Electronic supporting information

Application of hindered ether solvents for palladium catalyzed Suzuki-Miyaura, Sonogashira and cascade Sonogashira cross-coupling reactions

Suwiwat Sangon[a], Nontipa Supanchaiyamat[a], James Sherwood[b], Duncan J. Macquarrie[b], Pakin Noppawan[c], and Andrew J. Hunt[a,*].

[a]Materials Chemistry Research Center, Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen, 40002, Thailand. *Corresponding author: andrew@kku.ac.th

[b]Green Chemistry Centre of Excellence, Department of Chemistry, University of York, York, YO10 5DD, UK.

[c]Department of Chemistry, Faculty of Science, Mahasarakham University, Maha Sarakham, 44150, Thailand.

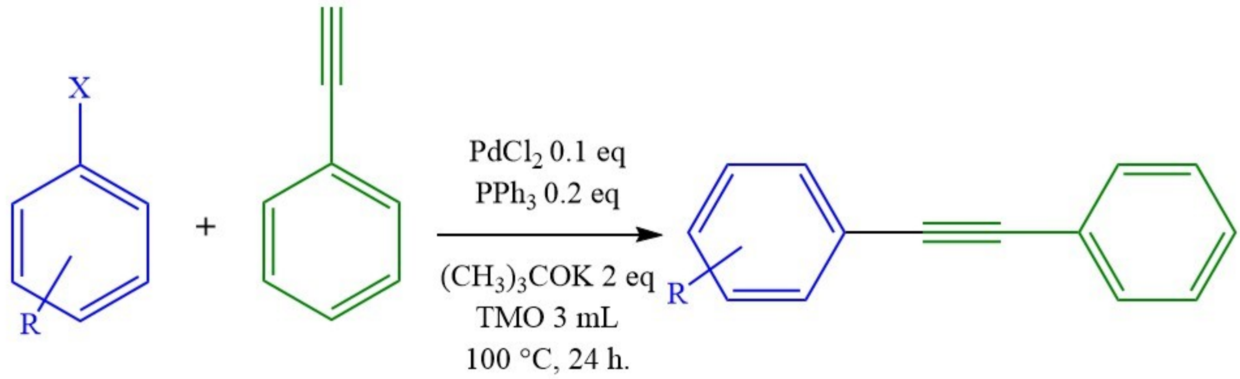
Contents

Table S1. Boiling point (BP), KAT parameters and Hansen solubility parameters of hindered ether solvents and traditional solvents.

Solvent	**BP /°C**	**α**	**β**	**π***	**δ_D /MPa$^{1/2}$**	**δ_P /MPa$^{1/2}$**	**δ_H /MPa$^{1/2}$**
TMO[1]	112	0.00	0.77	0.35	15.4	2.4	2.1
DEDMO[2]	162	0.00	0.62	0.32	16.2	3.1	2.2
Eucalyptol[3]	172	0.00	0.61	0.36	16.6	2.5	2.5
THF[1]	66	0.00	0.58	0.59	16.8	5.7	8.0
Toluene[1]	111	0.00	0.10	0.51	18.0	1.4	2.0

Key: BP, boiling point; α, hydrogen bond donating ability; β, hydrogen bond accepting ability; π*, dipolarity; δ_D, Hansen dispersion force solubility parameter; δ_P, Hansen polarity solubility parameter; δ_H, Hansen hydrogen bonding solubility parameter.

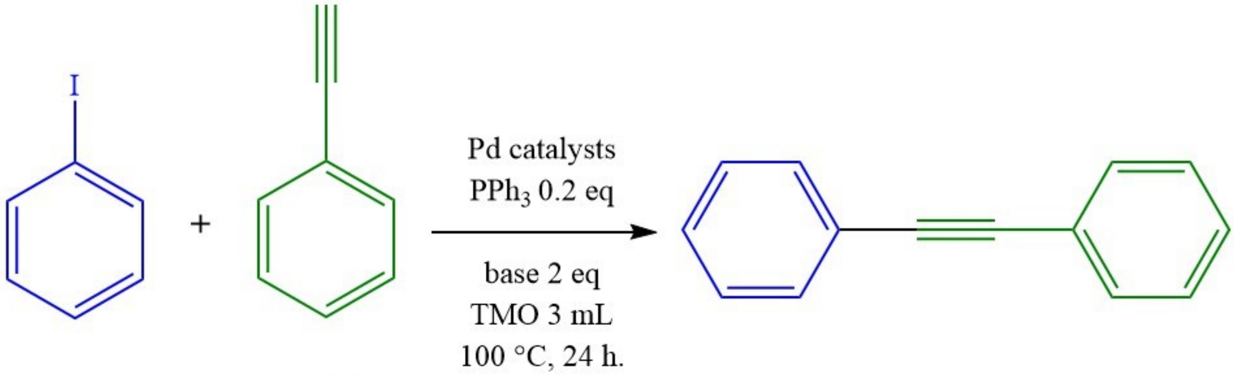
Table S2. Yields of Sonogashira reaction using halobenzene performed in TMO.



4′ **5′** **6′a,b,h-k**

Entry	X	R	Compound	Yields [a]
1	Cl	H	6a, 6′a	7%
2	Br	2-OMe	6′h	trace
3	Br	2-NO_2	6′i	trace
4	I	2-NH_2	6′j	trace
5	Br	4-OMe	6b, 6′b	78%
6	I	4-CH_3	6′k	73%

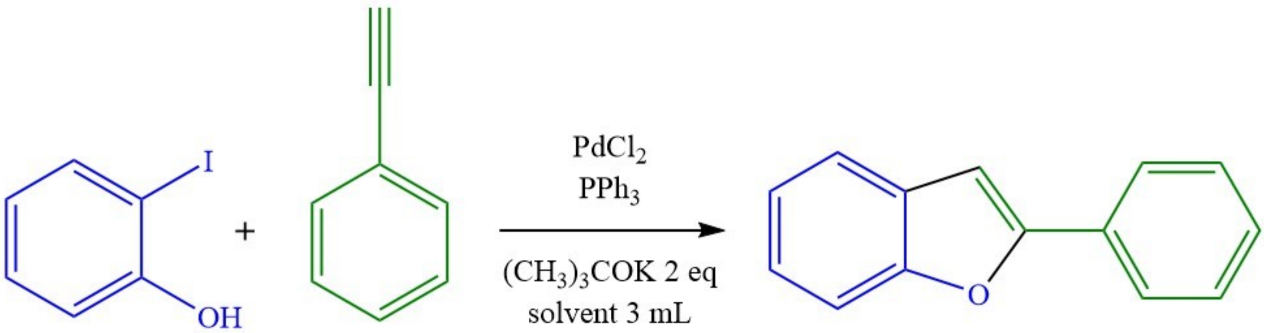
Table S3. Optimization of Sonogashira reaction using iodobenzene and phenylacetylene.



Entry	Catalyst (mol%)	Base	Yield [b]
1	$Pd(dba)_2$ (10%)	Cs_2CO_3	20%
2	$Pd(OAc)_2$ (10%)	Cs_2CO_3	25%
3	$PdCl_2$ (10%)	Cs_2CO_3	42%
4	$PdCl_2$ (10%)	Cs_2CO_3	34%[c]
5	$PdCl_2$ (20%)	Cs_2CO_3	56%
6	$PdCl_2$ (10%)	KO*t*-Bu	91%
7	$PdCl_2$ (5%)	KO*t*-Bu	98%
8	$PdCl_2$ (2.5%)	KO*t*-Bu	99%
9	$PdCl_2$ (1%)	KO*t*-Bu	98%

[a] Iodobenzene = 1mmol, Phenylacetylene = 1.5 mmol, base = 2 mmol, PPh_3 = 0.2 mmol, 100°C, 24 h, 3 mL of TMO as a solvent, [b] Isolated yield and [c] 10 h.

Table S4. Optimization of cascade Sonogashira reaction using iodobenzene and phenylacetylene.



Entry	Catalyst (mol%), PPh_3(mol%)	Time (h)	Temp. (°C)	Yield [b]
1	$PdCl_2$ (10%), PPh_3 (20%)	2	100	3%

2	$PdCl_2$ (10%), PPh_3 (20%)	5	100	8%
3	$PdCl_2$ (10%), PPh_3 (20%)	24	100	52%
4	$PdCl_2$ (10%), PPh_3 (20%)	24	110	43%

[a] 2-Iodophenol = 1 mmol, Phenylacetylene = 1.5 mmol, KO*t*-Bu = 2 mmol, 3 mL of TMO as a solvent.
[b] Isolated yield.

S5. Materials used for green metric calculation

Table S5. Materials used for green metric calculation.[2,4,5]

Chemicals	Suzuki reaction					Sonogashira reaction				
	TMO	DEDMO	Eucalyptol	THF	Tol	TMO	DEDMO	Eucalyptol	THF	Tol
Solvent	1.60	1.67	1.85	1.77	1.73	2.41	2.51	2.78	2.65	2.60
Product	0.1372	0.1326	0.1326	0.1311	0.1357	0.1622	0.1444	0.1355	0.1515	0.1426
Iodobenzene	1.00 mmol x 204.01 g mol^{-1} = 0.2040 g					1.00 mmol x 204.01 g mol^{-1} = 0.2040 g				
Phenyl boronic acid / Phenyl acetylene	1.25 mmol x 121.93 g mol^{-1} = 0.1524 g					1.50 mmol x 102.13 g mol^{-1} = 0.1532 g				
$Pd(dba)_2$/ $PdCl_2$	0.025 mmol x 575 g mol^{-1} = 0.0144 g					0.10 mmol x 177.33 g mol^{-1} = 0.0177 g				
PPh_3	0.15 mmol x 262.29 g mol^{-1} = 0.0393 g					0.20 mmol x 262.29 g mol^{-1} = 0.0524 g				
Reaction water	0.6667 mL x 1g mL^{-1} = 0.6667 g					-				
K_2CO_3/ KO*t*-Bu	2 mmol x 138.21 g mol^{-1} = 0.2764 g					2 mmol x 112.21 g mol^{-1} = 0.2244 g				
H_2O	10 mL x 1 g mL^{-1} = 10.00 g					10 mL x 1 g mL^{-1} = 10.00 g				
EtOAc	30 mL x 0.902 g mL^{-1} = 27.06 g					30 mL x 0.902 g mL^{-1} = 27.06 g				
$MgSO_4$	0.10 g					0.10 g				
Hexane	50 ml x 0.655 g mL^{-1} = 32.75 g					50 ml x 0.655 g mL^{-1} = 32.75 g				
silica	10.00 g					10.00 g				

$$\text{Process mass intensity (PMI)} = \frac{\text{total mass in process}}{\text{mass of product}}$$

$$\text{Reaction mass efficiency (RME)} = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$\text{Atom economy (AE)} = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

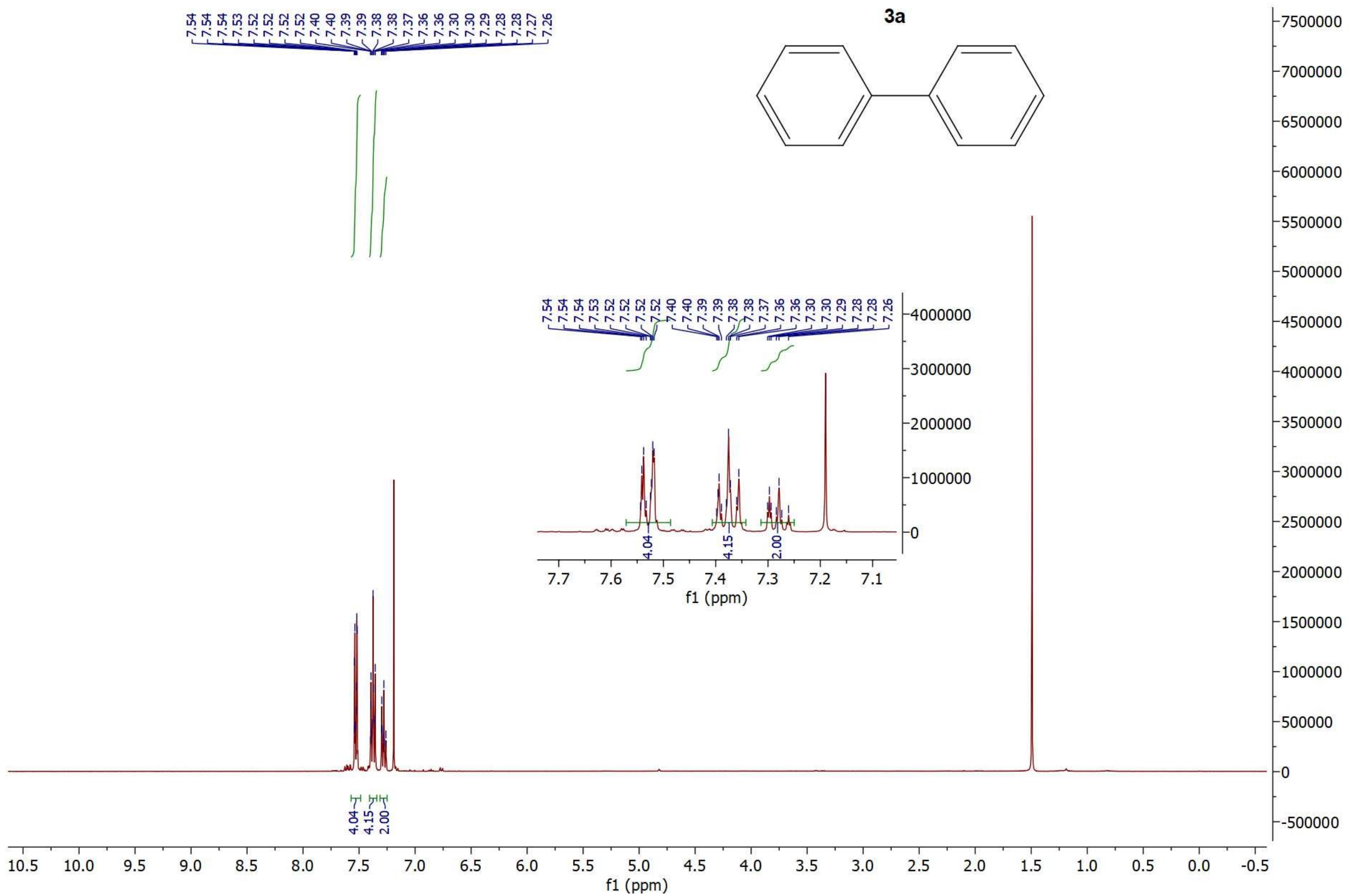
$$\text{Optimum efficiency (OE)} = \frac{\text{RME}}{\text{AE}} \times 100$$

Table S6. Green metric assessment of Suzuki-Miyaura and Sonogashira reactions.

