

Synthesis of 3-hetarylpyrroles by Suzuki–Miyaura cross-coupling

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Table S1. Comparison of protective groups

Protective group	Reaction conditions	Yield of protected pyrrole 1	Overall yield (two steps) of 3-halogenated pyrrole 2
4-MeC ₆ H ₄ SO ₂ –	TsCl, Bu ^t OK, DMF, 0°C	23%	11%
Bu ^t Me ₂ Si–	TBDMSCl, BuLi, THF, -78°C	55%	25%
Bu ^t Ph ₂ Si–	TBDPSCl, BuLi, THF, -78°C	42%	27%
	TBDPSCl, NaH, THF, 0°C	78%	50%

MATERIALS AND METHODS

General: Reactions were carried out using commercially available reagents (Acros, Aldrich, and Fluka). Anhydrous solvents were prepared according to standard procedures. Adsorption column chromatography was performed on Kieselgel 60 silica gel (40-60 μm , direct phase) (3x20 cm) (Merck, Germany). NMR spectra were recorded on an AMX III-800 spectrometer (Bruker) with an operating frequency of 400 MHz for ^1H -NMR and 100 MHz for ^{13}C -NMR; chemical shifts are shown on the scale relative to Me_4Si as internal standard for organic solvents. Thin layer chromatography (TLC) was performed on TLC Silica gel 60 F25.

High resolution mass spectra (HRMS) were registered on a Bruker Daltonics micrOTOF-Q II instrument using electrospray ionization (ESI). The measurements were acquired in a negative ion mode with the following parameters: interface capillary voltage – 3700 V; mass range from m/z 50 to 3000; external calibration (Electrospray Calibrant Solution, Fluka); nebulizer pressure – 0.3 Bar; flow rate – 3 $\mu\text{l min}^{-1}$; dry gas nitrogen (4.0 $\text{dm}^3 \text{min}^{-1}$); interface temperature was set at 180 or 190°C. A syringe injection was used.

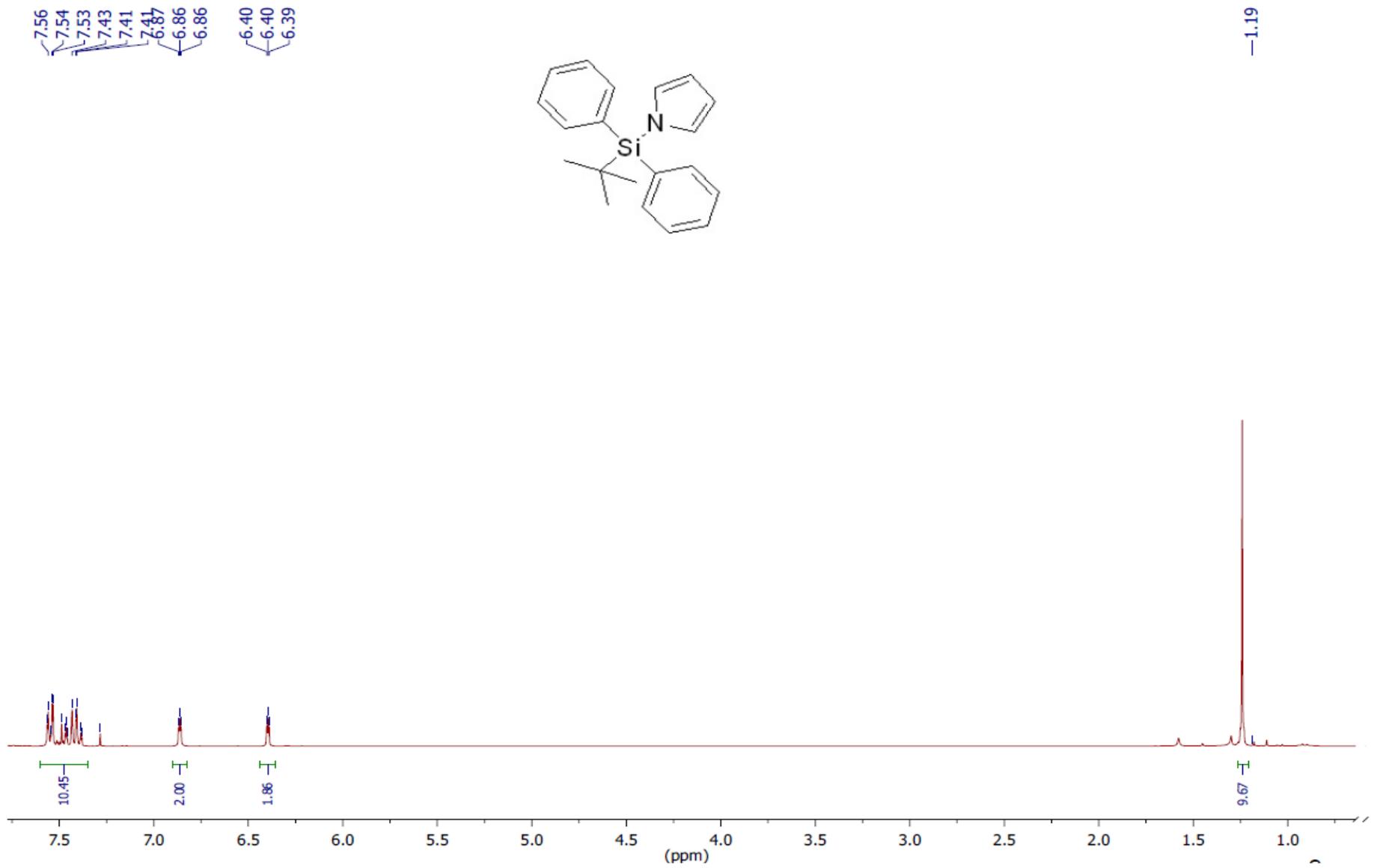
1-[*tert*-Butyl(diphenyl)silyl]pyrrole (1). Pyrrole (0.7 ml, 10 mmol) was dissolved in freshly distilled THF (10 ml) at 0°C. Sodium hydride (60% in mineral oil, 480 mg, 12 mmol) was quickly added in argon atmosphere. The resulting mixture was stirred for 10-15 minutes, while rapid evolution of hydrogen was observed. Then, *tert*-butyl(chloro)diphenylsilane (2.56 ml, 10 mmol) was added dropwise. The reaction mixture was stirred for 18 hours at room temperature. The resulting compound **1** was purified by silica gel column chromatography, eluted with hexane to give a white powder (2 g, 66% yield). ^1H NMR (CDCl_3): 7.56-7.46 (5H, m, Ph), 7.43-7.28 (5H, m, Ph), 6.87-6.86 and 6.40-6.39 (4H, m, Pyrr), 1.19 (9H, s, $-\text{Bu}^t$). ^{13}C NMR (CDCl_3): 135.72 (4 \times C), 132.39 (2 \times C), 130.22 (2 \times C), 128.0 (4 \times C), 125.84 (2 \times C), 110.83 (2 \times C), 28.08 (3 \times C), 19.38.

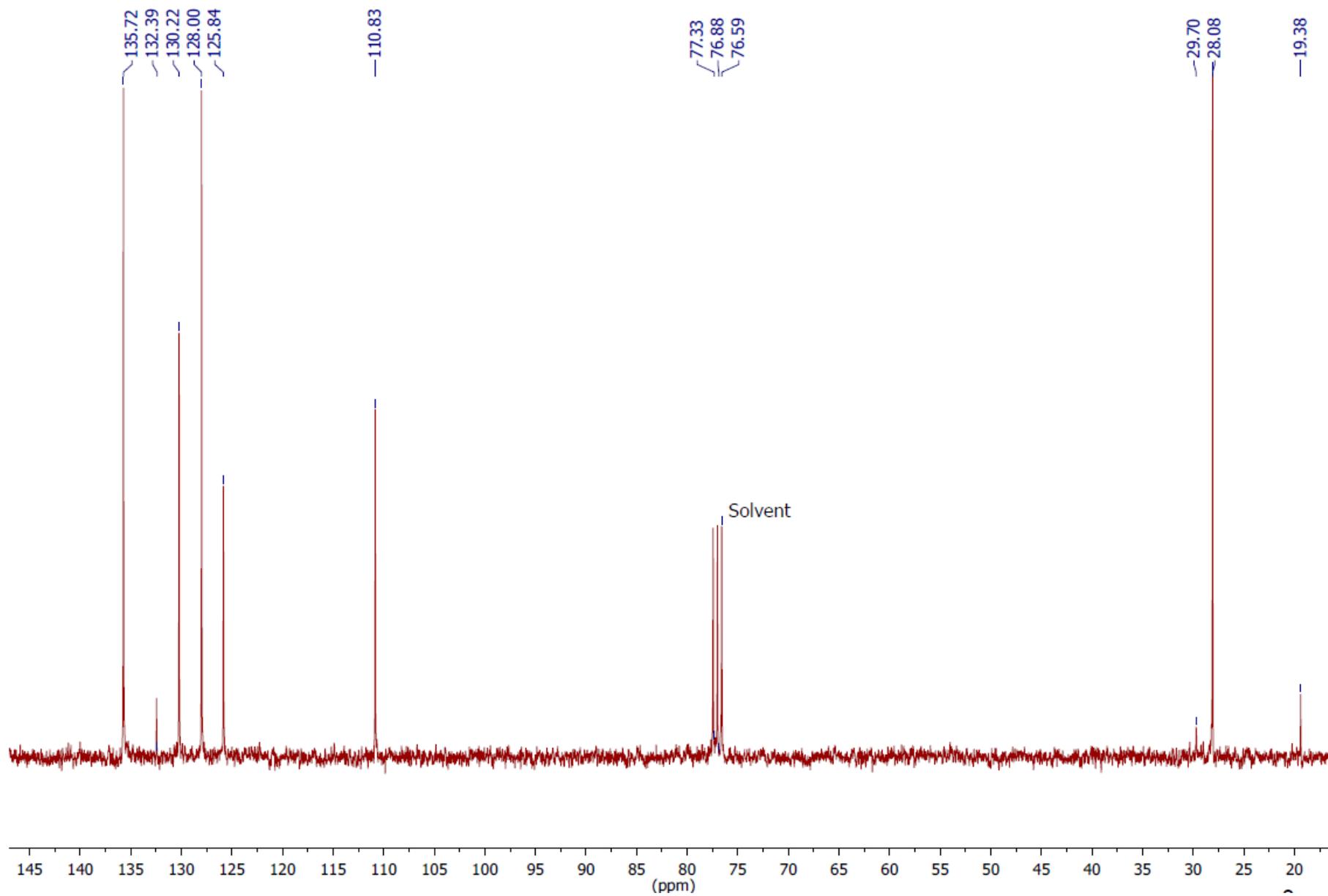
4-Benzoyloxy-5-bromopyrimidine (4'). To a solution of 5-bromo-4-(3*H*)-pyrimidone **4** (285 mg, 1.6 mmol) and triphenylphosphine (524 mg, 2 mmol) in DMF, diisopropyl azodicarboxylate (0.39 ml, 2 mmol) was added dropwise. Then the solution was cooled to 0°C, and benzyl alcohol (0.2 ml, 2 mmol) was added. The mixture was stirred at room temperature for 2 hours. The solvents were evaporated *in vacuo*, the mixture was subjected to column chromatography, first eluted with hexane/ethyl acetate (3:2) then with hexane/ethyl acetate (1:1) system to afford the product as a white powder (380 mg, 89% yield). ^1H NMR (CDCl_3 : CD_3OD , 3:1): 8.34 (1H, s, H6), 8.20 (1H, s, H2), 7.34-7.31 (5H, m, Bn), 4.14 (2H, s, CH_2). ^{13}C NMR (CDCl_3 : CD_3OD , 3:1): 157.85, 152.79, 150.45, 134.23, 129.1 (2 \times C), 128.78, 128.40 (2 \times C), 114.09, 51.19.

