Preparation of Nitriles from Aldehydes using Ammonium Persulfate by means of a Nitroxide-Catalysed Oxidative Functionalisation Reaction

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General Considerations

NMR spectra (^{1}H-, ^{13}C-, and ^{19}F-) were performed at 300 K using either a Brüker Avance Ultra Shield 300 MHz, Brüker DRX-400 400 MHz, or Brüker Avance 500 MHz spectrometer. ^{1}H-NMR spectra were referenced to residual $CHCl_3$ (7.26 ppm) in $CDCl_3$. ^{13}C-NMR spectra were referenced to $CDCl_3$ (77.16 ppm). ^{19}F-NMR spectra were referenced to hexafluorobenzene (-161.64 ppm).[1] Reactions were monitored by an Agilent Technologies 7820A gas chromatograph attached to a 5975 Mass Spectrometer, ^{19}F-NMR, and / or by TLC on silica gel plates (60 Å porosity, 250 μm thickness).

Chemicals

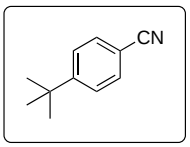
Deuterated chloroform ($CDCl_3$) was purchased from Cambridge Isotope Laboratories. 4-Acetamido-TEMPO (ACT, **2**) was prepared using a previously reported protocol.[2] Ammonium persulfate was purchased from Acros. Sodium persulfate were purchased from Sigma-Aldrich or Acros. Ammonium carbamate was purchased form Alfa Aesar. All the aldehydes and heterocycles used were purchased from Oakwood Chemicals, Sigma-Aldrich, or Alfa Aesar and distilled before use if required.

Procedure for the Oxidation of Aldehydes to Nitriles

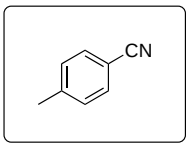
To a 4-dram reaction vial equipped with a stir bar were added the aldehyde (1 mmol, 1 eq), pyridine (565 μL, 7 eq), **2** (63 mg, 0.30 eq), ammonium persulfate (1.141 g, 5 equiv.), and acetonitrile (2 mL). The vial was closed tightly. The contents of the vial were then heated in an aluminium heating block at 50 ℃ for 24 h. Upon completion of the heating step, the reaction mixture was adhered to ~5 g of silica gel. The dry-packed material was gently added atop a silica gel plug. The desired product was eluted off the plug with Et_2O (for products **5a**-**f**, **5i**-**k**) or with a 90:10 by volume mixture of hexanes:EtOAc (for products. **5g**, **5h**, **5l**, **5m**-**o**[*]). The eluent was dried over sodium sulfate and the solvent removed in *vacuo* to afford the product.

[*] For products **5m**-**o**, a wash with 10 mL 0.5 M HCl was needed before drying the elute to remove traces of pyridine.

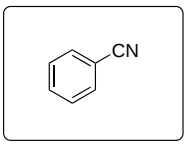
Product characterization



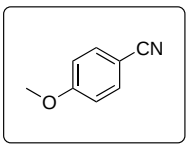
4-(*tert*-butyl)benzonitrile (5a). Obtained as a yellow oil (0.126 g, 79%). **^{1}H-NMR** (300 MHz, Chloroform-d) δ 7.64 – 7.54 (m, 2H), 7.53 – 7.43 (m, 2H), 1.33 (s, 9H).**^{13}C-NMR** (101 MHz, CDCl3) δ 156.79, 132.11, 126.31, 119.29, 109.48, 35.41, 31.09. Spectral data for this compound is consistent with that previously reported.[3]



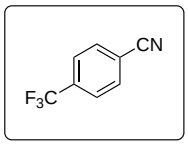
4-methylbenzonitrile (5b). Obtained as a white solid (0.096 g, 82%). **^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.54 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 2.42 (s, 3H).**^{13}C-NMR** (101 MHz, CDCl3) δ 143.81, 132.20, 129.97, 119.28, 109.50, 21.97. Spectral data for this compound is consistent with that previously reported.[3]



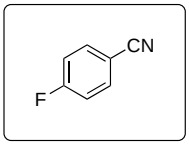
benzonitrile (5c). Obtained as a yellow oil (0.062 g, 60%).**^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.69 – 7.56 (m, 3H), 7.47 (td, J = 7.7, 1.5 Hz, 2H).**^{13}C-NMR** ((101 MHz, CDCl3) δ 132.87, 132.26, 129.23, 118.94, 112.58. Spectral data for this compound is consistent with that previously reported.[3]



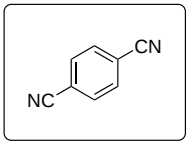
4-methoxybenzonitrile (5d). Obtained as a white solid (0.097 g, 73%).**^{1}H-NMR** (400 MHz, Chloroform-d) δ 7.63 – 7.55 (m, 2H), 6.99 – 6.91 (m, 2H), 3.86 (s, 3H).**^{13}C-NMR** (101 MHz, CDCl3) δ 162.99, 134.13, 119.35, 114.89, 104.15, 77.48, 77.16, 76.84, 55.68. Spectral data for this compound is consistent with that previously reported.[3]



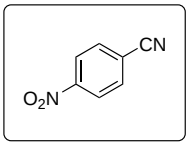
4-(trifluoromethyl)benzonitrile (5e). Obtained as a yellow solid (0.051 g, 30%).**^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.81 (d, *J* = 8.4 Hz, 0H), 7.76 (d, *J* = 8.5 Hz, 1H). **^{13}C-NMR** (126 MHz, Chloroform-*d*) δ 134.75 (q, *J* = 33.2 Hz), 132.84, 126.35 (q, *J* = 3.6 Hz), 123.20 (q, *J* = 272.4 Hz), 117.58, 116.24. **^{19}F-NMR** (376 MHz, $CDCl_3$) δ -63.43. Spectral data for this compound is consistent with that previously reported.[3]



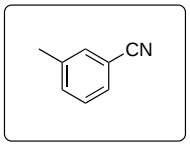
4-fluorobenzonitrile (5f). Obtained as a white solid (0.072 g, 59%) **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.73 – 7.64 (m, 2H), 7.23 – 7.12 (m, 2H).**^{13}C-NMR** (126 MHz, Chloroform-*d*) δ 165.20 (d, *J* = 256.5 Hz), 134.83 (d, *J* = 9.3 Hz), 118.16, 117.01 (d, *J* = 22.7 Hz), 108.73 (d, *J* = 3.5 Hz).**^{19}F-NMR** (376 MHz, Chloroform-*d*) δ -63.12. Spectral data for this compound is consistent with that previously reported.[4]



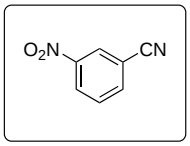
terephthalonitrile (5g). Obtained as a white powder (0.089 g, 69%) **^{1}H-NMR** (400 MHz, Chloroform-*d*) δ 7.80 (s, 4H).**^{13}C-NMR** (101 MHz, Chloroform-*d*) δ 132.94, 117.14, 116.90. Spectral data for this compound is consistent with that previously reported.[3]



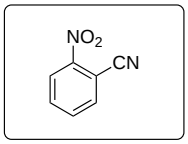
4-nitrobenzonitrile (5h). Obtained as white powder (0.089 g, 60%).**^{1}H-NMR** (300 MHz, Chloroform-*d*) δ 8.41 – 8.31 (m, 2H), 7.94 – 7.84 (m, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 150.11, 133.59, 124.37, 118.40, 116.90. Spectral data for this compound is consistent with that previously reported.[3]



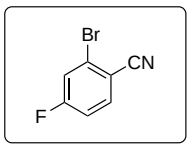
3-methylbenzonitrile (5i). Obtained as a yellow oil (0.093 g, 79%).**[1]H-NMR** (300 MHz, Chloroform-d) δ 7.49 – 7.44 (m, 2H), 7.41 (dt, J = 7.6, 2.0 Hz, 1H), 7.38 – 7.31 (m, 1H), 2.39 (s, 3H). **[13]C-NMR** (75 MHz, $CDCl_3$) δ 139.32, 133.75, 132.59, 129.38, 129.09, 119.16, 112.31, 21.25. Spectral data for this compound is consistent with that previously reported.[5]



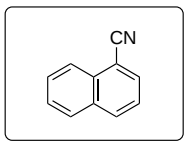
3-nitrobenzonitrile (5j). Obtained as a white powder (0.103 g, 70%). **[1]H-NMR** (300 MHz, Chloroform-*d*) δ 8.54 (t, *J* = 1.9 Hz, 1H), 8.48 (ddd, *J* = 8.4, 2.3, 1.1 Hz, 1H), 8.00 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H). **[13]C-NMR** (101 MHz, $CDCl_3$) δ 148.38, 137.72, 130.79, 127.65, 127.34, 116.64, 114.26. Spectral data for this compound is consistent with that previously reported.[3]



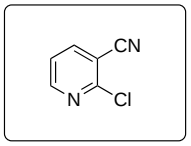
2-nitrobenzonitrile (5k). Obtained as a white solid (0.109 g, 74%).**[1]H-NMR** (400 MHz, Chloroform-*d*) δ 8.39 – 8.30 (m, 1H), 7.98 – 7.89 (m, 1H), 7.88 – 7.79 (m, 2H). **[13]C (75 MHz, $CDCl_3$)** δ 148.57, 135.69, 134.52, 133.91, 125.64, 115.06, 108.01, 77.58, 77.16, 76.74. Spectral data for this compound is consistent with that previously reported.[6]



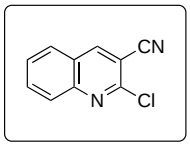
2-bromo-4-fluorobenzonitrile (5l). Obtained as a white solid (0.127 g, 47%).**[1]H-NMR** (400 MHz, Chloroform-*d*) δ 7.68 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.16 (ddd, *J* = 8.7, 7.7, 2.4 Hz, 1H). **[13]C-NMR** (126 MHz, Chloroform-*d*) δ 164.66 (d, *J* = 261.3 Hz), 136.16 (d, *J* = 9.8 Hz), 126.91 (d, *J* = 10.3 Hz), 121.39 (d, *J* = 25.3 Hz), 116.59, 115.83 (d, *J* = 22.3 Hz), 112.48 (d, *J* = 3.5 Hz). **[19]F-NMR** (376 MHz, Chloroform-*d*) δ -100.36 (td, *J* = 7.8, 5.5 Hz). Spectral data for this compound is consistent with that previously reported.[3]



1-napthonitrile (5m). Obtained as a yellow oil (0.079 g, 52%). **[1]H-NMR** (300 MHz, Chloroform-d) δ 8.25 (dd, J = 8.1, 1.3 Hz, 1H), 8.09 (dt, J = 8.4, 1.1 Hz, 1H), 8.03 – 7.88 (m, 2H), 7.67 (dddd, J = 23.6, 8.1, 6.9, 1.3 Hz, 2H), 7.53 (dd, J = 8.3, 7.2 Hz, 1H). **[13]C-NMR** (101 MHz, $CDCl_3$) δ 133.42, 133.09, 132.78, 132.53, 128.80, 128.75, 127.70, 125.32, 125.07, 117.95, 110.37. Spectral data for this compound is consistent with that previously reported.[3]



2-chloro-3-pyridinecarbonitrile (5n). Obtained as an off-white solid (0.116 g, 84%).**[1]H-NMR** (300 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 4.9, 1.9 Hz, 1H), 8.02 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.40 (dd, *J* = 7.7, 4.9 Hz, 1H). **[13]C-NMR** (101 MHz, $CDCl_3$) δ 152.98, 142.70, 122.32, 114.70, 111.12. Spectral data for this compound is consistent with that previously reported.[3]



2-chloroquinoline-3-carbonitrile (5o). Obtained as a white solid (0.183 g, 97%)**[1]H-NMR** (400 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 8.08 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.92 (td, *J* = 8.5, 1.6 Hz, 2H), 7.70 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H). **[13]C-NMR** (101 MHz, $CDCl_3$) δ 148.34, 148.31, 144.87, 133.95, 128.97, 128.75, 128.12, 125.19, 115.10, 107.97. Spectral data for this compound is consistent with that previously reported.[3]

