

Development of a Novel Route for Incorporation of Carbon-14 into the Pyridine Ring of RinskorTM Active

Pete Johnson

Process Chemistry, Corteva AgriscienceTM, 9330 Zionsville Rd., Indianapolis, IN 46268, USA

Supporting Information

Table of Contents

Figure S1-a. ¹ H NMR spectra (CDCl ₃) of 2,2,2-trifluoro-N-tritylethanimidoyl chloride (17).	4
Figure S1-b. ¹⁹ F NMR spectra (CDCl ₃) of 2,2,2-trifluoro-N-tritylethanimidoyl chloride (17).....	5
Figure S1-c. ¹³ C NMR spectra (CDCl ₃) of 2,2,2-trifluoro-N-tritylethanimidoyl chloride (17).	6
Figure S2-a. ¹ H NMR spectra (CDCl ₃) of <i>N</i> -[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).....	7
Figure S2-b. ¹⁹ F NMR spectra (CDCl ₃) of <i>N</i> -[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).....	8
Figure S2-c. ¹³ C NMR spectra (CDCl ₃) of <i>N</i> -[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).....	9
Figure S3-a. ¹ H NMR spectra (CDCl ₃) of 4-chloro-2-fluoro-3-methoxybenzaldehyde <i>O</i> -methyl oxime (20).....	10
Figure S3-b. ¹⁹ F NMR spectra (CDCl ₃) of 4-chloro-2-fluoro-3-methoxybenzaldehyde <i>O</i> -methyl oxime (20).....	11
Figure S3-c. ¹³ C NMR spectra (CDCl ₃) of 4-chloro-2-fluoro-3-methoxybenzaldehyde <i>O</i> -methyl oxime (20).....	12
Figure S4-a. ¹ H NMR spectra (CDCl ₃) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).13	
Figure S4-b. ¹⁹ F NMR spectra (CDCl ₃) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).14	
Figure S4-c. ¹³ C NMR spectra (CDCl ₃) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).15	

Figure S5-a. ^1H NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-tritylpyridin-4-amine (21).....	16
Figure S5-b. ^{19}F NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-tritylpyridin-4-amine (21).....	17
Figure S5-c. ^{13}C NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-tritylpyridin-4-amine (21).....	18
Figure S6-a. ^1H NMR spectra ($\text{DMSO}-d_6$) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).....	19
Figure S6-b. ^{19}F NMR spectra ($\text{DMSO}-d_6$) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).....	20
Figure S6-c. ^{13}C NMR spectra ($\text{DMSO}-d_6$) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).....	21
Figure S7-a. ^1H NMR spectra ($\text{DMSO}-d_6$) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).....	22
Figure S7-b. ^{19}F NMR spectra ($\text{DMSO}-d_6$) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).....	23
Figure S7-c. ^{13}C NMR spectra ($\text{DMSO}-d_6$) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).....	24
Figure S8-a. ^1H NMR spectra ($\text{DMSO}-d_6$) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).....	25
Figure S8-b. ^{19}F NMR spectra ($\text{DMSO}-d_6$) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).....	26
Figure S8-c. ^{13}C NMR spectra ($\text{DMSO}-d_6$) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).....	27
Figure S9-a. ^1H NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).	28
Figure S9-b. ^{19}F NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).	29
Figure S9-c. ^{13}C NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).	30
Figure S10. HPLC chromatograms for 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-trityl(4- ^{14}C)pyridin-4-amine (26).....	31
Figure S11. HPLC chromatograms for 4-Amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4- ^{14}C)pyridine-2-carbaldehyde (27).....	32
Figure S12. HPLC chromatograms for 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4- ^{14}C)pyridine-2-carbaldehyde (28).....	33
Figure S13. HPLC chromatograms for 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4- ^{14}C)pyridine-2-carboxylic acid (29).....	34

Figure S14. HPLC chromatograms for benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-¹⁴C)pyridine-2-carboxylate (30, Rinskor-Py-4-¹⁴C)..... 35

Figure S1-a. ^1H NMR spectra (CDCl_3) of 2,2,2-trifluoro-*N*-tritylethanimidoyl chloride (17).

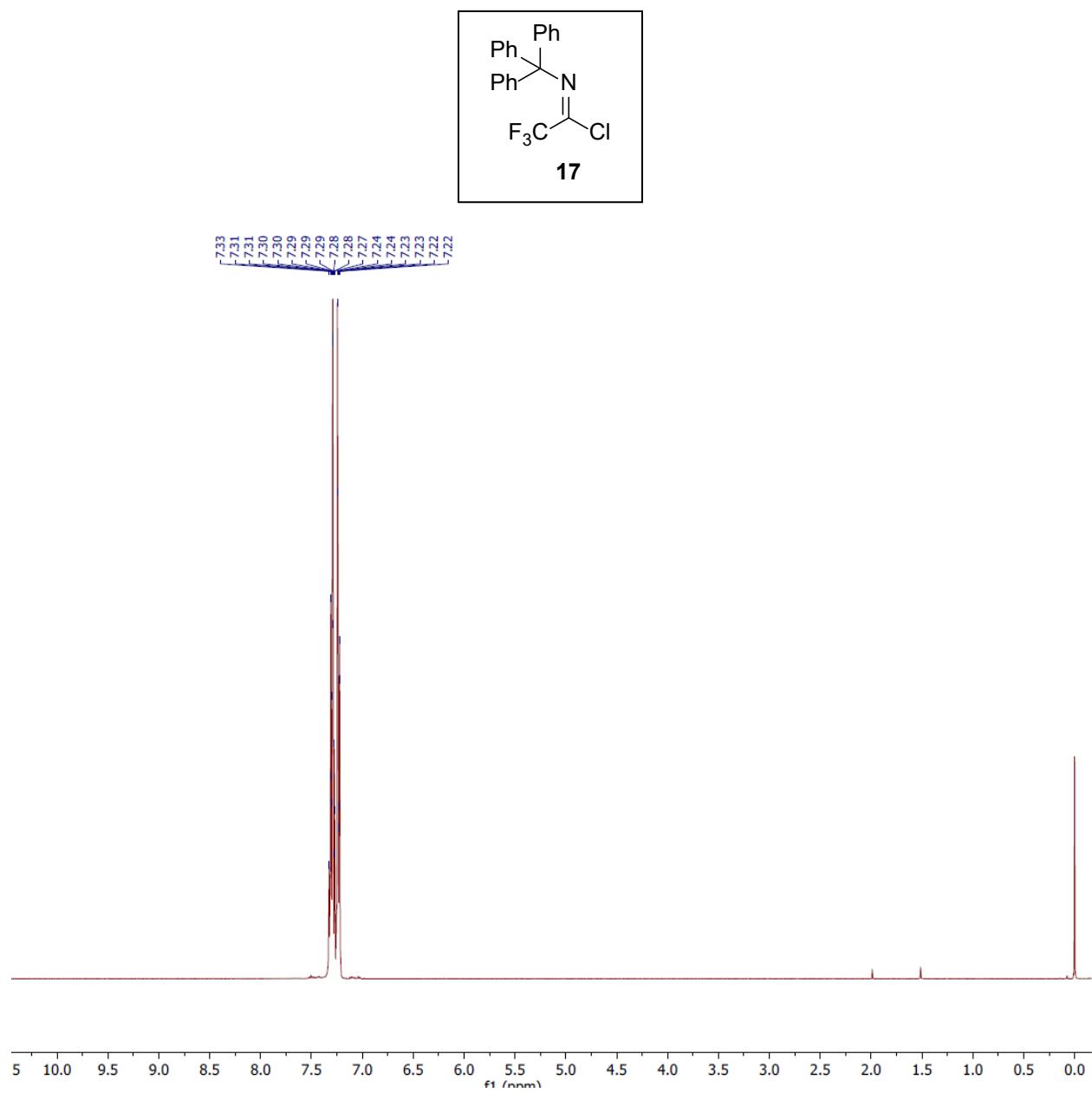


Figure S1-b. ^{19}F NMR spectra (CDCl_3) of 2,2,2-trifluoro-*N*-tritylethanimidoyl chloride (17).

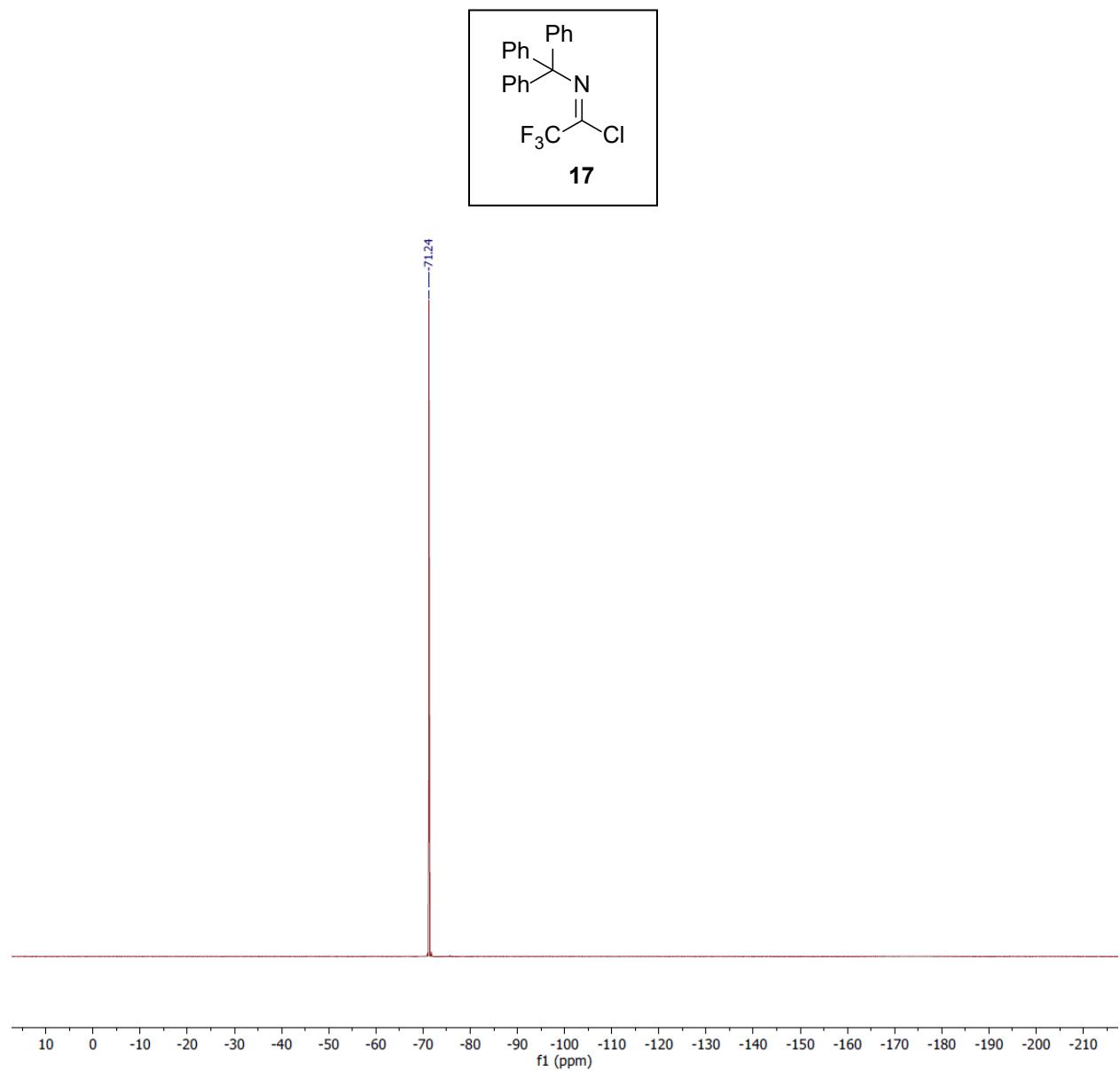


Figure S1-c. ^{13}C NMR spectra (CDCl_3) of 2,2,2-trifluoro-*N*-tritylethanimidoyl chloride (17).

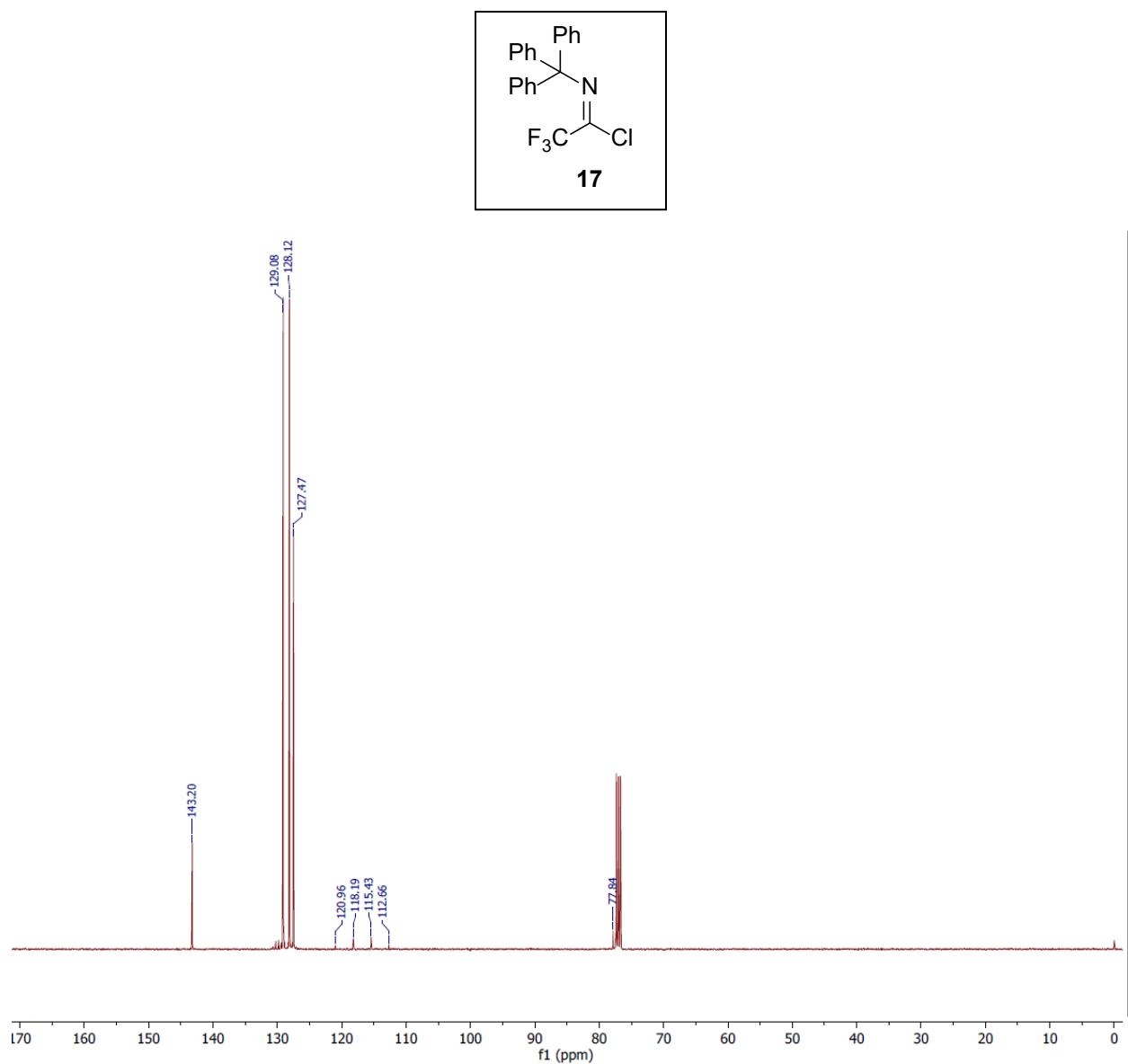


Figure S2-a. ^1H NMR spectra (CDCl_3) of *N*-[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).

