Metal-Ligand Binding Interactions in Rhodium /Palladium-Catalyzed Synthesis of Dihydroquinolines

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General Experimental Procedures. Unless otherwise noted, reactions were carried out under argon atmosphere, in single-neck, round bottom flasks fitted with a rubber septum, with magnetic stirring. Air- or water-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by successive freeze-pump-thaw cycles (≥ three iterations). Organic solutions were concentrated by rotary evaporation at 23–40 °C under 40 Torr (house vacuum). Analytical thin layer chromatography (TLC) was performed with silica gel normal phase aluminum plates (0.25 mm, 60-A pore size, 230-400 mesh). Visualization was done under a 254 nm UV light source and generally by immersion in acidic aqueous-ethanolic vanillin solution, or in potassium permanganate ($KMnO_4$), followed by heating using a heat gun. Purification of reaction products was generally done by flash chromatography with 230-400 mesh silica gel, as described by Still *et al*.[1]

Materials. Unless otherwise indicated, starting materials were obtained commerically and used without further purification. Rhodium and palladium catalysts were purchased from Strem. Tetrahydrofuran, 1,4-dioxane and toluene were purified by distillation under N_2 from Na/benzophenone immediately prior to use.

Instrumentation. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 23 °C with 400 MHz NMR spectrometers. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 23 °C with spectrometers at 100 MHz with complete proton decoupling. Recorded shifts for protons are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvents ($CHCl_3$: δ 7.26, $CHDCl_2$: δ 5.29, C_6HD_5: δ 7.15, CD_2HOD: δ 3.30). Chemical shifts for carbon resonances are reported in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.0, CH_2Cl_2: δ 53.8, C_6D_6: δ 128.0, CD_3OD: δ 49.2). Data are represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintuplet, sx = sextet, sp = septuplet, dd = doublet of doublets, m = multiplet, br = broad), and coupling constant (*J*, Hz). Infrared (IR) spectra were obtained using a FT-IR spectrometer as a neat film on a NaCl plate. Data is presented as follows: frequency of absorption (cm^{-1}). High resolution mass spectra were measured in EI or ESI mode, and the mass analyzer was TOF. Melting points are uncorrected.

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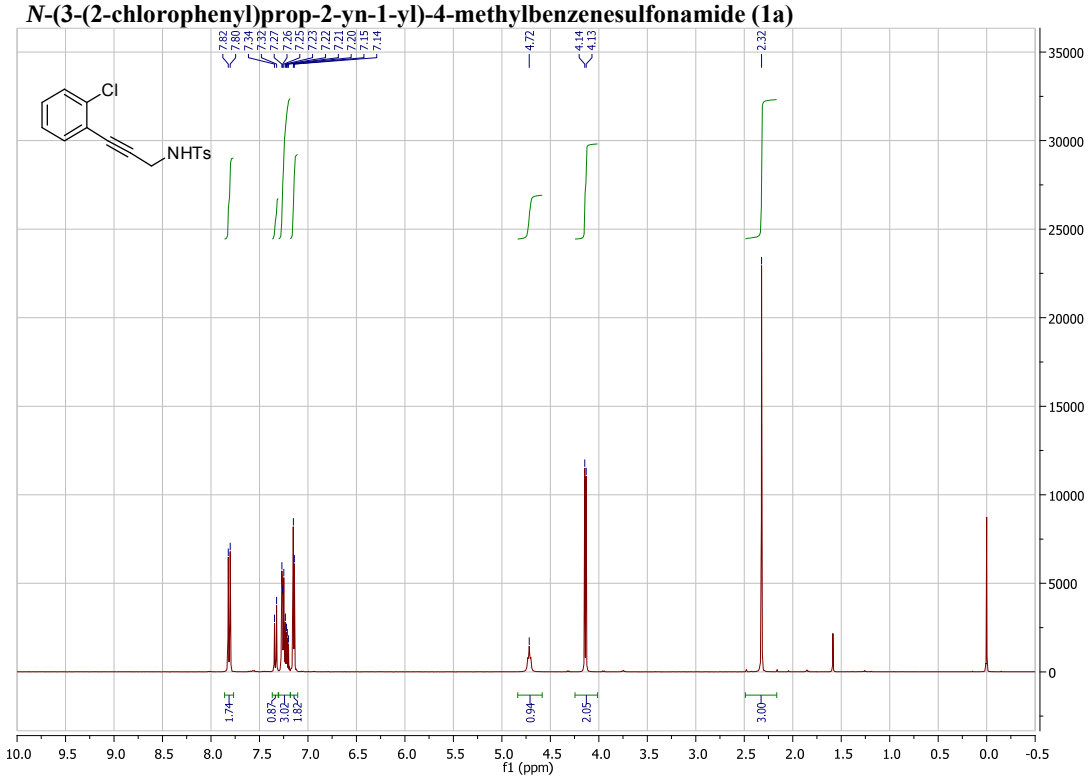

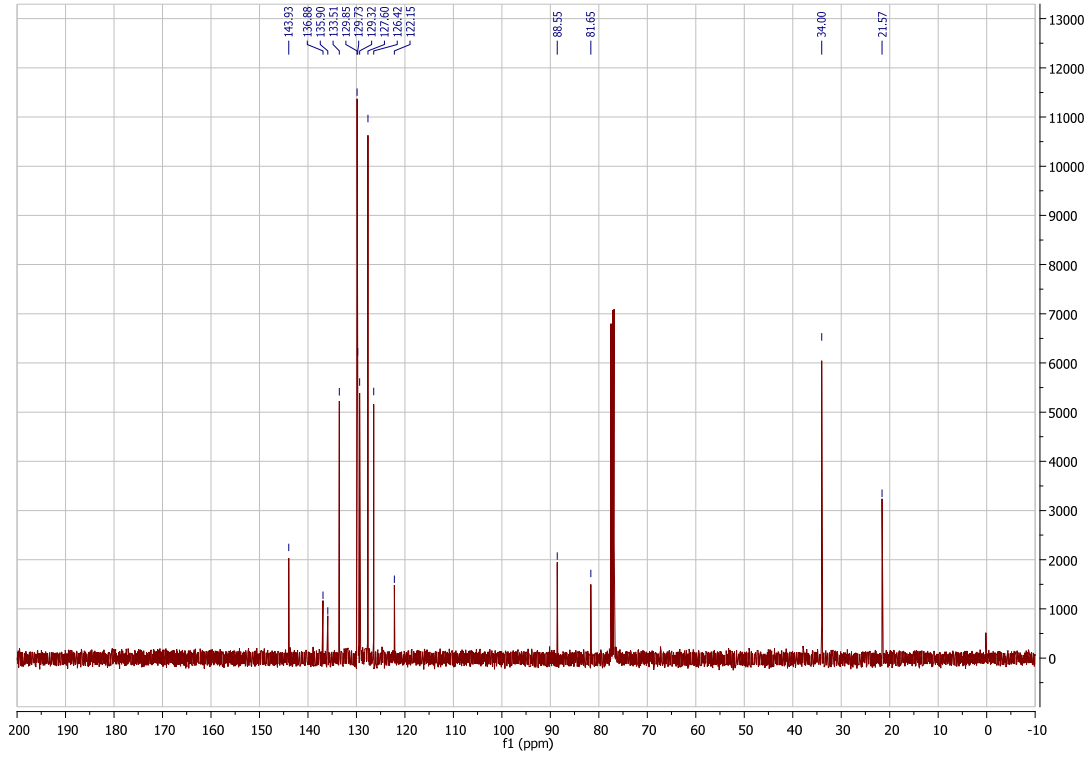

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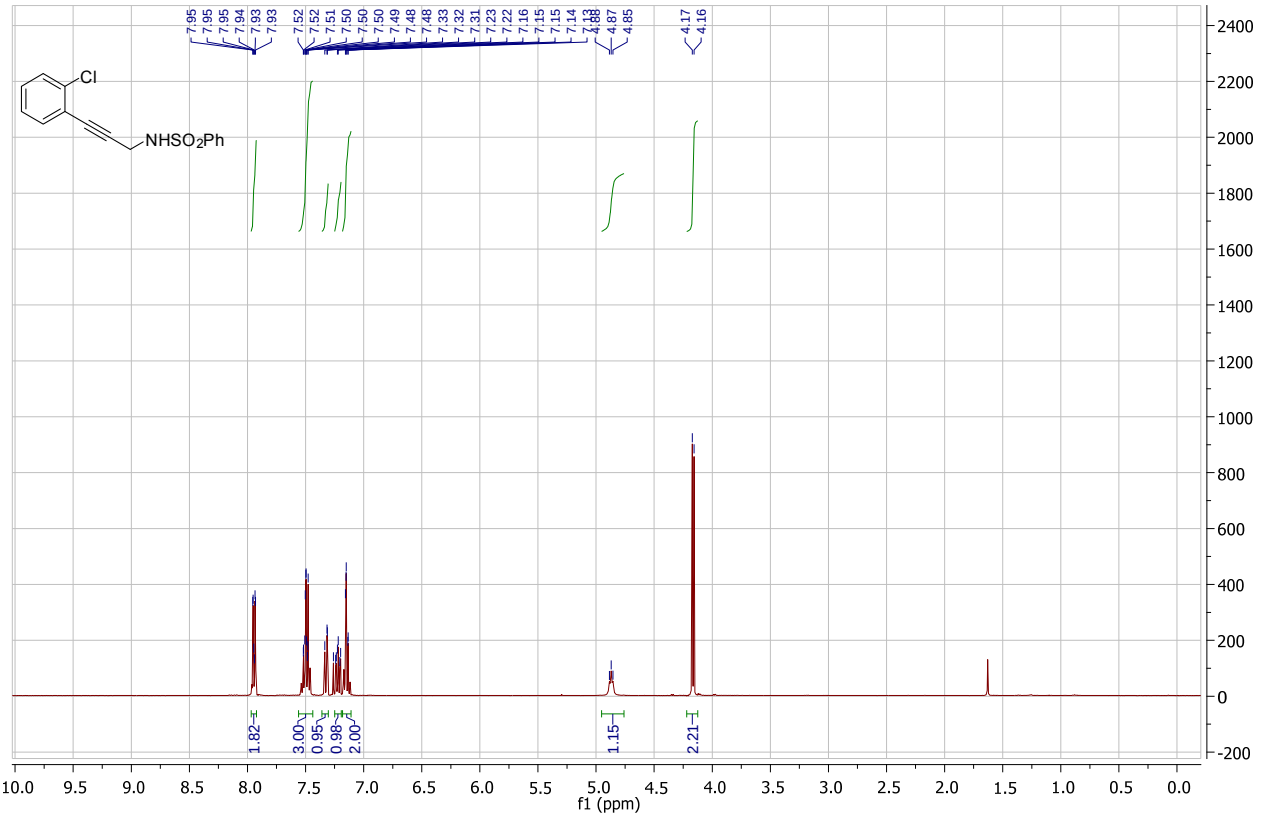

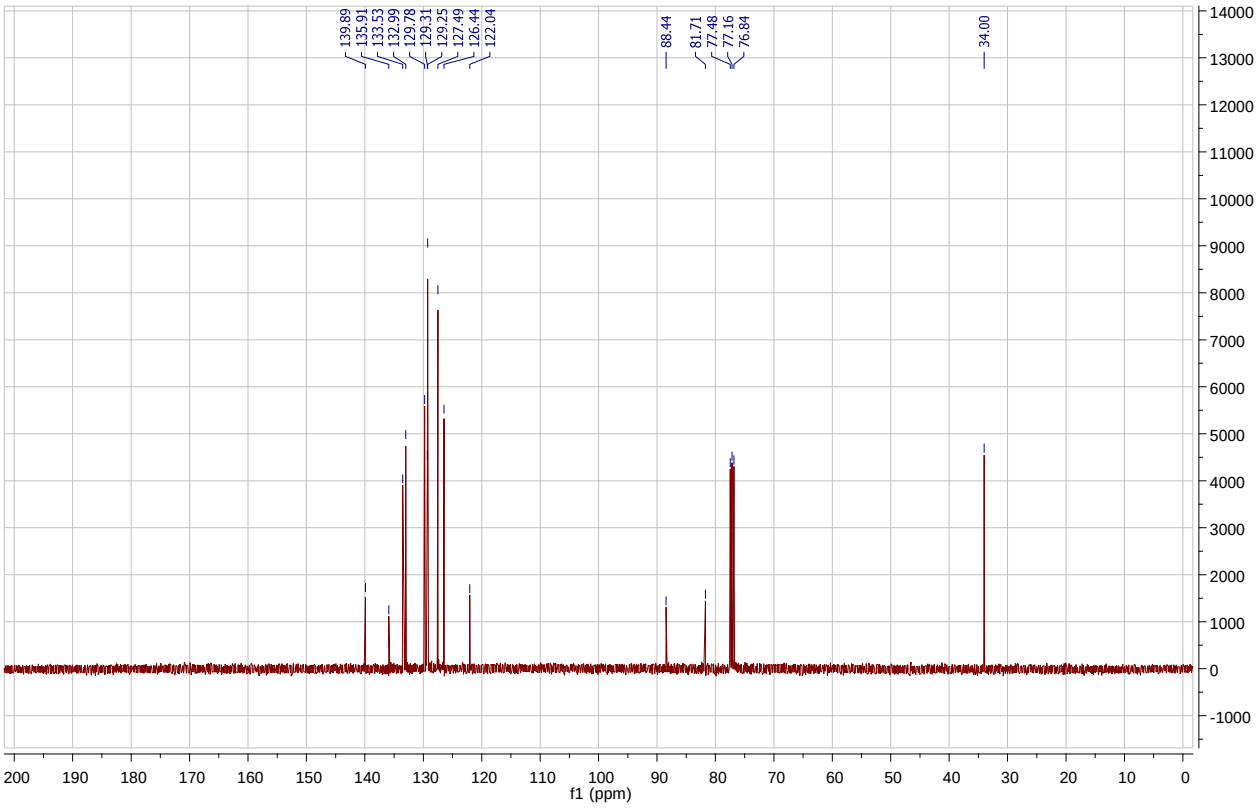

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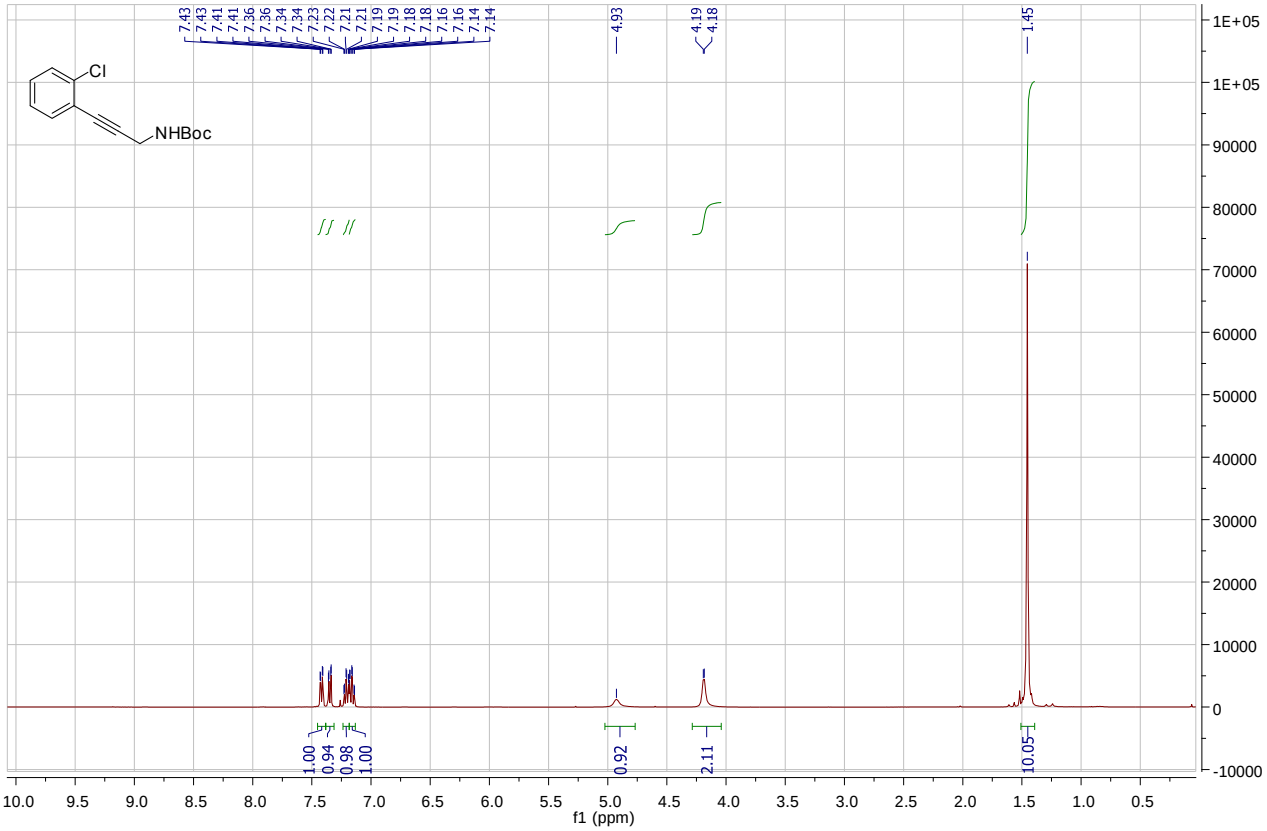

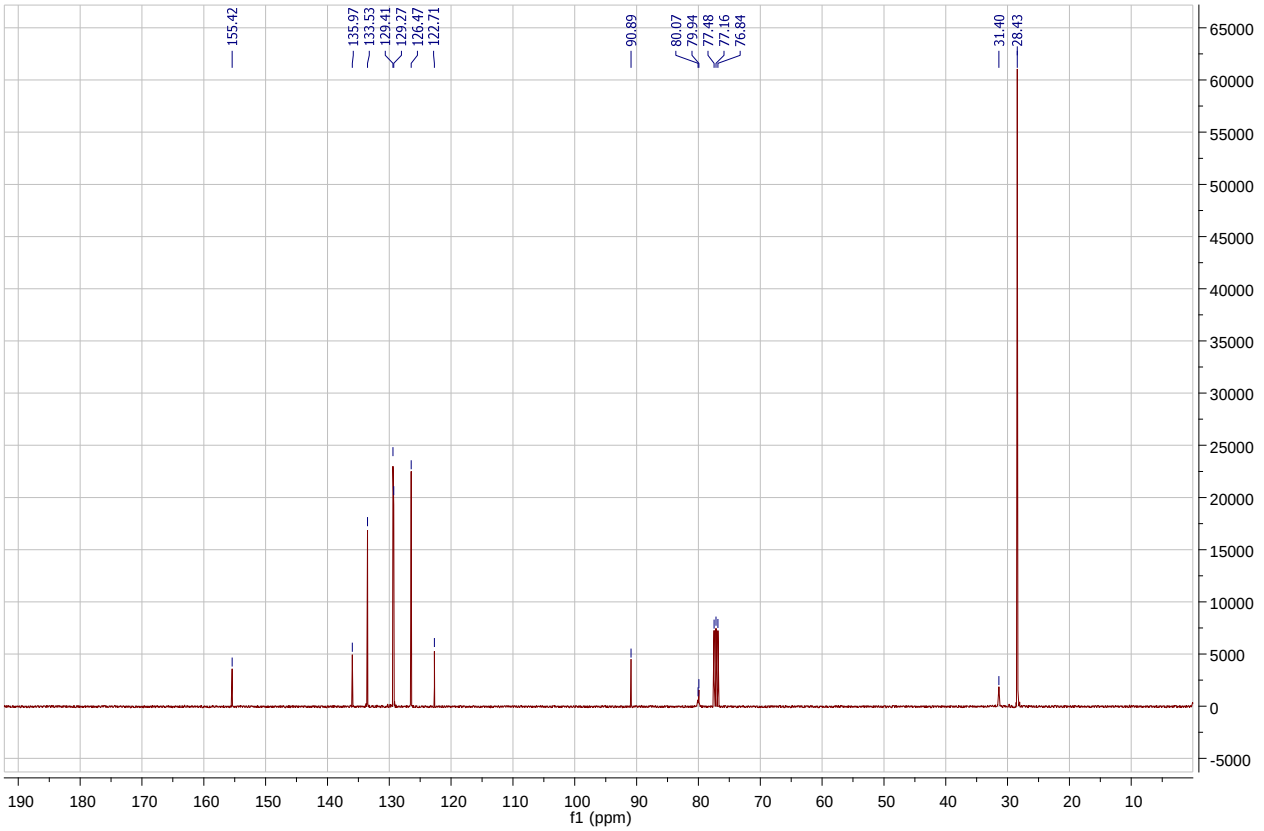

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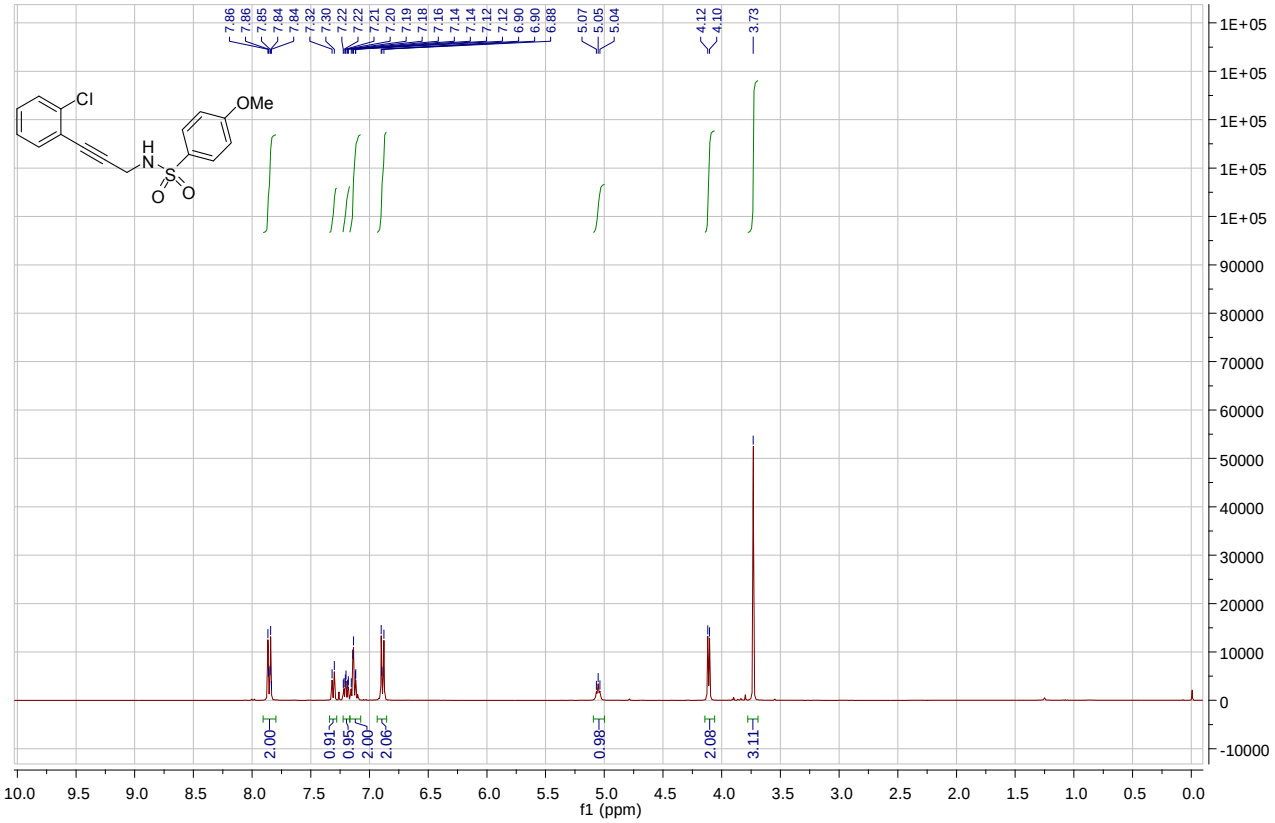

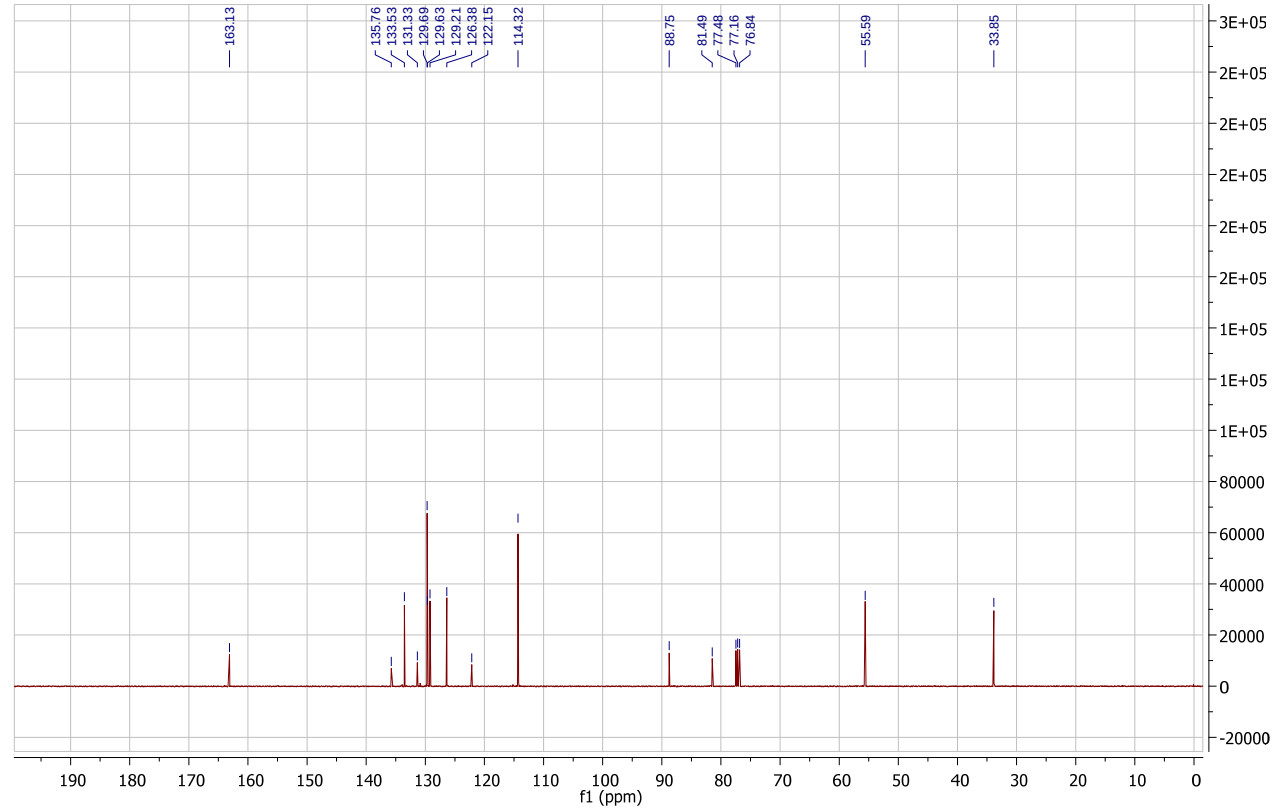

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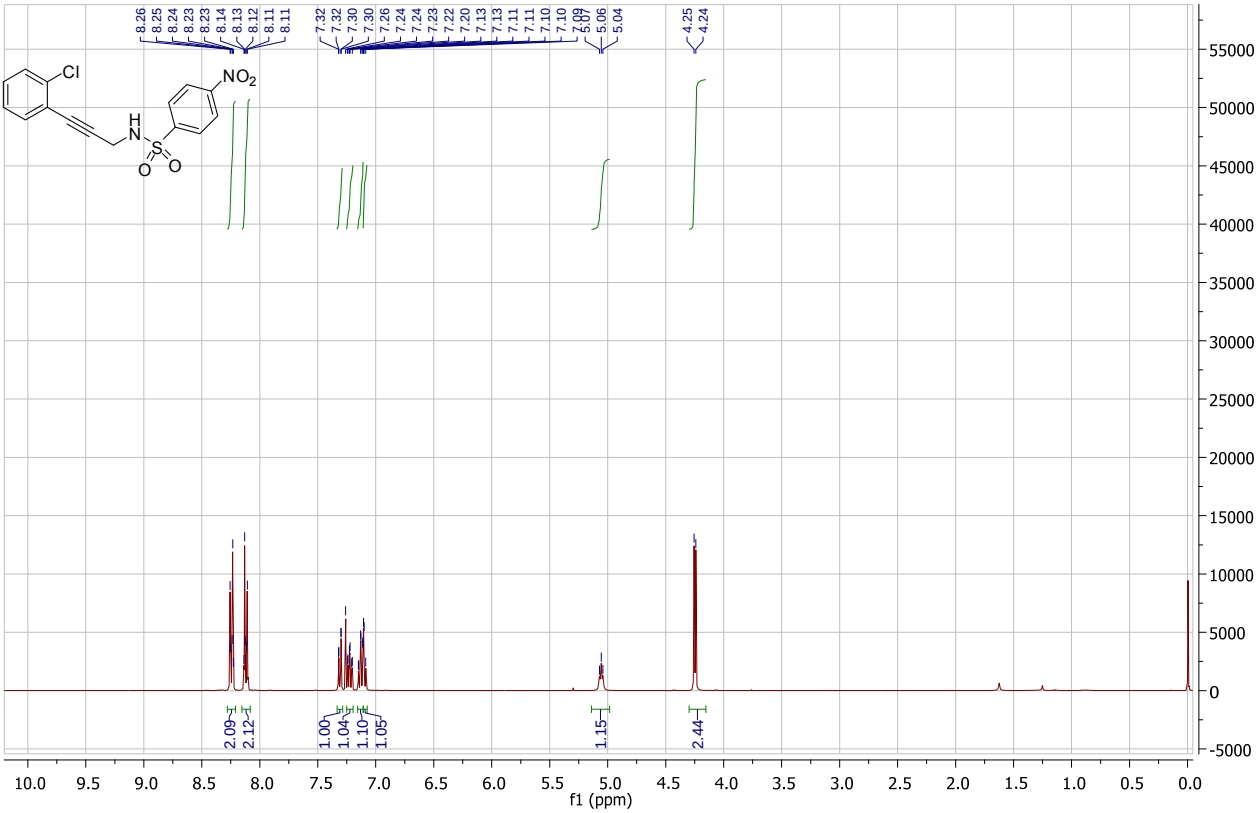

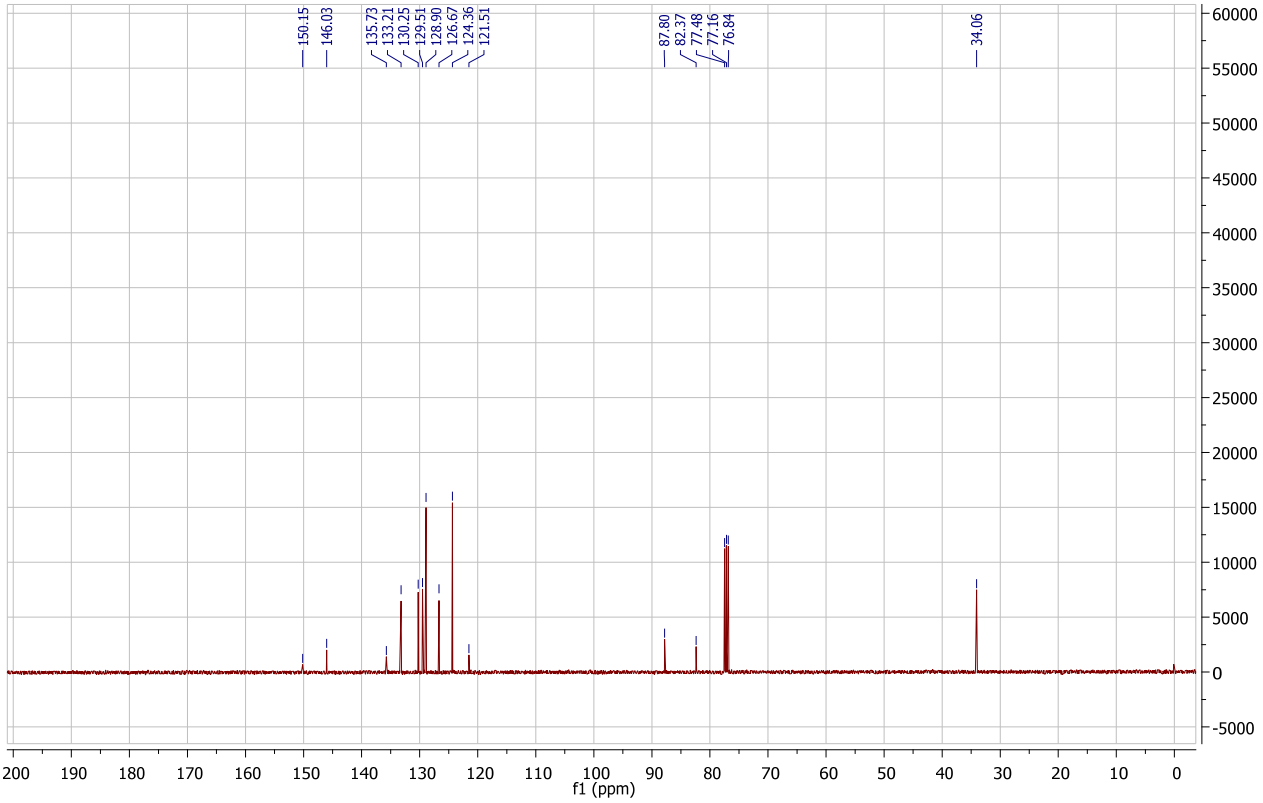

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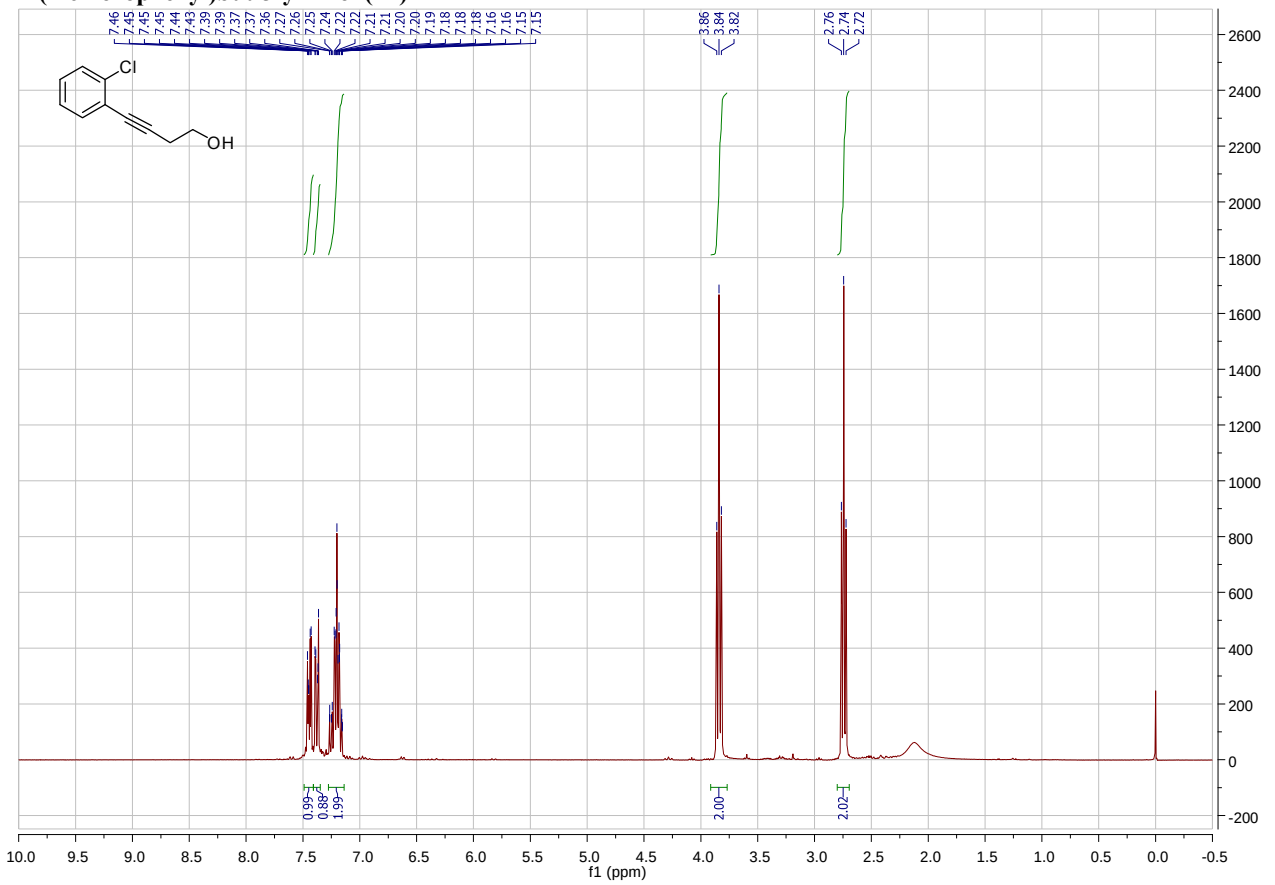

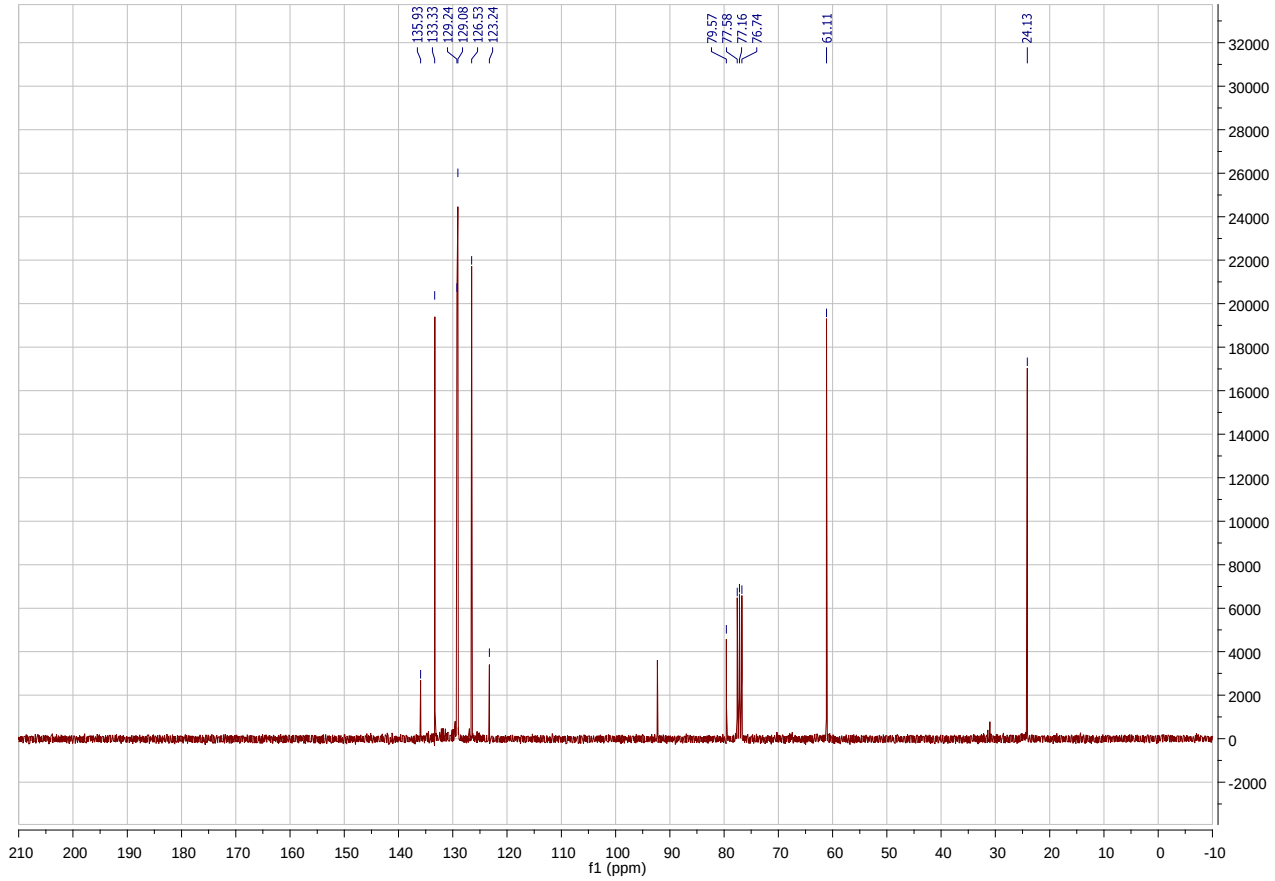

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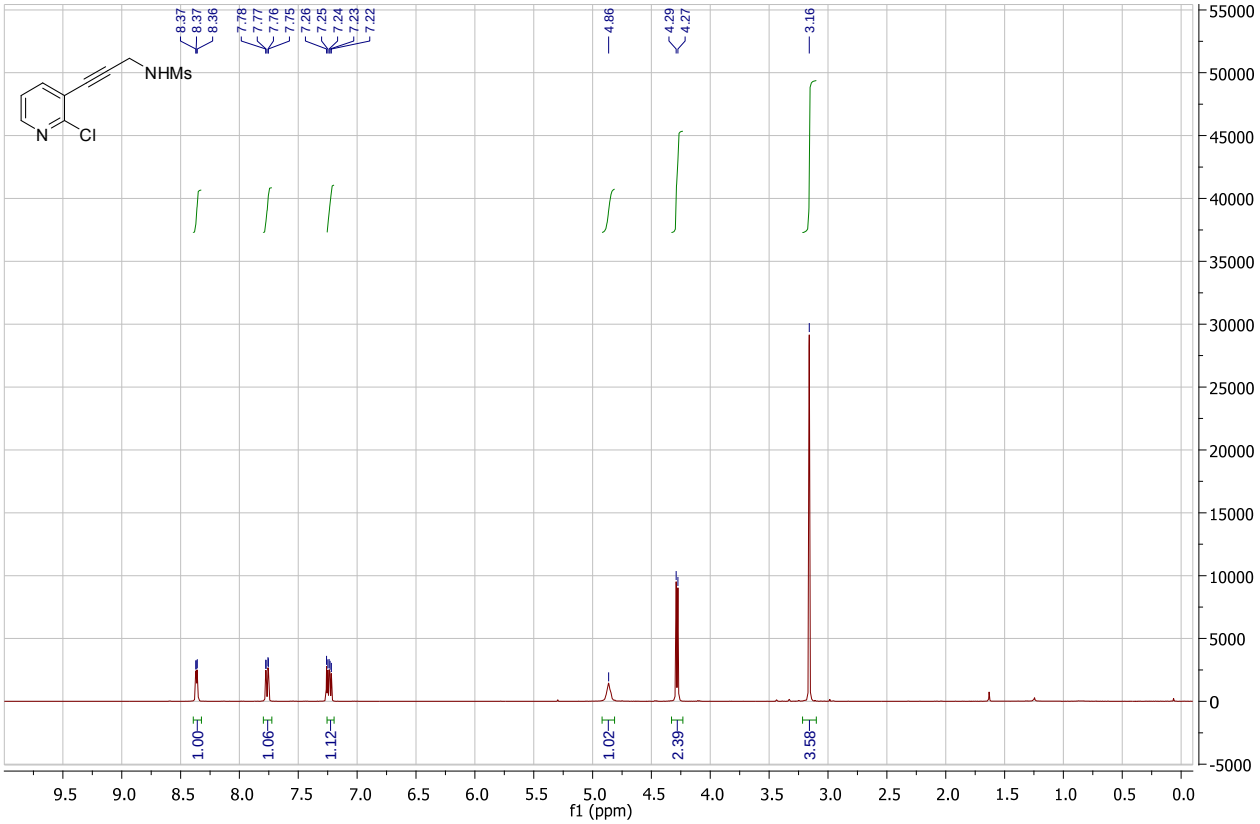