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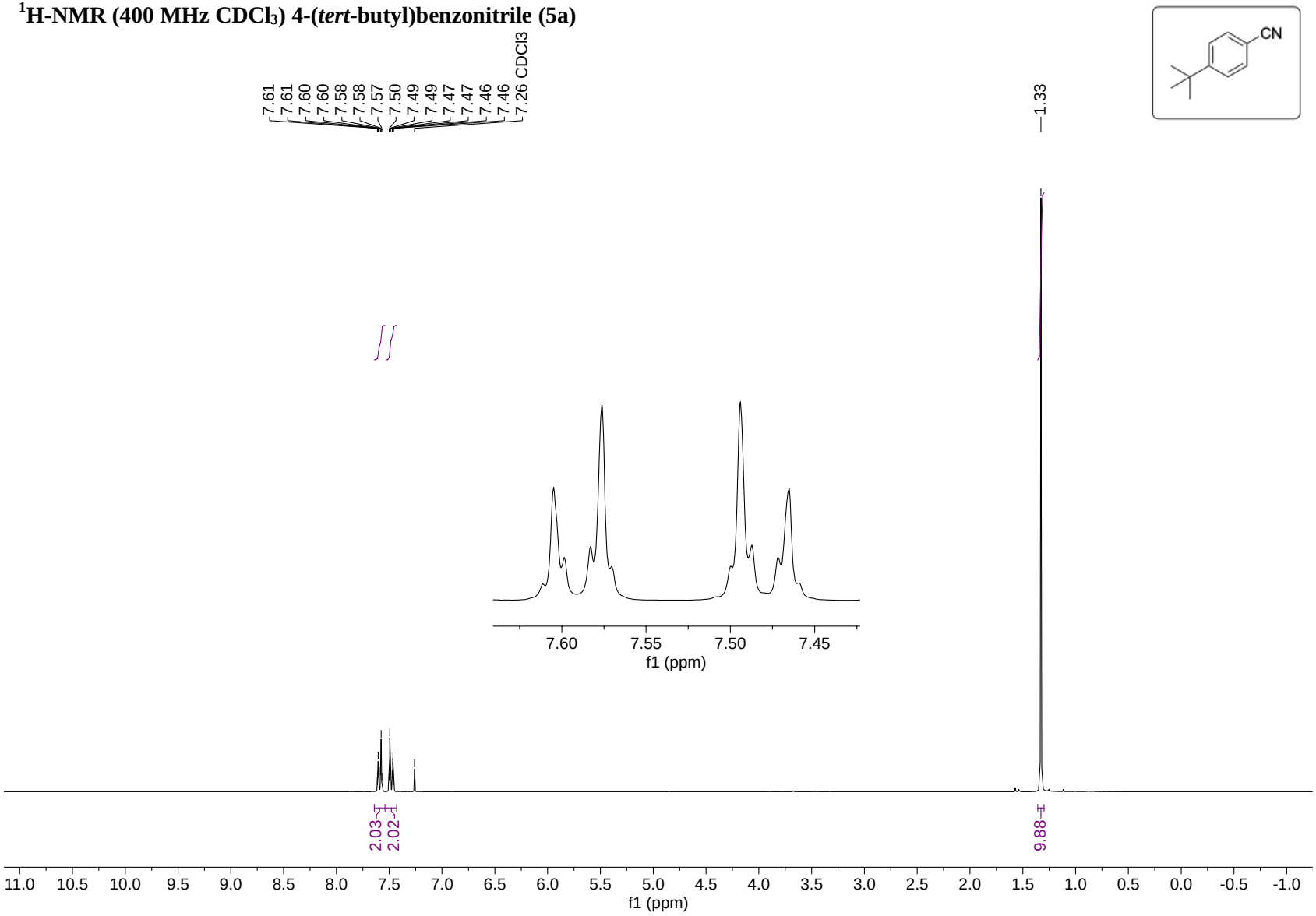
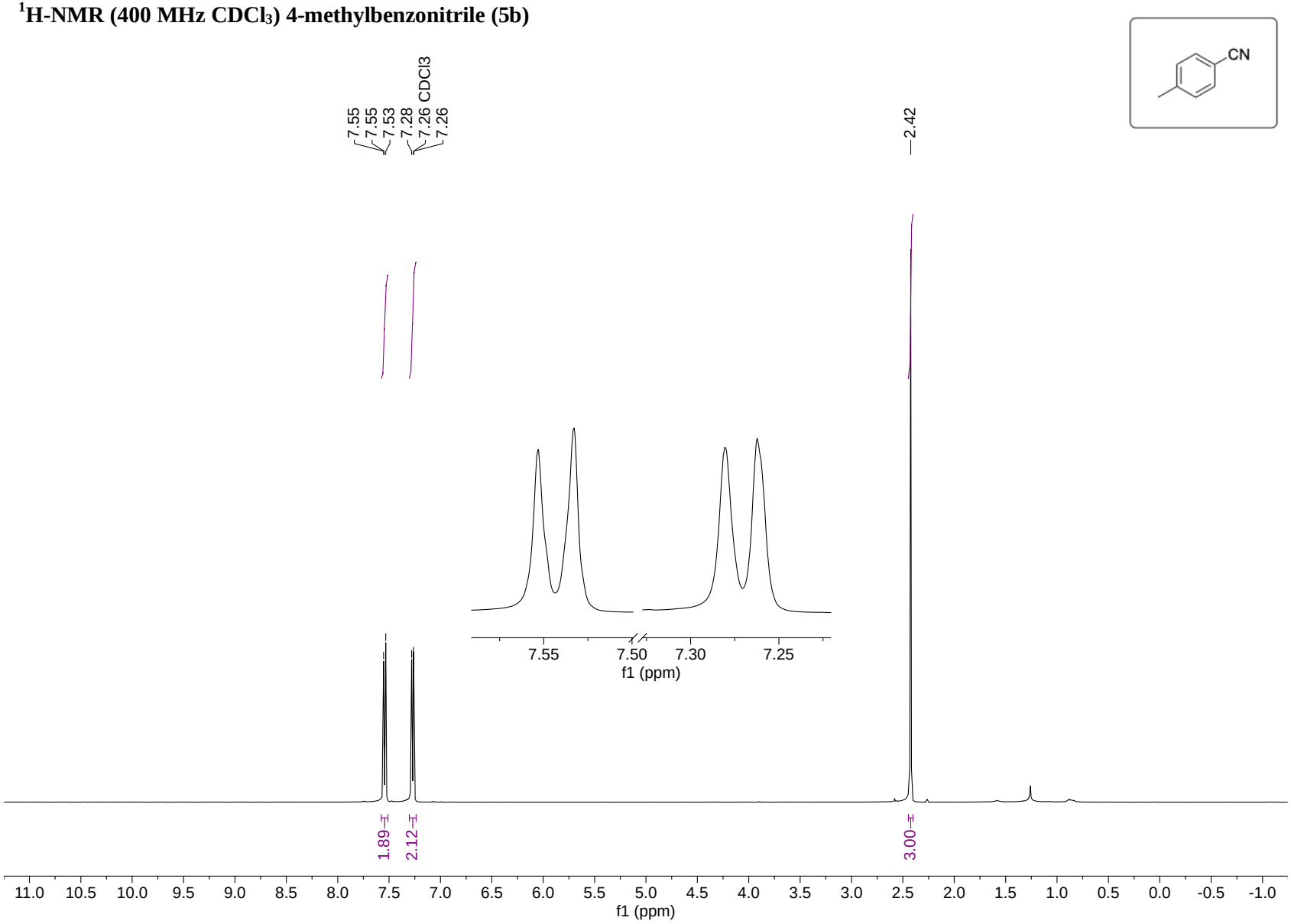
^{1}H-, ^{13}C- and ^{19}F-NMR Spectra of Compounds Prepared

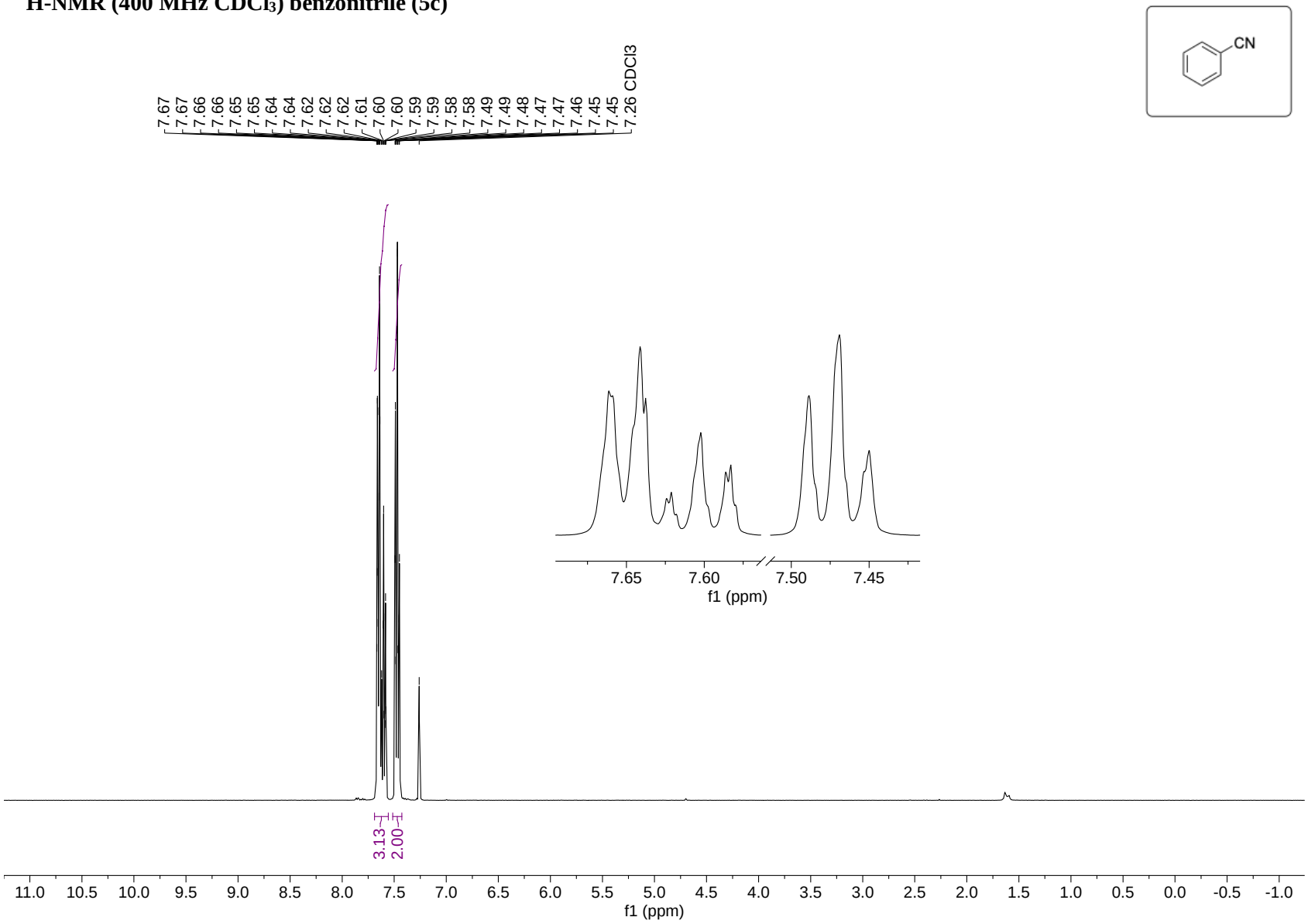
^{1}H-NMR (400 MHz $CDCl_3$) 4-(*tert*-butyl)benzonitrile (5a)



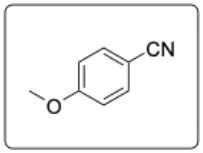
^{1}H-NMR (400 MHz $CDCl_3$) 4-methylbenzonitrile (5b)



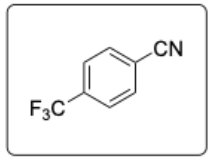
^{1}H-NMR (400 MHz $CDCl_3$) benzonitrile (5c)



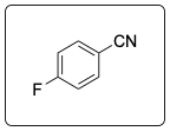
^{1}H-NMR (400 MHz $CDCl_3$) 4-methoxybenzonitrile (5d)

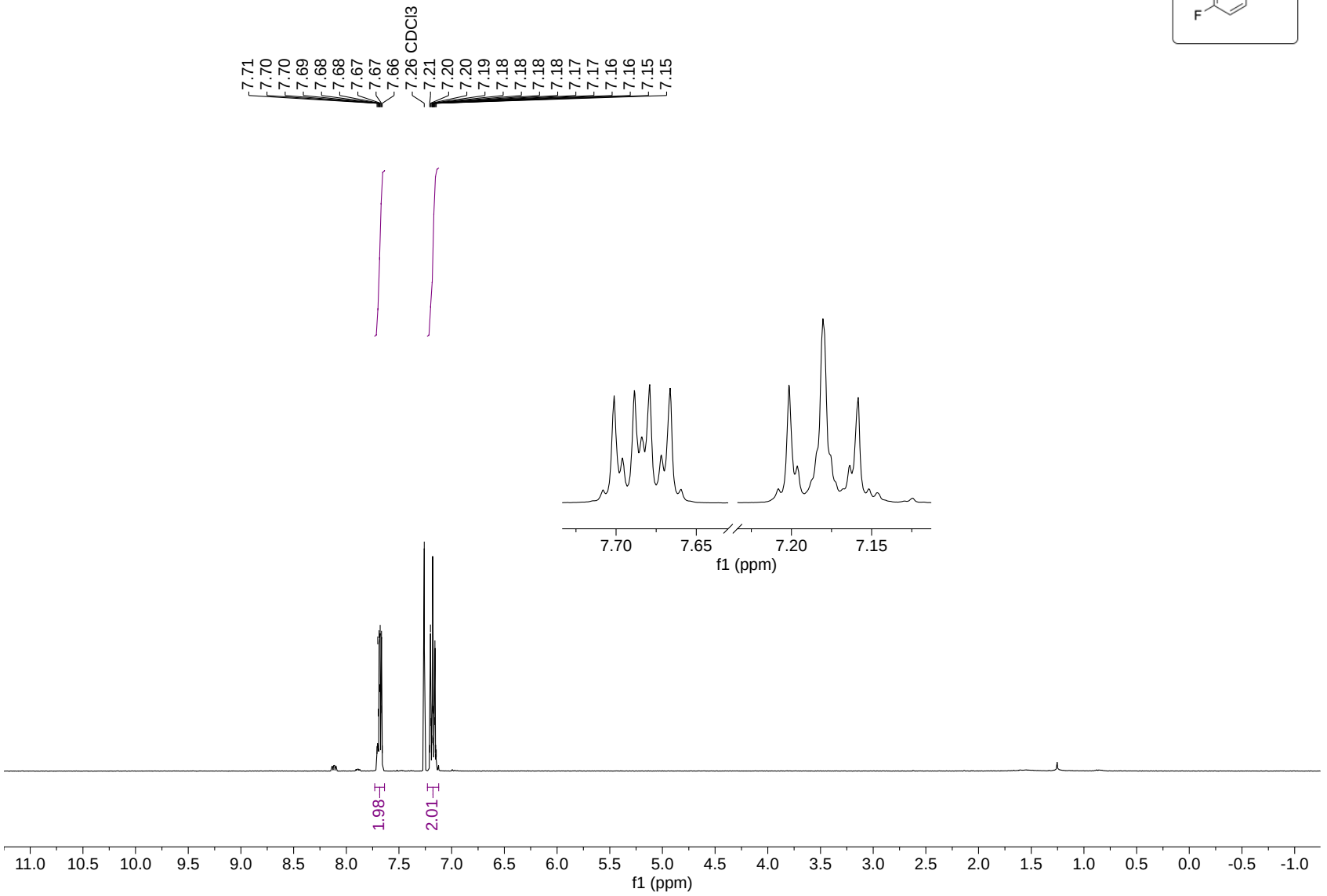


^{1}H-NMR (400 MHz $CDCl_3$) (4-(trifluoromethyl)benzonitrile (5e)

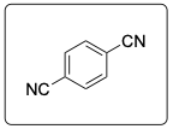


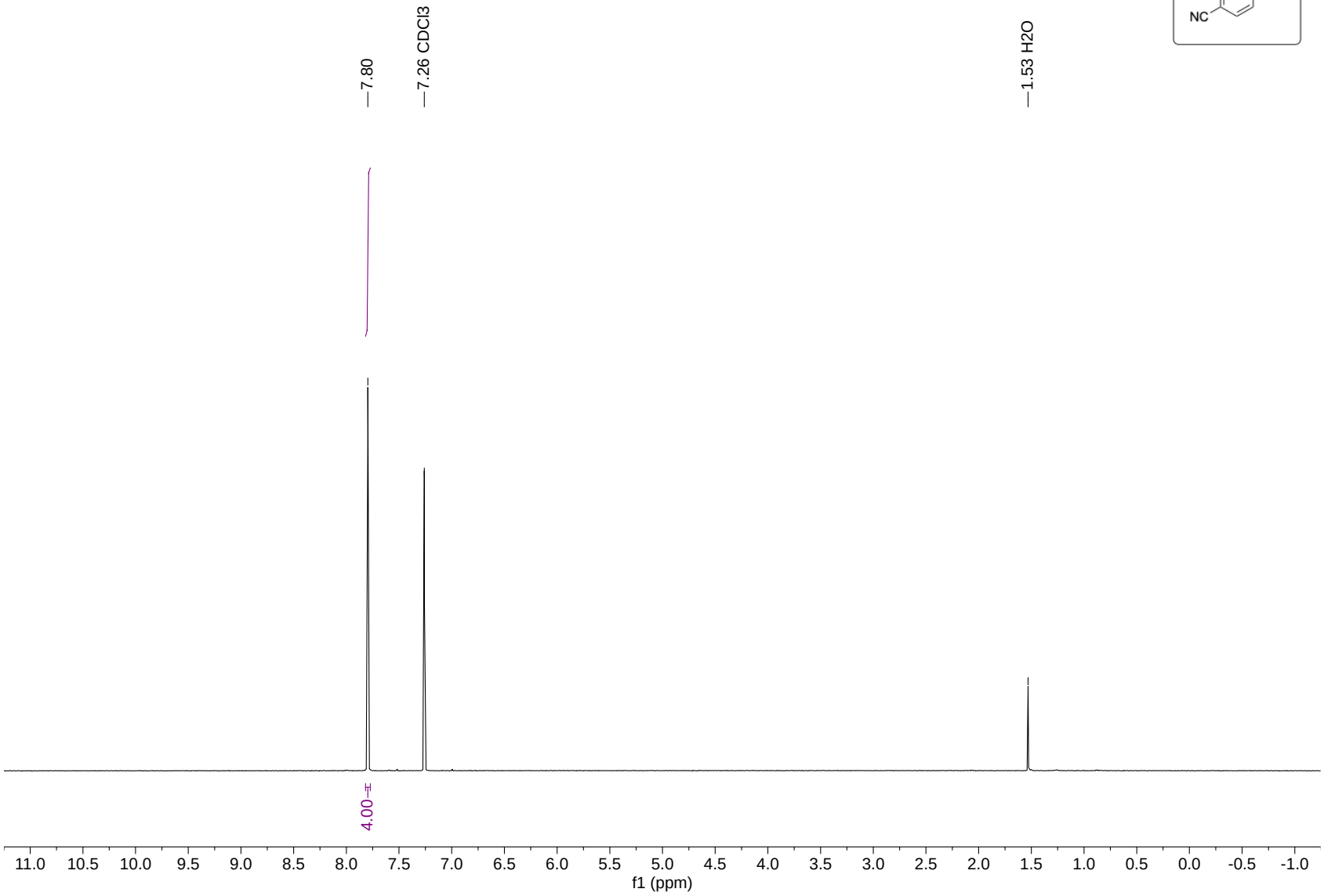
^{1}H-NMR (400 MHz $CDCl_3$) 4-fluorobenzonitrile (5f)



