Triple Zirconocene/Brønsted Acid/CuO Cooperative and Relay Catalysis System for Tandem Mannich Addition/C-C Formative Cyclization/Oxidation

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1. General procedures

^1H and ^{13}C NMR spectra were recorded on a Bruker EQUINX55 (400 MHz for ^1H; 101 MHz for ^{13}C) spectrometer in $CDCl_3$. For ^1H NMR, tetramethylsilane (TMS) served as internal standard (δ = 0) and ^1H NMR chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peak ($CDCl_3$ at 7.26 ppm) unless otherwise noted. The data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), and coupling constant in Hz. For ^{13}C NMR, $CDCl_3$ was used as internal standard (δ = 77.0) and spectra were obtained with complete proton decoupling. HRMS (ESI) analysis was performed and (HRMS) data were reported with sodium mass/charge (m/z) ratios as values in atomic mass units. Column chromatography was performed on silica gel (230-400 mesh) and analytical thin layer chromatography was carried out using 250 µm commercial silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance and stained with an iodine vapor.

2. Typical procedures for synthesis of substituted quinolines

A 10 mL test tube, equipped with a magnetic stirrer and a septum, was charged with *i*-PrOH (0.375mL), H_2O (0.125mL), aldehyde (1.0 mmol), amine (1.1 mmol) and ketone (1.5 mmol), in one portion. Cp_2ZrCl_2 (0.05mmol), trimellitic acid (0.05mmol), and CuO (0.05mmol) were added at 60 °C and stirred until the reaction was completed as indicated by TLC. Upon completion of the reaction, the reaction mixture was quenched with distilled water (5.0 mL). The aqueous phase was extracted with ether (3×5 mL), dried over Na_2SO_4 and concentrated in vacuo to give desired products. The corresponding solid products were obtained through column chromatography by using 100−200 mesh silica gels.

3. Optimization of reaction conditions for synthesis of substituted quinolines

To further investigate the effect of solvents, next we examined our reaction in different solvent systems. The catalytic activity of zirconocene dichloride, trimellitic acid and CuO in the reaction of anilines, aldehydes and ketones was sligthly influenced by solvents as show in Table S1. At first, non-polar solvent *n*-hexane was evaluated, we can found the catalyst almost inert in CH_2Cl_2, *n*-hexane only obtained 20% and 5% yield (entries 1 and 2). DMSO and THF can slightly accelerated Zr-Cu catalyst in this reaction obtained 20% and 32% yields respectively (entries 3, 4). More polar solvent such as EtOH was obviously accelerated Zr-Cu catalyst in this reaction obtained 48% yields (entry 5). So that, several alcohols were examined in this reaction, the result demonstrated that *i*-PrOH was best solvent in this coupling reaction, afforded 54% yield in this reaction (entries 6-12). At the same time, water as a solvent also sreened, only abtained 10%

substituted quinolines, but no byprduct was produced in this reaction. Concentrating this three components coupling reaction process fast in *i*-PrOH, so we combined water and *i*-PrOH, the best result obtained in *i*-PrOH:H_2O=3:1.

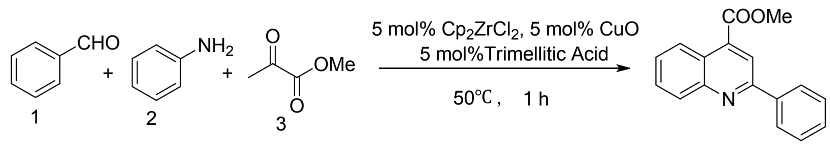


Table S1 Solvent screening of three-component coupling sequence reaction[a]

Entry	Solvent	Yield (%)[b]
1	CH_2Cl_2	29
2	*n*-hexane	5
3	DMSO	20
4	THF	32
5	EtOH	48
6	MeOH	43
7	PrOH	47
8	*i*-PrOH	54
9	BuOH	50
10	*t*-BuOH	44
11	$C_6H_{13}OH$	40
12	$C_6H_{15}OH$	37
13	H_2O	10
14	*i*-PrOH/H_2O=1:1	30
15	*i*-PrOH/H_2O=2:1	47
16	*i*-PrOH/H_2O=3:1	58
17	*i*-PrOH/H_2O=4:1	51

[a]All reactions were conducted using the aniline (1 mmol),benzaldehyde (1 mmol), methyl pyruvate (1.0 mmol), 50℃, 1h. [b]Isolated yields

Table S2 shows the effect of the catalyst amount with increasing of the molar ratio of catalyst trimellitic acid, Cp_2ZrCl_2 and CuO. When the loading of catalyst increased from 1 mol% to 5 mol%, the yield of product increased sharply from 15% to 58%. At a catalyst loading of 5 mol%, the best result can be obtained. Further increasing the amount of catalyst, the yield increase slightly, therefore 5mol% was selected as the best loading of catalyst. The ration trimellitic acid and Cp_2ZrCl_2 also screened, result demonstrated that 5 mol% trimellitic acid, Cp_2ZrCl_2 and CuO were best. Subsequently, we checked the effect of temperature on the progress of the reaction. According to Table S2, we can see that as the temperature increases the yield decreased, because byproducts increased with temperature increasing, so the optimum temperature is 60˚C. Reaction time was also screened, the optical time was 2h.

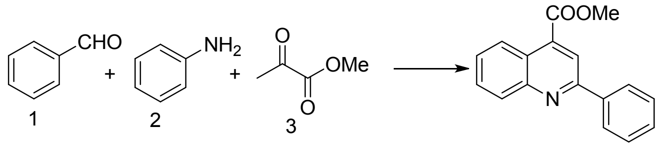


Table S2 Ratio of catalyst and time screening of three-component coupling sequence reaction[a]

Entry	Ratio of Cat.	Time	Temp(℃)	Yield(%)[b]
1	1%:1%:1%	1	50	15
2	2%:2%:2%	1	50	30
3	3%:3%:3%	1	50	43
4	5%:5%:5%	1	50	58
5	10%:10%:10%	1	50	60
6	5%:6%:5%	1	50	62
7	5%:7%:5%	1	50	63
8	5%:8%:5%	1	50	64
9	5%:9%:5%	1	50	65
10	5%:10%:5%	1	50	65
11	5%:5%:5%	1	60	70
12	5%:5%:5%	1	70	59
13	5%:5%:5%	1	80	57
14	5%:5%:5%	1	90	55
15	5%:5%:5%	1	100	53
17	5%:5%:5%	1.5	60	85
18	5%:5%:5%	2	60	87
19	5%:5%:5%	2.5	60	88
20	5%:5%:5%	3	60	89
21	5%:5%:5%	3.5	60	89

[a]All reactions were conducted using the aniline (1 mmol),benzaldehyde (1 mmol), methyl pyruvate (1.0 mmol), ratio of catalyst Cp_2ZrCl_2: trimellitic acid: CuO, 50℃, 1 h. [b]Isolated yields based on 2.

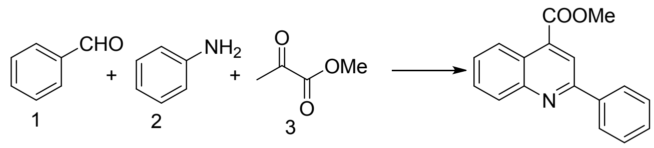


Table S3 Ratio of substrates screening of three-component coupling sequence reaction[a]

Entry	1/2/3	Yield(%)[b]
1	1:1:1	85
2	2:1:1	85
3	3:1:1	85
4	4:1:1	86
5	1:1.1:1	90
6	1:1.2:1	90
7	1:1.3:1	90
8	1:1.4:1	91
9	1:1.5:1	91
10	1:1.1:1.1	73
11	1:1.1:1.2	76
12	1:1.1:1.3	80
13	1:1.1:1.4	84
14	1:1.1:1.5	91
15	1:1.1:1.6	91
16	1:1.1:1.7	91
17	1:1.1:1.8	91
18	1:1.1:2	92

[a]All reactions were conducted using aldehyde (1.0 mmol); Cp_2ZrCl_2 (0.05 mmol, 5 mol%); CuO (0.05 mmol, 5 mol%); trimellitic acid (0.05 mmol, 5 mol%); i-PrOH : H_2O (3:1, 0.5 mL); All reactions were carried out at 60℃ for 2 h. [b]Isolated yield.

The ratio of substrates is show in Table S3. From this table, we can see the optical ratio of benzaldehyde, aniline and ketone are 1:1.1:1.5.

4. NMR experiments

The interplay of Cp_2ZrCl_2 and trimellitic acid were investigated by ^1H NMR in mechanistic scenario. A general procedure was as follows: Cp_2ZrCl_2 (10 μmol) and trimellitic acid (10 μmol) was placed in D_2O (0.5mL) and the solution was detected immediately as observed by ^1H NMR spectroscopy. The mixture was allowed to stand for 1 h and was conducted by ^1H NMR spectroscopyas confirmed by ^1H NMR spectroscopy. After 1.0 equiv. of trimellitic acid was added in the above solution, one new Cp protons singlet appeared at δ 6.57 ppm, but did not increase as time go on. After 2.0 equiv. aniline was added, Cp_2ZrCl_2 (**I**)was consumed gradually in D_2O in the presence of base and formed new zirconocene species $Cp_2Zr(OOC)_2PhCOOH$. (**II**).

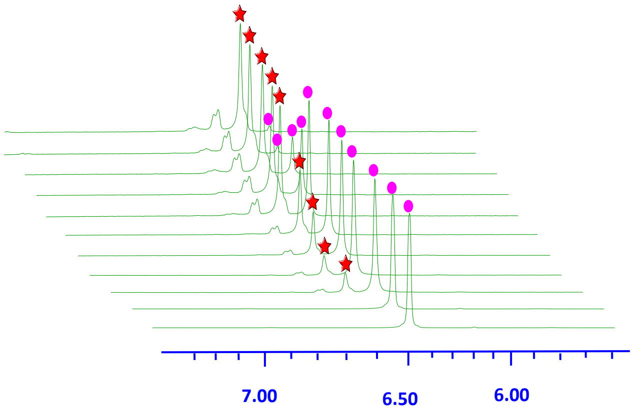


Fig. S1 Partial 400 MHz ^1H NMR spectra (D_2O) of a mixture of Cp_2ZrCl_2 (1.0 equiv) and trimellitic acid (1.0 equiv) with $PhNH_2$(2.0 equiv). 6.49 ppm **I**●[Cp_2ZrCl_2]; 6.57 ppm **II**★$Cp_2Zr(OOC)_2PhCOOH$.

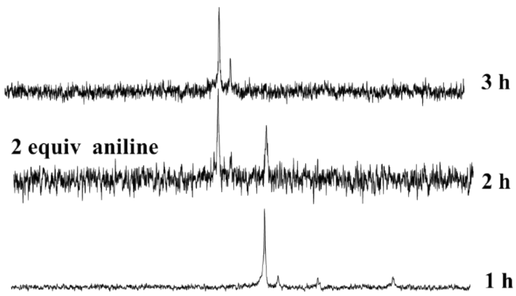


Fig. S2 Partial 400 MHz ^{13}C NMR spectra (D_2O) of a mixture of Cp_2ZrCl_2 (1.0 equiv) and trimellitic acid (1.0 equiv) with $PhNH_2$ (2.0 equiv).

5. HRMS analysis

Mass spectrometric measurements were performed in aBruker EVOQ tandem mass spectrometer. As a general rule, scan mode was Q1MS, positiveion mode (otherwise indicated), tube lens potential was optimized in each case or for aseries of measurements that required equal conditions, a time span of 1 minute was used to collectspectra and average them. The tube lens potential was adjusted in a way that the most interest ions had almost no attenuation (around 70 V).

For CID experiments, the cations of interest were mass-selected using the first quadrupole (Q1) and interacted with argon in the T-wave collision cell at variable collision energies (Elaboratory= 3-15 eV). The ionic products of fragmentation were analyzed with the time-offlight analyzer. The isolation width was 1Da and the most abundant isotopomer was mass-selected in the first quadrupole analyzer.

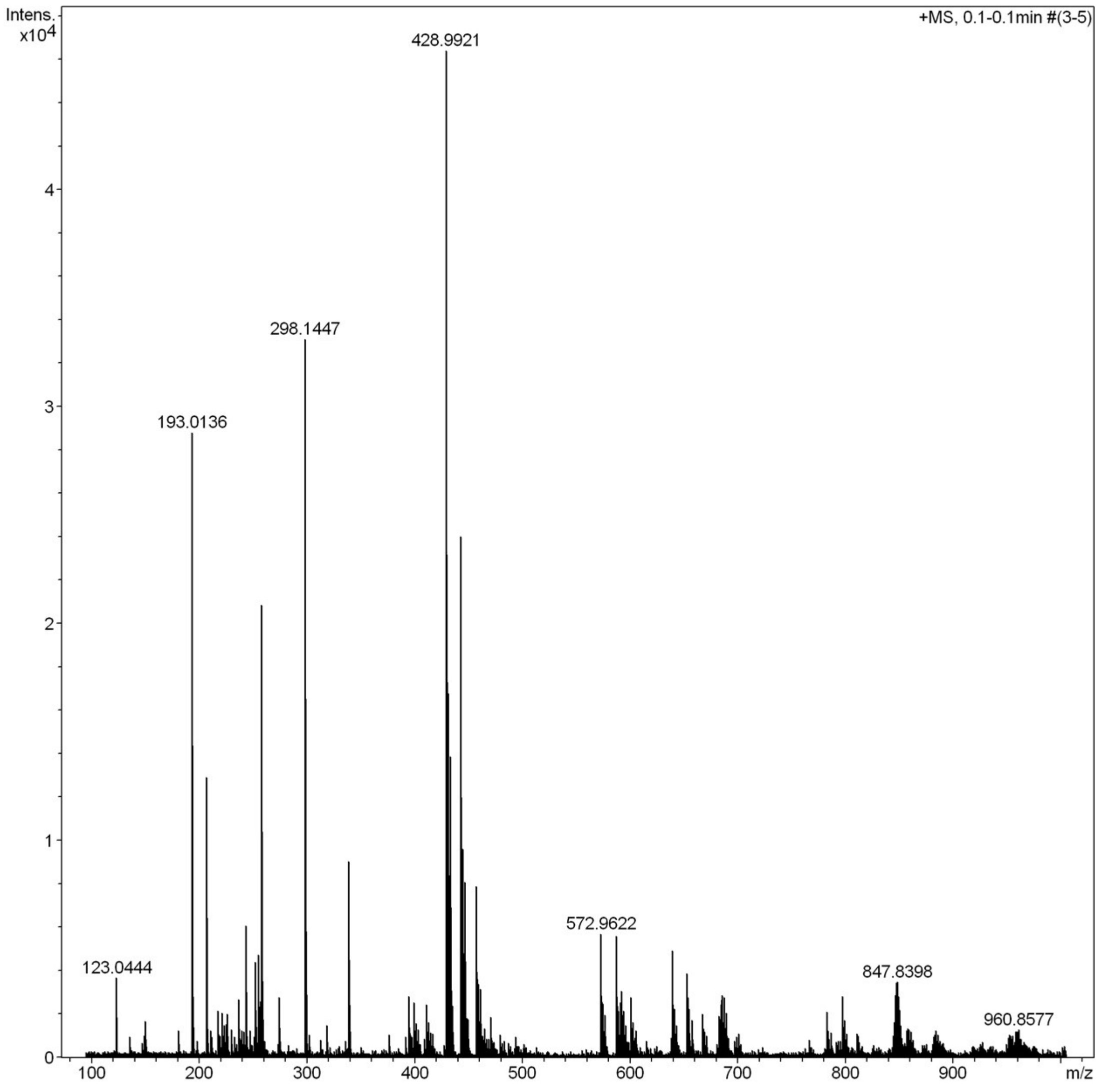


Fig. S3 The HRMS of trimellitic acid and Cp_2ZrCl_2 (m/z 100-1000)

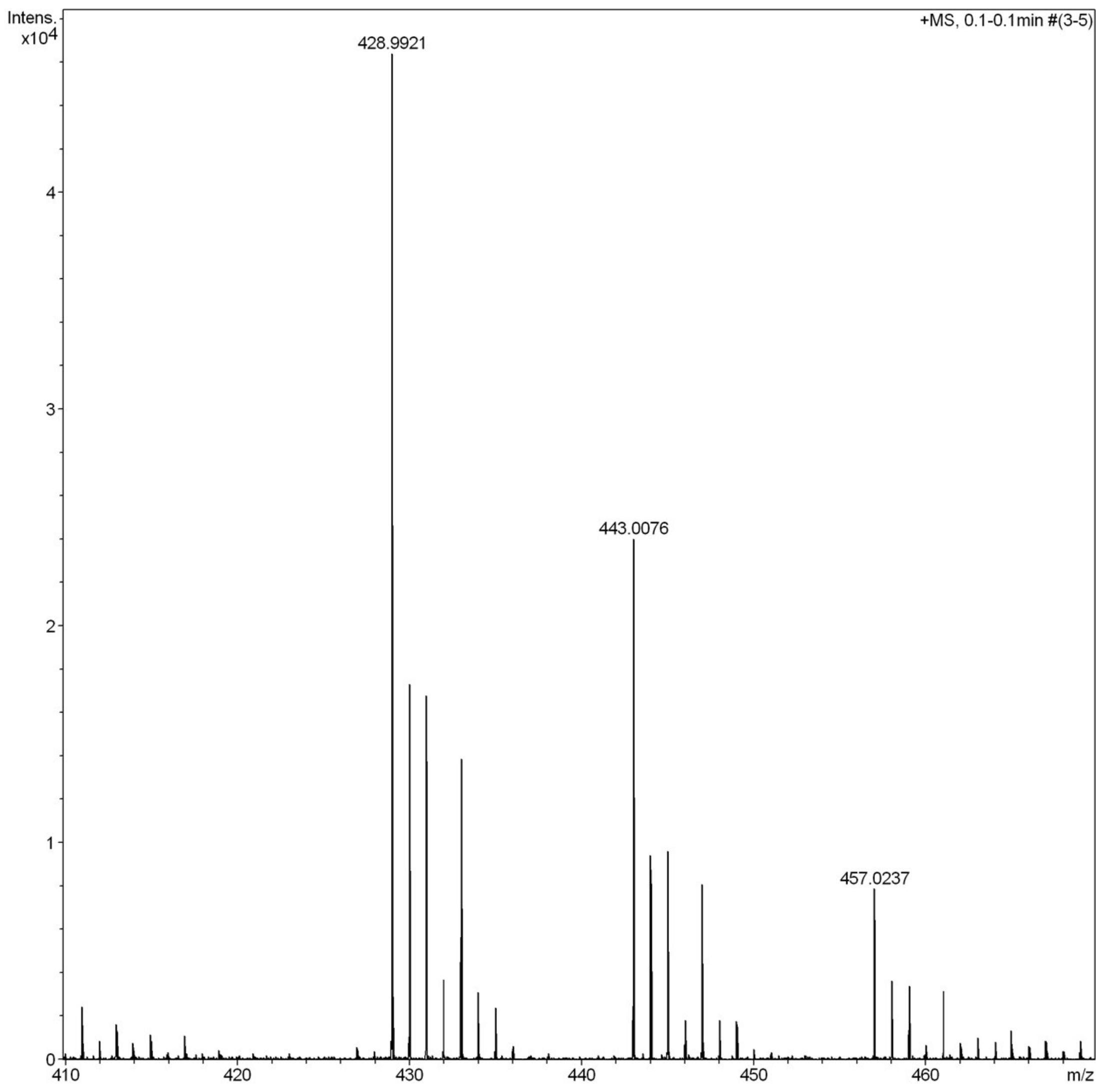


Fig. S4 The HRMS of trimellitic acid and Cp_2ZrCl_2 (m/z 410-470)

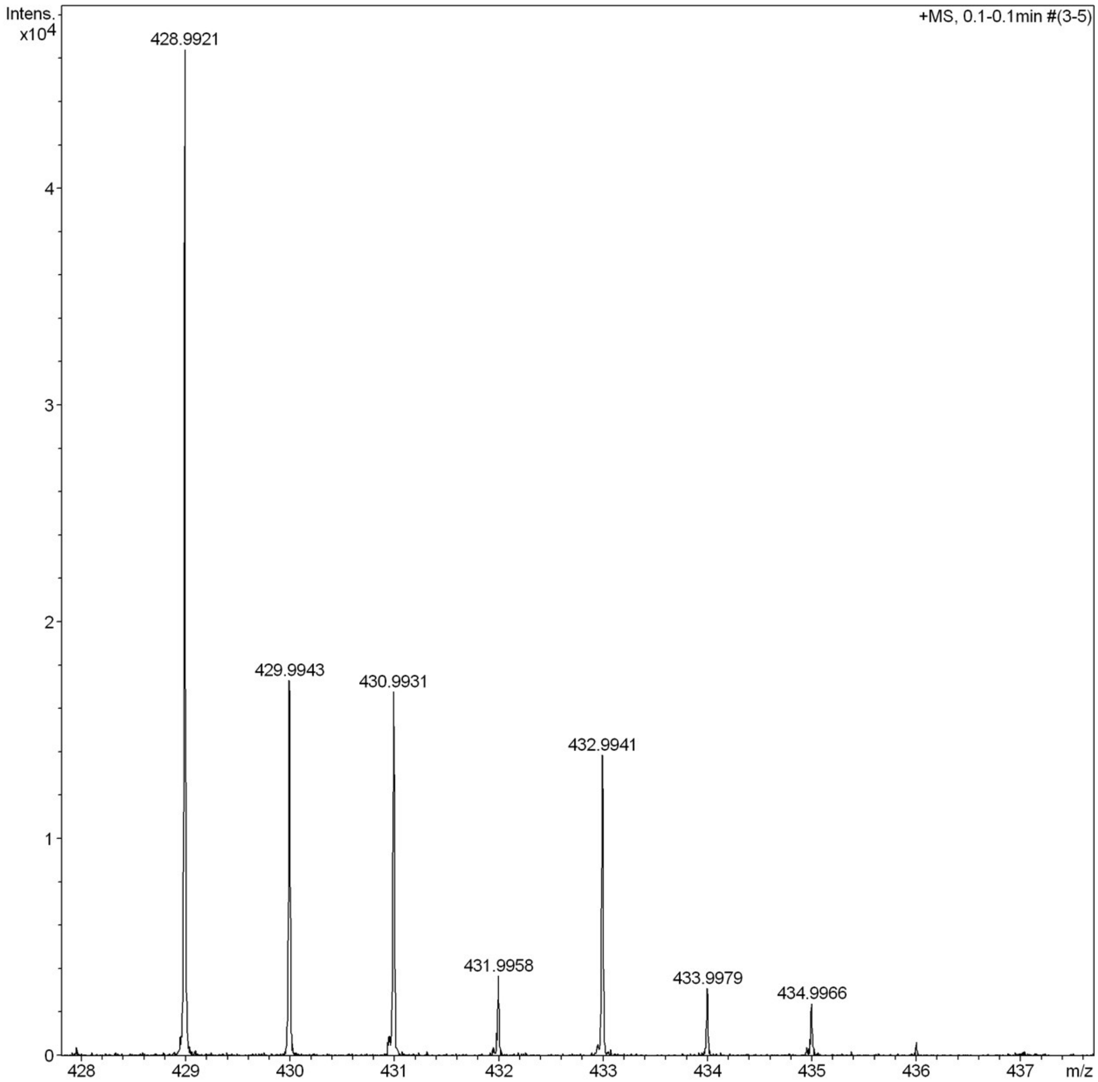


Fig. S5 The HRMS of trimellitic acid and Cp_2ZrCl_2 (m/z 428-438)

