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Chemistry & Drug Discovery

Supporting Information

7-Azamelatonin: Efficient Synthetic Routes, Excited-State Double Proton Transfer Properties and Biomedical Implication

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Supporting Information

3,3,5-Tribromo-2-oxo-1,3-dihydrophyrrolo [2,3-b] pyridine (2)

7-Azaindole (5 g, 42 mmol) was dissolved in a mixture of water (0.33 L) and *t*-butanol (0.33 L) at 298 K. After addition (dropwise) of bromine (27 mL, 525 mmol) to this solution and then stirring for 24 h, *t*-butanol was evaporated under reduced pressure and the aqueous phase was treated with a saturated solution of $NaHCO_3$ until pH = 9. After filtration the product was obtained, which was then dried under vacuum (10^{-2} torr). The desired tribrominated oxindole (**2**) (13.4 g, 85%) was isolated as a brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz) d 7.95 (d, *J* = 2.6 Hz, 1H), 8.30 (d, *J* = 2.6 Hz, 1H), 9.70 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) d 42.0, 114.7, 127.4, 136.4, 149.7, 149.9, 168.3. IR (KBr, cm^{-1}) 3091, 2981, 2813, 1746, 1612, 1593, 1459, 814. HRMS (EI^+) m/z calculated for $C_7H_3Br_3N_2O$ [M^+]: 369.7790, found: 369.7787.

5-Bromo-2-oxo-1,3-dihydropyrrolo[2,3-b]pyridine (3)

Zinc (4.40 g, 67.5 mmol) was added to a solution of compound 2 (2.5 g, 6.75 mmol) in acetic acid (50 mL) under purged N_2 at room temperature. The reaction was proceeded under stirring for ~5 h, and the solvent was then evaporated to dryness. After dilution with water, the crude mixture was extracted with ethyl acetate. After drying, the organic layers were coevaporated with toluene. The crude mixture was then purified by flash chromatography (eluent: methylene chloride/methanol, 95/5) to yield compound **3** (1.36 g, 95%) as an orange solid. ^{1}H NMR (DMSO-d_6, 400 MHz) d 3.57 (s, 2H), 7.75 (s, 1H), 8.14 (s, 1H), 11.12 (bs, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) d 35.4, 111.8, 122.8, 134.1, 146.0, 157.0, 175.1. IR (KBr, cm^{-1})

3102, 3080, 3021, 2819, 1728, 1620, 1594, 1209, 748. HRMS (EI^+) m/z calculated for $C_7H_5BrN_2O$ [M^+]: 211.9580, found: 211.9568.

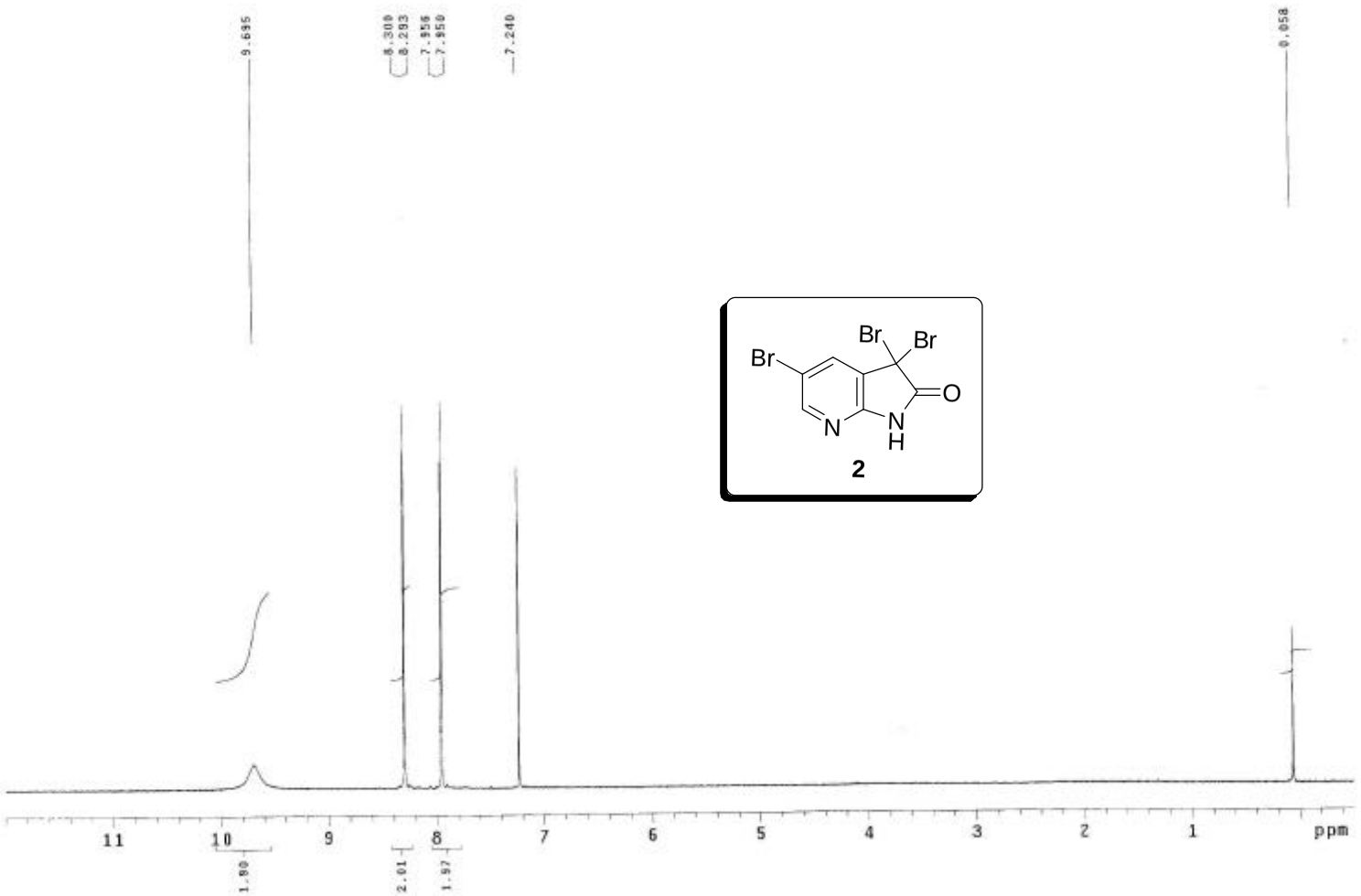
5-Bromo-1H-pyrrolo[2,3-b]pyridine (4)

Under N_2 purged condition, a solution of borane-tetrahydrofuran complex solution (1M) in anhydrous tetrahydrofuran (18.8 mL, 18.8 mmol) was added dropwise at 0 ^oC to a solution of compound **3** (1.0 g, 4.7 mmol) in anhydrous tetrahydrofuran (25 mL). The mixture was stirred for a period of ~50 min at room temperature. Solvent was then removed under reduced pressure (10^{-2} torr). The residue was diluted with a solution of hydrochloric acid (6 N) and heated until the complete dissolution of the solid. After cooling, the mixture was treated with sodium hydroxide (6 M) up to pH = 9 and extracted with ethyl acetate. The organic layers were dried and the solvent was removed under reduced pressure (10^{-2} torr). The crude mixture was used in the next step without further purification. As the next step, this crude compound was dissolved in acetic acid (10 mL) at room temperature and the resulting solution was added to a suspension of manganese(III) acetate (2.05 g, 7.64 mmol) in acetic acid (10 mL). After the stirring of 50 min, while the temperature was kept at 75 ^oC, the solvent was coevaporated with toluene. The crude mixture was then diluted with water, followed by the extraction with ethyl acetate, and the resulting organic layers were dried. After evaporation of the solvent under reduced pressure, the crude mixture was purified by flash chromatography (eluent: hexane/ethyl acetate, 5/1), yielding compound **4** (450 mg, 50%) as a yellowish solid. ^1H NMR ($CDCl_3$, 400 MHz) d 6.46 (d, *J* = 3.2 Hz, 1H), 7.37 (d, *J* = 3.2 Hz, 1H), 8.09 (s, 1H), 8.34 (s, 1H), 10.85 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) d 100.5, 111.4, 122.3, 126.8, 131.4, 142.3, 146.3. IR (KBr, cm^{-1}) 3132, 2862, 1558, 1282, 884, 740. HRMS (EI^+) m/z calculated for $C_7H_5BrN_2$ [M^+]: 195.9631, found: 195.9620.

