Supporting information

Nucleophilic Fluorination of Heteroaryl Chlorides and Aryl Triflates Enabled by Cooperative Catalysis

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Table of Contents

Purification and analytical details

Purification of desired compounds was performed by direct crystallization or chromatographic purification. Column chromatography was performed using a Teledyne ISCO CombiFlash® Rf+ chromatography system using prepacked single-use silica packed cartridges (RediSep® Rf Gold Normal-Phase Silica, 20–40 micron average particle size, 60 Å average pore size, with varying cartridge sizes ranging from 24 g (part number 69-2203-346), 40 g (part number 69-2203-347), 80 g (part number 69-2203-348) to 120 g SiO2 cartridges, part number 69-2203-349) operating with a flow rate of 35, 40, 80 and 85 mL/min, respectively, depending on the size of the cartridge.

Proton nuclear magnetic resonance (^{1}H NMR) spectra, proton decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra, and proton decoupled fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded at 25 °C unless stated otherwise on a Bruker DRX-500 spectrmeter or a Bruker Neo 600 MHz spectrometer equipped with an iProbe TBO. Chemical shifts for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual proton signals of the NMR solvent according to values reported in the literature.[1] Chemical shifts for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent according to values reported in the literature.[1] Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dt = doublet of triplets), coupling constants (J) in Hertz (Hz). High resolution mass spectra (HRMS) were obtained on an Agilent 1290 Infinity 2 equipped with a Binary Pump and DAD coupled to a Agilent 6230 TOF. High throughput screening was performed in a 24 well plate using stock solutions and multichannel pipettors.

Screening results

A 24-well reaction plate was used to evaluate initial conditions and performance of two tetramethylammonium salts for cooperative catalysis with various crown ethers on 0.05 mmol scale with respect to substrate (**1a**). These wells were charged with stir bars and 3 equiv. of KF or CsF. Stock solutions of (**1a**), tetramethylammonium chloride, tetramethylammonium hexafluorophosphate, 18-crown-6 ether, 15-crown-5 ether, dibenzo-18-crown-6 ether were prepared in MeCN in a nitrogen glovebox. These were dispensed accordingly to screen all combinations of tetramethylammonium salts (0.1 equiv) for cooperative catalysis in the presence of a phase transfer catalyst (0.1 equiv).

Well	F^- salt	TMA salt	Crown Ether	Evaluated	LC area % 2a
1	KF	-	-	Control	0
2	KF	-	18-c-6	18-c-6	4
3	KF	TMACl	-	TMACl	0
4	KF	TMACl	15-c-5	TMACl + 15-c-5	2
5	KF	TMACl	18-c-6	TMACl + 18-c-6	11
6	KF	TMACl	BZ-18-c-6	TMACl + BZ-18-c-6	1
7	KF	$TMABF_4$	-	$TMABF_4$	3
8	KF	$TMABF_4$	15-c-5	$TMABF_4$ + 15-c-5	2
9	KF	$TMABF_4$	18-c-6	$TMABF_4$+ 18-c-6	18
10	KF	$TMABF_4$	BZ-18-c-6	$TMABF_4$ + BZ-18-c-6	1
11	CsF	-	-	$TMABF_4$ + Control	5
12	CsF	-	18-c-6	$TMABF_4$ + 18-c-6	47
13	CsF	TMACl	-	TMACl	12
14	CsF	TMACl	15-c-5	TMACl + 15-c-5	95
15	CsF	TMACl	18-c-6	TMACl + 18-c-6	97
16	CsF	TMACl	BZ-18-c-6	TMACl + BZ-18-c-6	88
17	CsF	$TMABF_4$	-	$TMABF_4$	31
18	CsF	$TMABF_4$	15-c-5	$TMABF_4$+ 15-c-5	81
19	CsF	$TMABF_4$	18-c-6	$TMABF_4$ + 18-c-6	94
20	CsF	$TMABF_4$	BZ-18-c-6	$TMABF_4$ + BZ-18-c-6	95

Hygroscopicity studies of raw materials

The primary challenges with using highly hygroscopic reagents such as TMAF on manufacturing scale are two-fold. First, a reagent's ability to rapidly and efficiently absorb water from atmospheric conditions poses a challenge to water-sensitive chemistry by introducing a point of entry for uncontrolled amounts of water. Second, reagents that are hygroscopic to the degree of deliquescing at ambient humidities pose challenges from the perspective of raw material handling, even if the chemistry is tolerant to water. While solid, liquid, slurry, and gas reagents are well established for handling in a plant setting, deliquesing reagents can form wet clumpy solids, gels, or thick liquids, which pose a significant operational challenge.

To quantify the relative degrees of water uptake, samples of raw materials for this method and TMAF were aged open to the atmosphere under ambient laboratory conditions (40% relative humidity, 72 ^oF). These conditions can be used to approximate the conditions under which pilot plant subdivisions are typically carried out. A

representative subdivision operation to prepare 50 kg of a solid reagent can require time cycles of up to six hours of exposure of the raw material to ambient conditions. It was observed that at 22 hours of aging, TMAF had completely deliquesced into a thick gel, while TMACl, 18-crown-6 ether, and CsF were still well-behaved (albeit visibly wet) solids.

Water uptake in mg / g of reagent			
Reagent	**1 h**	**4 h**	**22 h**
TMAF	66	162	547
TMACl	23	49	148
18-c-6	1	2	2
CsF	7	13	43

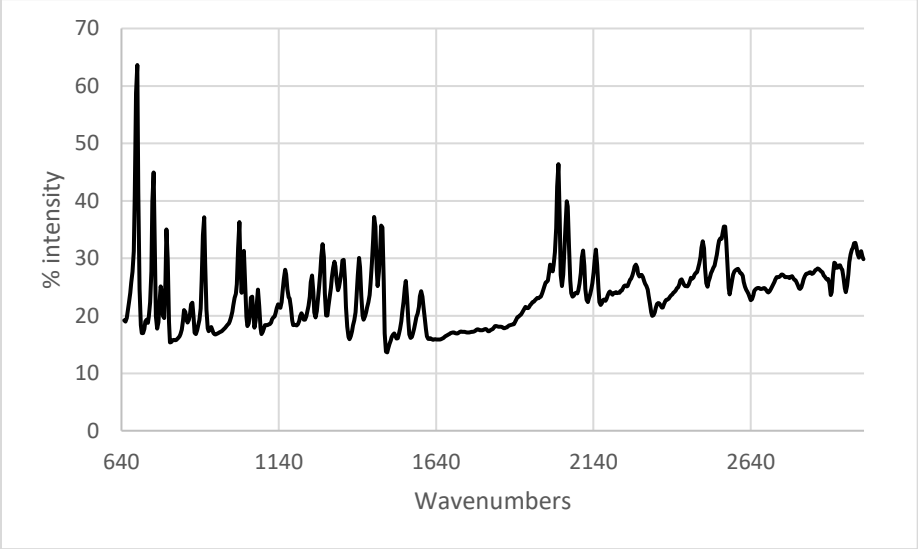
Impact of water content

To understand the tolerance of this method to water intrusion, the fluorination of **1a** was evaluted with varying degrees of water content in the acetonitrile used (measured in duplicate *via* Karl Fischer titration). Reaction profiles were evaluated at 16 hours by HPLC (210 nm). The reaction is notably tolerant to water intrusion, showing only minor deteroriation in the impurity profile and a slightly slowed reaction rate at high levels of water intrusion.

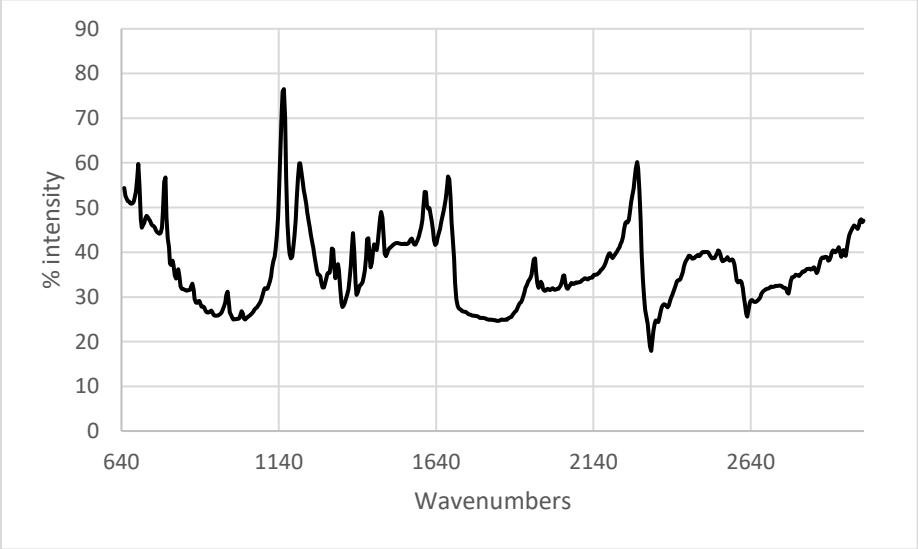
Water content (ppm) measured in duplicate	**Product (LC area %)**	**Starting Material (LC area %)**	**Impurities (LC area %)**
72.25	87.1	0.0	12.9
943.05	89.8	0.0	10.2
1955.70	89.1	0.0	10.9
3093.80	85.5	0.0	14.5
4094.50	84.6	4.0	11.4

IR data for previously unreported compounds

ethyl 4-fluoro-2-(trifluoromethyl)pyrimidine-5-carboxylate (2k)

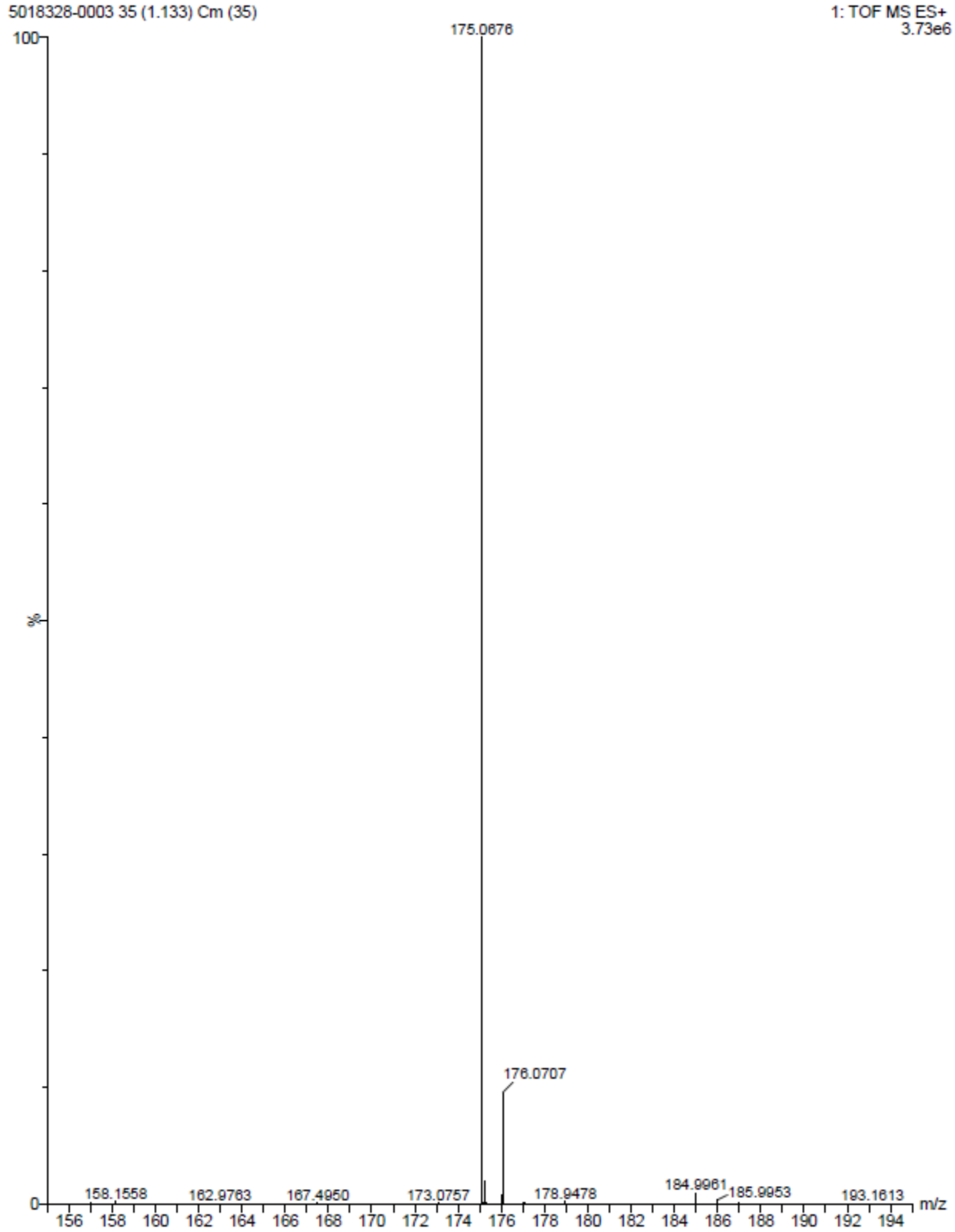


2-(chloromethyl)-4-fluoroquinazoline (2n)