	Suzuki-Miyaura reaction (Iodobenzene + Phenylboronic acid)					Sonogashira reaction (Iodobenzene + Phenylacetylene)				
Solvent	TMO	DEDMO	Eucalyptol	THF	Tol	TMO	DEDMO	Eucalyptol	THF	Tol
Yield (%)	89	86	86	85	88	91	81	76	85	80
PMI	604	625	627	633	612	512	575	615	549	583
RME (%)	38	37	37	36	38	45	40	38	42	40
AE (%)	47					55				
OE (%)	81	79	79	77	81	82	73	69	76	73

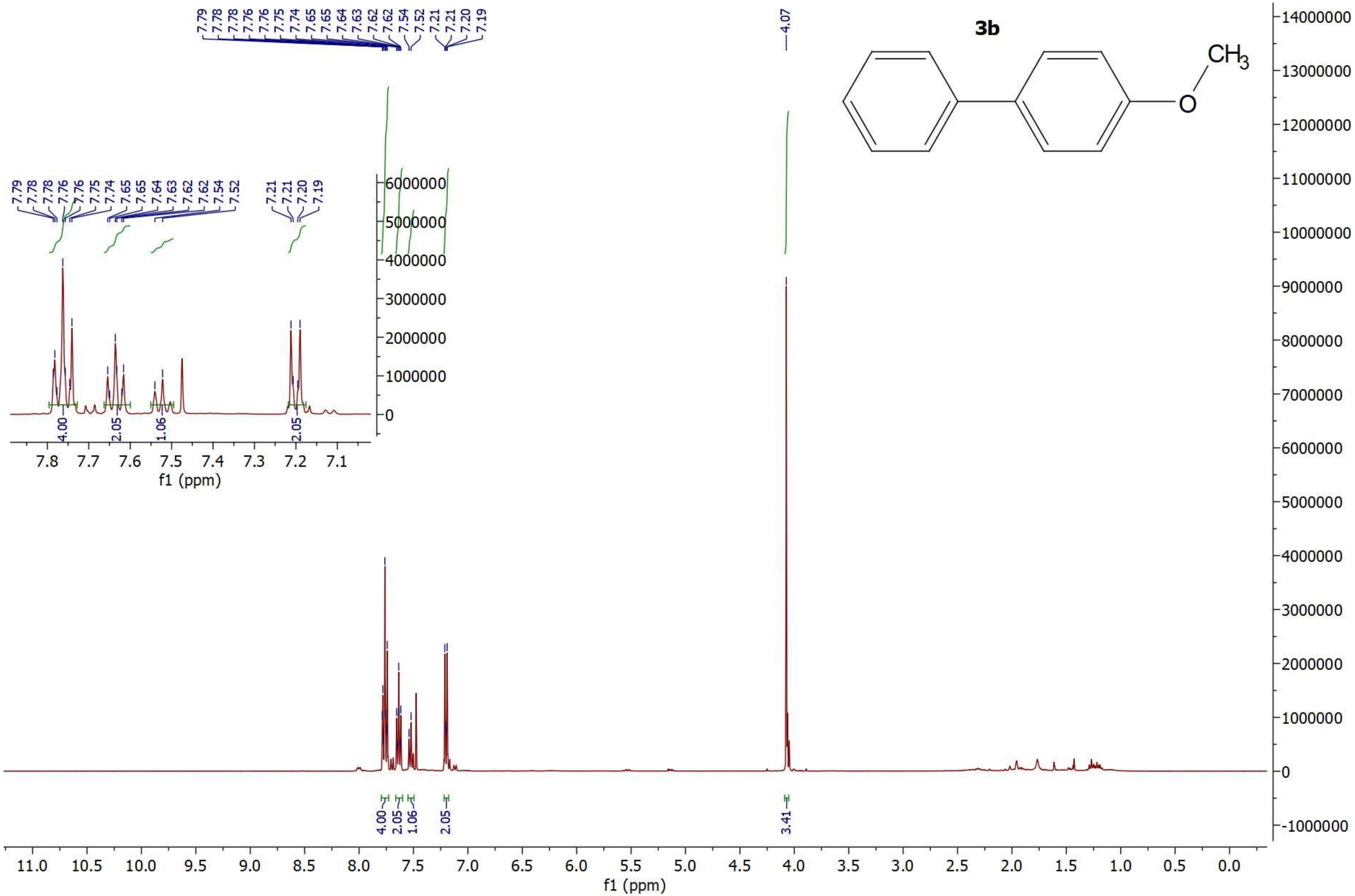
S7. ^{1}H and ^{13}C NMR Spectra of Synthesized Compounds

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 4H), 7.41 – 7.34 (m, 4H), 7.31 – 7.25 (m, 2H).

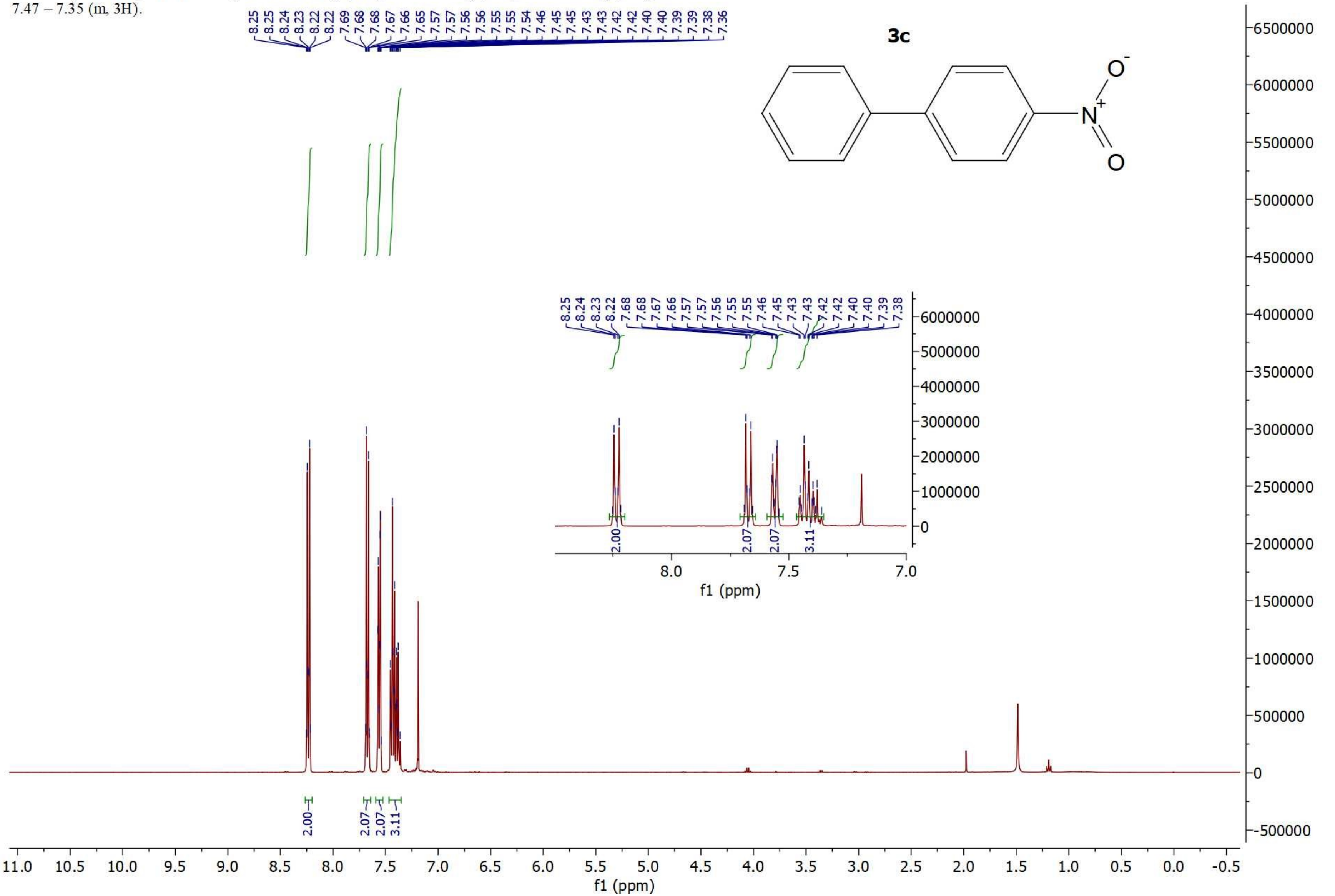


[1]H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.73 (m, 4H), 7.63 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.17 (m, 2H), 4.07 (s, 3H).

3b

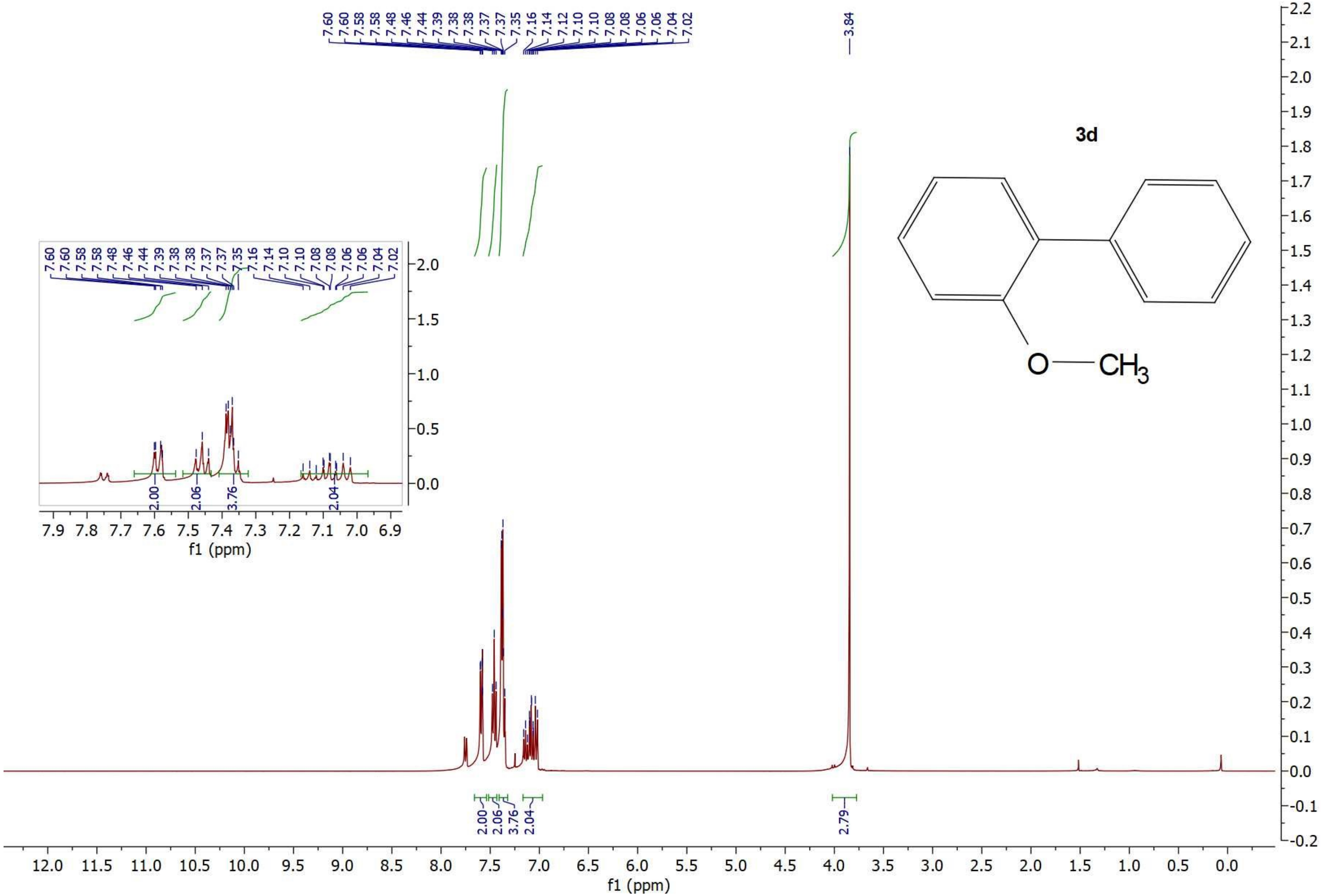


^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.21 (m, 2H), 7.70 – 7.65 (m, 2H), 7.58 – 7.54 (m, 2H), 7.47 – 7.35 (m, 3H).

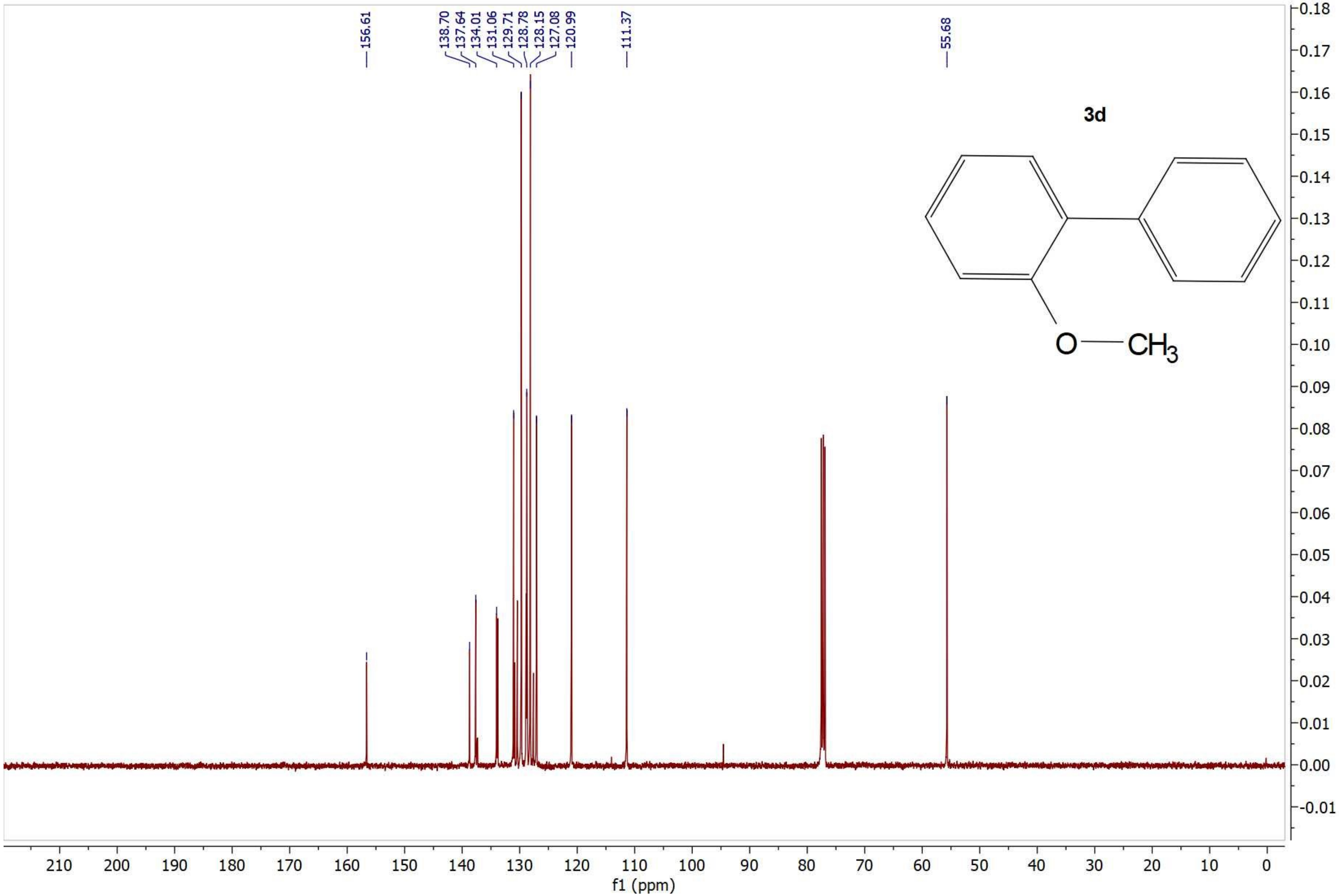


3c

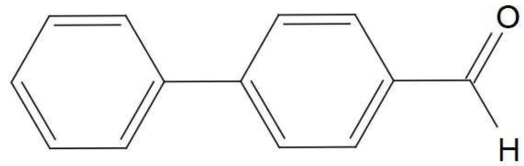
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.41 – 7.34 (m, 3H), 7.17 – 6.99 (m, 2H), 3.84 (s, 3H).