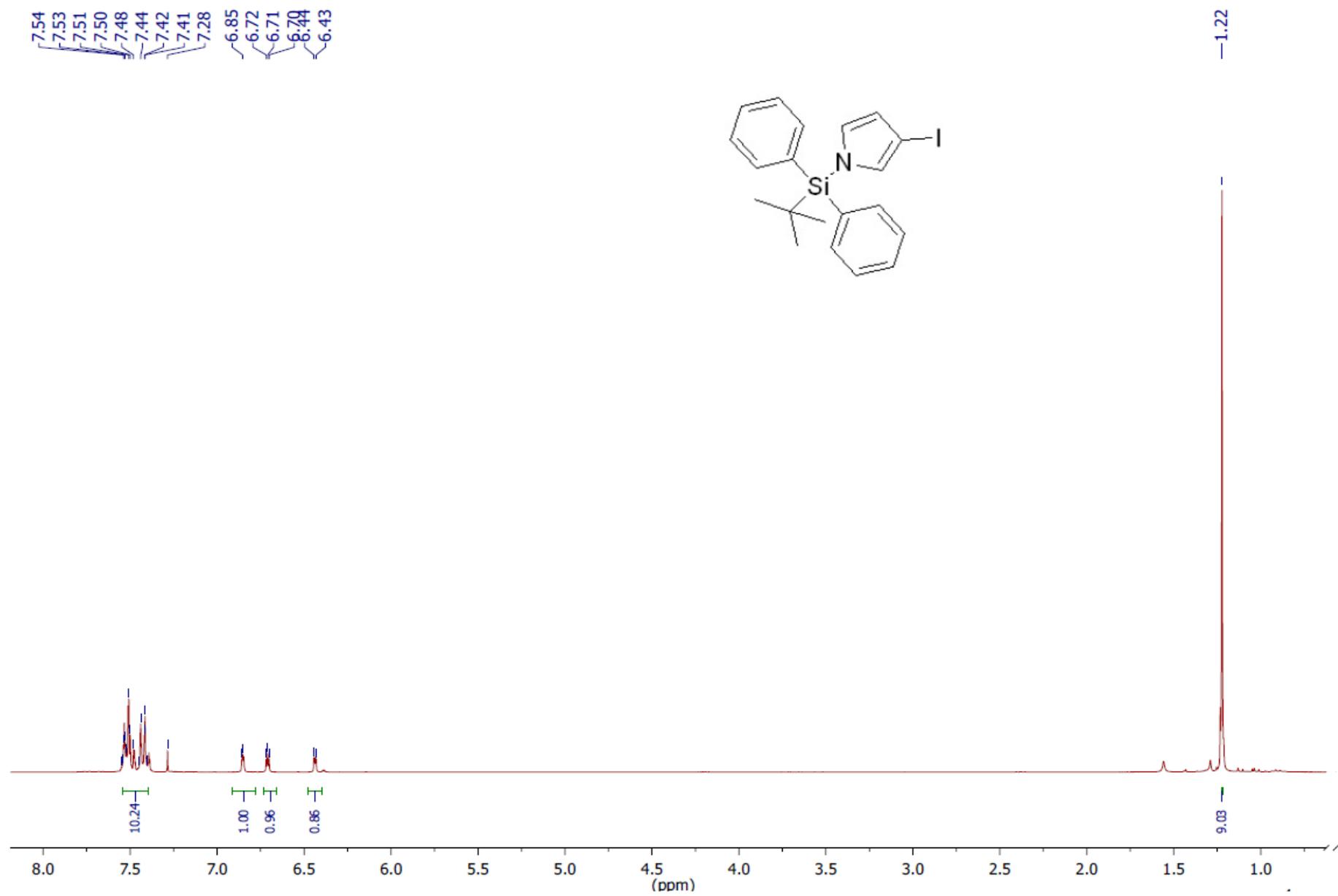
4-Acetylamino-3-bromopyridine (5'). 3-Bromo-4-aminopyridine **5** (1 g, 5.7 mmol) was

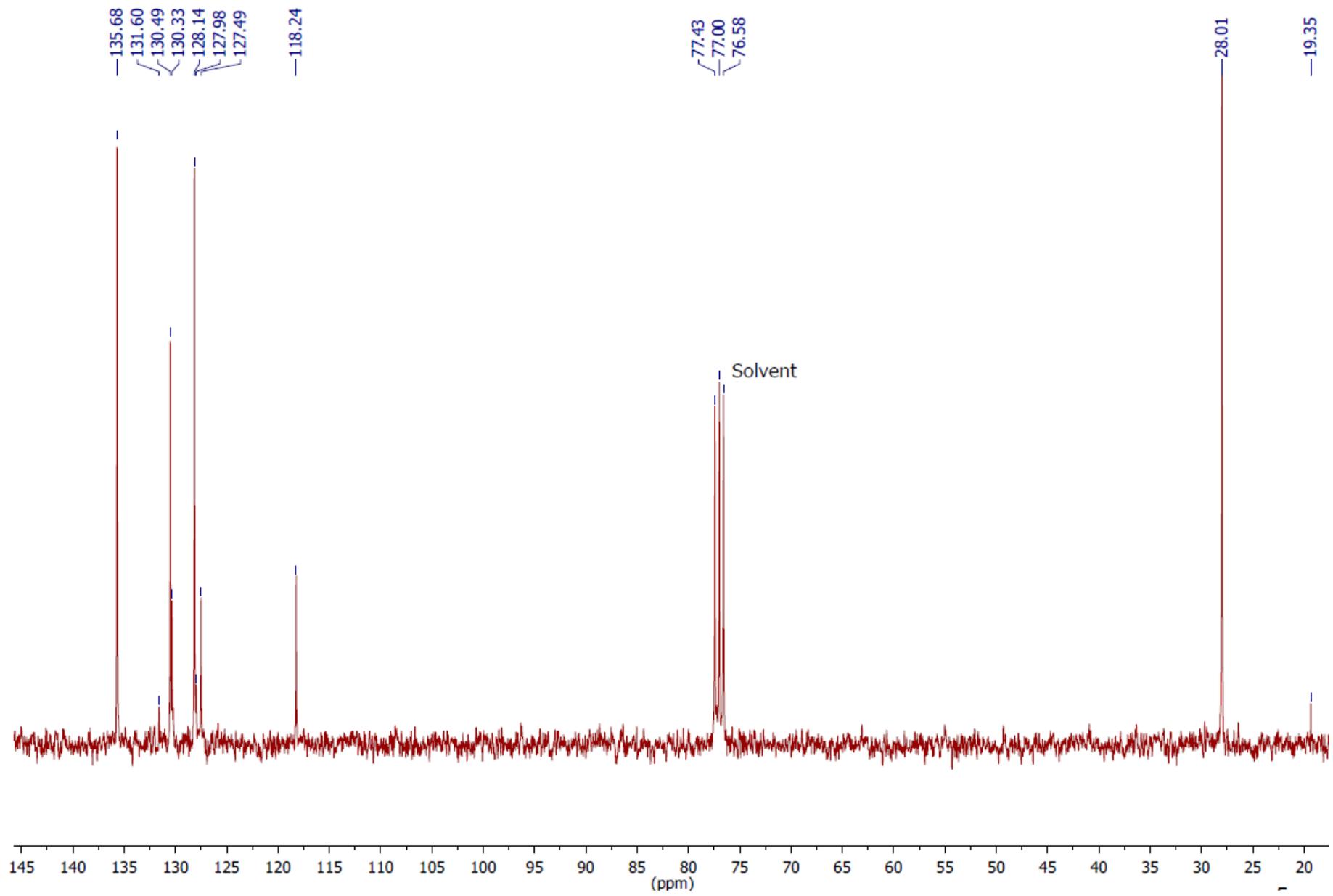
dissolved in freshly distilled acetone (50 ml), and Ac₂O (4.4 g, 8.55 mmol) was added under argon atmosphere. The reaction mixture was left overnight. The resulting compound **5'** was purified by column chromatography on silica gel, eluted with hexane/ethyl acetate (10:1) system to give a pale yellow powder (970 mg, 60% yield). ¹H NMR (CDCl₃): 8.57 (1H, s, H2), 8.40-8.39 (1H, m, H6), 8.24-8.22 (1H, m, H5), 7.21 (1H, s, NH), 2.78 (3H, s, CH₃). ¹³C NMR (CDCl₃): 177.96, 151.20 (2×C), 149.30, 114.80, 29.59, 25.08.