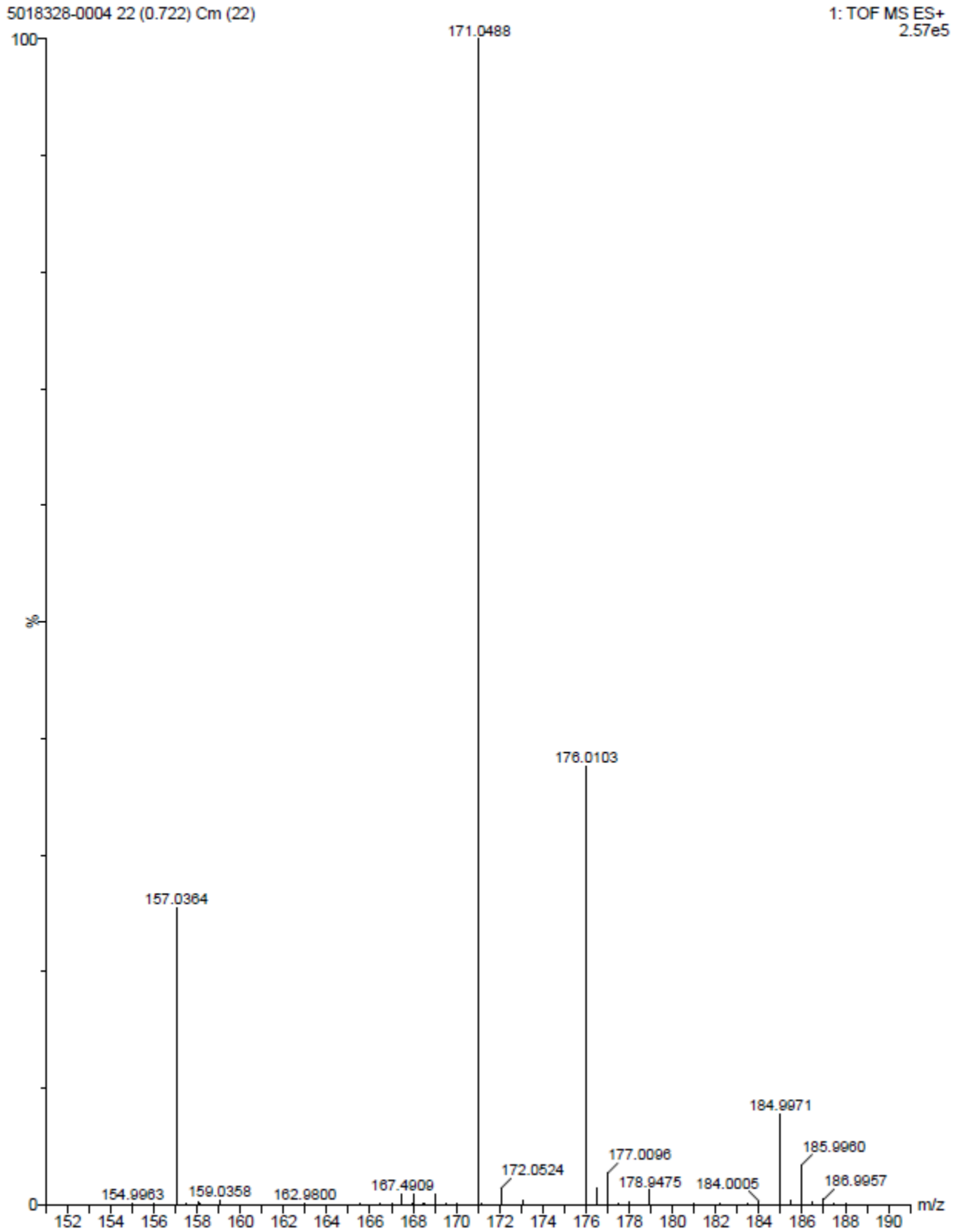


HRMS data for previously unreported and selected compounds

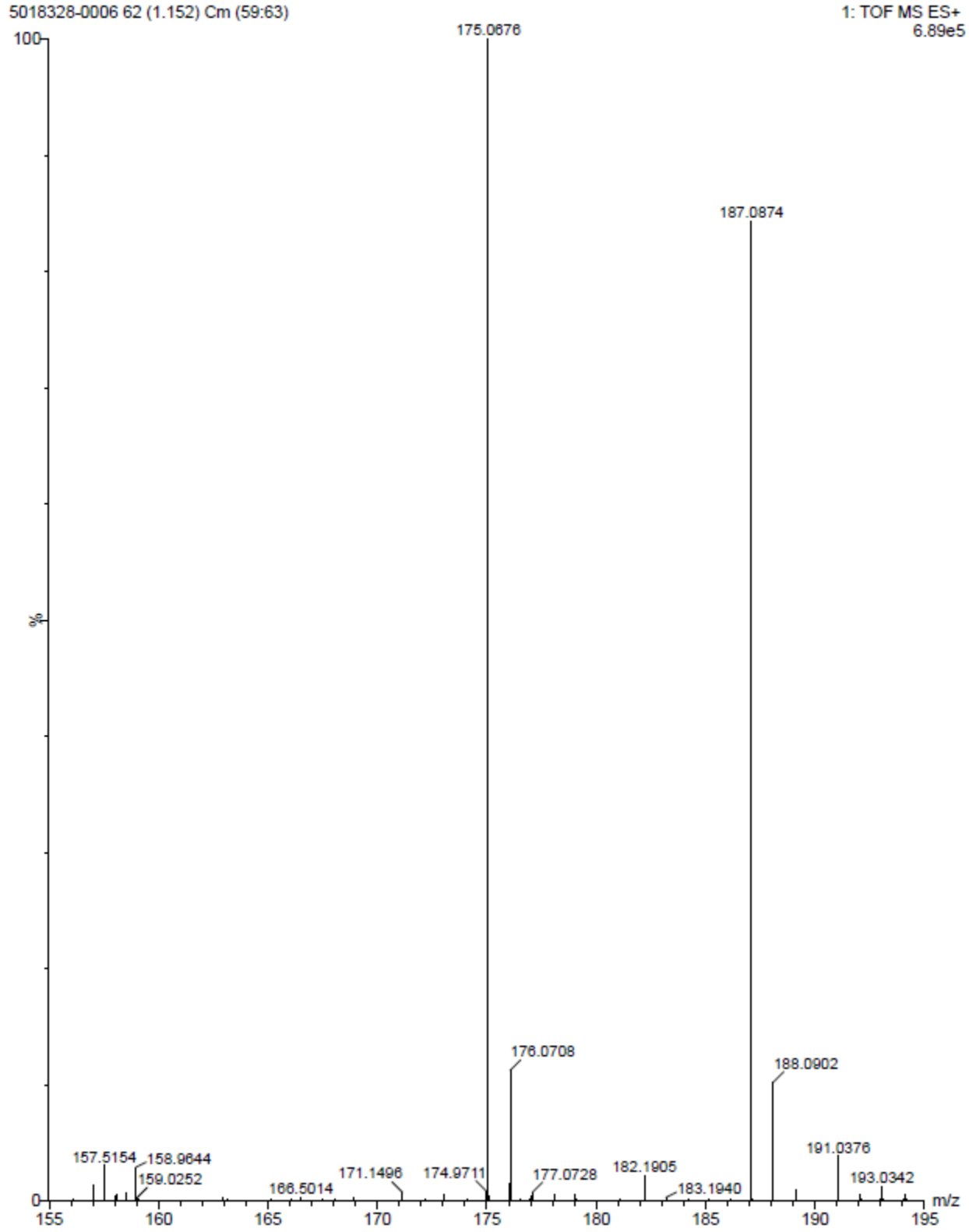
2-fluoro-4-phenylpyrimidine (2a)



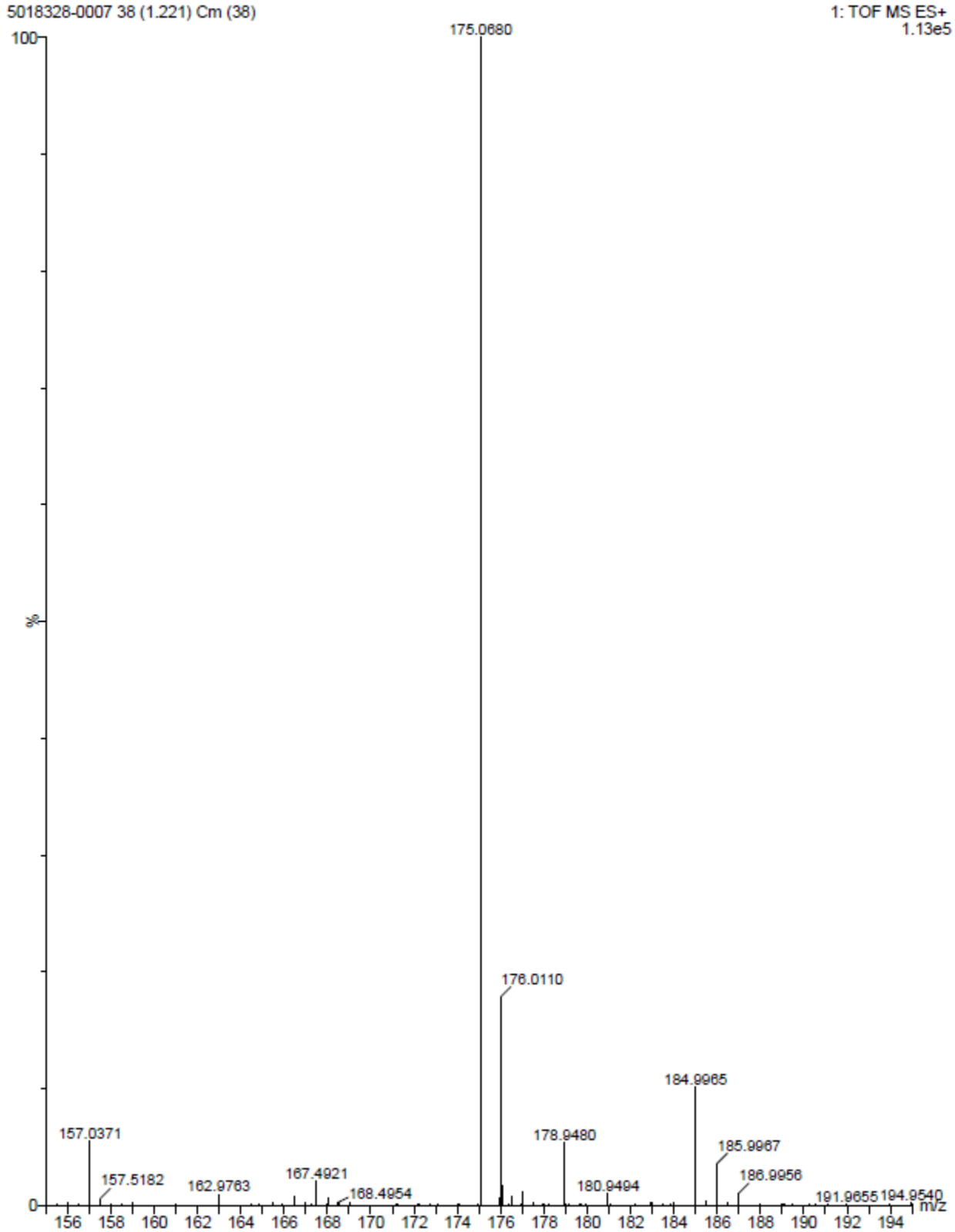
2,6-difluoro-9-methyl-9H-purine (2b)



