

Supporting Information

Tetrahydroindazole inhibitors of CDK2-cylin complexes

Jae Chul Lee,¹ Kwon Ho Hong,¹ Andreas Becker,² Joseph S. Tash,³ Ernst Schönbrunn,² and Gunda I. Georg^{1,*}

¹ Department of Medicinal Chemistry, Institute for Therapeutics Discovery and Development, College of Pharmacy, University of Minnesota, 717 Delaware Street, SE, Minneapolis, MN 55455, USA

² Drug Discovery Department, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA

³ Department of Molecular and Integrative Physiology, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160, USA

georg@umn.edu

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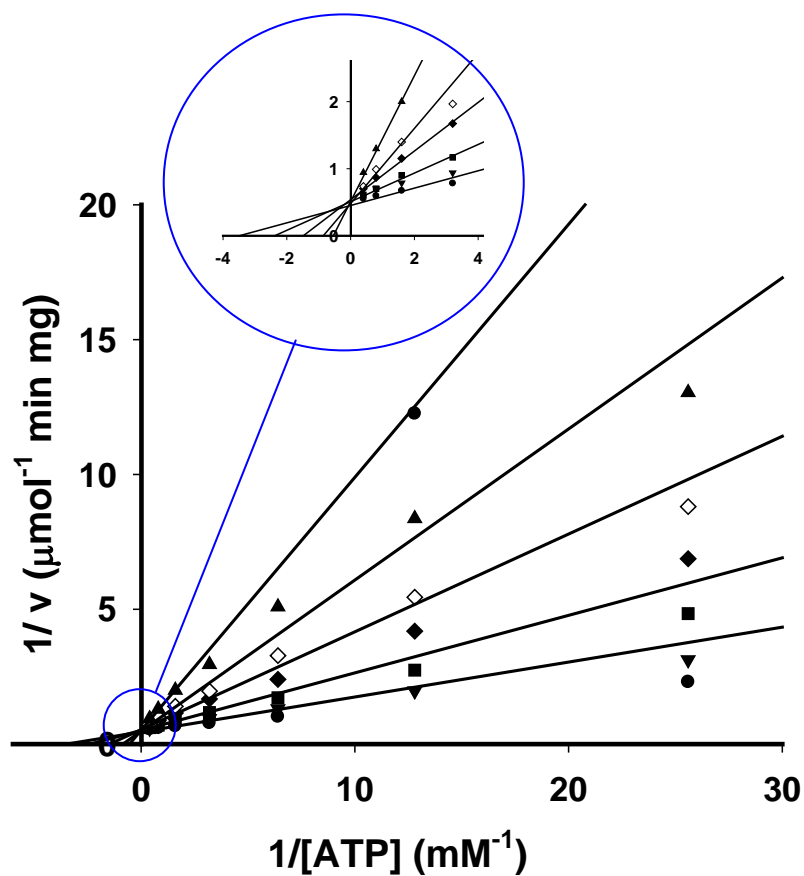


Fig. S1. Inhibition of the CDK2-cylin A complex by hit 3. Lineweaver-Burk presentation of initial velocities against ATP. The peptide substrate was held constant at 0.5 mM. Concentrations of **3** were (\bullet) 0 μM , (\blacktriangledown) 0.5 μM , (\blacksquare) 1.9 μM , (\blacklozenge) 3.9 μM , (\diamond) 7.8 μM , (\blacktriangle) 15.6 μM . The common y-axis intercept (circled view) indicates competitive inhibition. Data were fitted to the Michaelis-Menten equation $v = V_{\text{max}} * [\text{S}] / (K_{\text{mobs}}([\text{I}]) + [\text{S}])$ and K_i values were determined by fitting the observed K_m values = $K_m (1 + [\text{I}] / K_i)$.

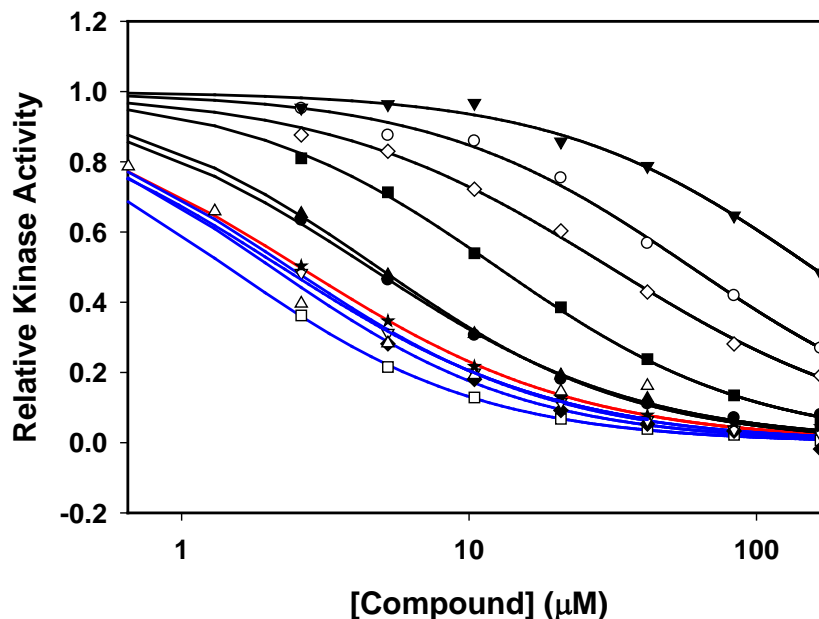


Fig. S2. SAR of hit 3 derivatives. Displayed are dose-response curves of selected analogues: (●) **12** (R6 = N₃; IC₅₀ = 4.5 +/- 0.2 μM), (▲) **18b-trans** (R5 = CH₃, H; IC₅₀ = 4.8 +/- 0.1 μM, for comparison (◇) **18b-cis** (R5 = H, CH₃; IC₅₀ = 31 +/- 0.9 μM), (■) **21** (R4 = -CH₂-NH-; IC₅₀ = 12 +/- 3 μM), (○) **23** (R3 = =NOH; IC₅₀ = 59 +/- 3 μM), (▼) **25** (R2 = H; IC₅₀ = 160 +/- 10 μM), (□) **59** (R1 = pyrimidin-4-yl; IC₅₀ = 1.5 +/- 0.03 μM), (△) **53** (R1 = thiazol-2-yl; IC₅₀ = 2.2 +/- 0.3 μM), (◆) **64** (R1 = methoxypyridin-2-yl; IC₅₀ = 2.1 +/- 0.3 μM), (▽) **72** (R1 = pyridin-3-yl-sulfamoylamide; IC₅₀ = 2.4 +/- 0.05 μM), and (★) **3** (IC₅₀ = 2.6 +/- 0.1 μM); IC₅₀ values were obtained by fitting the data to the equation $A/A_0 = 1/(1+([I]/IC_{50})^n)$. The blue lines represent compounds with increased inhibitory activity over the parent compound **3** (red line).

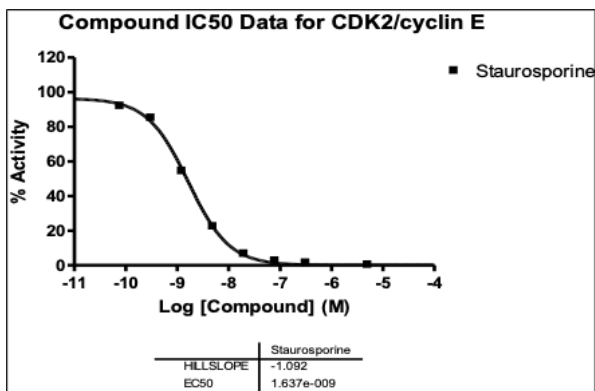
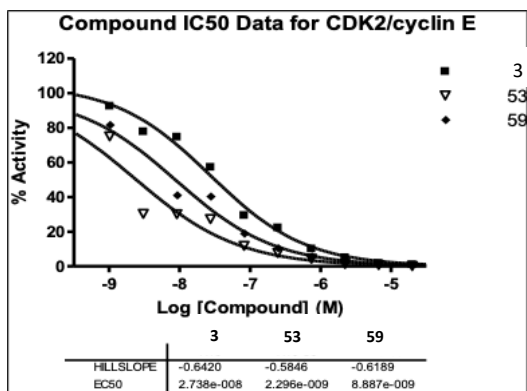
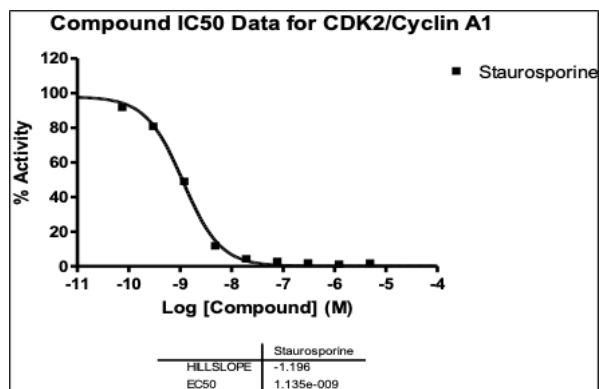
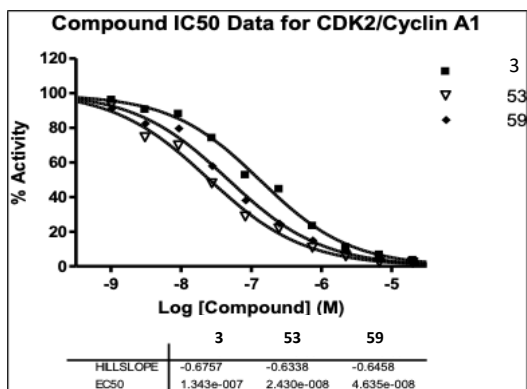
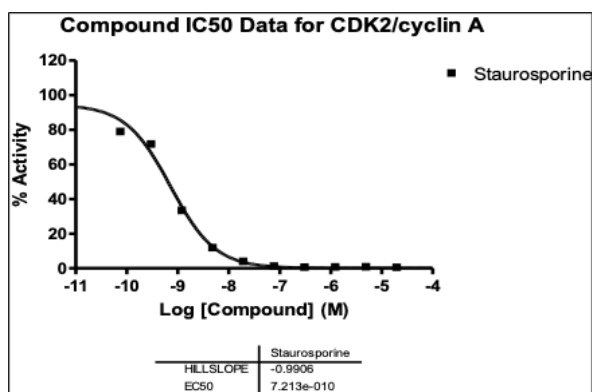
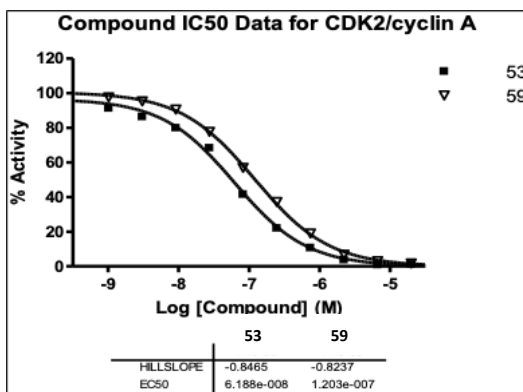


Fig. S3. IC₅₀ data generated by Reaction Biology for compounds **3**, **53** and **59** and staurosporine as the positive control for CDK2/cyclin complexes.

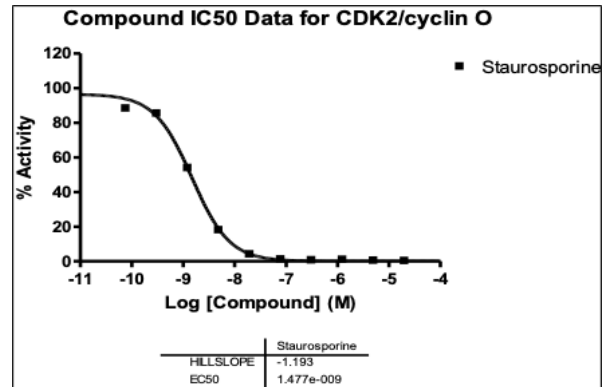
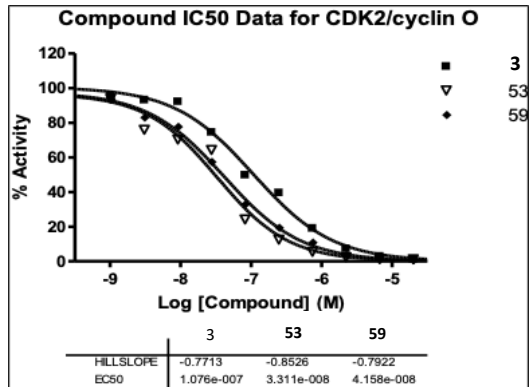
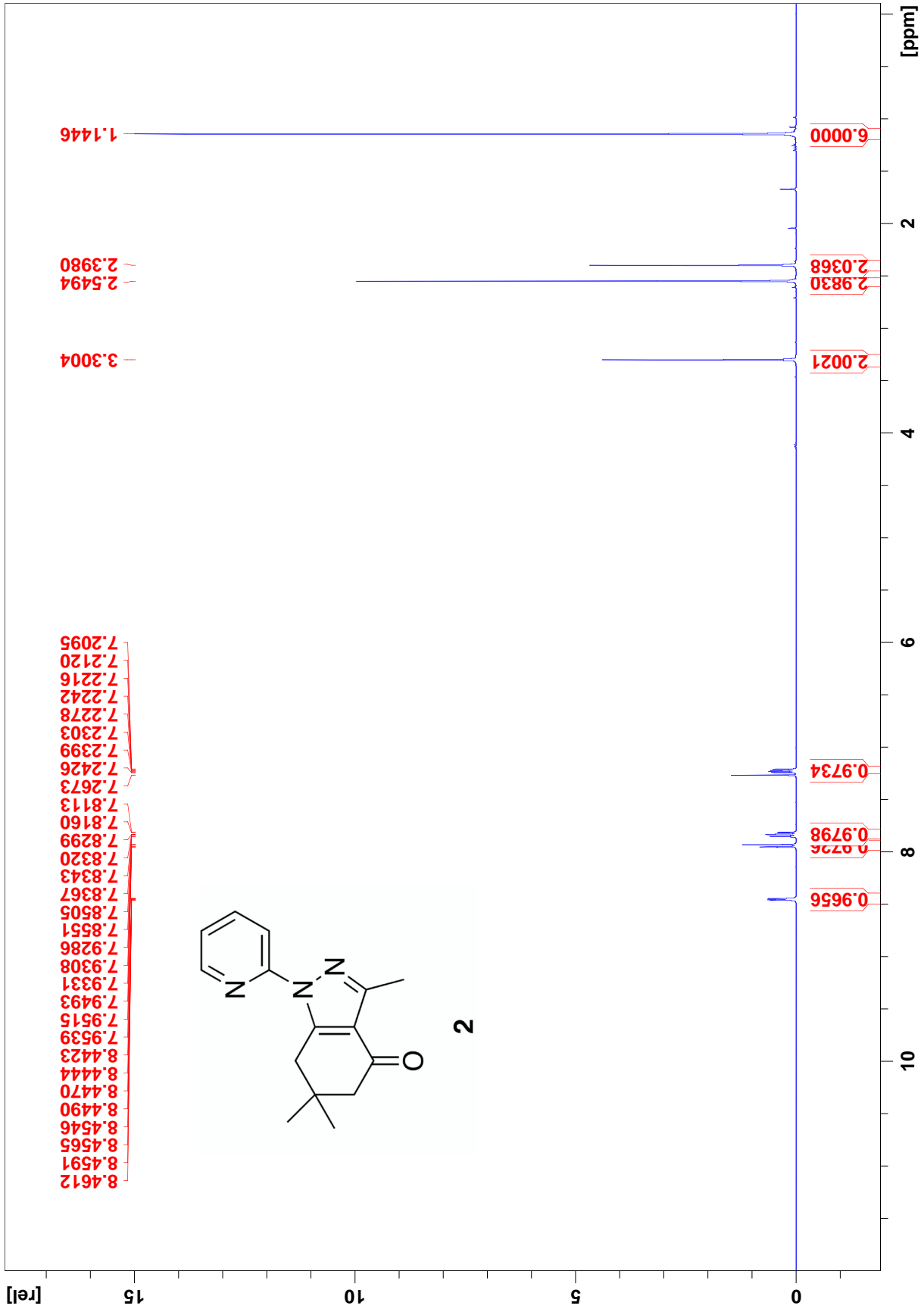


Fig. S3 cont. IC₅₀ data generated by Reaction Biology for compounds **3**, **53** and **59** and staurosporine as the positive control for CDK2/cyclin complexes.

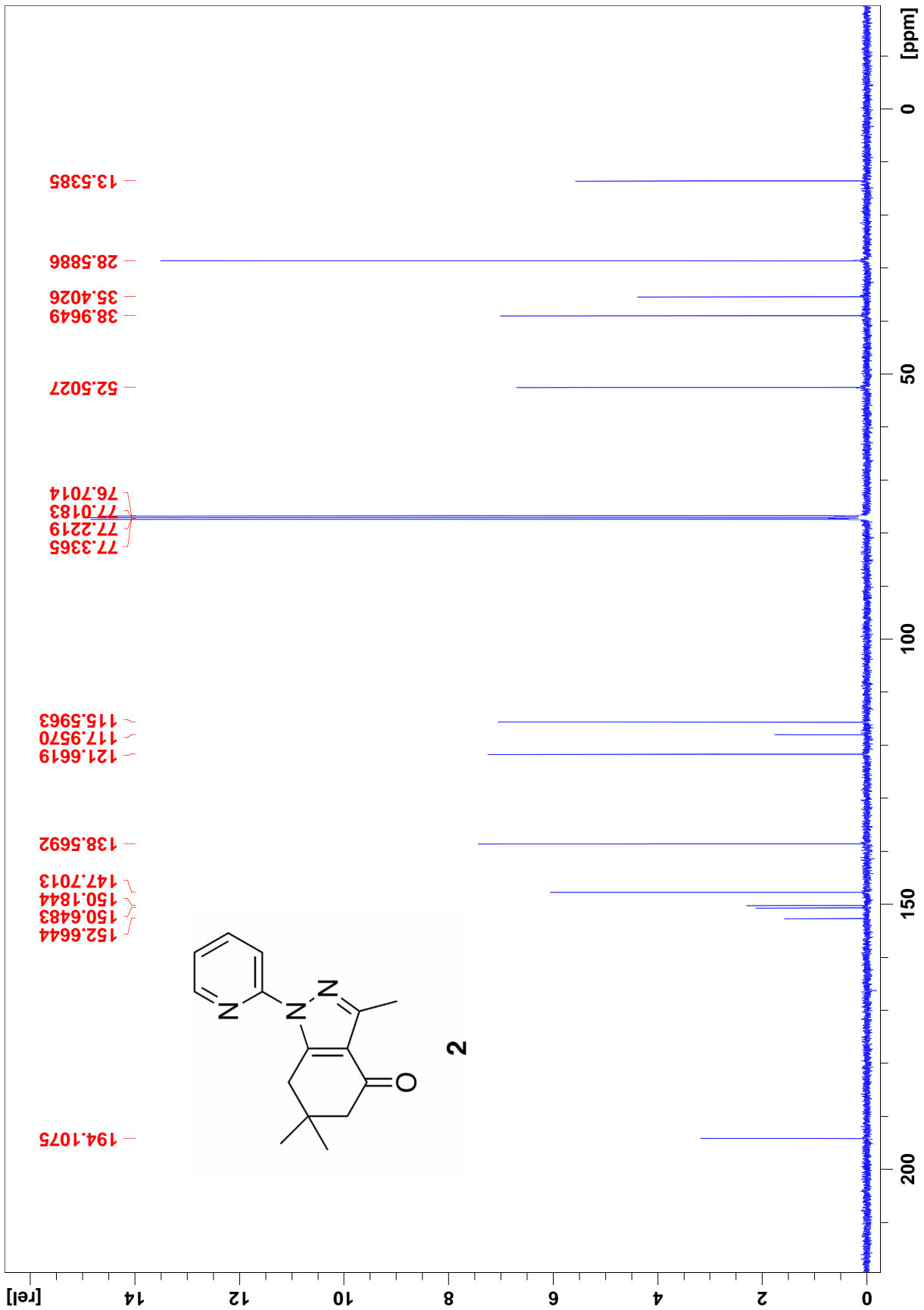
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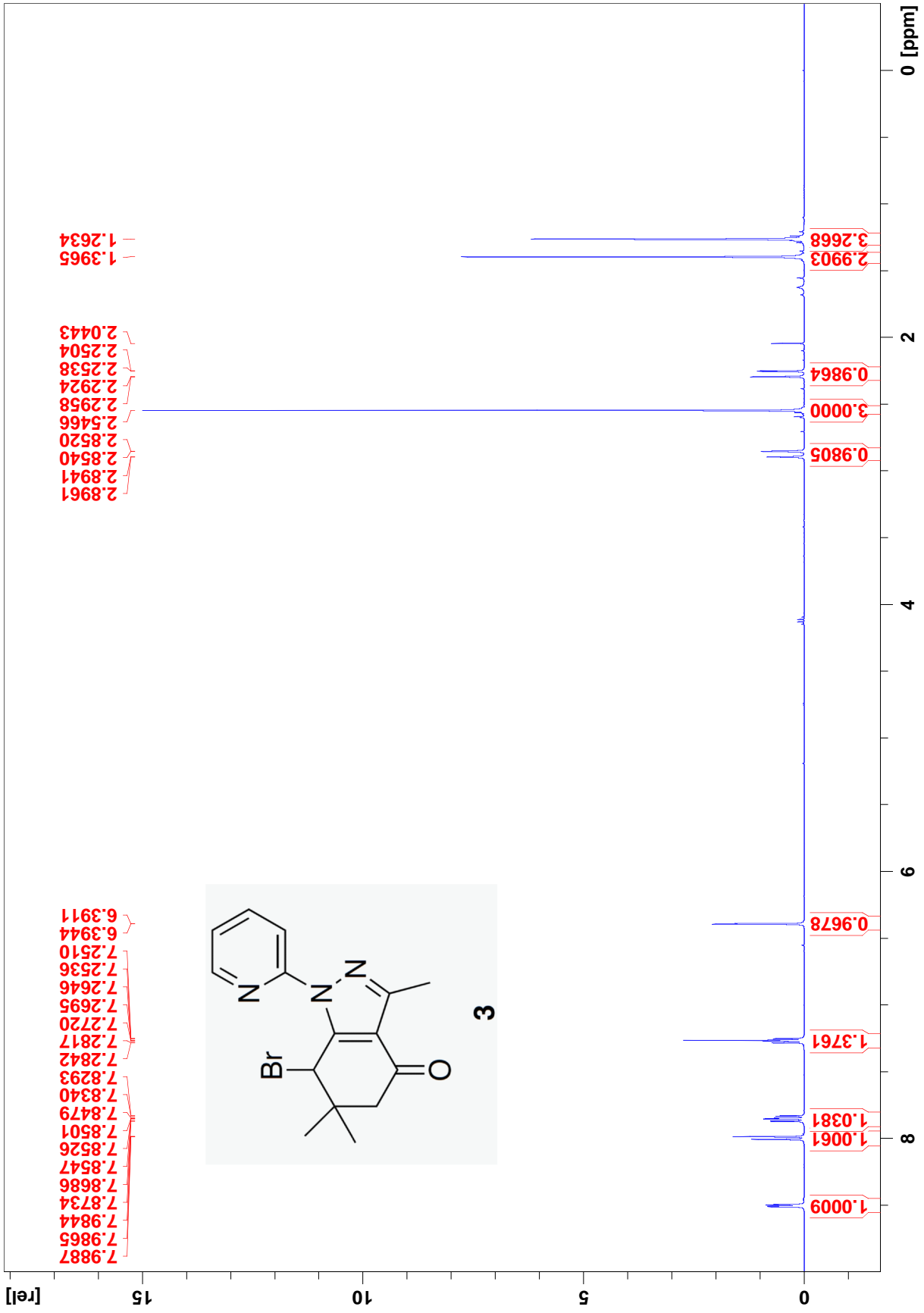
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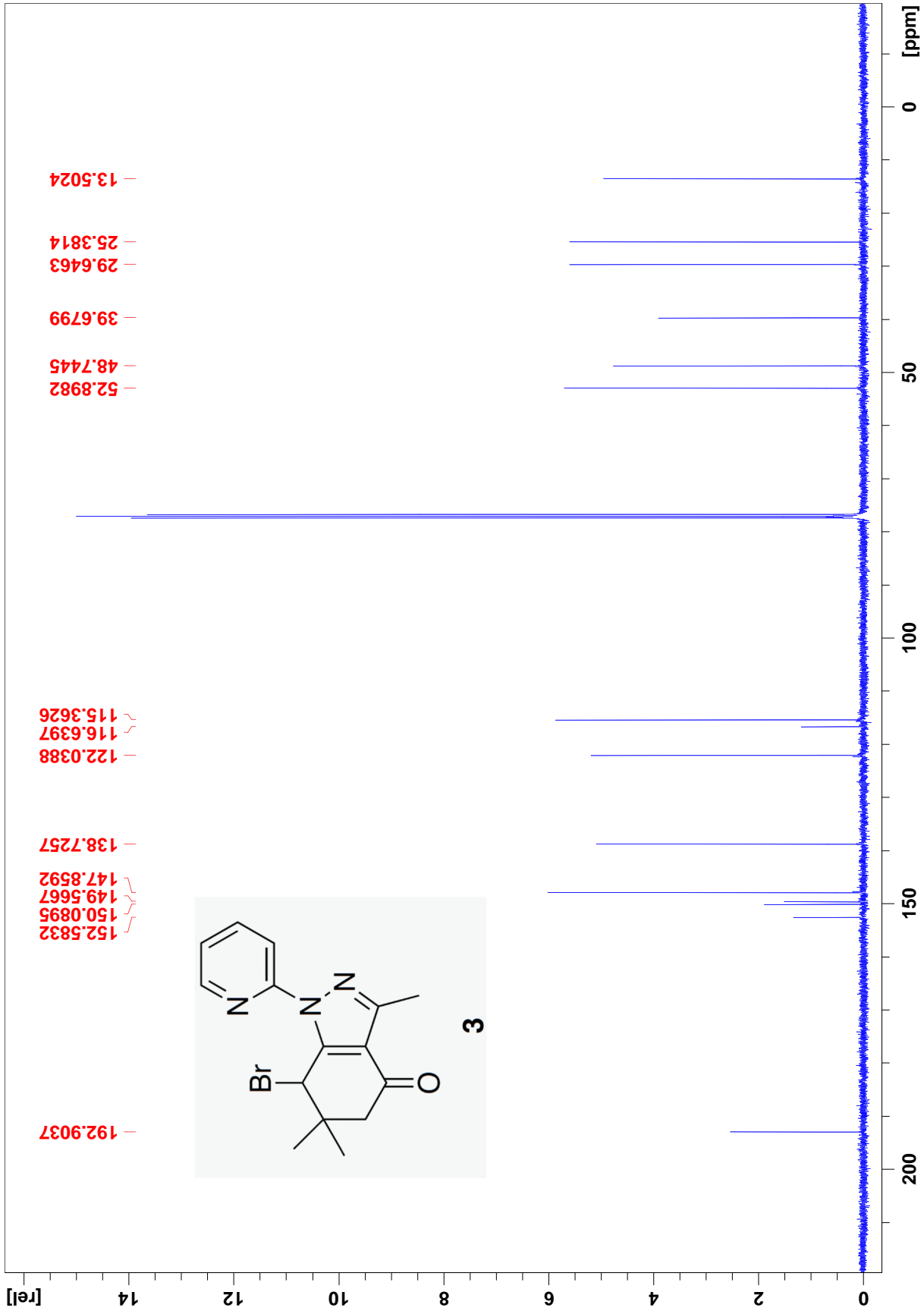
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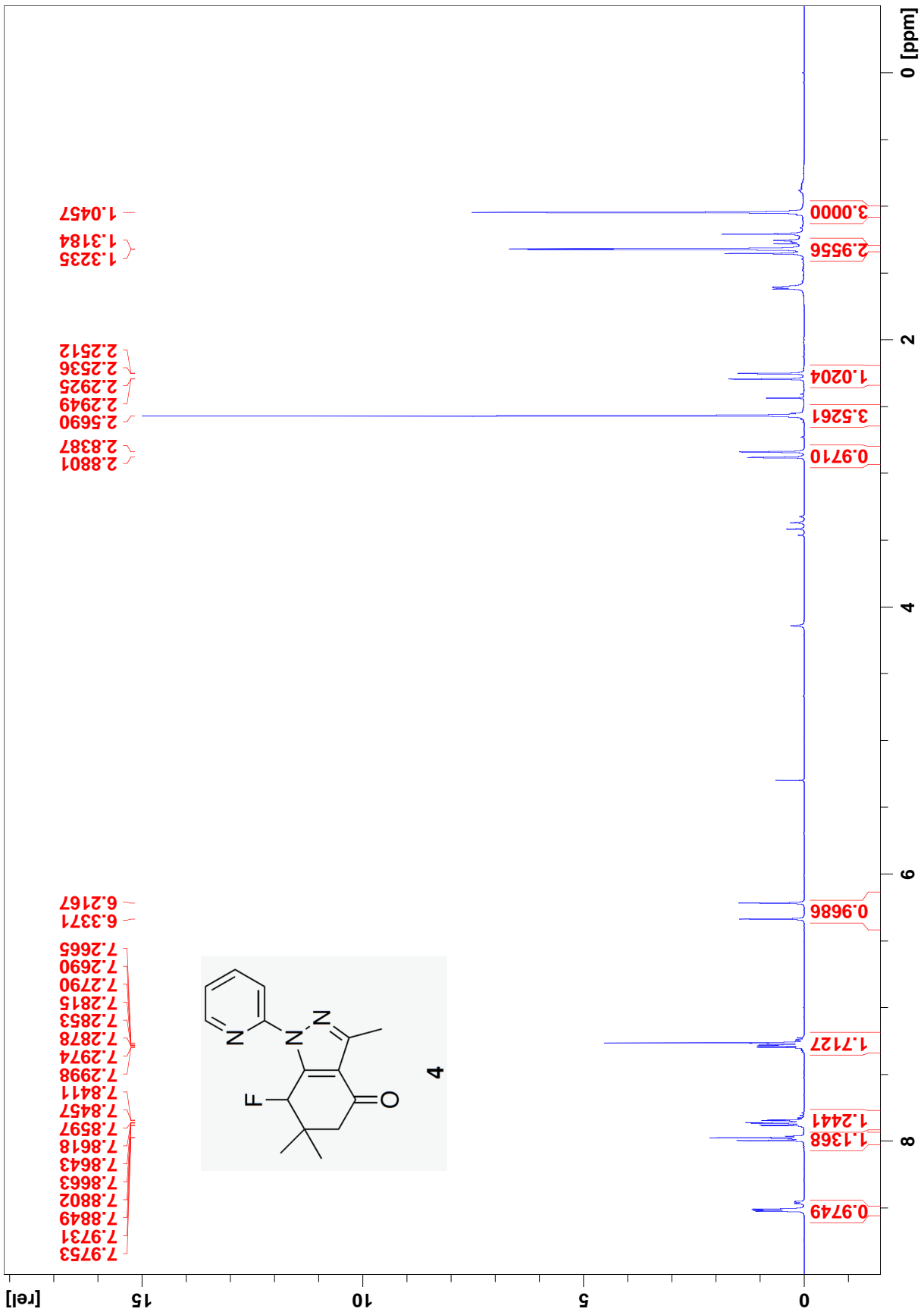
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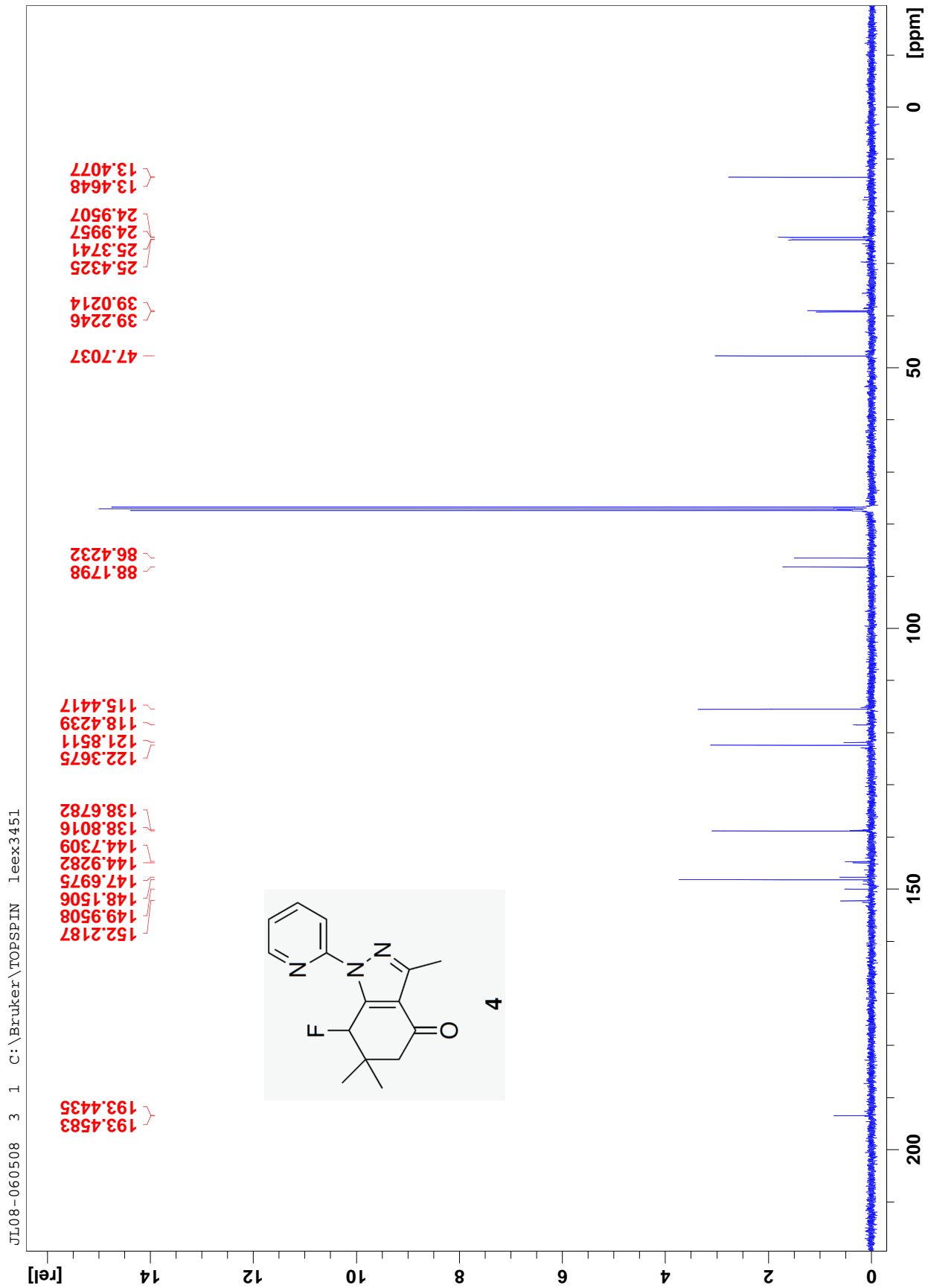


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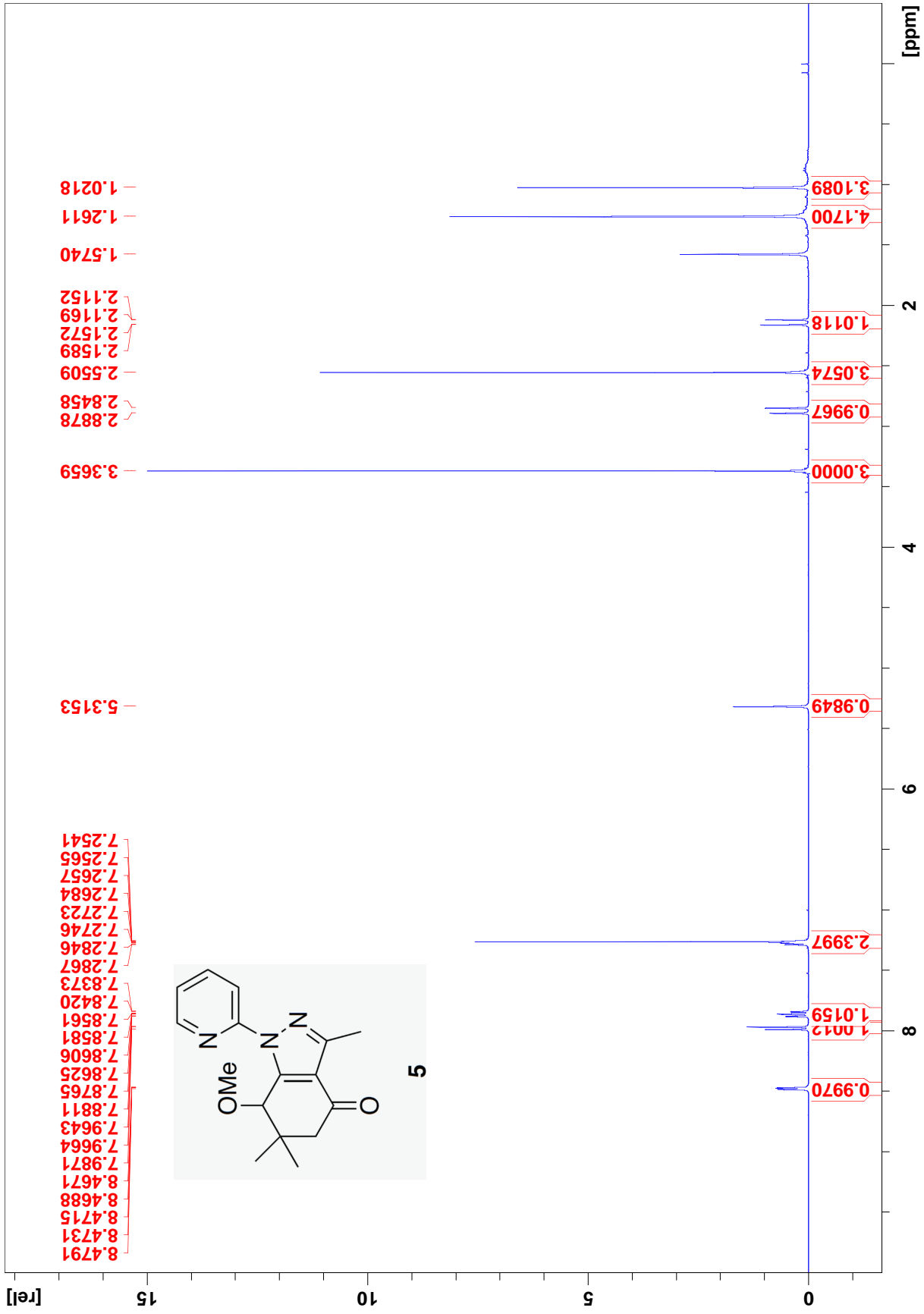


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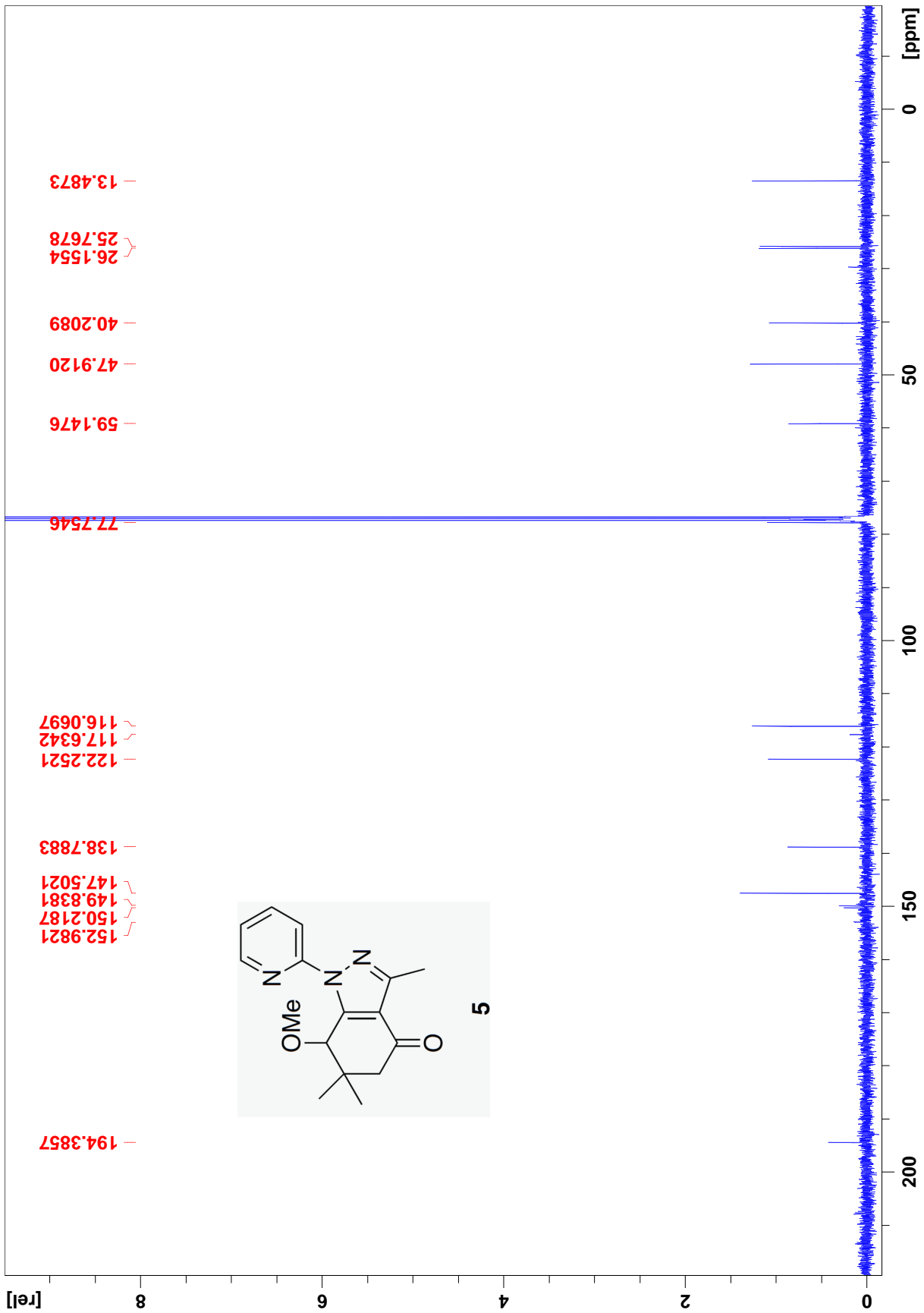
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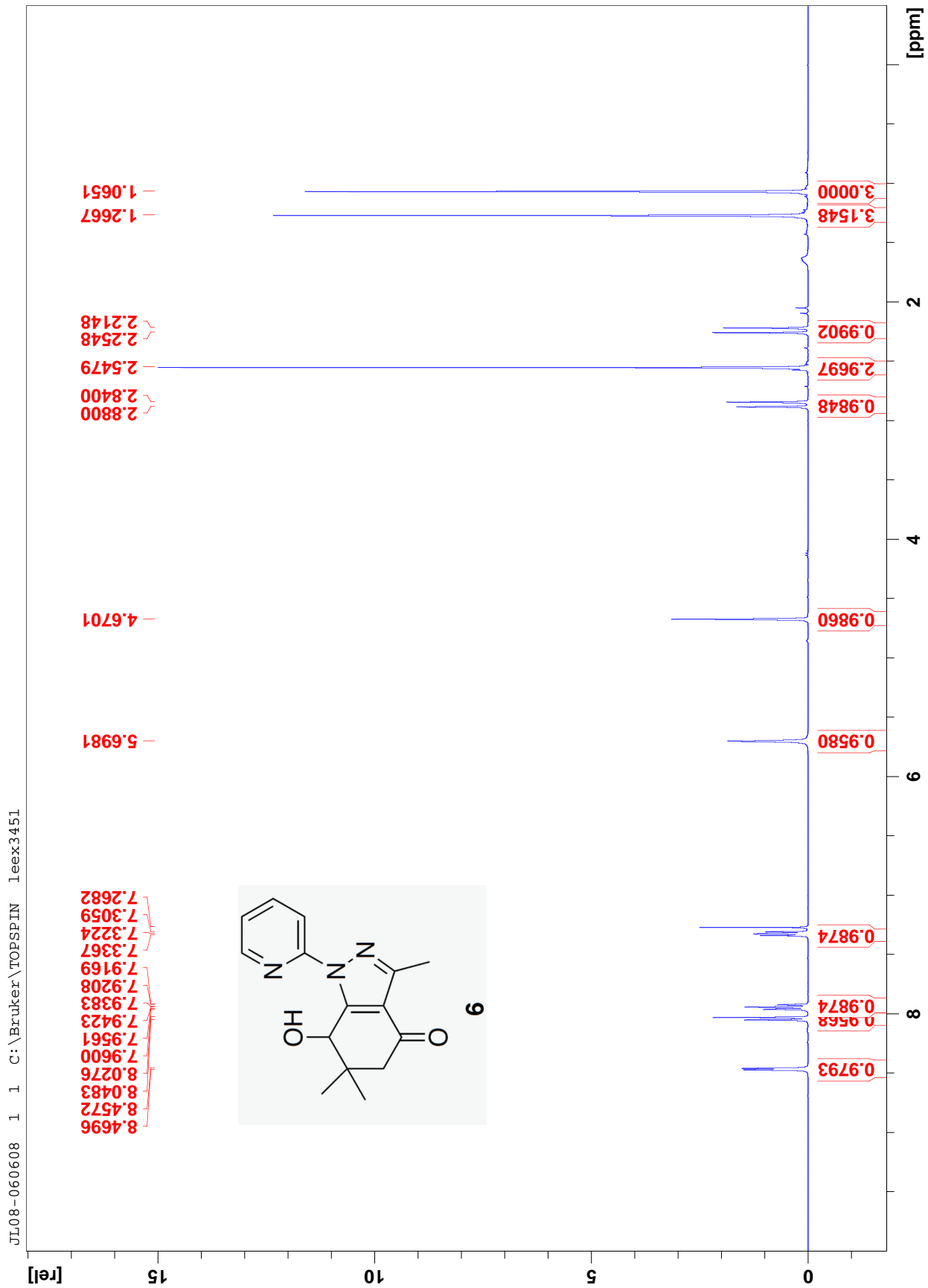


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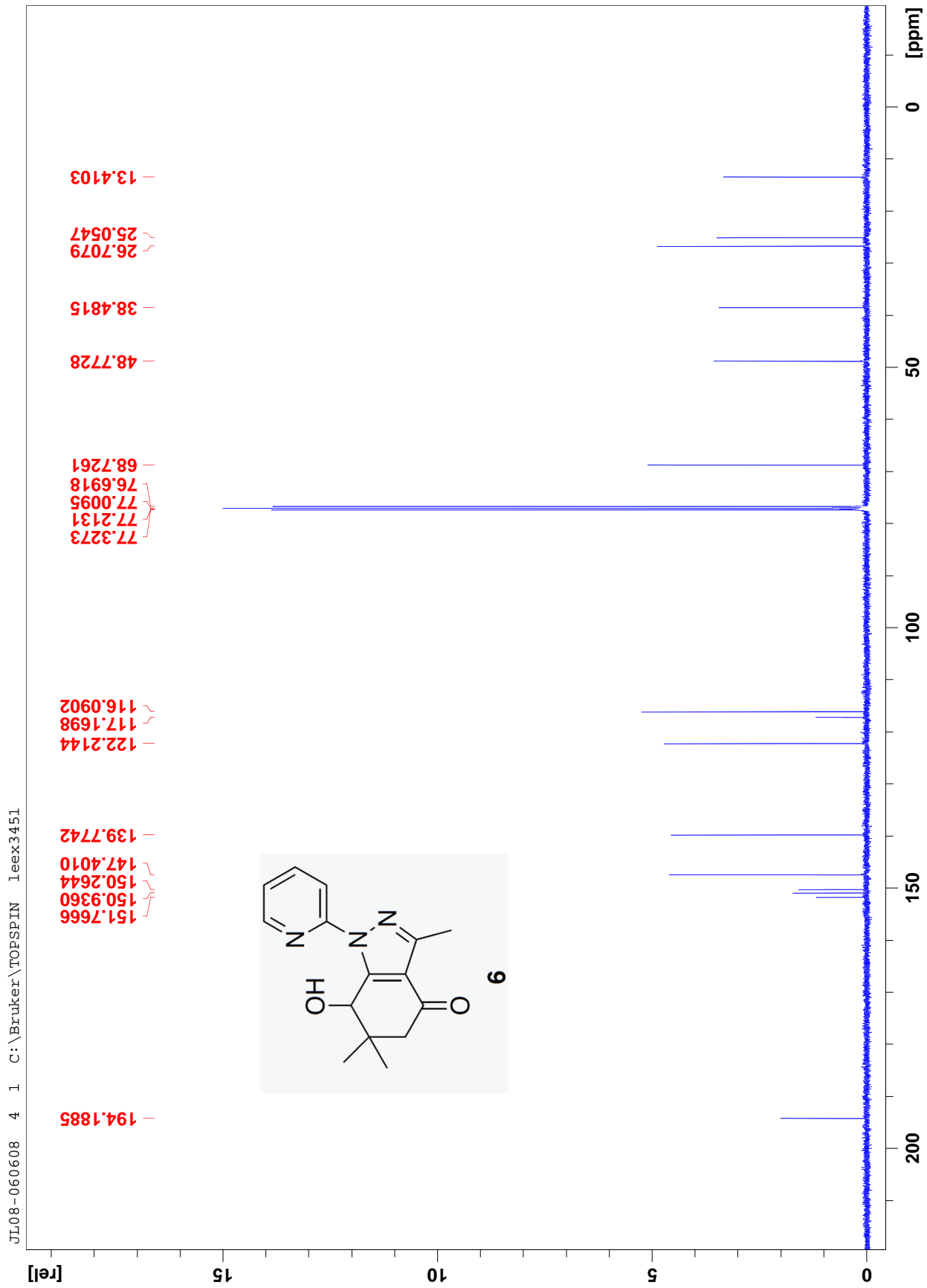
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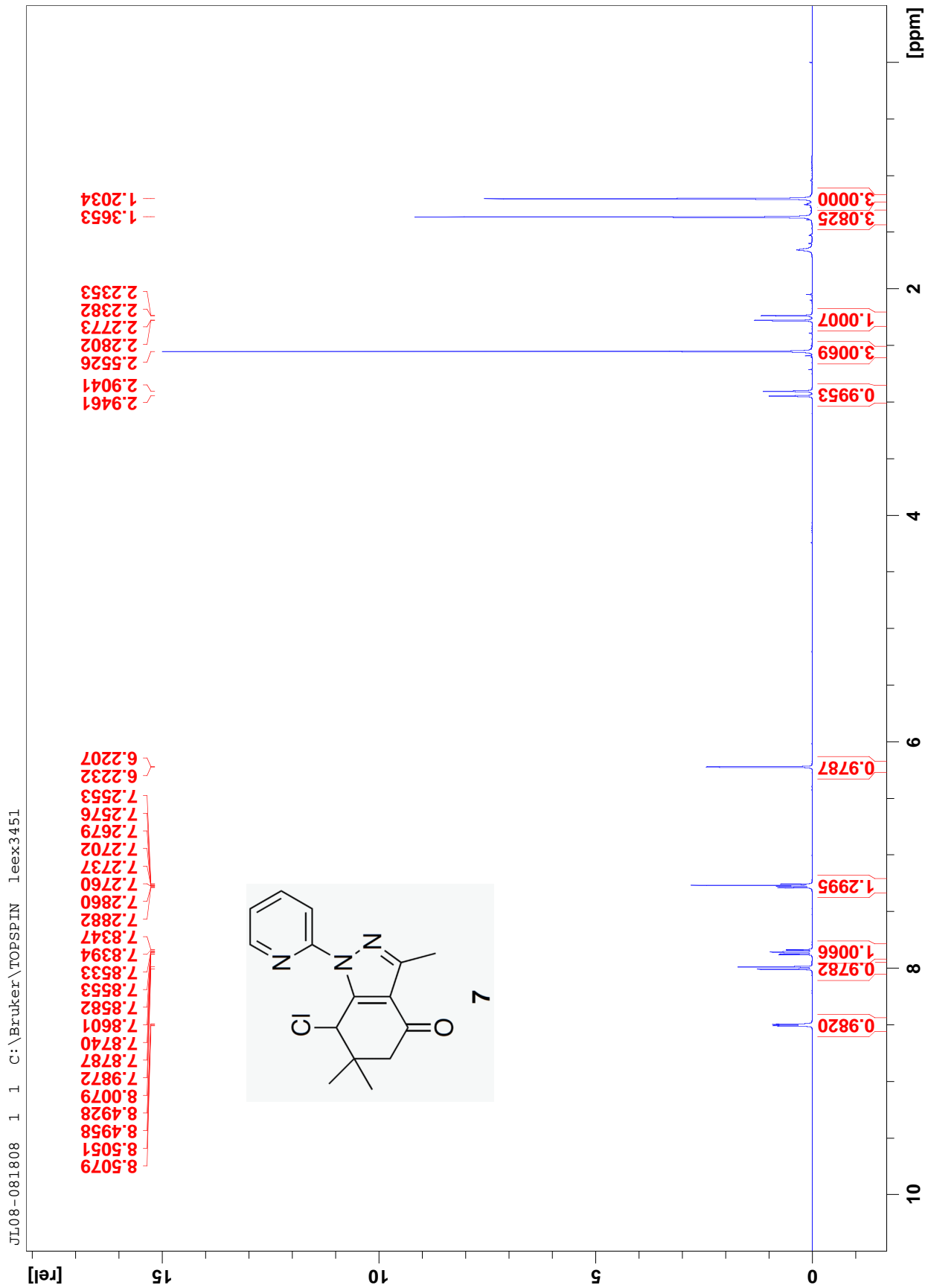
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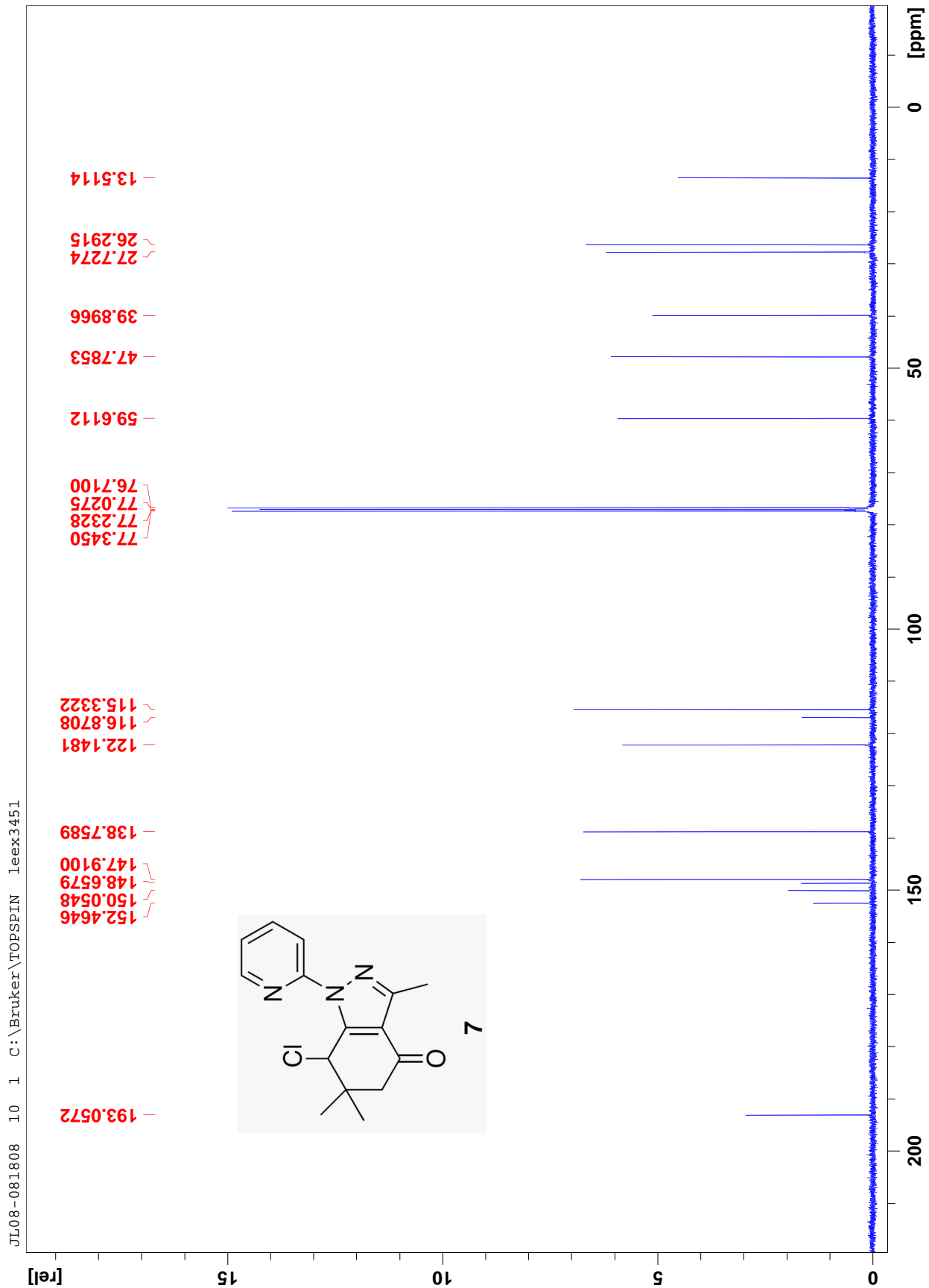
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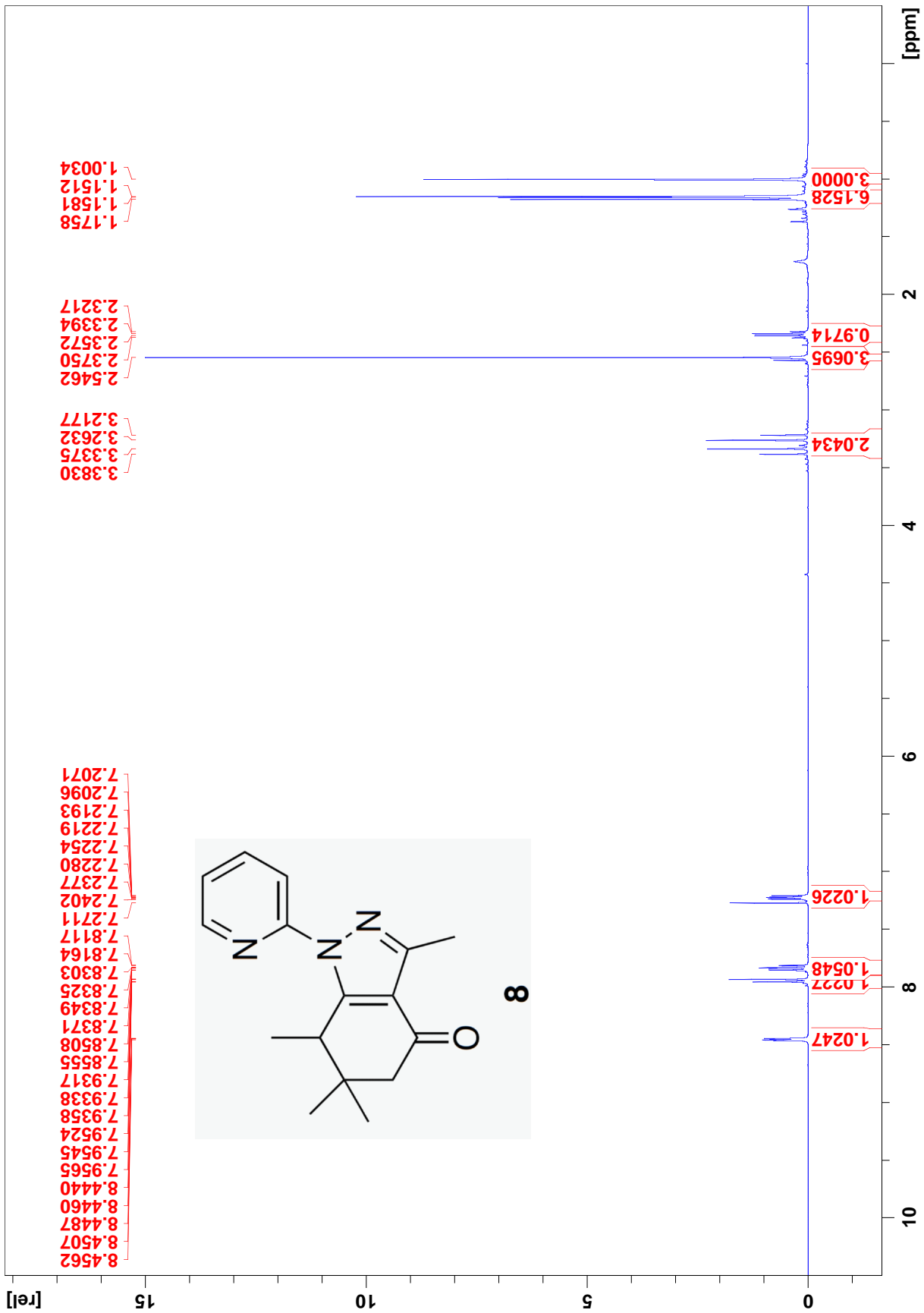


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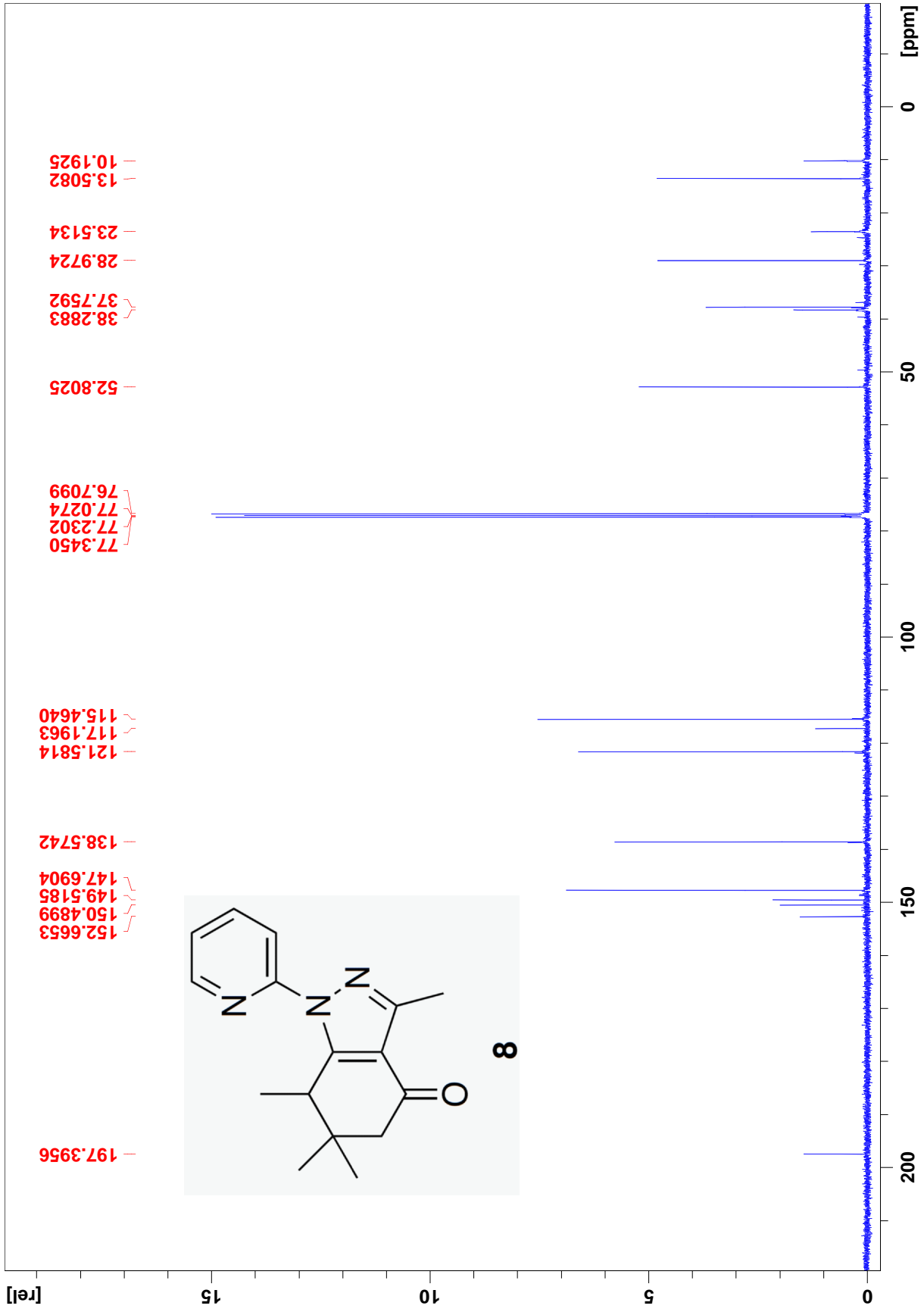
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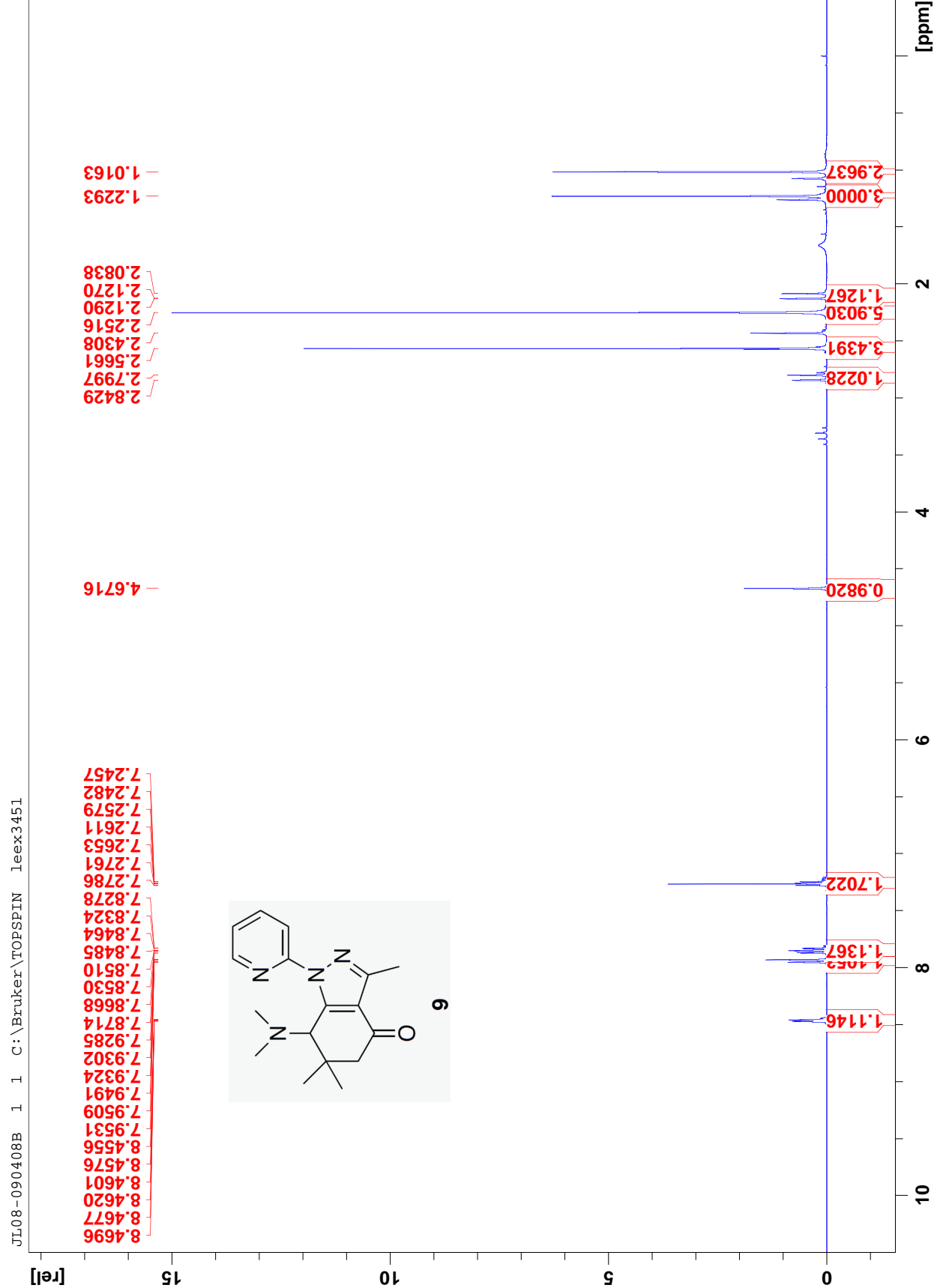


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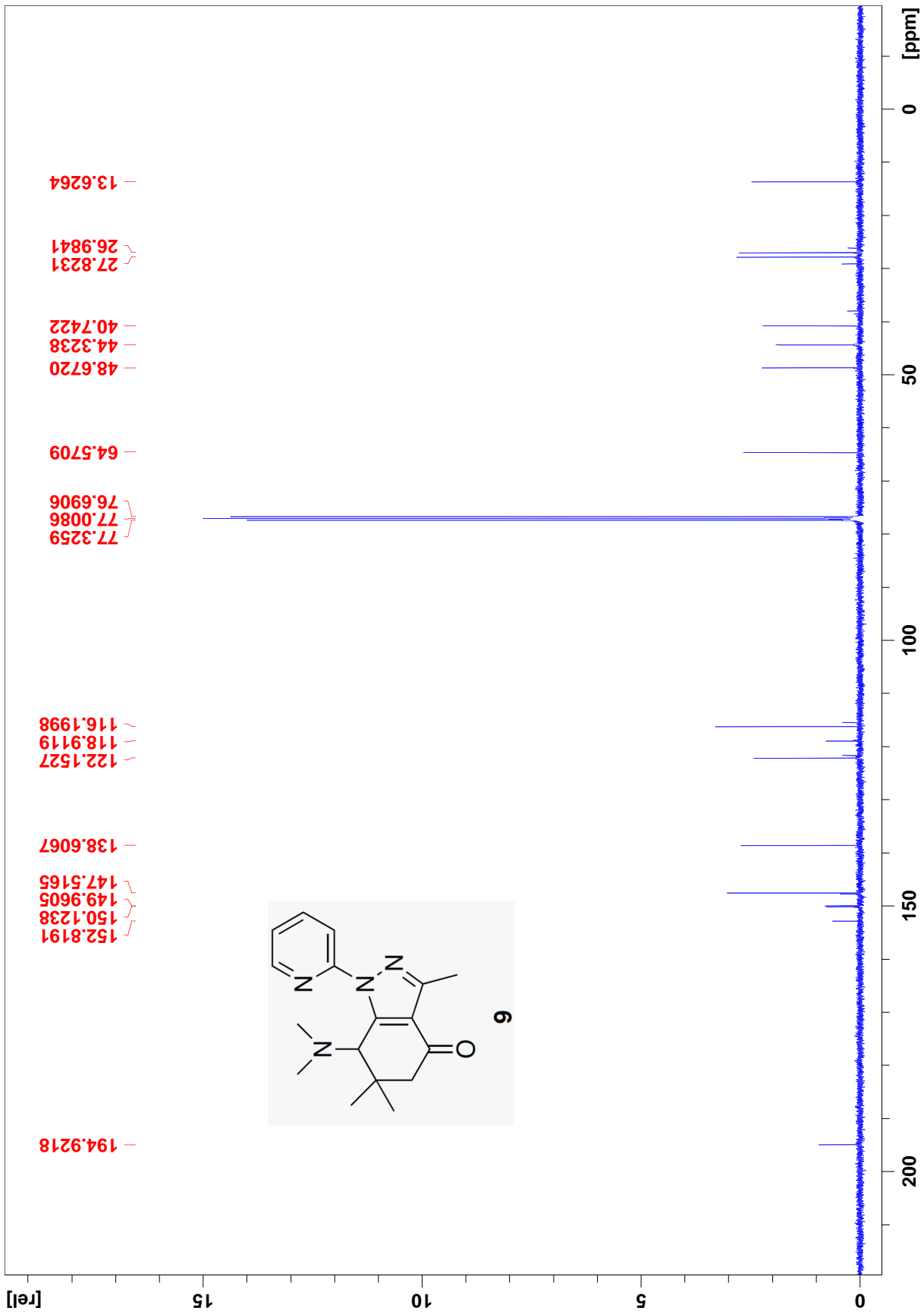


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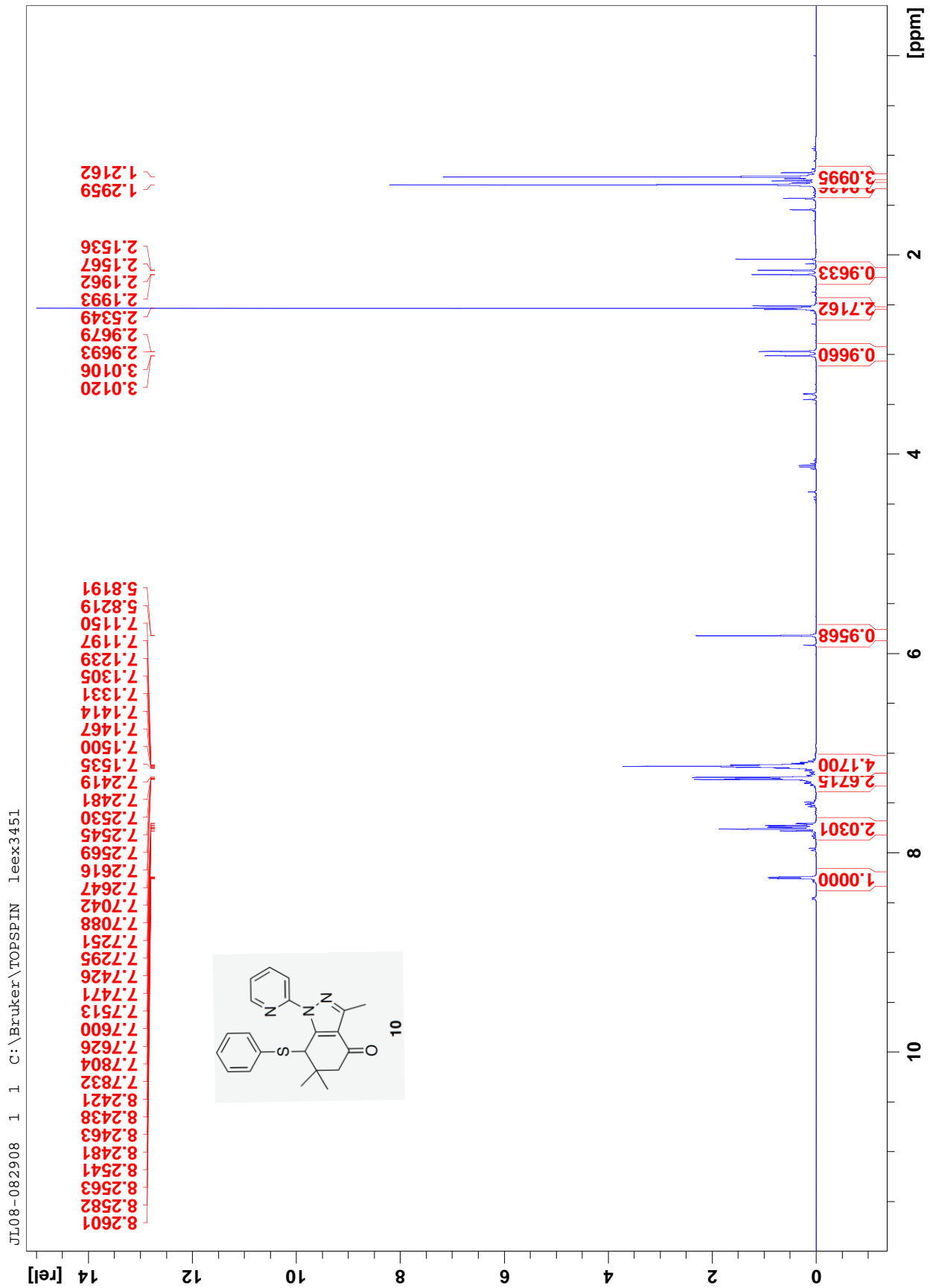


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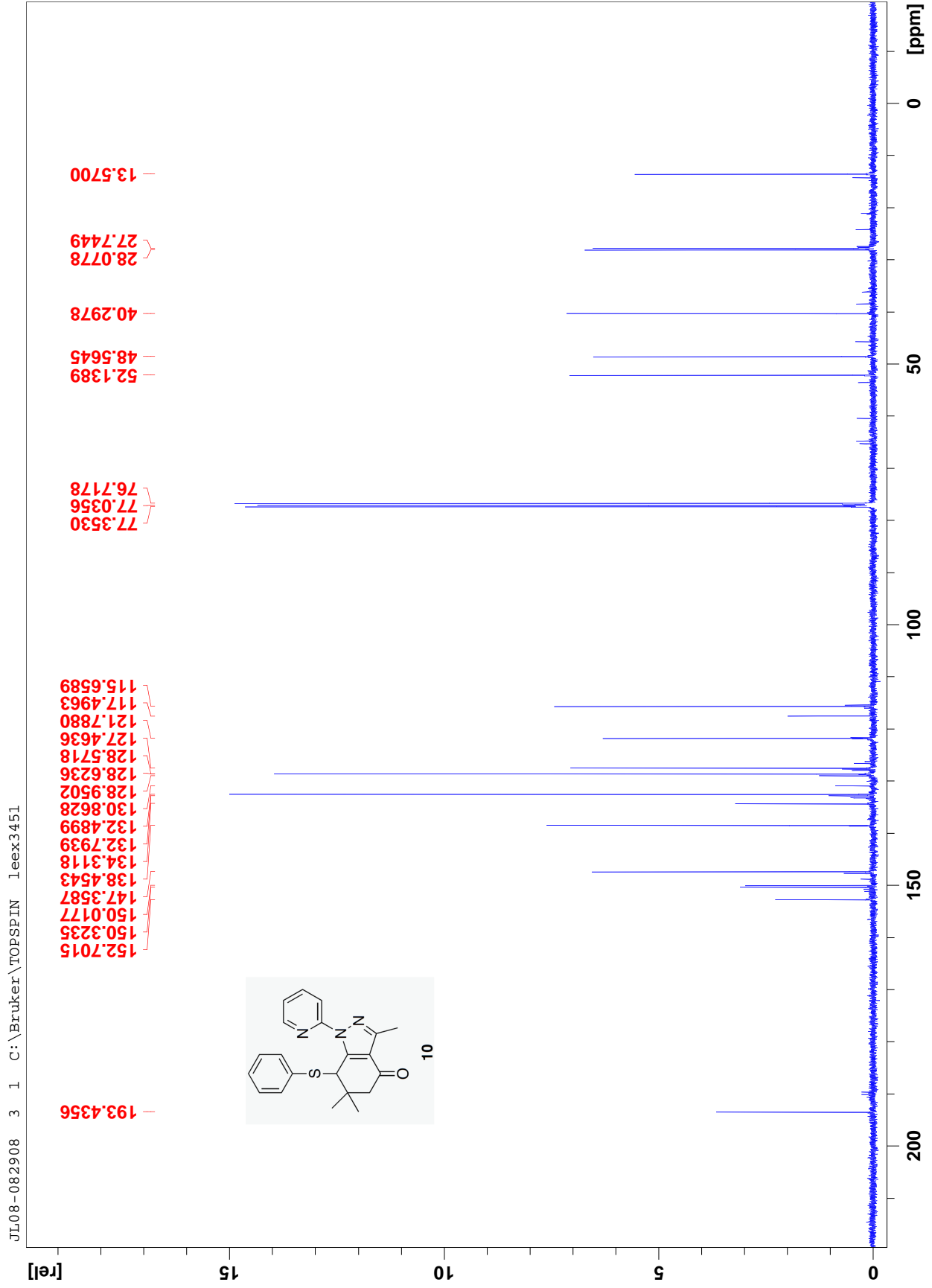
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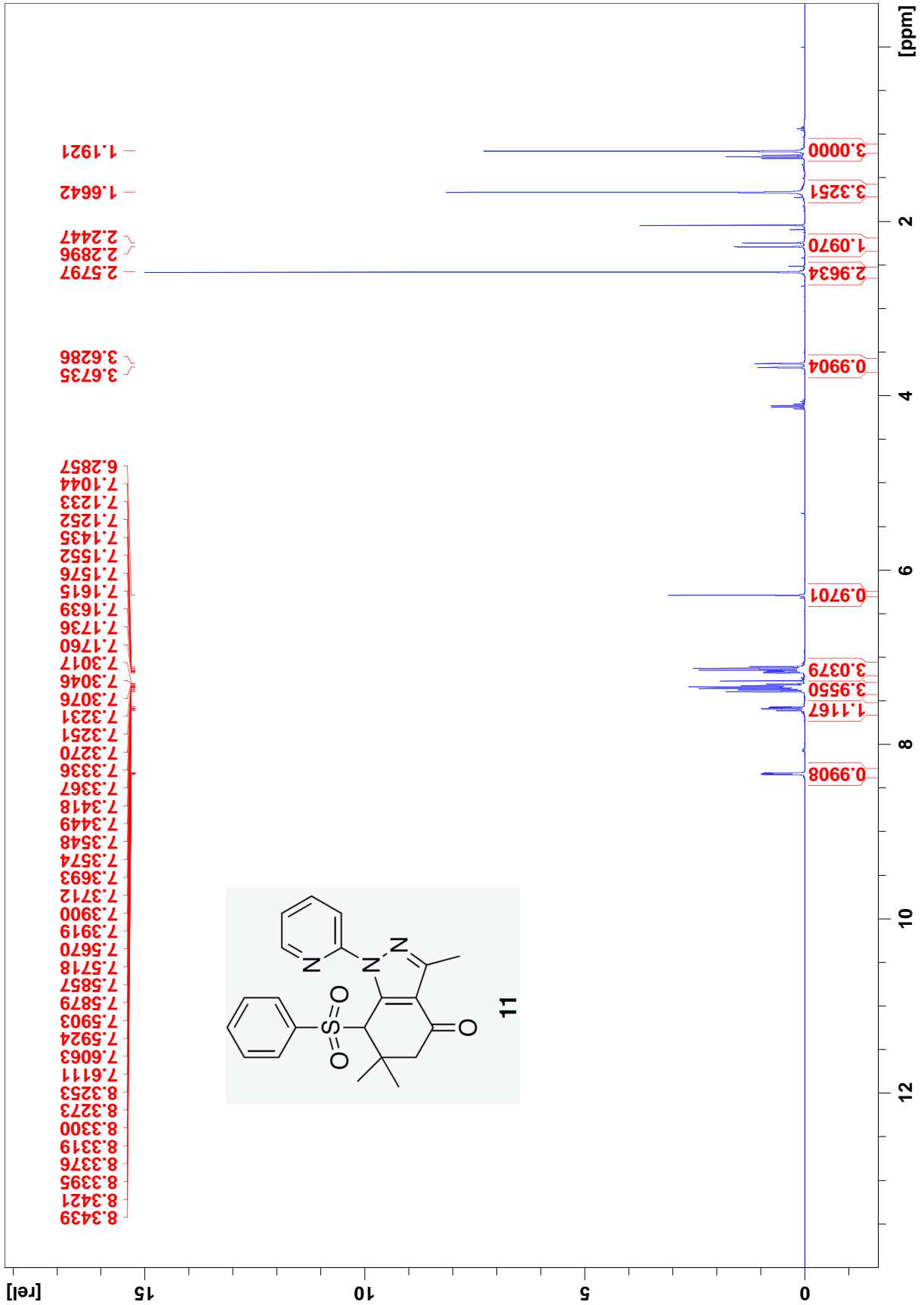


