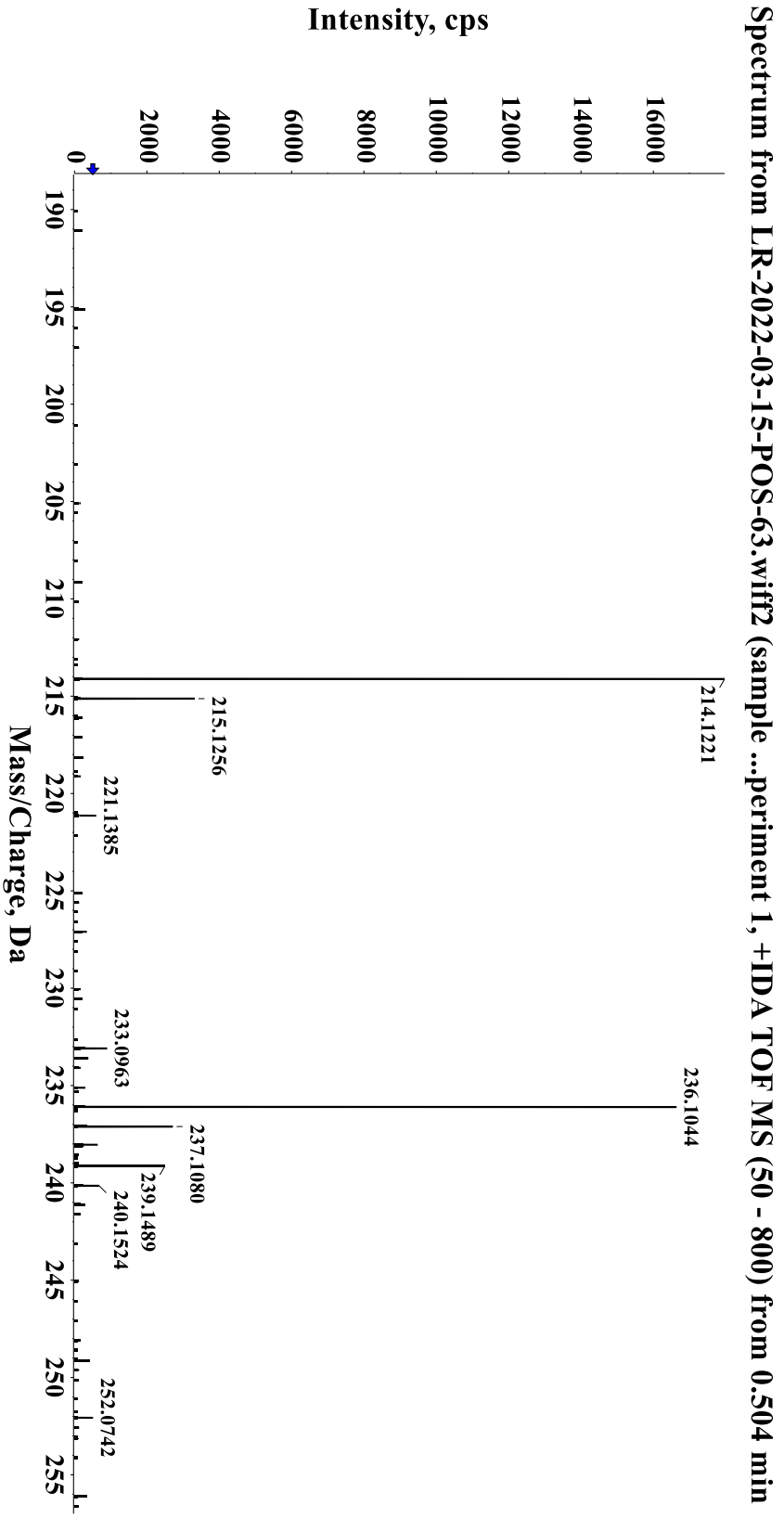
HRMS spectra of **3o**



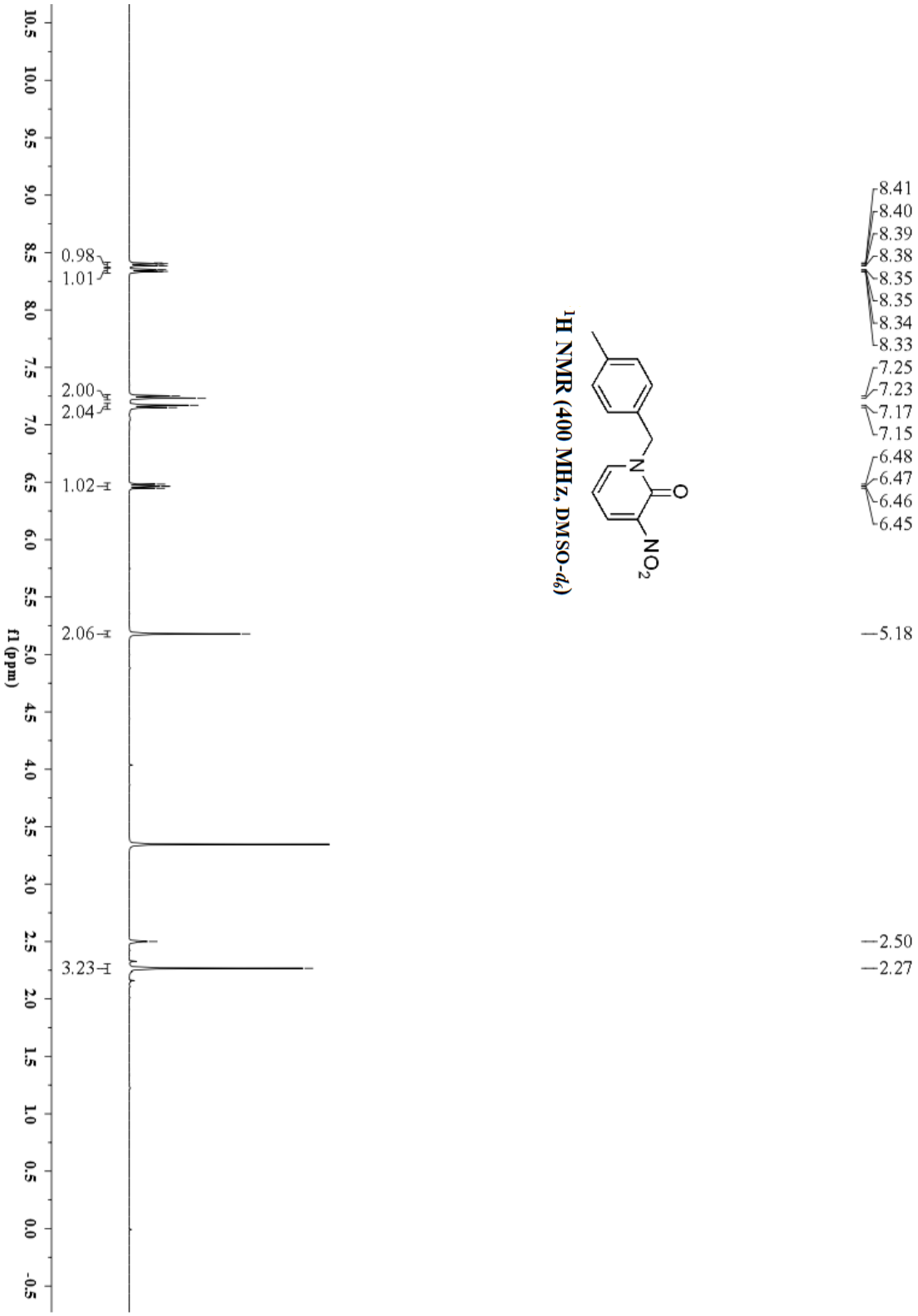
^{1}H NMR spectra of **3p**



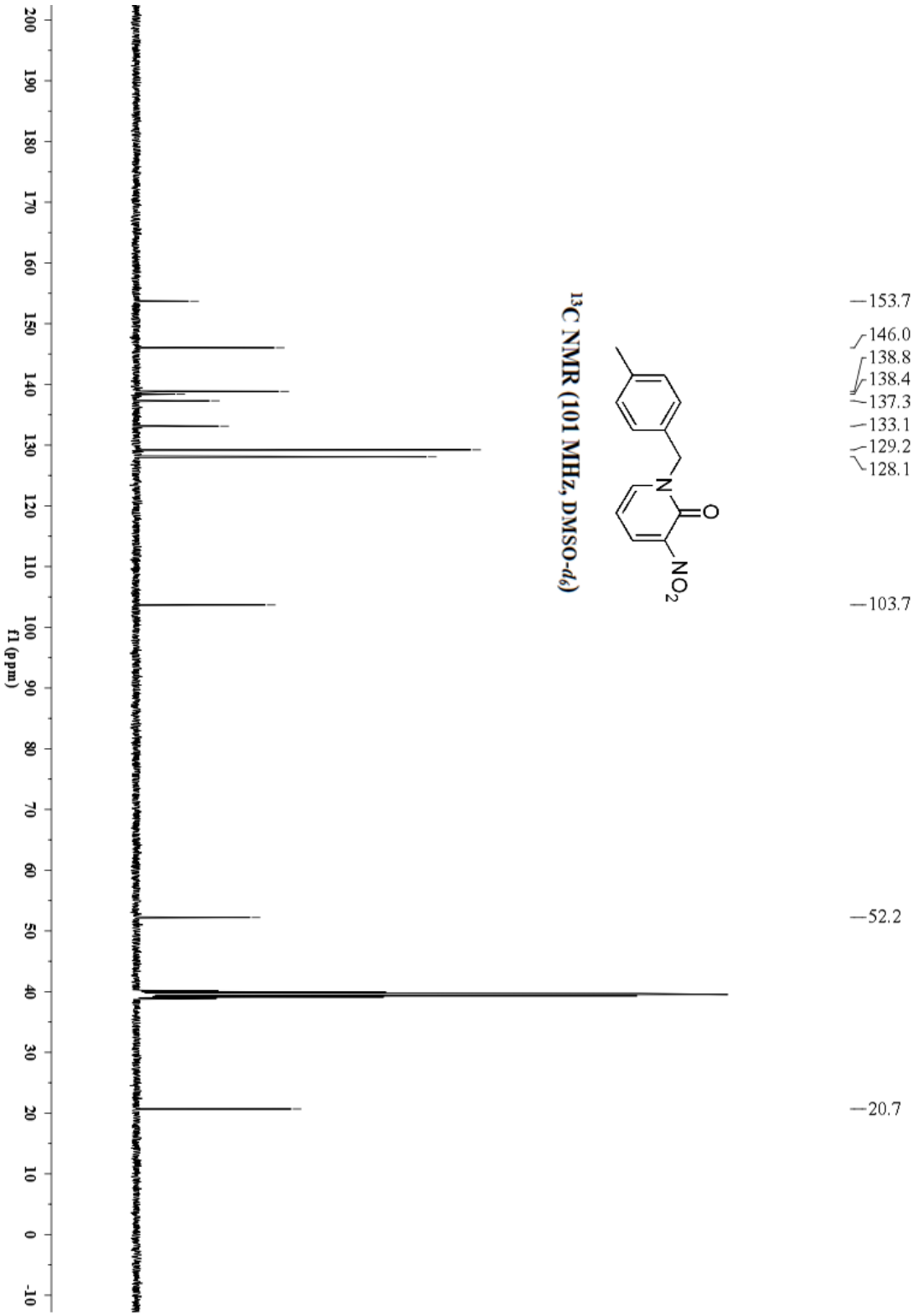
HRMS spectra of **3p**



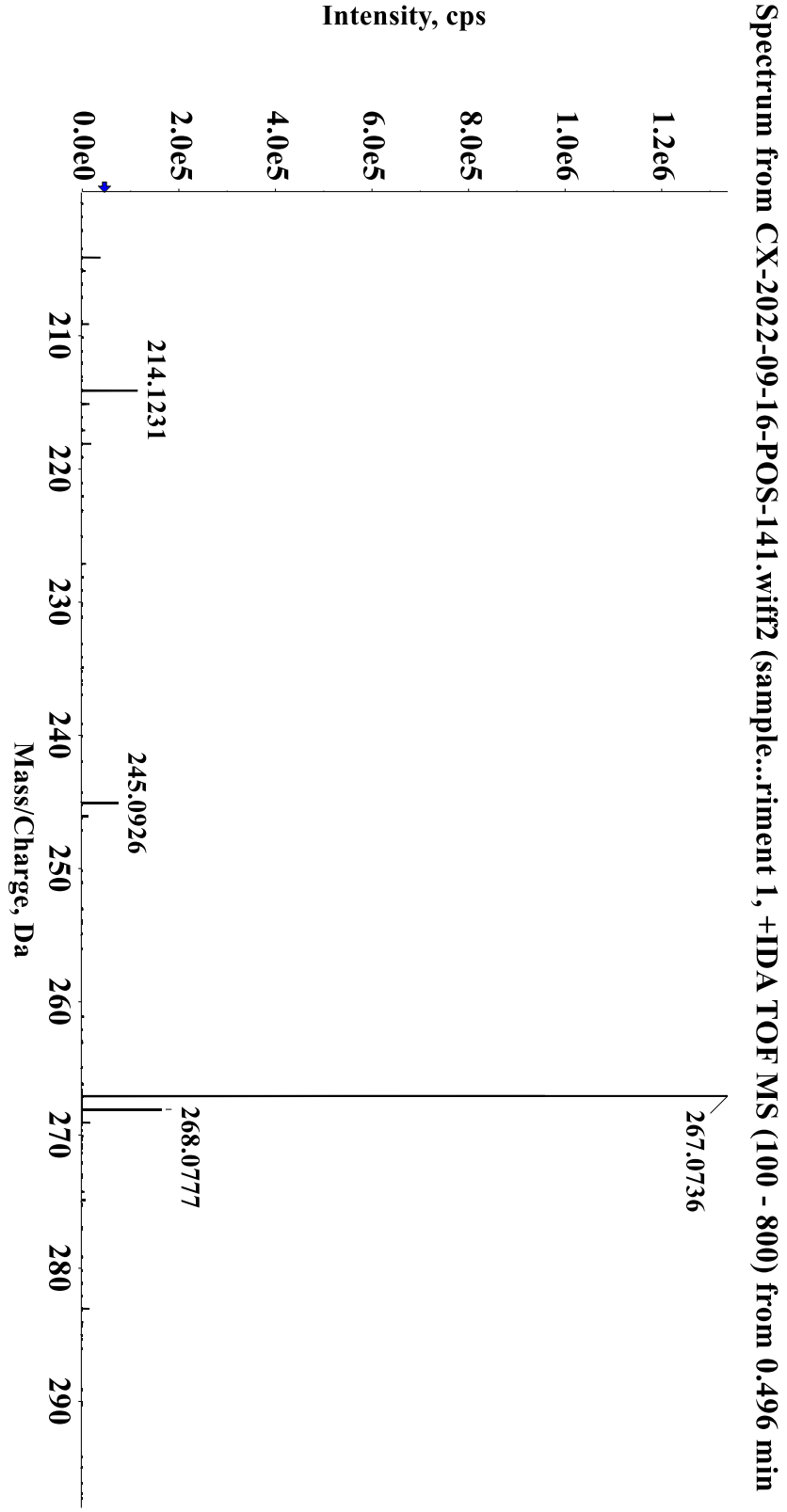
^{1}H NMR spectra of **3q**



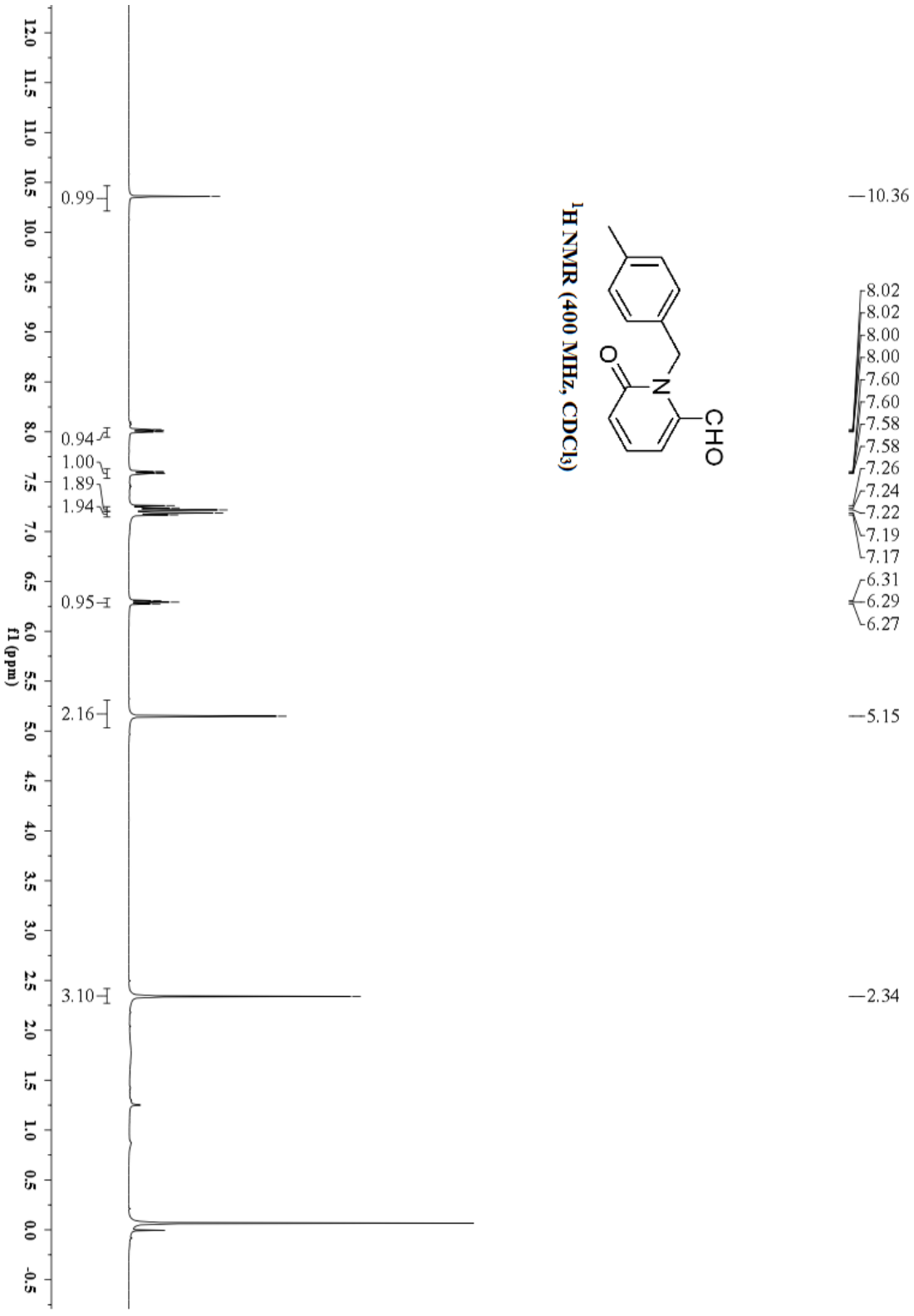
^{13}C NMR spectra of **3q**



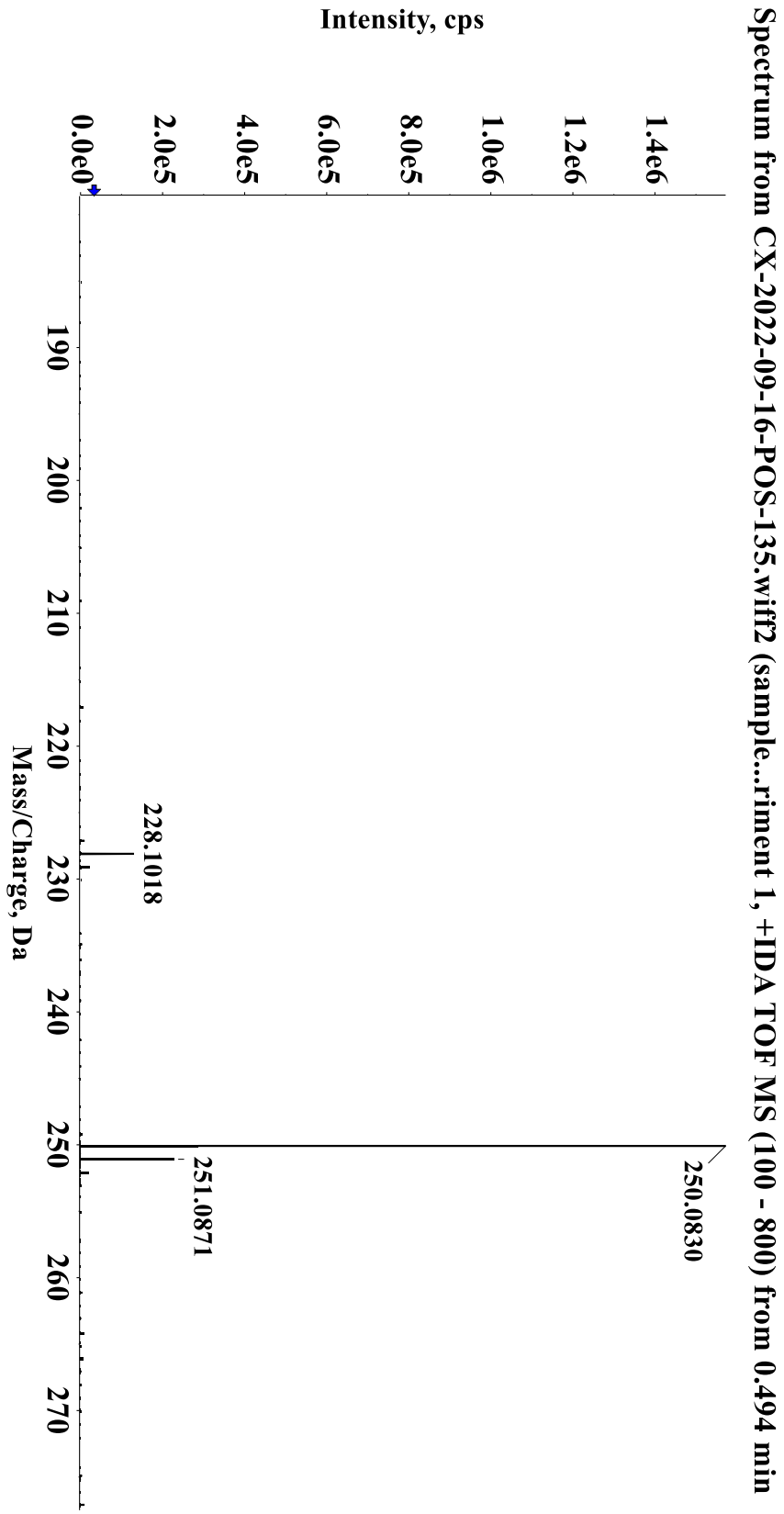
HRMS spectra of **3q**



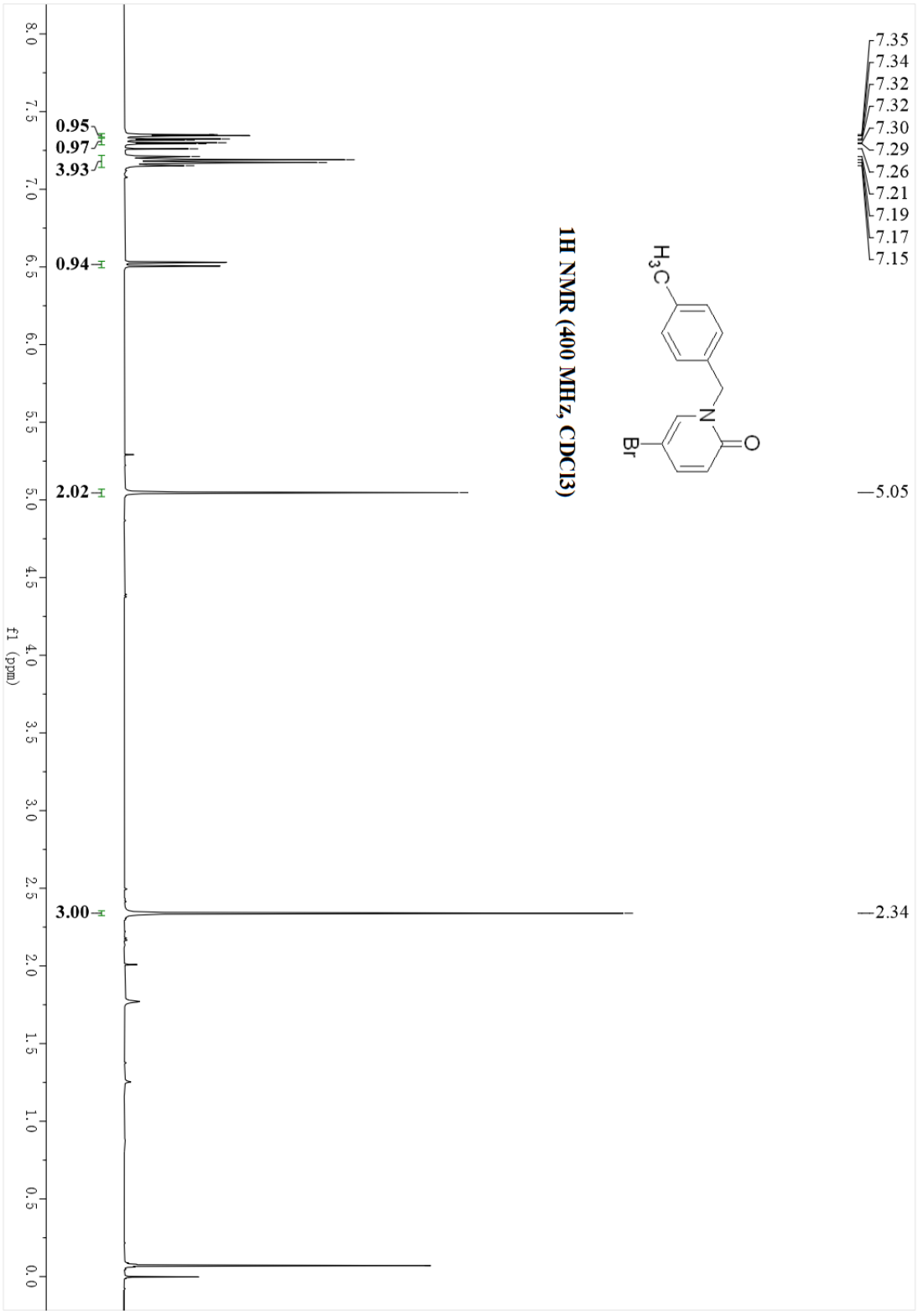
