Supporting Information for:

NHC-Copper Mediated Ligand-Directed Radiofluorination of Aryl Halides

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Table of Contents

1. General

The syntheses of organometallic complexes and preparation of stoichiometric and radiofluorination screening reactions were carried out in a N_2-filled glovebox. NMR spectra were obtained on a Varian VNMR 700 (699.76 MHz for ^{1}H; 175.95 MHz for ^{13}C), Varian VNMR 500 (500.09 MHz for 1H; 470.56 MHz for ^{19}F; 125.75 MHz for ^{13}C), or Varian VNMR 400 (401 MHz for ^{1}H; 376 MHz for ^{19}F; 123 MHz for ^{13}C) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. ^{19}F NMR chemical shifts are reported in ppm and are referenced to fluorobenzene (–113.52 ppm). Abbreviations used in the NMR data are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Yields of reactions that generated fluorinated products were determined by ^{19}F NMR spectroscopic analysis using a relaxation delay of 5 s. Mass spectral data were obtained on a Micromass Magnetic Sector Mass Spectrometer in electrospray ionization mode. X-ray crystallographic data were collected on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer. Flash chromatography was performed using a Biotage Isolera One system with cartridges containing high performance silica gel.

2. Materials and Methods

Unless otherwise stated, reagents were purchased from commercial suppliers and used as received. The following reagents were prepared according to literature procedures: IPrCuCl,[1] sIPrCuCl,[2] IAdCuCl,[3] sICyCuCl,[4] IPrCuOTf,[5] Cu(tBuCN)$_2$OTf,[6] **1-Br**,[7] **1-Cl**,[8] **1-I**,[9] **1-F,**[10] **2-F**,[11] **3-Br**,[12] **3-F**,[12] **6-Br**,[13] **7-F,**[14] **8-Br**[15] and 2-fluoro-5-(methoxyphenyl)boronic acid.[16] Imines **4-Br**,[17] **4-Cl**,[17] **9-Br,**[18] **11-Br**,[19] **18-Br**[20] and **18-F**[21] were prepared according to the general procedure described in Section 6.1 and spectra of these compounds matched those previously reported. IPrCuF,[22] sIPrCuF,[5] and sICyCuF[4] were prepared according to novel procedures (See Section 6.6), and spectral data for these compounds matched those in the literature. Cu(CH$_3$CN)$_4$OTf and Cu(CH$_3$CN)$_4$PF$_6$ were purchased from Millipore Sigma and recrystallized from a CH$_3$CN/Et$_2$O mixture under an inert atmosphere. Aldehydes were purchased from commercial suppliers. Potassium fluoride (KF) was supplied by The Dow Chemical Company. Tetramethylammonium fluoride (TMAF, anhydrous) was purchased from Millipore Sigma. N,N-dimethylformamide (DMF, 99.8%, Millipore Sigma), N,N-dimethylacetamide (DMA, 99%, Millipore Sigma), dimethylsulfoxide (DMSO, 99.8%, Acros), acetonitrile (CH$_3$CN, 99.9%, Millipore Sigma), N-methylpyrrolidinone (NMP), and N,N'-dimethylpropyleneurea (DMPU) were transferred directly into a N_2 glovebox prior to opening and dried over activated molecular sieves for at least 3 days prior to use. The water content in the DMF was determined to be 6 ppm via Karl Fischer titration. Tetrahydrofuran (THF), toluene, dichloromethane (DCM), and pentane were sparged with argon, dried over alumina columns using an Innovative Technologies solvent system, and further dried over activated molecular sieves for at least 3 days prior to use. Dioxane was purchased from Acros and dried over activated molecular sieves. THF and dioxane were further dried by the addition of a small amount of metallic sodium. Molecular sieves were activated under vacuum at 180 ºC for 3 days.

3. Stoichiometric Fluorination of Aryl Halides

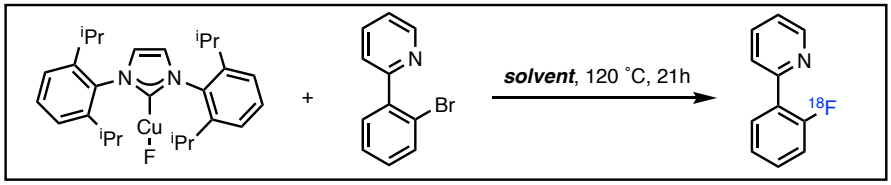
3.1 General procedure for the stoichiometric fluorination of aryl halides

In a N_2-containing glovebox, a 4 mL vial containing a stir bar was charged with dry, air-free DMF (450 µL), a stock solution of aryl halide in DMF (0.006 mmol aryl halide, 100 µL), and a stock solution of (NHC)CuF in DMF (0.006 mmol in 100 µL). The vial was capped with a PTFE-lined screw cap (Thermo Scientific™ 13 mm Autosampler Vial Screw Thread Caps with septa, catalog # 03-378-316), sealed with electrical tape, removed from the glovebox, and heated to 120 or 140 ºC on a hot plate equipped with an aluminum multi-reaction heating block. The homogeneous colorless to pale yellow solution was allowed to stir at this temperature for 21 h. After cooling to room temperature, α,α,α-trifluorotoluene or 4,4'-difluorobiphenyl was added as an internal standard, and the reaction yield was quantified using ^{19}F NMR spectroscopy. Product identity was confirmed by ^{19}F NMR spectroscopy by spiking the sample with the authentic product. Control reactions using other fluoride sources were carried out analogously to those with the (NHC)Cu complexes but with the following modification: the fluoride reagent was weighed into the 4 mL vial rather than using a stock solution, since the fluoride sources are not soluble in DMF at room temperature. Time-course reactions were run in screw-cap NMR tubes using the following modified

procedure: In a N_2-containing glovebox, an NMR tube fitted with a screw-cap was charged with dry, air-free DMF (350 µL), a stock solution of aryl halide in DMF (0.01 mmol aryl halide, 100 µL), a stock solution of (NHC)CuF in DMF (0.01 mmol in 100 µL) and a stock solution of and 4,4'-difluorobiphenyl in DMF (0.01 mmol in 100 µL) as the internal standard. The NMR tube was capped with a PTFE-lined screw cap, sealed with electrical tape, removed from the glovebox, and heated at 140 ˚C in an oil bath.

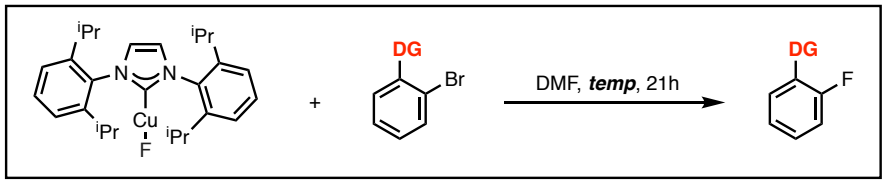
3.2 Additional screening

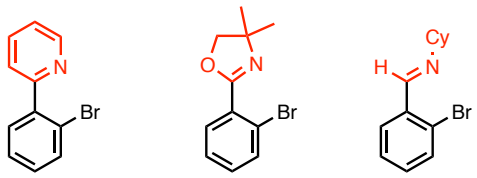
Table S1. Solvent screen for the stoichiometric fluorination of **1-Br.** The general procedure described in Section 3.1 was followed while varying the solvent.



Entry	Solvent	Yield (%)
1	DMPU	5
2	CH_3CN	12
3	dioxane	16
4	toluene	28
5	DMA	31
6	NMP	38
7	DMSO	61
8	DMF	65

Table S2. Temperature screen for the stoichiometric fluorination of **1-Br.** The general procedure described in Section 3.1 was followed while varying the temperature.



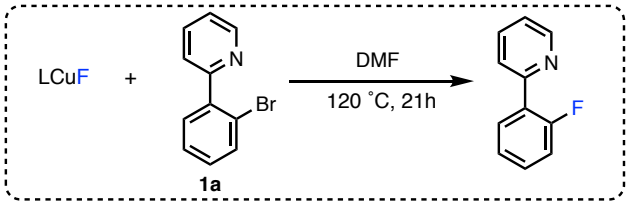


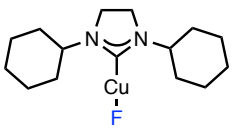
(**1-Br**) (**3-Br**) (**4-Br**)

Entry	Substrate	Temp (˚C)	Yield (%)
1	**1-Br**	120	65
2	**1-Br**	140	65
3	**2-Br**	120	12
4	**2-Br**	140	30
5	**3-Br**	120	18
6	**3-Br**	140	40[a]

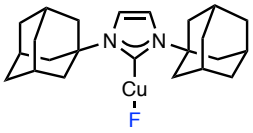
[a]Yield reported as sum of fluorinated imine product (37%) and a small amount of aldehyde (3%).

Table S3. NHC ligand screen for the stoichiometric fluorination of **1-Br.** The general procedure described in Section 3.1 was followed while varying the copper complex.

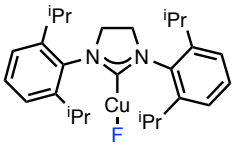




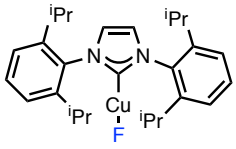
sICyCuF
3%



IAdCuF
36%

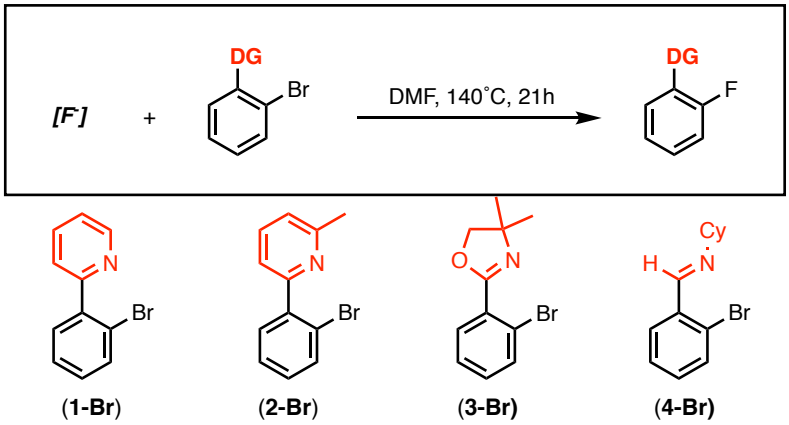


sIPrCuF
57%



IPrCuF
65%

Table S4. Screen of alternative fluoride sources. The general procedure described in Section 3.1 was followed while varying the fluoride source.

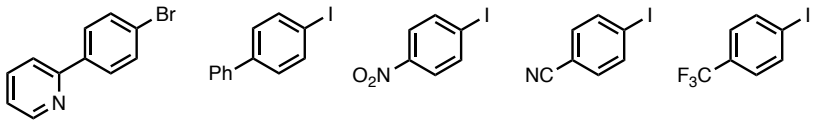


Entry	Substrate	Temp	[F⁻]	Yield (%)
1	**1-Br**	120	CuF_2	0
2	**1-Br**	120	TMAF	2
3	**1-Br**	120	AgF	1
4	**1-Br**	120	KF	0
5	**1-Br**	140	CuF_2	1
6	**1-Br**	140	TMAF	3
7	**1-Br**	140	AgF	3
8	**1-Br**	140	KF	0
9	**2-Br**	140	CuF_2	1
10	**2-Br**	140	TMAF	1
11	**2-Br**	140	AgF	0
12	**2-Br**	140	KF	0
13	**3-Br**	140	CuF_2	2
14	**3-Br**	140	TMAF	0
15	**3-Br**	140	AgF	0
16	**3-Br**	140	KF	0
17	**4-Br**	140	CuF_2	3
18	**4-Br**	140	TMAF	0
19	**4-Br**	140	AgF	0
20	**4-Br**	140	KF	0

3.3. Unsuccessful substrates

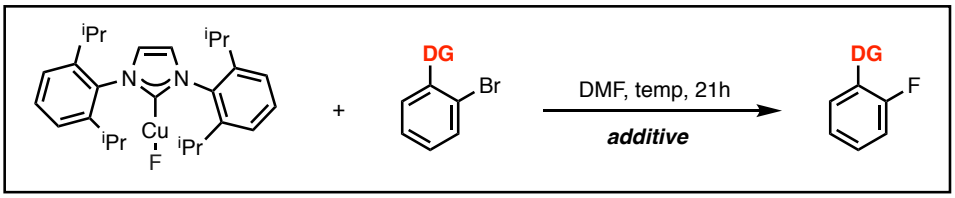
Figure S1. Attempted fluorination of non-directing substrates.

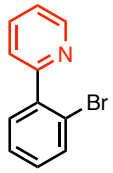
The following non-directing substrates yielded no observed fluorinated product when subjected to our optimized reaction conditions:



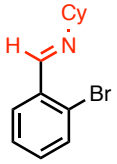
3.4. Effect of DMAP additive on the fluorination reaction

Table S5. Effect of DMAP additive on stoichiometric fluorination reaction. The general procedure described in Section 3.1 was followed.





(**1-Br**)

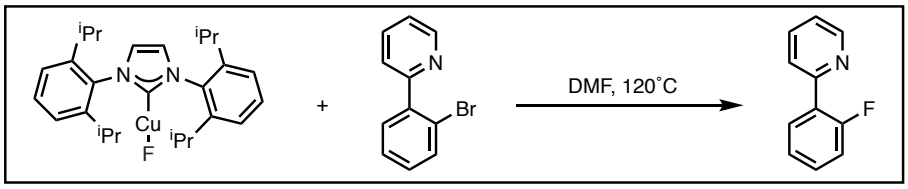


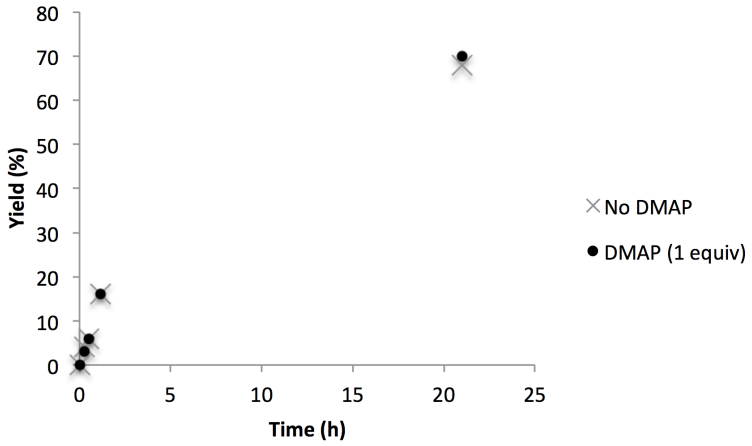
(**4-Br**)

Entry	Substrate	Additive (1 equiv)	Temp (˚C)	Yield (%)
1	**1-Br**	DMAP	120	66
2	**1-Br**	none	120	65
3	**4-Br**	DMAP	140	44[a]
4	**4-Br**	none	140	40[b]

[a]Yield reported as sum of fluorinated imine product (40%) and a small amount of aldehyde (4%).
[b]Yield reported as sum of fluorinated imine product (37%) and a small amount of aldehyde (3%).

Figure S2. Effect of DMAP on reaction rate[a,b]

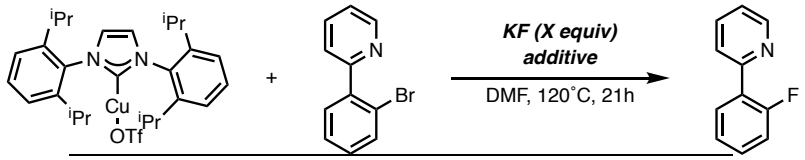




[a]Reactions were run in screw-cap NMR tubes. Yields were determined by integration vs. the internal standard 4,4'-difluorobiphenyl.
[b]The procedure for time-course reactions described in Section 3.1 was followed.

3.5. Fluorination using IPrCuOTf/KF[a]

Table S6. Fluorination with IPrCuOTf/KF[a]

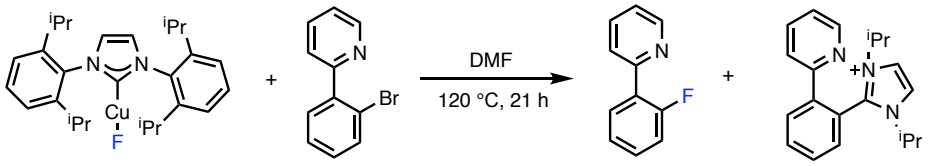


Entry	Additive (1 equiv)	Equiv. KF	Yield (%)
1	none	2	12
2	DMAP	2	13
3	none	1	32

[a]Conditions: IPrCuOTf (0.006 mmol), KF (1 or 2 equiv.), additive (0 or 1 equiv), substrate (1 equiv) DMF (0.01 M).

3.6. Identification of NHC-aryl side product

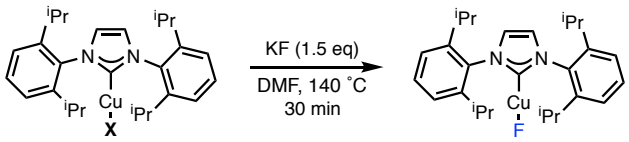
An NHC-aryl coupled species was identified by electrospray HRMS as a side product in the fluorination reaction. The observed mass (542.3535) closely matches that predicted for the compound (542.3533).



HRMS
m/z predicted: 542.3535
found: 542.3533

4. Synthesis of IPrCuF with KF

Scheme S1. Generation of IPrCuF with KF



X=Cl: 0%
X=OTf: 94%

Experimental Procedure:
In a N_2-containing glovebox, a 4 mL vial was charged with KF (0.009 mmol) and a stock solution of IPrCuX (X = Cl or OTF; 0.006 mmol, 650 µL DMF). The vial was capped with a PTFE-lined screw cap (Thermo Scientific™ 13mm Autosampler Vial Screw Thread Caps with septa, catalog # 03-378-316), removed from the glovebox, and heated at 140 ºC for 30 min with stirring. The mixture was cooled to room temperature, the vial was transferred into the glovebox, and 4,4'-difluorobiphenyl was added as an internal standard. The mixture was analyzed by ^{19}F NMR spectroscopy. IPrCuF was identified based on its ^{19}F NMR shift, and the yield was quantified by integration versus the internal standard.

5. Radiofluorination of Aryl Halides

5.1 Radiofluorination materials and methods

See the Materials and Methods (Section 2) for details on the synthesis and purification of chemicals. Unless otherwise stated, reagents were purchased from commercial suppliers and used as received. Solvents N,N-dimethylformamide (DMF, 99.8%, Millipore sigma), N,N-dimethylacetamide (DMA, 99%,

Millipore Sigma), dimethylsulfoxide (DMSO, 99.8%, Acros), and acetonitrile (CH_3CN, 99.9%, Millipore Sigma) were transferred directly into a N_2 glovebox prior to opening and dried over activated molecular sieves for 3 days prior to use. KOTf and K_2CO_3 were purchased from Fisher Scientific. Sterile product vials were purchased from Hollister-Stier. QMA-light Sep-Paks were purchased from Waters Corporation. QMA-light Sep-Paks were flushed with 10 mL of ethanol, followed by 10 mL of 90 mg/mL KOTf solution, and 10 mL of sterile water prior to use.

5.2 Preparation of $K^{18}F$

$K^{18}F$ was synthesized according to our previously reported procedure using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). Anhydrous, air-free DMF (4 mL) was transferred from a sealed vial to an argon-filled vial in the automated reactor using a syringe under a positive flow of argon. [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETTrace cyclotron (55 μA beam for 2–5 min generated ca. 150–375 mCi of [^{18}F]fluoride). The [^{18}F]fluoride was delivered to the synthesis module in a 2.5 mL bolus of [^{18}O]water and trapped on a QMA-light Sep-Pak preconditioned with potassium triflate (10 mL, 0.5 M) to remove [^{18}O]water and other impurities. [^{18}F]Fluoride was eluted into the reaction vessel using 550 μL of an aqueous solution containing 10 mg of potassium triflate and 50 μg of potassium carbonate. CH_3CN (1 mL) was added to the reaction vessel, and the resulting solution was dried by azeotropic distillation to provide anhydrous $K^{18}F$. Azeotropic drying/evaporation was achieved by heating the reaction vessel to 100 ºC and drawing vacuum for 6 min. The reaction vessel was then simultaneously subjected to an argon stream and vacuum draw for an additional 6 min. Anhydrous, air-free DMF was added to the dried reagent, and the sample was cooled to 40 ºC and then transferred to an S10 sterile vial for subsequent use in reactions. As an example, approximately 50 mCi of prepared $K^{18}F$ in 4 mL of DMF was isolated with a 3 min cyclotron beam. It should be noted that percent recovery data is only relevant for manual reactions, not automated one-pot syntheses. *Note: All loading operations were conducted under a positive flow of argon, which was used as a pressurizing gas during automated sample transfers.* $Ag^{18}F/K_{2.2.2}$ was prepared and dried according to our previously reported procedure[23] and eluted with DMF. $Ag^{18}F$ was prepared was prepared analogously but without the addition of $K_{2.2.2}$.

5.3 General procedure for the radiofluorination of aryl halides

In a N_2-containing glovebox, a 4 mL vial was charged with a stock solution of aryl halide in DMF (0.005 mmol, 100 μL), a stock solution of IPrCuOTf in DMF (0.005 mmol, 100 μL), and a stock solution of 4-dimethylaminopyridine (DMAP) in DMF (0.005 mmol, 25 μL). The vial was capped with a PTFE-lined screw cap (Thermo Scientific™ 13mm Autosampler Vial Screw Thread Caps with septa, catalog # 03-378-316), removed from the glovebox, and transferred to the University of Michigan PET center. Freshly prepared $K^{18}F$ in DMF (100 μL) was added to the capped vial through the septum, and the reaction mixture was heated at 120, 140 or 160 °C for 30 min on a hot plate equipped with an aluminum multi-reaction heating block. The time between preparation of the sample and the addition of $K^{18}F$ was generally 2–3 h. Radiochemical conversion (RCC) was quantified using radio-TLC (Eckert and Ziegler Bioscan AR 2000 Radio-TLC scanner) and product identity was confirmed by an HPLC unit equipped with a radiation detector (Eckert and Ziegler Flow Count). Reactions using Cu complexes other than IPrCuOTf were carried out analogously to those with IPrCuOTf, but with the following modification: Cu complexes not soluble in DMF at room temperature were weighed into the 4 mL vial rather than being drawn from a stock solution. Similarly, for reactions using additives not soluble in DMF, the additive was weighed directly into the vial rather than using a stock solution.

The following parameters were varied: Cu source; additives; fluoride source; temperature (120, 140, 160 °C).

5.4 Identification and quantification of radiofluorinated products

Radiochemical conversion (RCC) was determined using radio-TLC. The crude reaction mixture was spotted on a silica gel TLC plate using 1:1 ethyl acetate:hexane as the eluent. The distribution of ^{18}F was visualized using a Bioscan AR 2000 Radio-TLC scanner (Eckert and Ziegler), and the conversion was

determined by integrating the peak corresponding to the fluorinated product and dividing by the total integrated area of ^{18}F on the plate. For complex substrates **19-Br** and **20-Cl**, more polar developing mixtures (100% ethyl acetate (**19-Br**) and 4:1 DCM:methanol (**20-Cl**) were used. For these substrates, more than one ^{18}F-containing spot was observed on the TLC plate. The peak corresponding to the desired product was identified by co-spotting with the authentic ^{19}F product to determine the R_f of the desired product. Integrating this peak gave the radiochemical conversion, and its identity was further confirmed by radio-HPLC analysis (see below). The identity of the radiofluorinated products was determined through HPLC analysis. For each substrate, the crude reaction mixture was spiked with a small amount of the authentic ^{19}F-containing product and injected into the HPLC unit. Both UV and RAD traces were collected. The presence of the ^{18}F product was confirmed by the presence of a RAD peak with a retention time corresponding to that of the UV peak due to the co-injected authentic ^{19}F-containing product. The UV and RAD detectors are sequentially aligned (with the sample passing through the UV detector first), resulting in a ~0.2 min delay between the corresponding UV and RAD peaks.

5.5 HPLC conditions

HPLCs of reaction mixtures and authentic standards were run using the following method:
Column: Phenomenex Luna 5 µm C18(2) 100 Å 150 mm x 4.6 mm
Flow Rate: 2 mL/min
Solvent A: H_2O
Solvent B: MeCN
Gradient: 0–3 min, 5% B; 3–17 min, linear gradient, 5–95% B; 17–20 min, 95% B; 20–30 min, 5% B

Isocratic HPLC for compound **1-^{18}F** was run using a Gemini C18, 250 x 4.6 mm, 5 µm column with a flow rate of 2 mL/min. The eluent was 40% CH_3CN with 50 mM NH_4HCO_3 at pH 10.

5.6 Automated synthesis of 1-^{18}F

All loading operations were conducted under a positive flow of Ar, which was used as a pressurizing gas during automated sample transfers. $K^{18}F$ was prepared using a TRACERLab FX_{FN} automated radiochemistry synthesis module (General Electric, GE). [^{18}F]Fluoride was produced via the $^{18}O(p,n)^{18}F$ nuclear reaction using a GE PETtrace cyclotron. $K^{18}F$ was produced as indicated above. In a N_2-filled glovebox, stock solutions of **1-Br** (0.02 mmol in 0.5 mL of DMF), IPrCuOTf (0.02 mmol in 0.5 mL of DMF), and DMAP (0.02 mmol in 0.3 mL of DMF) were added to a 4 mL vial. The vial was capped with a PTFE-lined screw cap (Thermo Scientific™ 13mm Autosampler Vial Screw Thread Caps with septa, catalog # 03-378-316) and removed from the glovebox. The solution was transferred to an Ar-filled vial in the synthesis module under a positive flow of Ar. Subsequently, this solution was transferred to a reactor containing dry $K^{18}F$ by applying Ar gas through the valve containing the reagent solution. Open valves leading out of the reactor were closed, and the mixture was stirred for 30 min at 140 ºC. The mixture was then cooled to 50 ºC with compressed air cooling, and 2 mL of HPLC buffer (30% MeCN, 10 mM NH_4HCO_3, pH 10) was added to the reactor. This mixture was allowed to stir for approximately 1 min and was then transferred to an HPLC loop for injection and purification by semi-preparative chromatography (Phenomenex Gemini, 250 x 10 mm, 10µm, 4 mL/min). The product was collected and diluted in a flask containing H_2O (50 mL). Compound **1-^{18}F** was then trapped on a C18 extraction disk, washed with 10 mL of sterile water, eluted with 1 mL of EtOH, and then rinsed with 9 mL of saline solution. Compound **1-^{18}F** was produced in a 14.3 ± 3.2% decay corrected radiochemical yield (RCY, 119.9 mCi ± 28, n=2).

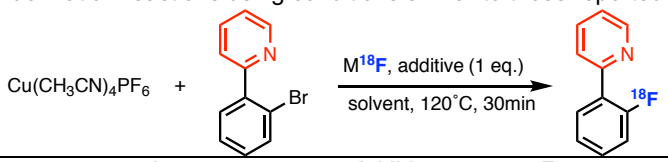
5.7 Molar activity calculations

An aliquot of the sample was injected onto an analytical HPLC using the isocratic conditions described in Section 5.5. The UV peak corresponding to the radiofluorinated product was determined by overlaying the UV and RAD traces (with a 0.2 min offset as described in the HPLC section). The UV area was then used to calculate the concentration of the product based on linear regression analysis of the appropriate fluoroarene standard. A standard curve was generated from the standard solutions, each run in duplicate (0.0001 mg/mL to 1.0 mg/mL). This provided the concentration of the product in mmol/mL. Dividing the activity concentration (Ci/mL) by the HPLC-derived concentration of product (mmol/mL) provided the

molar activity in Ci/mmol. This reflects an end of synthesis (EoS) molar activity. Compound **1-^{18}F** was produced with a molar activity of 1614 ± 353 Ci/mmol (n=2).

5.8 Additional radiofluorination screening

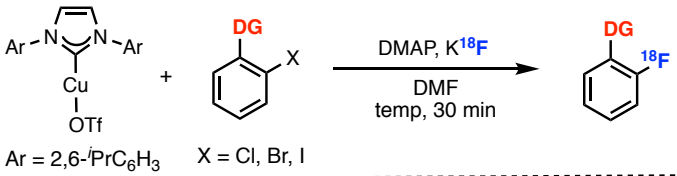
Table S7. Radiofluorination reactions using conditions similar to those reported in reference 25.

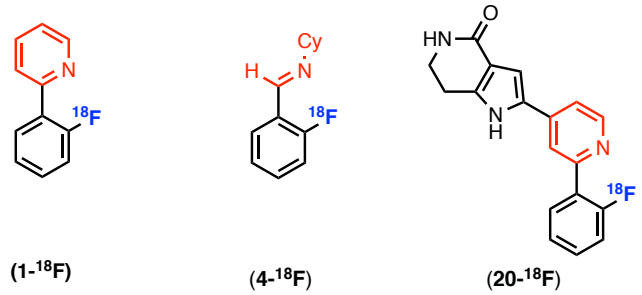


Entry	M^{18}F	solvent	Additive	Temperature (˚C)	RCC (%)
1[a]	Ag^{18}F[b]	CH_3CN	NBu_4PF_6	120	0[d,e]
2[a]	Ag^{18}F[b]	CH_3CN	DMAP	120	0
3[c]	K^{18}F	DMF	NBu_4PF_6	120	0
4[c]	K^{18}F	DMF	NBu_4PF_6	140	0
5[c]	K^{18}F	DMF	NBu_4PF_6, DMAP	140	0
6[c]	K^{18}F	DMF	DMAP	140	0
7[c]	K^{18}F	DMF	none	140	0

[a]Conditions (analogous to ref. 25): Substrate (0.05 mmol), additive (1 equiv), $Cu(CH_3CN)_4PF_6$ (0.2 equiv), Ag^{18}F solution in CH_3CN (0.25 mL).
[b]Ag^{18}F was prepared according to the procedure in ref. 23.
[c]Reactions were run under the general conditions described in Section 5.3 using $Cu(CH_3CN)_4PF_6$ and the specified additive(s).
[d]Substituting imine substrate **4-Br** for phenylpyridine **1-Br** also gave 0% RCC under these conditions.
[e]Carrier added reaction with 1 equiv of Ag^{19}F also gave no detected product.

Table S8. Radiofluorination temperature screen. The general procedure described in Section 5.3 was followed while varying the temperature.



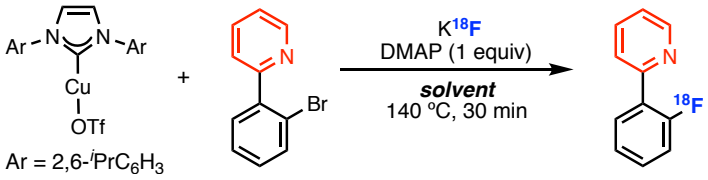


(**1-^{18}F**) (**4-^{18}F**) (**20-^{18}F**)

Entry	Substrate	Temp (ºC)	RCC (%)[a]
1	**1-Br**	120	47±9 (n=3)
2	**1-Br**	140	65±7 (n=18)
3	**1-Br**	160	71 (n=1)
4	**1-Cl**	140	8±2 (n=2)
5	**1-Cl**	160	11±3 (n=3)
6	**4-Cl**	140	1 (n=1)
7	**4-Cl**	160	6±2 (n=3)
8	**20-Cl**	140	3±1 (n=3)
9	**20-Cl**	160	5±1 (n=3)

[a]RCC determined by radio-TLC

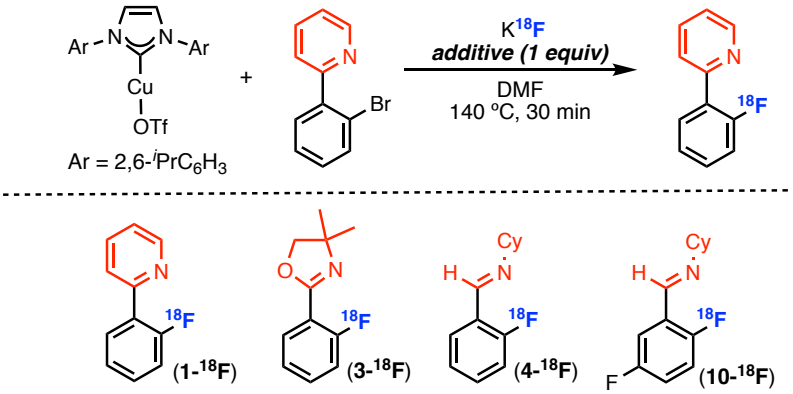
Table S9. Radiofluorination solvent screen.[a]



Entry	Solvent	RCY (%)[b]
1	DMF	65
2	DMA	62
3	DMSO	63

[a]The general procedure for automated synthesis in Section 5.6 was followed while varying the solvent. No chromatographic separation was carried out.
[b]RCY was calculated by determining the percent yield of activity in the crude reaction mixture and multiplying this by the radiochemical purity of the product as measured by radio-HPLC.

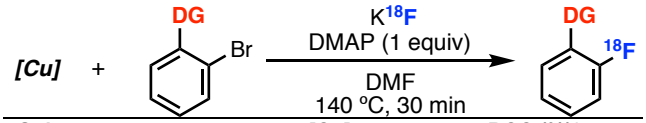
Table S10. Additive equivalents screen for radiofluorination. The general procedure described in Section 5.3 was followed while varying the additive.

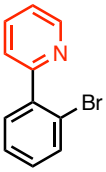
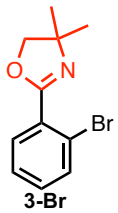
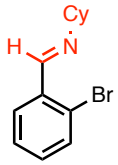
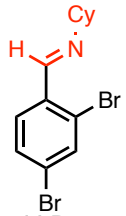
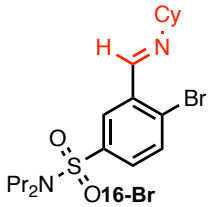


Entry	Substrate	Additive (equiv)	RCC (%)[a]
1	**1-Br**	none	10±6 (n=3)
2	**1-Br**	pyridine (1)	23±2 (n=2)
3	**1-Br**	pyridine (5)	32±6 (n=3)
4	**1-Br**	4-phenylpyridine (1)	3±1 (n=2)
5	**1-Br**	4-phenylpyridine (5)	0 (n=2)
6	**1-Br**	DMAP (0.5)	35±1 (n=2)
7	**1-Br**	DMAP (1)	65±7 (n=17)
8	**1-Br**	DMAP (5)	79±1 (n=3)[b]
9	**1-Br**	DBU (1)	30±14 (n=2)
10	**1-Br**	DBU (5)	7±1 (n=2)
11	**1-Br**	none	7±2 (n=2)
12	**3-Br**	DMAP (1)	54±6 (n=3)
13	**3-Br**	DMAP (5)	31±1 (n=2)
14	**4-Br**	DMAP (1)	53±10 (n=8)
15	**4-Br**	DMAP (5)	31±0 (n=2)
16	**10-Br**	DMAP (1)	28±9 (n=4)
17	**10-Br**	DMAP (5)	13±4 (n=2)

[a]RCC determined by radio-TLC. [b]Although 5 equiv of DMAP increased the yield for substrate **1-Br,** this was not general for other substrates (See entries 12–17). Therefore, 1 equiv of DMAP was used as standard conditions.

Table S11. Radiofluorination Cu source screen. The general procedure described in Section 5.3 was followed while varying the Cu source.

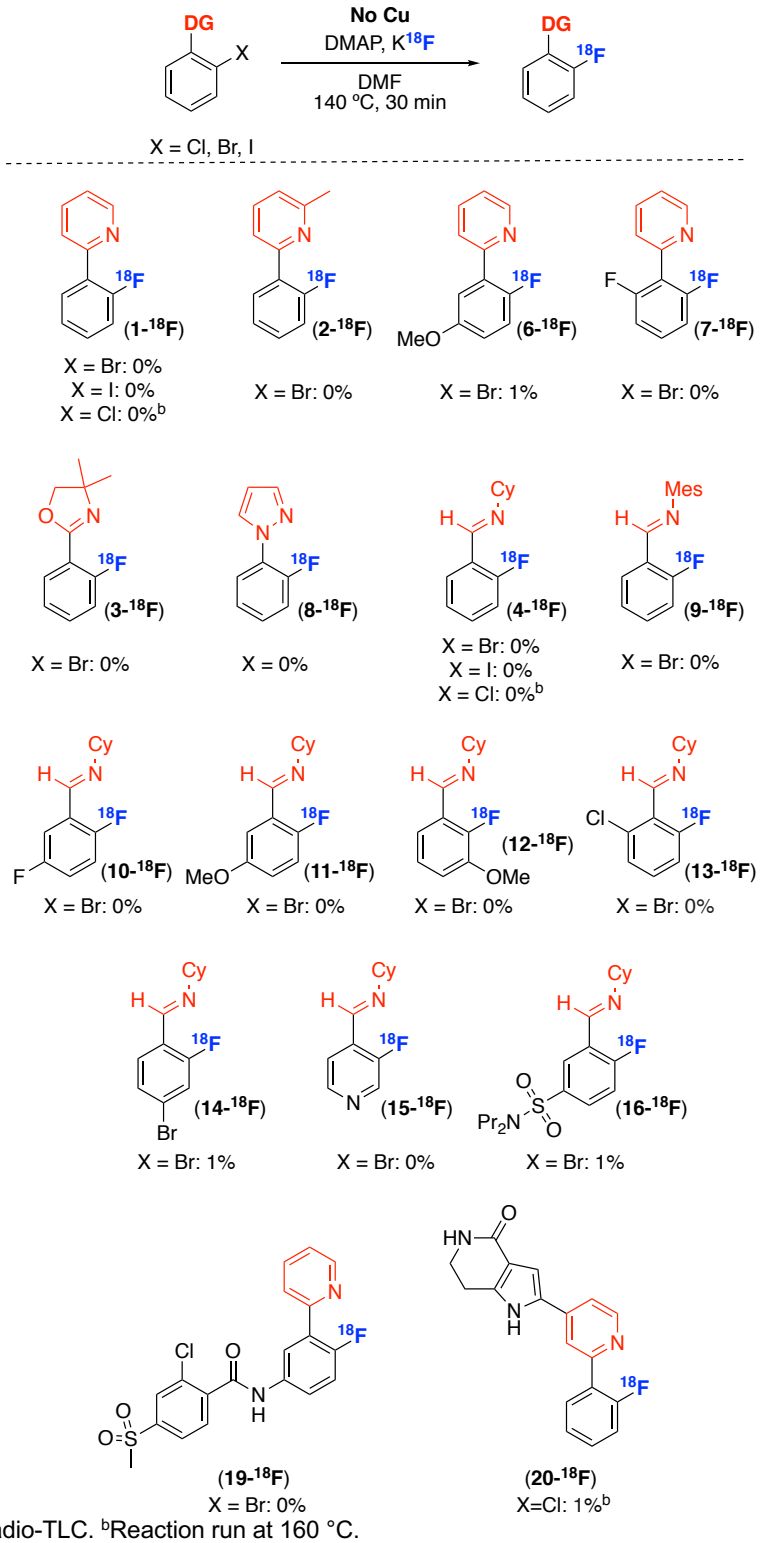


Substrate	[Cu]	RCC (%)[a]
 **1-Br**	IPrCuOTf	65±7 (n=18)
	IPrCuCl	0
	sICyCuOTf	0
	$Cu(CH_3CN)_4PF_6$	0
	$Cu(CH_3CN)_4OTf$	0
	$Cu(^tBuCN)_2OTf$	1
	$[CuOTf]_2C_6H_6$	1
	CuCl	0
	IPrCuOtBu	0
	$Cu(OTf)_2$	0
	IPr ligand only	0
	none	0
 **3-Br**	IPrCuOTf	54±6 (n=3)
	$Cu(CH_3CN)_4PF_6$	2±3 (n=3)
	$Cu(CH_3CN)_4OTf$	3±3 (n=3)
	$Cu(^tBuCN)_2OTf$	5±3 (n=4)
	$[CuOTf]_2C_6H_6$	2±1 (n=2)
	$Cu(OTf)_2$	3±1 (n=2)
	none	0
 **4-Br**	IPrCuOTf	53±10 (n=8)
	sICyCuOTf	0
	$Cu(CH_3CN)_4PF_6$	0
	$Cu(CH_3CN)_4OTf$	4±4 n=5
	$Cu(^tBuCN)_2OTf$	2±1 n=3
	$[CuOTf]_2C_6H_6$	2±1 n=3
	CuCl	0
	$Cu(OTf)_2$	1
	IPr ligand only	0
	none	0
 **14-Br**	IPrCuOTf	33±8 (n=3)
	$Cu(CH_3CN)_4PF_6$	0
	$Cu(CH_3CN)_4OTf$	1
	$Cu(^tBuCN)_2OTf$	0
	$[CuOTf]_2C_6H_6$	1
	$Cu(OTf)_2$	1
	none	1
 **16-Br**	IPrCuOTf	49±9 (n=3)
	$Cu(CH_3CN)_4OTf$	1
	$Cu(^tBuCN)_2OTf$	1
	none	1

Reactions with yield >1% were run at least twice. [a]RCC determined by radio-TLC. The RCCs using simple Cu salts [$Cu(CH_3CN)_4PF_6$, $Cu(CH_3CN)_4OTf$, $Cu(^tBuCN)_2OTf$, $[CuOTf]_2C_6H_6$, and $Cu(OTf)_2$] under identical conditions but in the absence of DMAP additive were comparable to or lower than those reported here.

5.9 Negative controls for optimized radiofluorination reaction

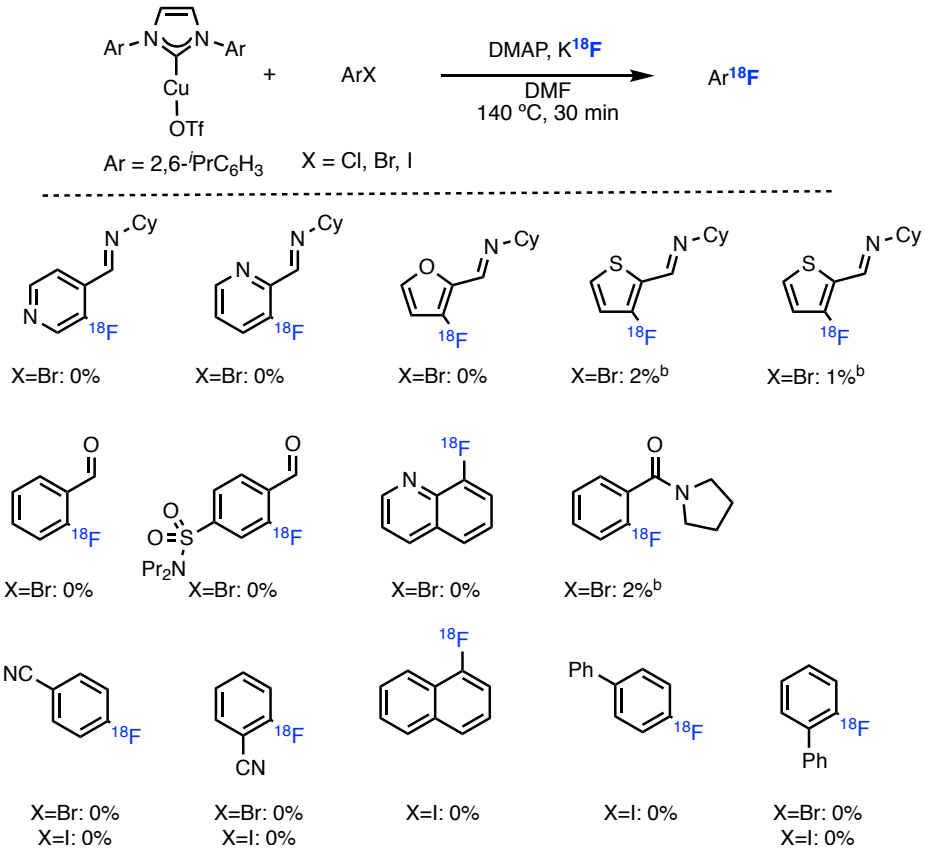
Table S12. Radiofluorination control reactions without Cu.[a,b] The general procedure described in Section 5.3 was followed but with no Cu added.



[a]RCC determined by radio-TLC. [b]Reaction run at 160 °C.

5.10 Unsuccessful substrates for radiofluorination

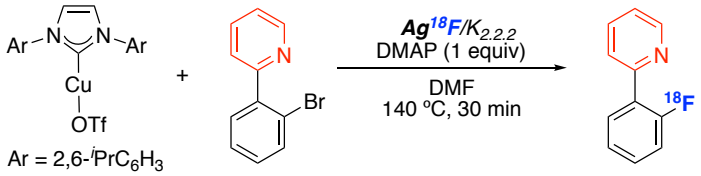
Table S13. Unsuccessful substrates under the optimized radiofluorination conditions.[a] The general procedure described in Section 5.3 was followed.



[a]RCC determined by radio-TLC. [b]Product identity not confirmed by radio-HPLC. Imine substrates were prepared using the procedure described in Section 6.1.

5.11 Reactions with $Ag^{18}F$

Scheme S2. Radiofluorination reactions with $Ag^{18}F$ and **1-Br**. The general procedure described in Section 5.3 was followed using $Ag^{18}F/K_{2.2.2}$ instead of $K^{18}F$.[a]

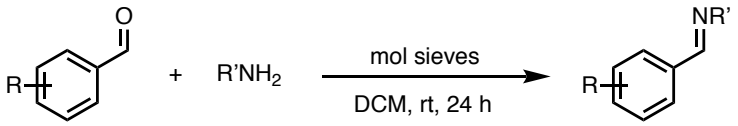


22 ± 4%
(n=3)

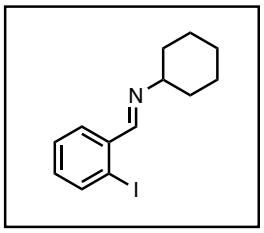
[a]$Ag^{18}F/K_{2.2.2}$ was prepared according to the procedure reported in ref. 23.

6. Synthesis of Novel Compounds

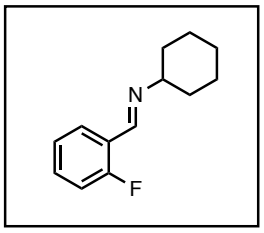
6.1 Preparation of imines



Imines were prepared using a previously reported procedure.[24] The respective aldehyde (1 mmol) and amine (1 mmol) were added to a 20 mL vial under N_2 and dissolved in DCM (4 mL). Activated molecular sieves (1 g) were added, and the reaction was allowed to stir at room temperature for 24 h. The solution was then filtered and concentrated *in vacuo* to afford the corresponding imine. The spectra of **4-Br**,[17] **4-Cl**,[17] **9-Br**[18], **18-Br**[20], and **18-F**[21] matched those reported in the literature.



2-Iodobenzaldehyde cyclohexylimine (4-I)
Colorless oil, 120 mg, 38% yield
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.41–7.31 (m, 1H), 7.13–7.02 (m, 1H), 3.38–3.23 (m, 1H), 1.96–1.51 (m, 7H), 1.48–1.21 (m, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 162.01, 139.61, 137.51, 131.79, 129.01, 128.50, 100.03, 69.73, 34.46, 25.76, 24.84.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{16}IN]H^+$ 314.0406; found: 314.0412



2-Fluorobenzaldehyde cyclohexylimine (4-^{19}F)

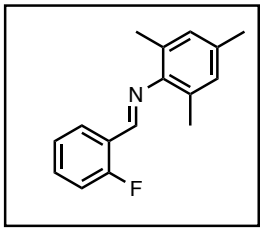
Colorless oil, 150 mg, 73% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.02–7.95 (m, 1H), 7.40–7.33 (m, 1H), 7.26 (s, 1H), 7.18–7.13 (m, 1H), 7.08–7.03 (m, 1H), 3.28–3.20 (m, 1H), 1.86–1.81 (m, 2H), 1.77–1.72 (m, 2H), 1.70–1.66 (m, 1H), 1.64–1.55 (m, 2H), 1.43–1.33 (m, 2H), 1.32–1.23 (m, 1H)

^{13}C NMR (176 MHz, $CDCl_3$): δ 162.30 (d, *J* = 251.5 Hz), 152.04 (d, *J* = 4.7 Hz), 131.95 (d, *J* = 8.6 Hz), 127.93 (d, *J* = 3.0 Hz), 124.39 (d, *J* = 3.5 Hz), 124.38 (d, *J* = 8.4 Hz), 115.75 (d, *J* = 21.2 Hz), 70.41, 34.48, 25.78, 24.90

^{19}F NMR (377 MHz, $CDCl_3$): δ –117.77 to –126.06 (m, 1F)

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{16}FN]H^+$ 206.1345; found: 206.1342



2-Fluorobenzaldehyde mesitylimine (9-^{19}F)

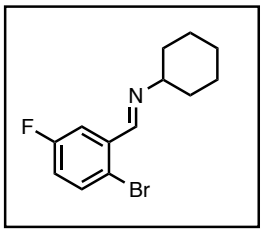
Yellow oil, 175 mg, 72% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 8.31–8.21 (m, 1H), 7.50 (dddd, *J* = 8.3, 7.3, 5.3, 1.8 Hz, 1H), 7.35–7.25 (m, 1H), 7.16 (dd, *J* = 10.6, 8.4 Hz, 1H), 6.92 (s, 2H), 2.31 (s, 3H), 2.15 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.91 (d, *J* = 253.2 Hz), 156.41 (d, *J* = 4.9 Hz), 148.92, 133.35, 133.01 (d, *J* = 8.6 Hz), 128.91, 127.73 (d, *J* = 2.7 Hz), 127.11, 124.60 (d, *J* = 3.5 Hz), 124.02 (d, *J* = 9.4 Hz), 116.05 (d, *J* = 21.1 Hz), 20.88, 18.35.