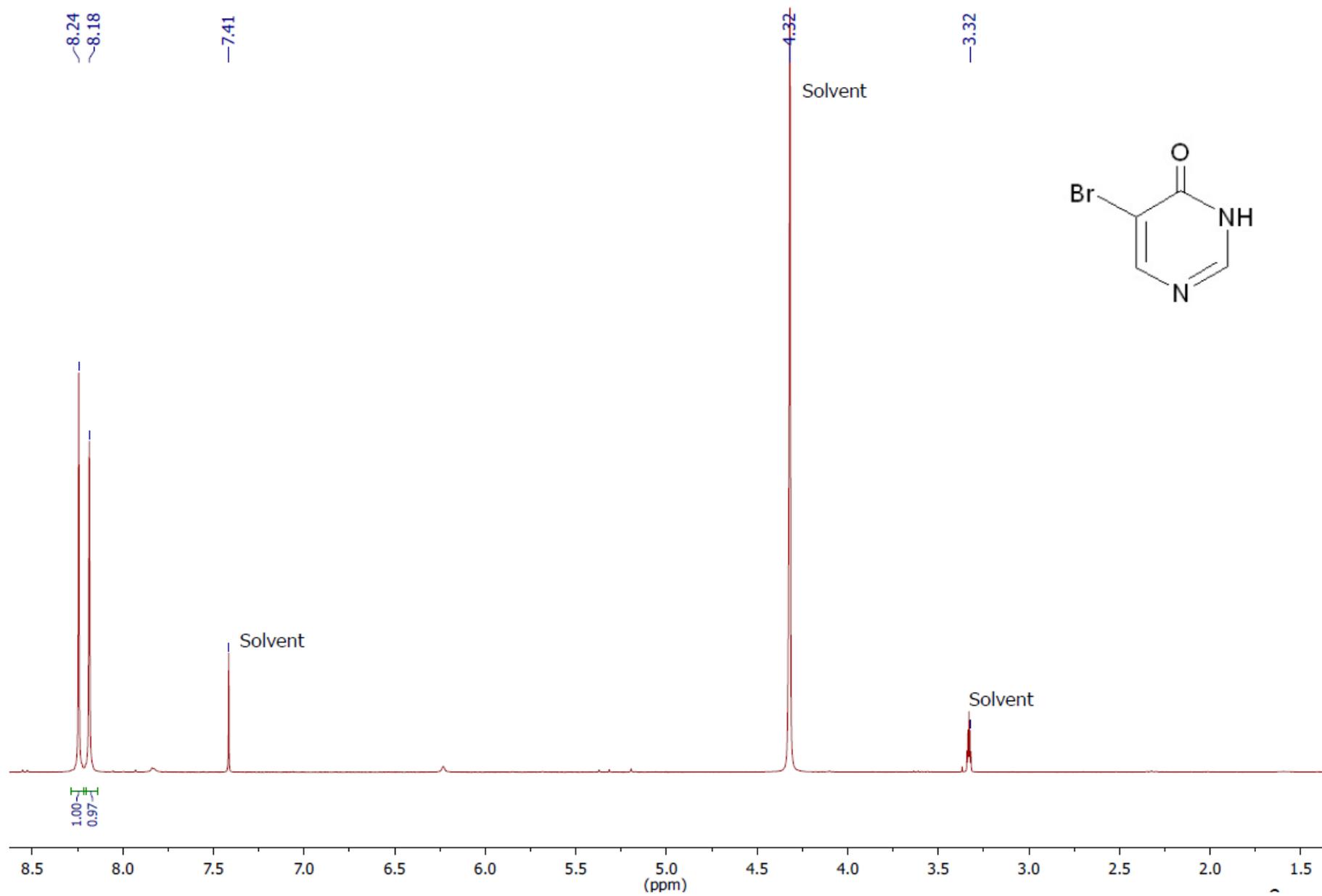
4-Acetylamino-5-(1H-pyrrol-3-yl)pyridine (7). Compound **5'** (200 mg, 0.7 mmol) was dissolved in 1,2-dimethoxyethane (20 ml) in a two-necked flask, and Pd(PPh₃)₄ (5 mol%) was added under argon atmosphere, and the mixture was stirred for 15 minutes. Then pyrrolylboronic acid **3** (245 mg, 0.7 mmol) dissolved in dimethoxyethane (20 ml) and sodium bicarbonate (10 ml) were added. The reaction mixture was refluxed at 90 °C for 4 hours. The resulting compound **7** was purified by column chromatography on silica gel, eluted with CDCl₃: methanol (95:5) system to give an off-white powder (60 mg, 30% yield). ¹H NMR (CDCl₃): 8.91 (1H, m, NH), 8.39-8.37 (2H, m, Py), 8.12 (1H, m, Py), 7.29 (1H, m, NH), 6.96-6.92 (2H, m, Pyr), 6.35-6.34 (H, m, Pyr), 2.06 (3H, s, Ac). ¹³C NMR (CDCl₃): 152.31, 150.27, 148.85, 143.18, 120.41, 119.94, 117.1, 111.88, 108.88, 81.55, 28.41. HRMS *m/z*: calculated for C₁₁H₁₁N₃O [M+nH] 202.0975; found [M+nH] 202.0994.