^{1}H NMR spectra of **3r**



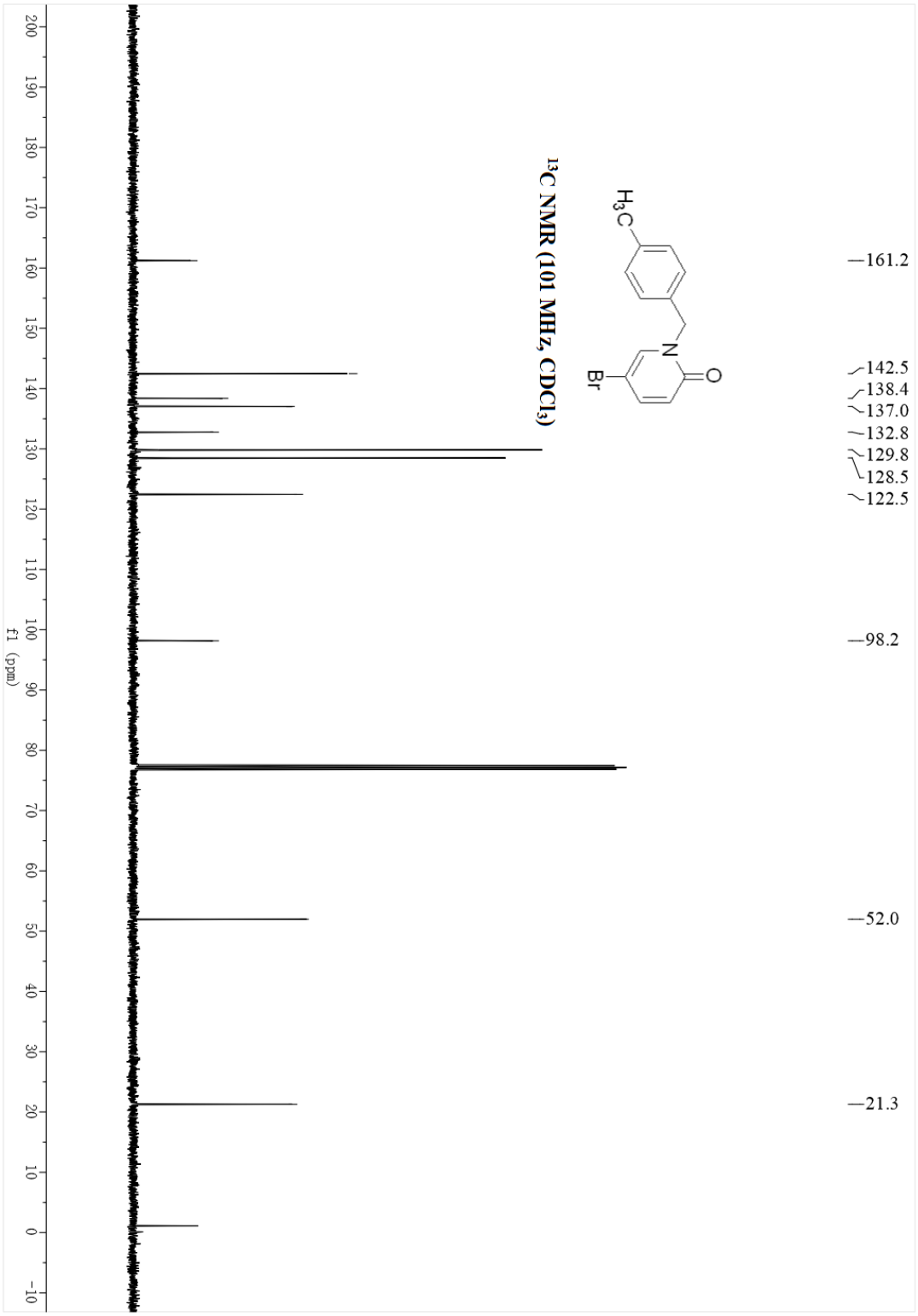
HRMS spectra of **3r**



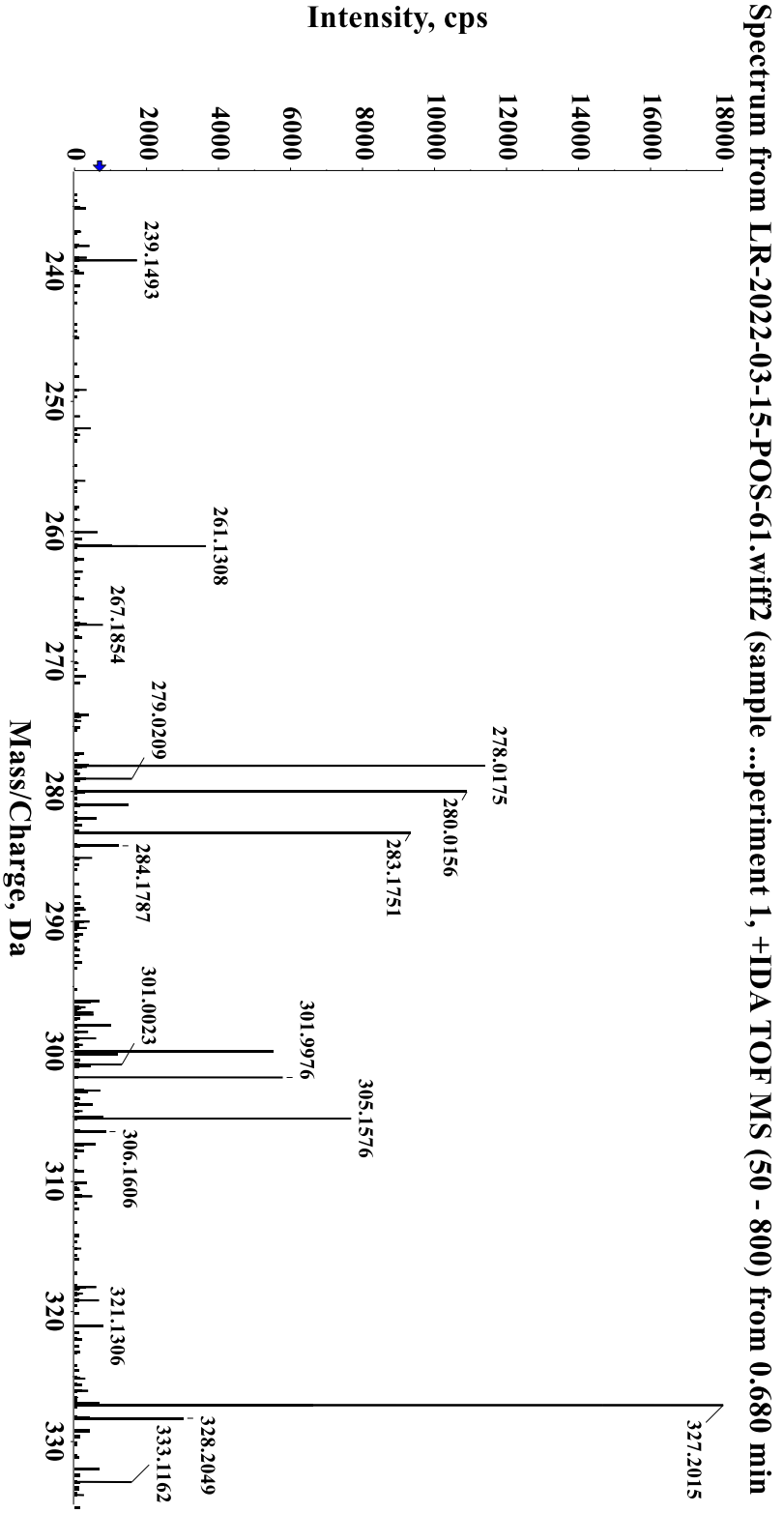
^{1}H NMR spectra of **3s**



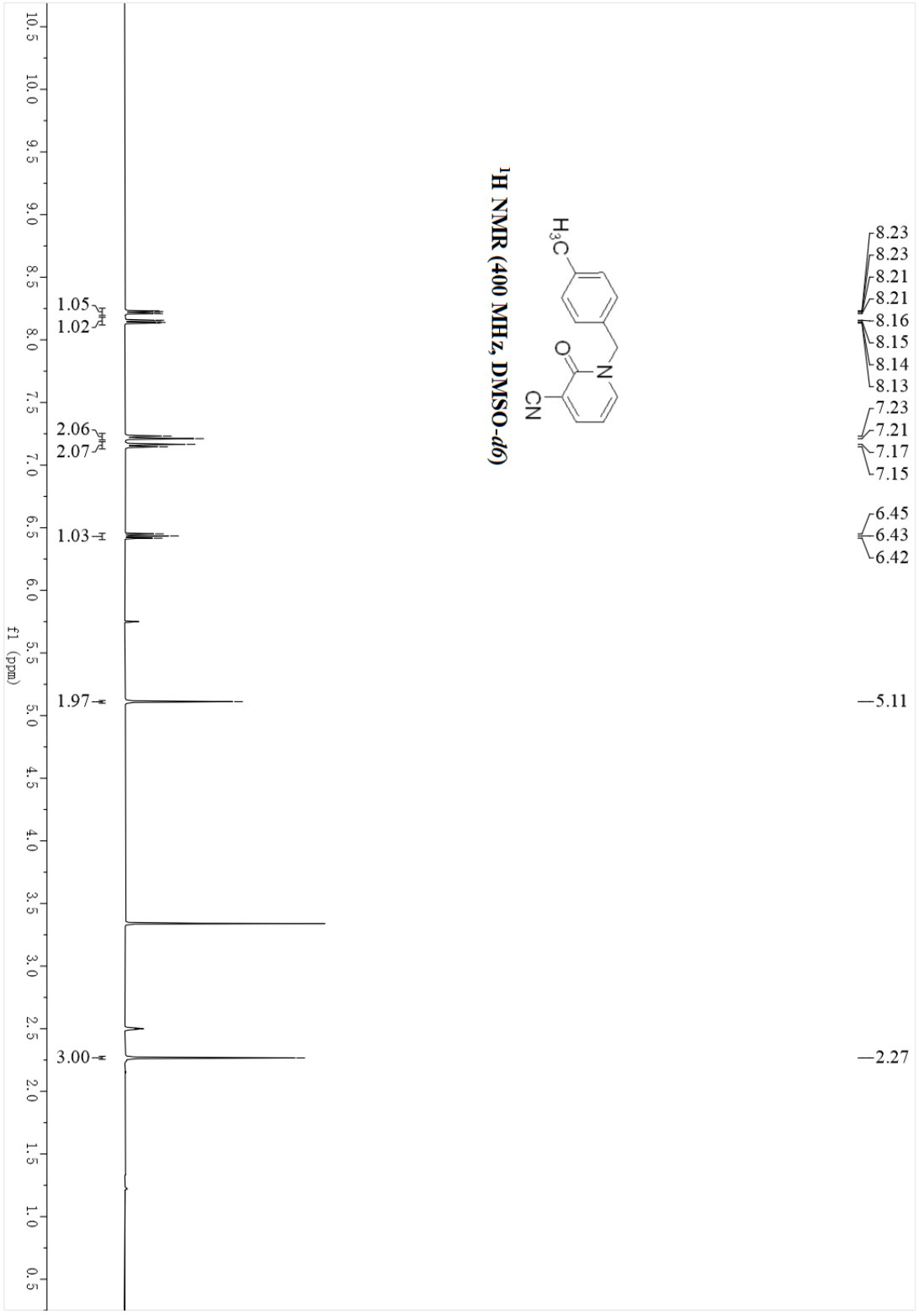
^{13}C NMR spectra of **3s**



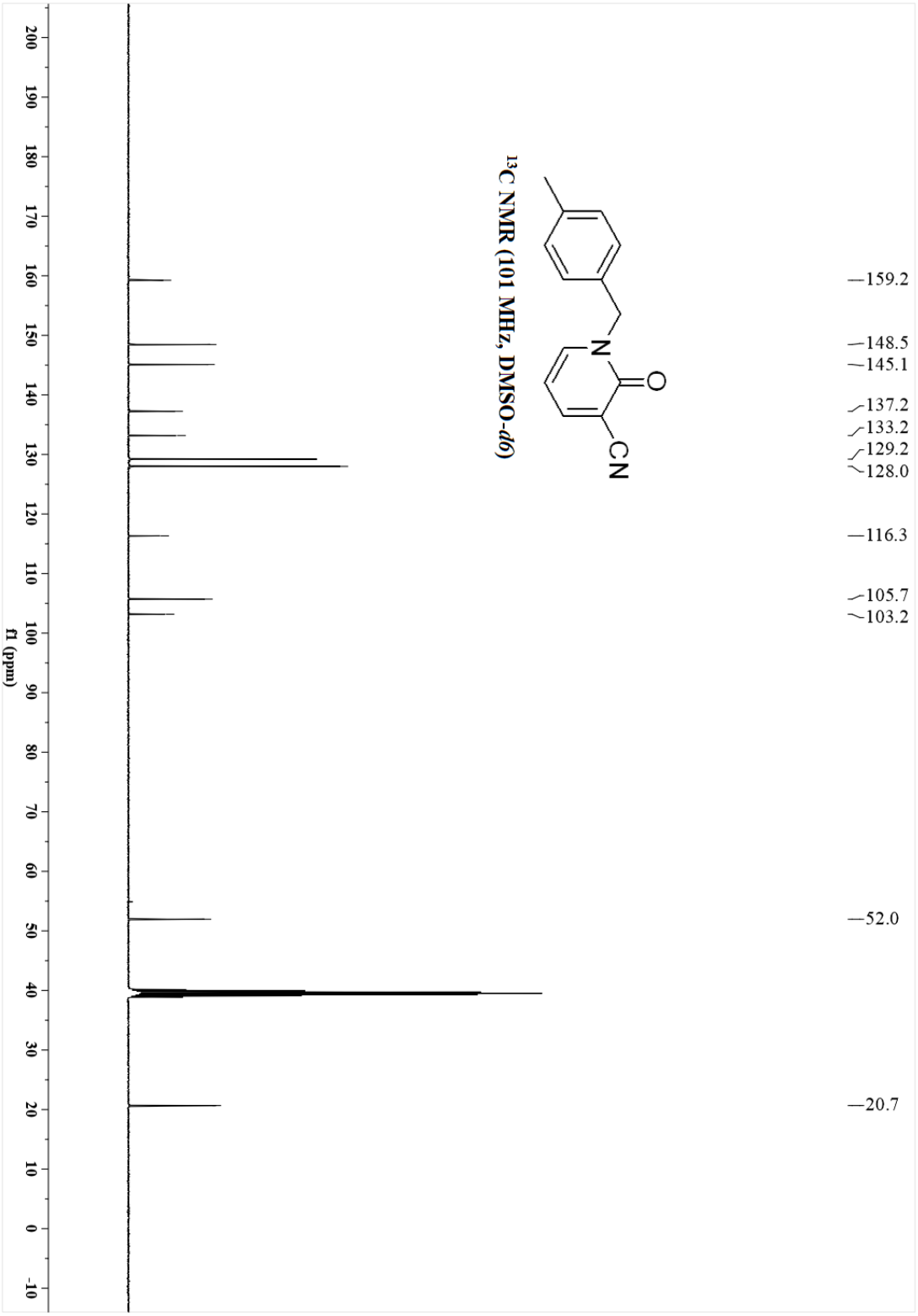
HRMS spectra of **3s**



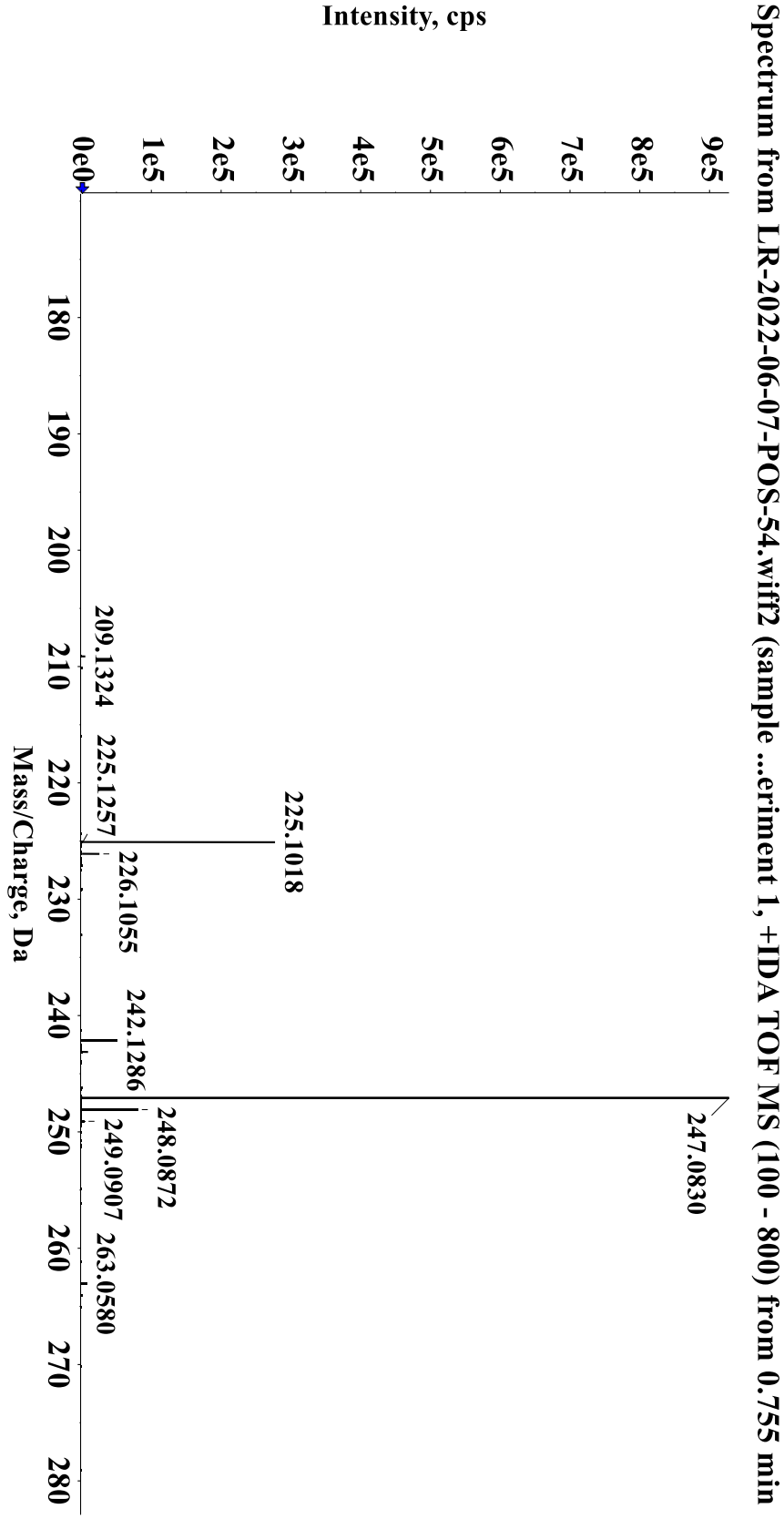
^{1}H NMR spectra of **3t**



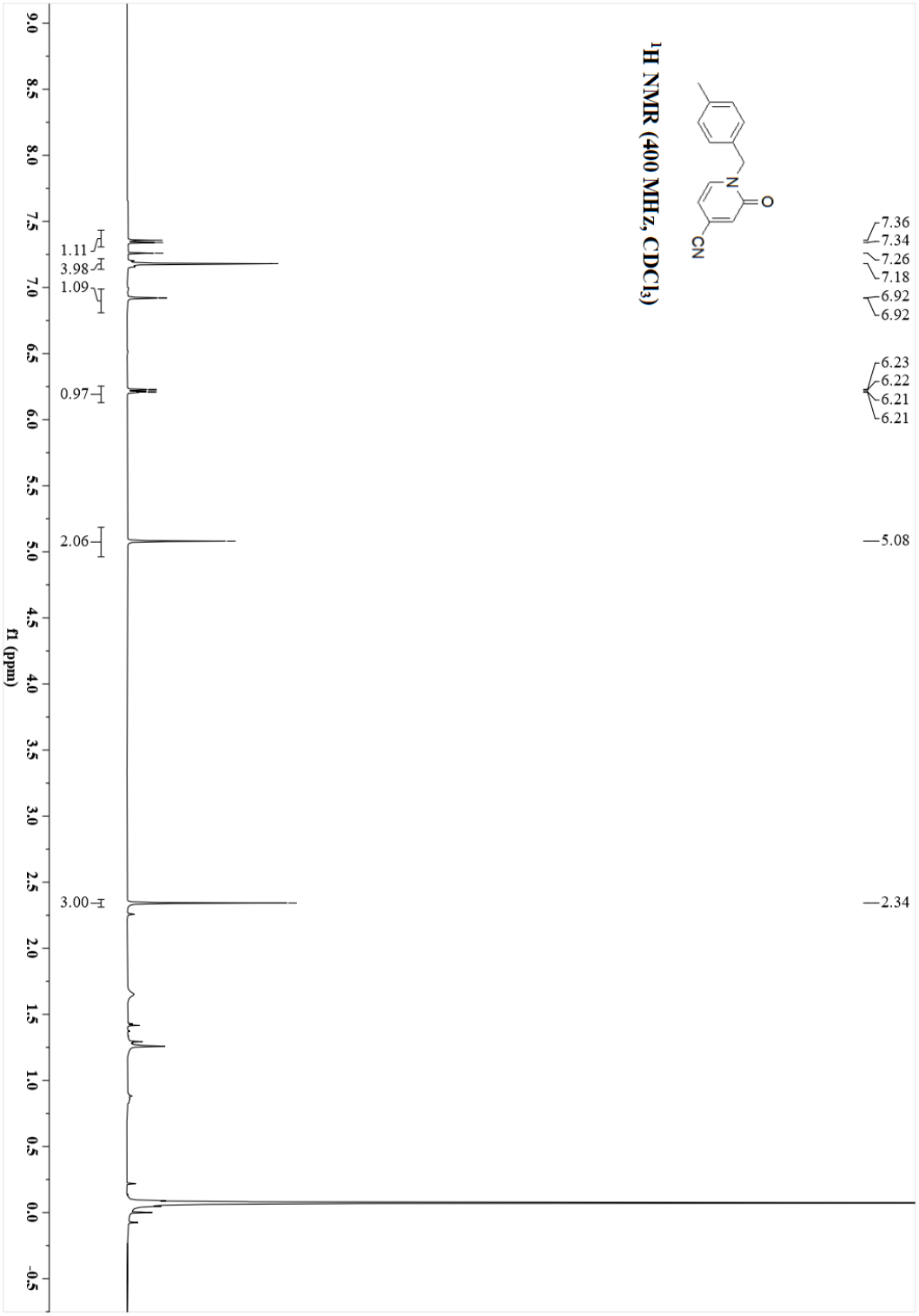
^{13}C NMR spectra of **3t**



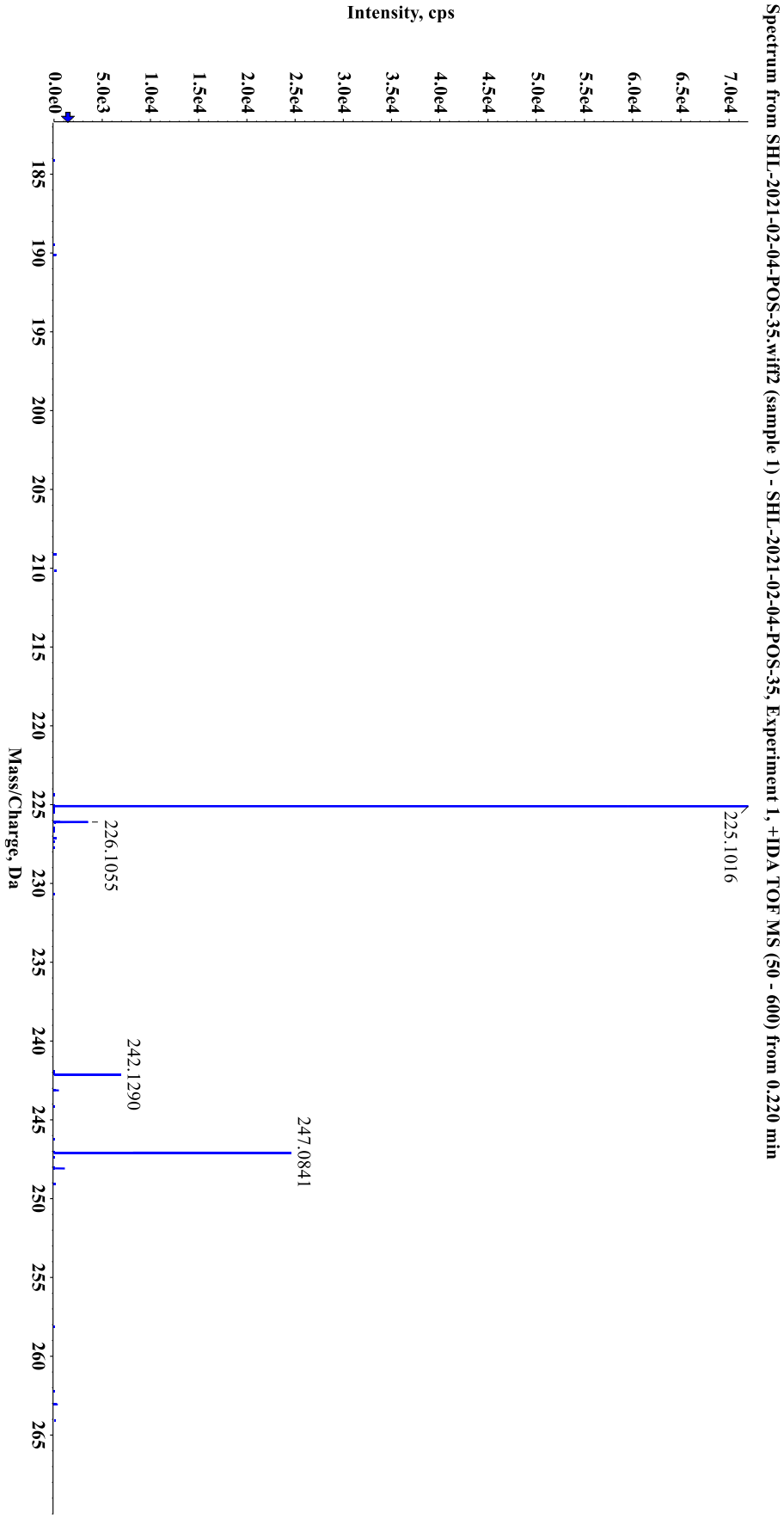