^{19}F NMR (376 MHz, $CDCl_3$): δ –119.53 to –124.14 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{16}H_{16}FN]H^+$ 242.1345; found: 242.1348



2-Bromo-5-fluorobenzaldehyde cyclohexylimine (10-Br)

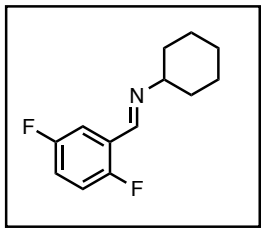
White crystalline solid, 240 mg, 85% yield, mp = 46.0–48.0 °C

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 9.4, 3.2 Hz, 1H), 7.51 (dd, *J* = 8.8, 5.0 Hz, 1H), 6.98 (ddd, *J* = 8.8, 7.6, 3.2 Hz, 1H), 3.35–3.27 (m, 1H), 1.88–1.80 (m, 2H), 1.78–1.71 (m, 2H), 1.71–1.65 (m, 1H), 1.62–1.53 (m, 2H), 1.43–1.34 (m, 2H), 1.33–1.24 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 162.20 (d, *J* = 247.5 Hz), 156.80 (d, *J* = 2.2 Hz), 136.95 (d, *J* = 7.3 Hz), 134.32 (d, *J* = 7.6 Hz), 118.94 (d, *J* = 3.2 Hz), 118.92 (d, *J* = 23.2 Hz), 115.66 (d, *J* = 24.1 Hz), 69.86, 34.40, 25.75, 24.77.

^{19}F NMR (377 MHz, $CDCl_3$): δ –112.77 to –115.66 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}BrFN]H^+$ 284.0450; found: 284.0453



2,5-Difluorobenzaldehyde cyclohexylimine (10-^{19}F)

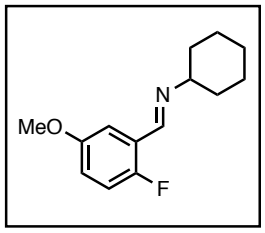
Colorless oil, 175 mg, 78% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.55 (d, *J* = 2.3 Hz, 1H), 7.68 (ddd, *J* = 8.7, 5.5, 3.1 Hz, 1H), 7.09–6.99 (m, 2H), 3.29–3.22 (m, 1H), 1.86–1.80 (m, 2H), 1.77–1.71 (m, 2H), 1.71–1.66 (m, 1H), 1.63–1.53 (m, 2H), 1.42–1.33 (m, 2H), 1.32–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 159.01 (dd, *J* = 242.8, 2.2 Hz), 158.27 (dd, *J* = 248.0, 2.2 Hz), 151.00 (dd, *J* = 4.2, 2.2 Hz), 125.75 (dd, *J* = 11.9, 7.6 Hz), 118.52 (dd, *J* = 24.9, 8.9 Hz), 117.00 (dd, *J* = 24.2, 8.4 Hz), 113.81 (dd, *J* = 25.0, 3.5 Hz), 70.20, 34.39, 25.75, 24.79.

^{19}F NMR (377 MHz, $CDCl_3$): δ –118.58 (ddt, *J* = 13.4, 6.7, 2.2 Hz, 1F), –127.54 to –128.91 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}F_2N]H^+$ 224.1251; found: 224.1249



2-Fluoro-5-methoxybenzaldehyde cyclohexylimine (11-^{19}F)

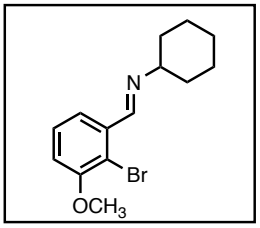
Pale tan oil, 175 mg, 74% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.58 (s, 1H), 7.46 (dd, *J* = 5.6, 3.2 Hz, 1H), 6.97 (t, *J* = 9.3 Hz, 1H), 6.90 (ddd, *J* = 9.0, 4.2, 3.2 Hz, 1H), 3.82 (s, 3H), 3.24 (tt, *J* = 10.6, 4.1 Hz, 1H), 1.83 (dt, *J* = 13.7, 3.7 Hz, 2H), 1.77–1.72 (m, 2H), 1.71–1.66 (m, 1H), 1.64–1.54 (m, 2H), 1.37 (qt, *J* = 12.7, 3.5 Hz, 2H), 1.32–1.22 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 157.02 (d, *J* = 244.4 Hz), 155.95 (d, *J* = 2.0 Hz), 152.01 (d, *J* = 4.3 Hz), 124.60 (d, *J* = 10.7 Hz), 118.96 (d, *J* = 8.4 Hz), 116.59 (d, *J* = 23.5 Hz), 110.25 (d, *J* = 2.8 Hz), 70.30, 56.07, 34.46, 25.78, 24.91.

^{19}F NMR (377 MHz, $CDCl_3$): δ –132.26 to –133.55 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{14}H_{18}FNO]H^+$ 236.1451; found: 236.1450



2-bromo-3-methoxybenzaldehyde cyclohexylimine (12-Br)

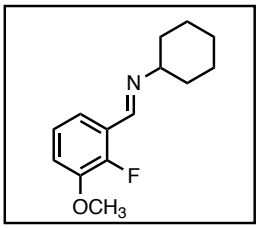
The title compound was synthesized using the general procedure described in Section 6.1 but on a 0.35 mmol scale.

Colorless solid, 79 mg, 77% yield, mp = 64.5–66.3 °C

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.29–7.26 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 3.92 (d, *J* = 2.1 Hz, 3H), 3.33–3.26 (m, 1H), 1.87–1.80 (m, 2H), 1.75 (d, *J* = 13.1 Hz, 2H), 1.71–1.66 (m, 1H), 1.63–1.55 (m, 2H), 1.43–1.34 (m, 2H), 1.31–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 158.22, 156.00, 136.69, 128.09, 121.02, 114.86, 113.21, 70.02, 56.62, 34.47, 25.78, 24.88.

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{14}H_{18}BrNO]H^+$ 296.0650; found: 296.0644



2-fluoro-3-methoxybenzaldehyde cyclohexylimine (12-^{19}F)

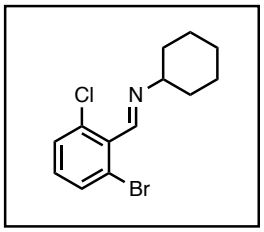
Colorless oil, 170 mg, 72% yield

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.54 (dd, *J* = 7.2, 3.8 Hz, 1H), 7.06 (dd, *J* = 8.1 Hz, 1H), 6.98 (dd, *J* = 8.1 Hz, 1H), 3.89 (s, 3H), 3.28–3.20 (m, 1H), 1.87–1.79 (m, 2H), 1.73 (d, *J* = 13.0 Hz, 2H), 1.70–1.64 (m, 1H), 1.63–1.54 (m, 2H), 1.41–1.32 (m, 2H), 1.31–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$) δ 152.40 (d, 252.1 Hz), 151.97 (d, *J* = 5.9 Hz), 147.90 (d, *J* = 10.3 Hz), 125.16 (d, *J* = 6.9 Hz), 123.98 (d, *J* = 4.5 Hz), 118.90 (d, *J* = 2.0 Hz), 114.83 (d, *J* = 2.0 Hz), 70.40, 56.50, 34.43, 25.75, 24.86.

^{19}F NMR (377 MHz, $CDCl_3$) δ –144.89 to –145.00 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{14}H_{18}FNO]H^+$ 236.1451; found: 236.1446



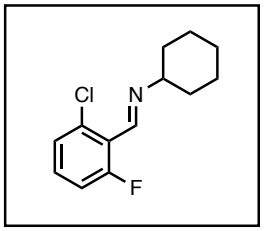
2-Bromo-6-chlorobenzaldehyde cyclohexylimine (13-Br)

Colorless oil, 250 mg, 83% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.50 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.35 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.14–7.09 (m, 1H), 3.37–3.31 (m, 1H), 1.88–1.81 (m, 4H), 1.71–1.61 (m, 3H), 1.44–1.35 (m, 2H), 1.32–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 155.60, 135.28, 134.28, 131.51, 130.28, 129.04, 123.37, 70.45, 33.99, 25.60, 24.59.

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}BrClN]H^+$ 300.0155; found: 300.0155



2-Chloro-6-fluoro cyclohexylimine (13-^{19}F)

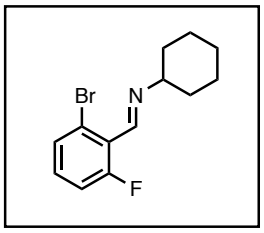
Colorless oil, 220 mg, 92% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.26–7.21 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.05–6.99 (m, 1H), 3.29–3.22 (m, 1H), 1.87–1.76 (m, 4H), 1.72–1.60 (m, 3H), 1.42–1.33 (m, 2H), 1.31–1.22 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 161.31 (d, *J* = 256.5 Hz), 152.06 (d, *J* = 2.1 Hz), 135.15 (d, *J* = 4.6 Hz), 130.72 (d, *J* = 9.8 Hz), 125.66 (d, *J* = 3.6 Hz), 123.66 (d, *J* = 13.9 Hz), 115.13 (d, *J* = 22.3 Hz), 71.33, 34.33, 25.70, 24.80.

^{19}F NMR (658 MHz, $CDCl_3$): δ –112.49 (d, *J* = 8.8 Hz, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}ClFN]H^+$ 240.0955; found: 240.0960



2-Bromo-6-fluoro cyclohexylimine (13-^{19}F')

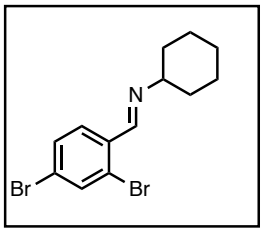
Colorless oil, 230 mg, 81% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.89–7.84 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.26 (dd, *J* = 9.9, 1.8 Hz, 1H), 3.27–3.20 (m, 1H), 1.86–1.80 (m, 2H), 1.75–1.70 (m, 2H), 1.72–1.64 (m, 1H), 1.61–1.53 (m, 2H), 1.41–1.32 (m, 2H), 1.31–1.22 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 161.82 (d, *J* = 256.2 Hz), 151.03 (d, *J* = 4.2 Hz), 129.03 (d, *J* = 3.7 Hz), 127.90 (d, *J* = 3.7 Hz), 124.78 (d, *J* = 9.8 Hz), 123.50 (d, *J* = 9.7 Hz), 119.40 (d, *J* = 24.5 Hz), 70.38, 34.39, 25.74, 24.82.

^{19}F NMR (377 MHz, $CDCl_3$): δ –118.61 to –121.12 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}BrFN]H^+$ 284.0450; found: 284.0446



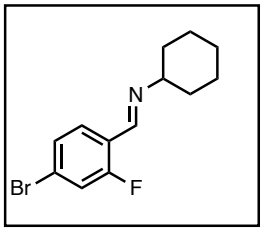
2,4-Dibromobenzaldehyde cyclohexylimine (14-Br)

White crystalline solid, 260 mg, 75% yield, mp = 43.7–45.4 °C

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.57 (d, *J* = 0.8 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.4, 1.9 Hz, 1H), 3.33–3.24 (m, 1H), 1.88–1.80 (m, 2H), 1.78–1.72 (m, 2H), 1.71–1.66 (m, 1H), 1.62–1.53 (m, 2H), 1.43–1.34 (m, 2H), 1.31–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 156.77, 135.34, 134.14, 131.00, 130.08, 125.30, 124.92, 70.02, 34.42, 25.75, 24.80.

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}Br_2N]H^+$ 345.9629; found: 345.9630



4-Bromo-2-fluorobenzaldehyde cyclohexylimine (14-^{19}F)

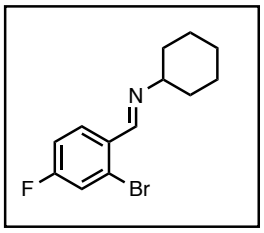
Colorless oil, 204 mg, 72% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.41 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.20–7.14 (m, 1H), 7.09–7.02 (m, 1H), 3.31–3.23 (m, 1H), 1.88–1.77 (m, 4H), 1.72–1.60 (m, 3H), 1.43–1.33 (m, 2H), 1.32–1.23 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 161.08 (d, *J* = 257.5 Hz), 153.74 (d, *J* = 2.6 Hz), 131.11 (d, *J* = 9.4 Hz), 128.80 (d, *J* = 3.7 Hz), 125.16 (d, *J* = 13.8 Hz), 124.14 (d, *J* = 3.7 Hz), 115.76 (d, *J* = 22.3 Hz), 71.09, 34.30, 25.71, 24.80.

^{19}F NMR (377 MHz, $CDCl_3$): δ –110.18 to –112.76 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}BrFN]H^+$ 284.0450; found: 284.0447



2-Bromo-4-fluorobenzaldehyde cyclohexylimine (14-^{19}F')

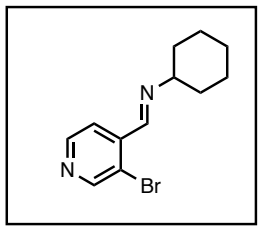
Colorless oil, 220 mg, 77% yield

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.03 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.29 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.07–7.02 (m, 1H), 3.31–3.24 (m, 1H), 1.87–1.80 (m, 2H), 1.77–1.71 (m, 2H), 1.71–1.65 (m, 1H), 1.61–1.53 (m, 2H), 1.42–1.33 (m, 2H), 1.31–1.22 (m, 1H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 163.60 (d, *J* = 254.5 Hz), 156.53, 131.56 (d, *J* = 3.5 Hz), 130.42 (d, *J* = 8.8 Hz), 125.06 (d, *J* = 9.7 Hz), 120.05 (d, *J* = 24.7 Hz), 115.24 (d, *J* = 21.2 Hz), 69.90, 34.47, 25.75, 24.83.

^{19}F NMR (377 MHz, $CDCl_3$): δ –108.29 to –109.17 (m, 1F).

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{15}BrFN]H^+$ 284.0450; found: 284.0450



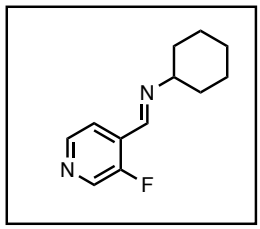
3-Bromo-4-pyridinecarboxaldehyde cyclohexylimine (15-Br)

Colorless oil, 165 mg, 78% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.57 (s, 1H), 8.50 (d, *J* = 5.0 Hz, 1H), 7.84 (d, *J* = 5.0 Hz, 1H), 3.41–3.24 (m, 1H), 1.96–1.10 (m, 10H).

^{13}C NMR (106 MHz, $CDCl_3$): δ 155.77, 152.78, 148.56, 141.81, 122.39, 122.18, 70.17, 34.19, 25.64, 24.60.

HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{12}H_{15}BrN_2]H^+$ 267.0497; found: 267.0491



3-Fluoro-4-pyridinecarboxaldehyde cyclohexylimine (15-^{19}F)

Colorless oil, 150 mg, 62% yield

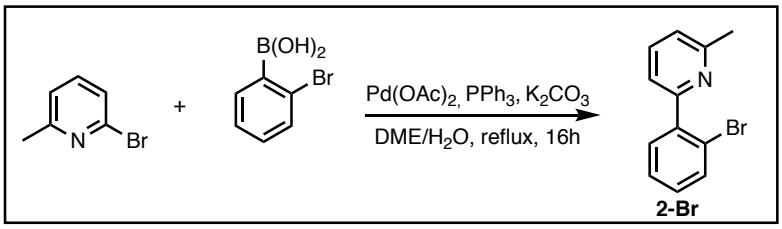
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.51 (s, 1H), 8.43 (d, *J* = 5.0 Hz, 1H), 7.84 (d, *J* = 5.0 Hz, 1H), 3.41–3.22 (m, 1H), 1.98–1.06 (m, 10H).

^{13}C NMR (106 MHz, $CDCl_3$): δ 158.28 (d, *J* = 260.9 Hz), 150.07 (d, *J* = 3.8 Hz), 146.03 (d, *J* = 5.2 Hz), 139.19 (d, *J* = 23.4 Hz), 130.78 (d, *J* = 7.8 Hz), 120.95, 70.51, 34.19, 25.66, 24.65.

^{19}F NMR (471 MHz, $CDCl_3$): δ –132.32 (d, *J* = 5.9 Hz, 1F).

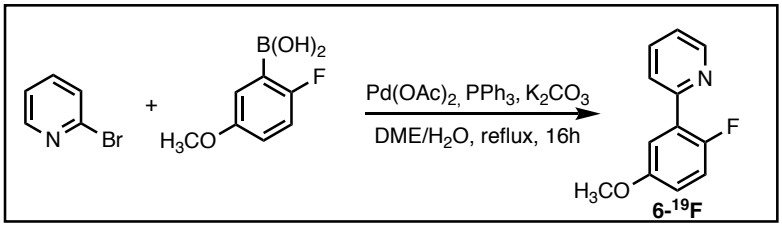
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{12}H_{15}FN_2]H^+$ 207.1298; found: 207.1297

6.2 Preparation of additional directed substrates



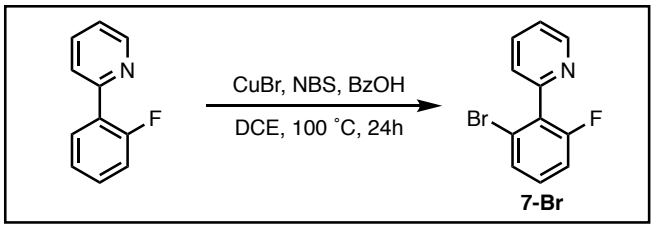
2-(2-bromophenyl)-6-methylpyridine (2-Br)
The title compound was prepared from a literature procedure.[25] To a 100 mL round bottom flask were added 2-bromophenylboronic acid (14.9 mmol, 1.0 equiv), 2-bromo-6-methylpyridine (14.9 mmol, 1.0 equiv), PPh_3 (3.0 mmol, 0.2 equiv), and dimethoxyethane (22 mL). After stirring for 3 min, K_2CO_3 (44.8 mmol, 3.0 equiv), water (23 mL), and $Pd(OAc)_2$ (1.24 mmol, 0.05 equiv) were added, and the mixture was heated at reflux for 16 h. The reaction mixture was then cooled to room temperature and extracted with EtOAc (3 x 30 mL). The organics were combined, concentrated *in vacuo*, and purified by column chromatography (0–10% EtOAc/hexanes) to give the title compound as a pale yellow oil (1.56 g, 42%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.60 (m, 2H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.43–7.34 (m, 2H), 7.27–7.20 (m, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 2.63 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$): δ 158.24, 157.89, 141.70, 136.13, 133.32, 131.50, 129.64, 127.65, 122.06, 122.01, 121.76, 24.77.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{12}H_{10}BrN]H^+$ 248.0075; found: 248.0072



2-(2-fluoro-5-methoxyphenyl)pyridine (6-^{19}F)
The title compound was prepared using a modified version of the literature procedure described for **2-Br**.[25] To a 100 mL round bottom flask were added (2-fluoro-5-methoxyphenyl)boronic acid (prepared according to literature procedure;[16] 5.9 mmol, 1.0 equiv), 2-bromo-6-methylpyridine (5.9 mmol, 1.0 equiv), PPh_3 (1.2 mmol, 0.2 equiv), and dimethoxyethane (10 mL). After stirring for 3 min, K_2CO_3 (17.6 mmol, 3.0 equiv), water (10 mL), and $Pd(OAc)_2$ (0.29 mmol, 0.05 equiv) were added, and the mixture was heated at reflux for 16 h. The reaction mixture was then cooled to room temperature and extracted with EtOAc (3 x 30 mL). The organics were combined, concentrated *in vacuo*, and purified by column chromatography (0–25% EtOAc/hexanes). The resulting mixture was purified via preparative silica gel TLC using a 500 μM plate (20% Et_2O in DCM) to give the title compound as a pale colorless oil (480 mg, 40%).

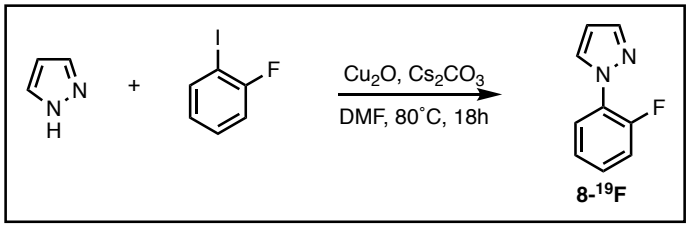
^{1}H NMR (700 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.7 Hz, 1H), 7.82–7.78 (m, 1H), 7.77–7.73 (m, 1H), 7.54–7.50 (m, 1H), 7.28–7.24 (m, 1H), 7.07 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.93–6.88 (m, 1H), 3.86 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 156.10 (d, *J* = 1.9 Hz), 155.10 (d, *J* = 242.4 Hz), 153.45 (d, *J* = 2.7 Hz), 149.84, 136.50, 127.84 (d, *J* = 13.1 Hz), 124.69 (d, *J* = 9.9 Hz), 122.62, 117.10 (d, *J* = 25.2 Hz), 116.77 (d, *J* = 8.4 Hz), 114.47 (d, *J* = 3.0 Hz), 56.03.
^{19}F NMR (377 MHz, $CDCl_3$) δ –144.89 to –145.00 (m, 1F).
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{12}H_{10}FNO]H^+$ 204.0825; found: 204.0821



2-(2-bromo-6-fluorophenyl)pyridine (7-Br)

The title compound was prepared from an adapted literature procedure.[26] To a 12 mL screw cap vial under N_2 were added CuBr (0.5 mmol, 1.0 equiv), *N*-bromosuccinimide (1.0 mmol, 2.0 equiv), benzoic acid (0.25 mmol, 0.5 equiv), 2-(2-fluorophenyl)pyridine (0.5 mmol, 1.0 equiv), and degassed dichloroethane (3 mL). The sealed tube was stirred rapidly at 100 °C for 24 h. After cooling to room temperature, a 10 wt % solution of Na_2S in EtOAc (5 mL) was added, and the mixture was stirred for 10 min. The crude reaction mixture was washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography gave the title compound as a colorless oil (60 mg, 48%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.76 (d, *J* = 4.9 Hz, 1H), 7.80 (ddd, *J* = 7.7, 1.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.34 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 7.28–7.23 (m, 1H), 7.14 (dd, *J* = 8.7 Hz, 1H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 160.51 (d, *J* = 250.7 Hz), 153.71, 149.77, 136.40, 130.65 (d, *J* = 9.2 Hz), 130.20 (d, *J* = 18.7 Hz), 128.75 (d, *J* = 3.6 Hz), 125.62 (d, *J* = 1.2 Hz), 123.76 (d, *J* = 3.4 Hz), 123.19, 115.13 (d, *J* = 22.7 Hz).
^{19}F NMR (377 MHz, $CDCl_3$): δ –111.32 (dd, *J* = 9.0, 5.8 Hz, 1F).
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{11}H_7BrFN]H^+$ 251.9824; found: 251.9823

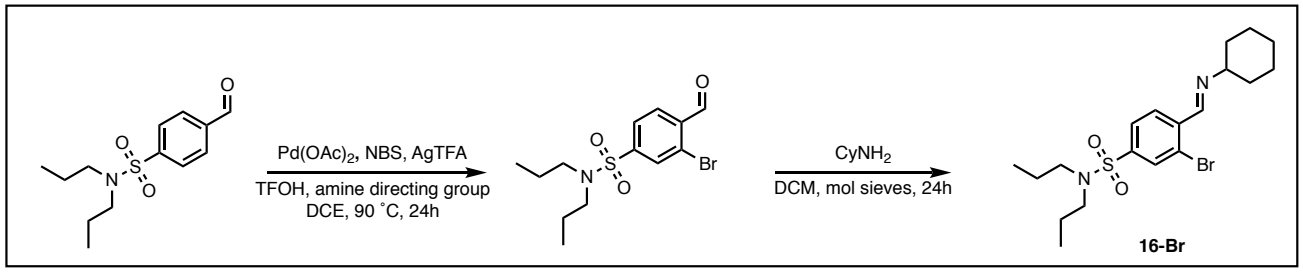


1-(2-fluorophenyl)-1*H*-pyrazole (8-^{19}F)

The title compound was prepared from a modified literature procedure.[27] To an 8 mL vial under N_2 were added pyrazole (1.44 mmol, 1 equiv), 2-fluoroiodobenzene (2.88 mmol, 2 equiv), Cu_2O (0.72 mmol, 0.5 equiv), Cs_2CO_3 (2.88 mmol, 2 equiv), and dry DMF (1 mL). The vial was capped and stirred at 80 °C for 18 h. The crude reaction mixture was filtered through a plug of silica. Then, 5 mL of water was added, and the mixture was extracted with Et_2O (5 x 10 mL). The organics were combined, dried over $MgSO_4$, concentrated *in vacuo*, and purified by silica gel column chromatography (8% EtOAc in hexane) to give the title compound as a colorless oil (40 mg, 17%).

^{1}H NMR (700 MHz, CD_2Cl_2): δ 8.09–7.98 (m, 1H), 7.94–7.86 (m, 1H), 7.72 (s, 1H), 7.36–7.21 (m, 3H), 6.56–6.43 (m, 1H).
^{13}C NMR (176 MHz, CD_2Cl_2): δ 154.10 (d, *J* = 248.3 Hz), 141.24, 131.26 (d, *J* = 10.3 Hz), 129.00 (d, *J* = 8.7 Hz), 128.24 (d, *J* = 7.7 Hz), 125.46 (d, *J* = 3.8 Hz), 124.88, 117.30 (d, *J* = 20.8 Hz), 107.88.
^{19}F NMR (377 MHz, CD_2Cl_2): δ –122.79 to –128.29 (m, 1F).
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_9H_7FN_2]H^+$ 163.0672; found: 163.0669

6.3 Preparation of probenecid derivatives



2-Bromo-4-dipropylsulfamoylbenzaldehyde

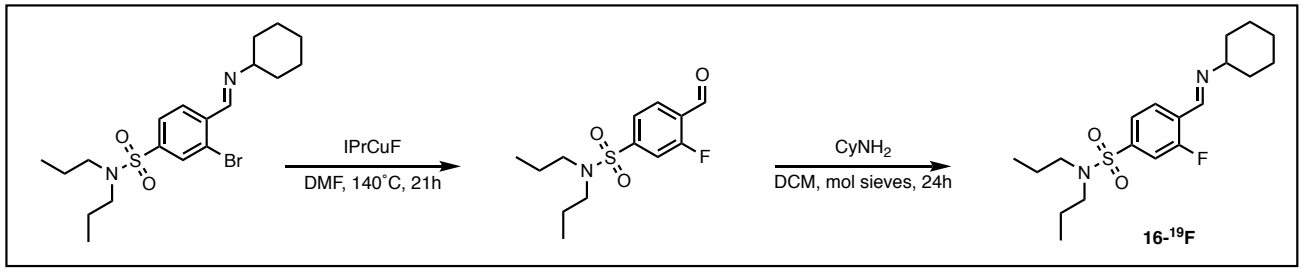
The title compound was prepared from a modified literature procedure.[28] To a 20 mL vial in air were added *N*-bromosuccinimide (0.59 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.197 mmol, 0.5 equiv), *p*-nitroanthranilic acid (0.197 mmol, 0.5 equiv), and AgTFA (0.039 mmol, 0.1 equiv). Subsequently, TfOH (0.197 mmol, 0.5 equiv) in 1 mL of DCE was added, followed by 4-dipropylsulfamoylbenzaldehyde (0.393 mmol, 1 equiv) in 2 mL of DCE. The reaction mixture was stirred rapidly at 90 °C for 24 h. The solvent was removed *in vacuo*, and the crude product was purified by silica gel column chromatography (0–60% EtOAc/hexane) to give the title compound as a tan crystalline solid (23 mg, 17%, mp = 66.9–67.4 °C).

^{1}H NMR (700 MHz, $CDCl_3$): δ 10.39 (s, 1H), 8.09 (d, *J* = 1.7 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.16–3.10 (m, 4H), 1.62–1.52 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 6H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 190.69, 146.67, 135.80, 132.35, 130.63, 127.27, 126.23, 50.13, 22.12, 11.29.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{13}H_{18}BrNO_3S]$ H^+ 348.0269; found: 348.0269

2-Bromo-4-dipropylsulfamoylbenzaldehyde cyclohexylimine (16-Br)

The title compound was prepared from 2-bromo-4-dipropylsulfamoylbenzaldehyde using the imine condensation procedure described in Section 6.1 to give imine **16-Br** as a white solid (25 mg, 88%, mp = 65.6–66.2 °C).

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 1.8 Hz, 1H), 7.71 (d, 1H), 3.38–3.29 (m, 1H), 3.12–3.05 (m, 4H), 1.84 (dt, *J* = 13.3, 3.7 Hz, 2H), 1.75 (d, *J* = 3.9 Hz, 2H), 1.69 (dd, *J* = 12.8, 3.8 Hz, 1H), 1.64–1.52 (m, 6H), 1.38 (qt, *J* = 12.7, 3.5 Hz, 2H), 1.33–1.23 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 6H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 156.56, 142.88, 138.44, 131.50, 129.59, 125.93, 124.94, 70.13, 50.12, 34.35, 25.69, 24.71, 22.10, 11.30.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{19}H_{29}BrN_2O_2S]H^+$ 429.1211; found: 429.1215



4-dipropylsulfamoyl-2-fluorobenzaldehyde

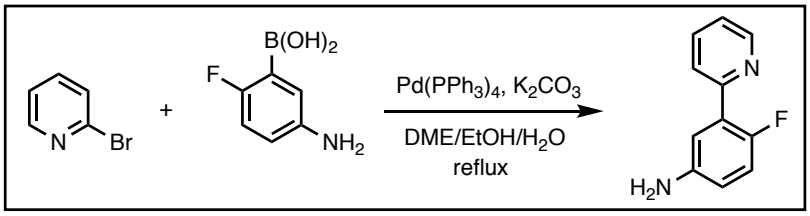
The title compound was prepared using a modified version of the (NHC)Cu-mediated fluorination procedure described in Section 3.1. In a N_2-containing glovebox, the imine (21 mg, 0.048 mol), IPrCuF (23 mg, 0.048 mol), and DMF (5.2 mL) were added to a 20 mL screw-cap vial. The reaction mixture was removed from the glovebox and allowed to stir at 140 °C for 21 h. Subsequently, solvent was removed *in vacuo* and the resulting residue was purified via preparative silica gel TLC using a 500 μM plate (20% EtOAc/hexane). The title compound was isolated as a colorless oil (3.3 mg, 22%).

^{1}H NMR (700 MHz, $CDCl_3$): δ 10.40 (d, *J* = 1.1 Hz, 1H), 8.03–7.98 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 9.4 Hz, 1H), 3.18–3.07 (m, 4H), 1.62–1.50 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 6H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 186.07 (d, *J* = 6.3 Hz), 164.23 (d, *J* = 263.2 Hz), 147.78 (d, *J* = 7.1 Hz), 129.82 (d, *J* = 1.9 Hz), 126.42 (d, *J* = 8.5 Hz), 123.07 (d, *J* = 4.0 Hz), 115.78 (d, *J* = 23.5 Hz), 50.12, 22.09, 11.27.
^{19}F NMR (377 MHz, $CDCl_3$): δ –118.88 (dd, *J* = 9.6, 6.6 Hz, 1F).
HRMS (ESI$^+$) [M+H]$^+$ calc. for $[C_{13}H_{18}FNO_3S]H^+$ 288.1070; found: 288.1070

4-dipropylsulfamoyl-2-fluorobenzaldehyde cyclohexylimine (16-^{19}F)
Imine **16-^{19}F** was prepared from 4-dipropylsulfamoyl-2-fluorobenzaldehyde using the imine condensation procedure described in Section 6.1 to give a colorless oil (3.3 mg, 89%).

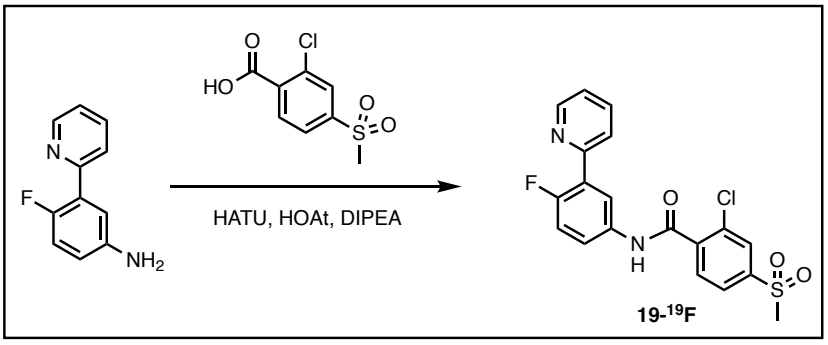
^{1}H NMR (700 MHz, CD_2Cl_2): δ 8.60 (s, 1H), 8.11 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 9.9 Hz, 1H), 3.29 (tt, *J* = 10.3, 4.1 Hz, 1H), 3.13–3.04 (m, 4H), 1.83 (dt, *J* = 13.4, 3.8 Hz, 2H), 1.77–1.65 (m, 3H), 1.61–1.50 (m, 6H), 1.39 (qt, *J* = 12.6, 3.5 Hz, 2H), 1.33–1.25 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 6H).
^{13}C NMR (176 MHz, CD_2Cl_2): δ 162.06 (d, *J* = 255.7 Hz), 150.85 (d, *J* = 4.1 Hz), 143.81 (d, *J* = 6.9 Hz), 129.14 (d, *J* = 3.1 Hz), 128.36 (d, *J* = 9.8 Hz), 123.25 (d, *J* = 3.6 Hz), 115.37 (d, *J* = 24.4 Hz), 70.79, 50.55, 34.80, 26.20, 25.12, 22.48, 11.47.
^{19}F NMR (377 MHz, CD_2Cl_2): δ –120.24 (dd, *J* = 9.8, 6.9 Hz, 1F).
HRMS (ESI$^+$) [M+H]$^+$ calc. for $[C_{19}H_{29}FN_2O_2S]H^+$ 369.2012; found: 369.2021

6.4 Preparation of vismodegib derivatives



4-fluoro-3-(pyridin-2-yl)aniline
The title compound was prepared using a modified literature procedure.[29] 5-amino-2-fluorophenylboronic acid (1.93 mmol, 1.0 equiv), K_2CO_3 (3.86 mmol, 2.0 equiv), and $Pd(PPh_3)_4$ (0.097 mmol, 5 mol%) were added to a 100 mL round bottom flask coupled to a condenser. The flask was placed under a N_2 atmosphere and a degassed solution of 2-bromopyridine (2.05 mmol, 1.06 equiv) in DME (8 mL), H_2O (5 mL), and EtOH (2.5 mL) was added. The reaction mixture was heated to reflux for 24 h, cooled to room temperature, and filtered. EtOAc (25 mL) was added, and the crude mixture was extracted with EtOAc (3 x 25 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated *in vacuo*. The title compound was purified by silica gel column chromatography (0–50% EtOAc/hexane) and isolated as a tan solid (220 mg, 61%, mp = 65.2–66.9 °C).

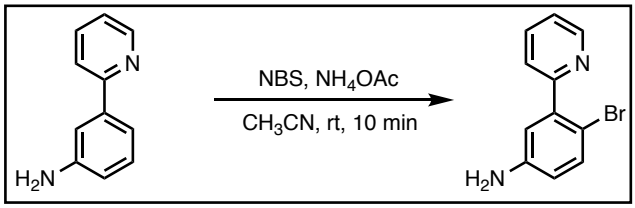
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.9 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.75–7.71 (m, 1H), 7.31–7.27 (m, 1H), 7.25–7.21 (m, 1H), 6.96 (ddd, *J* = 10.9, 8.7, 1.0 Hz, 1H), 6.70–6.64 (m, 1H), 3.64 (s, 2H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 154.26 (d, *J* = 230.1 Hz), 153.57 (d, *J* = 7.9 Hz), 149.72, 142.95 (d, *J* = 2.3 Hz), 136.45, 127.66 (d, *J* = 12.8 Hz), 124.70 (d, *J* = 9.8 Hz), 122.47, 116.91 (d, *J* = 7.9 Hz), 116.87 (d, *J* = 24.6 Hz), 116.59 (d, *J* = 2.5 Hz).
^{19}F NMR (377 MHz, $CDCl_3$): δ –130.72 (dd, *J* = 6.6, 4.5 Hz, 1F).
HRMS (ESI$^+$) [M+H]$^+$ calc. for $[C_{11}H_9FN_2]H^+$ 189.0828; found: 189.0831



2-chloro-*N*-(4-fluoro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (19-^{19}F)

The title compound was prepared using a modified literature procedure.[30] To a 20 mL screw-cap vial in air were added 4-fluoro-3-(pyridin-2-yl)aniline (0.4 mmol, 1.0 equiv), the carboxylic acid (0.6 mmol, 1.5 equiv), HATU (0.8 mmol, 2.0 equiv), HOAt (0.6 mmol, 1.5 equiv), diisopropylethylamine (2.4 mmol, 0.6 equiv), and anhydrous DCM (12 mL). The reaction mixture was stirred for 16 h at room temperature. Water (20 mL) was added, and the organics were extracted with DCM (3 x 20 mL). The combined extracts were washed with brine (20 mL) and concentrated *in vacuo* to give a red oil. Purification by silica gel column chromatography (0–65% EtOAc/hexanes) gave a tan solid, which was taken up in minimal DCM and crashed out with excess hexanes, affording the title compound as a colorless crystalline solid (110 mg, 68%, mp = 176.2–177.8 °C).

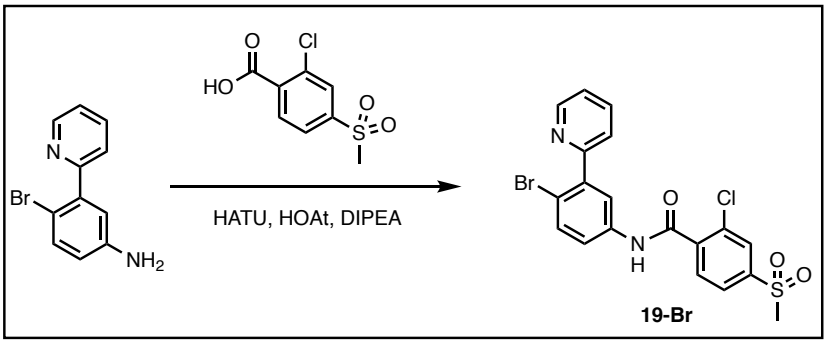
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.92 (s, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.14–8.08 (m, 1H), 8.00 (dd, *J* = 6.6, 2.8 Hz, 1H), 7.87 (d, *J* = 1.7 Hz, 1H), 7.79–7.72 (m, 3H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.25–7.19 (m, 2H), 3.05 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 163.49, 157.25 (d, *J* = 248.8 Hz), 152.60 (d, *J* = 2.3 Hz), 149.67, 142.99, 140.52, 137.02, 134.38 (d, *J* = 2.8 Hz), 132.21, 130.47, 129.13, 127.63 (d, *J* = 13.4 Hz), 126.02, 124.93 (d, *J* = 9.1 Hz), 123.03, 122.74 (d, *J* = 8.3 Hz), 122.35 (d, *J* = 2.8 Hz), 117.21 (d, *J* = 24.2 Hz), 44.51.
^{19}F NMR (377 MHz, $CDCl_3$): δ –121.21 (s, 1F).
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{19}H_{14}FClN_2O_3S]$ H^+ 405.0476; found: 405.0475



4-bromo-3-(pyridin-2-yl)aniline

The title compound was prepared through a modified literature procedure.[31] To a solution of 2-(3-aminophenyl)pyridine (0.441 mmol, 1.0 equiv) and NH_4OAc (0.0441 mmol, 0.1 equiv) in acetonitrile (2 mL) open to air was added *N*-bromosuccinimide (0.463 mmol, 1.05 equiv). After stirring for 10 min at room temperature, the solvent was removed *in vacuo*. The resulting oil was dissolved in 5 mL of water and extracted with EtOAc (3 x 5 mL). The organics were combined, dried over Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (0–50% EtOAc/hexane) to give a purple solid. This solid was then dissolved in minimal Et_2O and recrystallized with excess hexane. The resulting solid was dissolved in DCM and washed with water (3 x 5 mL) to give the title compound as a grey solid (15 mg, 14%).

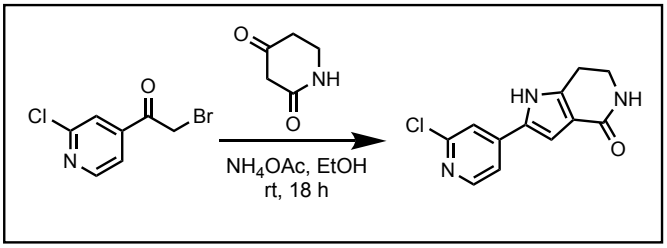
^{1}H NMR (401 MHz, CD_2Cl_2): δ 8.65 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.75 (ddd, *J* = 7.7, 1.8 Hz, 1H), 7.57 (ddd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.28 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 6.84 (d, *J* = 2.9 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.85 (s, 2H).
^{13}C NMR (176 MHz, CD_2Cl_2): δ 159.05, 149.80, 146.87, 142.38, 136.21, 134.19, 125.15, 122.88, 118.23, 116.90, 109.42.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{11}H_9BrN_2]H^+$ 249.0027; found: 249.0027



***N*-(4-bromo-3-(pyridin-2-yl)phenyl)-2-chloro-4-(methylsulfonyl)benzamide (19-Br)**
Compound **19-Br** was prepared from 4-bromo-3-(pyridin-2-yl)aniline using the same procedure described for compound **19-^{19}F** to give a colorless crystalline solid (15 mg, 58%, mp = 172–174 °C).

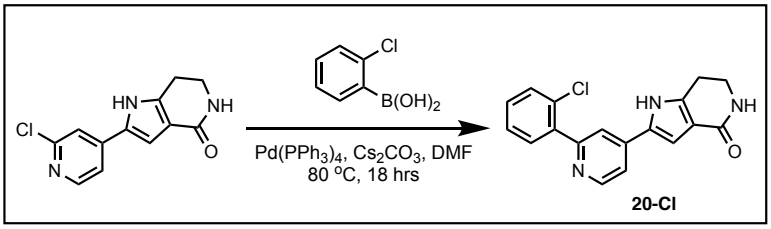
^{1}H NMR (700 MHz, CD_3CN): δ 9.05 (s, 1H), 8.71–8.63 (m, 1H), 8.04 (d, *J* = 1.7 Hz, 1H), 7.94 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.88–7.82 (m, 2H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.67–7.61 (m, 2H), 7.42–7.36 (m, 1H), 3.12 (s, 3H).
^{13}C NMR (176 MHz, CD_3CN): δ 164.99, 158.68, 150.36, 144.33, 142.87, 141.68, 138.78, 137.15, 134.66, 132.72, 130.86, 129.65, 127.04, 125.57, 123.87, 123.49, 122.13, 116.91, 44.27.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{19}H_{14}BrClN_2O_3S]H^+$ 464.9675; found: 464.9677

6.5 Preparation of MK-2 inhibitor derivatives



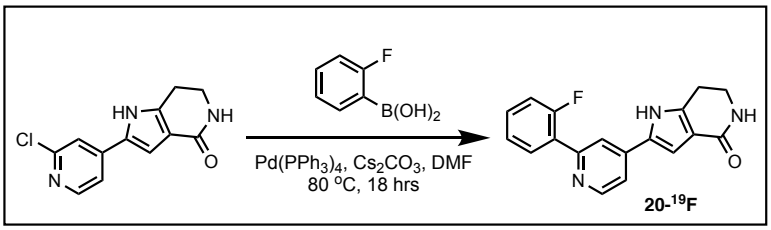
2-(2-chloropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one
The title compound was prepared according to a previously reported procedure.[32] In a flame-dried flask, 2-bromo-1-(2-chloropyridin-4-yl)ethan-1-one (600 mg, 2.56 mmol) and 2,4-piperidinedione (0.3767 g, 3.33 mmol) were dissolved in dry EtOH (25.6 mL). NH_4OAc (789 mg, 10.24 mmol) was then added, and the solution was stirred for 18 h at room temperature. Upon completion, the reaction was diluted with water (25 mL), filtered, and the resulting solid was further washed with water (5 mL) and Et_2O (5 mL) to give the title compound as a grey powder (398 mg, 63%).

^{1}H-NMR (401 MHz, DMSO-d_6): δ 12.04 (broad s, 1H), 8.29 (d, *J* = 5.4 Hz, 1H), 7.75 (s, 1H), 7.64 (dd, *J* = 5.4, 1.5 Hz, 1H), 7.14 (s, 1H), 7.12 (broad s, 1H), 3.41 (dt, *J* = 6.8, 2.4 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H).
^{13}C-NMR (100 MHz, DMSO-d_6): δ 165.00, 151.66, 150.51, 142.79, 140.23, 127.62, 117.35, 116.38, 108.46, 40.46, 22.25.
HRMS (ESI$^+$) $[M+H]^+$ calc. for $[C_{12}H_{10}ClN_3O]H^+$: 248.0585; found: 248.0593.



2-(2-(2-chlorophenyl)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (20-Cl).
The title compound was prepared according to a previously reported procedure.[32] 2-(2-chloropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (200 mg g, 0.807 mmol) and 2-chlorophenylboronic acid (189 mg, 1.21 mmol) were suspended in DMF (4 mL). To this suspension, an aqueous solution of Cs_2CO_3 (1.2 mL, 2M) was added, and the vessel was purged with argon. Tetrakis(triphenylphosphine)palladium (46.7 mg, 0.0404 mmol) was added, and the reaction was stirred at 80 °C for 18 h. The reaction was then cooled to room temperature, quenched with brine (50 mL), extracted with EtOAc (3 x 50 mL) and the organic layers were combined and dried over Na_2SO_4. The mixture was then purified by flash chromatography (10 g silica, 1:4 MeOH: DCM) to give **20-Cl** as a yellow oil (168 mg, 64%).

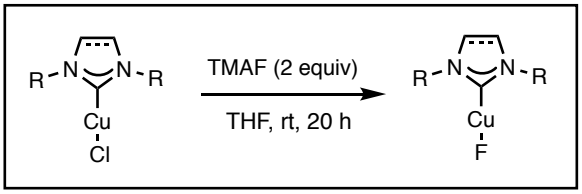
^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.95 (broad s, 1H), 8.55 (d, *J* = 5.3 Hz, 1H), 7.83 (d, *J* = 1.1 Hz, 1H), 7.63 (dd, *J* = 5.4, 1.8 Hz, 1H), 7.57 (m, 2H), 7.46 (m, 2H), 7.07 (broad s, 1H), 7.04 (d, *J* = 2.3 Hz, 1H), 3.39 (td, *J* = 6.9, 2.4 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 2H).
^{13}C-NMR (100 MHz, DMSO-d_6): δ 165.19, 162.73, 157.36, 150.14, 139.62, 131.96, 131.68, 130.44, 130.28, 128.75, 127.72, 118.42, 116.98, 116.15, 107.15, 36.22, 22.27.
HRMS (ESI+) $[M+H]^+$ calc. for $[C_{18}H_{14}ClN_3O]H^+$: 324.0898; found: 324.0910.



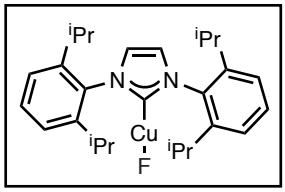
2-(2-(2-fluorophenyl)pyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (20-^{19}F).
The title compound was prepared according to a previously reported procedure.[32] 2-(2-chloropyridin-4-yl)-1,5,6,7-tetrahydro-4H-pyrrolo[3,2-c]pyridin-4-one (200 mg, 0.807 mmol) (100 mg, 0.404 mmol) and 2-chlorophenylboronic acid (85 mg, 0.61 mmol) were suspended in dimethylformamide (2 mL). To this suspension, an aqueous solution of Cs_2CO_3 (0.6 mL, 2M) was added, and the vessel was purged with argon. Tetrakis(triphenylphosphine)palladium (23 mg, 0.02 mmol) was added, and the reaction was stirred at 80 °C for 18 h. The reaction was then cooled to room temperature, quenched with brine (50 mL), extracted with ethyl acetate (3 x 50 mL), and the organic layers were combined and dried over Na_2SO_4. The mixture was then purified by flash chromatography (10 g silica, 1:4 MeOH: DCM) to give **20-^{19}F** as a yellow powder (73 mg, 59%).