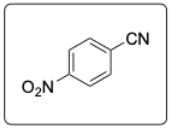


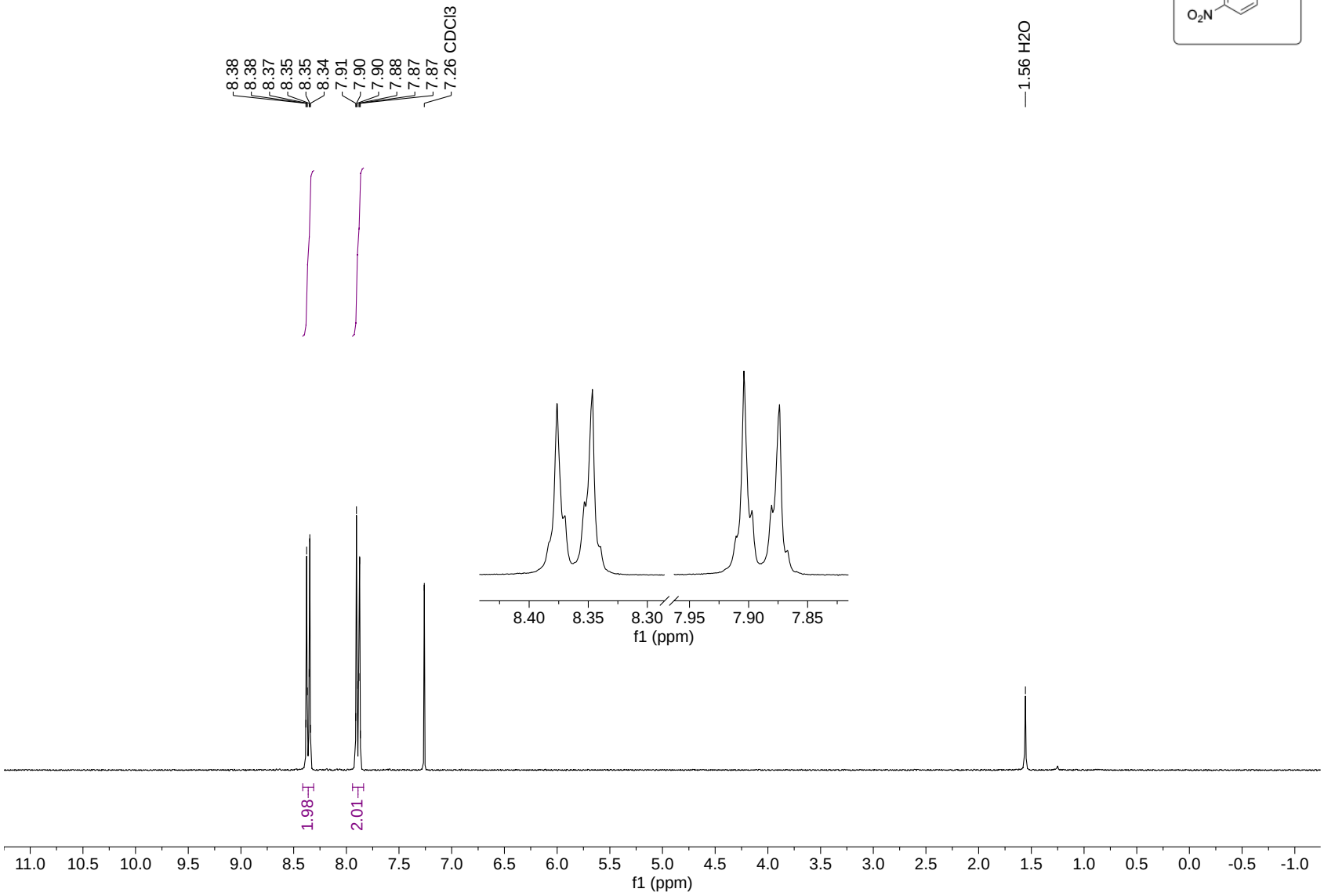
^{1}H-NMR (400 MHz $CDCl_3$) terephthalonitrile (5g)



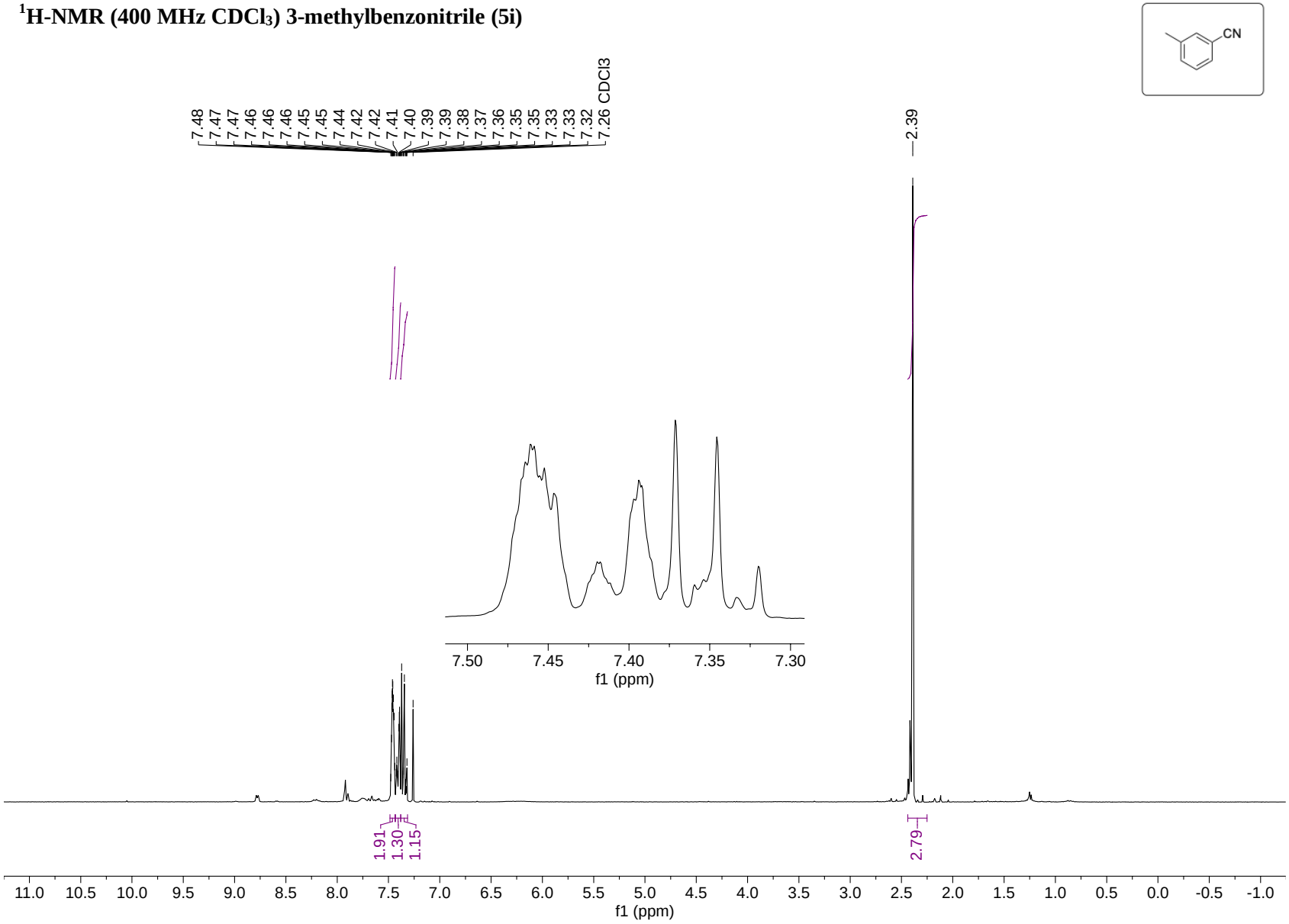


^{1}H-NMR (300 MHz $CDCl_3$) 4-nitrobenzonitrile (5h)

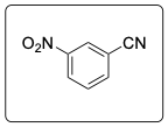




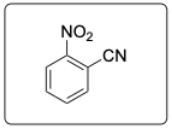
^{1}H-NMR (400 MHz $CDCl_3$) 3-methylbenzonitrile (5i)

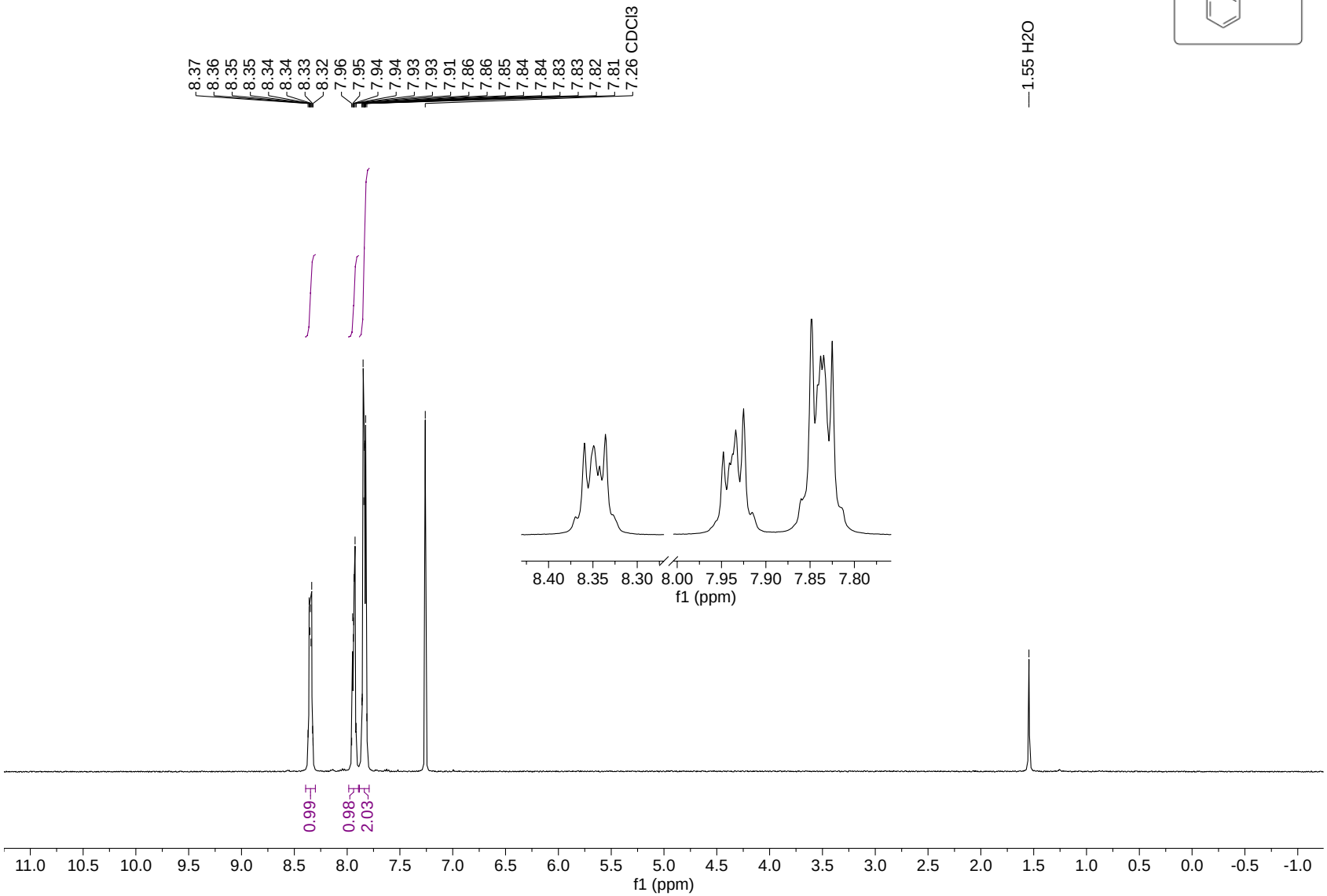


^{1}H-NMR (300 MHz $CDCl_3$) 3-nitrobenzonitrile (5j)

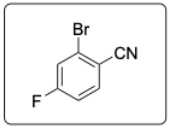


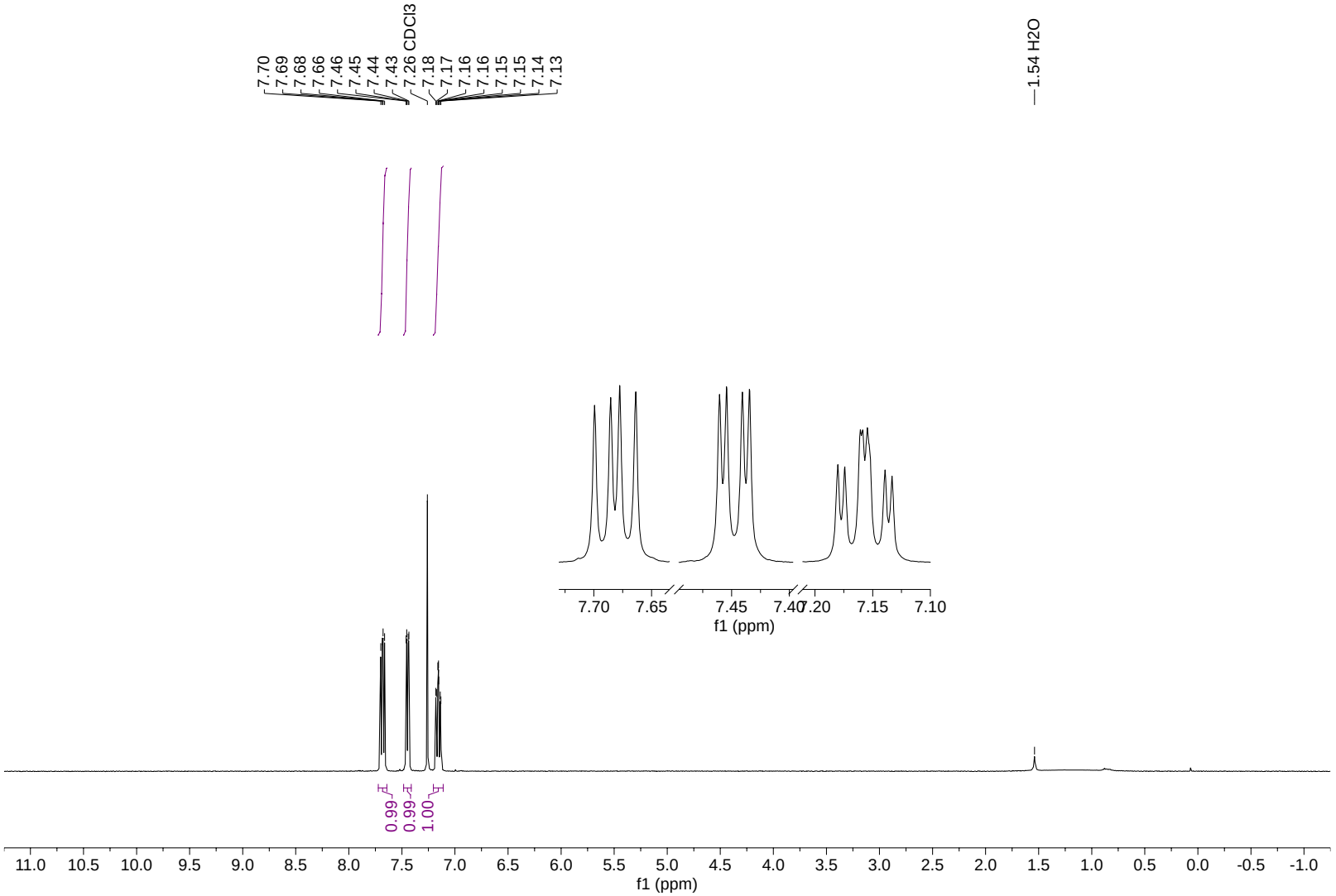
^{1}H-NMR (400 MHz $CDCl_3$) 2-nitrobenzonitrile (5k)



