

Electronic Supplementary Information

Coupling reaction between electron-rich pyrimidinones and α -amino acids promoted by phosphonium salts

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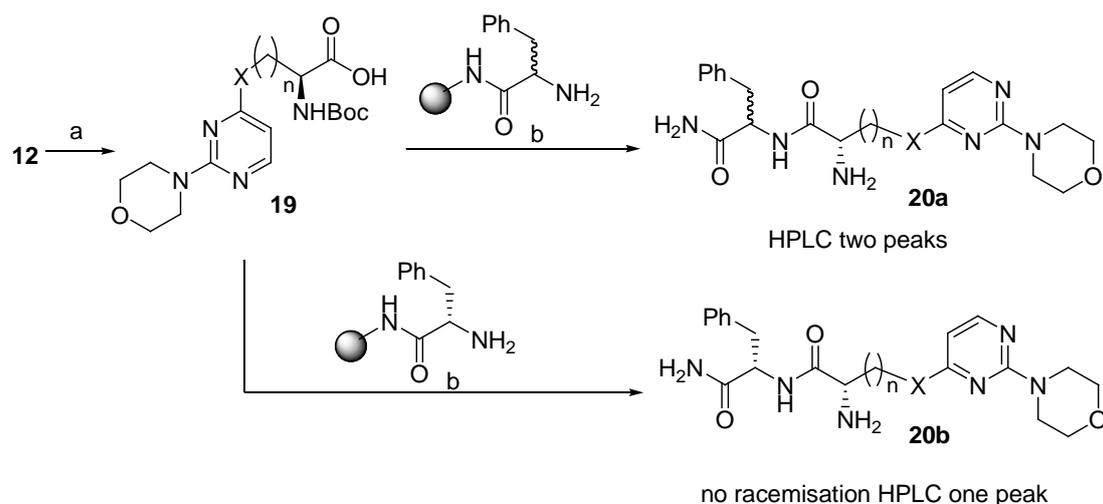
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Instruments

High performance liquid chromatography (HPLC) was performed on a Summit Dionex instruments composed of P680 binary pump, UVD 170U 4-Channel UV-Vis Detector, ASI-100 Autosampler and the Chromaleon 6.60 software from Dionex, on a C18 Kromasil reverse-phase column (4.6 x 40 mm; 3.5 μm particle size). ESI-MS analyses were performed with an Esquire 6000 ESI ion Trap LC/MS (Bruker Daltonics) instrument equipped with an electrospray ion source. The instrument was operated in the positive ESI(+) ion mode.

Analysis of optical purity of pyrimidin-4-yl amino esters **12**

The optical purity of compounds **12** was verified by coupling with both racemic phenylalanine and L-phenylalanine in order to measure the degree of racemisation by HPLC. Thus, samples of N^α -Boc amino esters **12** were deprotected using lithium hydroxide to give amino acids **19** in near quantitative yield. These compounds were first coupled to resin bound racemic phenylalanine **20a** using standard protocols for solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy. After cleavage from the resin, the HPLC analyses of the resulting dipeptides **20a** showed the formation of two diastereoisomers. Dipeptides **20b** were then synthesized analogously by coupling N^α -Boc amino acids **12** to L-phenylalanine resin bound **20b**. When no reasonable racemisation occurred during the synthesis of **12**, HPLC analyses of **20b** showed the formation of one single diastereoisomer (Scheme 1).¹



Scheme 1. Solid-phase synthesis of dipeptides **20**. Reagents and conditions: (a) LiOH, THF/MeOH/H₂O (1:2:2), room temp., 3–4 h. (b) (i) HBTU, DIEA, DMF, room temp., 3 h; (ii) TFA/H₂O/TIS (95:2.5:2.5), room temp., 2 h.

¹ Optical purity of compounds **10** and **12e** was also verified following Scheme 2.

Synthesis of Dipeptides 20 General procedure. Dipeptides **20** were prepared manually by solid-phase method using Fmoc-Rink-MBHA resin (0.64 mmol/g) as solid support following standard Fmoc-strategy. Coupling of amino acids were mediated by HBTU (3 equiv) and DIEA (3 equiv) in DMF at room temperature for 3 h. Monitoring was carried out by ninhydrin test.² Washings were performed with DMF (6 x 1 min). Fmoc group was removed by treating the resin with 30% piperidine in DMF (v/v) and washed with DMF (6 x 1 min). The Fmoc-Rink-MBHA resin (10 mg) was placed into a plastic syringe fitted with a polypropylene frit to remove the Fmoc group and subsequently couple Fmoc-Phe-OH. After Fmoc group removal resin was treated with pyrimidinyl amino acid **19** under coupling conditions. The resulting dipeptides were deprotected and cleaved from resin by treatment with TFA/H₂O/TIS (95:2.5:2.5) for 2 h. Then the solvents were evaporated to dryness and the crude dipeptides **20** were dissolved in H₂O, lyophilized and tested for purity on HPLC. Electrospray ionisation mass spectrometry was used to confirm peptide identity.

HPLC conditions

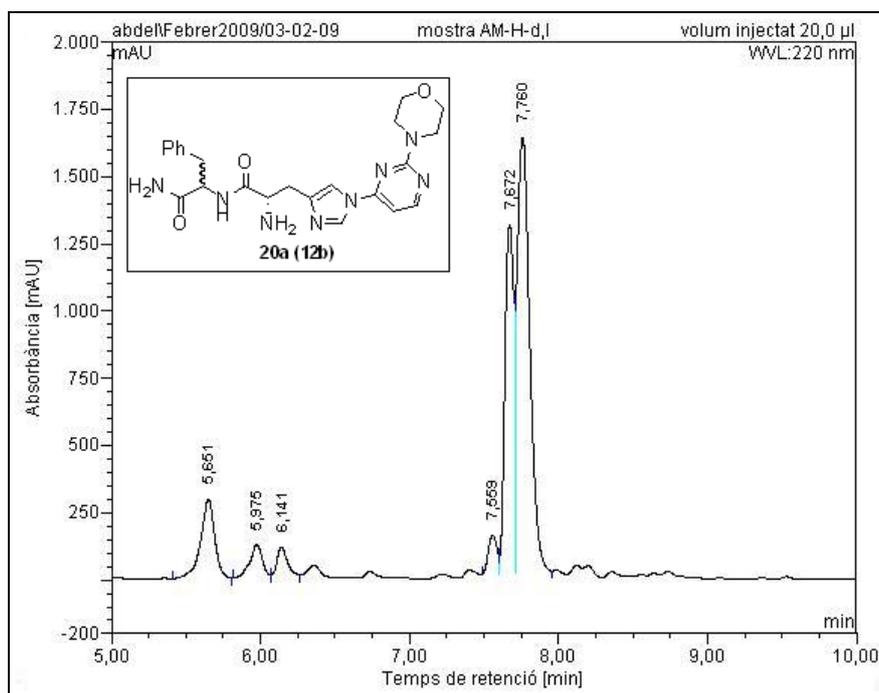
Solvent A: H₂O/0.1% TFA

Solvent B: CH₃CN/0.1% TFA

Linear gradient of (2-100%) B at flow rate of 1.0 mL/min over 17 min.

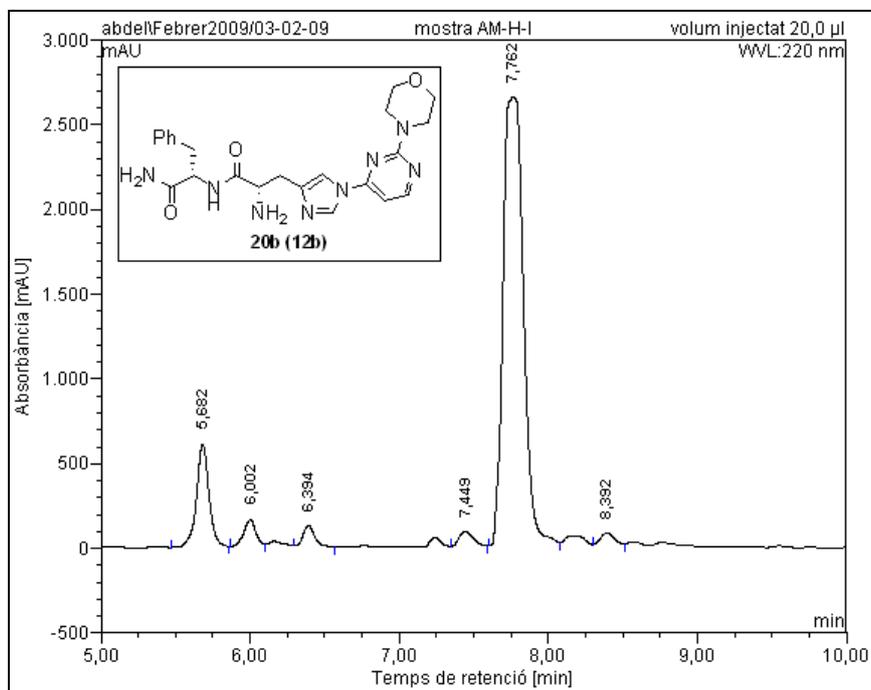
² Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595-598

HPLC of dipeptide 20a (12b)

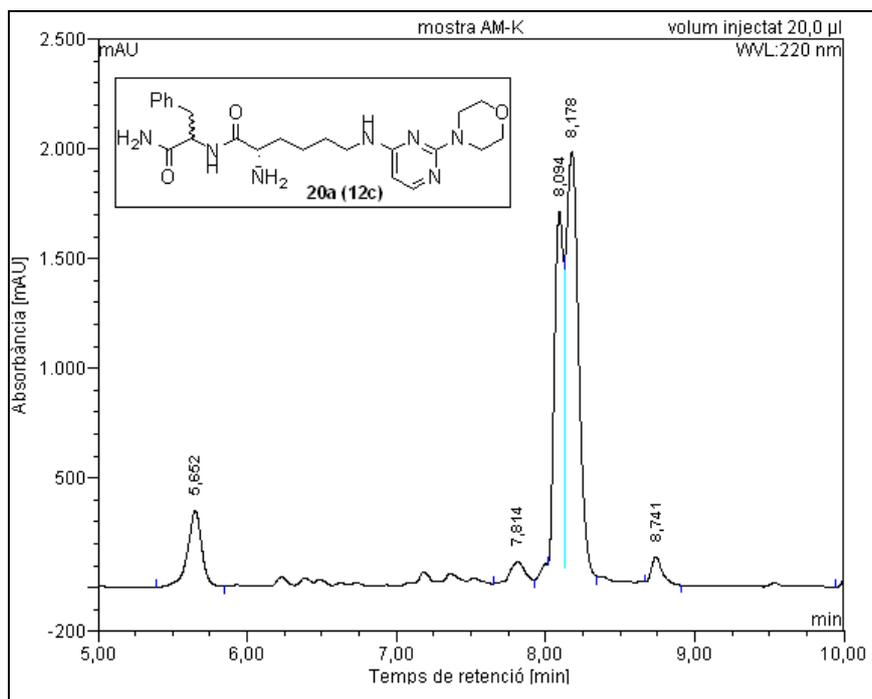


HPLC of dipeptide 20b (12b)

Reaction performed with conditions D at 50°C (entry 6, Table 3)

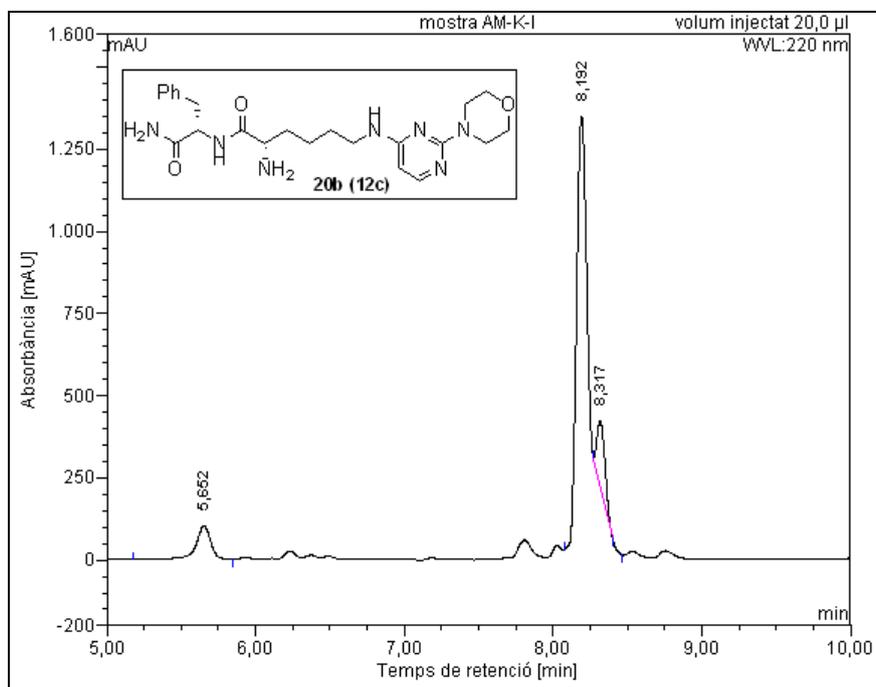


HPLC of dipeptide 20a (12c)



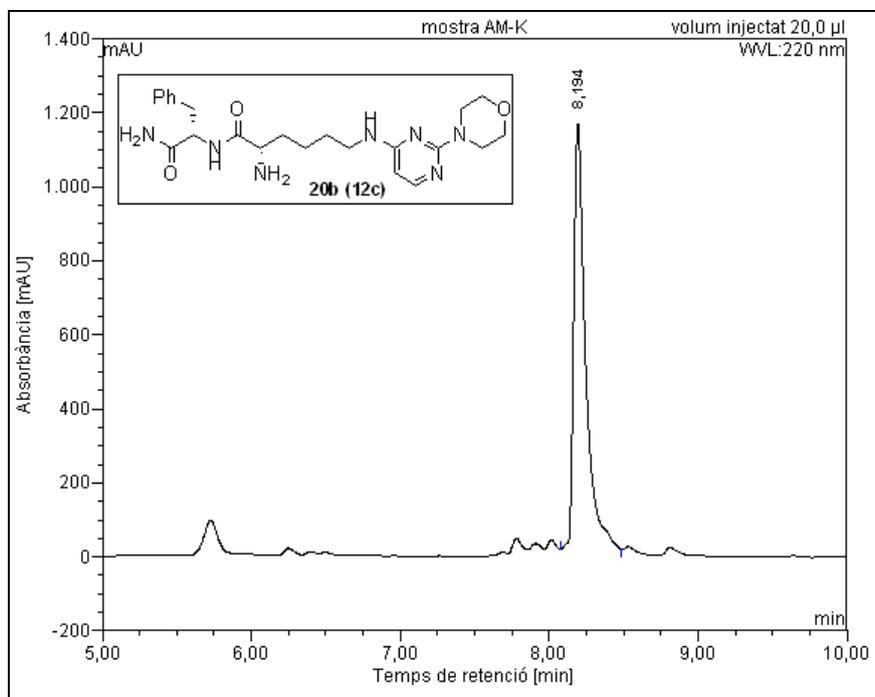
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Reaction performed with conditions B at 50°C (entry 7, Table 3)

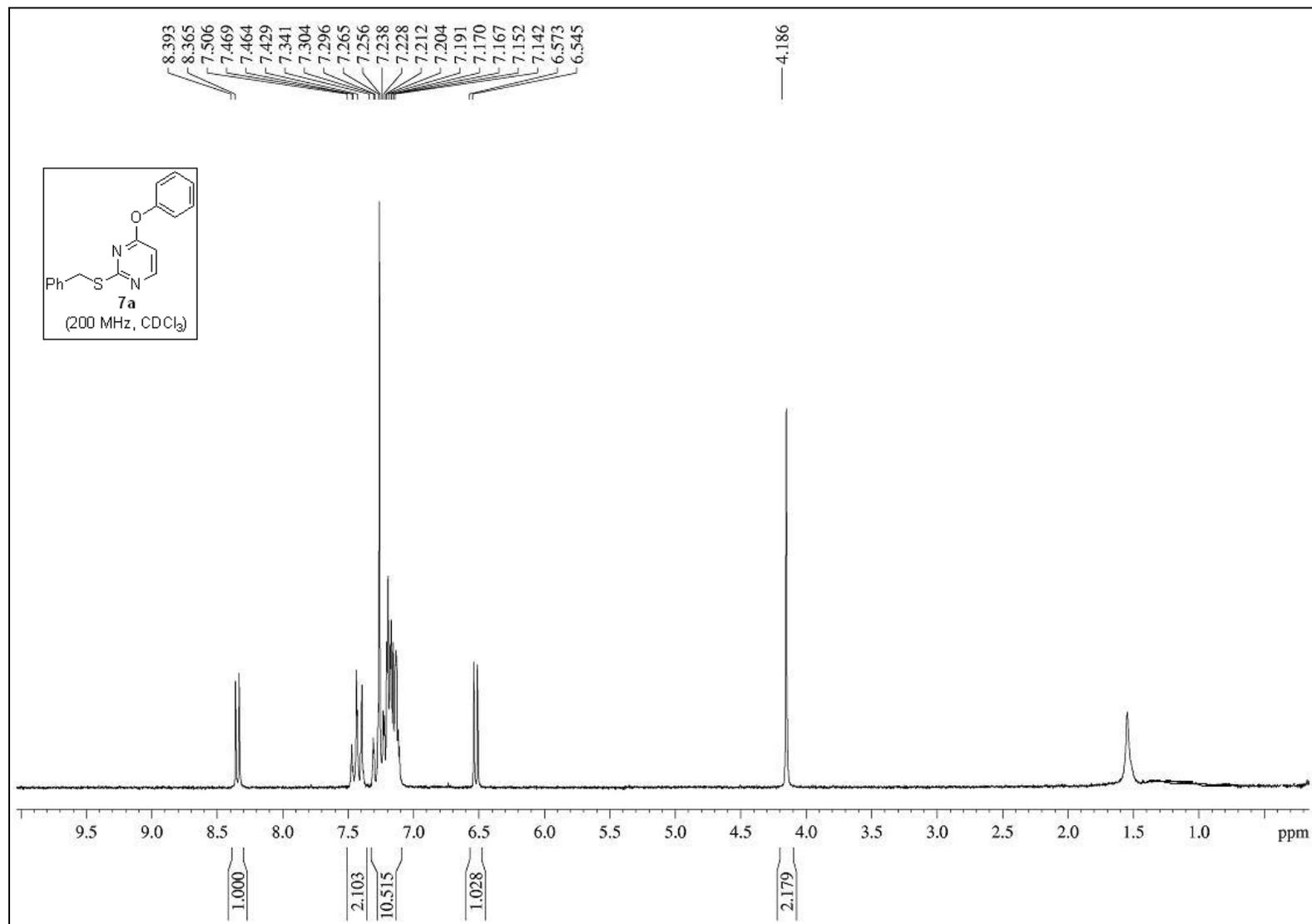


HPLC of dipeptide 20b (12c)

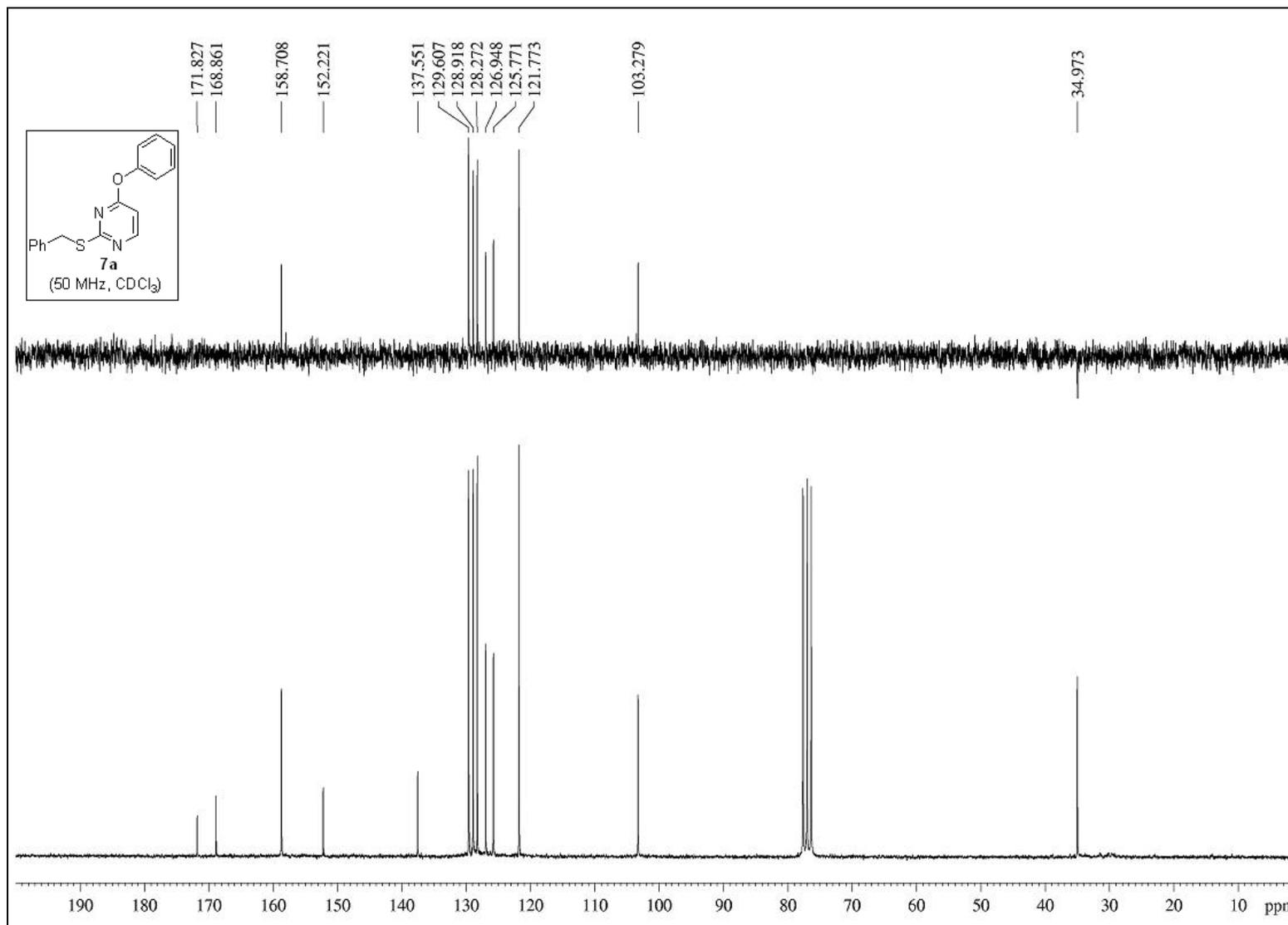
Reaction performed with conditions D at 40°C (entry 10, Table 3)