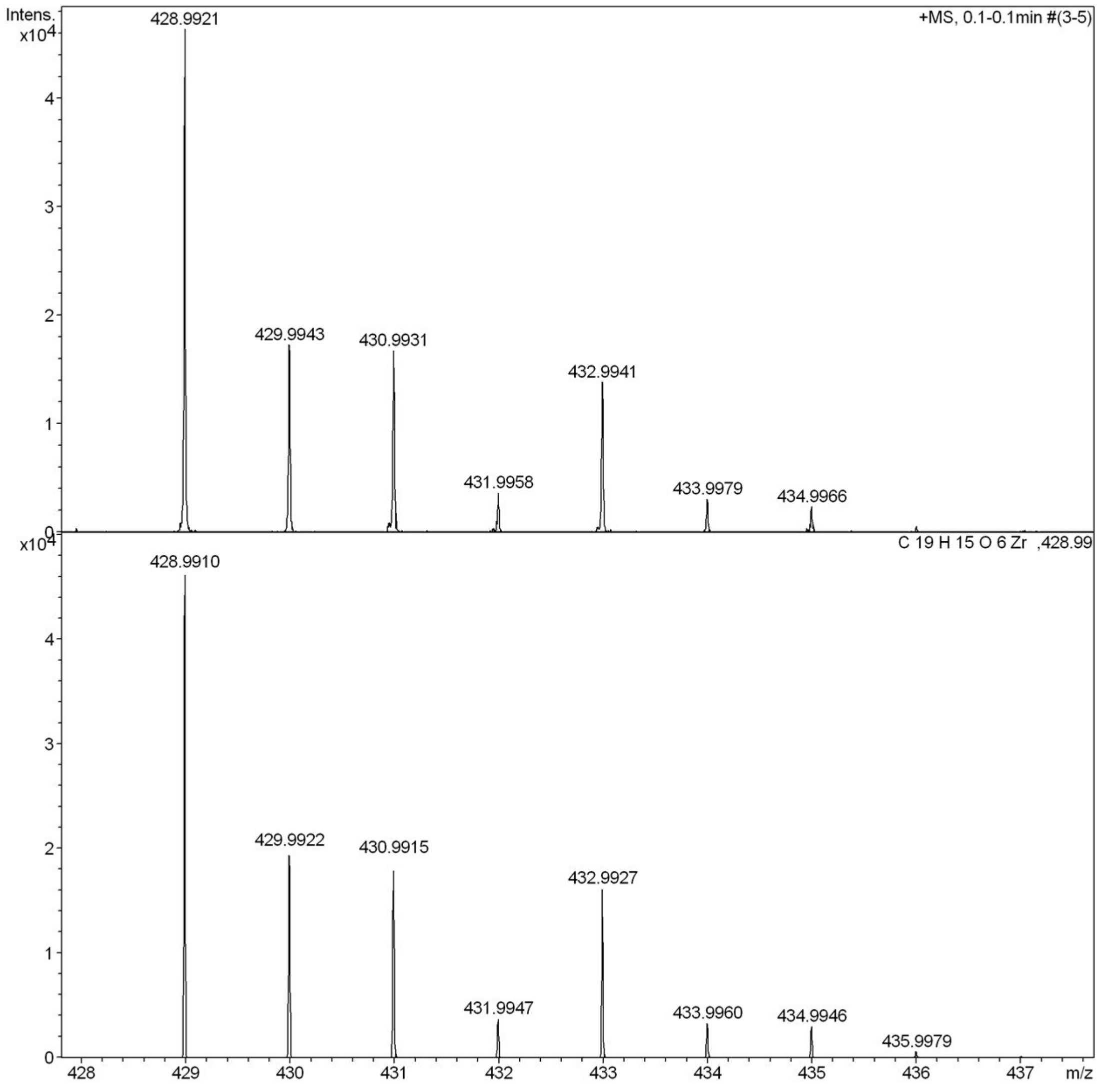
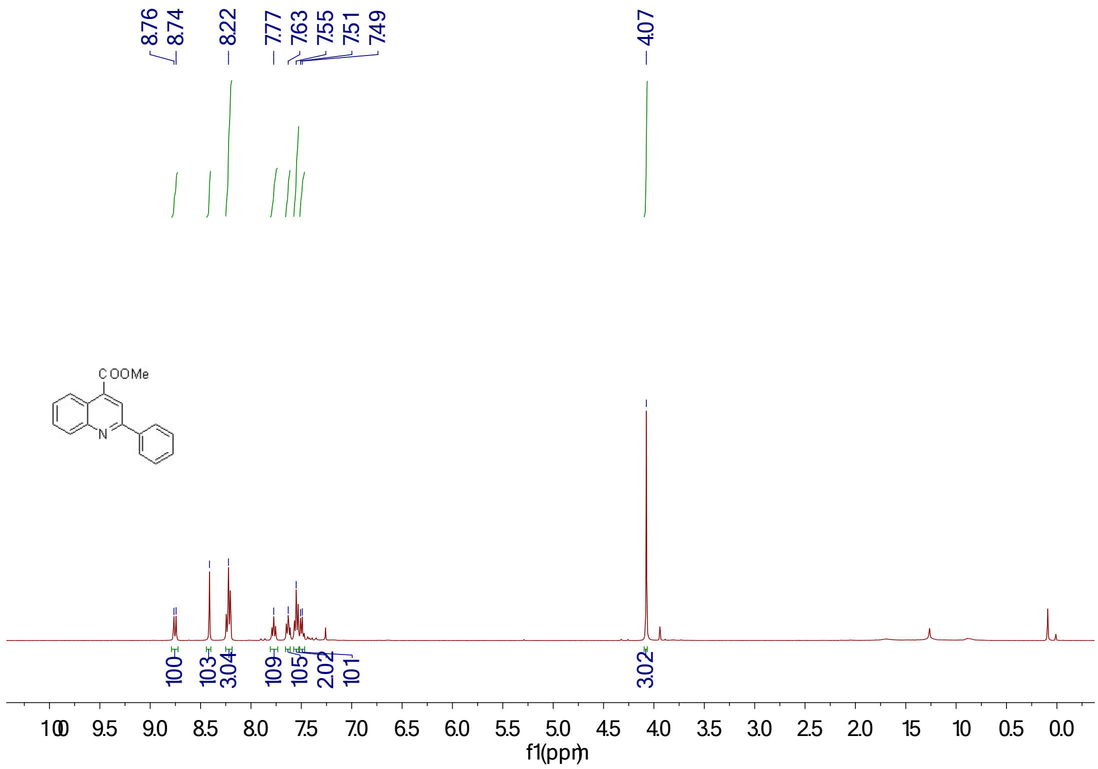


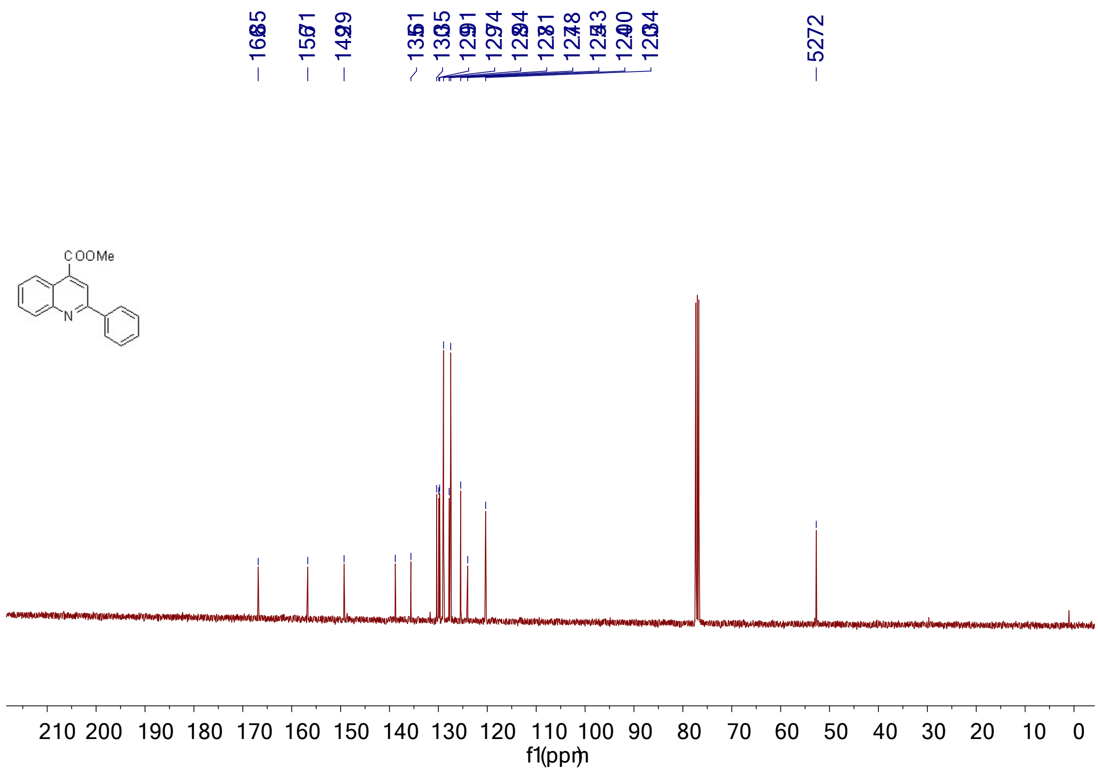
Fig. S6 The HRMS of trimellitic acid and Cp_2ZrCl_2

6. ^{1}H NMR and ^{13}C NMR Spectra for All Compounds:

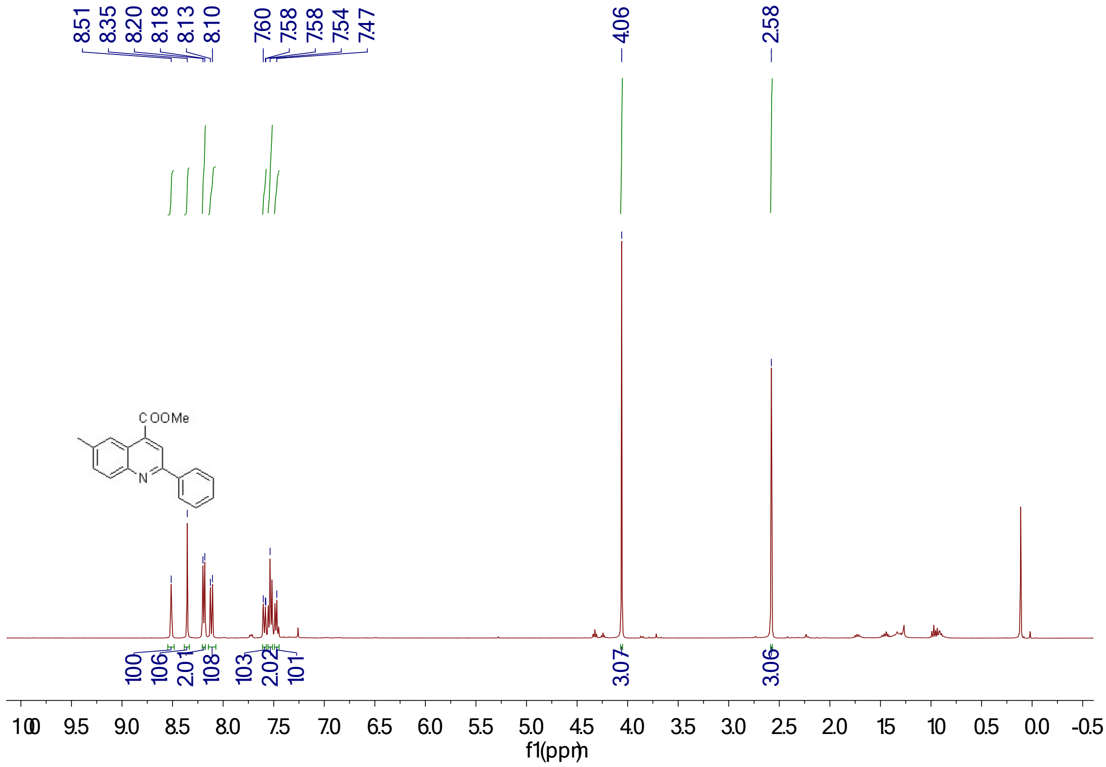
4aa ^{1}HNMR spectrum



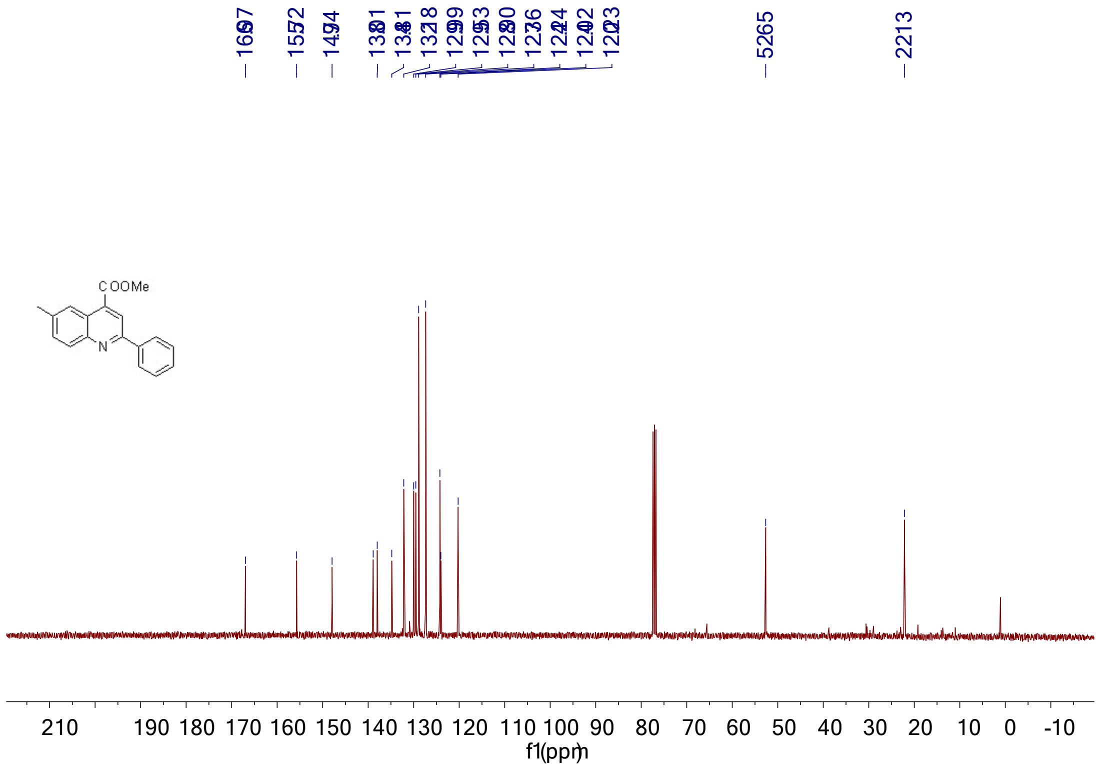
4aa ^{13}C NMR spectrum



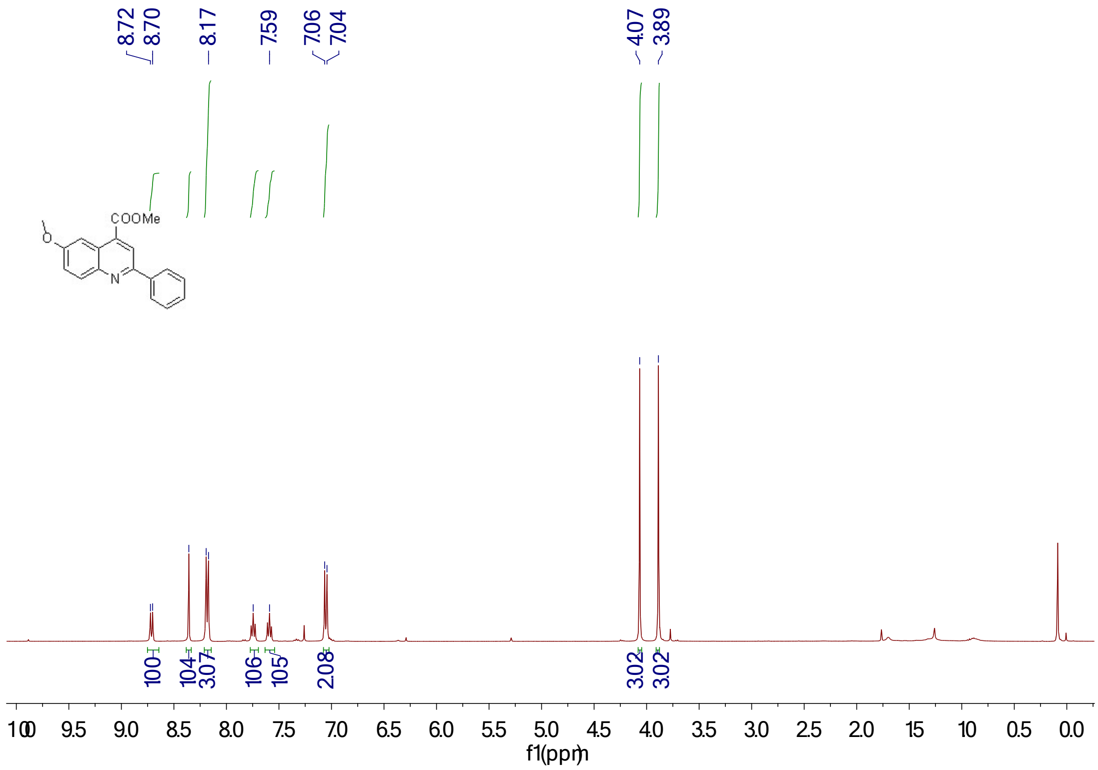
4ab ^{1}HNMR spectrum



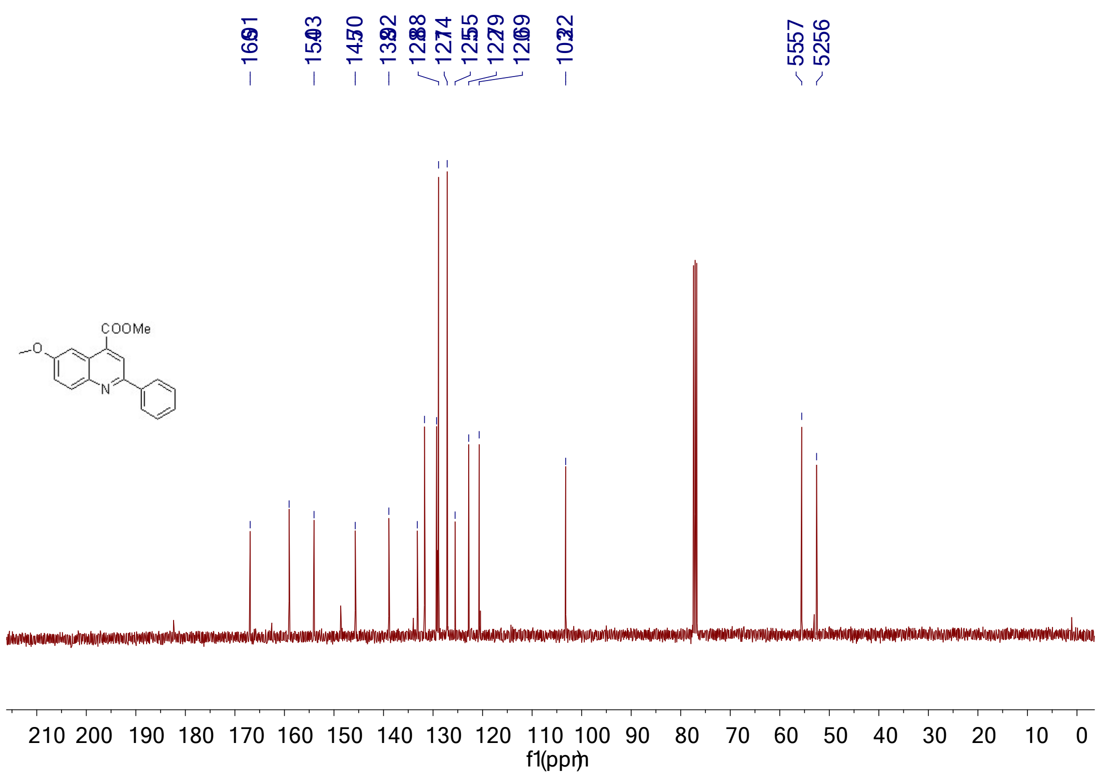
4ab ^{13}C NMR spectrum



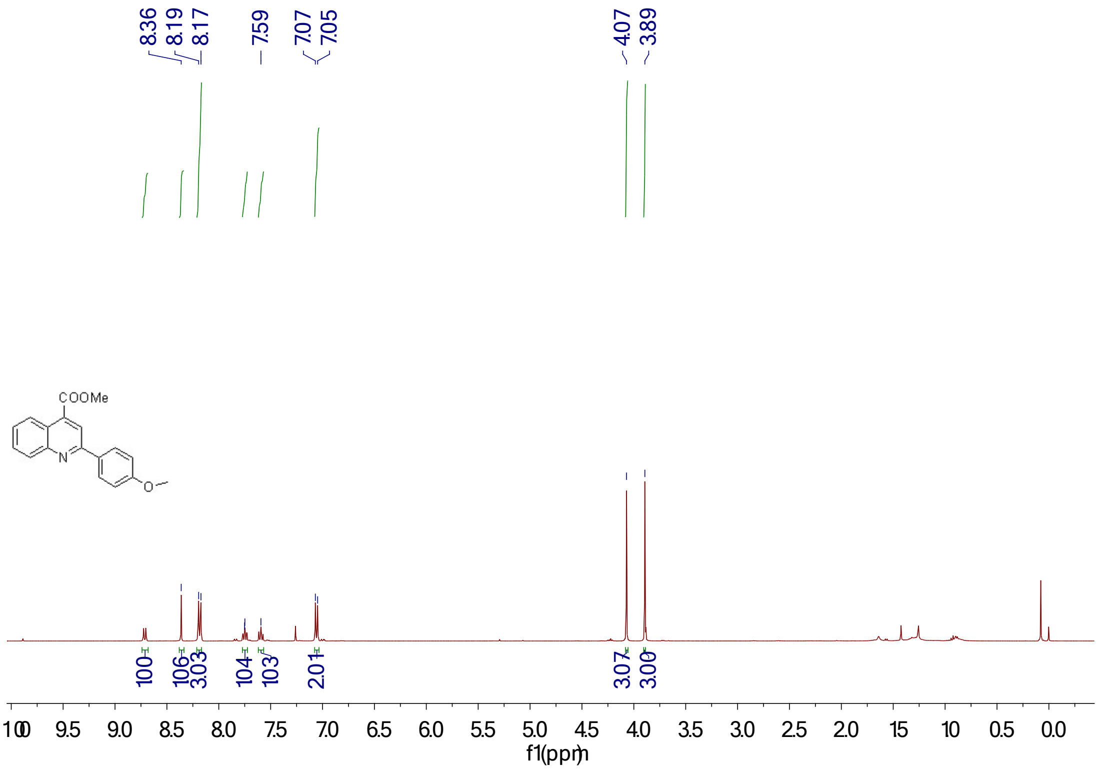
4ac ^{1}HNMR spectrum



4ac ^{13}C NMR spectrum



4ad ^{1}HNMR spectrum



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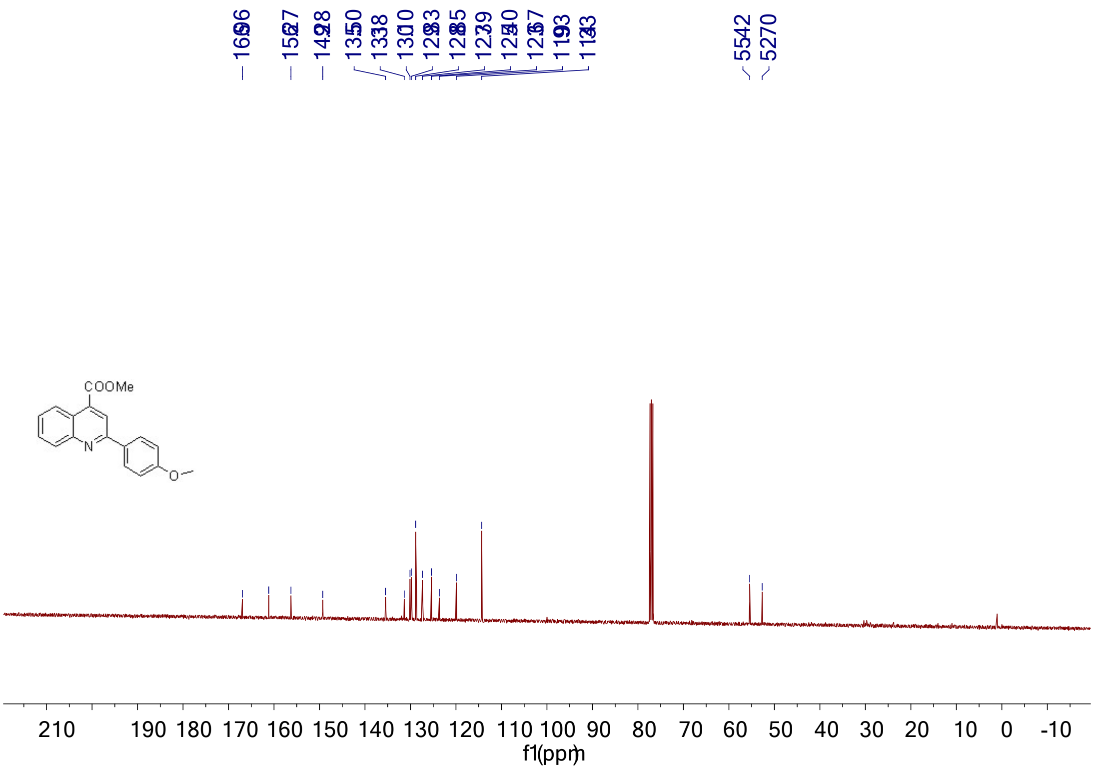
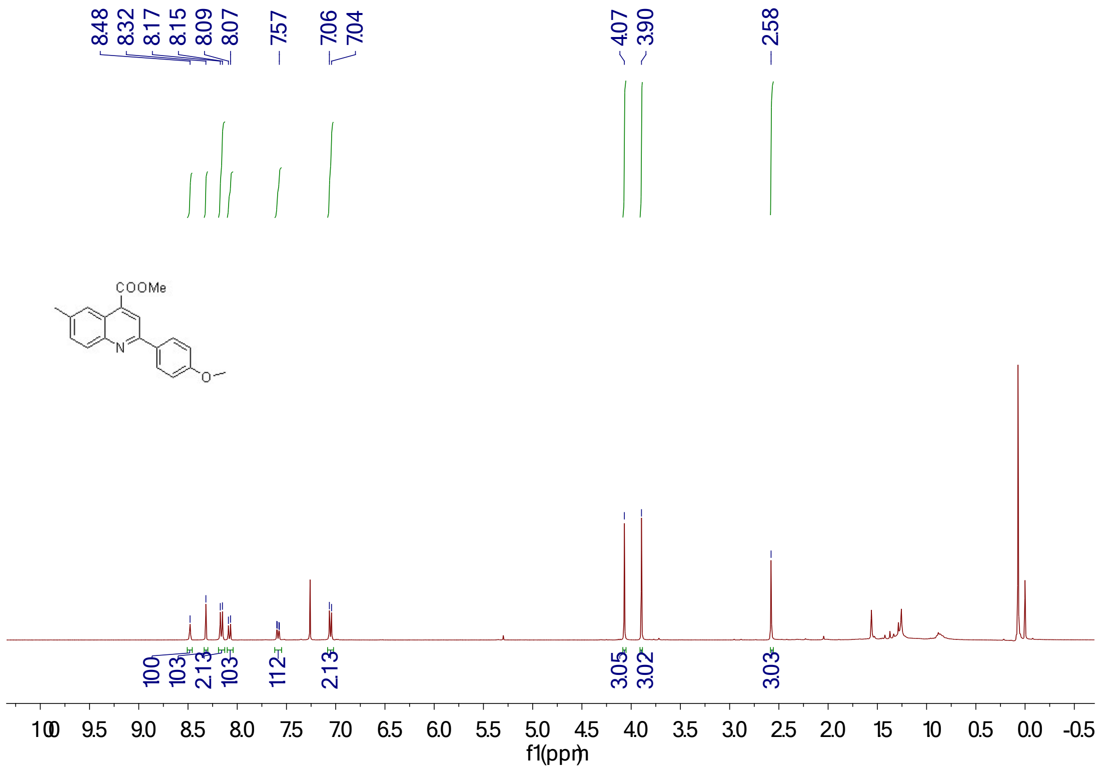