5-Methoxy-1H-pyrrolo[2,3-b]pyridine (5)

Under N_2 purged atmosphere, **4** (1.0 g, 5.07 mmol) was dissolved in a mixture of *N,N*-dimethylformamide (32 mL) and methanol (20 mL). Then, sodium methoxide (14.5 g, 268.7 mmol) and copper(I) bromide

(1.45 g, 10.1 mmol) were added to this solution at room temperature. The mixture was heated and refluxed for 3 h. After cooling, the solvents were removed under reduced pressure and the residue was hydrolyzed, followed by the extraction with ethyl acetate. The organic layers were dried, followed by removal of the solvent under reduced pressure. The crude mixture was purified by flash chromatography (eluent: methylene chloride/methanol, 99/1) to provide compound 5 (639 mg, 85%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) d 3.89 (s, 3H), 6.45 (d, *J* = 3.2 Hz, 1H), 7.34 (d, *J* = 3.2 Hz, 1H), 7.53 (s, 1H), 8.06 (s, 1H), 10.01 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) d 56.6, 100.7, 113.6, 121.1, 126.5, 131.0, 142.5, 151.5. IR (KBr, cm^{-1}) 3134, 2875, 1493, 1314, 1248, 1028, 786. HRMS (EI^+) m/z calculated for $C_8H_8N_2O$ [M^+]: 148.0631, found: 148.0640.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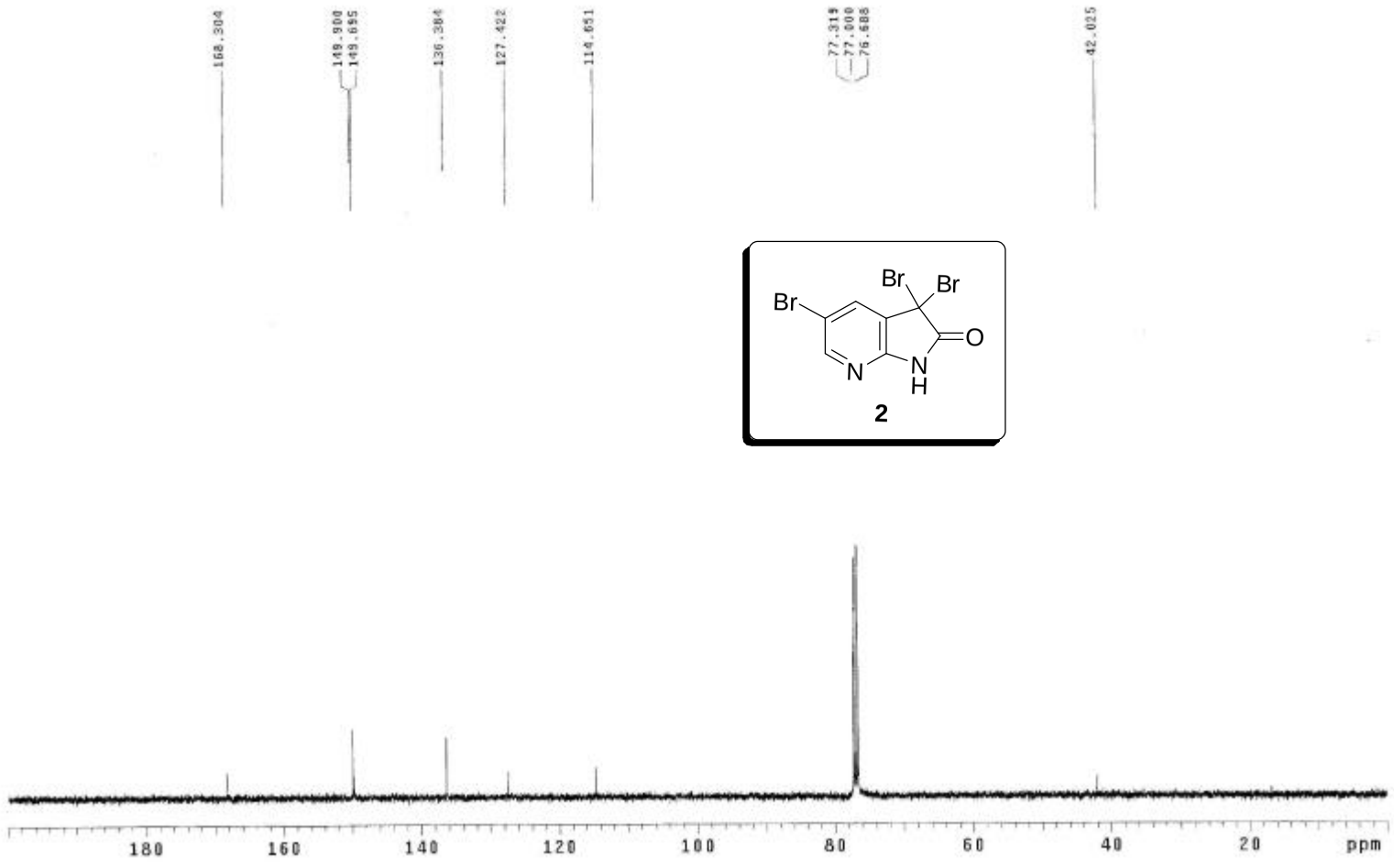
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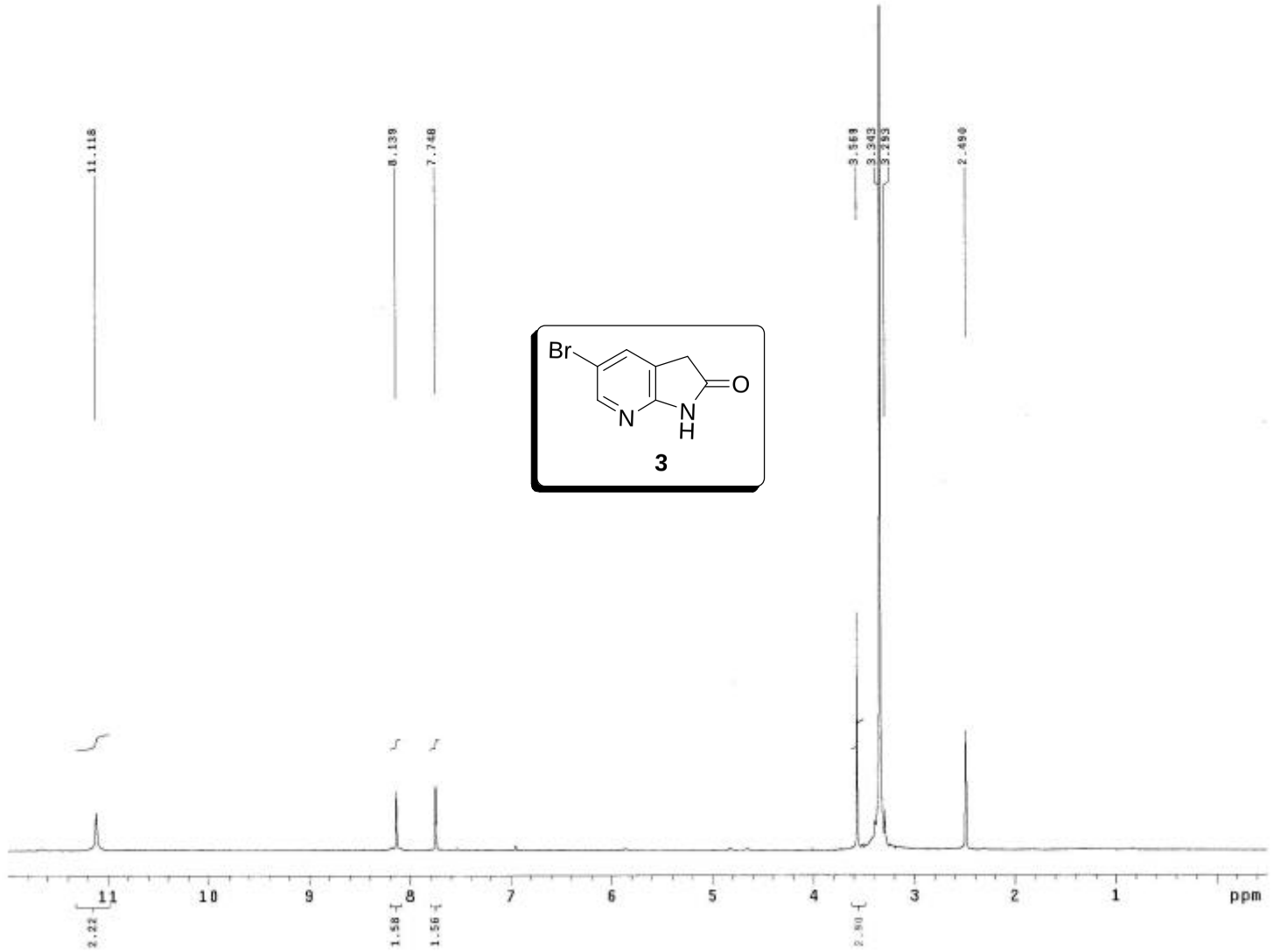