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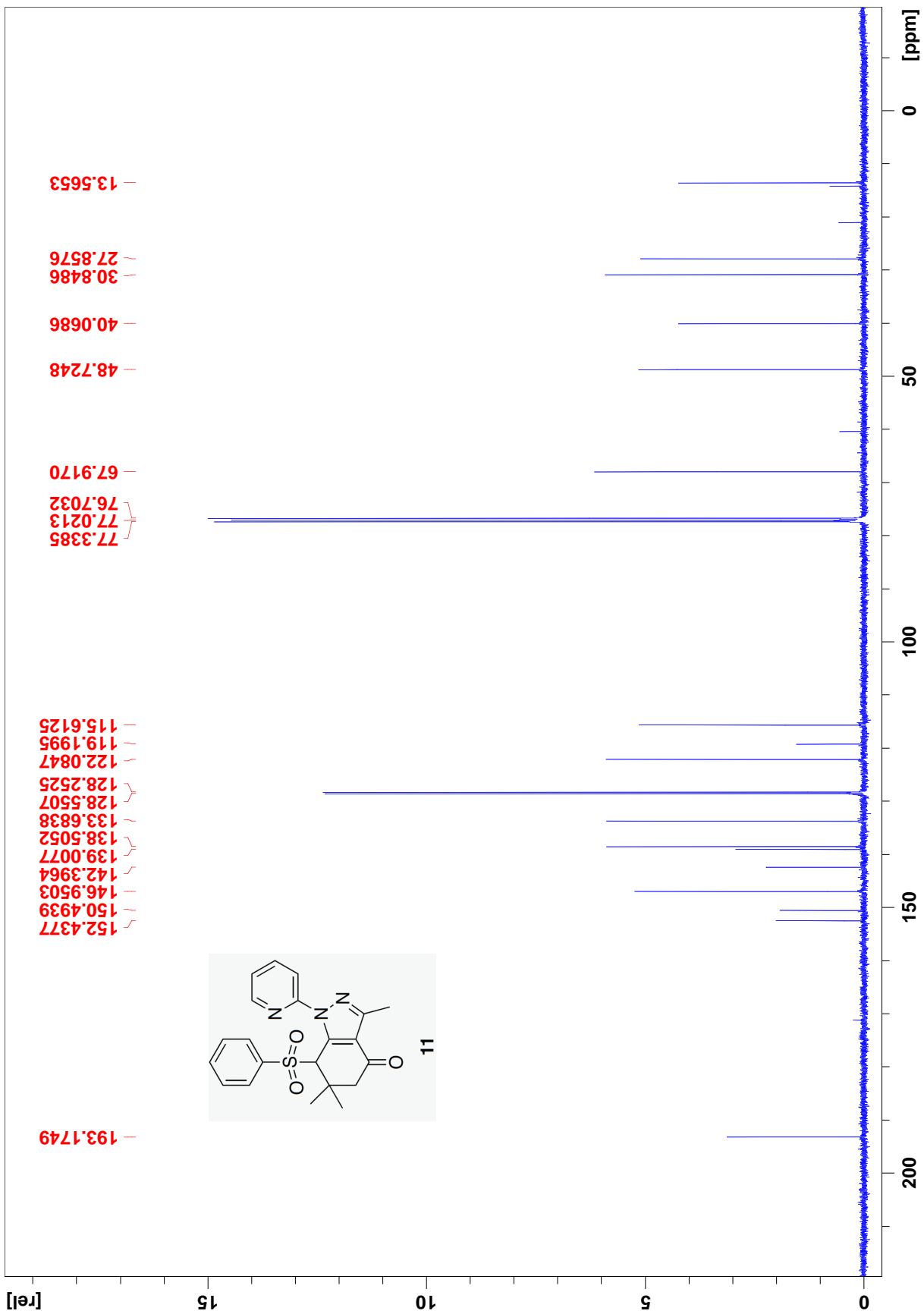
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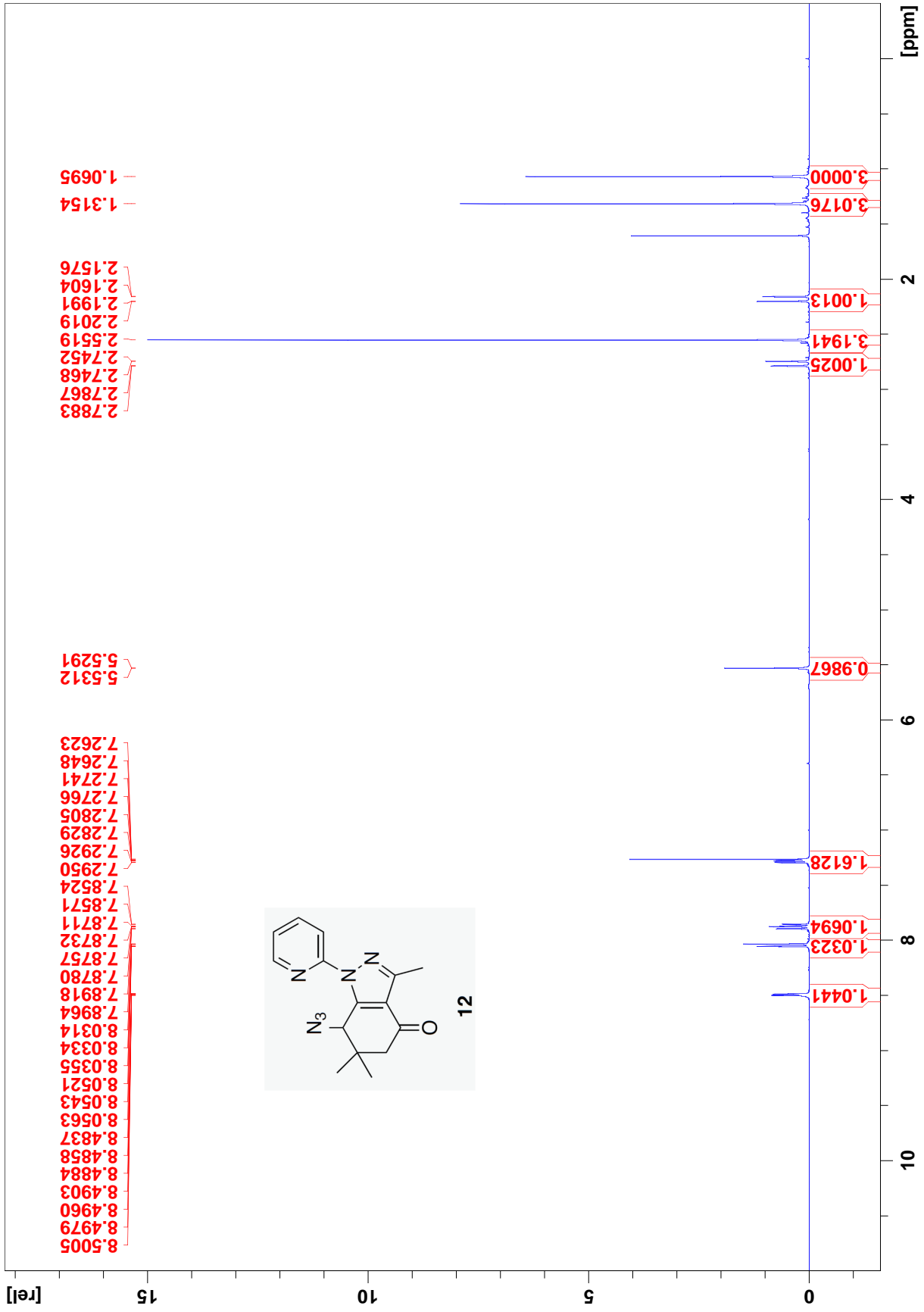
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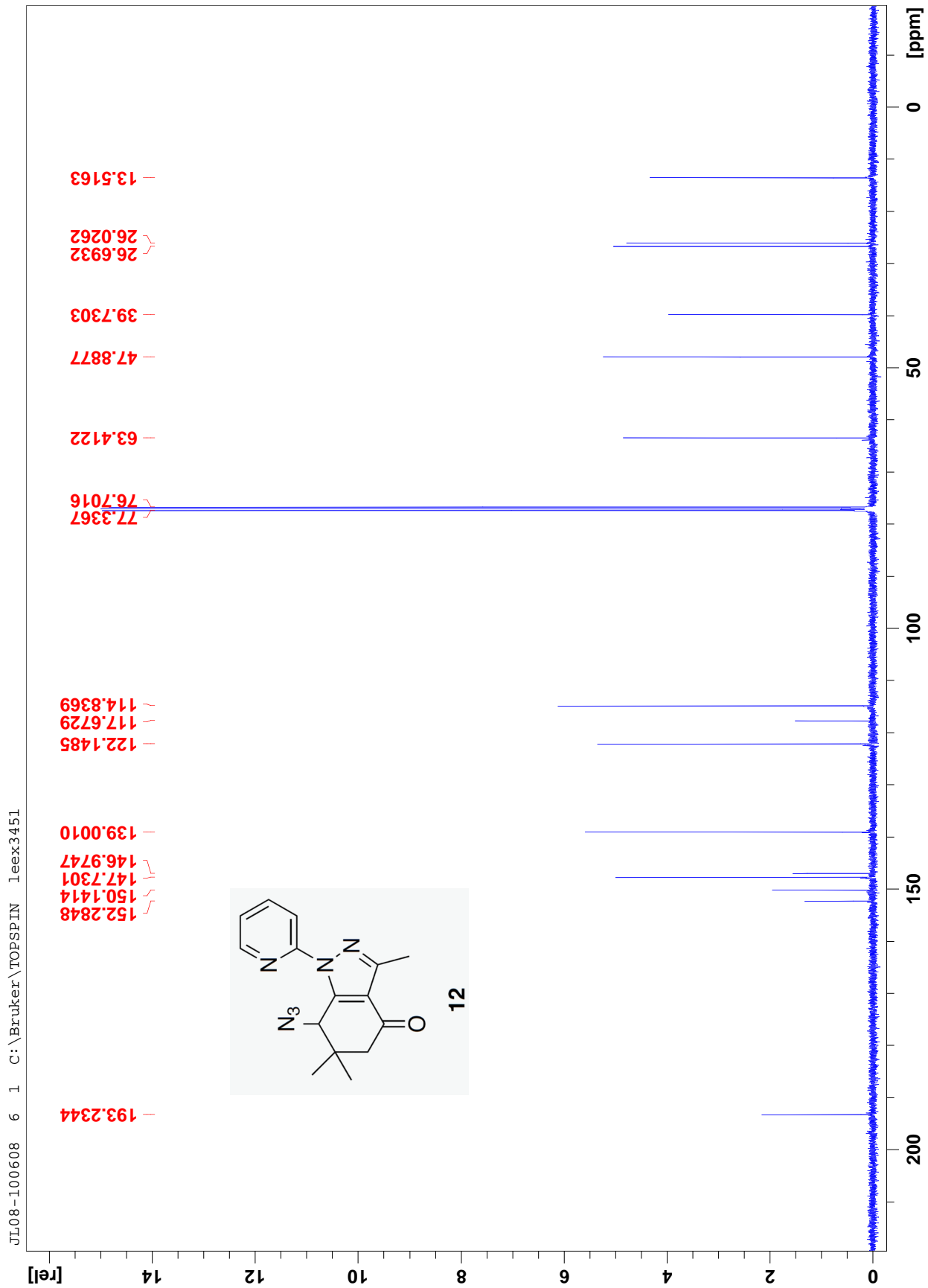


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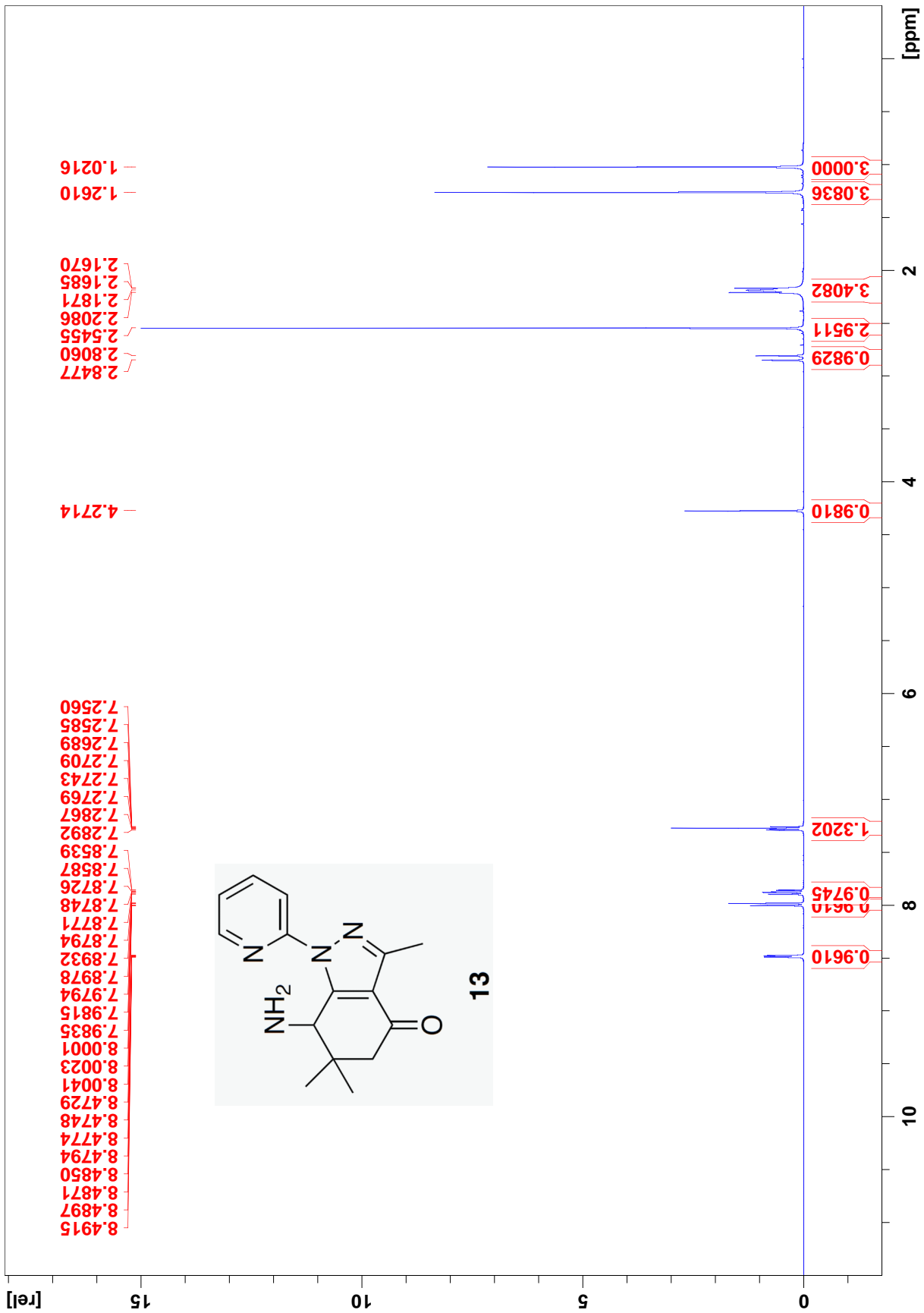


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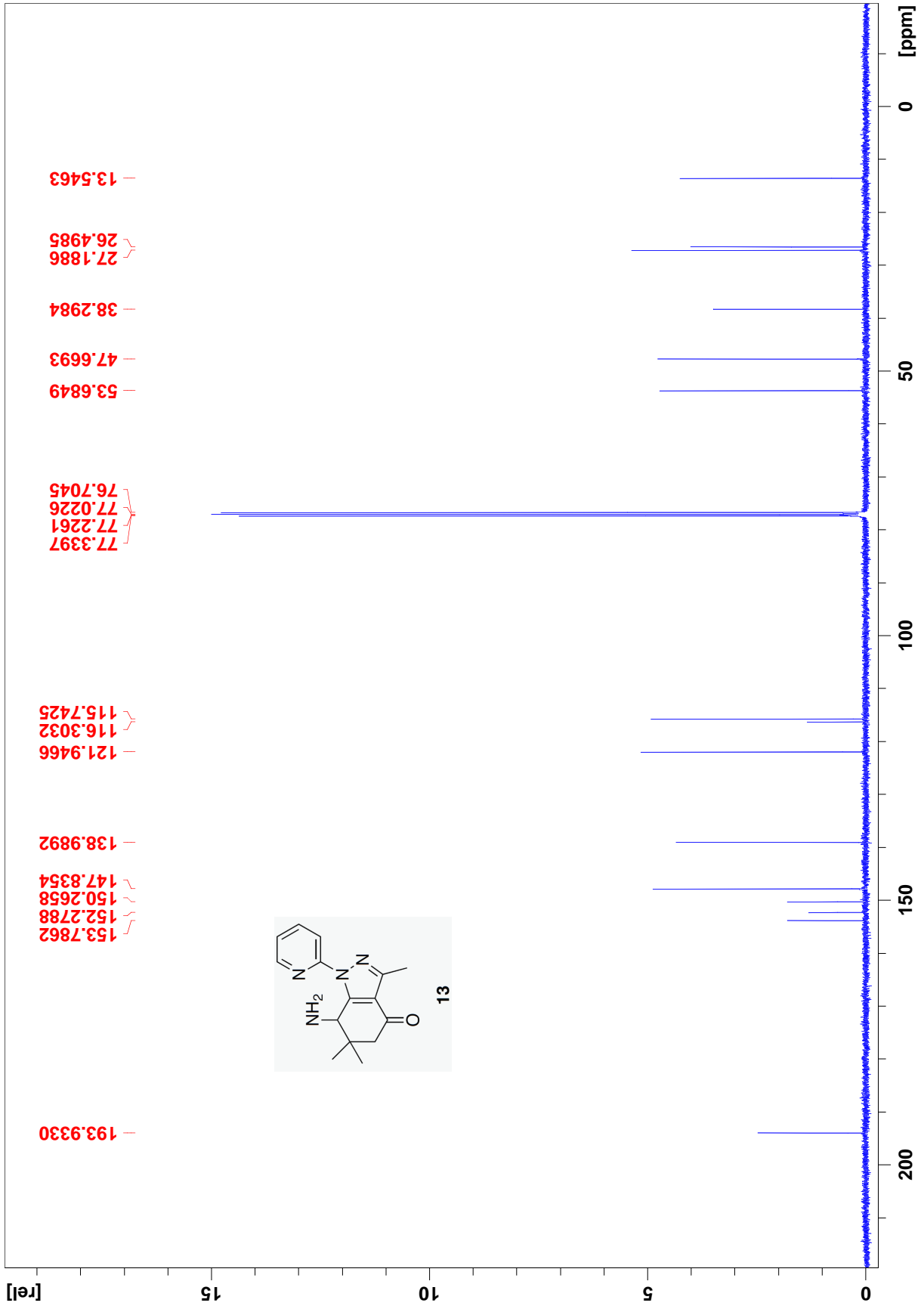
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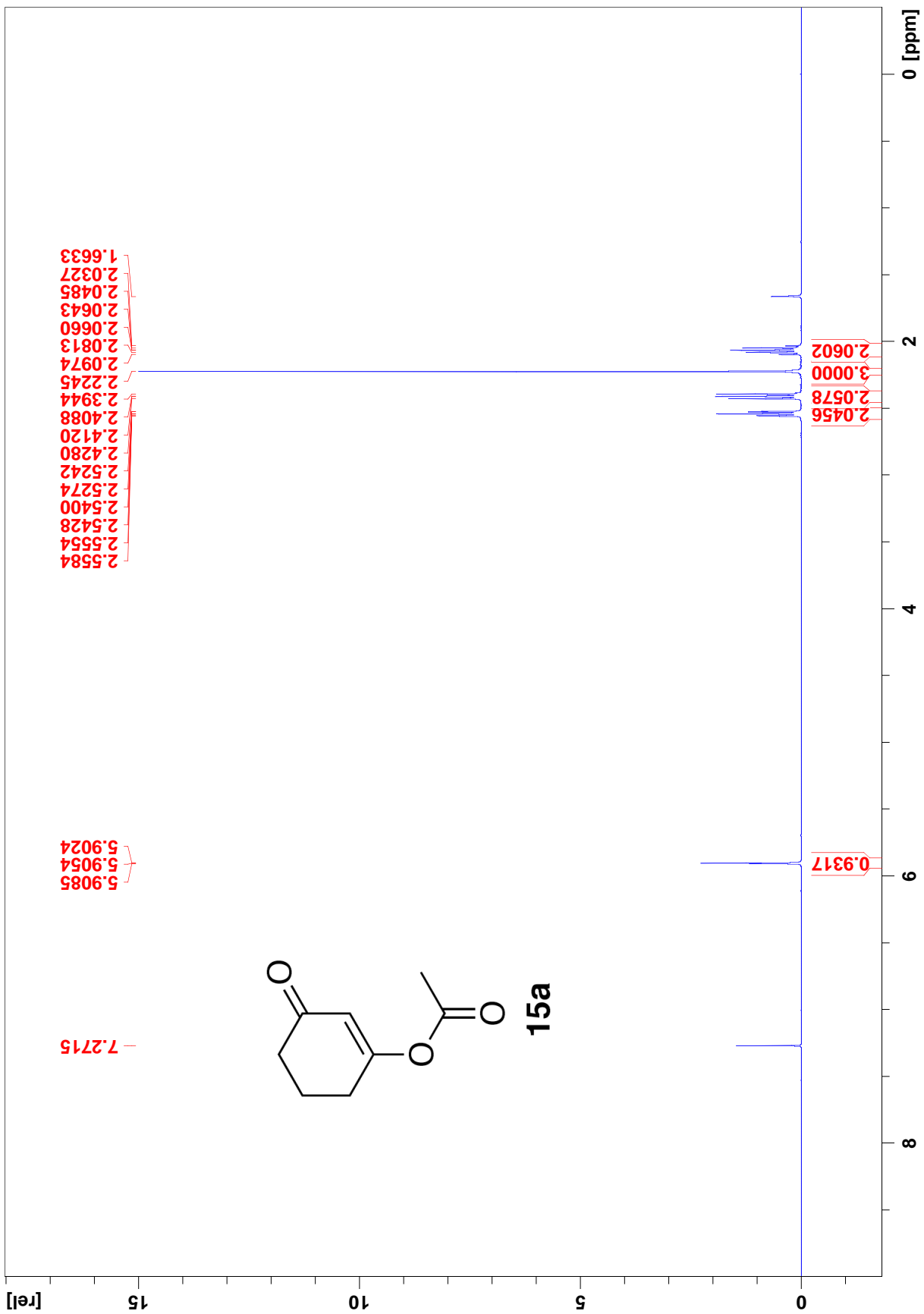
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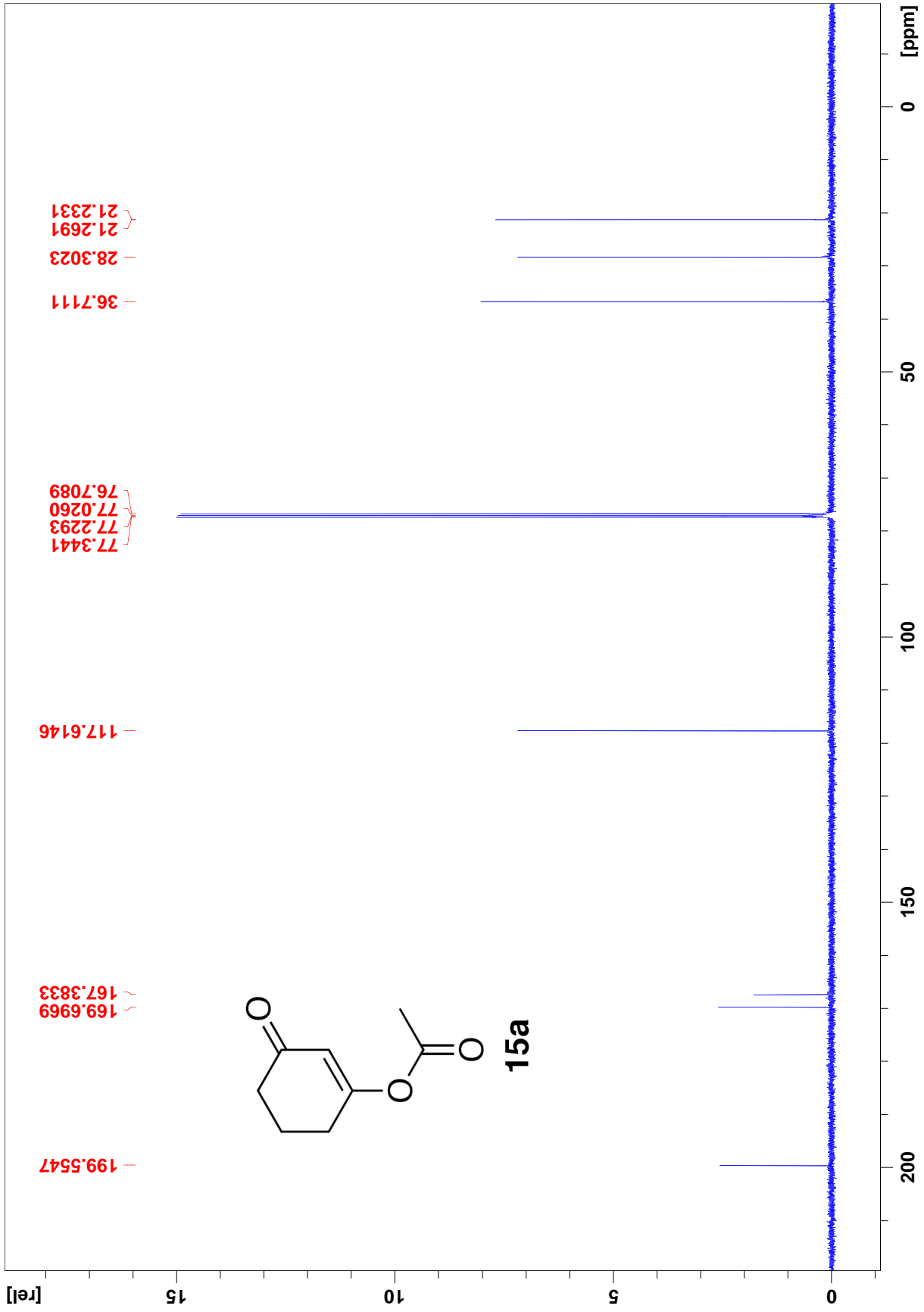
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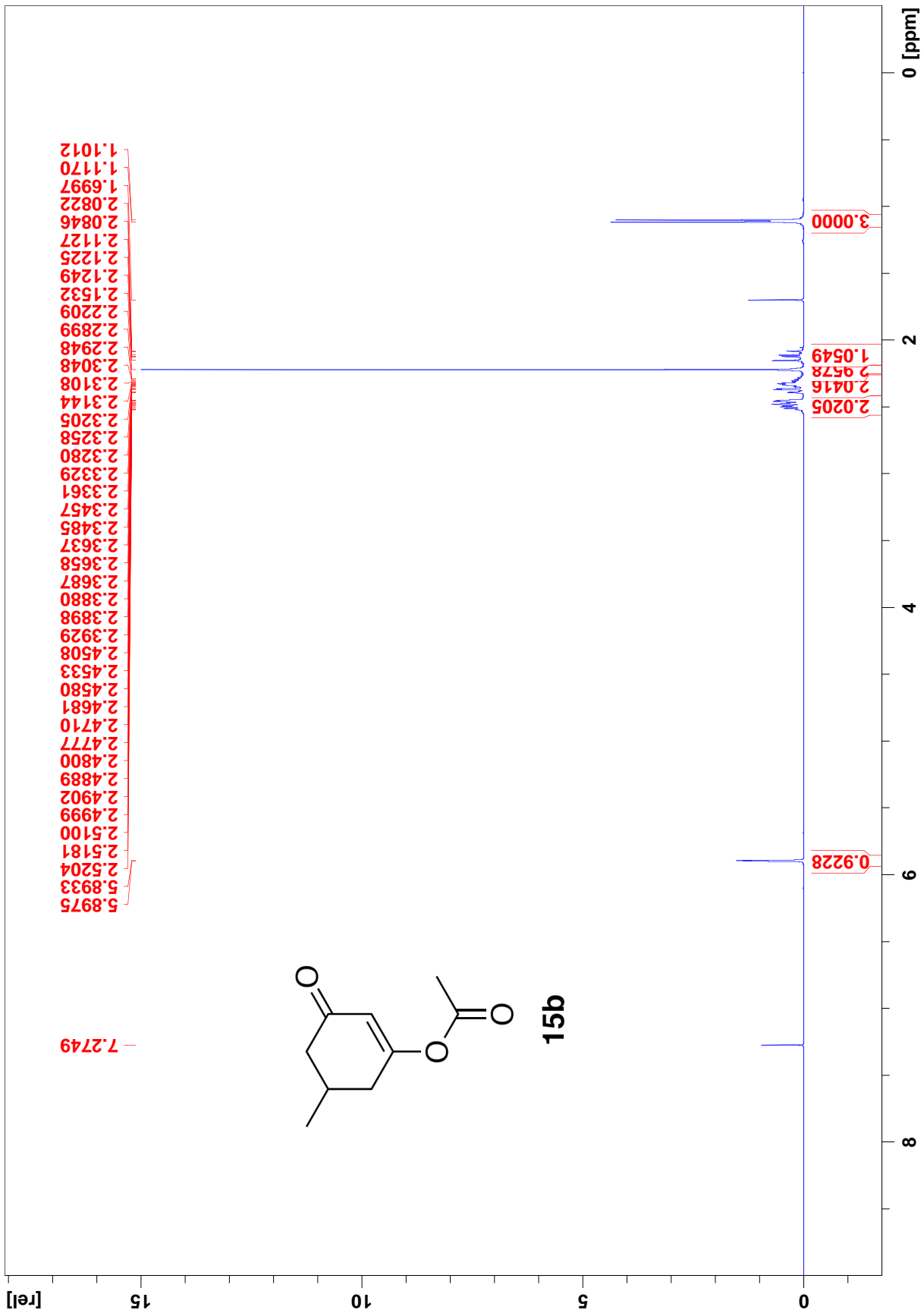
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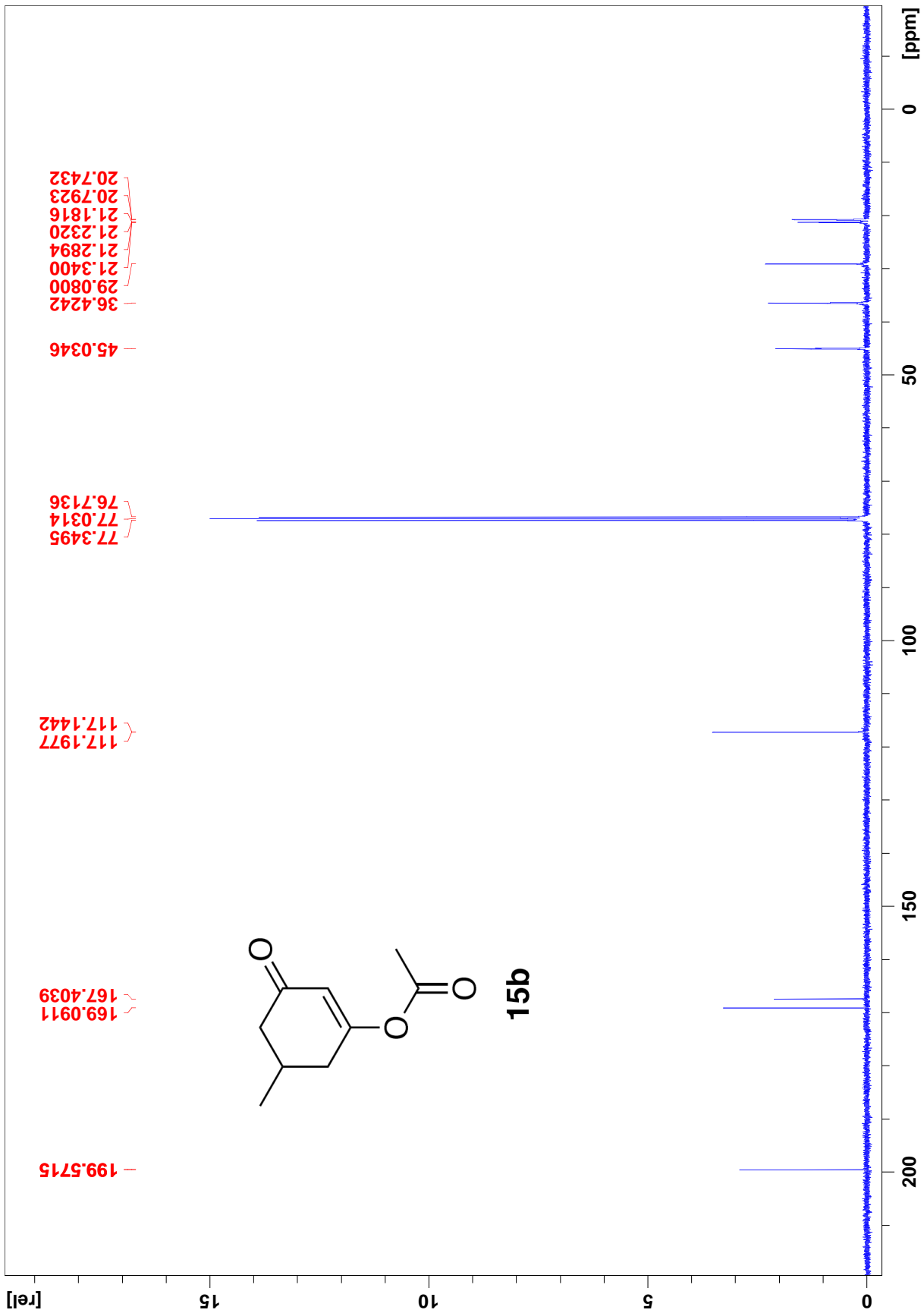
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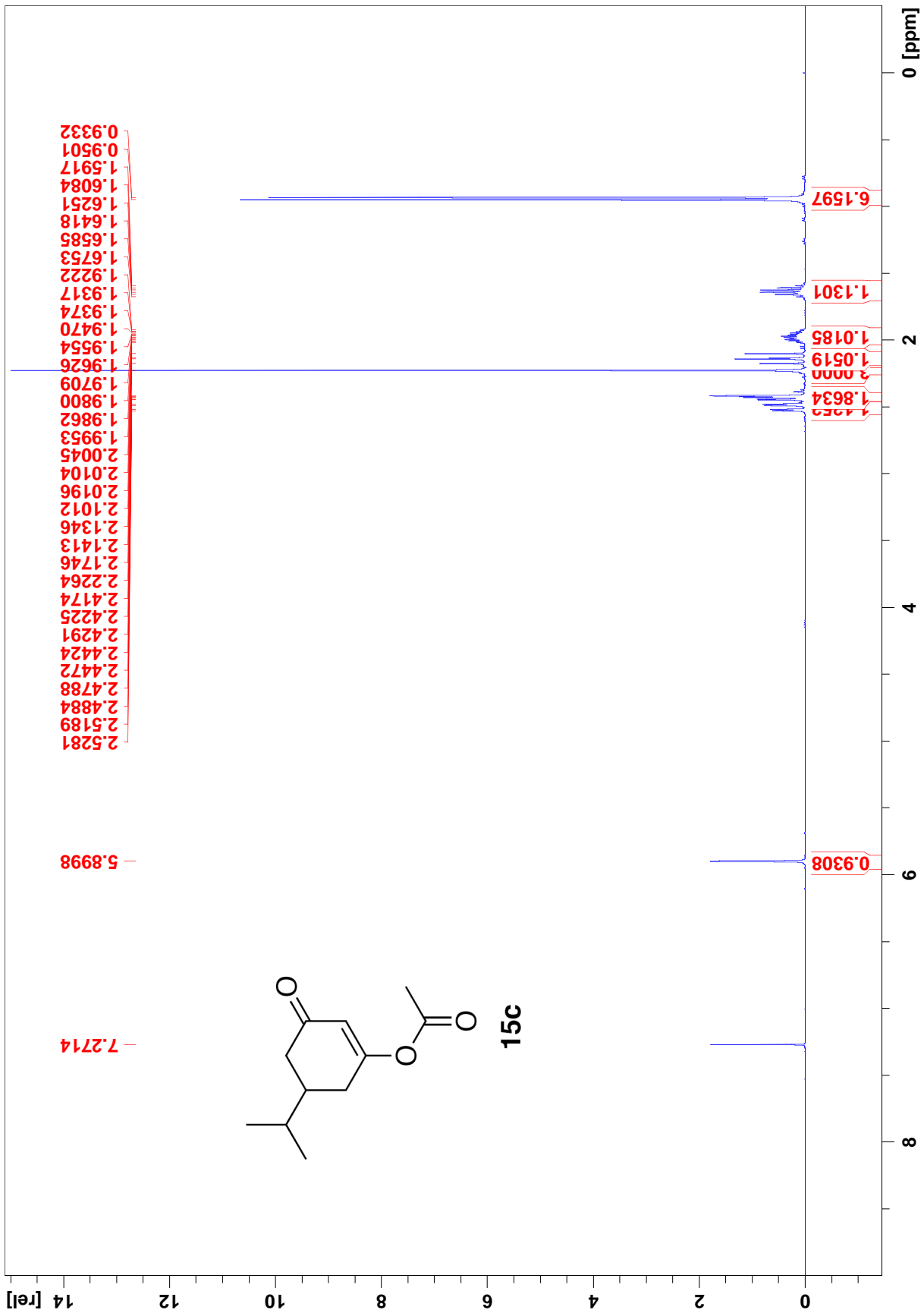
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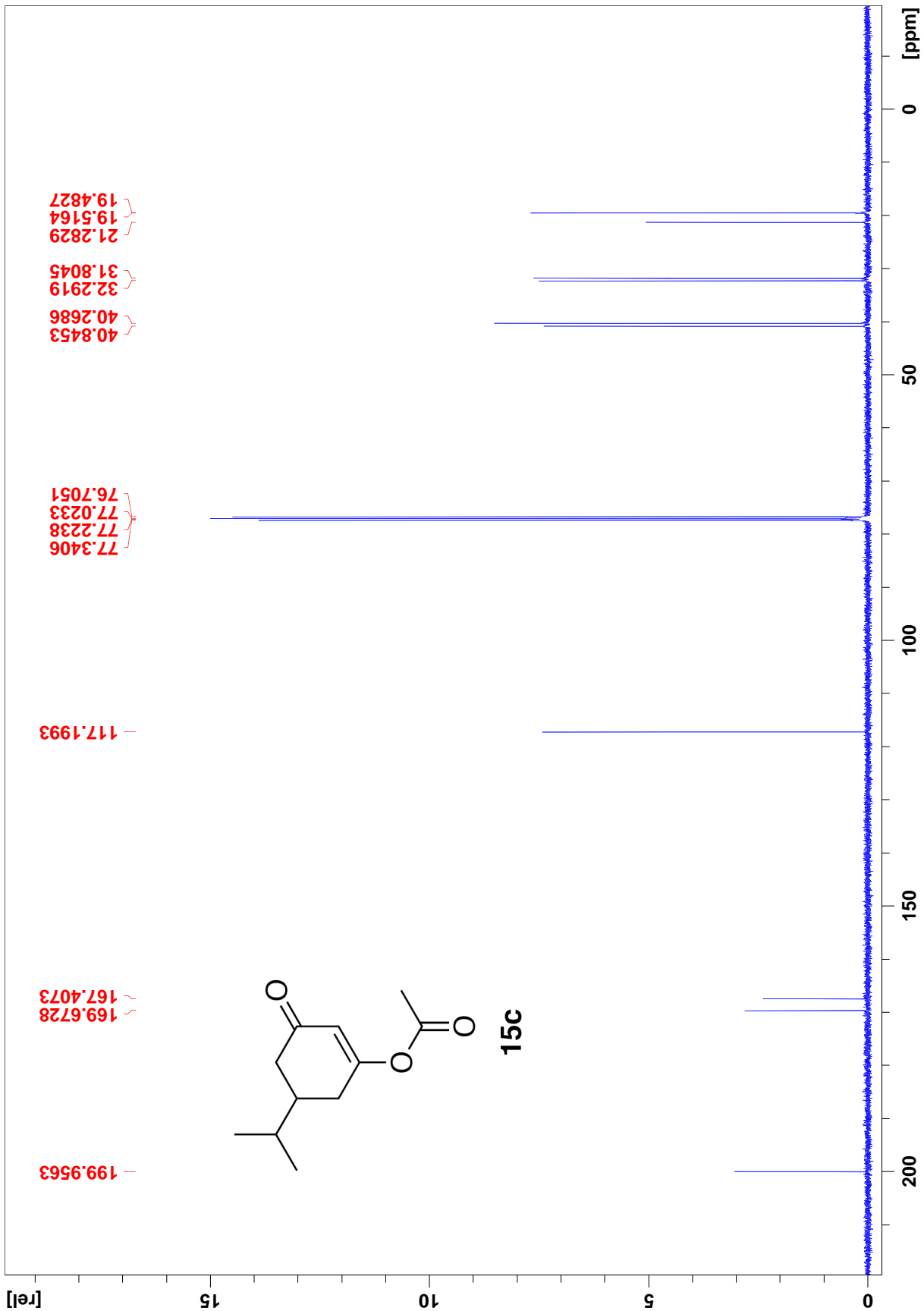
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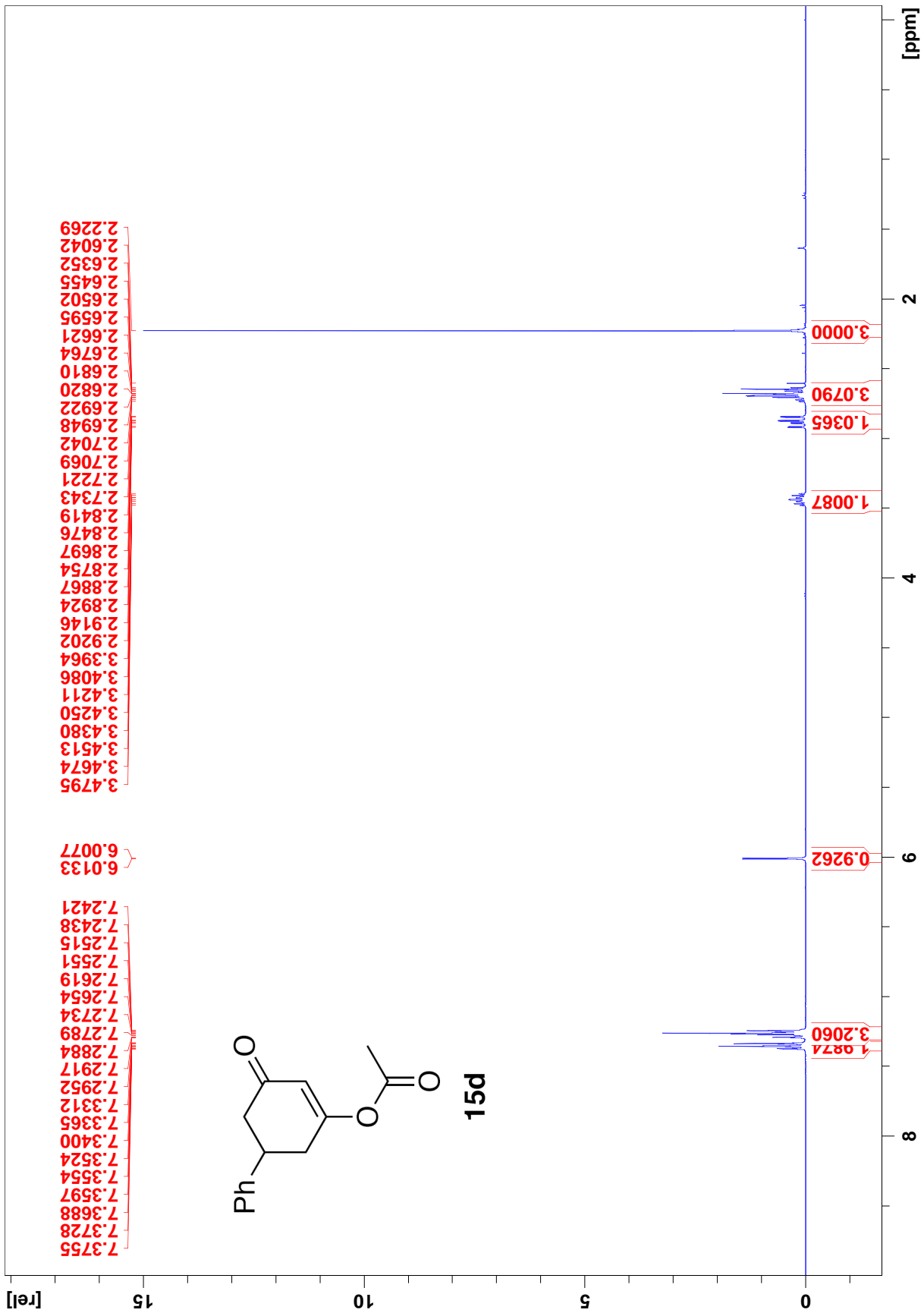
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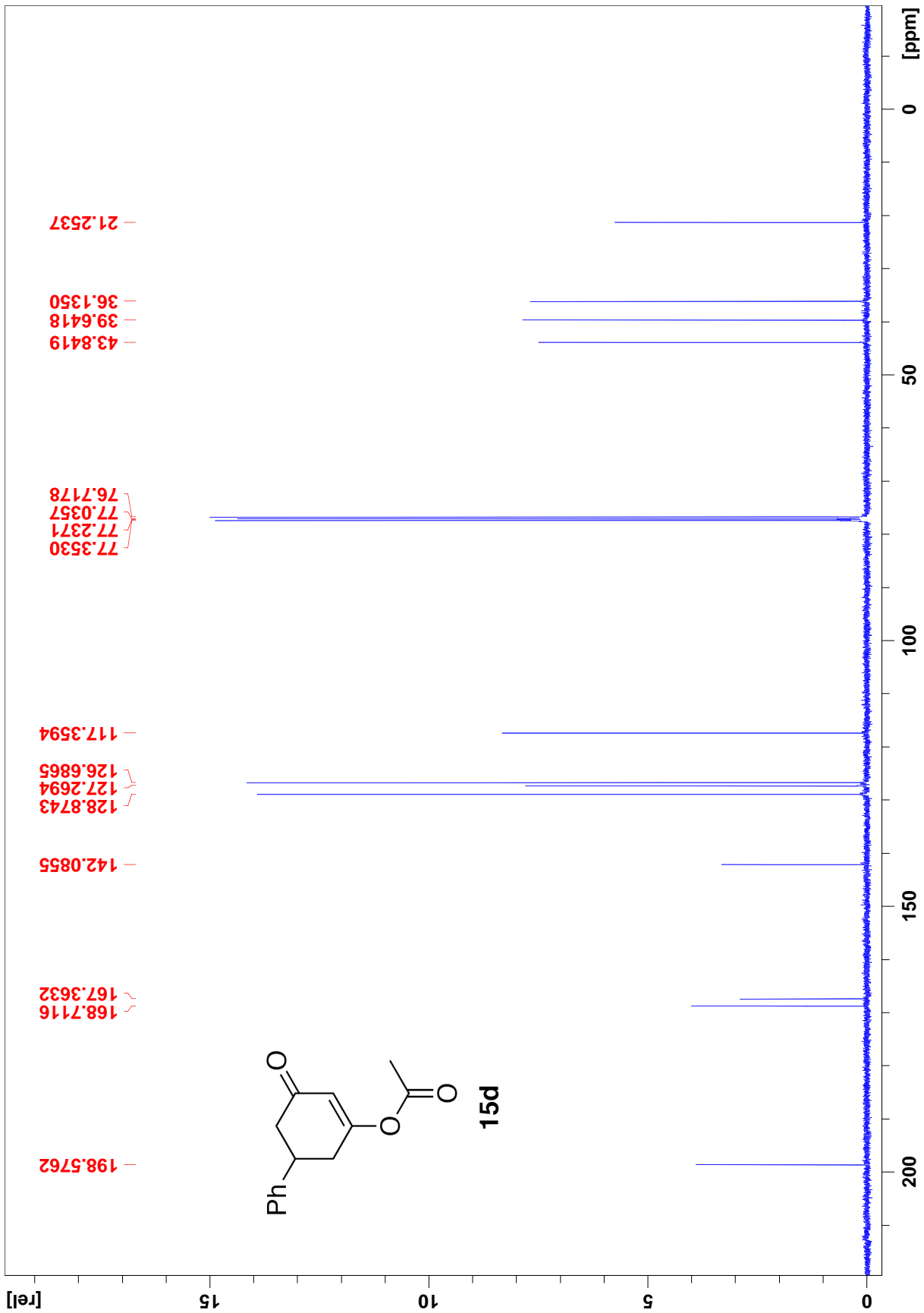
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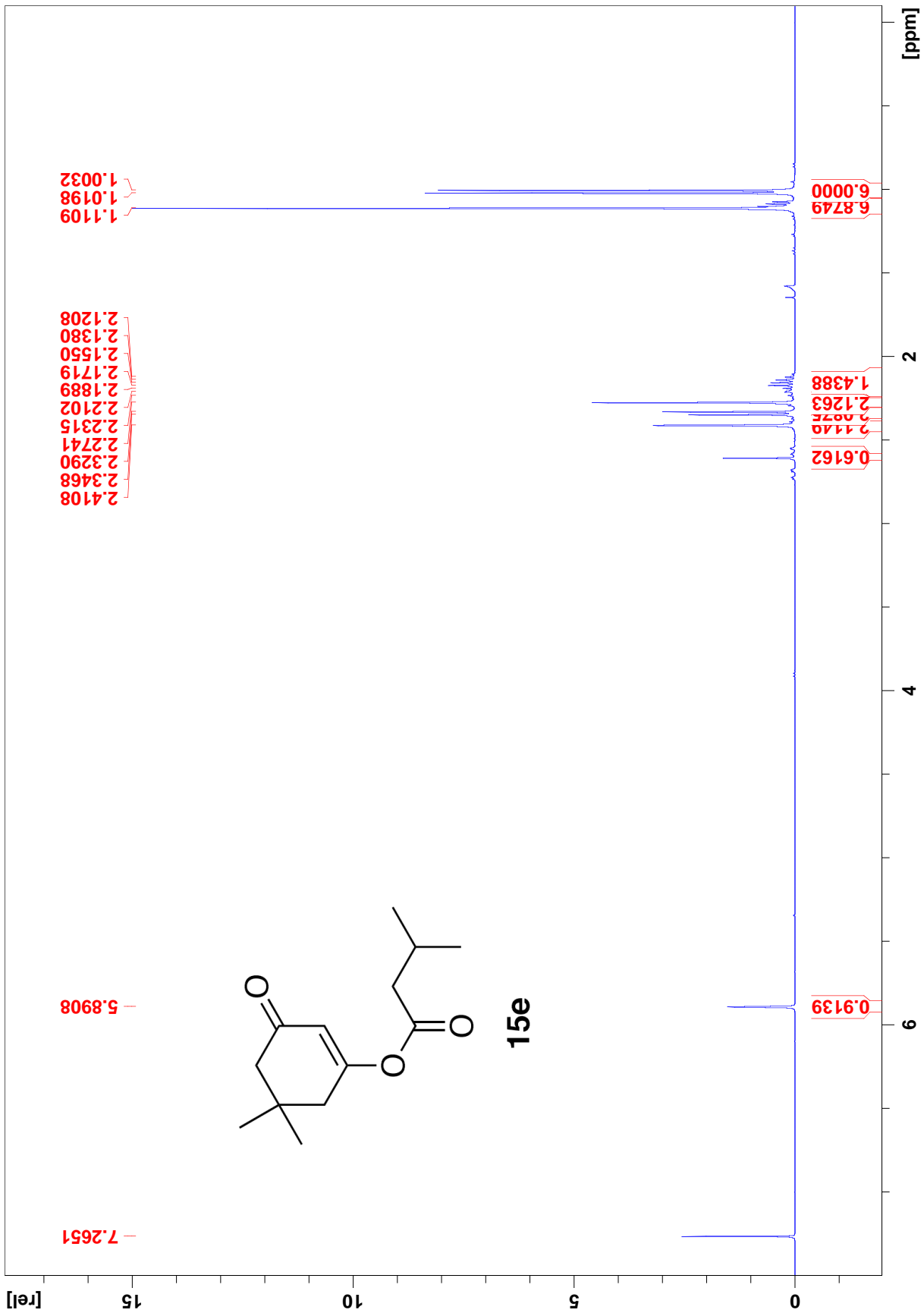
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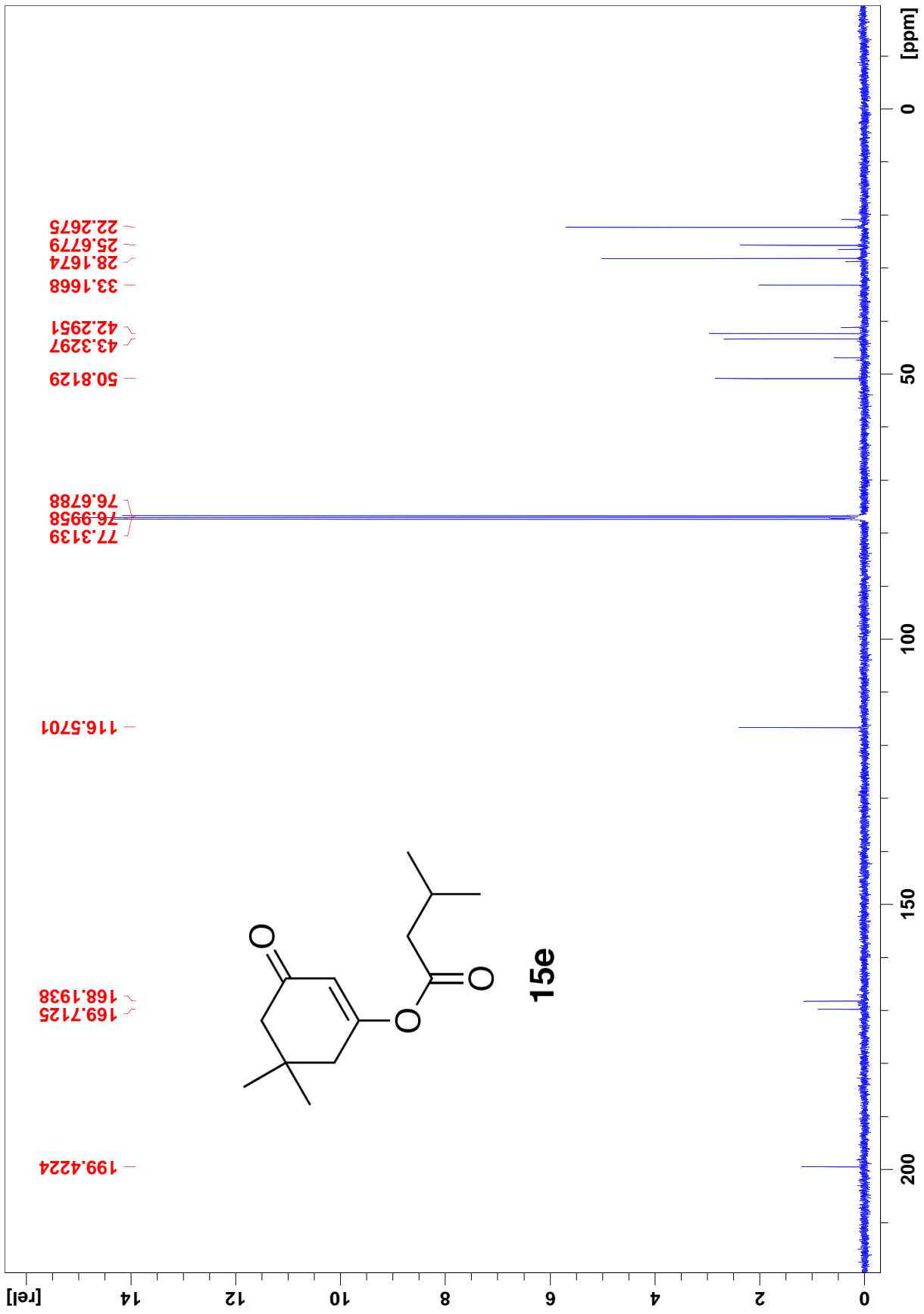
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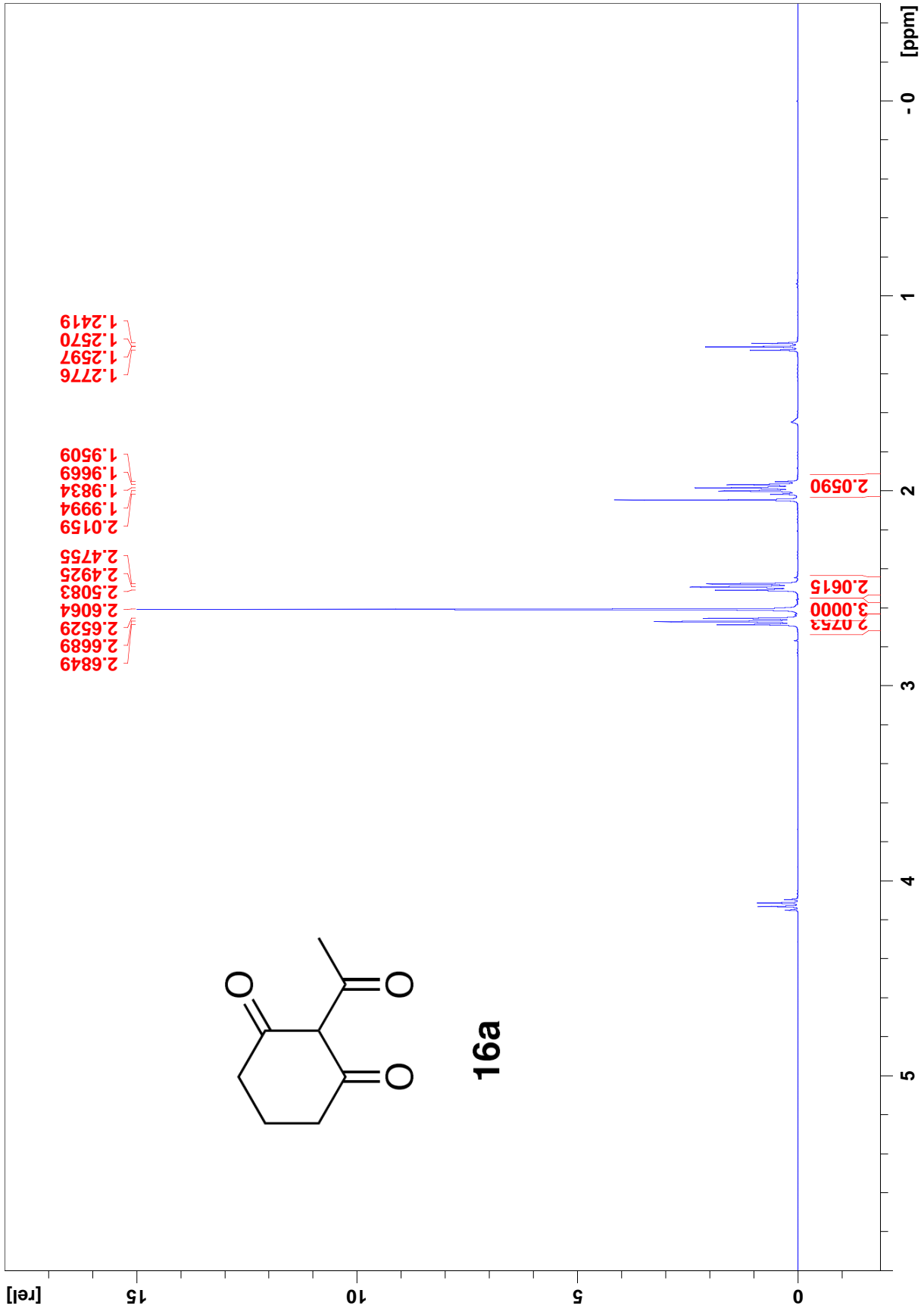
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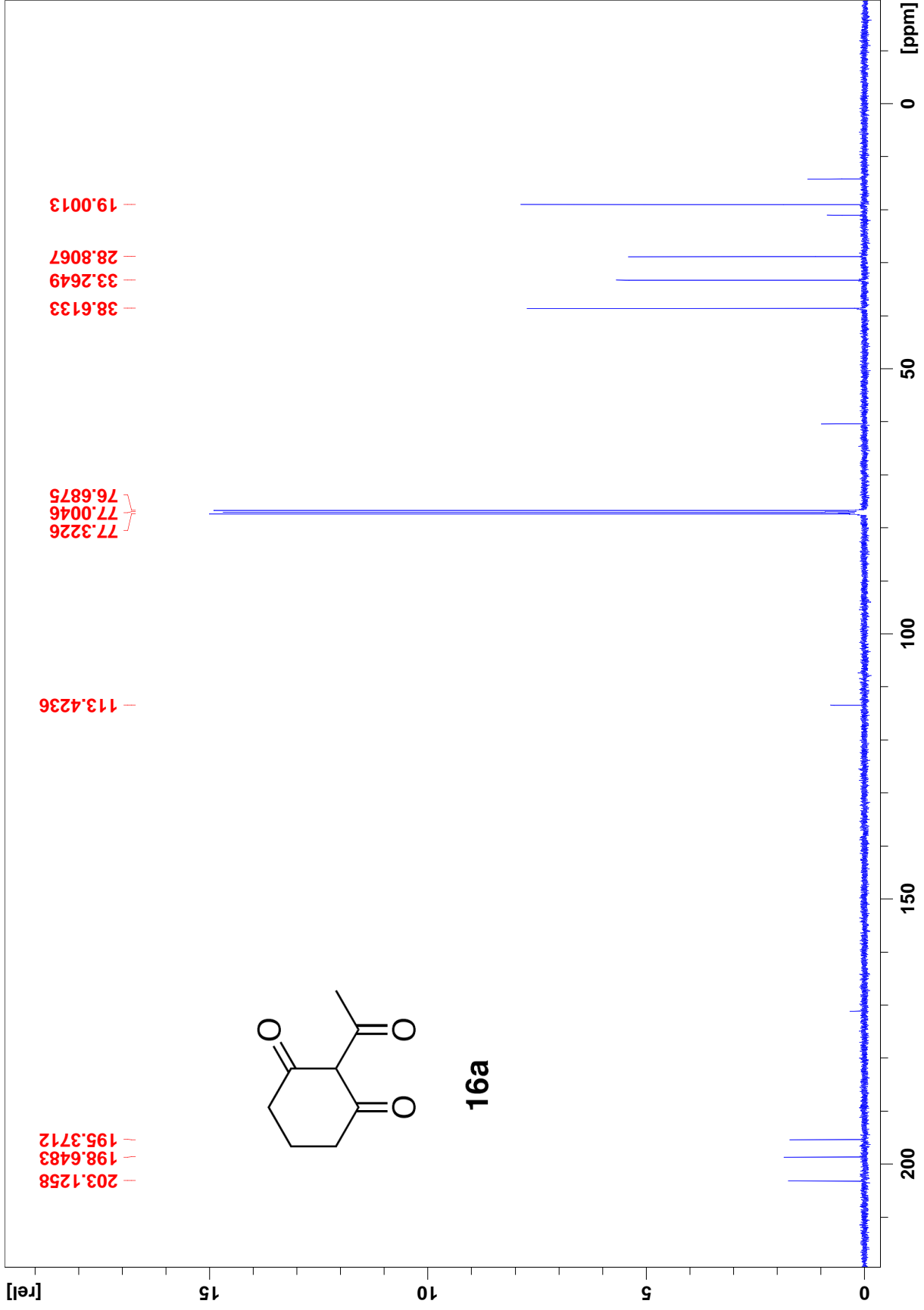
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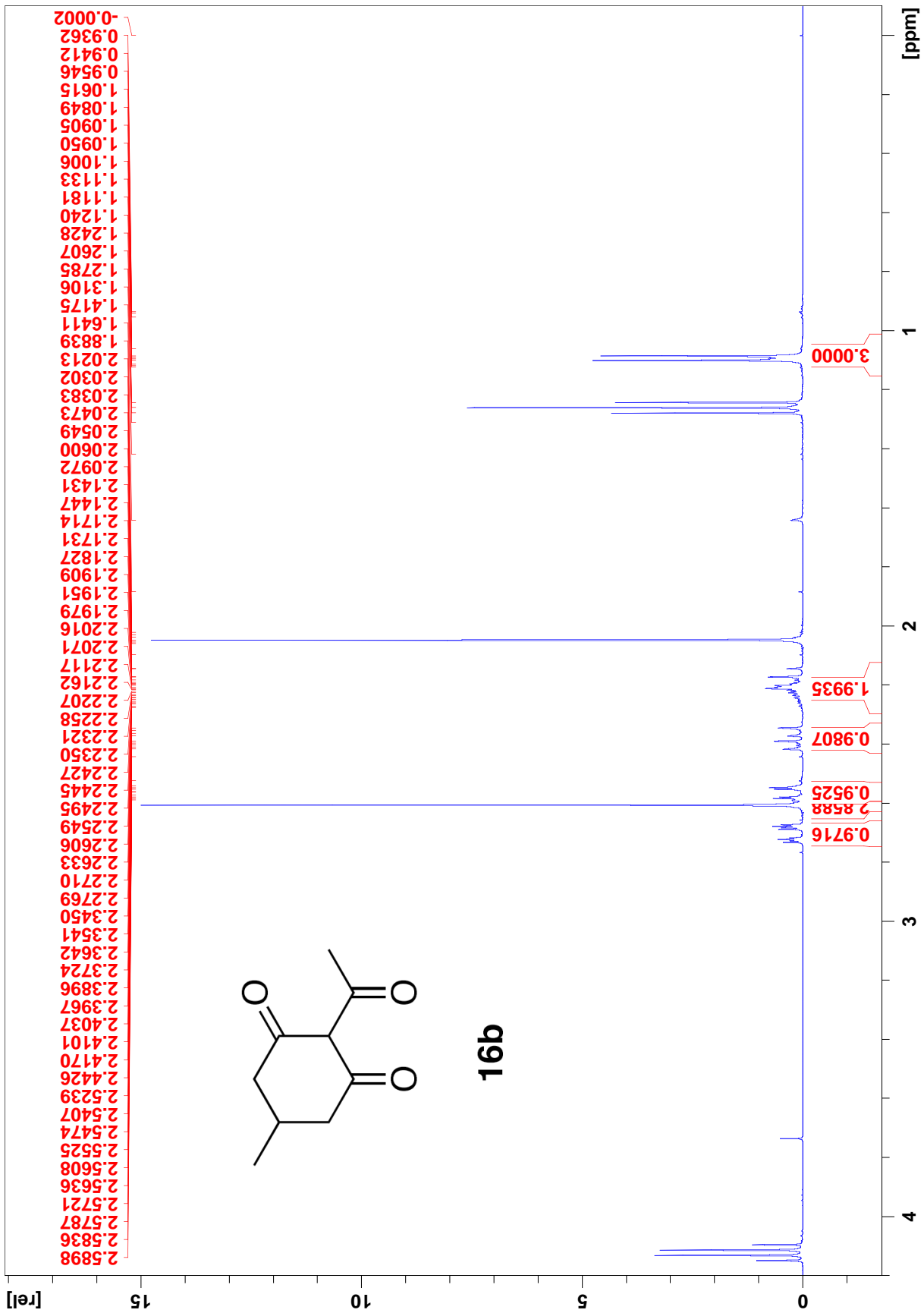
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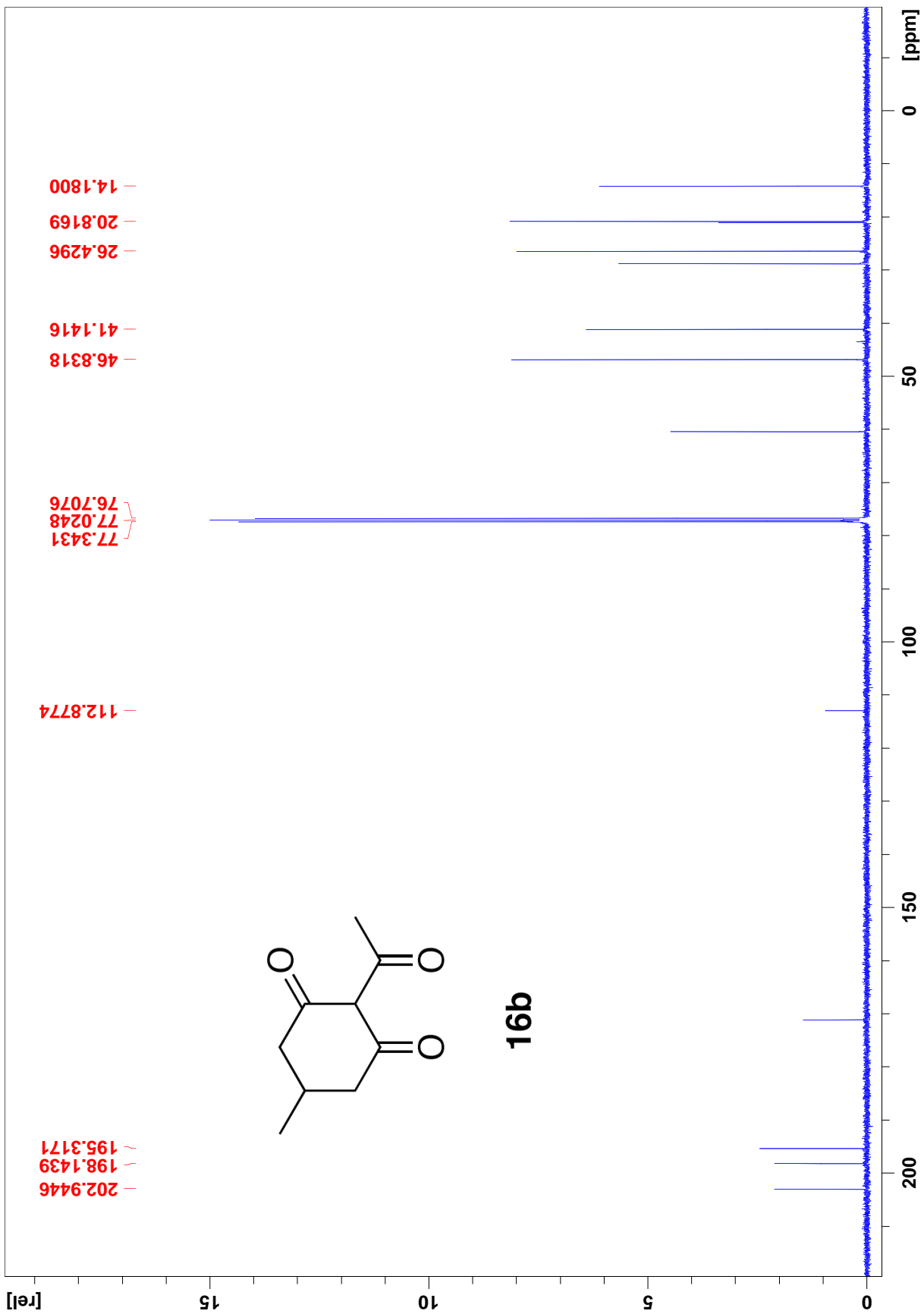
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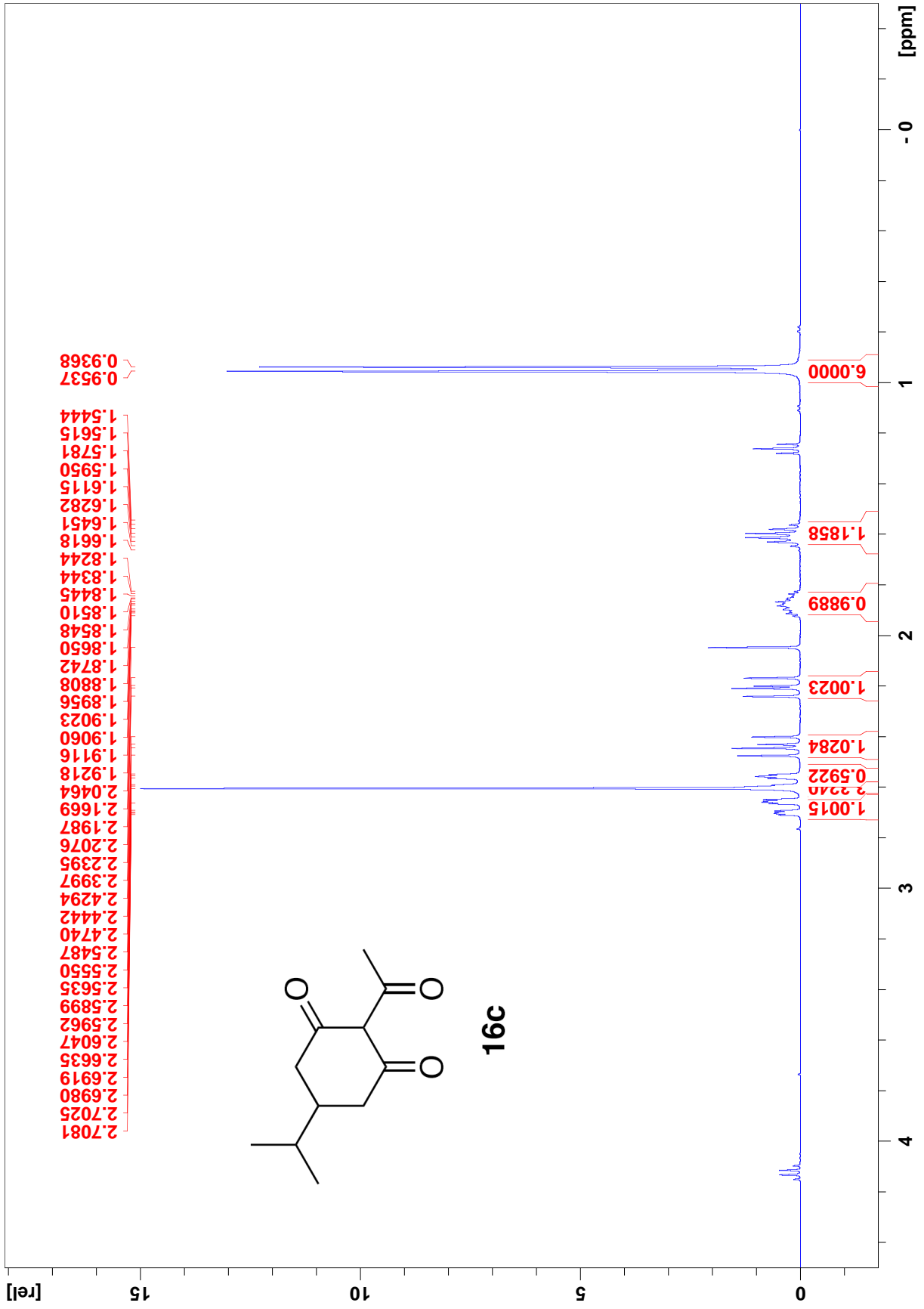
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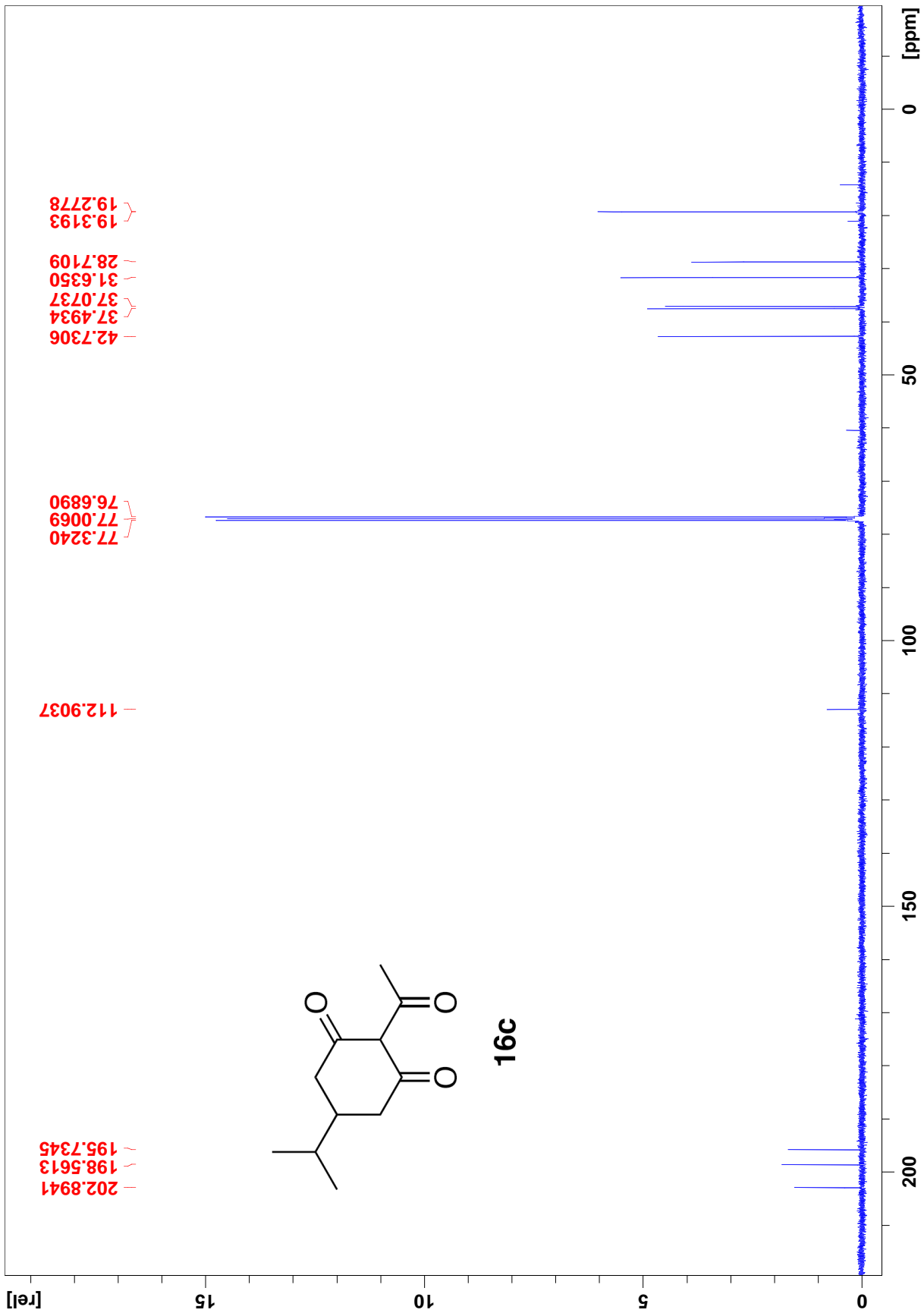
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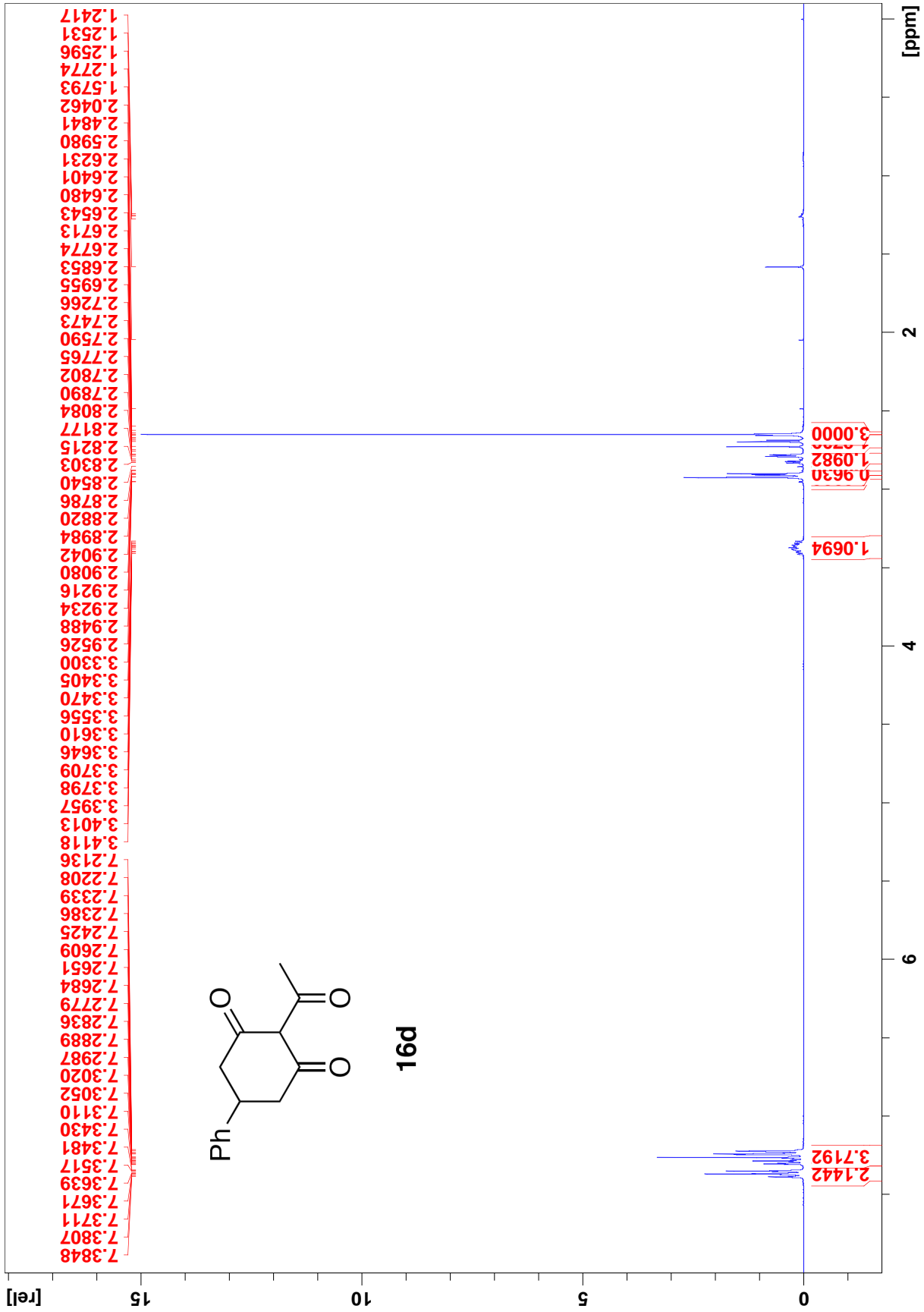
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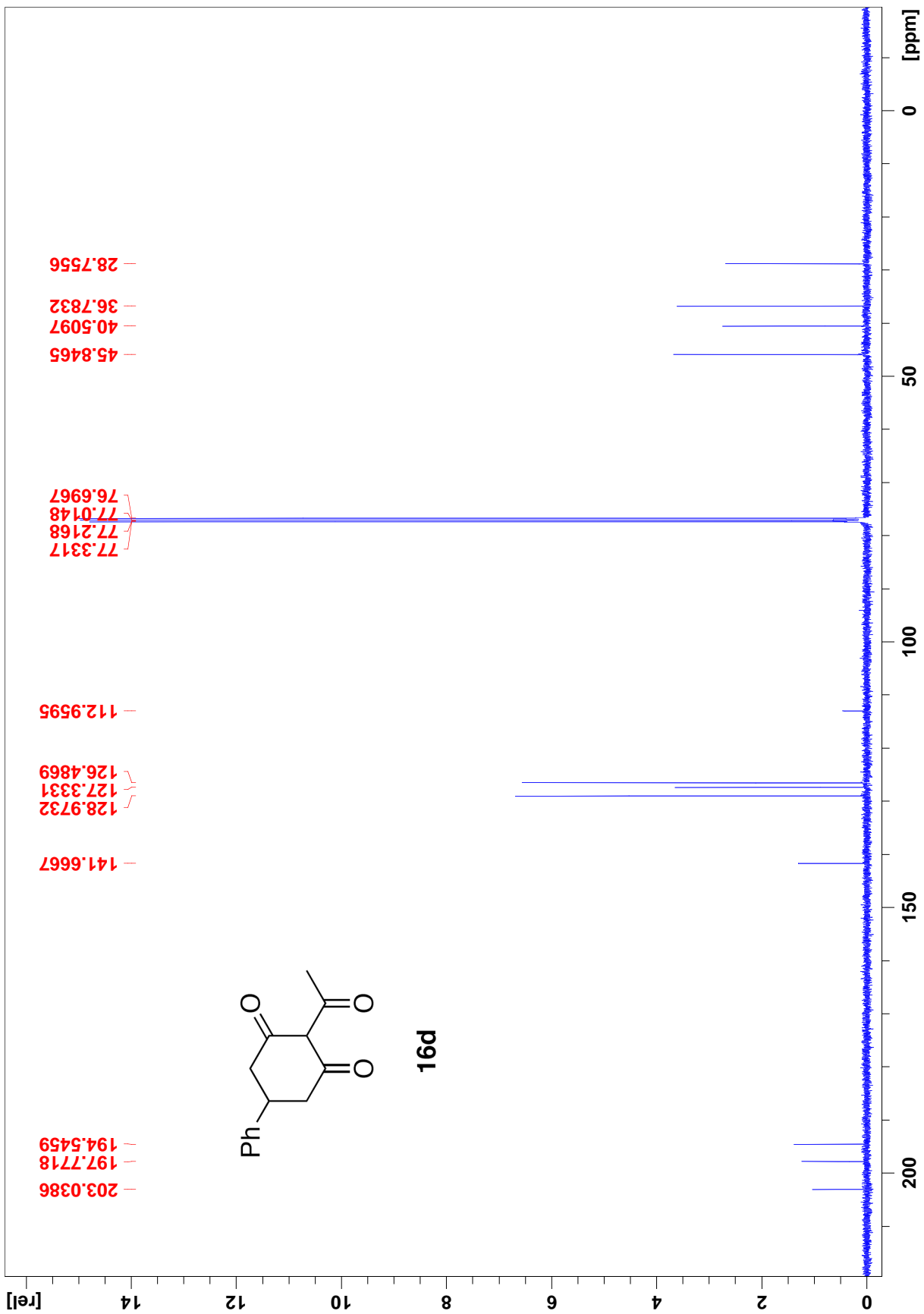
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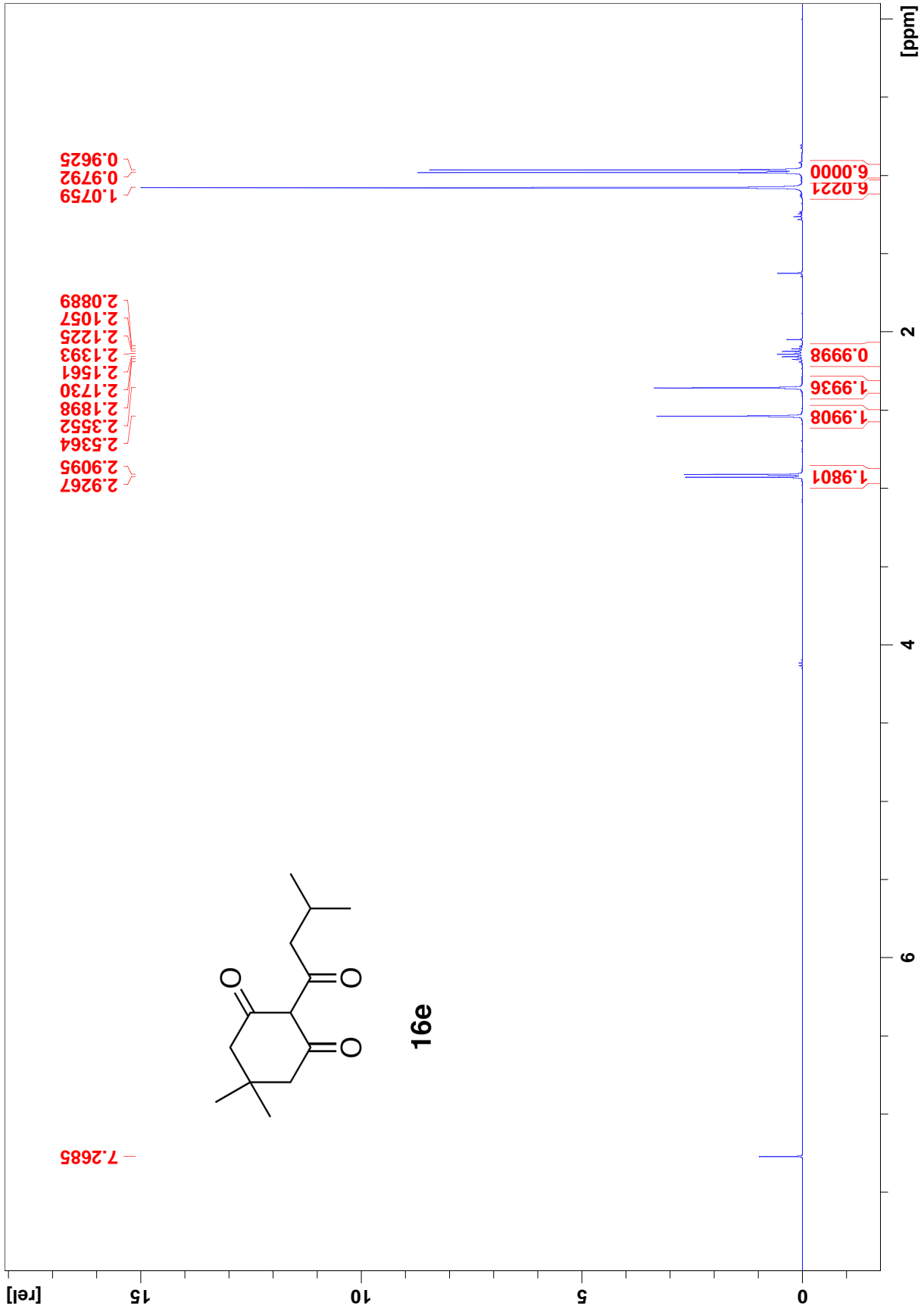
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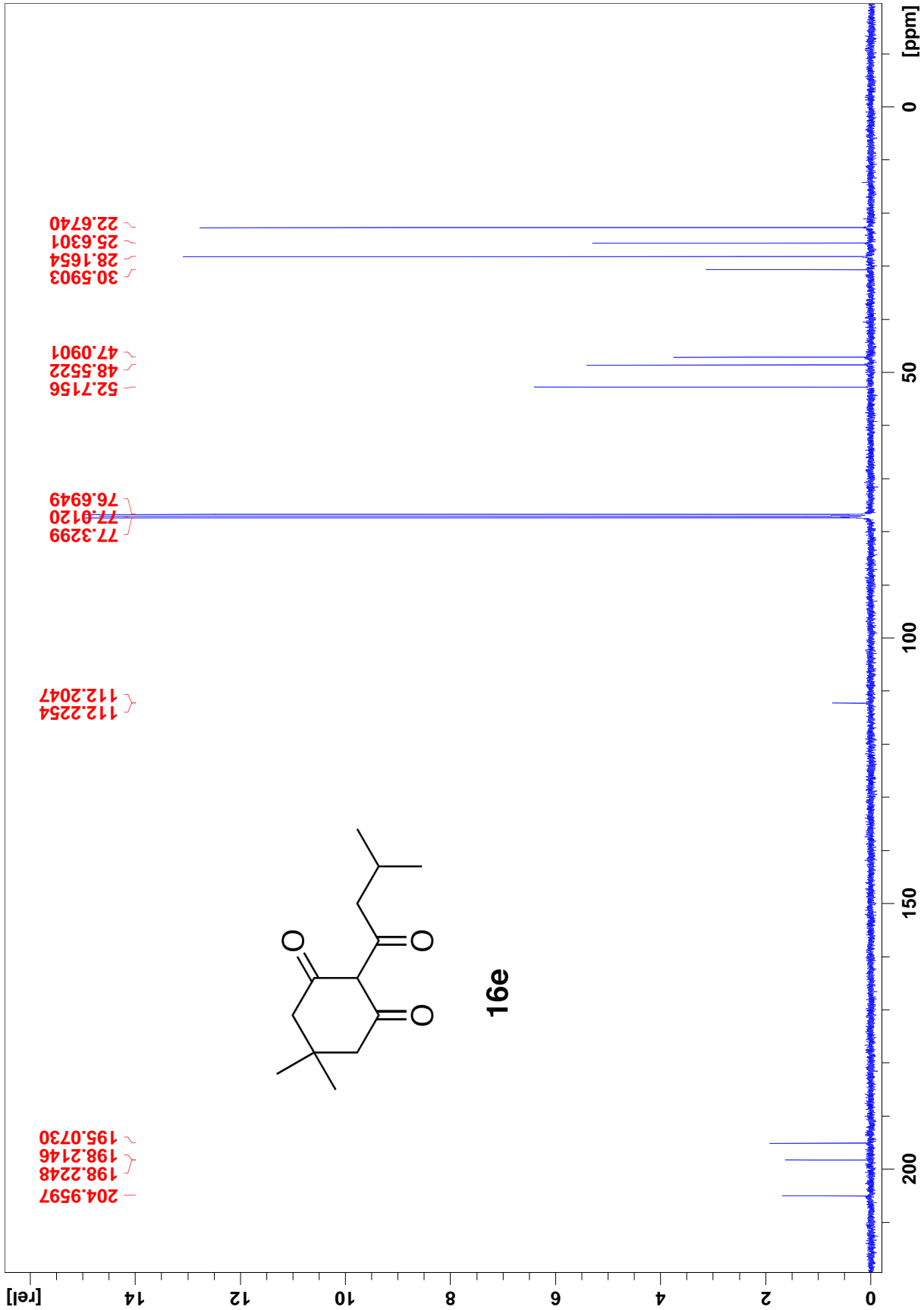
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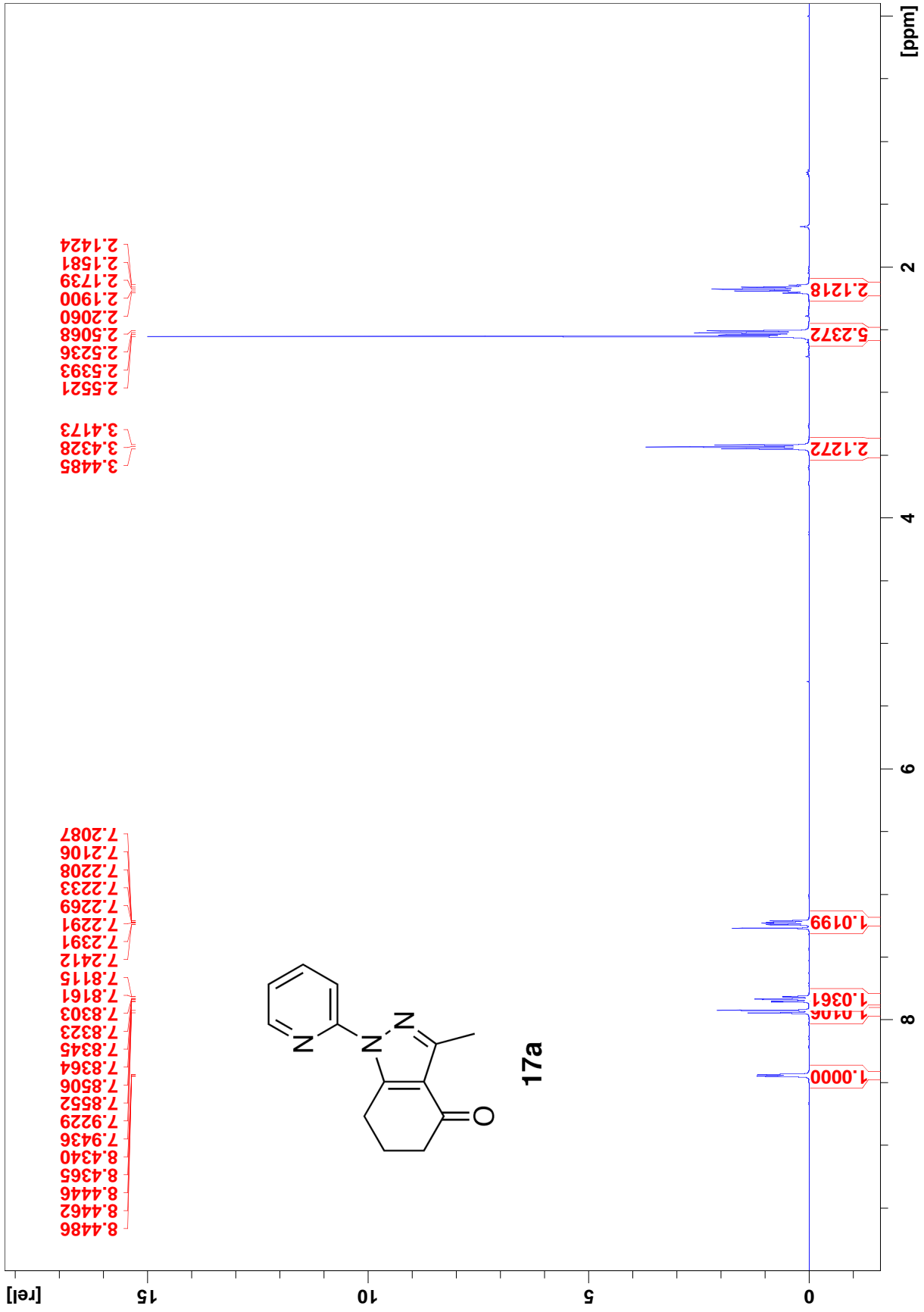
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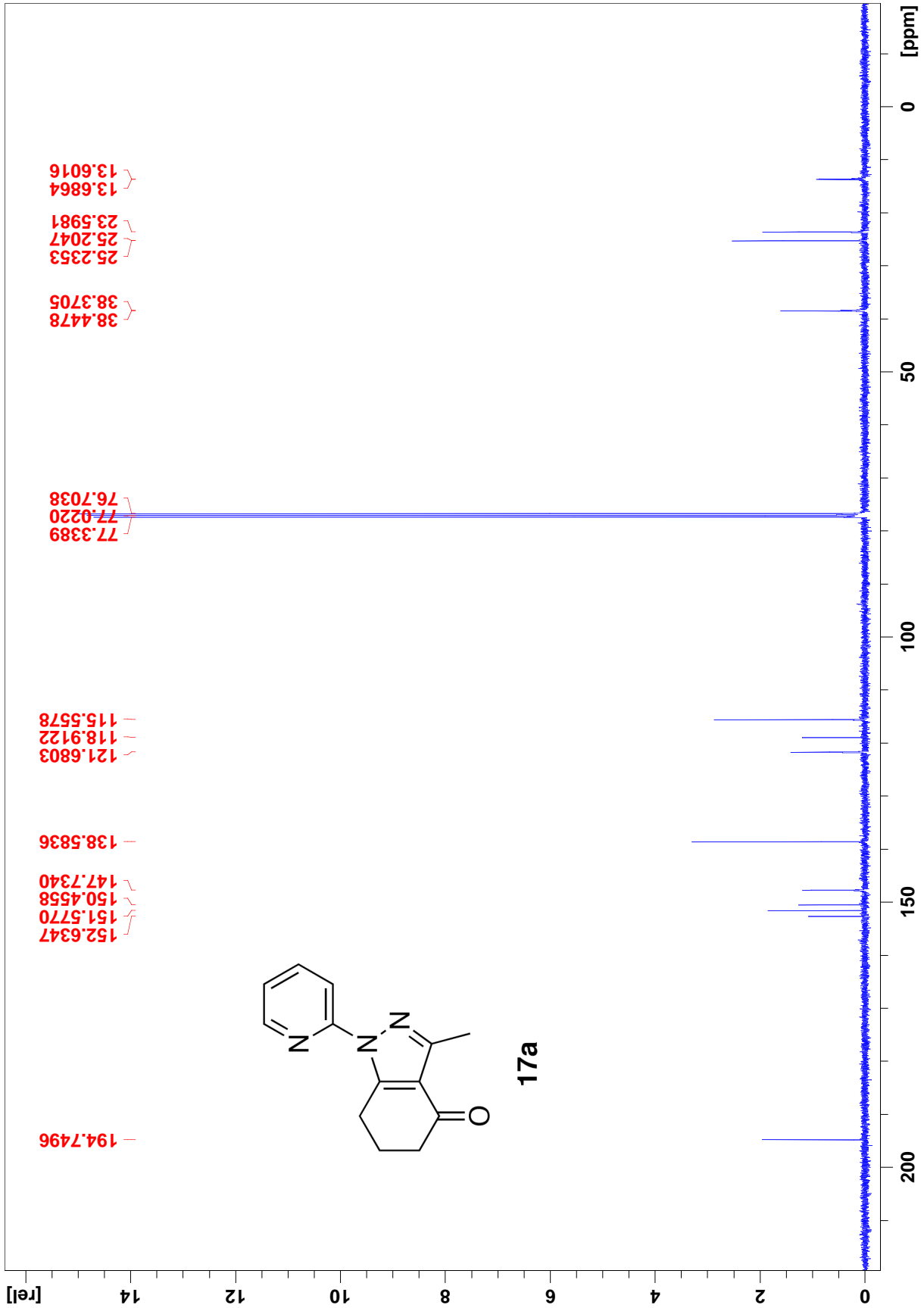
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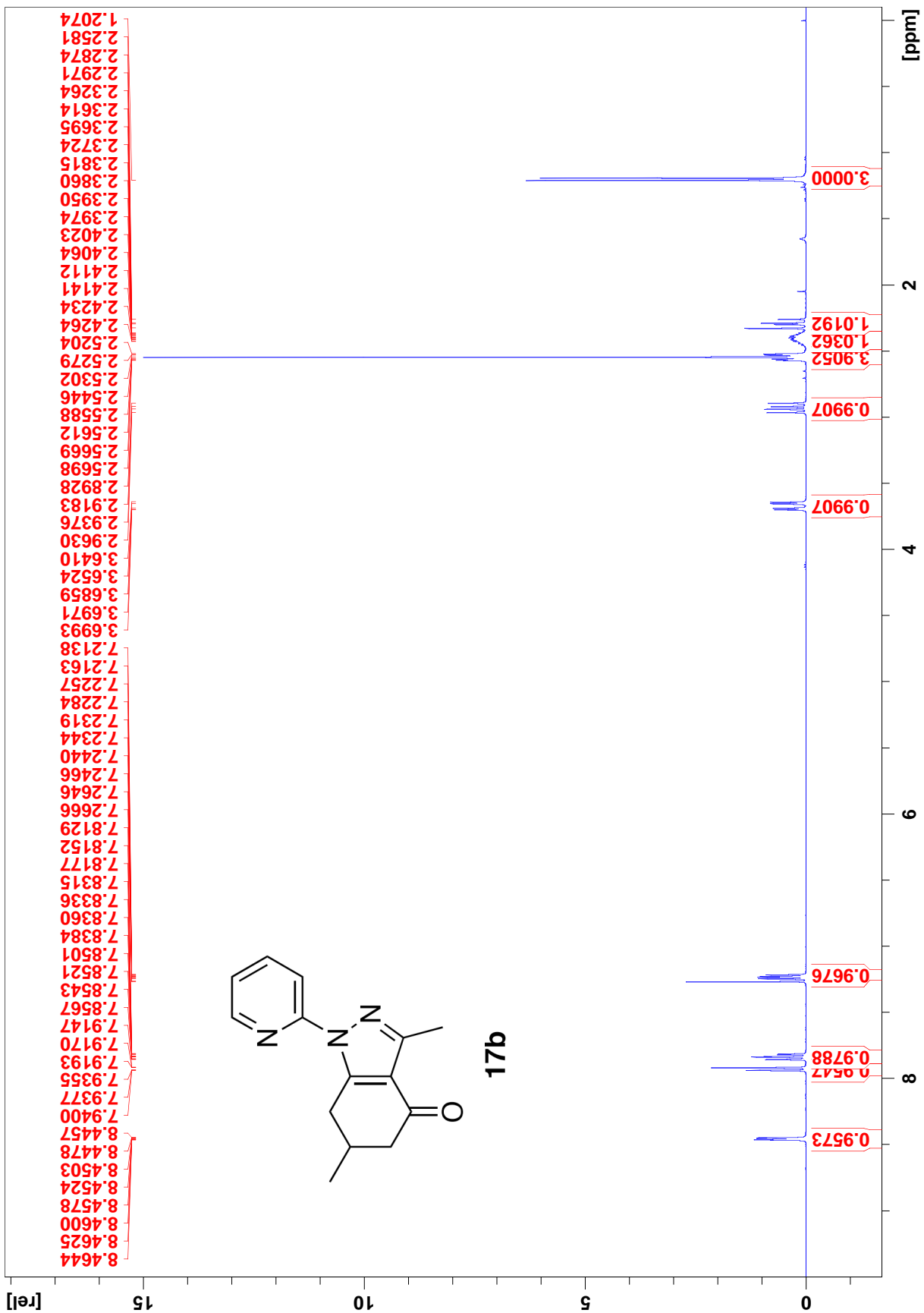
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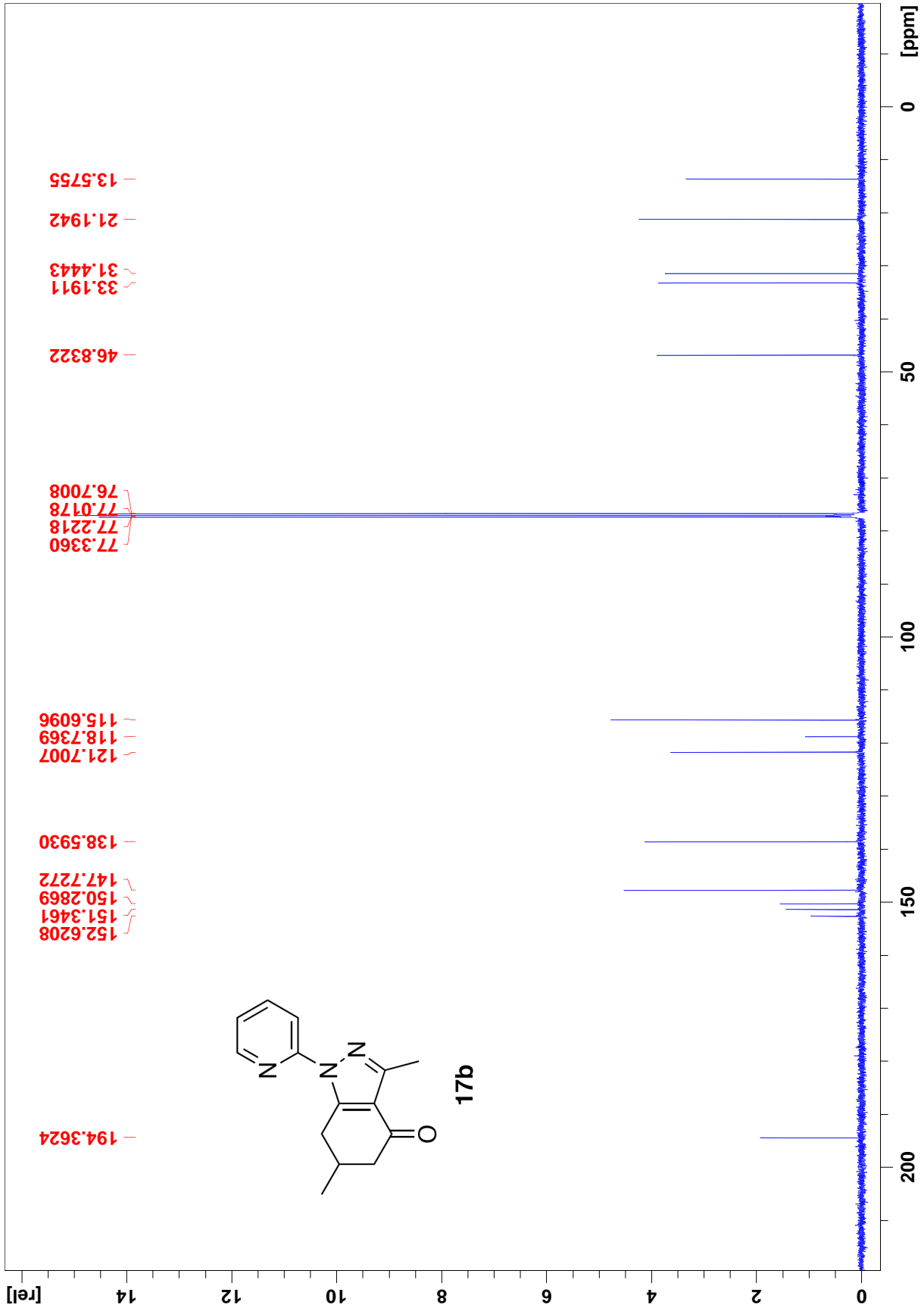
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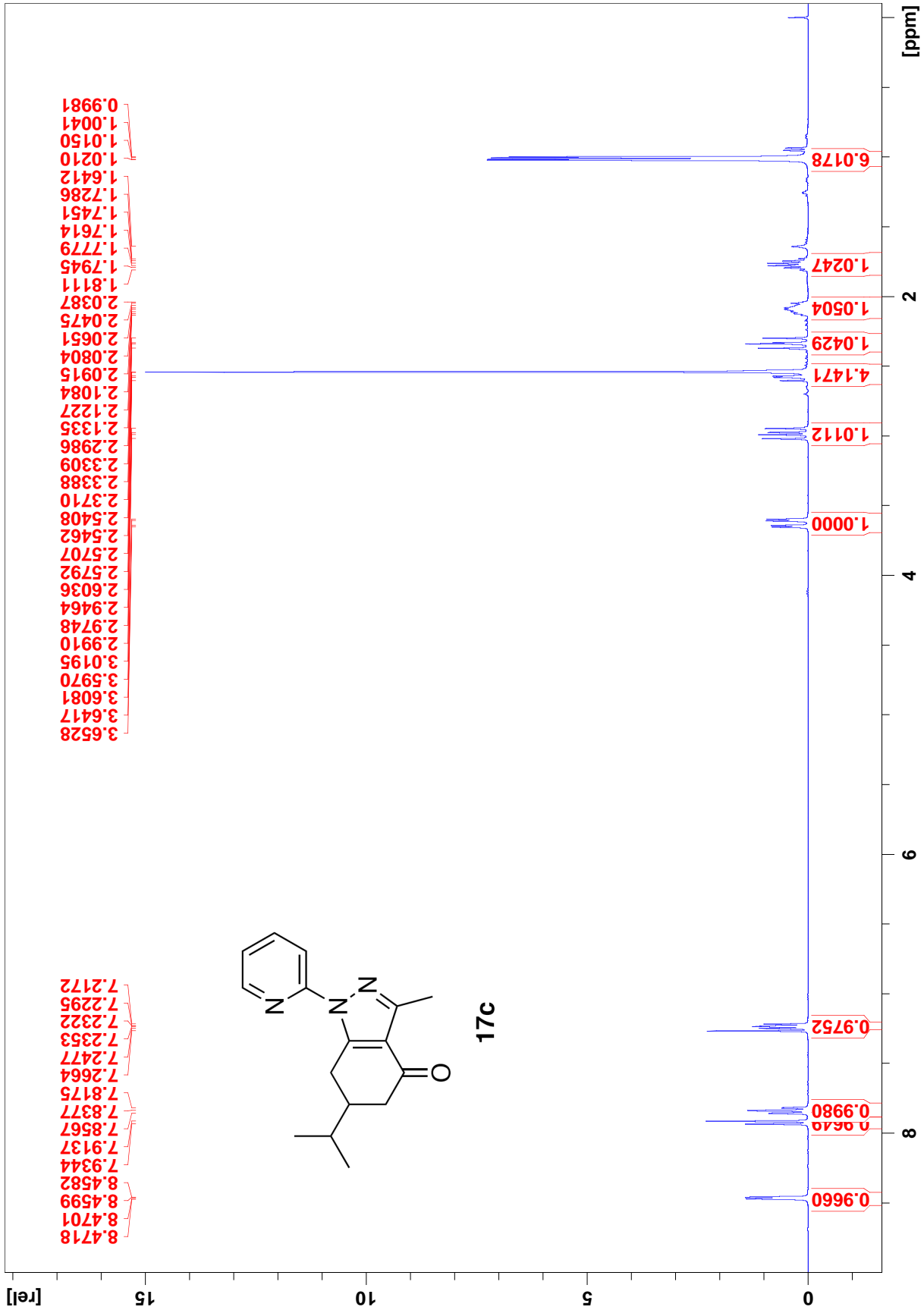
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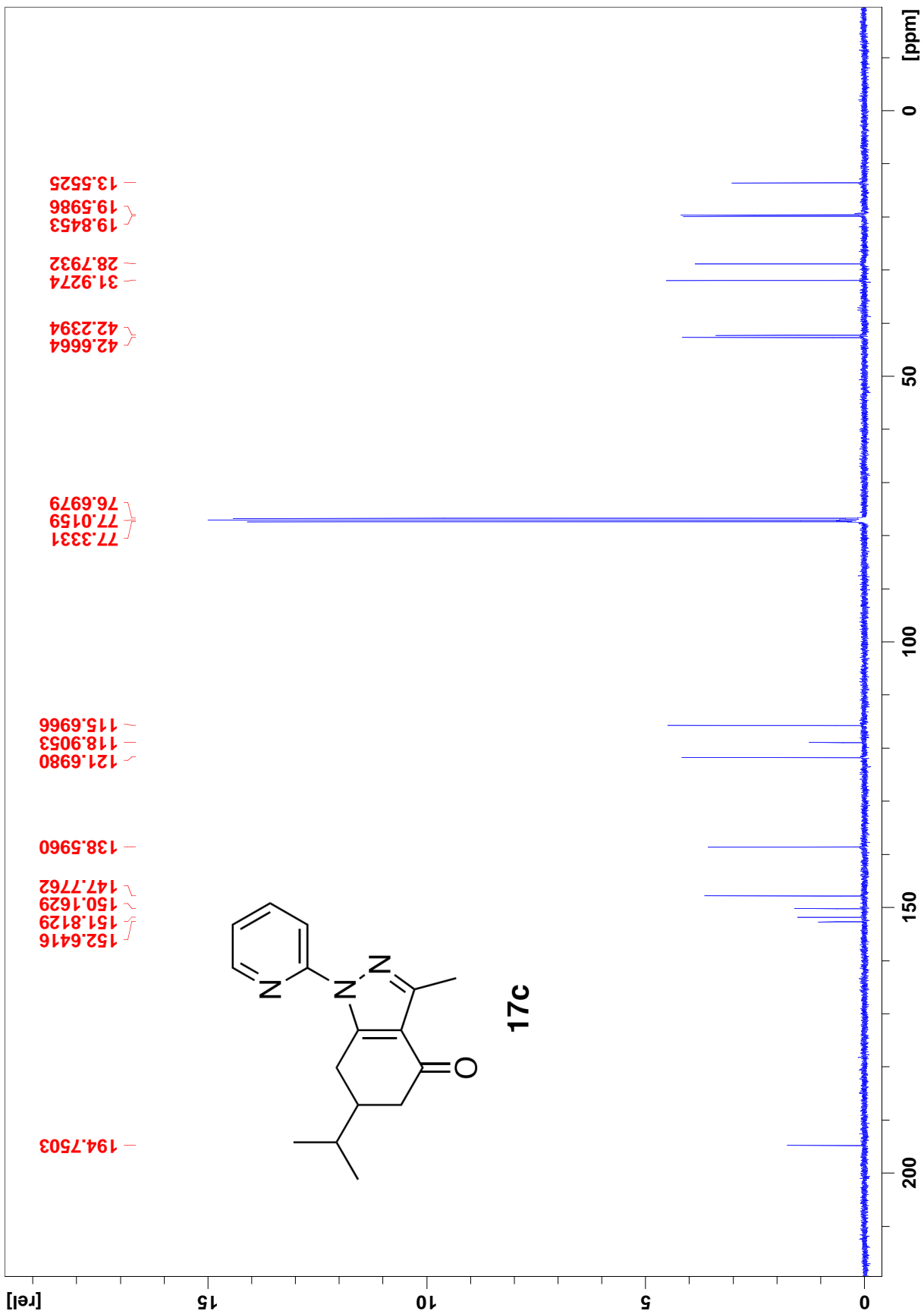
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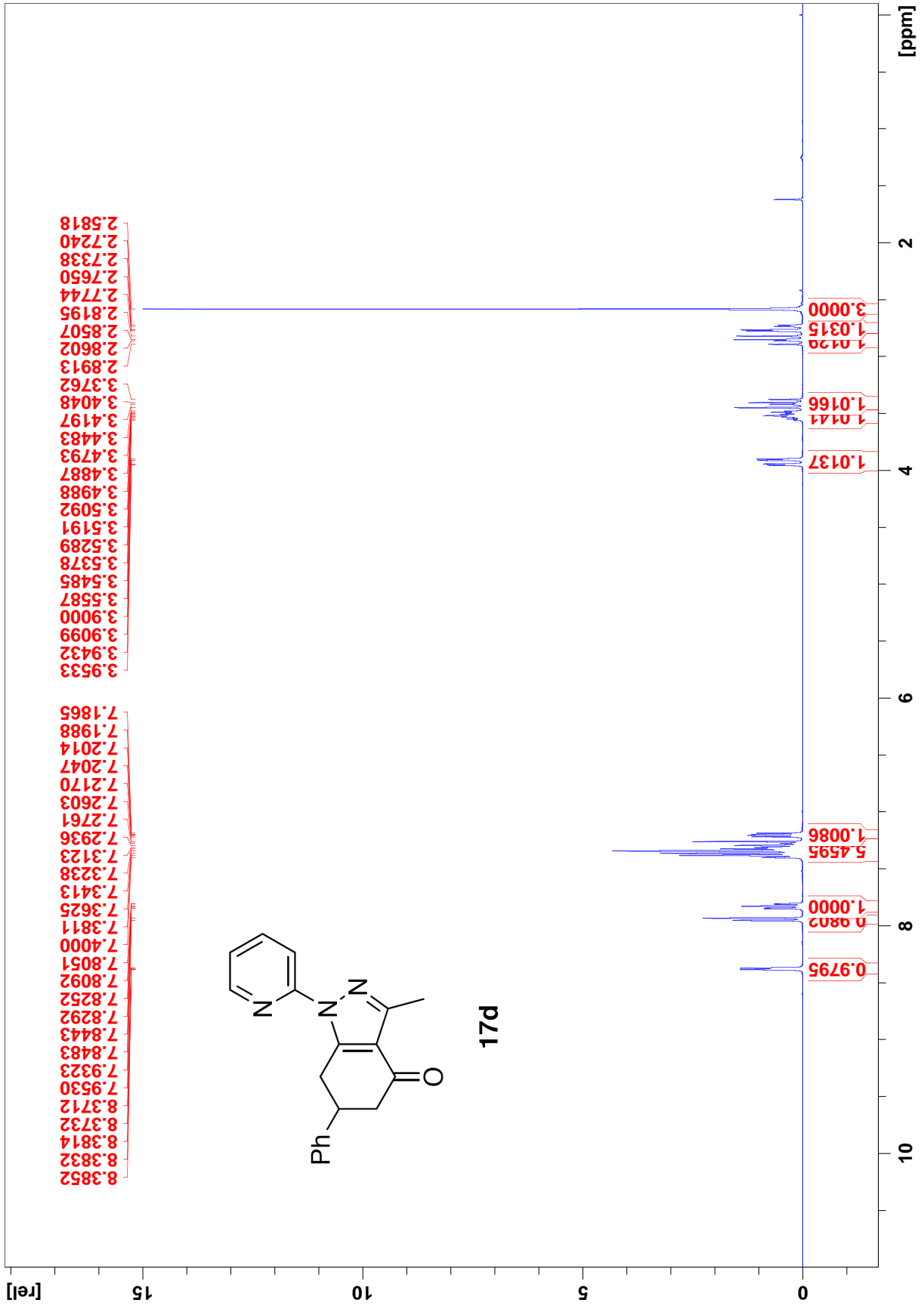
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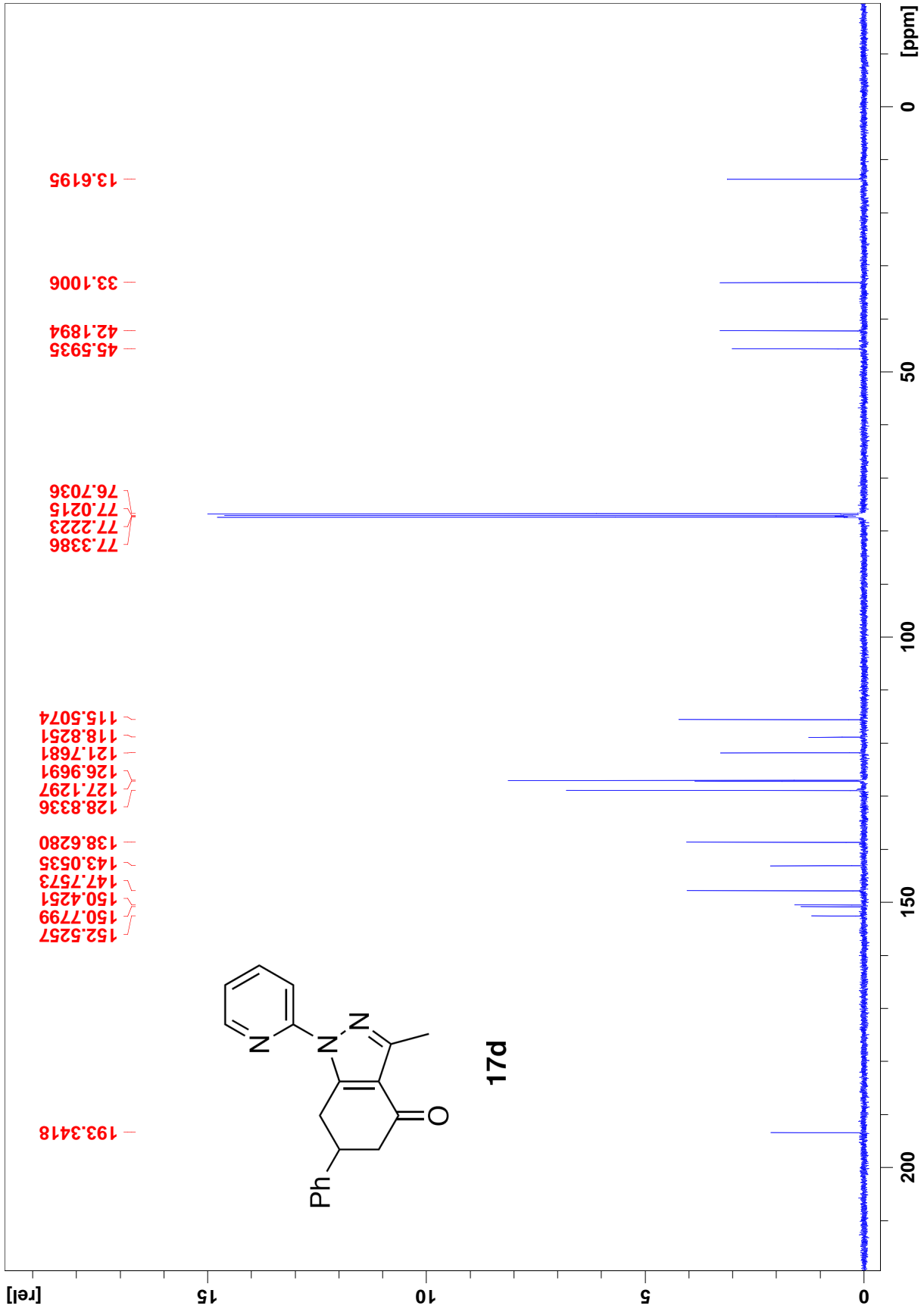
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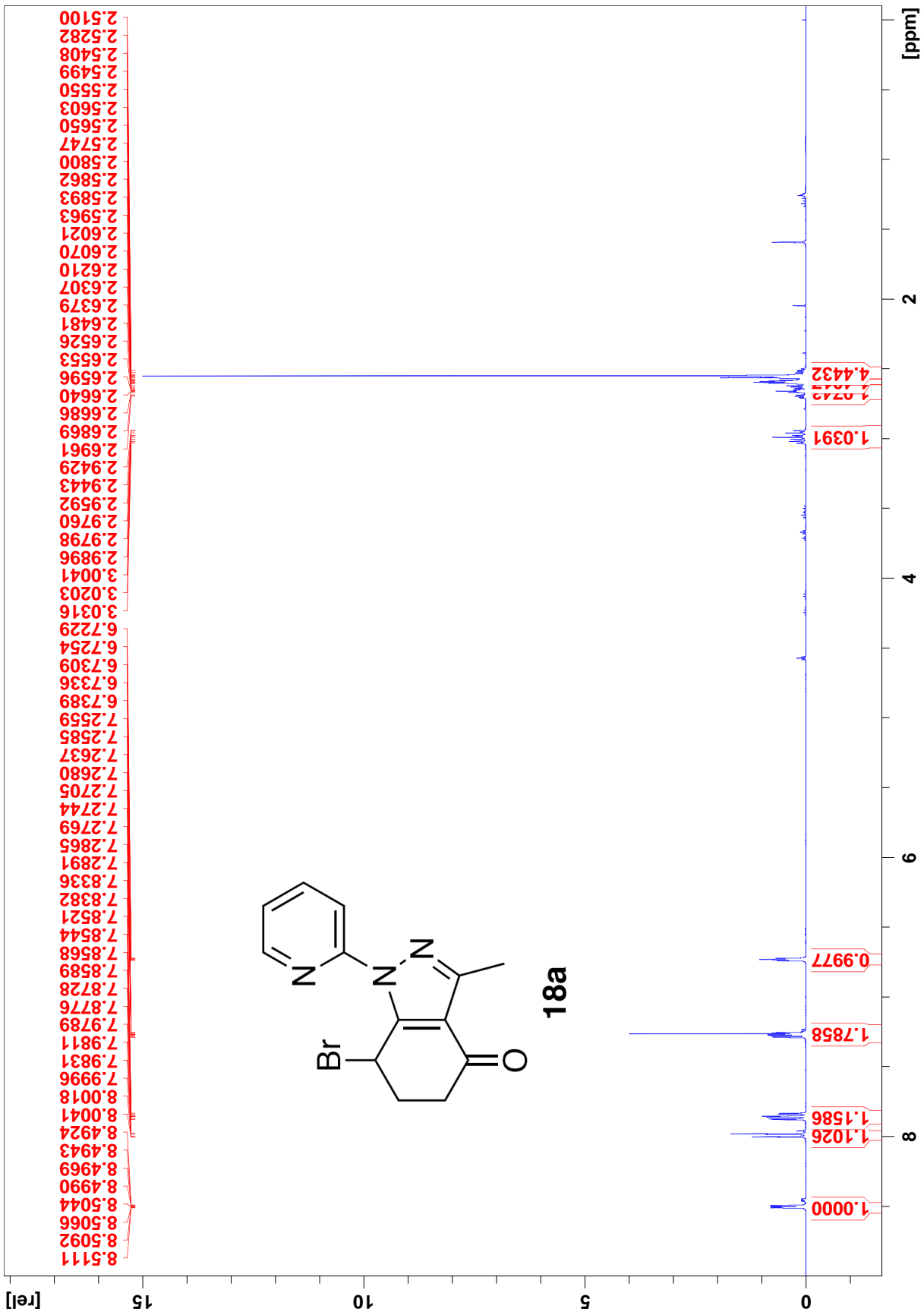
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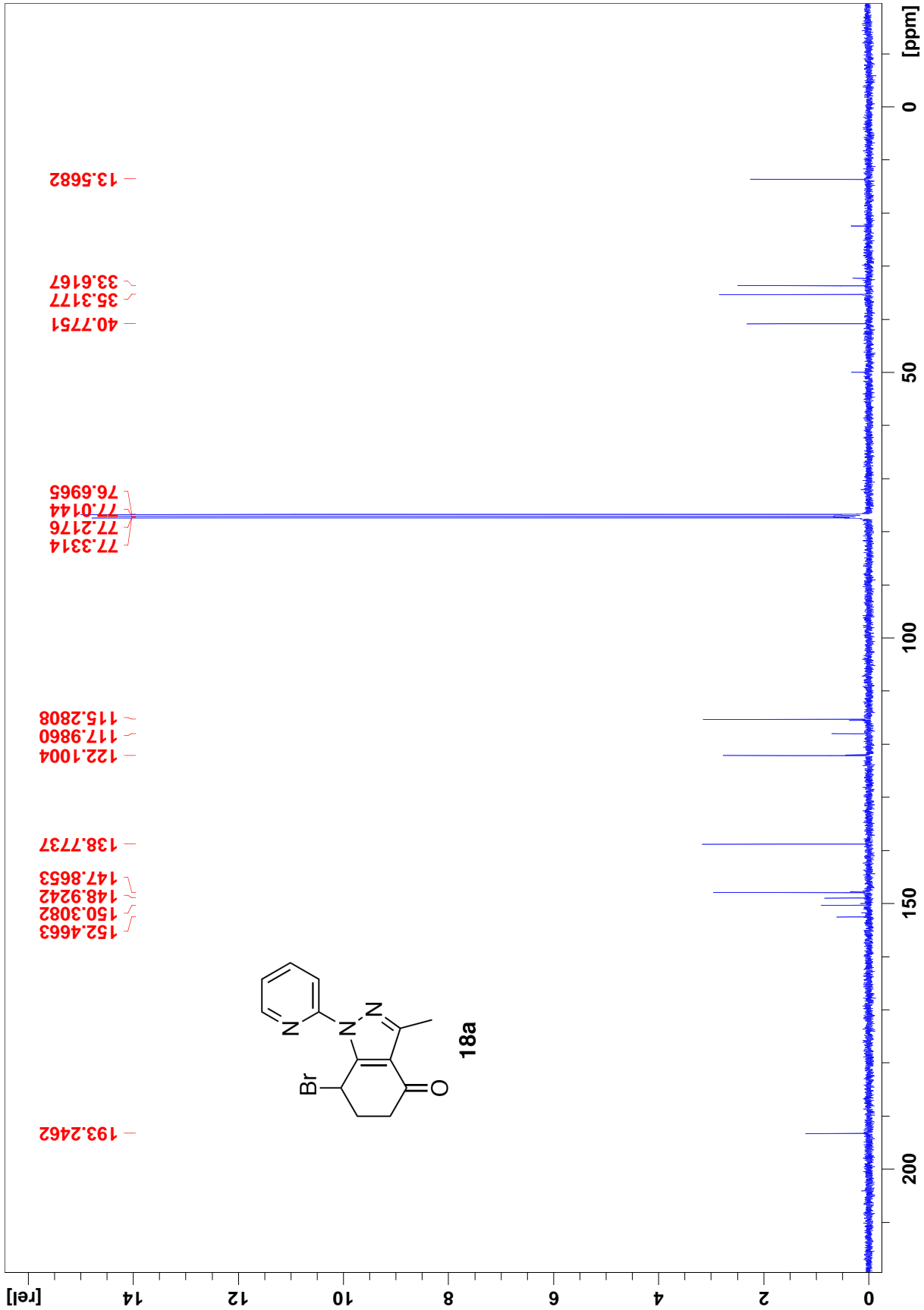
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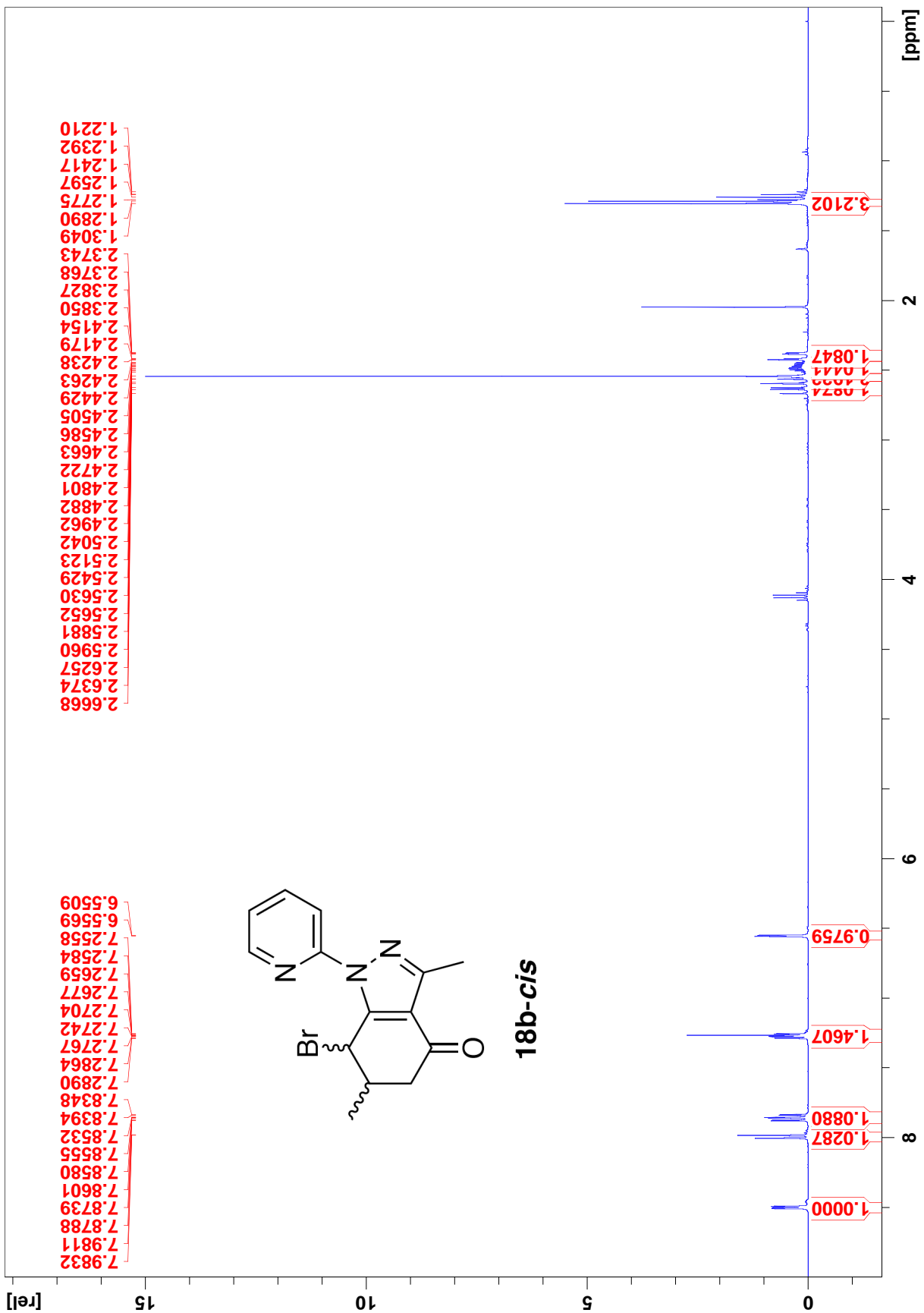
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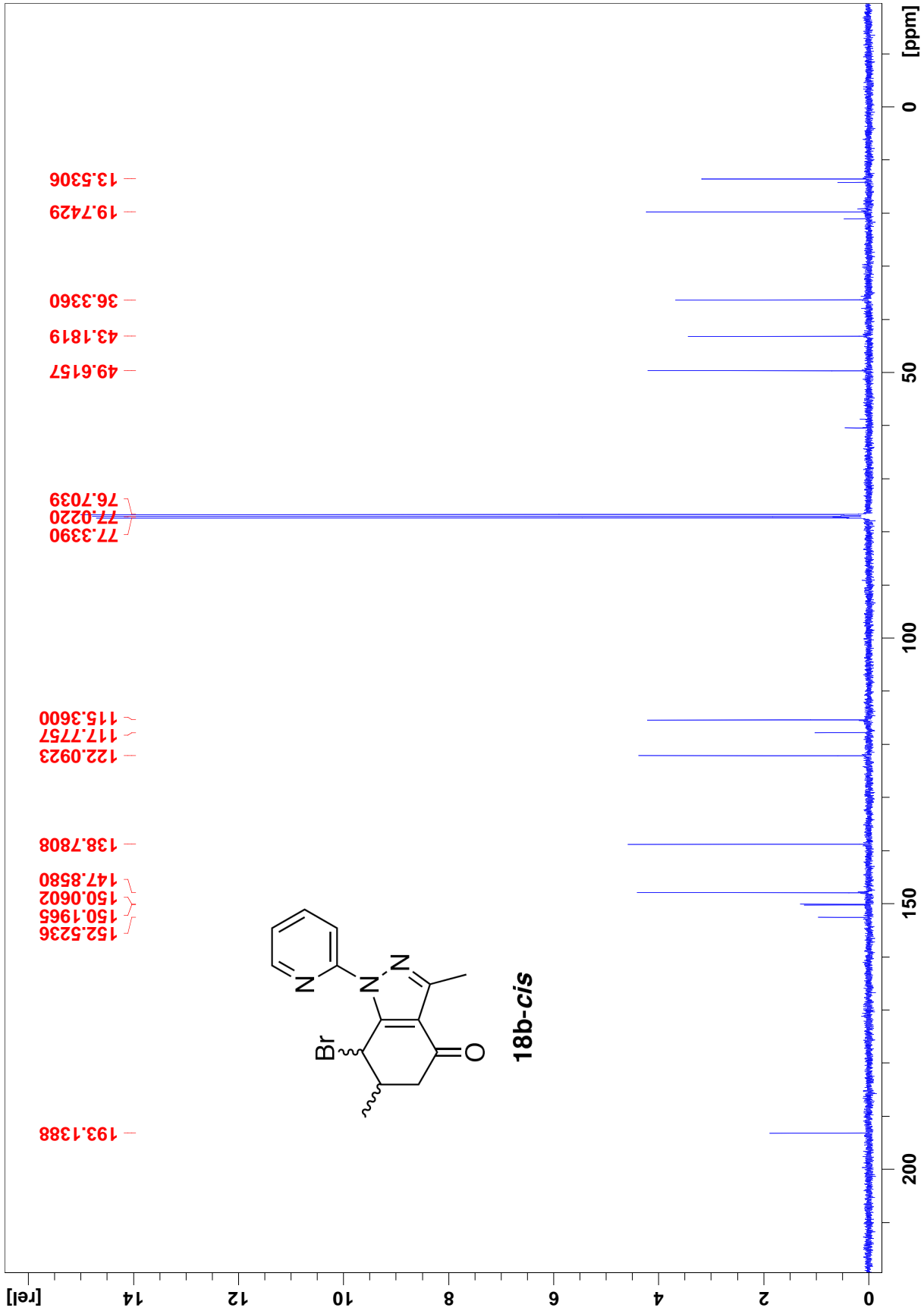
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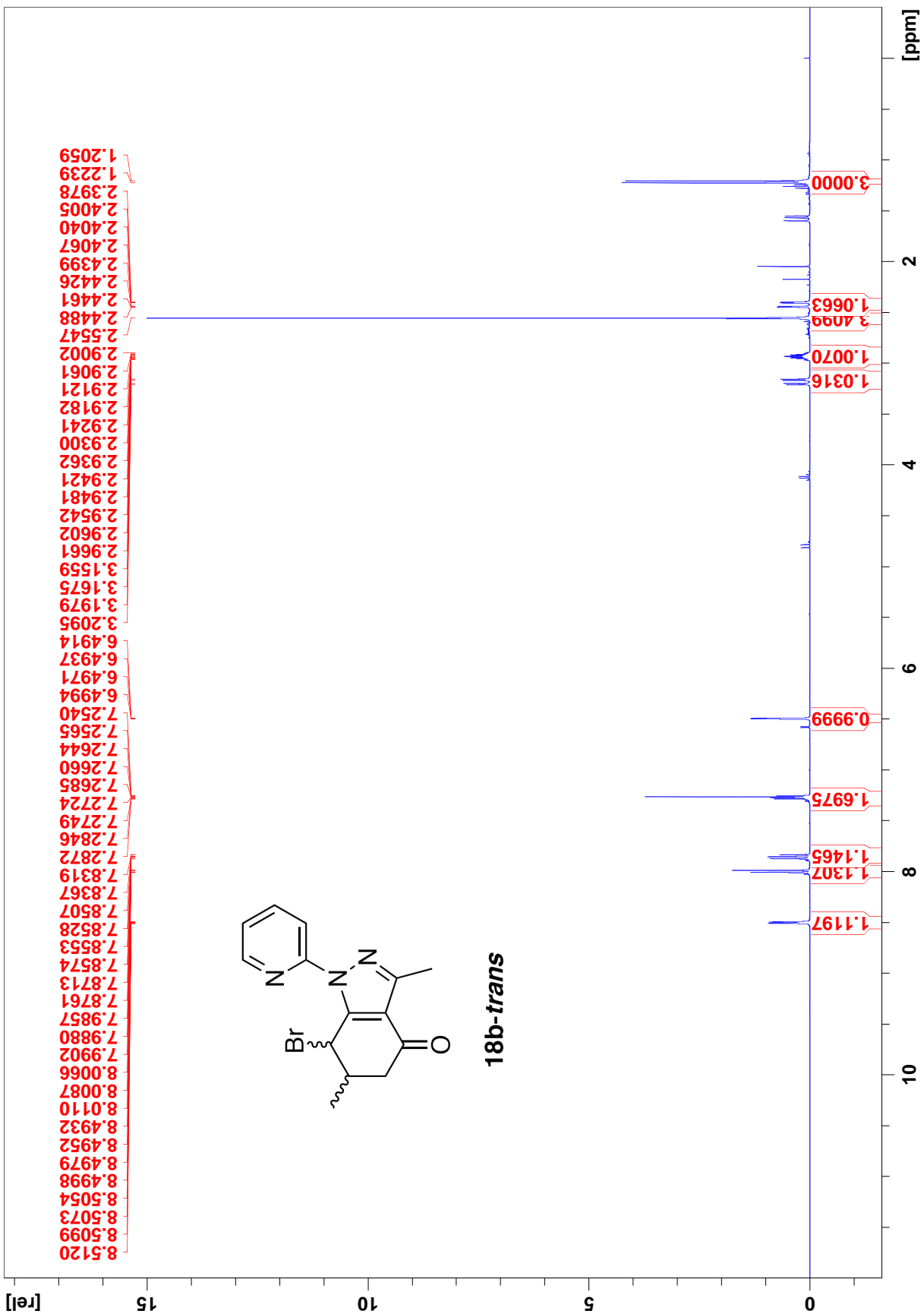
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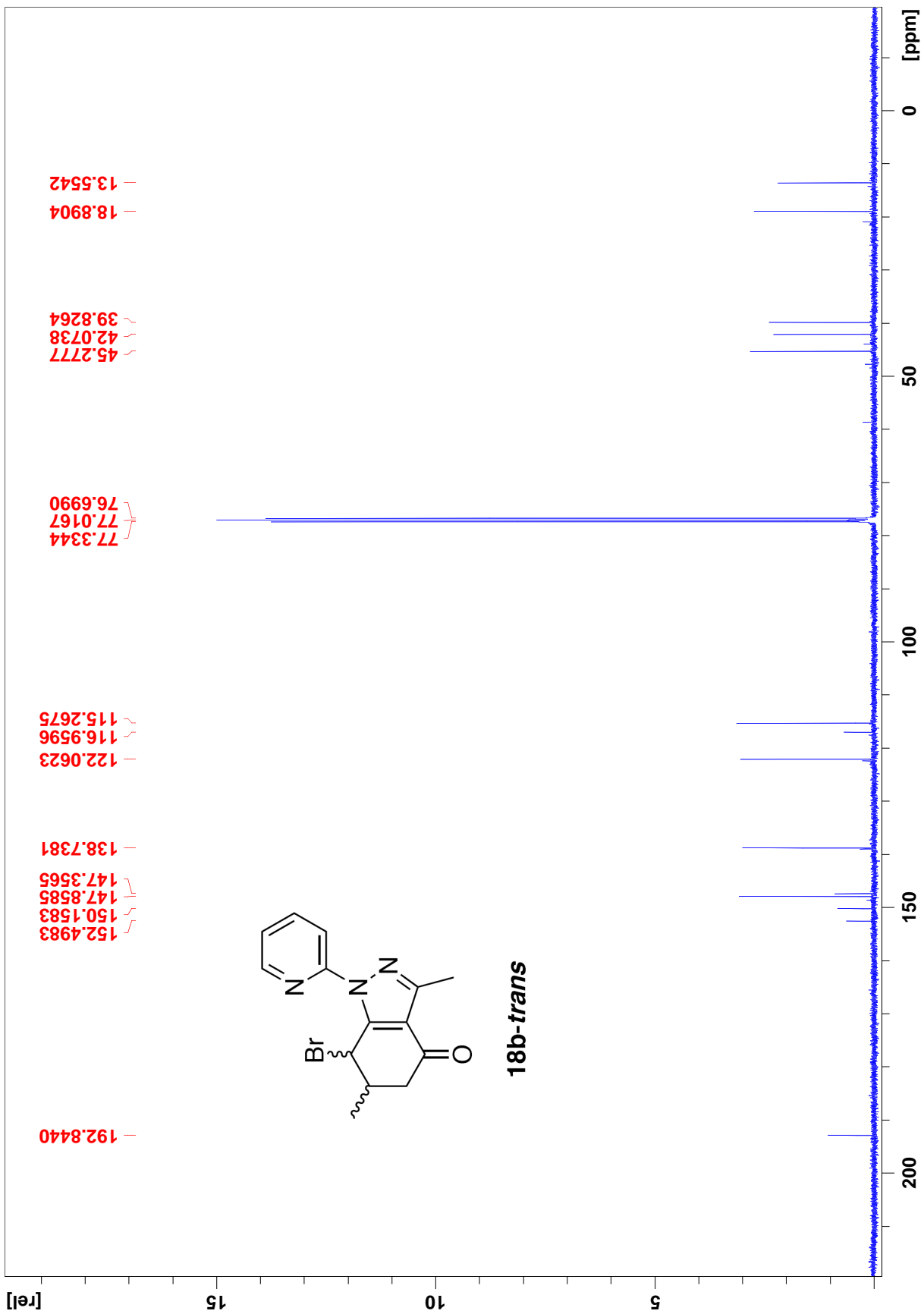
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JL09-011409B 1 1 C:\Bruker\TOPSPIN leex3451