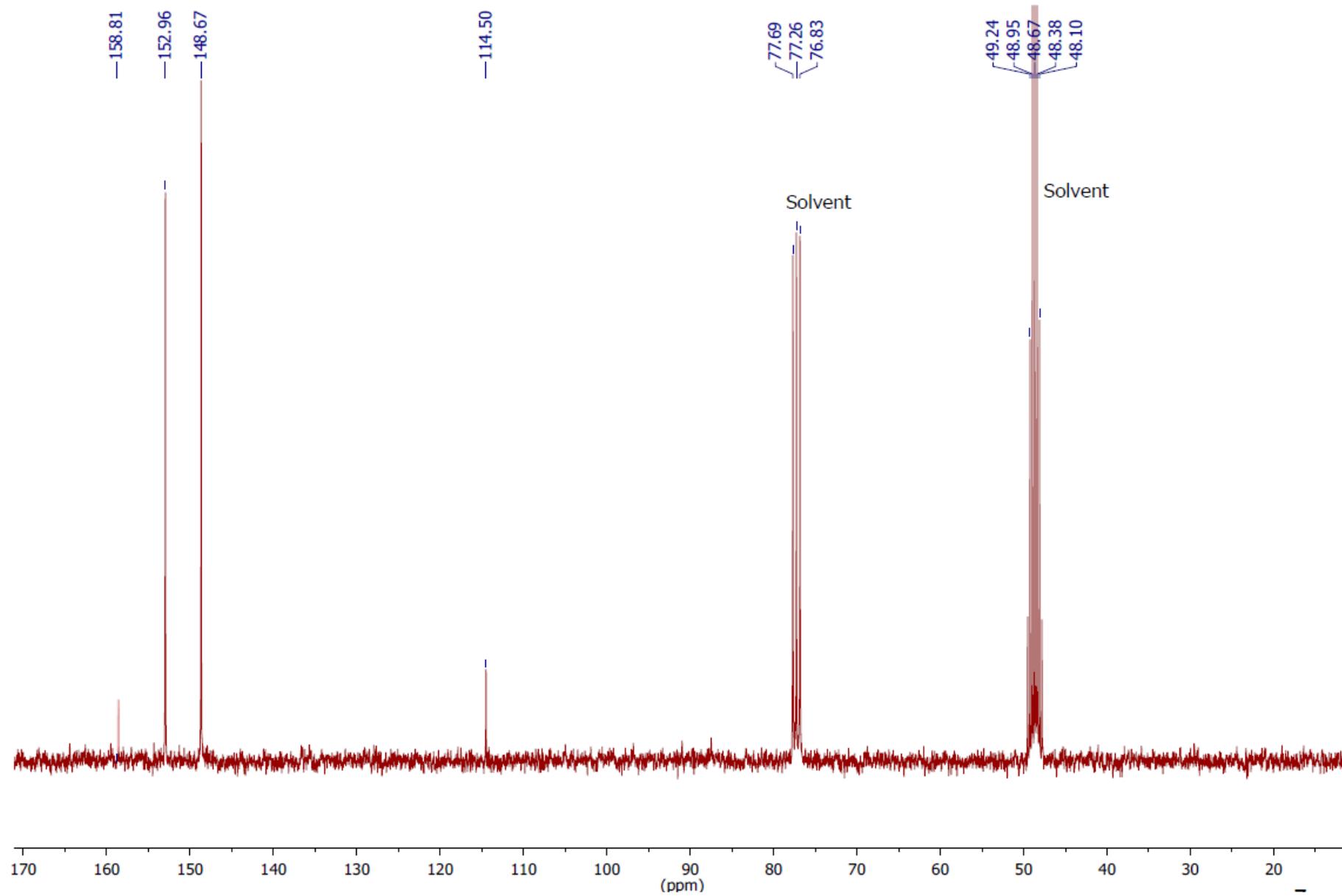


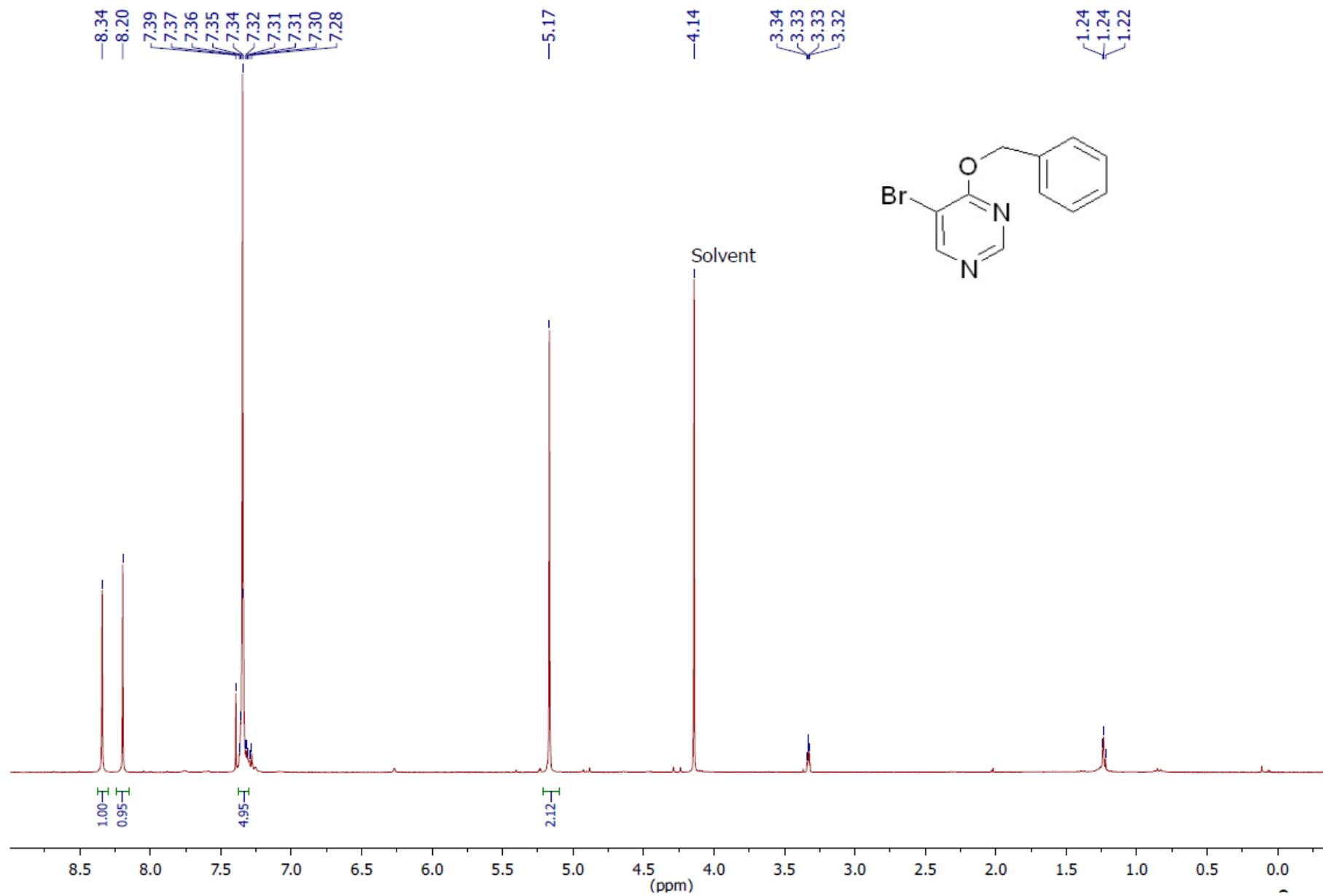


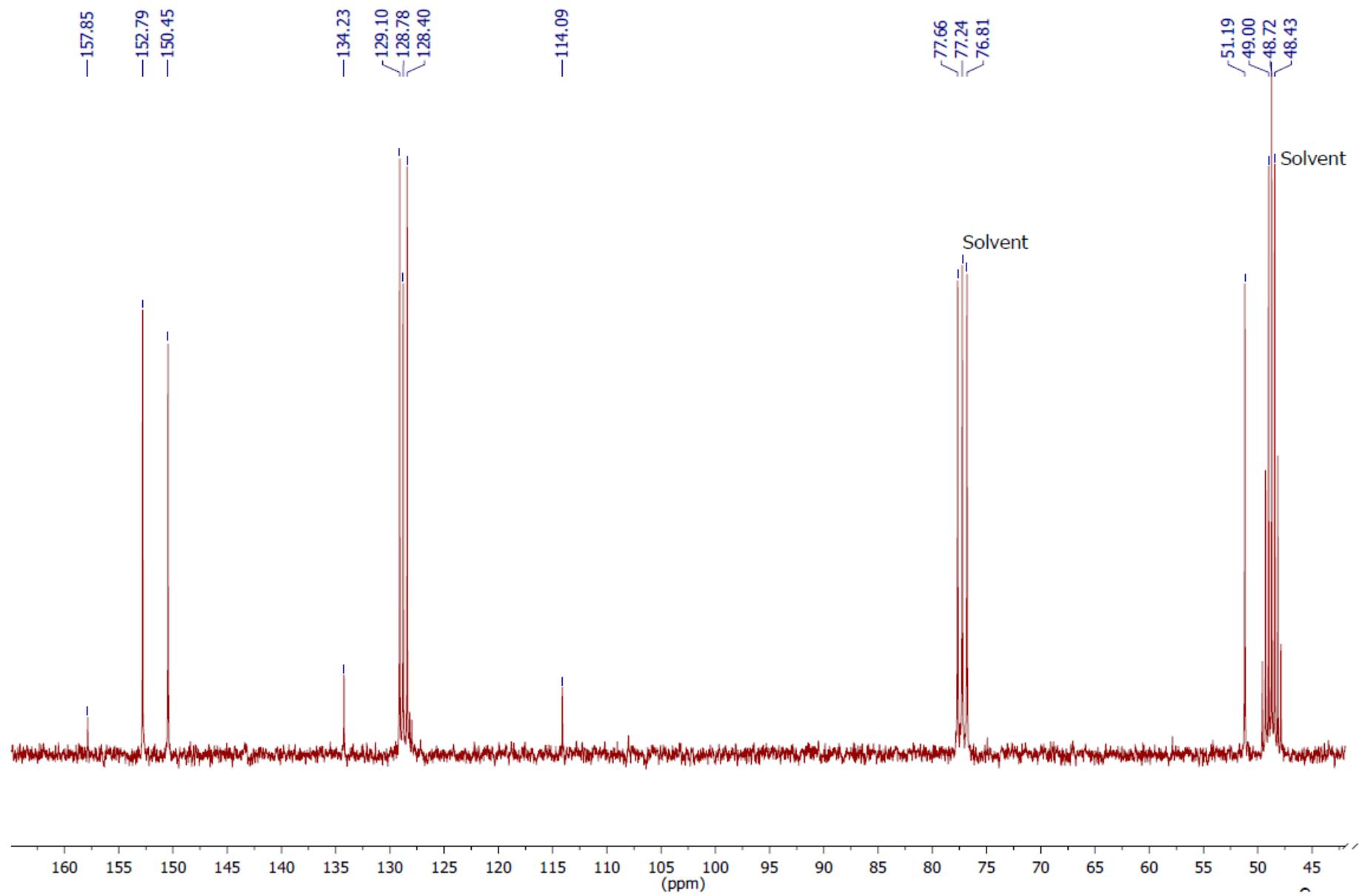


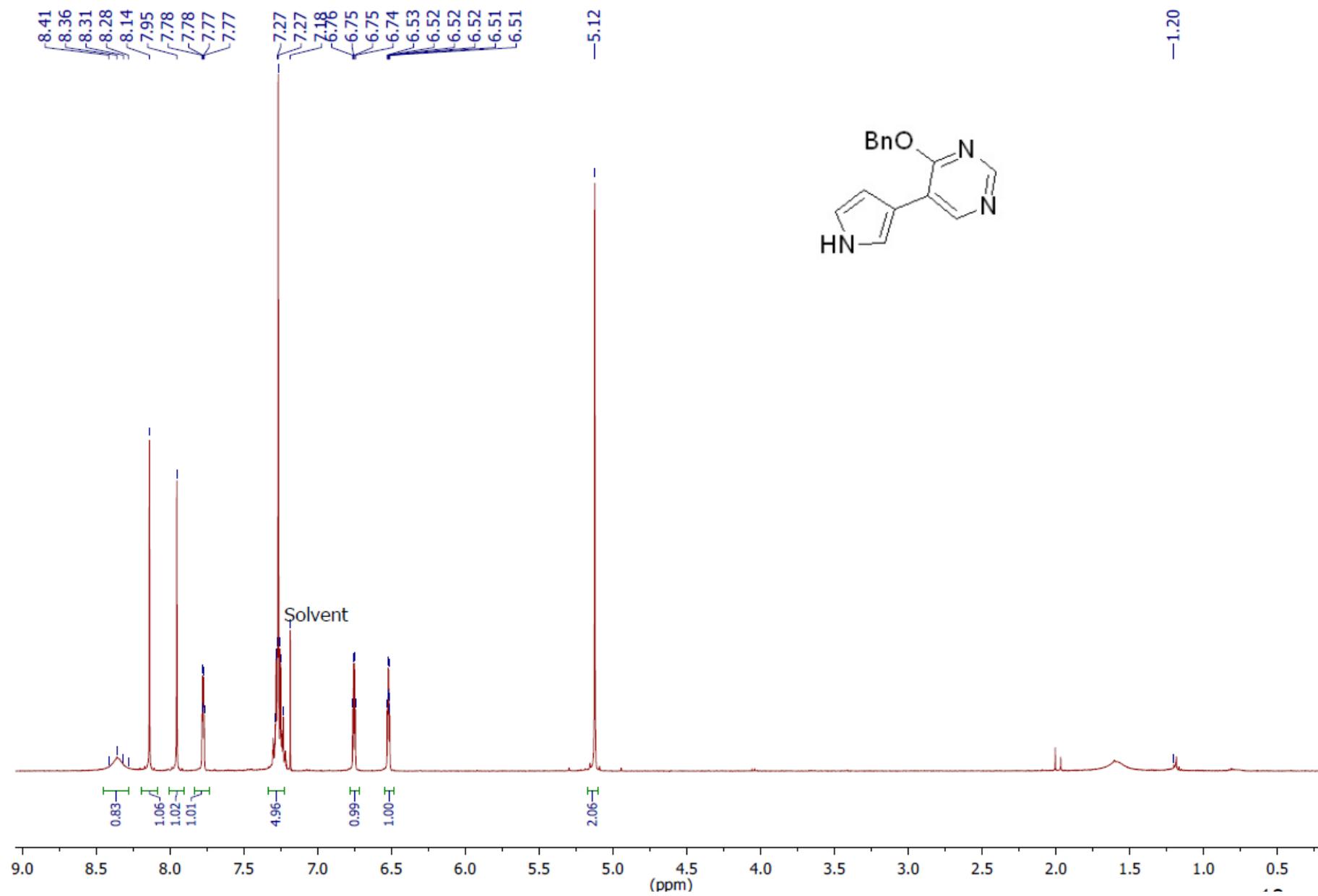


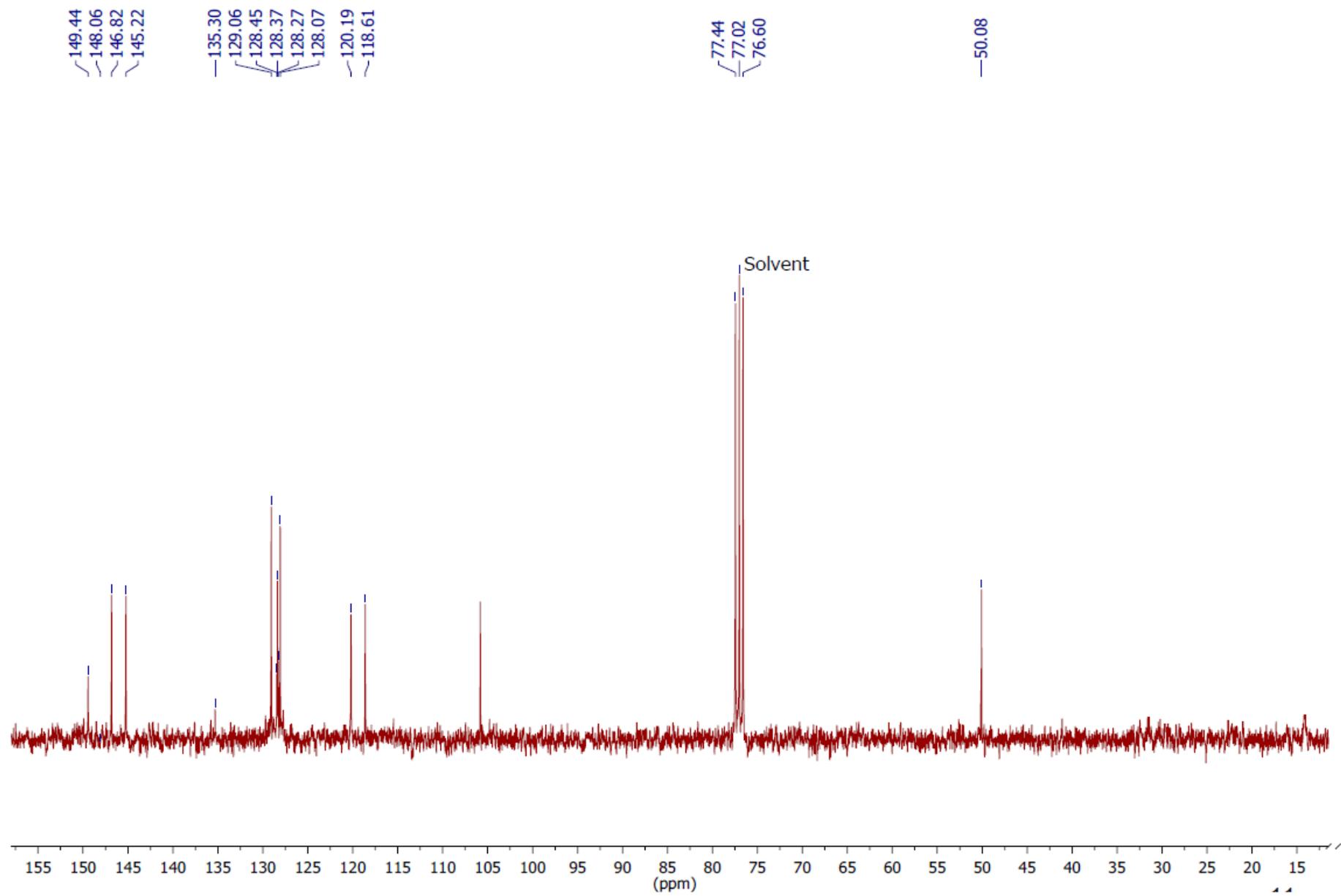