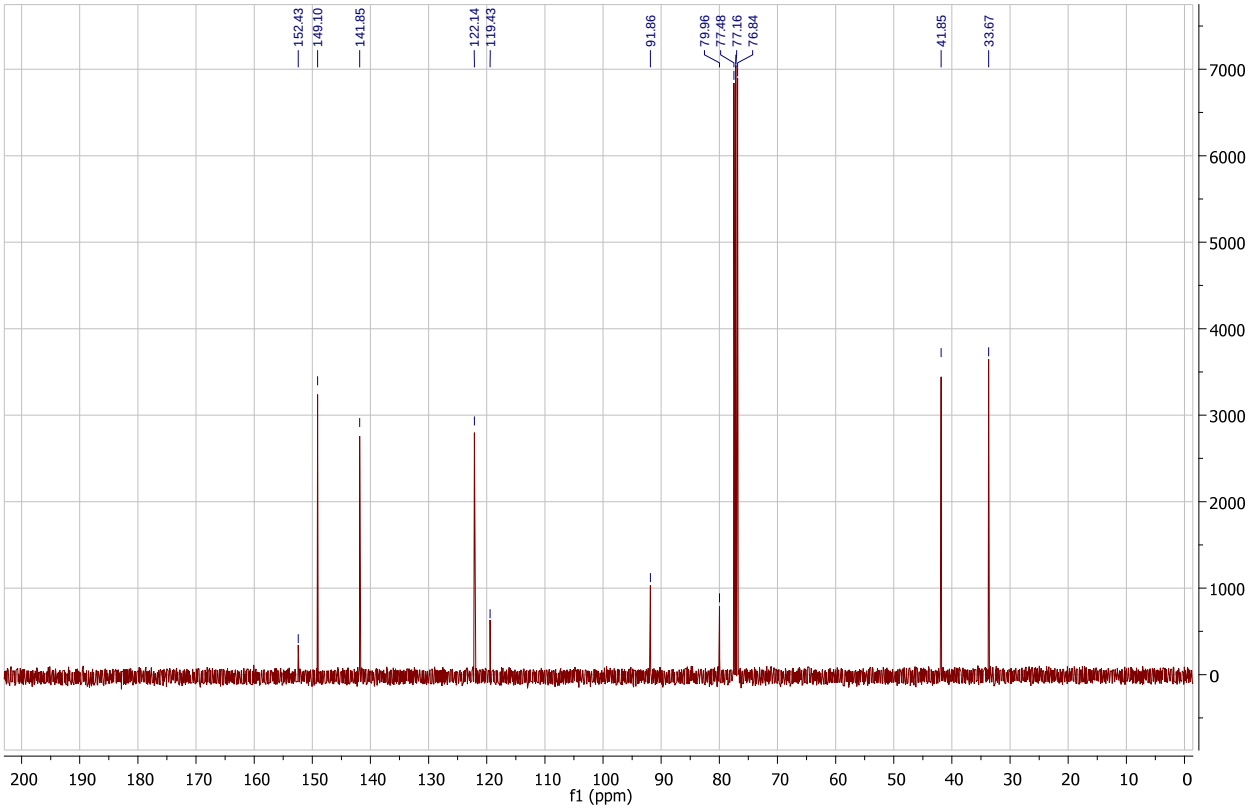

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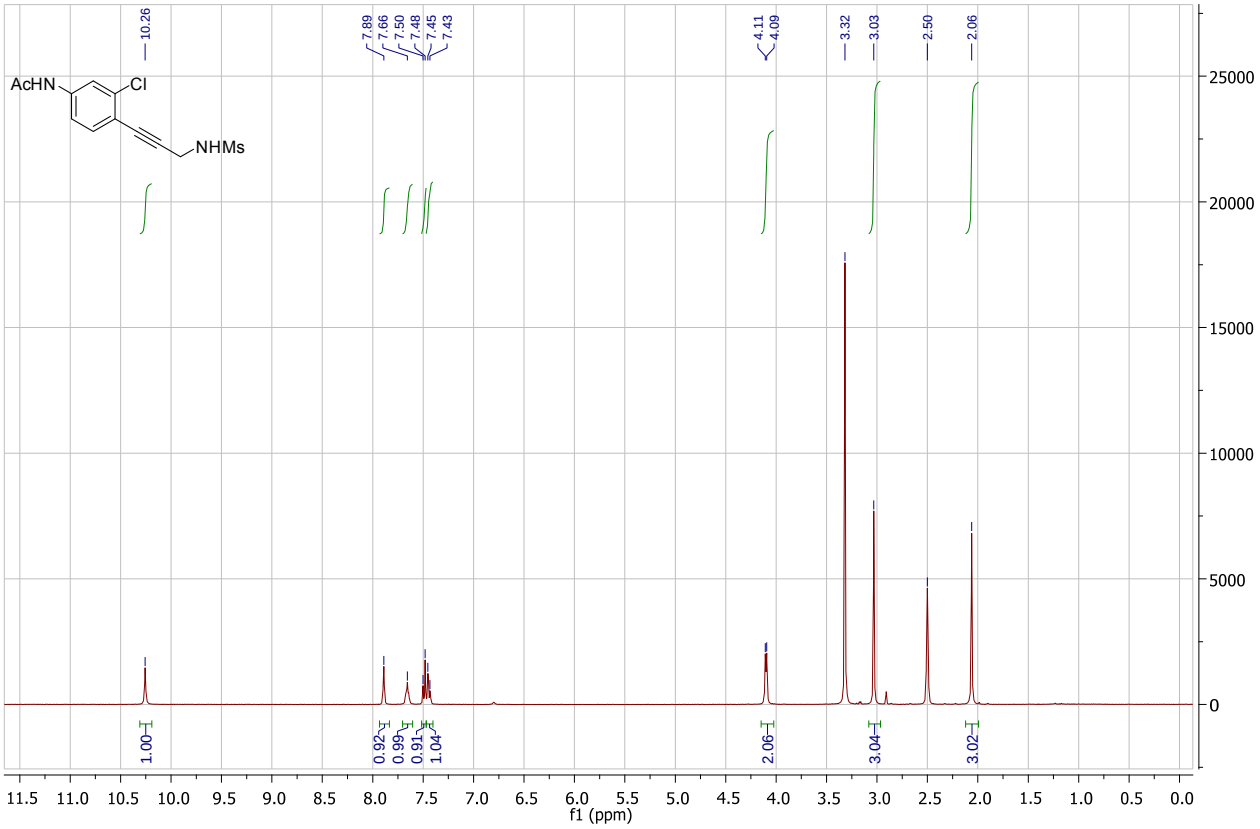

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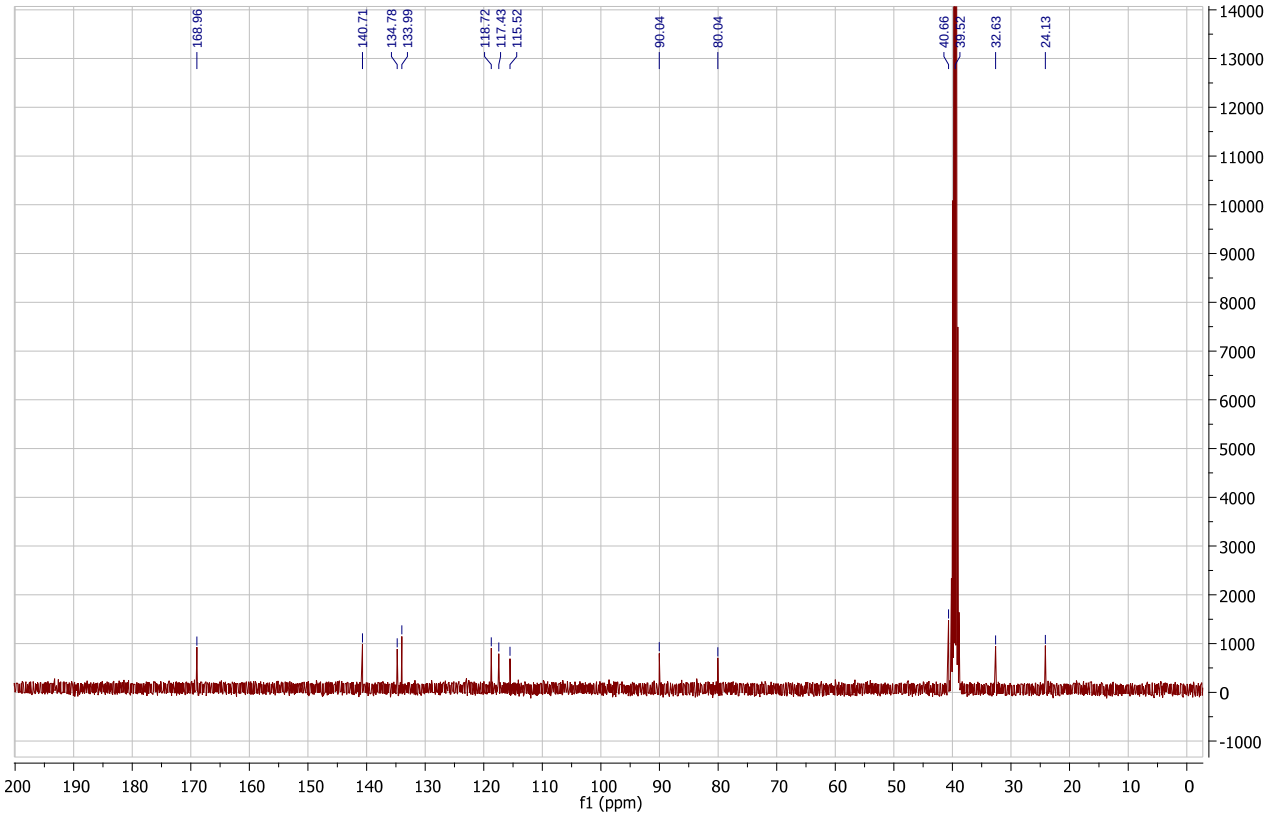

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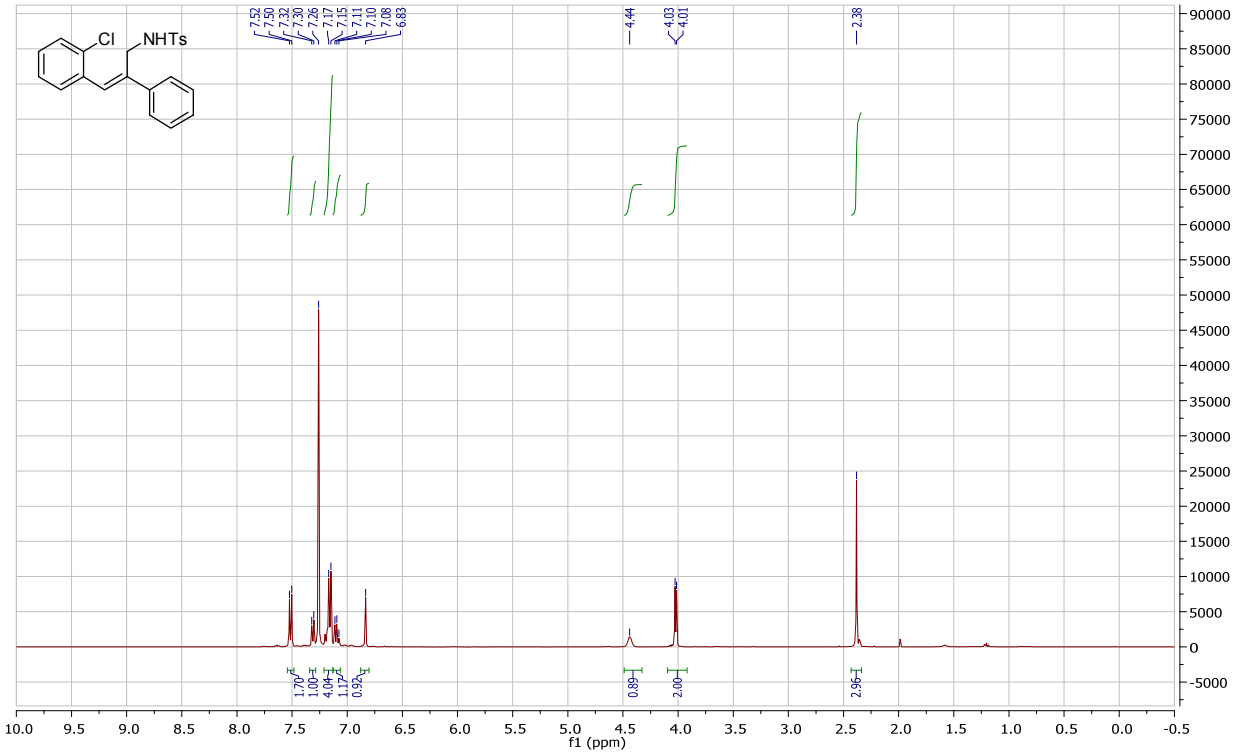

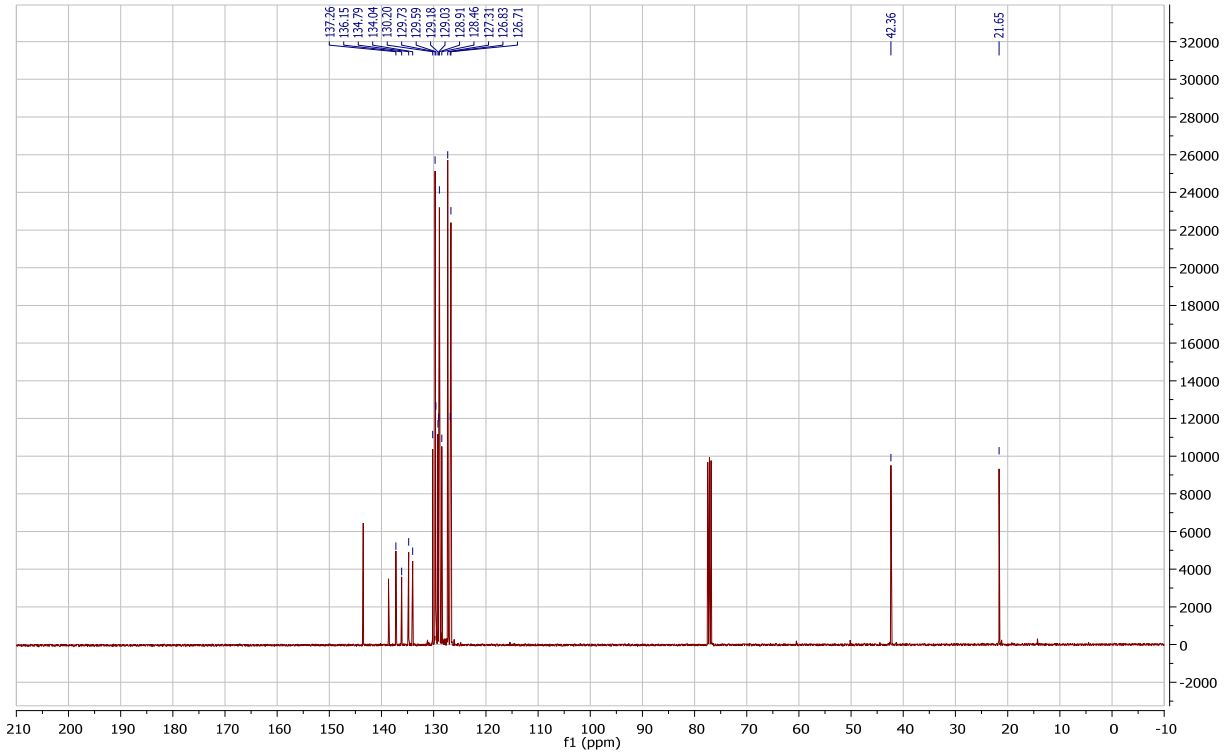

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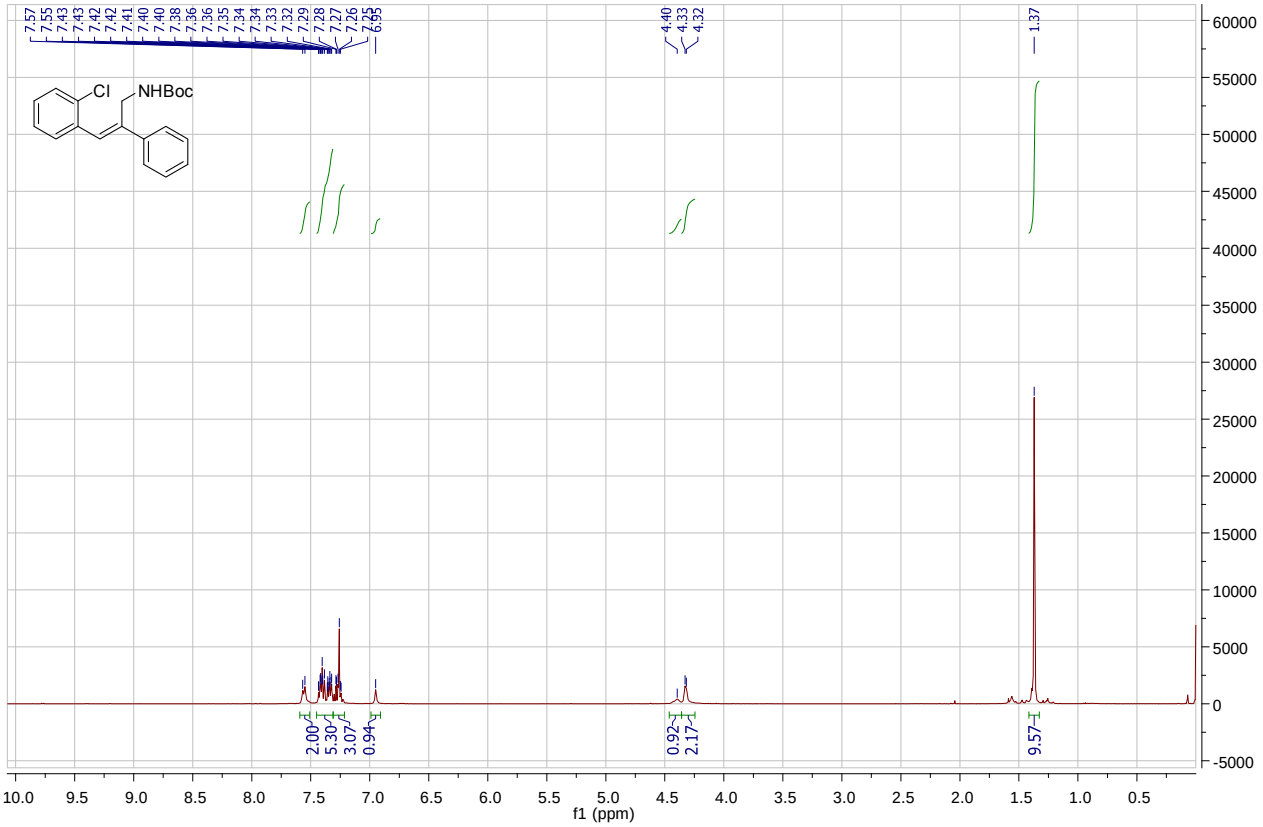

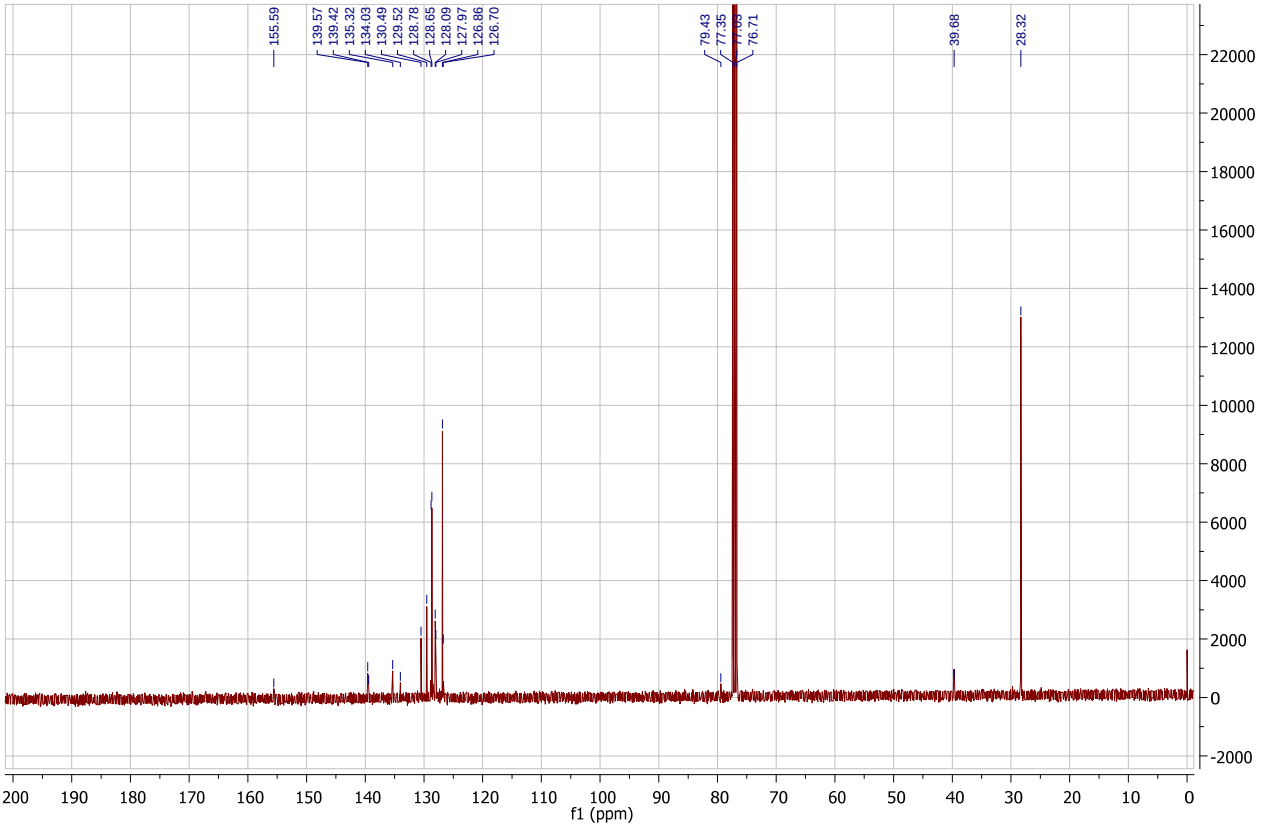

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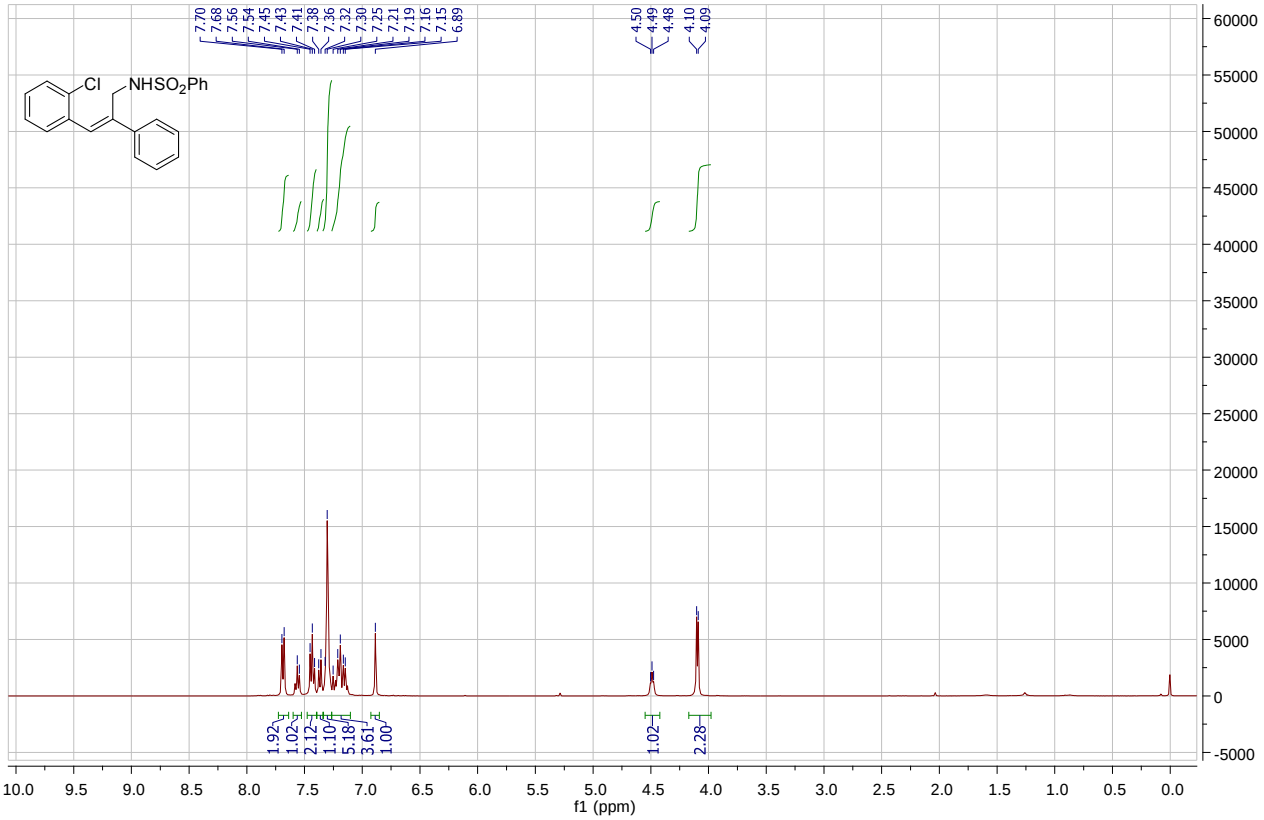

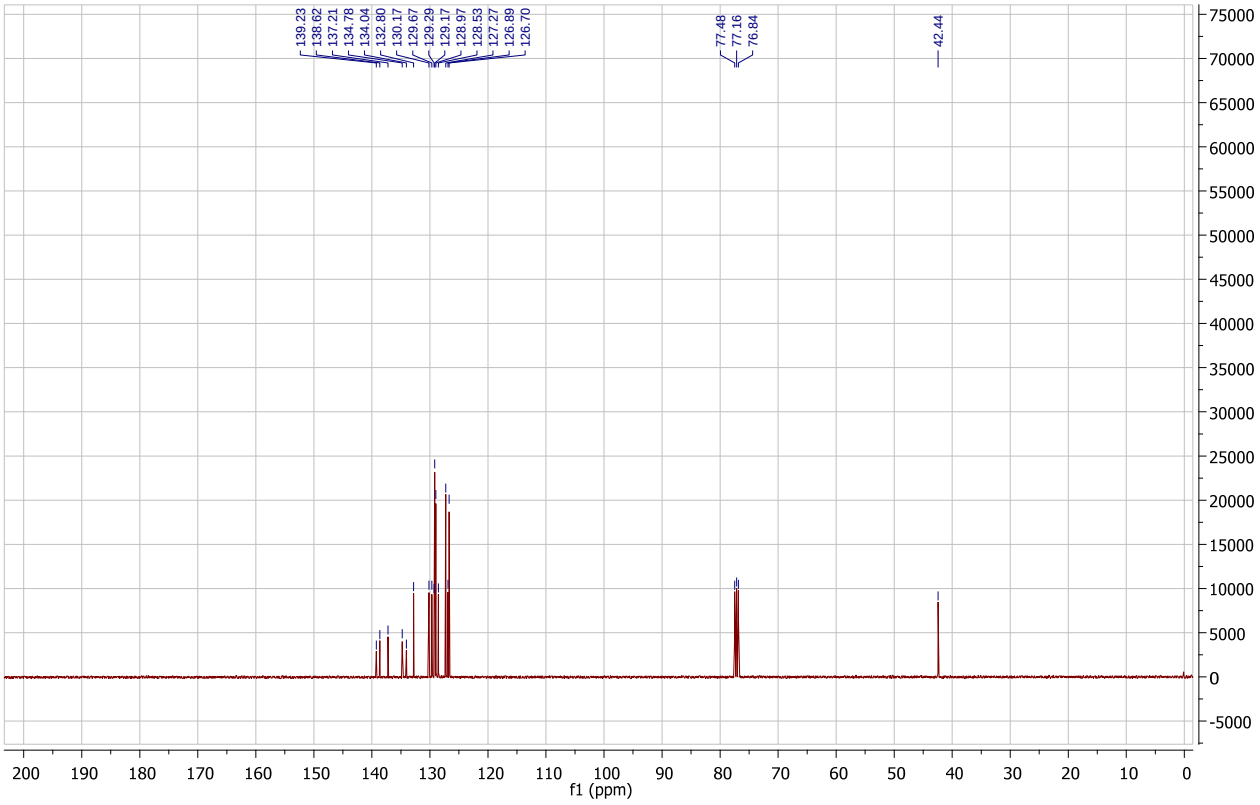

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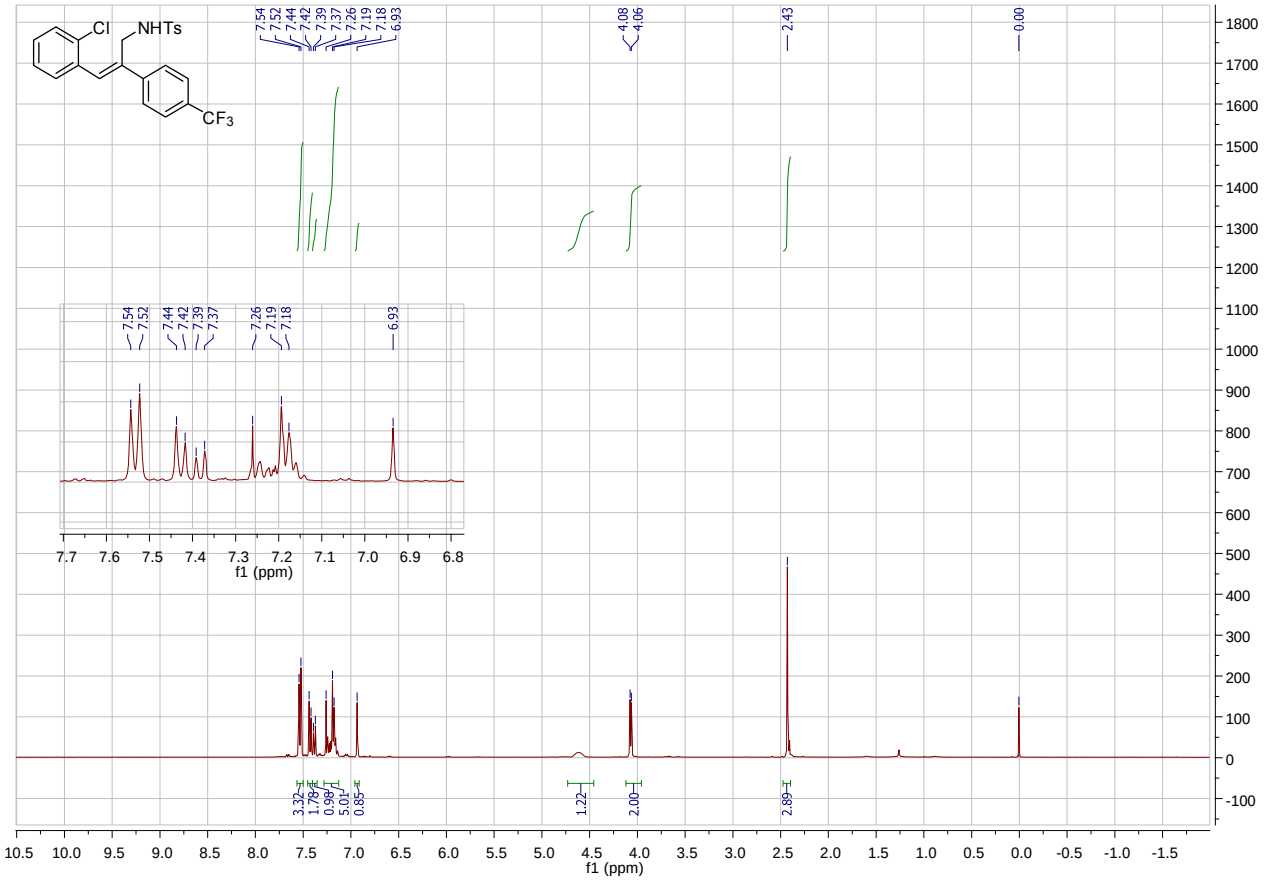

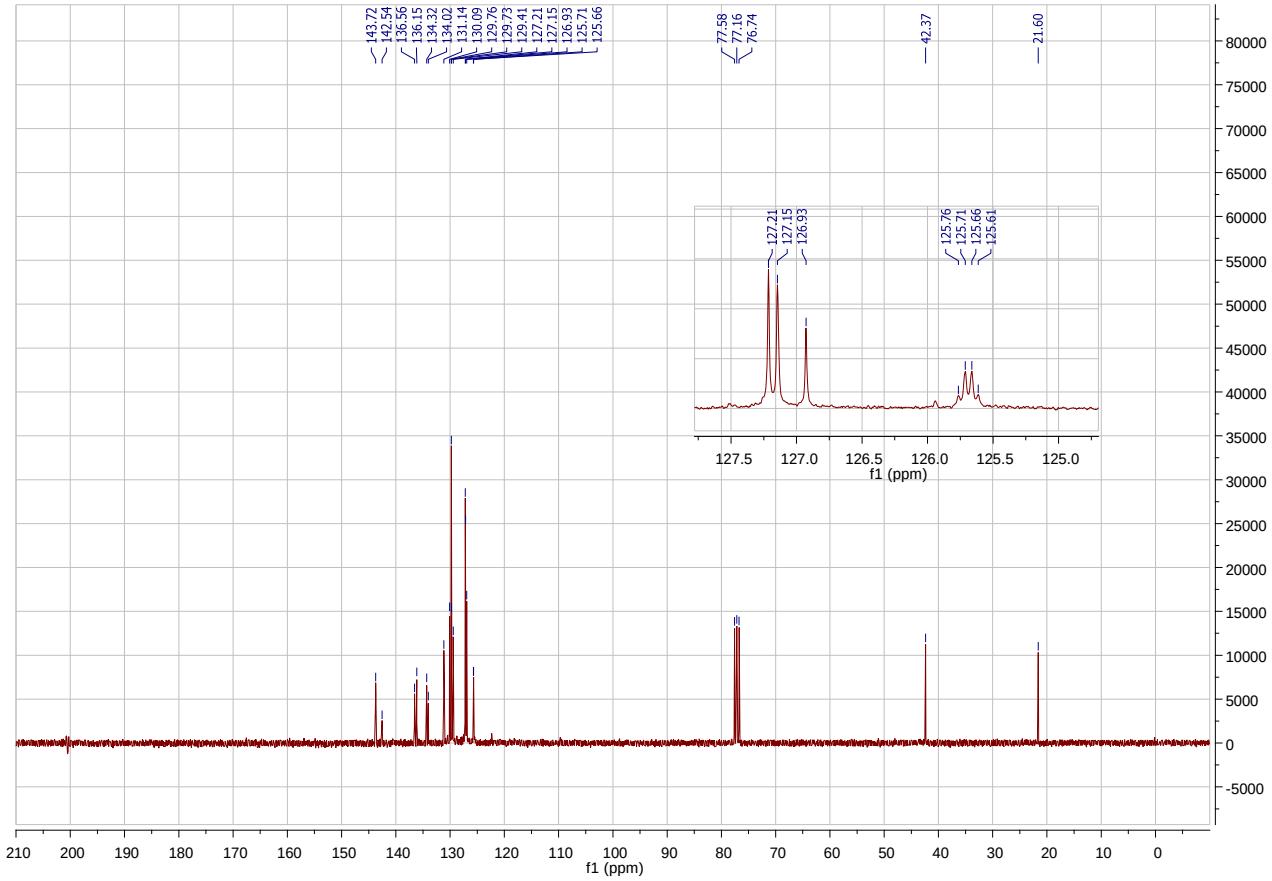

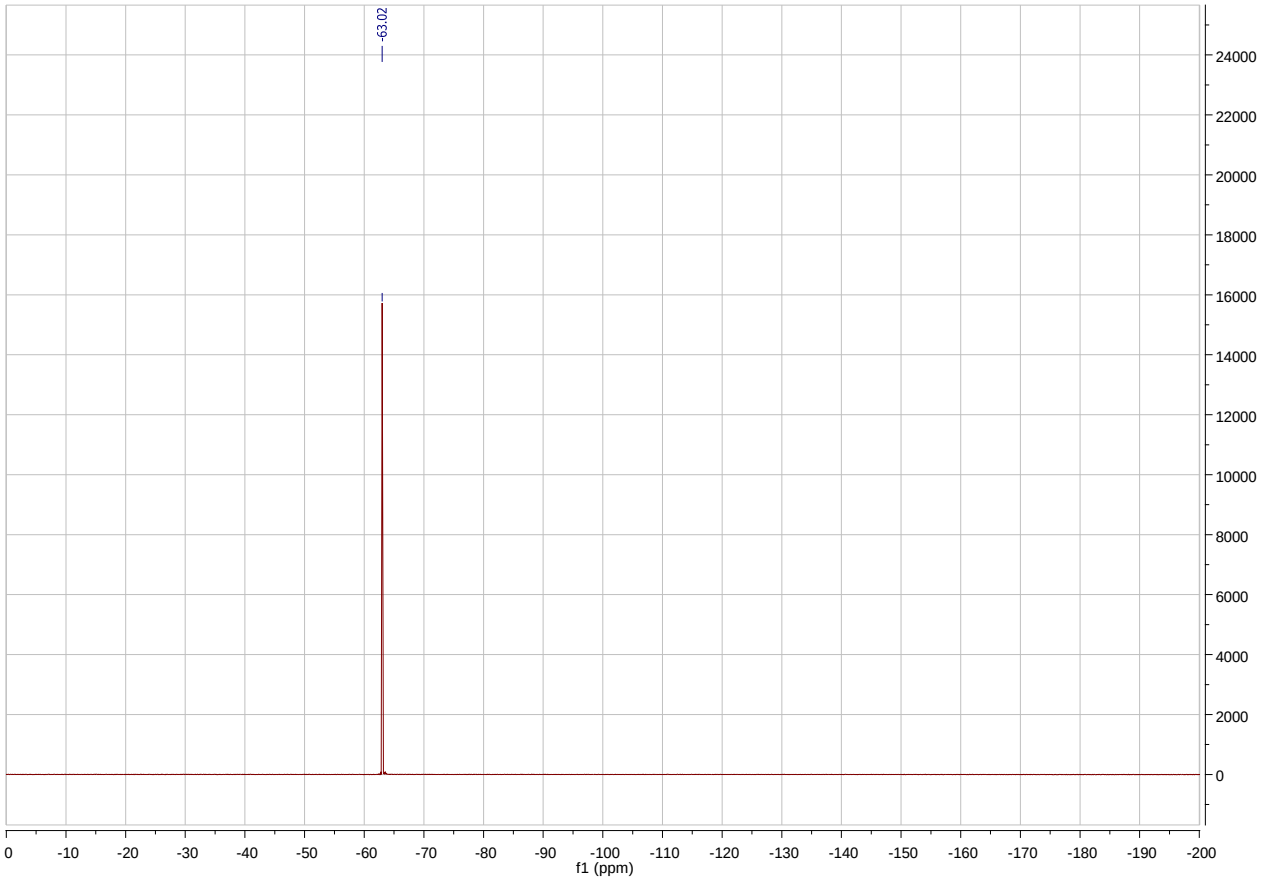
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20000
18000
16000
14000
12000
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4000
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-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

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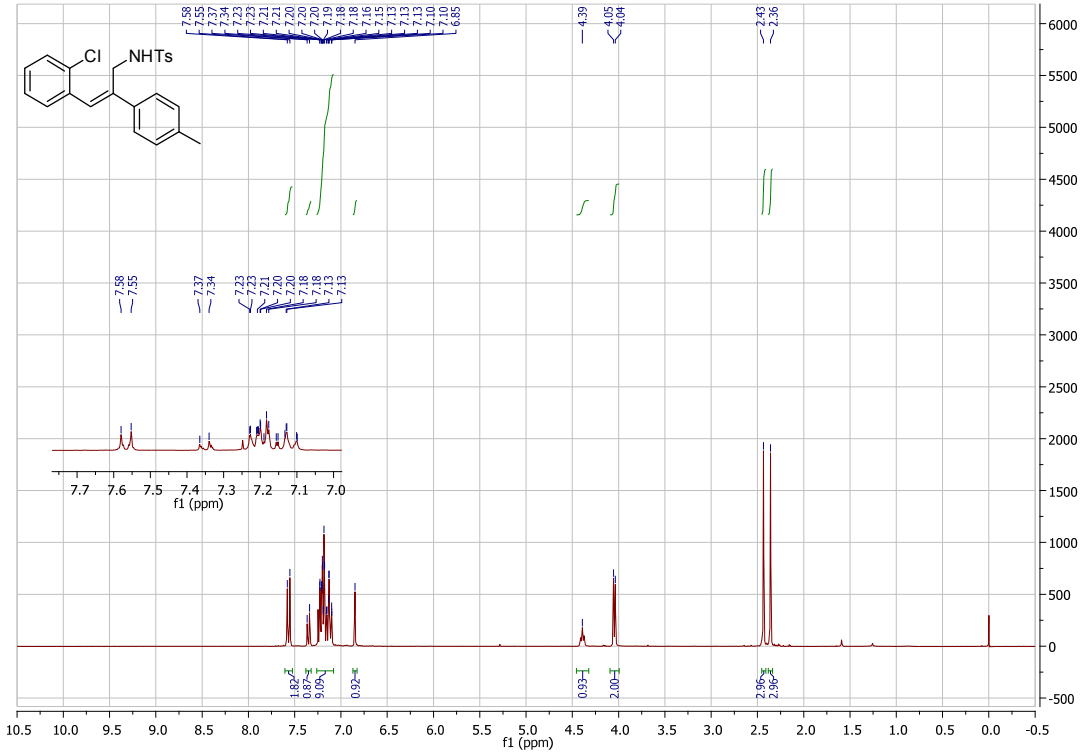

