

Supporting Information

Metal-Free Synthesis of Carbamoylated Dihydroquinolinones via Cascade Radical Annulation of Cinnamamides with Oxamic Acids

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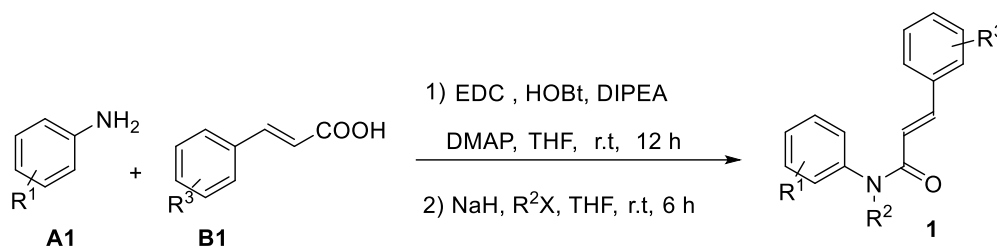
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1. General Information.

All reagents and solvents were purchased from GLR INNOVATIONS, Loba Chemie Pvt. Ltd., and Spectrochem Pvt. Ltd. and used as received. Thin layer chromatography (TLC) was used to monitor the reactions using silica gel GF₂₅₄. Compounds **1**^[4] and **2**^[1-3] were prepared by reported procedure. Dimethyl sulphoxide (DMSO) was used as the reaction solvent with H₂O in a 6:1 ratio. All the reactions were performed in an oven-dried 5 mL round bottom flask in air. Column chromatography was performed on silica gel (60-120 mesh) using ethyl acetate-hexane as eluents. NMR spectra were recorded on JEOL RESONANCE ECZ600R, 600MHz spectrometer (¹H: 600MHz and ¹³C{¹H}: 150 MHz) in chloroform-d. Tetramethylsilane (TMS; δ = 0.00 ppm) served as an internal standard for ¹H NMR, and the corresponding solvent signal (CDCl₃; δ = 77.00 ppm) was used as an internal standard for (¹³C {¹H}) NMR. The ¹H NMR data were recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, coupling constant in Hz, and integration). The ¹³C NMR data were reported in terms of chemical shift (δ, ppm). High resolution mass spectra (HRMS) were obtained using XEVO G2-XS QTOF mass spectrometry. GCMS data was recorded by SHIMADZU, GCMS-QP2010 Ultra.

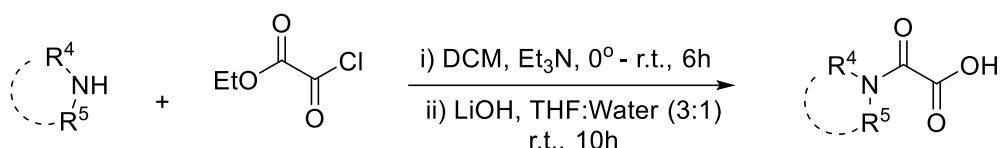
2. General Synthetic Procedure for Cinnamamide^[4]



General Procedure: Aryl-amine (**A1**) (1.0 equiv, 5.0 mmol) was taken in a 50 ml round-bottom flask and THF (10 mL) was added, followed by addition of cinnamic acid derivative (**B1**) (1.0 equiv, 5.0 mmol), EDC (1.2 equiv, 6.0 mmol), HOBT (1.2 equiv, 6.0 mmol), DIPEA (2.0 equiv, 10.0 mmol) and DMAP (0.2 equiv, 1.0 mmol). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (TLC), the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was combined, washed with brine and dried over Na₂SO₄. Organic solvent was removed under reduced pressure and the residue obtained was subjected to precipitation using DCM-Hexane to get the desired cinnamamides. The obtained cinnamamide (1.0 equiv, 3.0 mmol) was portion wise added to a

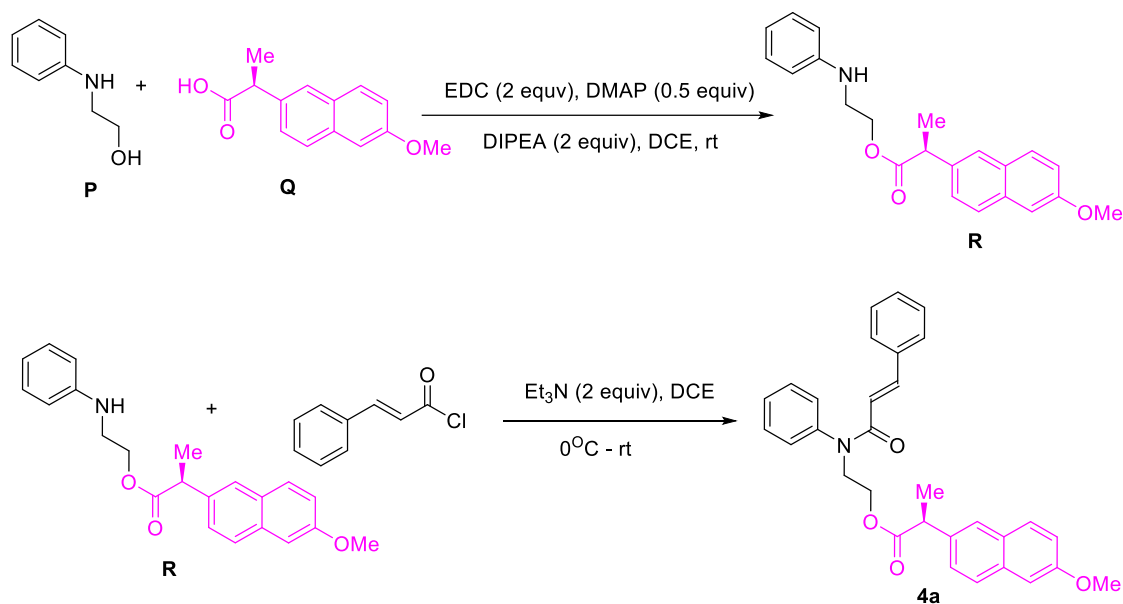
round-bottom flask containing sodium hydride (1.5 equiv, 4.5 mmol) in THF (5 mL) at room temperature. The mixture was stirred for 30 min, followed by slow addition of alkyl halide (1.5 equiv, 4.5 mmol). After completion of the reaction (TLC), excess sodium hydride was quenched with few drops of cold water and the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography with silica gel (60–120 mesh) using ethyl acetate-hexane (1:3) as eluent to obtain the desired cinnamamide in good to excellent yields.

3. General procedure for the synthesis of oxamic acids^[1-3]



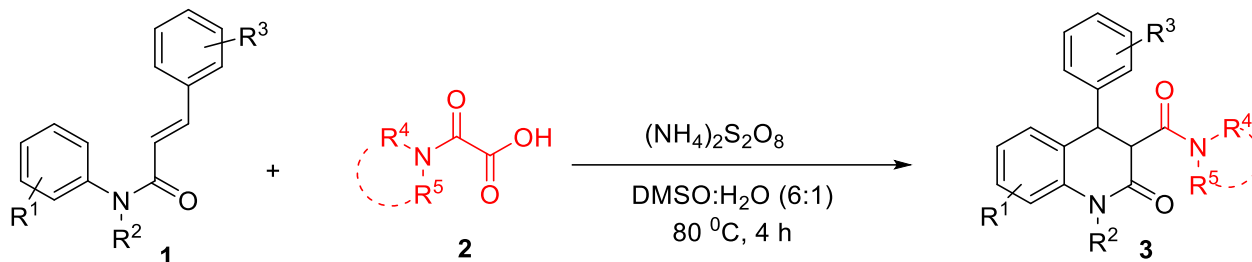
General Procedure: In a 50 mL round bottom flask a solution of amine (5.0 mmol, 1equiv.) in dichloromethane (30 mL) was added Et₃N (6 mmol, 1.2 equiv.) and then ethyl chlorooxoacetate (6 mmol, 1.2 equiv.) was added to the solution slowly at 0 °C. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction (TLC), the reaction mixture was then treated with 1.0 M HCl (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated on reduced pressure and the residue obtained was directly subjected to hydrolysis. The residue was dissolved in THF (9 mL) and water (3 mL), and LiOH (25 mmol, 5 equiv.) was added to the solution. The resulting reaction mixture was stirred for 10 h at room temperature. After completion of hydrolysis, aqueous phase was separated and acidified with 1.0 M aqueous HCl solution. The resulting mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed in reduced pressure and the residue obtained was recrystallized by dichloromethane-hexanes to obtain oxamic acids.

4. Synthetic Procedure for 2-(*N*-phenylcinnamamido)ethyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanoate^[4]



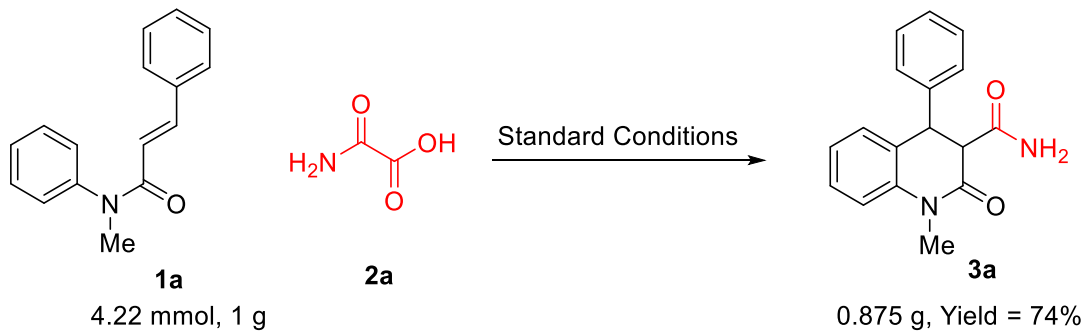
Synthetic Procedure: In a 50 ml round-bottom flask, 2-(phenylamino)ethan-1-ol (**P**) (1.0 equiv, 3.0 mmol), Naproxen (**Q**) (1.0 equiv, 3.0 mmol), EDC (2 equiv, 6.0 mmol), DIPEA (2.0 equiv, 6.0 mmol) and DMAP (0.5 equiv, 1.5 mmol) were taken and dissolved in THF (15 mL). The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction (TLC), the crude mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The organic layer was combined, washed with brine, dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue obtained was precipitated using DCM-Hexane to get the ester **R**. The compound **R** was then added slowly to a solution of cinnamoyl chloride (1.5 equiv, 4.5 mmol) and trimethylamine (2.0 equiv, 6.0 mmol) in DCE (10 mL) at 0 °C and the resultant mixture was stirred at room temperature for 10 h. After completion of the reaction (TLC), the crude mixture was diluted with water (20 mL) and extracted with DCM (2 x 30 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography with silica gel (60–120 mesh) using ethyl acetate-hexane (1:4) as eluent to get the desired Naproxen-derived cinnamamide **4a** as white solid.

5. Synthesis Procedure for Dihydroquinolinone-3-carboxamide



General Procedure: Cinnamamide **1** (1.0 equiv, 0.21 mmol) was taken in a 5 mL round bottom flask and dissolved in Dimethyl sulphoxide (DMSO) and water (1.5 mL). The oxamic acid **2** (2.0 equiv, 0.42 mmol) was further added to the solution followed by the addition of ammonium persulfate (2.0 equiv, 0.42 mmol) and the mixture was stirred for 4 h at 80 °C. Reaction progress was checked by TLC. After completion, the reaction solvent was removed under reduced pressure and the residue obtained was diluted with water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography with silica gel (60-120 mesh) using ethyl acetate-hexane (gradient elution, 5 to 30% ethyl acetate-hexane) to afford the carbamoylated dihydroquinolinone **3** in good to excellent yields.

6. Gram-scale Reaction



Cinnamamide **1a** (1.0 equiv, 4.22 mmol, 1.0 g) was taken in a 25 mL round bottom flask and dissolved in Dimethyl sulphoxide (DMSO) and water (15 mL). The oxamic acid **2a** (2.0 equiv, 8.44 mmol, 0.75 g) was further added to the solution followed by the addition of ammonium persulfate (2.0 equiv, 8.44 mmol, 1.92 g) and the reaction mixture was stirred for 4 h at 80 °C.

Reaction progress was checked by TLC. After completion, the reaction solvent was removed under reduced pressure and the residue obtained was diluted with water (30 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography with silica gel (60-120 mesh) using ethyl acetate-hexane (gradient elution, 5 to 30% ethyl acetate-hexane) to afford **3a** (0.875 g, 74%).

7. Control Experiments

General procedure for radical trapping: In a 5 mL round bottom flask, cinnamamide **1a** (1.0 equiv, 0.21 mmol) and TEMPO/BHT (2.0 equiv, 0.42 mmol) were taken and dissolved in Dimethyl sulphoxide (DMSO) and water (6:1, 1.5 mL). The oxamic acid **2** (2.0 equiv, 0.42 mmol) was added to the solution, followed by the addition of ammonium persulfate (2.0 equiv, 0.42 mmol) and the mixture was stirred for 4 h at 80 °C. Reaction mixture was analyzed by TLC and GC-MS. The mass peak corresponding to BHT-Carbamoyl adduct (**6a**) was detected.

7. (a) Radical Trapping by BHT

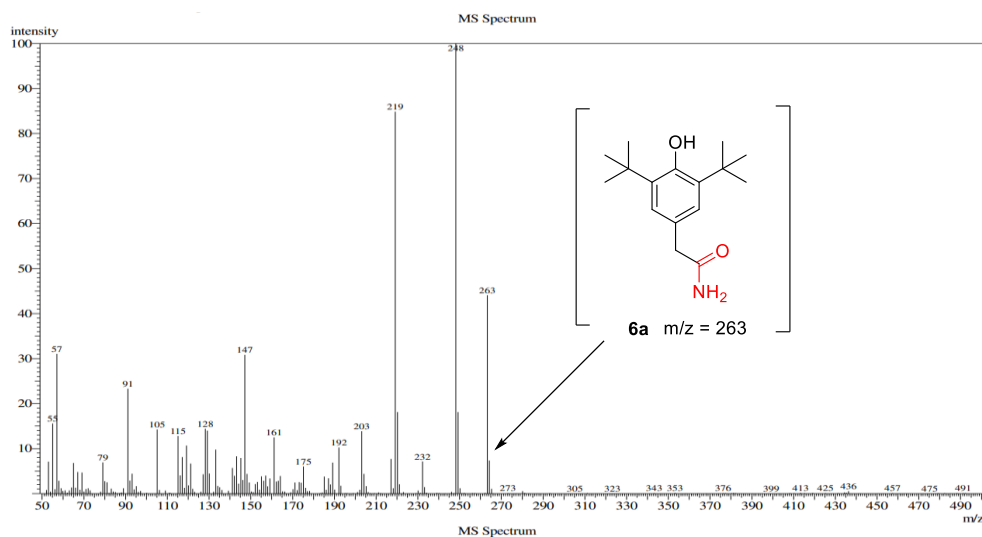
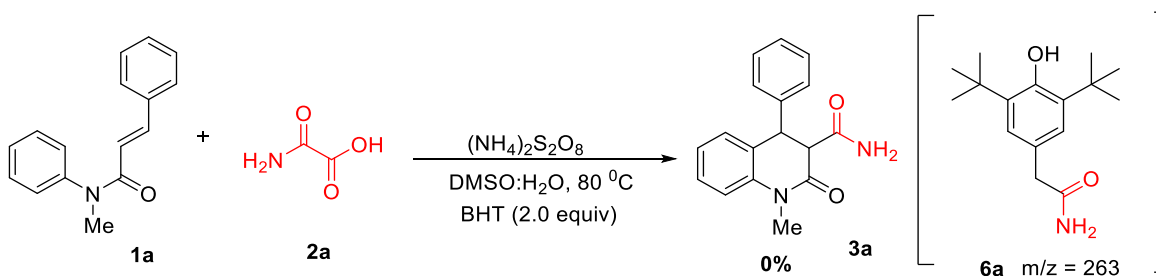
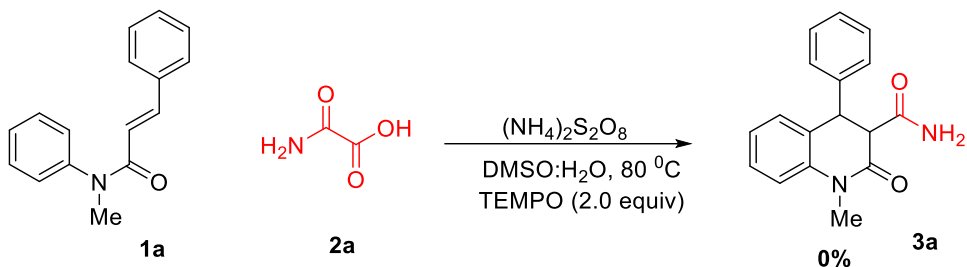


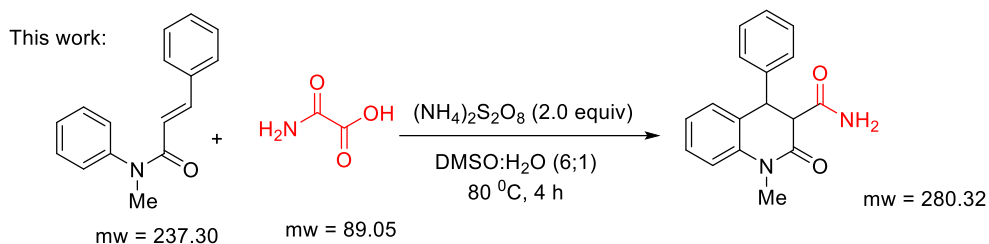
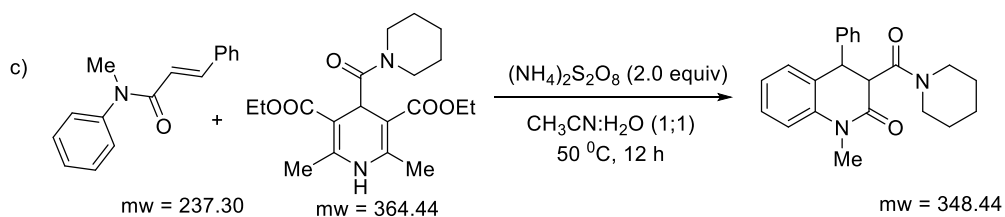
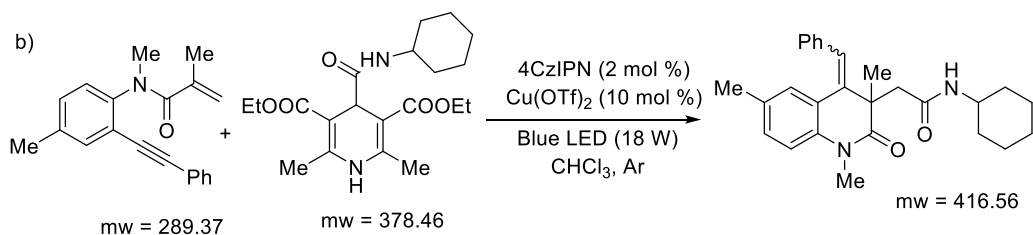
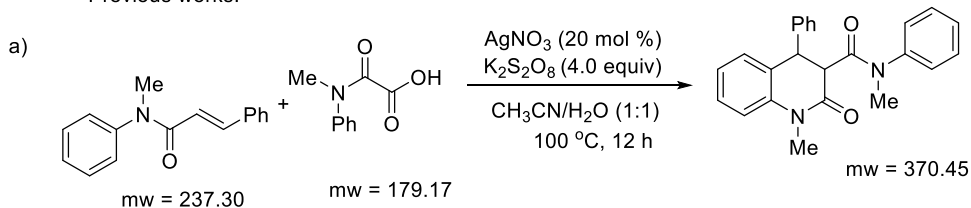
Figure S1. GC-MS Study for BHT Reaction

7. (b) Radical Trapping by TEMPO



8. Calculation of atom economy

Previous works:



$$\text{Atom Economy (AE)} = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100\% = \frac{370.4}{237.3 + 179.2} \times 100\% = 88.9$$

(a)

$$\text{Atom Economy (AE)} = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100\% = \frac{416.5}{289.4 + 378.5} \times 100\% = 62.3$$

(b)

$$\text{Atom Economy (AE)} = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100\% = \frac{348.4}{237.3 + 364.4} \times 100\% = 57.9$$

(c)

$$\text{Atom Economy (AE)} = \frac{\text{Molecular weight of product}}{\text{Total molecular weight of reactants}} \times 100\% = \frac{280.3}{237.3 + 89.0} \times 100\% = 85.9$$

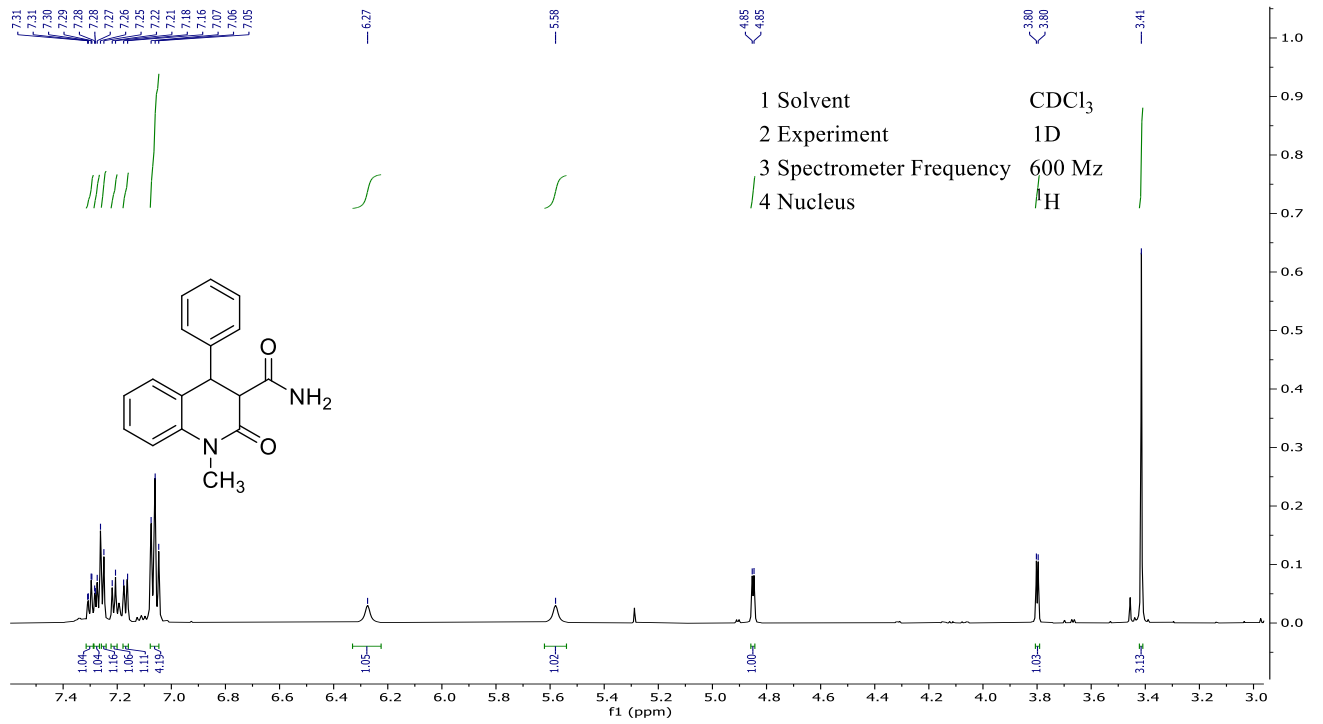
(this work)

9. References:

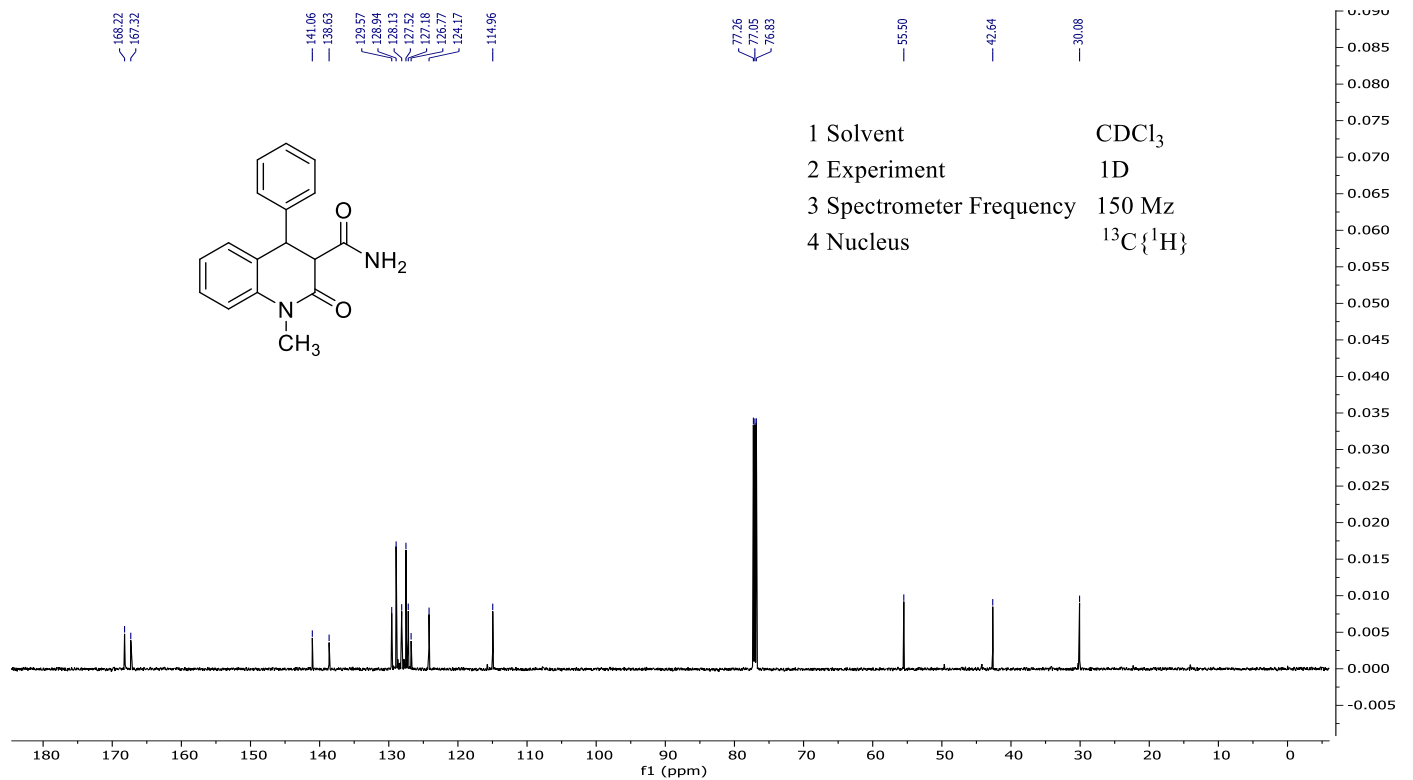
1. G. G. Pawar, F. Robert, E. Grau, H. Cramail and Y. Landais, *Chem. Commun.*, 2018, **54**, 9337-9340.
2. V. S. Bhat and A. Lee, *Eur. J. Org. Chem.*, 2021, **2021**, 3382-3385.
3. Q.-F. Bai, C. Jin, J.-Y. He and G. Feng, *Org. Lett.*, 2018, **20**, 2172-2175.
4. C. S. Nishad, P. Suman, H. Saha and B. Banerjee, *J. Org. Chem.*, 2023, **88**, 11010-11022.

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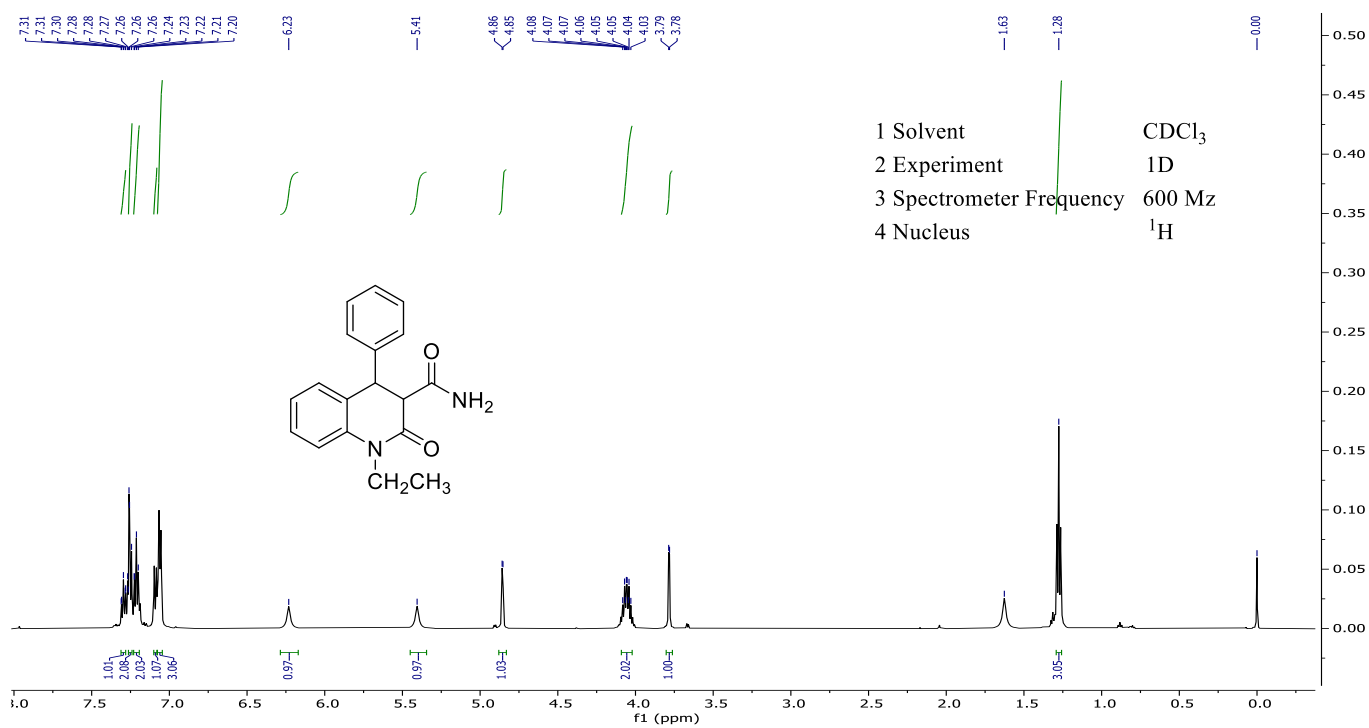
^1H NMR of **3a**