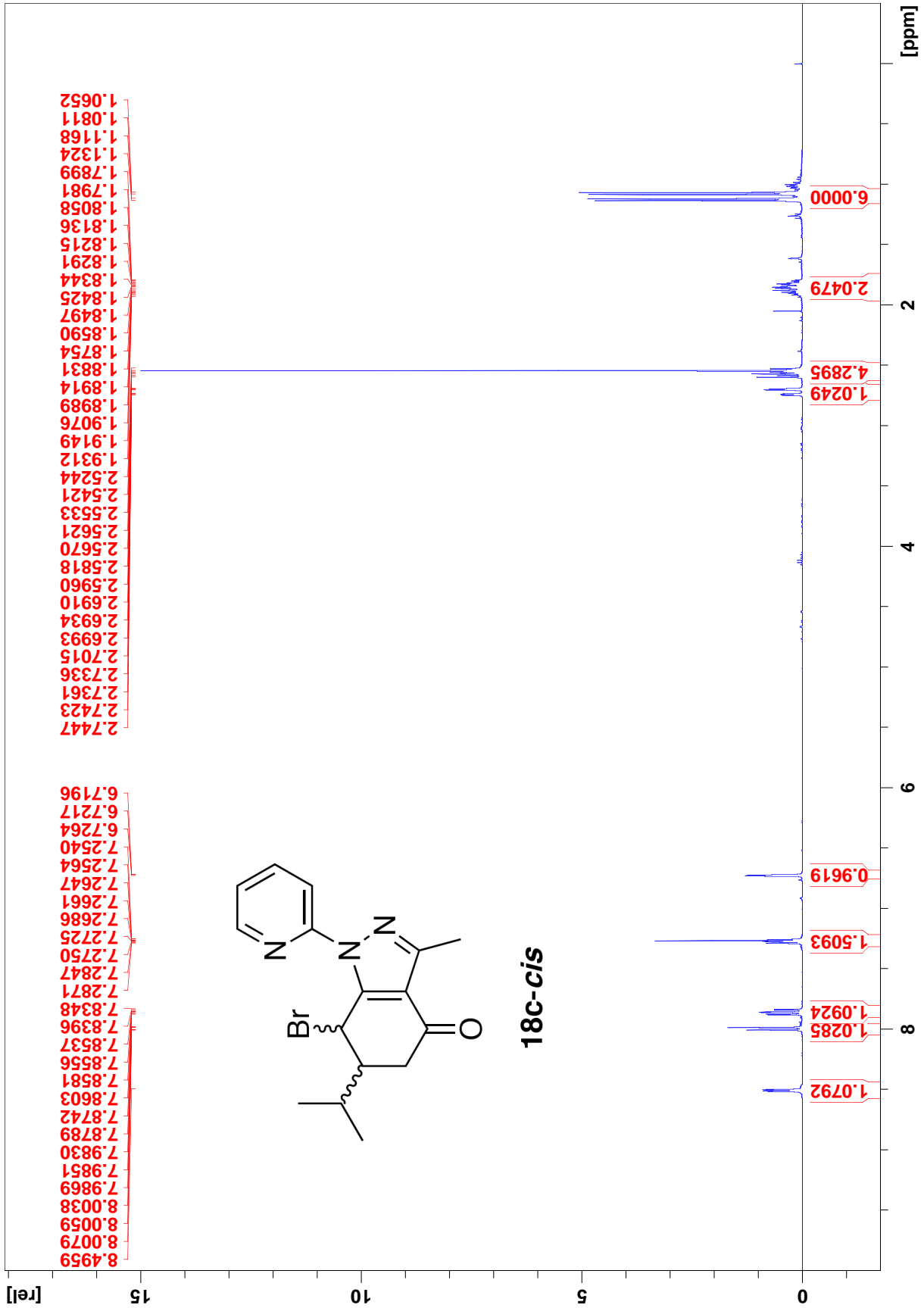
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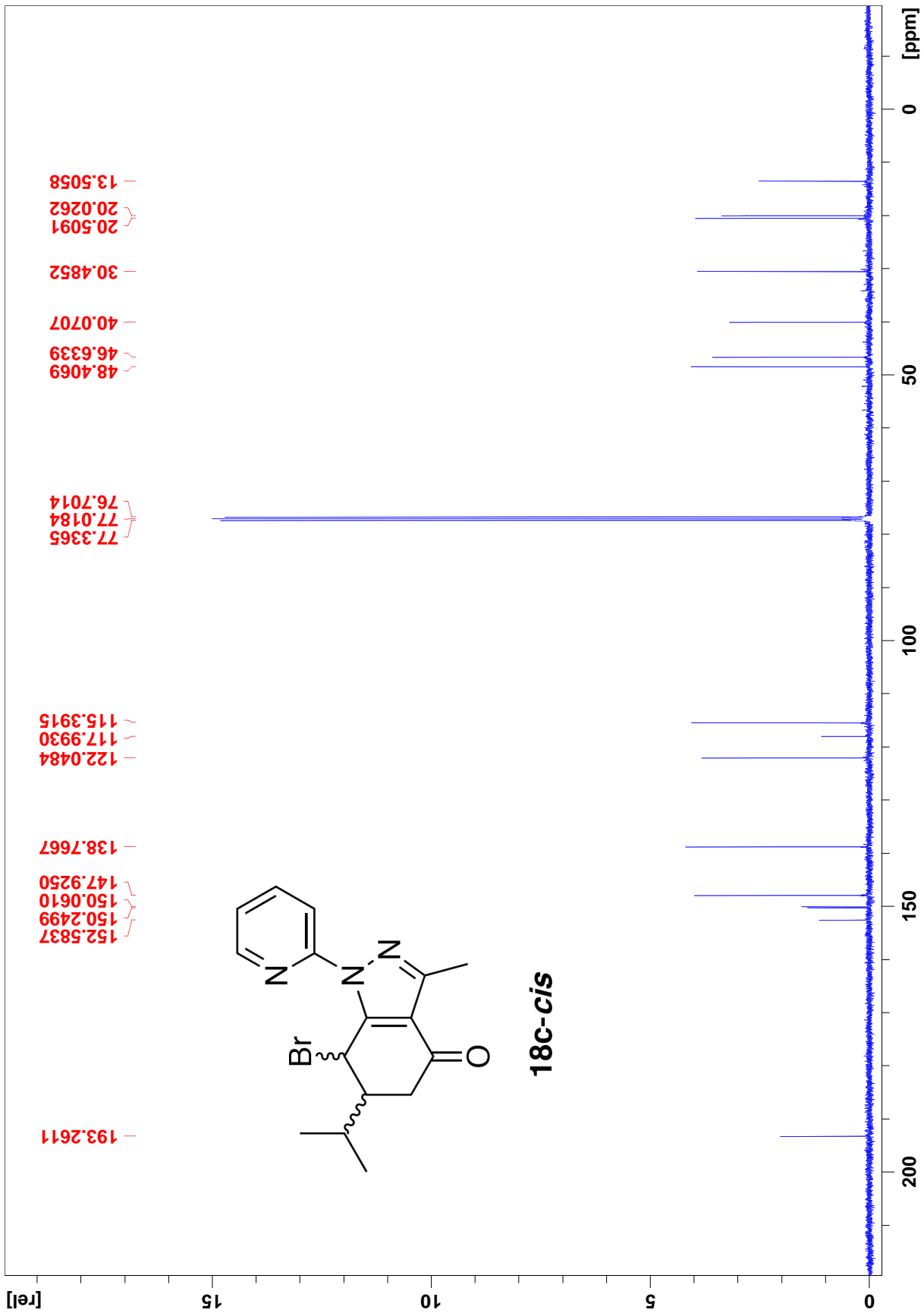
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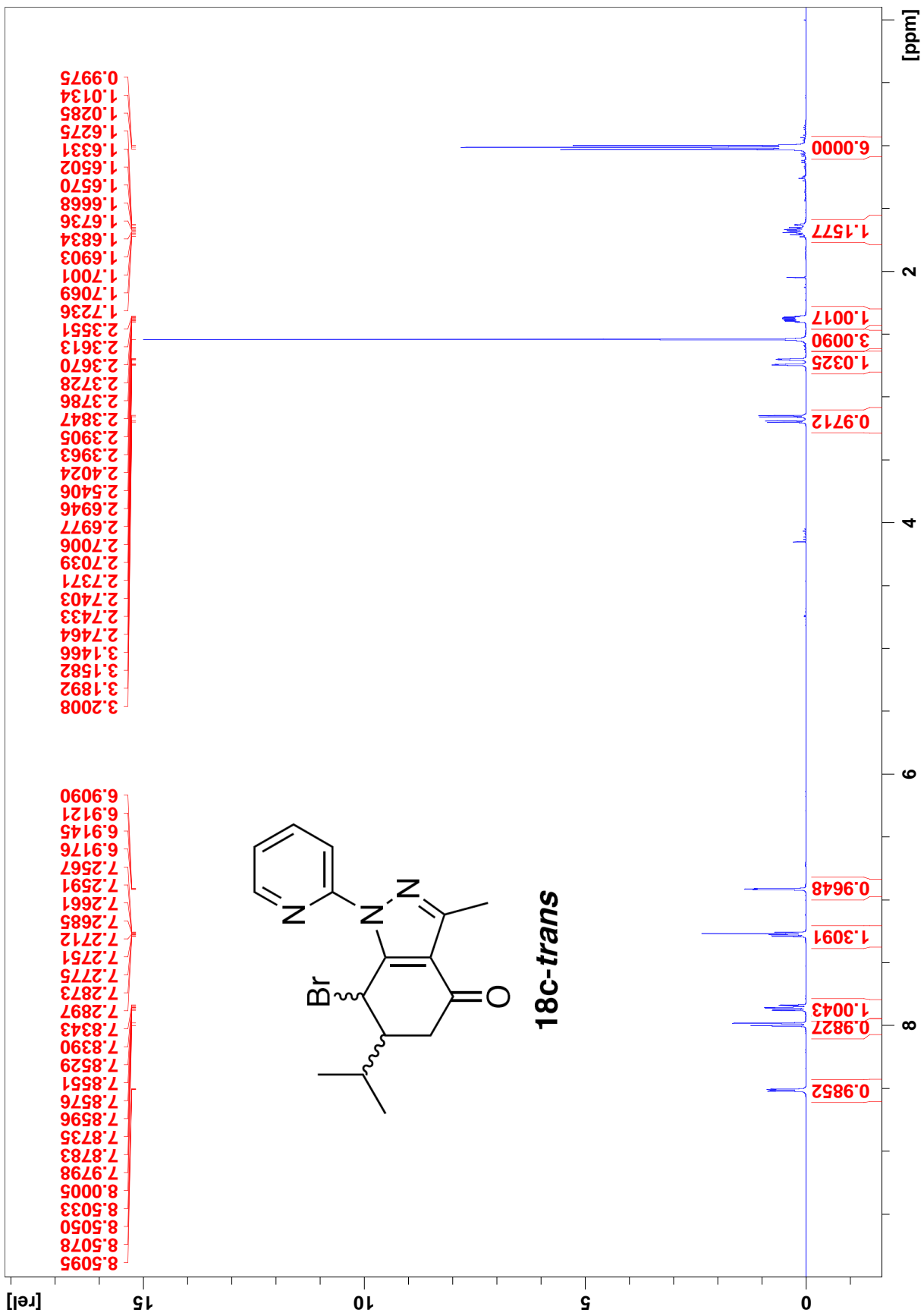
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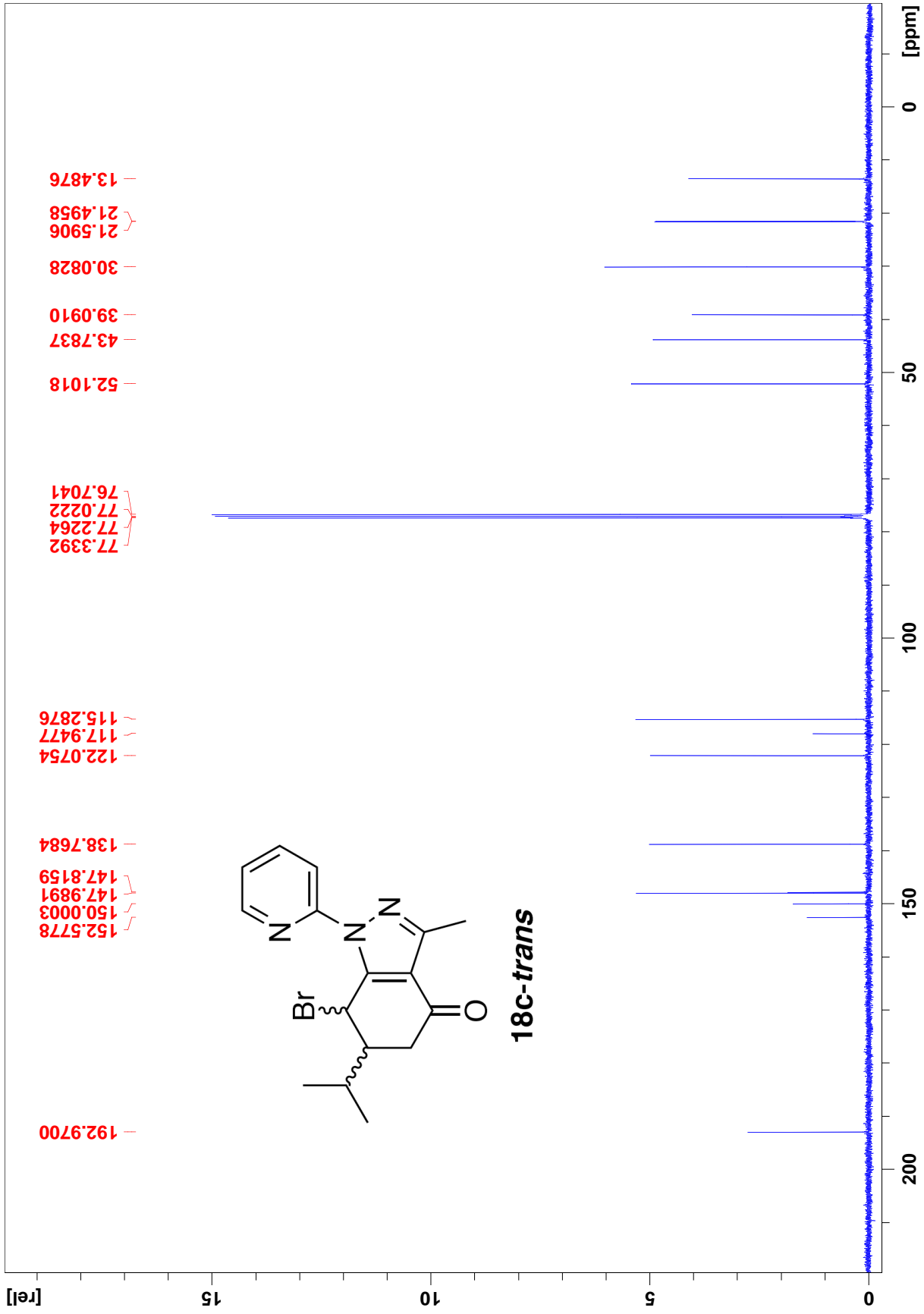
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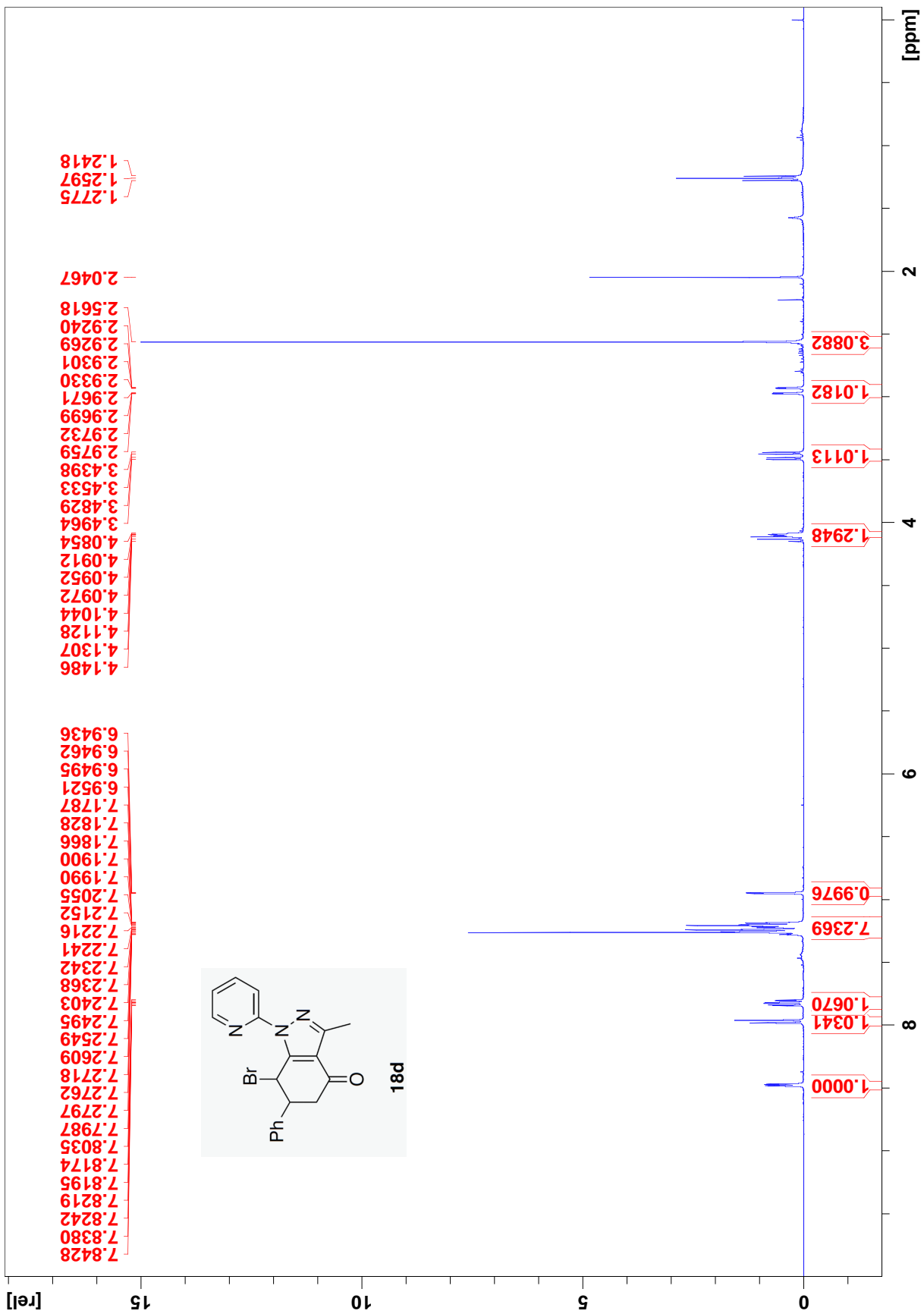
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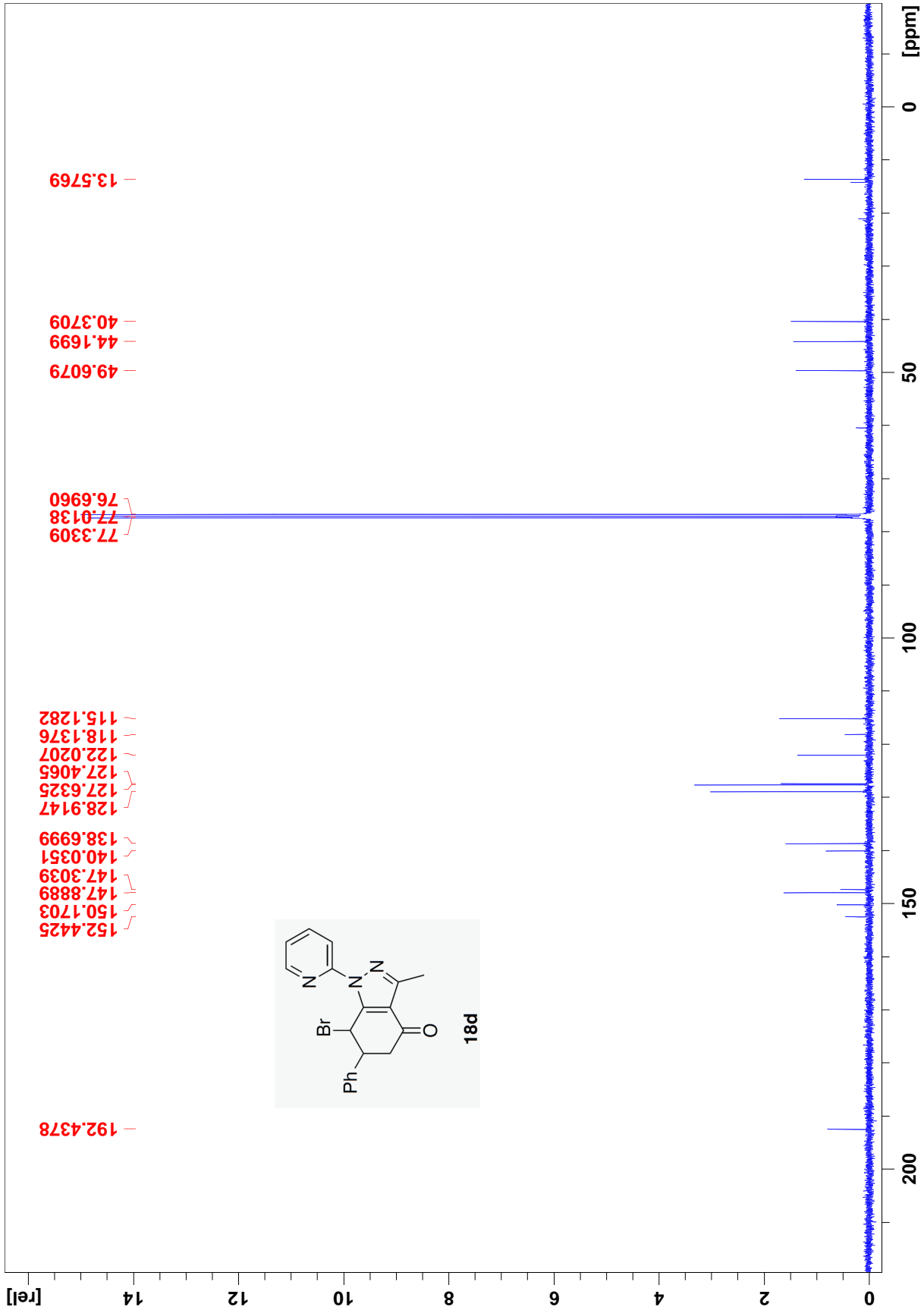
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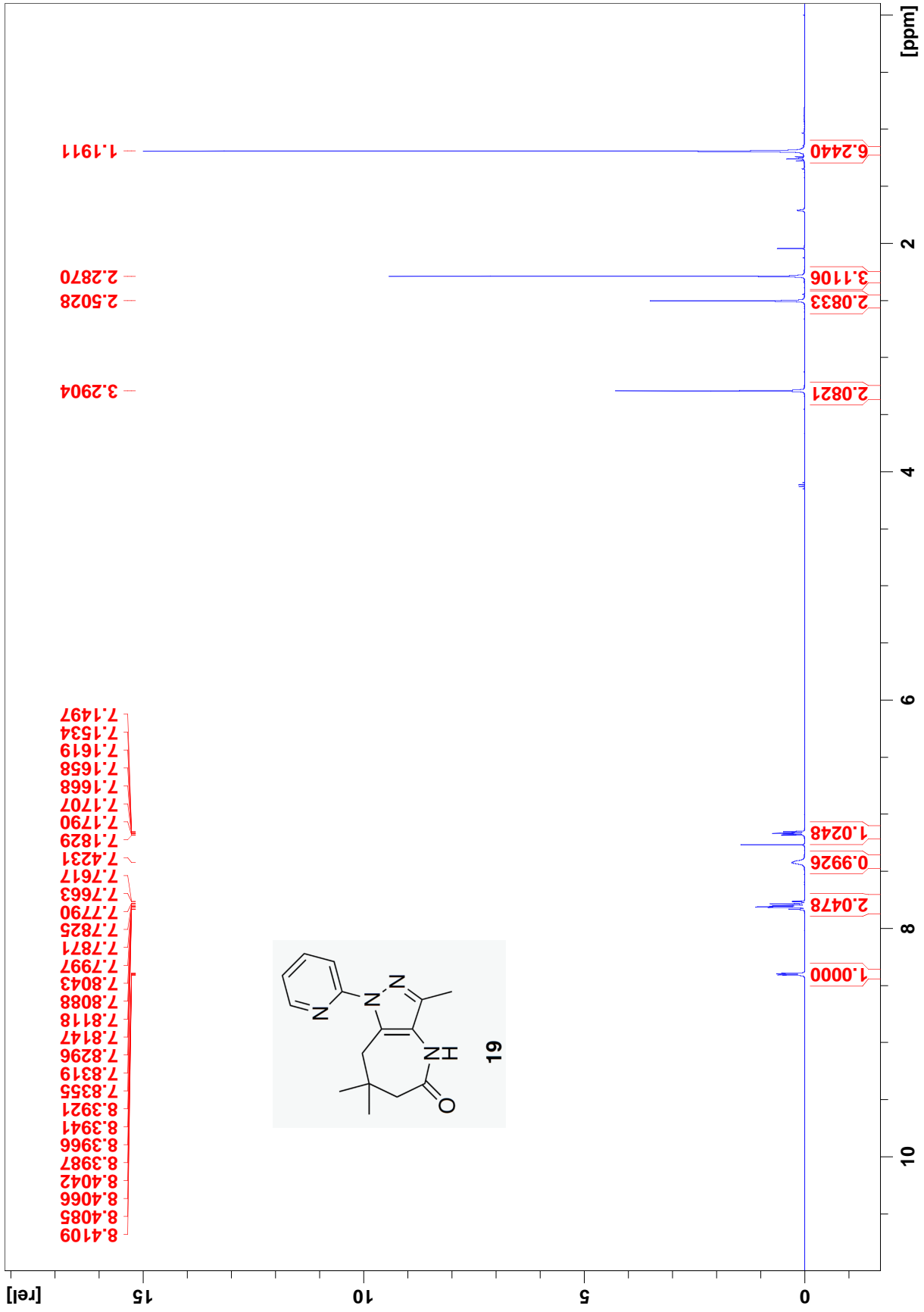
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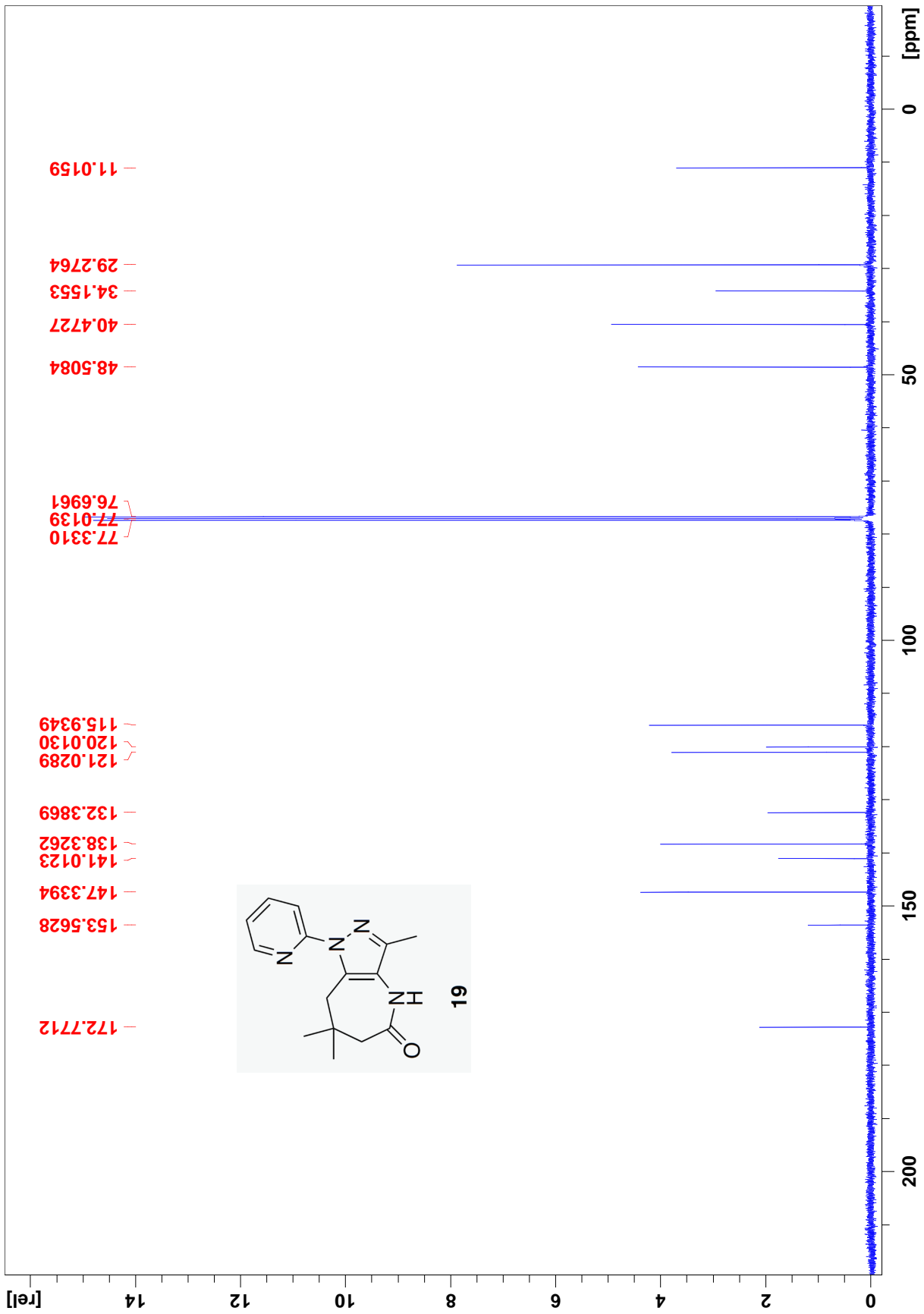
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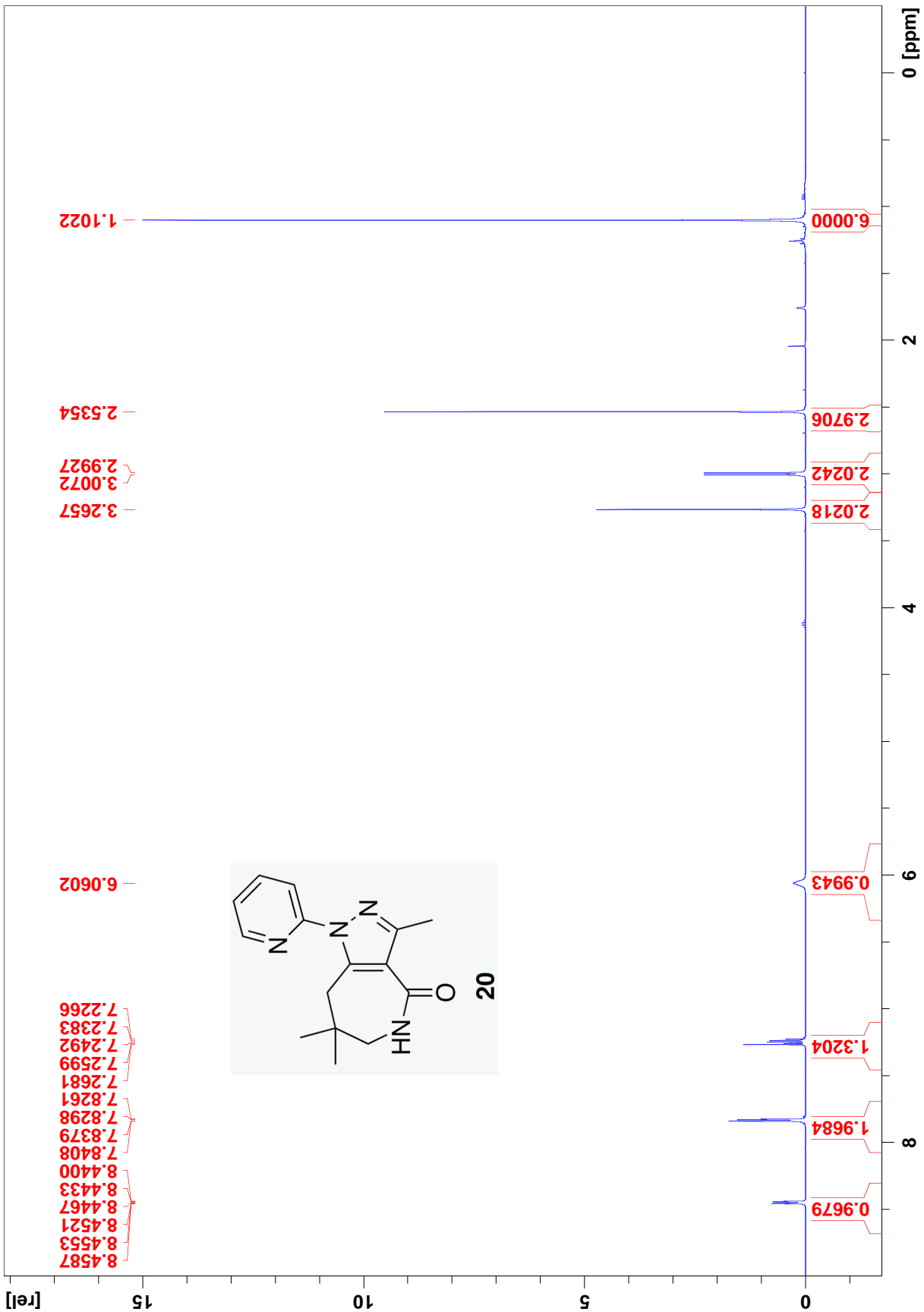
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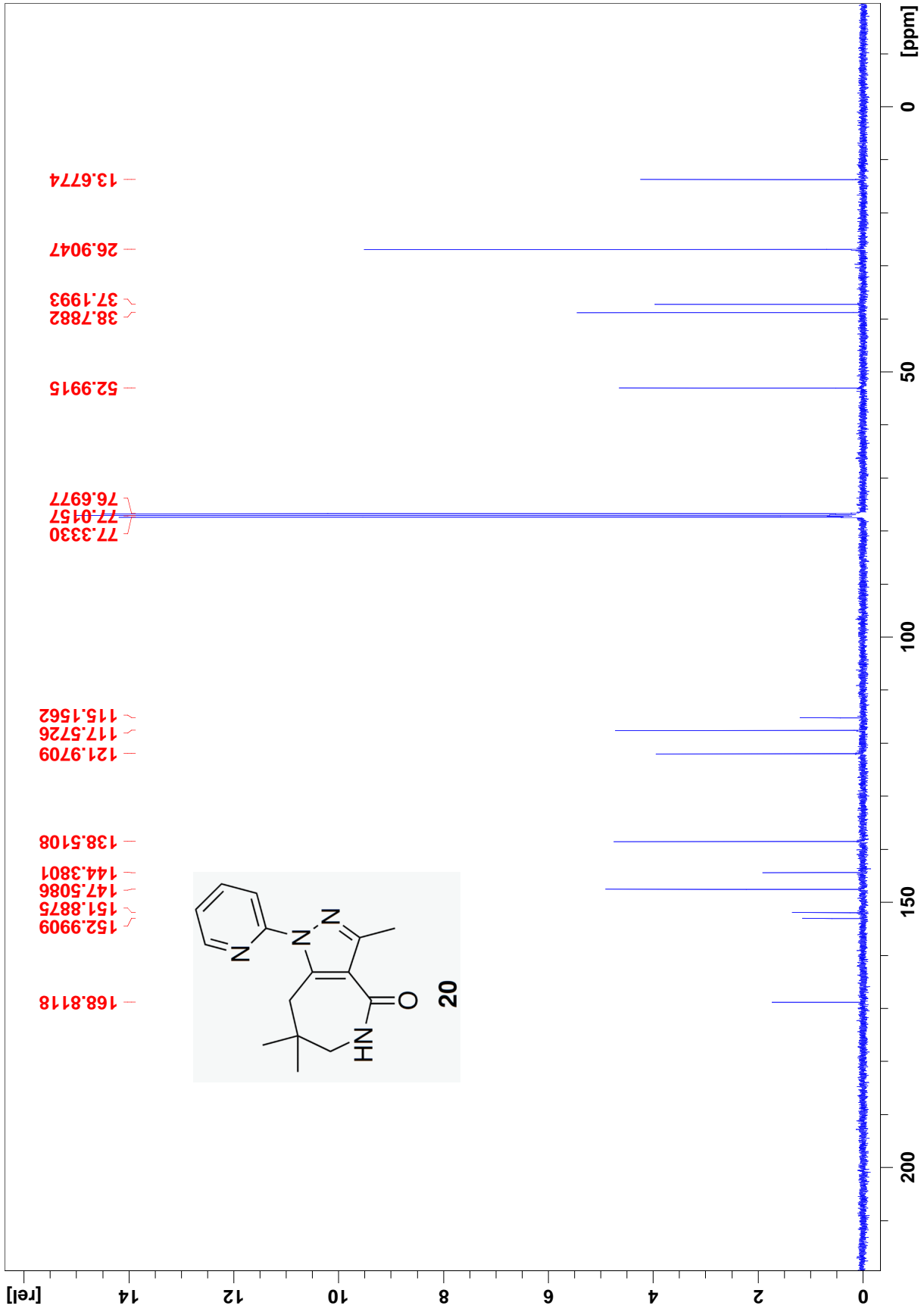
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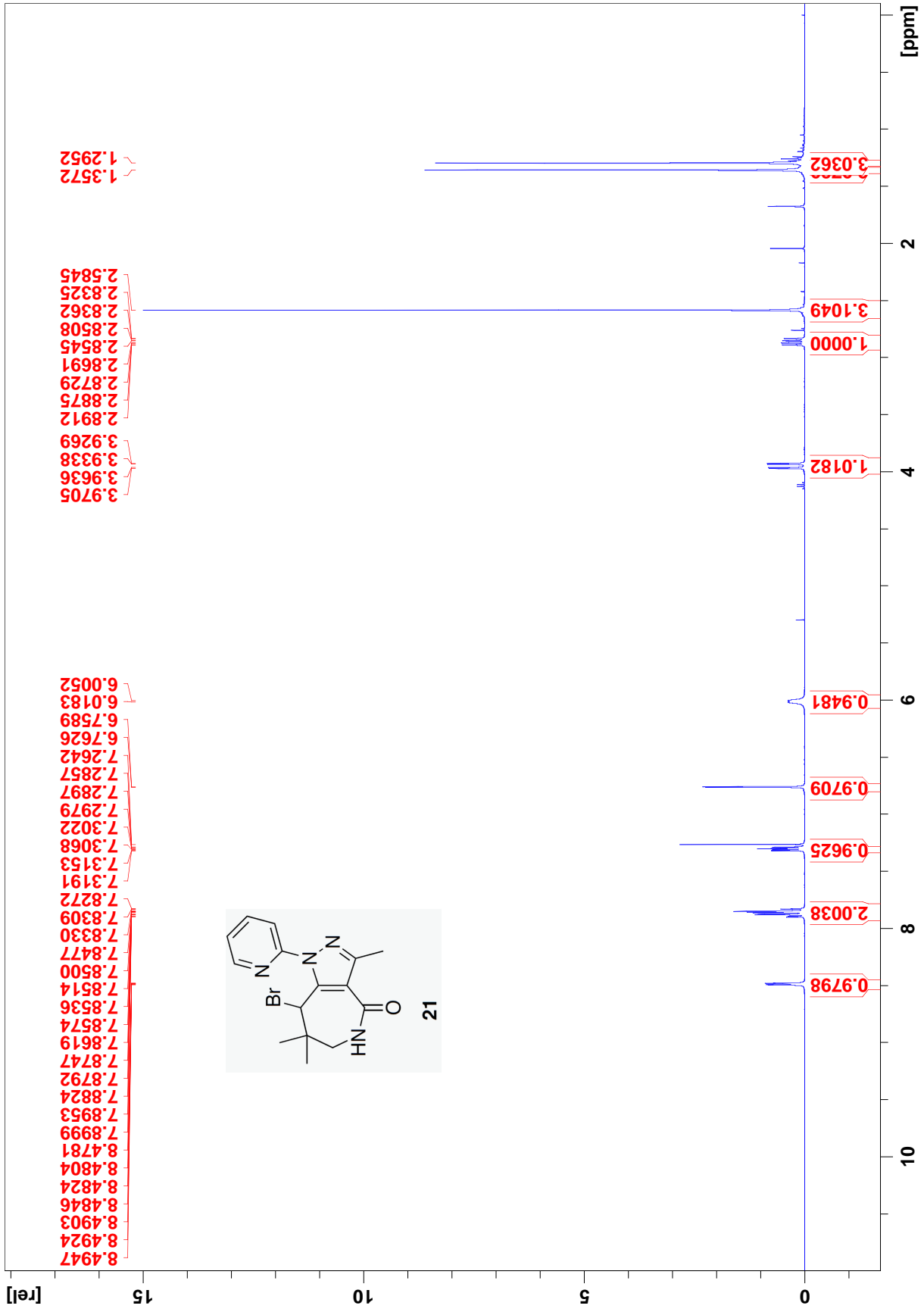
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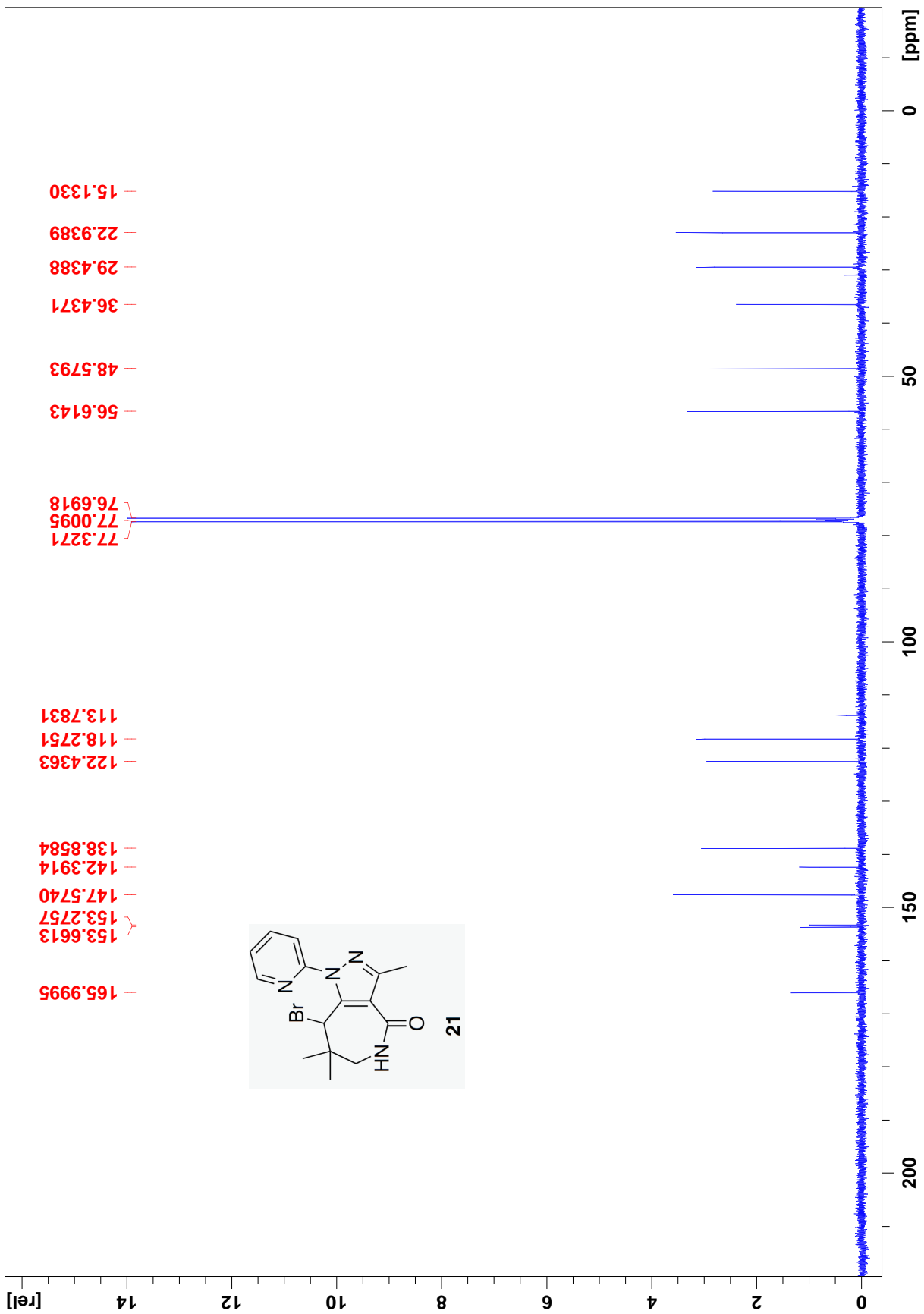
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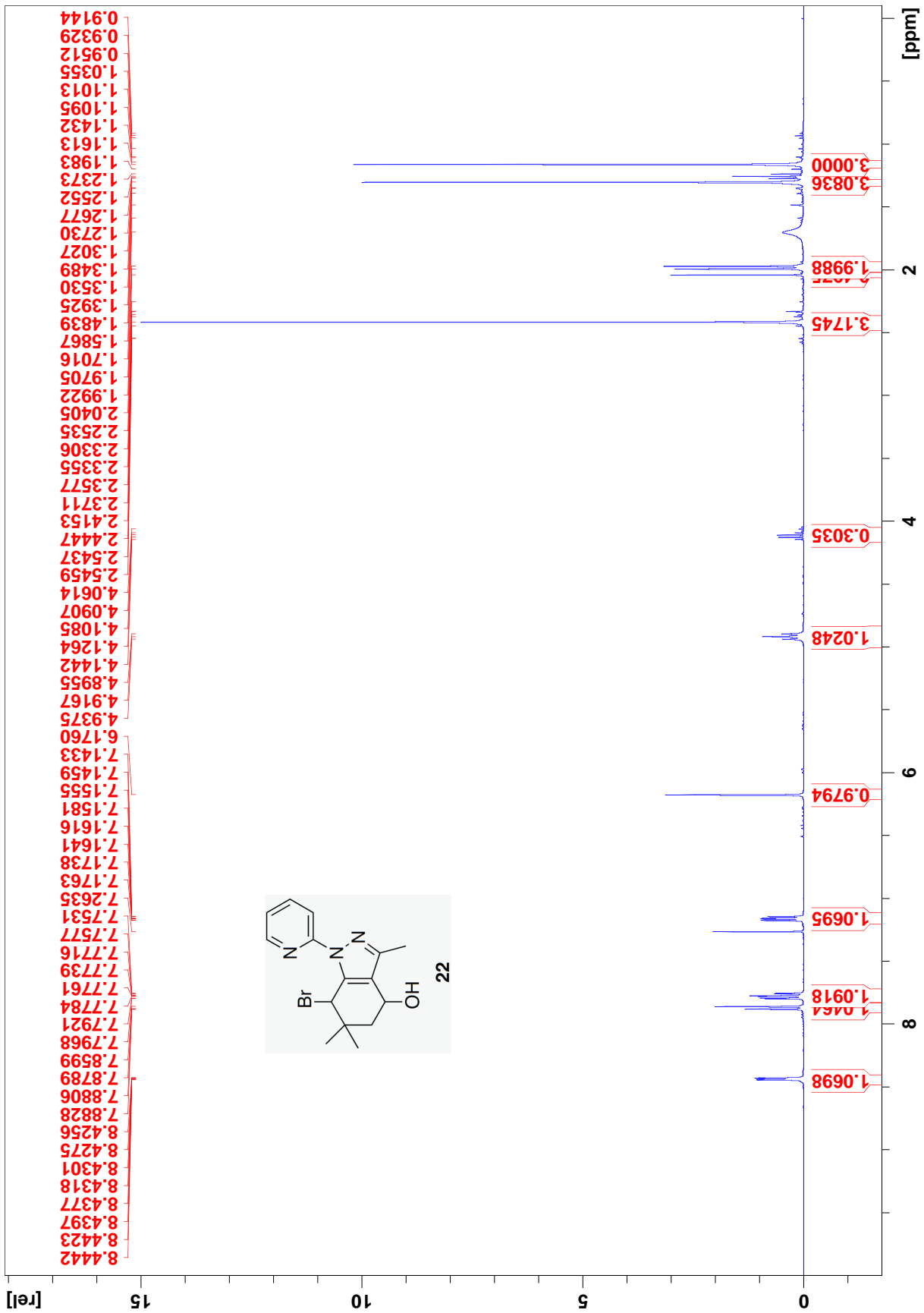
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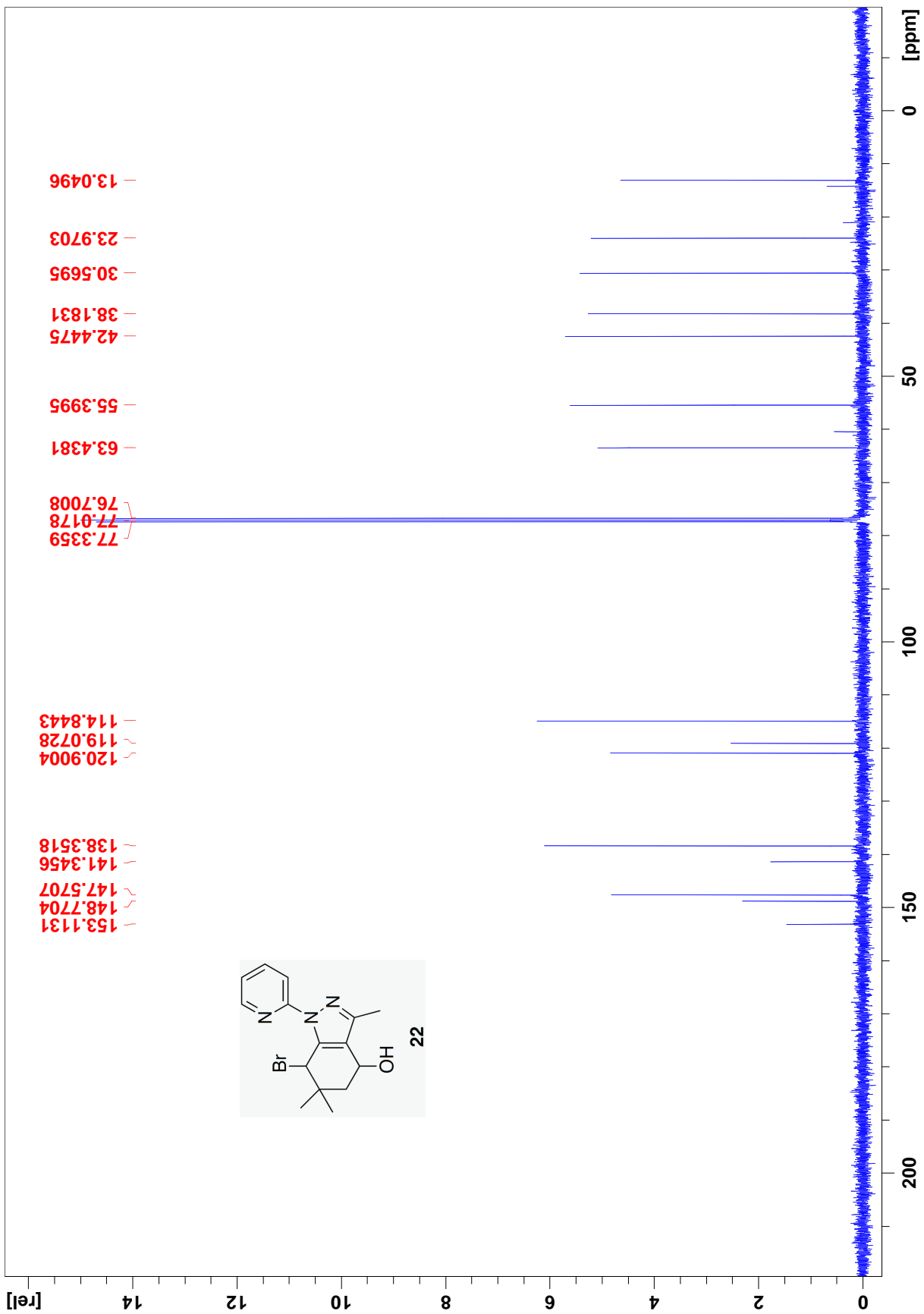
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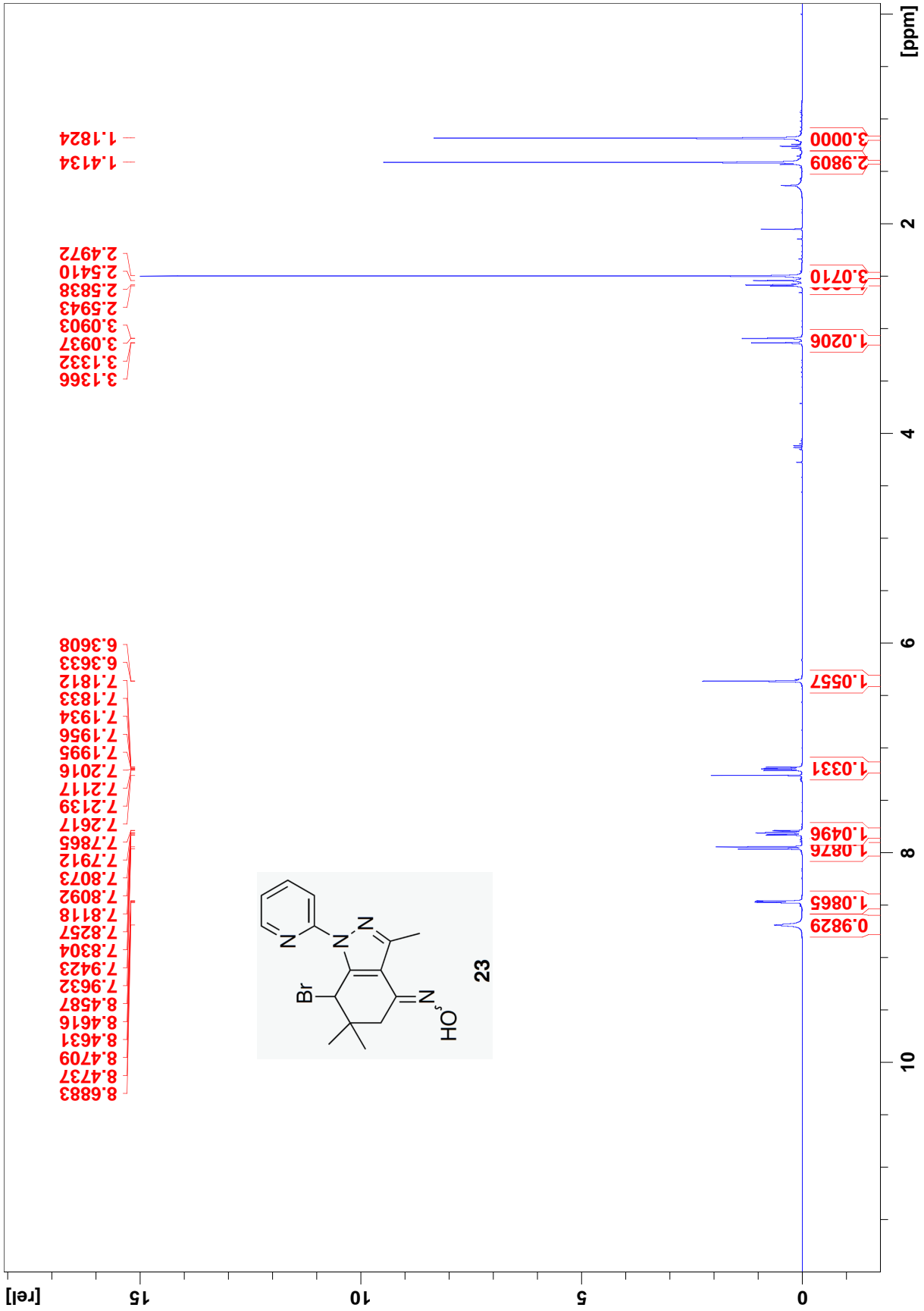
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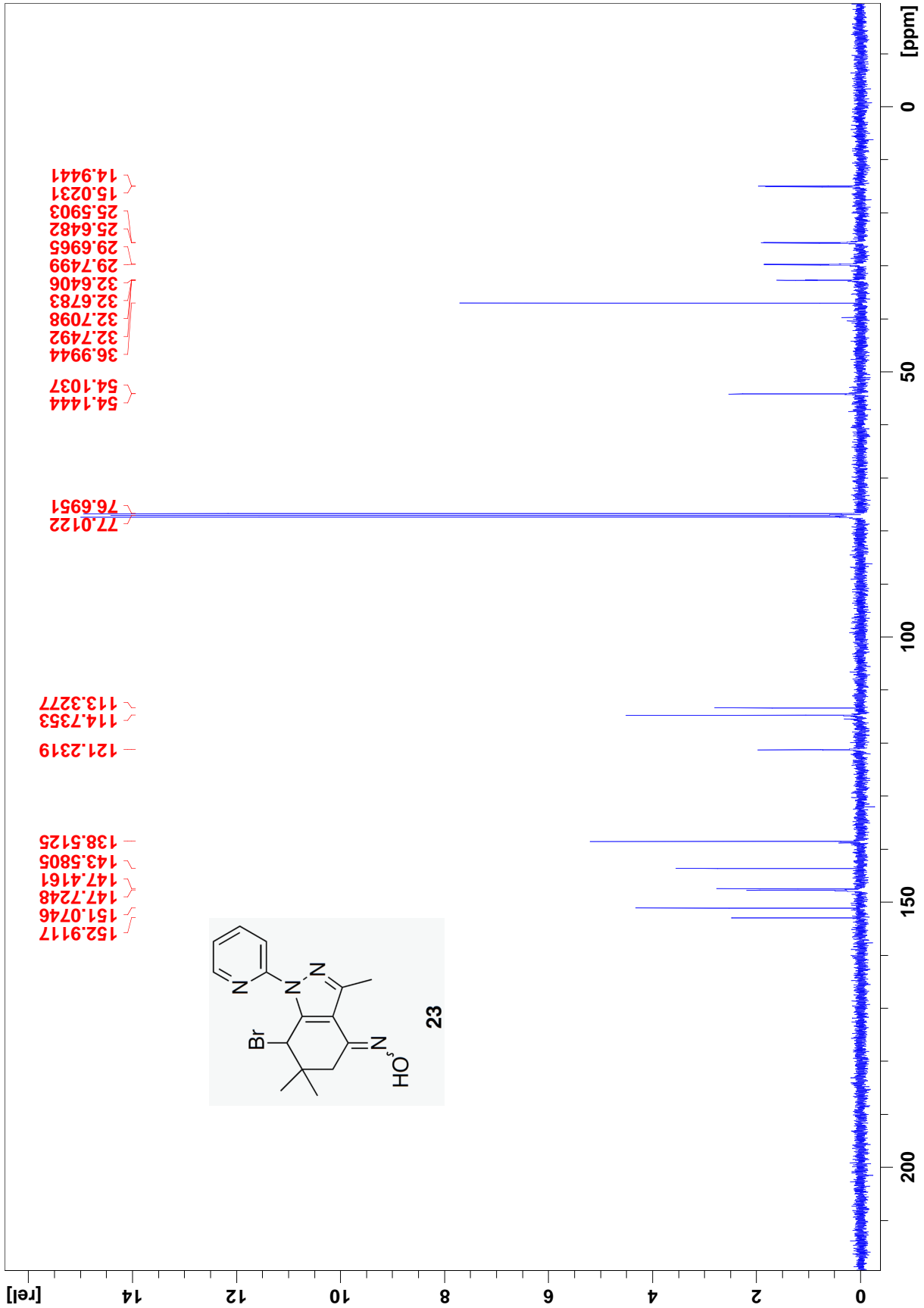
1H-NMR