^{1}H-NMR (401 MHz, DMSO-d_6): δ 12.06 (broad s, 1H), 8.58 (d, *J* = 5.3 Hz, 1H), 7.96 (s, 1H), 7.86 (td, *J* = 7.8, 1.9 Hz, 1H), 7.62 (dd, *J* = 5.3, 1.7 Hz, 1H), 7.48 (m, 1H), 7.33 (m, 2H), 7.09 (broad s, 1H), 7.04 (d, *J* = 1.9 Hz, 1H), 3.40 (td, *J* = 6.9, 2.4 Hz, 2H), 2.84 (t, *J* = 6.9 Hz, 2H).
^{13}C-NMR (100 MHz, DMSO-d_6): δ 165.29, 161.35, 158.88, 153.81, 150.51, 139.96, 139.71, 131.44, 128.79, 127.96, 127.84, 125.13, 118.04, 117.09, 116.75, 116.53, 116.08, 109.99, 107.05, 49.03, 22.26.
^{19}F-NMR (377 MHz, DMSO-d_6): δ –77.80 (m, 1F).
HRMS (ESI+) $[M+H]^+$ calc. for $[C_{18}H_{14}FN_3O]H^+$: 308.1194; found: 308.1204.

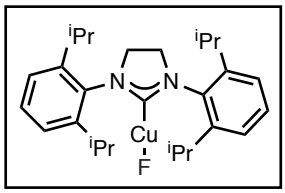
6.6 Preparation of (NHC)CuF complexes



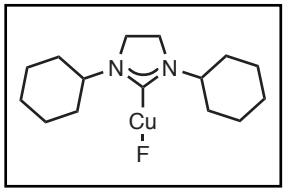
General procedure for the preparation of (NHC)CuF complexes with TMAF:
In a N_2 glovebox, the corresponding (NHC)CuCl (0.2 mmol, 1.0 equiv) and anhydrous TMAF (0.4 mmol, 2.0 equiv) were added to a 20 mL vial. Anhydrous THF (4 mL) was then added, and the resulting suspension was stirred vigorously for 20 h at room temperature. The suspension was then transferred to a 15 mL centrifuge tube, taken out of the glovebox, and centrifuged for 5 min. The tube was returned to the glovebox, and the colorless supernatant was decanted and concentrated to <0.5 mL. Excess pentane was added, leading to precipitation of (NHC)CuF as a white or tan powder (89–94%). Spectral data for complexes IPrCuF,[22] sIPrCuF,[5] and sICyCuF[4] match those in the literature.



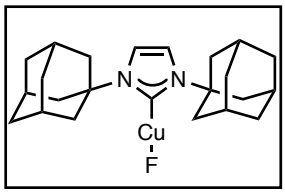
IPrCuF
IPrCuF was synthesized according to the general procedure.
White powder, 84 mg, 89% yield
Spectral data matched those previously reported for this complex.[22]



sIPrCuF
sIPrCuF was synthesized according to the general procedure with a slight modification: 8 mL of THF was used to ensure that all of the sIPrCuF product remained in solution for the filtration step (using less THF led to lower yields).
White powder, 86 mg, 91% yield
Spectral data matched those previously reported for this complex.[5]

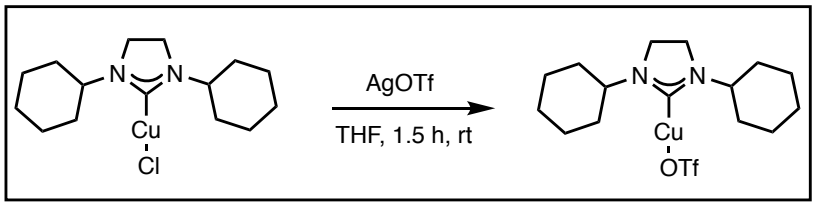


sICyCuF
sICyCuF was synthesized according to a modified version of the general procedure. After completion of the reaction, the slurry was filtered through a pipette filter in the glovebox instead of centrifuging. sICyCuF appears to be more air and/or moisture sensitive than the other NHCCuF complexes, and some decomposition occurred if the solution was transferred into a centrifuge tube and removed from the box.
Off-white powder, 57 mg, 90% yield
Spectral data matched those previously reported for this complex.[4]



IAdCuF

IAdCuF was synthesized according to the general procedure.
White powder, 78 mg, 93% yield
^{1}H NMR (700 MHz, CD_2Cl_2): δ 7.08 (s, 2H), 2.42 (s, 12H), 2.26 (s, 6H), 1.78 (s, 12H).
^{13}C NMR (176 MHz, CD_2Cl_2): δ 171.17 (weak), 116.11, 58.36, 45.37, 36.41, 30.59.
^{19}F NMR (377 MHz, CD_2Cl_2): δ –248.39 (s, 1F).
HRMS (ESI$^+$) $[M]^+$ calc. for $[C_{25}H_{35}CuN_3]^+$ ([IAdCu]$^+$ complexed with acetonitrile, the HRMS elution solvent) 440.2127; found: 440.2130.
Diffraction quality crystals were grown by layering a DCM solution of IAdCuF with pentane and allowing for slow diffusion at –30 °C over several days.



sICyCuOTf

The title complex was synthesized from a modified literature procedure.[33] In a N_2-containing glovebox, sICyCuCl (0.2 mmol, 1.0 equiv), AgOTf (0.2 mmol, 1.0 equiv), and anhydrous THF (2 mL) were added to a 20 mL vial. Immediate precipitation of AgCl was observed. The suspension was stirred for 1.5 h at room temperature, filtered, and concentrated *in vacuo* until <0.5 mL of the solution remained. Excess pentane was then added to give sICyCuOTf as a colorless precipitate. Diffraction quality crystals were grown by layering a DCM solution of sICyCuOTf with pentane and allowing for slow diffusion at –30 °C over several days.

^{1}H NMR (700 MHz, CD_2Cl_2): δ 3.76–3.67 (m, 2H), 3.52 (d, *J* = 2.6 Hz, 4H), 1.88–1.78 (m, 8H), 1.71–1.63 (m, 2H), 1.55–1.44 (m, 4H), 1.43–1.32 (m, 4H), 1.18–1.06 (m, 2H).
^{13}C NMR (176 MHz, CD_2Cl_2): δ 195.59 (weak), 60.61, 45.14, 32.69, 25.93, 25.75.
^{19}F NMR (377 MHz, CD_2Cl_2): δ –248.39 (s, 3F).
HRMS (ESI$^+$) $[M]^+$ calc. for $[C_{17}H_{29}CuN_3]^+$ ([sICyCu]$^+$ complexed with acetonitrile, the HRMS elution solvent) 338.1657; found: 338.1659.

7. X-Ray Crystallography

IAdCuF

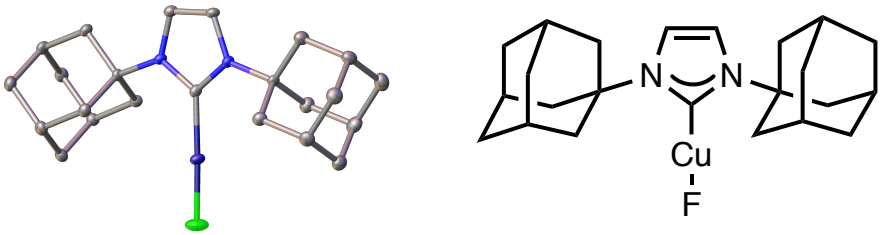


Figure S3. Crystal structure of IAdCuF with thermal ellipsoids at 40% probability. Hydrogen atoms and co-crystallized dichloromethane molecule have been omitted for clarity.

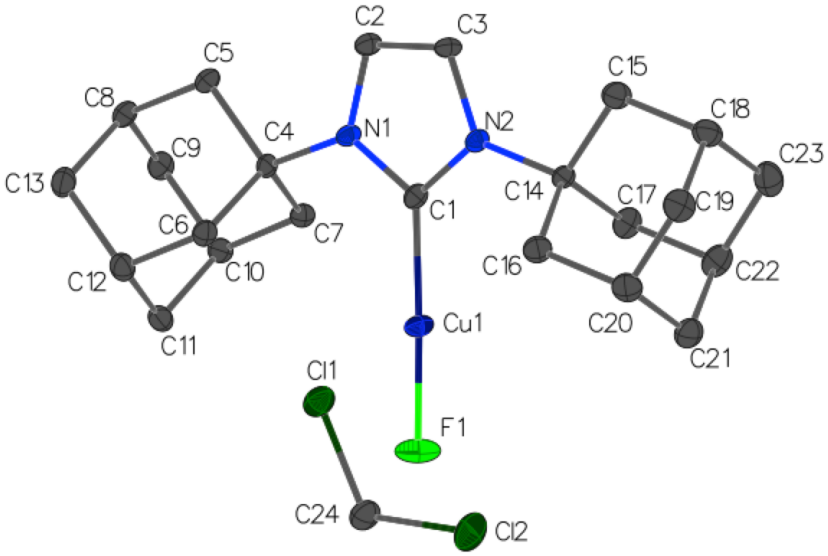


Figure S4. Numbering scheme for IAdCuF, including co-crystallized molecule of DCM solvent. Hydrogen atoms have been removed for clarity.

Structure Determination of IAdCuF

Colorless needles of IAdCuF were grown from a layered DCM/pentane solution of the compound at –30 °C. A crystal of dimensions 0.08 x 0.07 x 0.04 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 85(2) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 s for the low angle images, 6 s for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 17545 reflections to a maximum 2θ value of 138.710° of which 4140 were independent and 3872 were greater than 2σ(I). The final cell constants (Table S13) were based on the xyz centroids 10843 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2014/7) software package, using the space group P-1 with Z = 2 for the

formula $C_{24}H_{34}Cl_2CuFN_2$ (2 molecules in asymmetric unit). All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. There is one molecule of dichloromethane solvent in the asymmetric unit. Full matrix least-squares refinement based on F2 converged at R1 = 0.0396 and wR2 = 0.1011 [based on I > 2sigma(I)], R1 = 0.0421 and wR2 = 0.1057 for all data. Two reflections with Error/esd > 10 were omitted during refinement. These reflections may have been due to the beam stop or secondary extinction. Additional details are presented in Table S14 and are given as Supporting Information in a CIF file. The CIF file has been deposited in the Cambridge Crystallographic Data Centre (CCDC) under deposition number 1985172.

Table S14. Crystal data and structure refinement for IAdCuF.

Identification code	ls2ad	
Empirical formula	C24 H34 Cl2 Cu F N2	
Formula weight	503.97	
Temperature	85(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4835(6) Å	a= 87.075(5)°
	b = 11.9653(8) Å	b= 80.401(5)°
	c = 12.0408(7) Å	g = 71.730(6)°
Volume	1144.37(13) $Å^3$	
Z	2	
Density (calculated)	1.463 Mg/m^3	
Absorption coefficient	3.666 mm^{-1}	
F(000)	528	
Crystal size	0.080 x 0.070 x 0.040 mm^3	
Crystal color and habit	colorless needle	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	3.723 to 69.355°	
Index ranges	–10<=h<=9, –14<=k<=14, –14<=l<=14	
Reflections collected	17545	
Independent reflections	4140 [R(int) = 0.0515]	
Observed reflections (I > 2sigma(I))	3872	
Completeness to theta = 67.684°	97.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.75217	
Solution method	SHELXT (Sheldrick, 2014)	
Refinement method	SHELXL-2014/6 (Sheldrick, 2014)	
Data / restraints / parameters	4140 / 0 / 271	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.1011	
R indices (all data)	R1 = 0.0421, wR2 = 0.1057	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.891 and –0.592 e.$Å^{-3}$	

sICyCuOTf

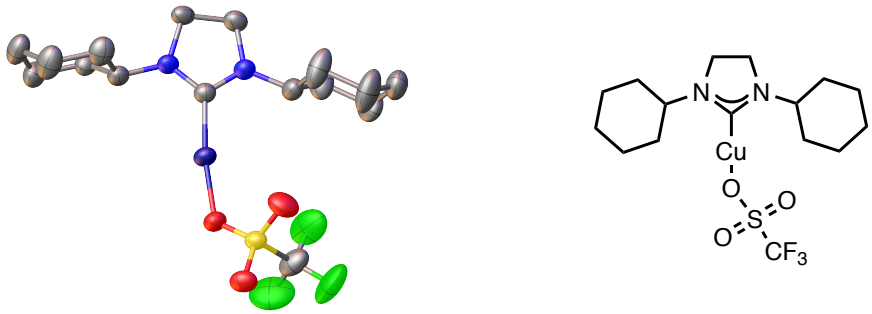


Figure S5. Crystal structure of sICyCuOTf with thermal ellipsoids at 40% probability. Hydrogen atoms have been omitted for clarity and only one of the two independent molecules of sIPrCuOTf in the asymmetric unit is shown.

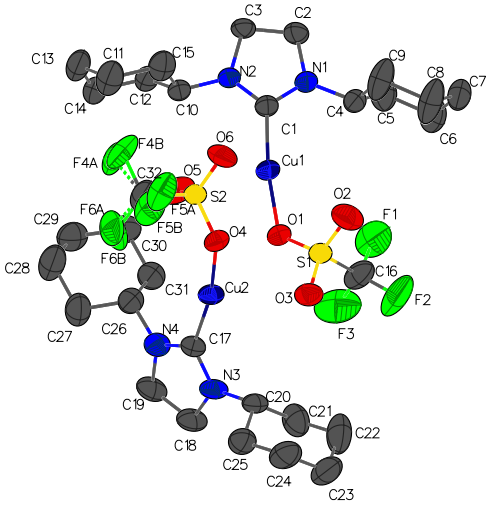


Figure S6. Numbering scheme for sICyCuOTf (2 molecules in asymmetric unit). Hydrogen atoms have been removed for clarity.

Structure Determination of sICyCuOTf

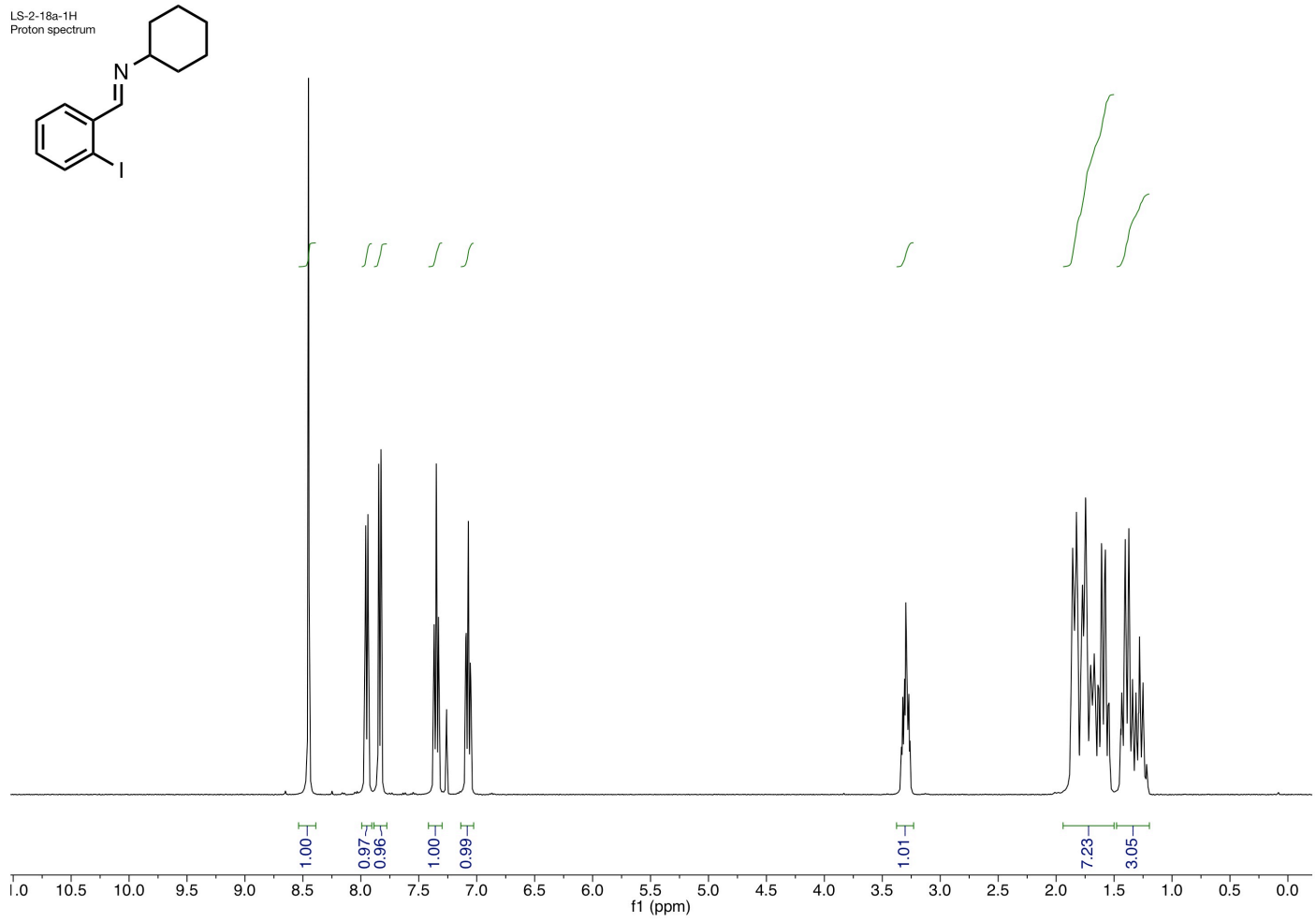
Colorless plates of sICyCuOTf were grown from a layered DCM/pentane solution of the compound at –30 °C. A crystal of dimensions 0.24 x 0.24 x 0.05 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target micro-focus rotating anode (λ = 1.54187 A) operated at 1.2 kW power (40 kV, 30 mA). The X-ray intensities were measured at 225(1) K with the detector placed at a distance 42.00 mm from the crystal. A total of 2028 images were collected with an oscillation width of 1.0° in ω. The exposure times were 1 s for the low angle images, 6 s for high angle. Rigaku d*trek images were exported to CrysAlisPro for processing and corrected for absorption. The integration of the data yielded a total of 60156 reflections to a maximum 2θ value of 138.808° of which 7460 were independent and 7203 were greater than 2σ(I). The final cell constants (Table S14) were based on the xyz centroids 38342 reflections above 10σ(I). Analysis of the data showed negligible decay during data collection. The structure was solved and refined with the Bruker SHELXTL (version 2014/7) software package, using the space group C2/c with Z =8 for the formula $C_{32}H_{52}Cu_2F_6N_4O_6S_2$ (2 molecules in asymmetric unit). All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed in idealized positions. There are two crystallographically independent complexes in the asymmetric unit. For one of the complexes, the CF_3 group of the triflate ligand is disordered. Full matrix least-squares refinement based on F^2 converged at R1 = 0.0407 and wR2 = 0.1070 [based on I > 2sigma(I)], R1 = 0.0415 and wR2 = 0.1078 for all data.

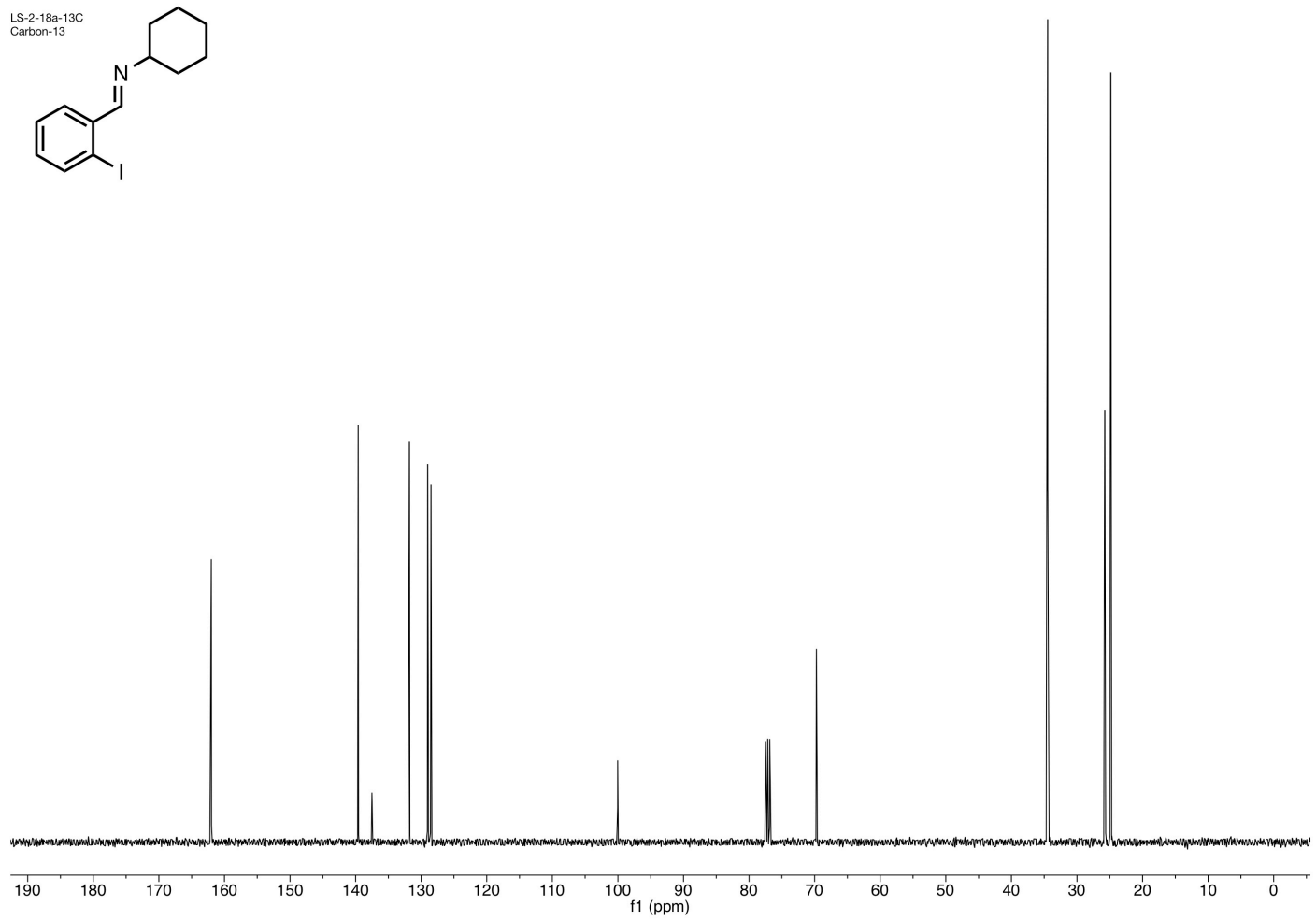
The disordered CF_3 group of one triflate ligand was modeled as two orientations, and site occupancy for each contribution was freely refined. The C-F bond distances in this group were made to be similar using SADI restraints. Additionally, a rigid bond restraint was used to normalize the thermal ellipsoids for this CF3 group. One reflection with high Error/esd was omitted during refinement. This reflection may have been due to the beam stop or secondary extinction. Additional details are presented in Table S15 and are given as Supporting Information in a CIF file. The CIF file has been deposited in the Cambridge Crystallographic Data Centre (CCDC) under deposition number 1985171. Acknowledgement is made for funding from NSF grant CHE-0840456 for X-ray instrumentation.

Table S15. Crystal data and structure refinement for sICyCuOTf.

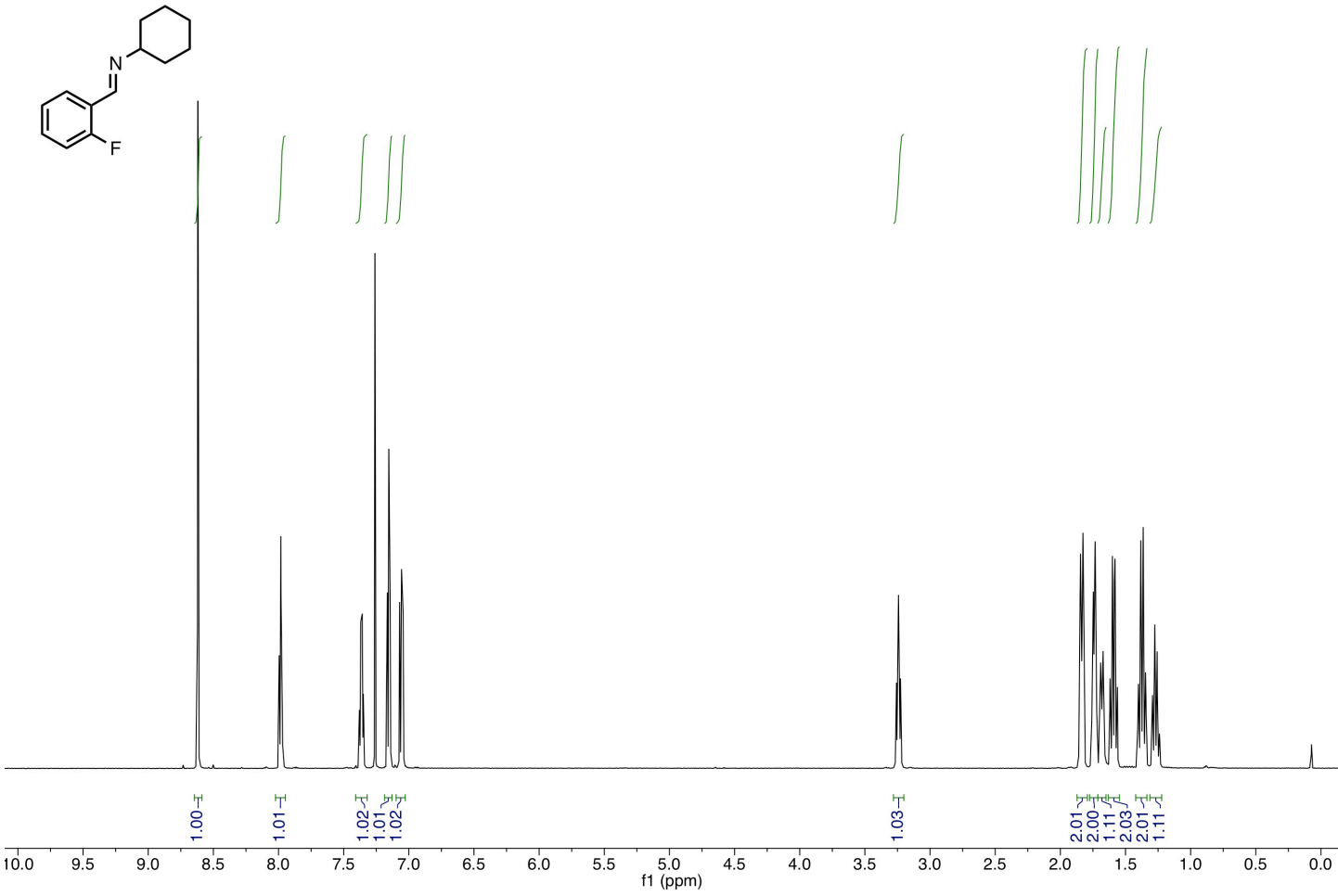
Identification code	ls110c	
Empirical formula	$C_{32}H_{52}Cu_2F_6N_4O_6S_2$	
Formula weight	893.97	
Temperature	225(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 23.2214(3) Å	a= 90°
	b = 20.51134(17) Å	b= 109.0793(14)°
	c = 17.8080(2) Å	g = 90°
Volume	8016.04(17) $Å^3$	
Z	8	
Density (calculated)	1.482 Mg/m^3	
Absorption coefficient	2.924 mm^{-1}	
F(000)	3712	
Crystal size	0.240 x 0.240 x 0.050 mm^3	
Crystal color and habit	colorless plate	
Diffractometer	Rigaku Saturn 944+ CCD	
Theta range for data collection	2.949 to 69.404°.	
Index ranges	–28<=h<=27, –24<=k<=24, –-20<=l<=21	
Reflections collected	60156	
Independent reflections	7461 [R(int) = 0.0490]	
Observed reflections (I > 2sigma(I))	7203	
Completeness to theta = 67.684°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.45978	
Solution method	SHELXT (Sheldrick, 2014)	
Refinement method	SHELXL-2014/6 (Sheldrick, 2014)	
Data / restraints / parameters	7461 / 51 / 498	
Goodness-of-fit on F^2	1.056	
Final R indices [I>2sigma(I)]	R1 = 0.0407, wR2 = 0.1070	
R indices (all data)	R1 = 0.0415, wR2 = 0.1078	
Extinction coefficient	0.000304(19)	
Largest diff. peak and hole	0.514 and –0.495 e.$Å^{-3}$	

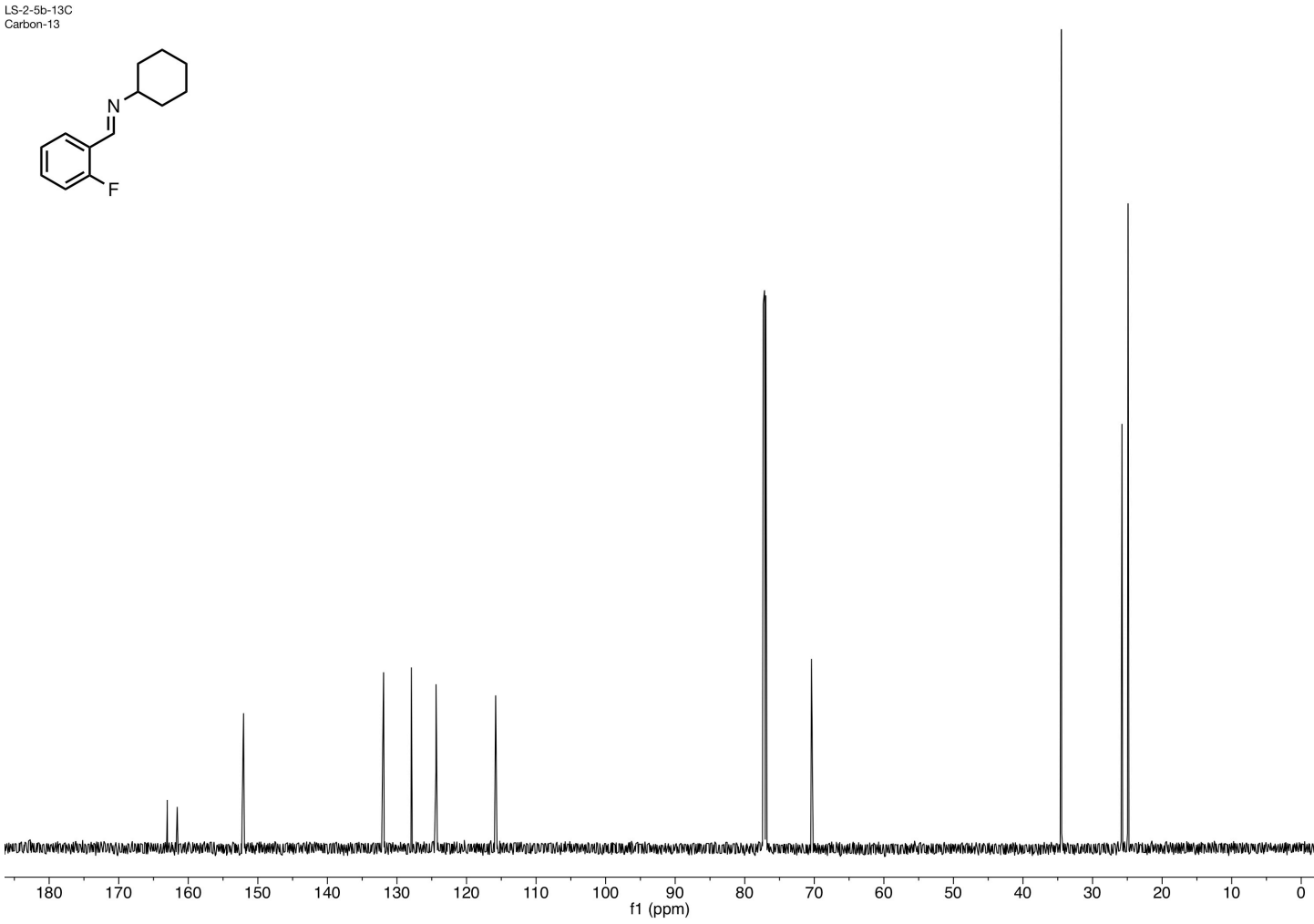
8. NMR Spectra of Novel Compounds



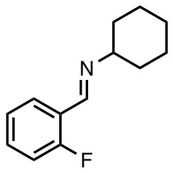

LS-2-18a-13C
Carbon-13
N
I
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-5b-1H
Proton Spectrum

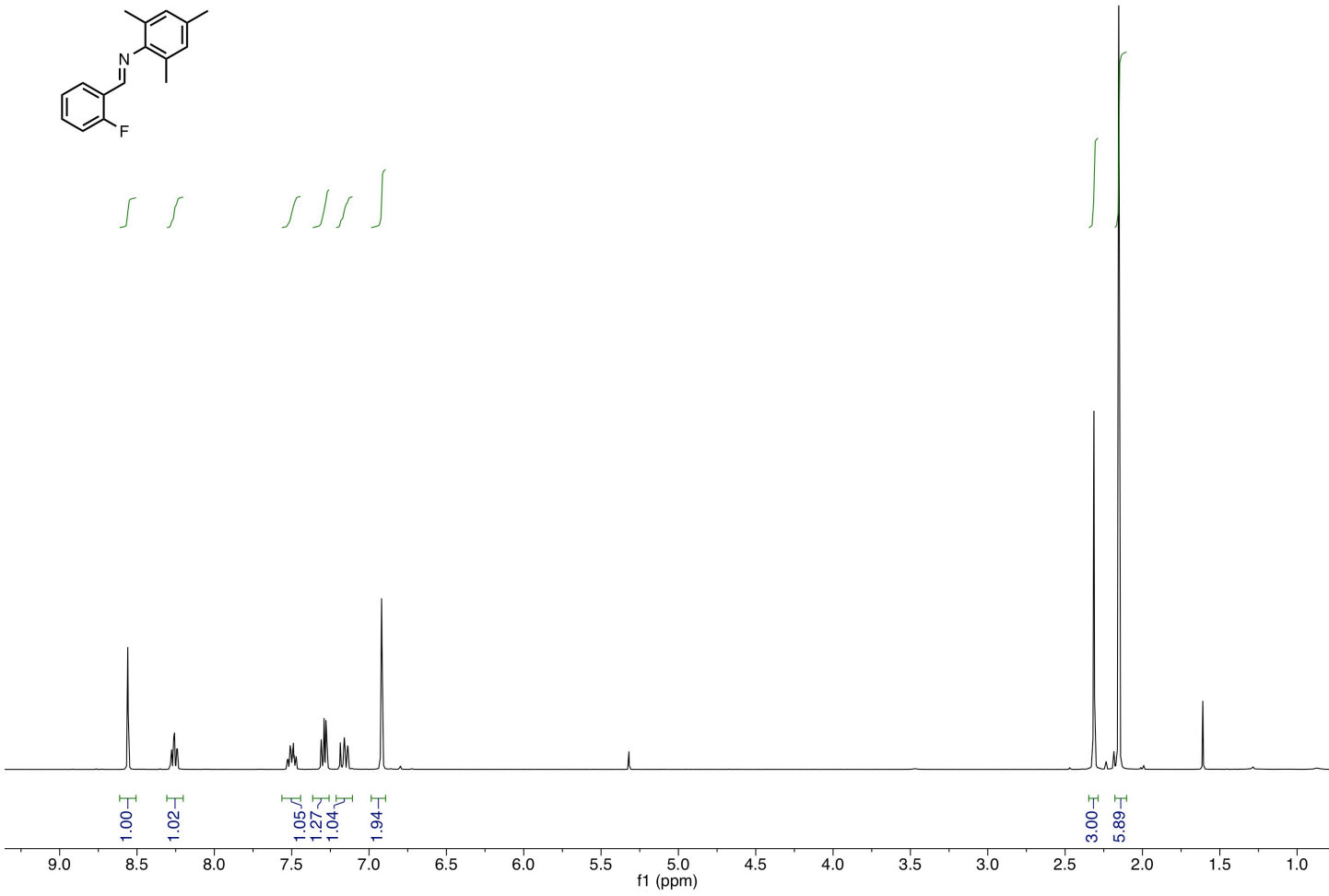


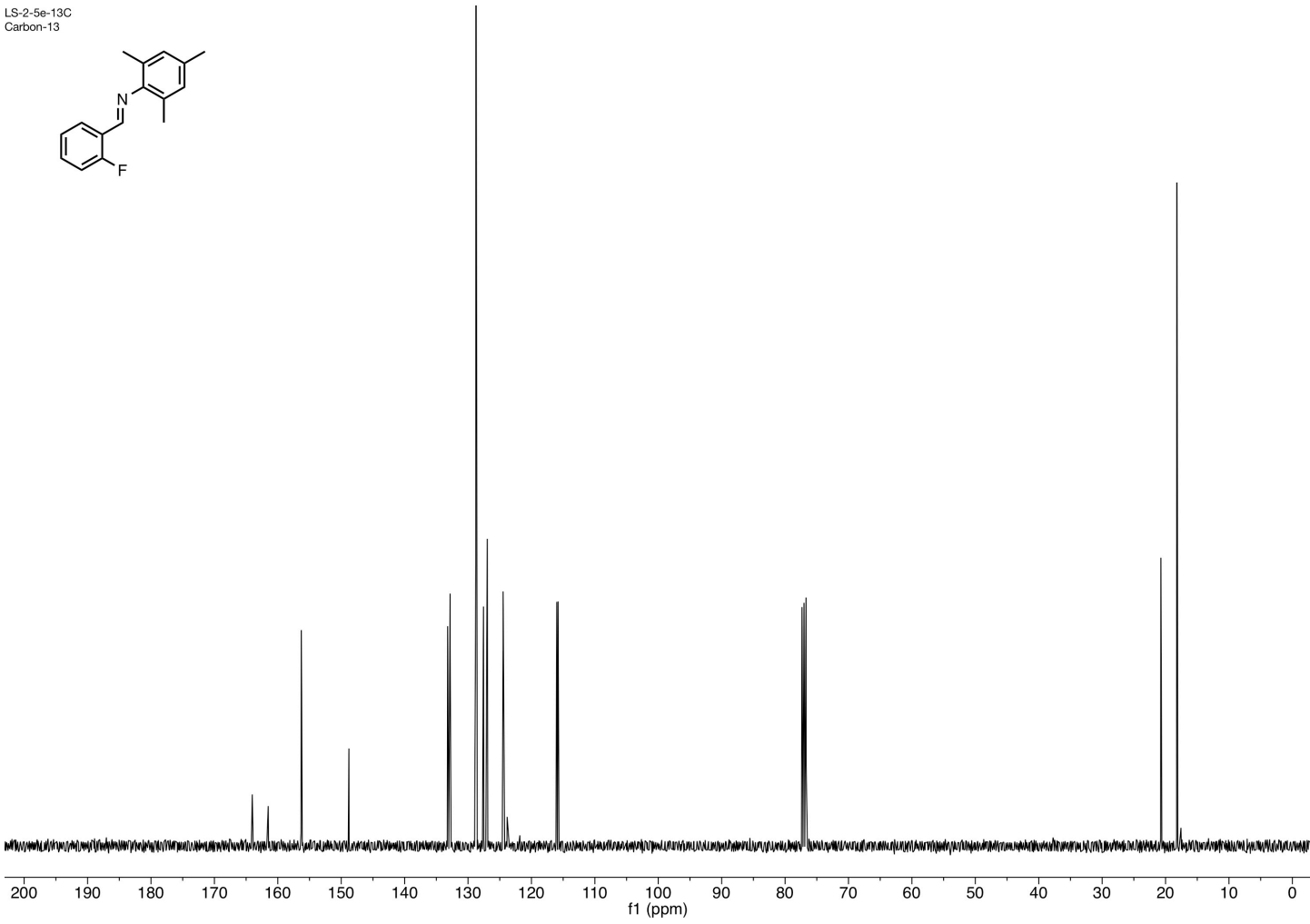

LS-2-5b-13C
Carbon-13
N
F
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-5b-19F
STANDARD FLUORINE PARAMETERS

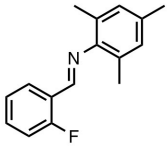


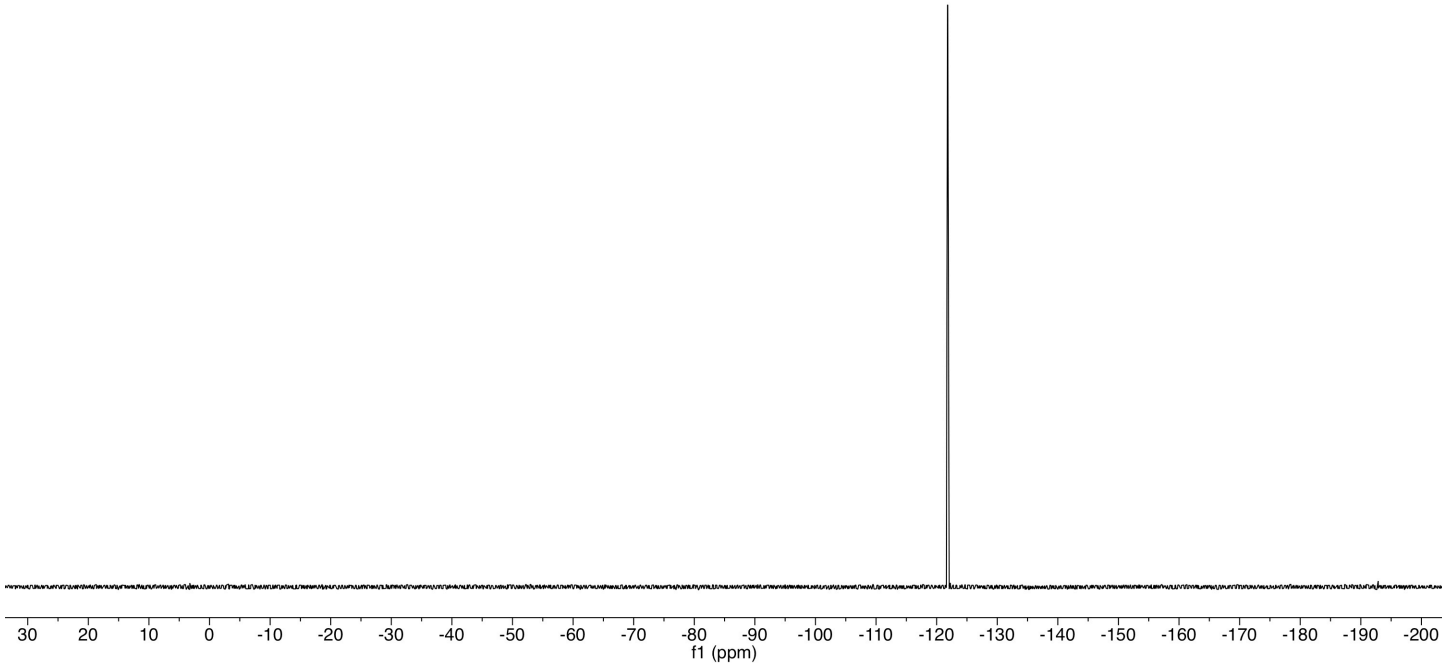
LS-2-5e-crude
Proton Spectrum



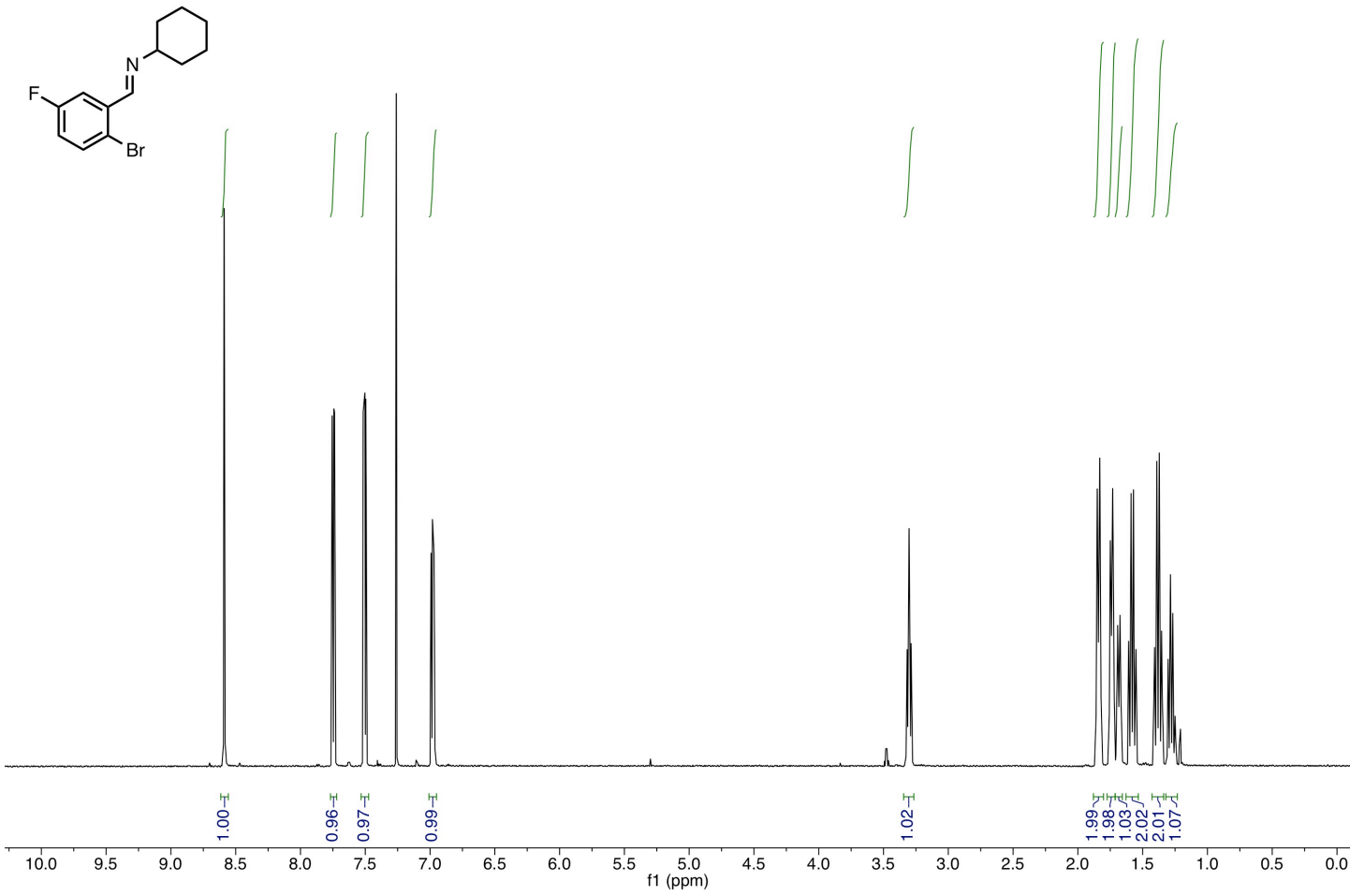

LS-2-5e-13C
Carbon-13
N
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-5e-crude-19F
Fluorine-19

