

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF PEPTIDOMIMETIC N-SUBSTITUTED CBZ-4-HYP-HPA-AMIDES AS NOVEL INHIBITORS OF *PLASMODIUM FALCIPARUM*

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b) National Center for Natural Products Research, University of Mississippi, University, MS 38677, United States

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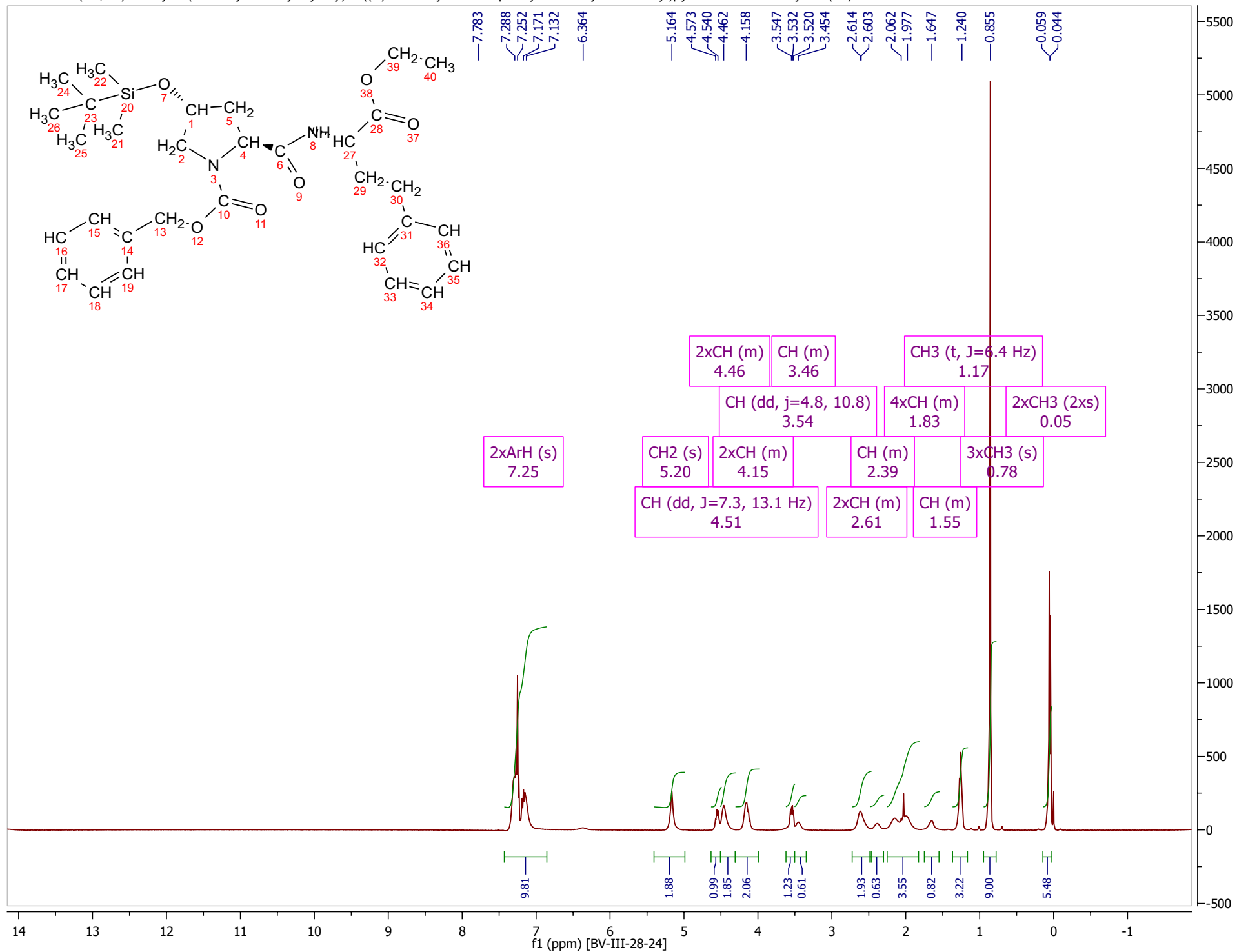
A new series of peptidomimetic N-substituted Cbz-4-Hyp-Hpa-amides were designed, synthesized and evaluated for inhibition of the *Plasmodium falciparum*. Substituents on the N atom of the amide group were selected alkyl-, allyl-, aryl-, 2-hydroxyethyl-, 2-cyanoethyl-, cyanomethyl-, 2-hydroxyethyl-, 2,2-diethoxyethyl-, or 2-ethoxy-2-oxoethylamino groups, and about of forty new compounds were synthesized and evaluated for anti-plasmodial activity in vitro. Antimalarial activity has been investigated as for the final peptide mimetics, and their immediate predecessors, carrying TBDMS or TBDPS protecting groups on 4-hydroxyproline residue and eighteen derivatives exhibited toxicity against *P. falciparum*. Of these agents, compound **23e** was shown to have potent antimalarial activity with IC₅₀ 528 ng/mL.

Supporting Information

NMR spectra of obtained compounds.

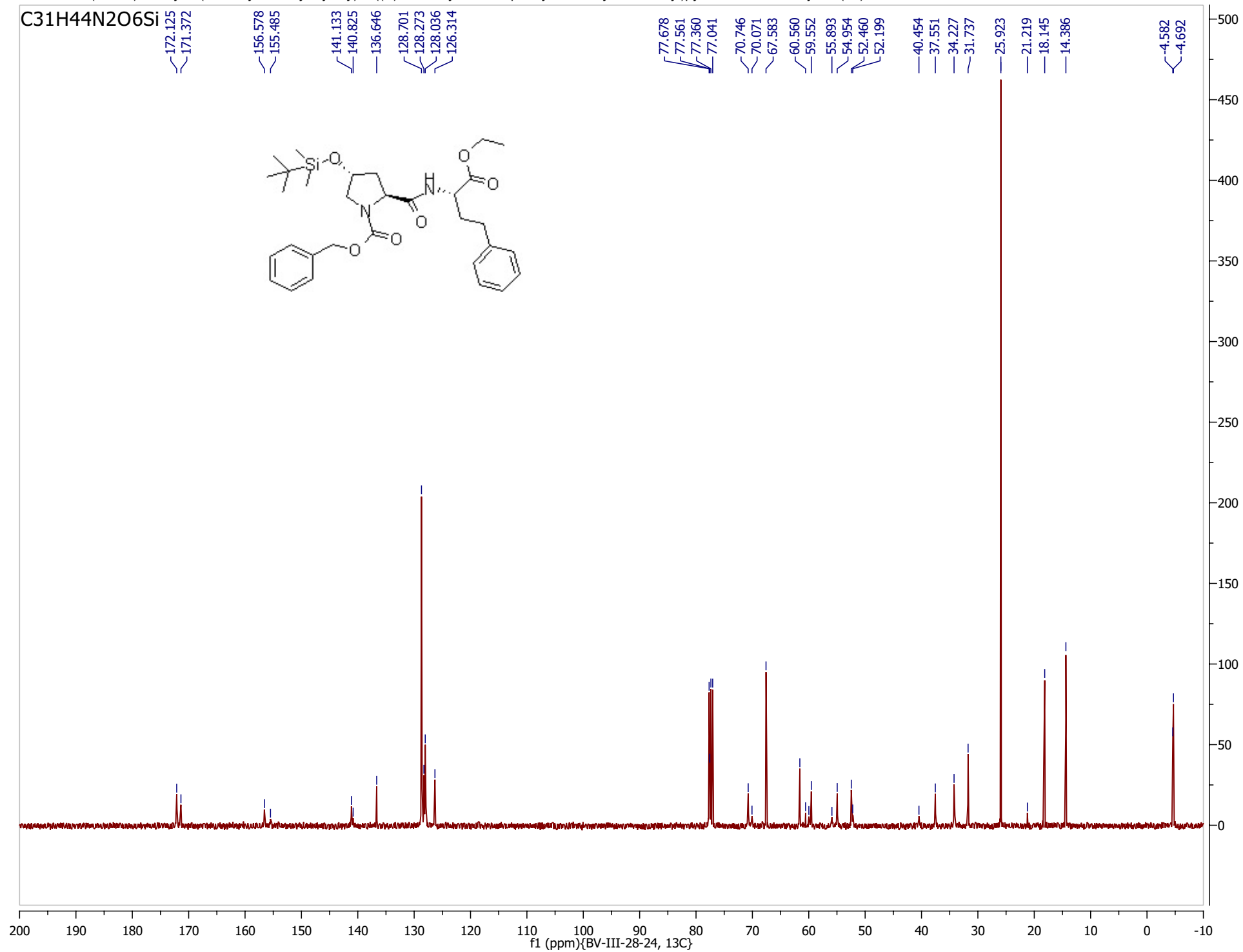
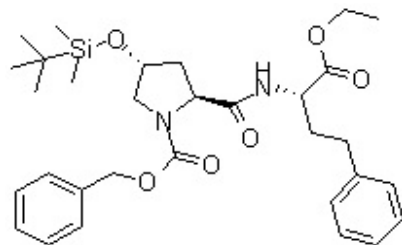
¹H NMR and ¹³C NMR spectra were determined on Bruker 400 MHz spectrometer in CDCl₃ or DMSO-d₆ solution at 25 °C. Chemical shifts (δ) were expressed in ppm downfield from internal standard TMS.

(2S,4R)-Benzyl 4-(tert-butylidimethylsilyloxy)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (16)



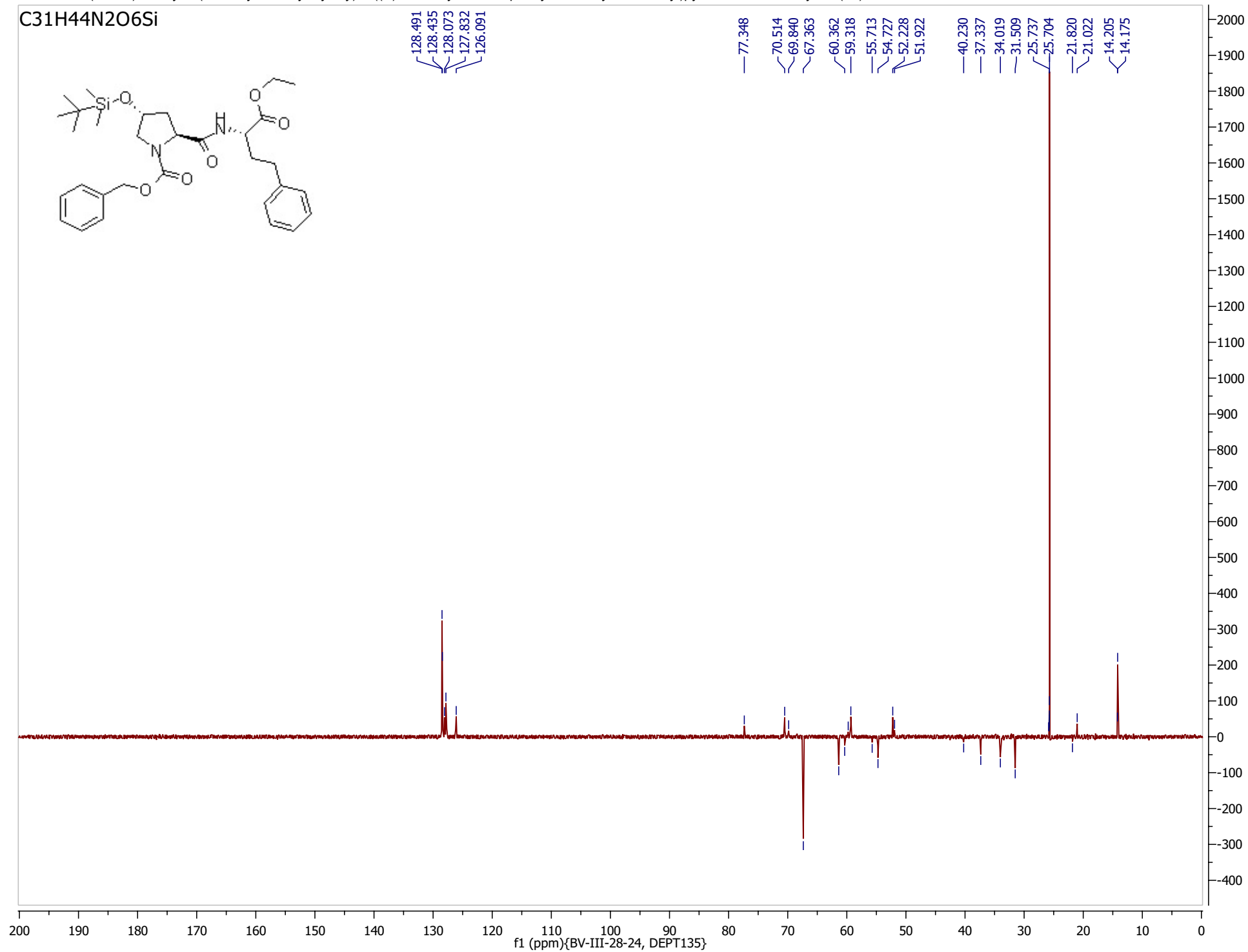
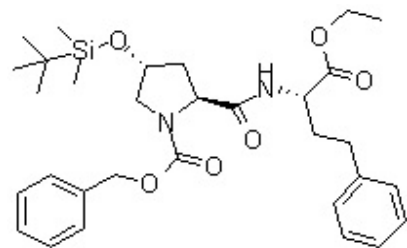
(2S,4R)-Benzyl 4-(tert-butyl dimethylsilyloxy)-2-((S)-1-ethoxy-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (16)

C31H44N2O6Si

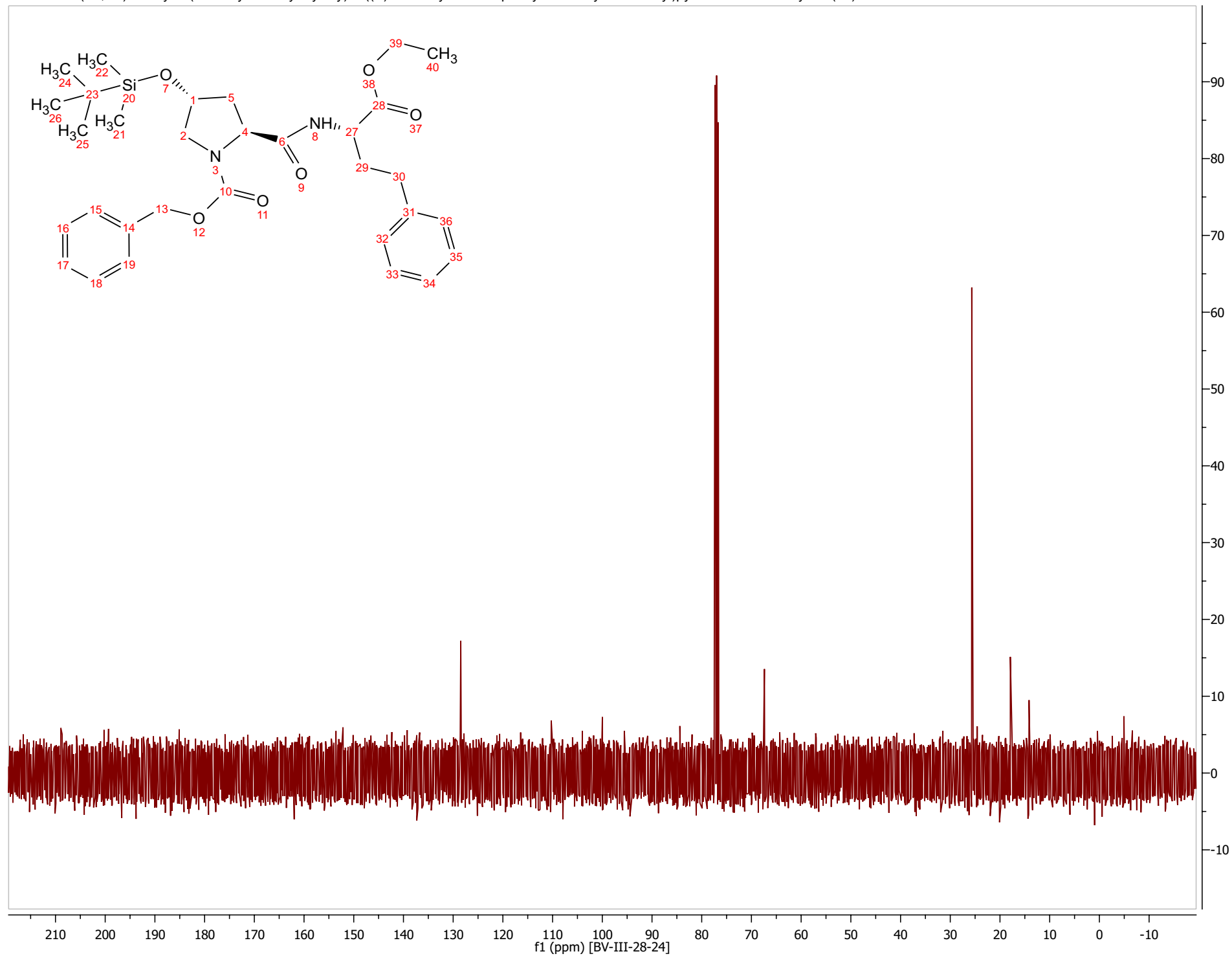


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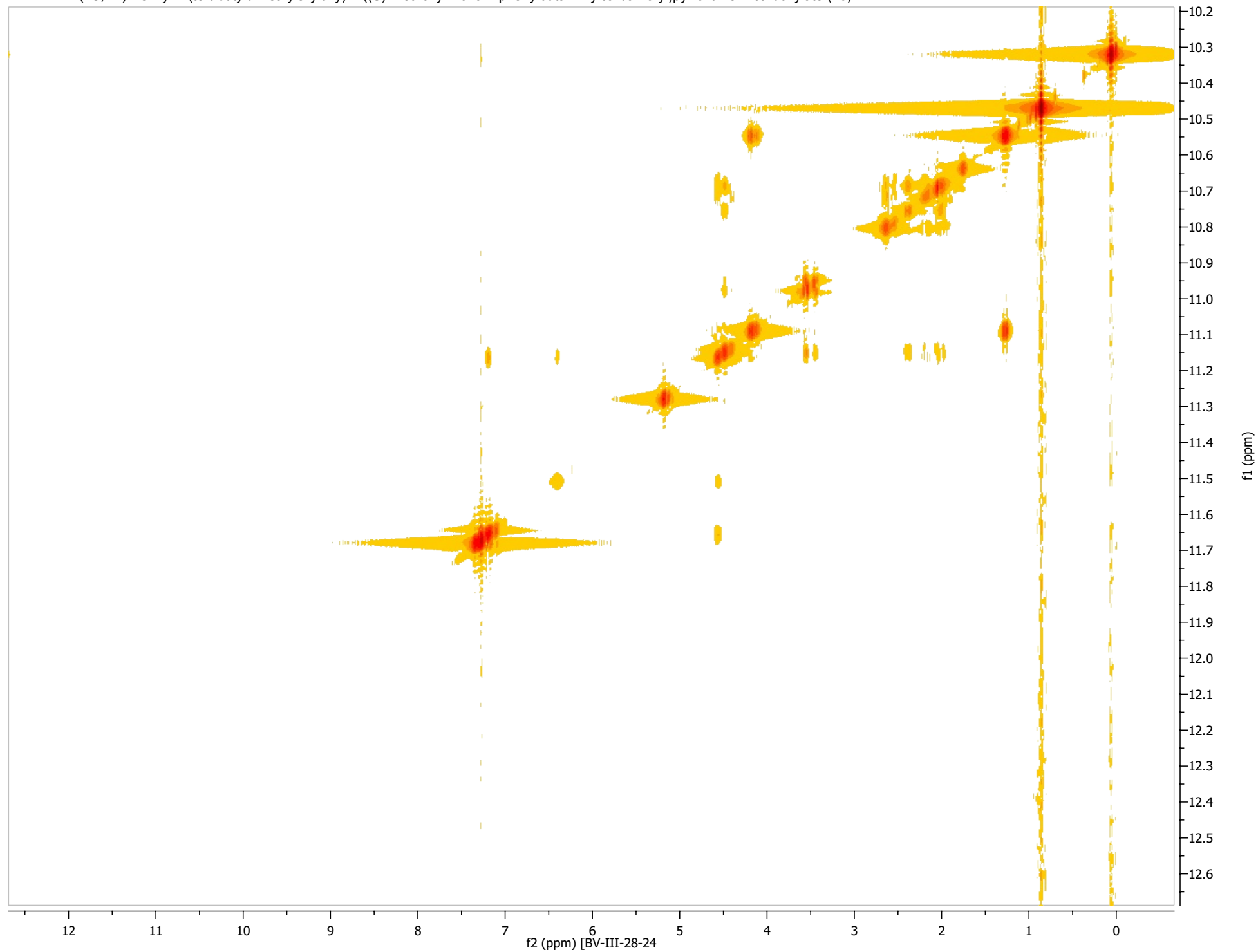
C₃₁H₄₄N₂O₆Si