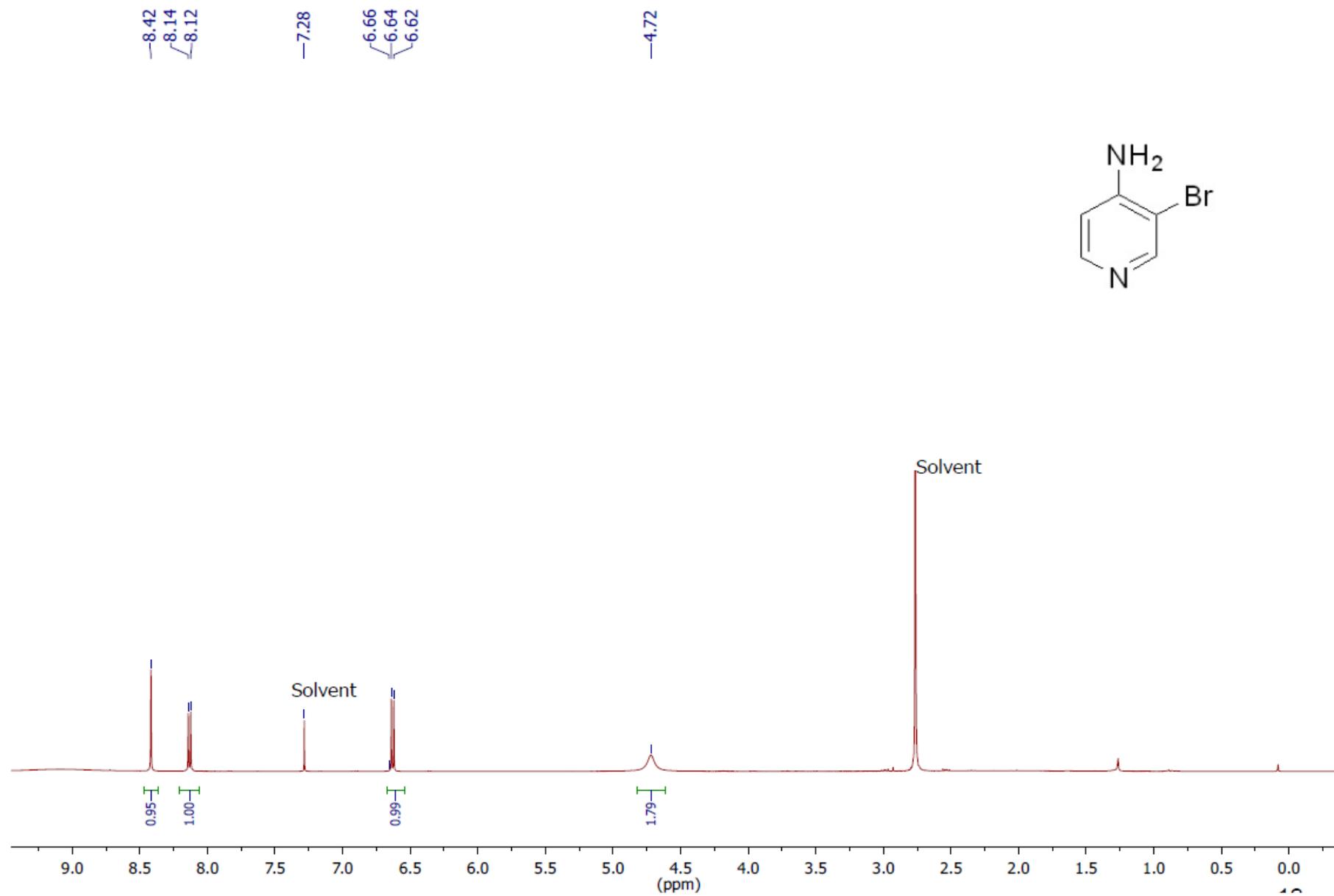


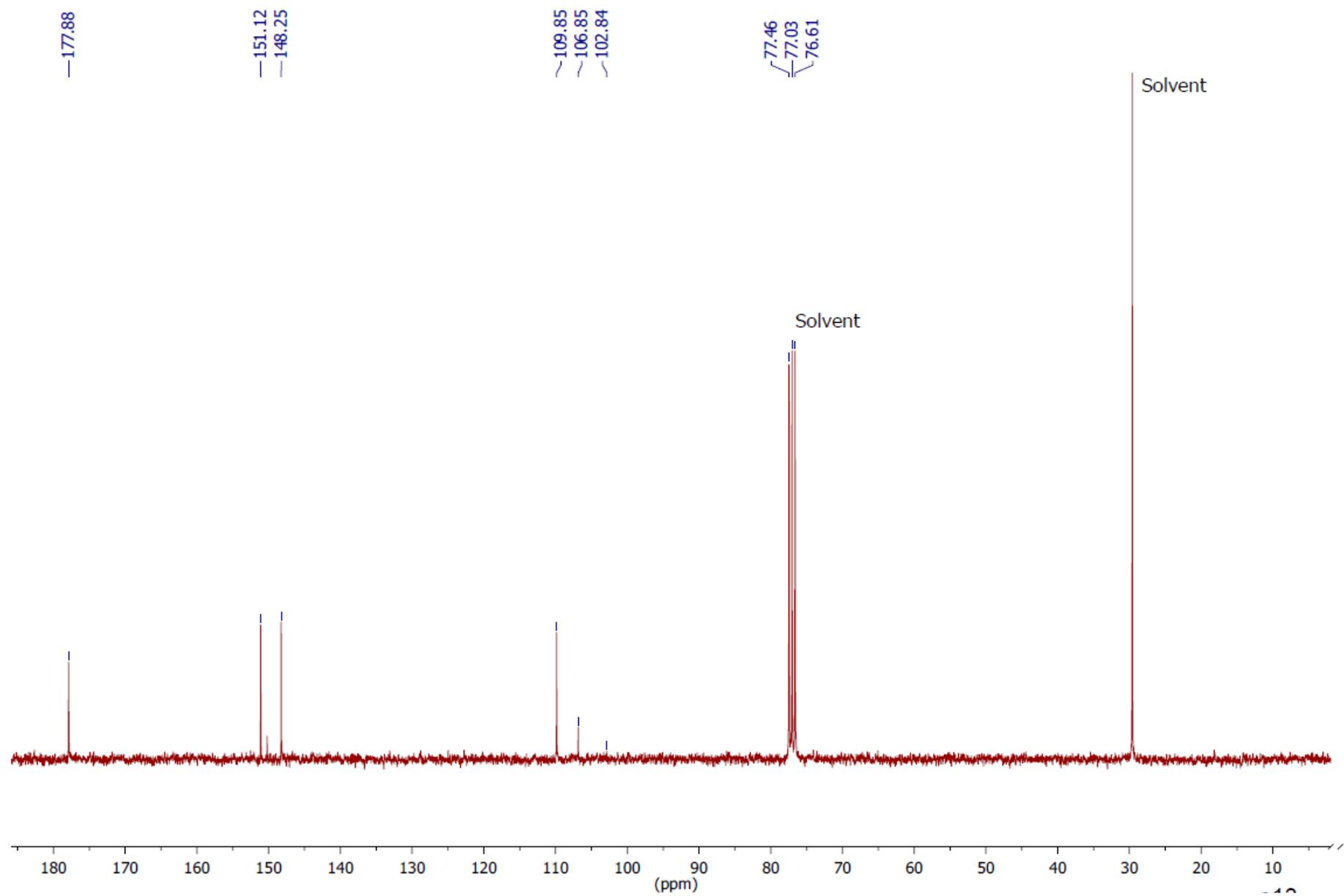


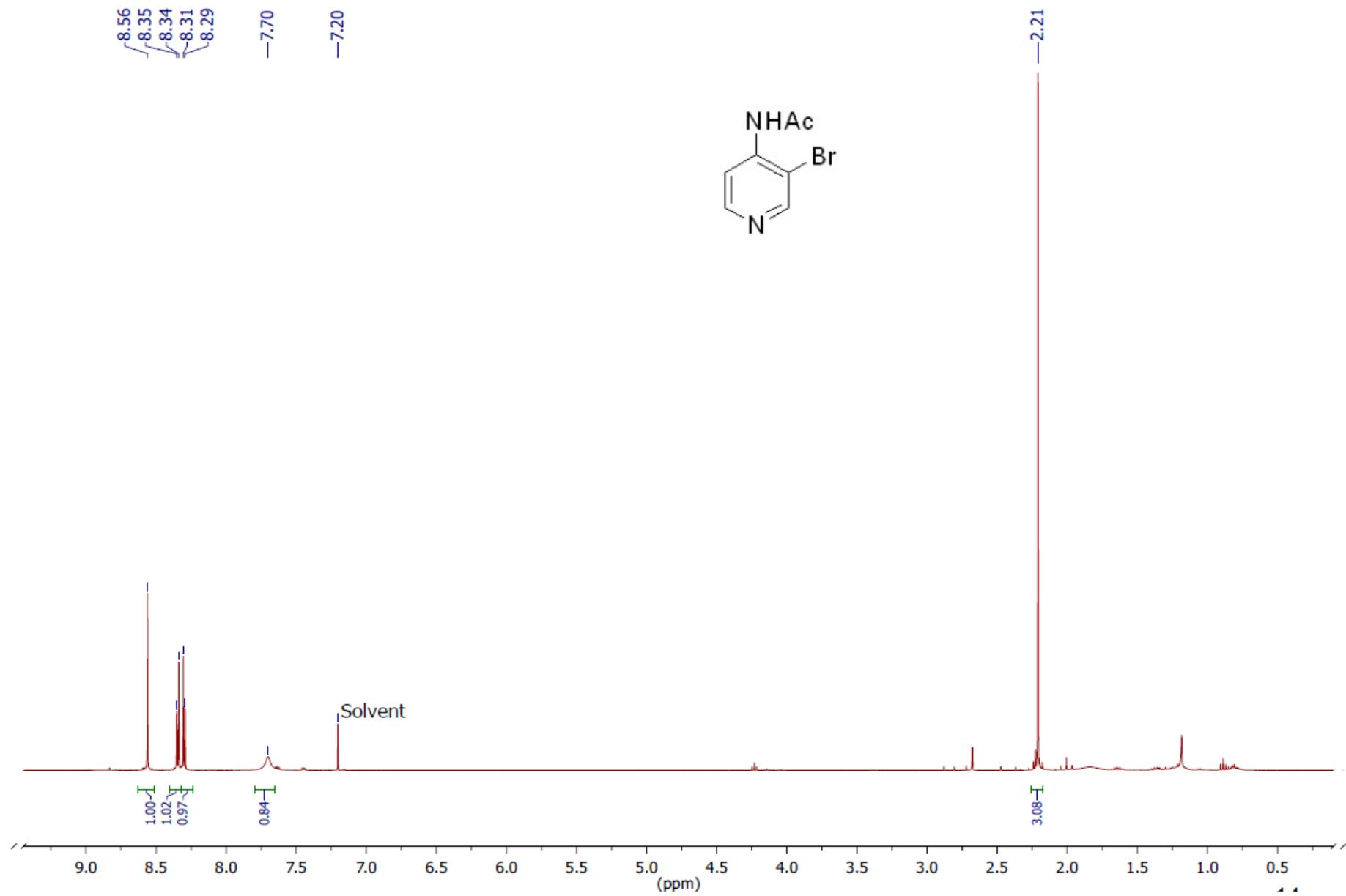


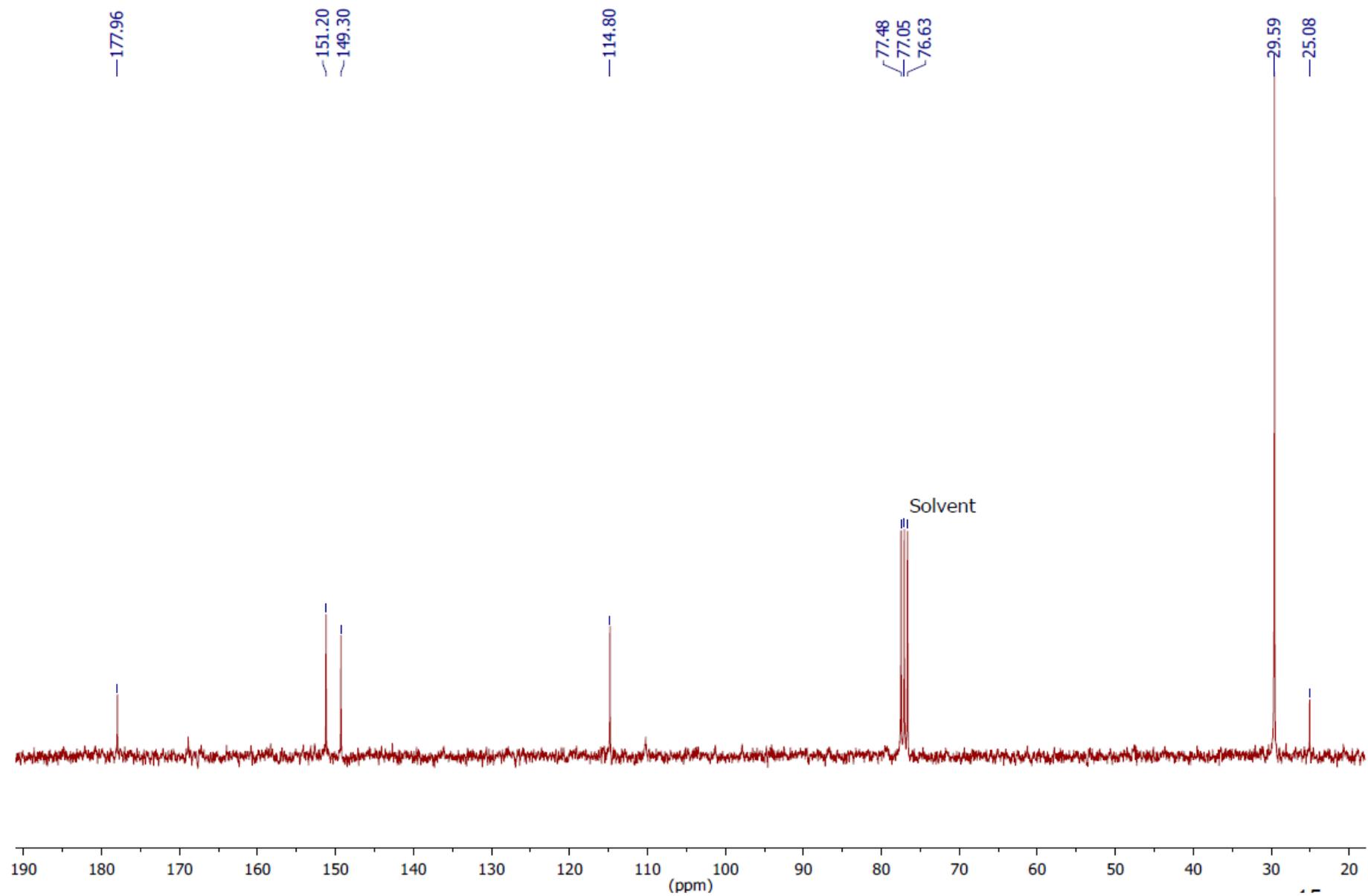


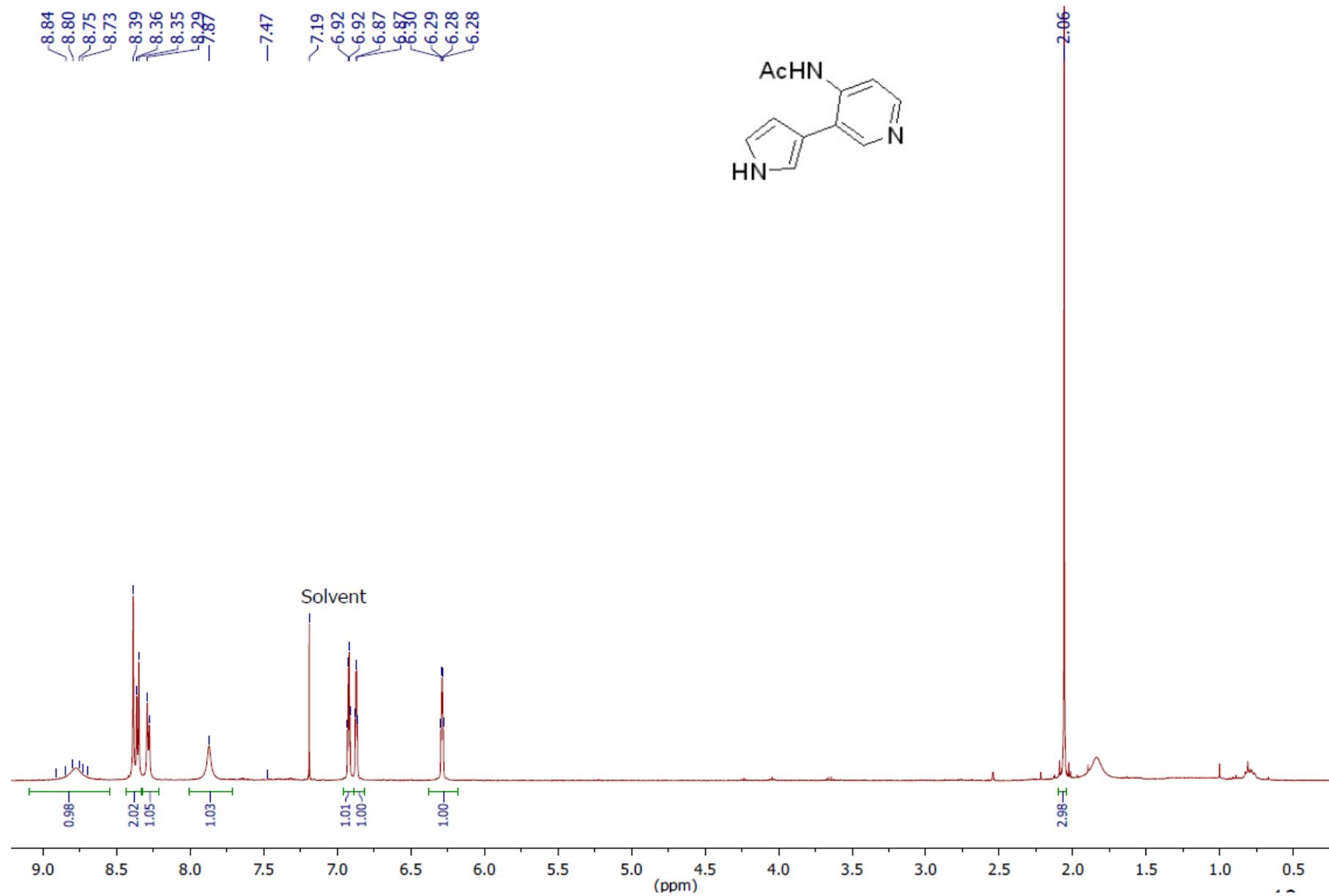