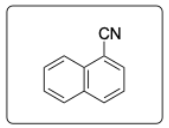


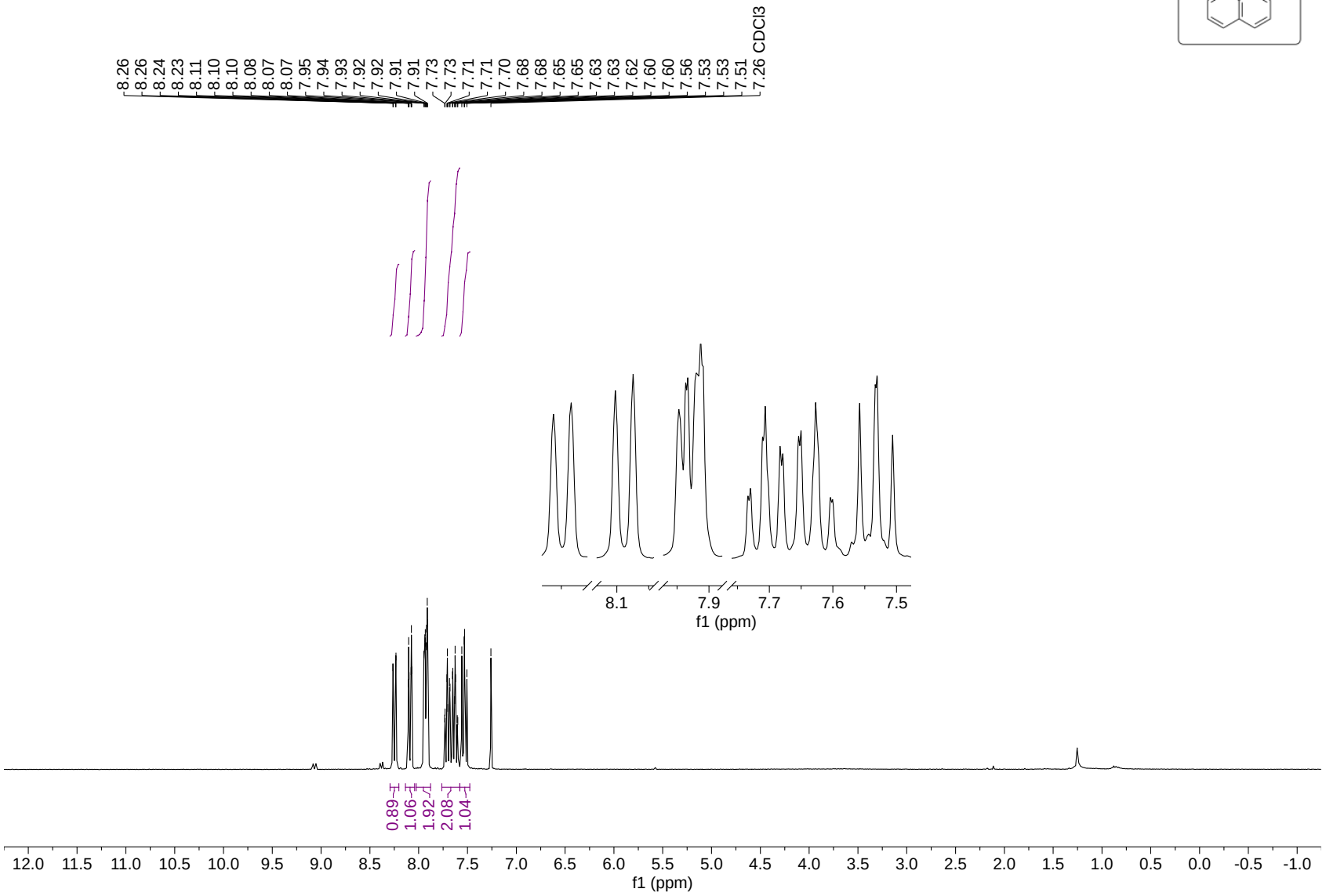
^{1}H-NMR (400 MHz $CDCl_3$) 2-bromo-4-fluorobenzonitrile (5l)



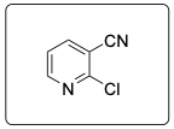


^{1}H-NMR (300 MHz $CDCl_3$) 1-napthonitrile (5m)

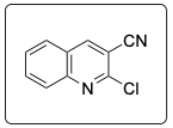




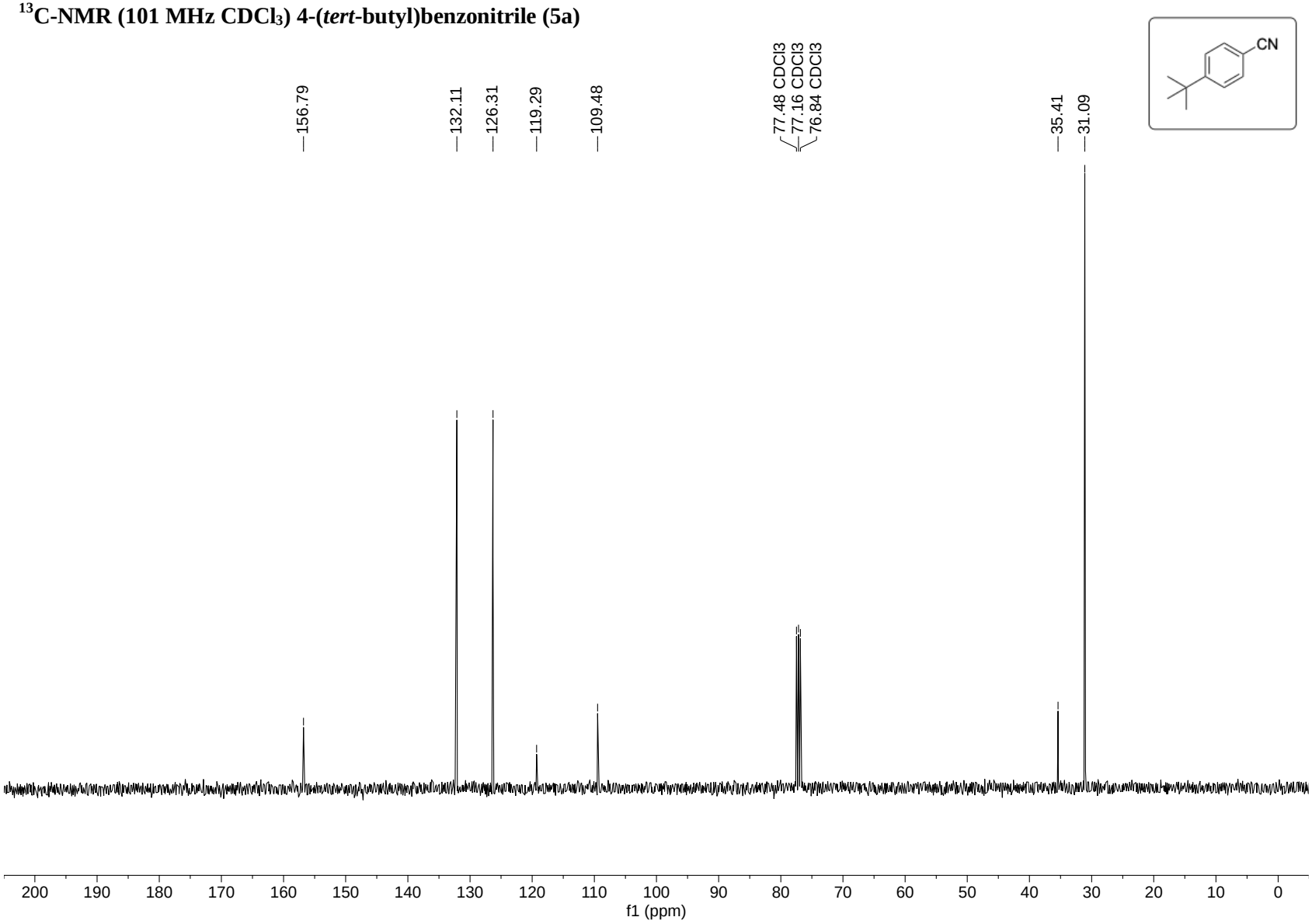
^{1}H-NMR (300 MHz $CDCl_3$) 2-chloro-3-pyridinecarbonitrile (5n)



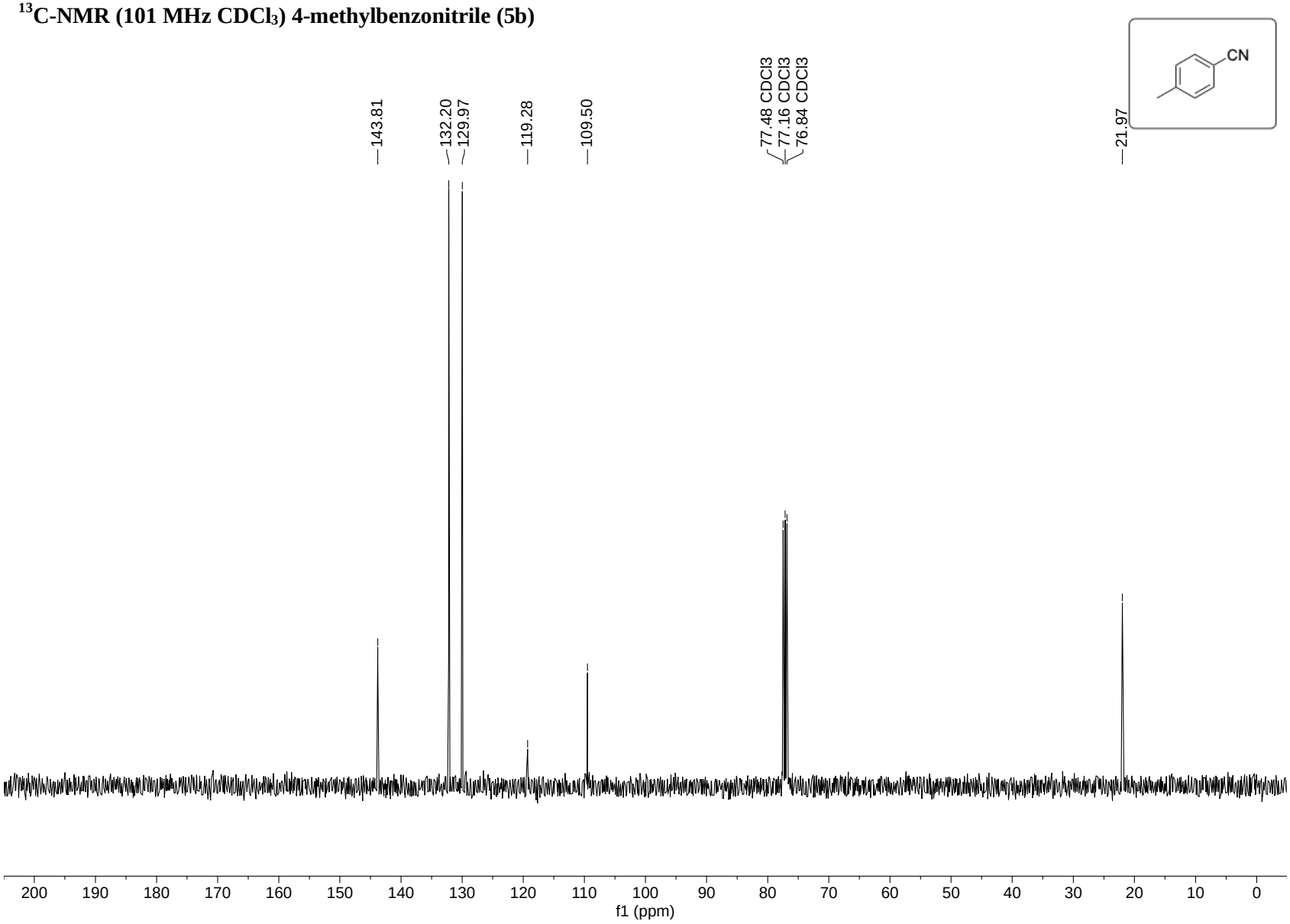
^{1}H-NMR (400 MHz $CDCl_3$) 2-chloroquinoline-3-carbonitrile (5o)



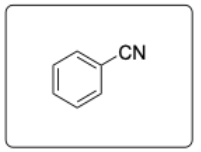
^{13}C-NMR (101 MHz $CDCl_3$) 4-(*tert*-butyl)benzonitrile (5a)



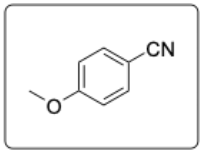
^{13}C-NMR (101 MHz $CDCl_3$) 4-methylbenzonitrile (5b)



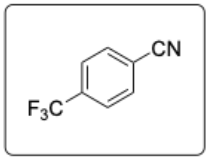
^{13}C-NMR (101 MHz $CDCl_3$) benzonitrile (5c)



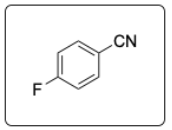
^{13}C-NMR (101 MHz $CDCl_3$) 4-methoxybenzonitrile (5d)

