Supporting Information For

An Efficient Coupling of *N*-Tosylhydrazones with 2-Halopyridines: Synthesis of 2-α-Styrylpyridines Endowed with Antitumor Activity

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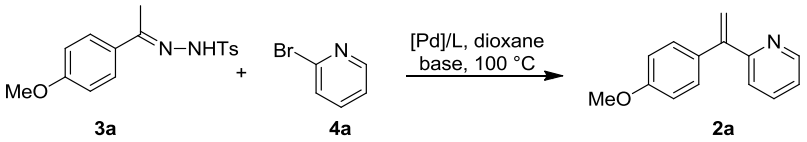
List of Contents

Table 1. Optimization Coupling Reaction of *N*-Tosylhydrazones 3a with 2-Bromopyridine 4a under Various Conditions.[a] 1

Experimental procedures for the synthesis of starting materials 4d, 4i, 4j. 4

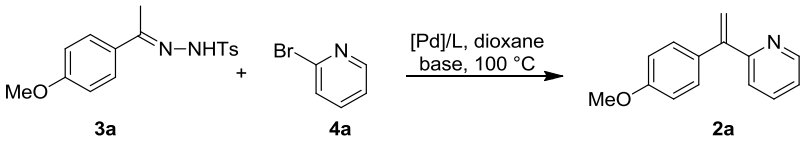
^{1}H NMR and ^{13}C Spectra 7

Table 1. Optimization Coupling Reaction of *N*-Tosylhydrazones 3a with 2-Bromopyridine 4a under Various Conditions.[a]



3a 4a 2a

Essais	[Pd]	Ligand	Solvent	Base	Yield of **2a**[b]	
1	**Pd_2dba_3**	Xphos	dioxane	LiO^tBu	15	Effect of base source
2	**$PdCl_2(MeCN)_2$**	DPPP	dioxane	Cs_2CO_3	22	
3	$PdCl_2(MeCN)_2$	DPPP	dioxane	LiO^tBu	42	
4	$PdCl_2(MeCN)_2$	DPPP	dioxane	NaO^tBu	32	
5	$PdCl_2(MeCN)_2$	DPPP	dioxane	KO^tBu	27	
6	$PdCl_2(MeCN)_2$	DPPP	dioxane	NaOMe	5	
7	$PdCl_2(MeCN)_2$	DPPB	dioxane	LiO^tBu	30	Effect of ligand source
8	$PdCl_2(MeCN)_2$	DPPE	dioxane	LiO^tBu	28	
9	$PdCl_2(MeCN)_2$	DPPM	dioxane	LiO^tBu	27	
10	**$PdCl_2(MeCN)_2$**	**DPPF**	**dioxane**	**LiO^tBu**	**84**[c]	
11	$PdCl_2(MeCN)_2$	D^iPrPF	dioxane	LiO^tBu	25	
12	$PdCl_2(MeCN)_2$	D^tBPF	dioxane	LiO^tBu	28	
13	$PdCl_2(MeCN)_2$	PPh_3	dioxane	LiO^tBu	33	
14	$PdCl_2(MeCN)_2$	DPEPhos	dioxane	LiO^tBu	32	
15	$PdCl_2(MeCN)_2$	JohnPhos	dioxane	LiO^tBu	6	
16	$PdCl_2(MeCN)_2$	DavePhos	dioxane	LiO^tBu	44	
17	$PdCl_2(MeCN)_2$	PCy_3	dioxane	LiO^tBu	31	
18	$PdCl_2(MeCN)_2$	$^tBu_3P\text{-}HBF_4$	dioxane	LiO^tBu	8	
19	**$PdCl_2(MeCN)_2$**	**$^tBu_2MeP\text{-}HBF_4$**	**dioxane**	**LiO^tBu**	**82**	

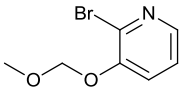


3a **4a** **2a**

Essais	[Pd]	Ligand	Solvent	Base	Yield of **2a**[b]	
20	**$PdCl_2(MeCN)_2$**	**DPPF**	**dioxane**	**LiO^{t}Bu**	**84**	**Effect of solvent**
21	$PdCl_2(MeCN)_2$	DPPF	CPME[d]	LiO^{t}Bu	46	
22	$PdCl_2(MeCN)_2$	DPPF	Toluene	LiO^{t}Bu	51	
23	$PdCl_2(MeCN)_2$	DPPF	THF	LiO^{t}Bu	62	
24	$PdCl_2(MeCN)_2$	DPPF	CH_3CN	LiO^{t}Bu	60	
25	$PdCl_2(MeCN)_2$	DPPF	DMF	LiO^{t}Bu	46	
26	$PdCl_2(MeCN)_2$	DPPF	PhF	LiO^{t}Bu	40	
27	$PdCl_2(MeCN)_2$	DPPF	DME	LiO^{t}Bu	53	
28	Pd_2dba_3	DPPF	dioxane	LiO^{t}Bu	40	**Effect of Pd source**
29	$PdCl_2(PhCN)_2$	DPPF	dioxane	LiO^{t}Bu	45	
30	$Pd(OAc)_2$	DPPF	dioxane	LiO^{t}Bu	35	
31	$PdCl_2$(dppf)	-	dioxane	LiO^{t}Bu	60	
32	$PdCl_2$(dppf)	^{t}Bu$_2$MeP-HBF$_4$	dioxane	LiO^{t}Bu	58	
33	$PdCl_2$(dppf)	DavePhos	dioxane	LiO^{t}Bu	51	
34	$PdCl_2(PPh_3)_2$	-	dioxane	LiO^{t}Bu	30	
35	-	DPPF	dioxane	LiO^{t}Bu	0	
36	$PdCl_2(MeCN)_2$	-	dioxane	LiO^{t}Bu	15	

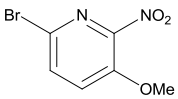
[a] The reactions were carried out in a sealed tube with **3a** (1.5 mmol), **4a** (1 mmol), [Pd] (5 mol %), Ligand (10 mol %), base (2.2 equiv) at 100 °C in 3.0 mL of solvent. [b] Isolated yield of **2a**. [c] Performing the coupling with a ratio of Pd/ligand (1:1) give the desired product **2a** in 60% isolated yield. [d] Cyclopentyl methyl ether (CPME).

Experimental procedures for the synthesis of starting materials 4d, 4i, 4j.

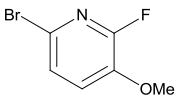


2-Bromo-3-(methoxymethoxy)pyridine 4d.[1] To a solution of 2-bromopyridin-3-ol (1.0 g, 5.75 mmol, 1.0 equiv) in dry THF (20 mL) in a dry flask under an argon atmosphere was added anhydrous DIPEA (1.5 mL, 8.6 mmol, 1.5 equiv). The suspension was stirred for 15 min then cooled to 5 °C and a solution of technical grade chloromethyl methyl ether (0.8 mL, 8.6 mmol, 1.5 equiv) in dry THF (5 mL) was added in one portion. The suspension was stirred at 5-10 °C for 2 h, then warmed to room temperature and stirred for 15 h at reflux. The reaction was poured into water (60 mL), extracted with diethyl ether (4 x 50 mL), then the combined organic phases were washed with water (1 x 50 mL) and brine (1 x 50 mL) before being dried over $MgSO_4$. Removal of solvents *in vacuo* yielded a clear oil which was purified by flash chromatography on silica gel (4 x 15 cm) eluting with 1:4 ethyl acetate/hexanes to afford **4d** as colorless crystals, yield 0.68 g, 55%; mp 44-46 °C; TLC: R_f = 0.8 (EtOAc/Cyclohexane, 5/5, SiO_2); IR (neat) 1566, 1453, 1418, 1401, 1308, 1271, 1206, 1155, 1134, 1095, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.44 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.16 – 7.10 (m, 1H), 5.23 (s, 2H), 3.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 149.6 (C), 141.9 (CH), 141.5 (C), 123.6 (CH), 123.2 (CH), 95.1 (OCH_2O), 56.4 (OCH_3); HRMS (ESI): for $C_7H_9BrNO_2$ $(M + H)^+$: *m/z* calcd 217.9817, found 217.9825.

(1) Robert, N.; Hoarau, C.; Célanire, S.; Ribéreau, P.; Godard, A.; Quéguiner, G.; Marsais, F., *Tetrahedron* **2005**, *61*, 4569.



6-Bromo-3-methoxy-2-nitropyridine 4i.[2] A mixture of 6-bromo-3-hydroxy-2-nitropyridine (2.87 g, 13.71 mmol), and potassium carbonate (3.78 g, 27.4 mol) in acetone (30 mL) was treated with iodomethane (1.8 ml, 28 mmol) and stirred at 50°C. Two further additions of 1.2 equivalents of iodomethane were made over a period of approximately four hours. The solvent was filtered, evaporated, and the residue dissolved in ethyl acetate (50 mL) and washed with water (30 mL), saturated sodium hydrogen carbonate solution (30 mL), water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and evaporated. Purification by column chromatography eluting with 0- 100% ethyl acetate in hexane gave the title compound as a cream yellow solid (3.1 g, 98% yield); mp 98-100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): ^{1}H NMR (300 MHz,) δ 7.71 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 147.5 (C), 133.3 (CH), 128.5 (2C), 125.6 (CH), 57.2 (OCH_3). HRMS (ESI): for $C_6H_6BrN_2O_3$ $(M + H)^+$ calcd 232.9556, found 232.9572.



6-Bromo-2-fluoro-3-methoxypyridine 4j.[3] To a stirred solution of 6-bromo-2-fluoropyridin-3-ol (1.55 g, 8.06 mmol) and sodium methoxide (0.46 mg, 8.45 mmol) in DMF (17 mL) was added iodomethane (0.53 mL, 8.45 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 hours. The mixture was treated with H_2O and extracted with ethyl acetate. The combined organic layer was dried and evaporated. The residue was purified by chromatography on silica gel, eluting with ethyl acetate/cyclohexane (5/5) afford compound **4j** as a yellow solid (0.57 g, 44%); mp 58-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30 (d, *J* = 8.2 Hz, 1H), 7.18 (dd, *J* = 9.6, 8.2 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 151.9

(2) Blaney, E. L.; King, N. P.; Witherington, J. Piperazine derivatives as growth hormone secretagogue (GHS) receptor agonists. WO/2007/113202A1, 2007.
(3) Kazuo, A.; HIROTA, M. 1-2-(4-Hydroxyphenyl)-2-hydroxyethyl-piperidin-4-ol compounds as NMDA receptor antagonists. WO2005035522A1, 2005.

(d, J = 240 Hz) (C), 142.45 (d, J = 23.3 Hz) (C), 125.6 (d, J = 2.25 Hz) (CH), 125.5 (C), 124.2 (d, J = 4.5 Hz) (CH), 56.60 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ -80.03.

^{1}H NMR and ^{13}C Spectra

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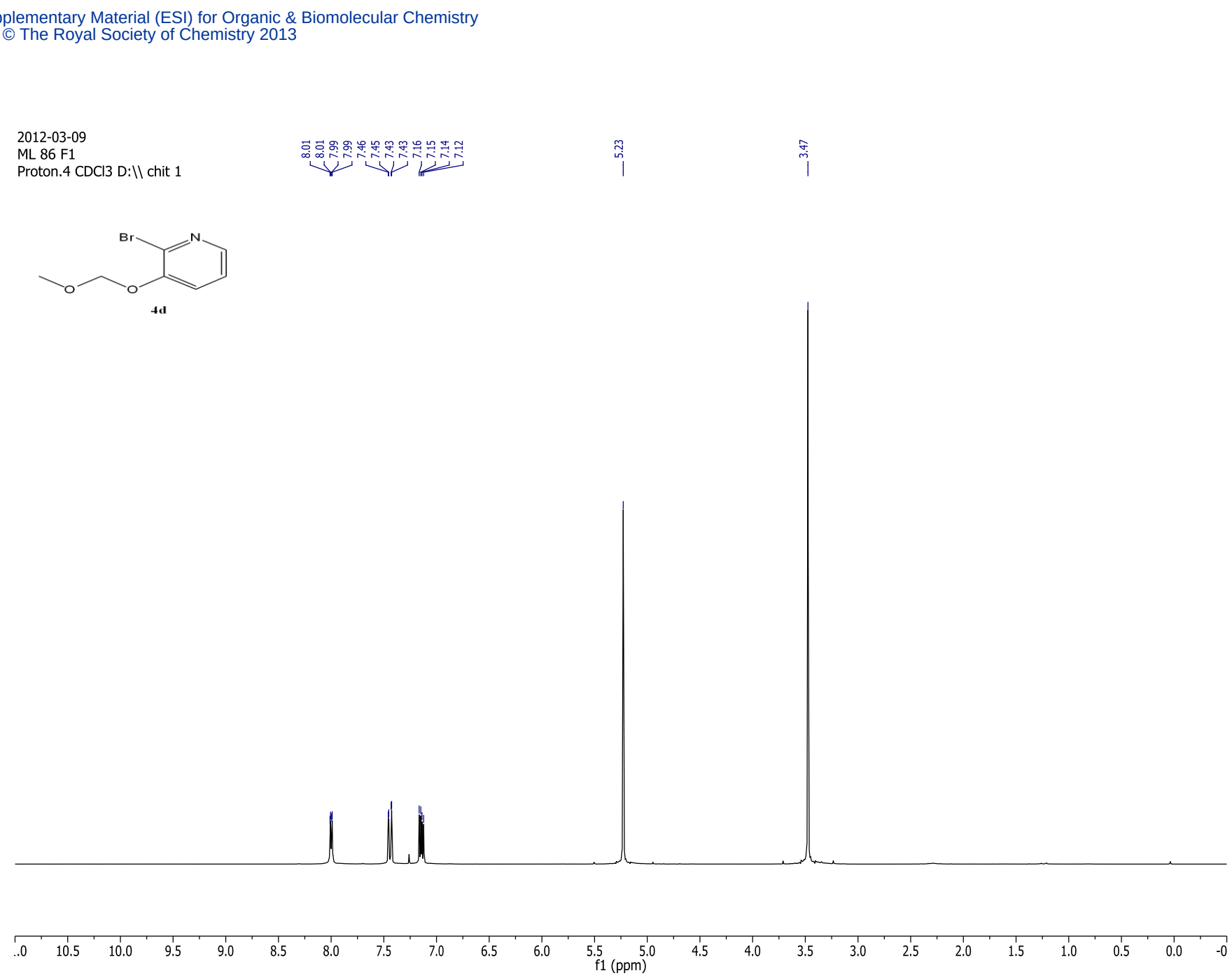

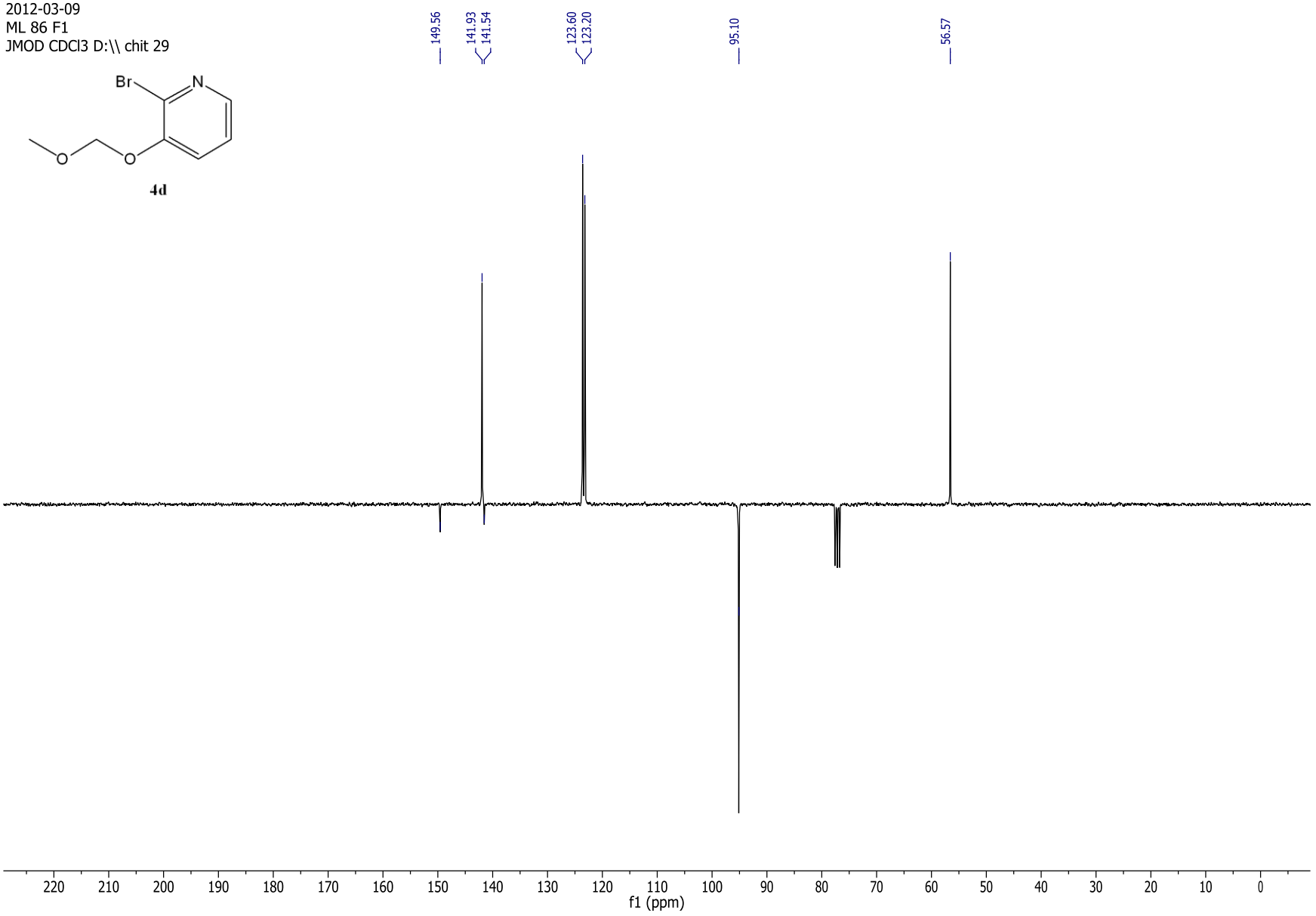

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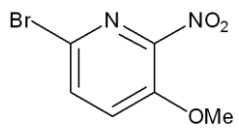
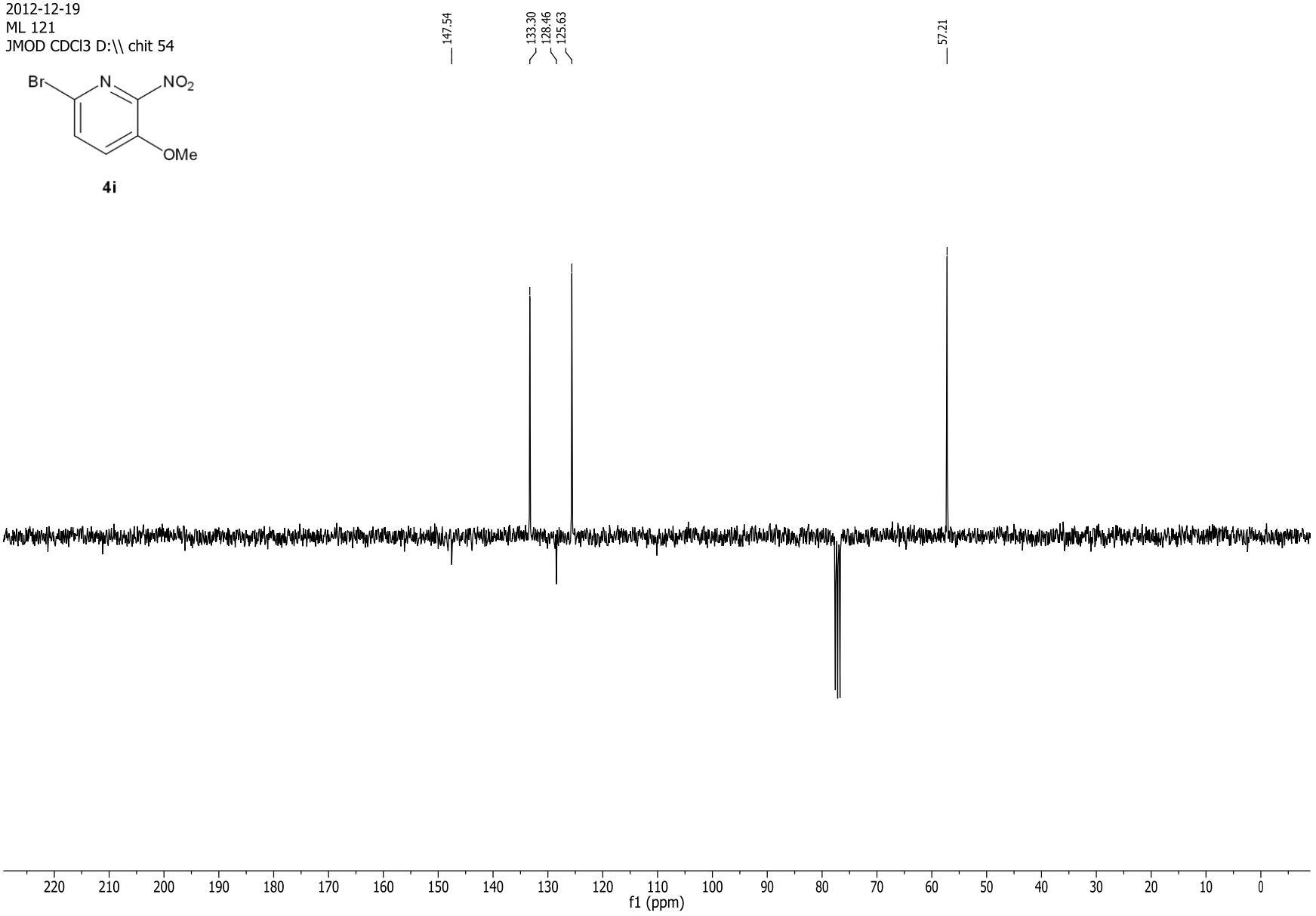