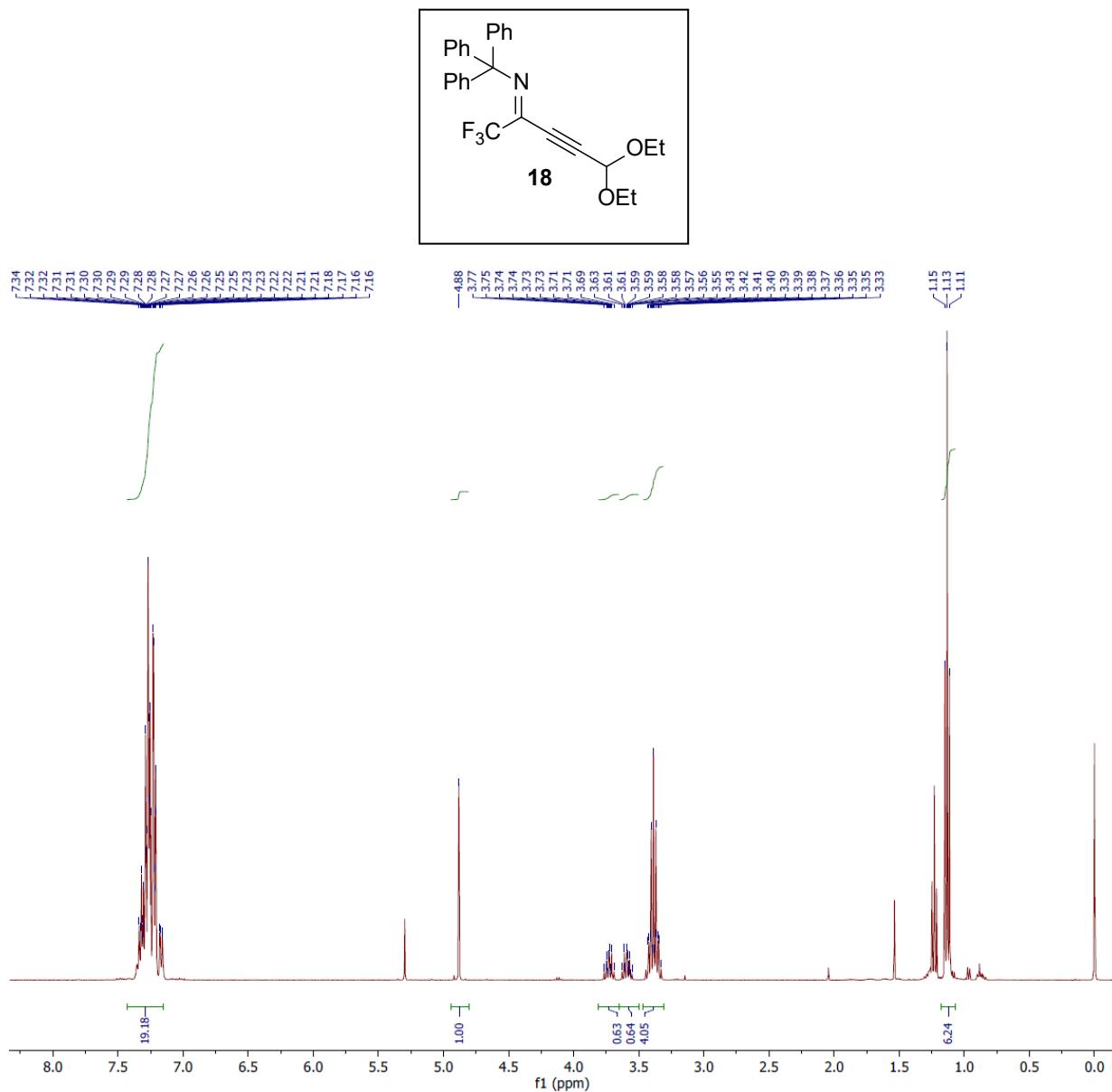


Figure S2-b. ^{19}F NMR spectra (CDCl_3) of *N*-[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).

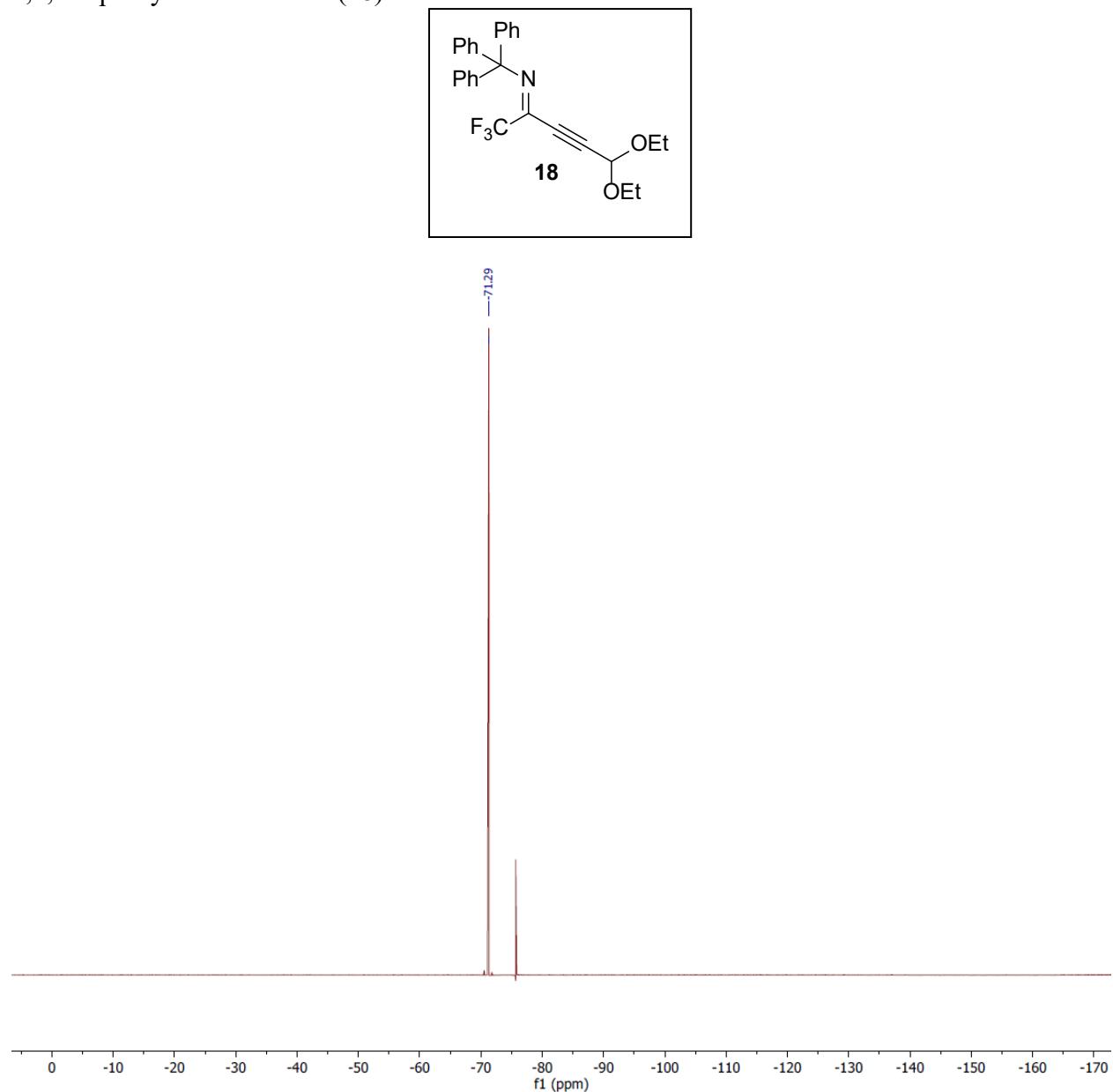


Figure S2-c. ^{13}C NMR spectra (CDCl_3) of *N*-[5,5-Diethoxy-1,1,1-trifluoropent-3-yn-2-ylidene]-1,1,1-triphenylmethanamine (18).

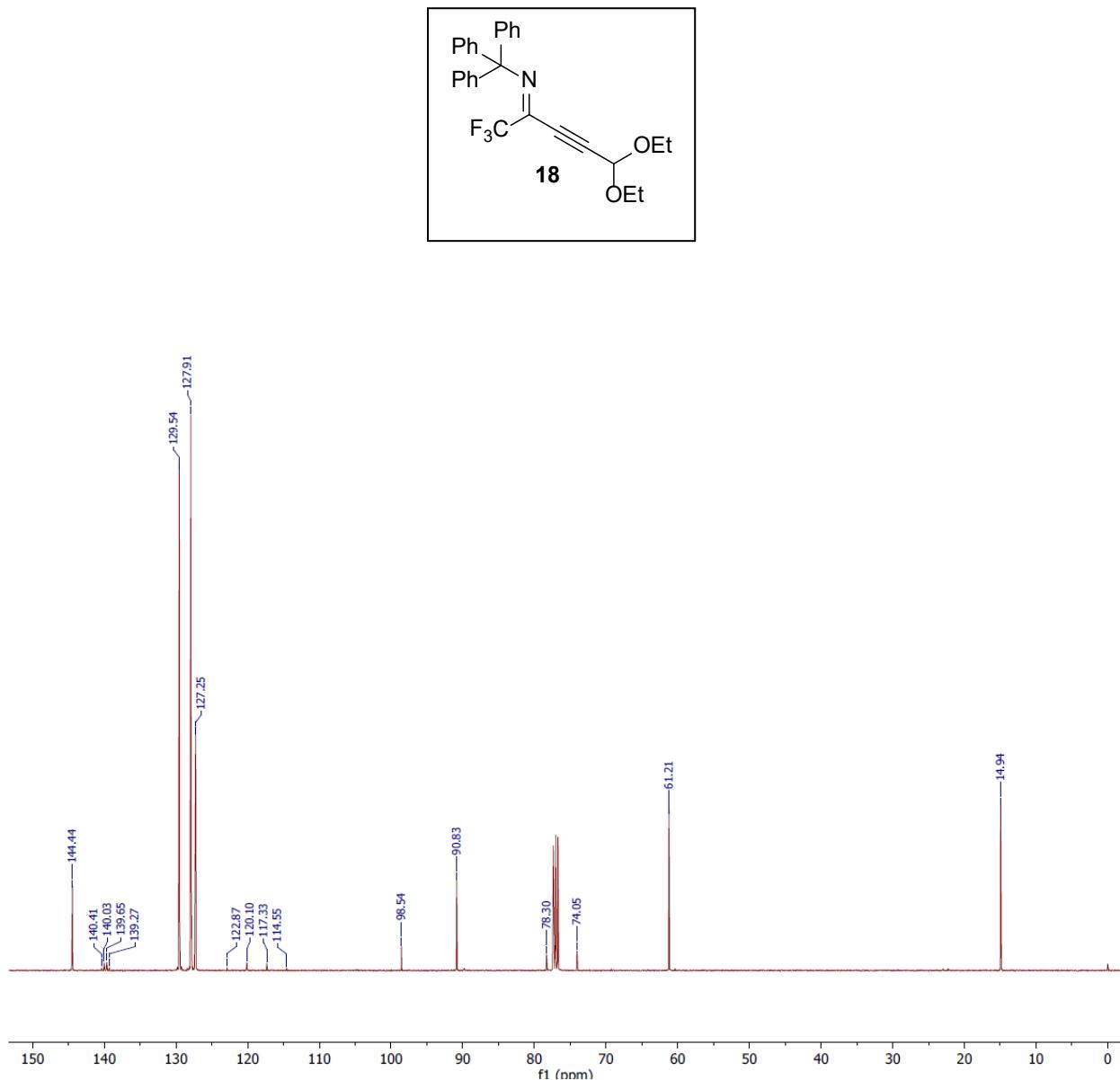


Figure S3-a. ^1H NMR spectra (CDCl_3) of 4-chloro-2-fluoro-3-methoxybenzaldehyde *O*-methyl oxime (20).

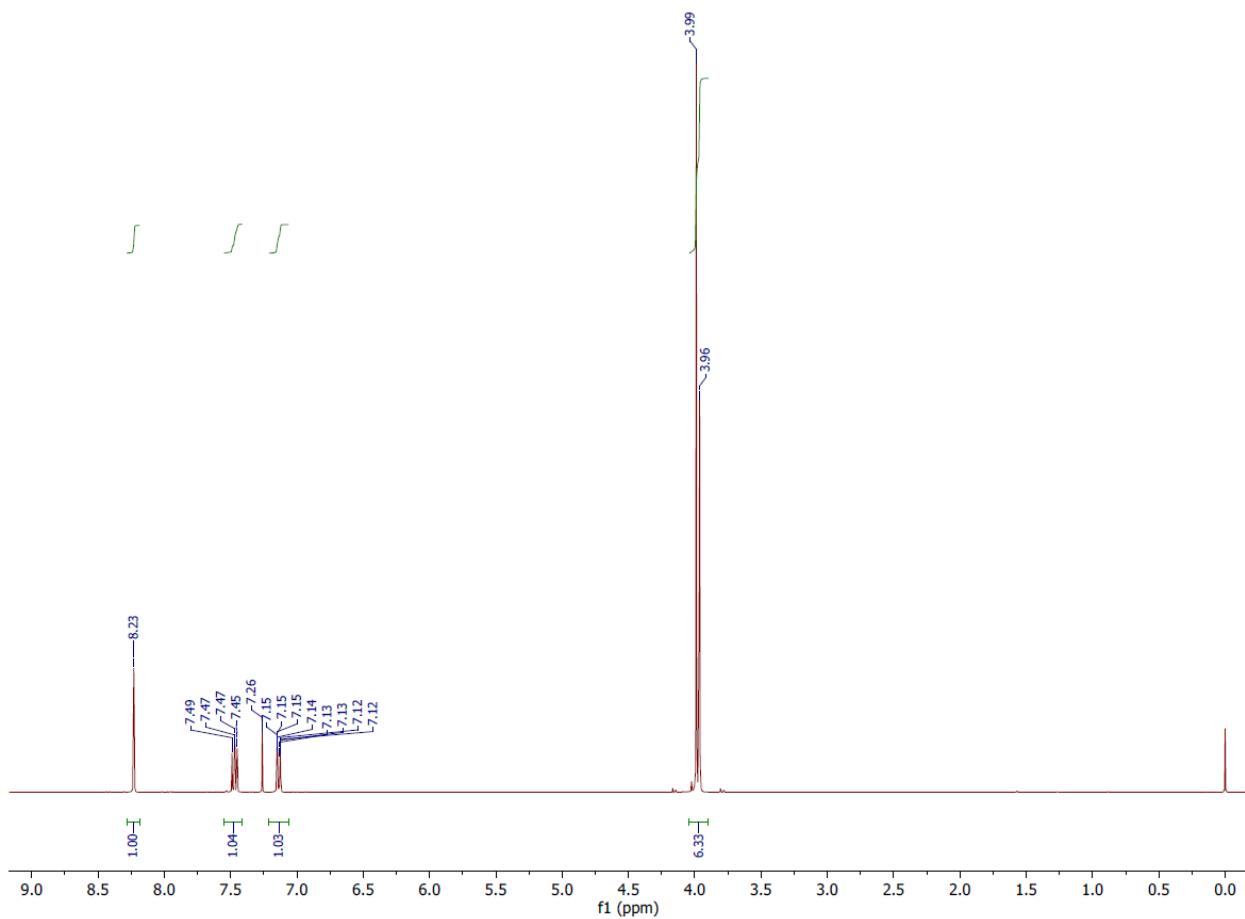
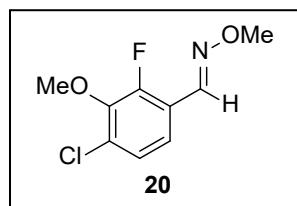


Figure S3-b. ^{19}F NMR spectra (CDCl_3) of 4-chloro-2-fluoro-3-methoxybenzaldehyde *O*-methyl oxime (20).