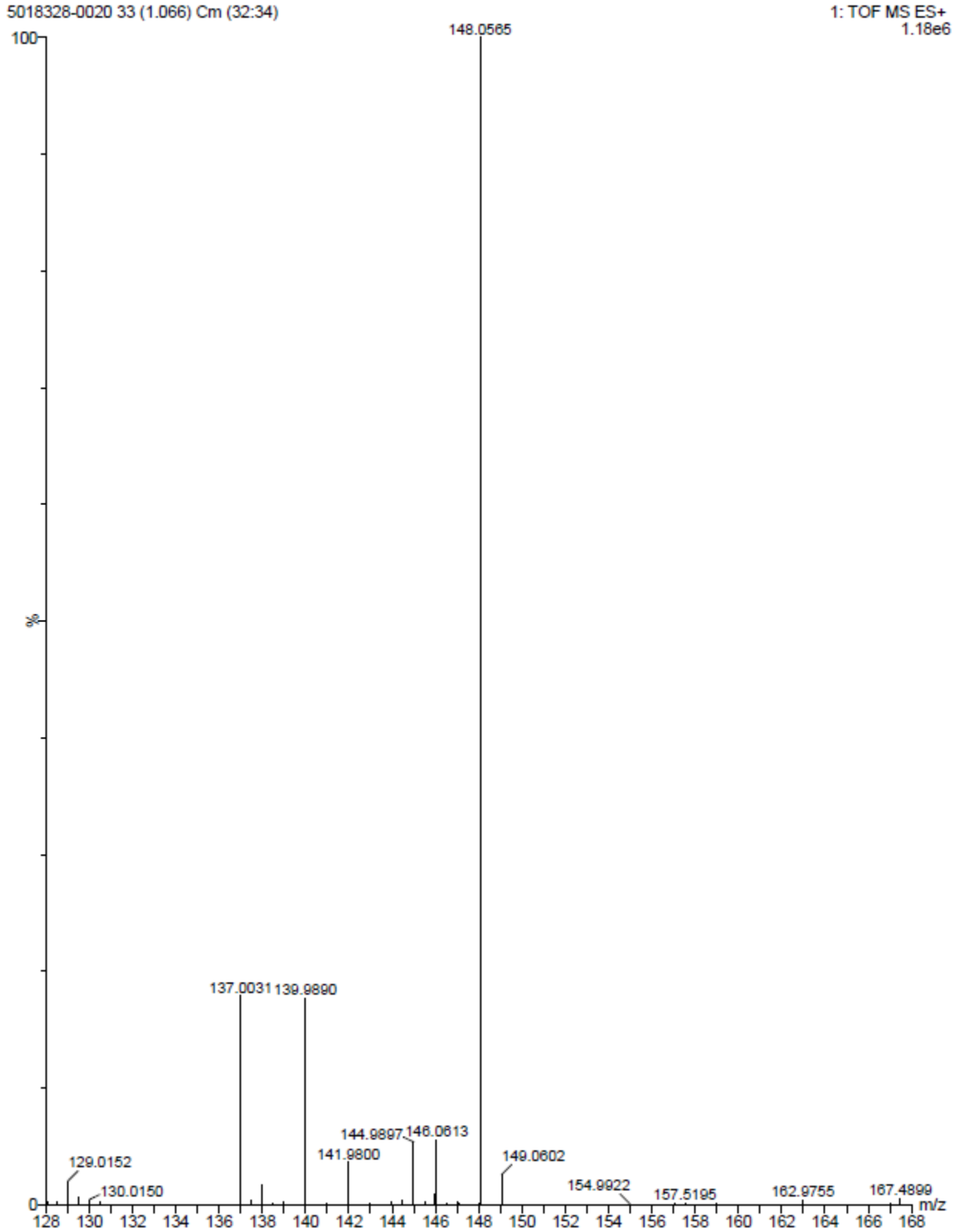
3-fluoro-6-phenylpyridazine (2d)



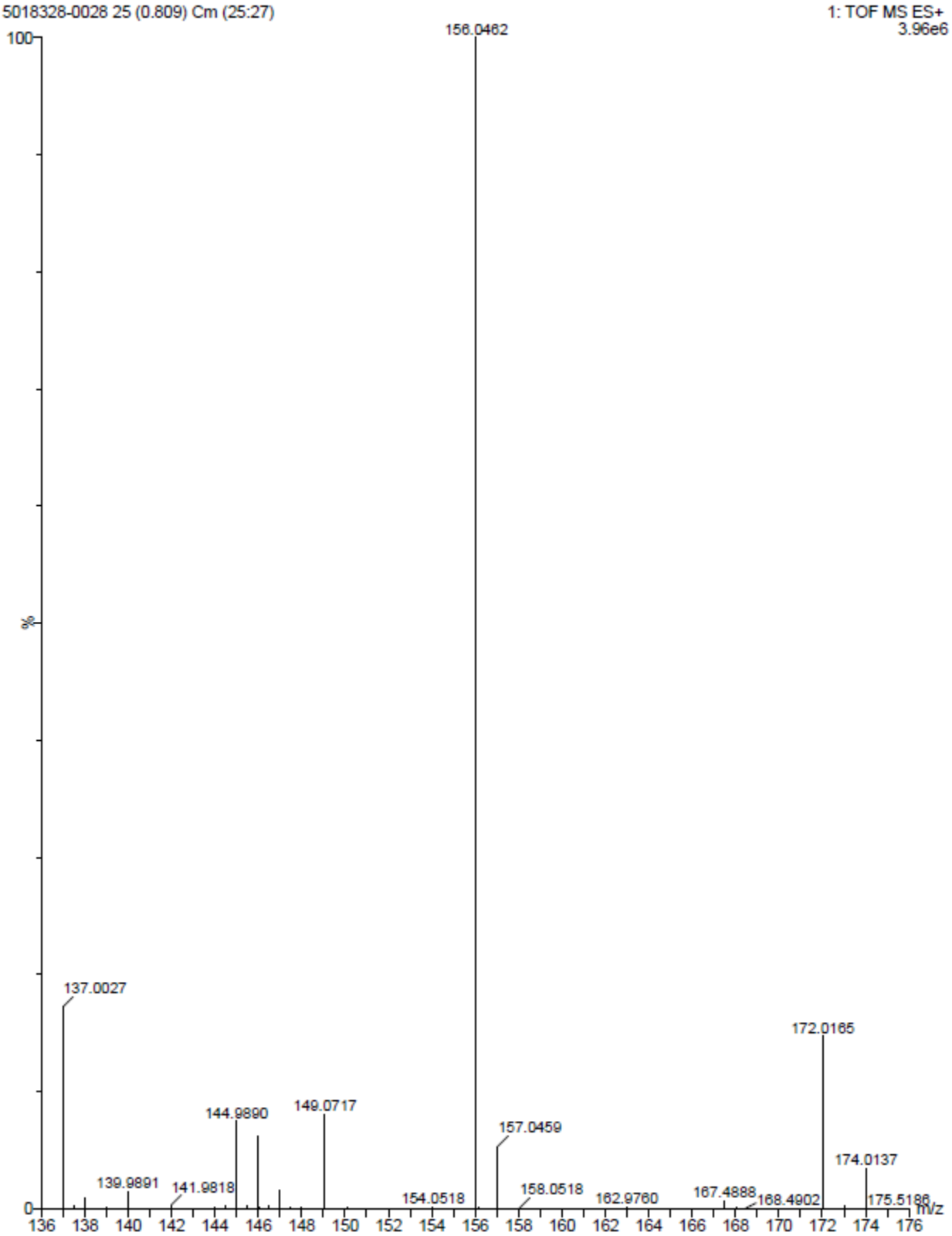
2-fluoro-5-phenylpyrazine (2g)



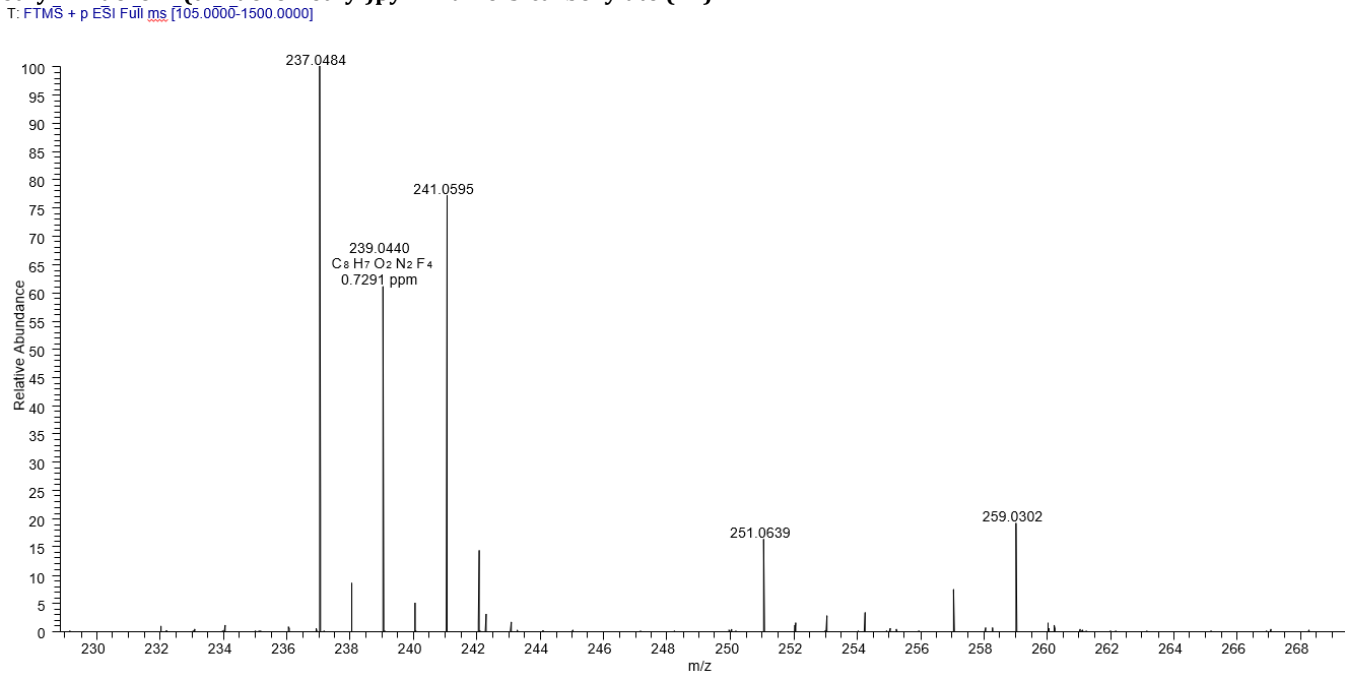
2-fluoroquinoline (2h)



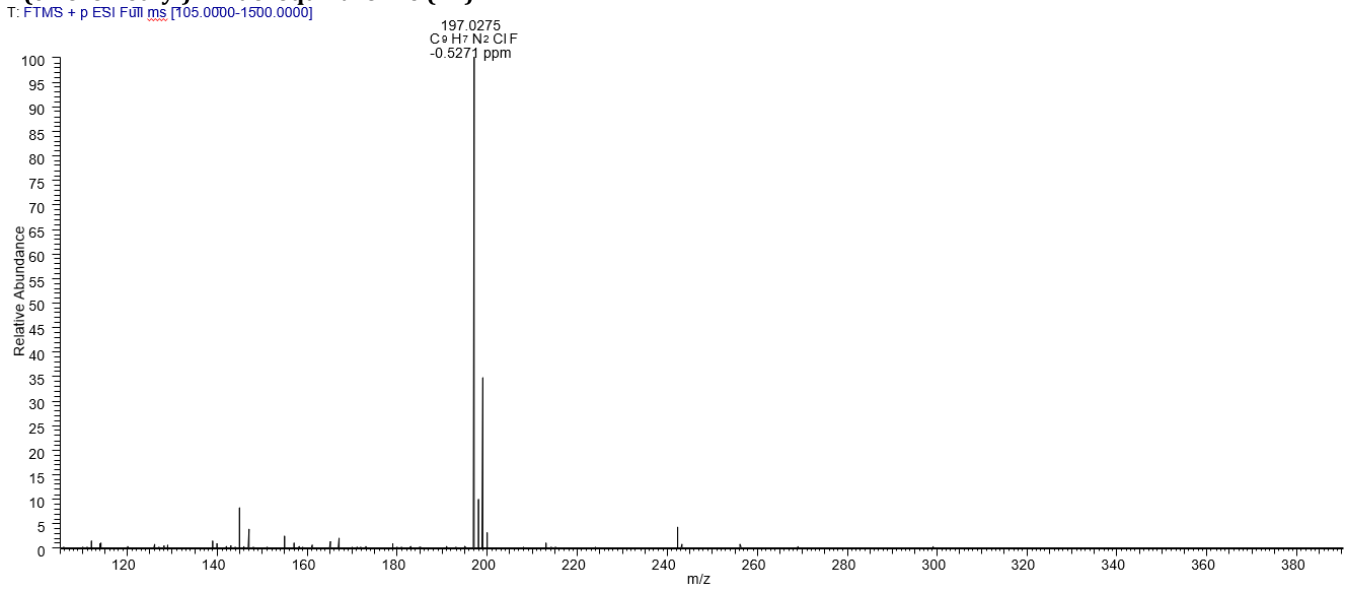
methyl 2-fluoronicotinate (2j)



ethyl 4-fluoro-2-(trifluoromethyl)pyrimidine-5-carboxylate (2k)



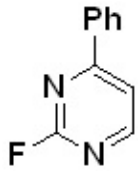
2-(chloromethyl)-4-fluoroquinazoline (2n)



References

1. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics*. **2010**, *29*, 2176–2179.