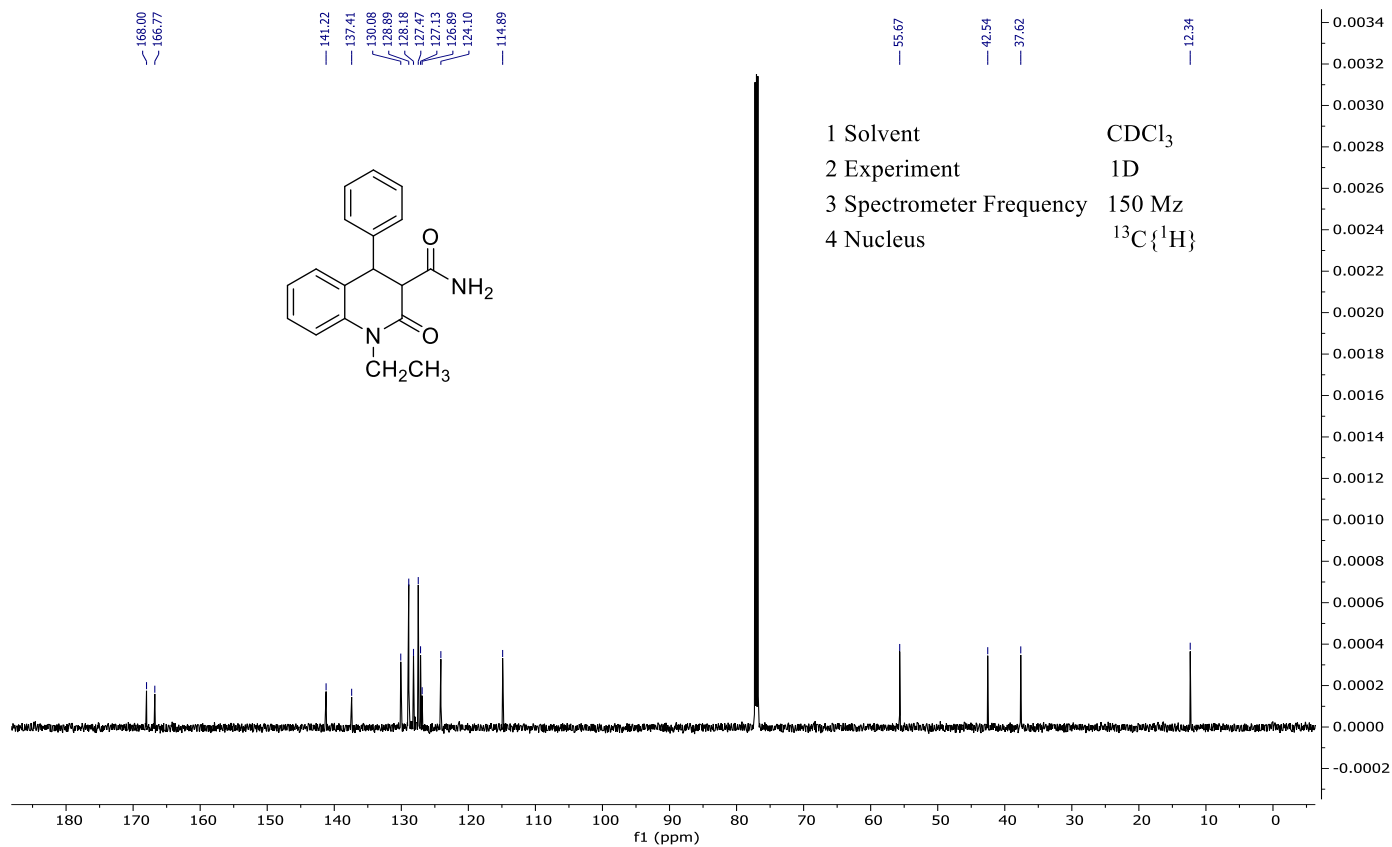
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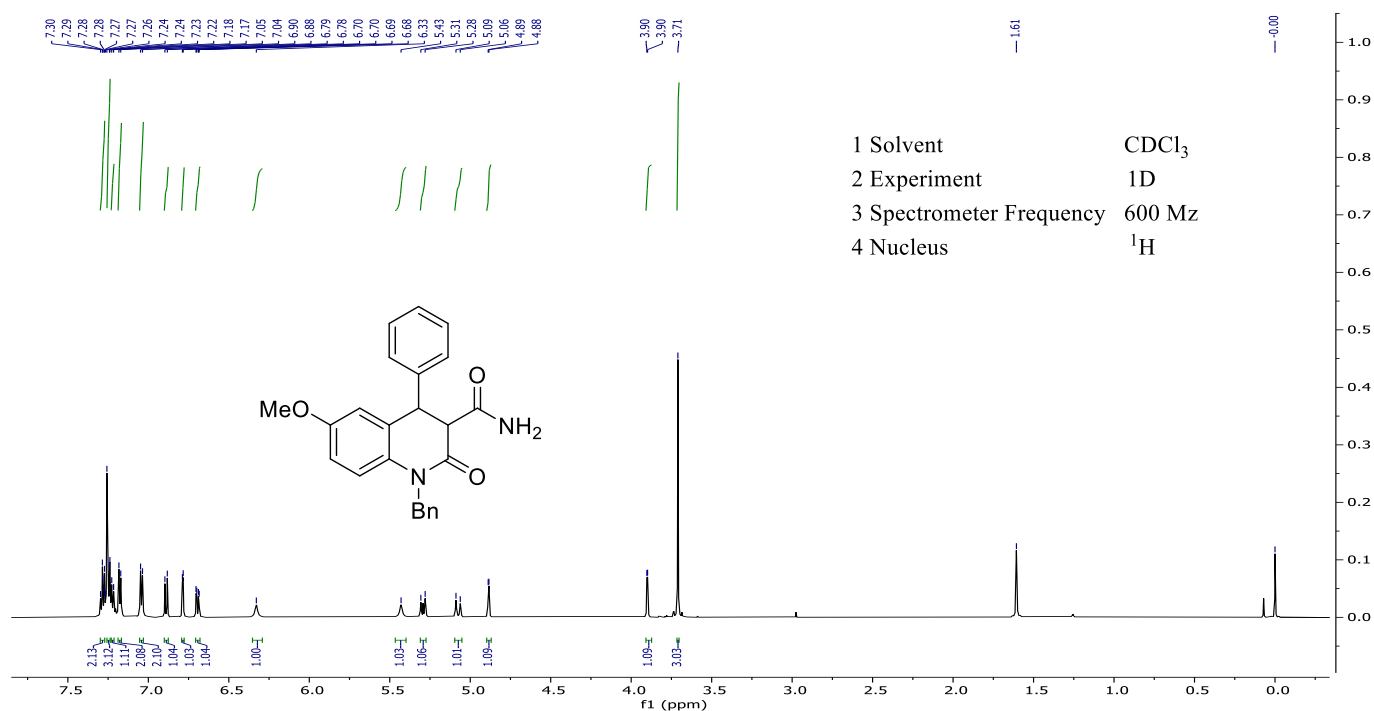
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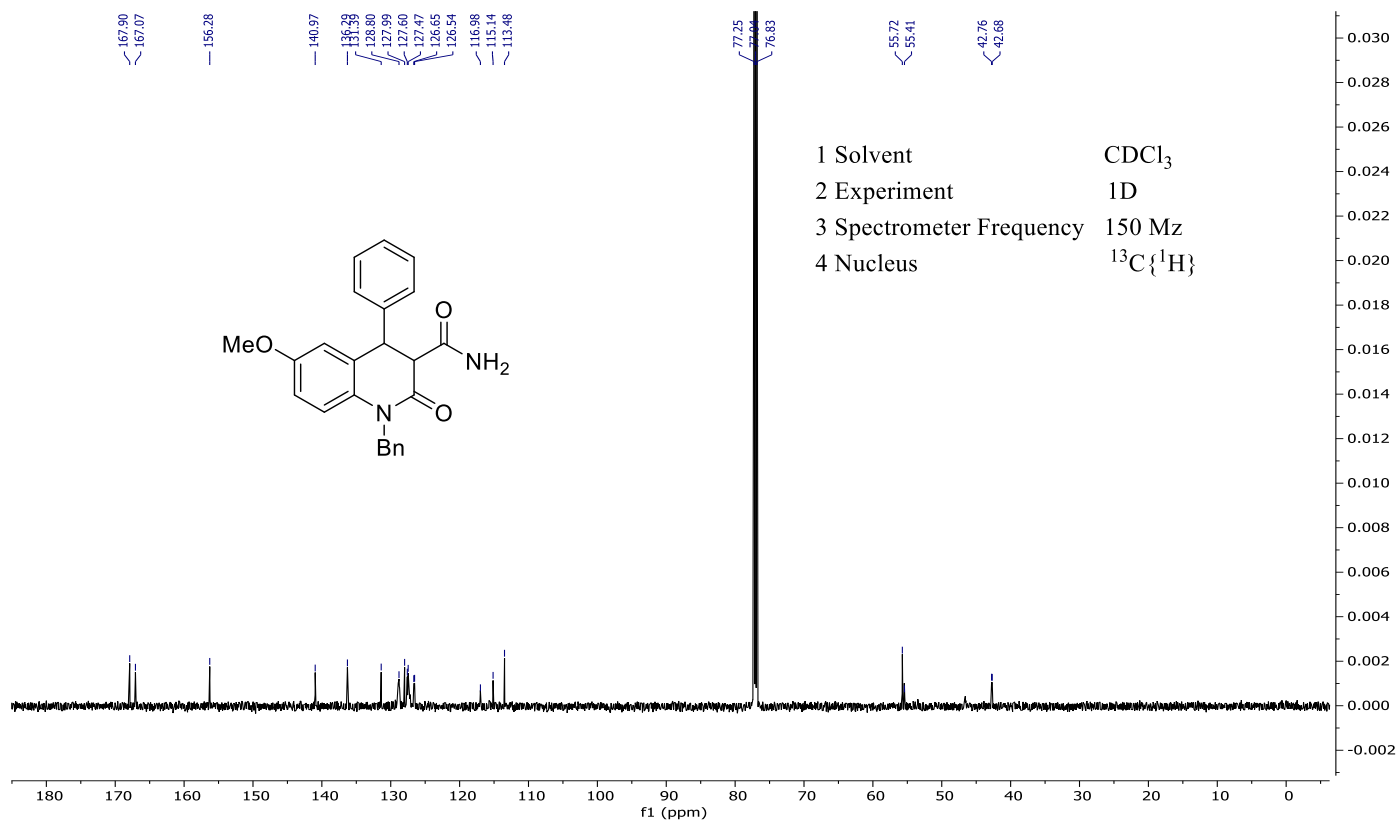
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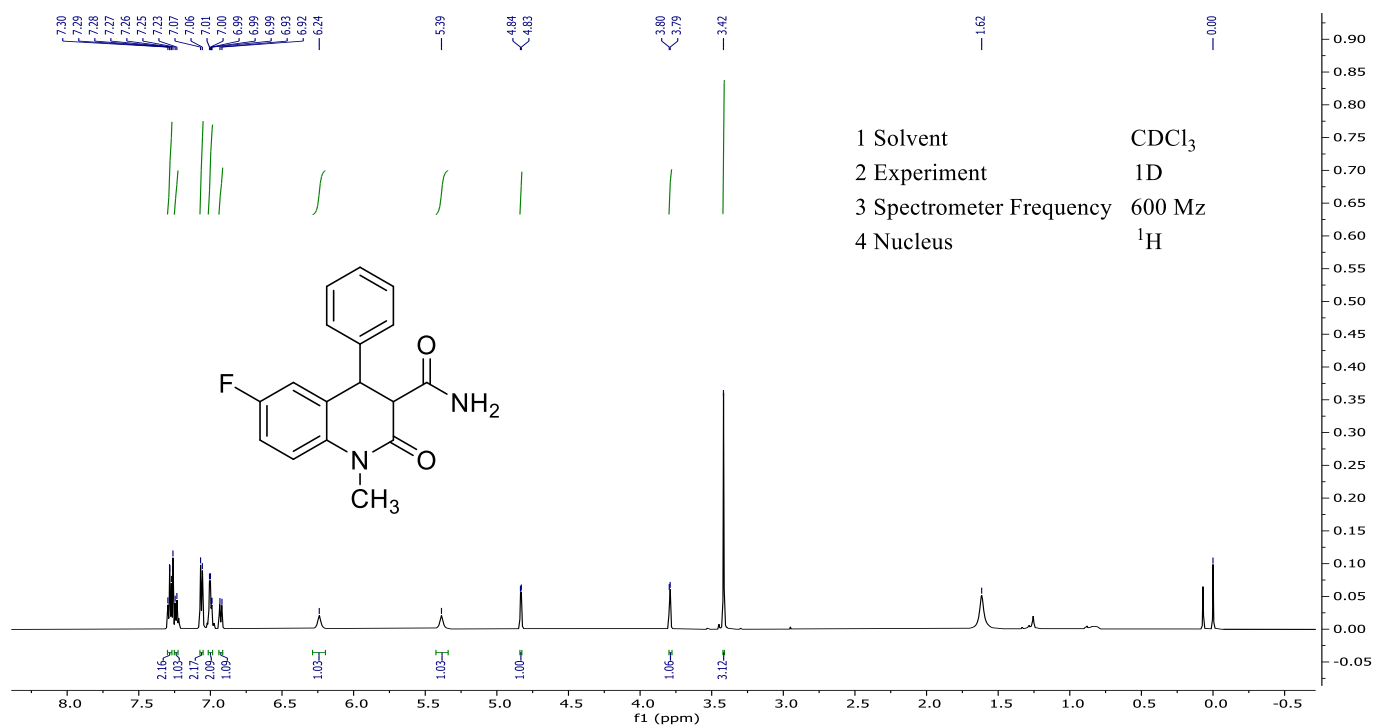
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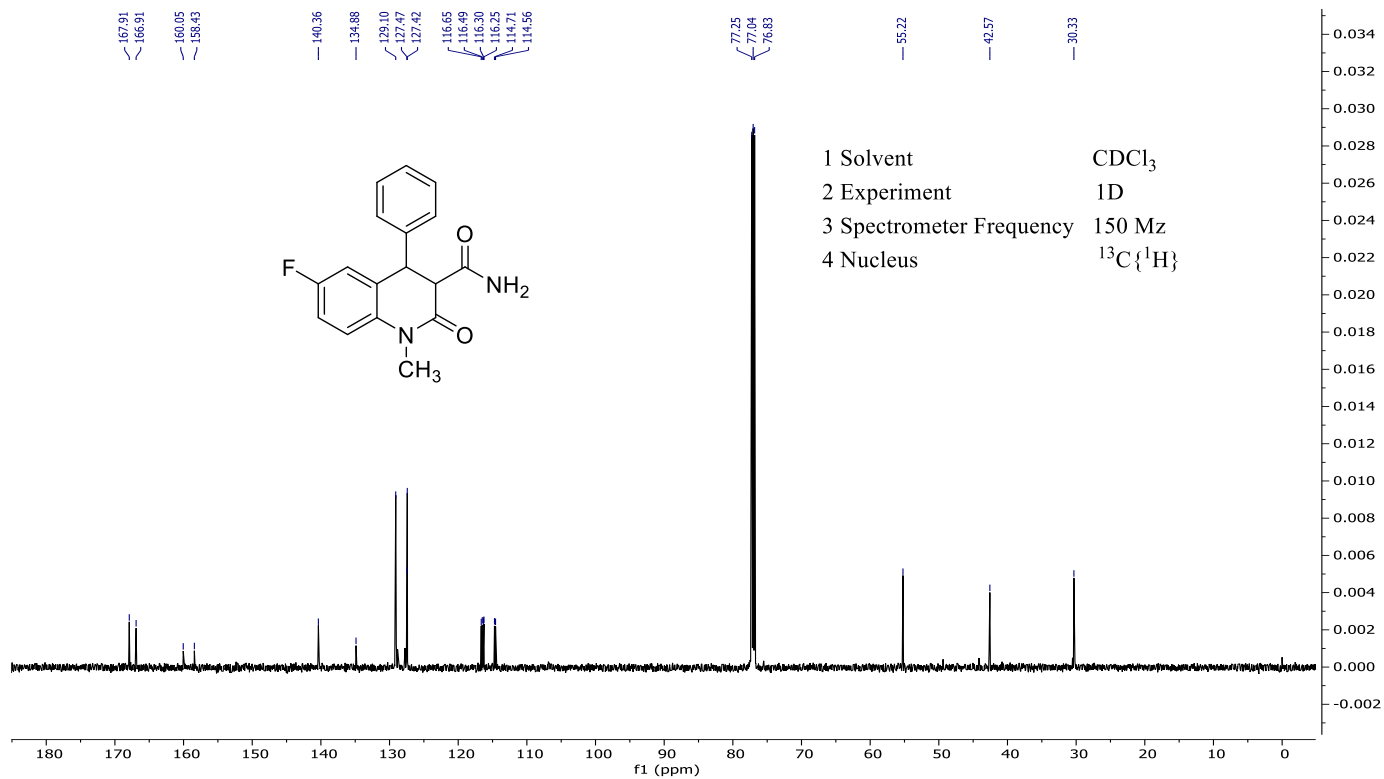
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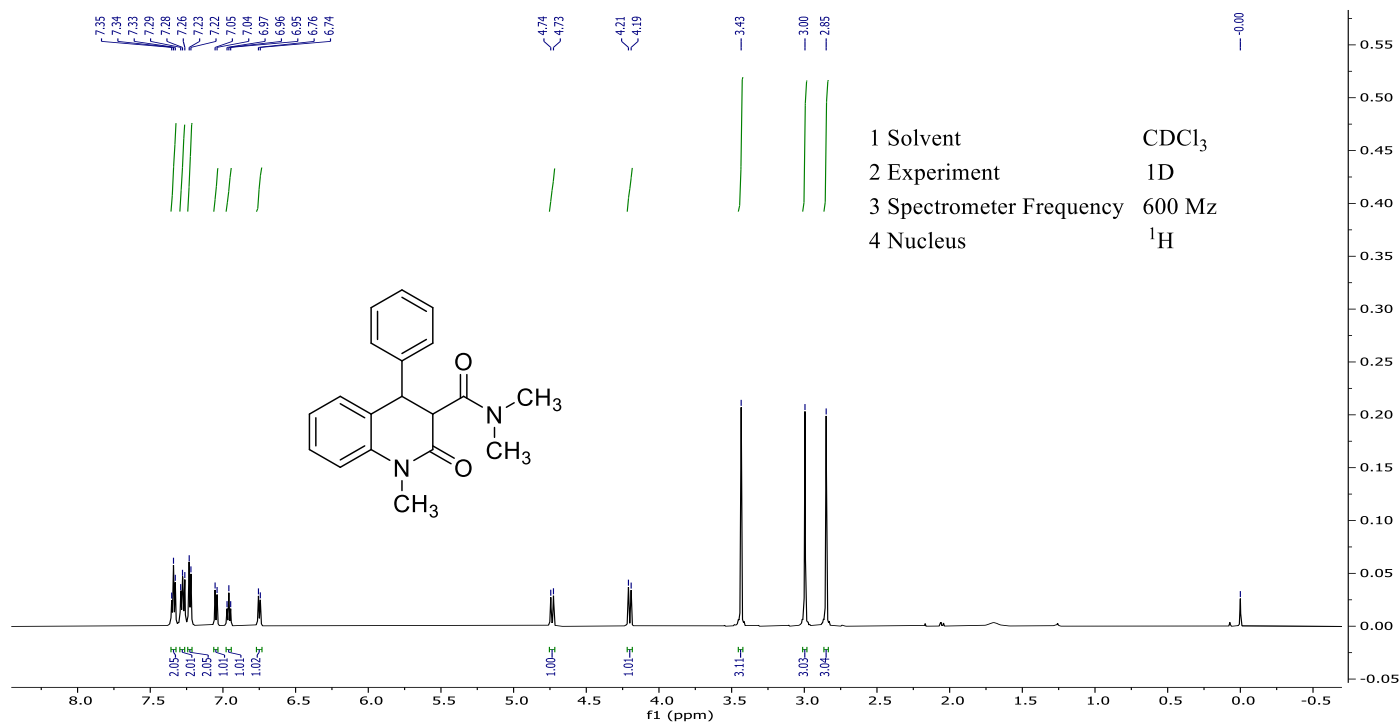
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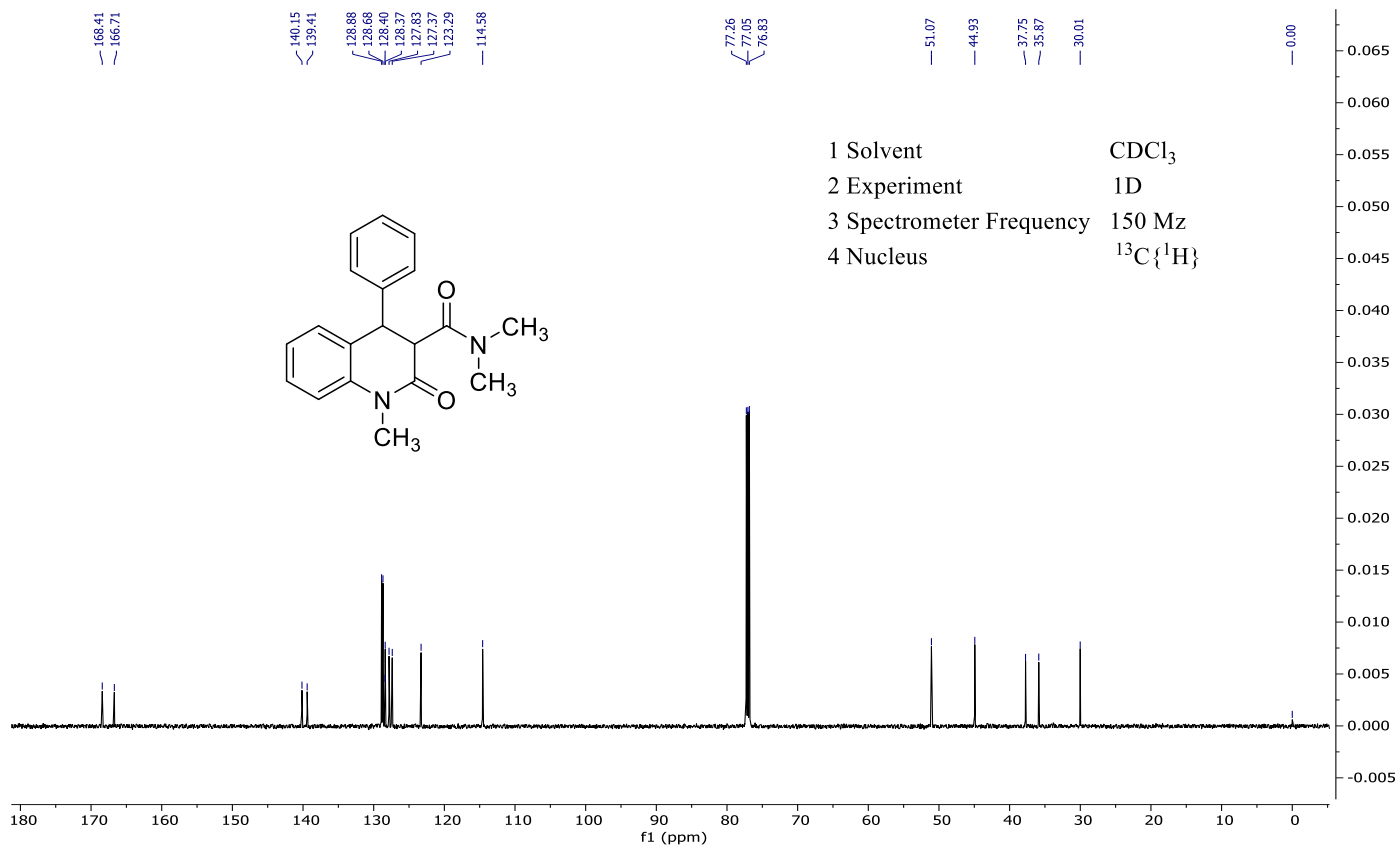
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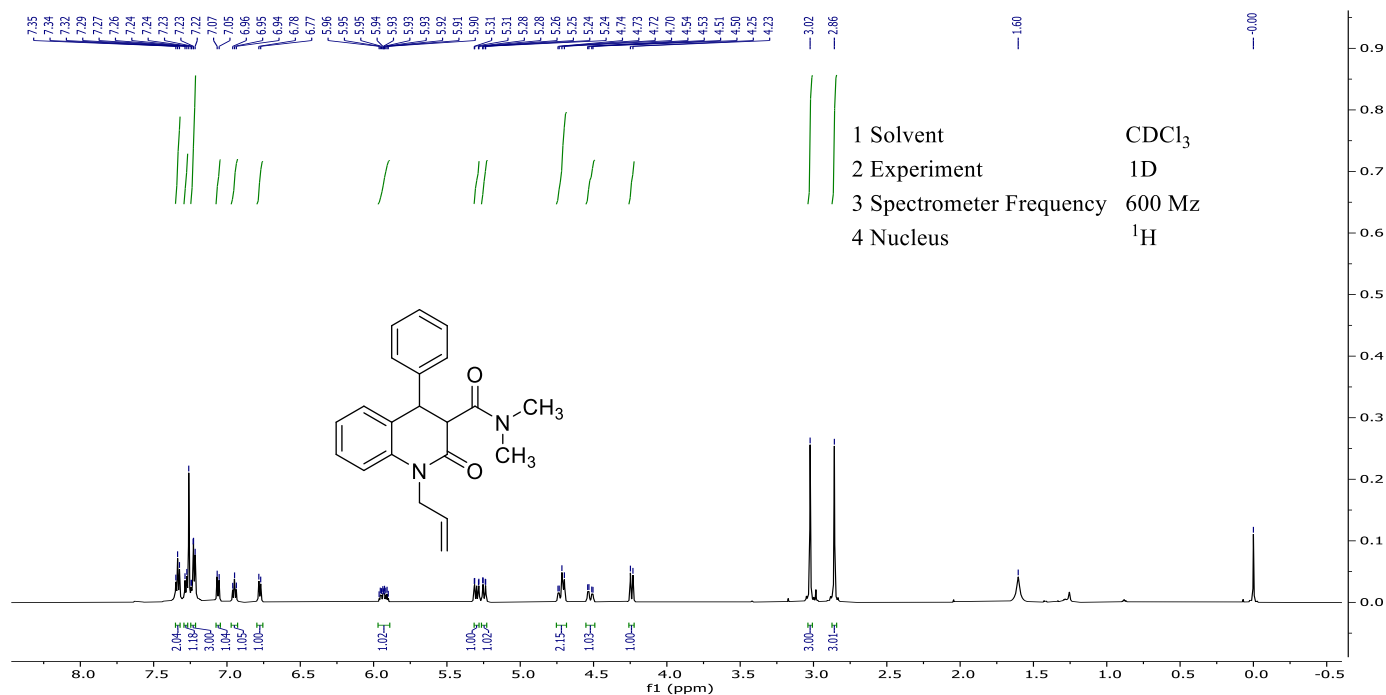
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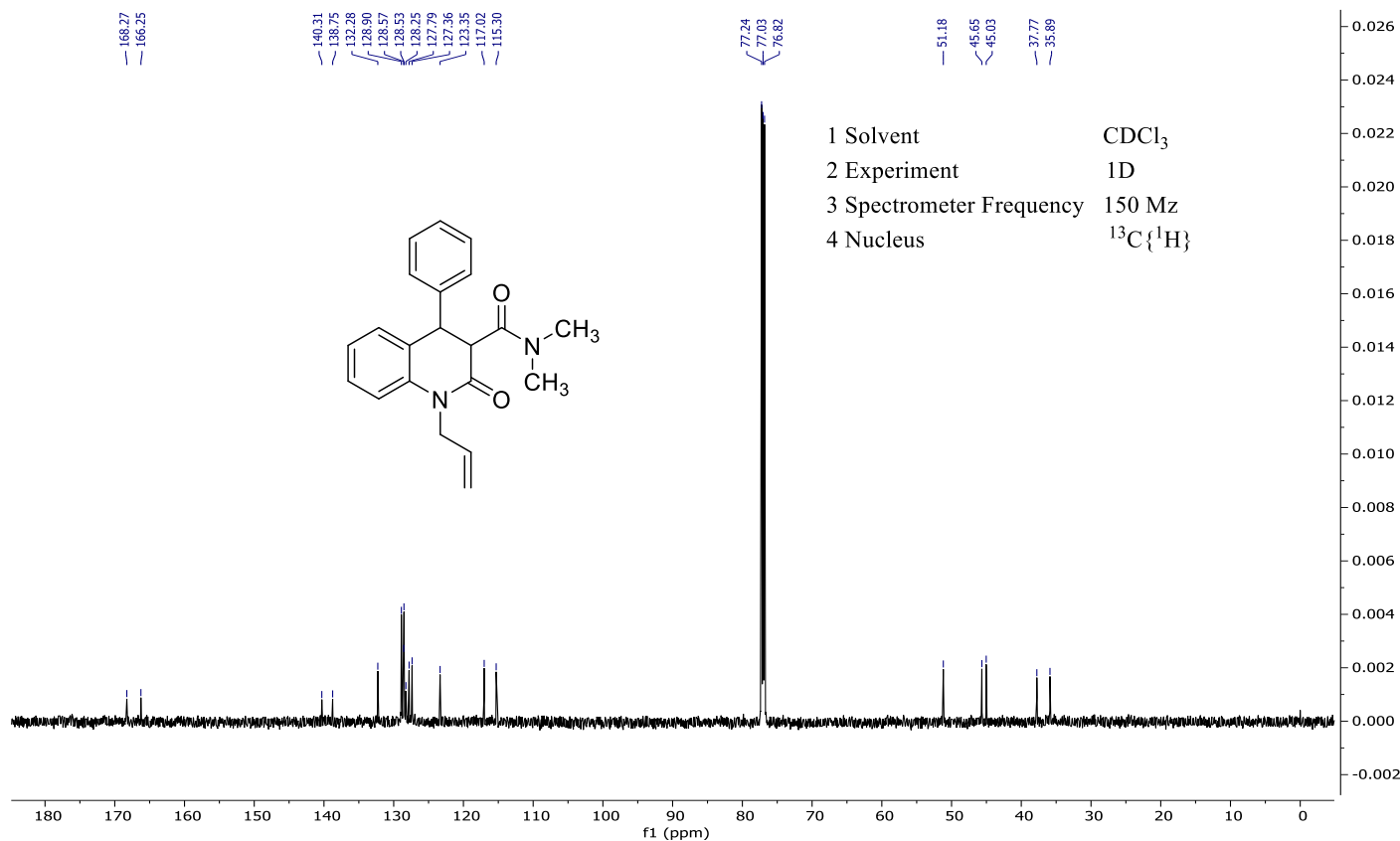
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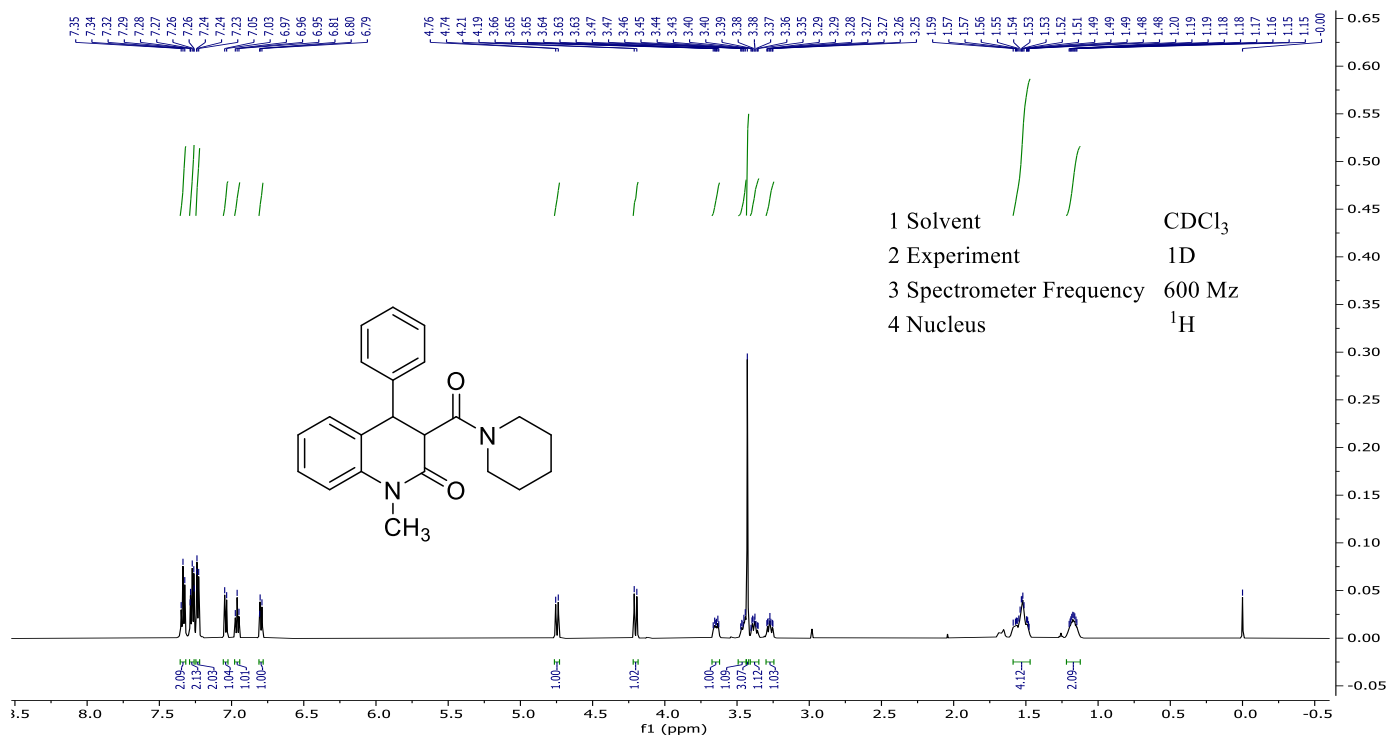