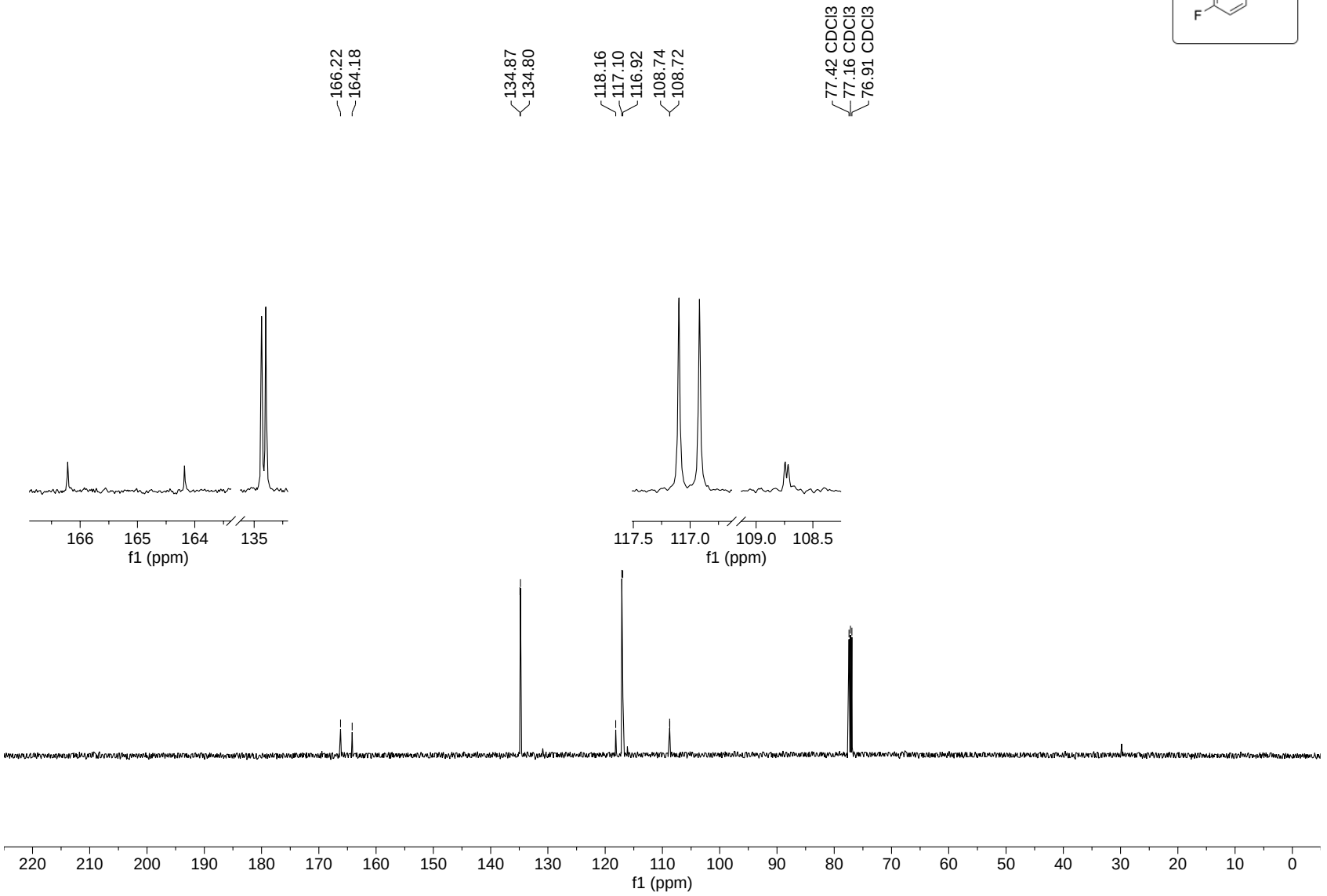


^{13}C-NMR (126 MHz $CDCl_3$) (4-(trifluoromethyl)benzonitrile (5e)

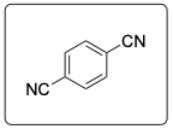


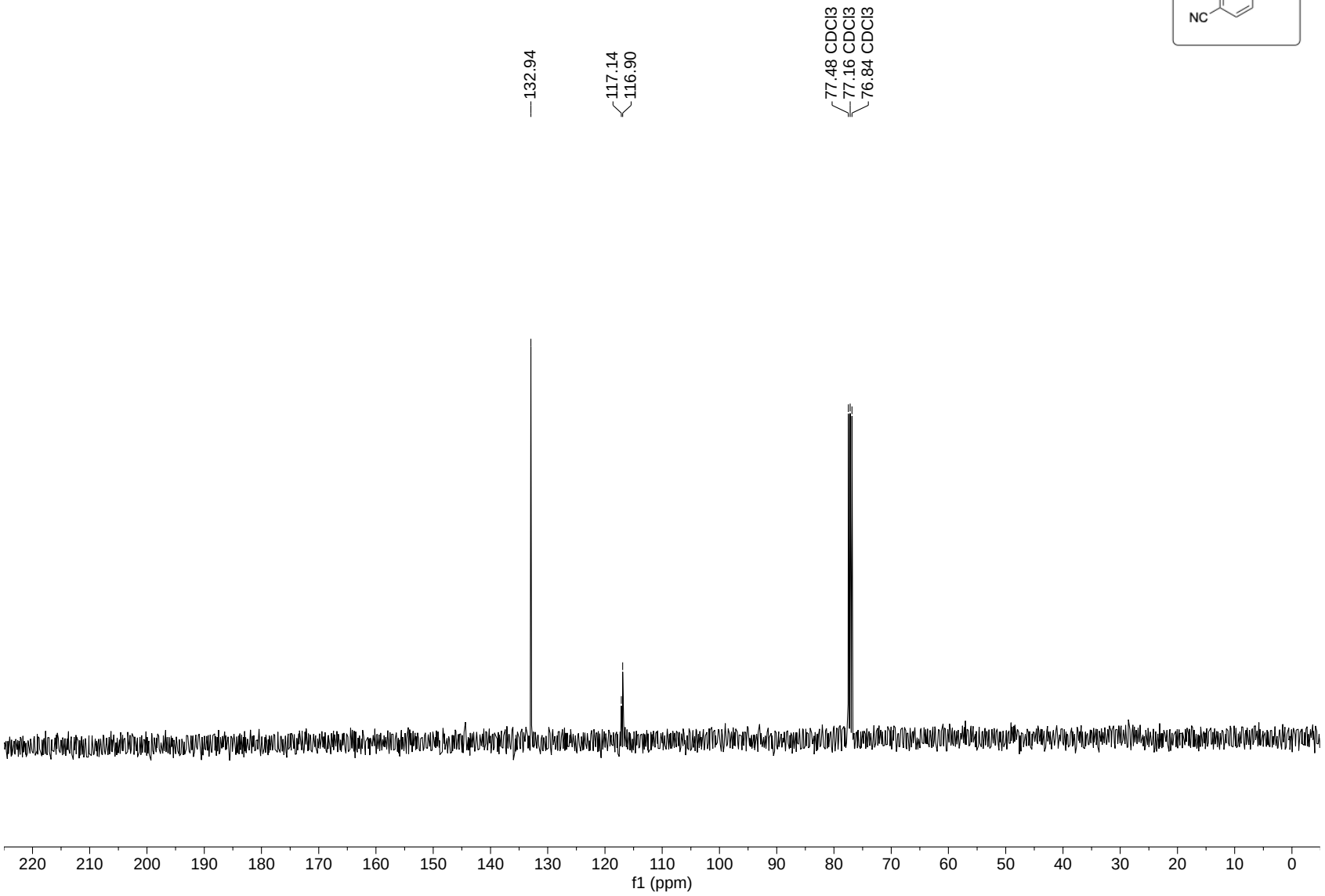
^{13}C-NMR (126 MHz $CDCl_3$) 4-fluorobenzonitrile (5f)



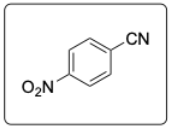


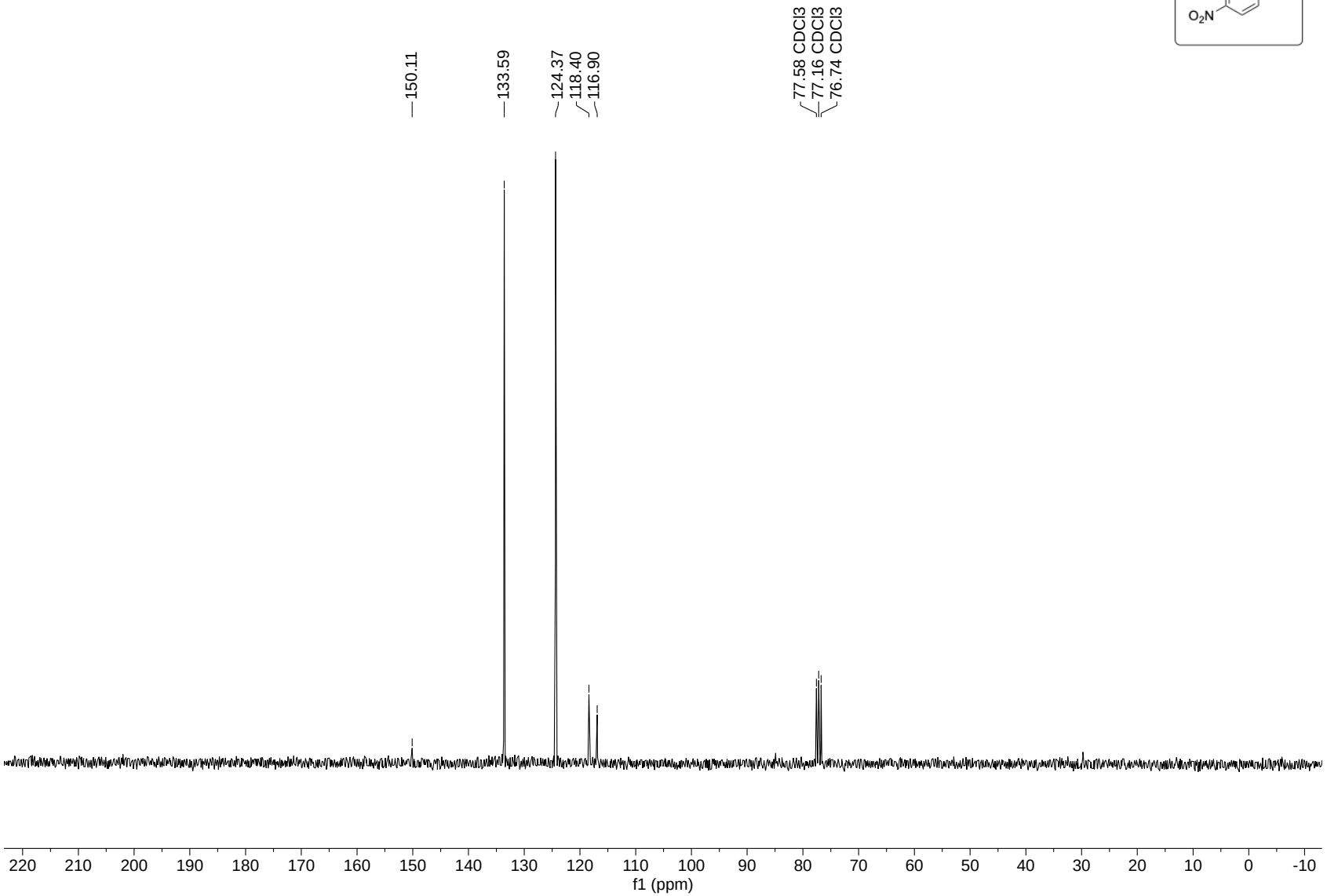
^{13}C-NMR (101 MHz $CDCl_3$) terephthalonitrile (5g)



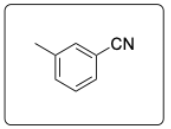


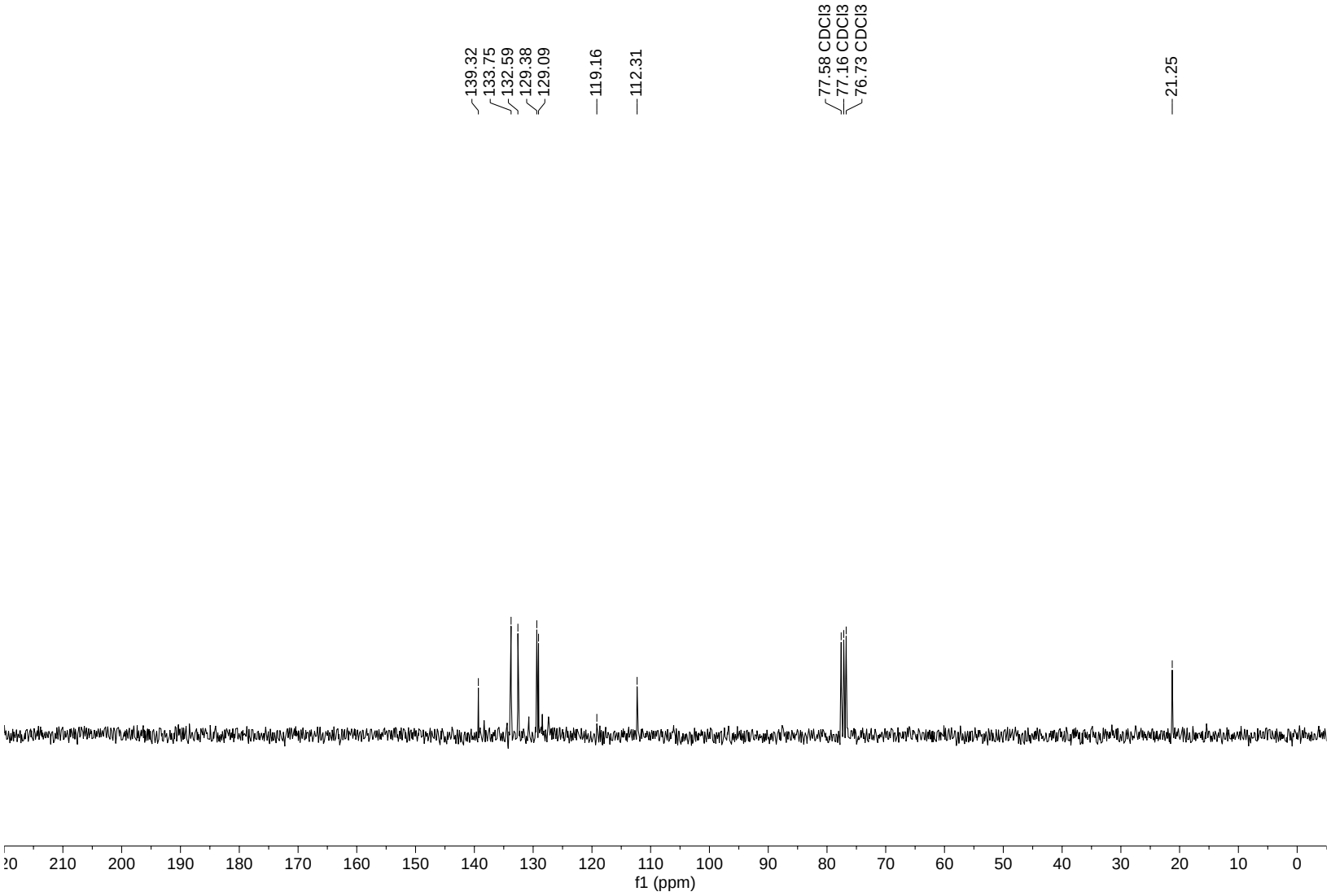
^{13}C-NMR (75 MHz $CDCl_3$) 4-nitrobenzonitrile (5h)