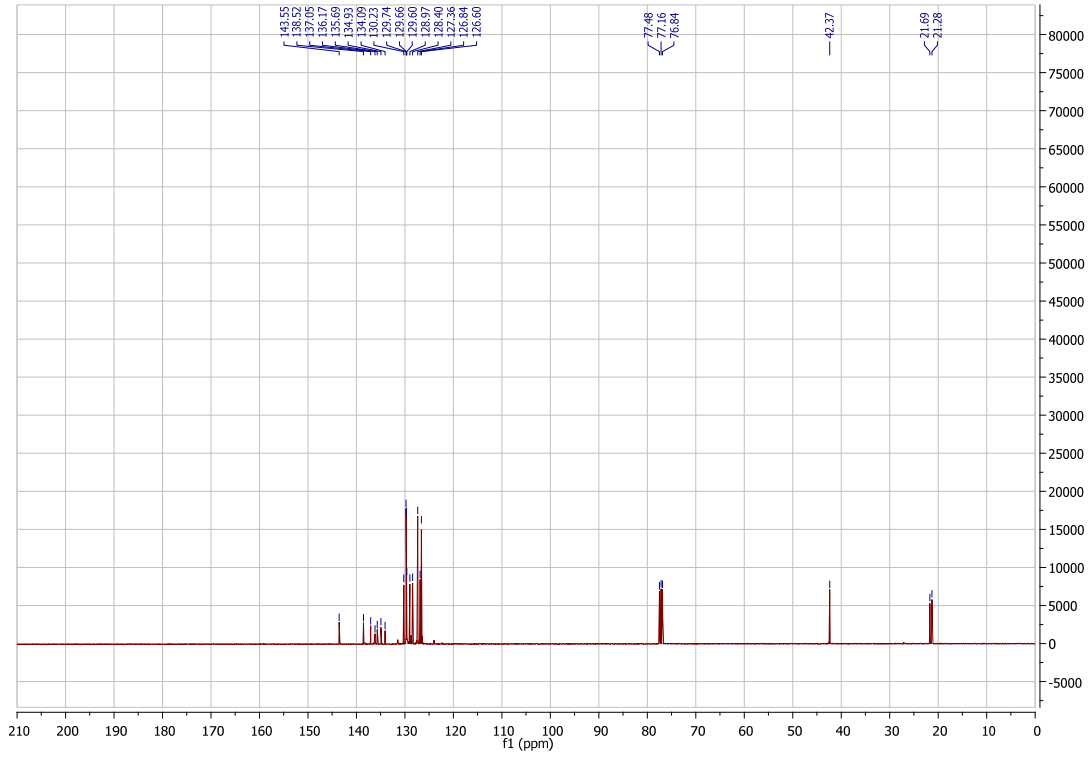

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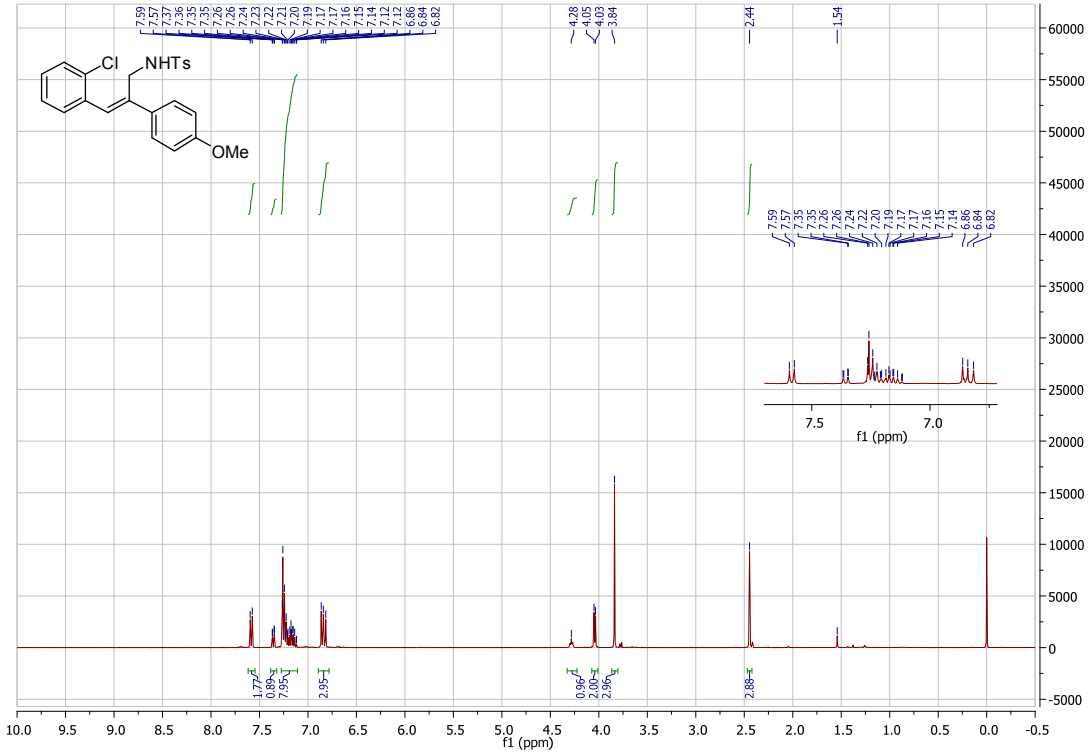

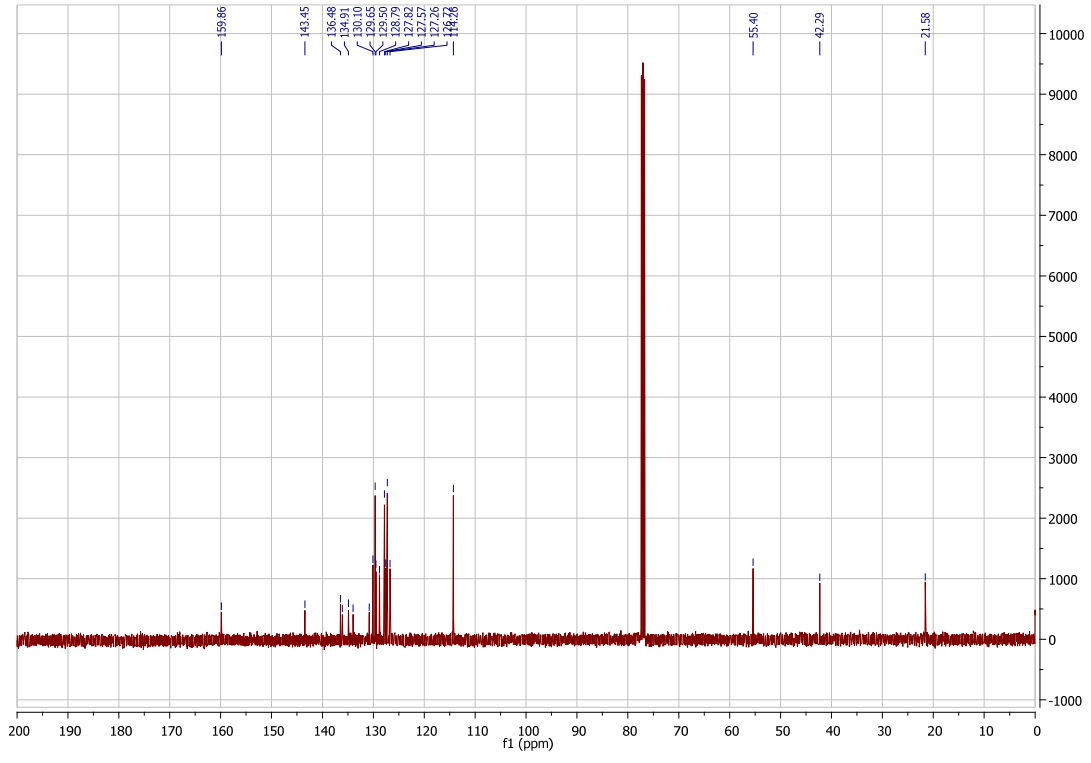

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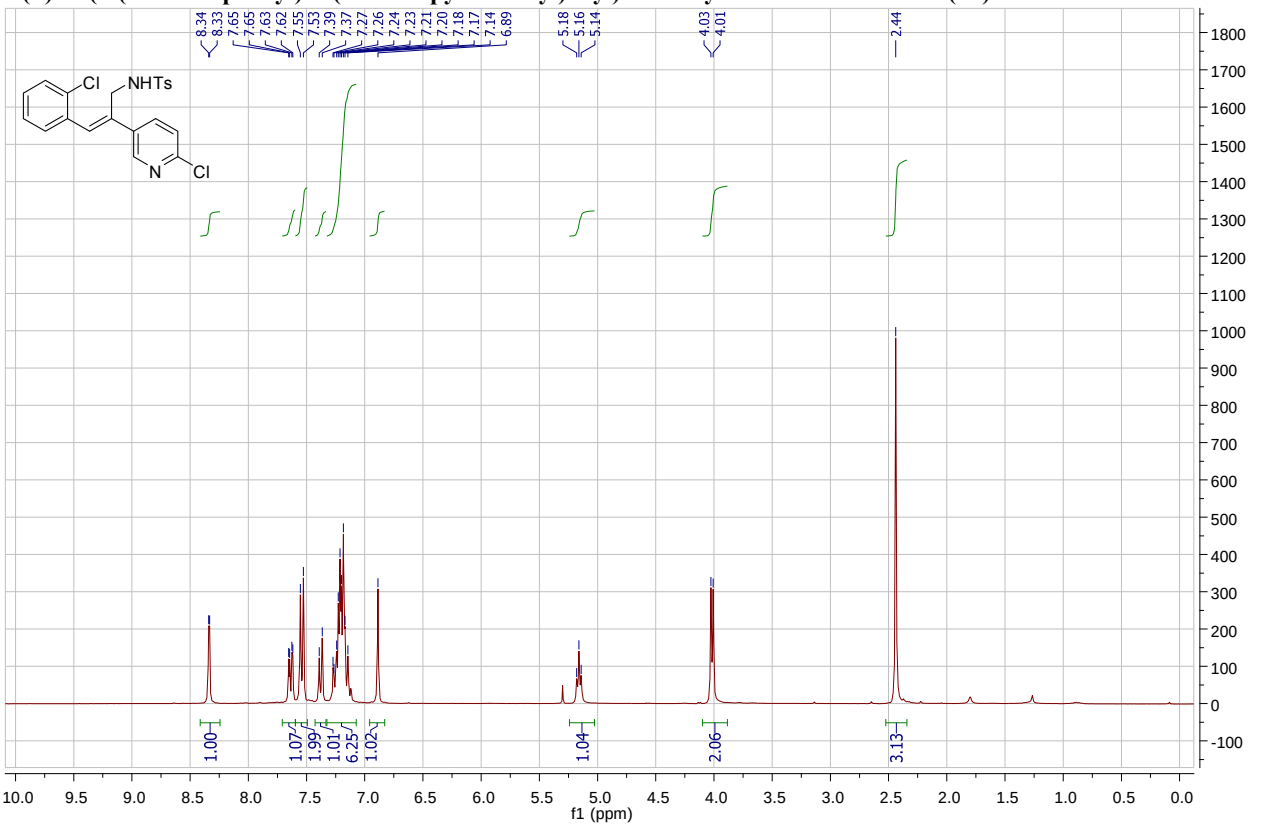

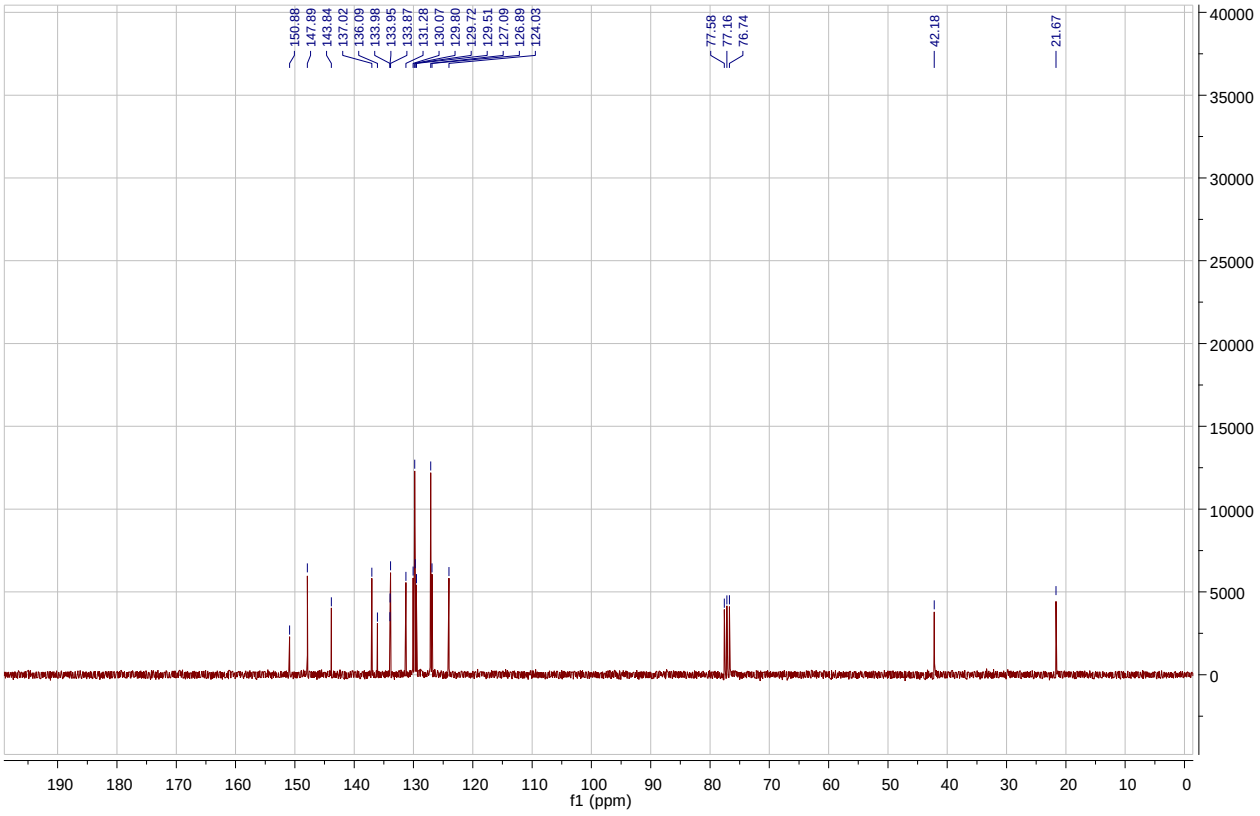

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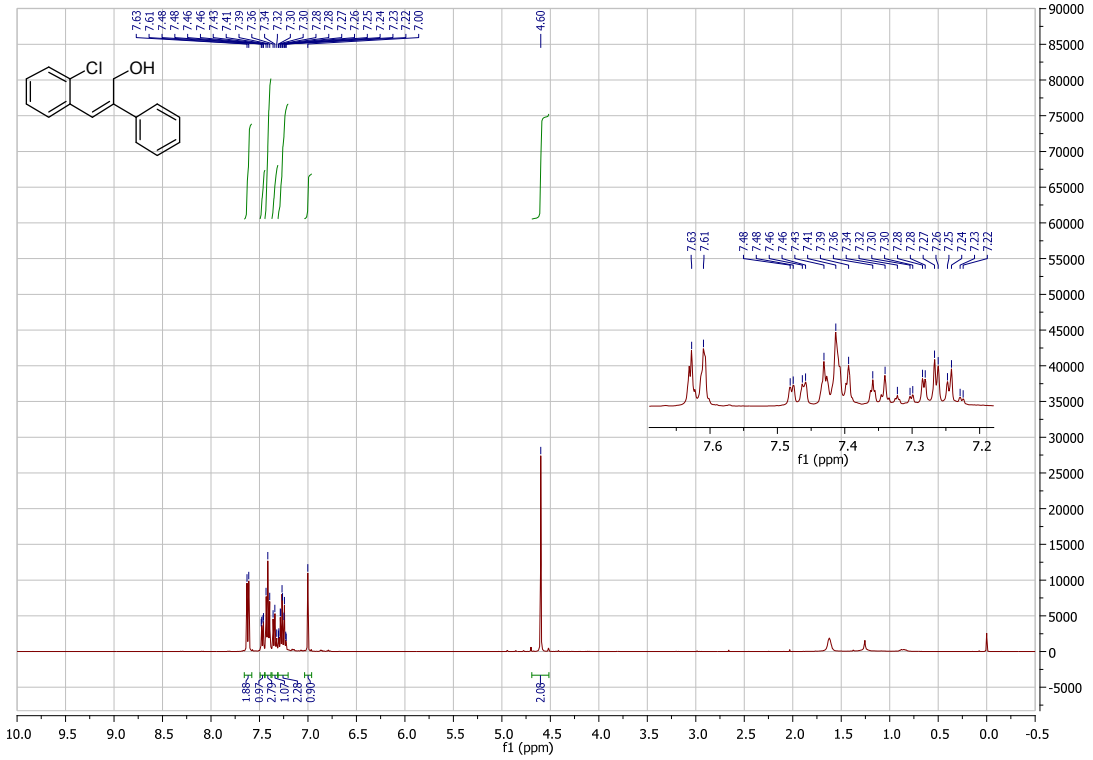

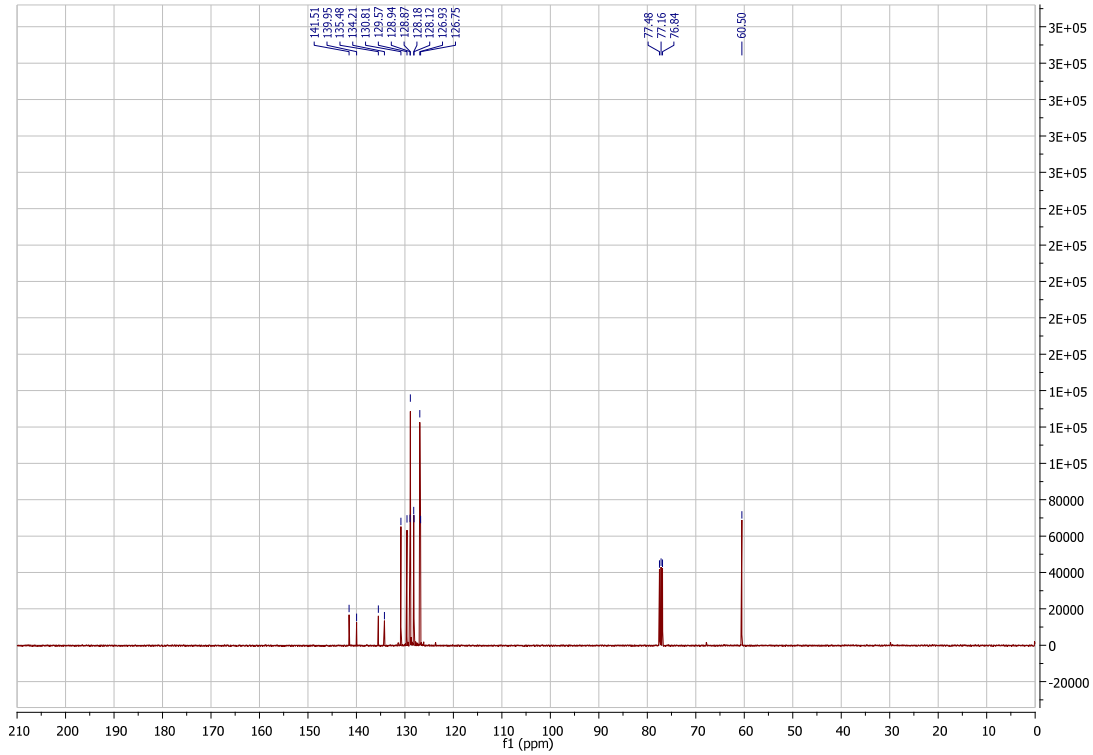

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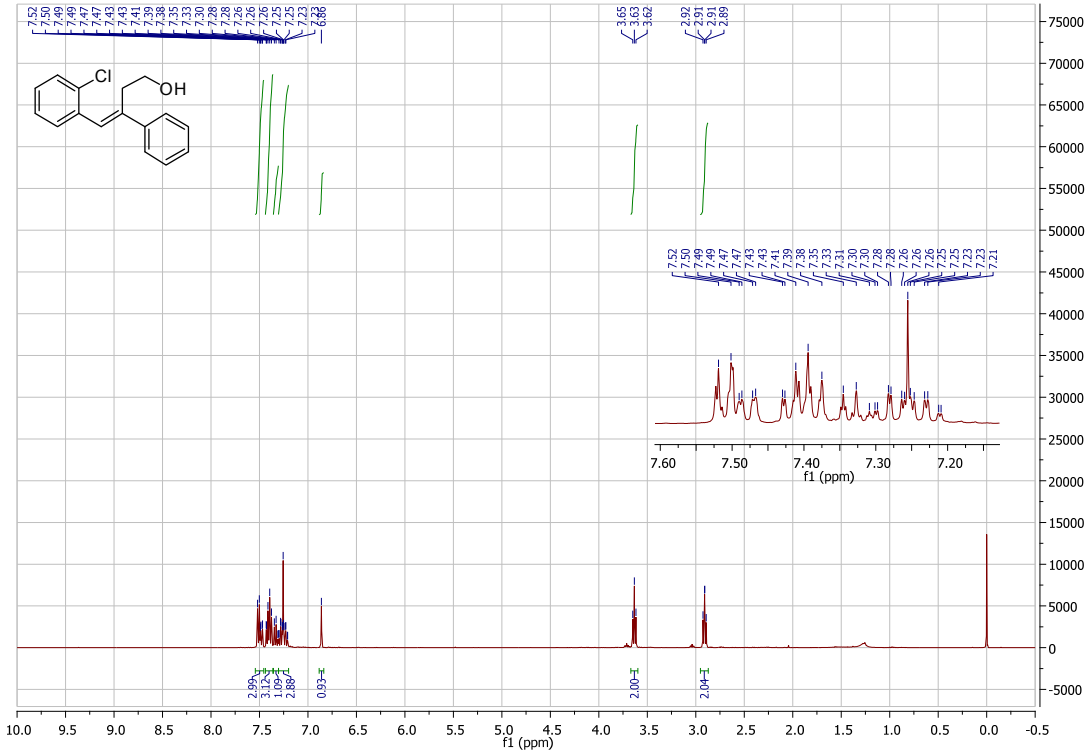

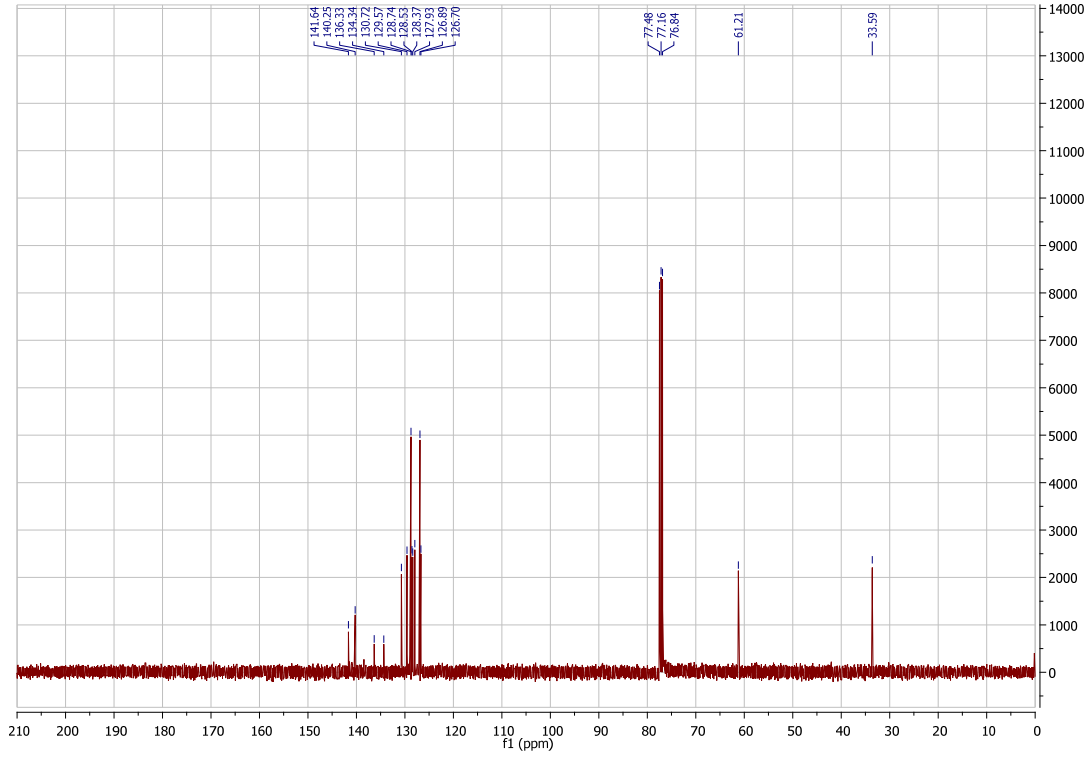

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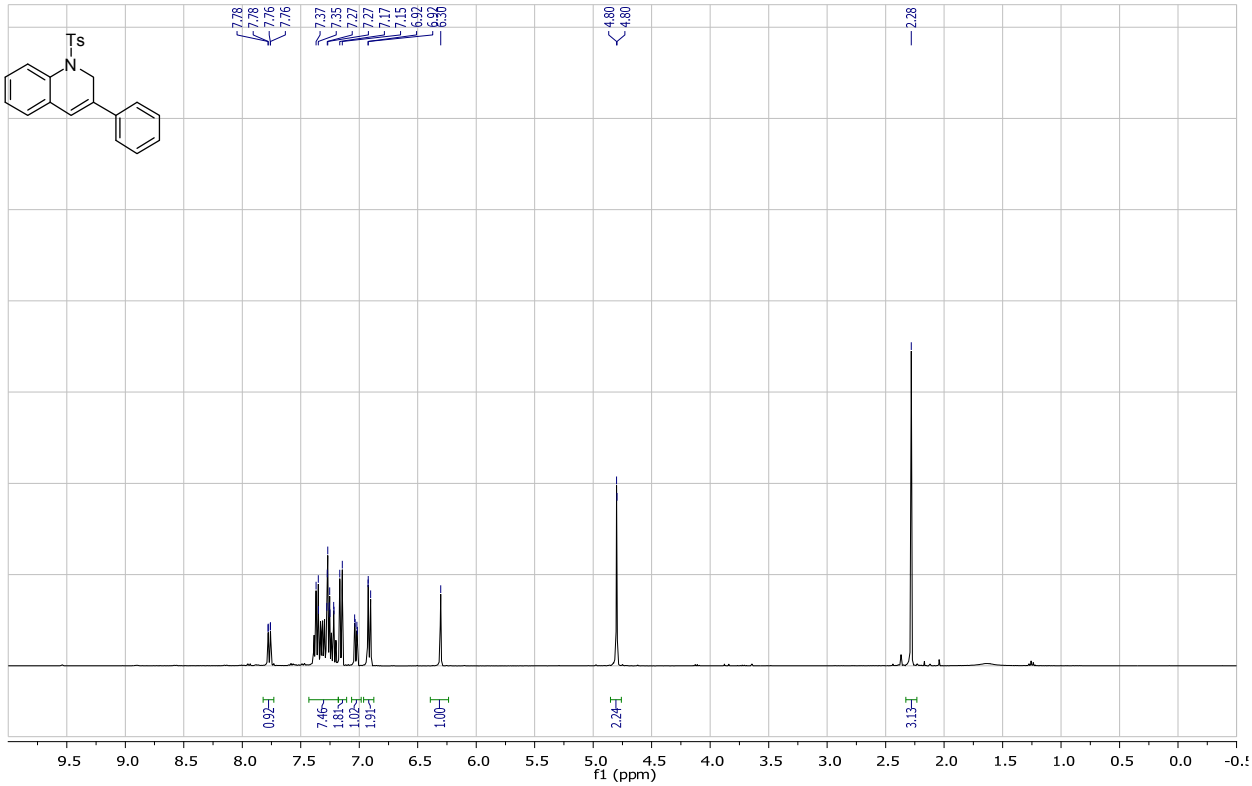

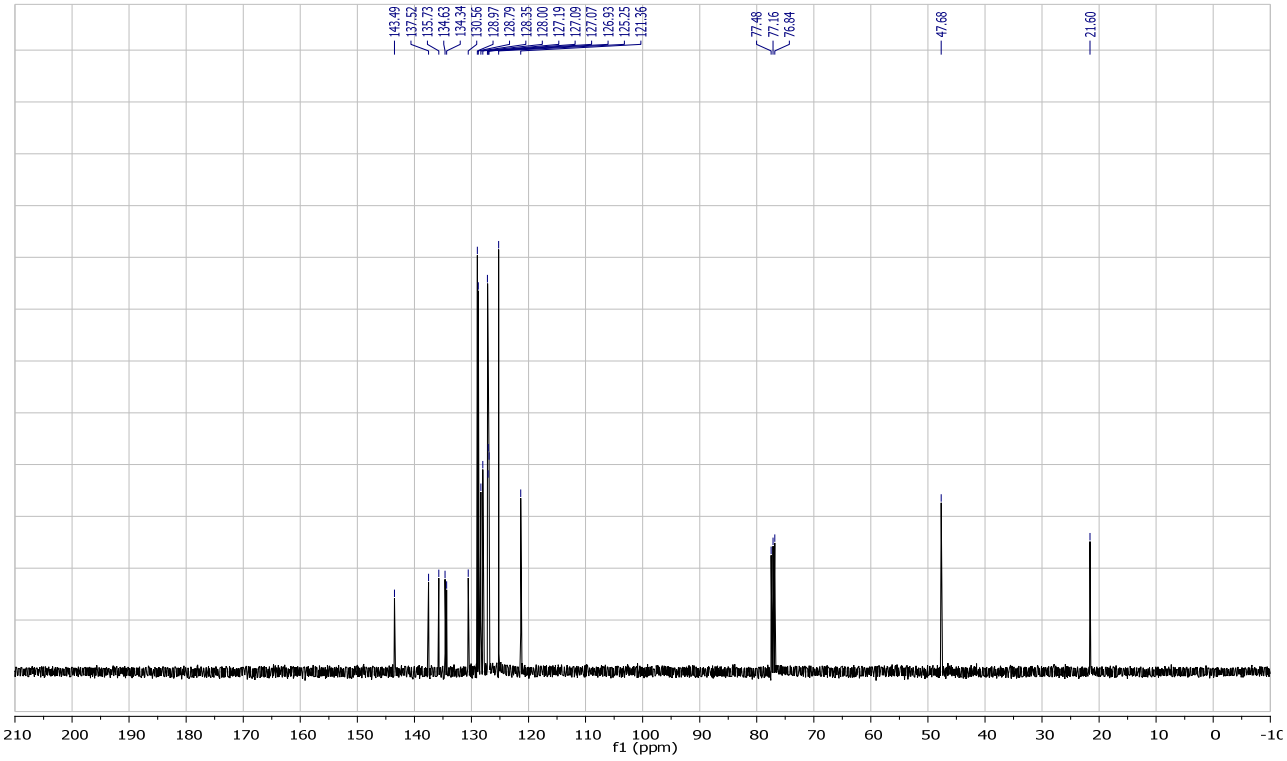

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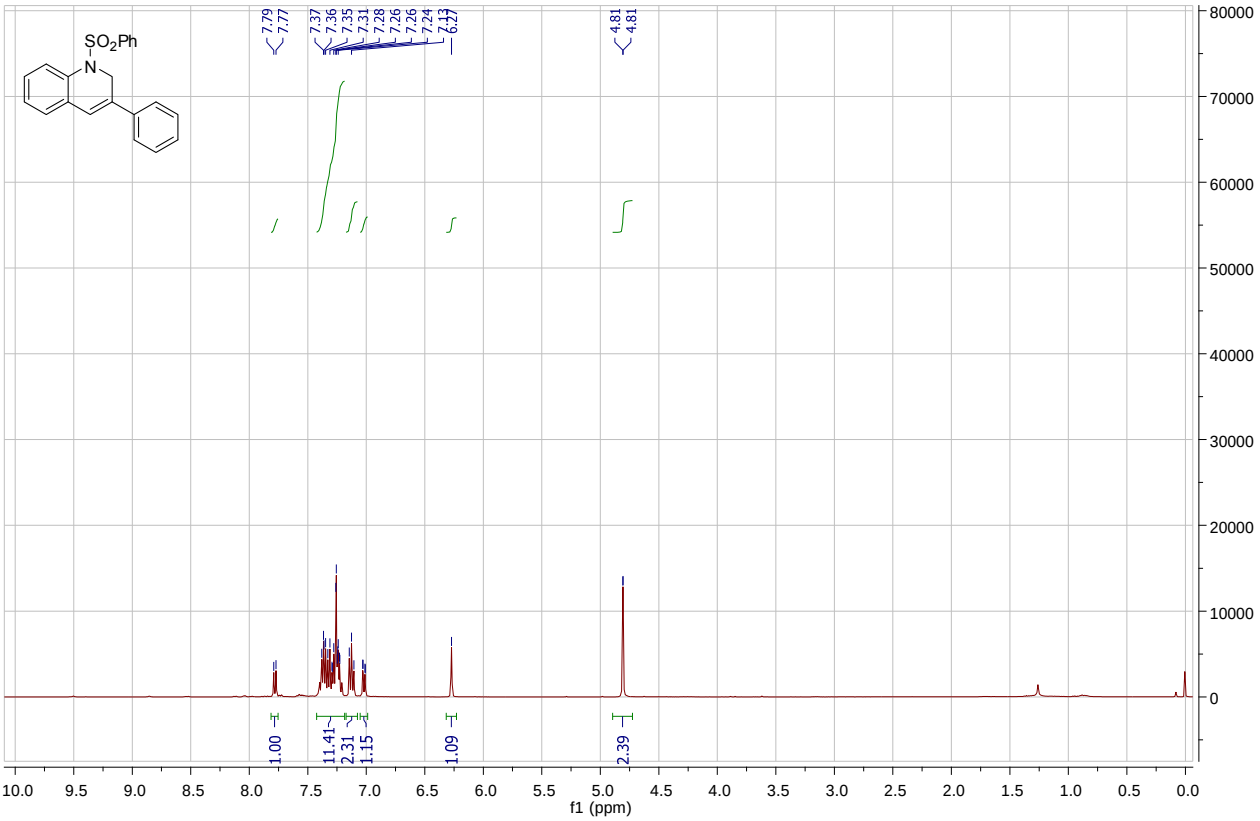

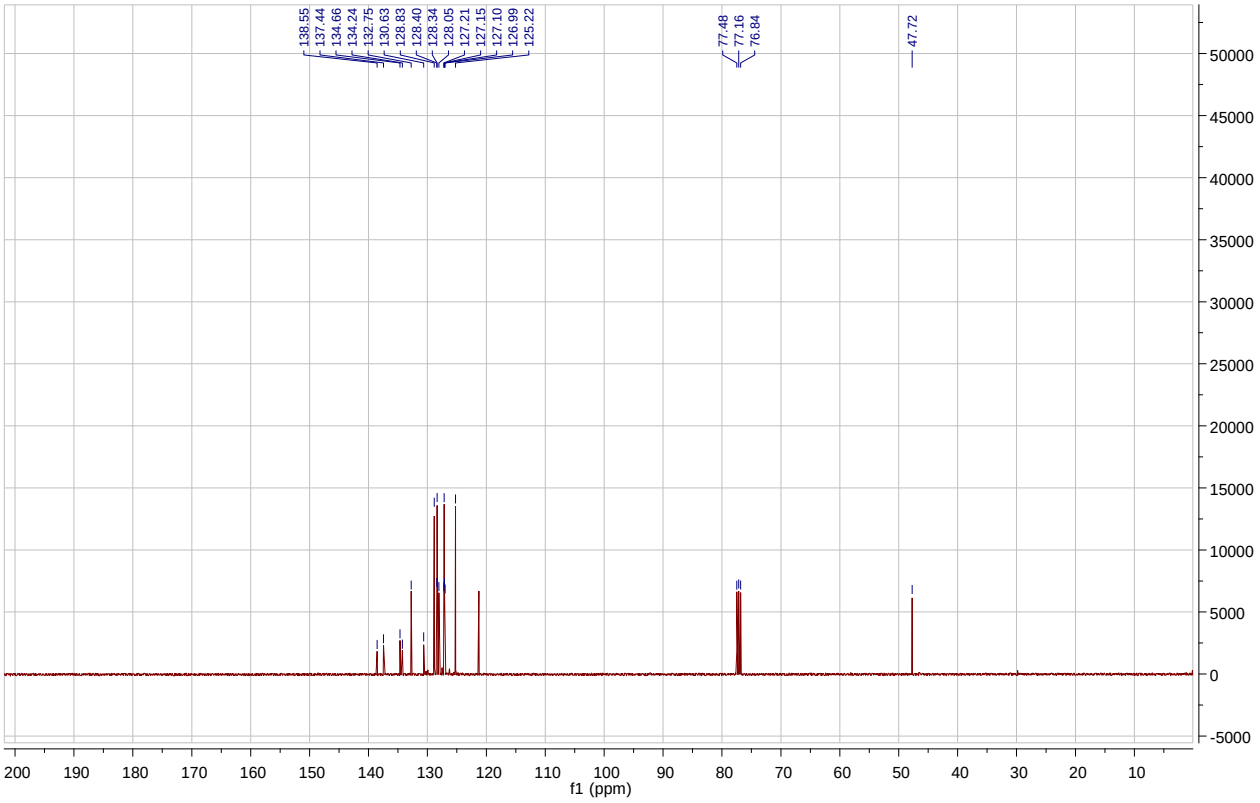

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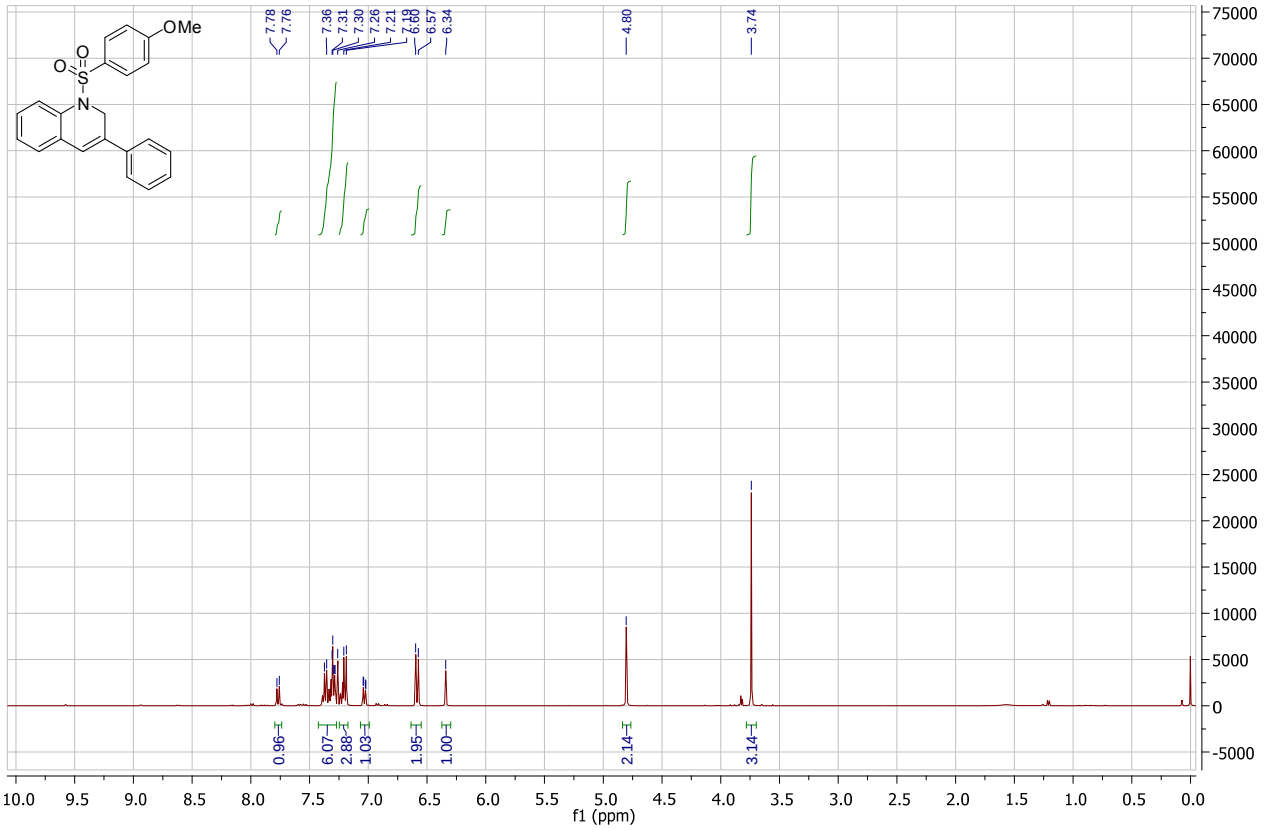

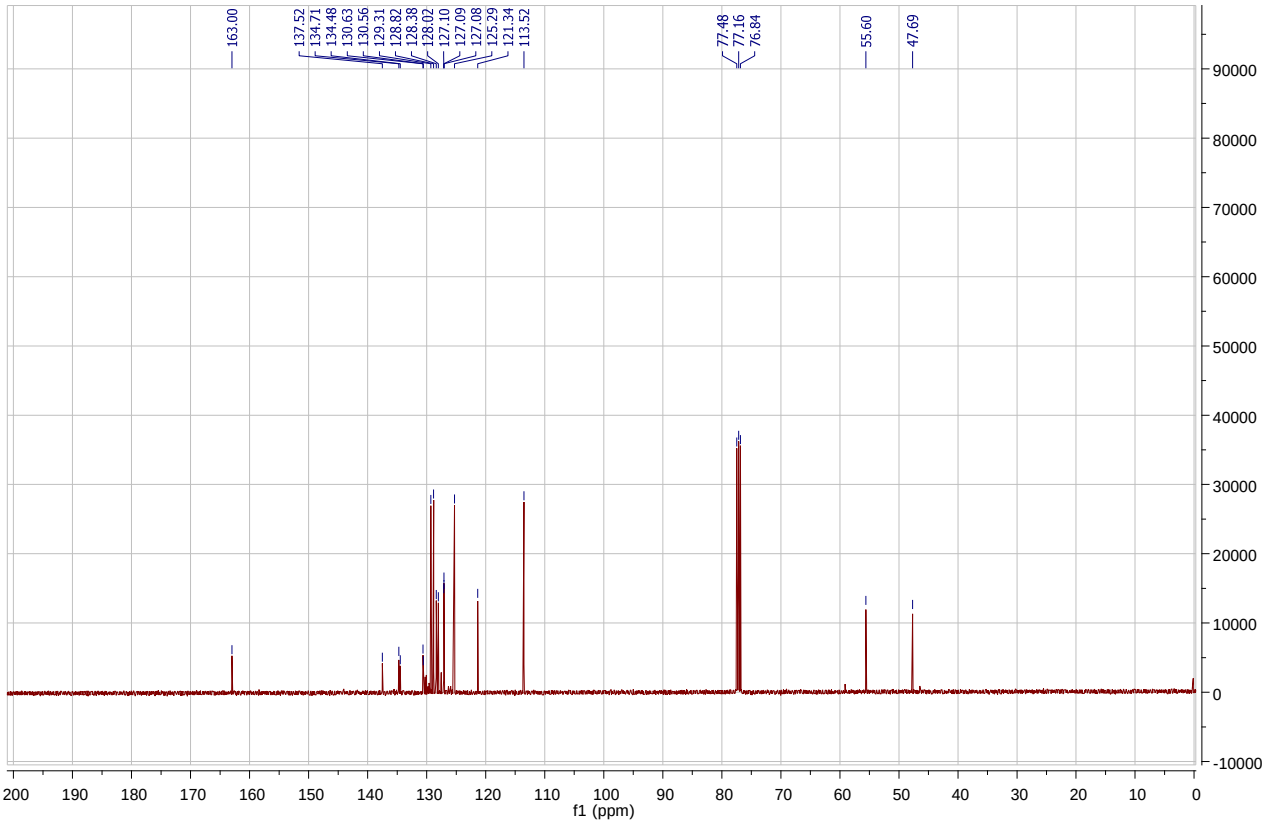

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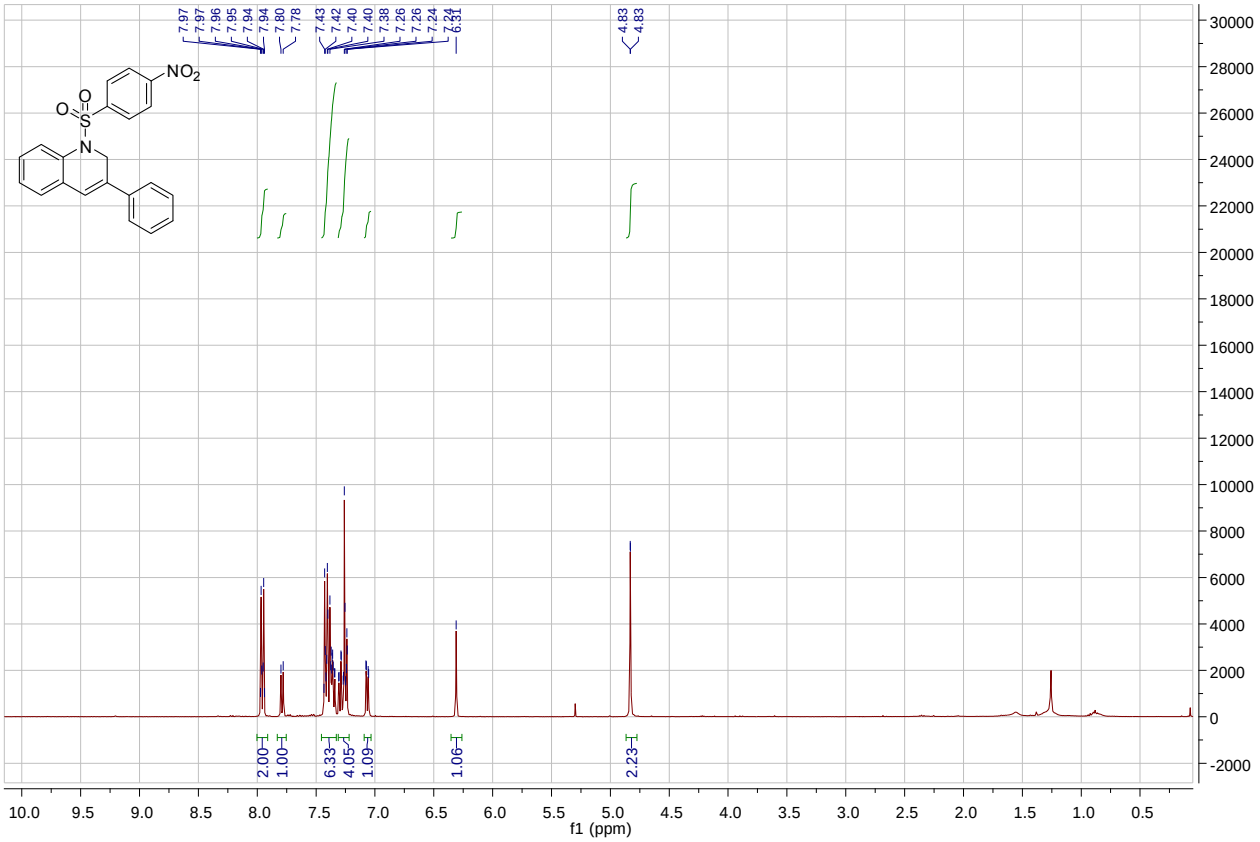