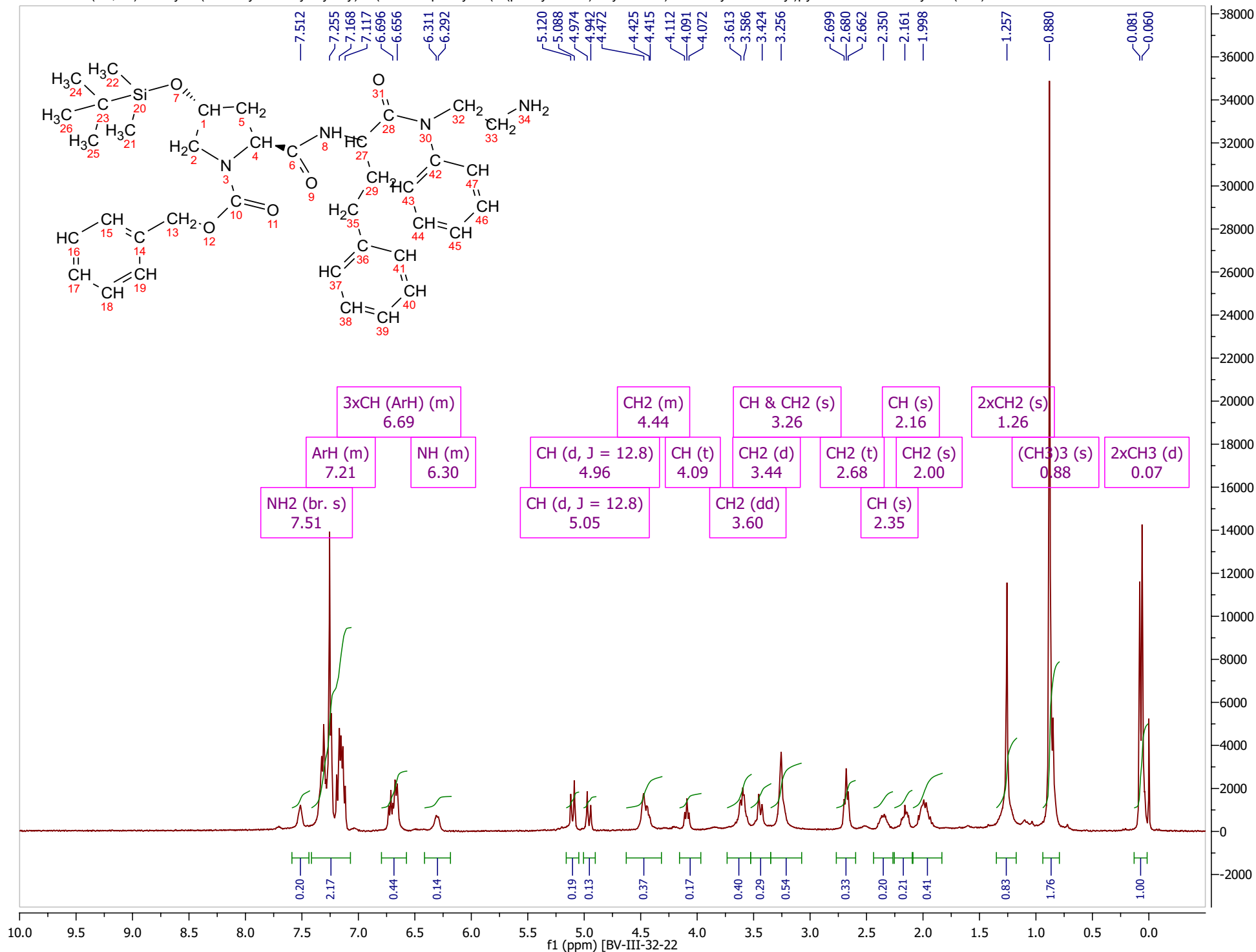
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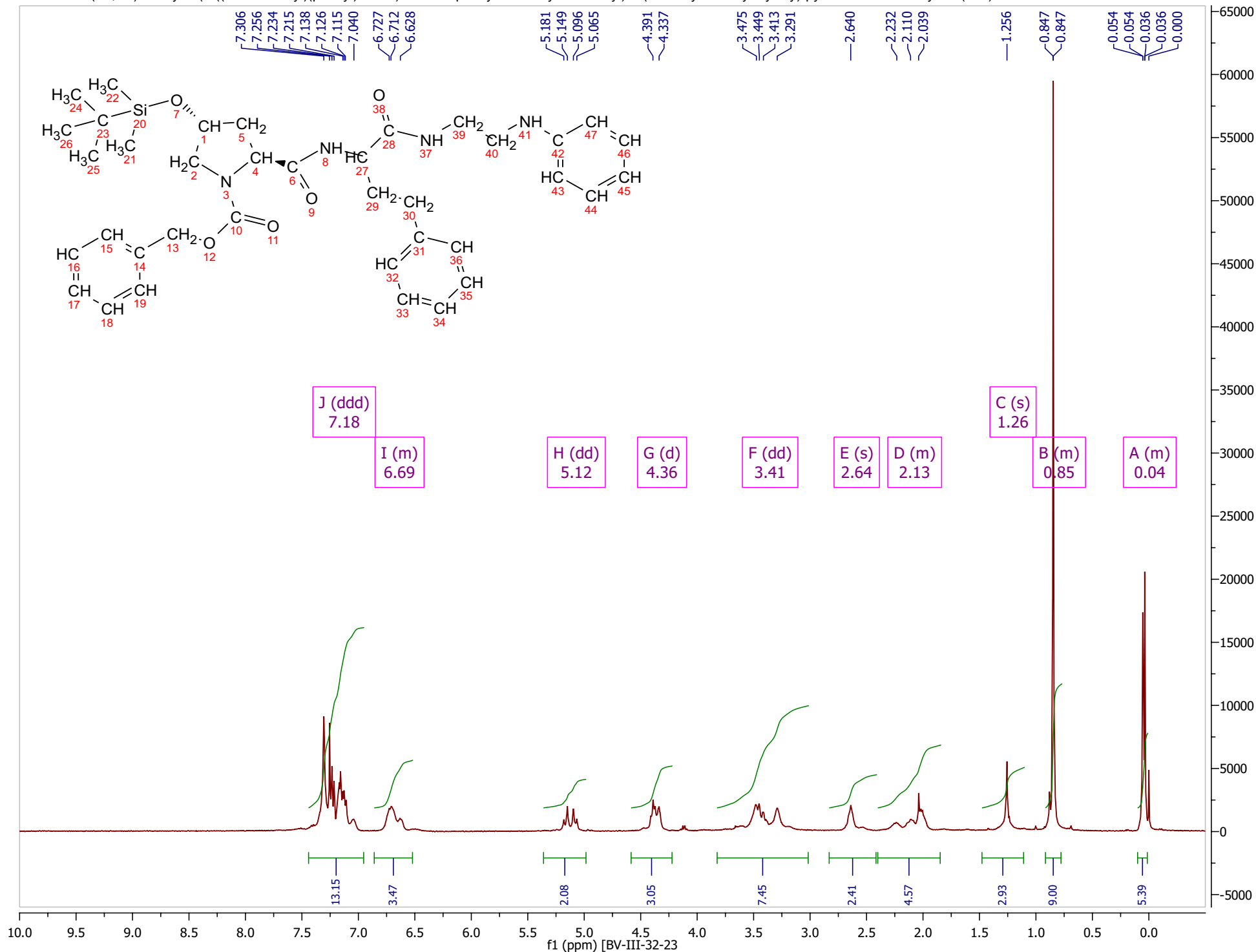
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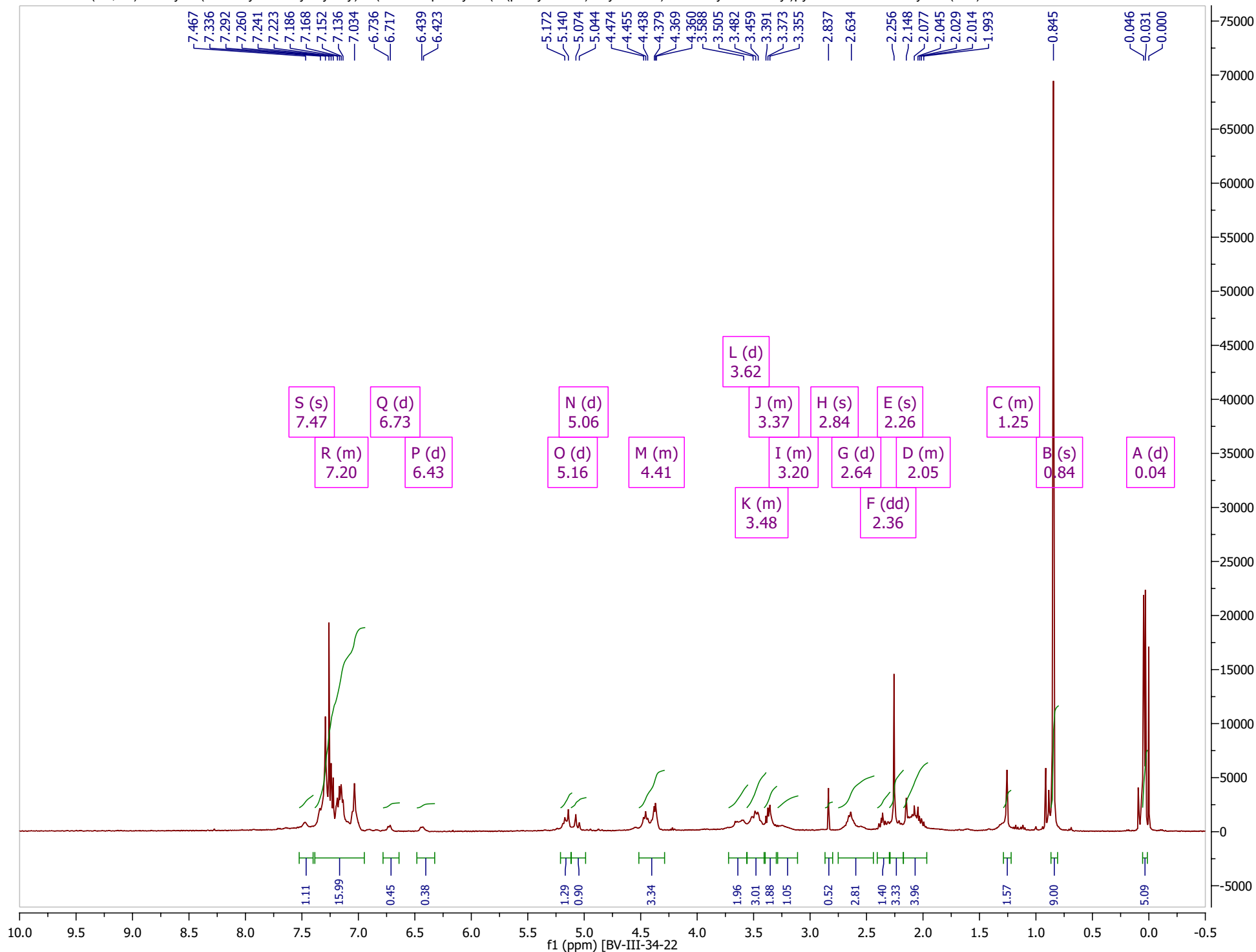
(2S,4R)-Benzyl 4-(tert-butylidimethylsilyloxy)-2-(1-oxo-4-phenyl-1-(2-(phenylamino)ethyl-amino)butan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (19a)



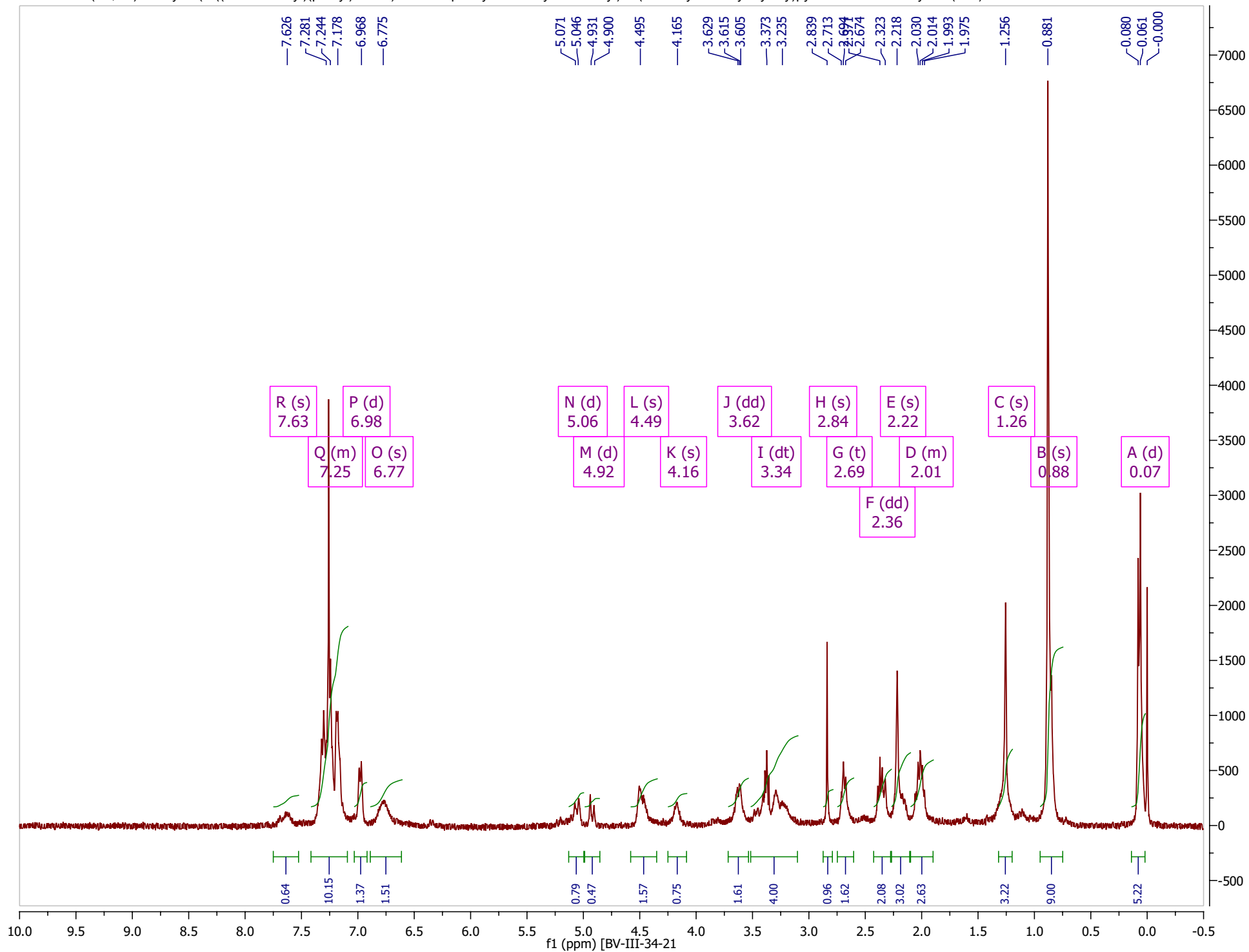
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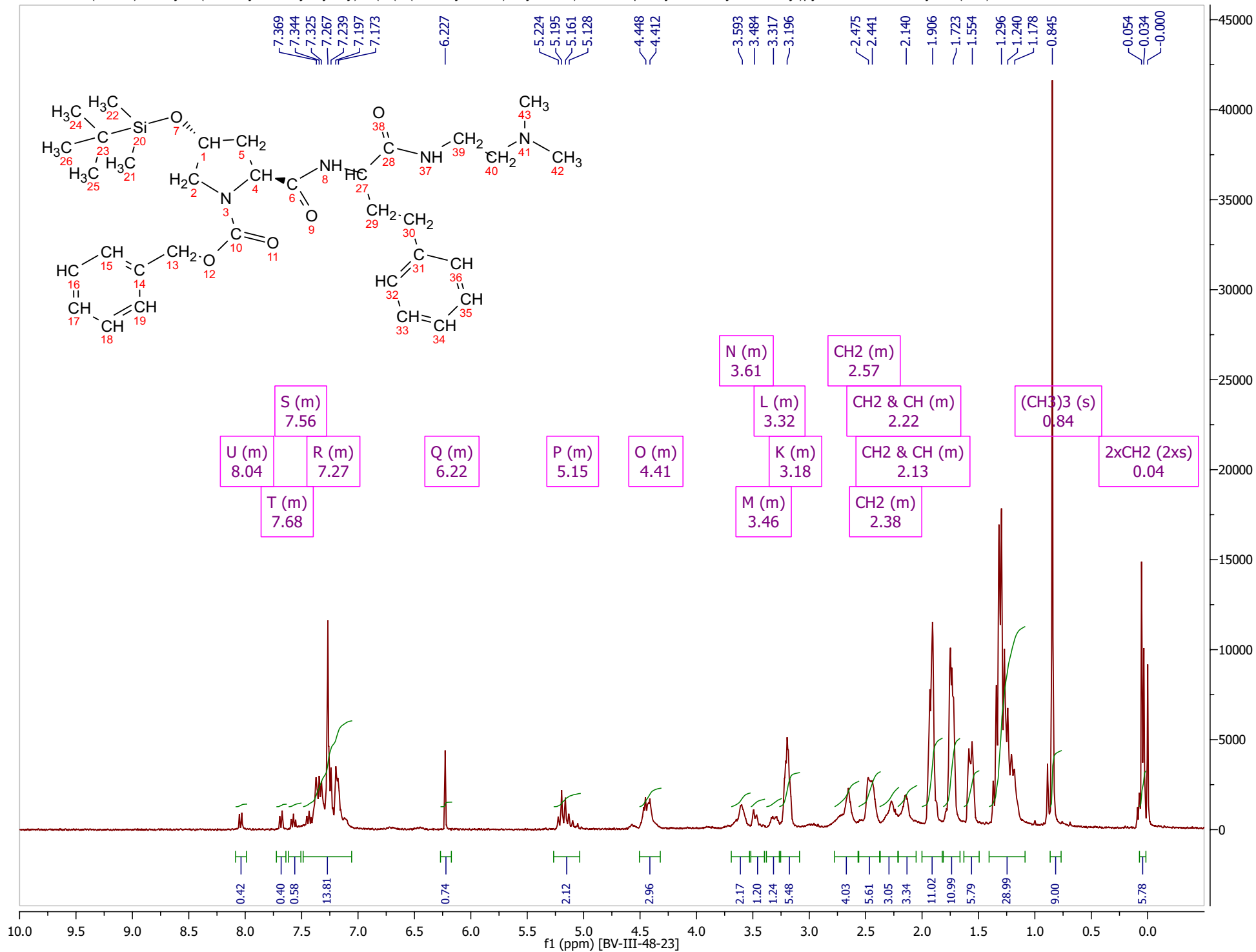
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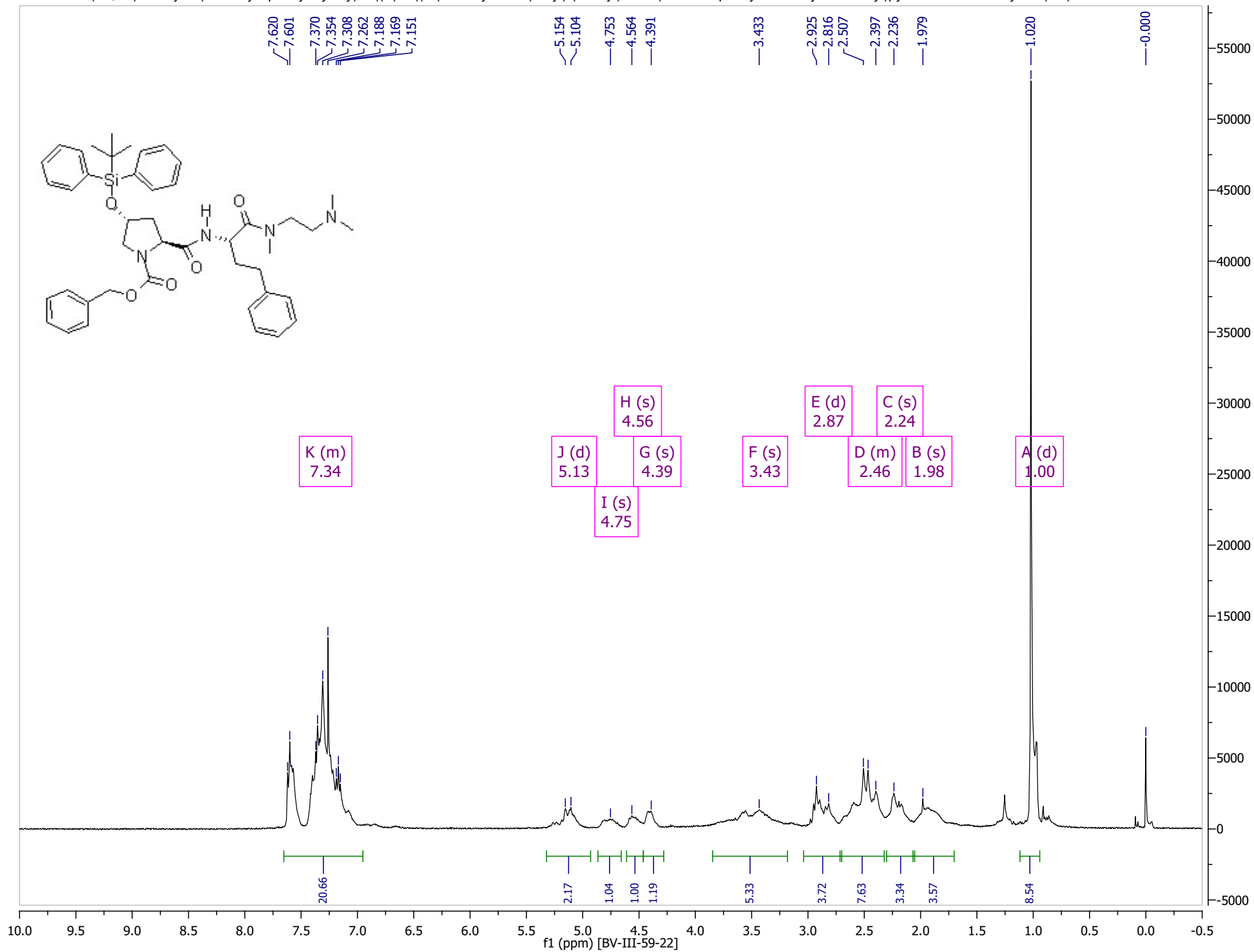
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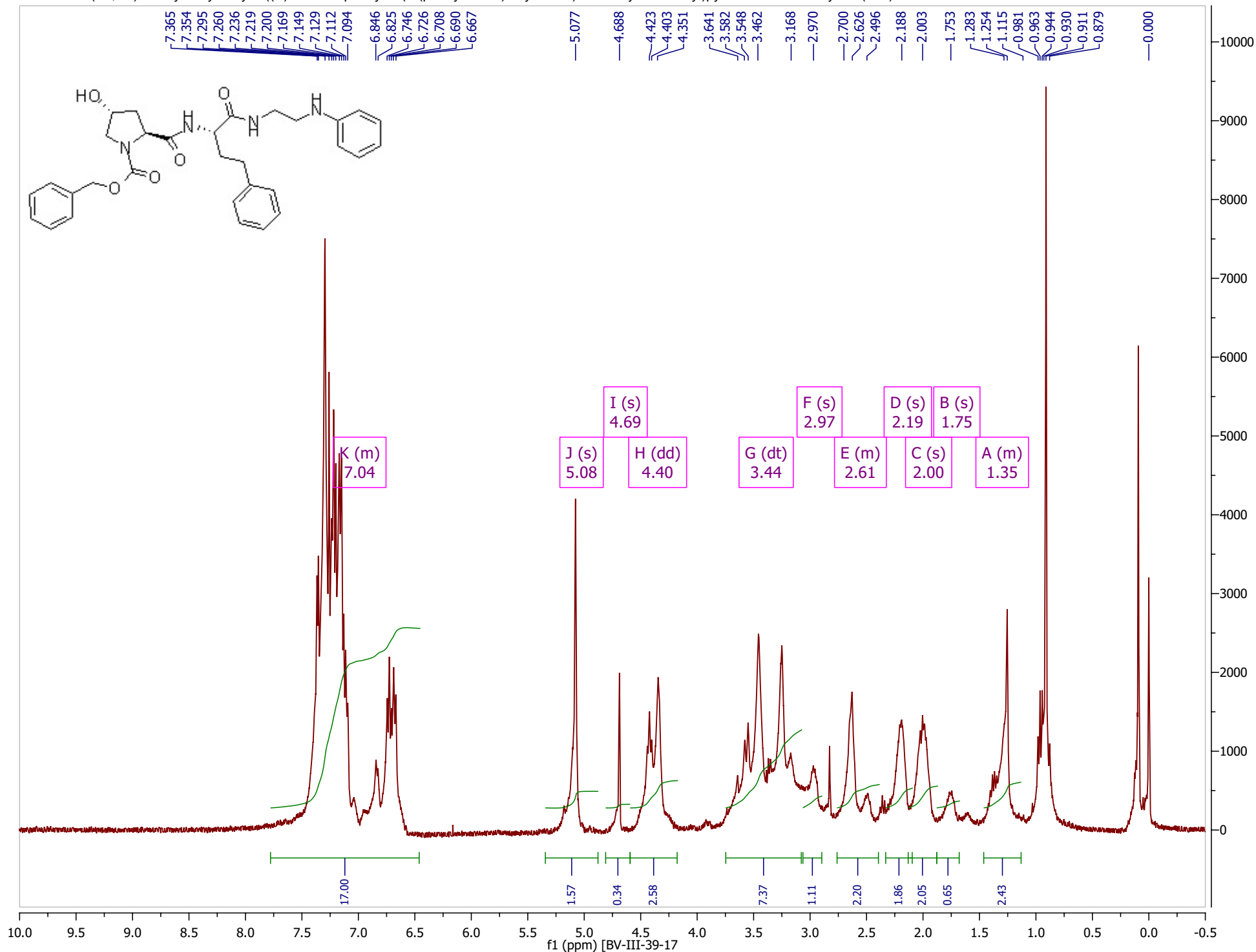
(2S,4R)-Benzyl 4-(tert-butyl(dimethyl)silyloxy)-2-(1-(2-(dimethylamino)ethylamino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (19e)