JL08-091808B 1 1 C:\Bruker\TOPSPIN leex3451



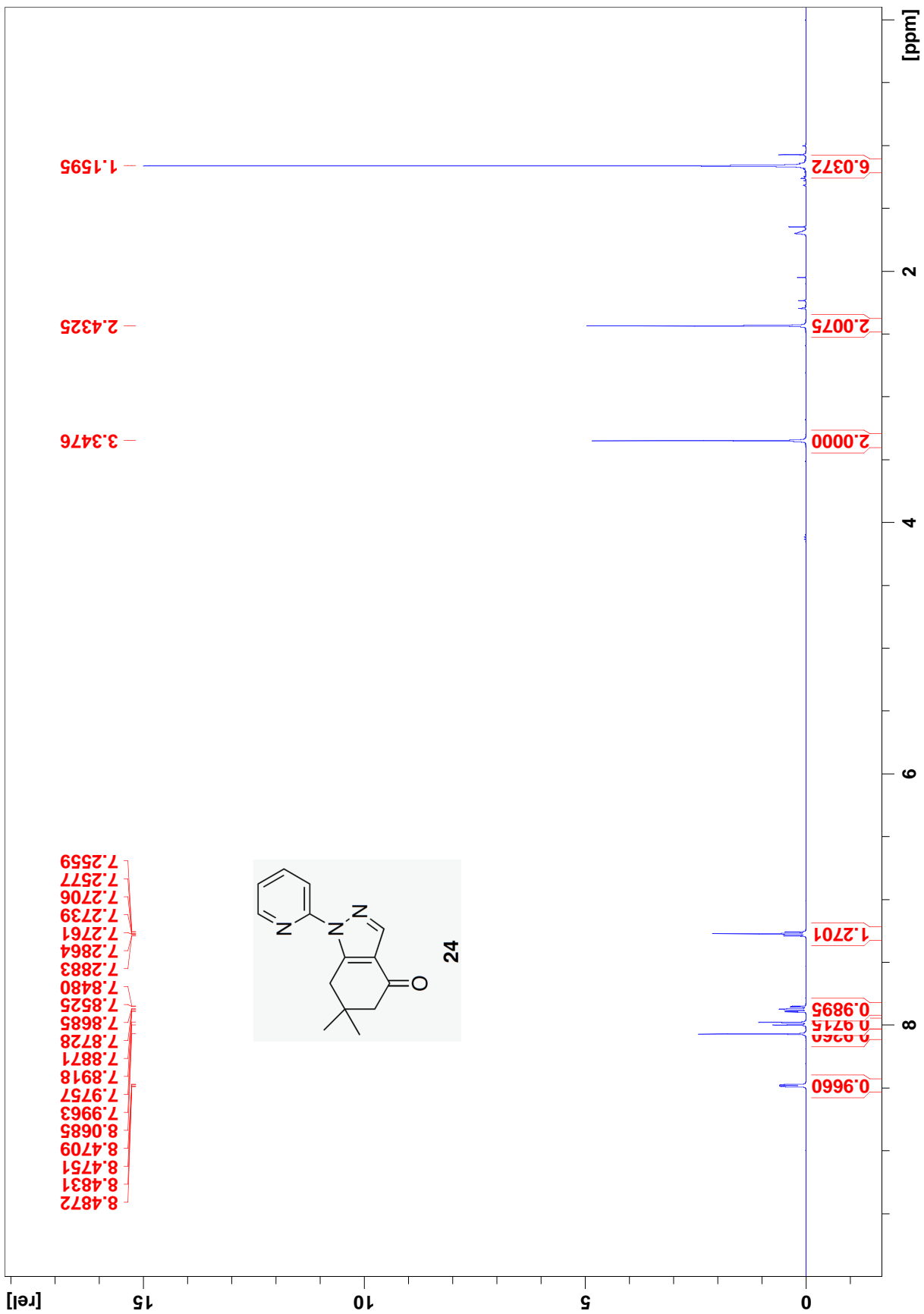
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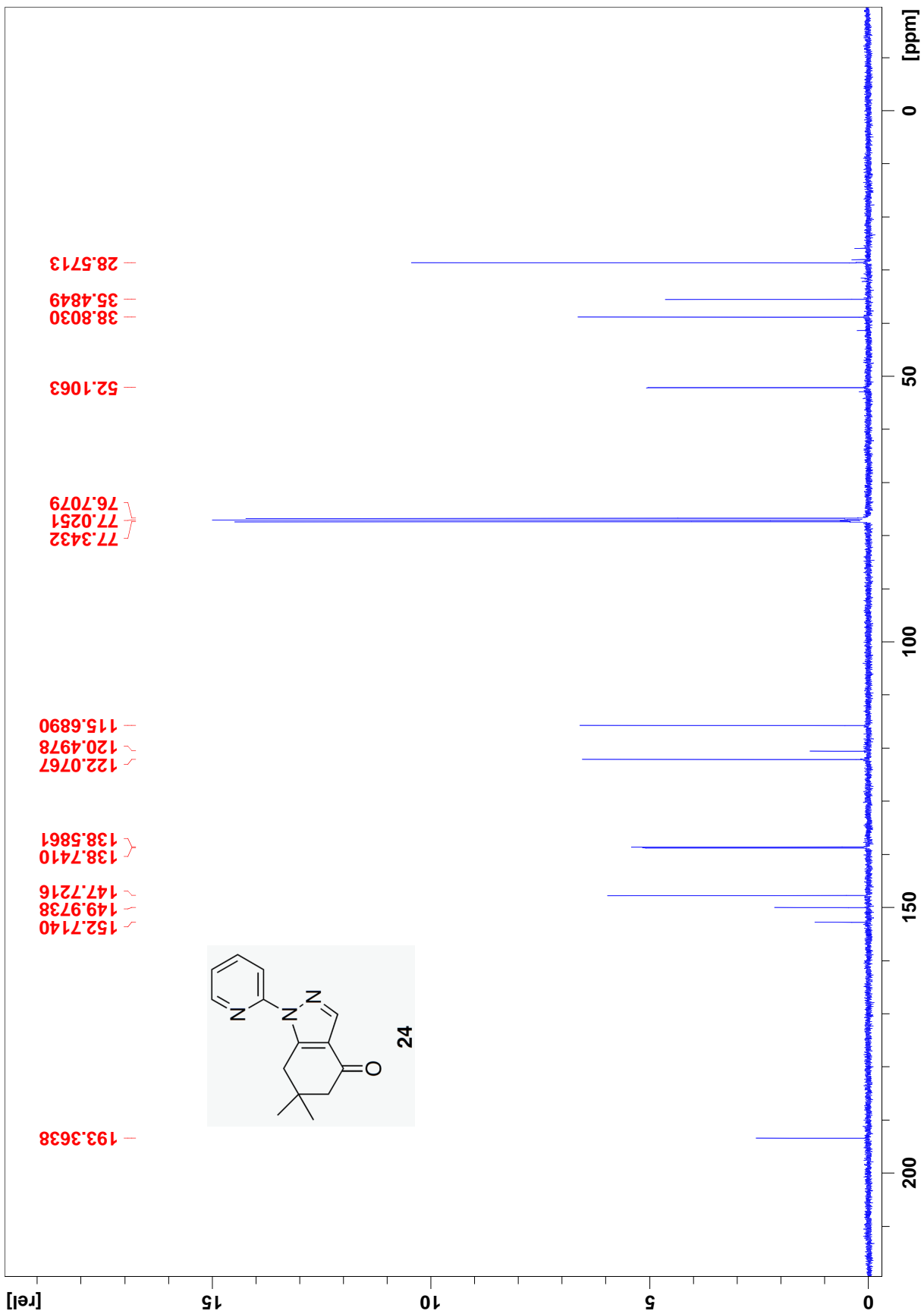
1H-NMR

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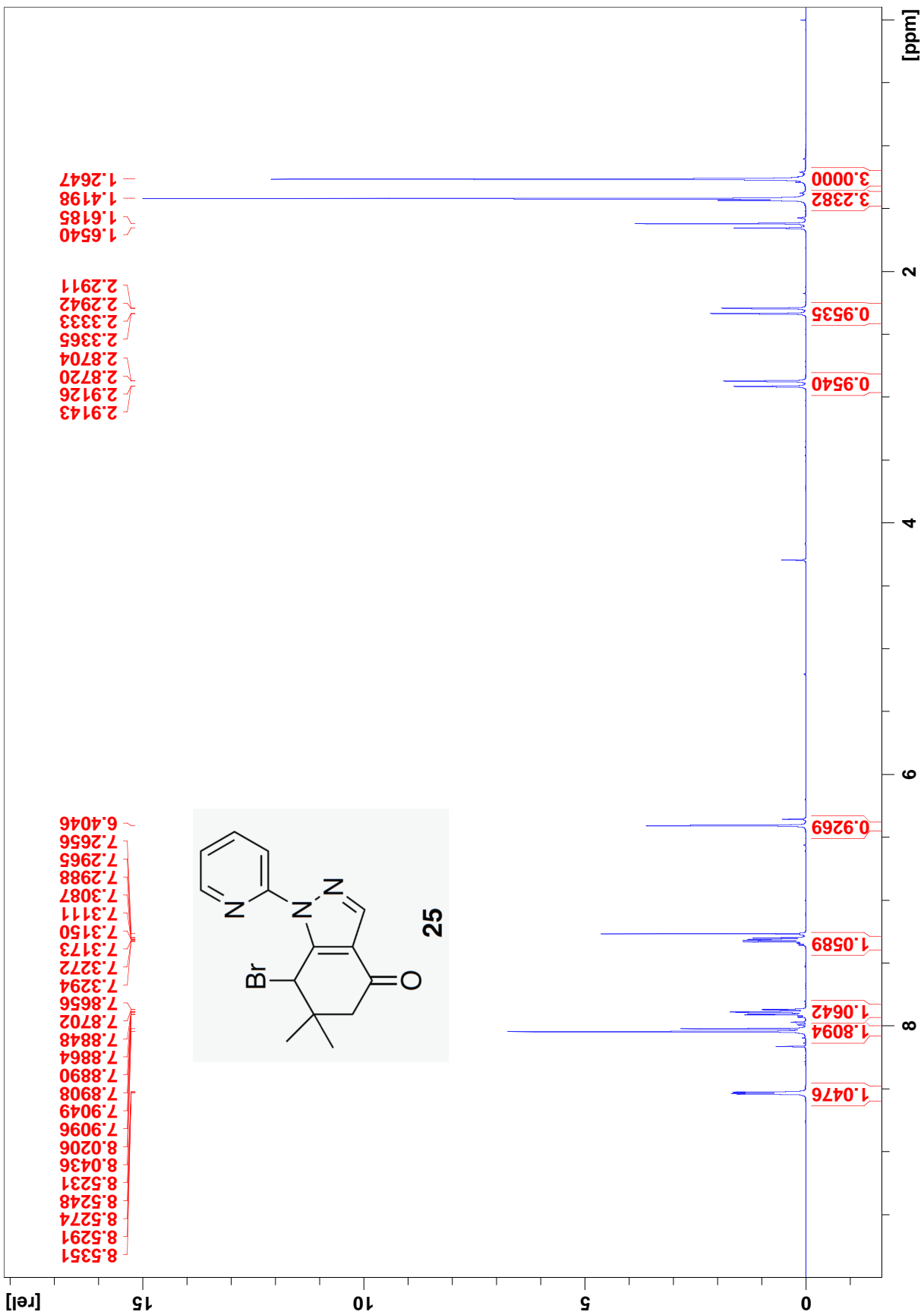
13C-NMR

JL08-101408 3 1 C:\Bruker\TOPSPIN leex3451



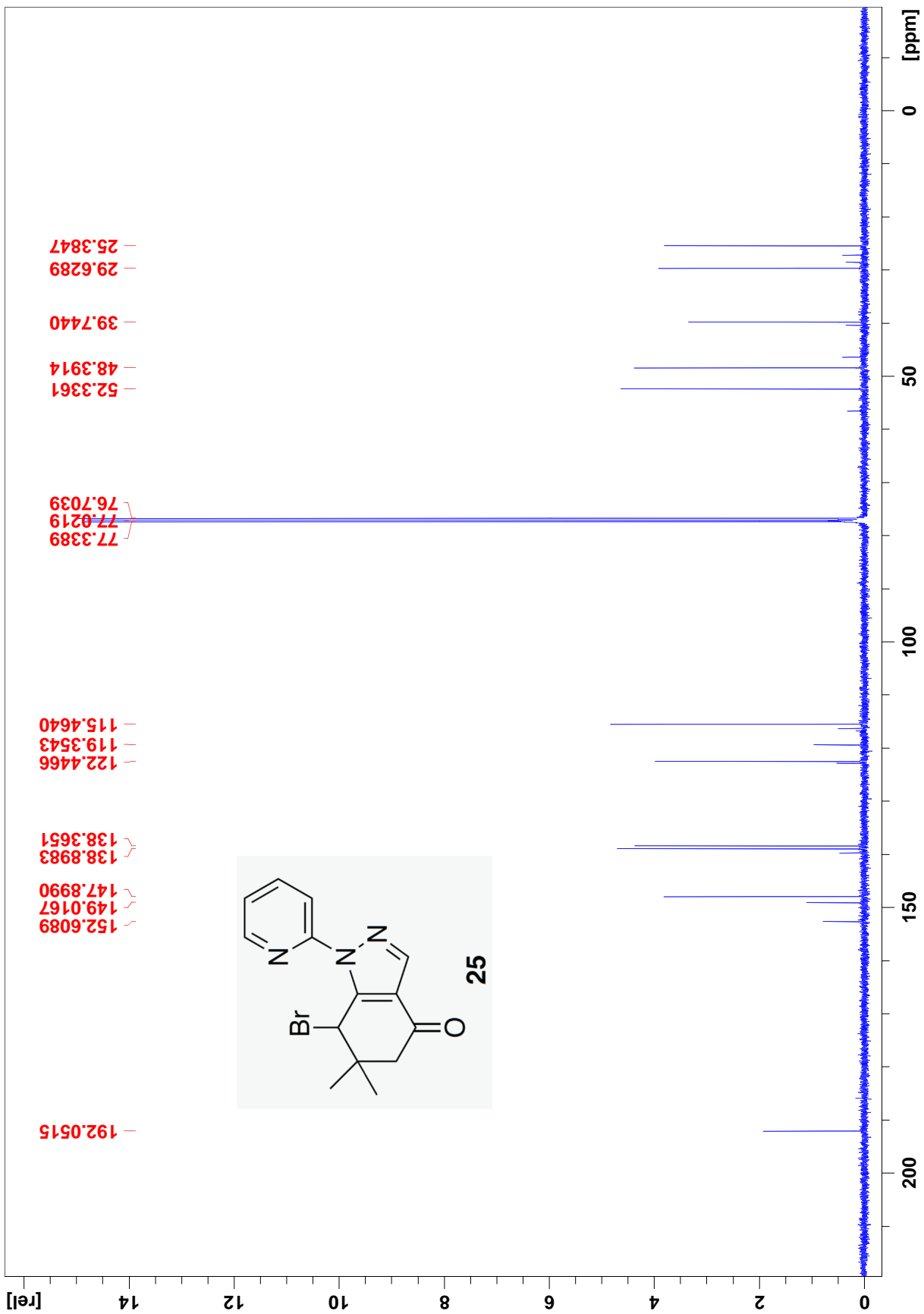
1H-NMR

JL08-101508-1 1 1 C:\Bruker\TOPSPIN leex3451



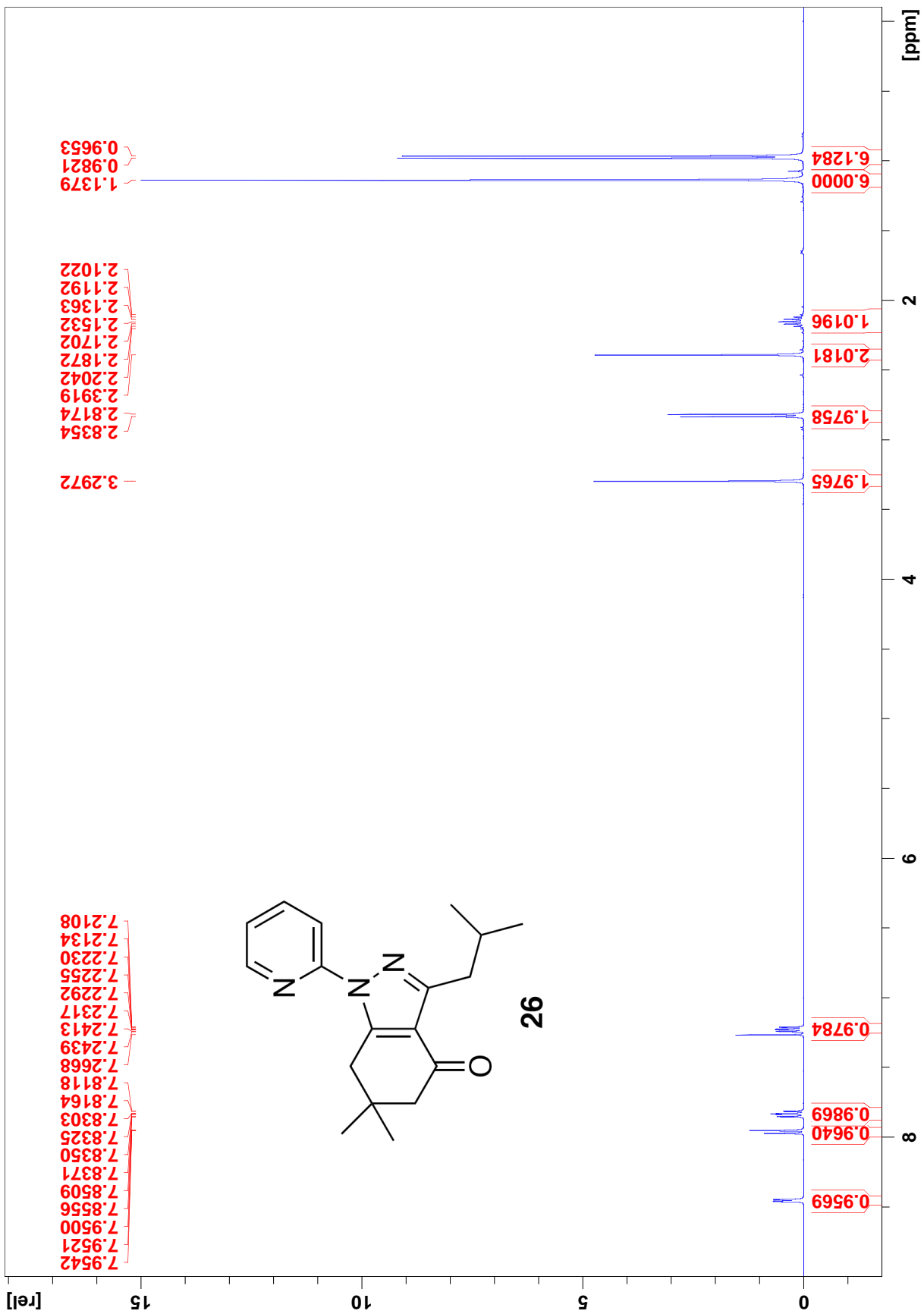
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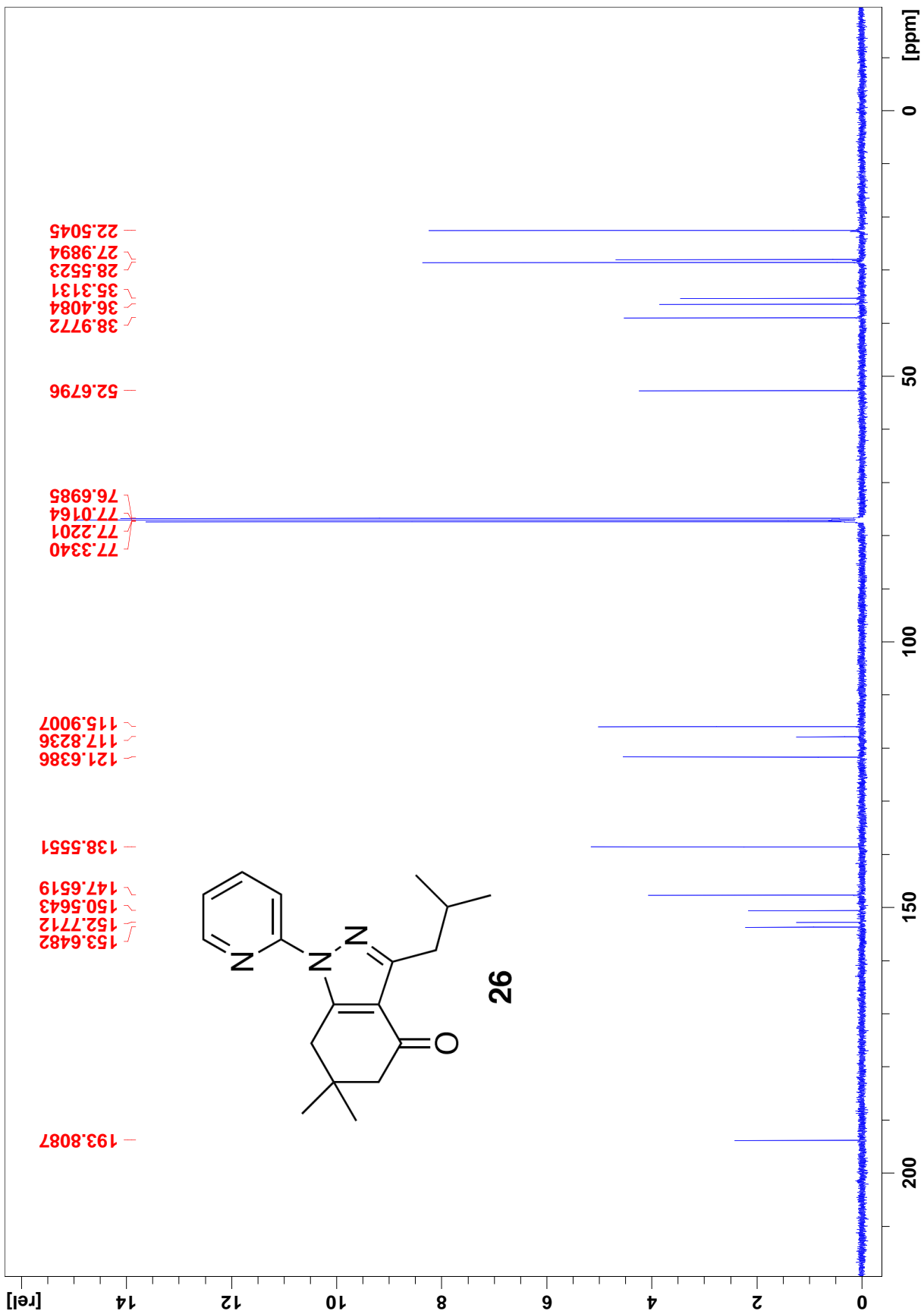
1H-NMR

JL08-11.2608 1 1 C:\Bruker\TOPSPIN leex3451



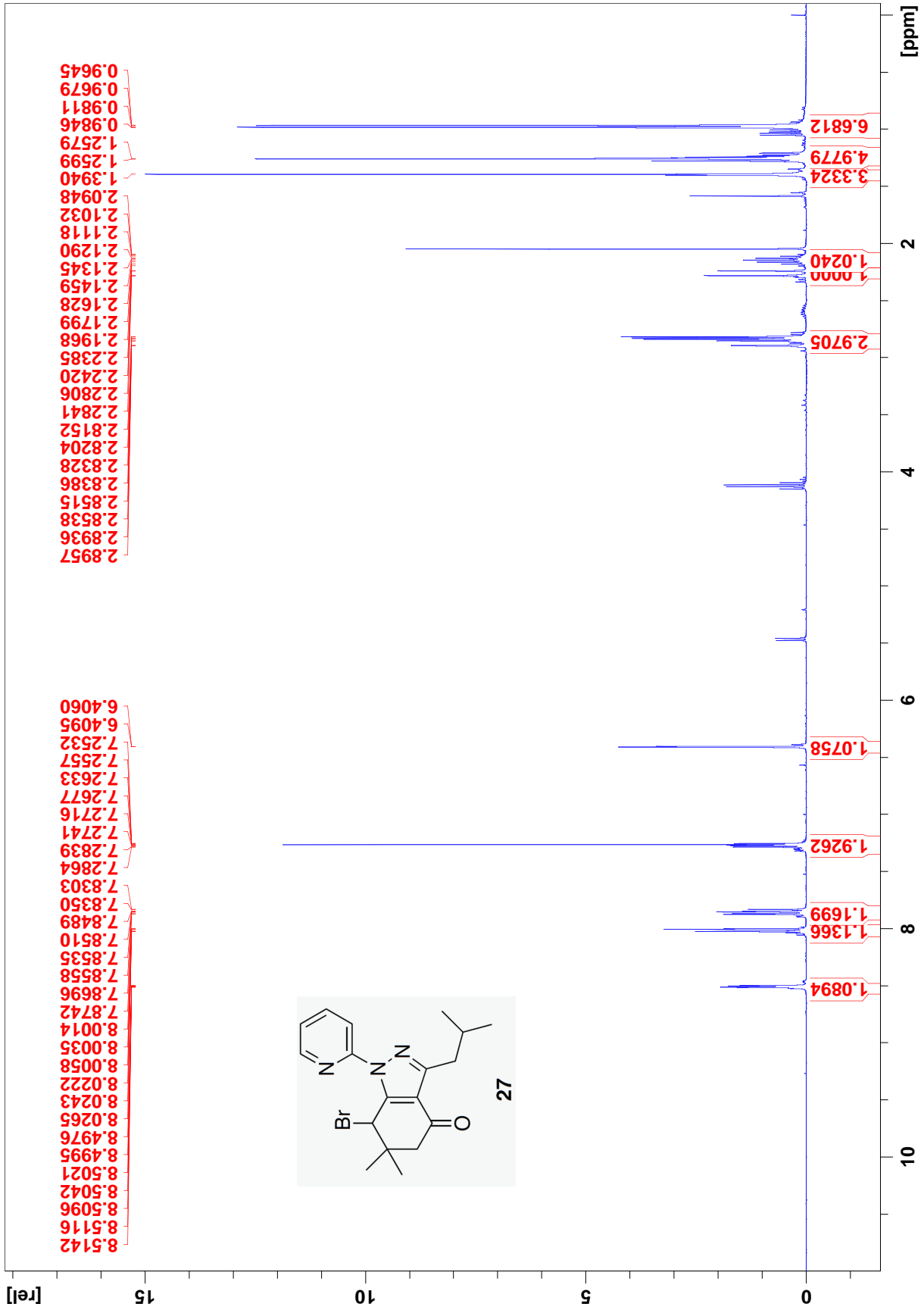
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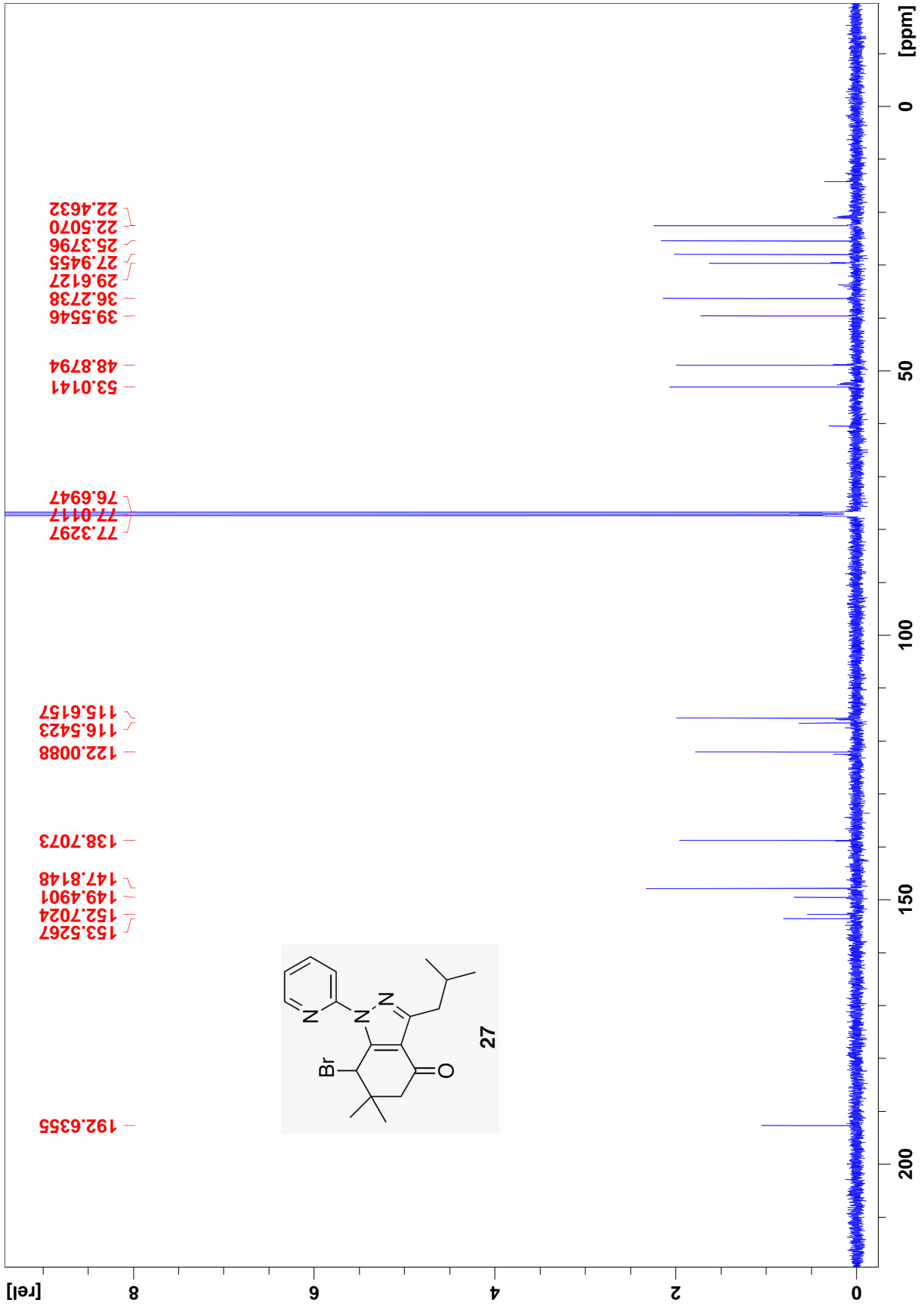
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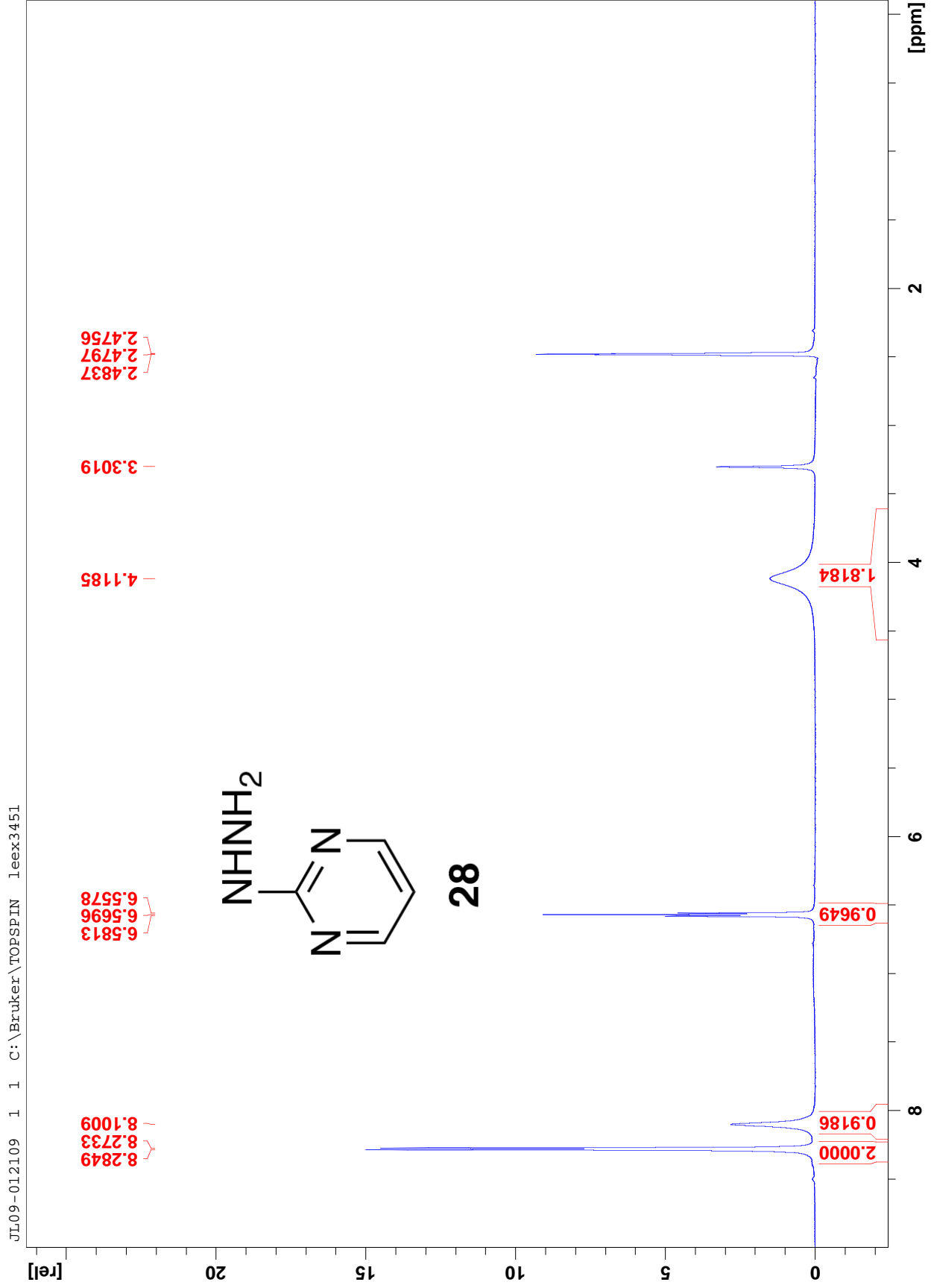


13C-NMR

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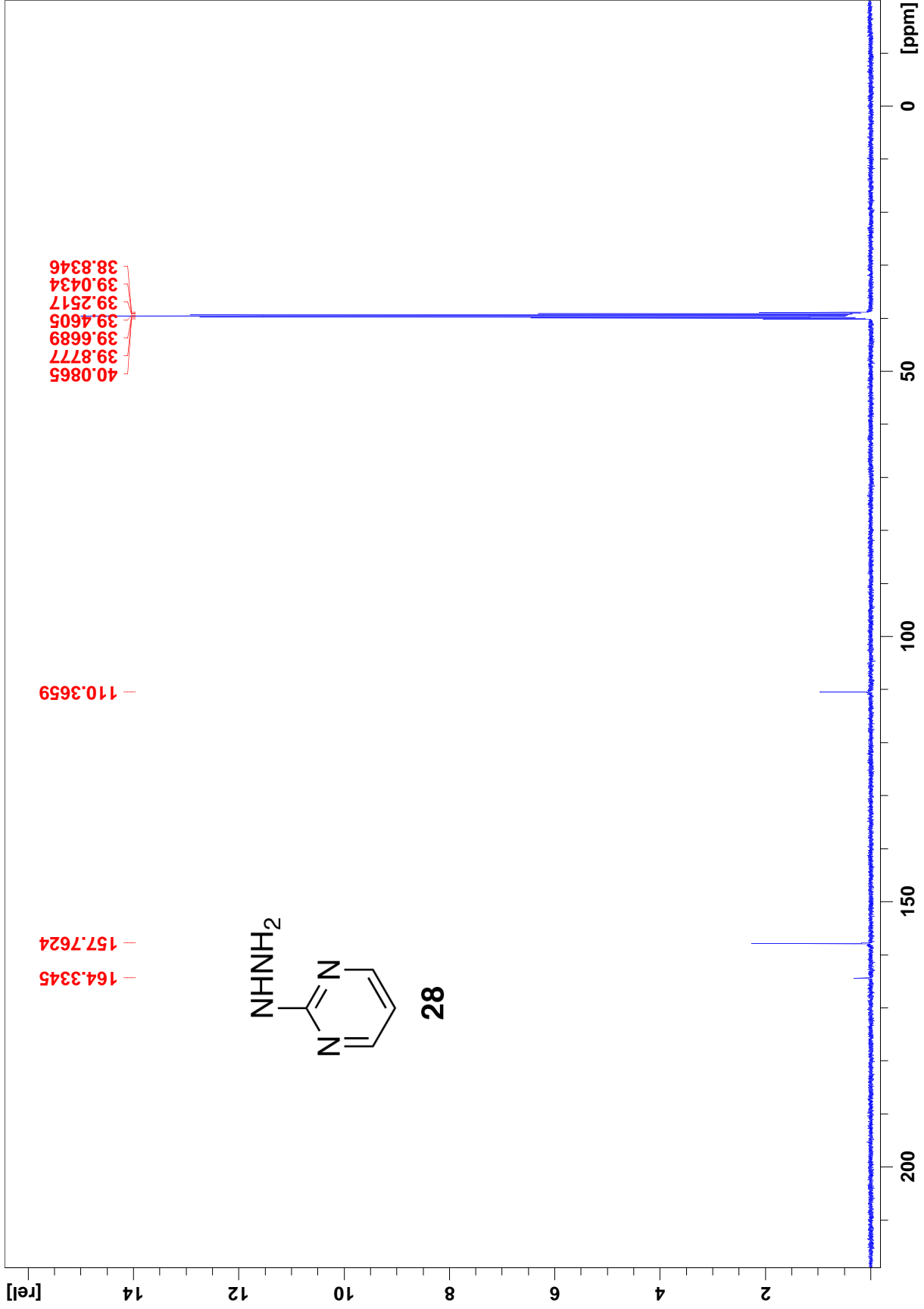


1H-NMR



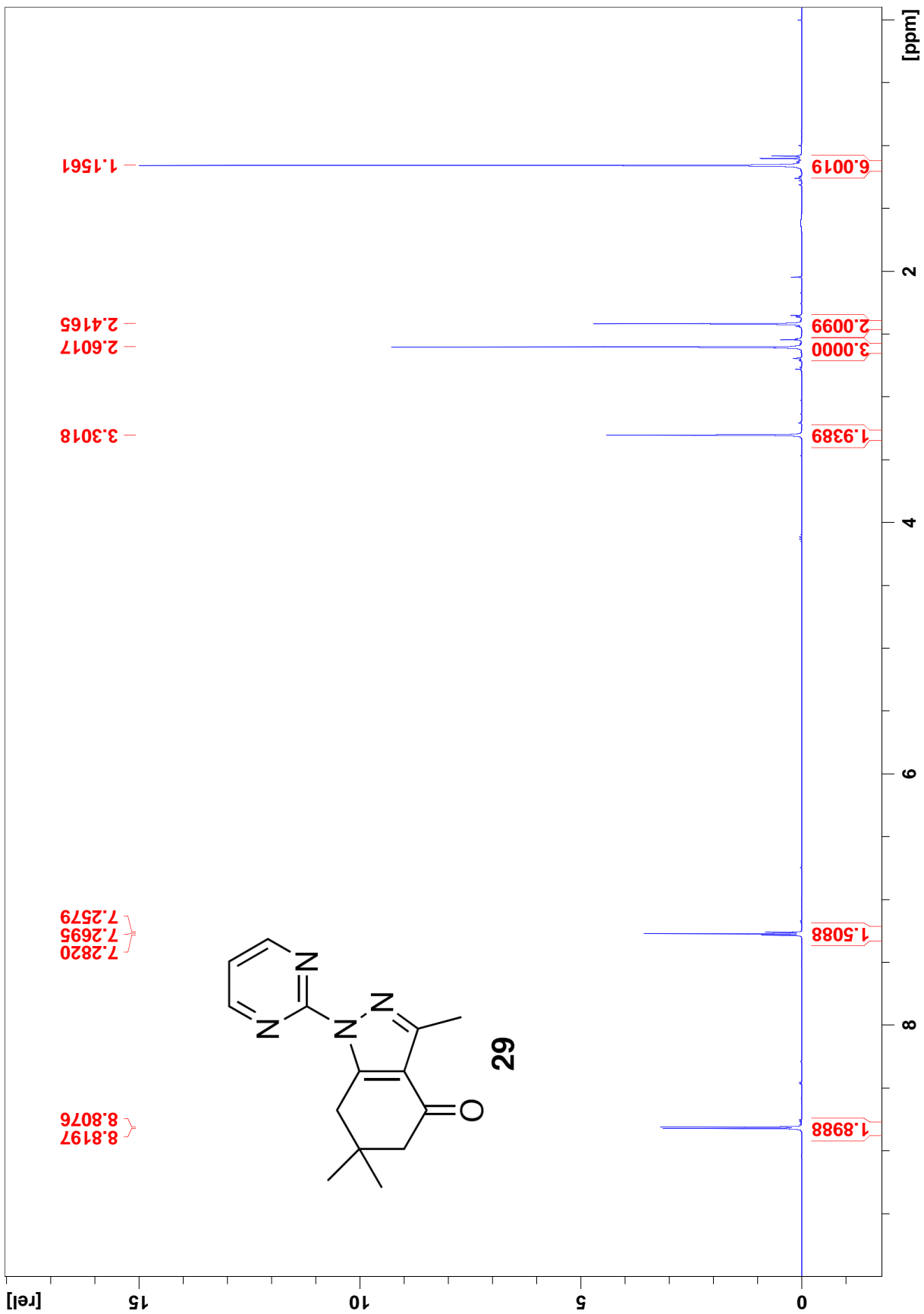
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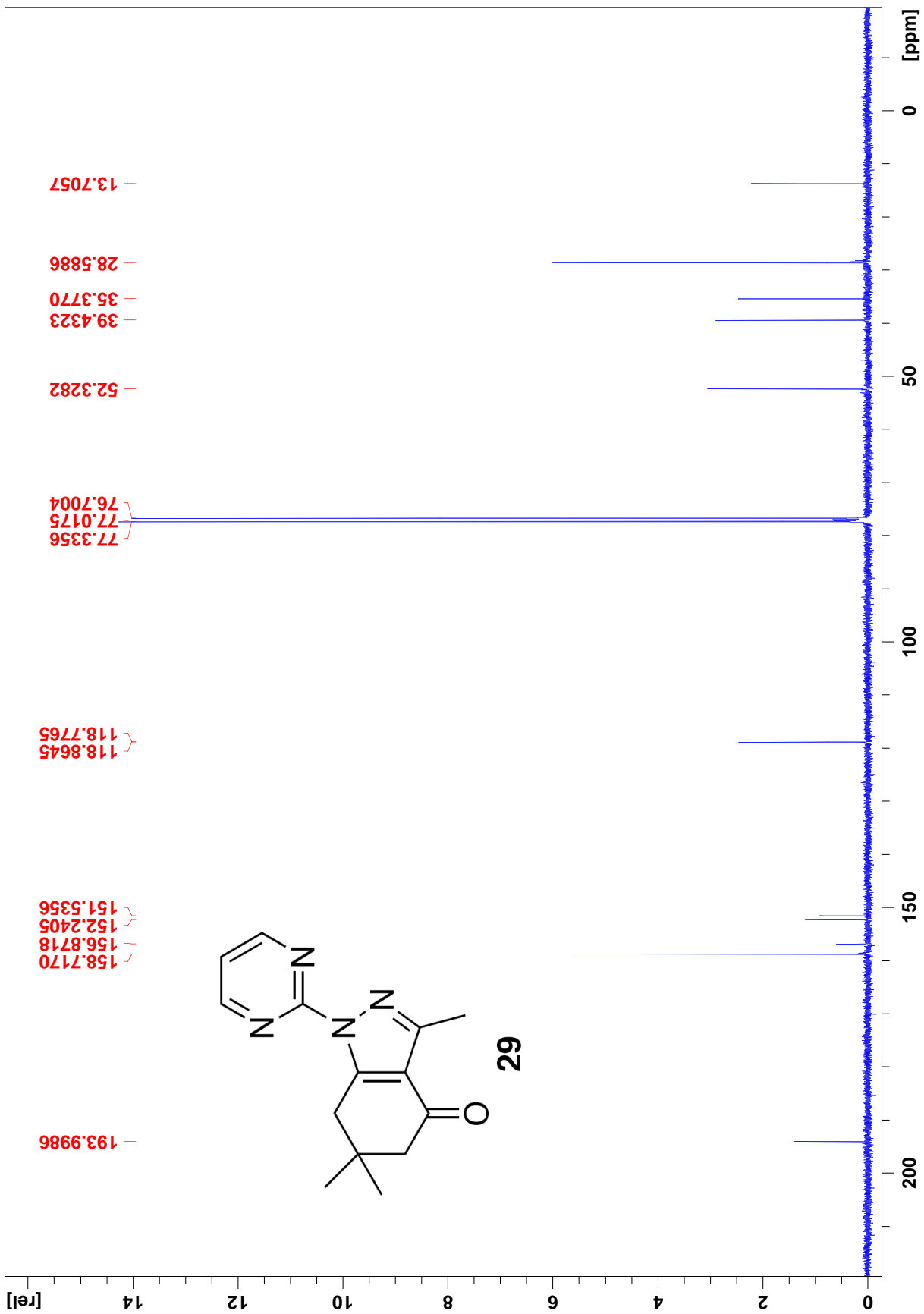
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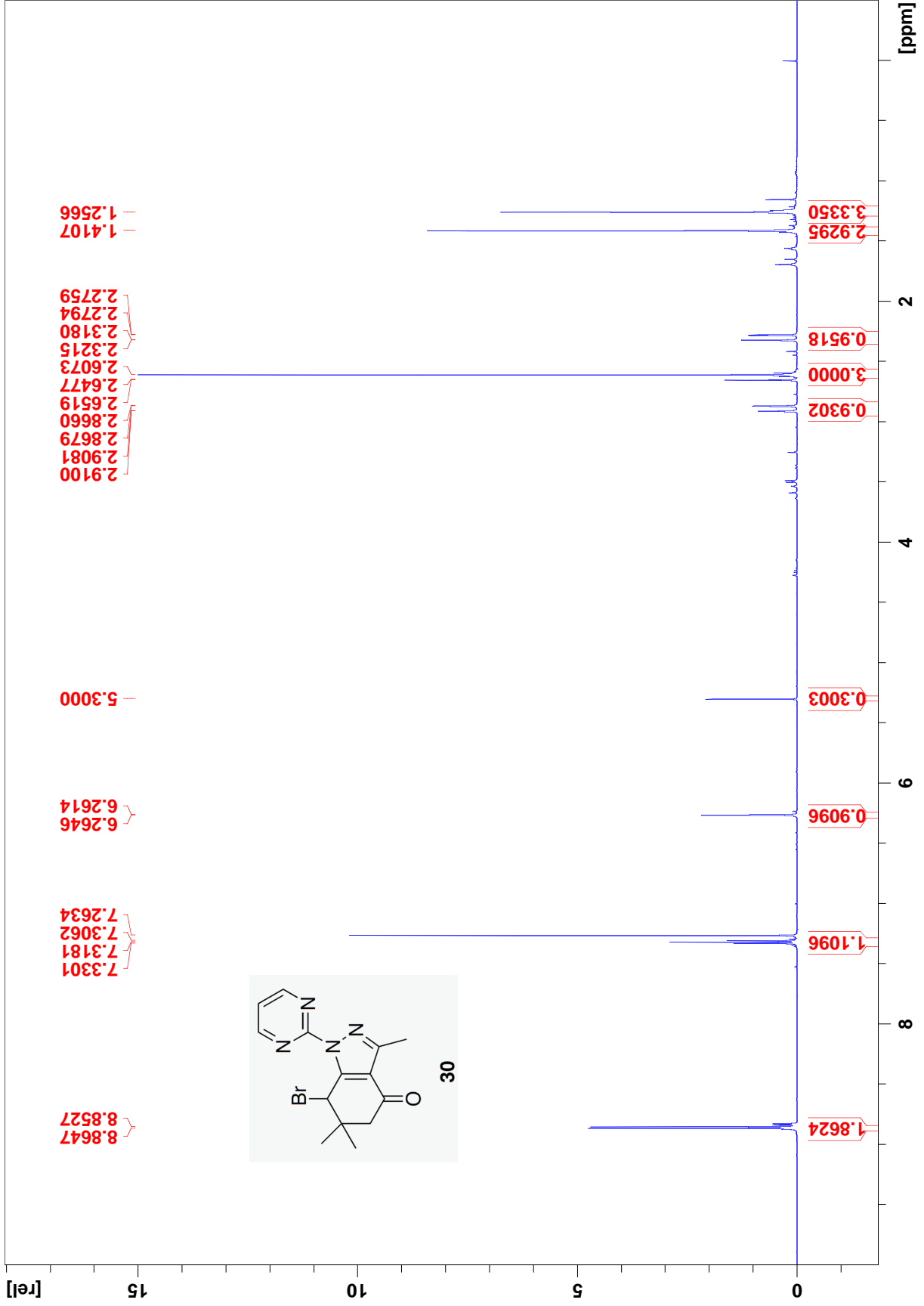
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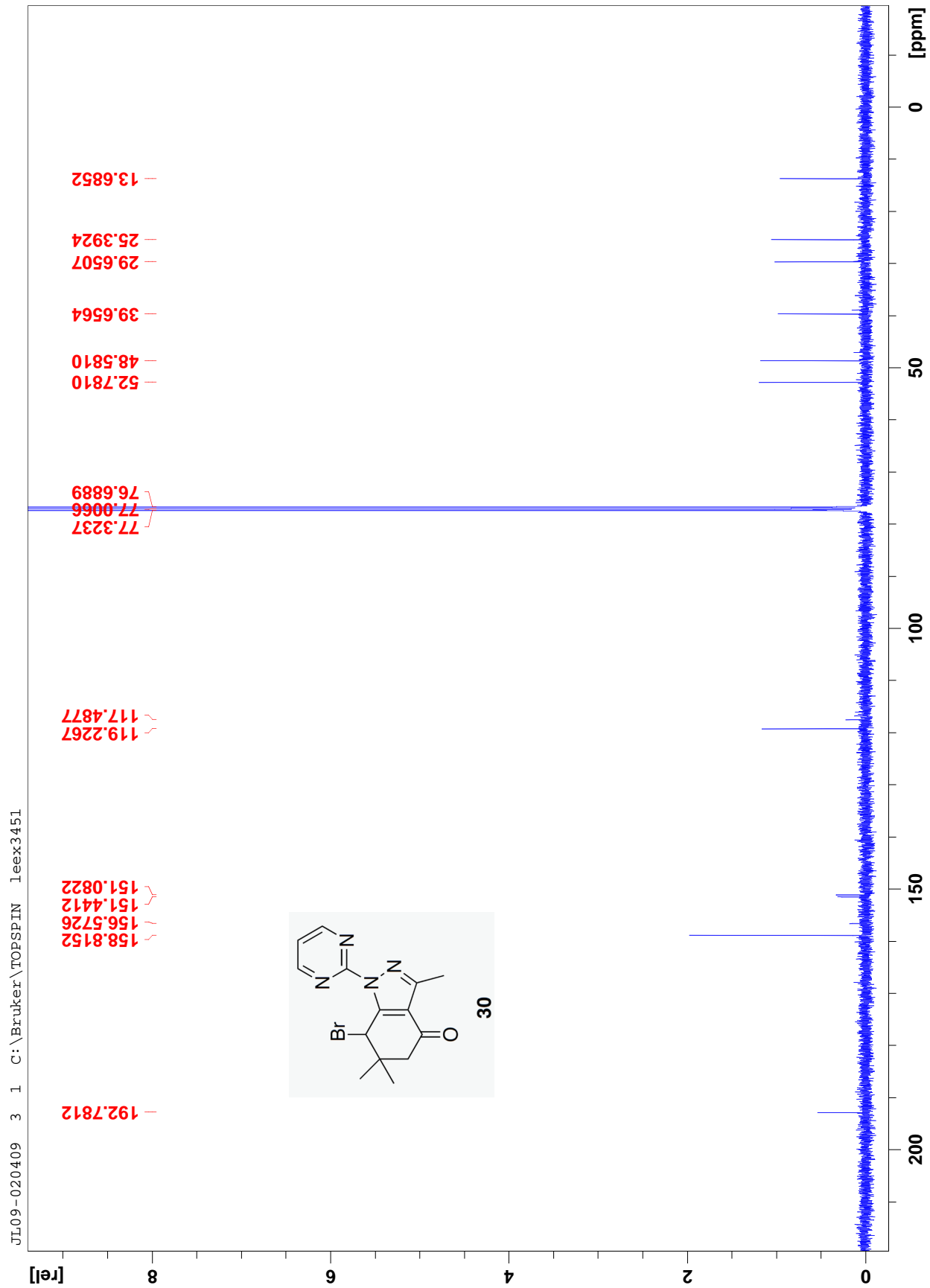