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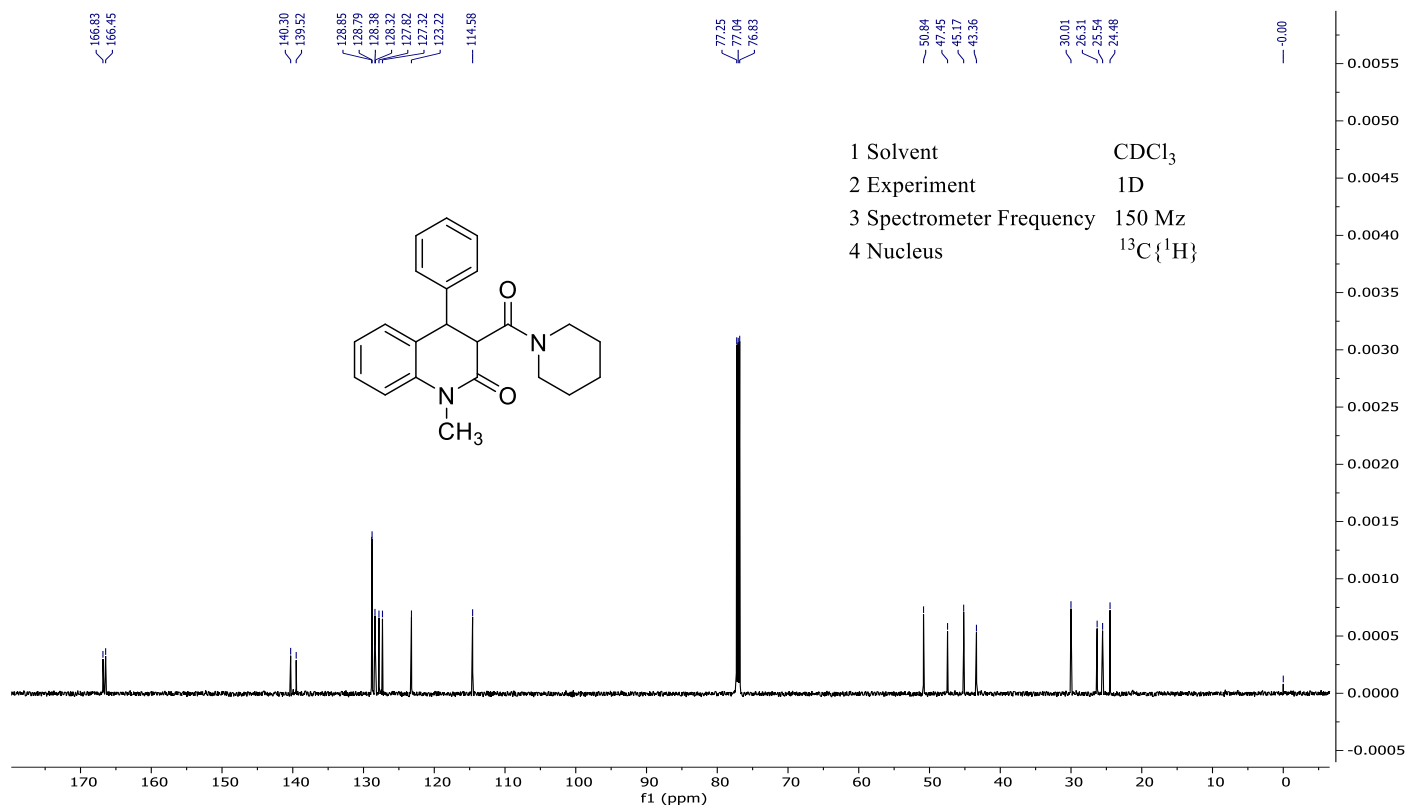
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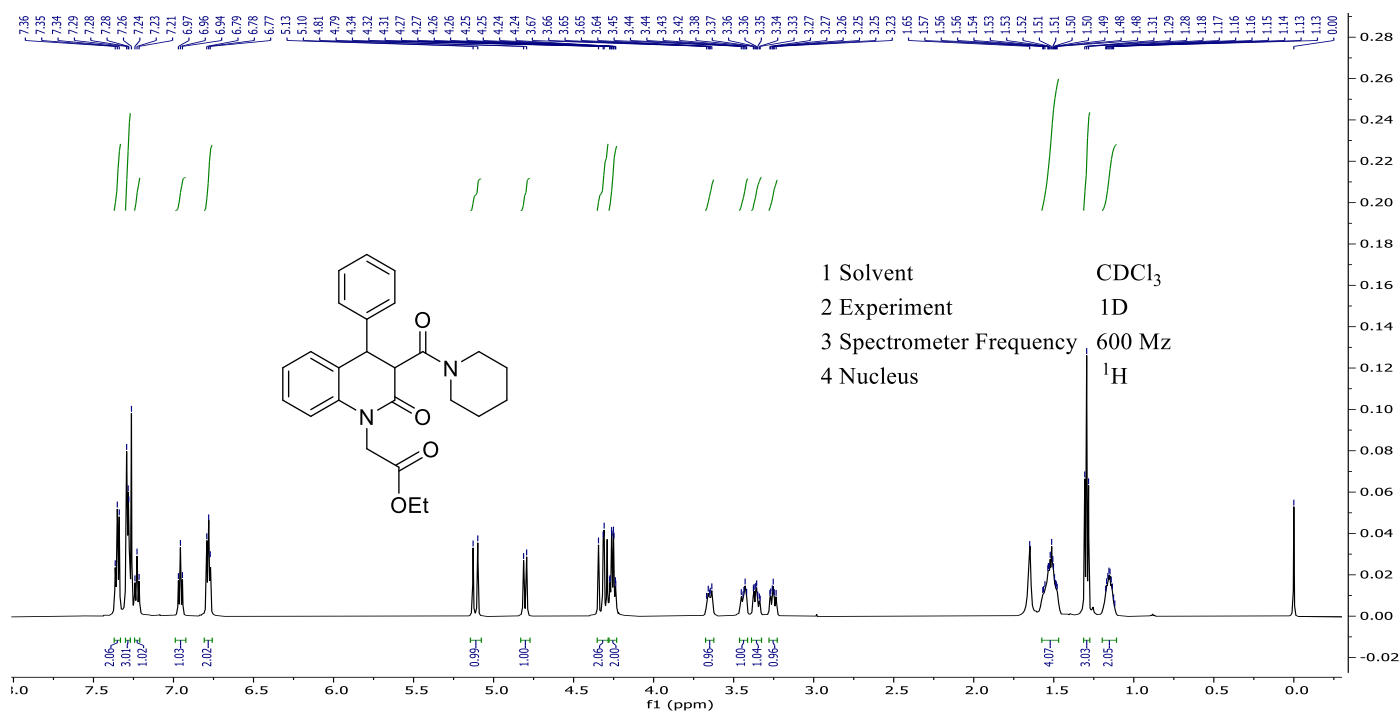
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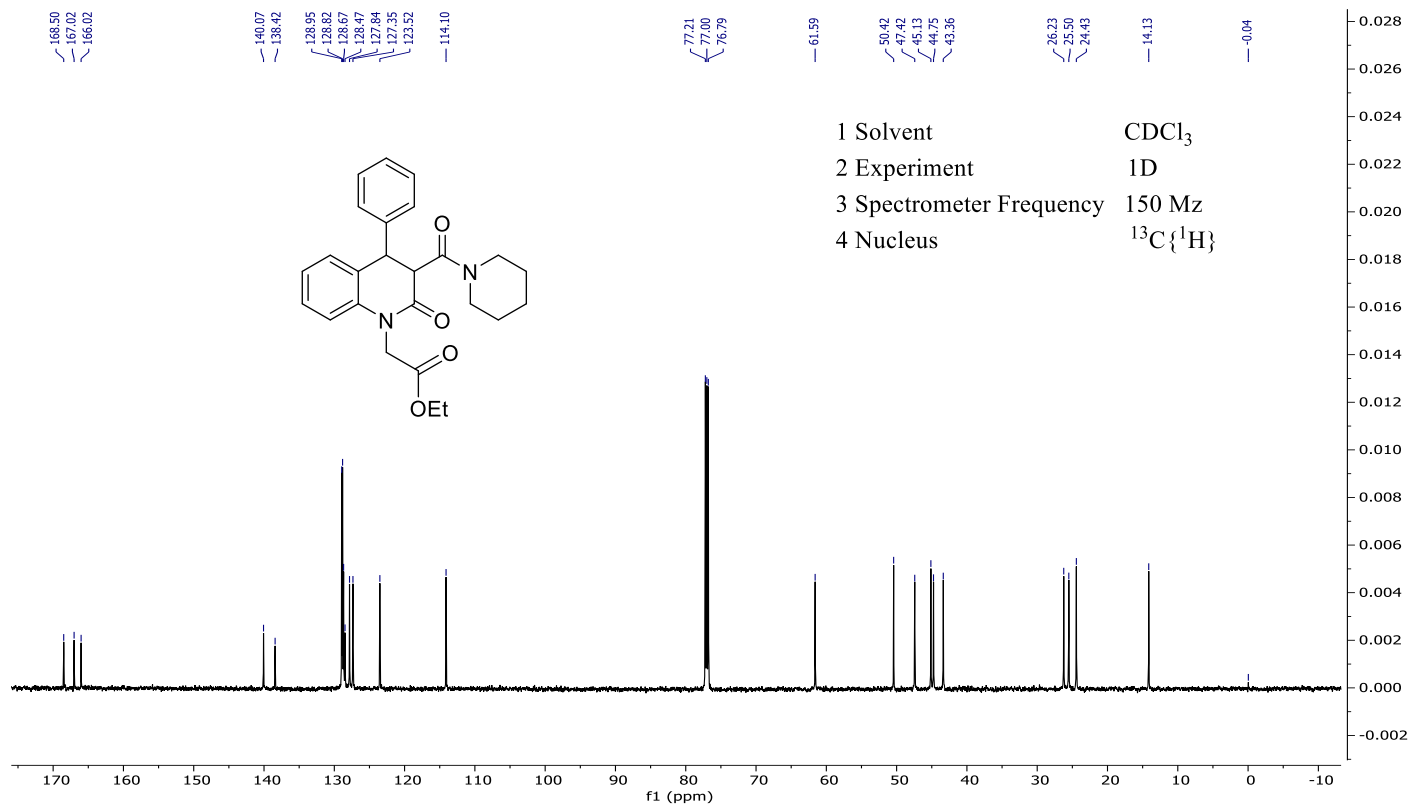
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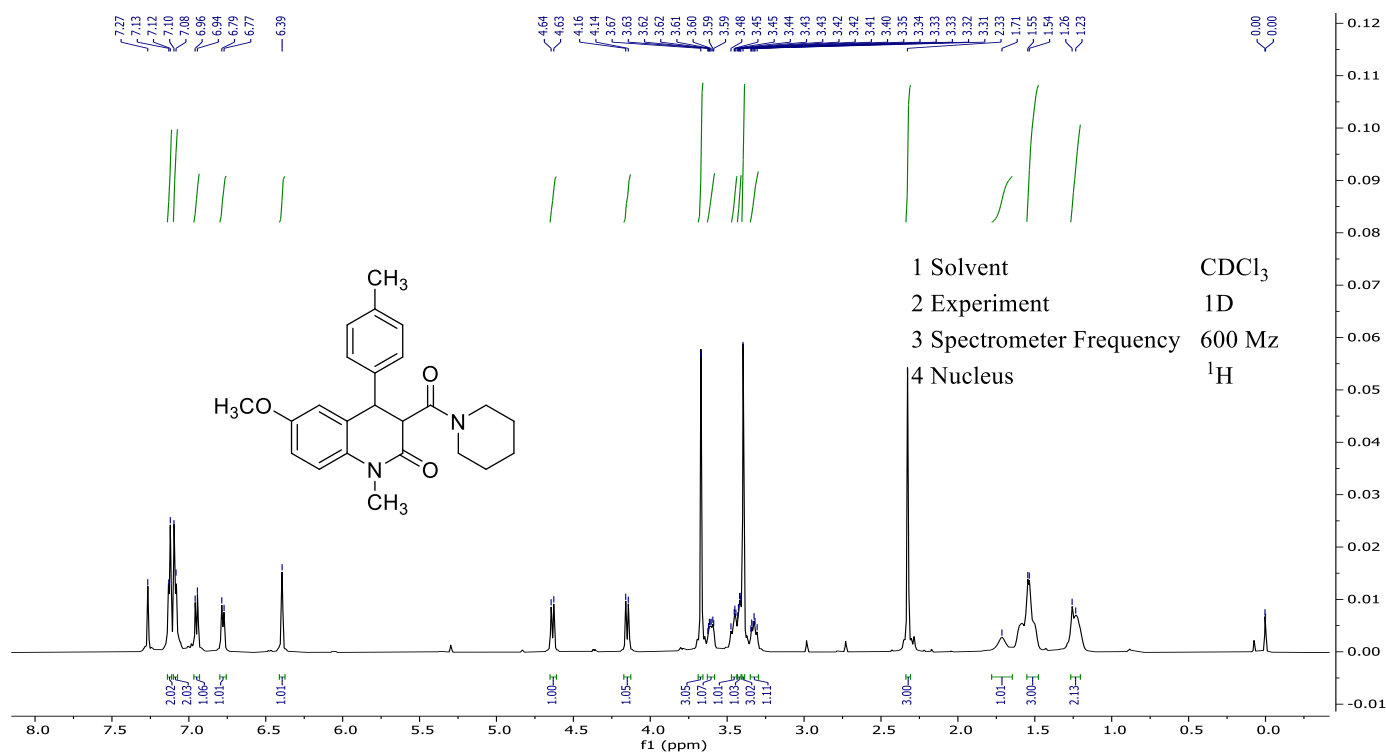
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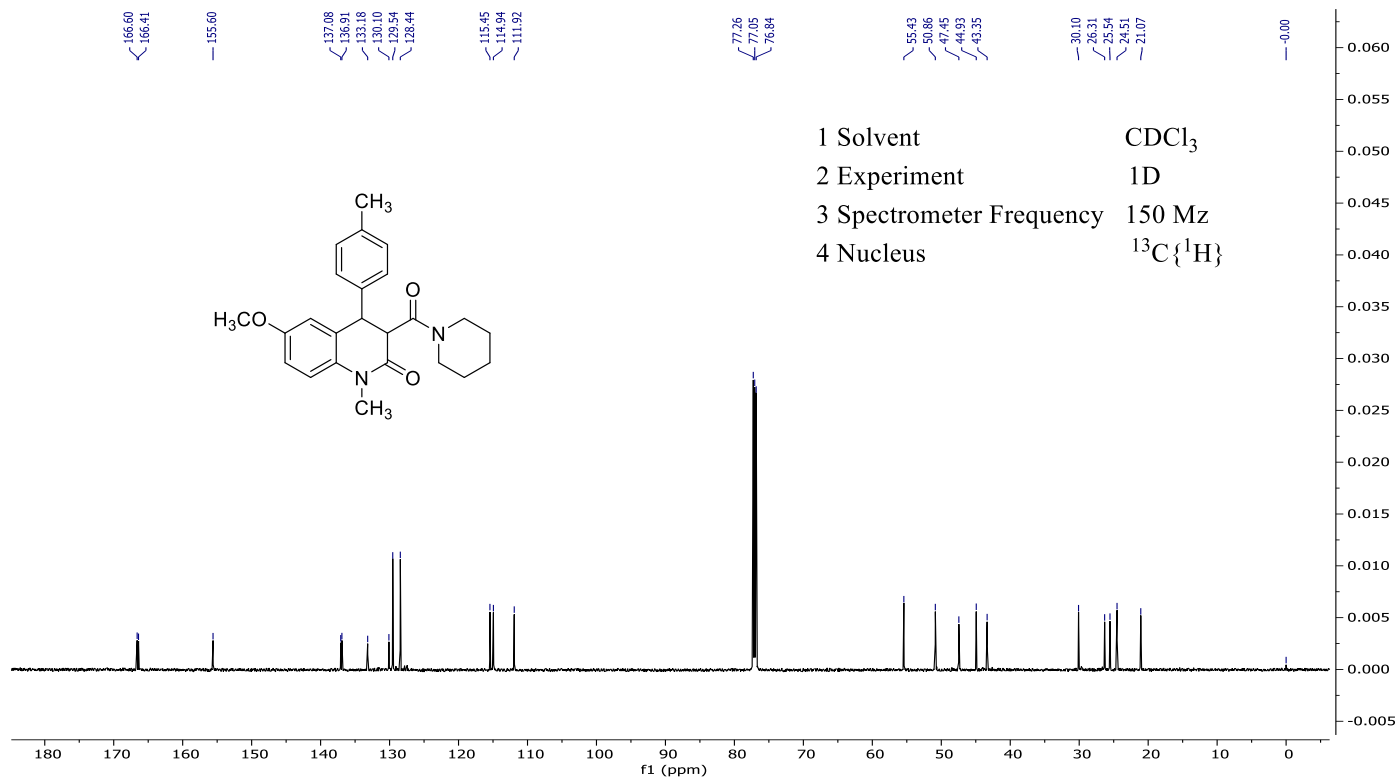
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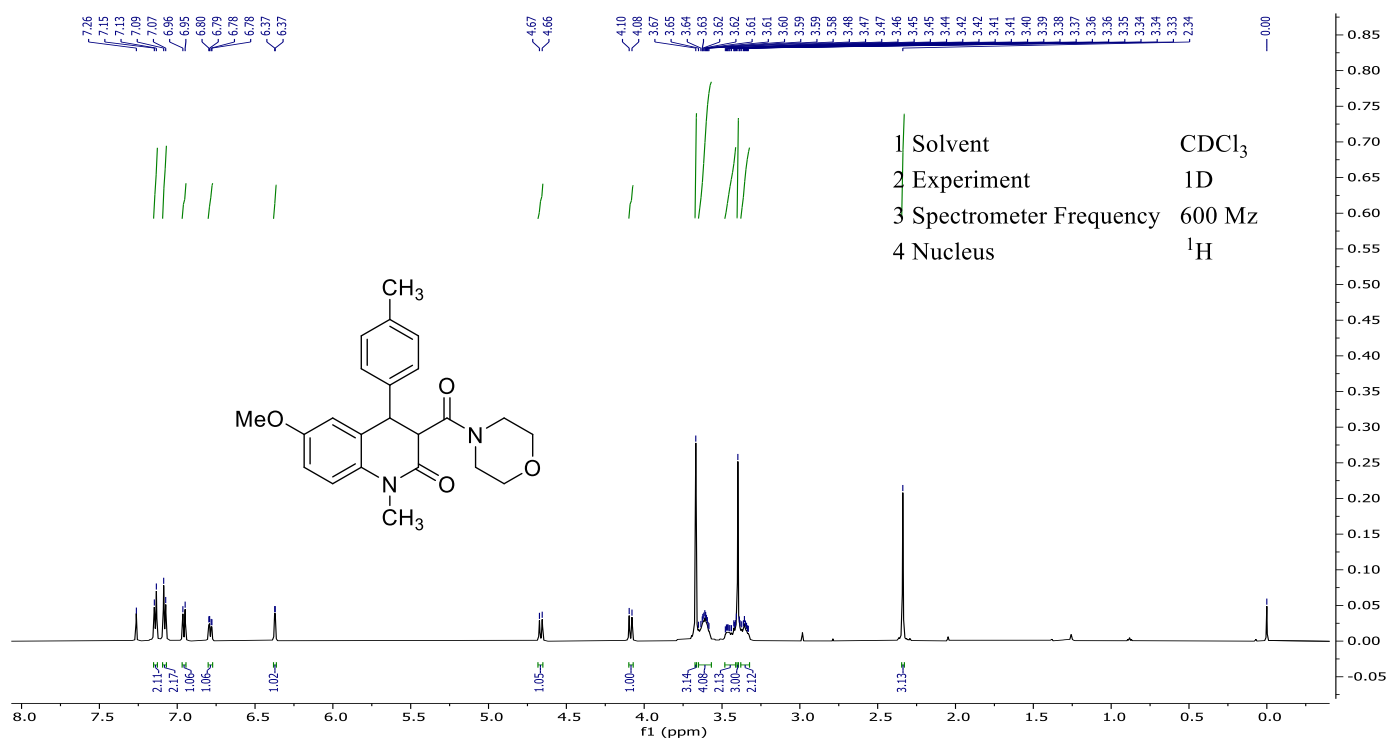
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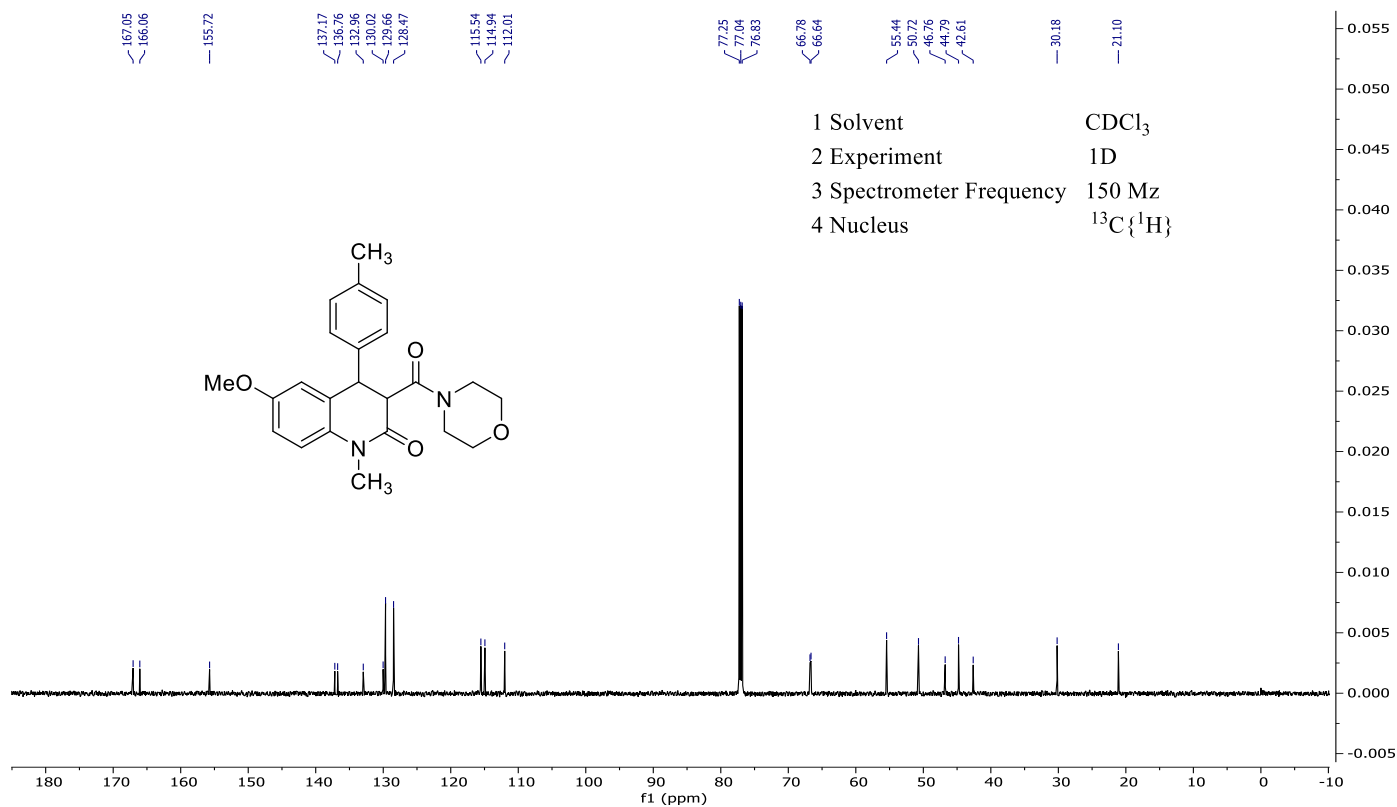
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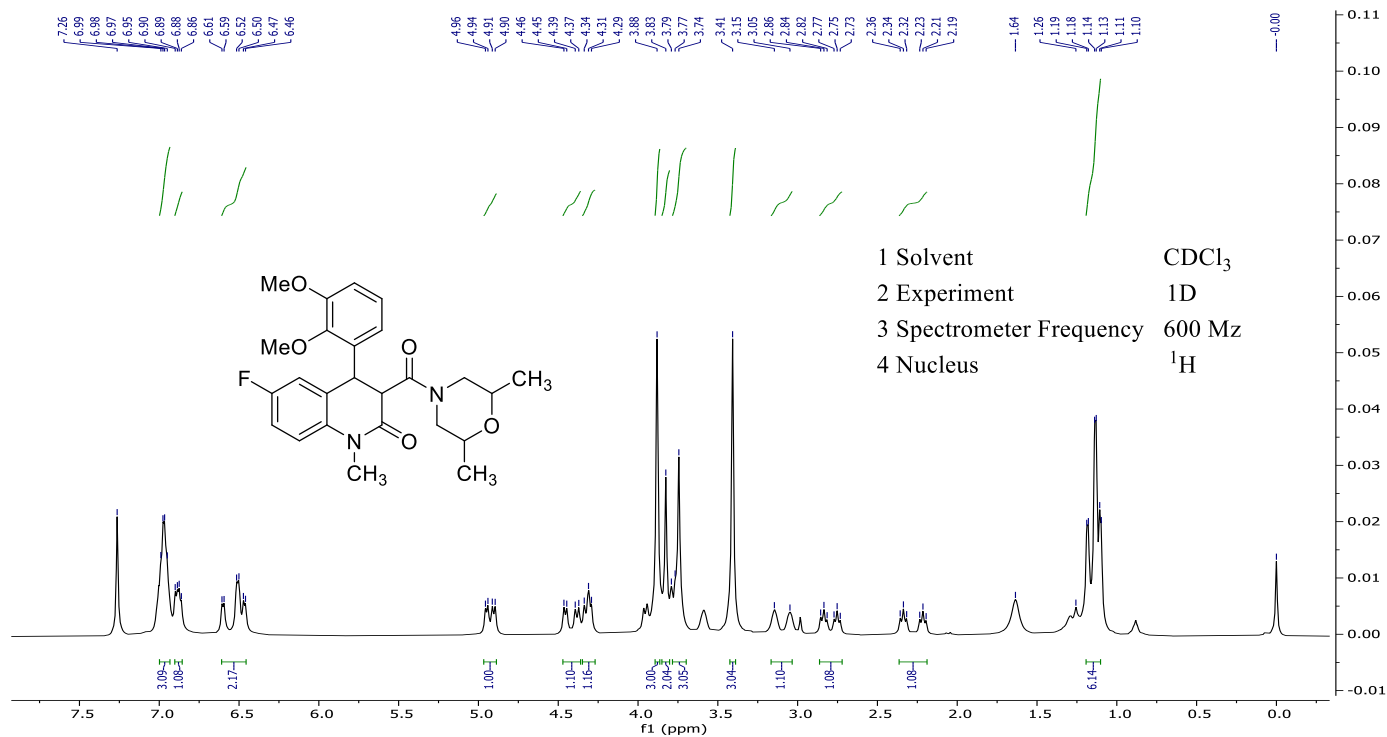
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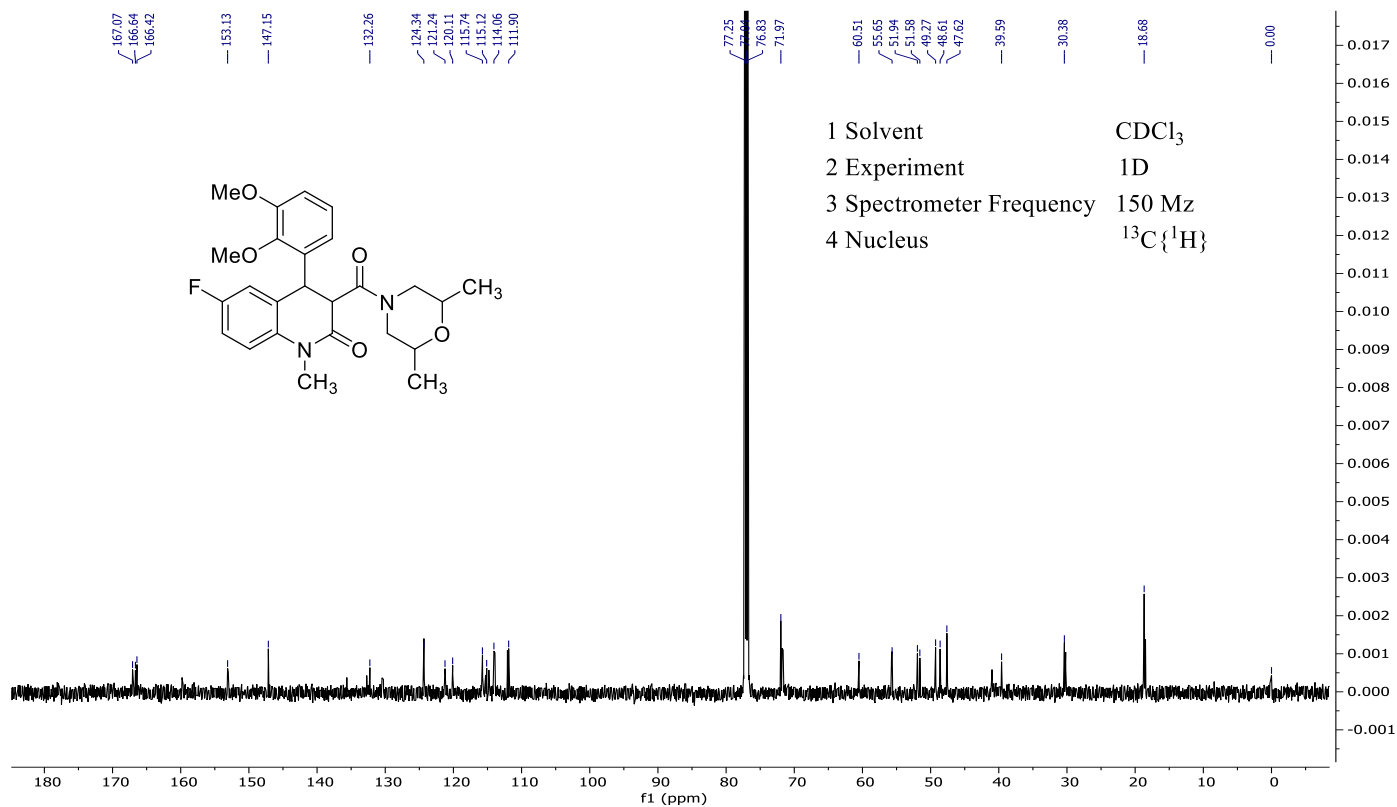
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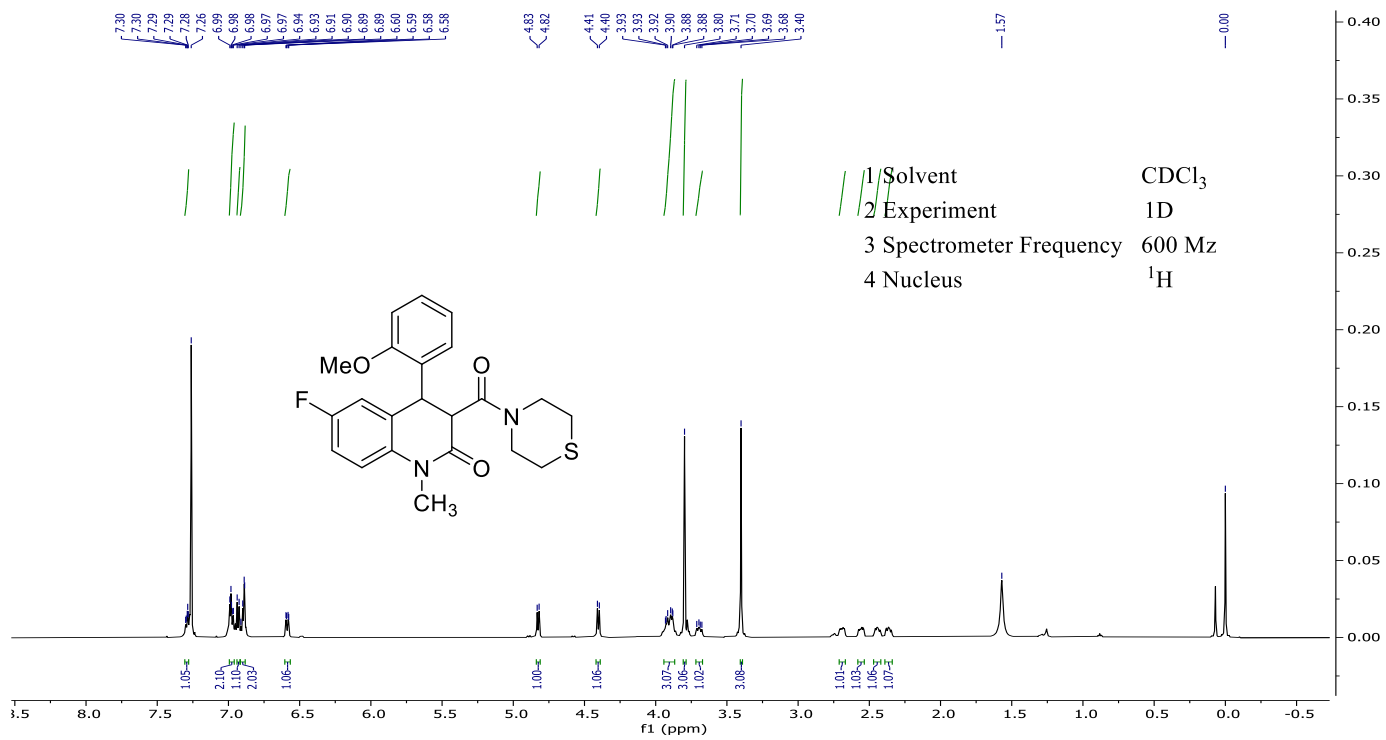