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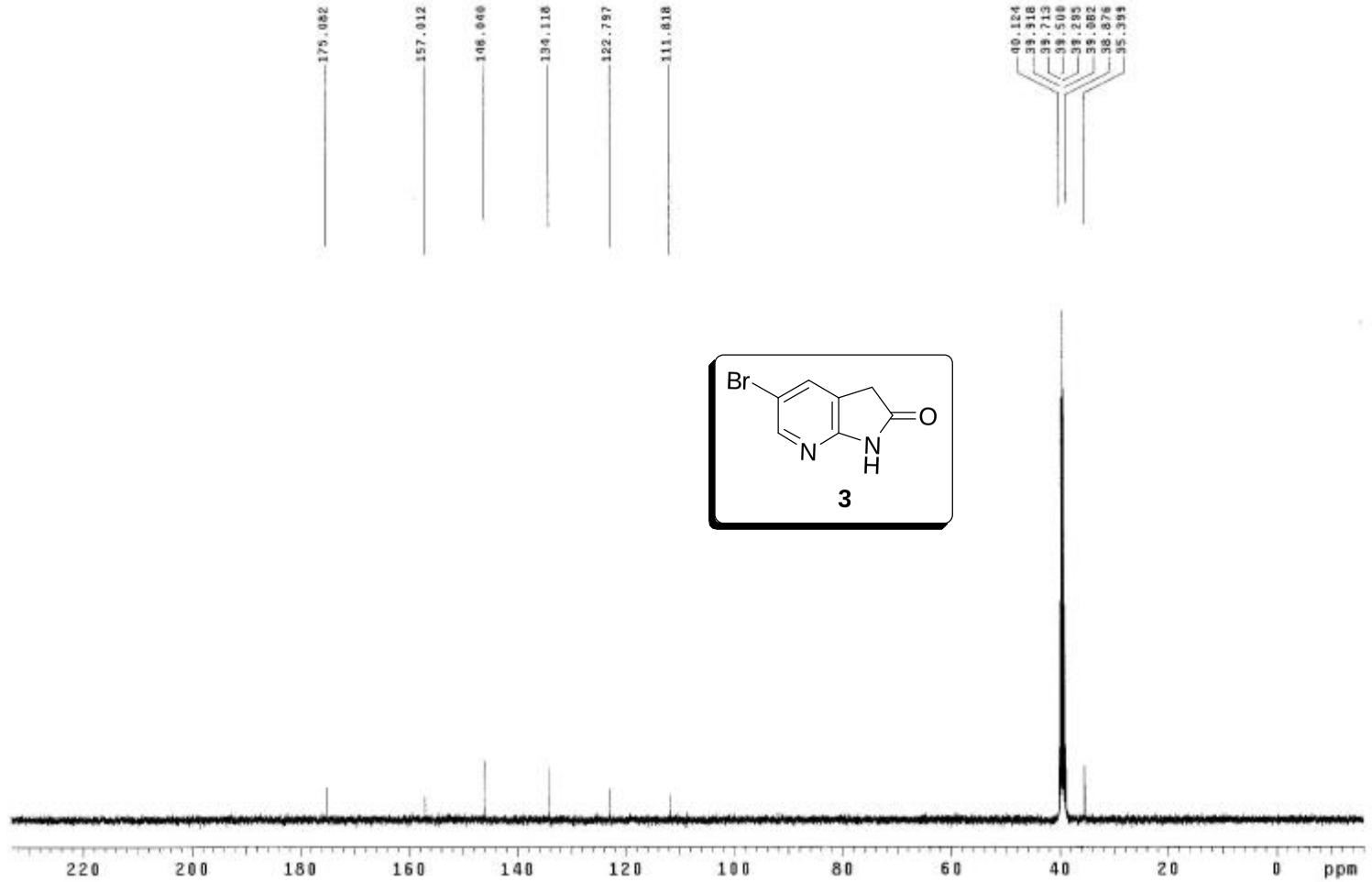
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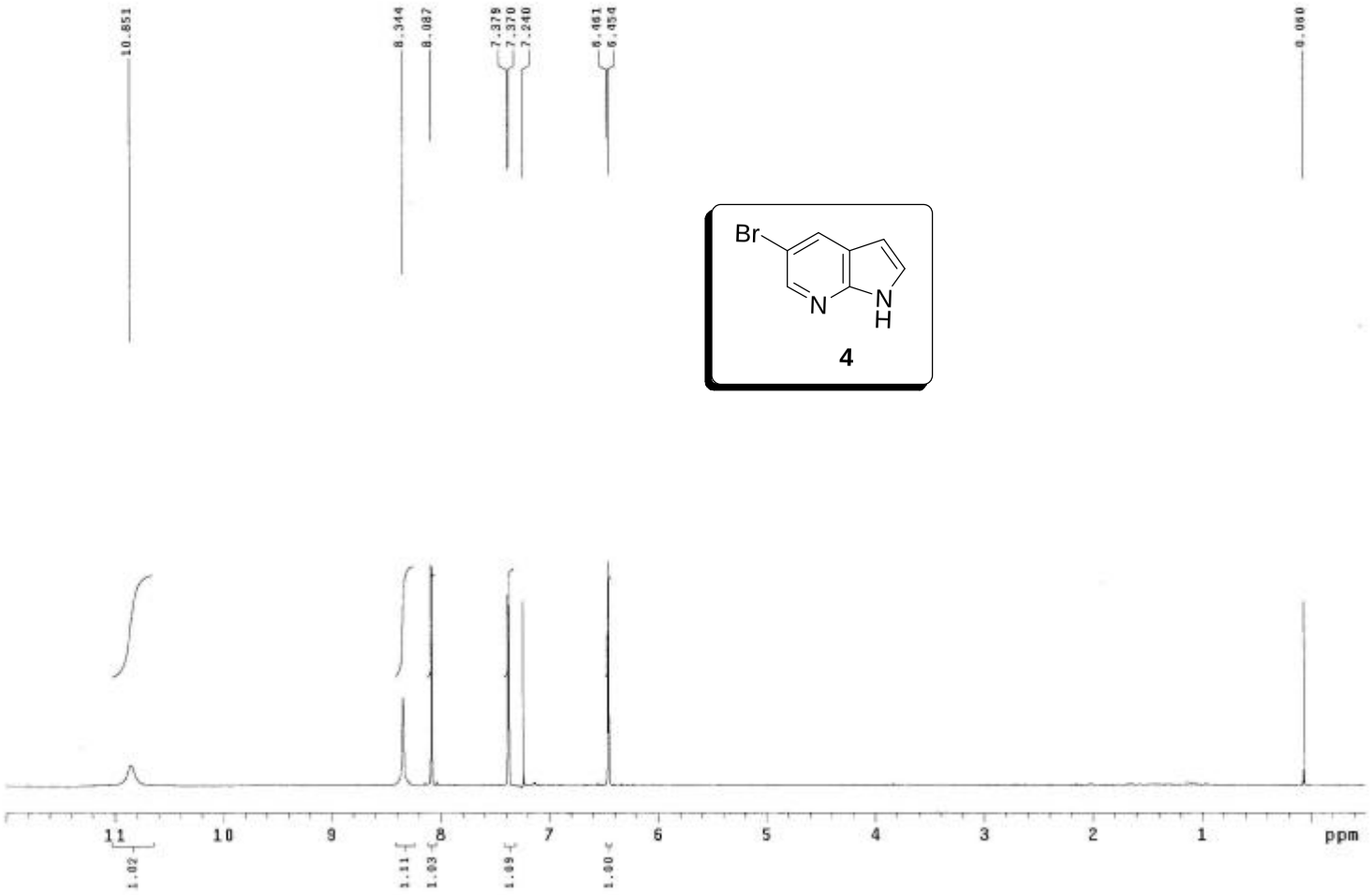
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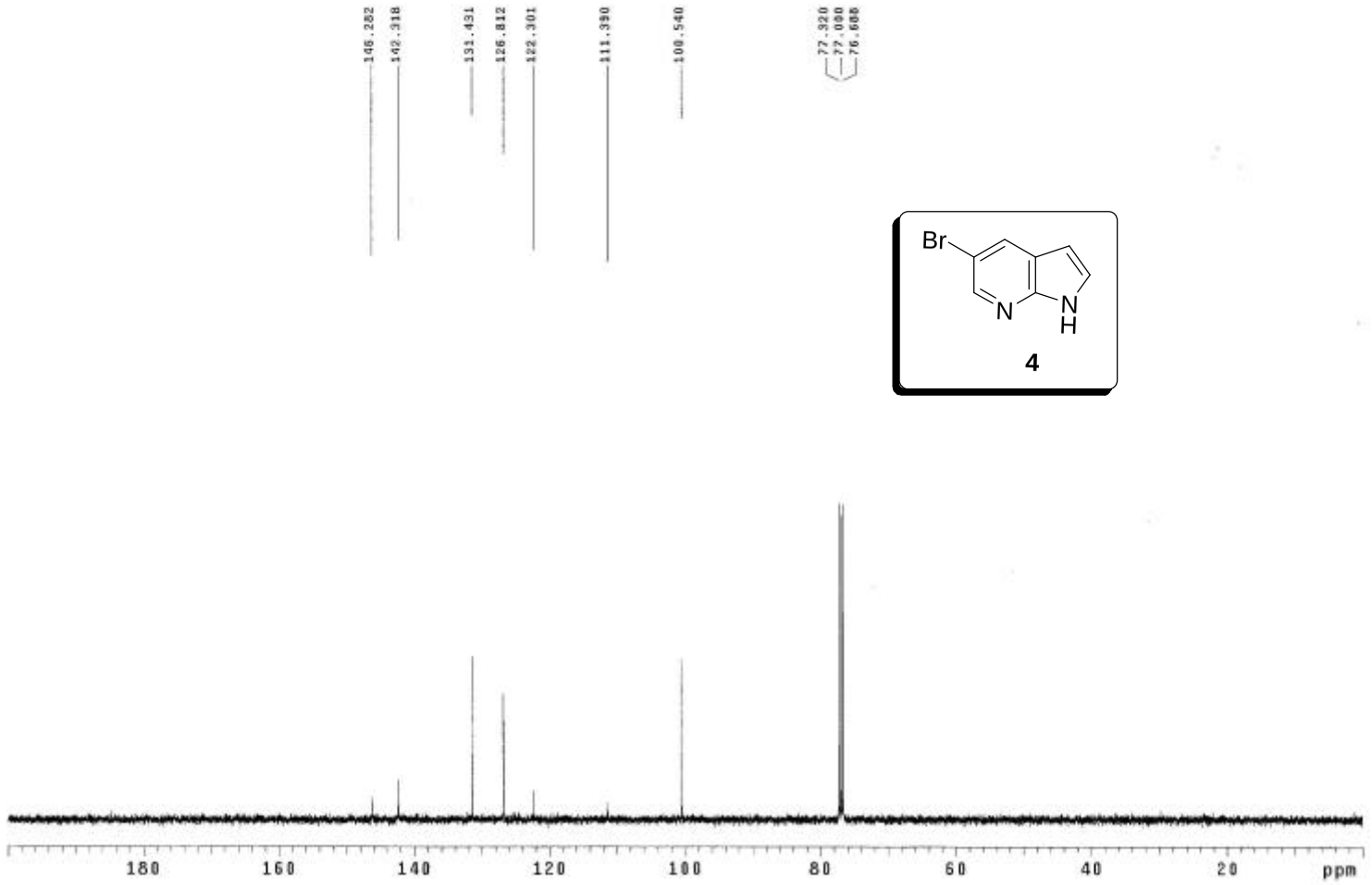
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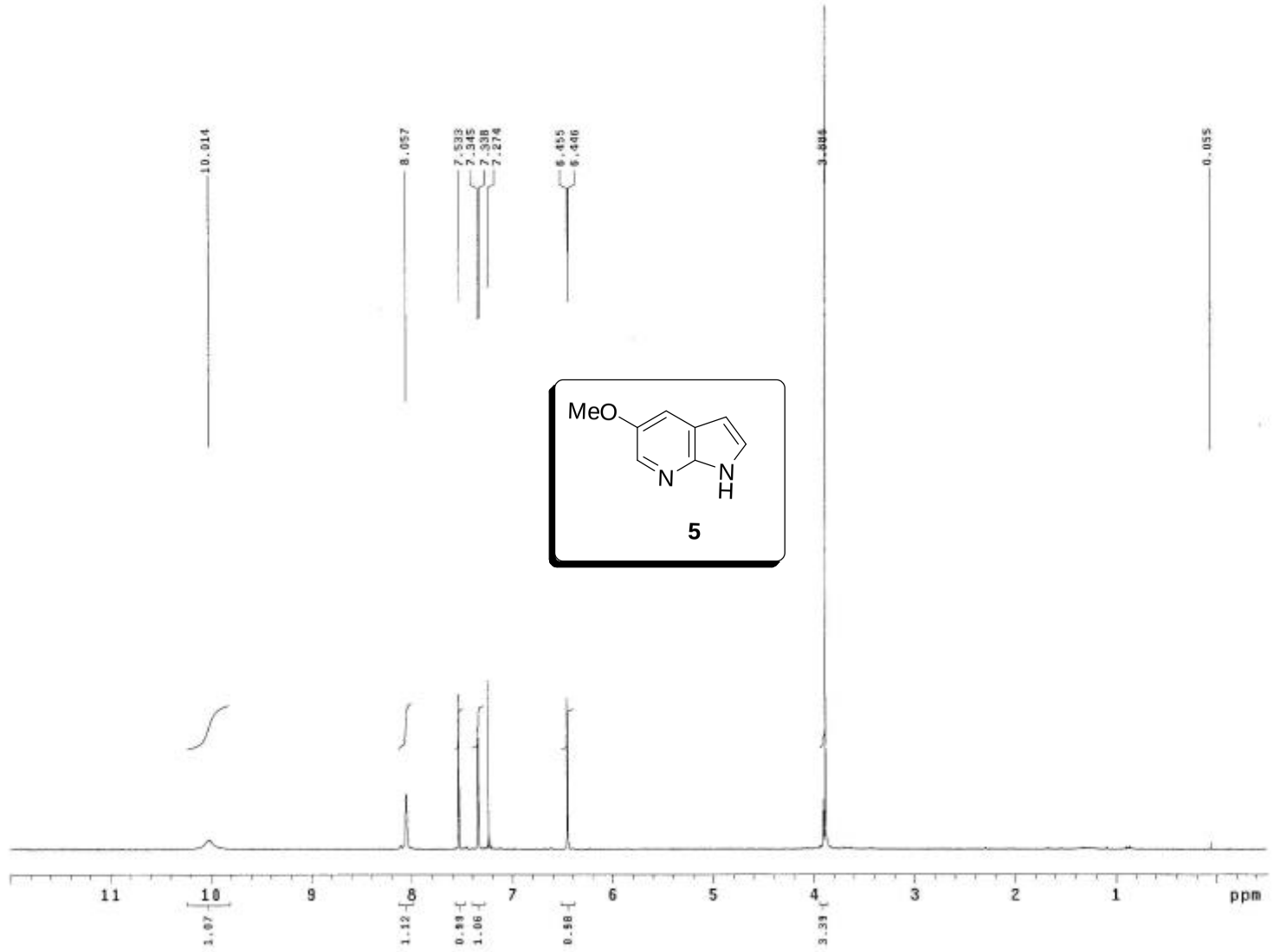