4ae ^{1}HNMR spectrum



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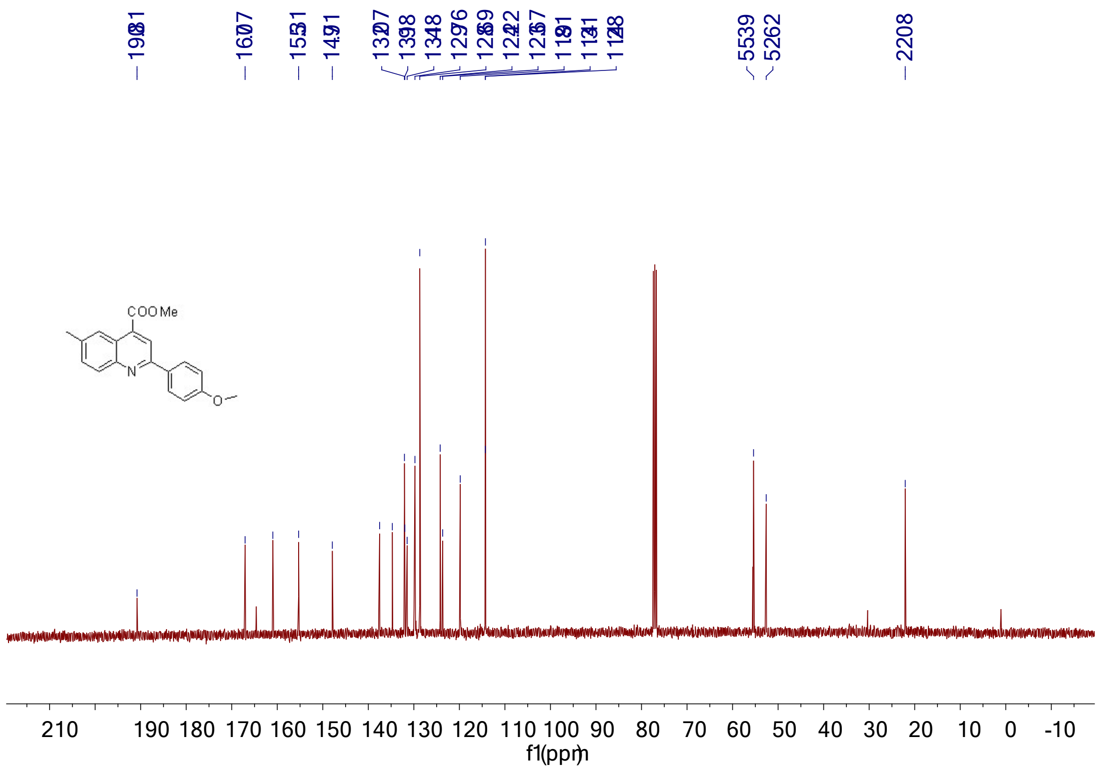

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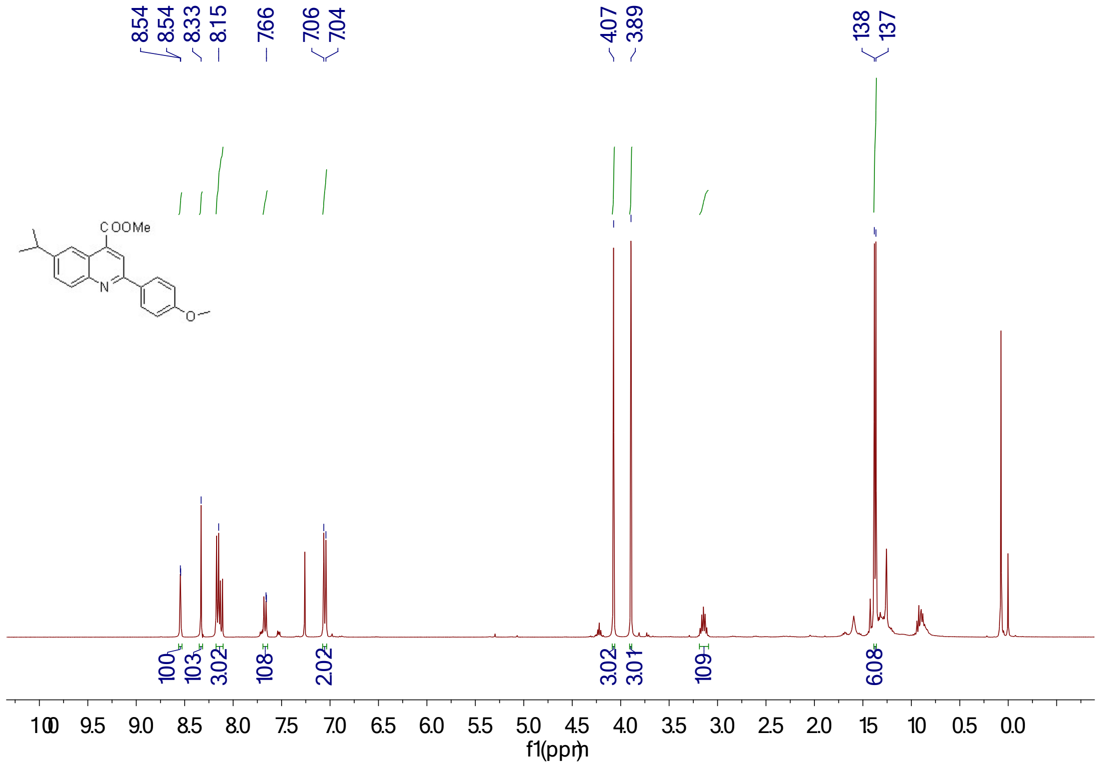

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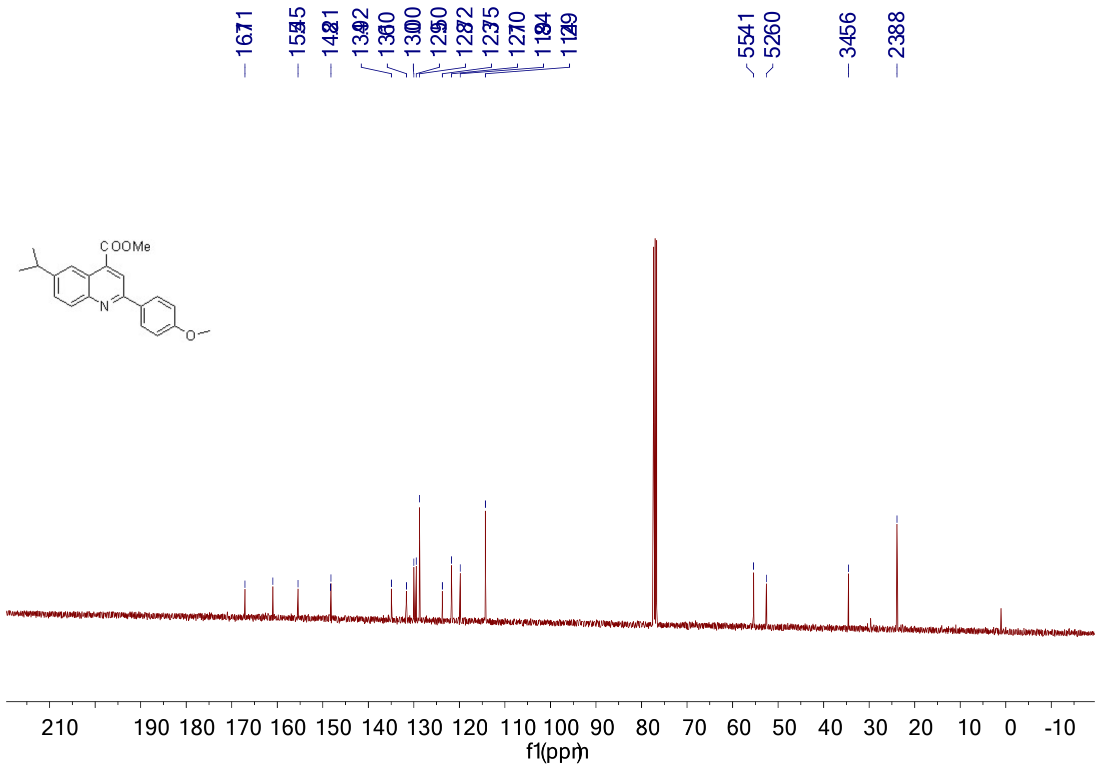

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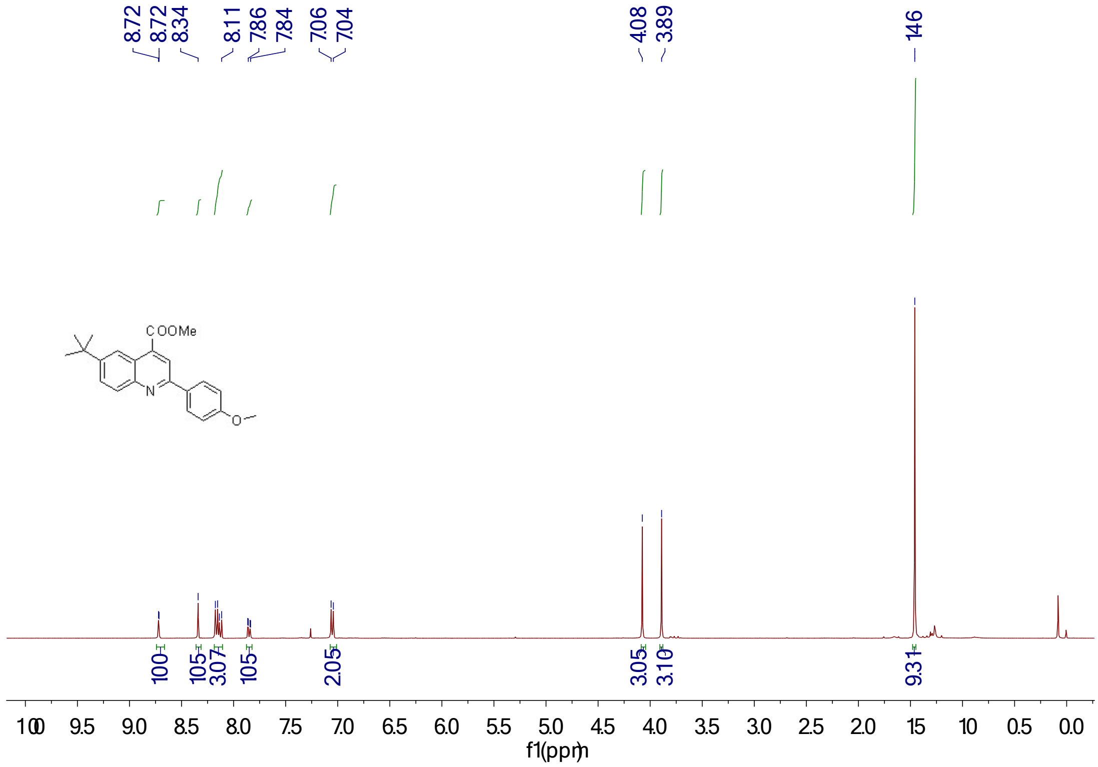

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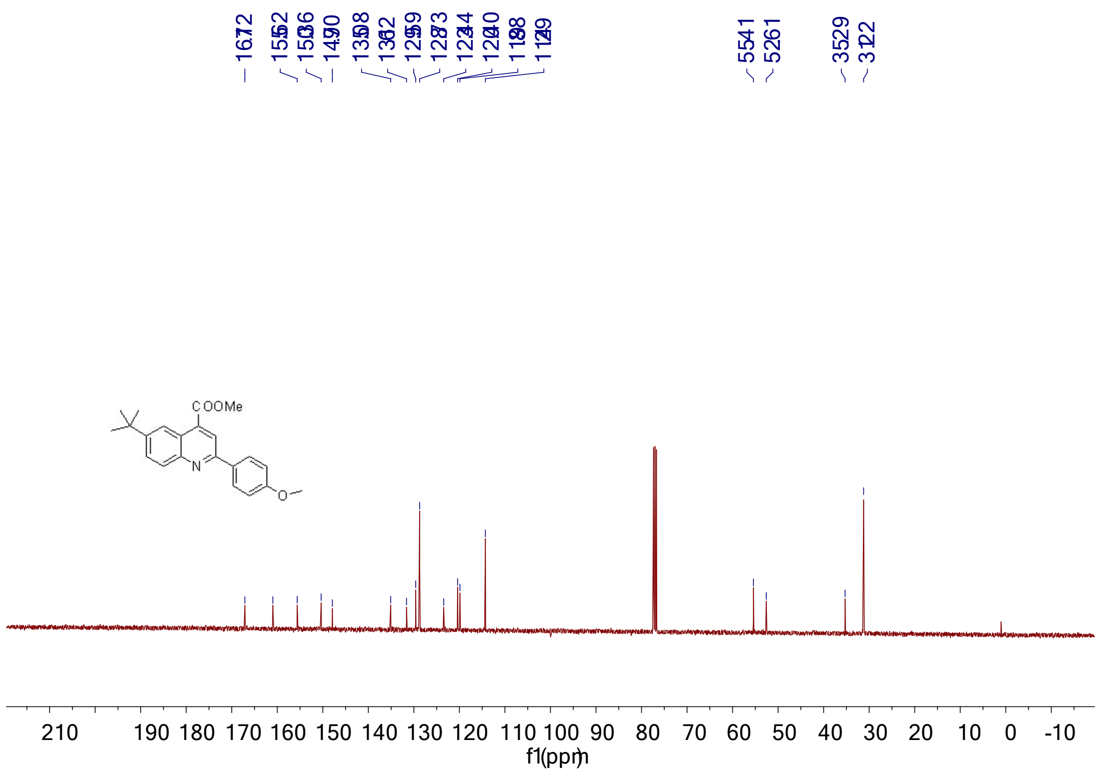

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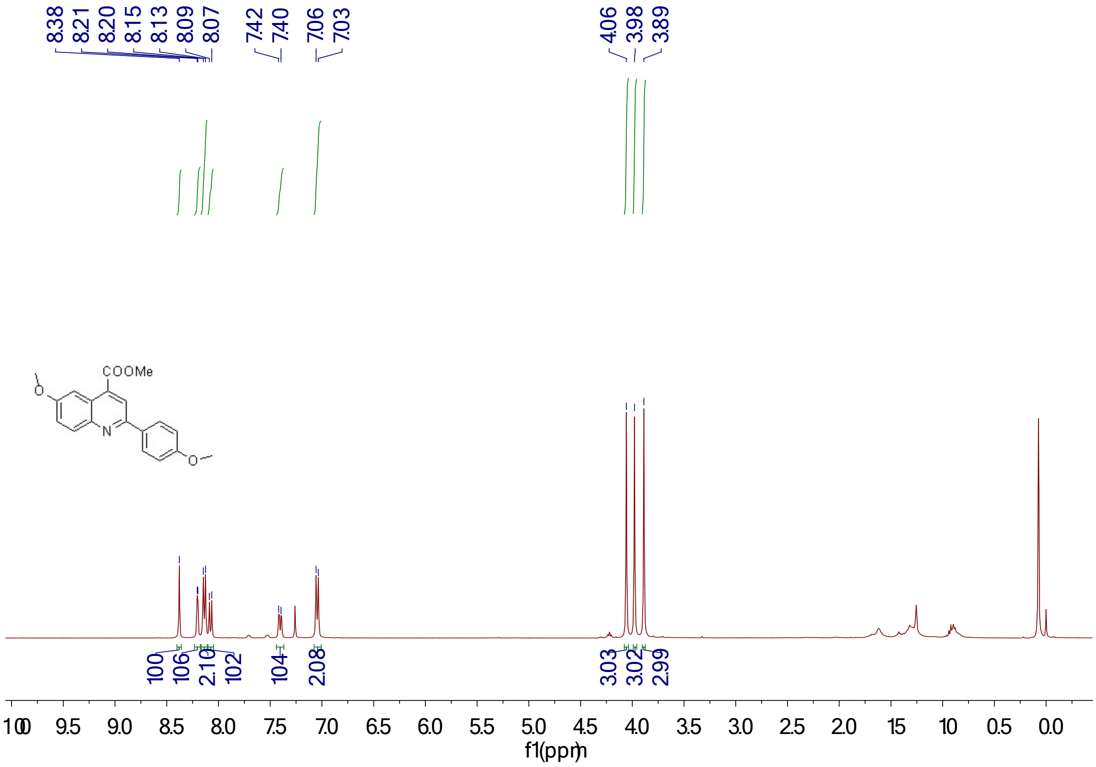

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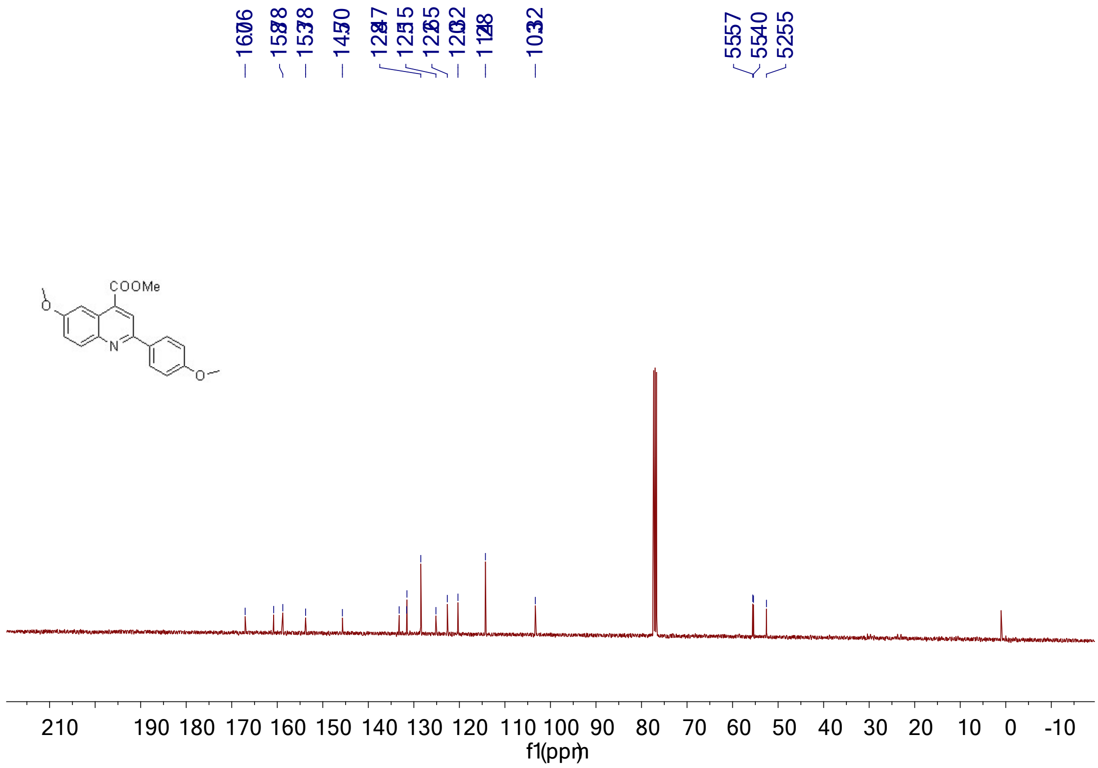

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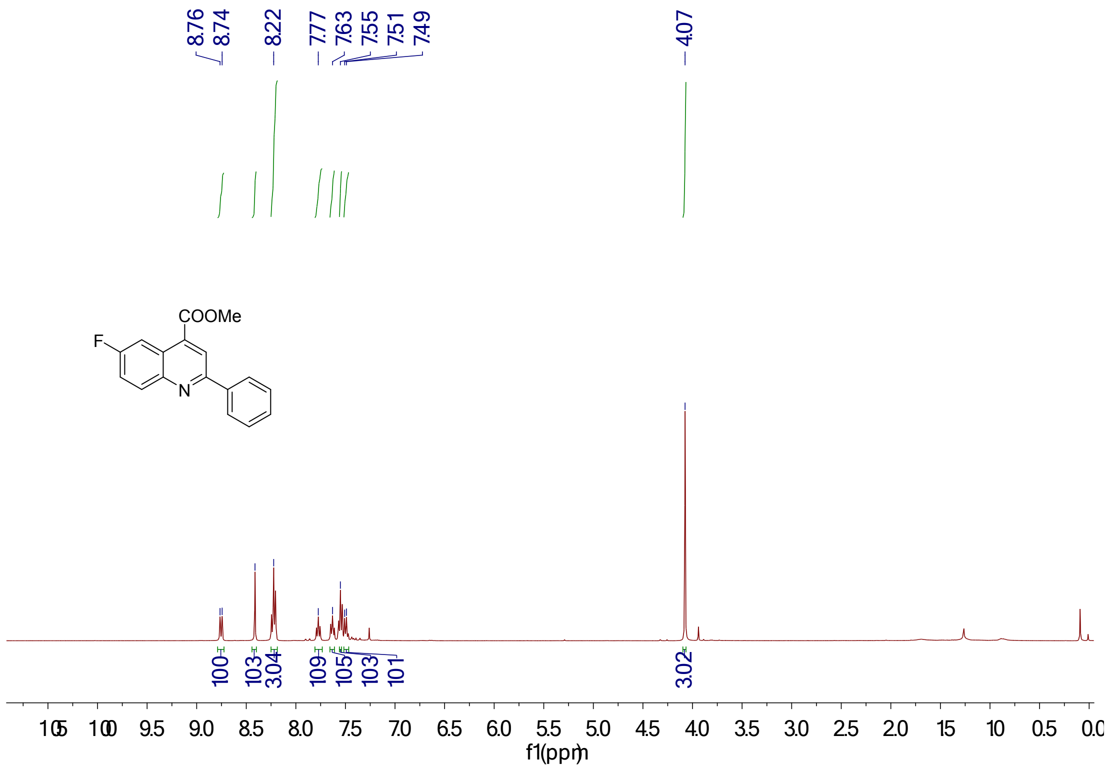

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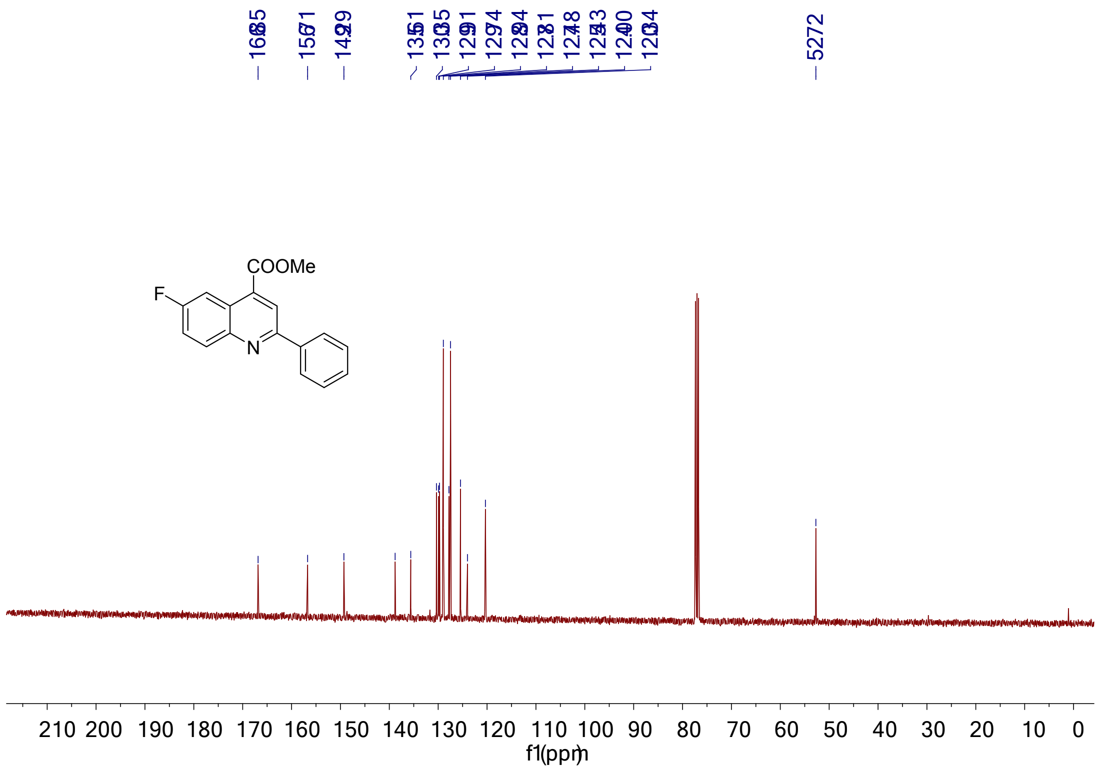
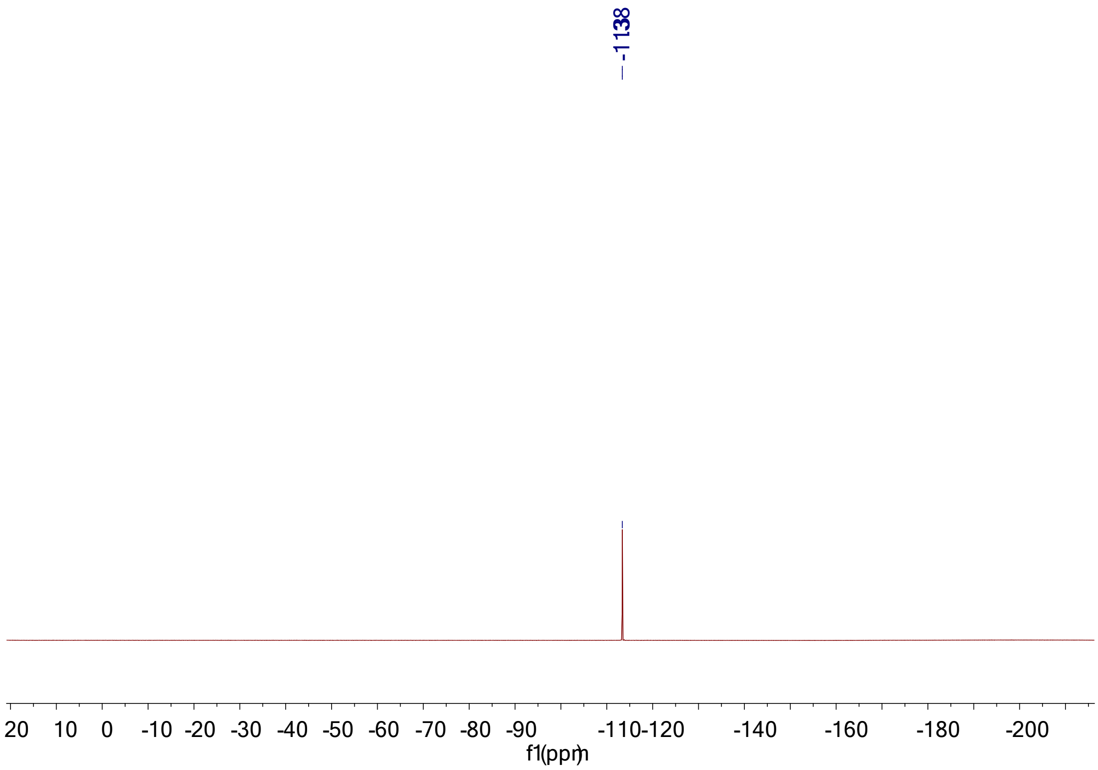