Copies of NMR data



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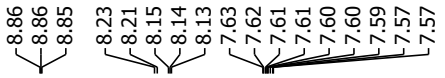

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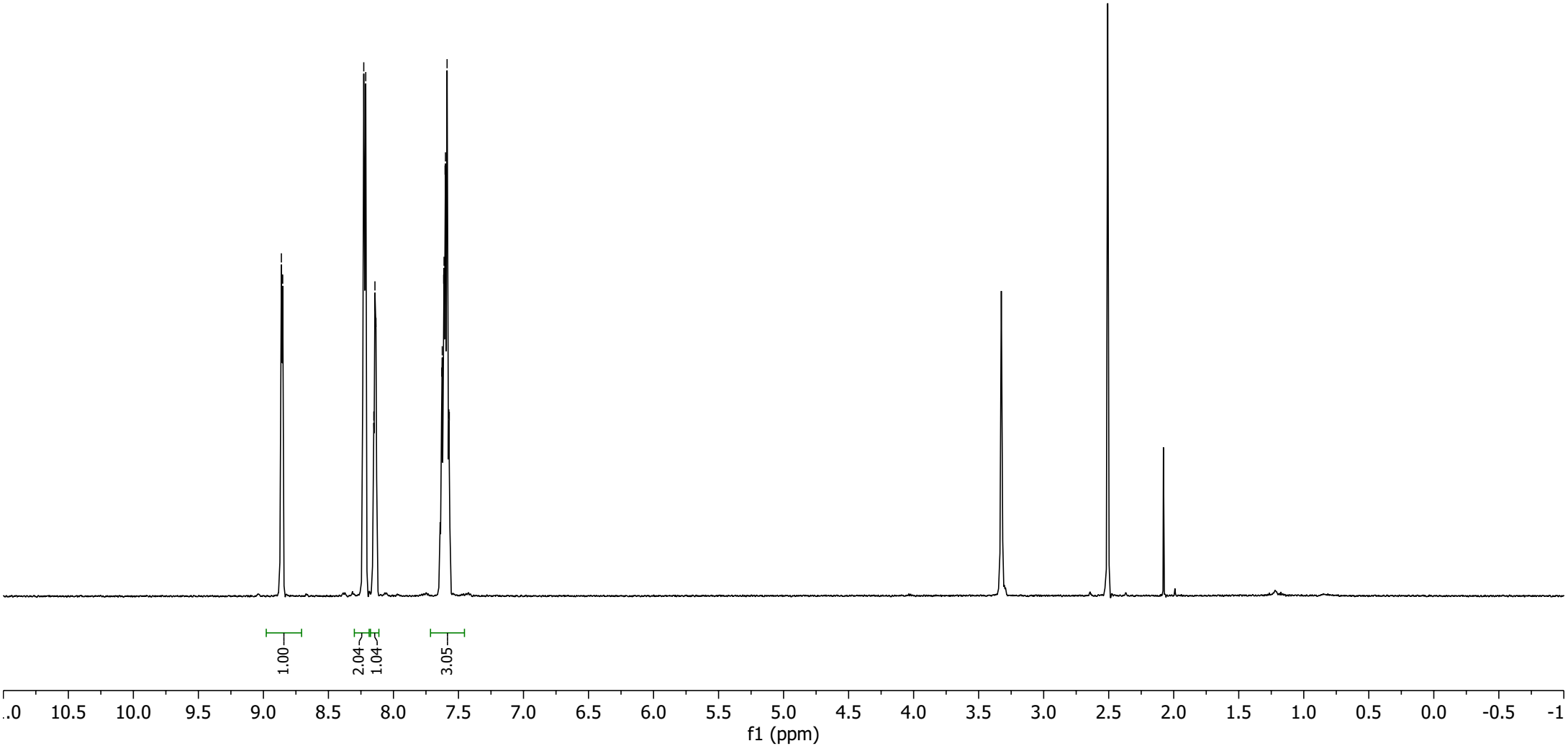

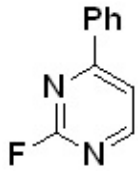

2a

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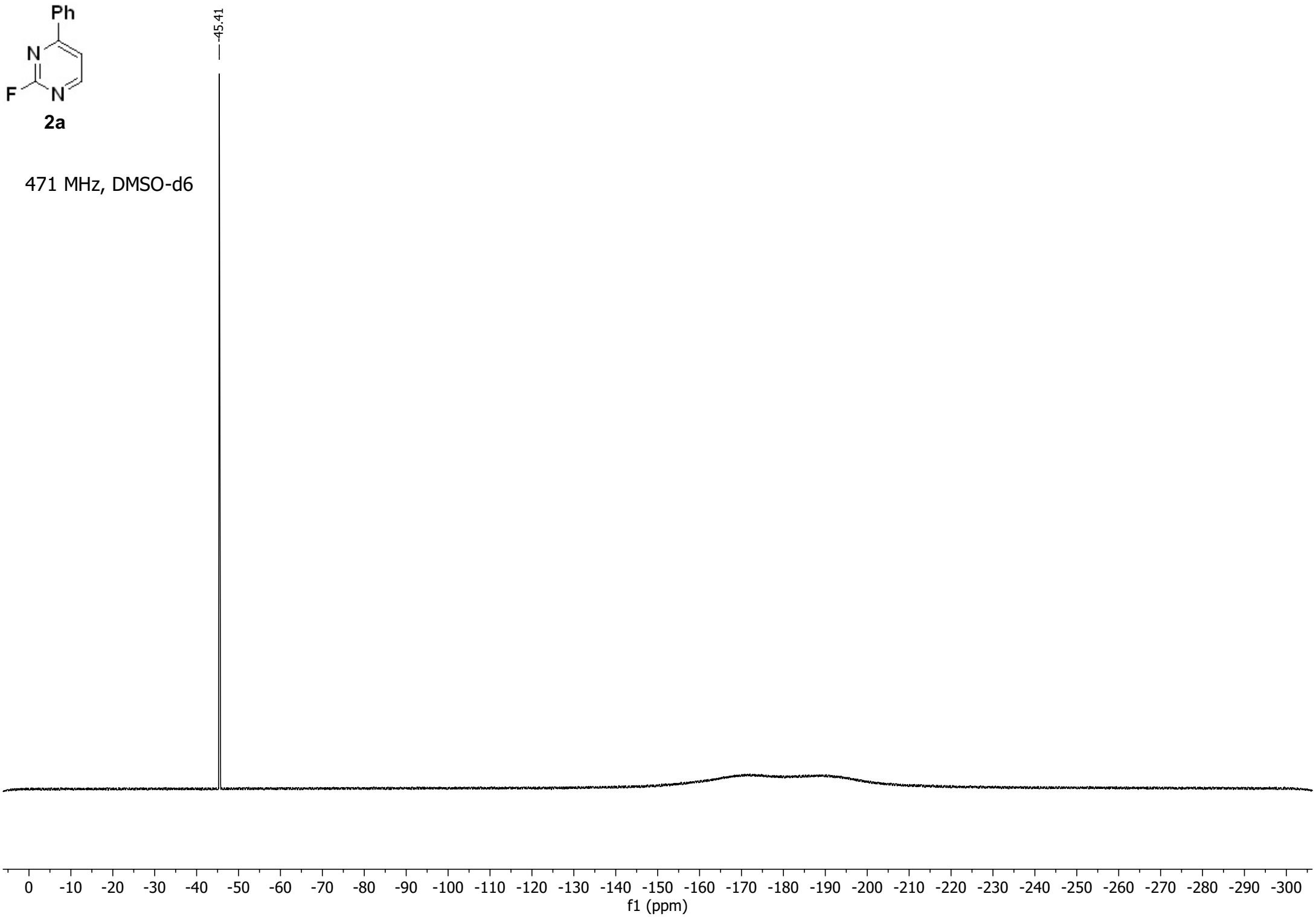
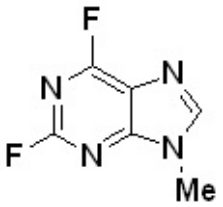
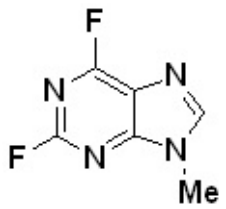

Ph
N
F
N
2a
-45.41
471 MHz, DMSO-d6
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300
f1 (ppm)



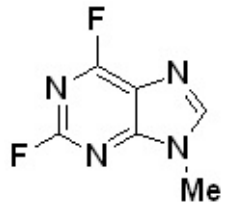
2b

500 MHz, DMSO-d6



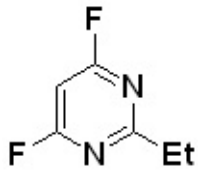
2b

126 MHz, DMSO-d6


F
N
N
F
N
N
Me

2b

-52.13
-70.53
-70.54
471 MHz, DMSO-d6
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290 -300
f1 (ppm)



2c

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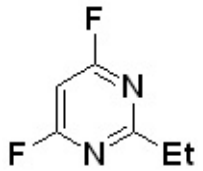
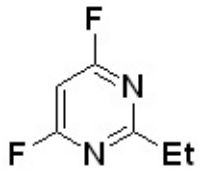


2c

126 MHz, $CDCl_3$



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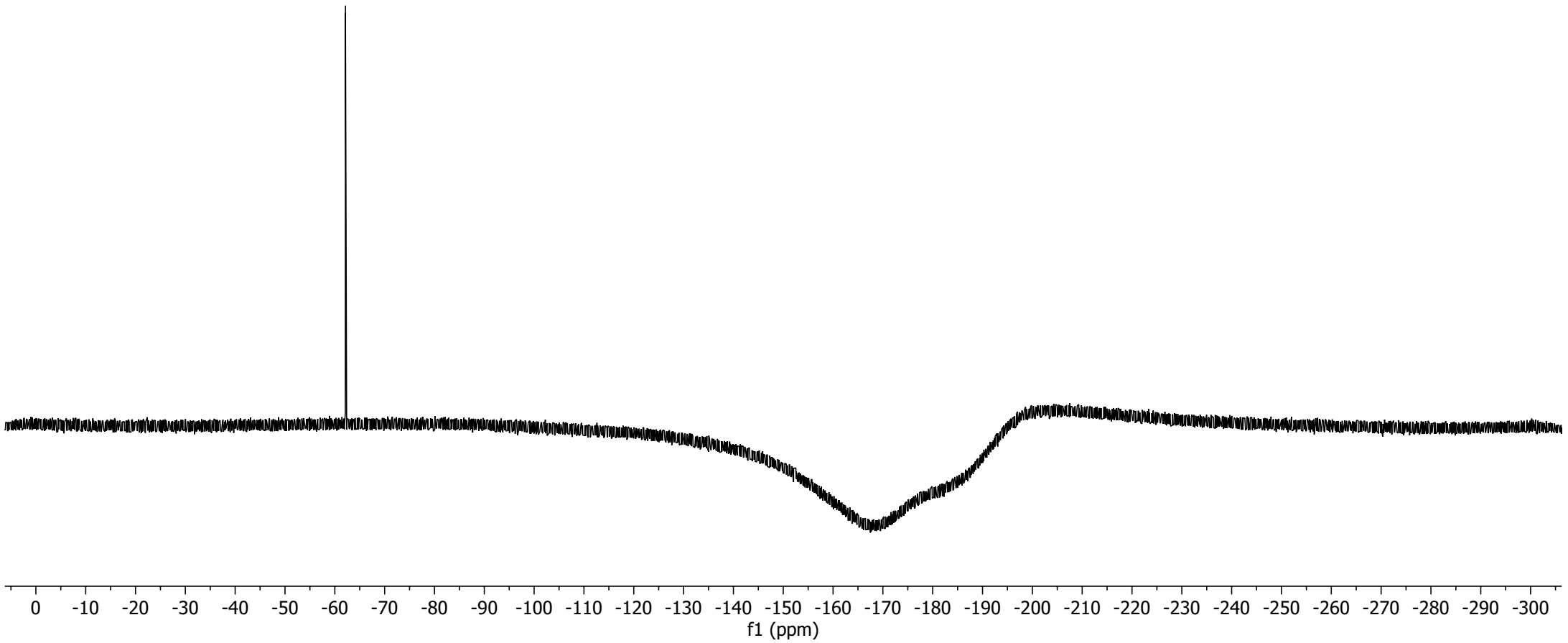
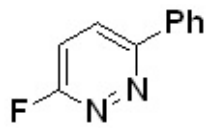
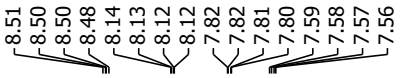
471 MHz, $CDCl_3$





2d



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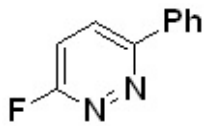