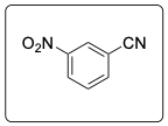


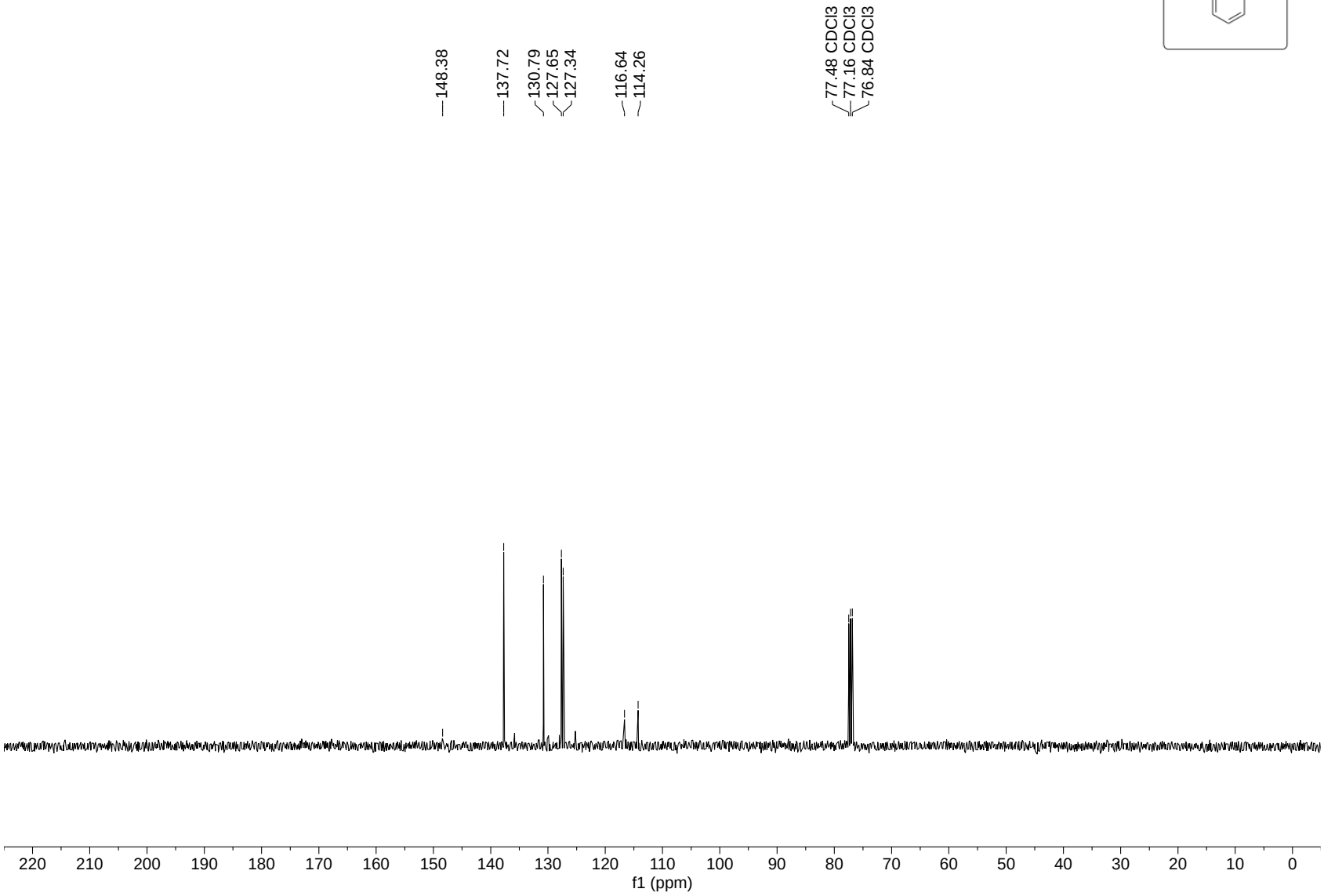
^{13}C-NMR (75 MHz $CDCl_3$) 3-methylbenzonitrile (5i)



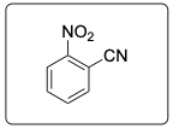


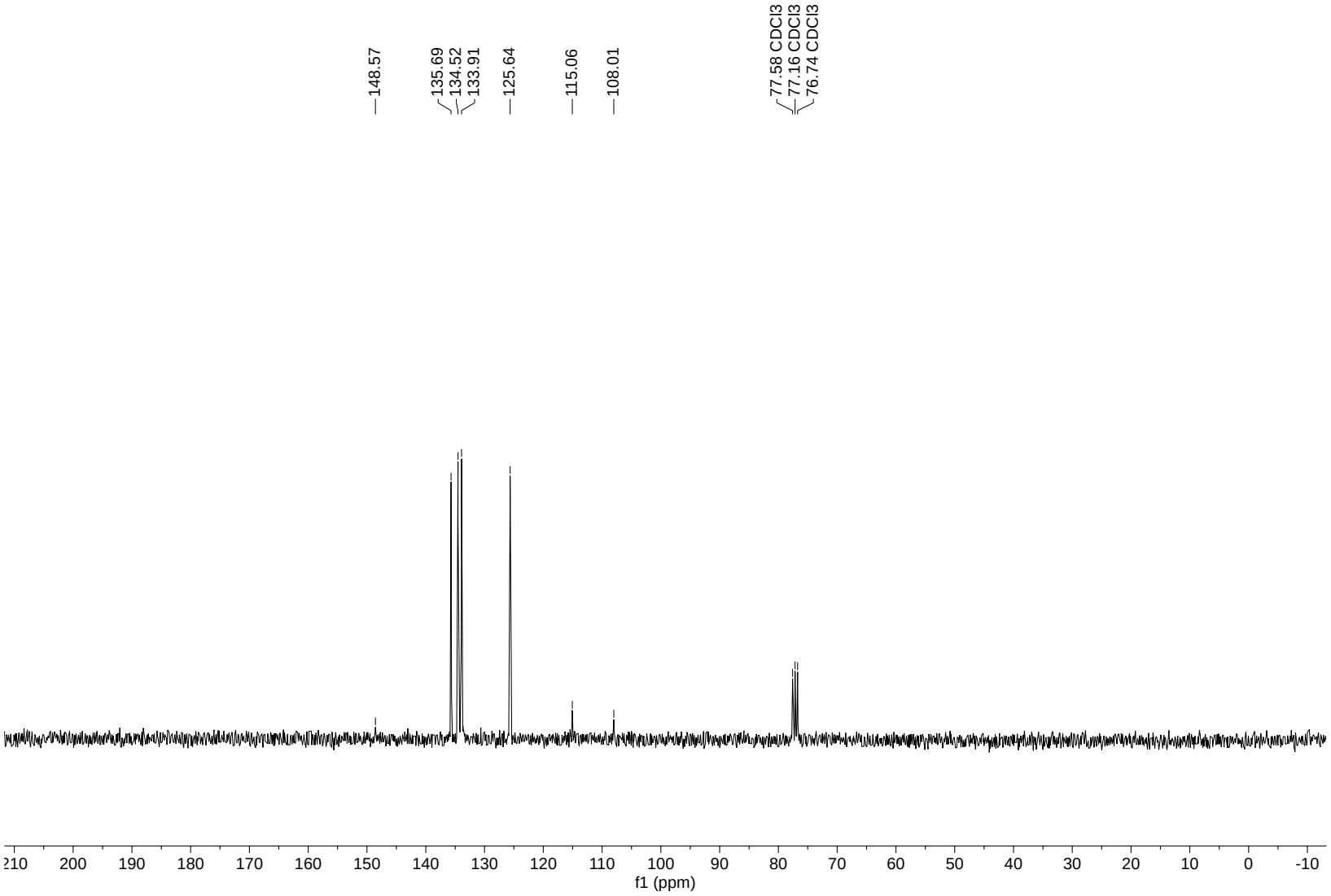
^{13}C-NMR (101 MHz $CDCl_3$) 3-nitrobenzonitrile (5j)



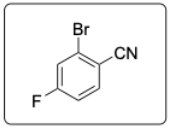


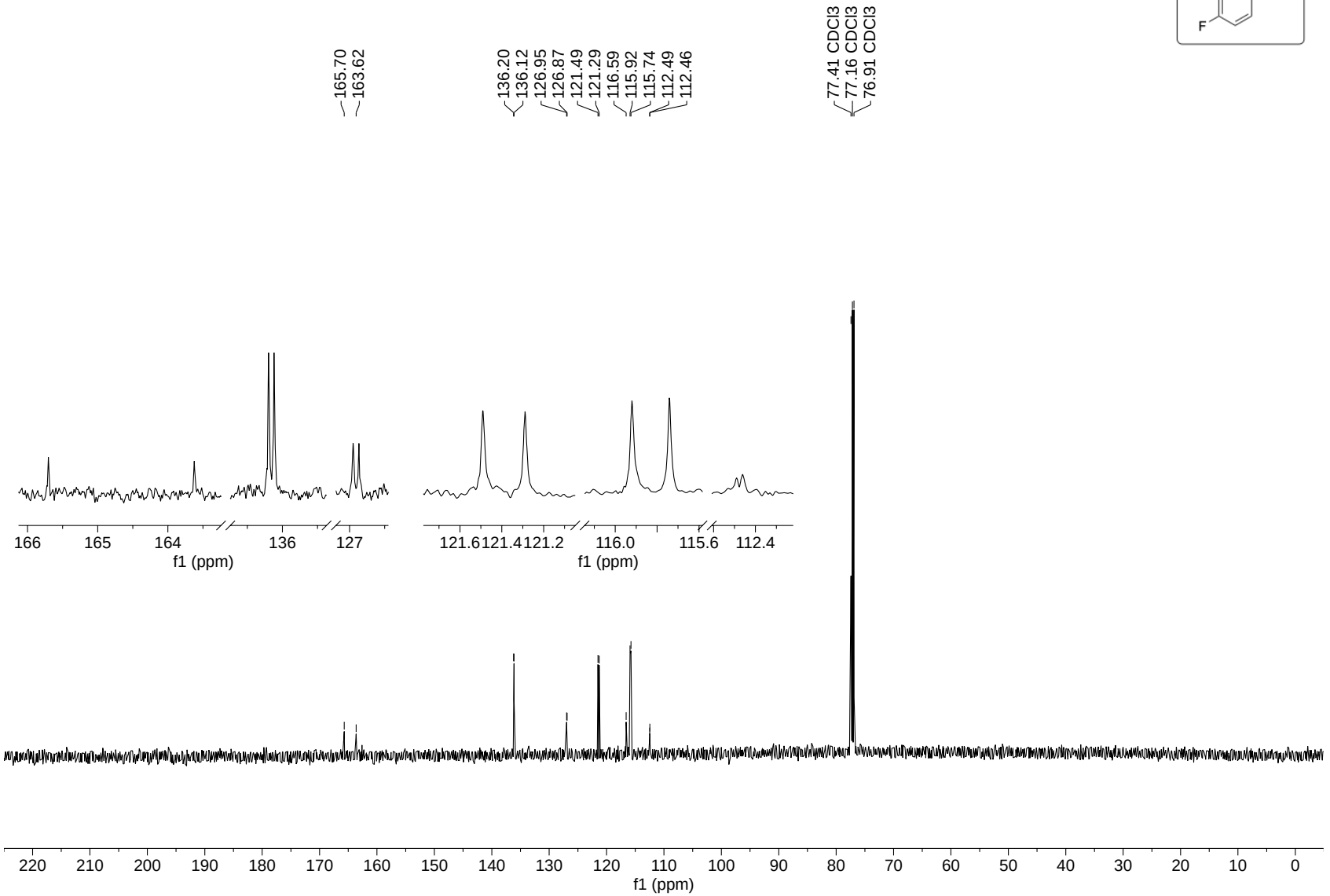
^{13}C-NMR (75 MHz $CDCl_3$) 2-nitrobenzonitrile (5k)



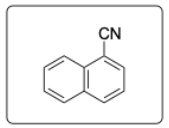


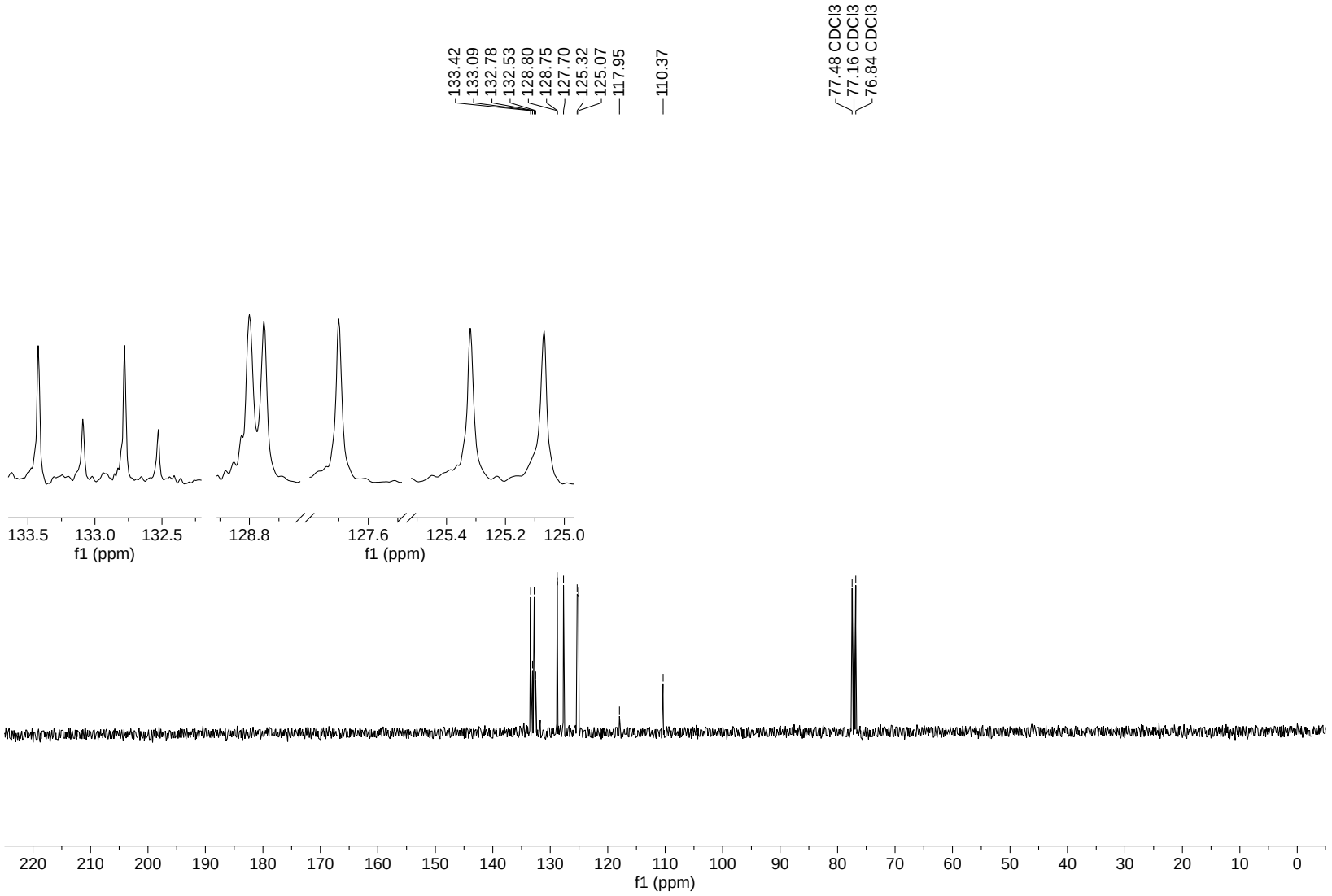
^{13}C-NMR (126 MHz $CDCl_3$) 2-bromo-4-fluorobenzonitrile (5l)