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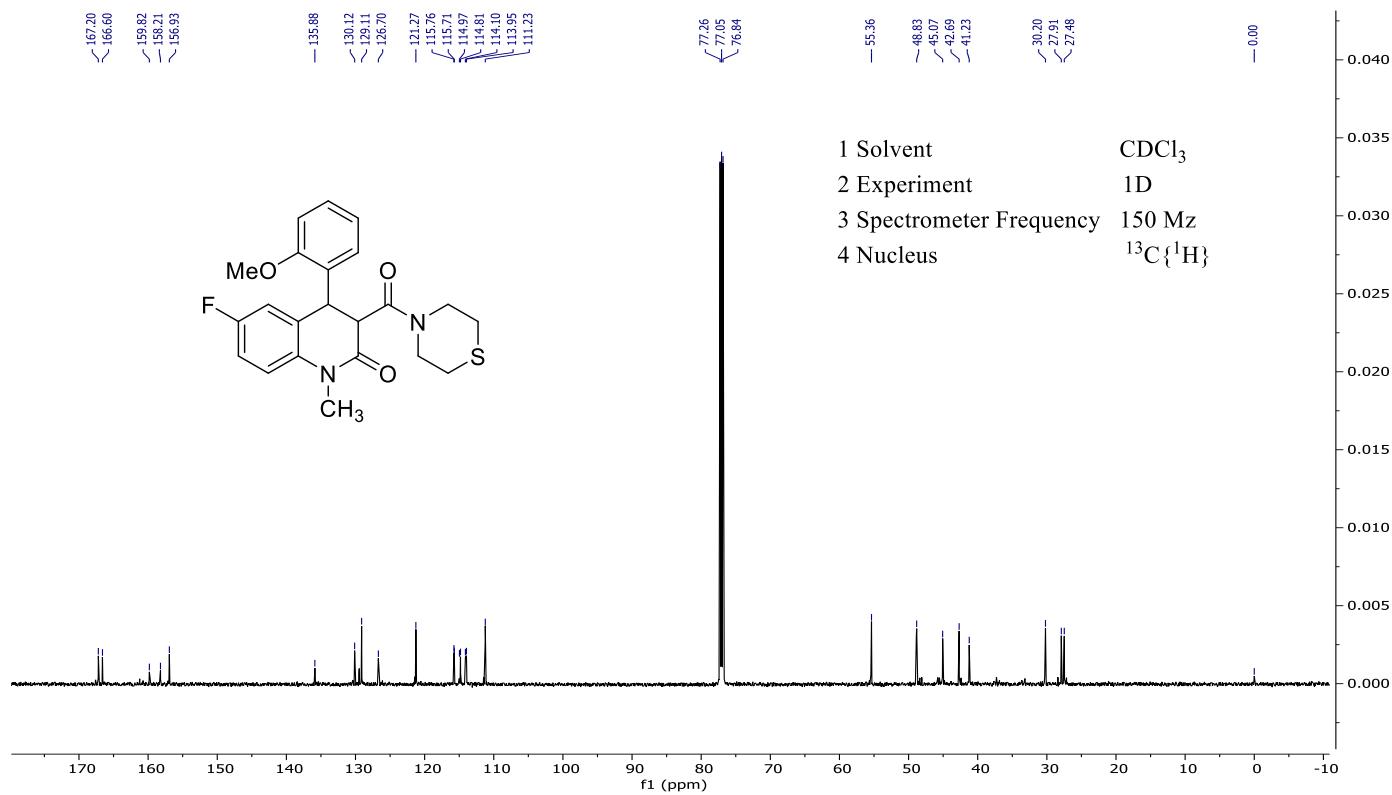
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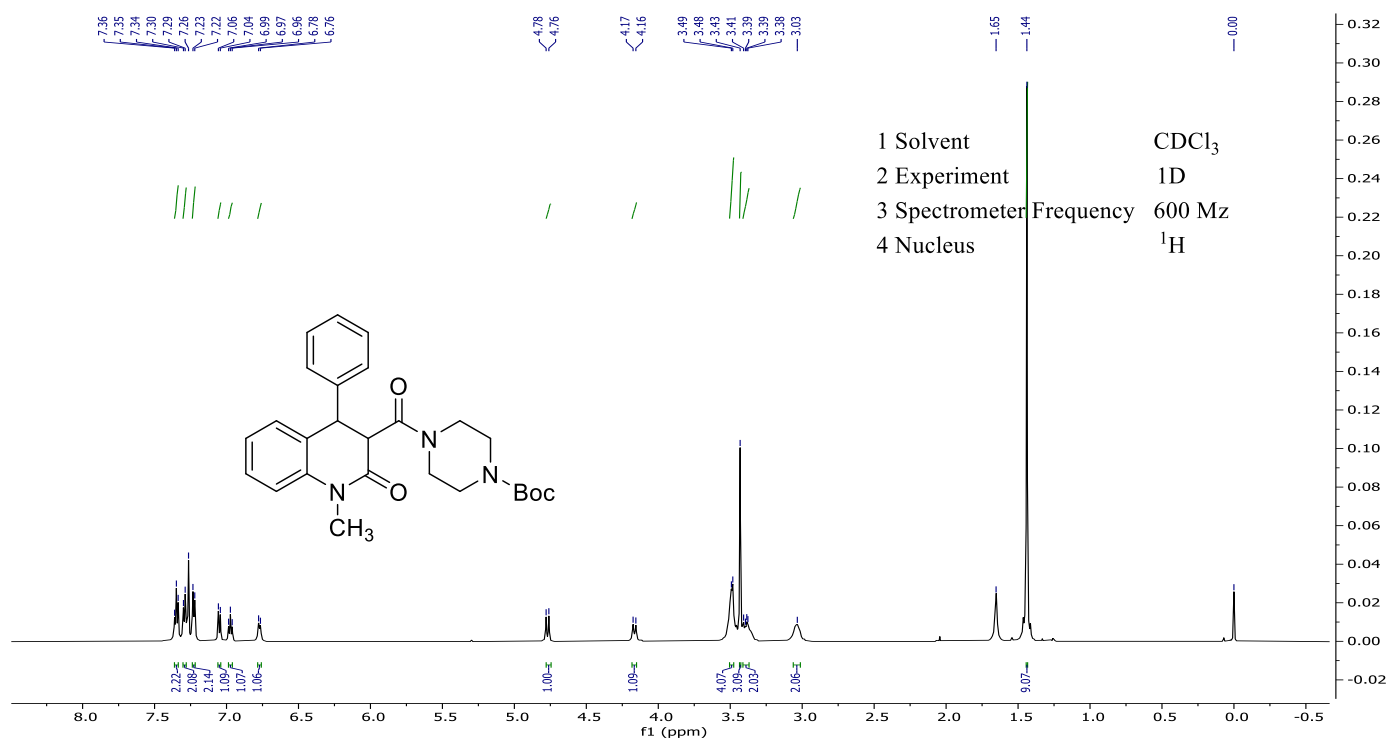
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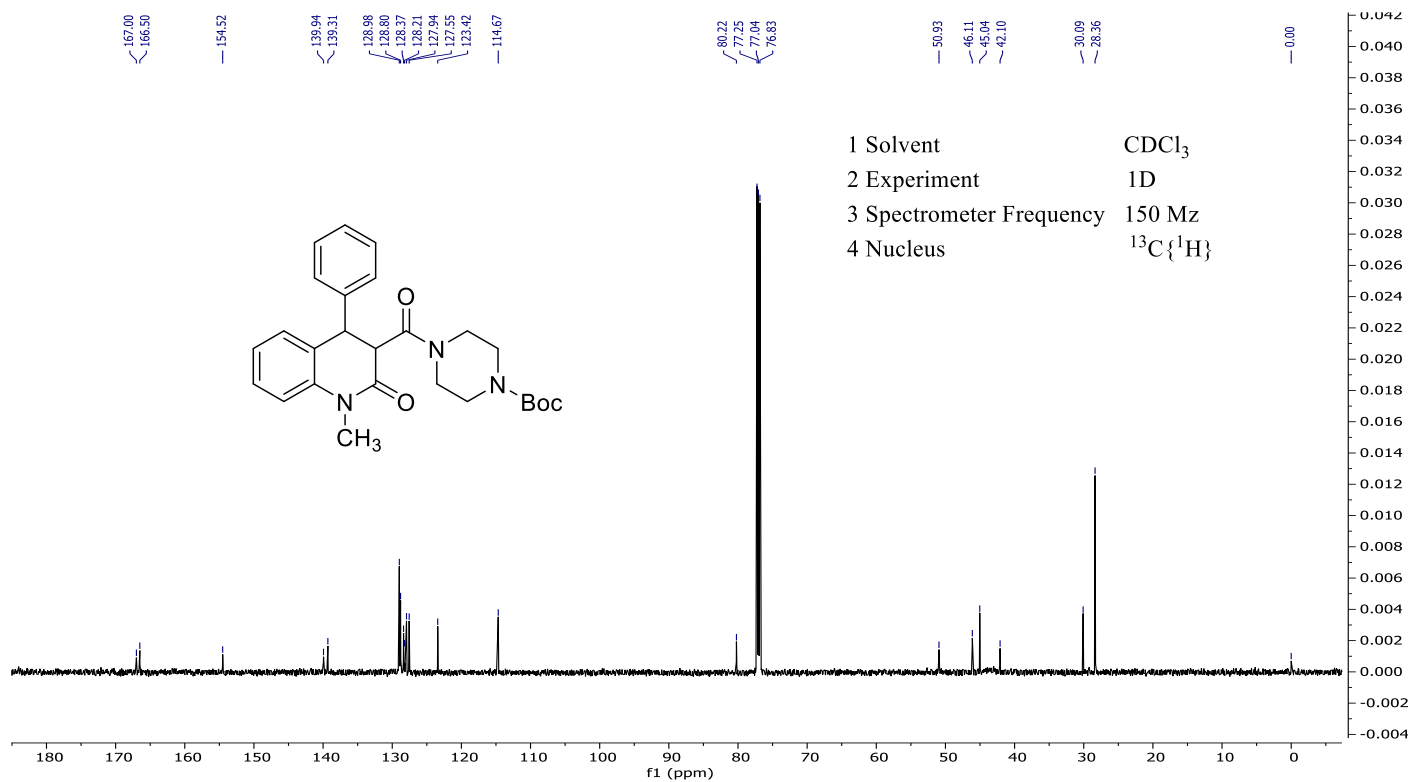
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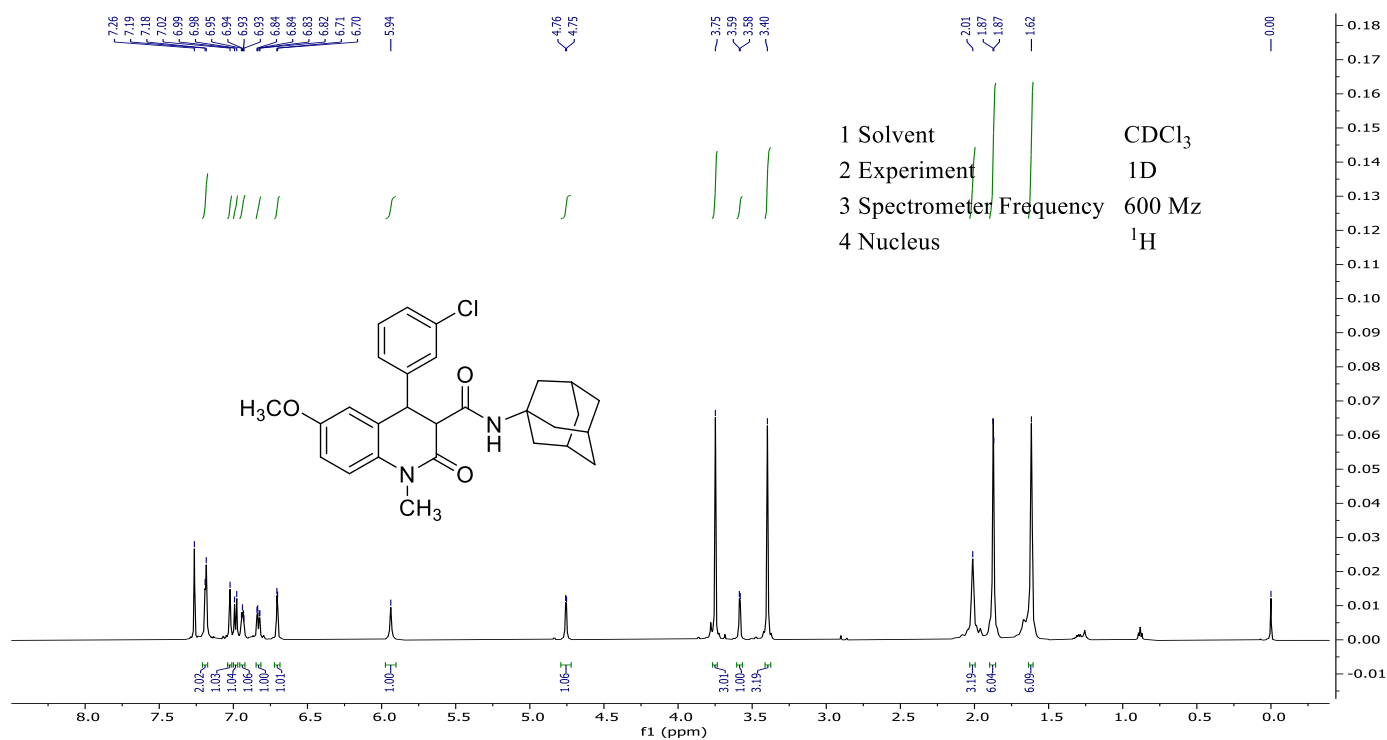
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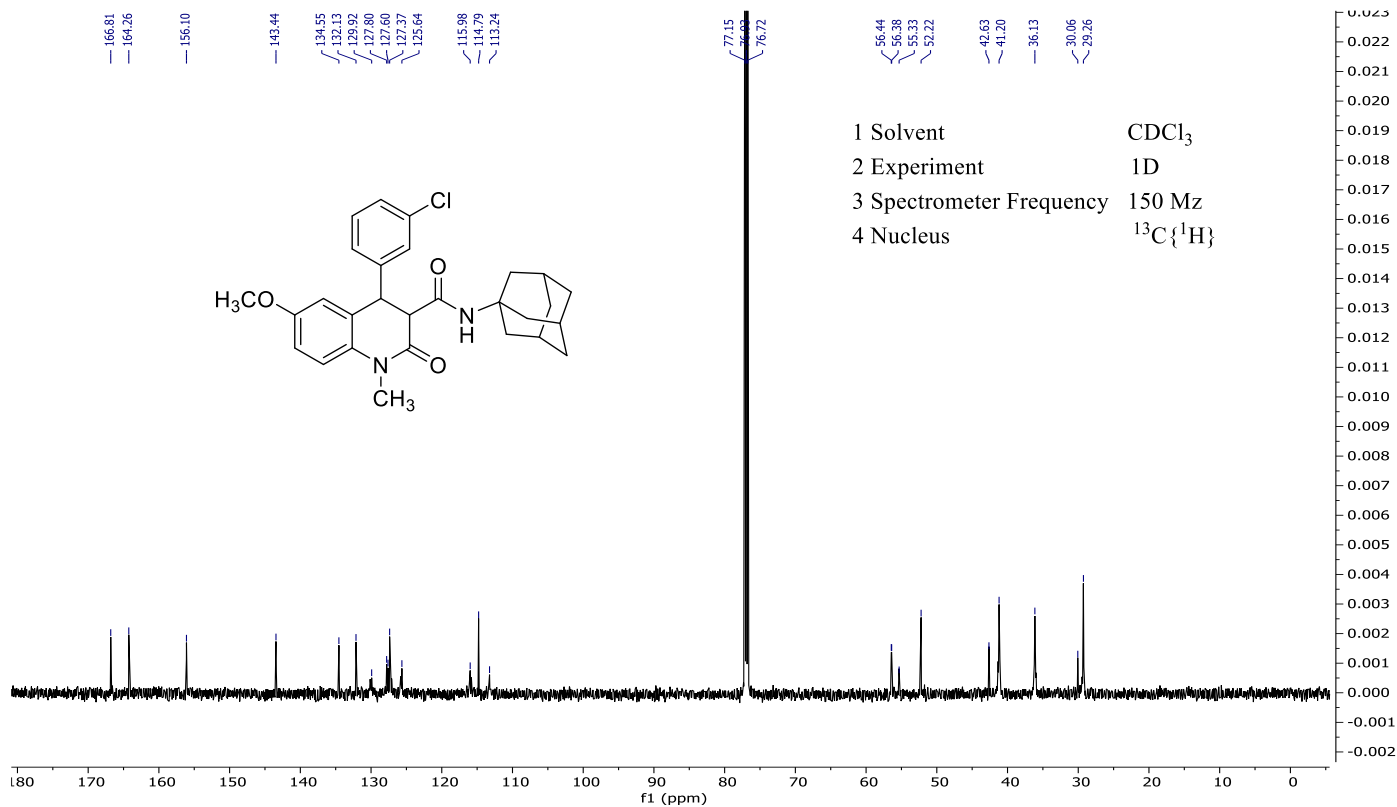
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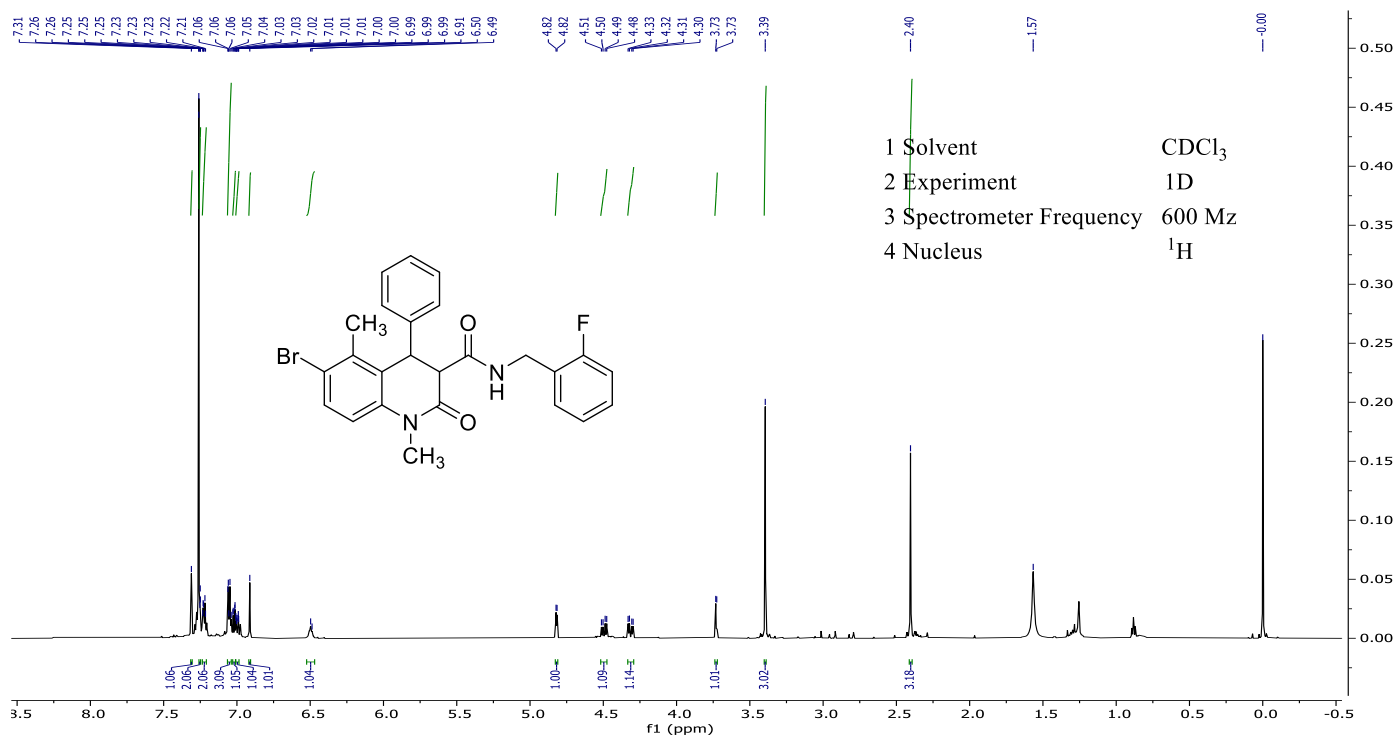
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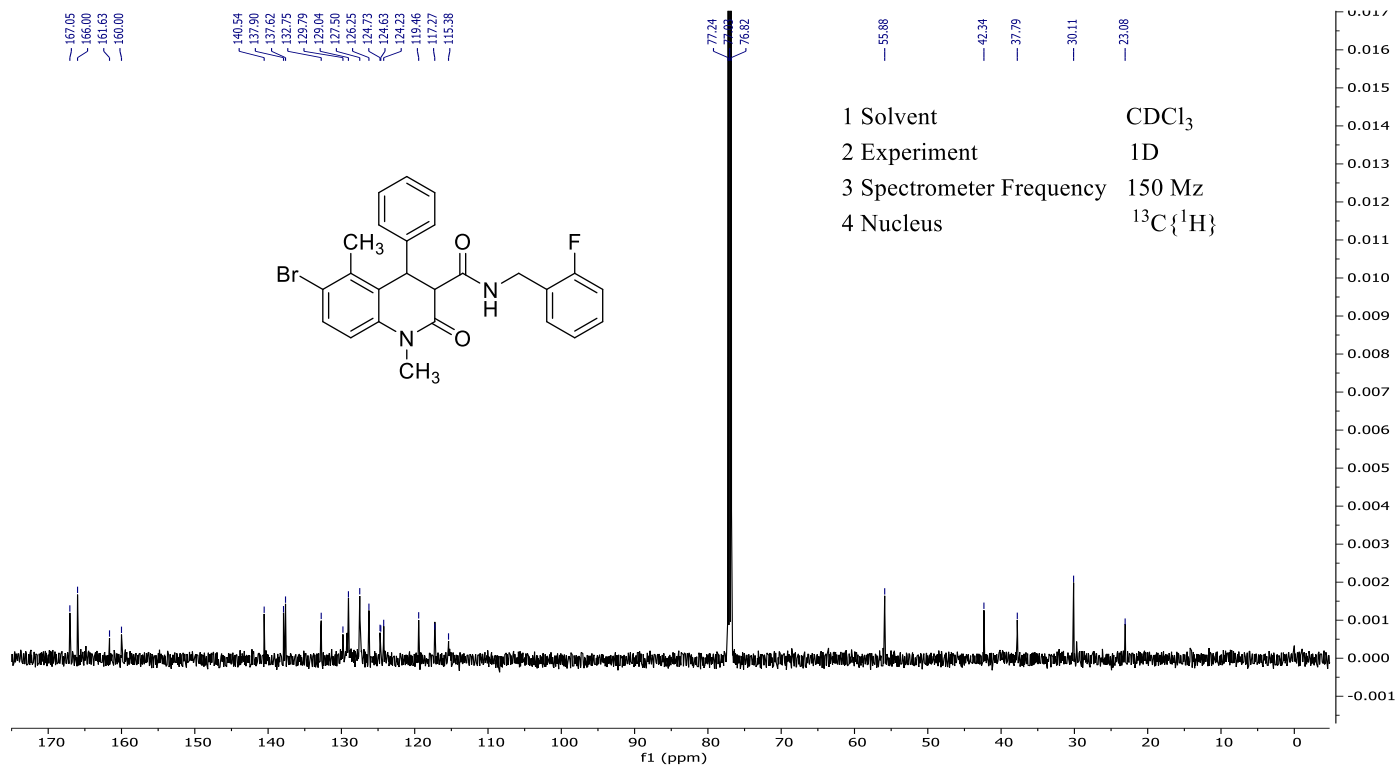
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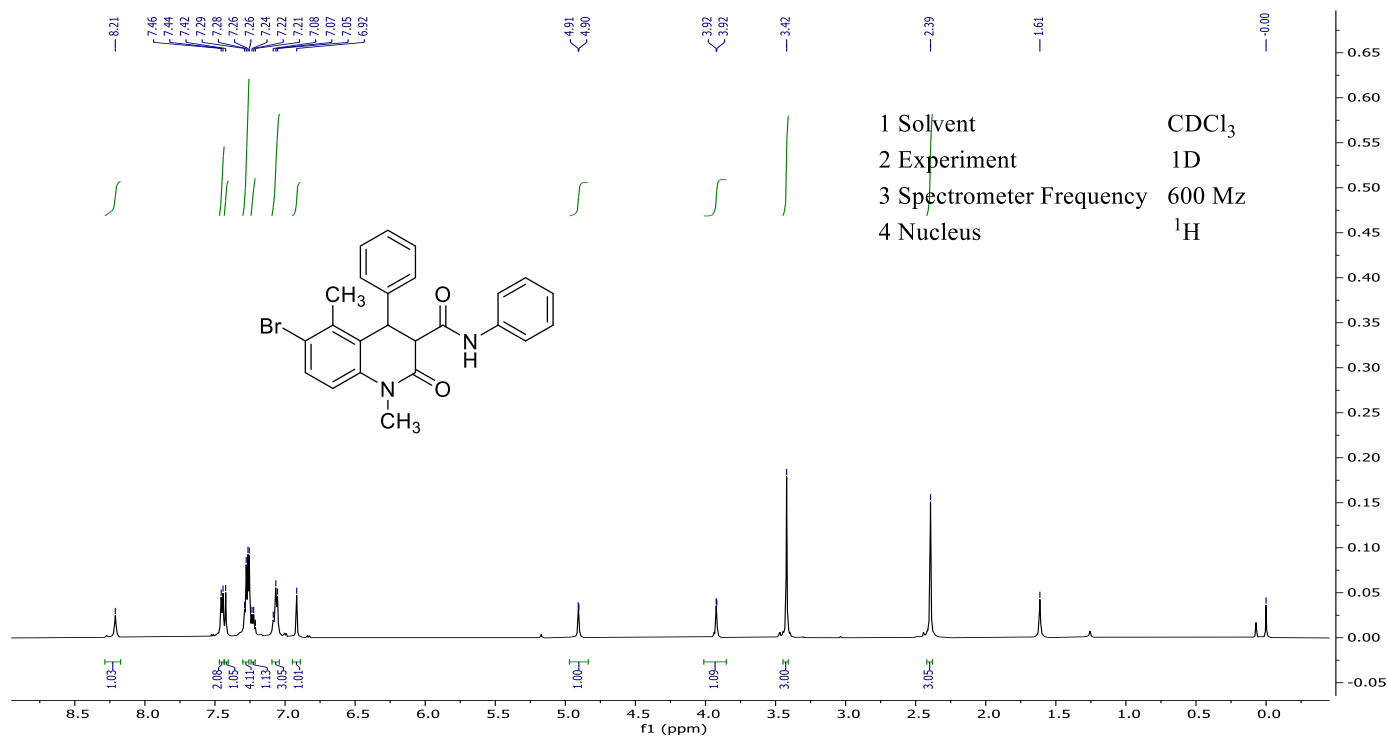
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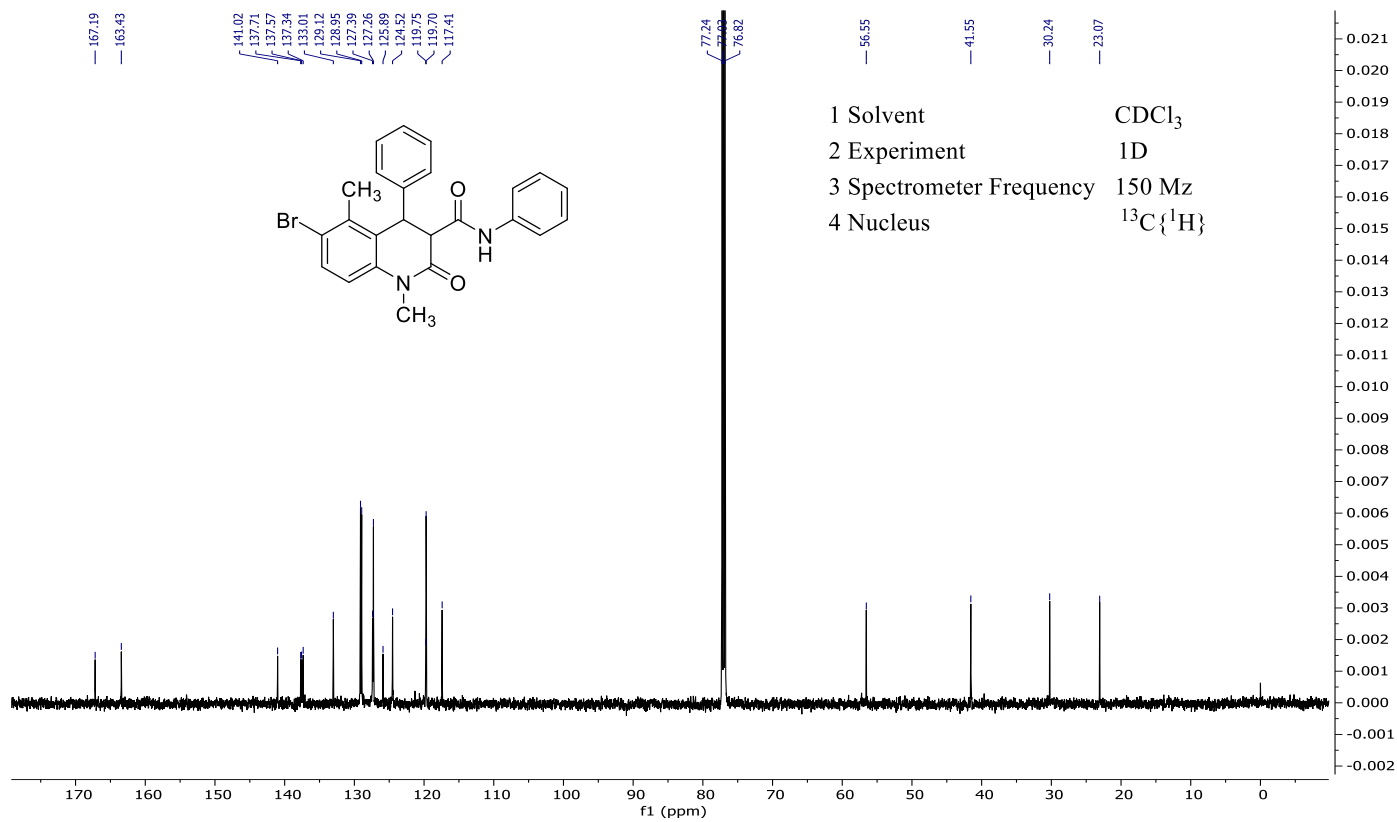
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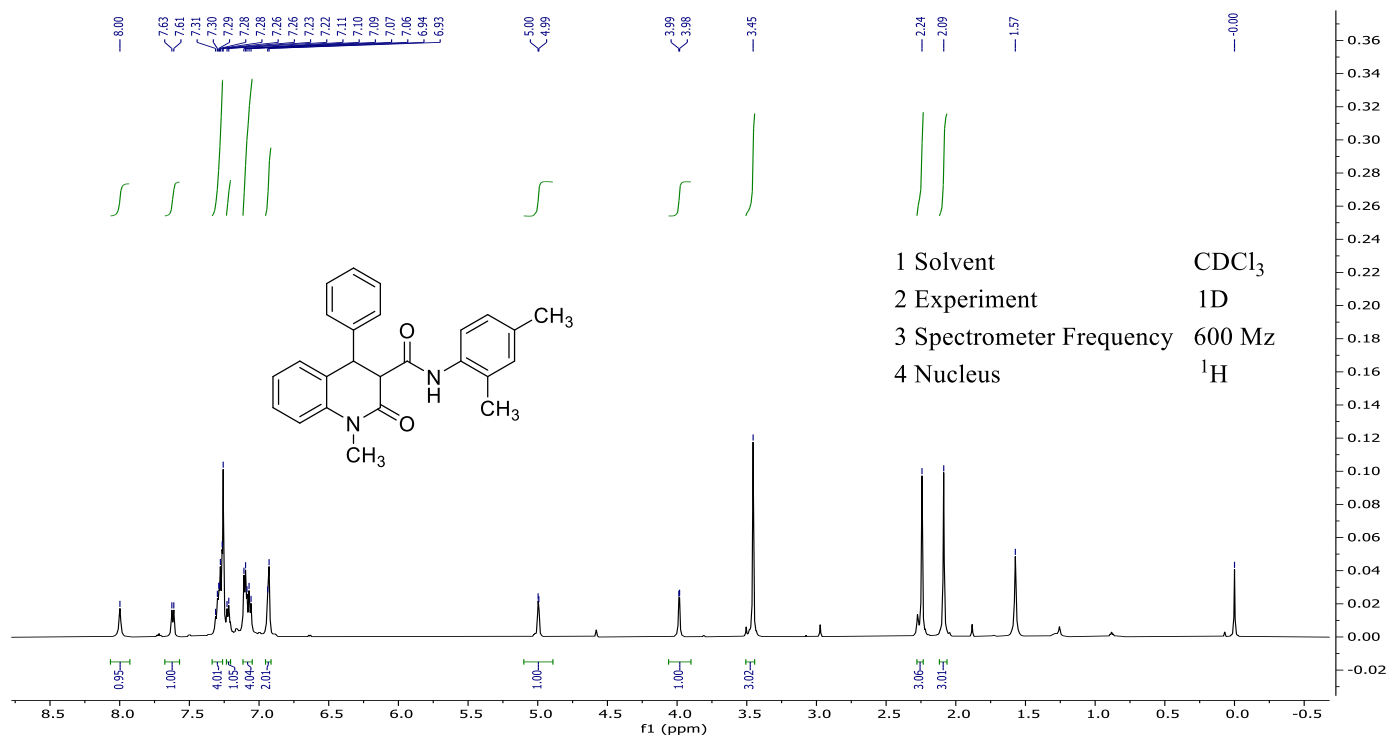