2d

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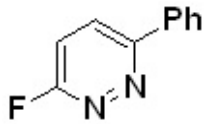

2d

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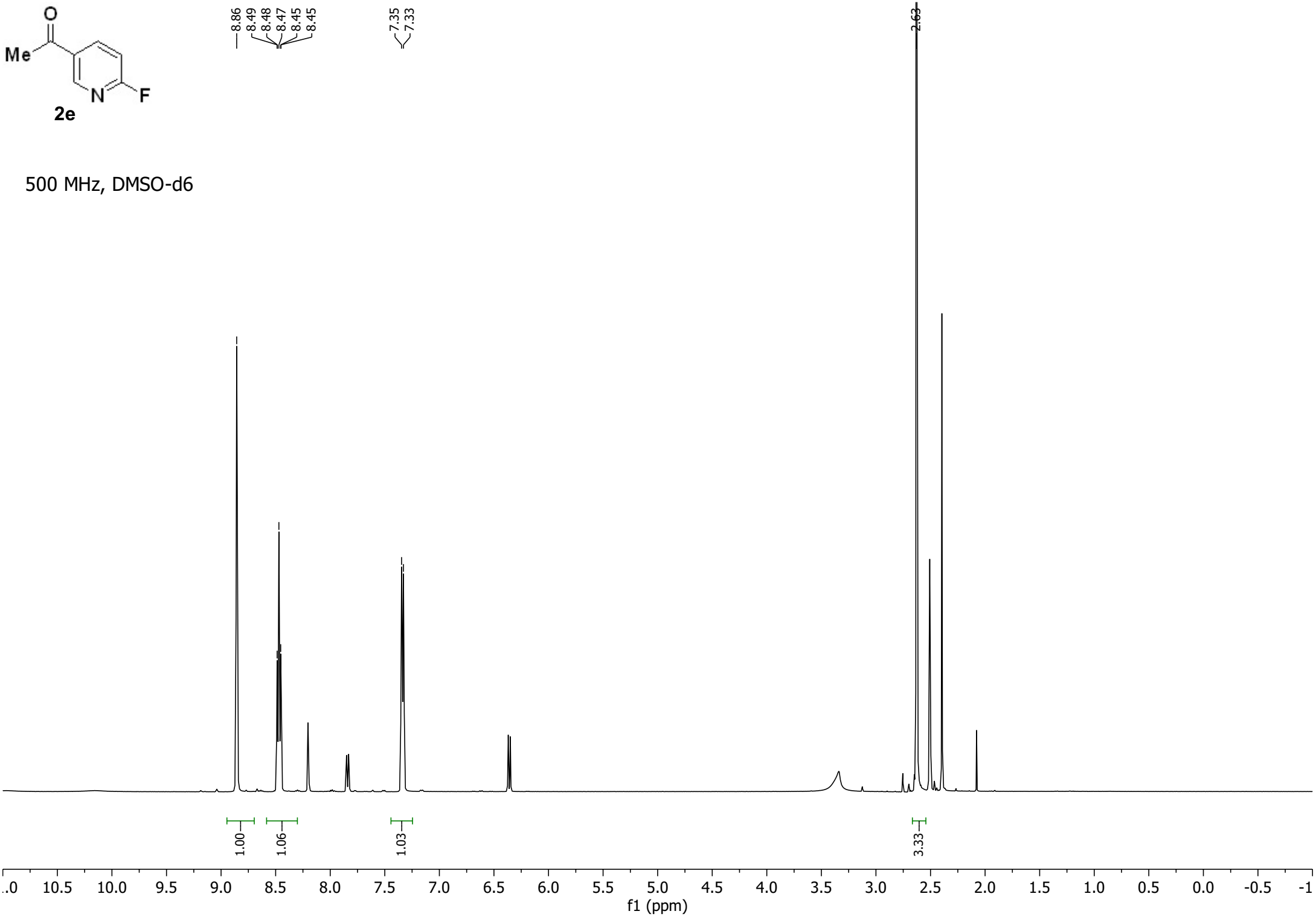
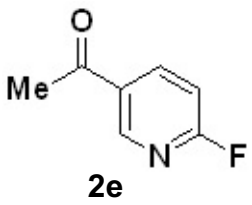

O
Me
N
F
2e
8.86
8.49
8.48
8.47
8.45
8.45
7.35
7.33
2.63
500 MHz, DMSO-d6
1.00
1.06
1.03
3.33
f1 (ppm)



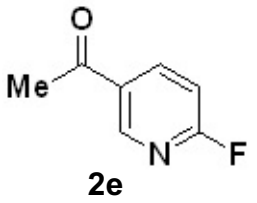
2e

196.23
166.35
164.42
149.76
149.63
142.50
142.43
131.64
131.61
110.51
110.21
27.45

126 MHz, DMSO-d6

260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60

f1 (ppm)



2e

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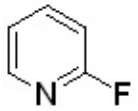

2f

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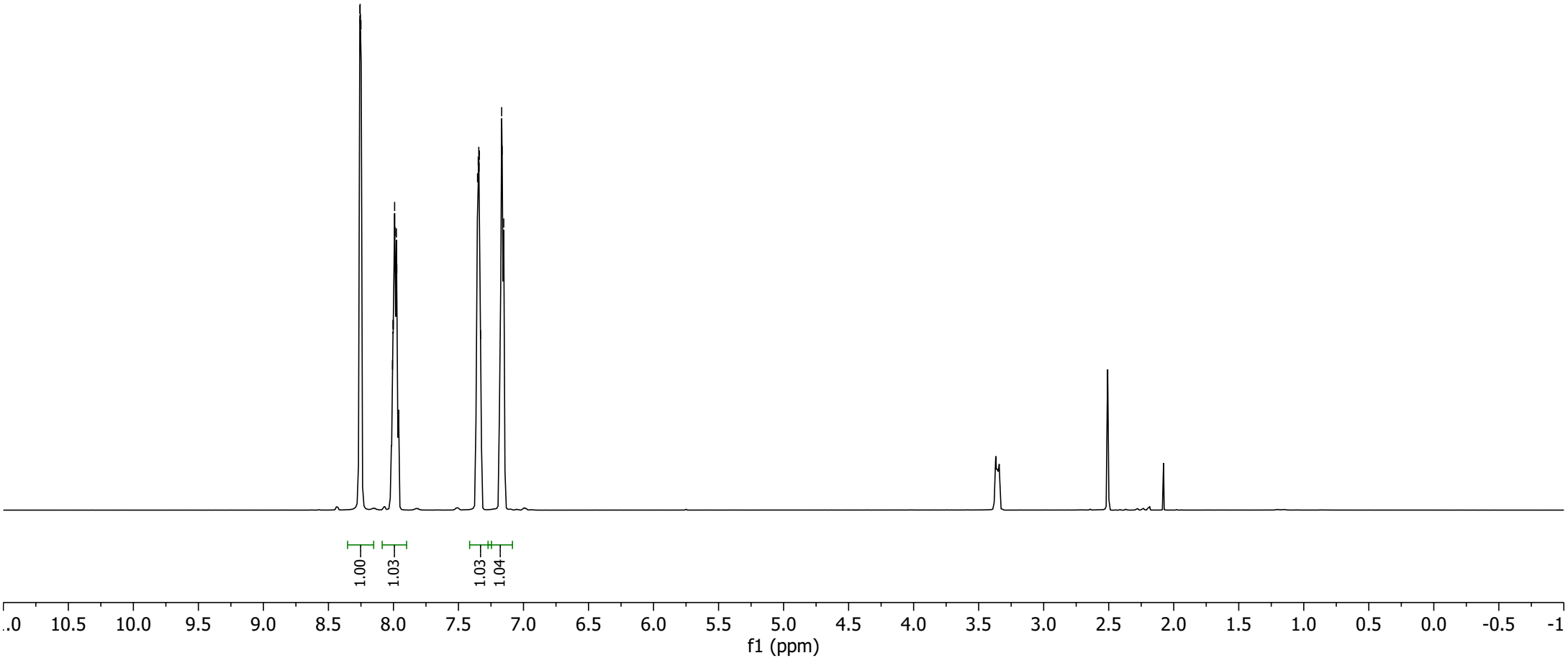
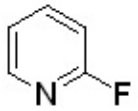




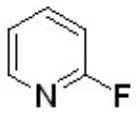
2f

164.40
162.53
148.17
148.06
142.55
142.49
122.39
110.21
109.92

126 MHz, DMSO-d6

260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60

f1 (ppm)



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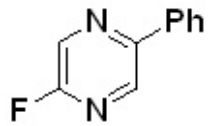
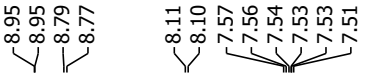


2g



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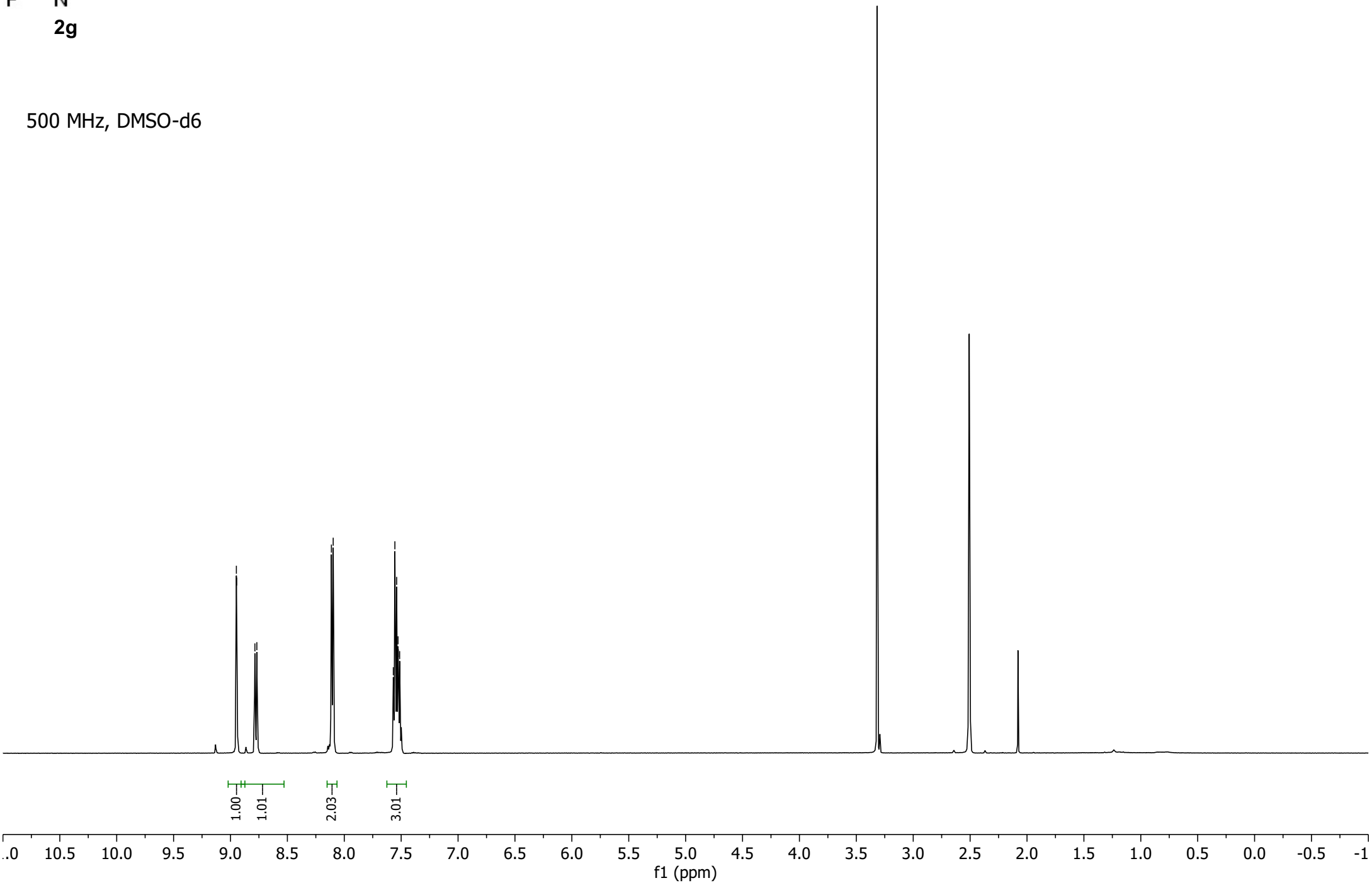

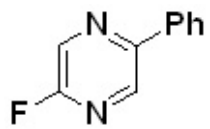

2g

160.70
158.72
150.14
139.07
139.00
135.38
133.44
133.14
130.27
129.55
127.08

126 MHz, DMSO-d6

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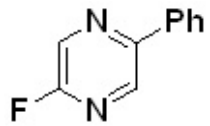
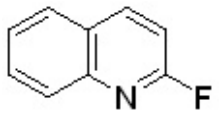
f1 (ppm)