HRMS spectra of **3t**



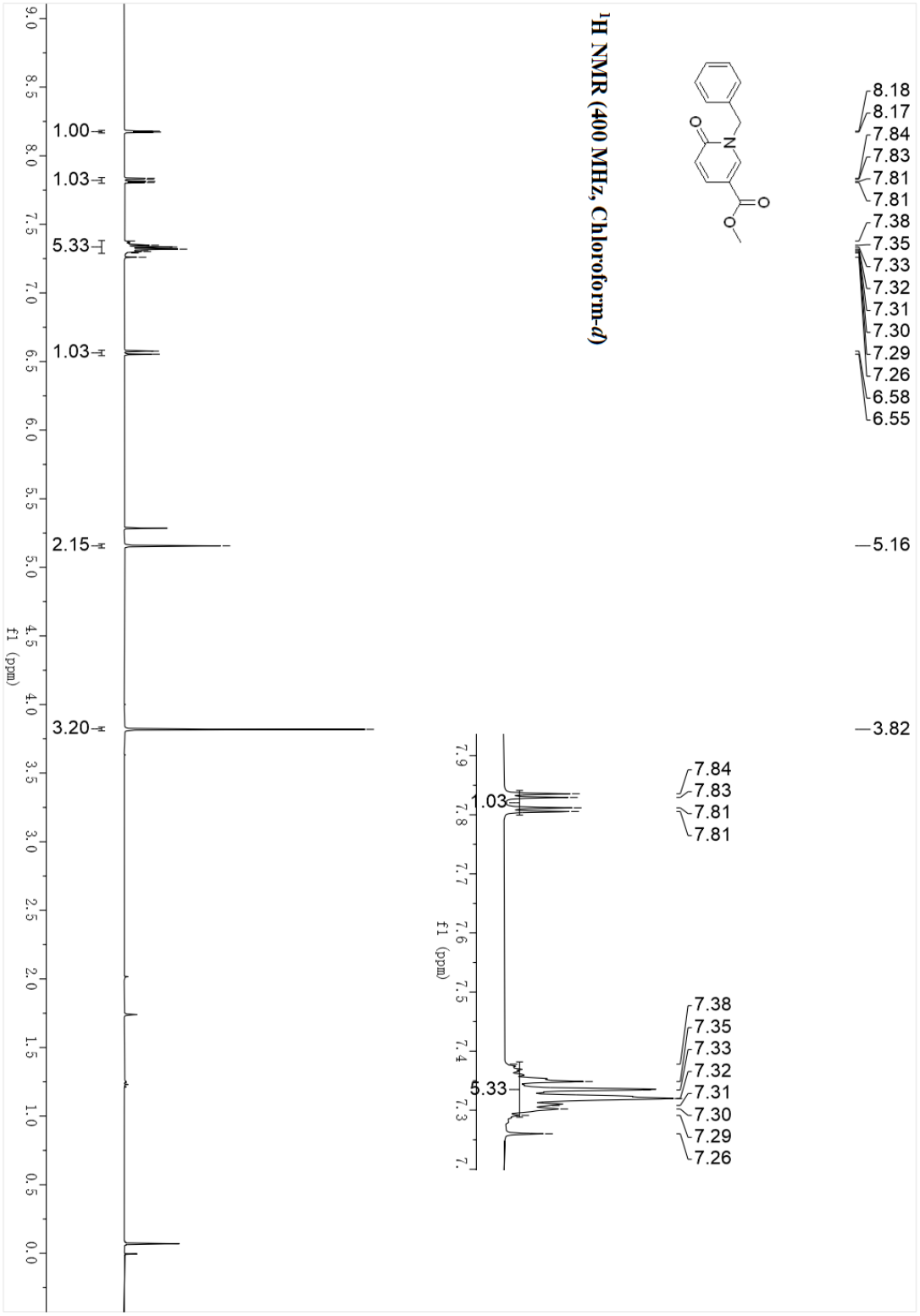
^{1}H NMR spectra of **3u**



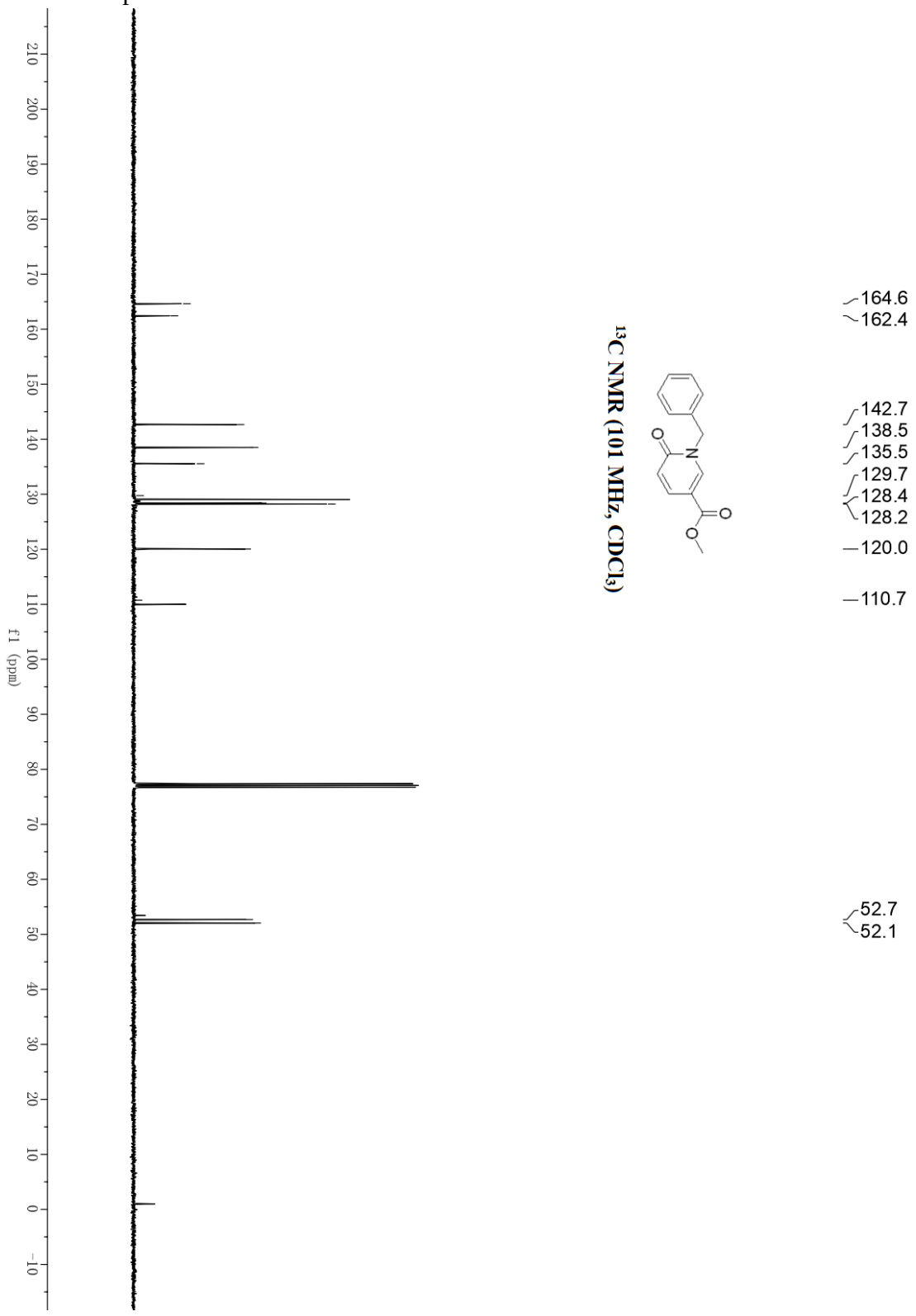
HRMS spectra of **3u**



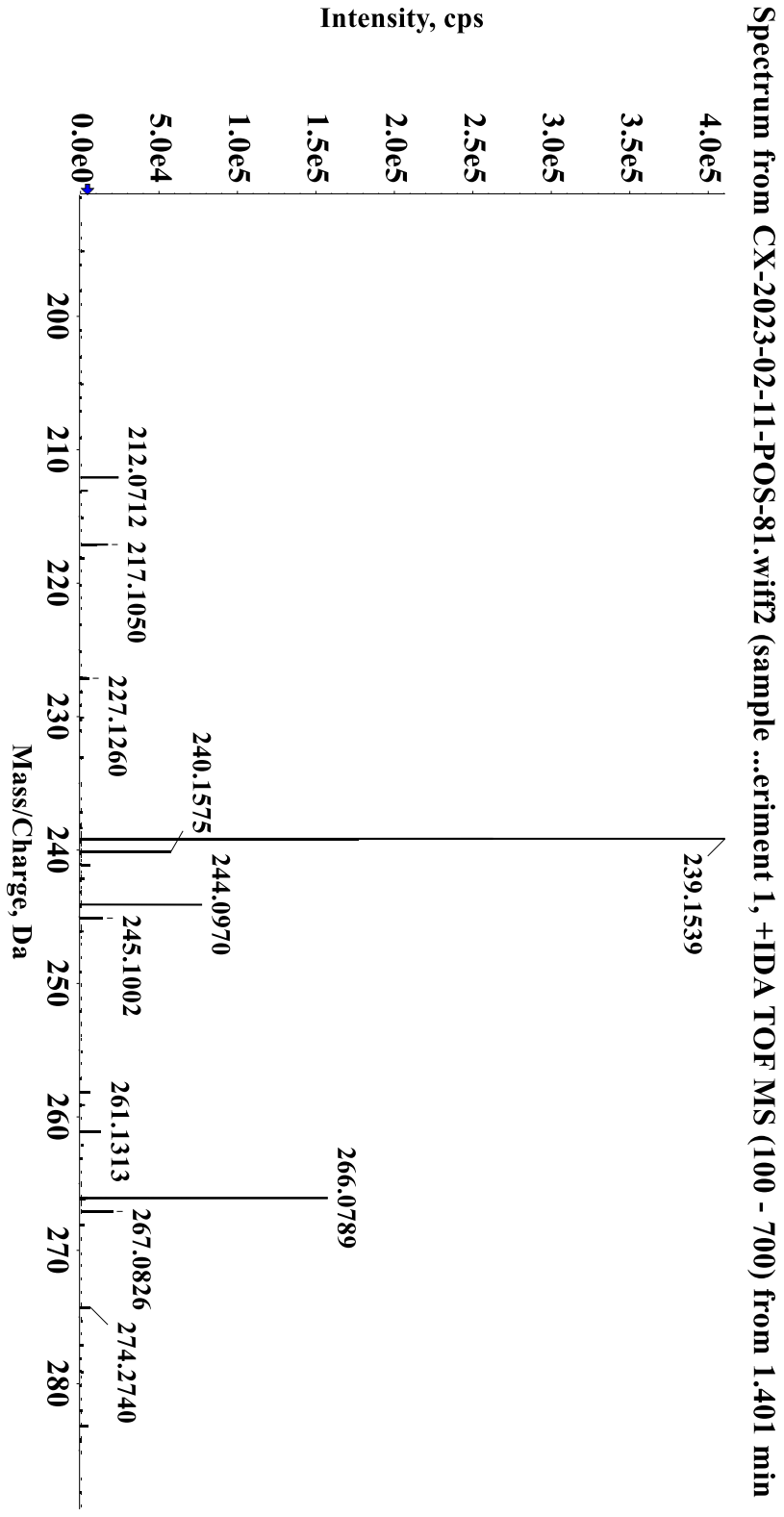
^{1}H NMR spectra of **3v**



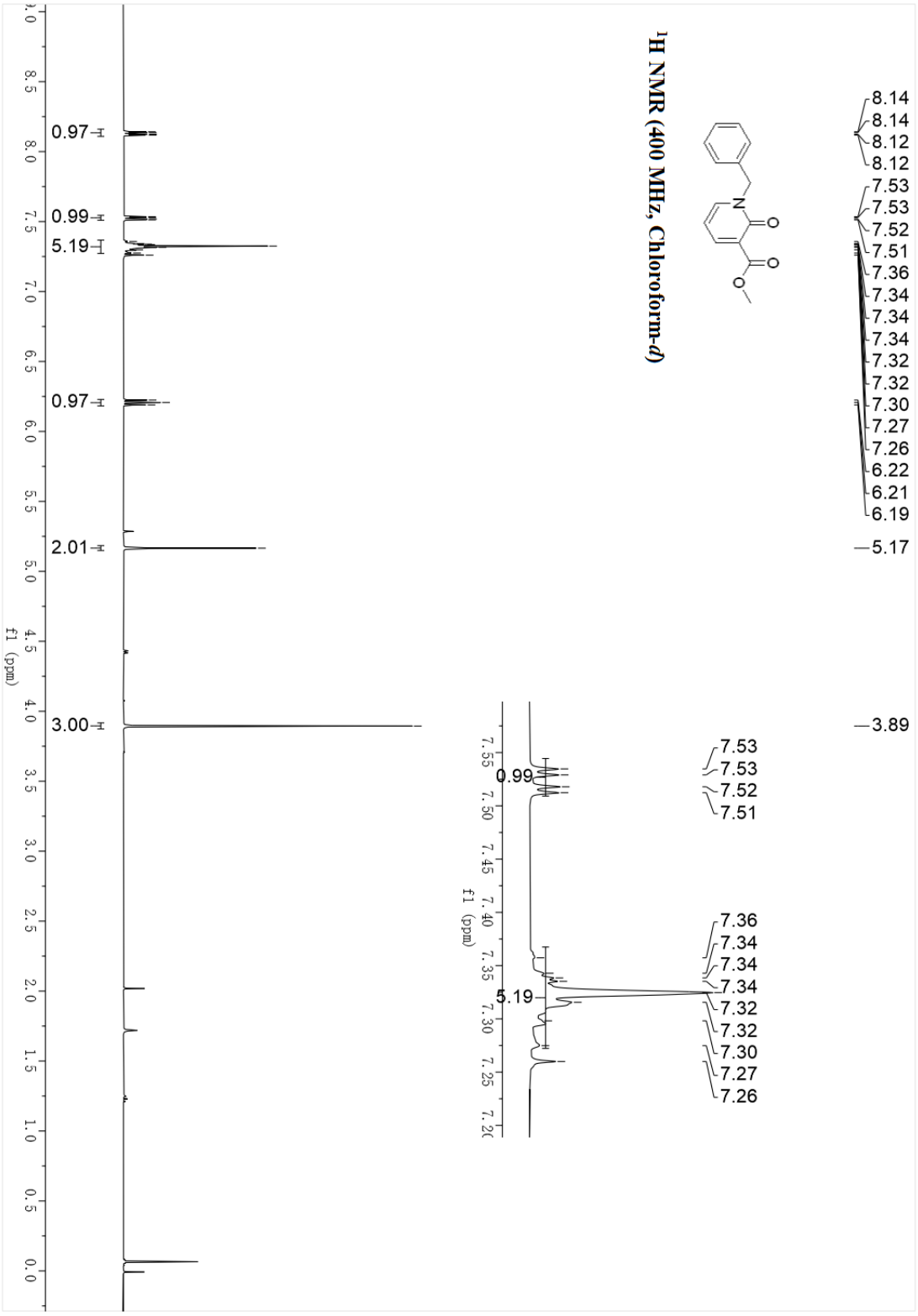
^{13}C NMR spectra of **3v**



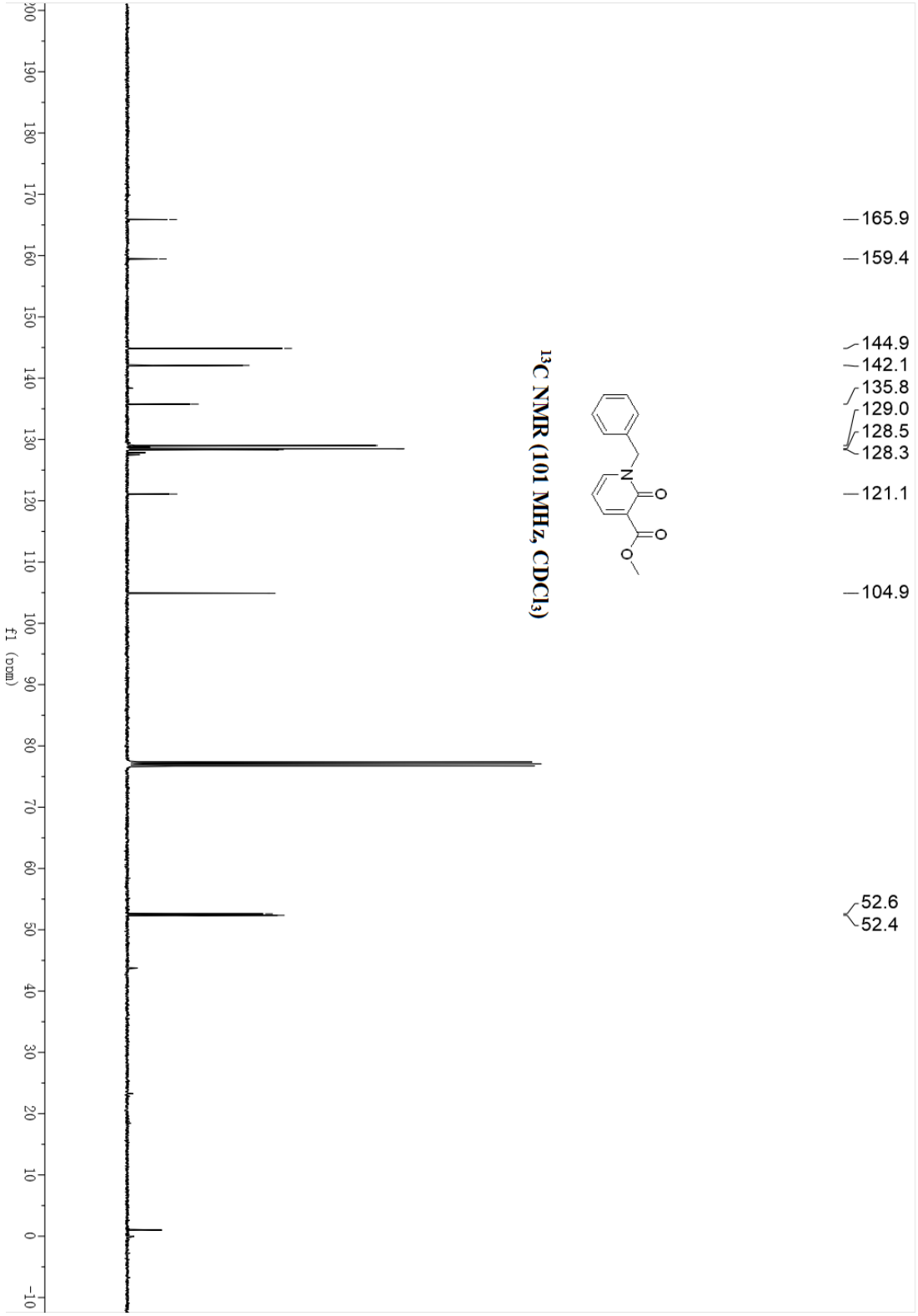
HRMS spectra of **3v**



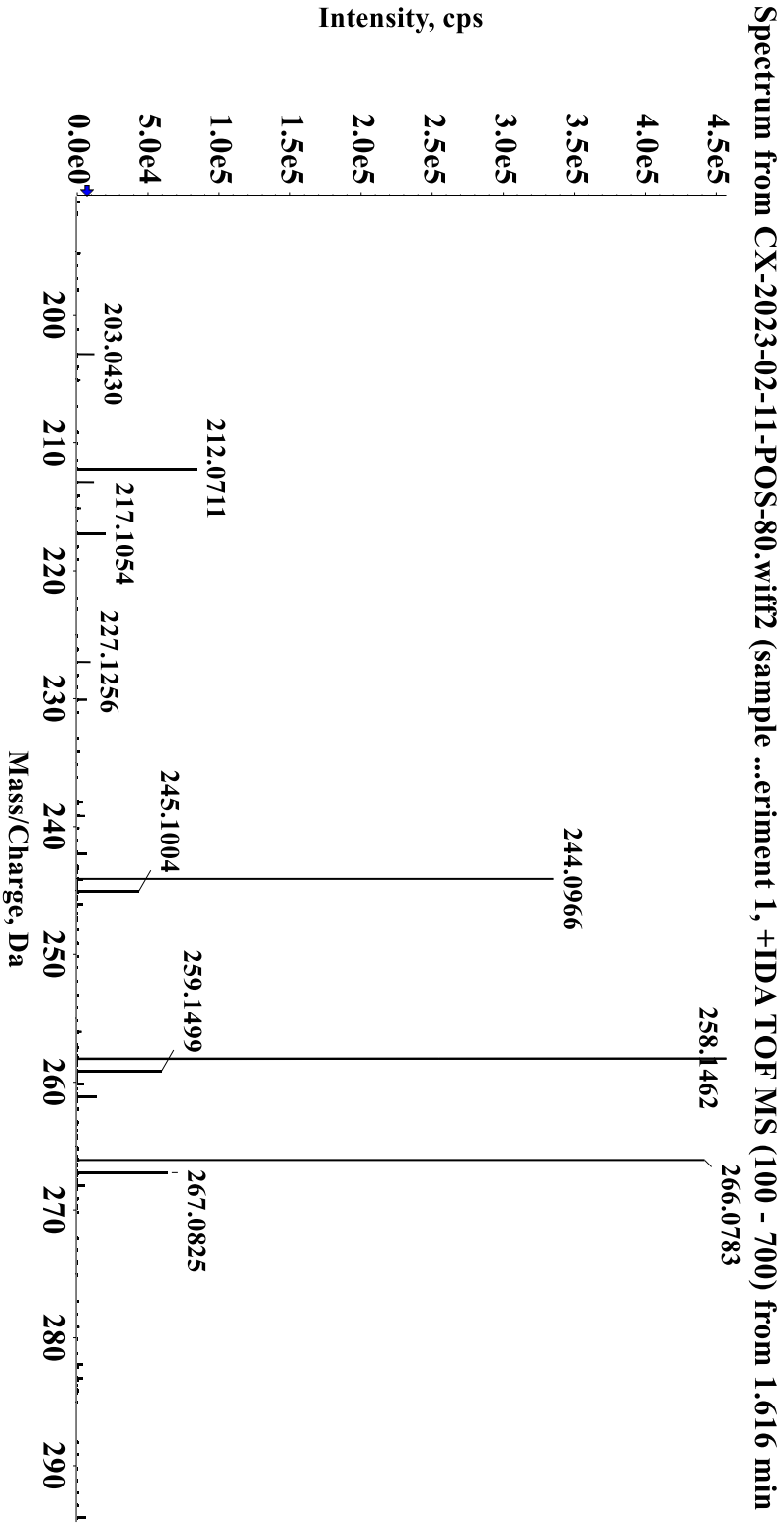
^{1}H NMR spectra of **3w**



