

Supplementary informations

Novel synthesis and cytotoxic activity of 1,4-disubstituted 3-methylidene-3,4-dihydroquinolin-2(1H)-ones

General method for the synthesis of Diethyl [(2-formylphenyl)carbamoyl]methylphosphonate **7**:

To a solution of 2-aminobenzaldehyde **5** (0.434 g, 4.00 mmol) and 2,6-lutidine (0.463 mL, 4.00 mmol) in toluene (5 ml) under nitrogen atmosphere a solution of diethyl 2-chloro-2-oxoethylphosphonate (0.858 g, 4.00 mmol) in toluene (5 ml) was added dropwise maintaining the temperature below 0 °C. When the addition was completed, the mixture was stirred at room temperature for 45 min. The mixture was washed with H₂O (10 mL) and brine (10 mL) and dried over MgSO₄. The solvent was removed in vacuo to yield an oil which was purified by chromatography on silica gel eluted with toluene/ethyl acetate 4/1.

General methods for the synthesis of 3-diethoxyphosphorylquinolin-2-one **8**:

Method A (from **7**):

Diethyl [(2-formylphenyl)carbamoyl]methylphosphonate **7** (1.20 g, 4.00 mmol) was dissolved in dry toluene (12 mL) in argon atmosphere and then piperidine (34.2 μL, 0.40 mmol) was added. The mixture was stirred in Dean-Stark apparatus for 8 hours at reflux. Then it was condensed in vacuo and the residue was triturated with Et₂O to give off-white solid.

Method B (from **15**):

Ethyl 2-(diethoxyphosphoryl)-3-(2-nitrophenyl)prop-2-enoate **15** (1.43 g, 4.00 mmol) was dissolved in AcOH (15 mL) and then to the intensively stirred solution reduced iron powder (1.34 g, 24.00 mmol) was added. The mixture was warmed to 80 °C and stirred for 6 hours. Then it was filtered through celite cake and the solid residue was washed with AcOH (15 mL) and AcOEt (15 mL). The filtrate was evaporated. The dark residue was dissolved in AcOEt (15 mL) and washed with 5% NaHCO₃ (2 * 15mL), then with water (10 mL) and brine (10 mL) and dried over Na₂SO₄. Obtained brown solid was purified by chromatography on silica gel eluted with ethyl acetate/CH₂Cl₂ 1/1.

General method for the synthesis of ethyl Z-2-(diethoxyphosphoryl)-3-(2-nitrophenyl)prop-2-enoate **15**:

To dry THF (60 mL) in argon atmosphere at 0 °C the solution of TiCl₄ (5.04 mL, 45.65 mmol) in CCl₄ (15 mL) was added dropwise followed by the triethyl phosphonoacetate (4.57 mL, 22.83 mmol) and N-methylmorpholine (10.37 mL, 94.30 mmol). It was stirred for 30 min at 0 °C and then the solution of 2-nitroaldehyde (3.0 g, 19.85 mmol) in THF (15 mL) was added portionwise. The reaction mixture was slowly warmed to rt and stirred for 5 h. Then water was added (100 mL) and the mixture was extracted with Et₂O (2*80 mL). Combined organic layers were washed with brine, dried over MgSO₄ and evaporated under reduced pressure, affording the crude product that was purified by chromatography on silica gel eluted with CH₂Cl₂/AcOEt.

General synthetic procedure for the synthesis of **16 a-d**:

To the solution of 3-diethoxyphosphorylquinolin-2-one **7** (5.0 mmol) in DMF (15 mL) under argon atmosphere, provided with water bath, sodium hydride (5.5 mmol) was added portionwise. The reaction mixture was stirred for 10 min. Then the alkyl halide (6.0 mmol) was added in one portion and the reaction mixture was stirred at rt overnight (for **12 b-d**) or for 6 h (for **12a**). Then solvent was removed under reduced pressure and the residue was separated between ethyl acetate (25 mL) and water (25 mL). The water layer was extracted with the second portion of ethyl acetate (25 mL). Combined organic layers were washed with brine, dried over MgSO₄ and evaporated under reduced pressure, affording the crude product that was purified by chromatography on silica gel eluted with CH₂Cl₂/AcOEt.

General synthetic procedure for the synthesis of **18 a-o**:

To the solution of 1-alkyl-3-diethoxyphosphorylquinolin-2-one **16** (1.0 mmol) in THF (5 mL) under argon atmosphere, provided with water bath, Grignard reagent (3.0 mmol as 2.0 M THF solution) was added dropwise. The reaction mixture was stirred at ambient temperature overnight. Then to the mixture saturated ammonium chloride solution in water (10 mL) was added and it was extracted with ethyl acetate (2*10 mL). Combined organic layers were washed with brine, dried over MgSO₄ and evaporated under reduced pressure, affording the crude product which was purified by chromatography on silica gel eluted with CH₂Cl₂/AcOEt.

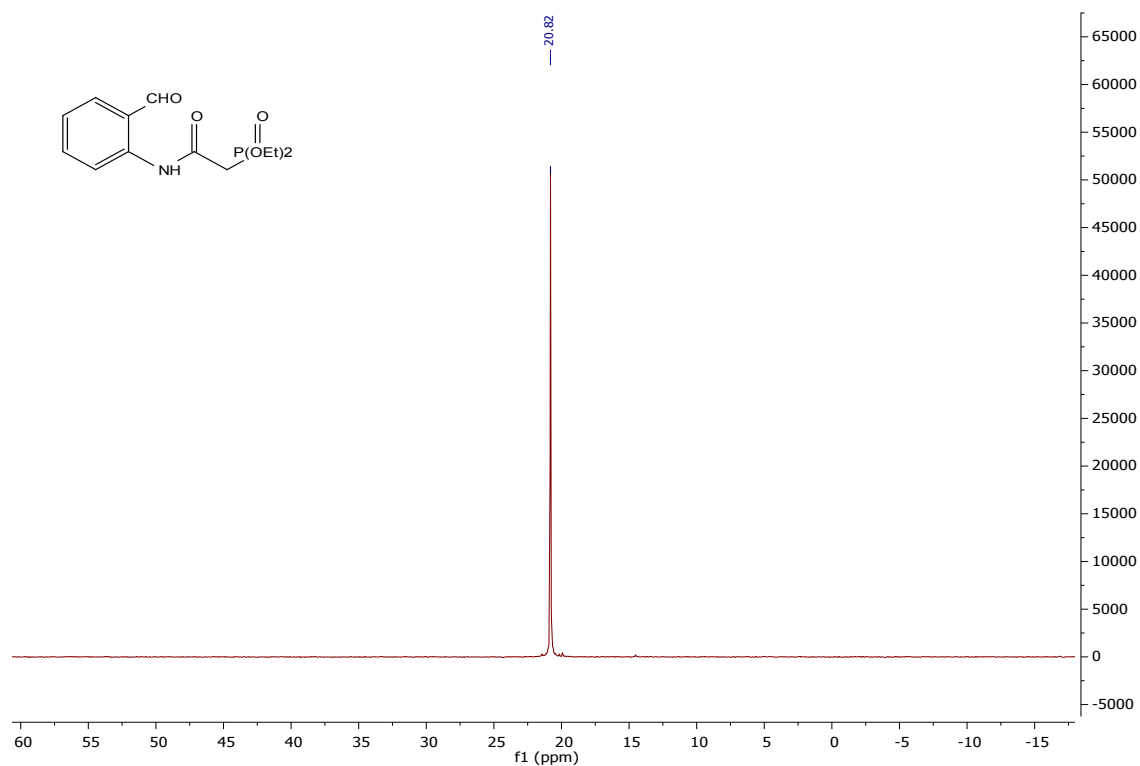
General synthetic procedure for the synthesis of **20 a-o**:

To the solution of 1,4-alkyl or aryl 3-diethoxyphosphorylquinolin-2-one **18** (0.5 mmol) in THF (2 mL) under argon atmosphere, sodium hydride (0.55 mmol) was added in one portion. The reaction mixture was stirred at ambient temperature for 5 min. Then formaldehyde (2.5 mmol) was added. After 4 hours water was added (3 mL) and the mixture was extracted with dichloromethane (2*5 mL). Combined organic layers were washed with brine, dried over MgSO₄ and evaporated under reduced pressure, affording the crude product which was purified by column chromatography (CH₂Cl₂).

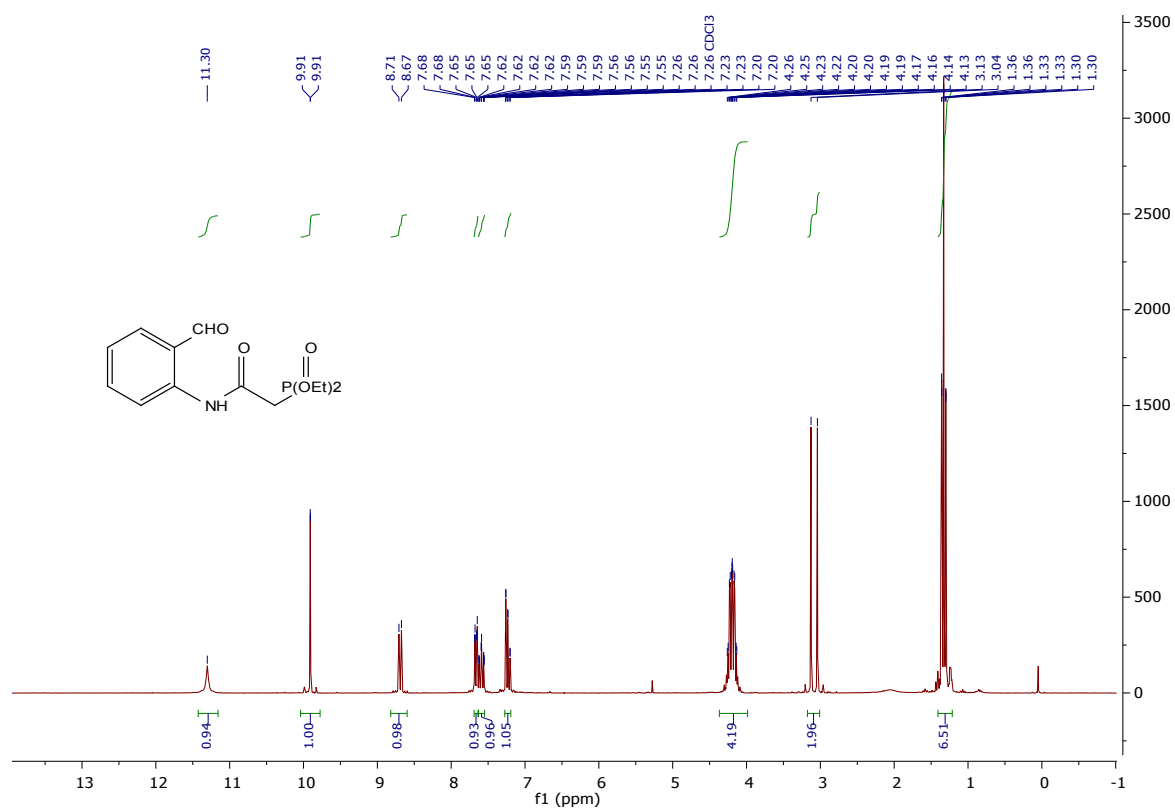
¹H ³¹P and ¹³C spectra of 7, 8, 9, 15, 16 a-d, 17 b-d, 18 a-o, 19 b,f,i,m and 20 a-m, o:

Compound 7

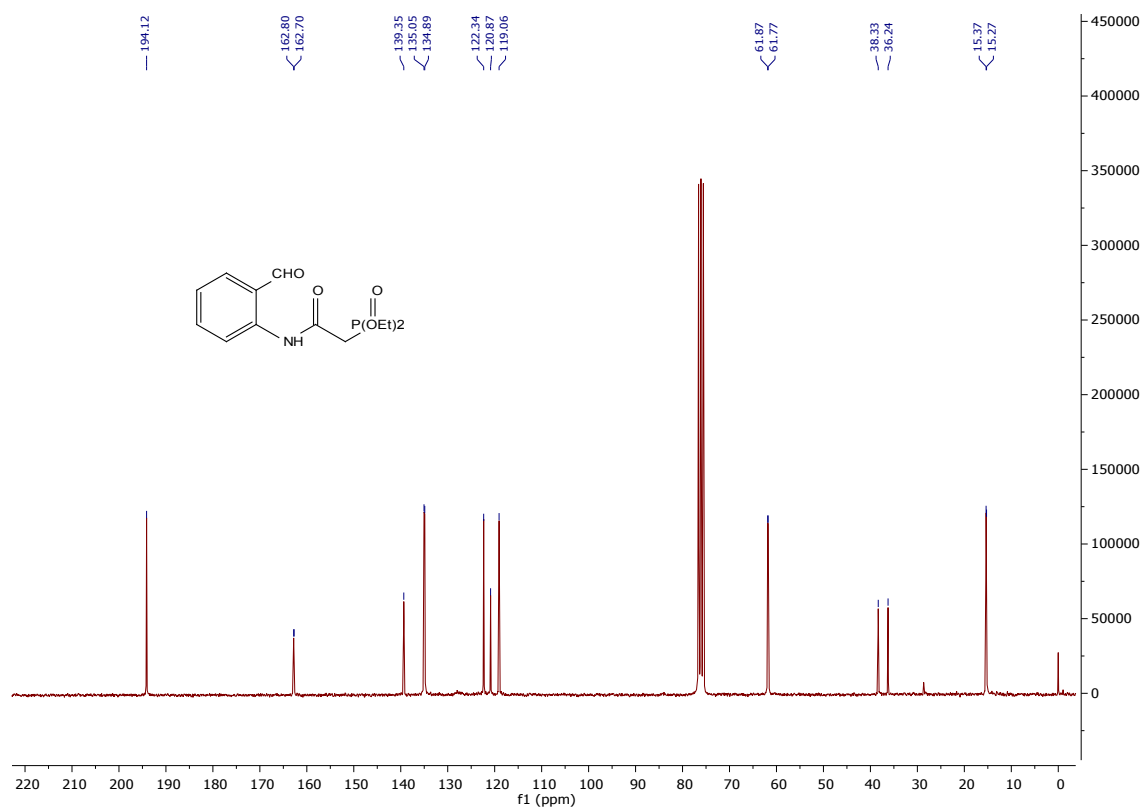
³¹P NMR



¹H NMR

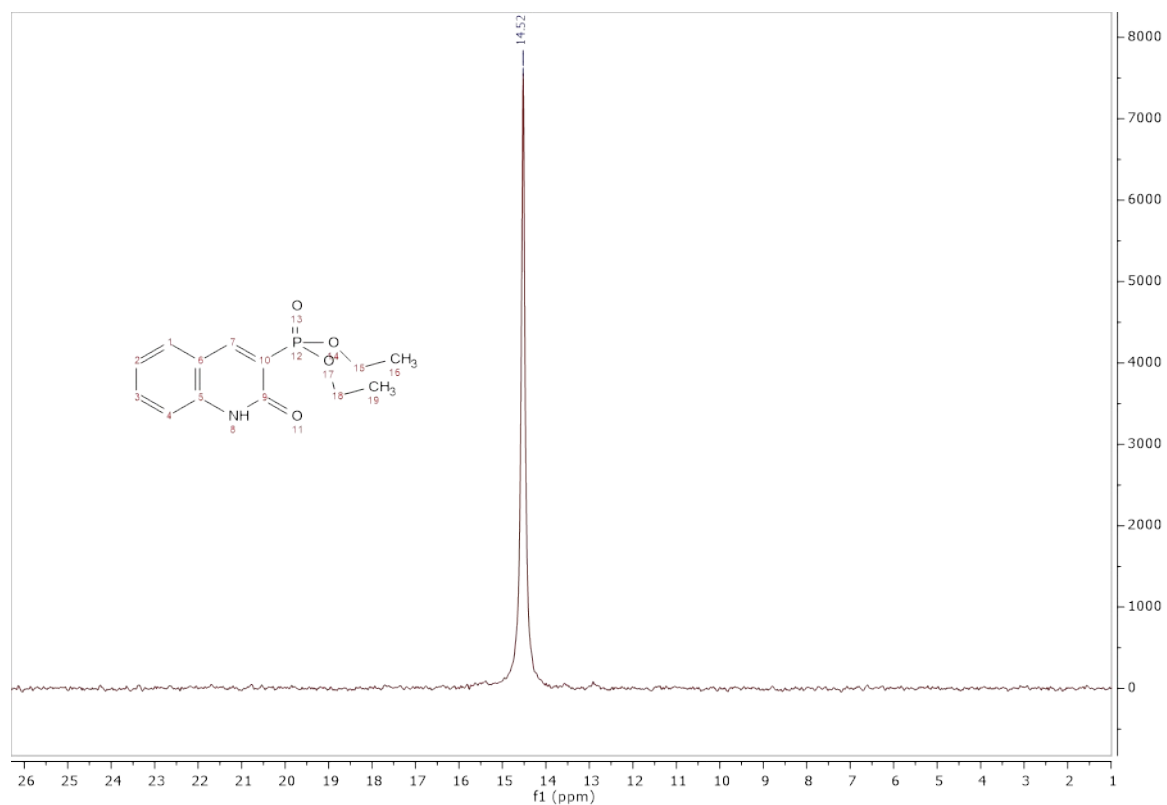


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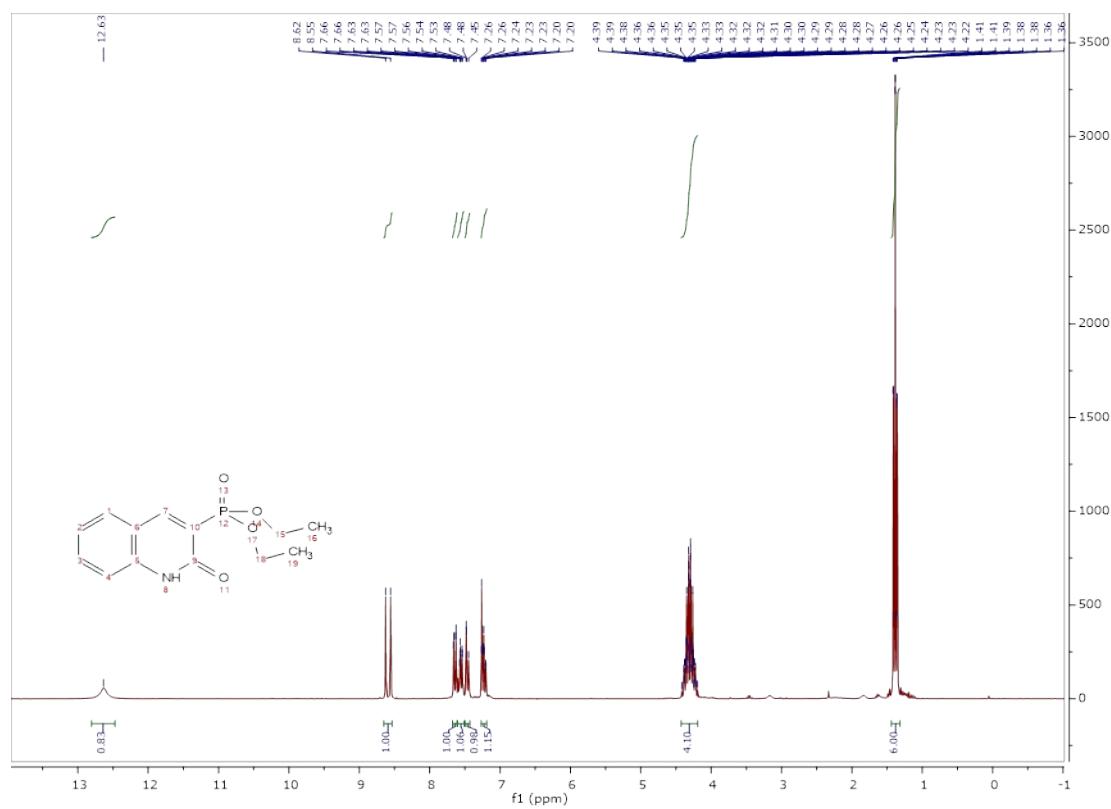


Compound 8

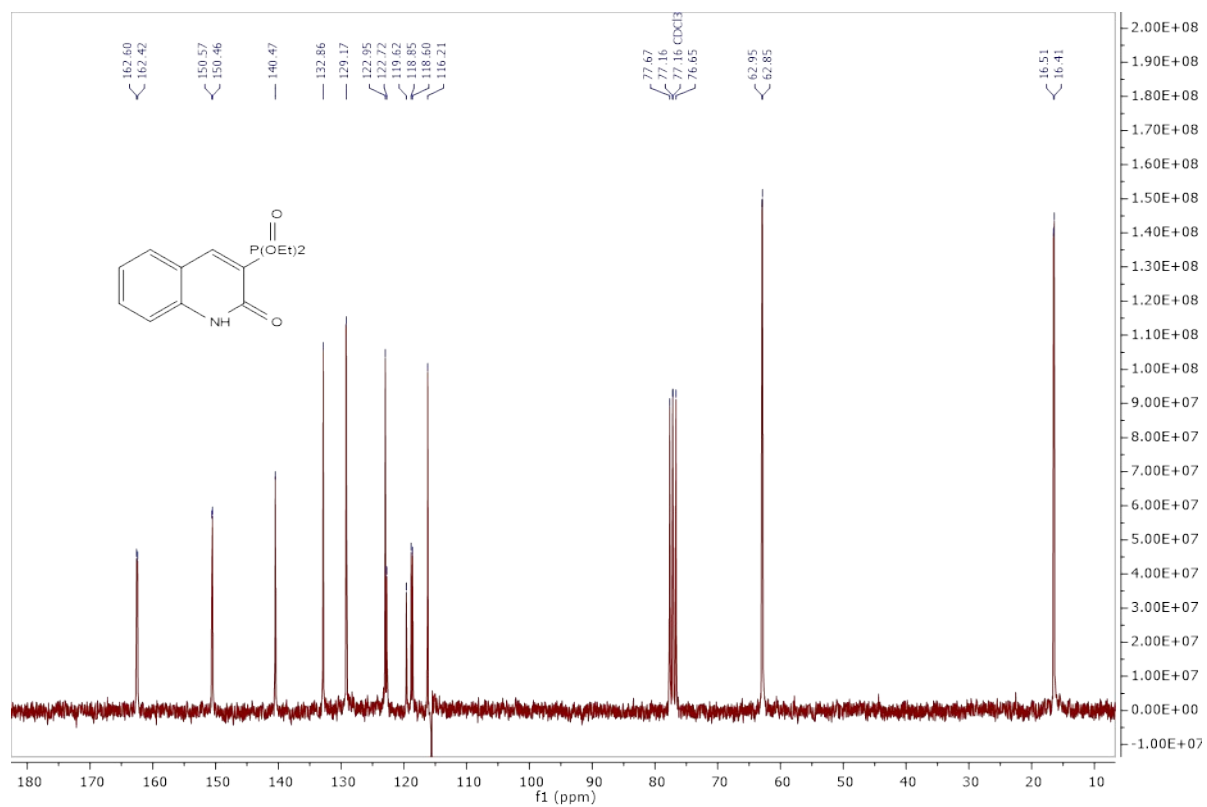
^{31}P NMR



^1H NMR

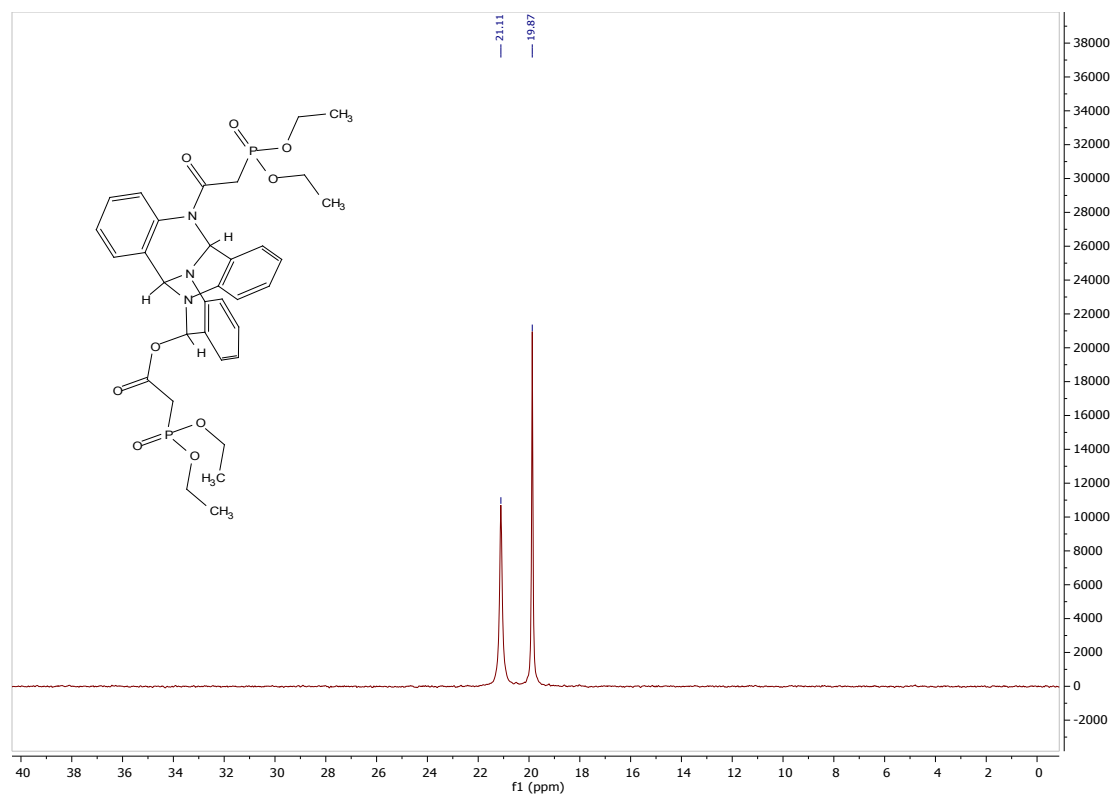


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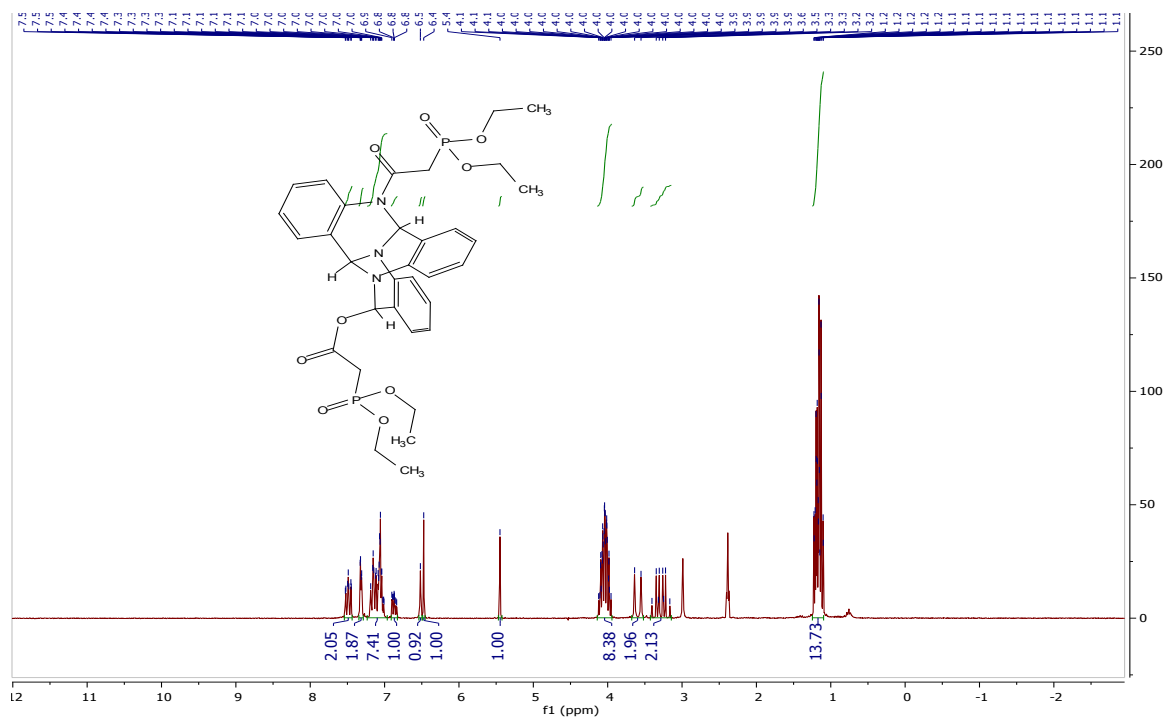


Compound 9

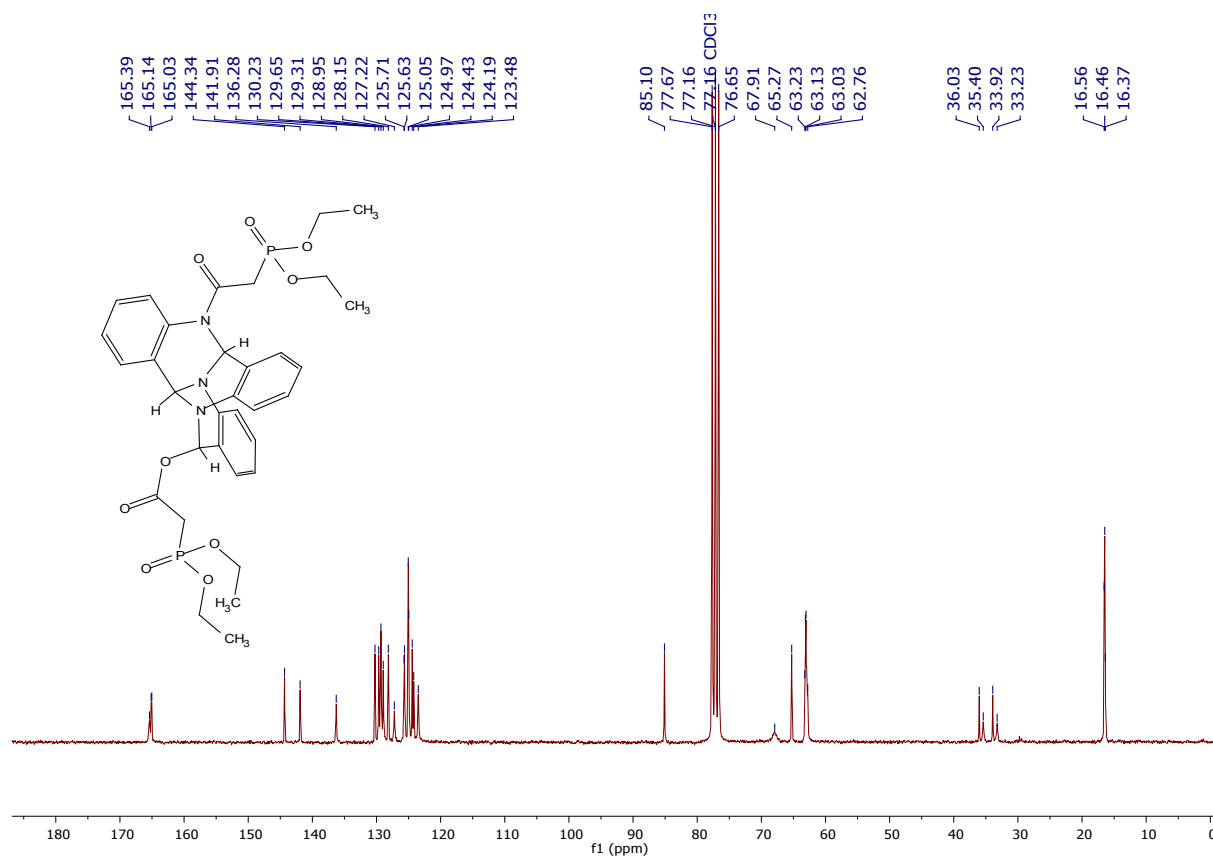
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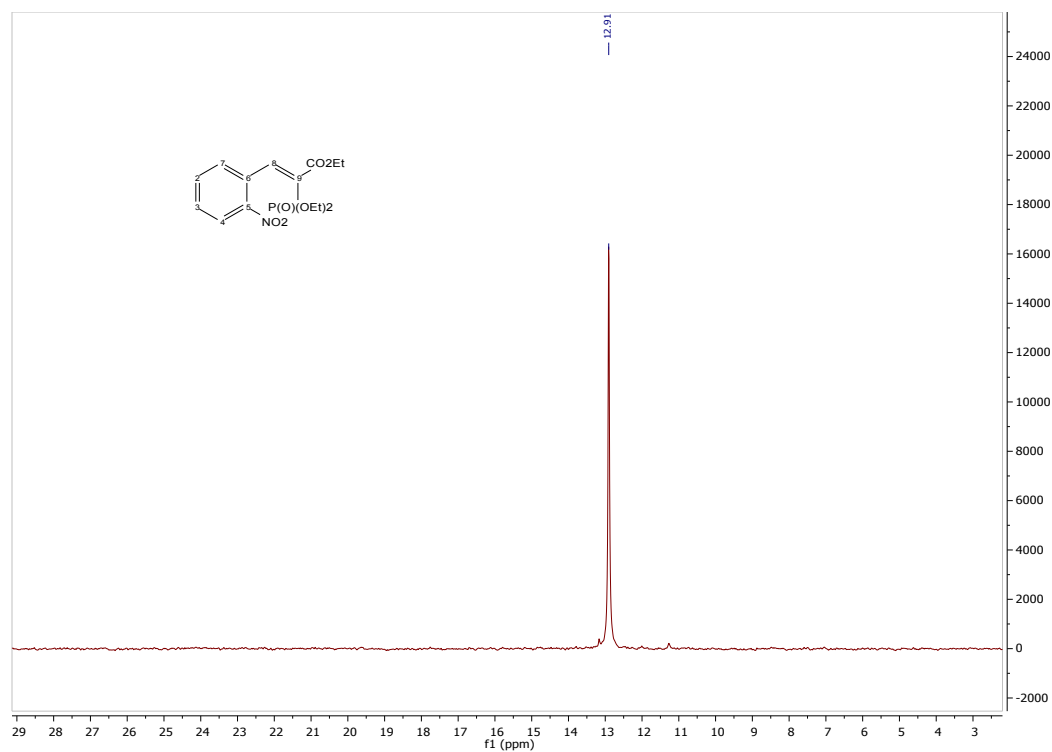


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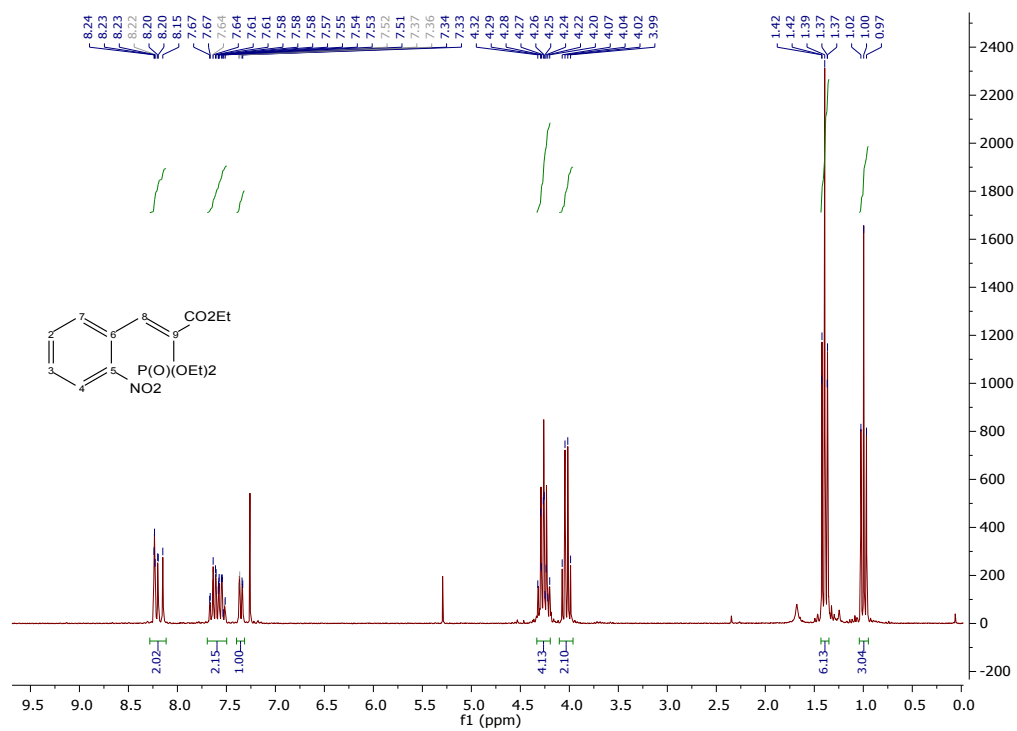


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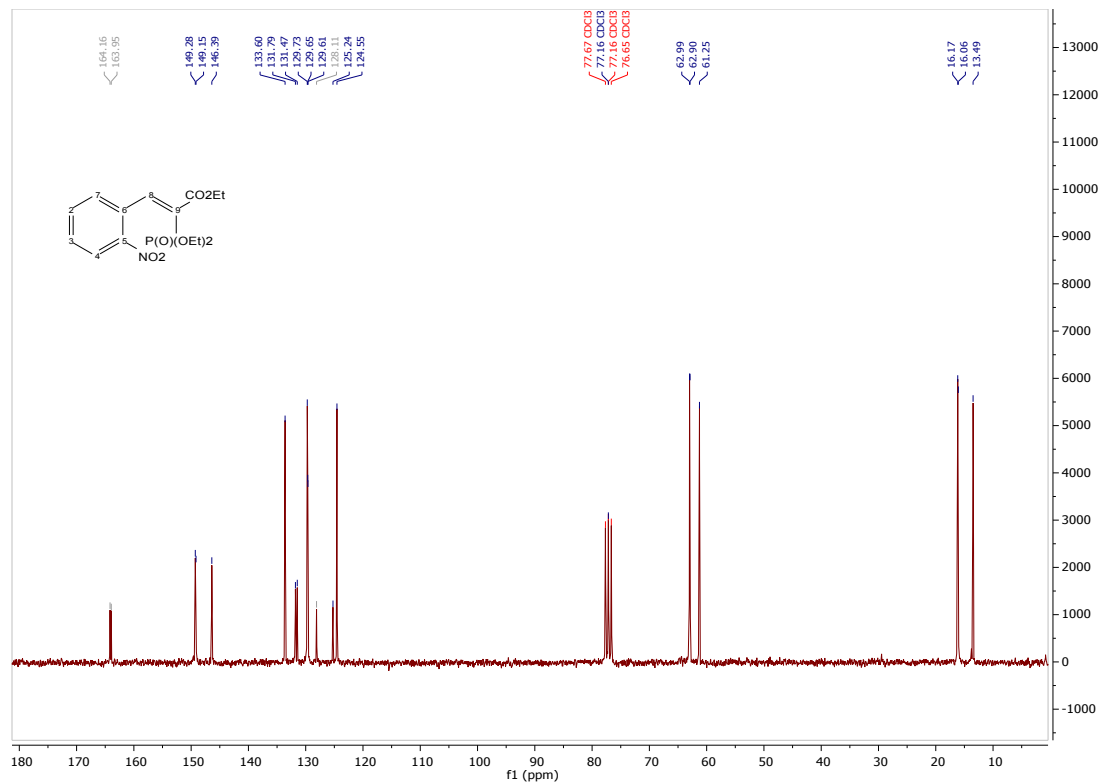
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^1H NMR

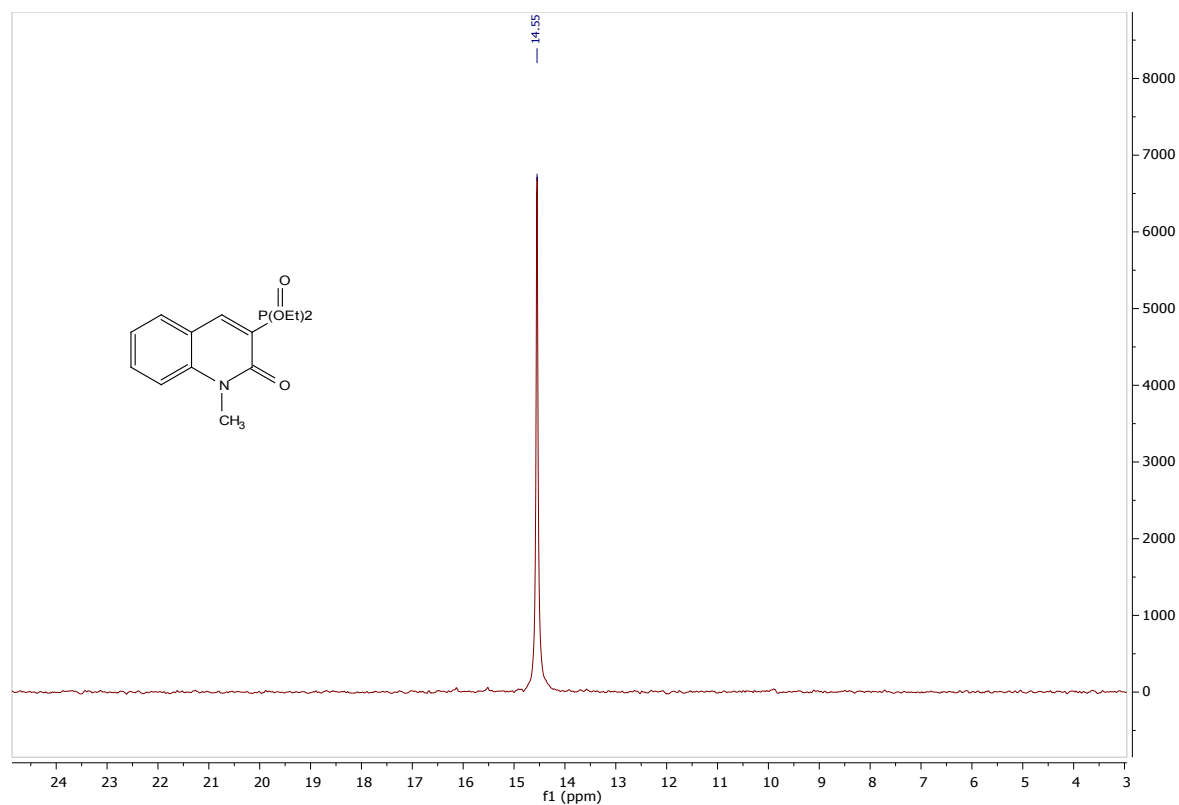


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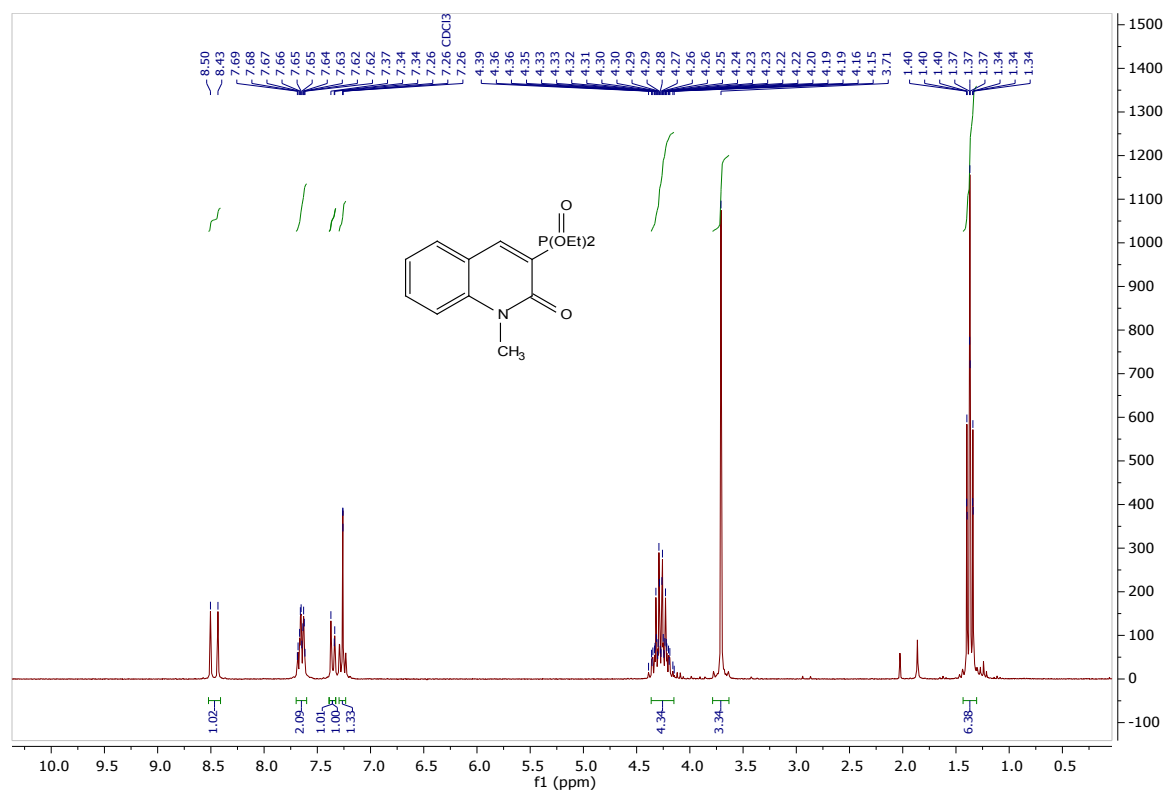