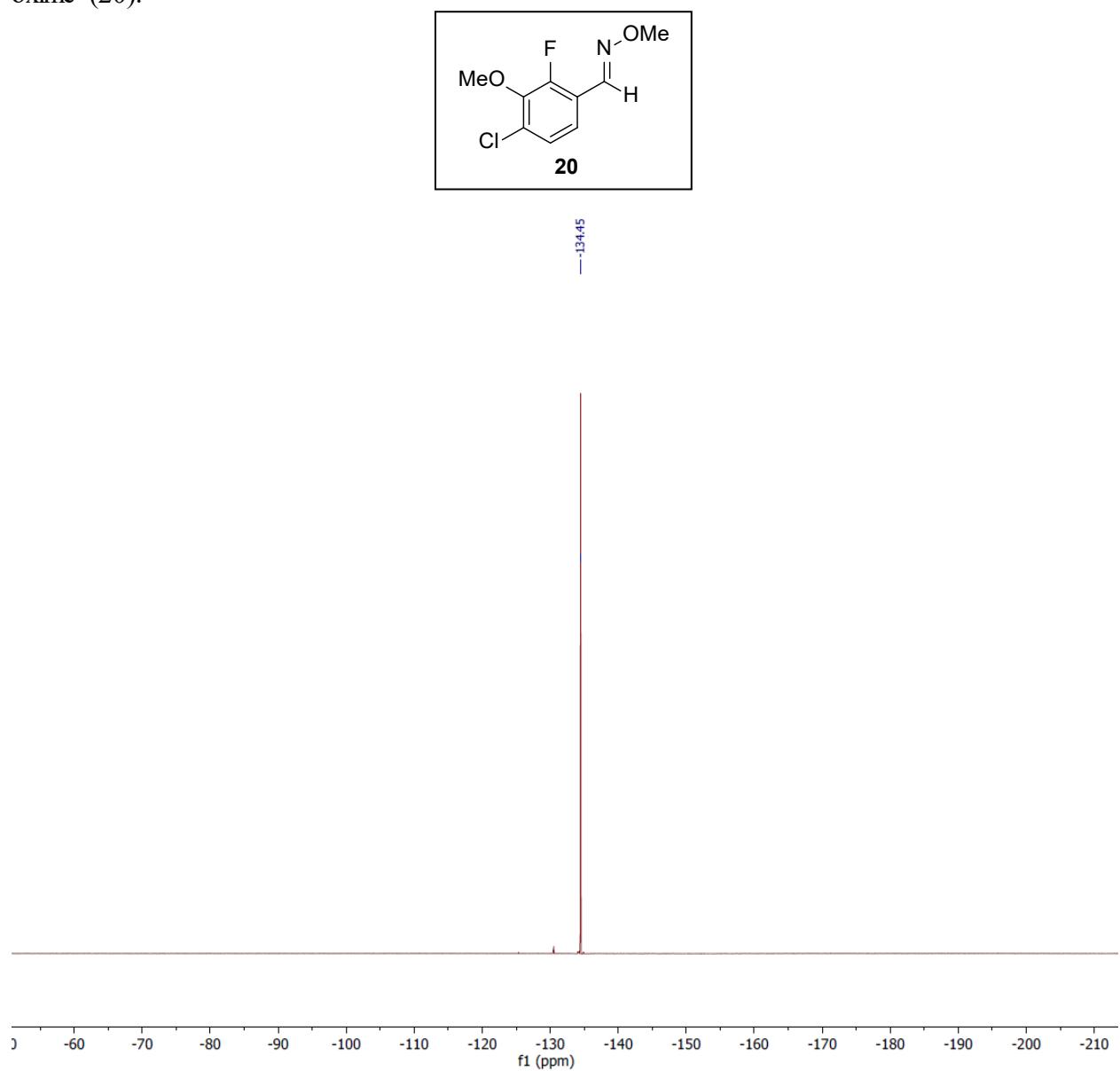


Figure S3-c. ^{13}C NMR spectra (CDCl_3) of 4-chloro-2-fluoro-3-methoxybenzaldehyde *O*-methyl oxime (20).

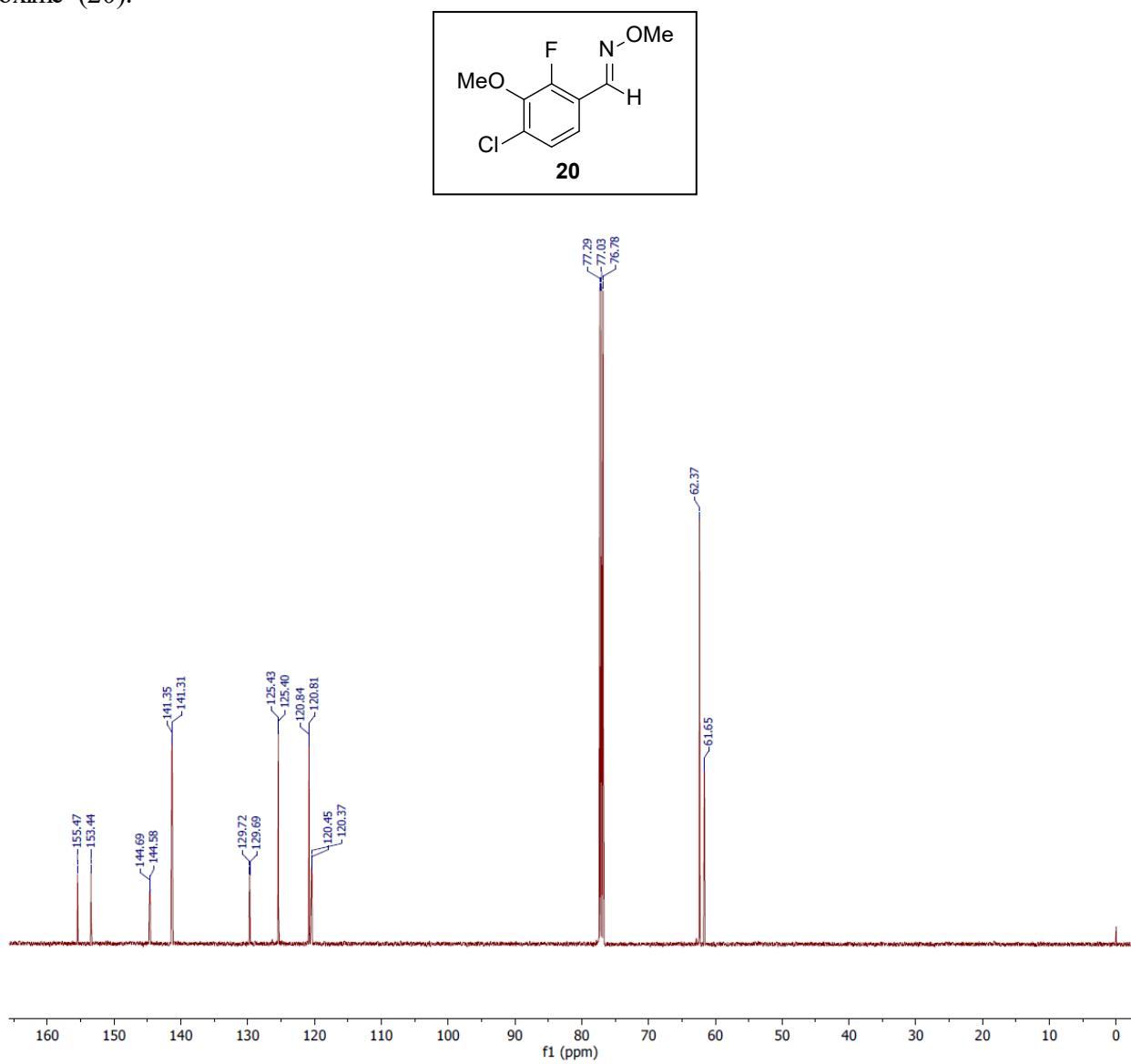


Figure S4-a. ^1H NMR spectra (CDCl_3) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).

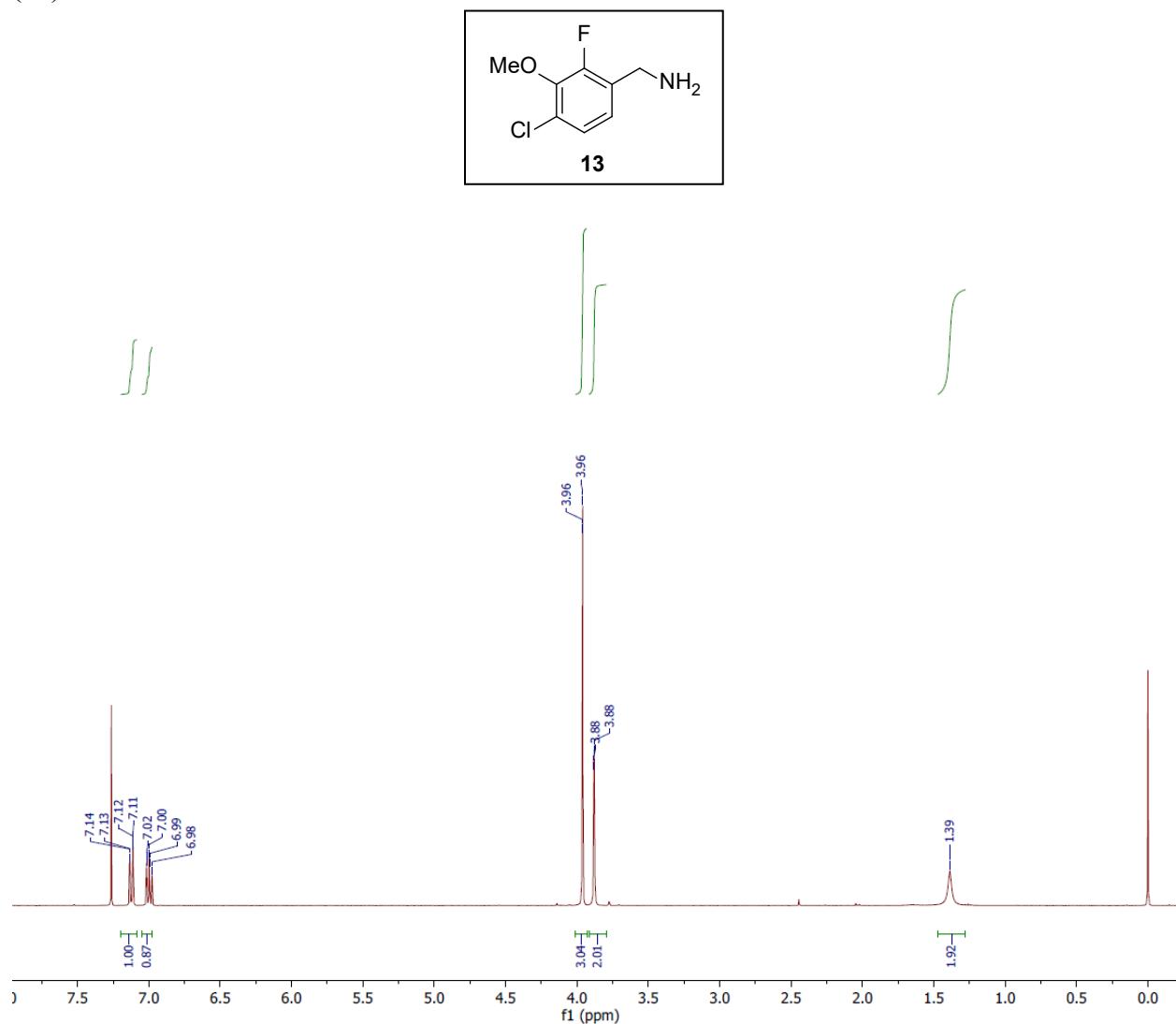


Figure S4-b. ^{19}F NMR spectra (CDCl_3) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).

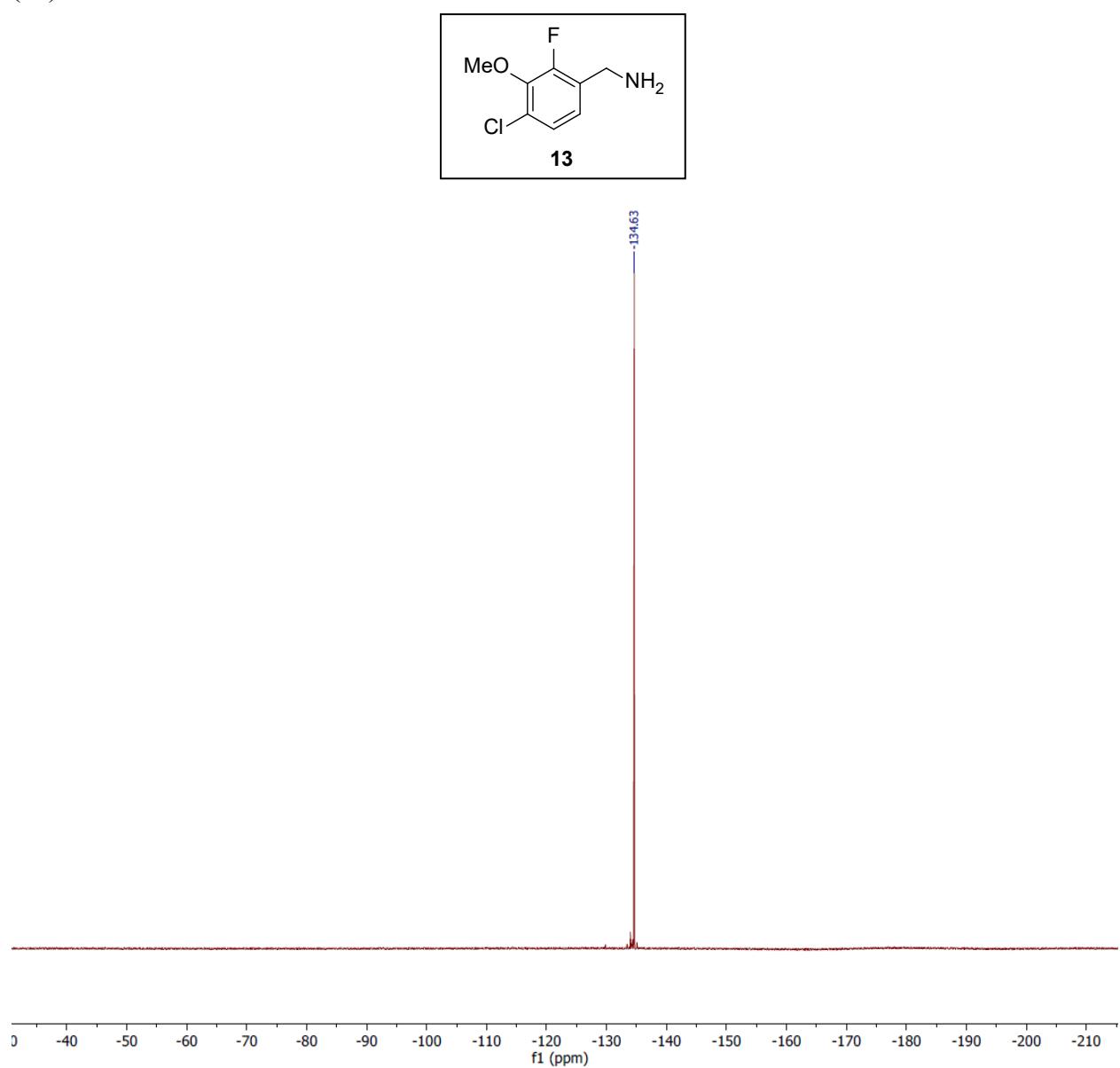


Figure S4-c. ^{13}C NMR spectra (CDCl_3) of 1-(4-chloro-2-fluoro-3-methoxyphenyl)-methanamine (13).