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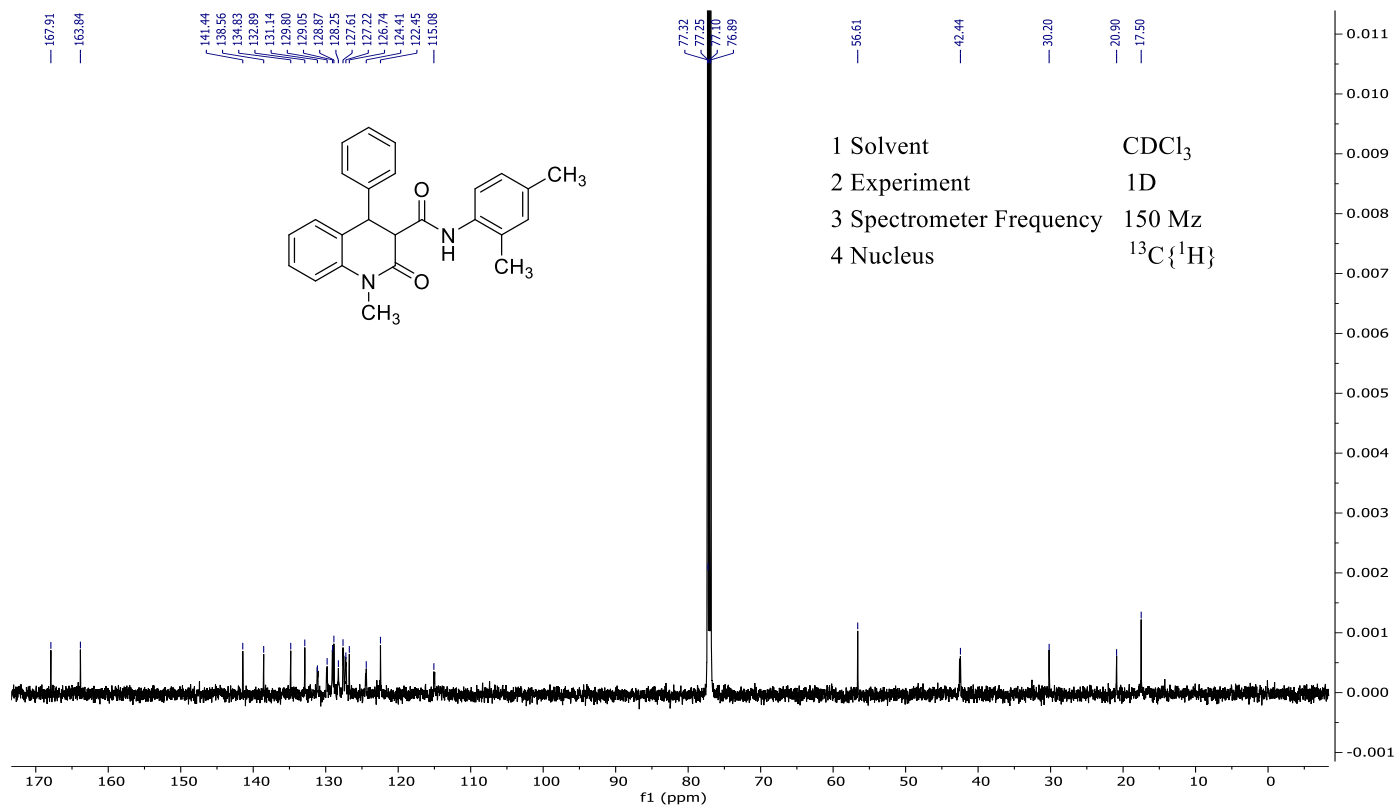
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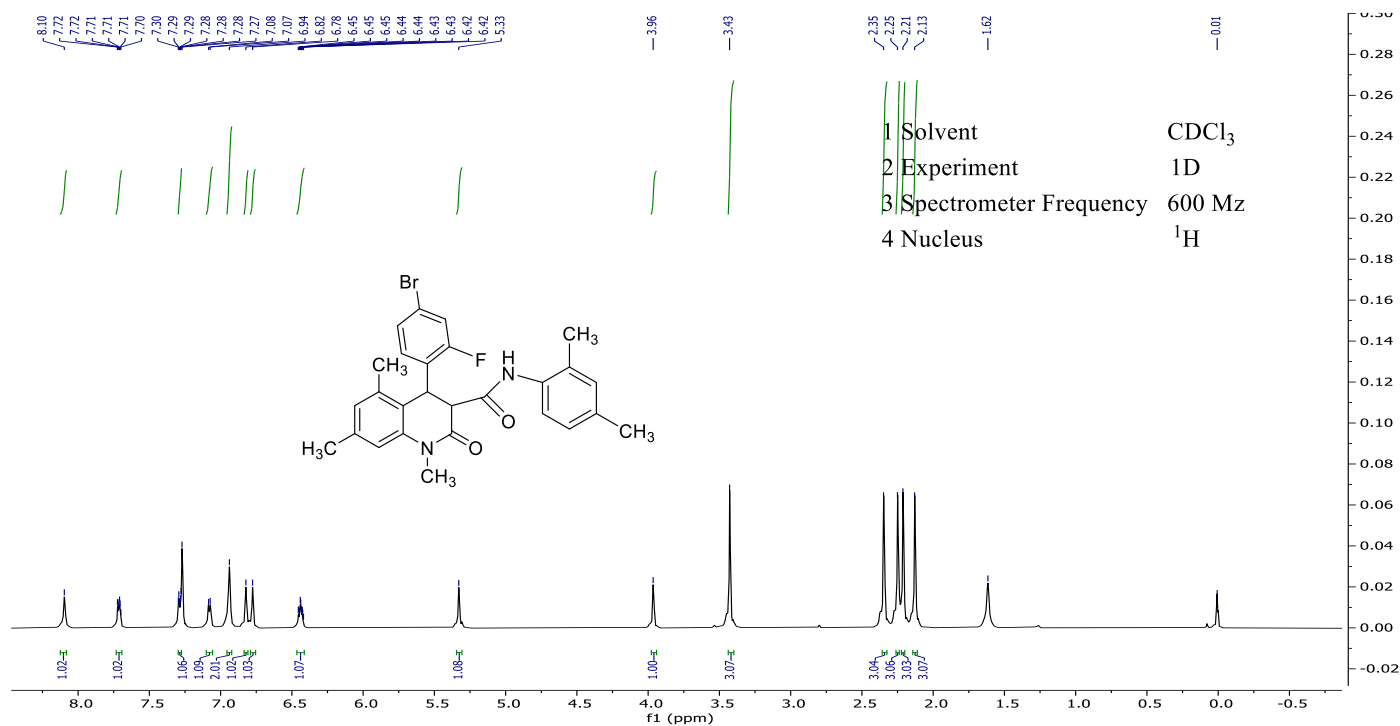
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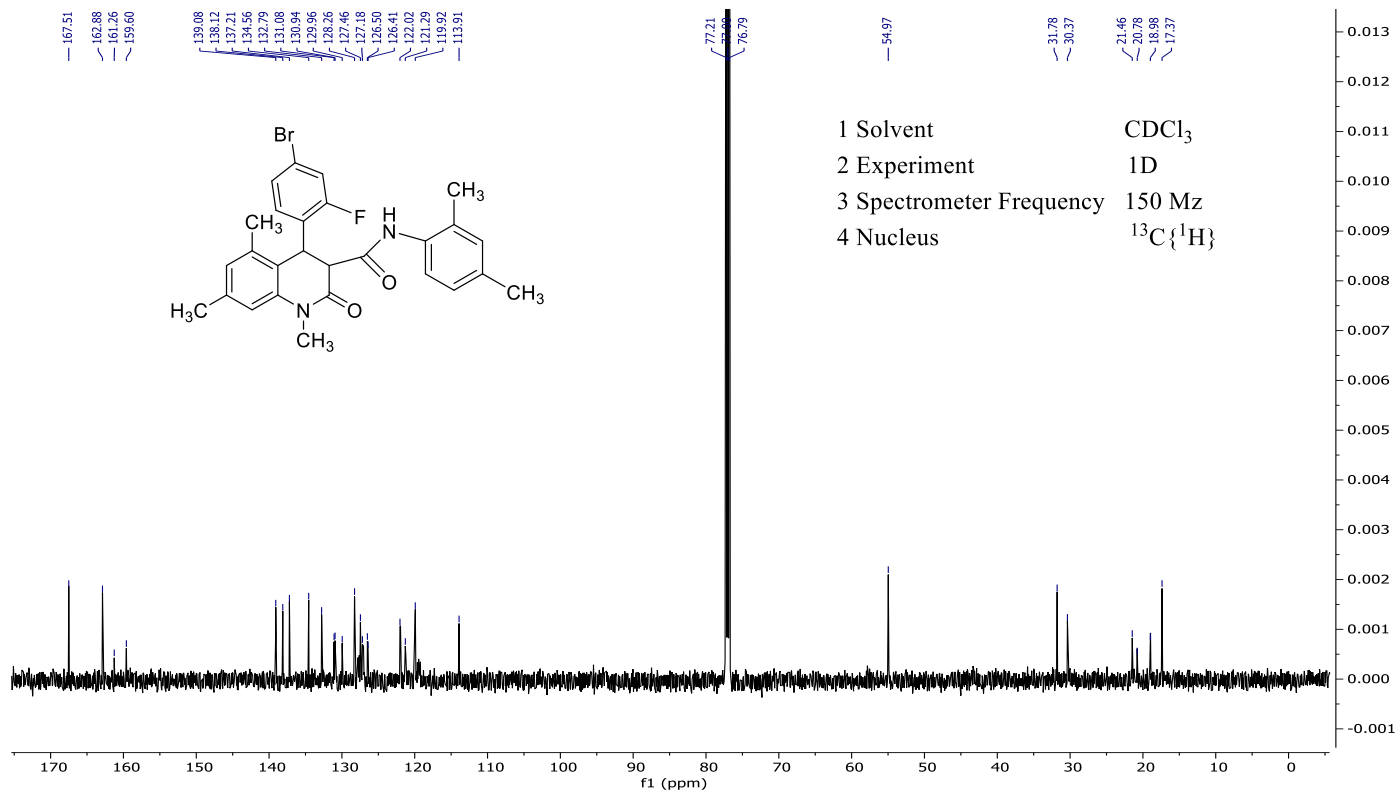
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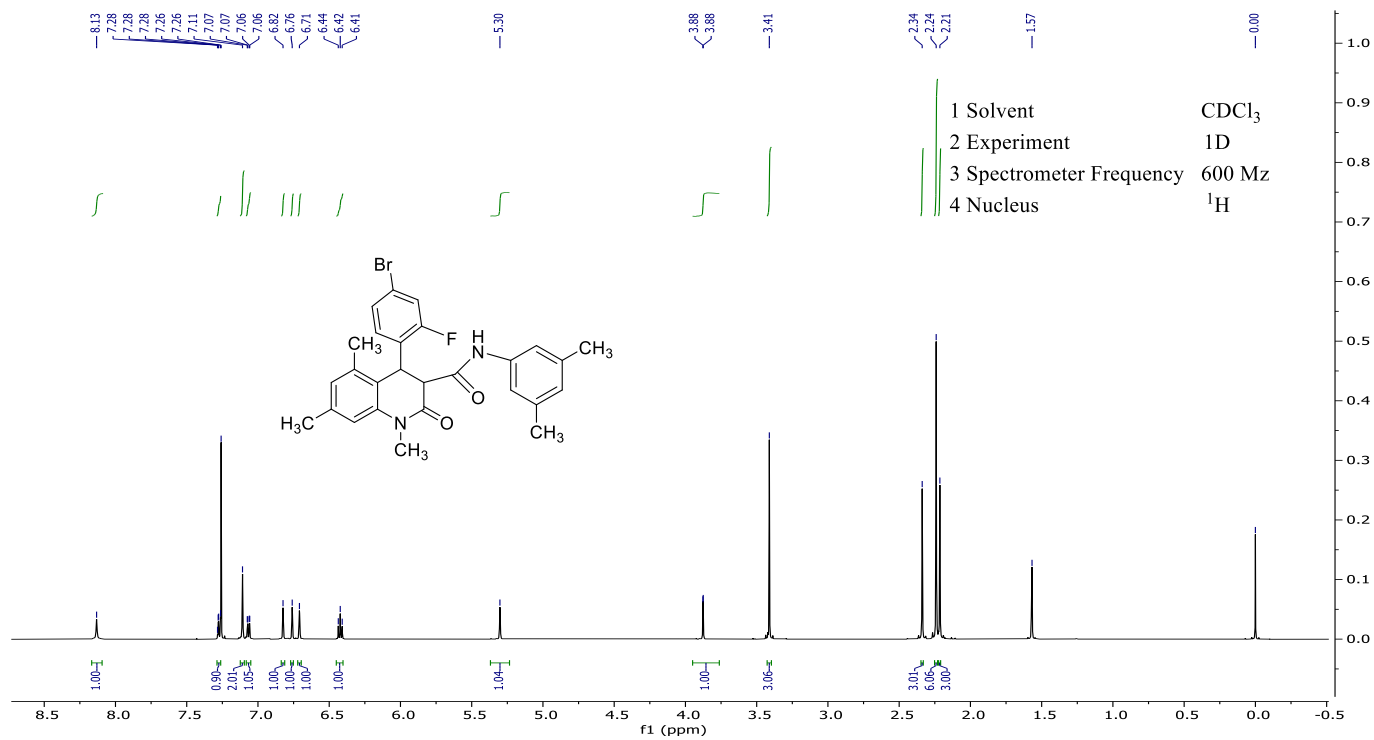
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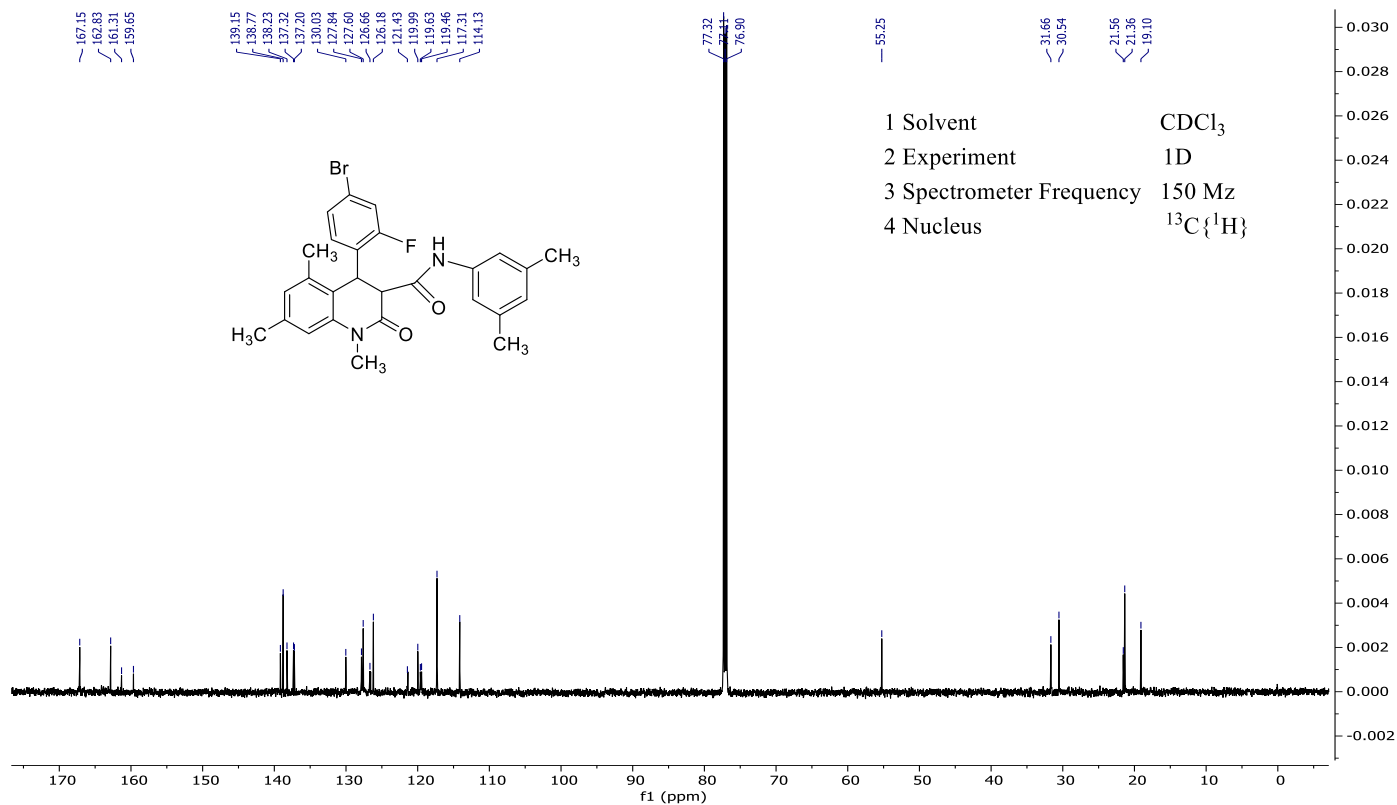
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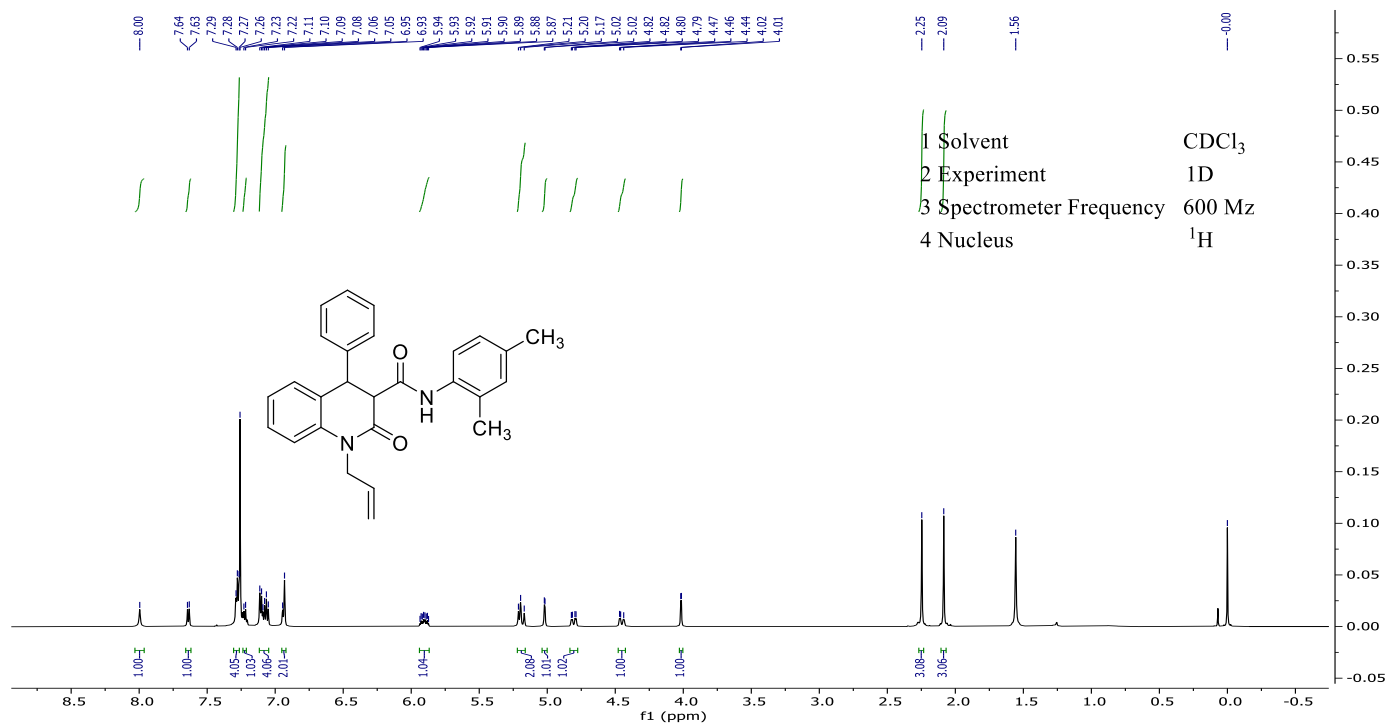
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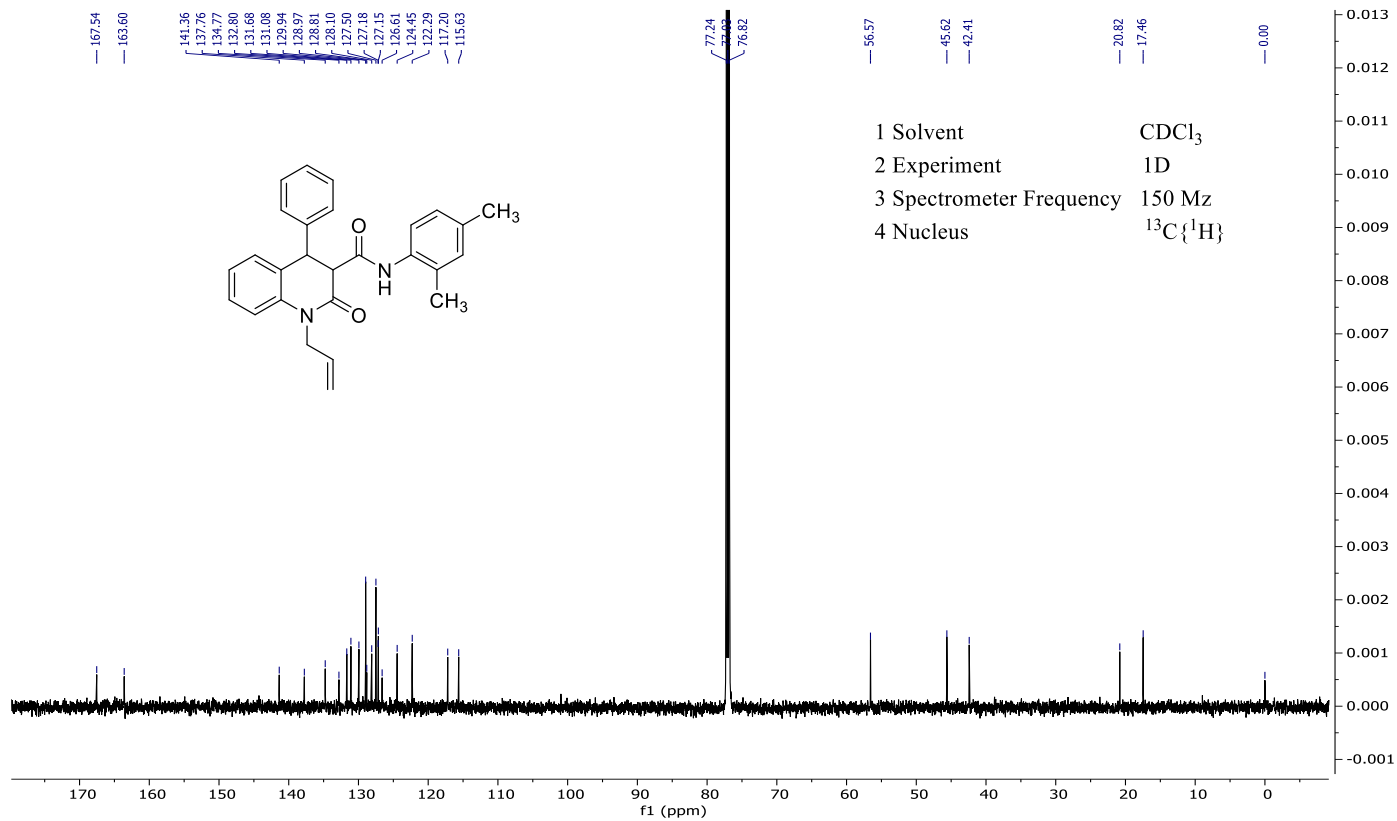
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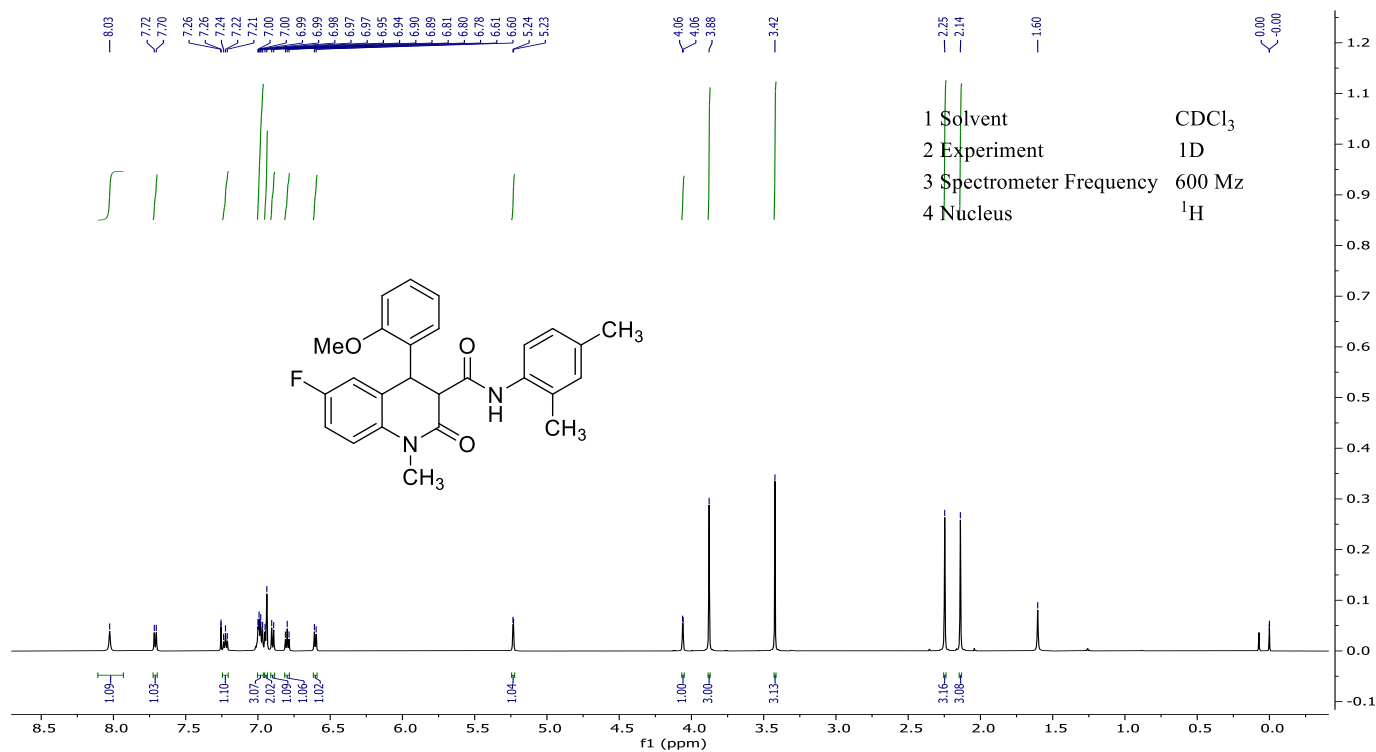
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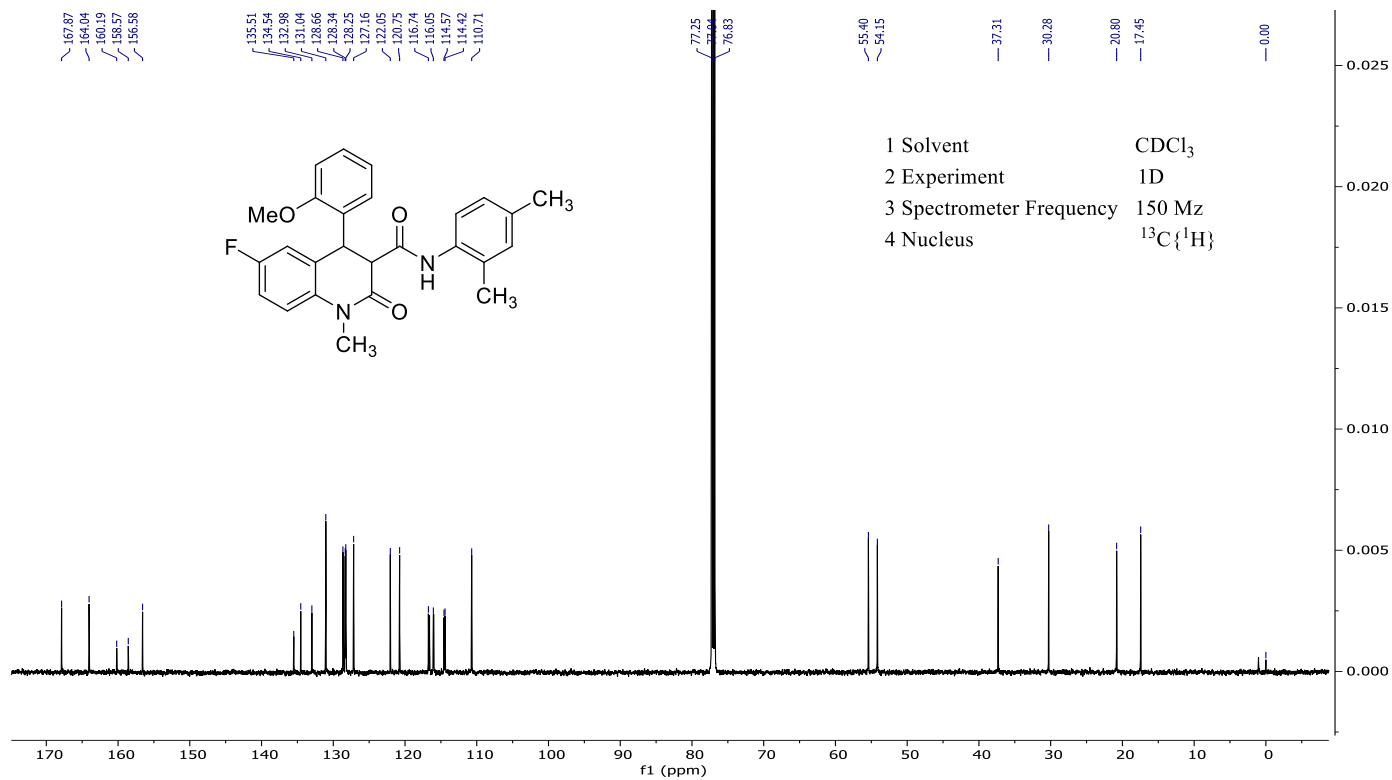
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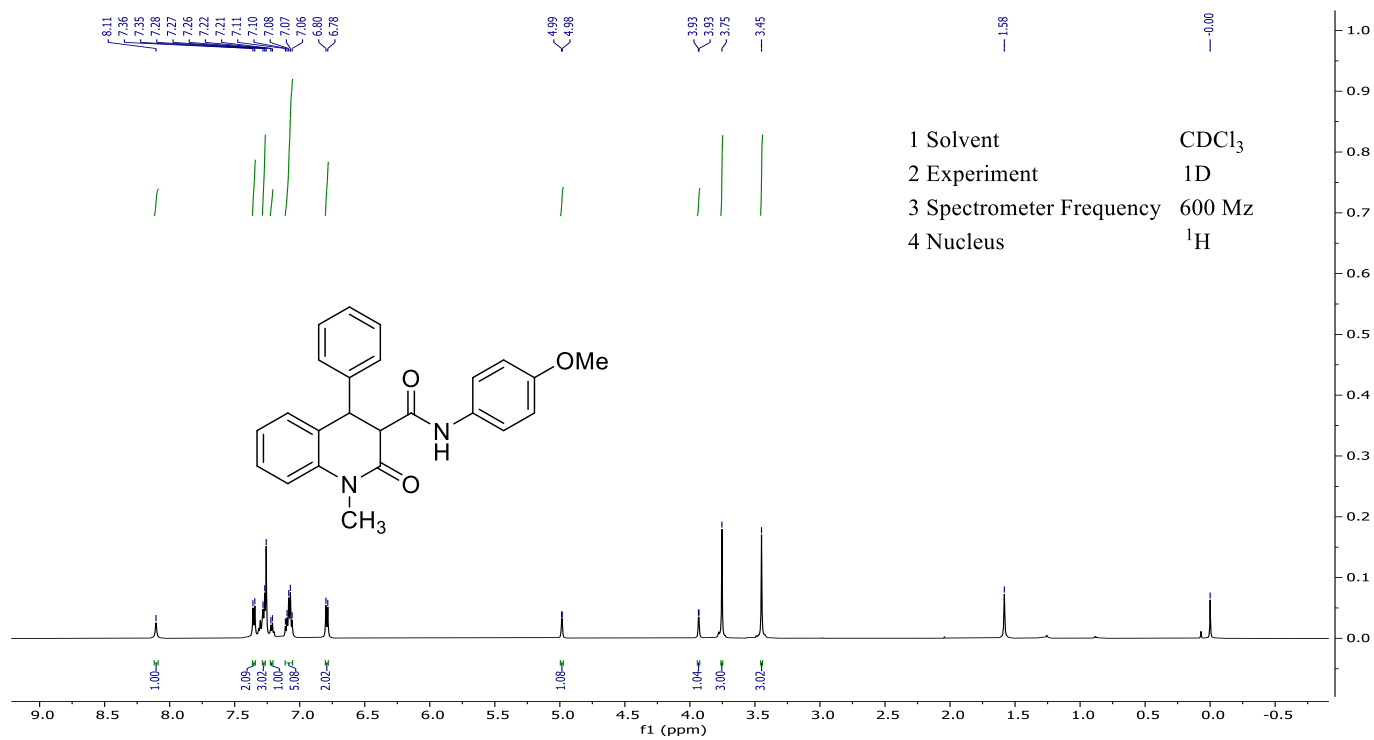
¹H NMR of 3u