Compound 16a

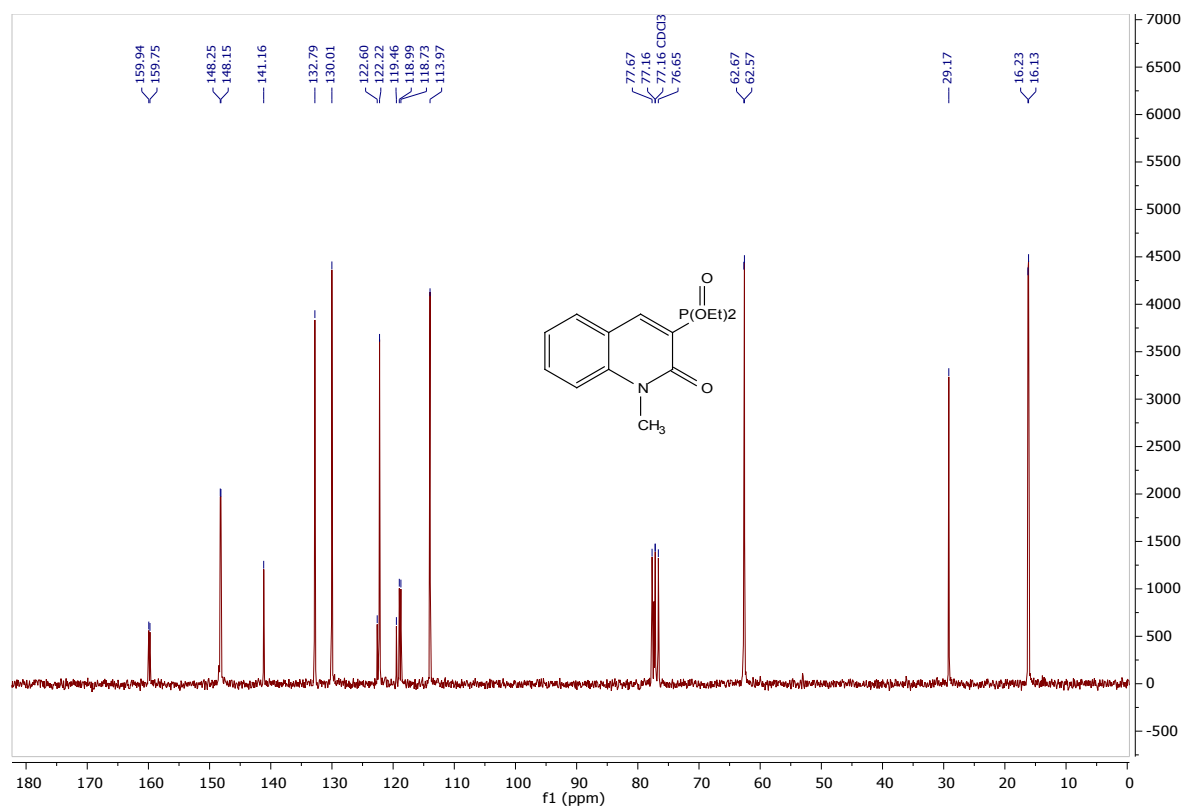
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¹H NMR

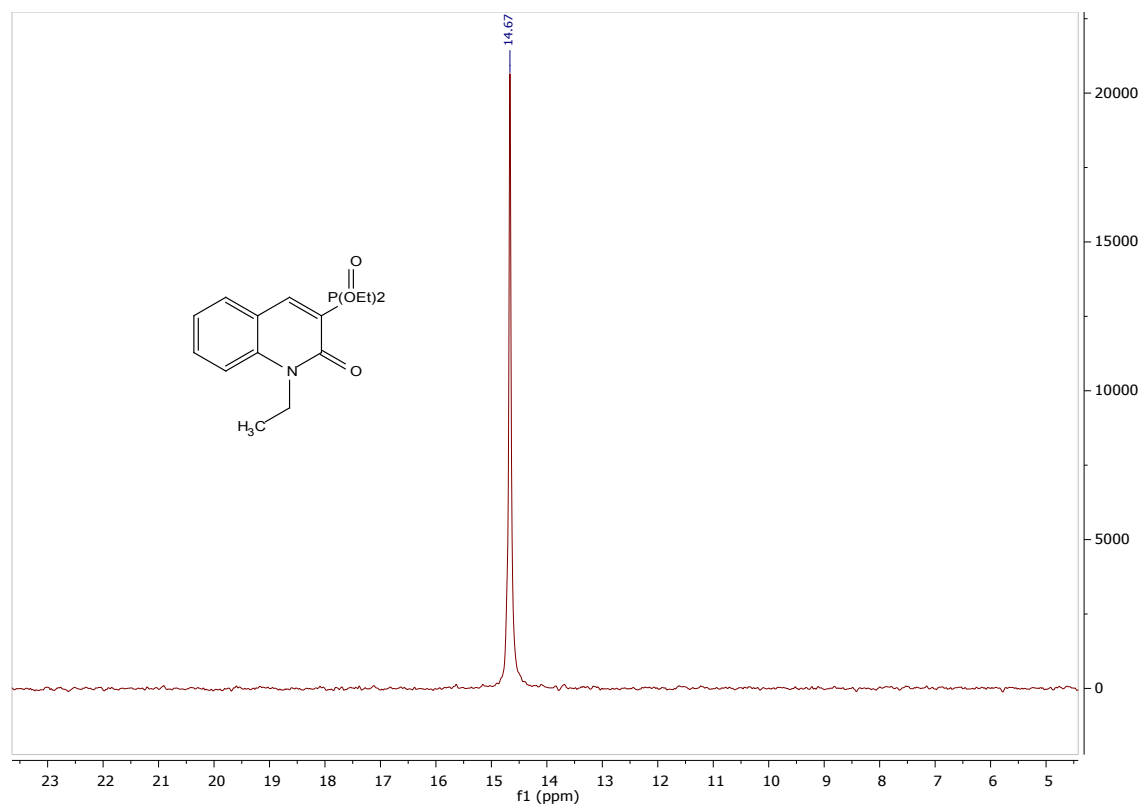


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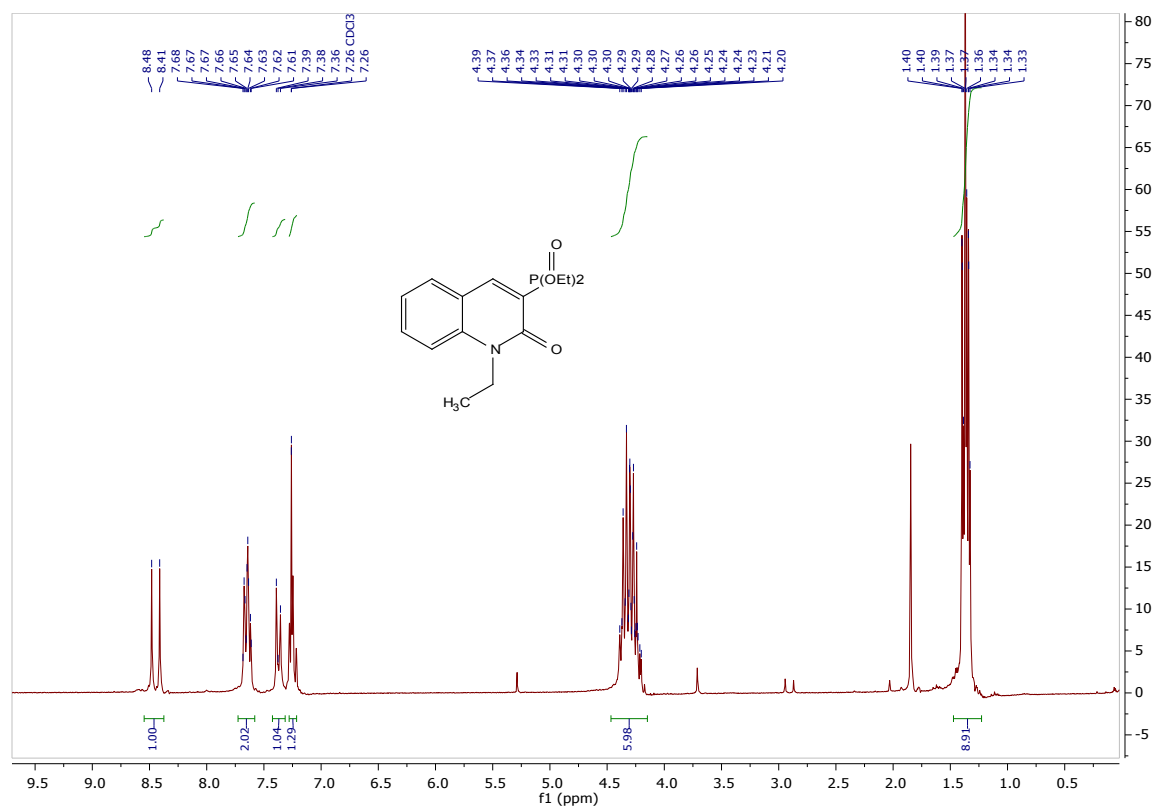


Compound 16b

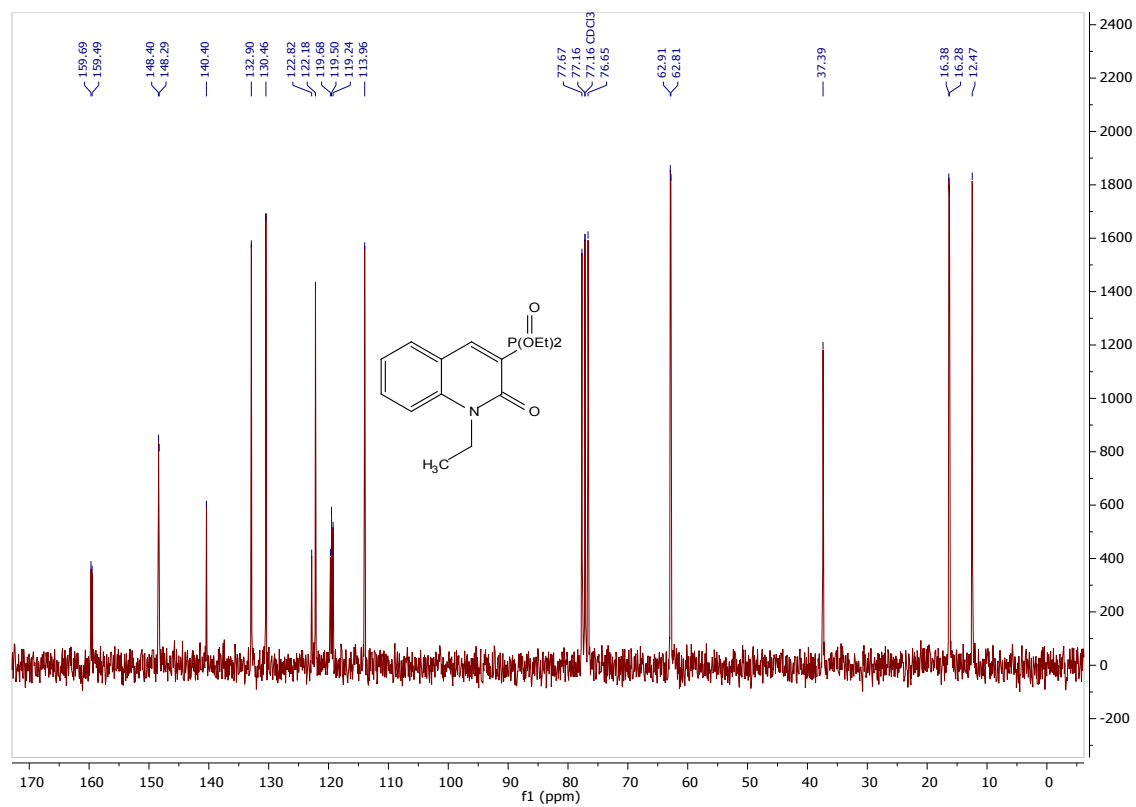
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¹H NMR

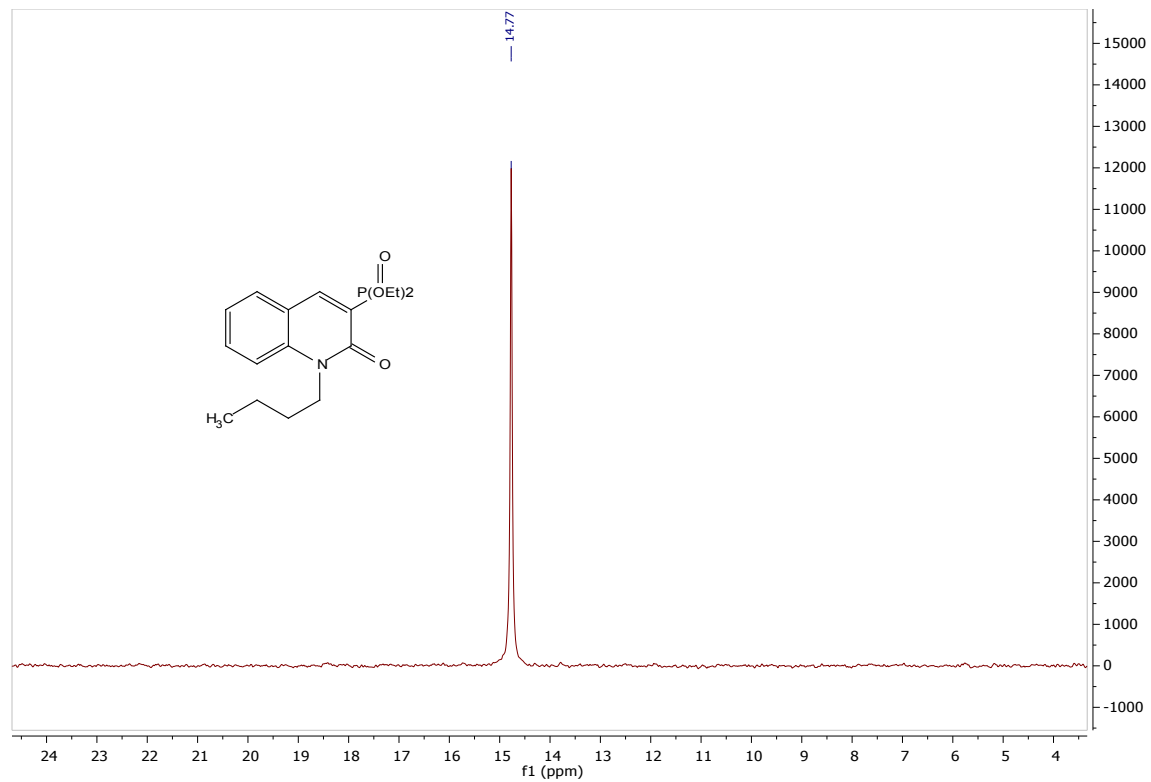


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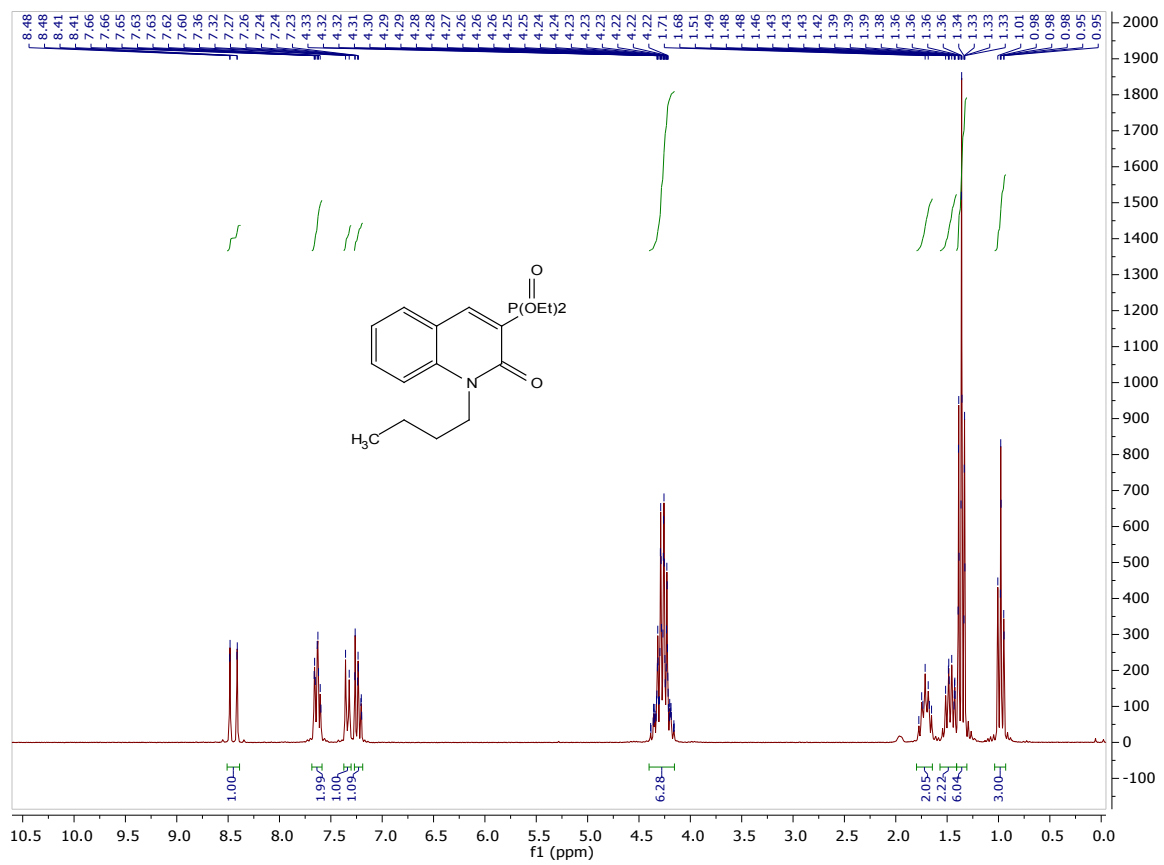


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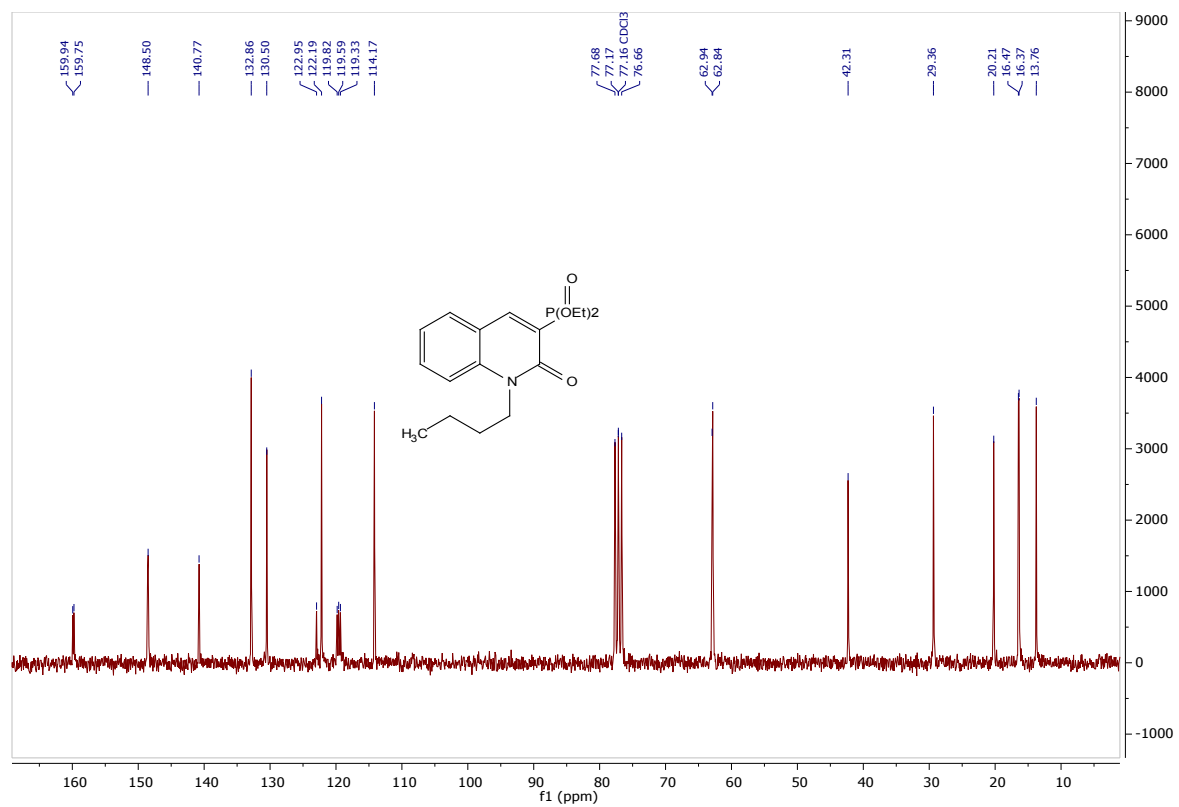
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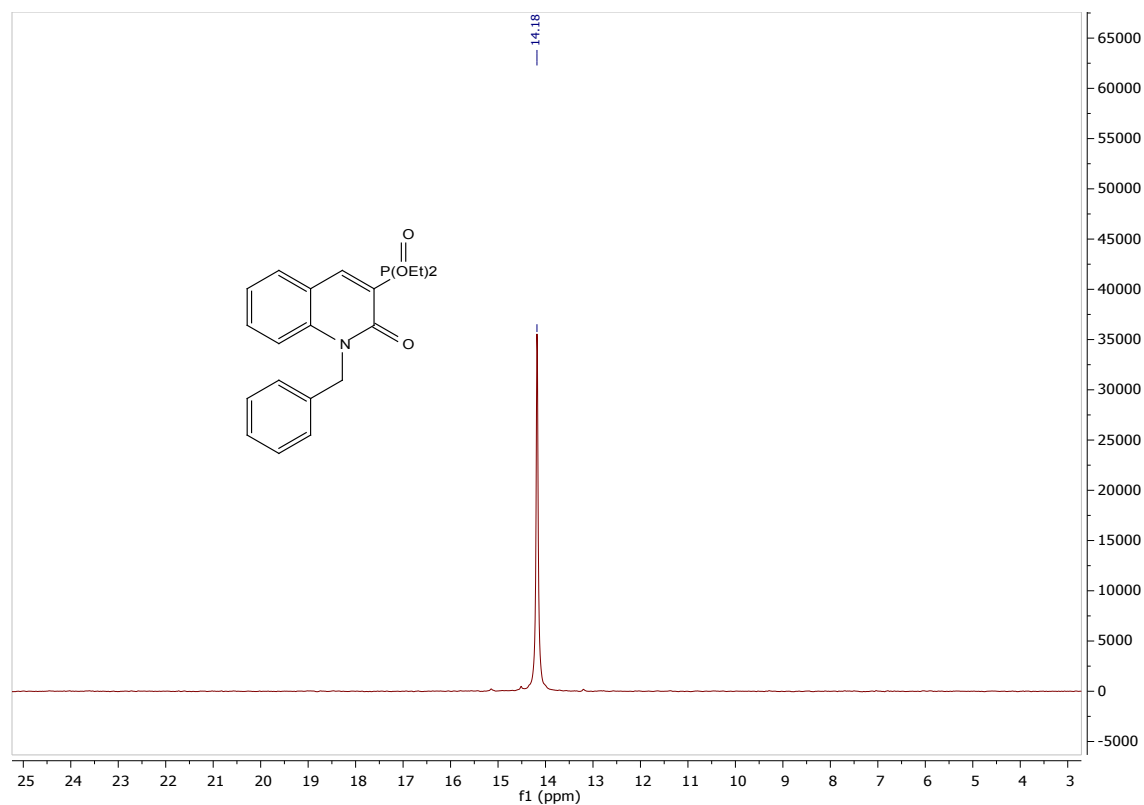


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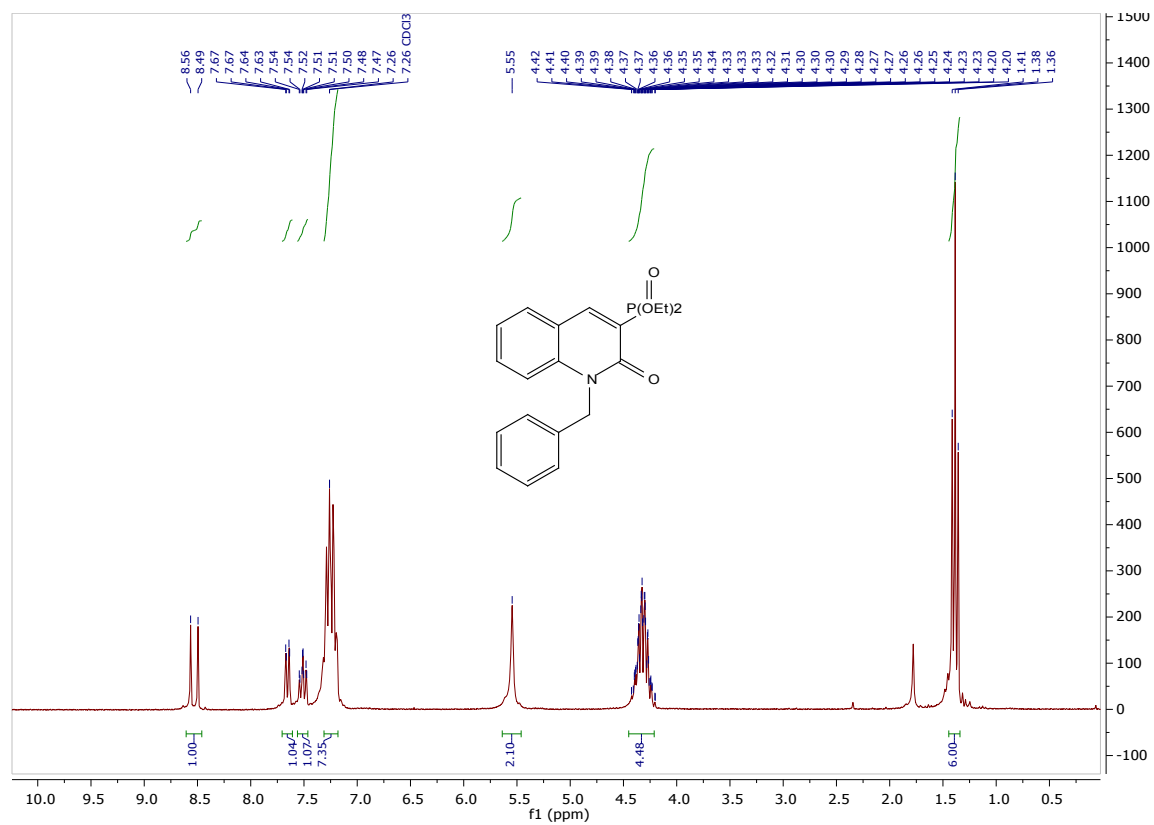


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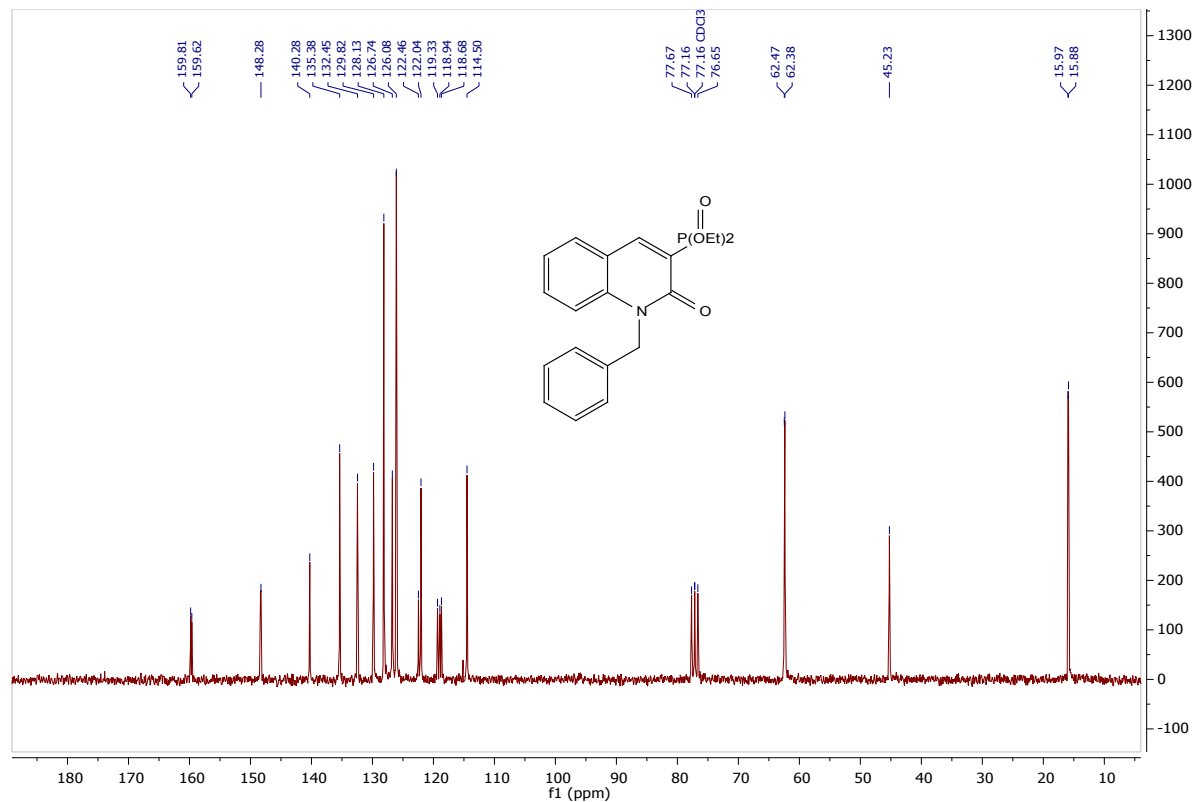
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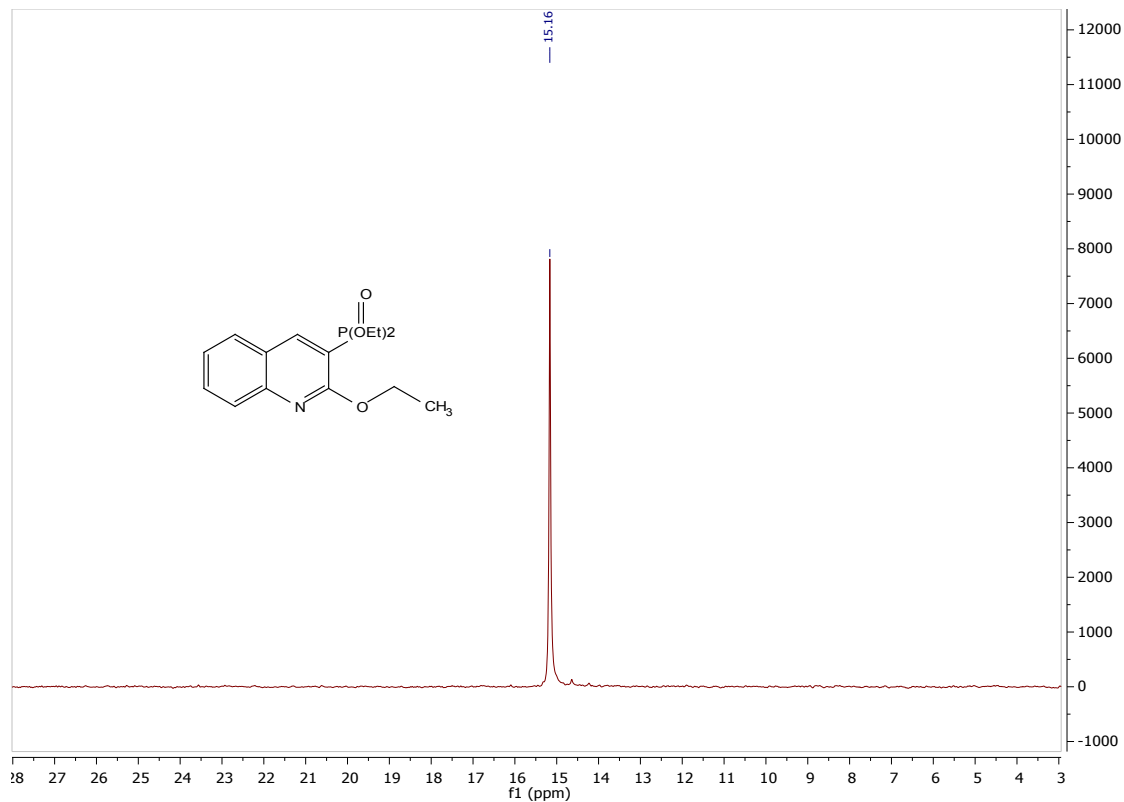


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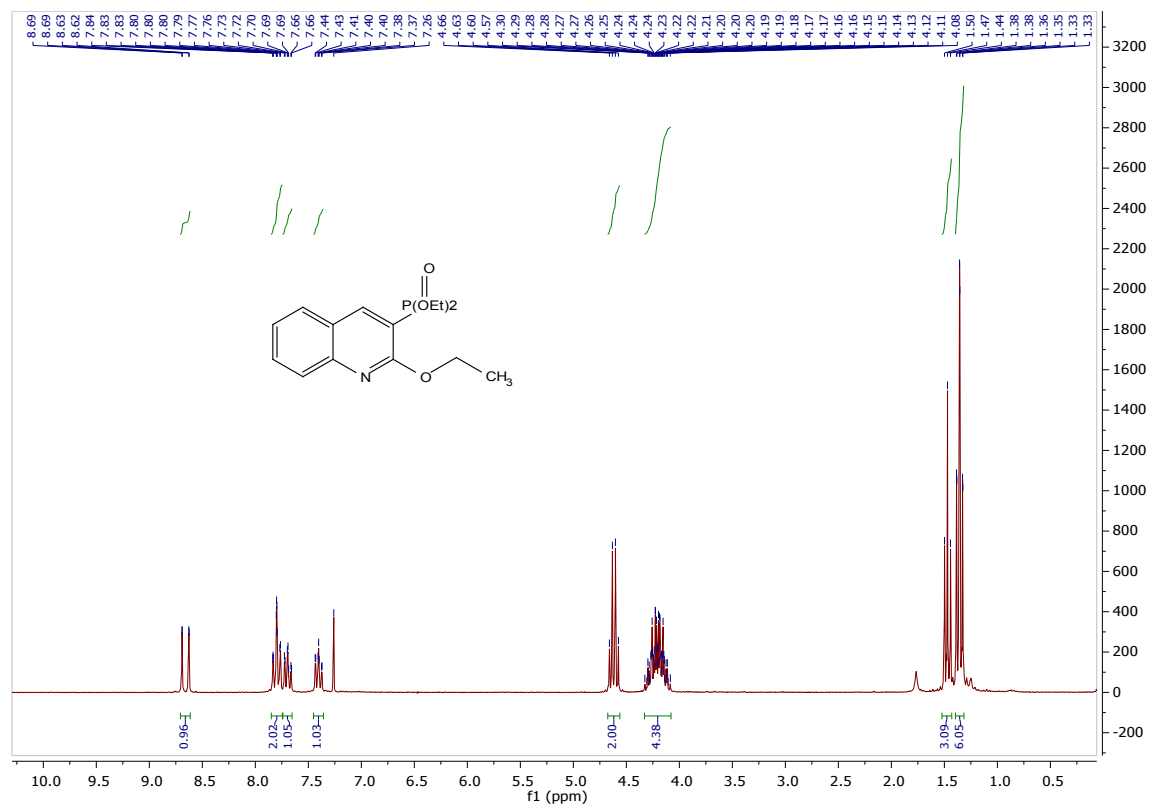


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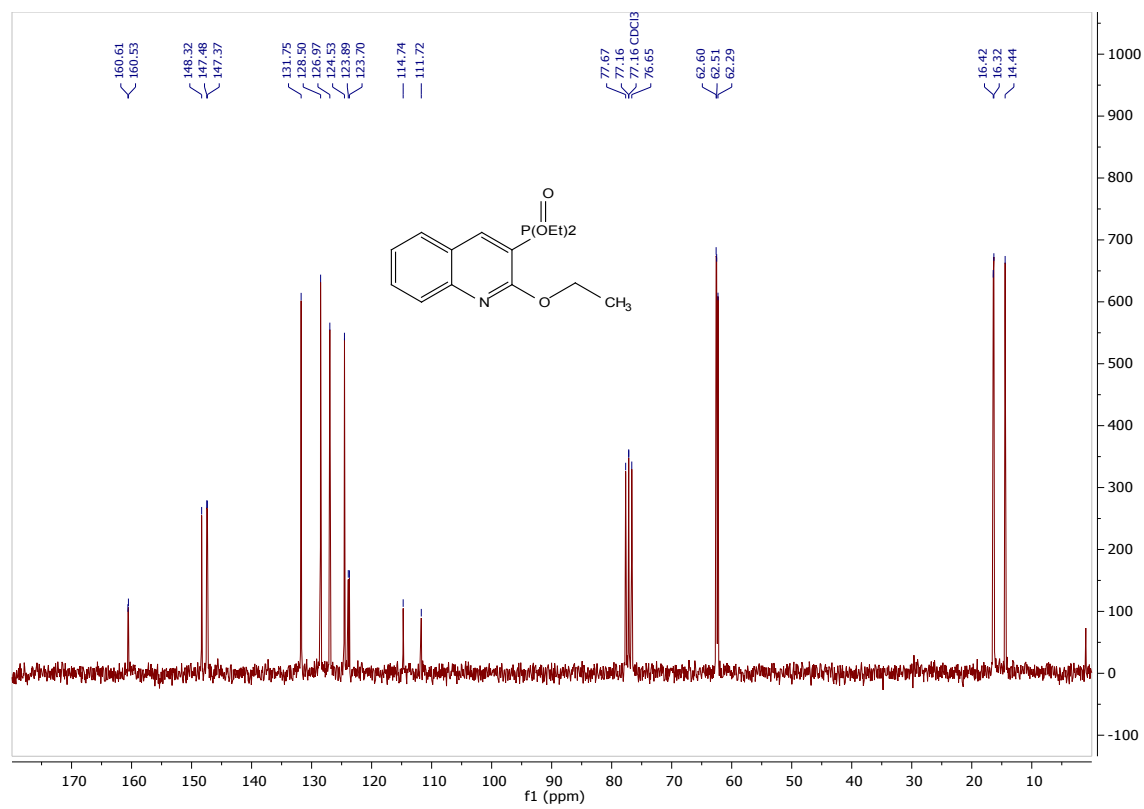
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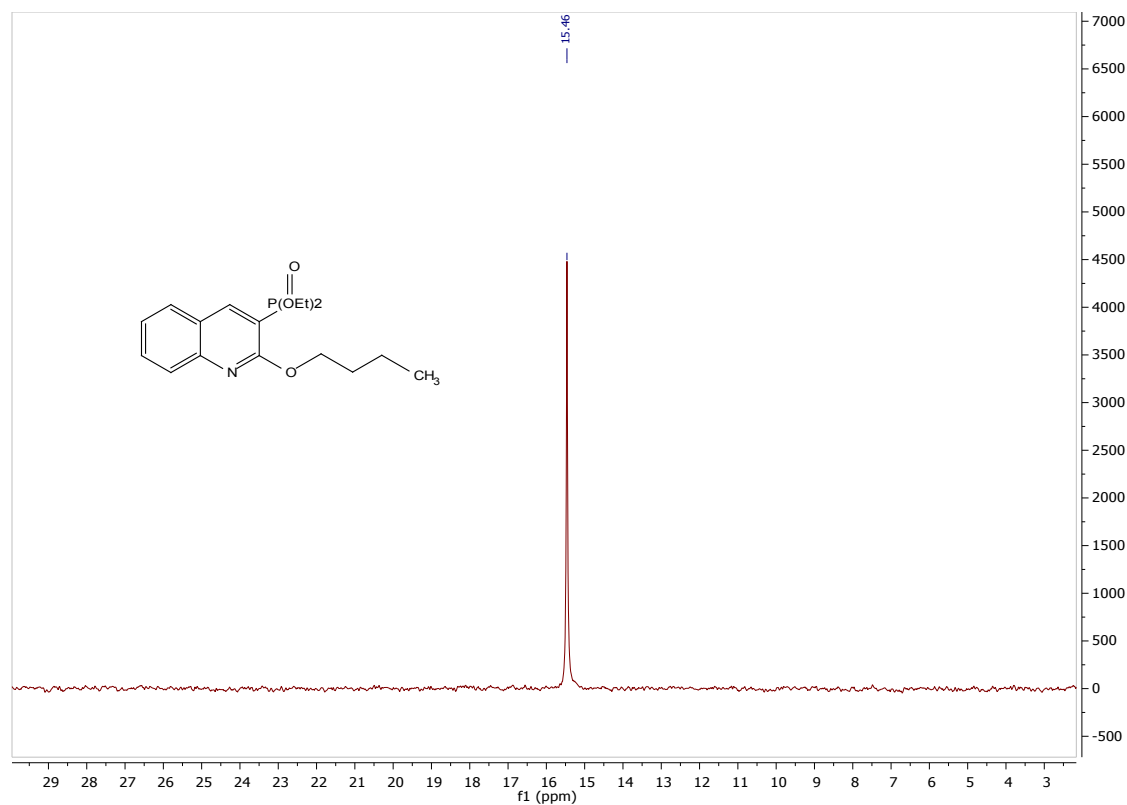