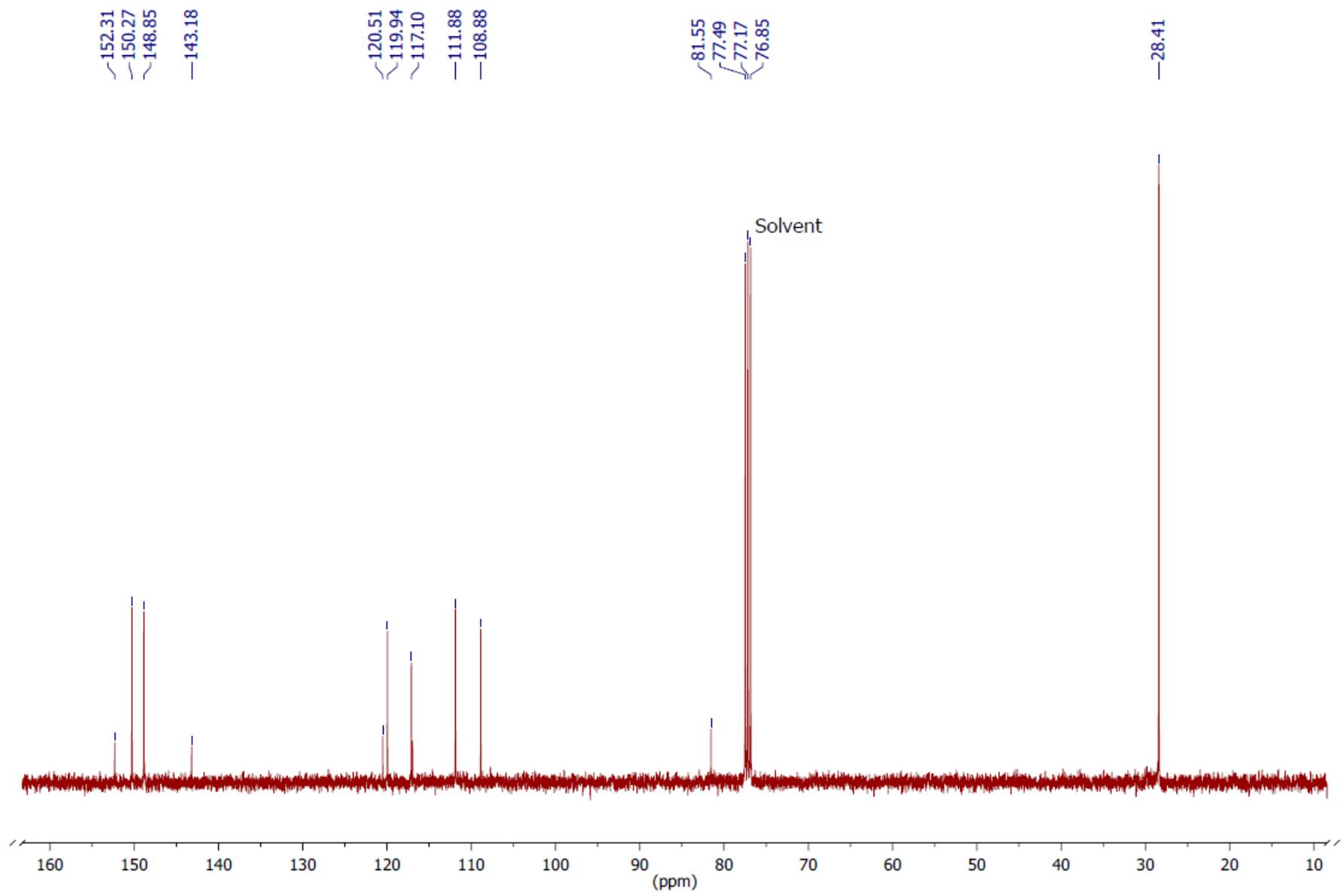












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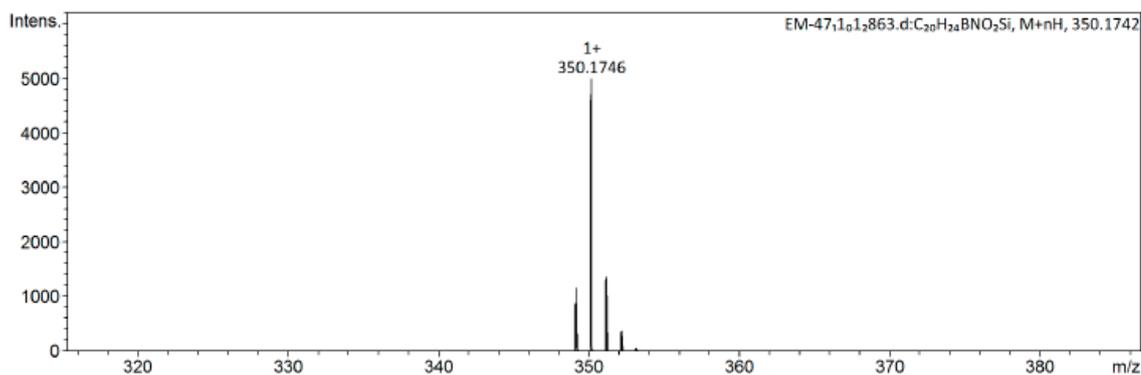
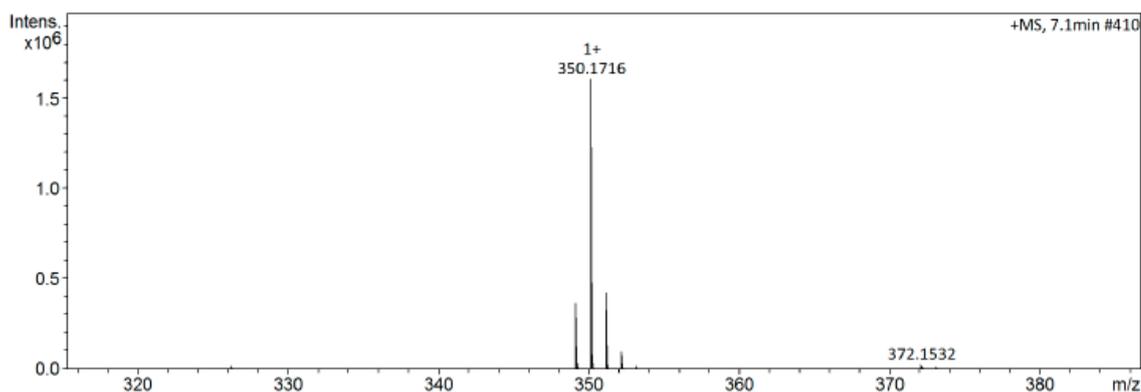