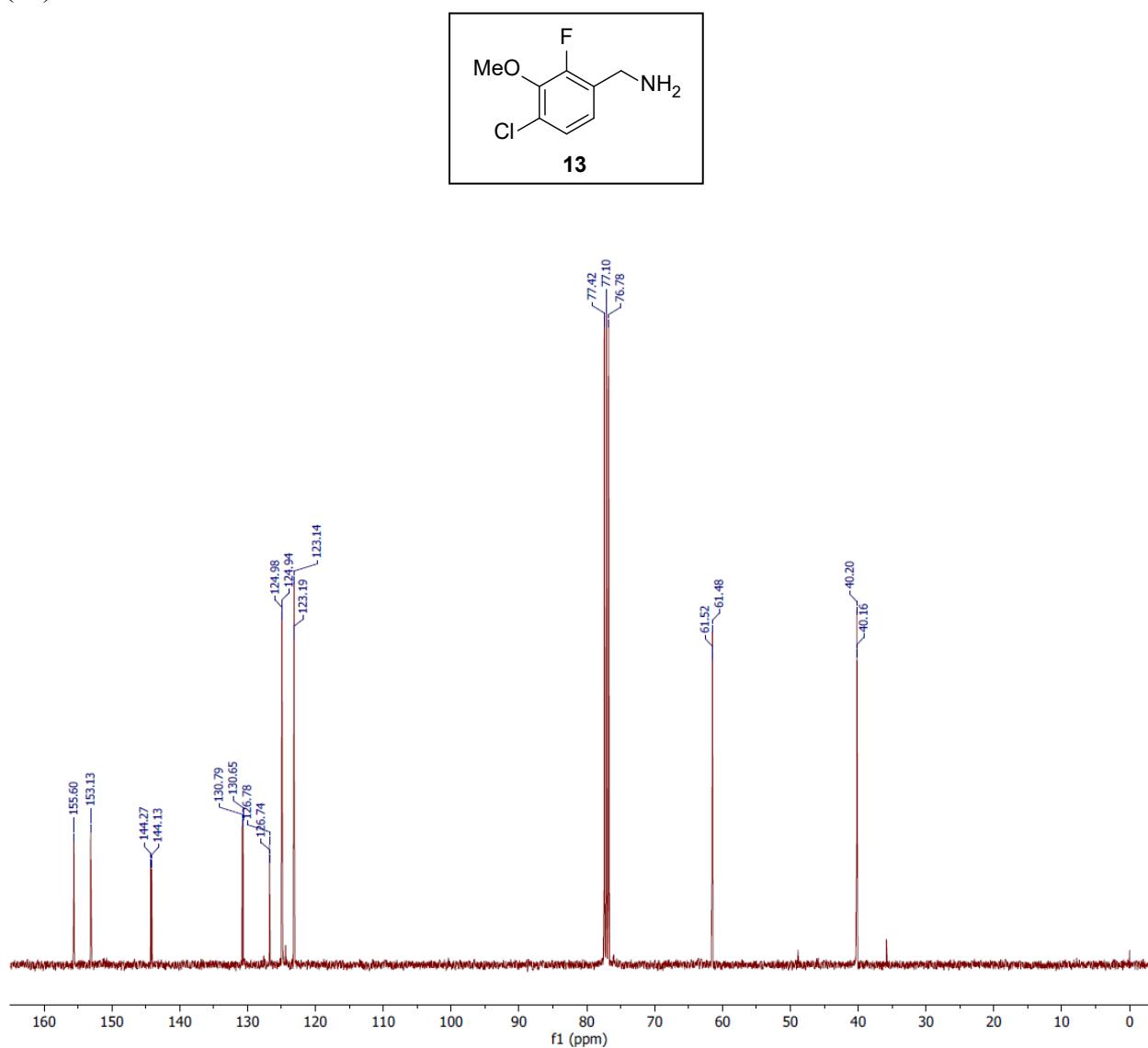


Figure S5-a. ^1H NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-tritylpyridin-4-amine (21).

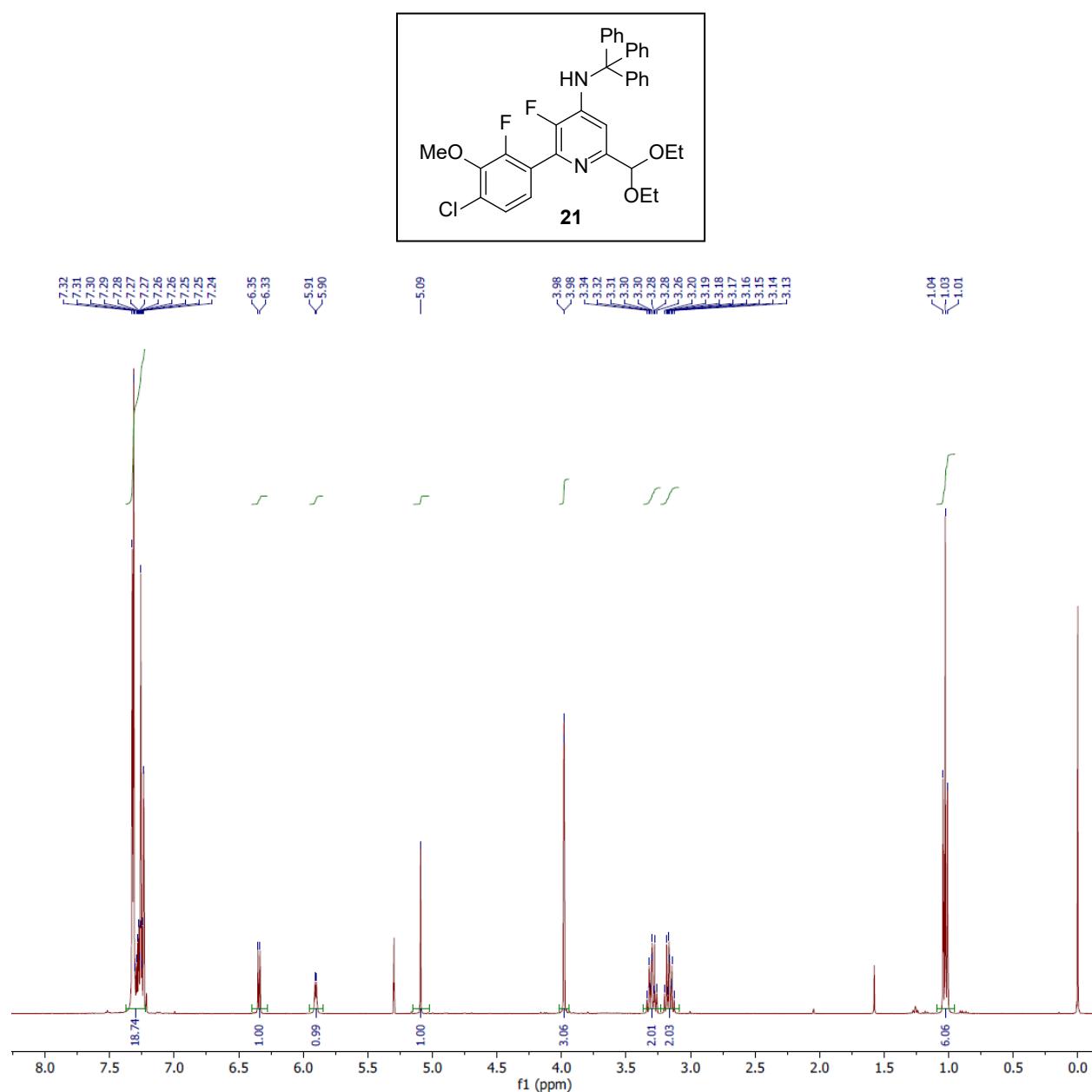


Figure S5-b. ^{19}F NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-*N*-tritylpyridin-4-amine (21).

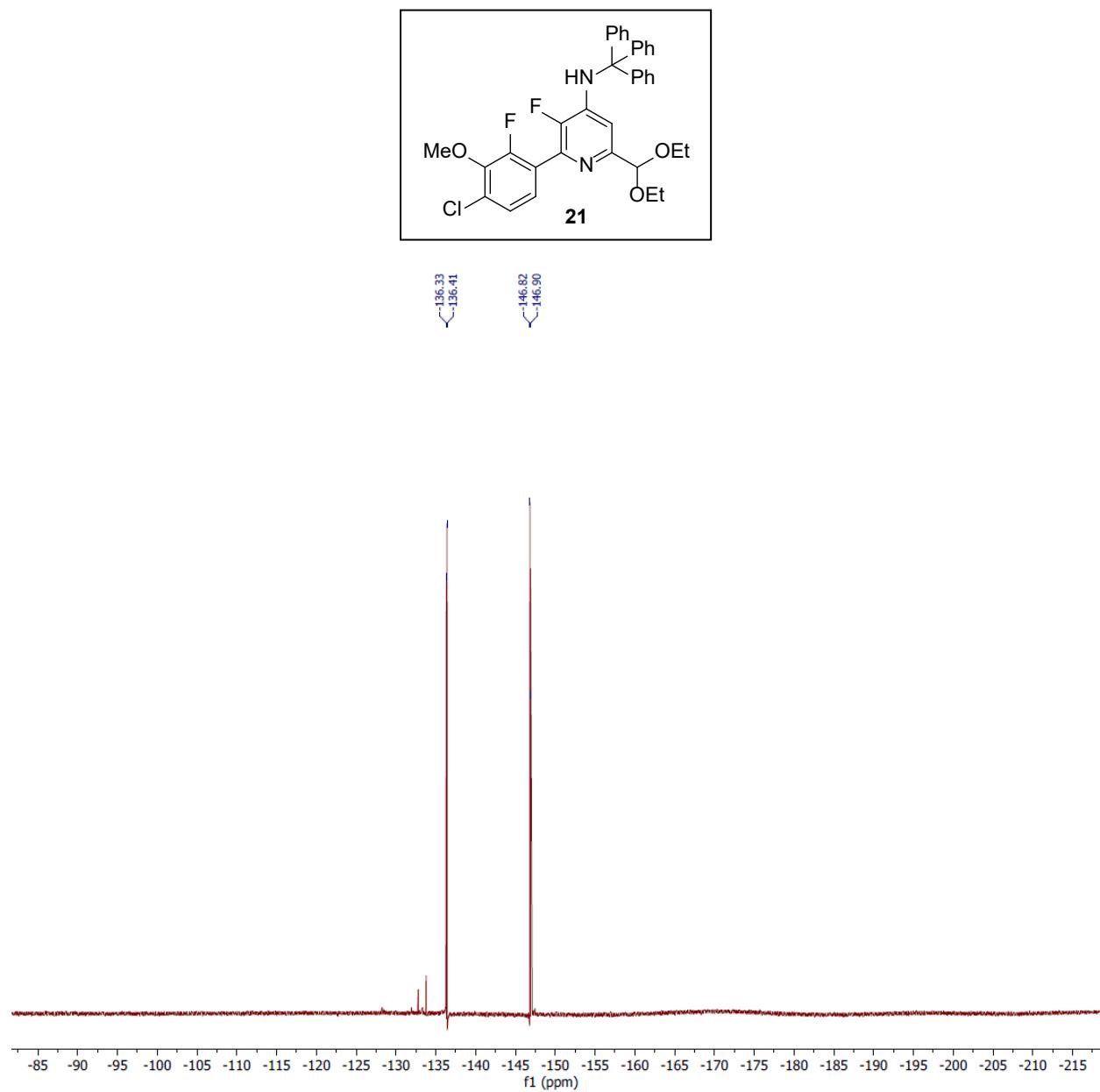


Figure S5-c. ^{13}C NMR spectra (CDCl_3) of 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-tritylpyridin-4-amine (21).

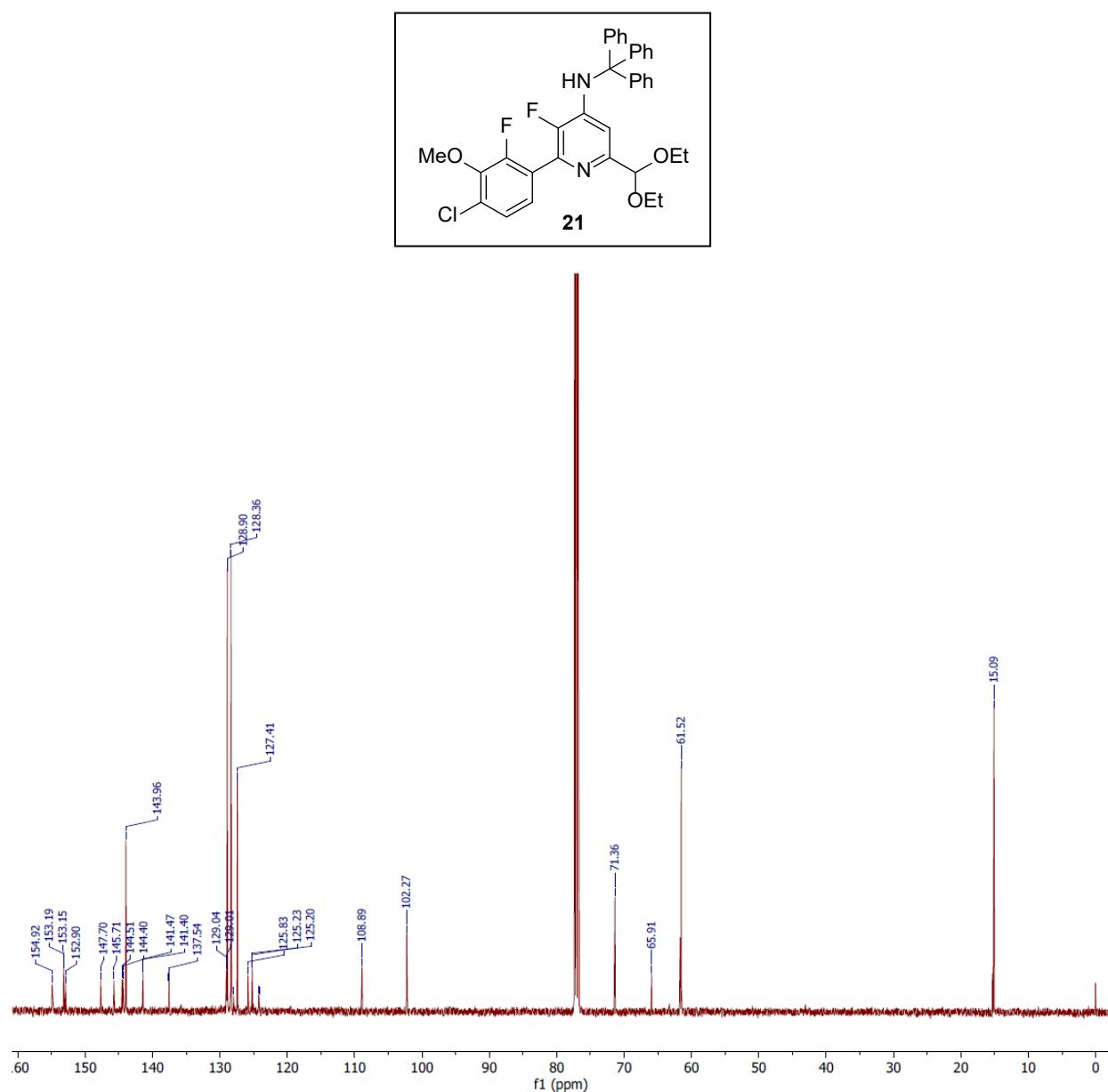


Figure S6-a. ^1H NMR spectra (DMSO- d_6) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).