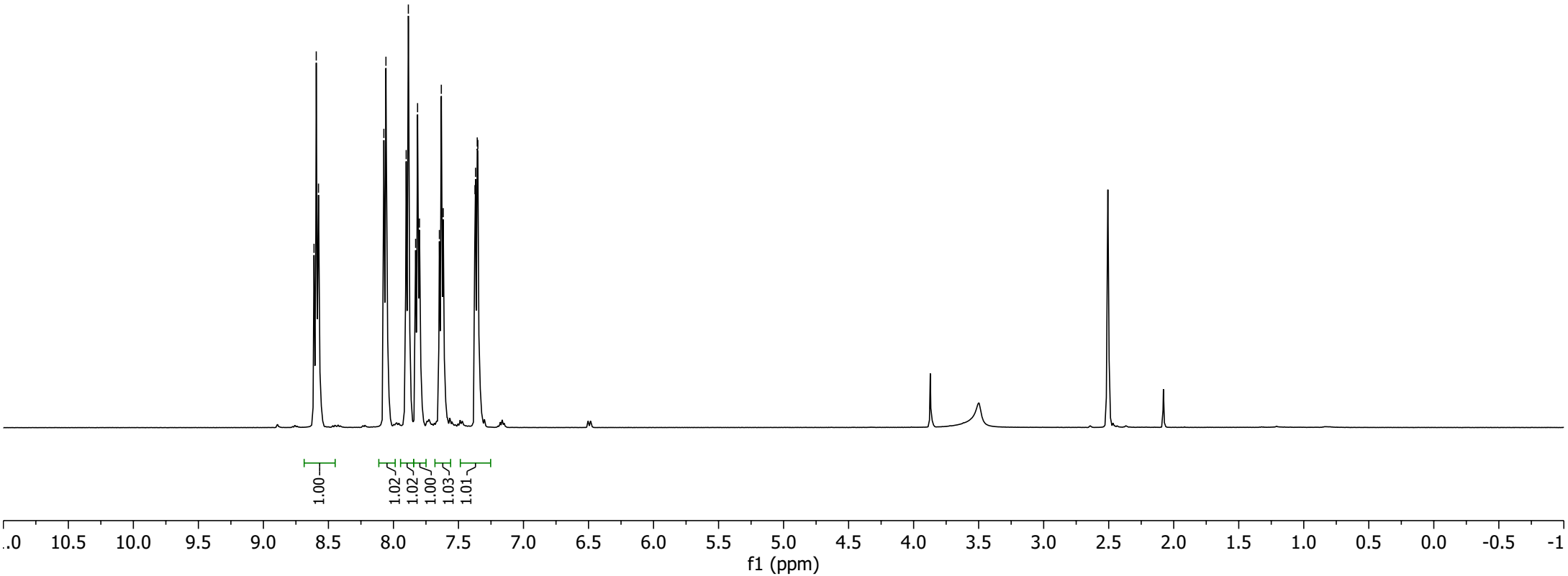
2g

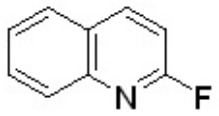
471 MHz, DMSO-d6



2h

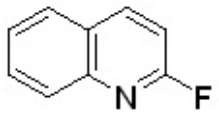
500 MHz, DMSO-d6





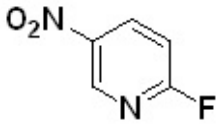
2h

126 MHz, DMSO-d6



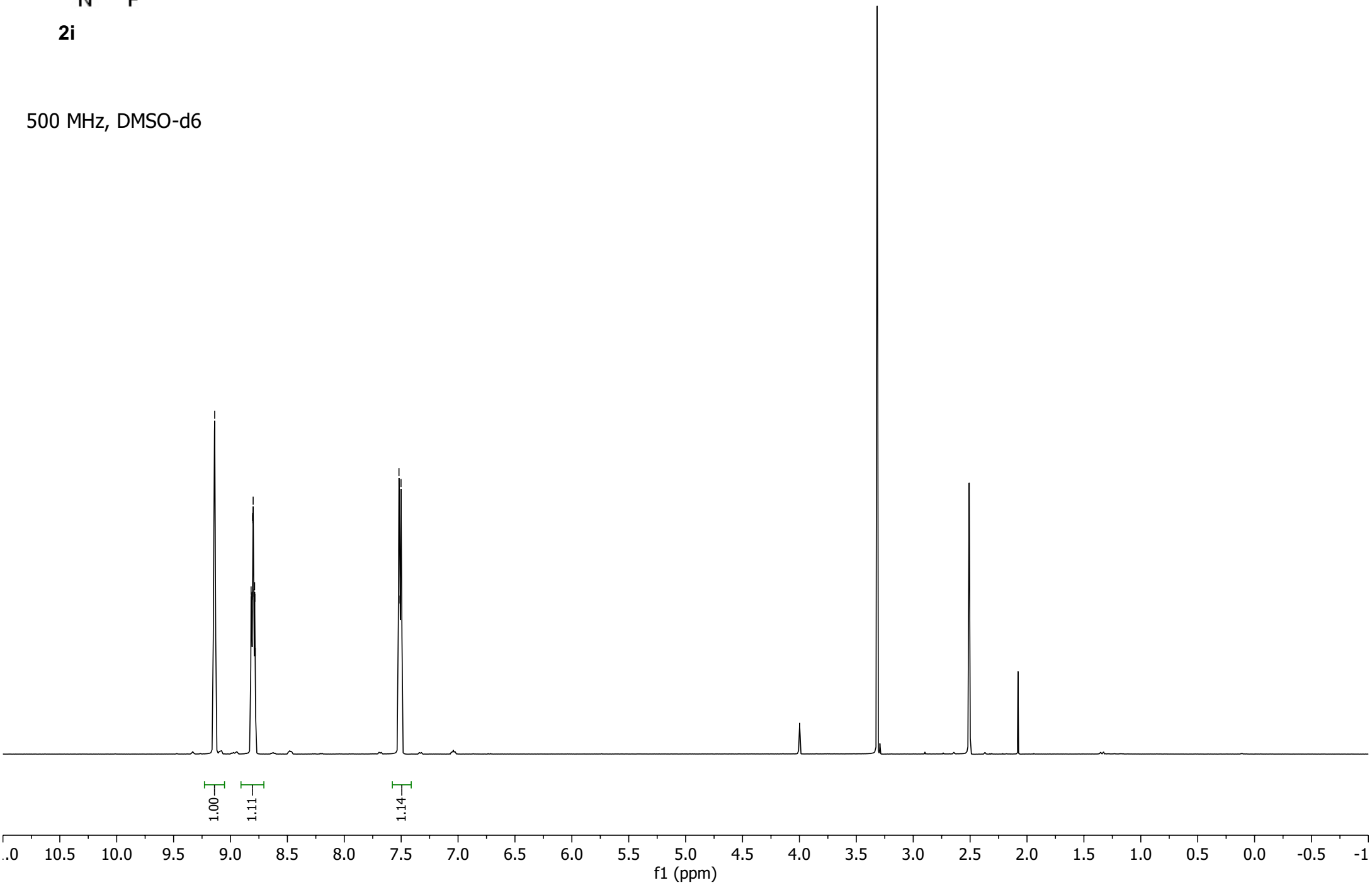
2h

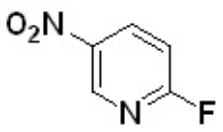
471 MHz, DMSO-d6



2i

500 MHz, DMSO-d6



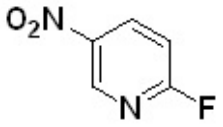


2i

126 MHz, DMSO-d6

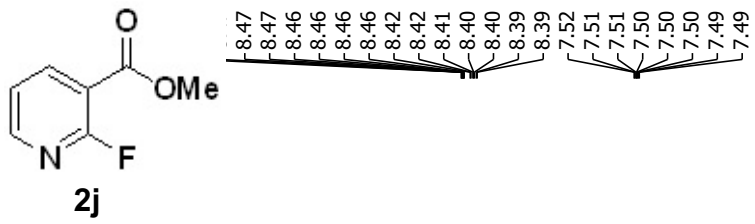
166.56
164.61
145.26
145.11
143.56
138.65
138.57
111.48
111.17

f1 (ppm)