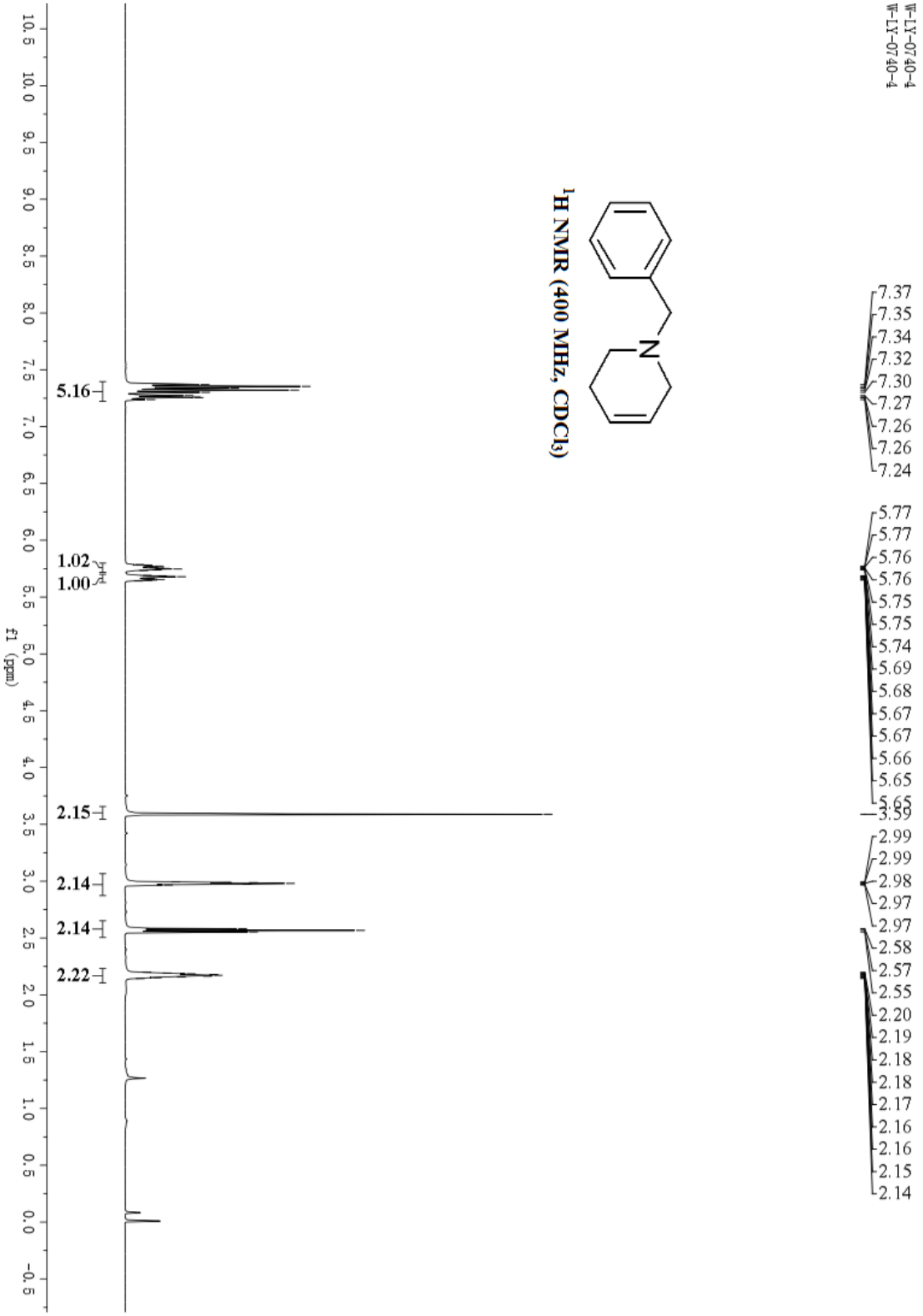
^{13}C NMR spectra of **3w**



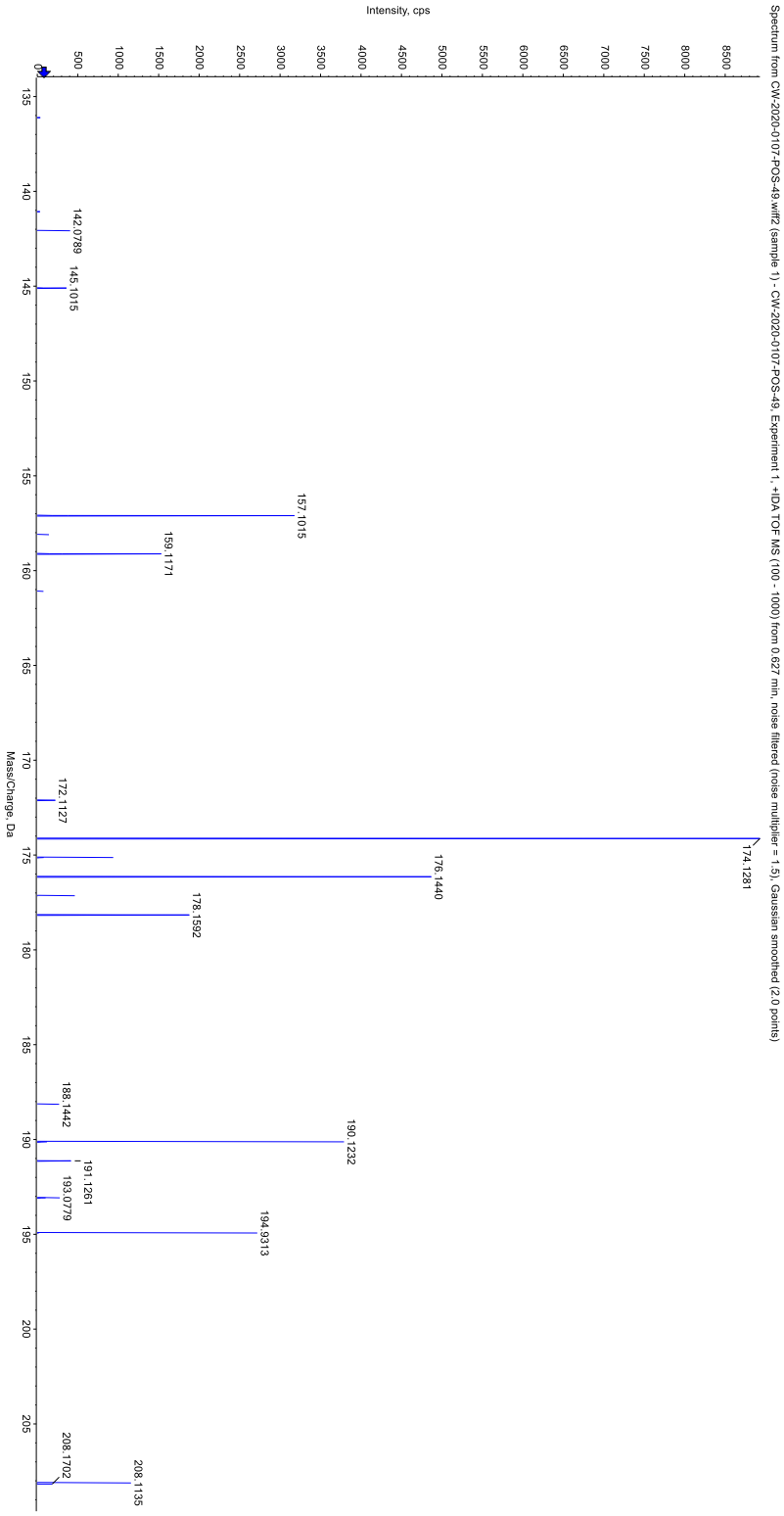
HRMS spectra of **3w**



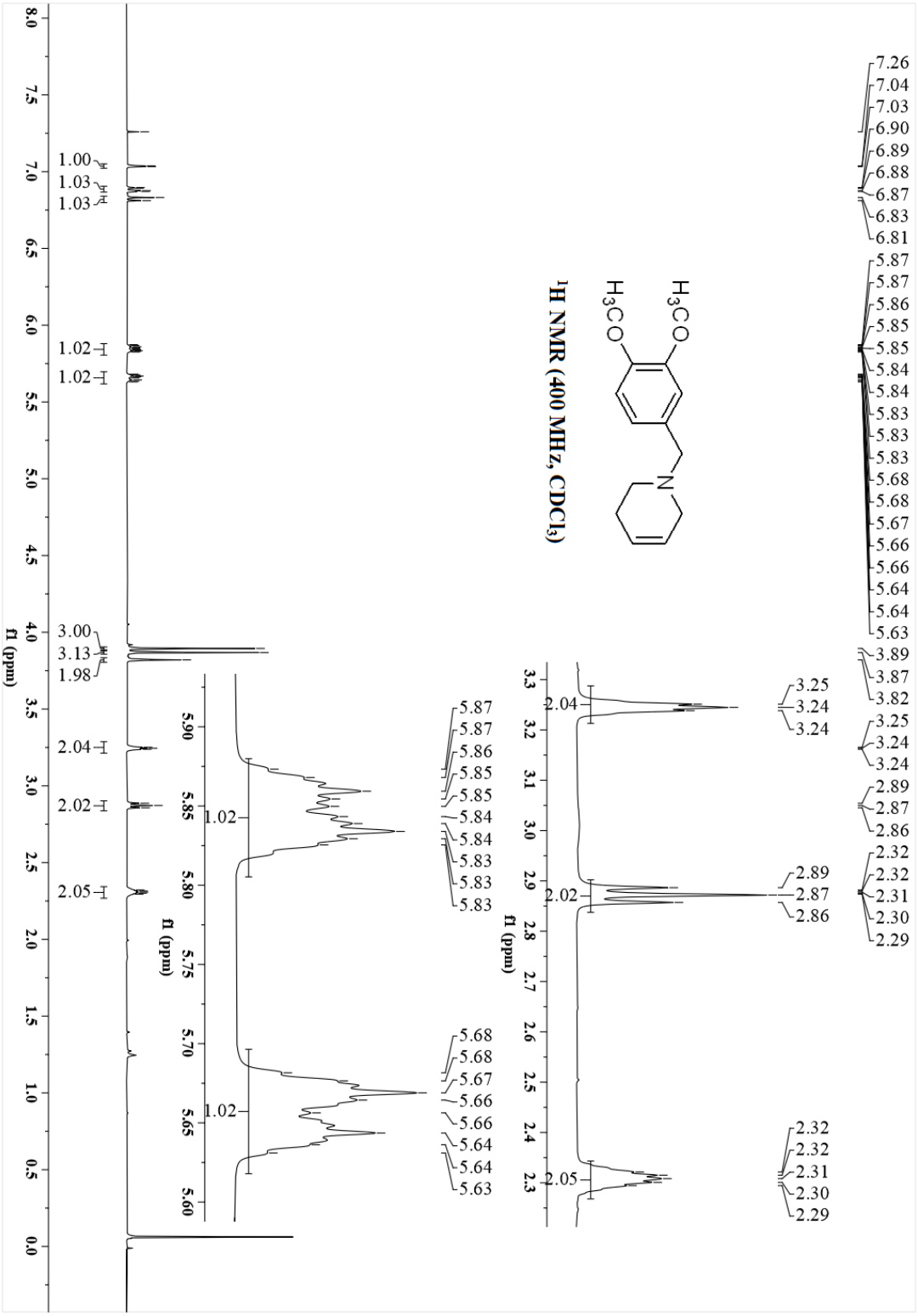
^{1}H NMR spectra of **4a**



HRMS spectra of **4a**



^{1}H NMR spectra of **4b**



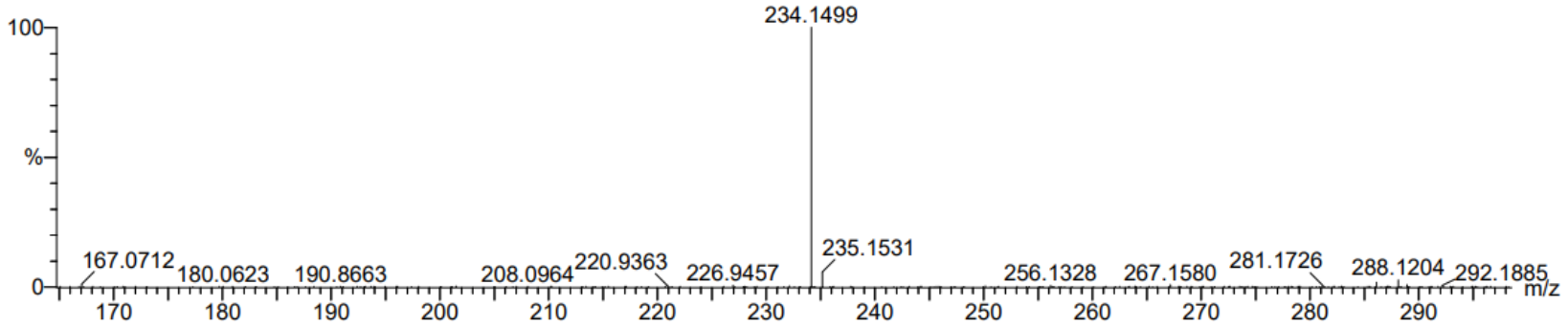
HRMS spectra of **4b**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
446 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:
C: 14-14 H: 20-20 N: 0-20 O: 0-100 Na: 0-4