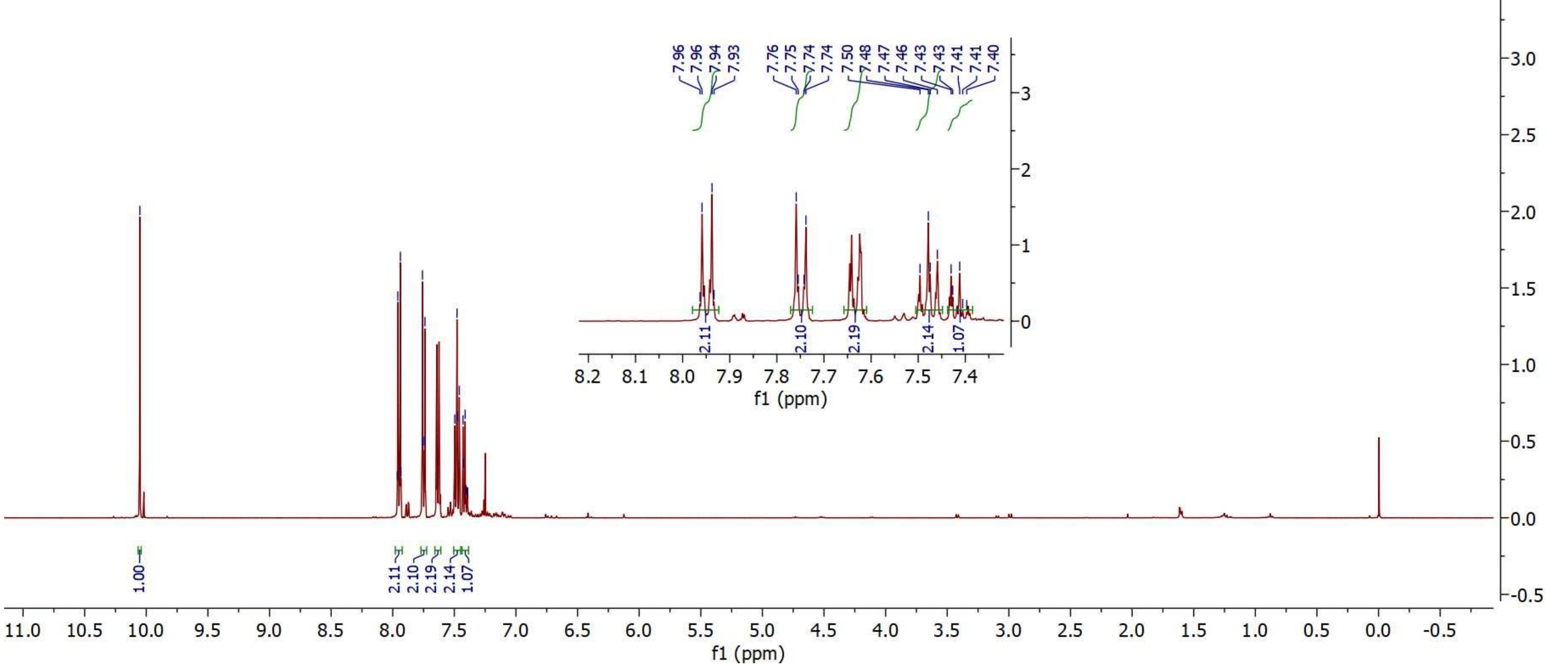
^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 156.61, 138.70, 137.64, 134.01, 131.06, 129.71, 128.78, 128.15, 127.08, 120.99, 111.37, 55.68.



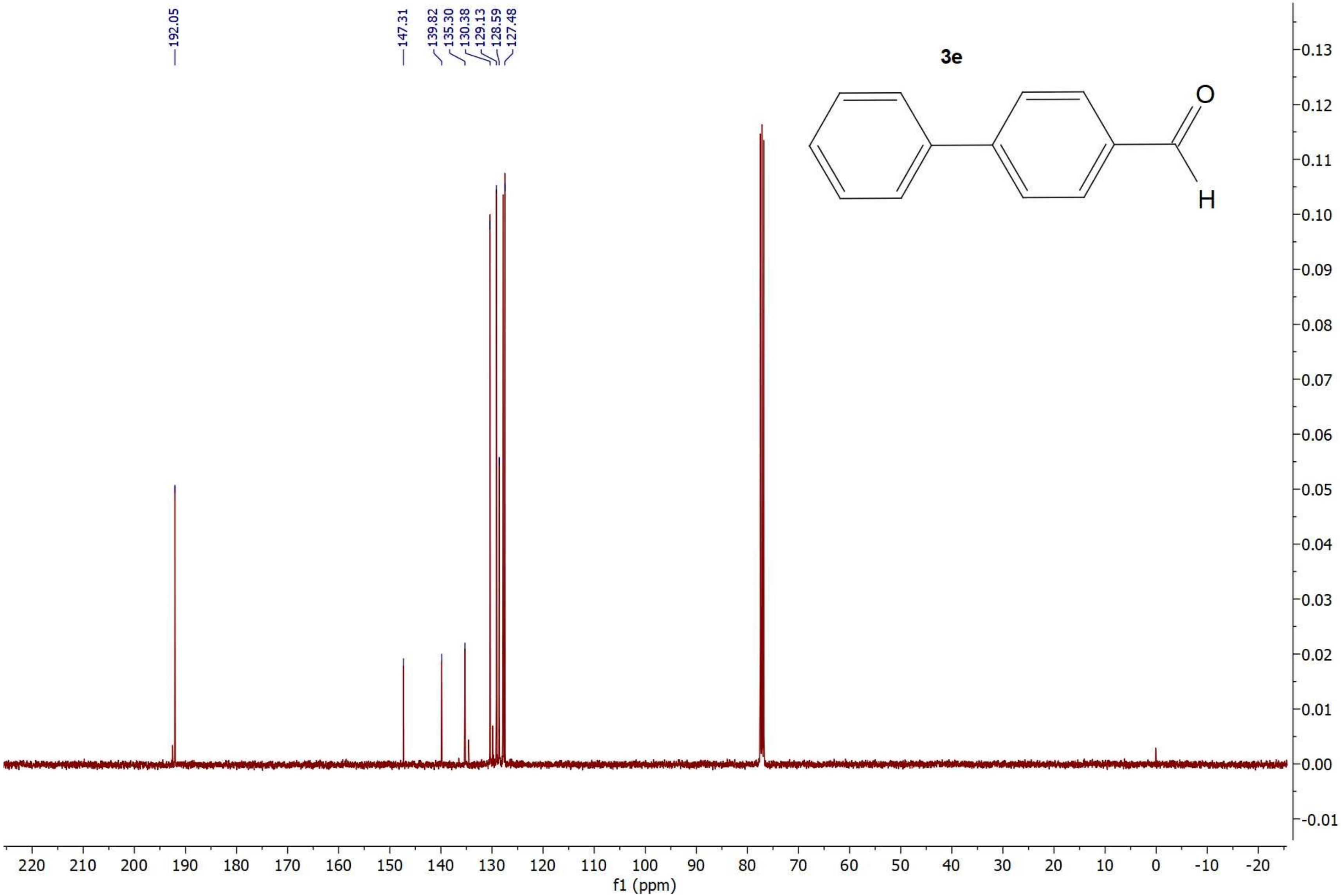
[1]H NMR (400 MHz, Chloroform-*d*) δ 10.05 (s, 1H), 7.98 – 7.92 (m, 2H), 7.78 – 7.72 (m, 2H), 7.67 – 7.60 (m, 2H), 7.50 – 7.44 (m, 2H), 7.44 – 7.37 (m, 1H).



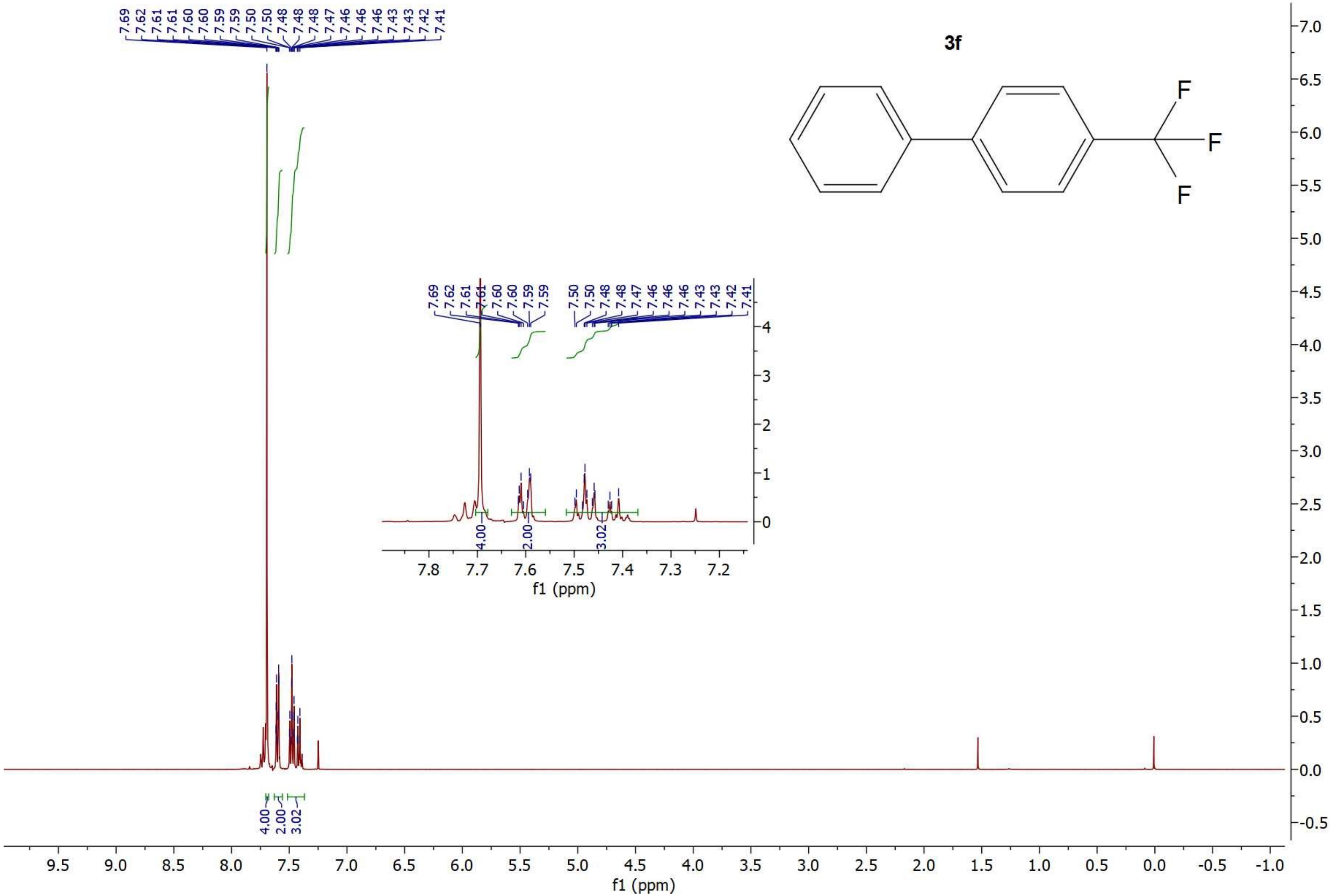
3e



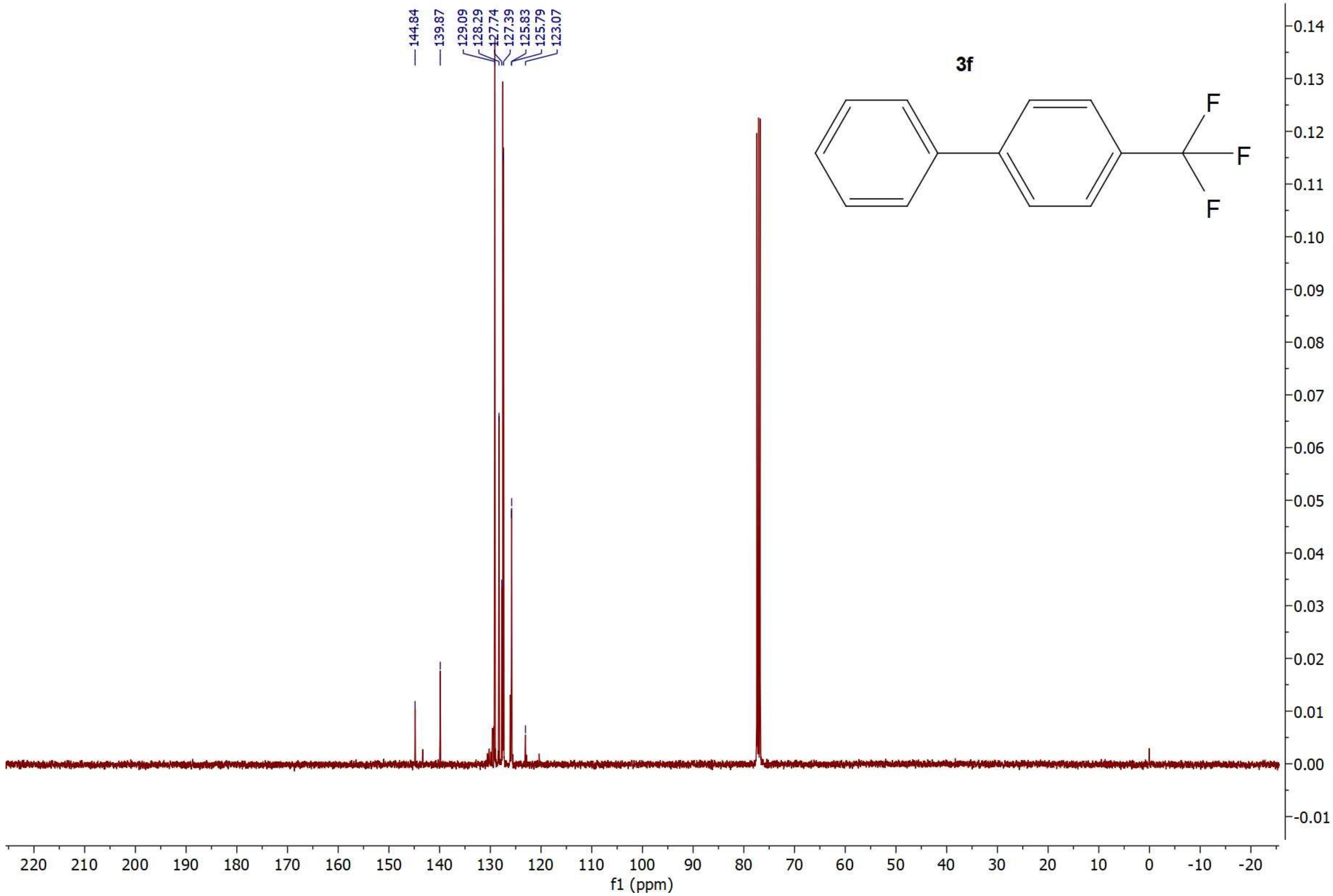
^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 192.05, 147.31, 139.82, 135.30, 130.38, 129.13, 128.59, 127.48.