4ai ^{19}F NMR spectrum



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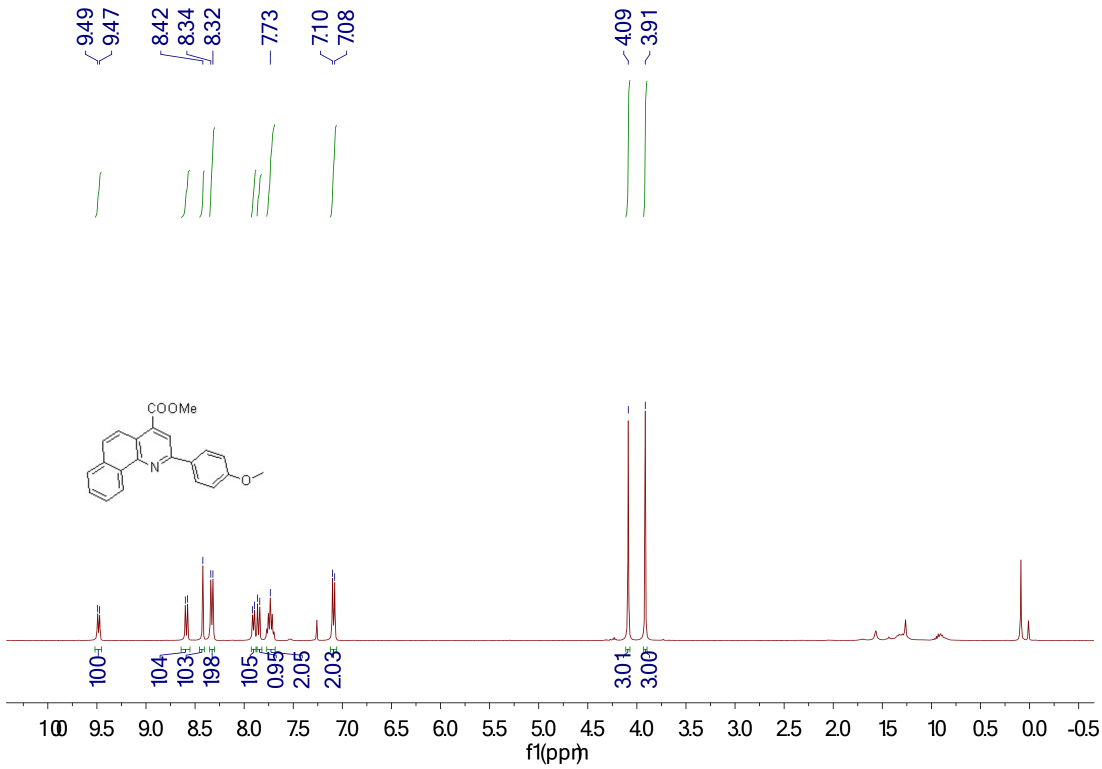

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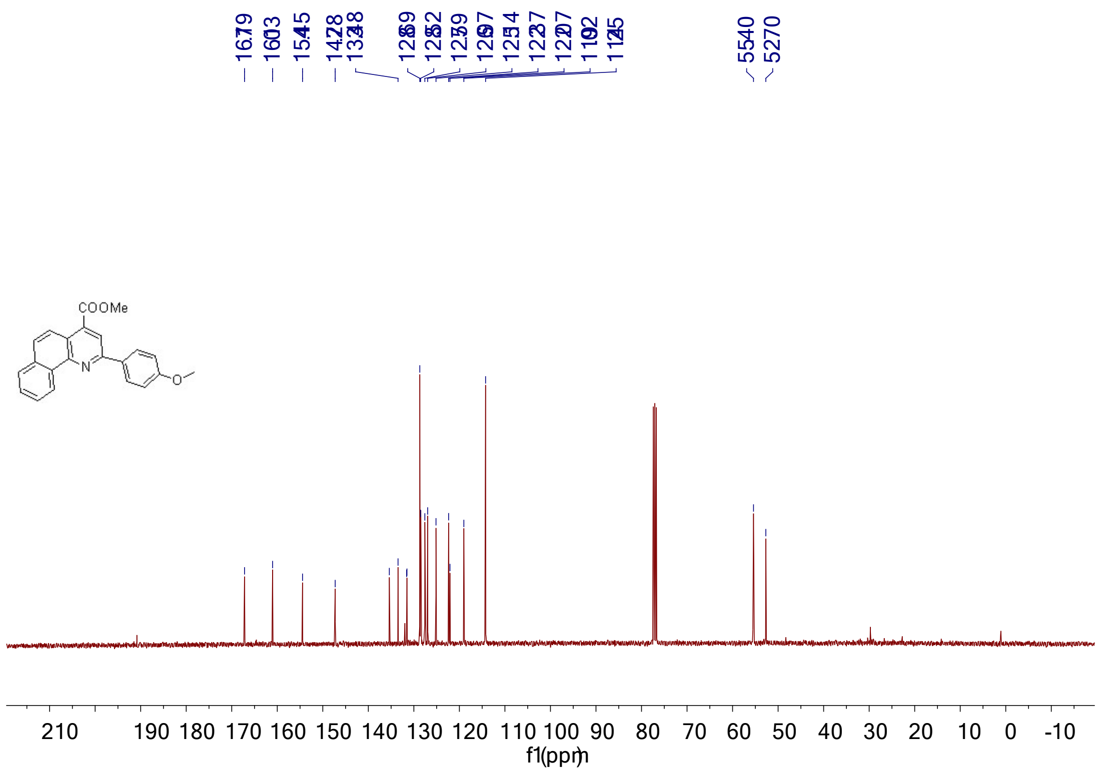

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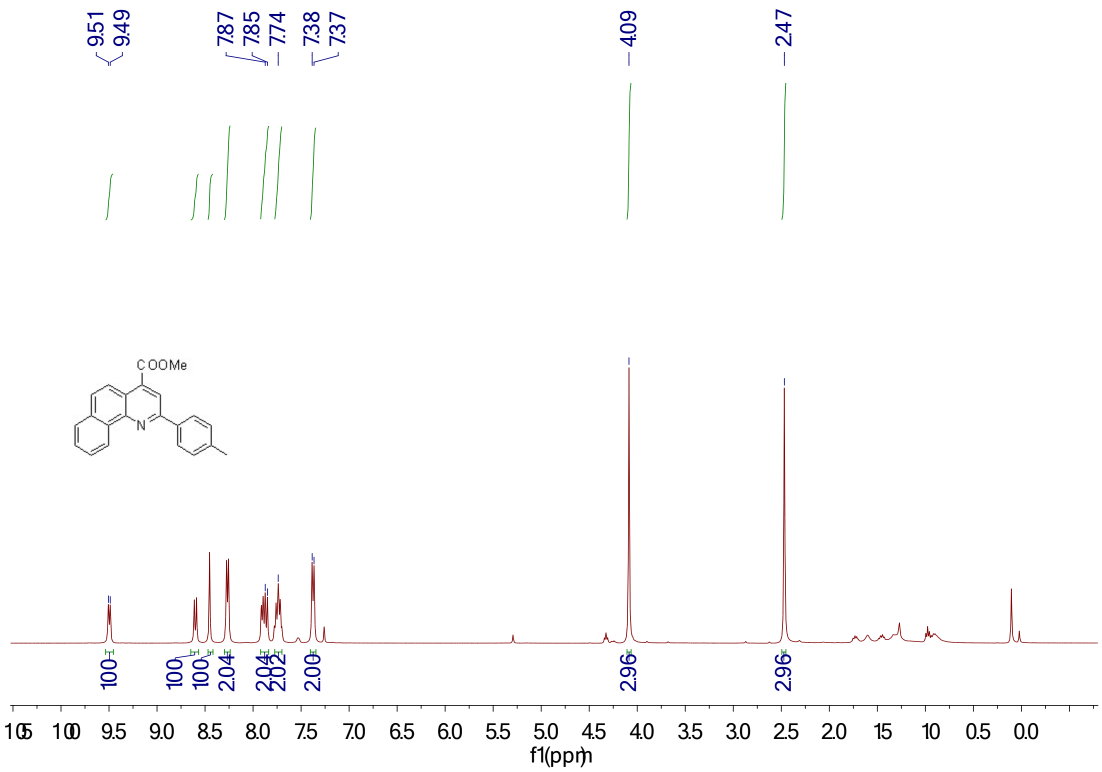

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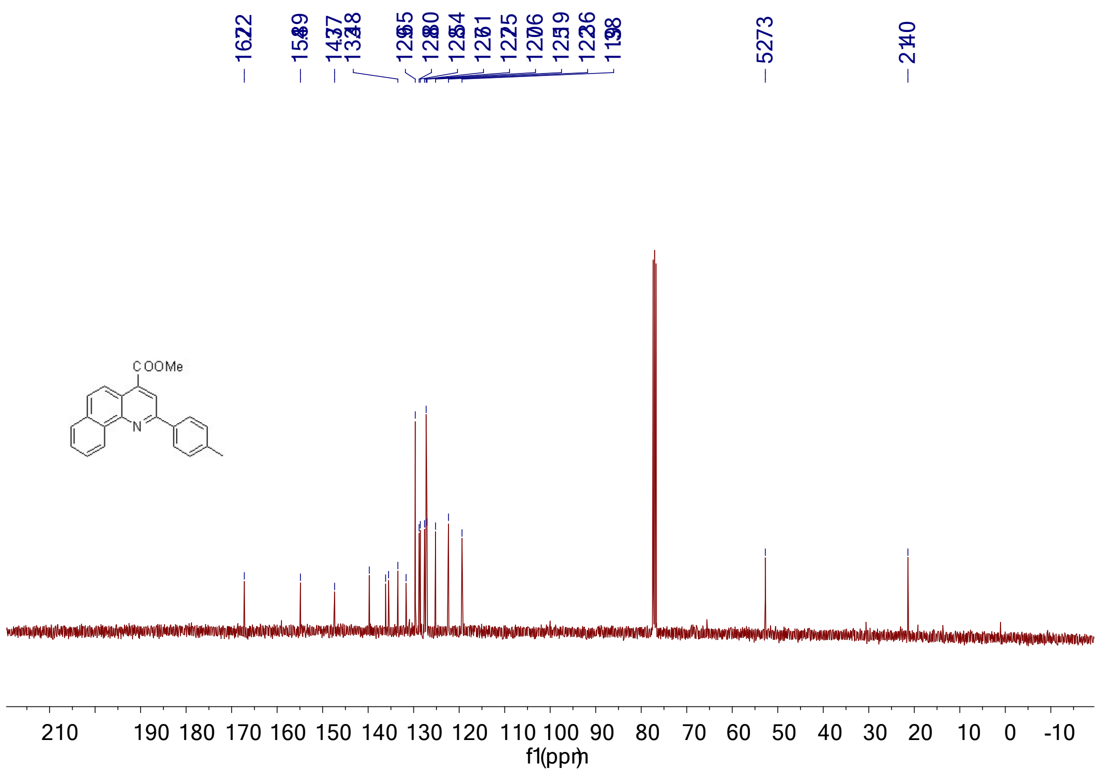

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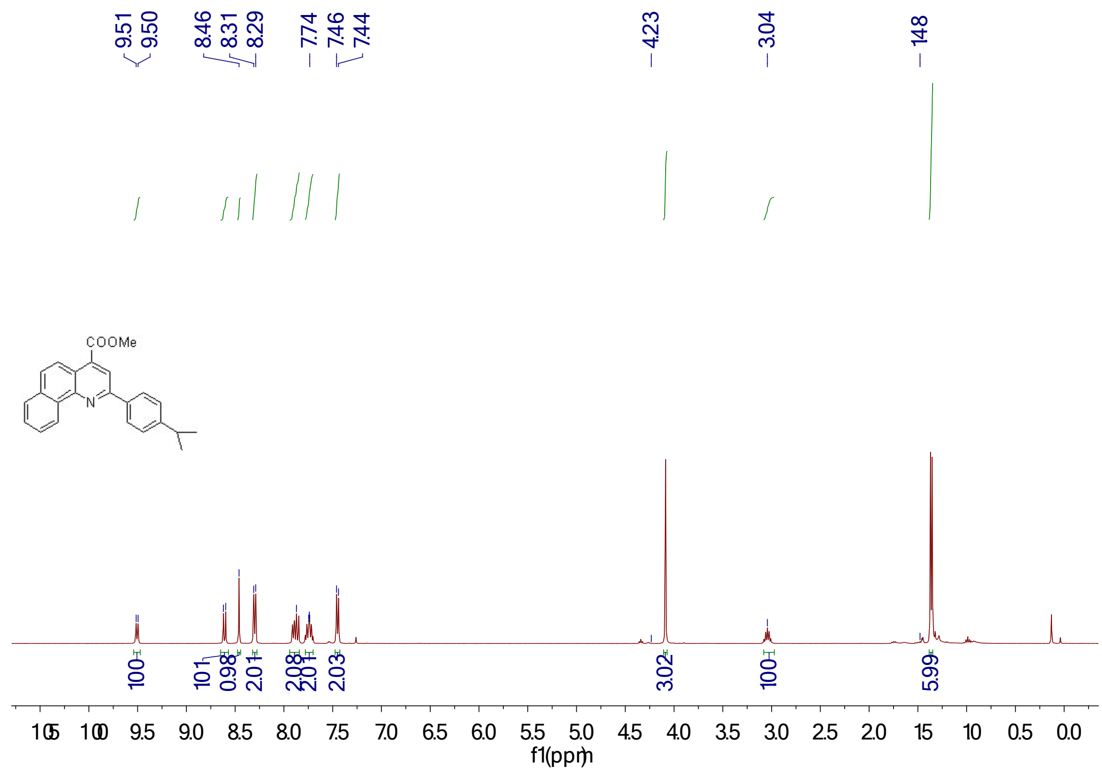

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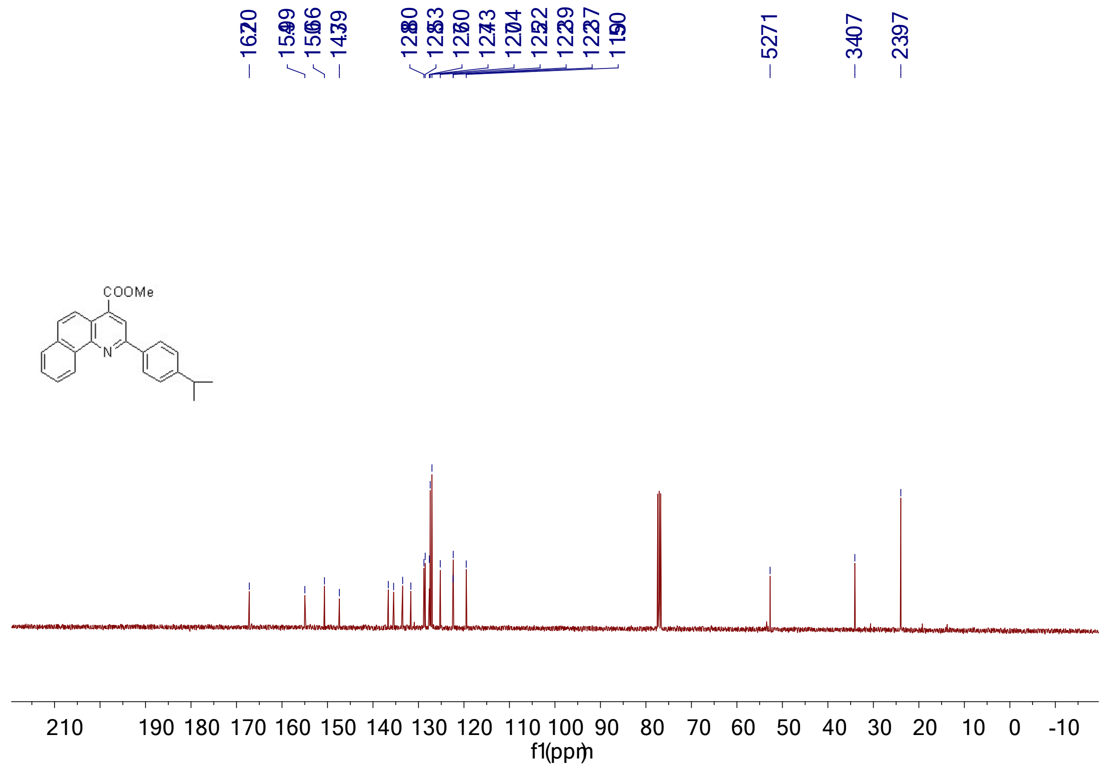

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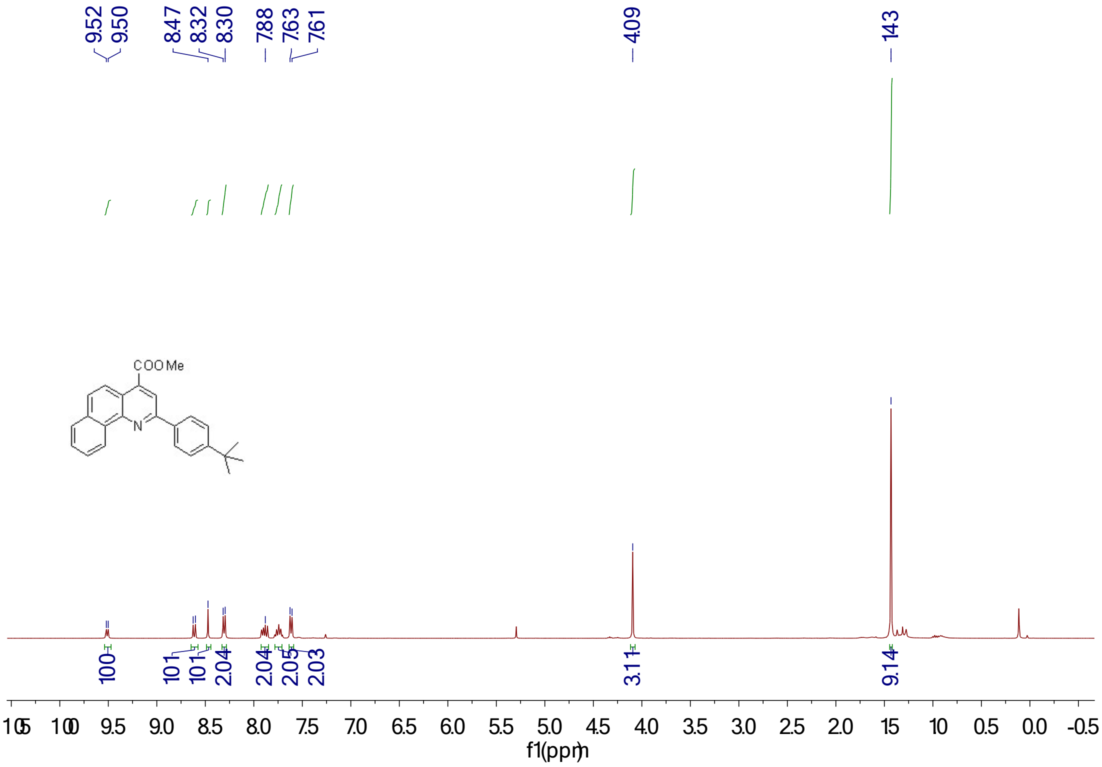
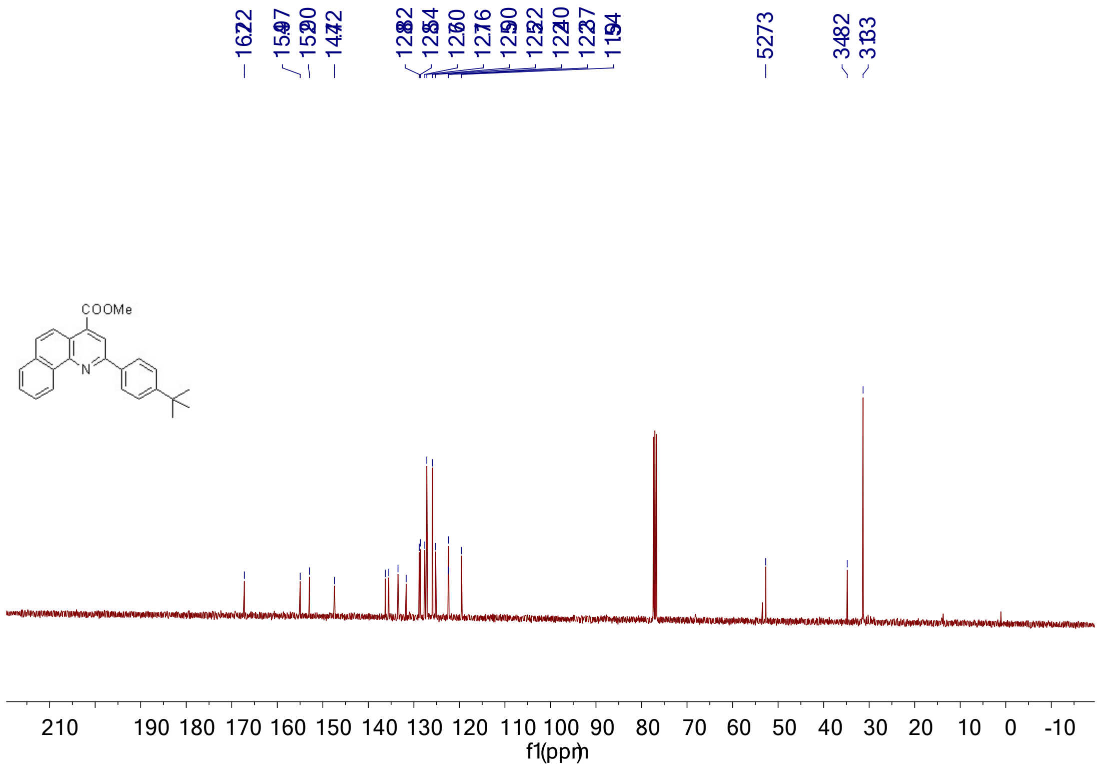
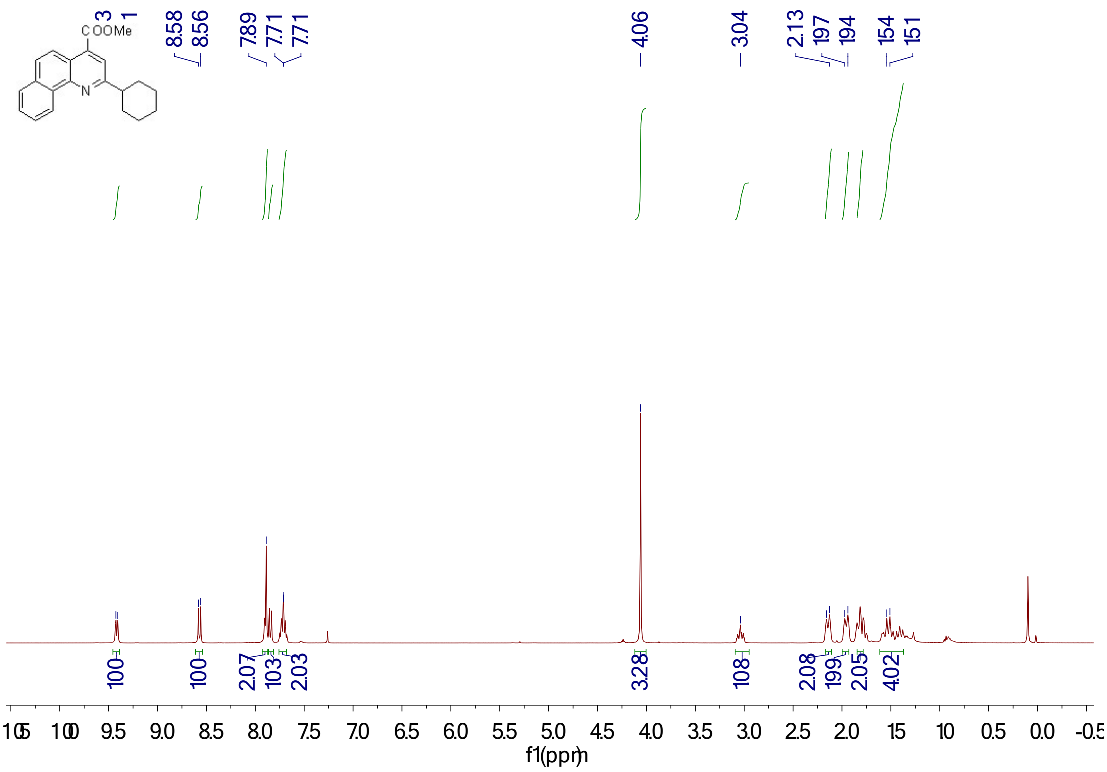