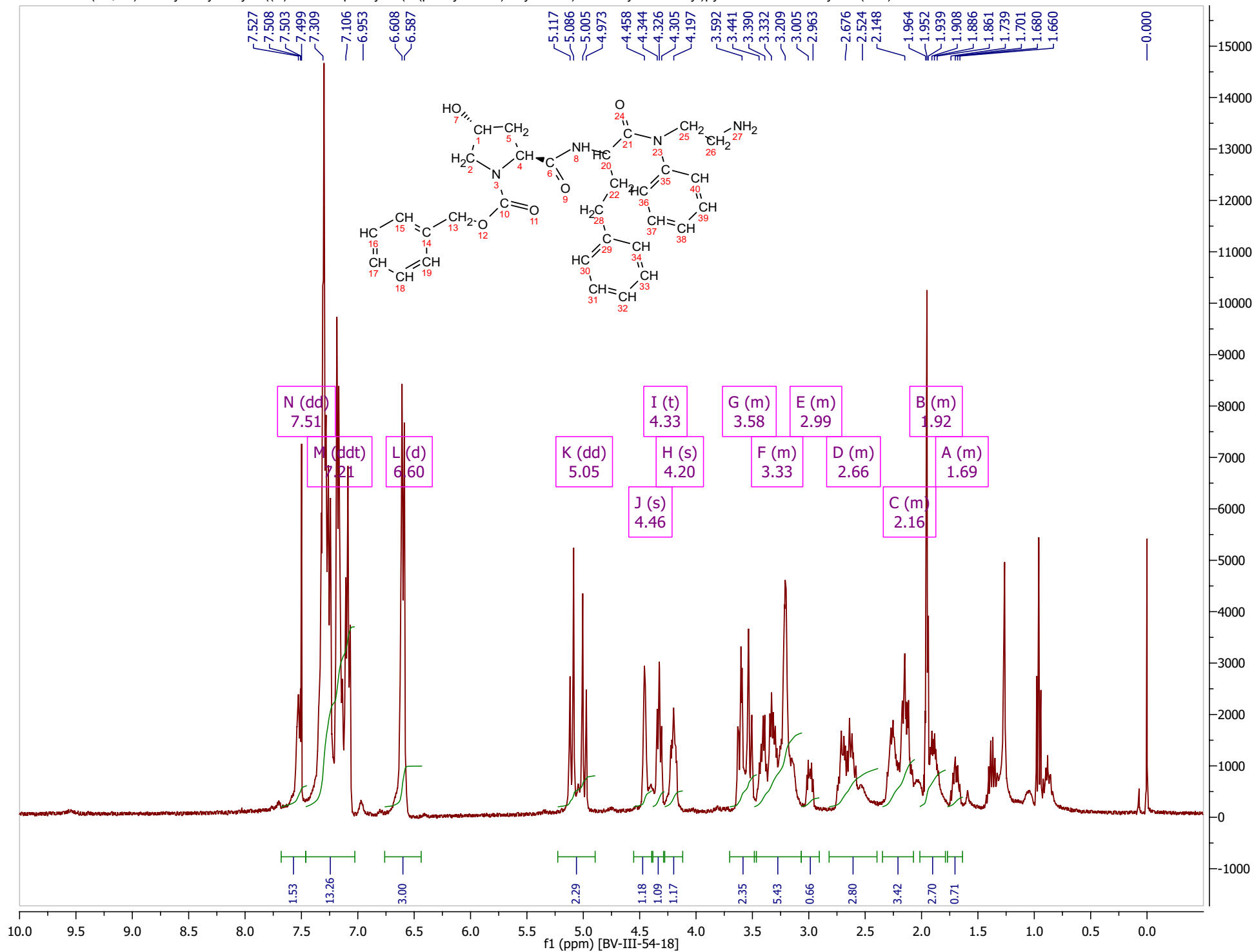
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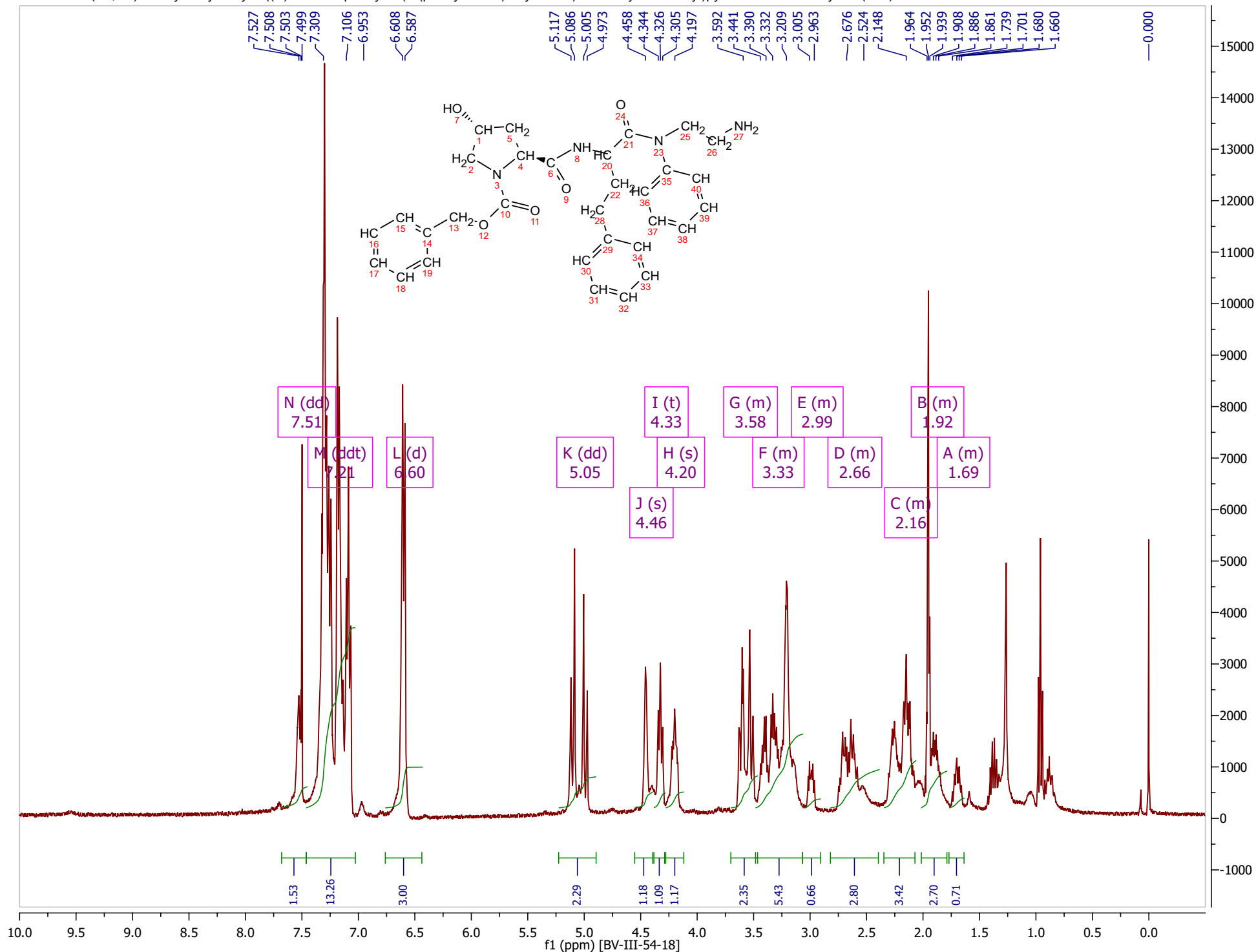
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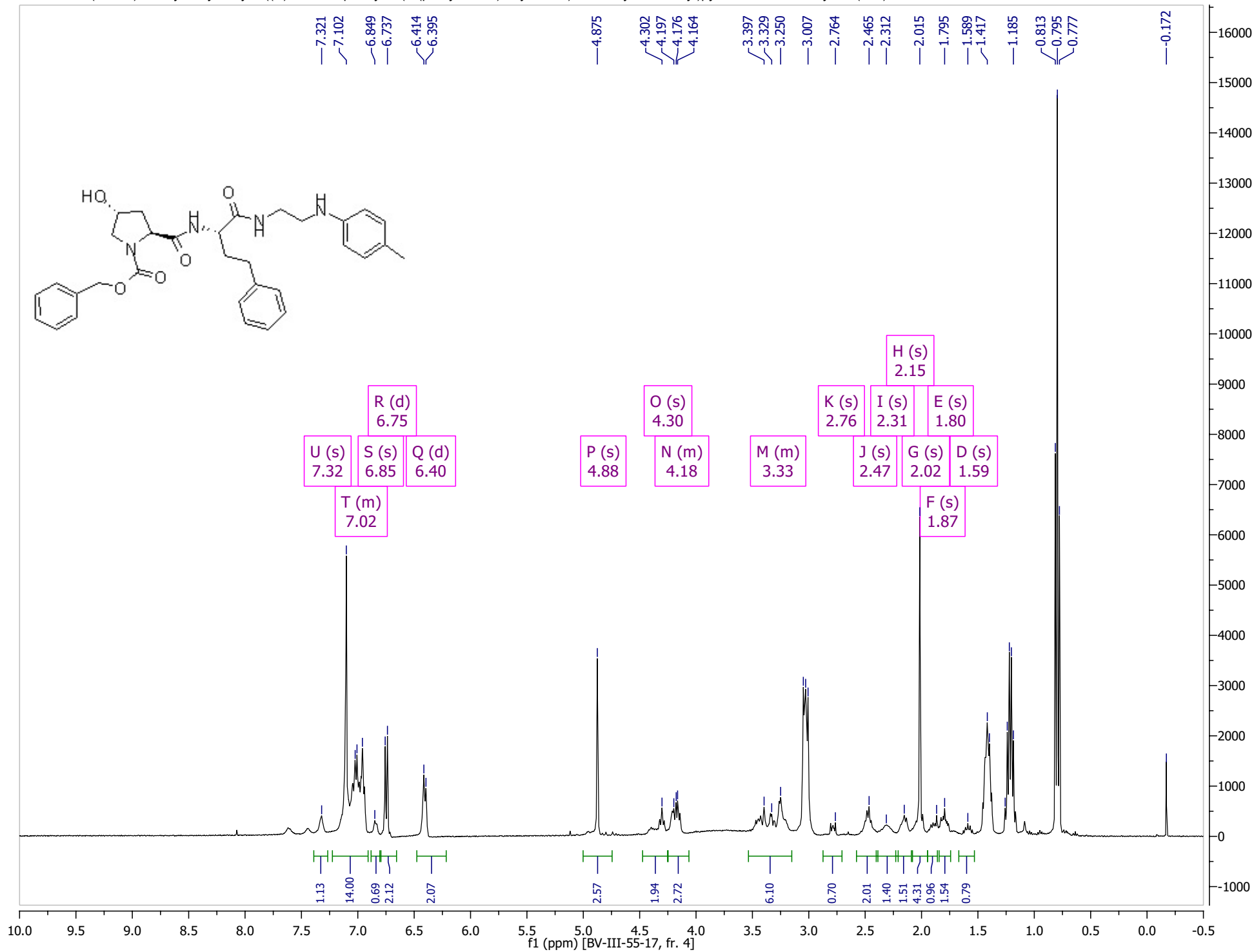
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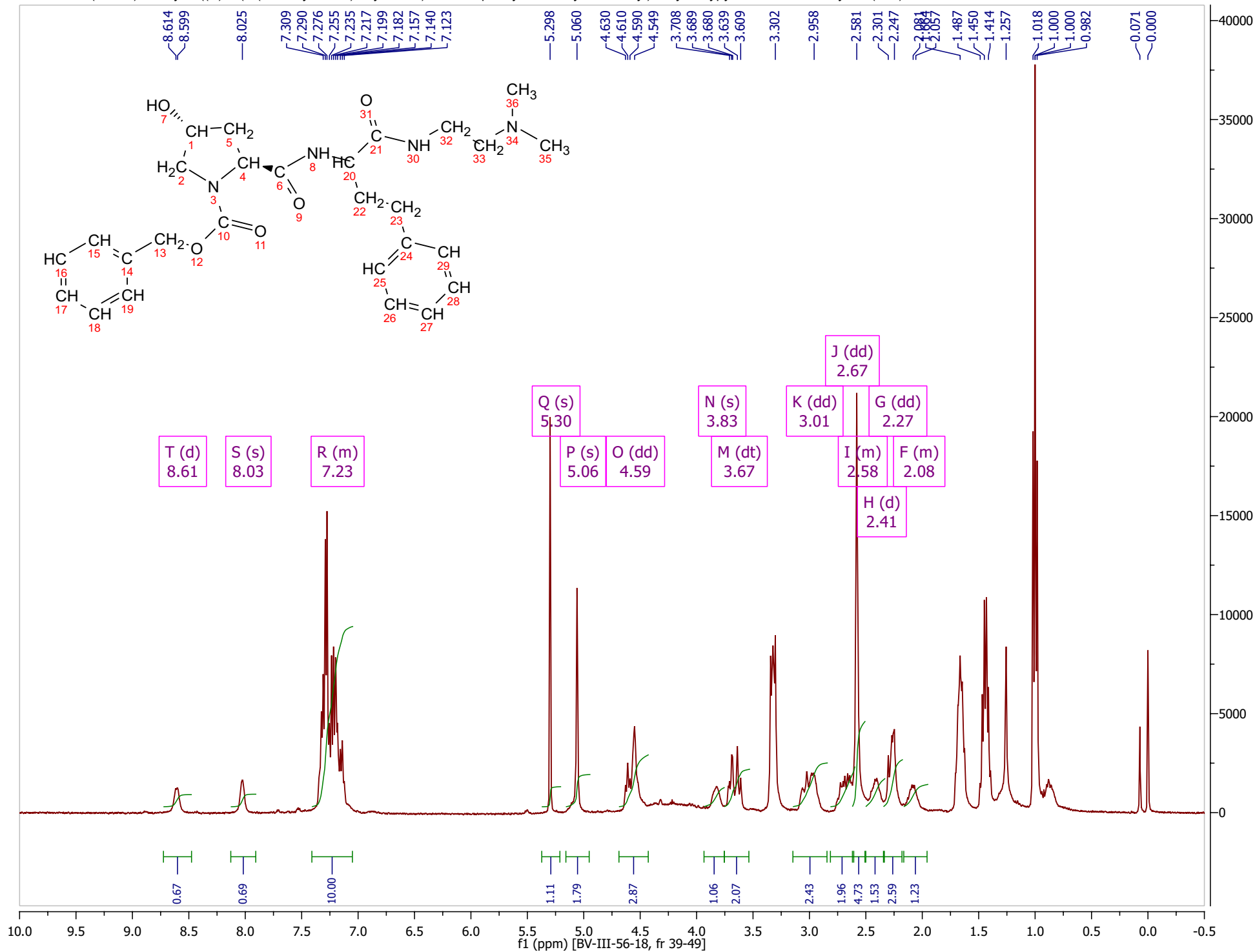
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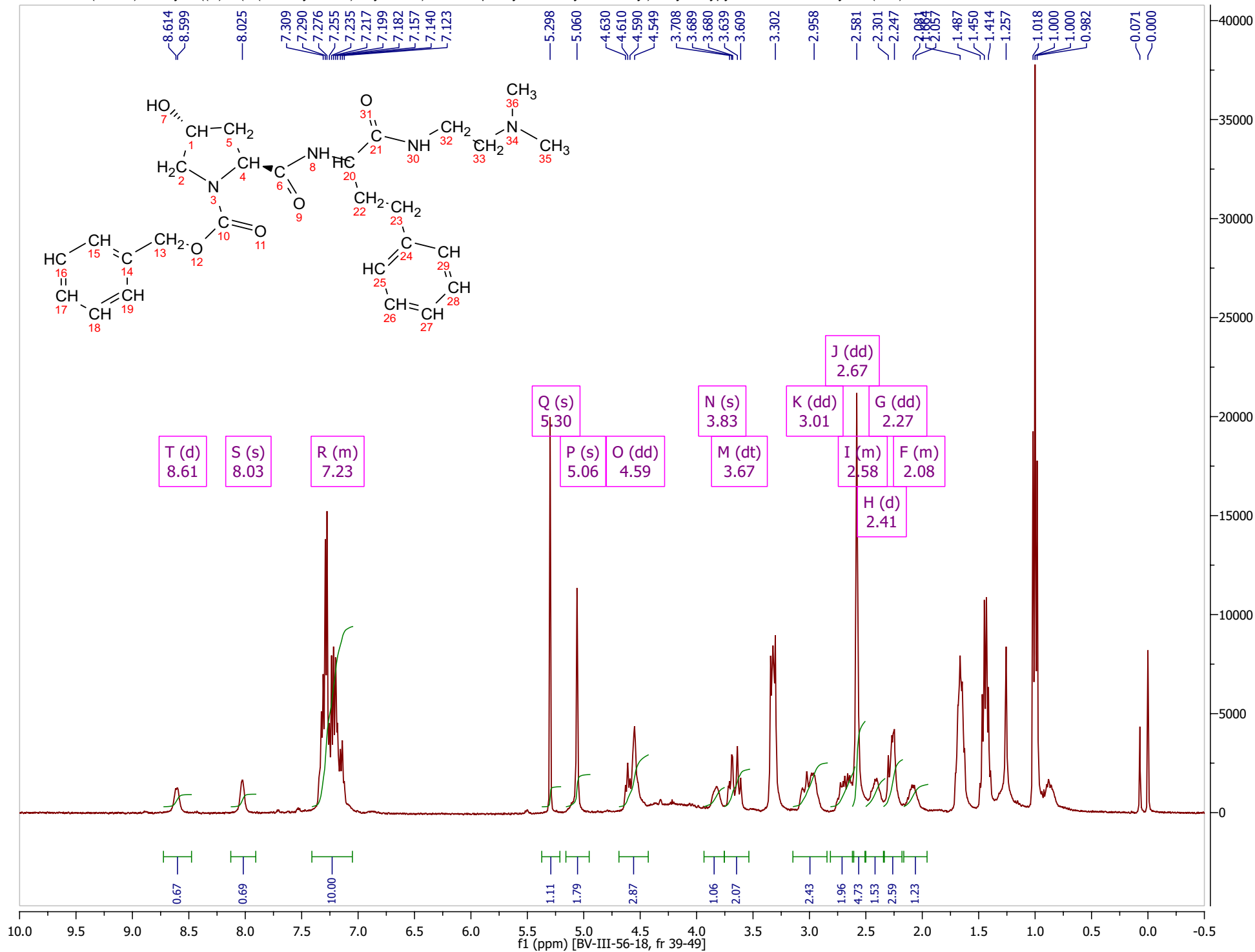
(2S,4R)-Benzyl 4-hydroxy-2-((S)-1-oxo-4-phenyl-1-(2-(p-tolylamino)ethylamino)butan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (20c)