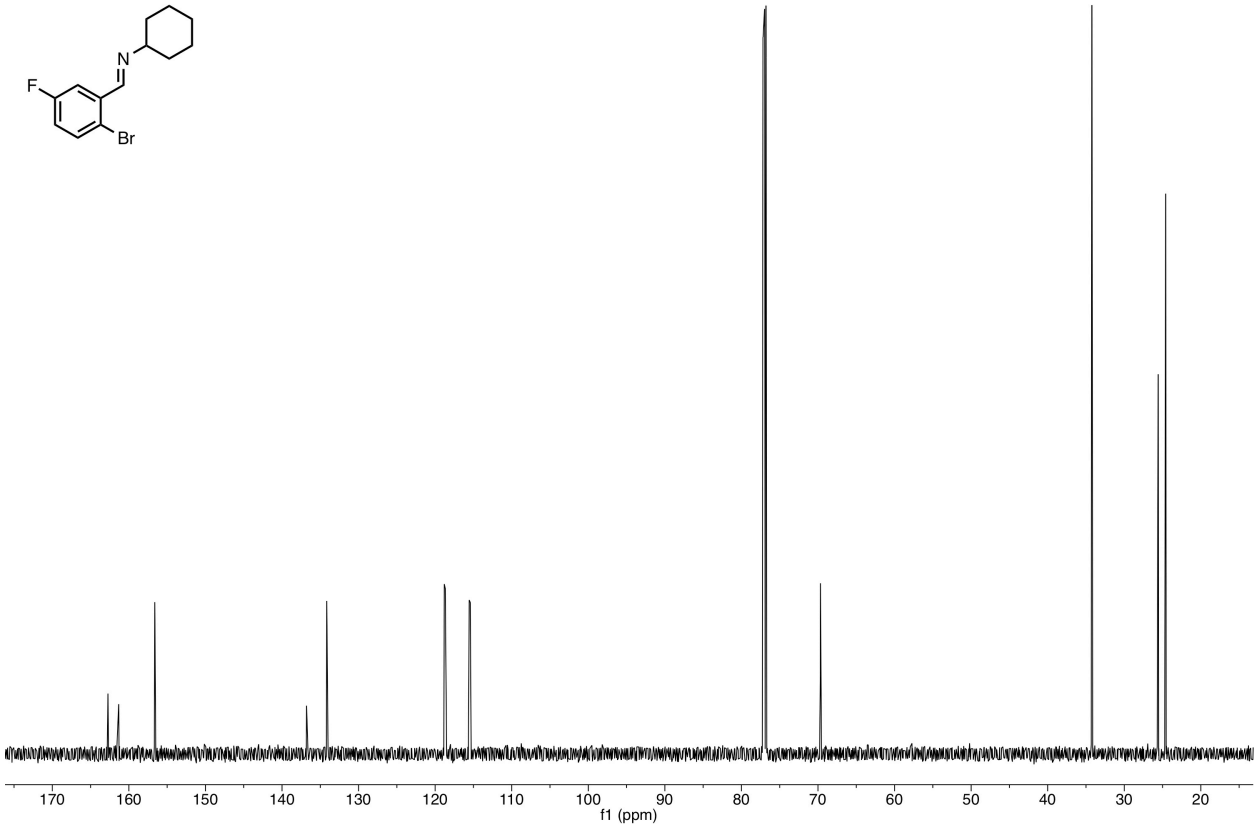




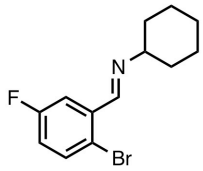
LS-2-18C-1H
Proton Spectrum

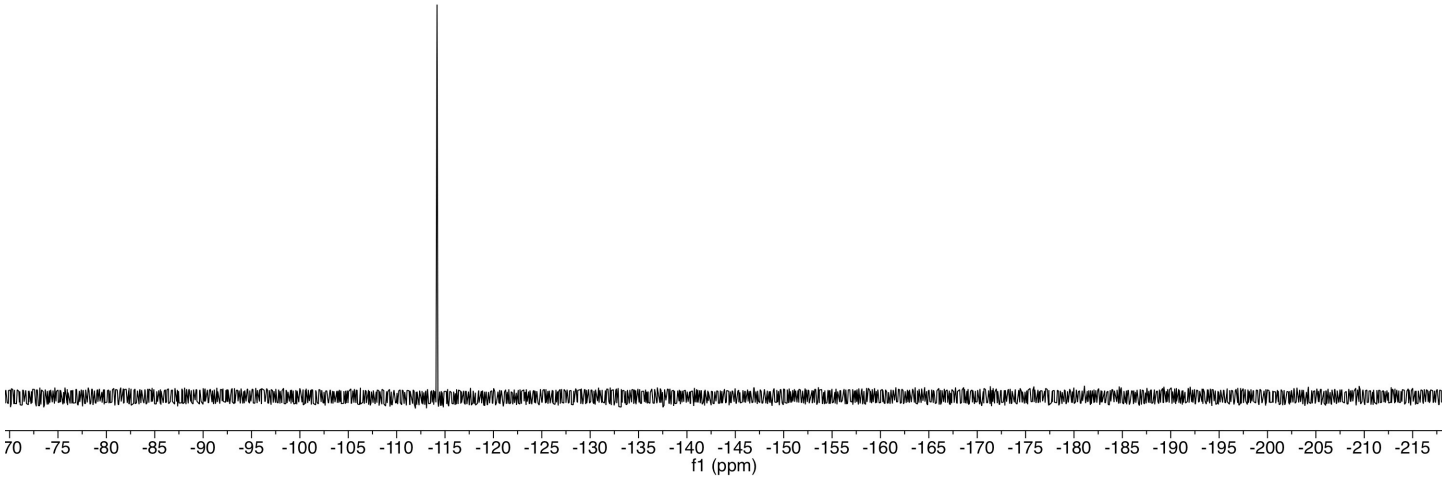


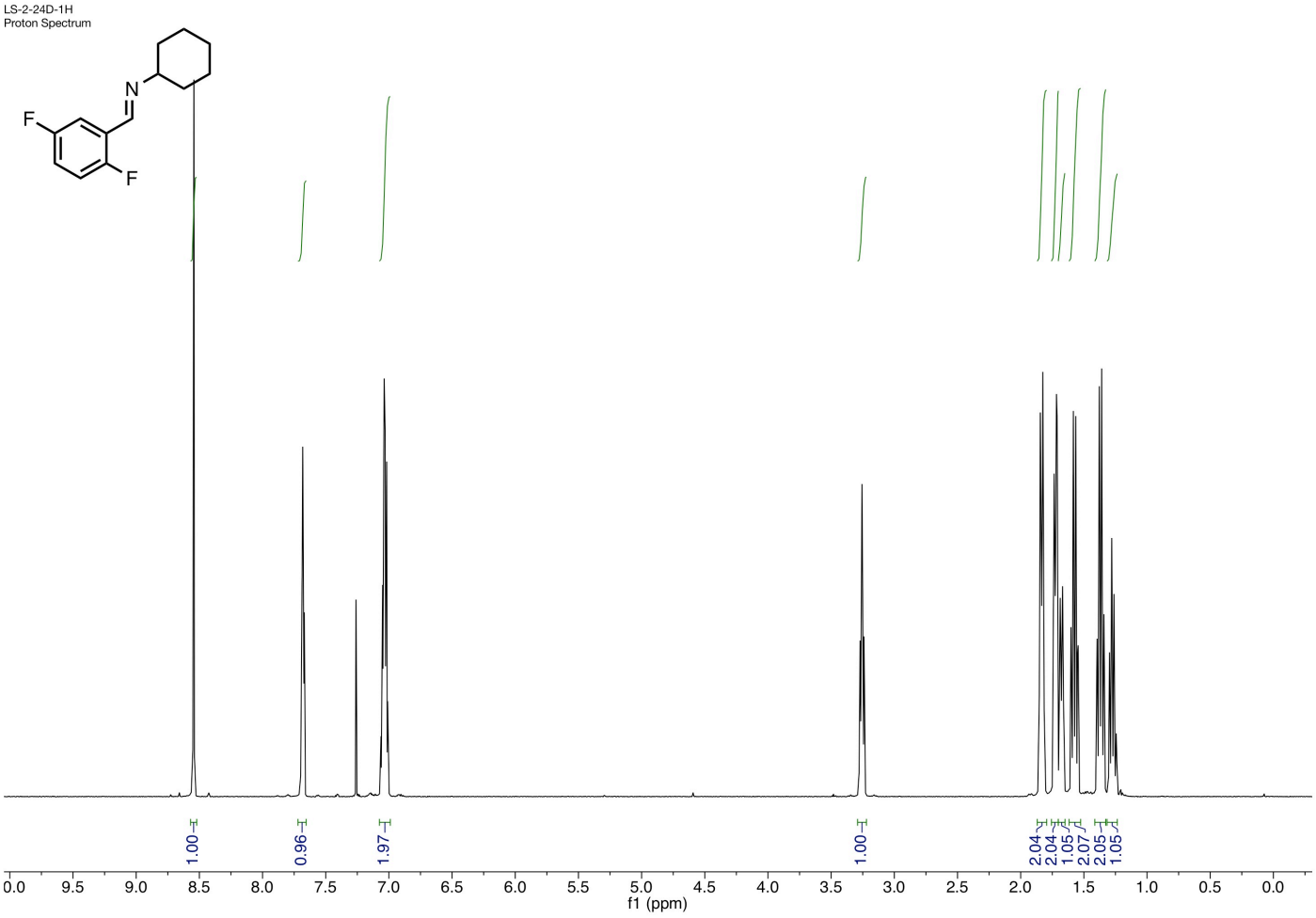
LS-2-18C-13C
Carbon-13

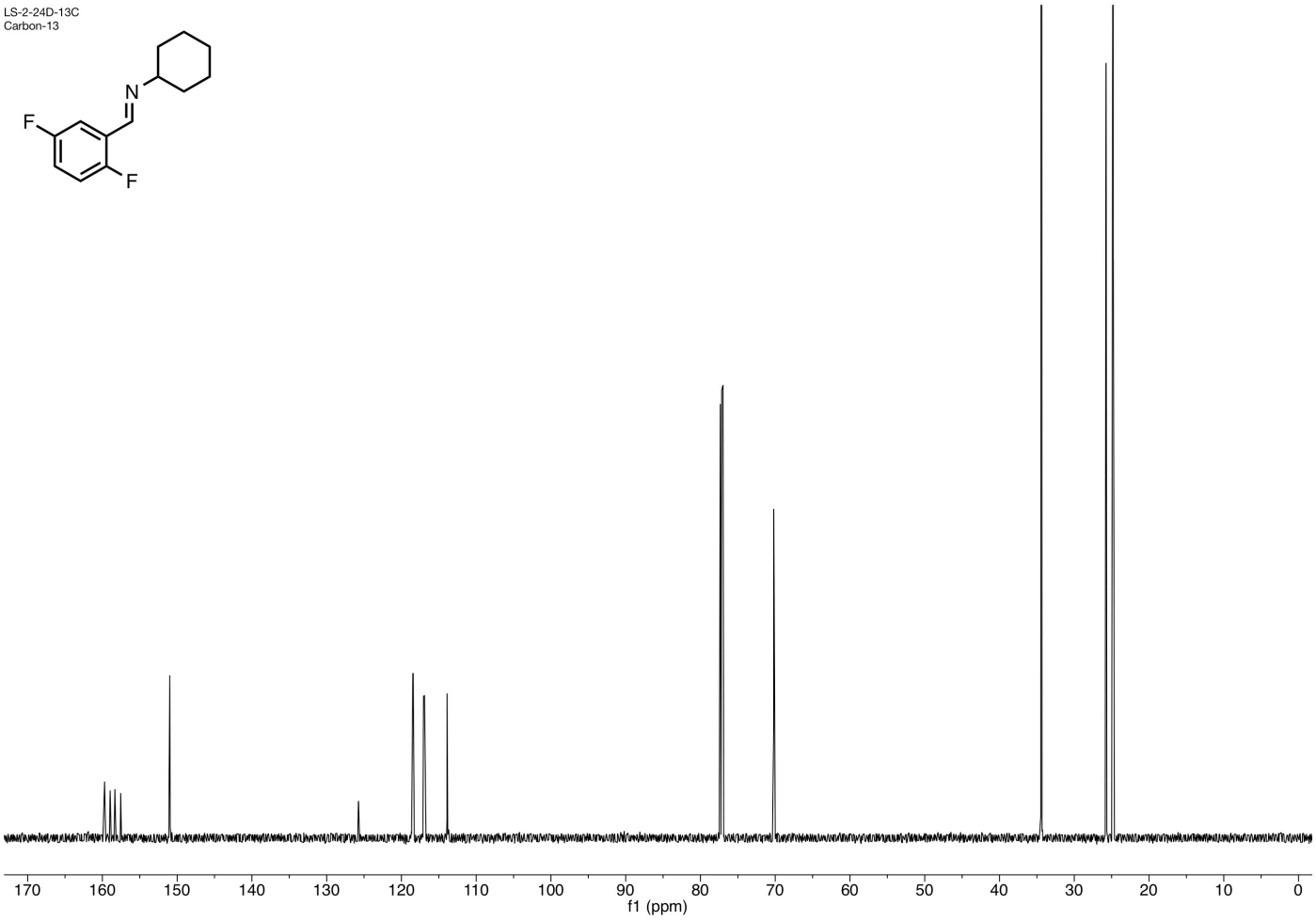


LS-2-18C-19F-TFT
STANDARD FLUORINE PARAMETERS

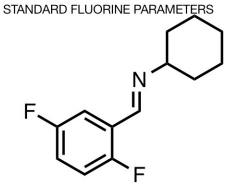


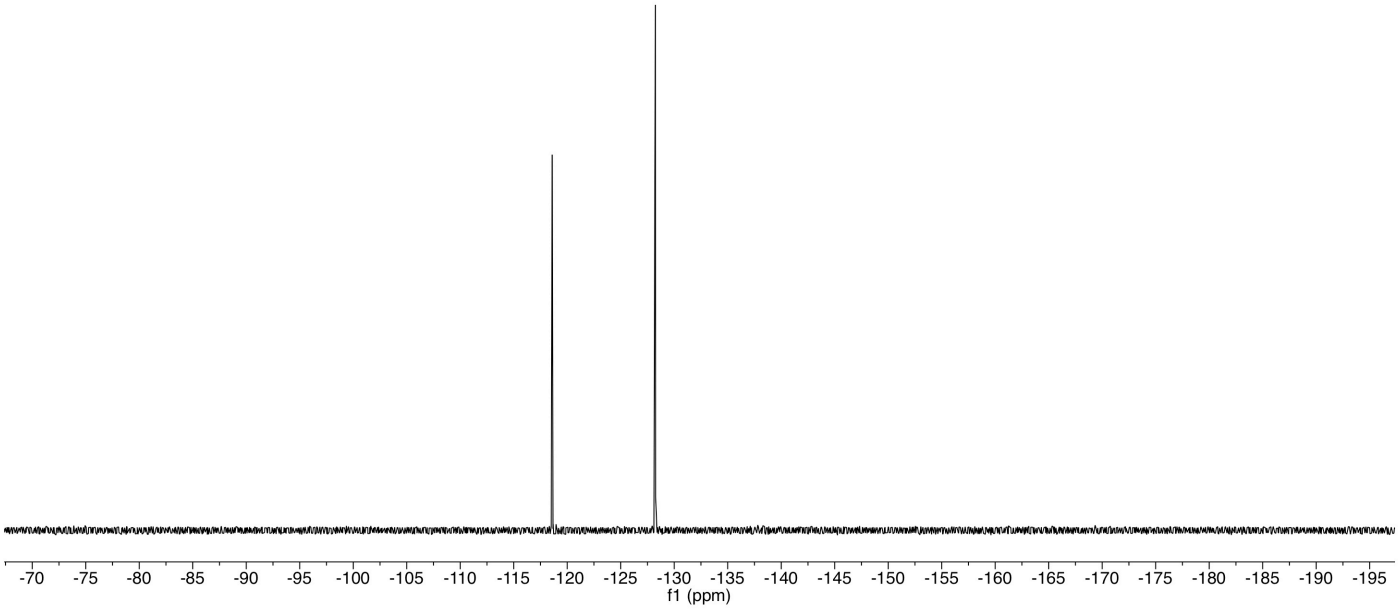


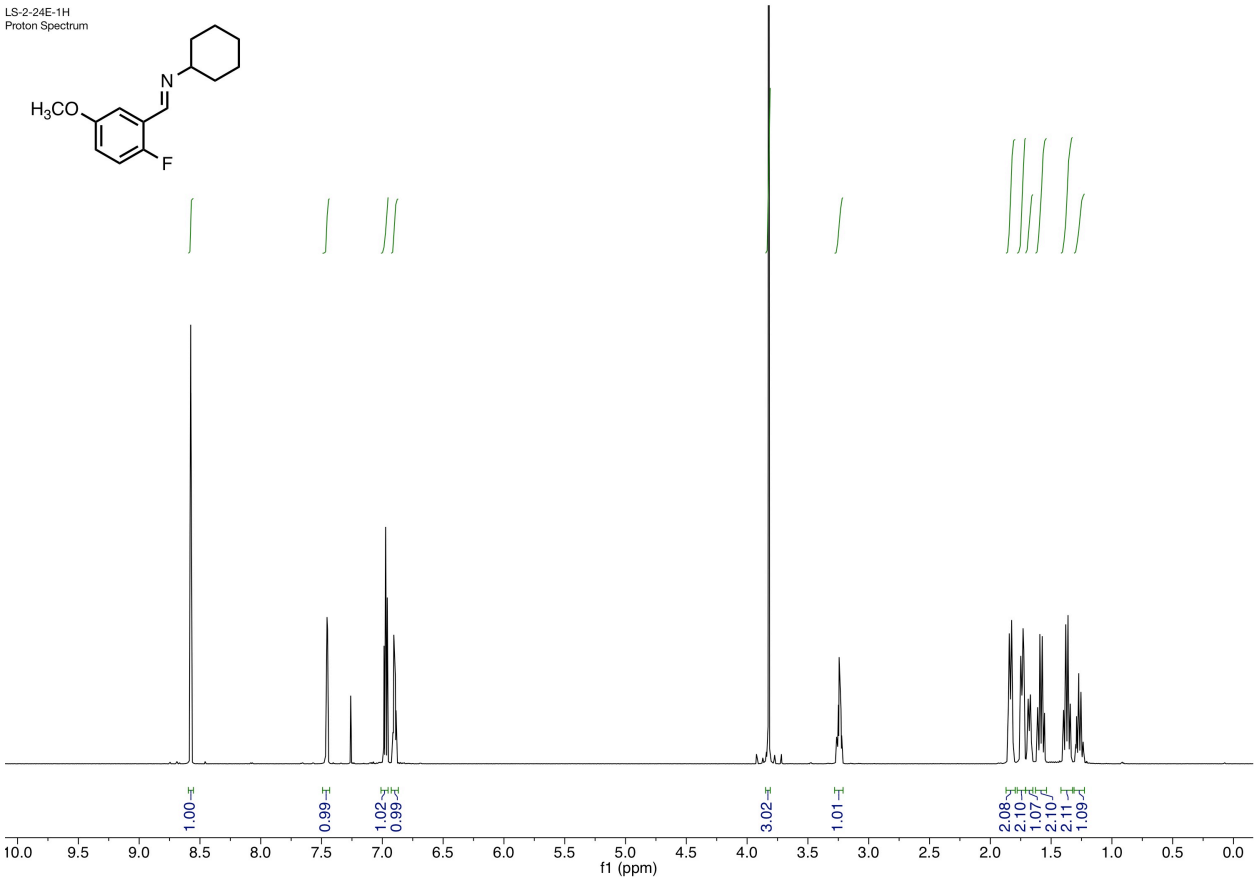

LS-2-24D-1H
Proton Spectrum
N
F
F
1.00
0.96
1.97
1.00
2.04
2.04
1.05
2.07
2.05
1.05
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

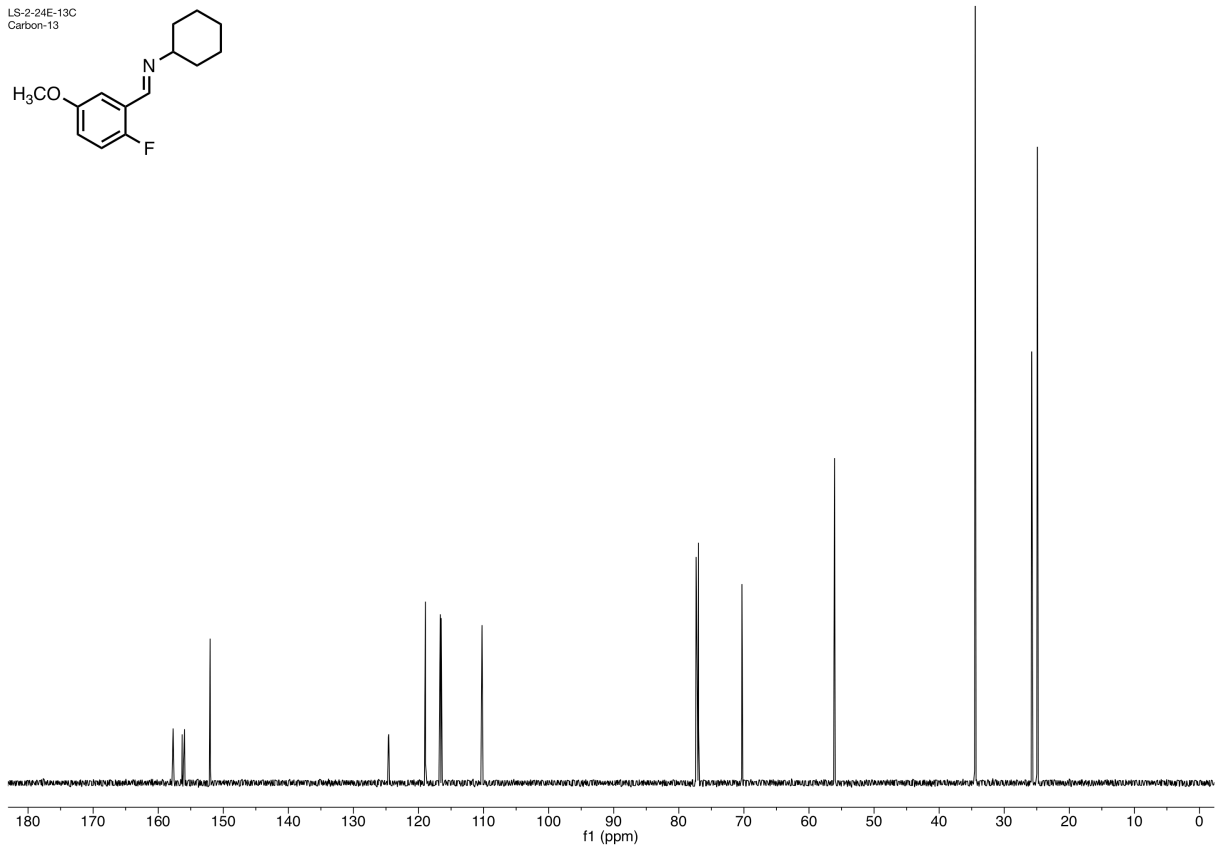

LS-2-24D-13C
Carbon-13
N
F
F
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

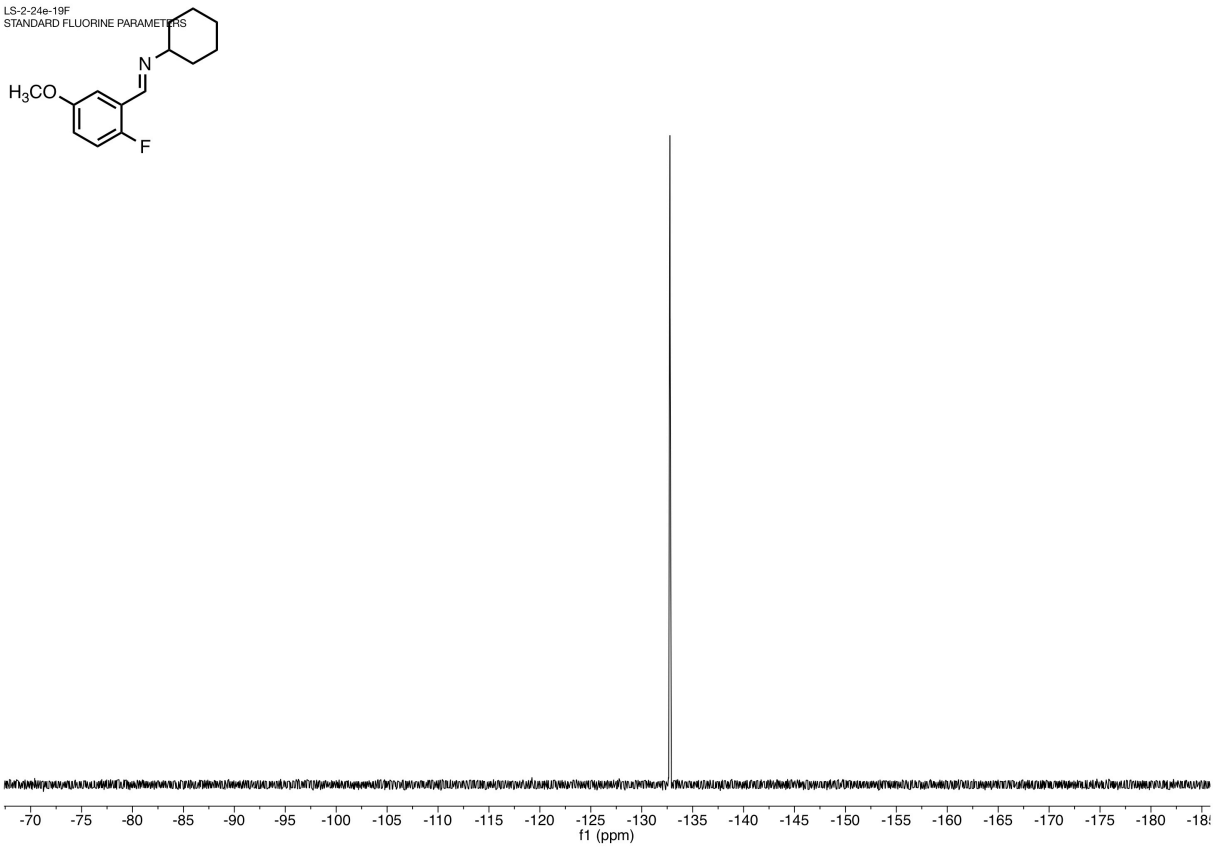
LS-2-24D-19F
STANDARD FLUORINE PARAMETERS

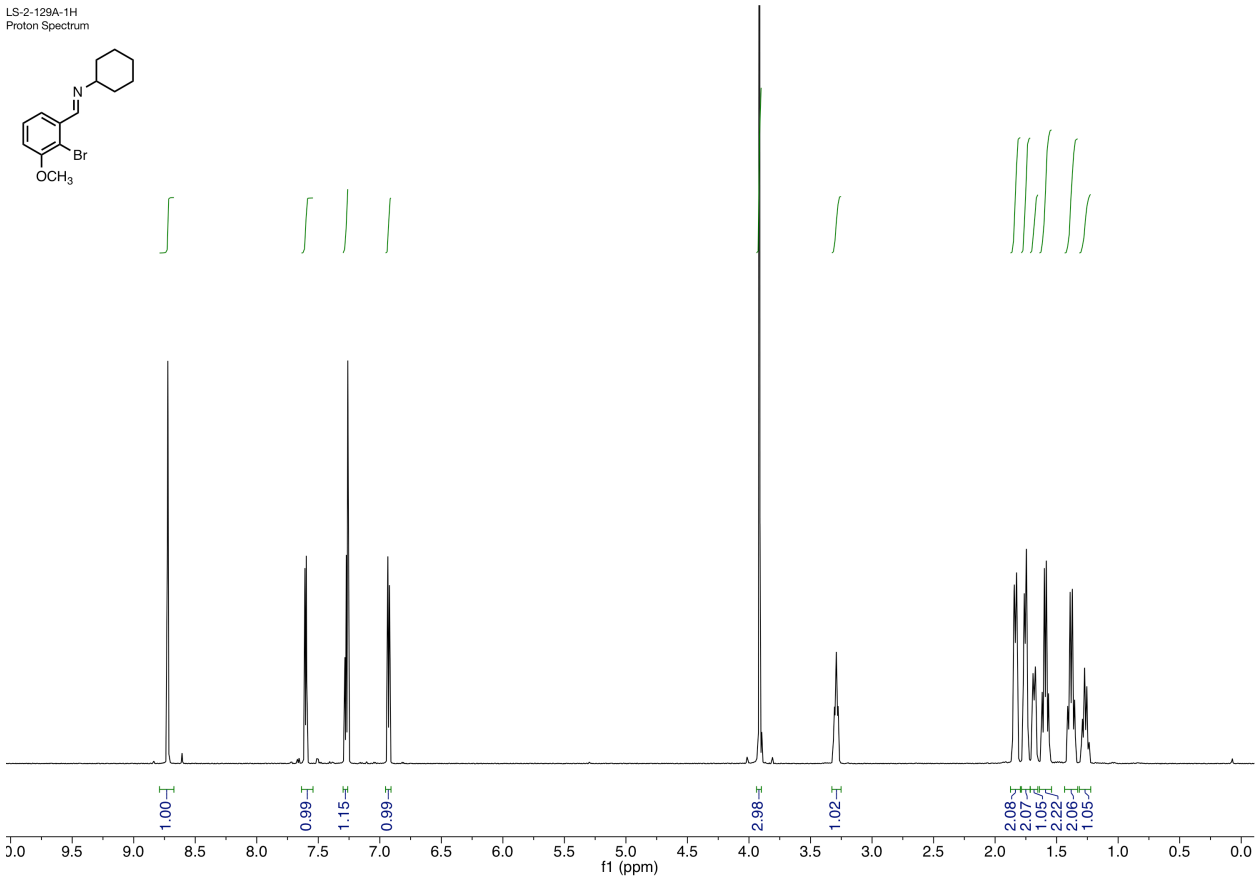


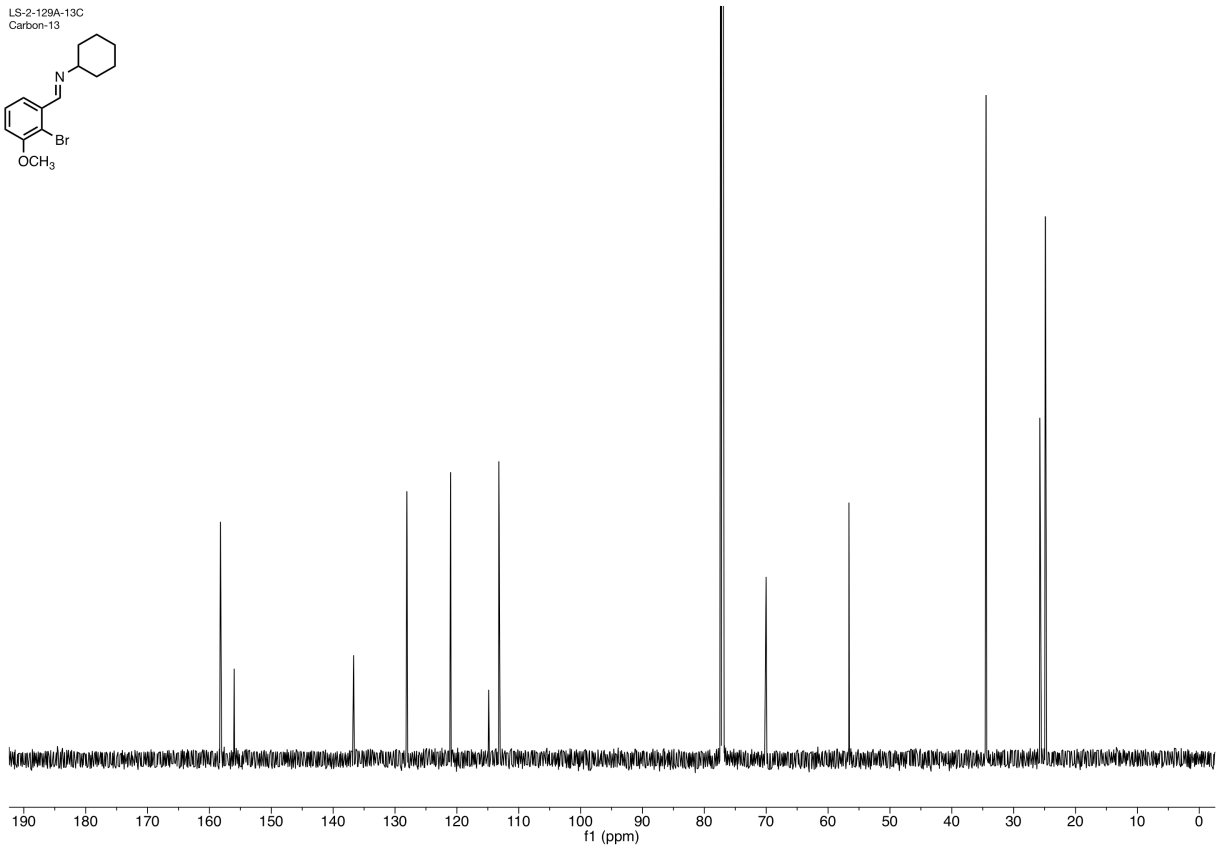


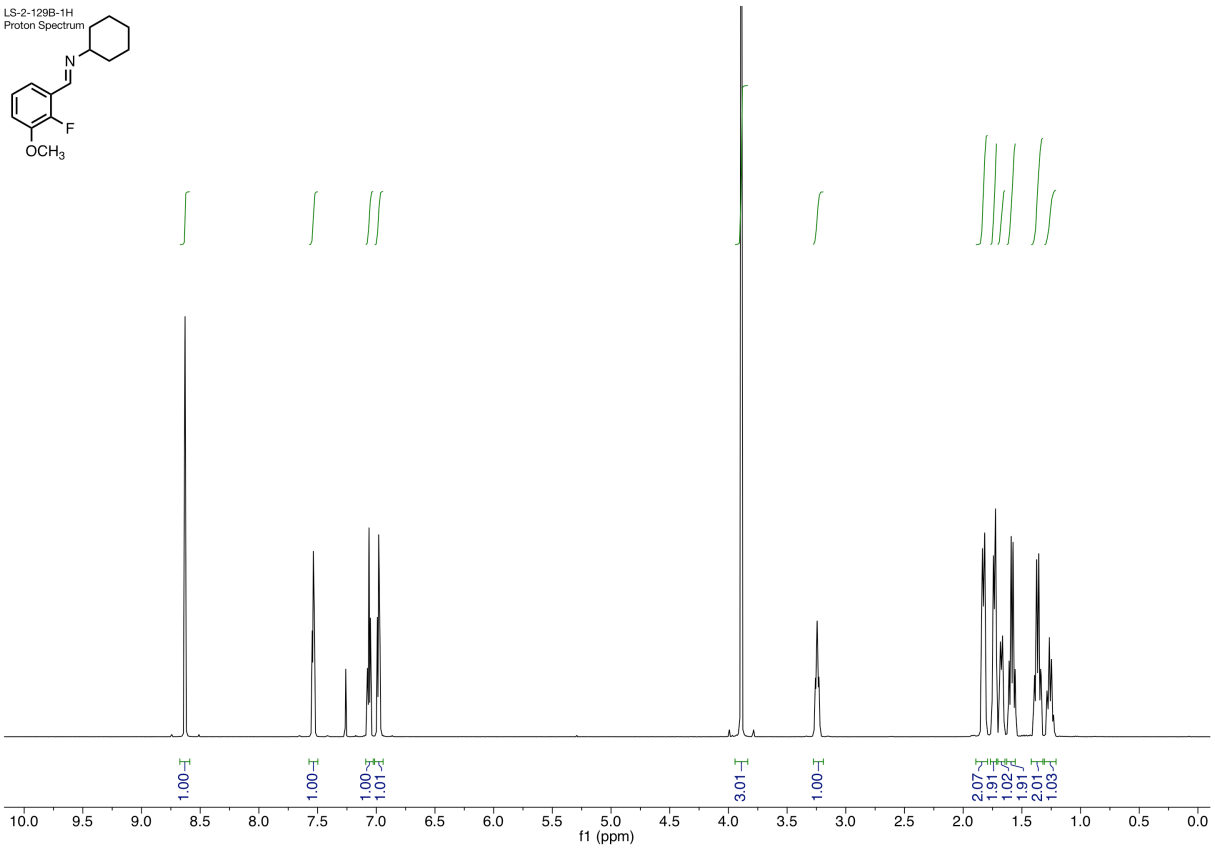

LS-2-24E-1H
Proton Spectrum
N
H3CO
F
1.00
0.99
1.02
0.99
3.02
1.01
2.08
2.10
1.07
2.10
2.11
1.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

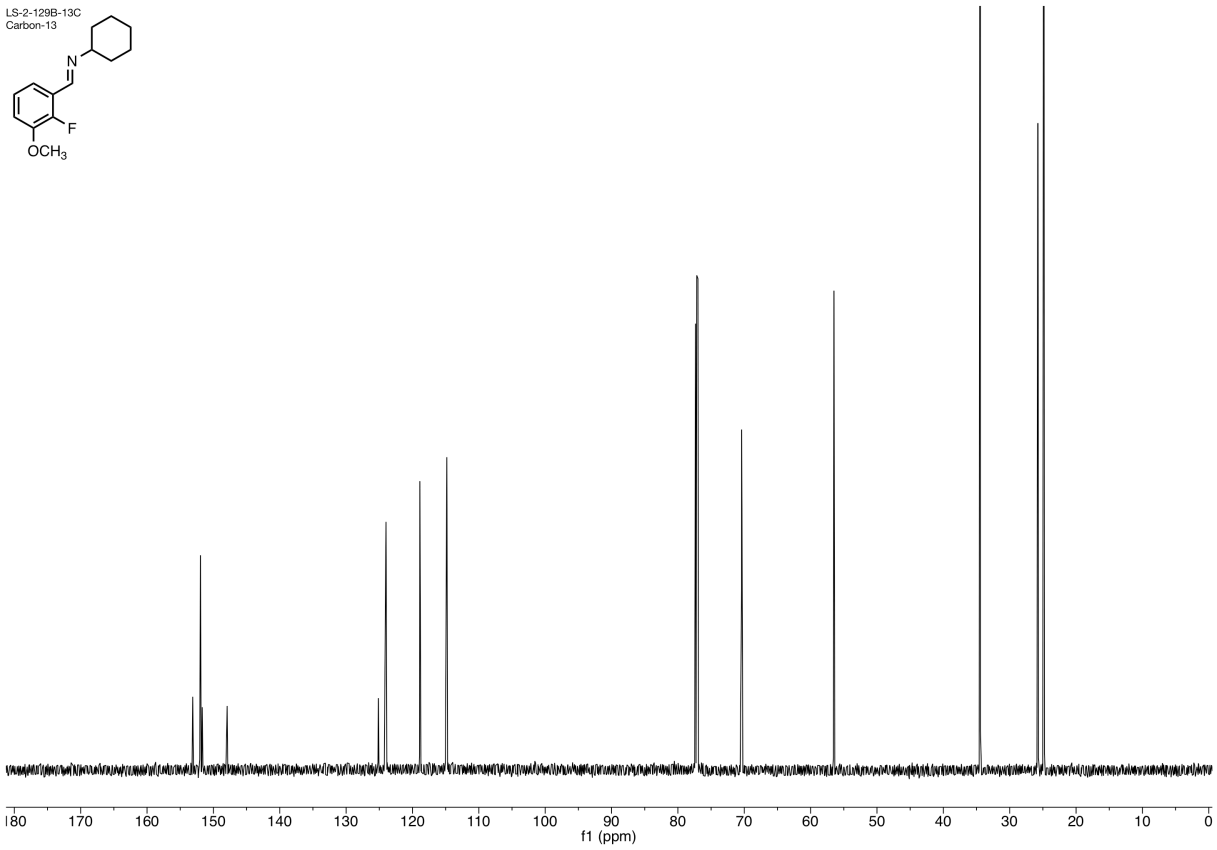

LS-2-24E-13C
Carbon-13
N
H3CO
F
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


LS-2-24e-19F
STANDARD FLUORINE PARAMETERS
N
H3CO
F
-70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160 -165 -170 -175 -180
f1 (ppm)

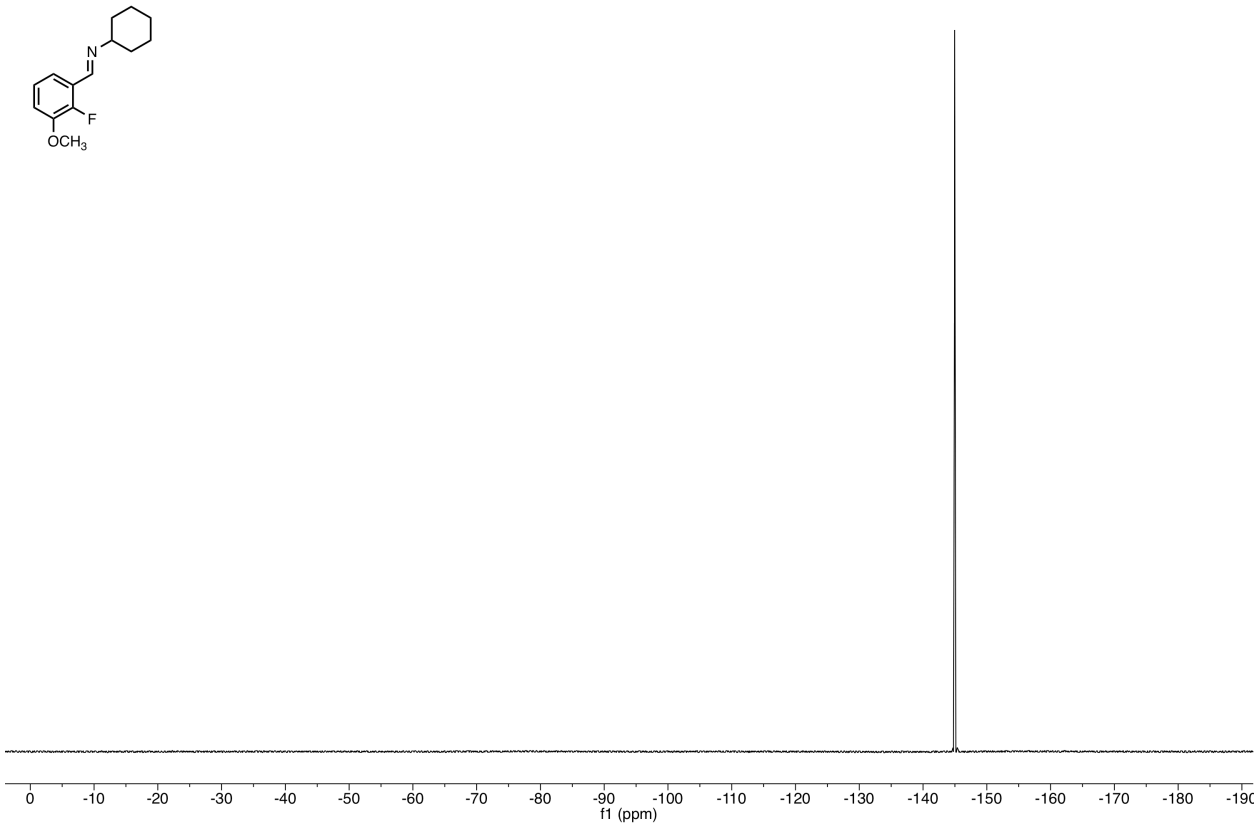

LS-2-129A-1H
Proton Spectrum
N
Br
OCH3
1.00
0.99
1.15
0.99
2.98
1.02
2.08
2.07
1.05
2.22
2.06
1.05
f1 (ppm)

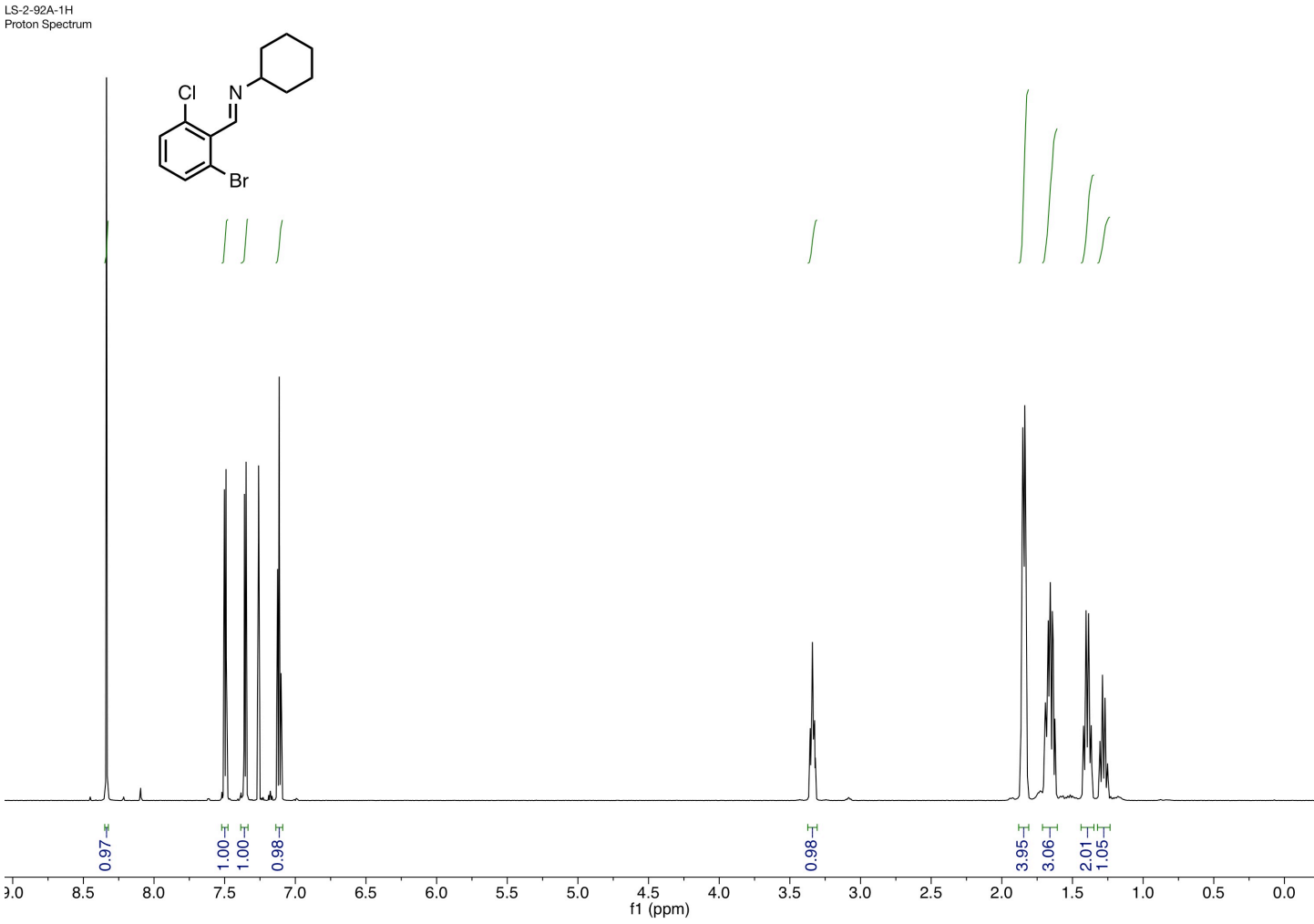

LS-2-129A-13C
Carbon-13
N
Br
OCH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

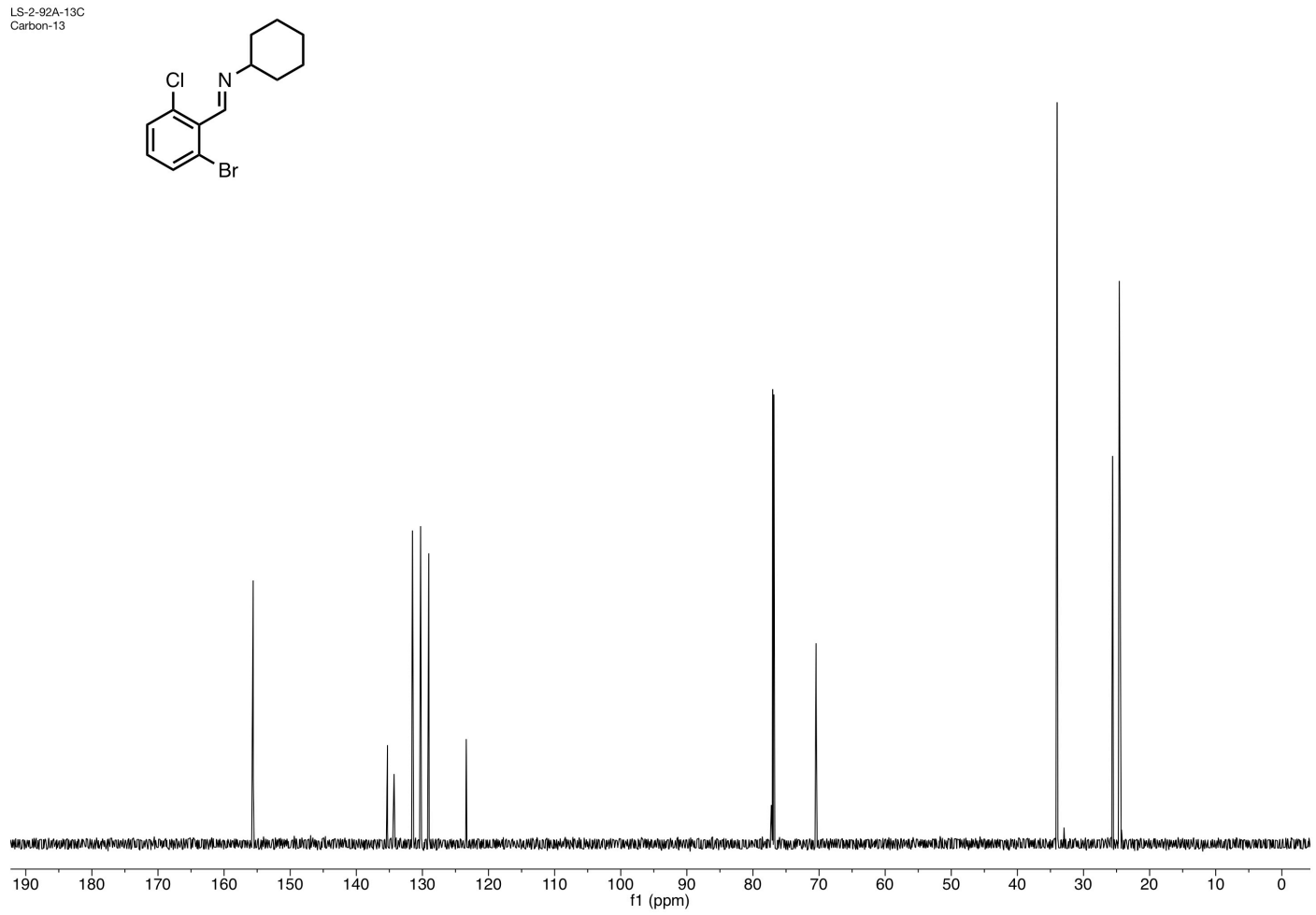

LS-2-129B-1H
Proton Spectrum
N
F
OCH3
1.00
1.00
1.00
1.01
3.01
1.00
2.07
1.91
1.02
1.91
2.01
1.03
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