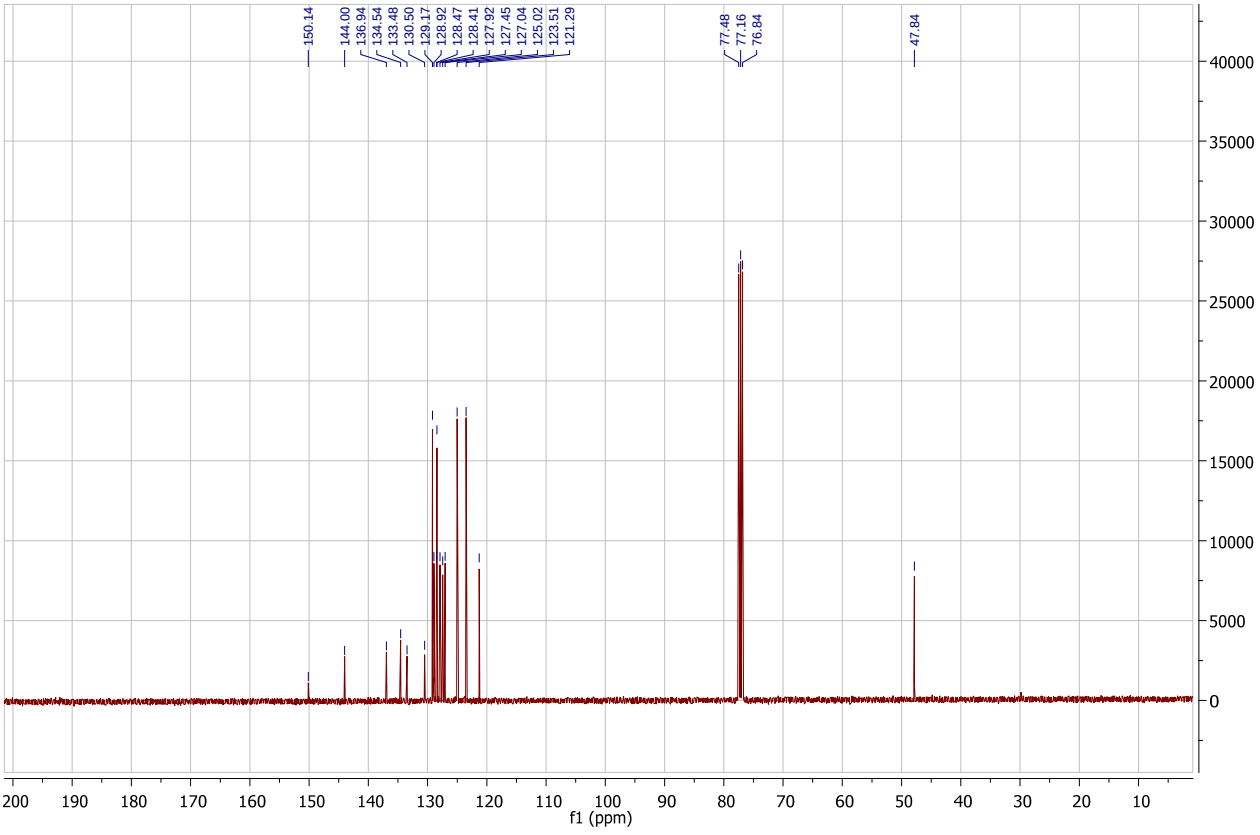

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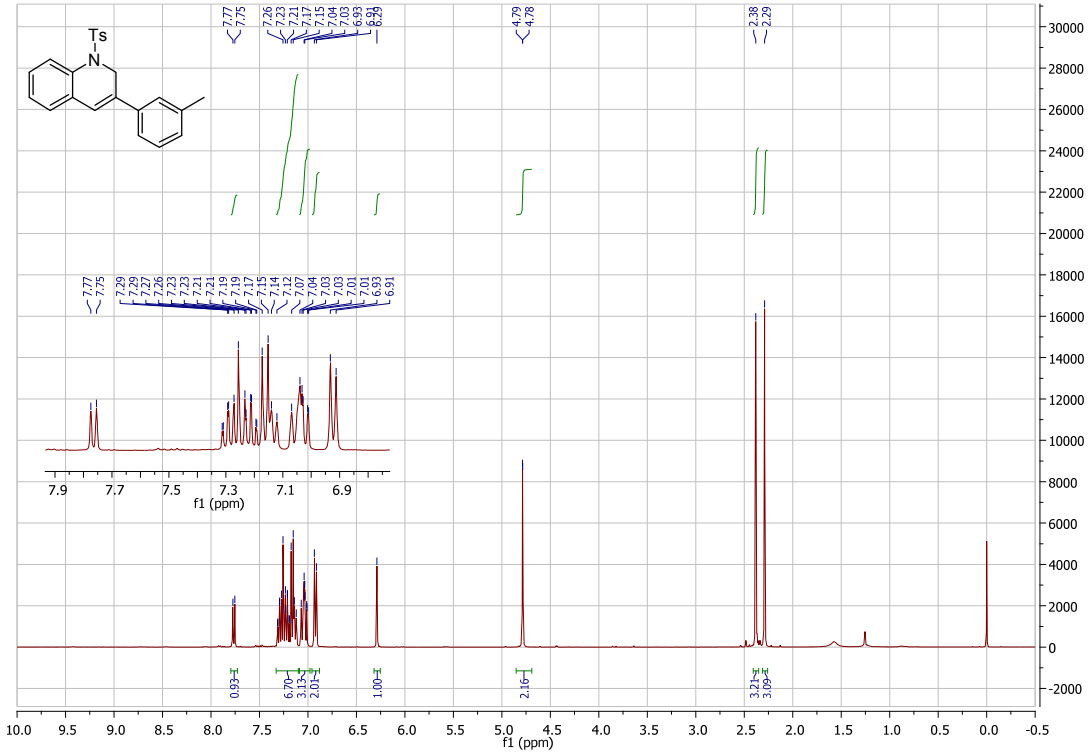

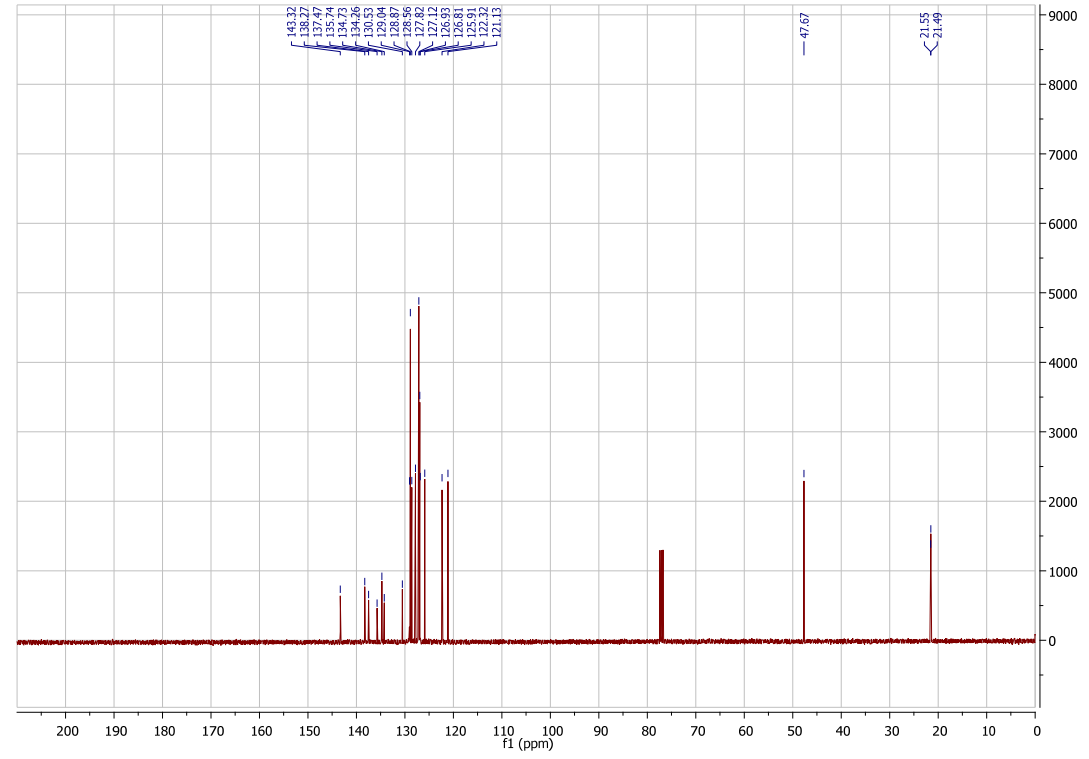

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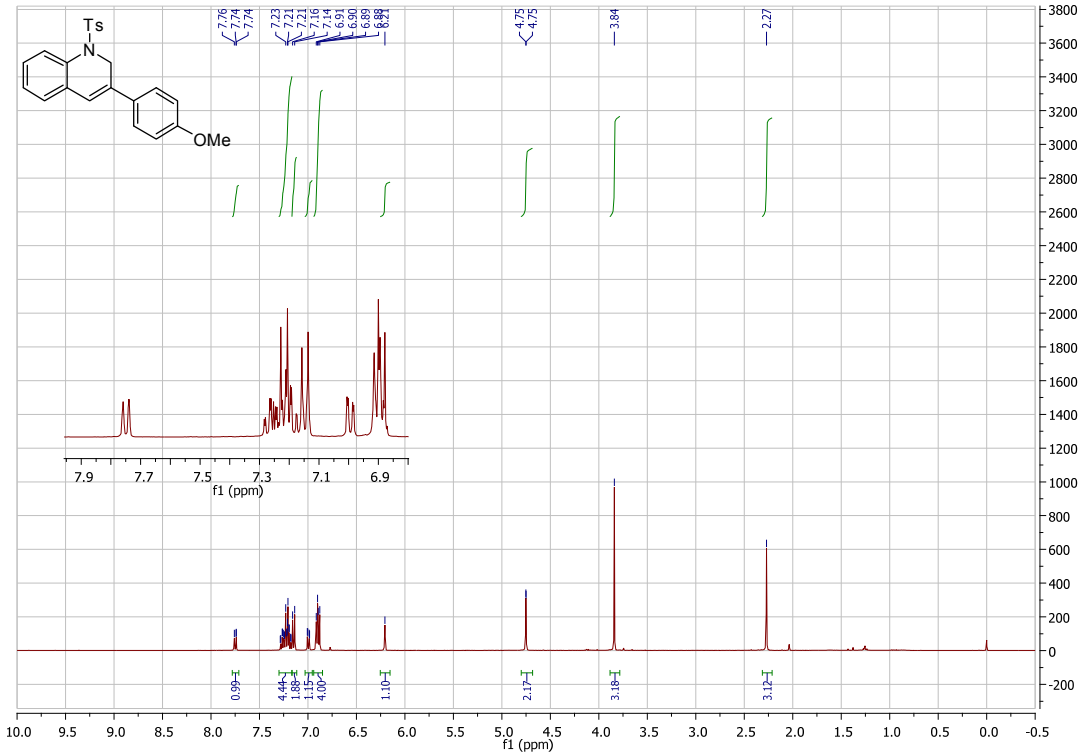

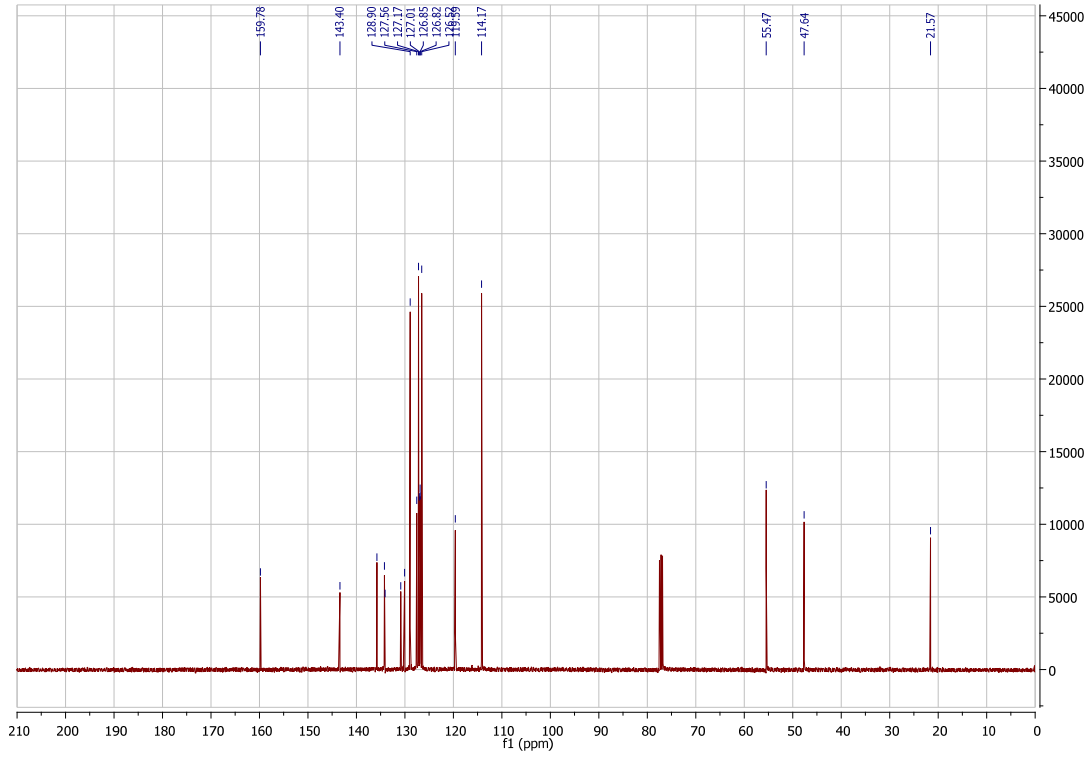

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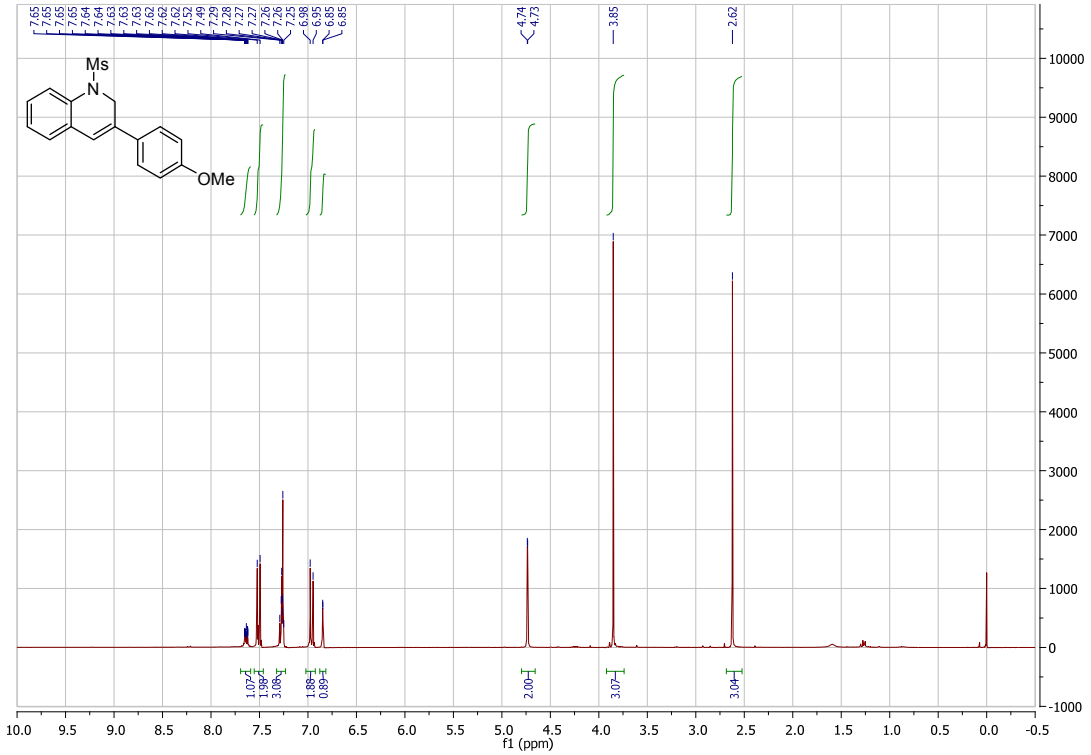
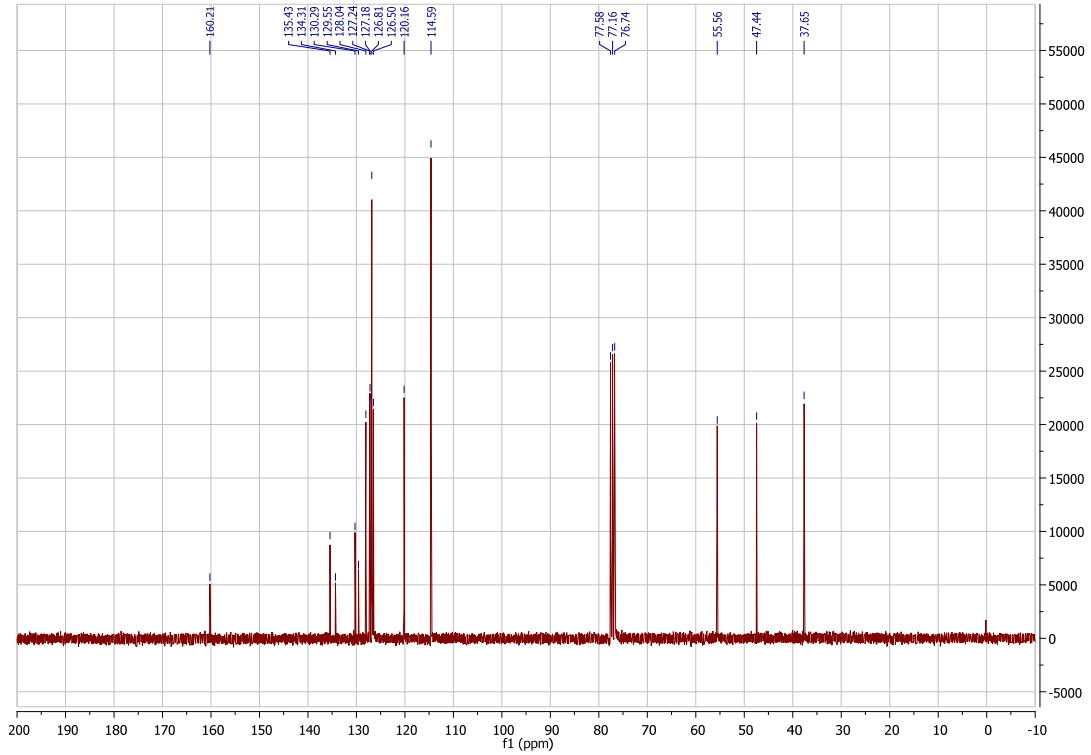
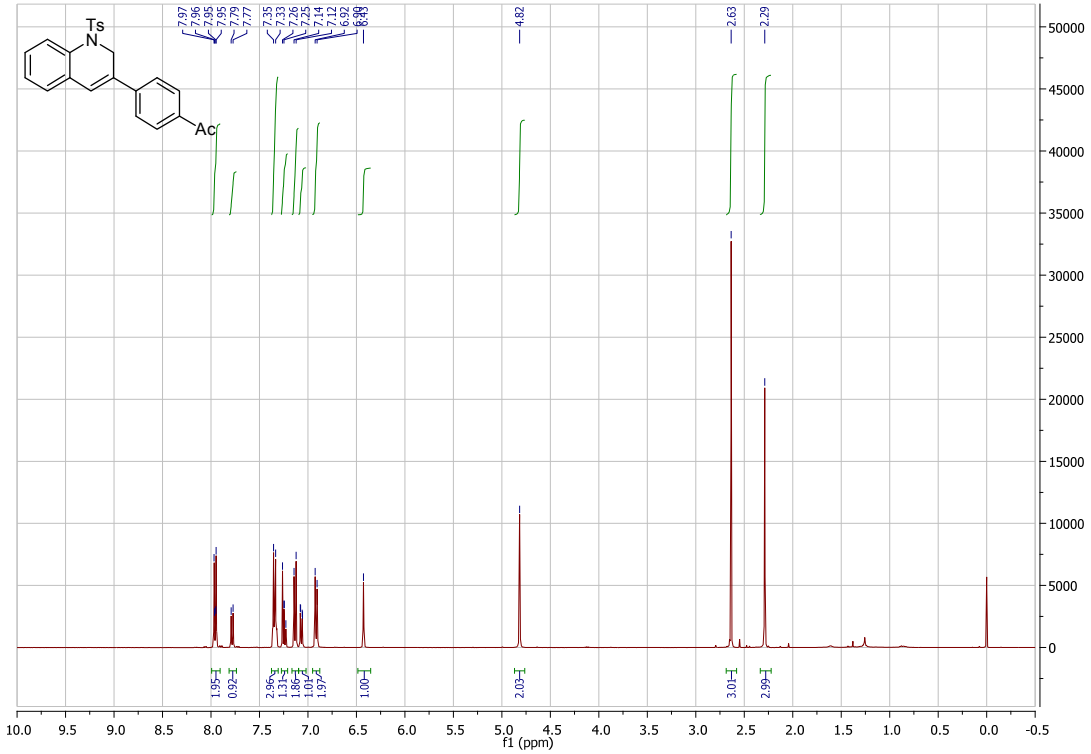
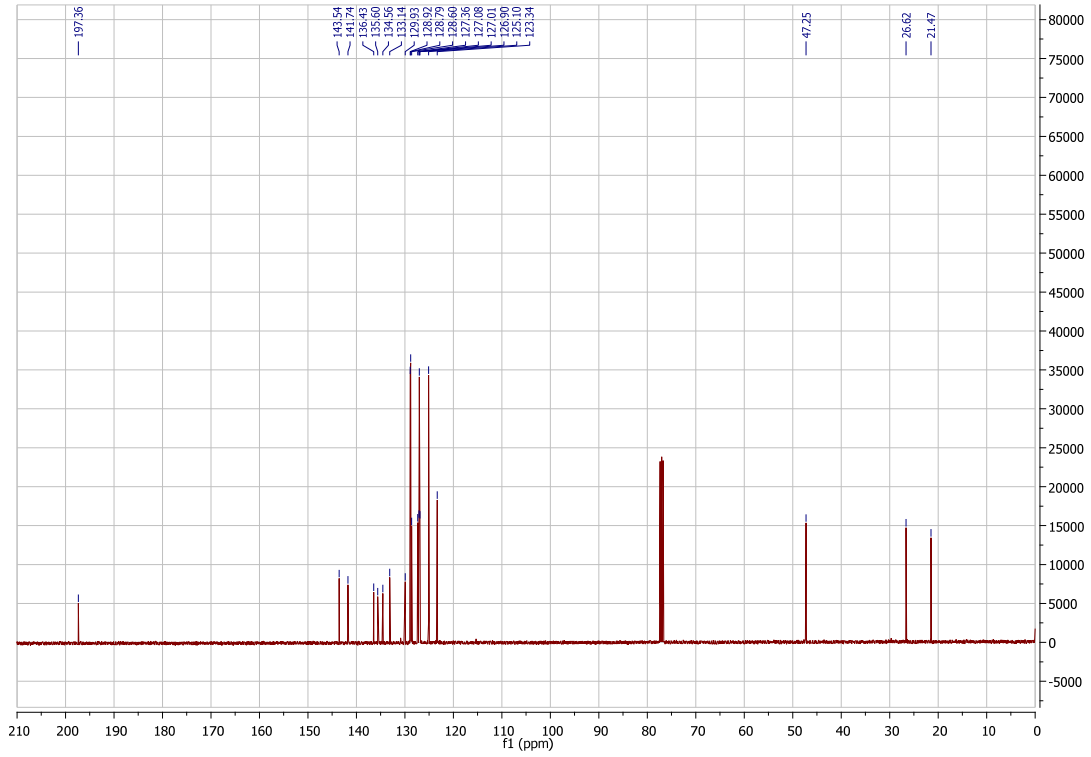


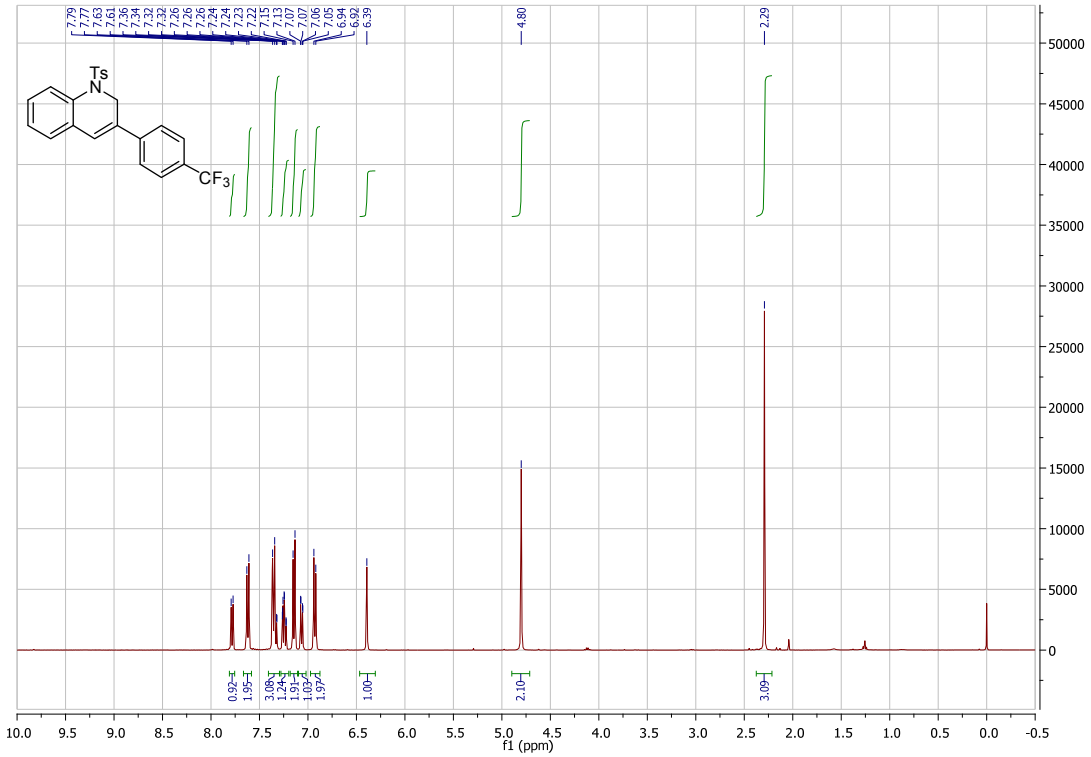


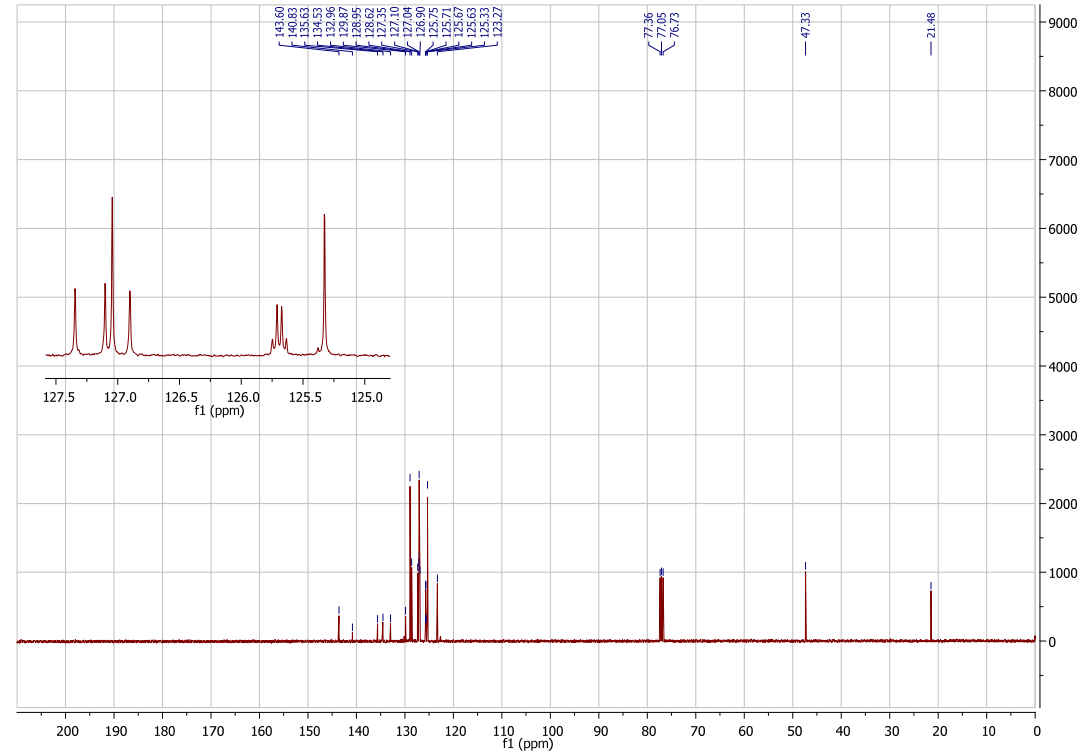
1-(4-(1-tosyl-1,2-dihydroquinolin-3-yl)phenyl)ethanone (3j)

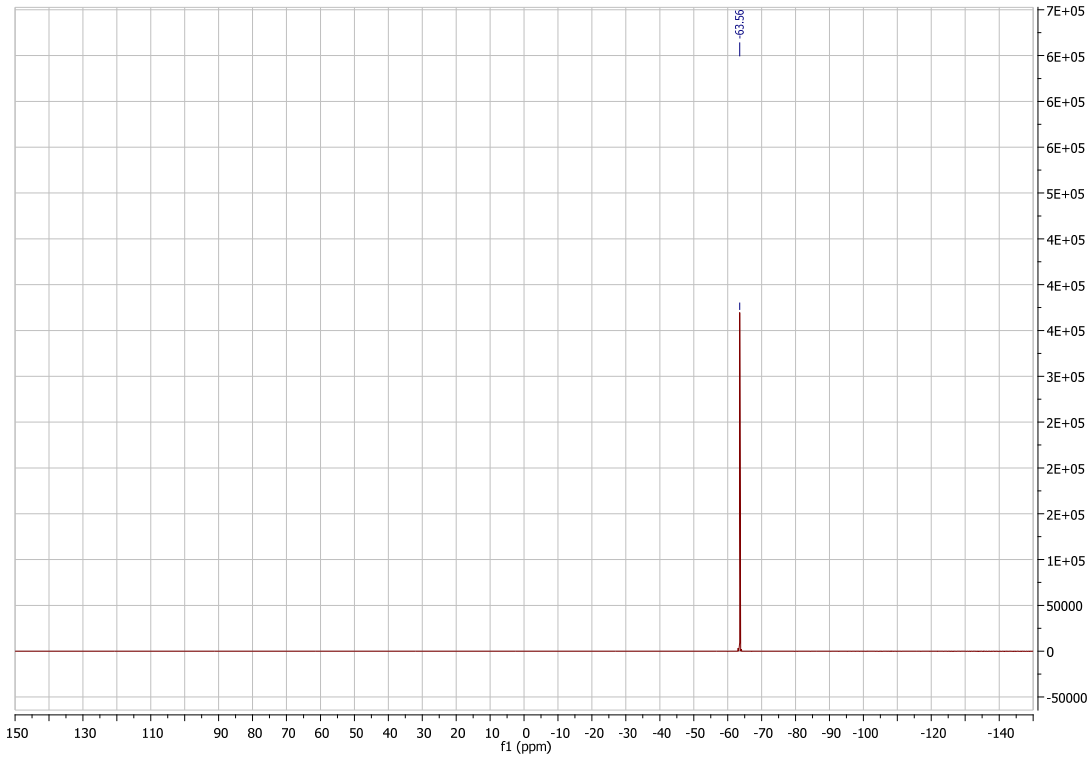




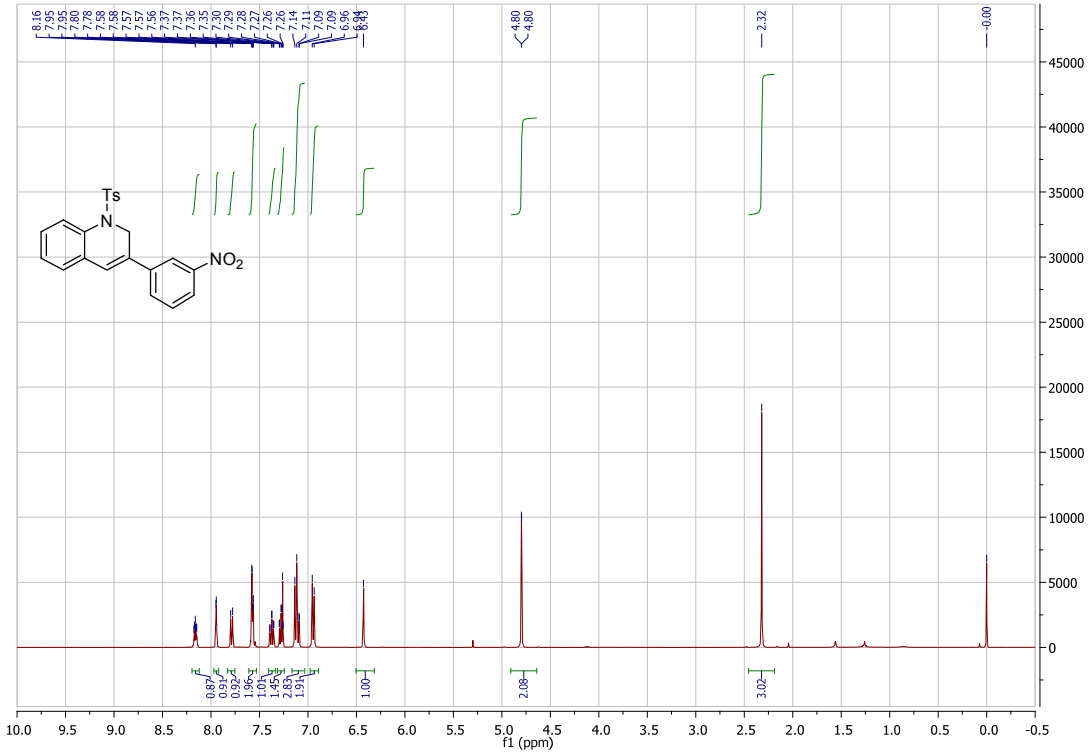
1-tosyl-3-(4-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (3e)

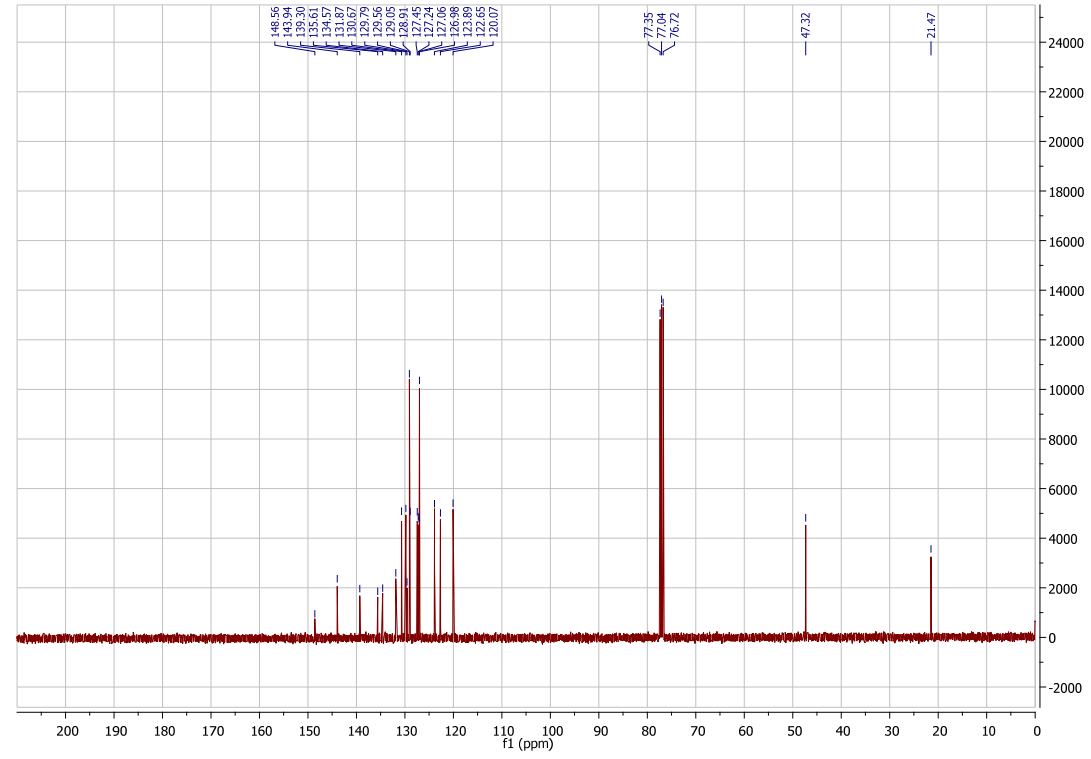




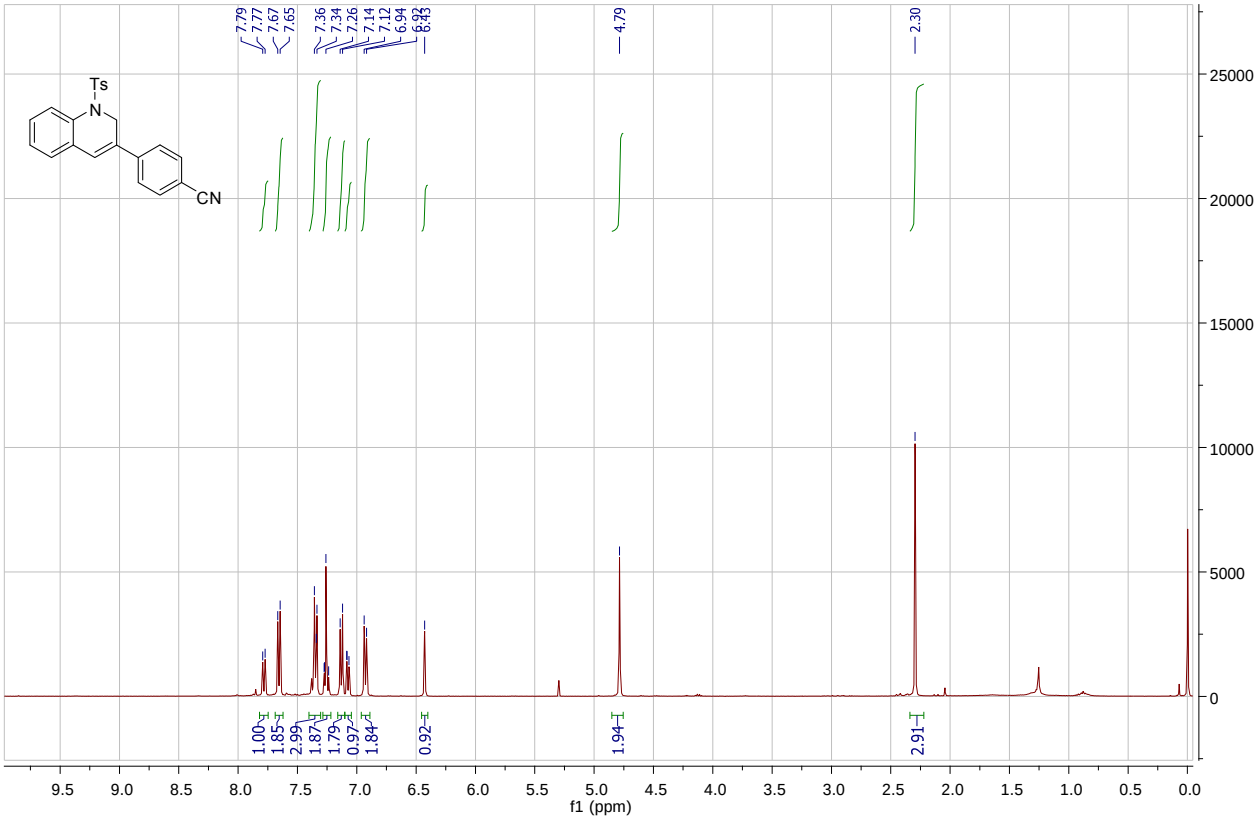

-63.56
7E+05
6E+05
6E+05
6E+05
5E+05
4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
-50000
150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140
f1 (ppm)