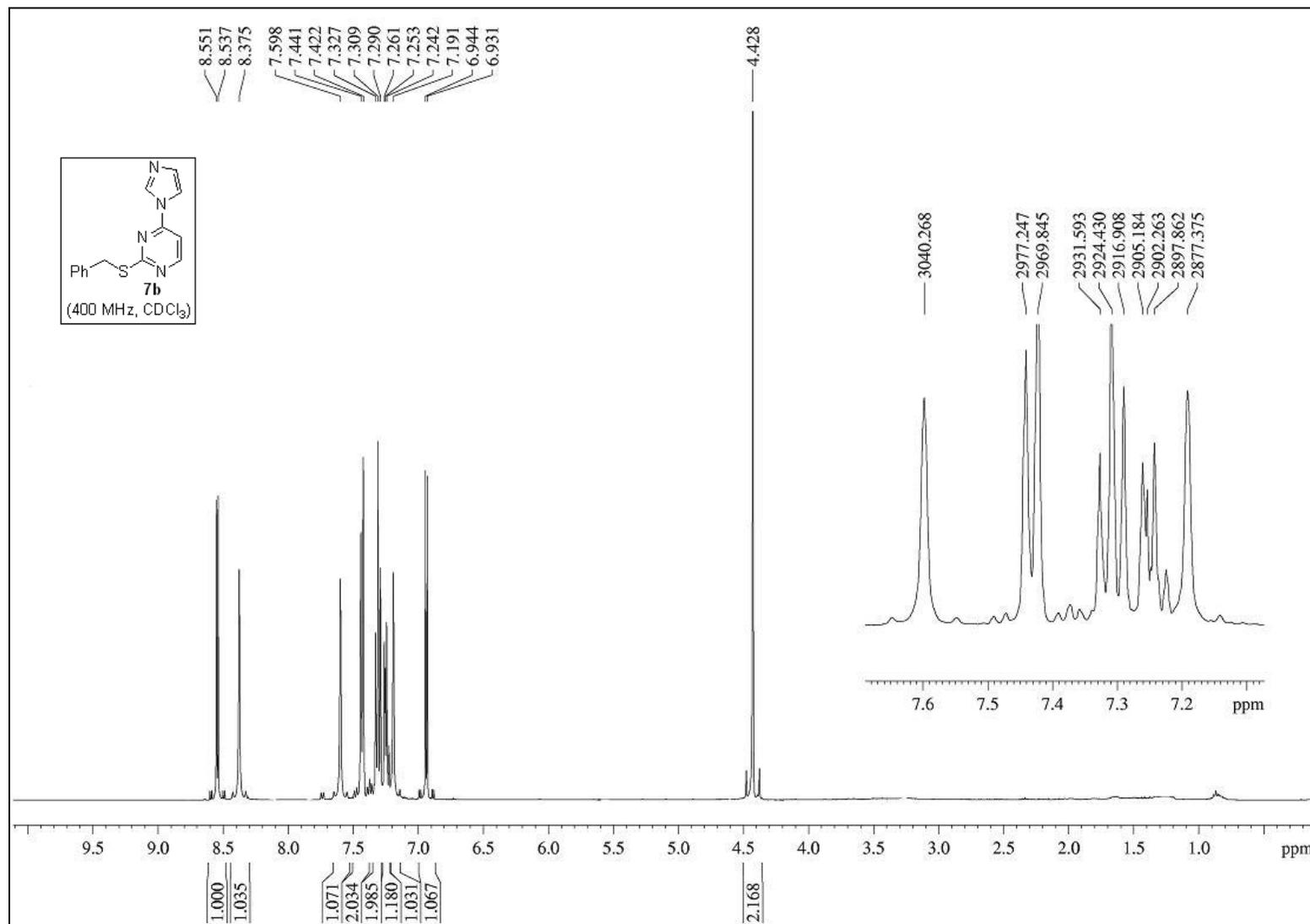
¹H-NMR of compound 7a



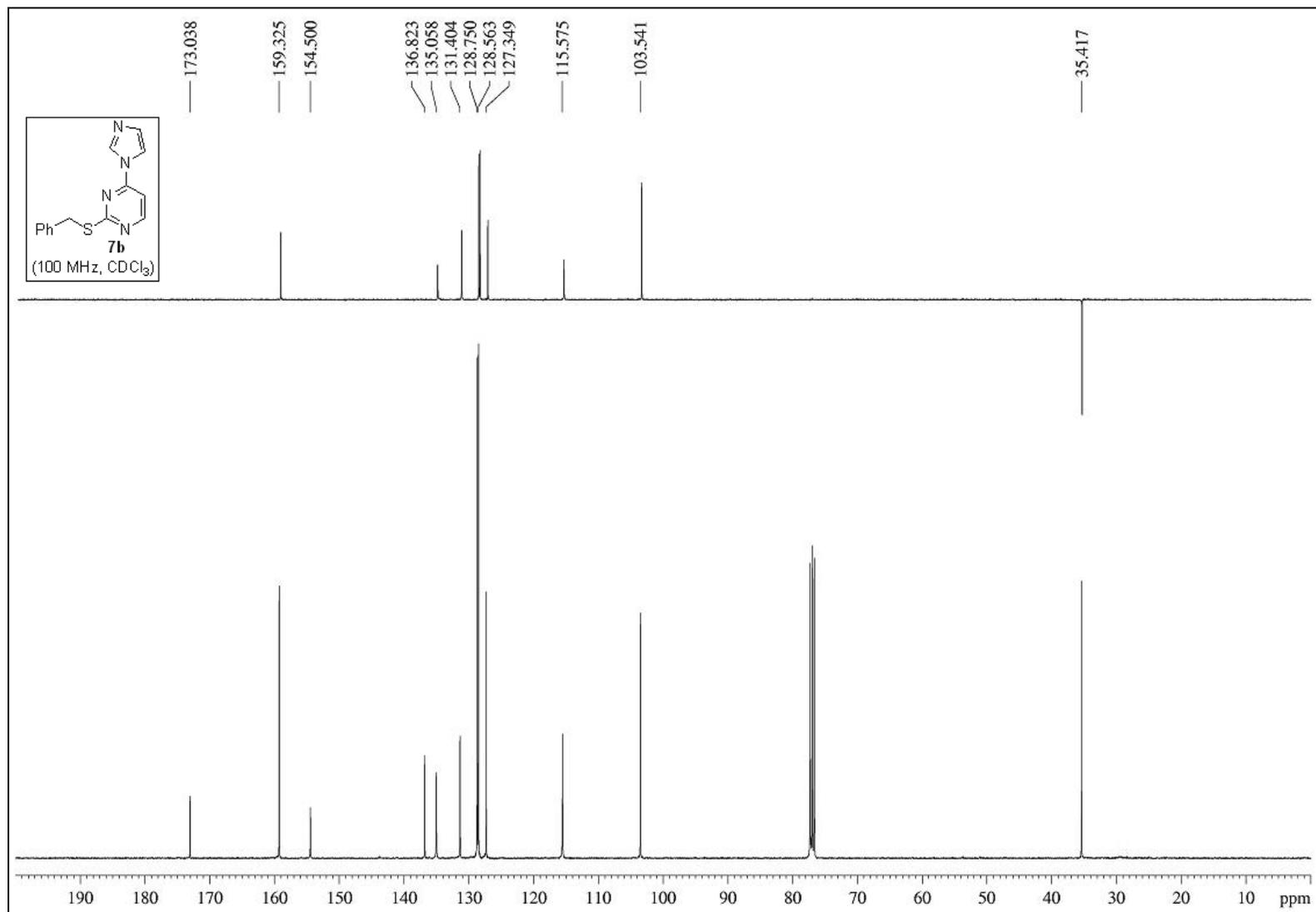
¹³C-NMR and DEPT experiment of compound 7a



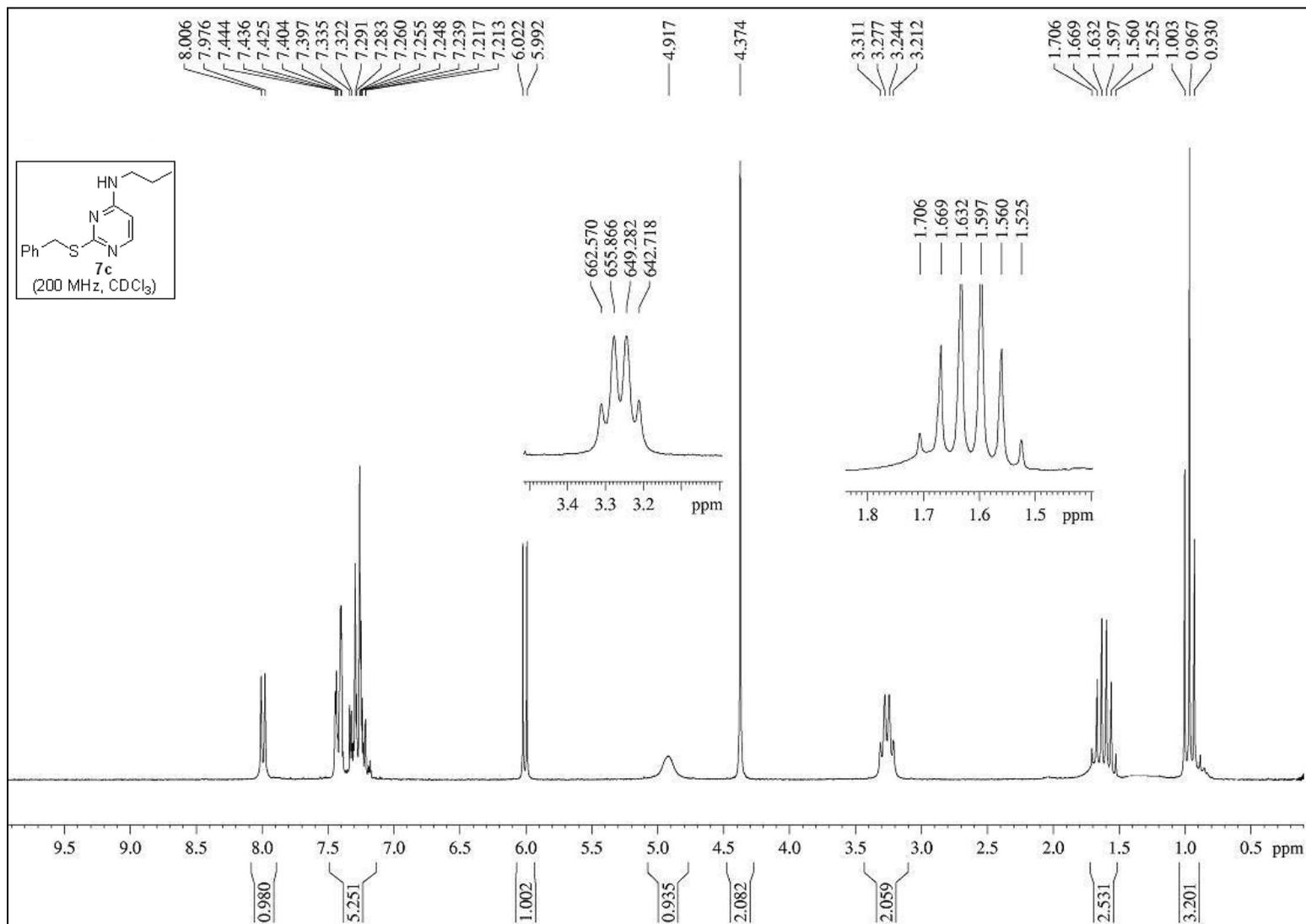
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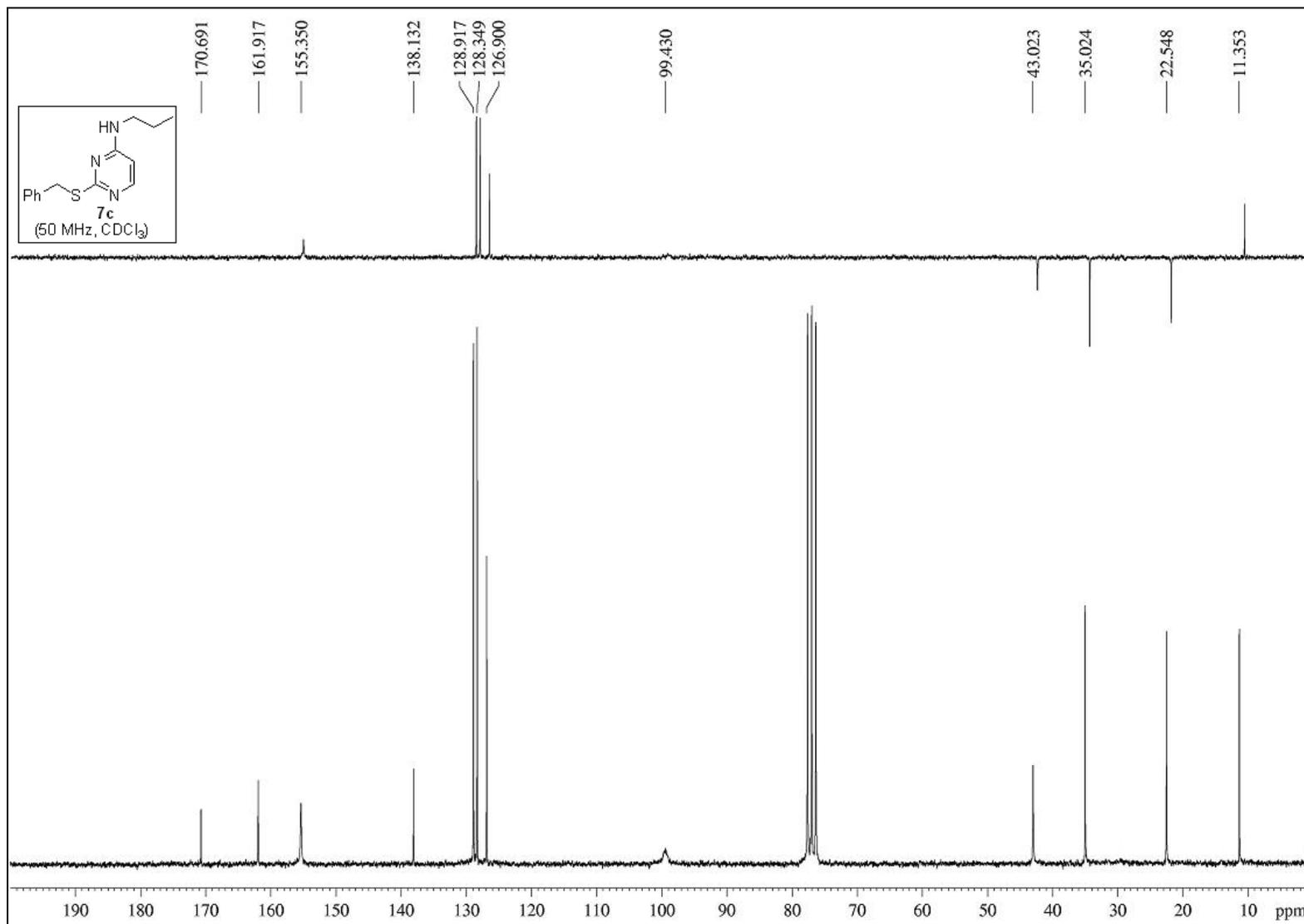
¹³C-NMR and DEPT experiment of compound **7b**



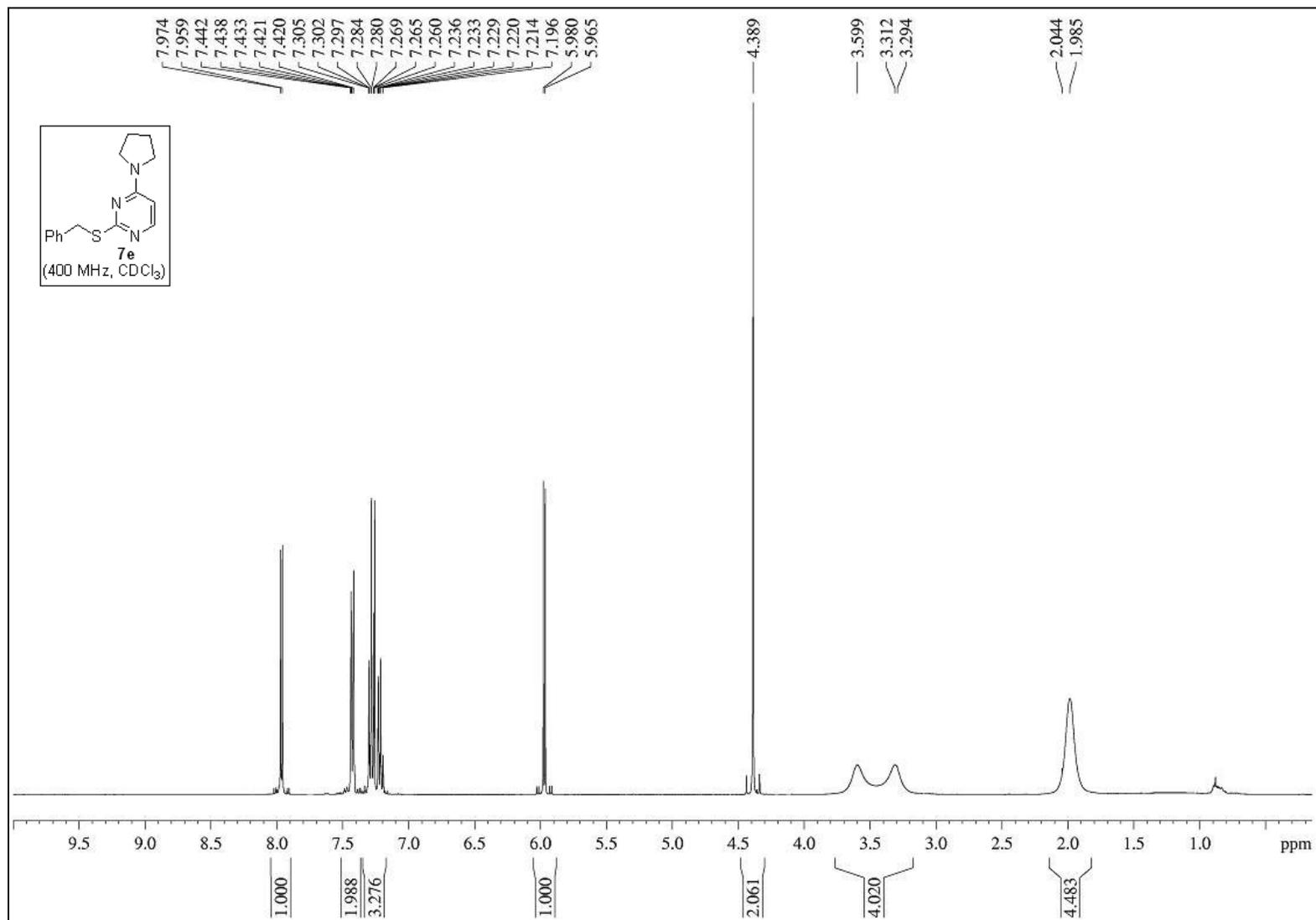
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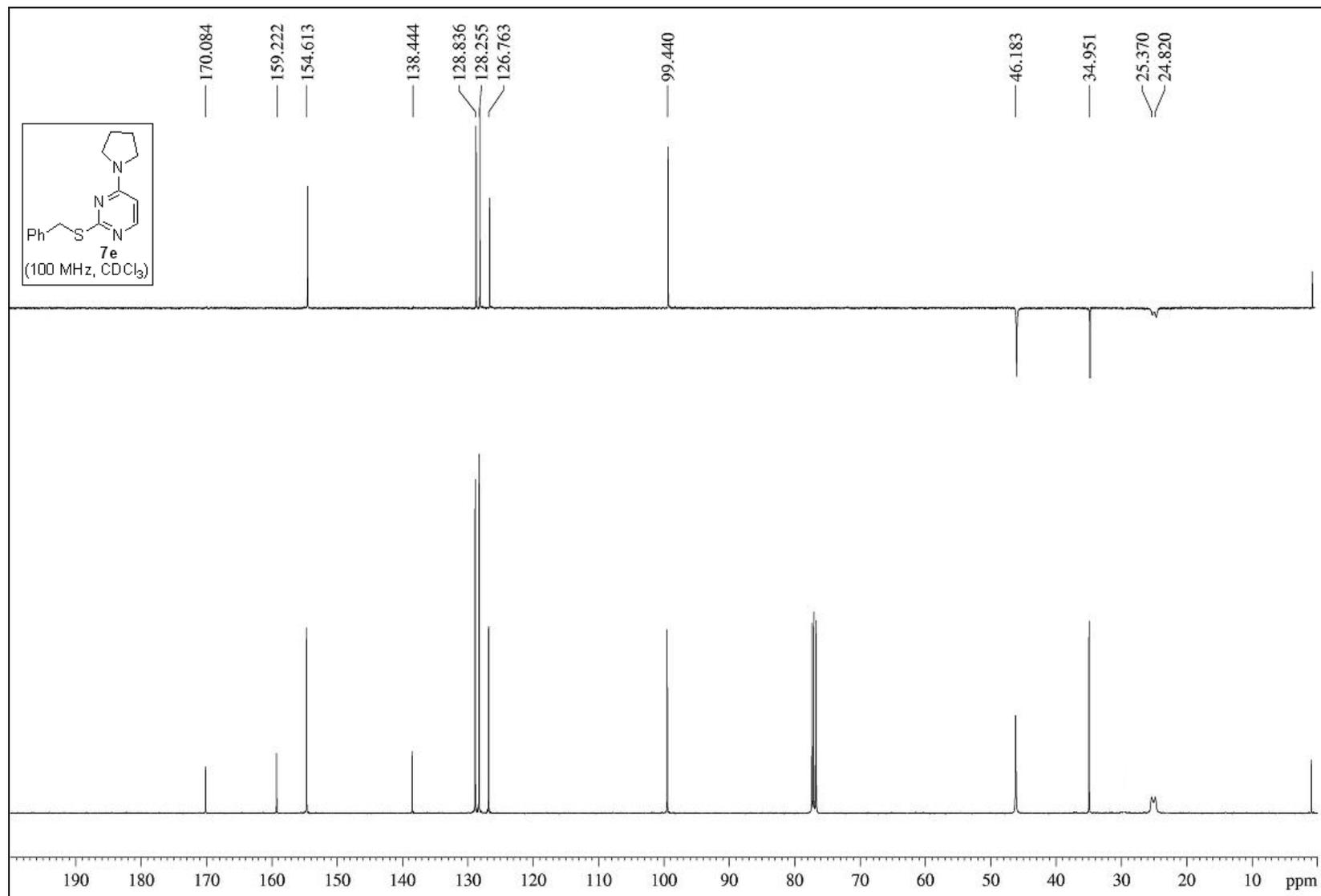
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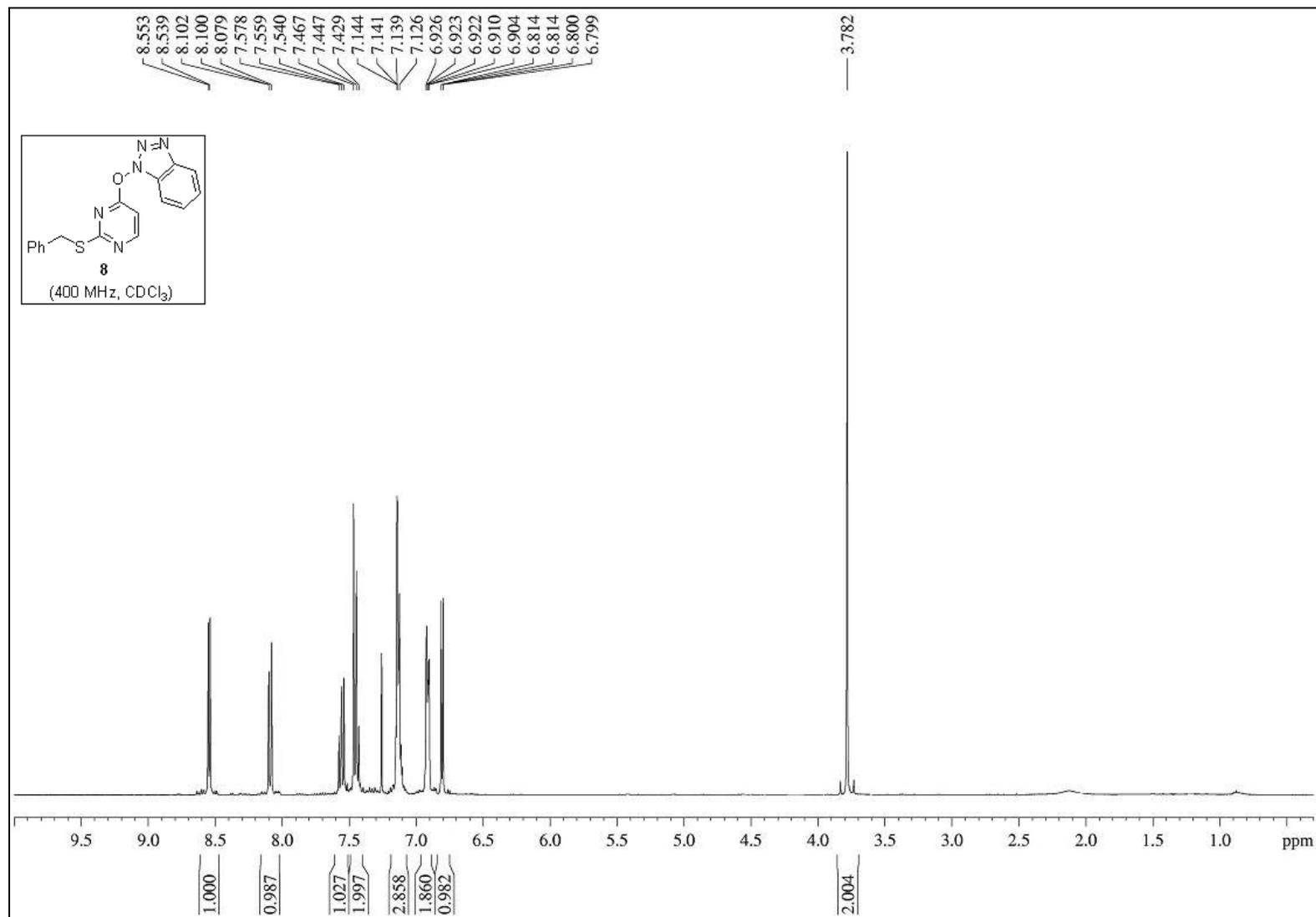
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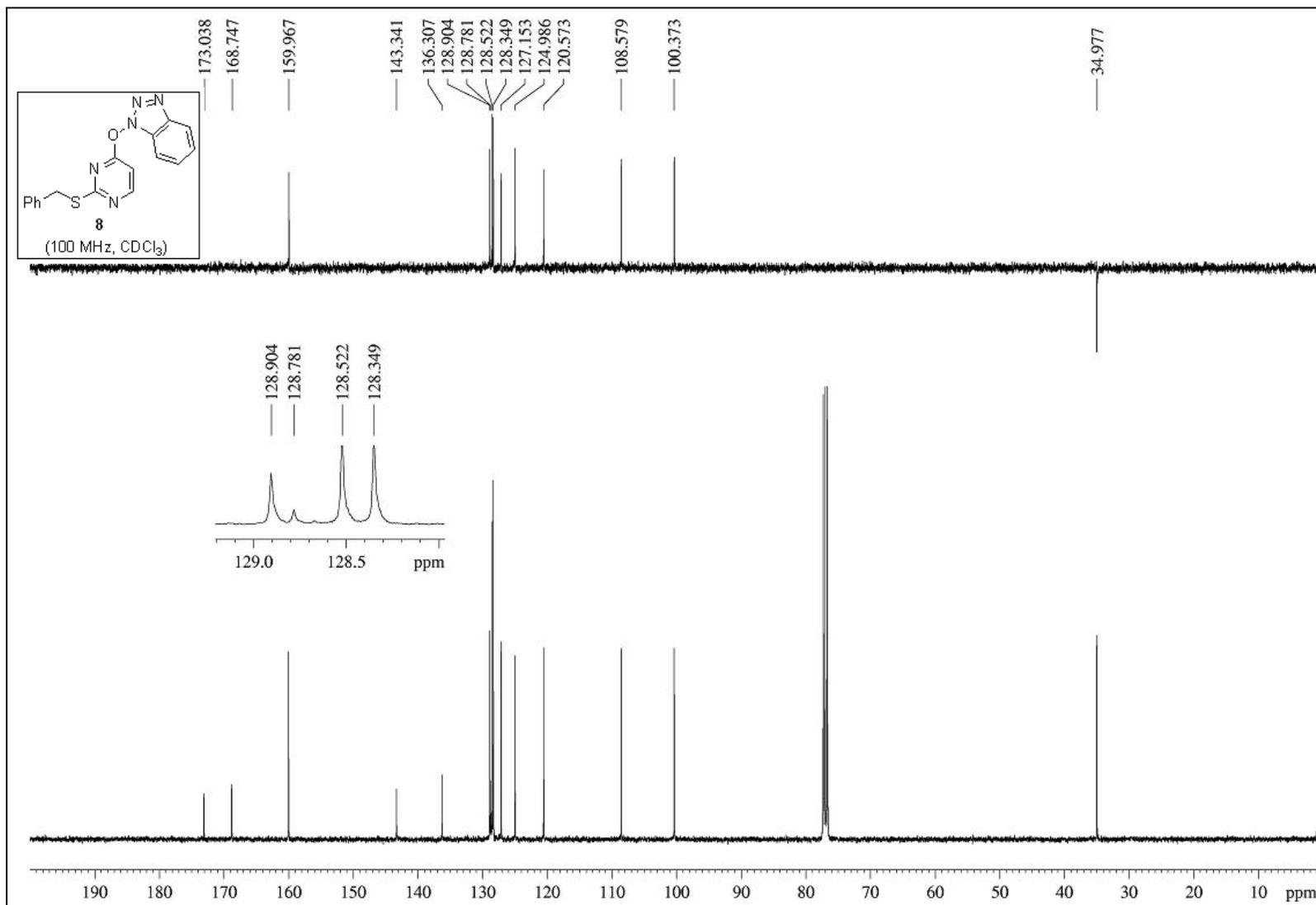
^{13}C -NMR and DEPT experiment of compound **7e**