LS-2-129B-13C
Carbon-13
N
F
OCH3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

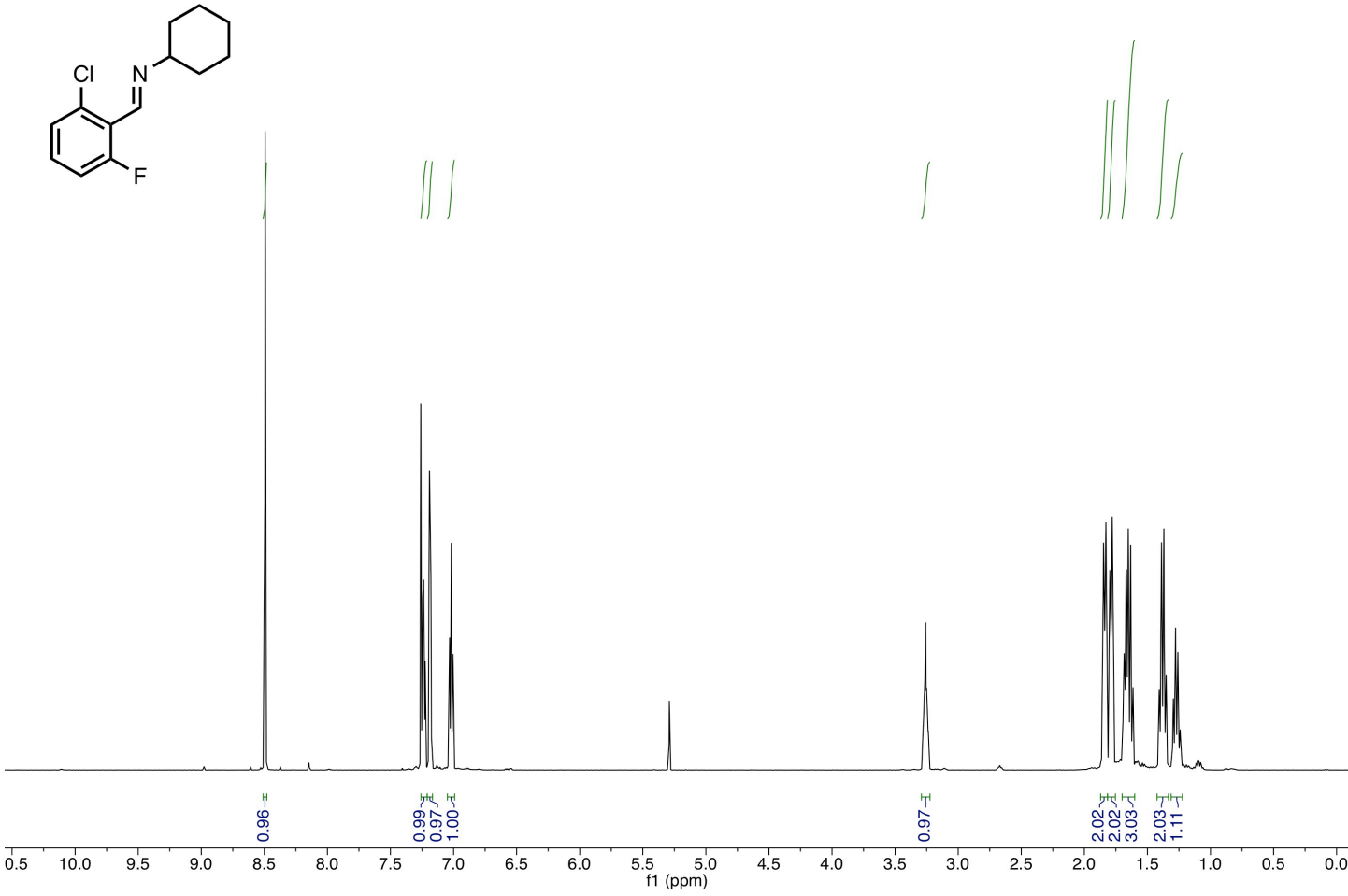
LS-2-129B-CyImoOMeF-19F
STANDARD FLUORINE PARAMETERS

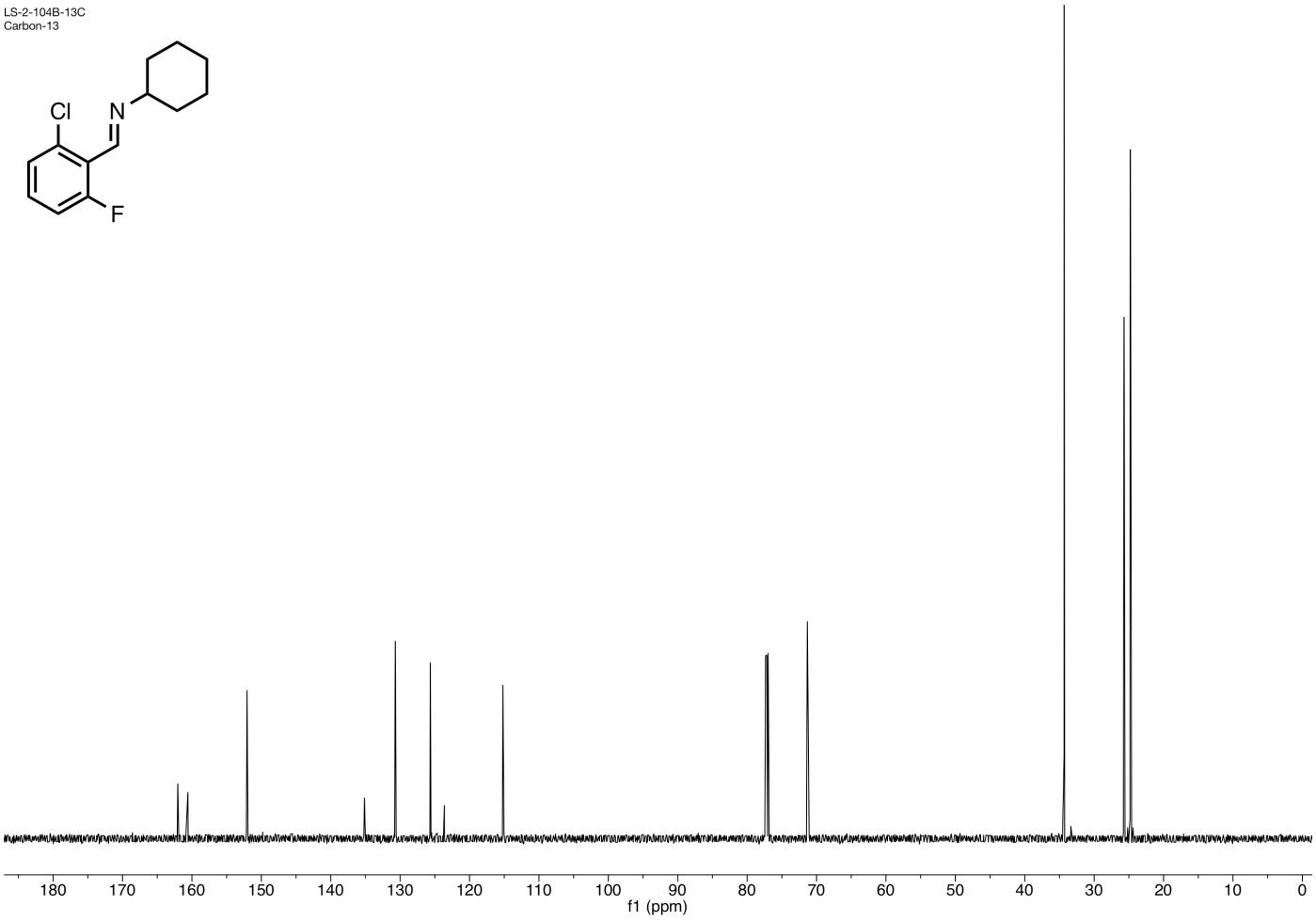



LS-2-92A-1H
Proton Spectrum
Cl
N
Br
0.97
1.00
1.00
0.98
0.98
3.95
3.06
2.01
1.05
f1 (ppm)

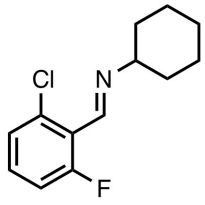

LS-2-92A-13C
Carbon-13
Cl
N
Br
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

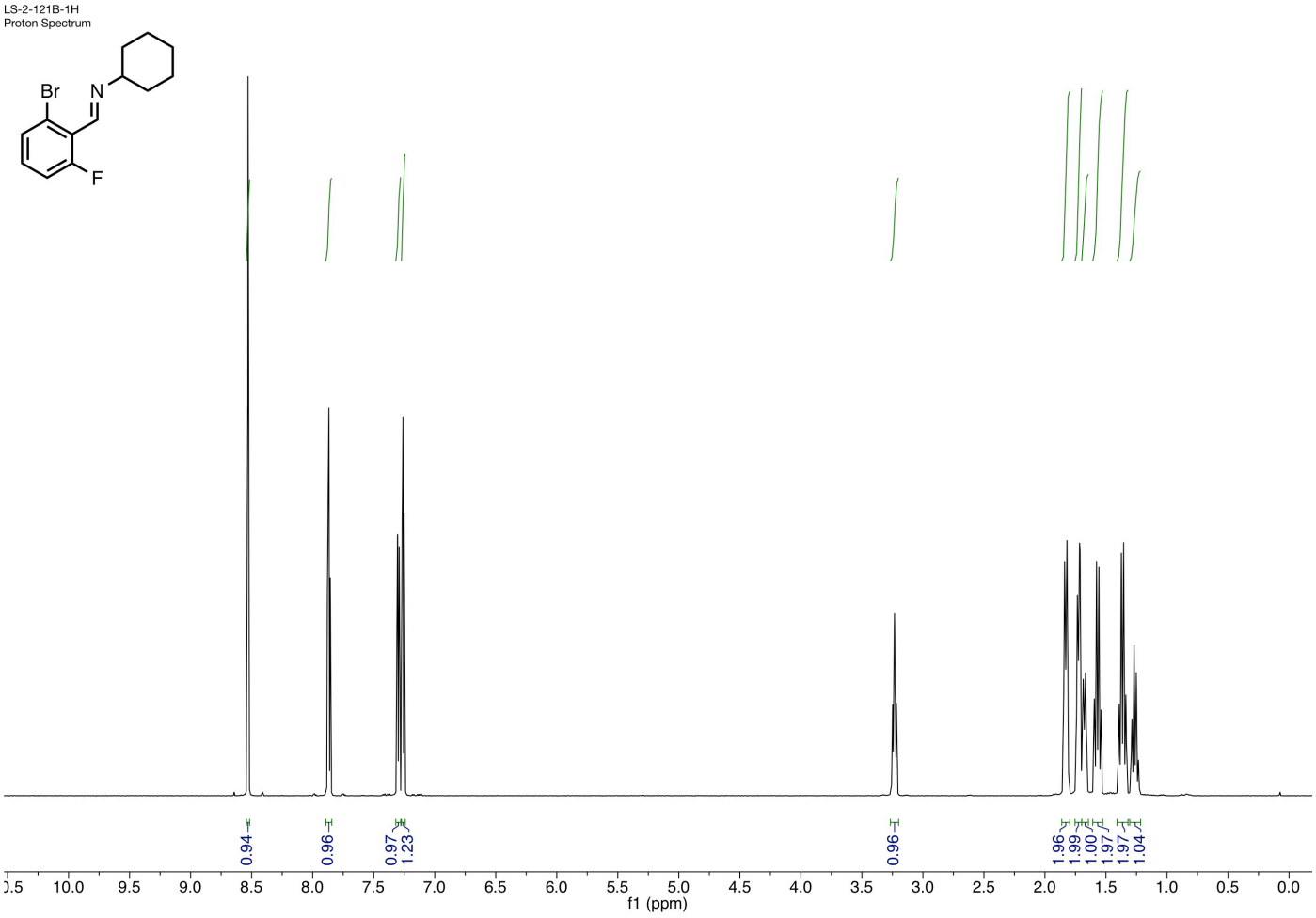
LS-2-104B-1H
Proton Spectrum

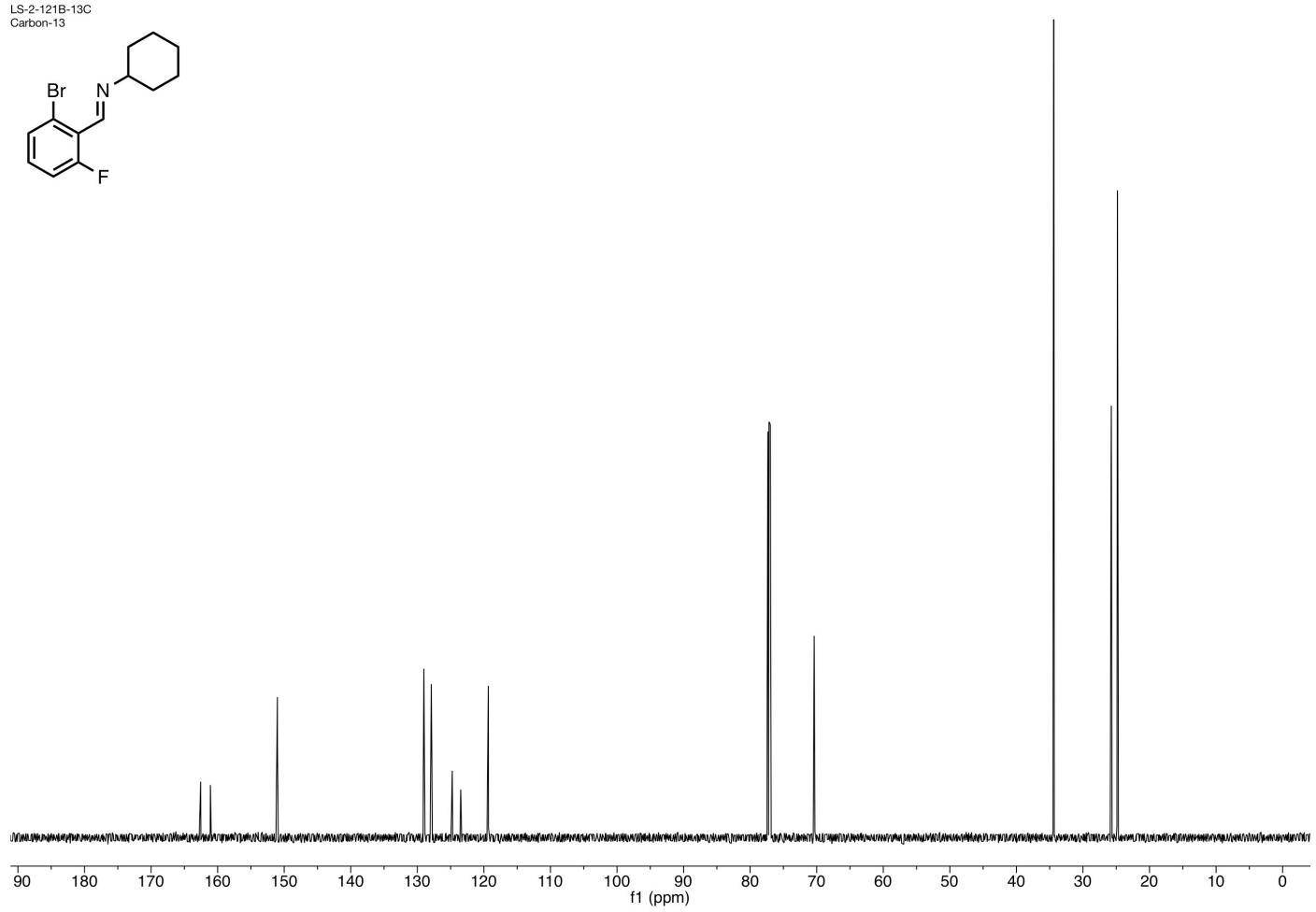



LS-2-104B-13C
Carbon-13
Cl
N
F
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

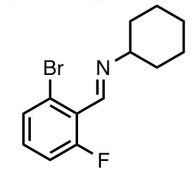
LS-2-104B-19F
Fluorine-19

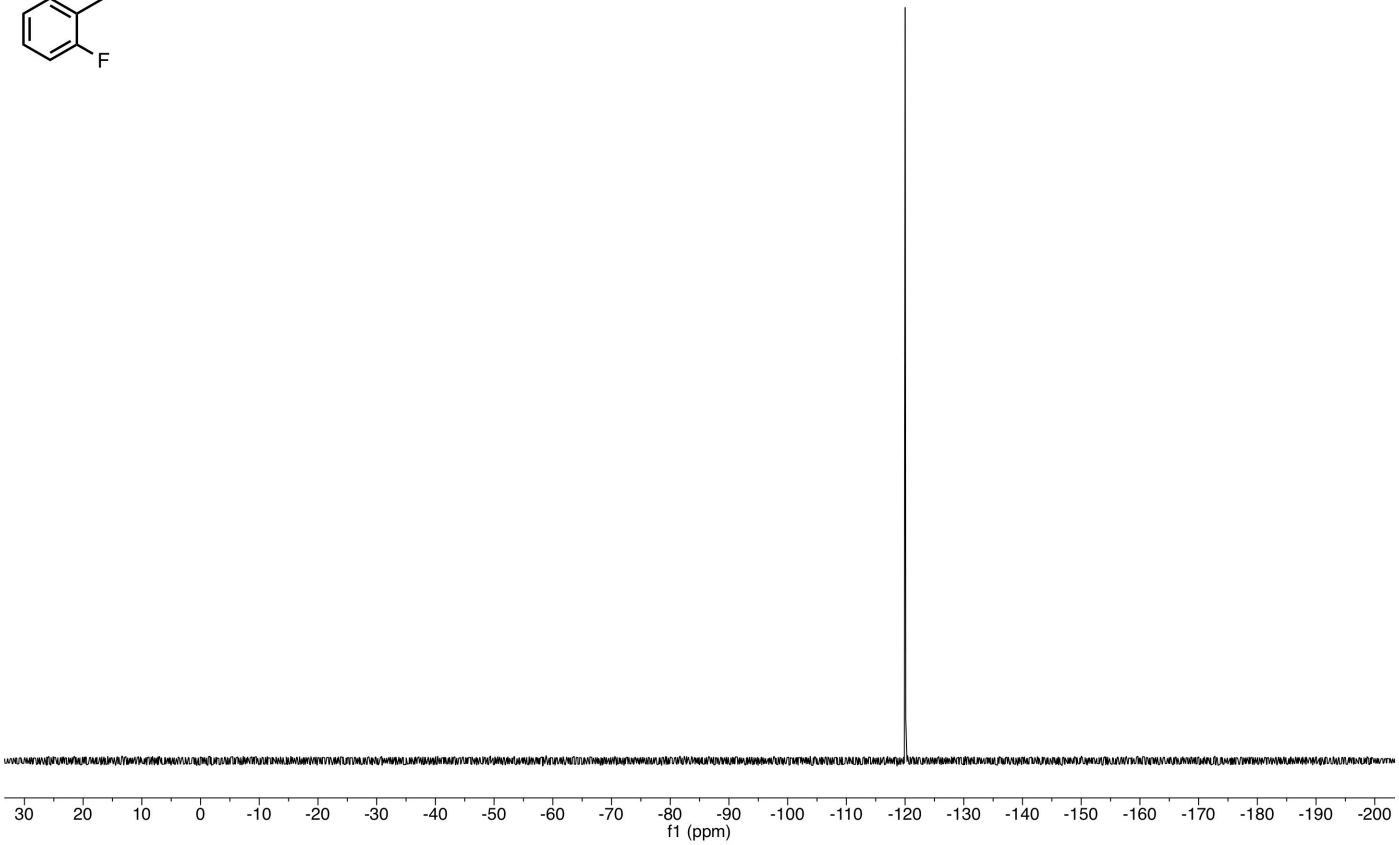


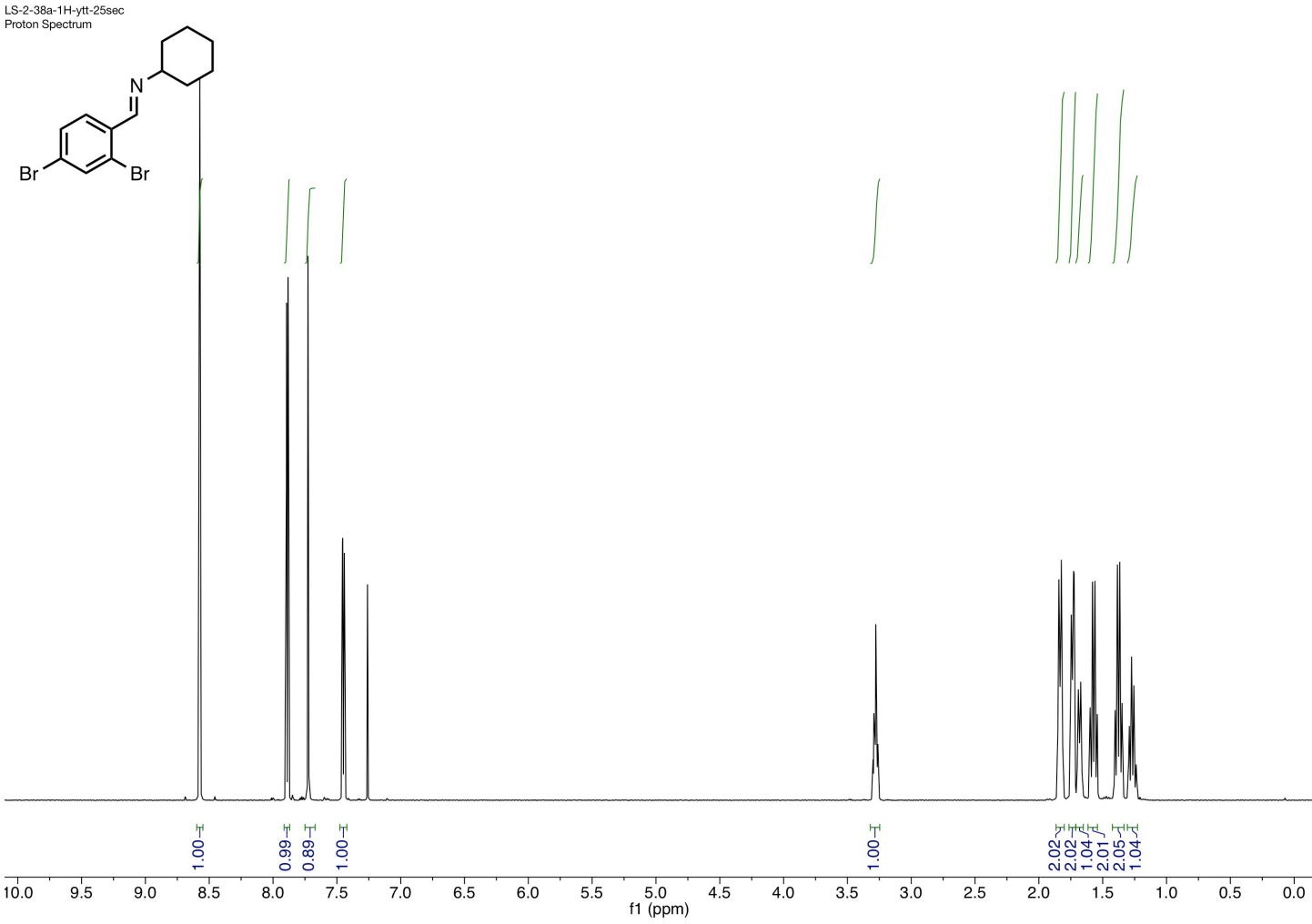

LS-2-121B-1H
Proton Spectrum
Br
N
F
0.94
0.96
0.97
1.23
0.96
1.96
1.99
1.00
1.97
1.97
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

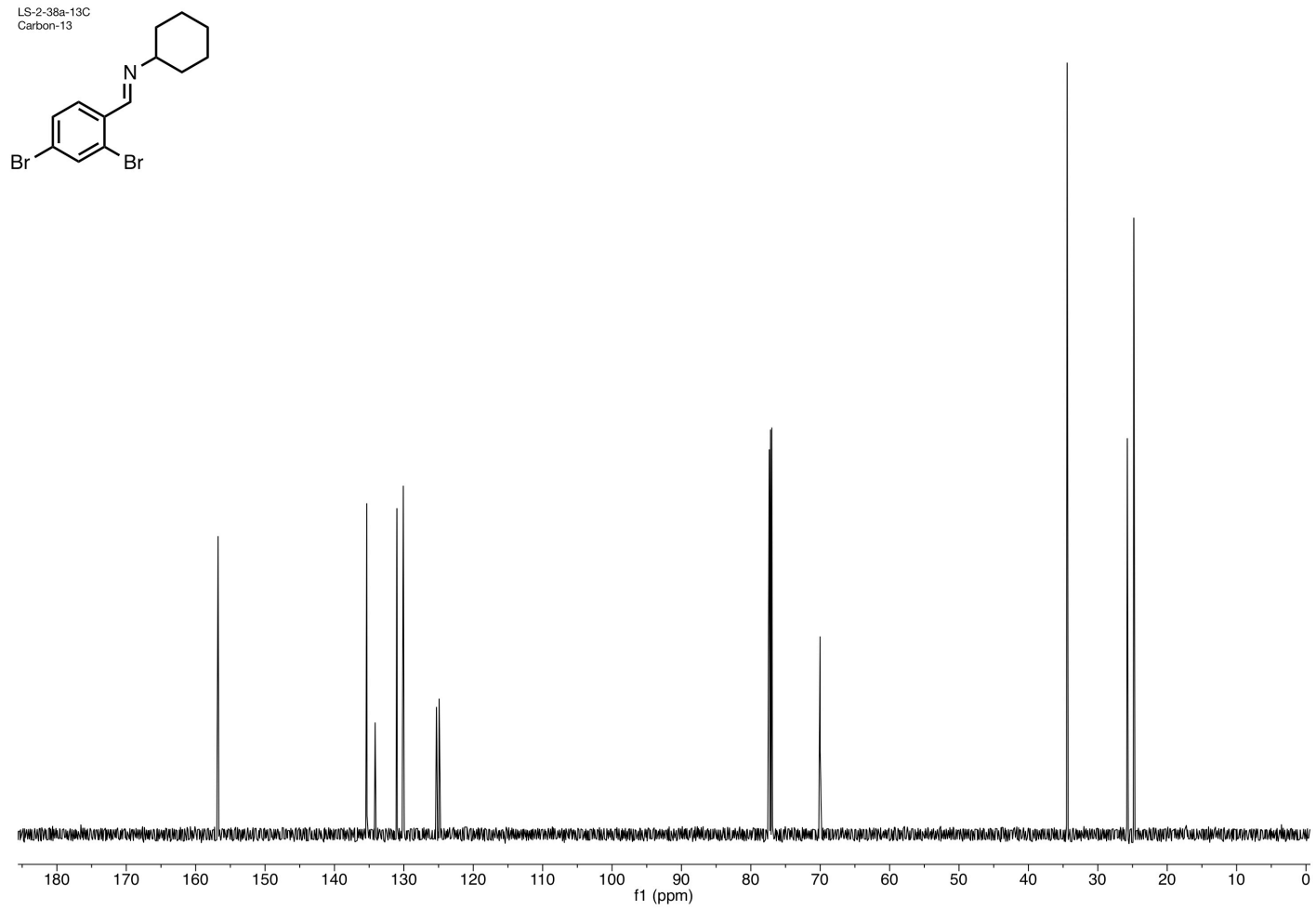

LS-2-121B-13C
Carbon-13
Br
N
F
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

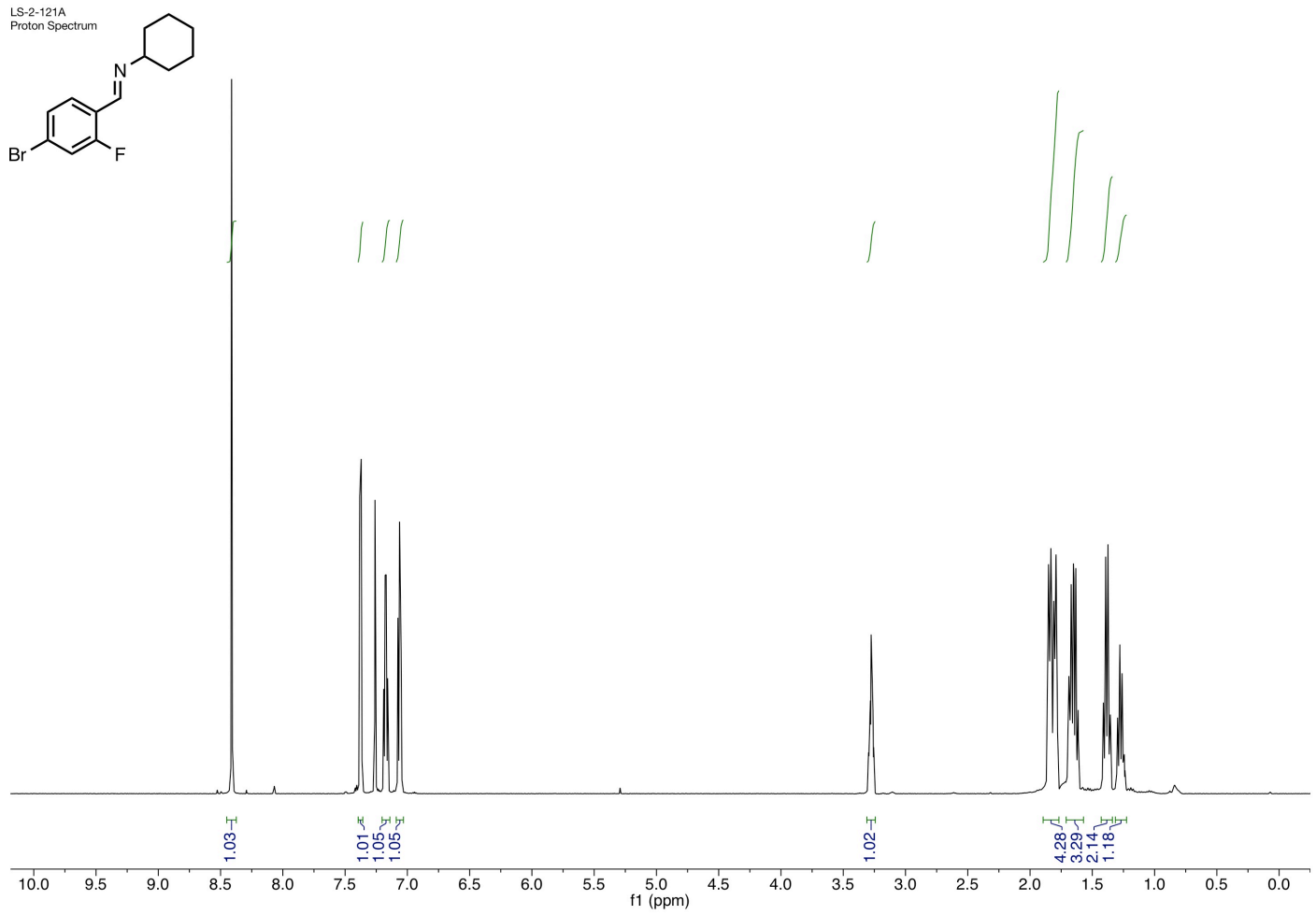
LS-2-121B-19F
STANDARD FLUORINE PARAMETERS

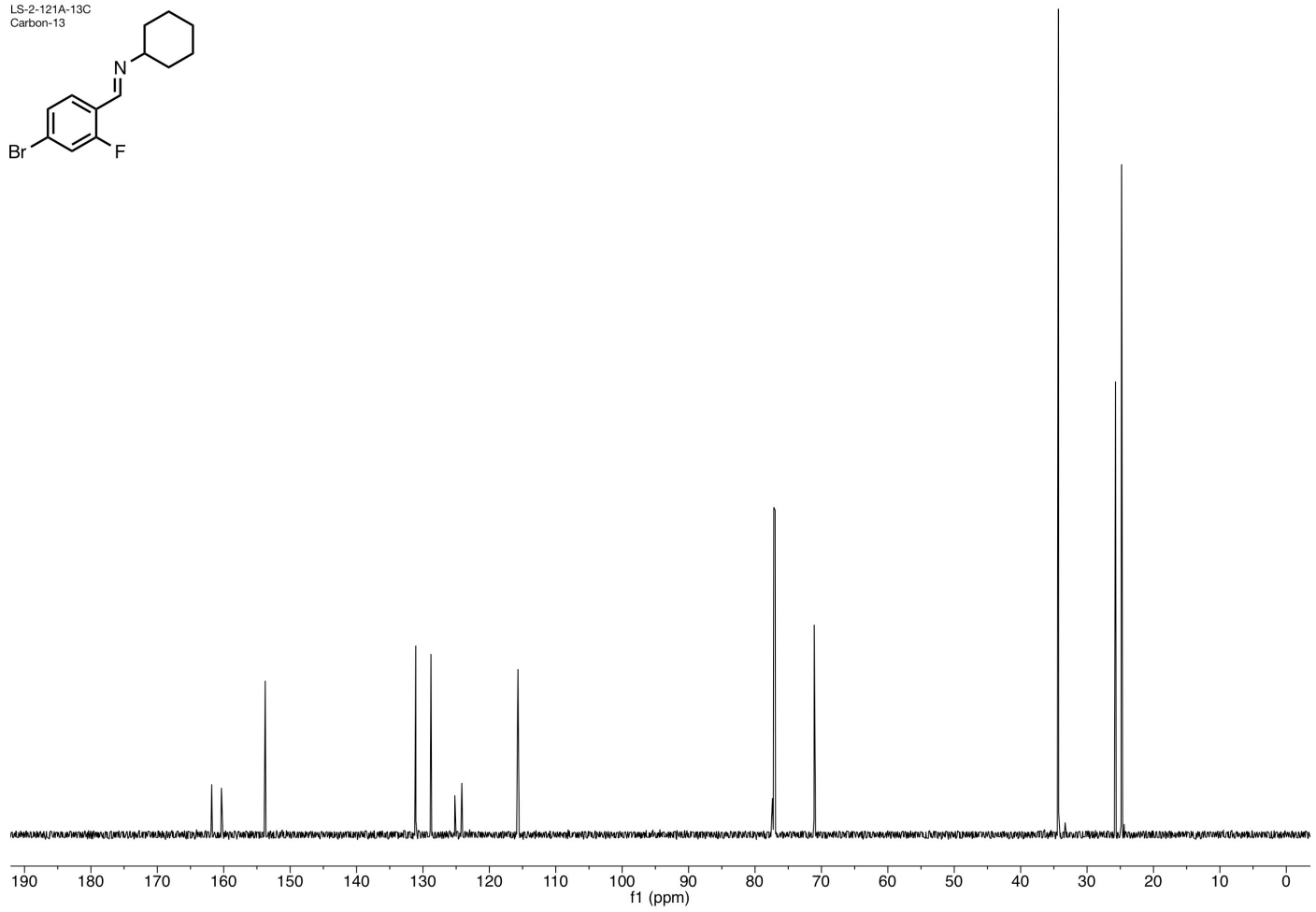


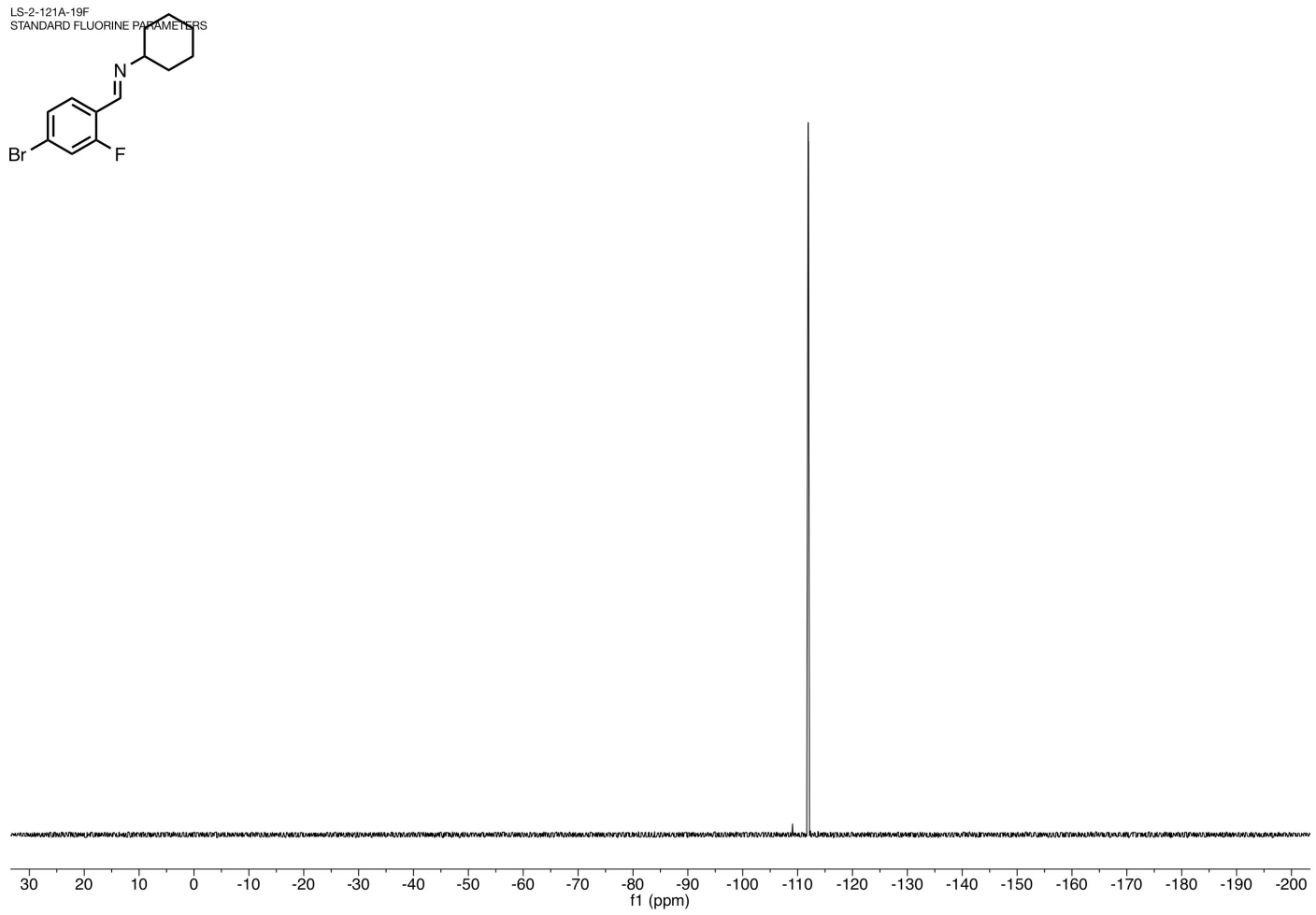


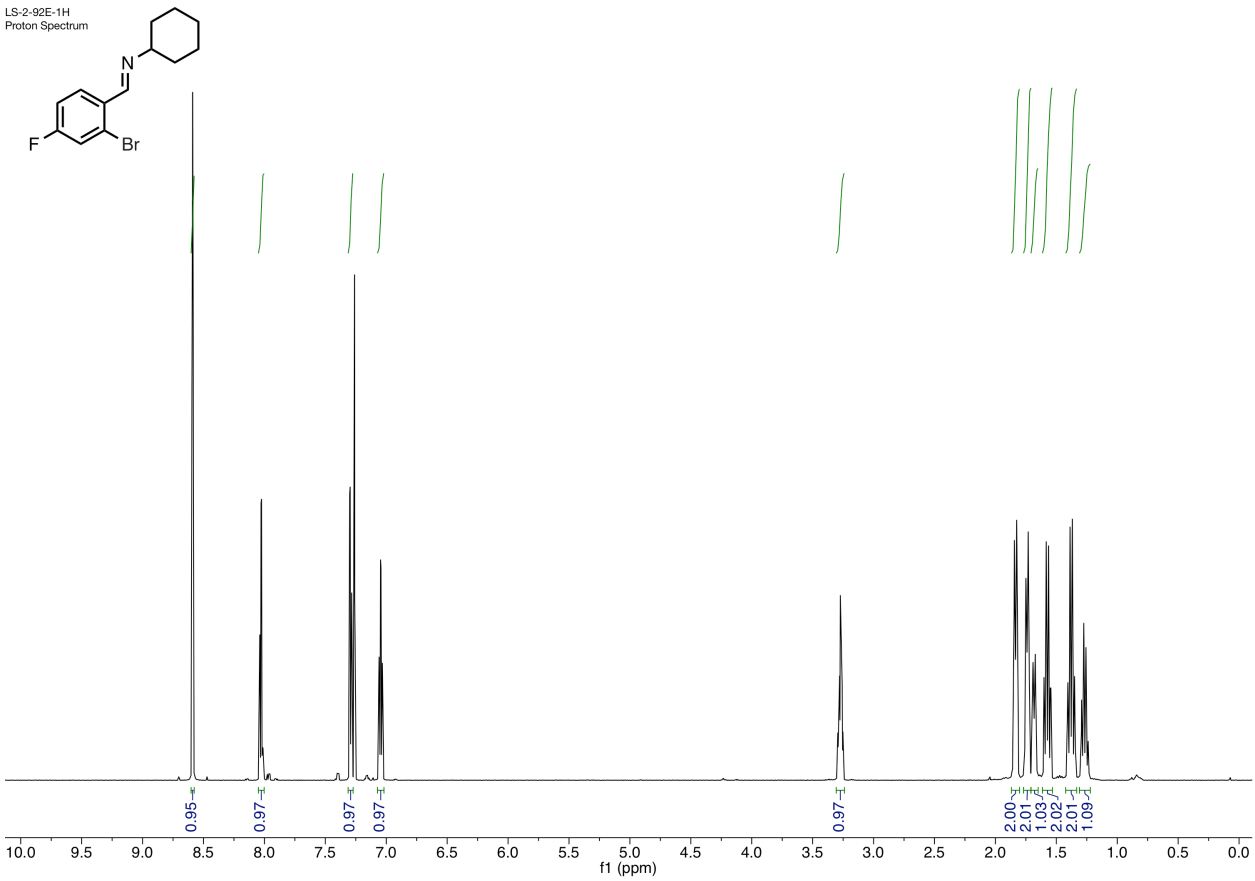

LS-2-38a-1H-ytt-25sec
Proton Spectrum
N
Br
Br
1.00
0.99
0.89
1.00
1.00
2.02
2.02
1.04
2.01
2.05
1.04
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

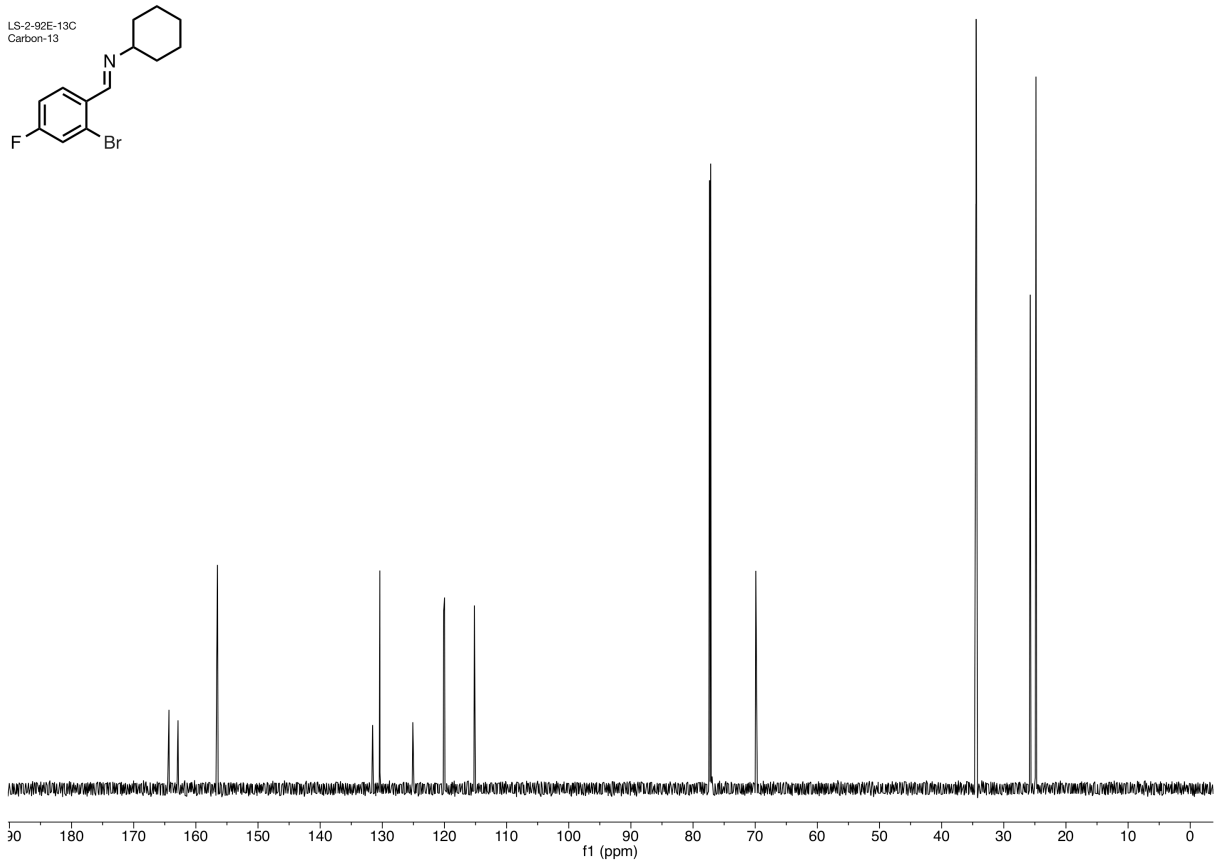

LS-2-38a-13C
Carbon-13
N
Br
Br
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

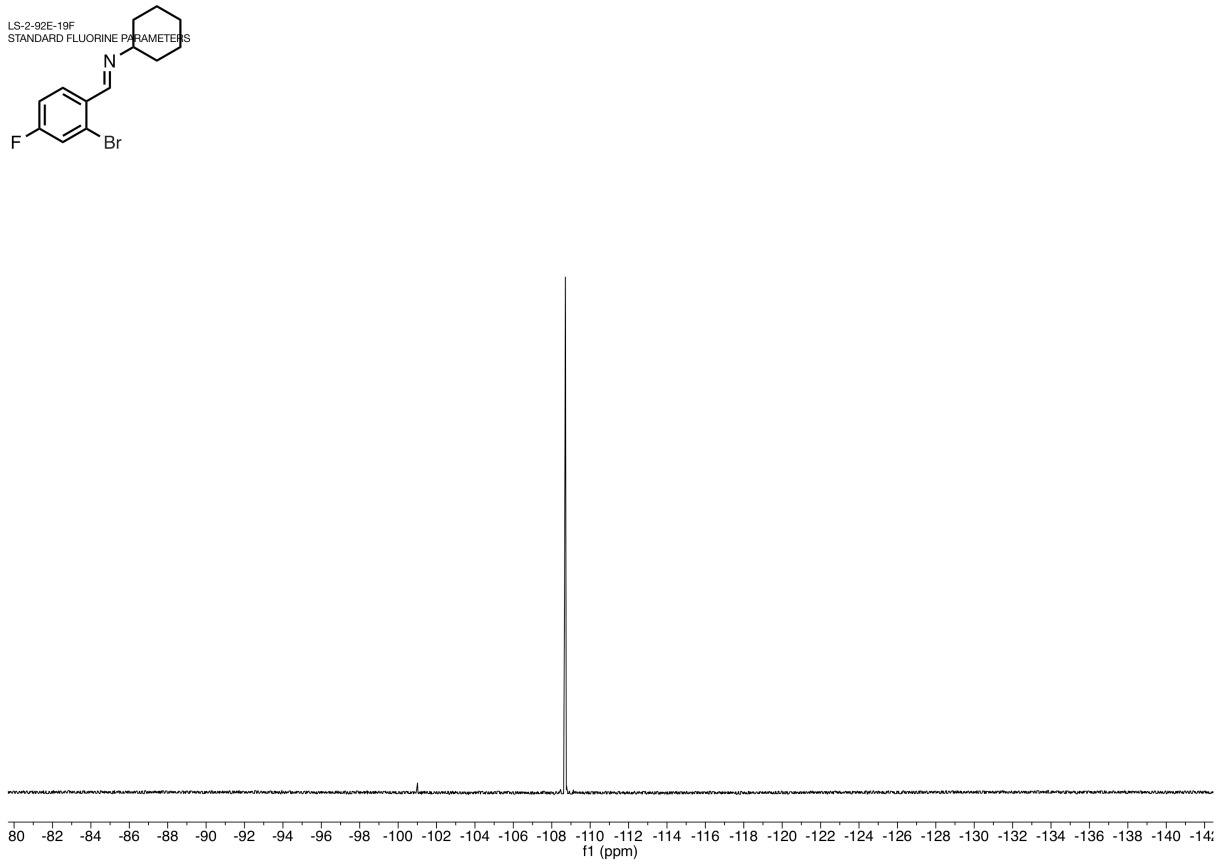

LS-2-121A
Proton Spectrum
N
Br
F
1.03
1.01
1.05
1.05
1.02
4.28
3.29
2.14
1.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