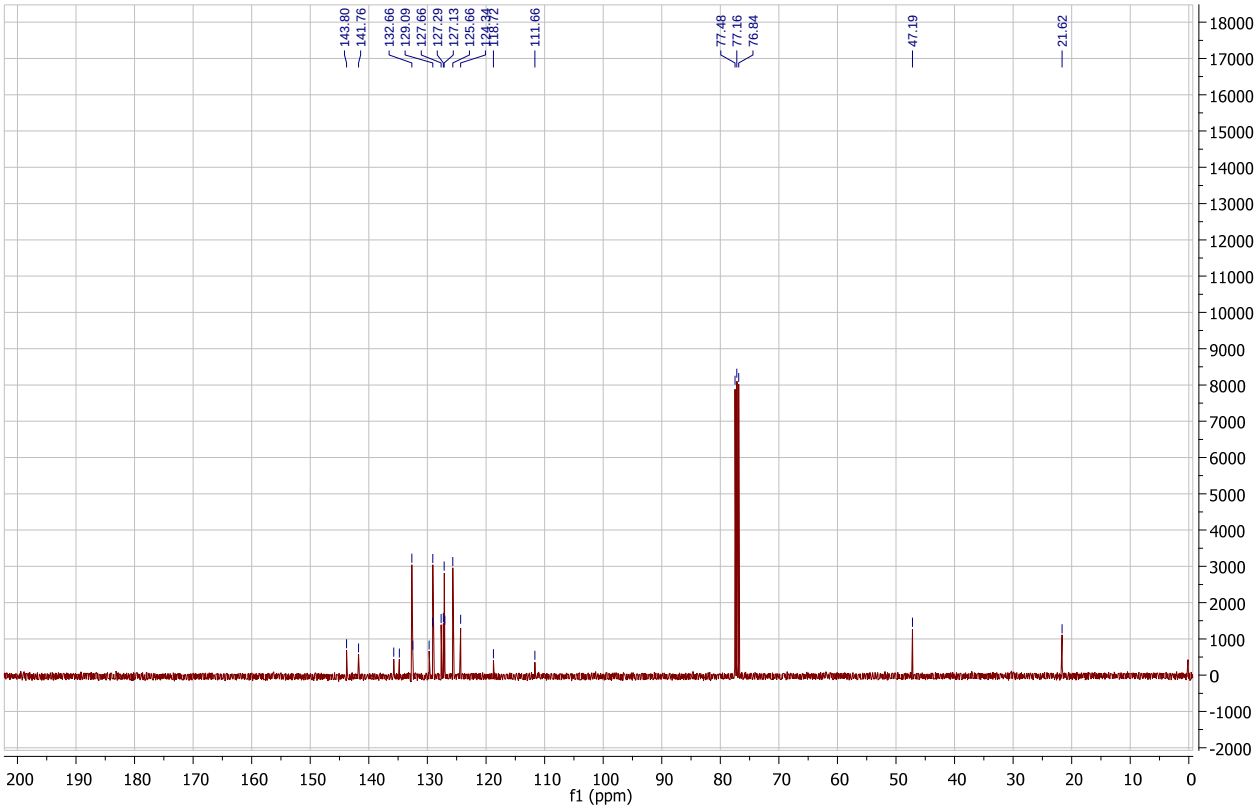
3-(3-nitrophenyl)-1-tosyl-1,2-dihydroquinoline (3k)



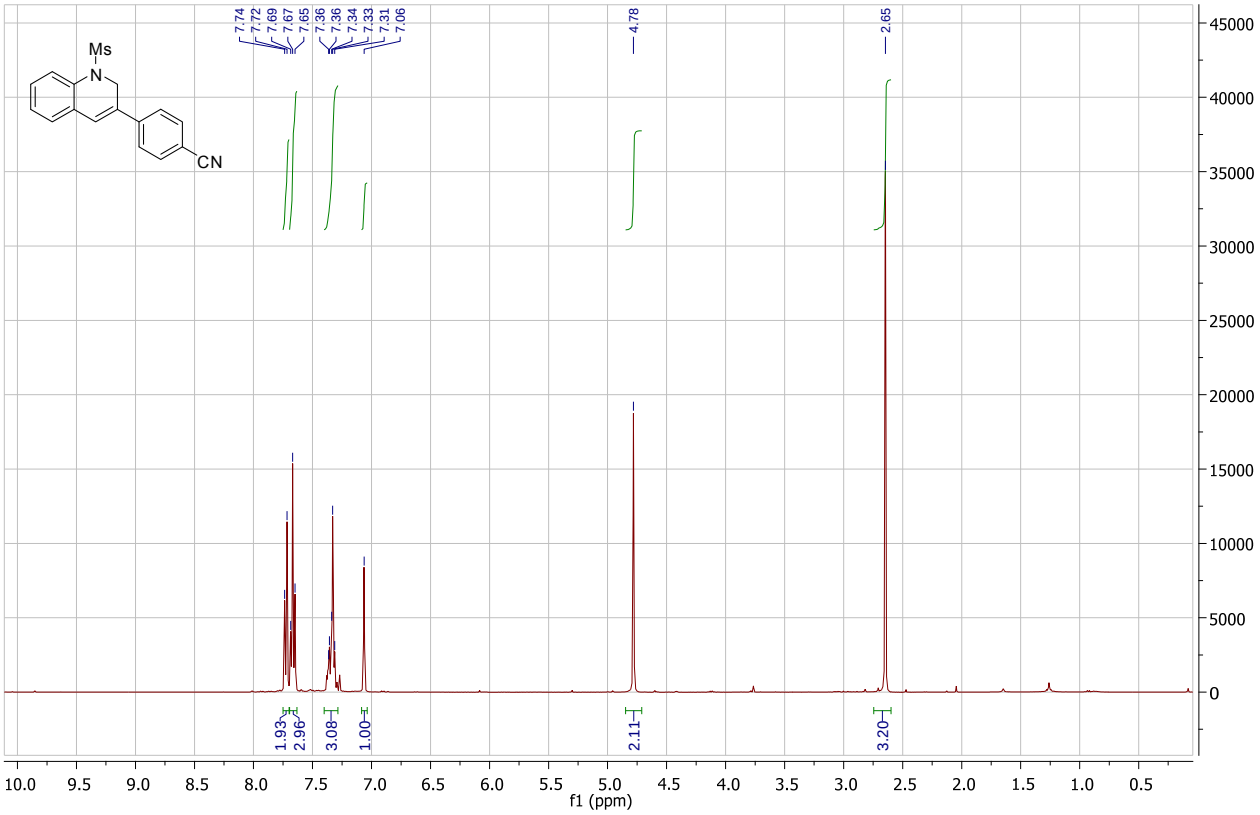


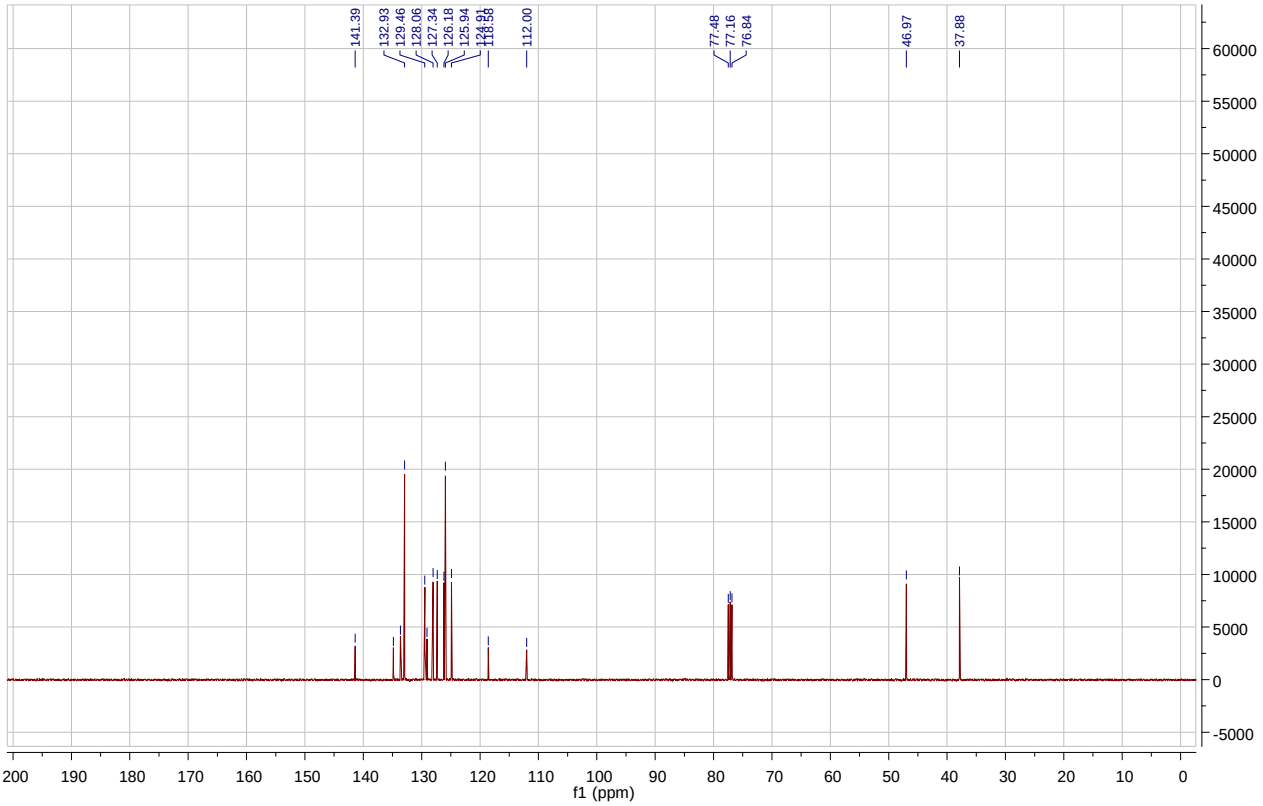
4-(1-Tosyl-1,2-dihydroquinolin-3-yl)benzonitrile(3la)



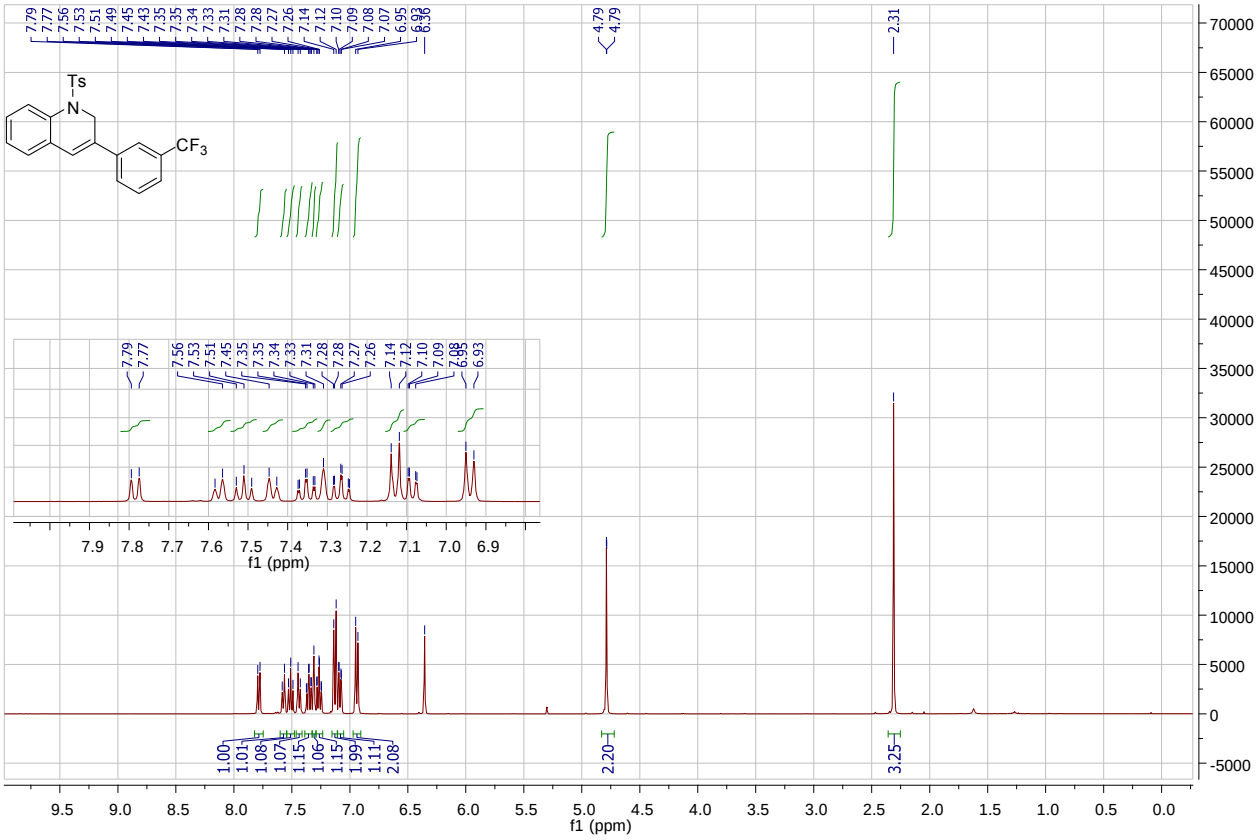


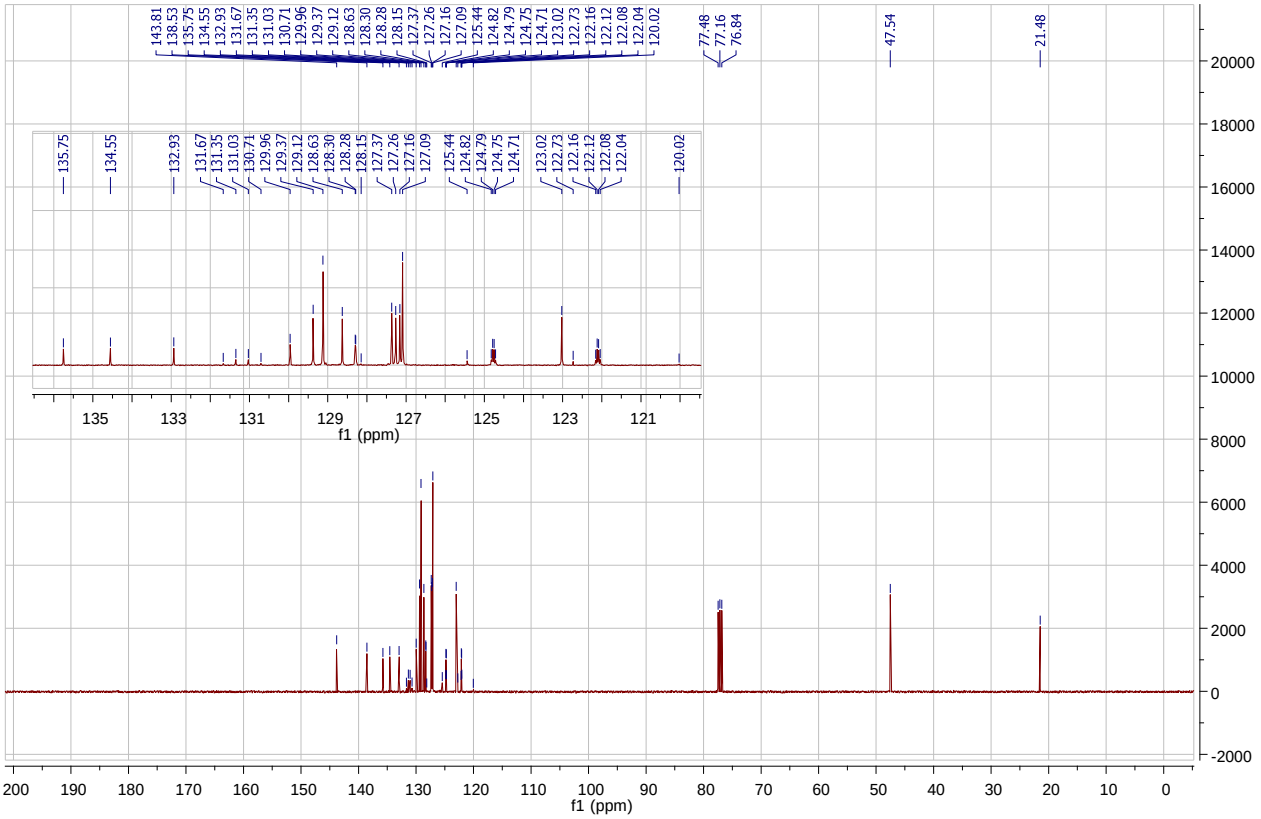
4-(1-(Methylsulfonyl)-1,2-dihydroquinolin-3-yl)benzonitrile (3lb)

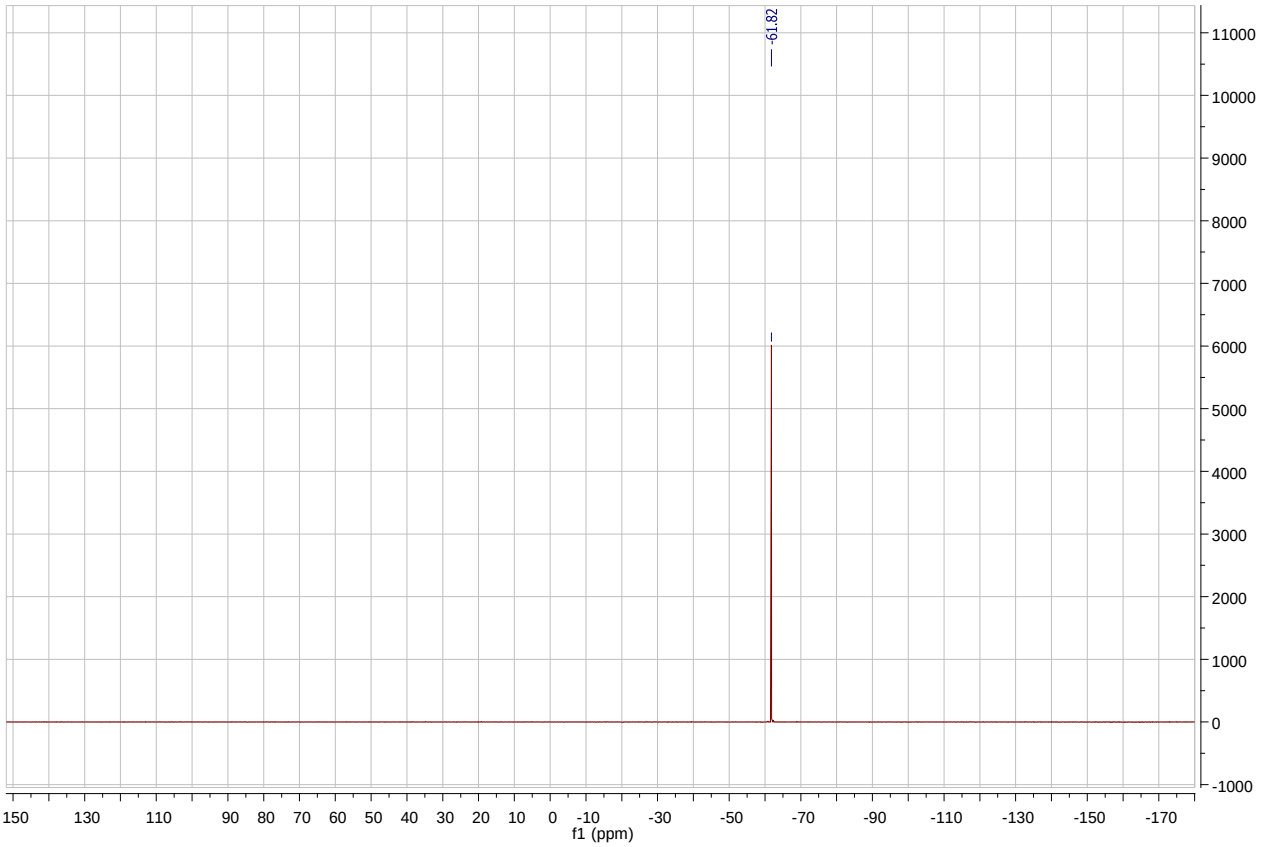




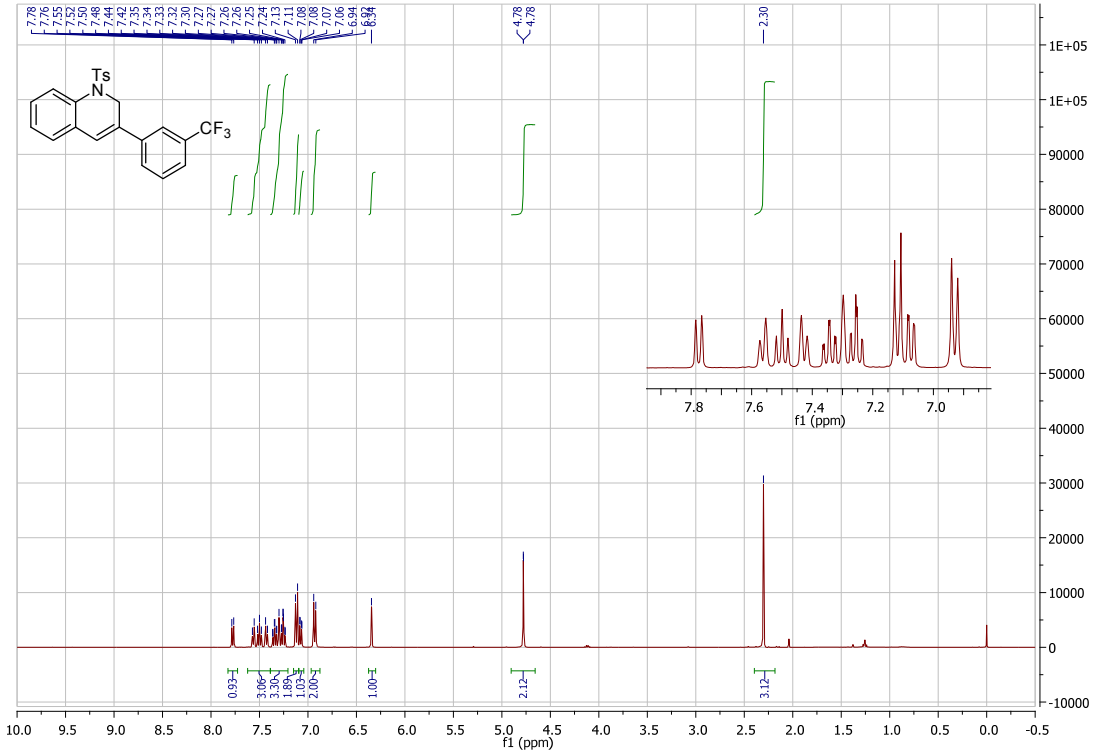
1-Tosyl-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline(3ma)

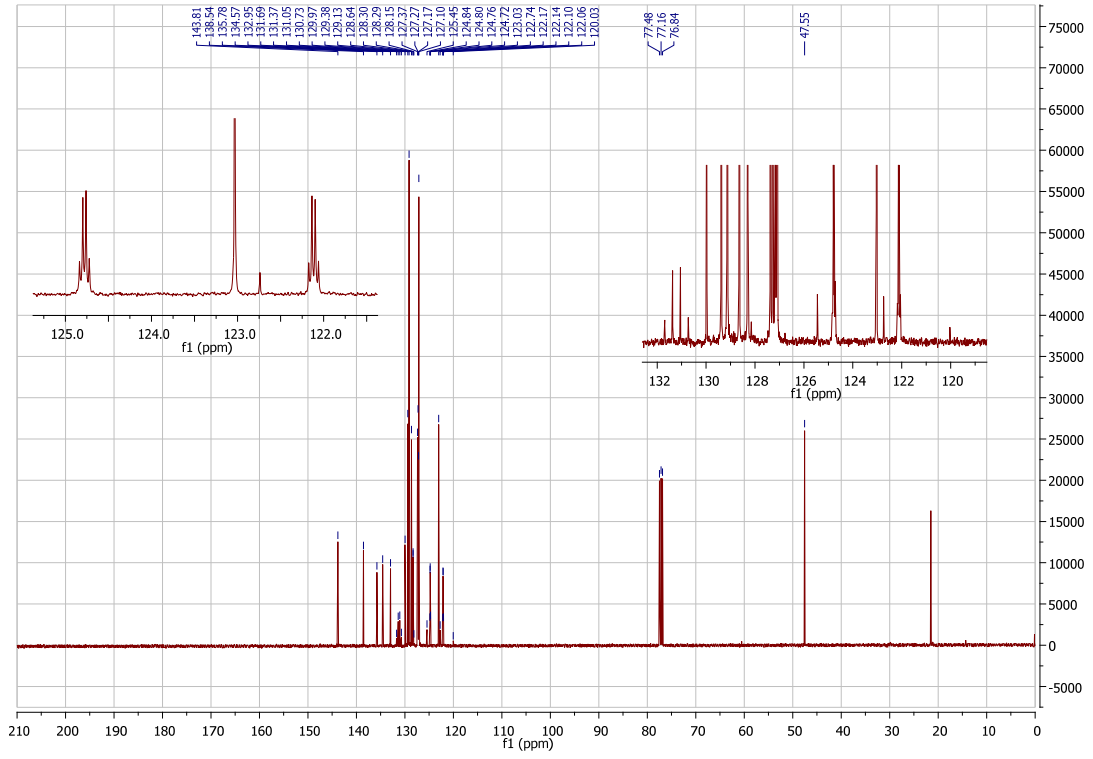


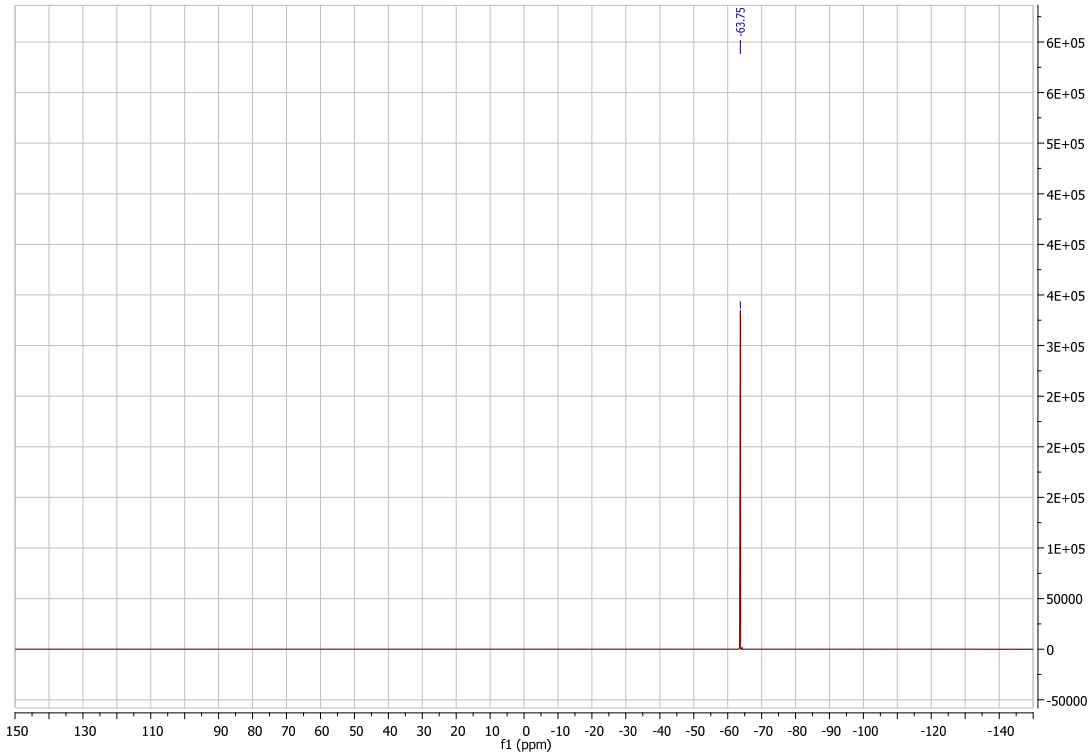



-61.82
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-30
-50
-70
-90
-110
-130
-150
-170
f1 (ppm)

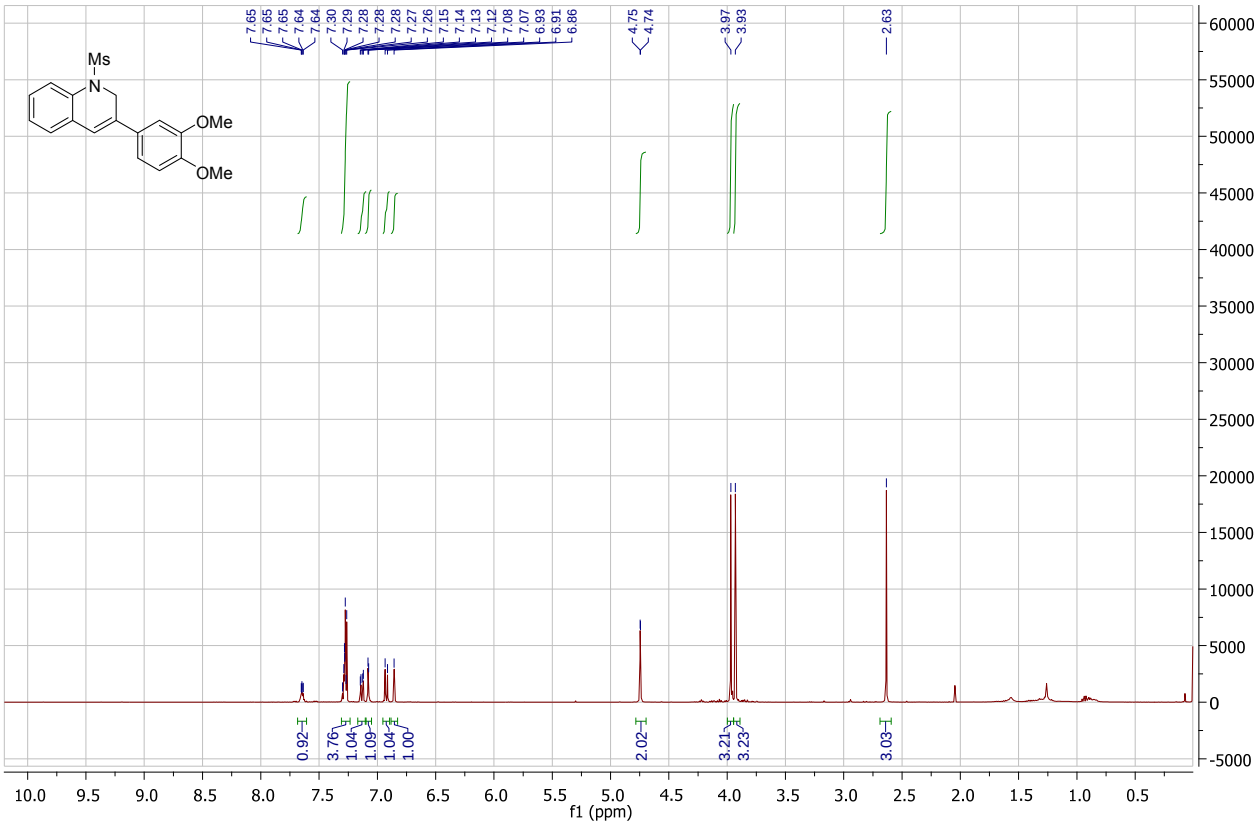
1-tosyl-3-(3-(trifluoromethyl)phenyl)-1,2-dihydroquinoline (3mb)

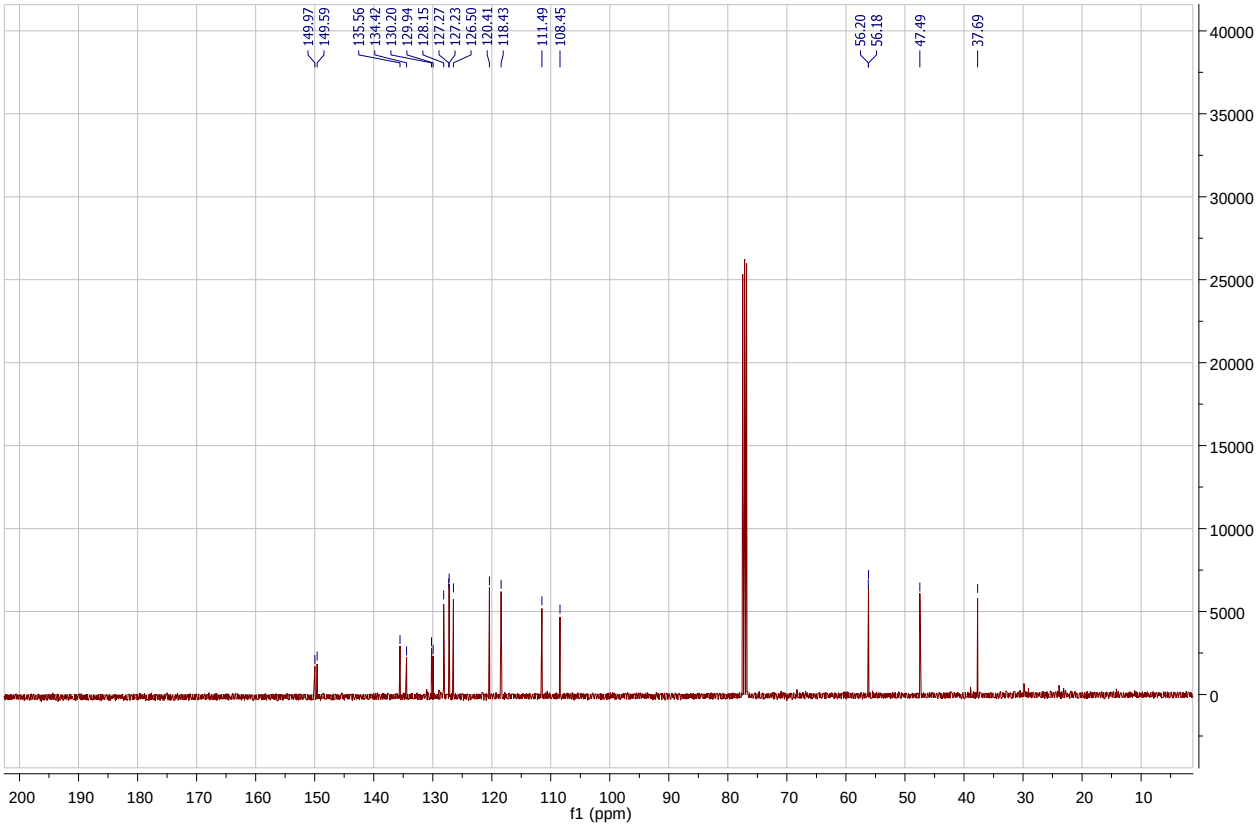




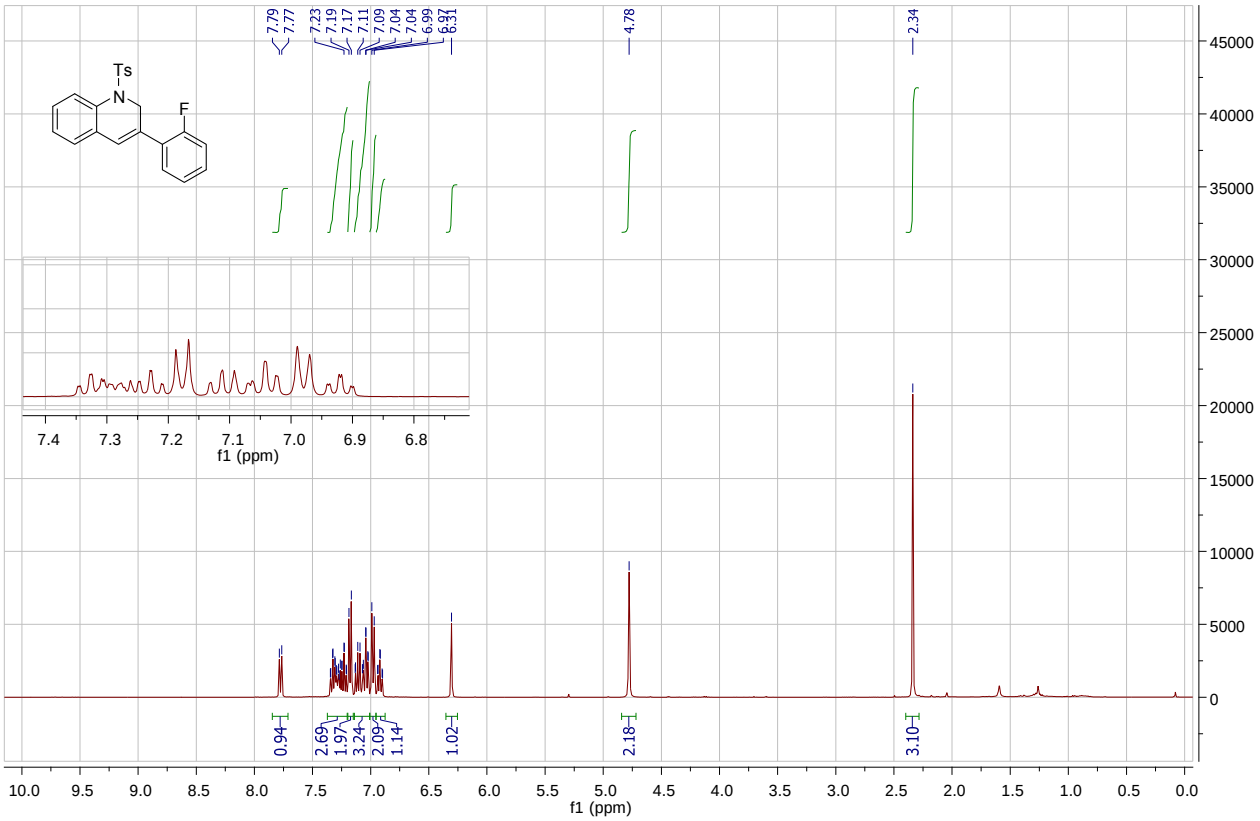

-63.75
6E+05
6E+05
5E+05
4E+05
4E+05
4E+05
3E+05
2E+05
2E+05
2E+05
1E+05
50000
0
-50000
150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -120 -140
f1 (ppm)

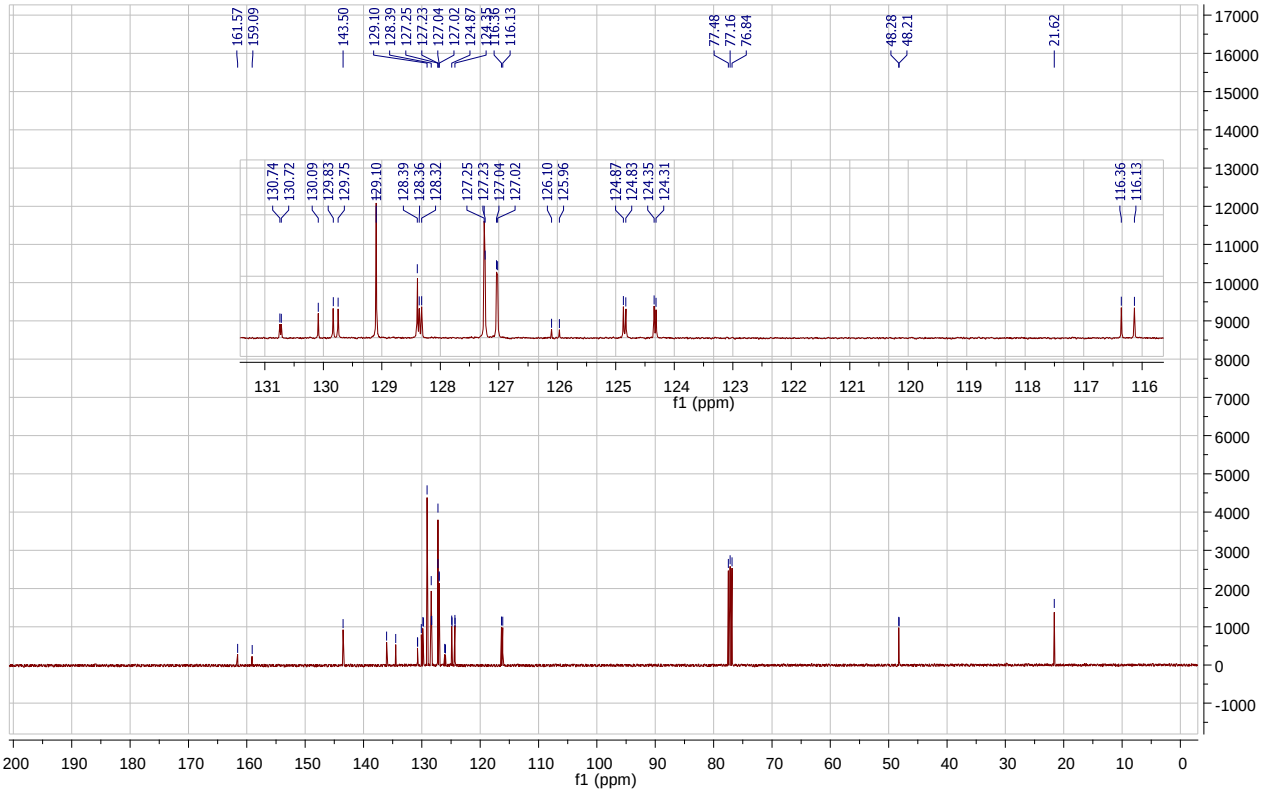
3-(3,4-Dimethoxyphenyl)-1-(methylsulfonyl)-1,2-dihydroquinoline(3n)