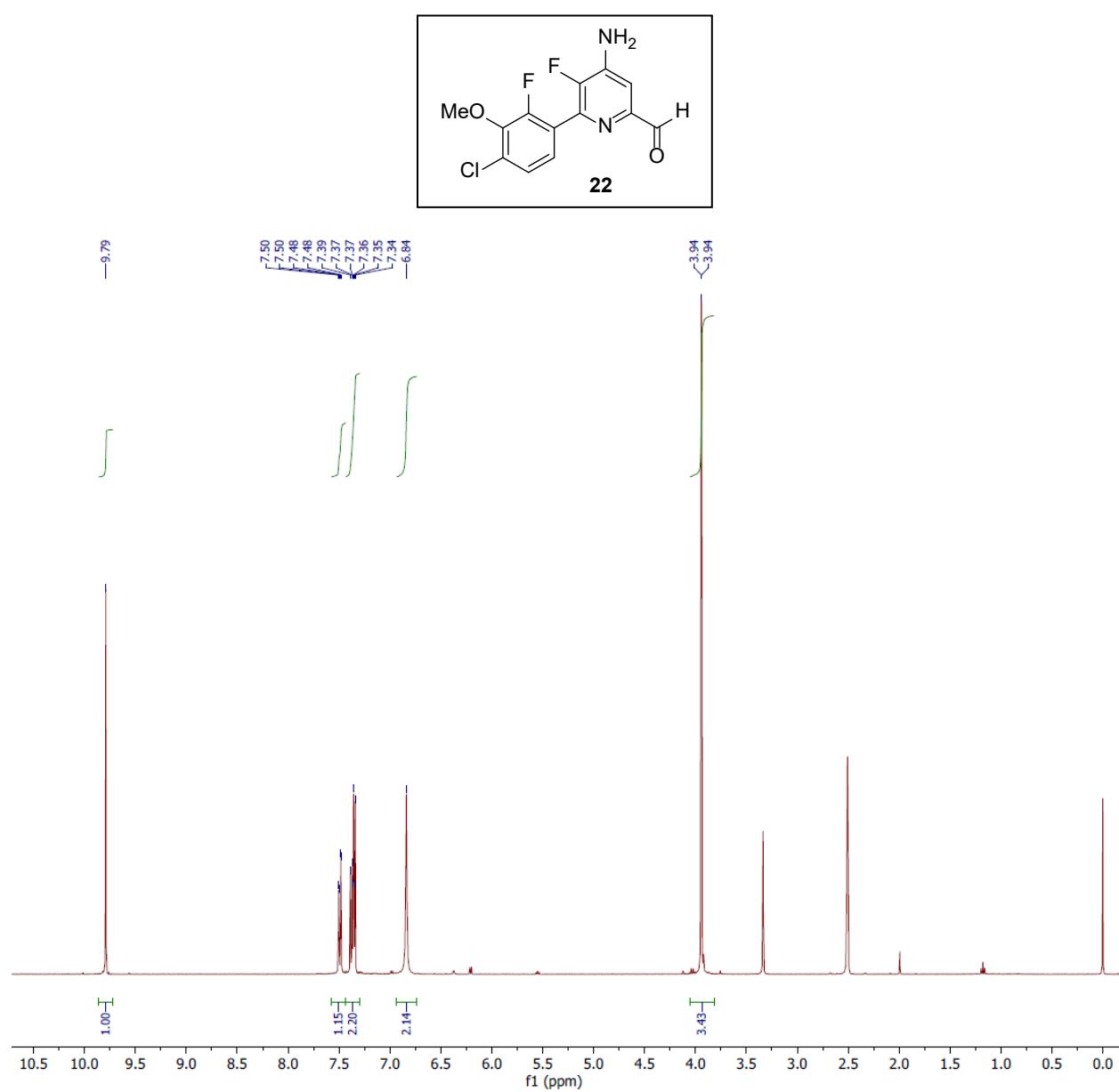


Figure S6-b. ^{19}F NMR spectra (DMSO- d_6) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).

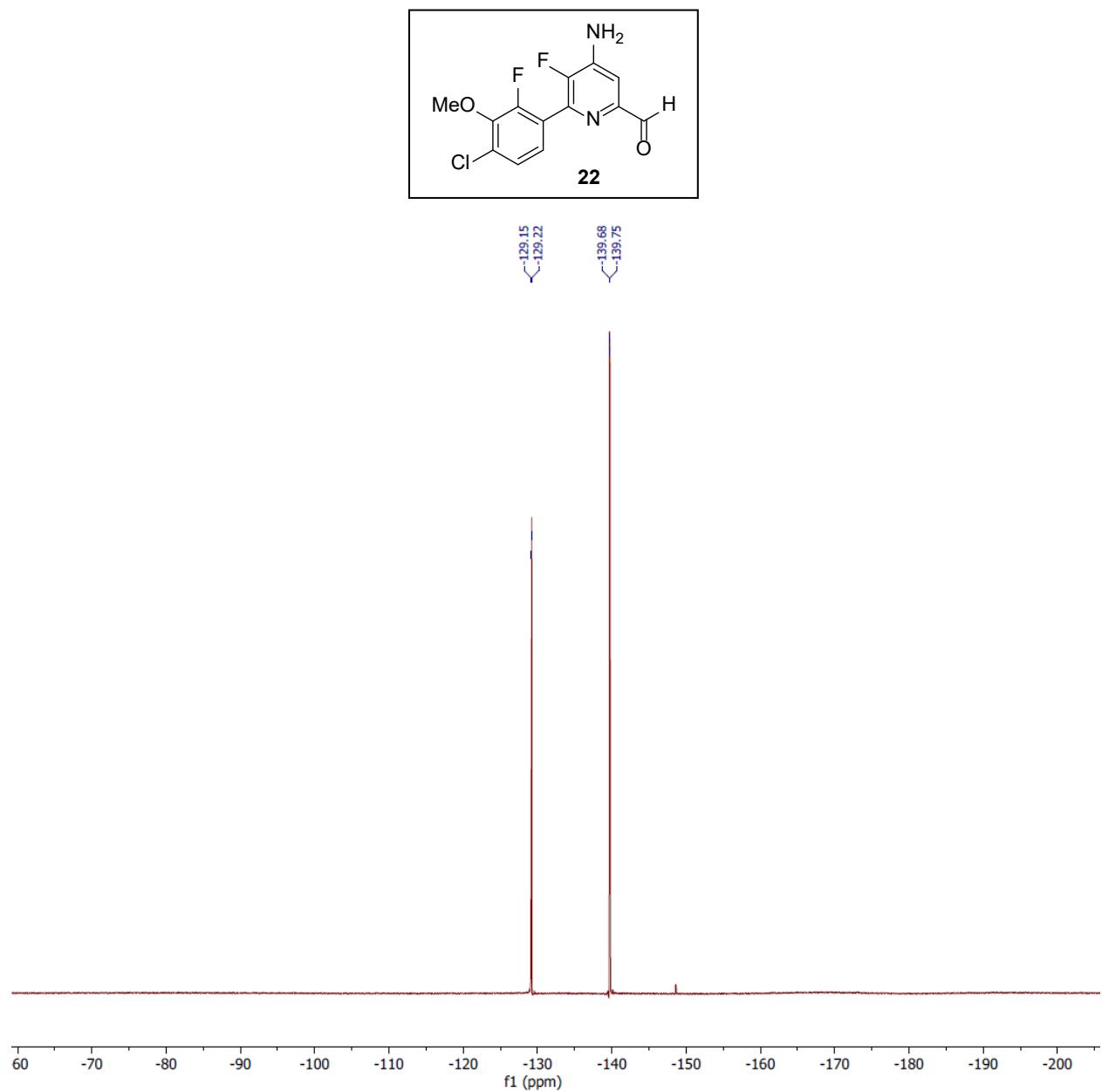


Figure S6-c. ^{13}C NMR spectra (DMSO- d_6) of 4-amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (22).

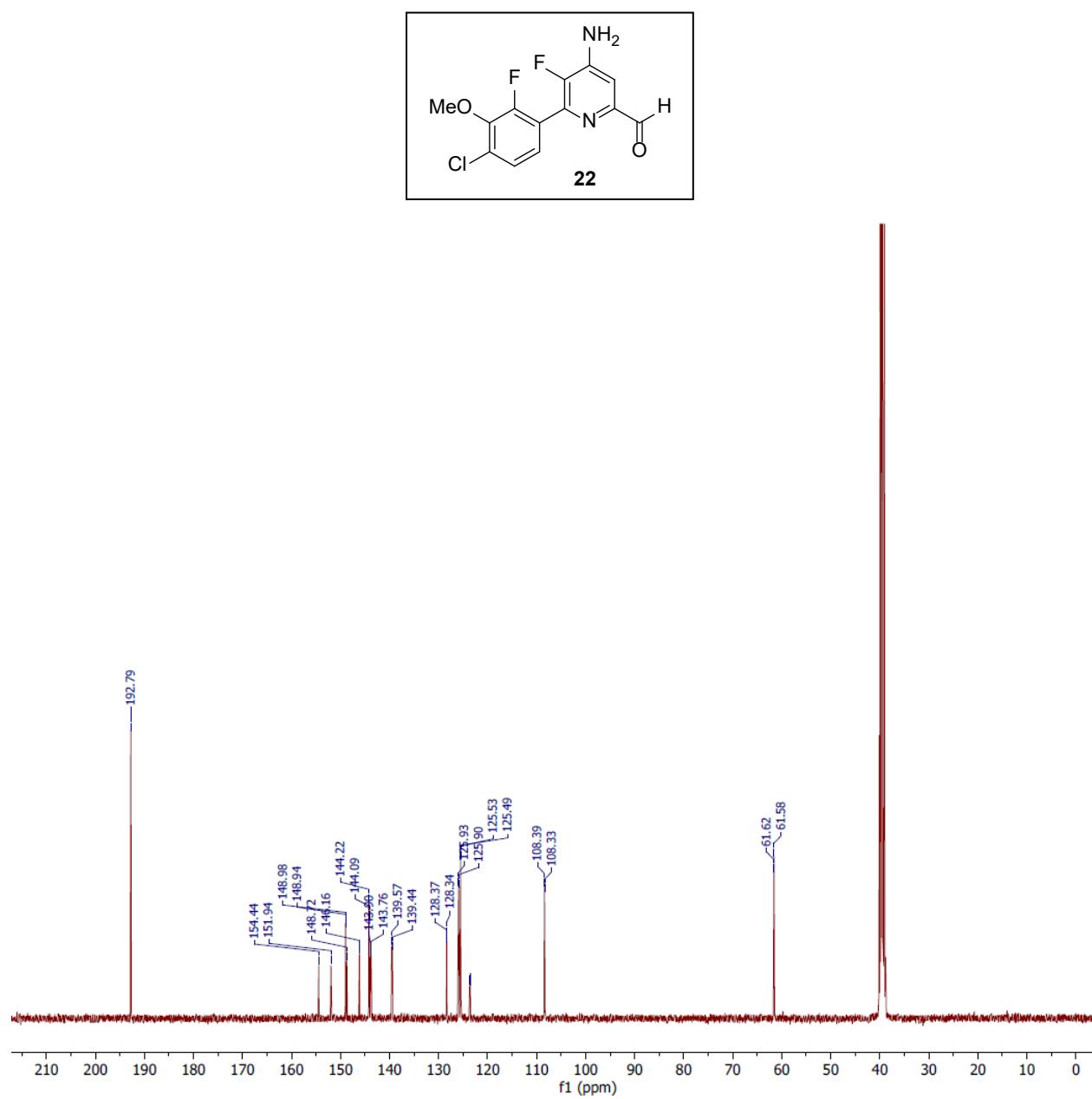


Figure S7-a. ^1H NMR spectra ($\text{DMSO}-d_6$) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).

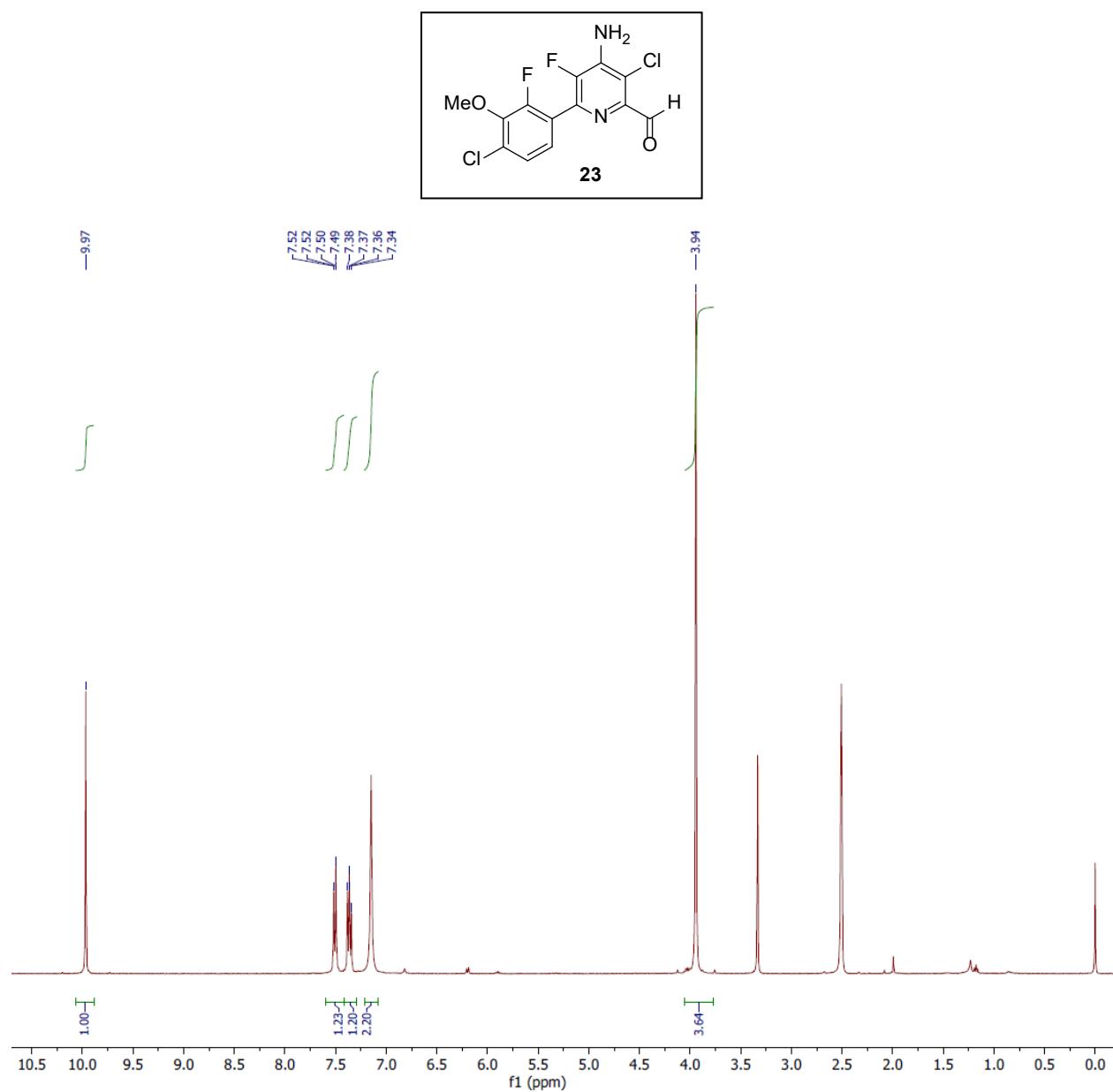


Figure S7-b. ^{19}F NMR spectra (DMSO- d_6) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).