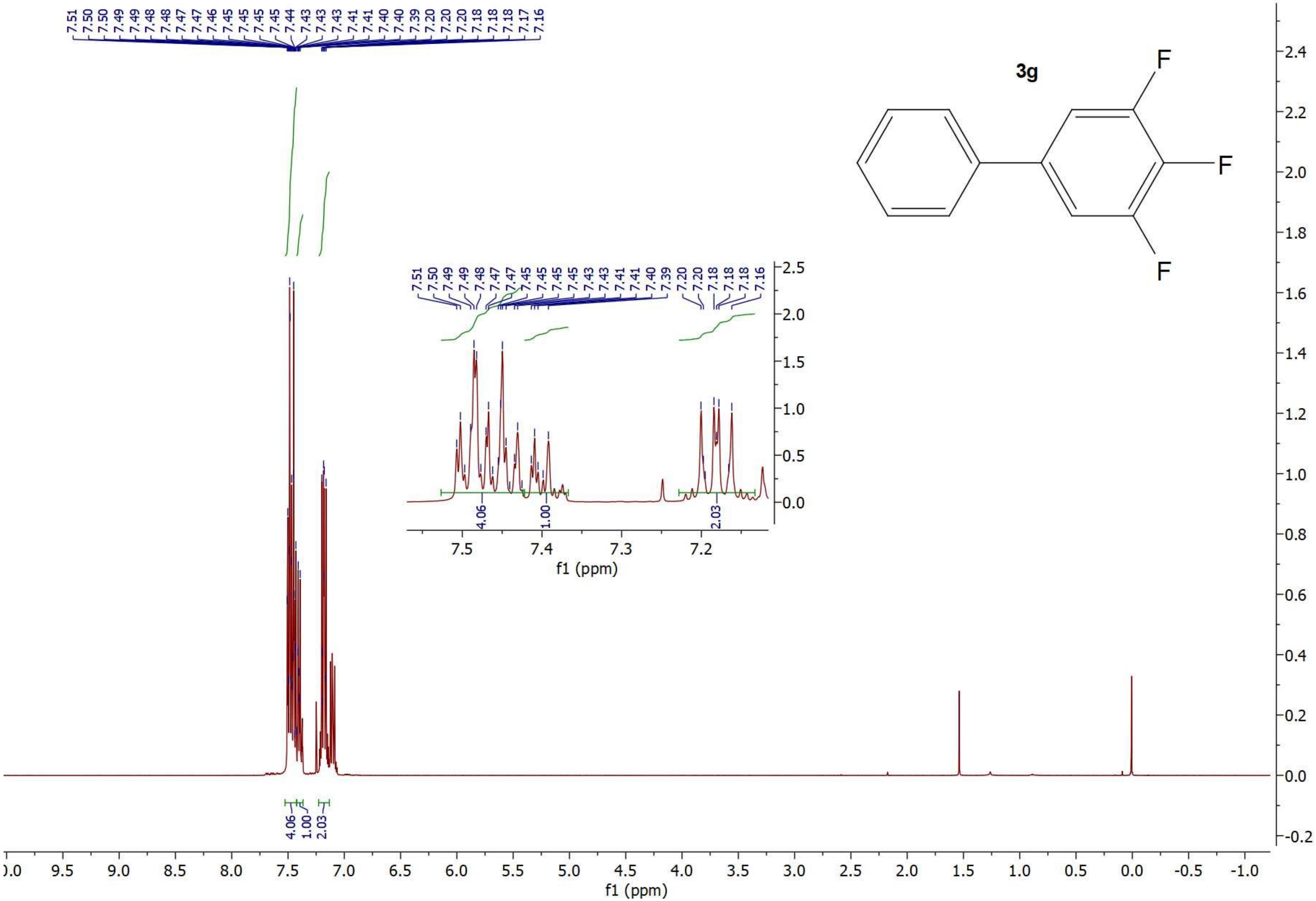
[1]H NMR (400 MHz, Chloroform-*d*) δ 7.69 (s, 4H), 7.63 – 7.58 (m, 2H), 7.51 – 7.38 (m,3H).



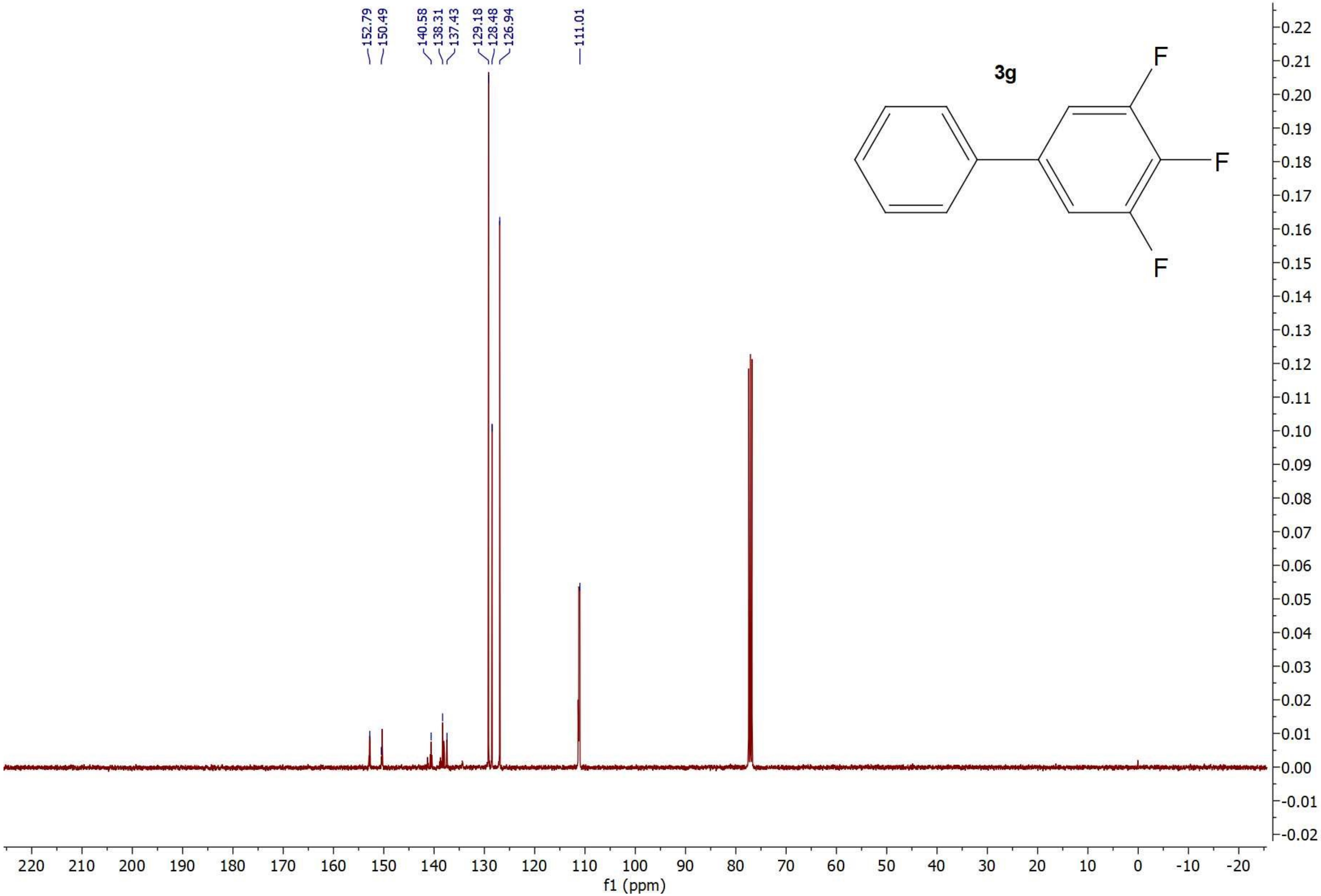
^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 144.84, 139.87, 129.09, 128.29, 127.74, 127.39, 125.83, 125.79, 123.07.



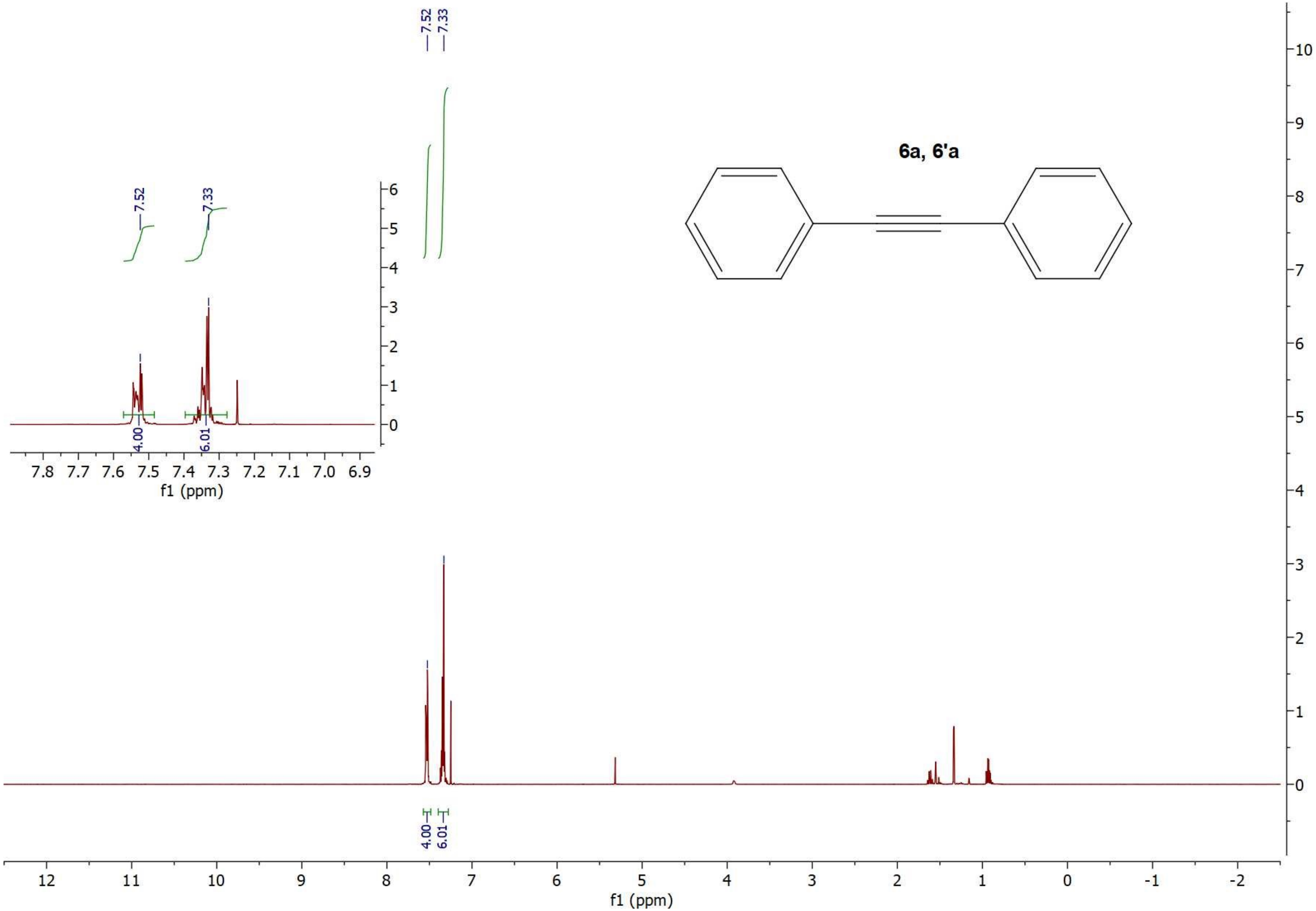
[1]H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.42 (m, 4H), 7.42 – 7.37 (m, 1H), 7.23 – 7.13 (m, 2H).



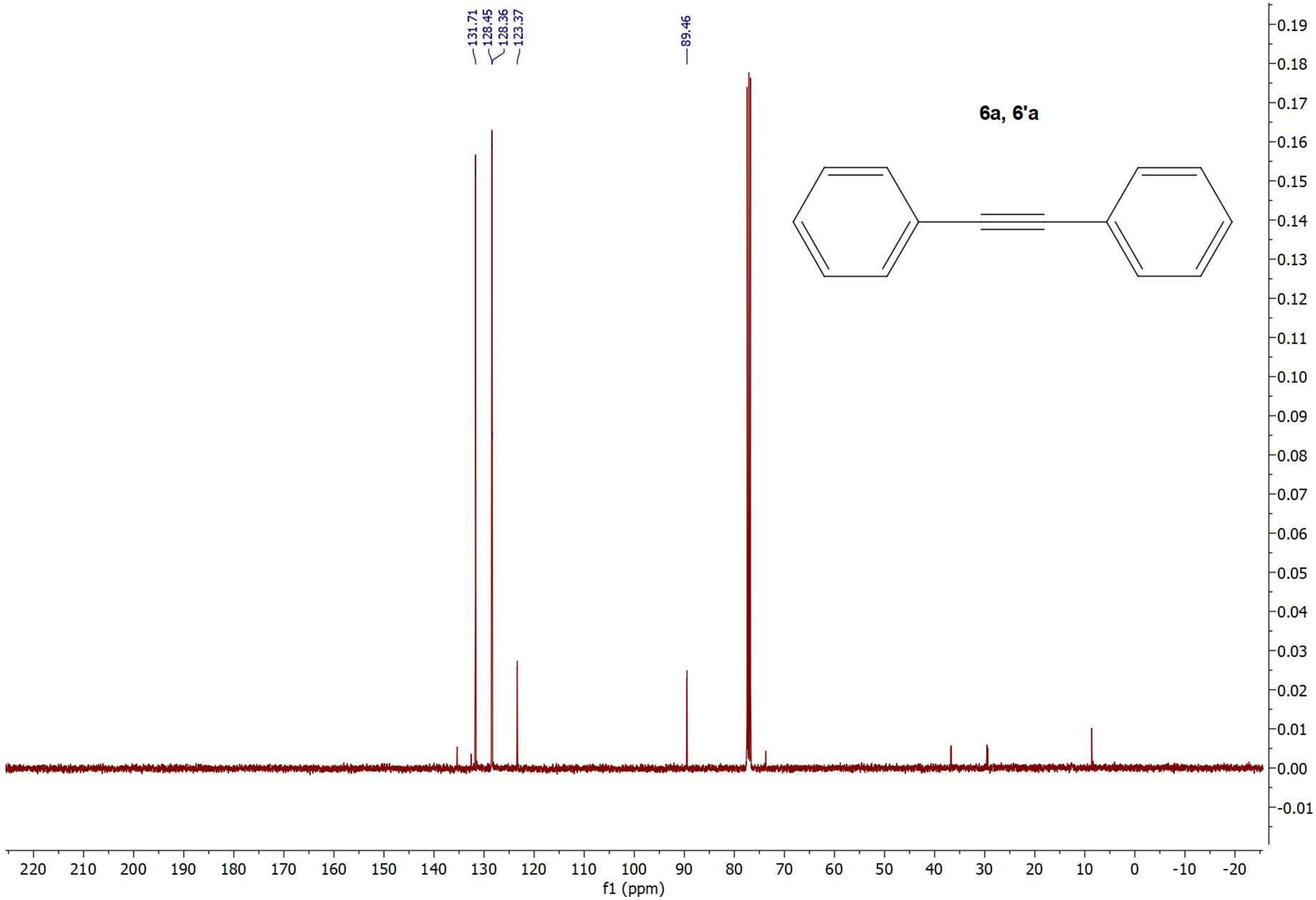
^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 152.79, 150.49, 140.58, 138.31, 137.43, 129.18, 128.48, 126.94, 111.01.