4i



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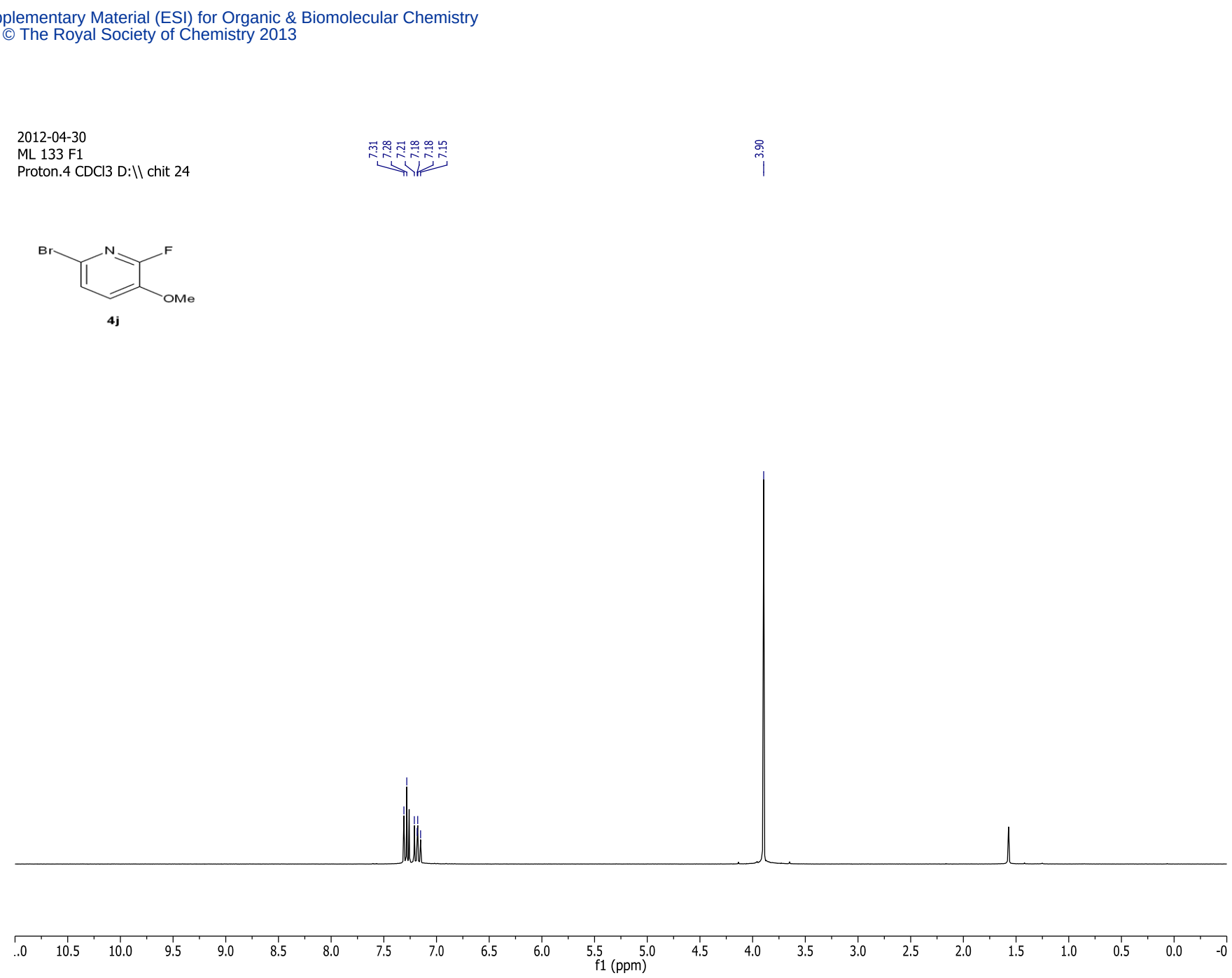

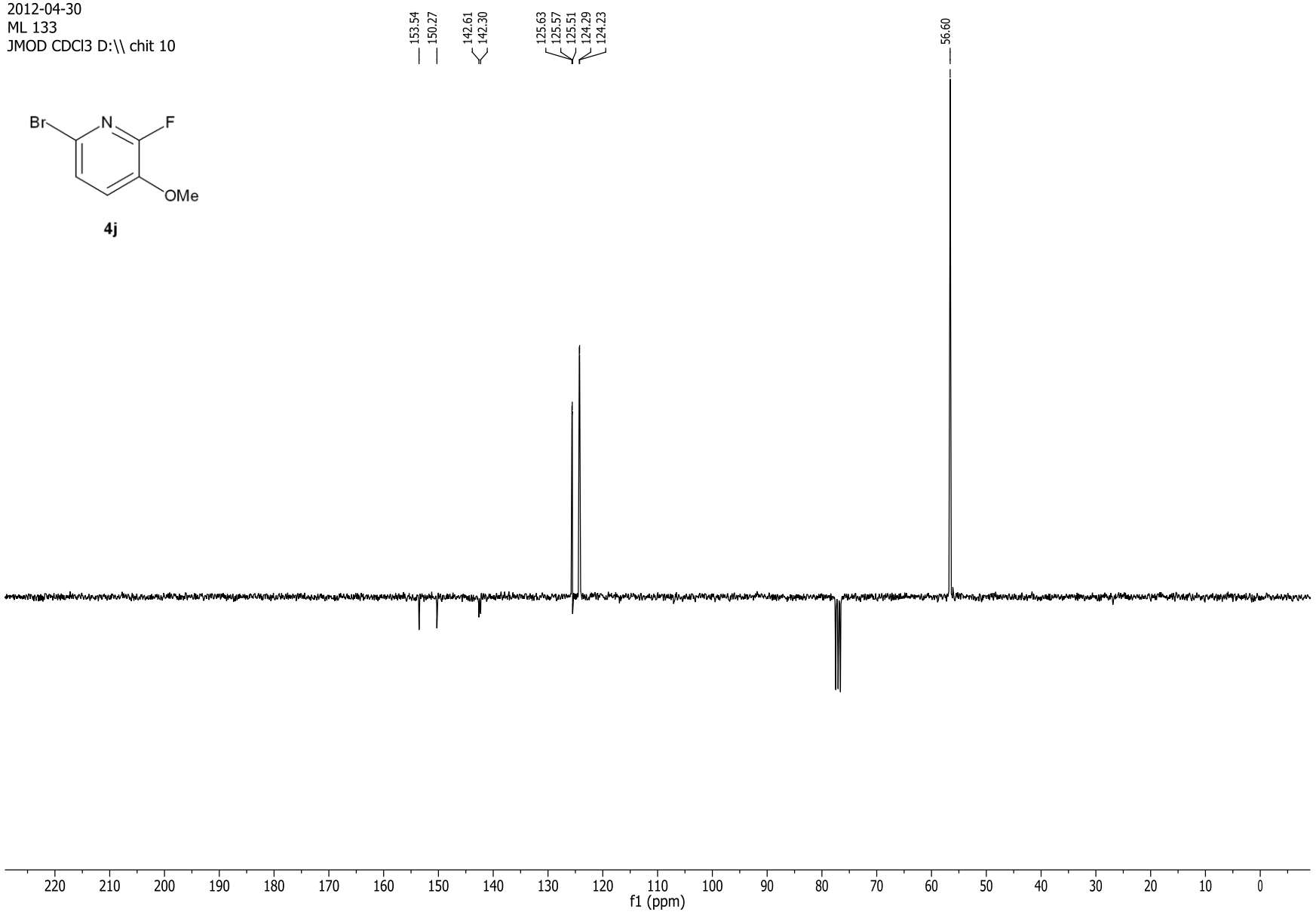

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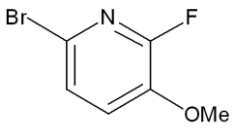

4j

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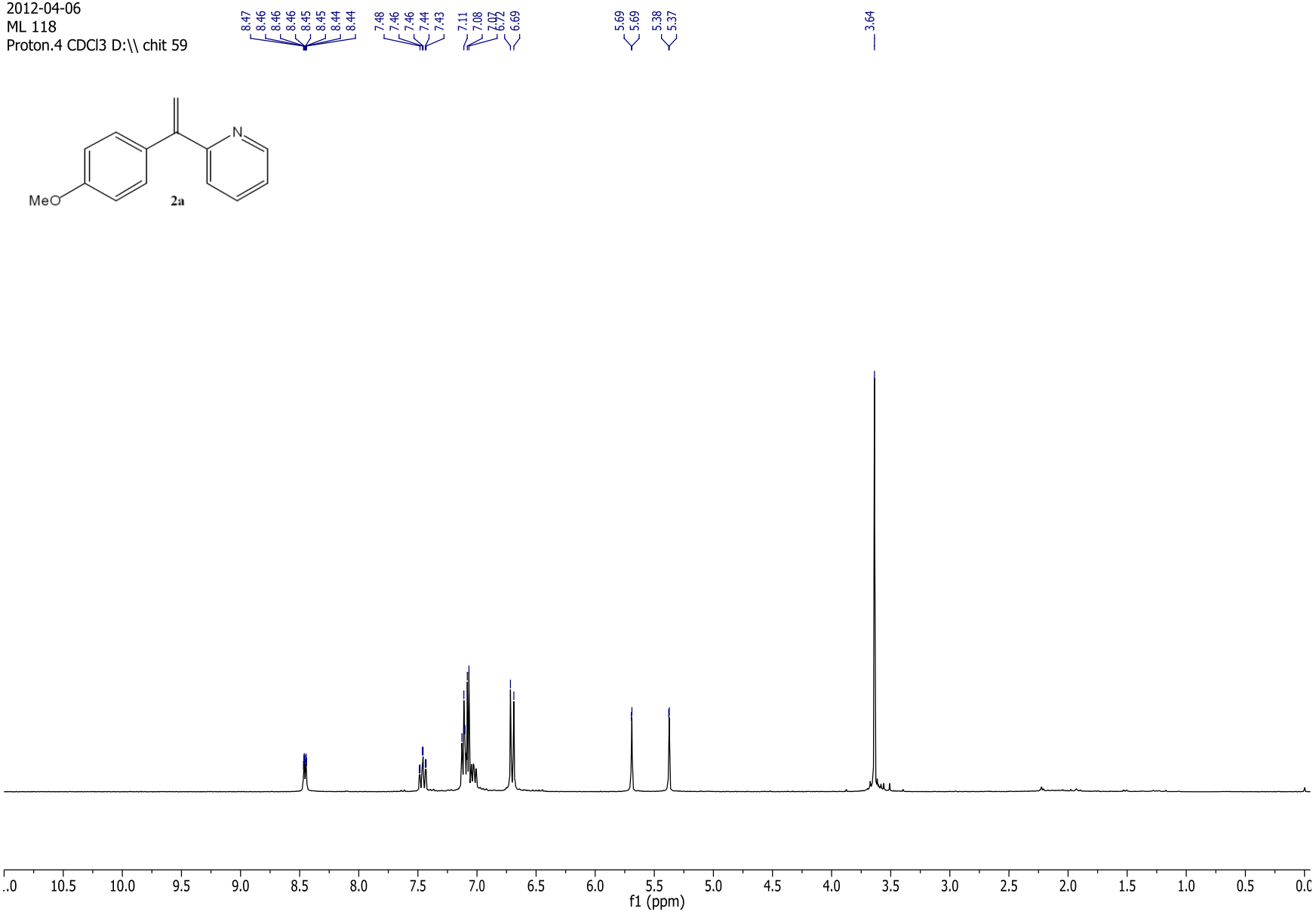

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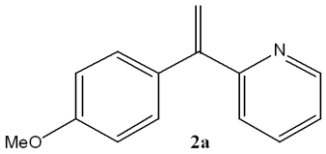
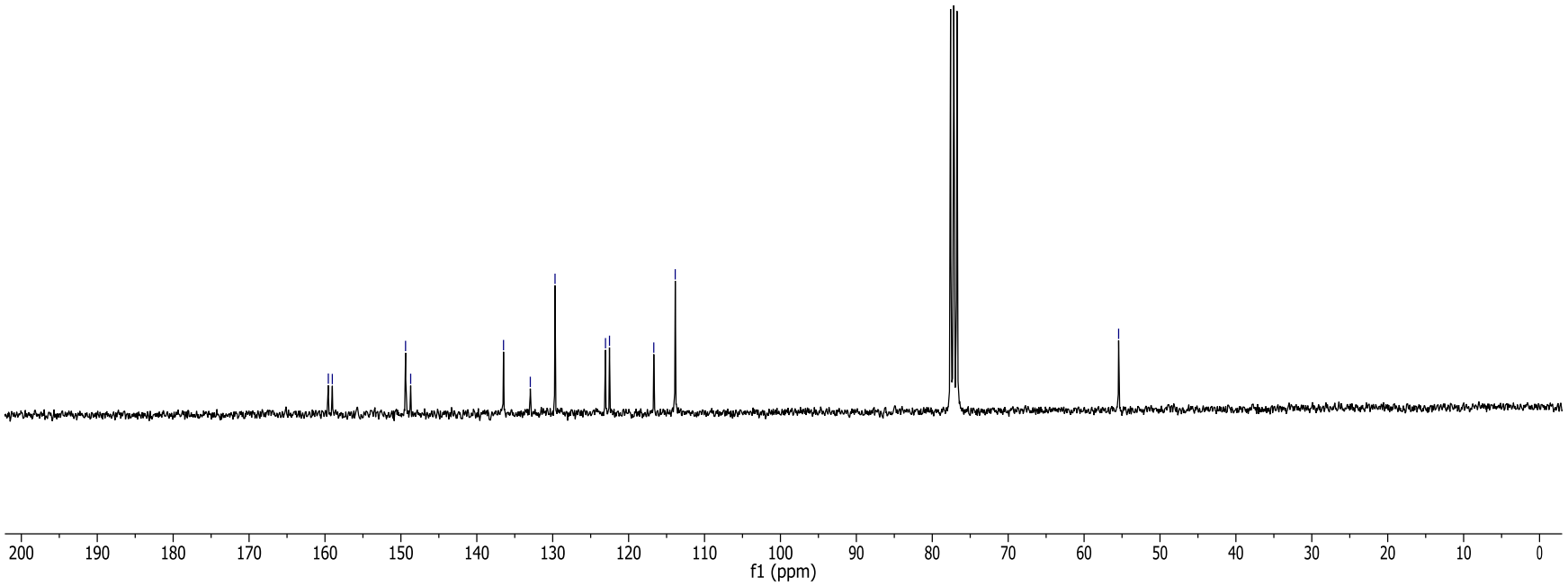


2a



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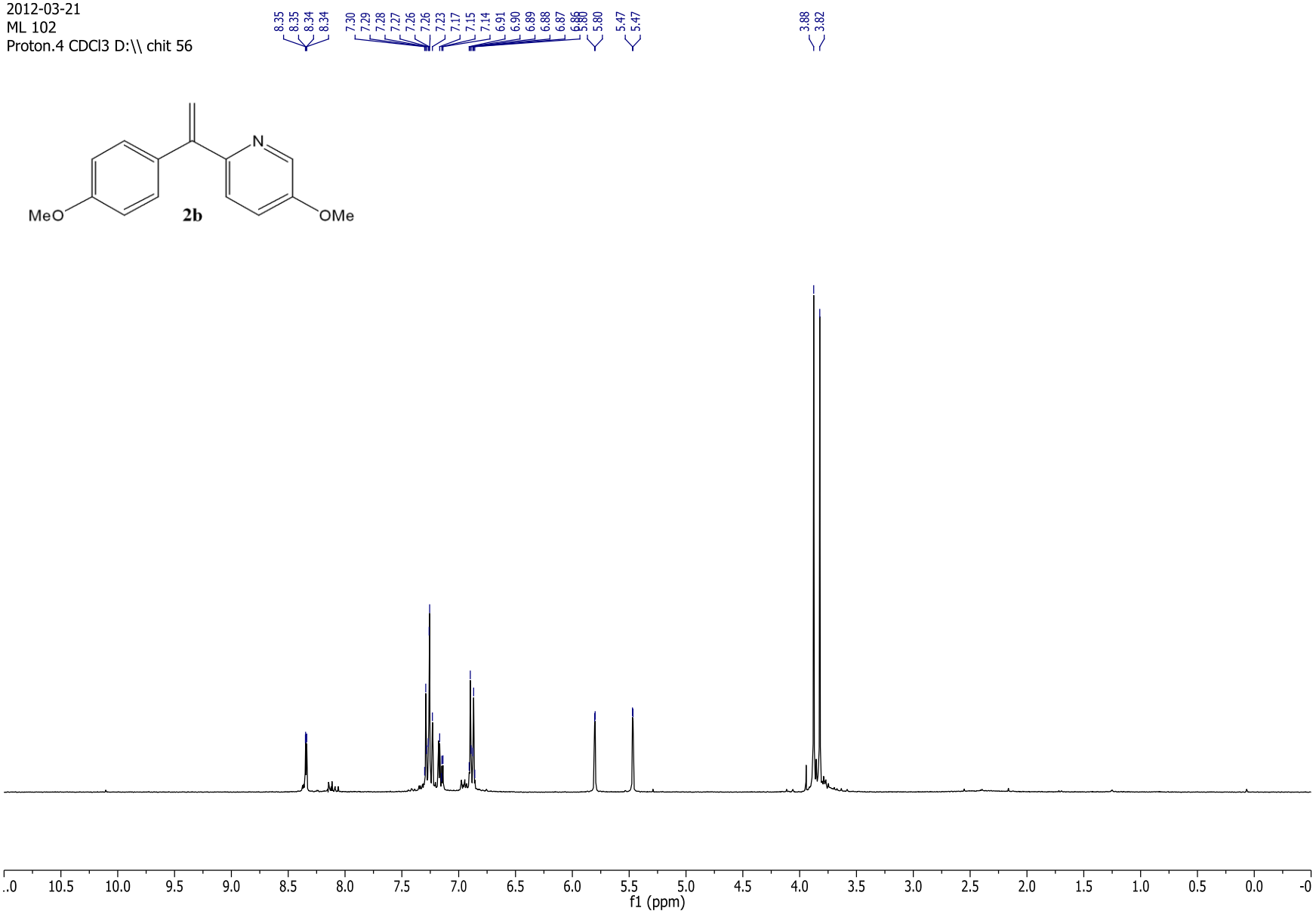

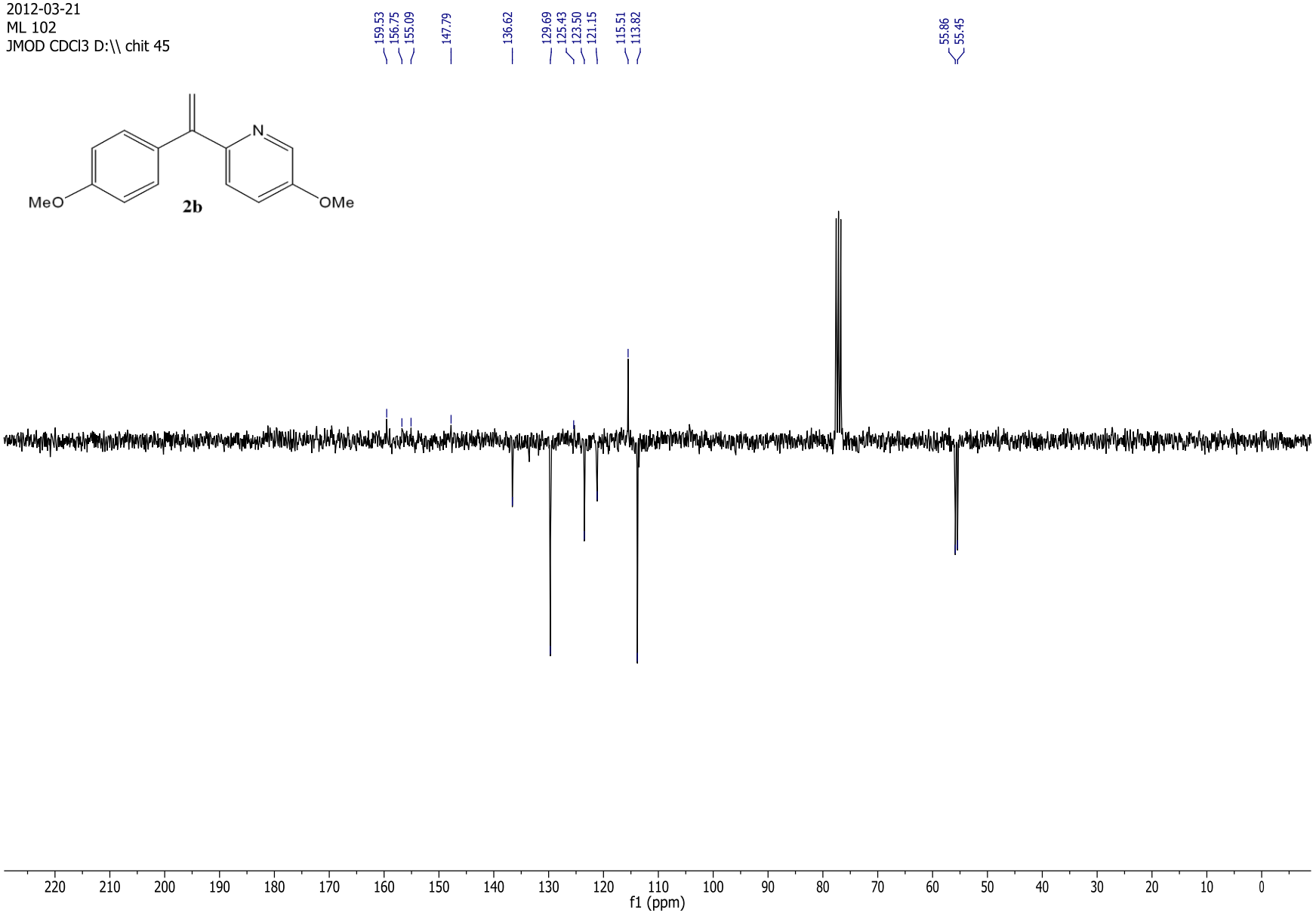

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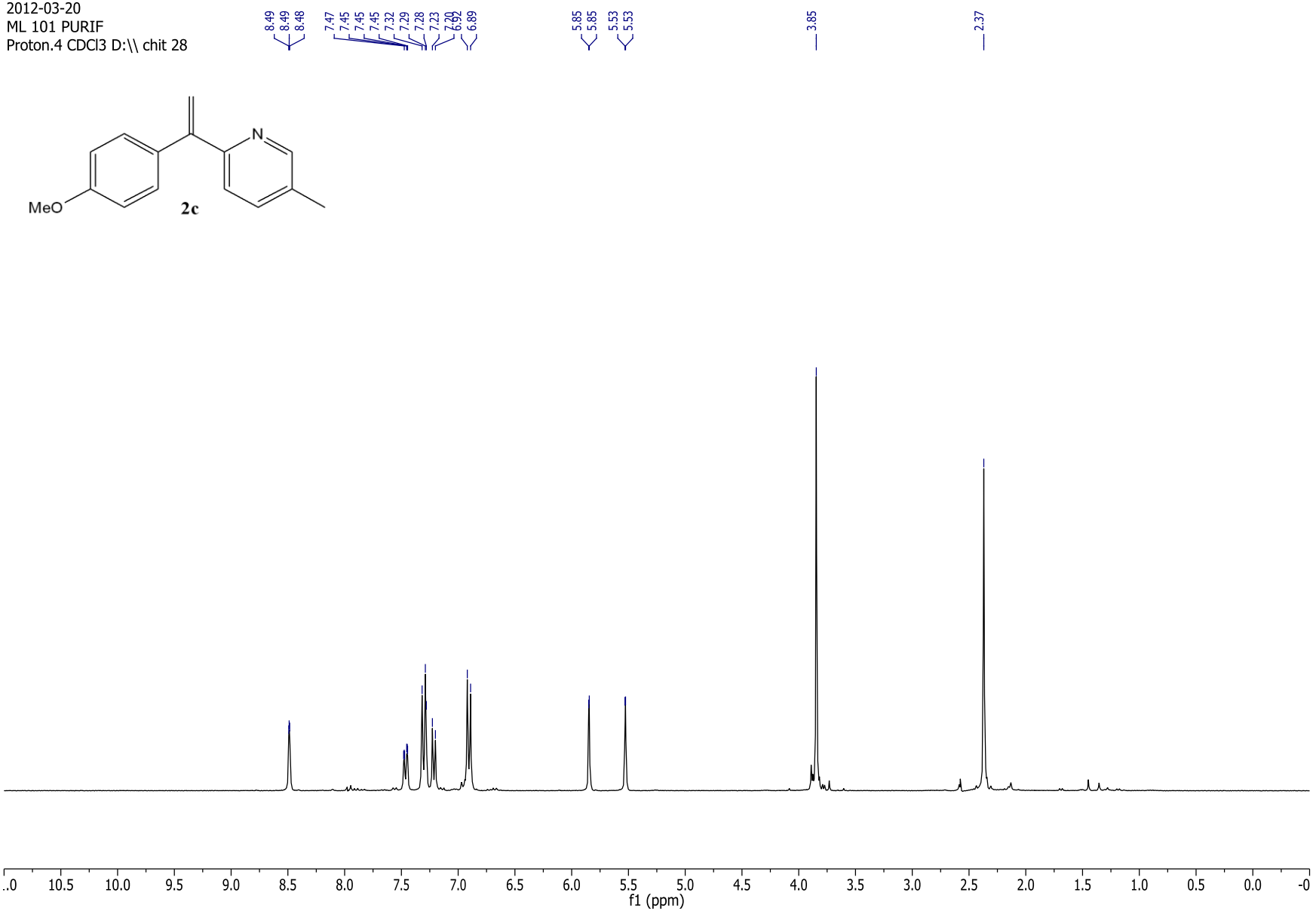