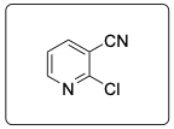


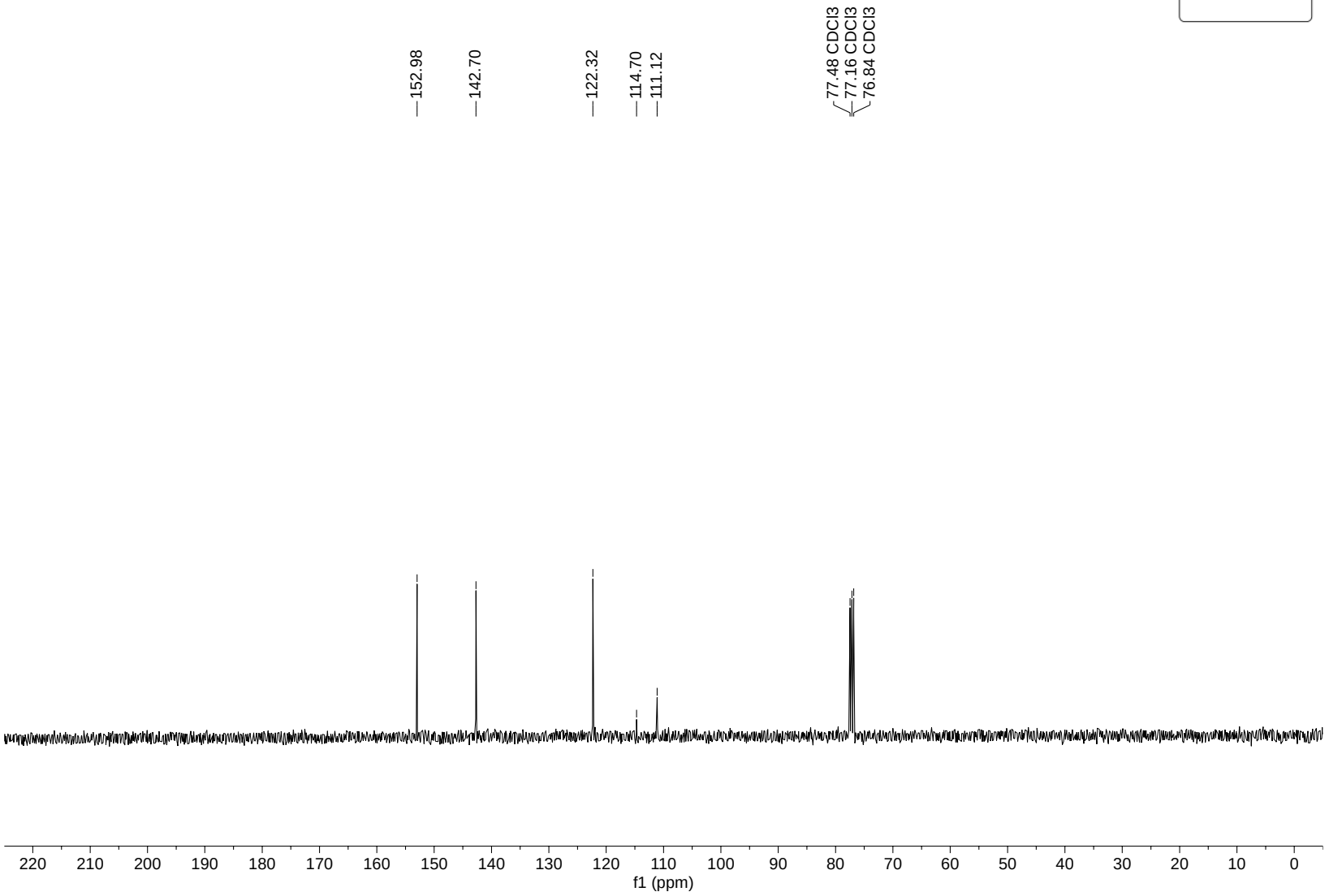
^{13}C-NMR (101 MHz $CDCl_3$) 1-napthonitrile (5m)



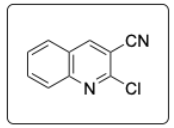


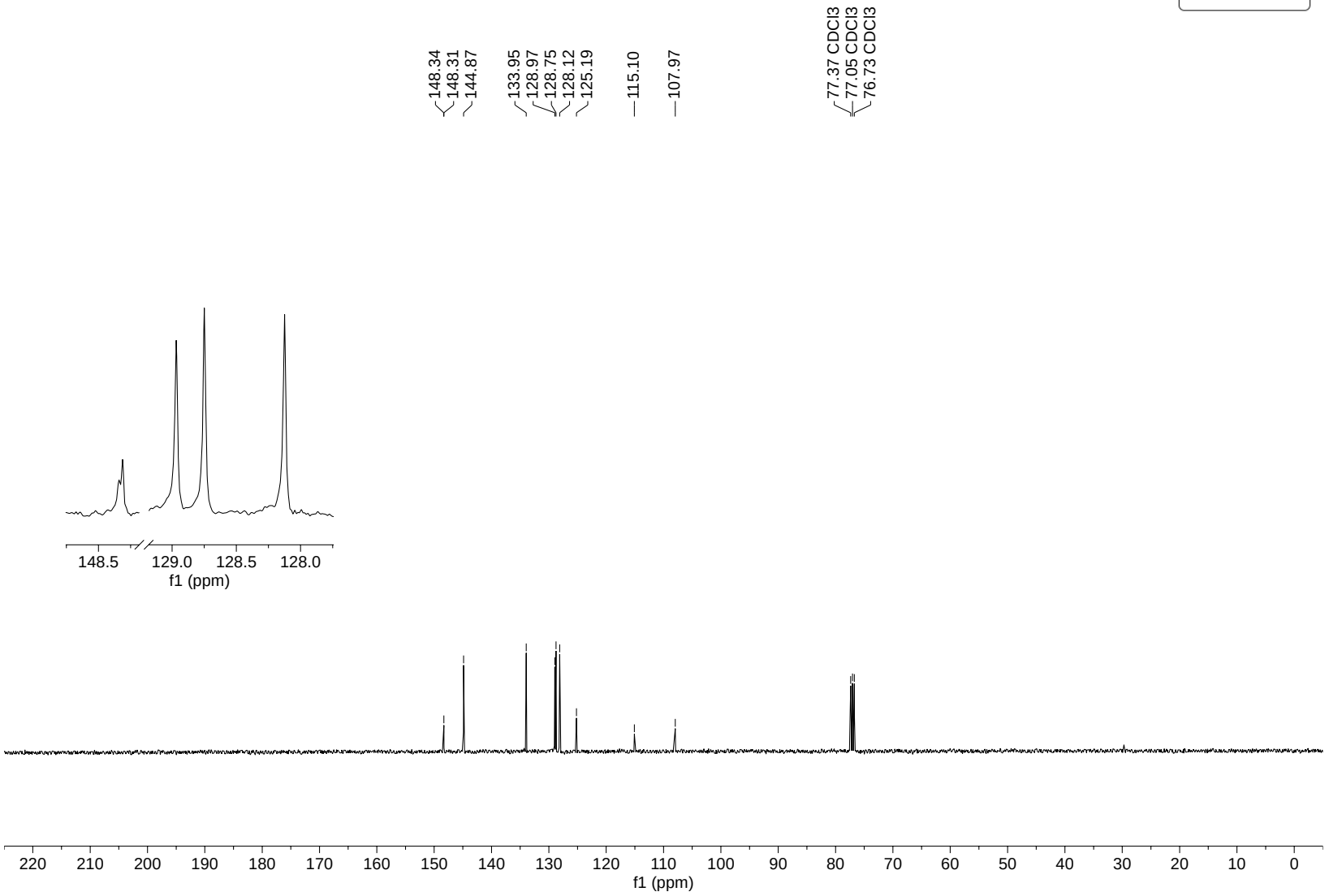
^{13}C-NMR (101 MHz $CDCl_3$) 2-chloro-3-pyridinecarbonitrile (5n)



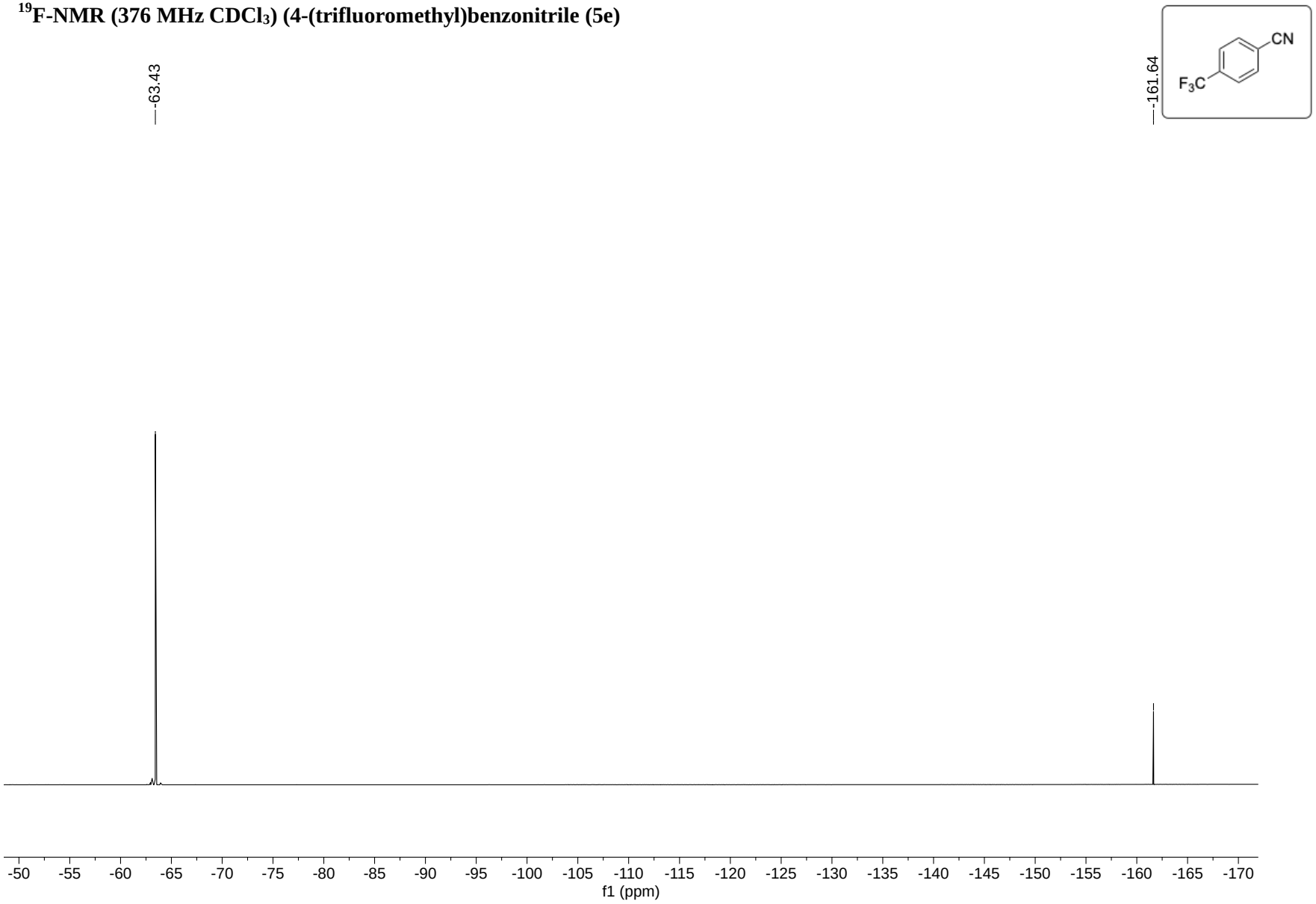


^{13}C-NMR (101 MHz $CDCl_3$) 2-chloroquinoline-3-carbonitrile (5o)

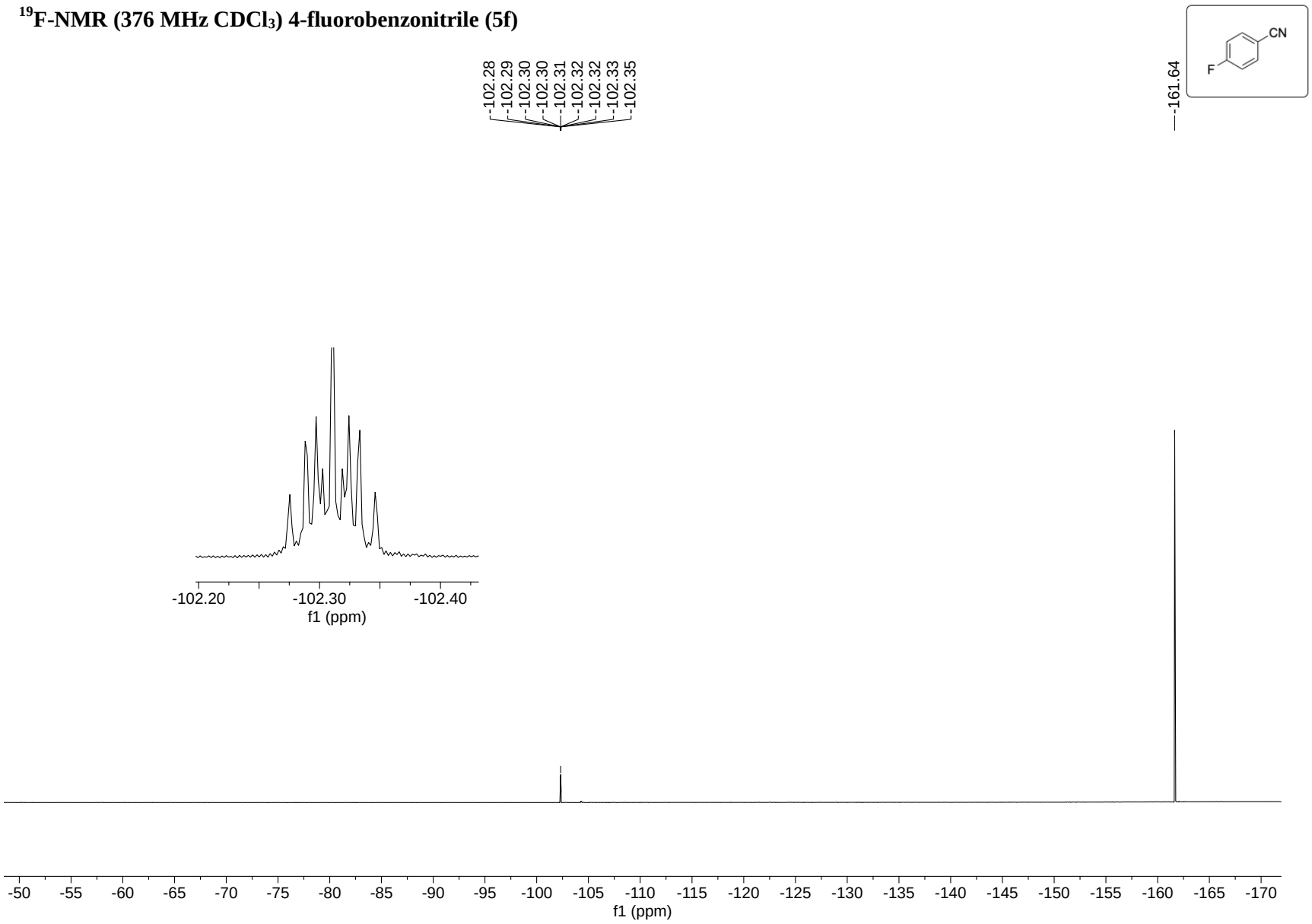




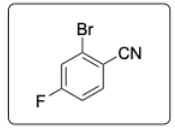
^{19}F-NMR (376 MHz $CDCl_3$) (4-(trifluoromethyl)benzonitrile (5e)