4am ¹³C NMR spectrum



4an ^{1}HNMR spectrum



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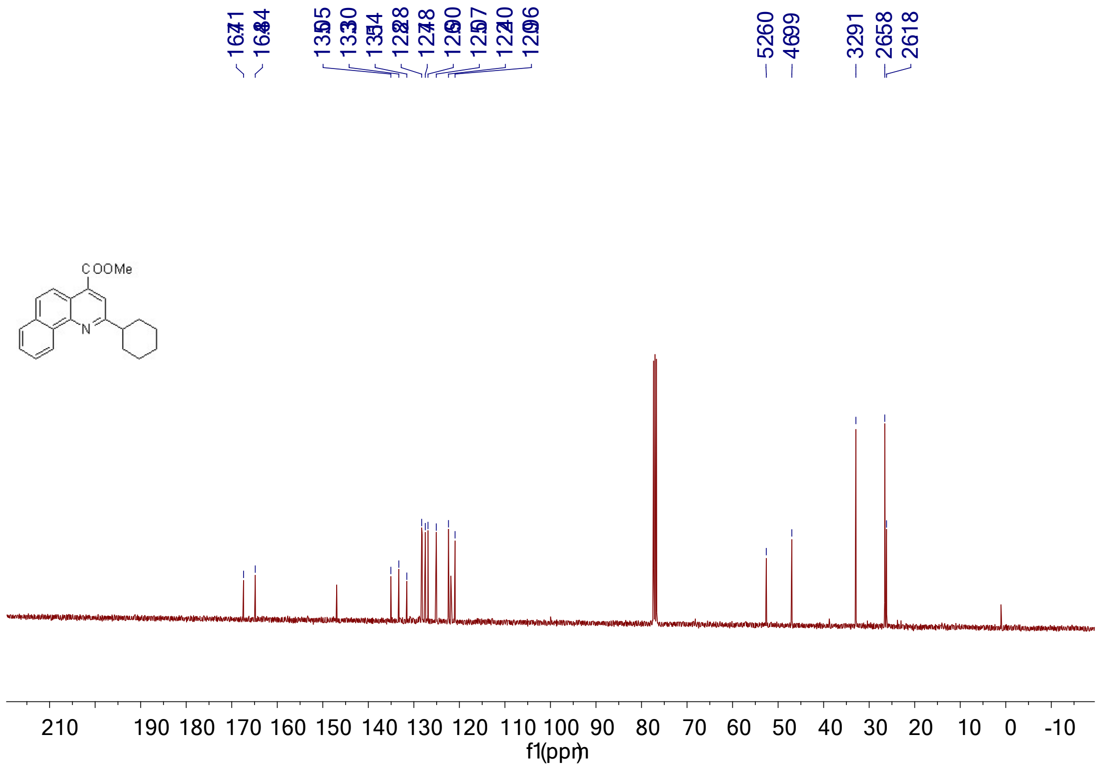

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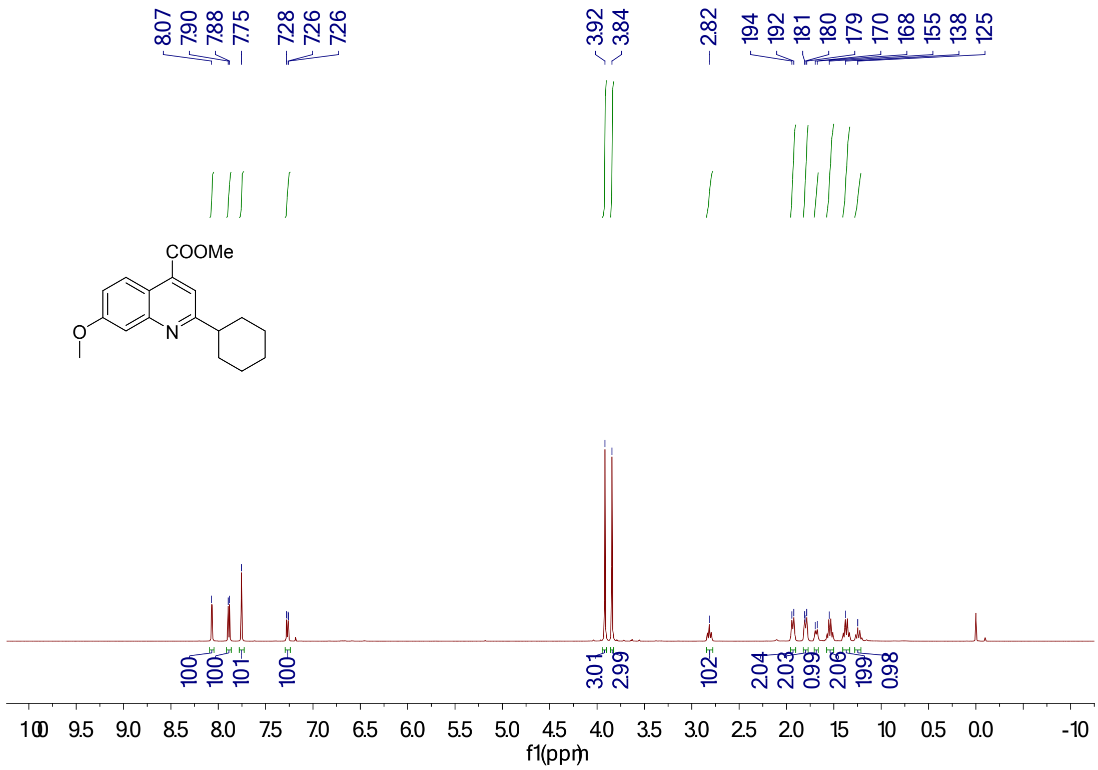

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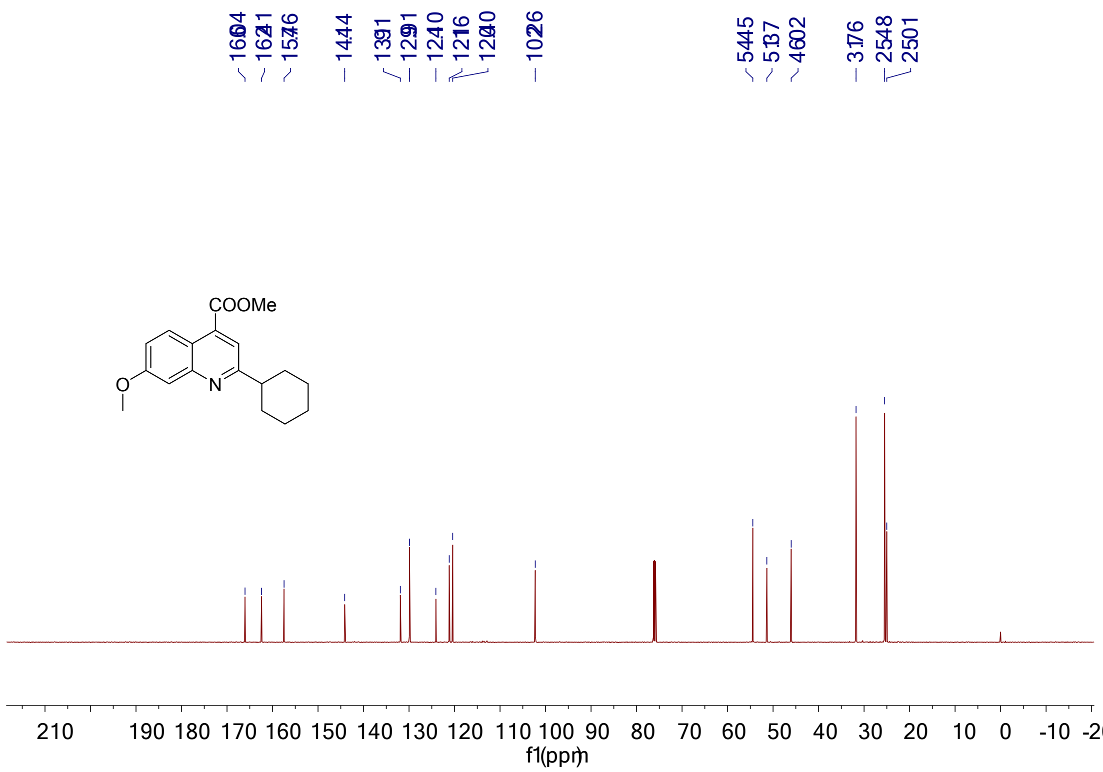

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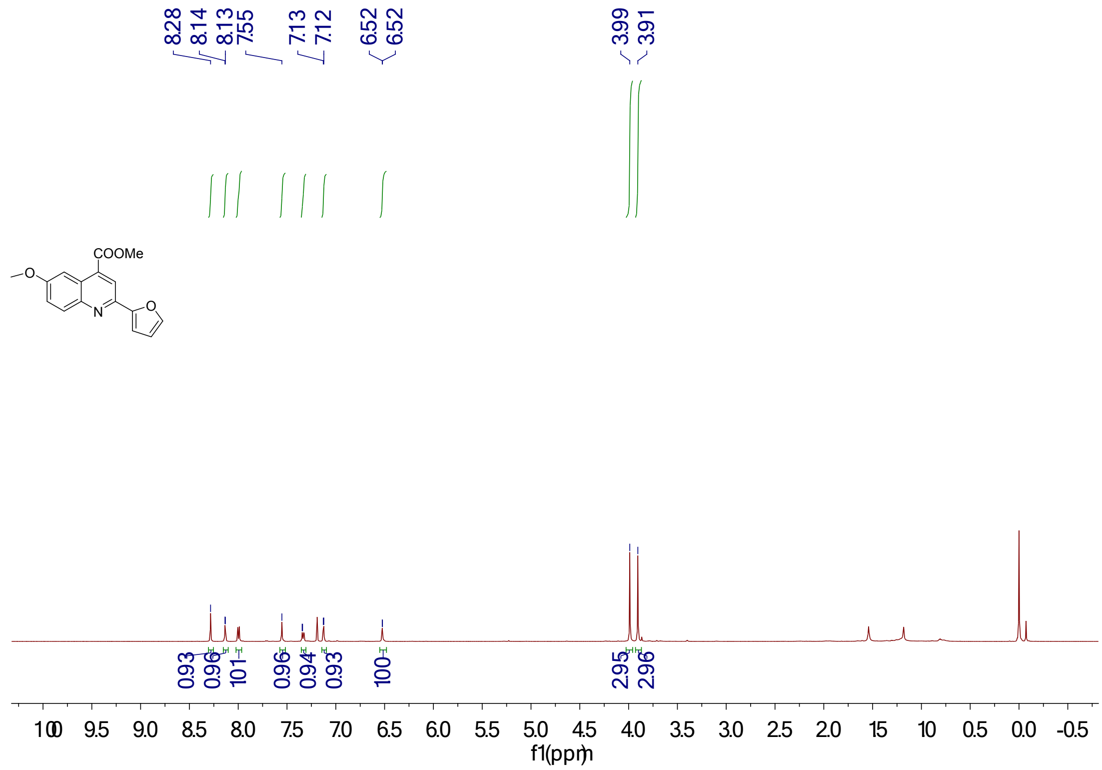

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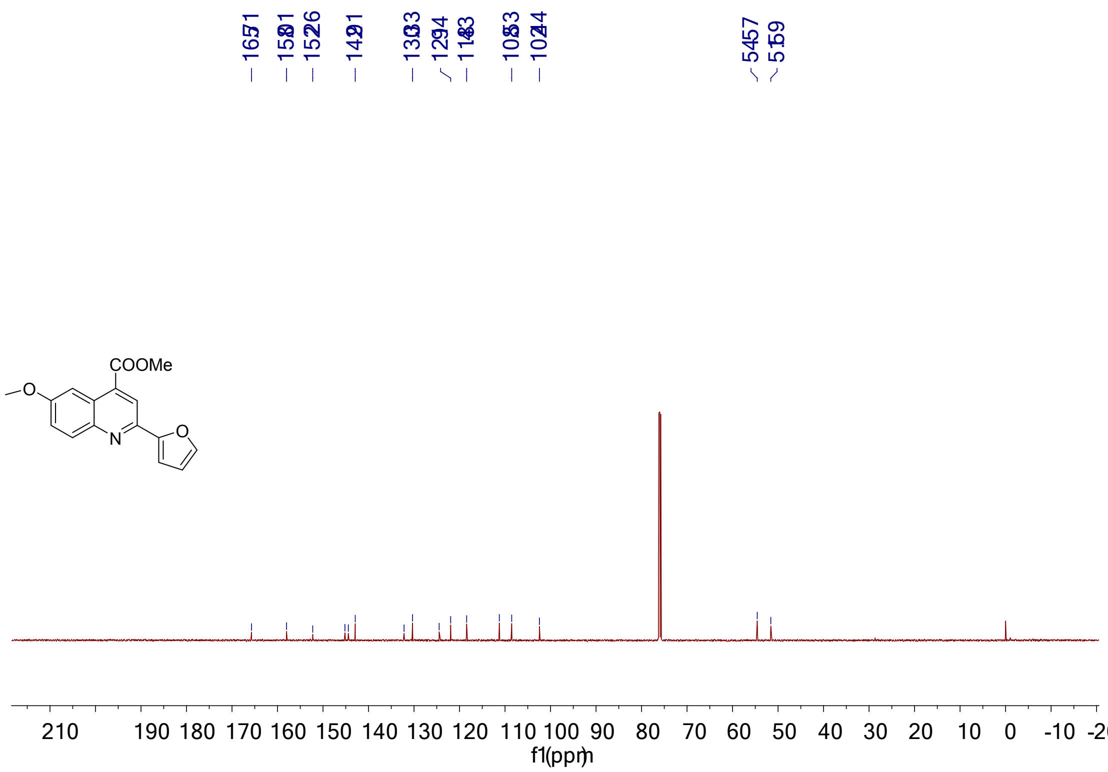

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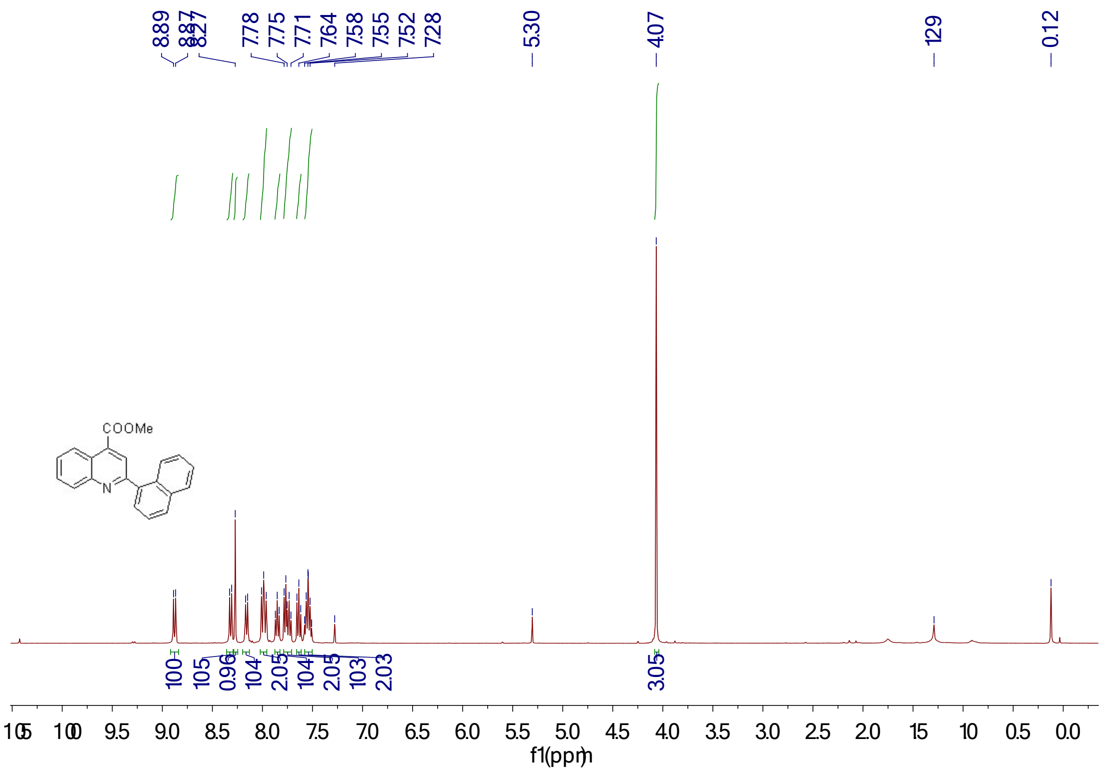

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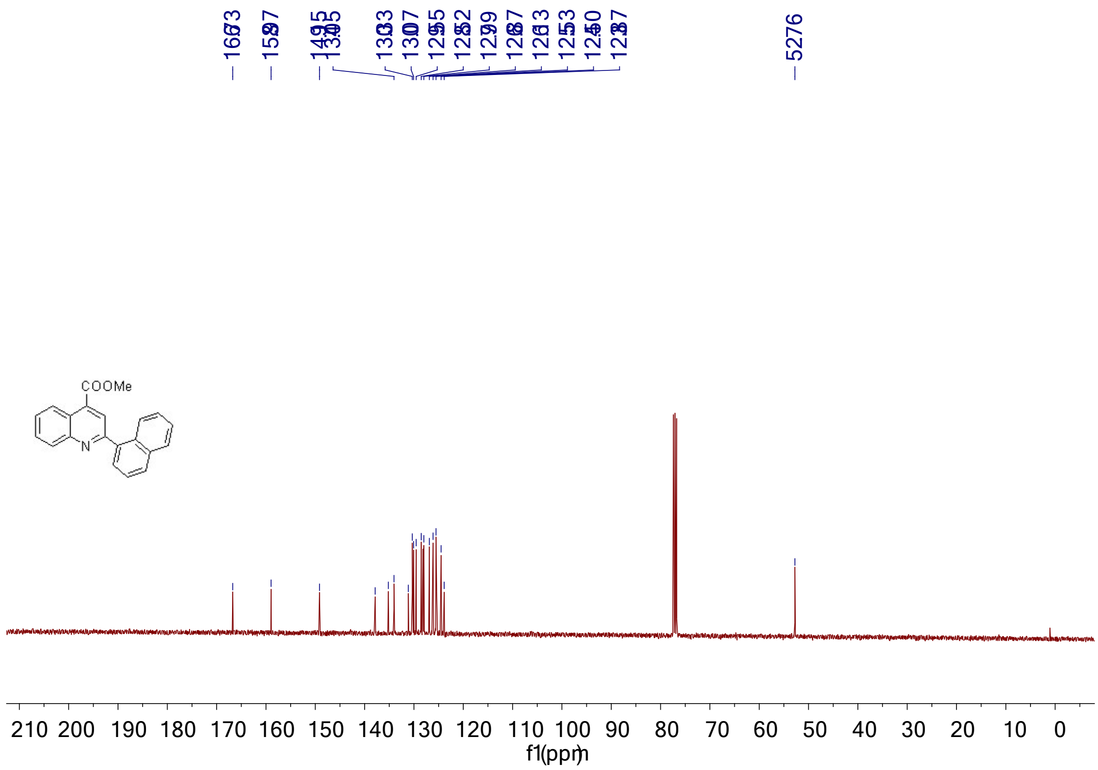
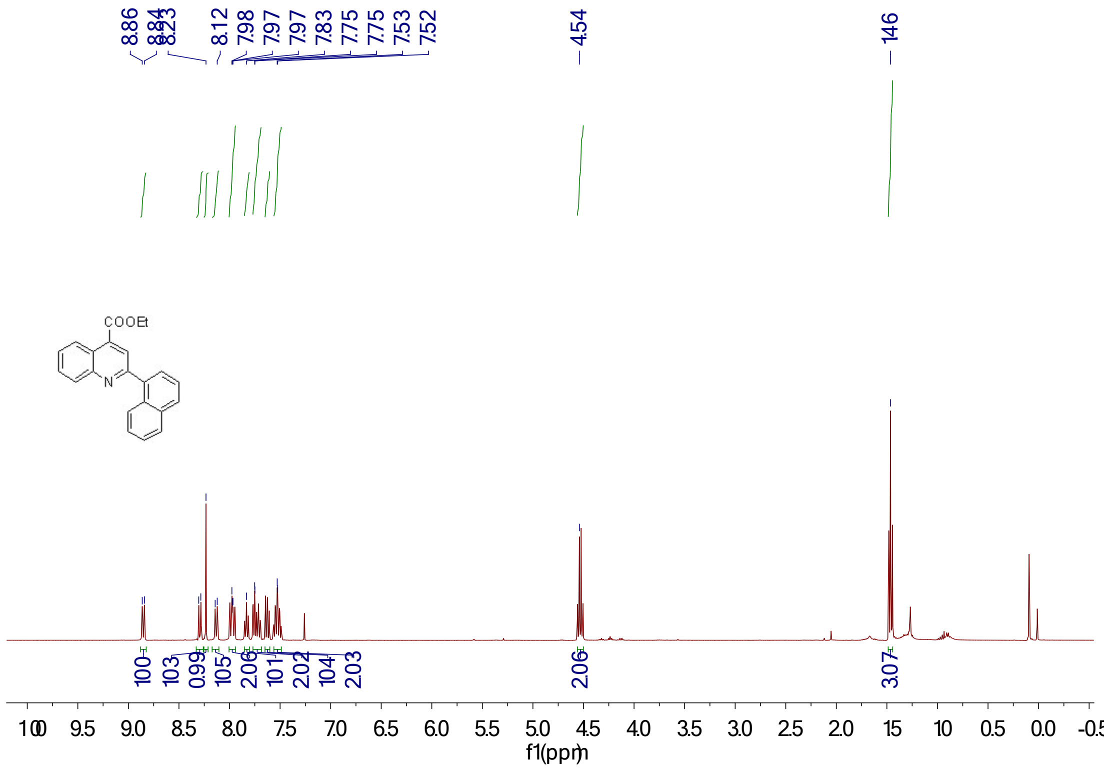
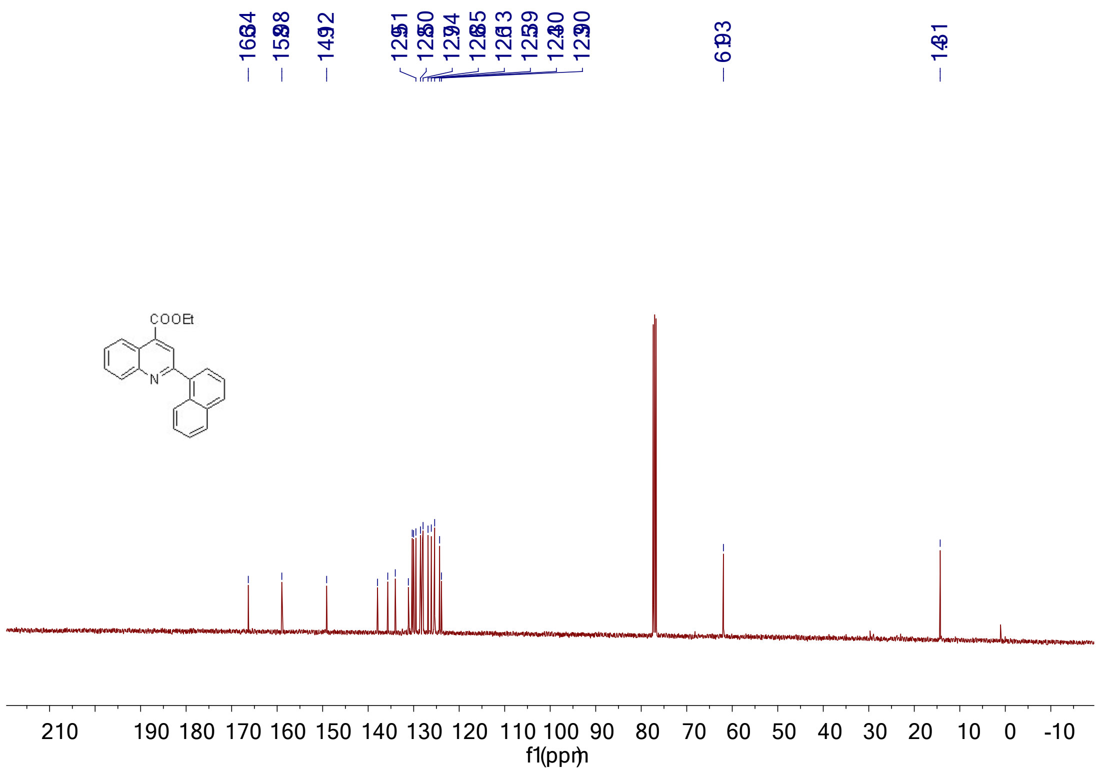