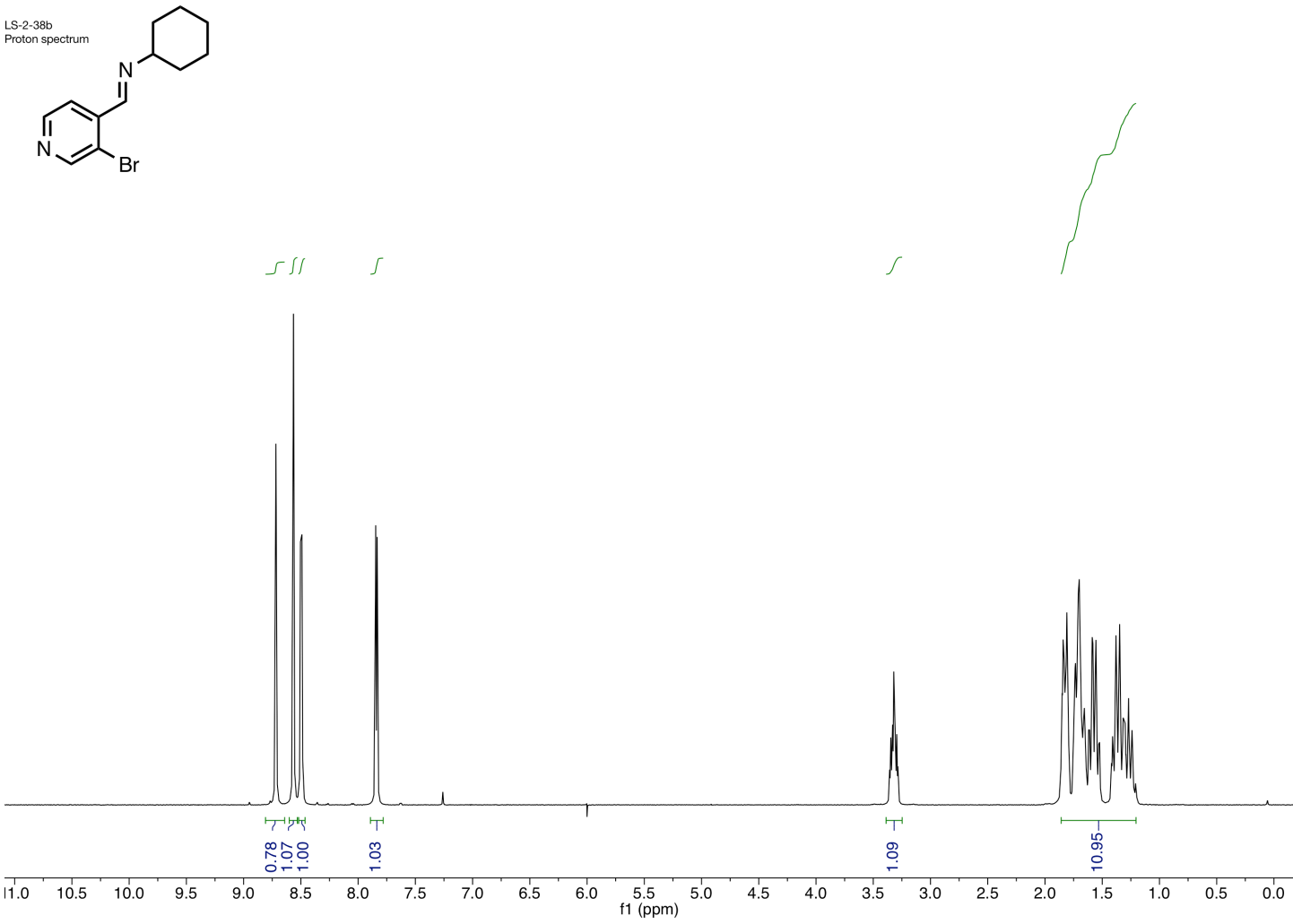

LS-2-121A-13C
Carbon-13
N
Br
F
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

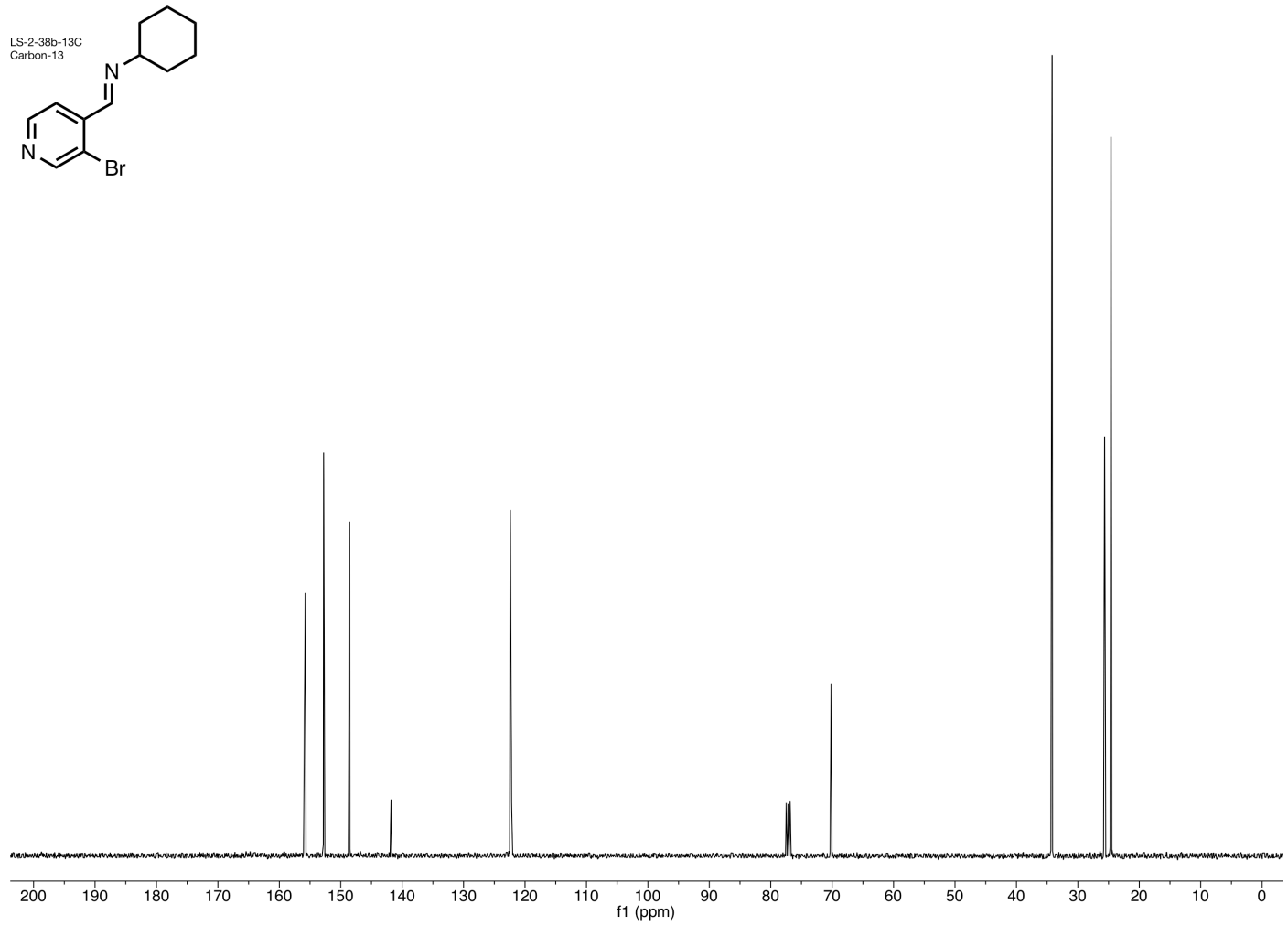

LS-2-121A-19F
STANDARD FLUORINE PARAMETERS
N
Br
F
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

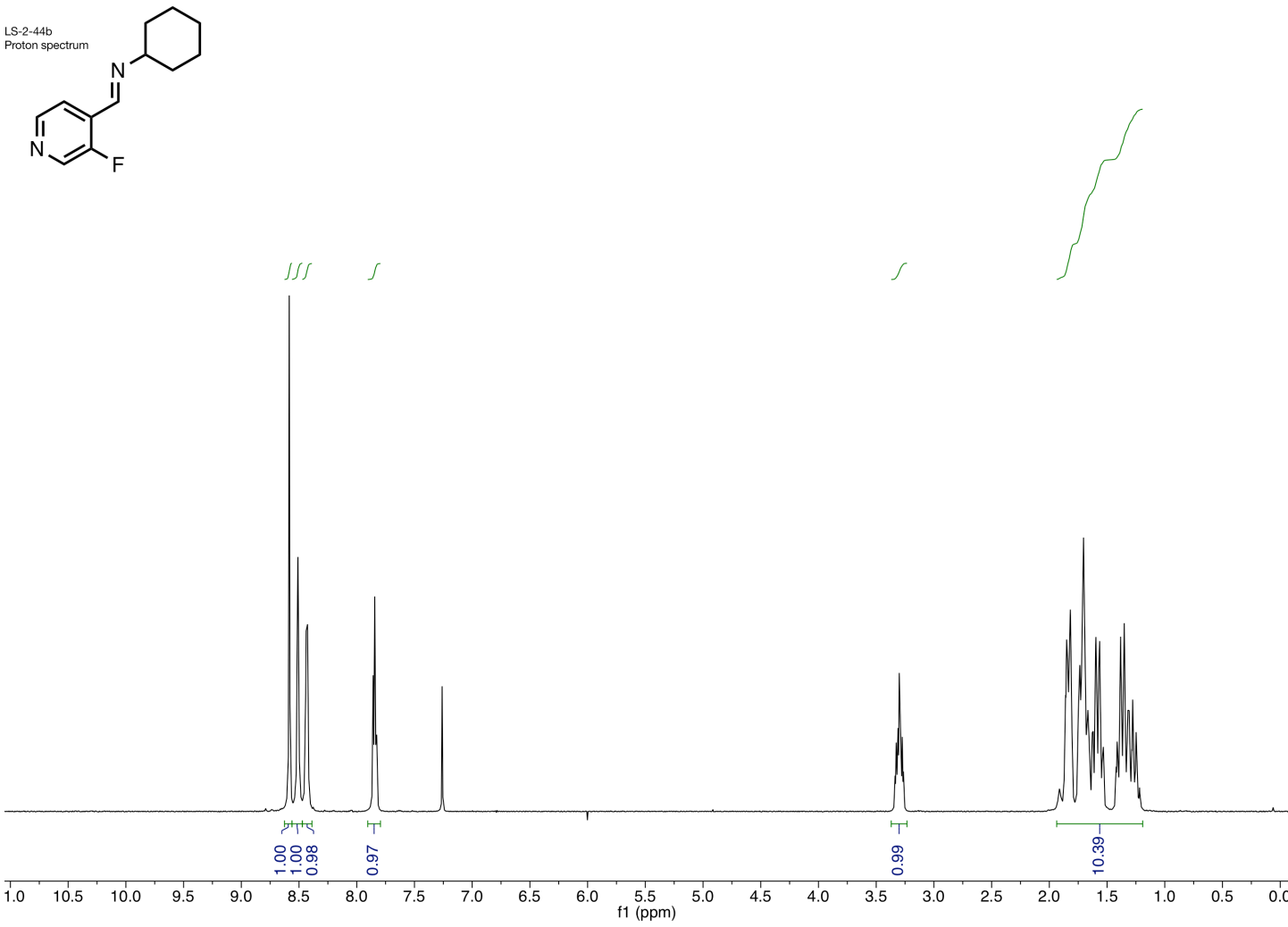

LS-2-92E-1H
Proton Spectrum
N
F
Br
0.95
0.97
0.97
0.97
0.97
2.00
2.01
1.03
2.02
2.01
1.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

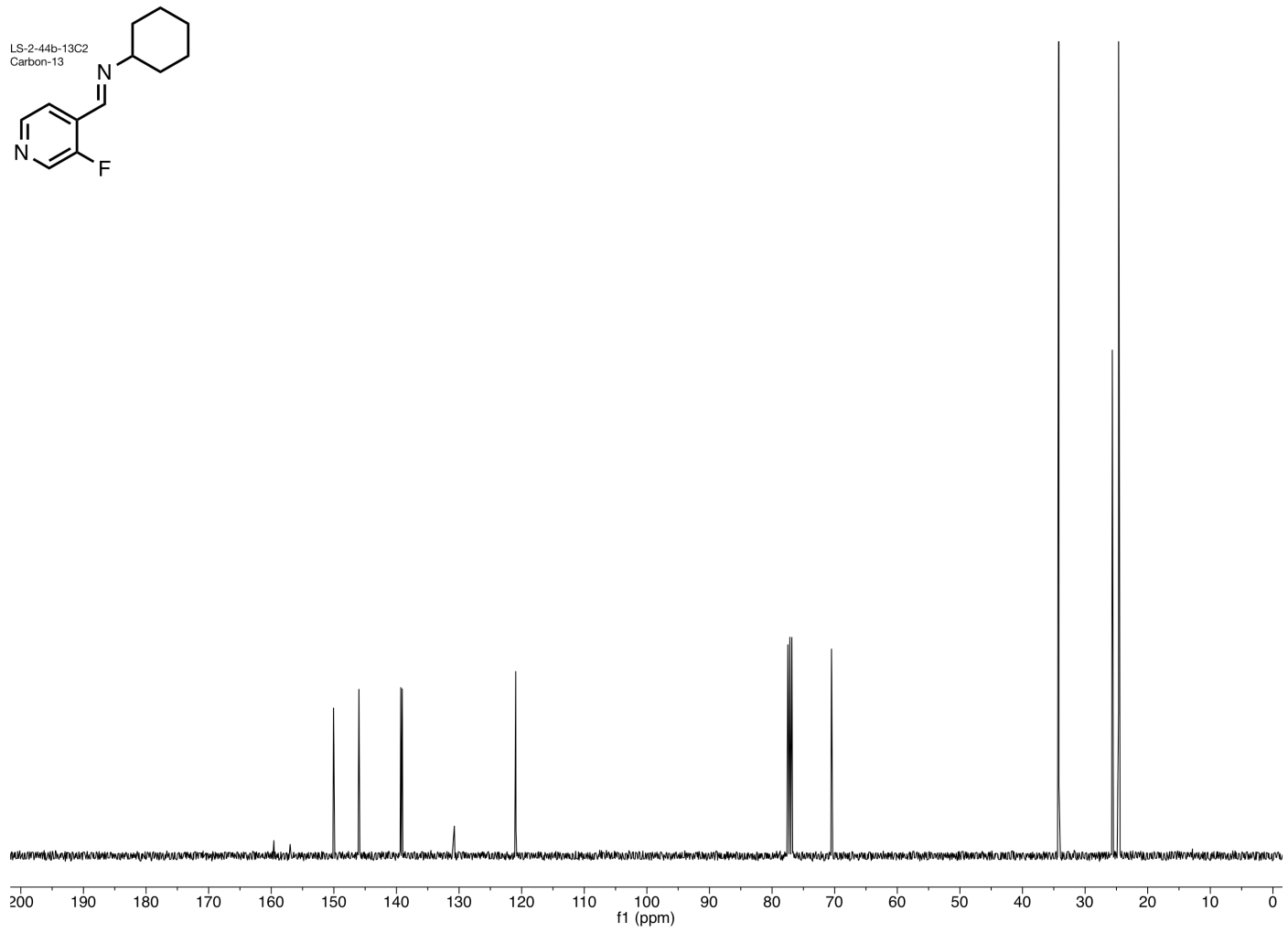

LS-2-92E-13C
Carbon-13
N
F
Br
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

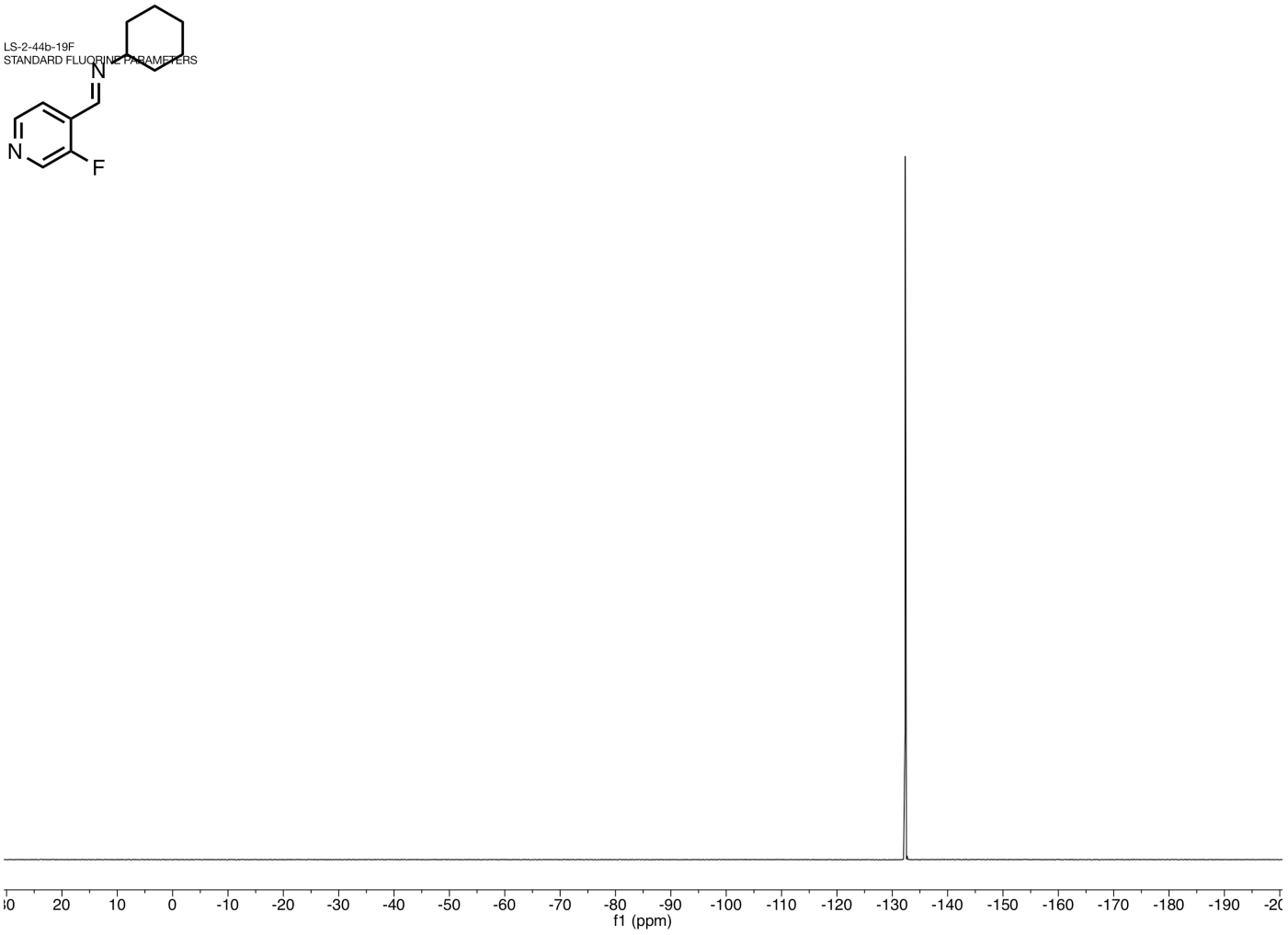

LS-2-92E-19F
STANDARD FLUORINE PARAMETERS
N
F
Br
80 -82 -84 -86 -88 -90 -92 -94 -96 -98 -100 -102 -104 -106 -108 -110 -112 -114 -116 -118 -120 -122 -124 -126 -128 -130 -132 -134 -136 -138 -140
f1 (ppm)

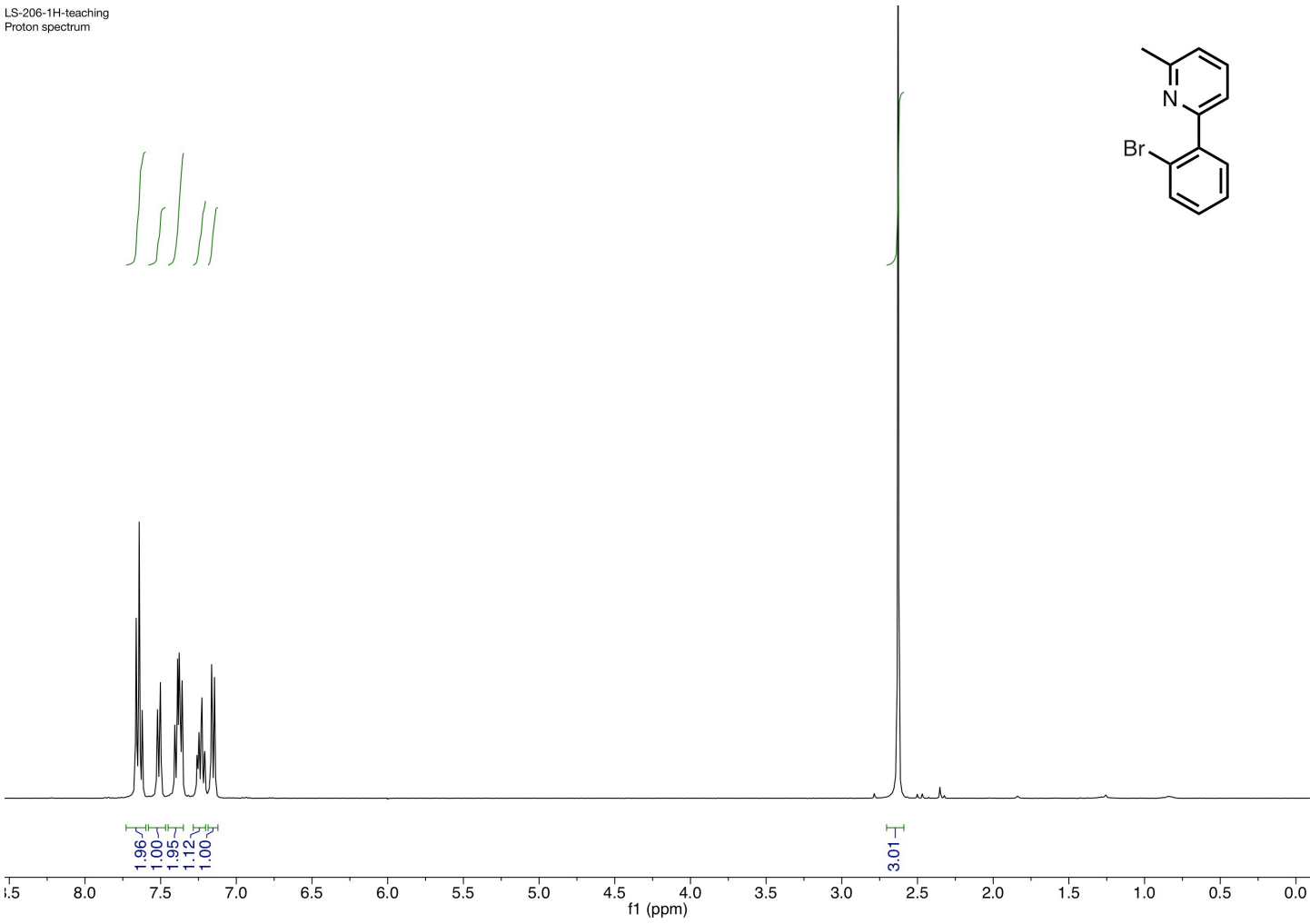

LS-2-38b
Proton spectrum
N
N
Br
0.78
1.07
1.00
1.03
1.09
10.95
f1 (ppm)

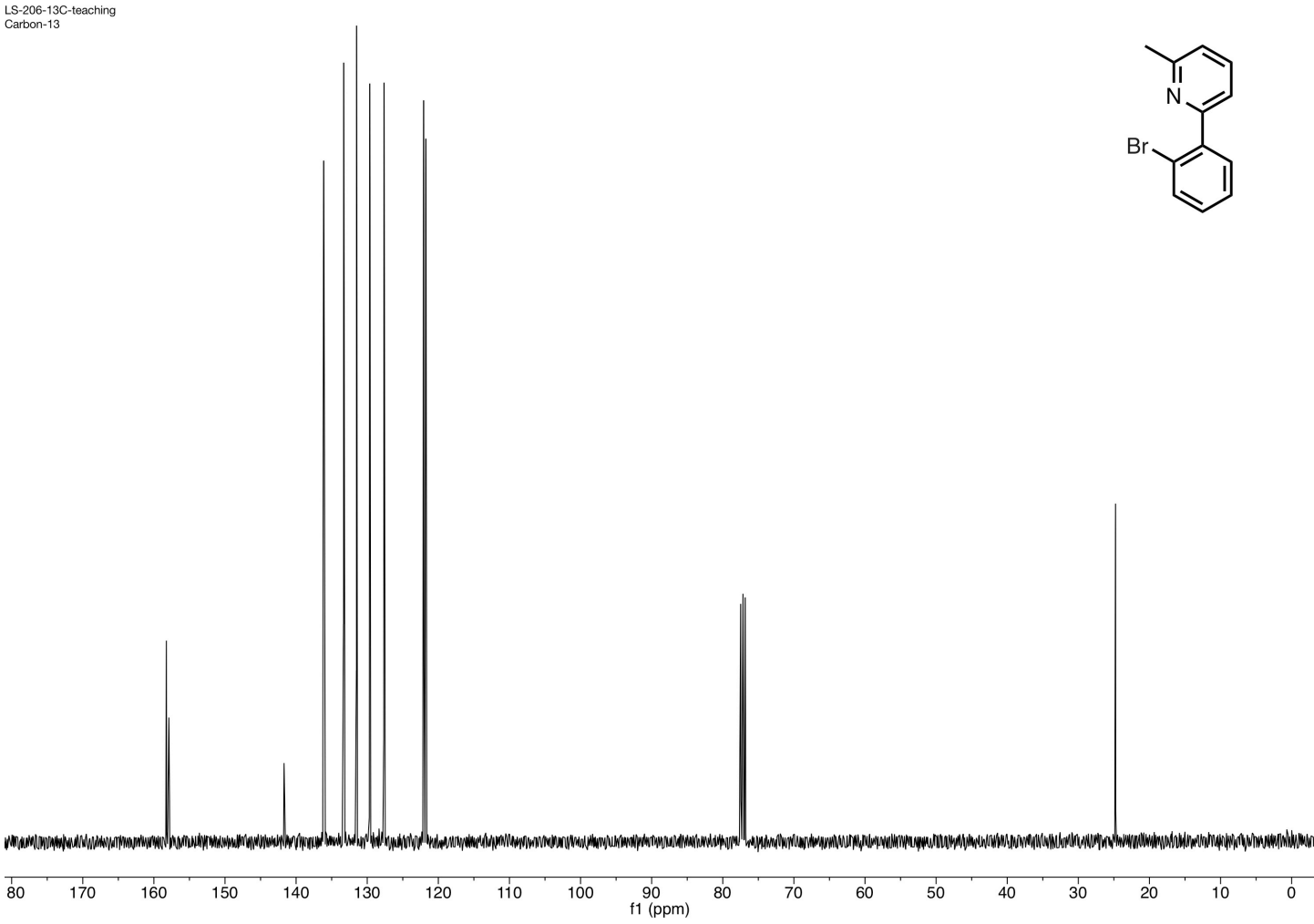

LS-2-38b-13C
Carbon-13
N
N
Br
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

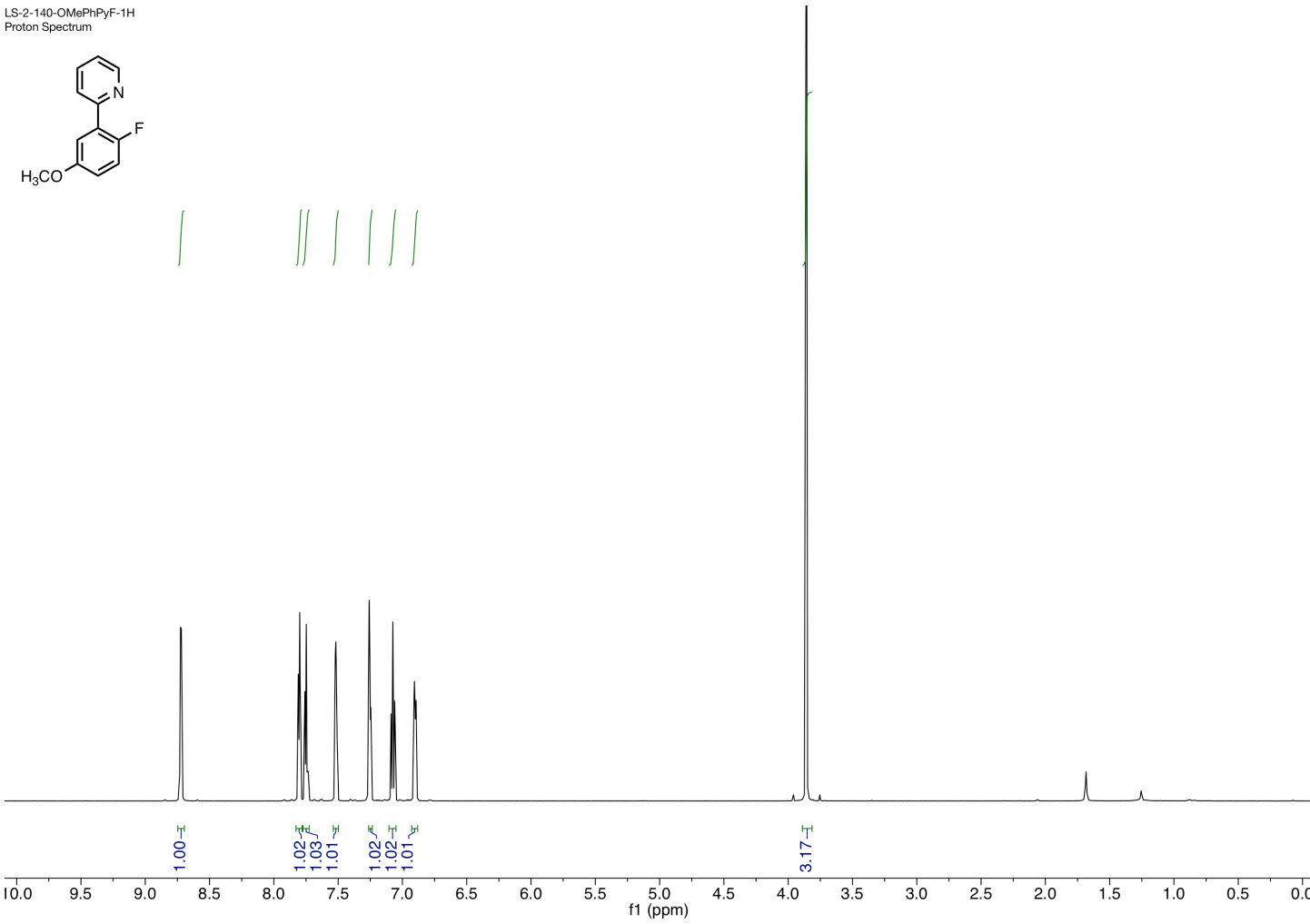

LS-2-44b
Proton spectrum
N
N
F
1.00
1.00
0.98
0.97
0.99
10.39
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

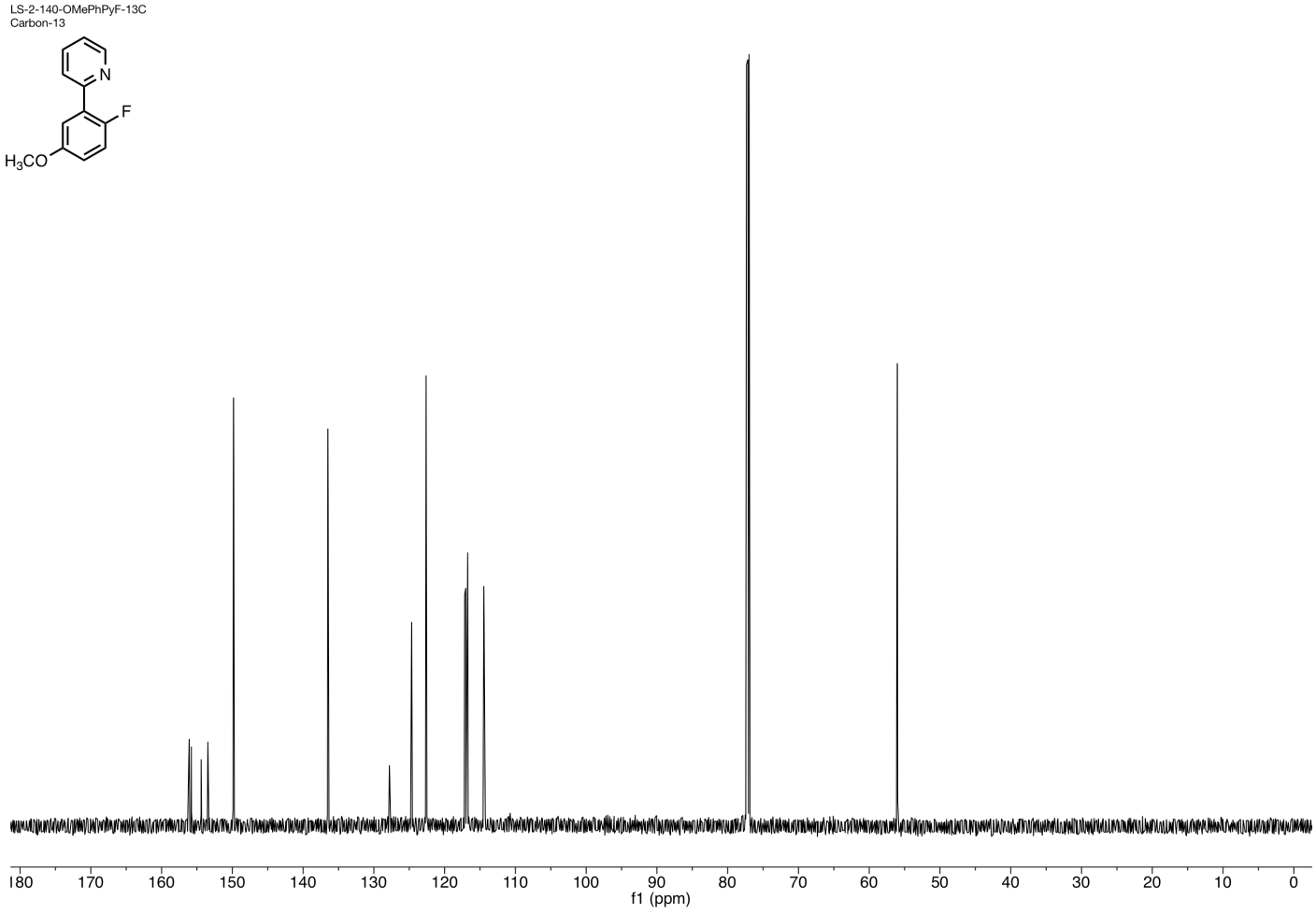

LS-2-44b-13C2
Carbon-13
N
N
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


LS-2-44b-19F
STANDARD FLUORINE PARAMETERS
N
N
F
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

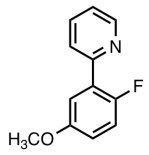

LS-206-1H-teaching
Proton spectrum
N
Br
1.96
1.00
1.95
1.12
1.00
3.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


LS-206-13C-teaching
Carbon-13
N
Br
80
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

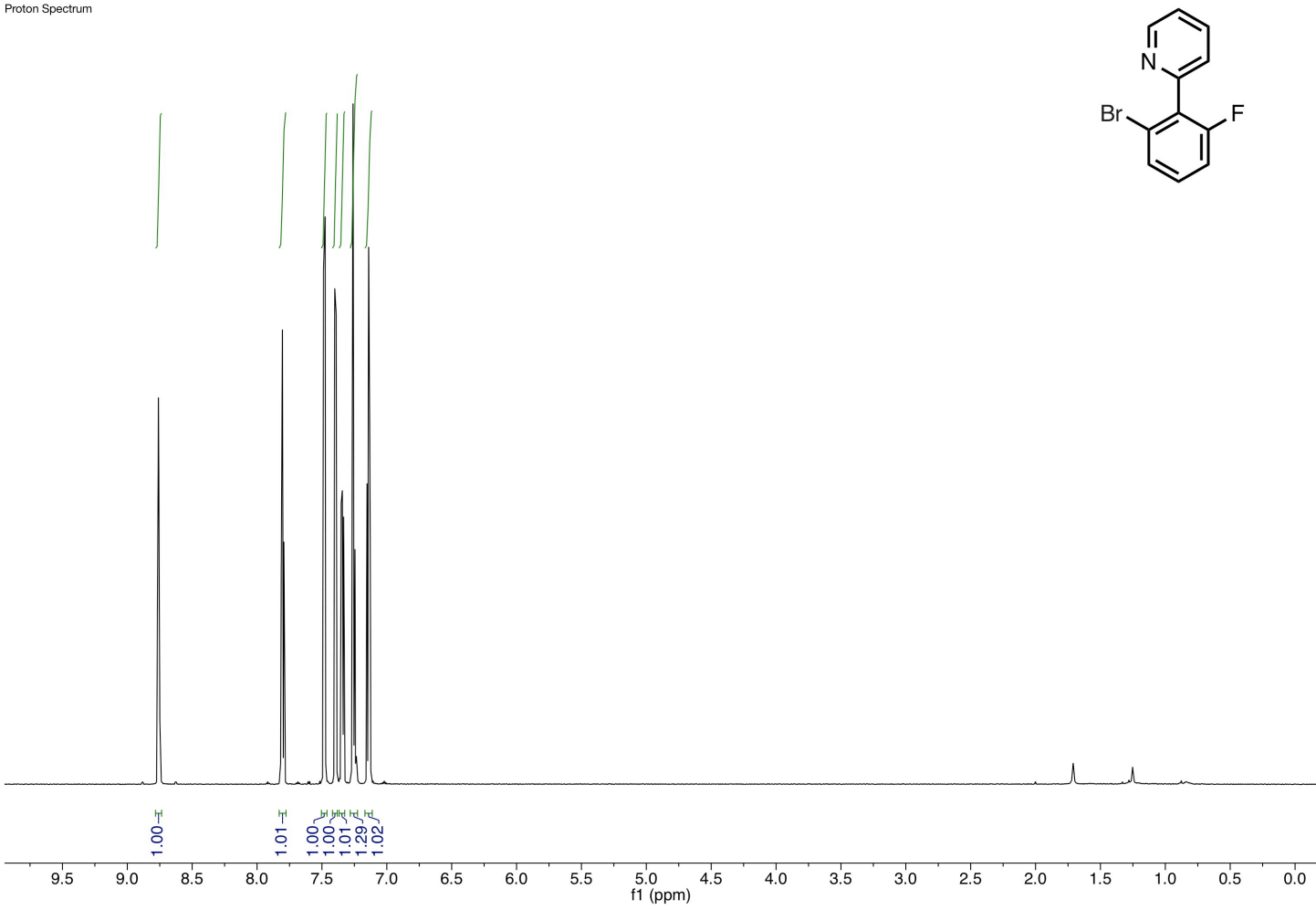

LS-2-140-OMePhPyF-1H
Proton Spectrum
N
F
H3CO
1.00
1.02
1.03
1.01
1.02
1.02
1.01
3.17
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

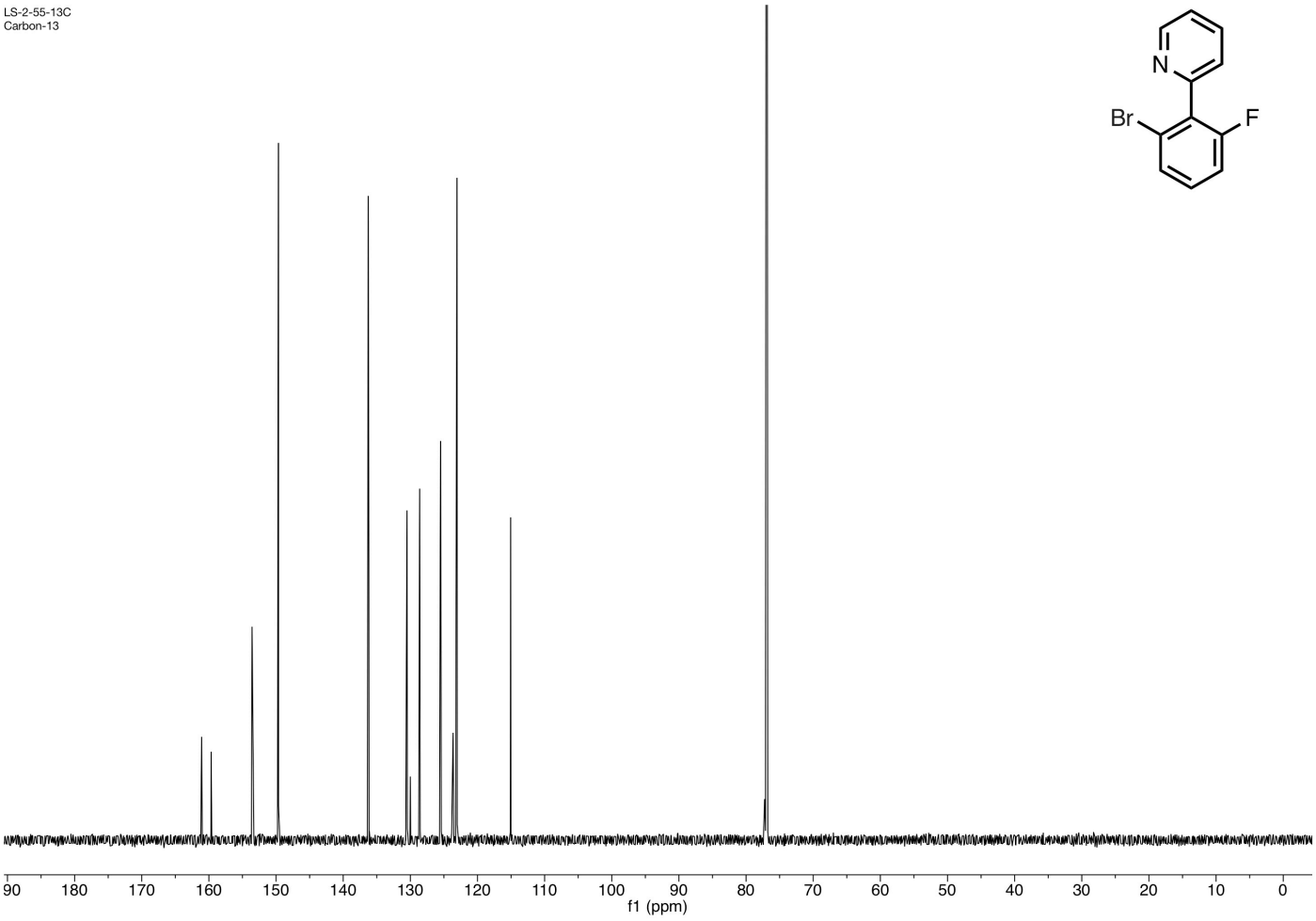

LS-2-140-OMePhPyF-13C
Carbon-13
N
F
H3CO
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-140-19F
STANDARD FLUORINE PARAMETERS

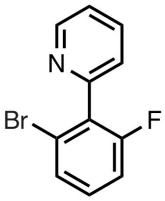


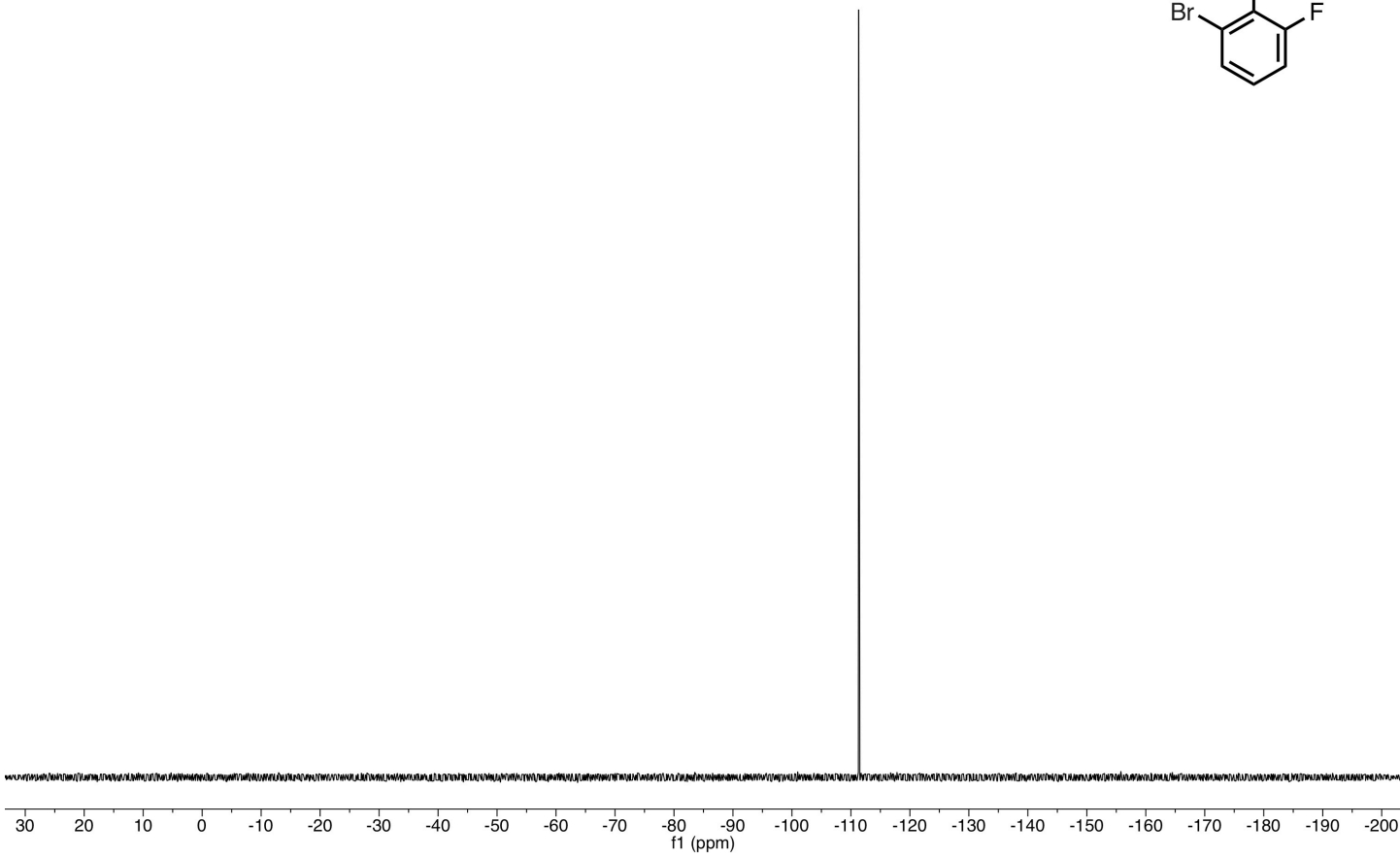
LS-2-55-1H
Proton Spectrum



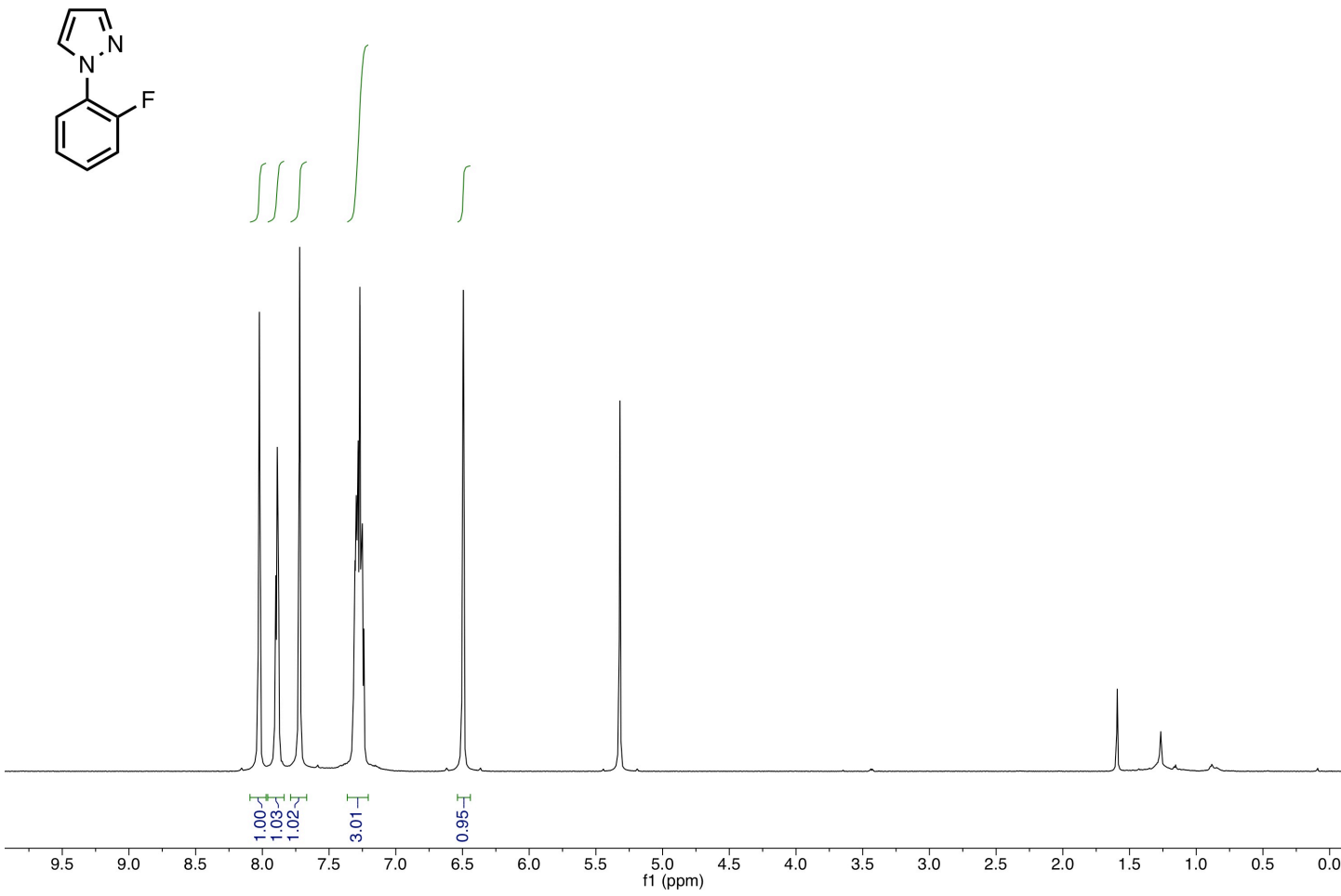

LS-2-55-13C
Carbon-13
N
Br
F
90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