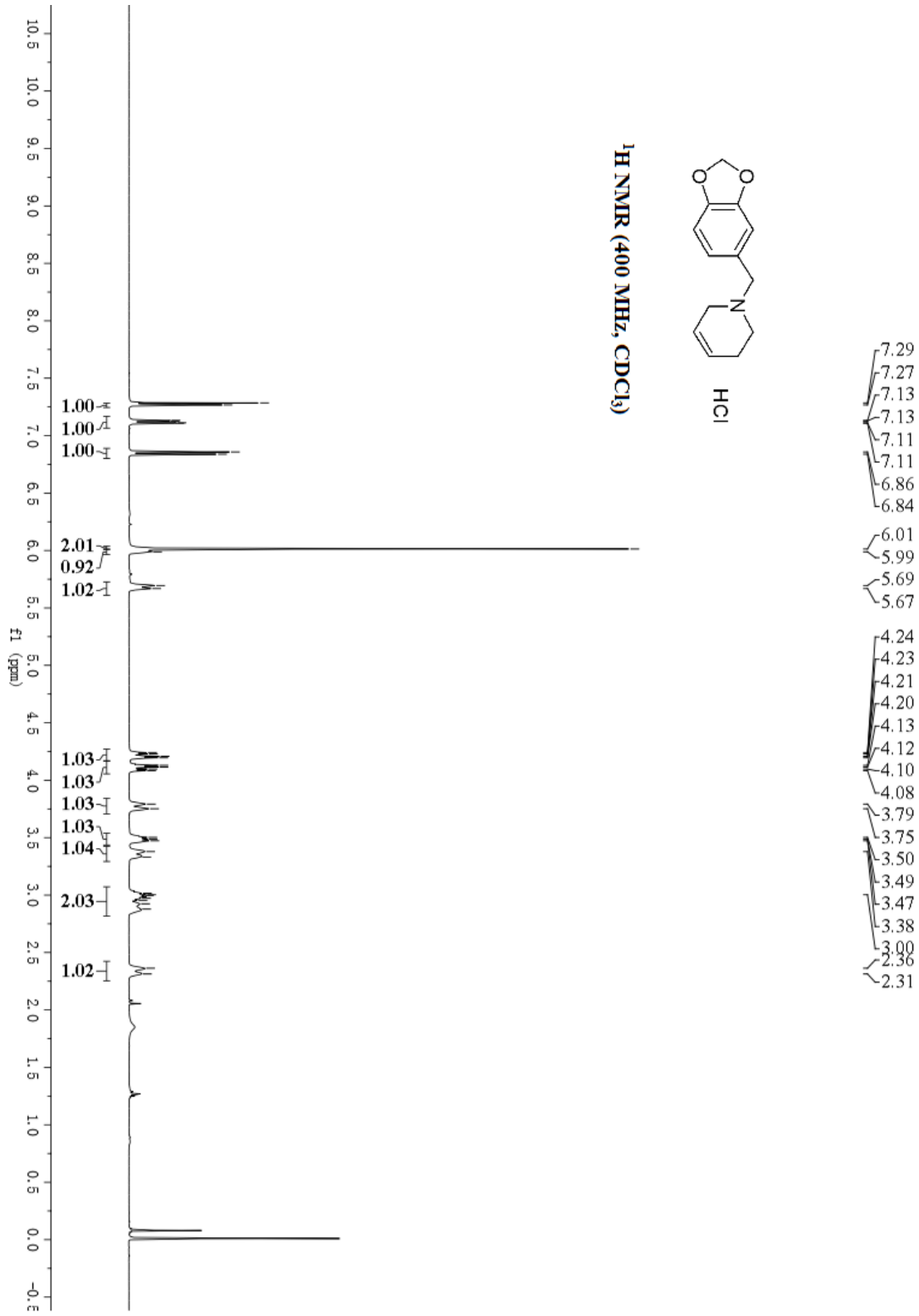
10
230105-9-ly-0754-1 29 (0.127)

1: TOF MS ES+
3.40e+004

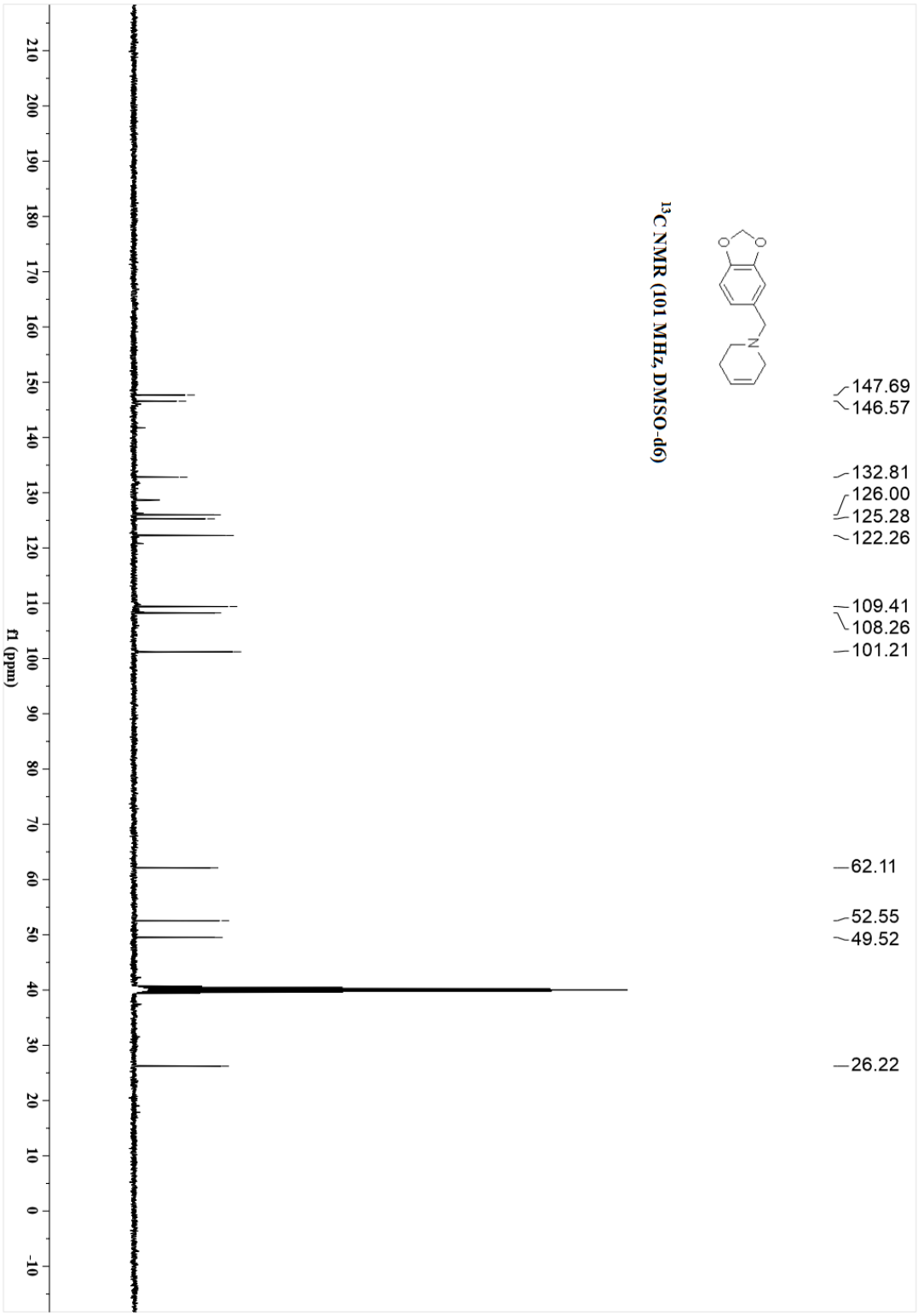


Minimum:				-1.5				
Maximum:		5.0	10.0	50.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
234.1499	234.1494	0.5	2.1	5.5	72.8	n/a	n/a	C14 H20 N O2