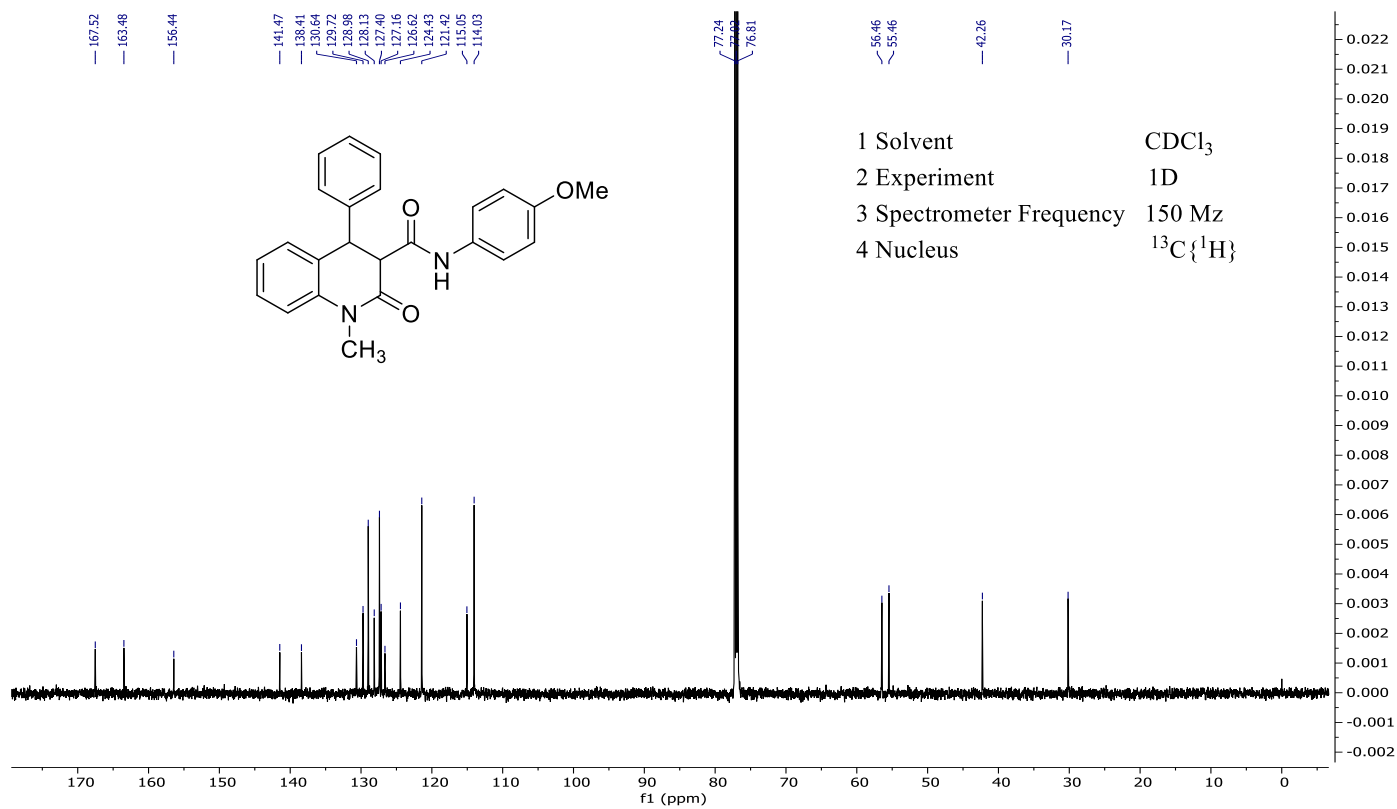
¹³C{¹H} of 3u



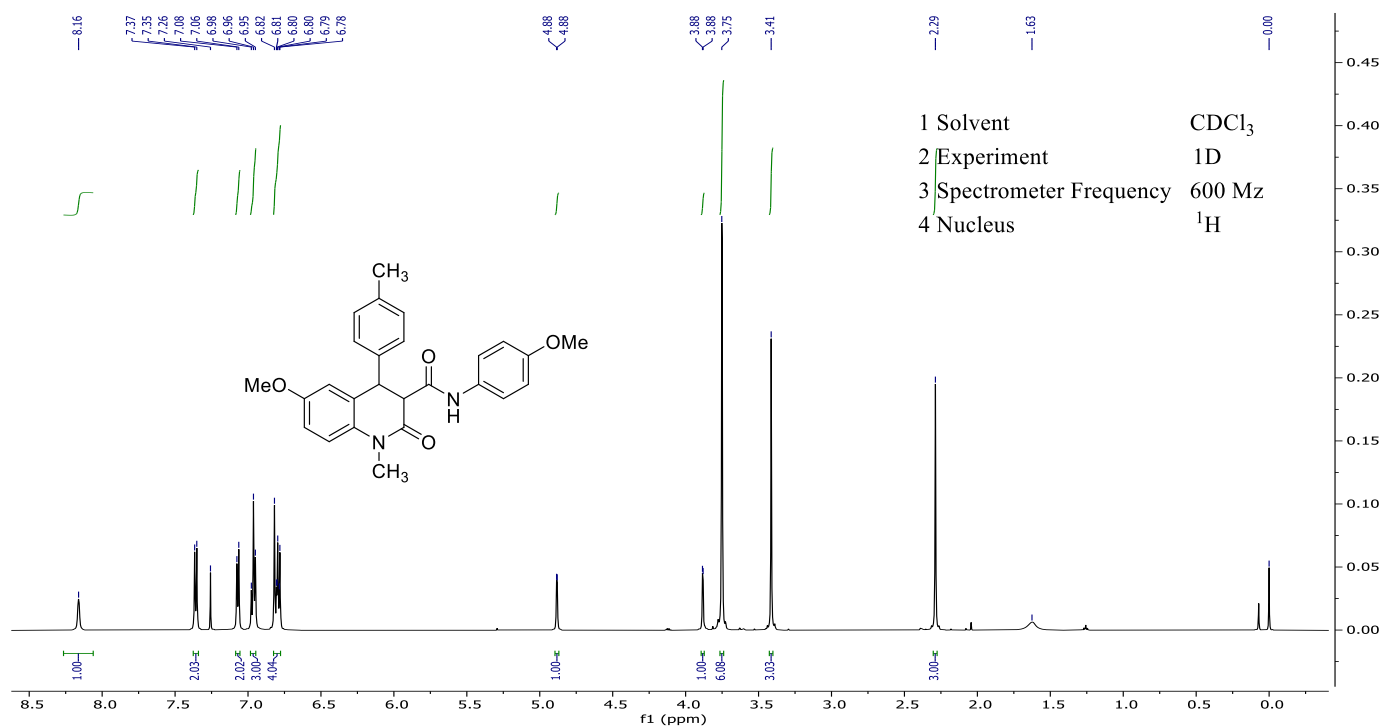
¹H NMR of 3v



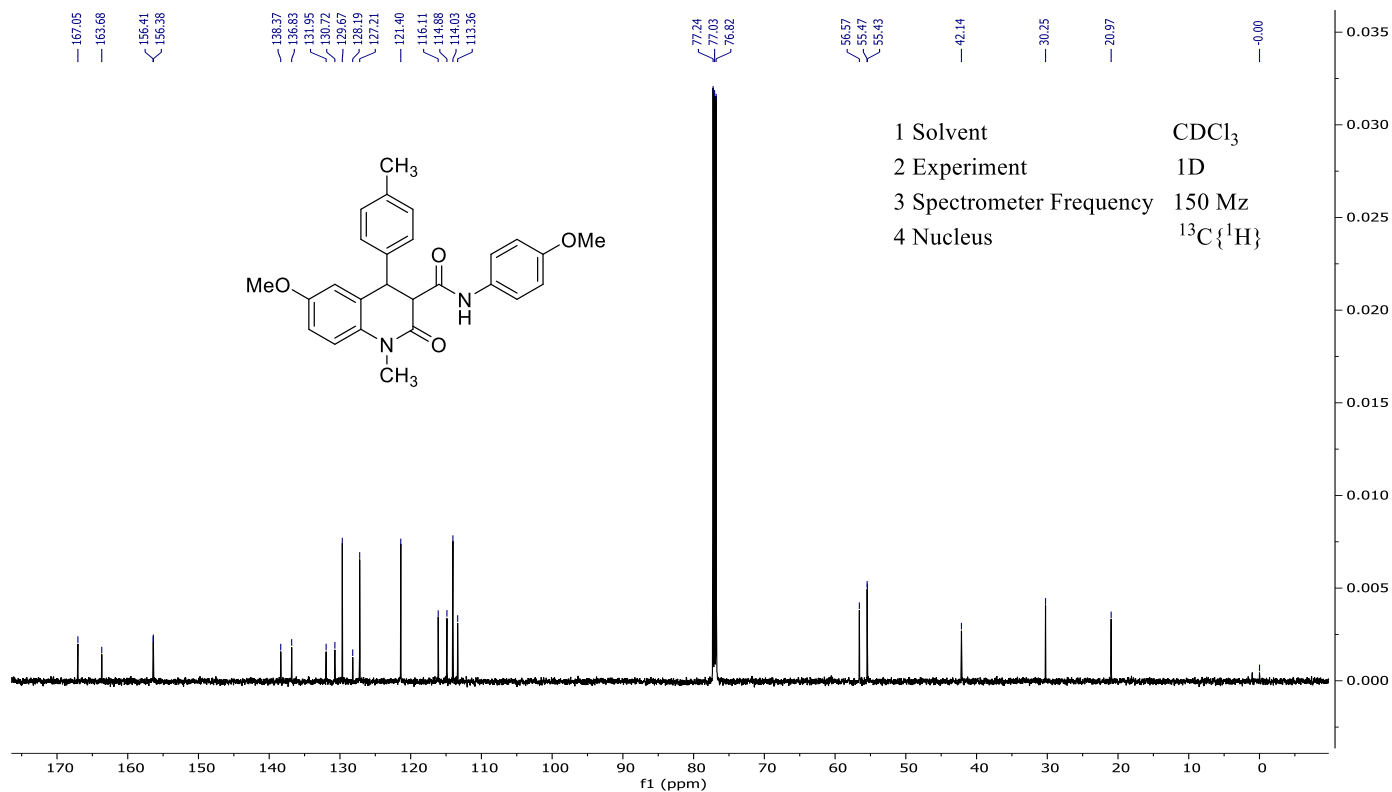
¹³C{¹H} of 3v



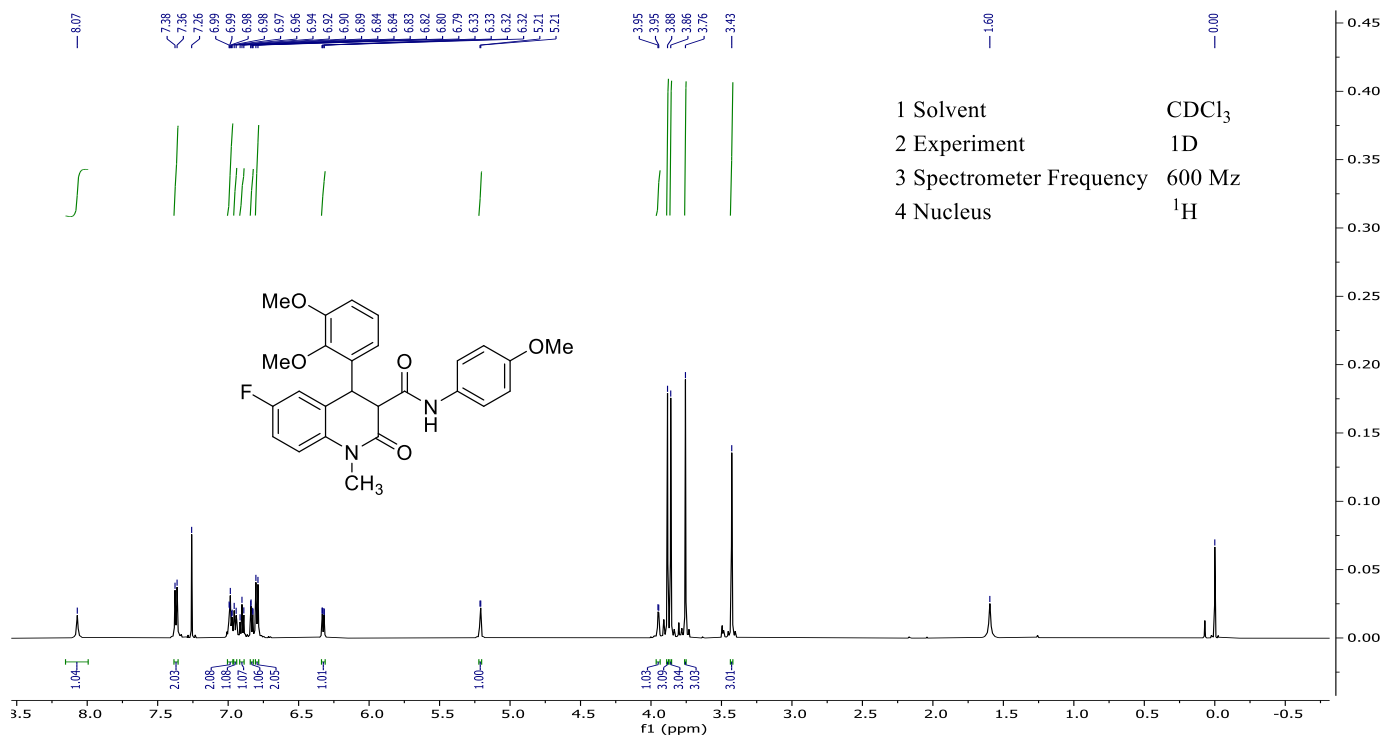
¹H NMR of 3w



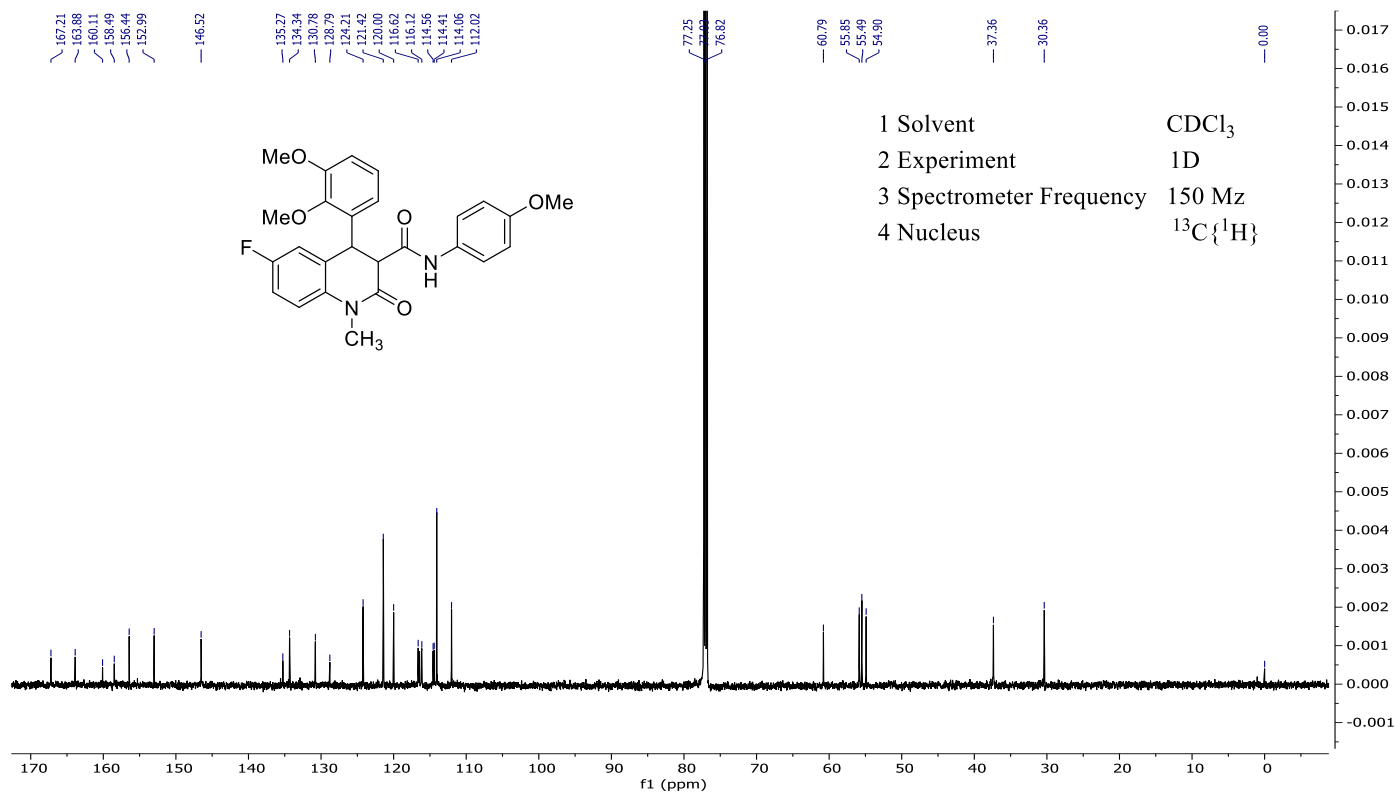
¹³C{¹H} of 3w



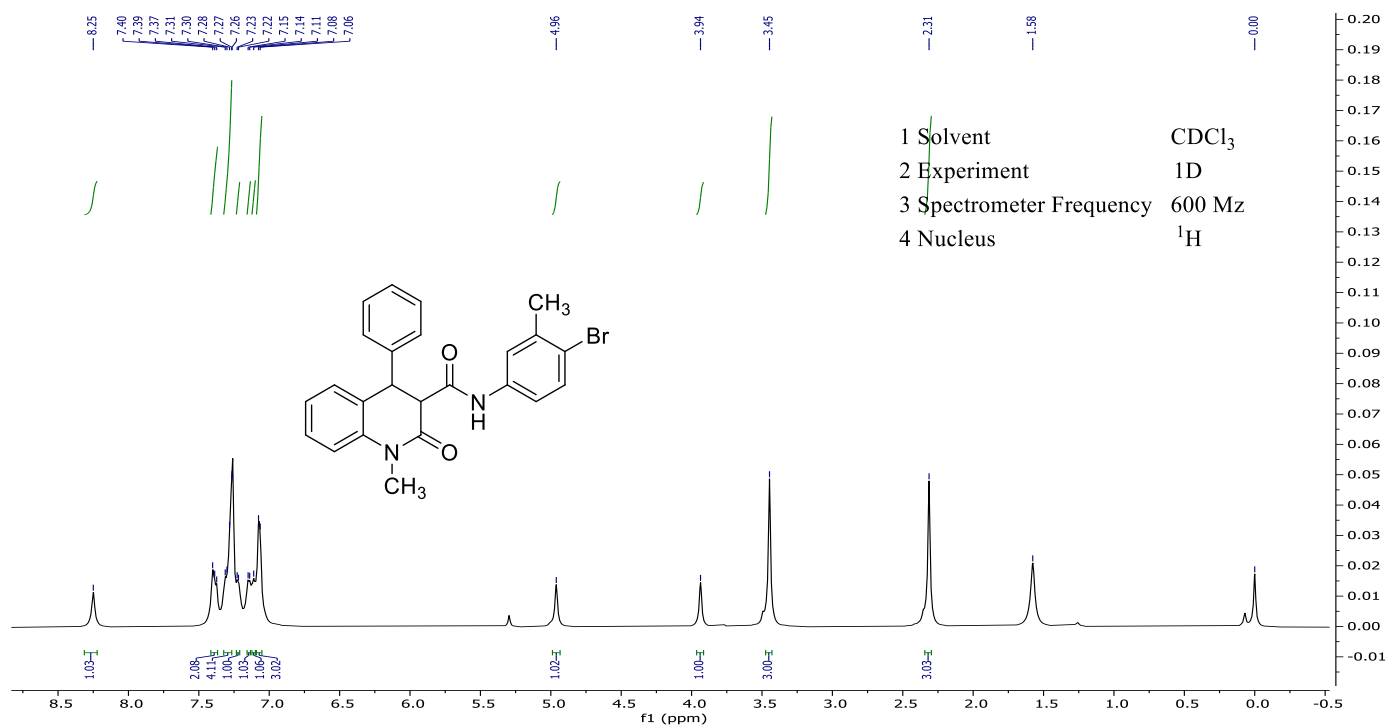
¹H NMR of 3x



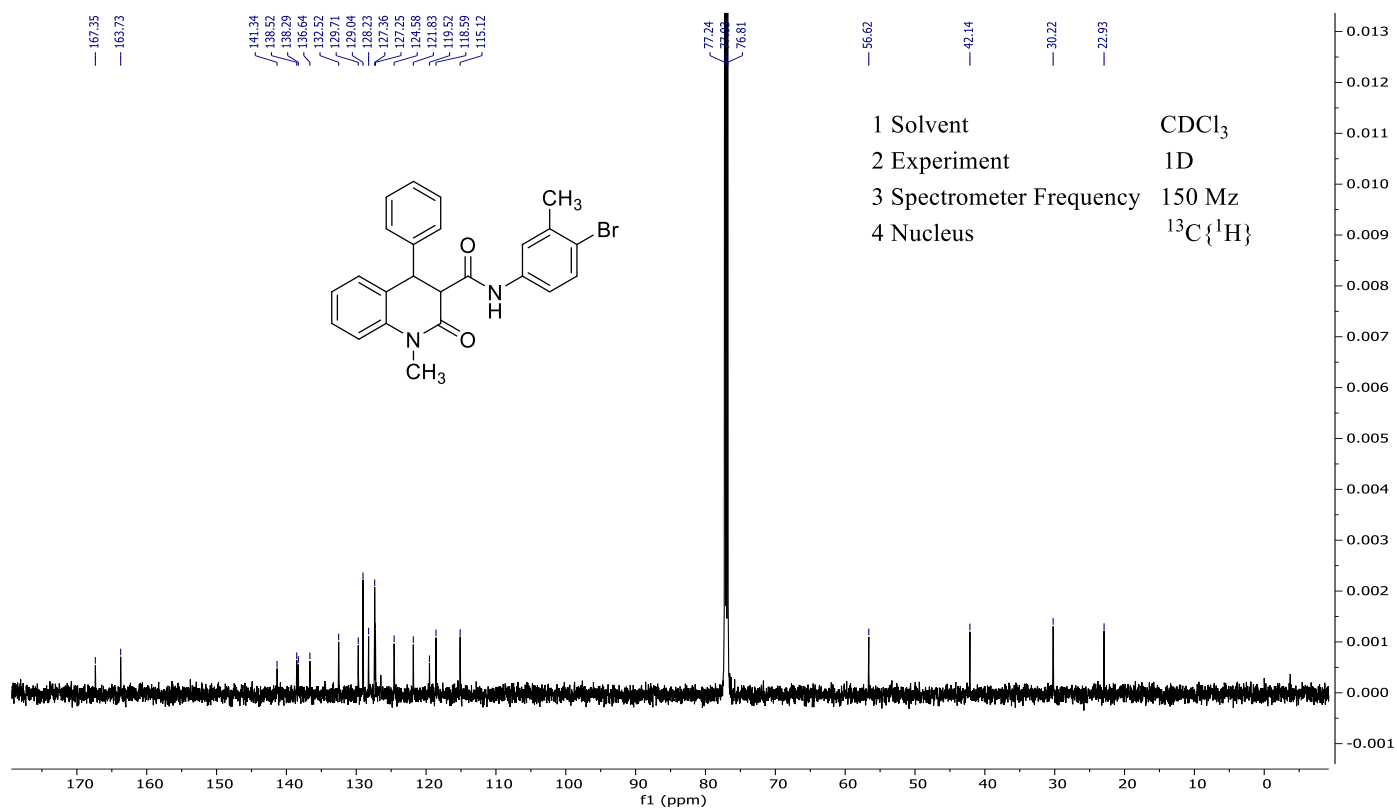
¹³C{¹H} of 3x



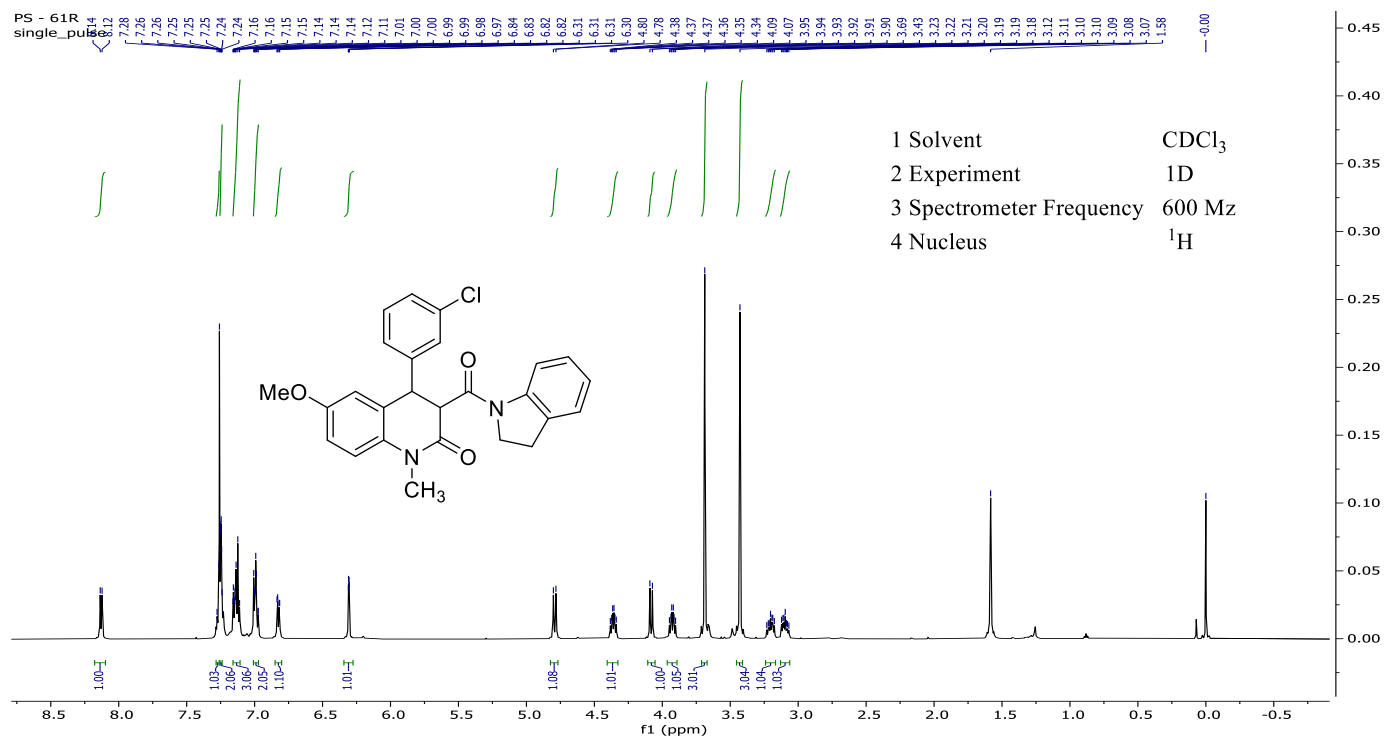
¹H NMR of 3y



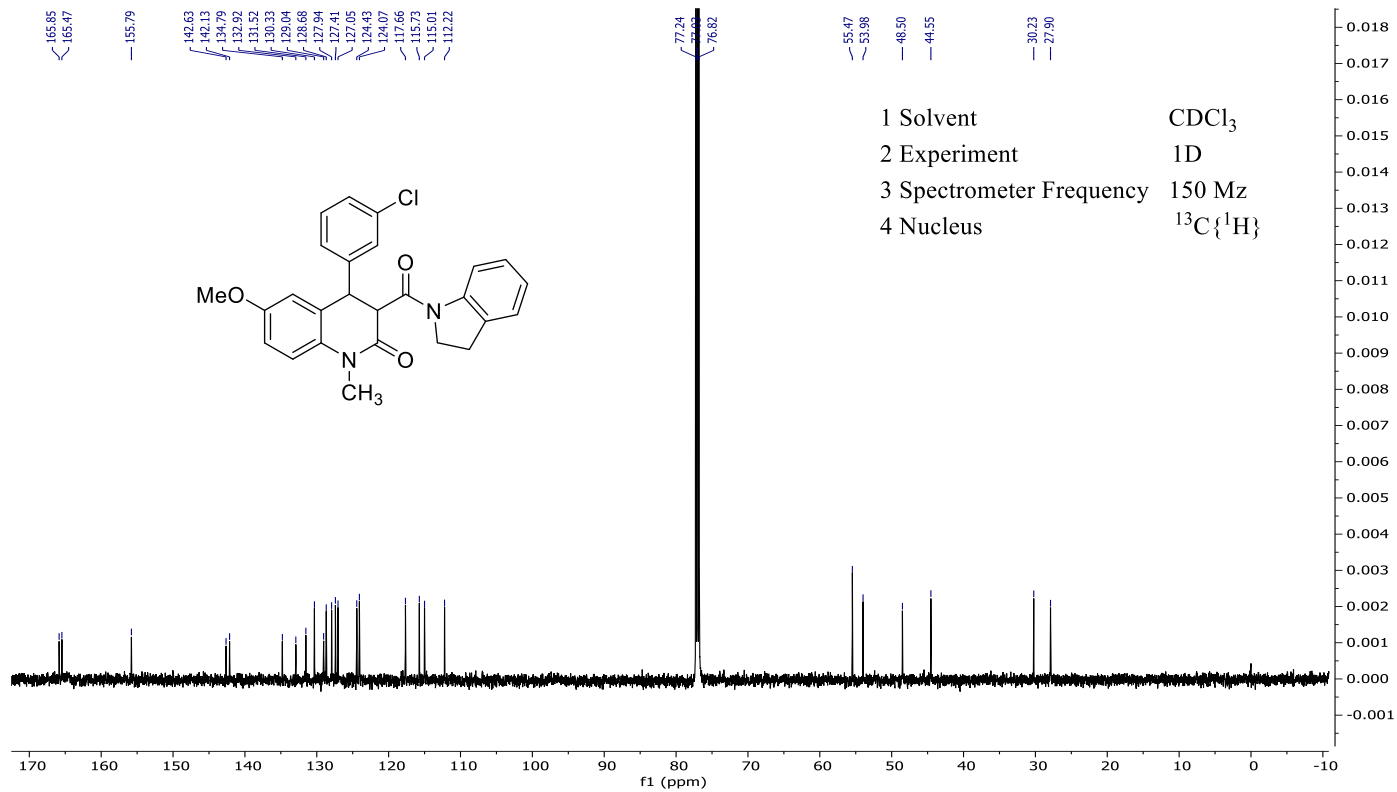