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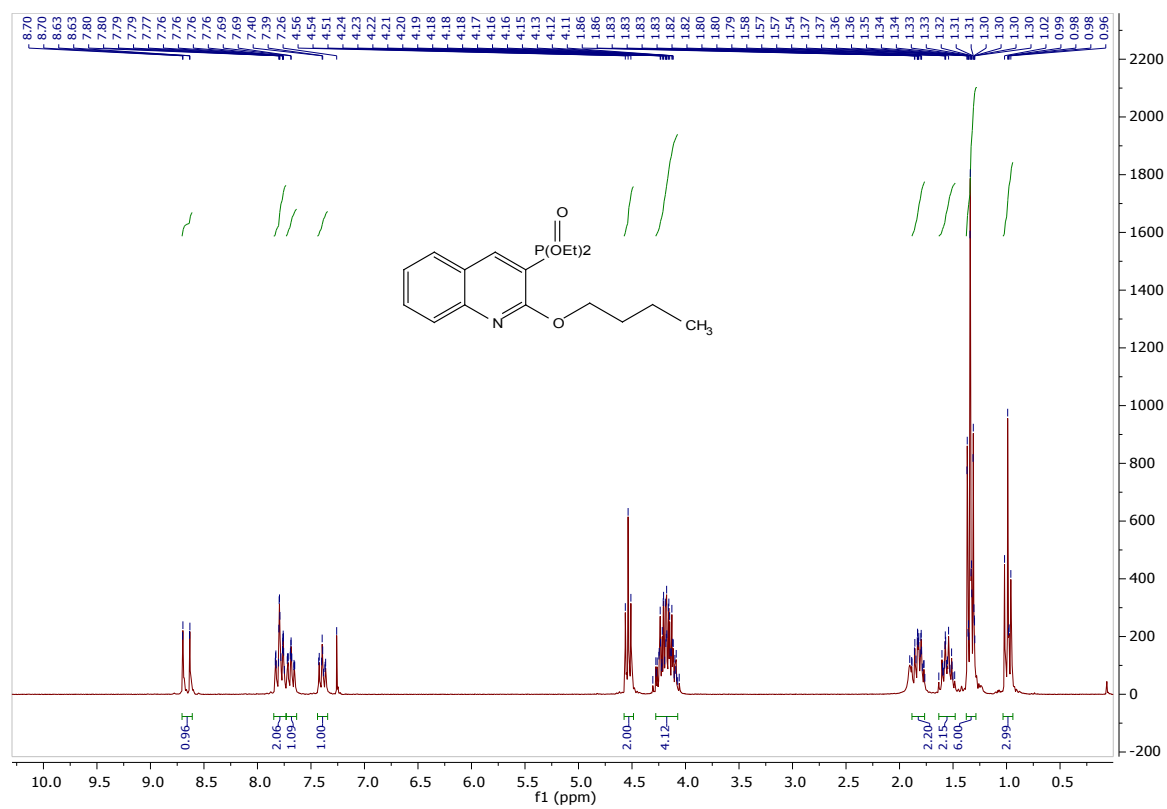


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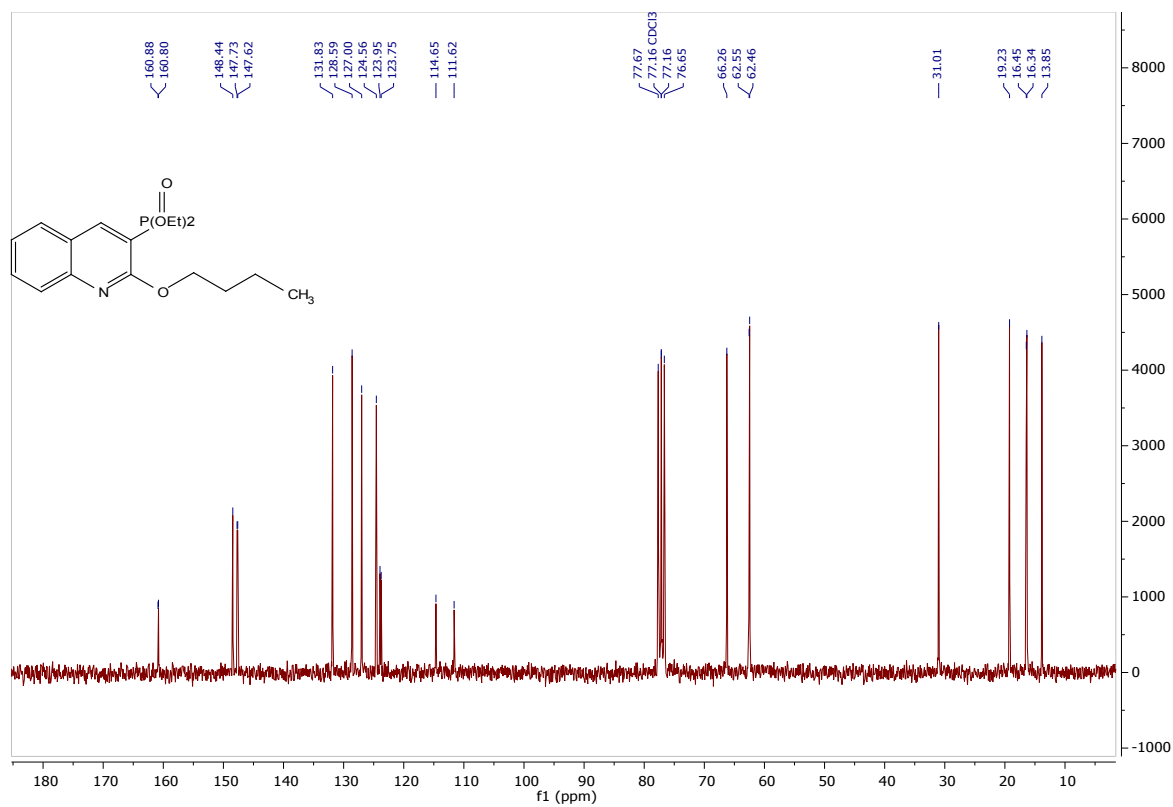
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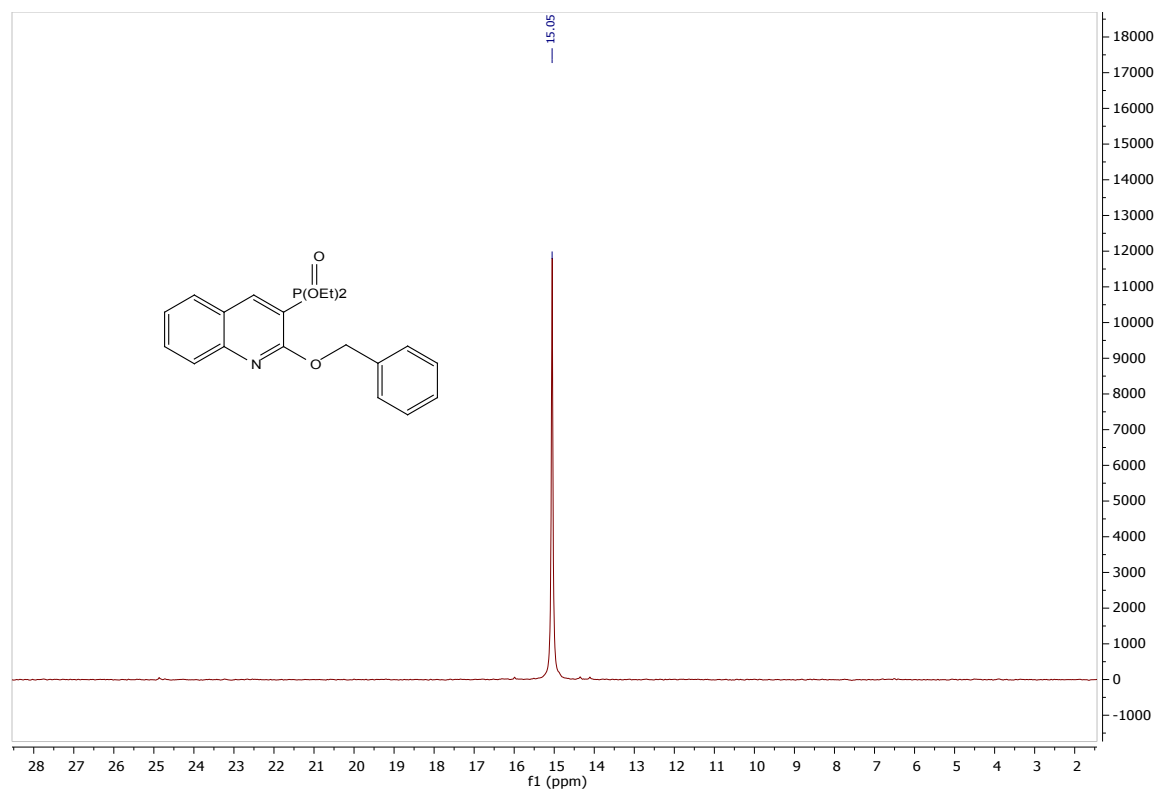


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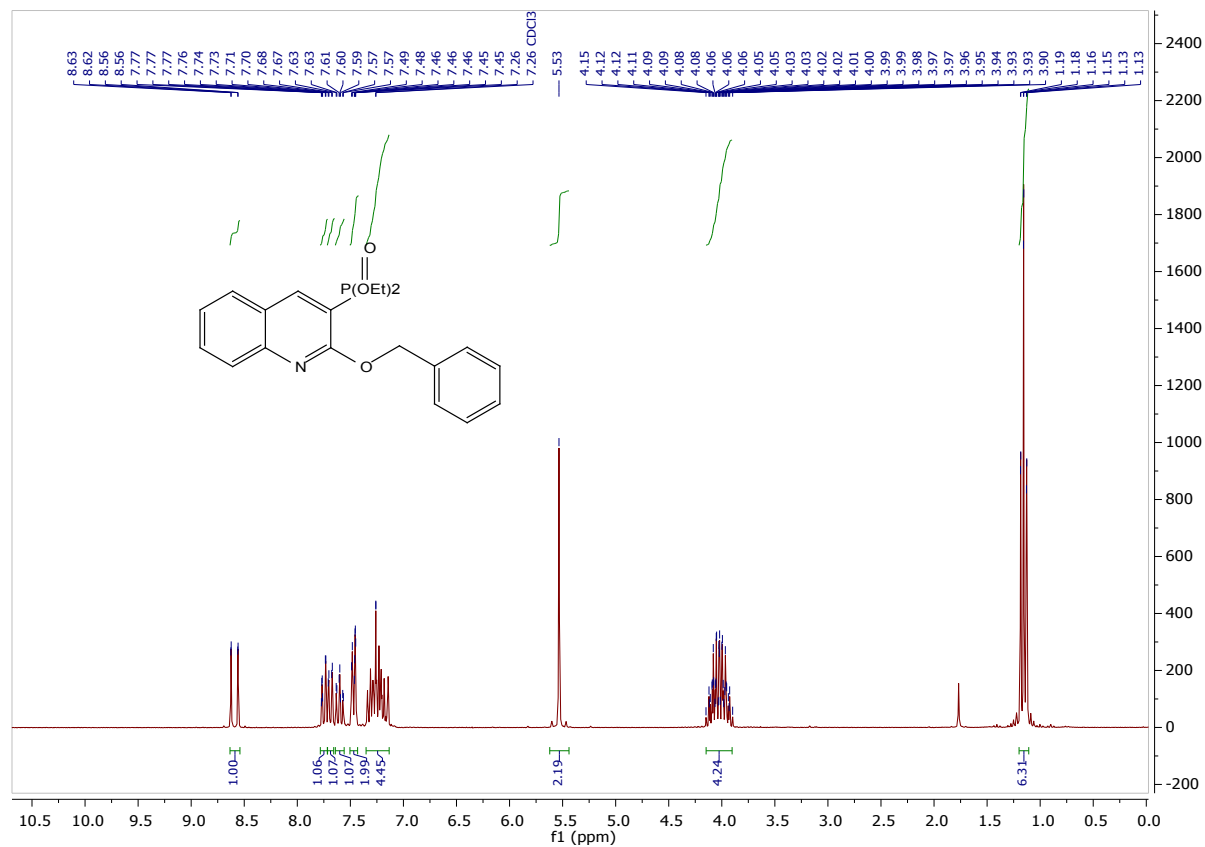


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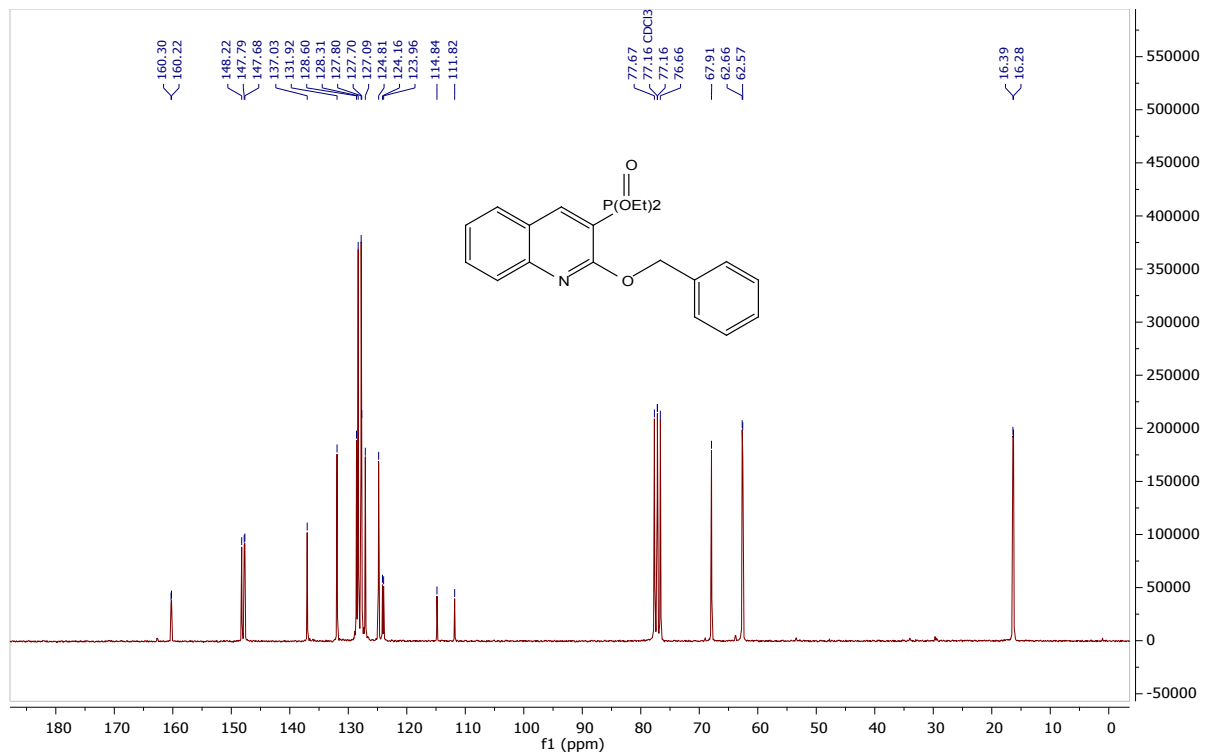
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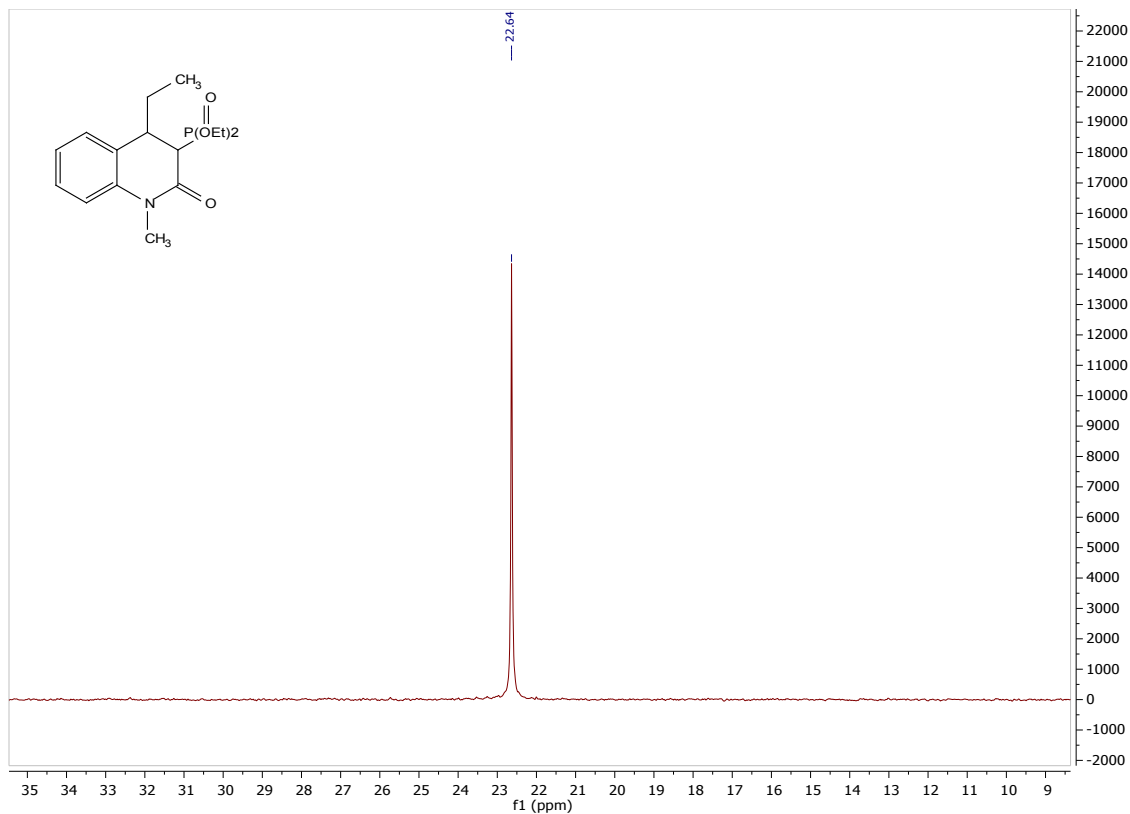


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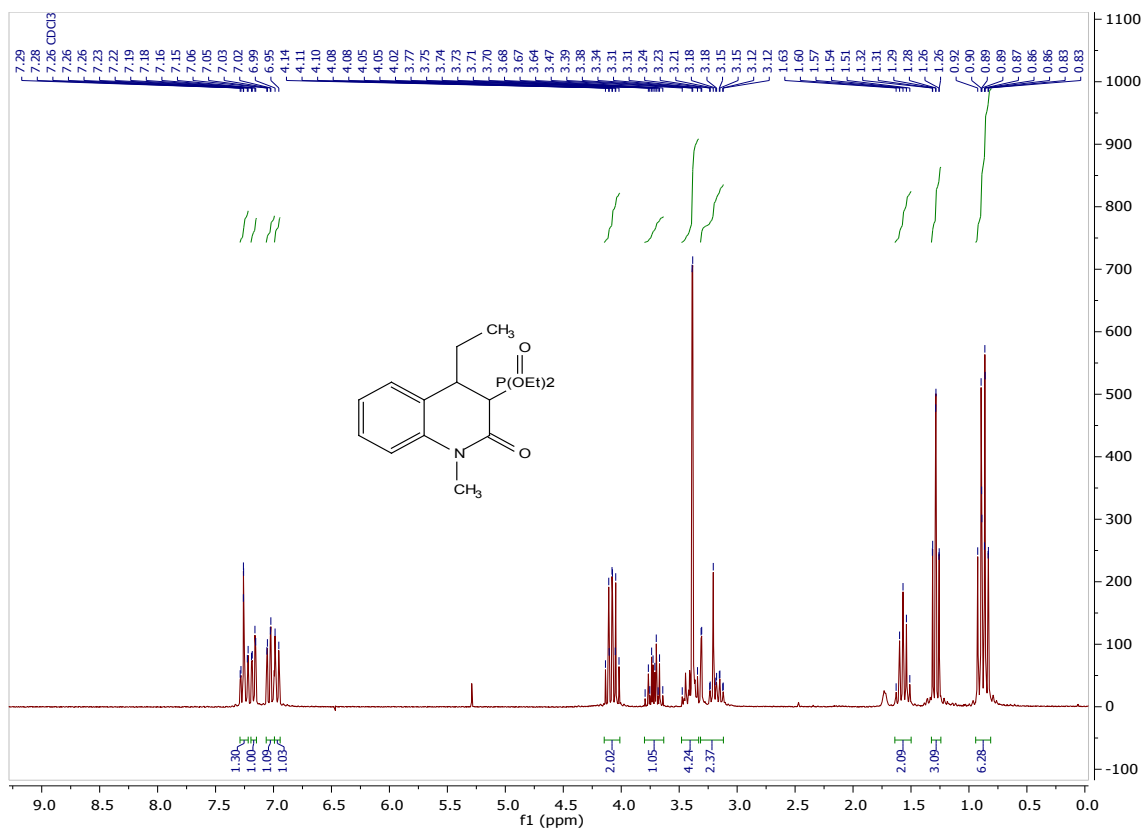


Compound 18a

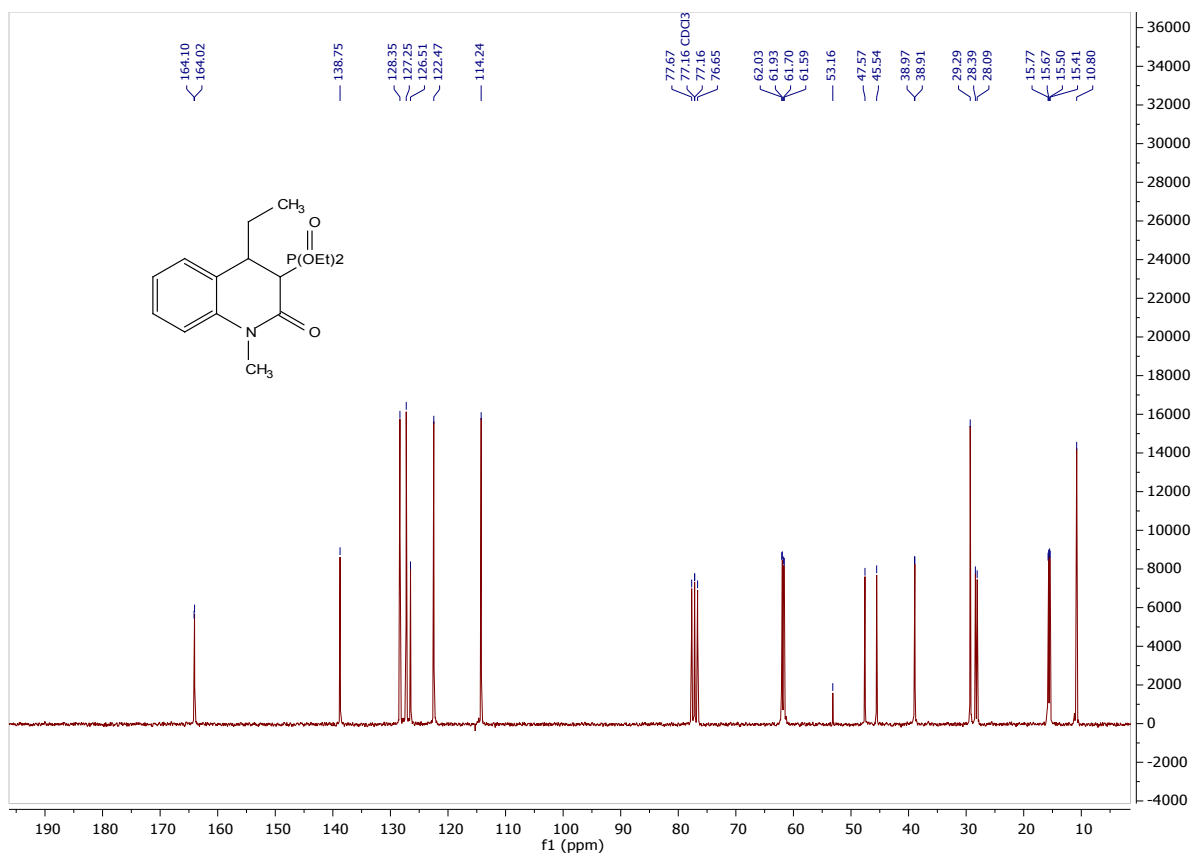
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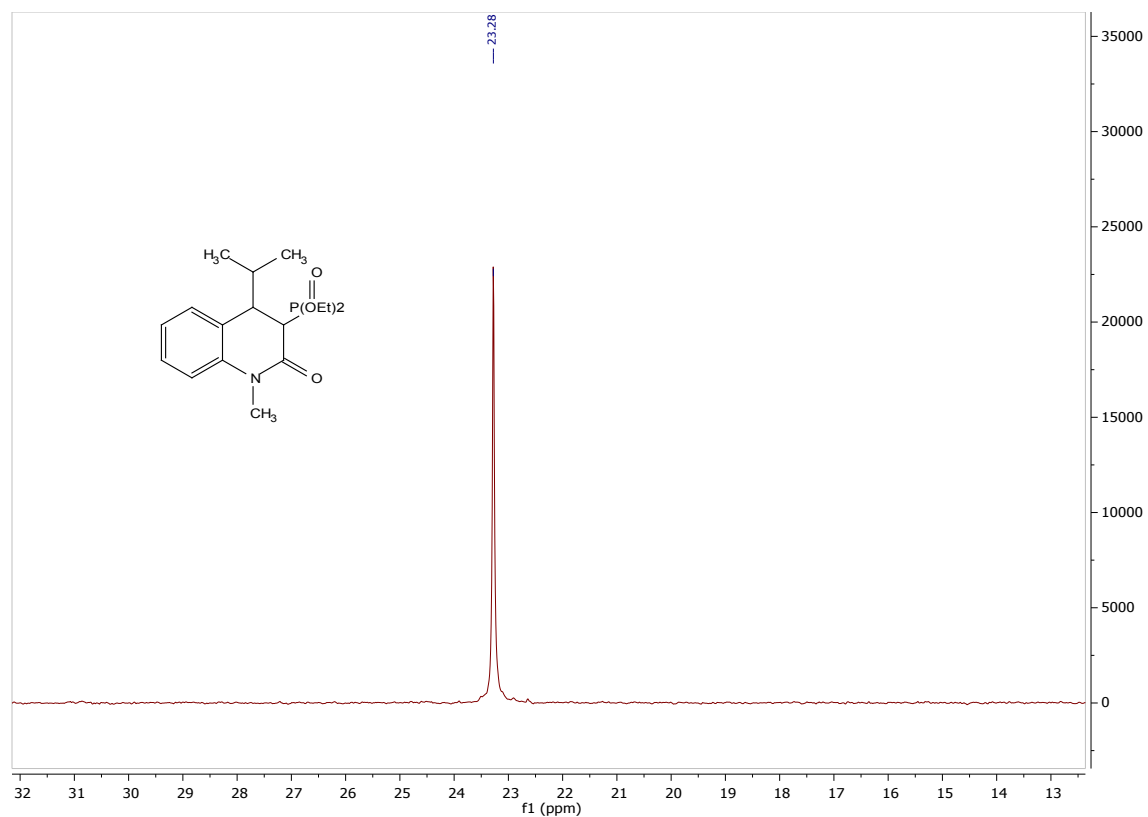


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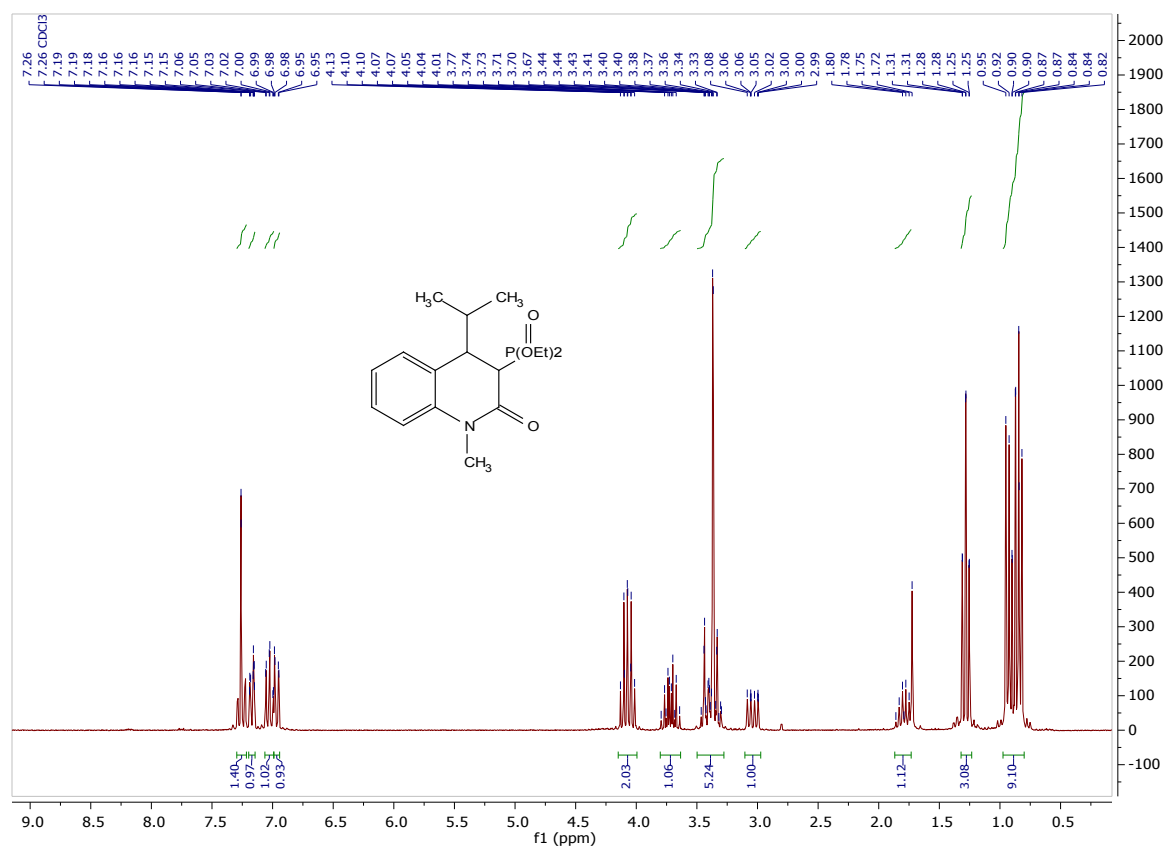


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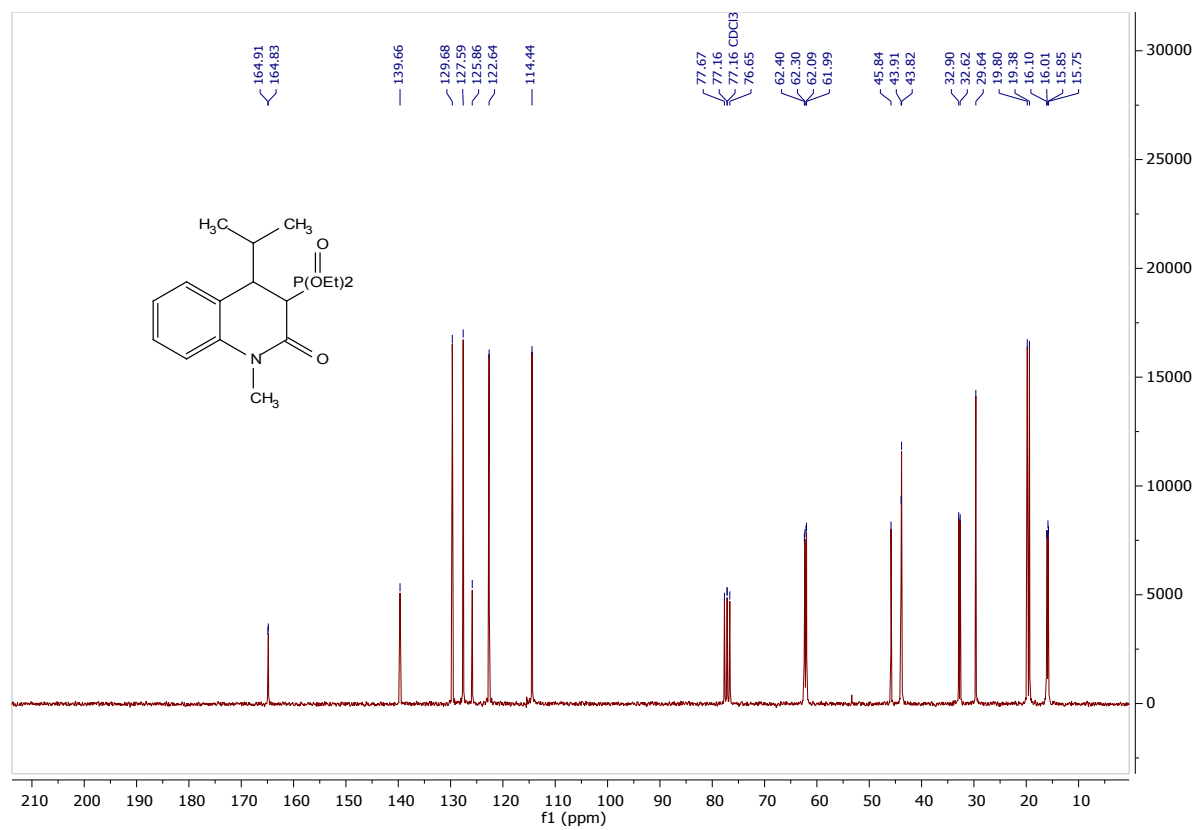
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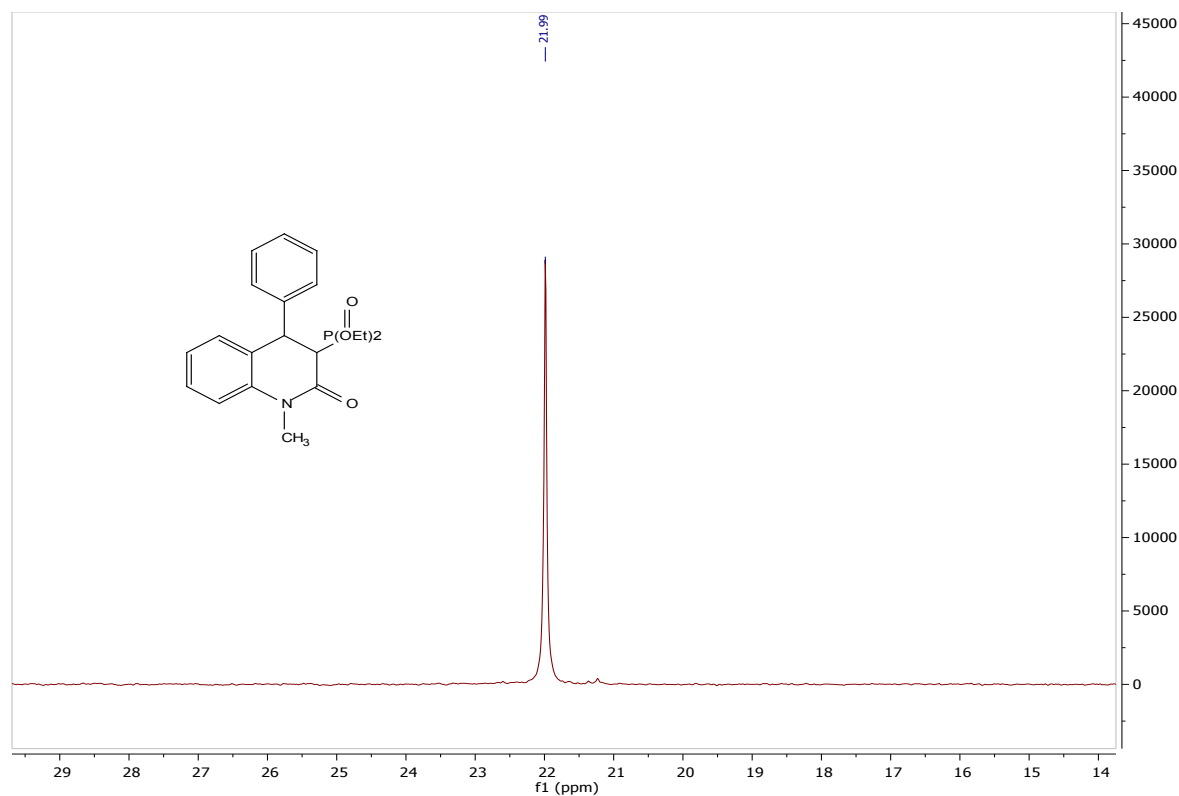


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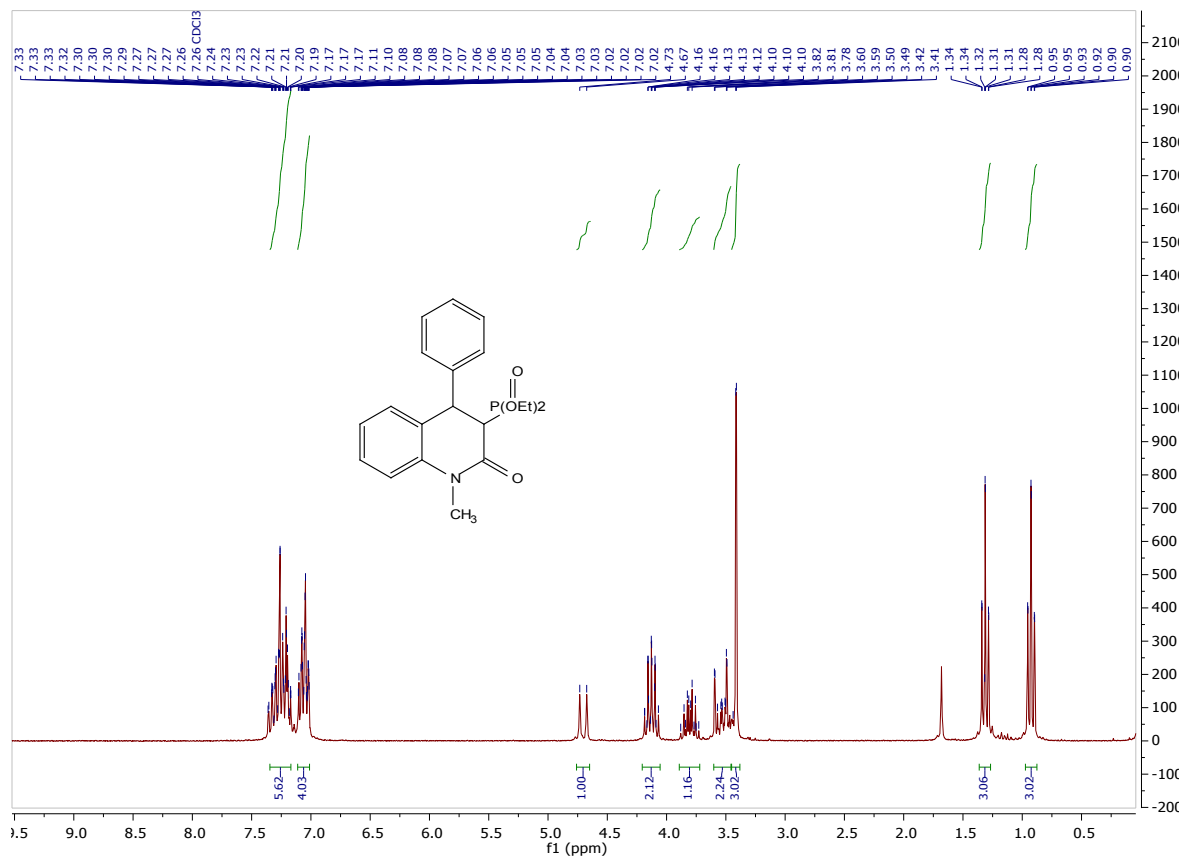


Compound 18c

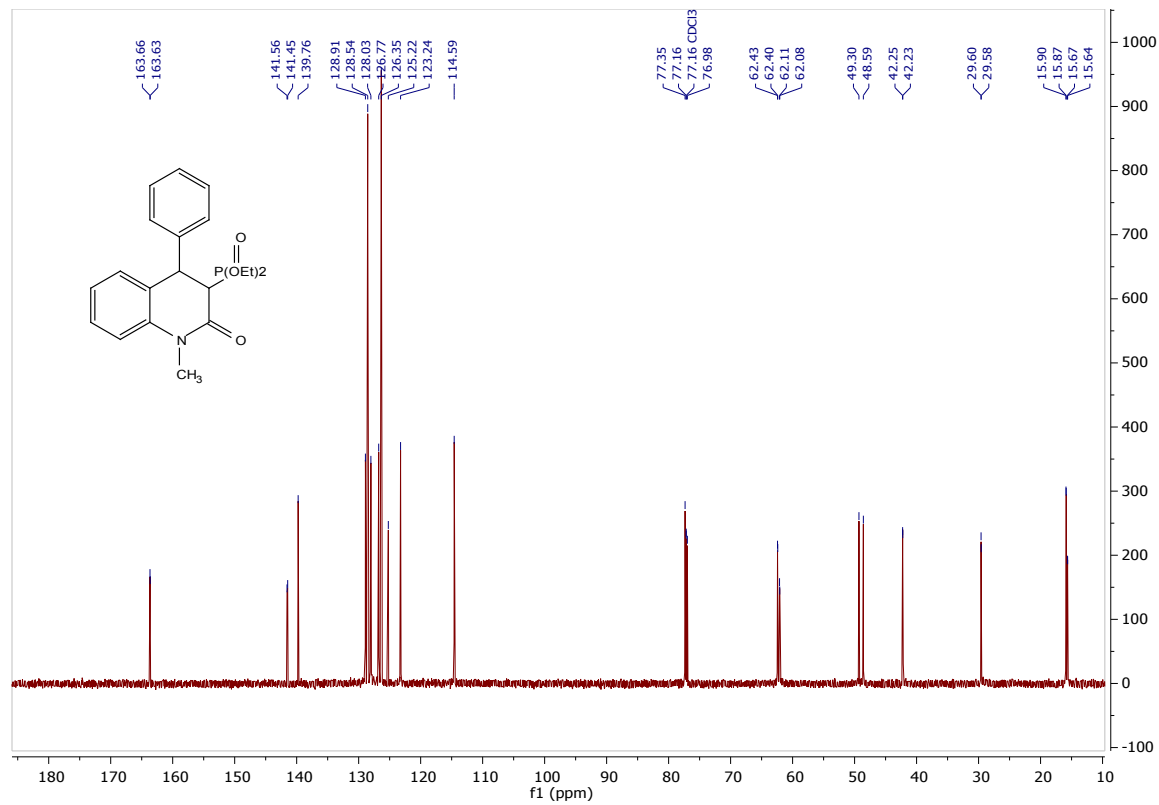
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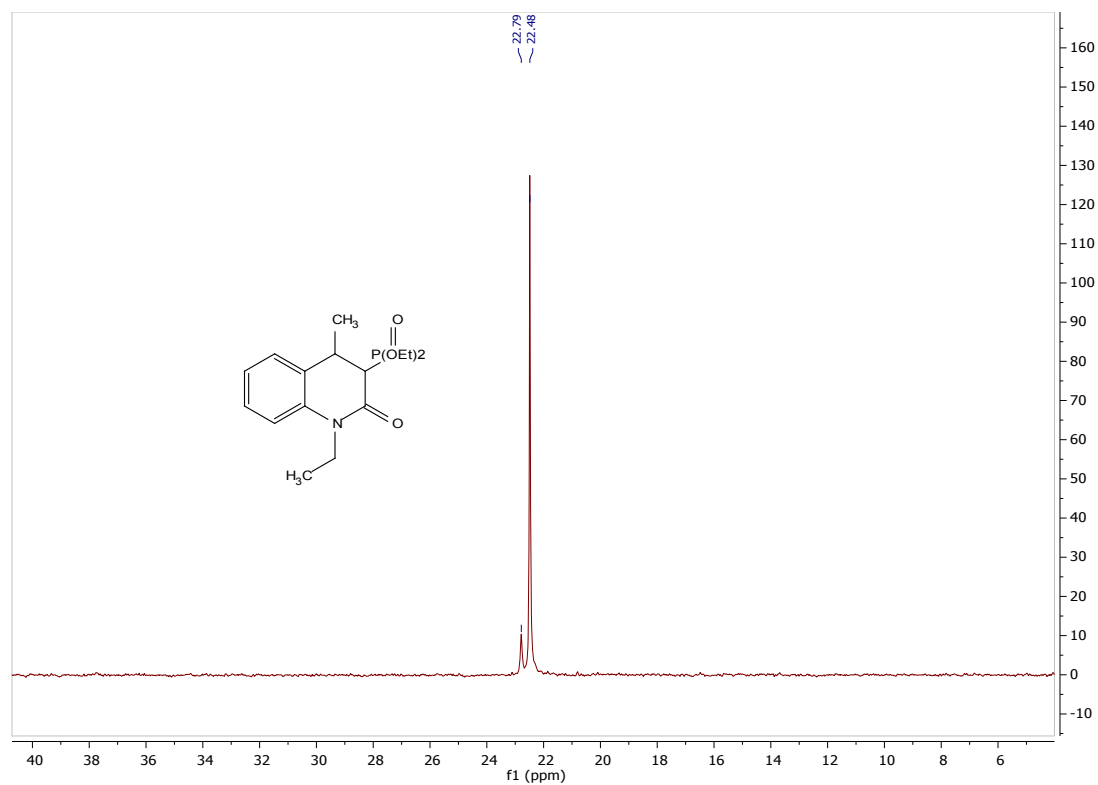