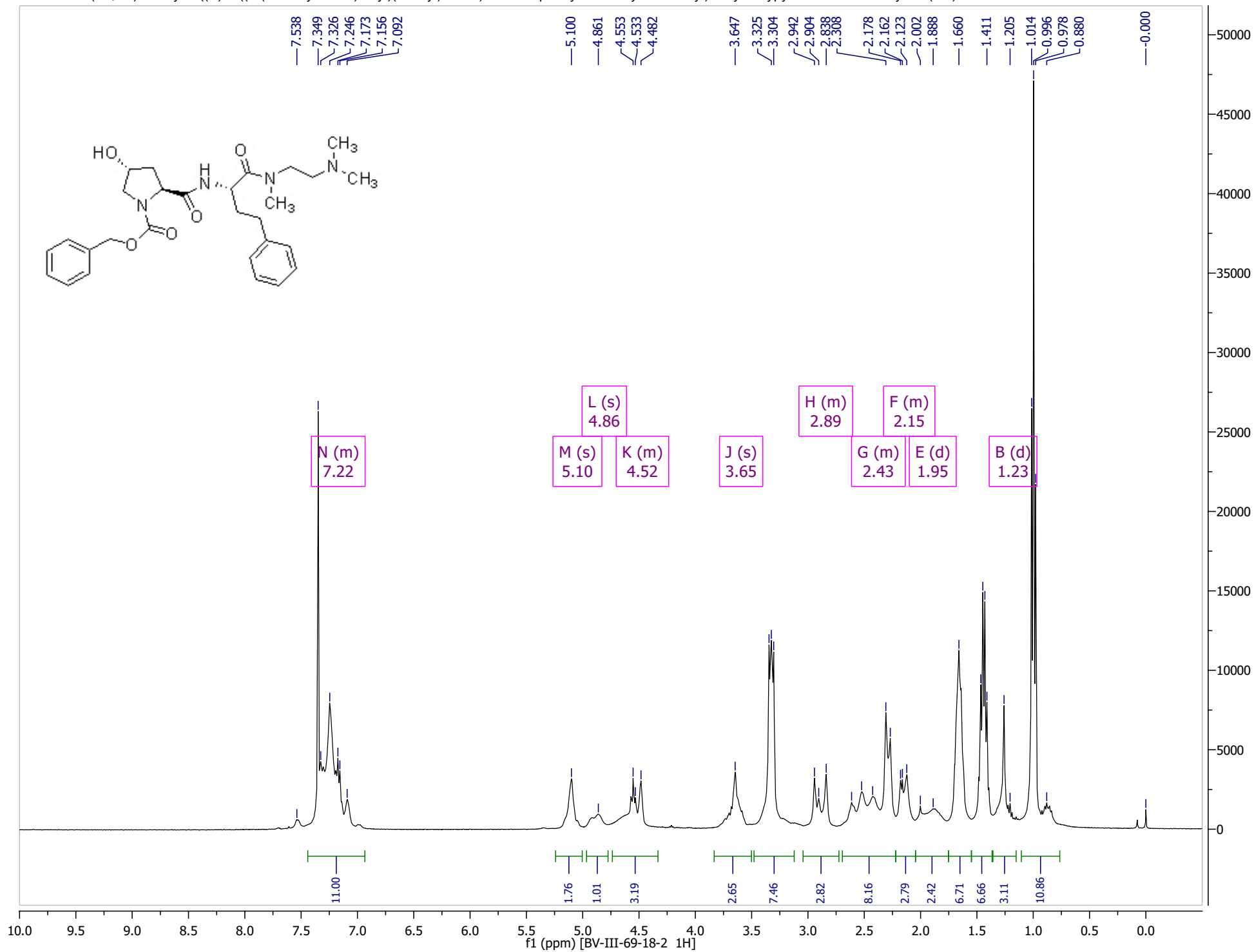
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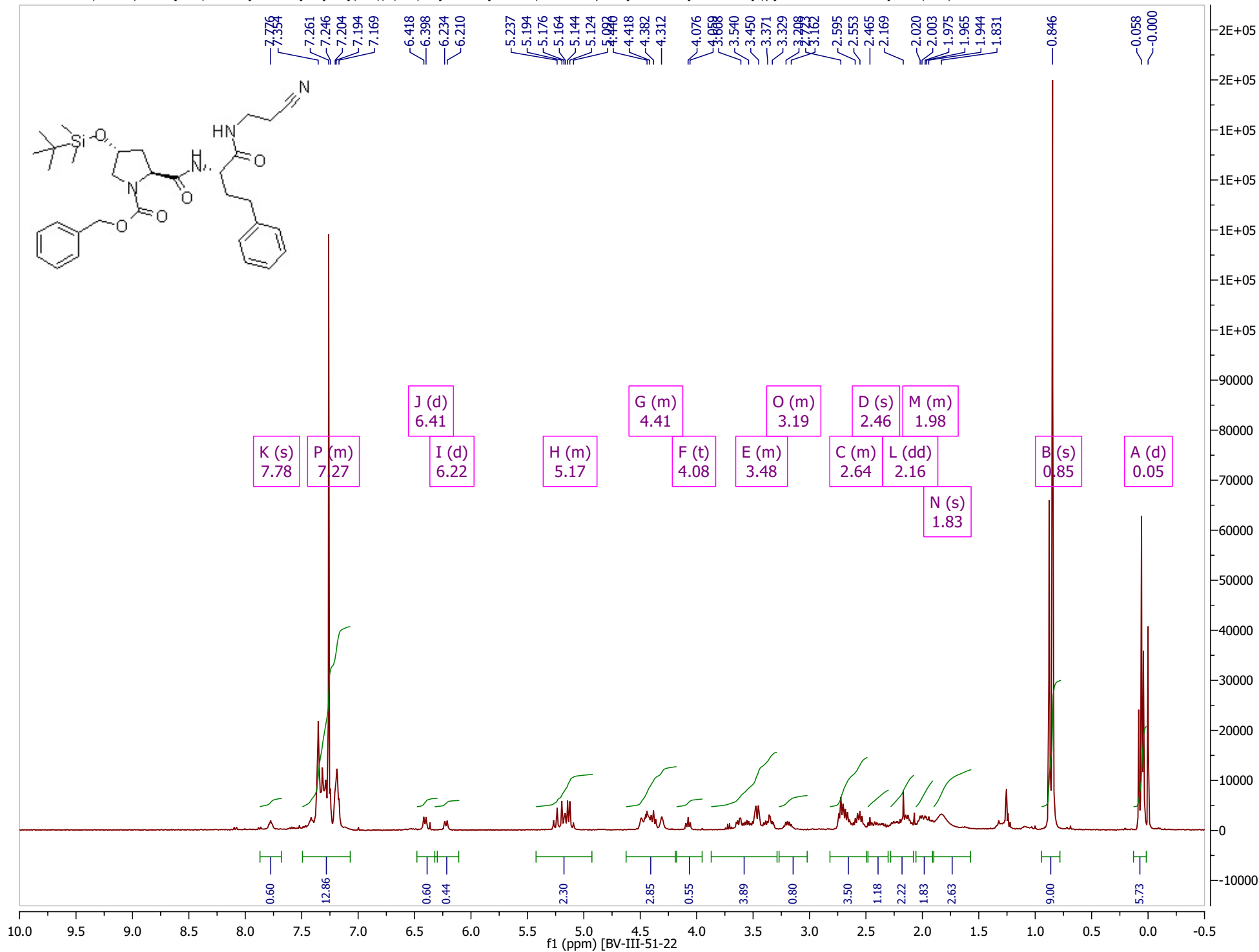
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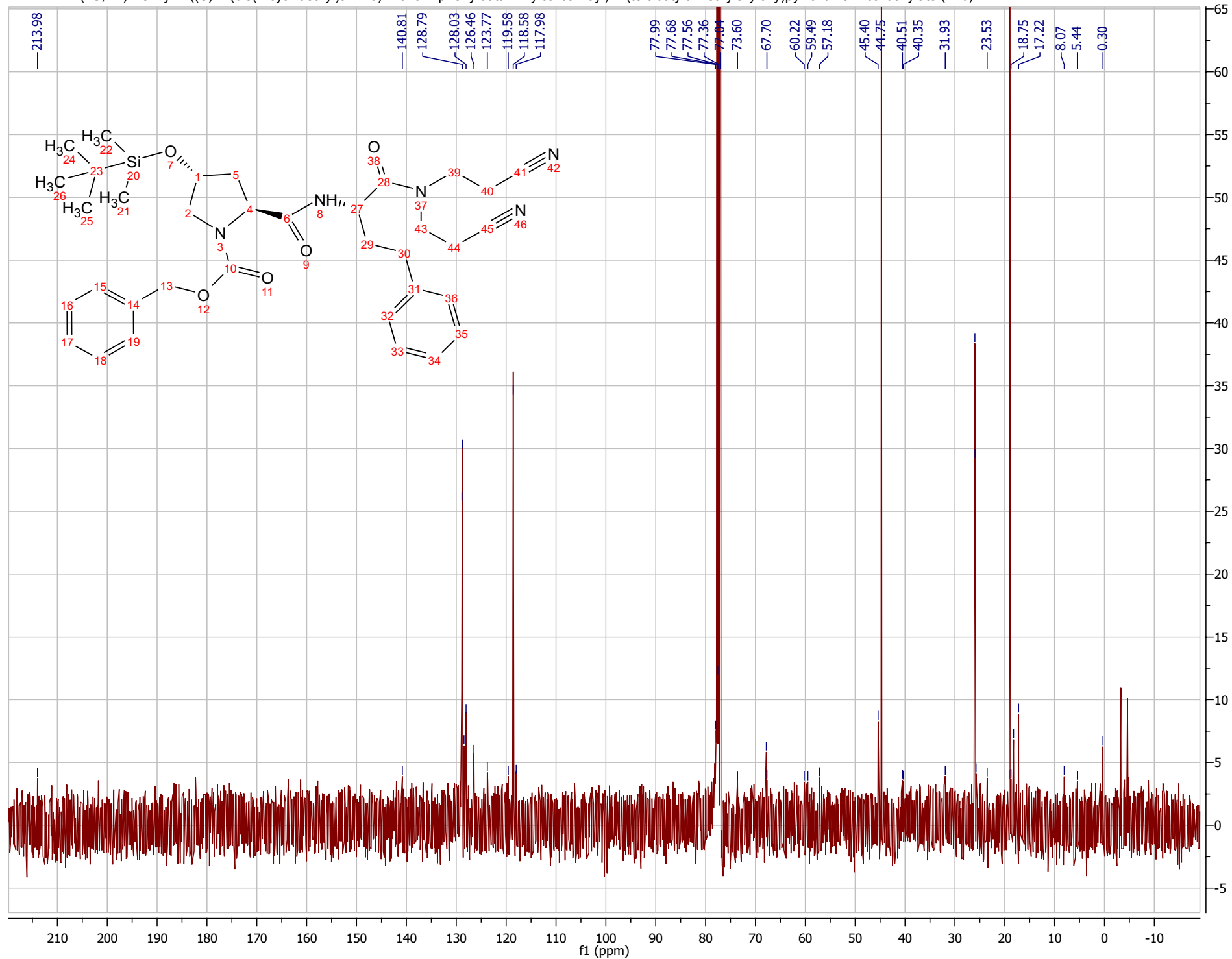
(2S,4R)-Benzyl 2-((S)-1-((2-(dimethylamino)ethyl)(methyl)amino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)-4-hydroxypyrrolidine-1-carboxylate (20f)