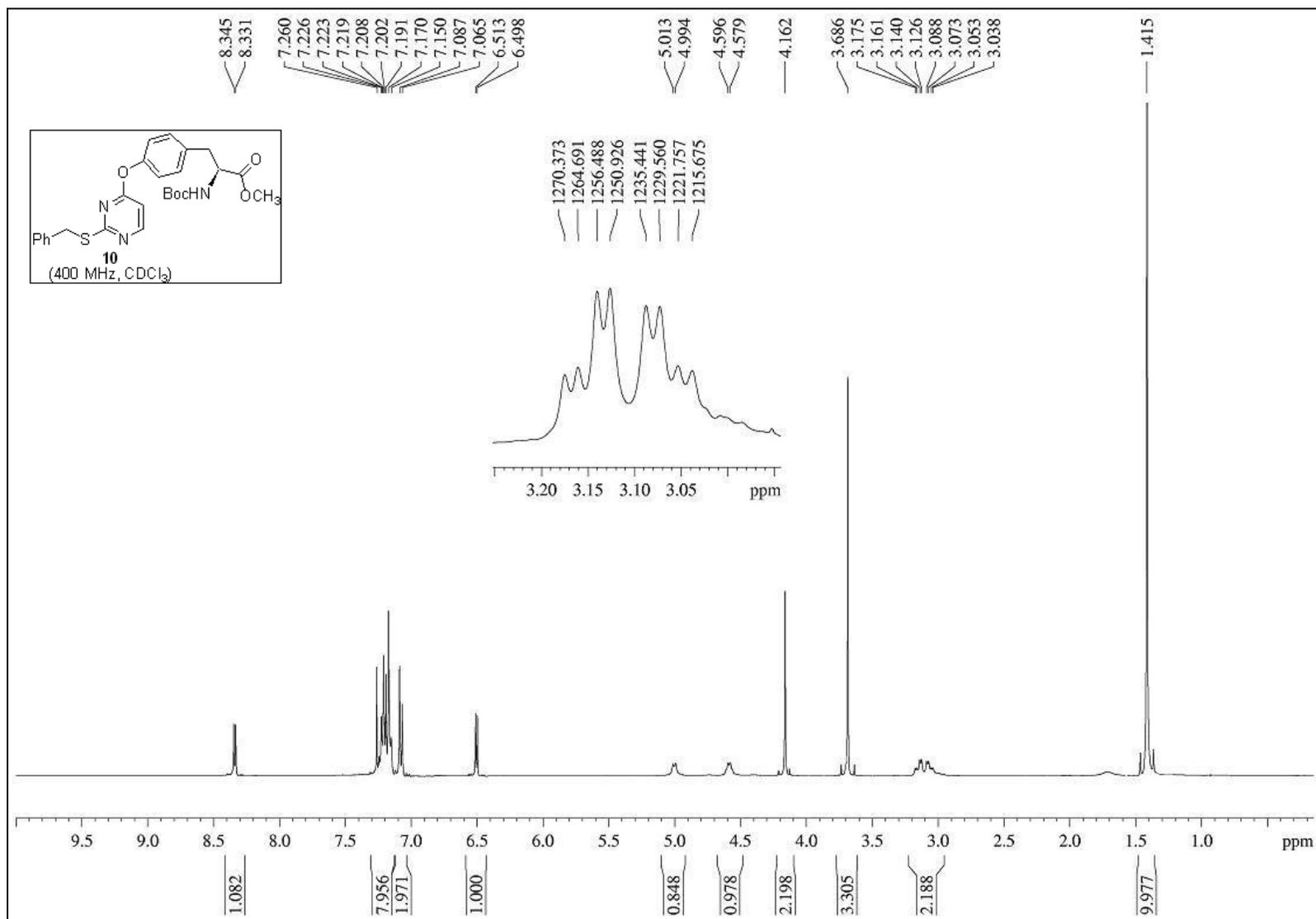
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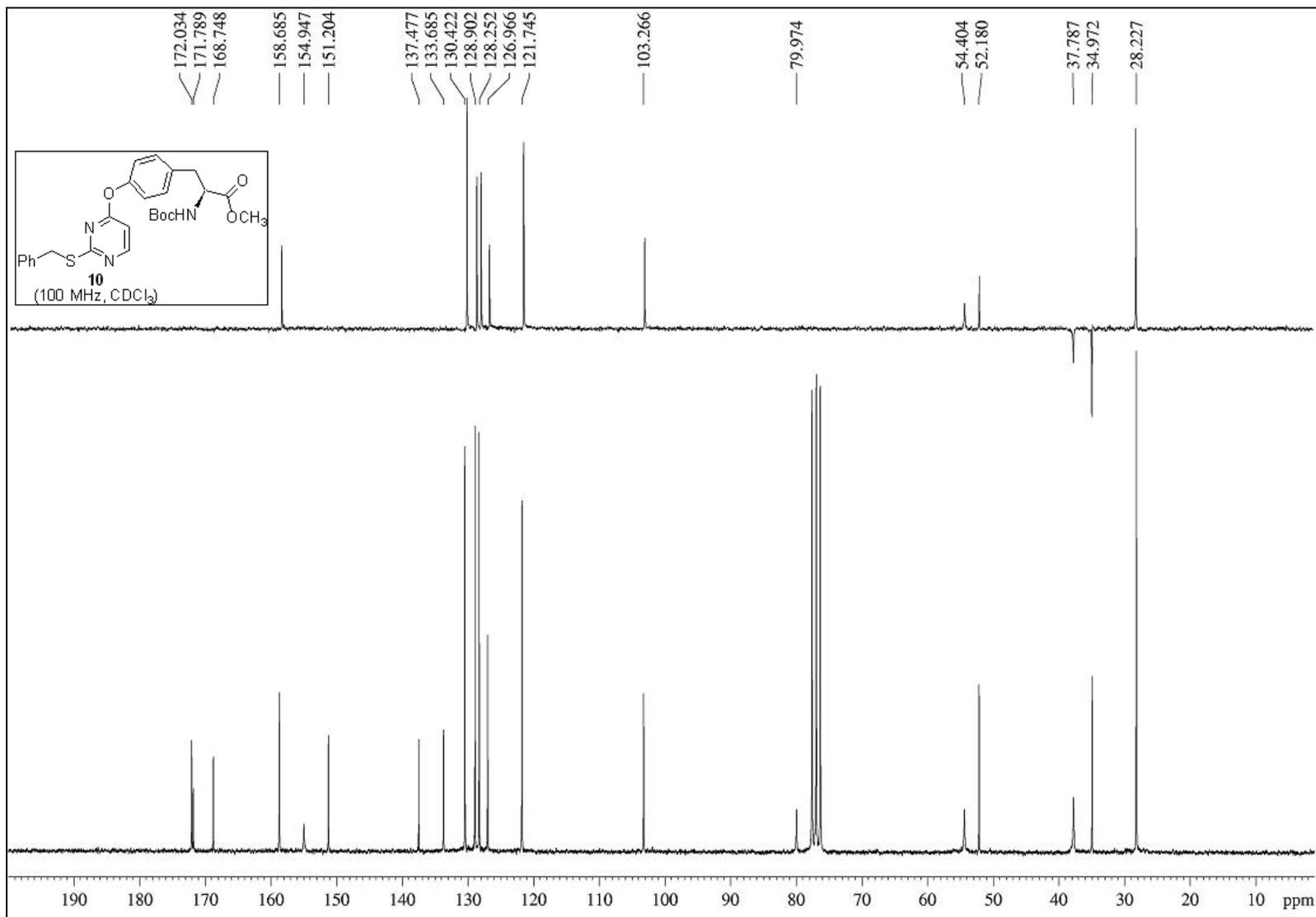
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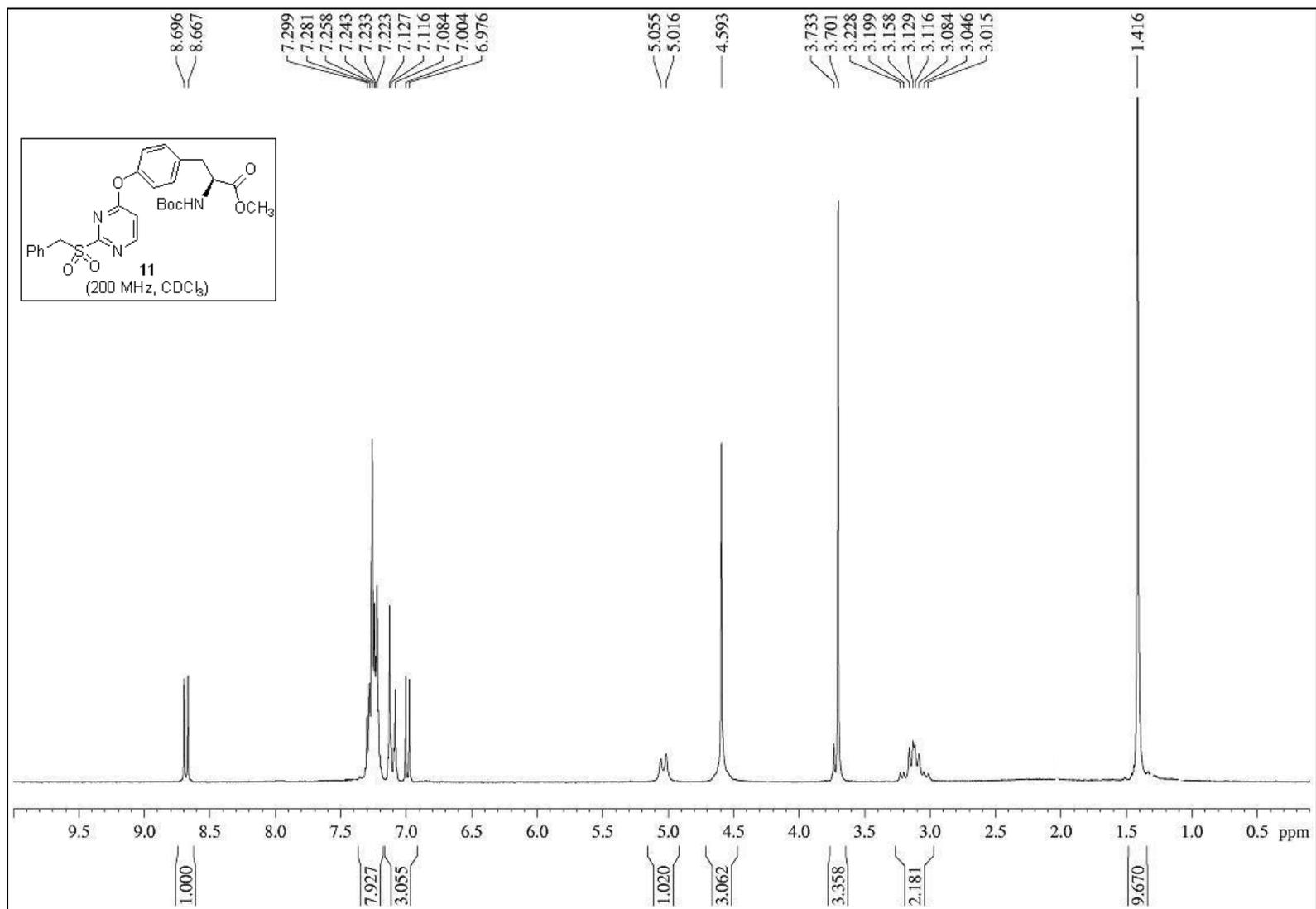
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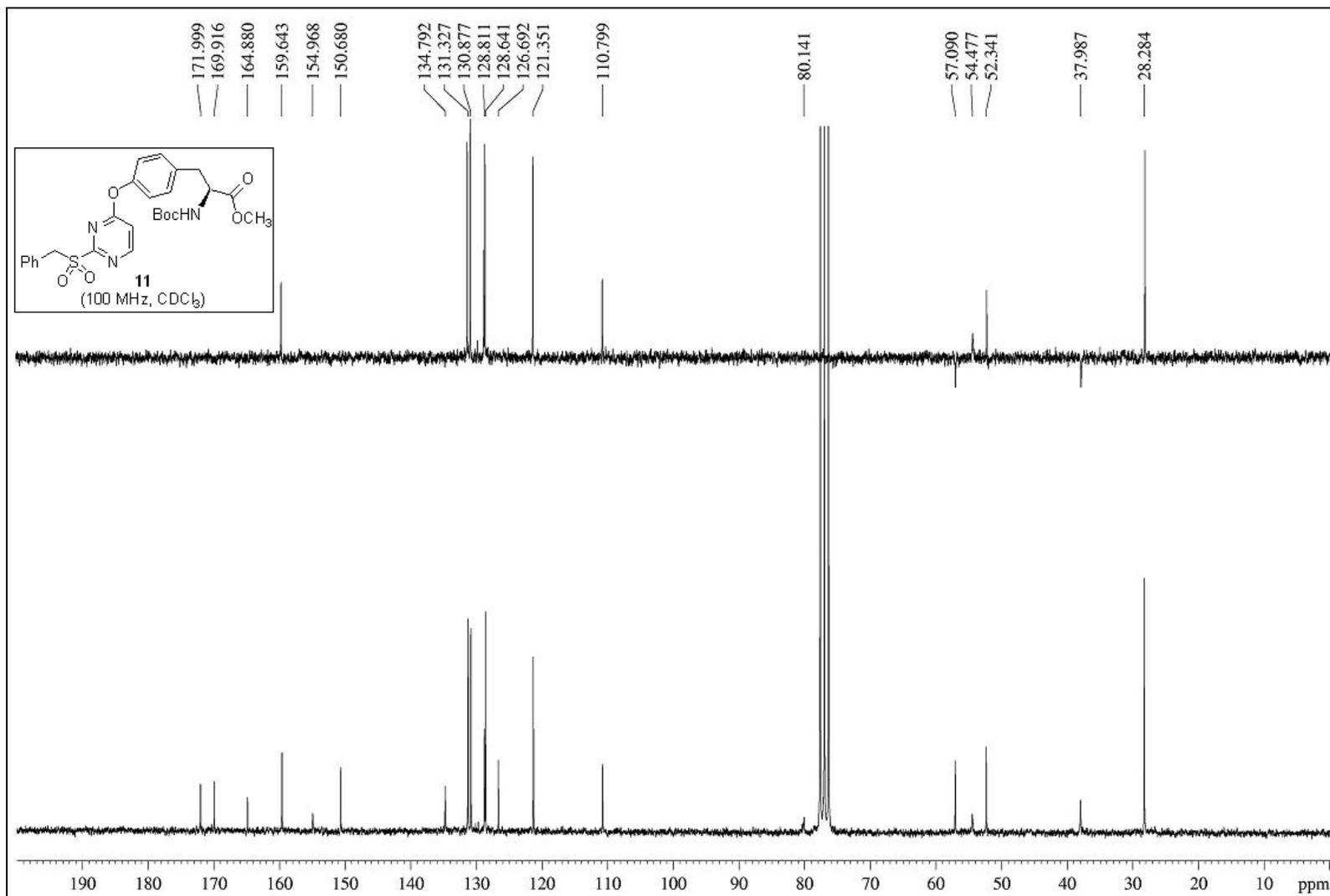
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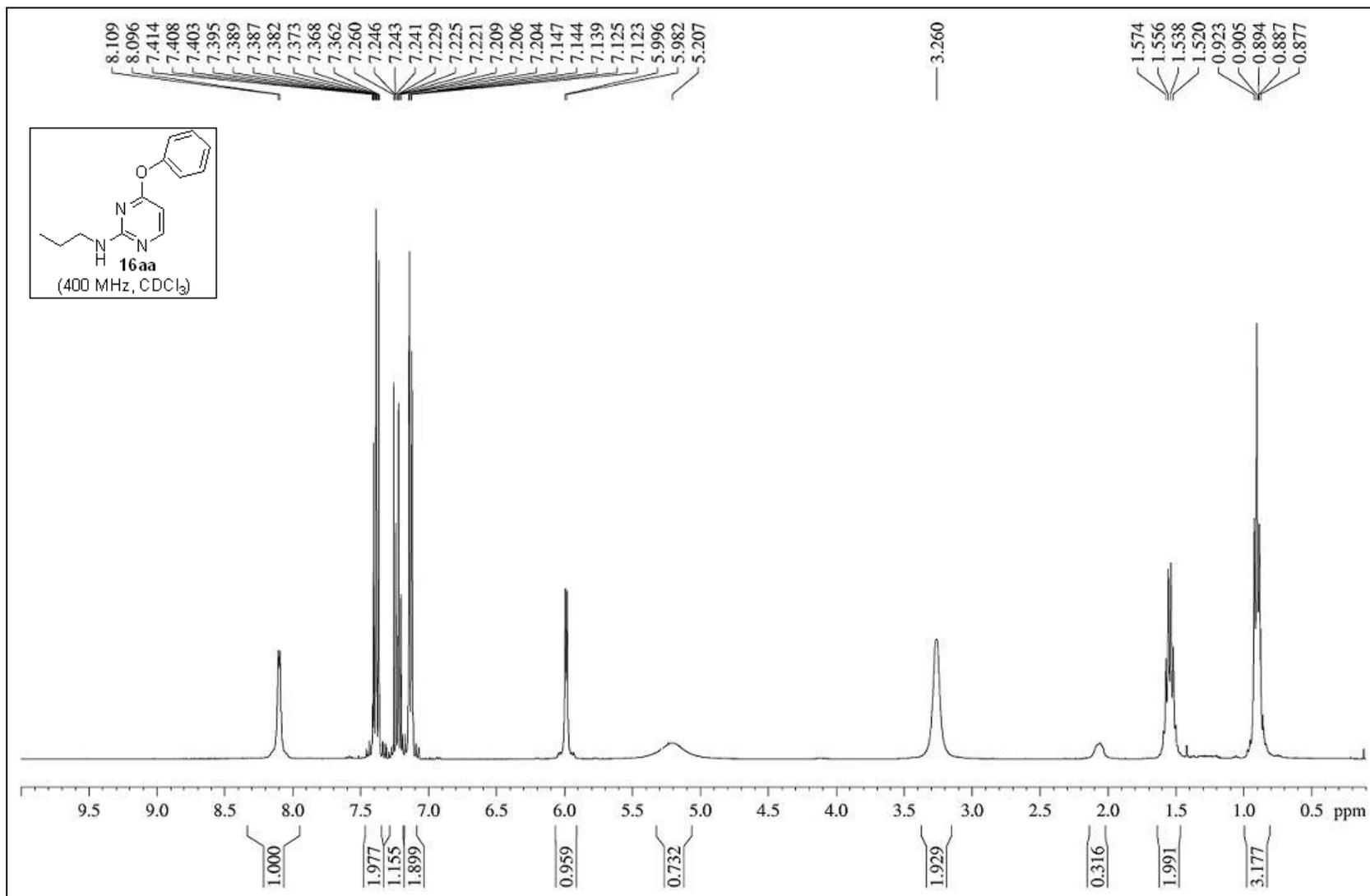
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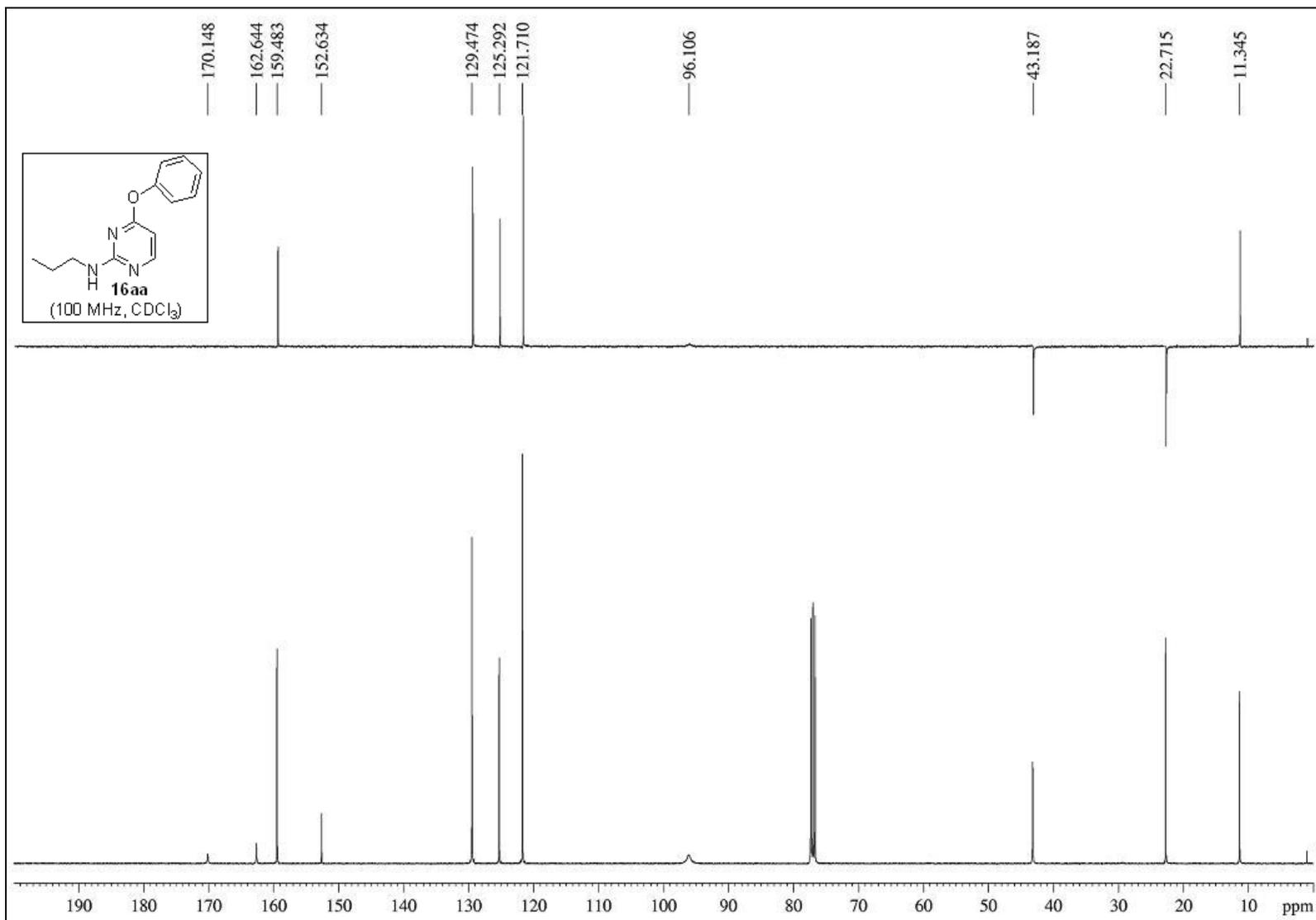
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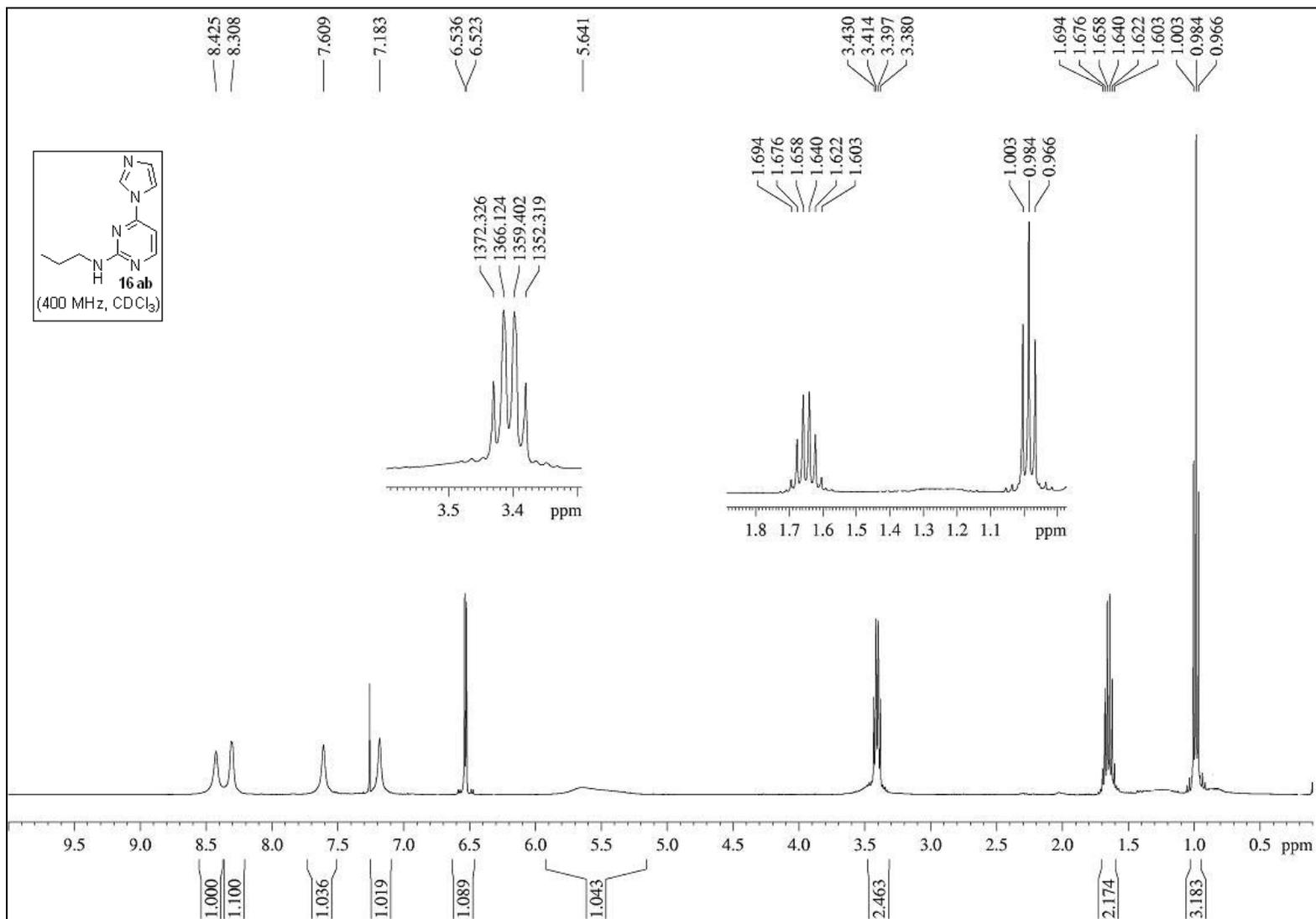
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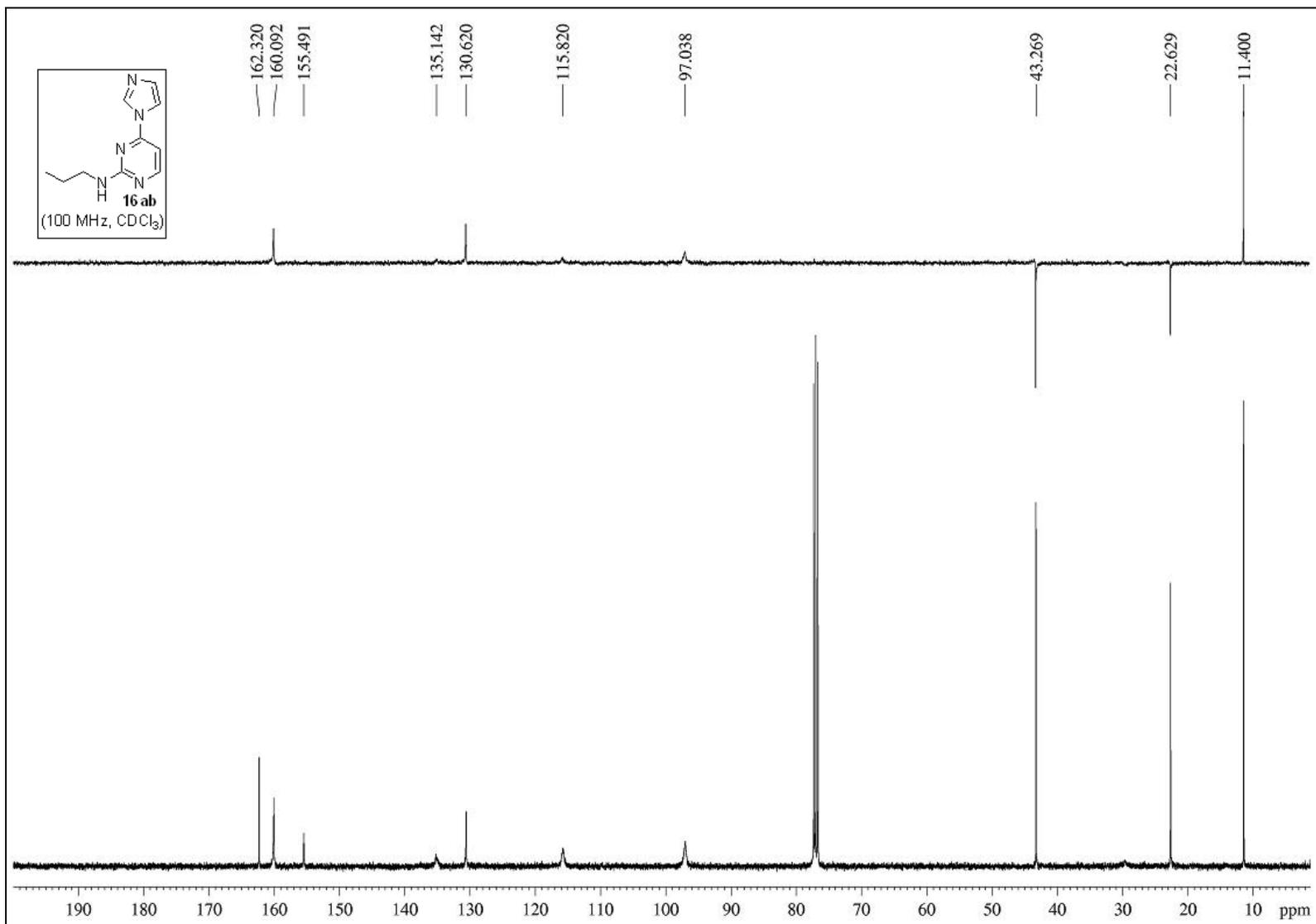