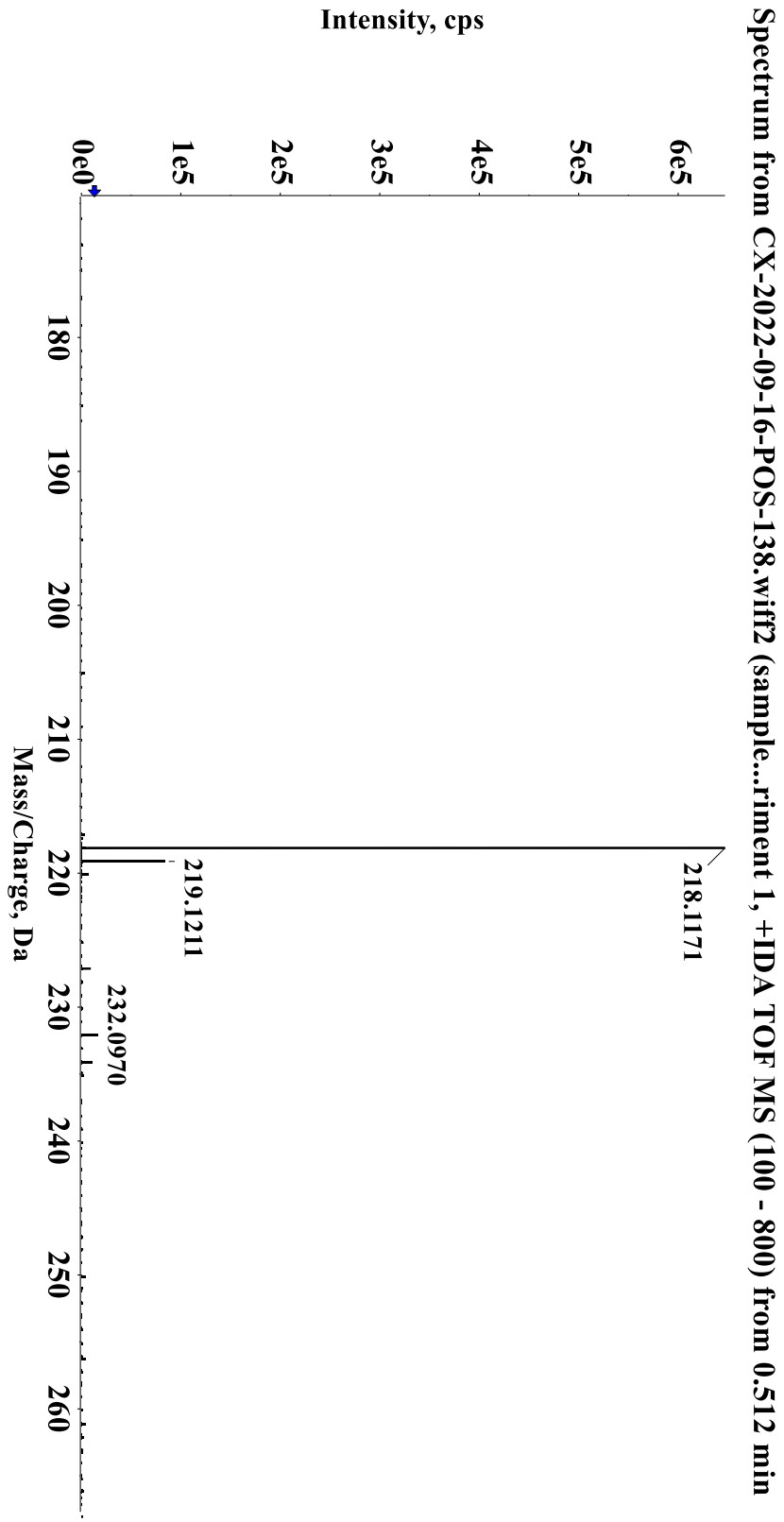
^{1}H NMR spectra of **4c**



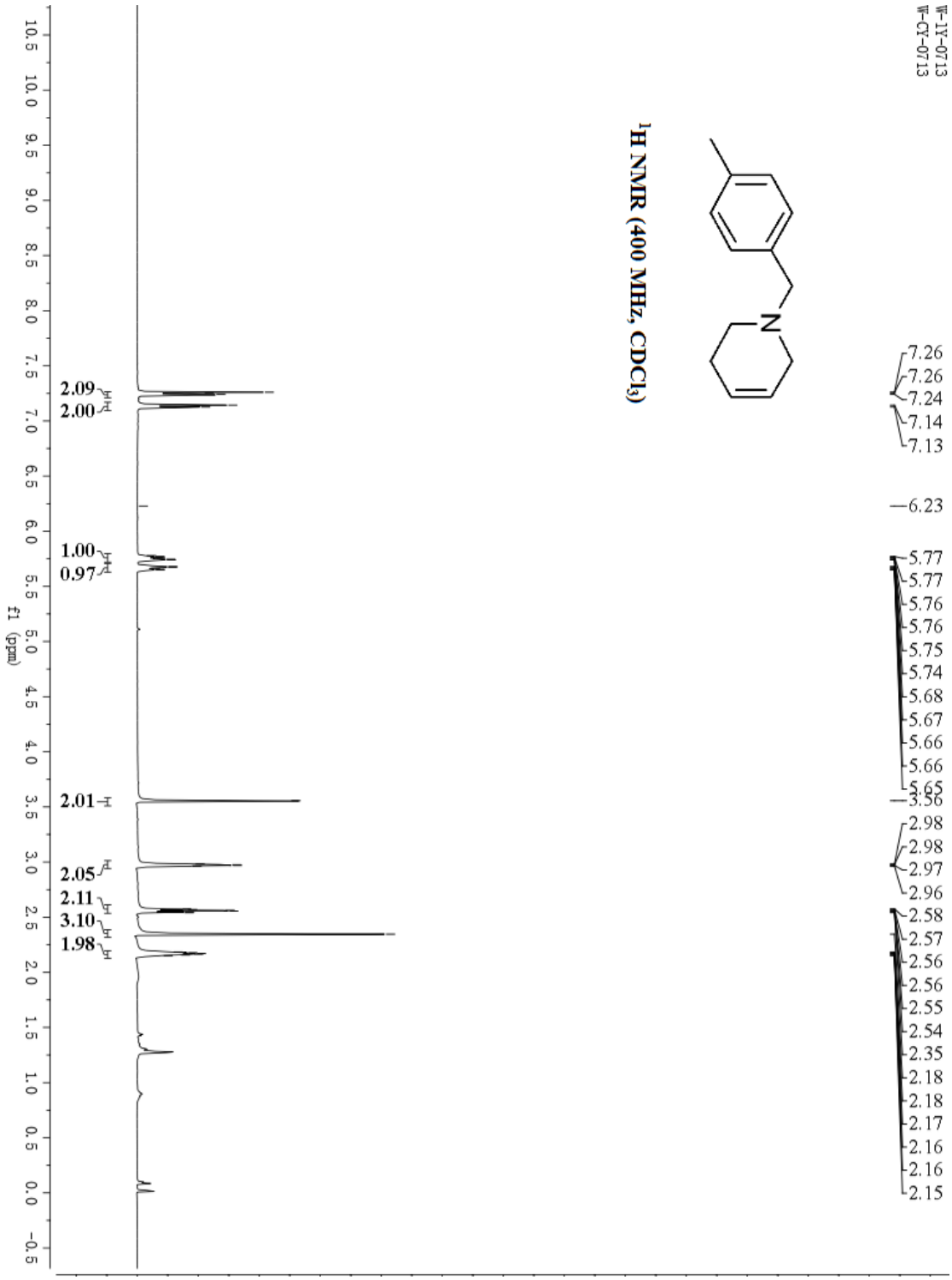
^{13}C NMR spectra of **4c**



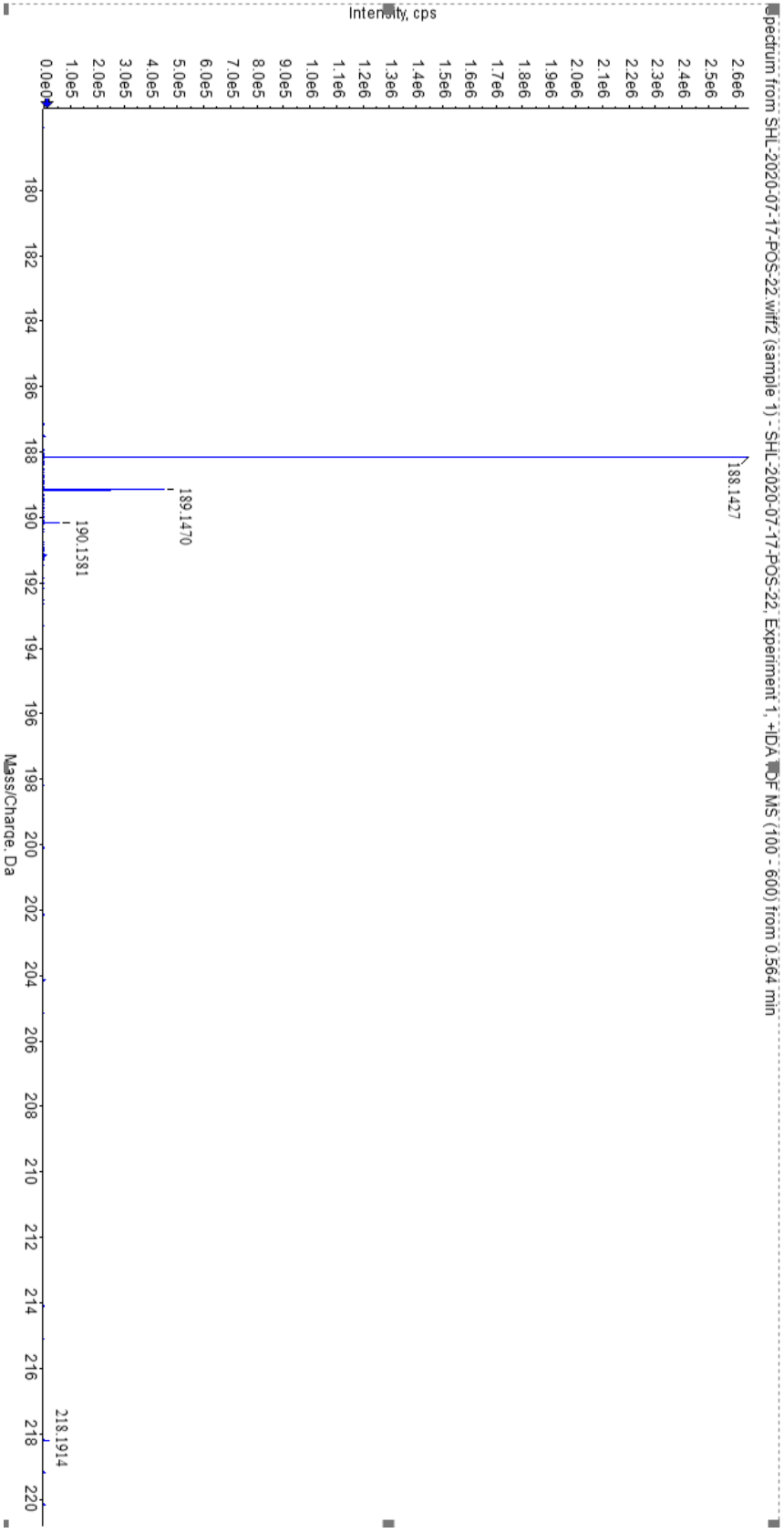
HRMS spectra of **4c**



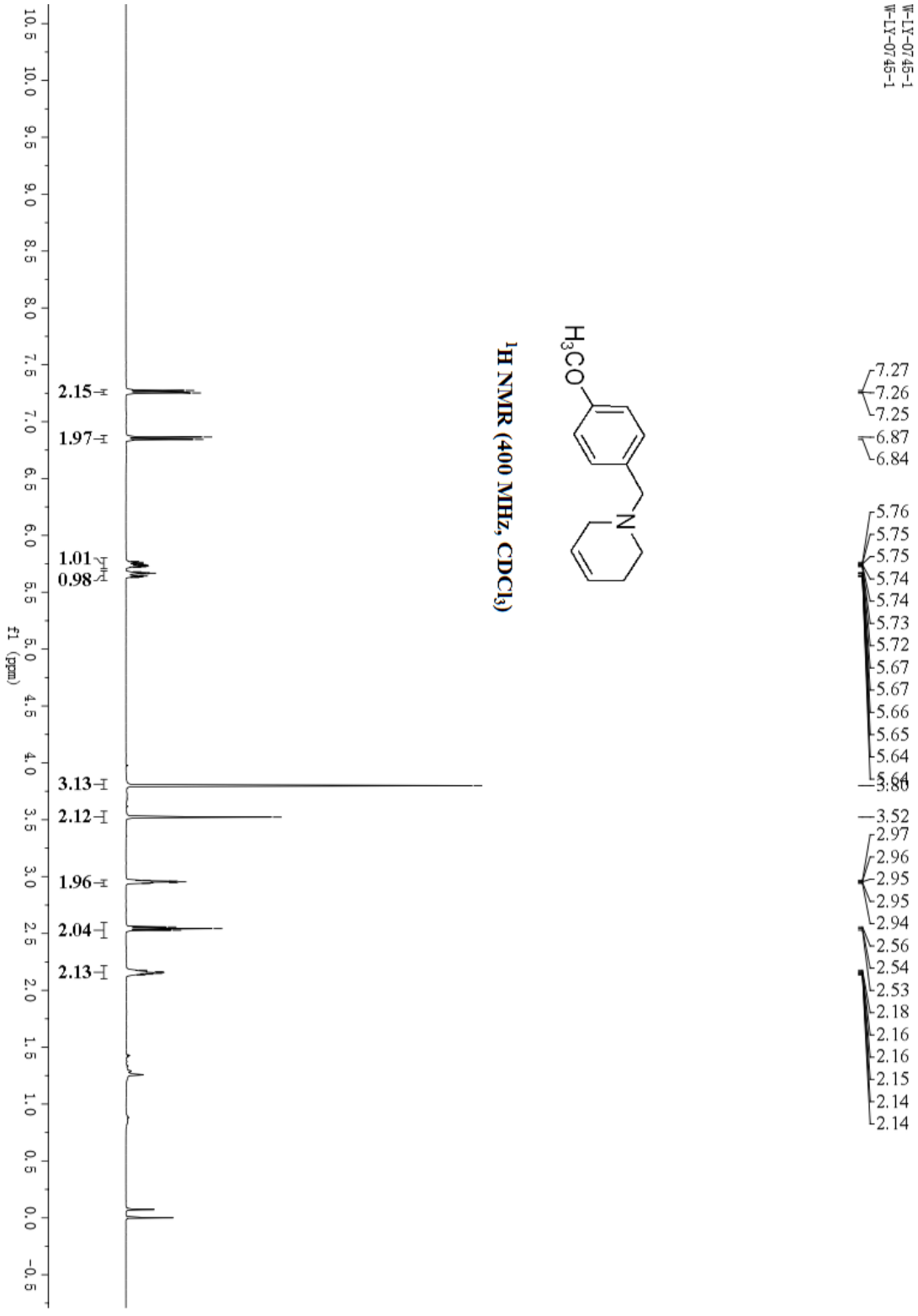
^{1}H NMR spectra of **4d**



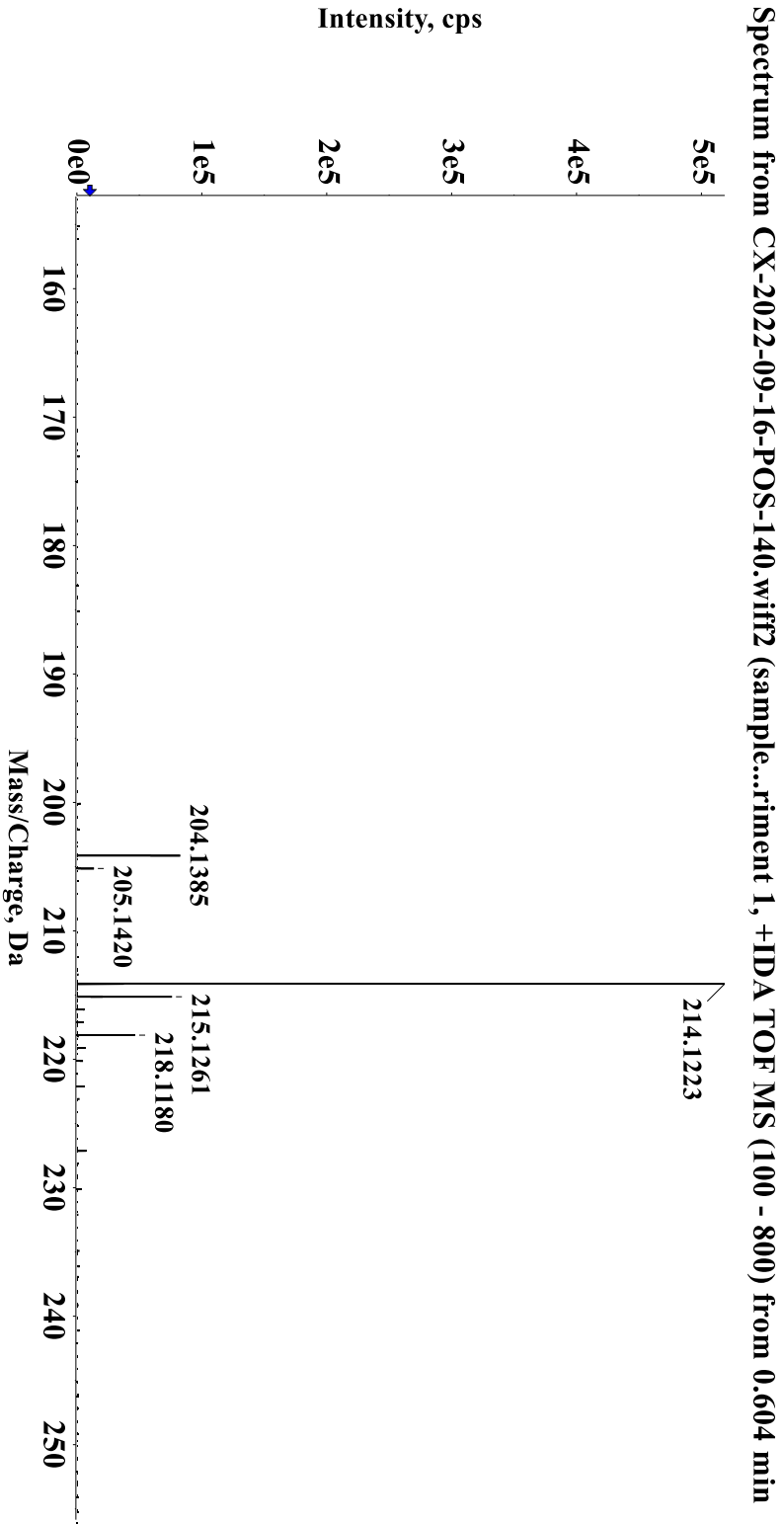
HRMS spectra of **4d**



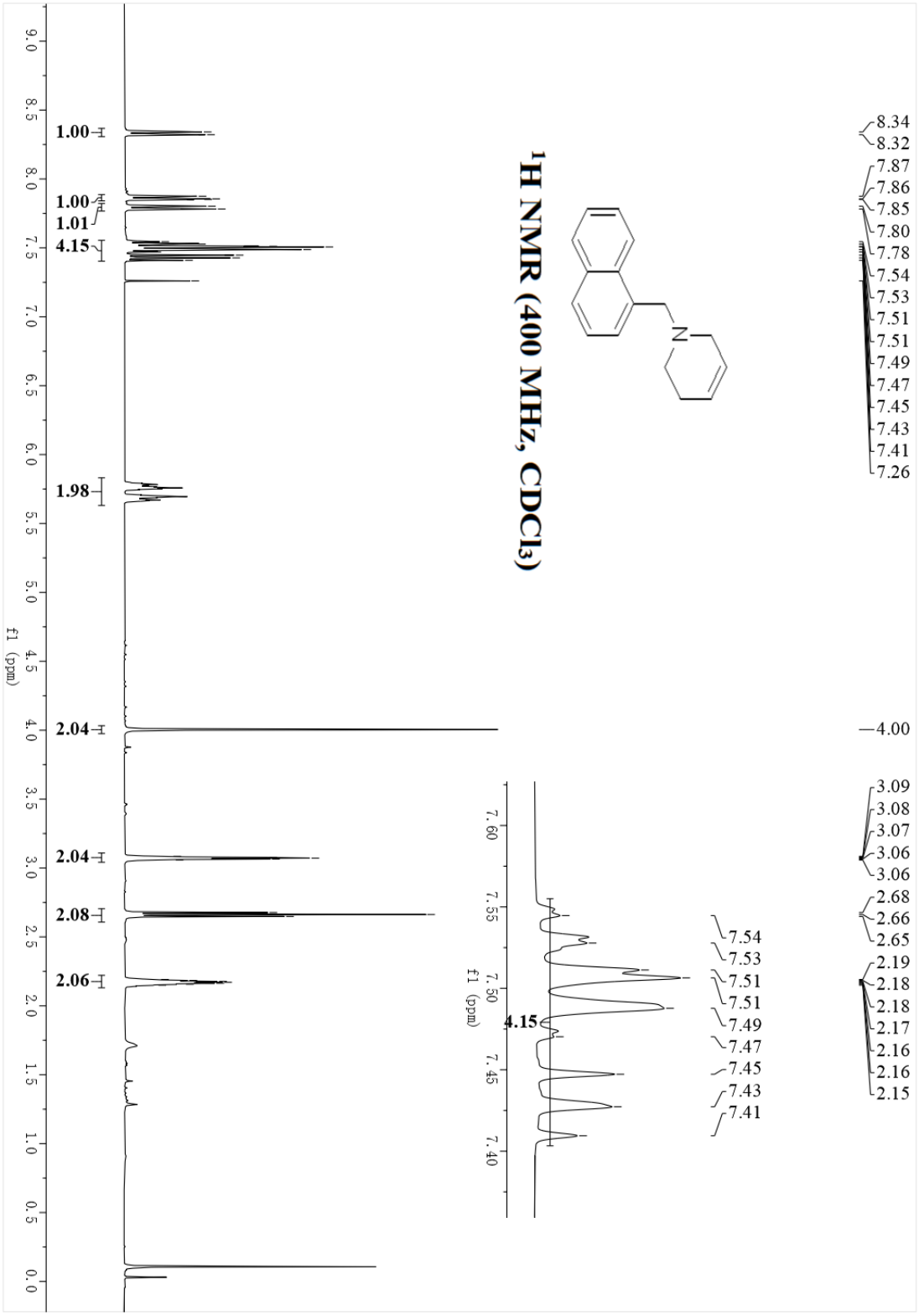
^{1}H NMR spectra of **4e**



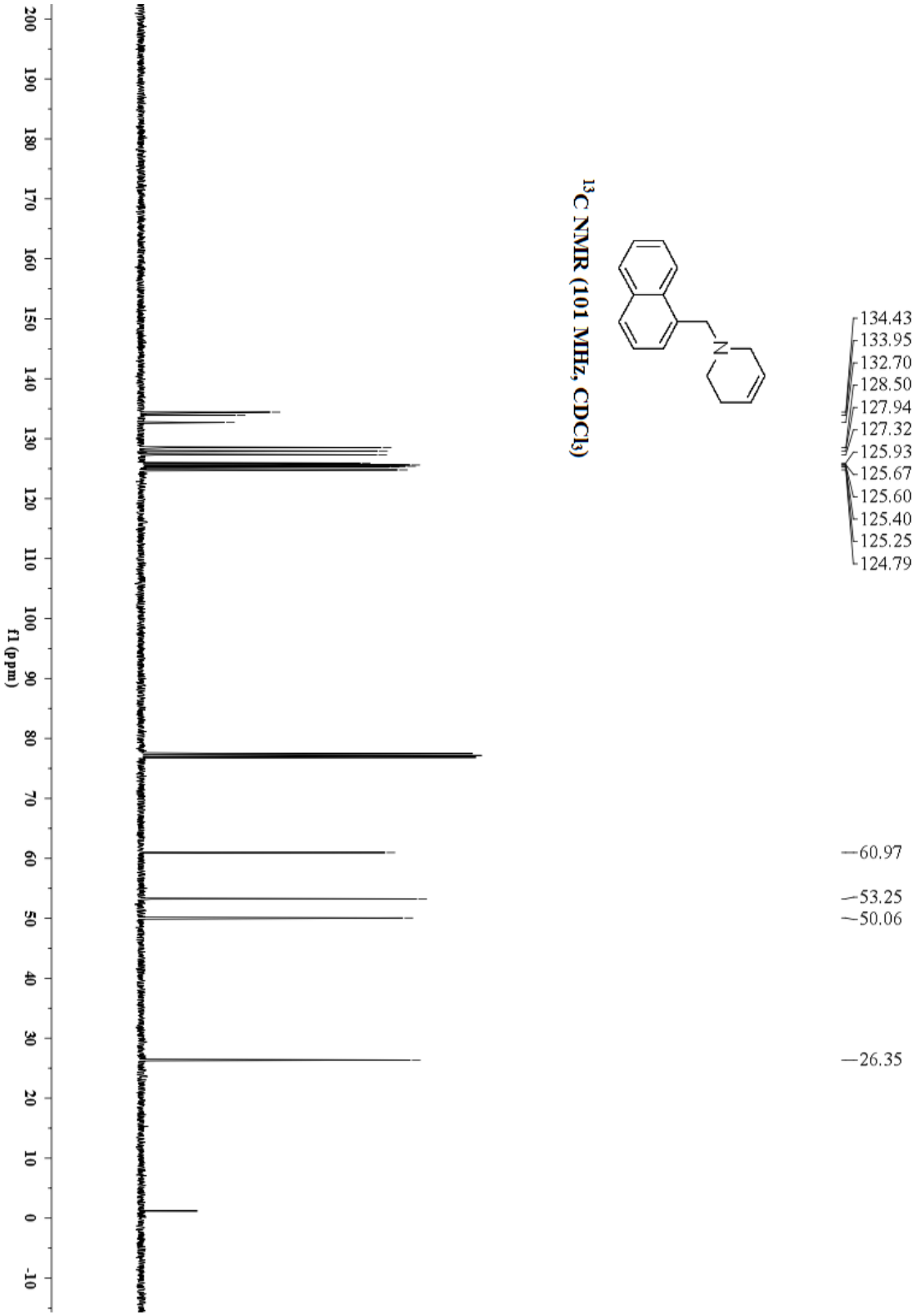
HRMS spectra of **4e**



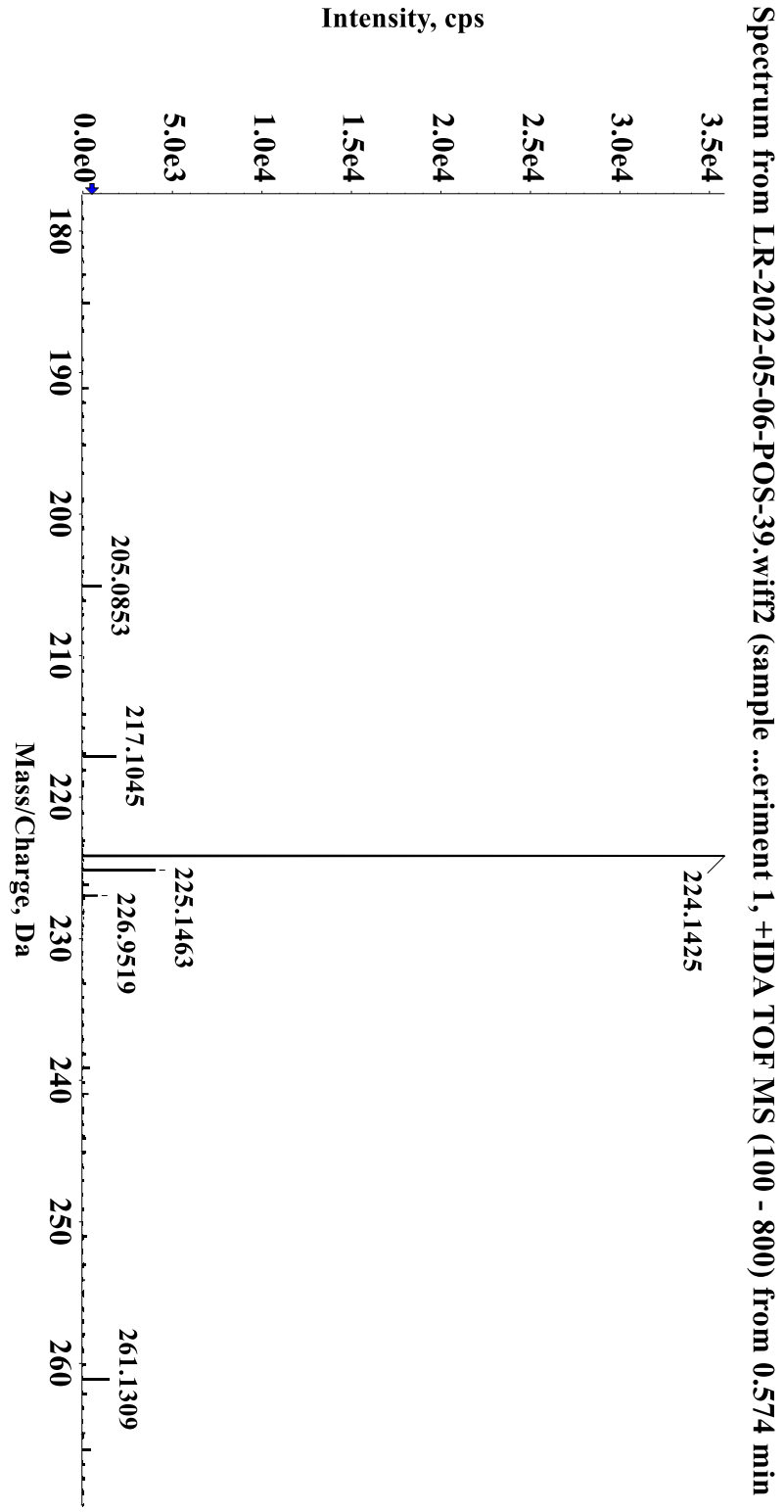