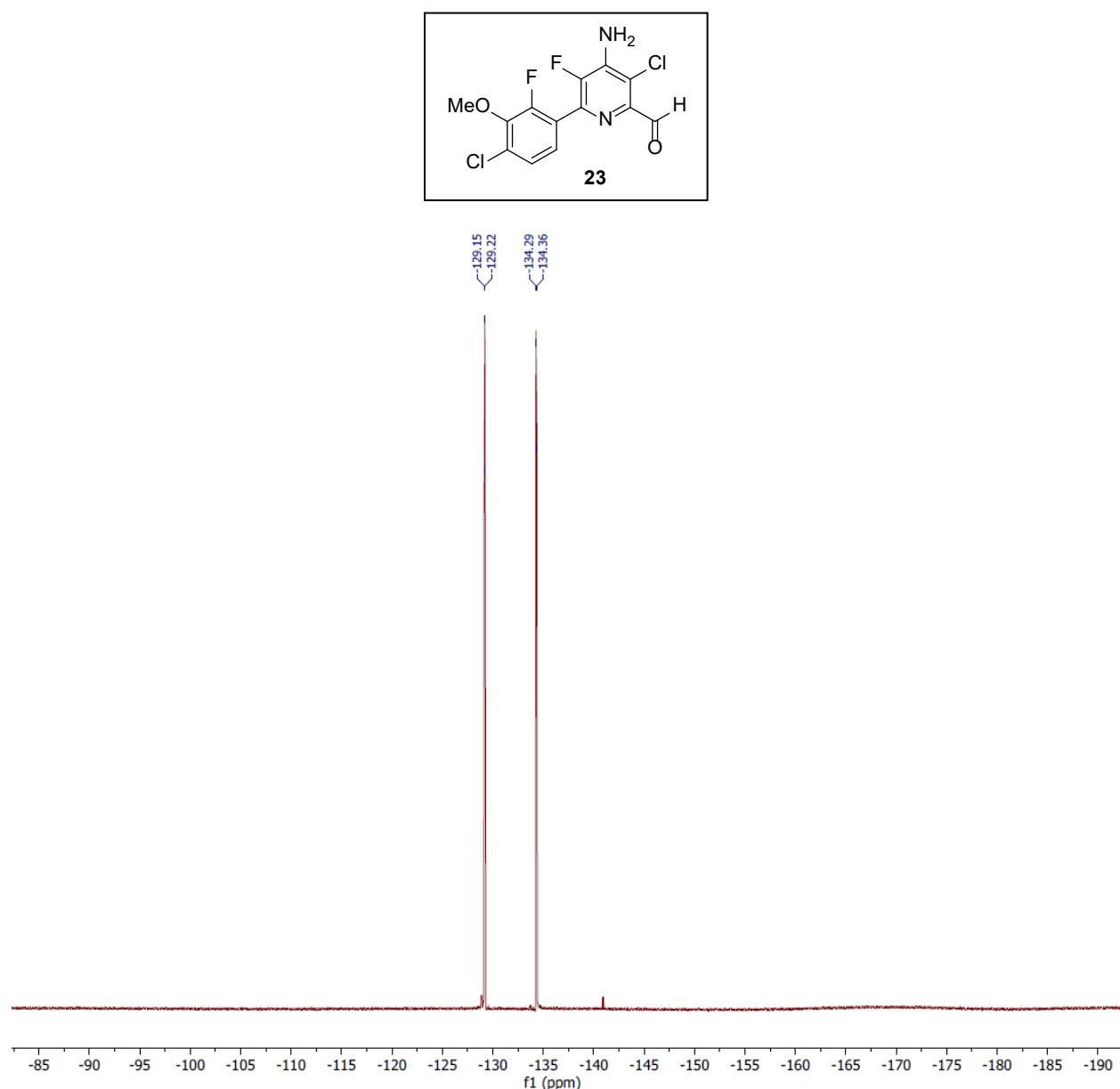


Figure S7-c. ^{13}C NMR spectra (DMSO- d_6) of 4-Amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carbaldehyde (23).

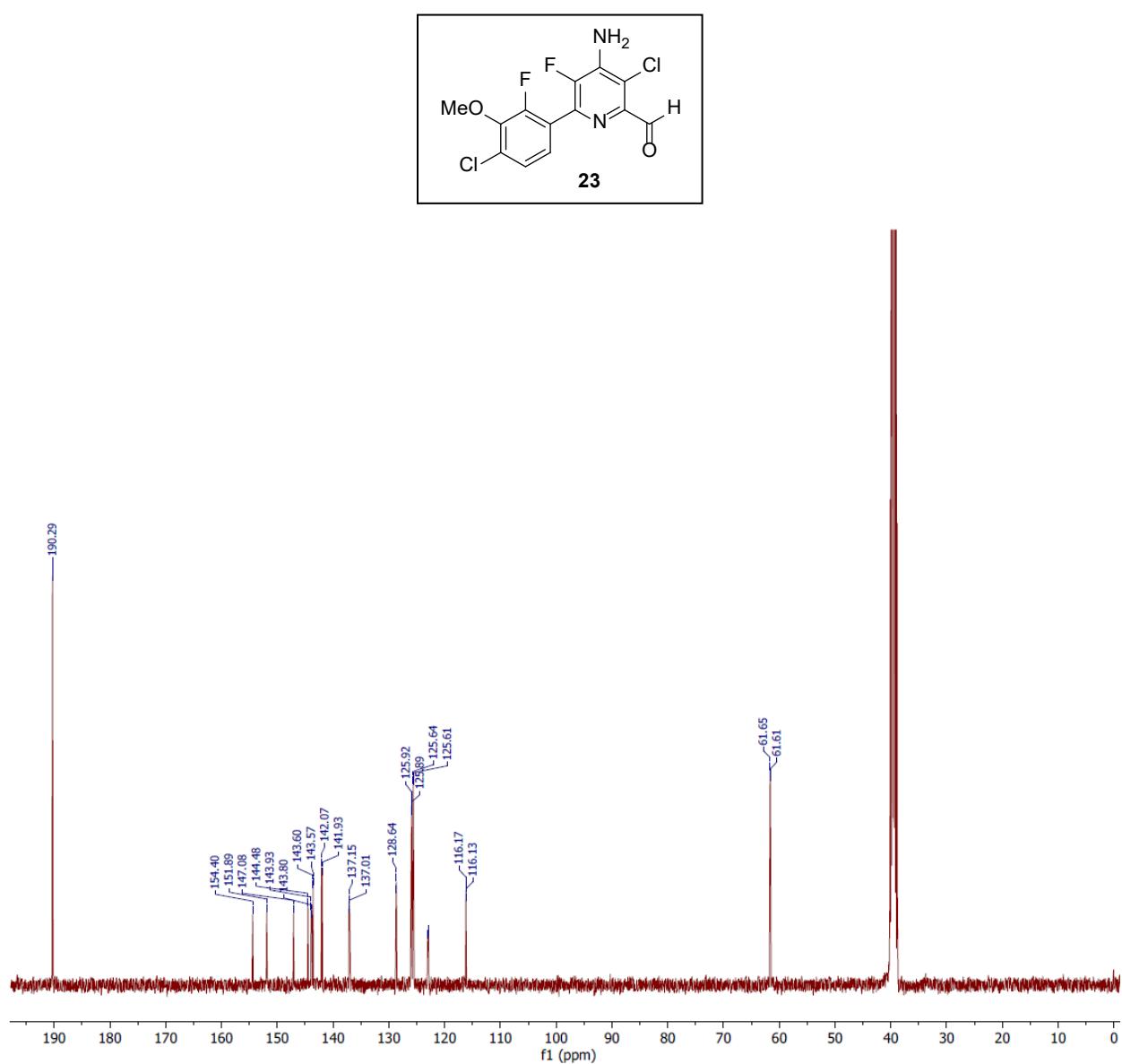


Figure S8-a. ^1H NMR spectra (DMSO-*d*₆) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).

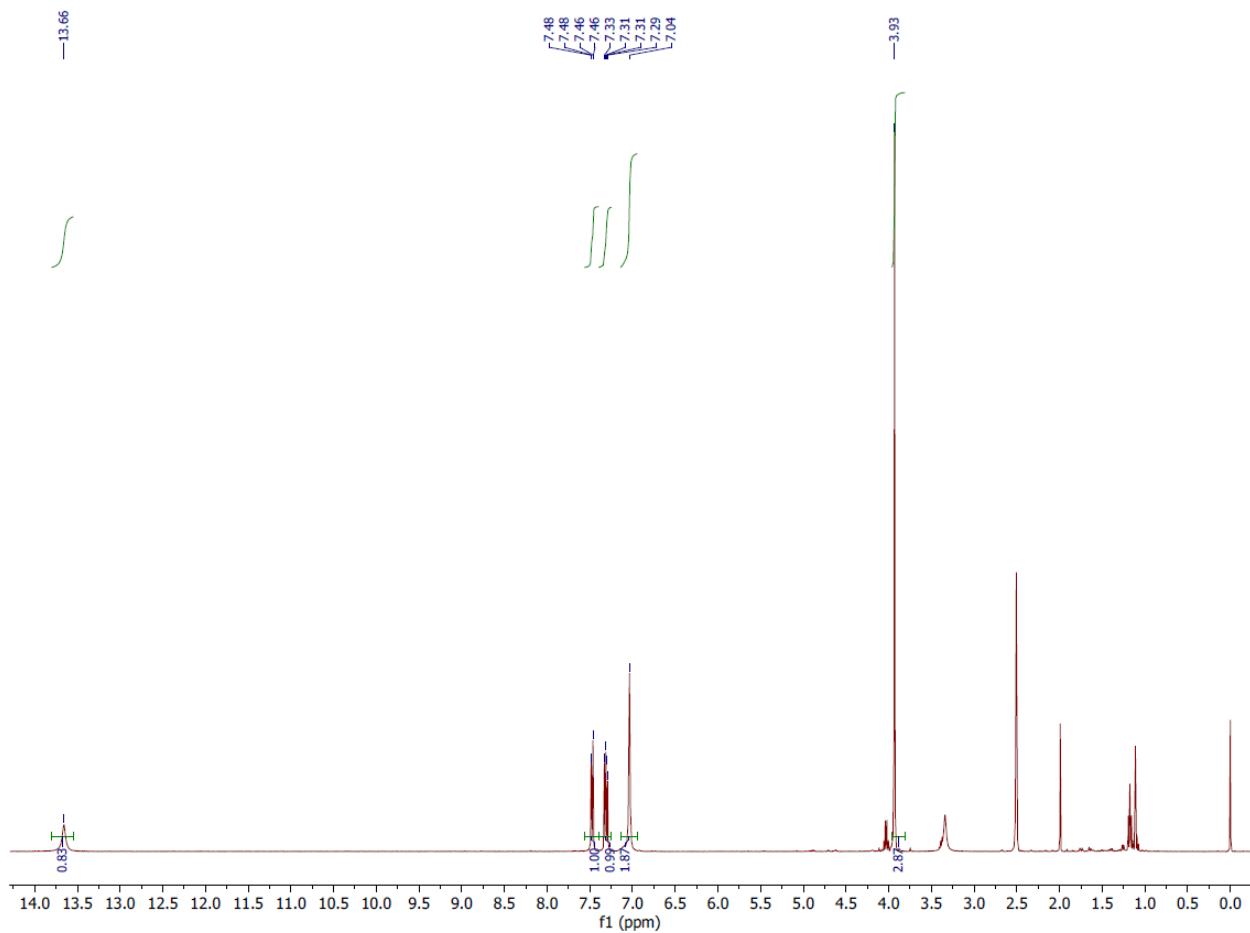
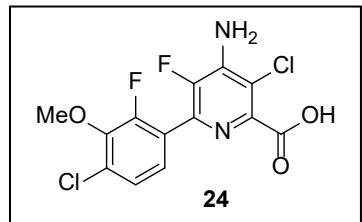


Figure S8-b. ^{19}F NMR spectra (DMSO- d_6) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).

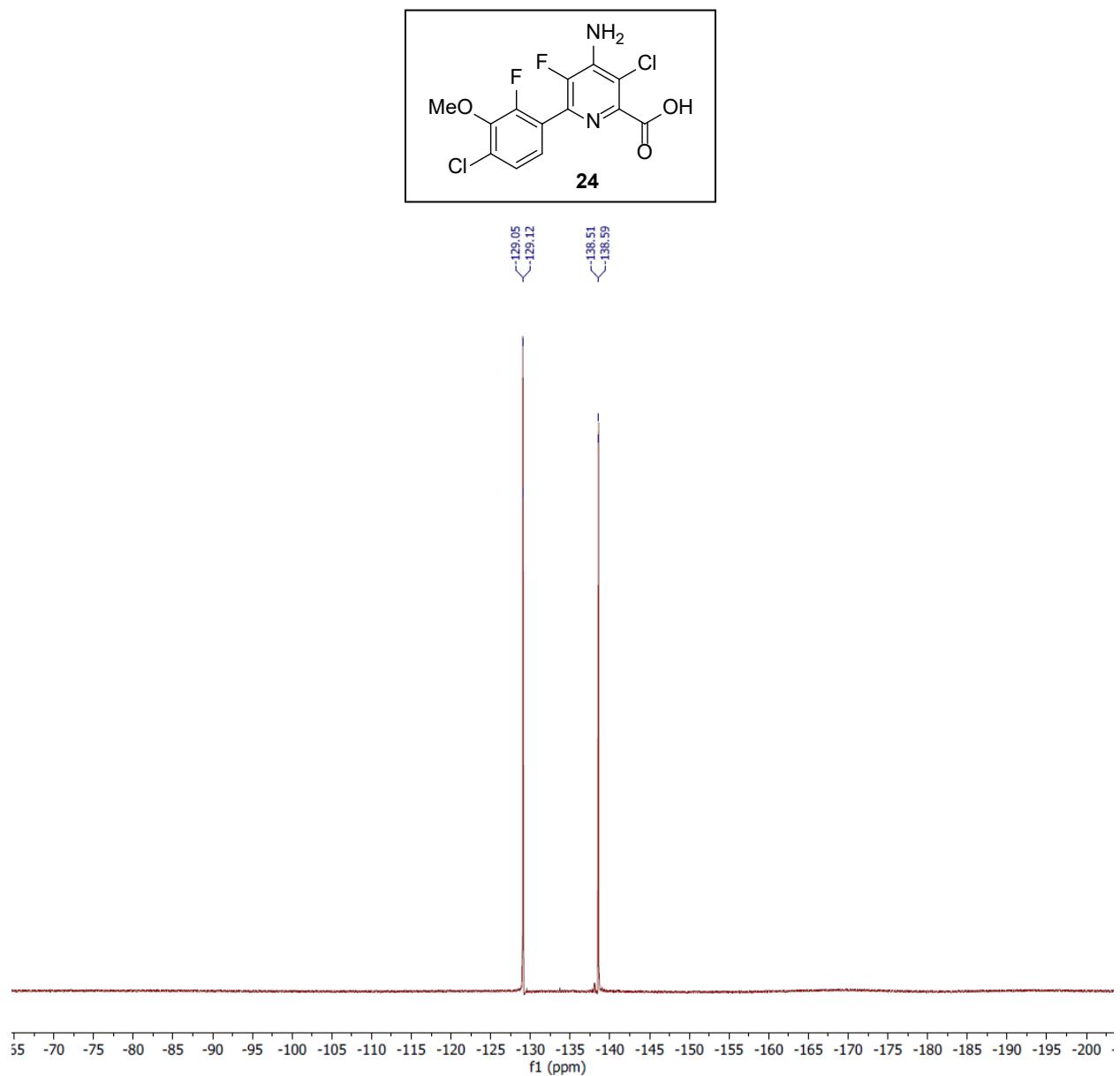


Figure S8-c. ^{13}C NMR spectra (DMSO- d_6) of 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylic acid (24).