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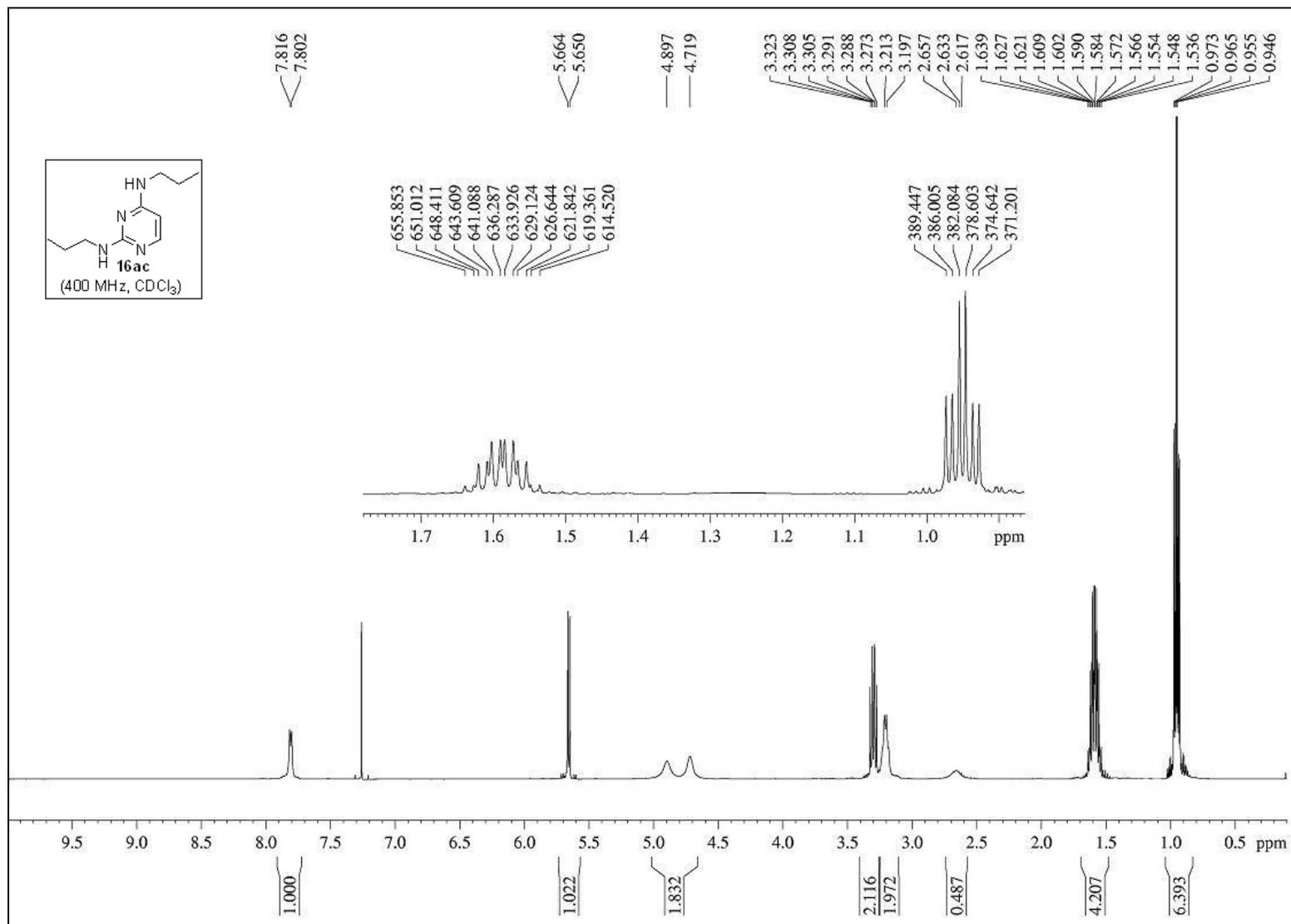
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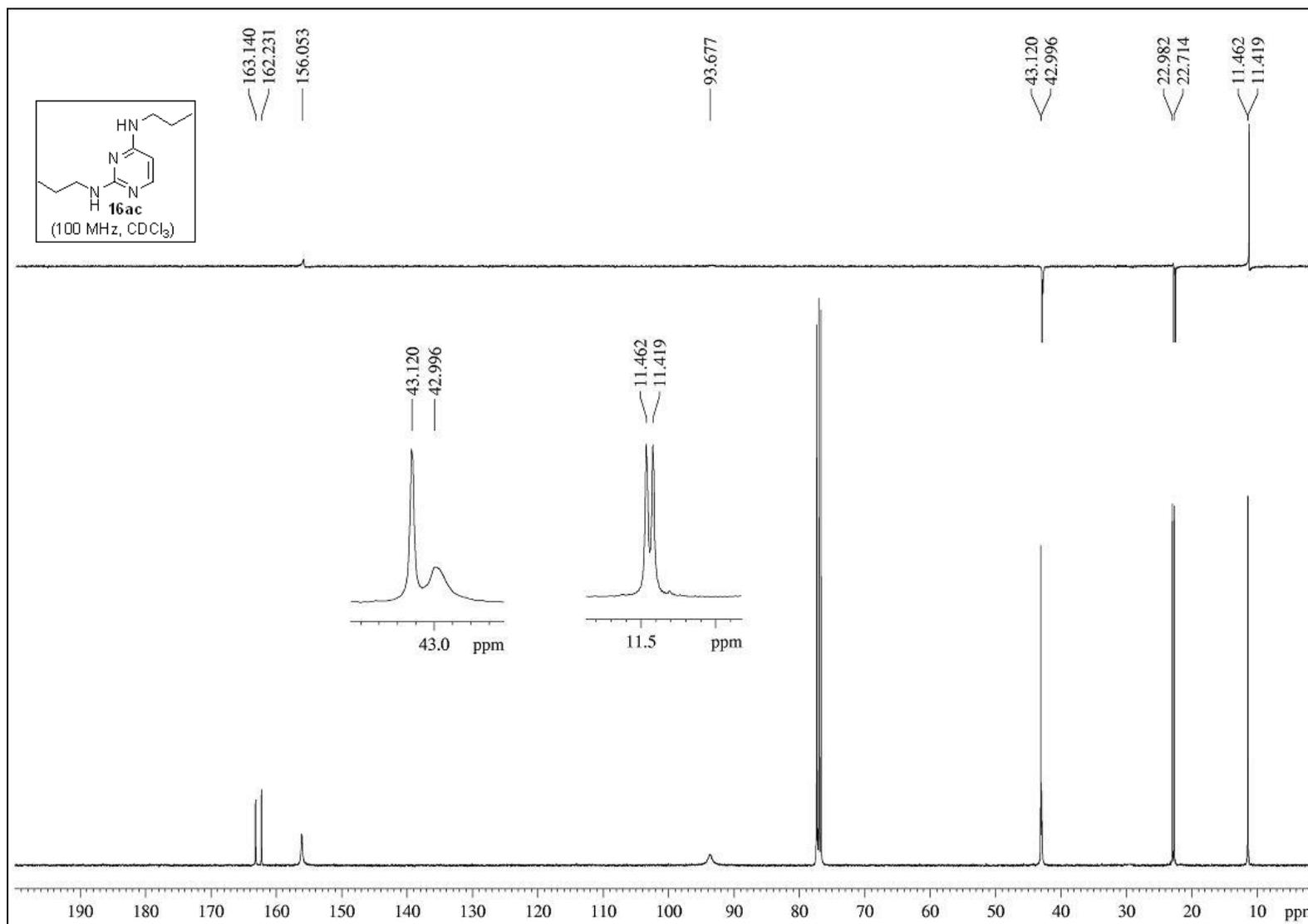
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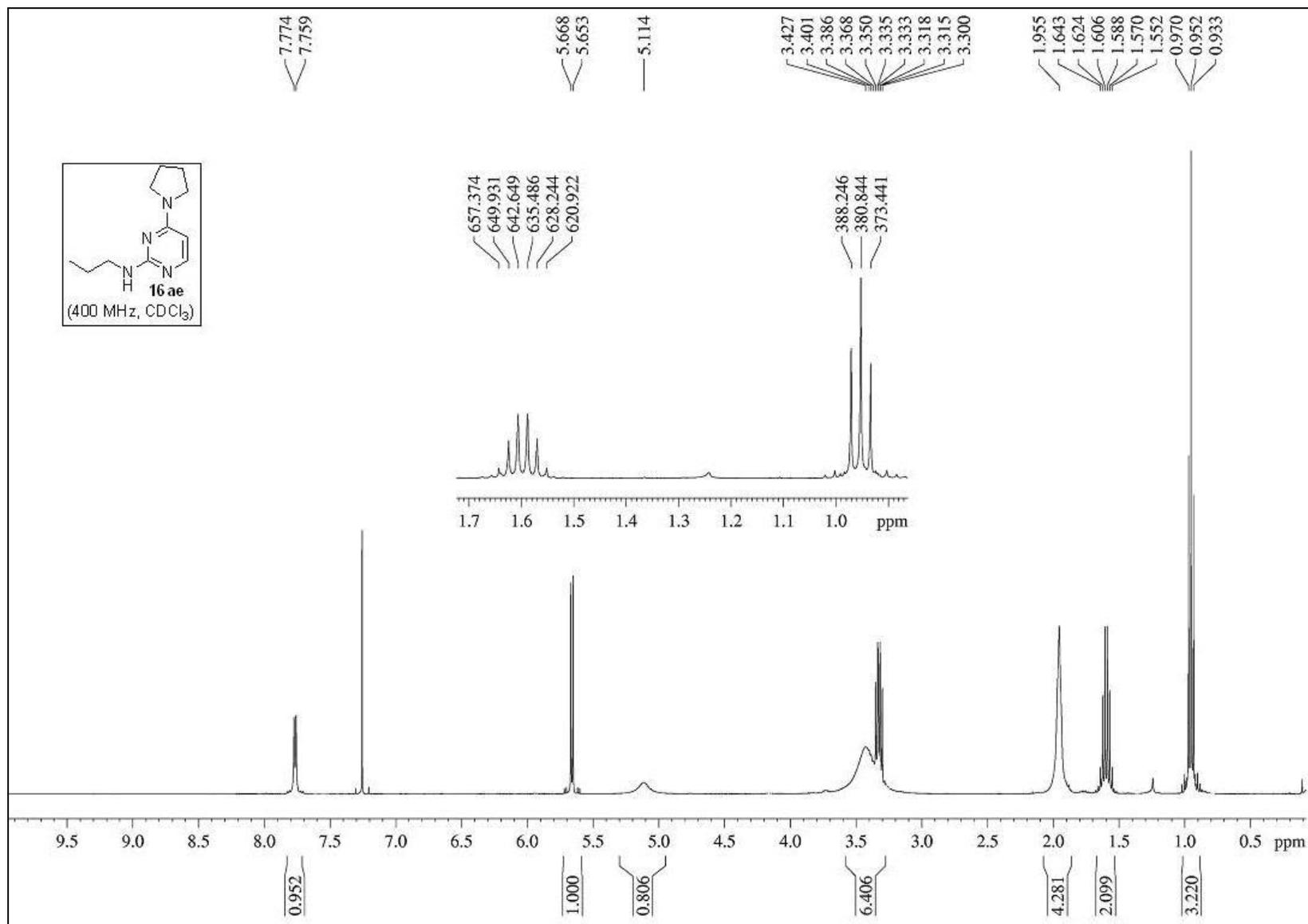
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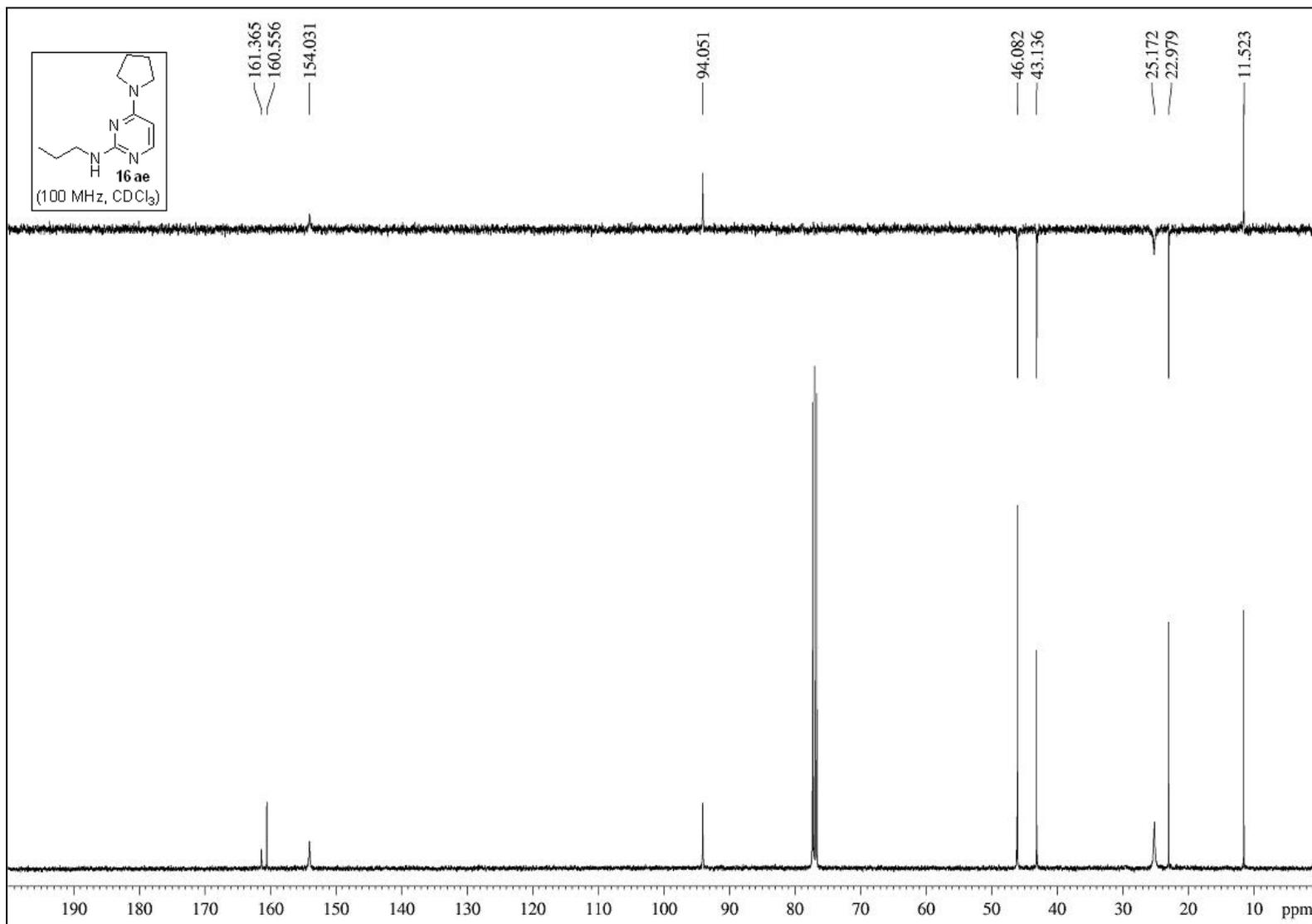
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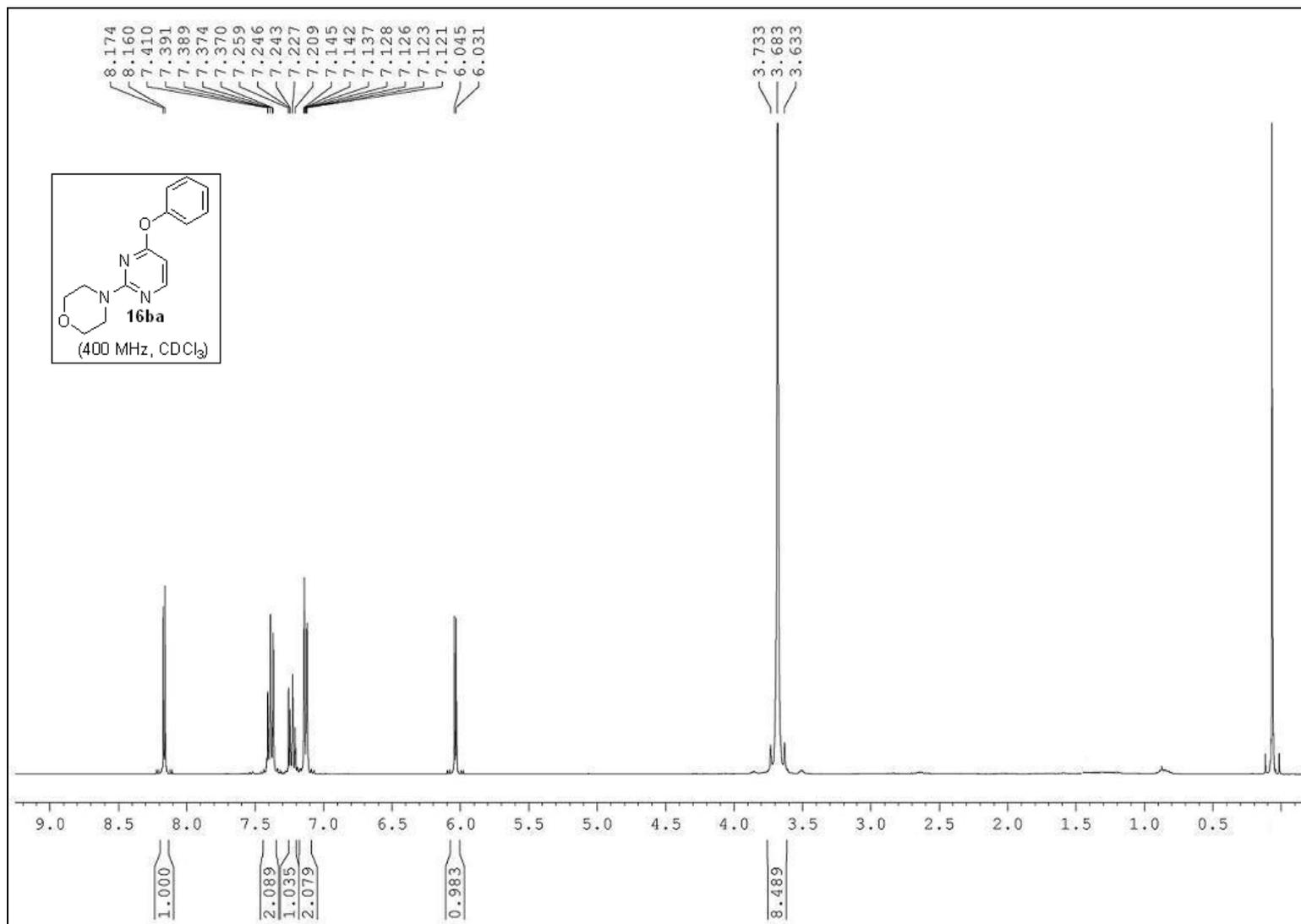
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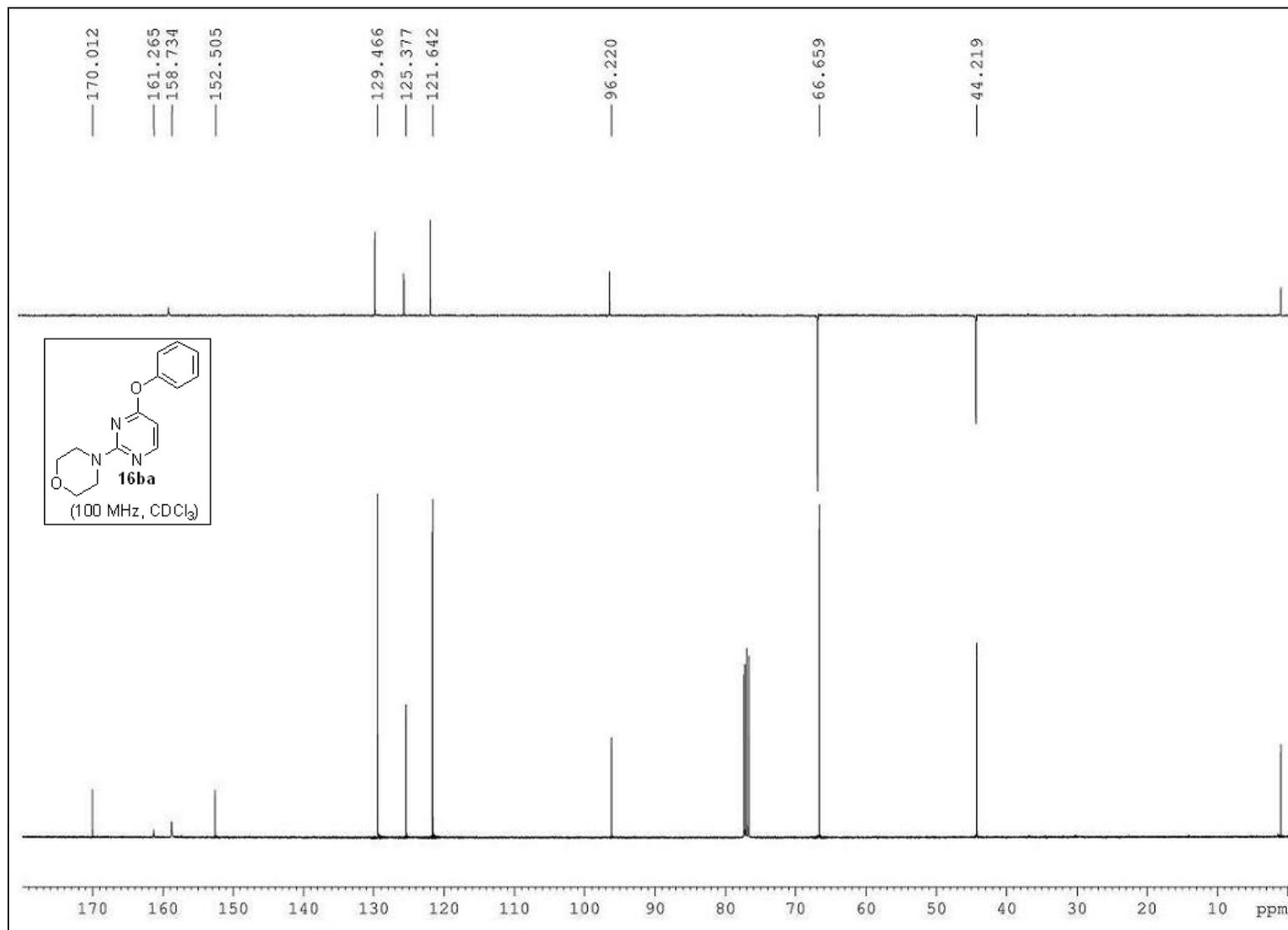