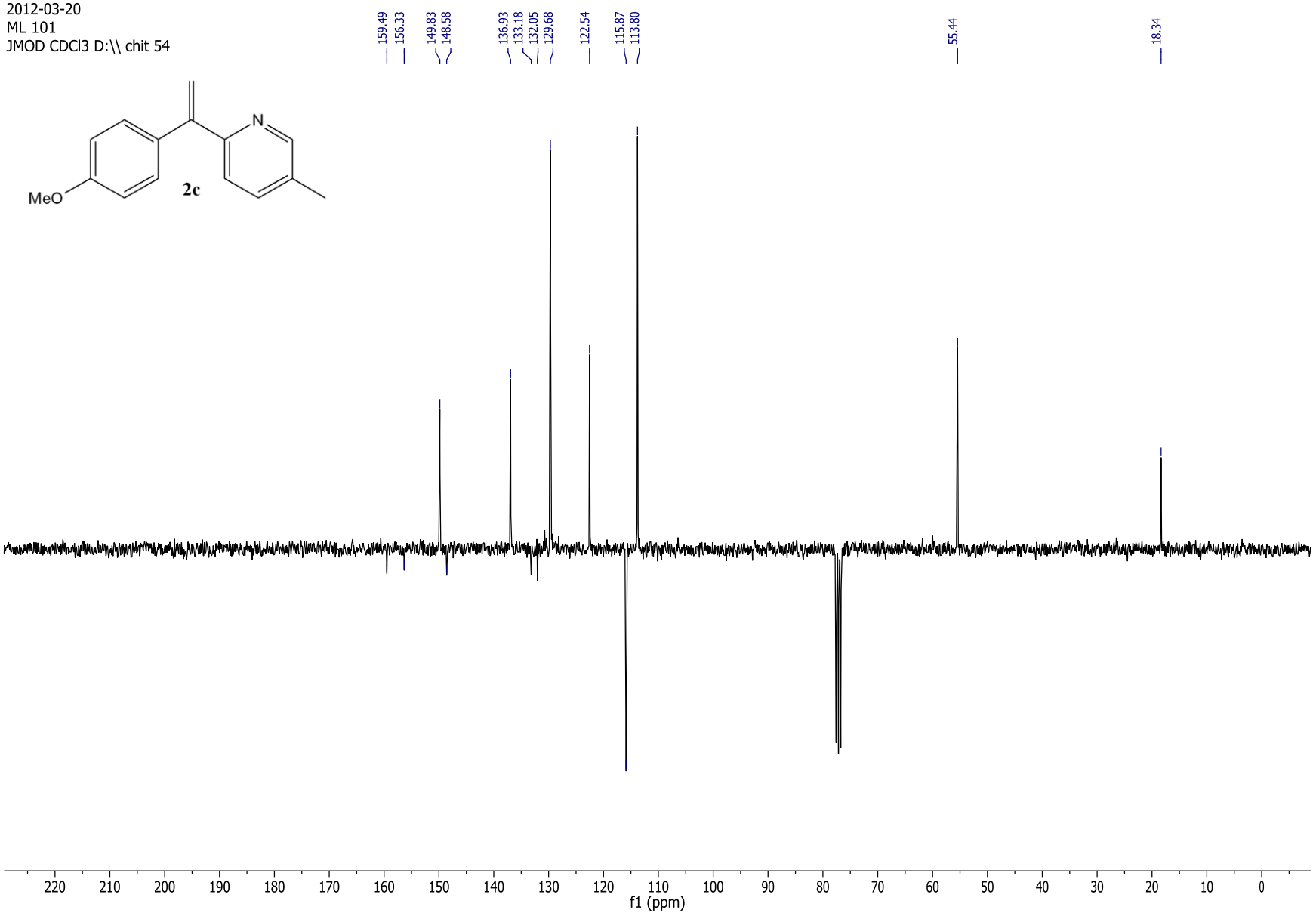

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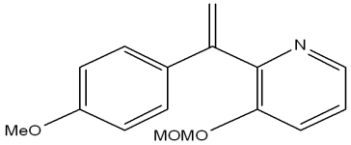

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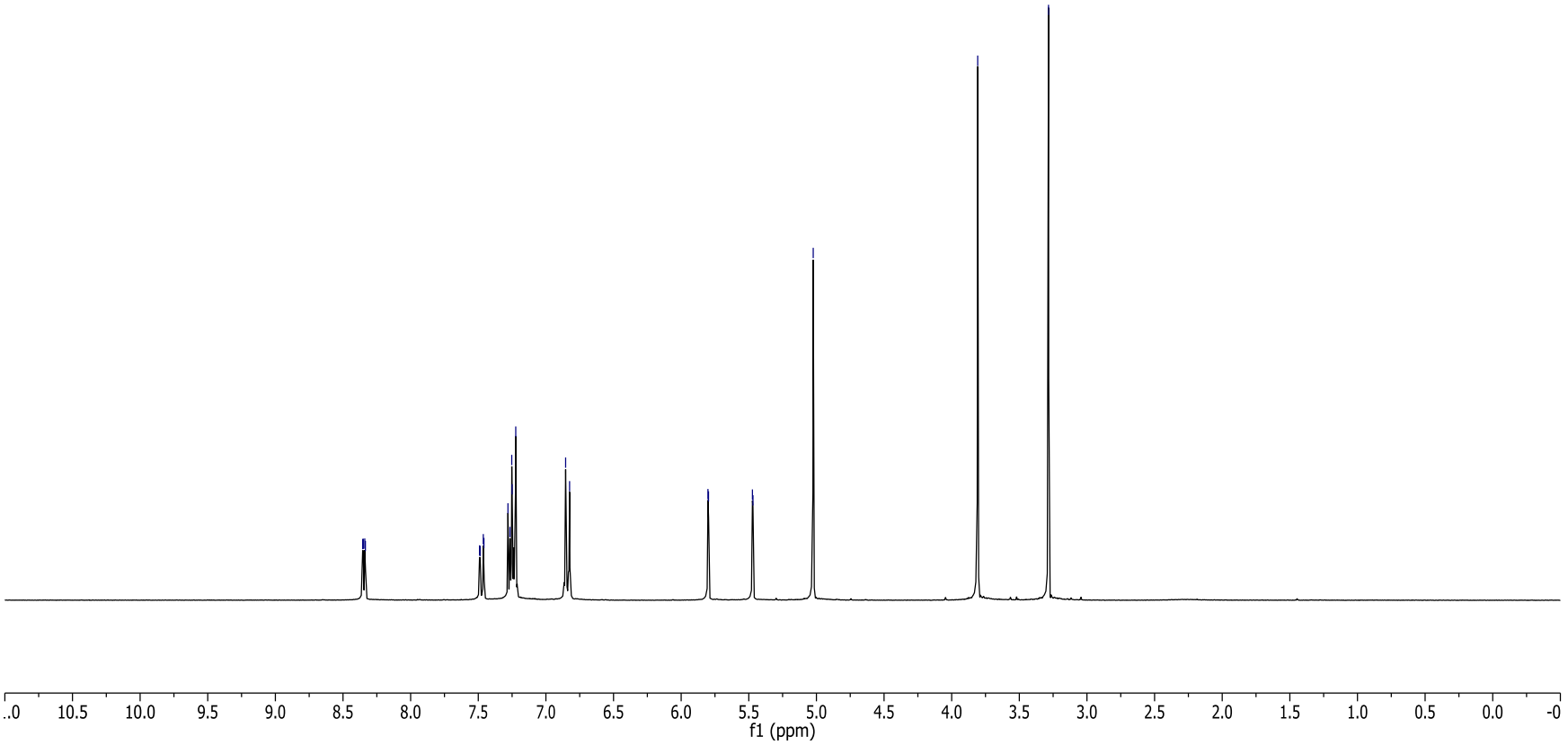

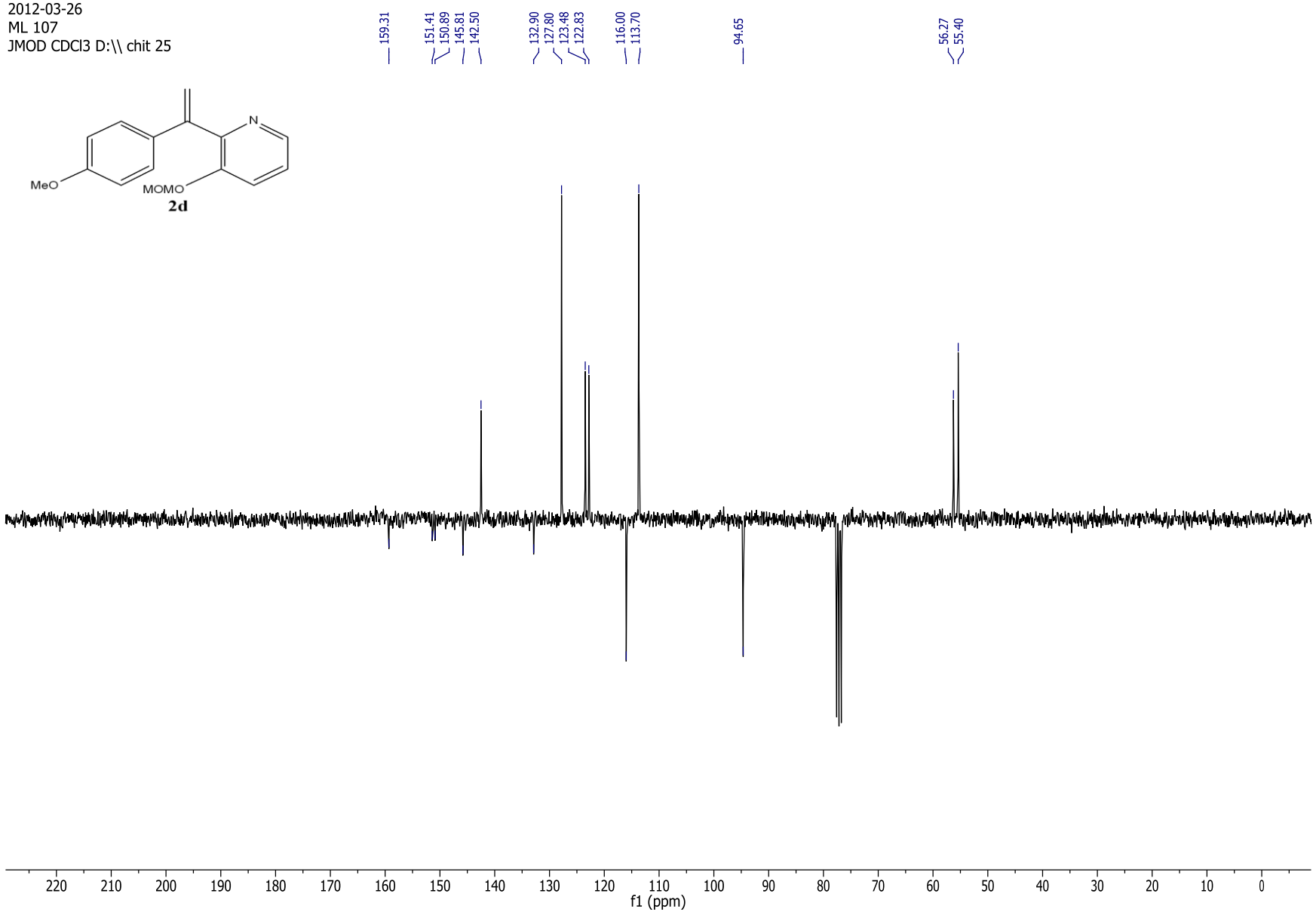

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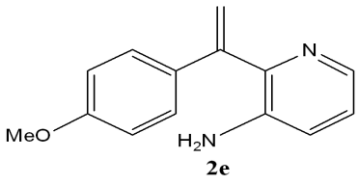

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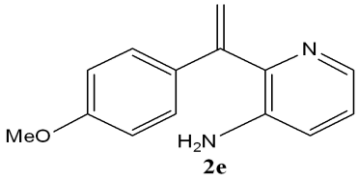

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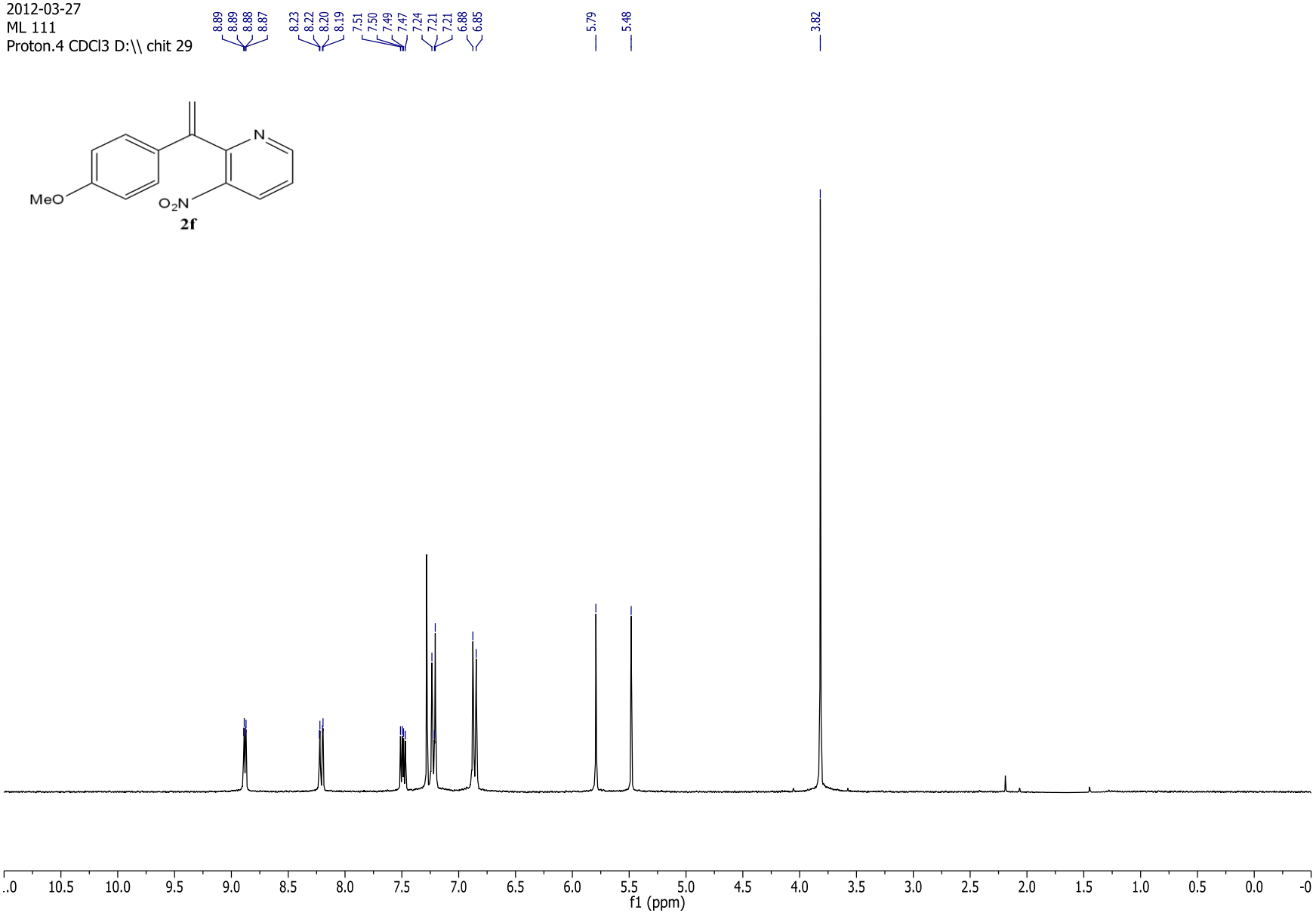

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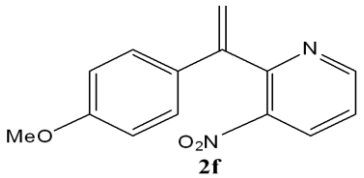

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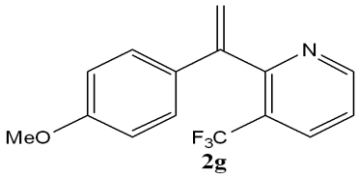

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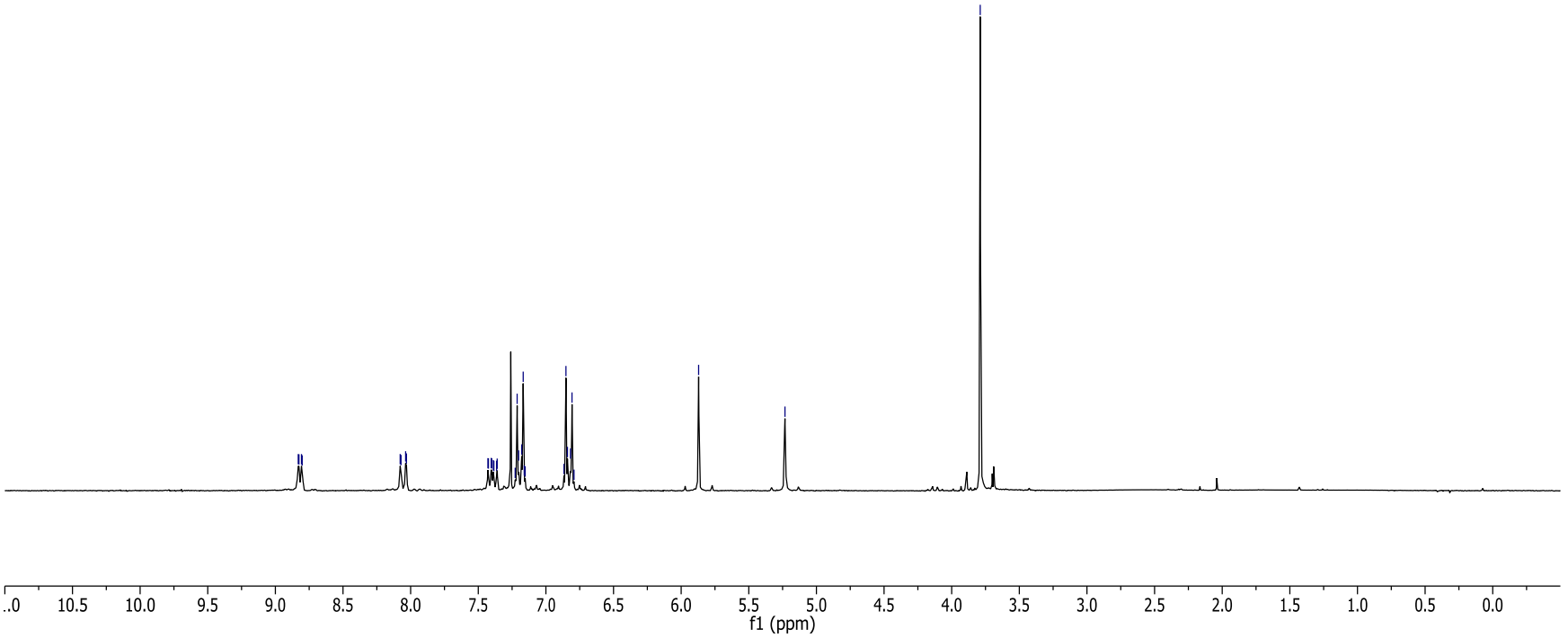

2012-05-25
JA 128
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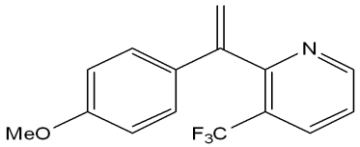

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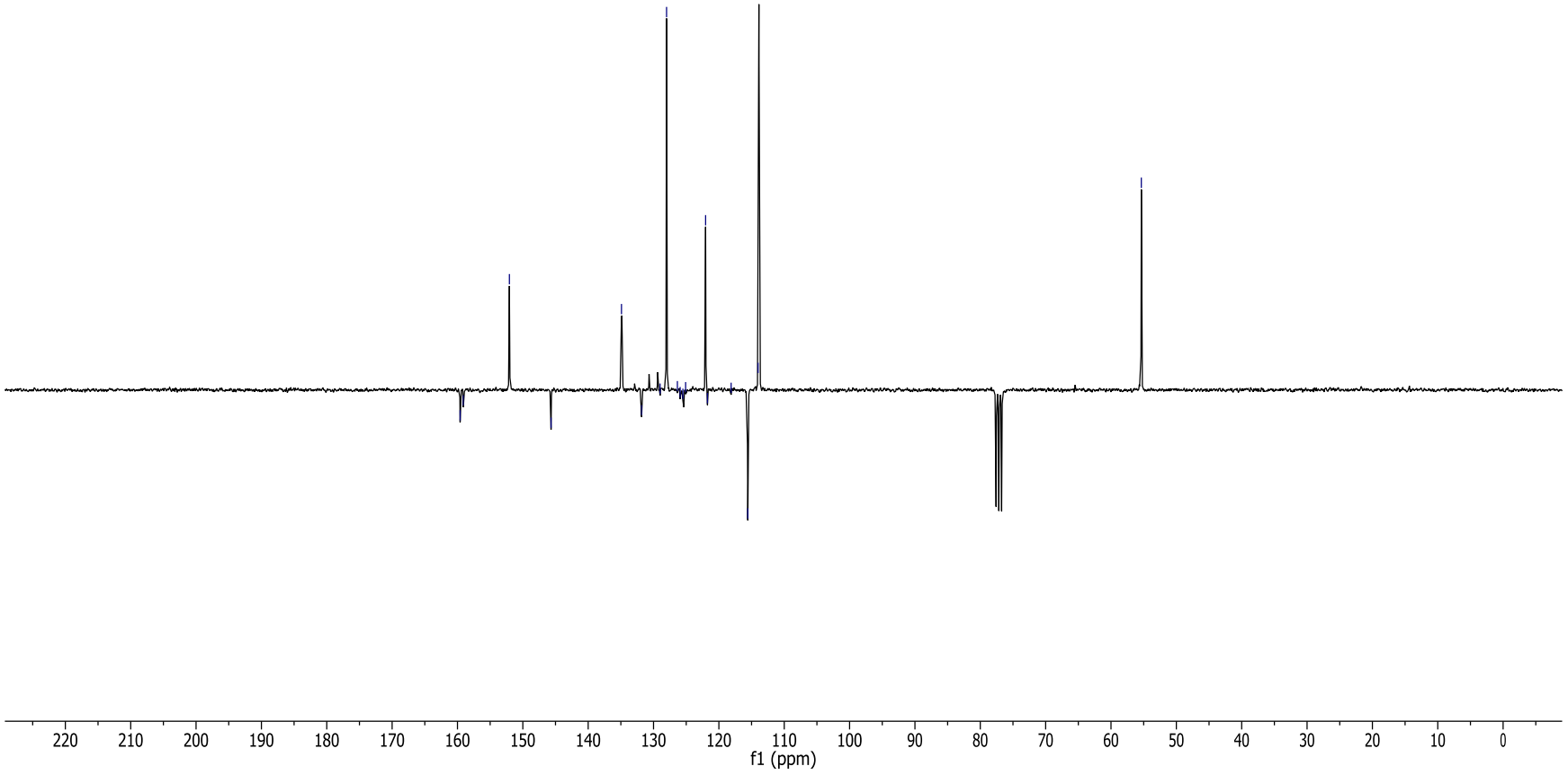