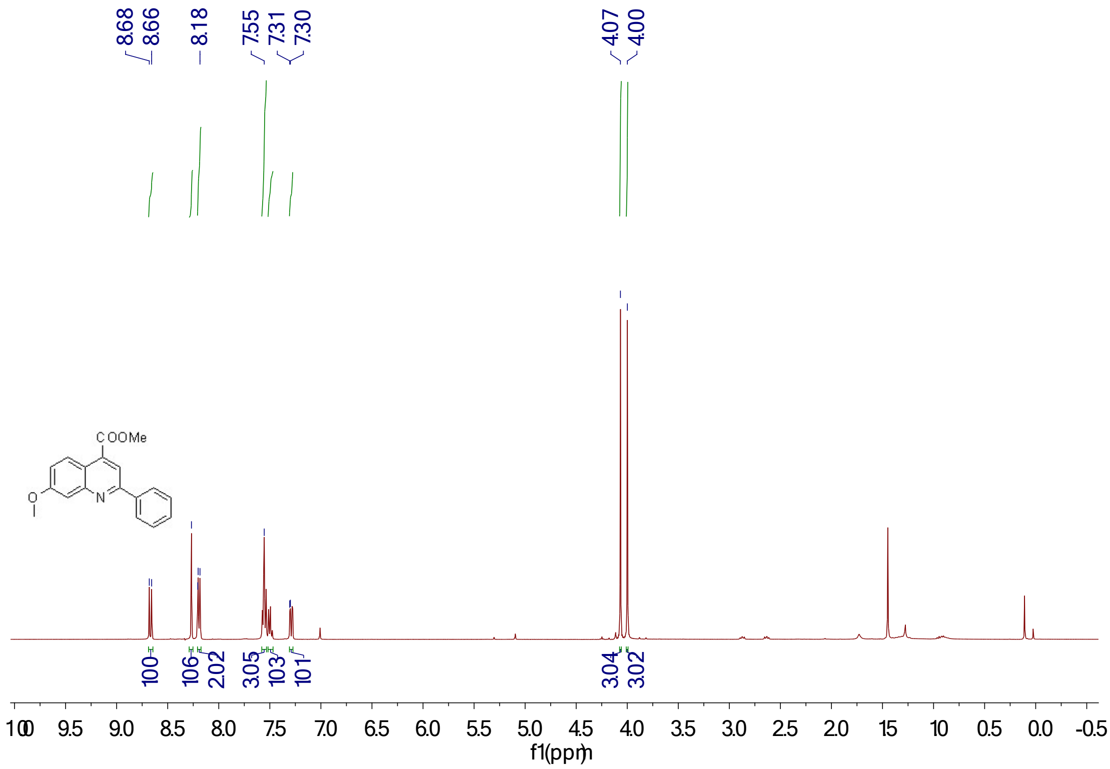
4ar ^{1}HNMR spectrum



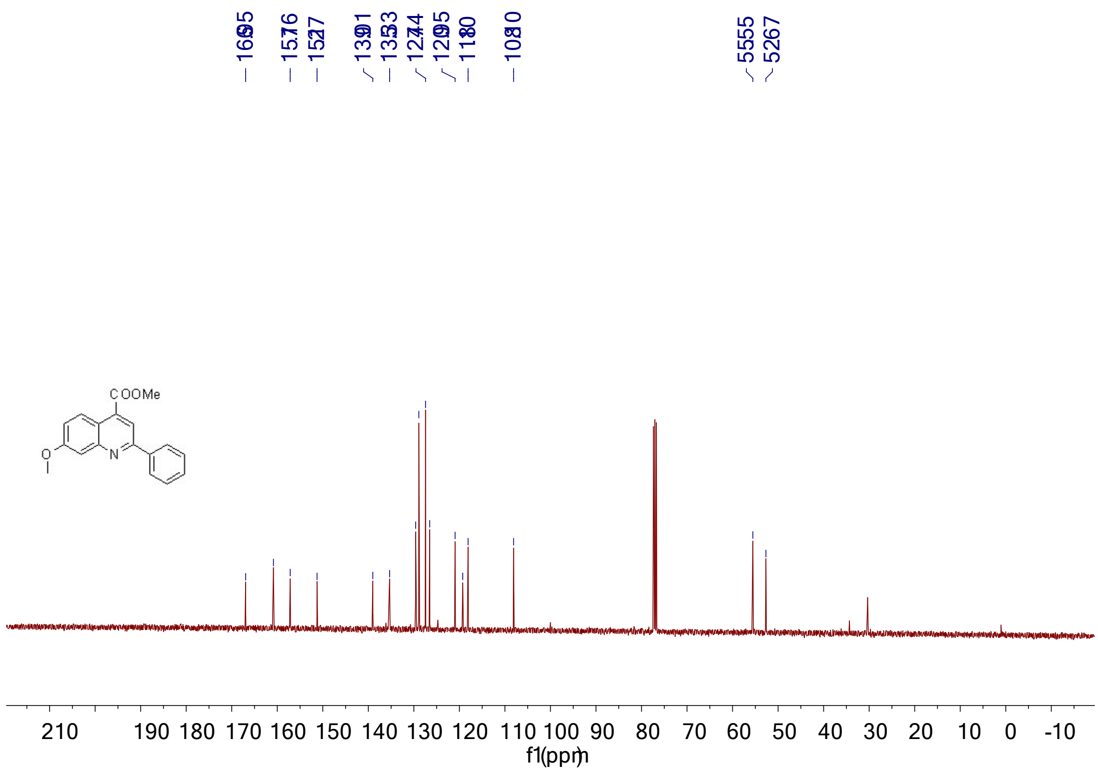
4ar ^{13}C NMR spectrum



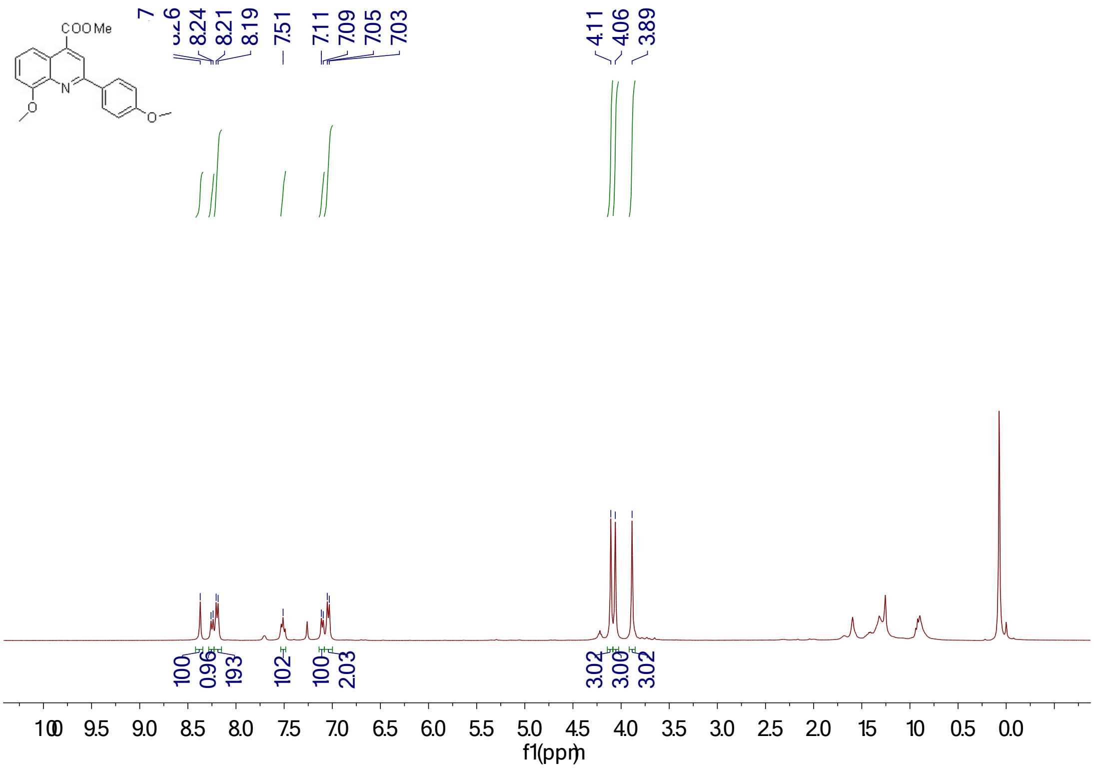
4as ^{1}HNMR spectrum



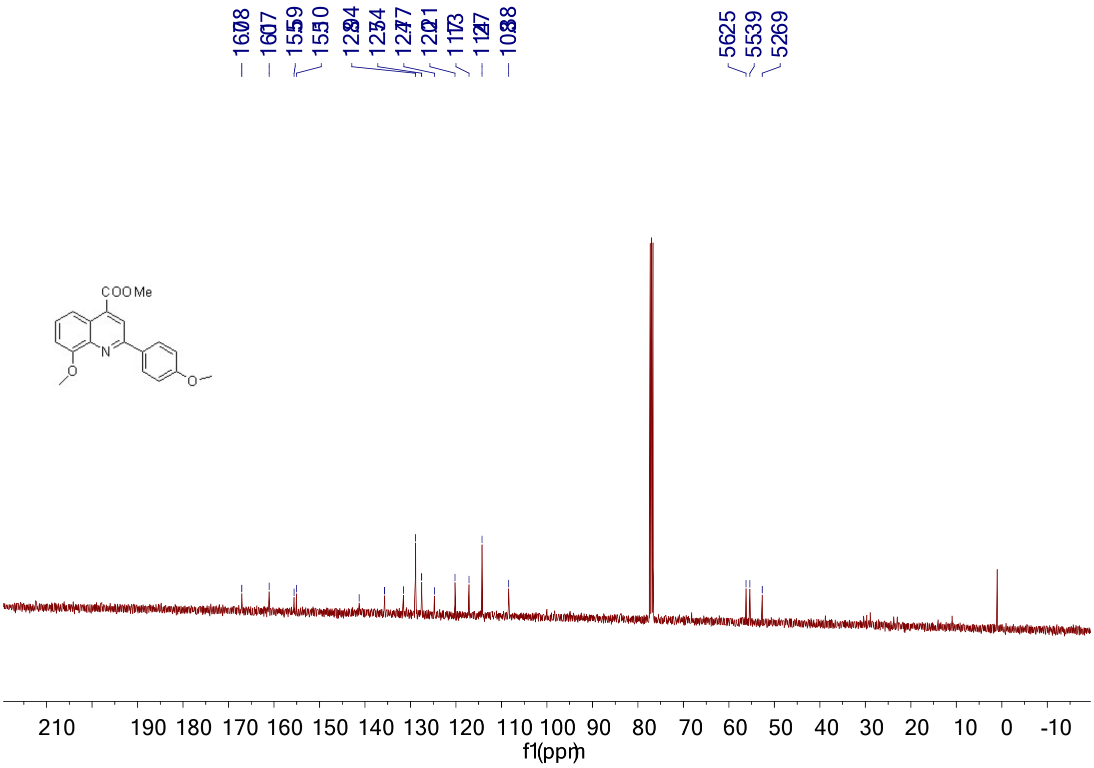
4as ^{13}C NMR spectrum



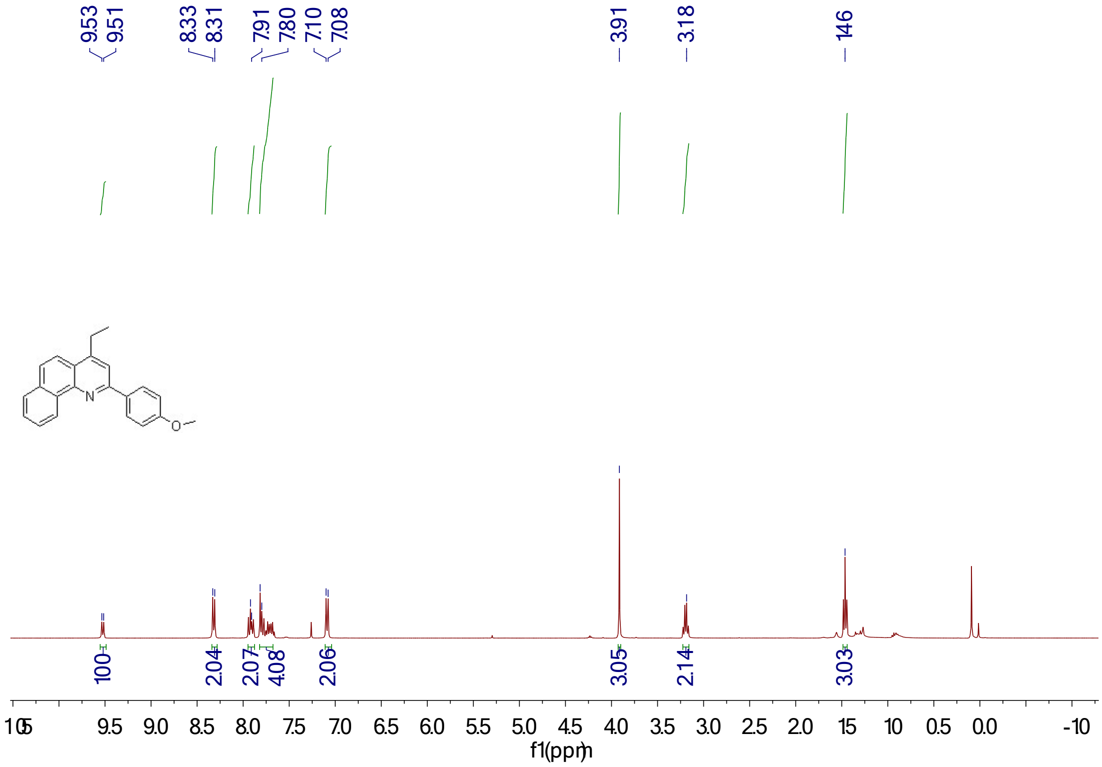
4at ^{1}HNMR spectrum



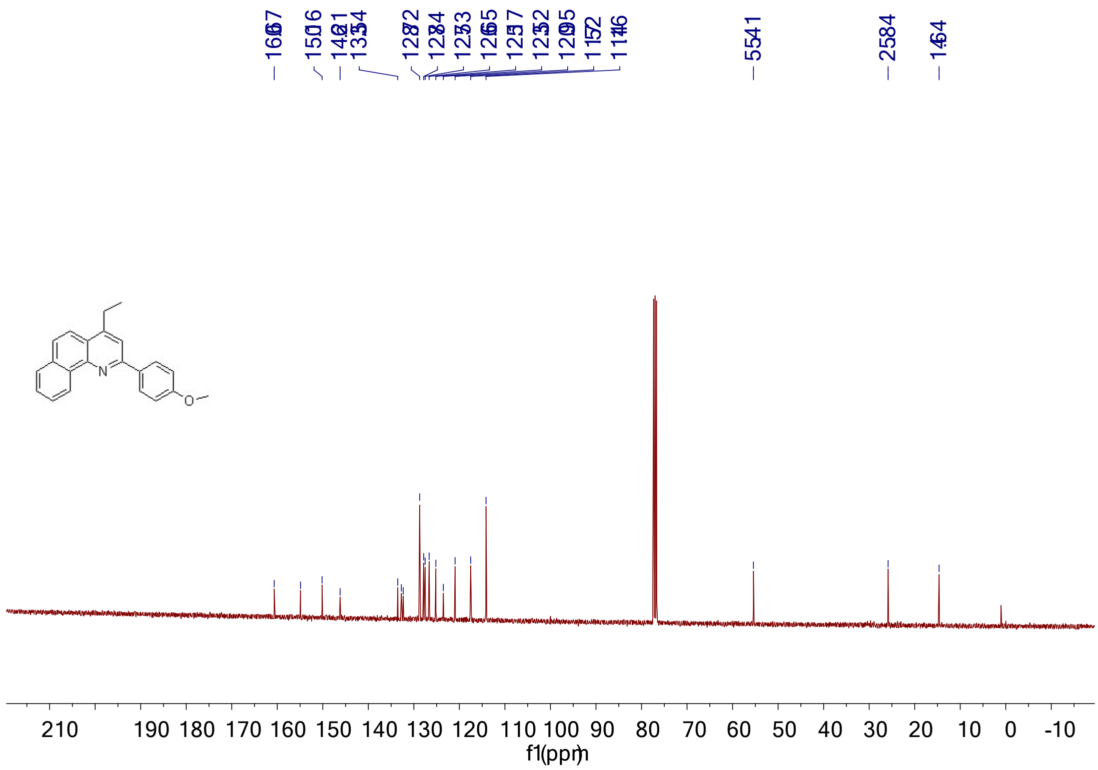
4at ^{13}C NMR spectrum



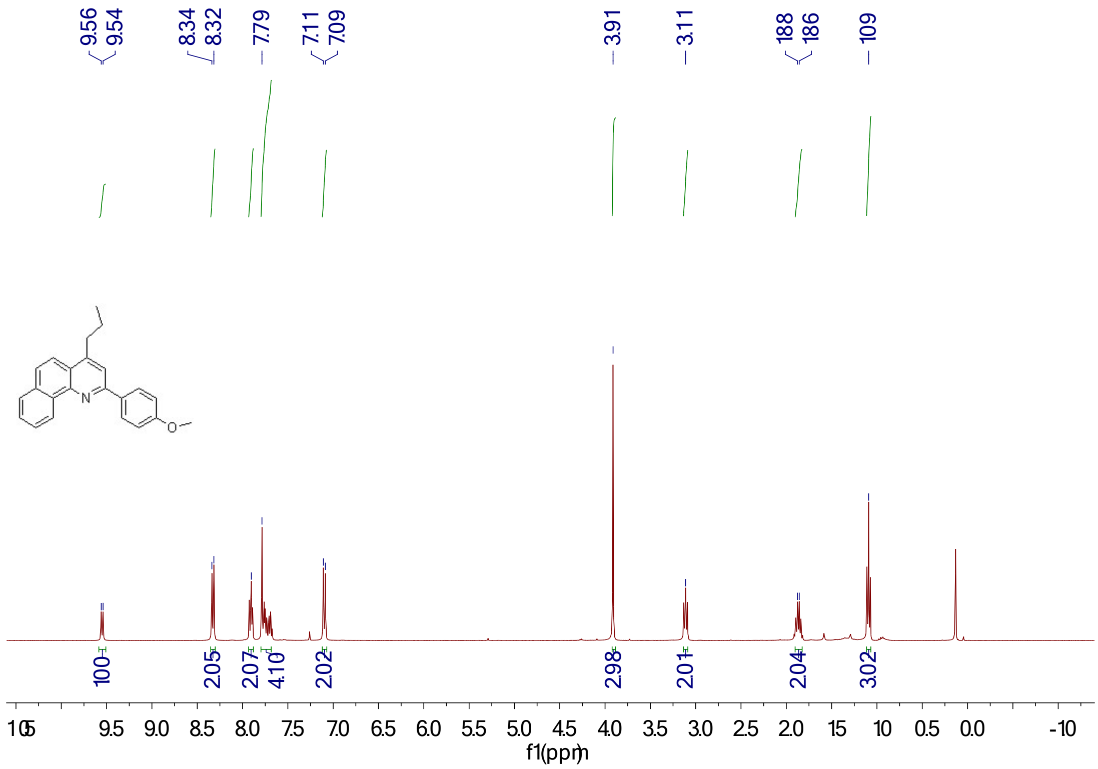
4bb 1HNMR spectrum



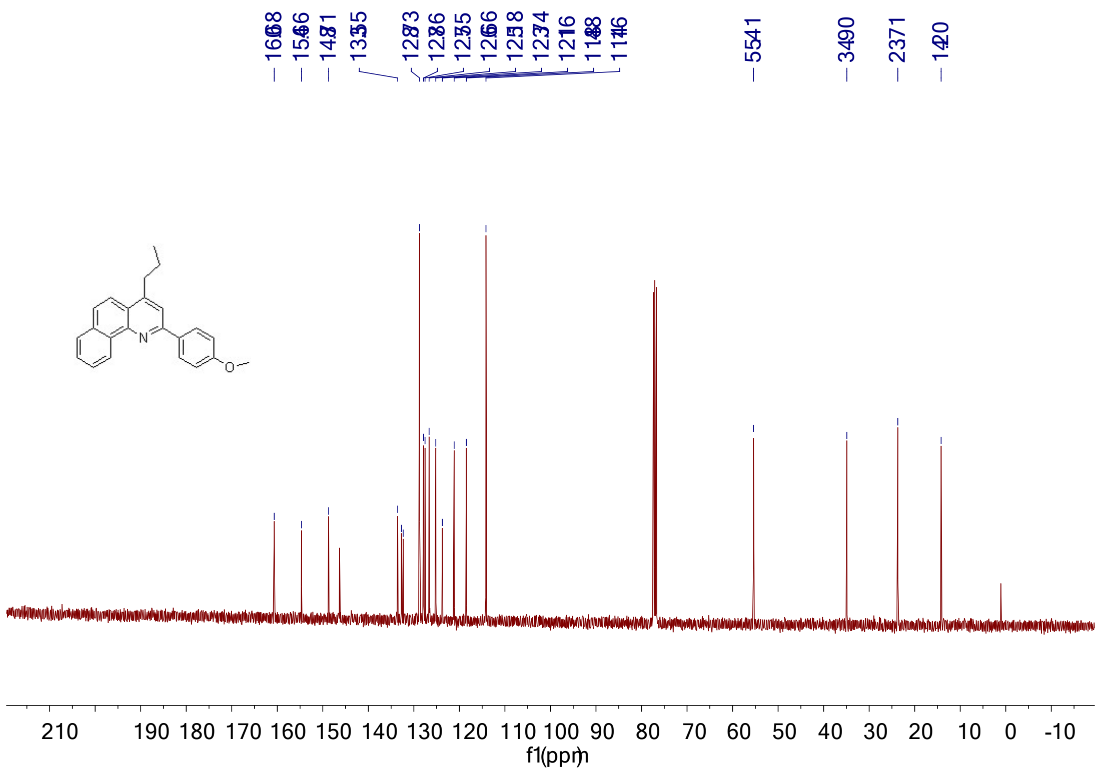
4bb 13C NMR spectrum



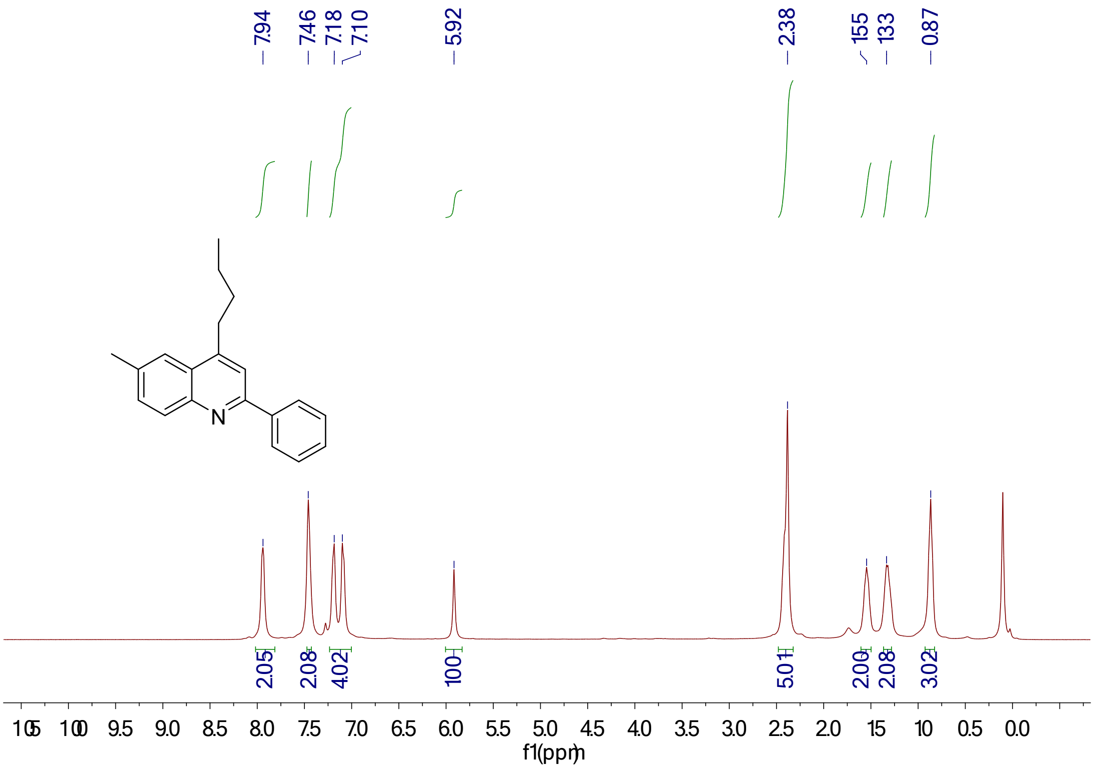
4bc ^{1}HNMR spectrum



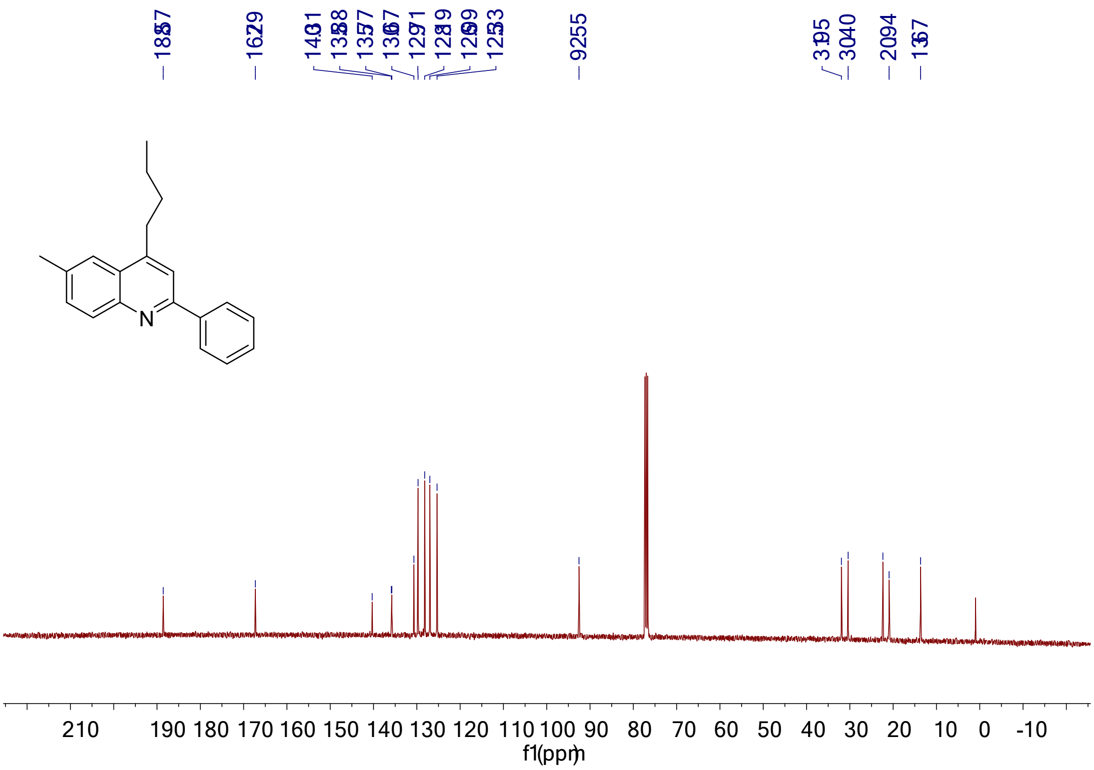
4bc ^{13}C NMR spectrum



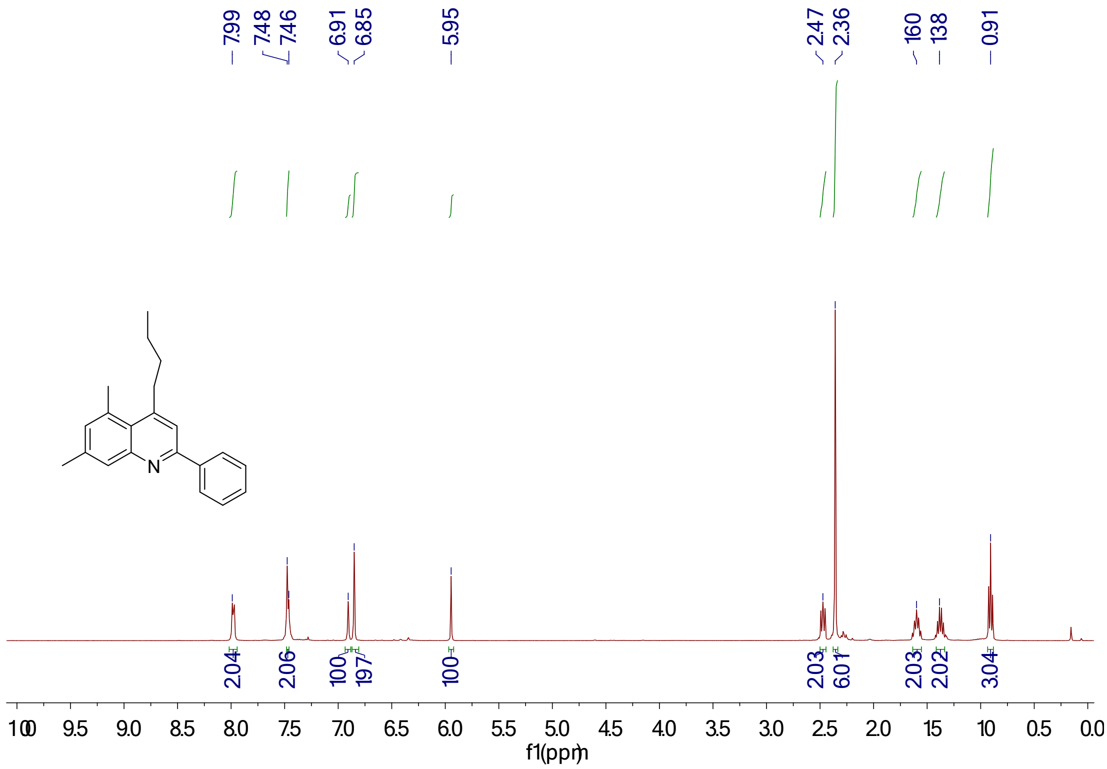
4bd ^{1}HNMR spectrum



4bd ^{13}C NMR spectrum



4be ^{1}HNMR spectrum



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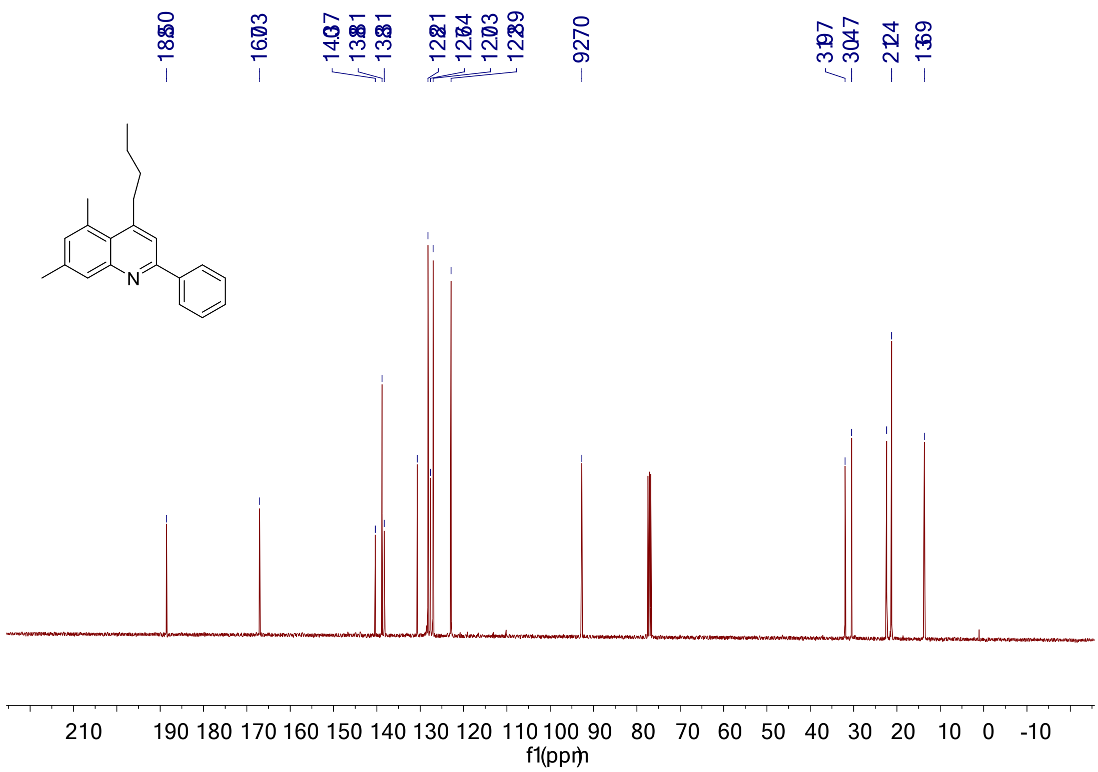
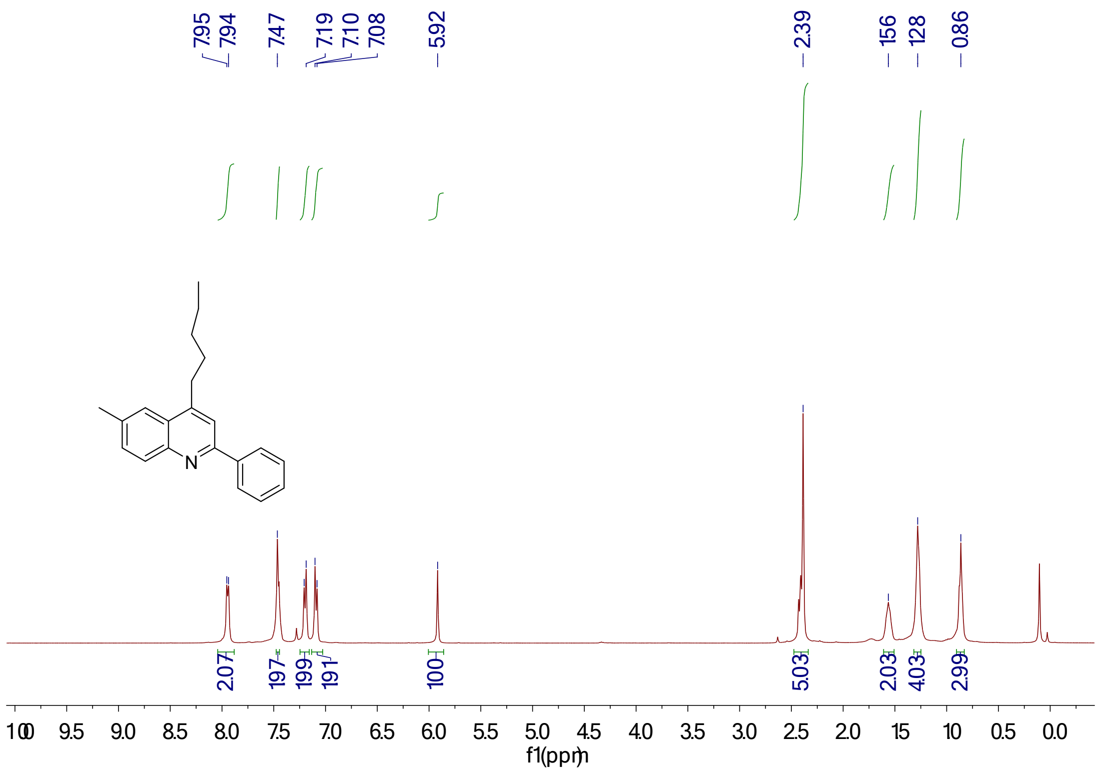
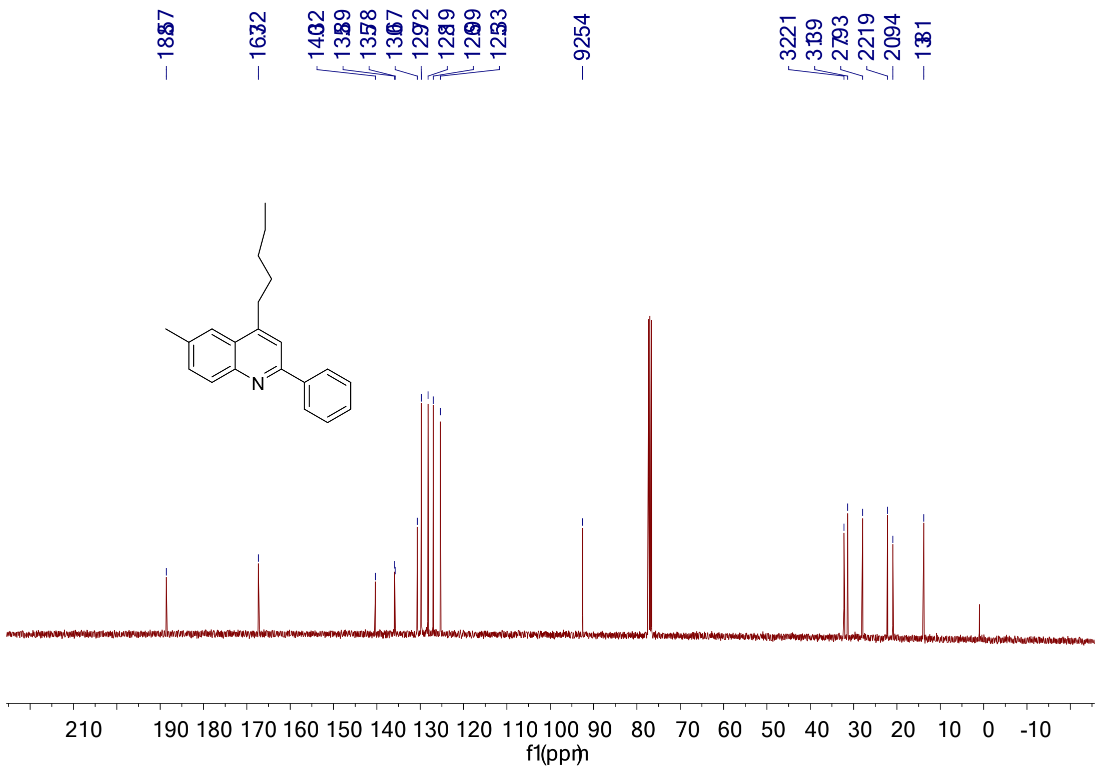