^{1}H NMR spectra of **4f**



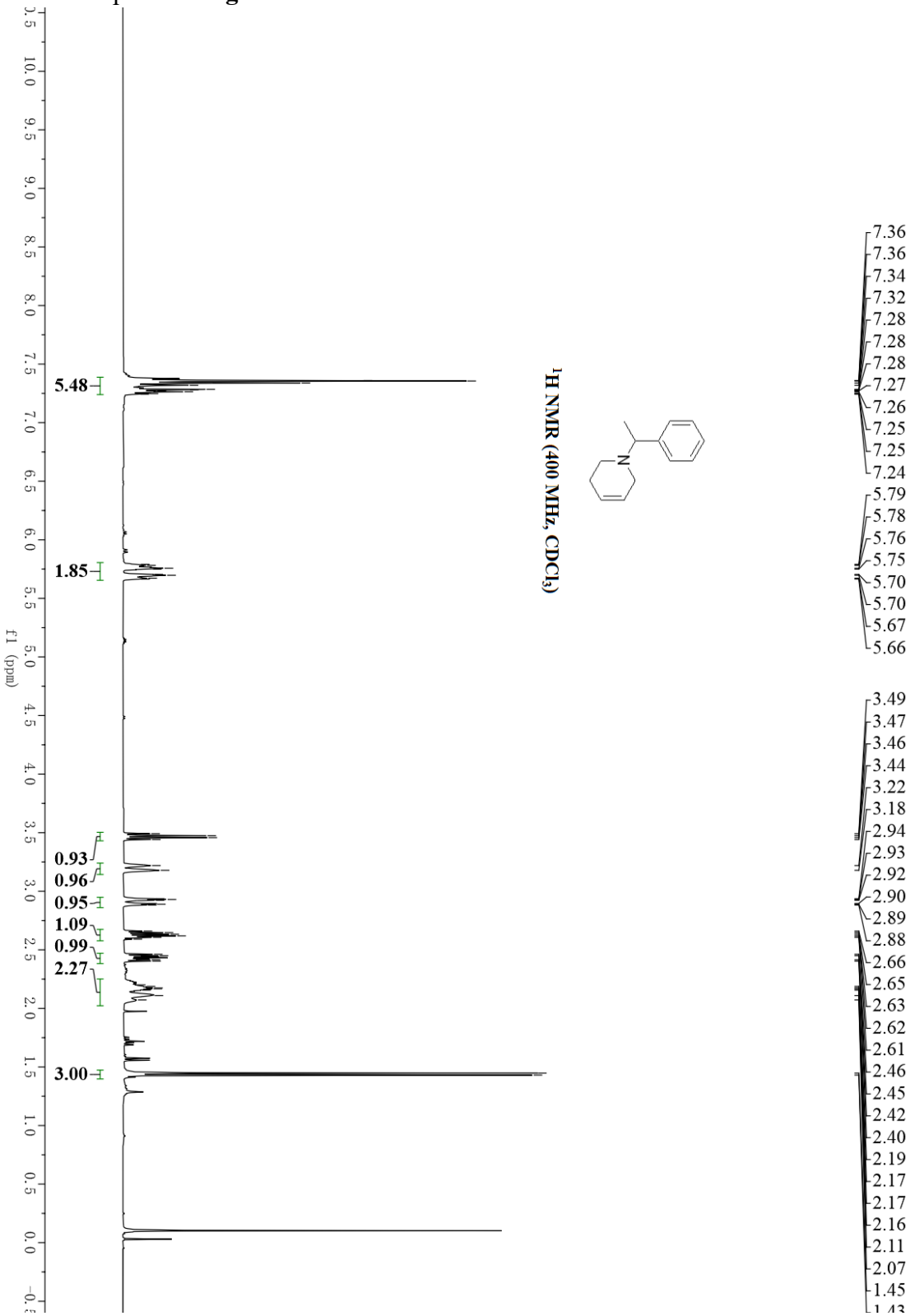
^{13}C NMR spectra of **4f**



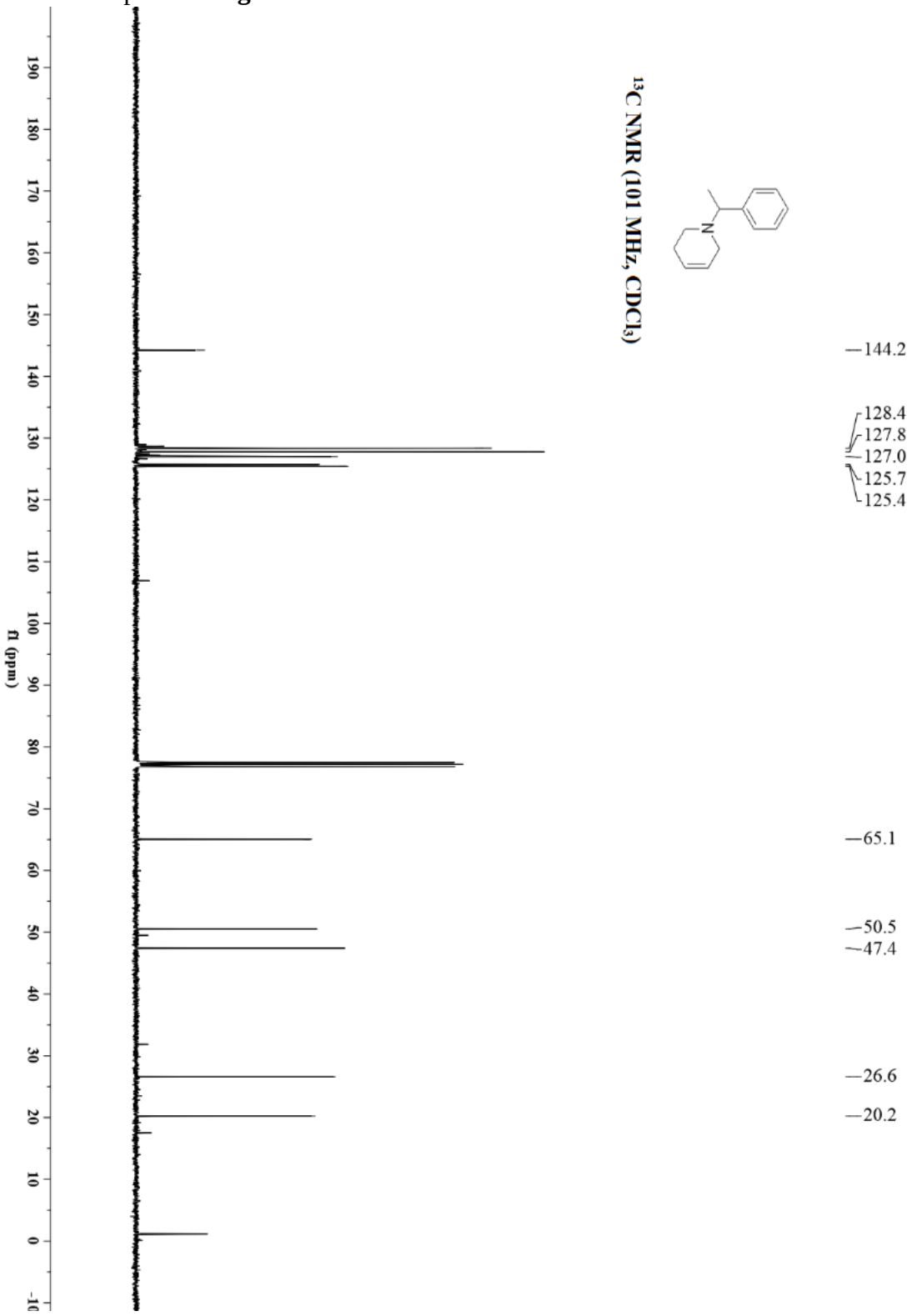
HRMS spectra of **4f**



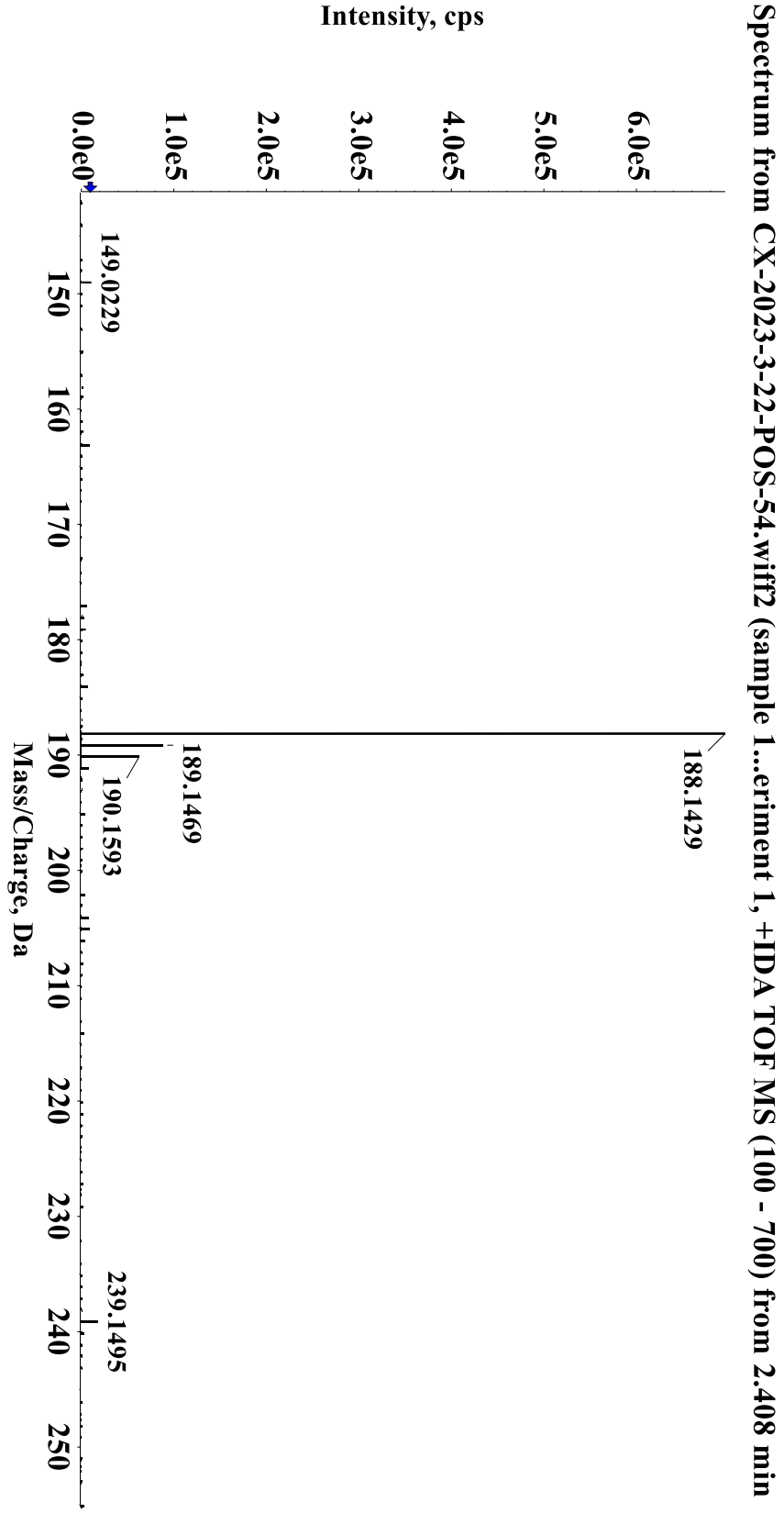
^{1}H NMR spectra of **4g**



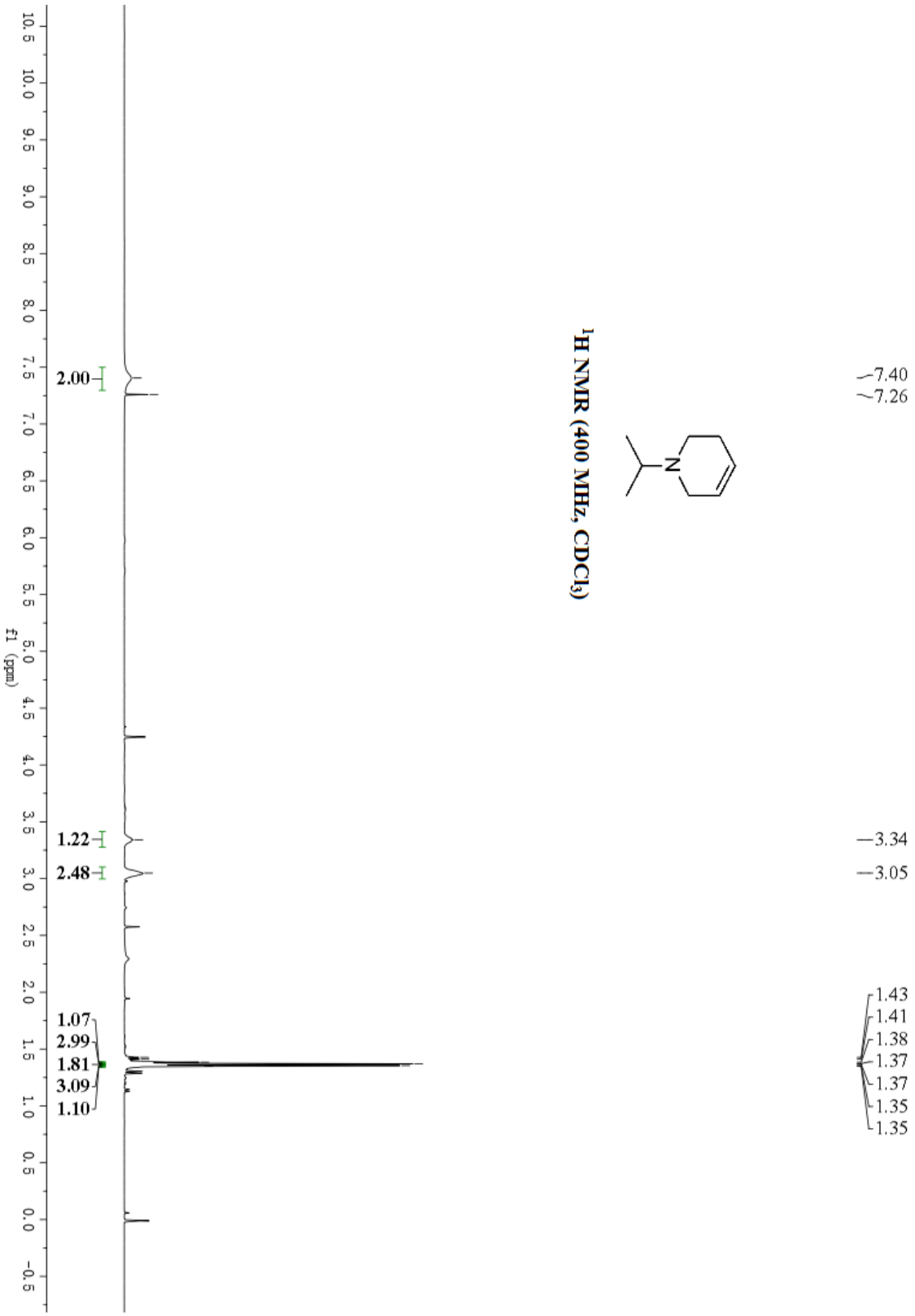
^{13}C NMR spectra of **4g**



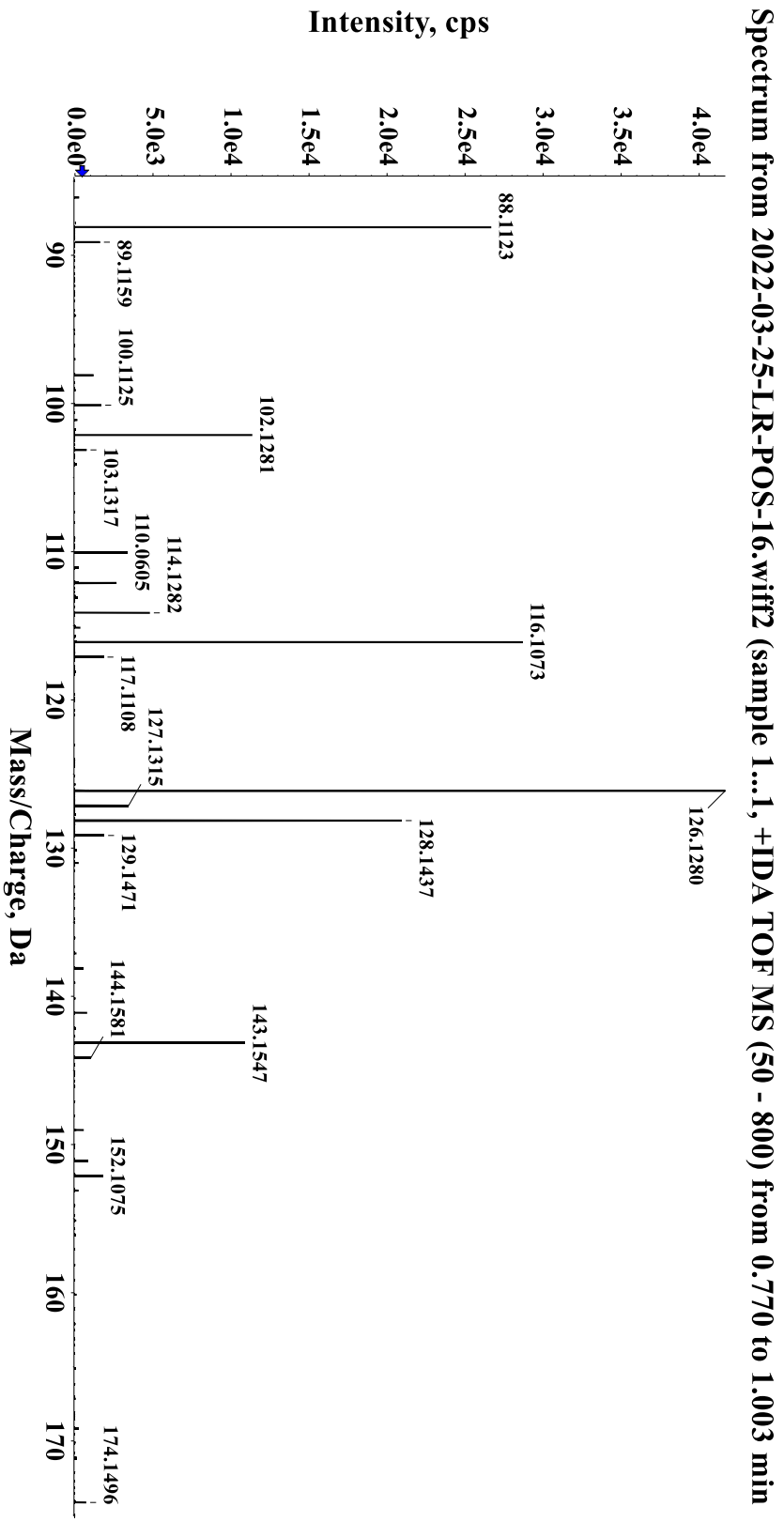
HRMS spectra of **4g**



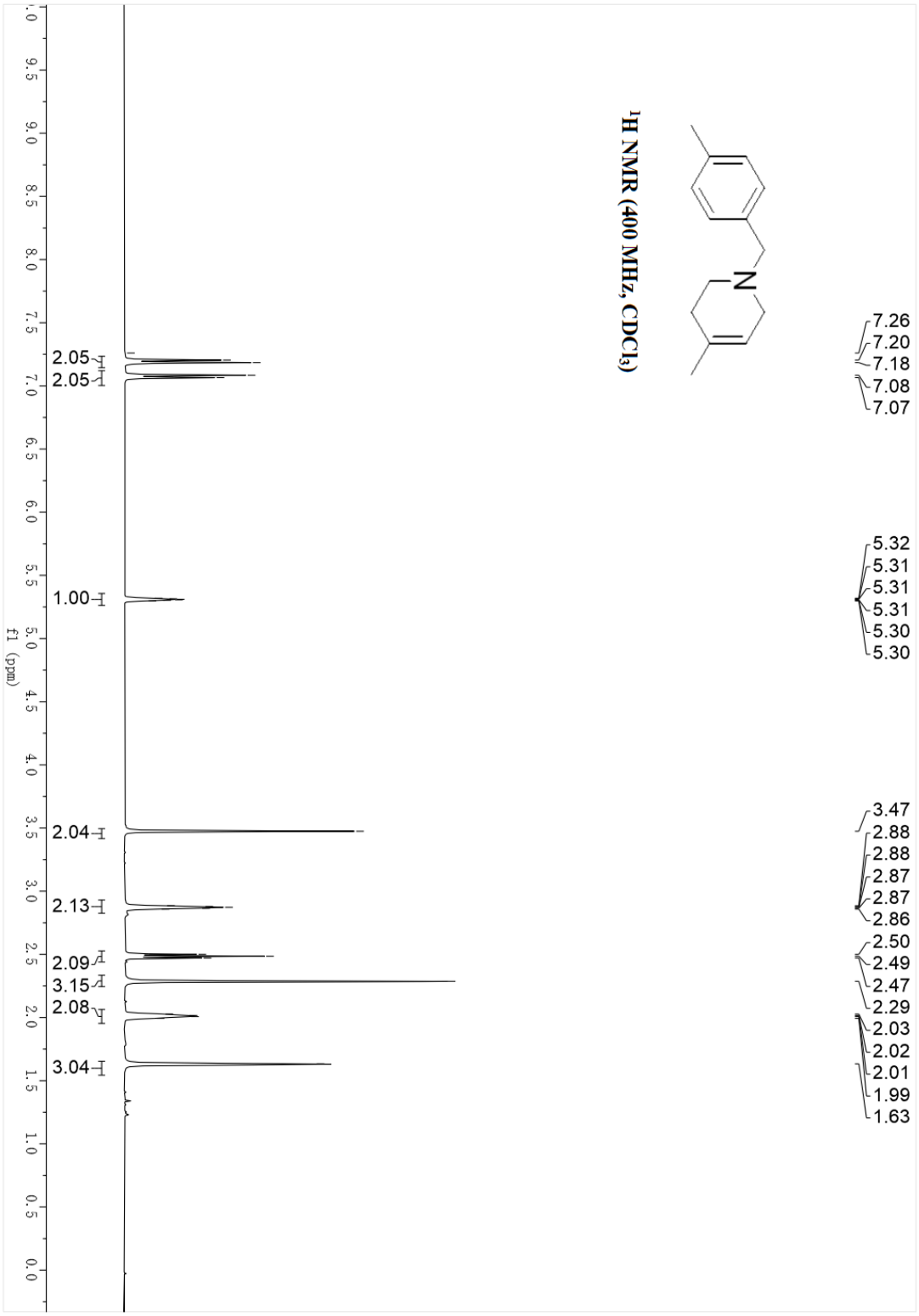
^{1}H NMR spectra of **4h**



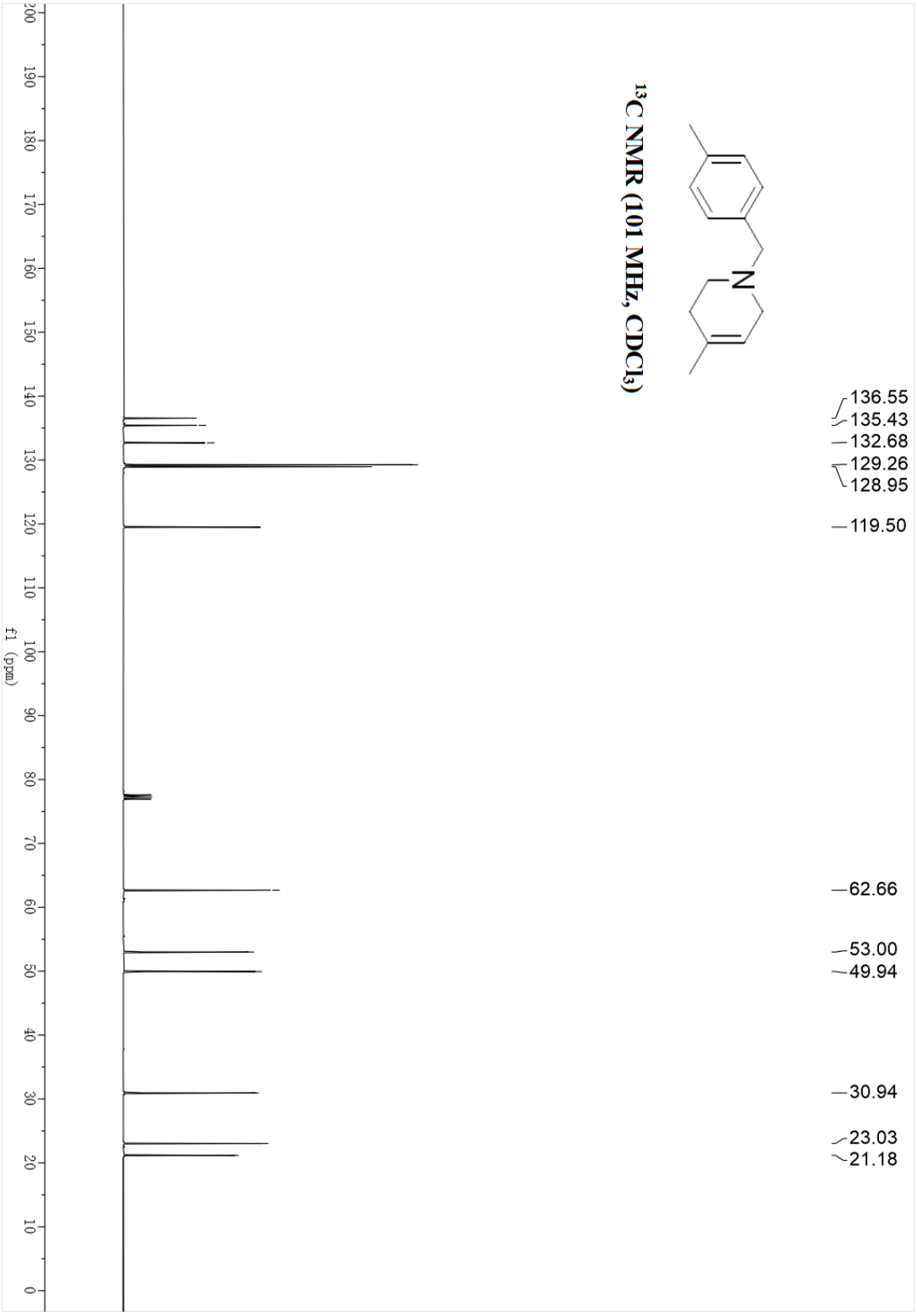
HRMS spectra of **4h**



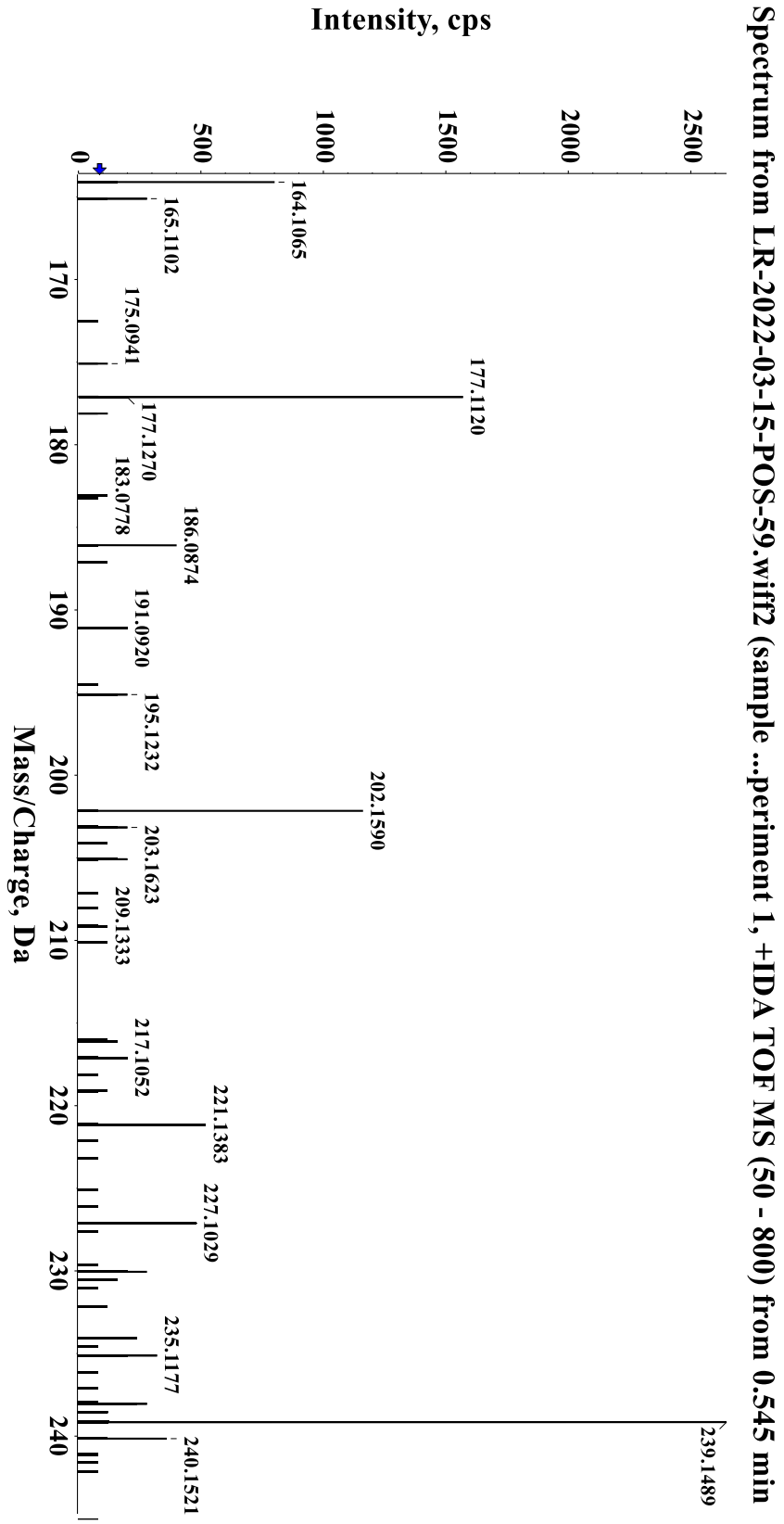