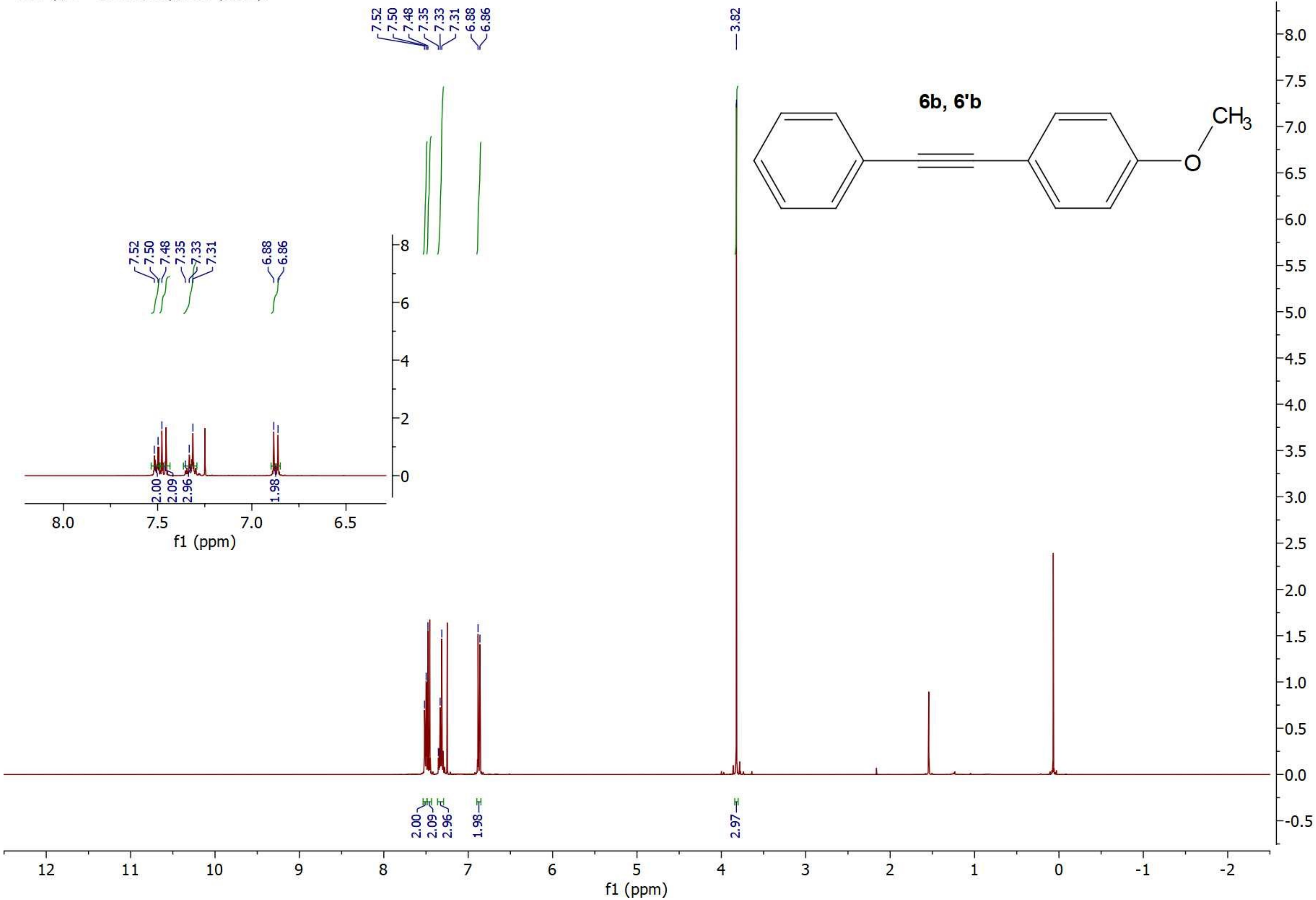
[1]H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.48 (m, 4H), 7.40 – 7.28 (m, 6H).



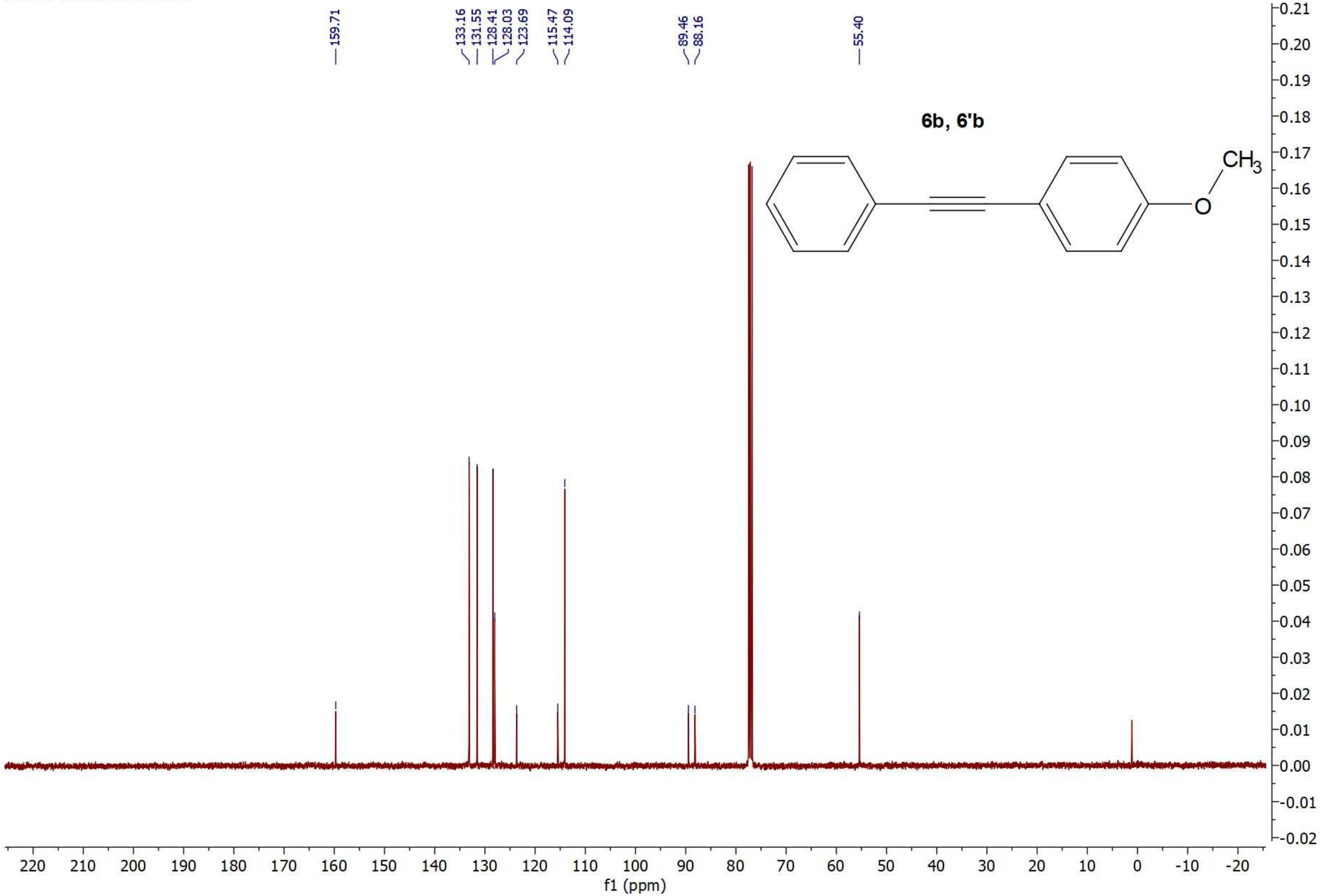
[13]C NMR (101 MHz, Chloroform-*d*) δ 131.71, 128.45, 128.36, 123.37, 89.46



[1]H NMR (400 MHz, Chloroform-*d*) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.48 (s, 2H), 7.36 – 7.29 (m, 3H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H).

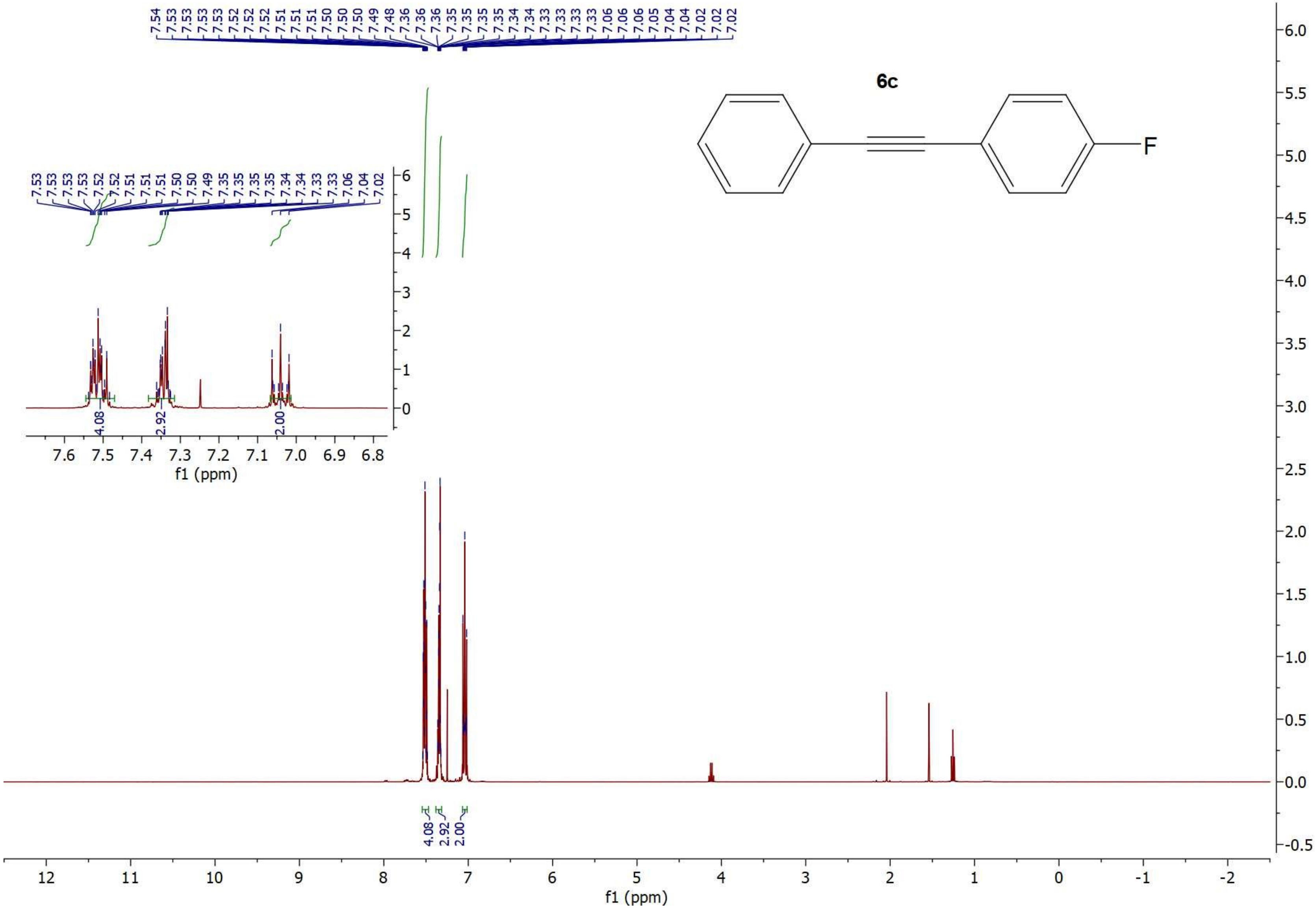


^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.71, 133.16, 131.55, 128.41, 128.03, 123.69, 115.47, 114.09, 89.46, 88.16, 55.40.

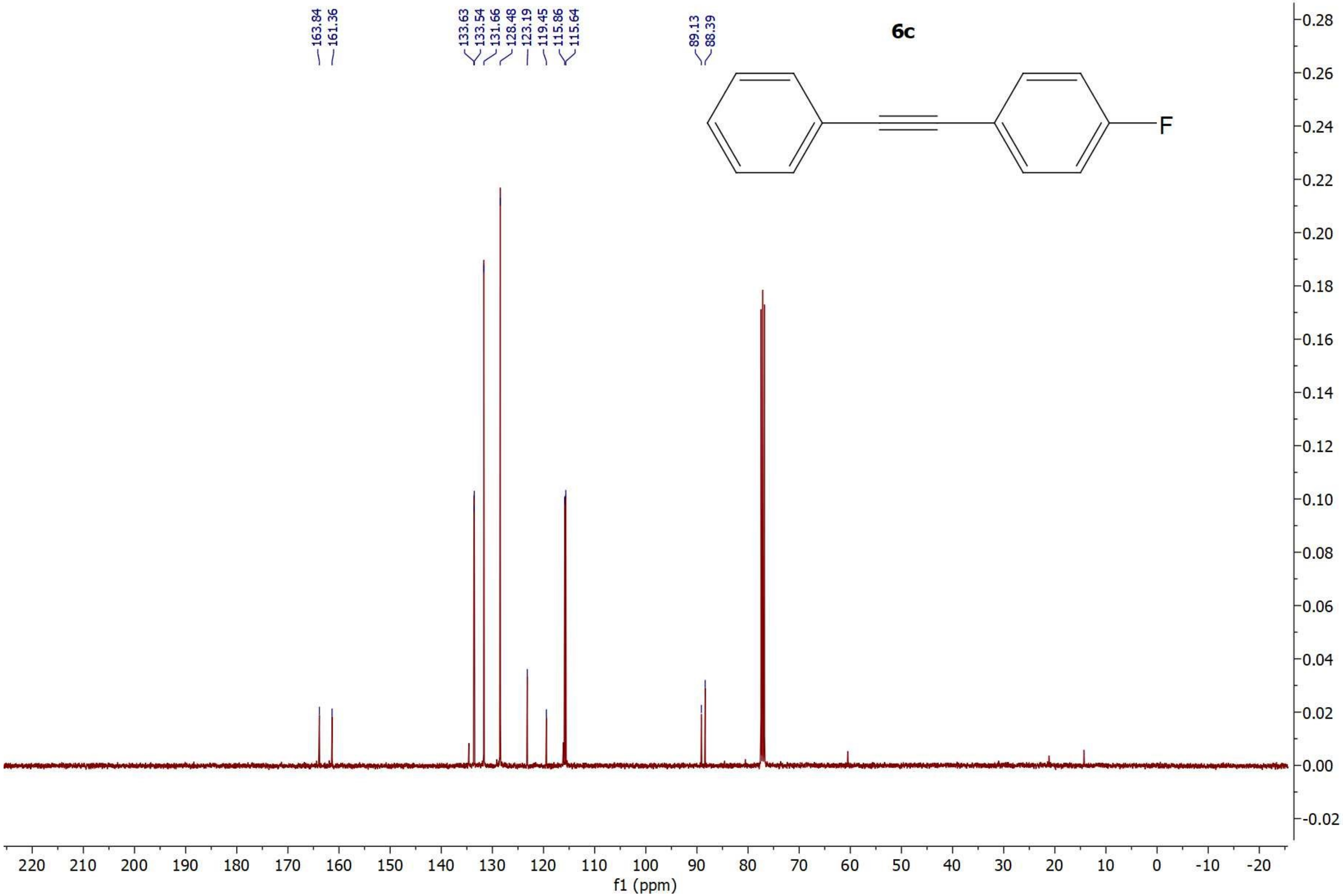


[1]H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.48 (m, 4H), 7.36 – 7.29 (m, 3H), 7.07 – 6.99 (m, 2H).