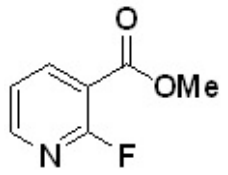
2i

471 MHz, DMSO-d6



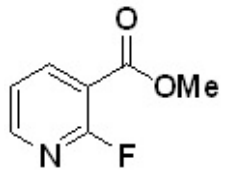
2j

500 MHz, DMSO-d6



2j

126 MHz, DMSO-d6

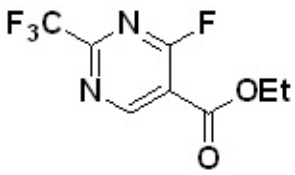


2j

471 MHz, DMSO-d6

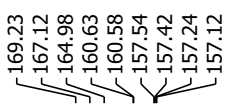
2k

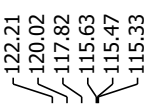
500 MHz, DMSO-d6

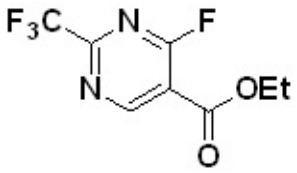


2k

126 MHz, DMSO-d6





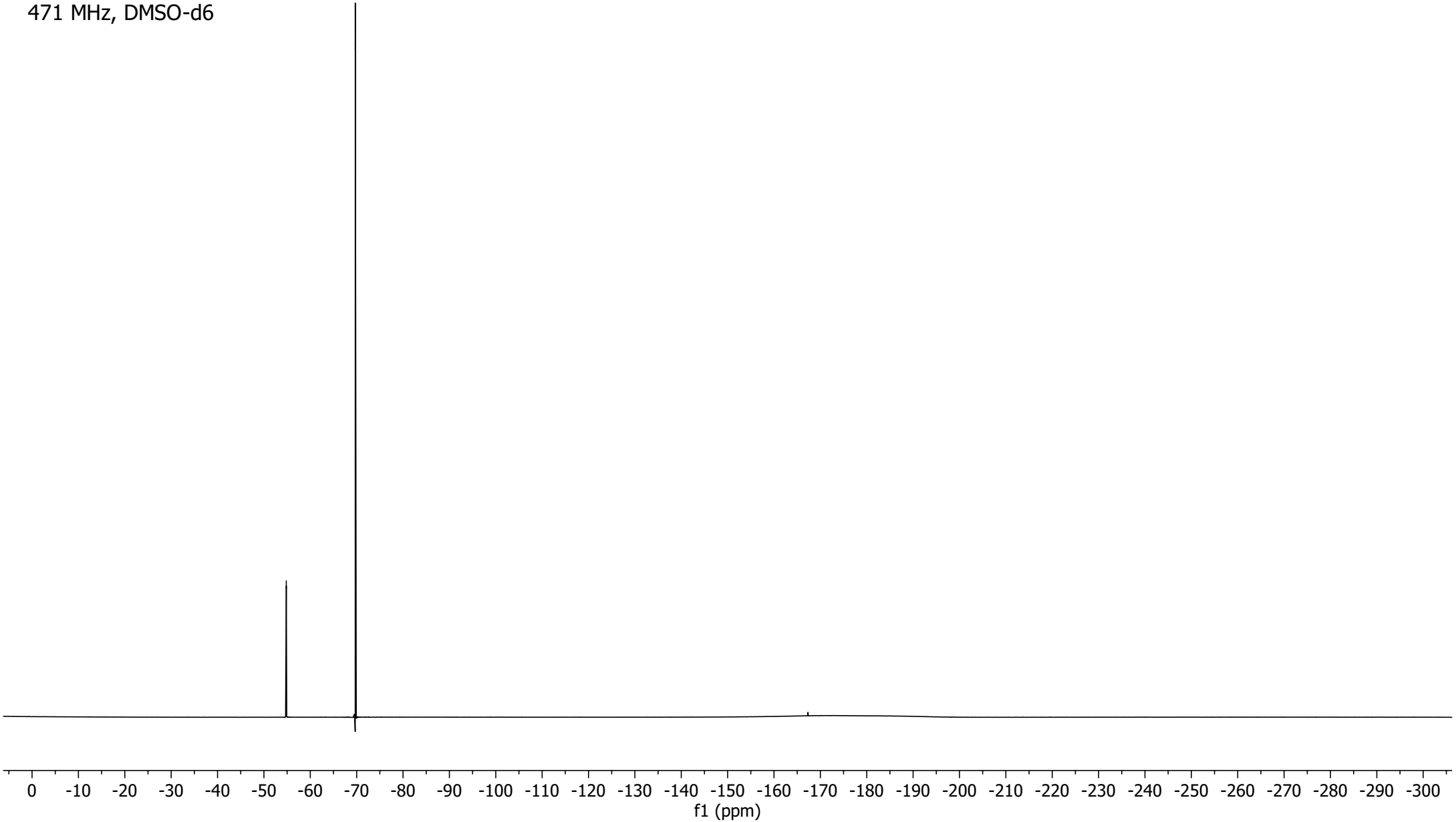


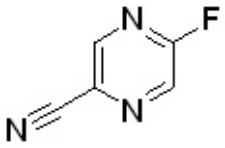
2k

-54.83

-69.70

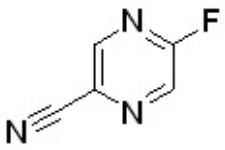
471 MHz, DMSO-d6





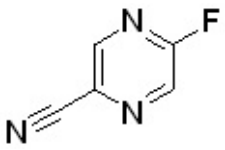
2l

500 MHz, CD_3CN



2l

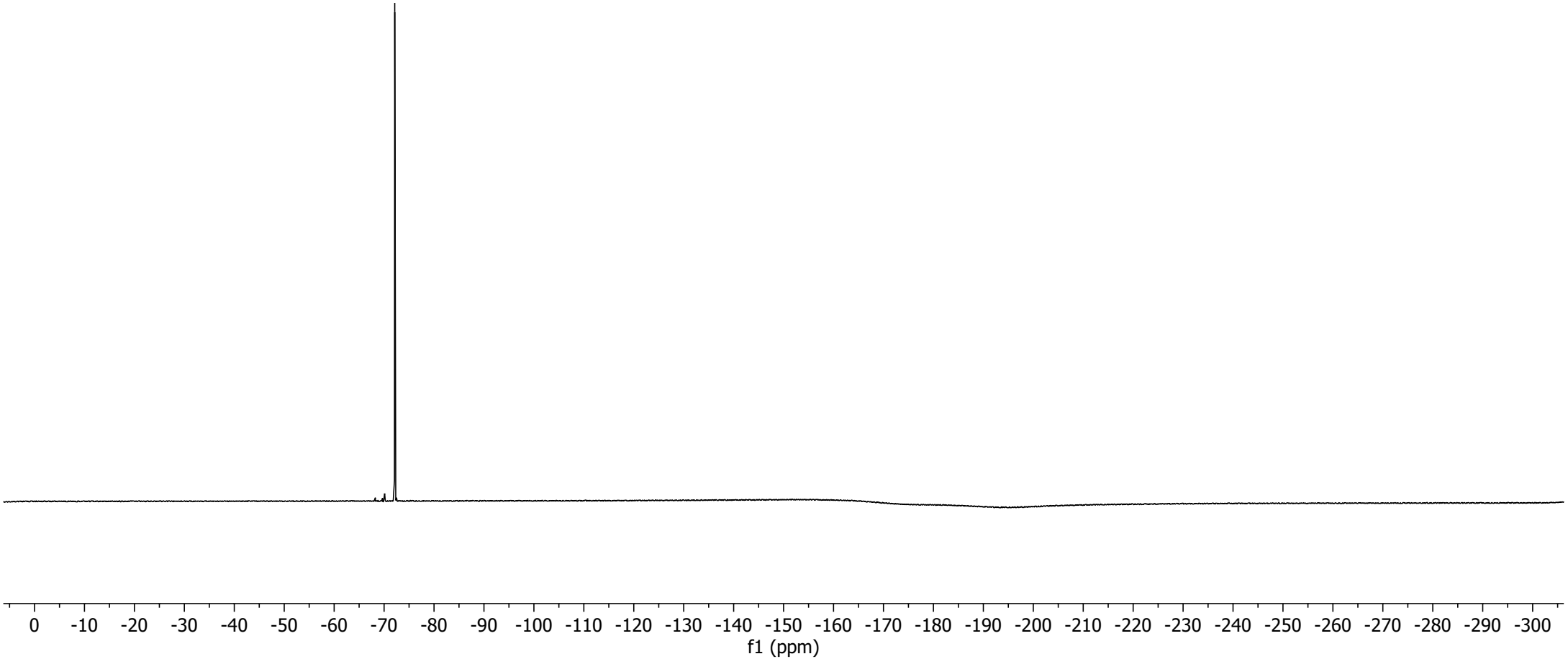
126 MHz, CD_3CN



2l

-72.13

471 MHz, CD_3CN

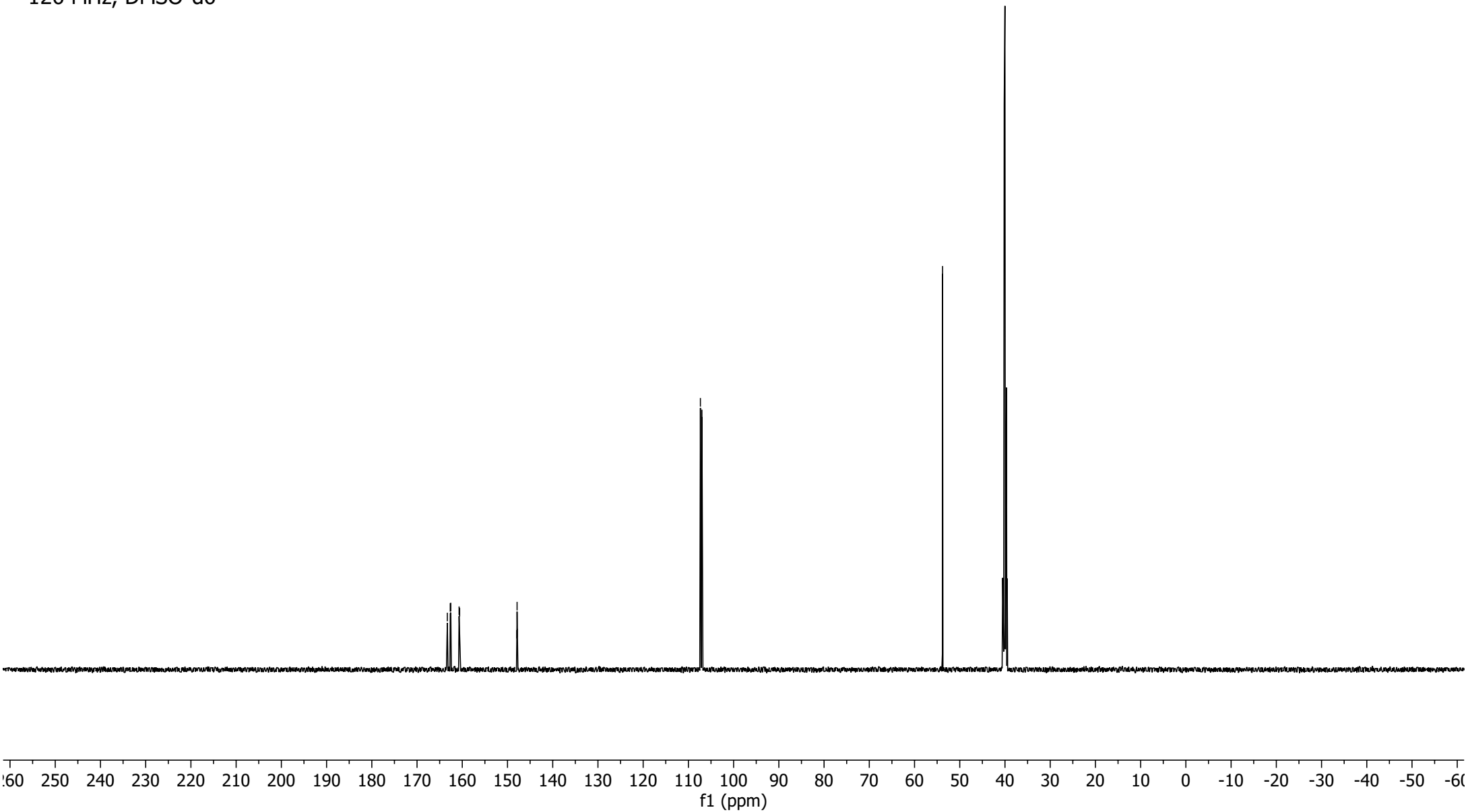


2m

500 MHz, DMSO-d6

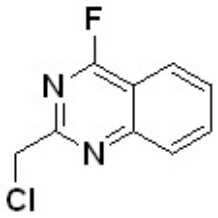
2m

126 MHz, DMSO-d6



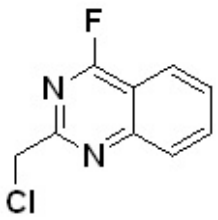
2m

471 MHz, DMSO-d6



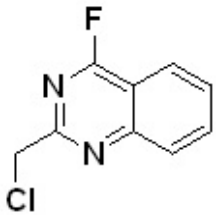
2n

500 MHz, DMSO-d6



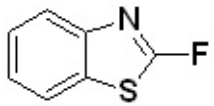
2n

126 MHz, DMSO-d6



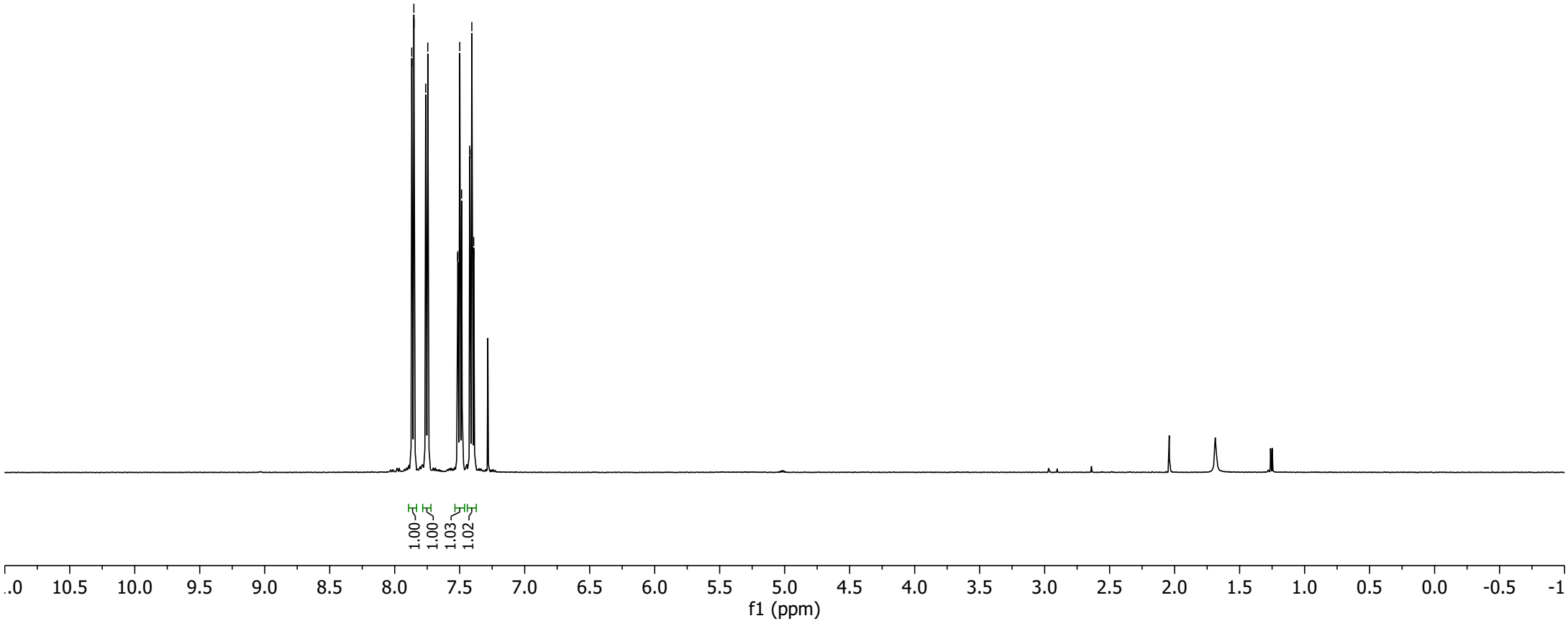
2n

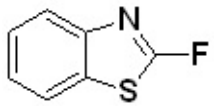
471 MHz, DMSO-d6



2o

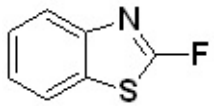
500 MHz, $CDCl_3$





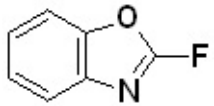
2o

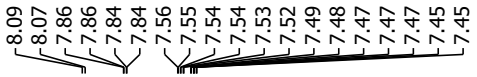
126 MHz, $CDCl_3$



2o