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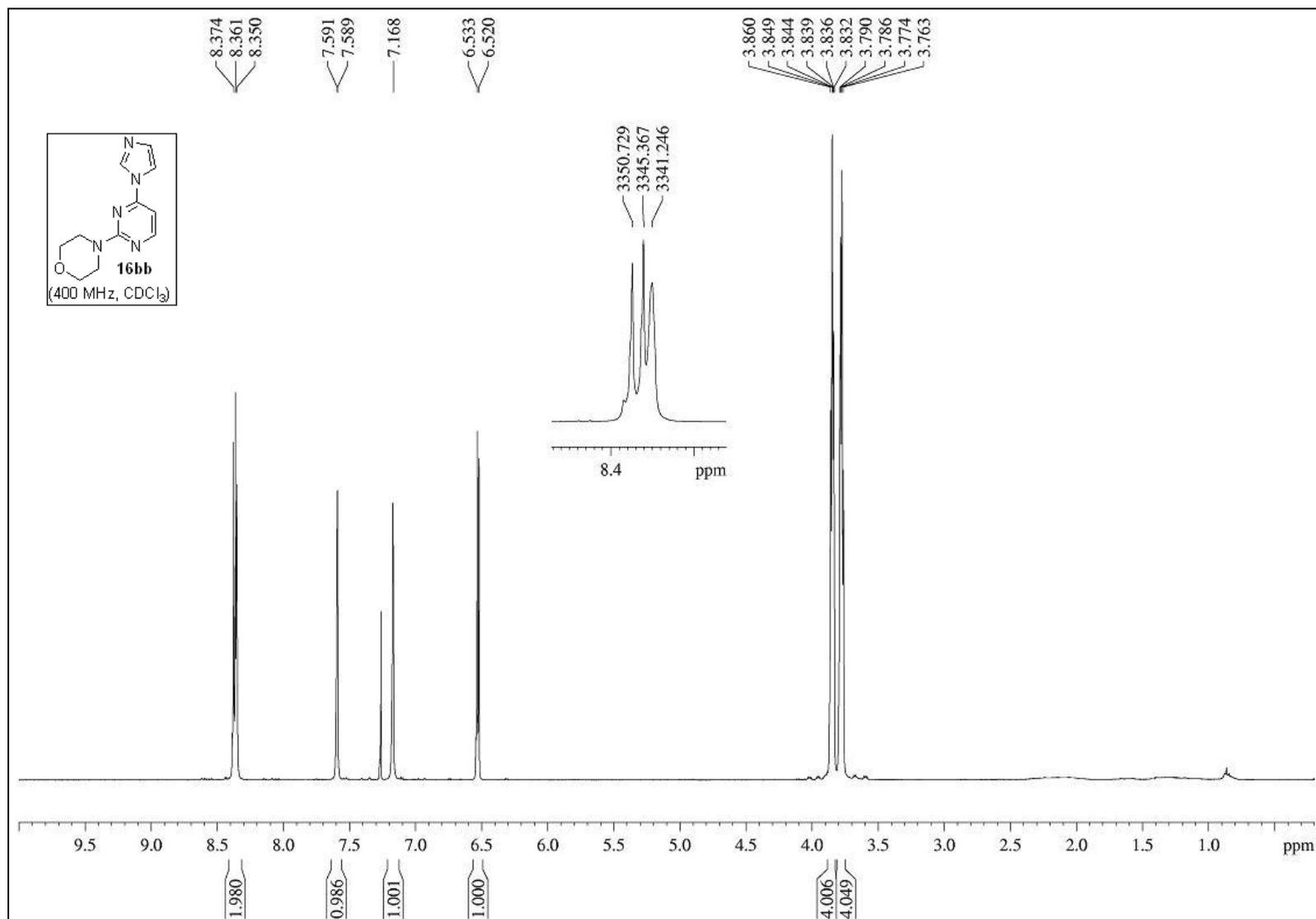
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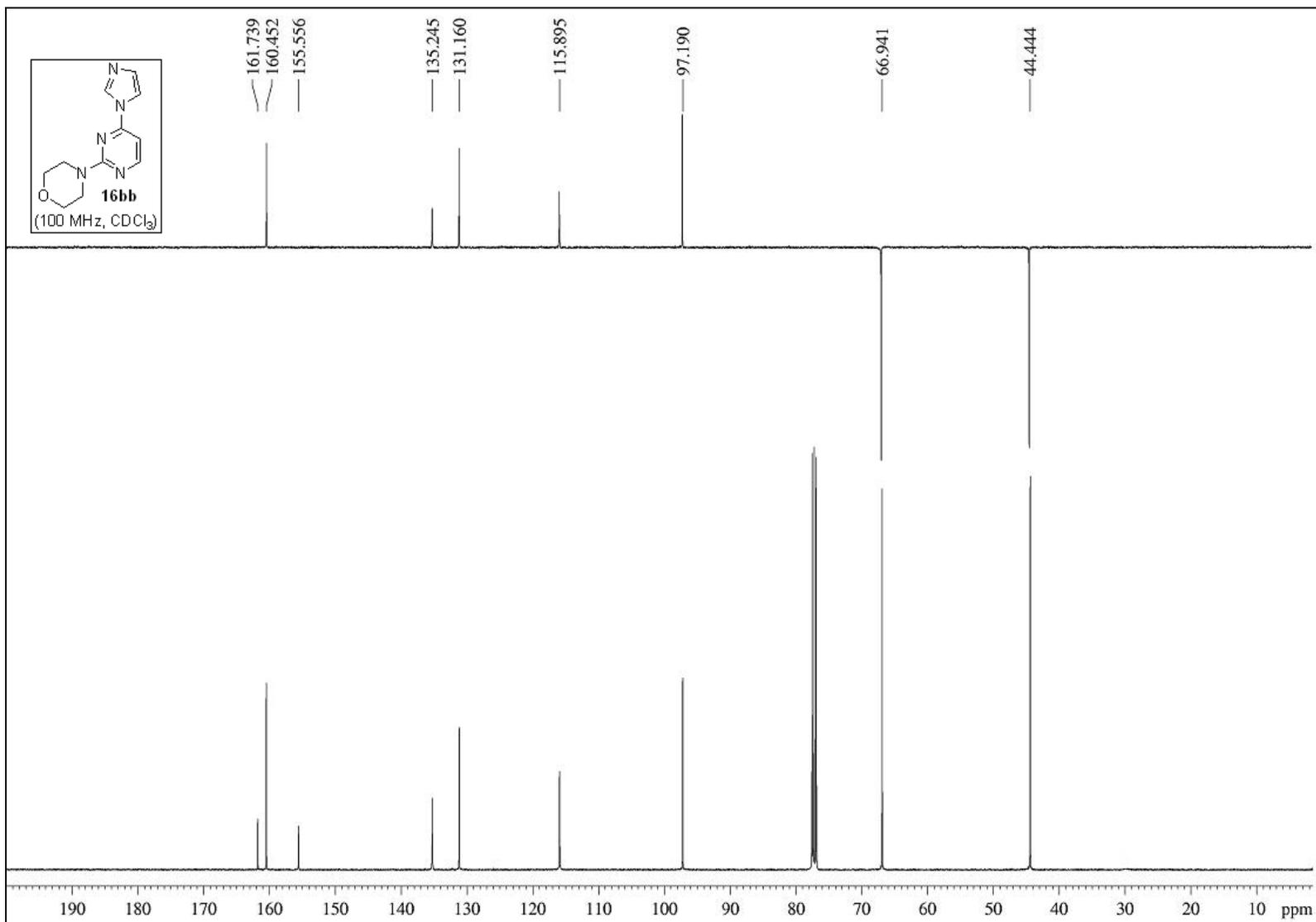
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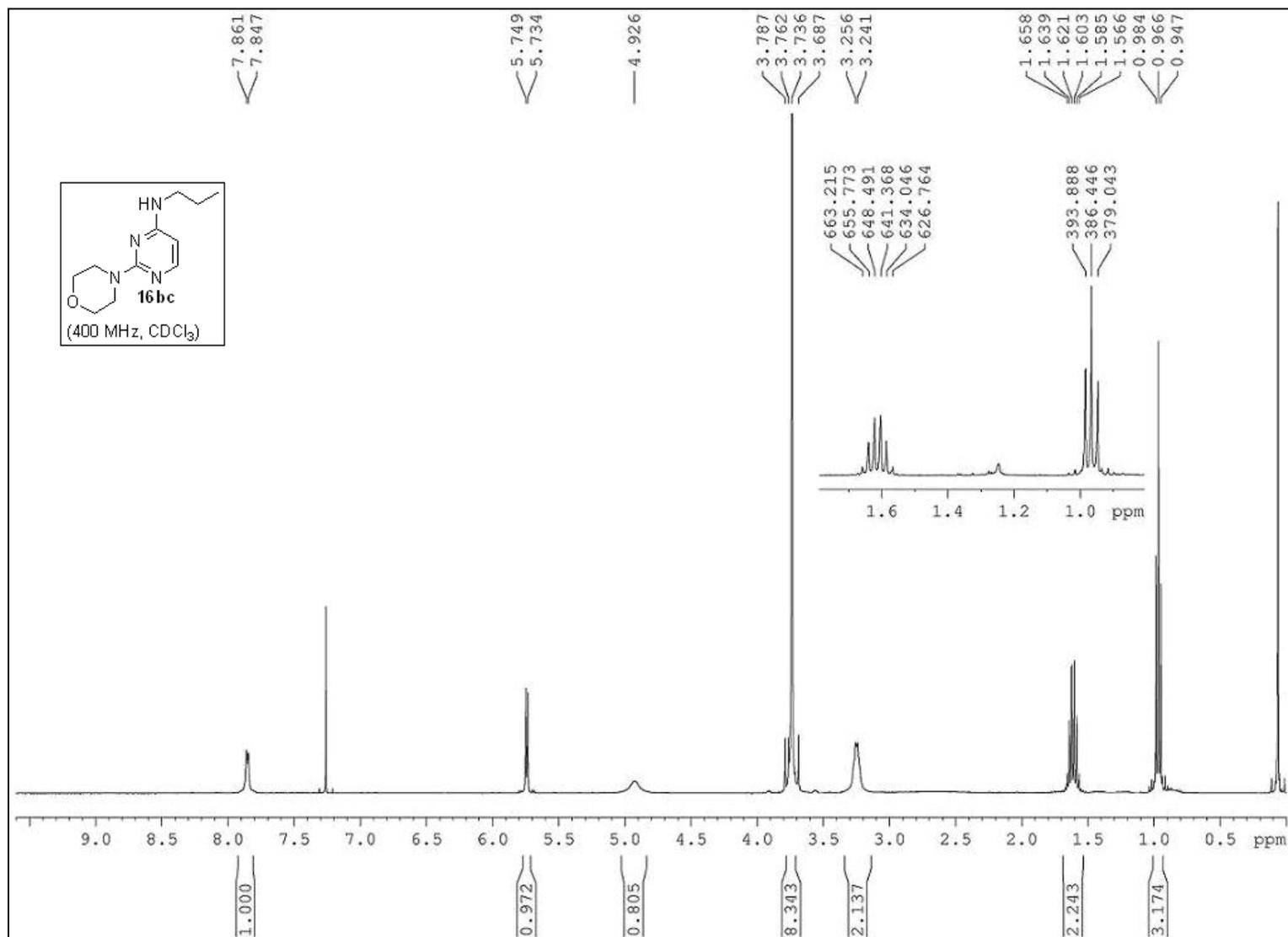
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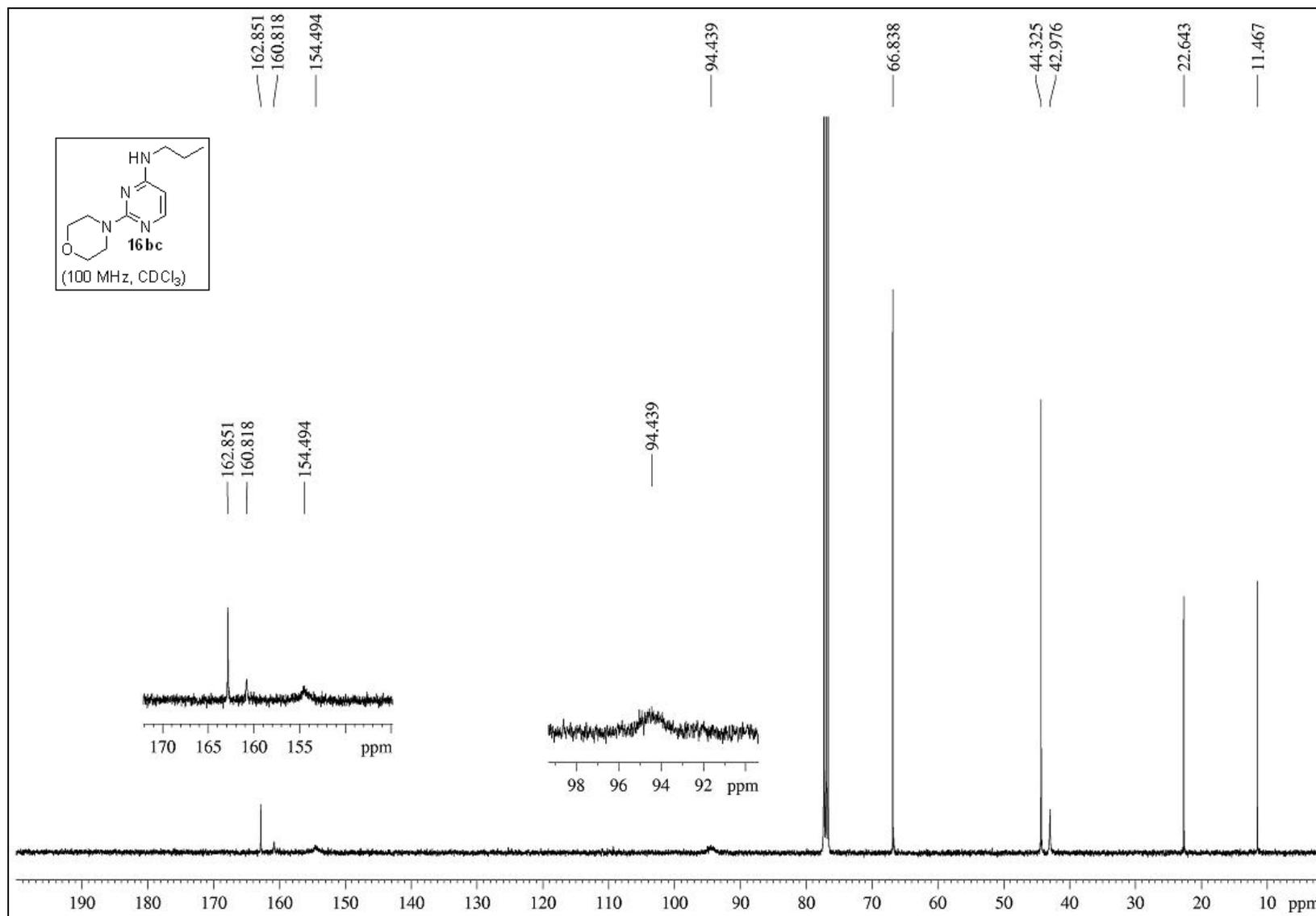
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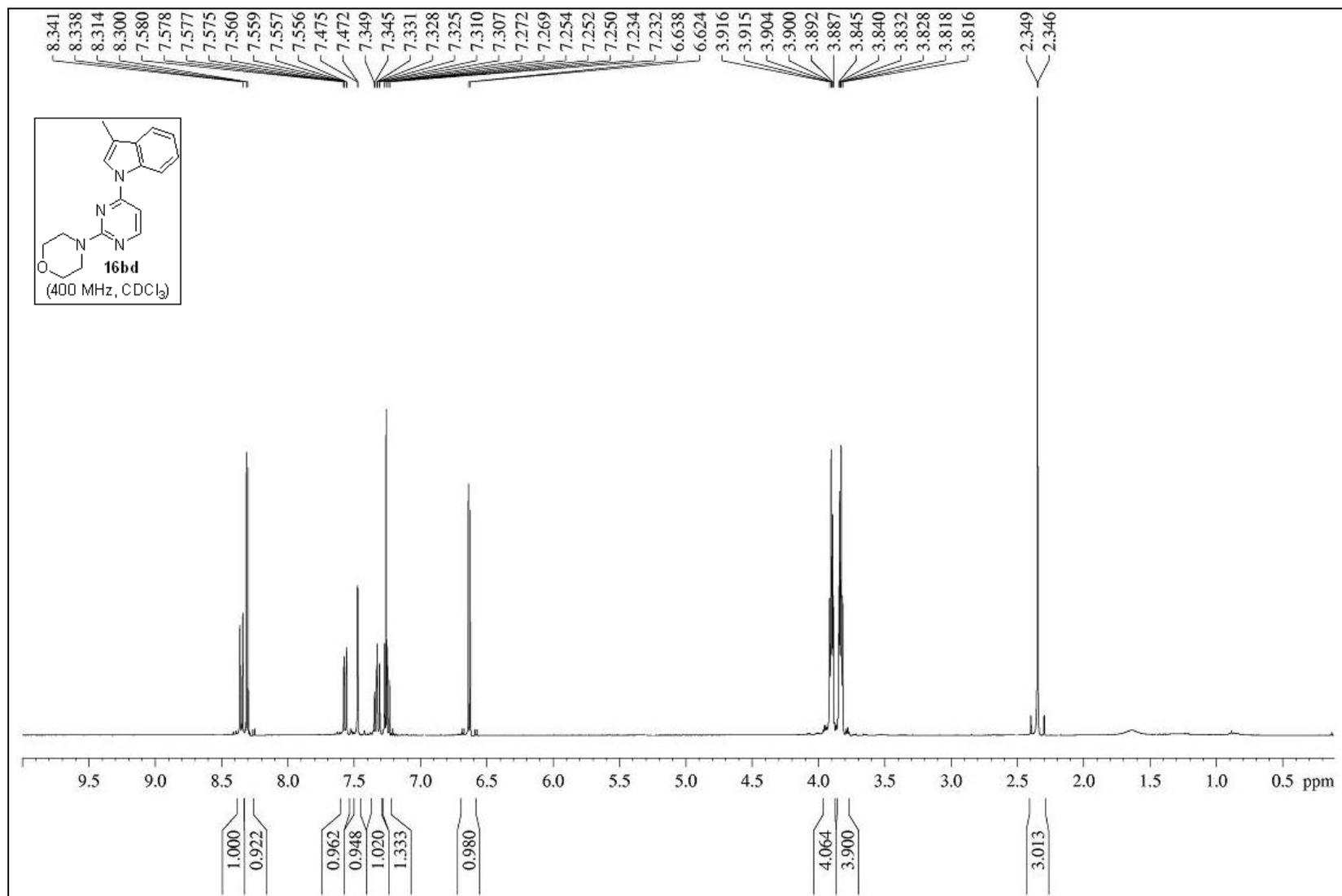
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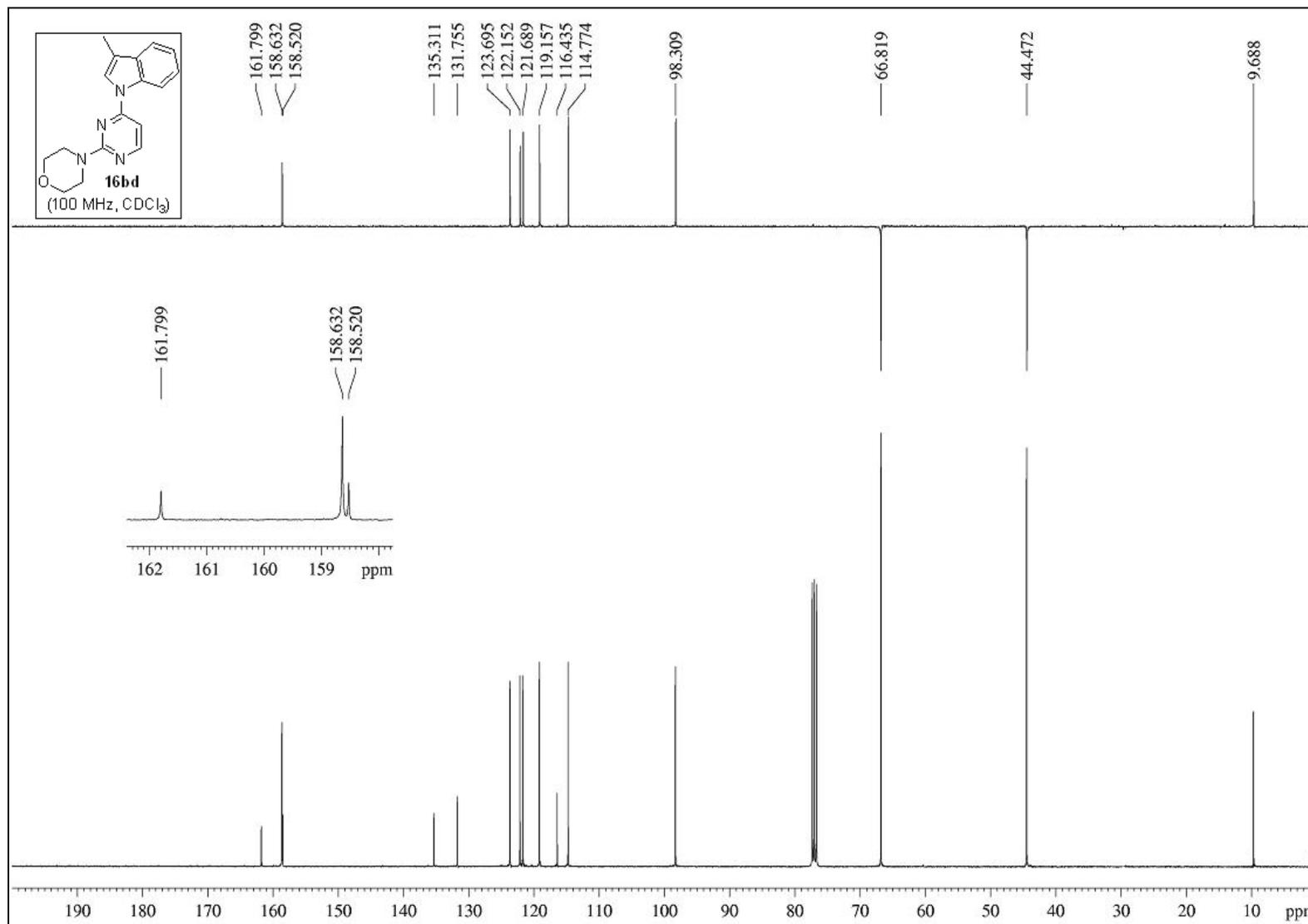
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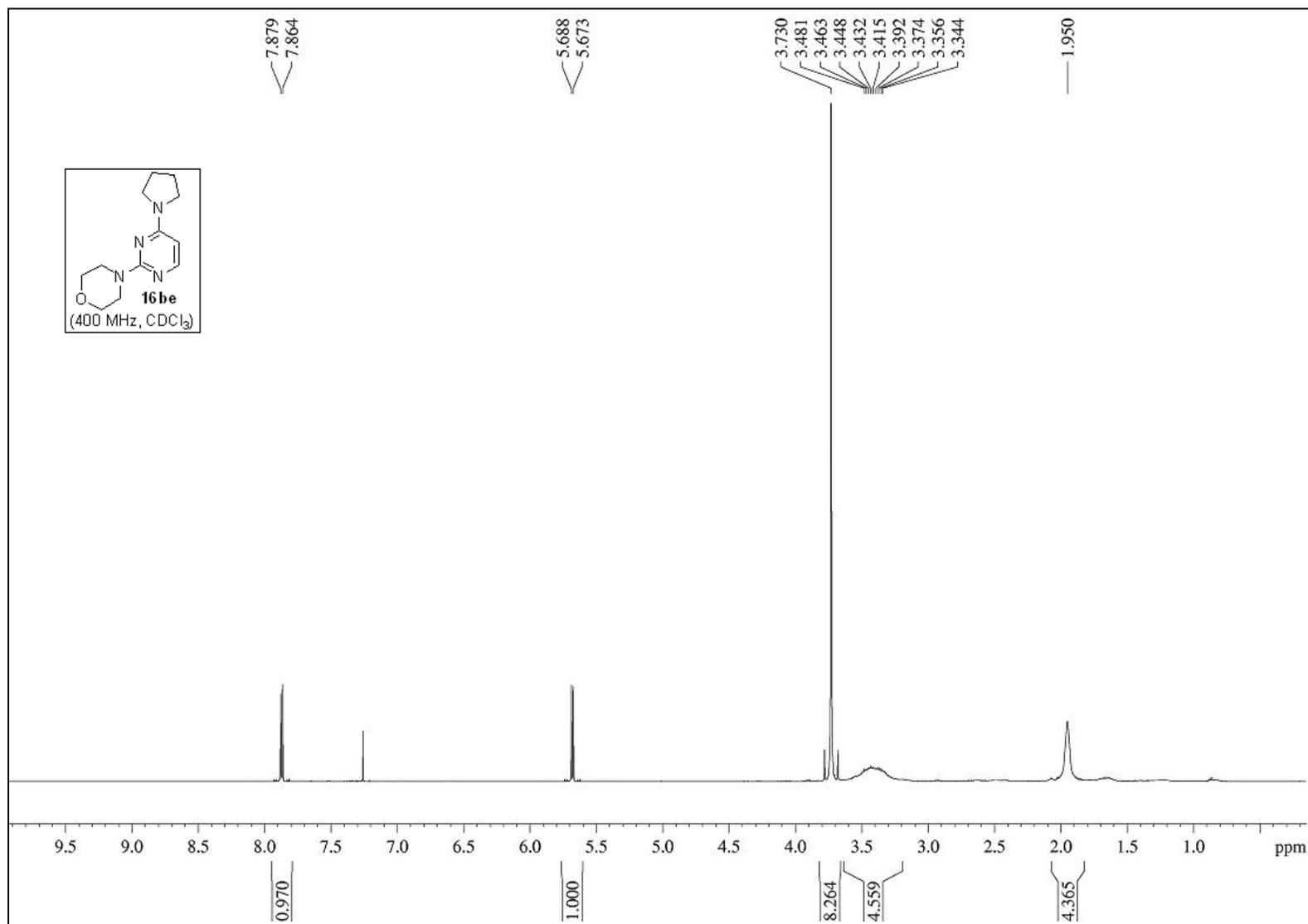