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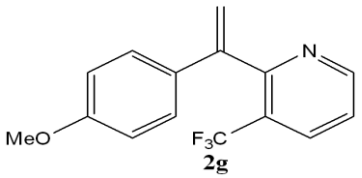

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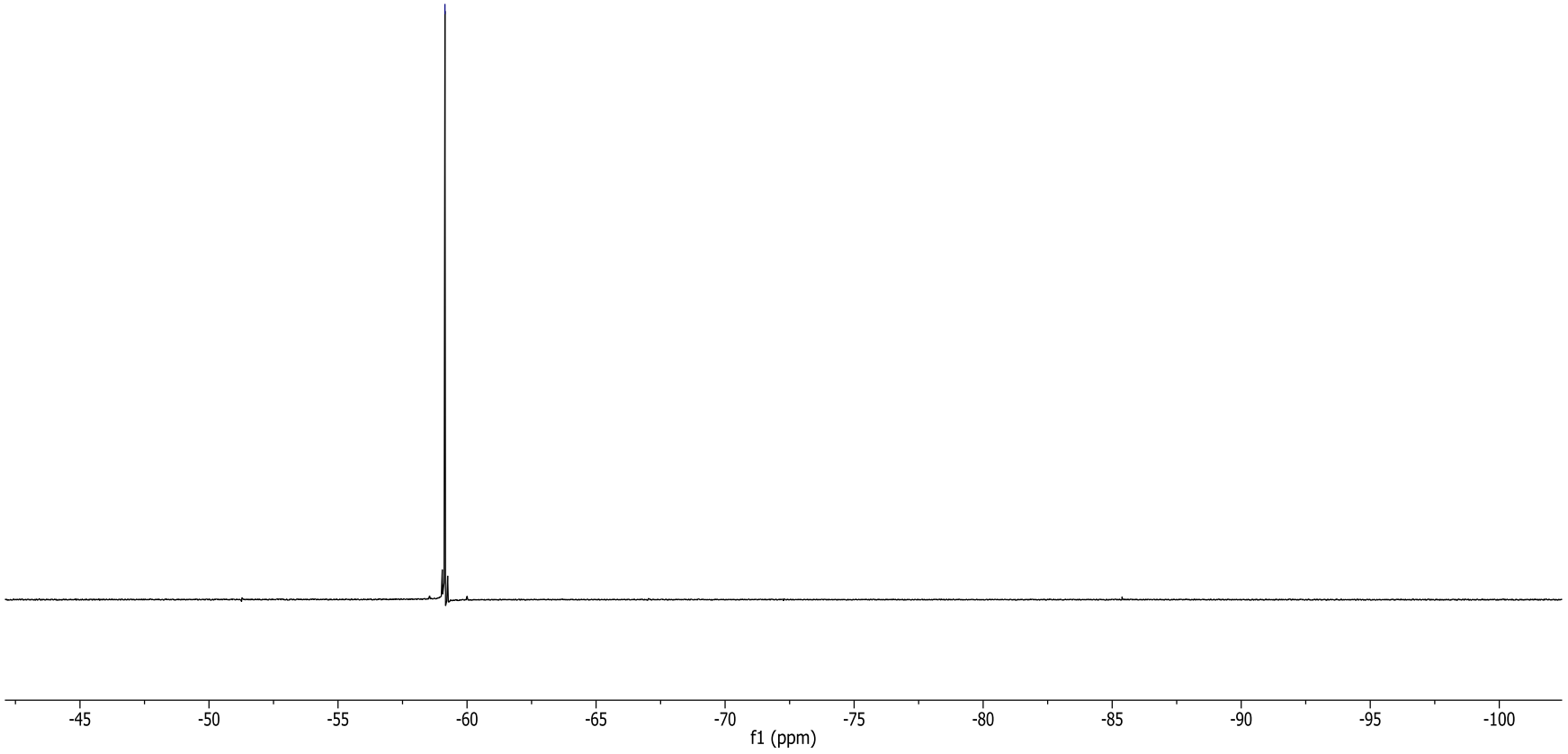
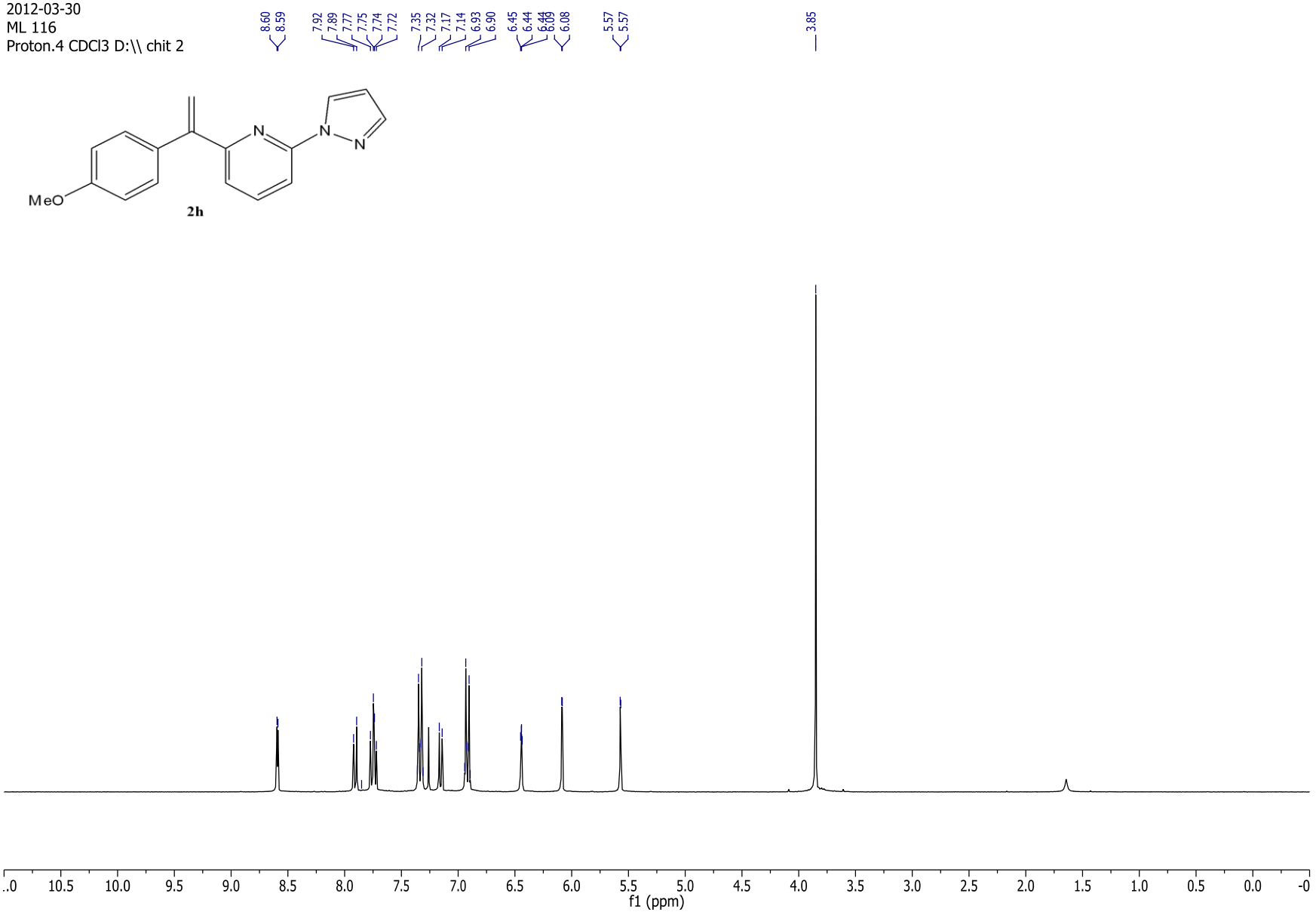
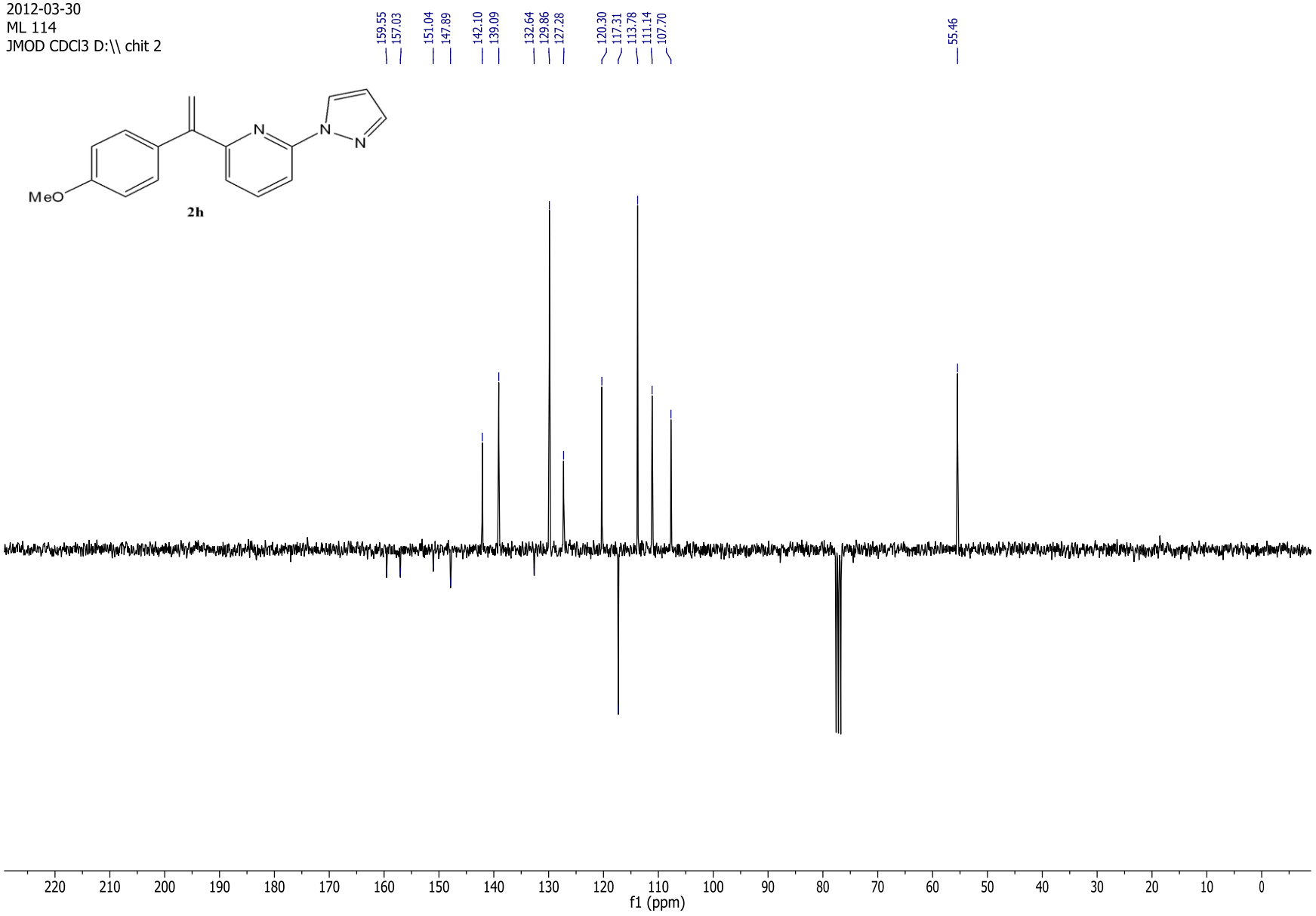
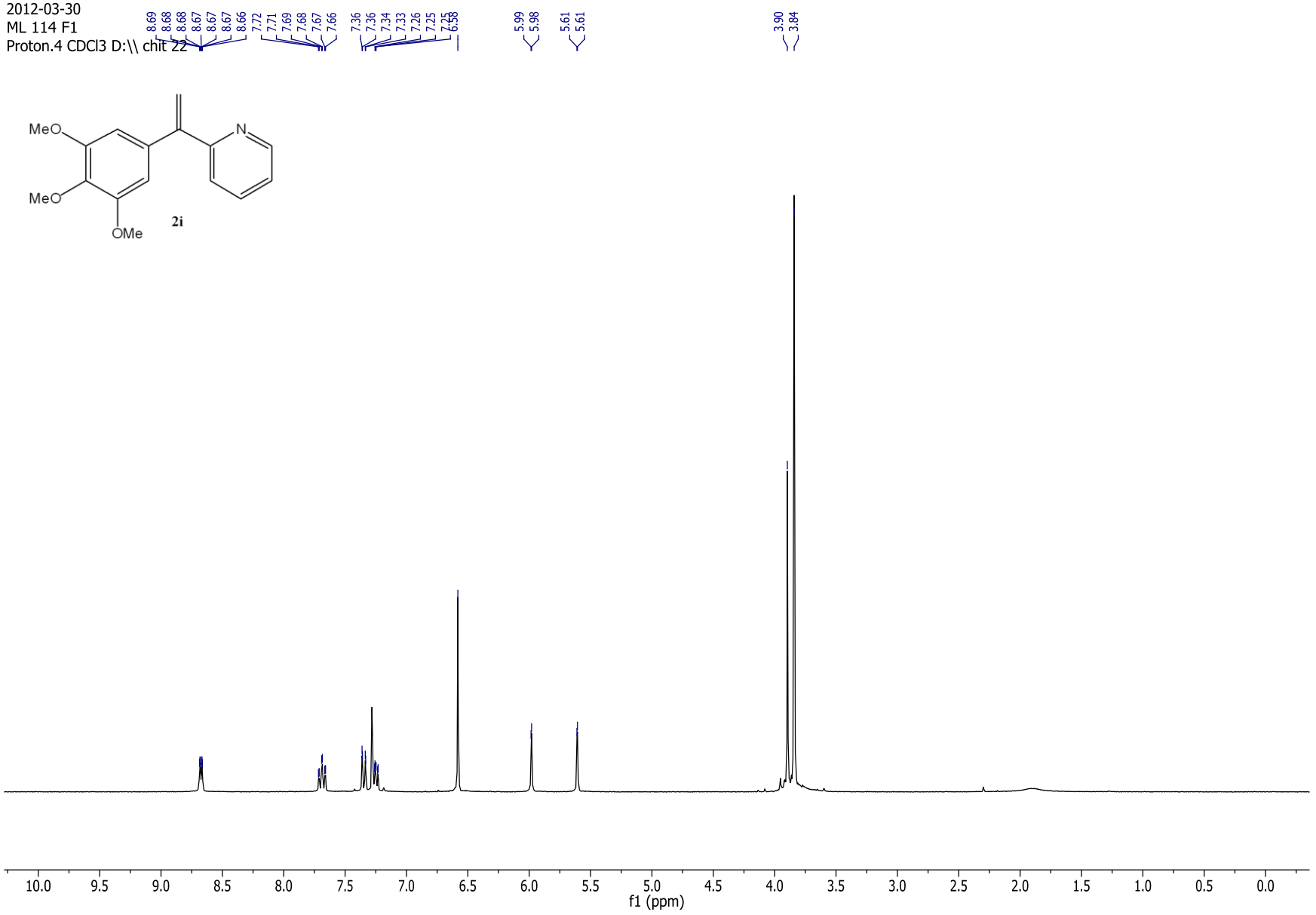
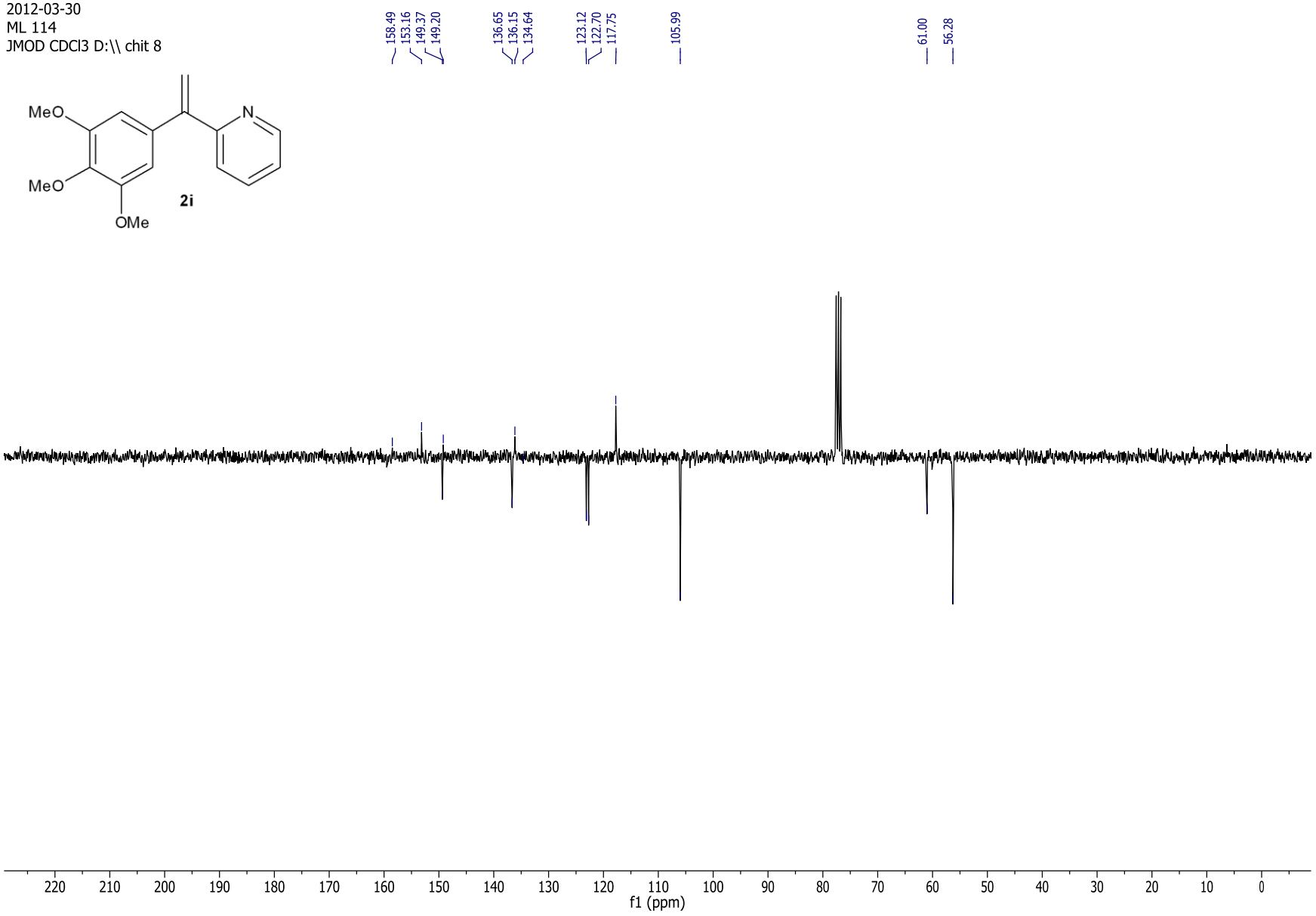
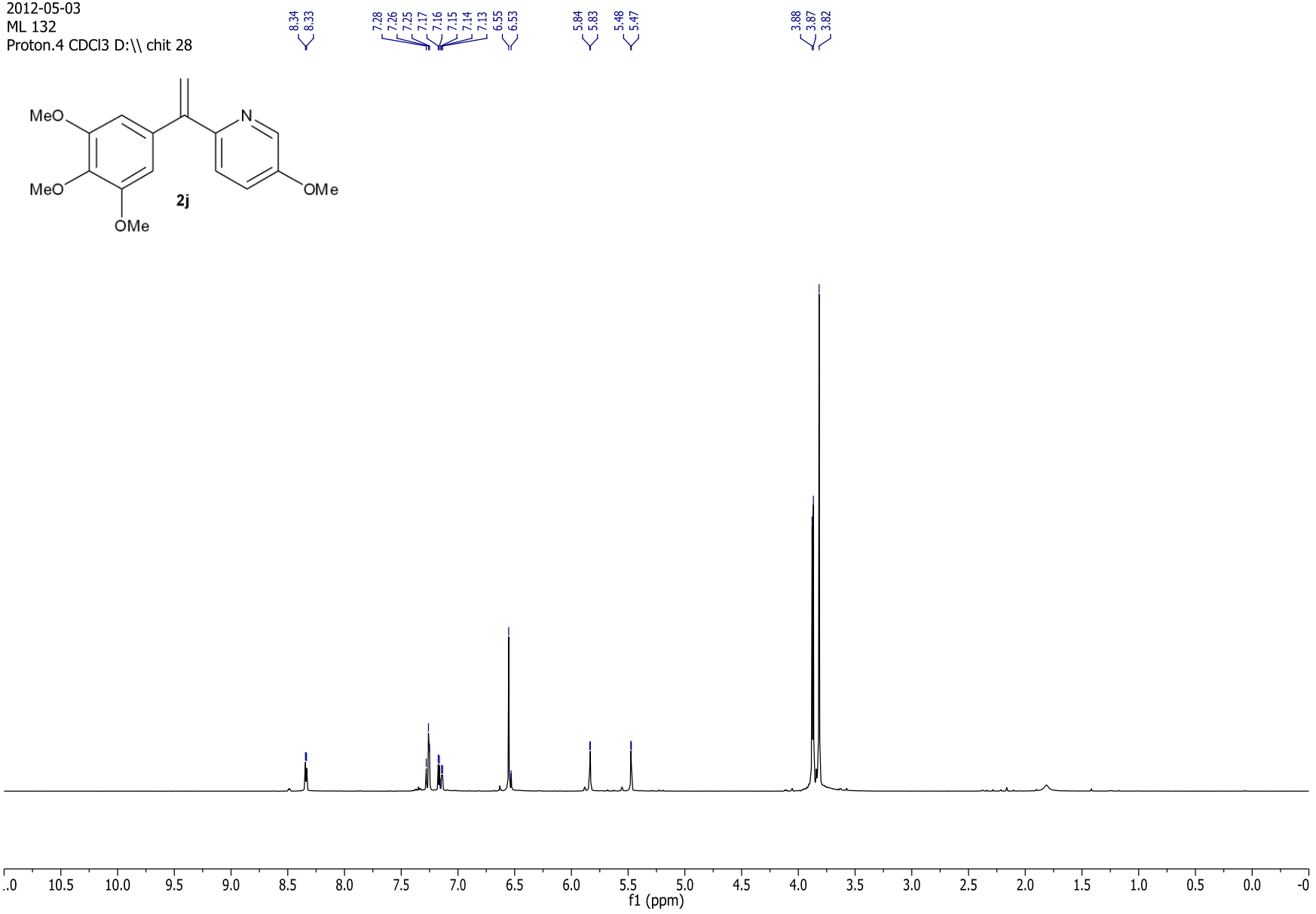