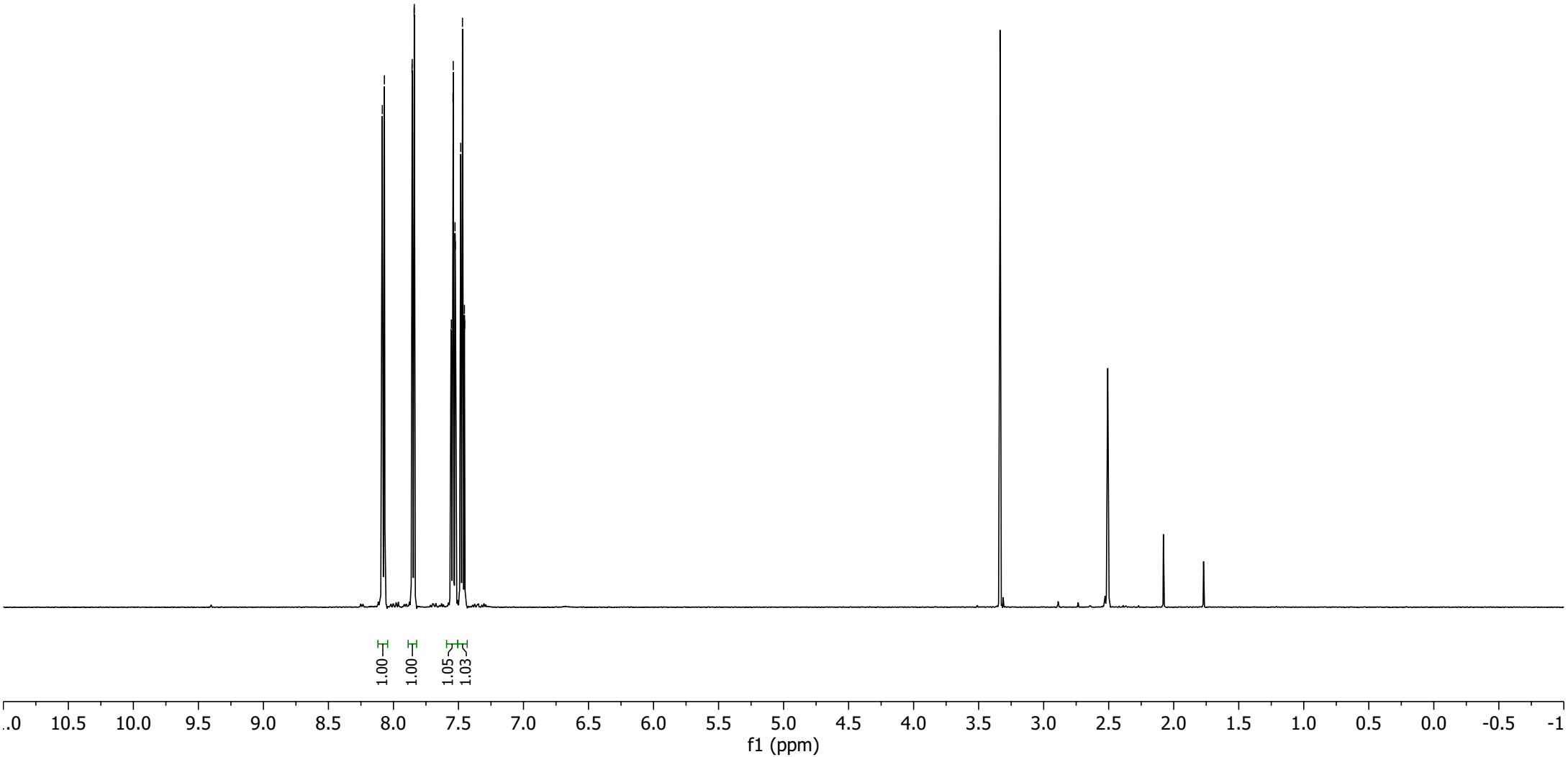
471 MHz, $CDCl_3$

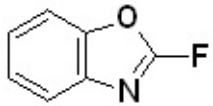




2p

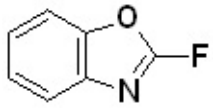
500 MHz, DMSO-d6





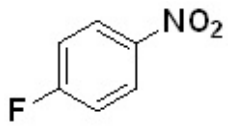
2p

126 MHz, DMSO-d6

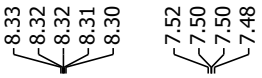


2p

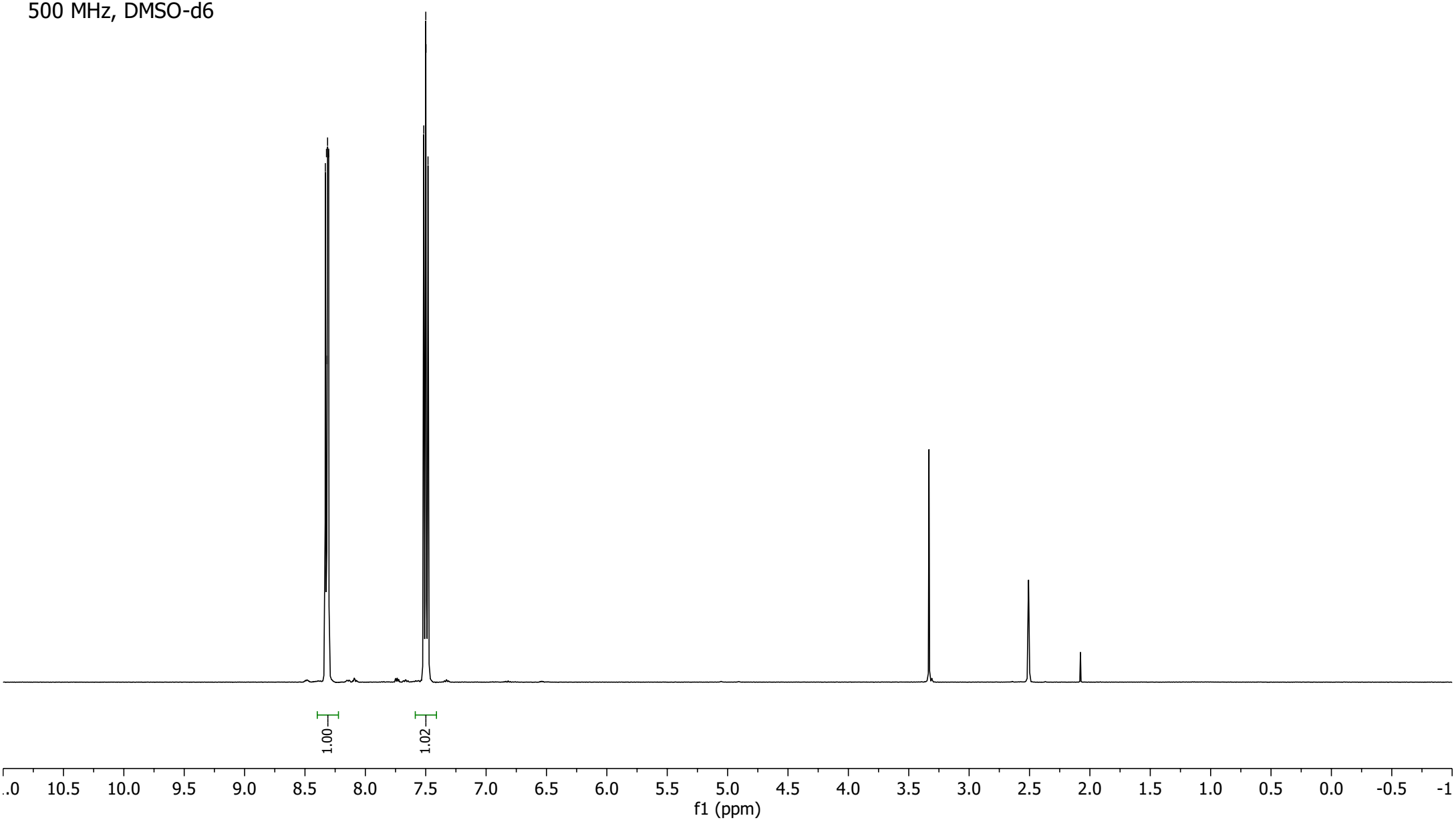
471 MHz, DMSO-d6

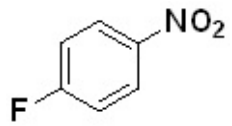


4a



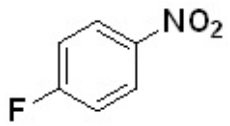
500 MHz, DMSO-d6





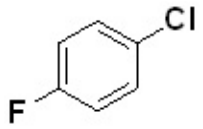
4a

126 MHz, DMSO-d6



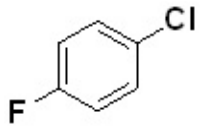
4a

471 MHz, DMSO-d6



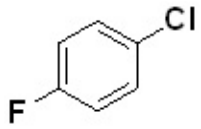
4b

500 MHz, DMSO-d6



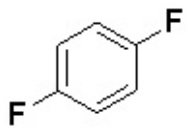
4b

126 MHz, DMSO-d6



4b

471 MHz, DMSO-d6



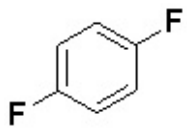
4c

7.26
7.25
7.23

500 MHz, DMSO-d6

19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4 -5 -6

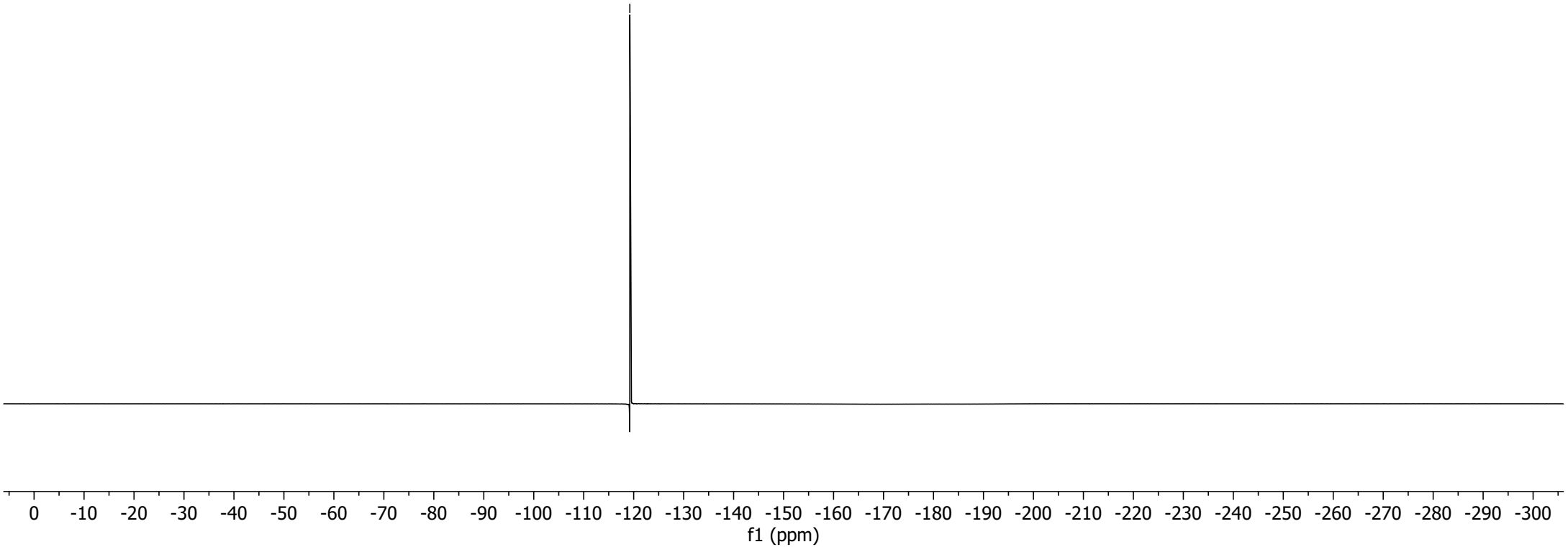
f1 (ppm)

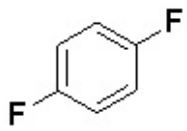


4c

-119.23

126 MHz, DMSO-d6





4c

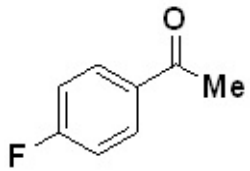
159.78
159.75
157.86
157.83

117.38
117.34
117.23
117.18
117.08
117.04

471 MHz, DMSO-d6

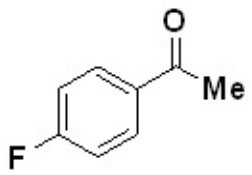
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60

f1 (ppm)



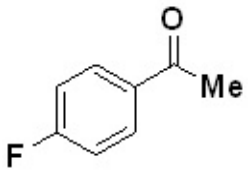
4d

500 MHz, CD_3CN



4d

126 MHz, CD_3CN



4d

471 MHz, CD_3CN