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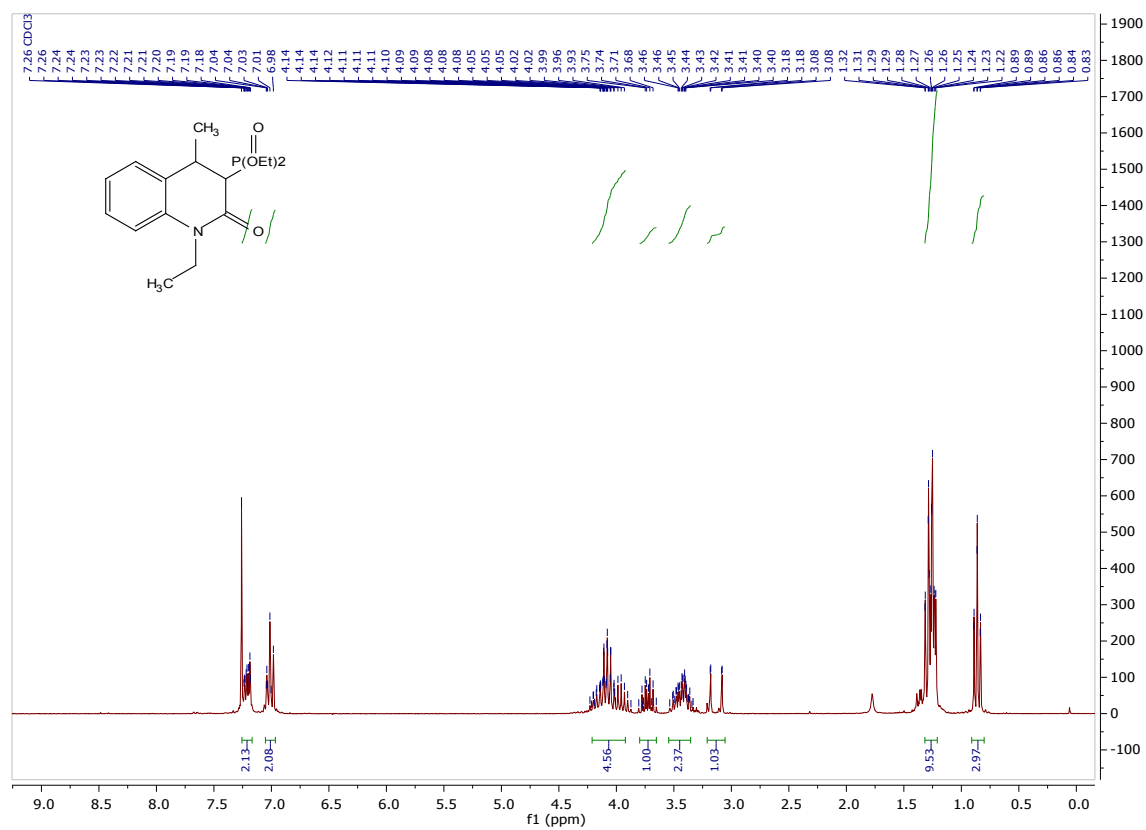


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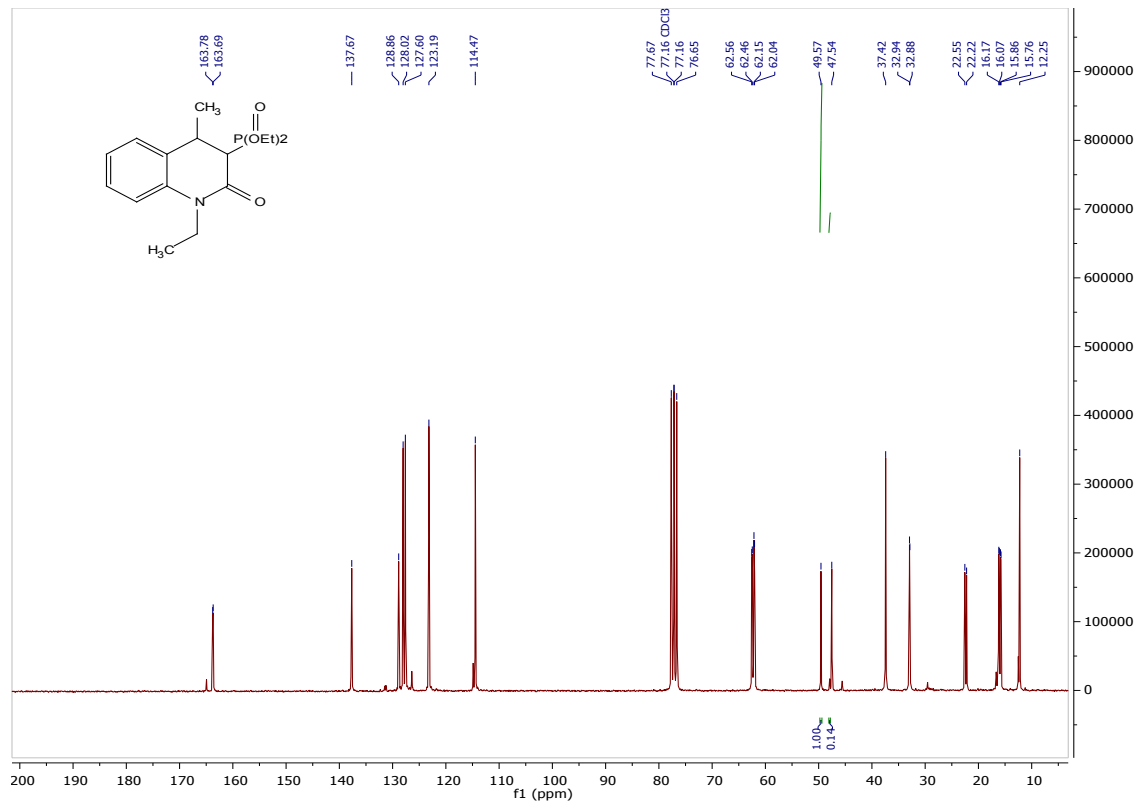
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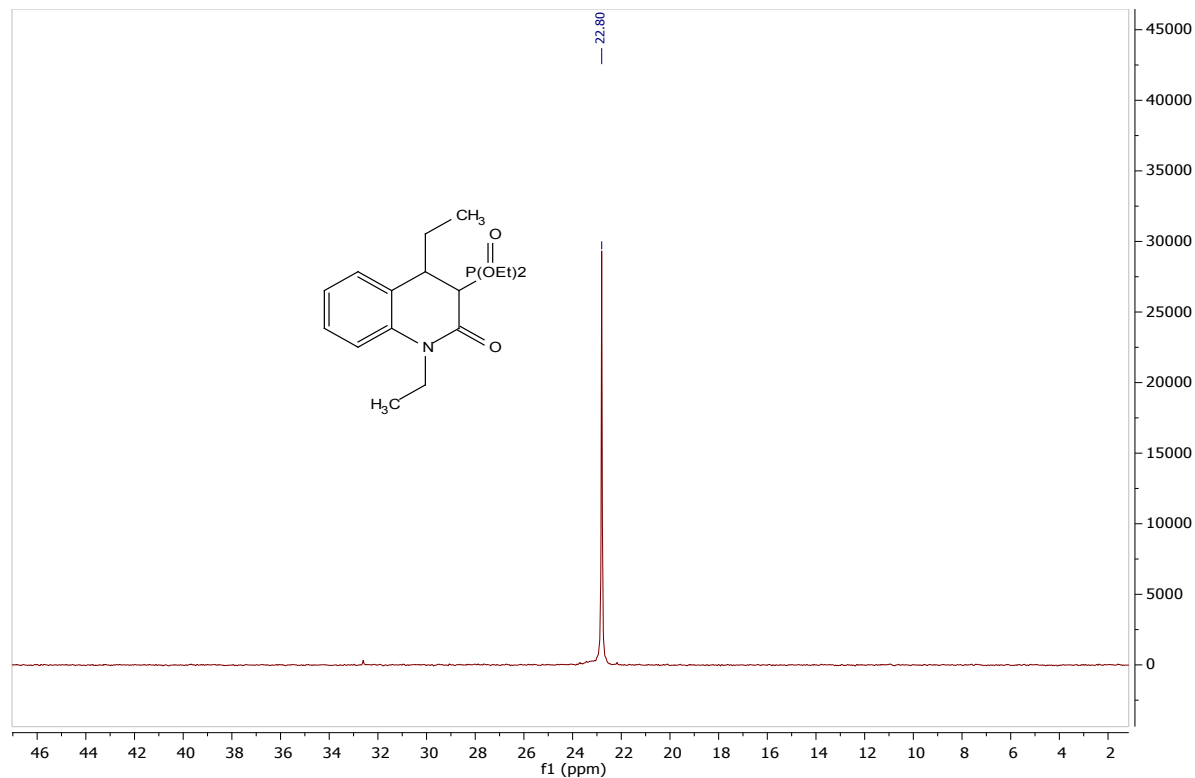


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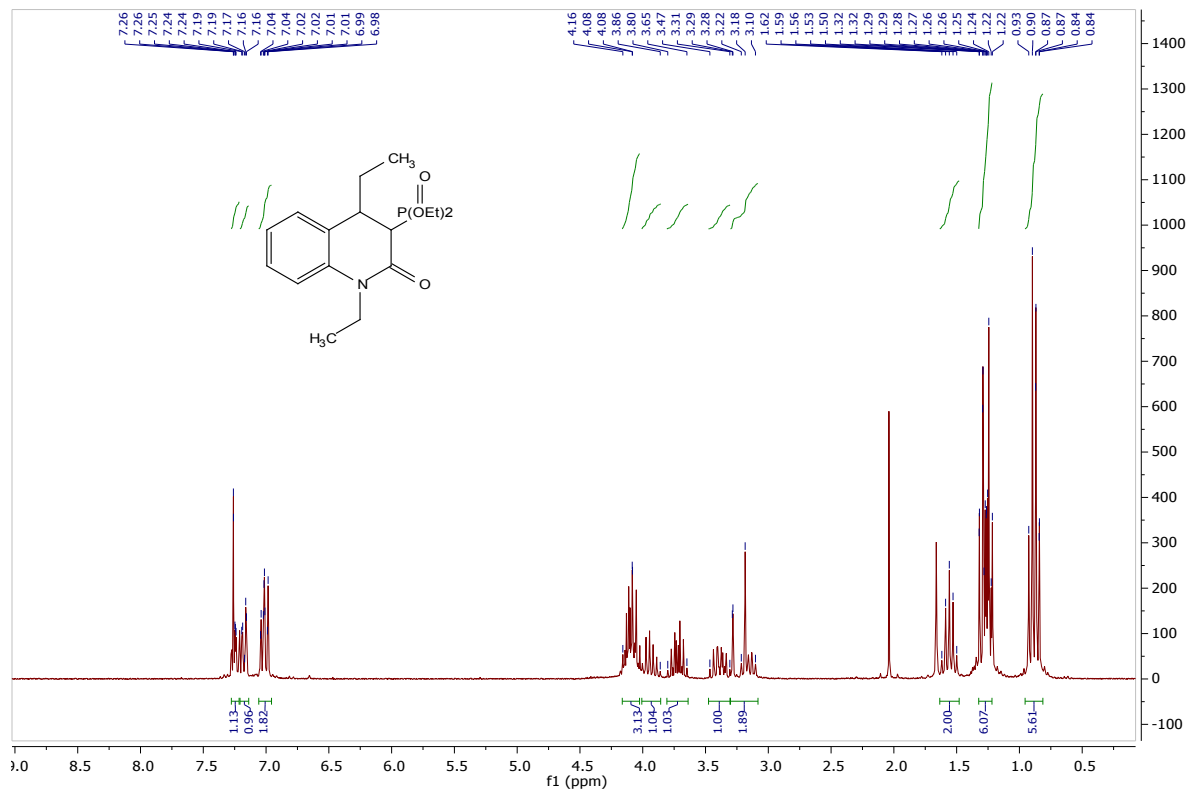


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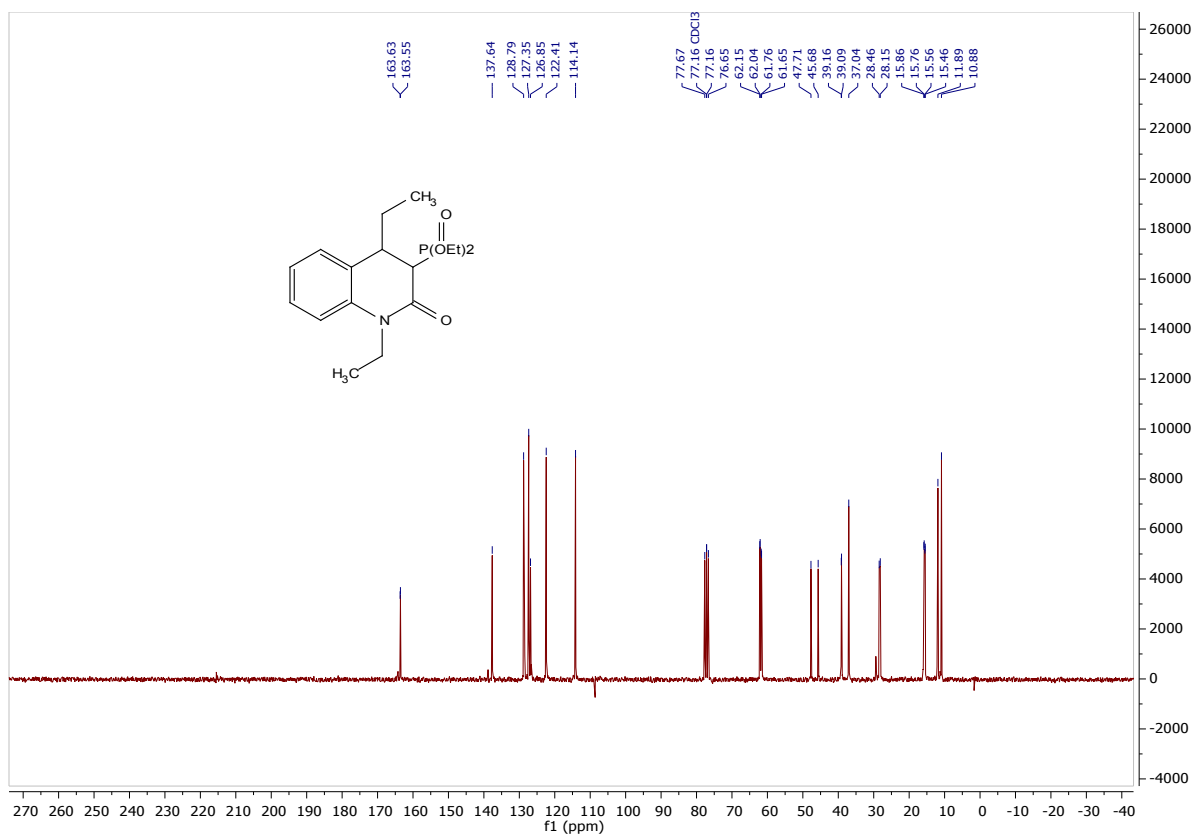
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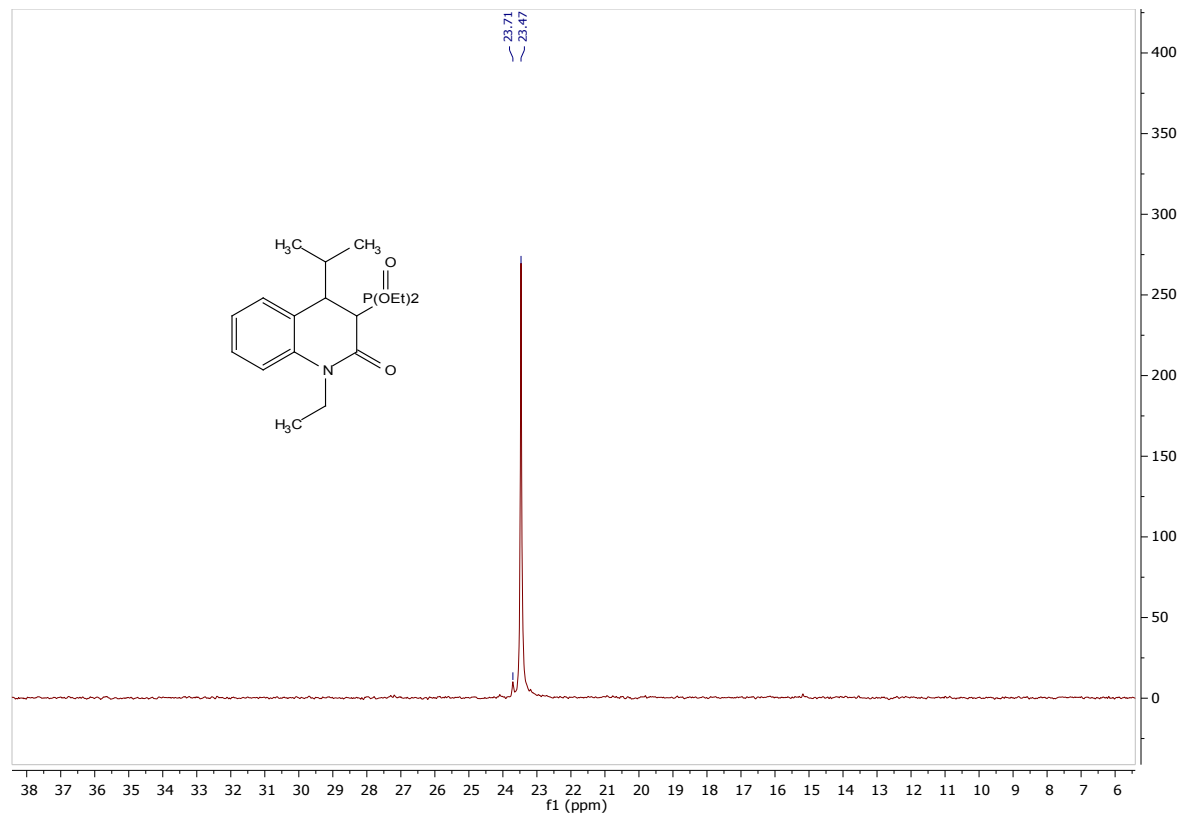


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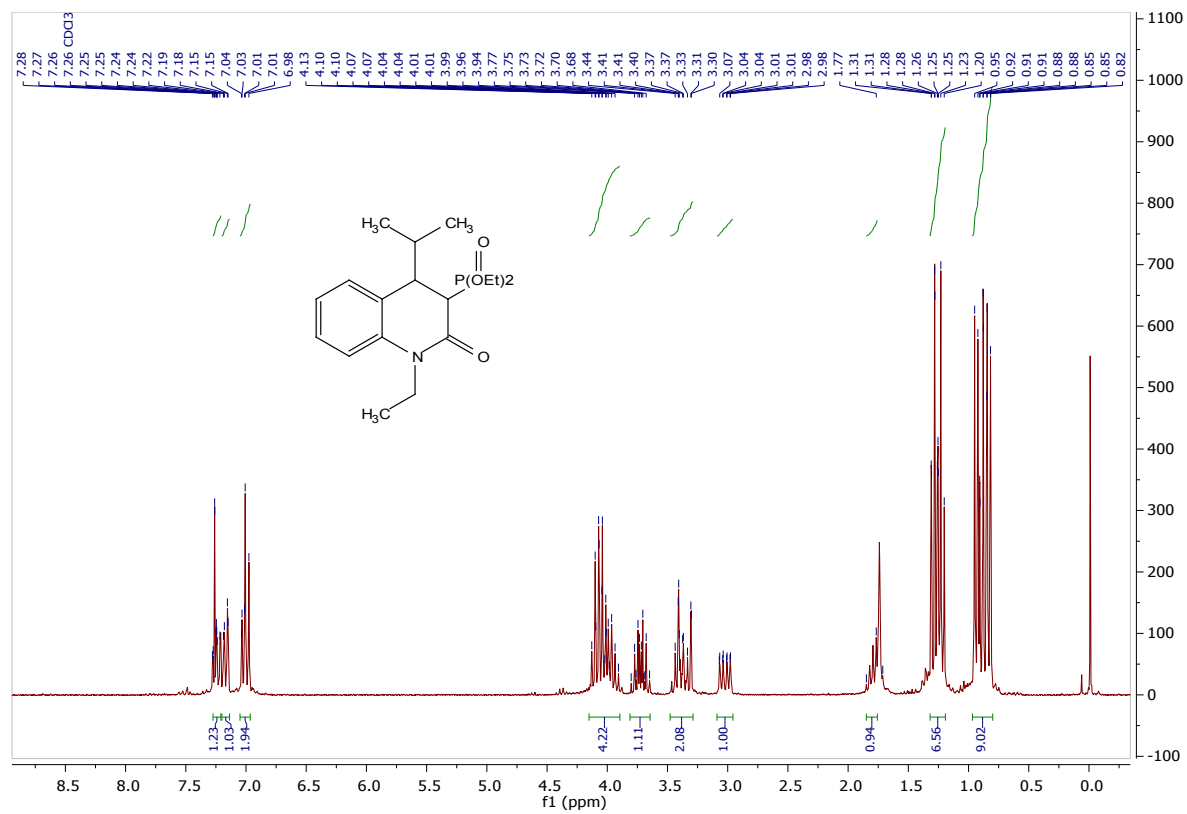


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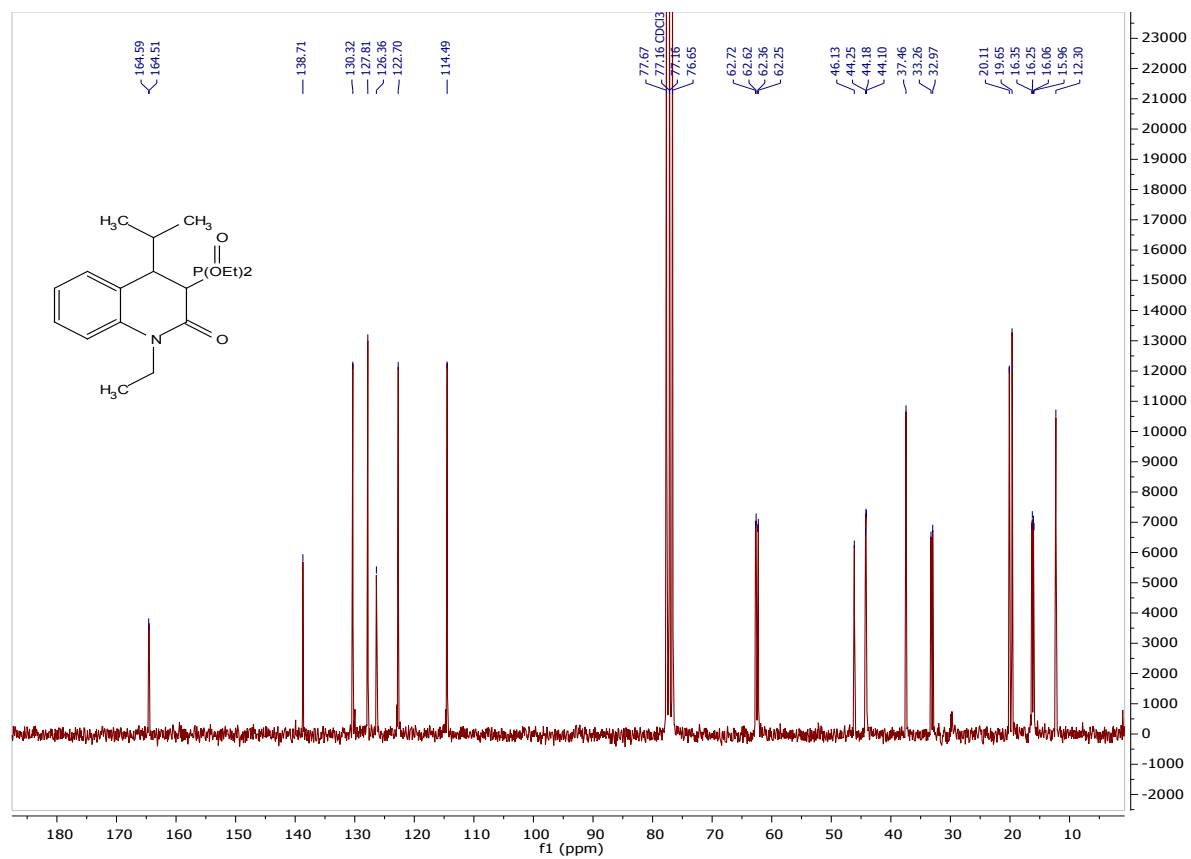
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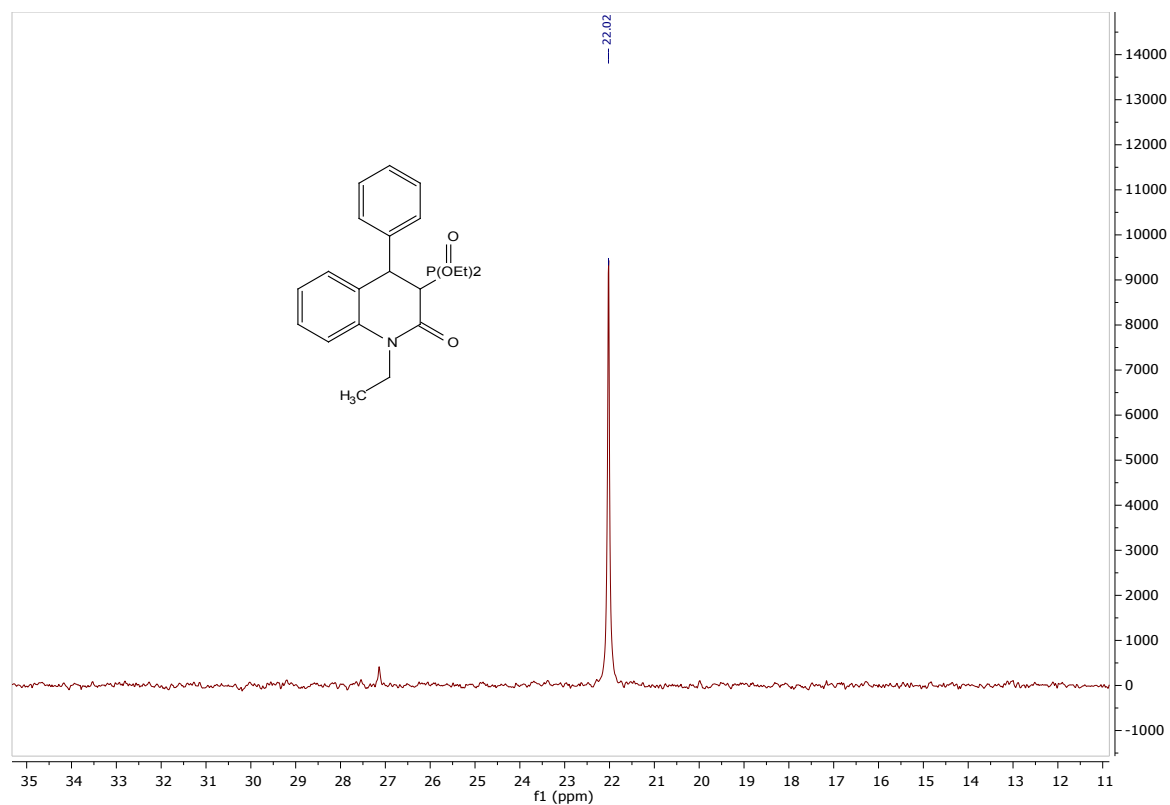


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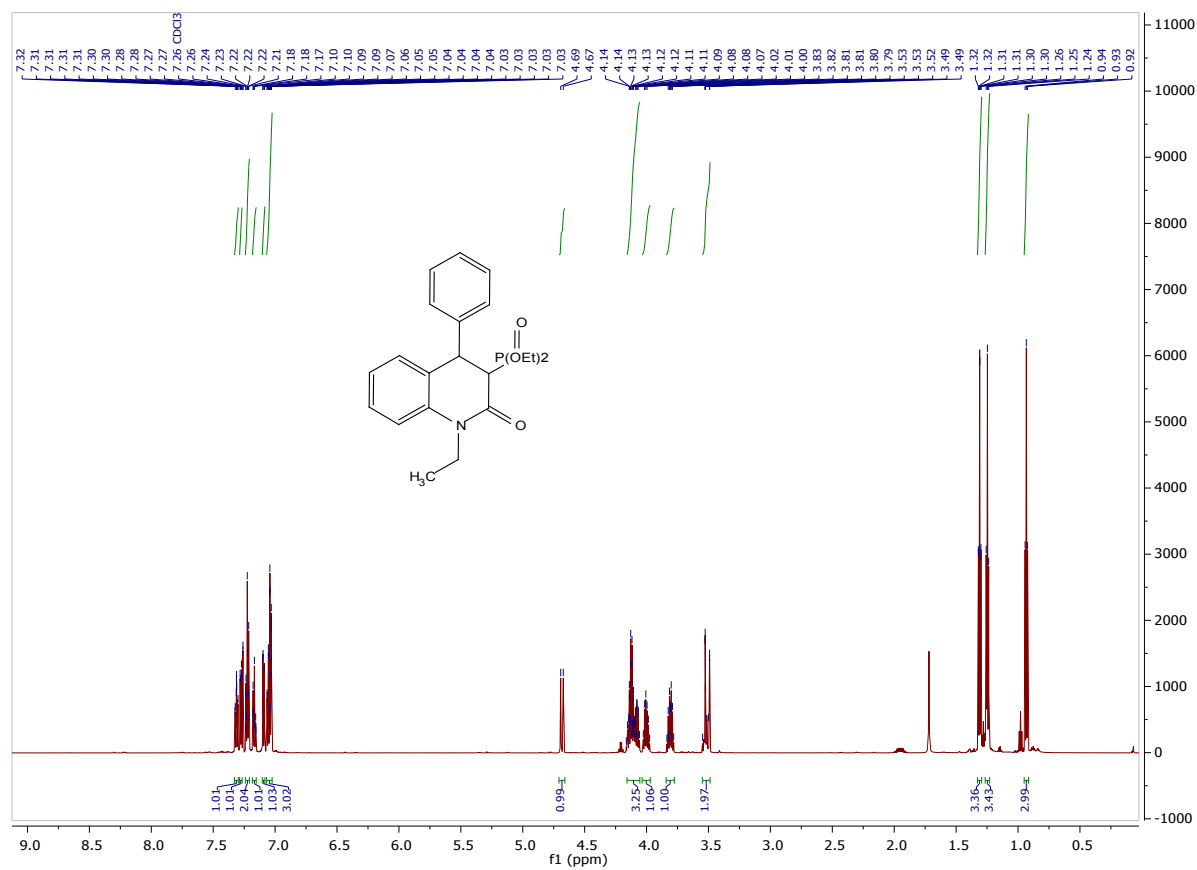


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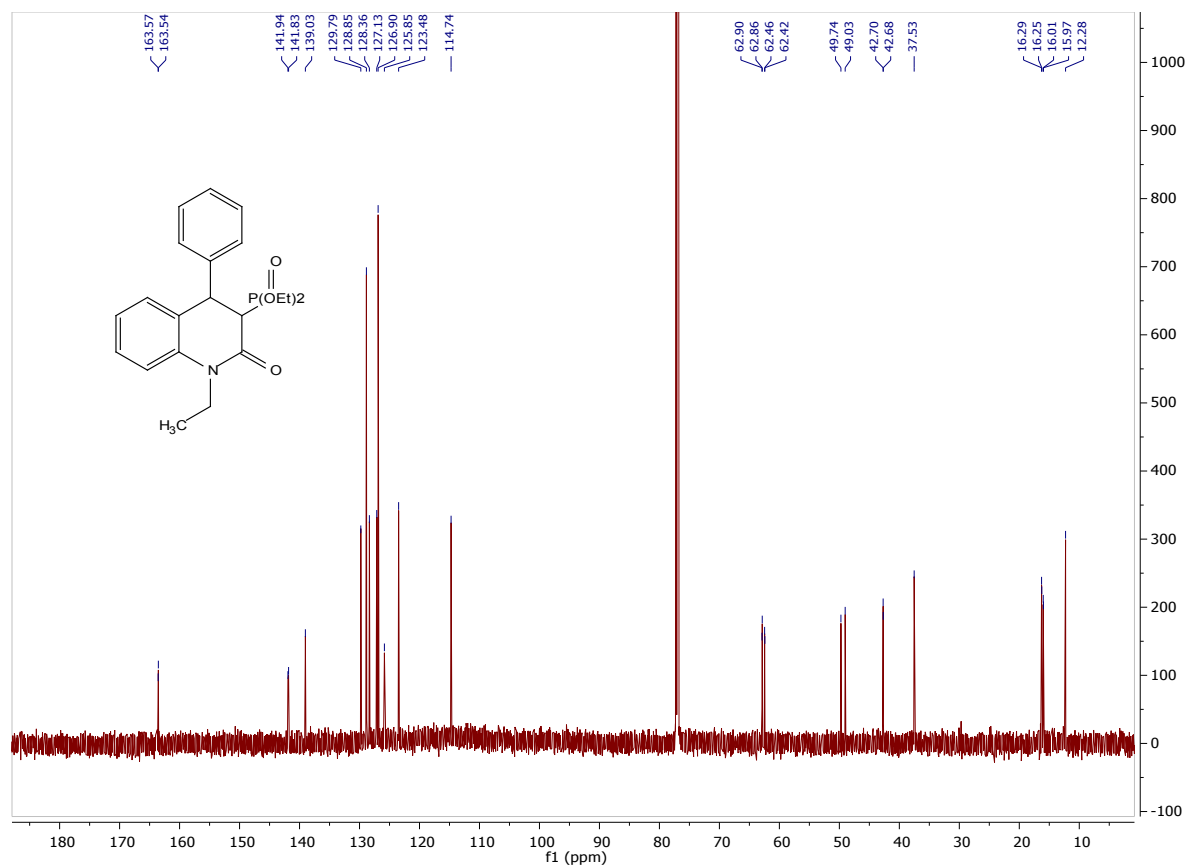
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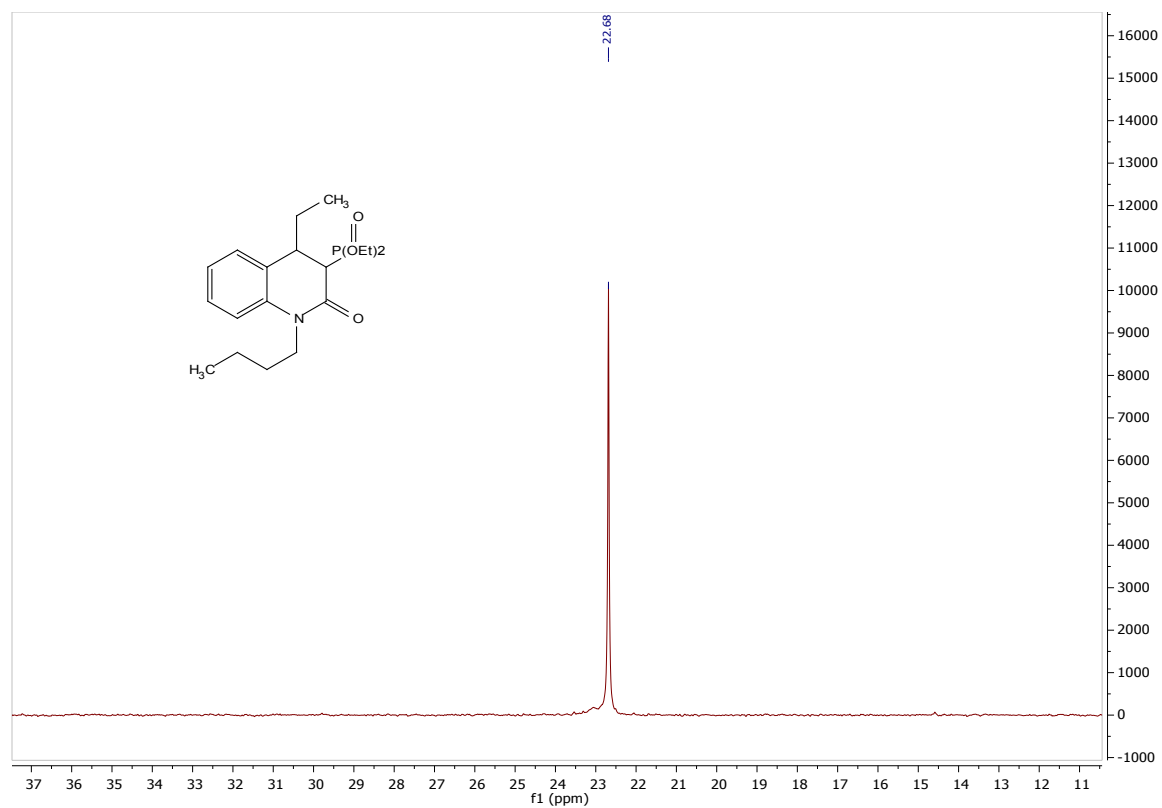


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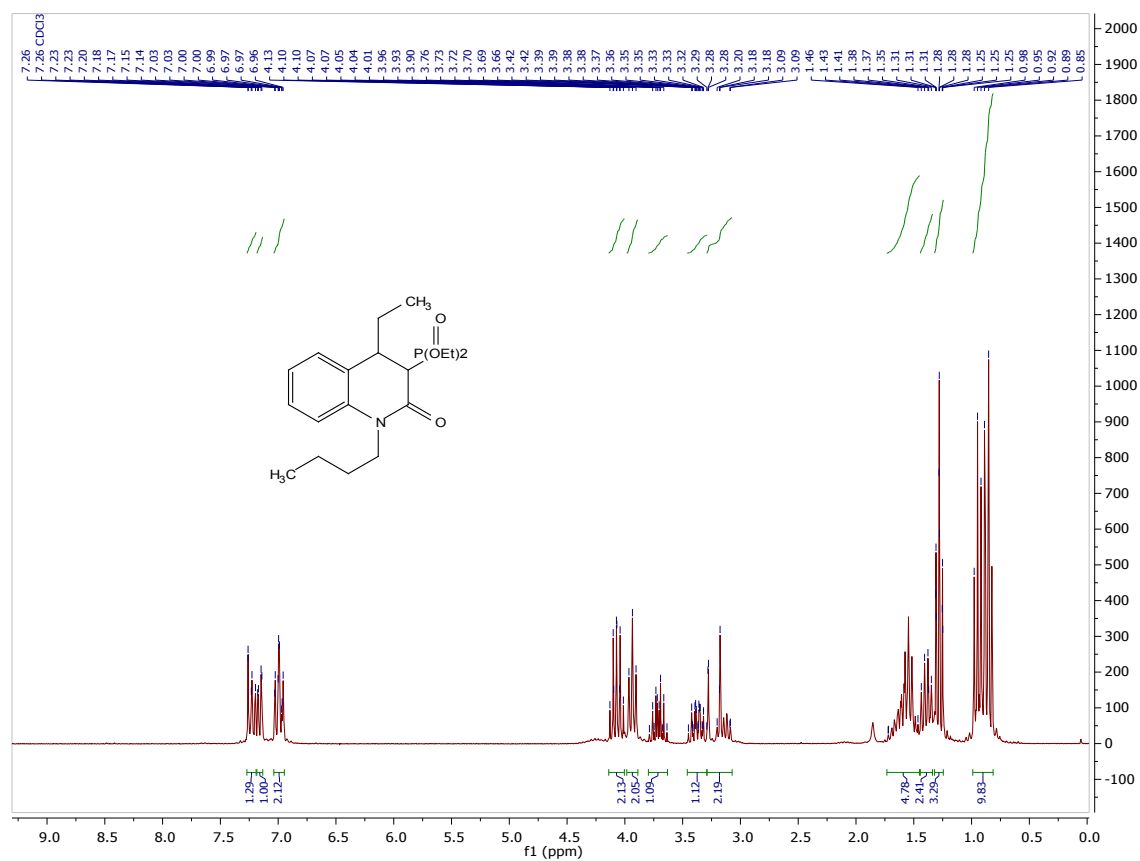