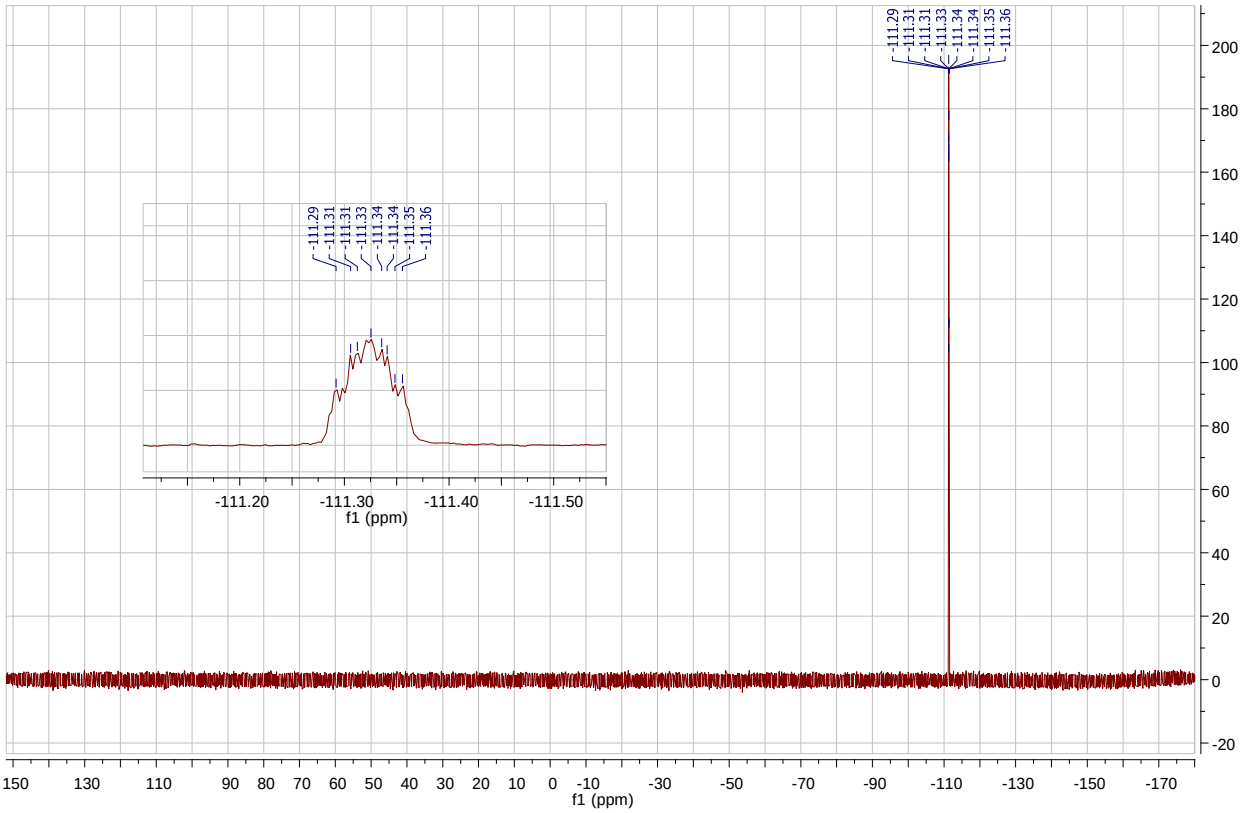




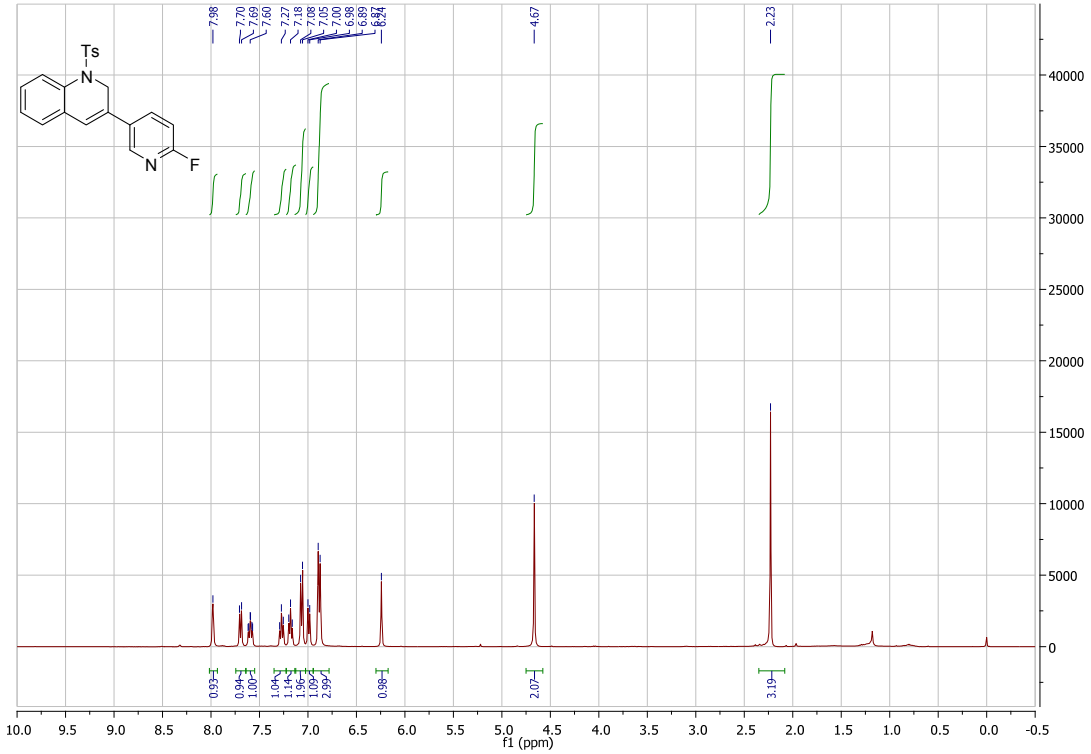
3-(2-Fluorophenyl)-1-tosyl-1,2-dihydroquinoline(3o)

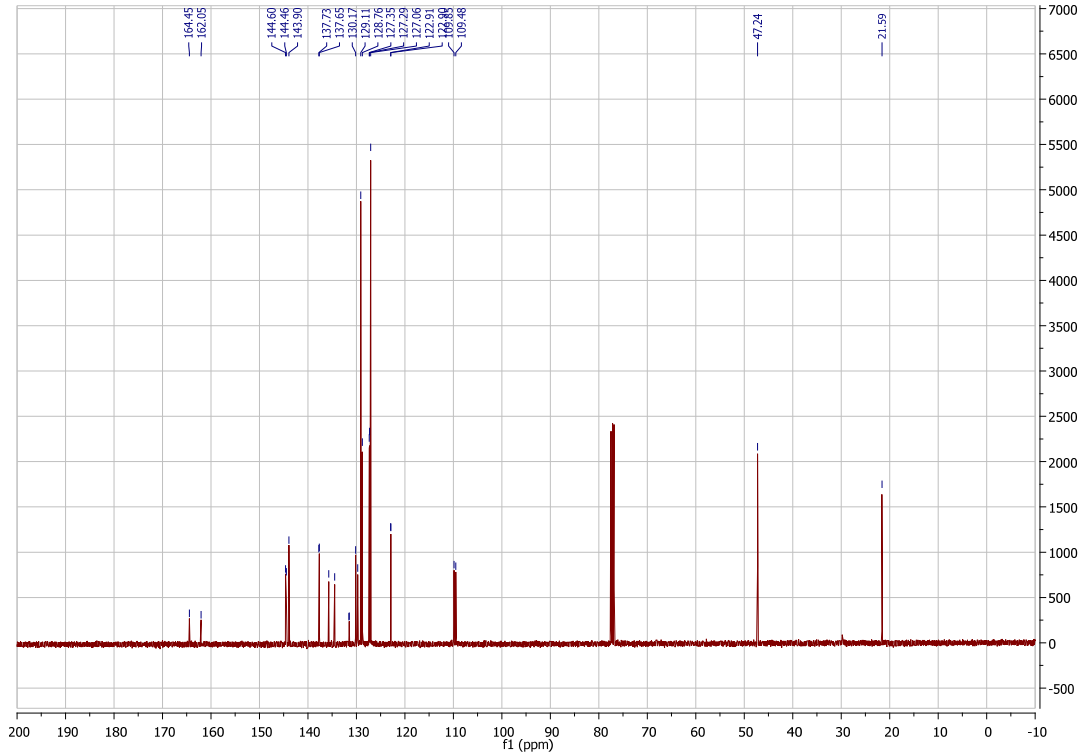


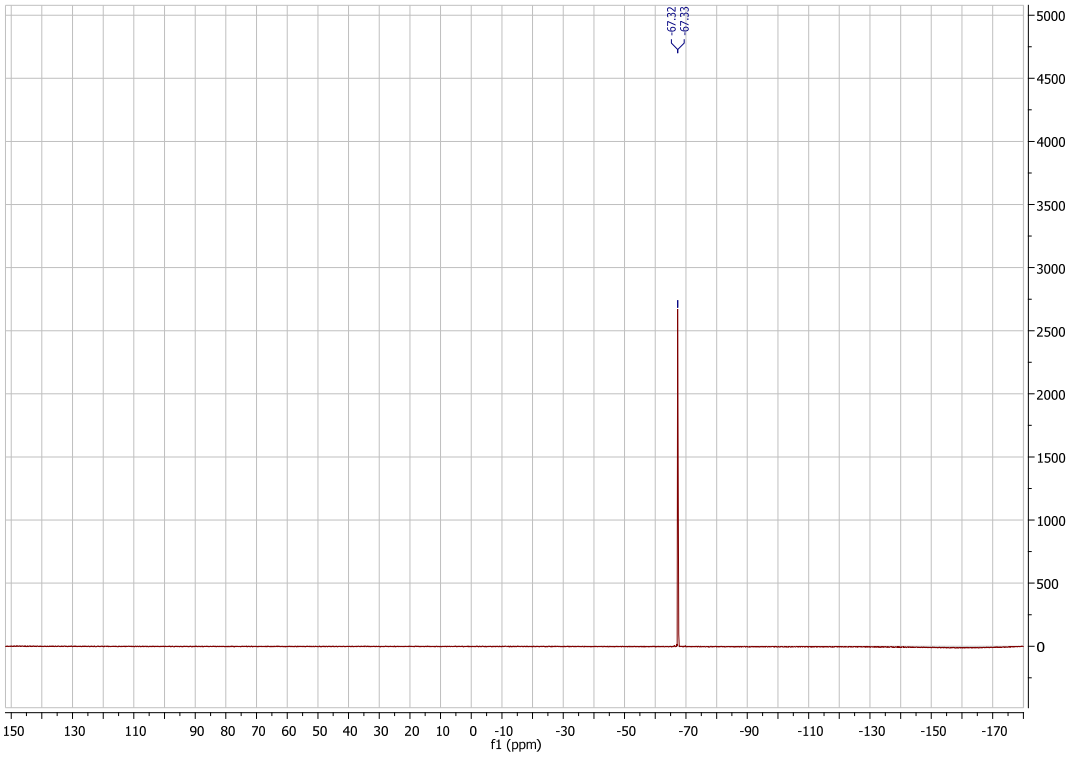



-111.29
-111.31
-111.31
-111.33
-111.34
-111.34
-111.35
-111.36
200
180
160
140
120
100
80
60
40
20
0
-20
-111.20
-111.30
-111.40
-111.50
f1 (ppm)
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-30
-50
-70
-90
-110
-130
-150
-170
f1 (ppm)

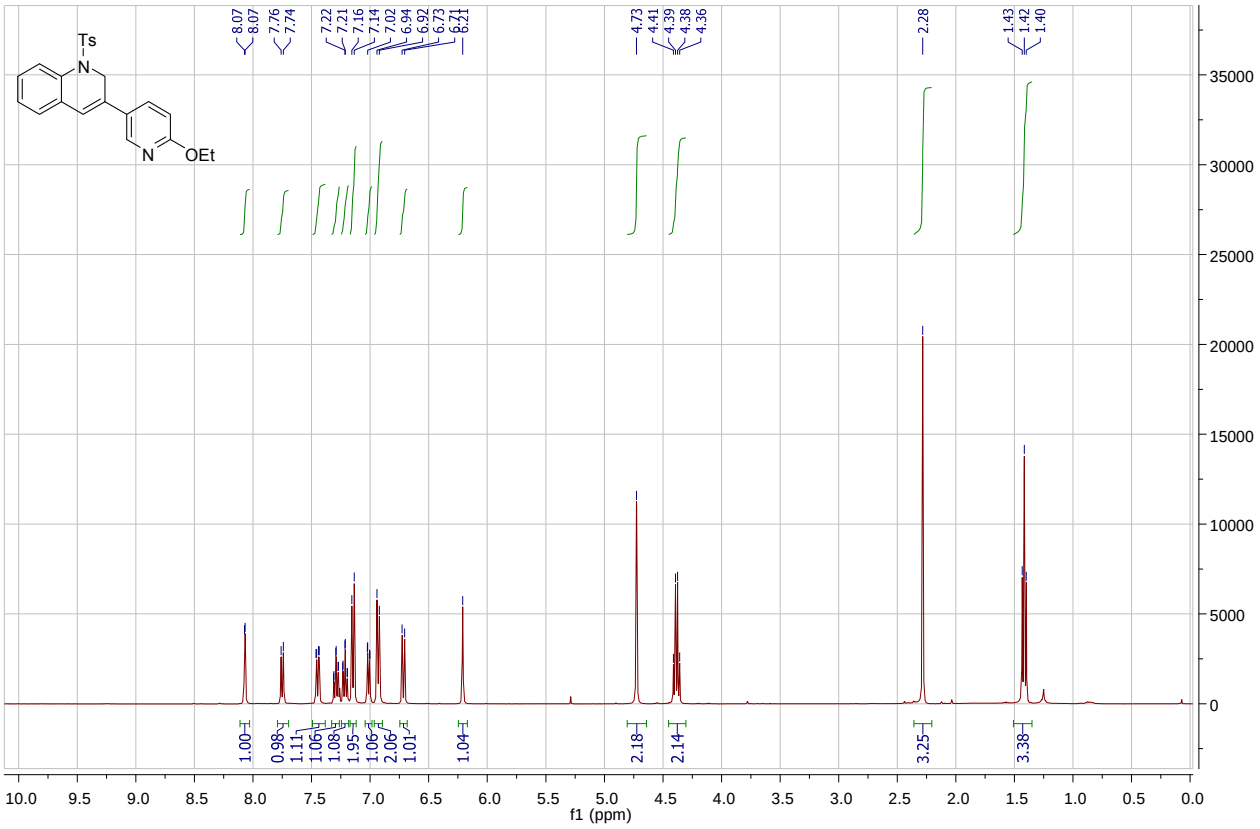
3-(6-Fluoropyridin-3-yl)-1-tosyl-1,2-dihydroquinoline (3p)

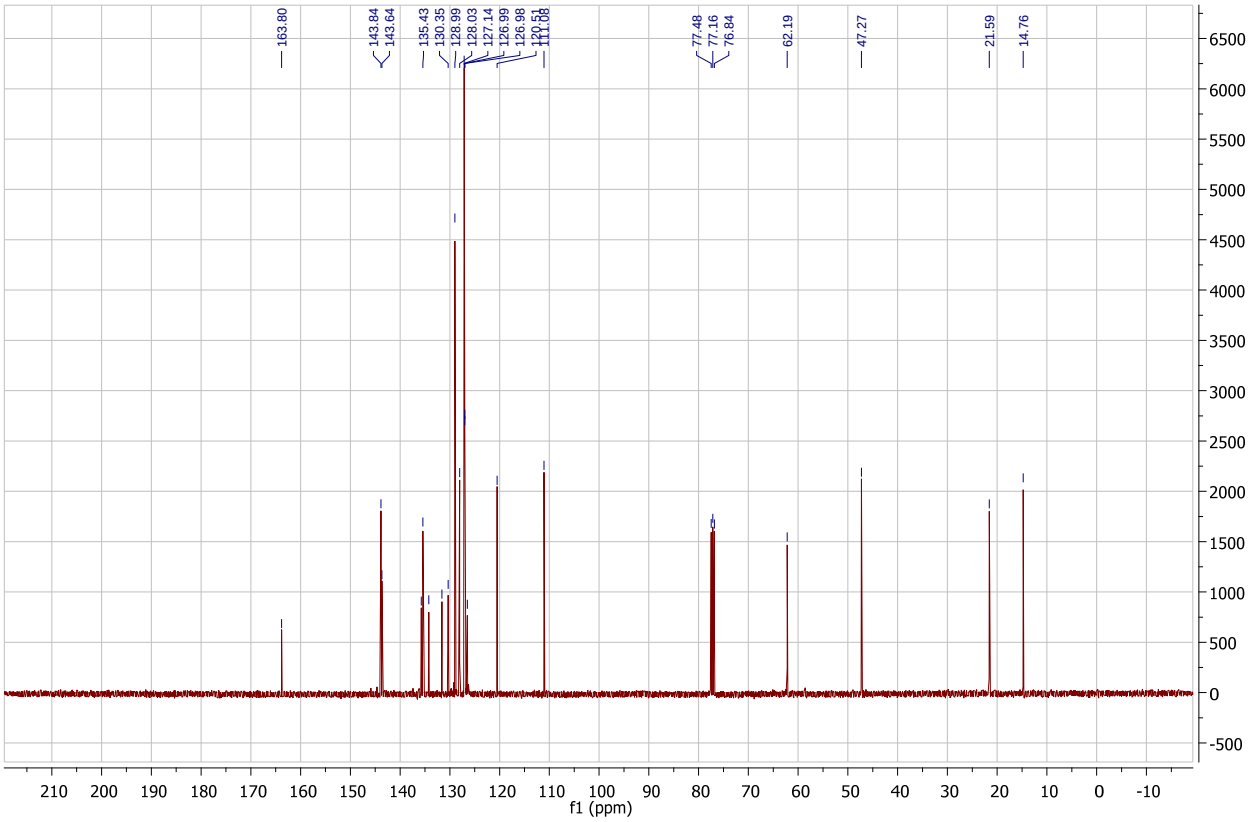




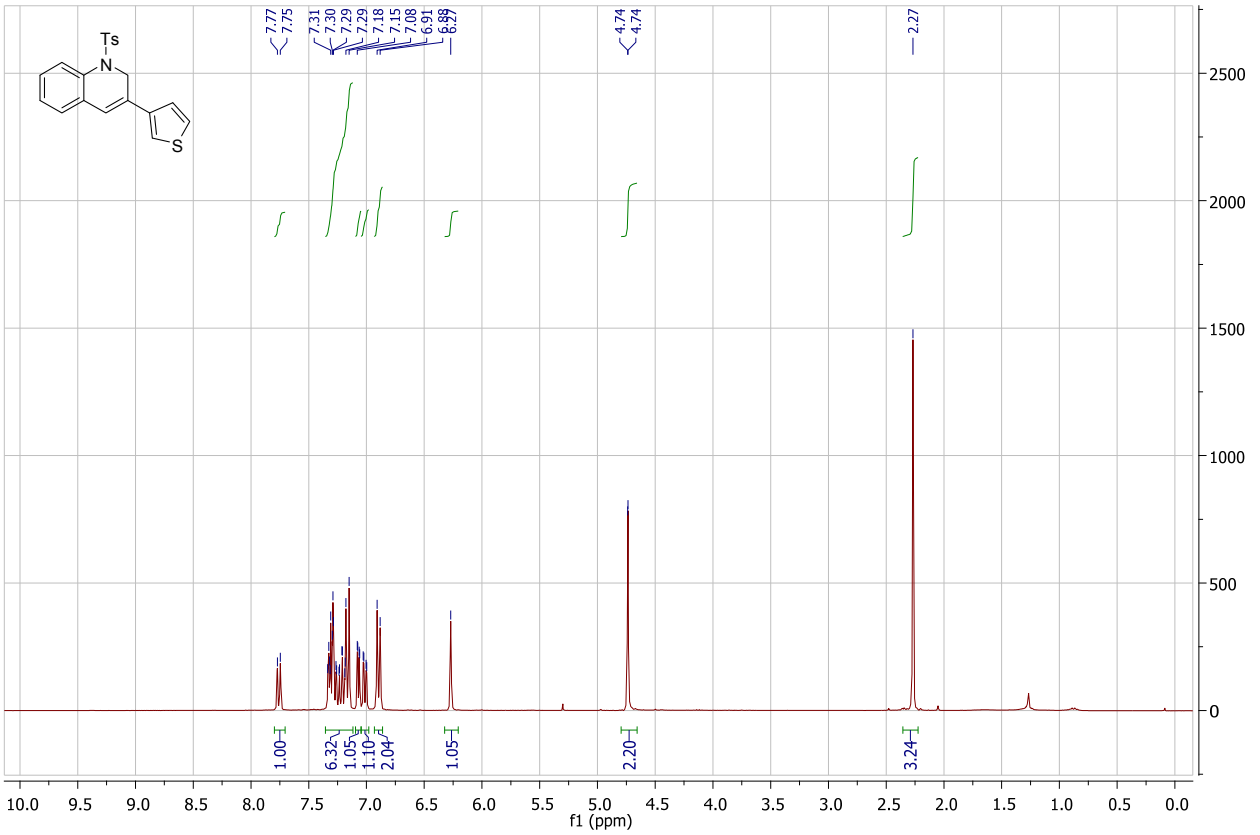

-67.32
-67.33
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
150 130 110 90 80 70 60 50 40 30 20 10 0 -10 -30 -50 -70 -90 -110 -130 -150 -170
f1 (ppm)

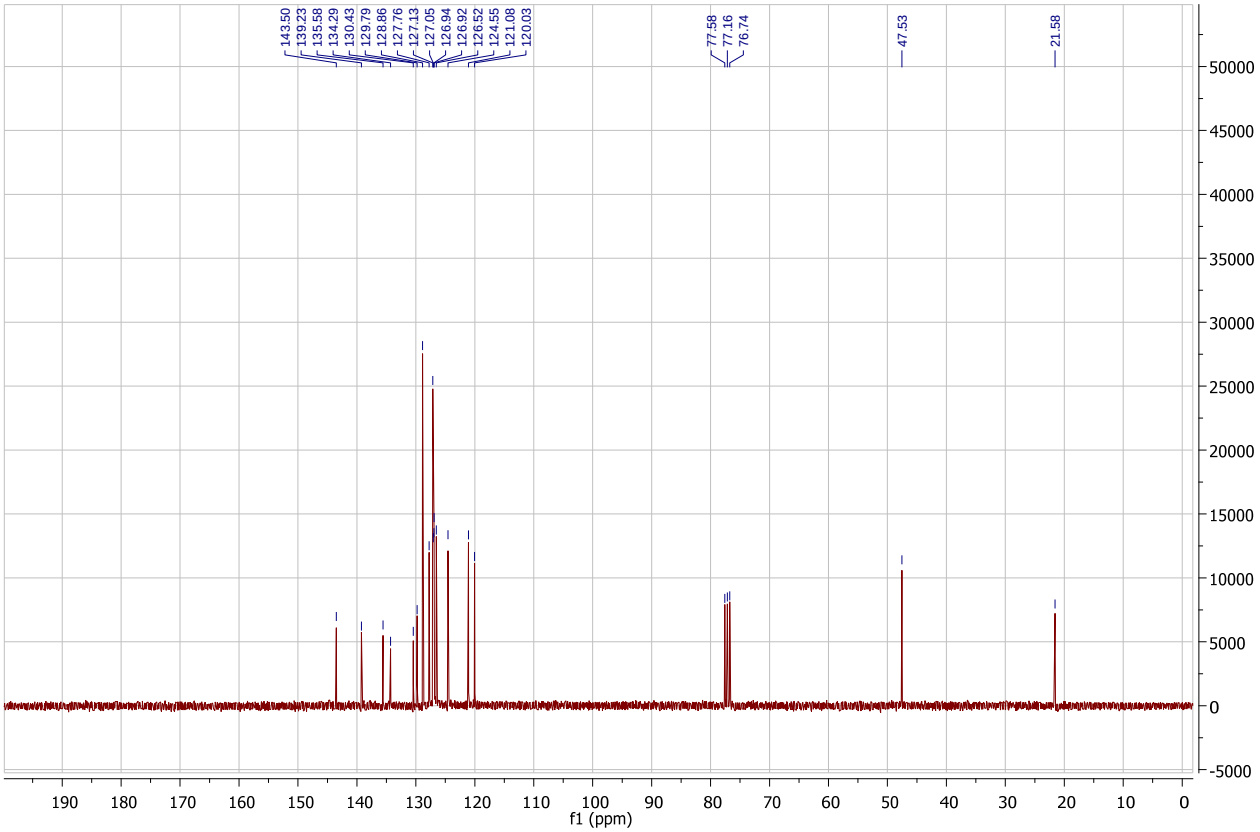
3-(6-Ethoxypyridin-3-yl)-1-tosyl-1,2-dihydroquinoline(3qa)



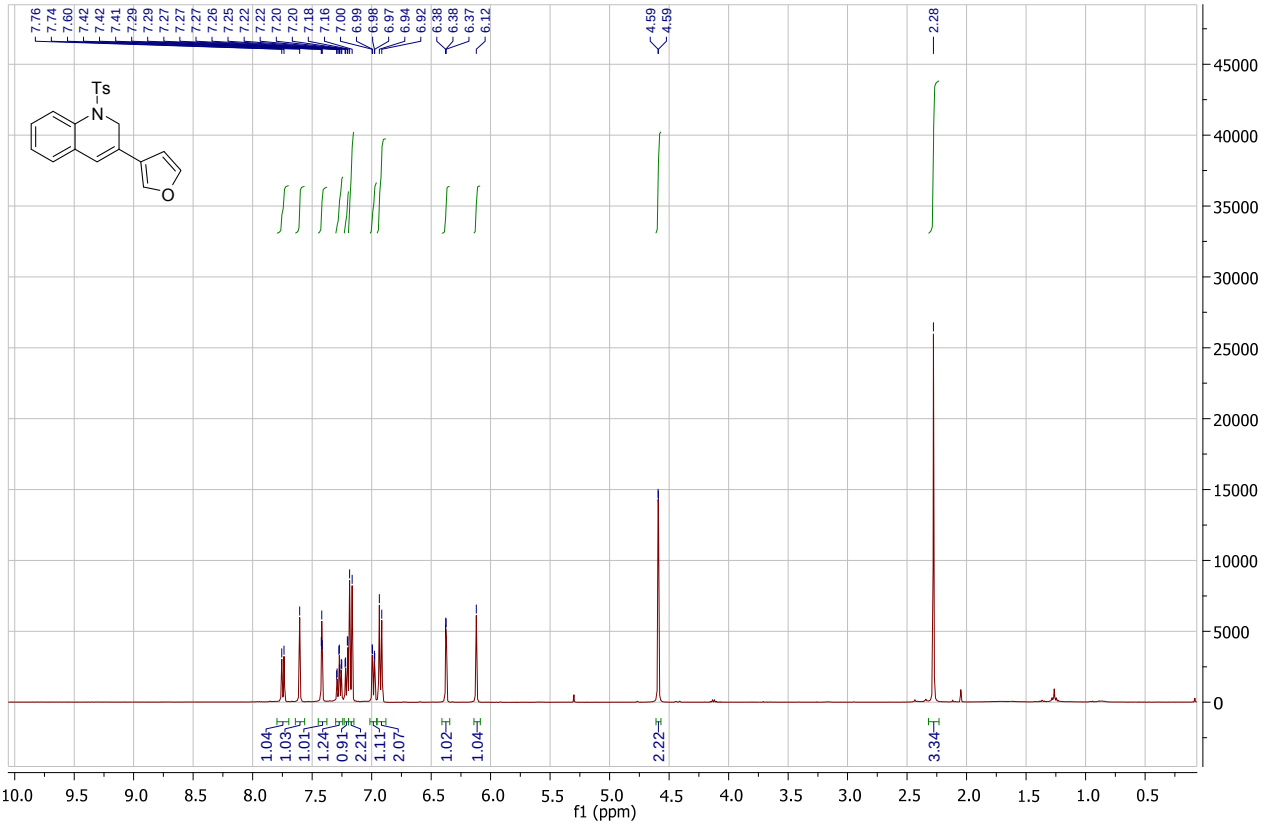


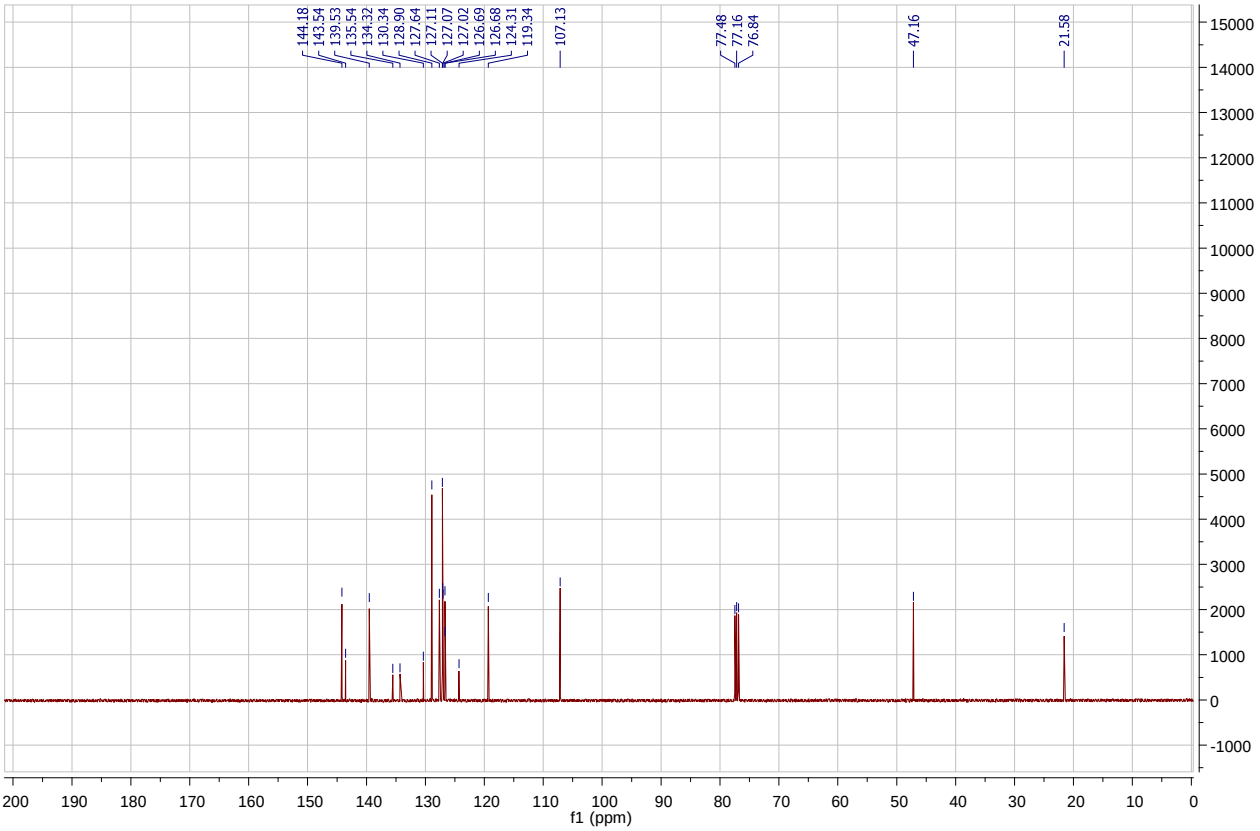
3-(Thiophen-3-yl)-1-tosyl-1,2-dihydroquinoline(3ra)



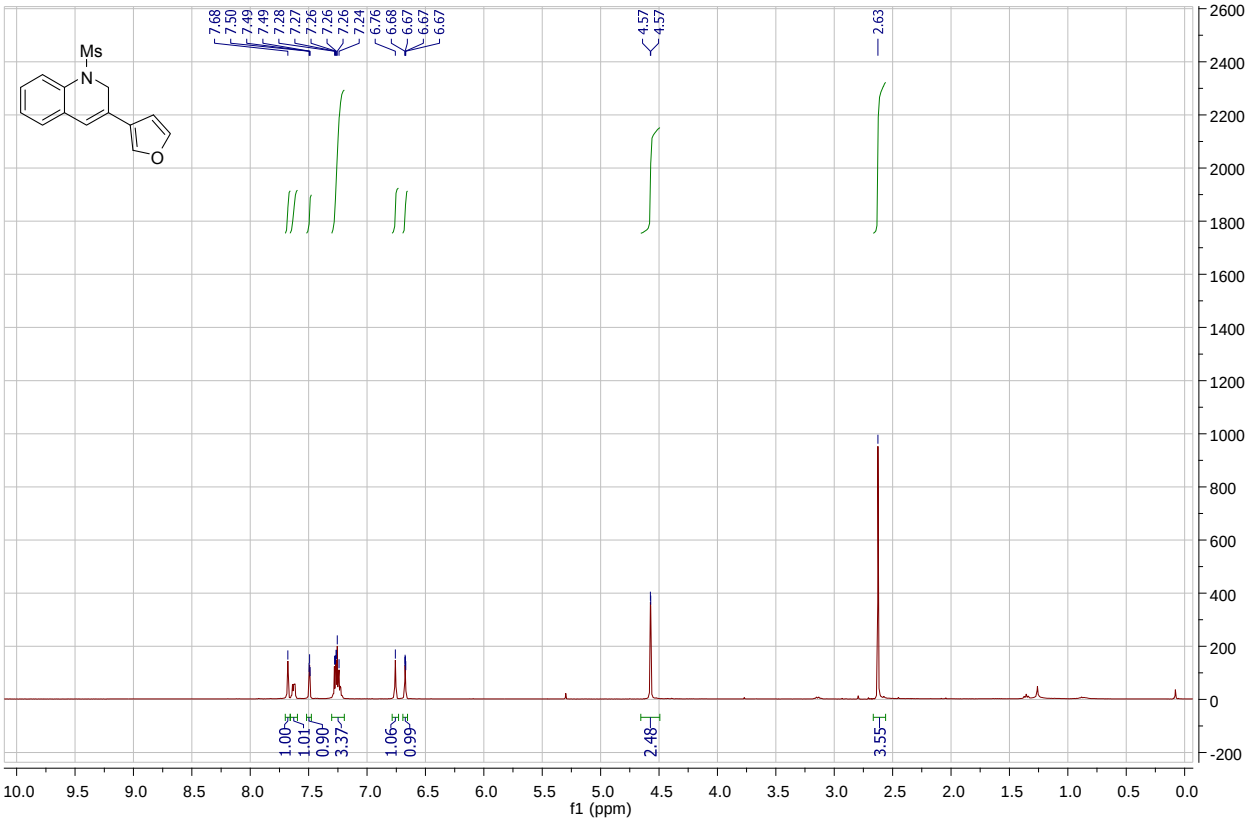


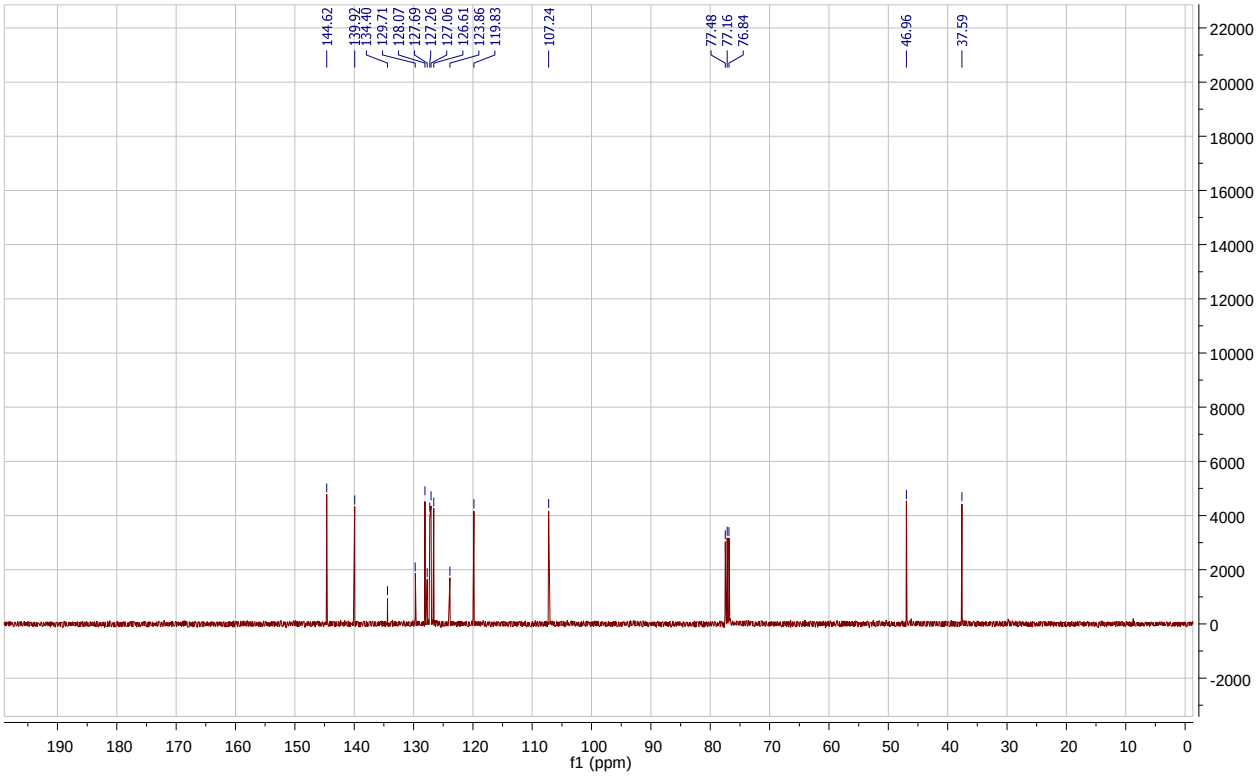
3-(Furan-3-yl)-1-tosyl-1,2-dihydroquinoline(3sa)



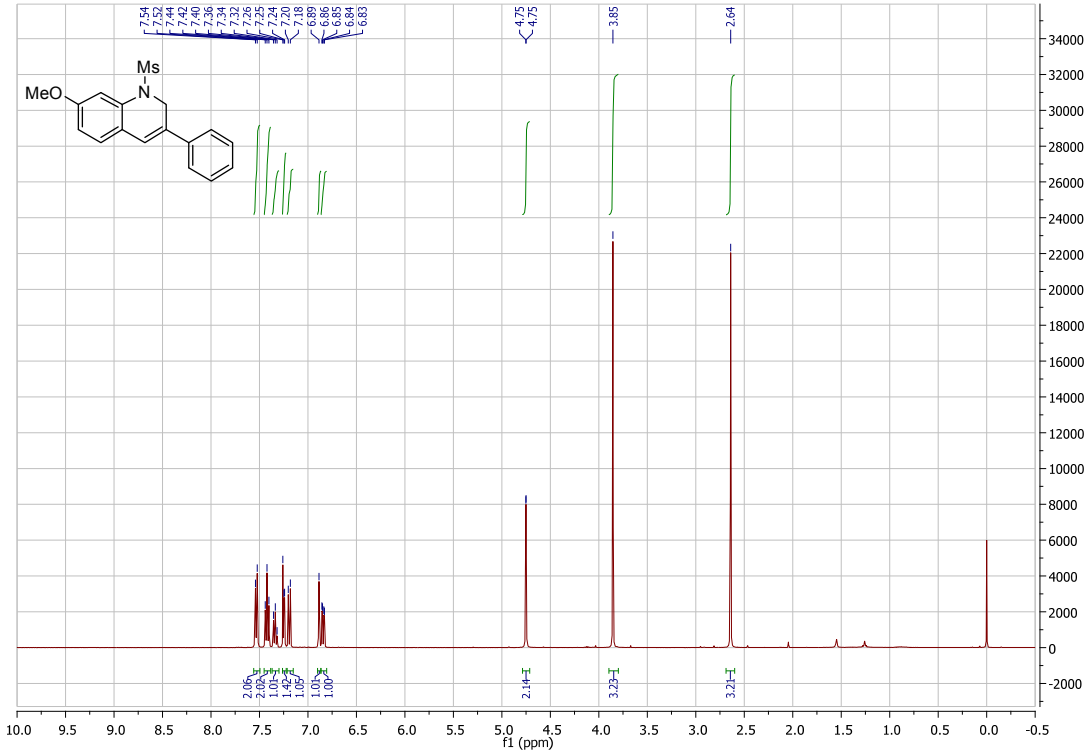


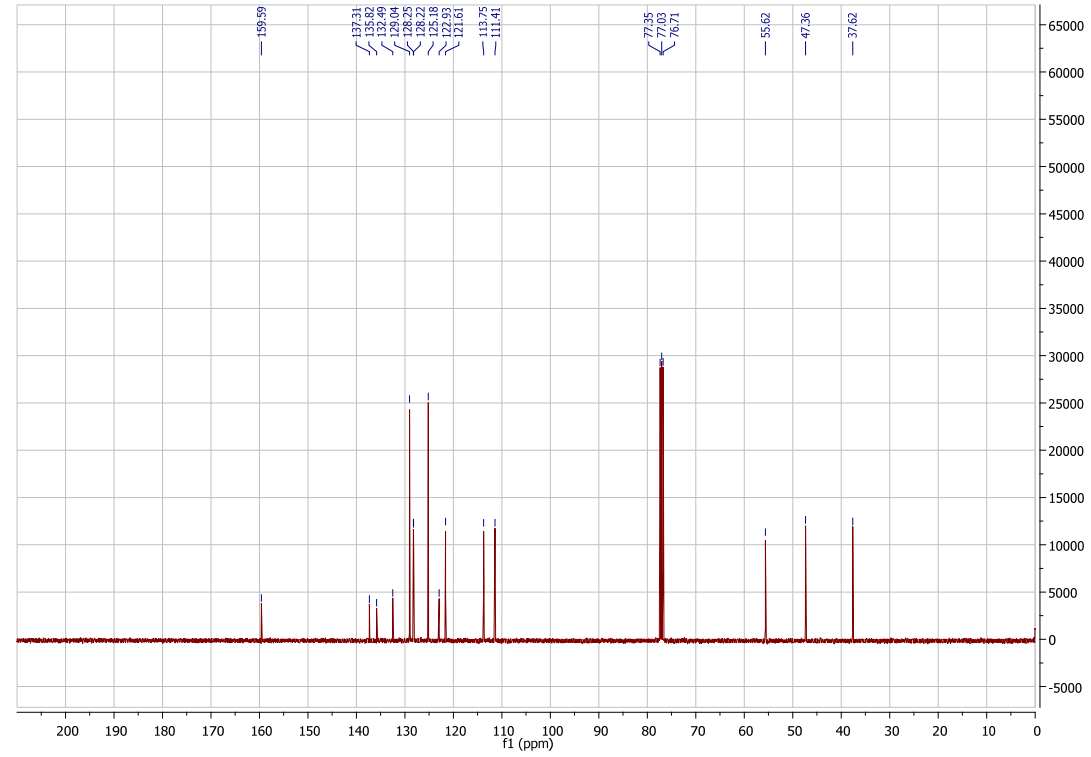
3-(Furan-3-yl)-1-(methylsulfonyl)-1,2-dihydroquinoline(3sb)



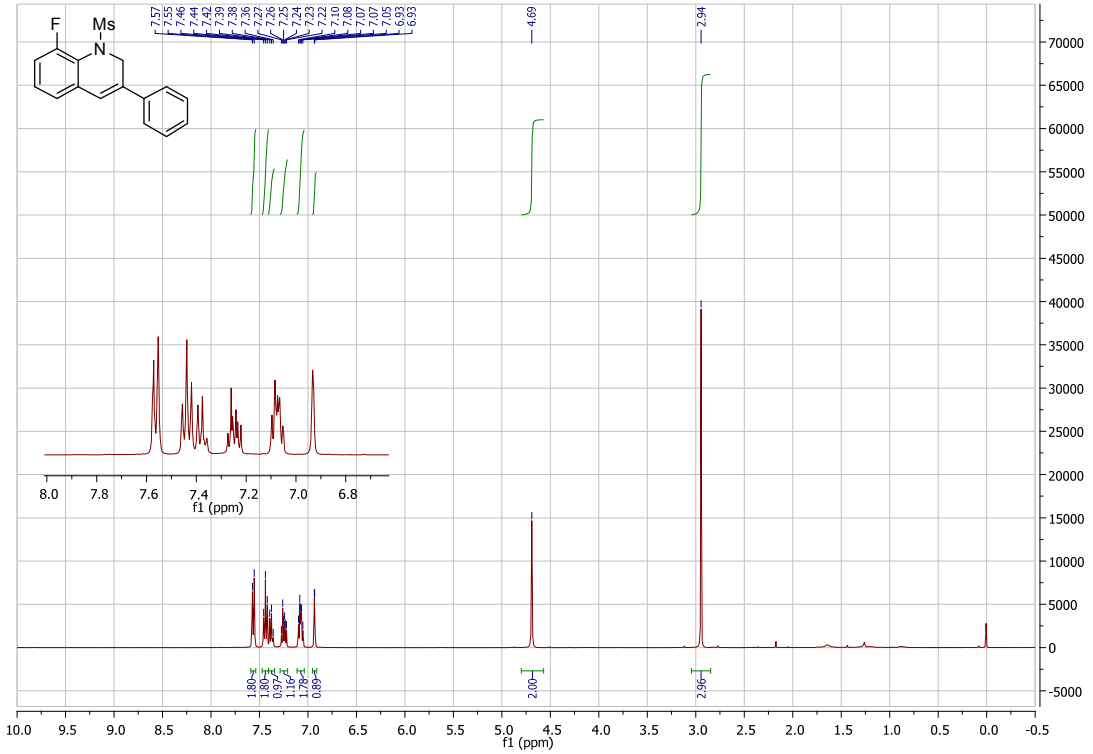


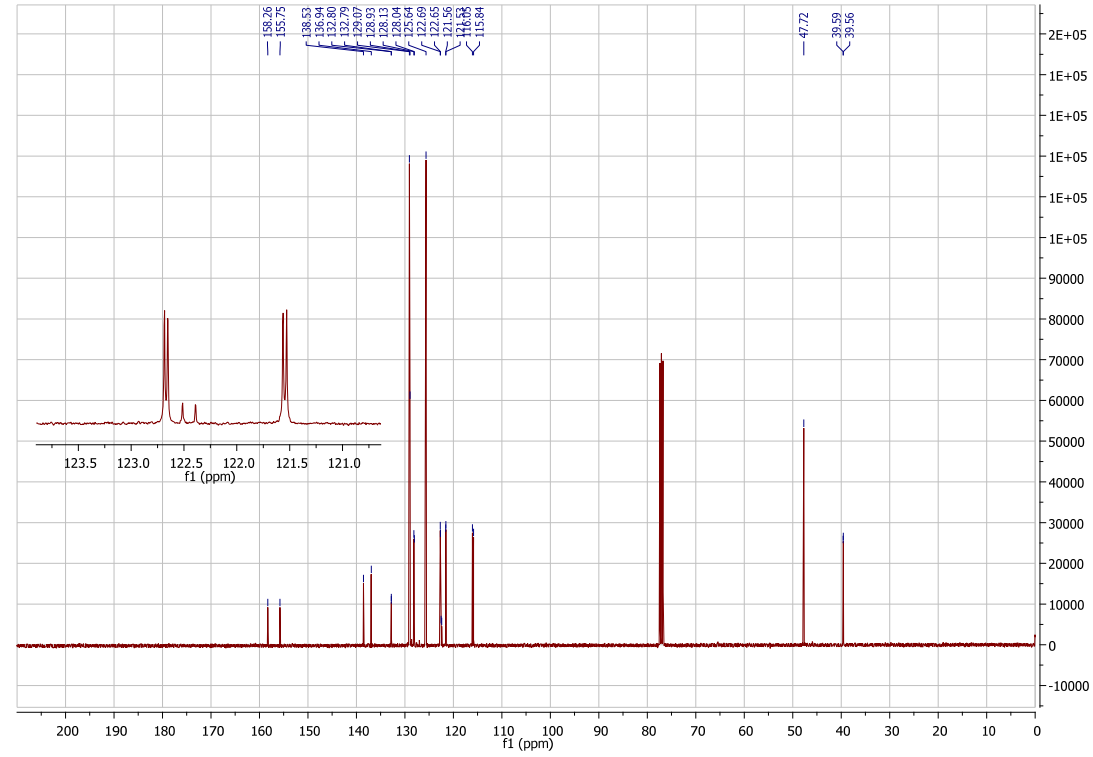
7-methoxy-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (3t)