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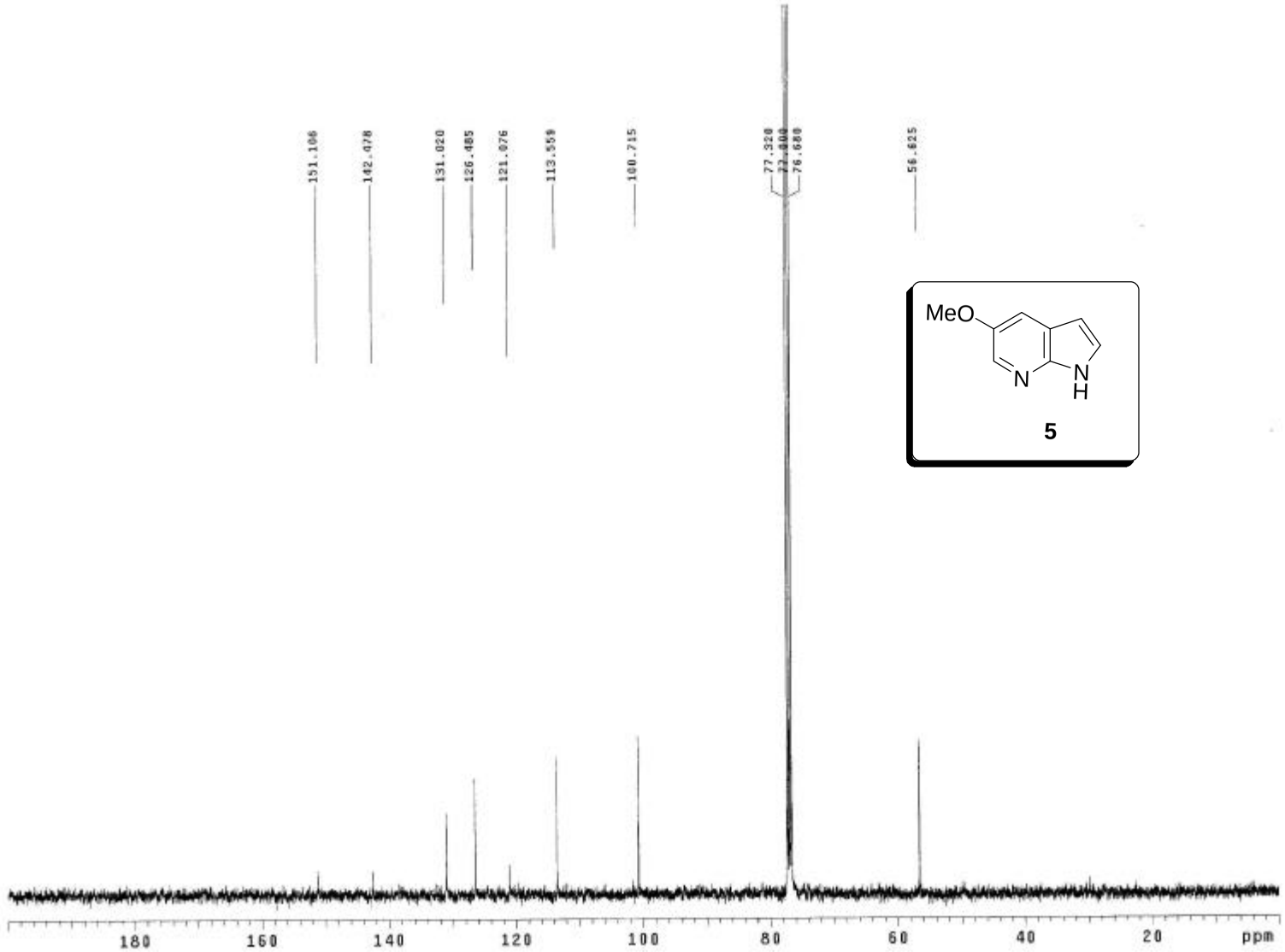
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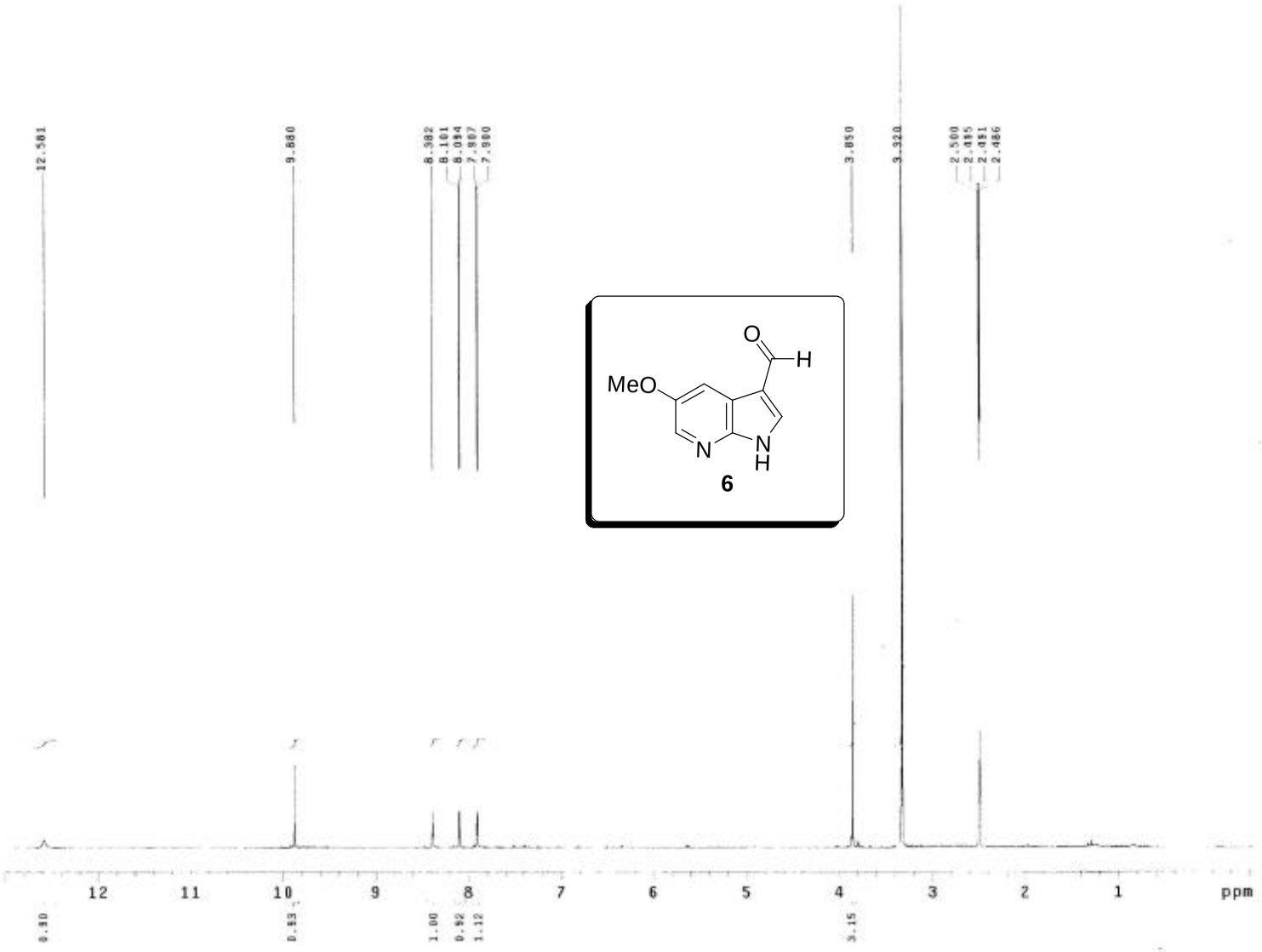
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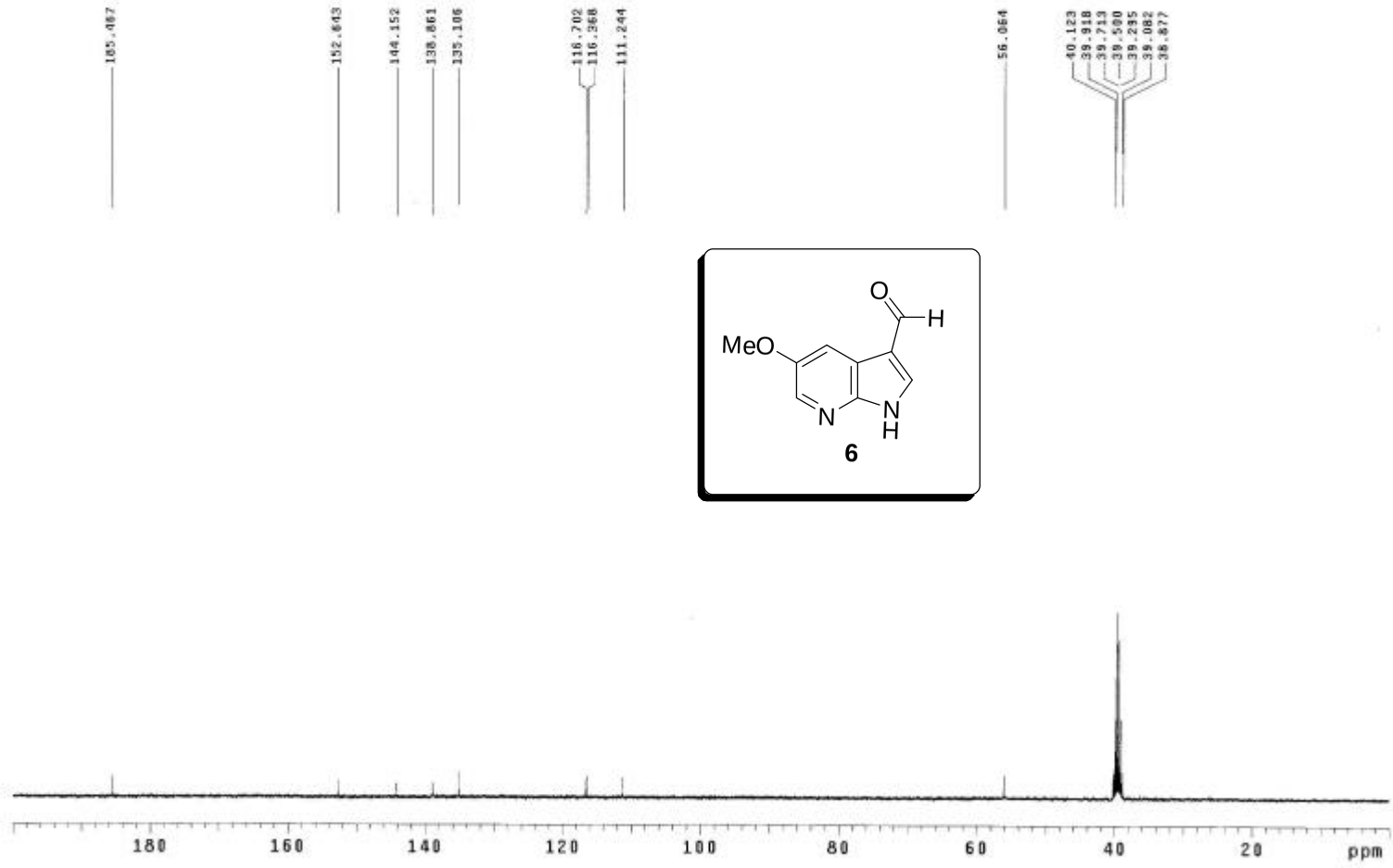