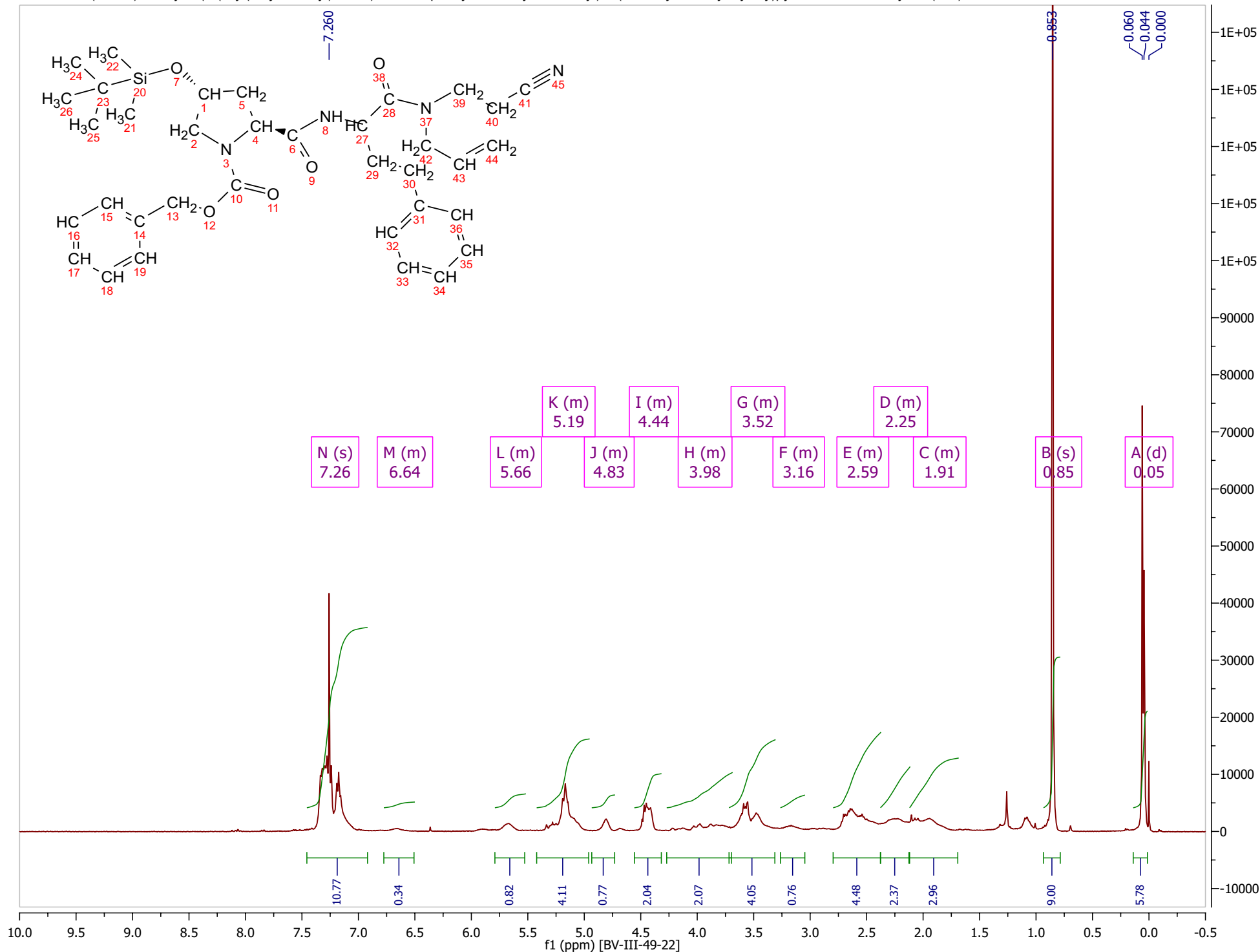
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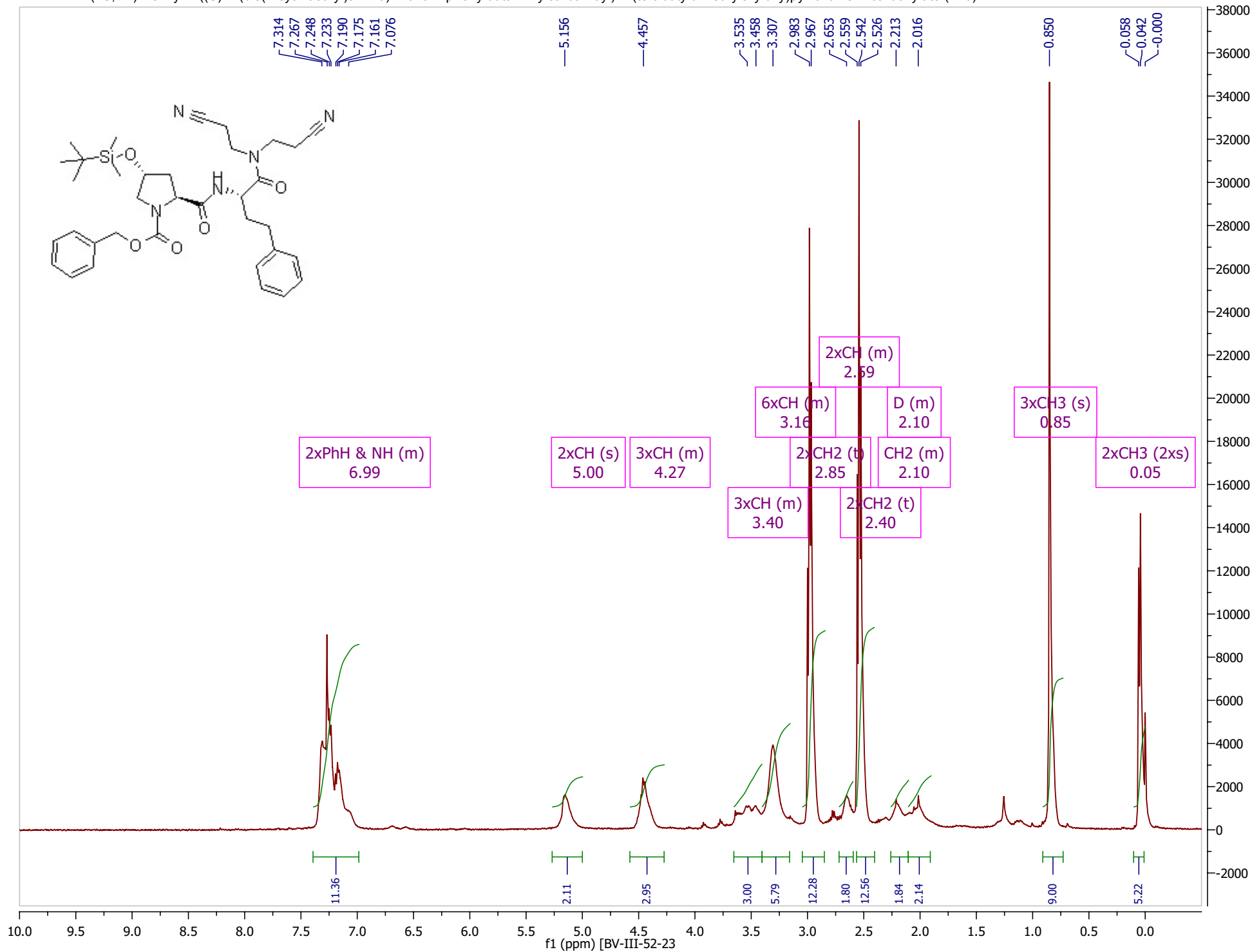
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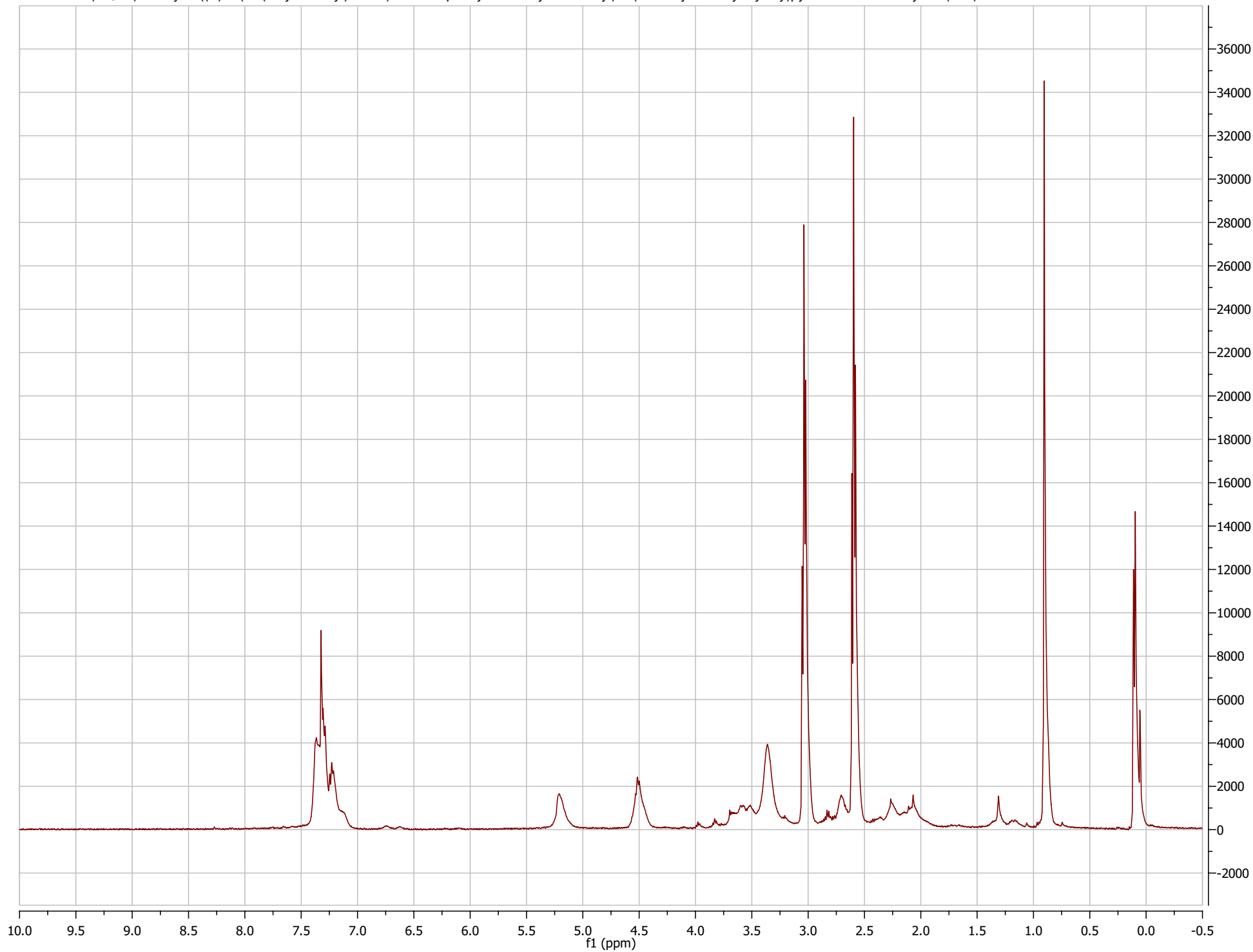
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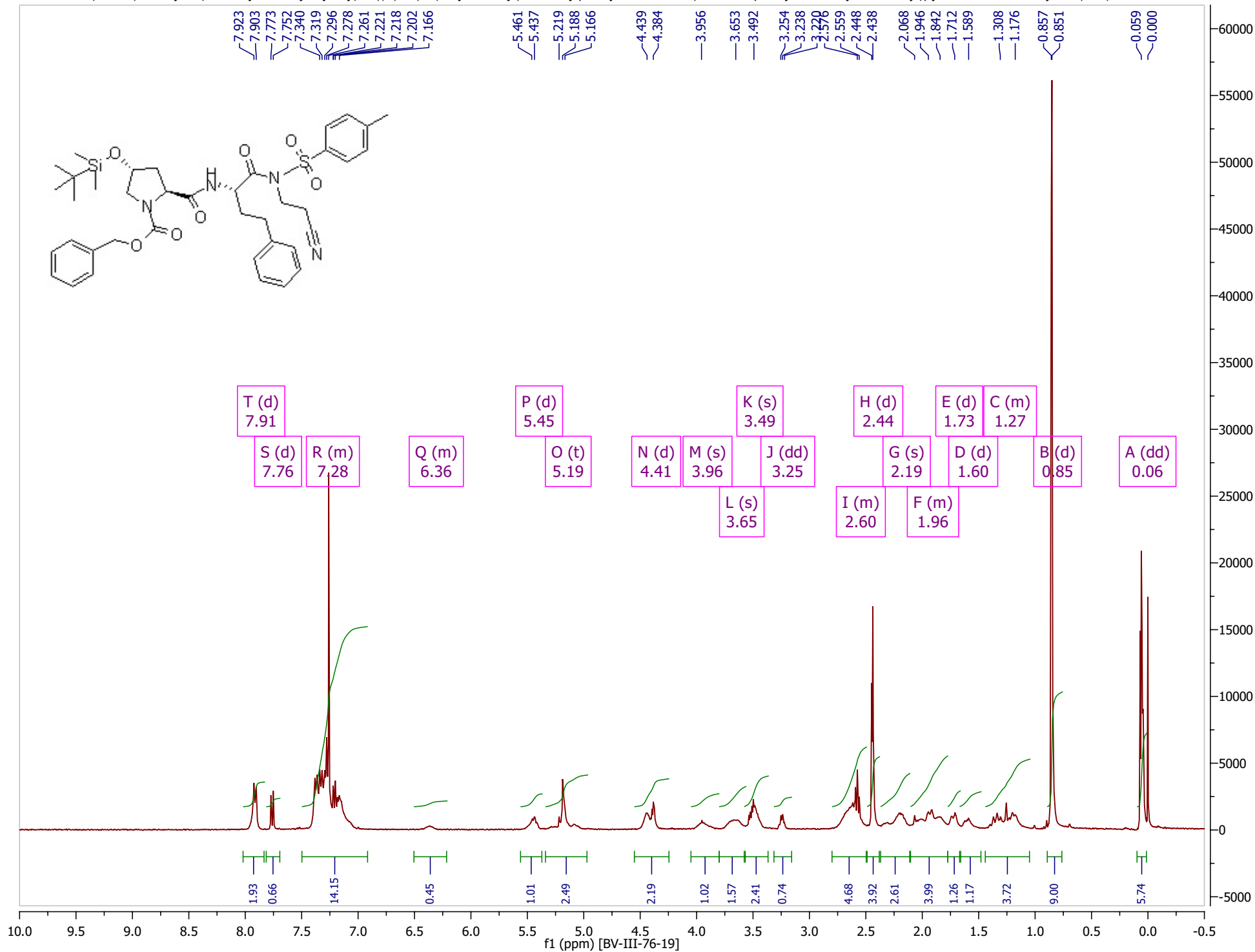
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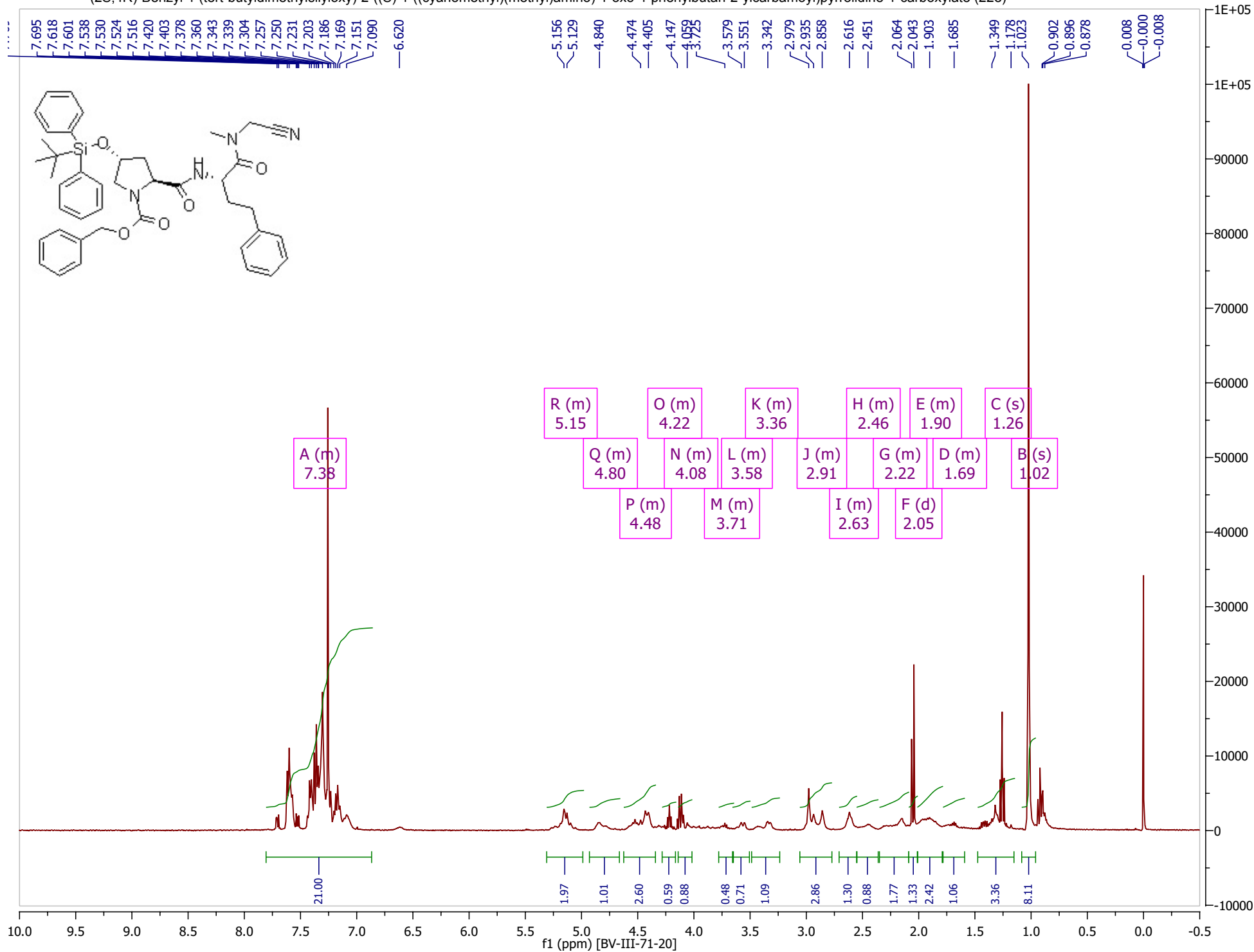
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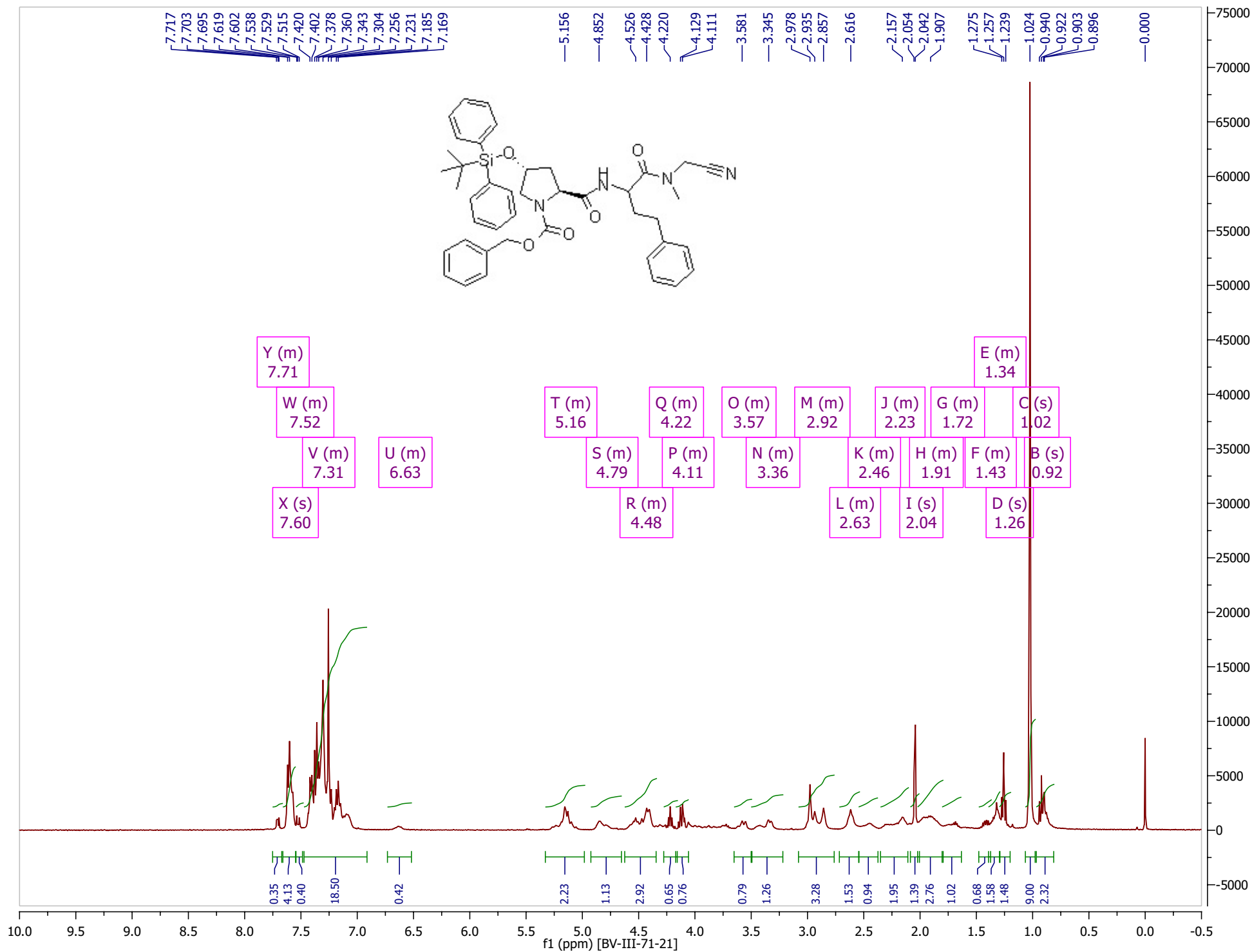
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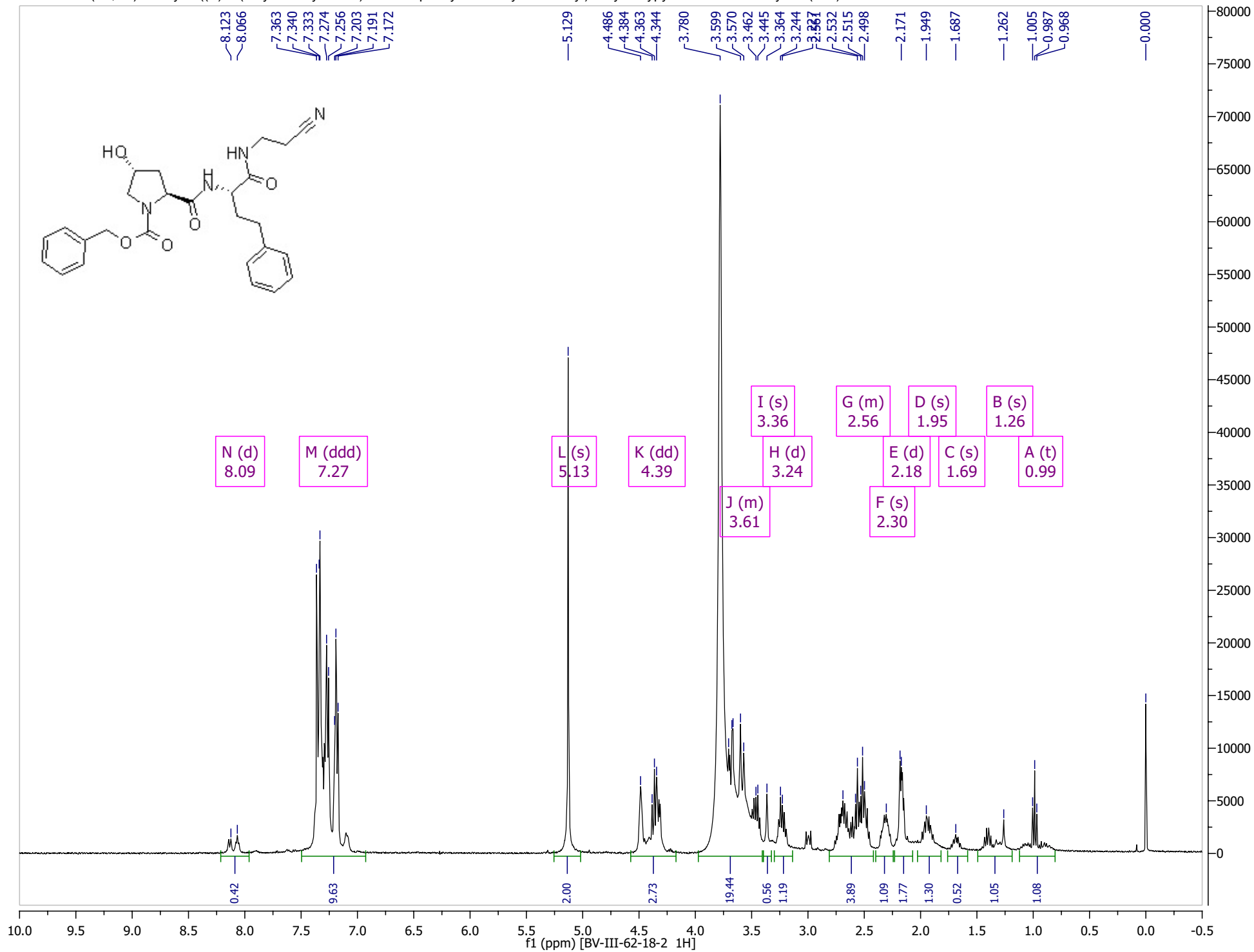
(2S,4R)-Benzyl 4-(tert-butylidimethylsilyloxy)-2-((S)-1-((cyanomethyl)(methyl)amino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (22e)



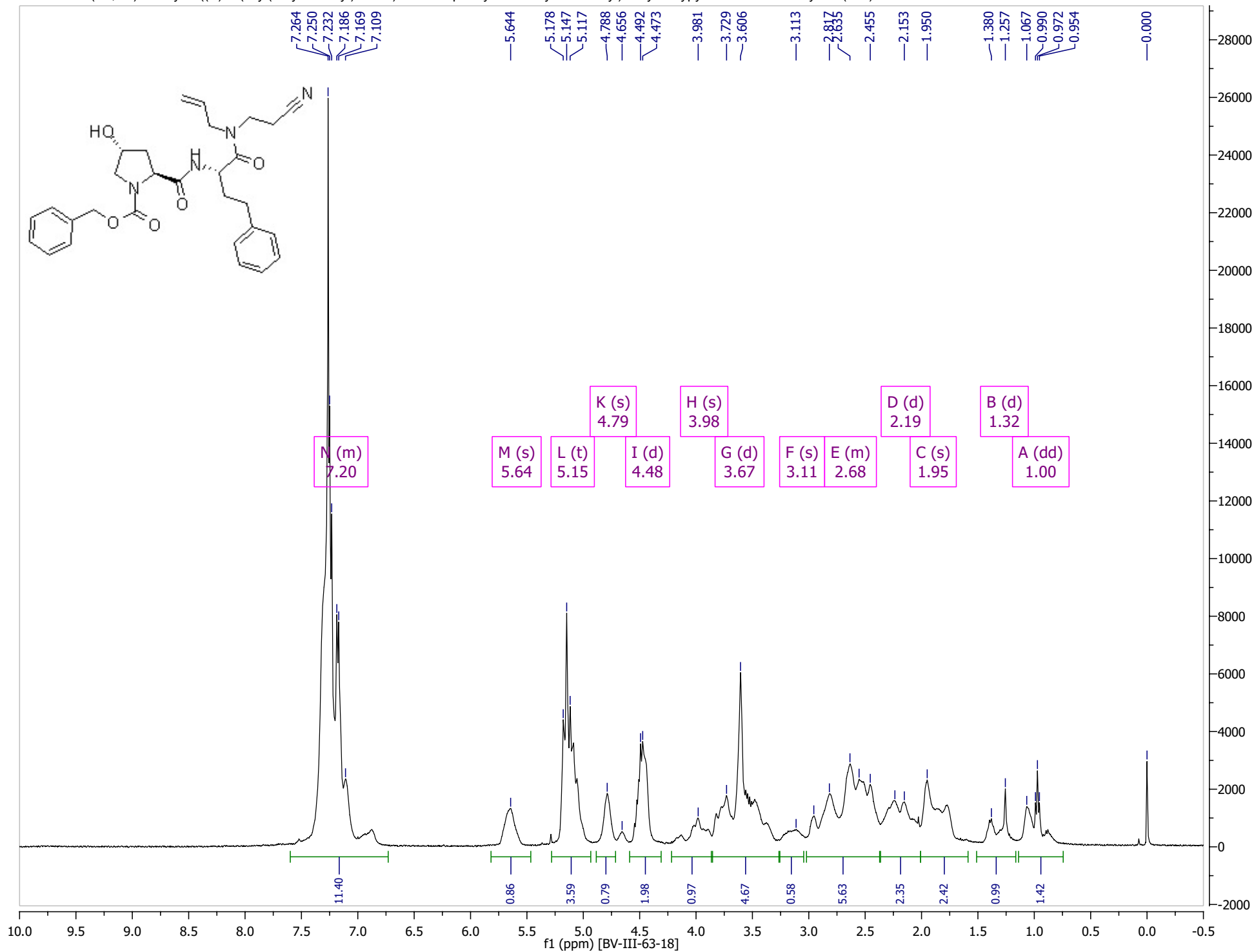
(2S,4R)-benzyl 4-(tert-butylidiphenylsilyloxy)-2-((S)-1-((cyanomethyl)(methyl)amino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (22e)
Chemical Formula: C₄₂H₄₈N₄O₅Si; Exact Mass: 716.3394