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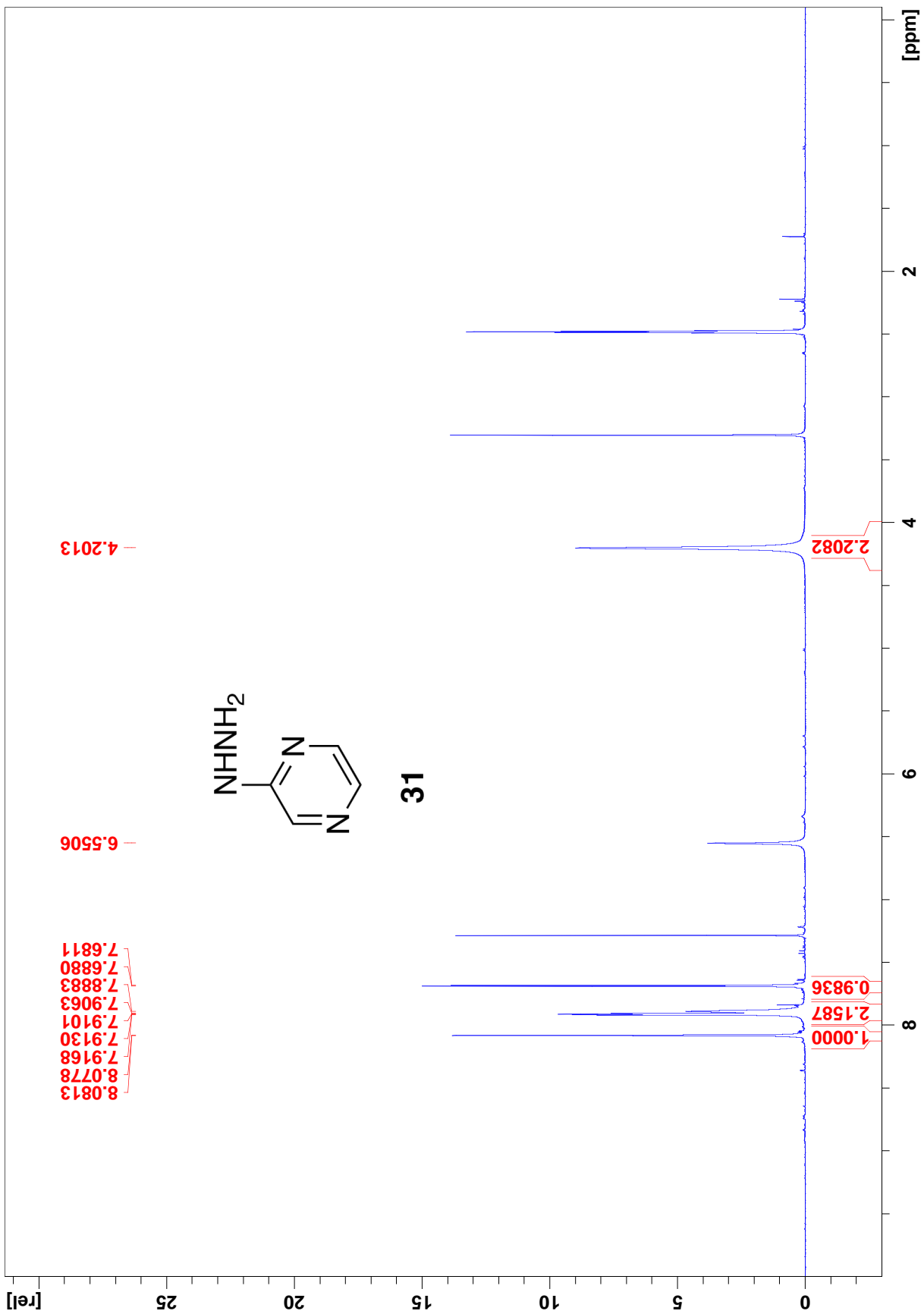


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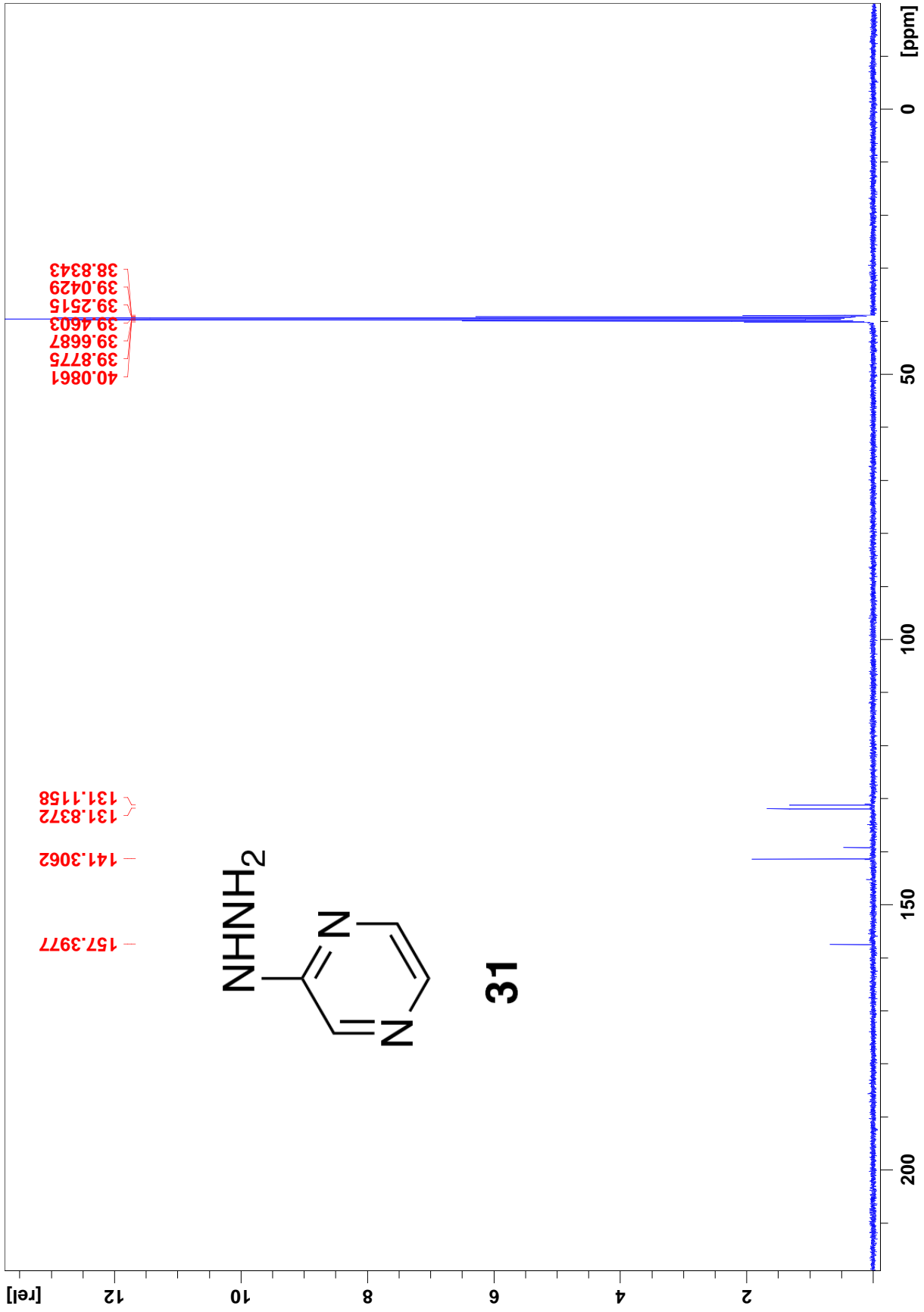
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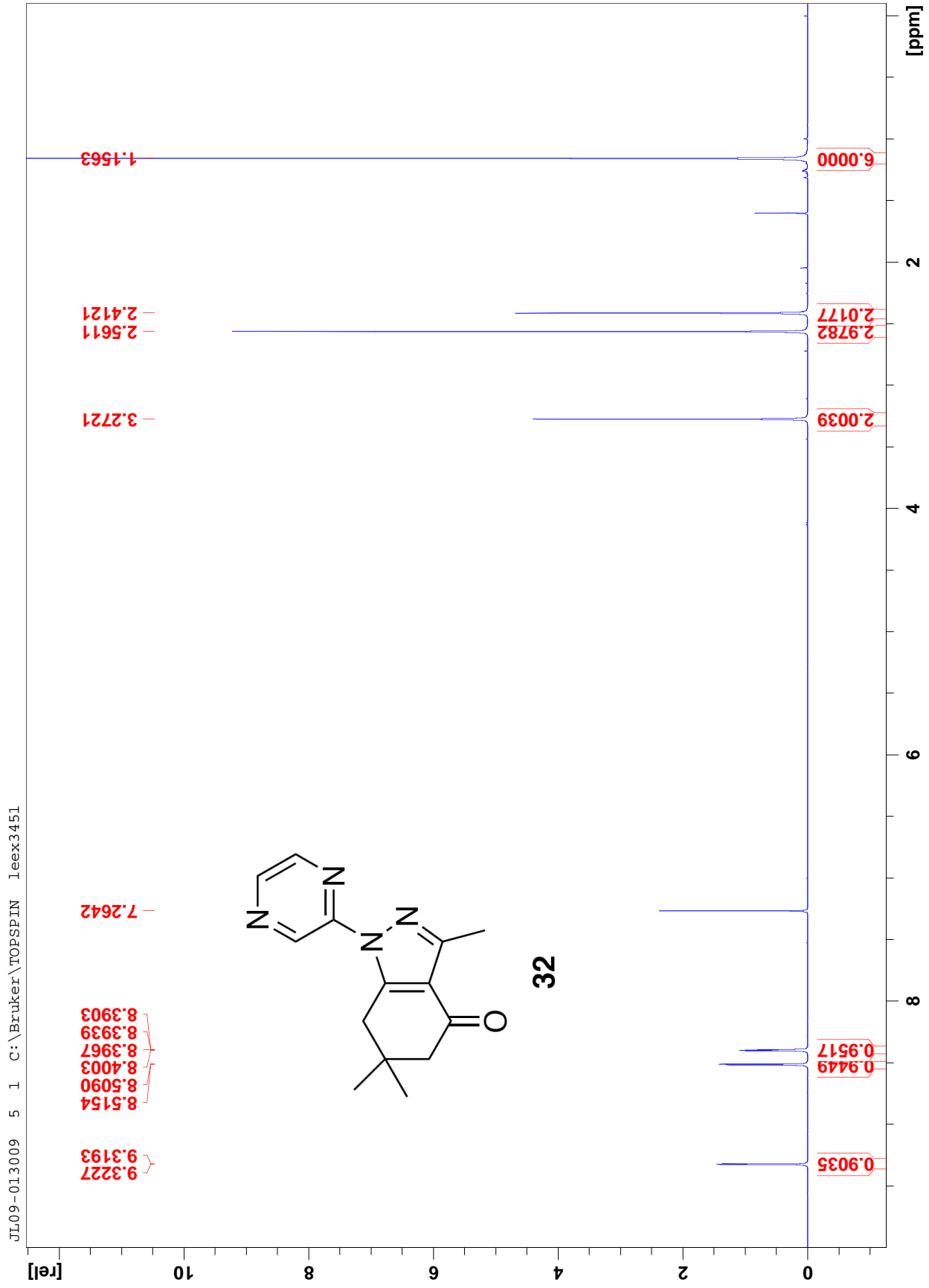


13C-NMR

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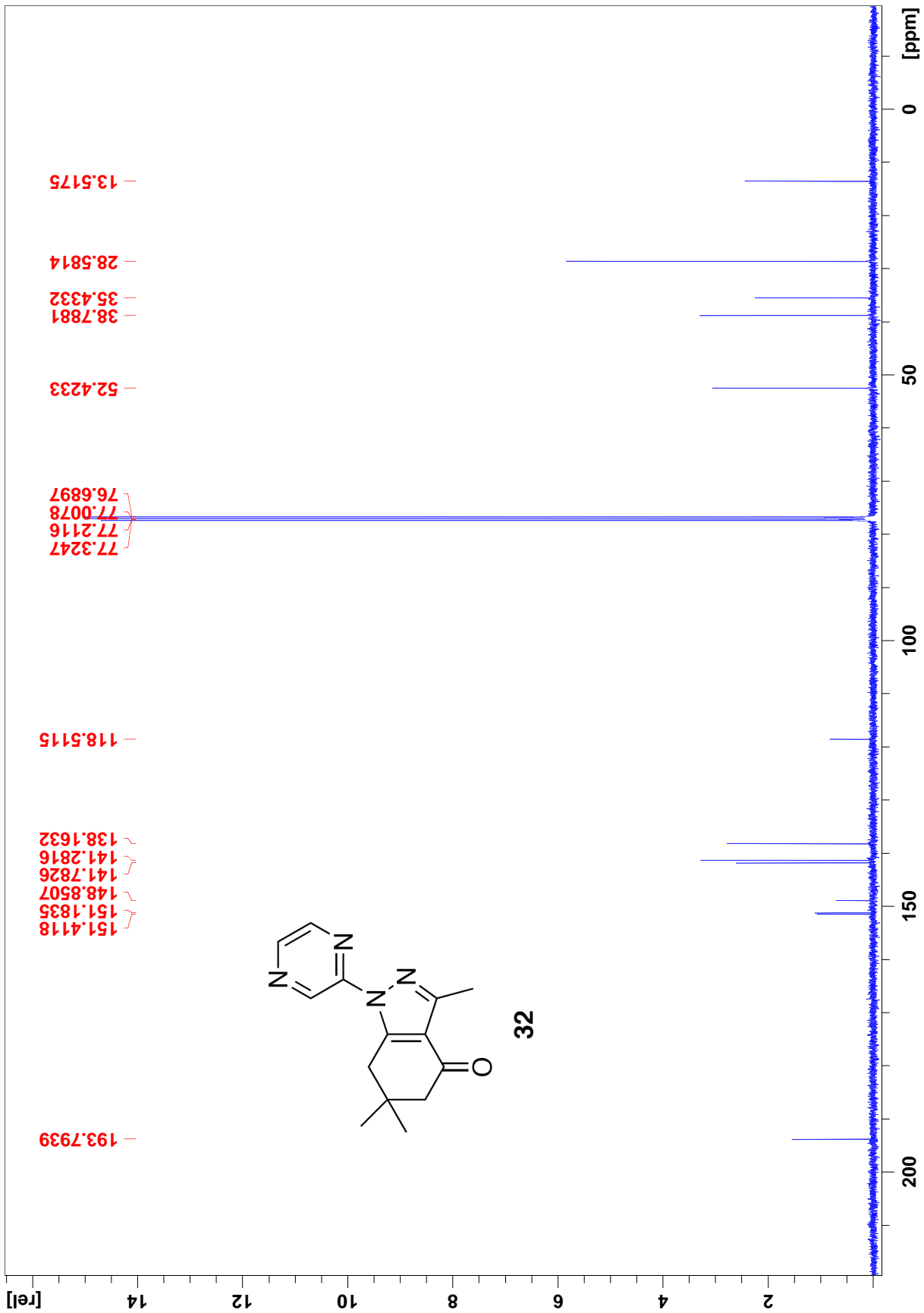


1H-NMR



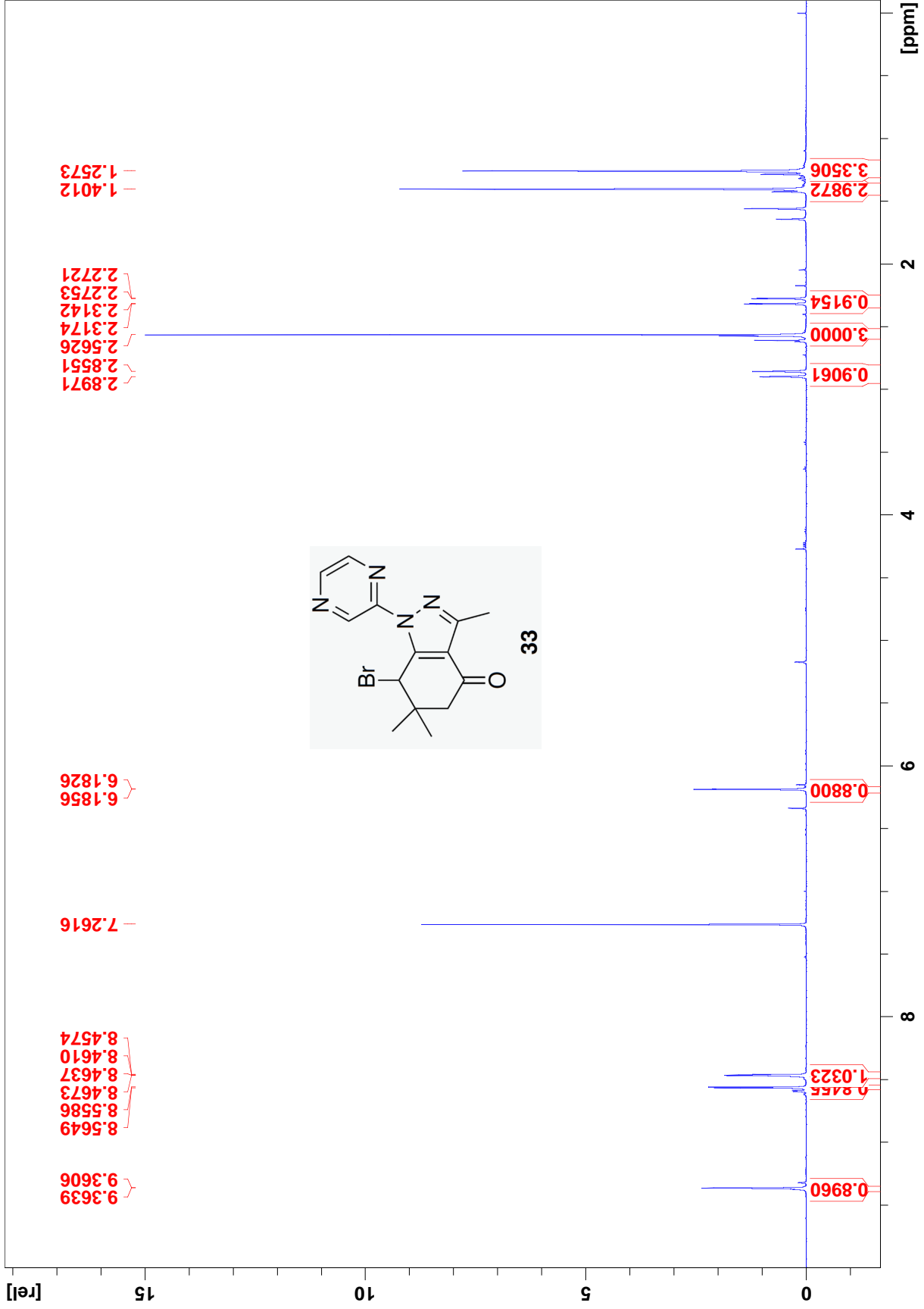
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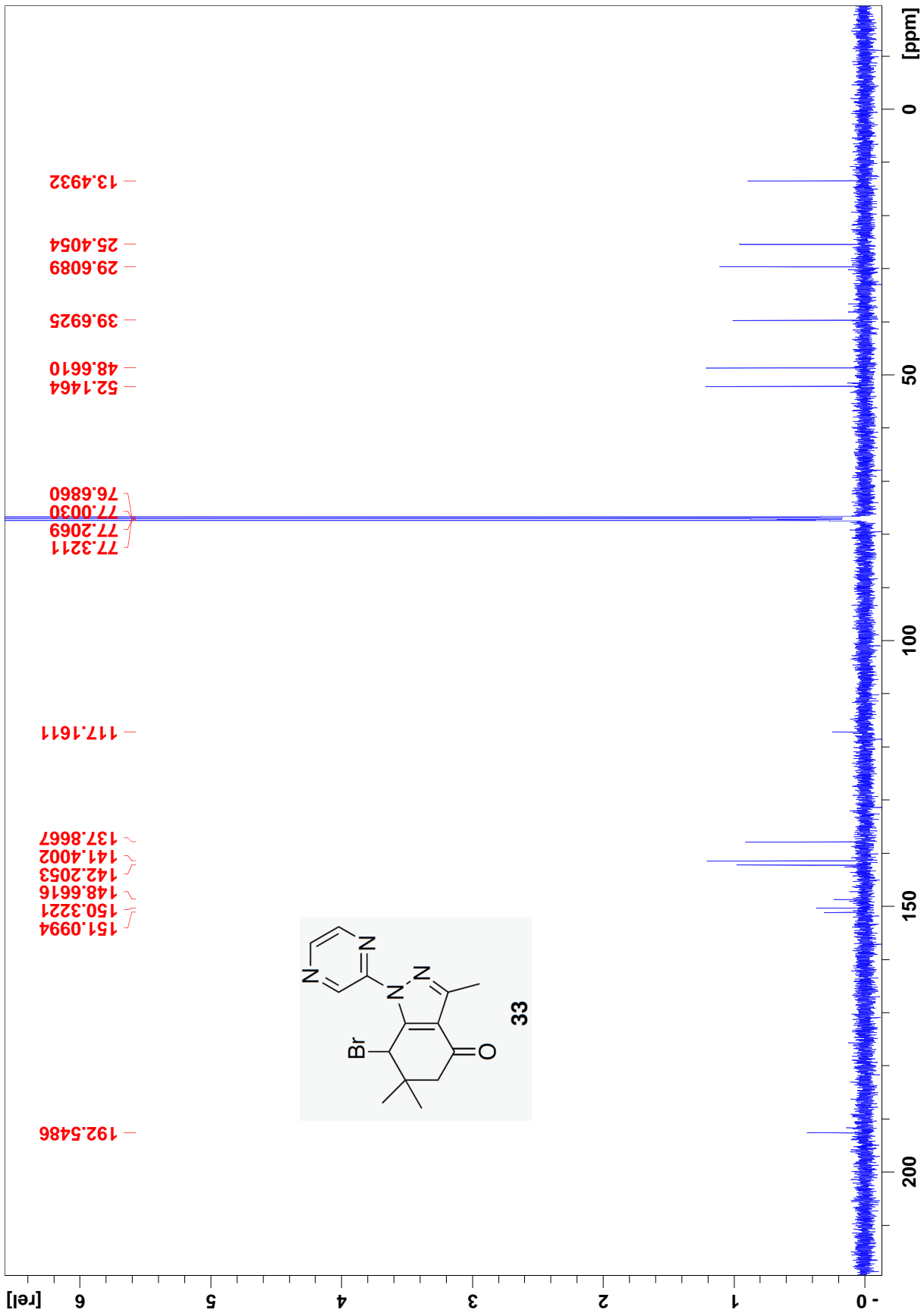
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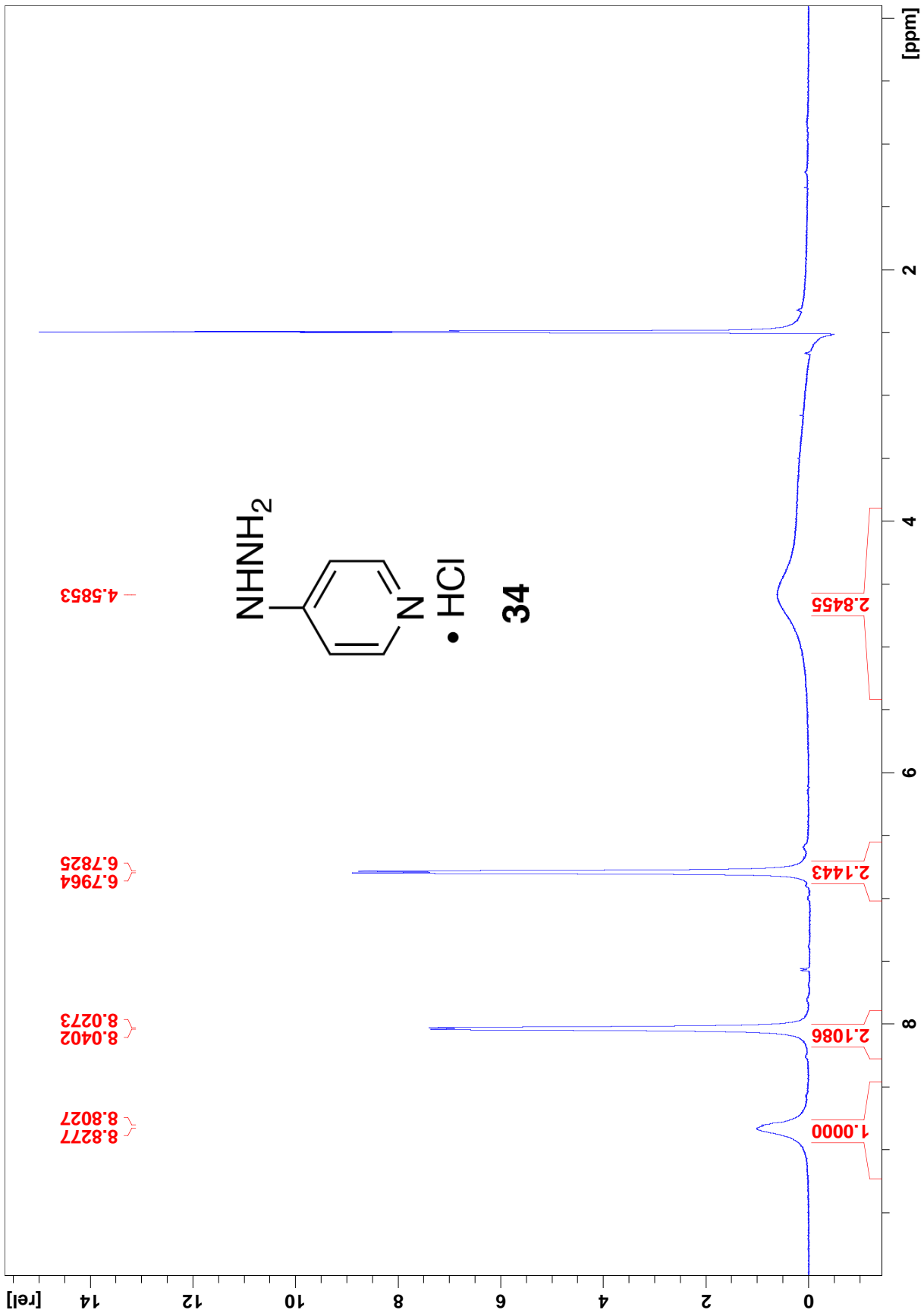
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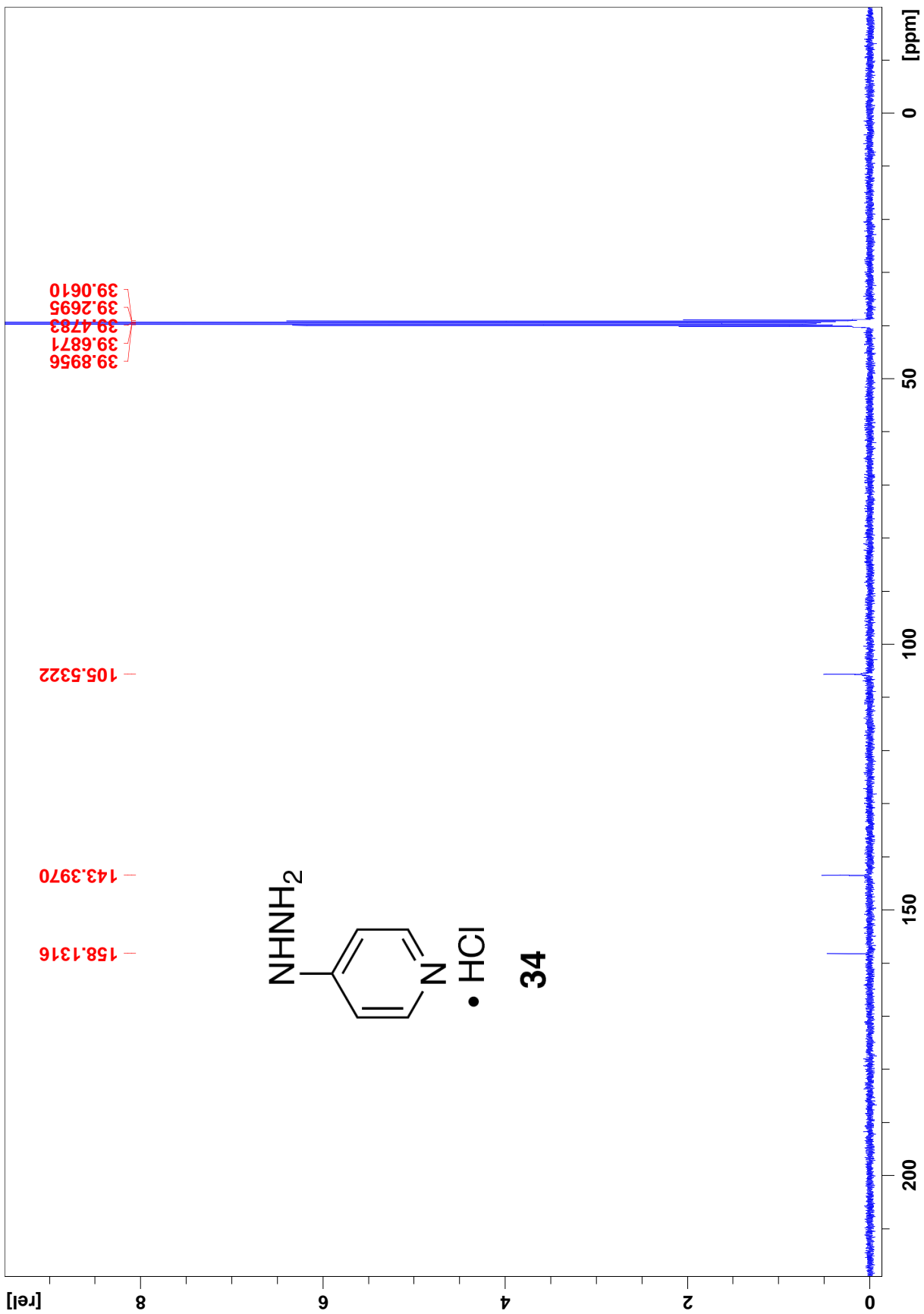
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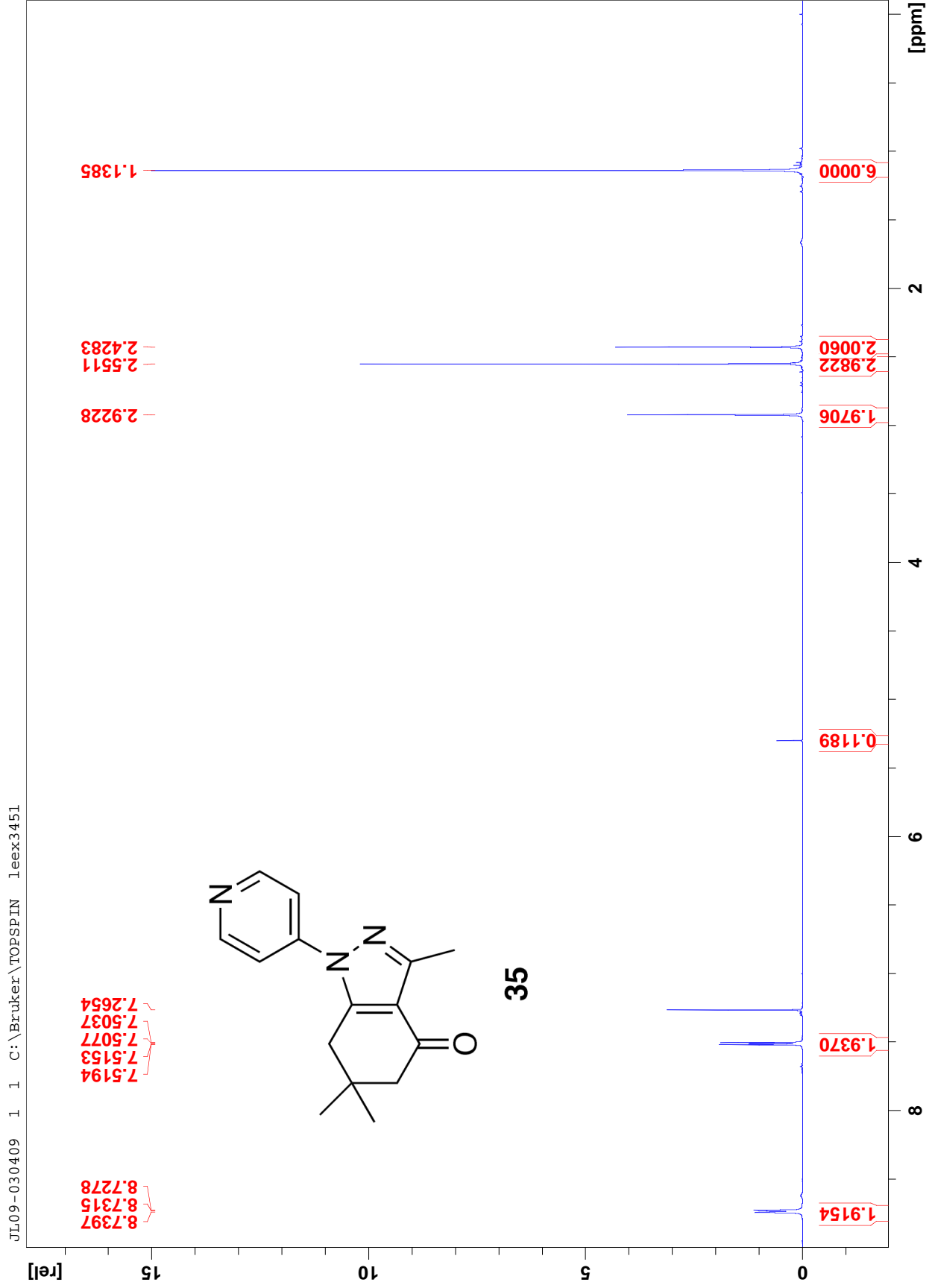


13C-NMR

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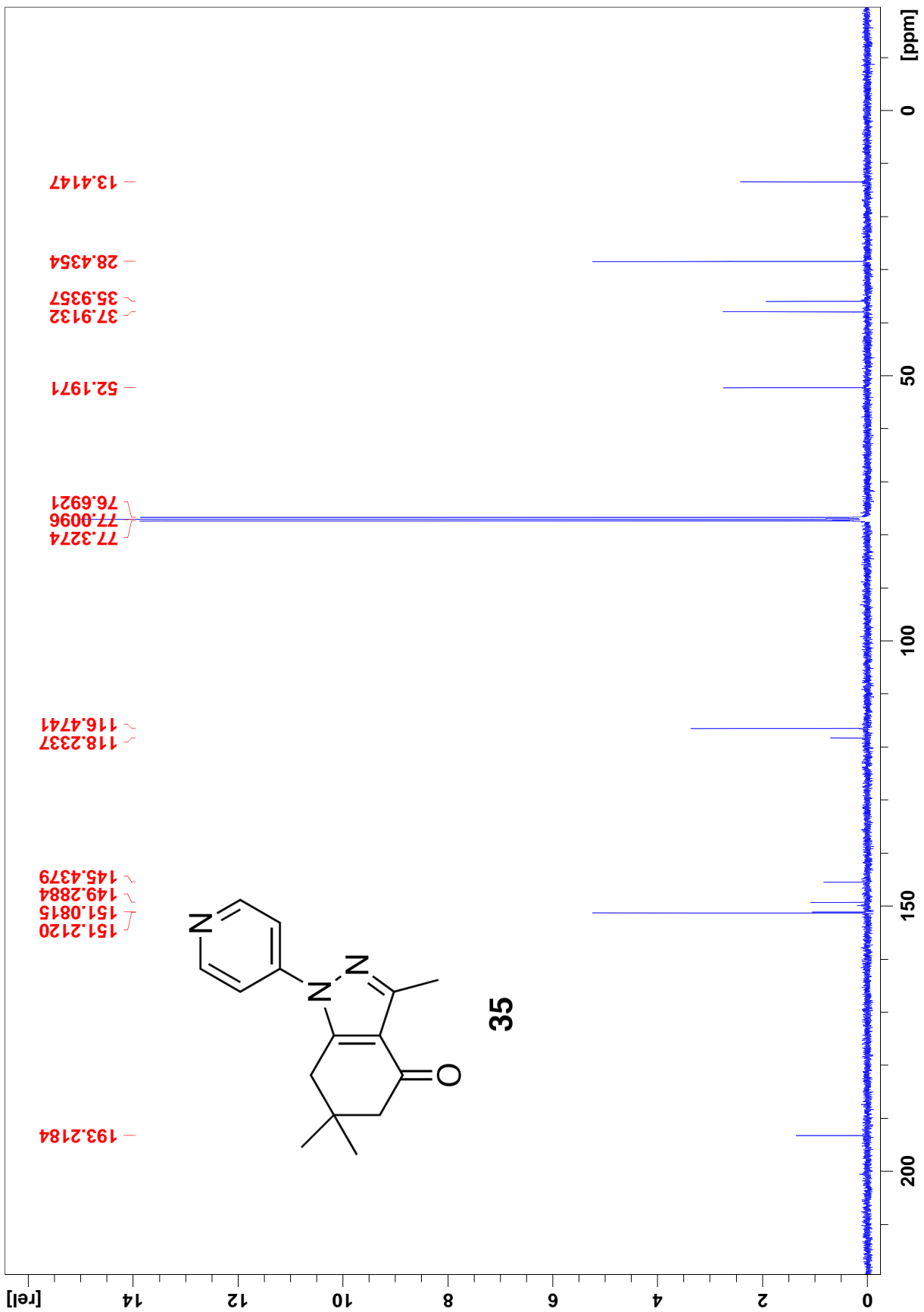


1H-NMR



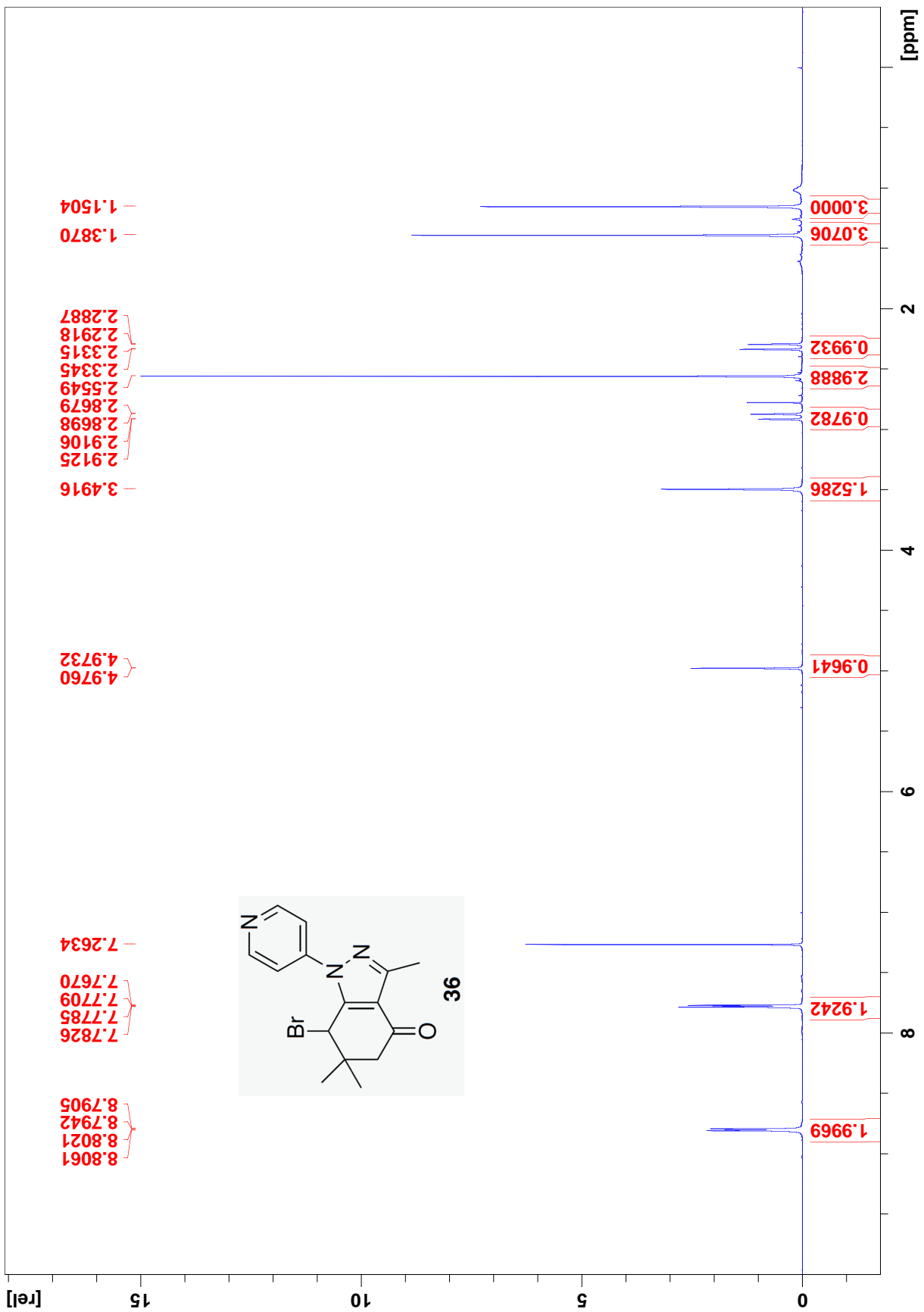
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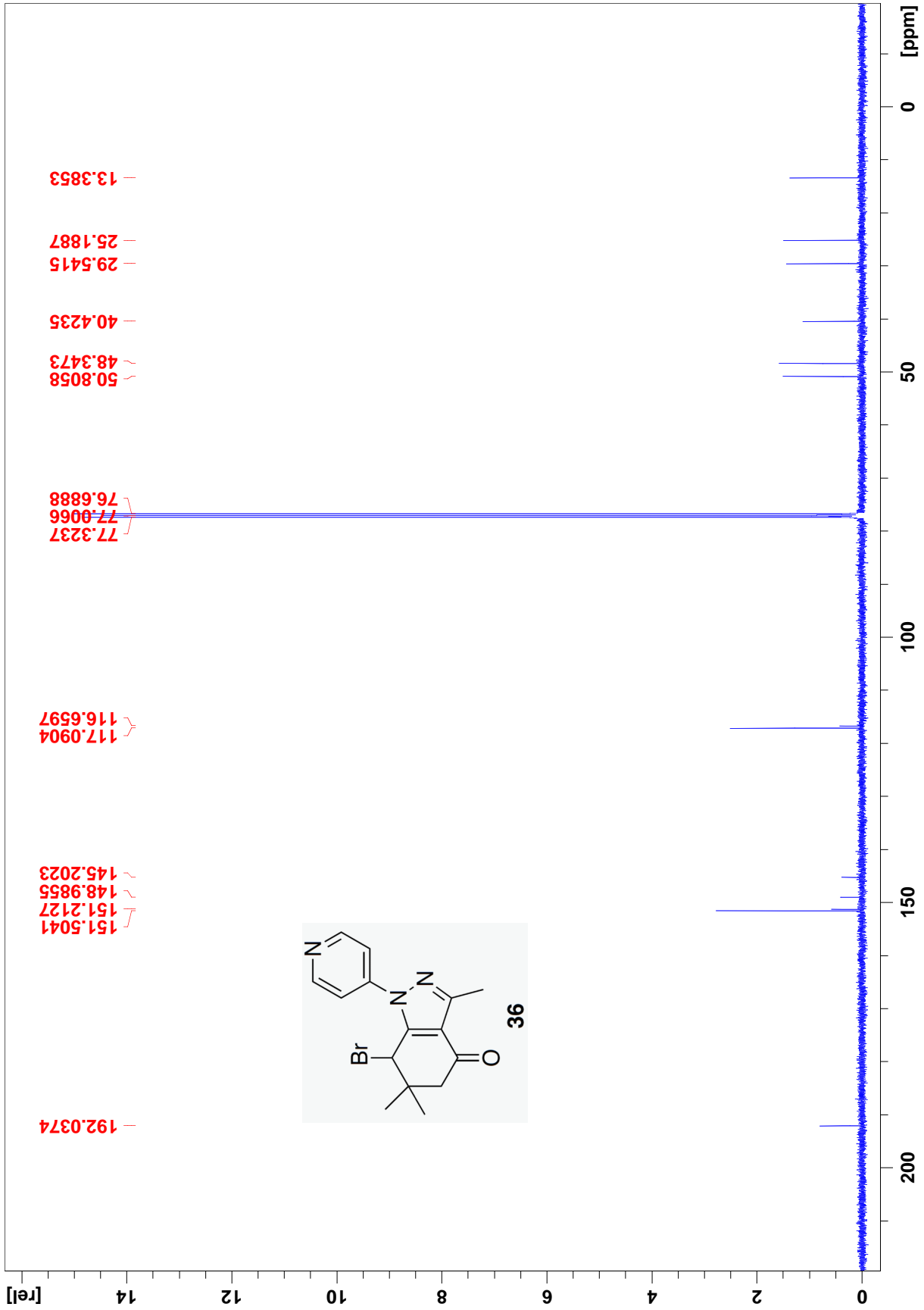
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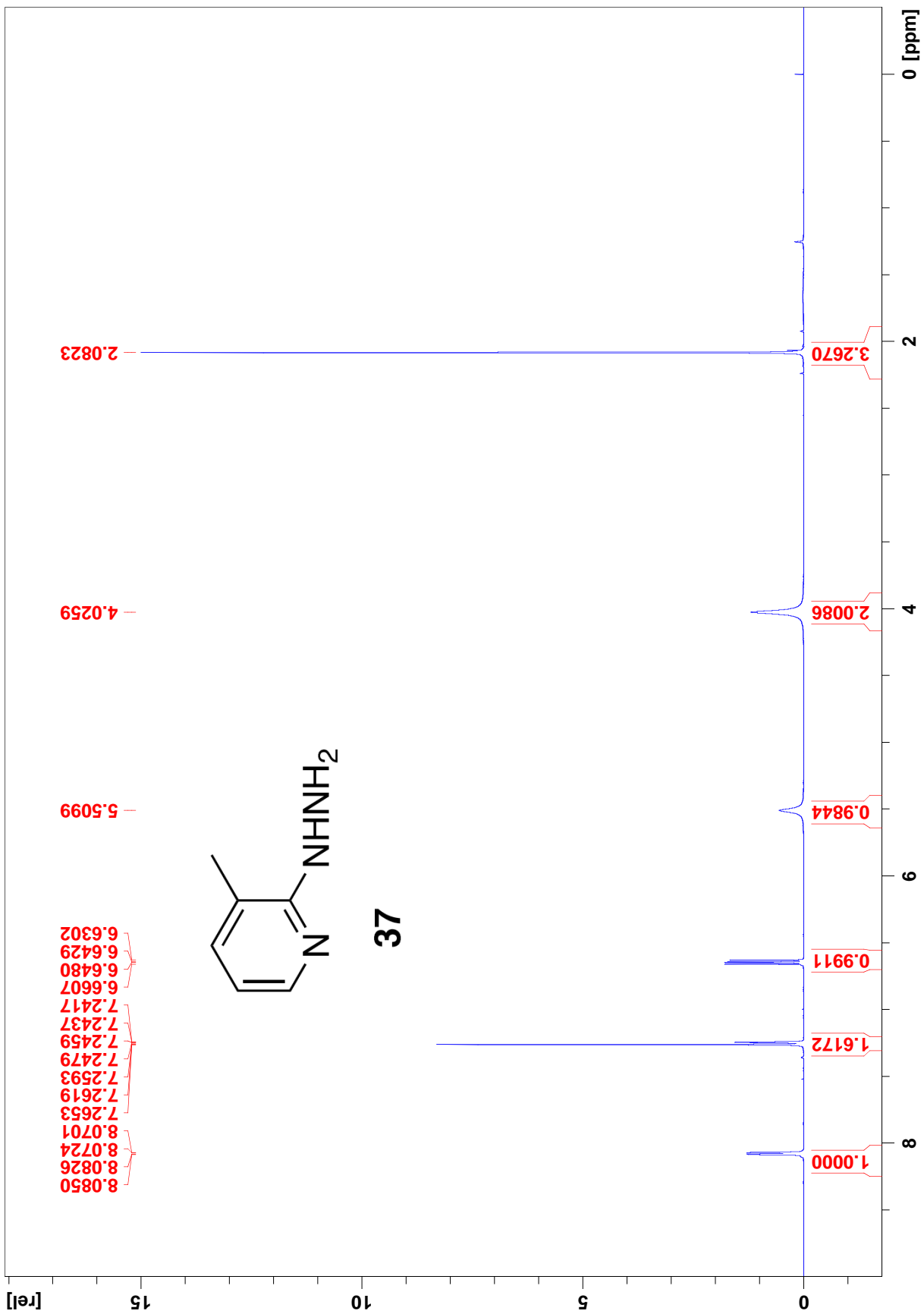
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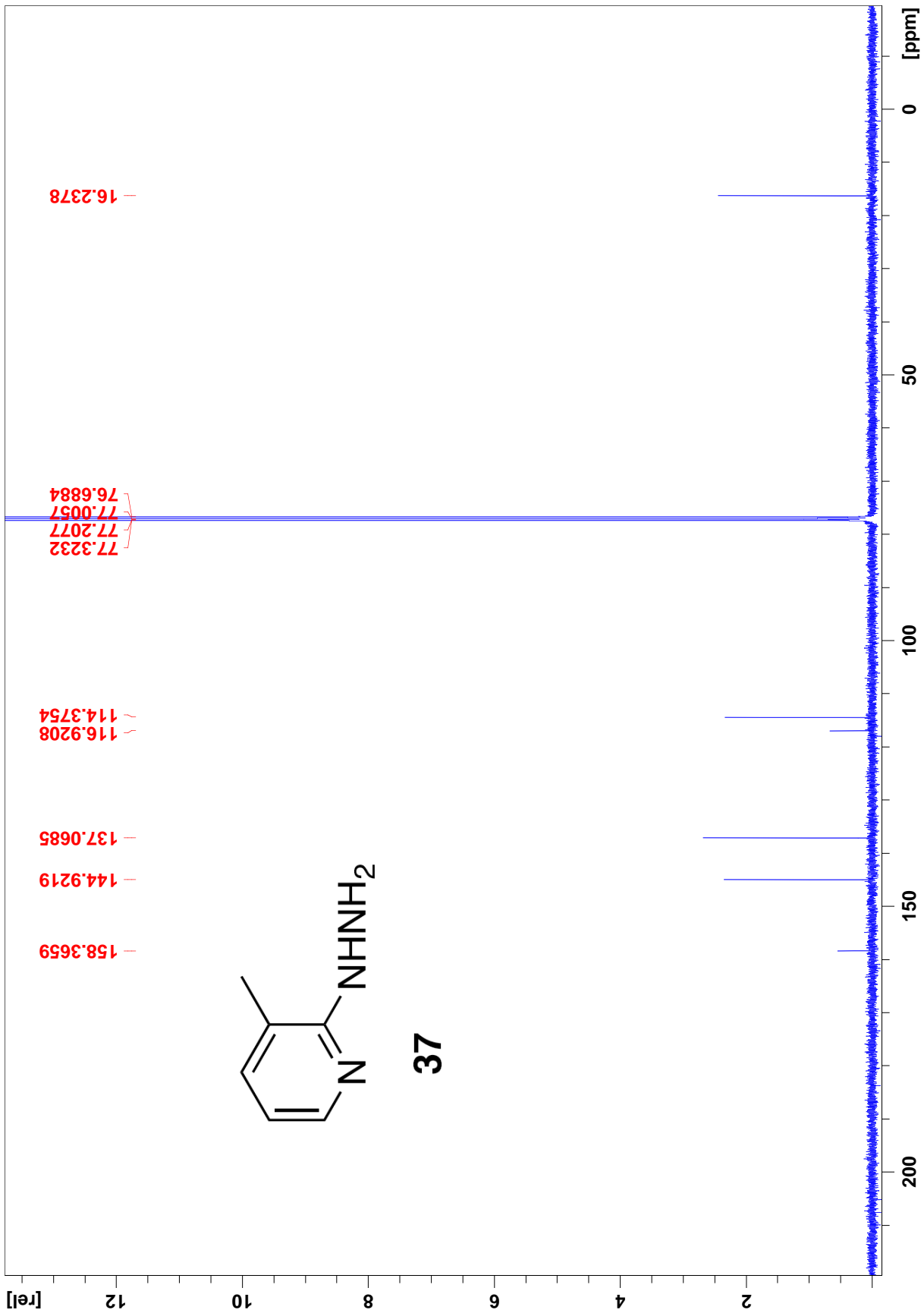
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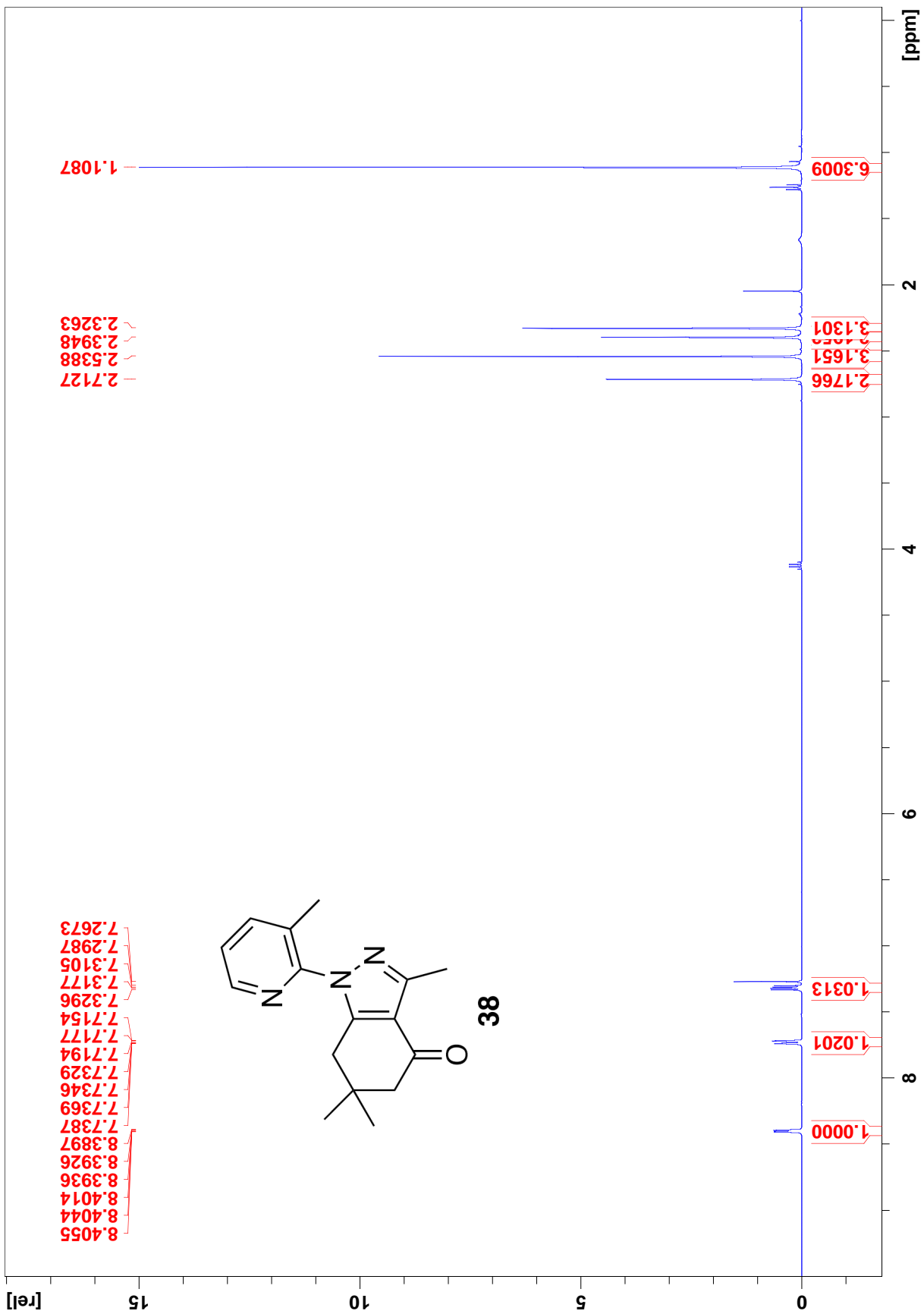
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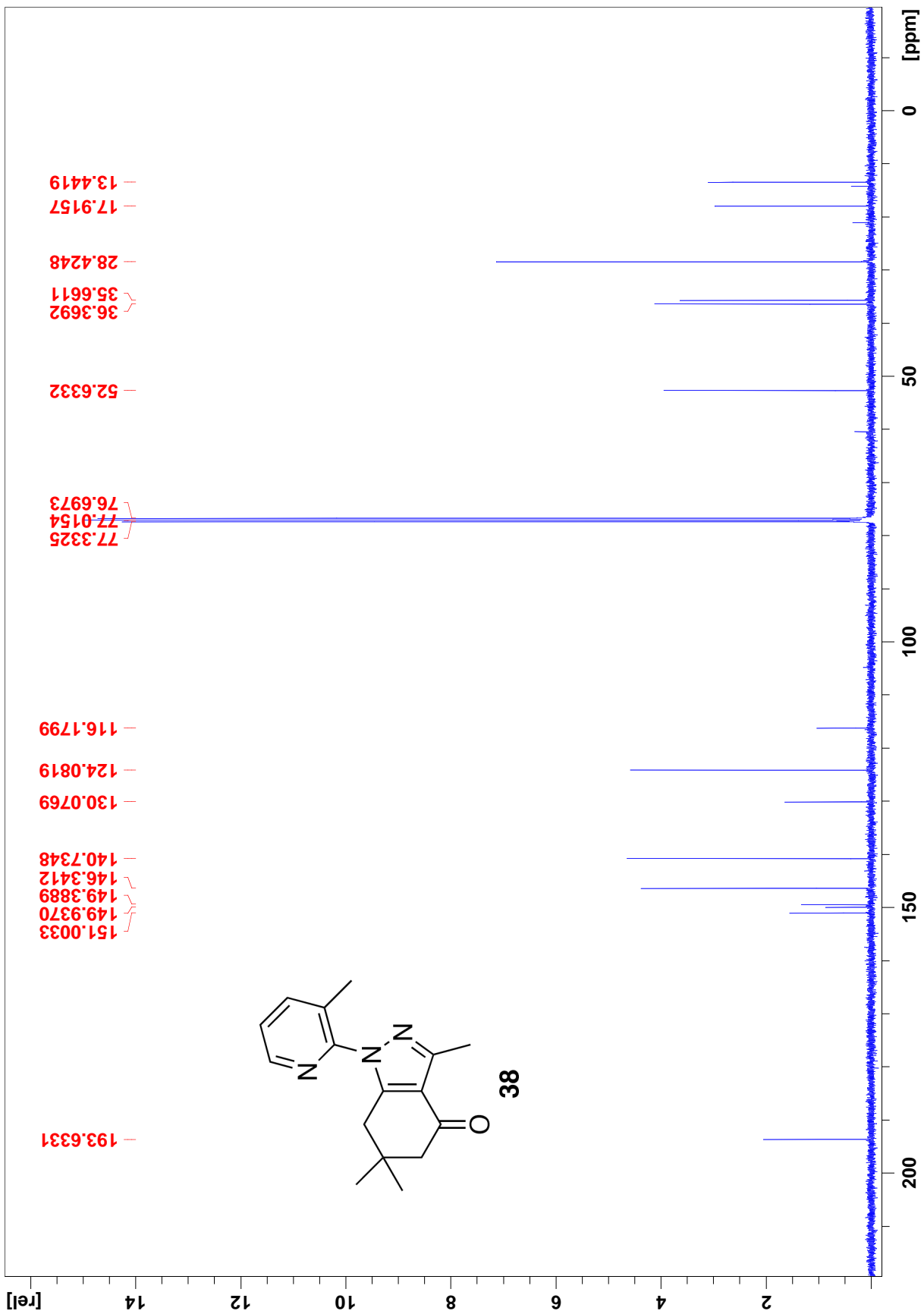
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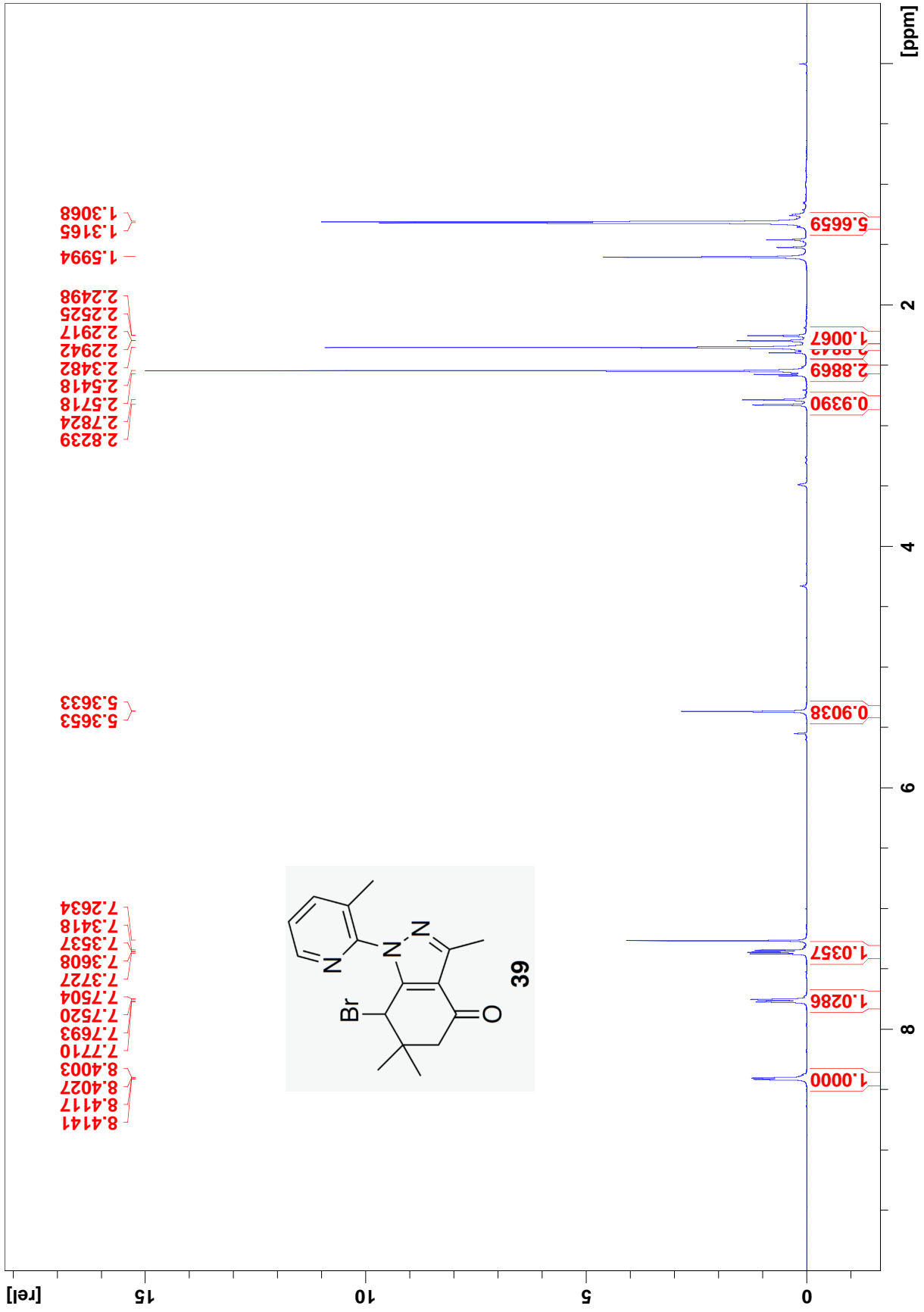
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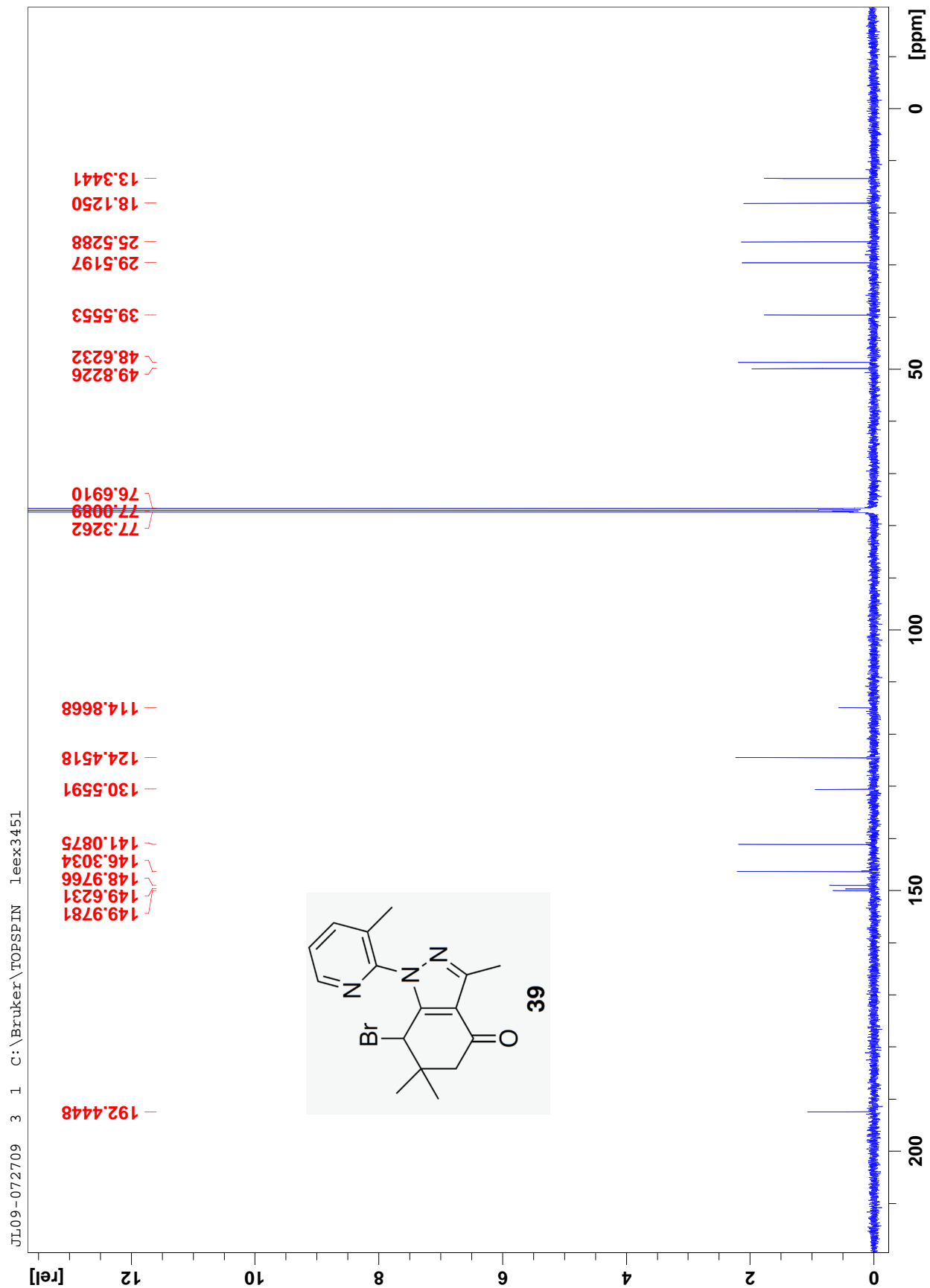


1H-NMR

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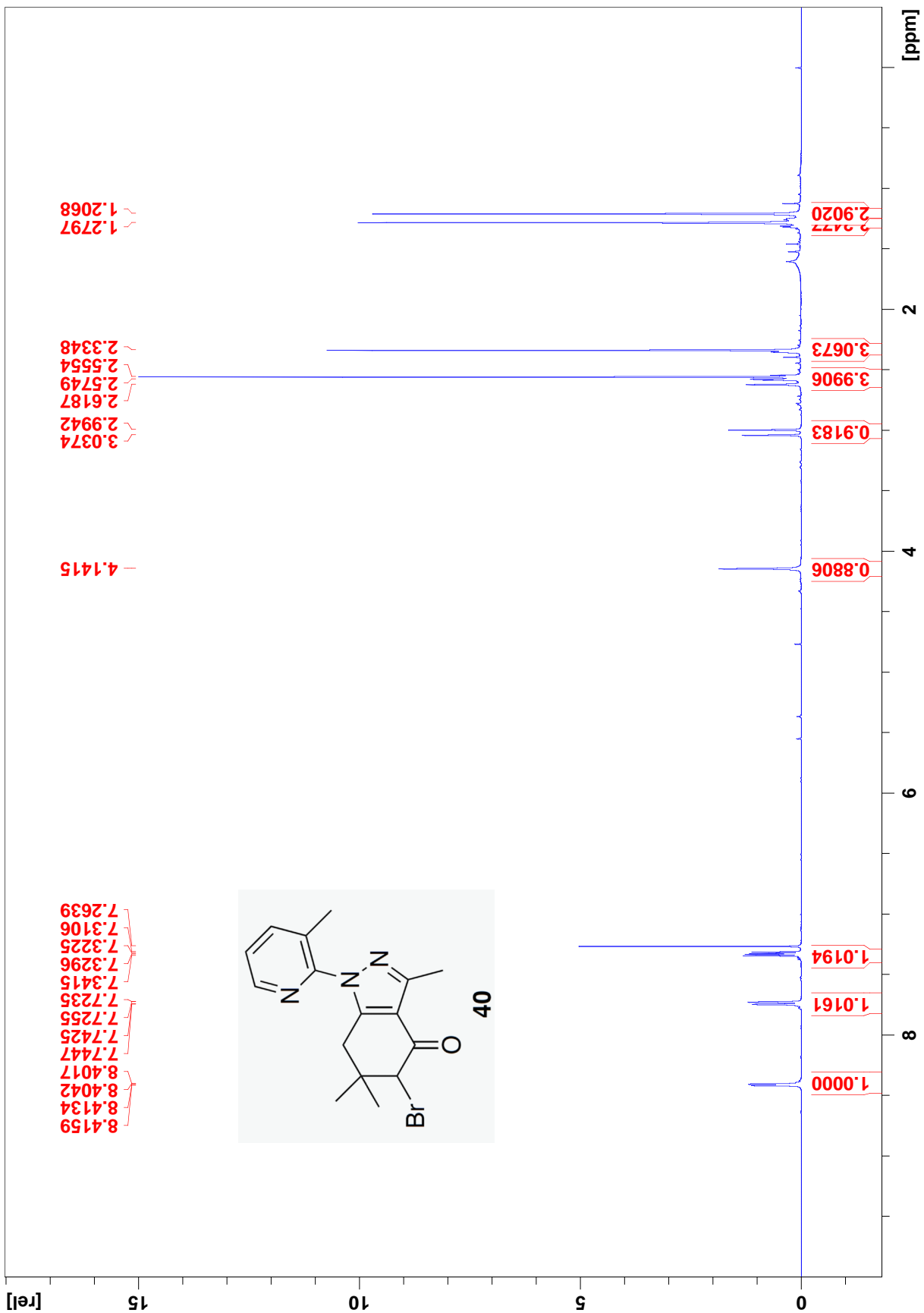


13C-NMR



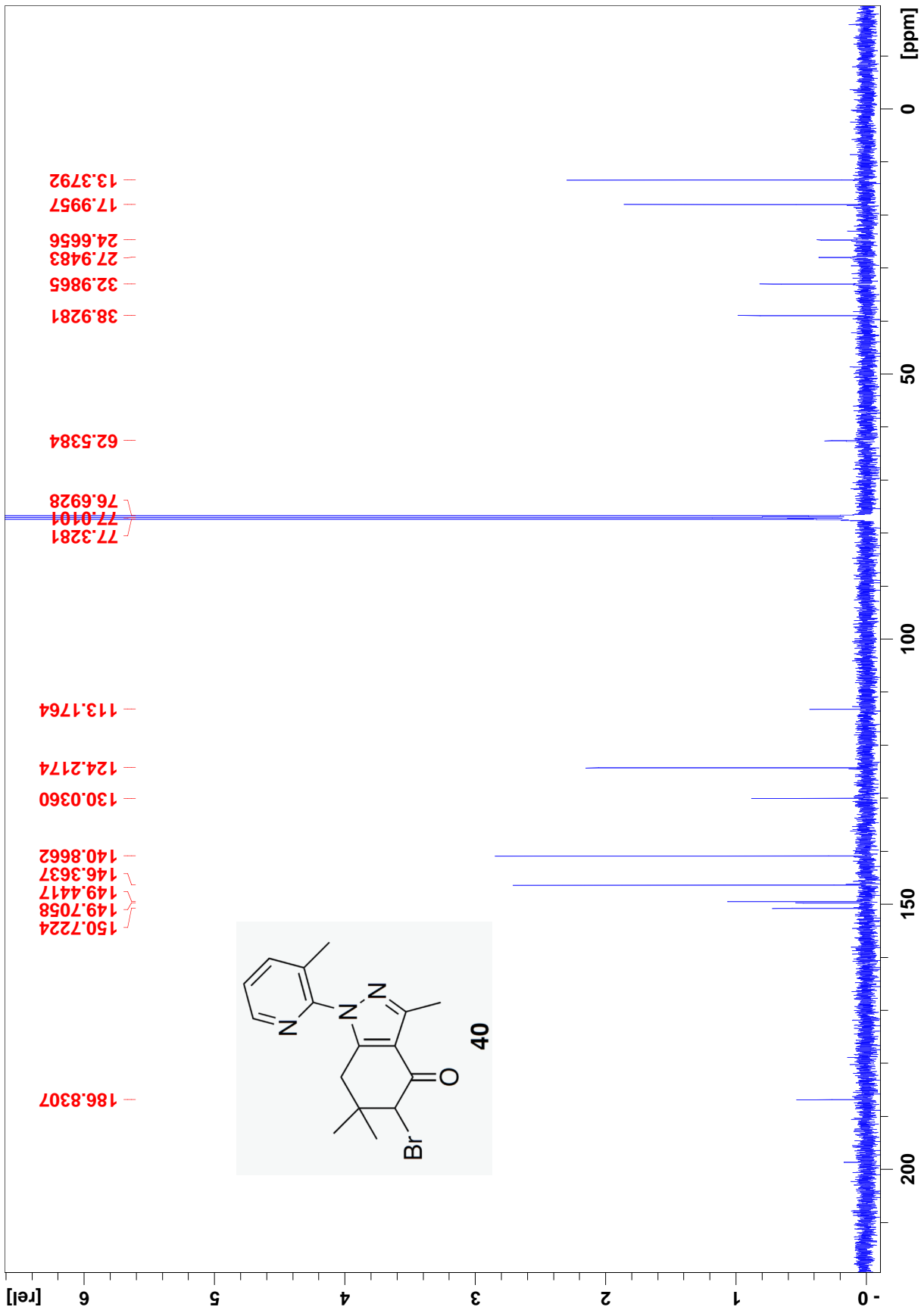
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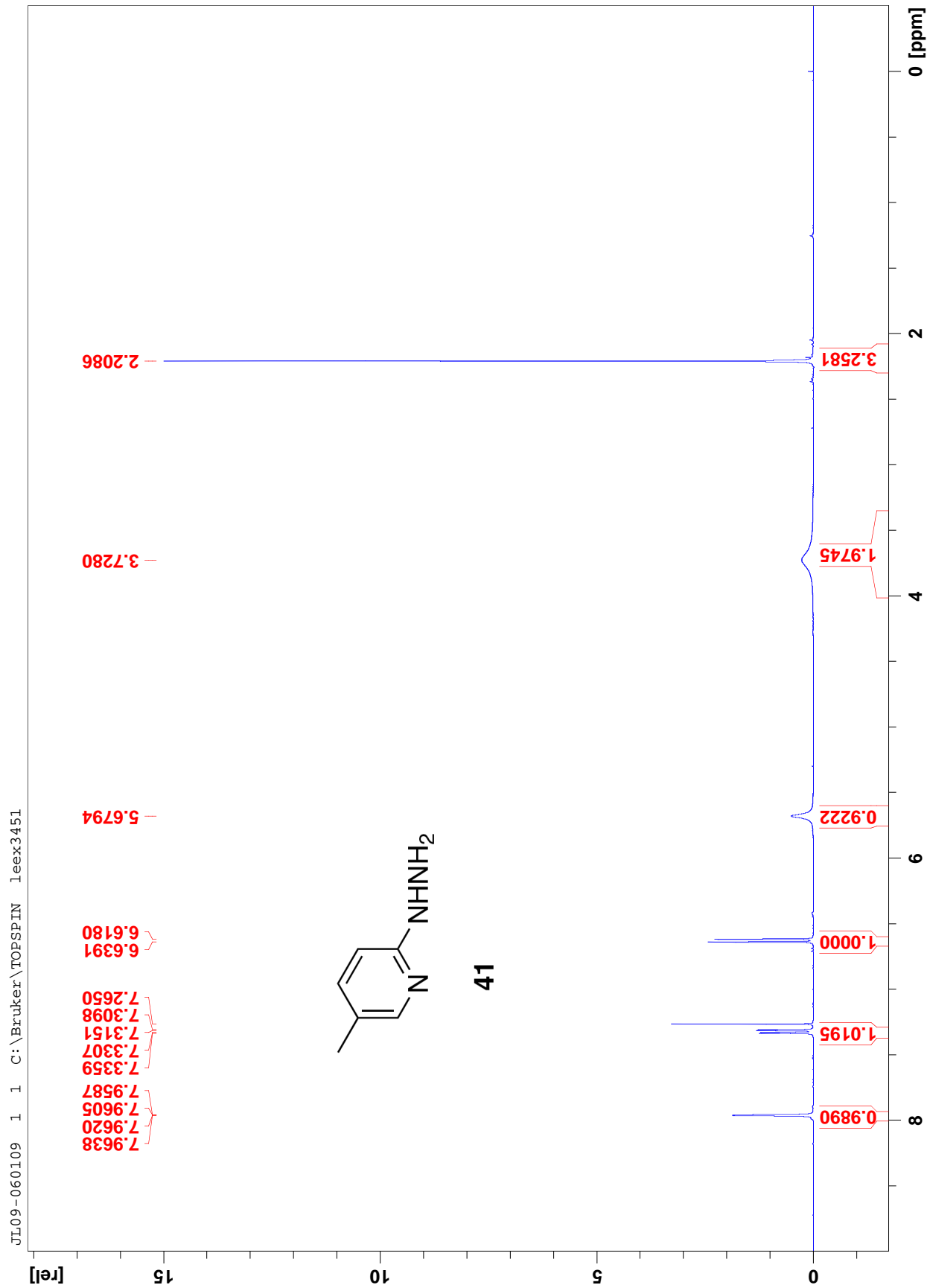


13C-NMR

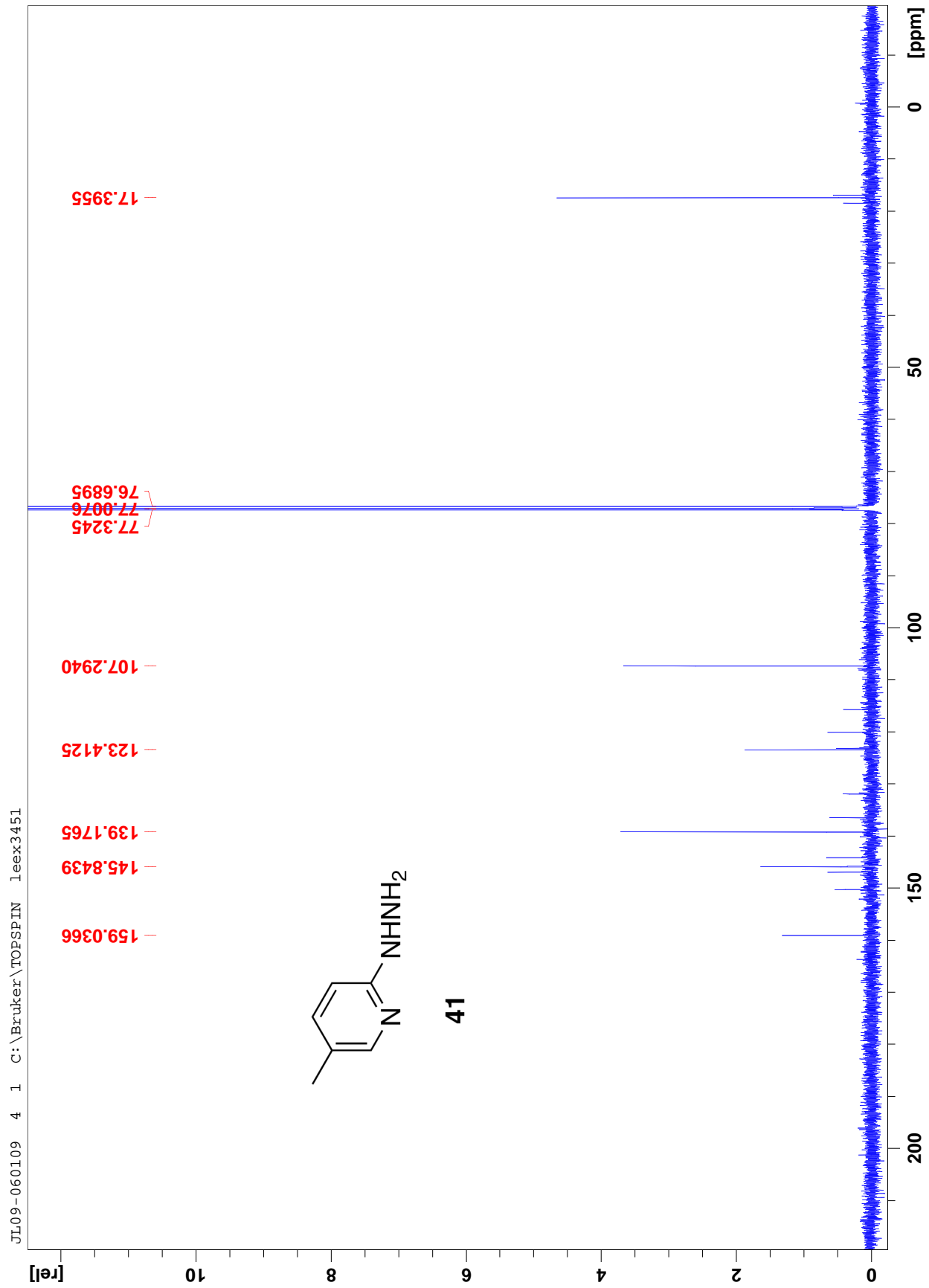
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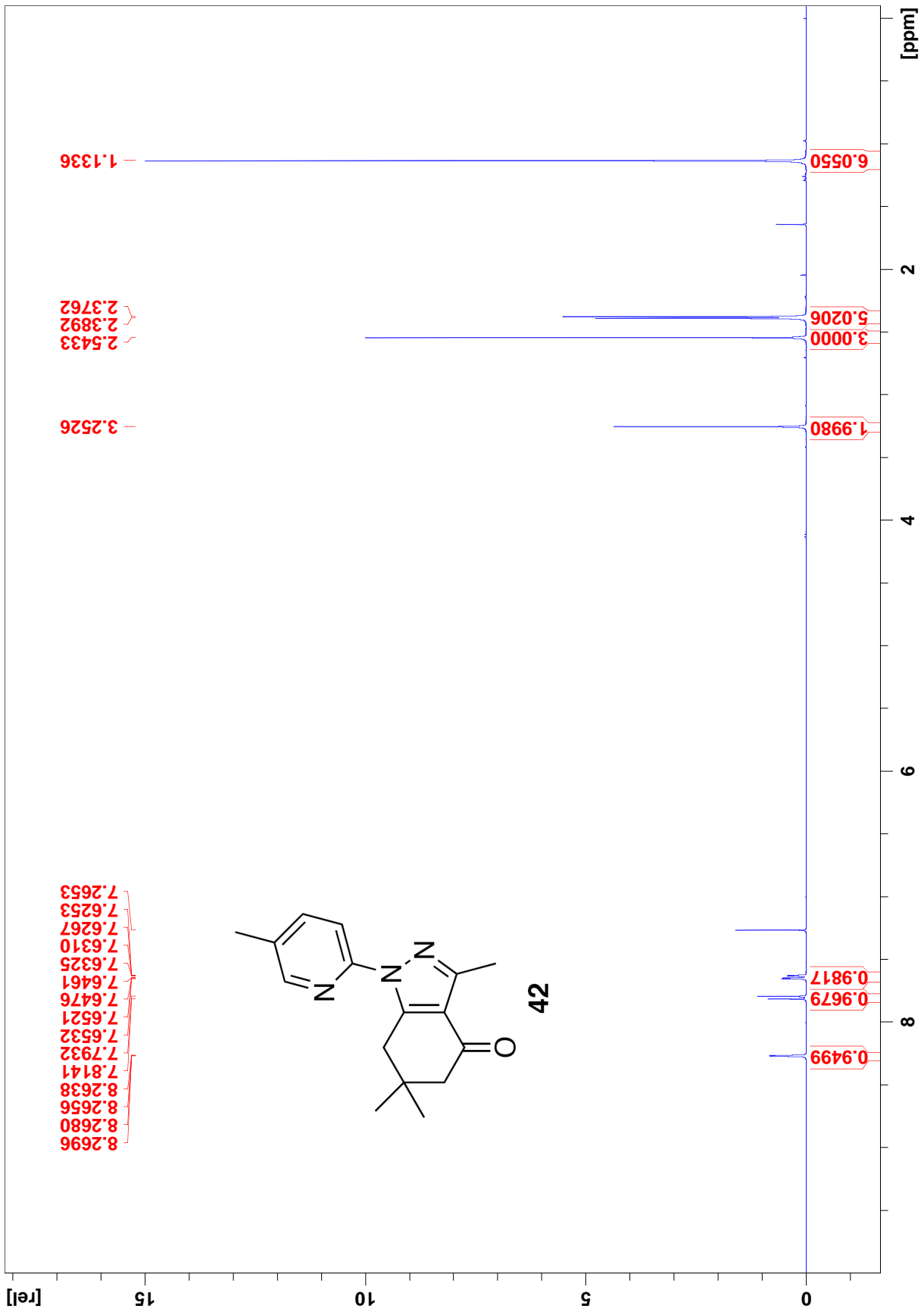