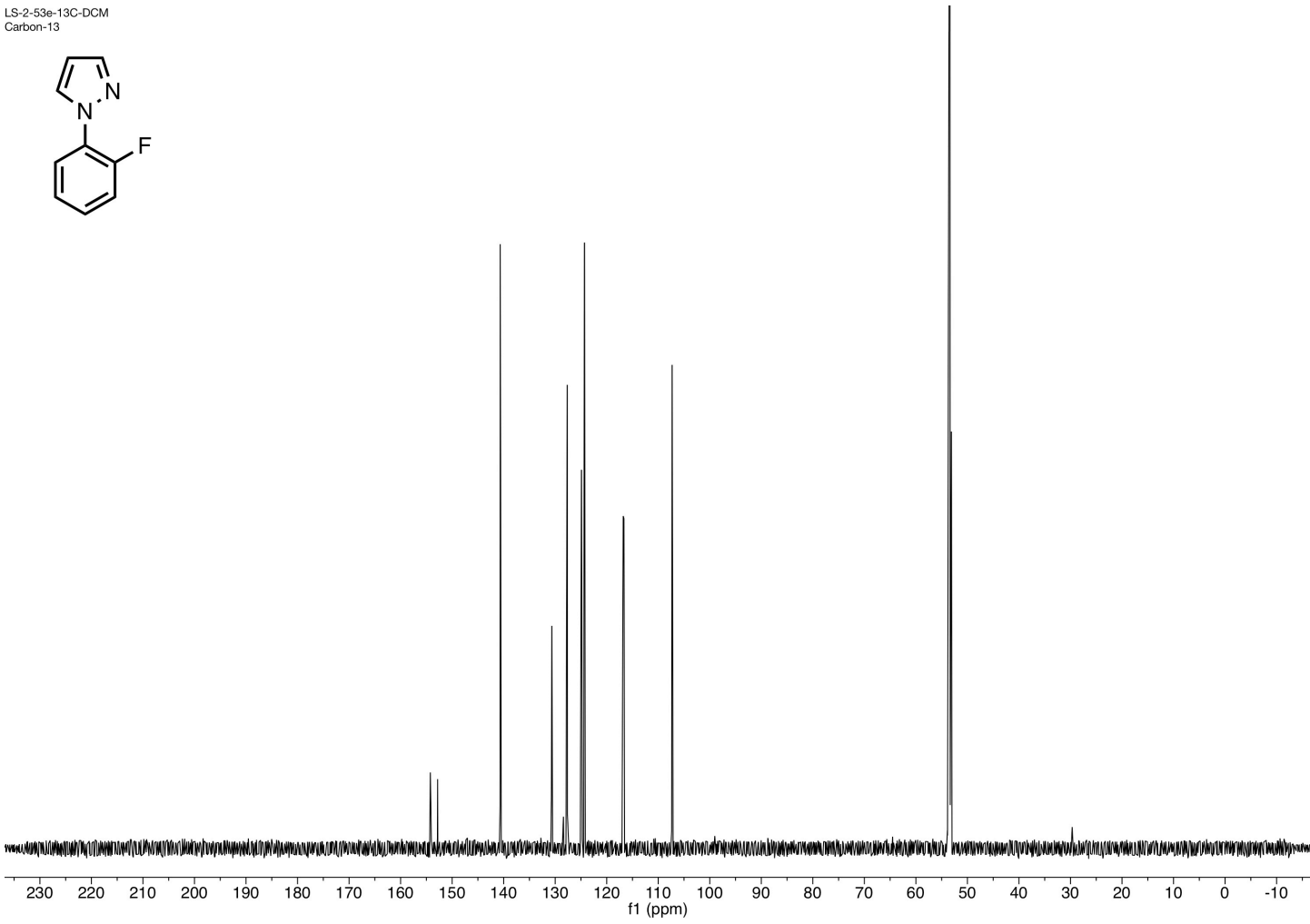
LS-2-55-19F
STANDARD FLUORINE PARAMETERS



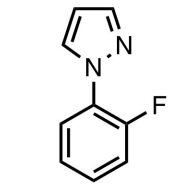


LS-2-53e-DCM
Proton Spectrum

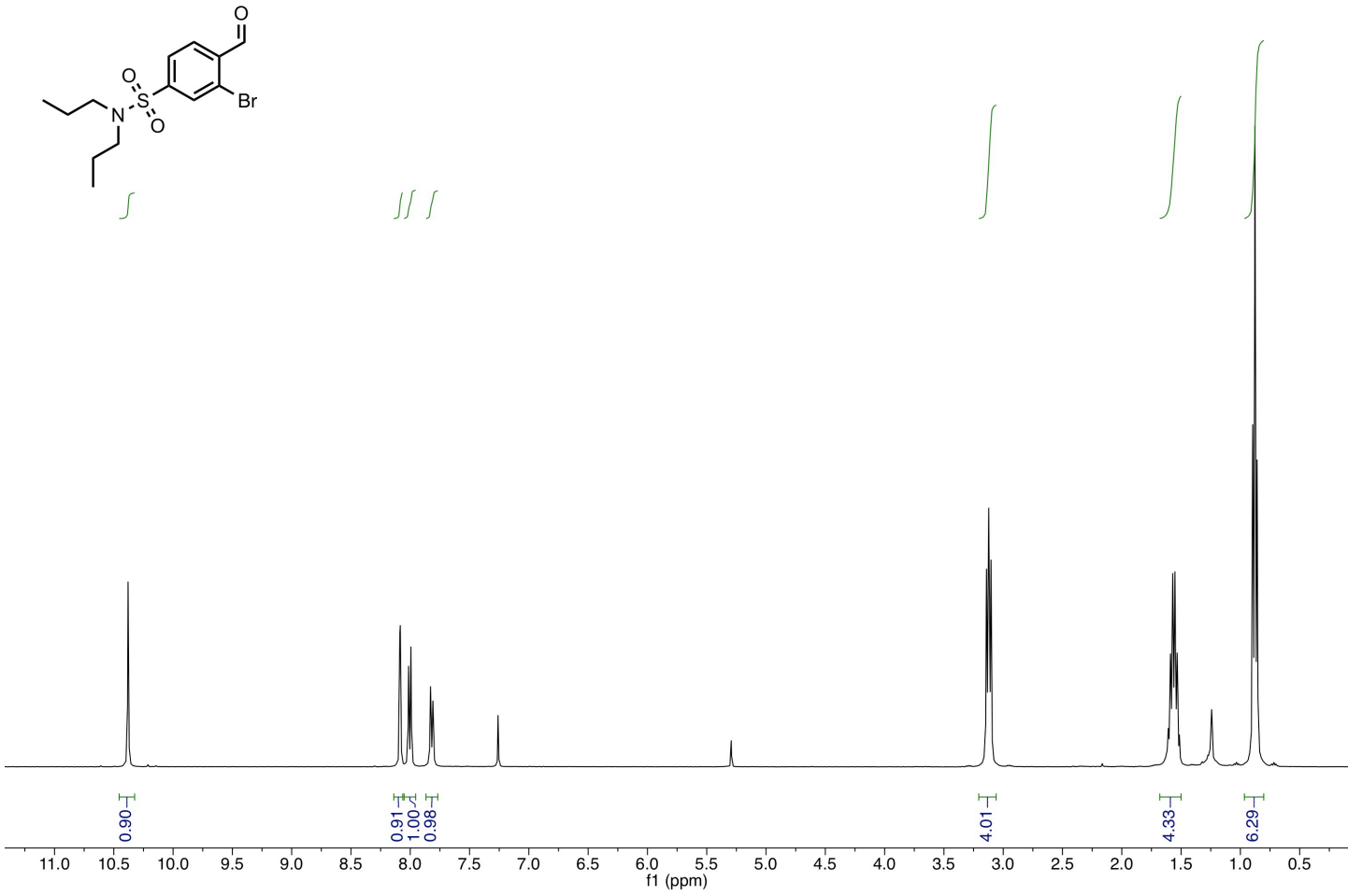



LS-2-53e-13C-DCM
Carbon-13
N
N
F
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

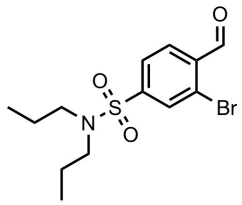
LS-2-53e-19F-CD2Cl2
STANDARD FLUORINE PARAMETERS

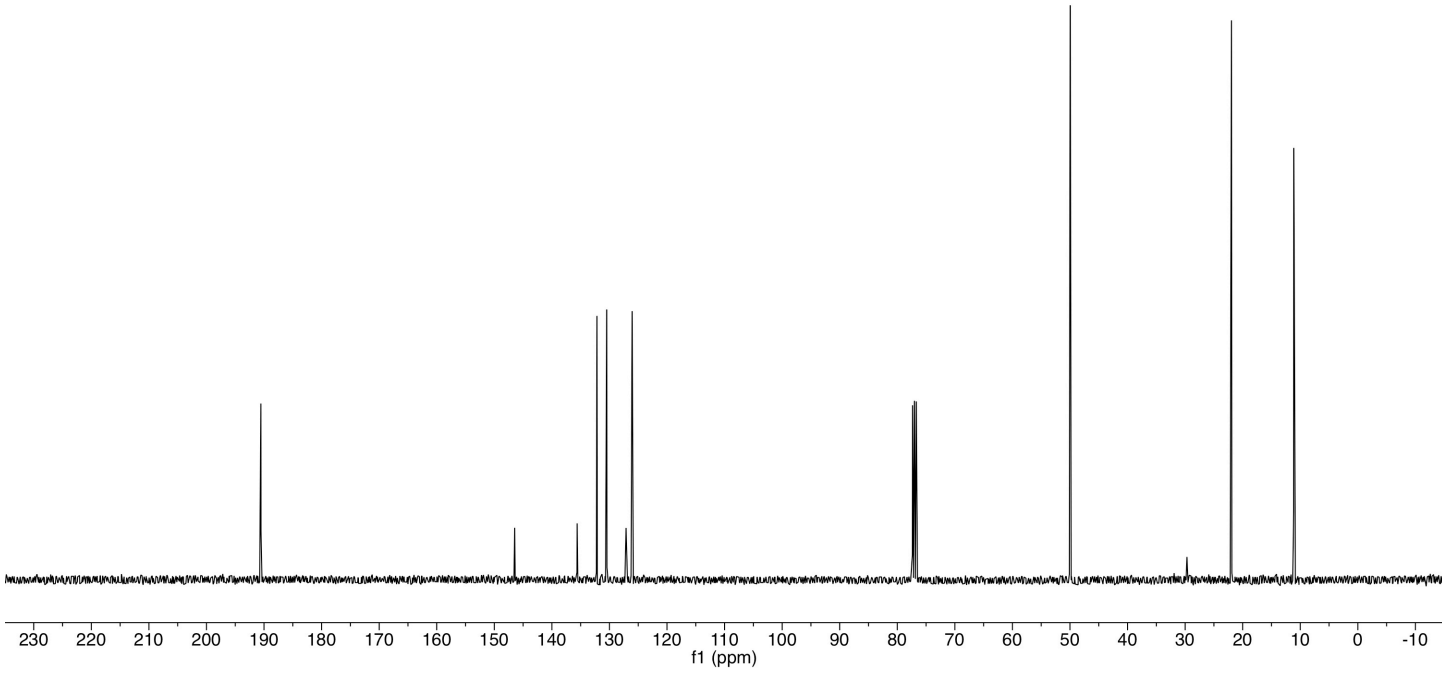


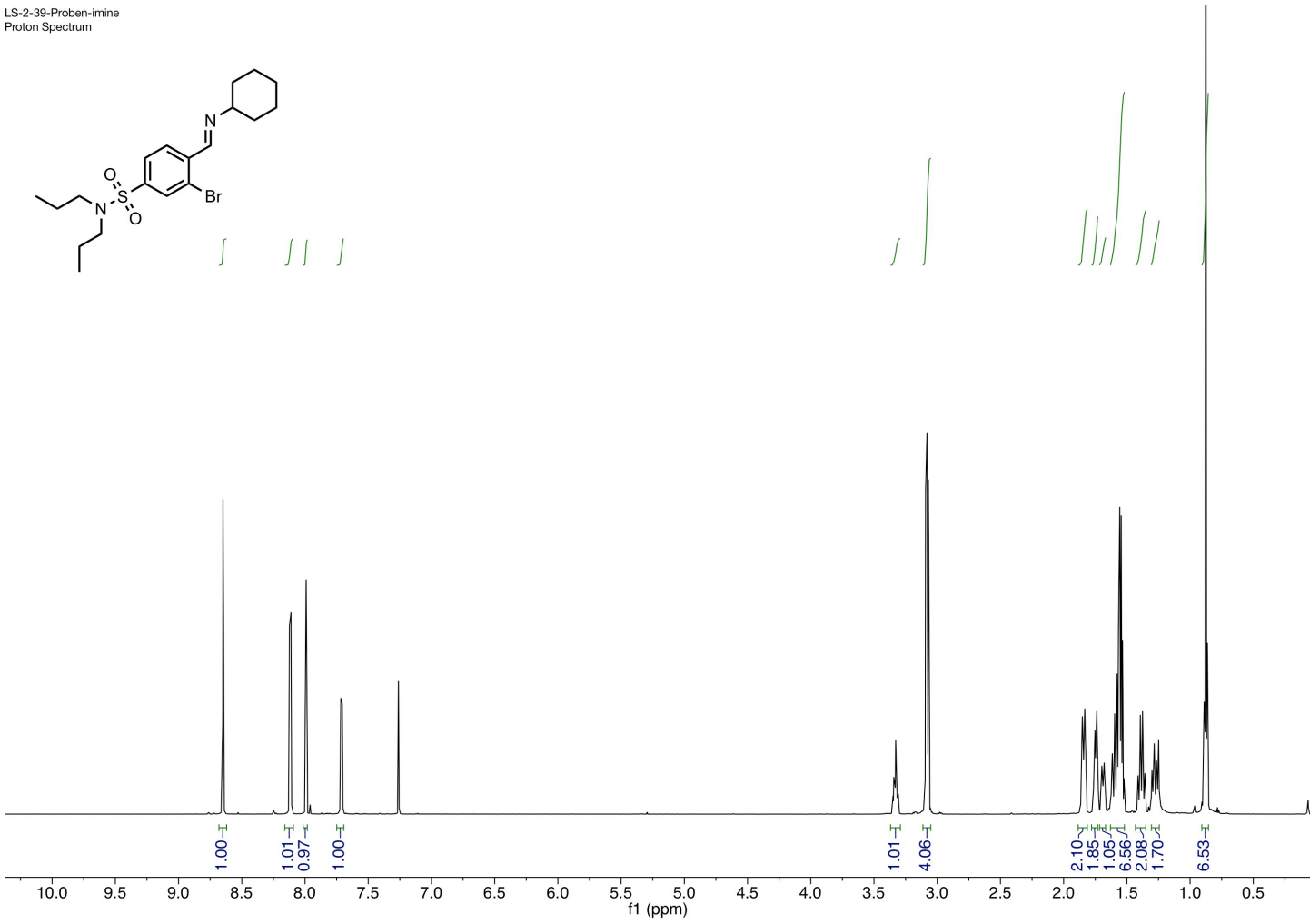
LS-2-35-columned-1H-longrelax-teachingNMR
Proton spectrum



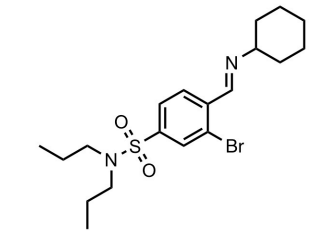
LS-2-35-columned-13C-teachingNMR
Carbon-13

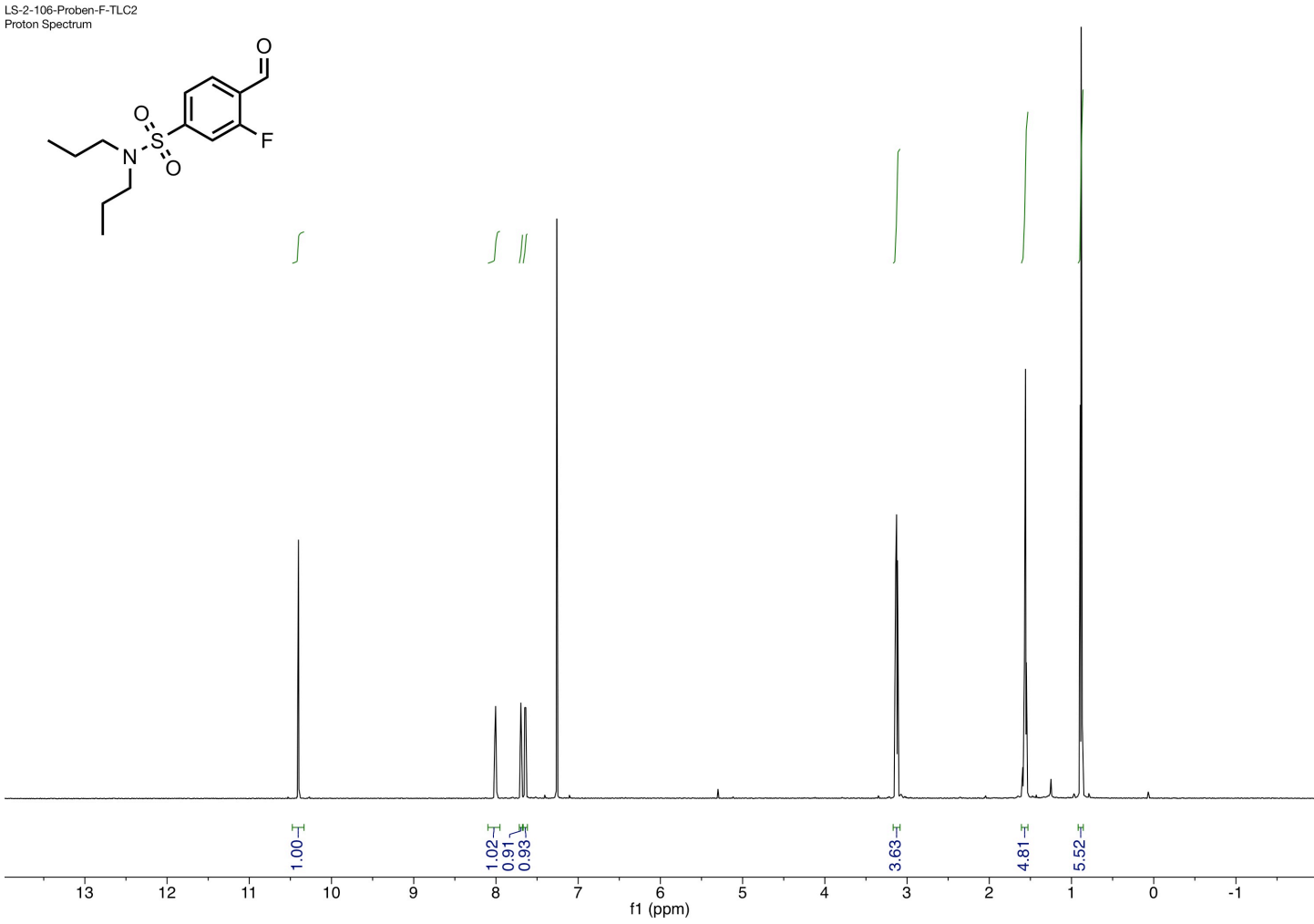


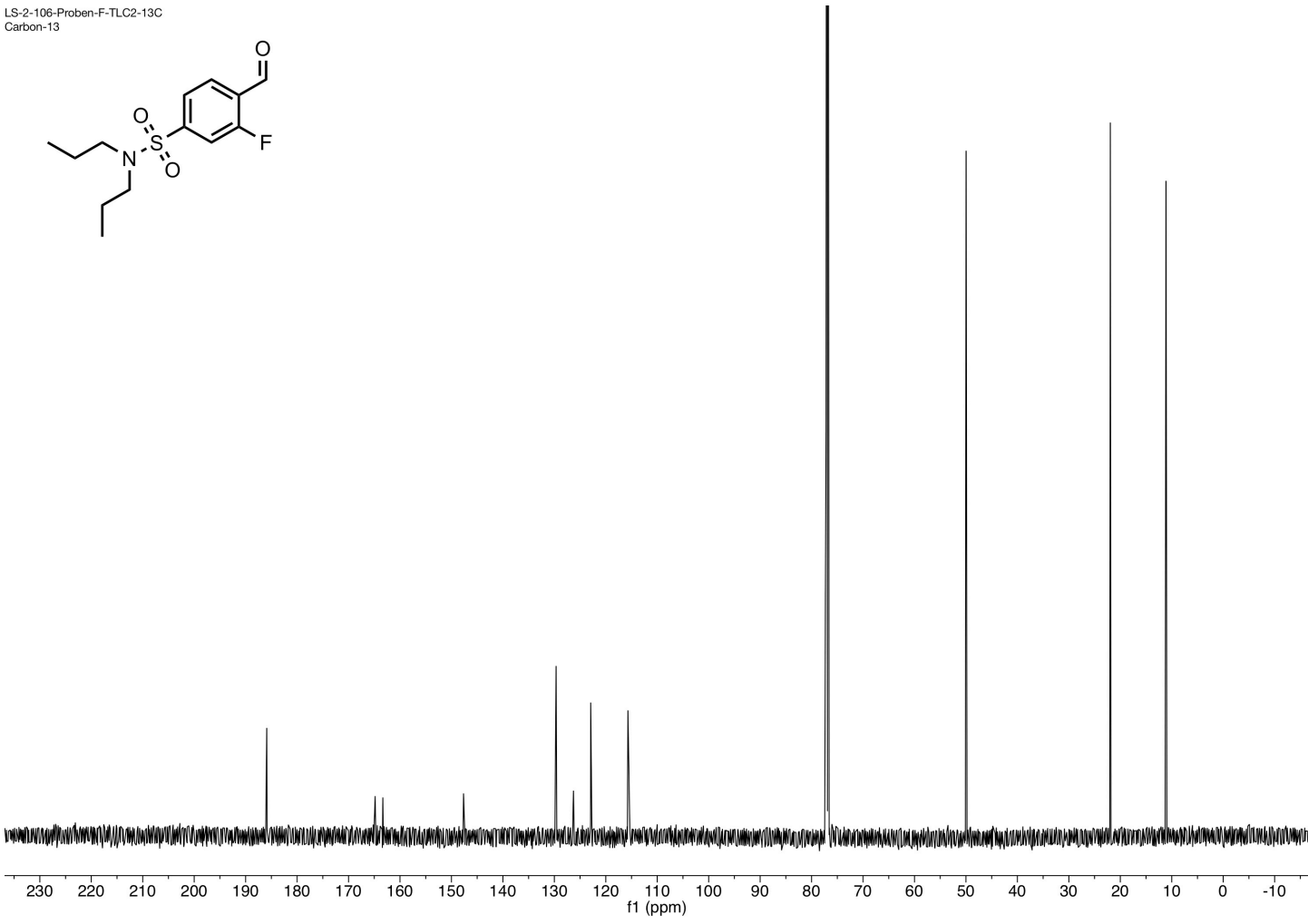



LS-2-39-Proben-imine
Proton Spectrum
N
O
S
O
N
Br
1.00
1.01
0.97
1.00
1.01
4.06
2.10
1.85
1.05
6.56
2.08
1.70
6.53
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

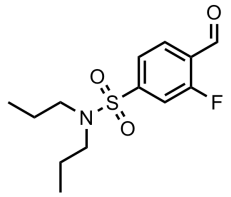
LS-2-39-Proben-imine-13C
Carbon-13

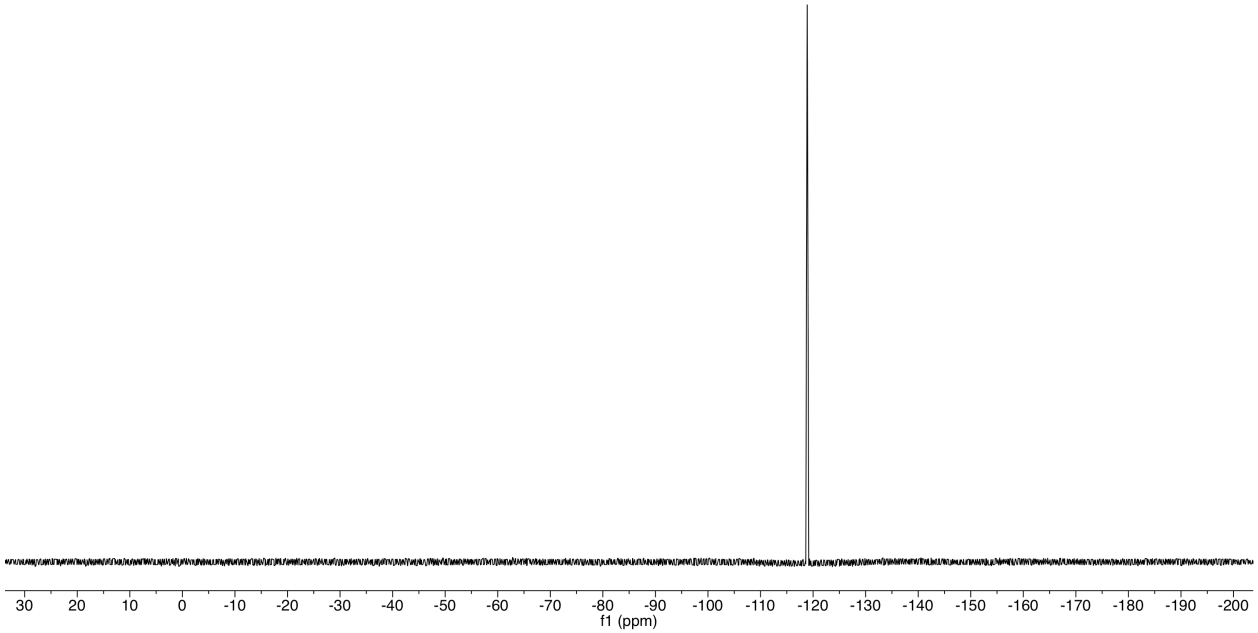


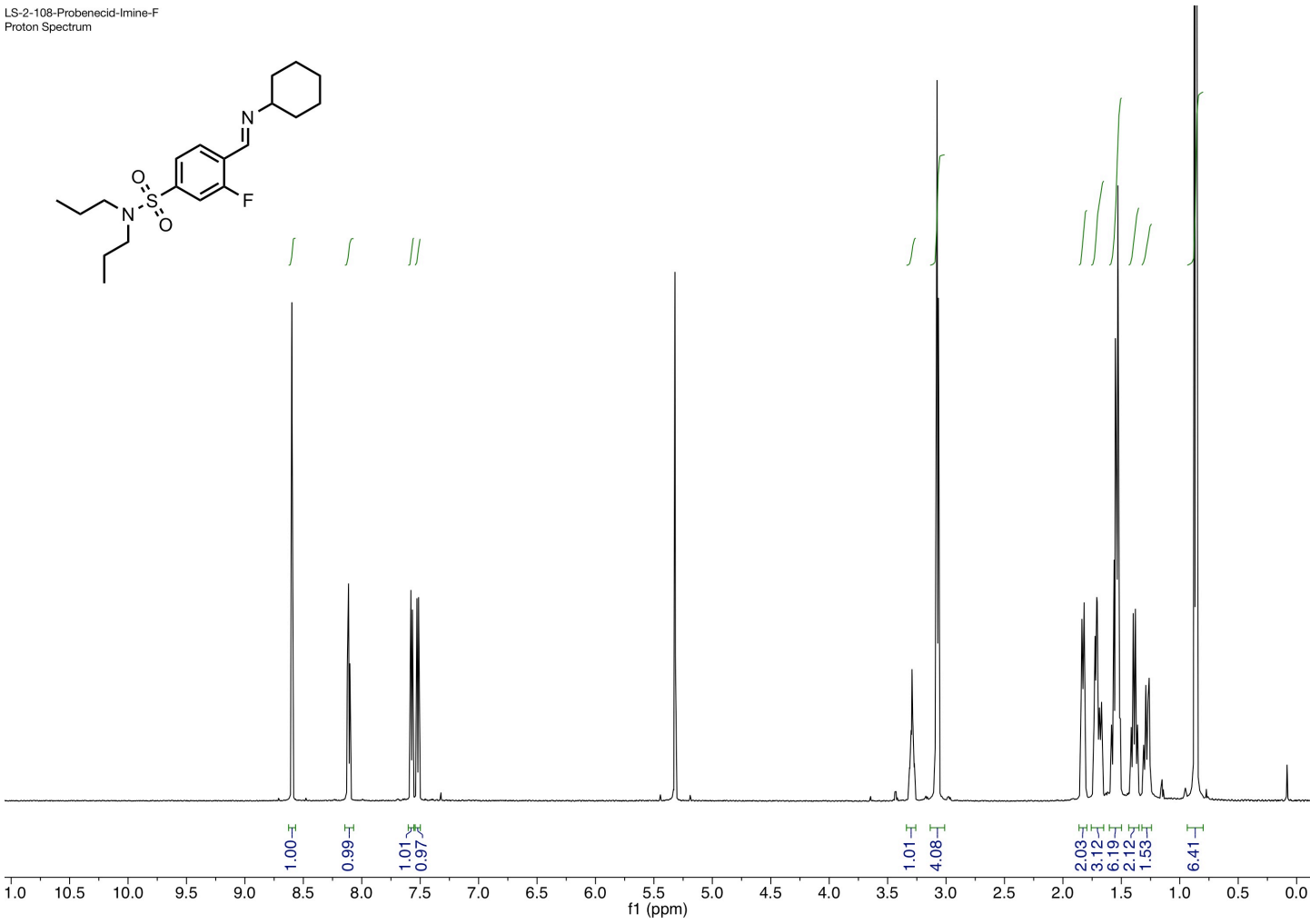

LS-2-106-Proben-F-TLC2
Proton Spectrum
O
O
S
O
N
F
1.00
1.02
0.91
0.93
3.63
4.81
5.52
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

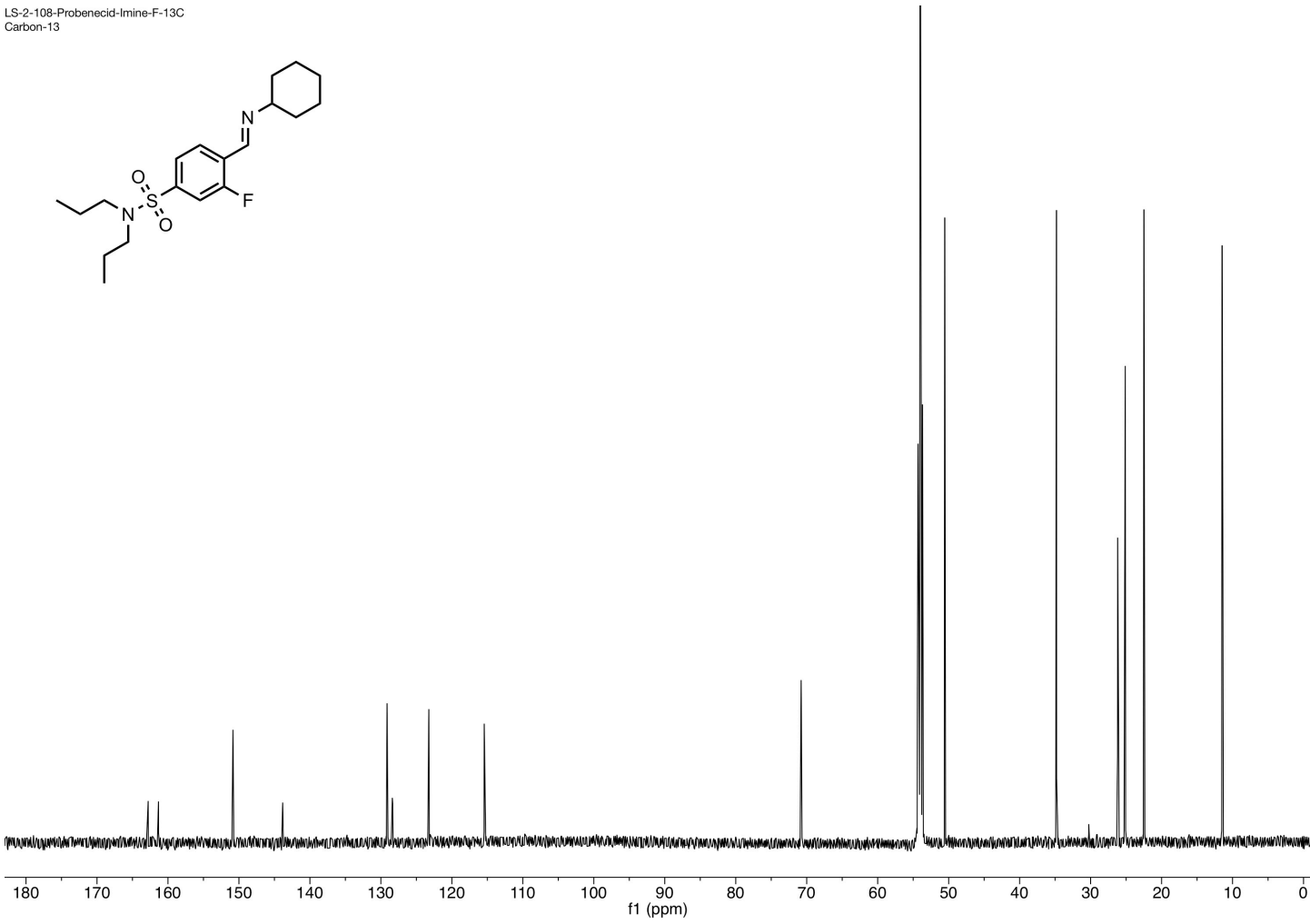

LS-2-106-Proben-F-TLC2-13C
Carbon-13
O
O
S
N
O
F
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

LS-2-106-Probenecid-F-19F
Fluorine-19

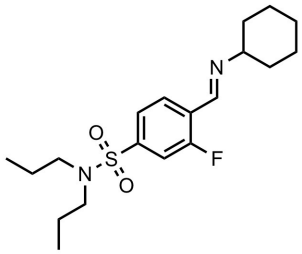


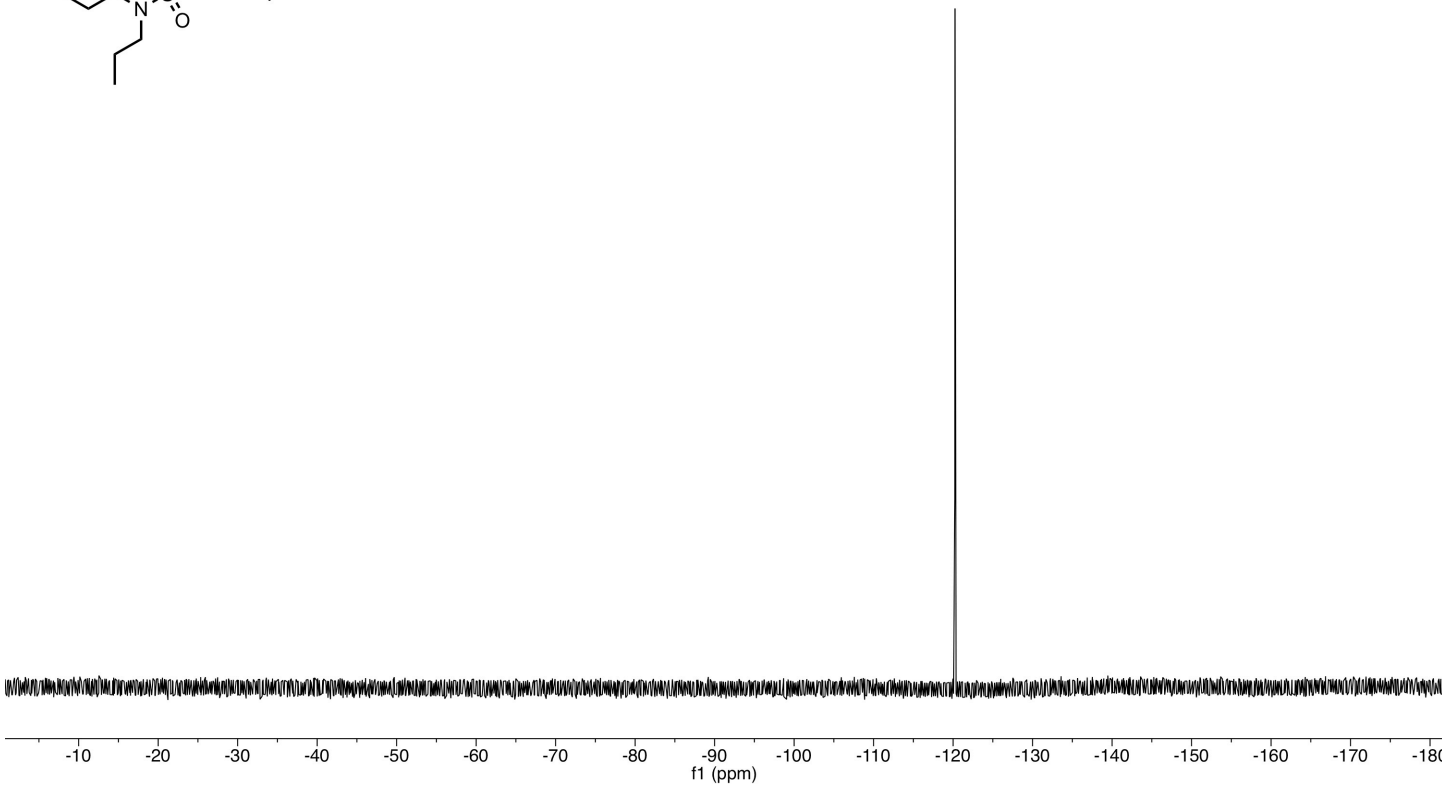


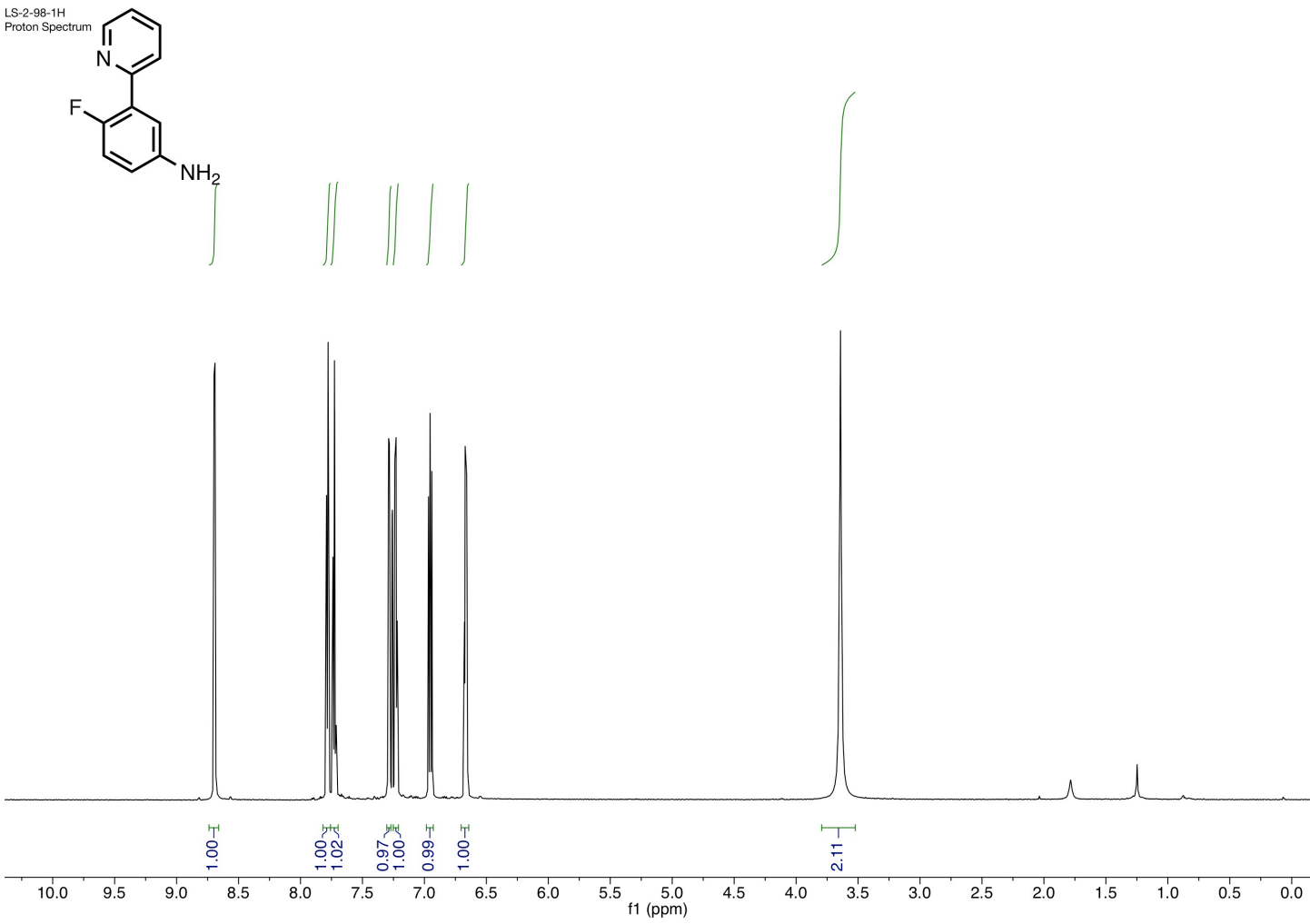

LS-2-108-Probenecid-Imine-F
Proton Spectrum
N
O
S
O
N
F
1.00
0.99
1.01
0.97
1.01
4.08
2.03
3.12
6.19
2.12
1.53
6.41
1.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

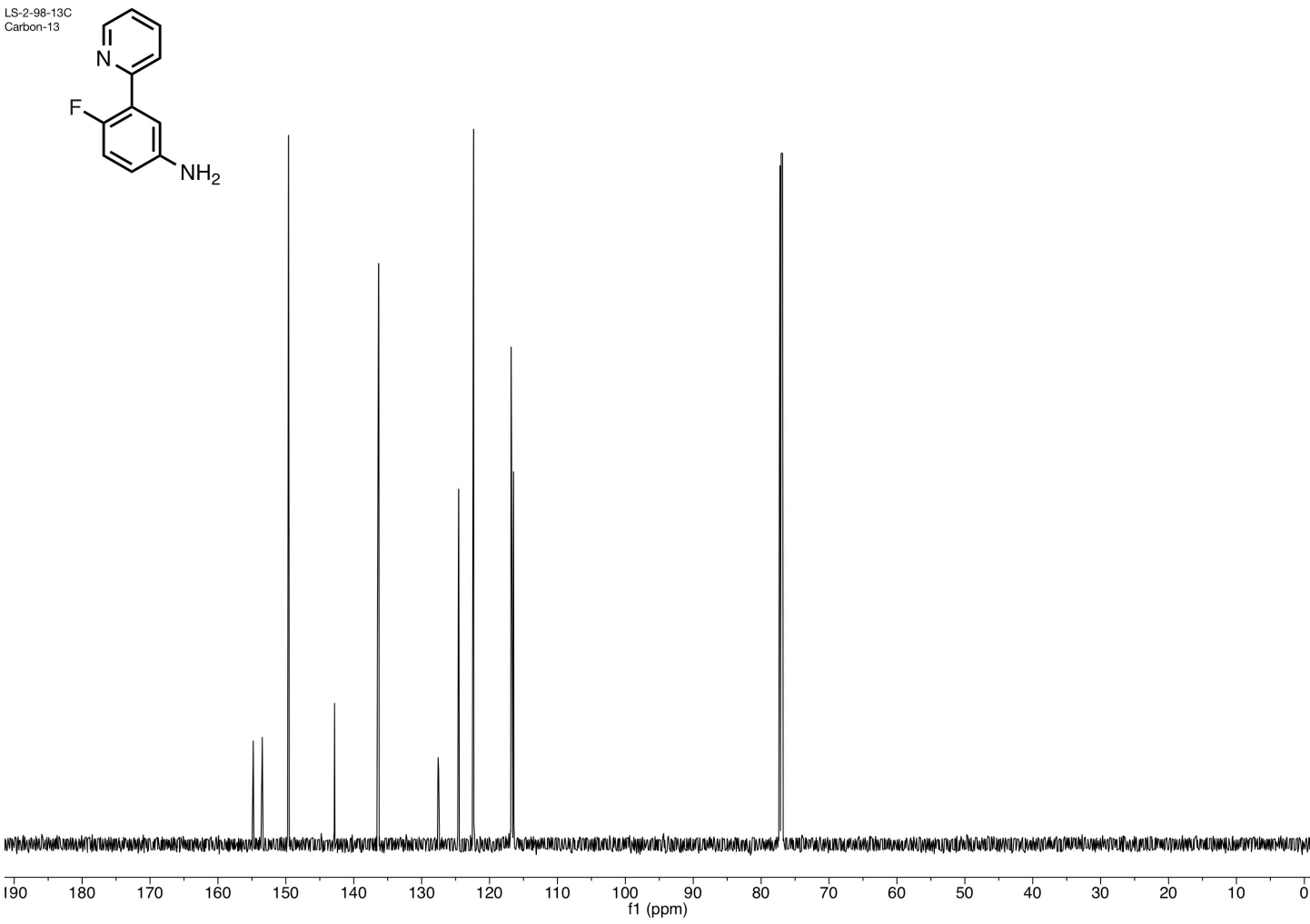

LS-2-108-Probenecid-Imine-F-13C
Carbon-13
N
O
S
O
N
F
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-108-Proben-Imine-19F
STANDARD FLUORINE PARAMETERS