¹³C{¹H} of 3y



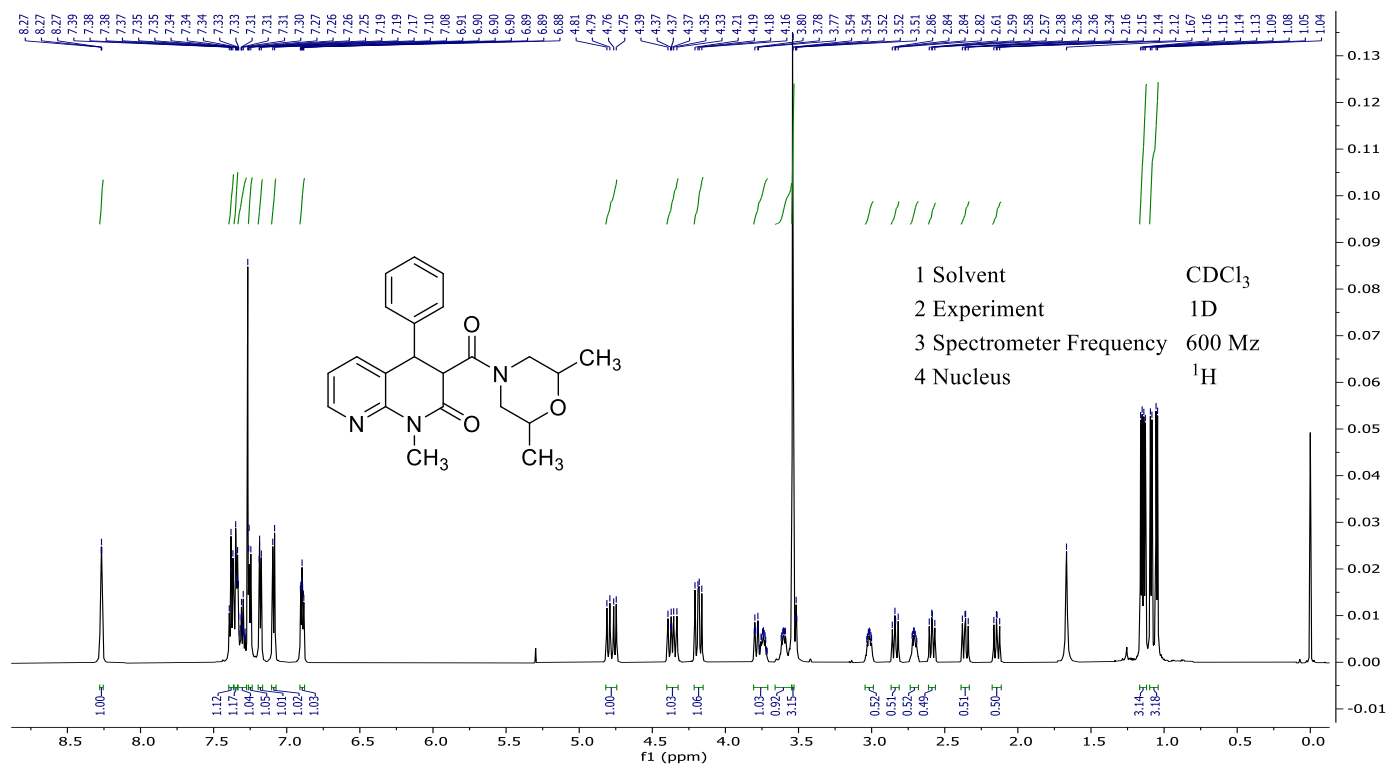
¹H NMR of 3z



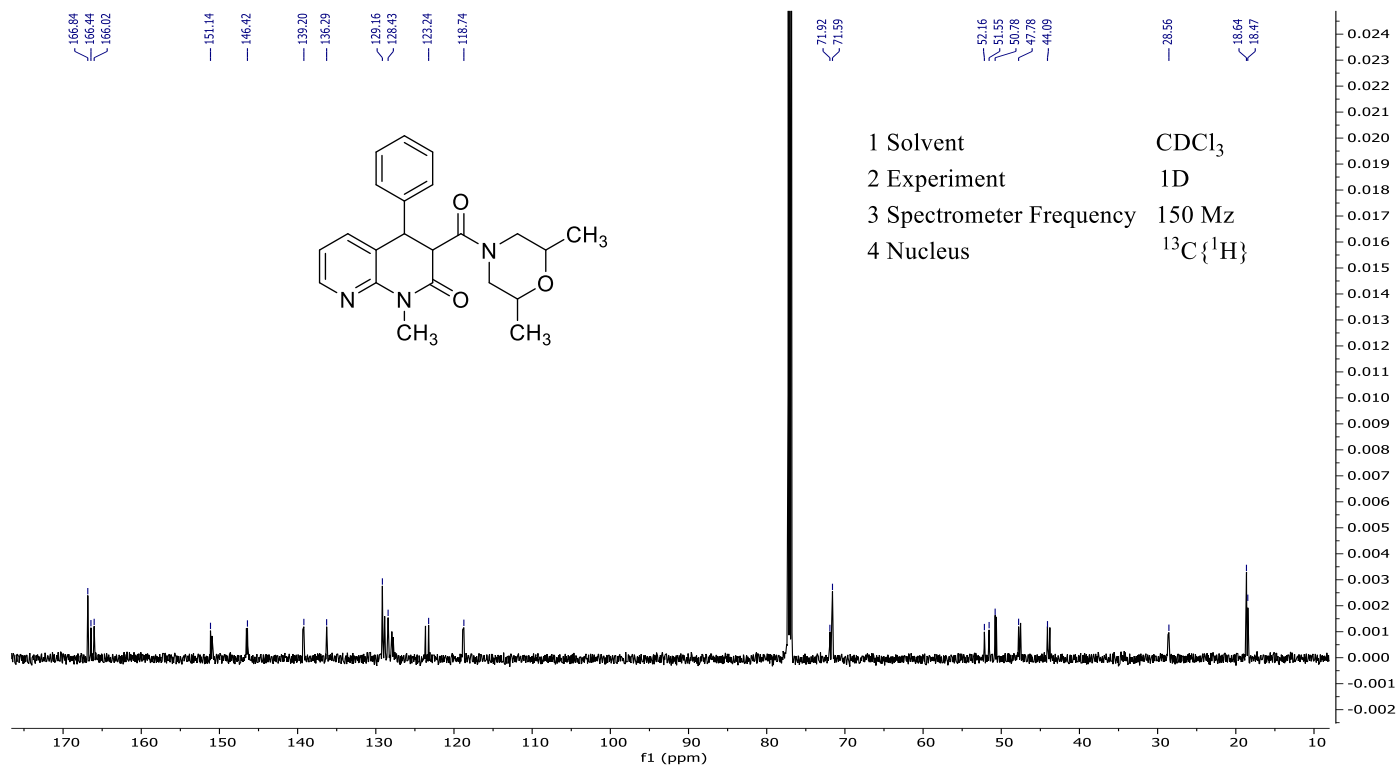
¹³C{¹H} of 3z



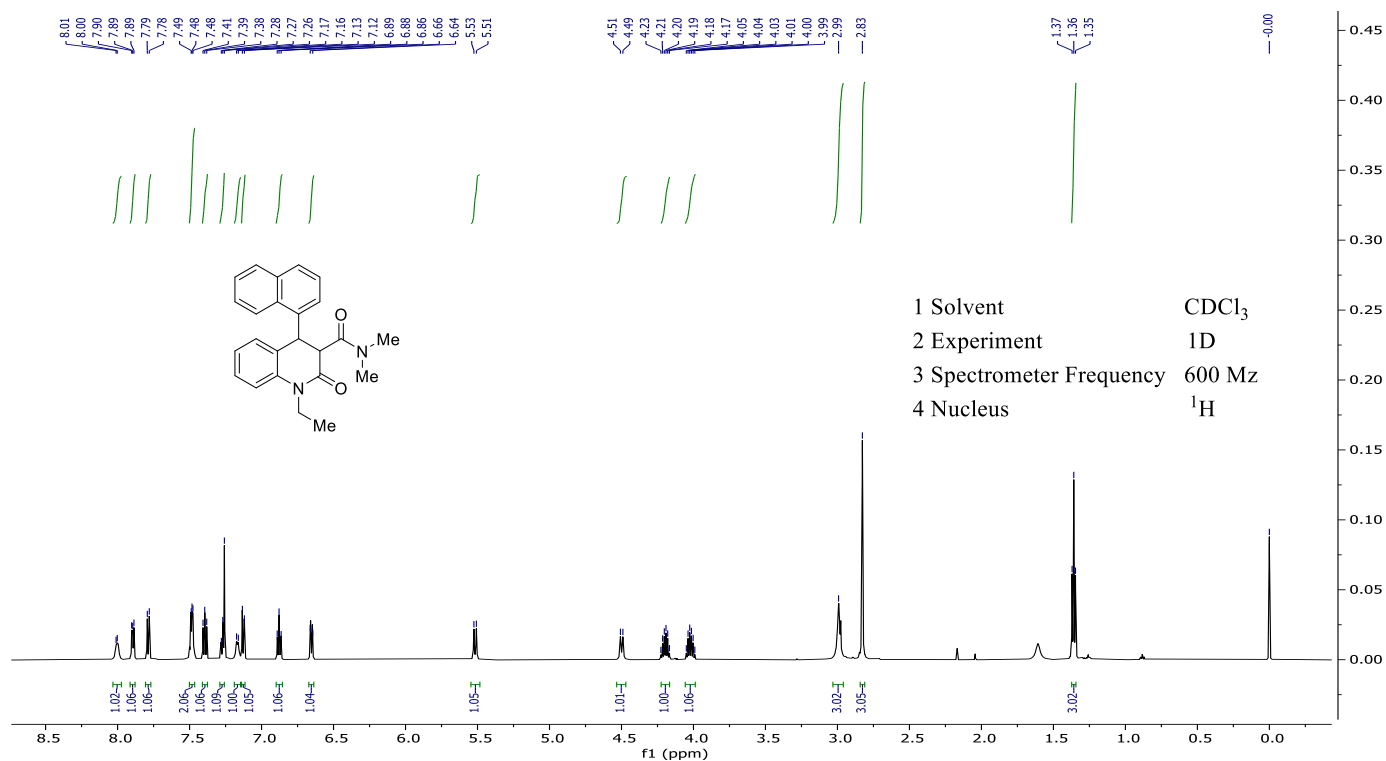
¹H NMR of 3aa



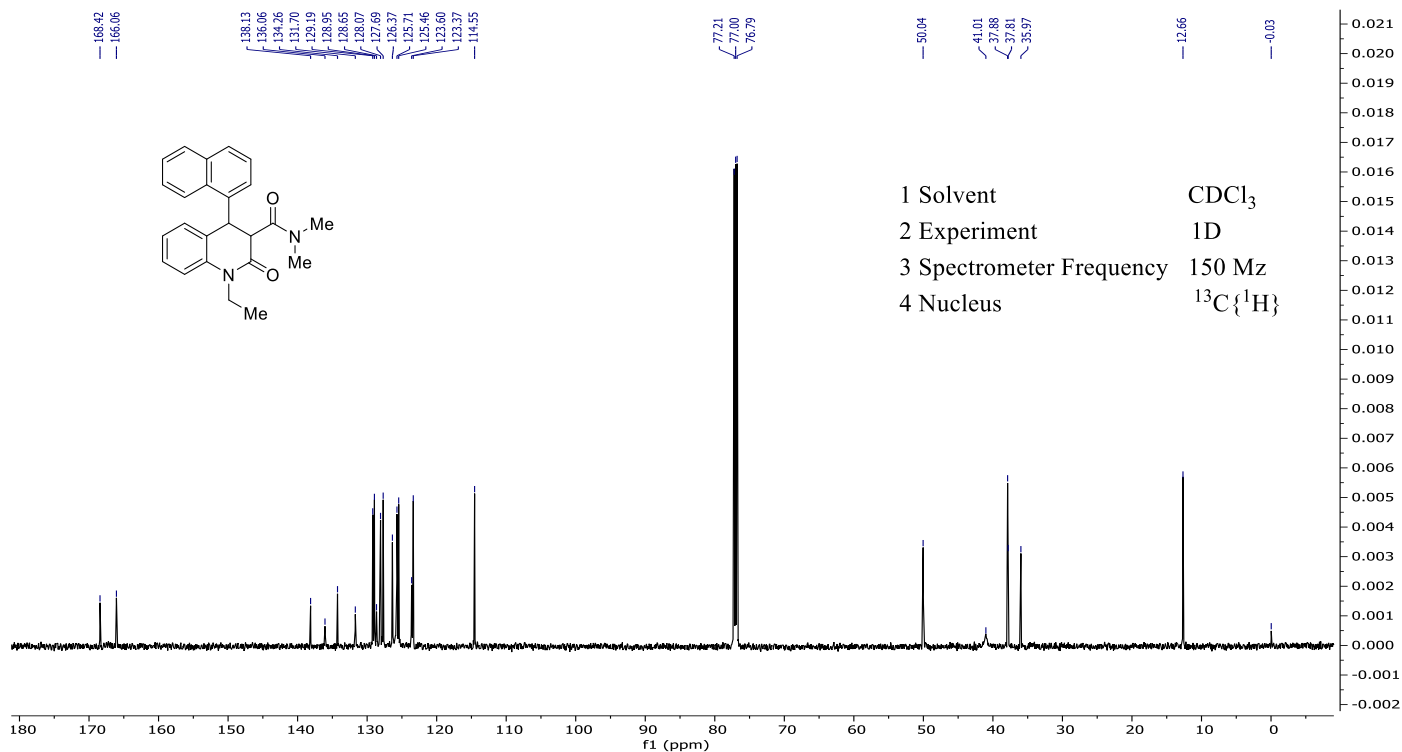
¹³C{¹H} of 3aa



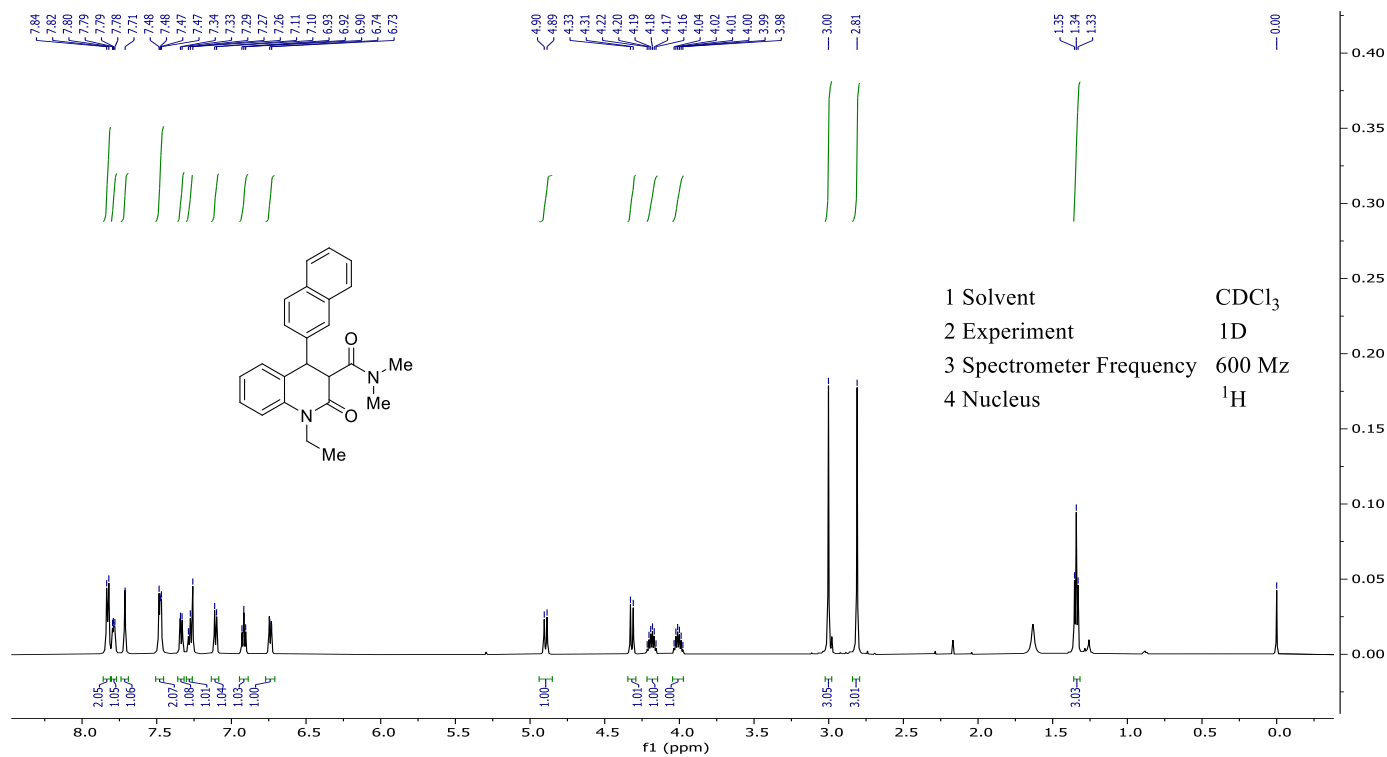
¹H NMR of 3bb



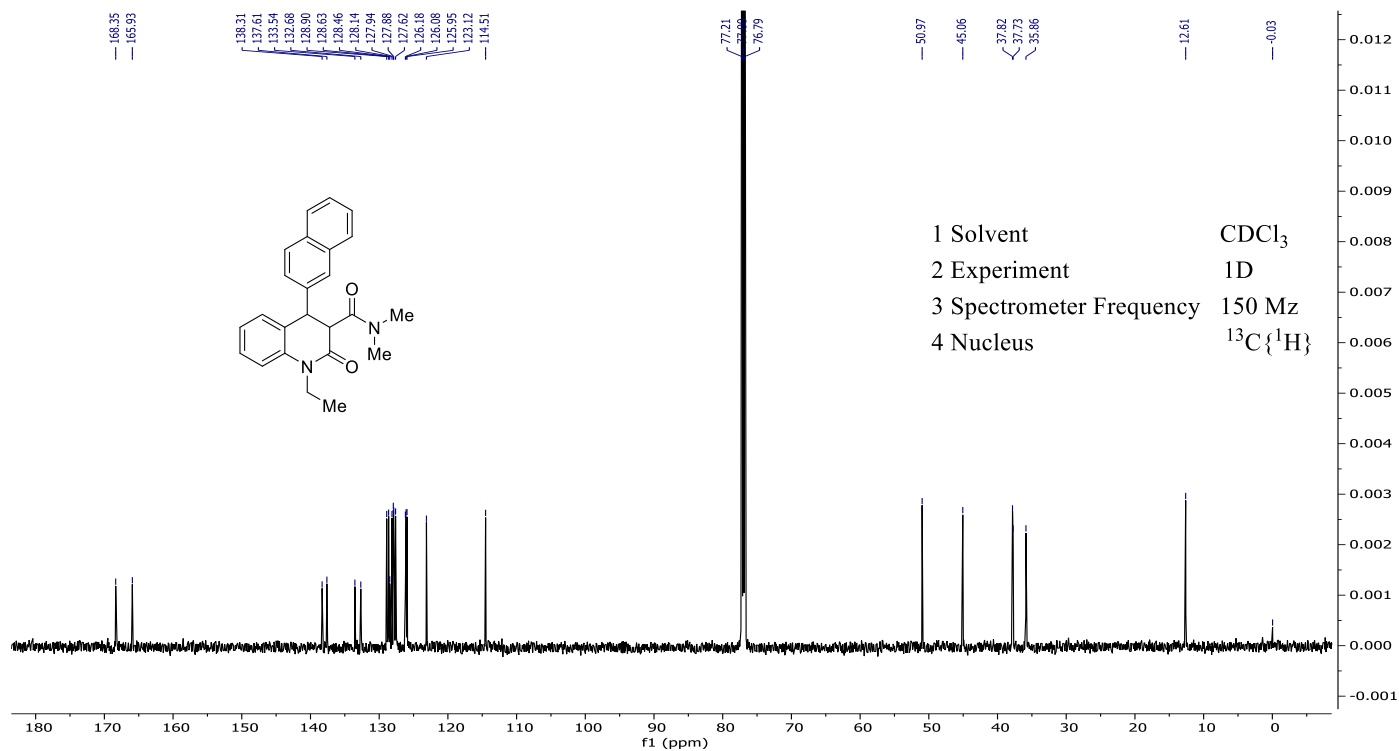
¹³C{¹H} of 3bb



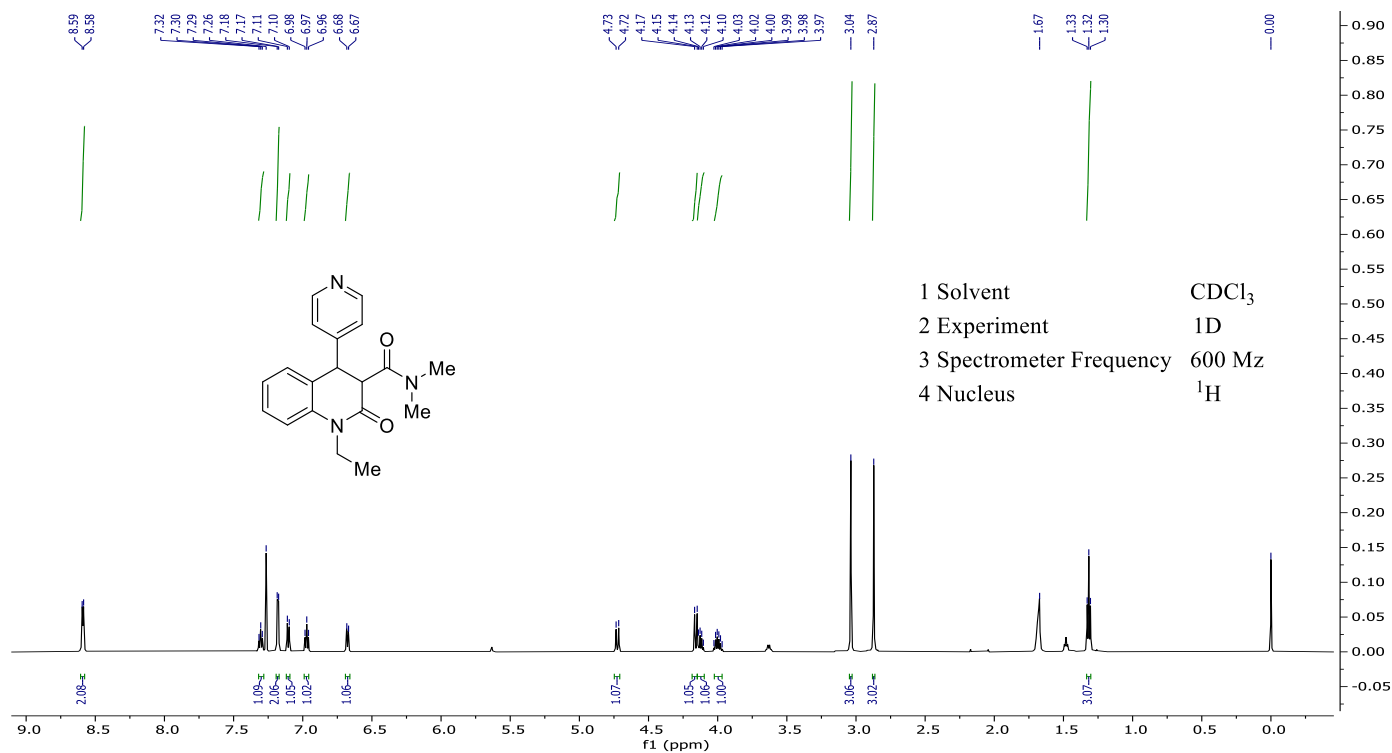
^1H NMR of **3cc**



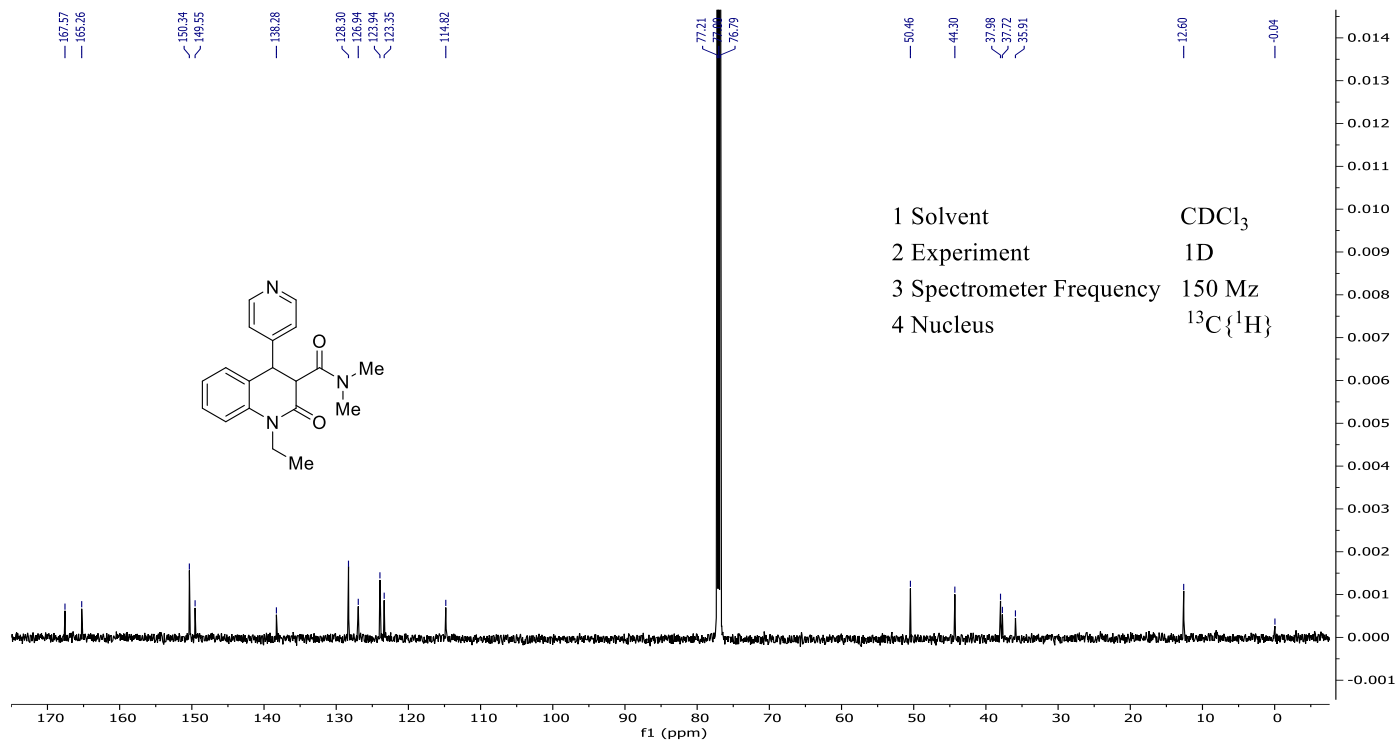
$^{13}\text{C}\{^1\text{H}\}$ of **3cc**