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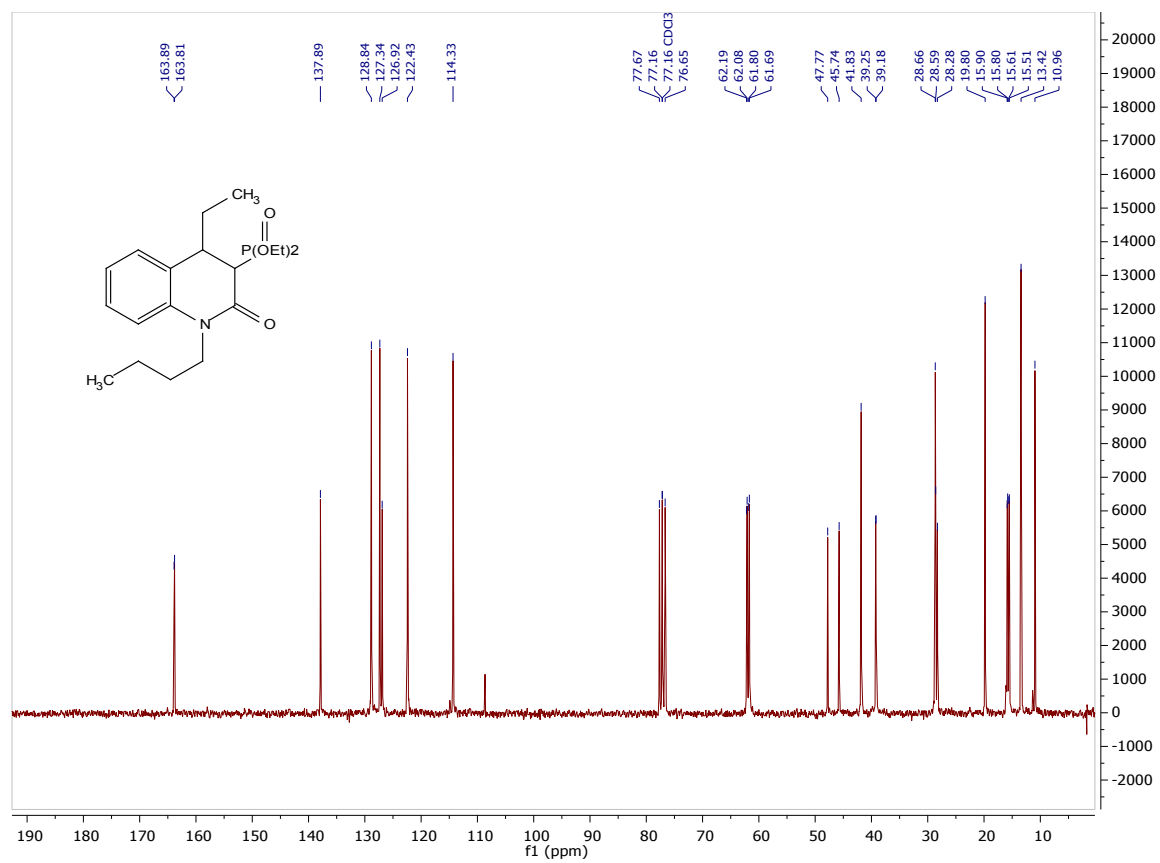
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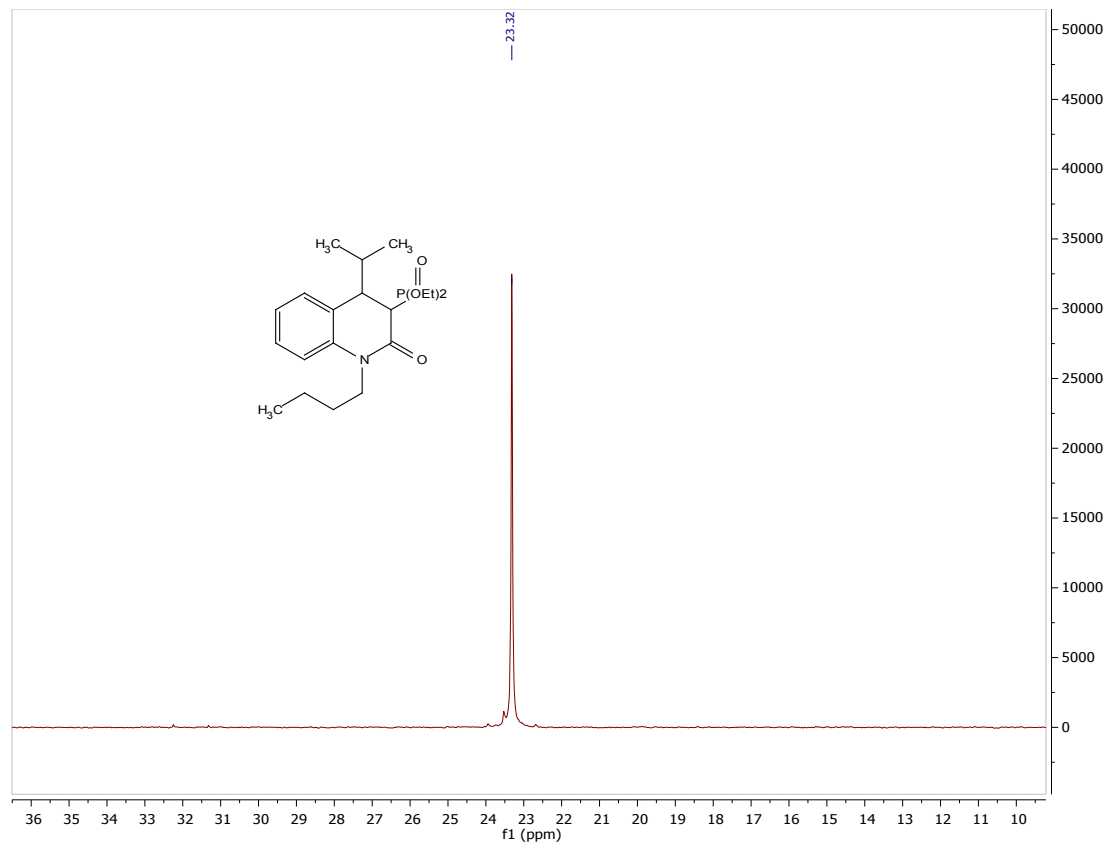


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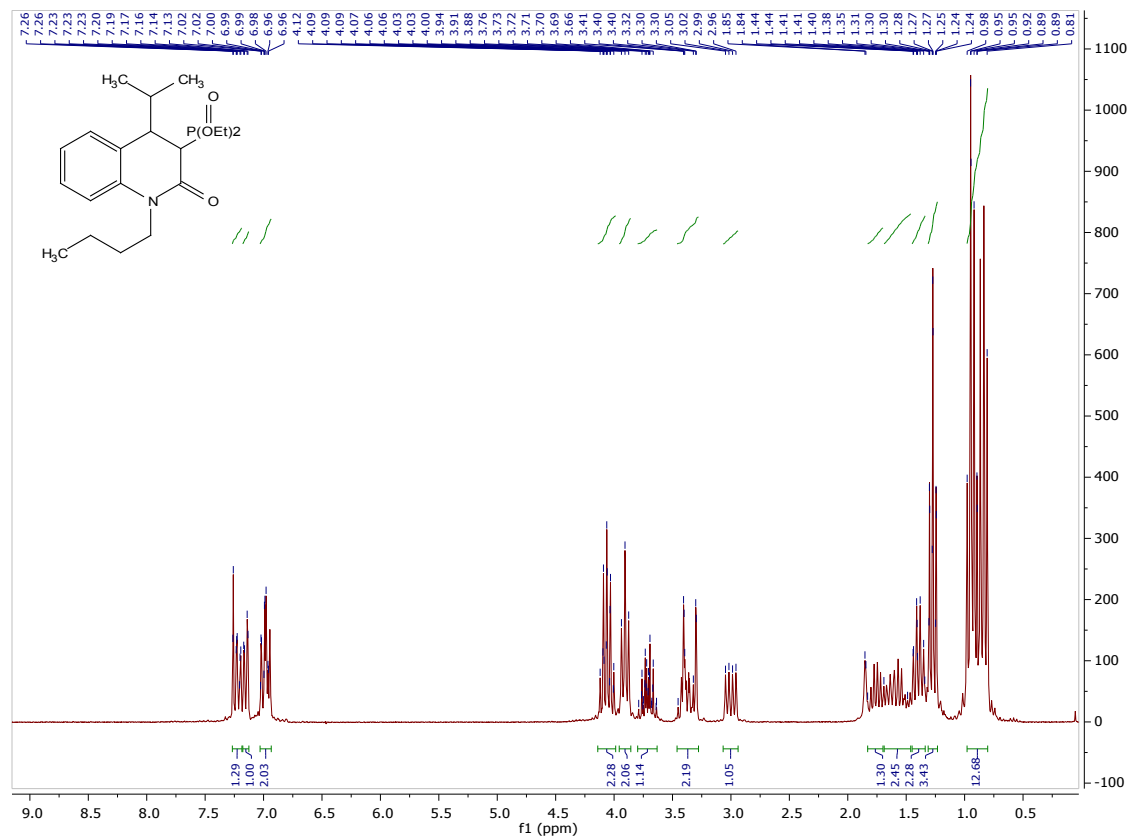


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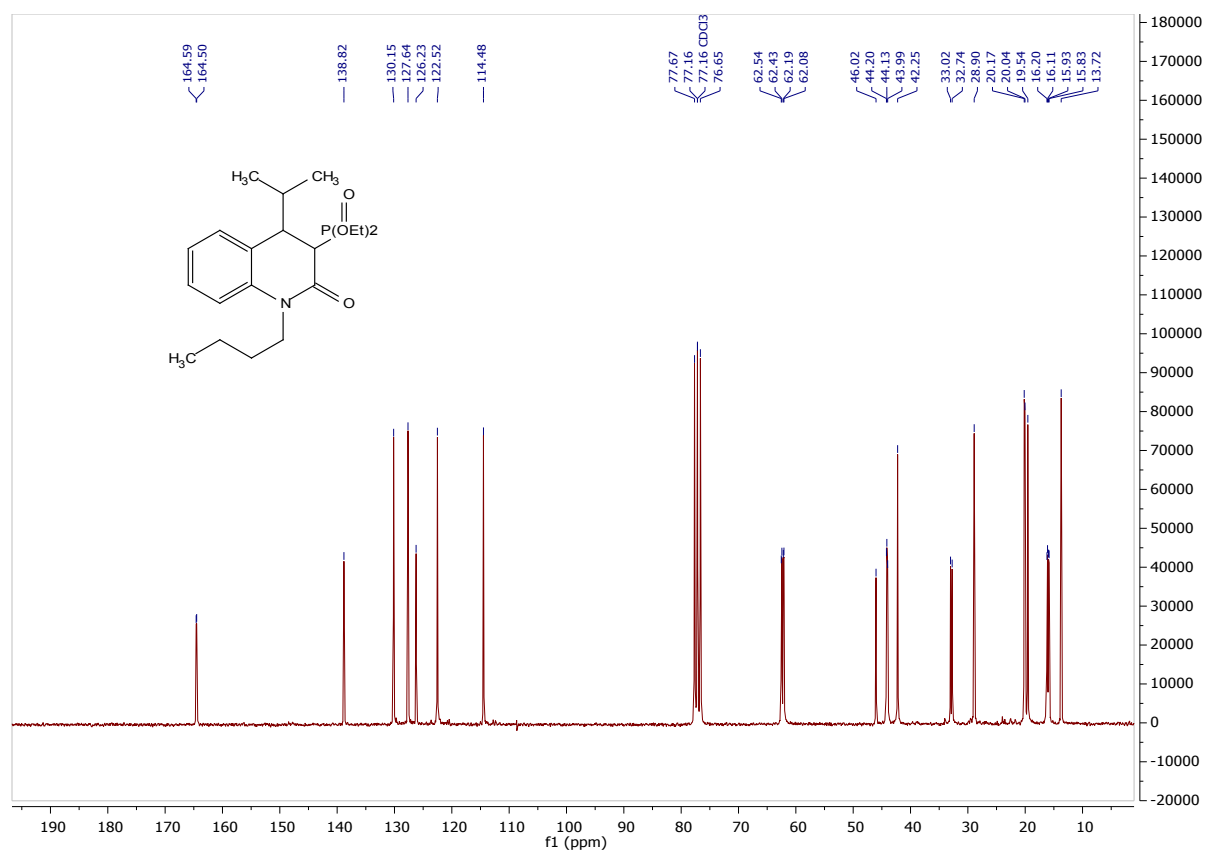
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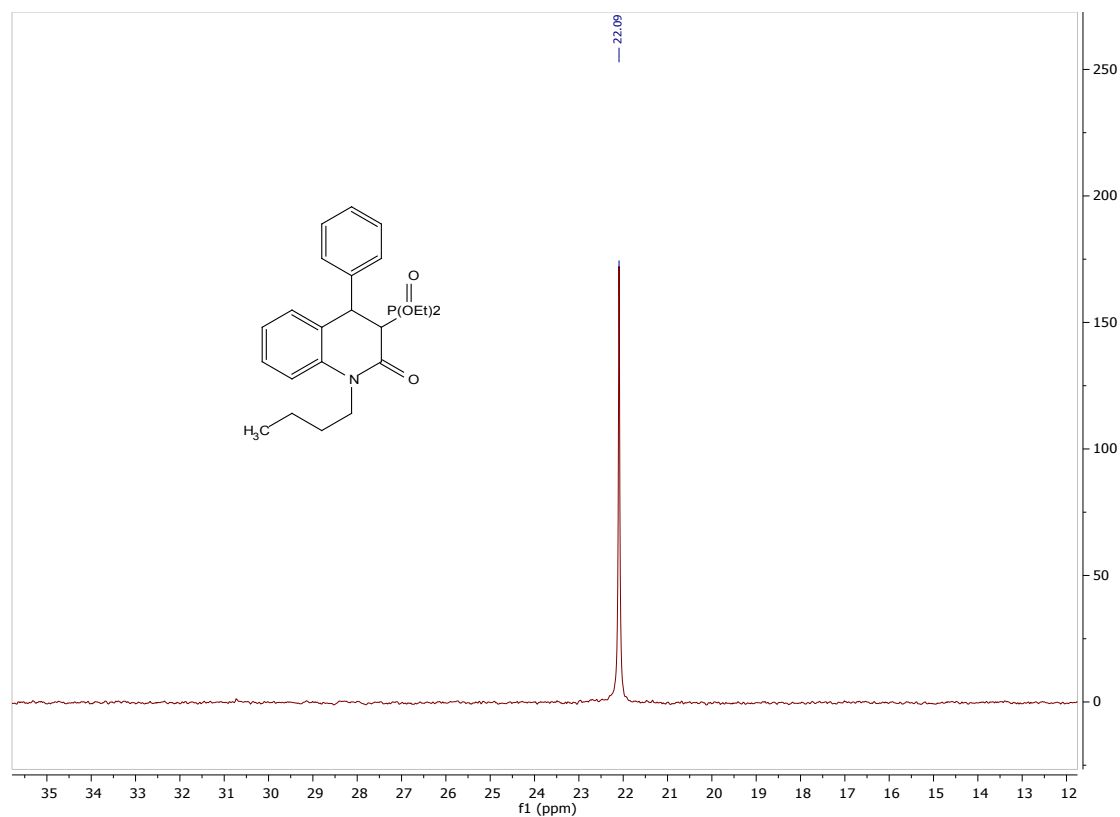


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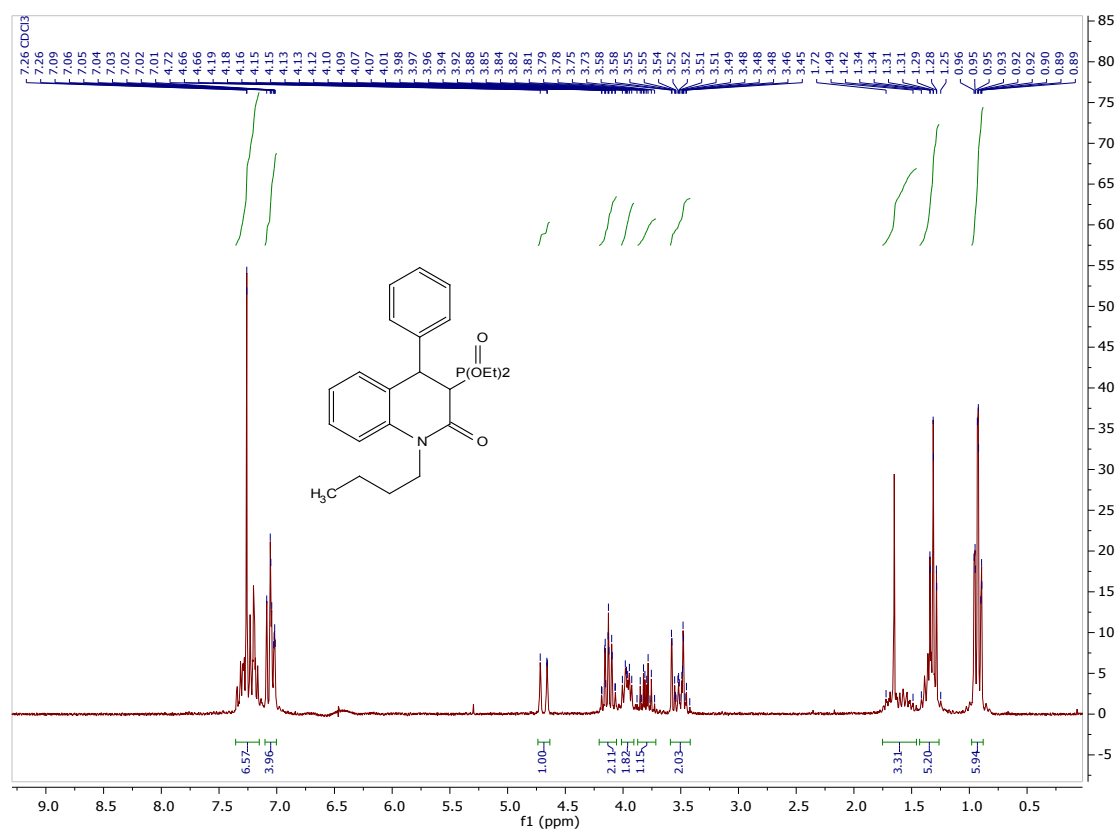


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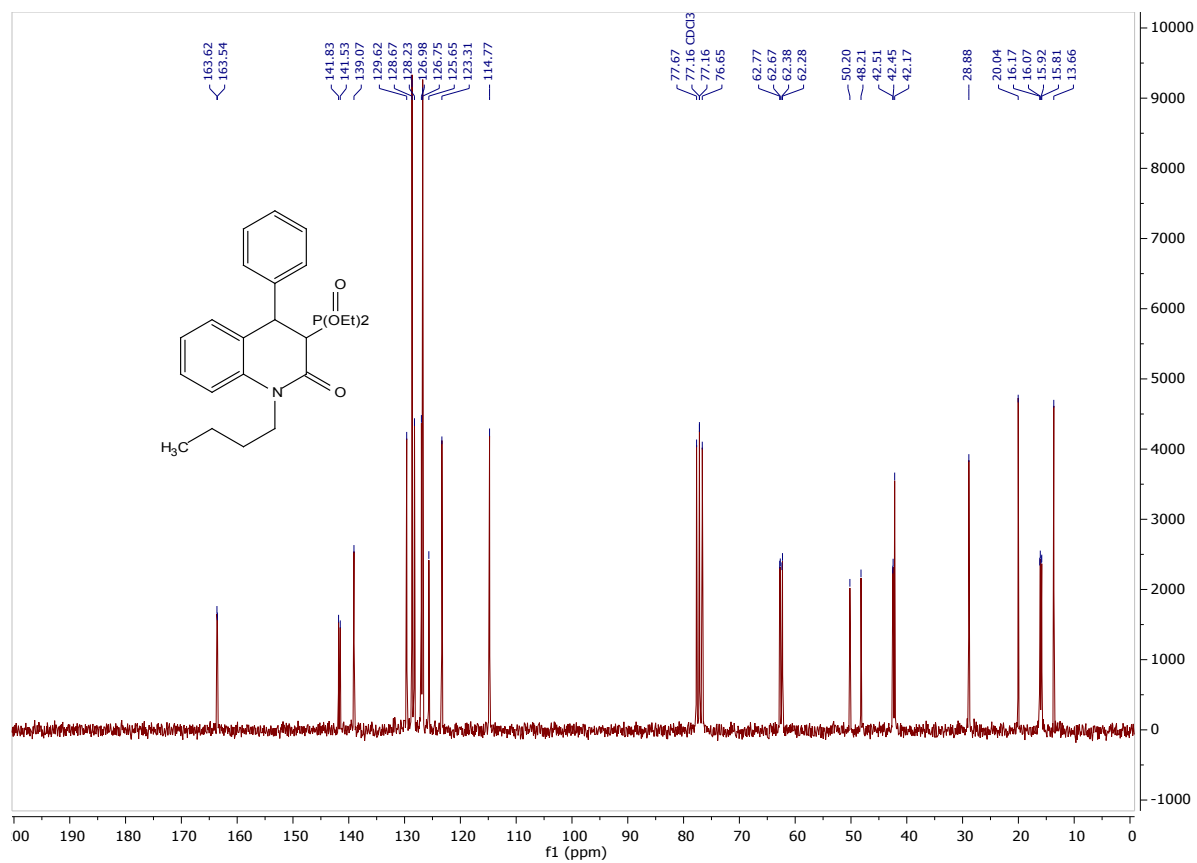
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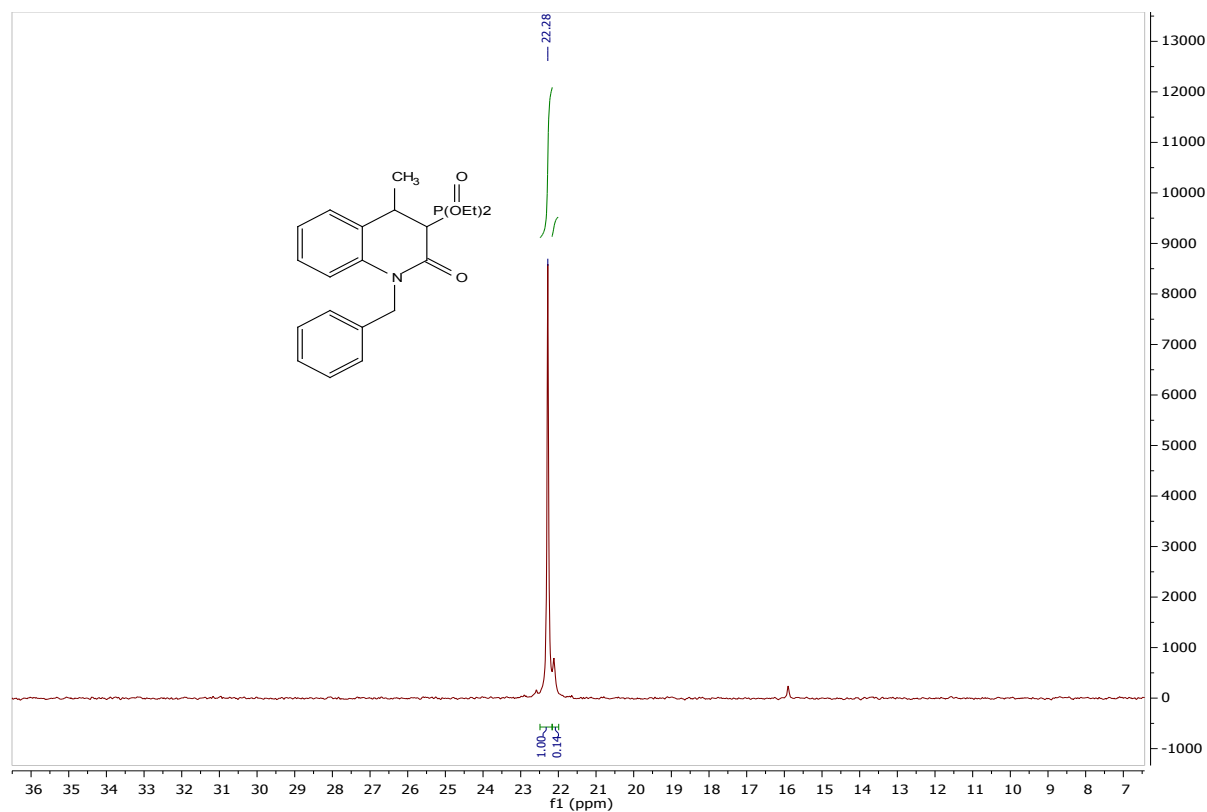


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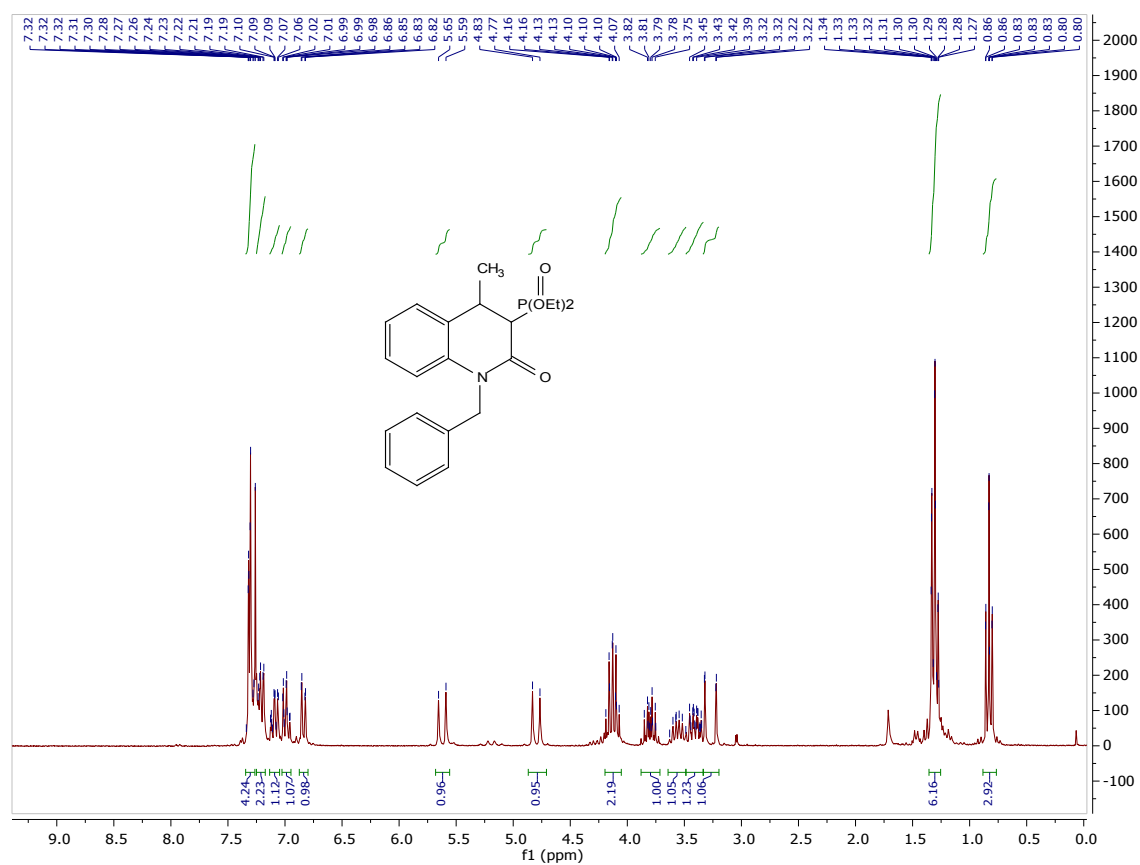


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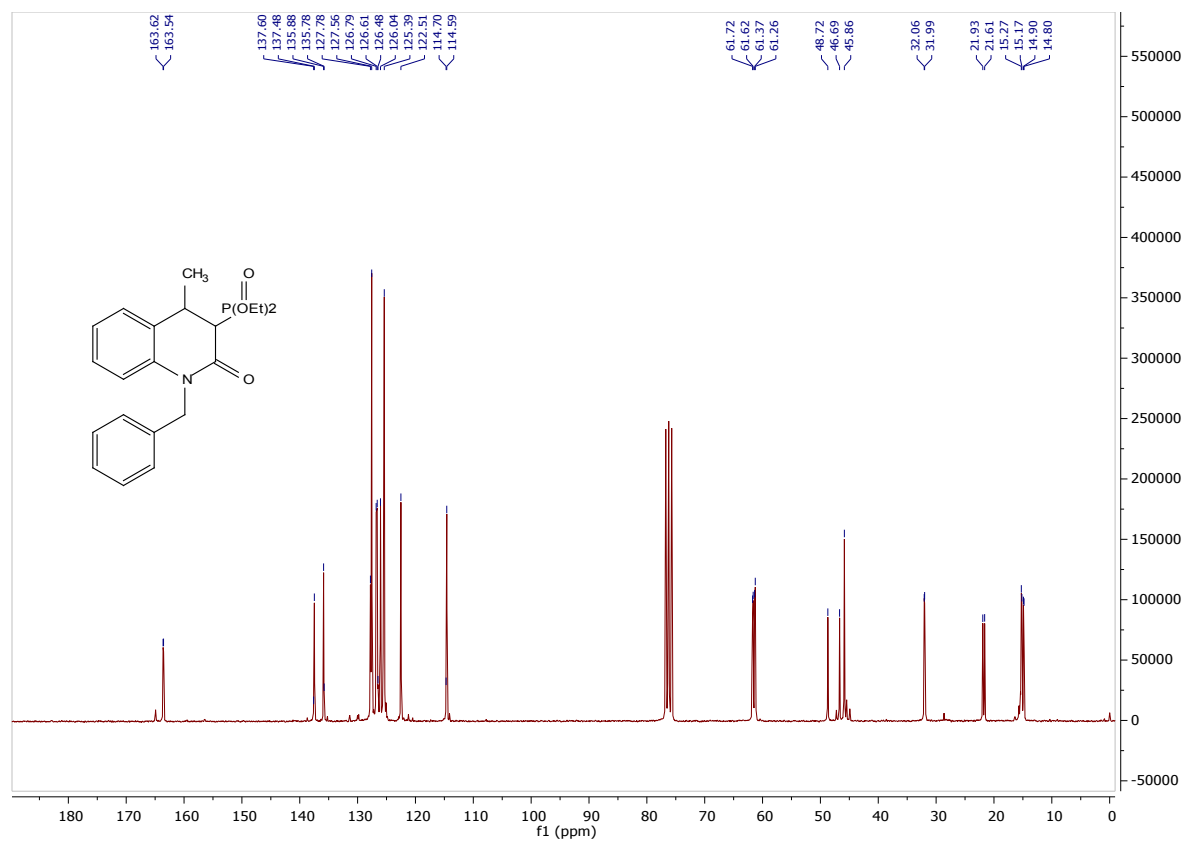
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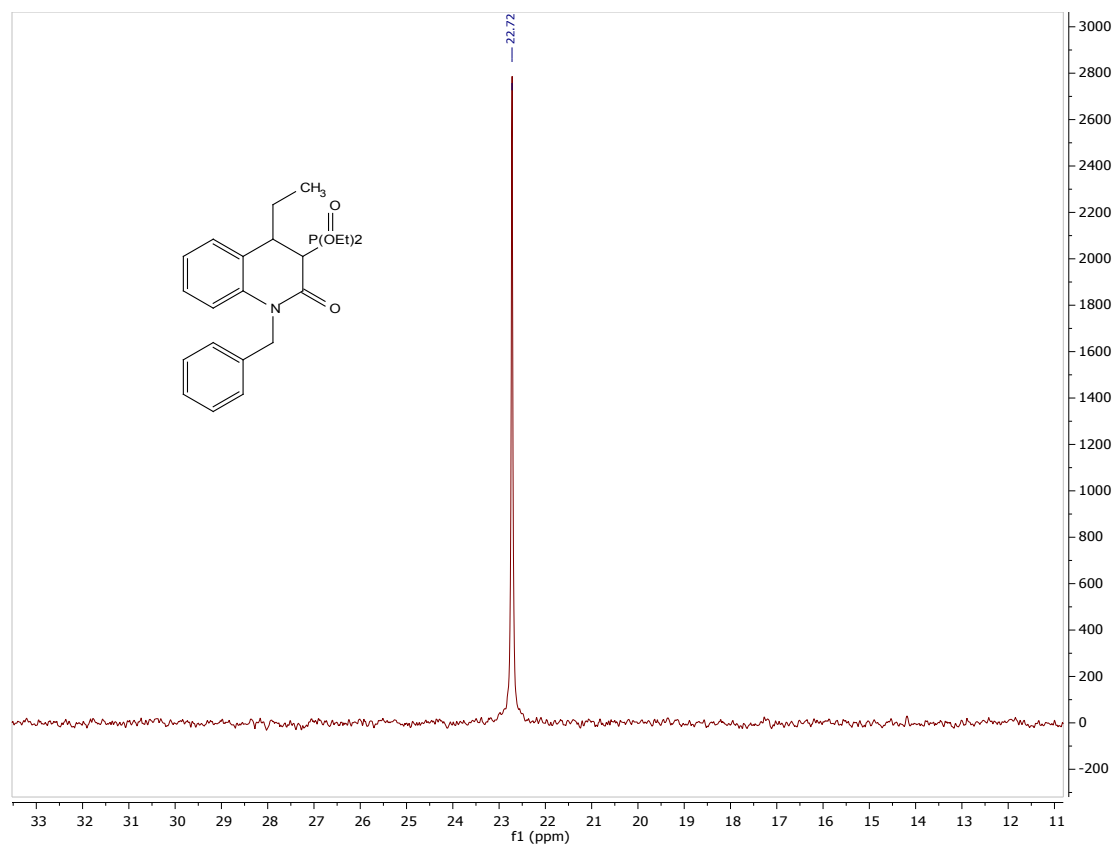


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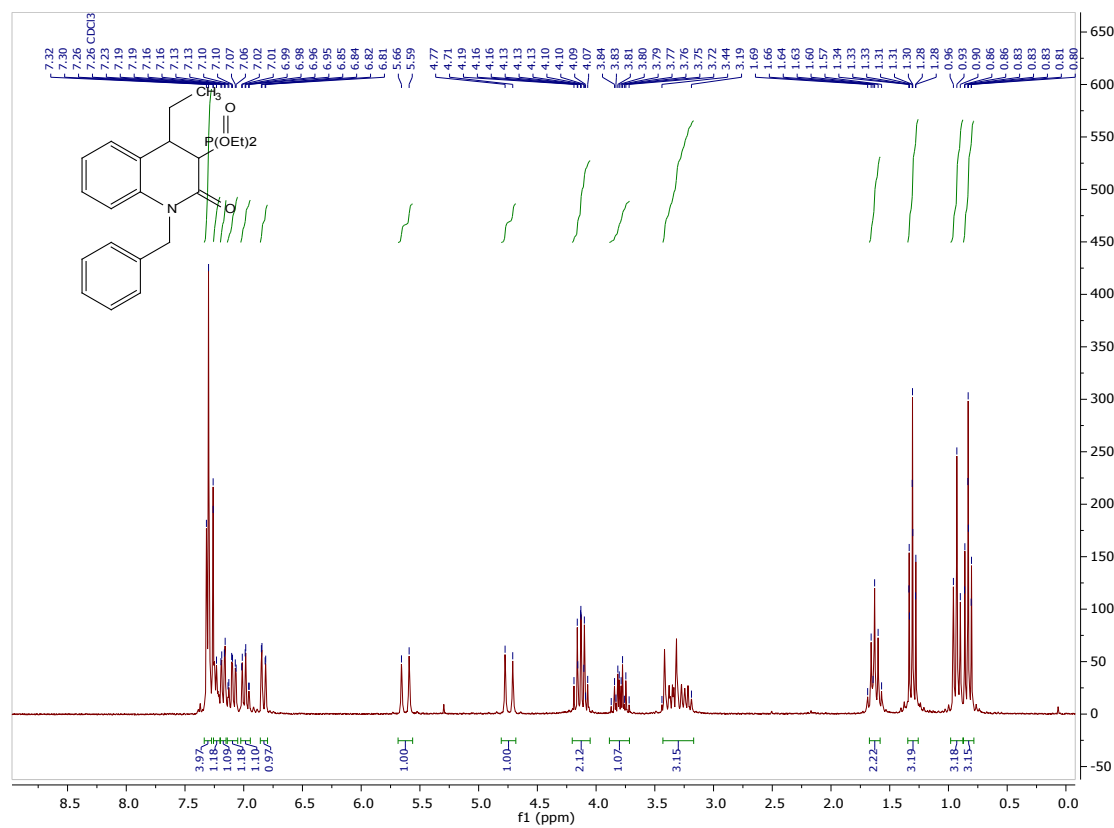


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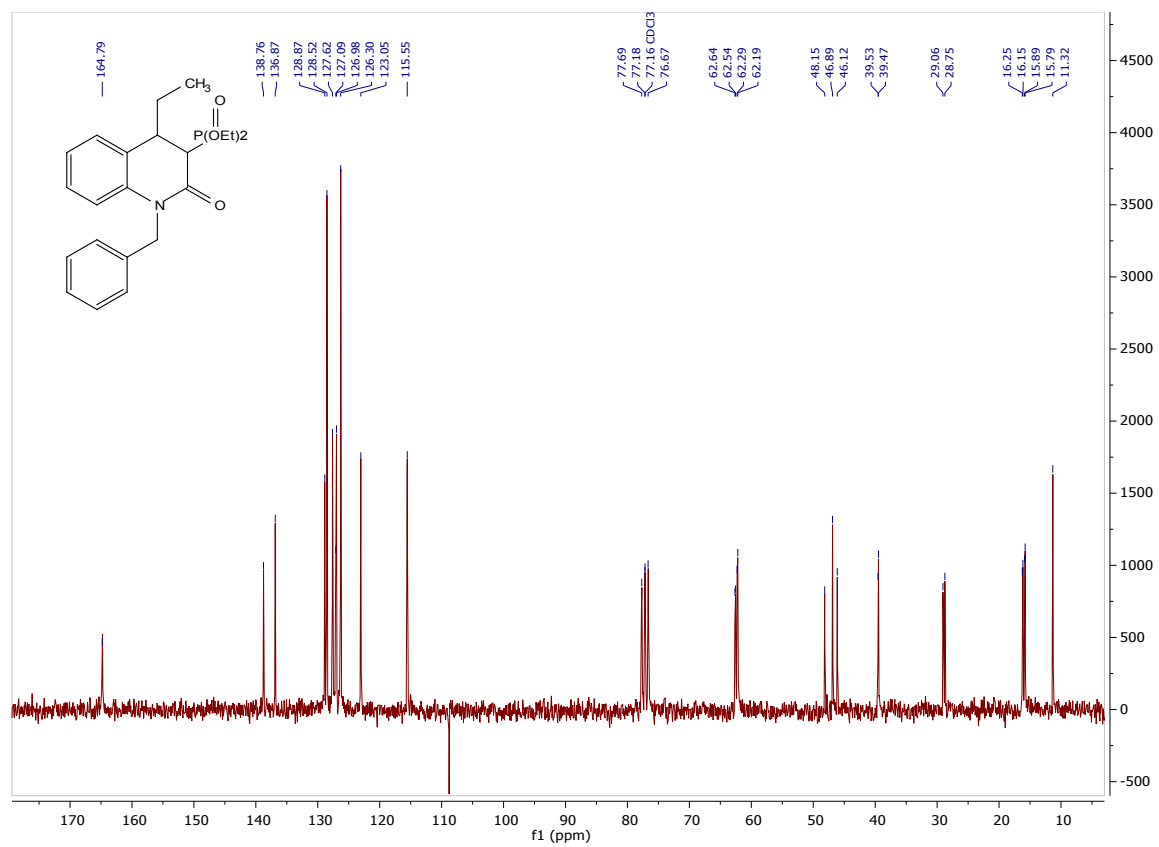
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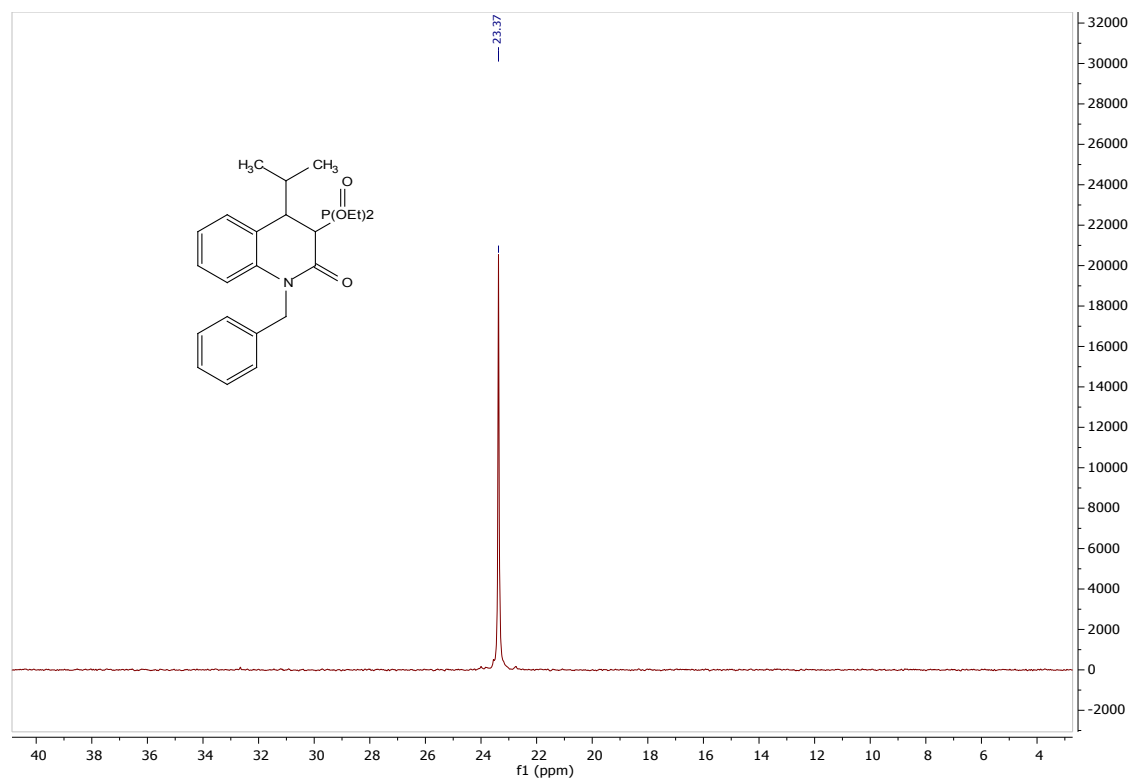


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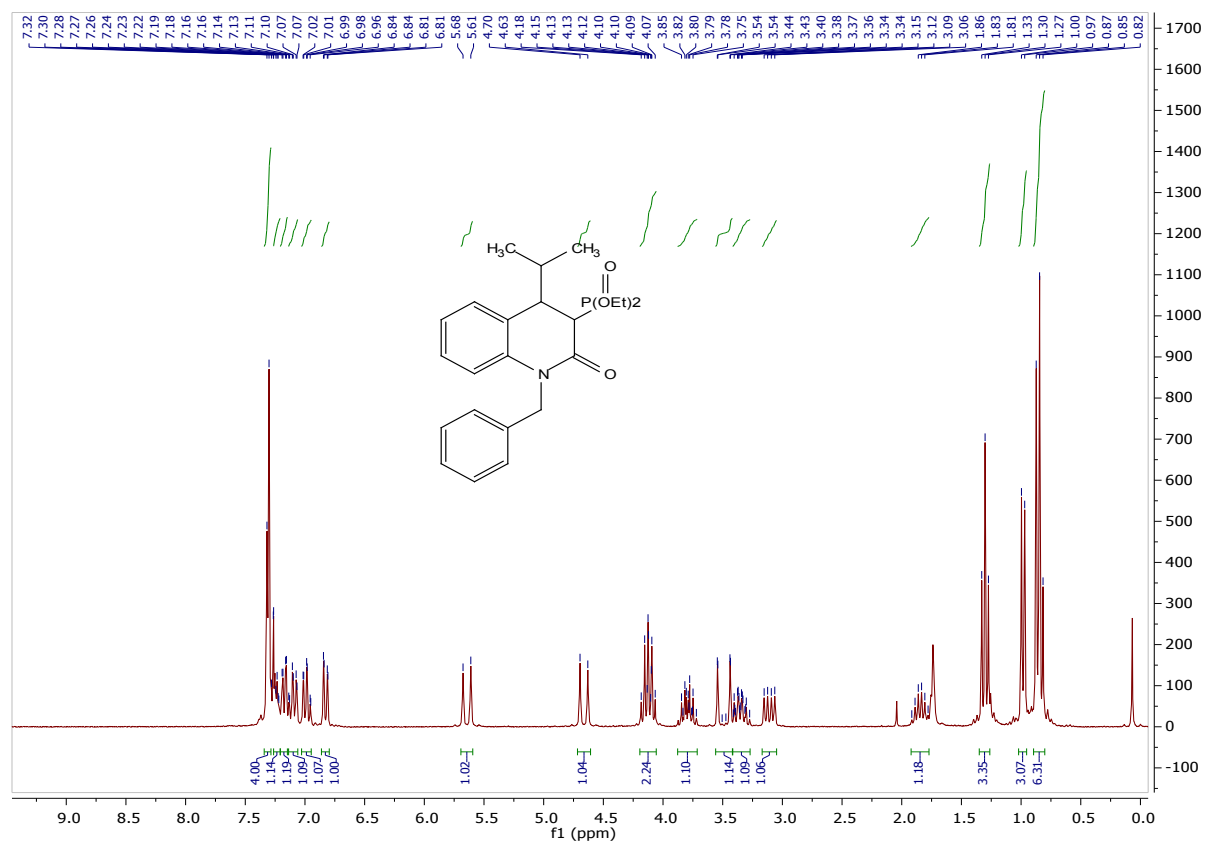