^{1}H NMR spectra of **4i**



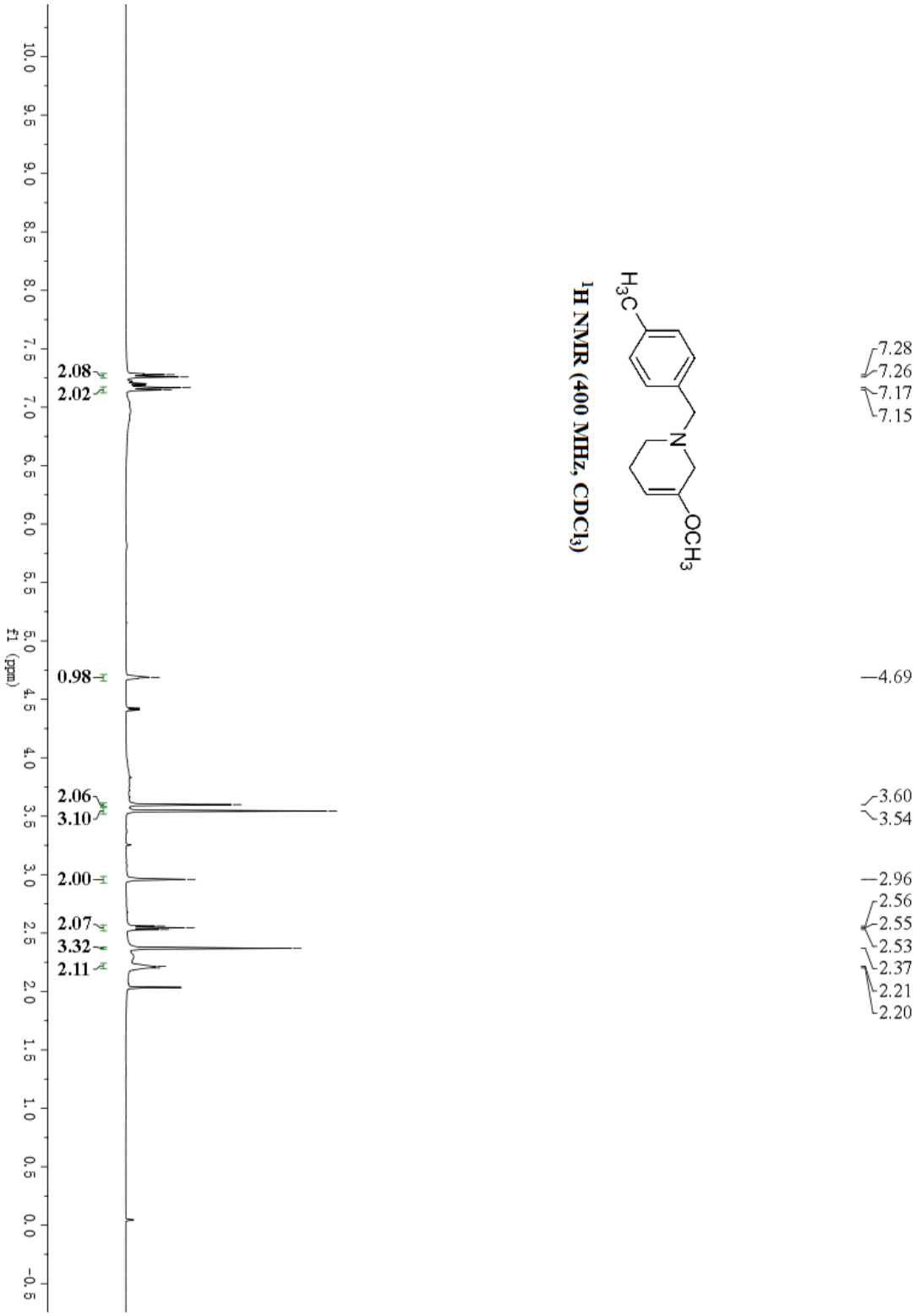
^{13}C NMR spectra of **4i**



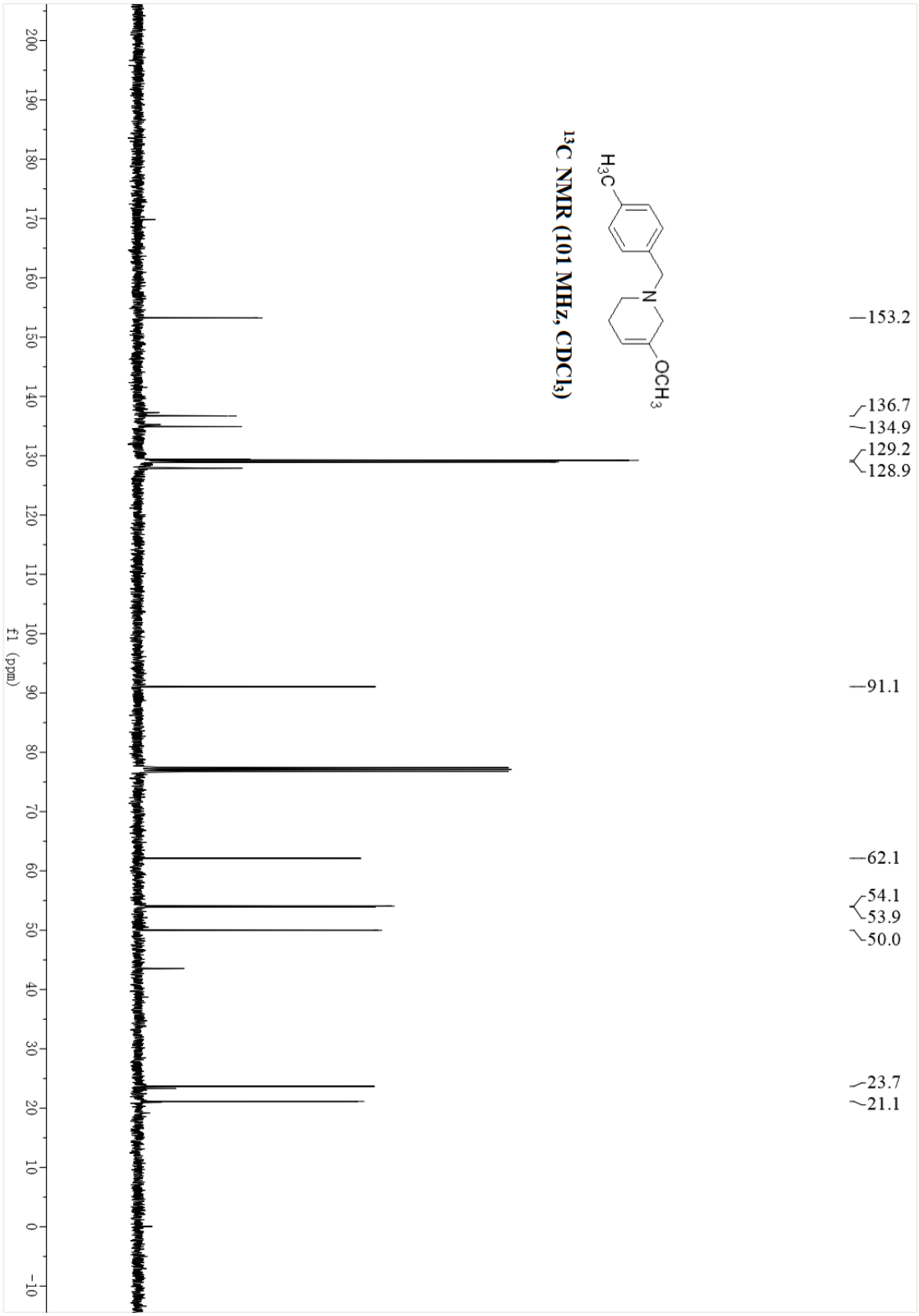
HRMS spectra of **4i**



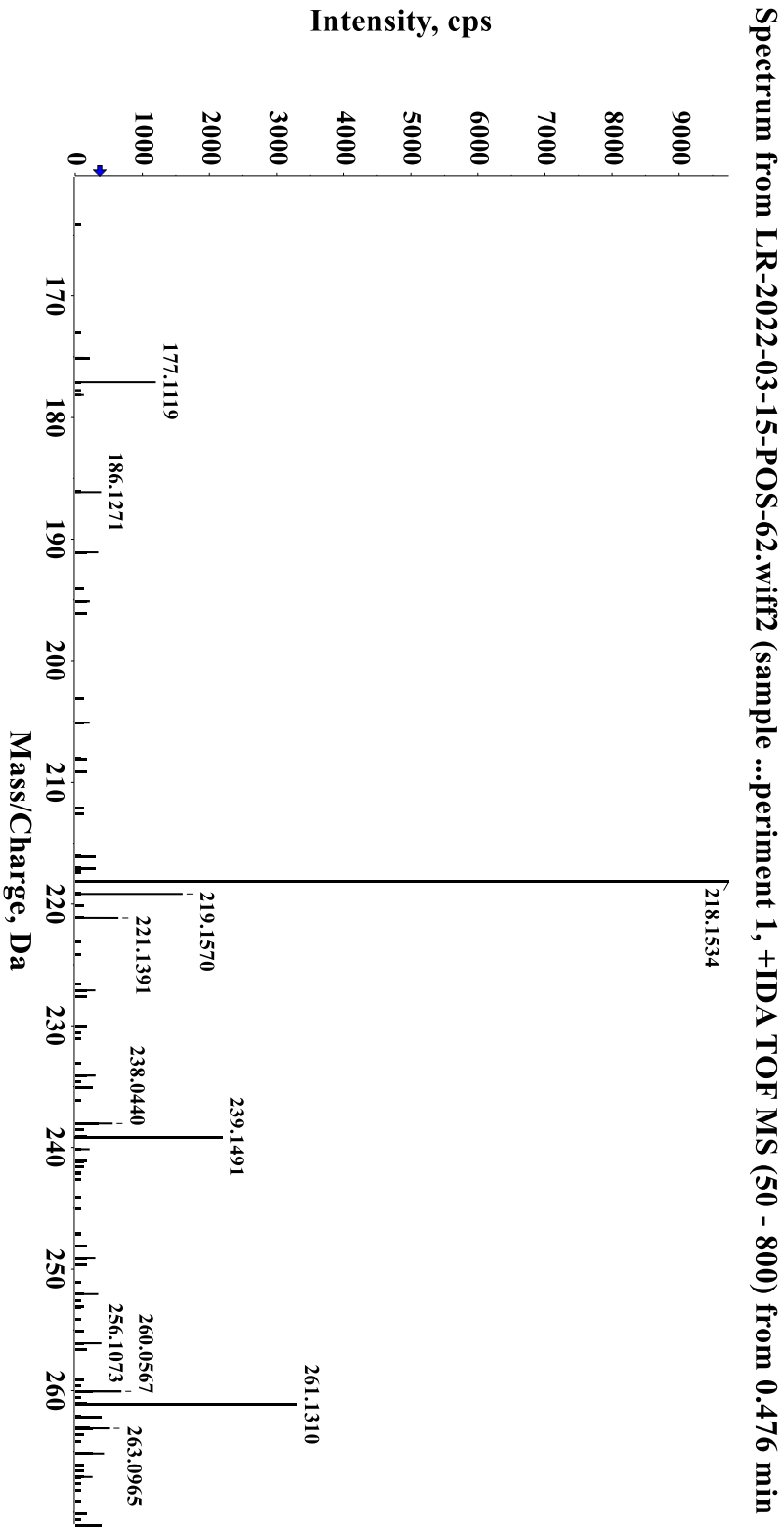
^{1}H NMR spectra of **4j**



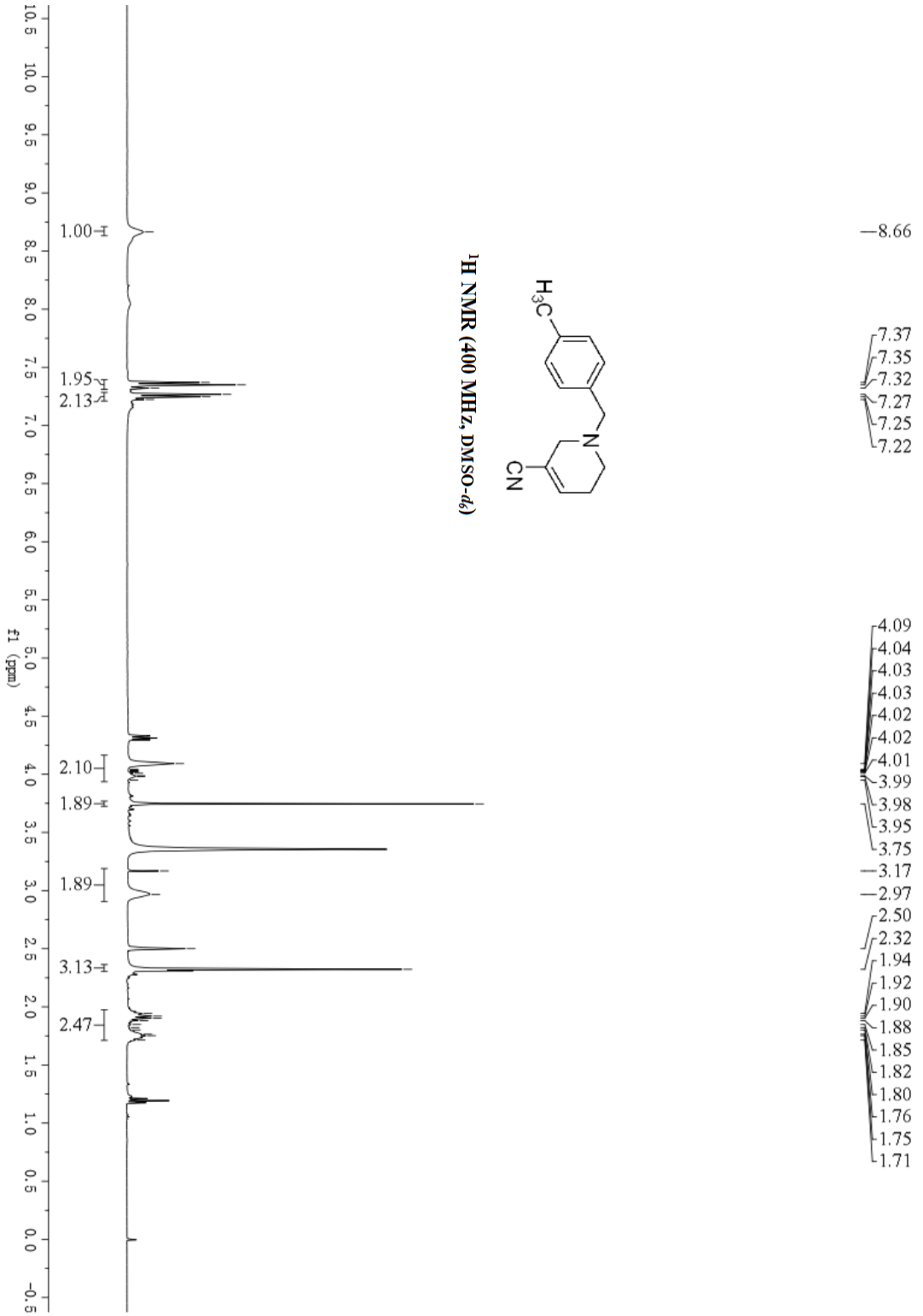
^{13}C NMR spectra of **4j**



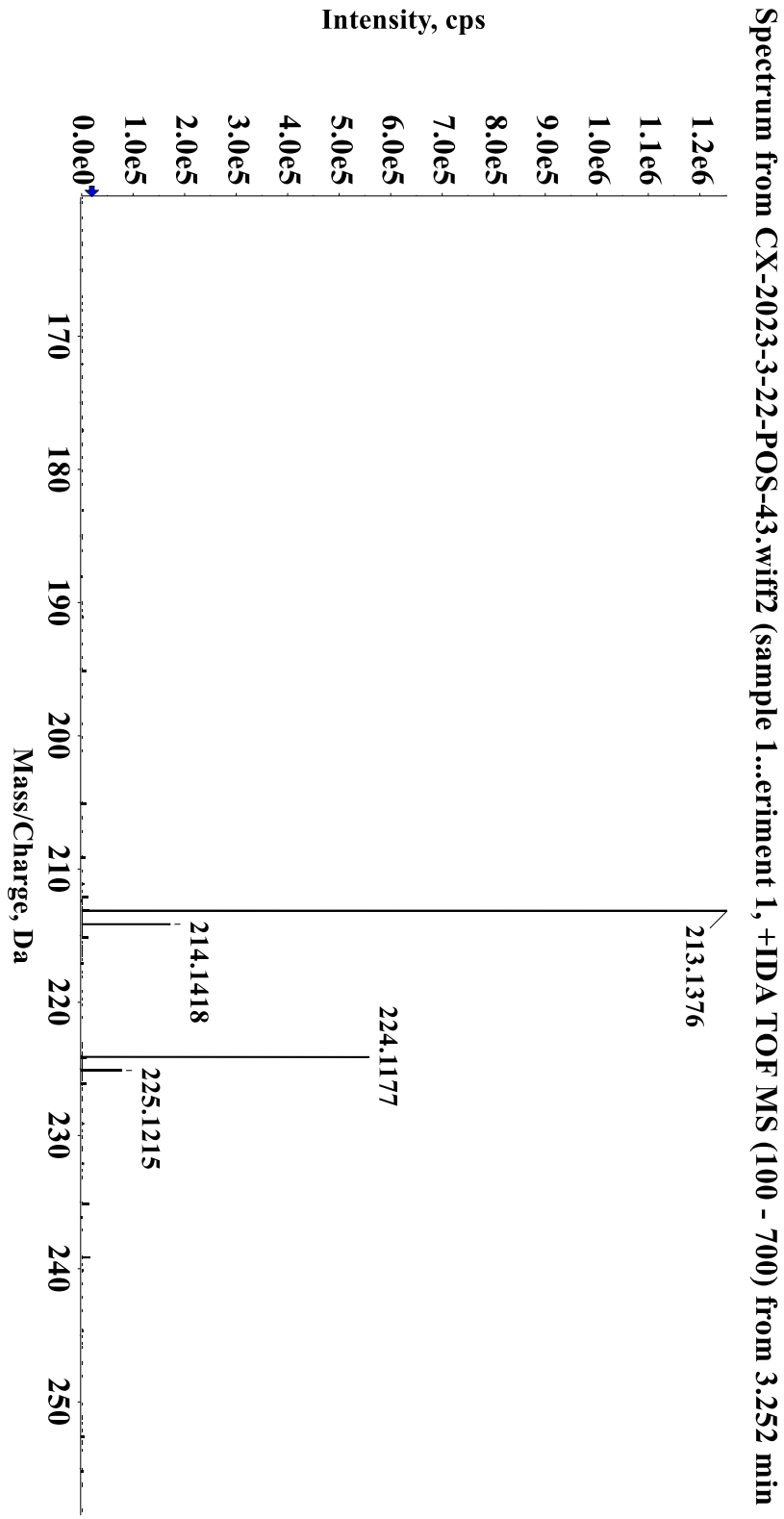
HRMS spectra of **4j**



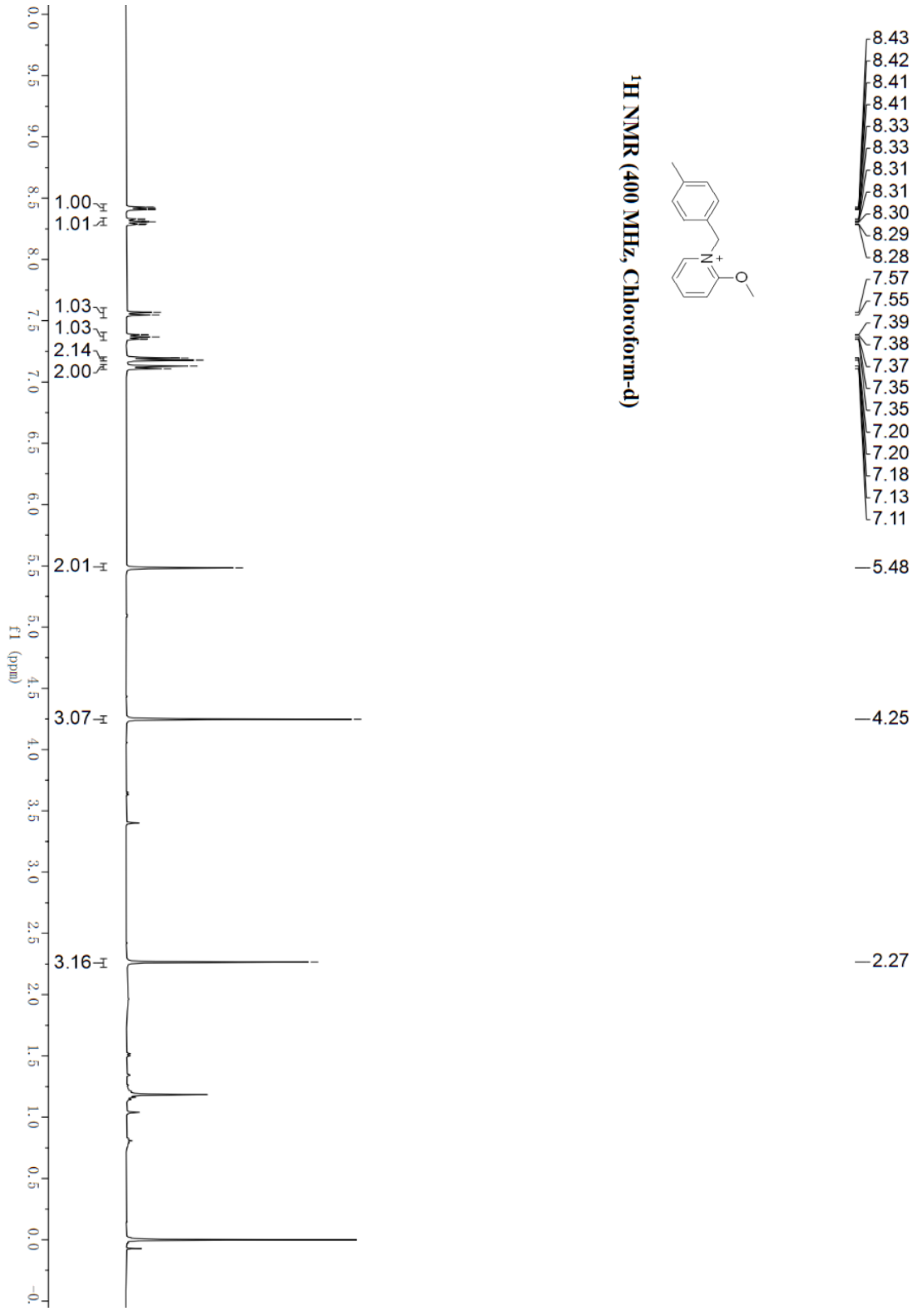
^{1}H NMR spectra of **4k**



HRMS spectra of **4k**



^{1}H NMR spectra of **10**



HRMS spectra of **10**