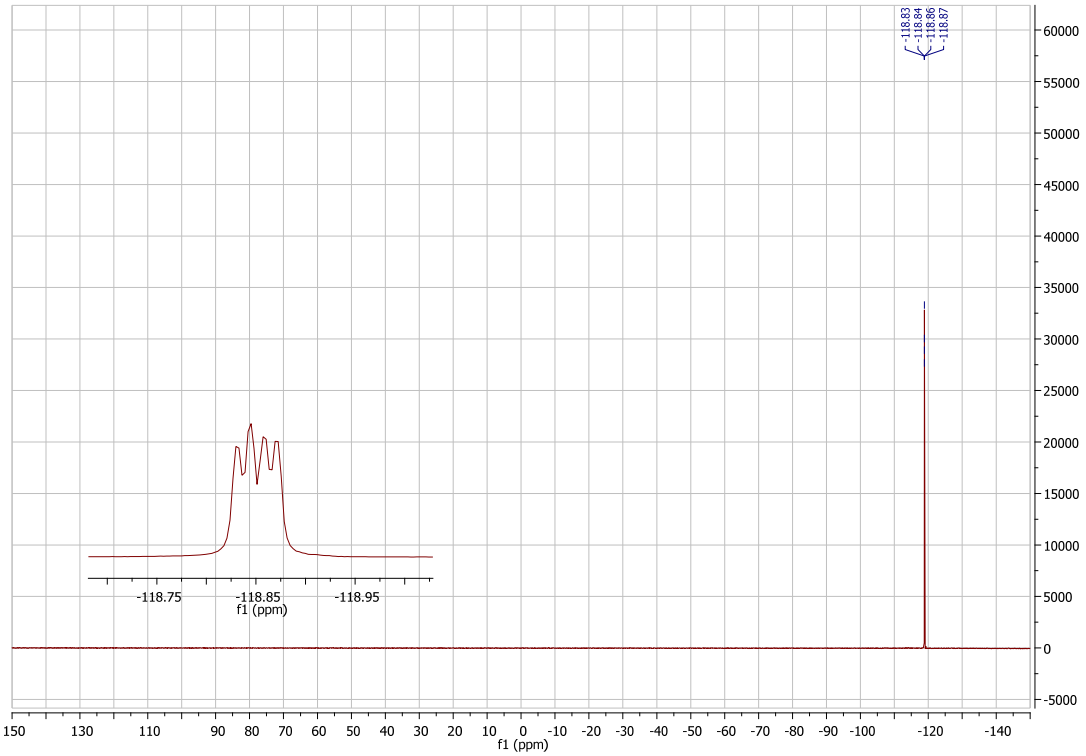




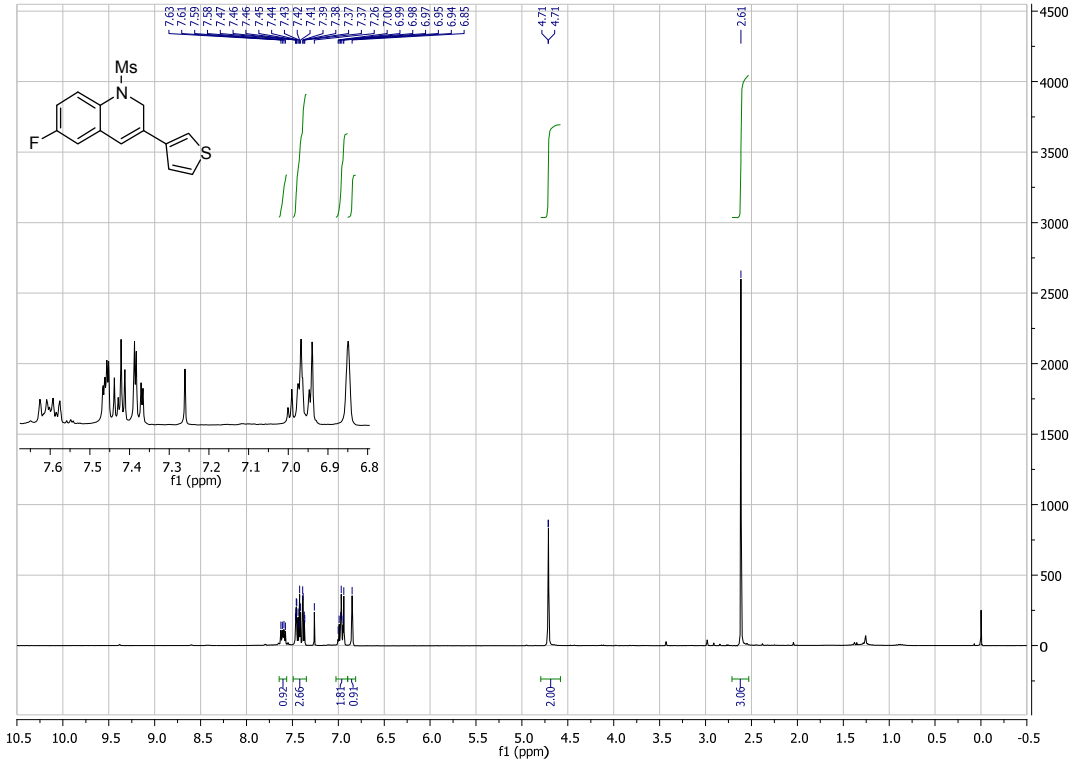
8-fluoro-1-(methylsulfonyl)-3-phenyl-1,2-dihydroquinoline (3u)

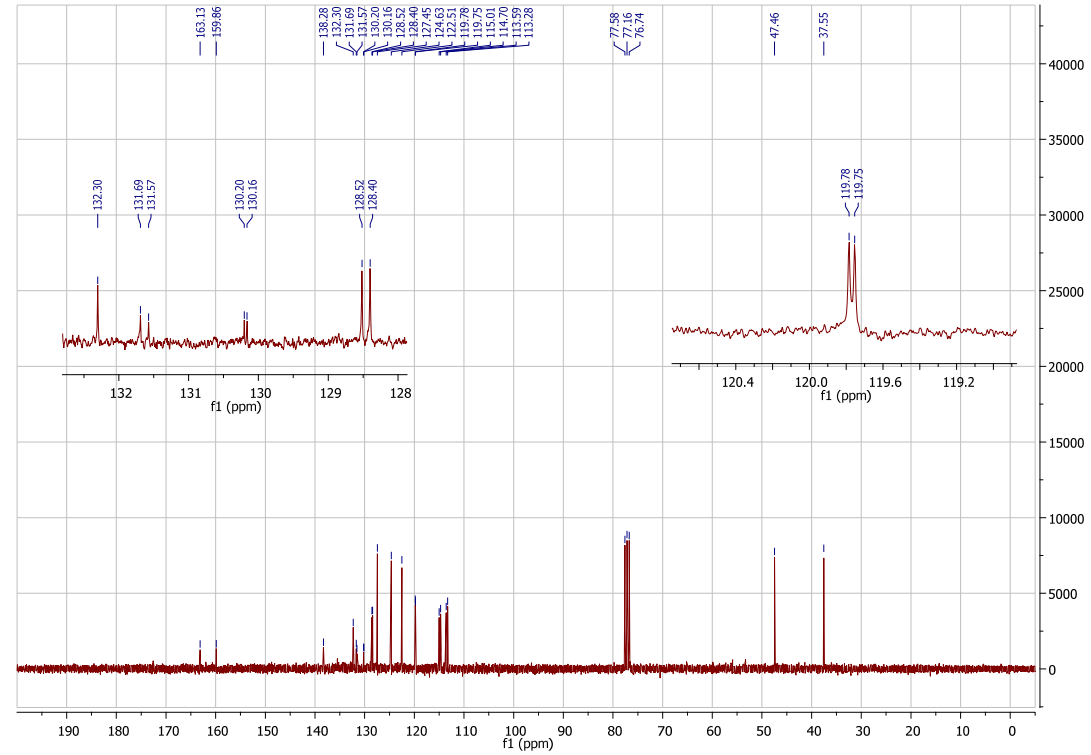


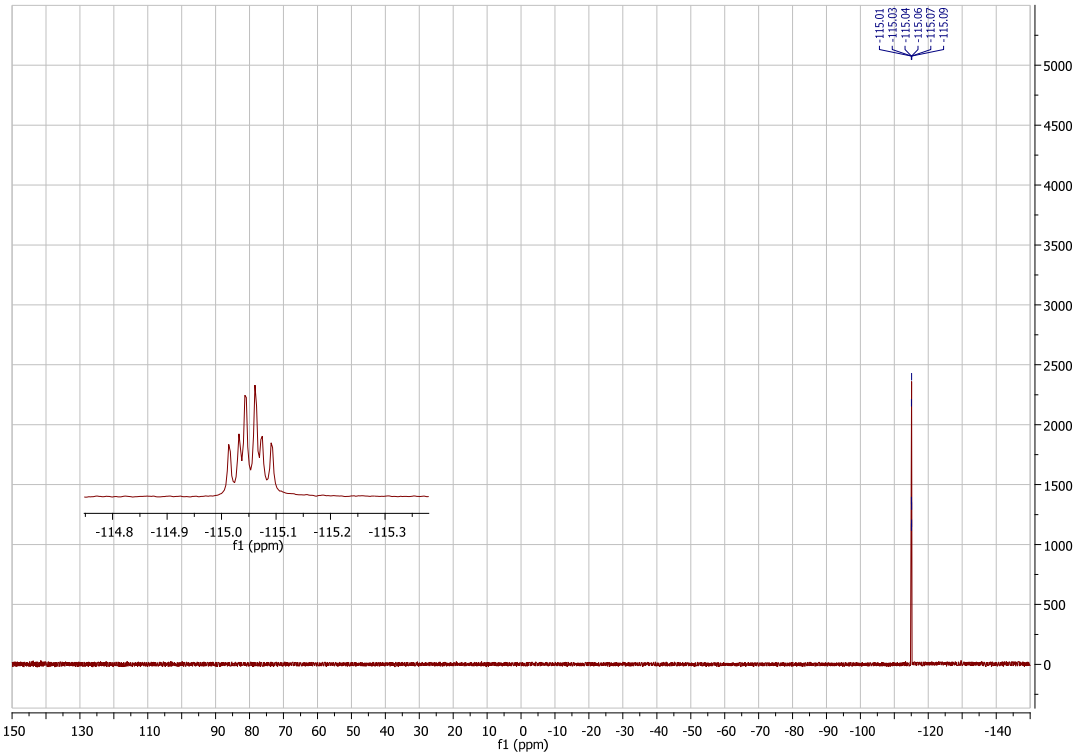



-118.83
-118.84
-118.86
-118.87
-118.75
-118.85
-118.95
f1 (ppm)
f1 (ppm)

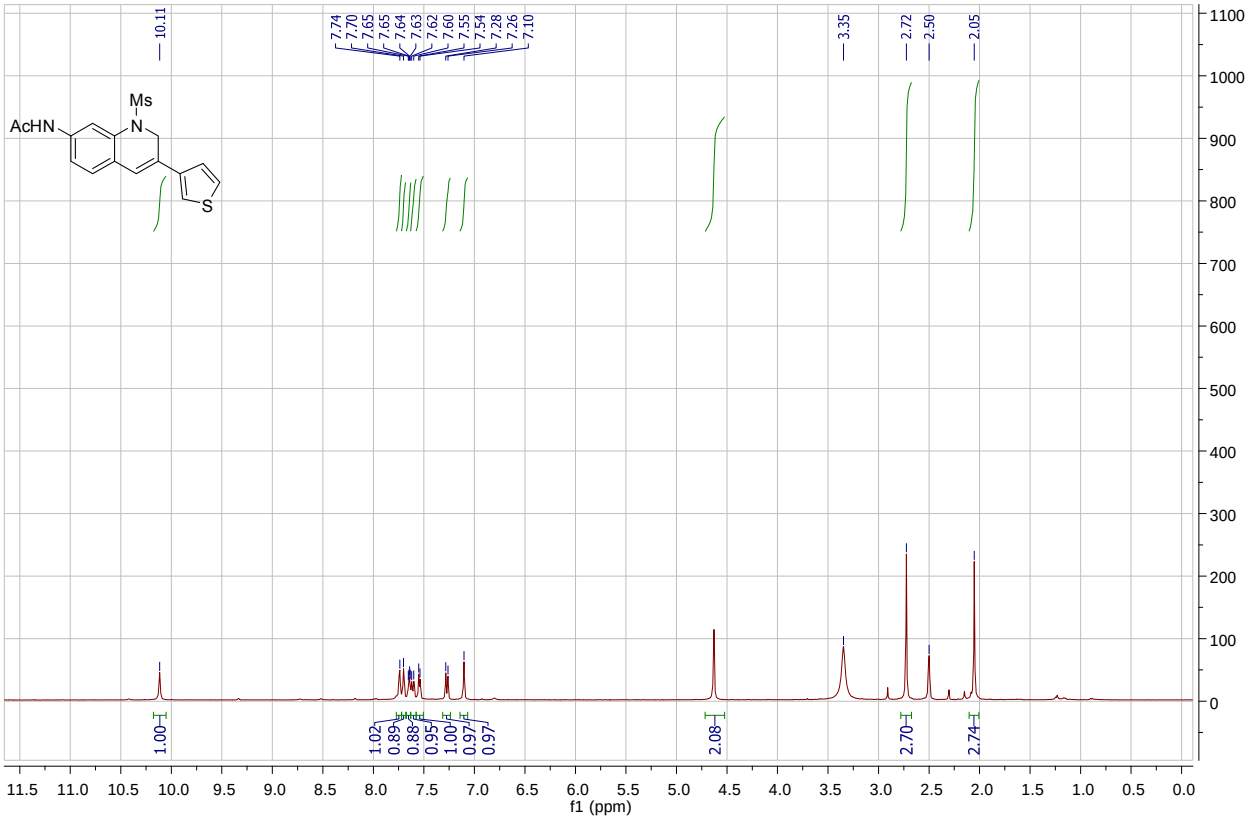
6-fluoro-1-methanesulfonyl-3-thiophen-3-yl-1,2-dihydro-quinoline (3x)

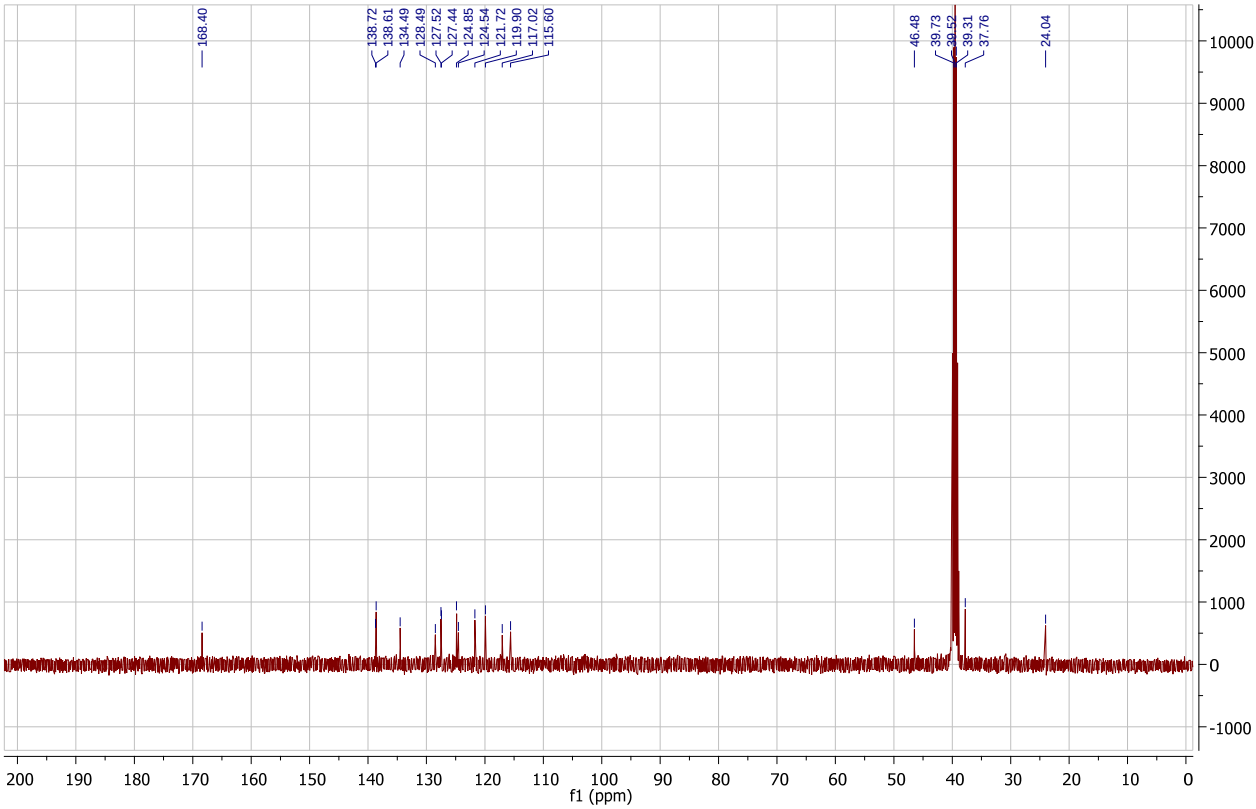




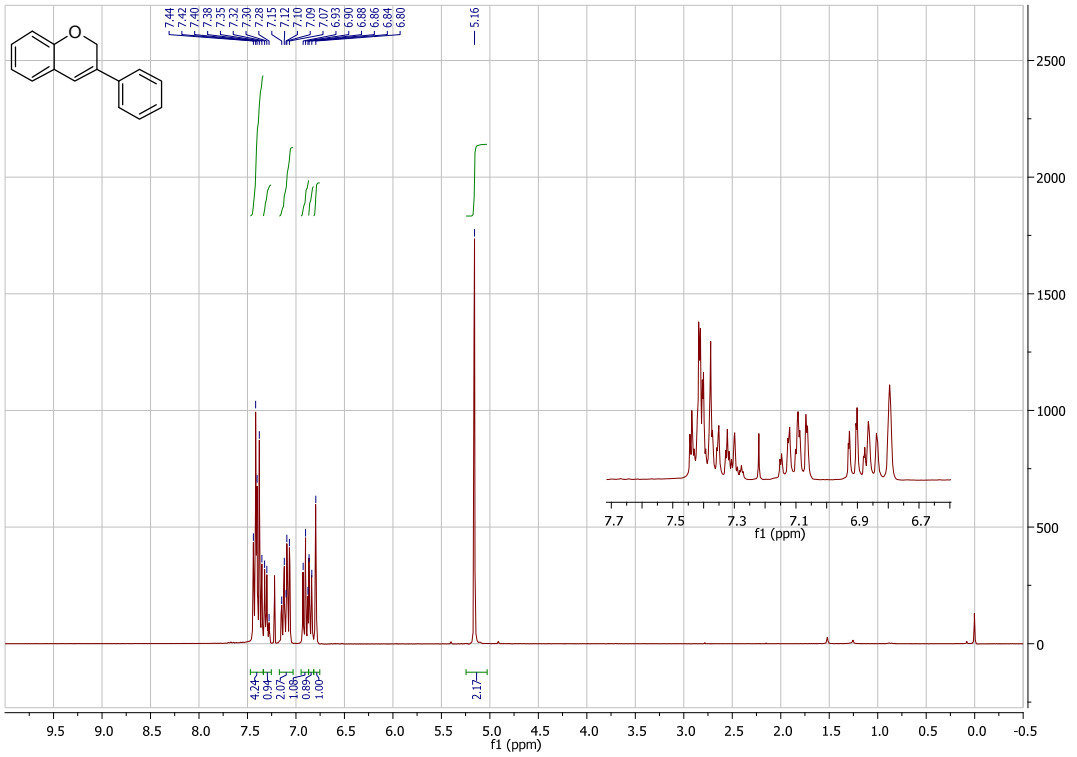

-115.01
-115.03
-115.04
-115.06
-115.07
-115.09
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-114.8
-114.9
-115.0
-115.1
-115.2
-115.3
f1 (ppm)
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-120
-140
f1 (ppm)

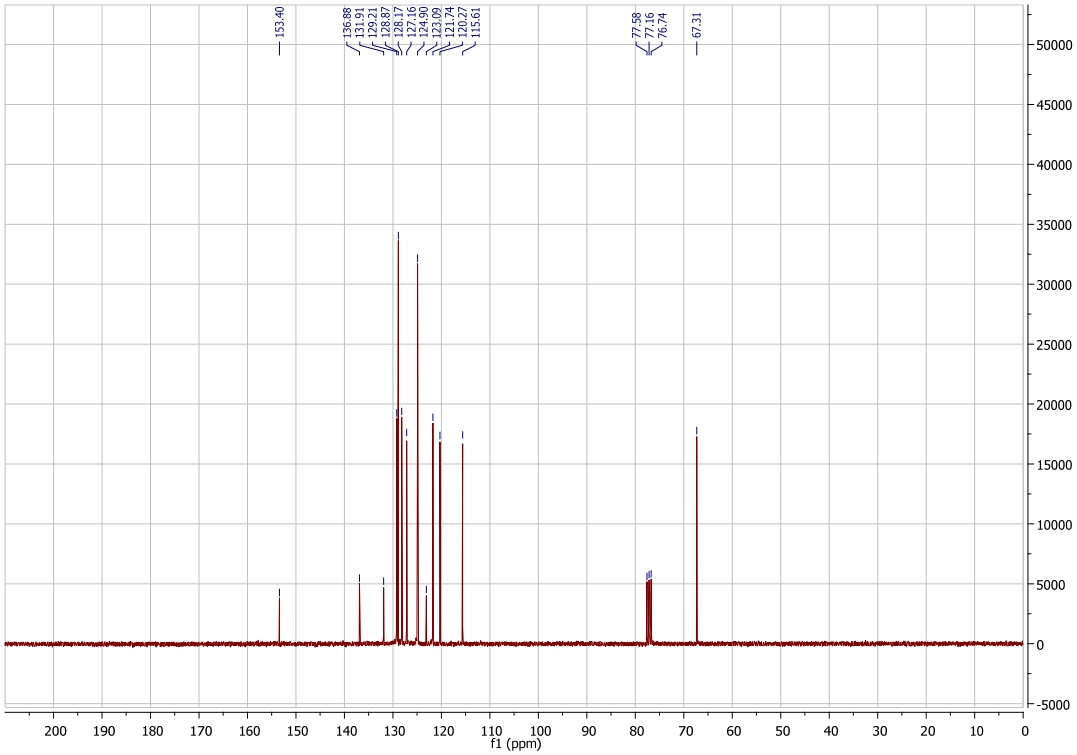
N-(1-(Methylsulfonyl)-3-(thiophen-3-yl)-1,2-dihydroquinolin-7-yl)acetamide (3z)



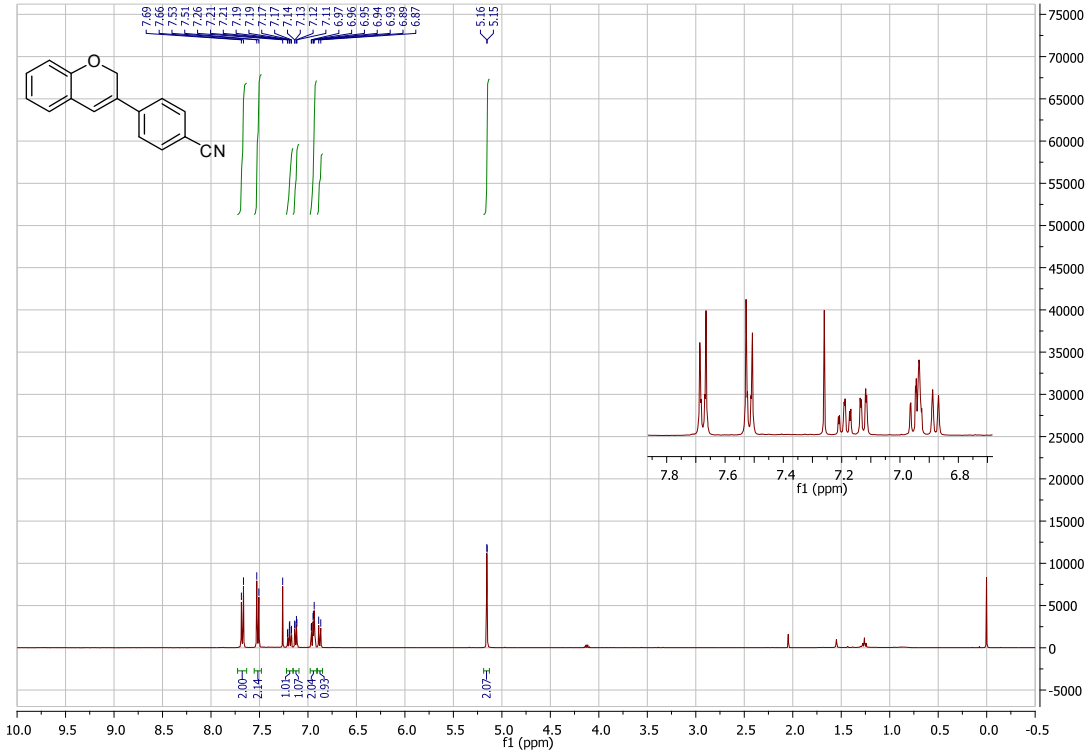


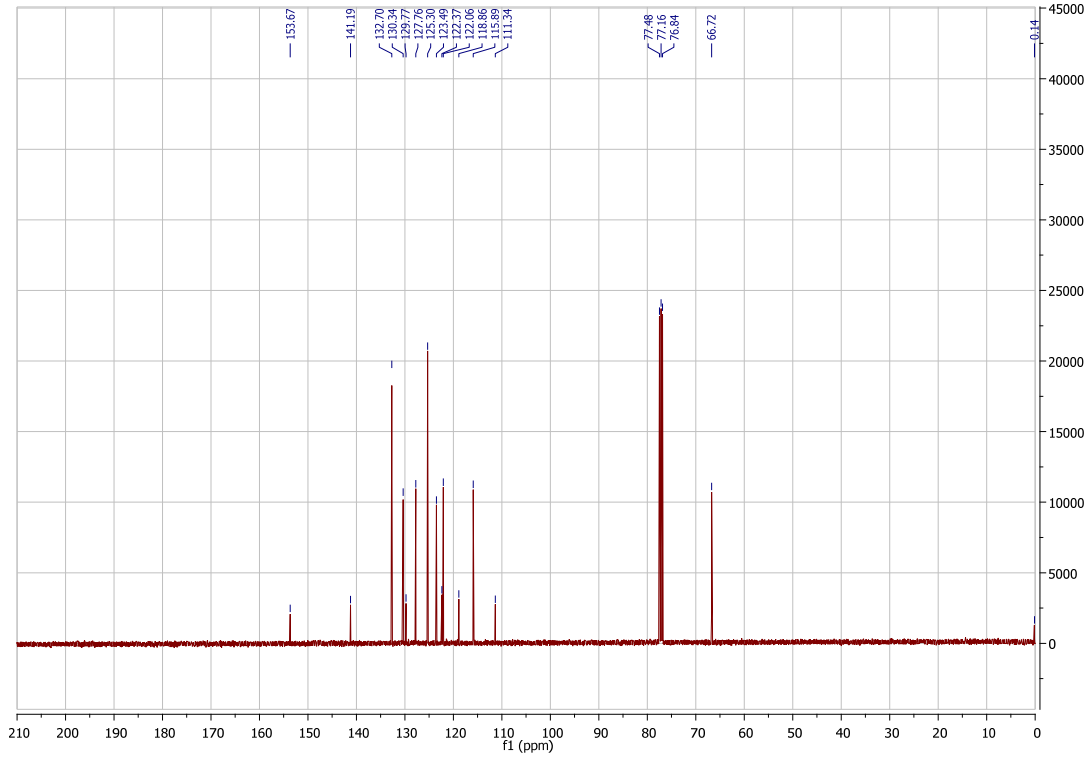
3-phenyl-2H-chromene (4a)



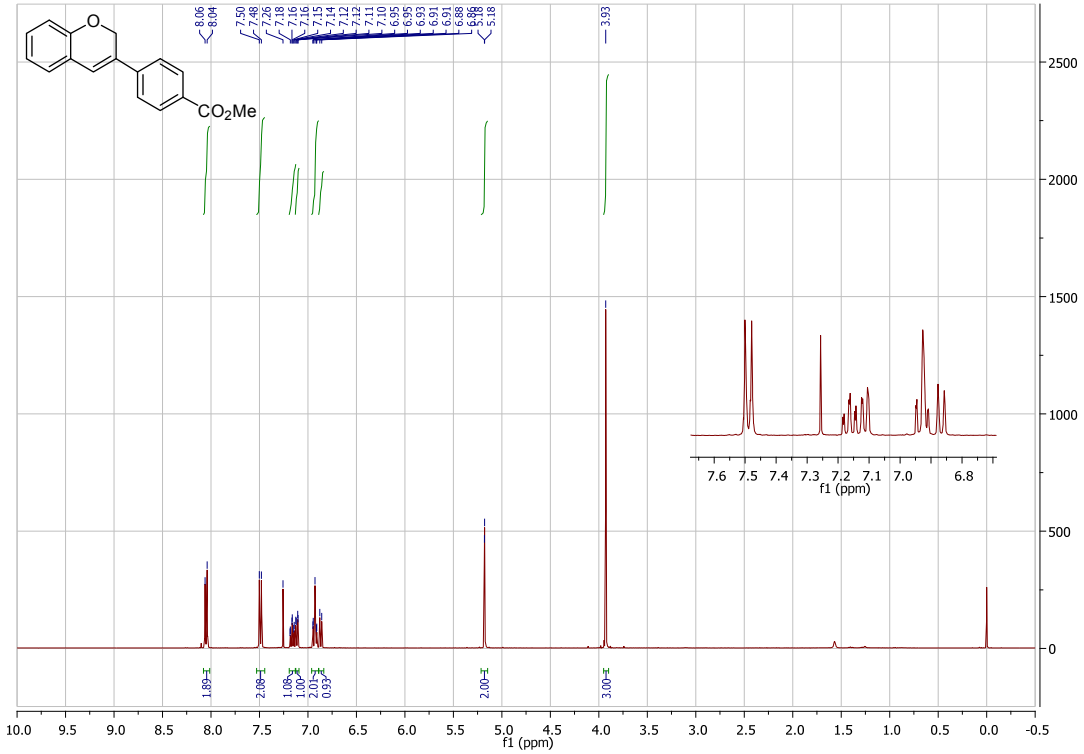


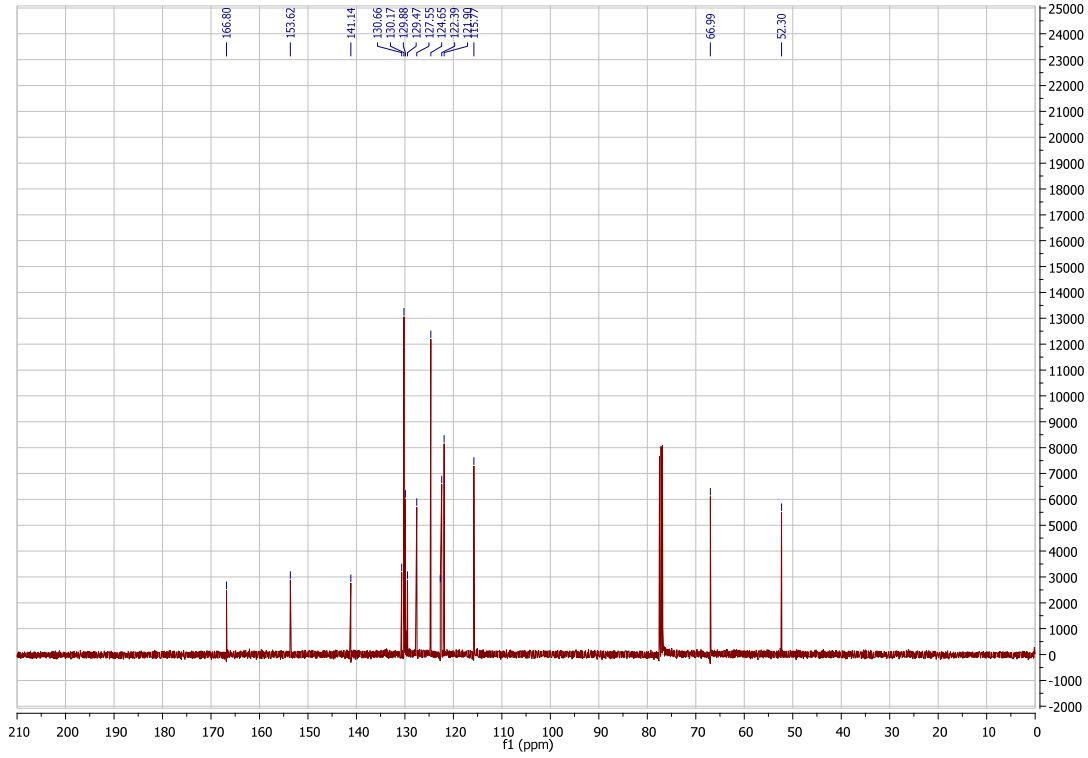
4-(2H-chromen-3-yl)benzonitrile (4b)



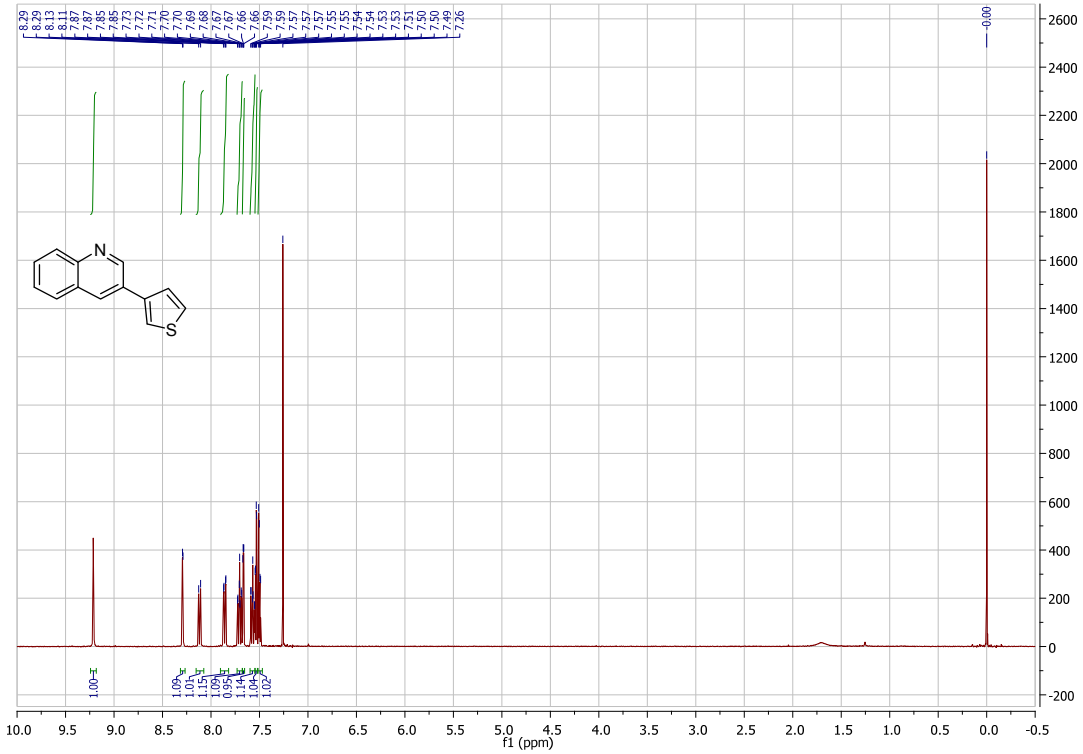


methyl 4-(2H-chromen-3-yl)benzoate (4c)

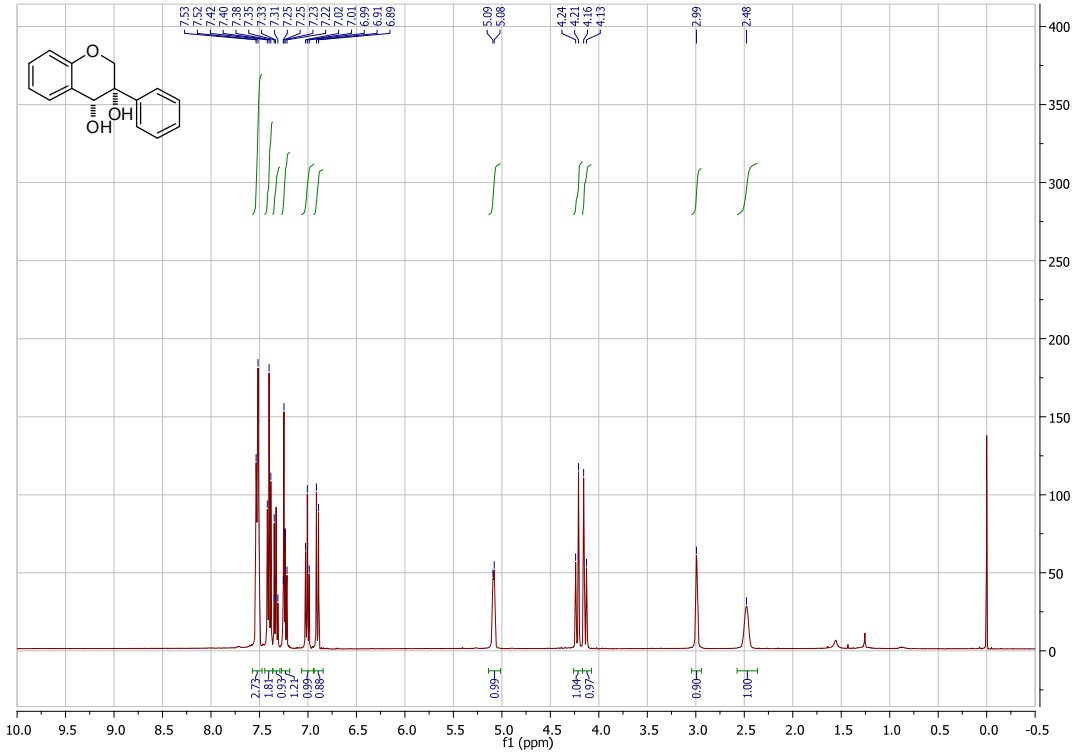


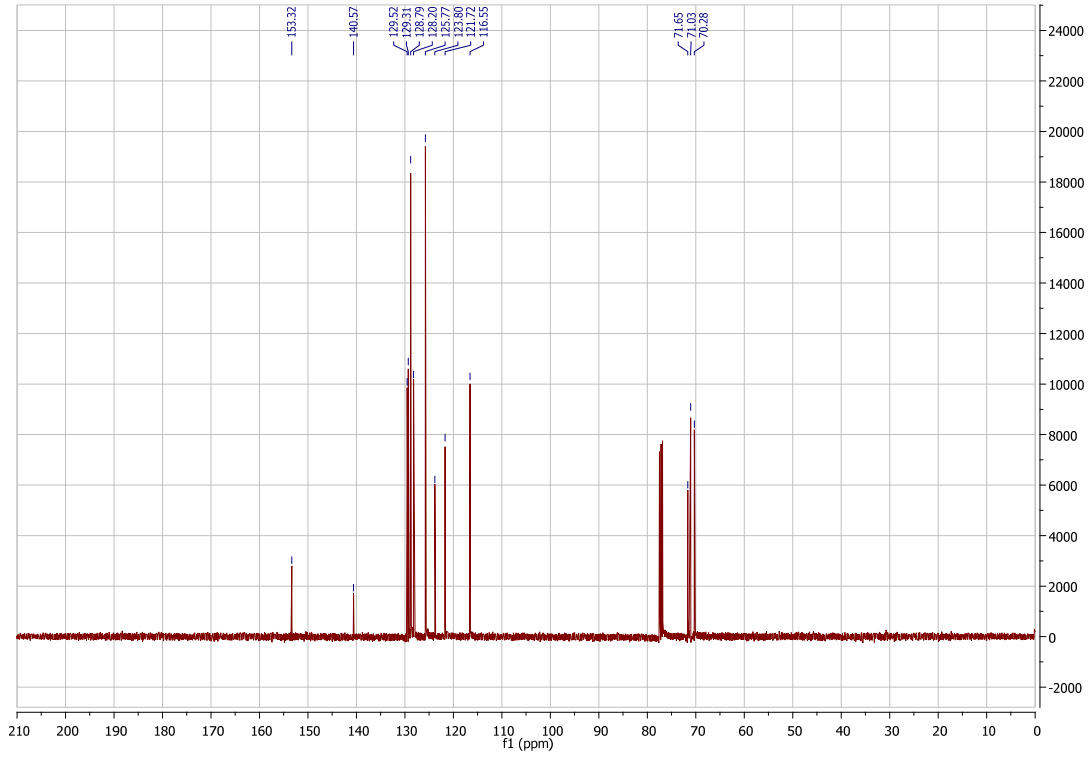


3-(thiophen-3-yl)quinoline 7



(3*S*,4*R*)-3-phenylchroman-3,4-diol 8





^{31}P NMR spectra of catalyst-ligand mixtures

^{31}P NMR spectra of Rh-ligand mixtures in benzene

$[Rh(cod)OH]_2$ + 4 X-Phos ⟶ $[Rh(cod)OH]_2$ + 4 X-Phos

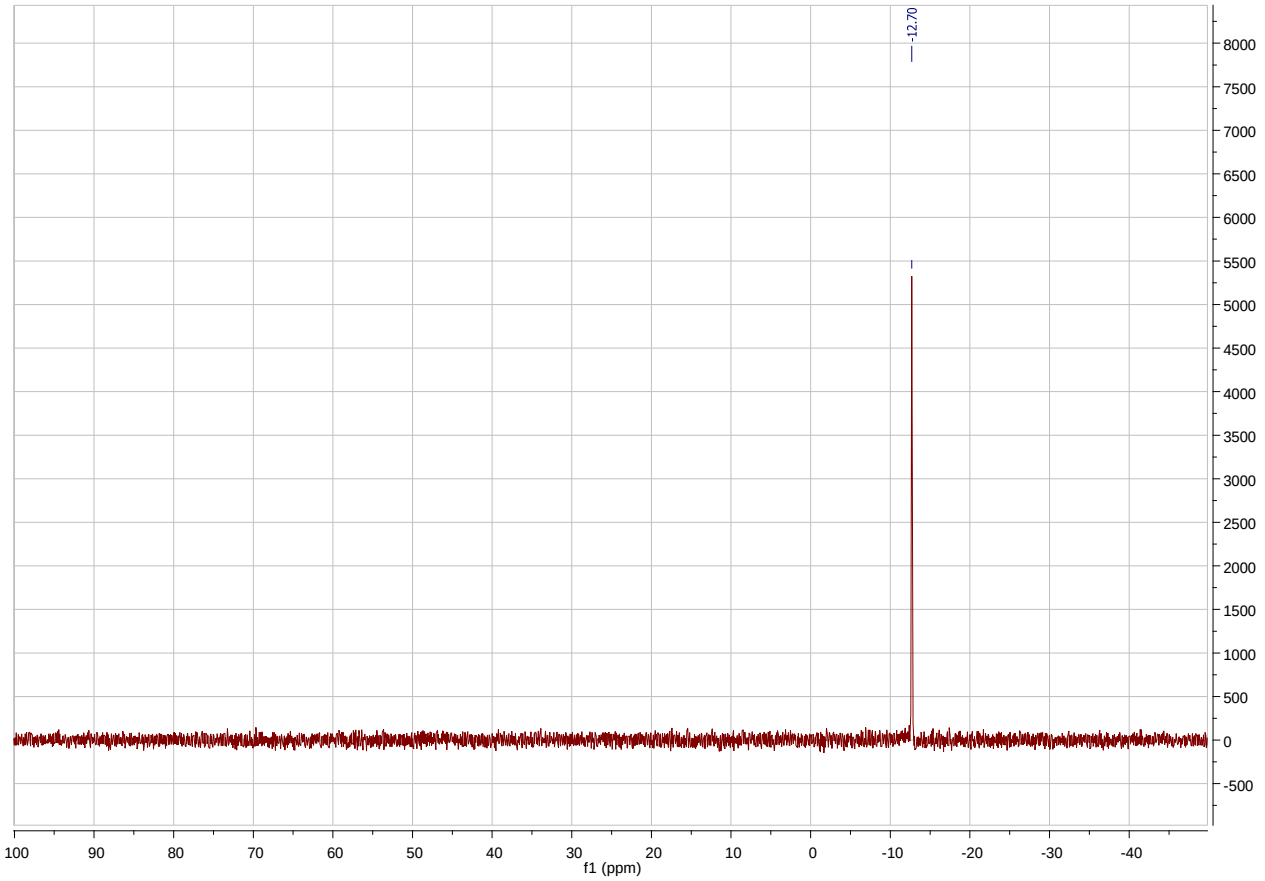


Figure 2, entry 1: $[Rh(cod)OH]_2$ (4.6 mg, 0.01 mmol) and X-Phos (19.07 mg, 0.04 mmol) were dissolved in benzene and left standing for 15min.