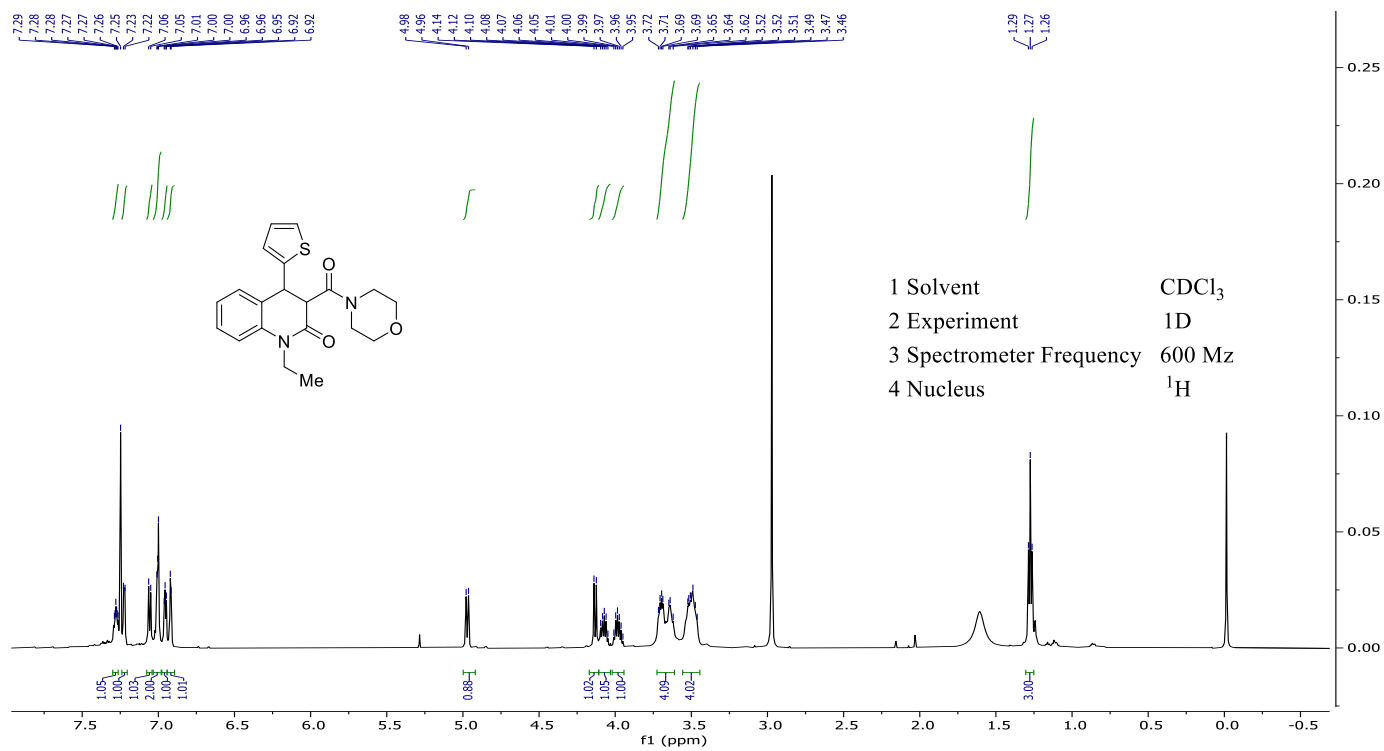
¹H NMR of 3dd



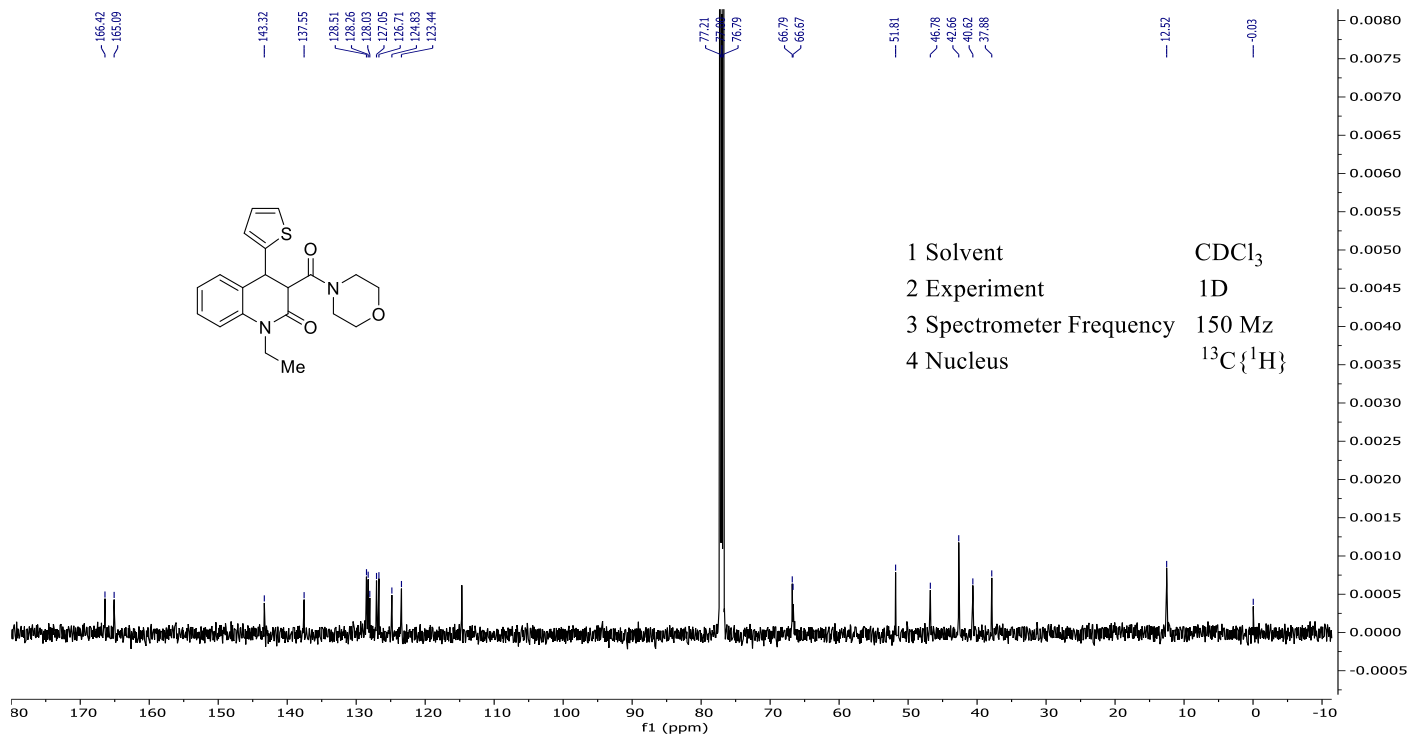
¹³C{¹H} of 3dd



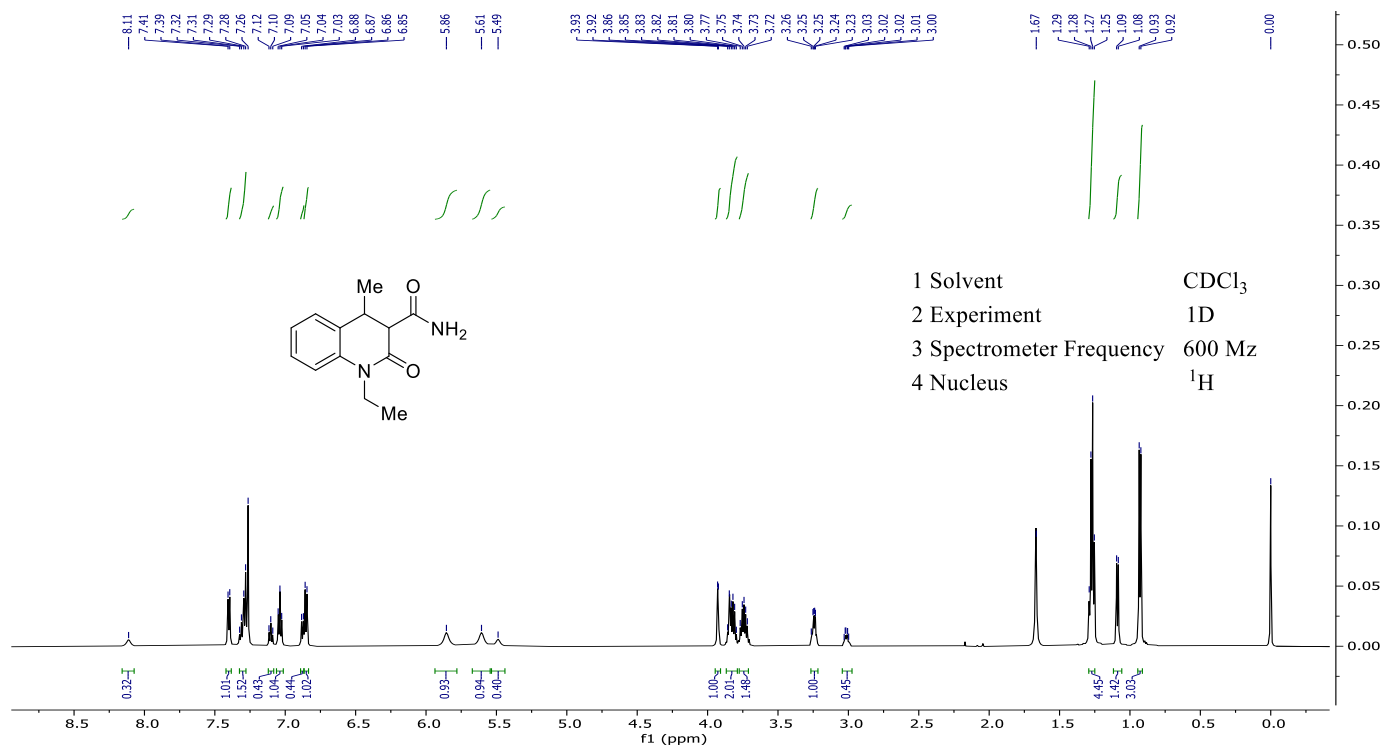
¹H NMR of 3ee



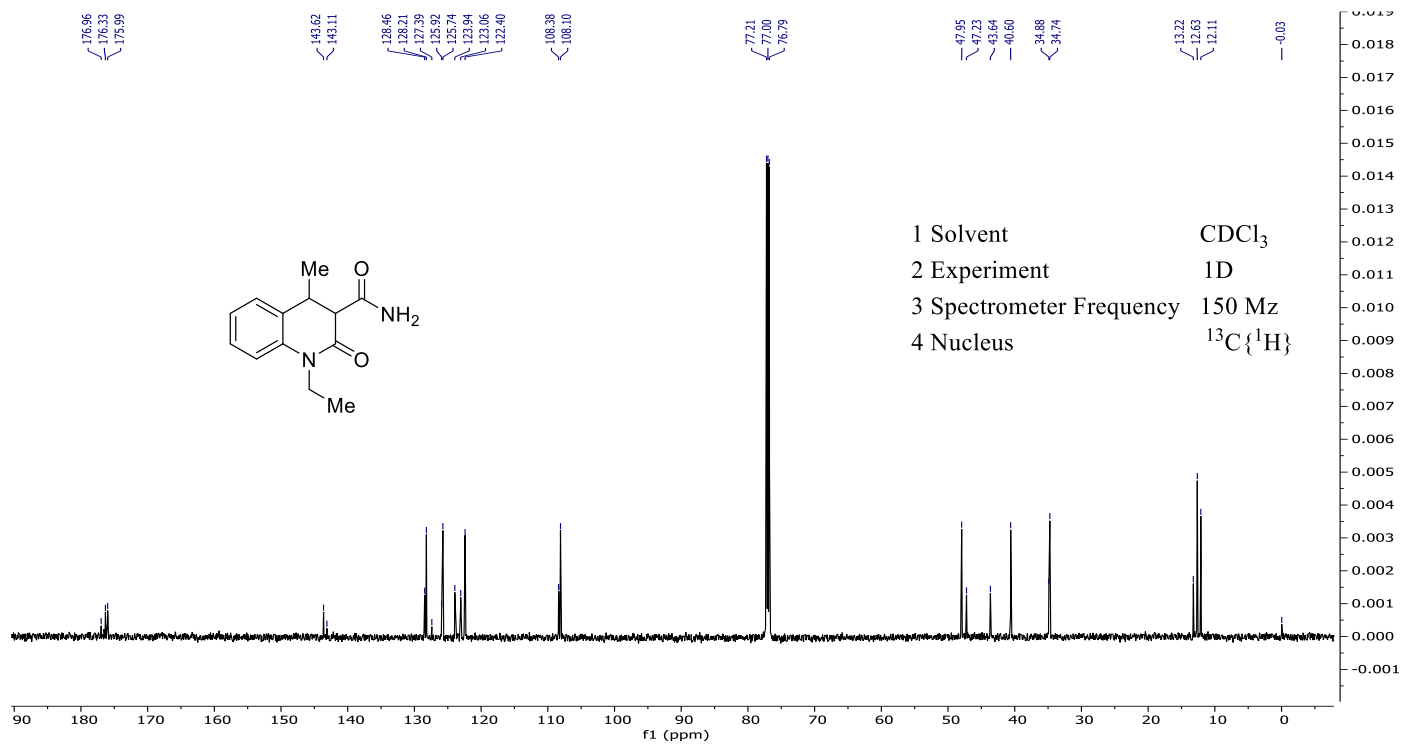
¹³C{¹H} of 3ee



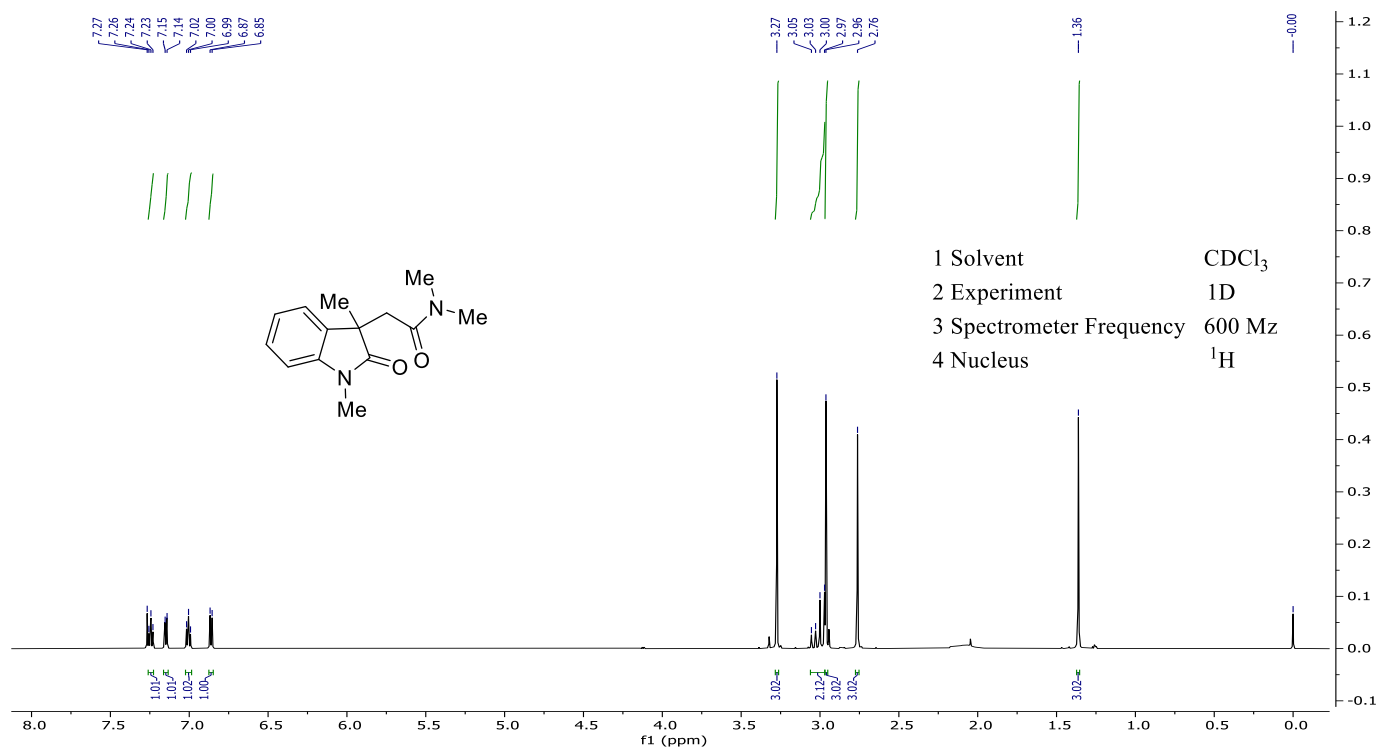
^1H NMR of **3ff** (mixture of isomers)



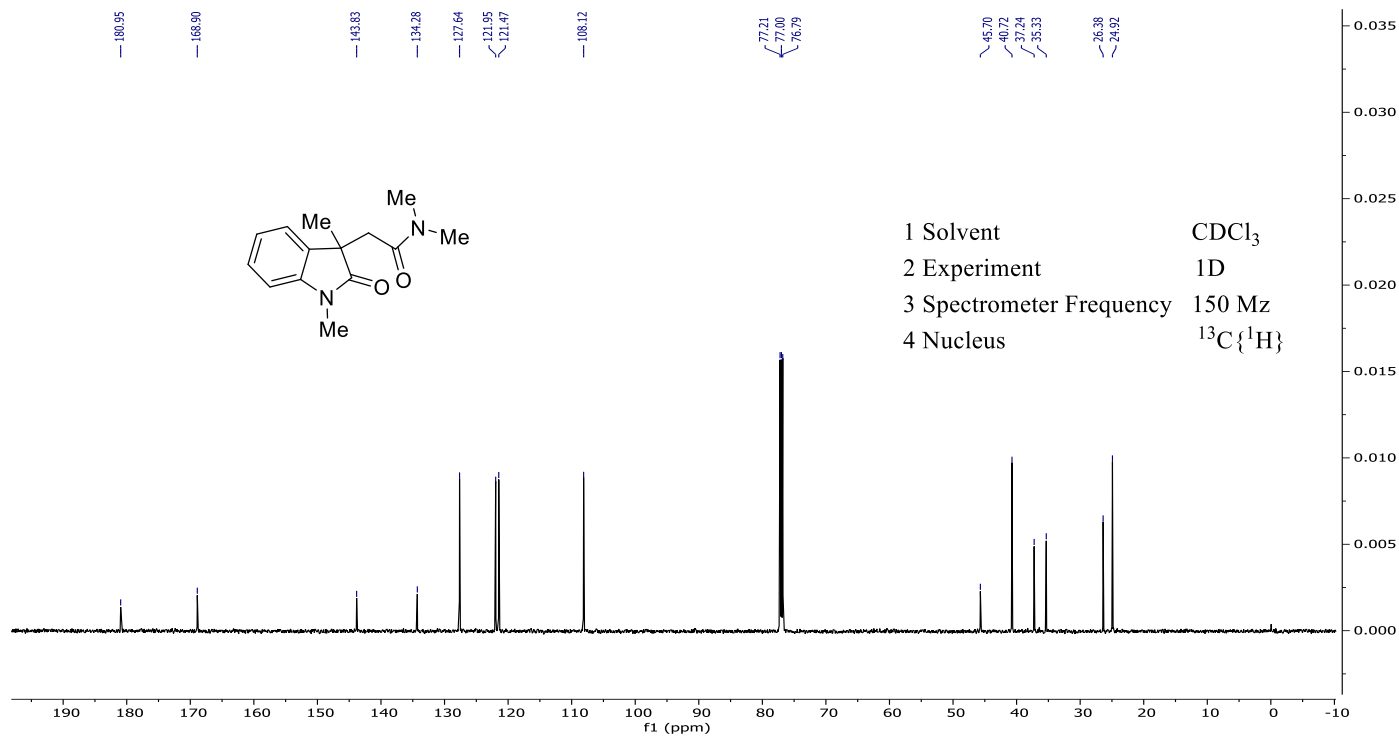
$^{13}\text{C}\{^1\text{H}\}$ of **3ff** (mixture of isomers)



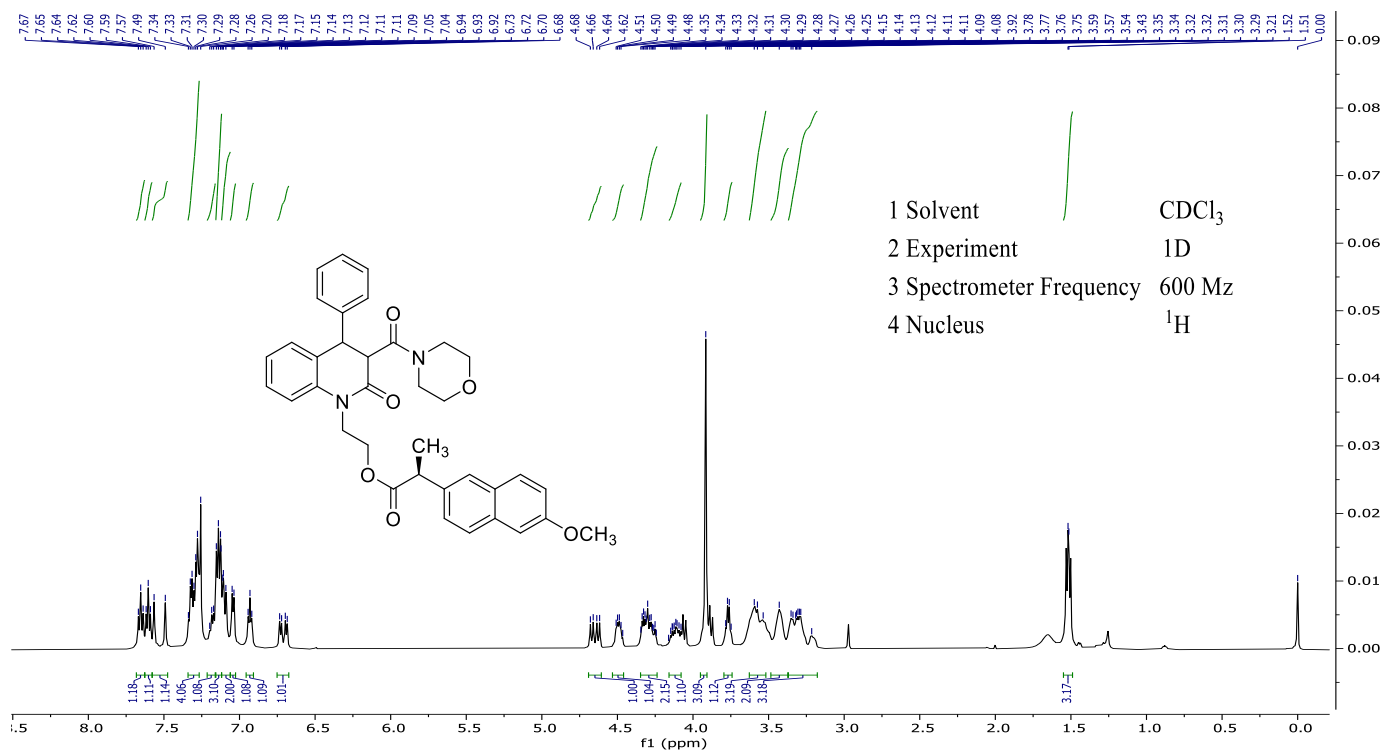
¹H NMR of **3gg**



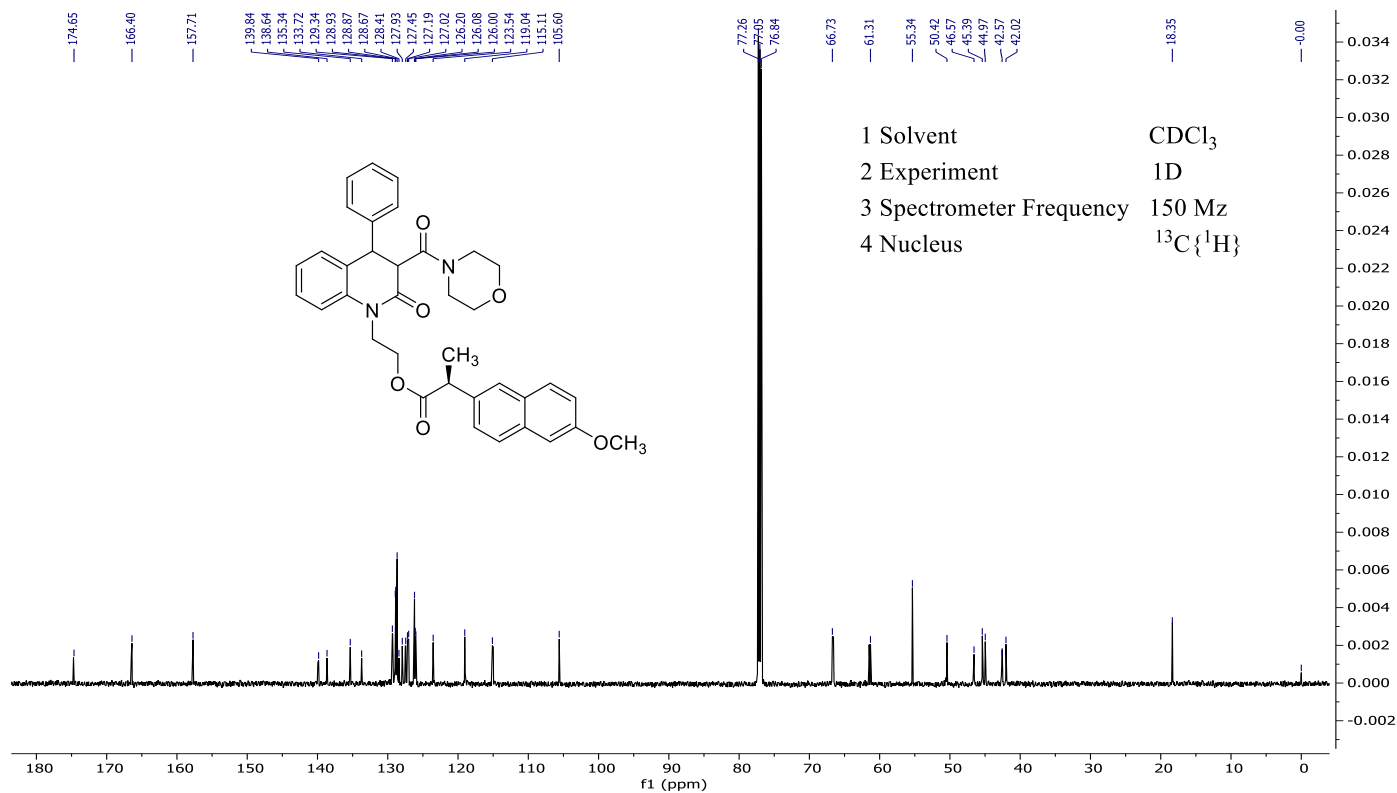
¹³C{¹H} of **3gg**



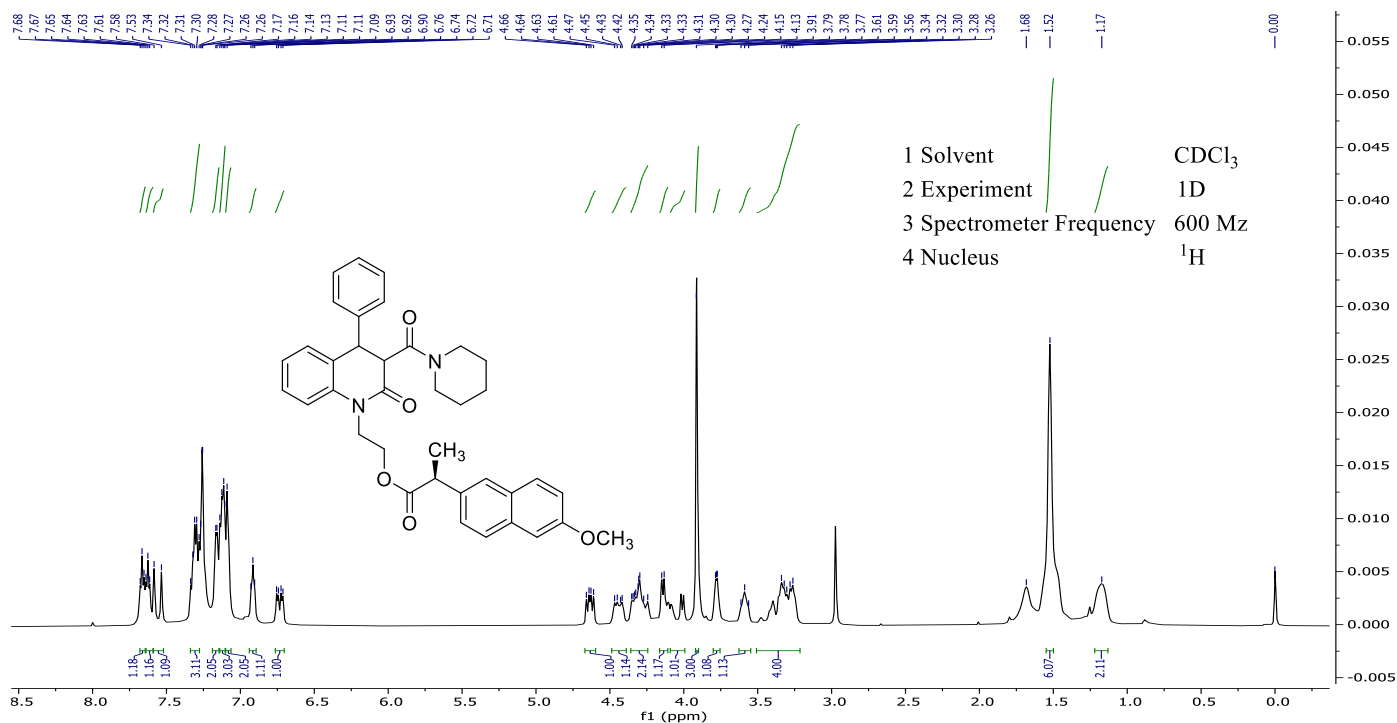
¹H NMR of 5a



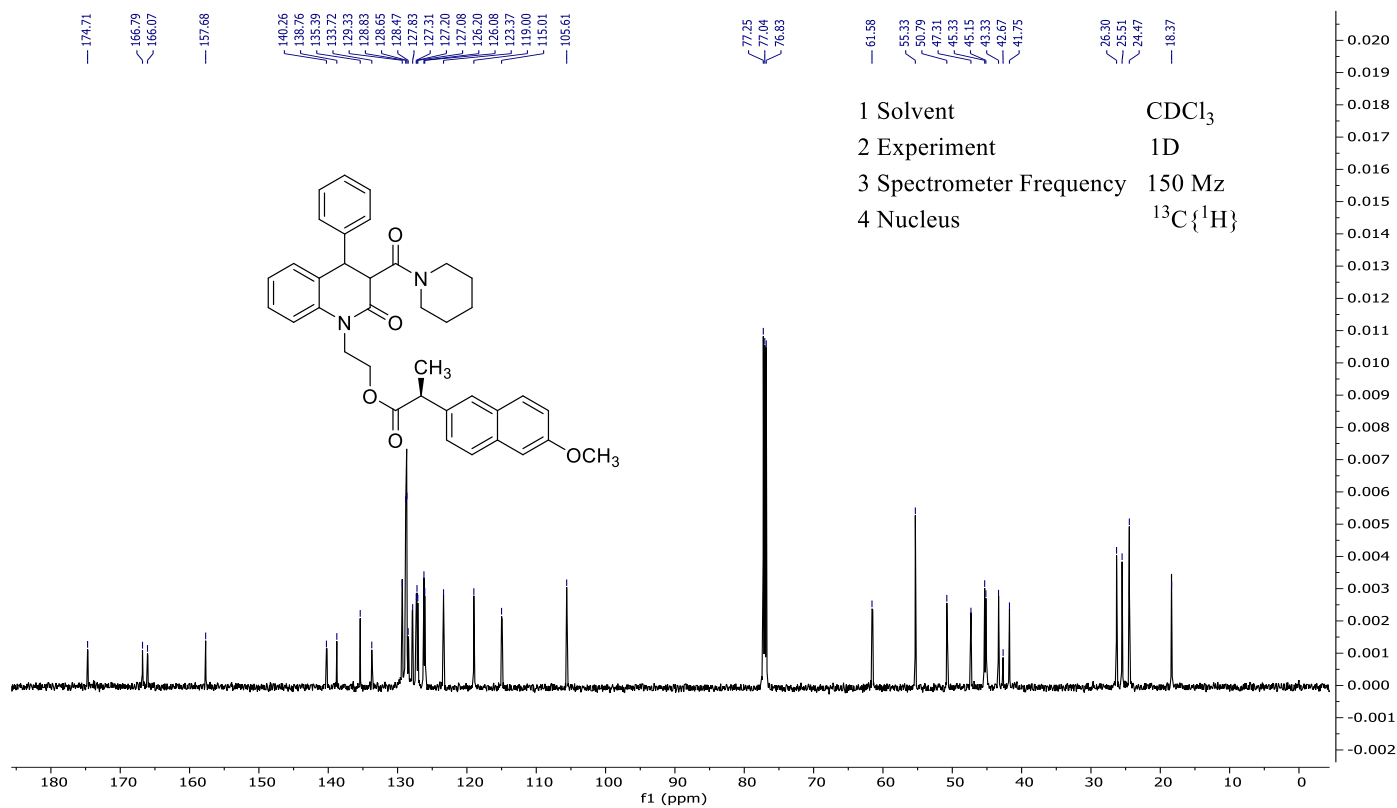
¹³C{¹H} of 5a



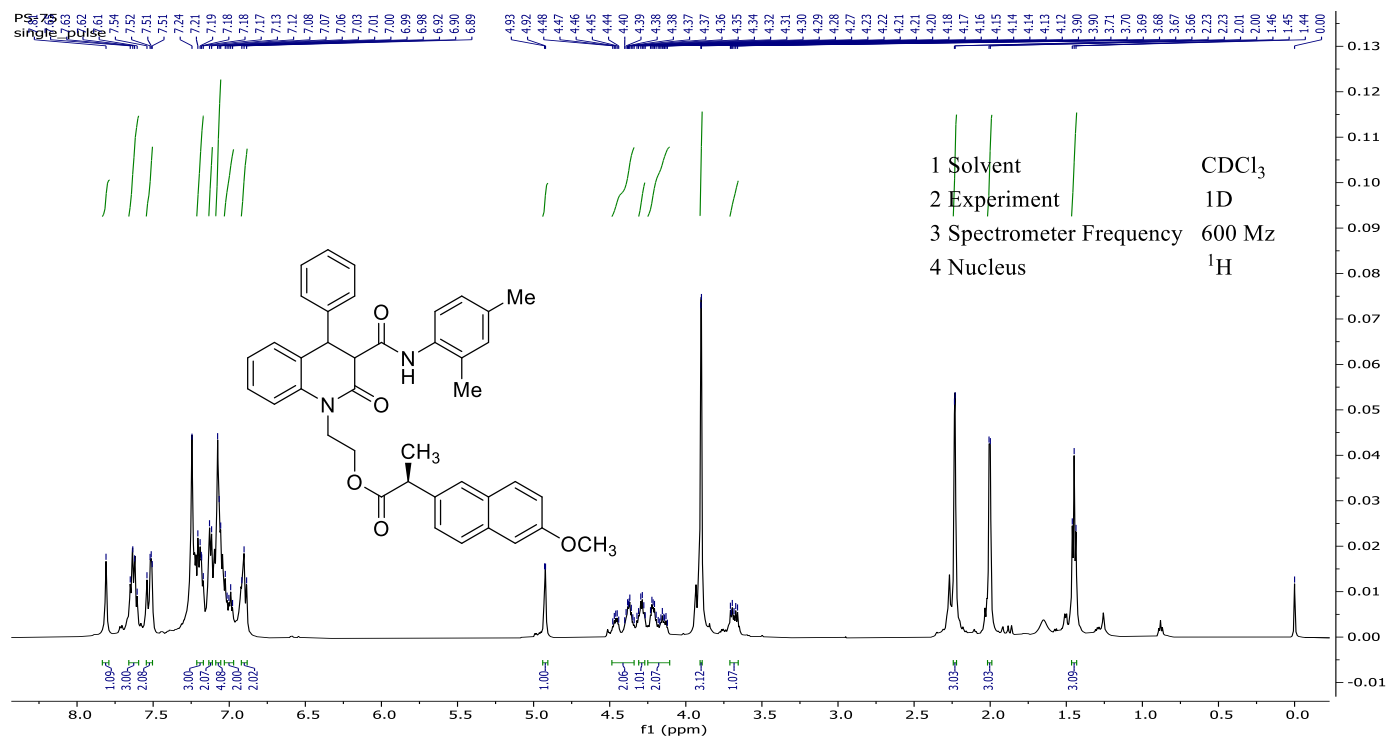
¹H NMR of 5b



¹³C{¹H} of 5b



¹H NMR of 5c



¹³C{¹H} of 5c