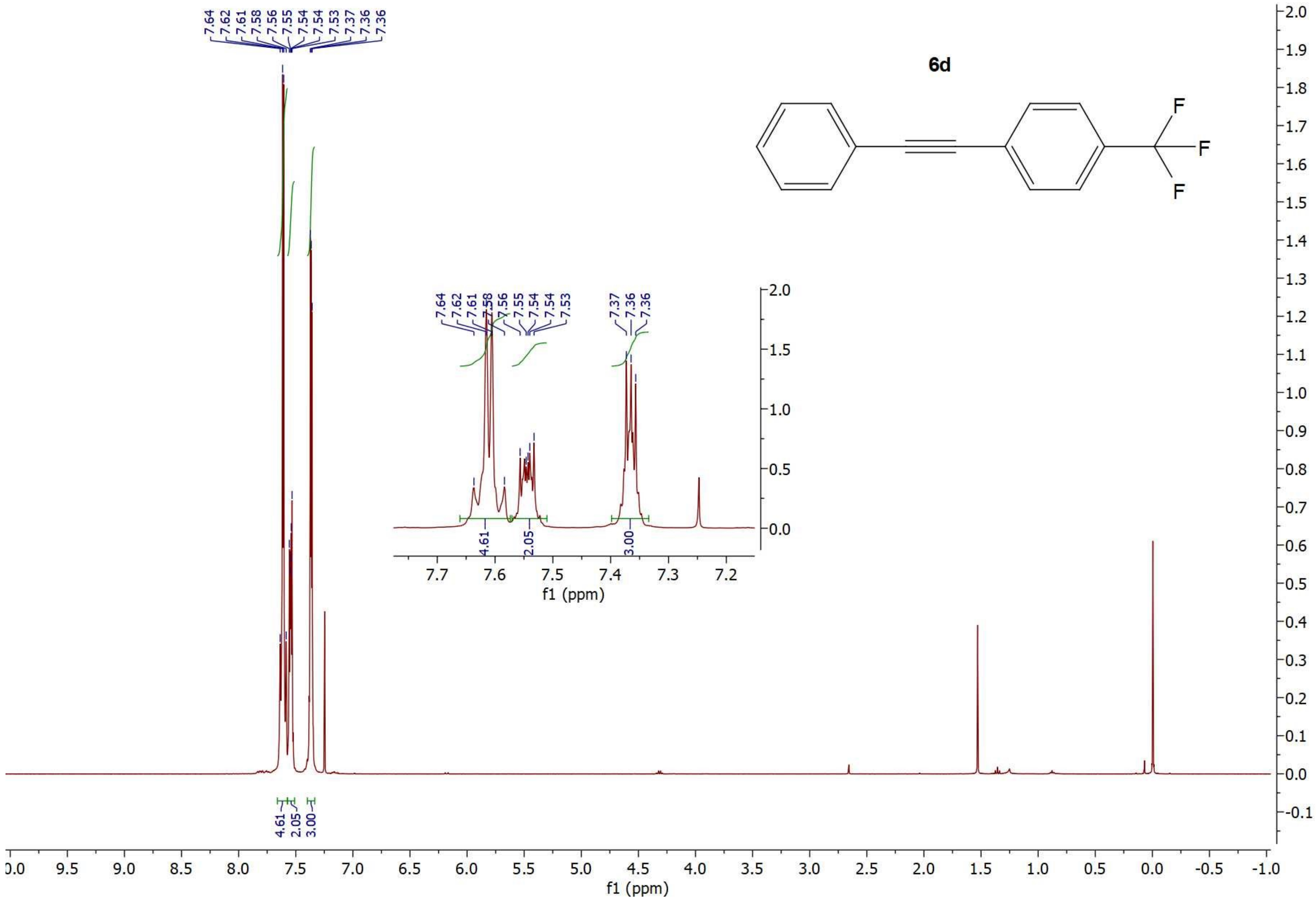
6c



^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.84, 133.63, 133.54, 131.66, 128.48, 123.19, 119.45, 115.86, 115.64, 89.13, 88.39.

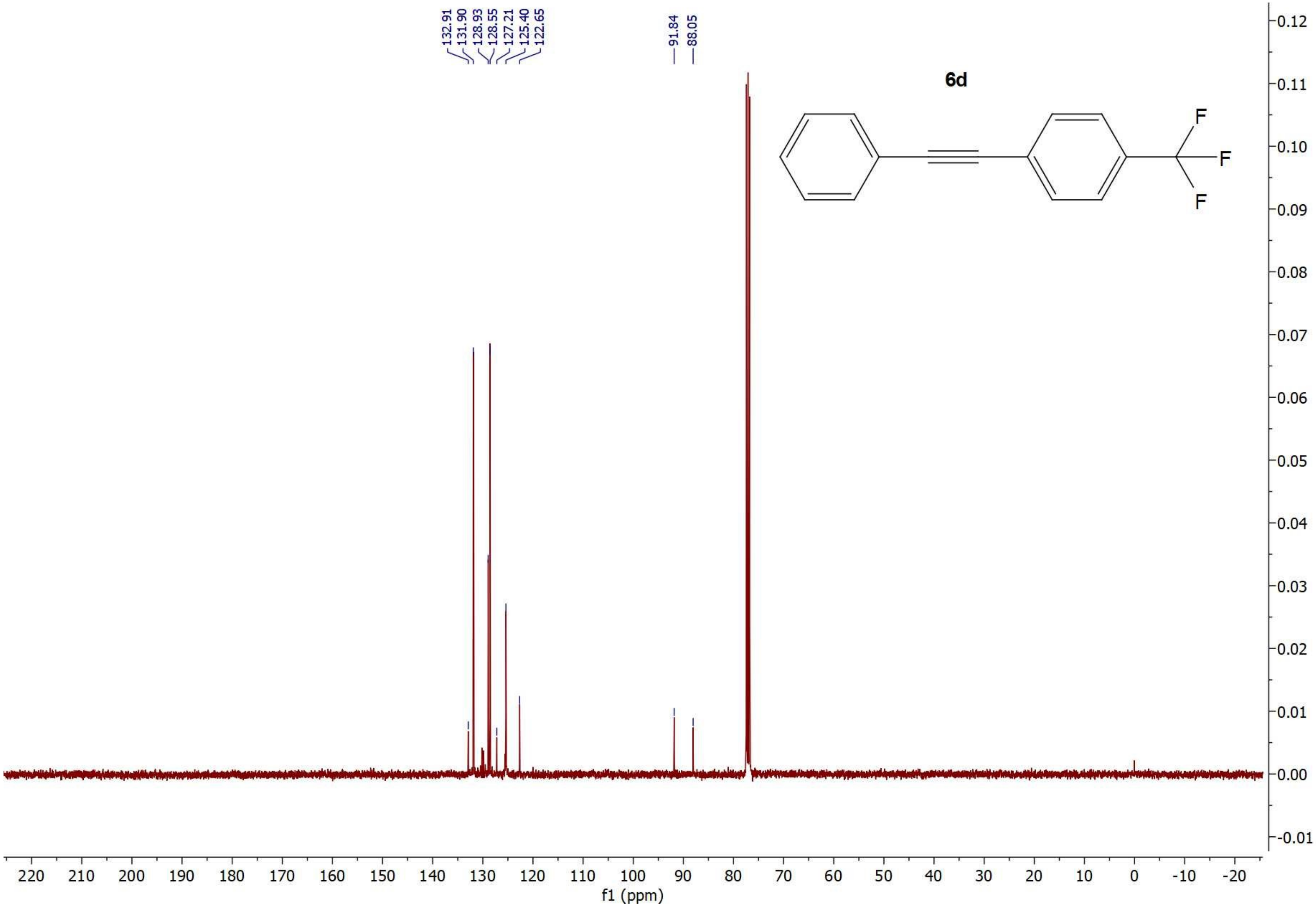


[1]H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.58 (m, 4H), 7.57 – 7.51 (m, 2H), 7.40 – 7.33 (m, 3H).

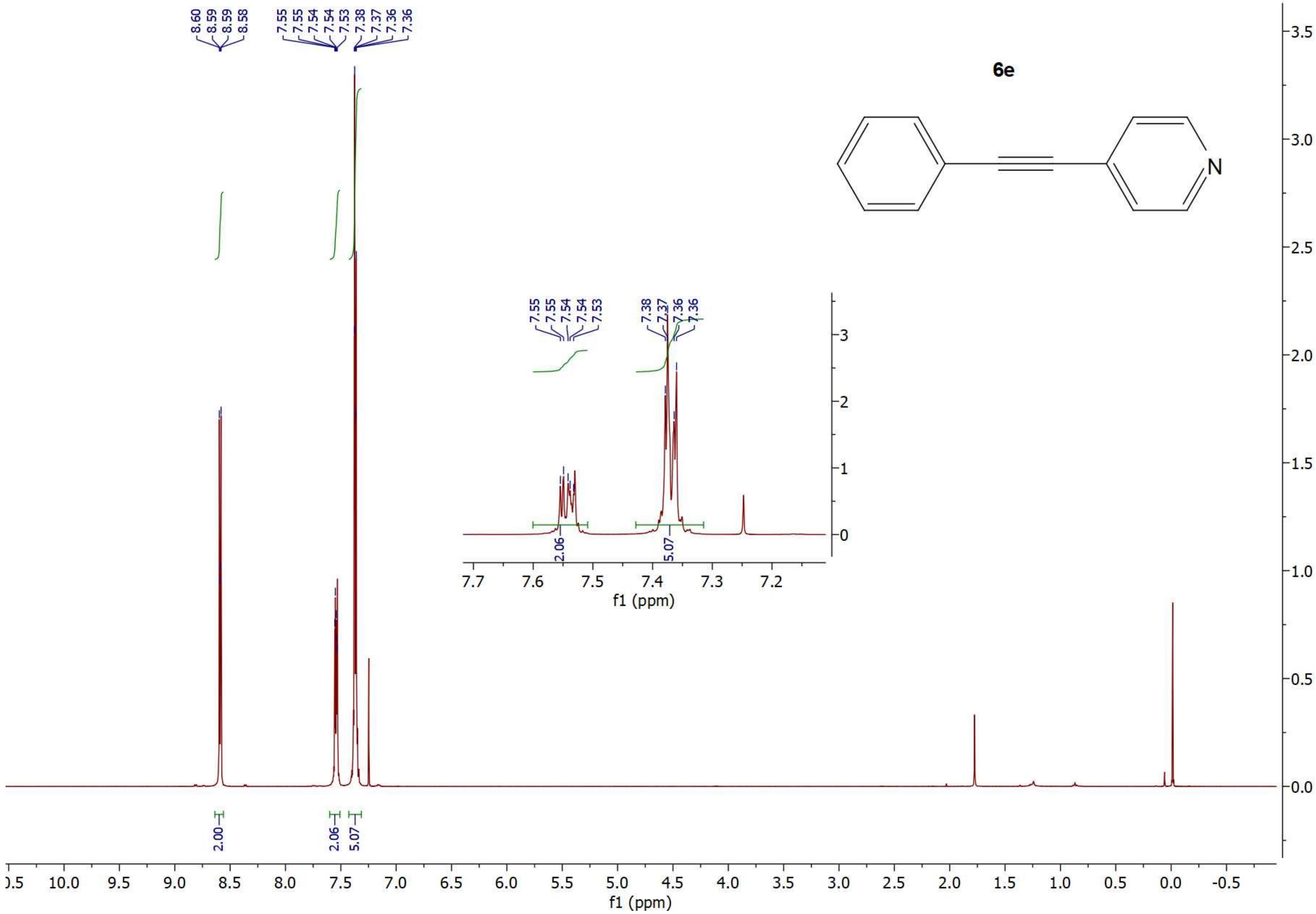


^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 132.91, 131.90, 128.93, 128.55, 127.21, 125.40, 122.65, 91.84, 88.05.

6d

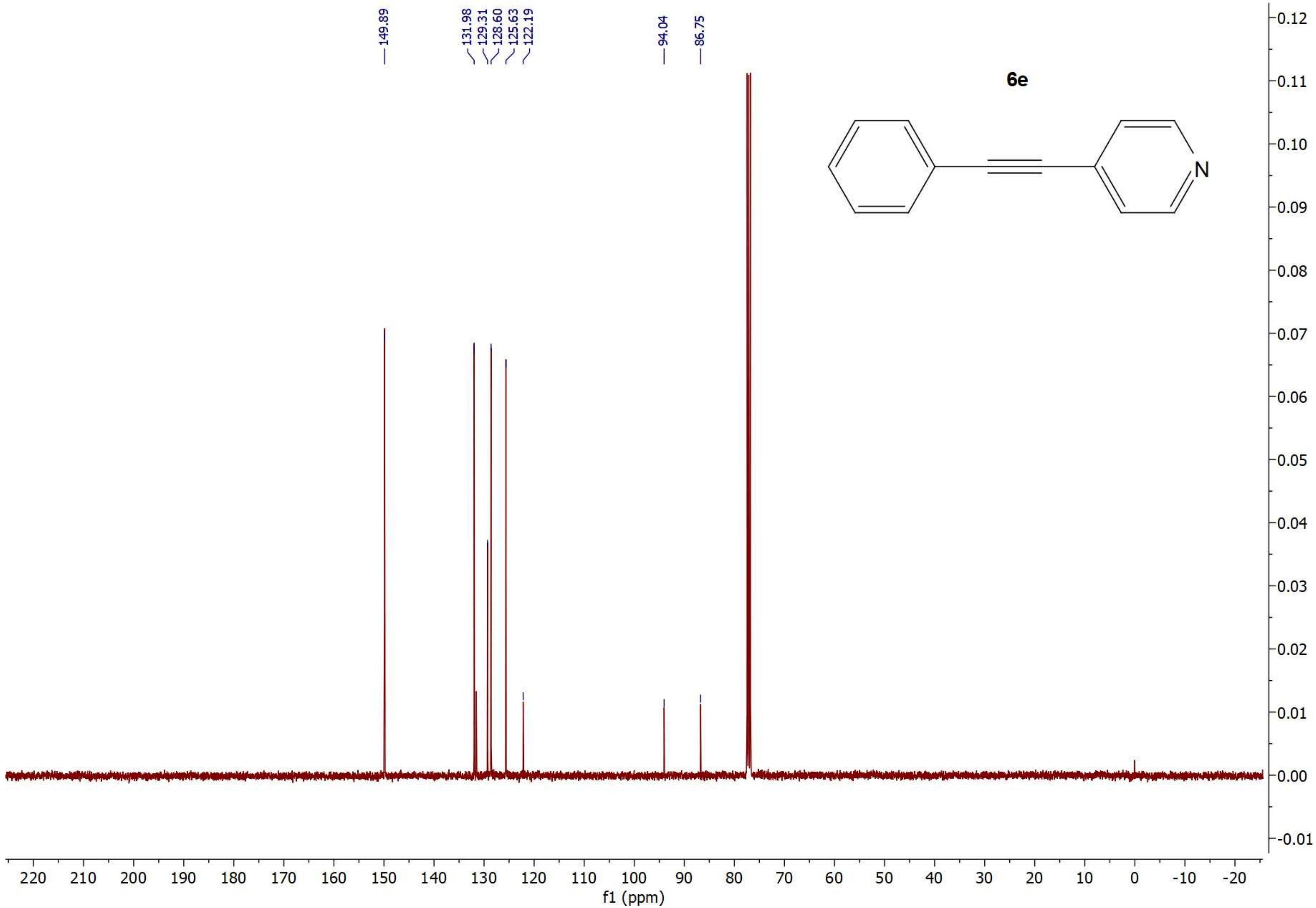


[1]H NMR (400 MHz, Chloroform-*d*) δ 8.62 – 8.56 (m, 2H), 7.58 – 7.50 (m, 2H), 7.41 – 7.31 (m, 5H).