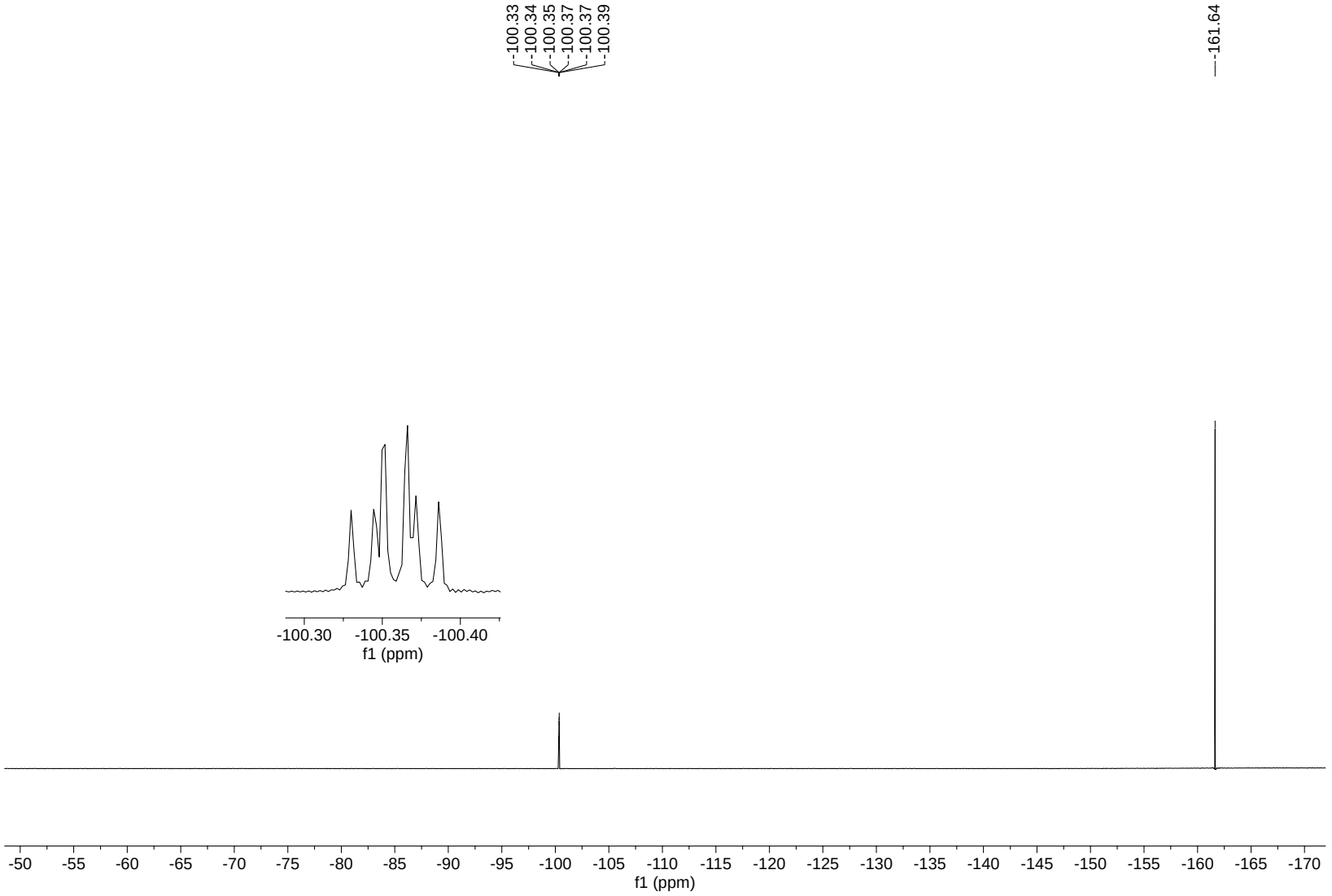


^{19}F-NMR (376 MHz $CDCl_3$) 4-fluorobenzonitrile (5f)



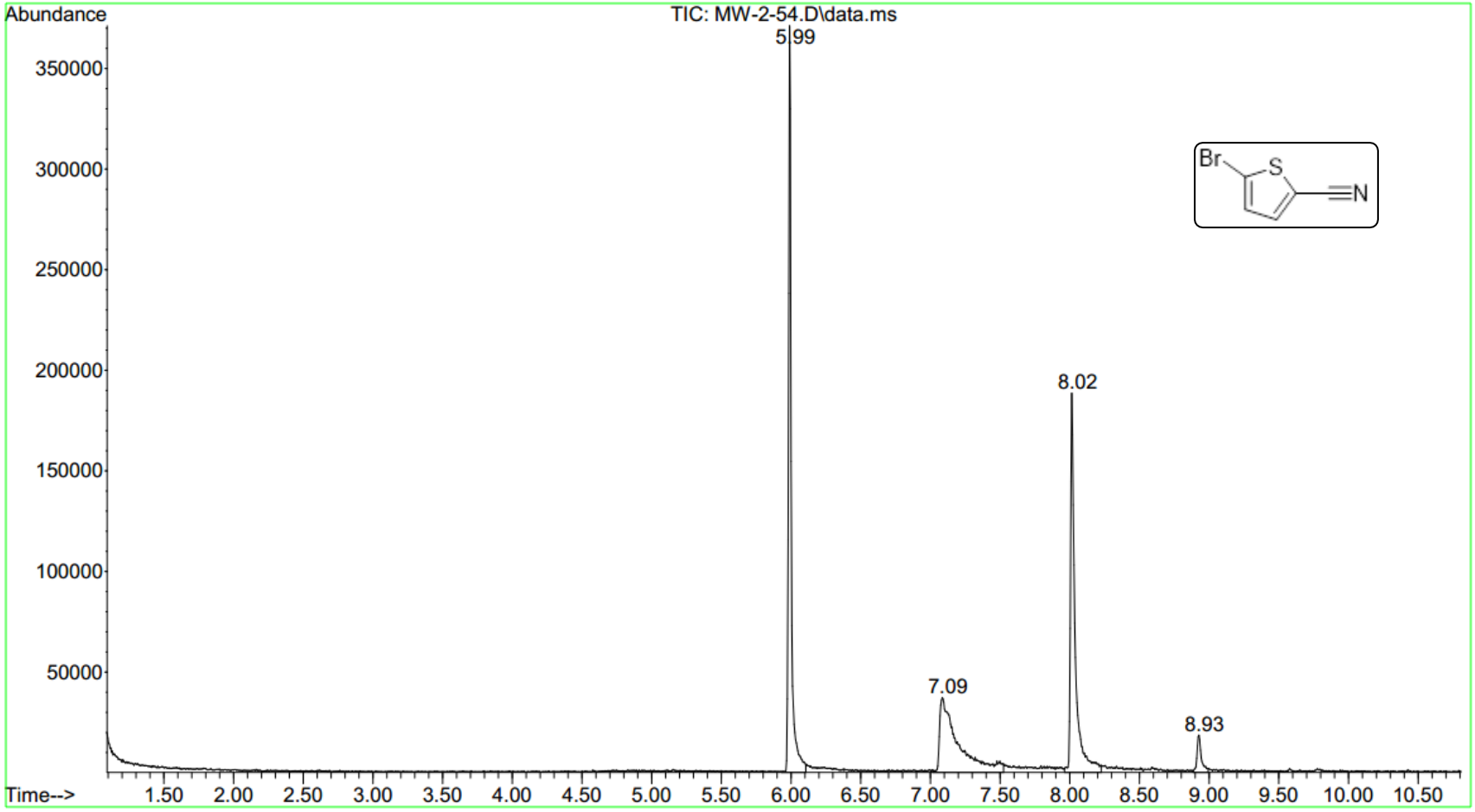
^{19}F-NMR (376 MHz $CDCl_3$) 2-bromo-4-fluorobenzonitrile (5l)





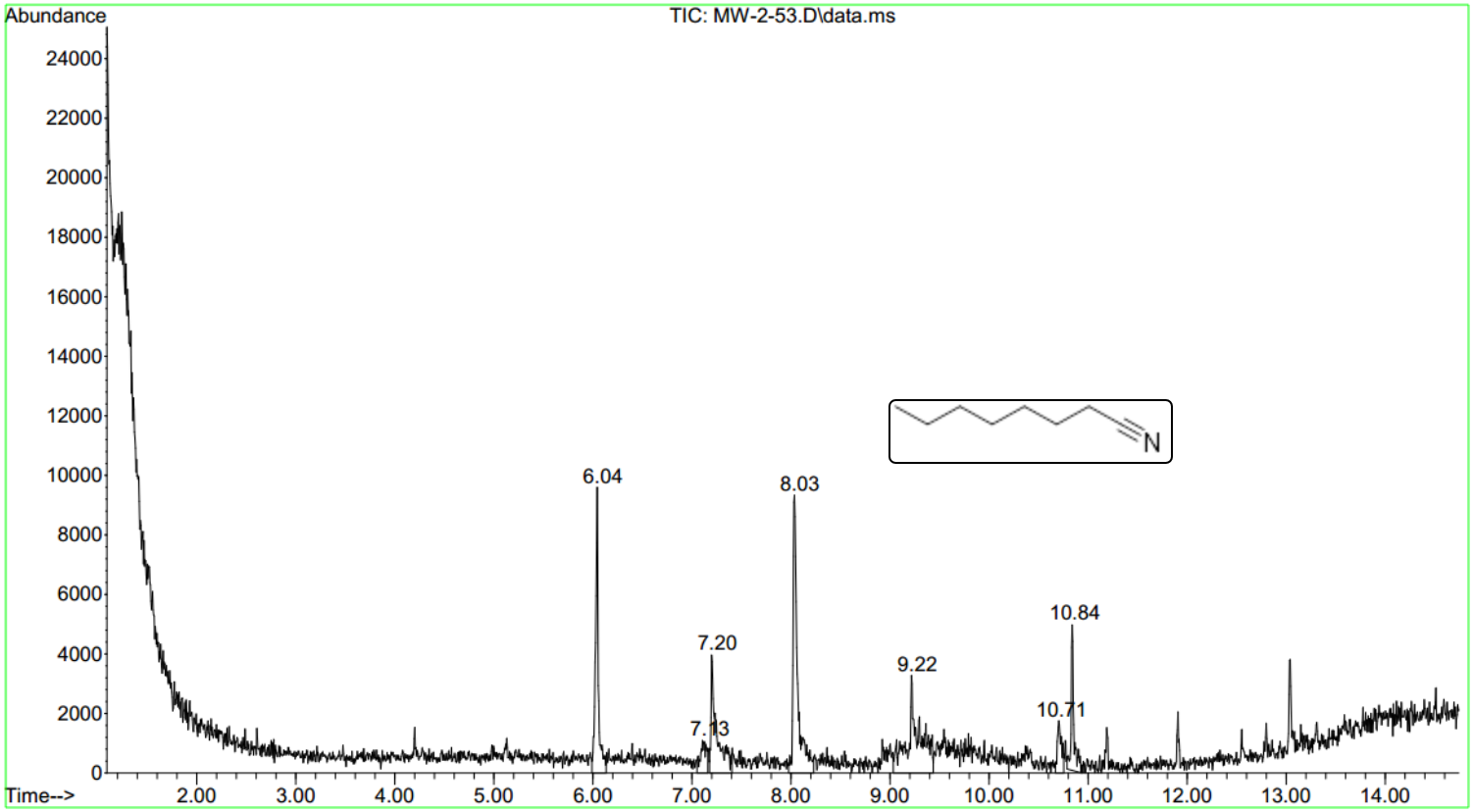
GC-MS Chromatograms of Compounds 5p, 5q, and 5r

5-bromo-2-thiophenecarbonitrile(5p)



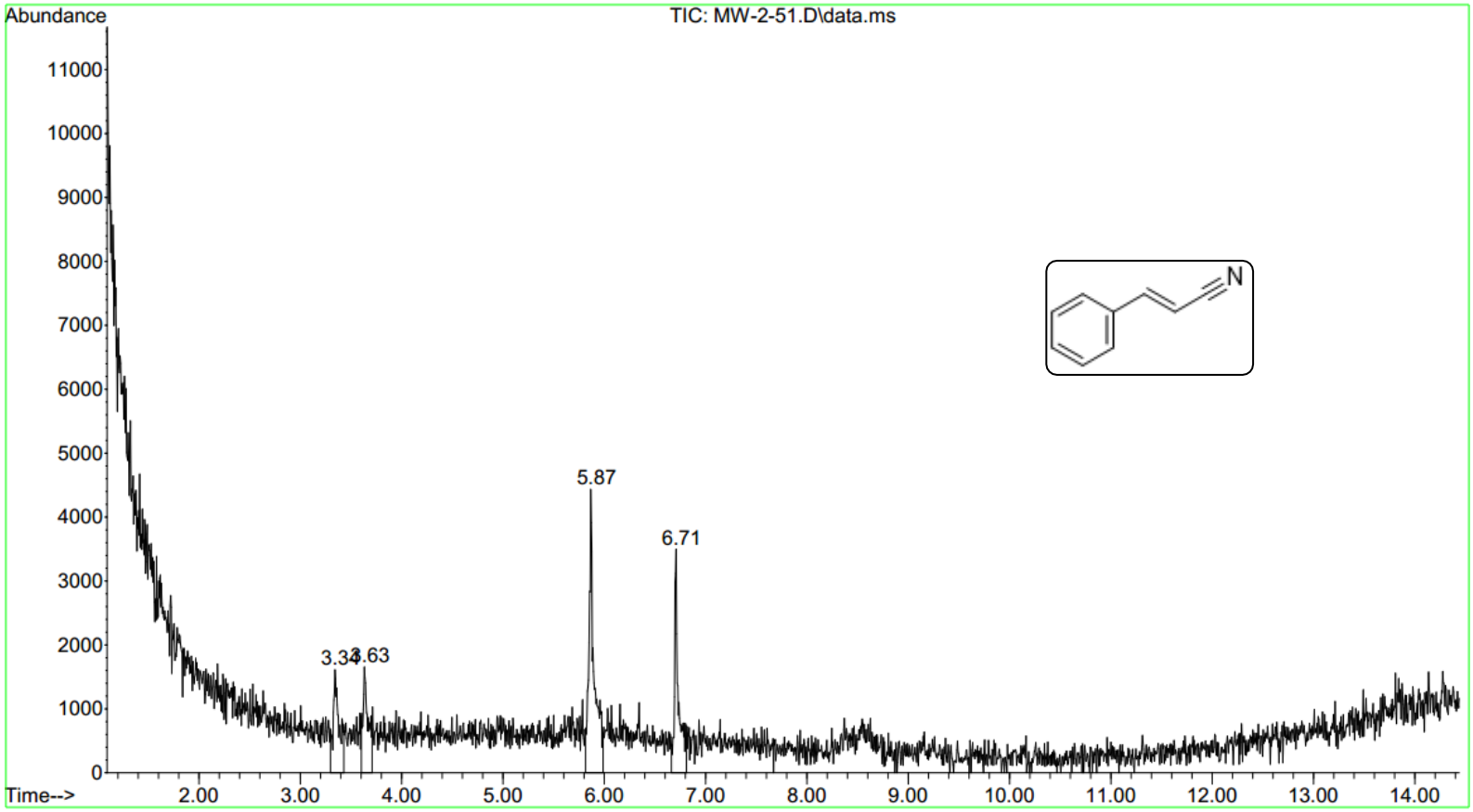
No.	Peak MW	Ret. time (min)	Area (mAU*min)	Height (mAU)	Identity	% of total
1	187	5.991	5044057	377171	Nitrile product	38.27
2	207	7.086	3412988	37286	Carboxylic acid byproduct	25.90
3	213	8.015	4313345	189526	ACT, **2**	32.73
4	435	8.926	409603	18609	Unknown	3.11

Caprylnitrile(5q)



No.	Peak MW	Ret. time (min)	Area (mAU*min)	Height (mAU)	Identity	% of total
1	115	6.043	189606	9627	Carboxylic acid byproduct	17.30
2	191	7.126	48987	1094	Unknown	4.47
3	86	7.200	158331	4152	Amide byproduct	14.45
4	281	8.035	298461	9372	Unknown	27.23
5	125	9.219	257100	3338	Nitrile product	23.46
6	213	10.705	50863	1759	ACT, **2**	4.64
7	223	10.839	92555	4892	Unknown	8.45

Cinnamonitrile (5r)



No.	Peak MW	Ret. time (min)	Area (mAU*min)	Height (mAU)	Identity	% of total
1	106	3.343	67717	1623	Aldehyde starting material	17.380
2	103	3.633	60786	1669	Amide byproduct	15.601
3	122	5.867	167339	4502	Carboxylic acid byproduct	42.947
4	129	6.708	93795	3565	Nitrile product	24.072

1. C. P. Rosenau, B. J. Jelier, A. D. Gossert and A. Togni, *Angew. Chemie - Int. Ed.*, 2018, **57**, 9528.
2. M. A. Mercadante, C. B. Kelly, J. M. Bobbitt, L. J. Tilley and N. E. Leadbeater, *Nat. Protoc.*, 2013, **8**, 666.