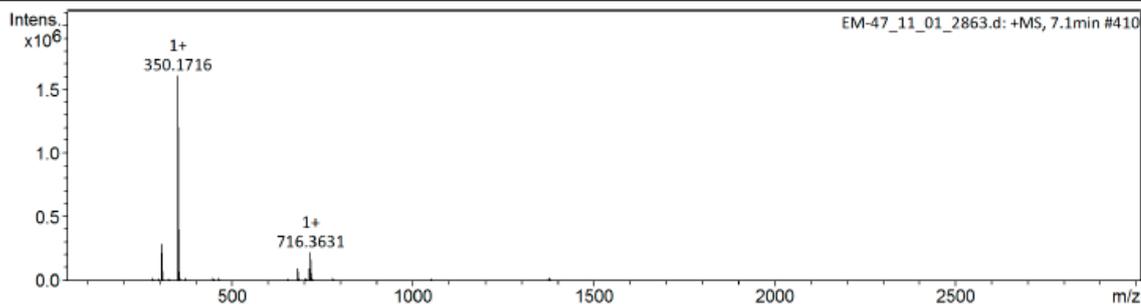
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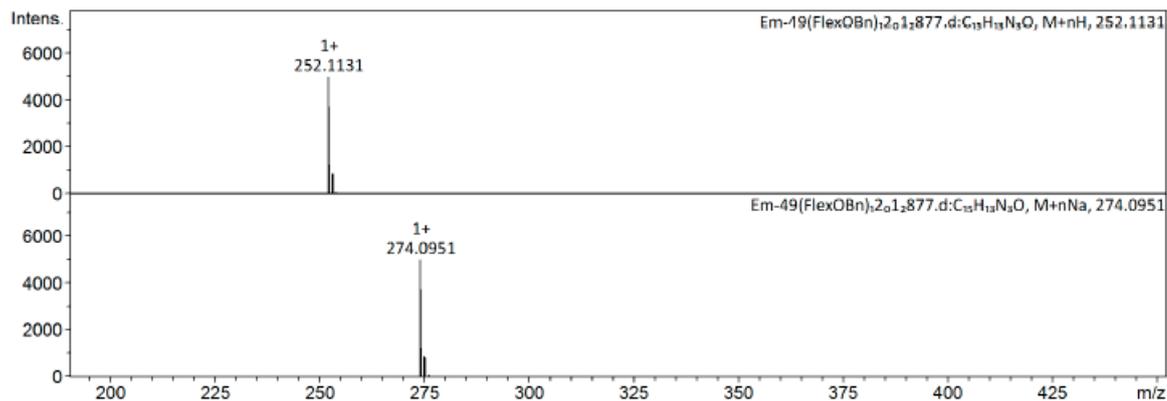
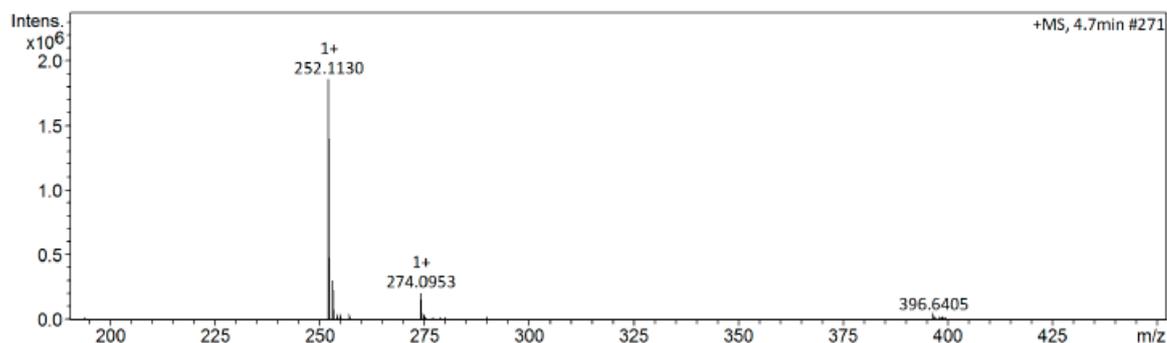
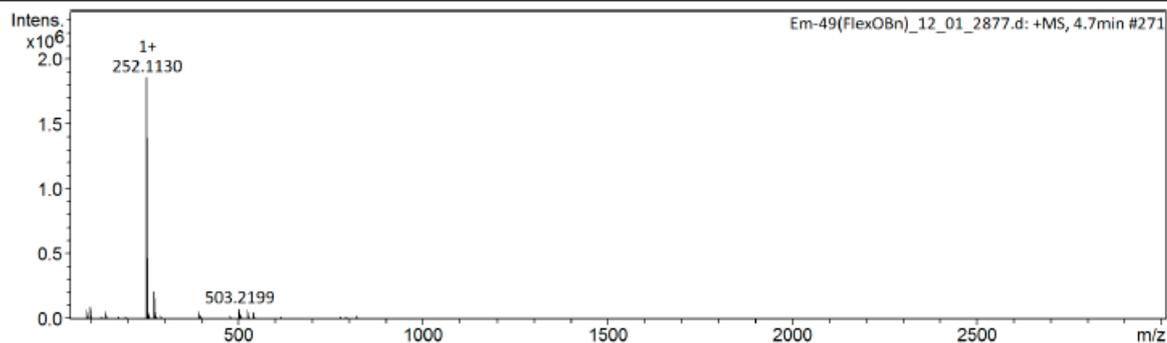