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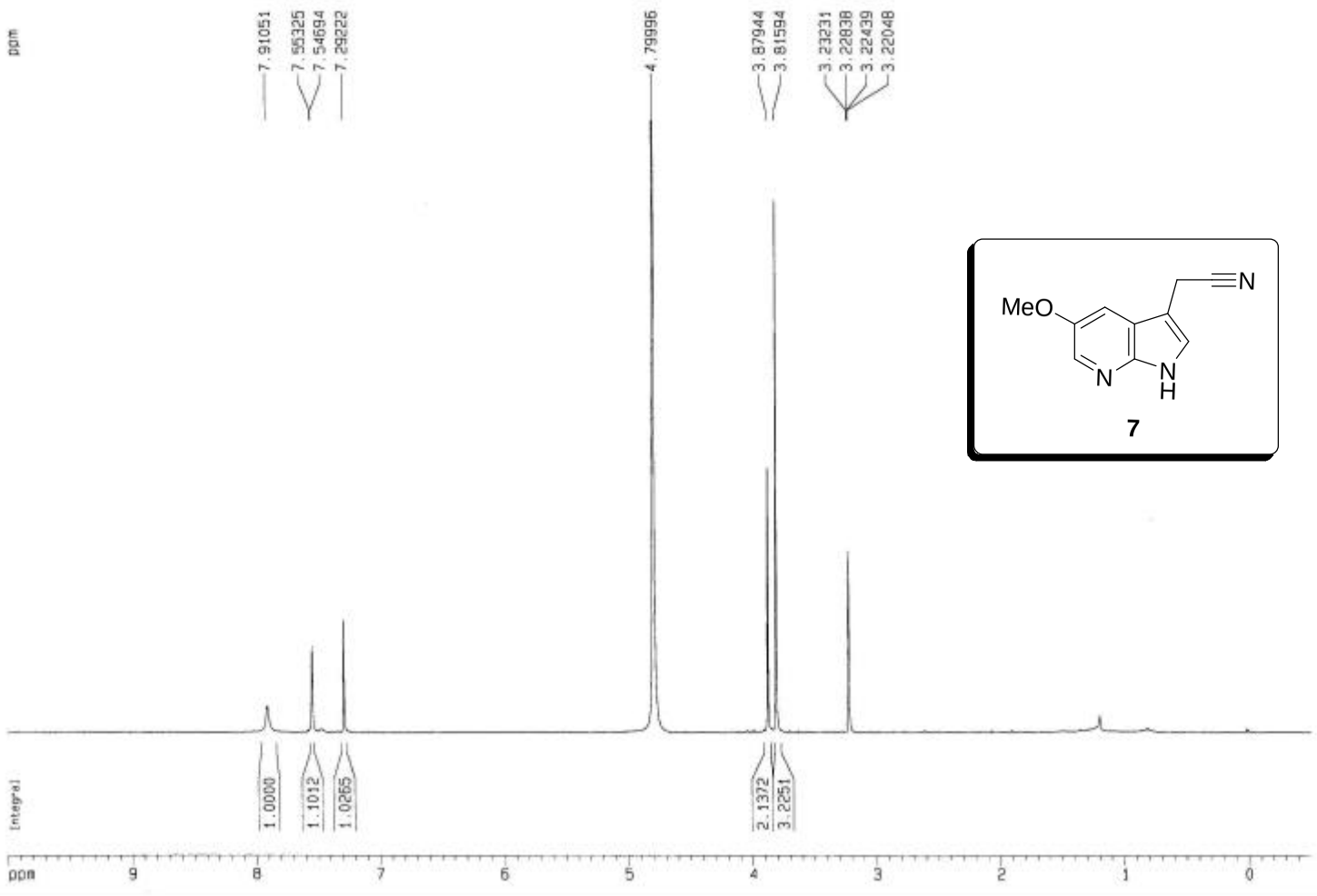
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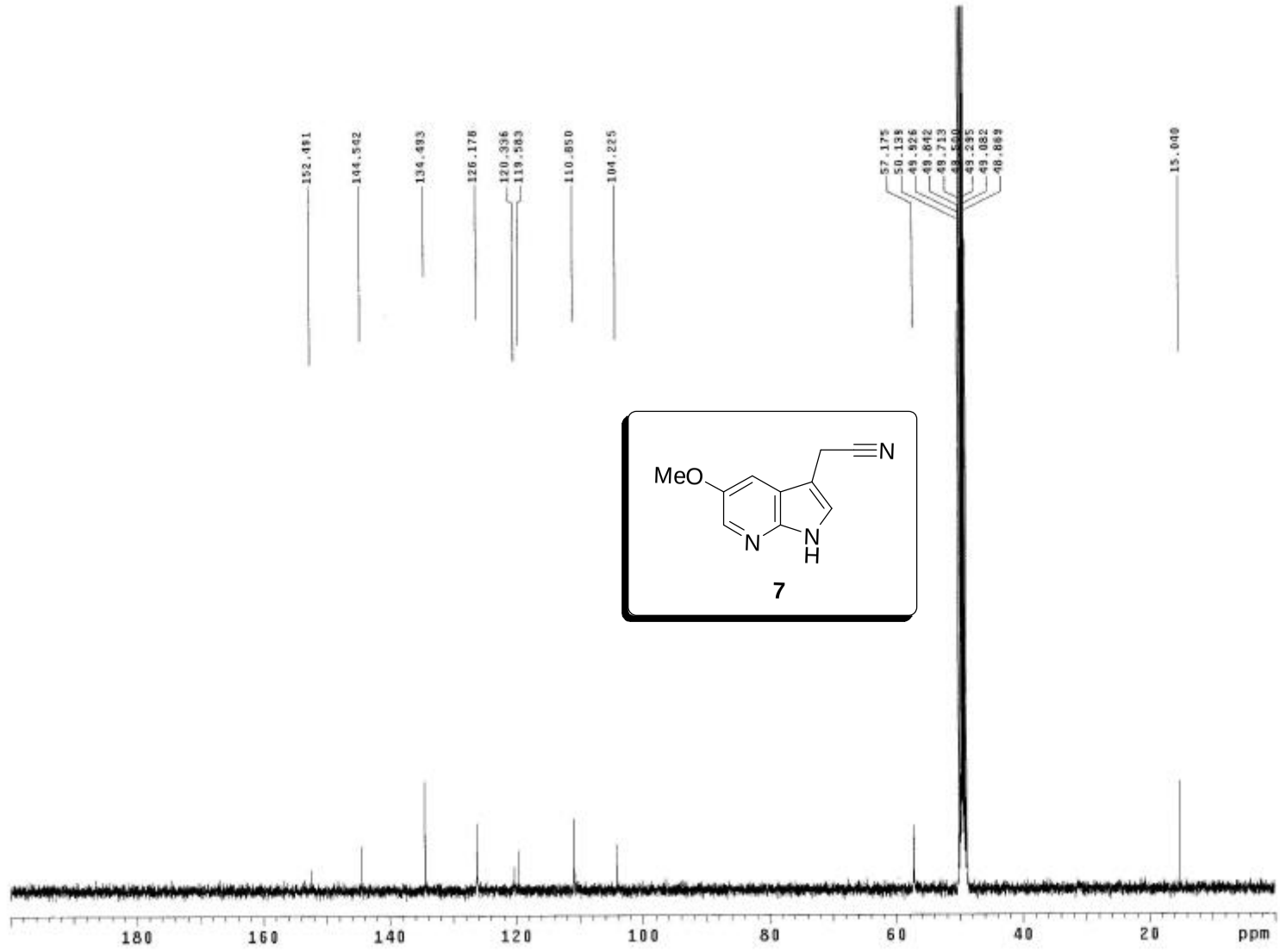
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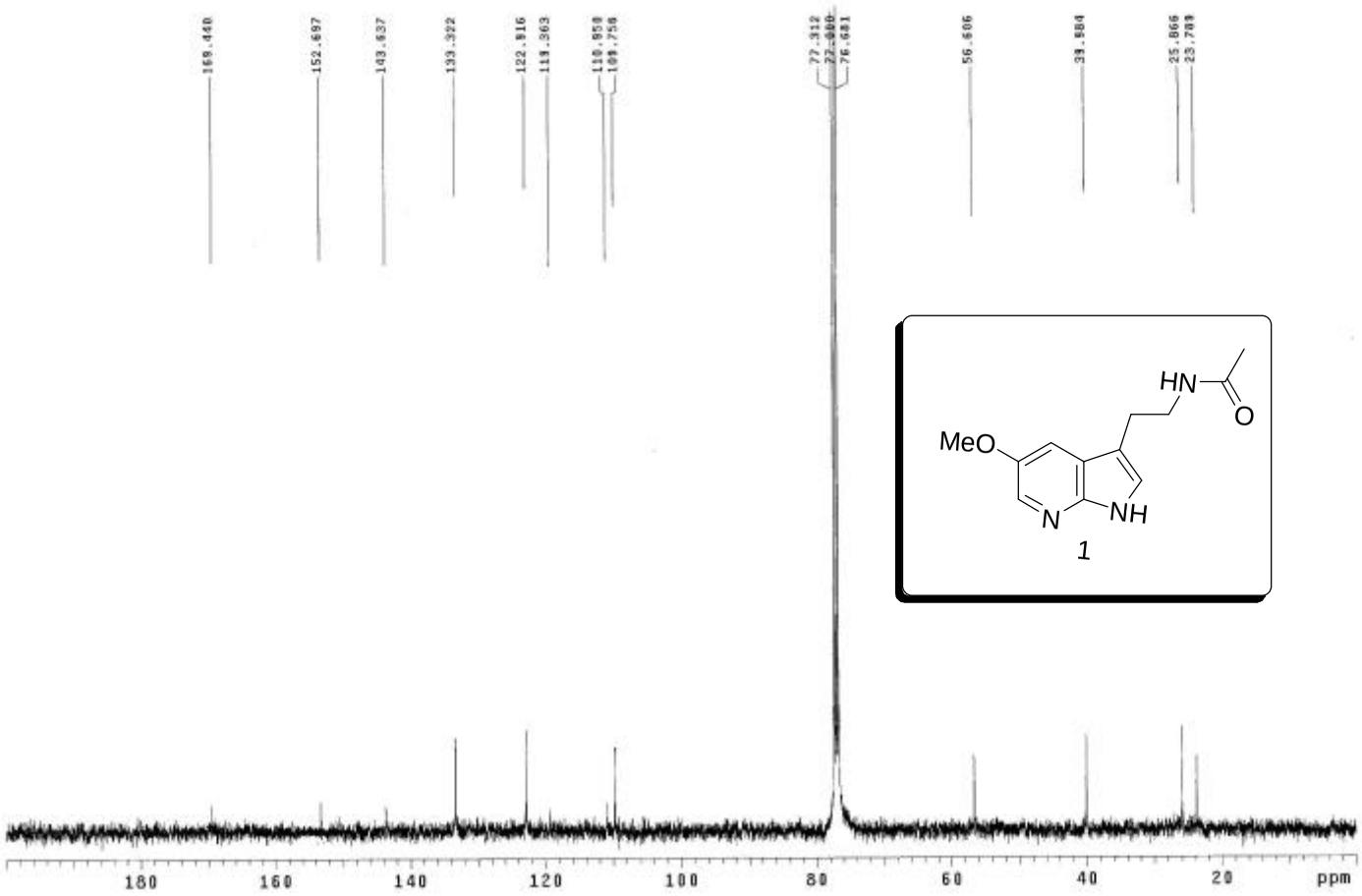
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