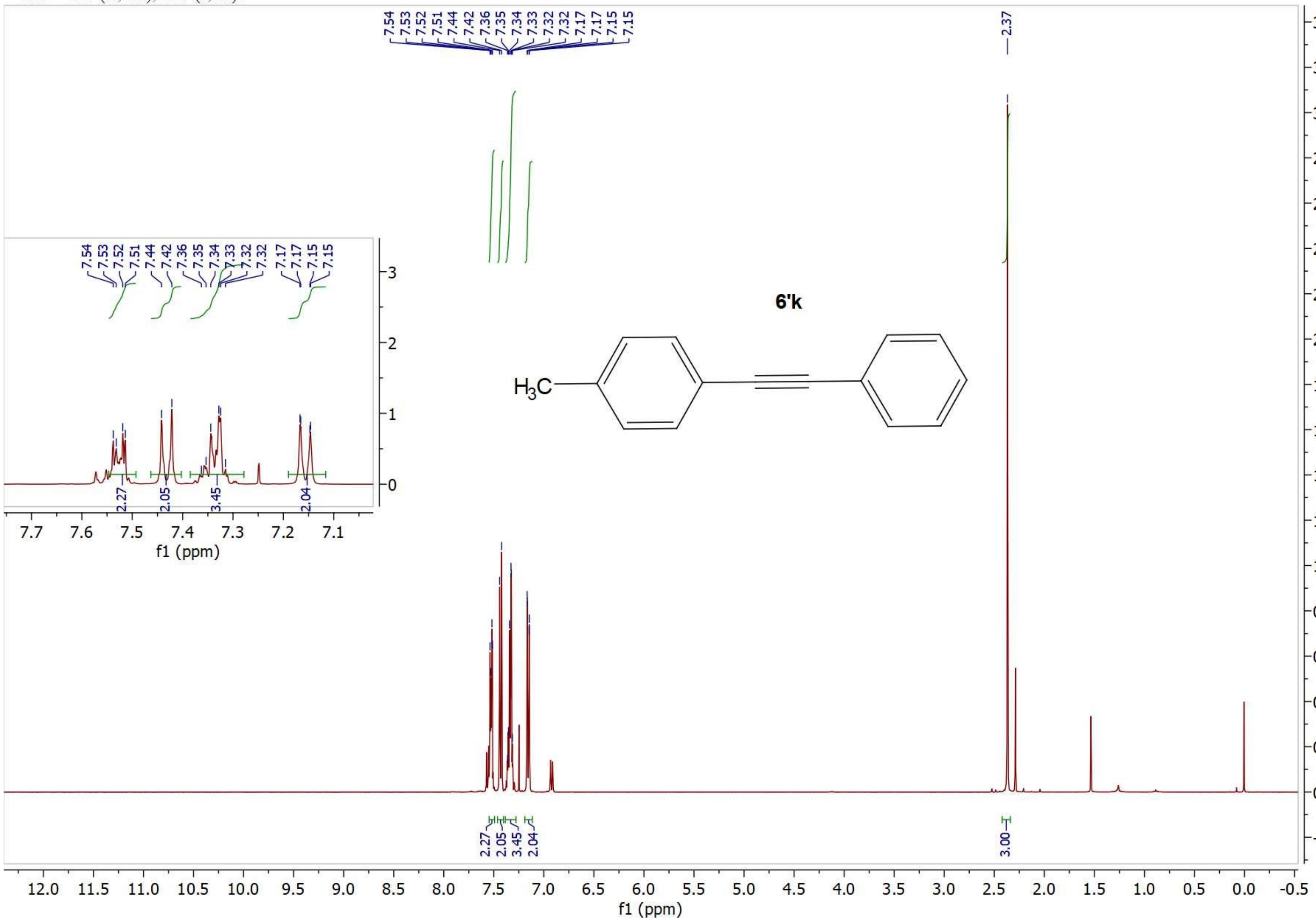


6e

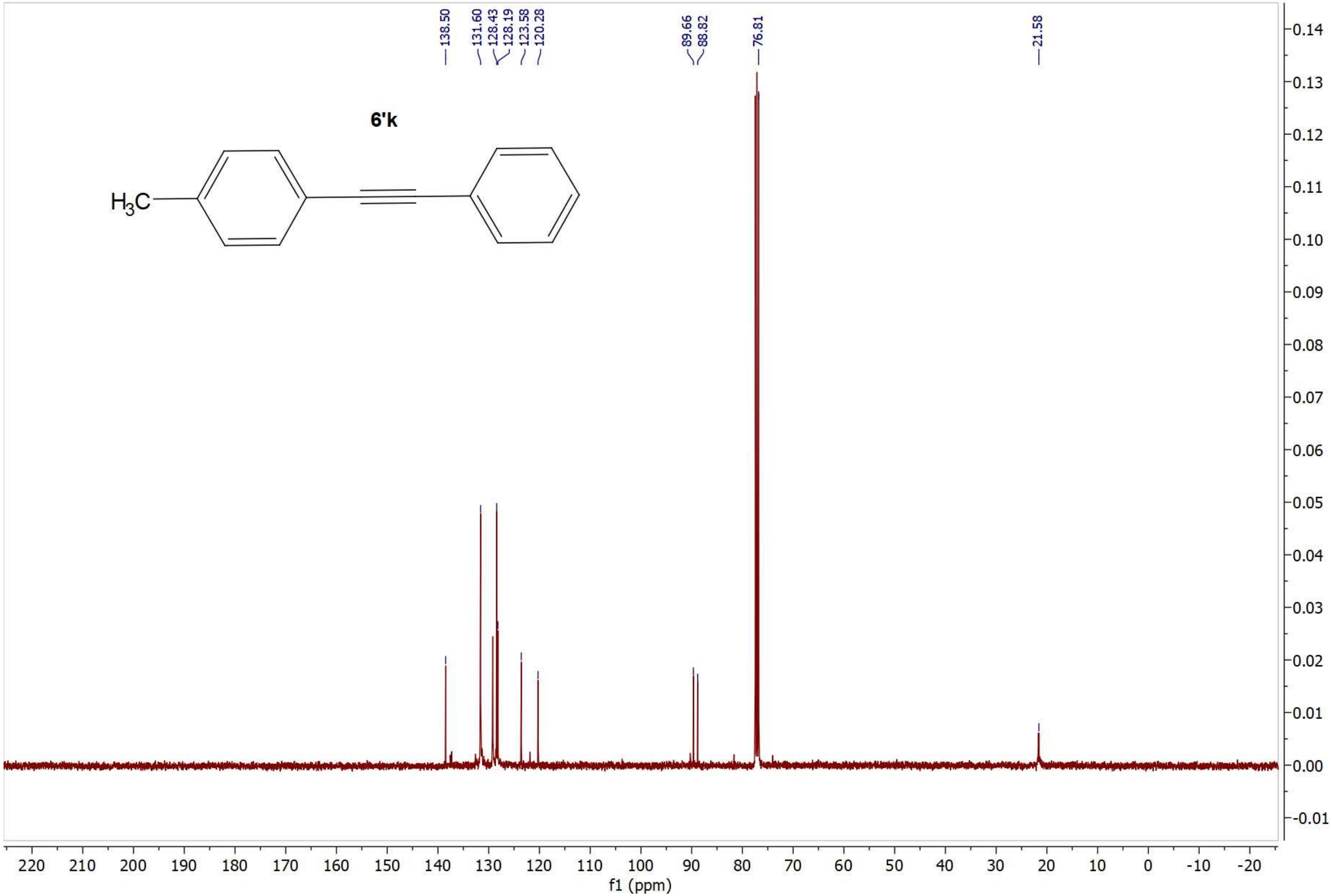
^{13}C NMR (101 MHz, CHLOROFORM-*D*) δ 149.89, 131.98, 129.31, 128.60, 125.63, 122.19, 94.04, 86.75.



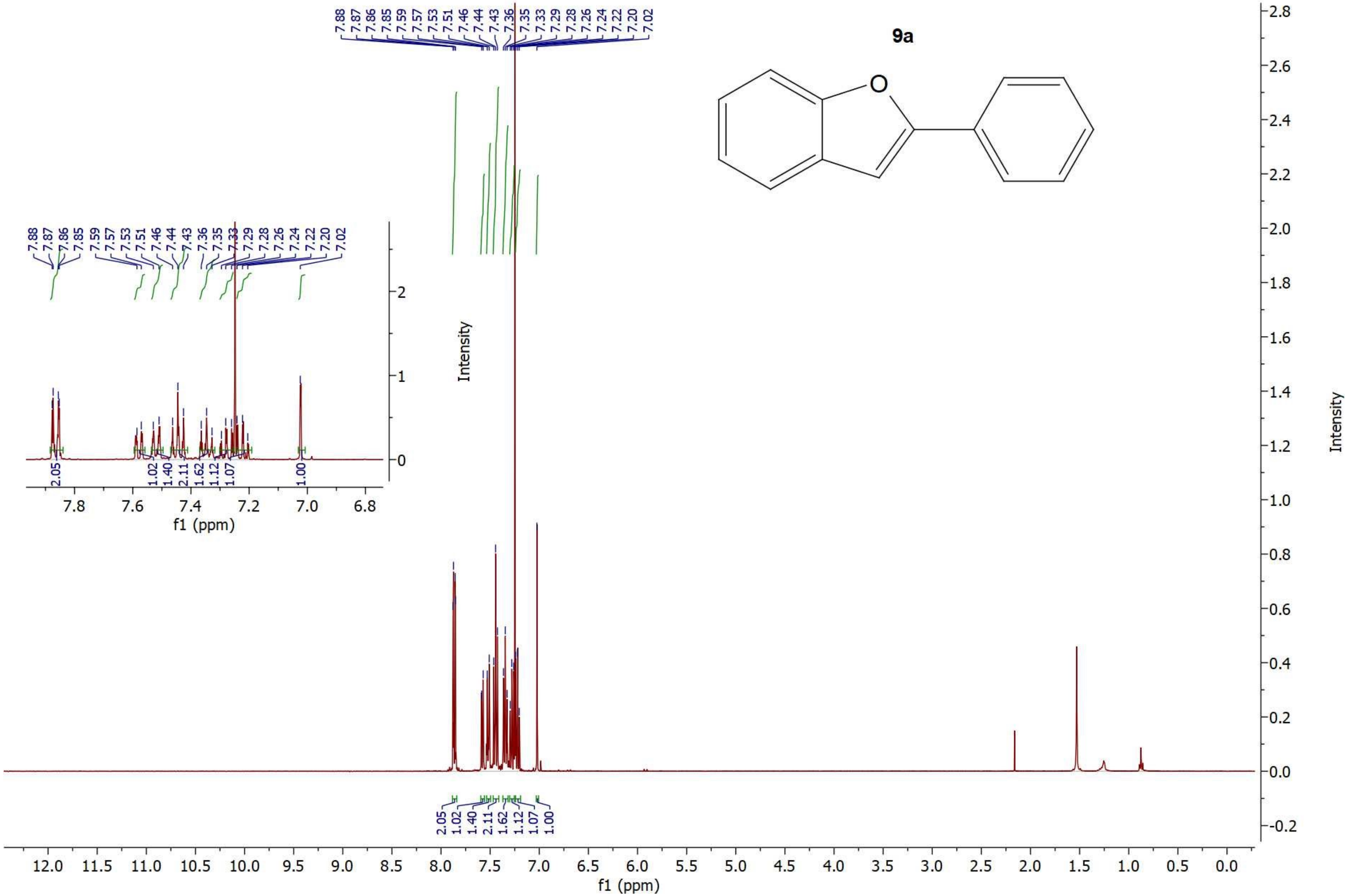
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.50 (m, 2H), 7.47 – 7.38 (m, 2H), 7.37 – 7.27 (m, 3H), 7.20 – 7.10 (m, 2H), 2.37 (s,3H).



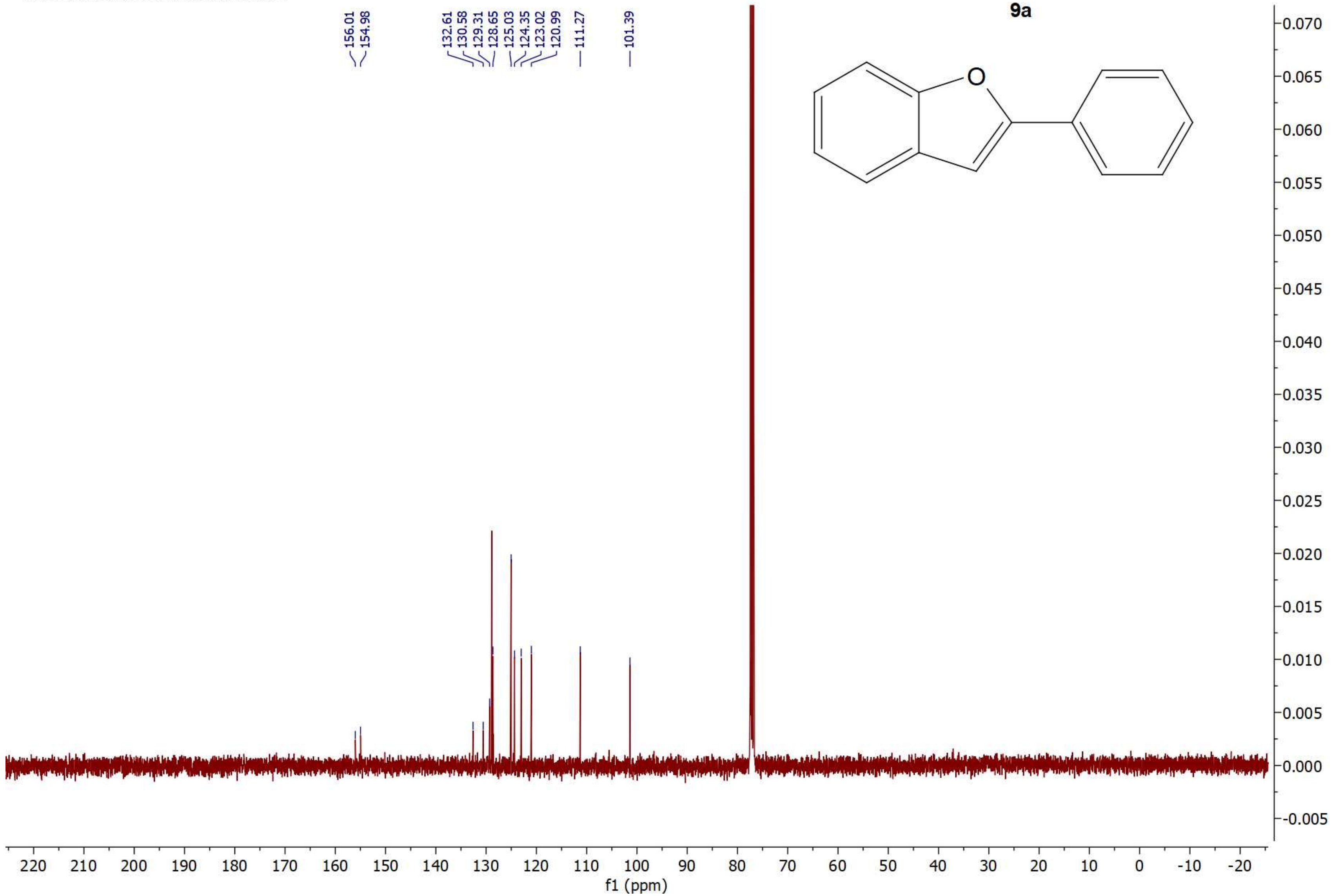
^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.50, 131.60, 128.43, 128.19, 123.58, 120.28, 89.66, 88.82, 21.58.