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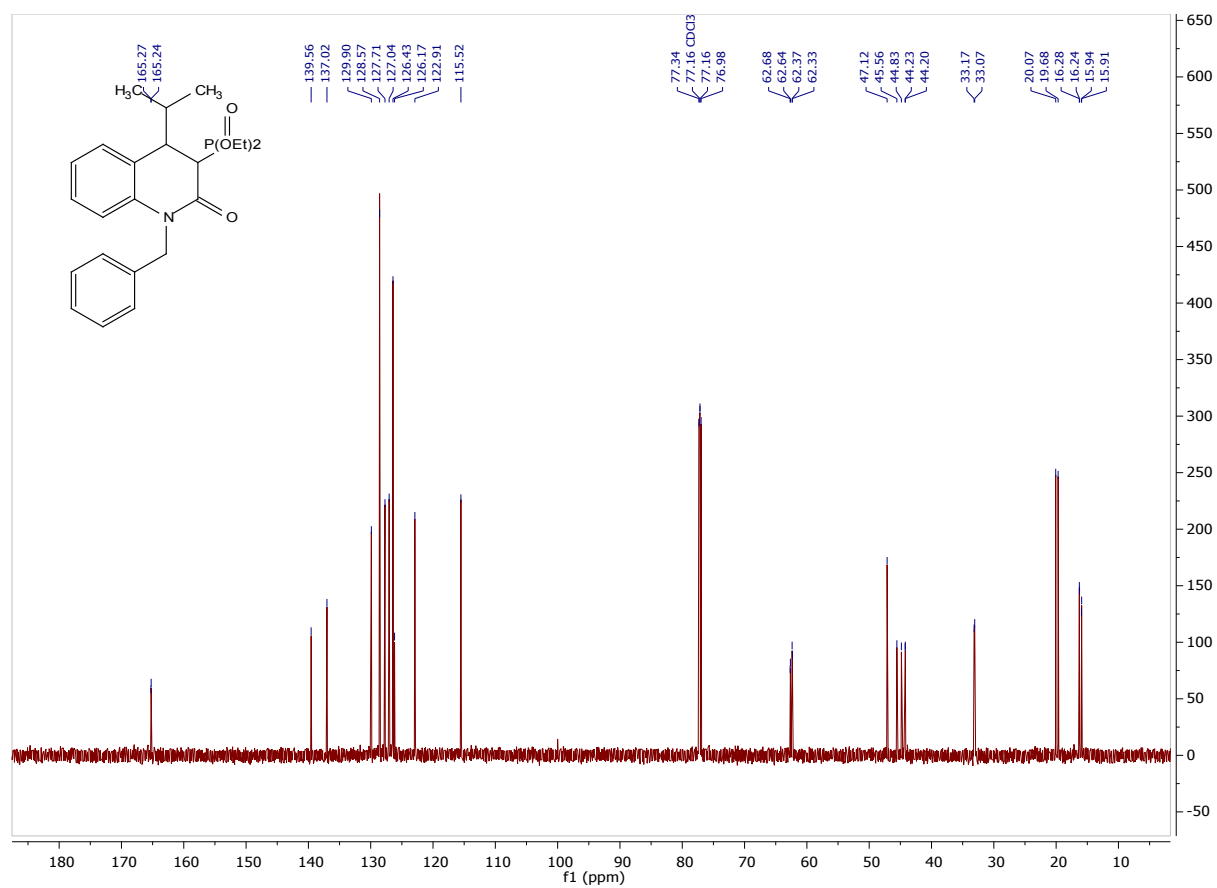
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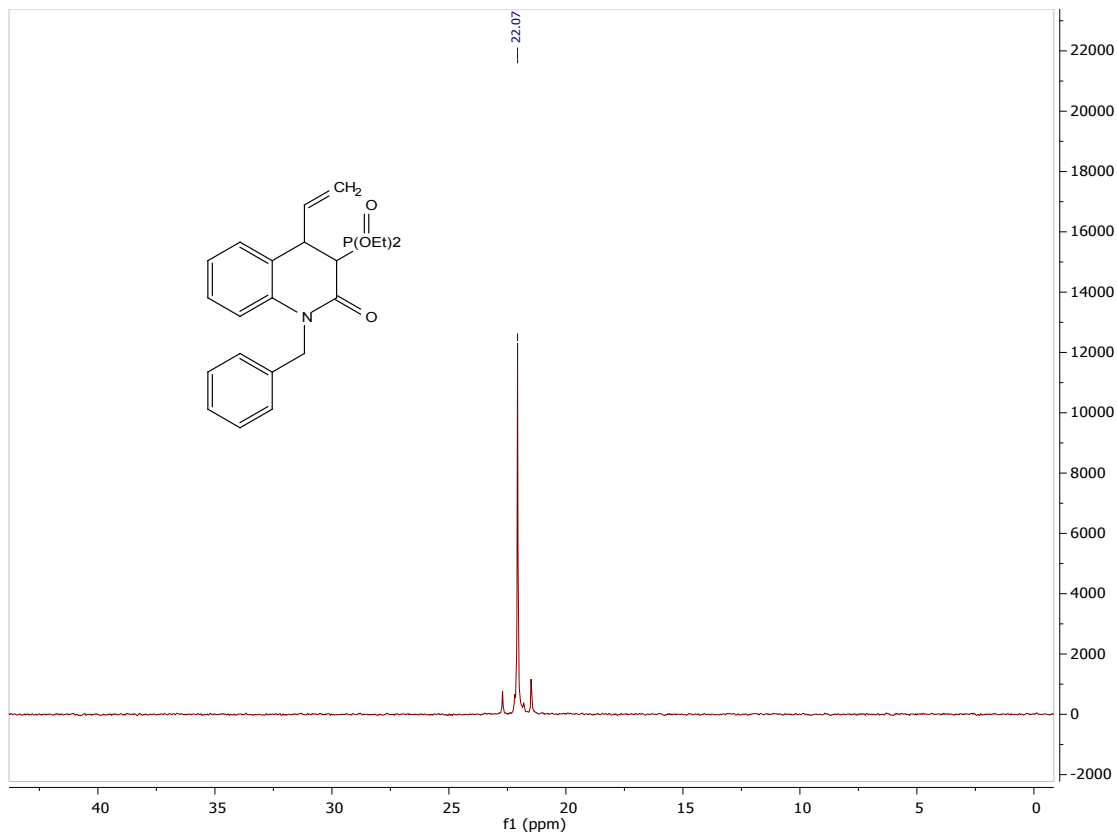