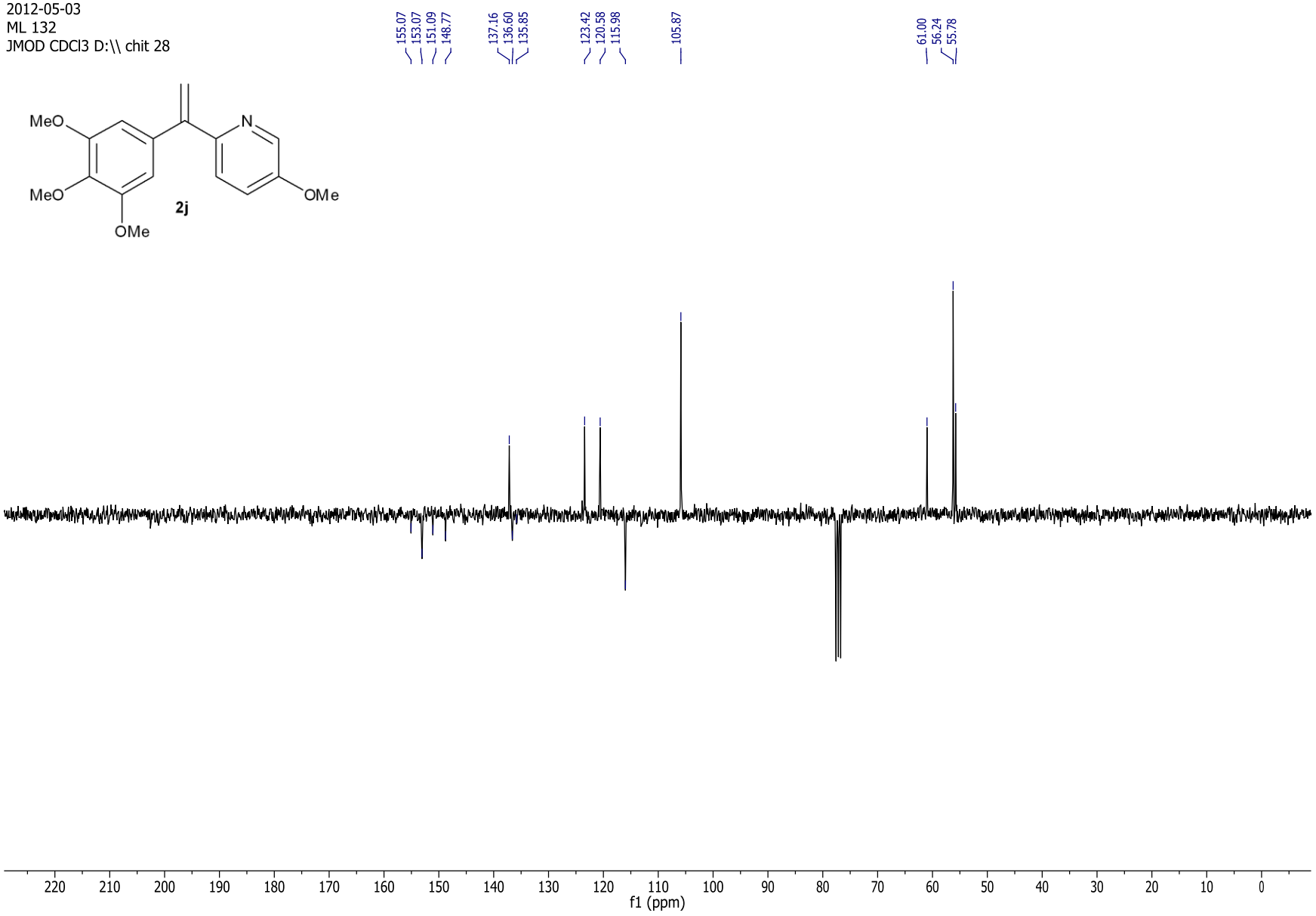




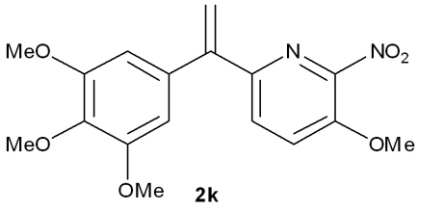




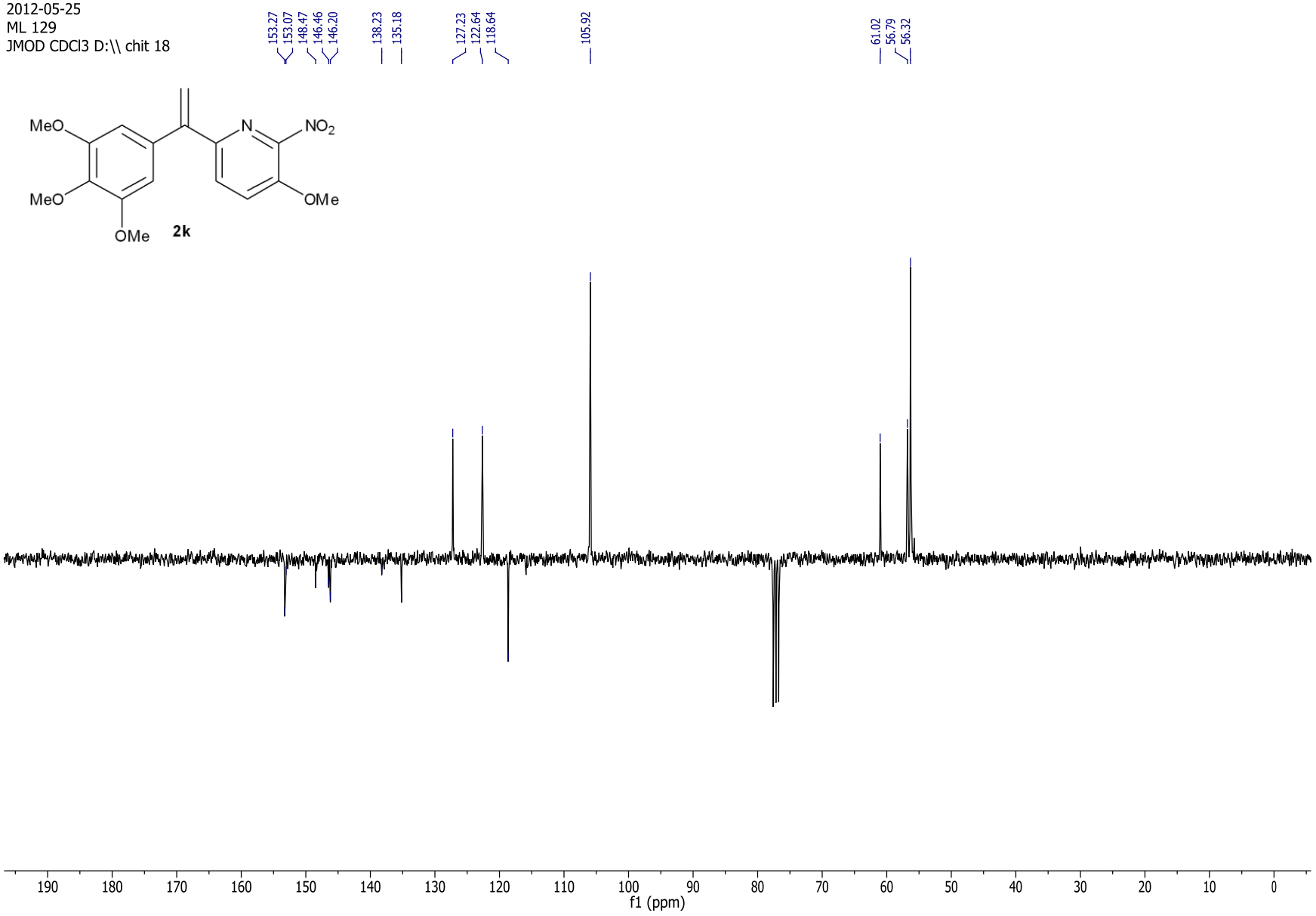




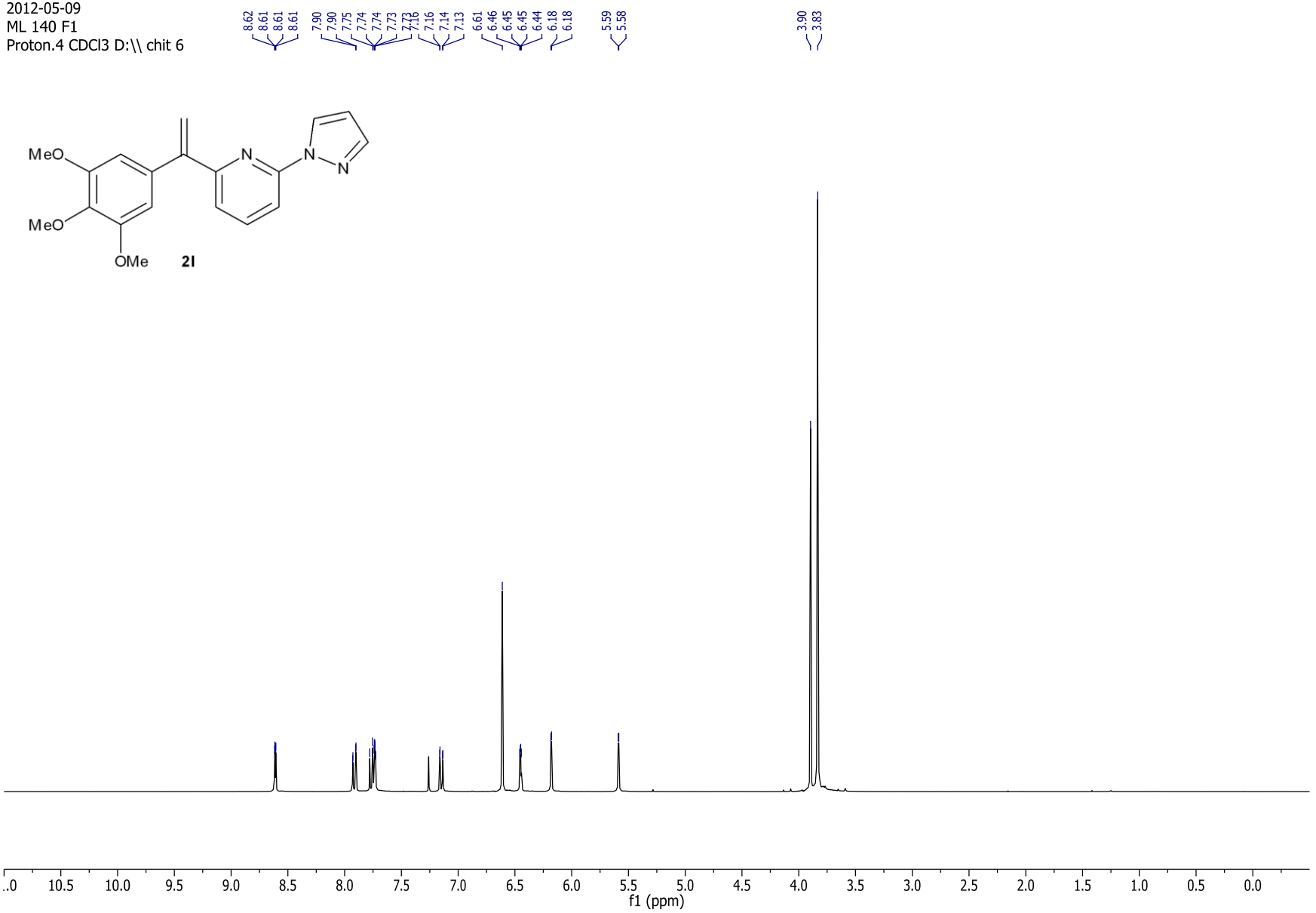
2012-04-26
ML 129
Proton.4 CDCl3 D:\\ chit 50

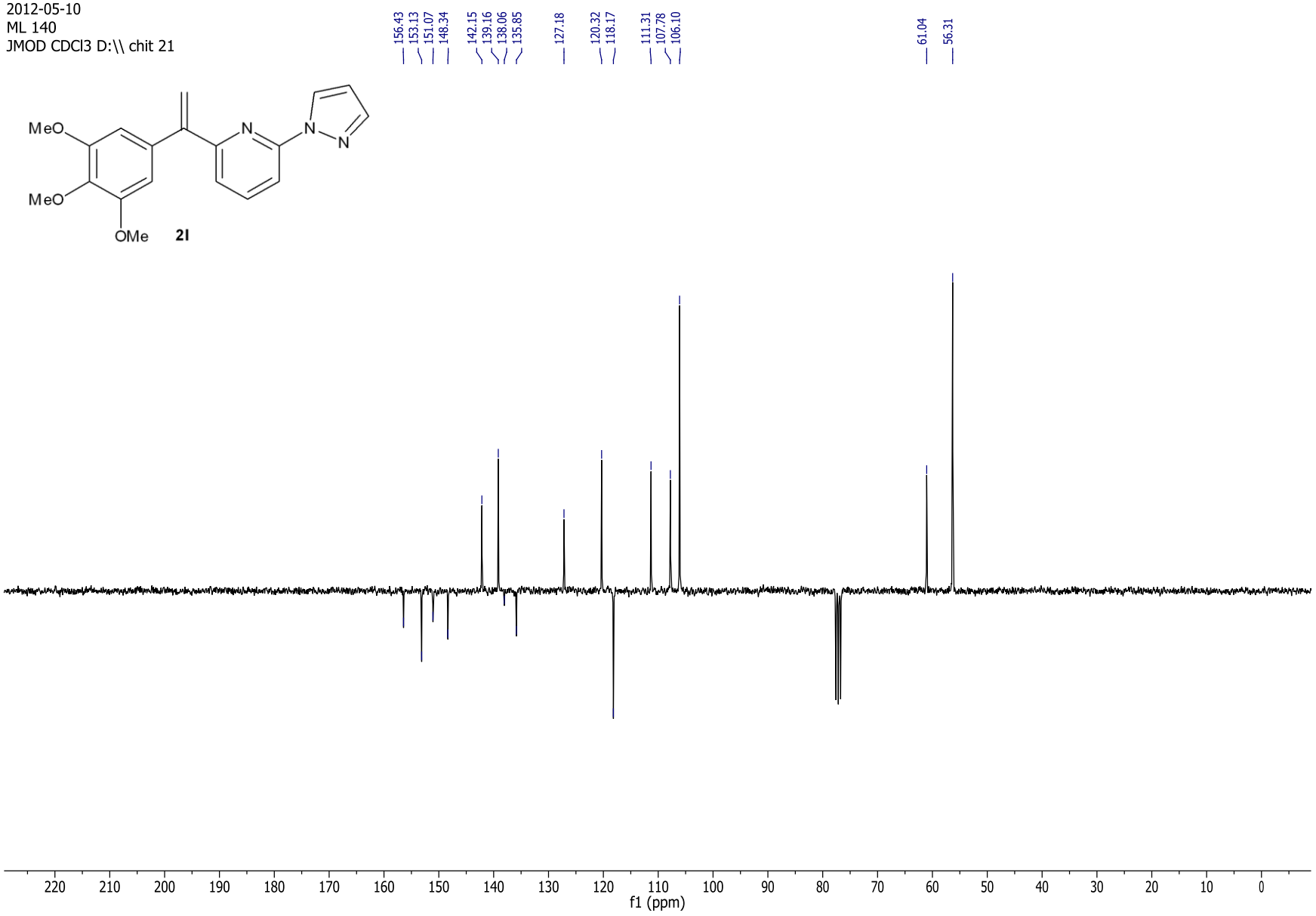


2k

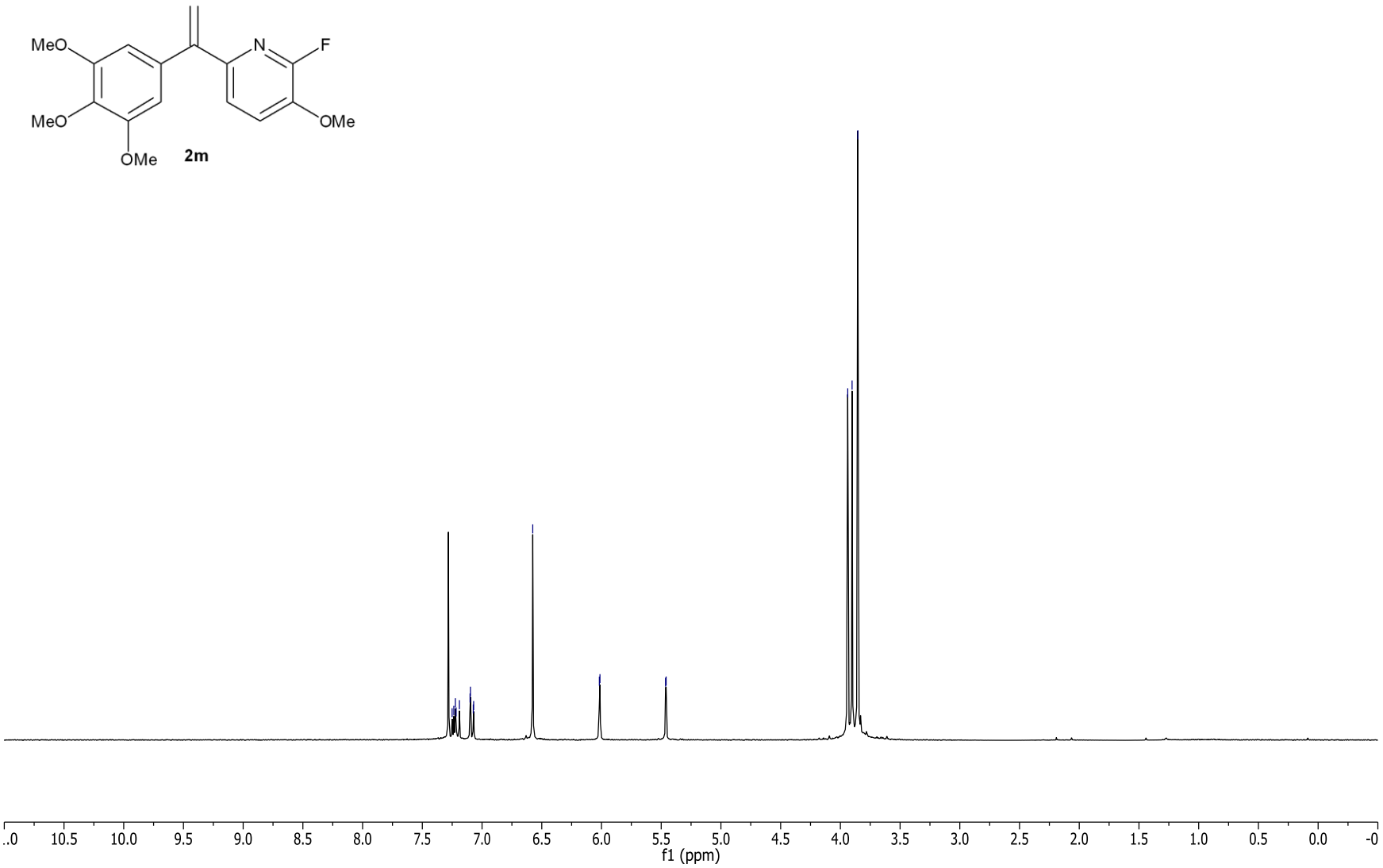


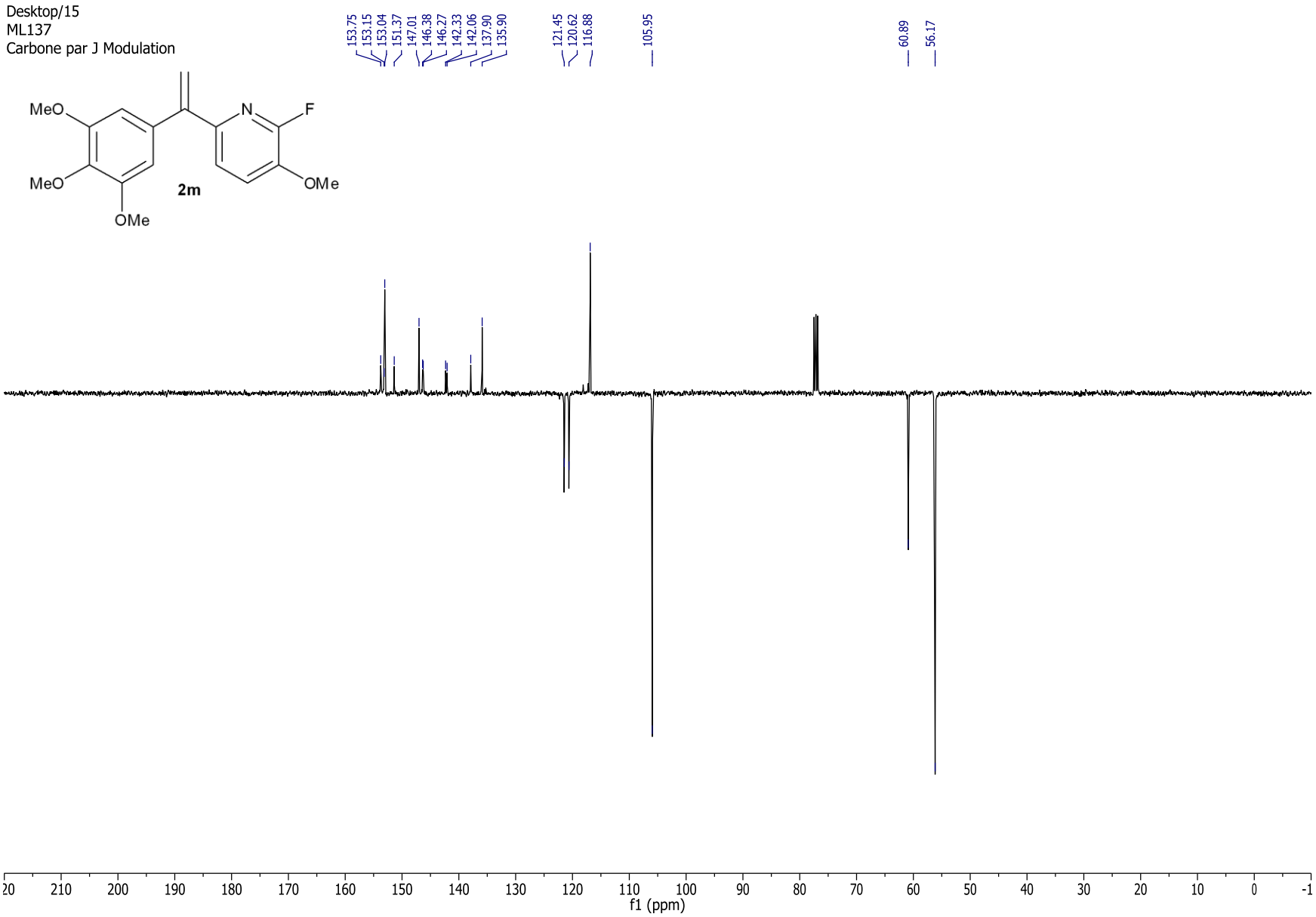
2012-05-09
ML 140 F1
Proton.4 CDCl3 D:\\ chit 6