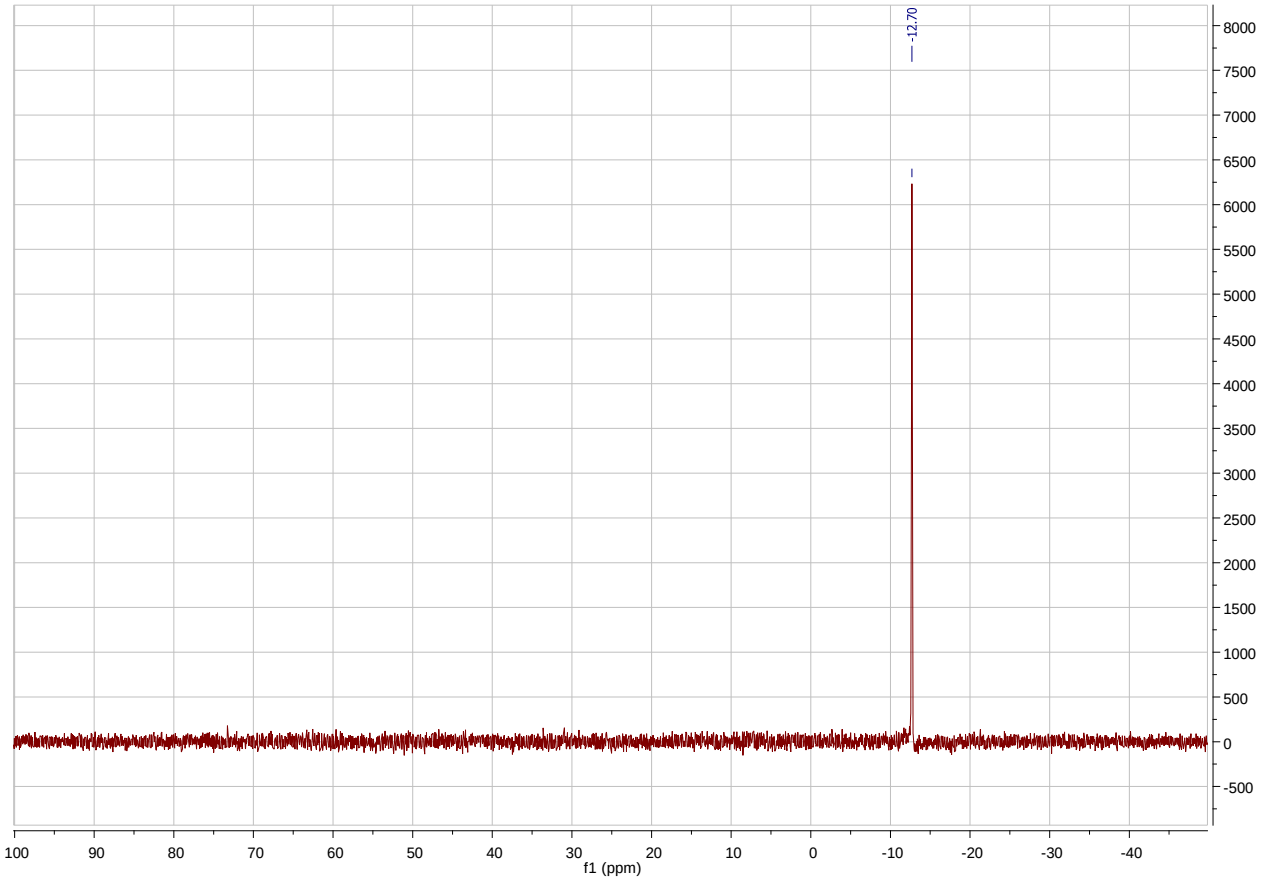


Figure 2, entry 2: The sample prepared in entry 1 was heated at 50 °C in an oil bath for 1 h.

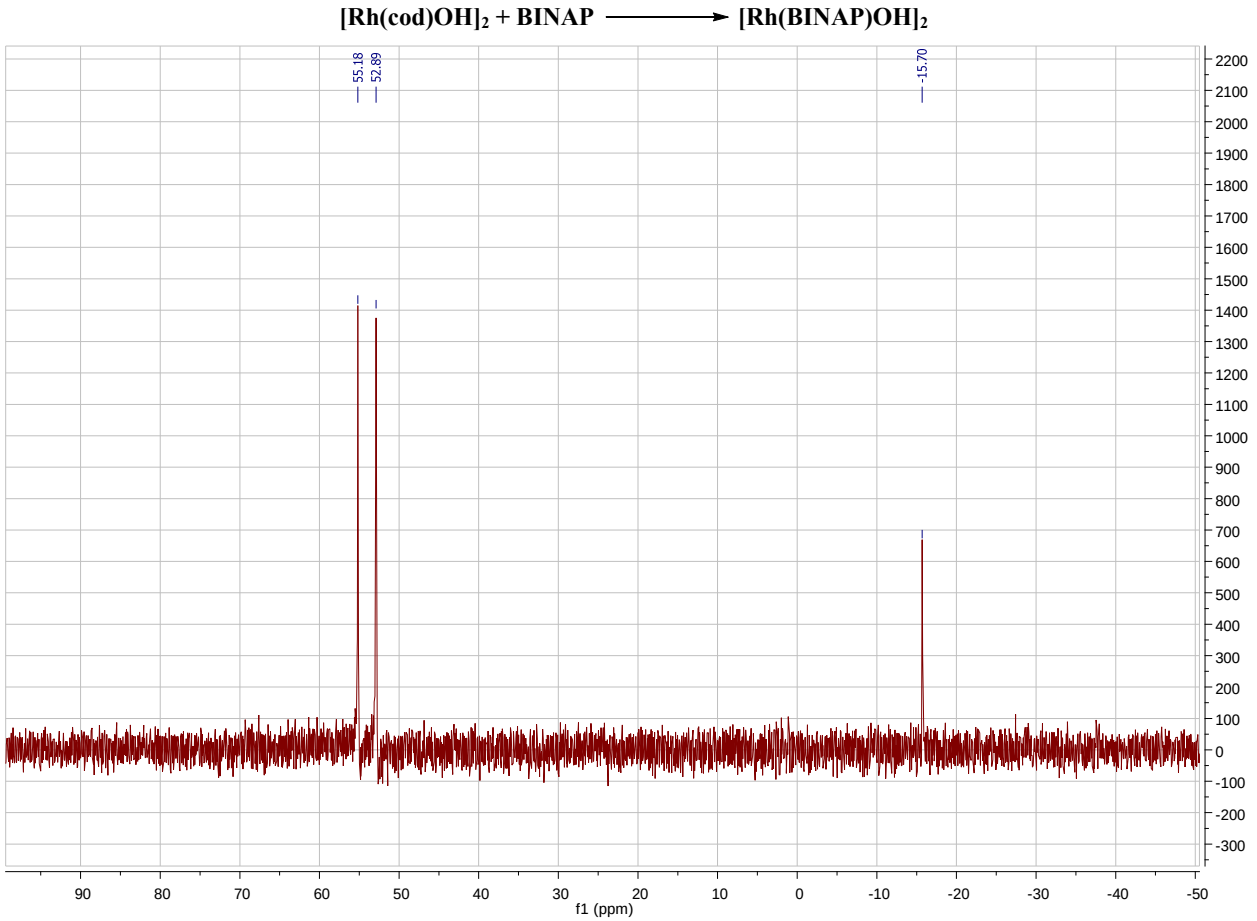


Figure 2, entry 3 $[Rh(cod)OH]_2$ (4.6 mg, 0.01 mmol) and BINAP (12.4 mg, 0.02 mmol) were dissolved in benzene and heated at 50 °C for 1 h.

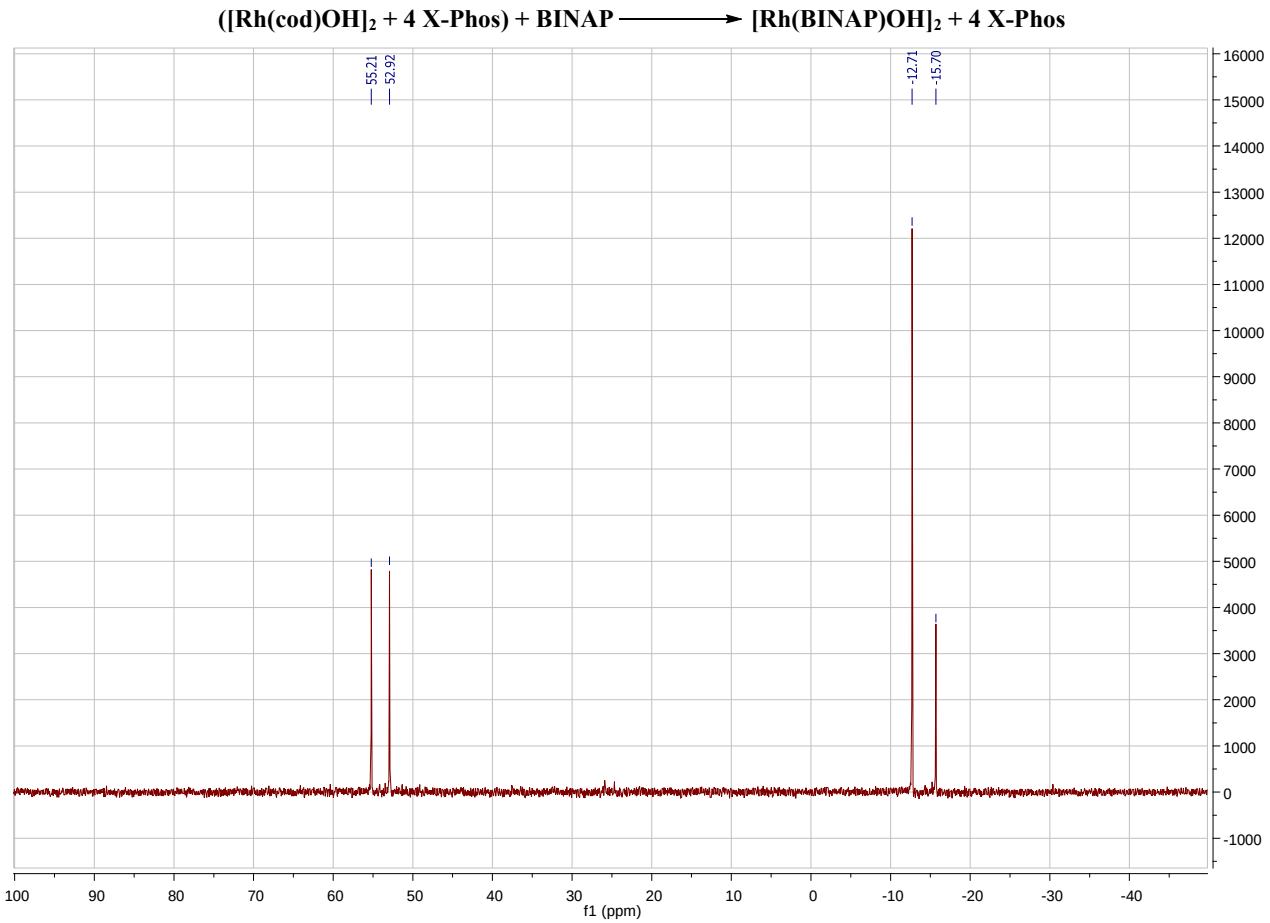


Figure 4, entry 1: $[Rh(cod)OH]_2$ (4.6 mg, 0.01 mmol) and X-Phos (19.07 mg, 0.04 mmol) were dissolved in benzene and left standing for 1 h. To that solution was added BINAP (12.4 mg, 0.02 mmol) and heated in an oil bath at 50 °C for 2 h.

^{31}P NMR spectra of Pd-ligand mixtures in dioxane

$$Pd(OAc)_2 + 2\ \text{X-Phos} \longrightarrow [Pd(\text{X-Phos})_2OAc_2]$$

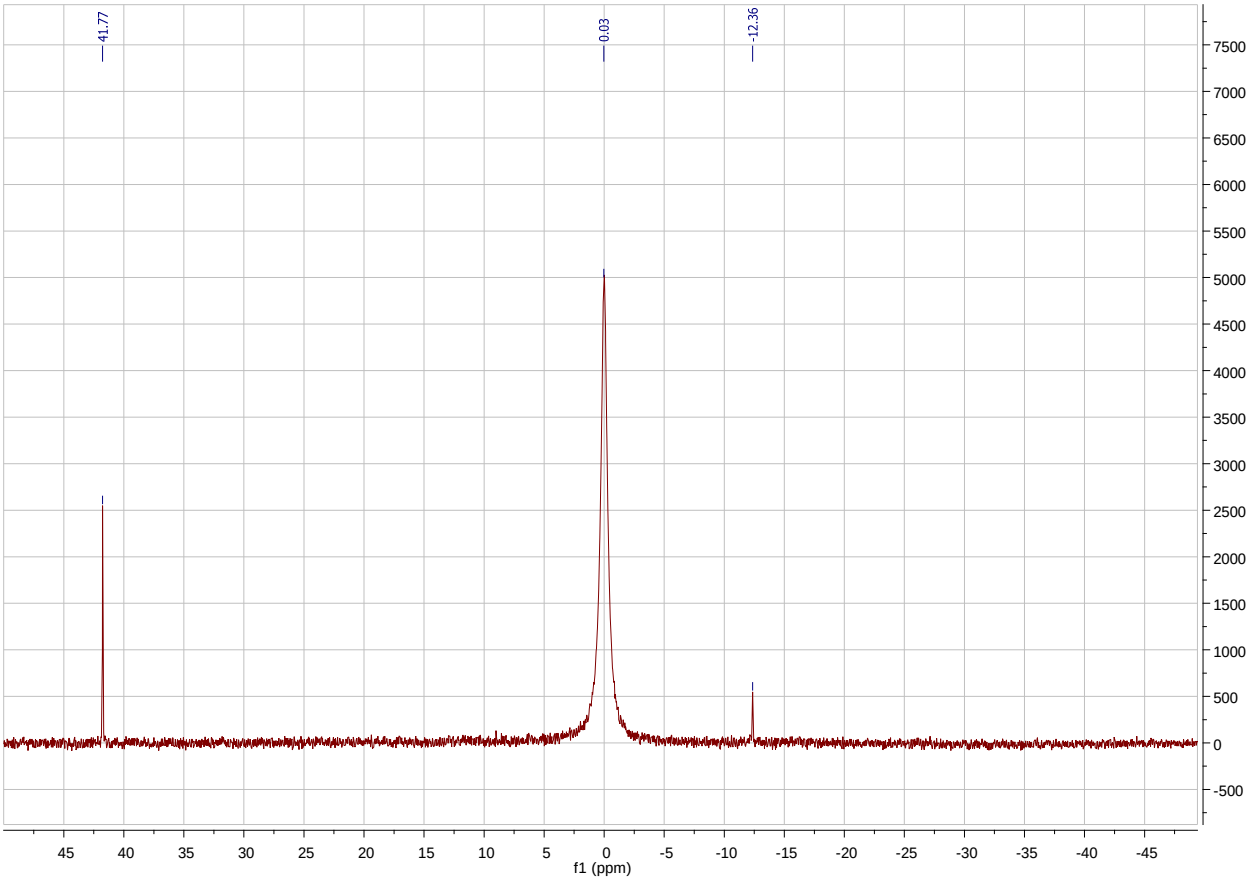
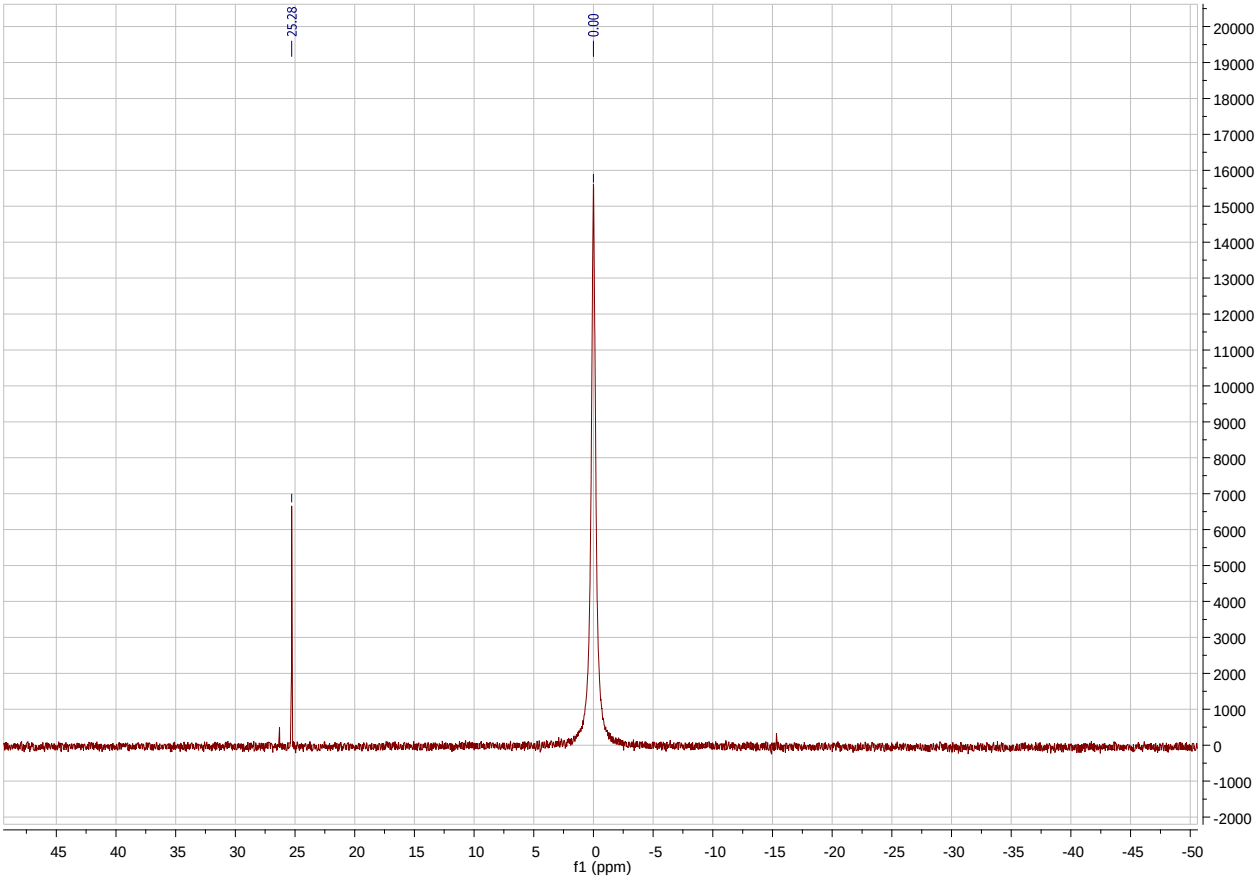


Figure 4, entry 1: $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and X-Phos (19.07 mg, 0.04 mmol) were weighed into a 2 dram vial, which was equipped with a stirring bar and fitted with a septum. Dioxane (2 ml) was added and the mixture was stirred at room temperature for 30 minutes. An NMR tube was equipped with a sealed tube of H_3PO_4 in D_2O (1:5, reference), fitted with a septum and purged with argon. An aliquot of the catalyst solution (0.5 ml) was transferred via syringe into the NMR tube.

$$Pd(OAc)_2 + (R)\text{-BINAP} \longrightarrow [Pd((R)\text{-BINAP})(OAc)_2]$$



Scheme 1: $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and (*R*)-BINAP (12.45mg, 0.02 mmol) were weighed into a 2 dram vial, which was equipped with a stirring bar and fitted with a septum. Dioxane (2 ml) was added and the mixture was stirred at room temperature for 30 minutes. An NMR tube was equipped with a sealed tube of H_3PO_4 in D_2O (1:5, reference), fitted with a septum and purged with argon. An aliquot of the catalyst solution (0.5 ml) was transferred via syringe into the NMR tube.

[Pd(XPhos)$_2$(OAc)$_2$] + (R)-BINAP (1 equiv) ⟶ [Pd((R)-BINAP)] + [Pd(X-Phos)] + X-Phos + (R)-BINAP

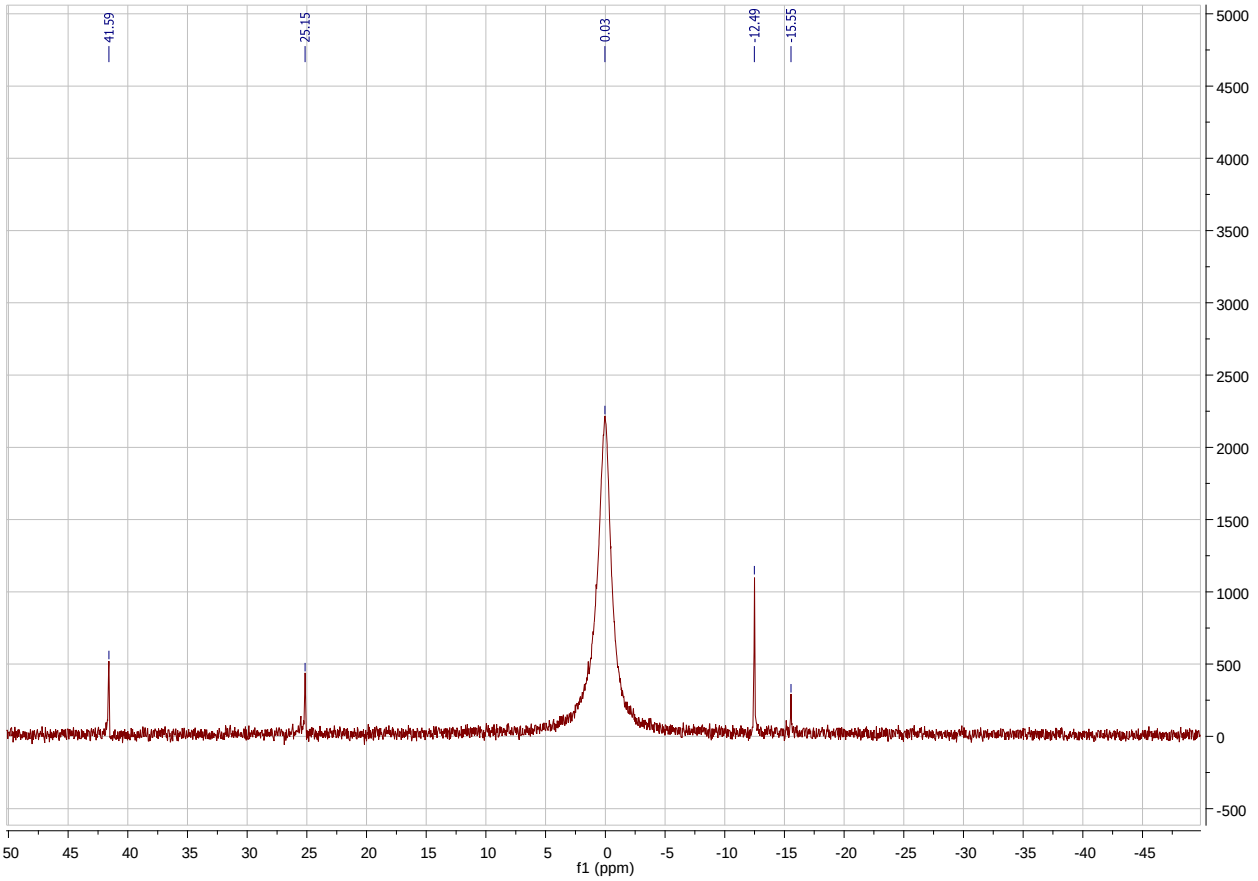


Figure 4, entry 2: [Pd(XPhos)$_2$(OAc)$_2$]solution was prepared as described above in entry 1. To this solution was added (R)-BINAP (1 equiv to Pd). This solution was stirred at r.t. for 30 min, and an aliquot was transferred to an NMR tube for analysis.

[Pd(XPhos)$_2$(OAc)$_2$] + (R)-BINAP (2 equiv) ⟶ [Pd((R)-BINAP)] + [Pd(X-Phos)] + X-Phos + (R)-BINAP

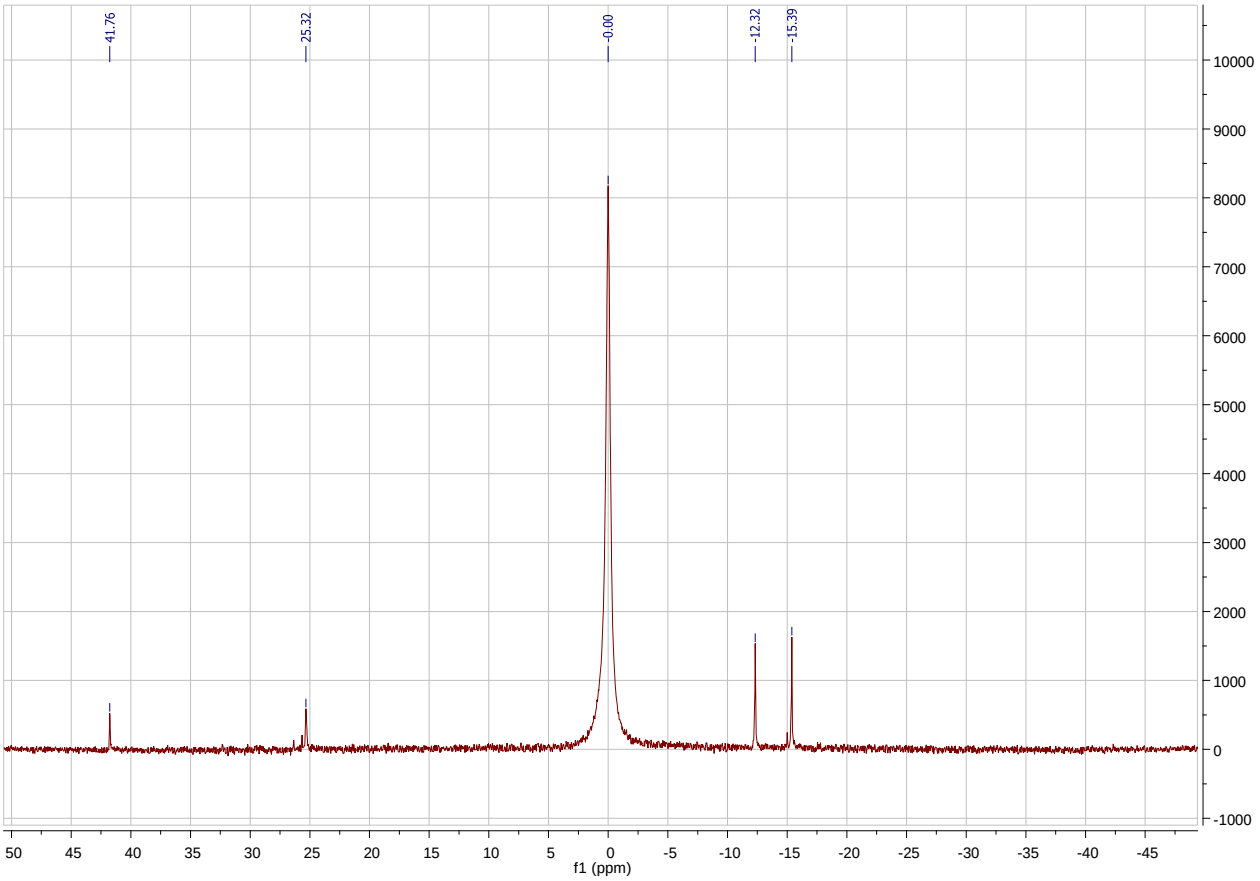


Figure 4, entry 3: [Pd(XPhos)$_2$(OAc)$_2$]solution was prepared as described above in entry 1. To this solution was added (R)-BINAP (2 equiv to Pd). This solution was stirred at r.t. for 30 min, and an aliquot was transferred to an NMR tube for analysis.

[Pd(XPhos)$_2$(OAc)$_2$] + (R)-BINAP (4 equiv) ⟶ [Pd((R)-BINAP)] + [Pd(X-Phos)] + X-Phos + (R)-BINAP + (R)-BINAP(O)

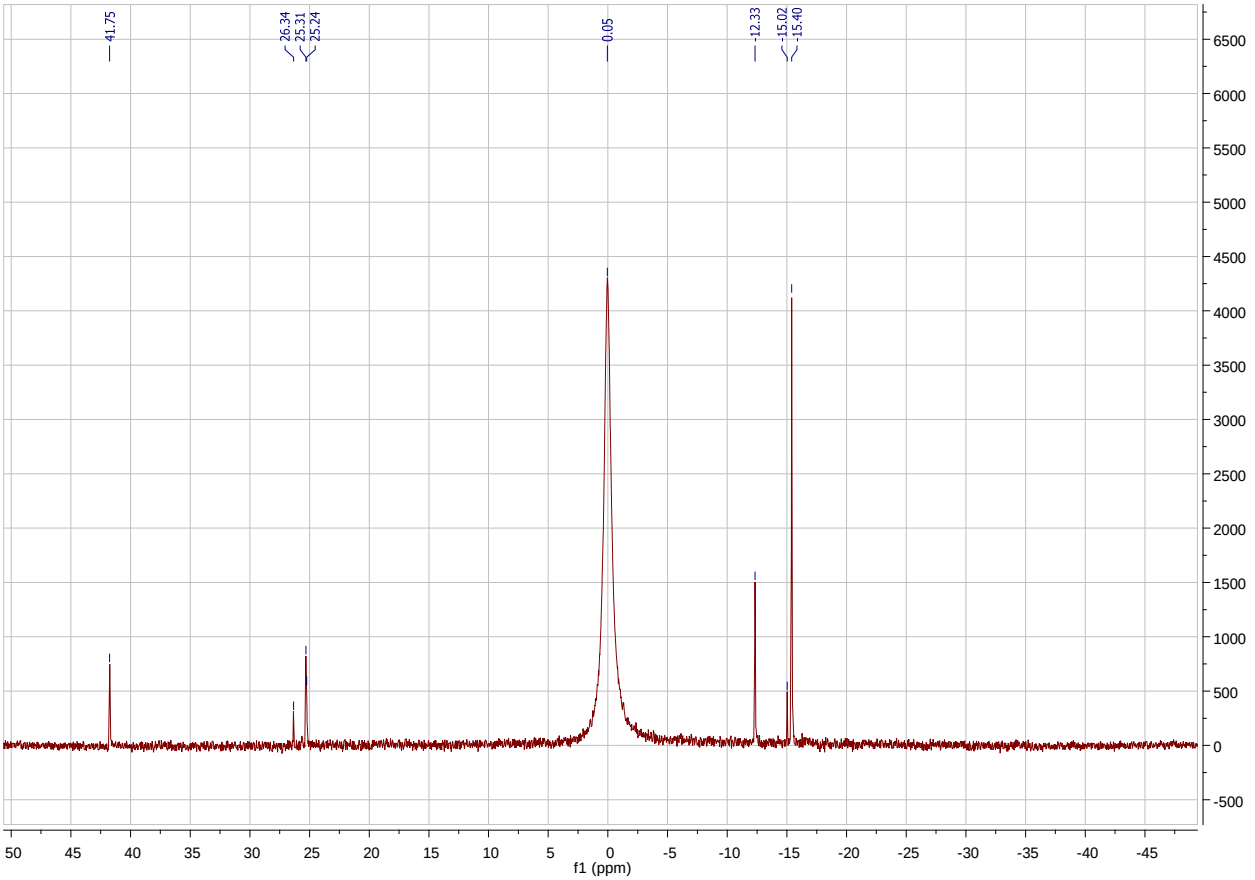


Figure 4, entry 4: [Pd(XPhos)$_2$(OAc)$_2$]solution was prepared as described above in entry 1. To this solution was added (R)-BINAP (4 equiv to Pd). This solution was stirred at r.t. for 30 min, and an aliquot was transferred to an NMR tube for analysis. The observation of (R)-BINAP(O) was identified with literature data described in references 20.

[Pd((R)-BINAP)(OAc)$_2$] + X-Phos (2 equiv) ⟶ [Pd(BINAP)] + X-Phos + (R)-BINAP

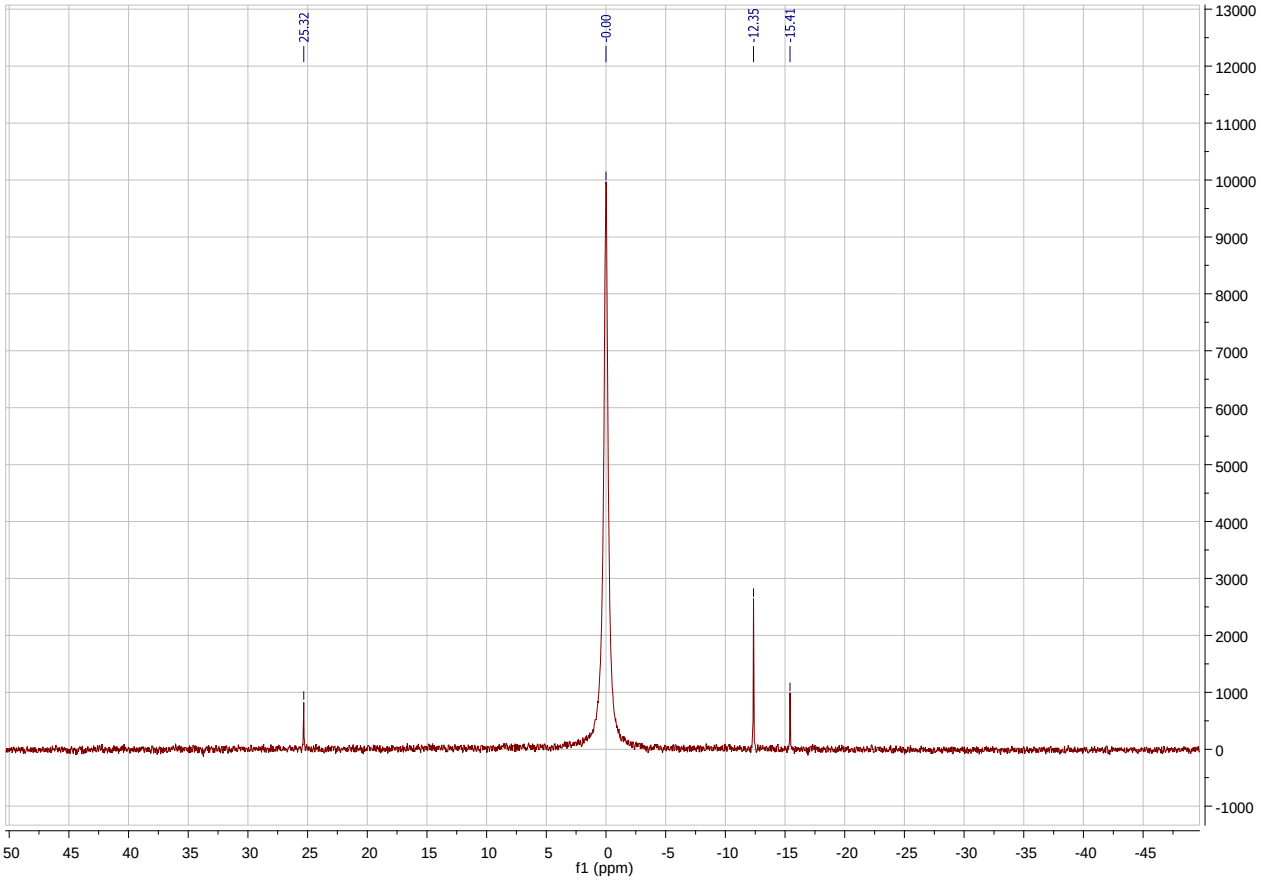


Figure 4, entry 5: Palladium-BINAP solution was prepared as described above in **Scheme 1**. To this solution was added X-Phos (2 equiv to Pd). This solution was stirred at r.t. for 30 mins, after which an aliquot was transferred to an NMR tube for analysis.

[Pd((R)-BINAP)(OAc)$_2$] + X-Phos (4 equiv) ⟶ [Pd(BINAP)] + X-Phos + (R)-BINAP

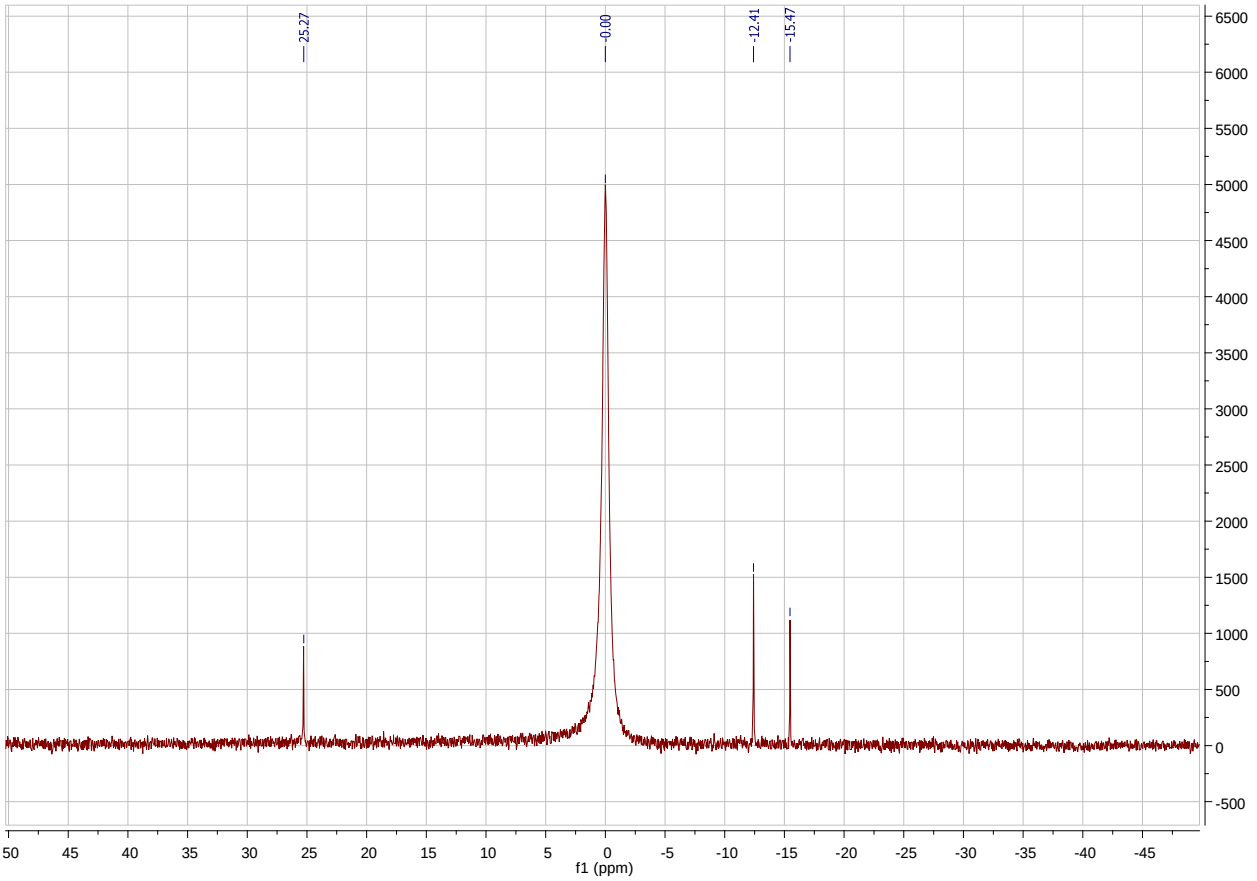


Figure 4, entry 5: Palladium-BINAP solution was prepared as described above in **Scheme 1**. To this solution was added X-Phos (4 equiv to Pd). This solution was stirred at r.t. for 30 mins, after which an aliquot was transferred to an NMR tube for analysis.

References

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.