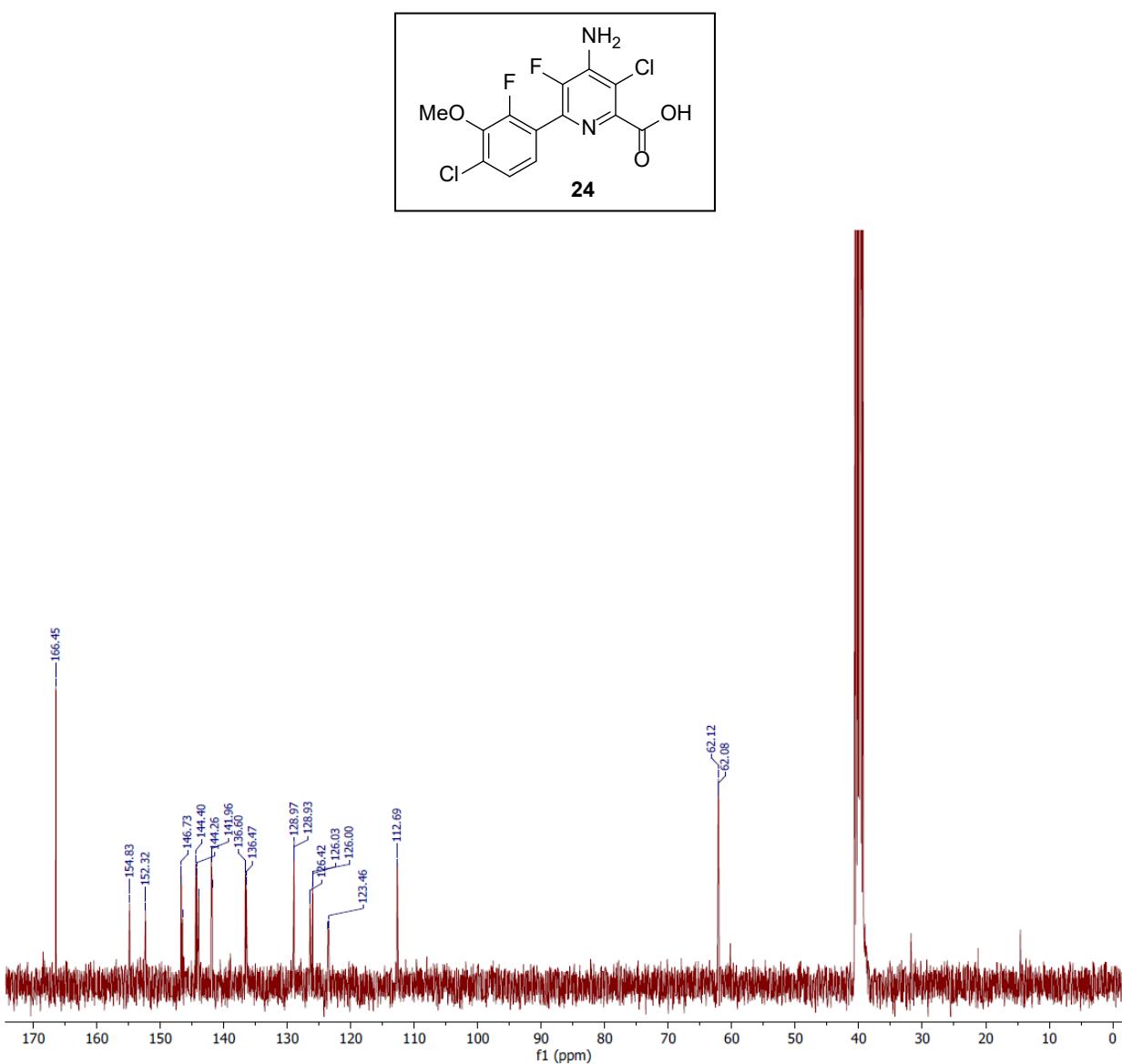


Figure S9-a. ^1H NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).

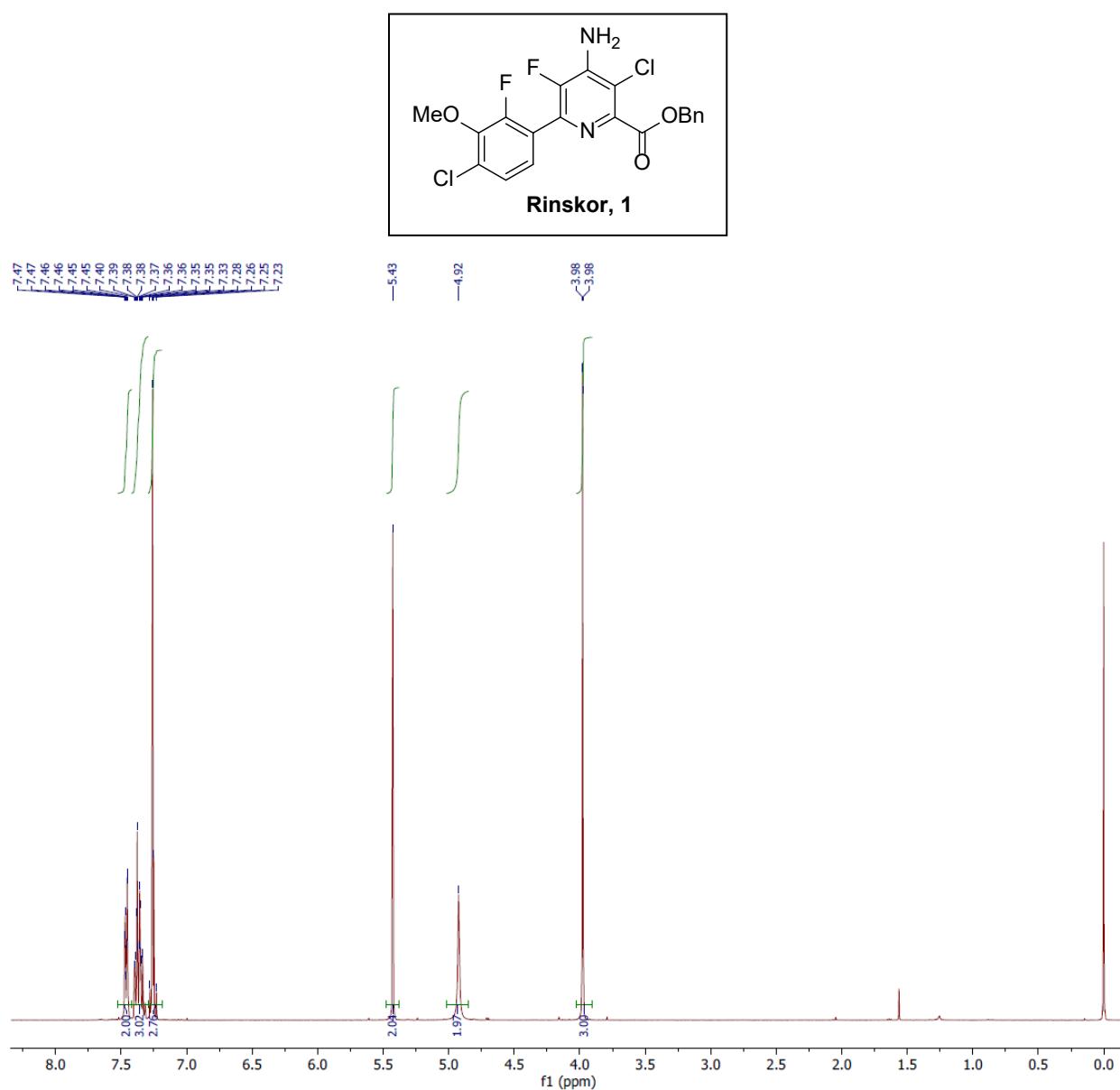


Figure S9-b. ^{19}F NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).

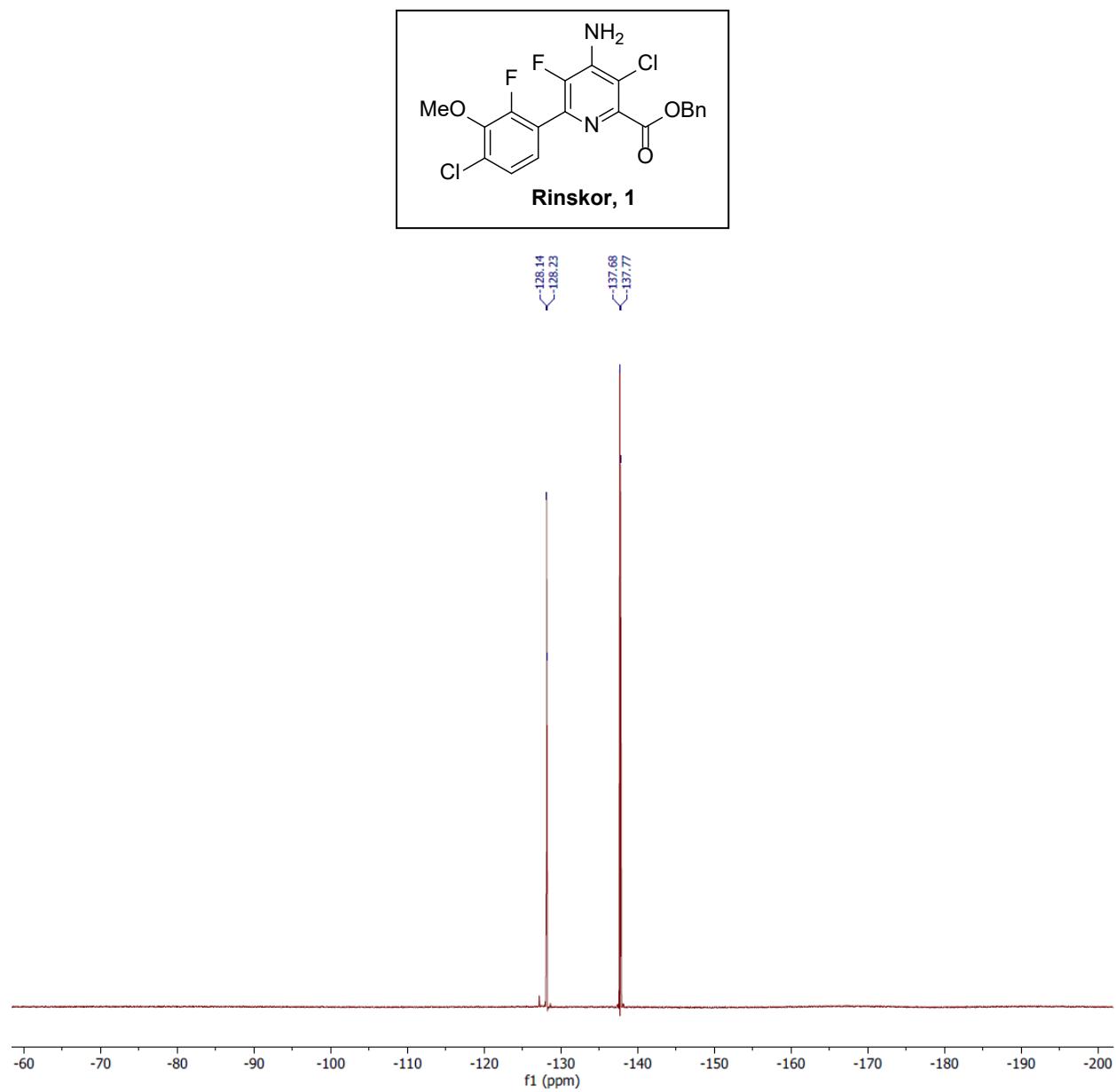


Figure S9-c. ^{13}C NMR spectra (CDCl_3) of benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoropyridine-2-carboxylate (Rinskor, 1).

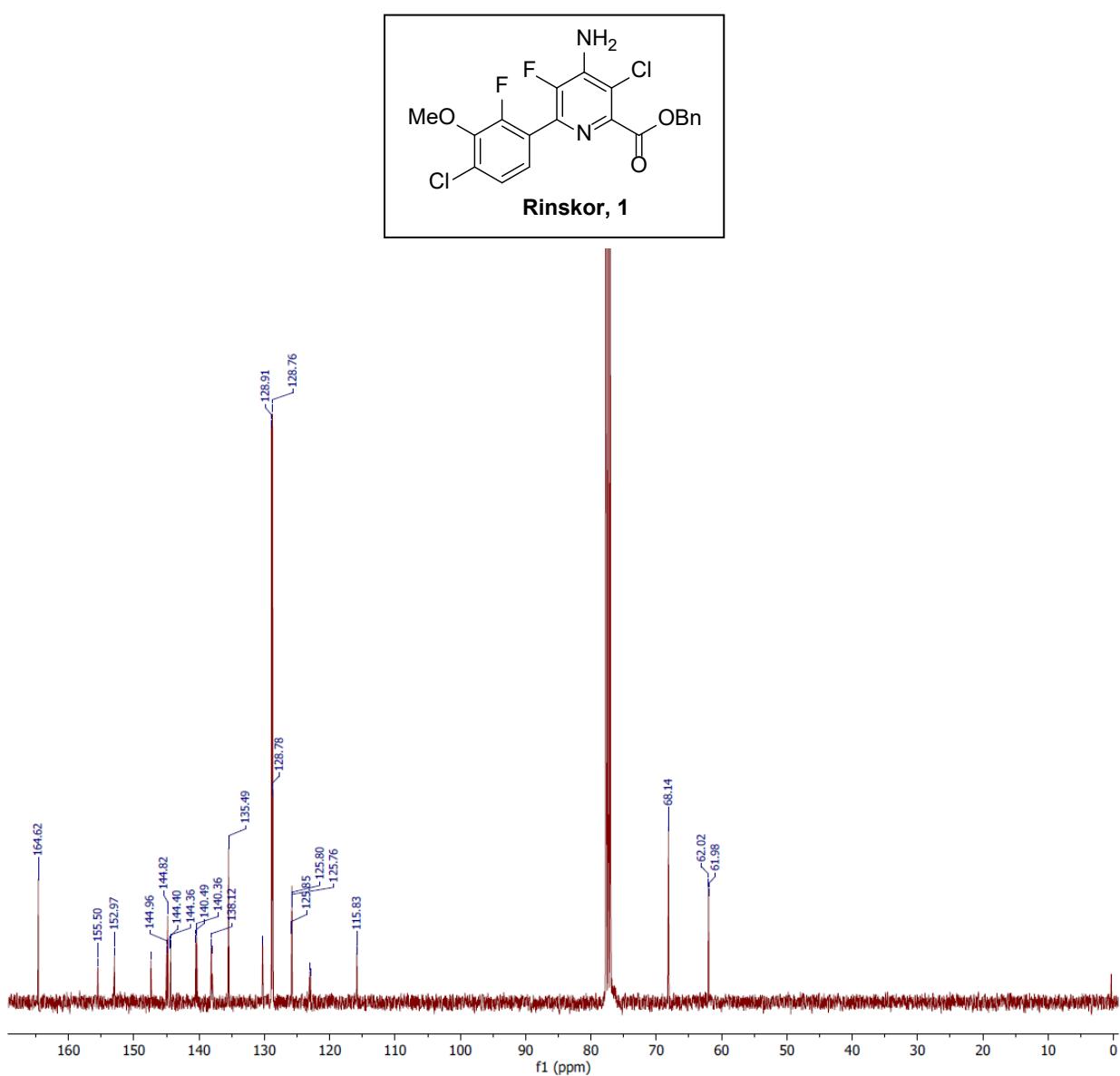
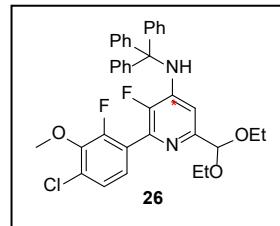
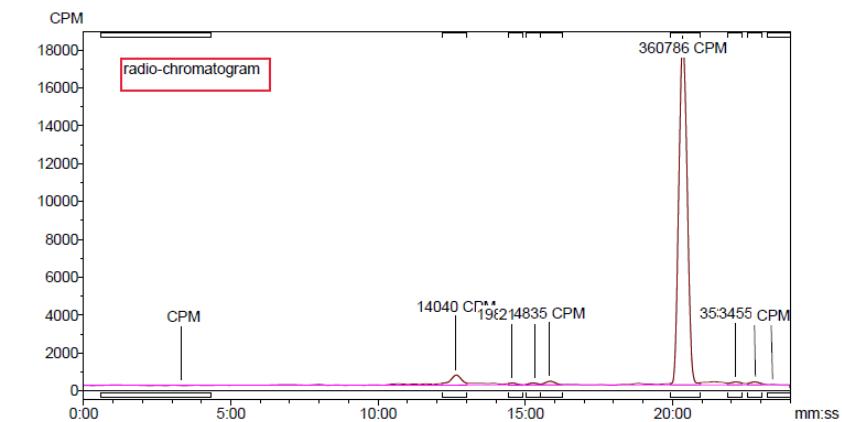


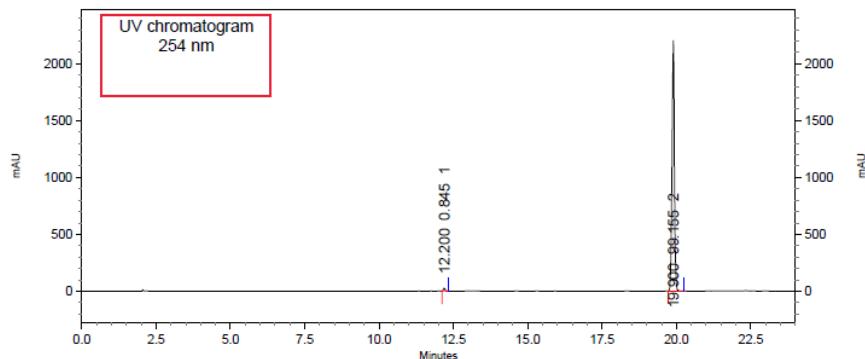
Figure S10. HPLC chromatograms for 2-(4-chloro-2-fluoro-3-methoxyphenyl)-6-(diethoxymethyl)-3-fluoro-N-trityl(4-¹⁴C)pyridin-4-amine (26).