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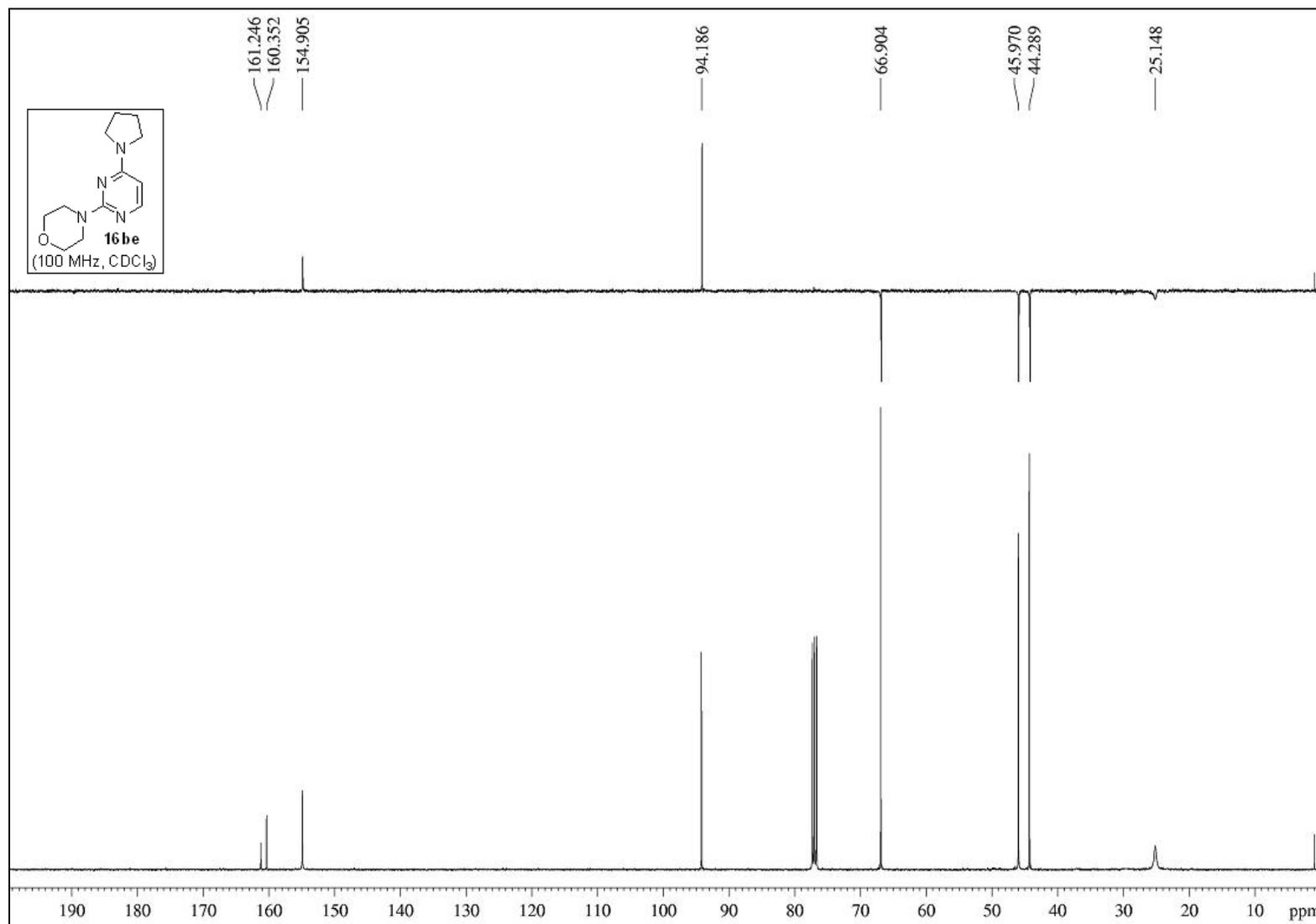
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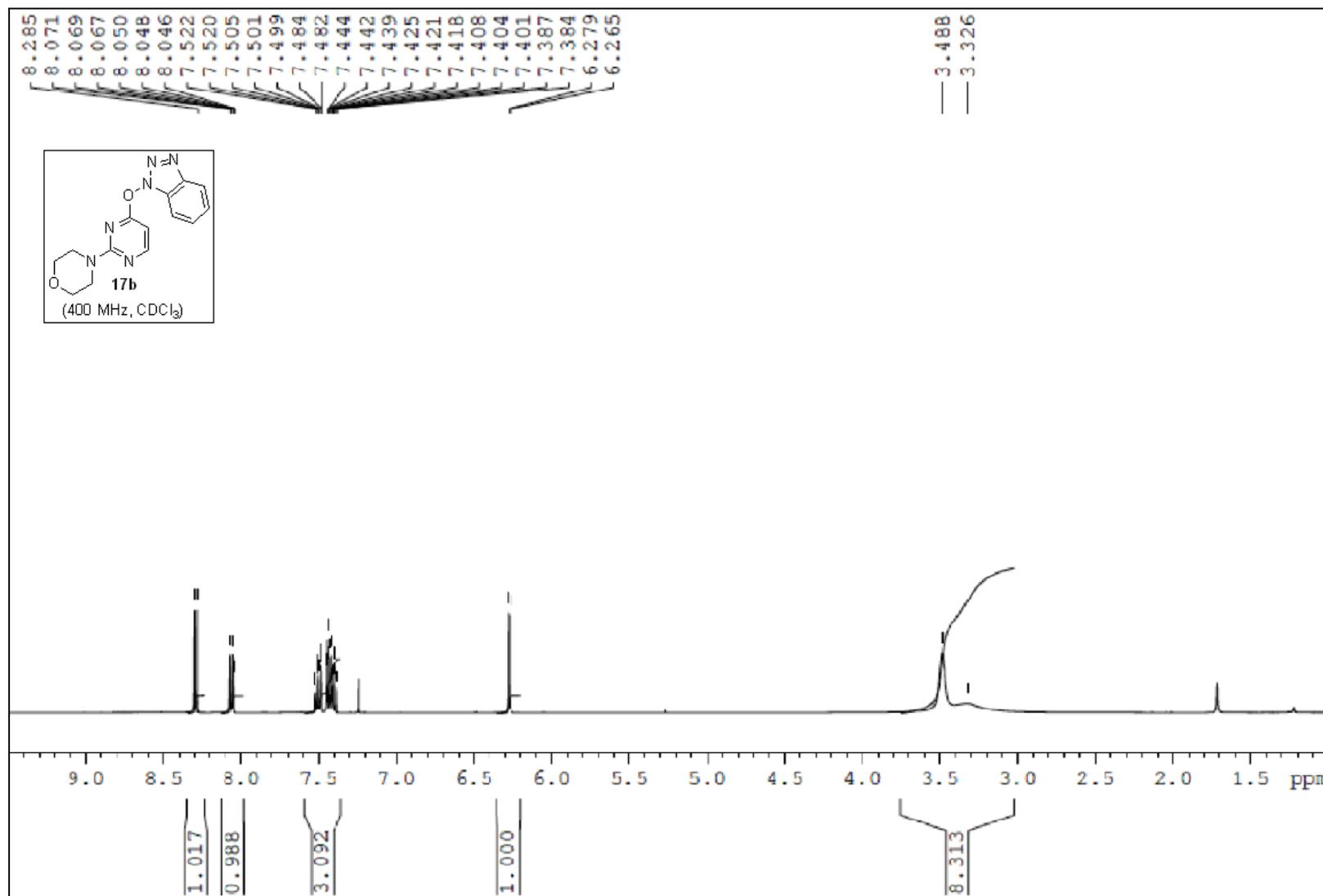
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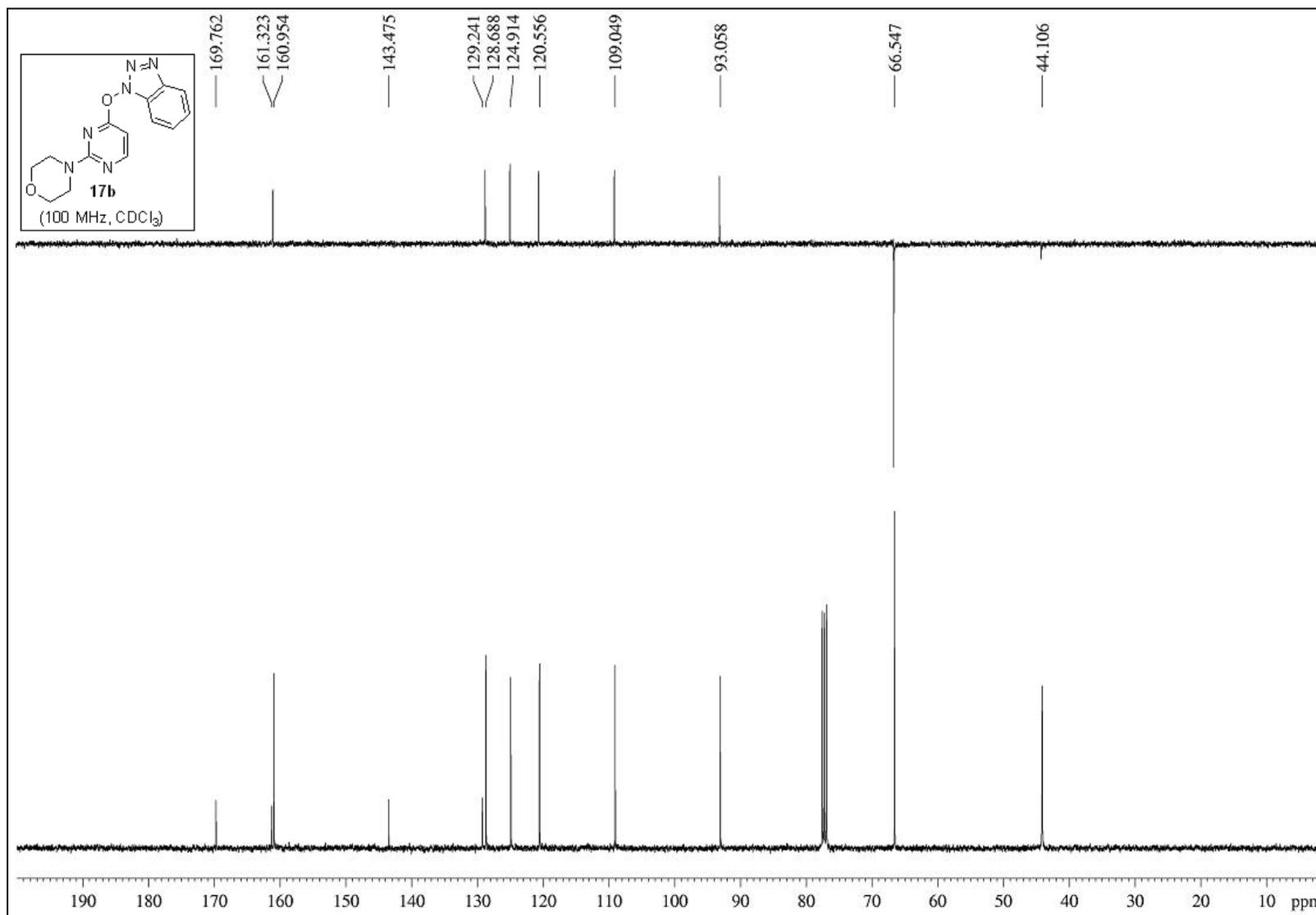
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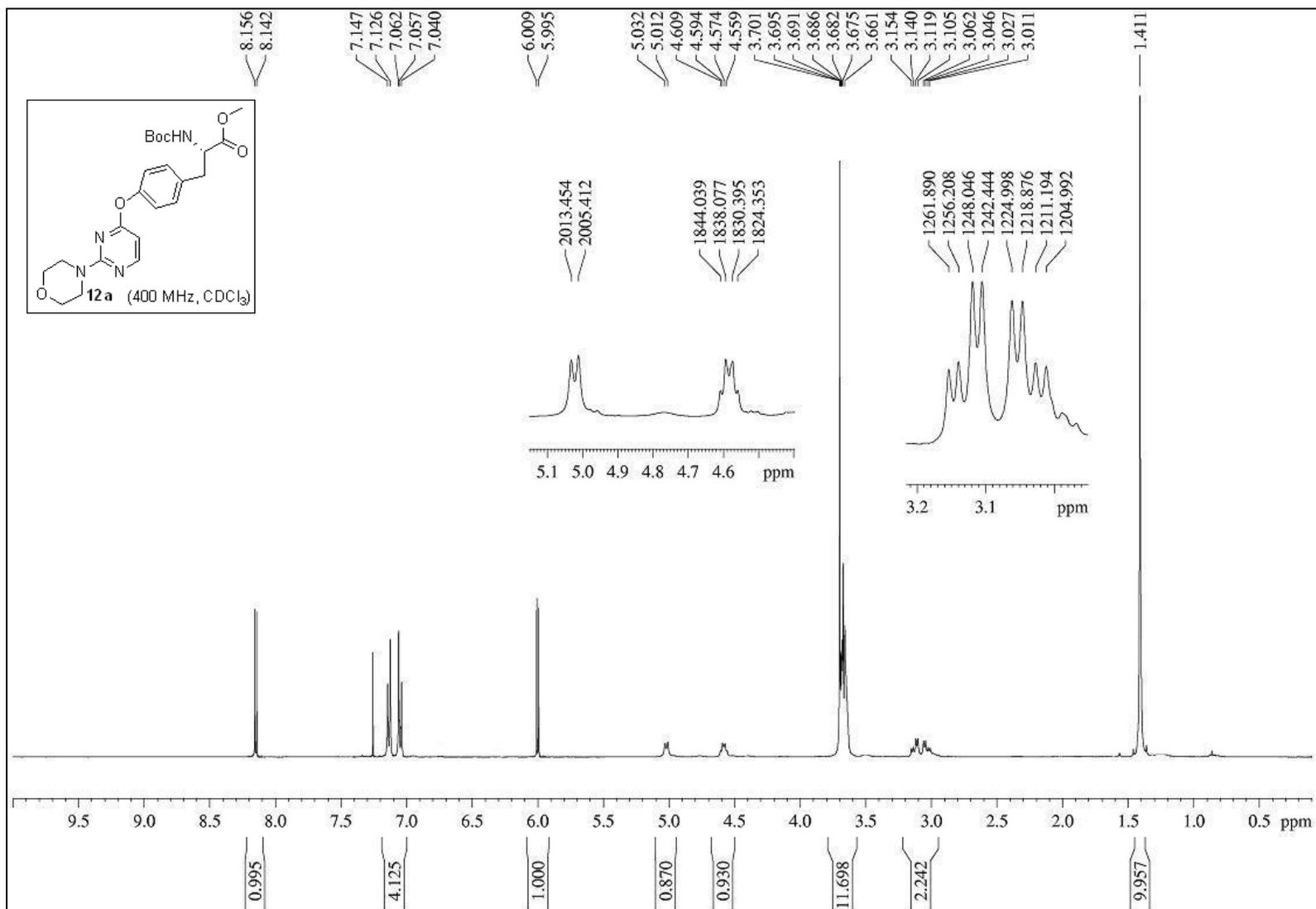
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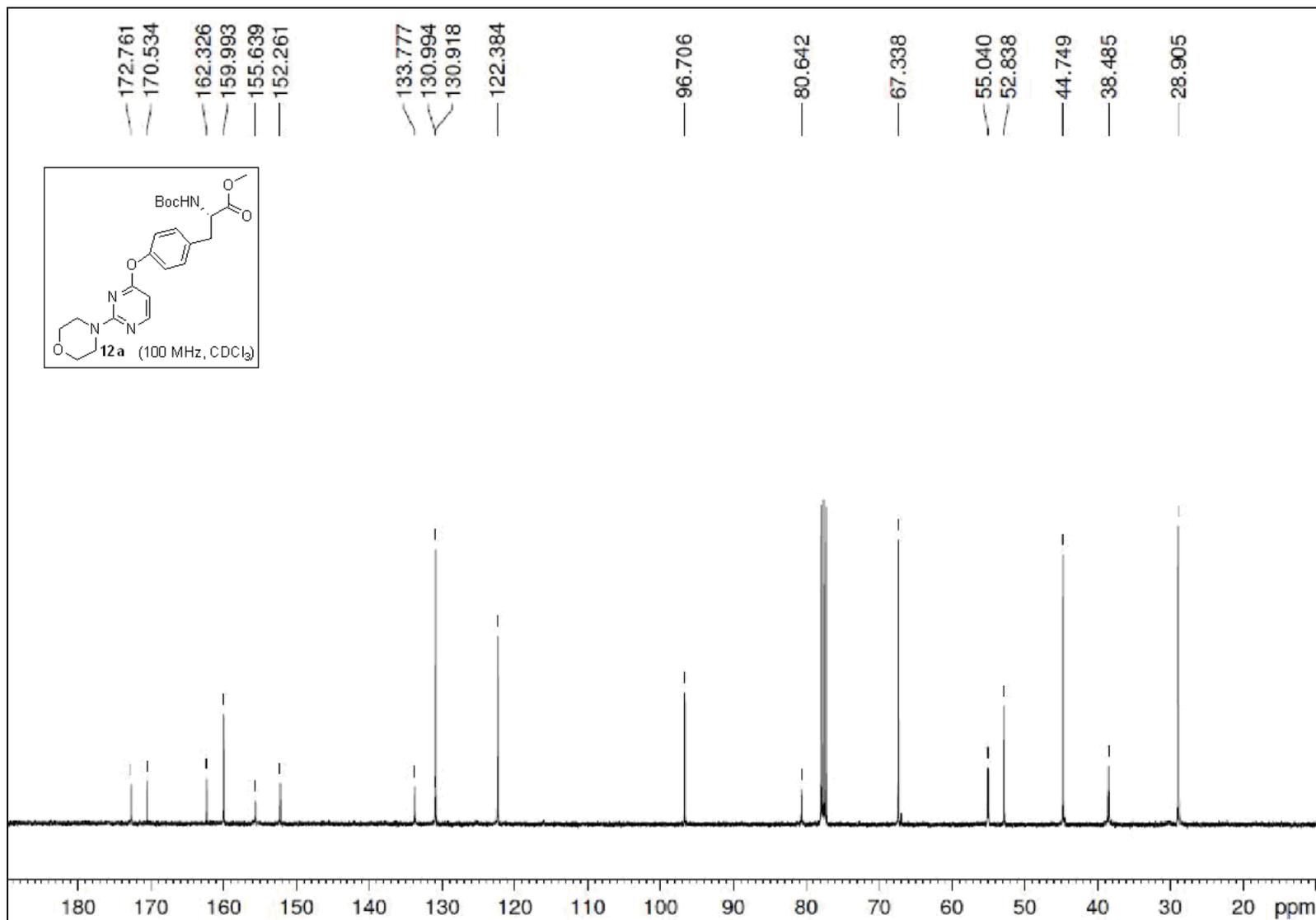
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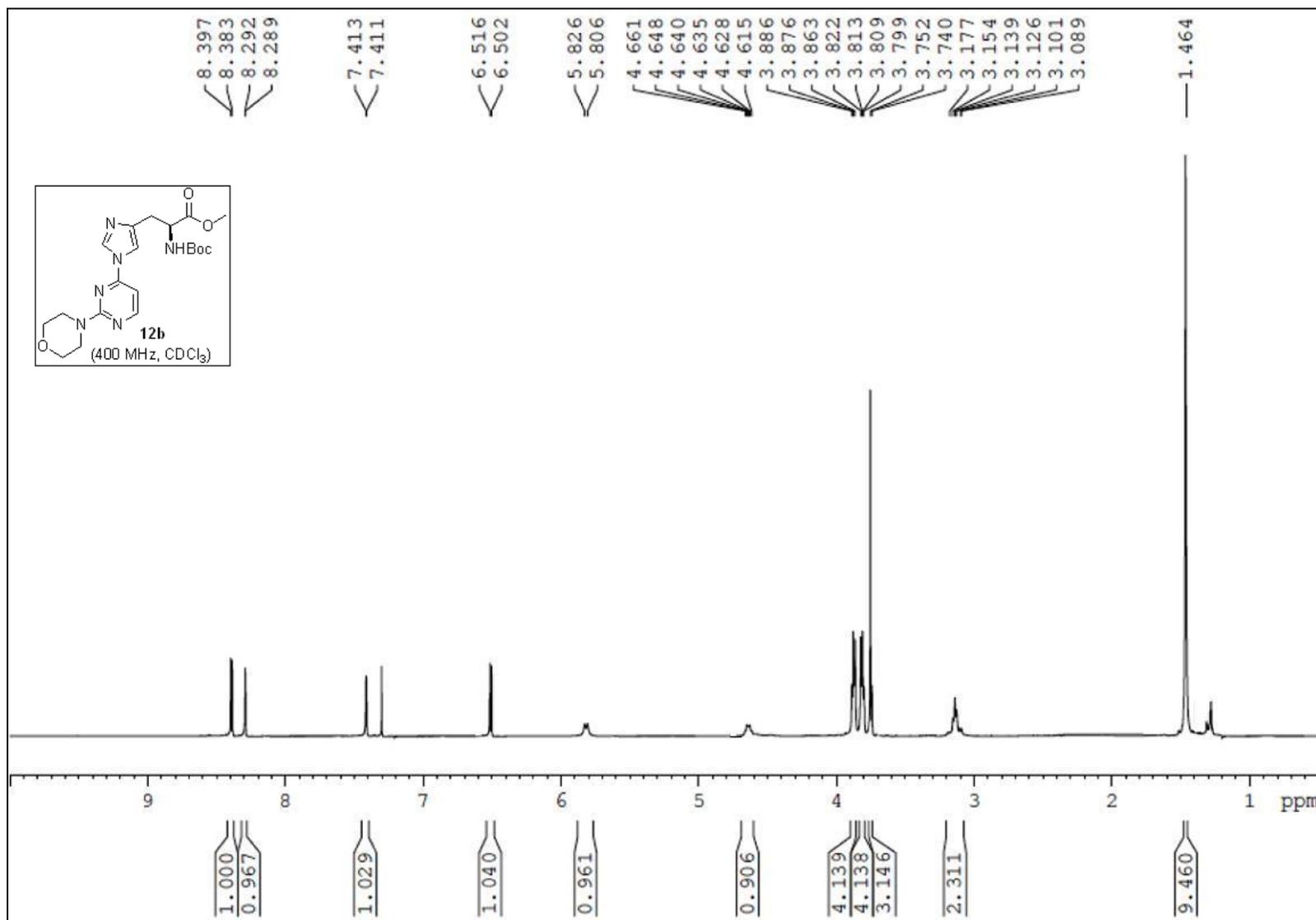
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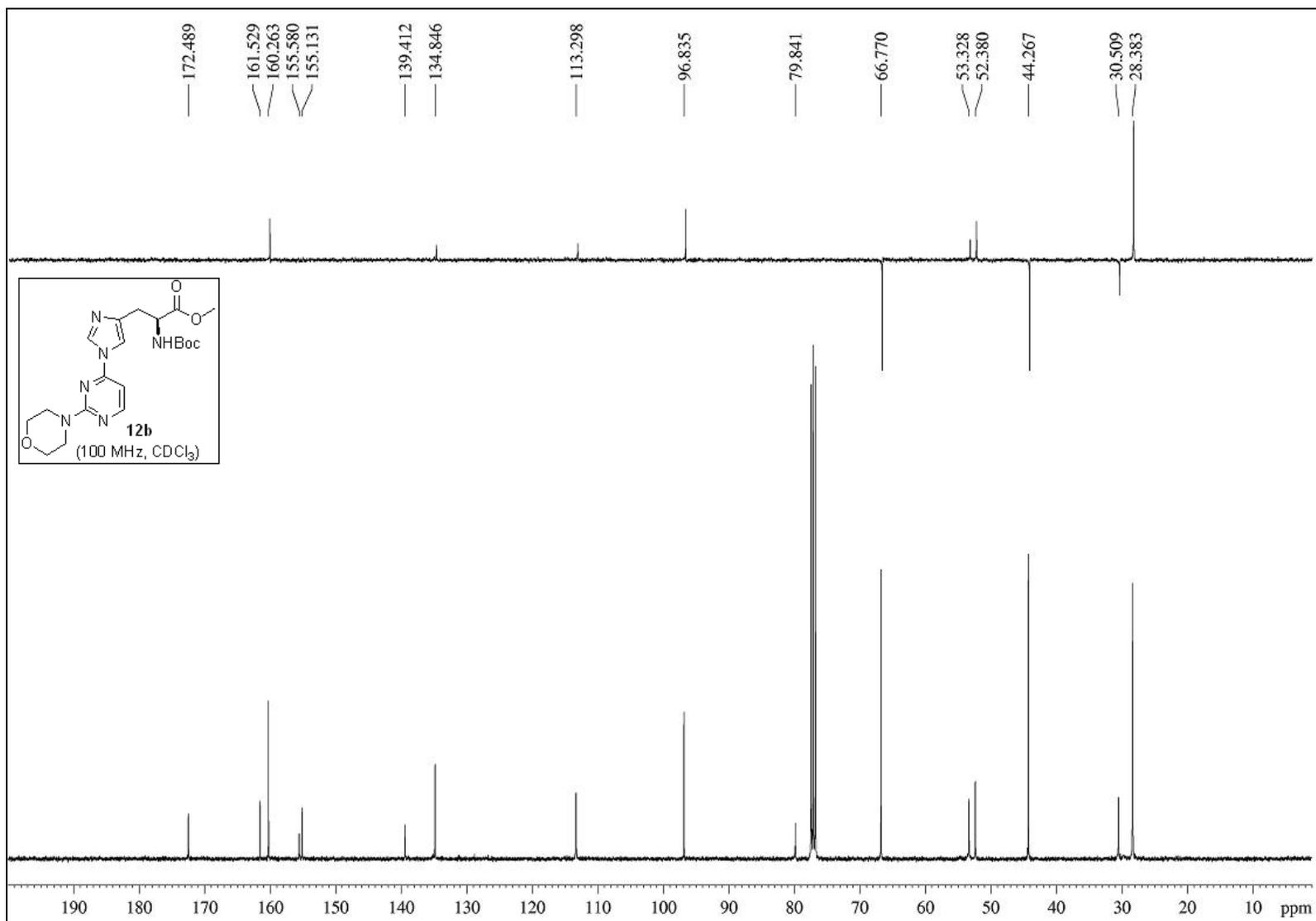