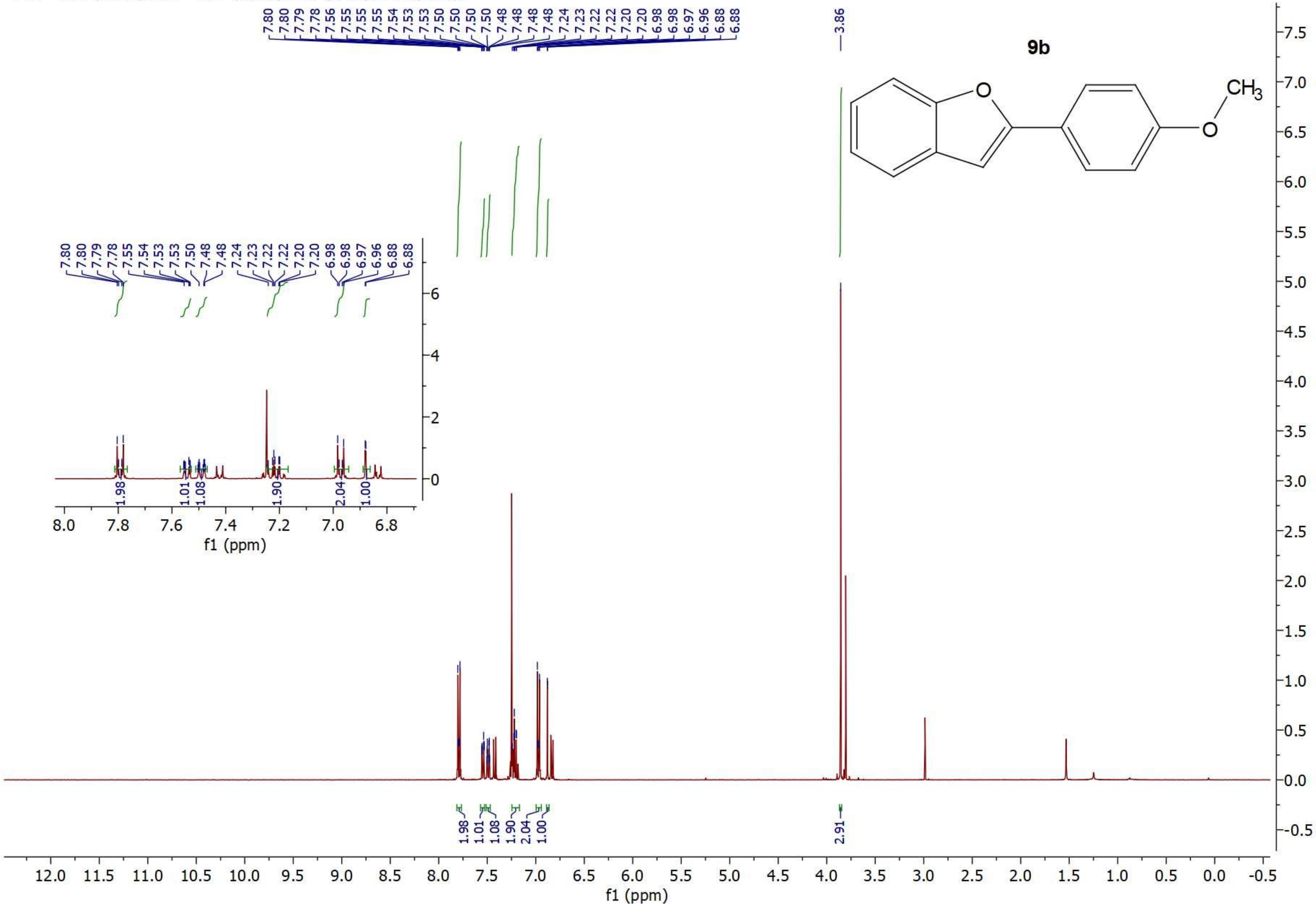
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 – 7.84 (m, 2H), 7.58 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.47 – 7.41 (m, 2H), 7.38 – 7.32 (m, 1H), 7.31 – 7.26 (m, 1H), 7.22 (m, 1H), 7.02 (s, 1H).



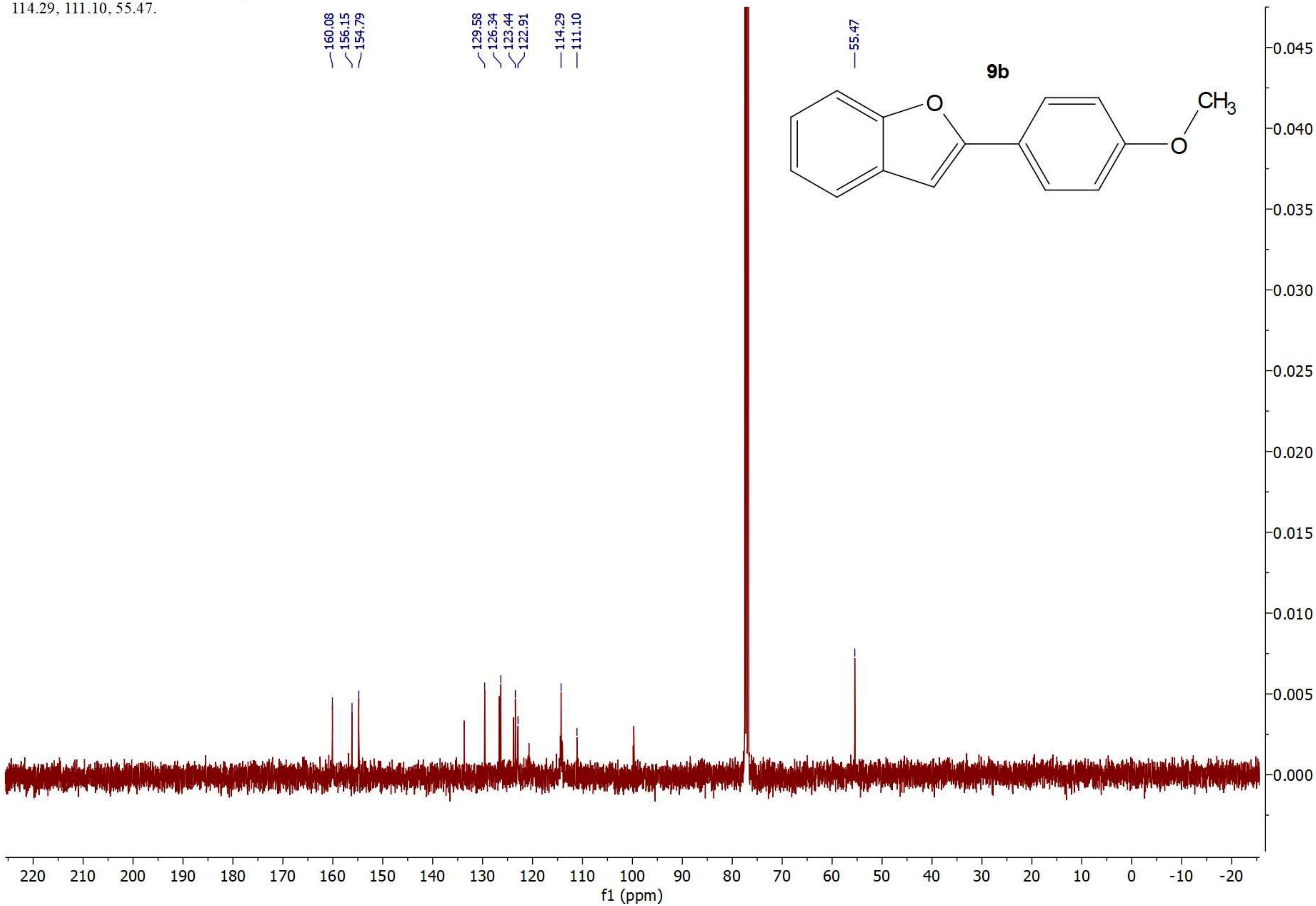
^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.01, 154.98, 132.61, 130.58, 129.31, 128.65, 125.03, 124.35, 123.02, 120.99, 111.27, 101.39.



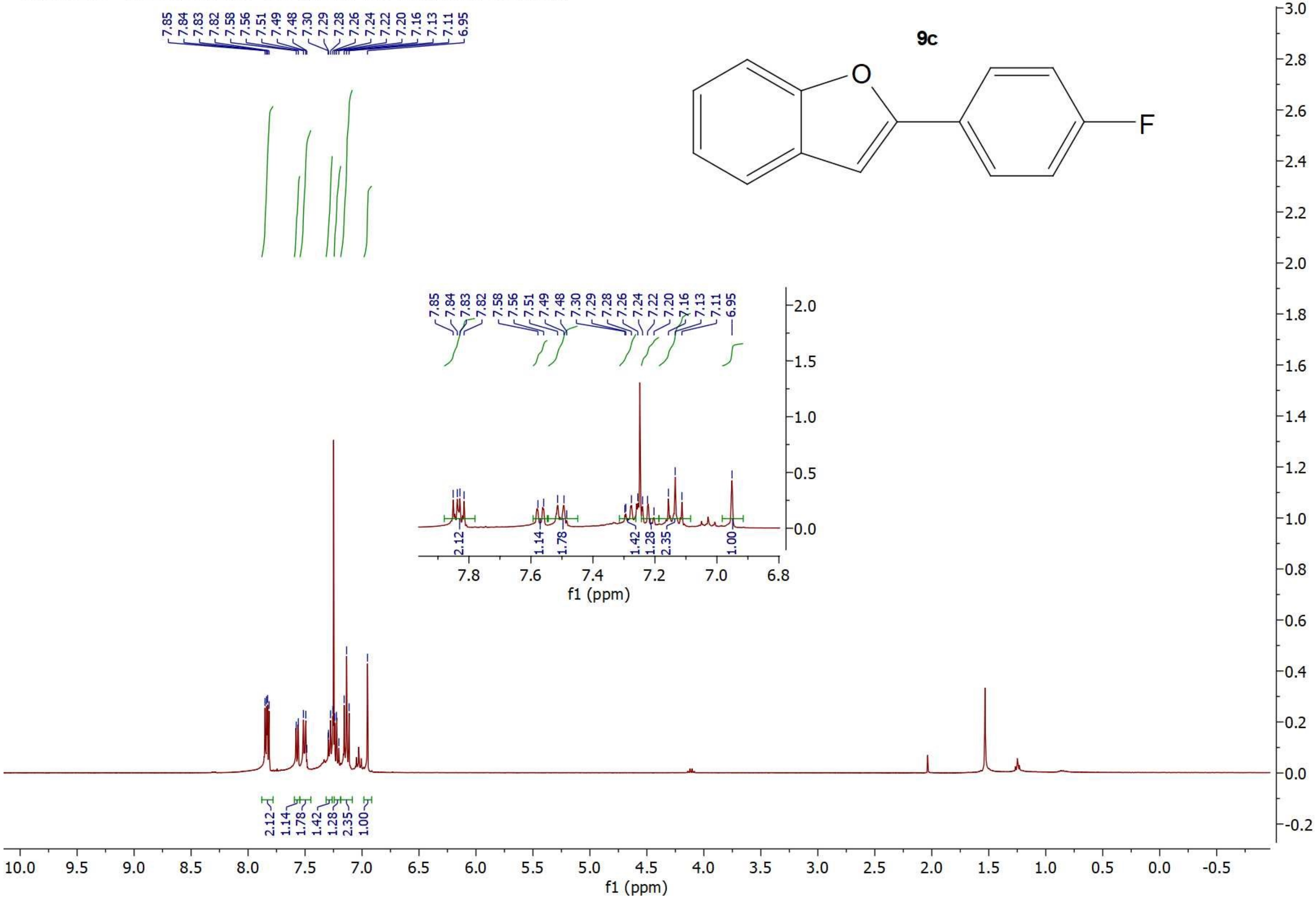
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.81 – 7.76 (m, 2H), 7.56 – 7.52 (m, 1H), 7.50-7.48 (m, 1H), 7.24 – 7.17 (m, 2H), 6.99 – 6.95 (m, 2H), 6.88 (s, 1H), 3.86 (s, 3H).



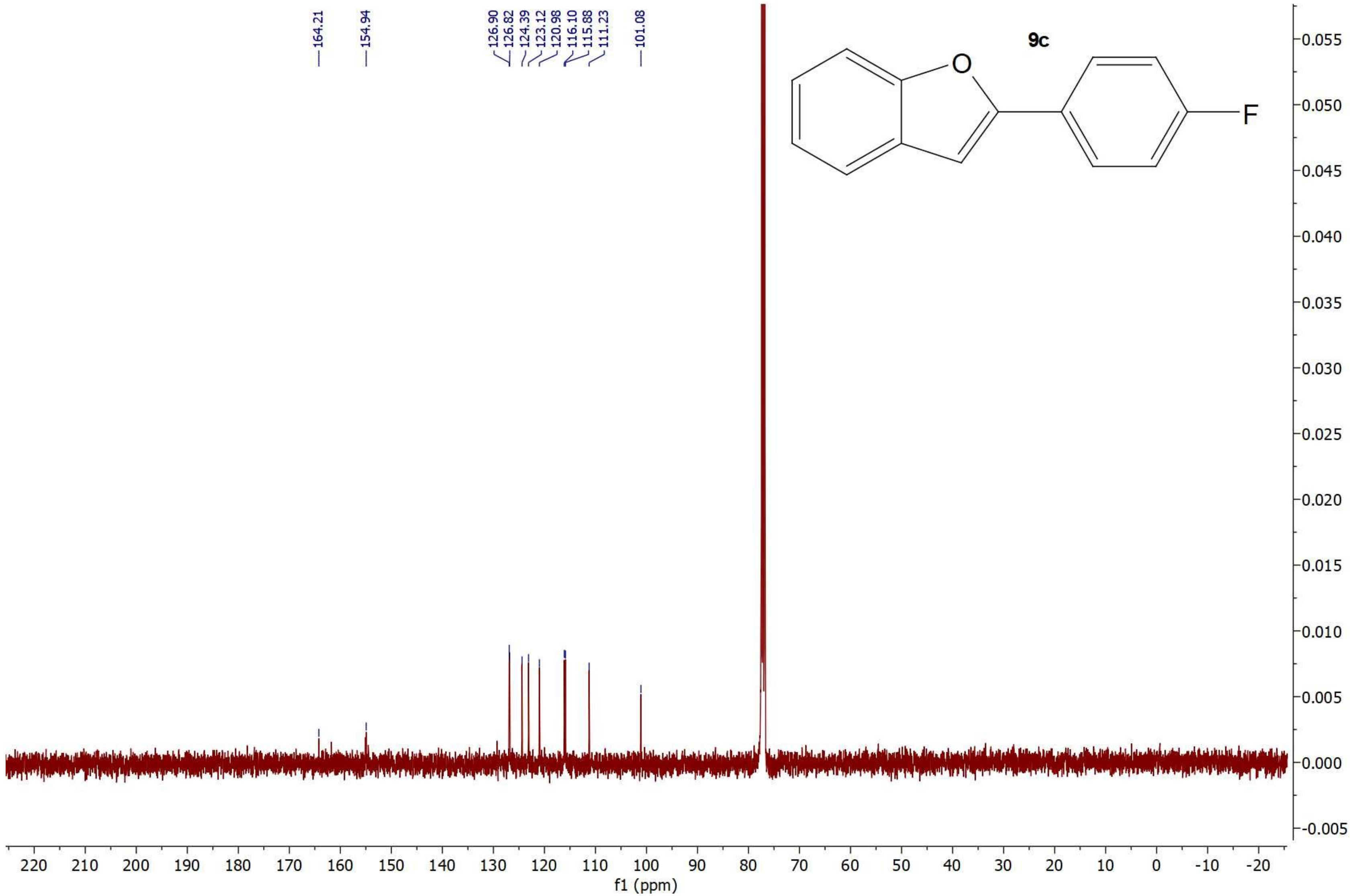
[13]C NMR (101 MHz, Chloroform-*d*) δ 160.08, 156.15, 154.79, 129.58, 126.34, 123.44, 122.91, 114.29, 111.10, 55.47.



[1]H NMR (400 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.51 – 7.48 (m, 1H), 7.30 – 7.28 (m, 1H), 7.26 – 7.20 (m, 1H), 7.16-7.11 (m, 2H), 6.95 (s, 1H)



^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.21, 154.94, 126.90, 126.82, 124.39, 123.12, 120.98, 116.10, 115.88, 111.23, 101.08, 77.42.



S8. References

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