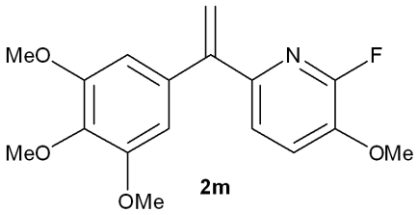


2012-05-04
ML 137 F2
Proton.4 CDCl3 D:\\ chit 2



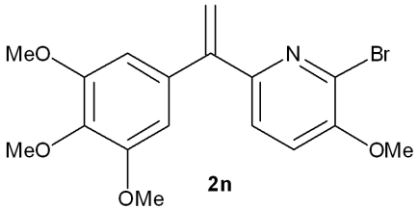


2012.05.04
ml 137
F19CPD CDCl3 v biocis 10



2m

2012-04-30
ML 134 F1
Proton.4 CDCl3 D:\\ chit 13



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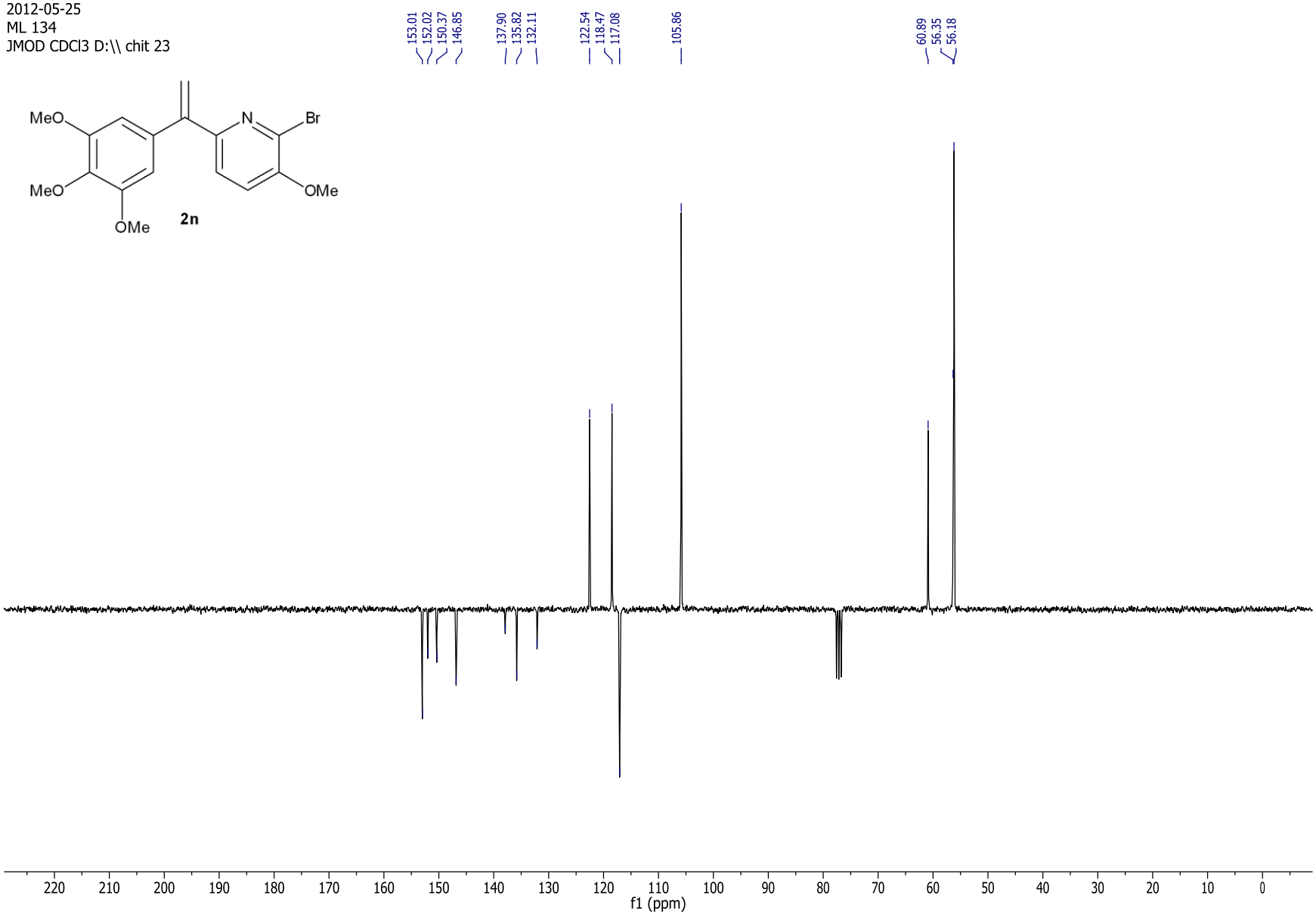
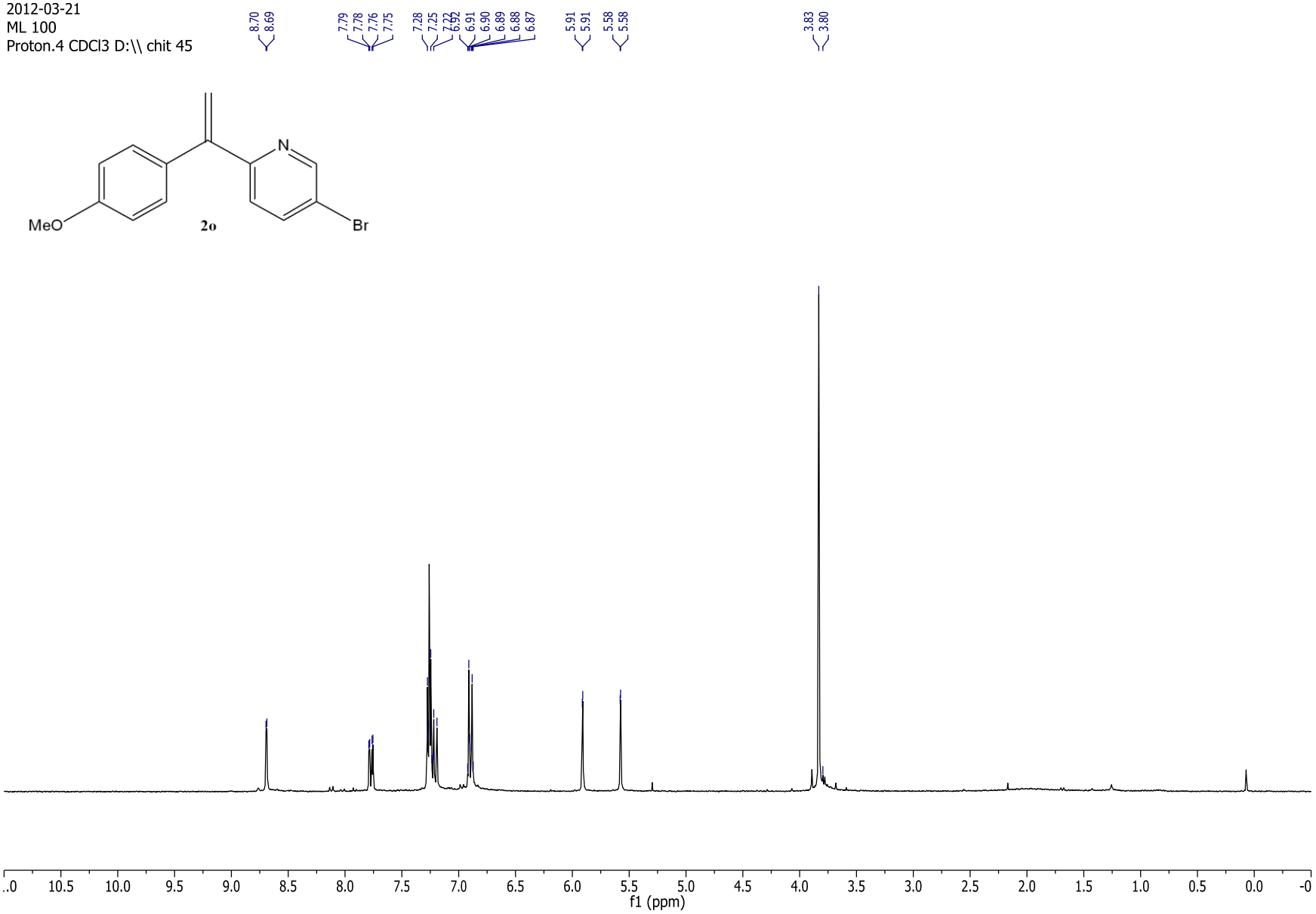
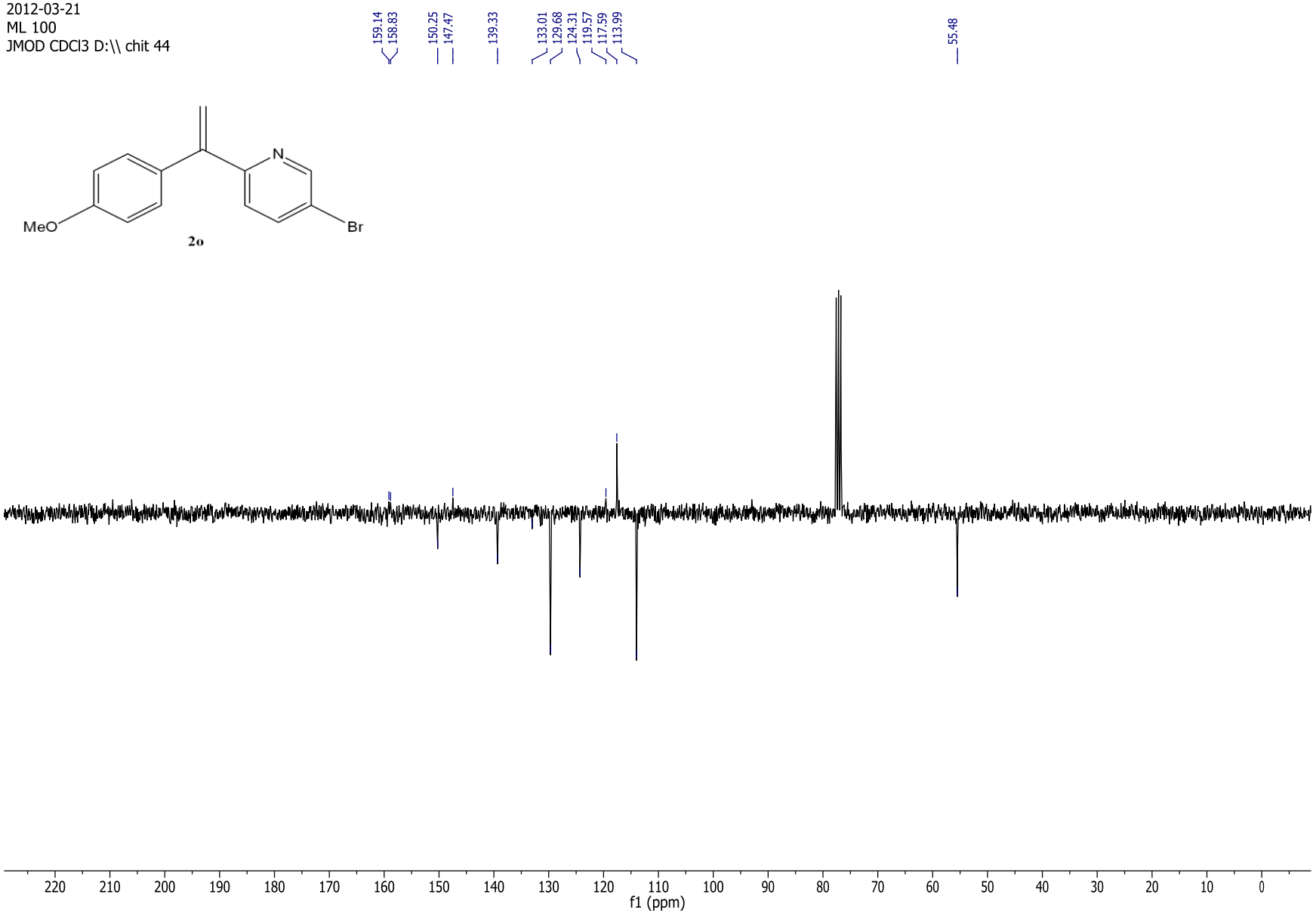
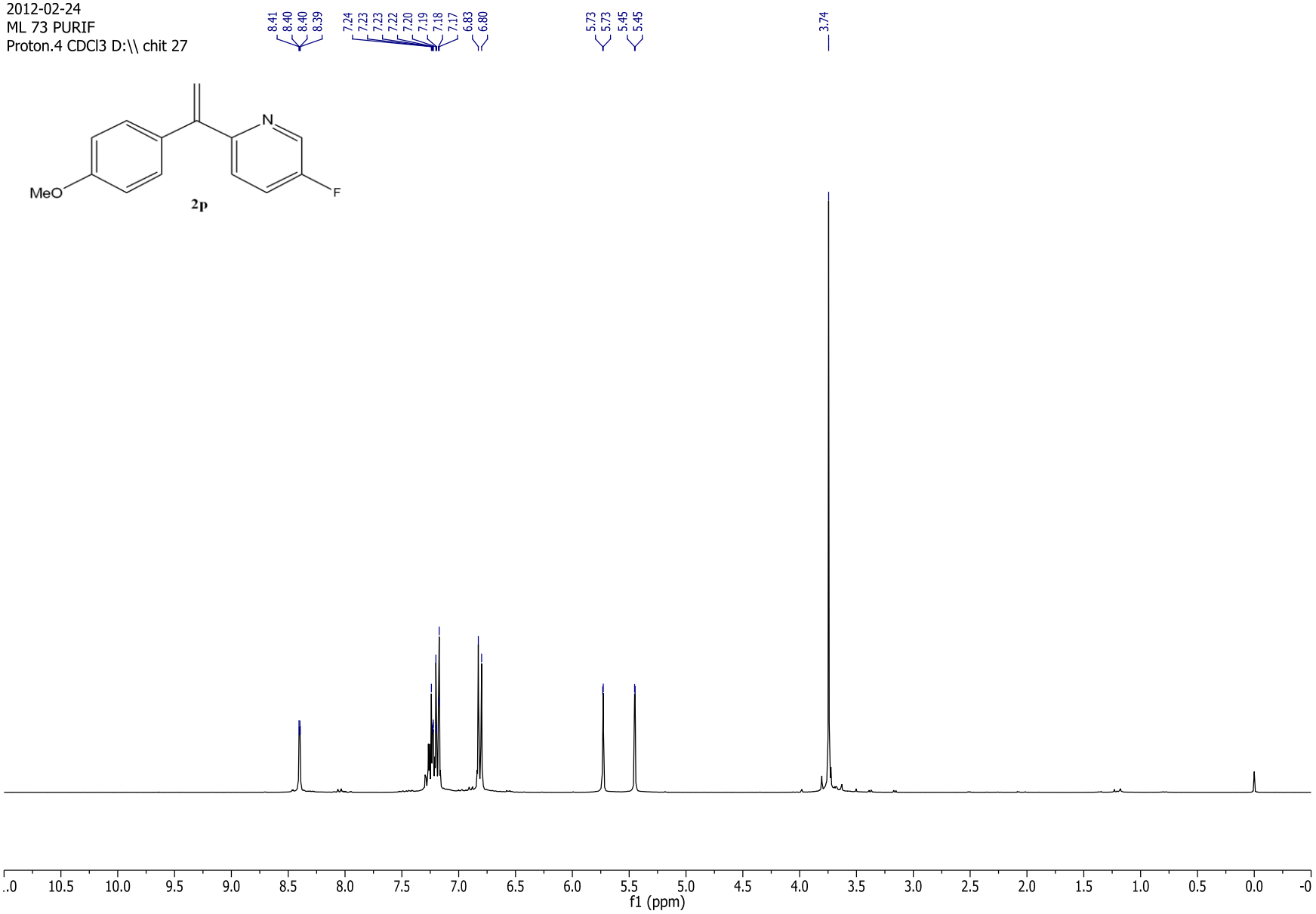
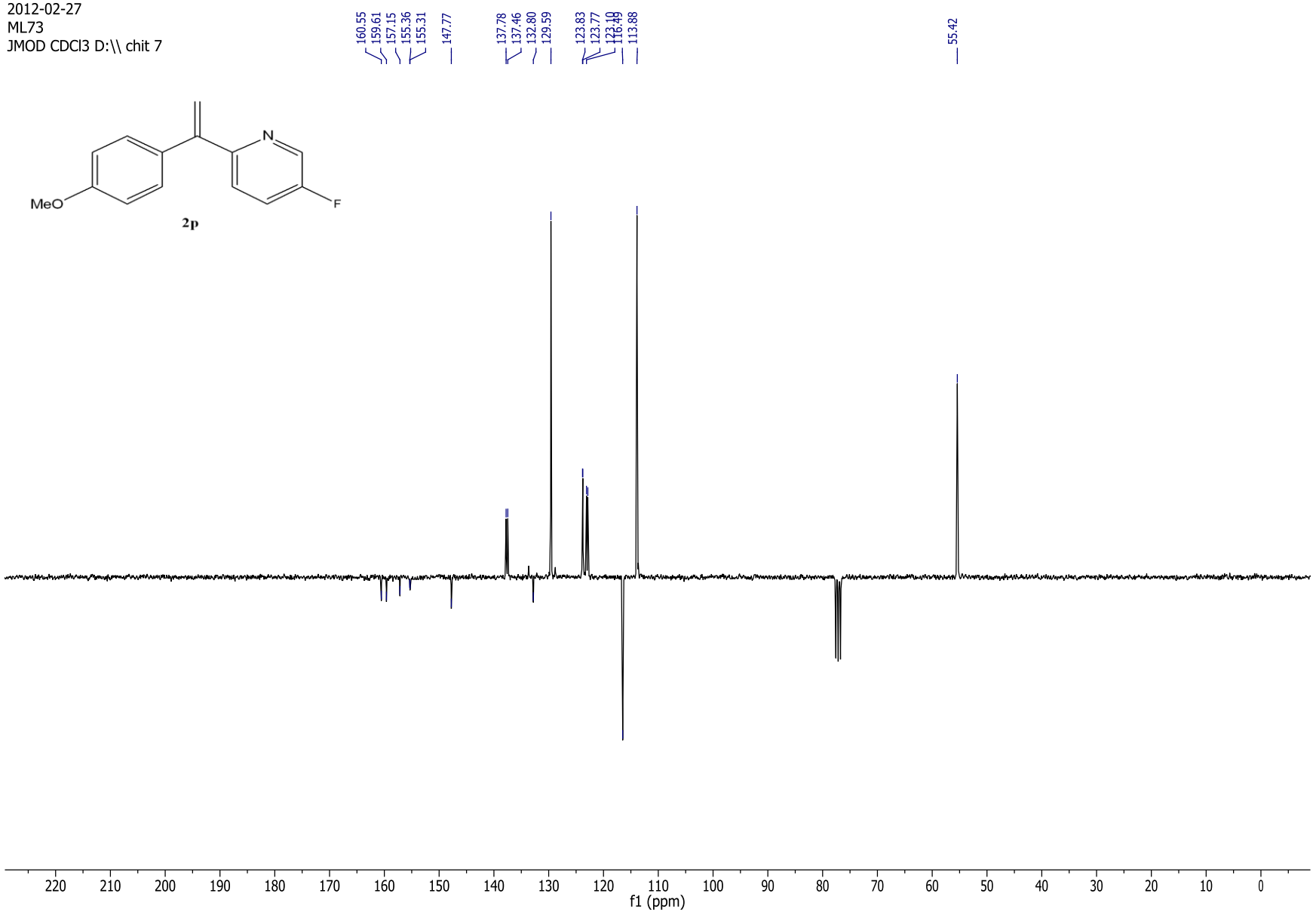


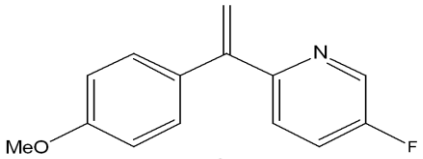







2012-02-27
ML73
JMOD CDCl3 D:\\ chit 7
160.55
159.61
157.15
155.36
155.31
147.77
137.78
137.46
132.80
129.59
123.83
123.77
123.10
116.48
113.88
55.42
MeO
F
N
2p
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

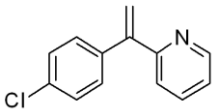
2012.02.27
ml 73
F19CPD CDCl3 v biocis 7



2p

2012-11-06
ML 210
Proton.4 CDCl3 D:\\ chit 30

8.61 8.60 7.66 7.65 7.63 7.63 7.61 7.60 7.31 7.28 7.26 7.24 7.23 7.22 7.20 7.20 7.18 5.95 5.58