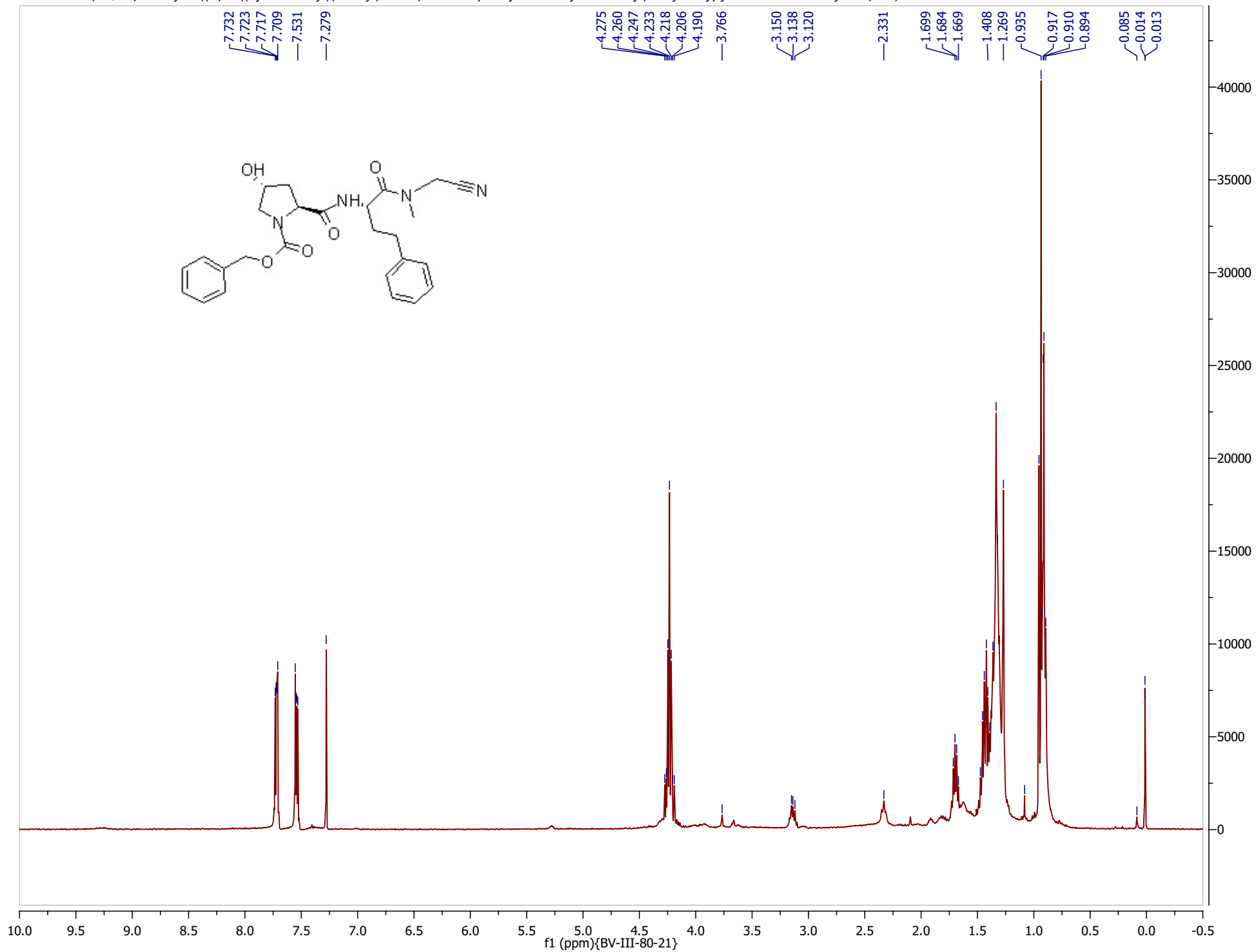
(2S,4R)-Benzyl 2-((S)-1-(2-cyanoethylamino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)-4-hydroxypyrrolidine-1-carboxylate (23a)