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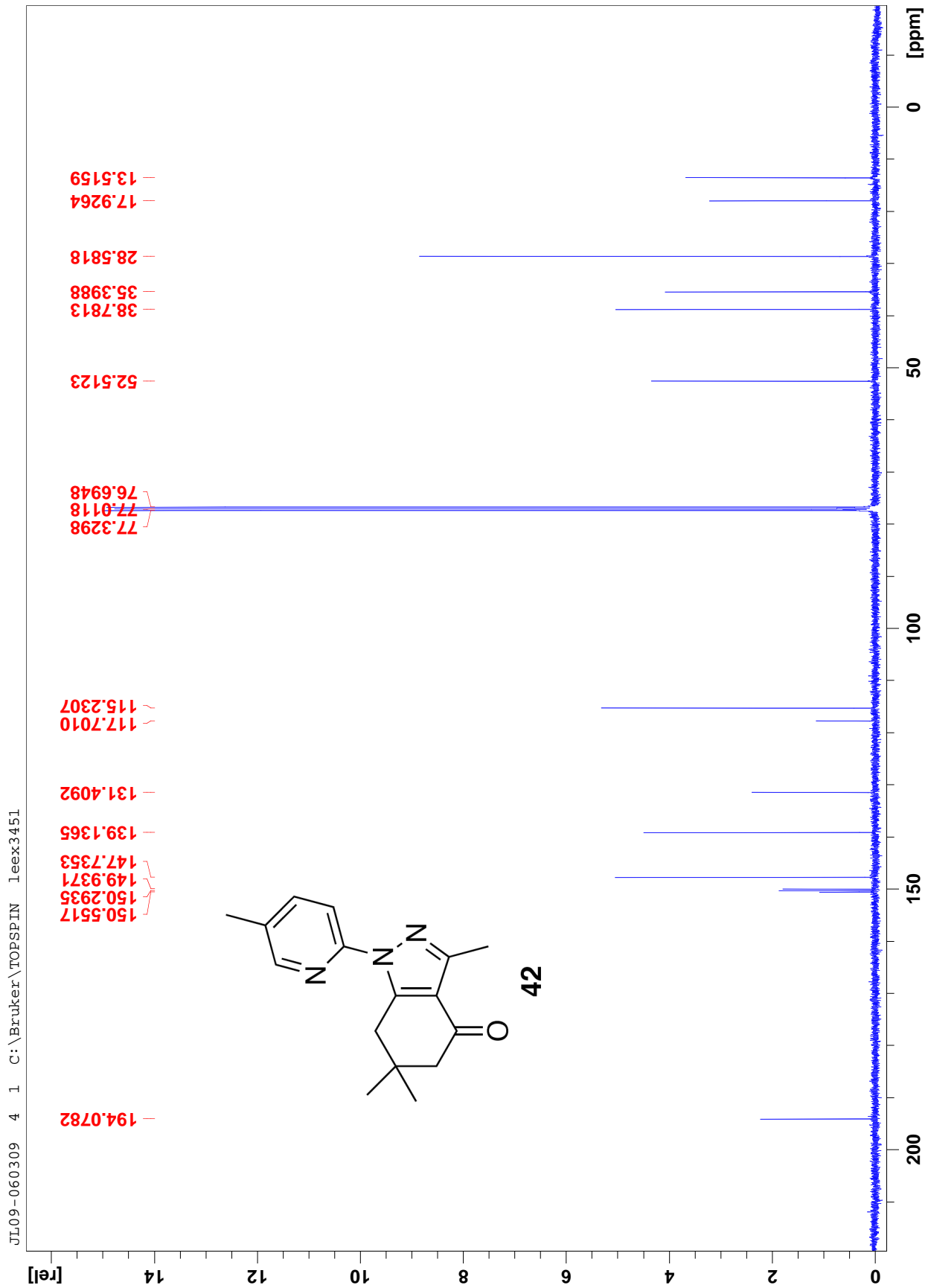


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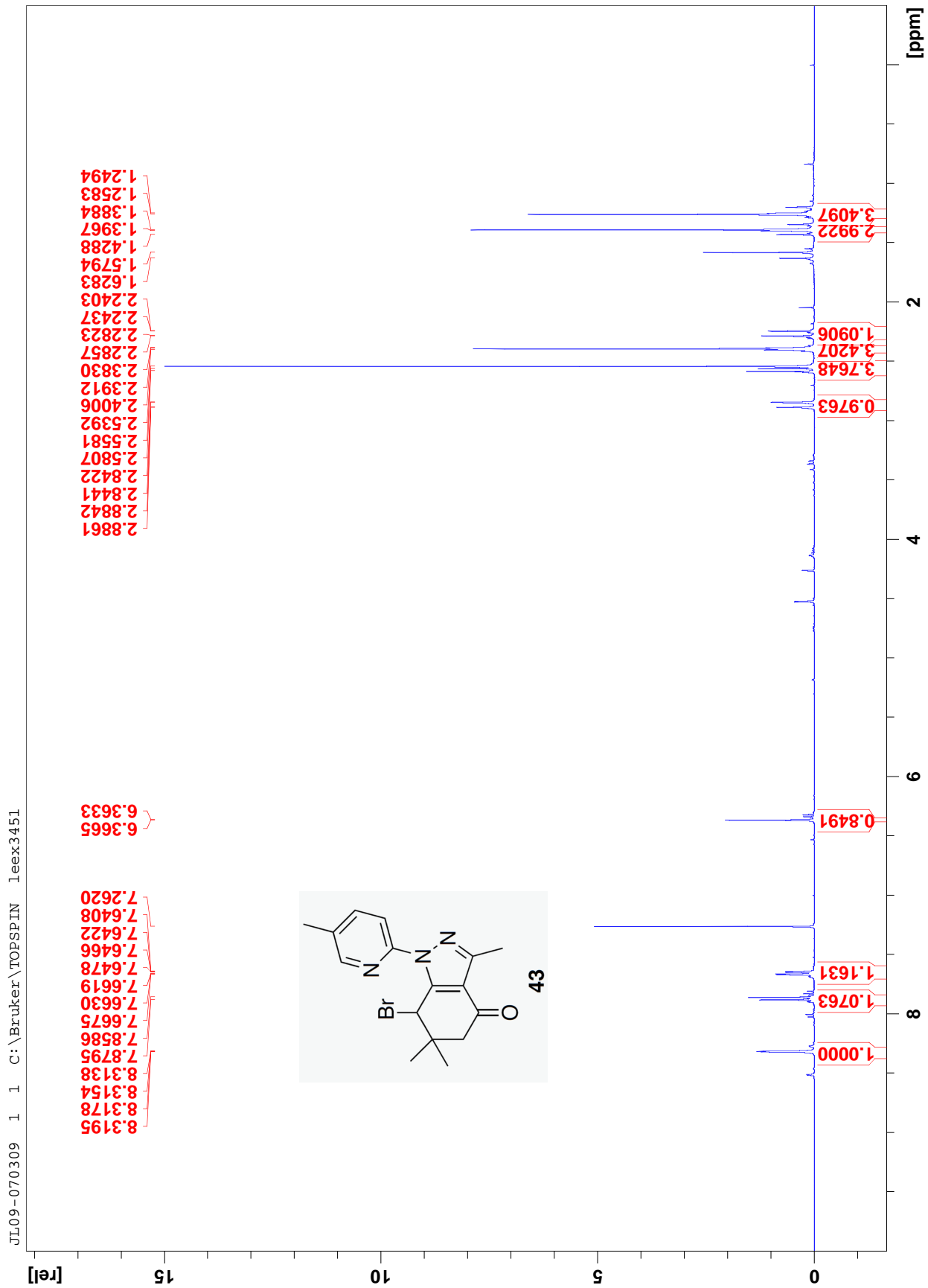
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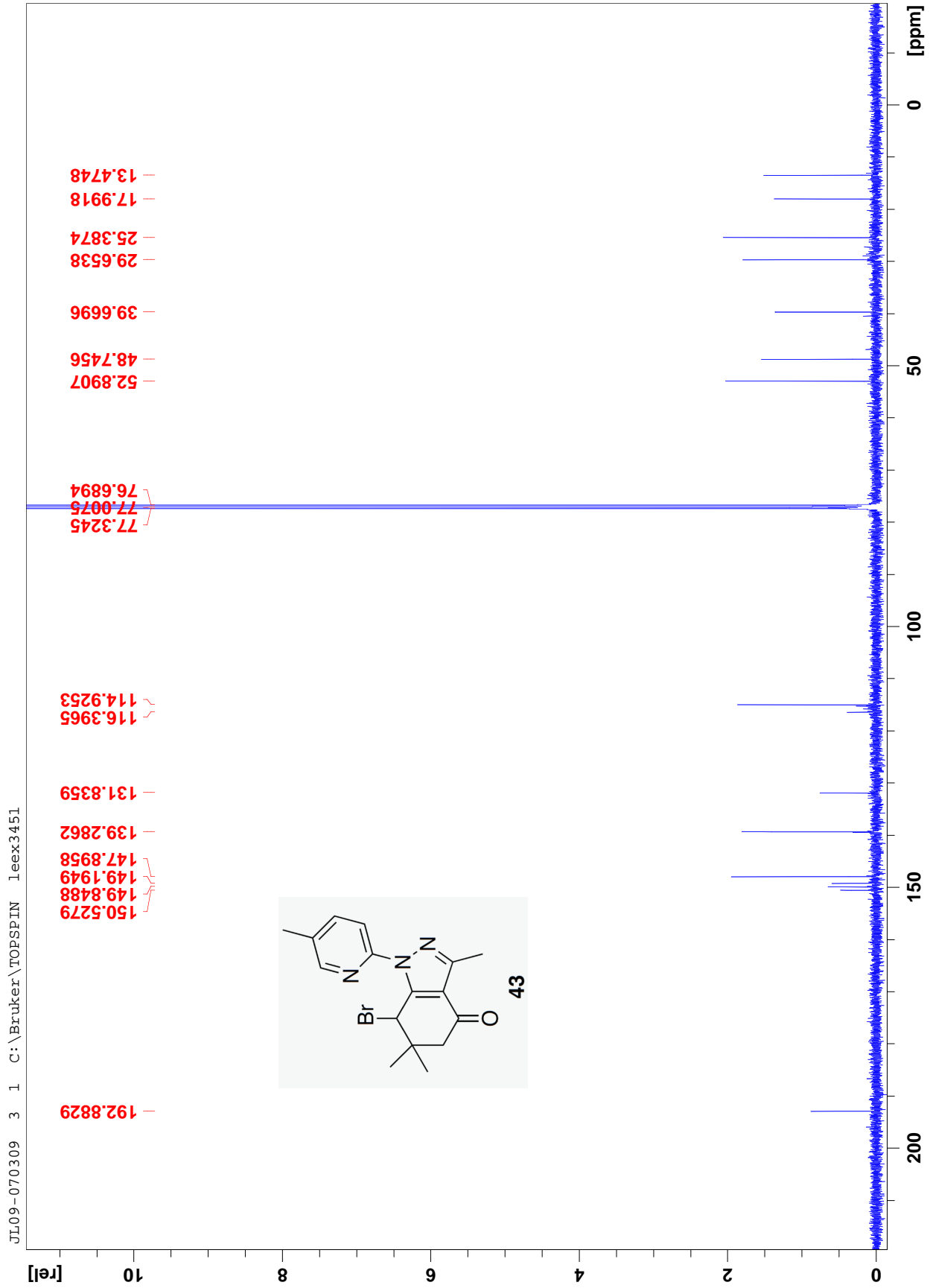
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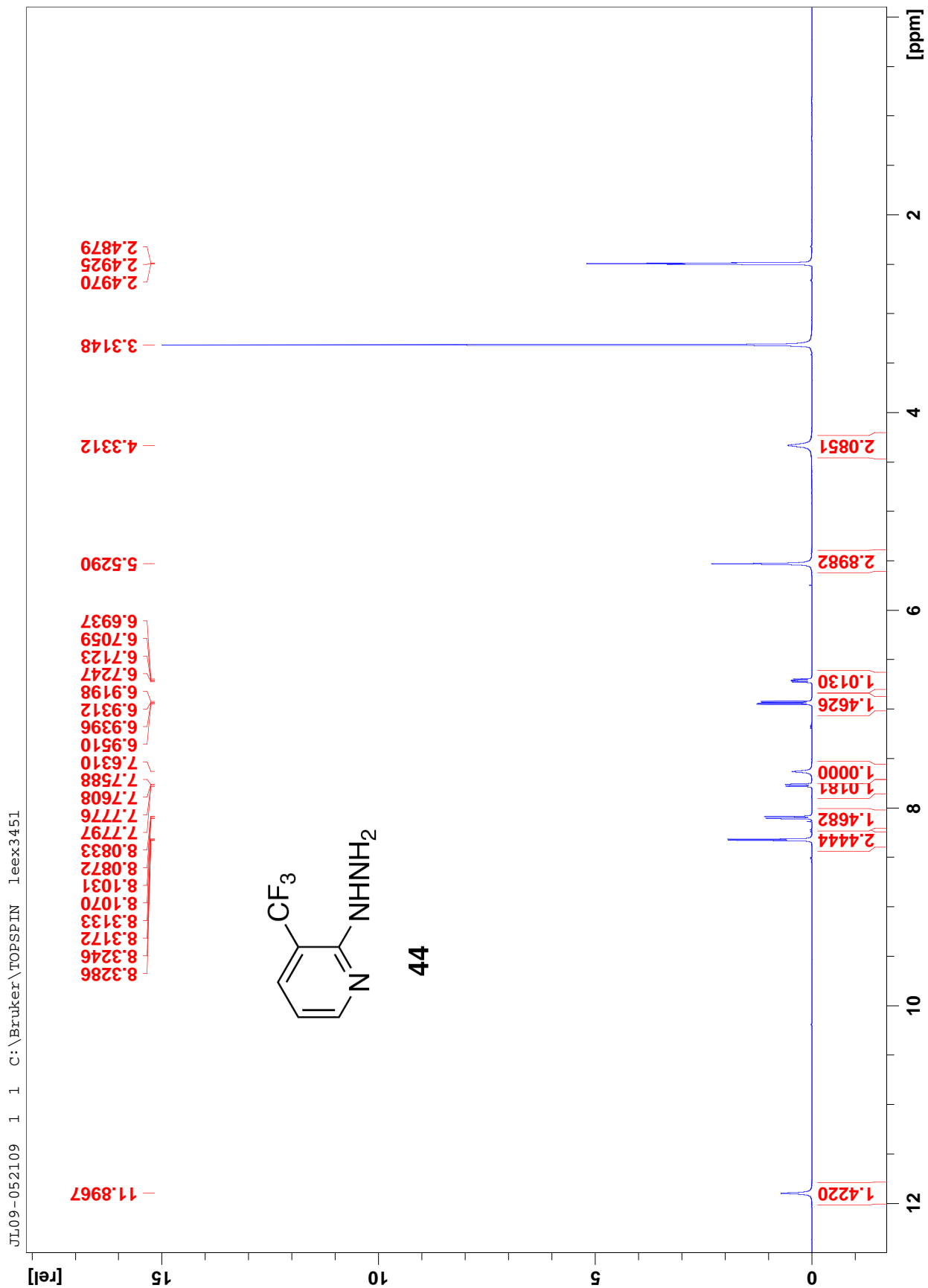
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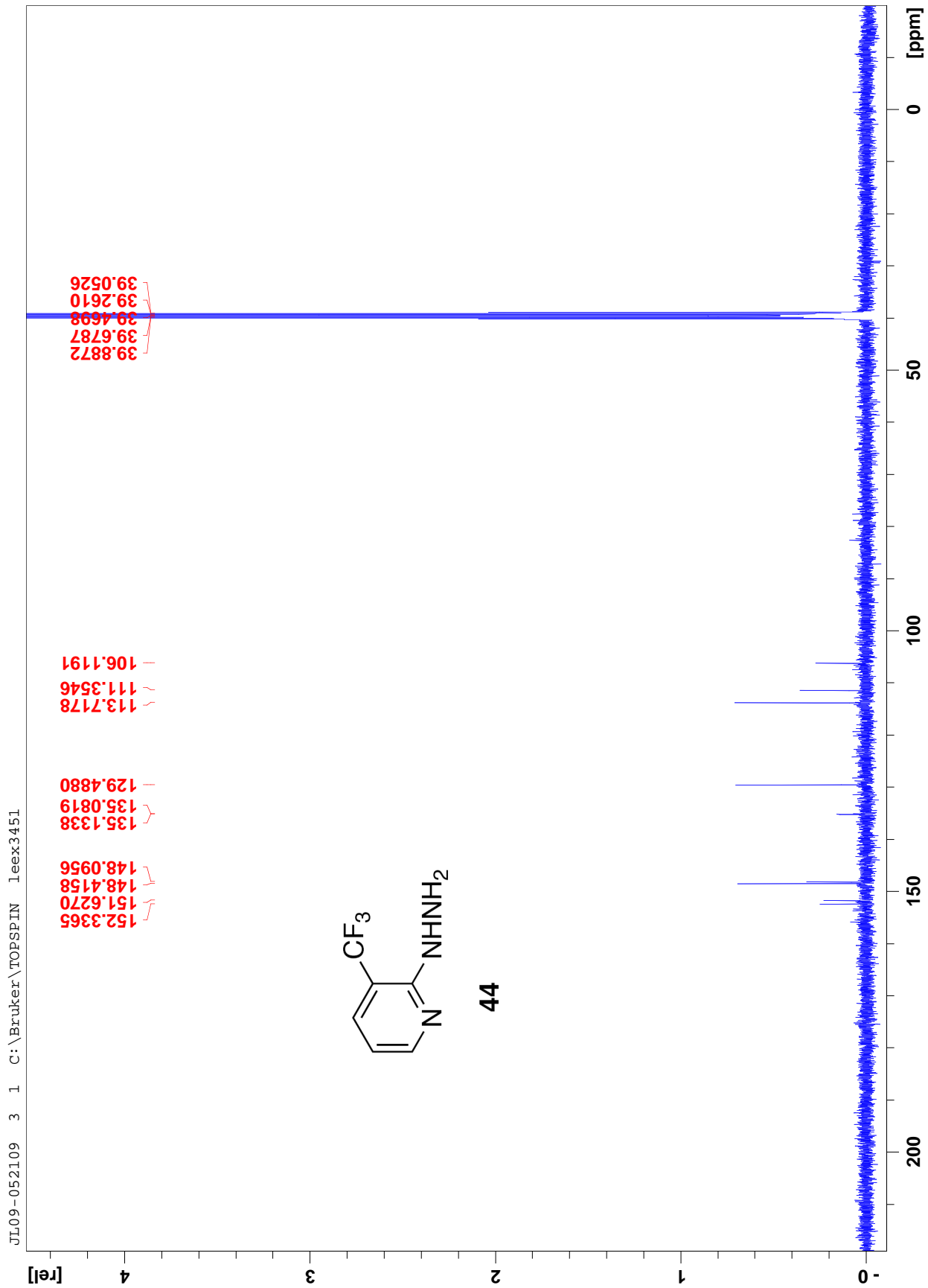
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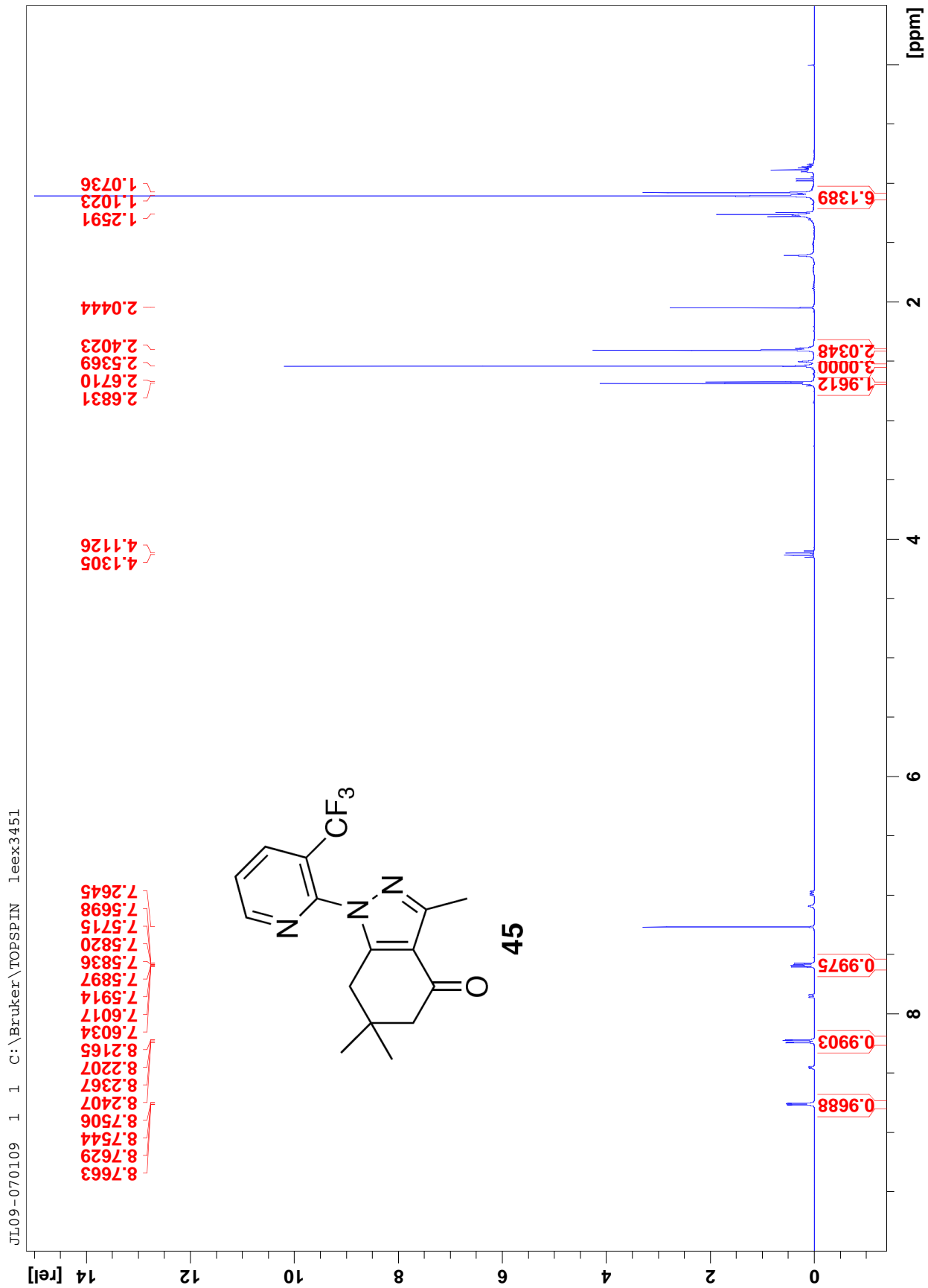
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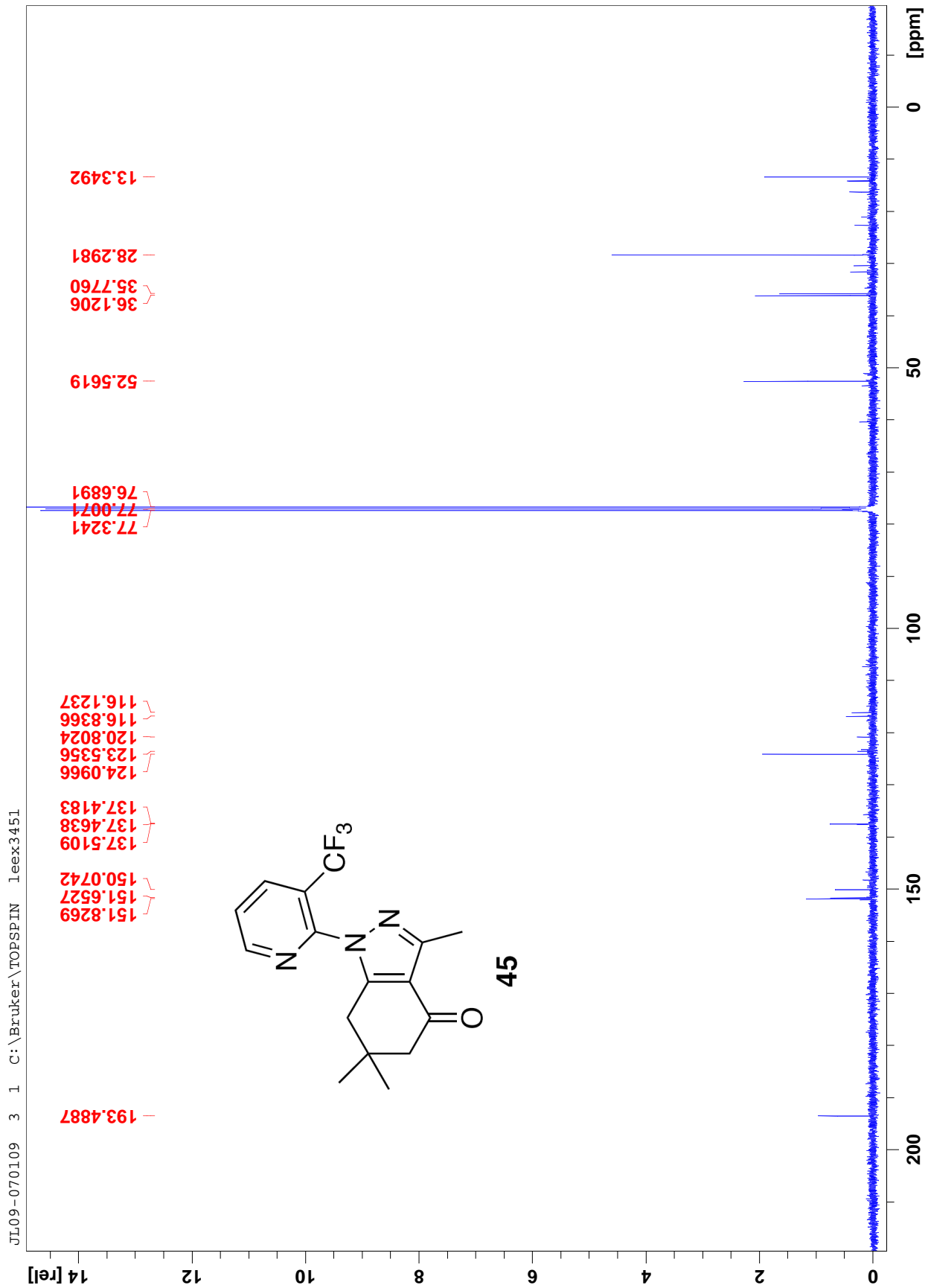
13C-NMR



1H-NMR

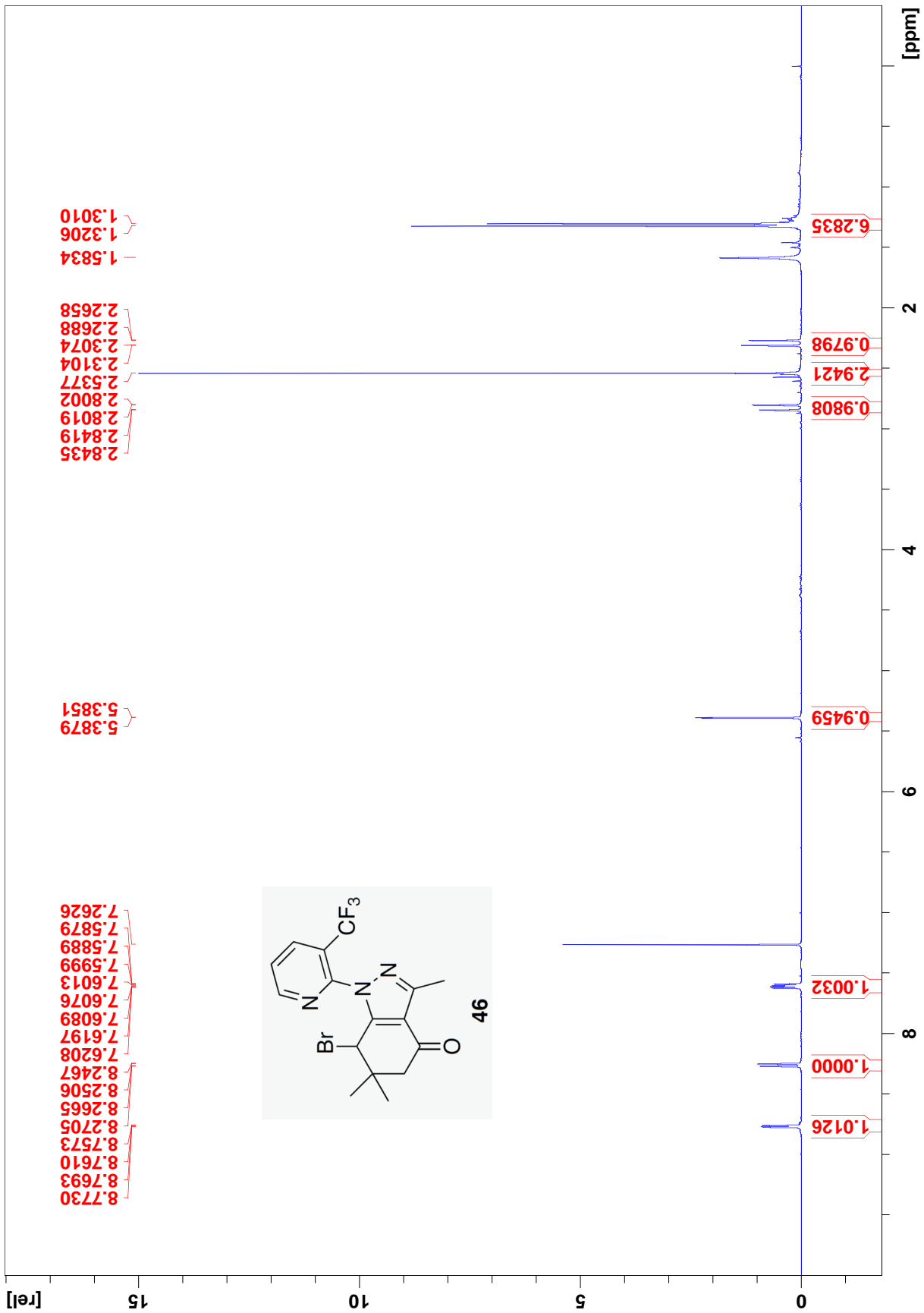


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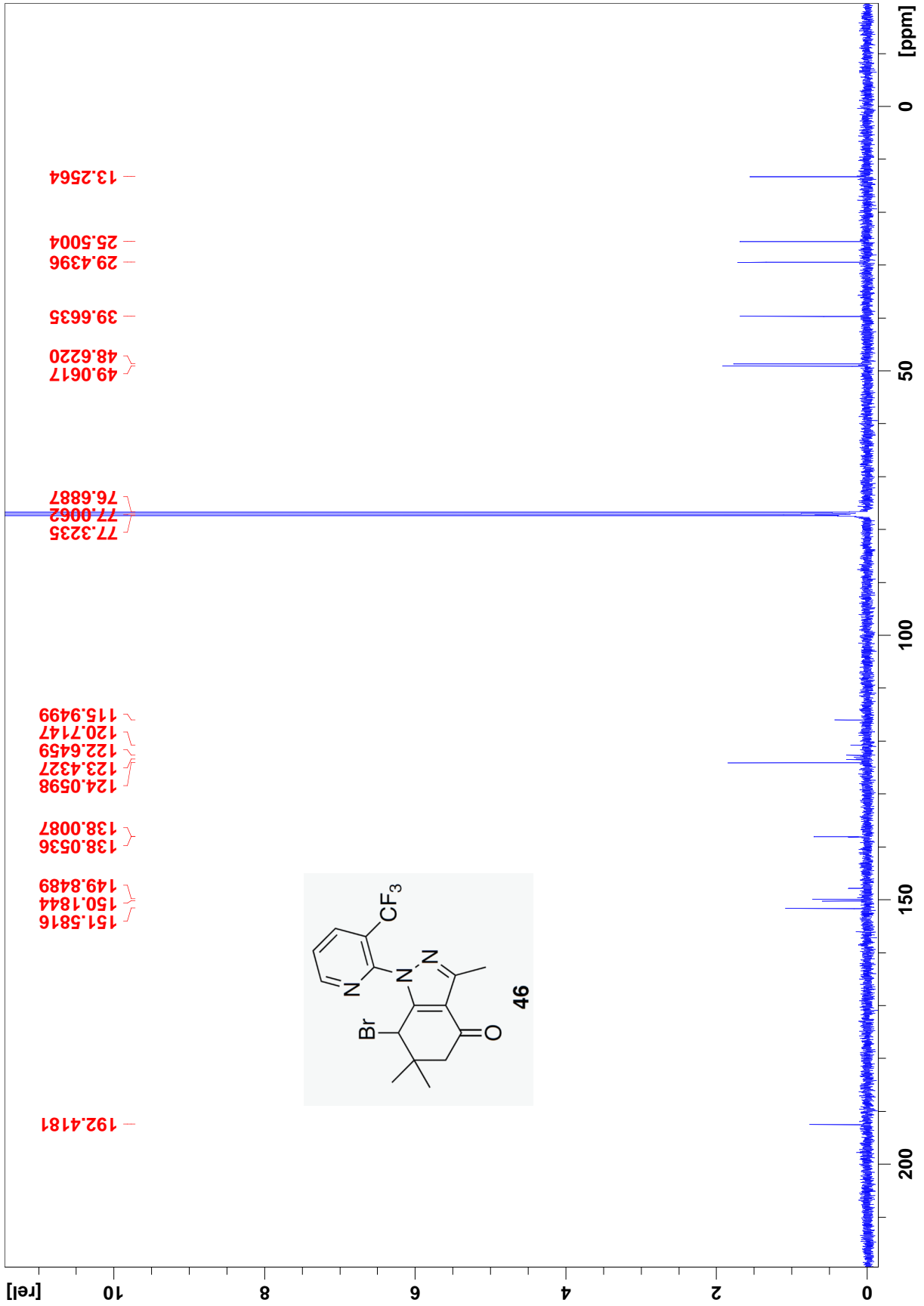
1H-NMR

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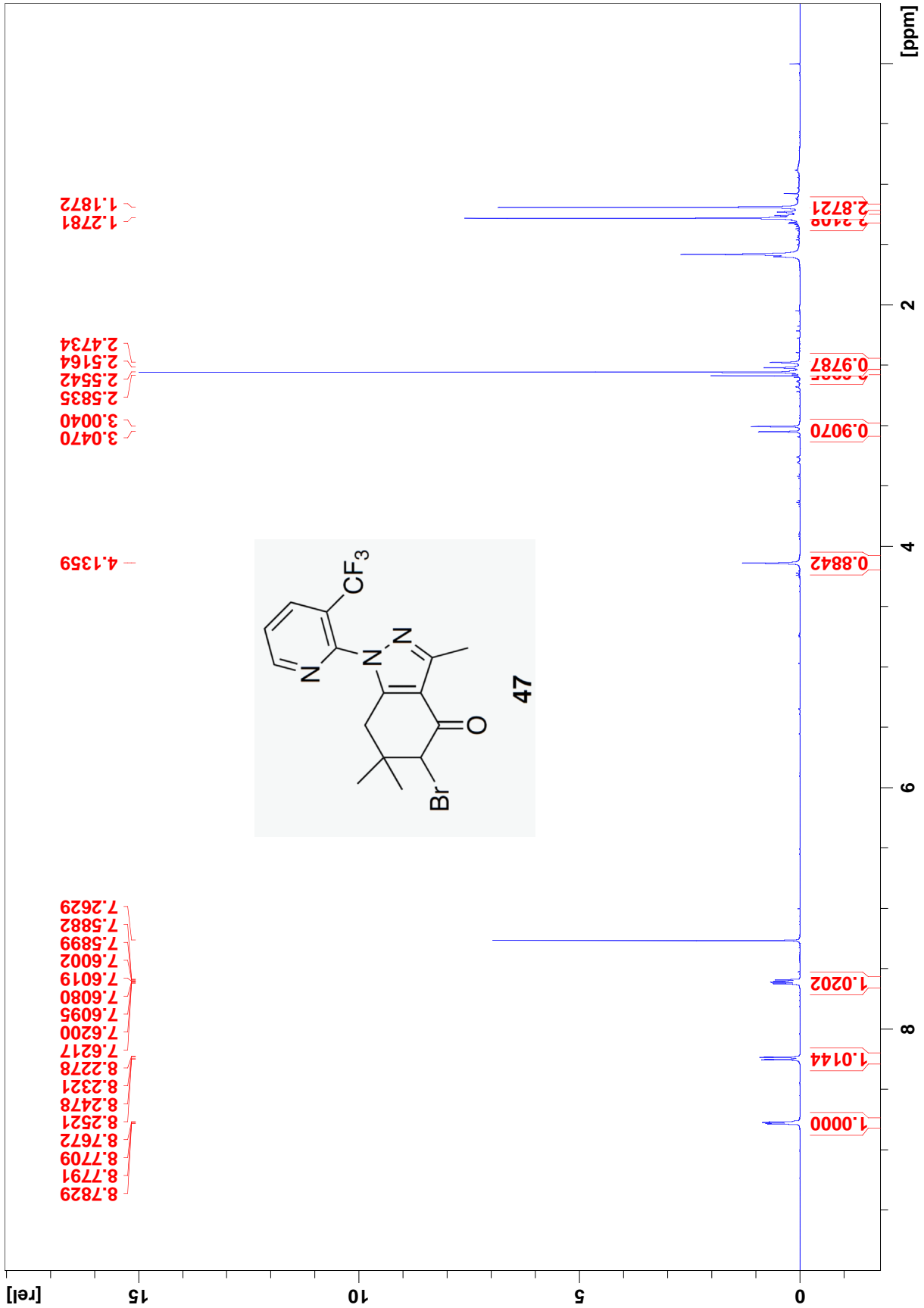
13C-NMR

JL09-072409A 4 1 C:\Bruker\TOPSPIN leex3451

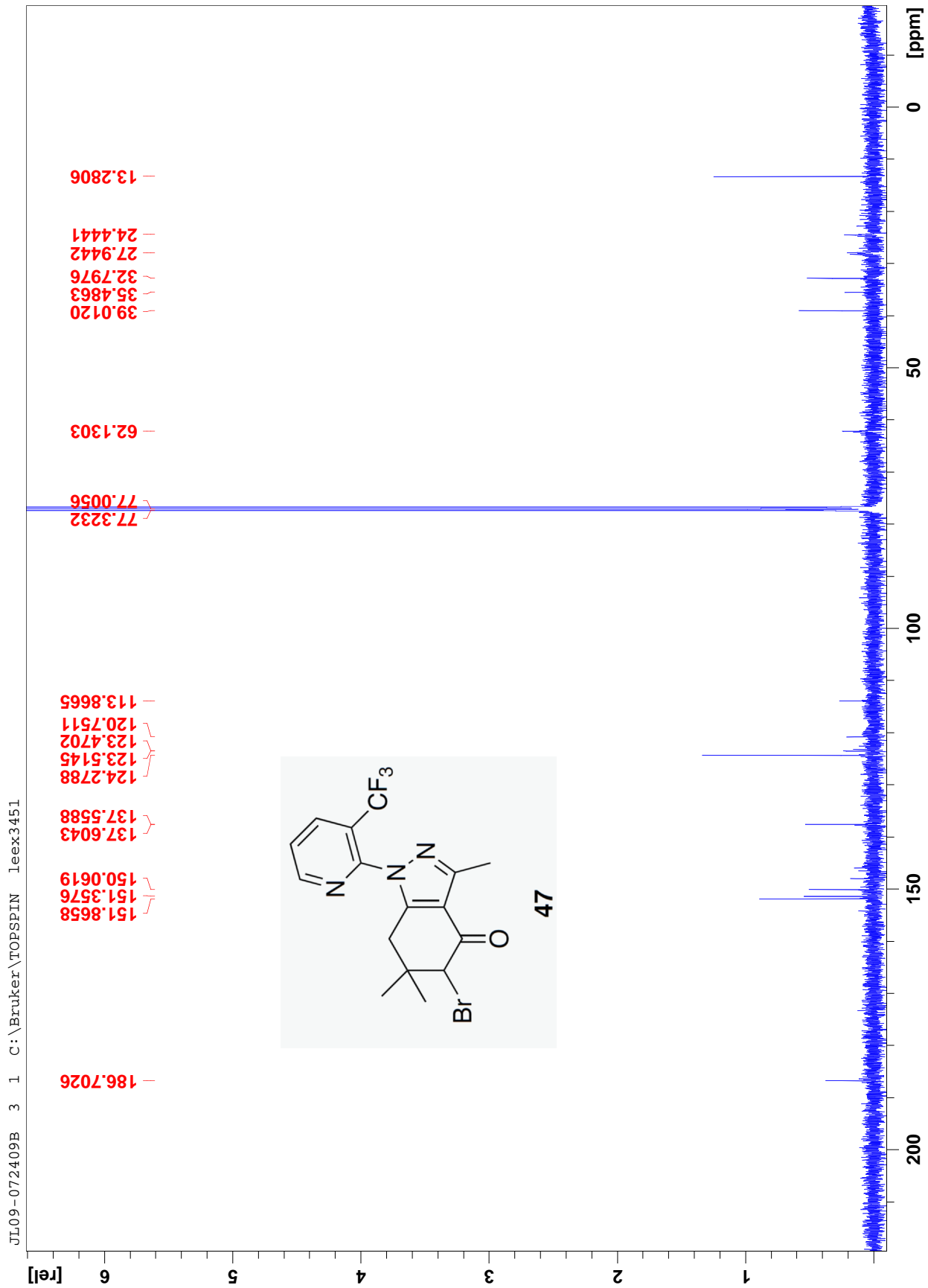


1H-NMR

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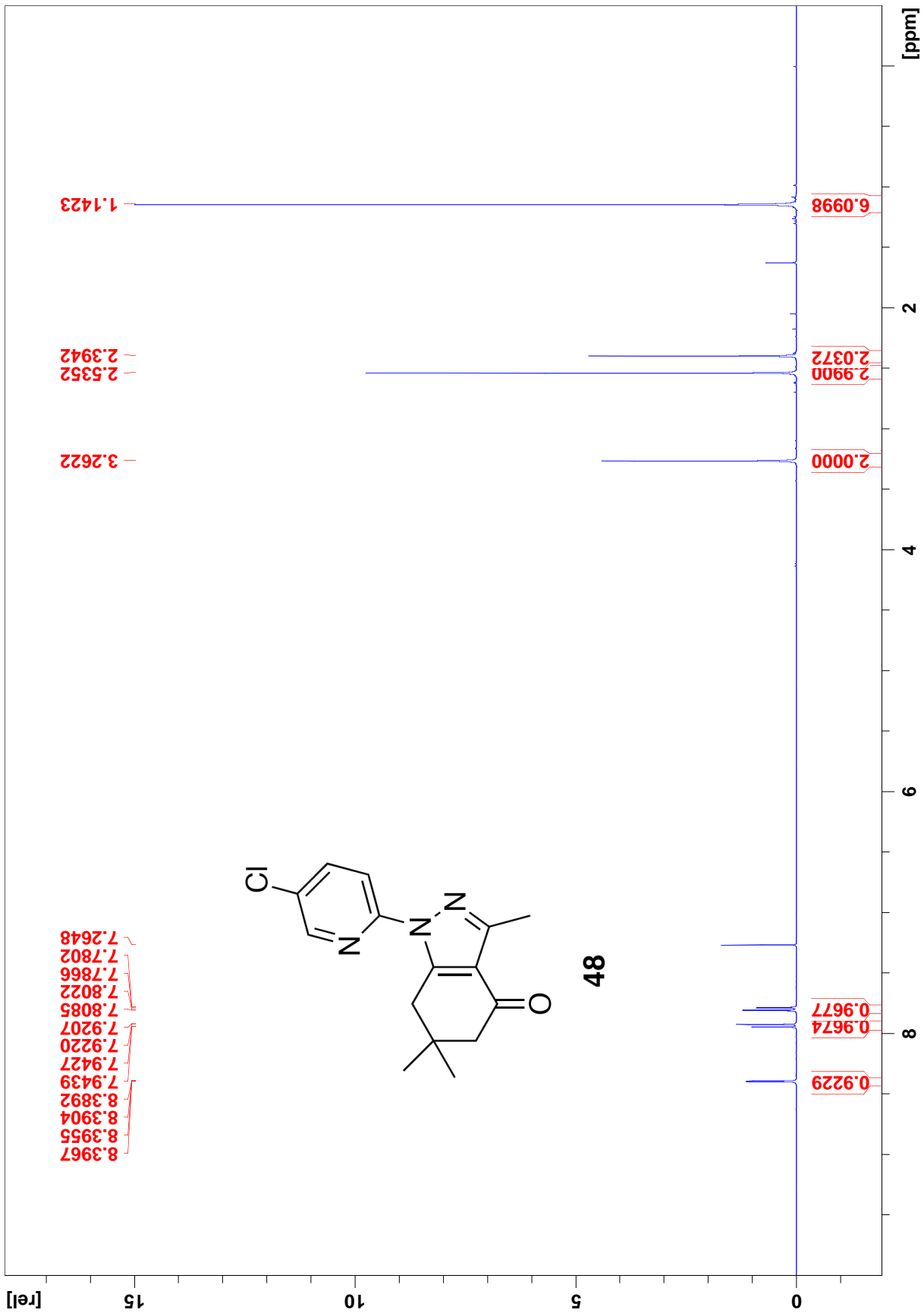


13C-NMR

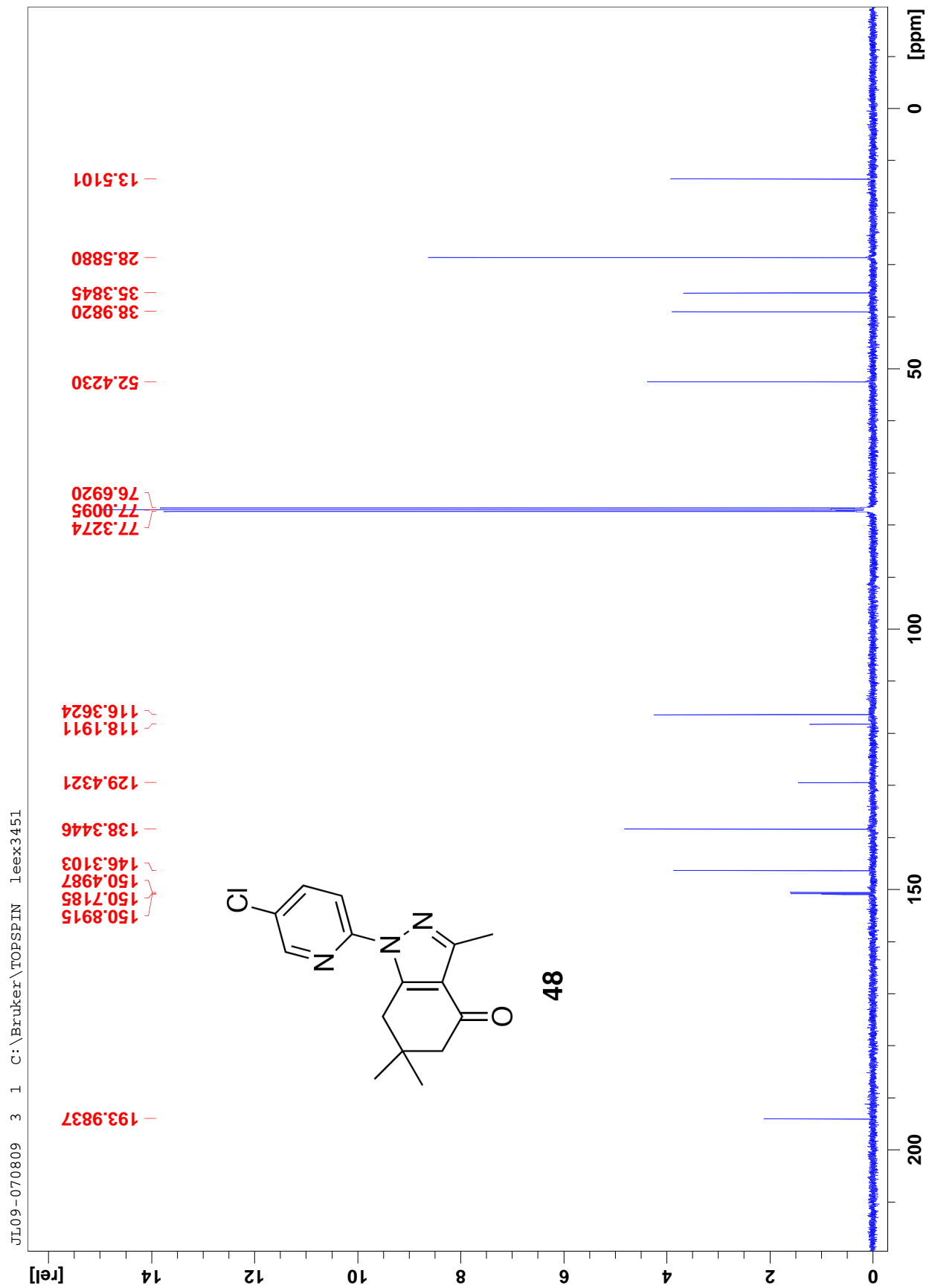


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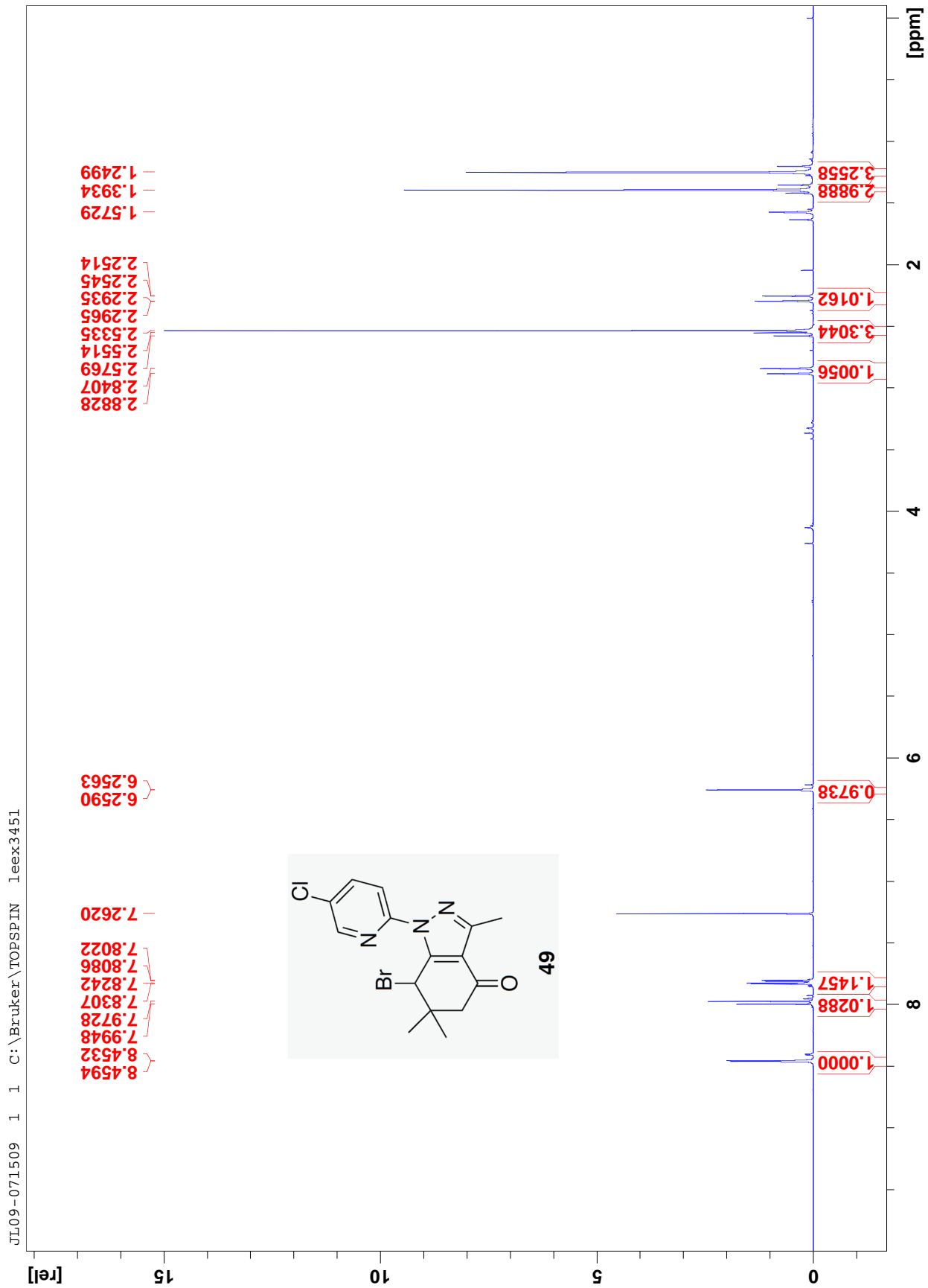
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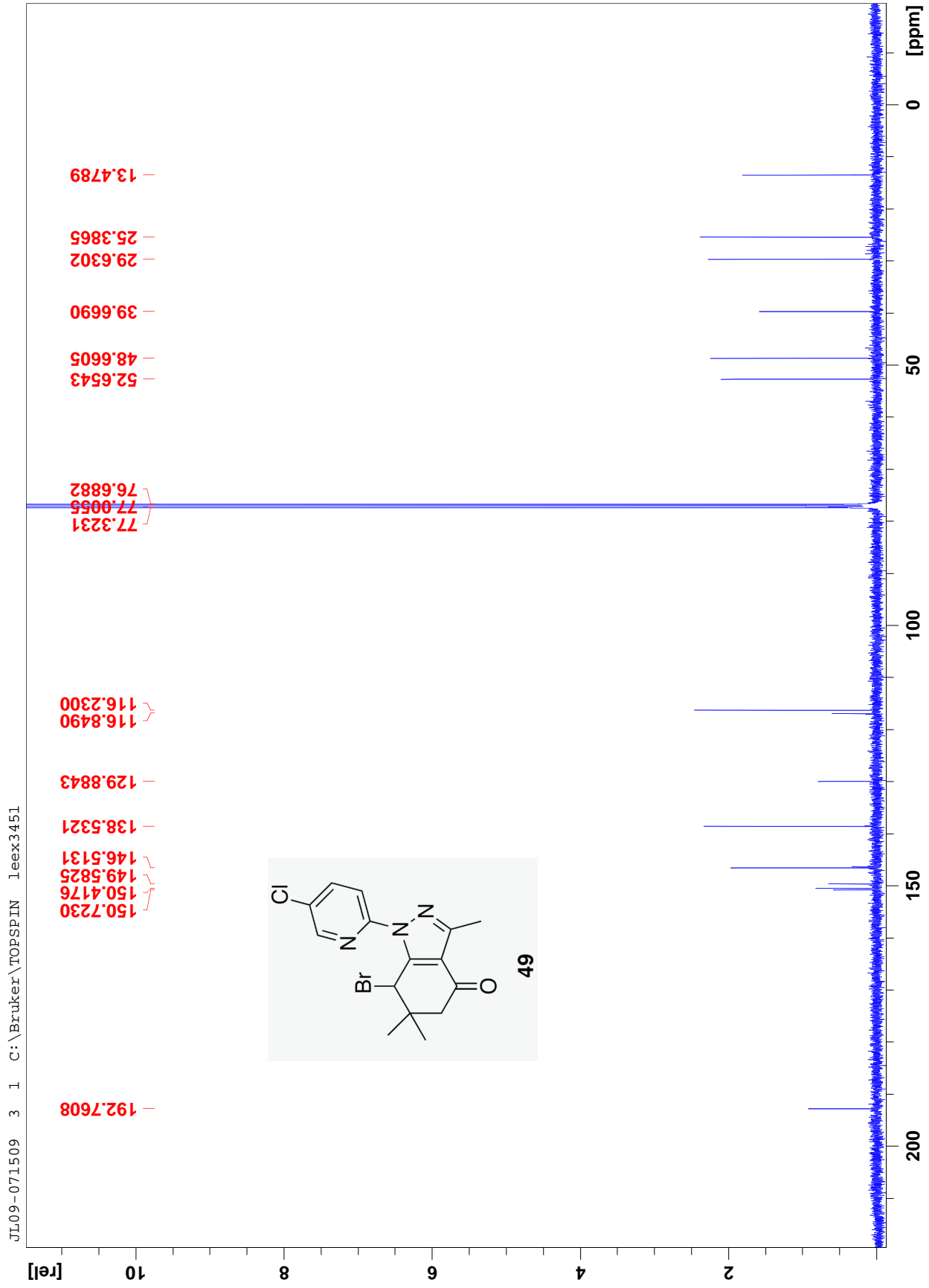
13C-NMR



1H-NMR

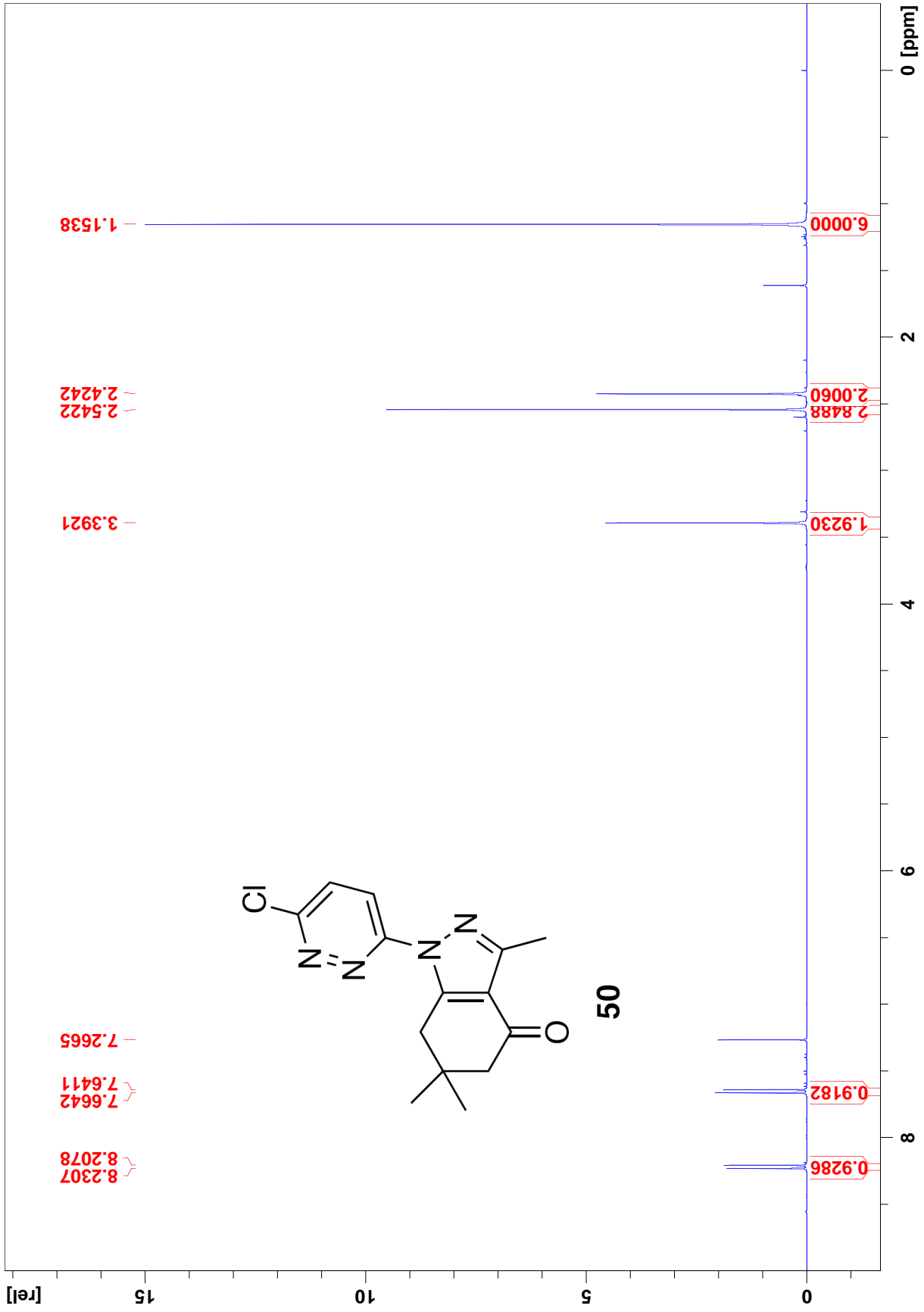


13C-NMR



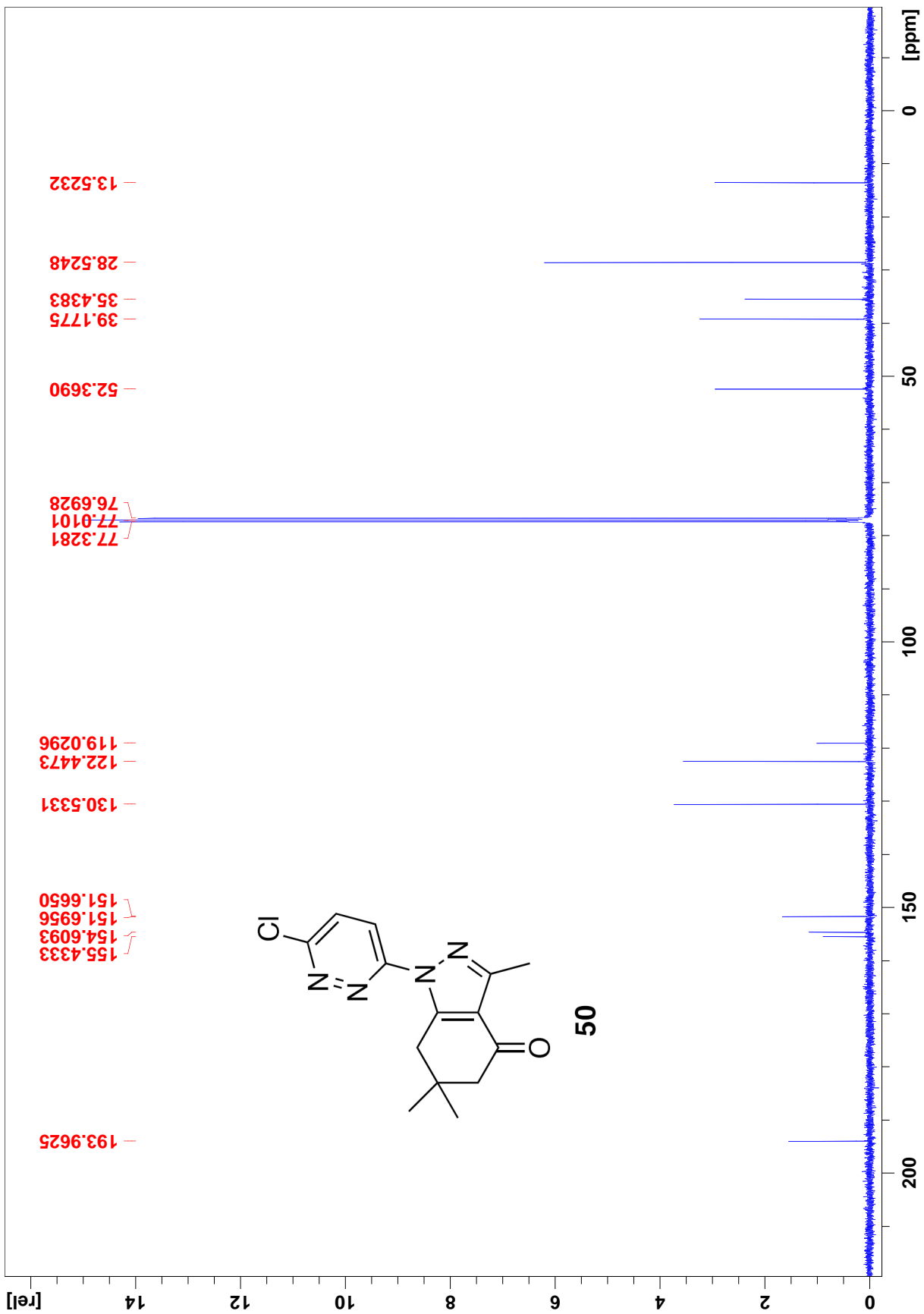
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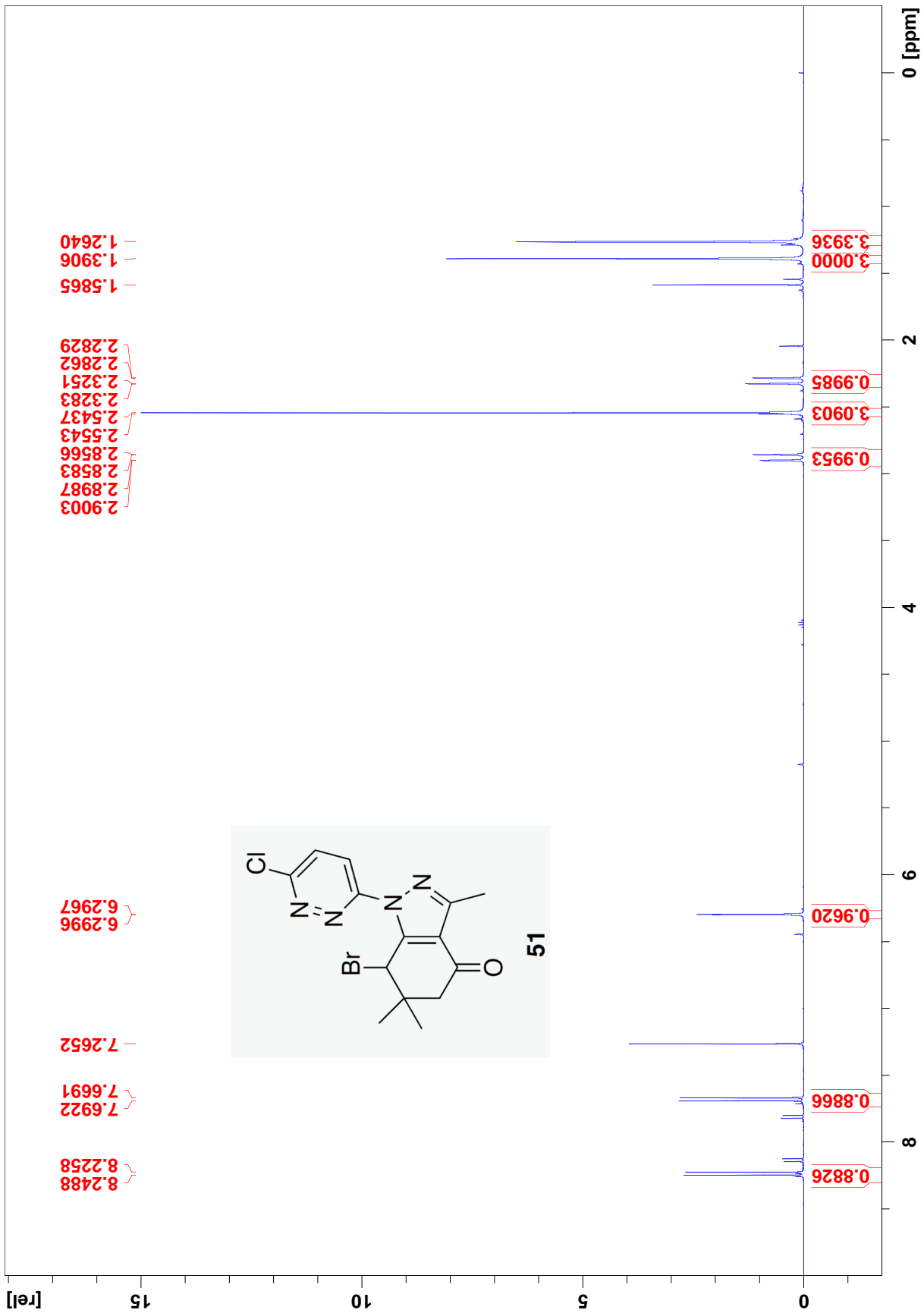
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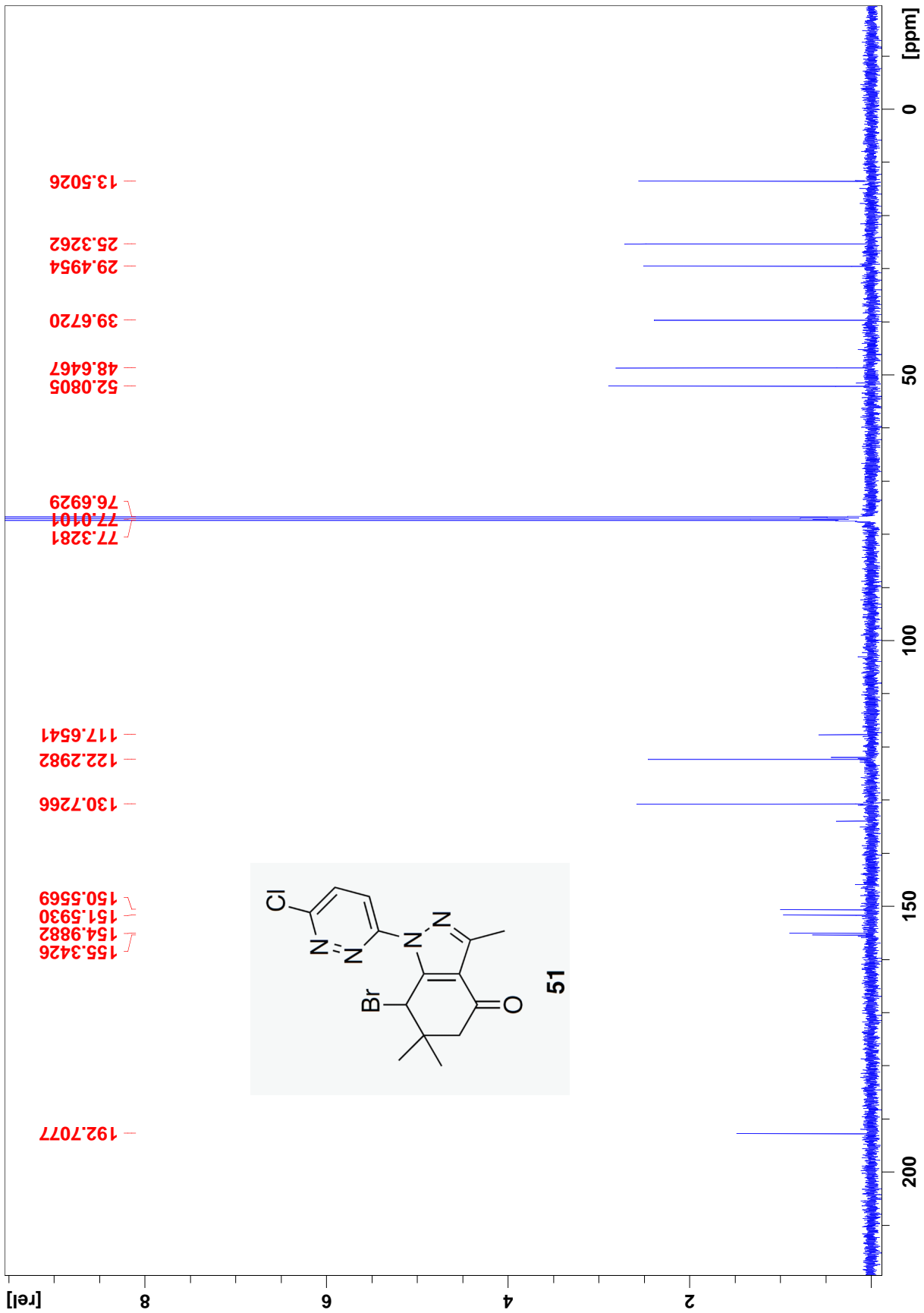
1H-NMR

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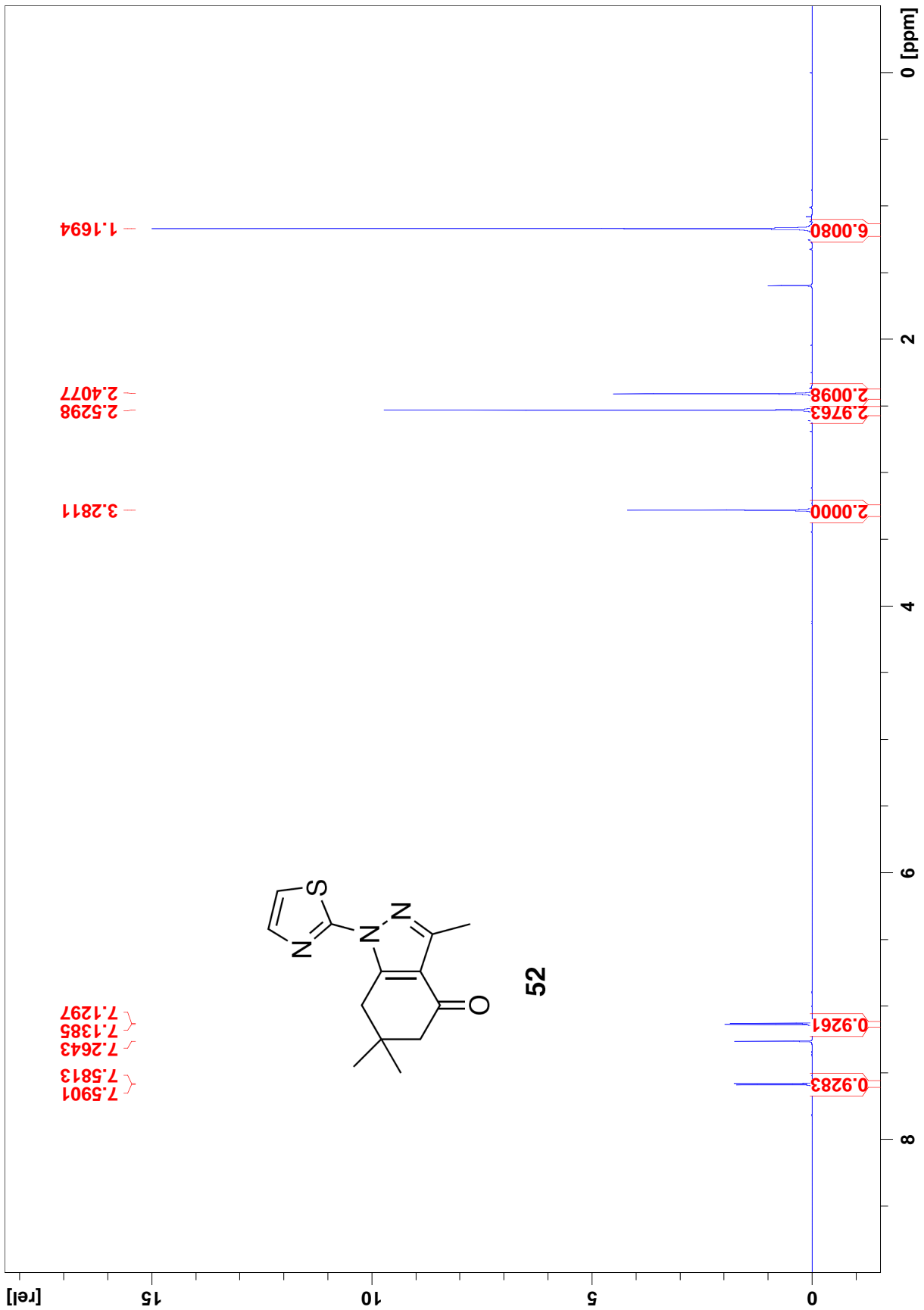
13C-NMR

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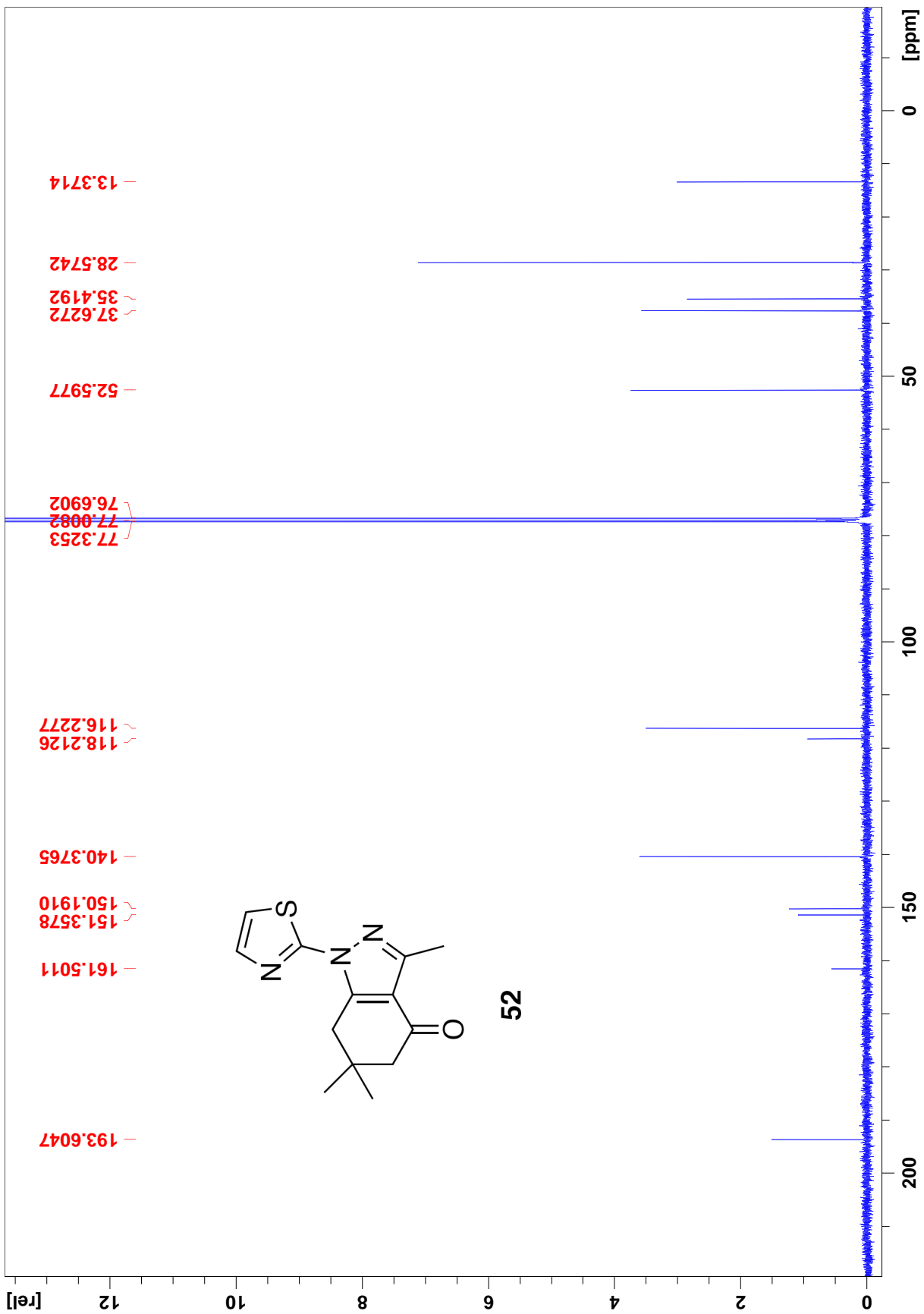
1H-NMR