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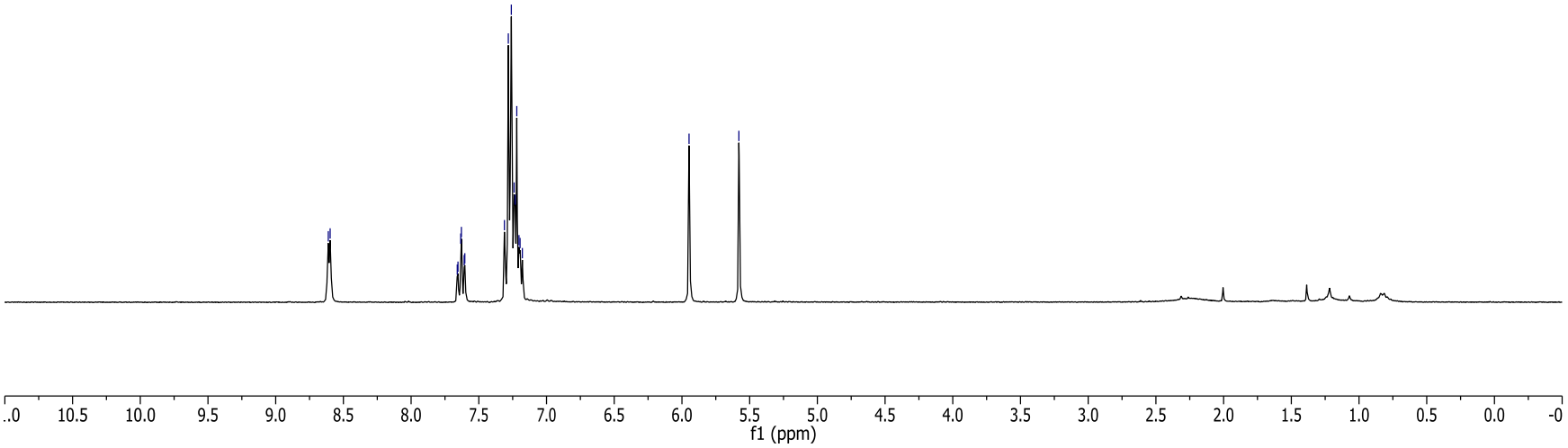
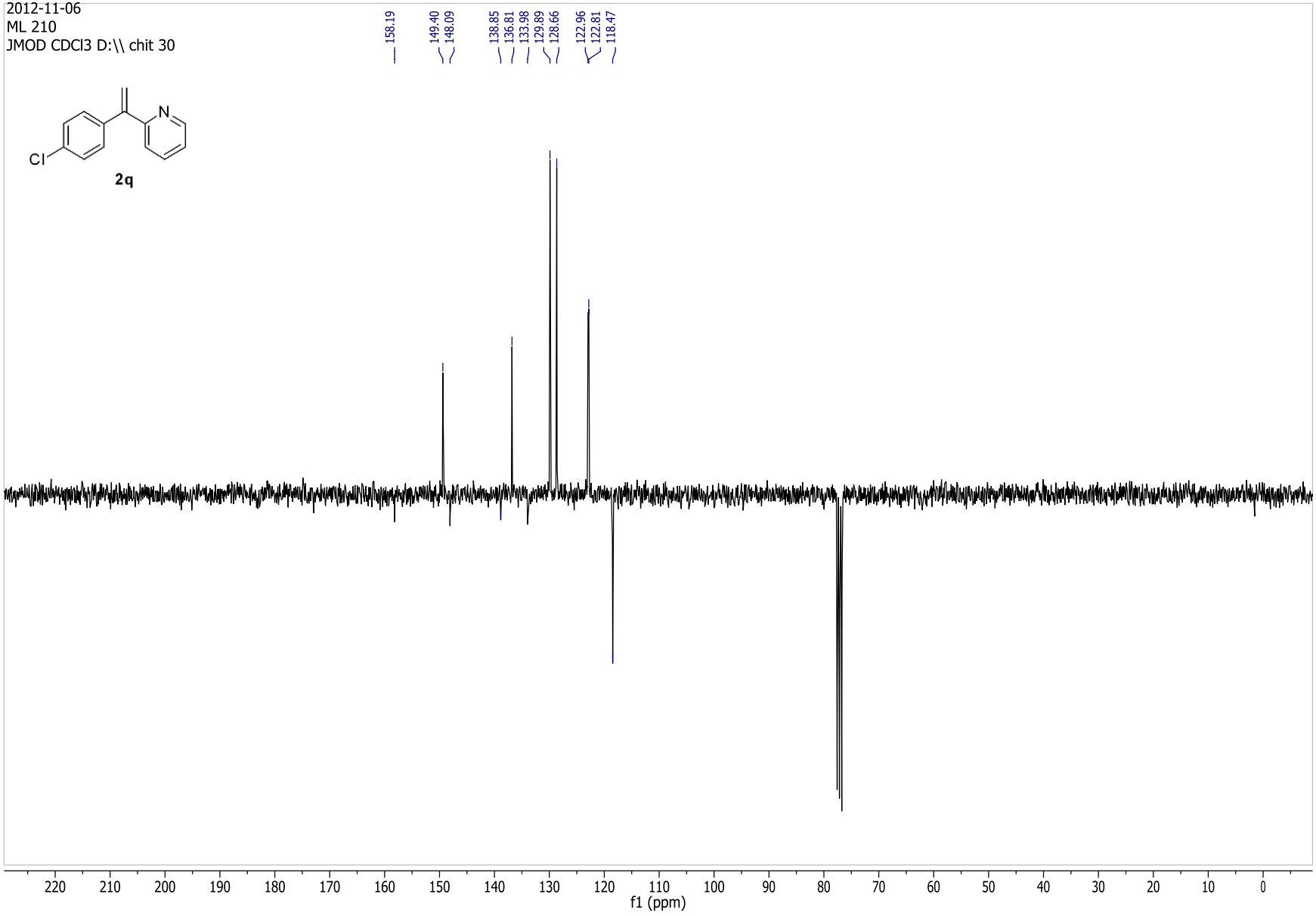
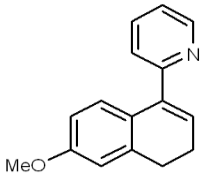


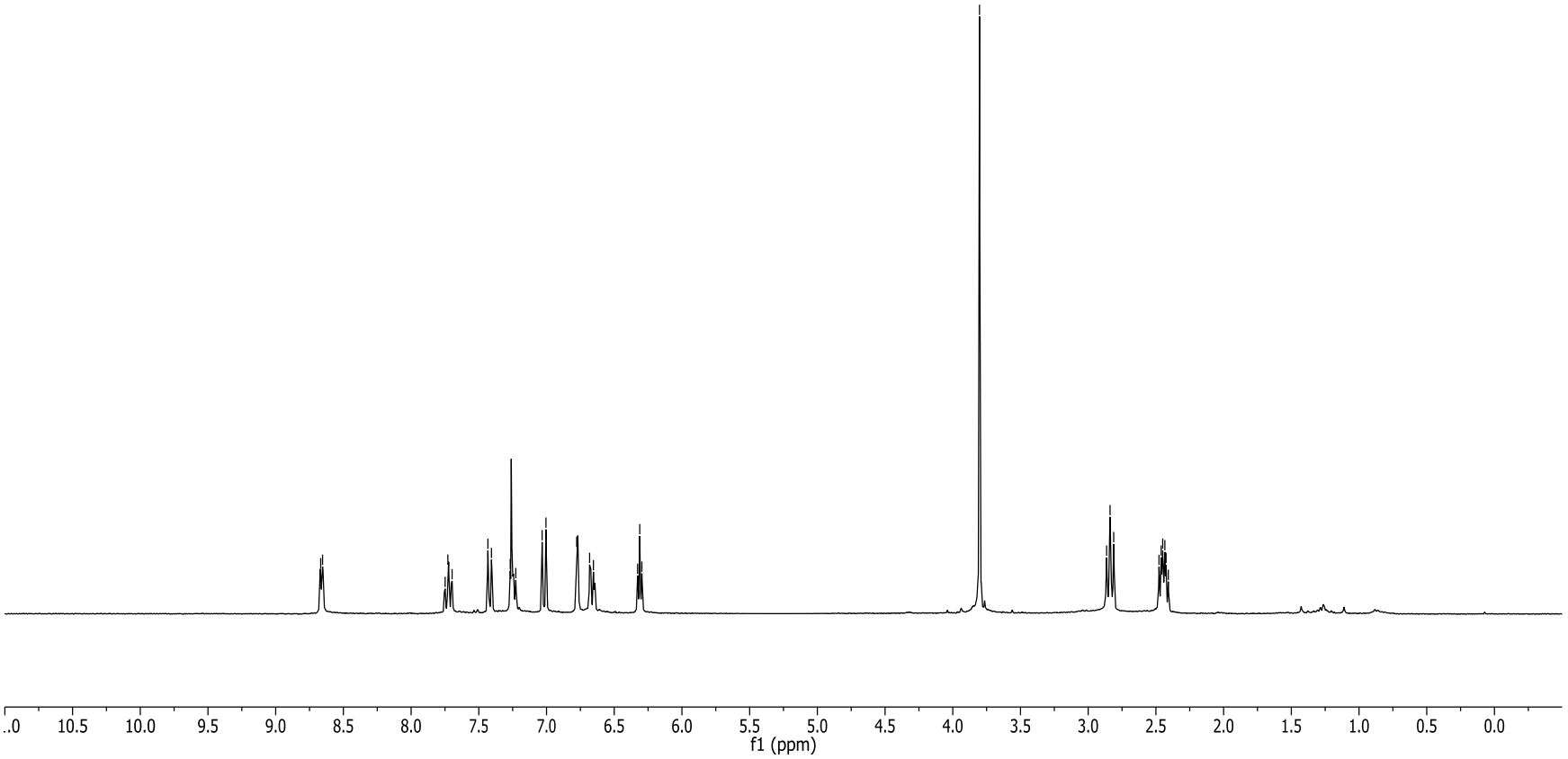


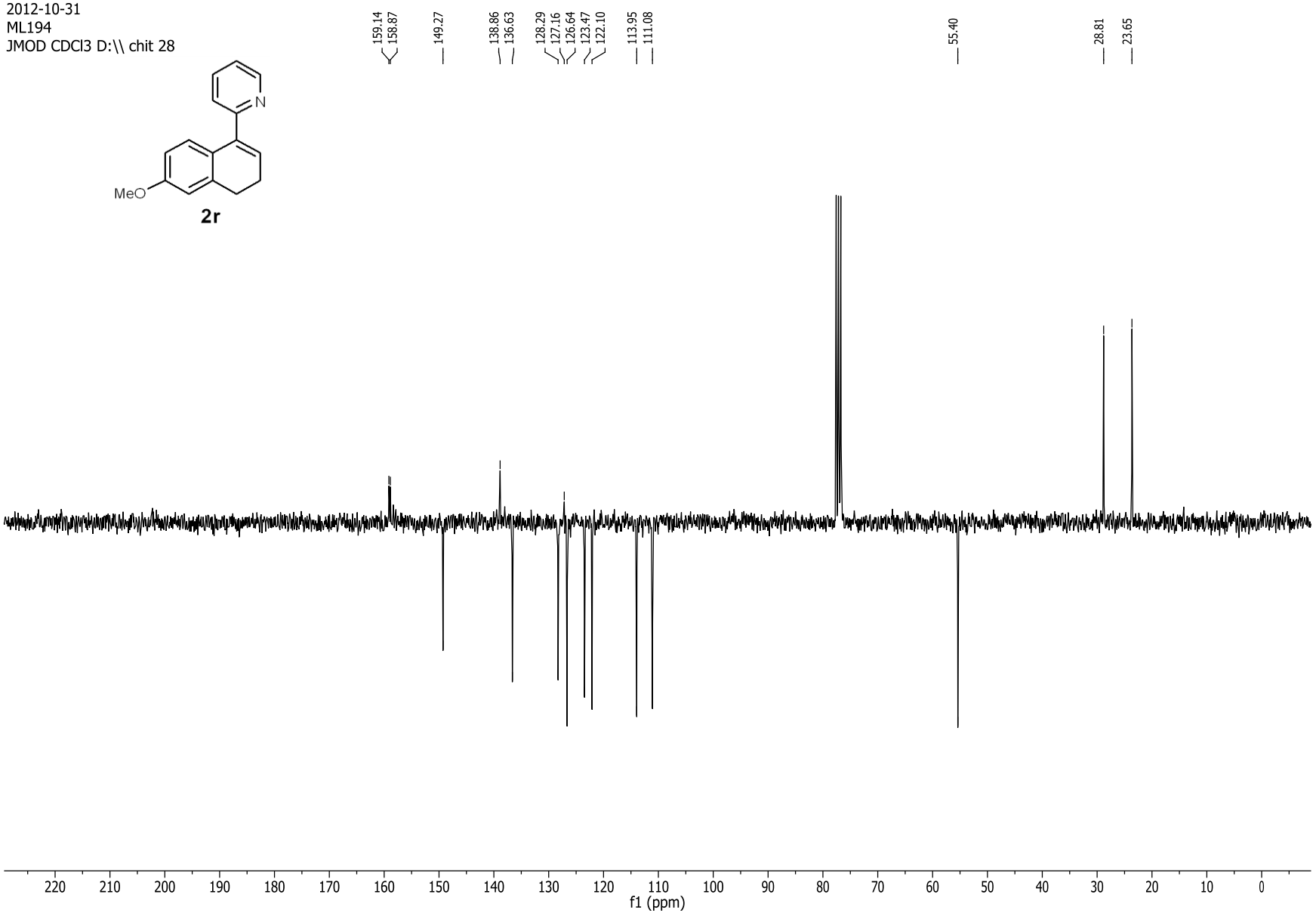
2012-11-05
ML 204
Proton.4 CDCl3 D:\\ chit 49

8.67 8.65 7.75 7.73 7.70 7.43 7.41 7.27 7.03 7.00 6.78 6.68 6.65 6.33 6.31 6.30 3.80 2.86 2.84 2.81 2.48 2.46 2.45 2.43 2.42 2.41



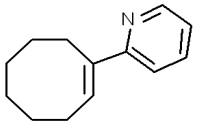
2r



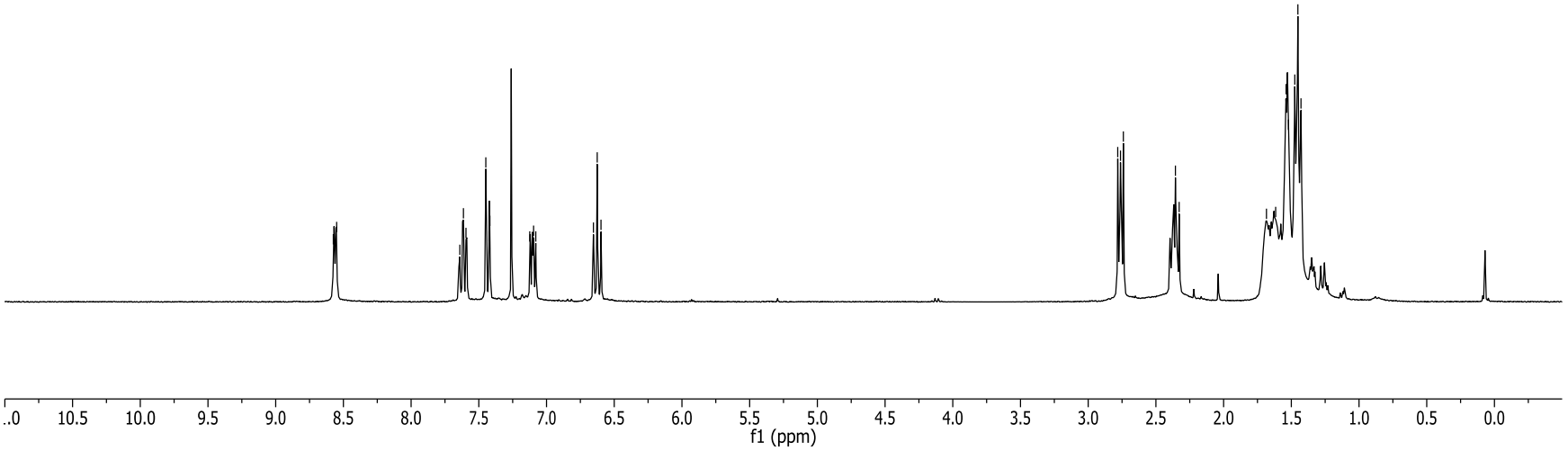


2012-11-06
ML 205
Proton.4 CDCl3 D:\\ chit 29

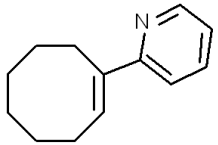
8.57 8.55 7.64 7.61 7.59 7.45 7.42 7.42 7.12 7.10 7.08 6.65 6.63 6.60 2.78 2.76 2.74 2.36 2.33 1.68 1.62 1.54 1.52 1.47 1.45 1.43