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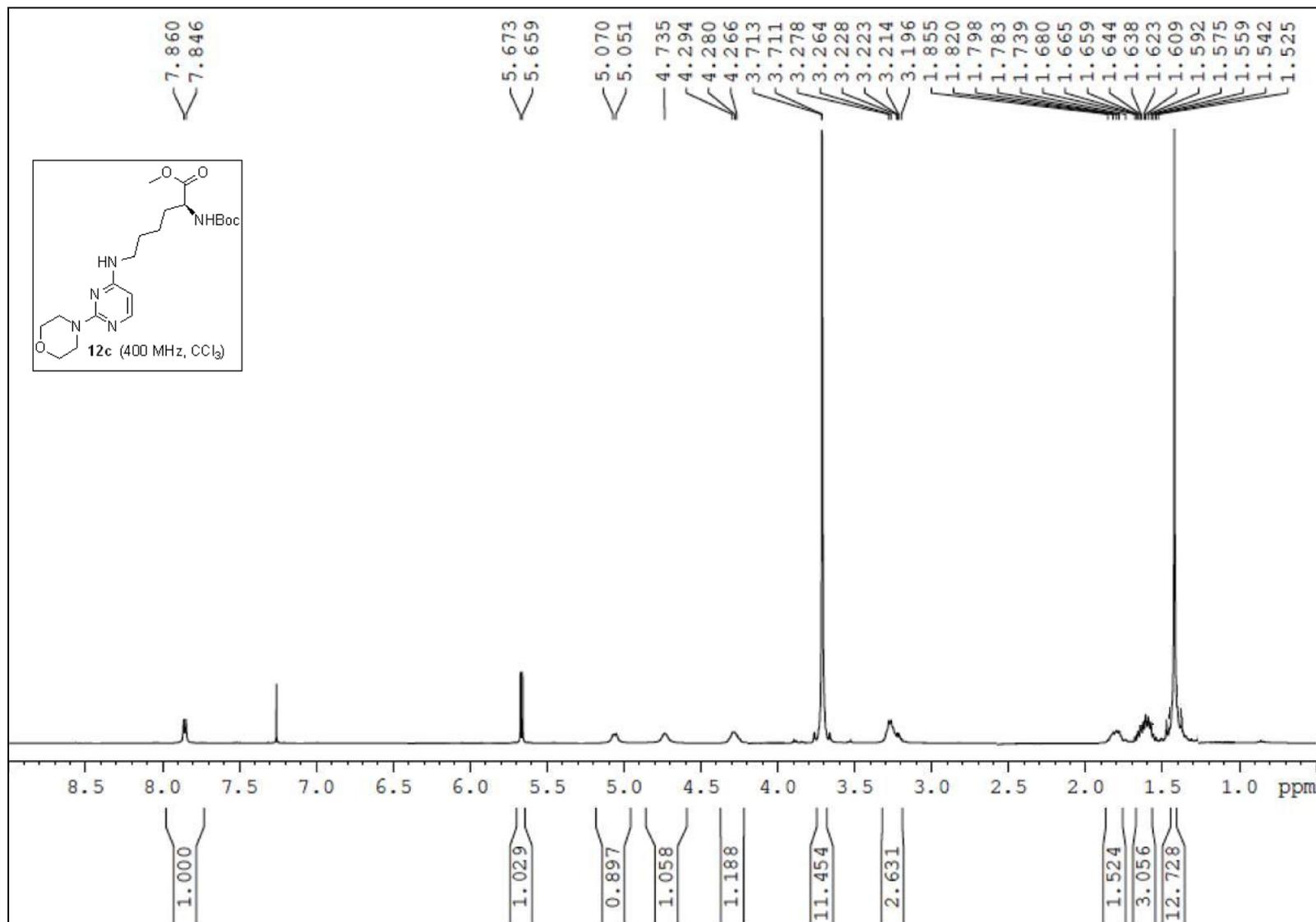
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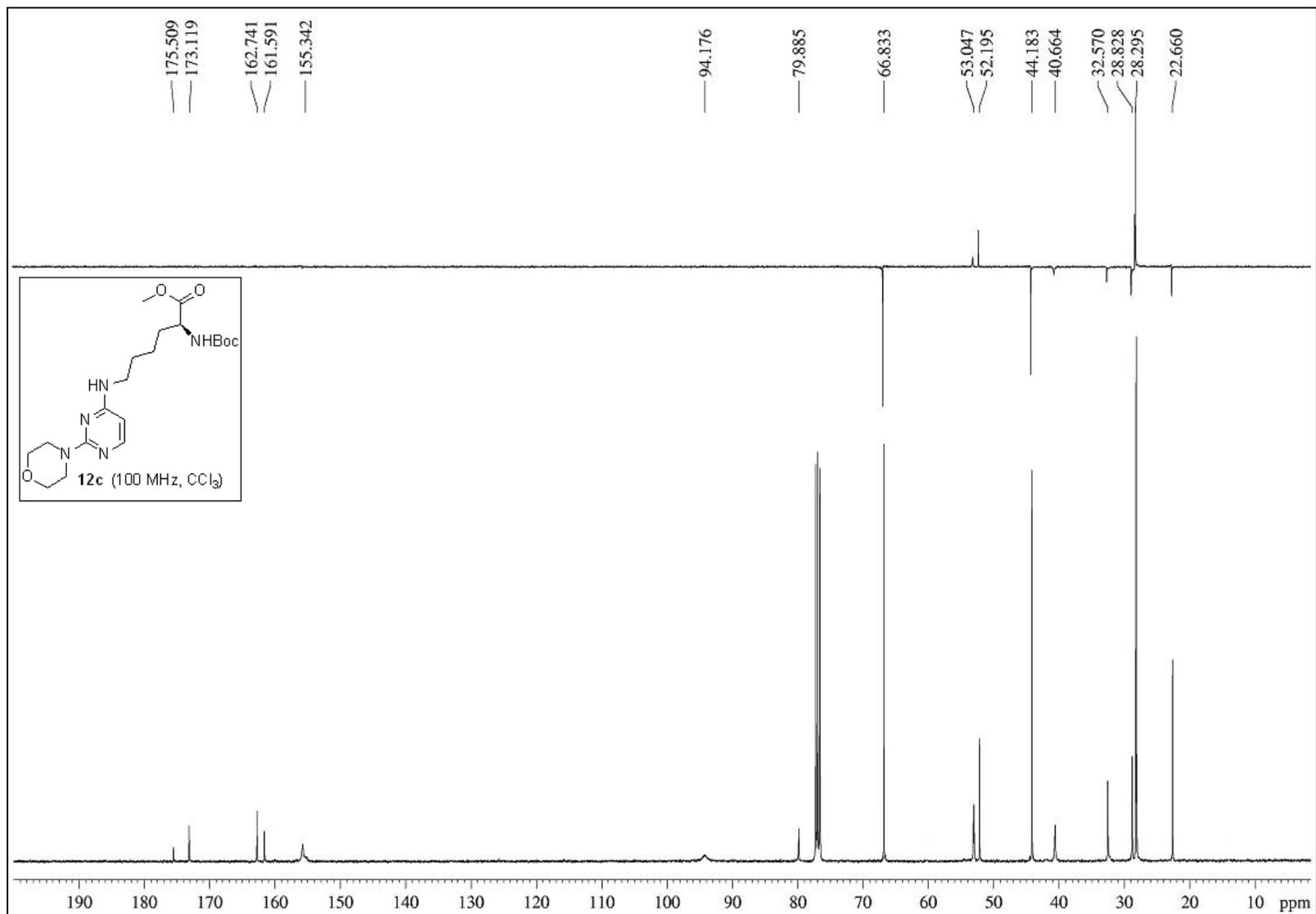
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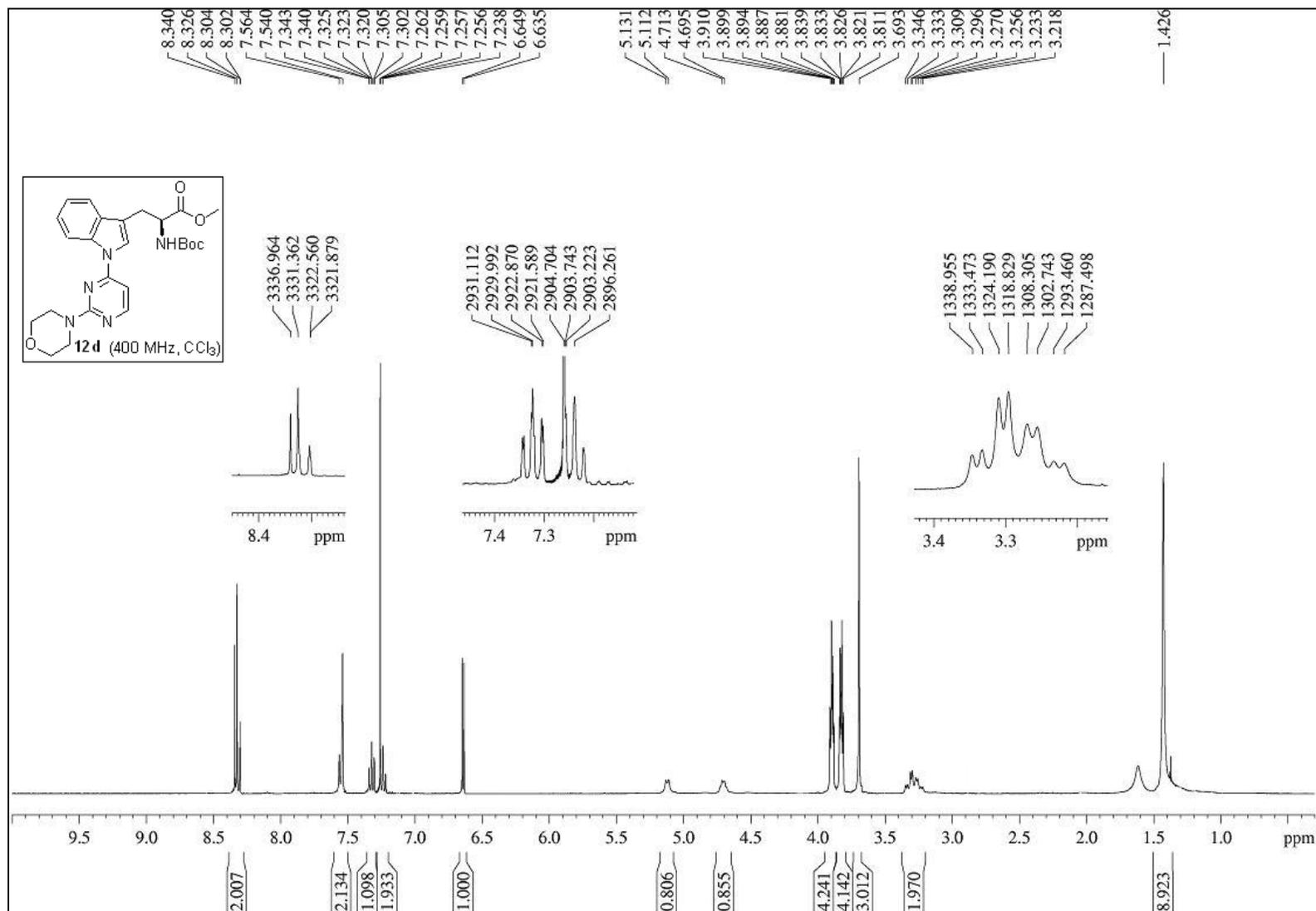
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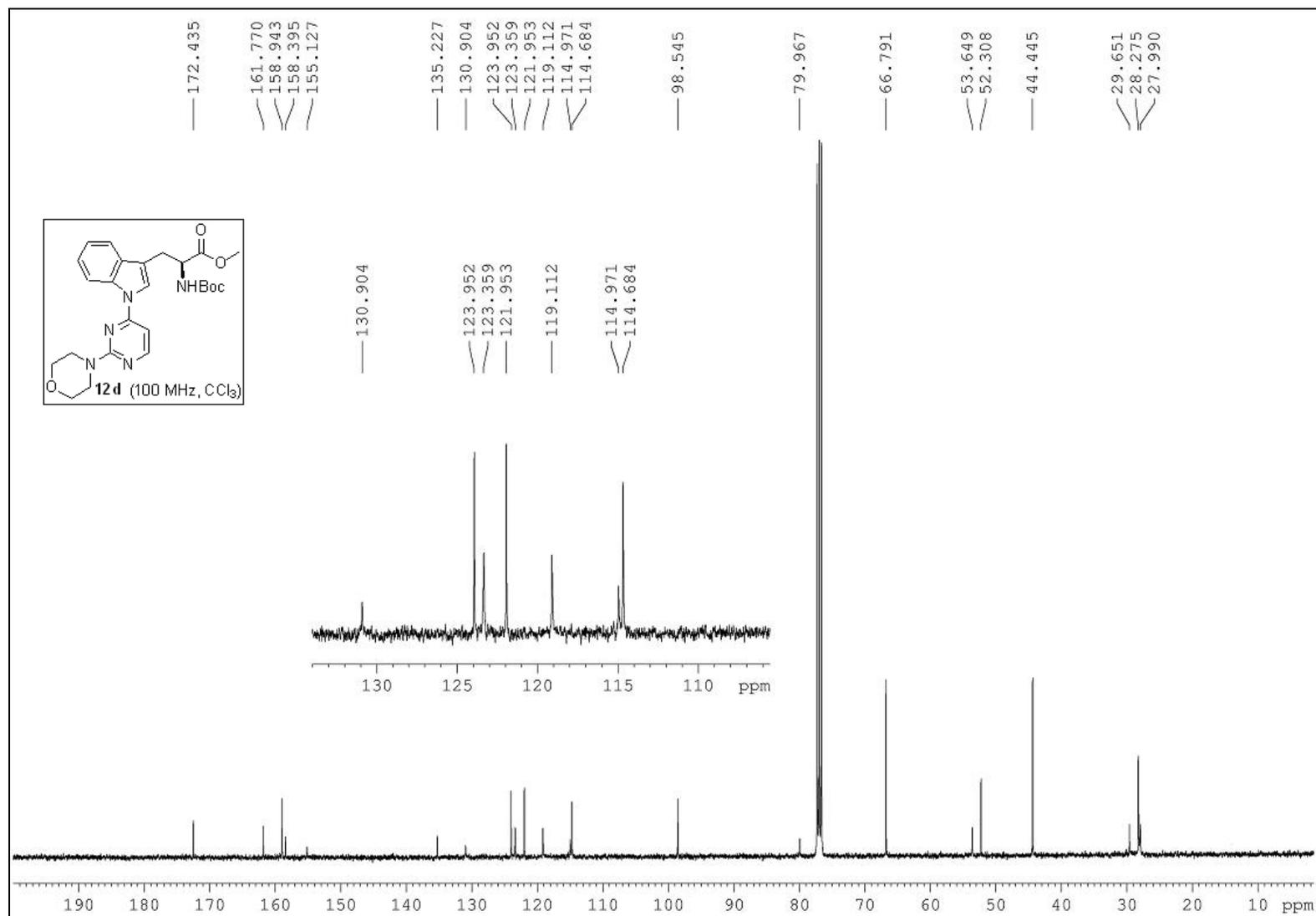
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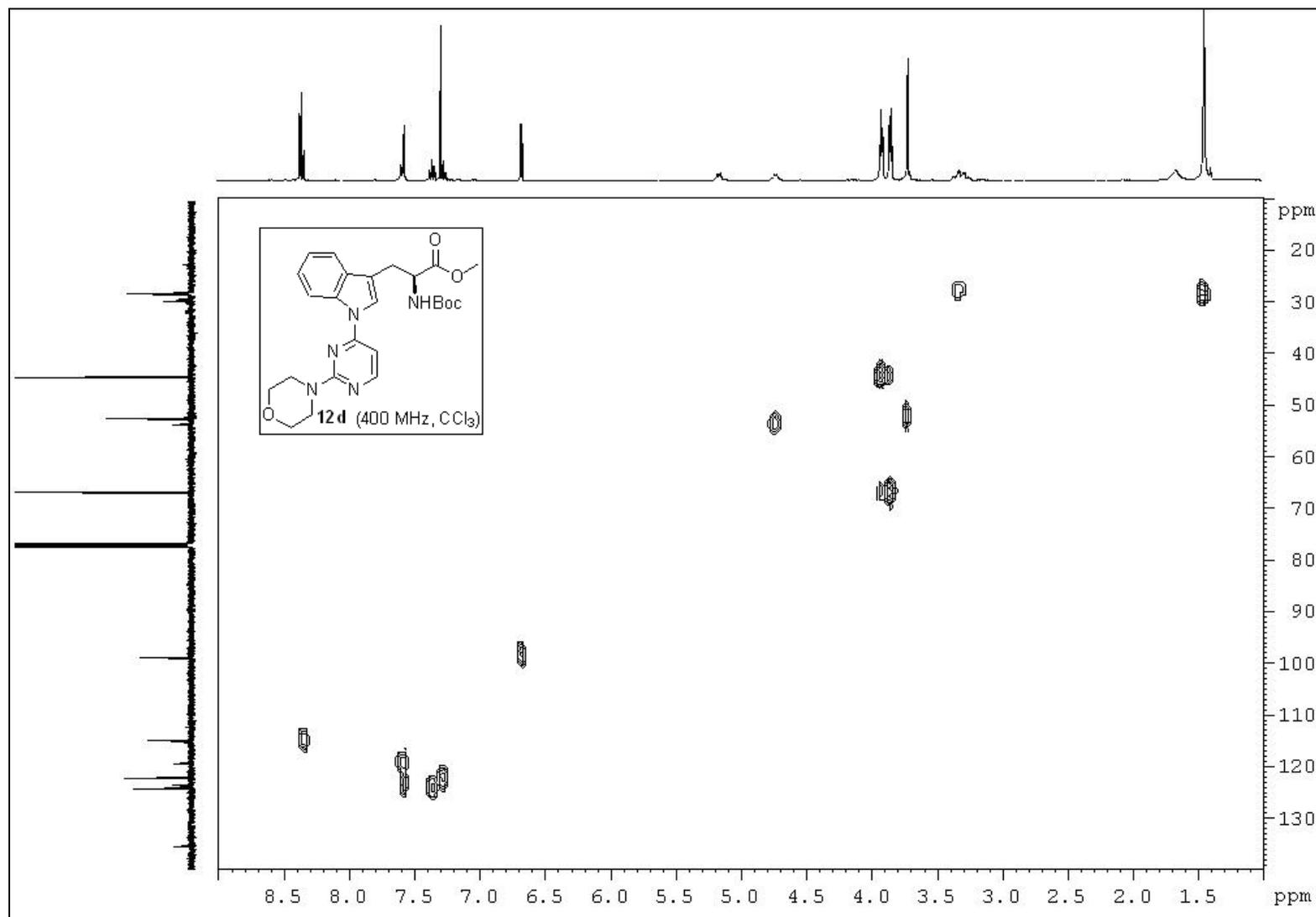
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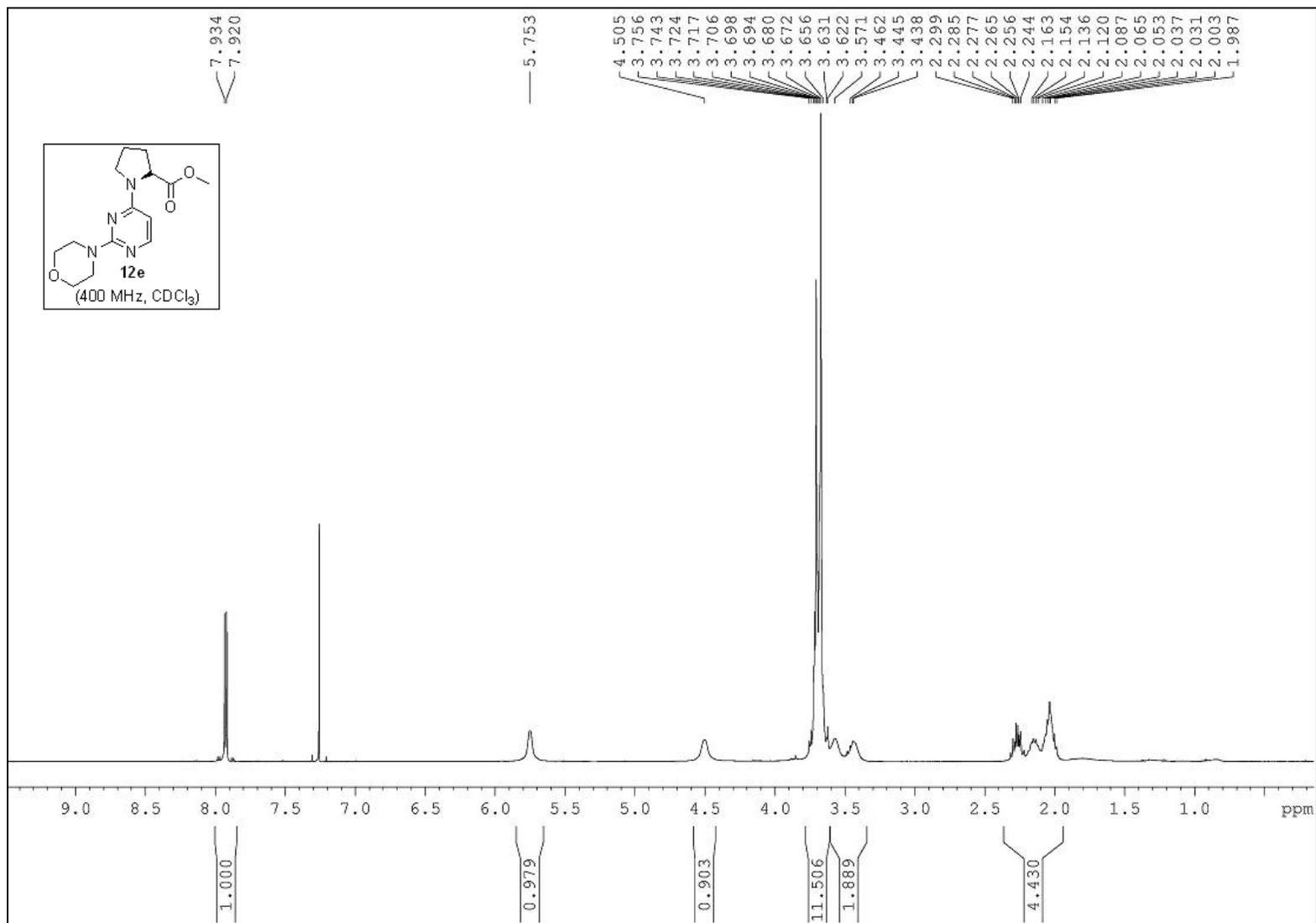
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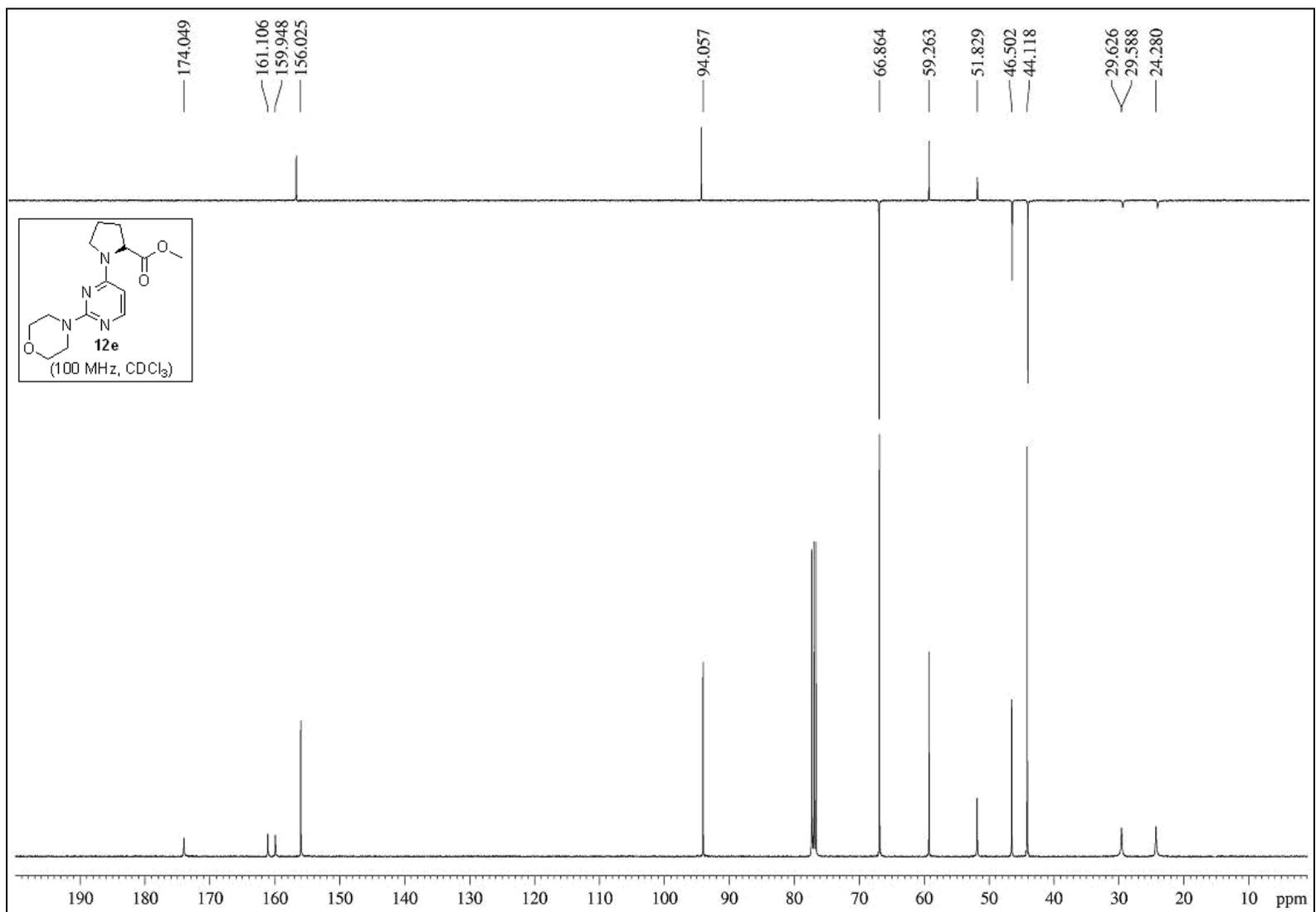
HSQC-ed experiment of compound 12d