¹³C NMR

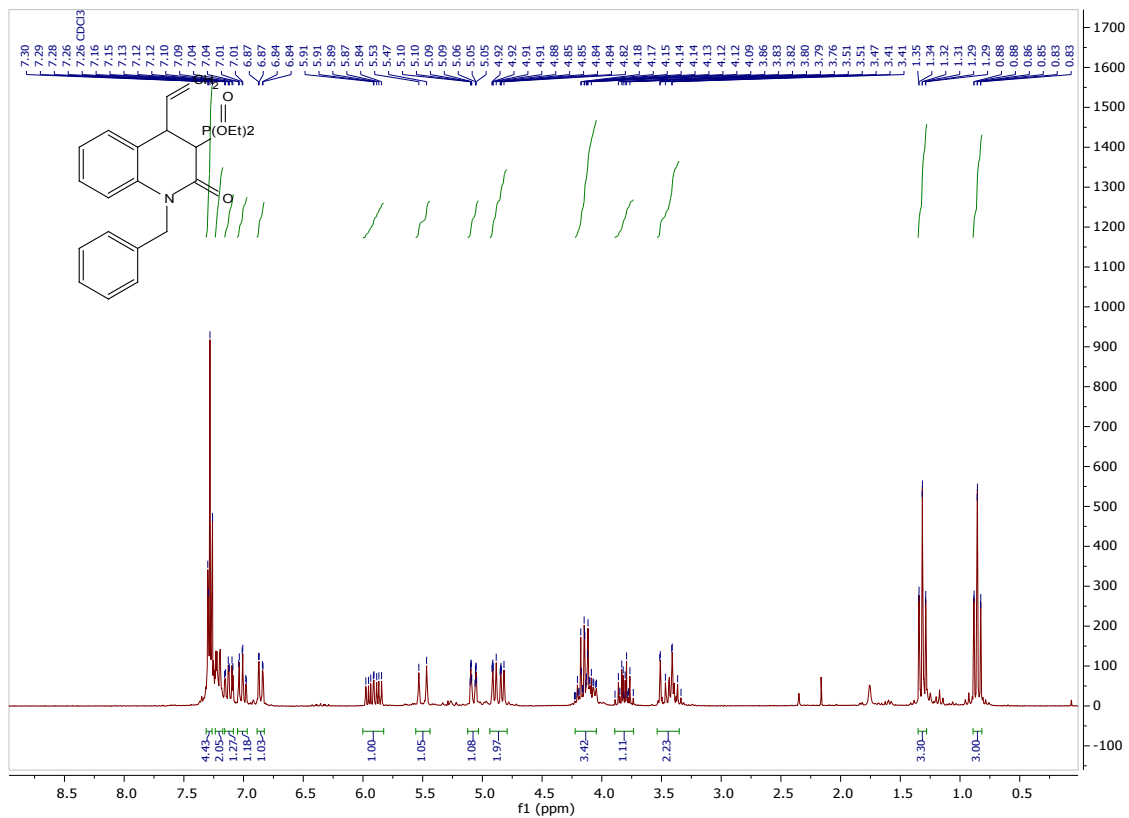


Compound 18n

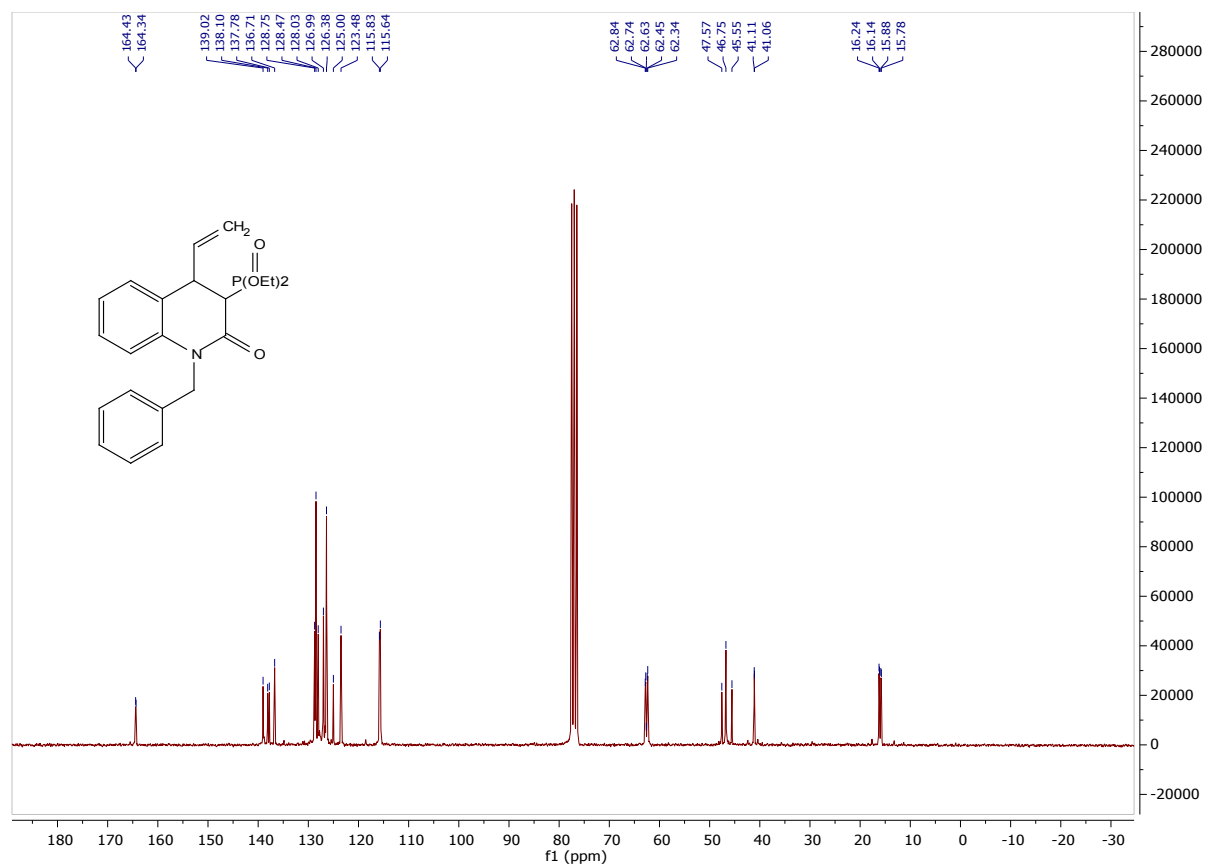
³¹P NMR



¹H NMR

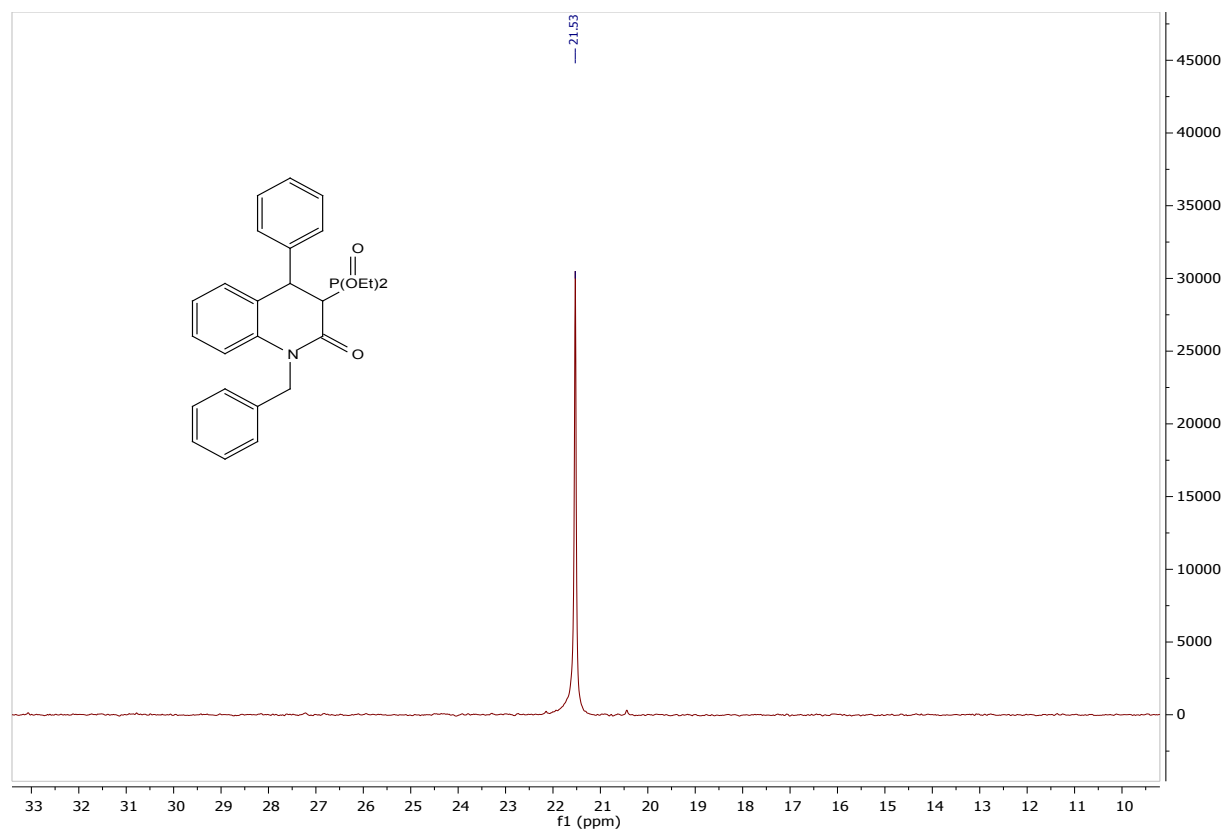


¹³C NMR

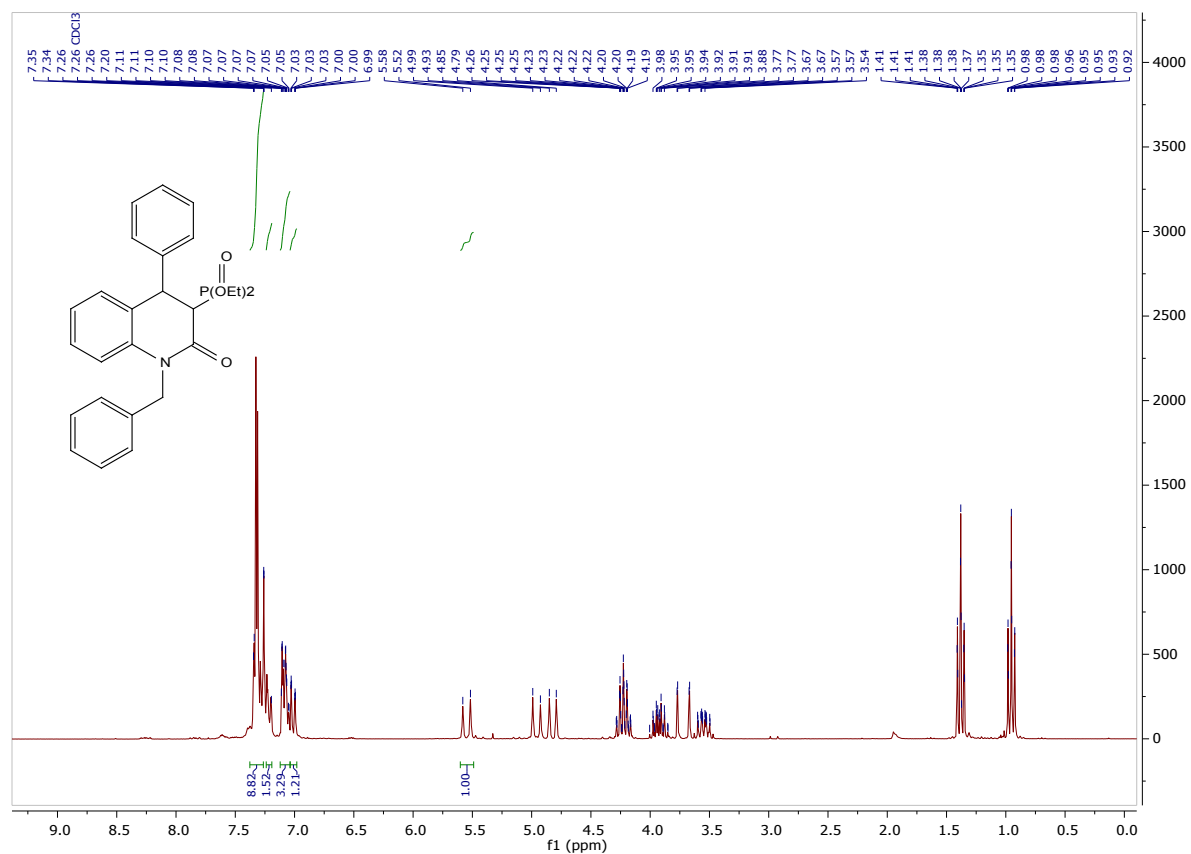


Compound 18o

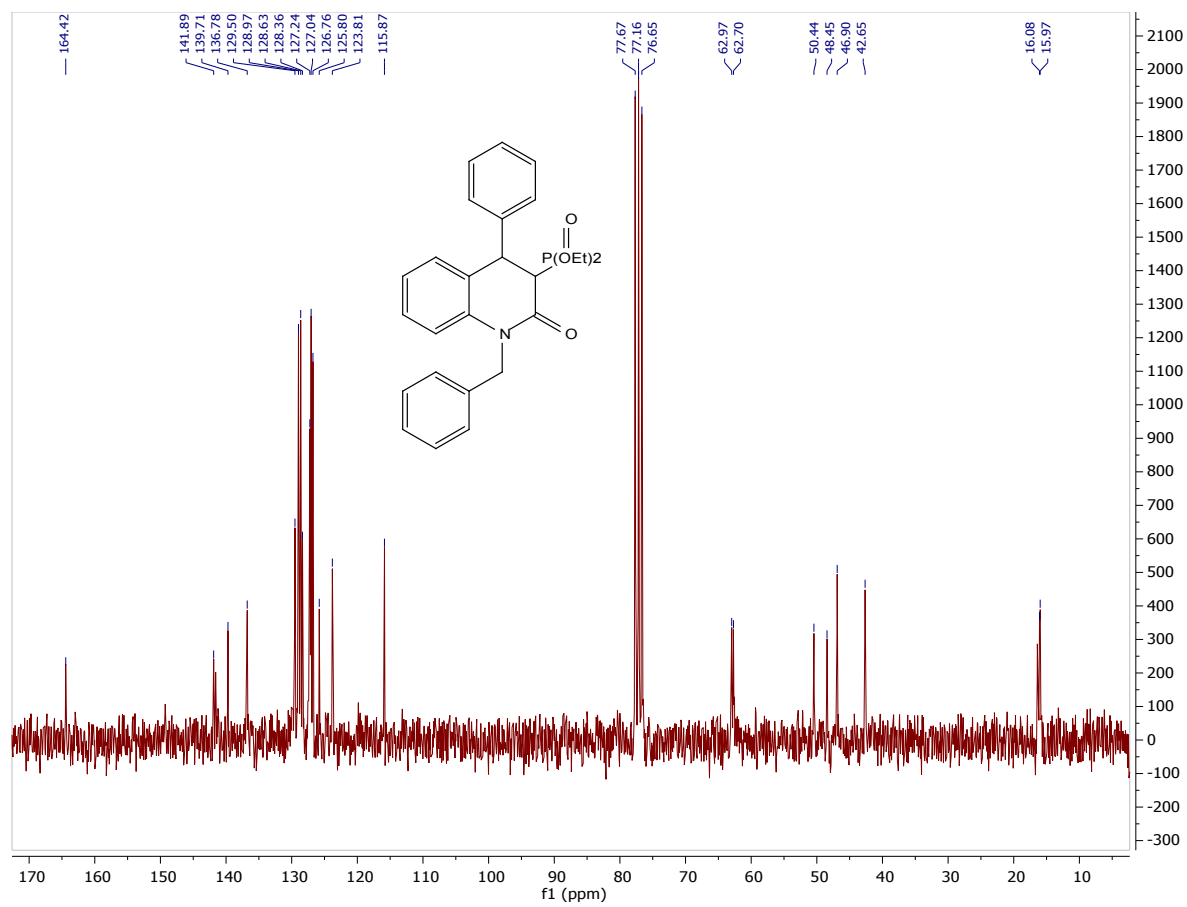
³¹P NMR



¹H NMR

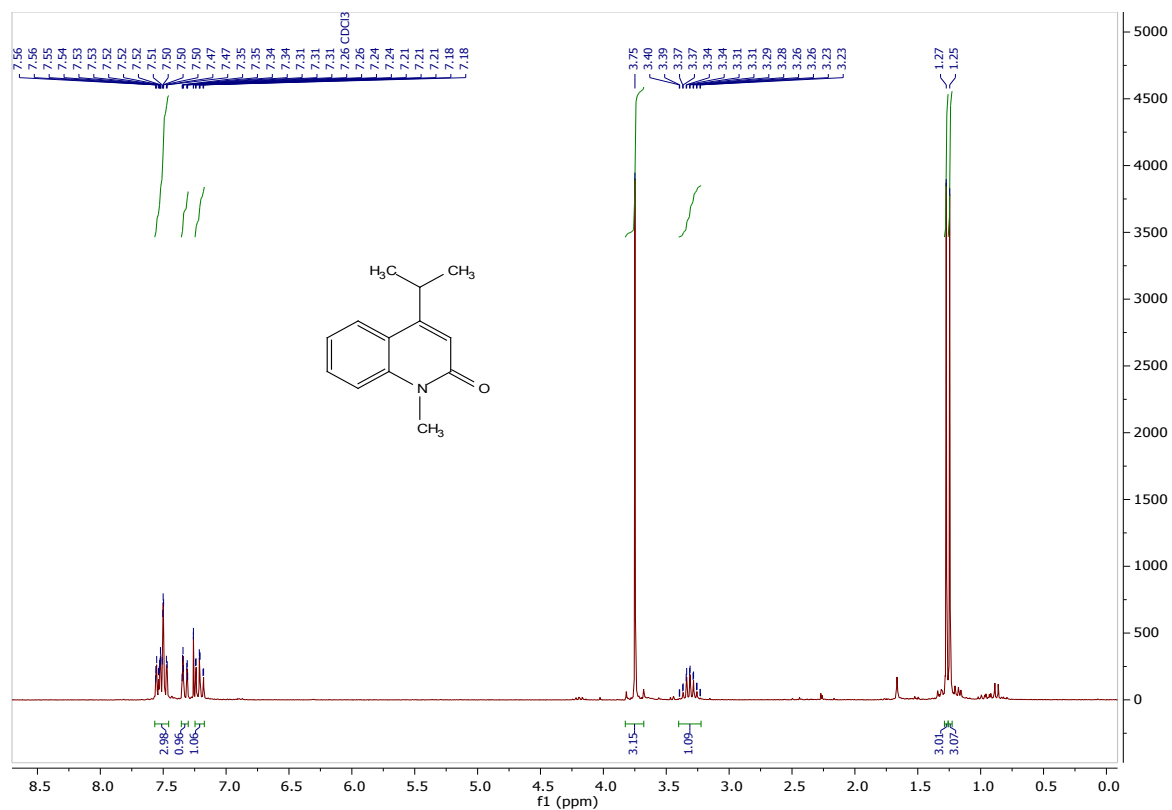


¹³C NMR

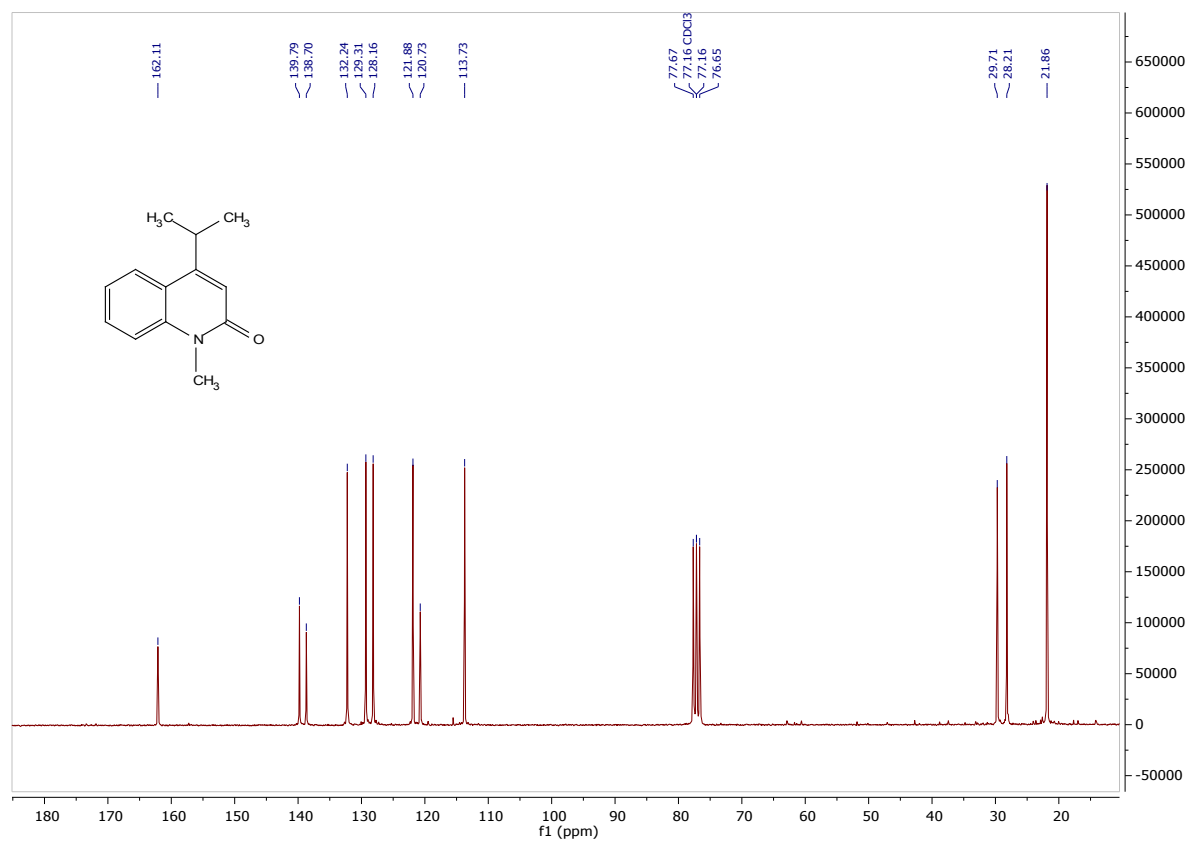


Compound 19b

¹H NMR

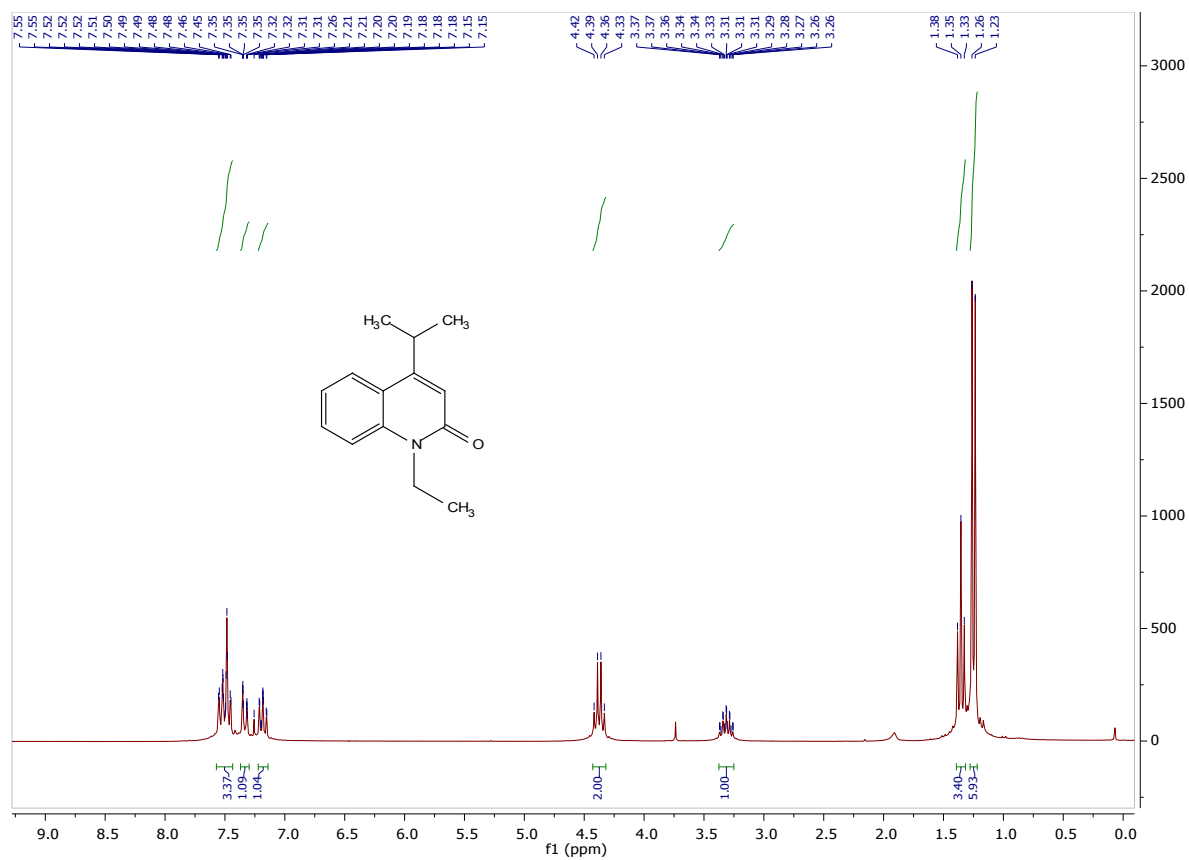


¹³C NMR

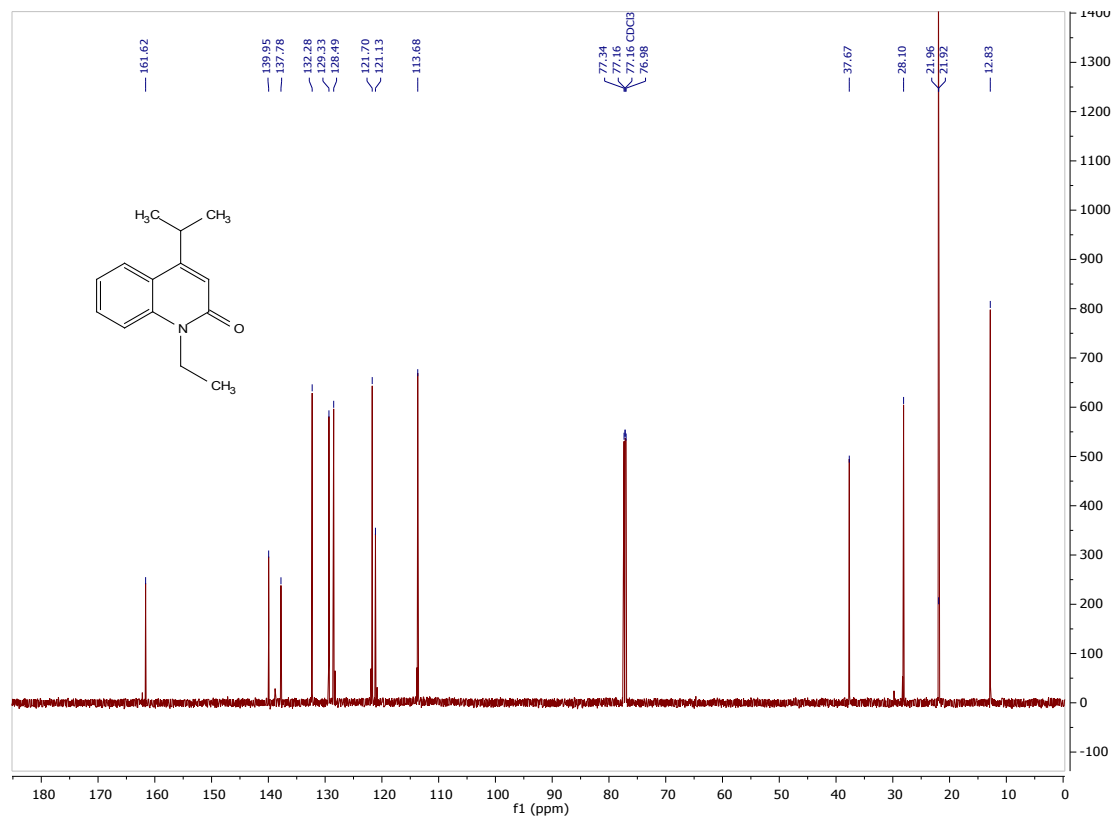


Compound 19f

¹H NMR

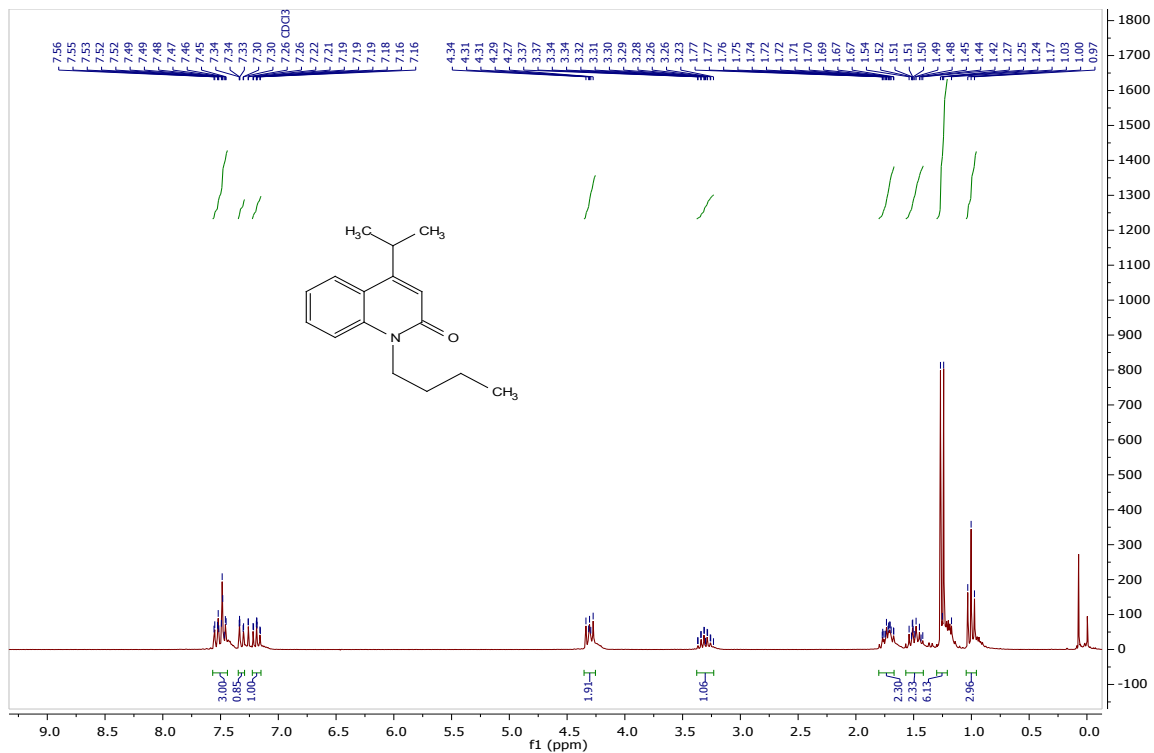


¹³C NMR

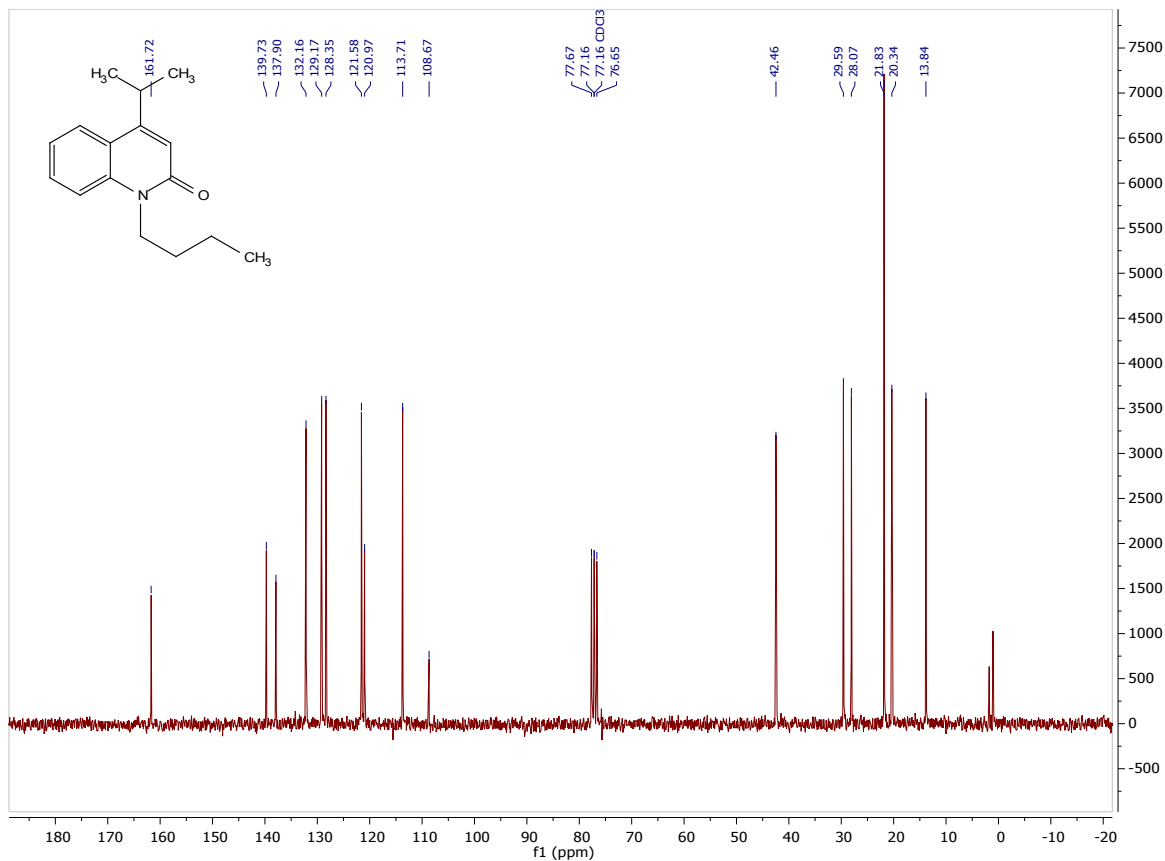


Compound 19i

¹H NMR

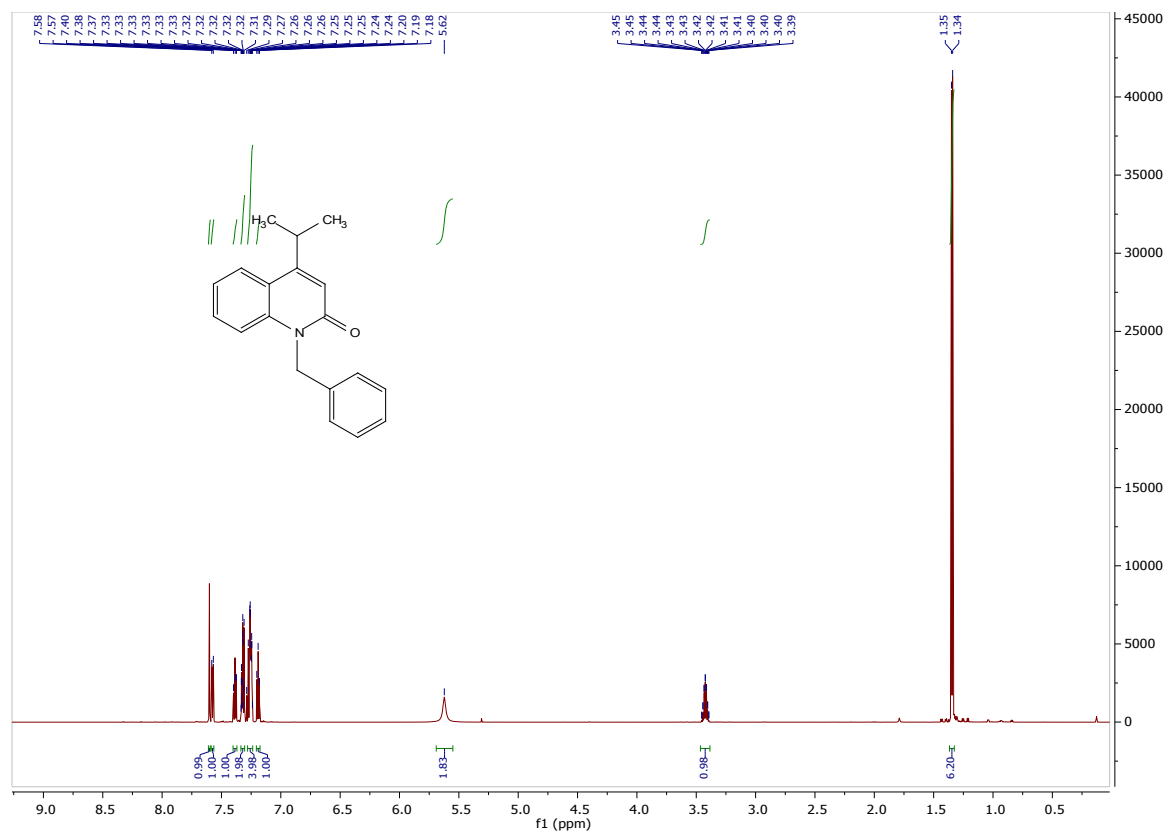


¹³C NMR

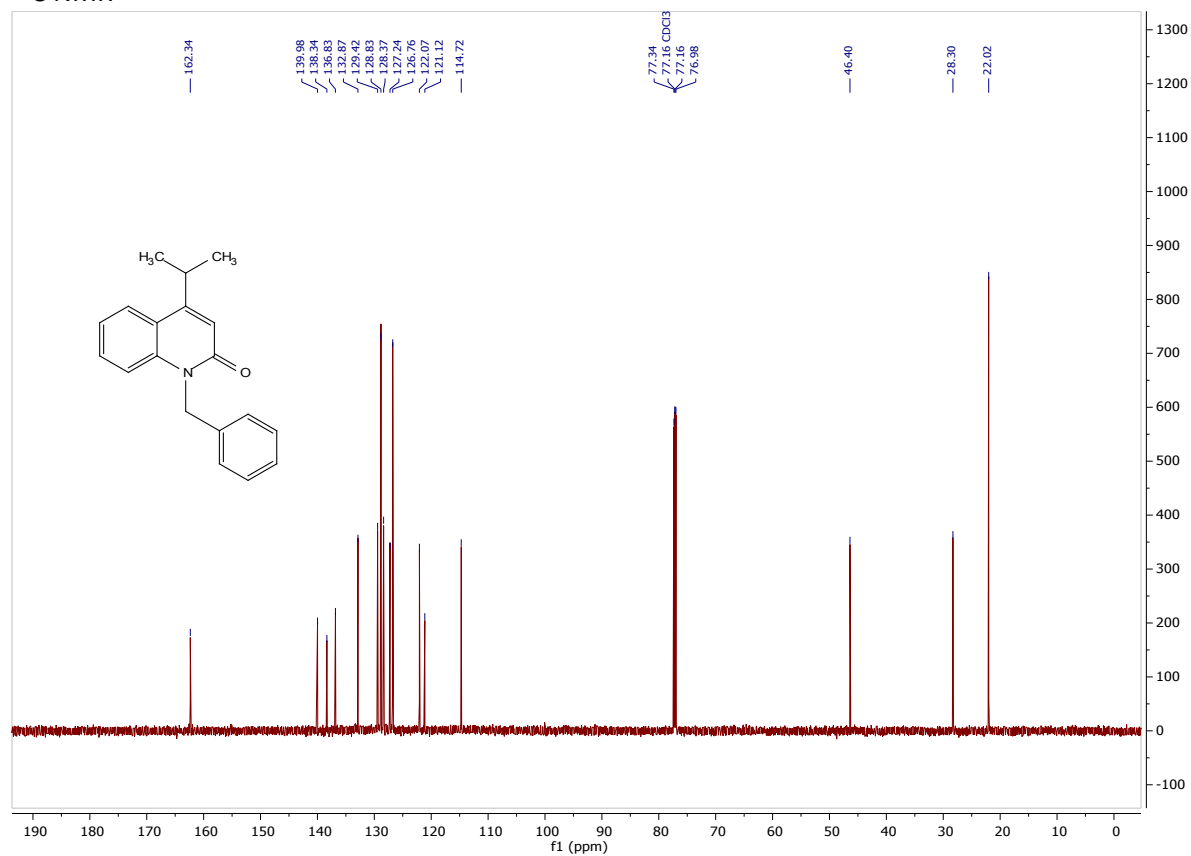


Compound 19m

¹H NMR

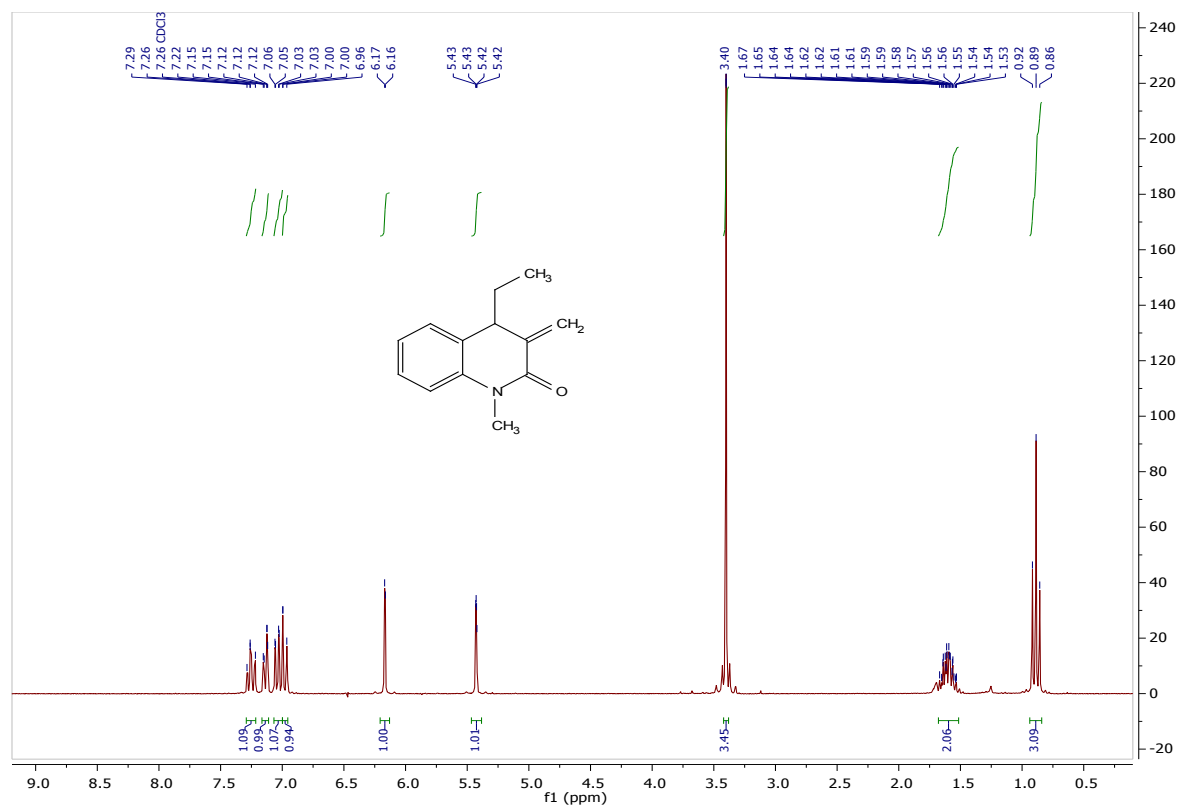


¹³C NMR

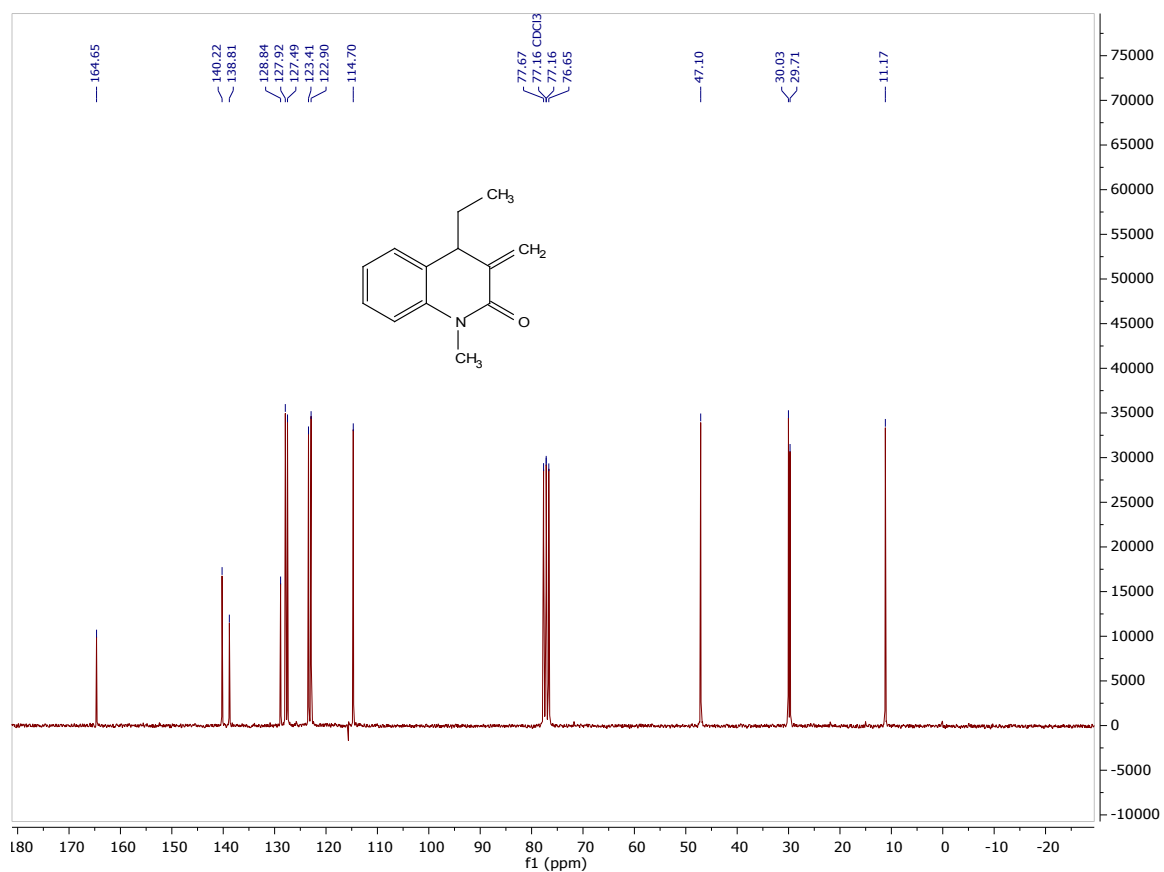


Compound 20a

¹H NMR

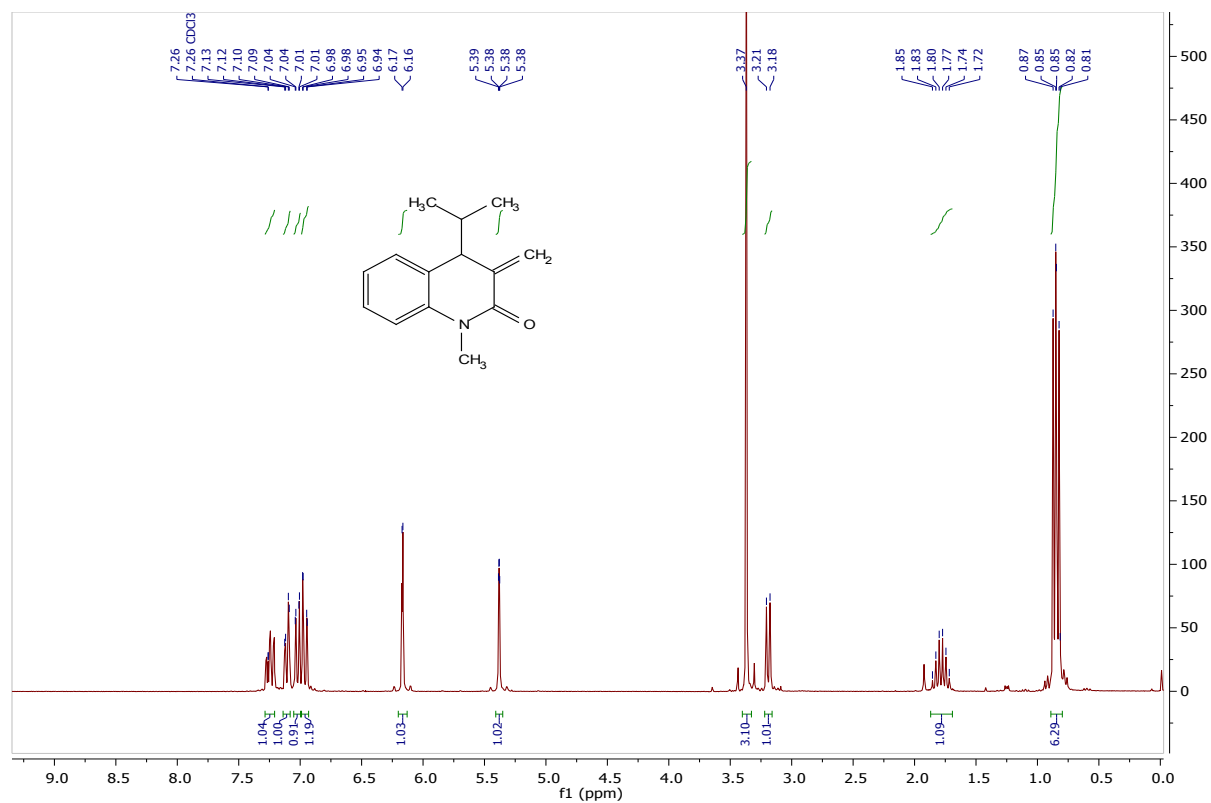


¹³C NMR

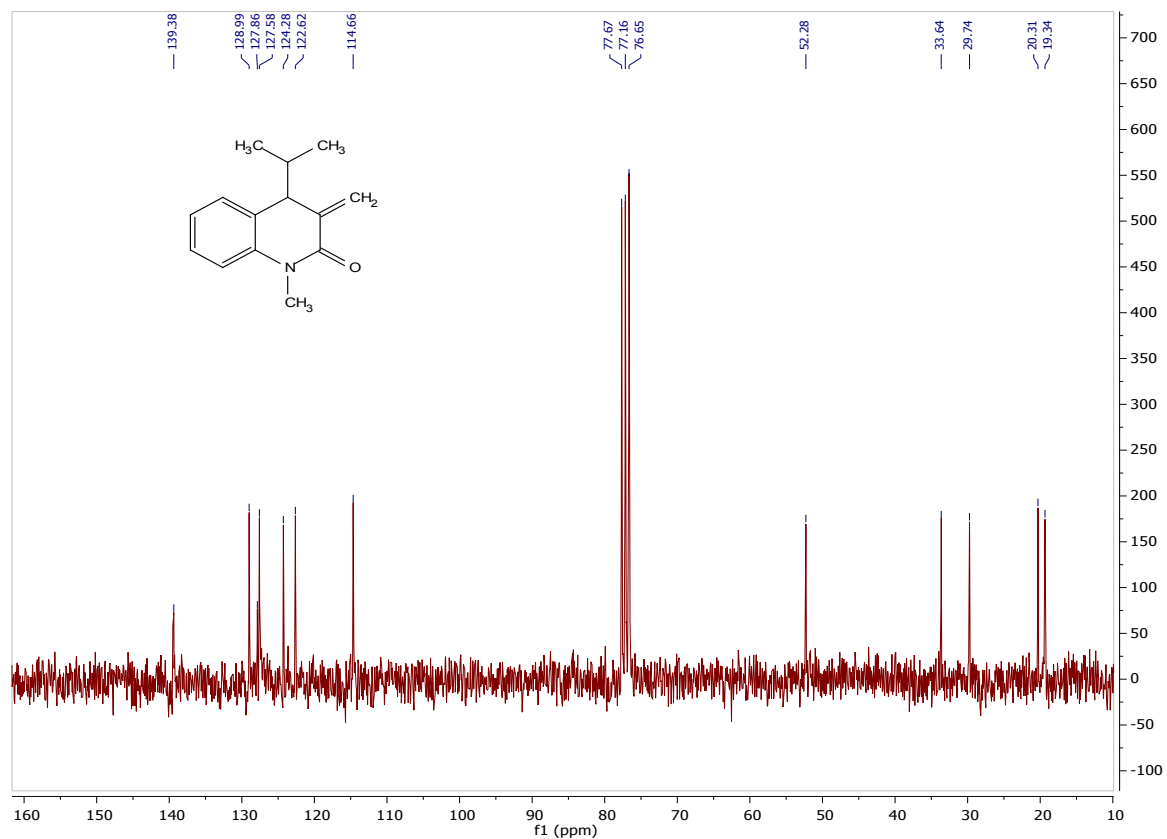


Compound 20b

¹H NMR

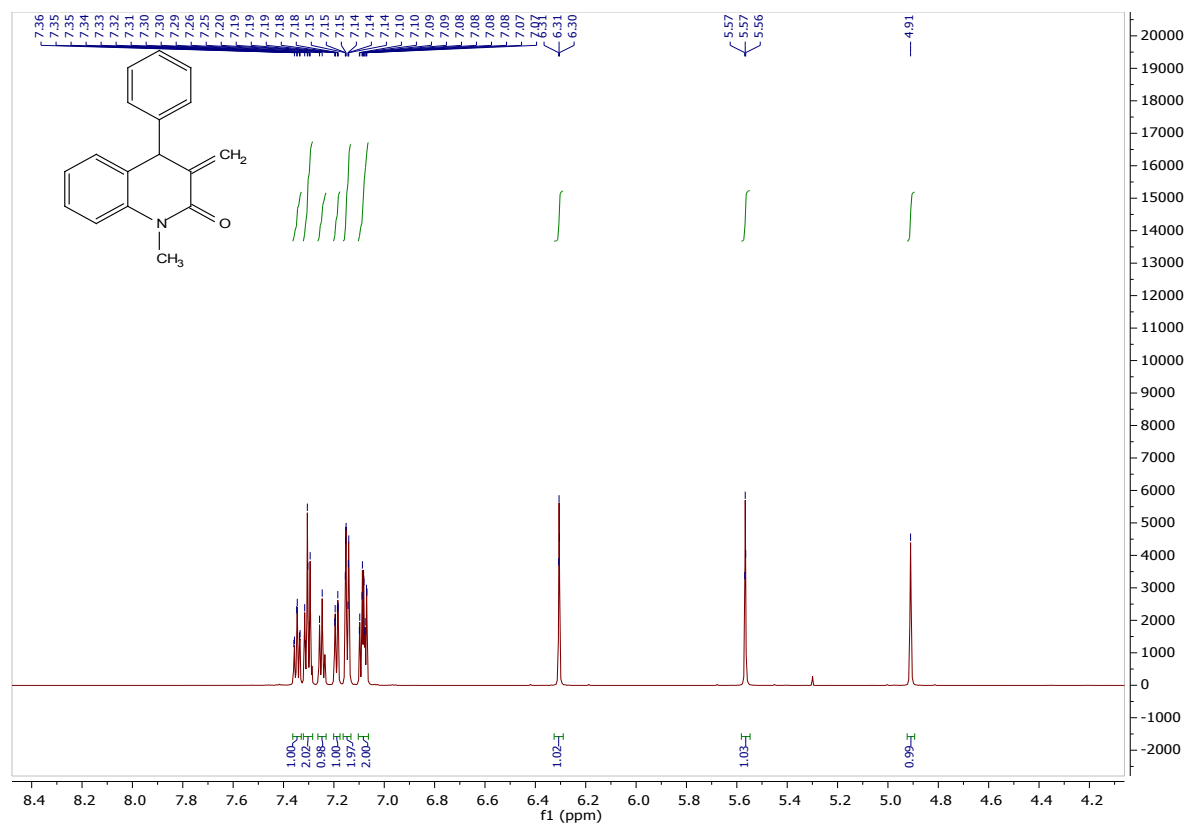


¹³C NMR

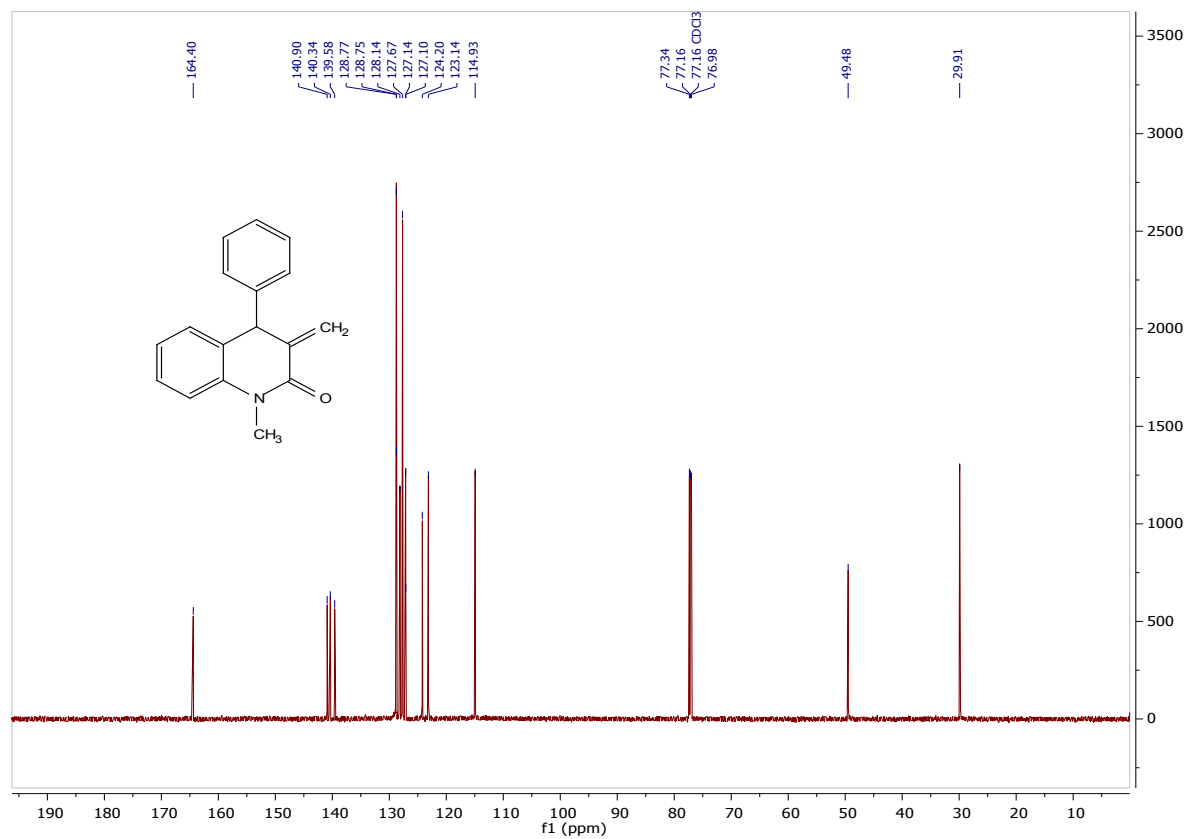


Compound 20c

¹H NMR

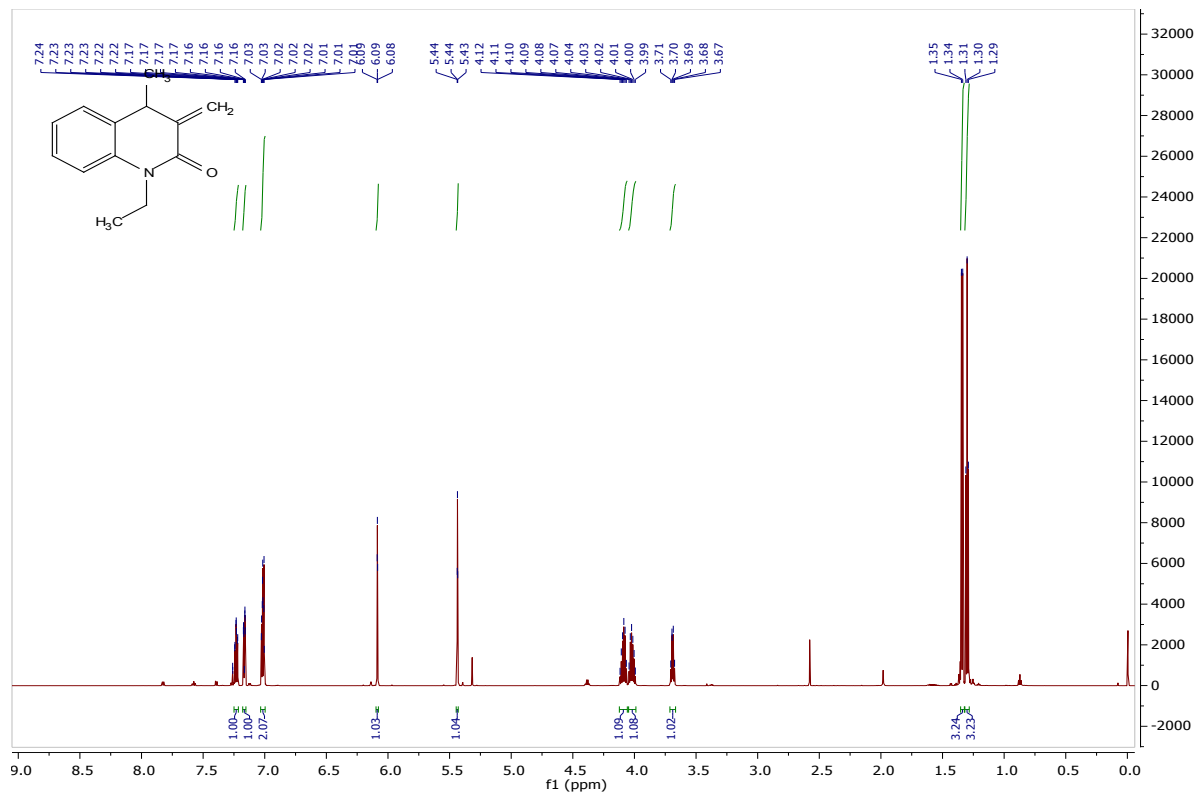


¹³C NMR