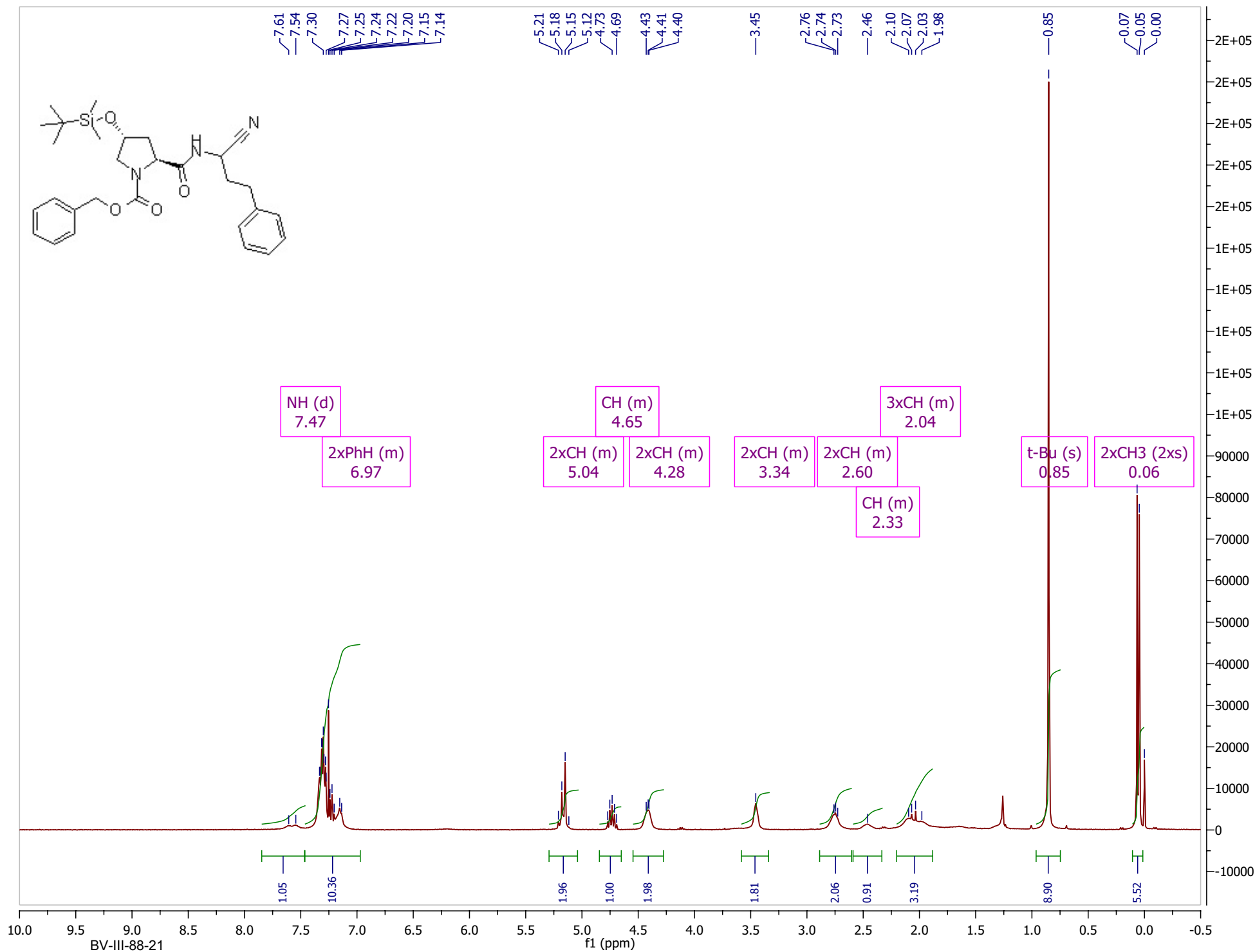
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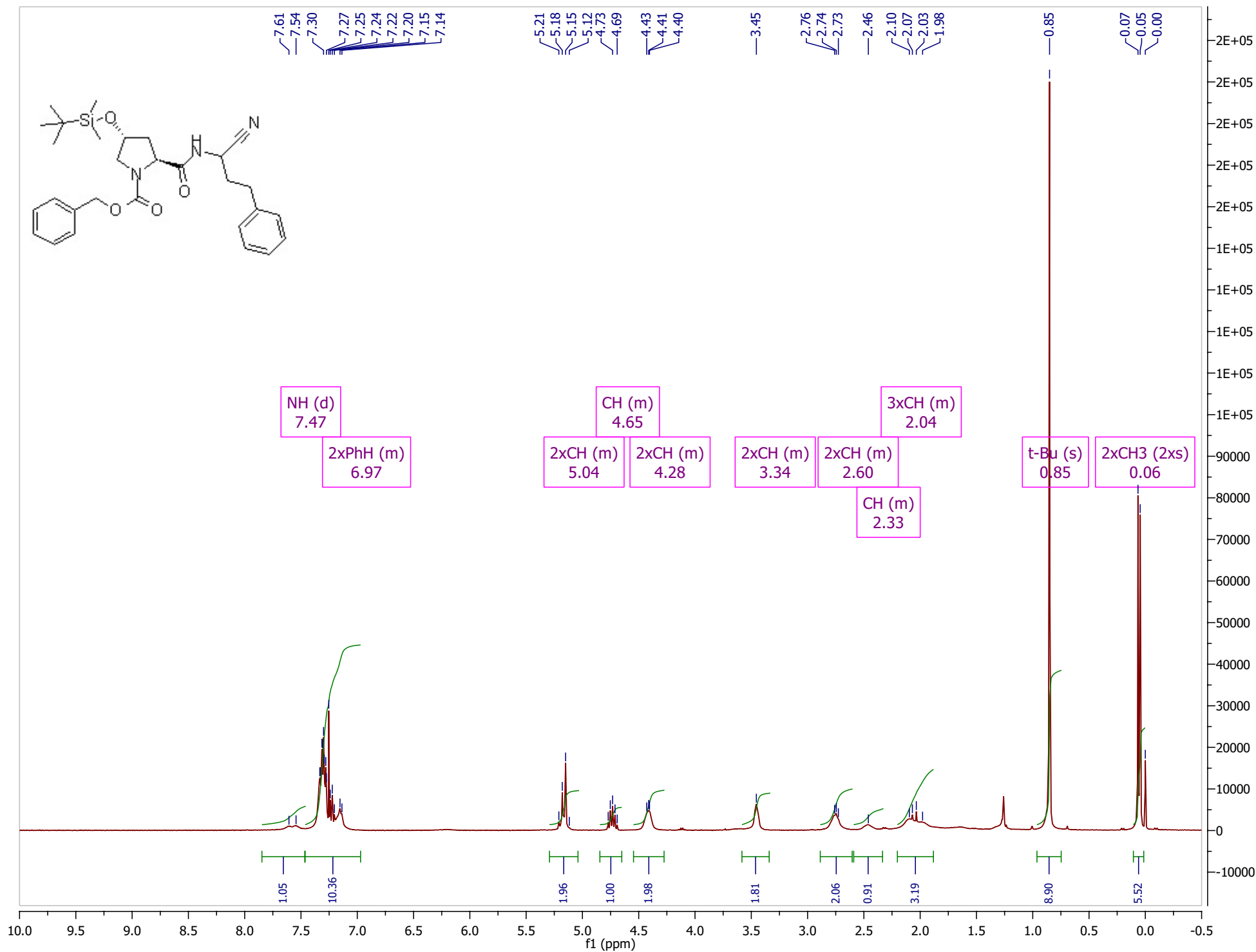
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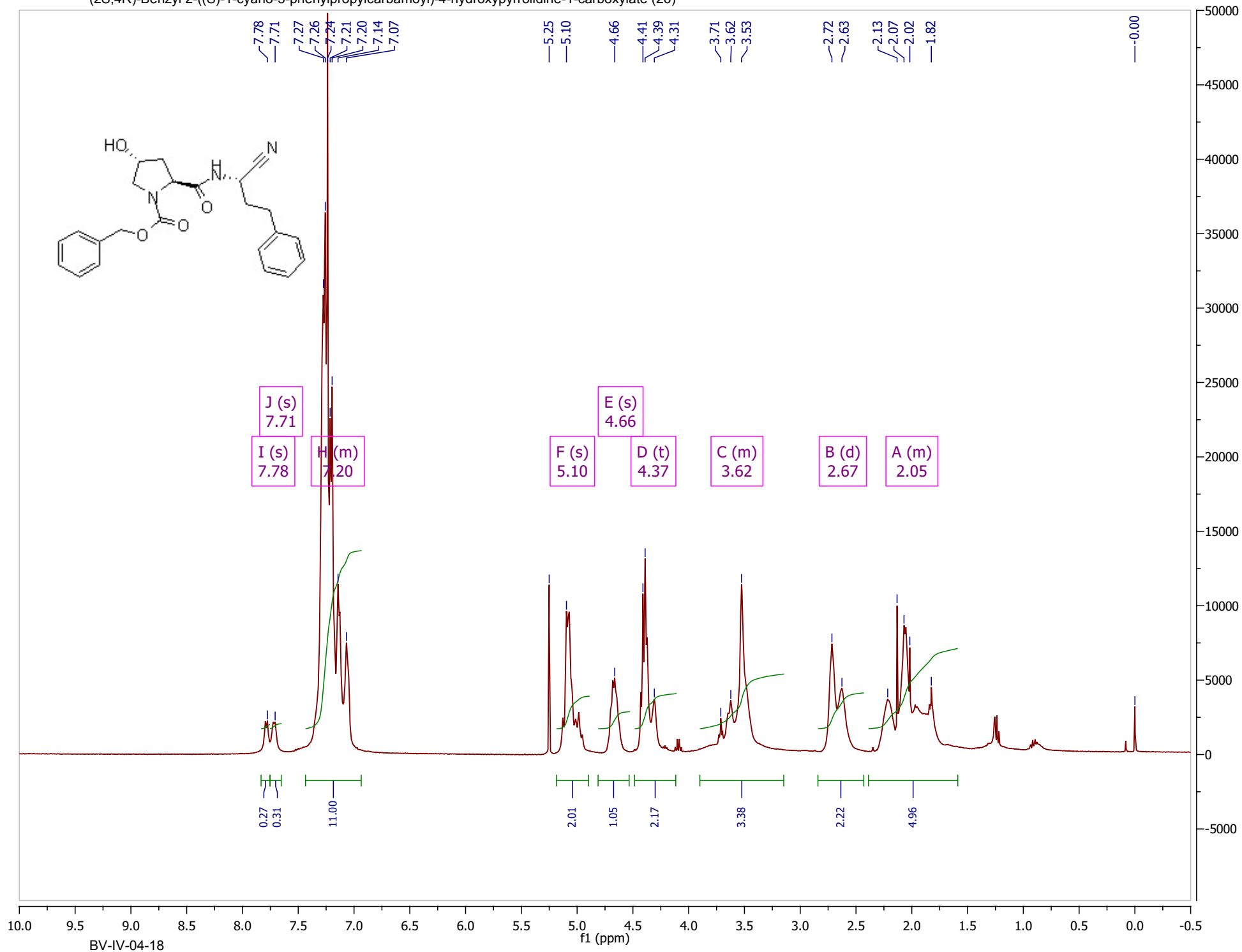
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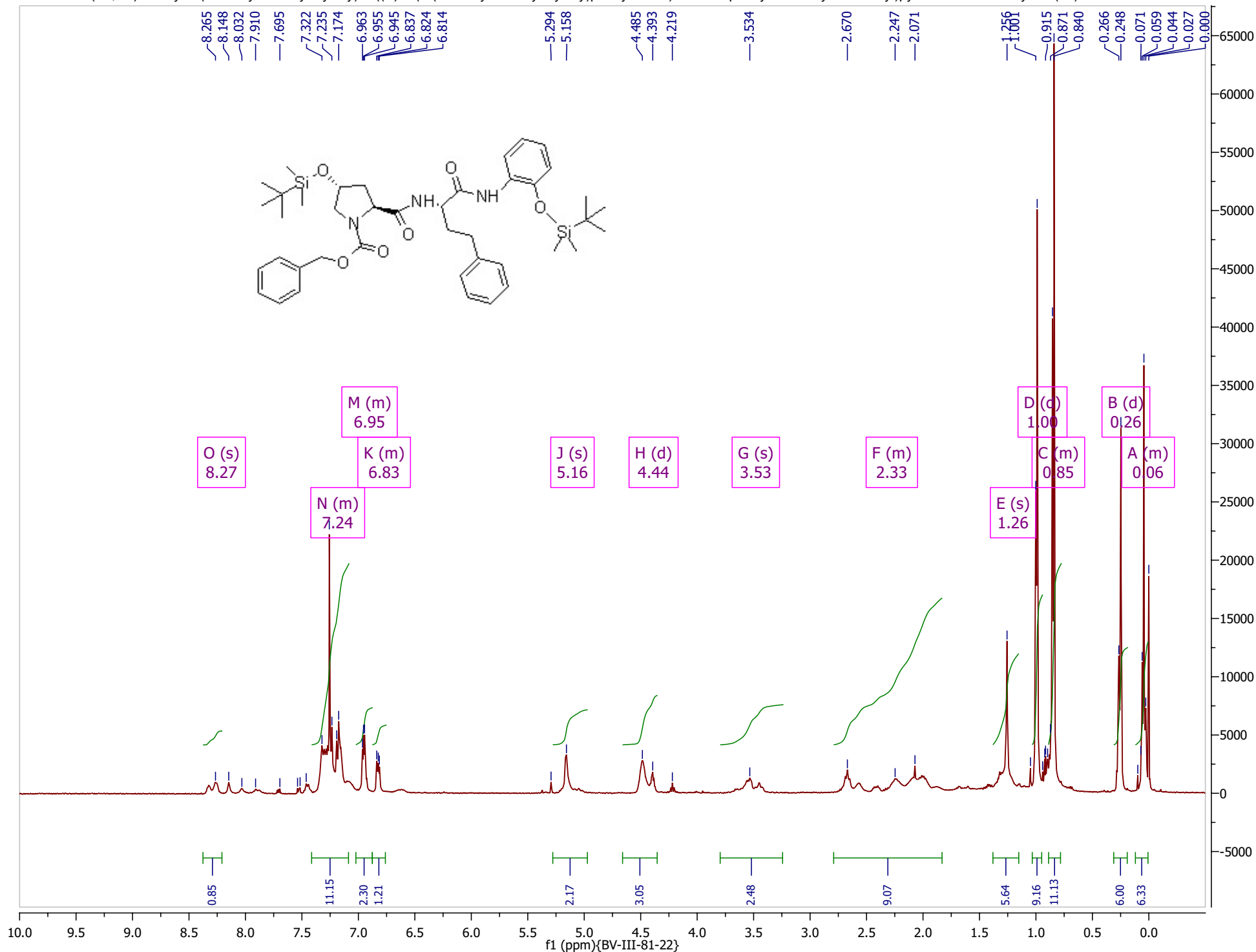
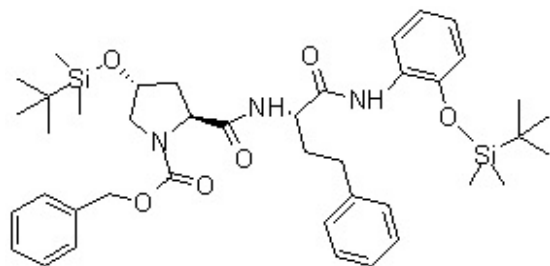
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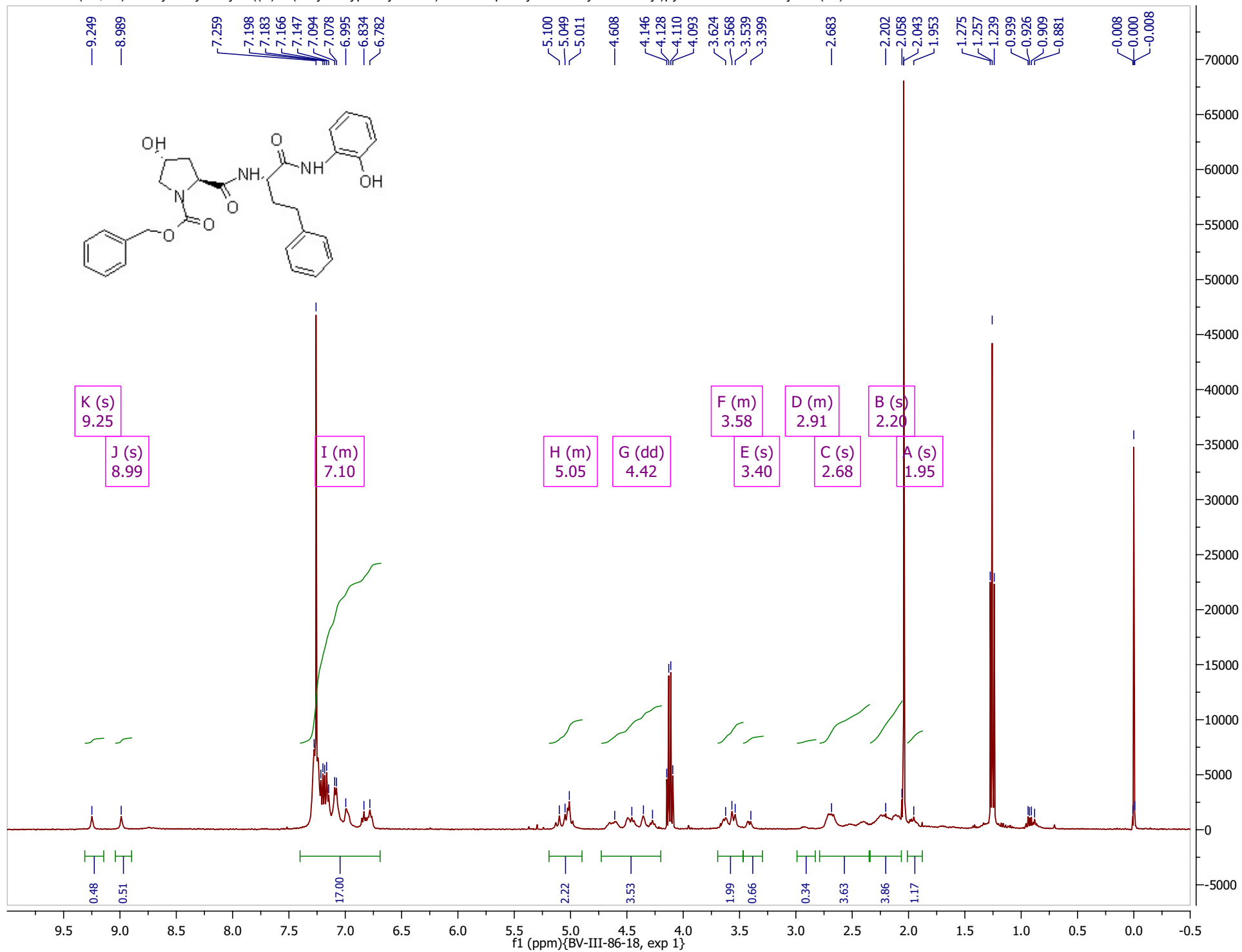
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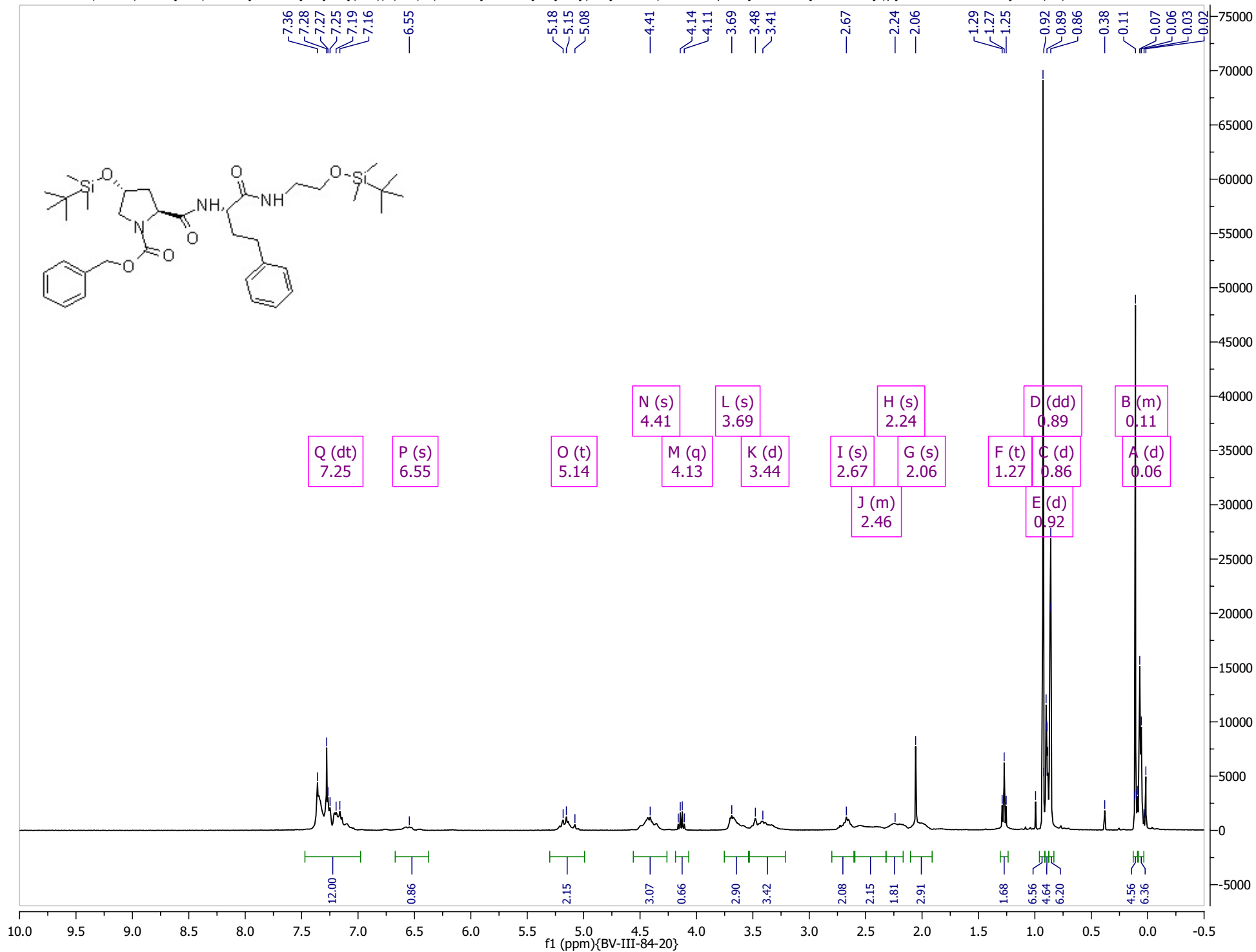
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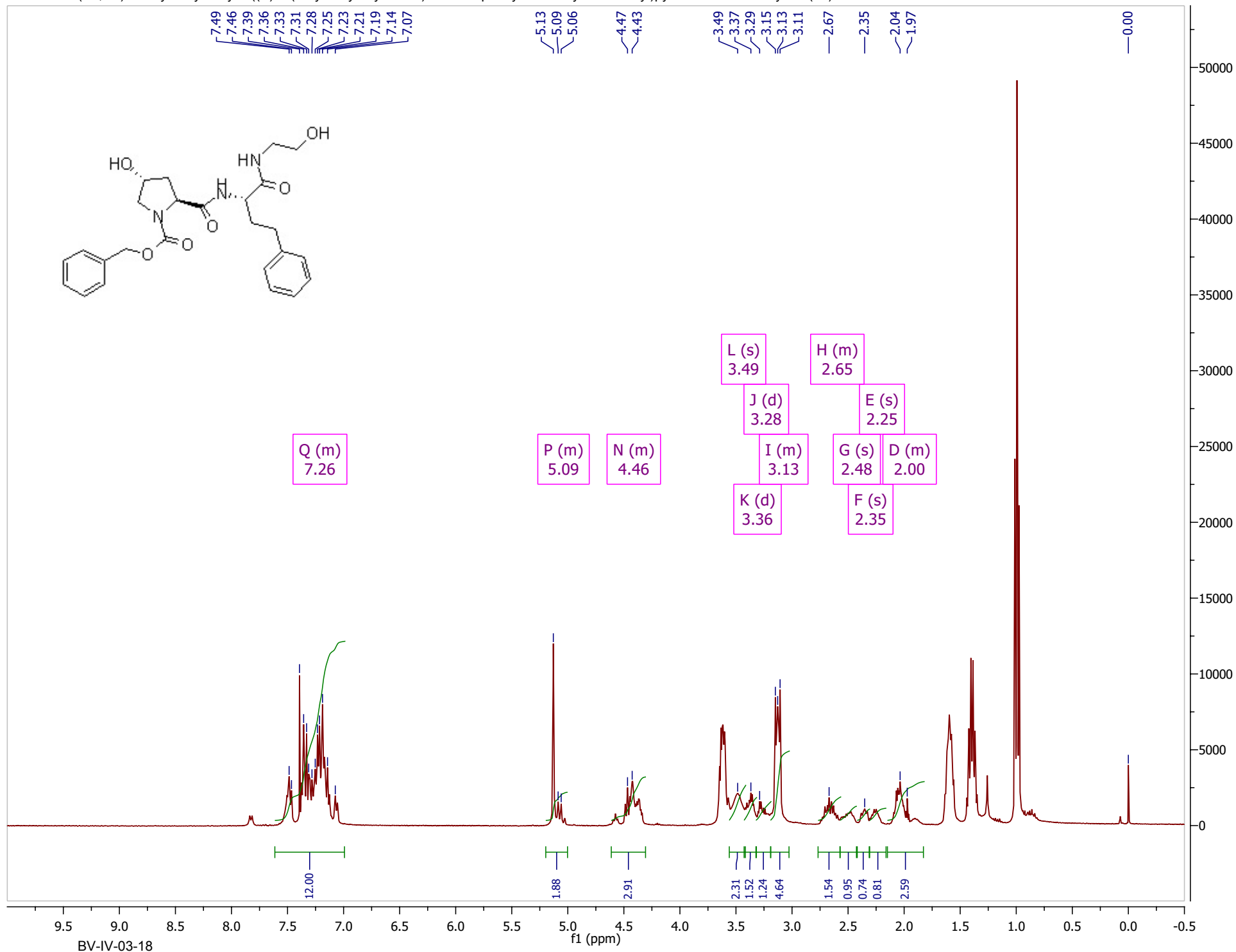
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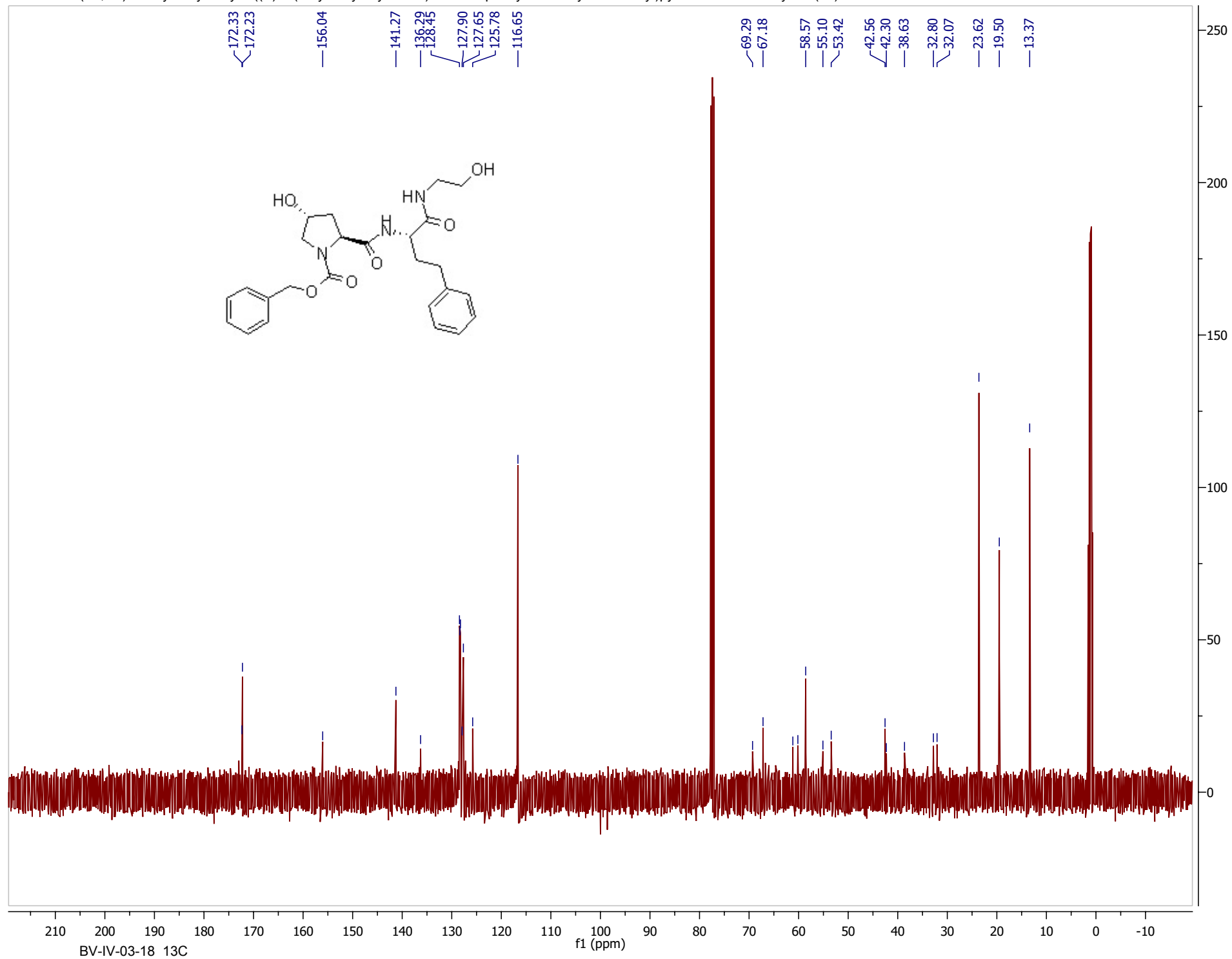
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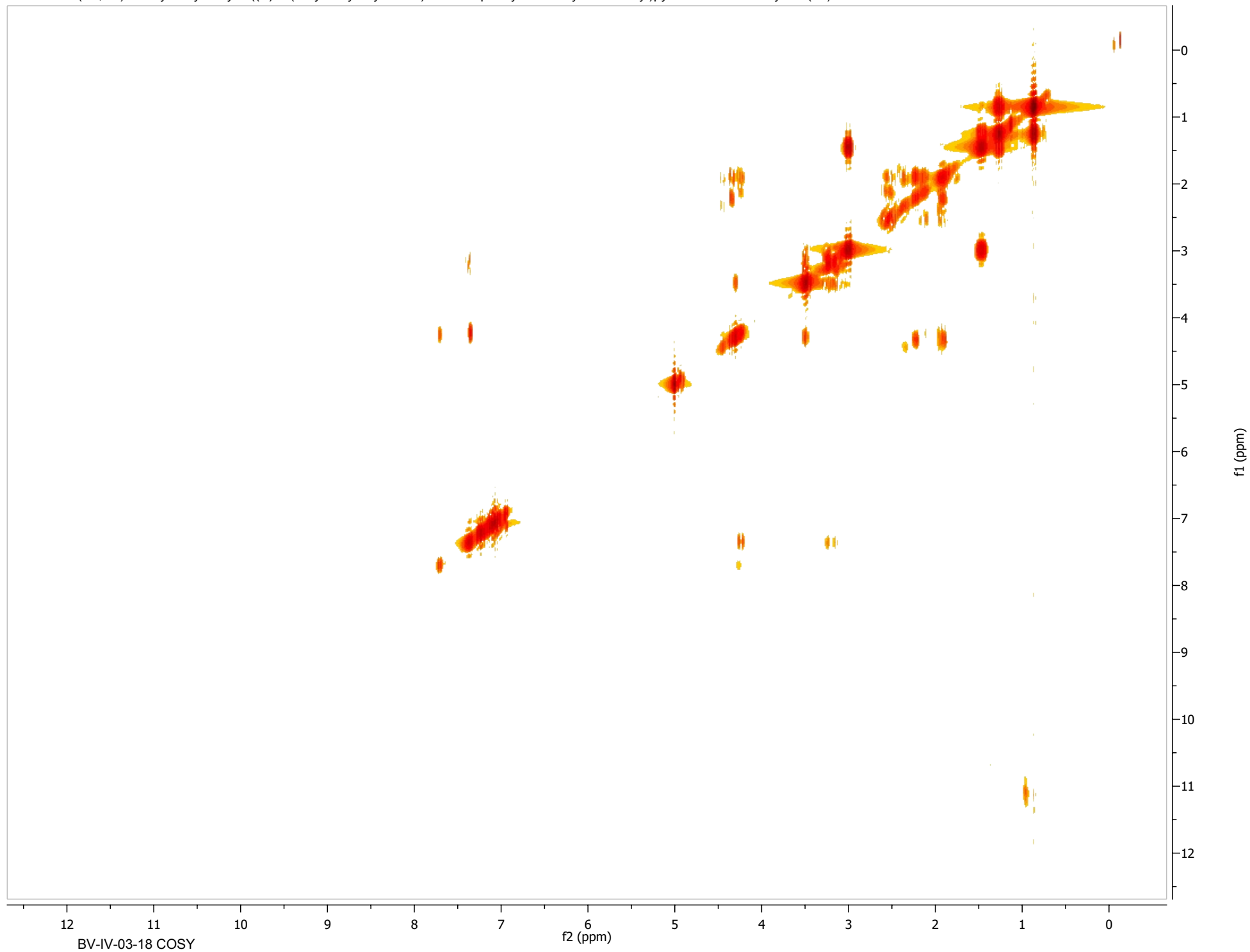
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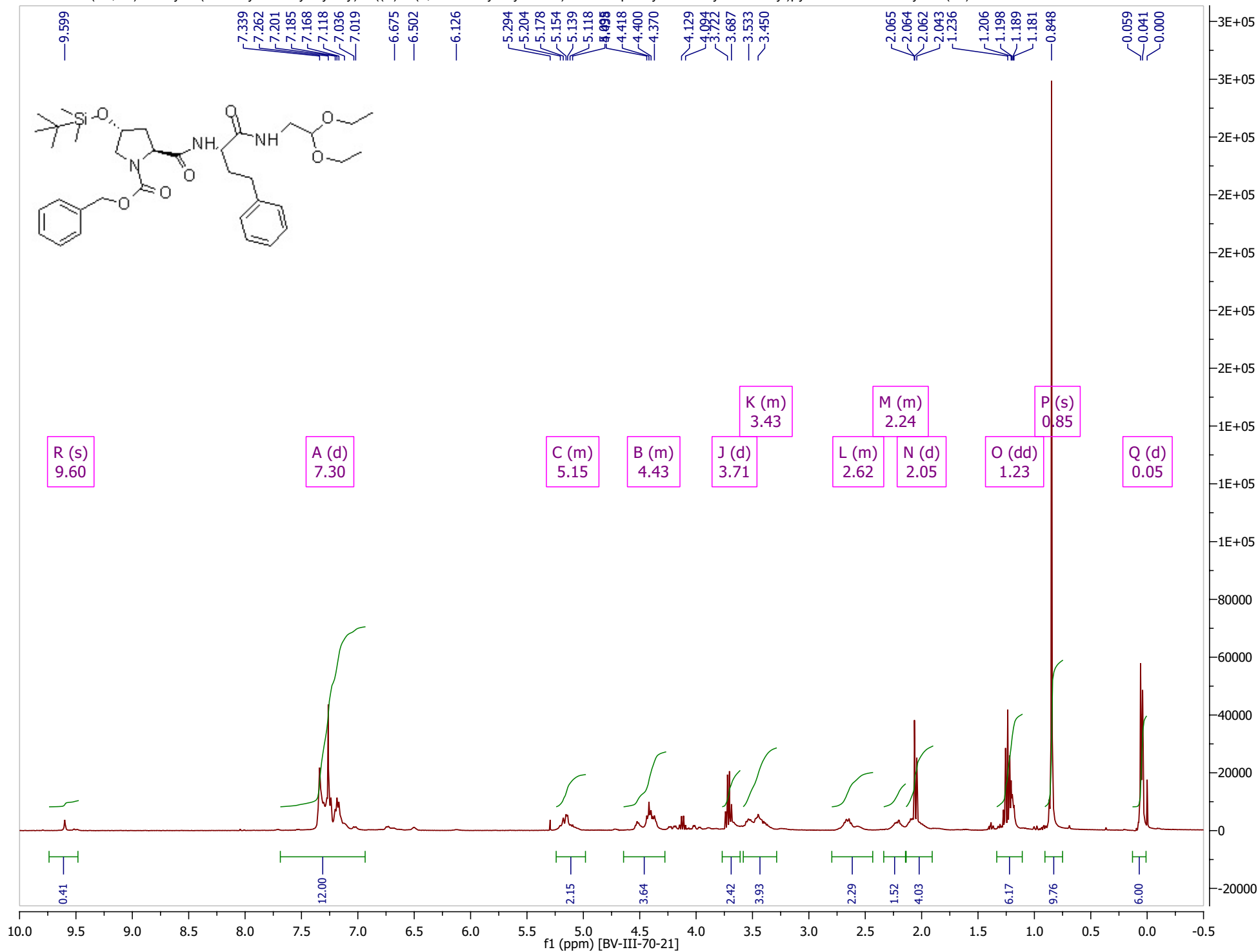