JL09-071309 1 1 C:\Bruker\TOPSPIN leex3451



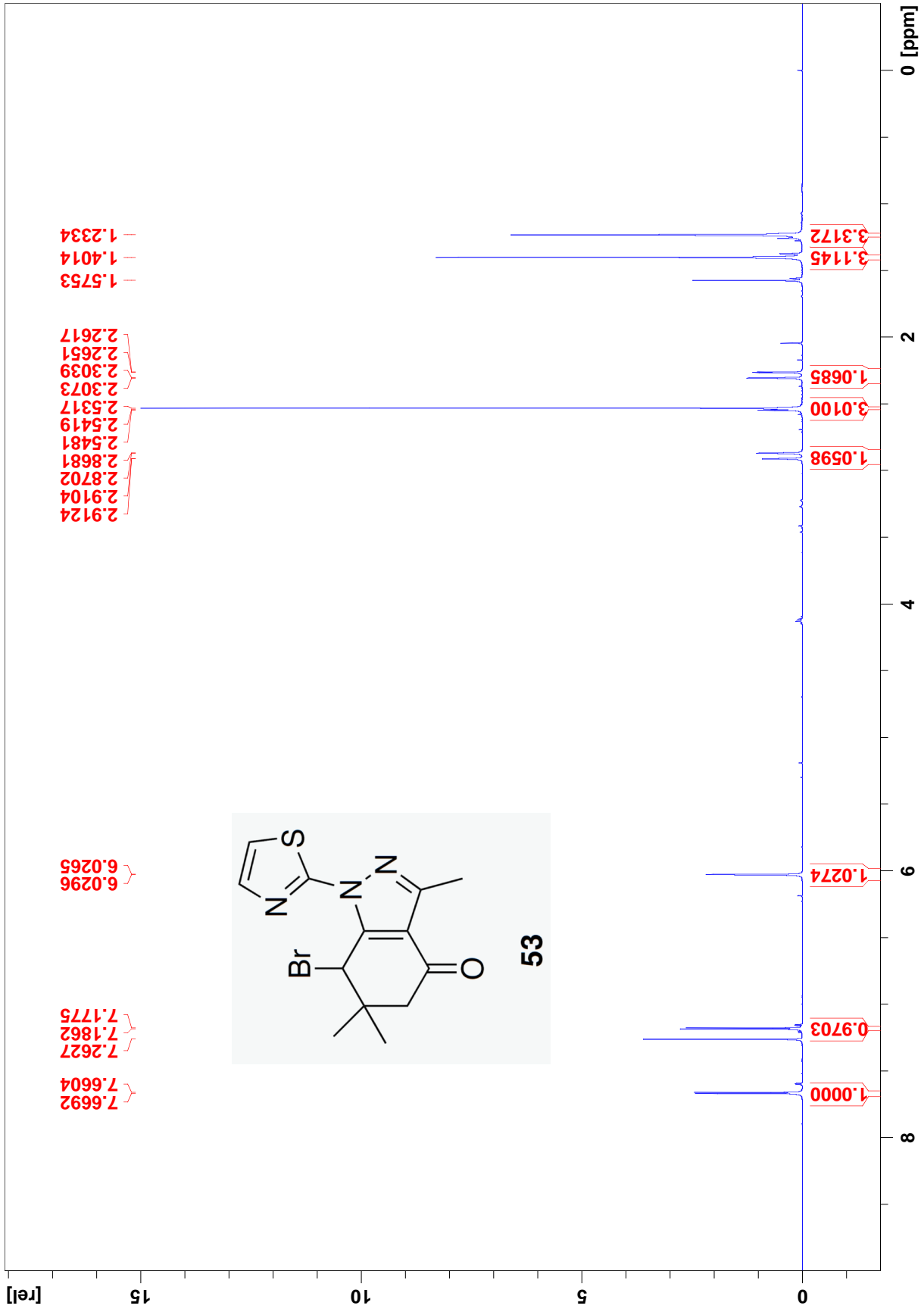
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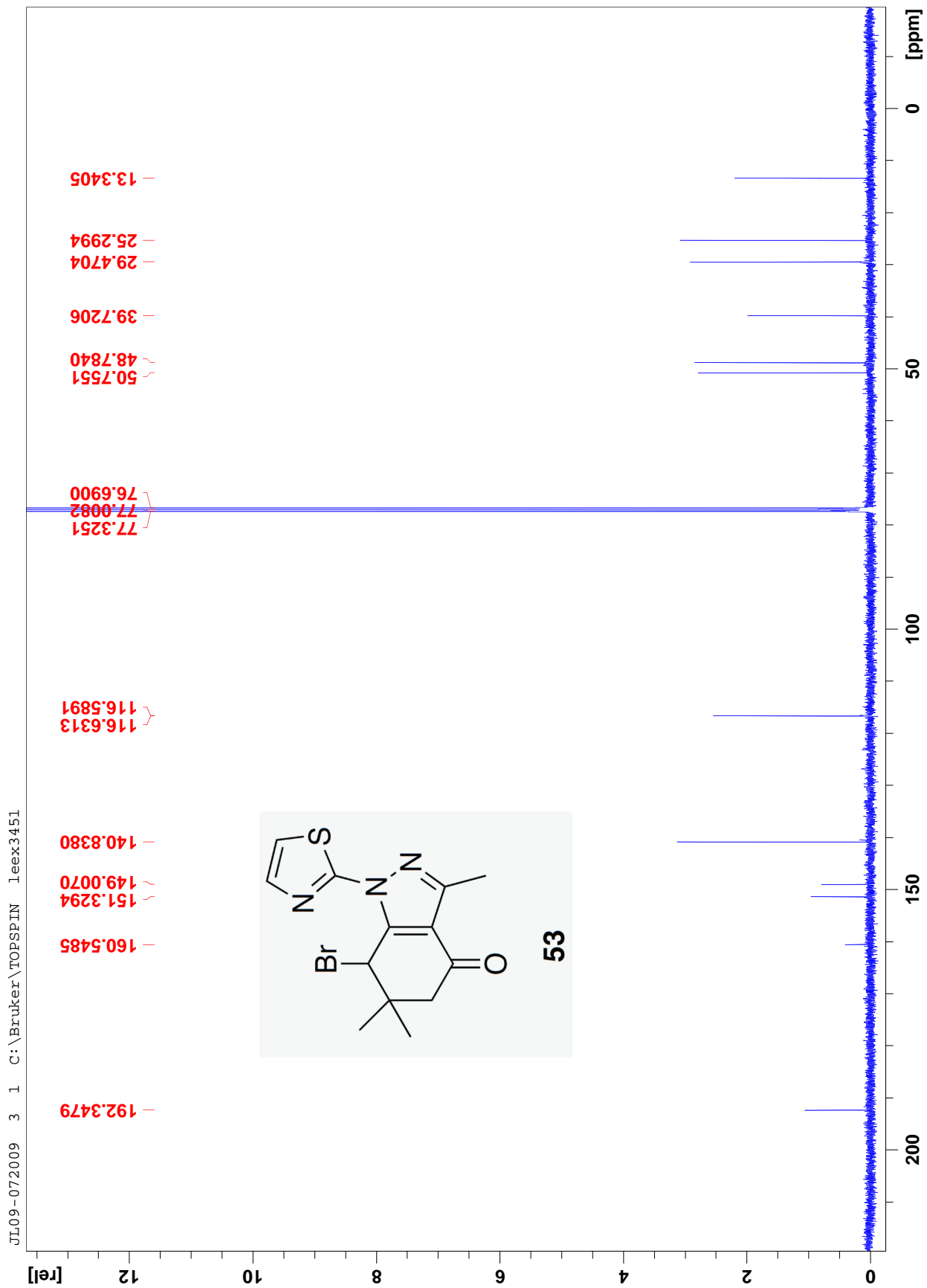


1H-NMR

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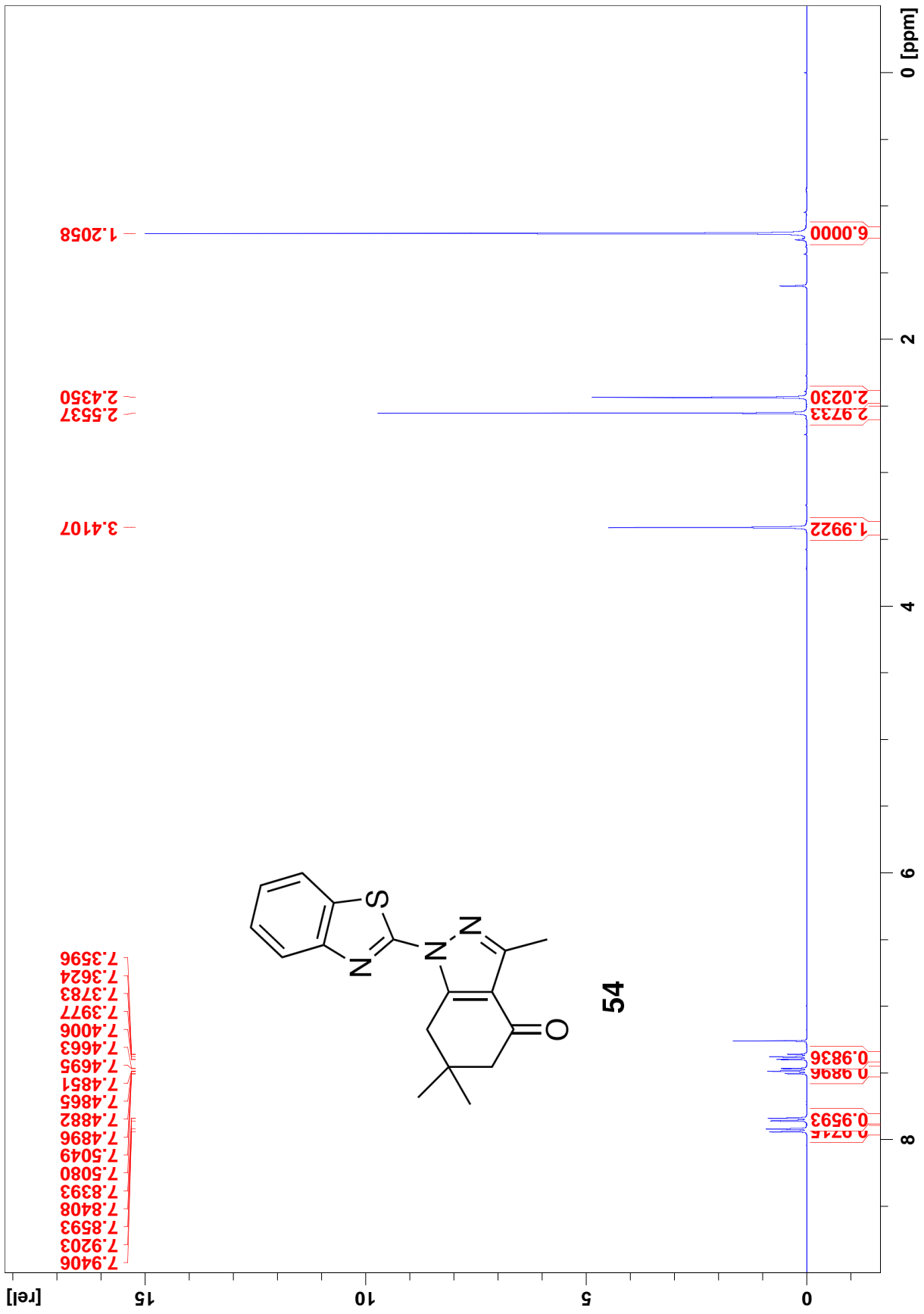


13C-NMR



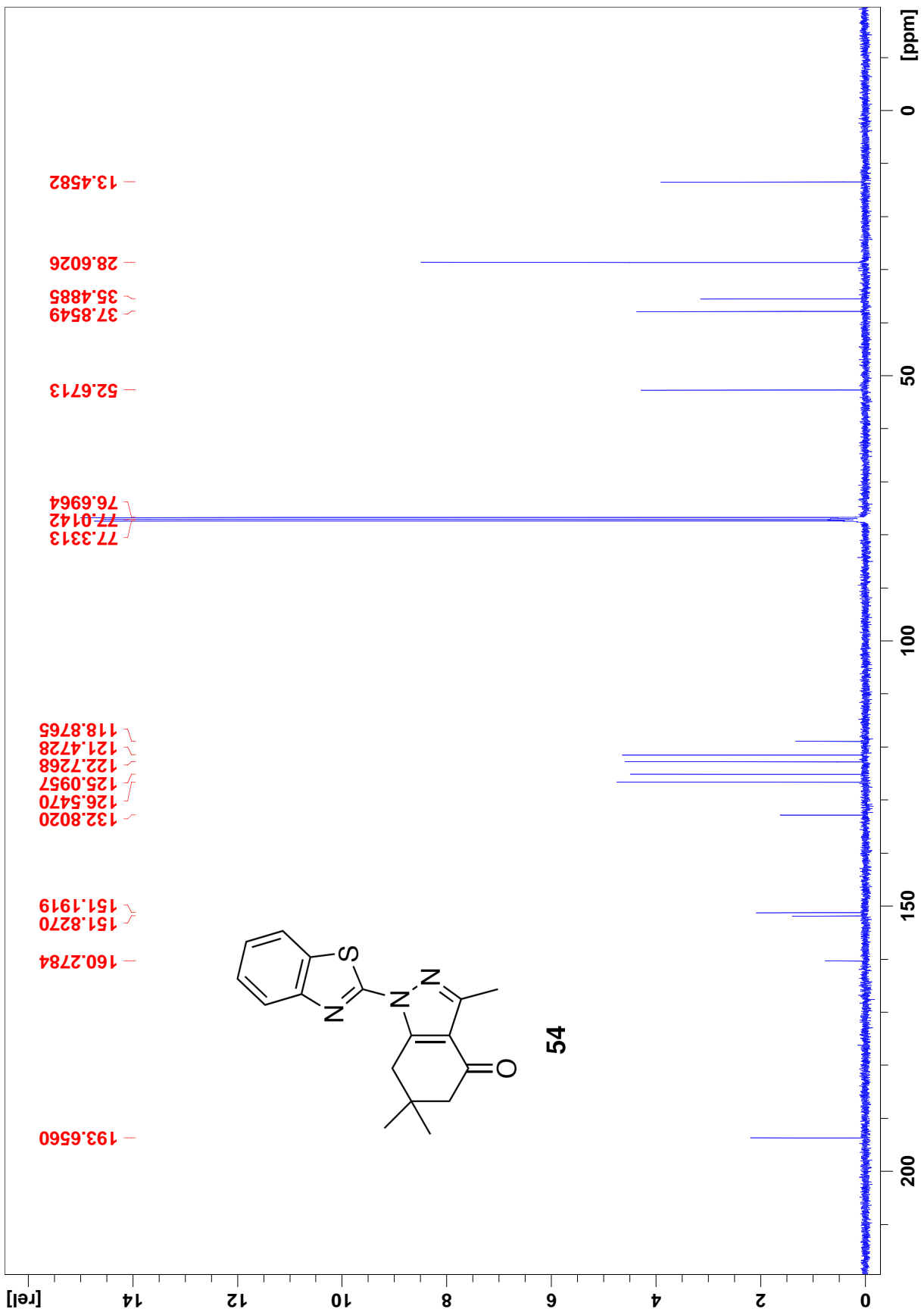
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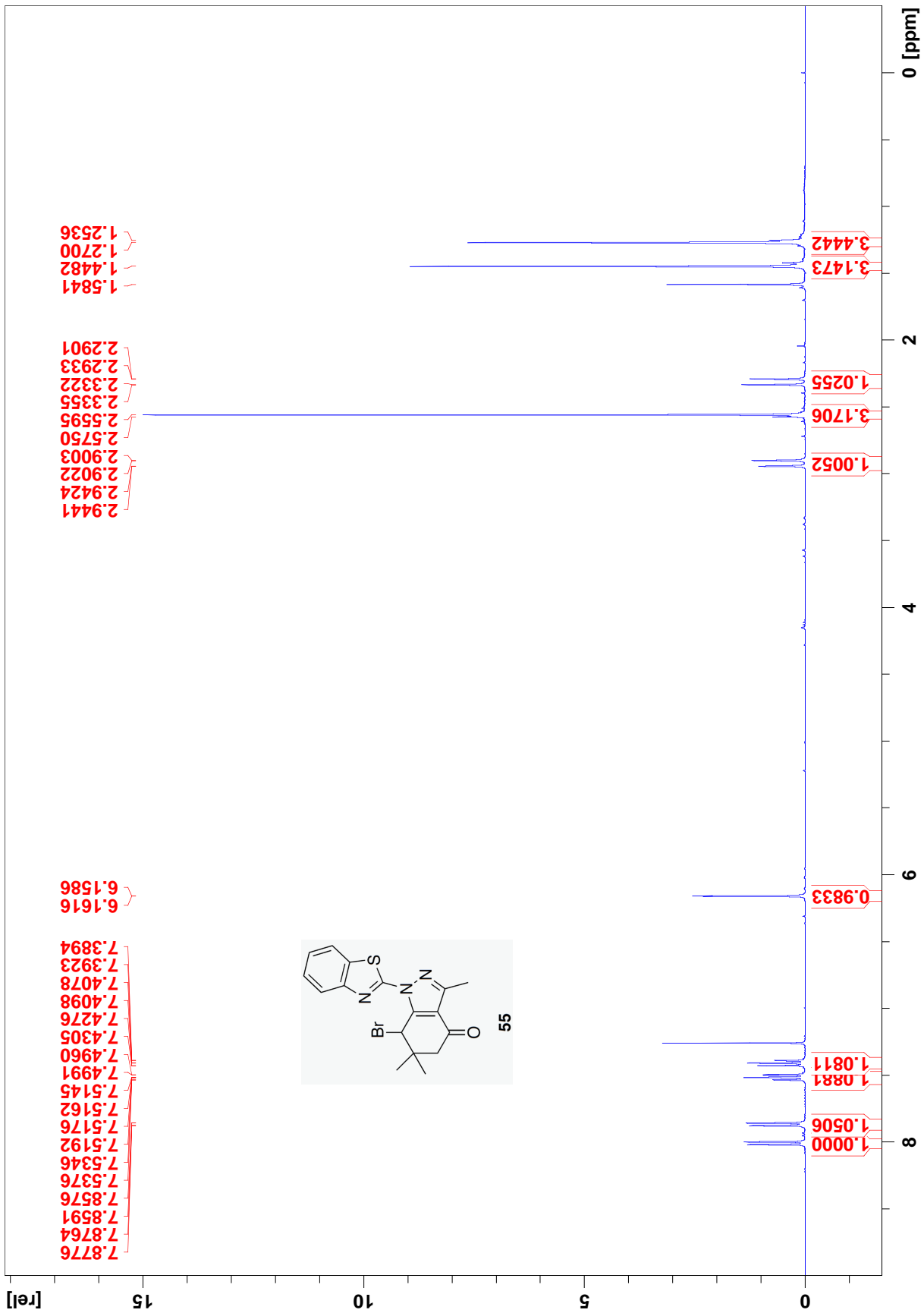
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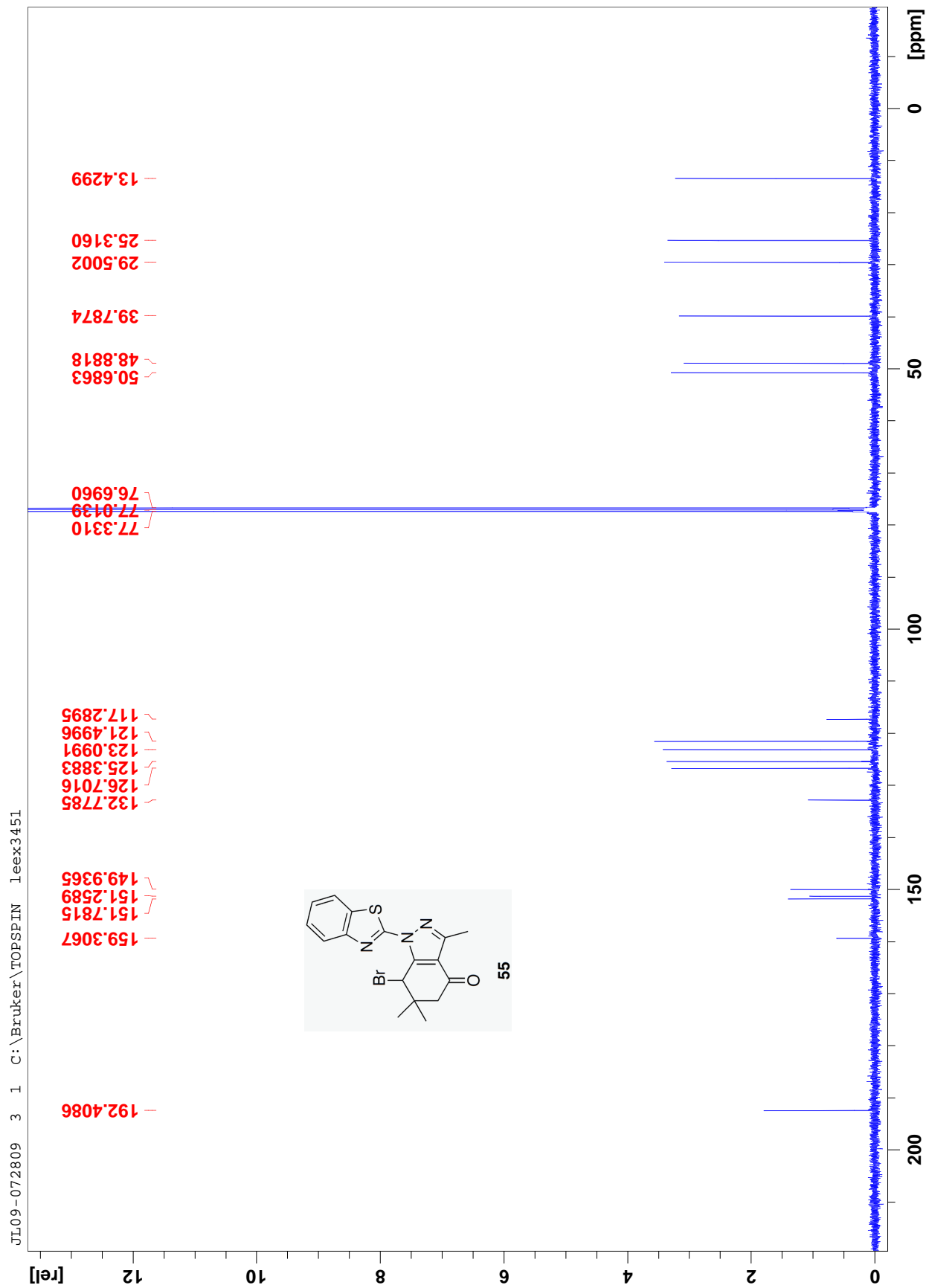


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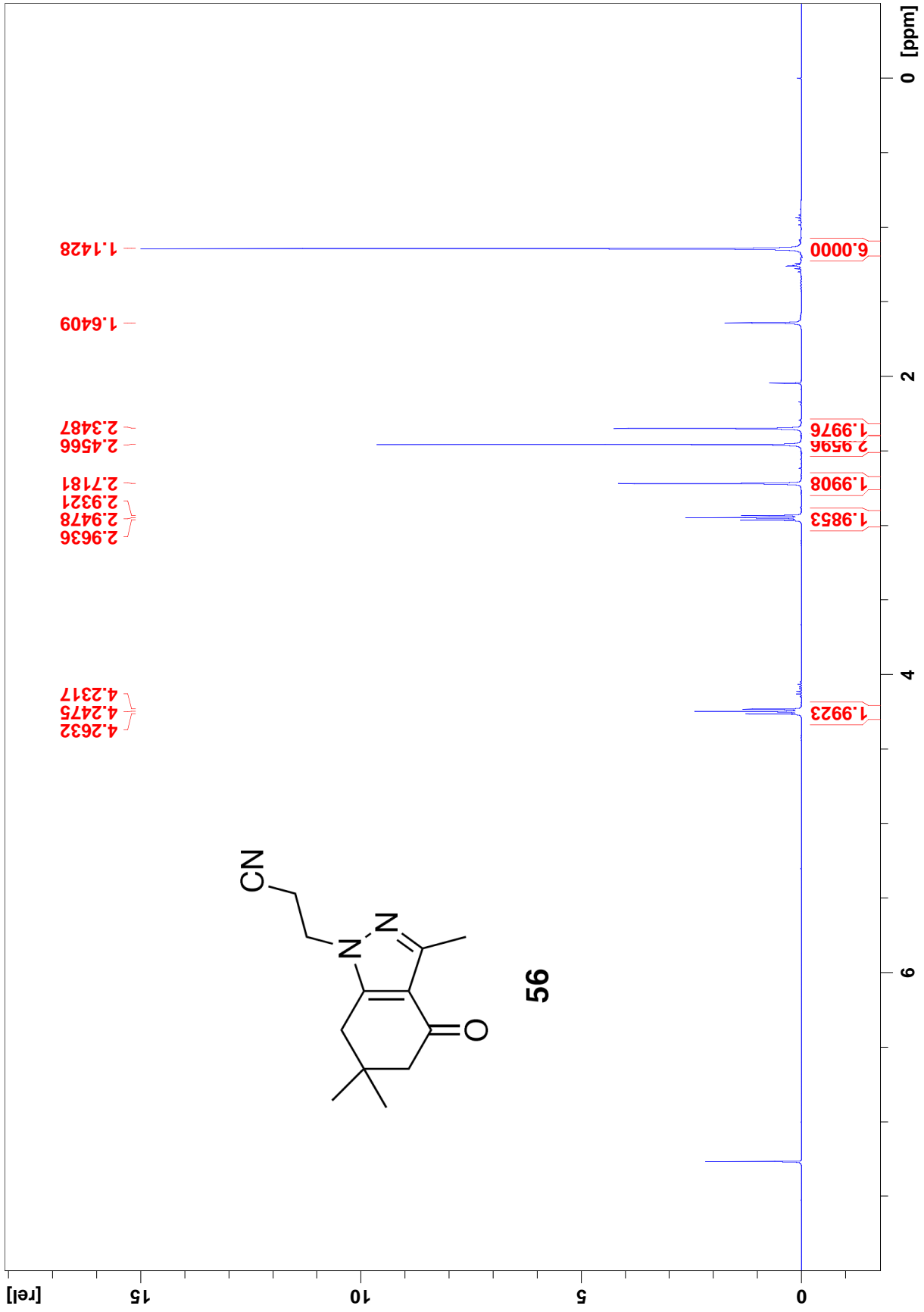


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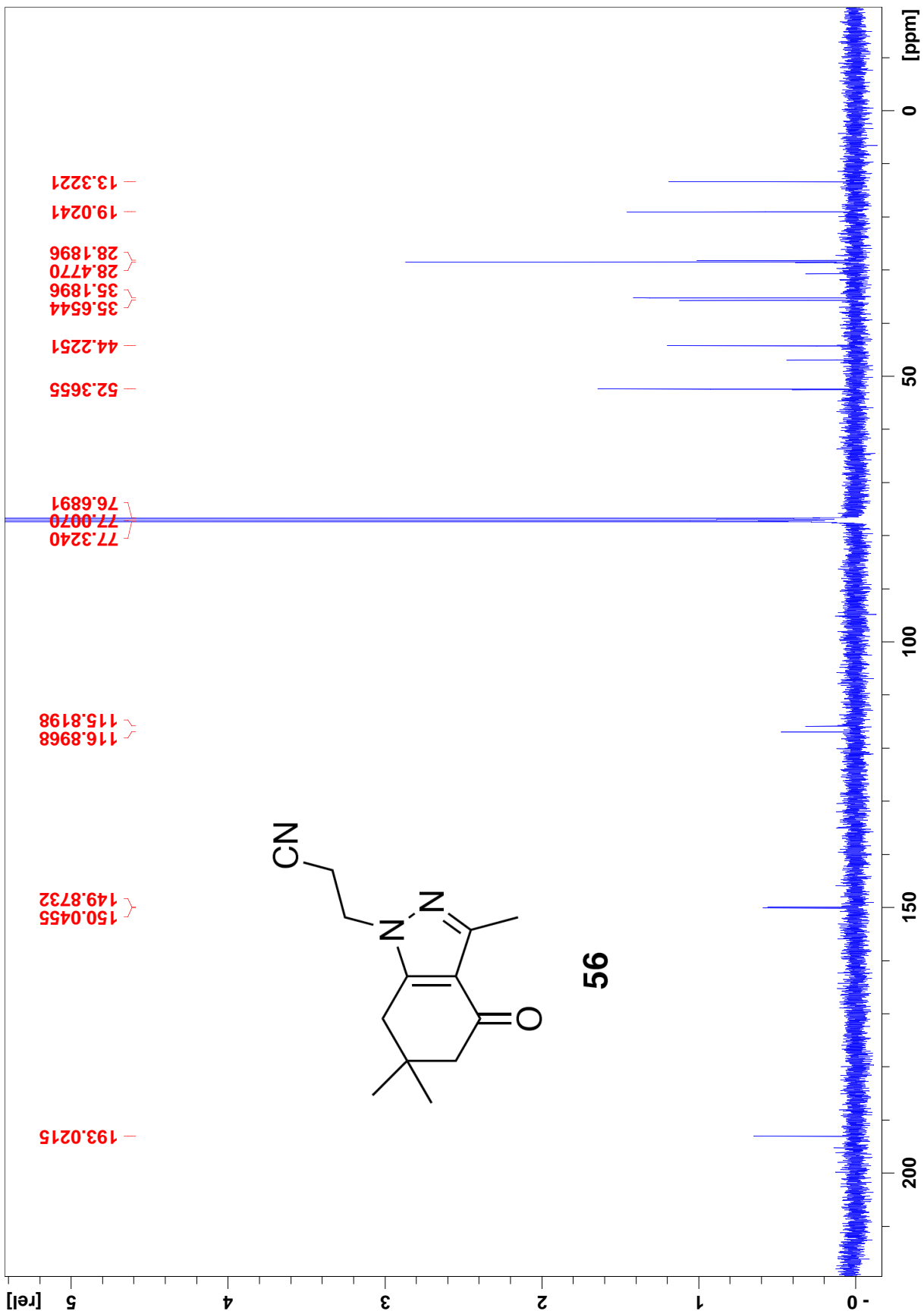
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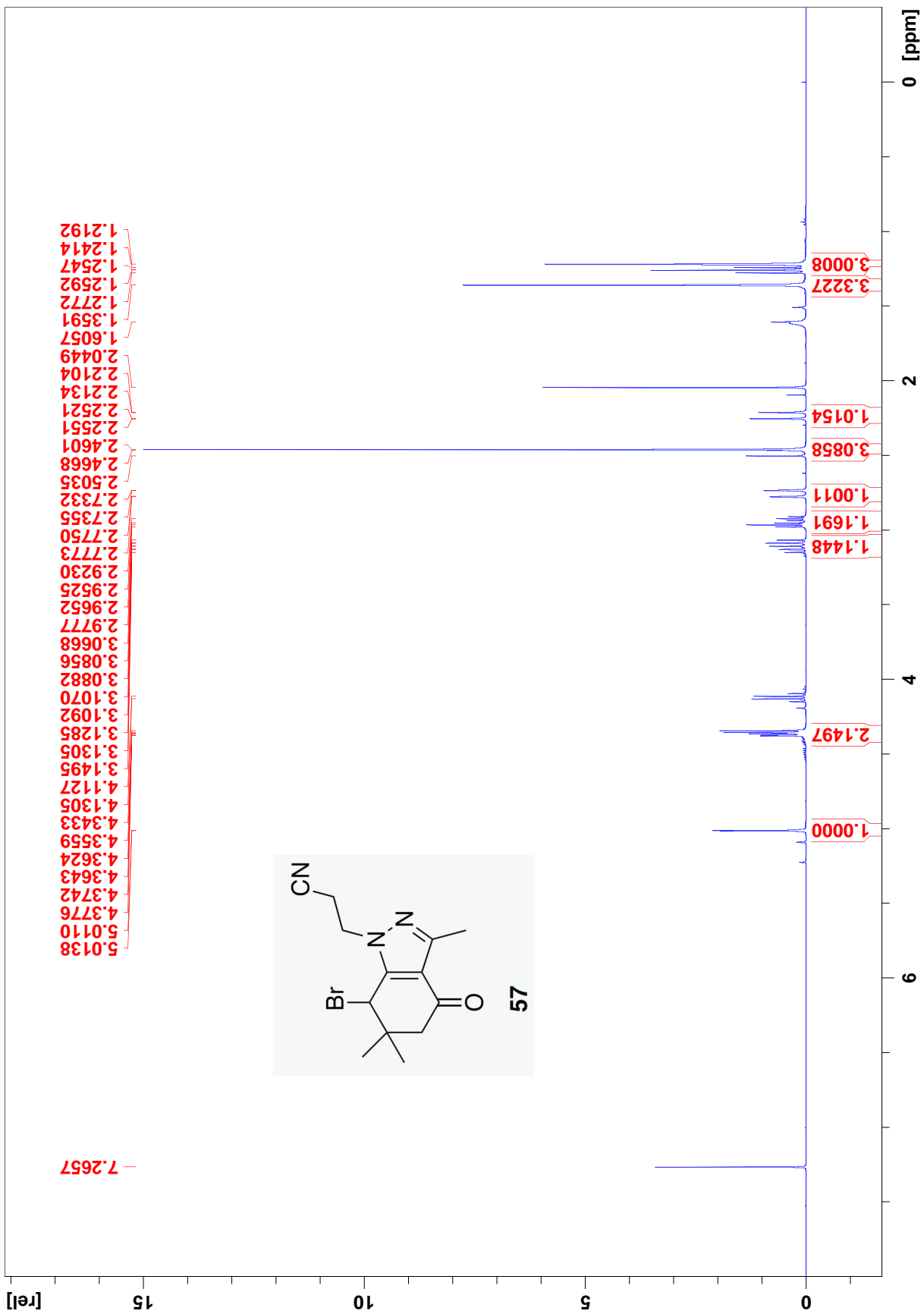
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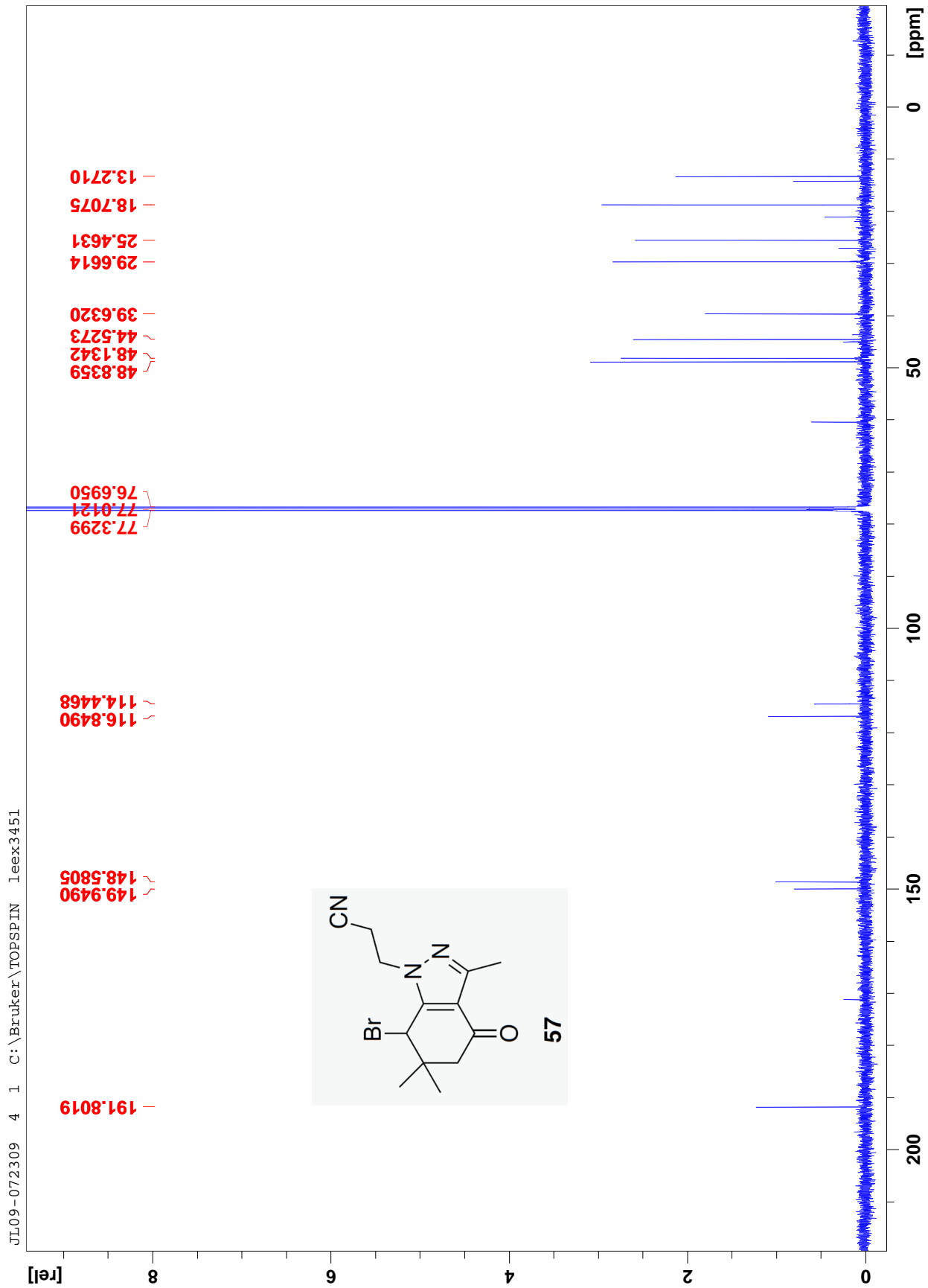


1H-NMR

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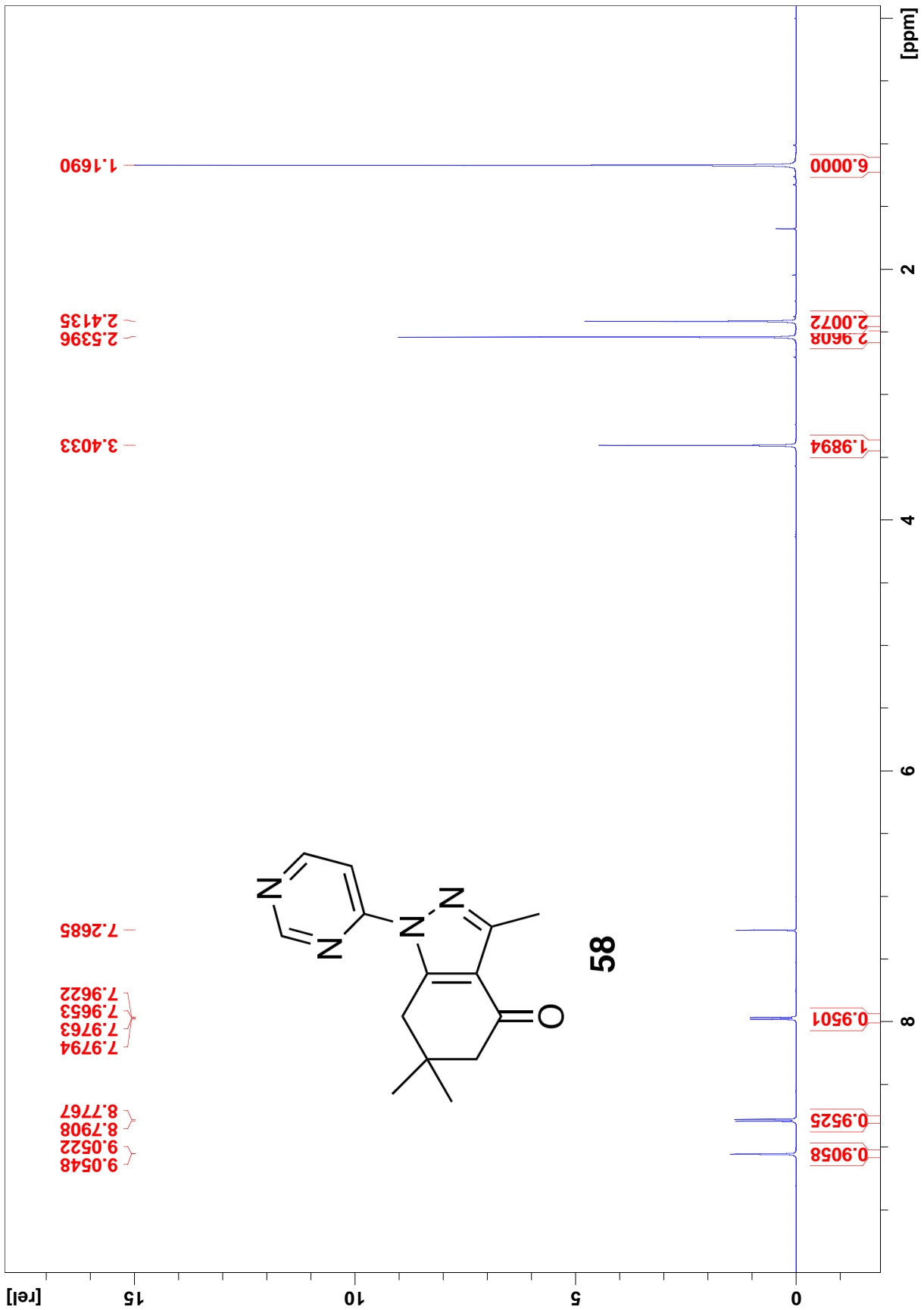


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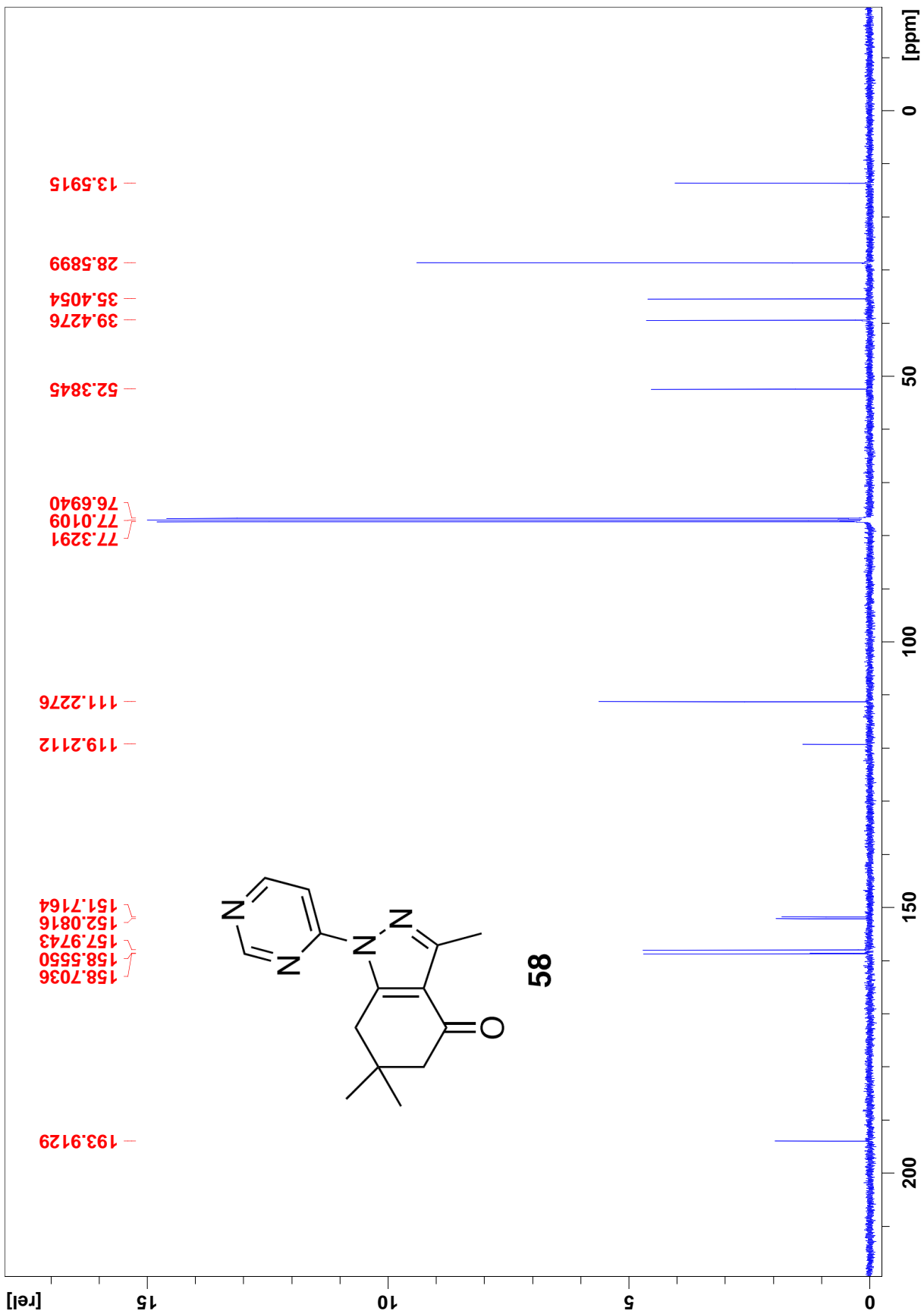
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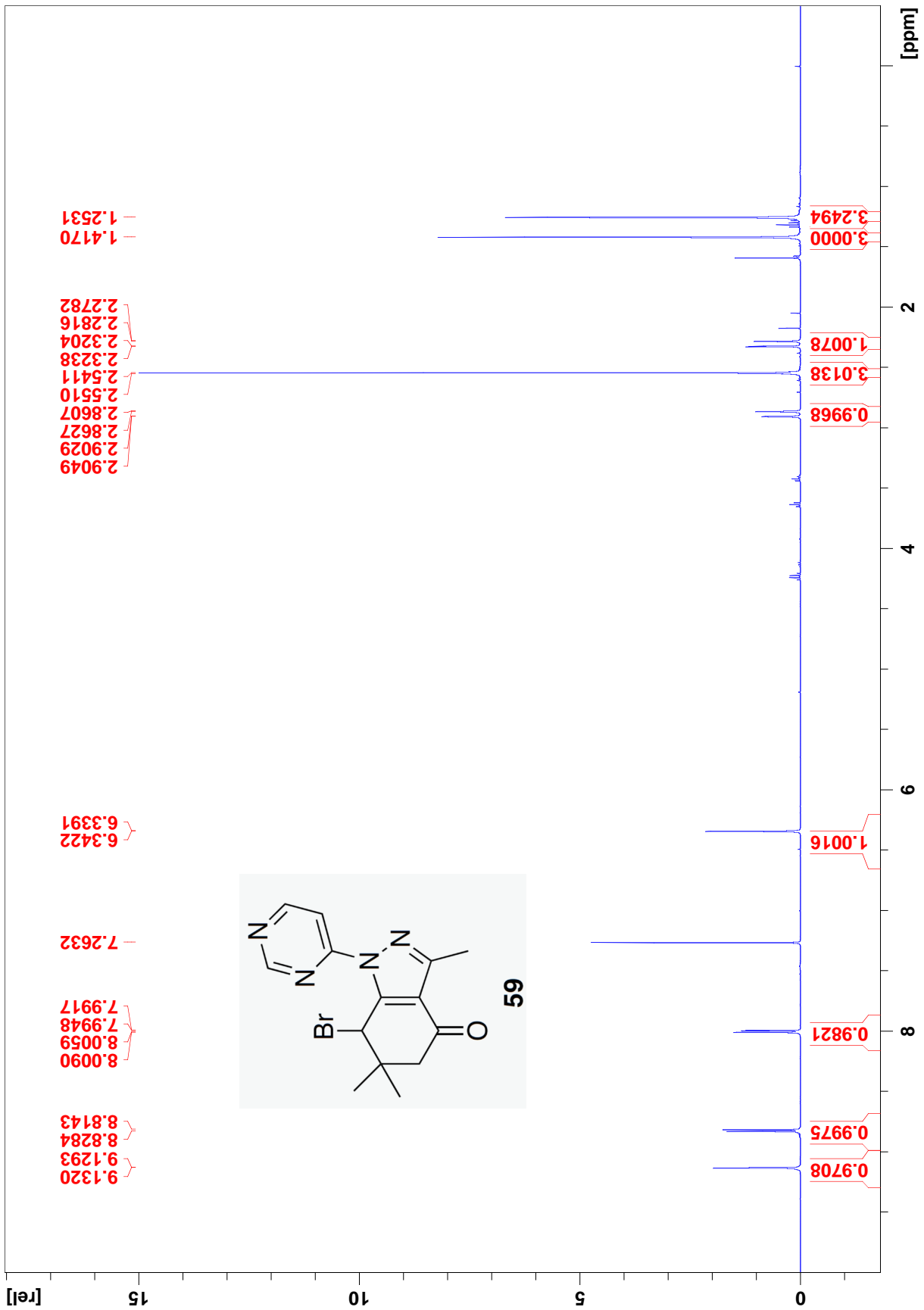
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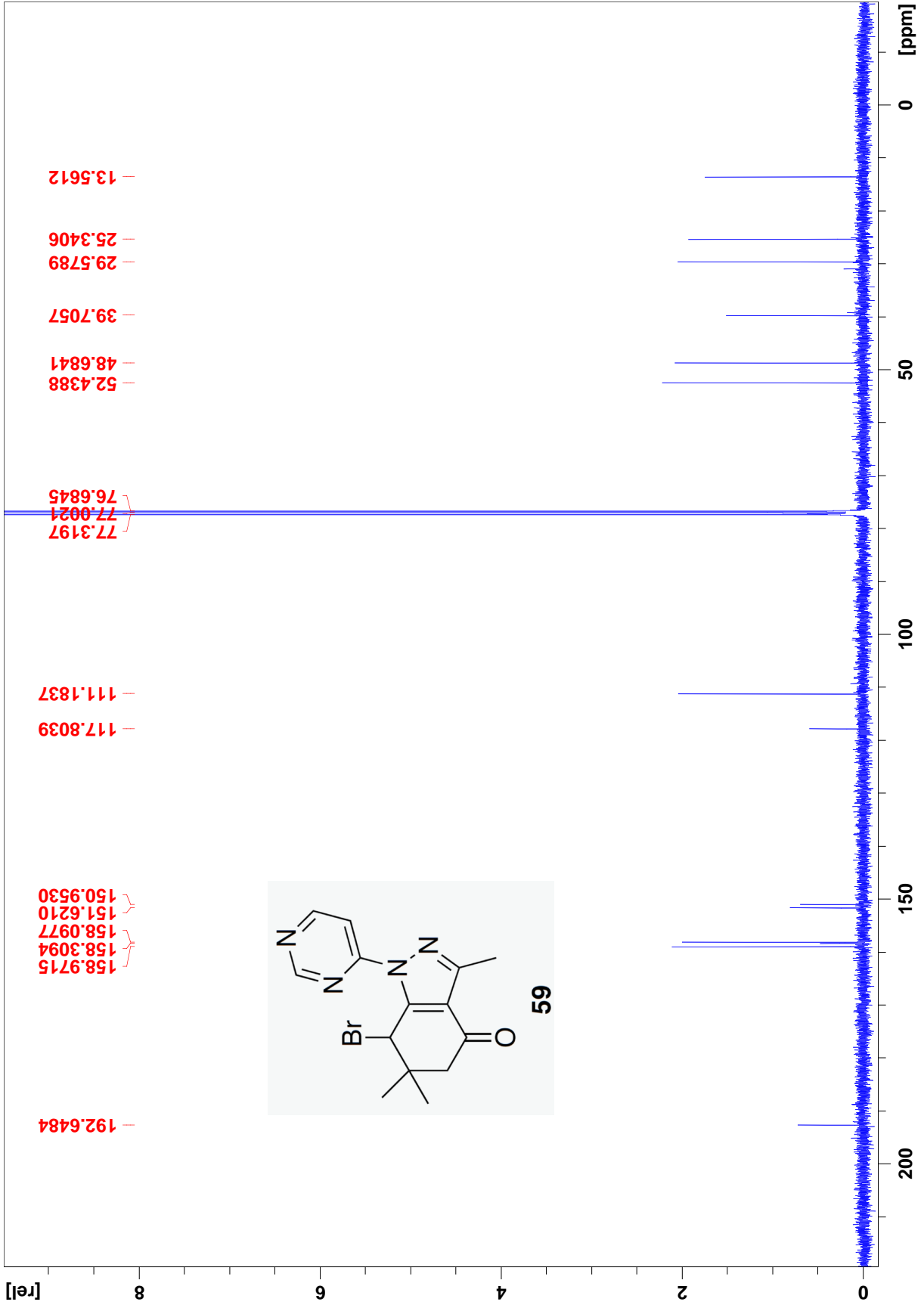
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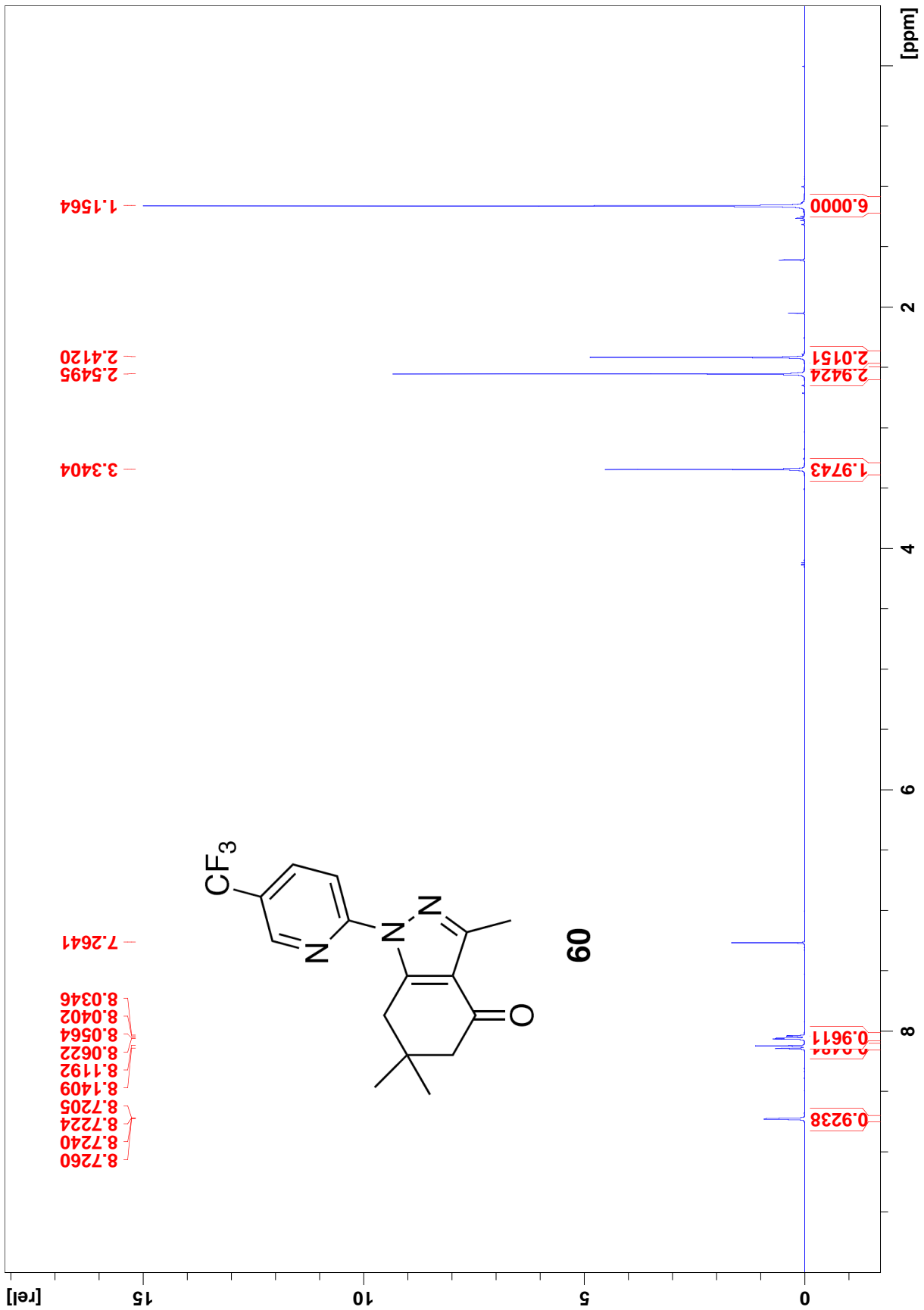
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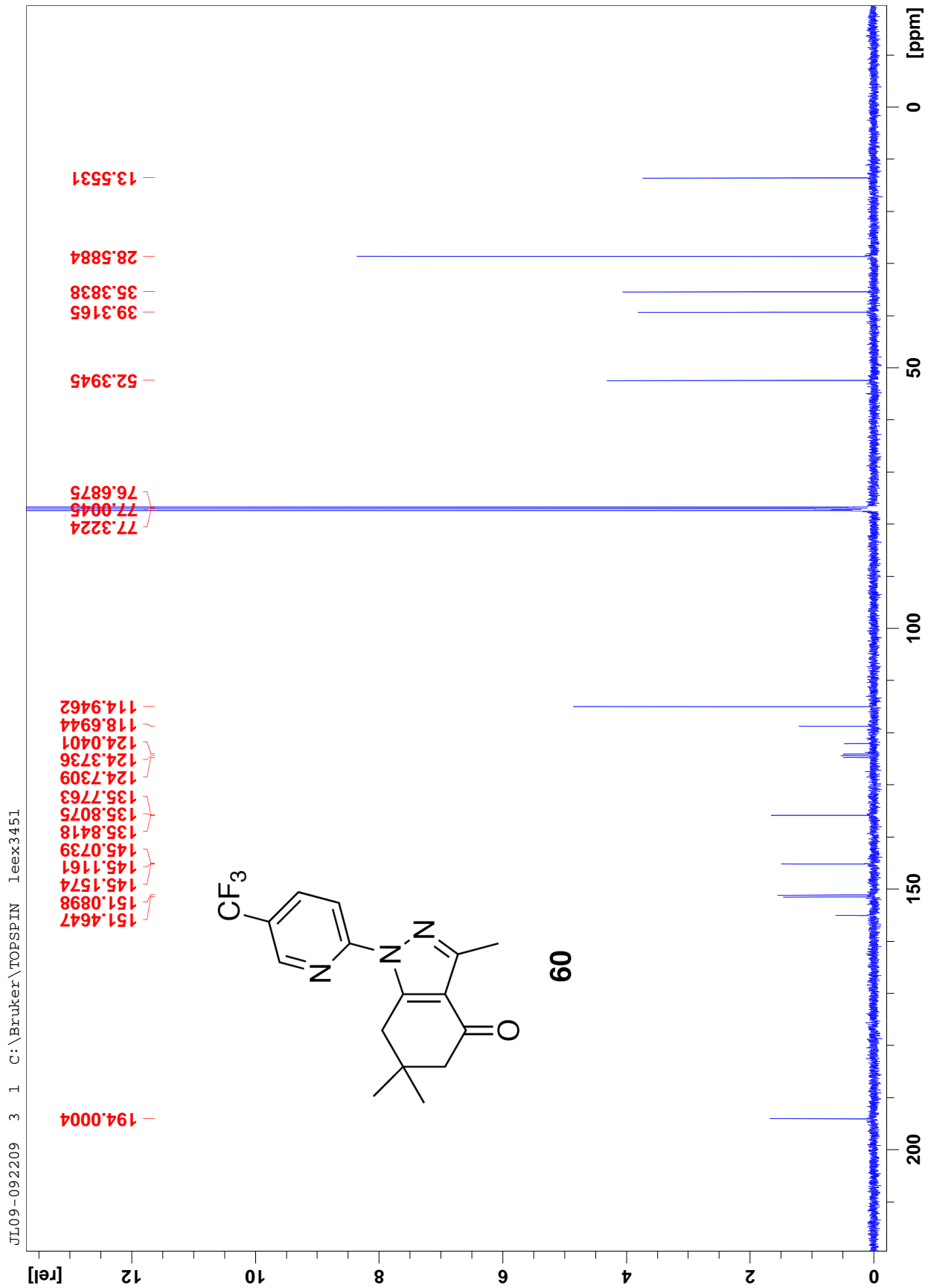


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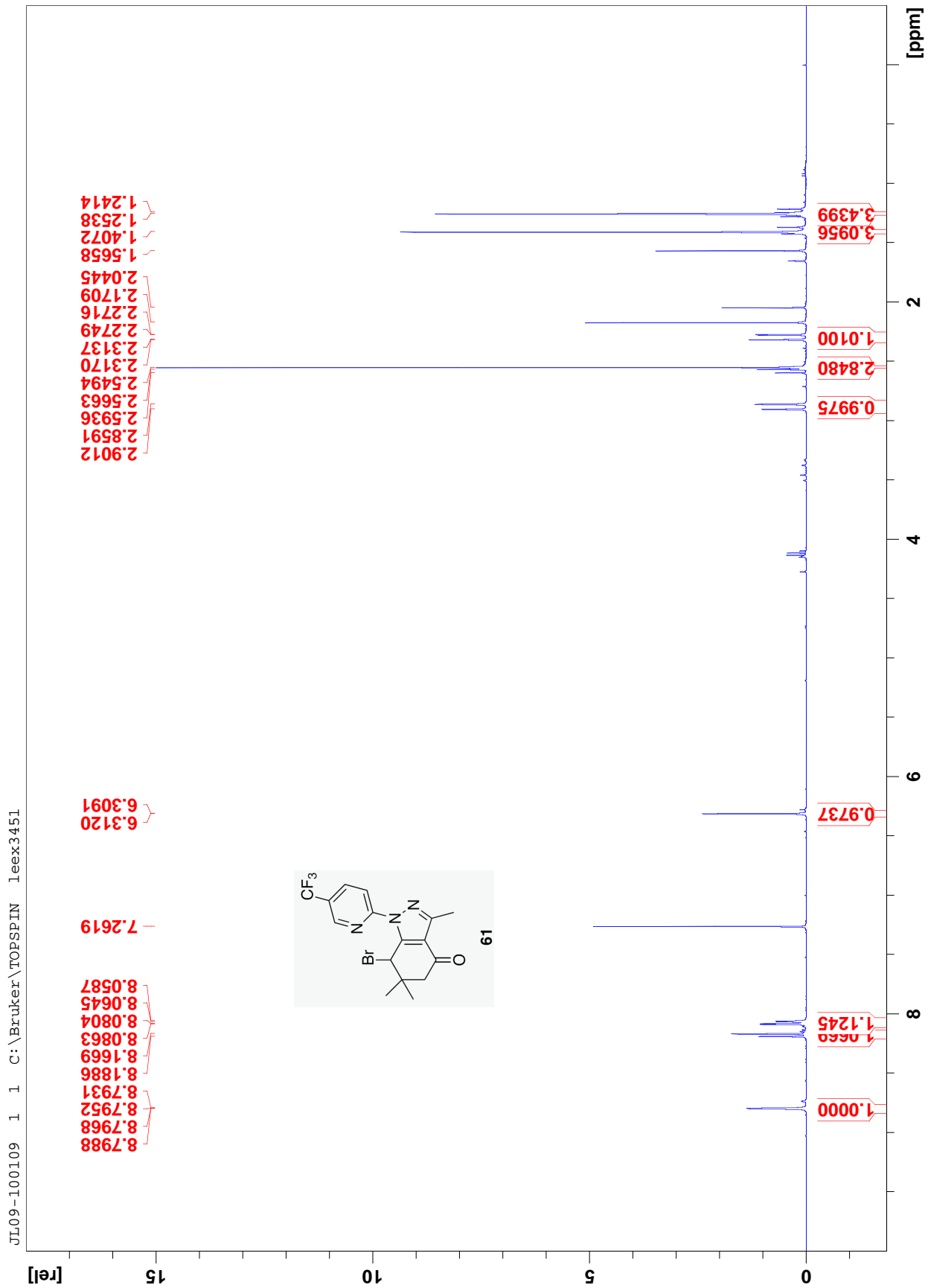
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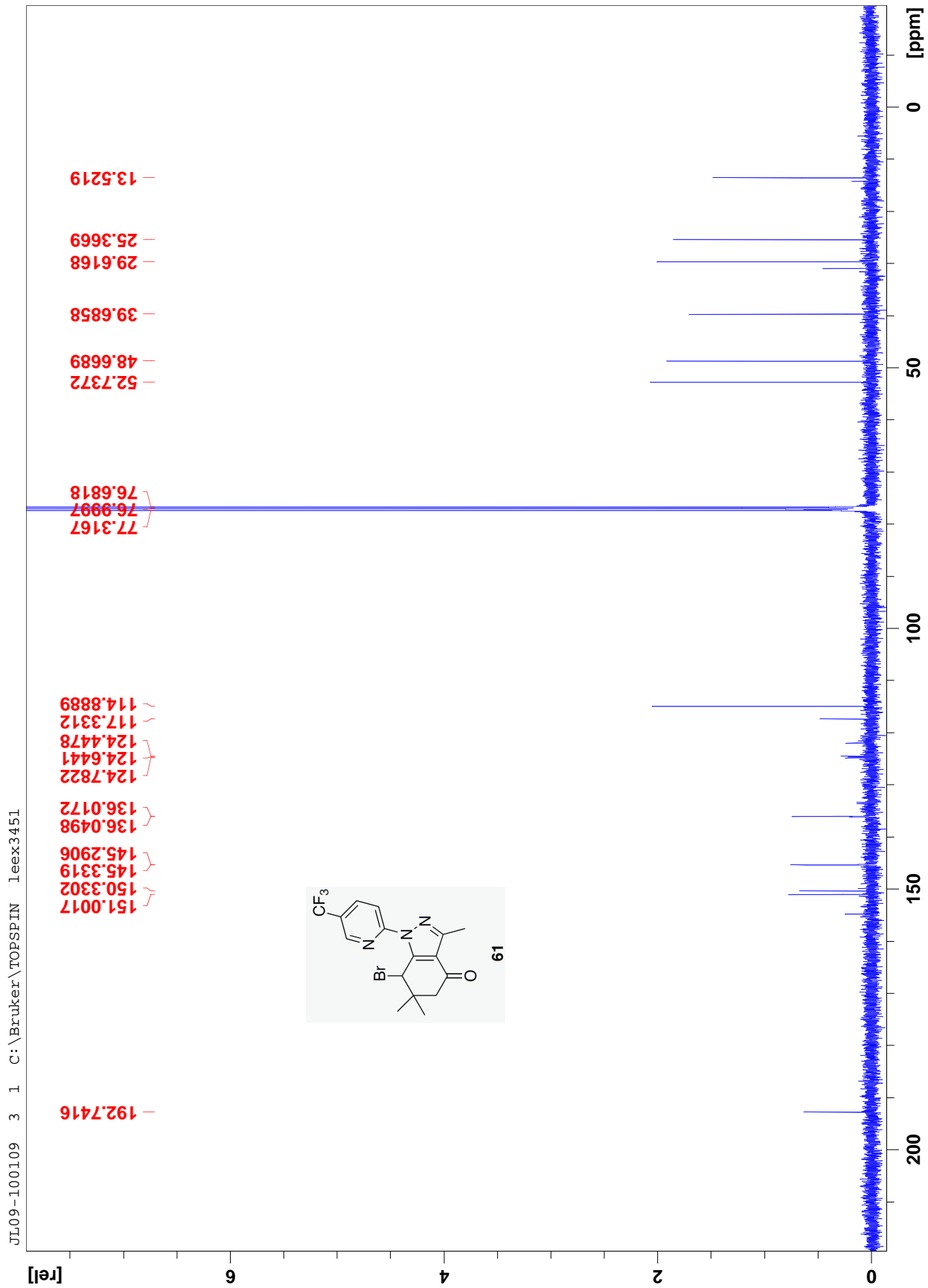
13C-NMR



1H-NMR

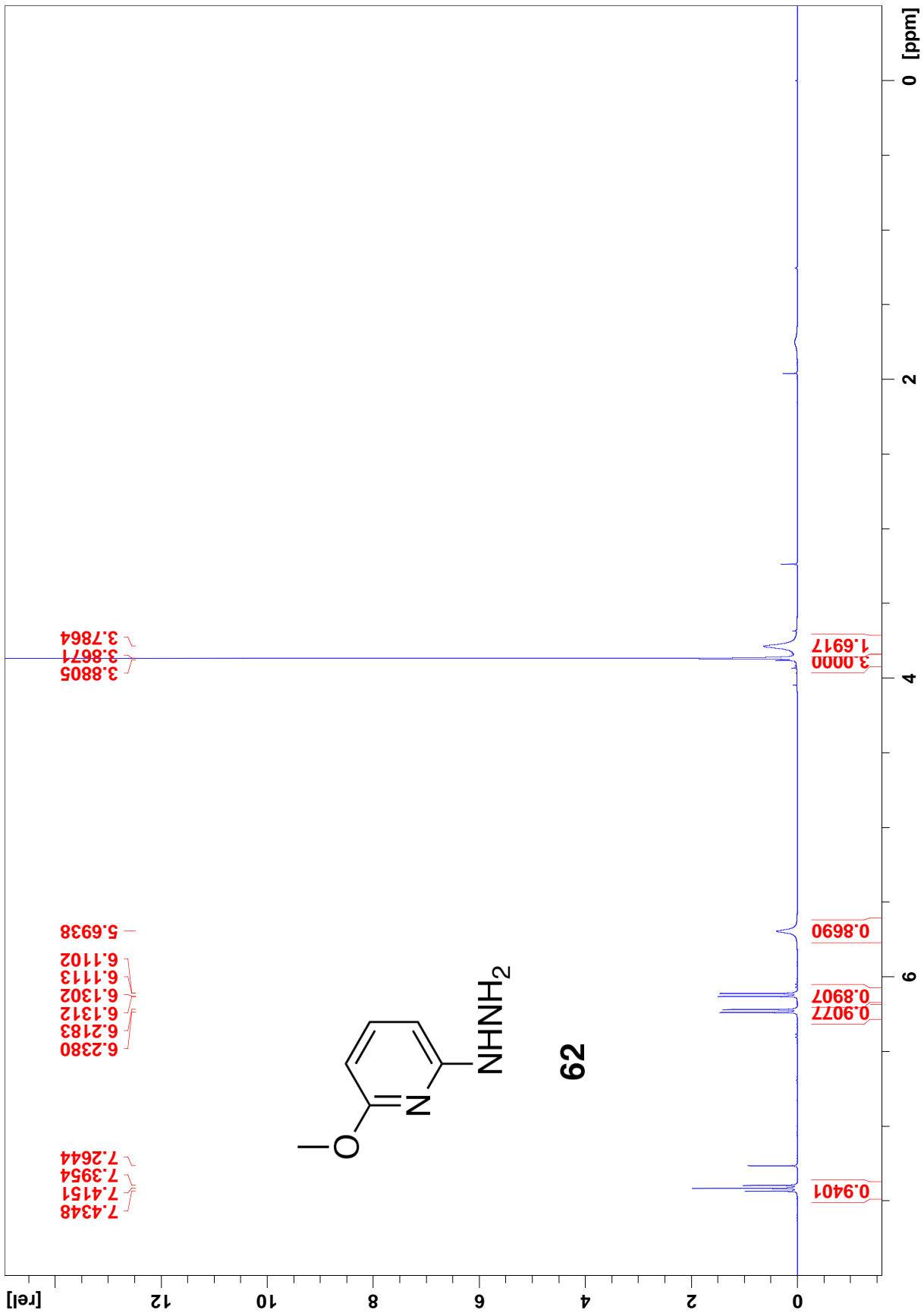


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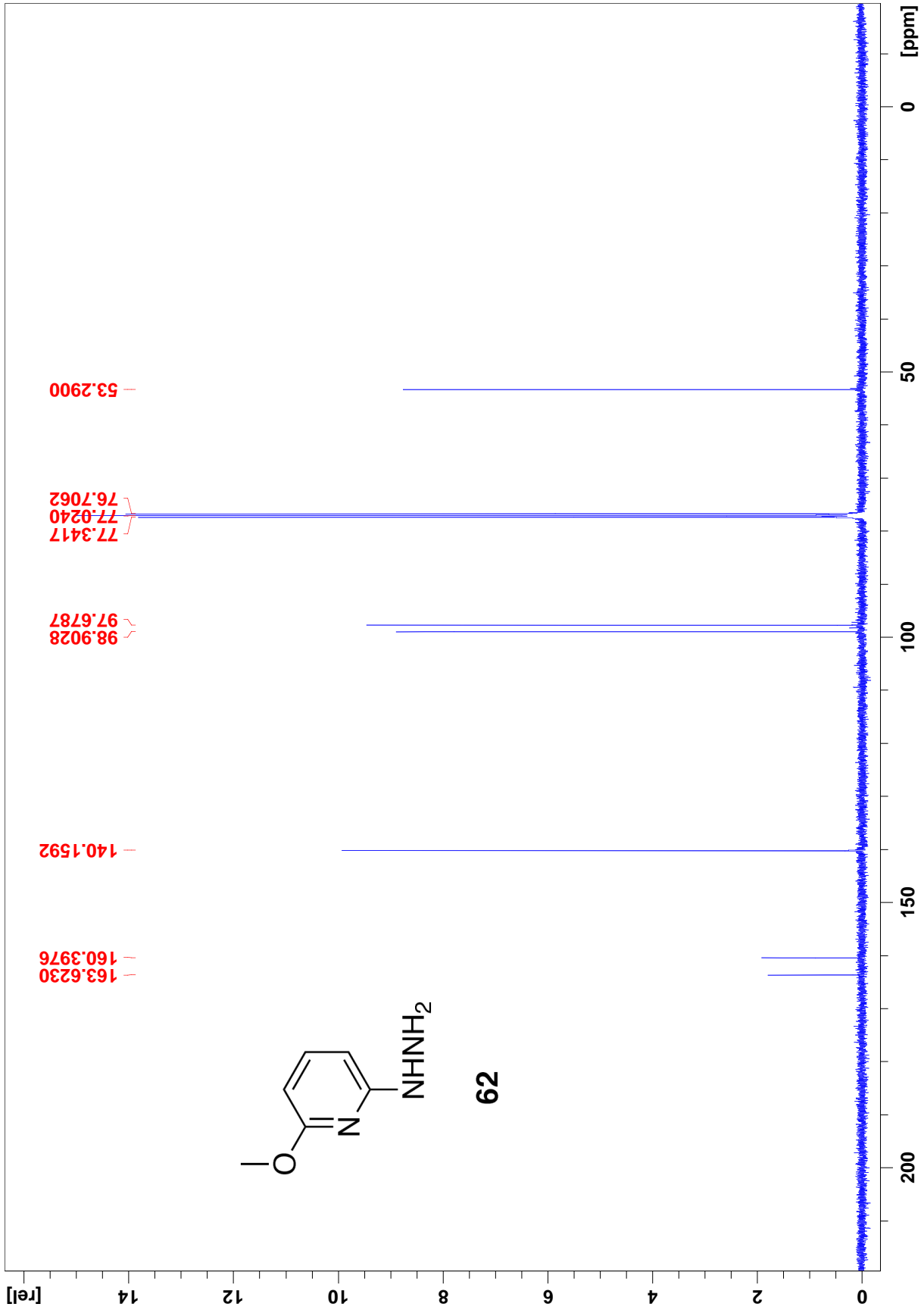
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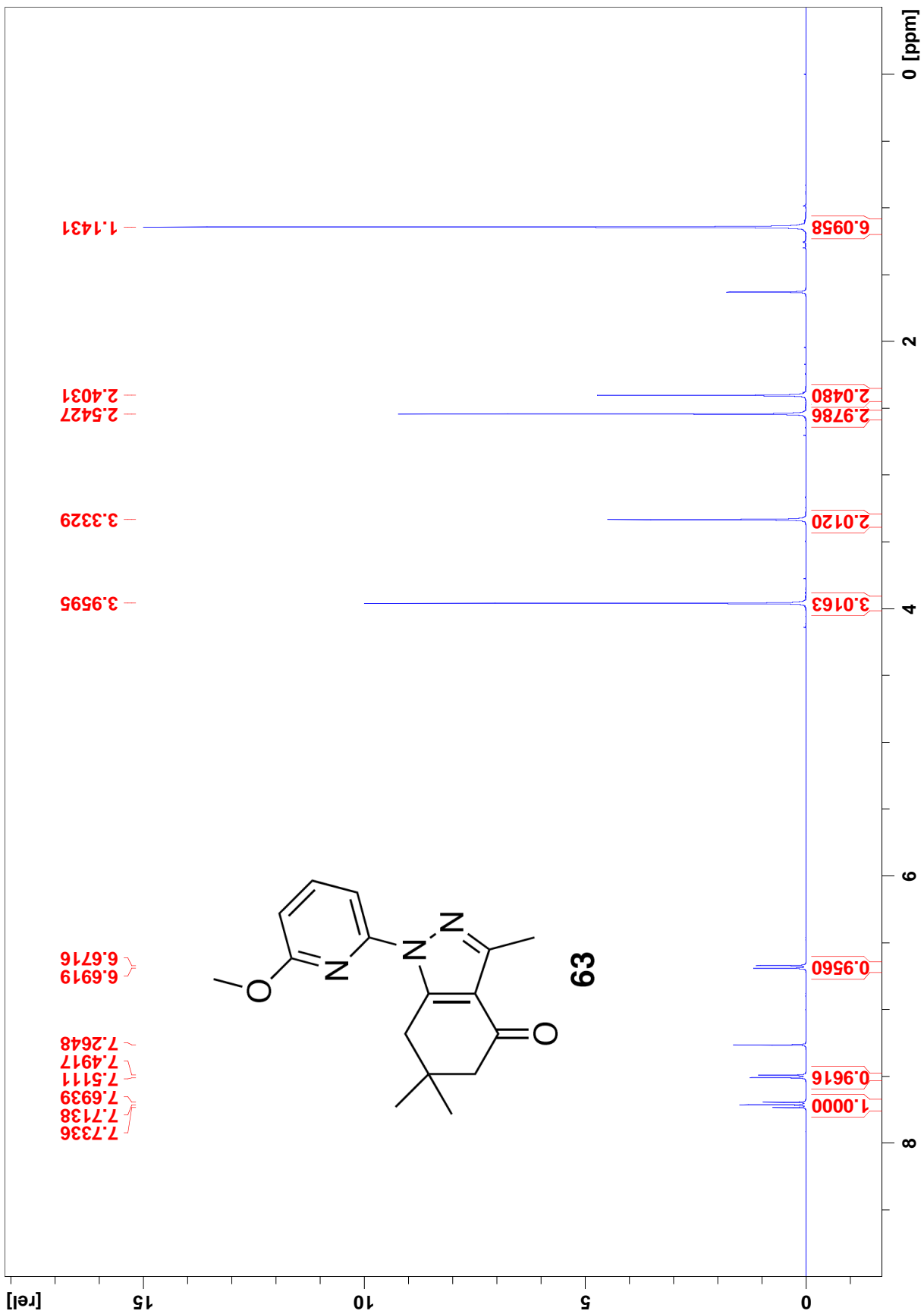
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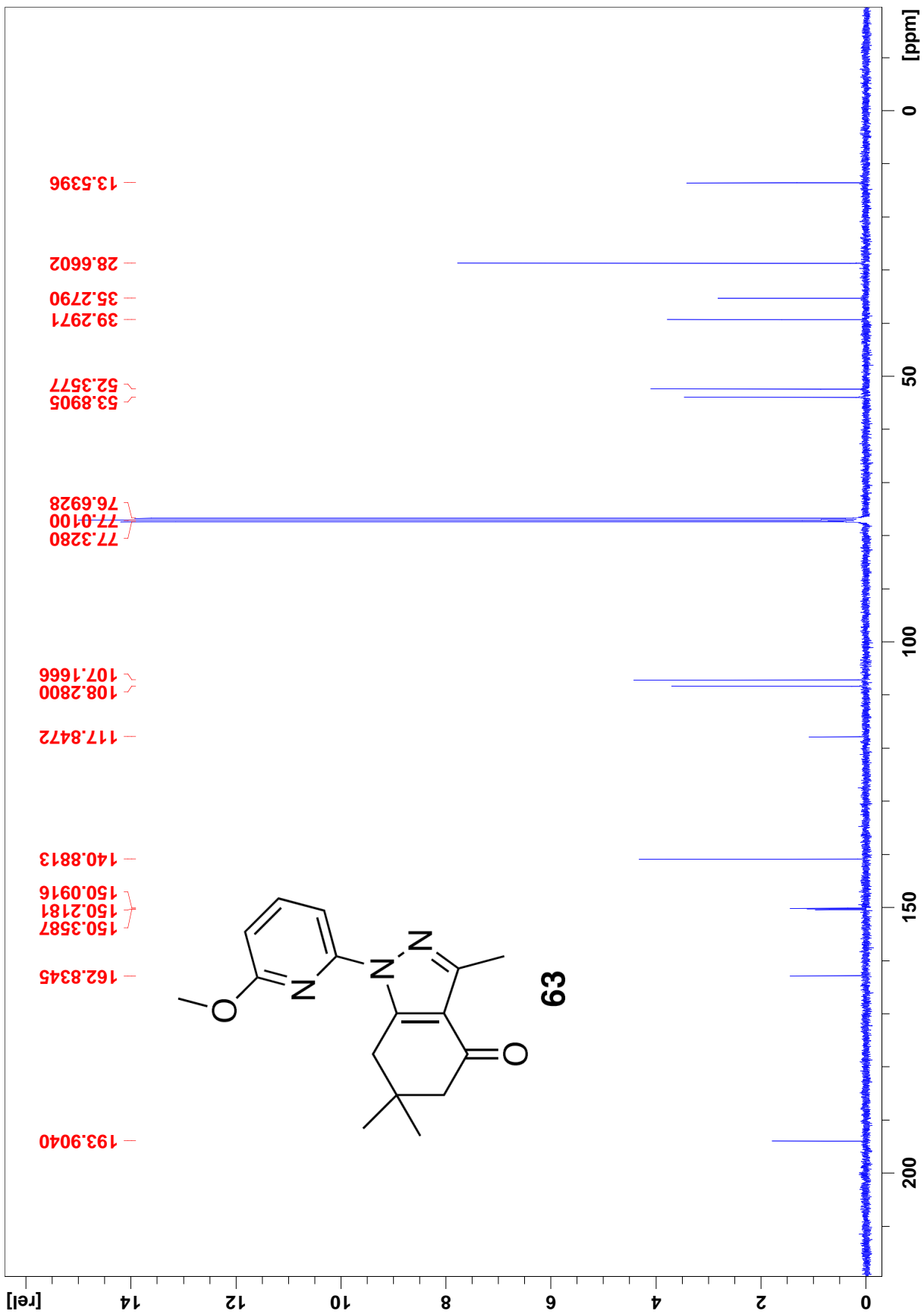
1H-NMR

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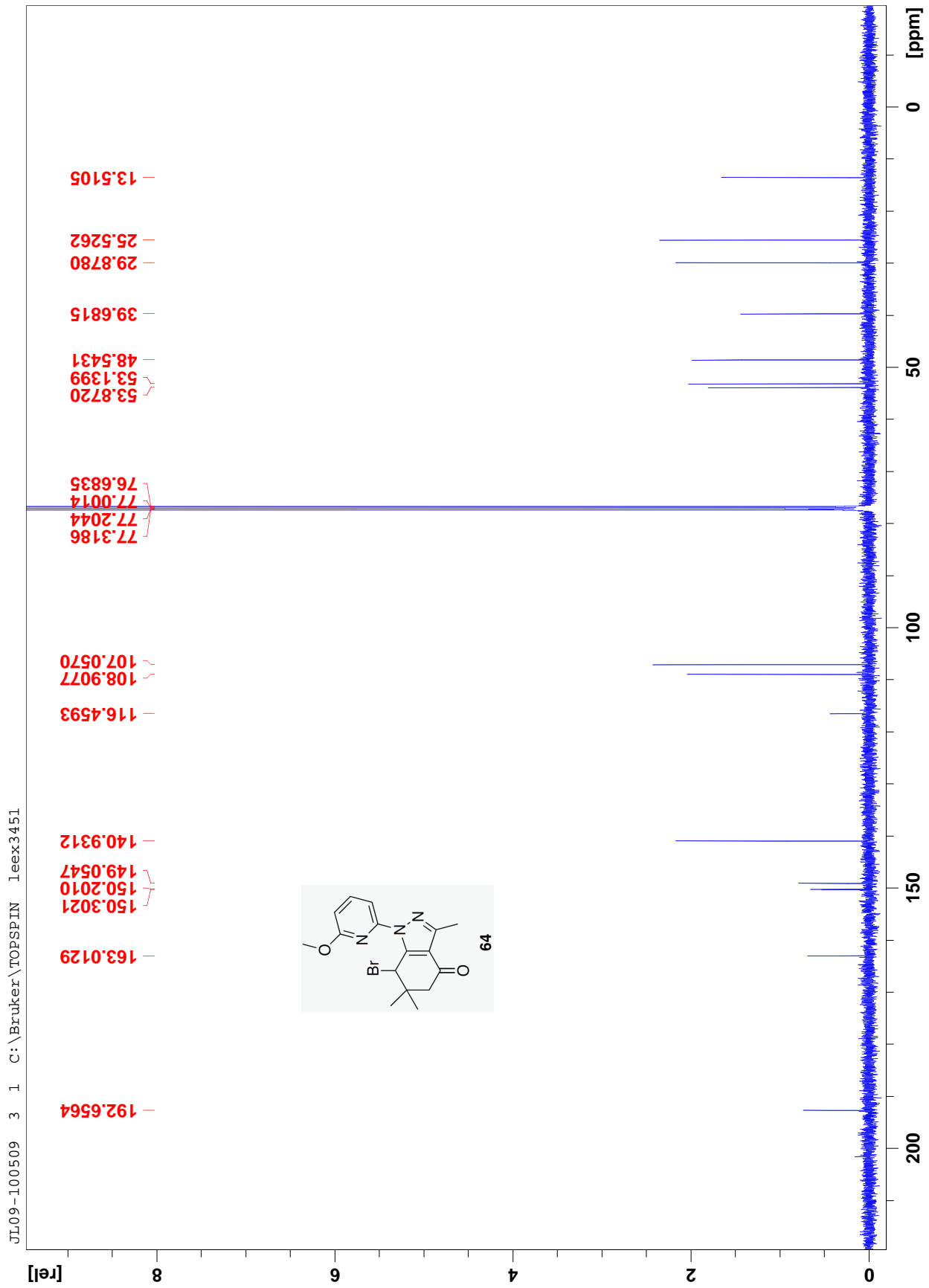