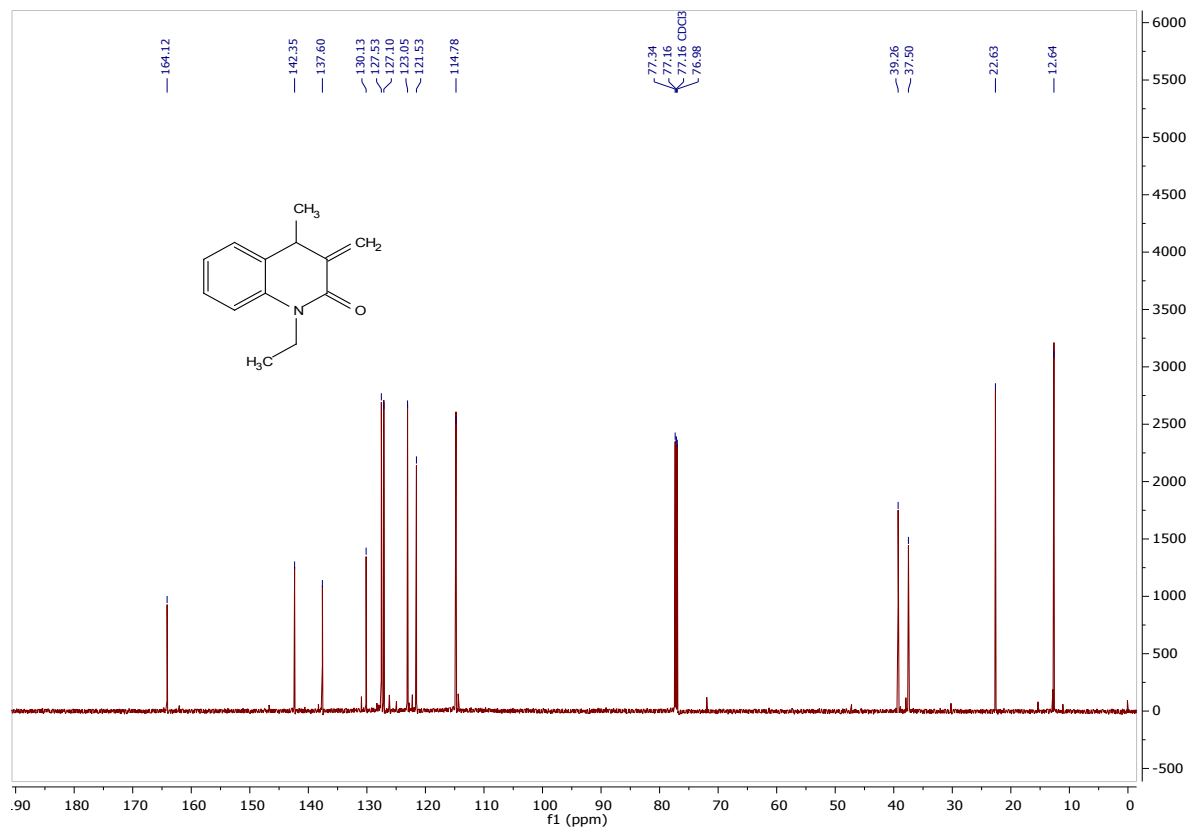


Compound 20d

¹H NMR

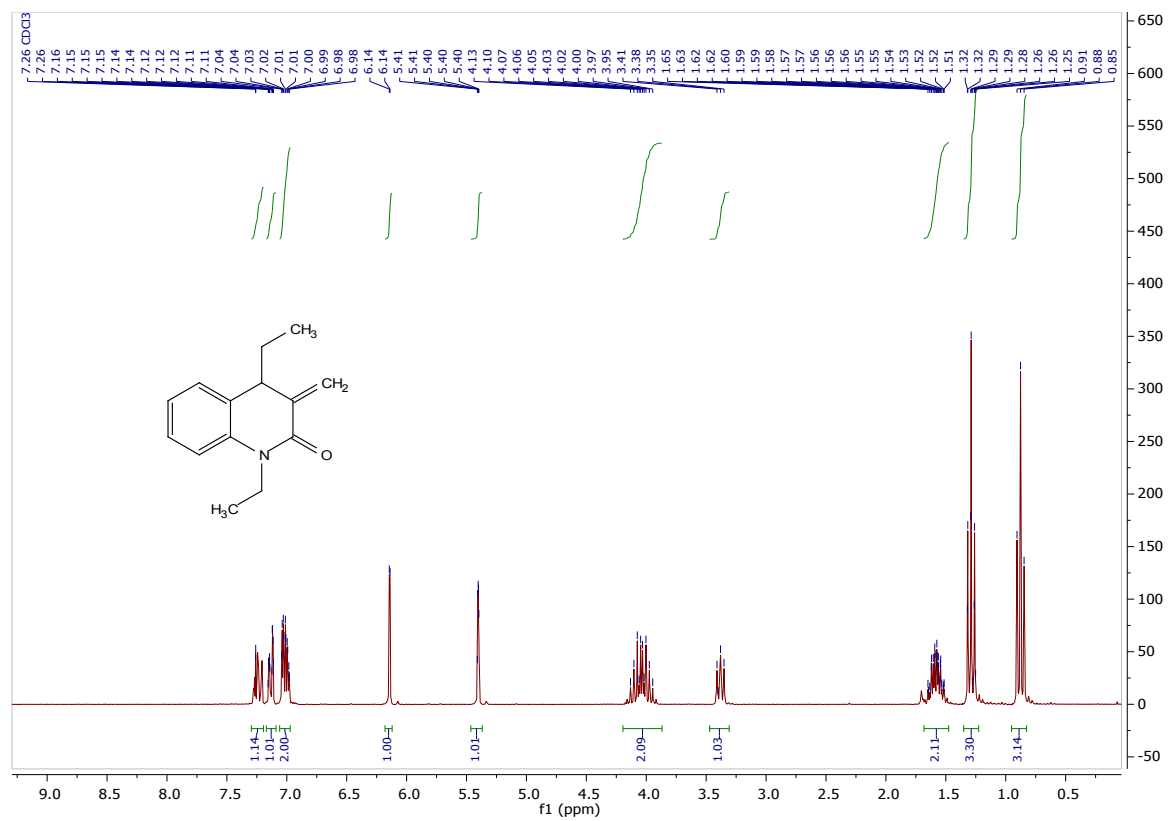


¹³C NMR

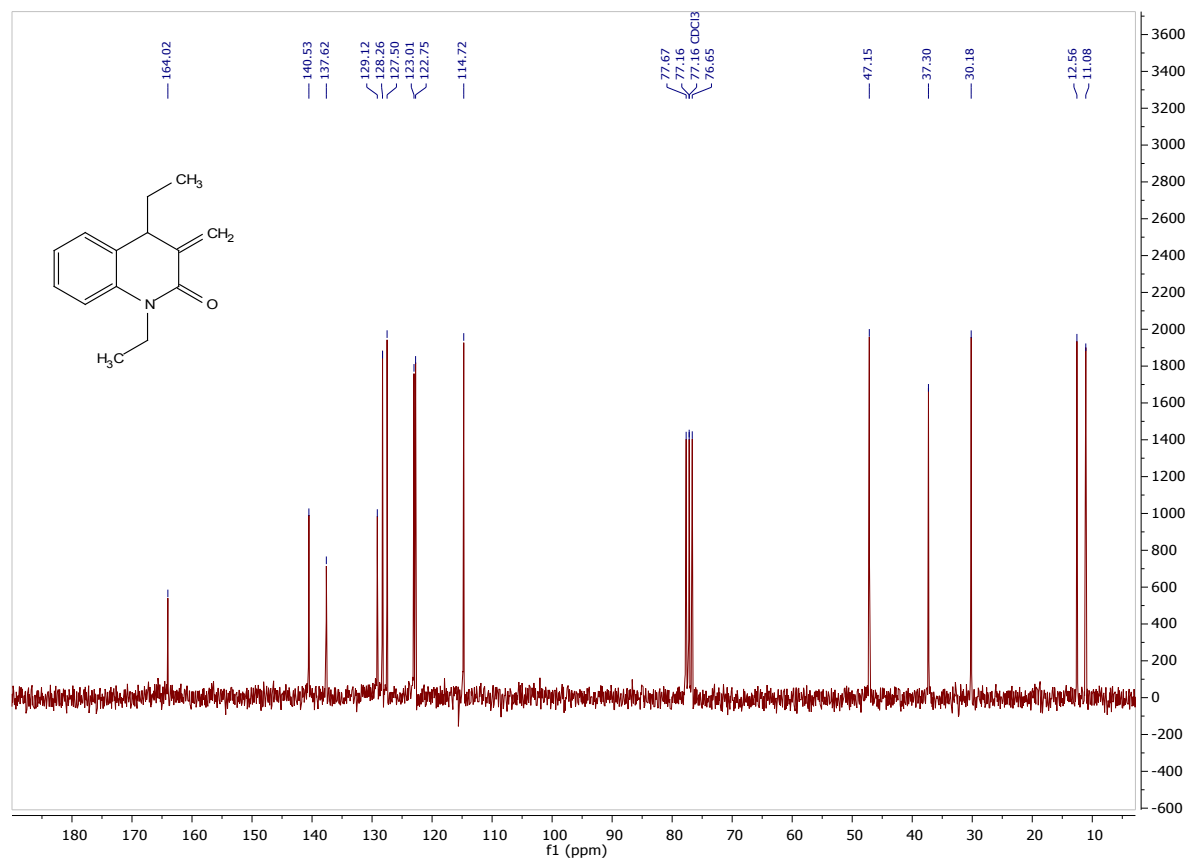


Compound 20e

¹H NMR

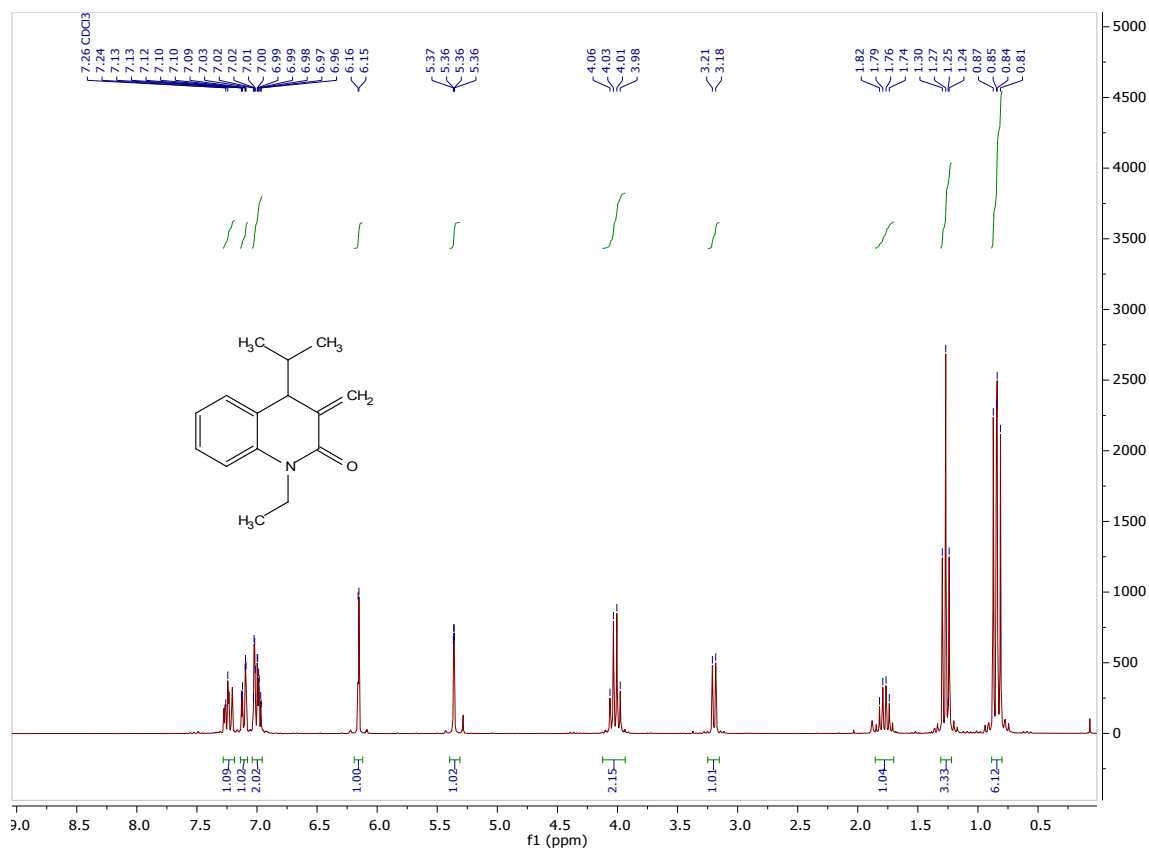


¹³C NMR

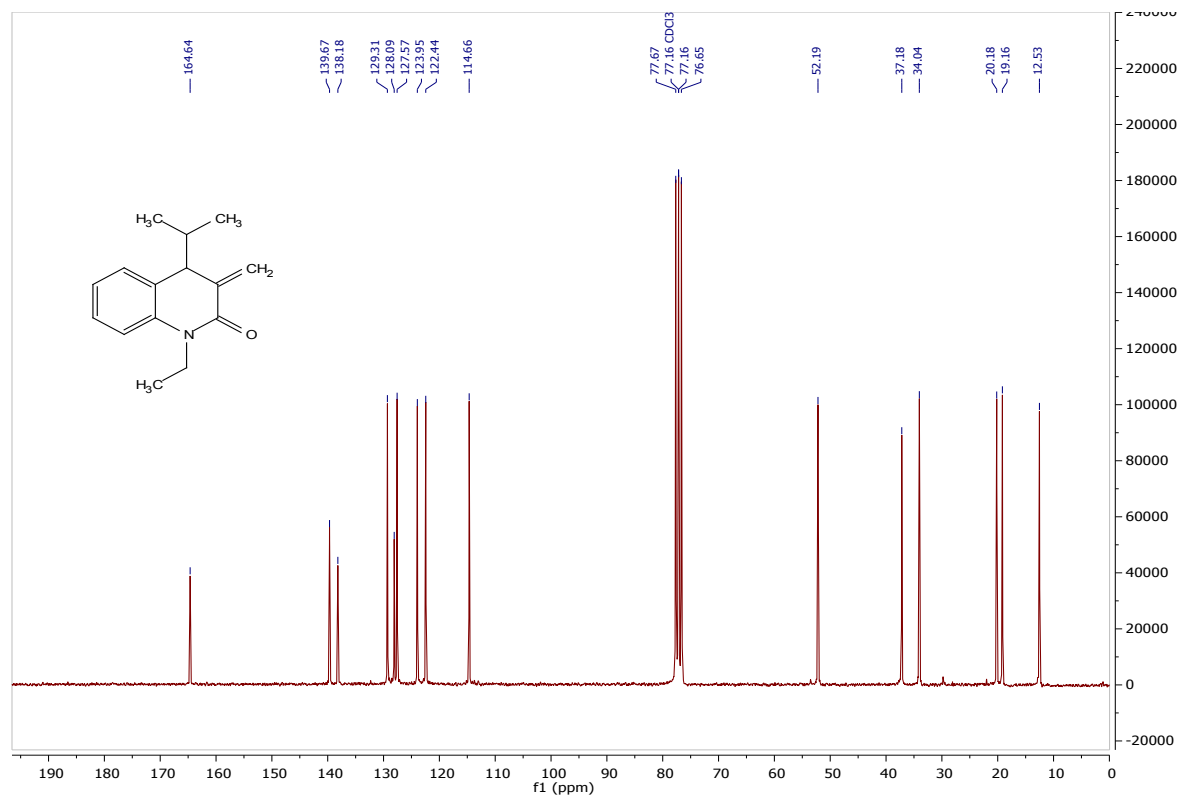


Compound 20f

¹H NMR

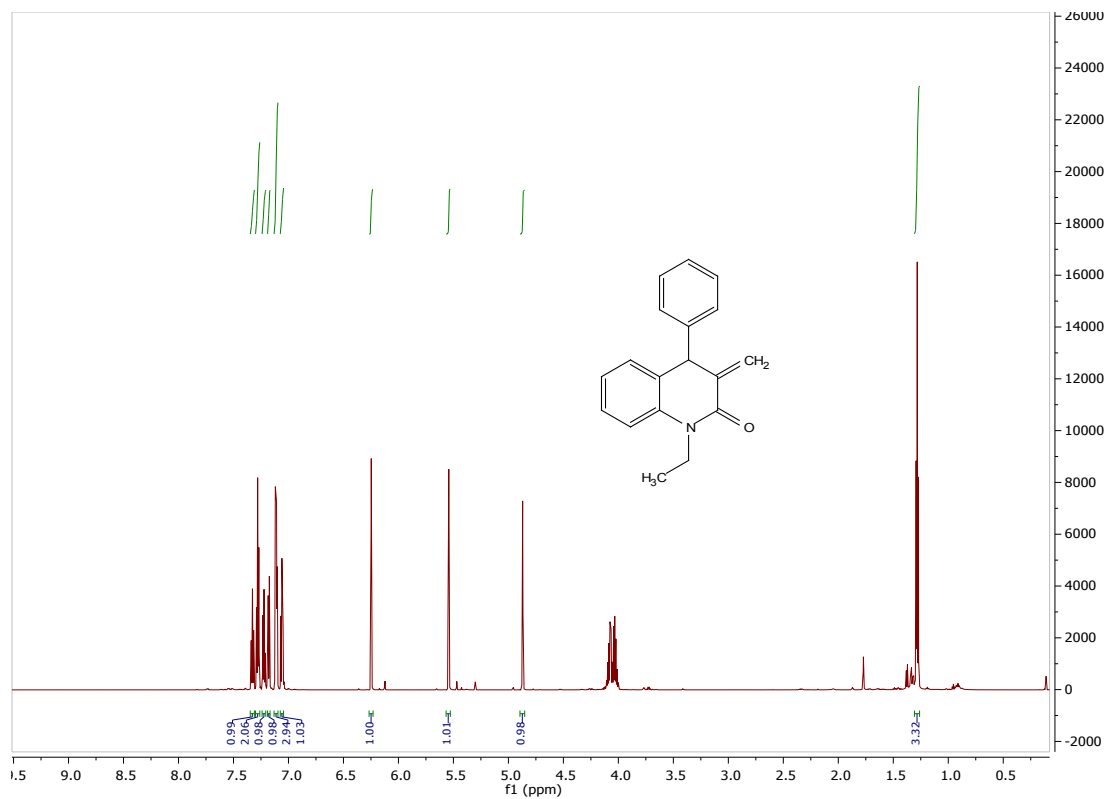


¹³C NMR

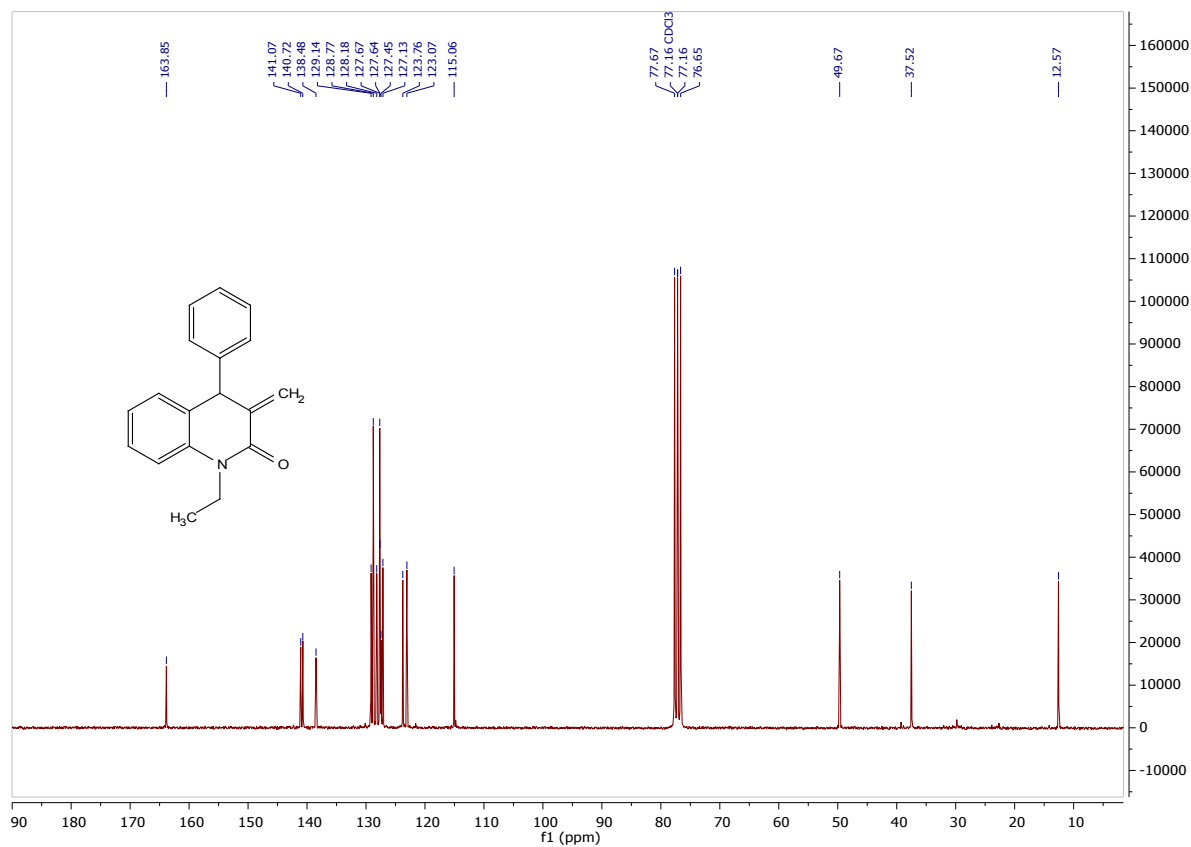


Compound 20g

¹H NMR

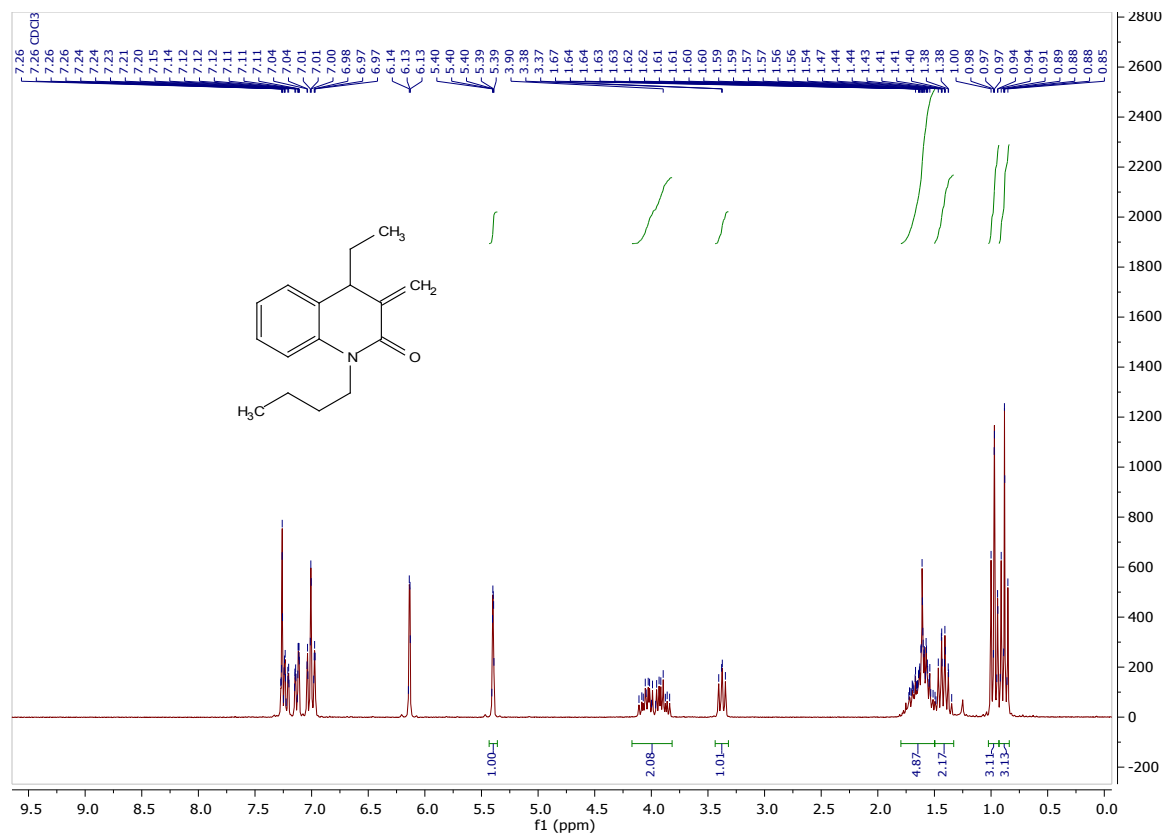


¹³C NMR

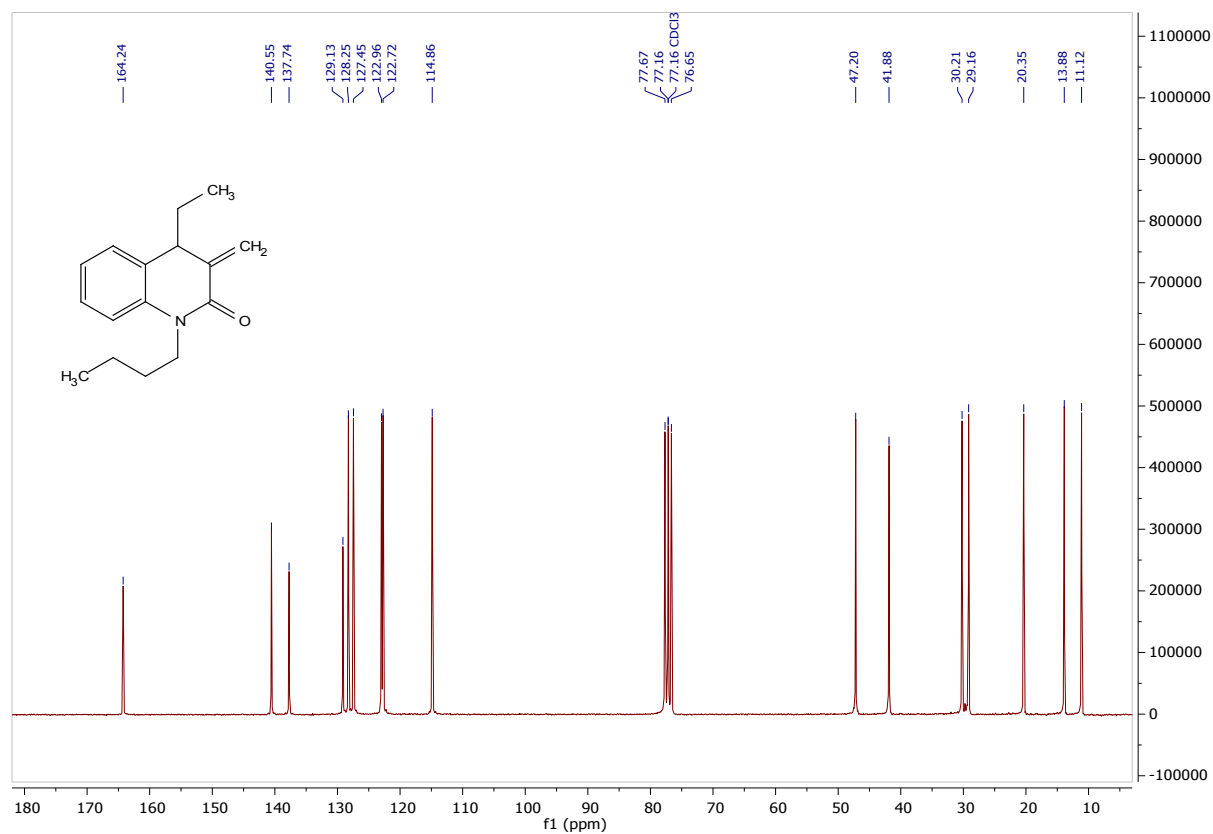


Compound 20h

¹H NMR

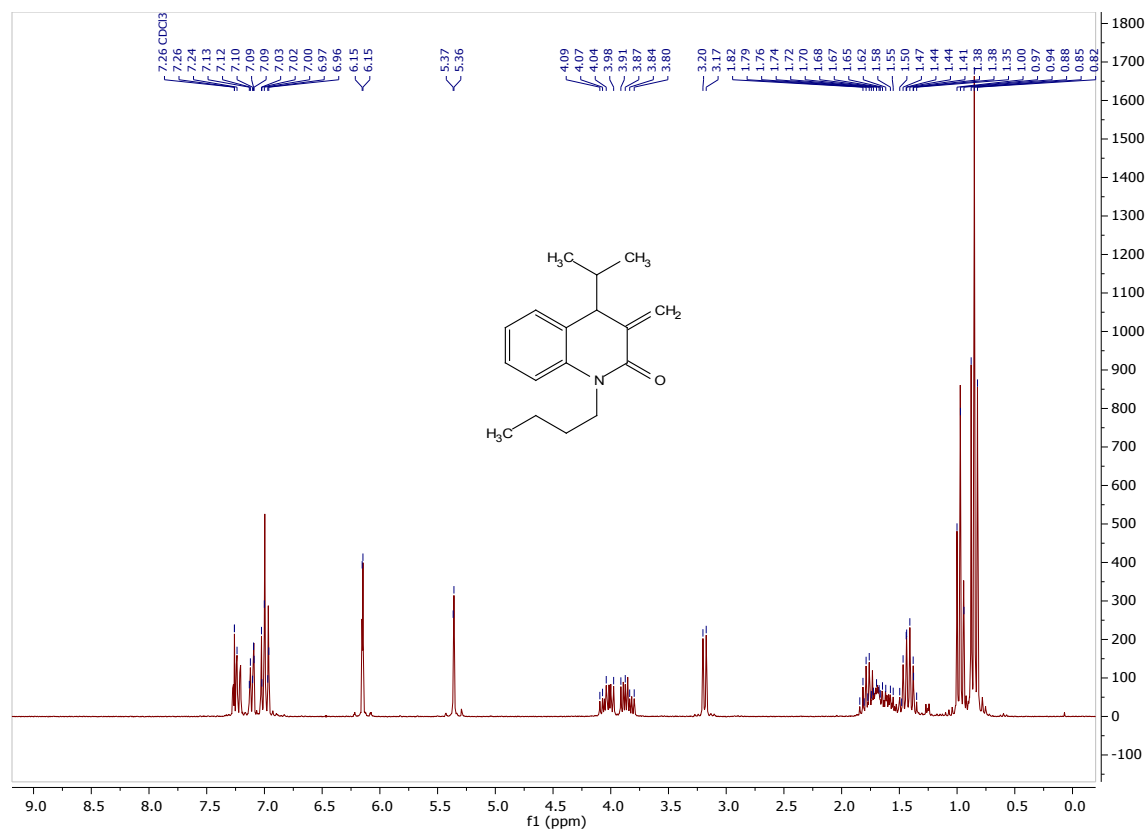


¹³C NMR

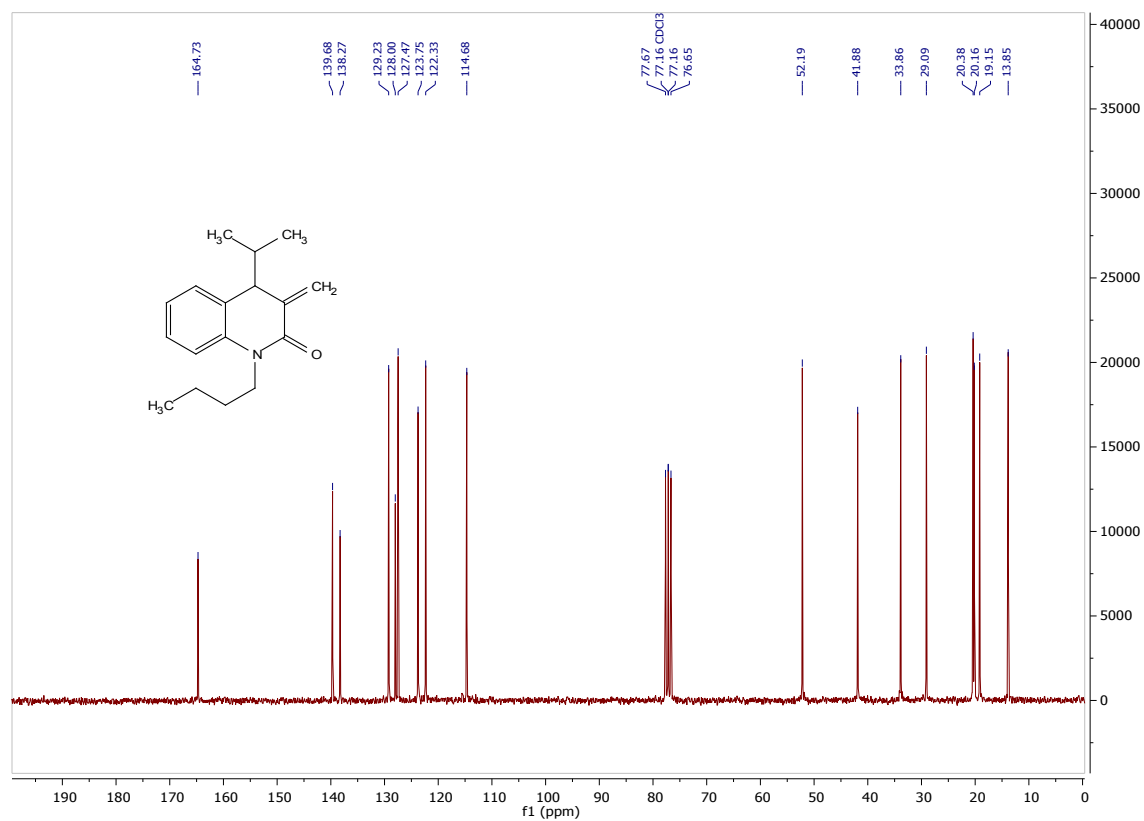


Compound 20i

¹H NMR

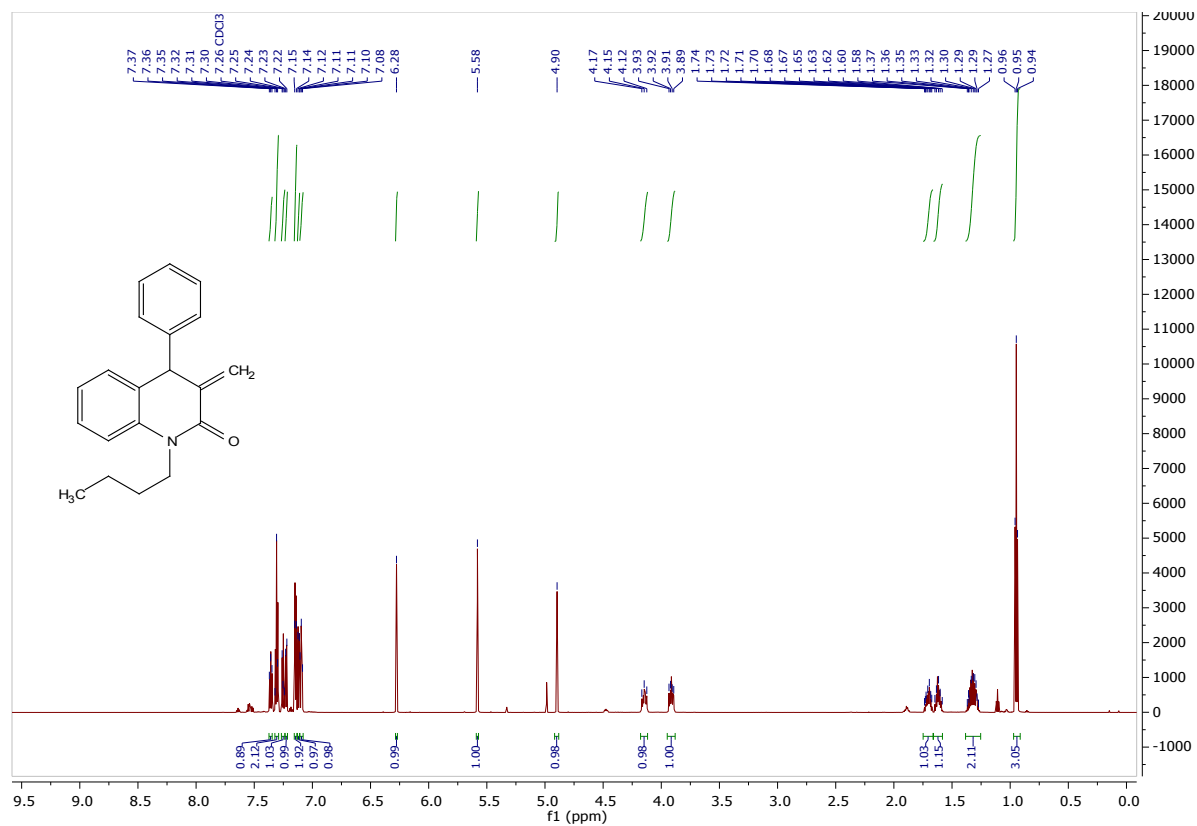


¹³C NMR

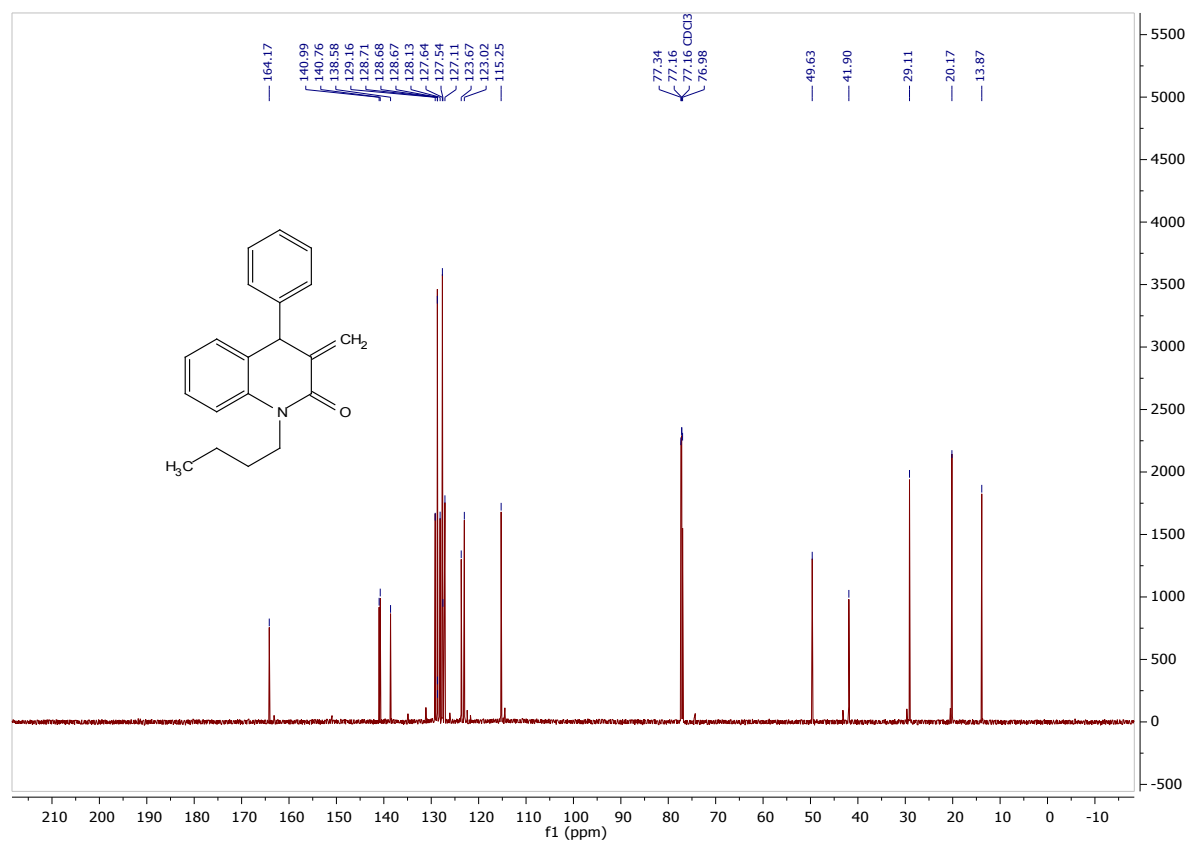


Compound 20j

¹H NMR

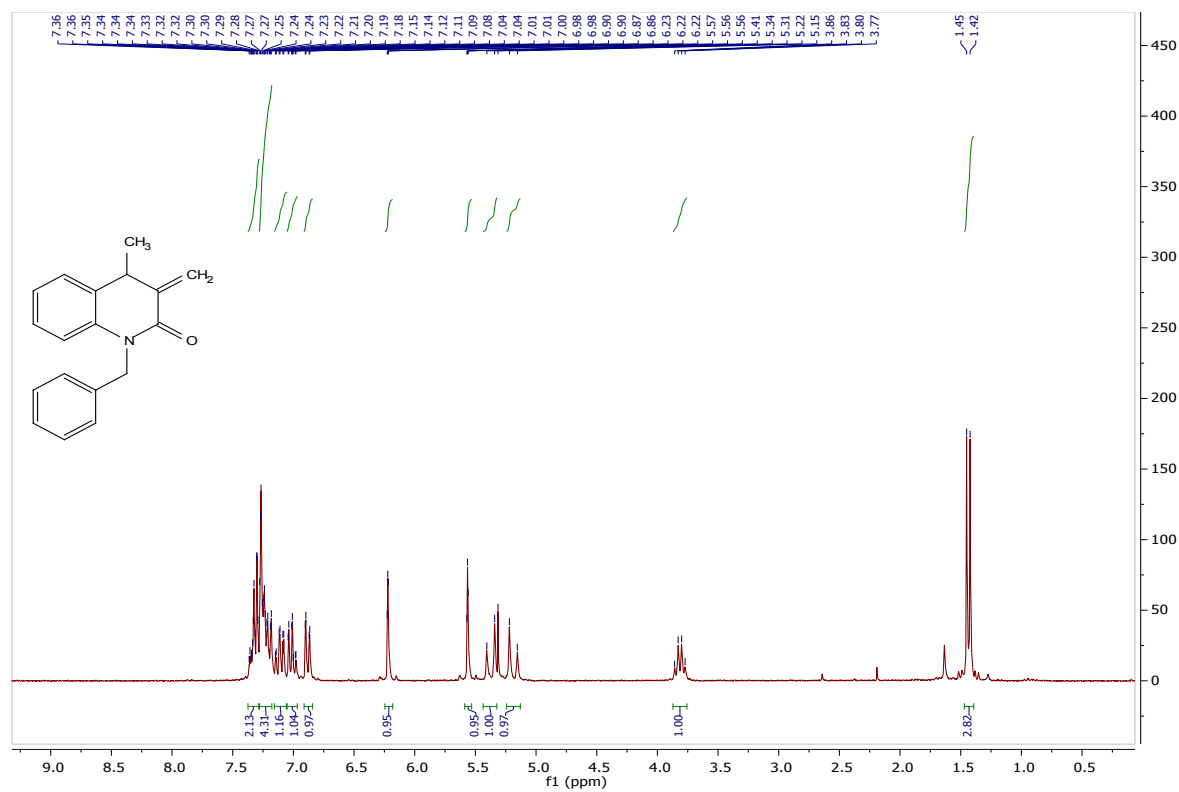


¹³C NMR

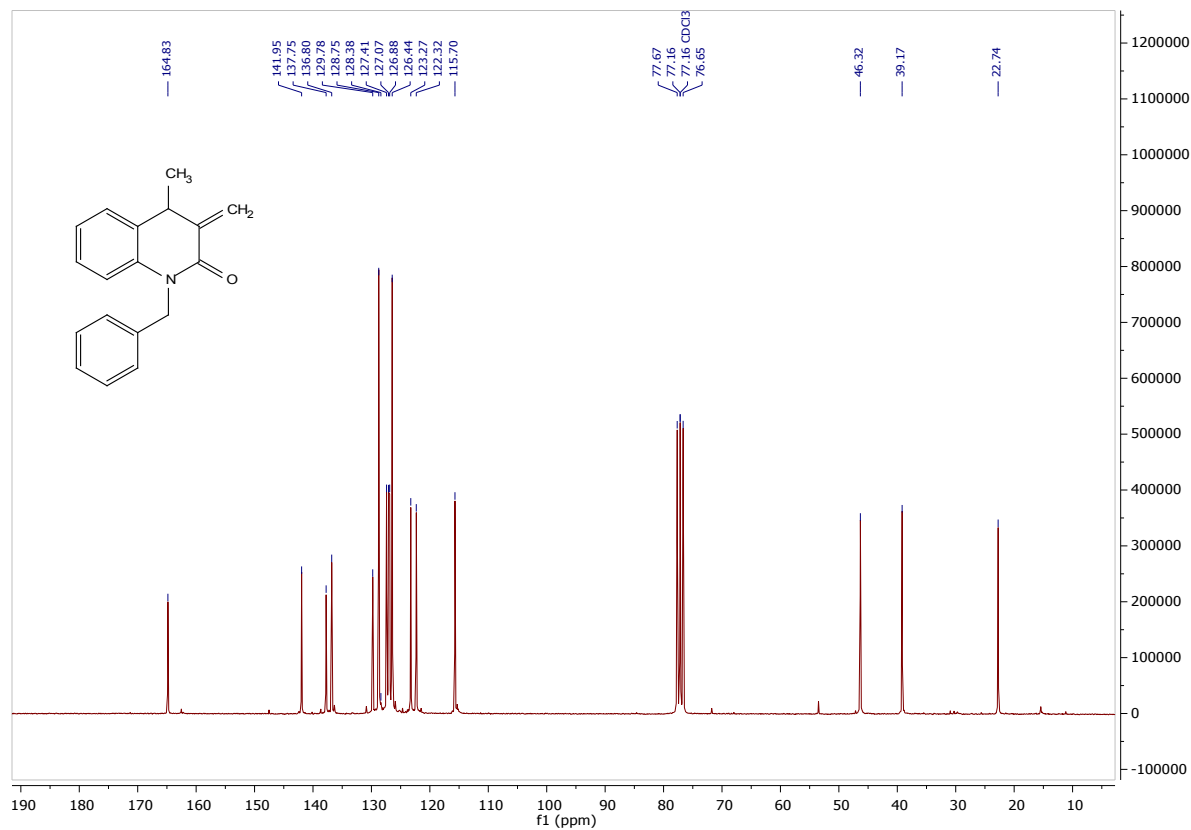


Compound 20k

¹H NMR

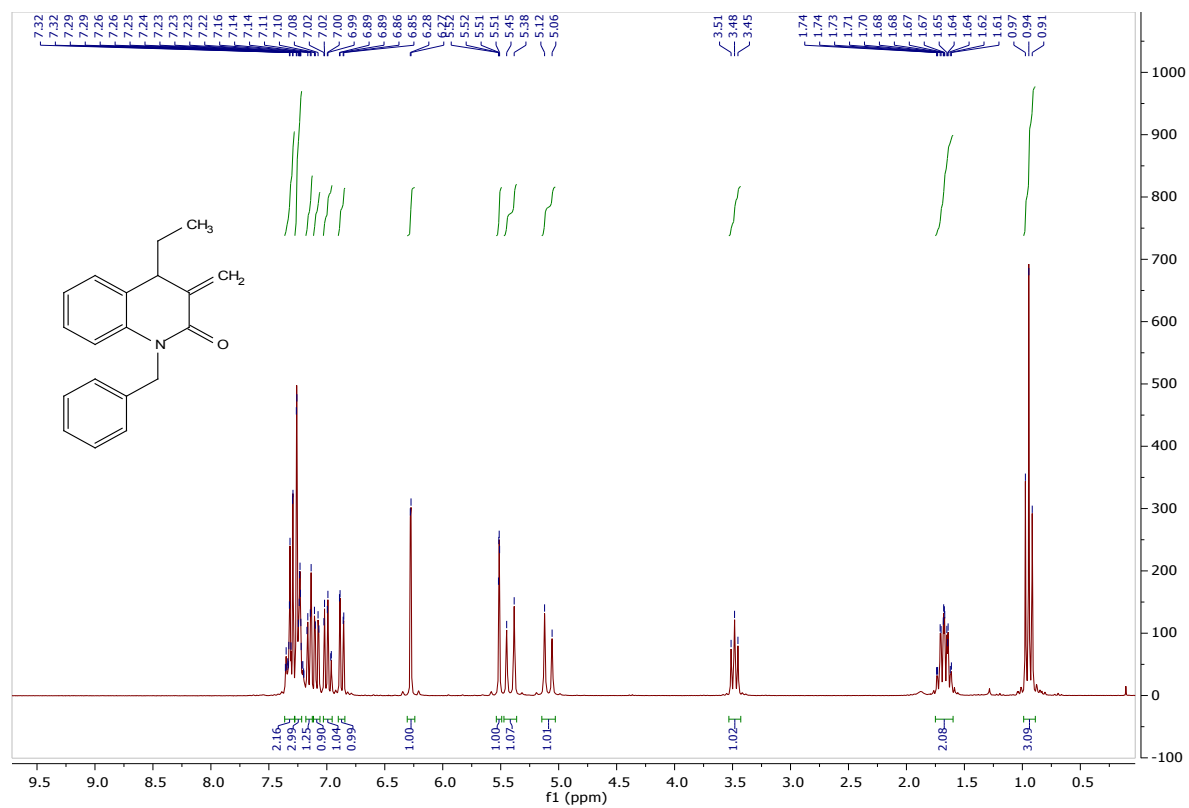


¹³C NMR

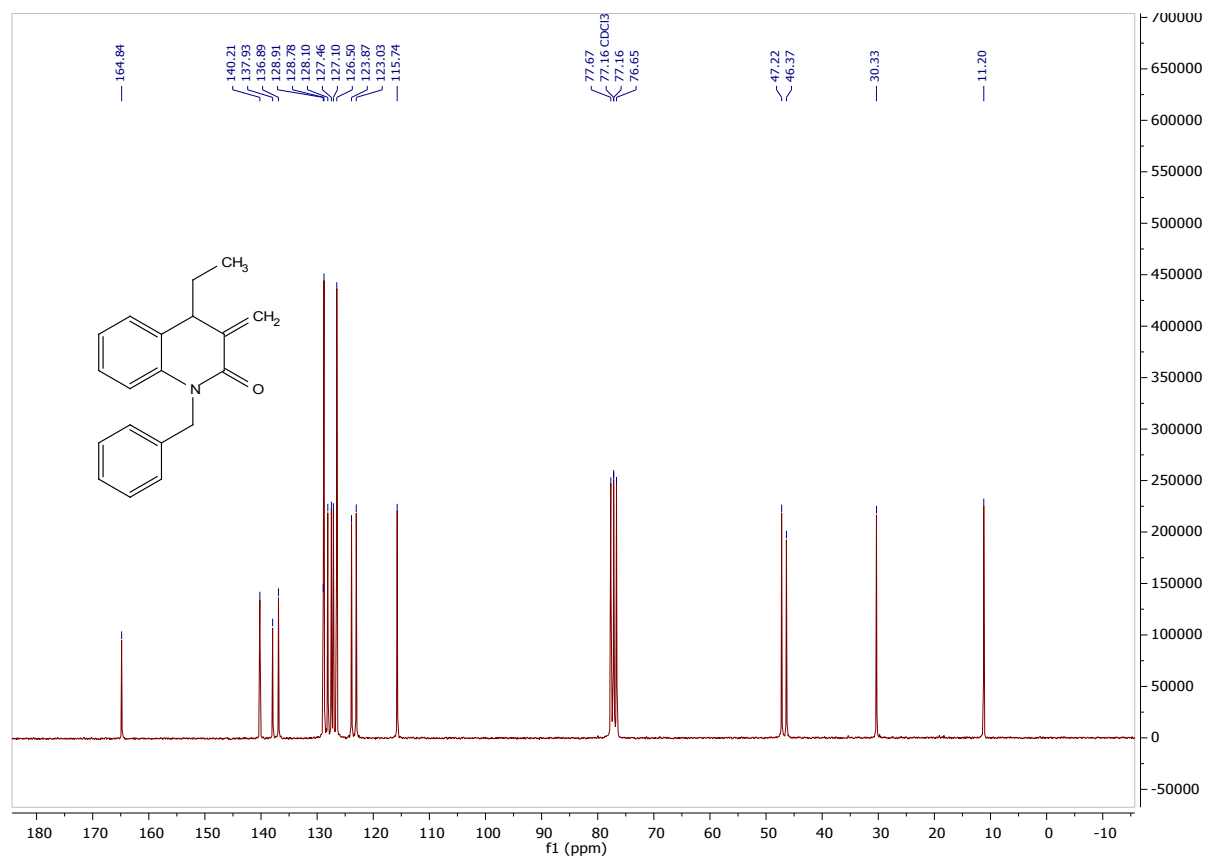


Compound 20l

¹H NMR

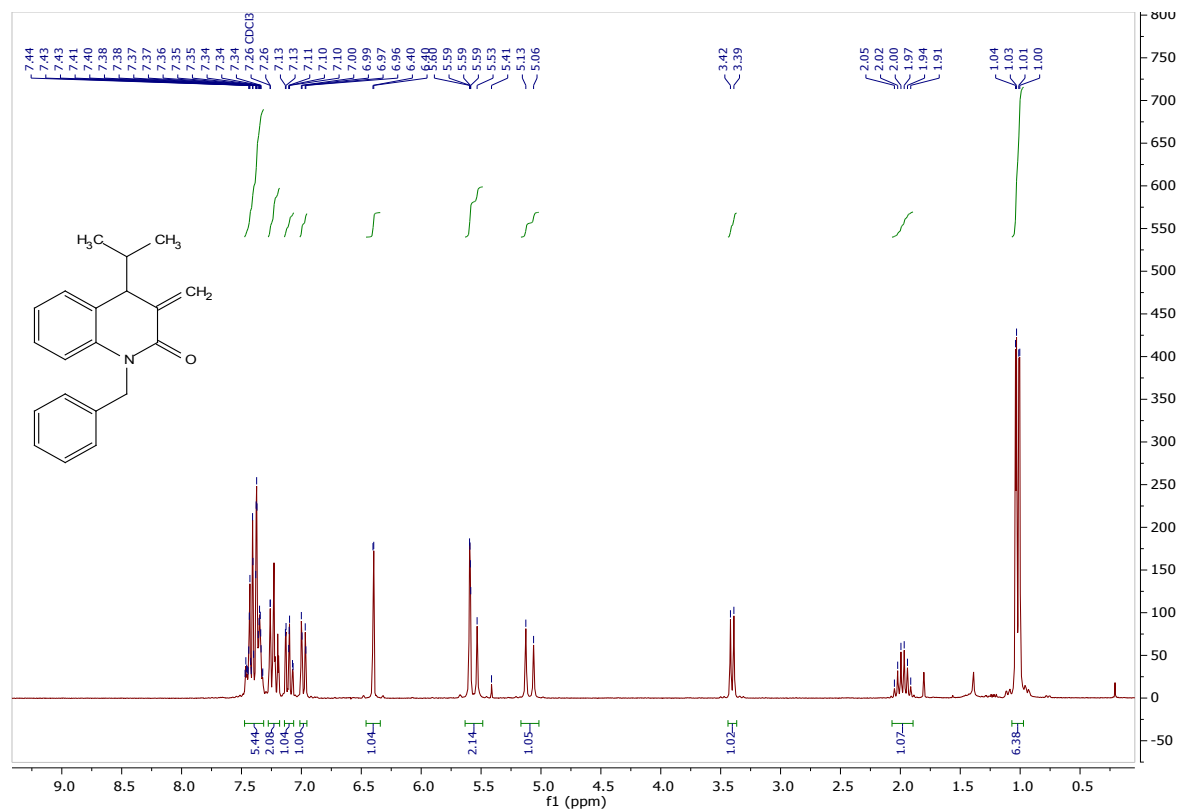


¹³C NMR

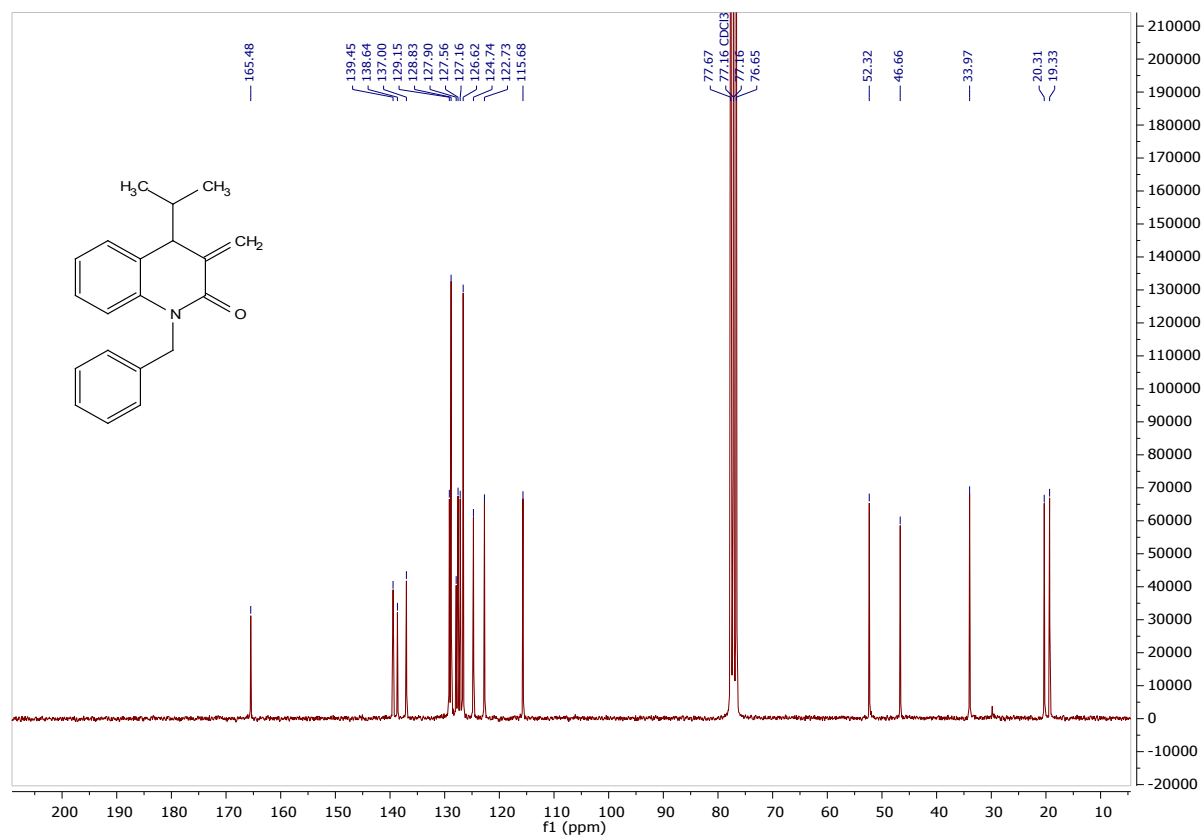


Compound 20m

¹H NMR

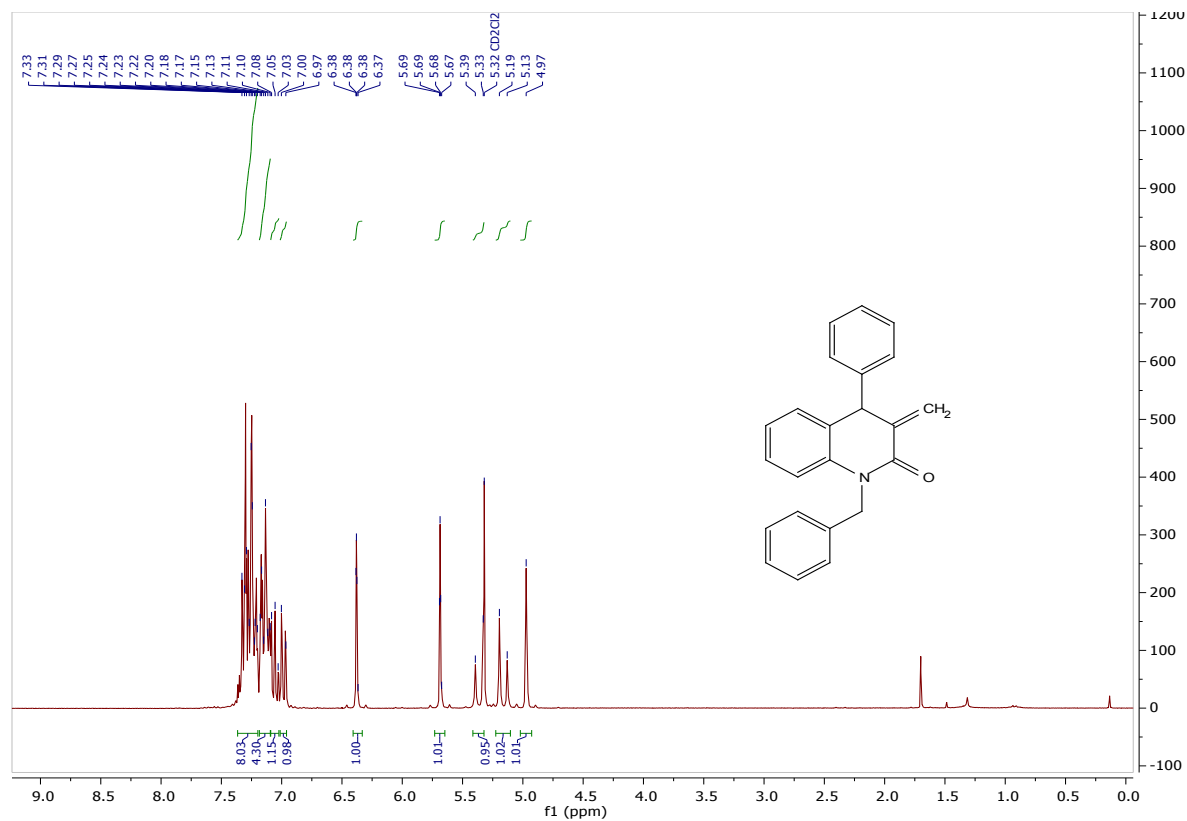


¹³C NMR



Compound 20o

¹H NMR



¹³C NMR