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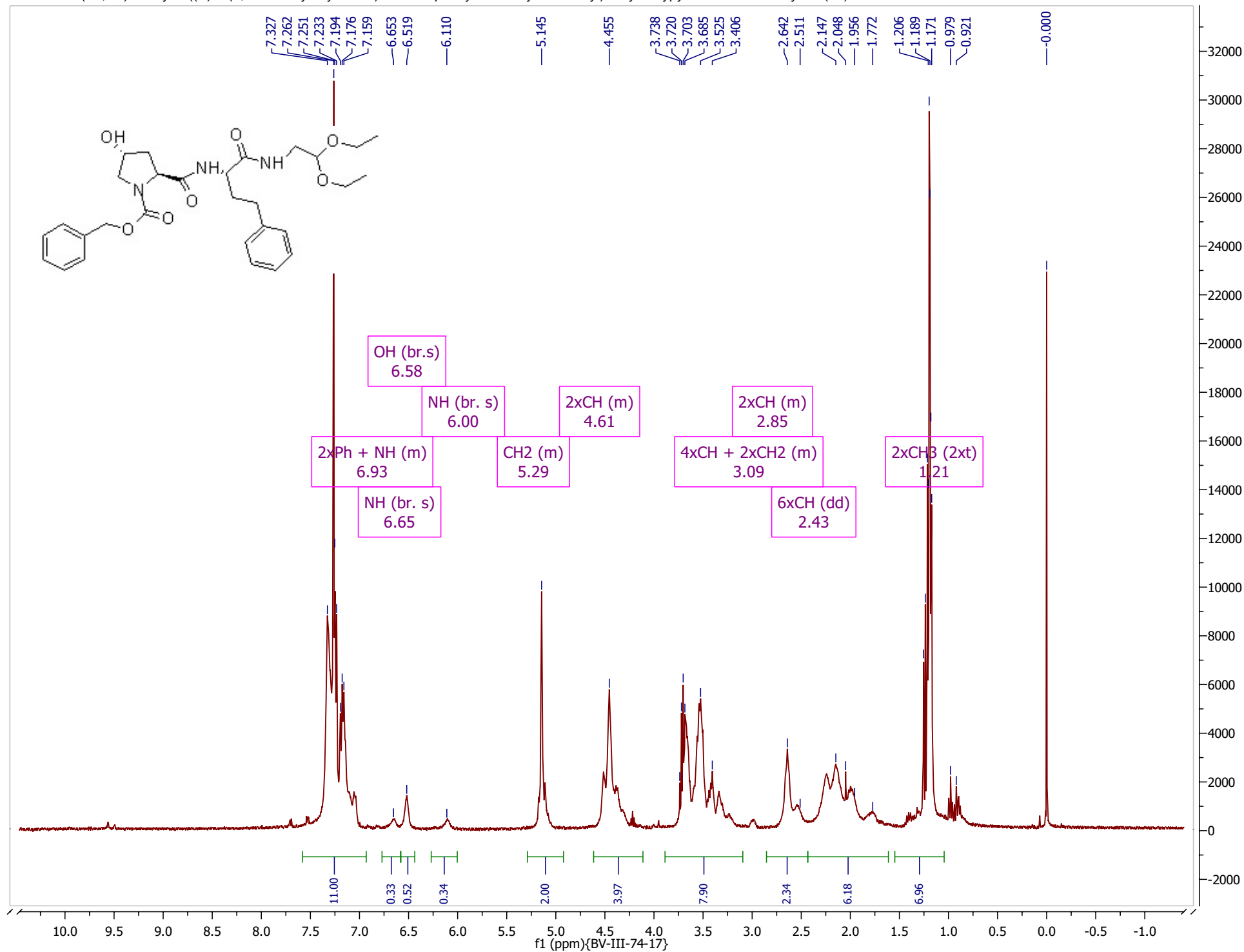
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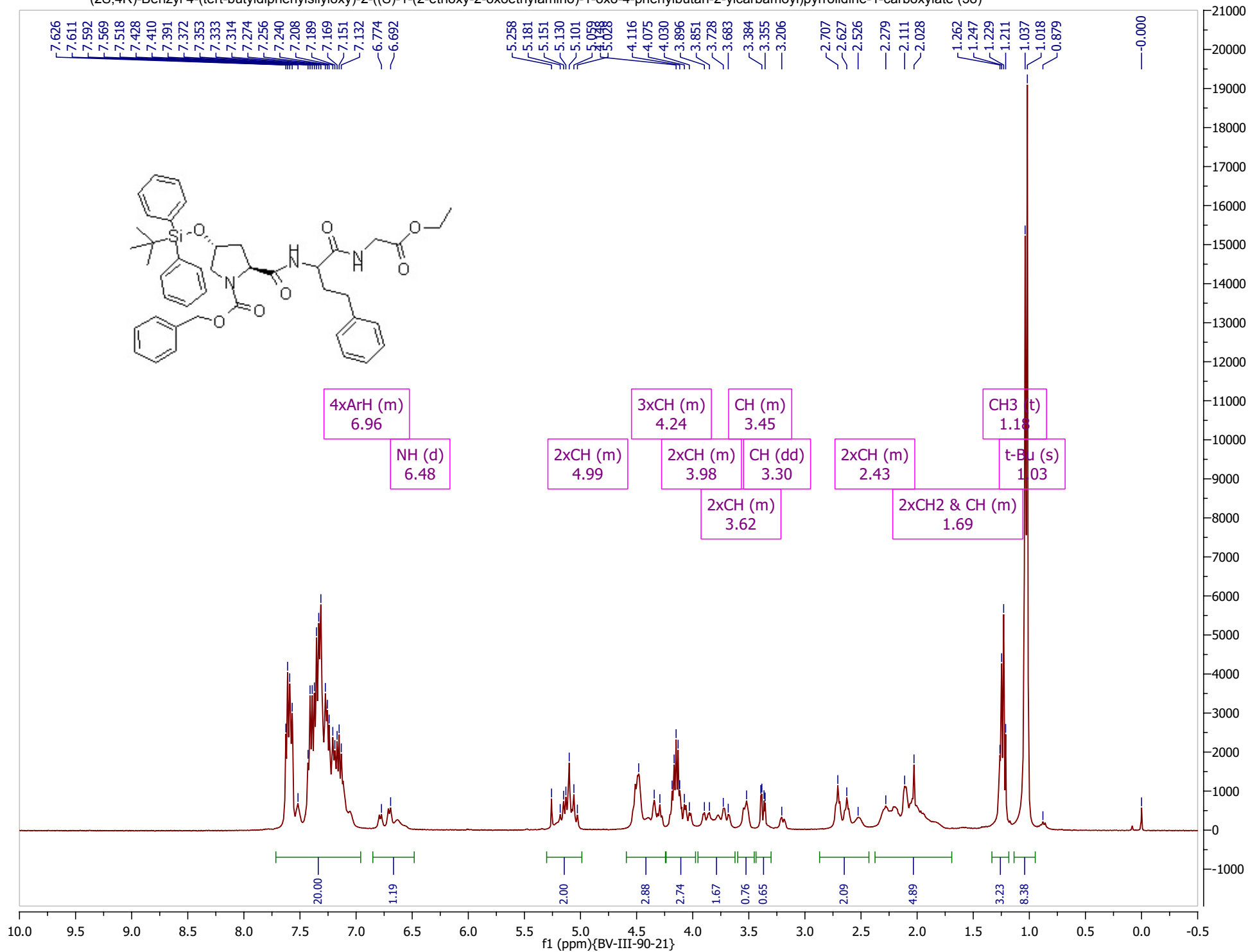
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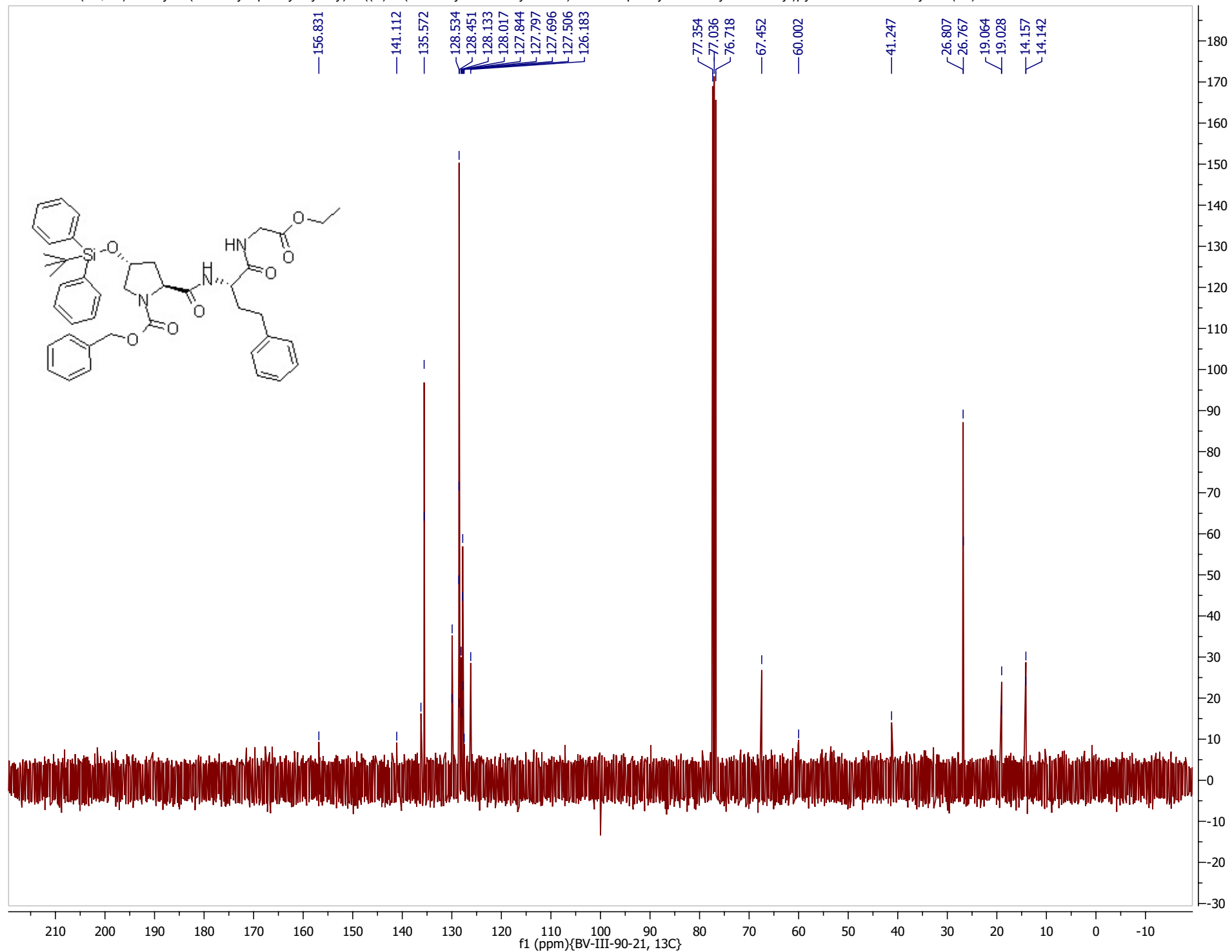
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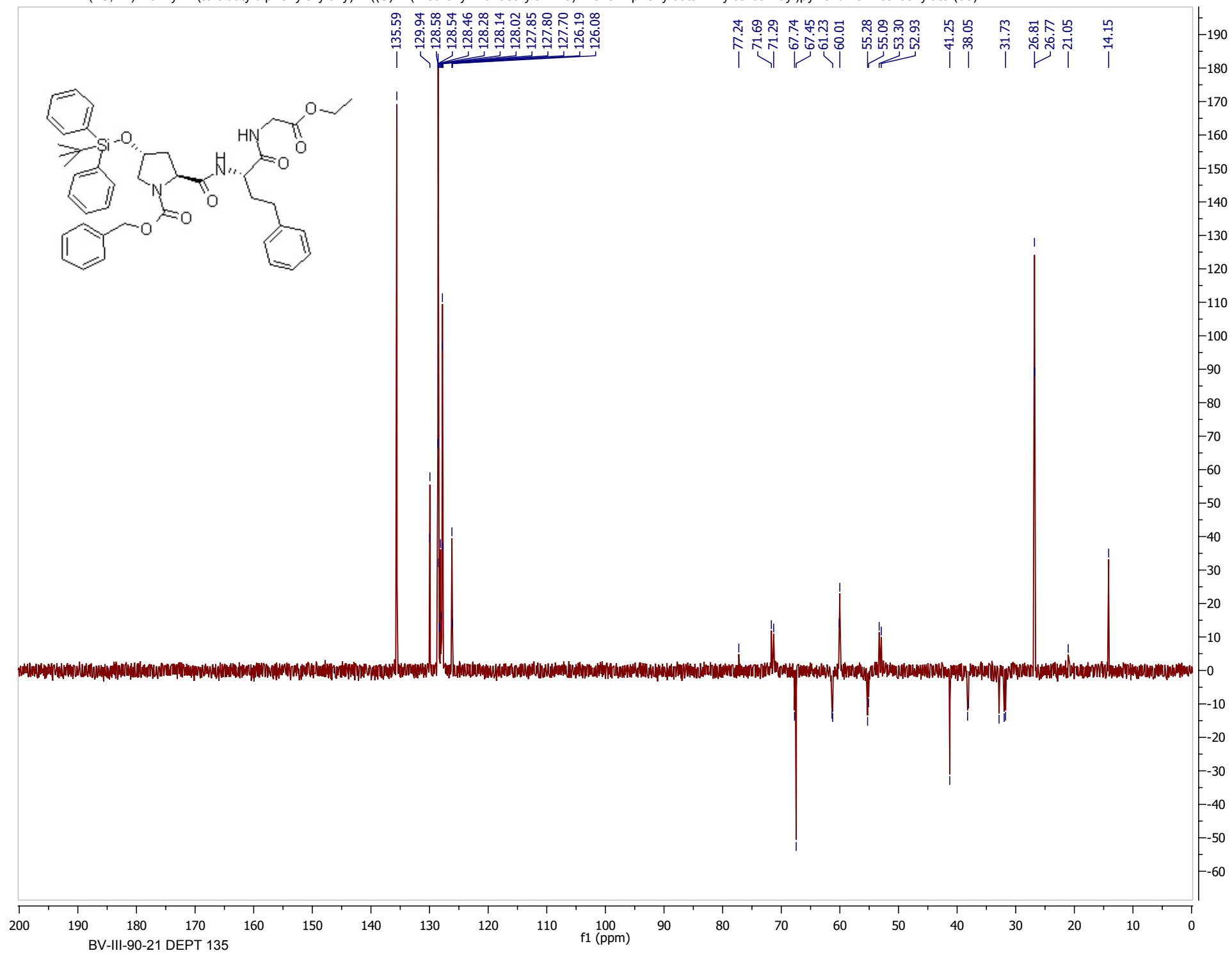
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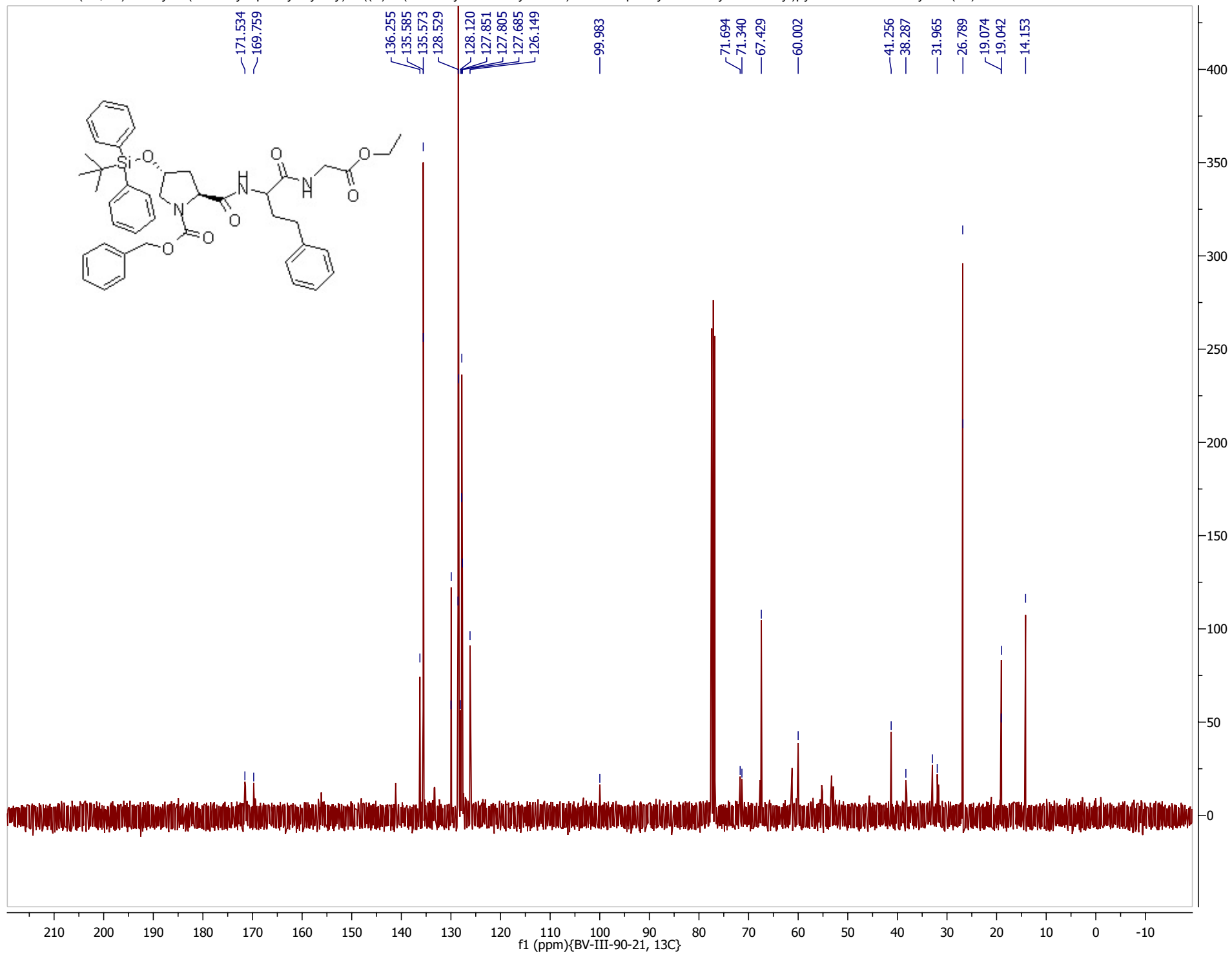
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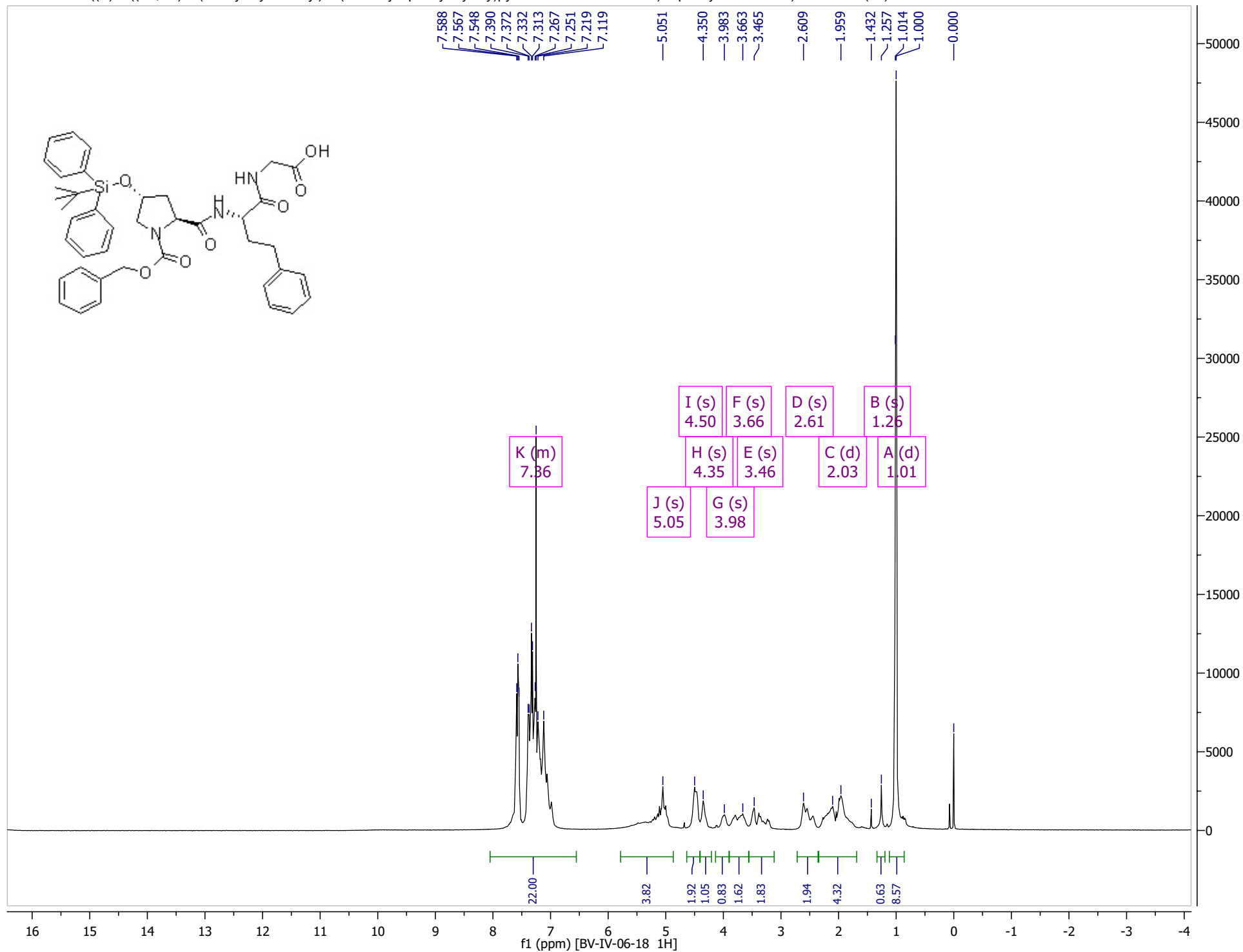
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(2S,4R)-Benzyl 4-(tert-butyldiphenylsilyloxy)-2-((S)-1-(2-ethoxy-2-oxoethylamino)-1-oxo-4-phenylbutan-2-ylcarbamoyl)pyrrolidine-1-carboxylate (38)



2-((S)-2-((2S,4R)-1-(Benzyloxycarbonyl)-4-(tert-butylidiphenylsilyloxy)pyrrolidine-2-carboxamido)-4-phenylbutanamido)acetic acid (39)



(R)-Benzyl 2-(phenyl(tosyl)carbamoyl)pyrrolidine-1-carboxylate (42)