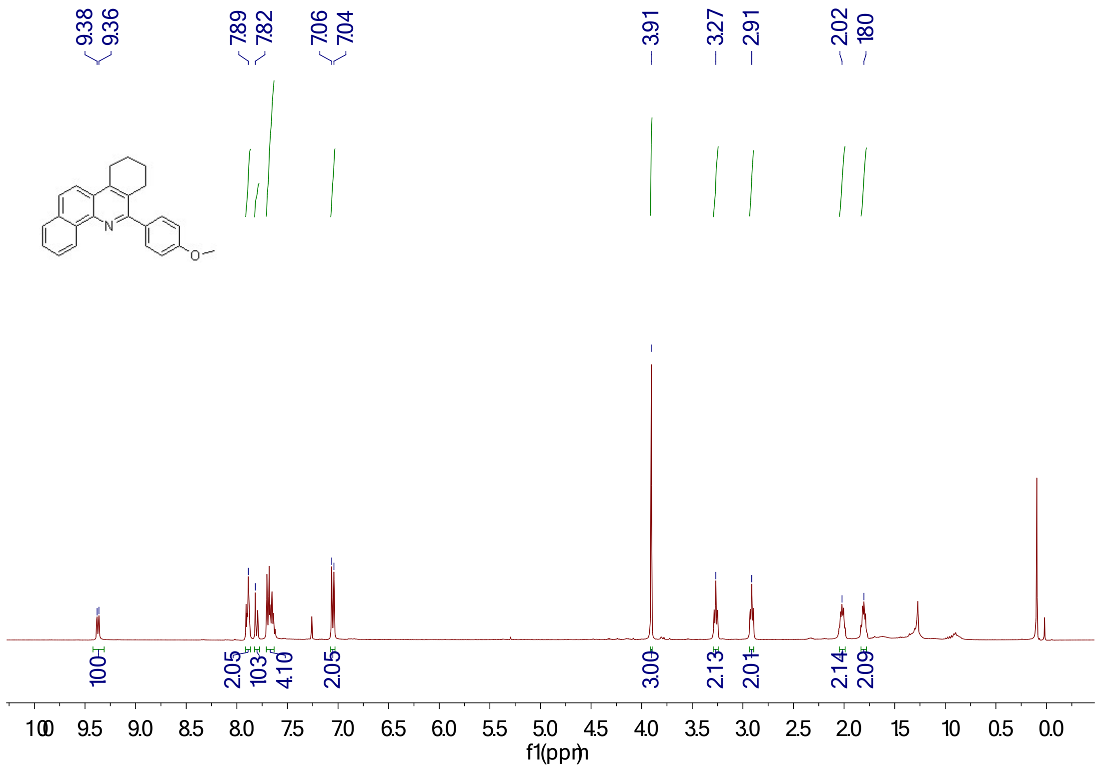
4bf ^{1}HNMR spectrum



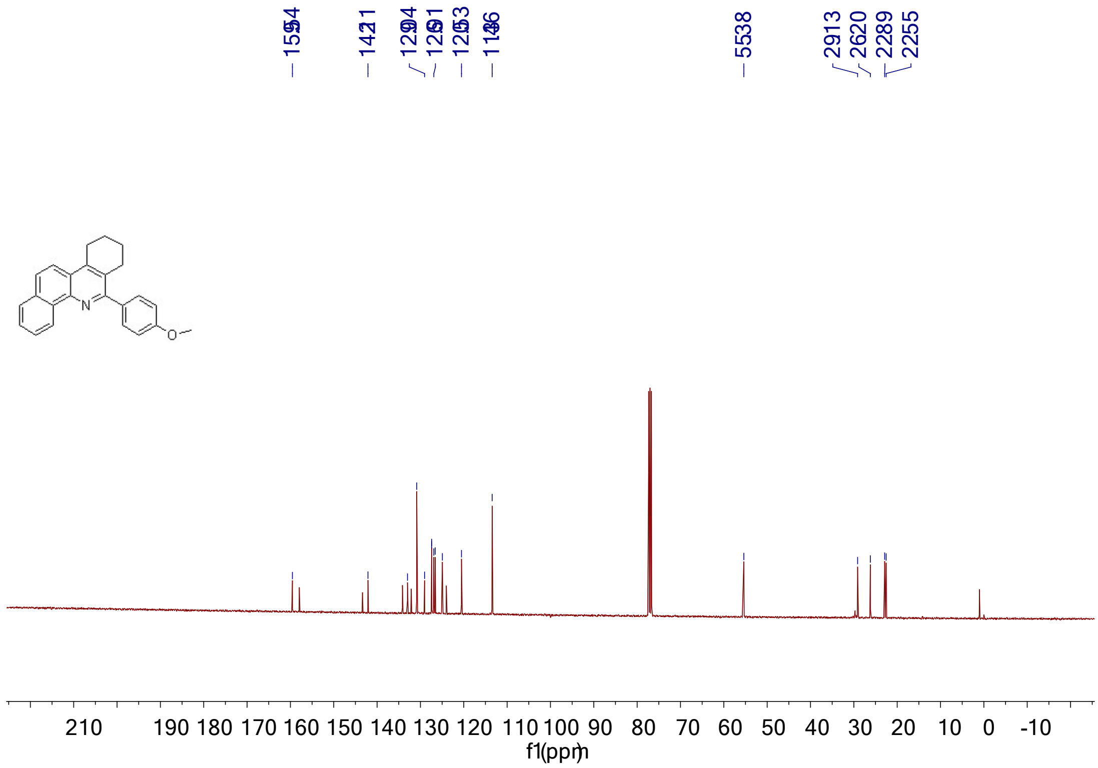
4bf ^{13}C NMR spectrum



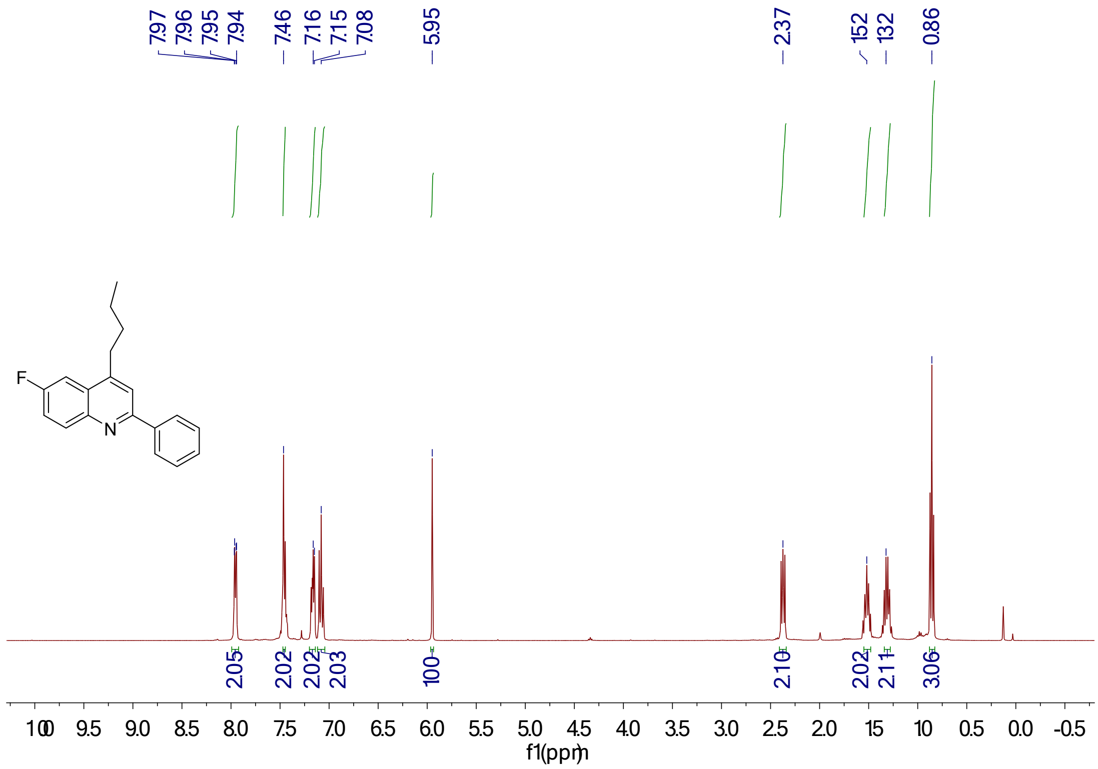
4bg ^{1}HNMR spectrum



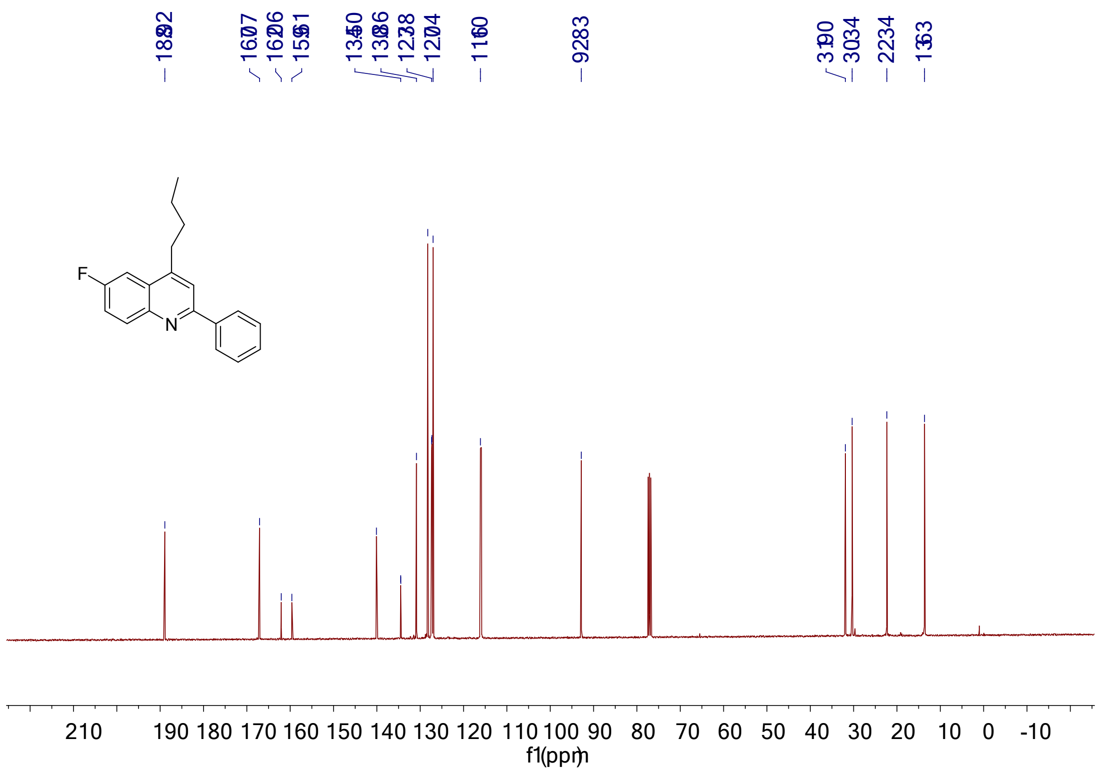
4bg ^{13}C NMR spectrum



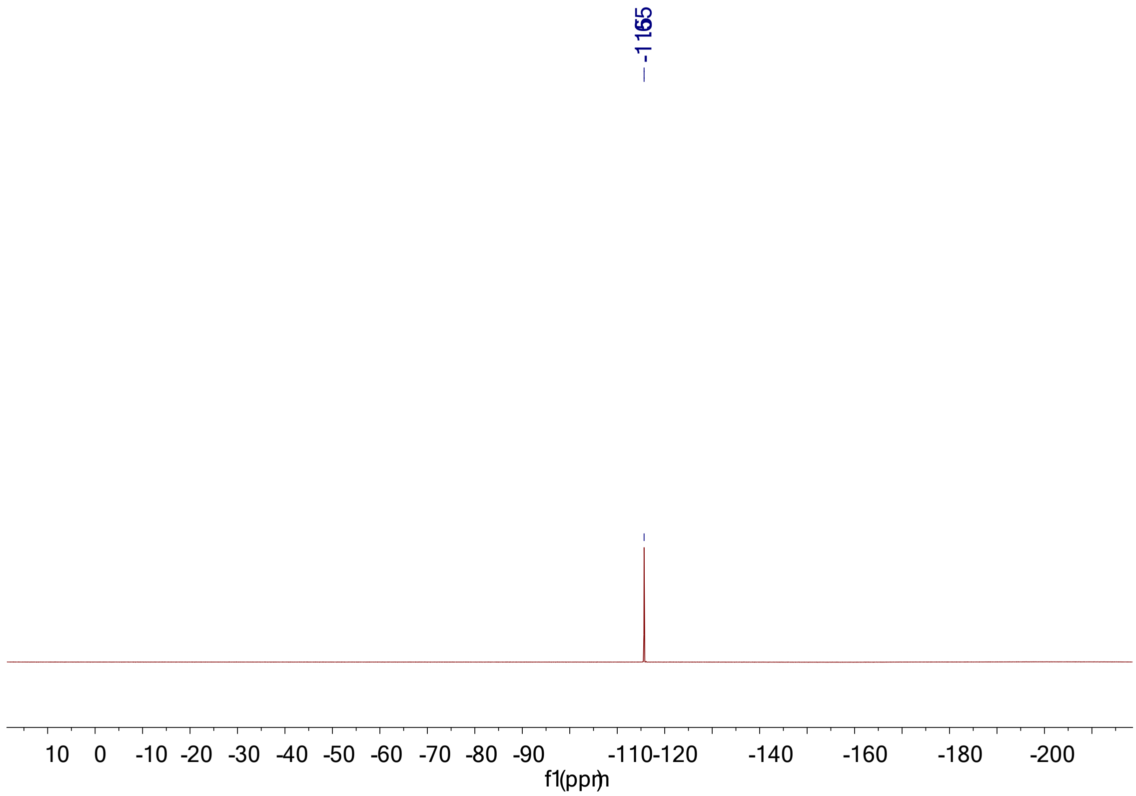
4bh ^{1}HNMR spectrum



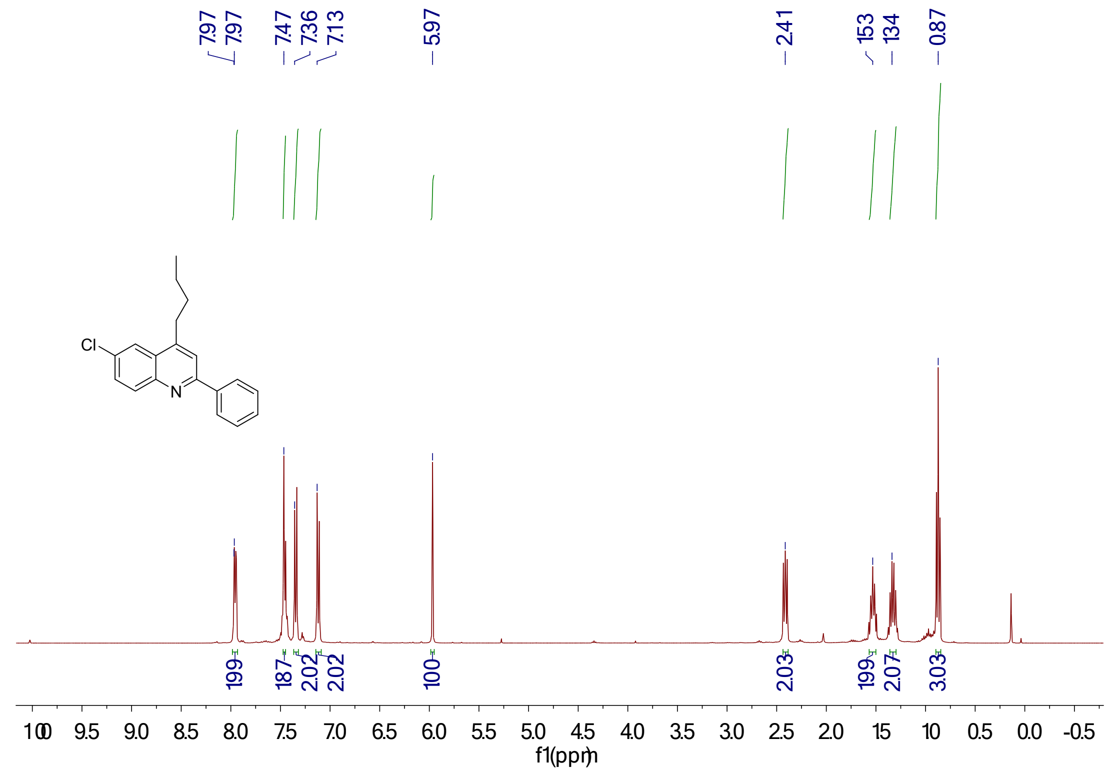
4bh ^{13}C NMR spectrum



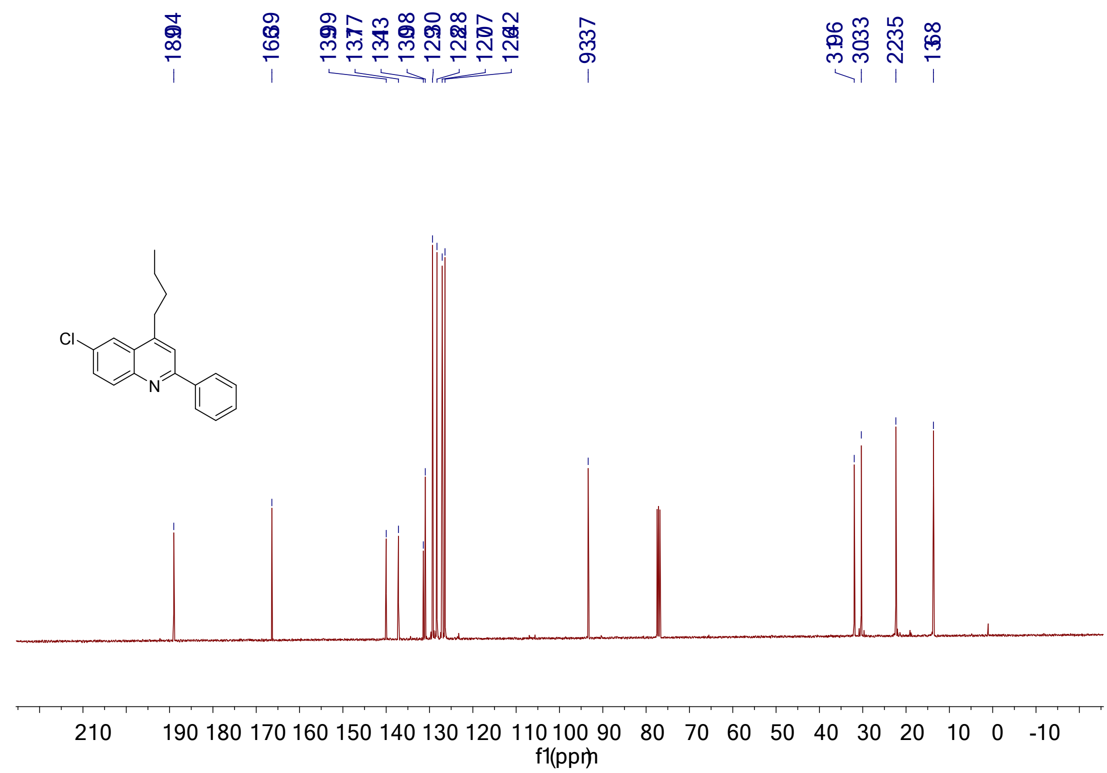
4bh ^{19}F NMR spectrum



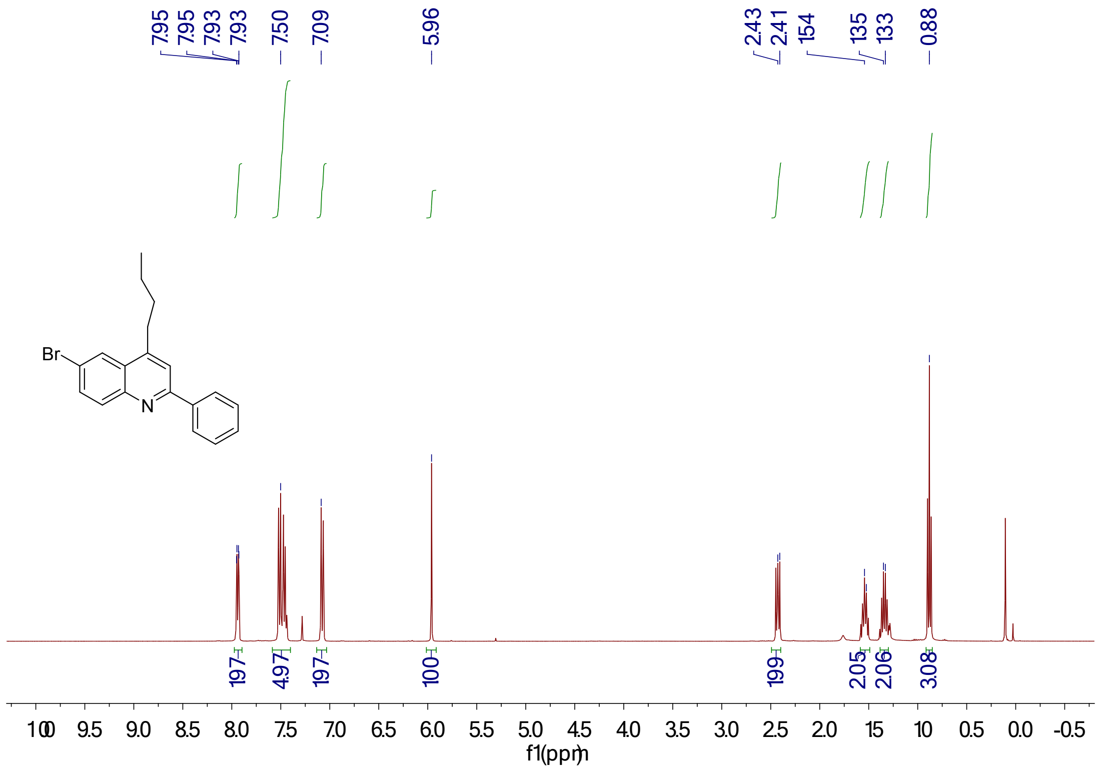
4bi ^{1}HNMR spectrum