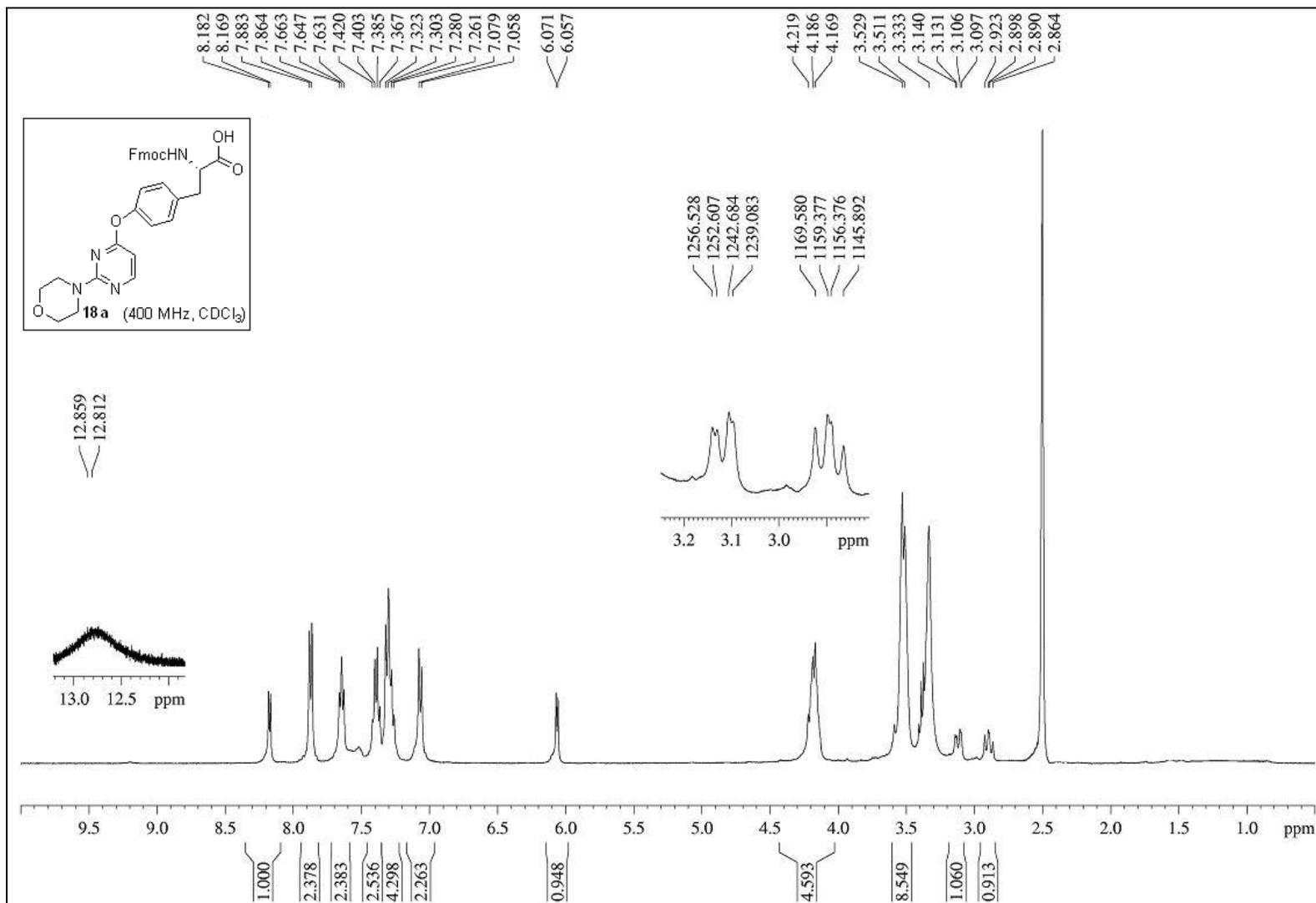
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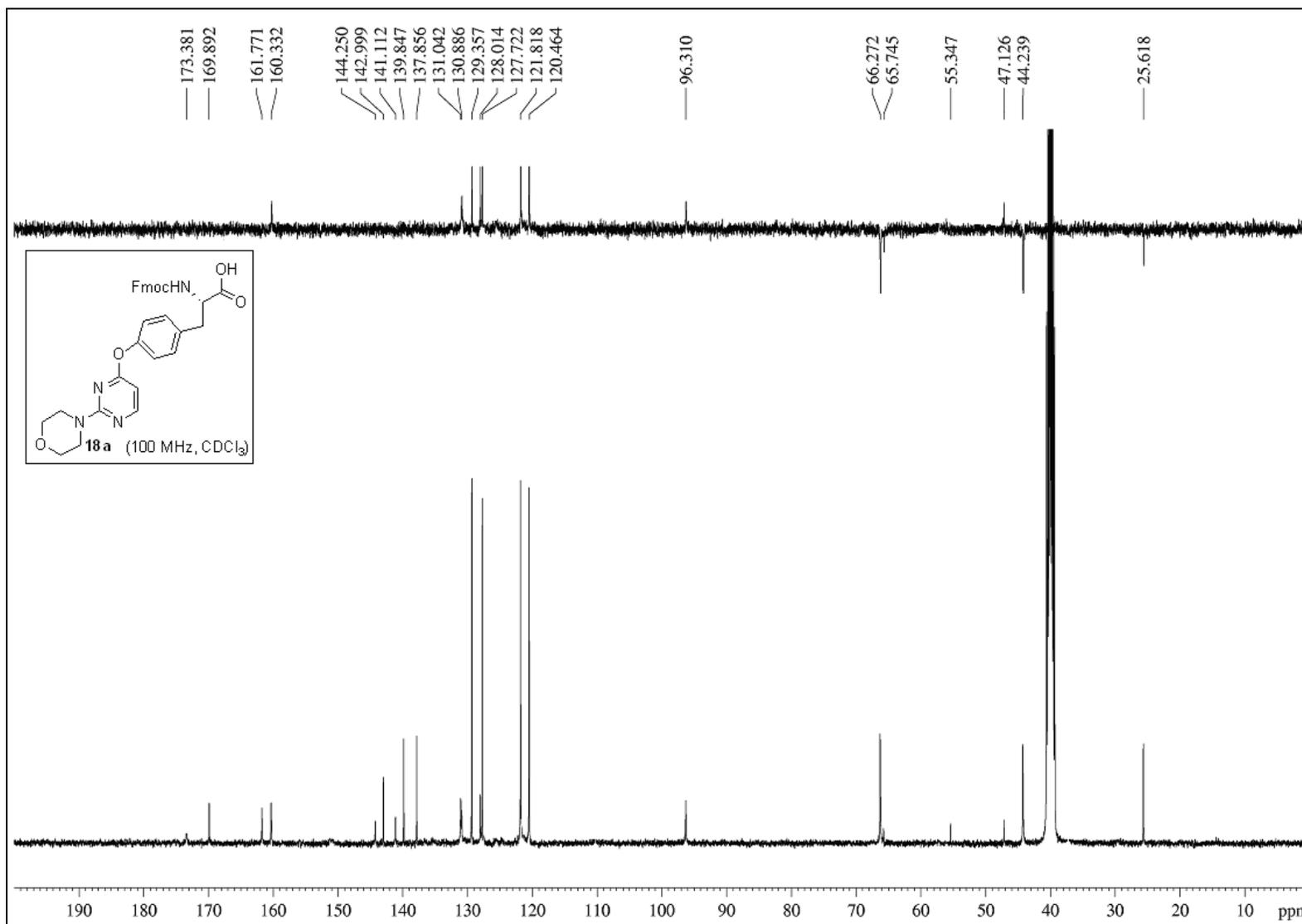
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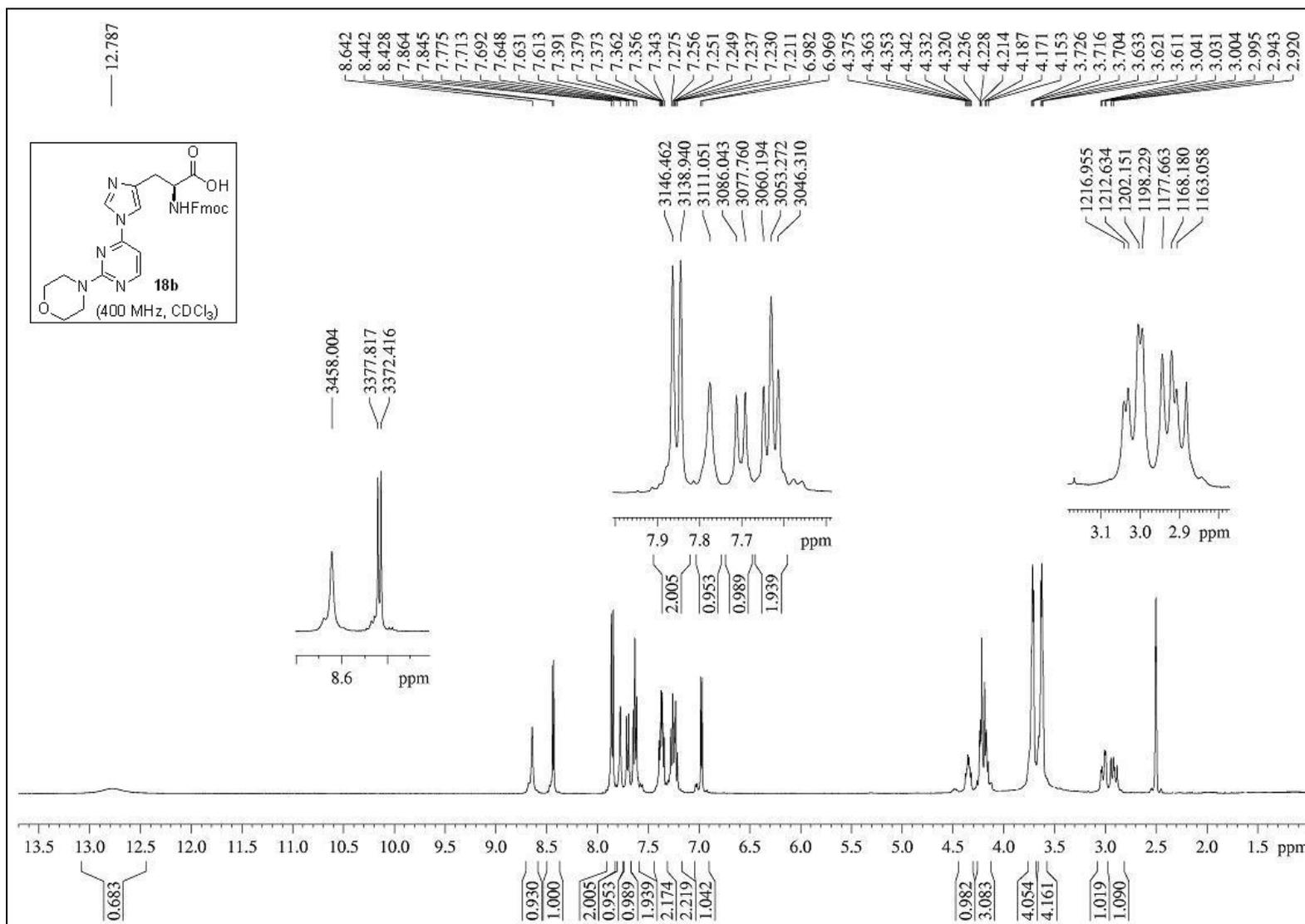
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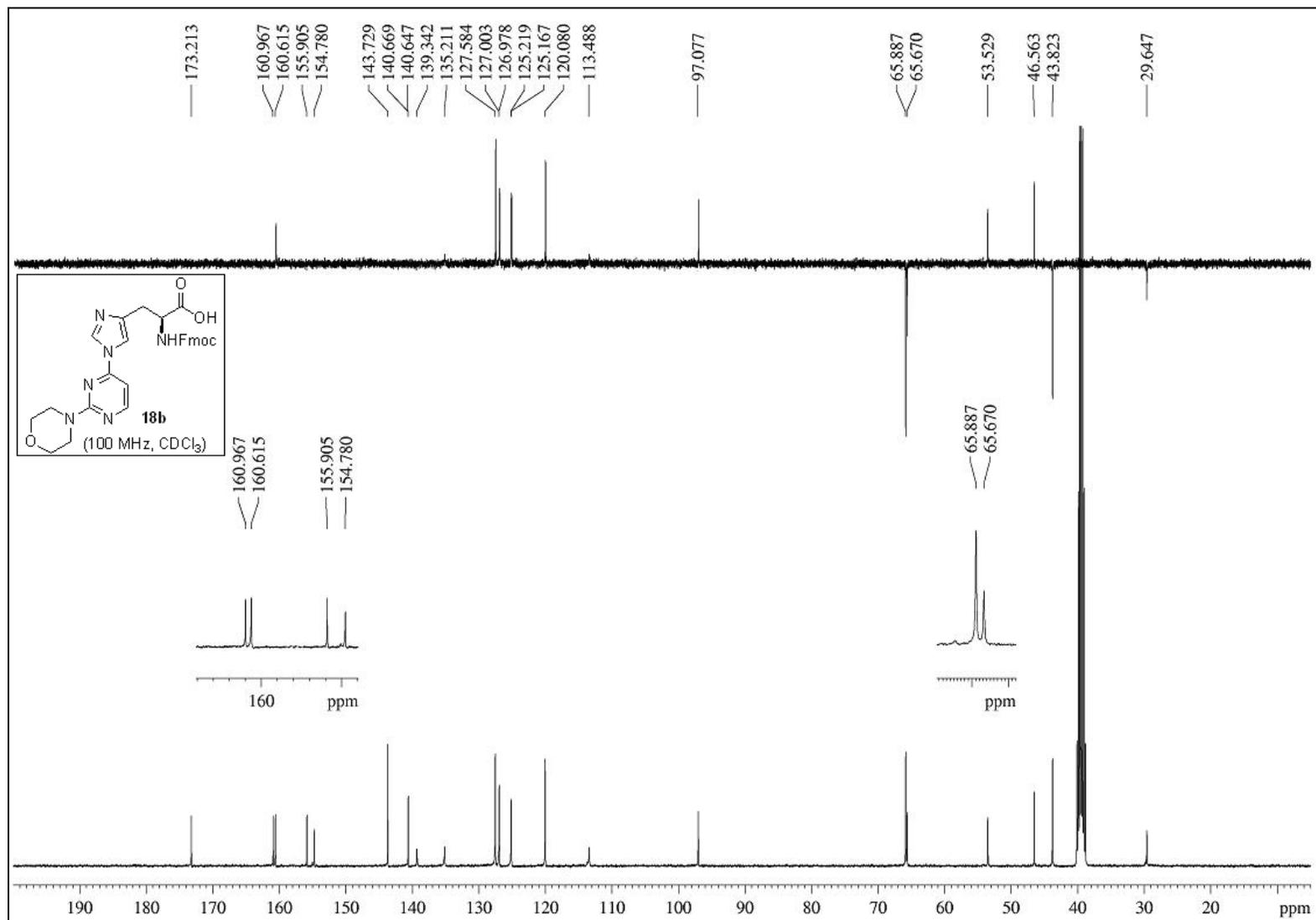
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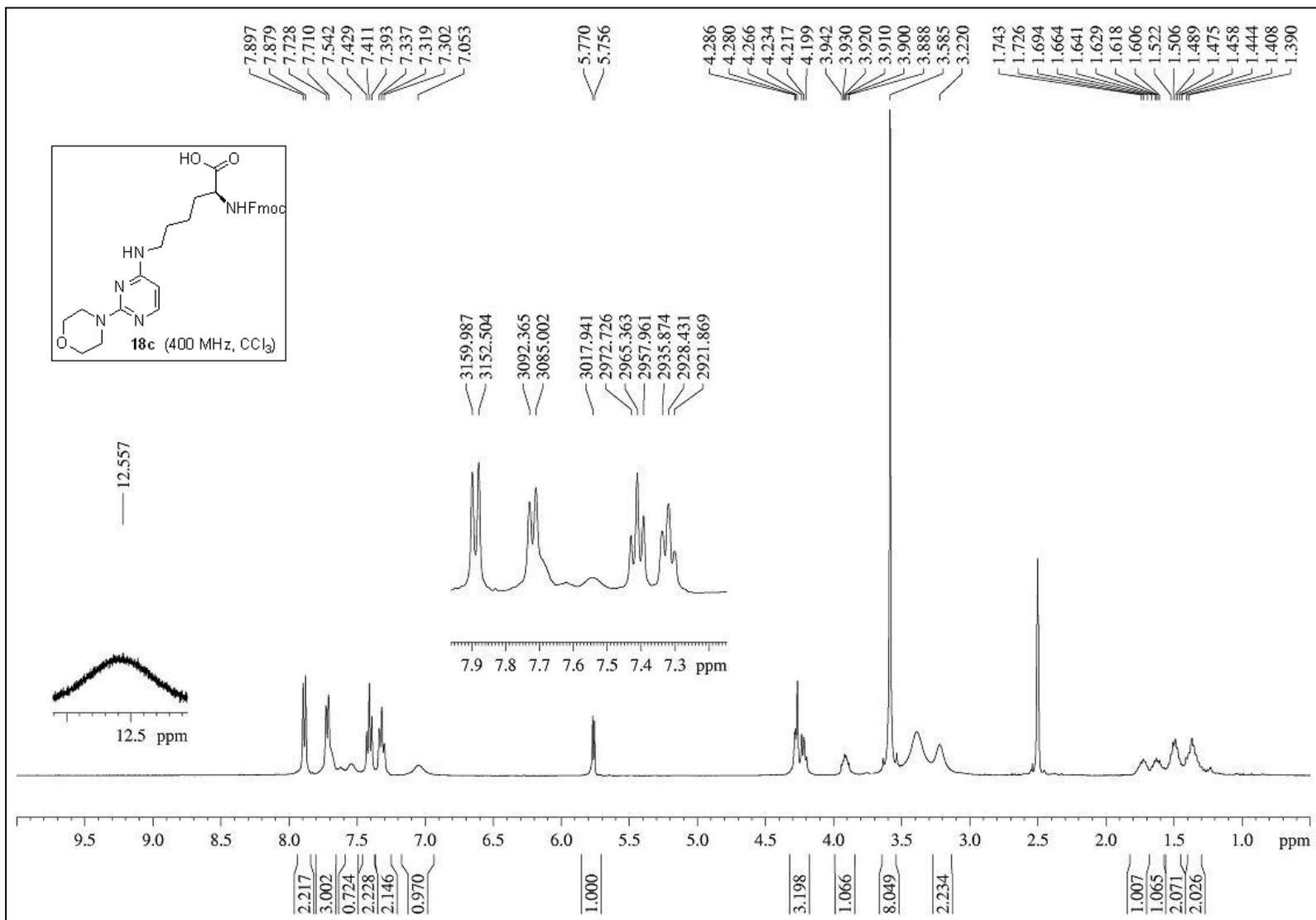
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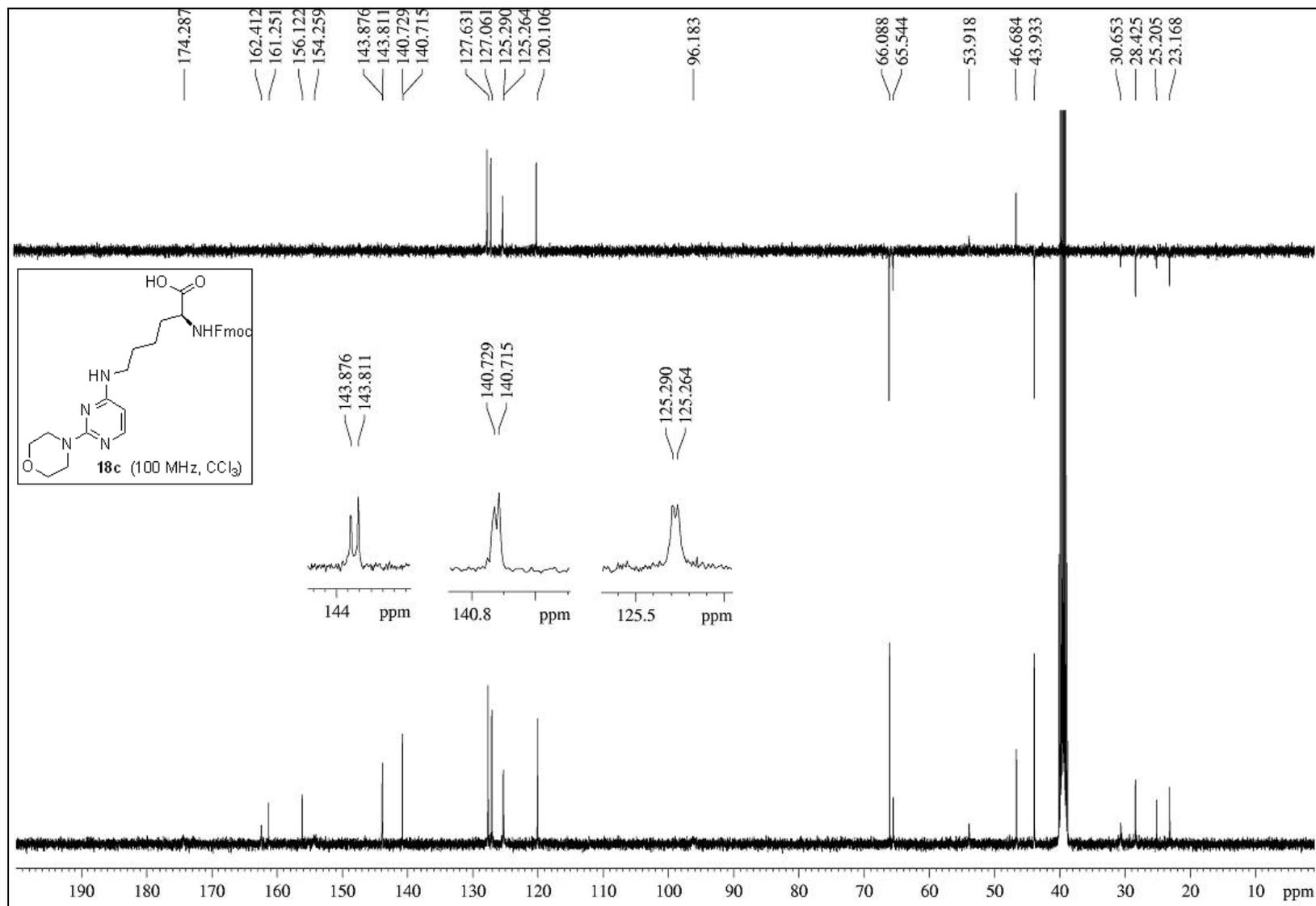
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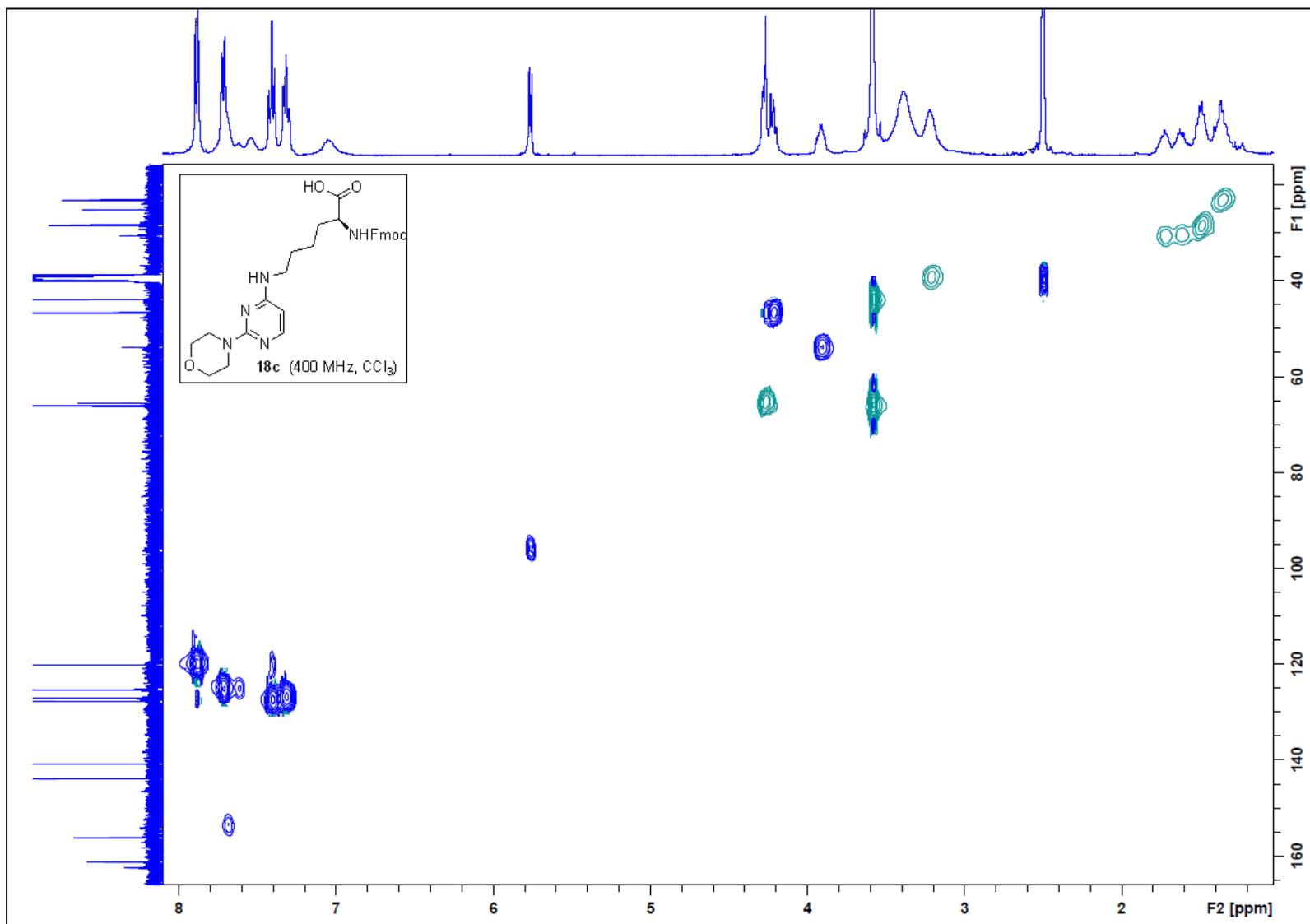
¹H-NMR of compound 18c



¹³C-NMR and DEPT experiment of compound 18c



HSQC-ed experiment of compound 18c



NOESY experiment of compound 12b