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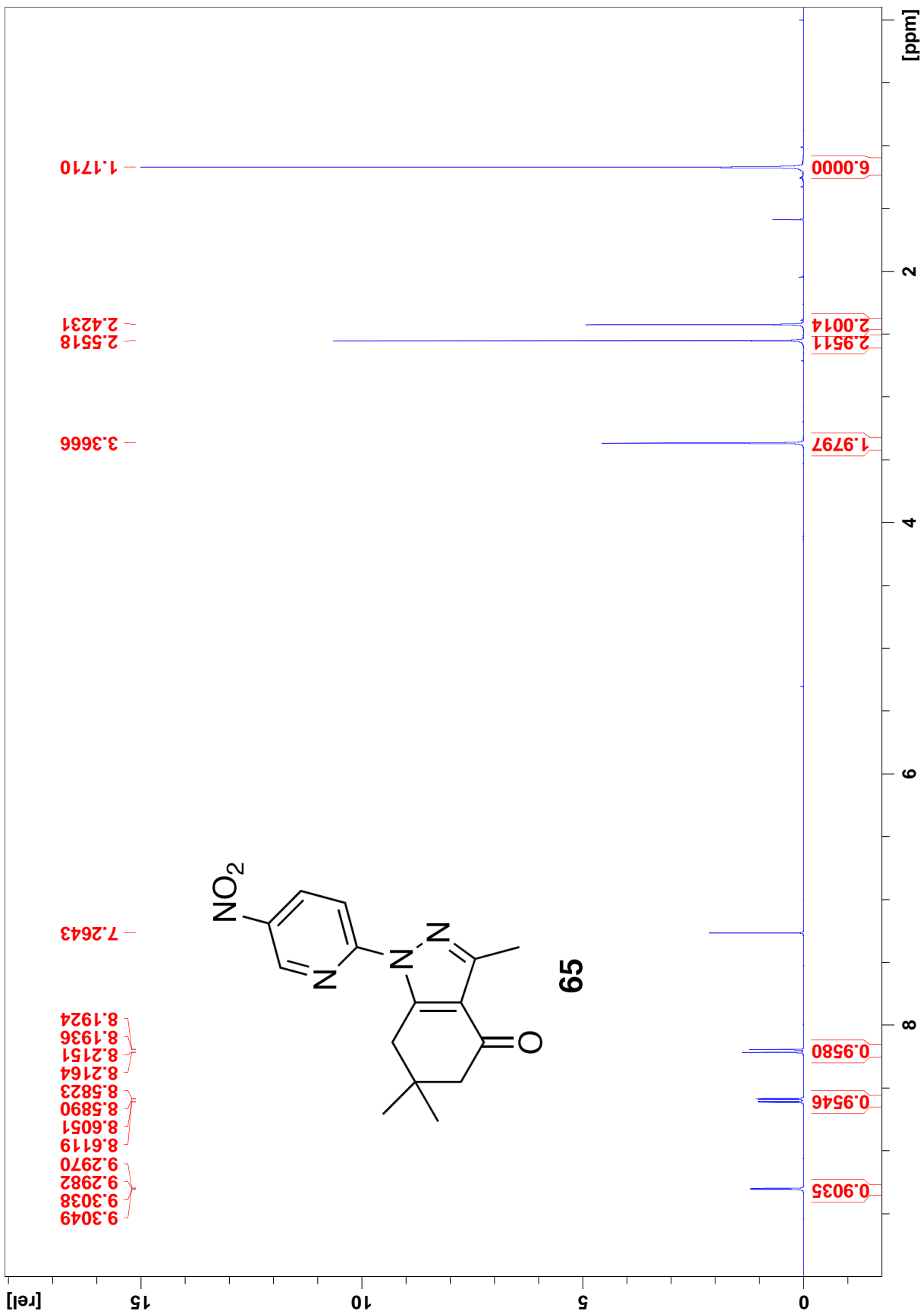


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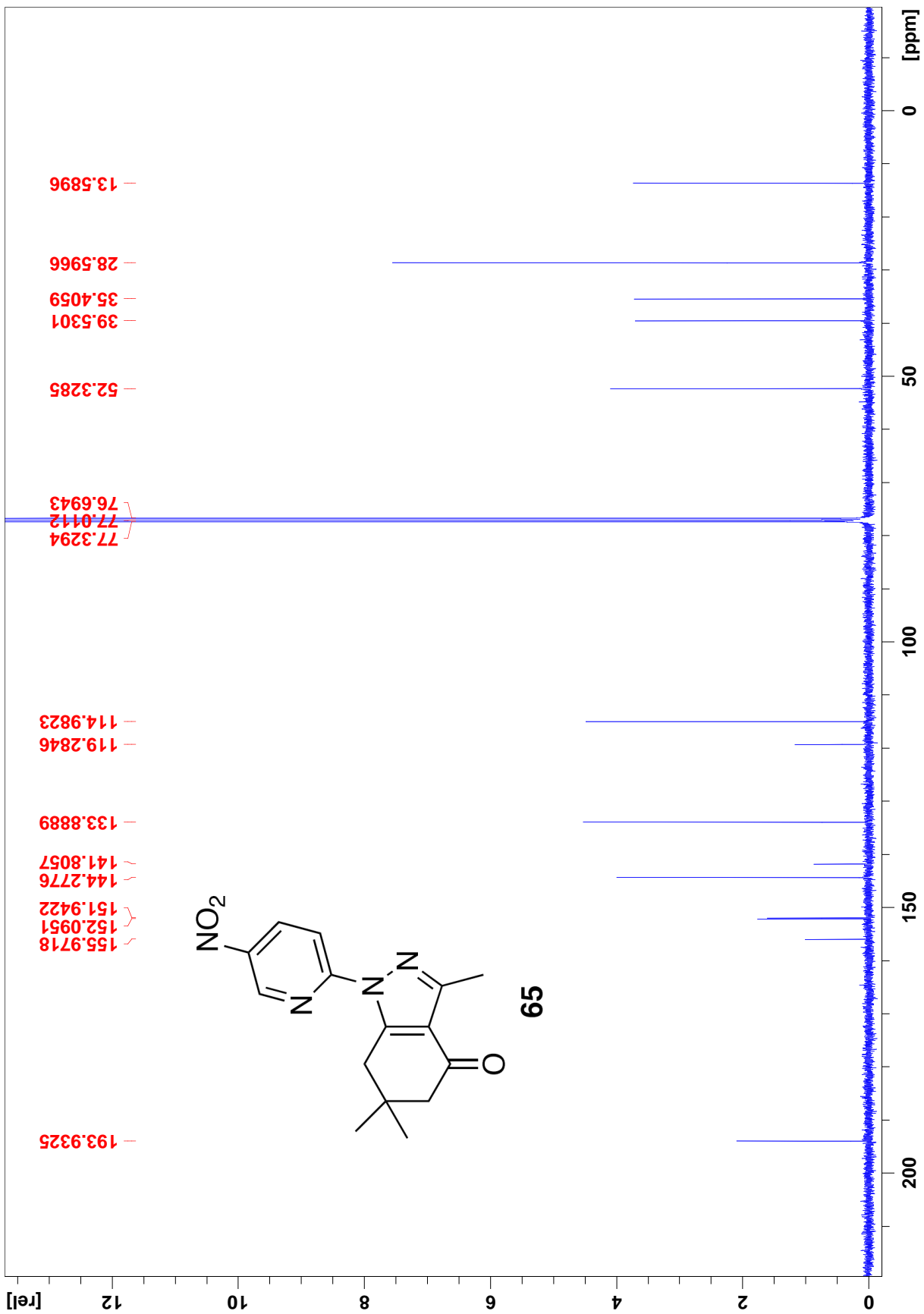
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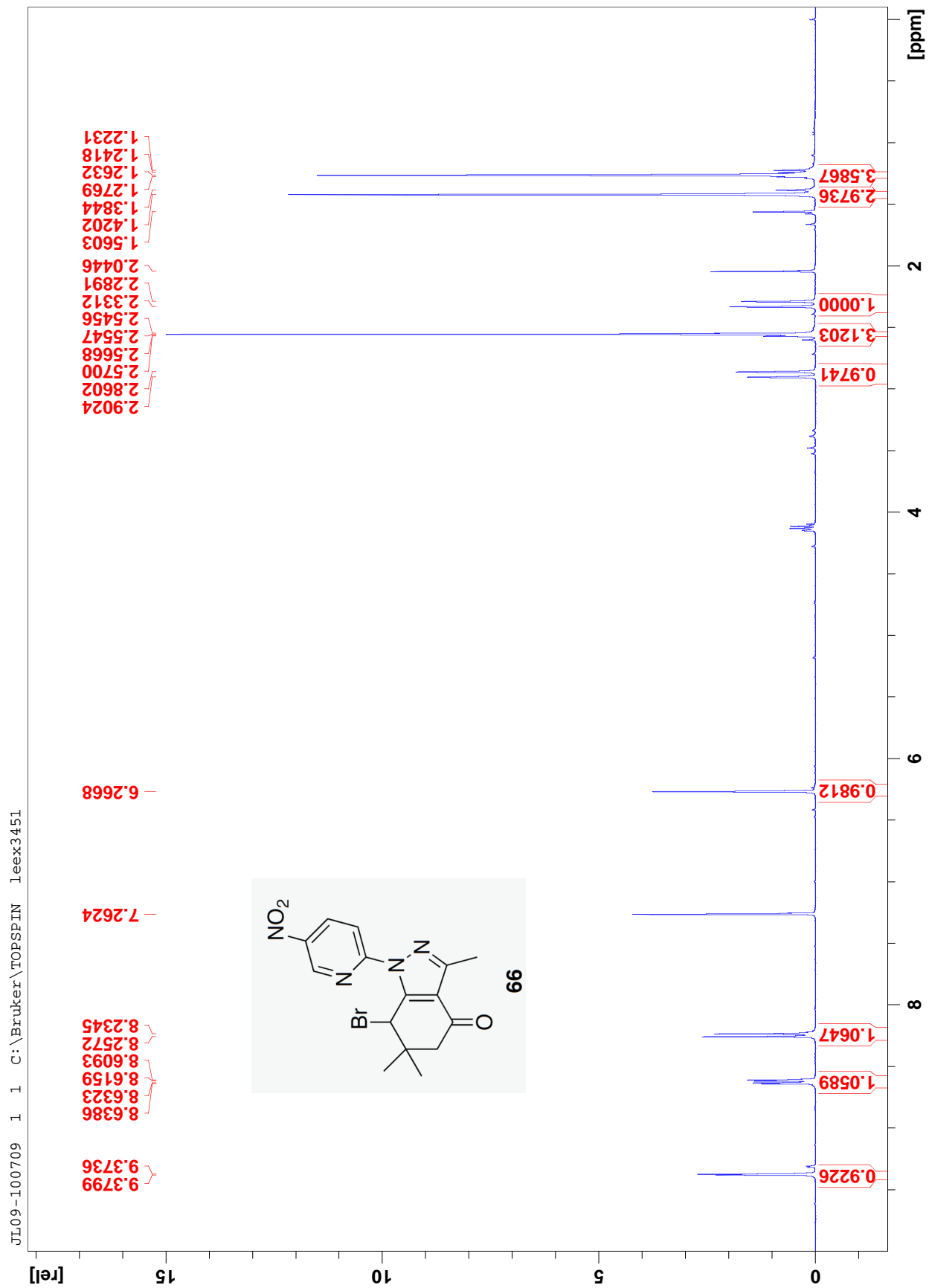


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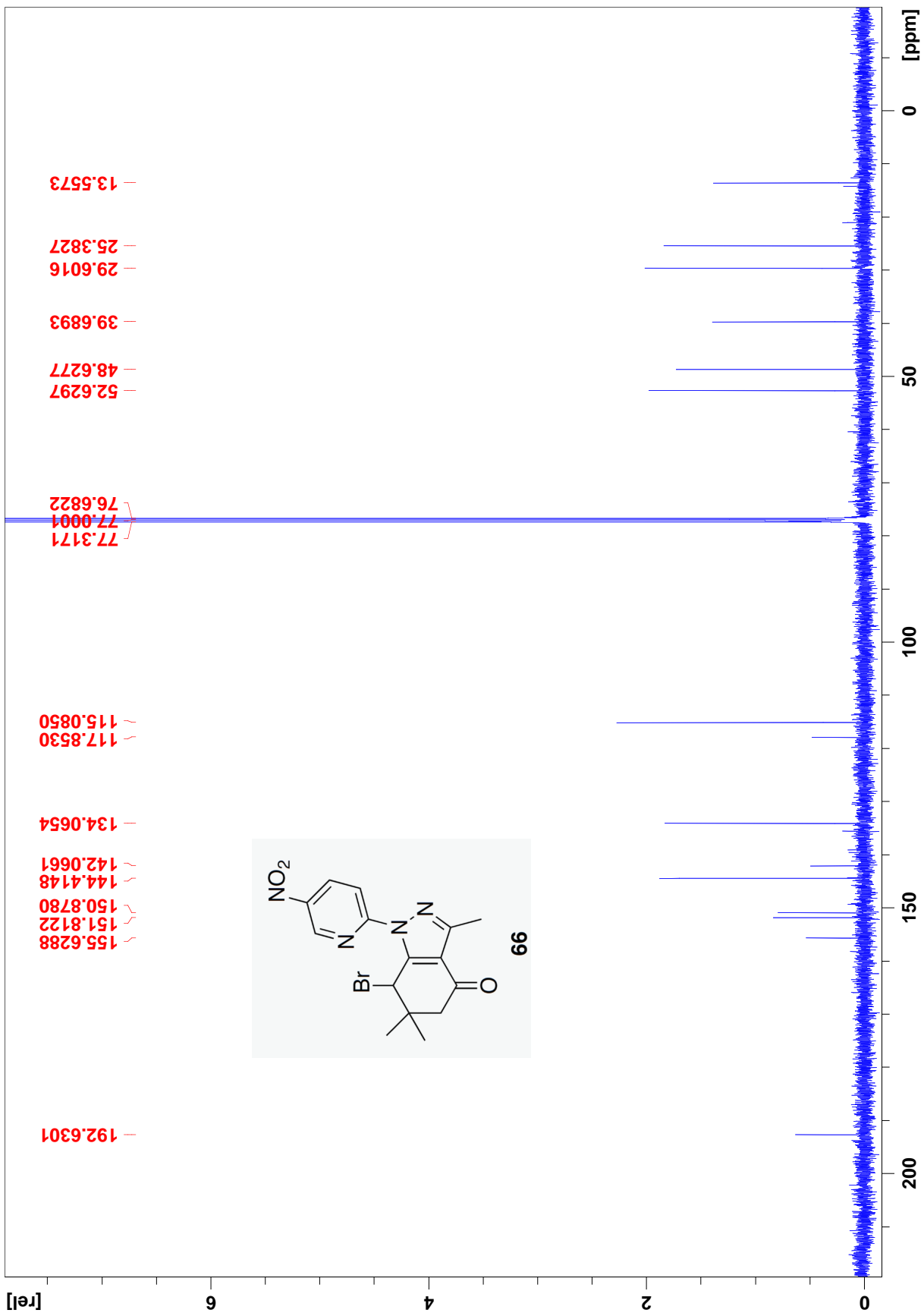


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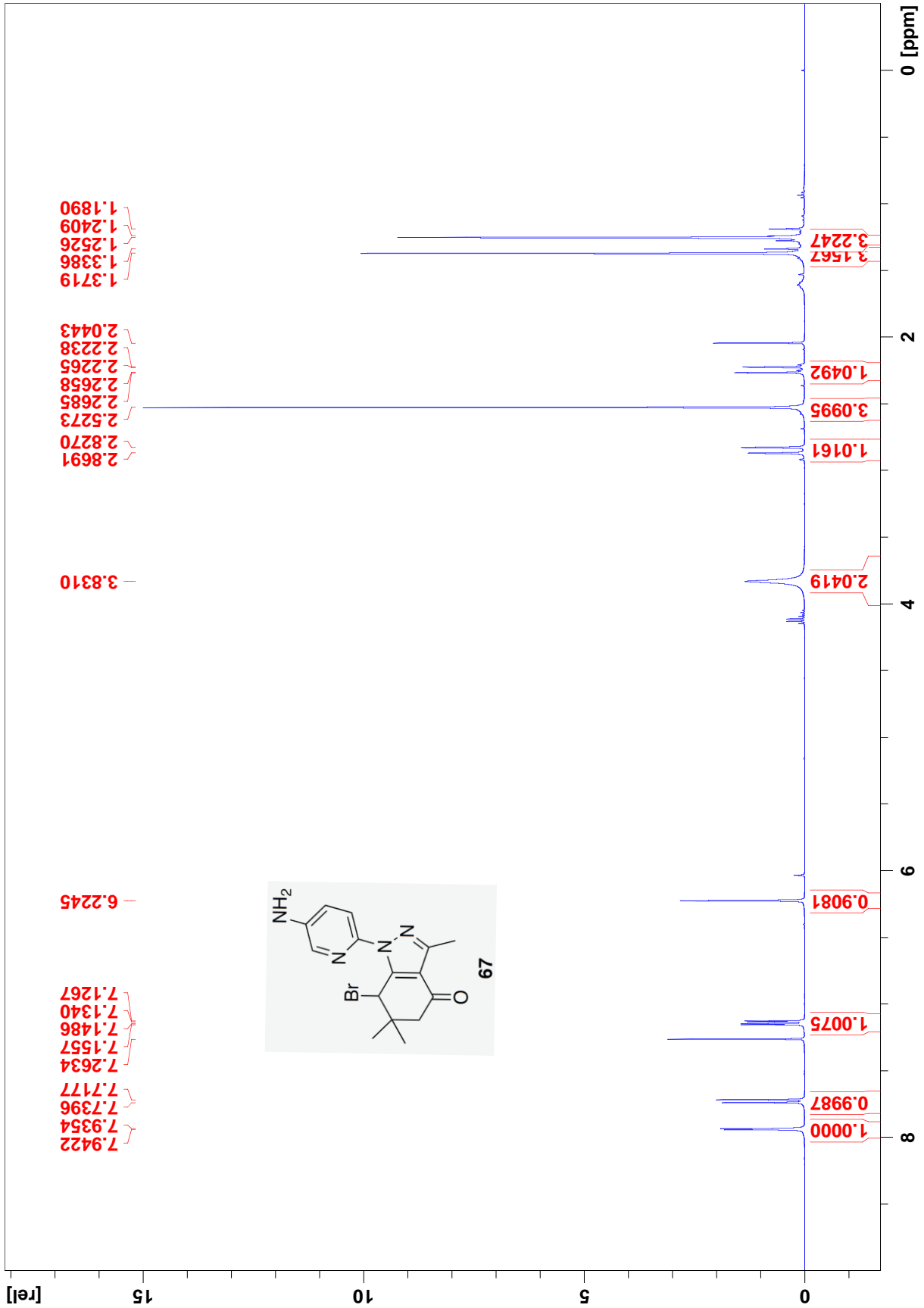
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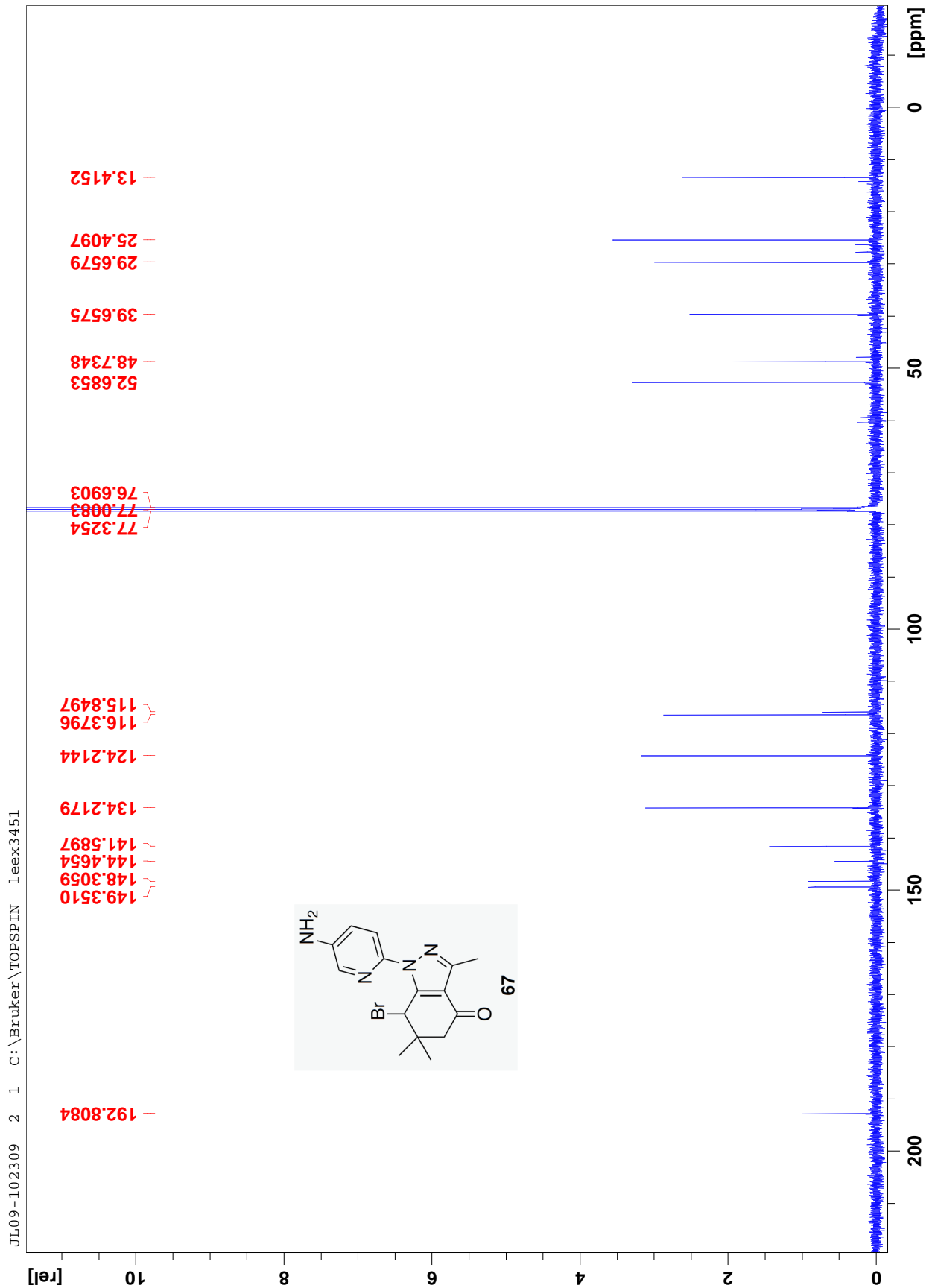


1H-NMR

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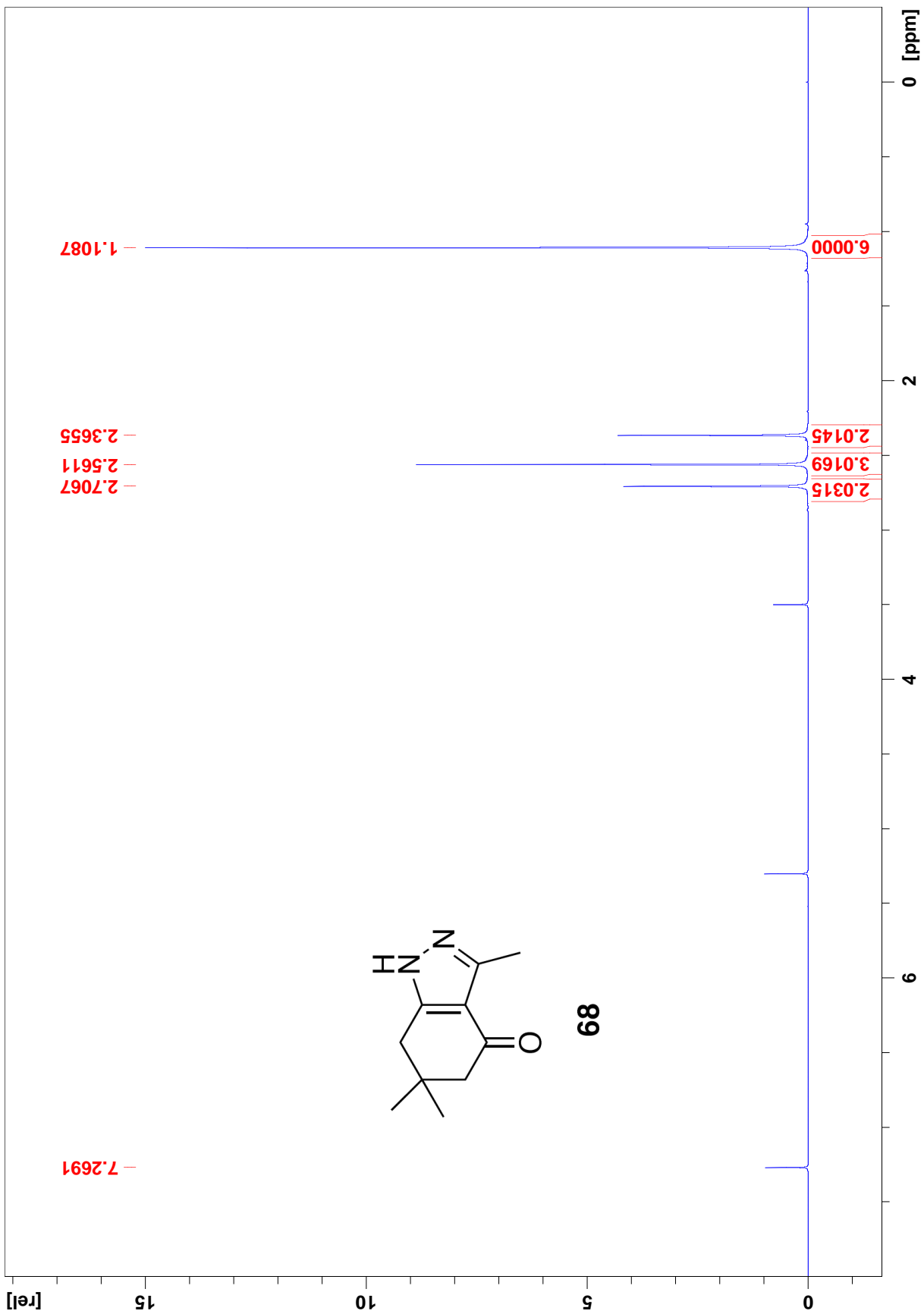


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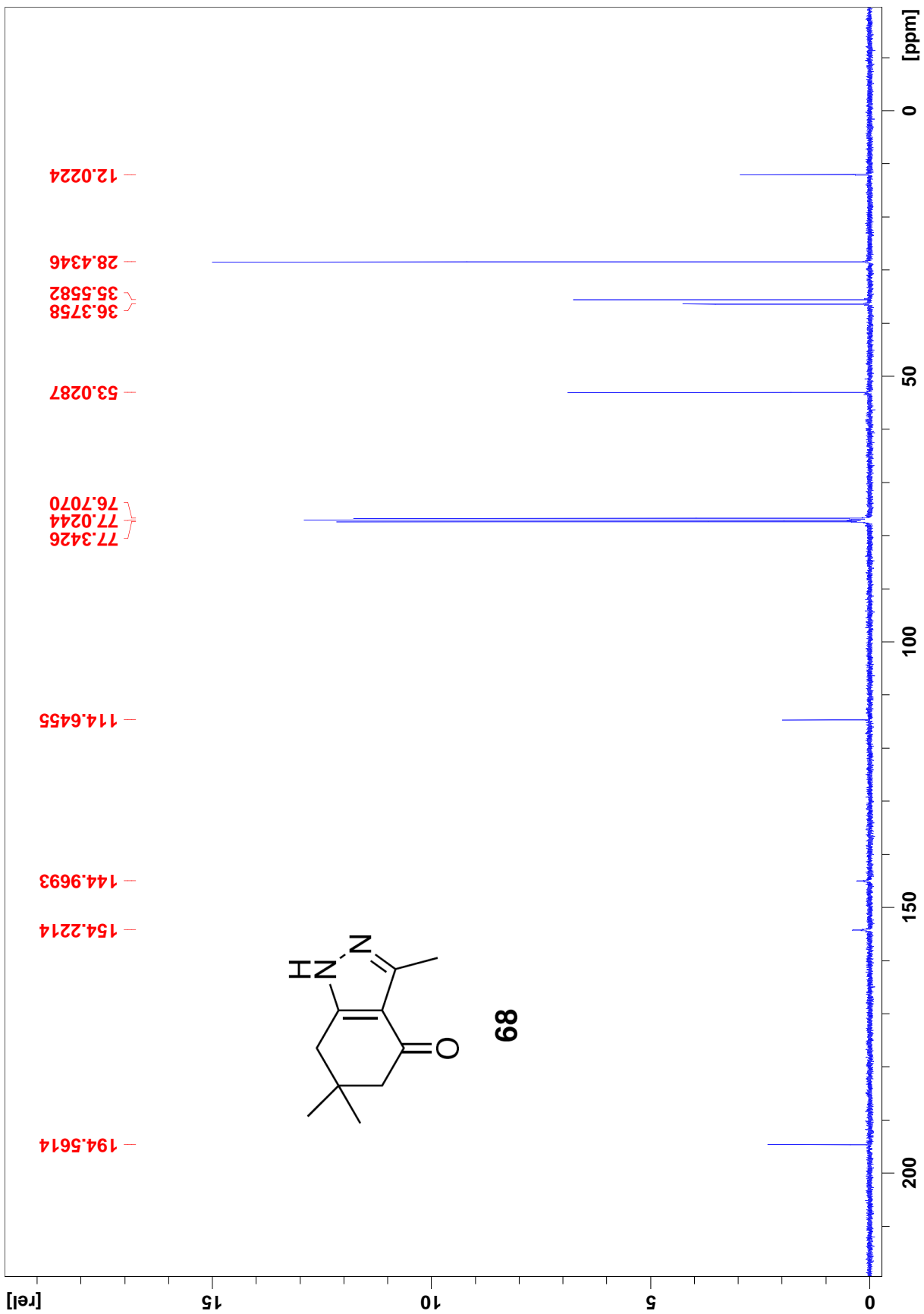
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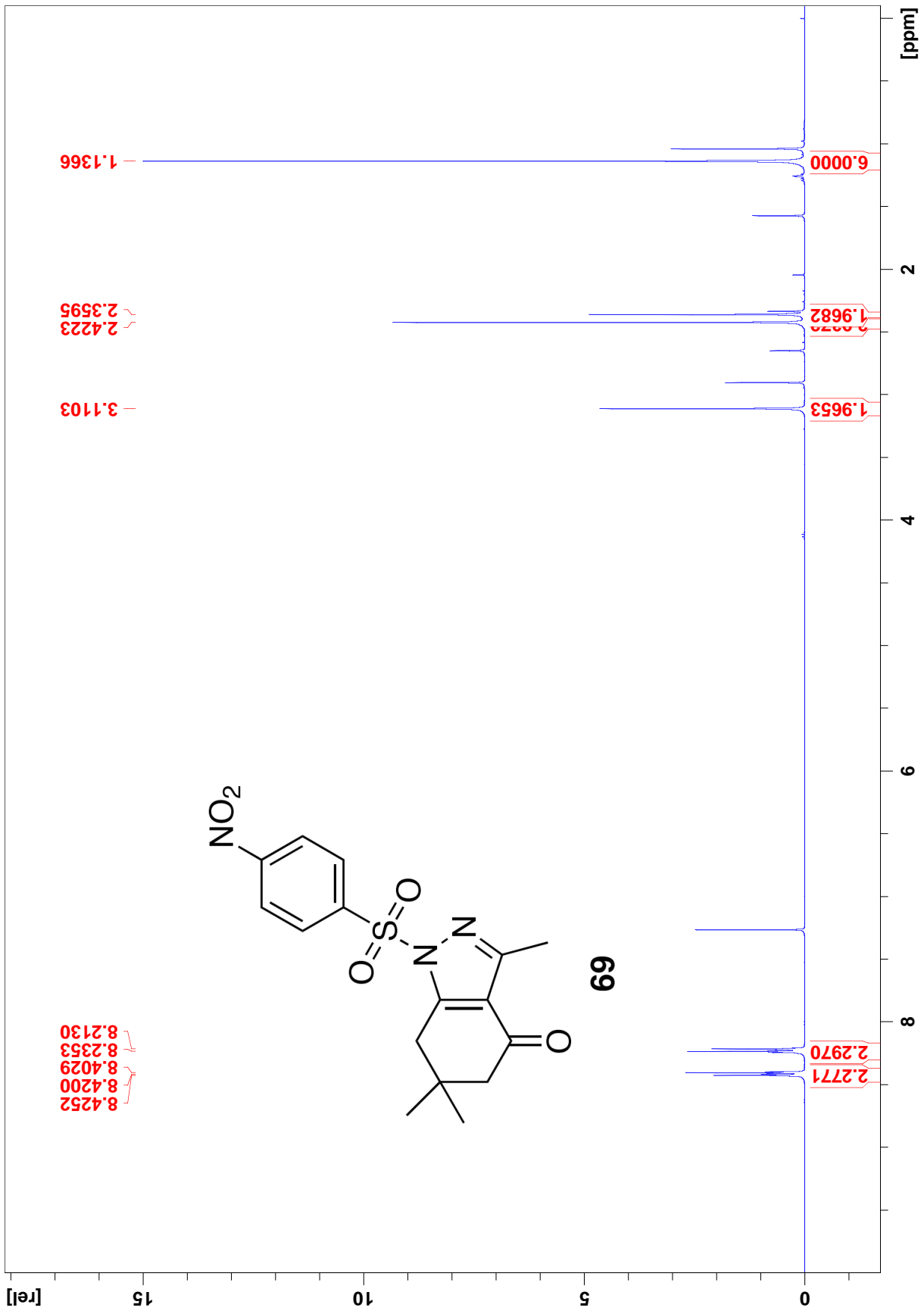
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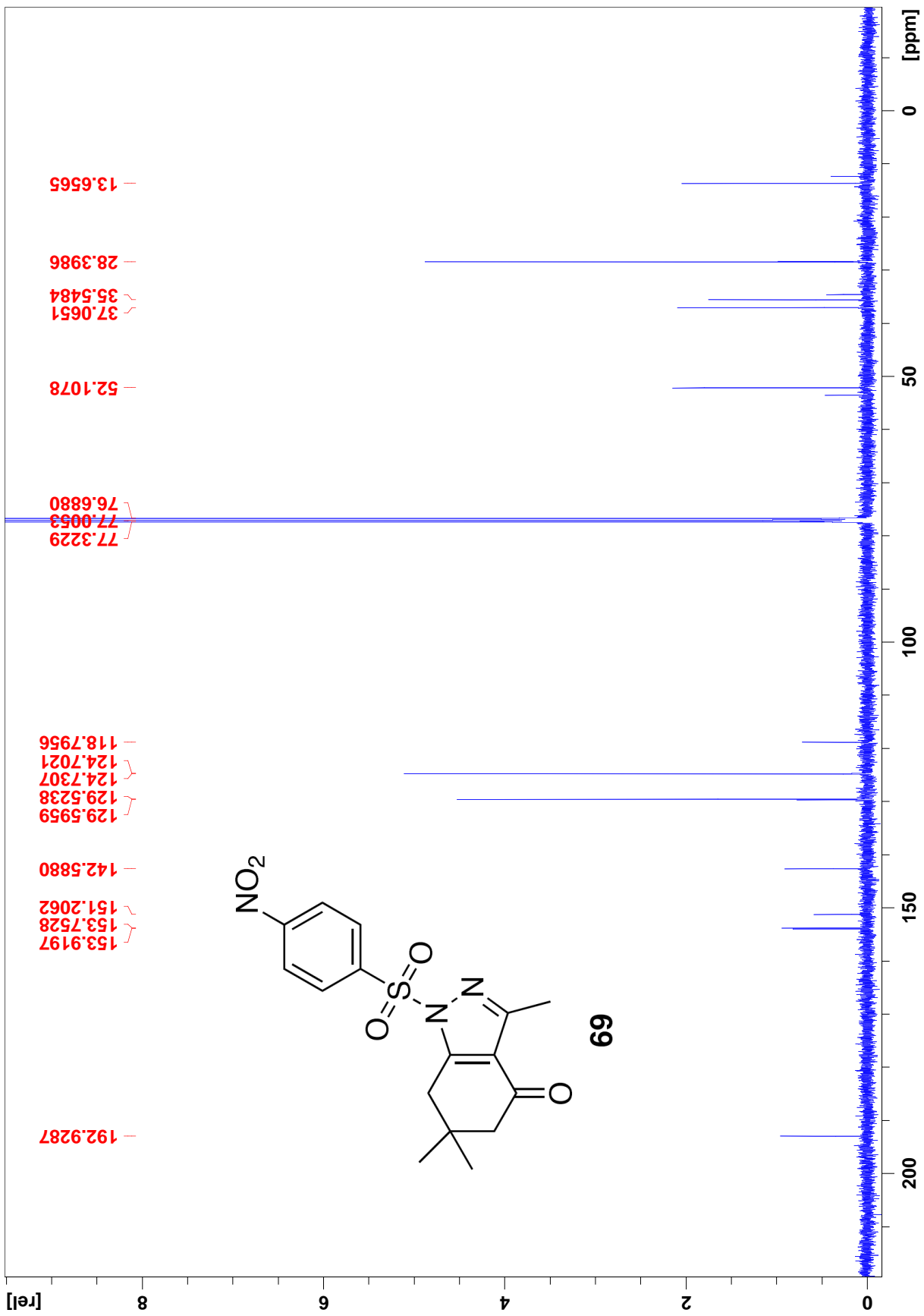
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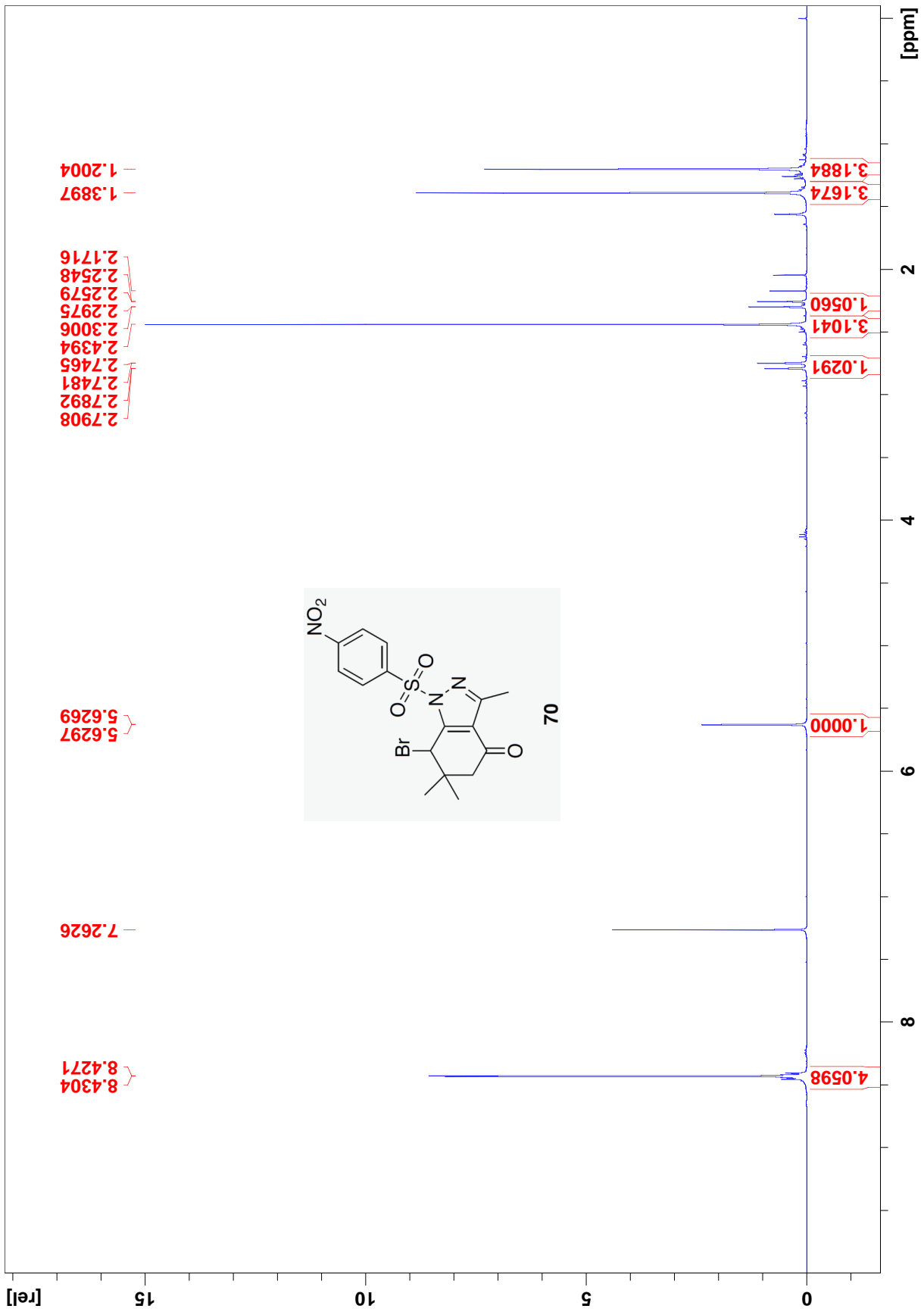
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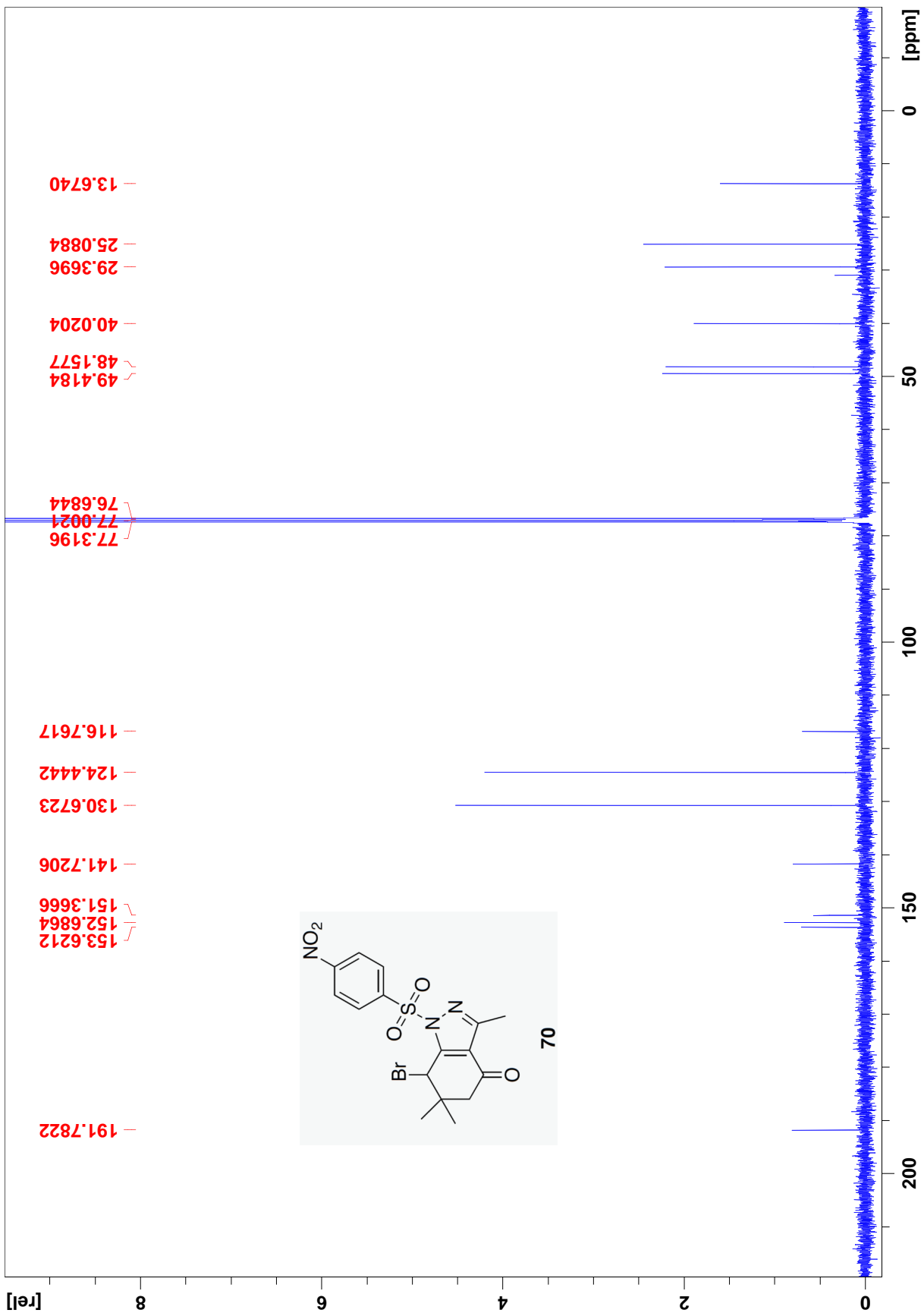
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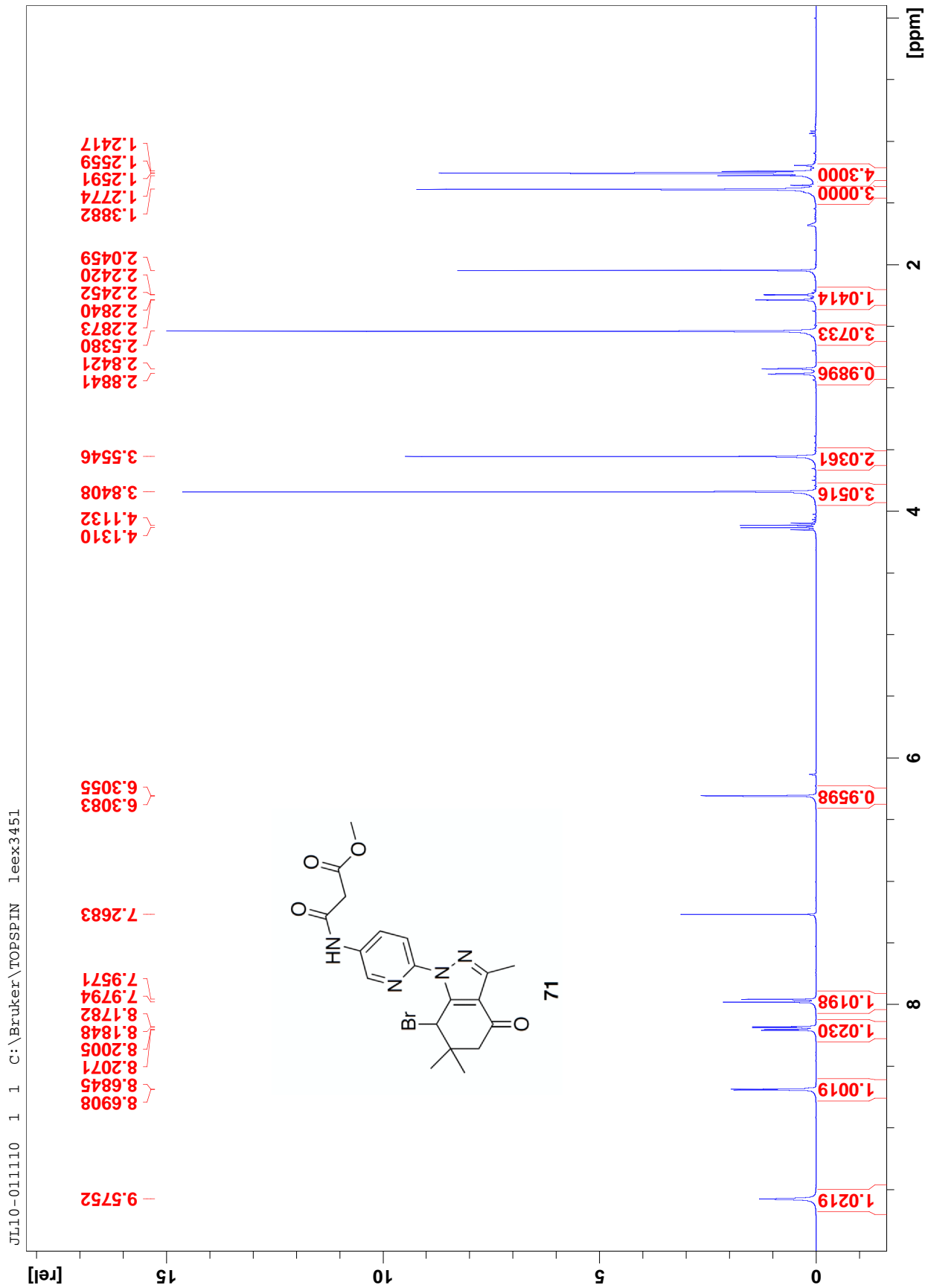


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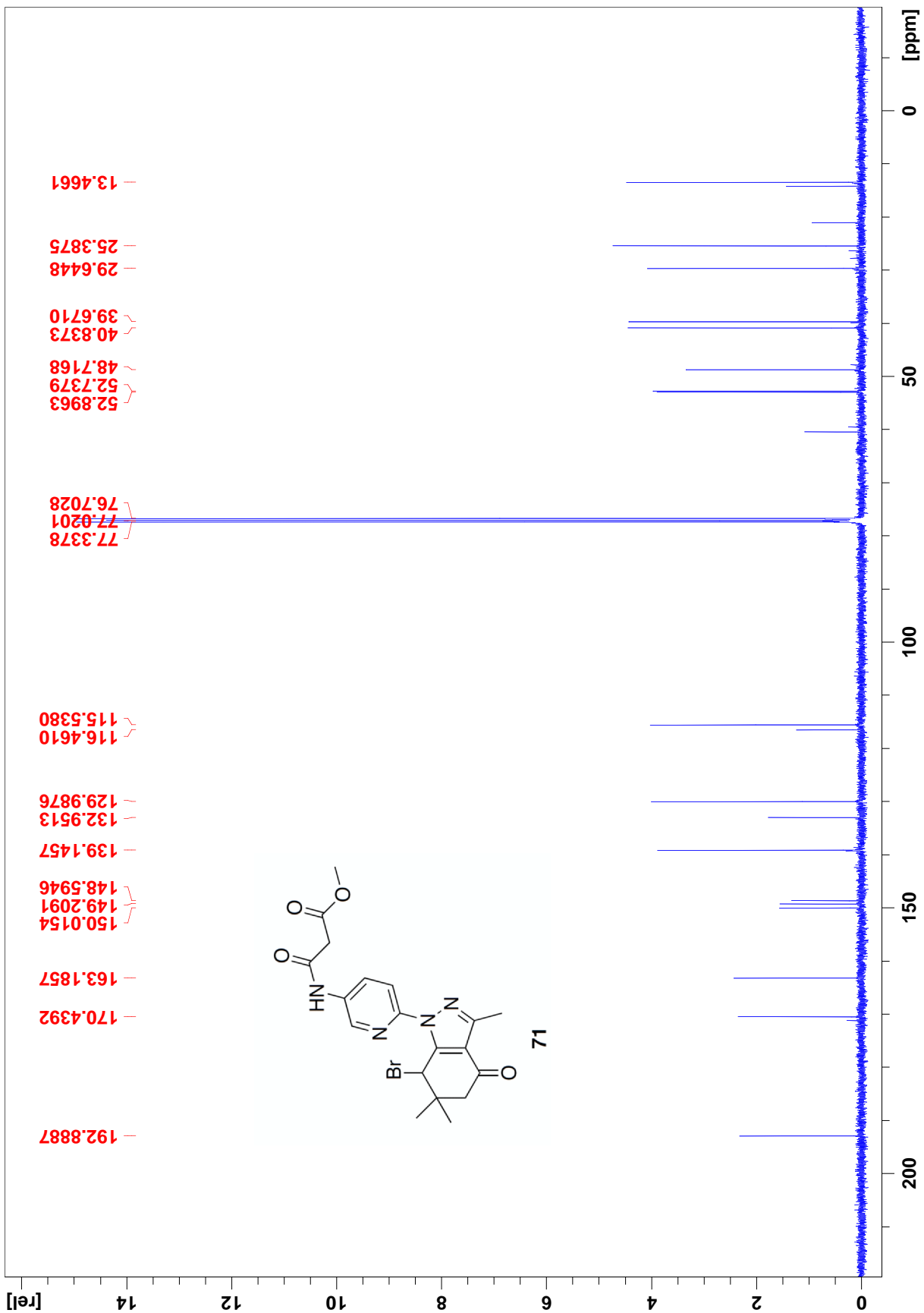


1H-NMR



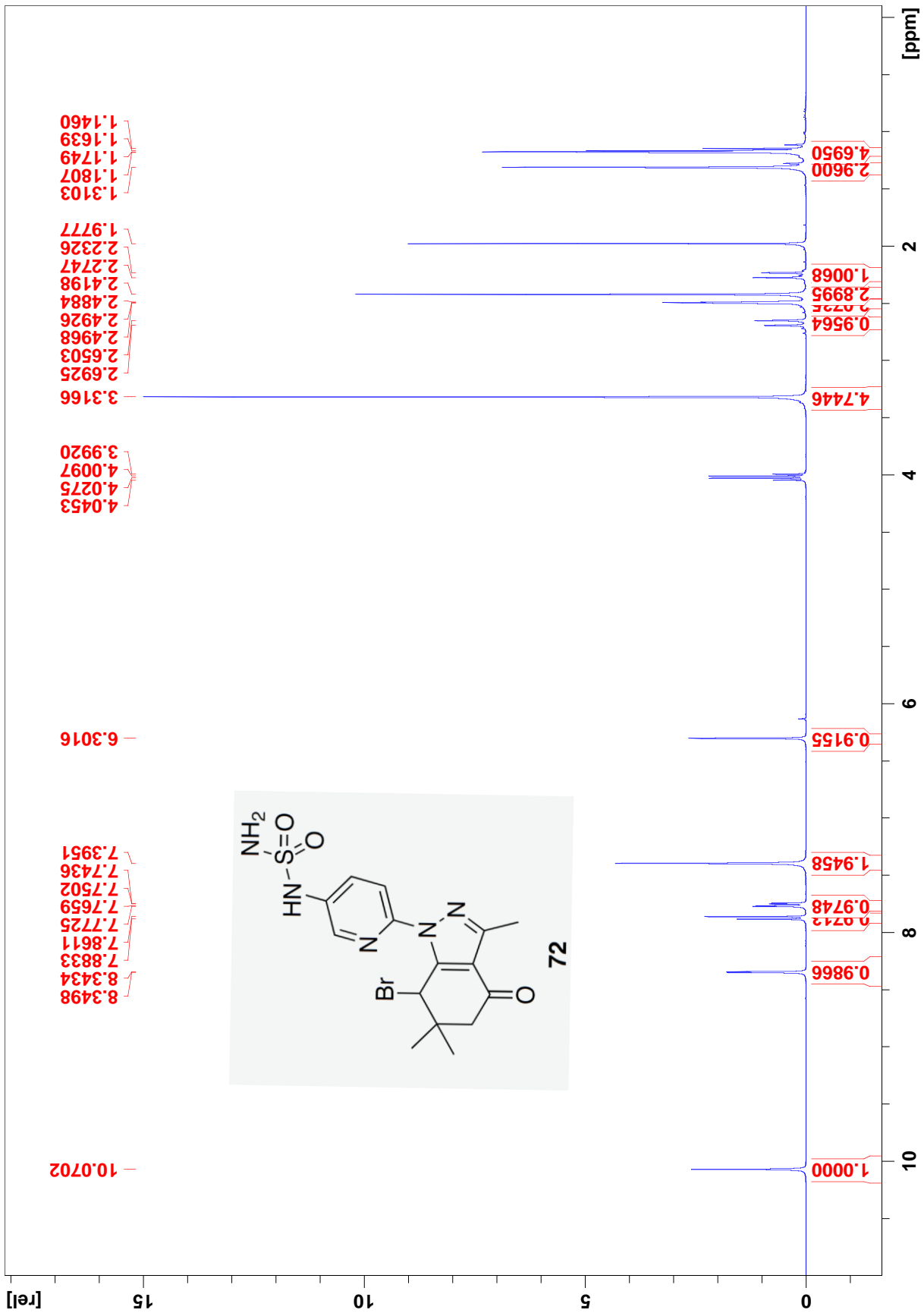
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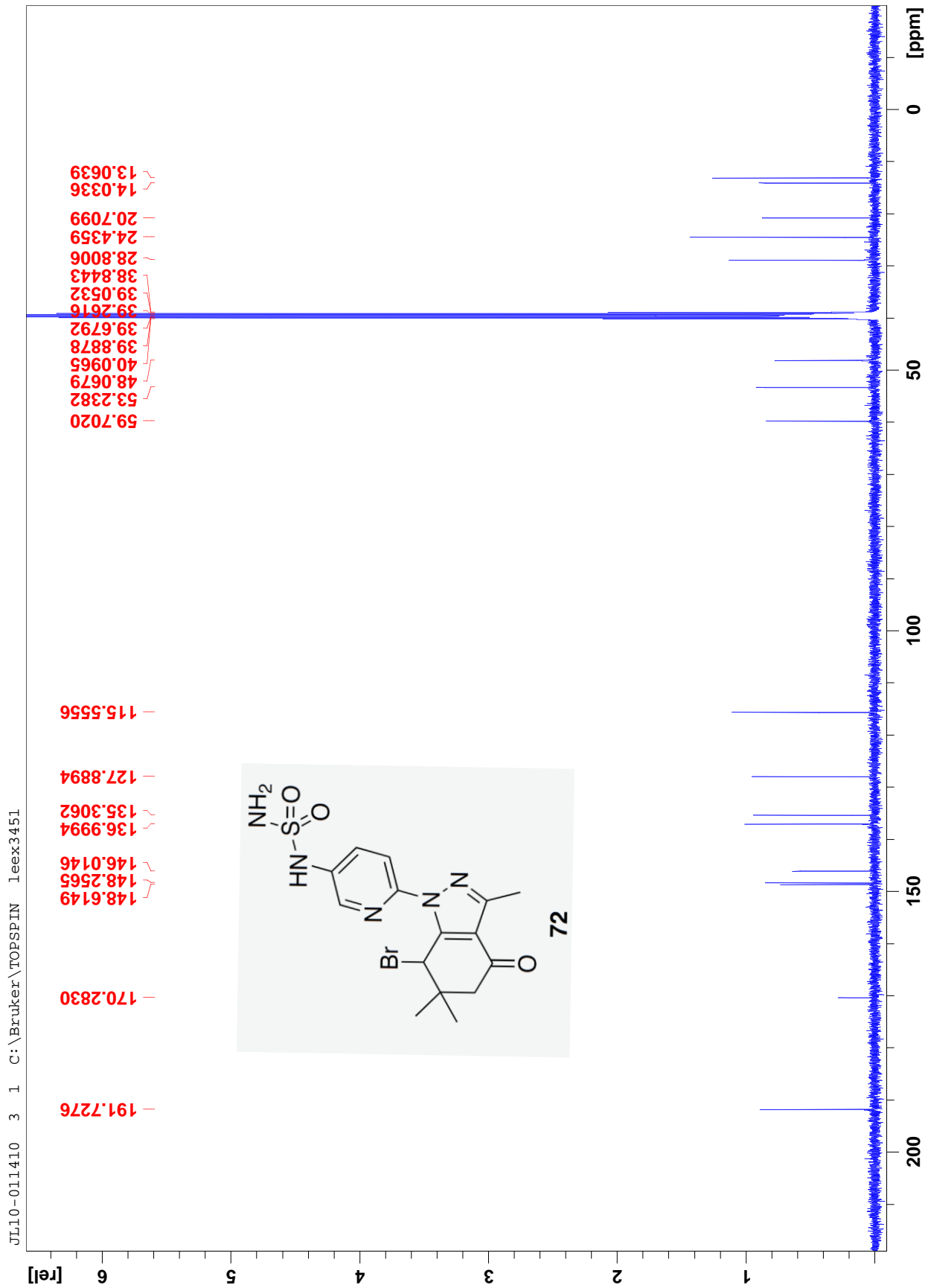


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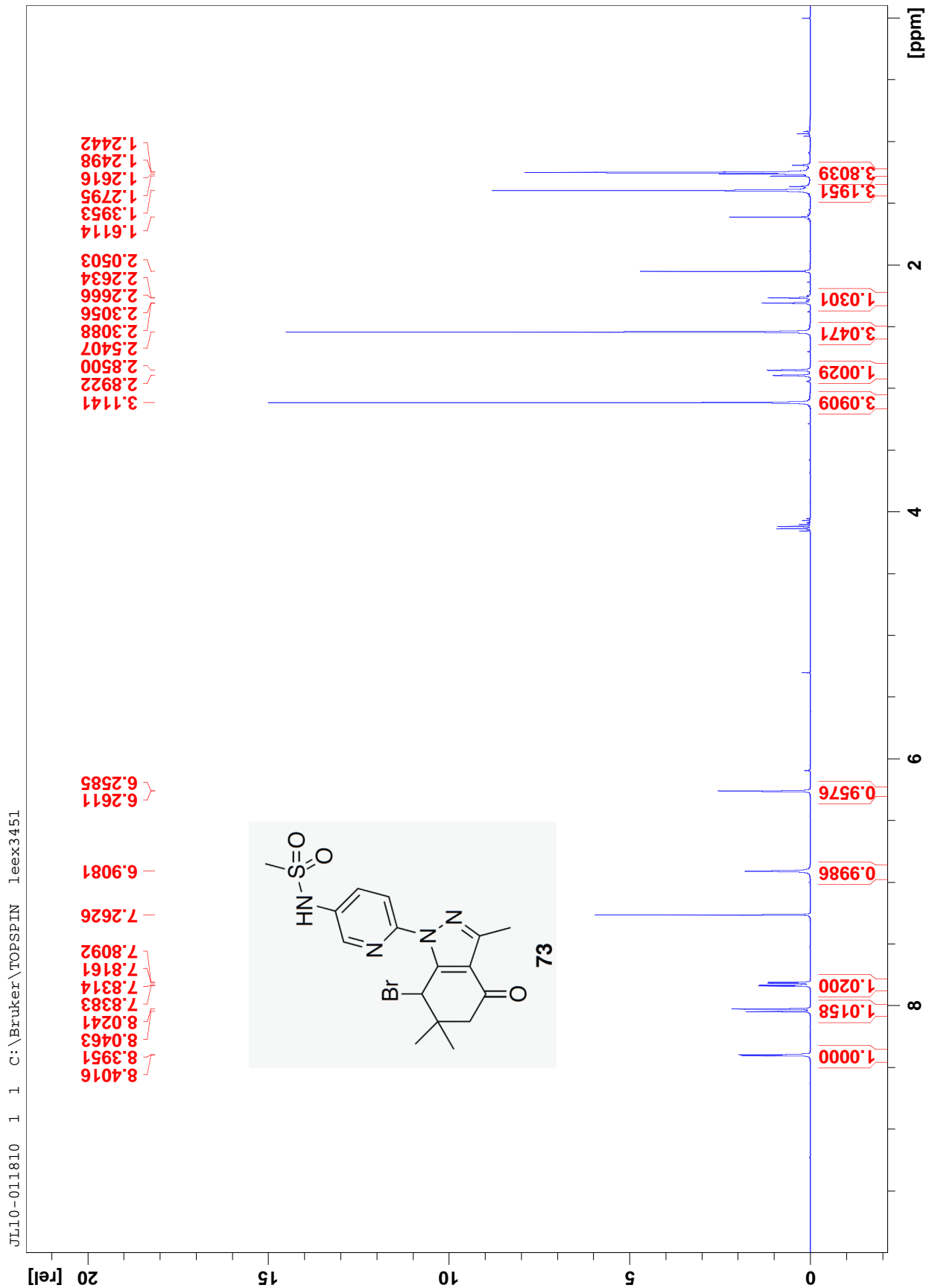
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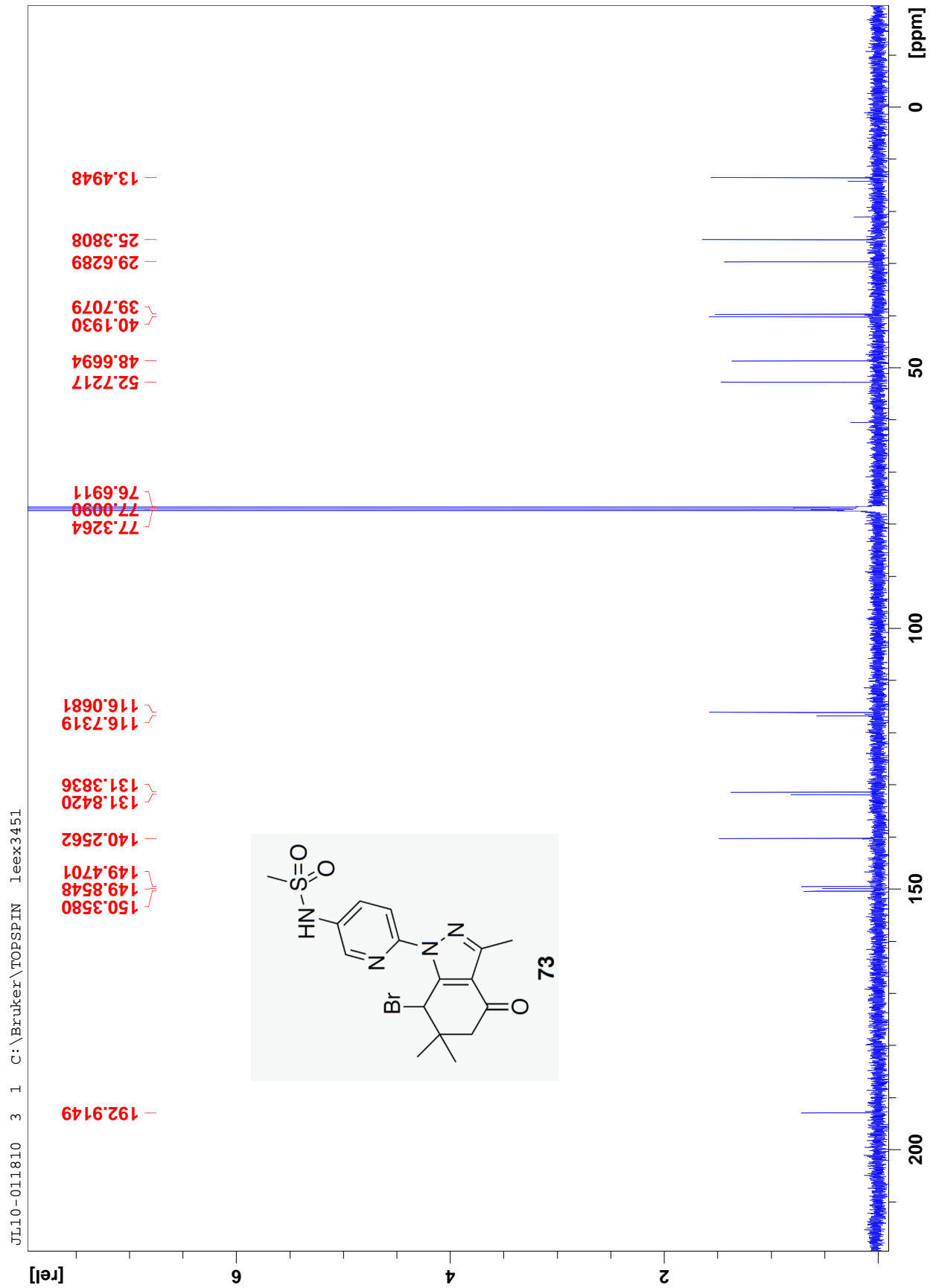
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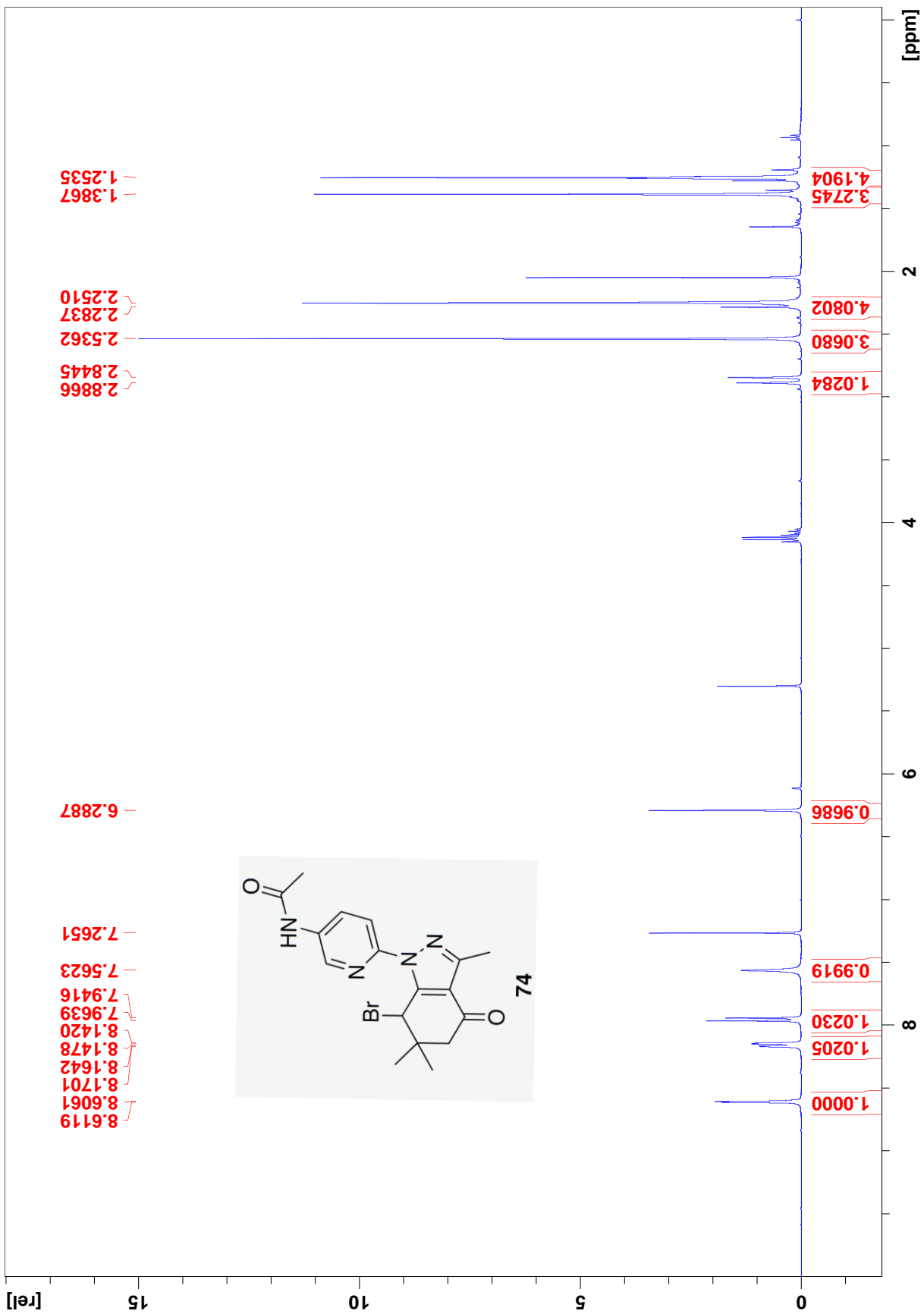


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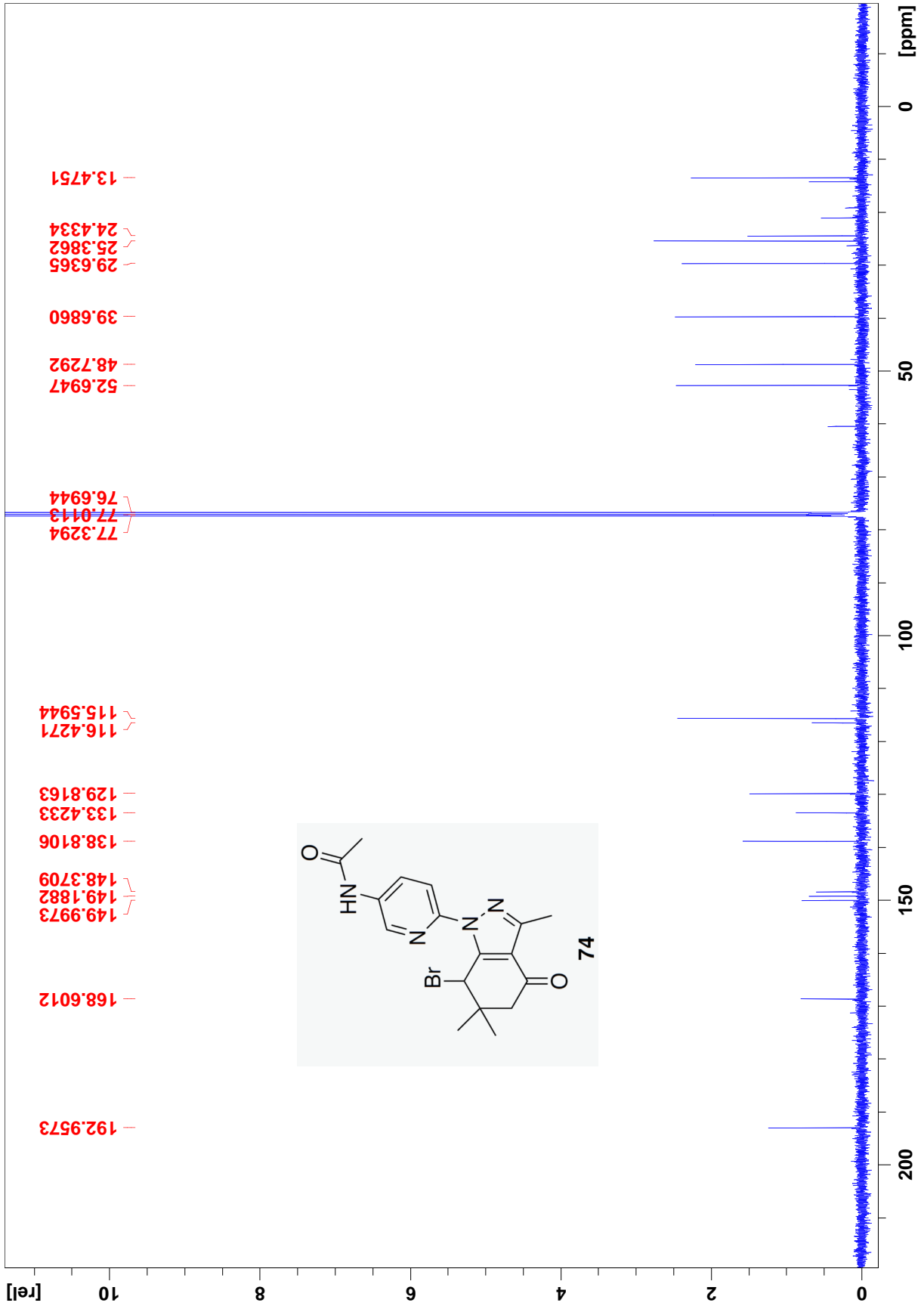
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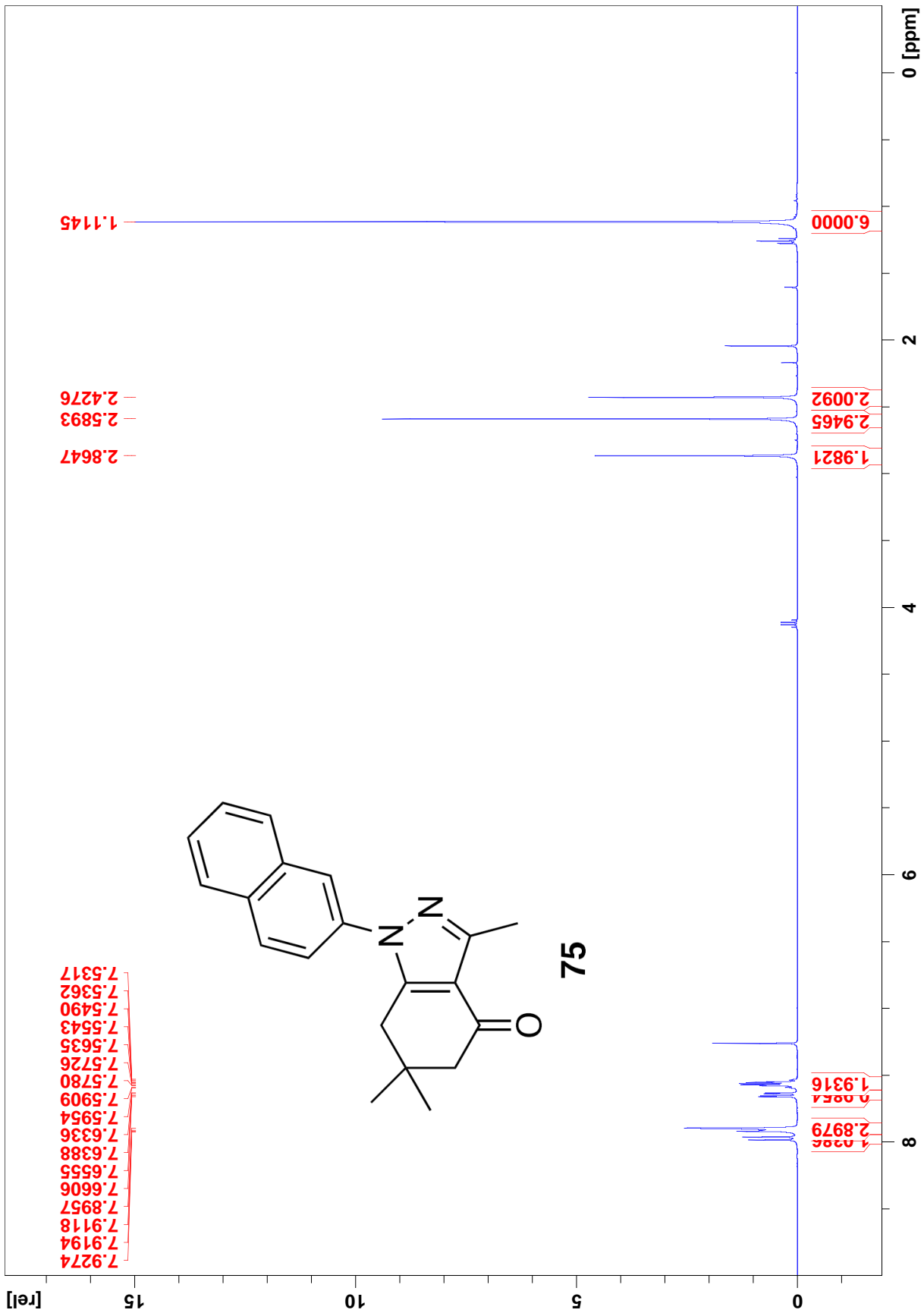
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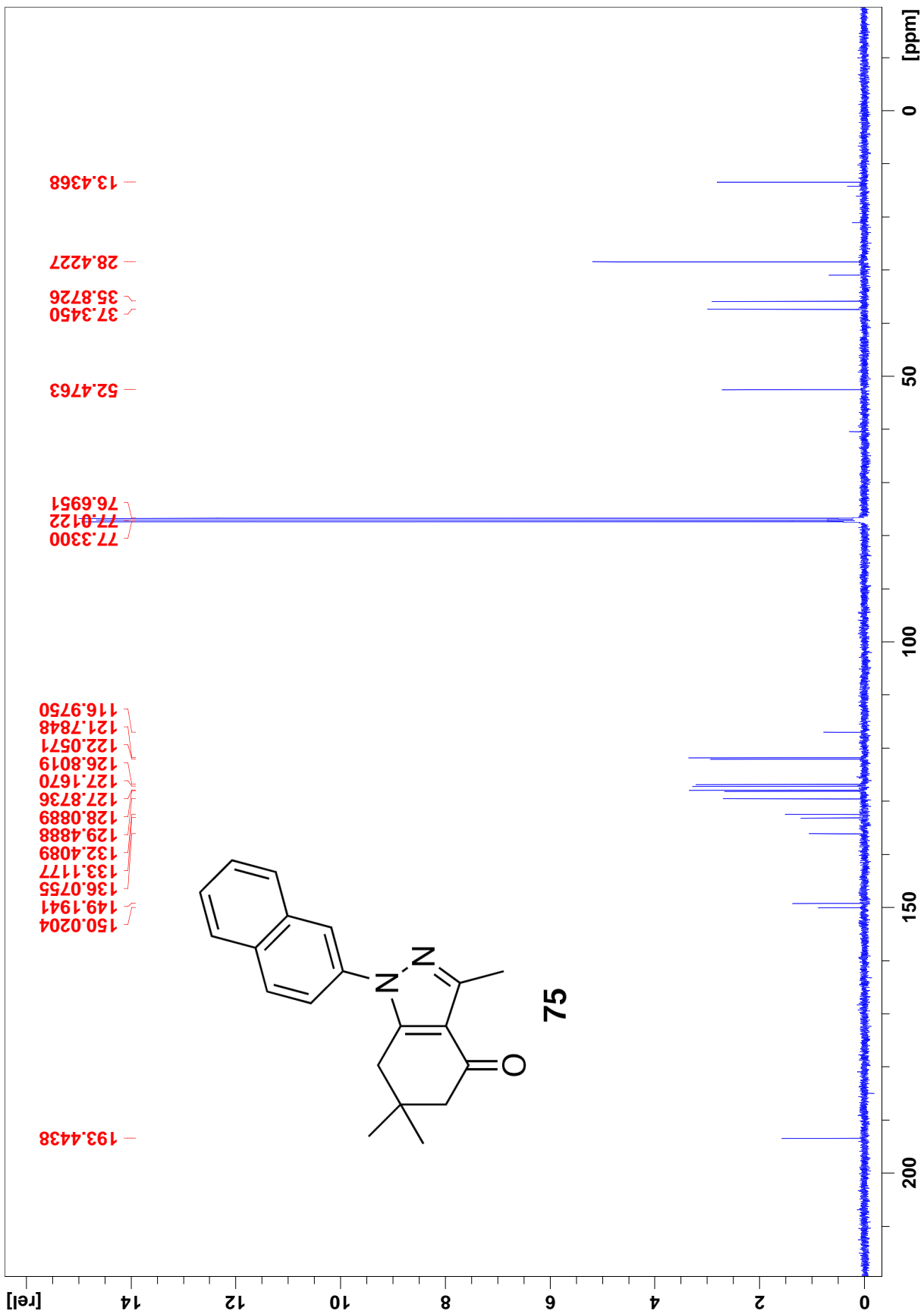
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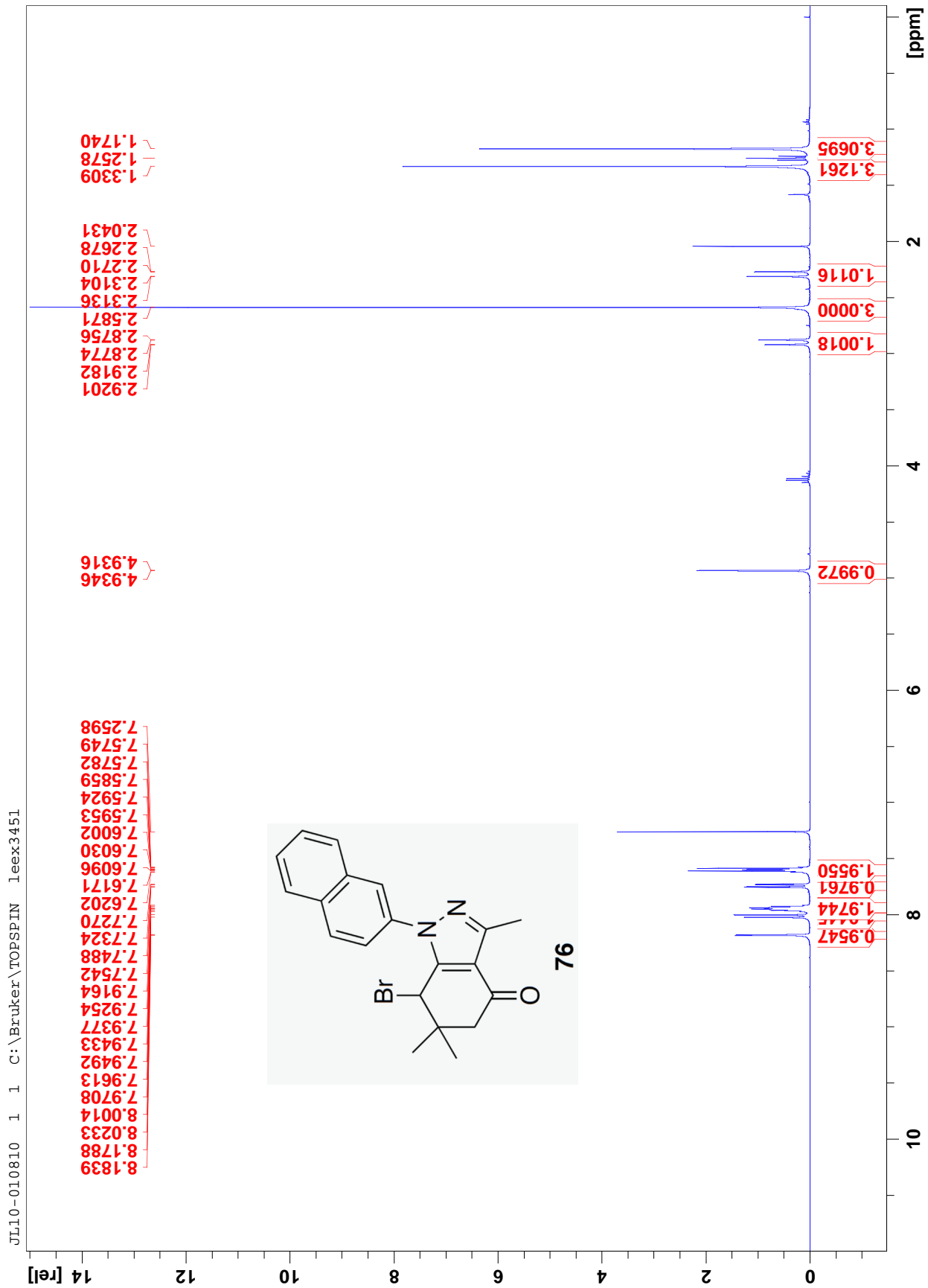


13C-NMR

JL10-010510B 3 1 C:\Bruker\TOPSPIN leex3451



1H-NMR



13C-NMR