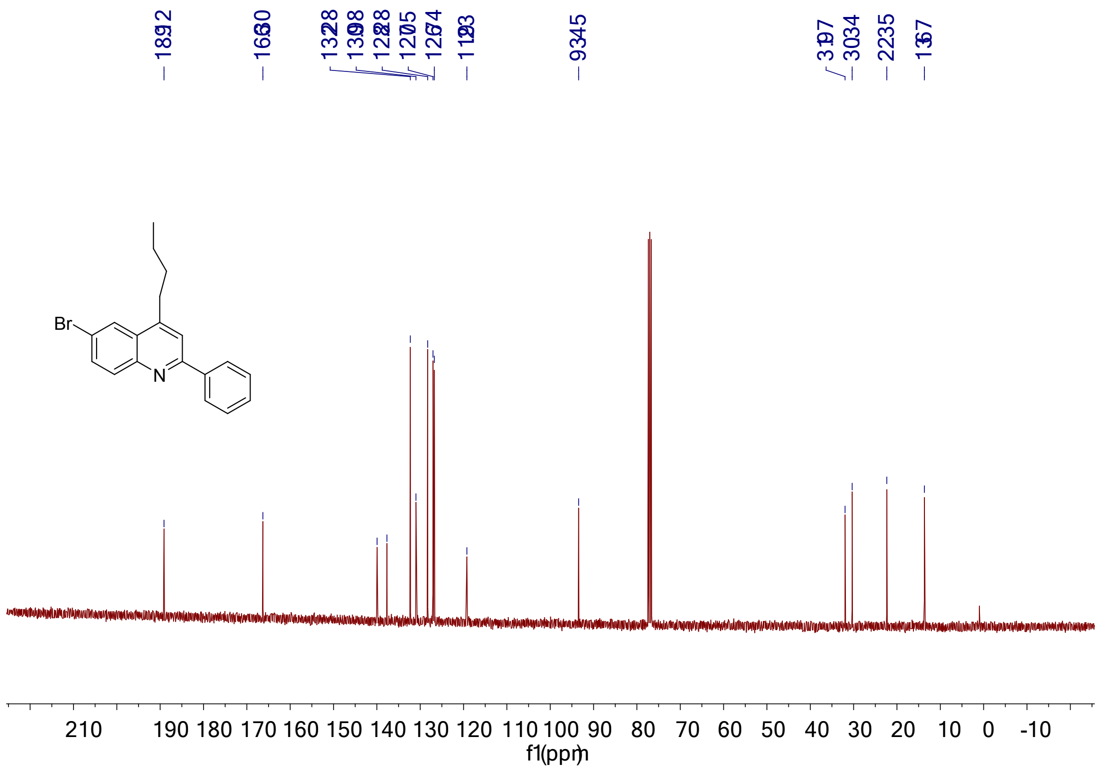
4bi ^{13}C NMR spectrum



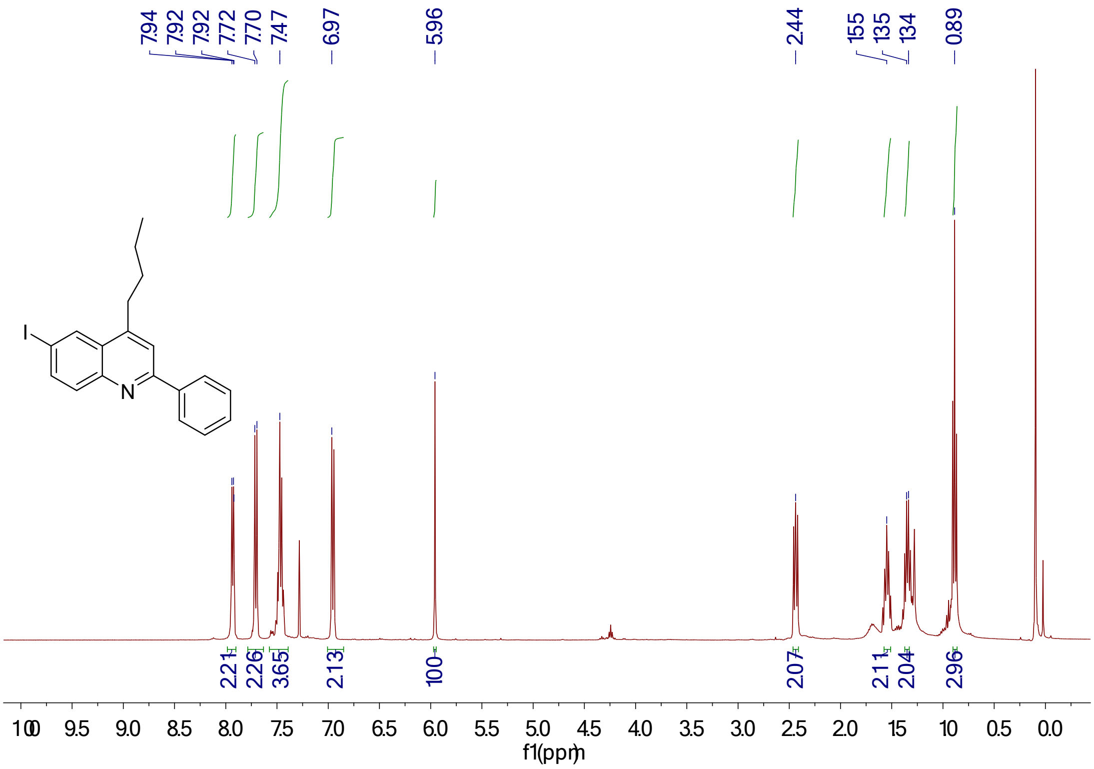
4bj ^{1}HNMR spectrum



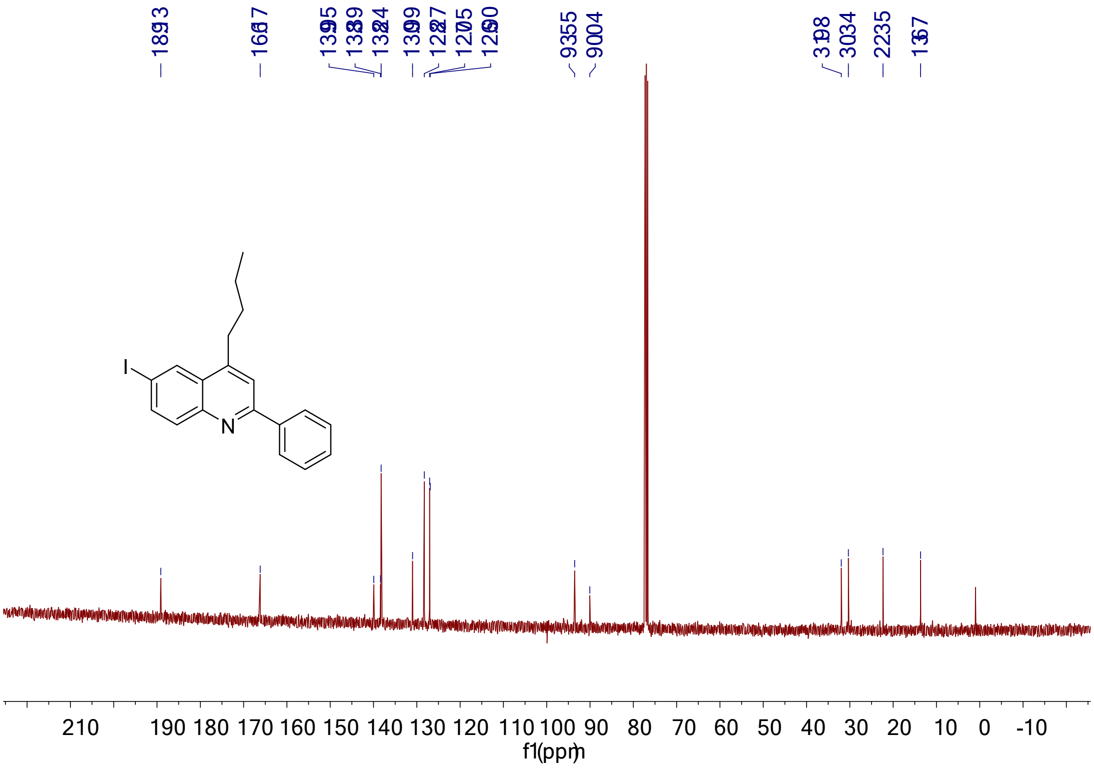
4bj ^{13}C NMR spectrum



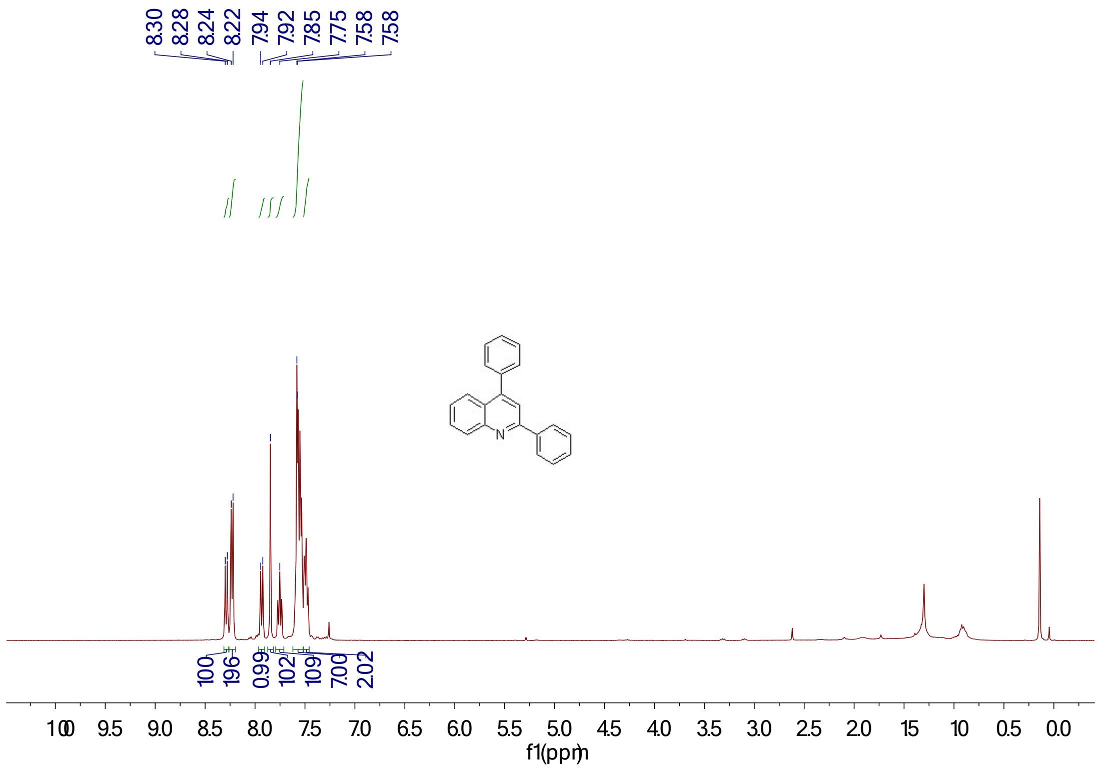
4bk ^{1}HNMR spectrum



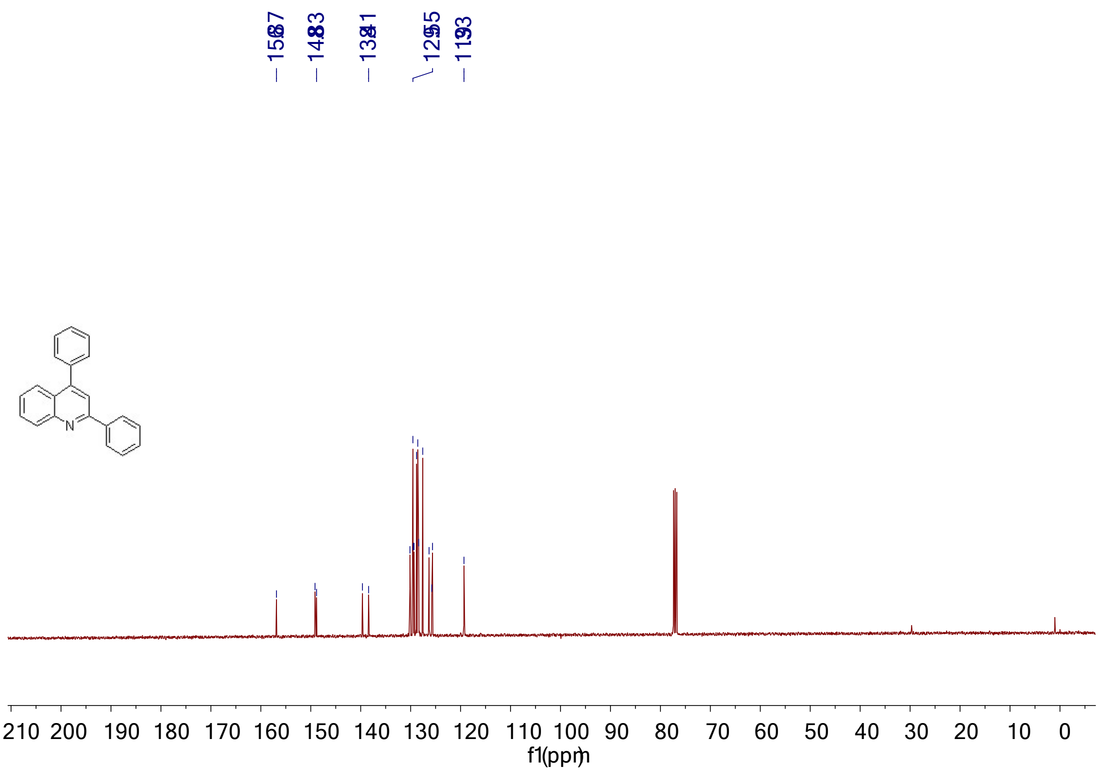
4bk ^{13}C NMR spectrum



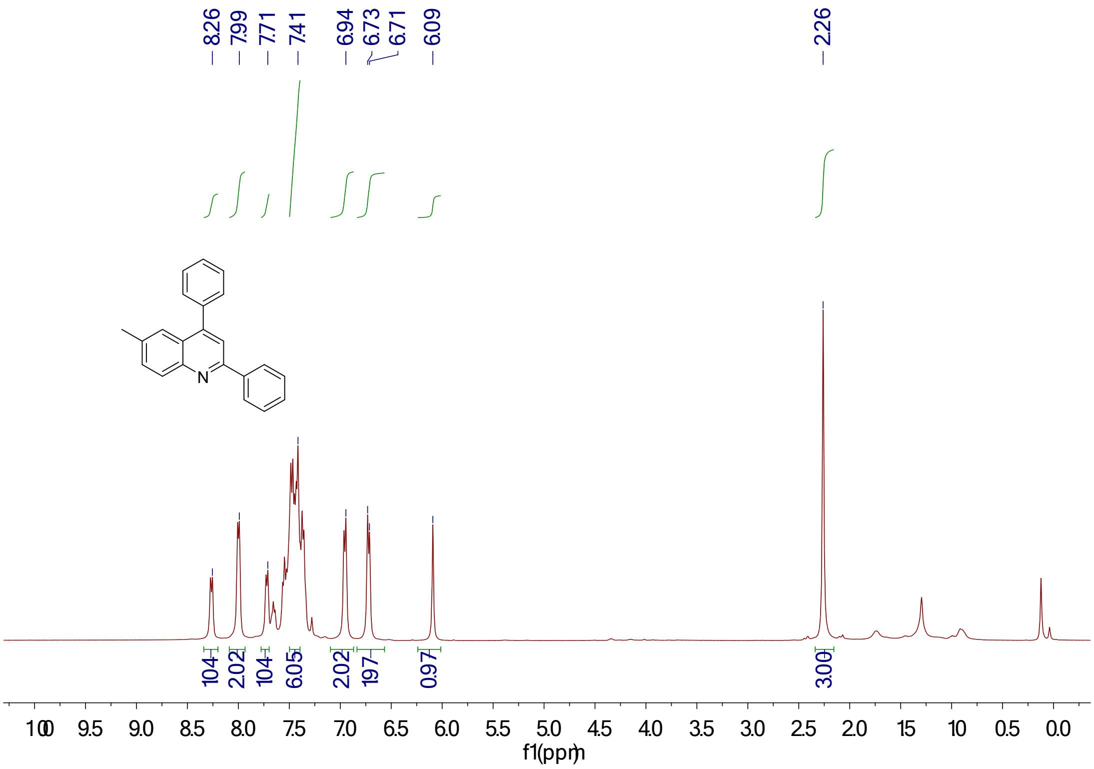
4bl ^{1}HNMR spectrum



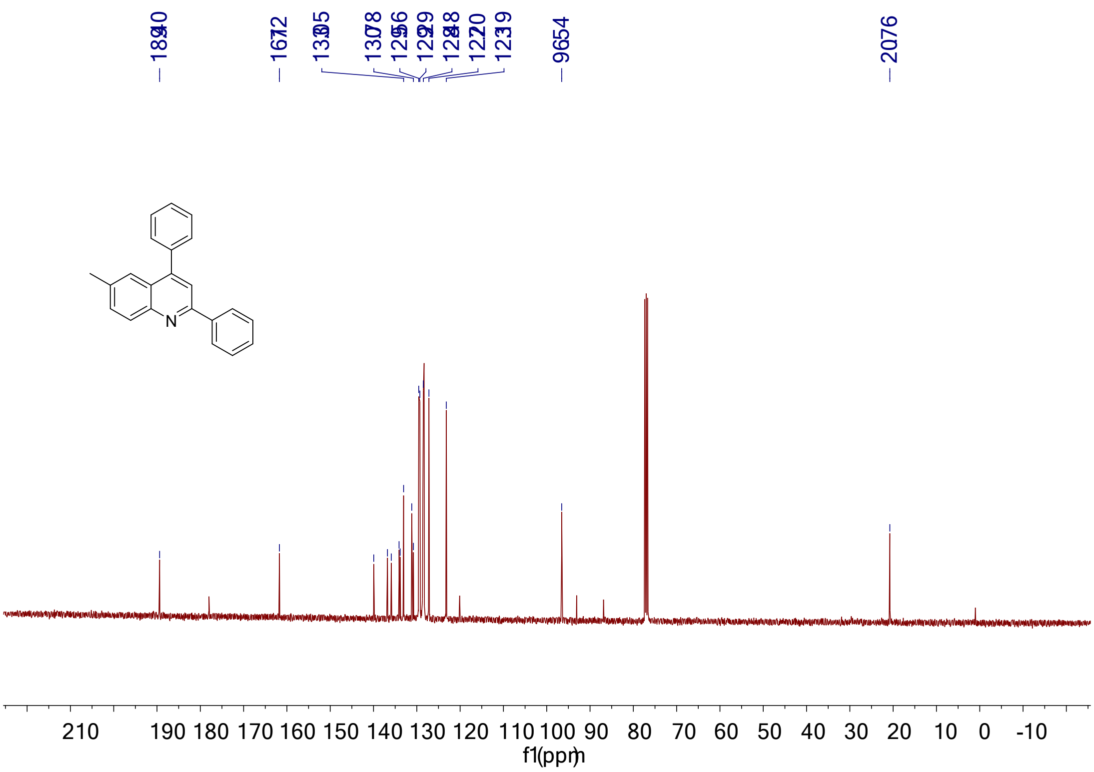
4bl ^{13}CNMR spectrum



4bm ^{1}HNMR spectrum



4bm ^{13}CNMR spectrum



4bm ^{1}HNMR spectrum