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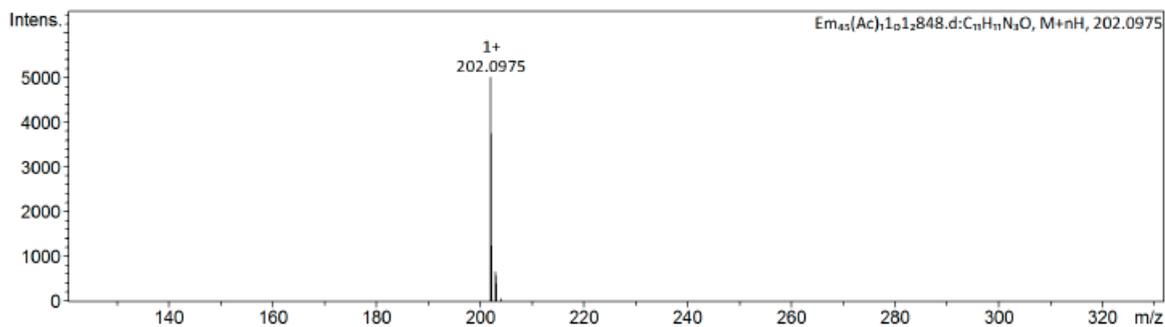
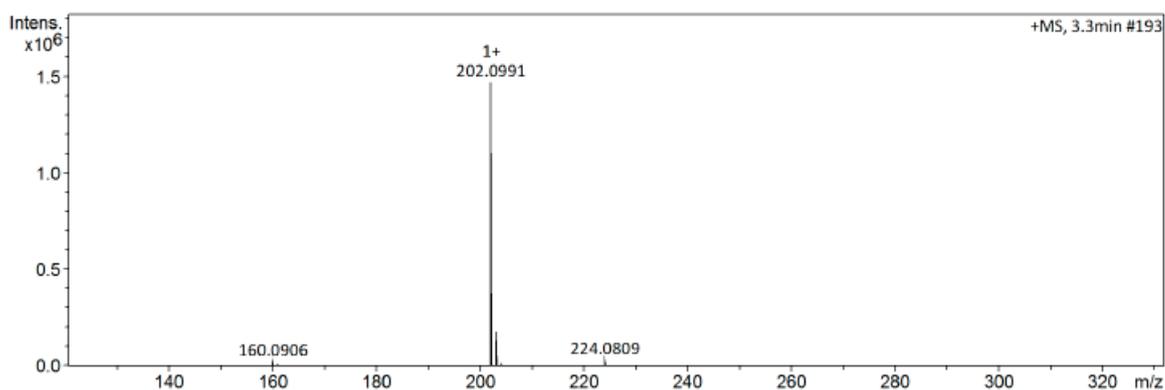
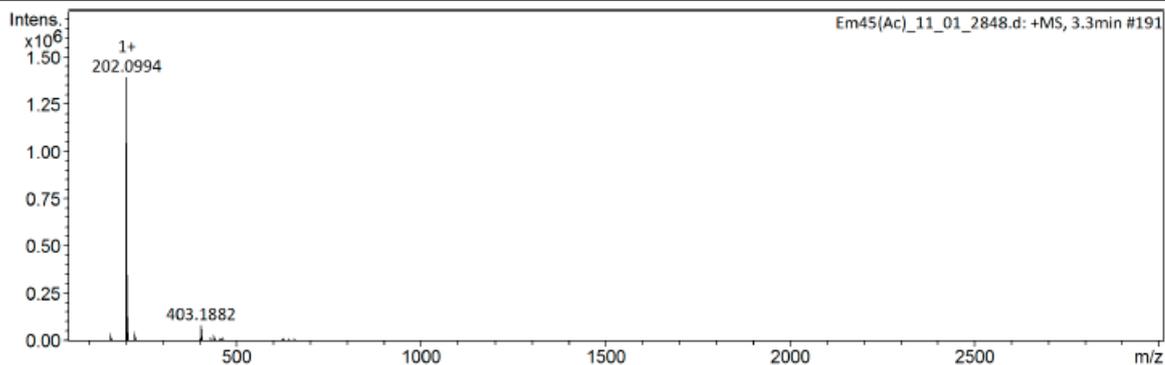
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