Chromatogram: ¹⁴C



Regions: ¹⁴C Detector: β -RAM

Name	Start (mm:ss)	End (mm:ss)	Retention (mm:ss)	Area (CPM)	%ROI (%)	%Total (%)
Bkg 1	0:36	4:19	3:19			
Region 1	12:10	13:01	12:39	14040	3.59	3.34
Region 2	14:26	14:55	14:33	1980	0.51	0.47
Region 3	15:01	15:30	15:19	2191	0.56	0.52
Region 4	15:31	16:15	15:49	4835	1.24	1.15
Region 5	19:56	20:57	20:21	360786	92.31	85.79
Region 6	21:52	22:21	22:08	3539	0.91	0.84
Region 7	22:33	23:02	22:49	3455	0.88	0.82
Bkg 2	23:14	24:00	23:24			
7 Peaks				390826	100.00	92.93



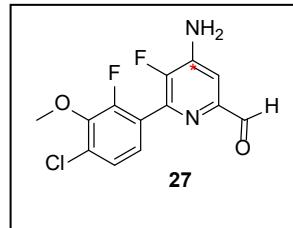
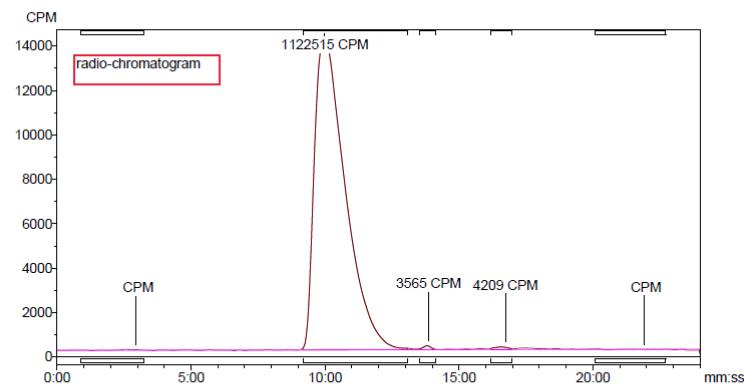
1: 254 nm, 4 nm

Results

Pk #	Retention Time	Area	Area Percent
1	12.200	103122	0.85
2	19.900	12095071	99.15
Totals		12198193	100.00

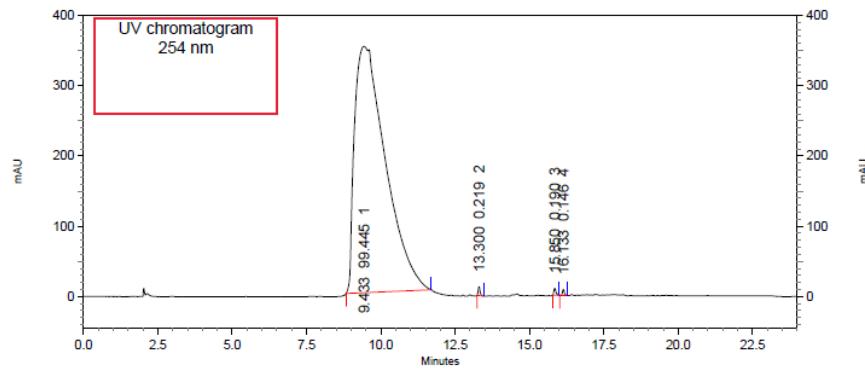
Figure S11. HPLC chromatograms for 4-Amino-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-¹⁴C)pyridine-2-carbaldehyde (27).

Chromatogram: ¹⁴C



Regions: ¹⁴C Detector: B-RAM

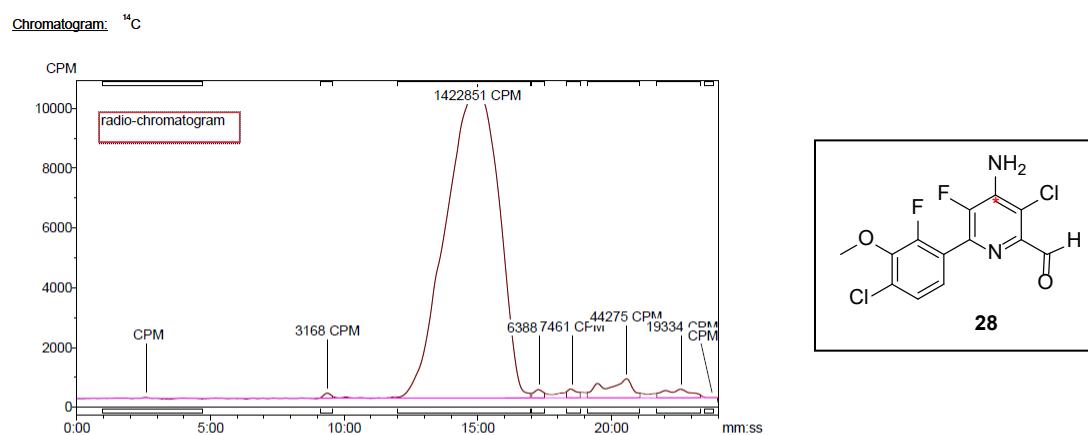
Name	Start (mm:ss)	End (mm:ss)	Retention (mm:ss)	Area (CPM)	%ROI (%)	%Total (%)
Bkg 1	0.53	3.15	2.57			
Region 1	9.11	13.05	9.59	1122515	99.31	98.98
Region 2	13.32	14.08	13.52	3565	0.32	0.31
Region 3	16.12	16.58	16.44	4209	0.37	0.37
Bkg 2	20.05	22.43	21.54			
3 Peaks				1130289	100.00	99.66



Results
1: 254 nm, 4 nm

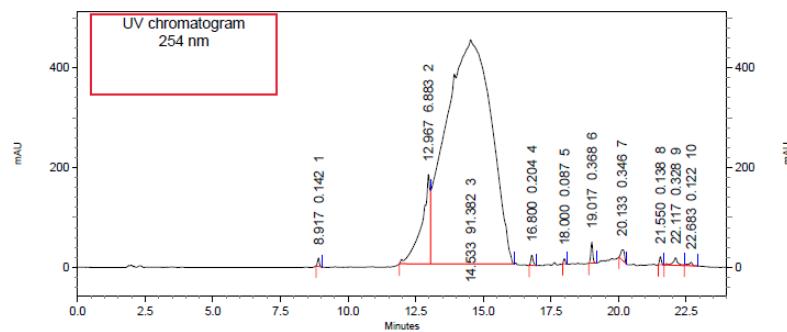
Pk #	Retention Time	Area	Area Percent
1	9.433	25357760	99.45
2	13.300	55895	0.22
3	15.850	48377	0.19
4	16.133	37247	0.15
Totals		25499279	100.00

Figure S12. HPLC chromatograms for 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-¹⁴C)pyridine-2-carbaldehyde (28).



Regions: ¹⁴C Detector: β -RAM

Name	Start (mm:ss)	End (mm:ss)	Retention (mm:ss)	Area (CPM)	%ROI (%)	%Total (%)
Bkg 1	0:58	4:41	2:36			
Region 1	9:07	9:34	9:22	3168	0.21	0.21
Region 2	12:00	16:58	14:59	1422851	94.64	93.74
Region 3	17:01	17:30	17:18	6388	0.42	0.42
Region 4	18:19	18:50	18:32	7461	0.50	0.49
Region 5	19:06	21:04	20:33	44275	2.94	2.92
Region 6	21:42	23:20	22:38	19334	1.29	1.27
Bkg 2	23:29	23:50	23:46			
6 Peaks				1503476	100.00	99.05



1: 254 nm, 4 nm
Results

Pk #	Retention Time	Area	Area Percent
1	8.917	81290	0.14
2	12.967	3938098	6.88
3	14.533	52285977	91.38
4	16.800	116819	0.20
5	18.000	49776	0.09
6	19.017	210318	0.37
7	20.133	198113	0.35
8	21.550	78918	0.14
9	22.117	187787	0.33
10	22.683	69587	0.12
Totals		57216683	100.00

Figure S13. HPLC chromatograms for 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-¹⁴C)pyridine-2-carboxylic acid (29).

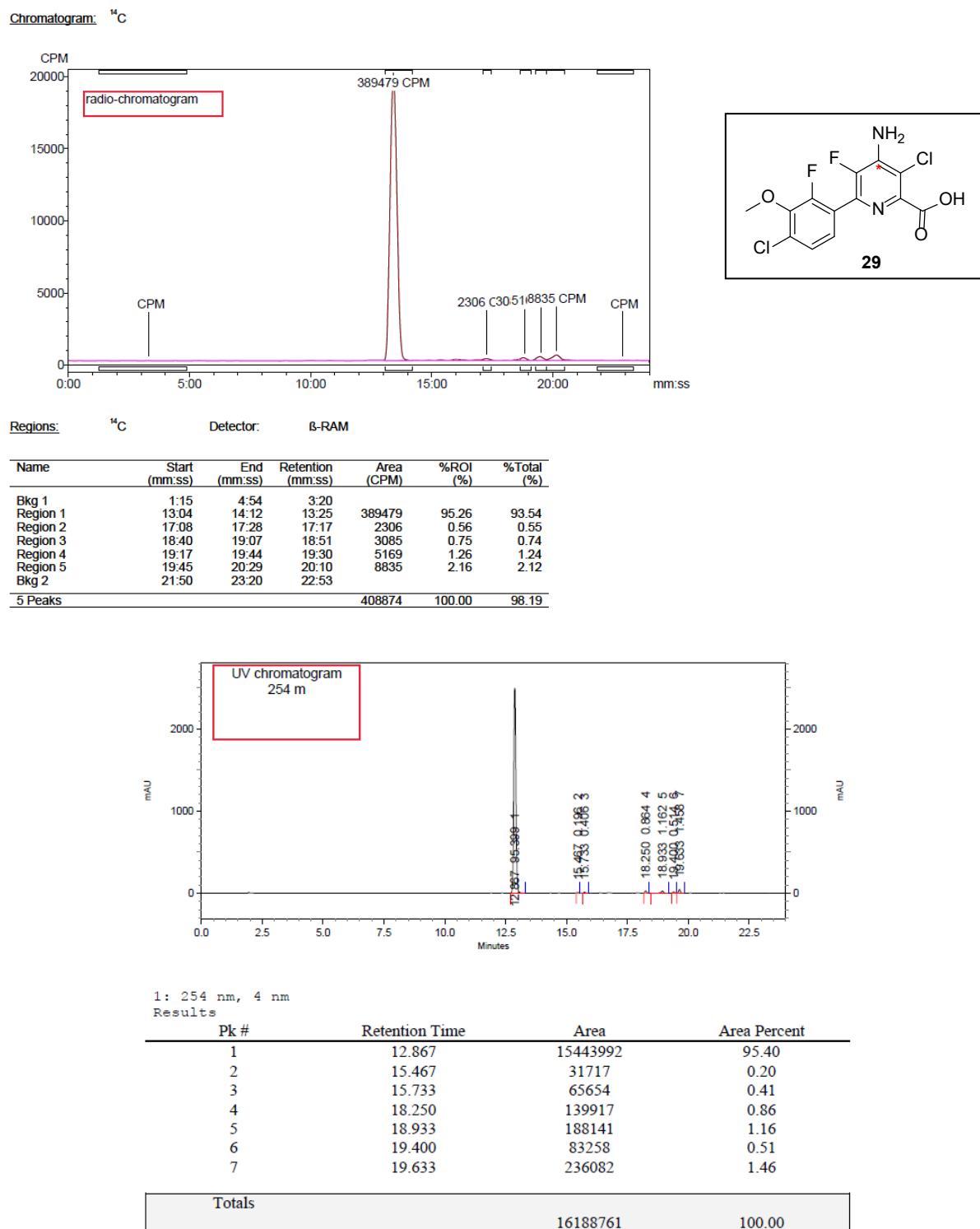
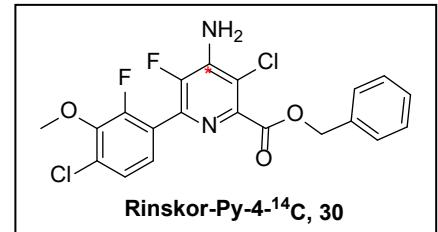
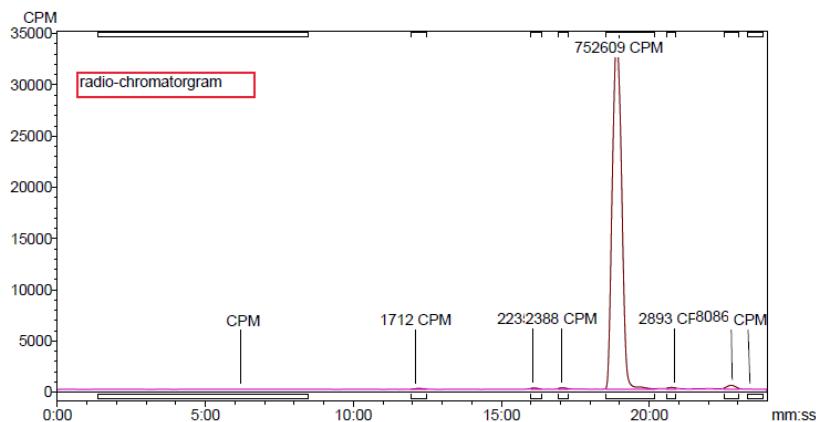


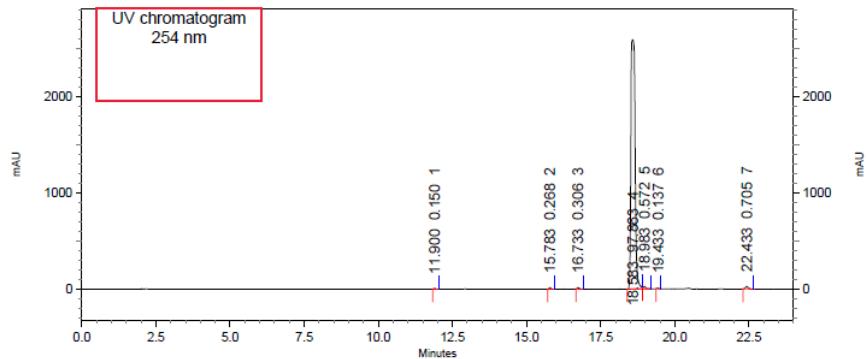
Figure S14. HPLC chromatograms for benzyl 4-amino-3-chloro-6-(4-chloro-2-fluoro-3-methoxyphenyl)-5-fluoro(4-¹⁴C)pyridine-2-carboxylate (30, Rinskor-Py-4-¹⁴C).

Chromatogram: ¹⁴C



Regions: ¹⁴C Detector: β -RAM

Name	Start (mm:ss)	End (mm:ss)	Retention (mm:ss)	Area (CPM)	%ROI (%)	%Total (%)
Bkg 1	1:21	8:29	6:12			
Region 1	11:57	12:28	12:06	1712	0.22	0.22
Region 2	16:00	16:21	16:04	2235	0.29	0.29
Region 3	16:56	17:15	17:01	2388	0.31	0.31
Region 4	18:33	20:11	18:58	752609	97.75	96.49
Region 5	20:36	20:54	20:51	2893	0.38	0.37
Region 6	22:32	23:01	22:48	8086	1.05	1.04
Bkg 2	23:20	23:51	23:24			
6 Peaks				769922	100.00	98.71



1: 254 nm, 4 nm
Results

Pk #	Retention Time	Area	Area Percent
1	11.900	38738	0.15
2	15.783	69118	0.27
3	16.733	78986	0.31
4	18.583	25267155	97.86
5	18.983	147641	0.57
6	19.433	35326	0.14
7	22.433	181917	0.70
Totals		25818881	100.00