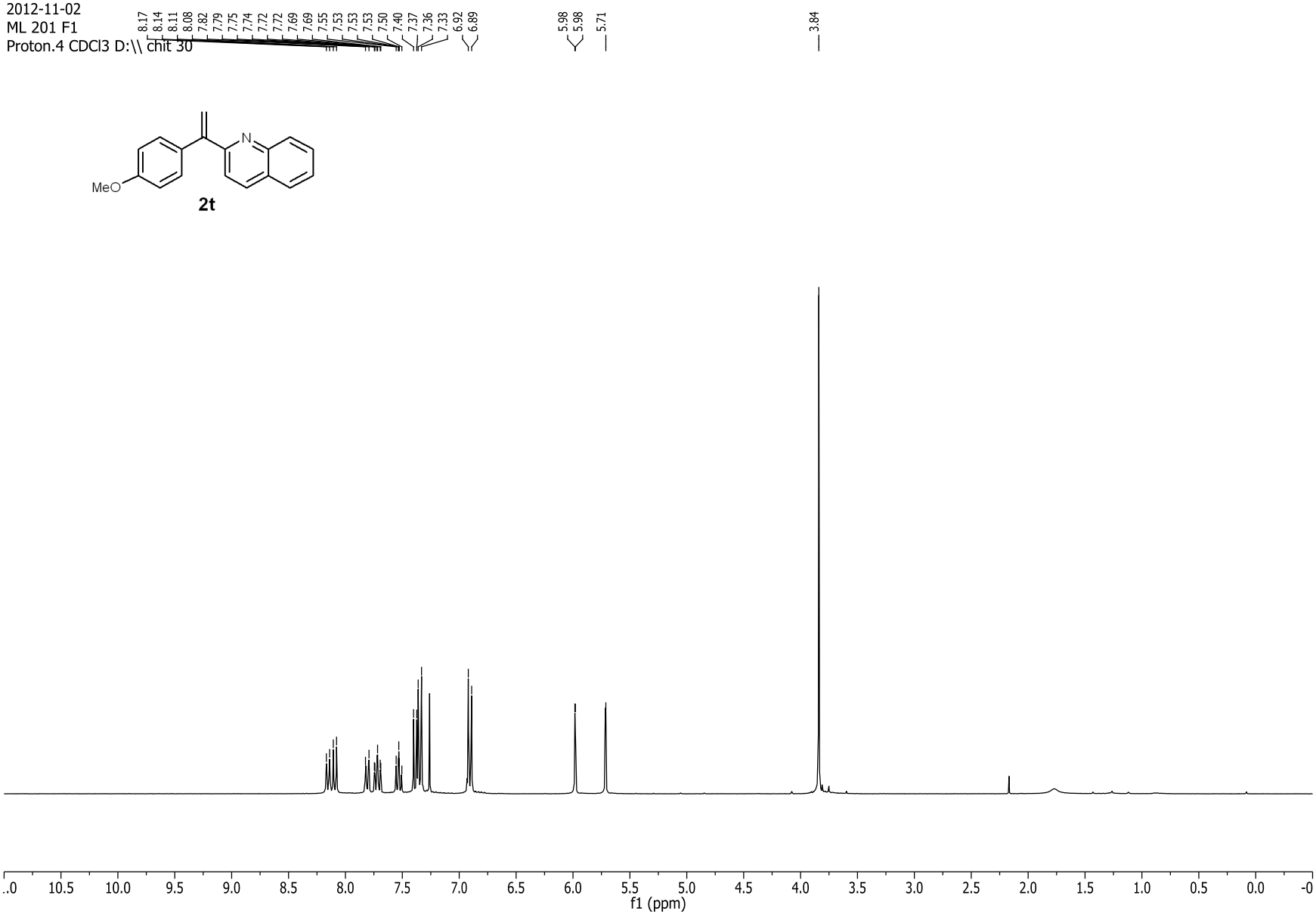
2s

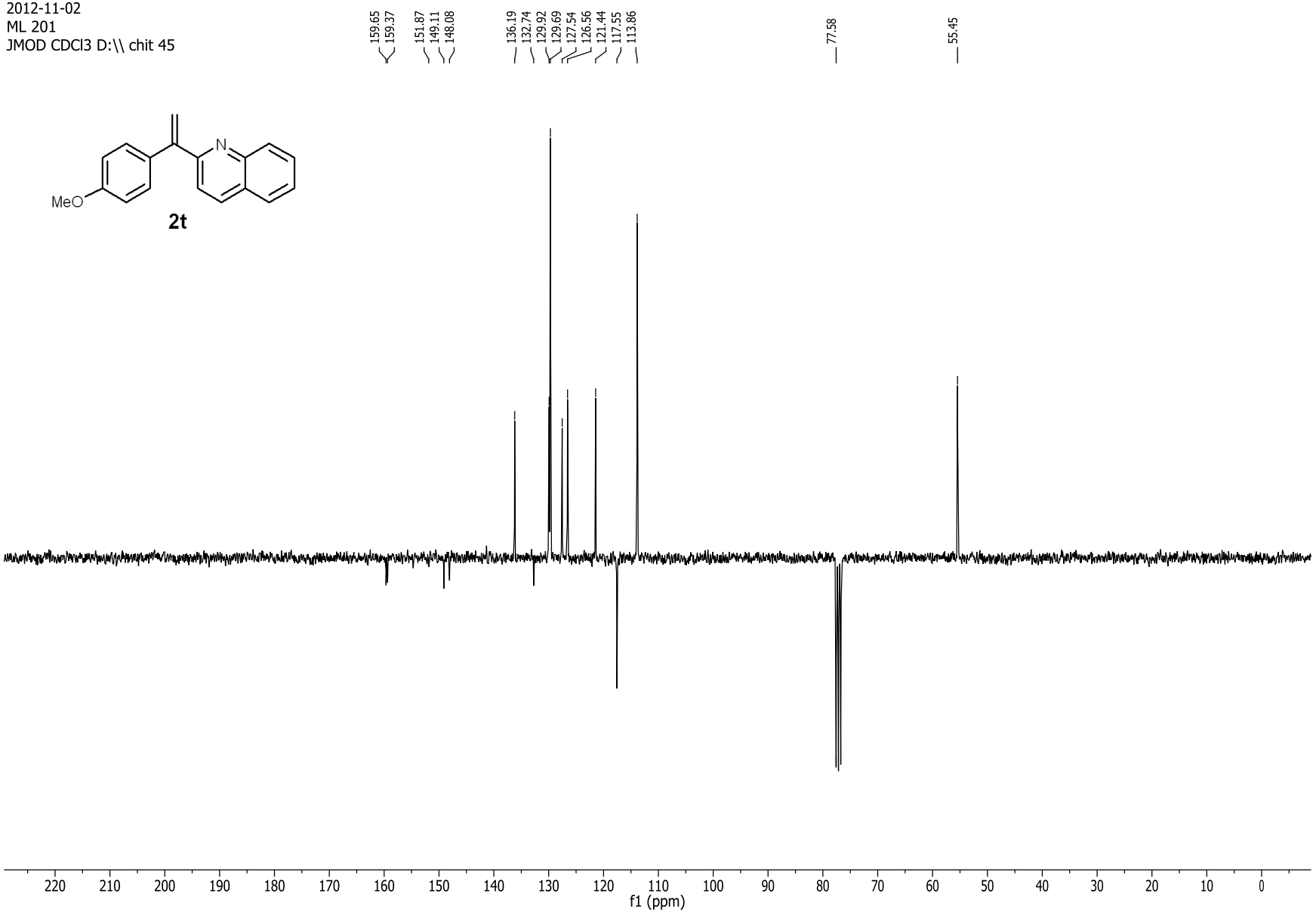


2012-11-07
ML 205
JMOD CDCl3 D:\\ chit 36

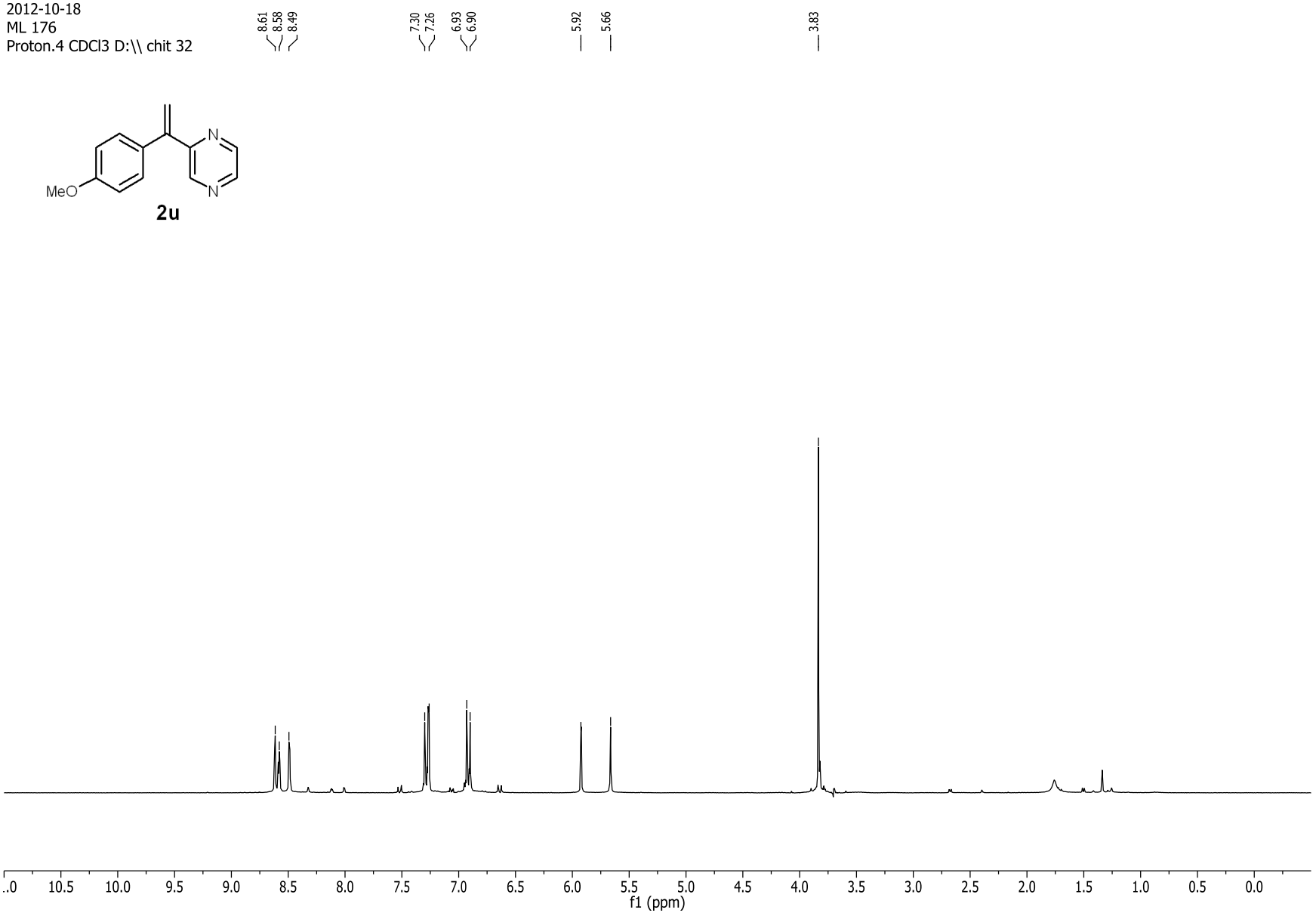


2s

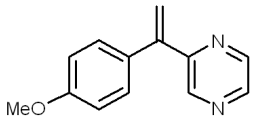




2012-10-18
ML 176
Proton.4 CDCl3 D:\\ chit 32

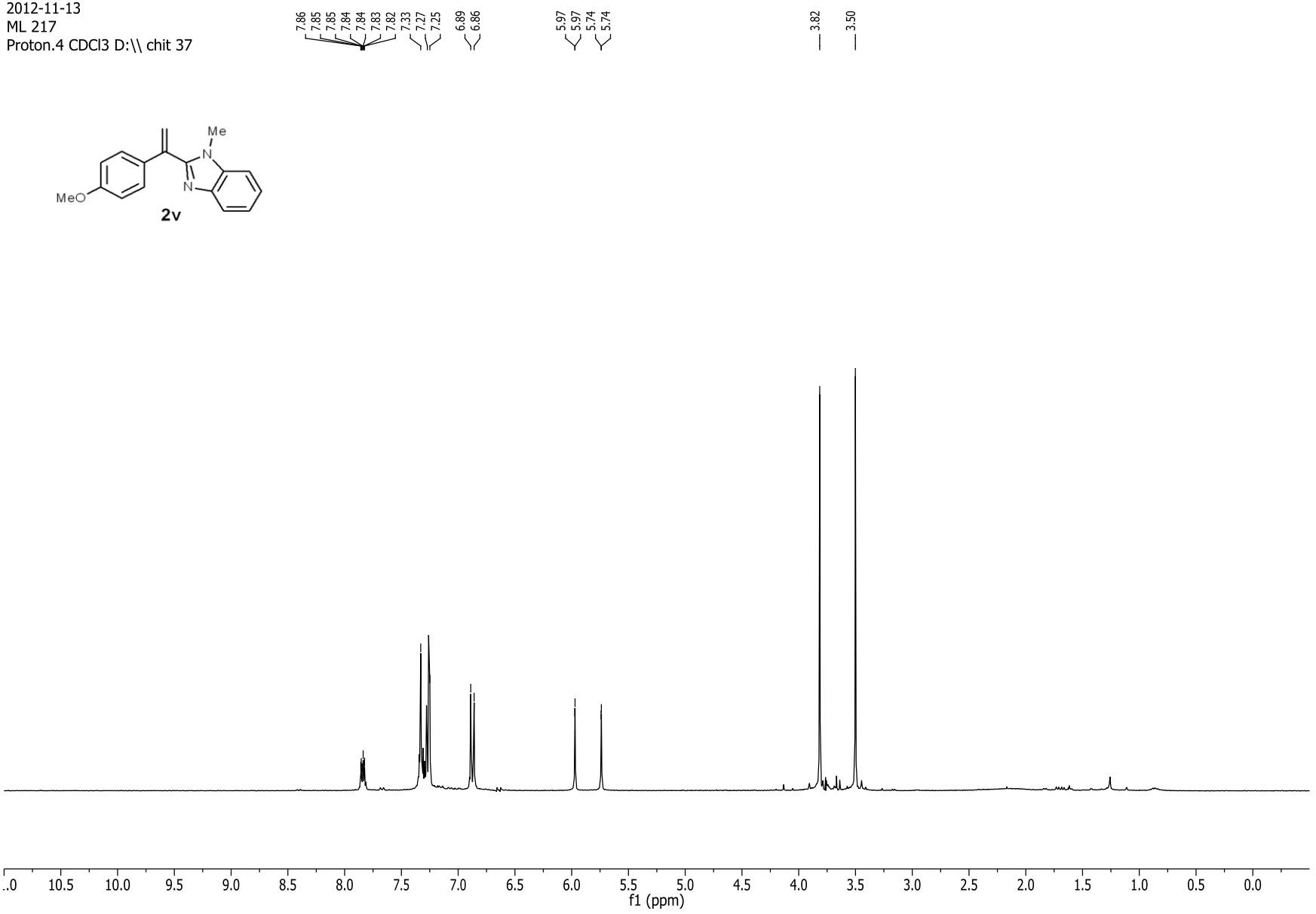


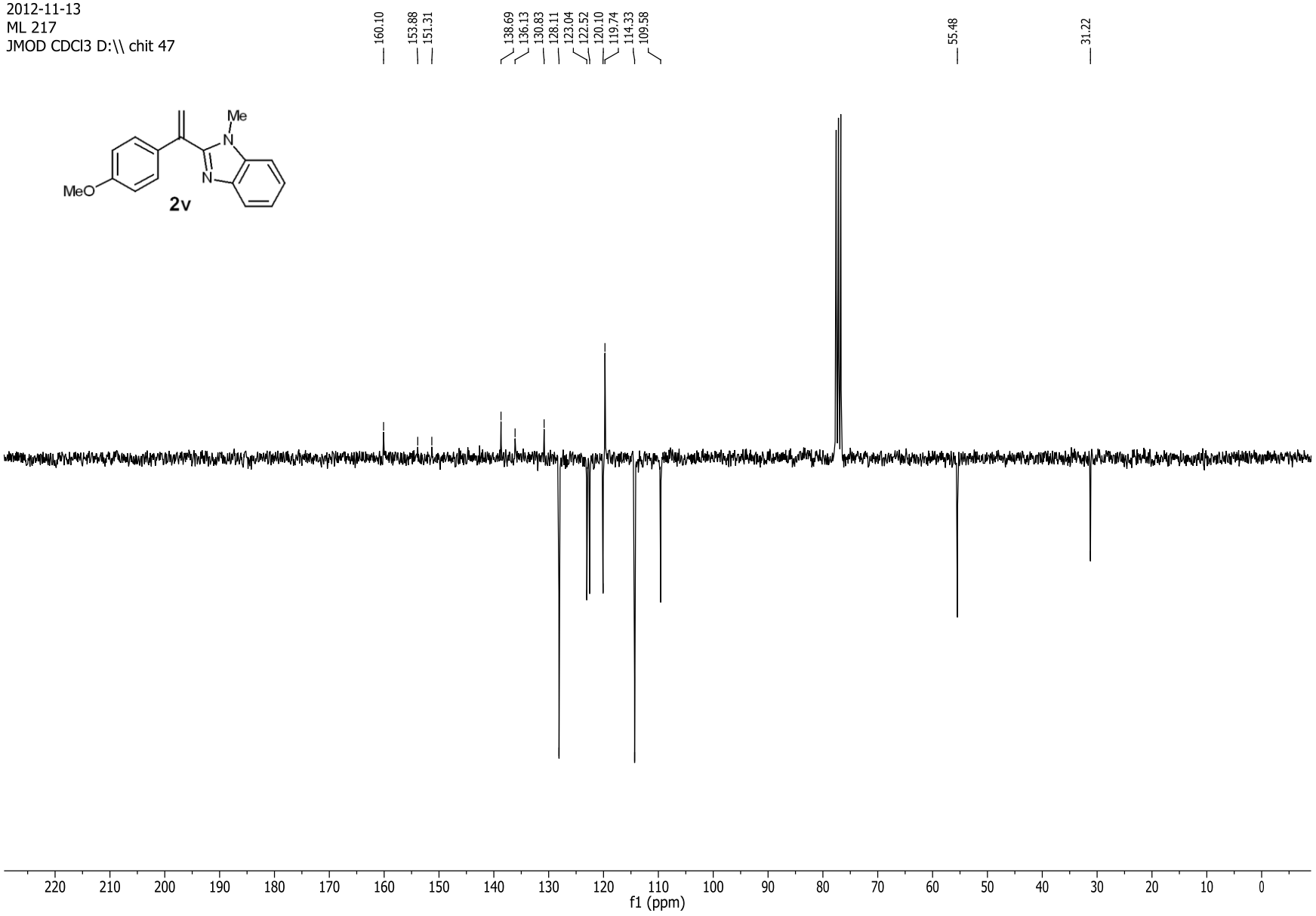
2012-12-05
ML 224
JMOD CDCl3 D:\\ chit 55



2u

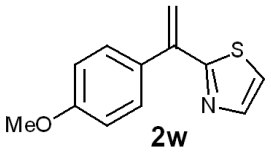
2012-11-13
ML 217
Proton.4 CDCl3 D:\\ chit 37





2012-10-04
ML 162
Proton.4 CDCl3 D:\\ chit 51

8.83
7.37
7.34
7.11
7.10
6.93
6.90
6.89
6.05
6.04
5.44
5.44
3.84



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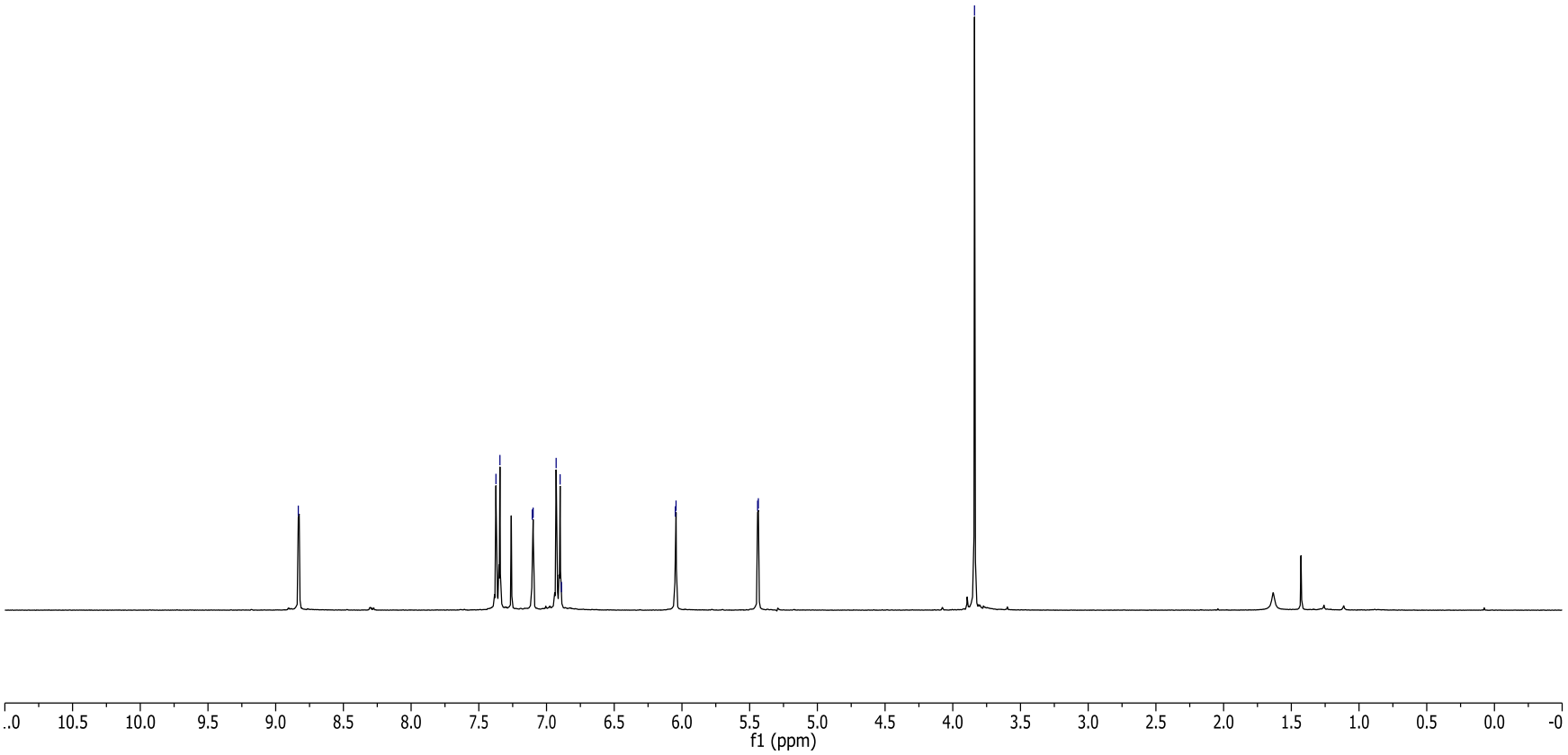
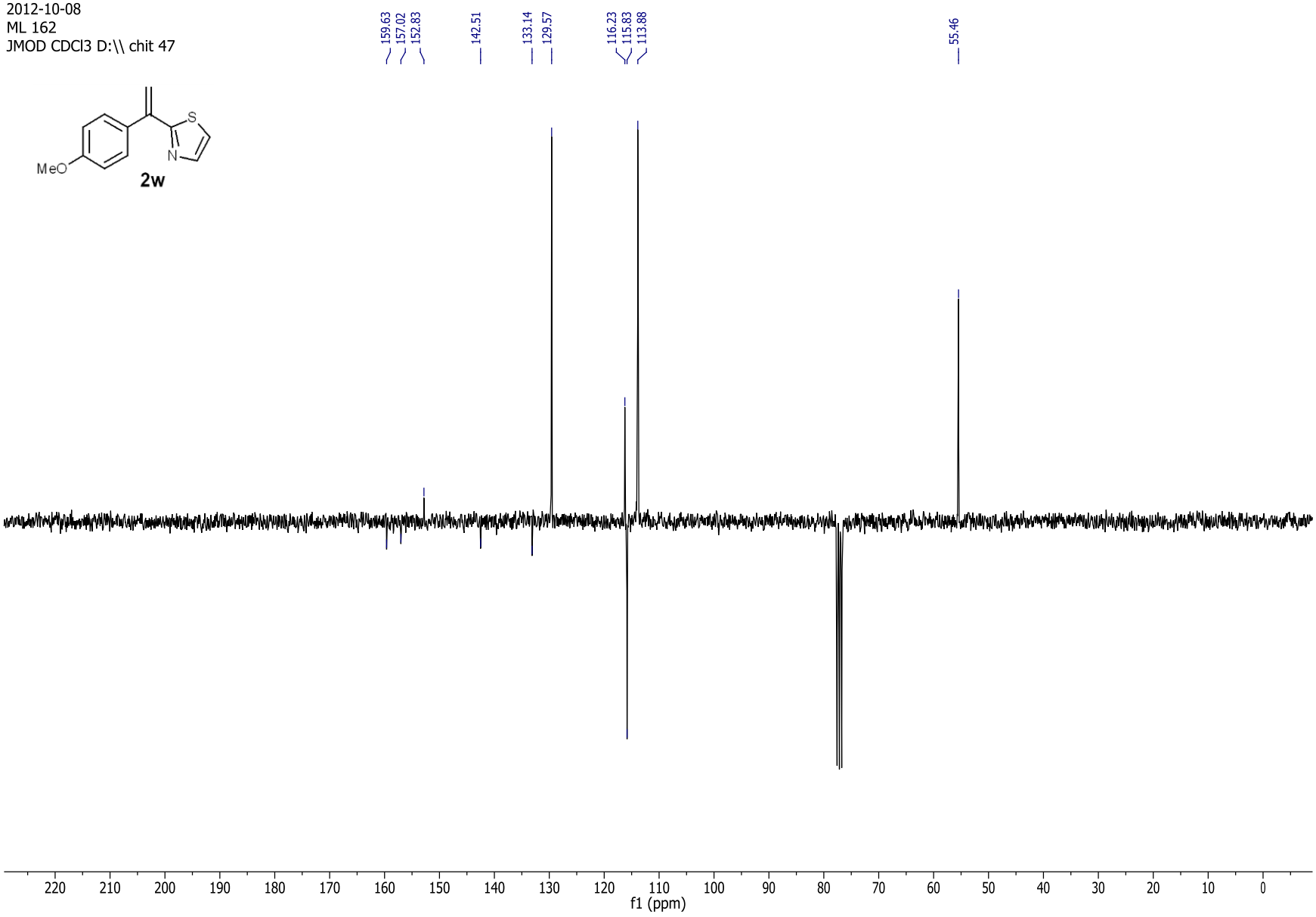
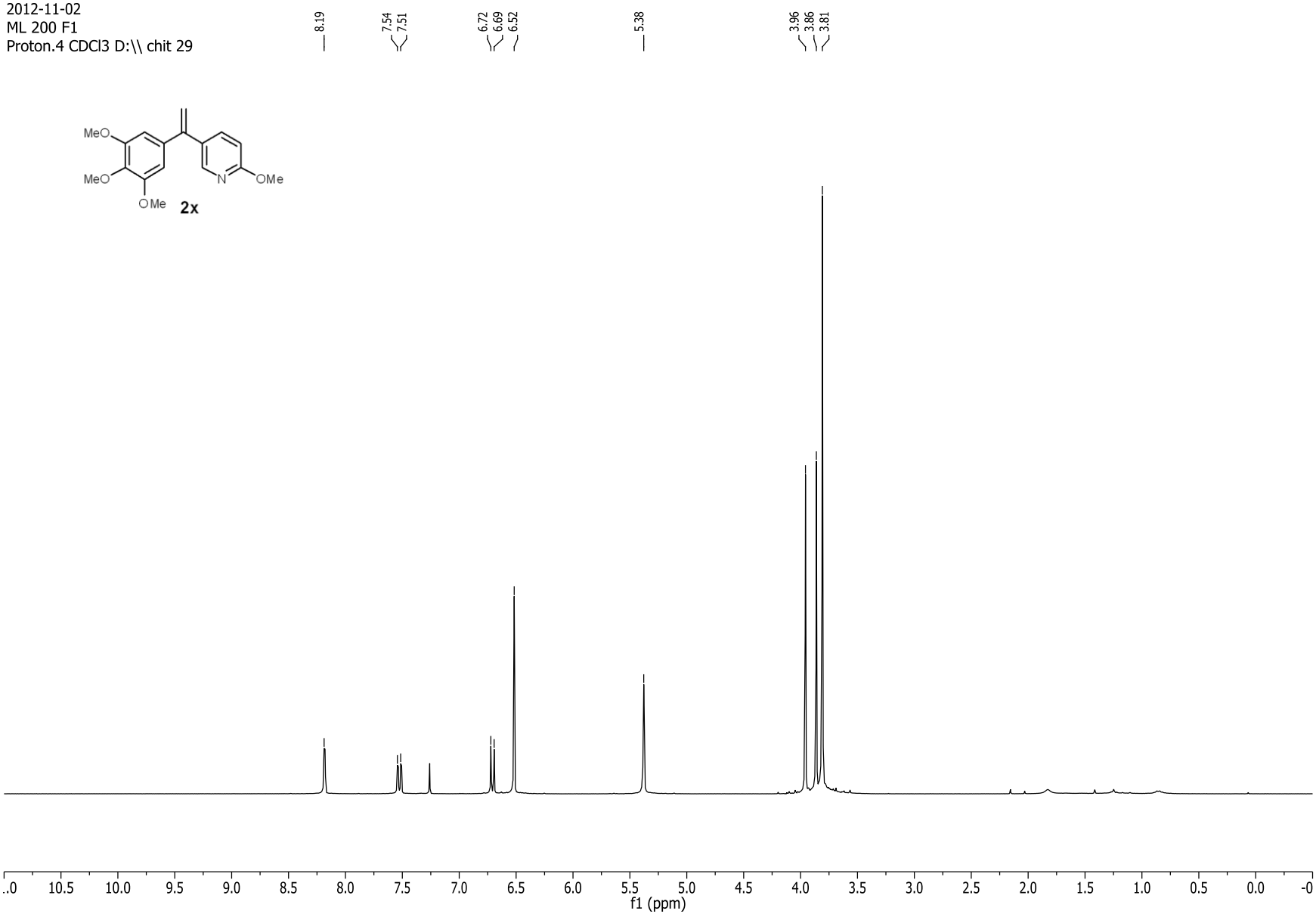
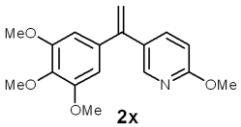






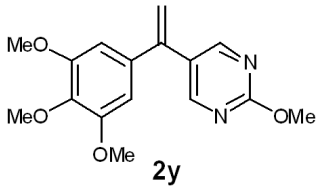
2012-11-02
ML 200
JMOD CDCl3 D:\\ chit 40



2x

2012-10-15
ML 167 T1
Proton.4 CDCl3 D:\\ chit 18

8.49 6.50 5.47 5.42 4.04 3.87 3.82



2y