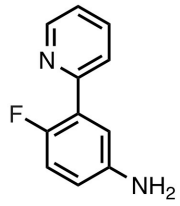


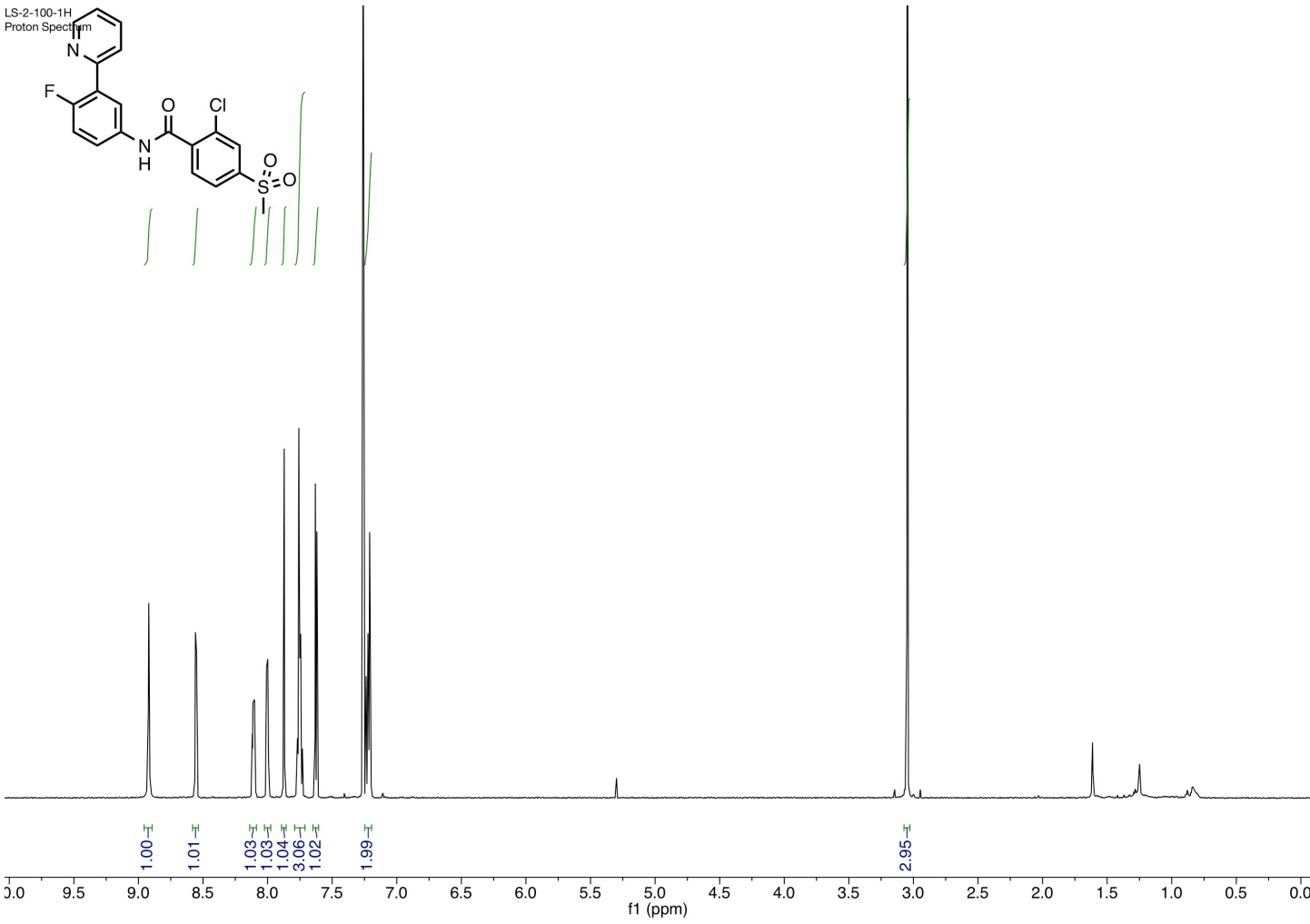


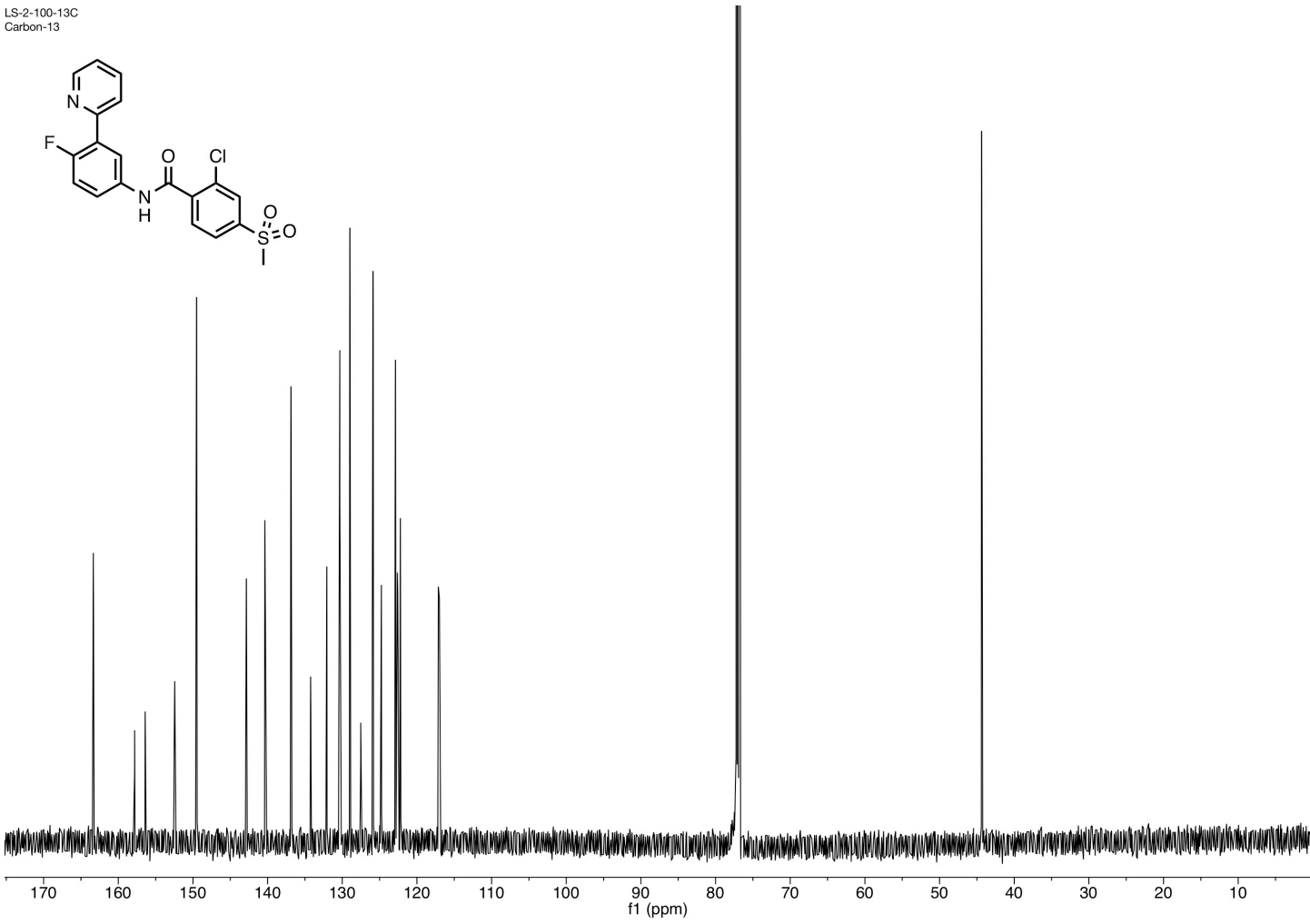

LS-2-98-1H
Proton Spectrum
N
F
NH2
1.00
1.00
1.02
0.97
1.00
0.99
1.00
2.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


LS-2-98-13C
Carbon-13
N
F
NH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

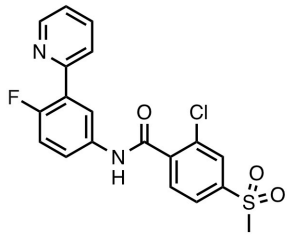
LS-2-98-PhPyImF-19F
STANDARD FLUORINE PARAMETERS

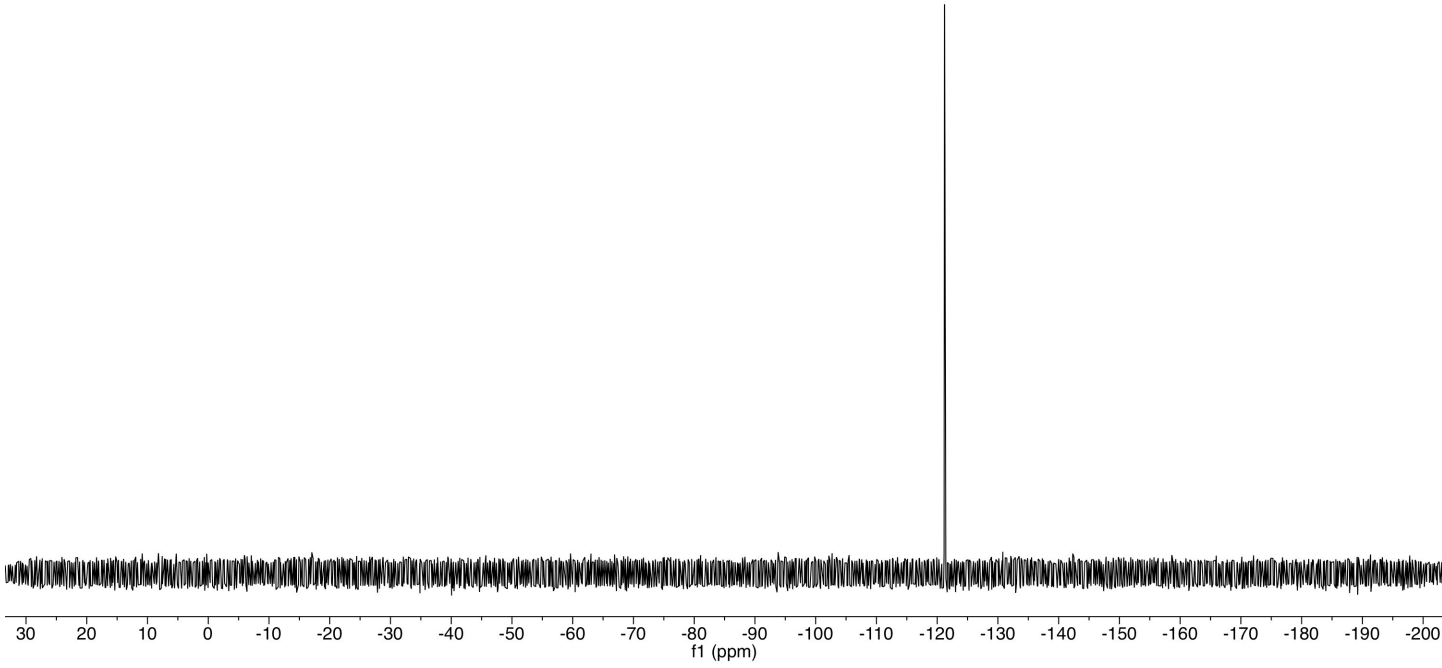



LS-2-100-1H
Proton Spectrum
F
N
H
O
Cl
S
O
O
1.00
1.01
1.03
1.03
1.04
3.06
1.02
1.99
2.95
f1 (ppm)

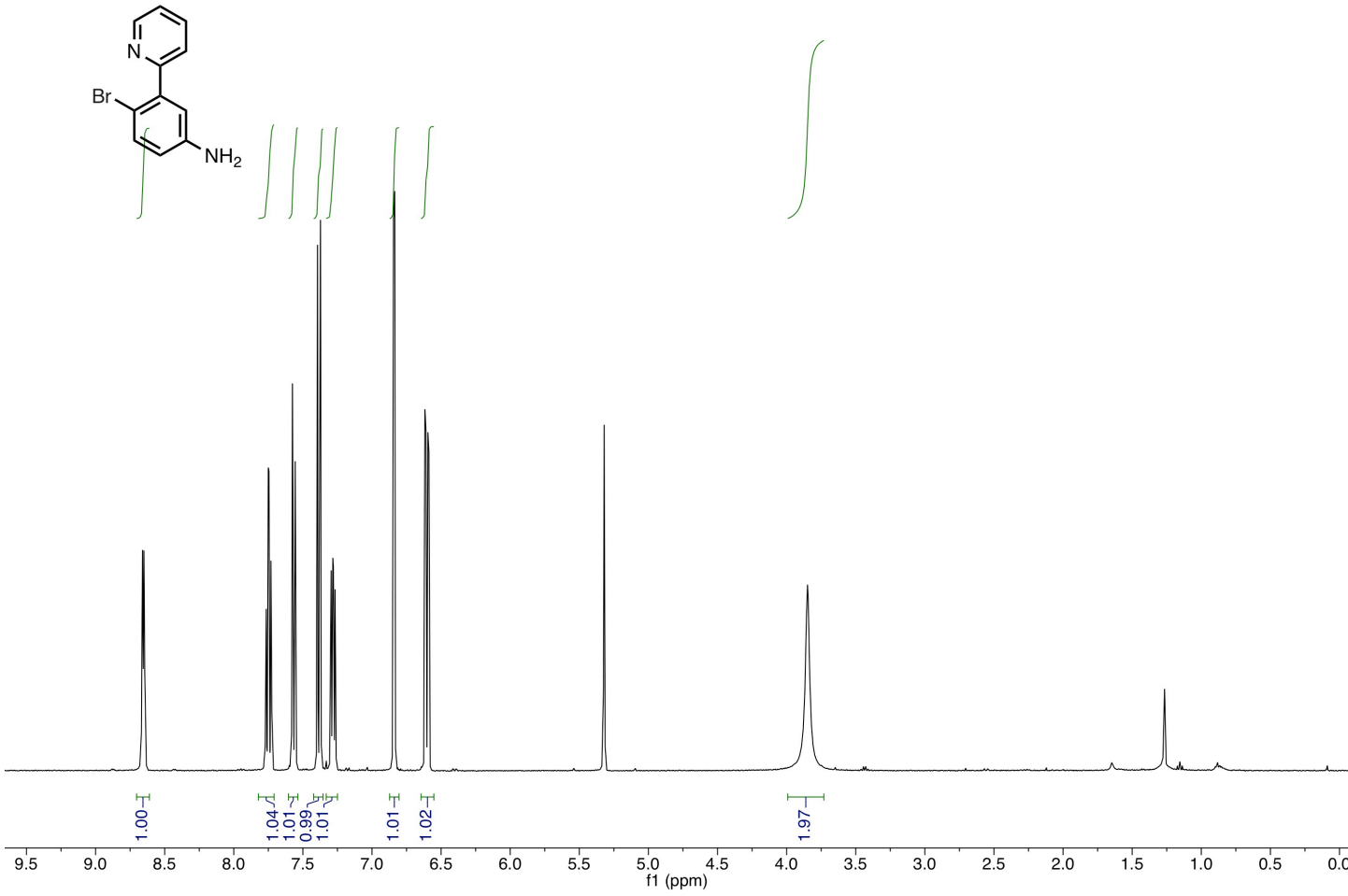

LS-2-100-13C
Carbon-13
N
F
O
Cl
N
H
O
S
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

LS-2-100-19F
STANDARD FLUORINE PARAMETERS

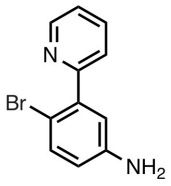


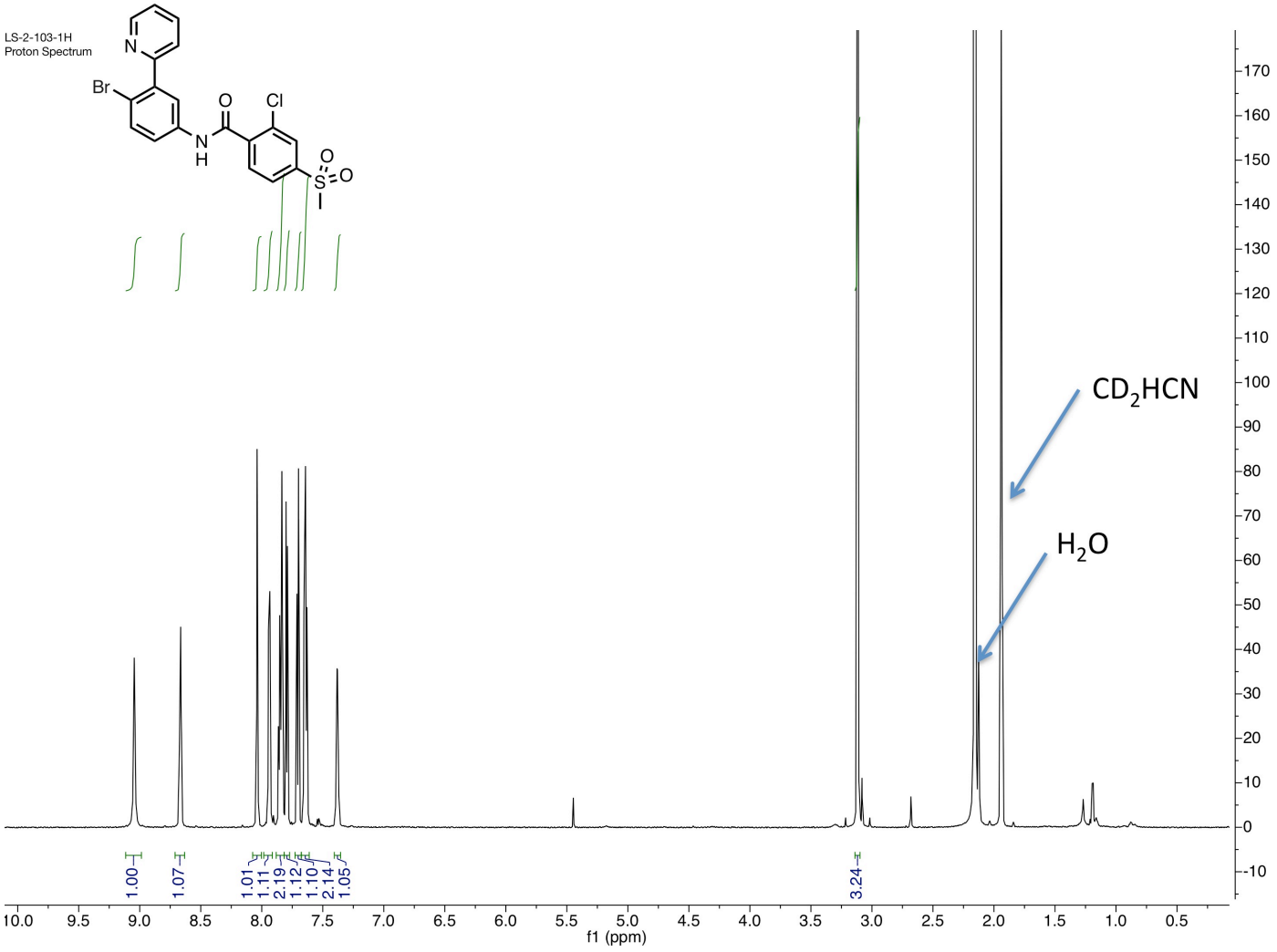


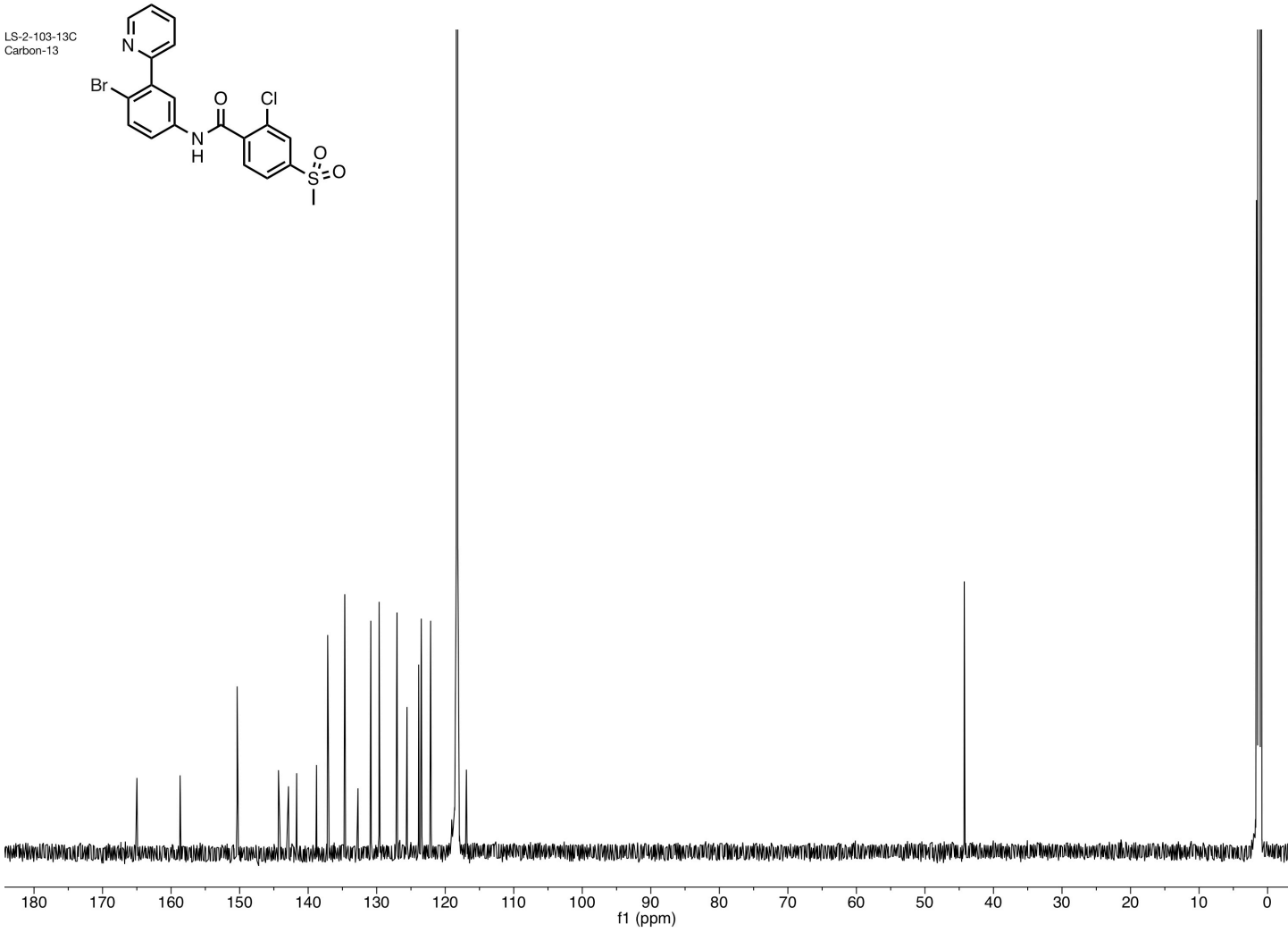
LS-2-102-pure-final
Proton Spectrum

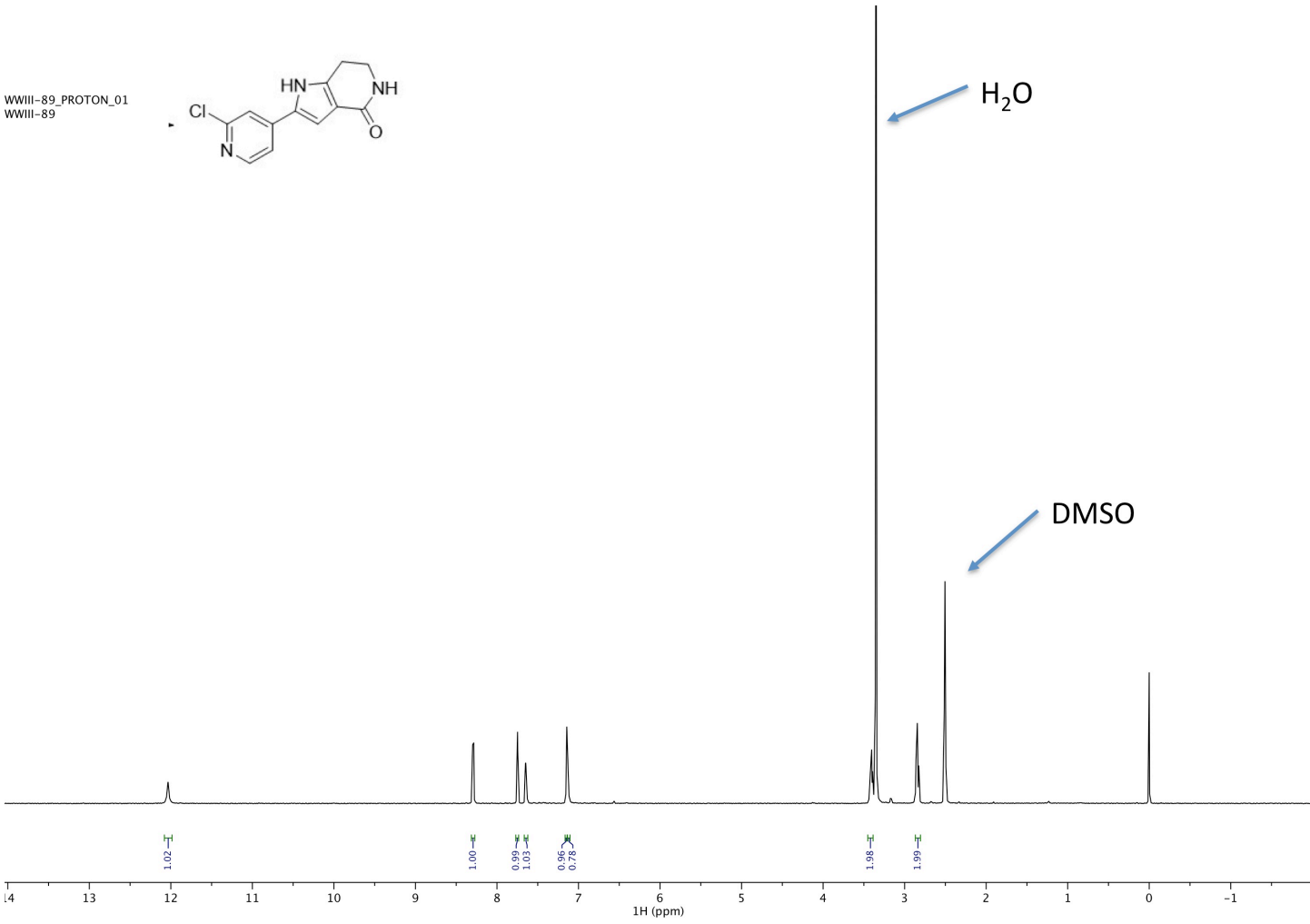


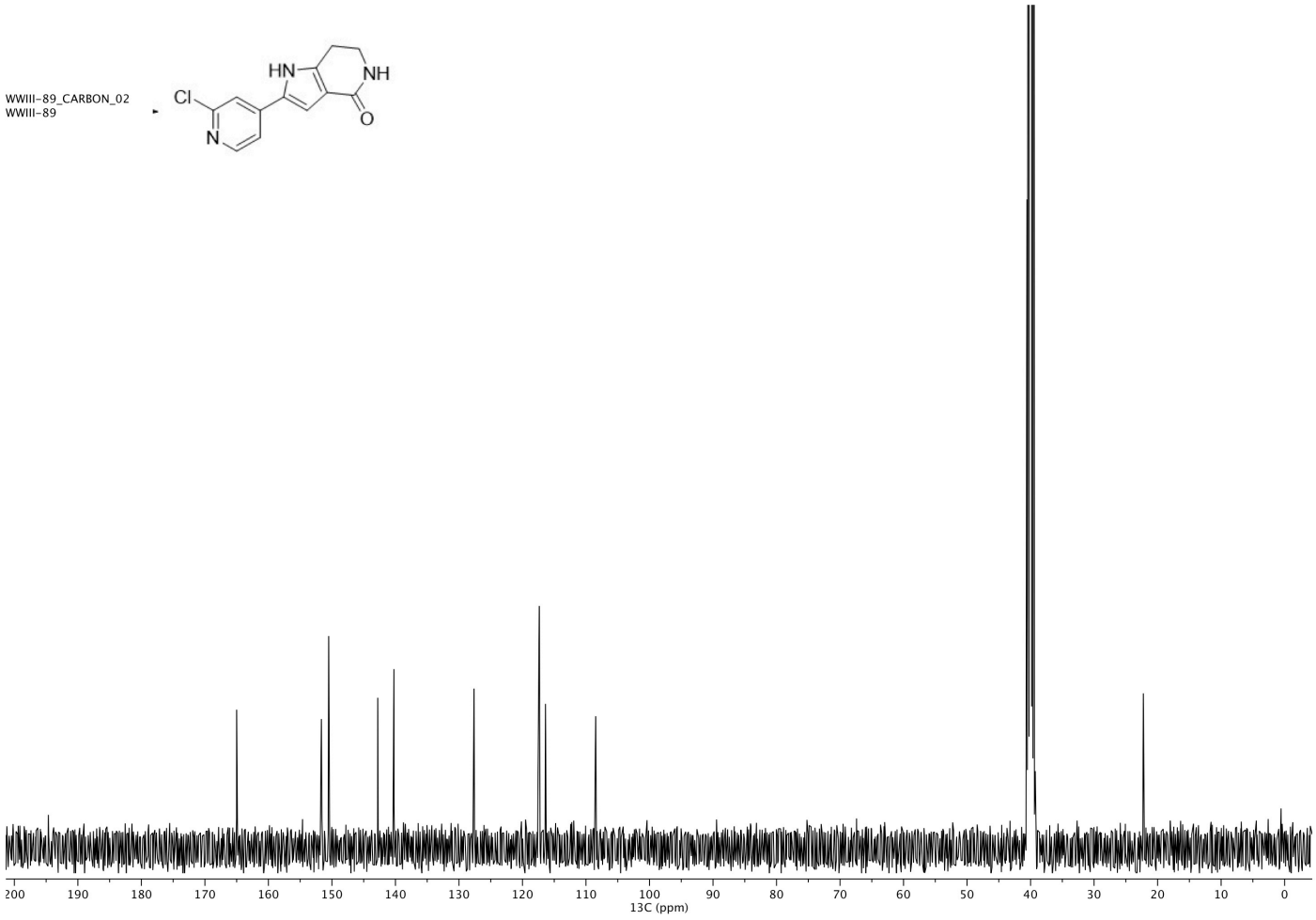
LS-2-102-washed-13C
Carbon-13

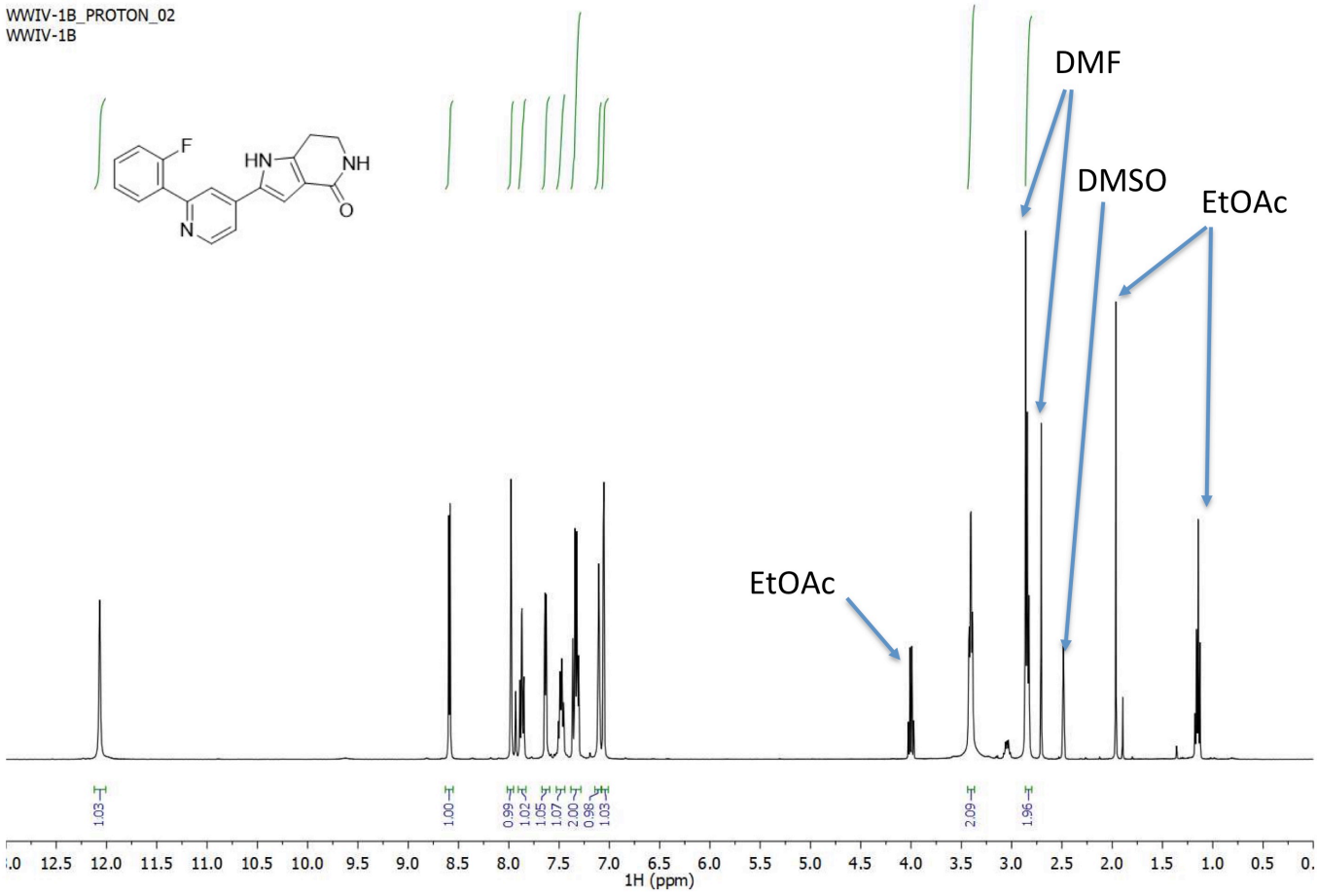


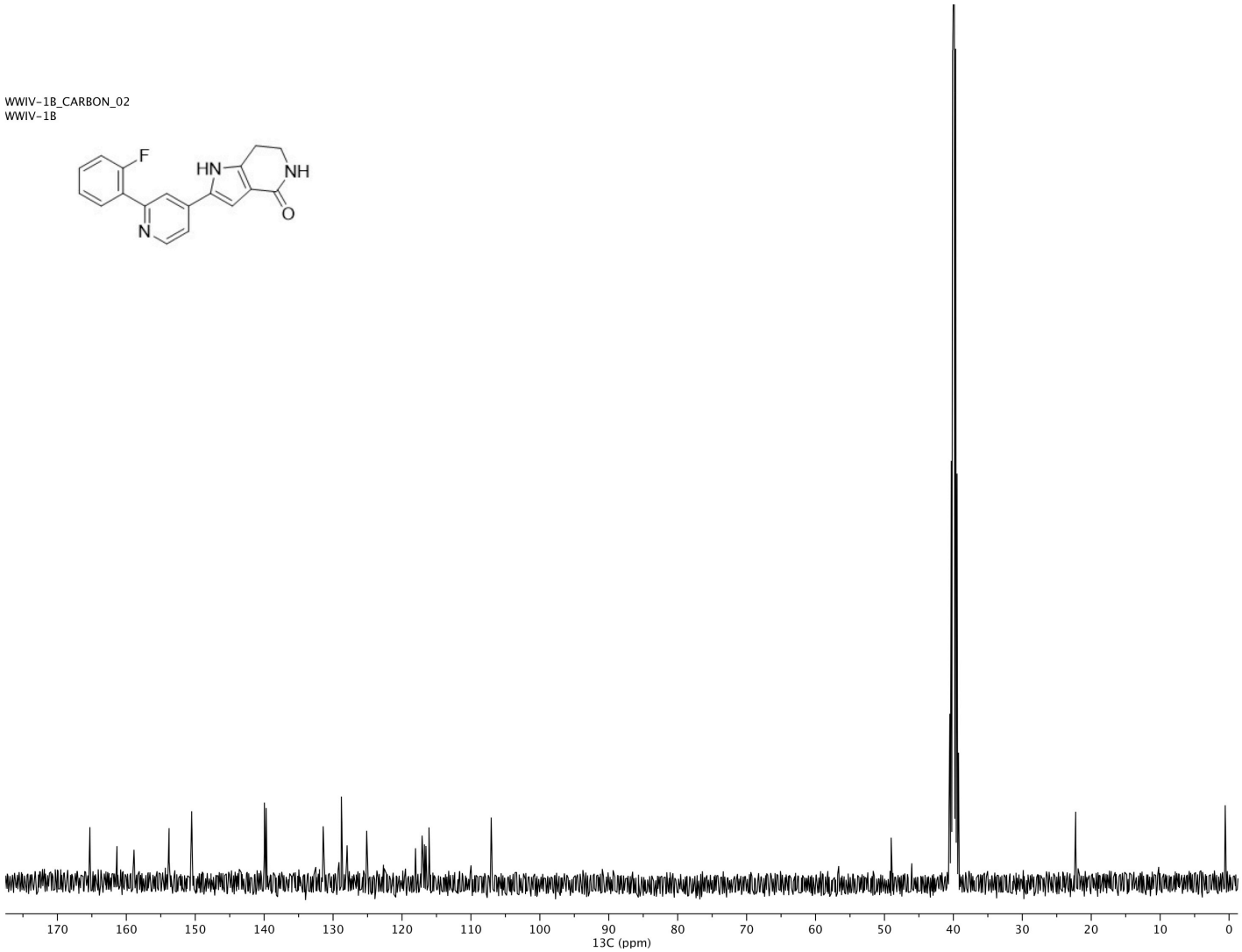

LS-2-103-1H
Proton Spectrum
Br
N
O
Cl
N
H
O
S
O
CD2HCN
H2O
1.00
1.07
1.01
1.11
2.19
1.12
1.10
2.14
1.05
3.24
f1 (ppm)


LS-2-103-13C
Carbon-13
N
Br
O
Cl
N
H
O
S
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

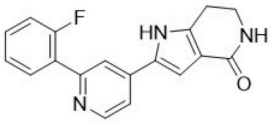

WWIII-89_PROTON_01
WWIII-89
HN
NH
Cl
N
O
H2O
DMSO
1.02
1.00
0.99
1.03
0.96
0.78
1.98
1.99
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
1H (ppm)

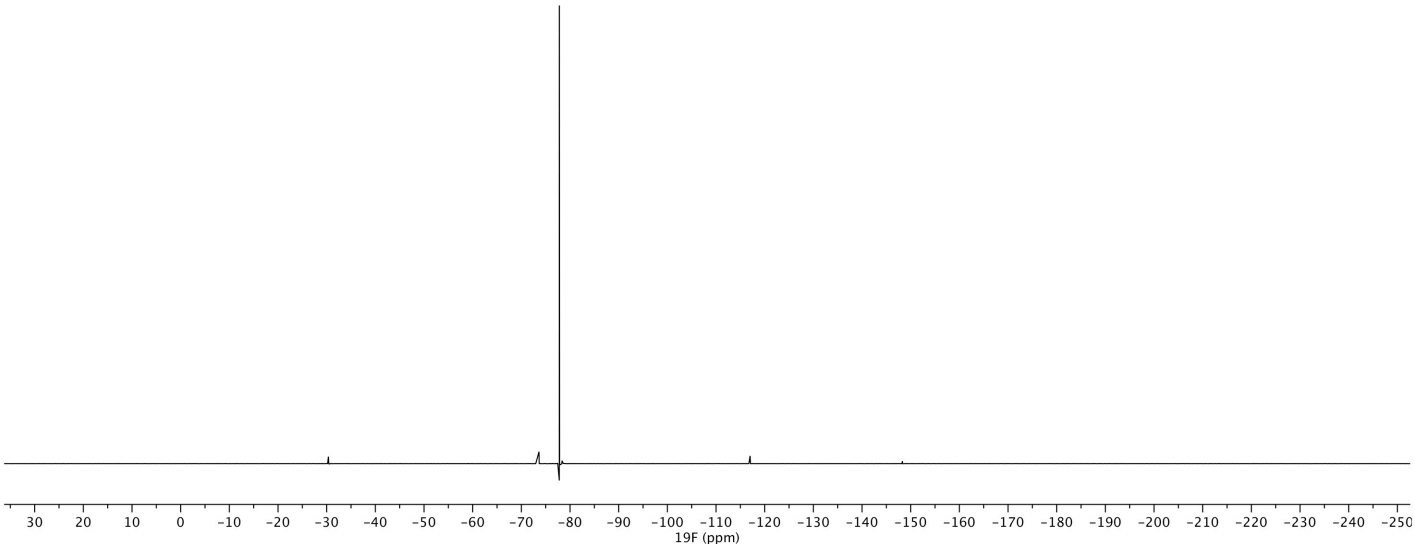

WWIII-89_CARBON_02
WWIII-89
HN
NH
Cl
N
O
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)

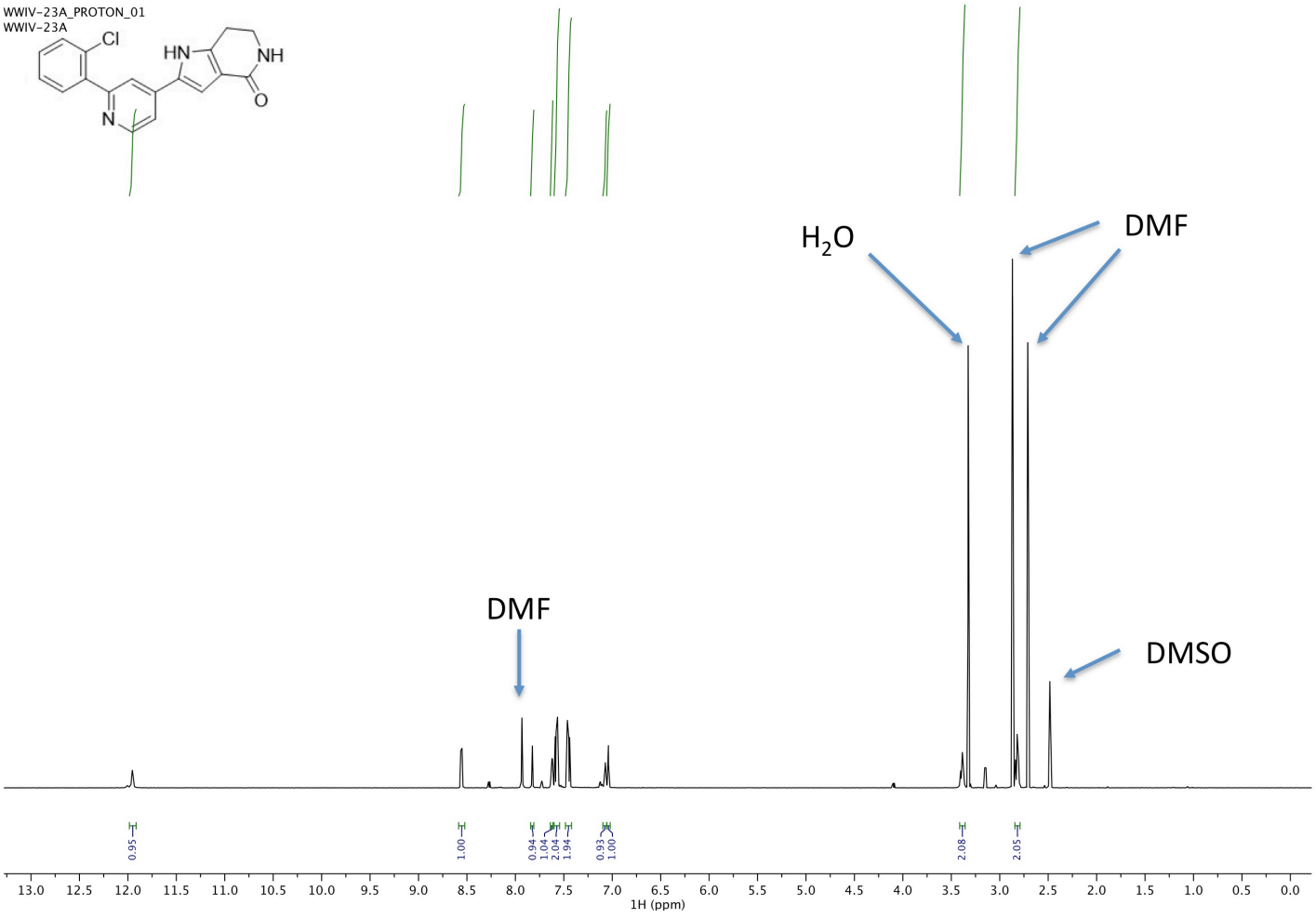

WWIV-1B_PROTON_02
WWIV-1B
F
HN
NH
O
N
DMF
DMSO
EtOAc
EtOAc
1.03
1.00
0.99
1.02
1.05
1.07
2.00
0.98
1.03
2.09
1.96
1H (ppm)

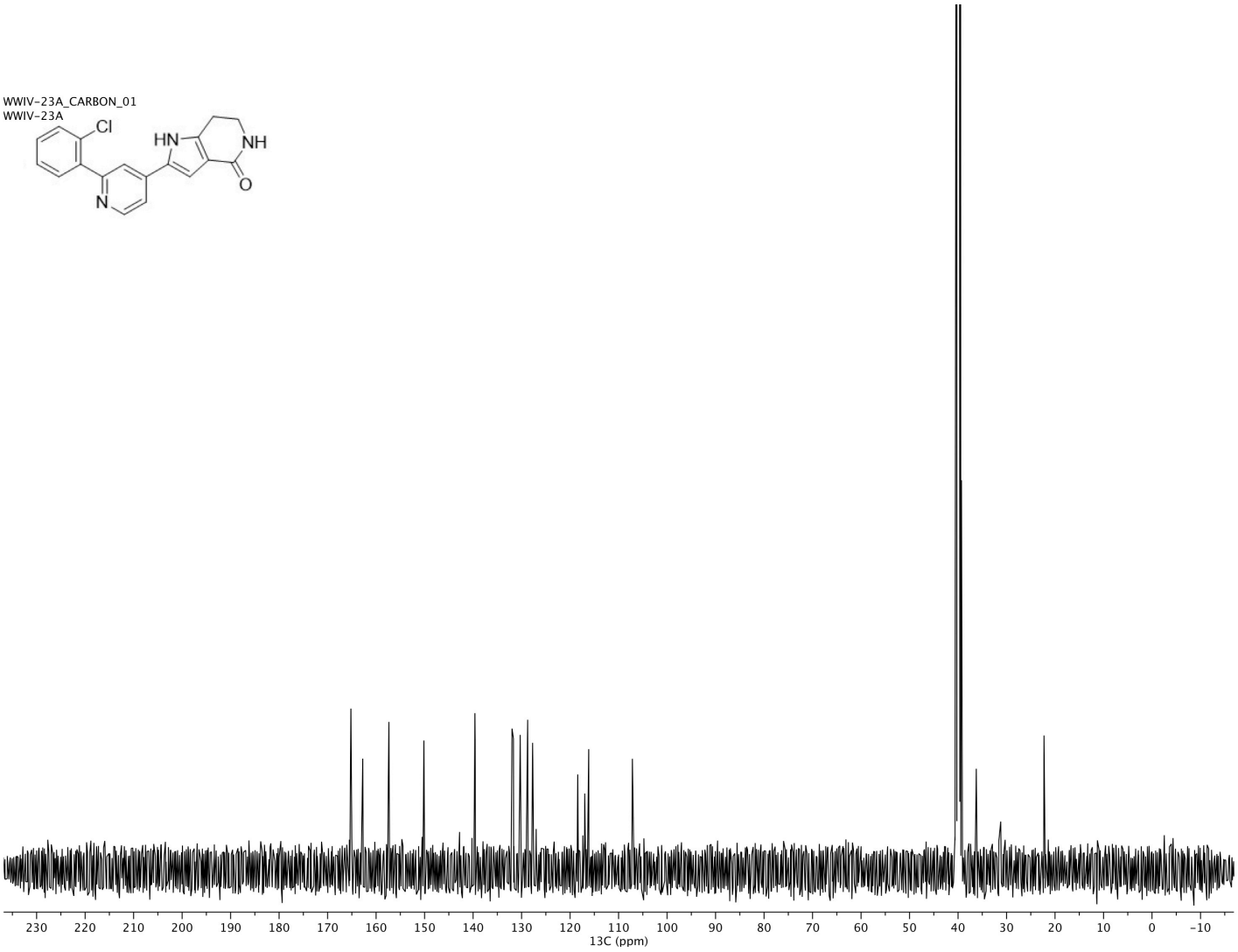

WWIV-1B_CARBON_02
WWIV-1B
F
HN
NH
O
N
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13C (ppm)

WWIV-1B_FLUORINE_01
WWIV-1B

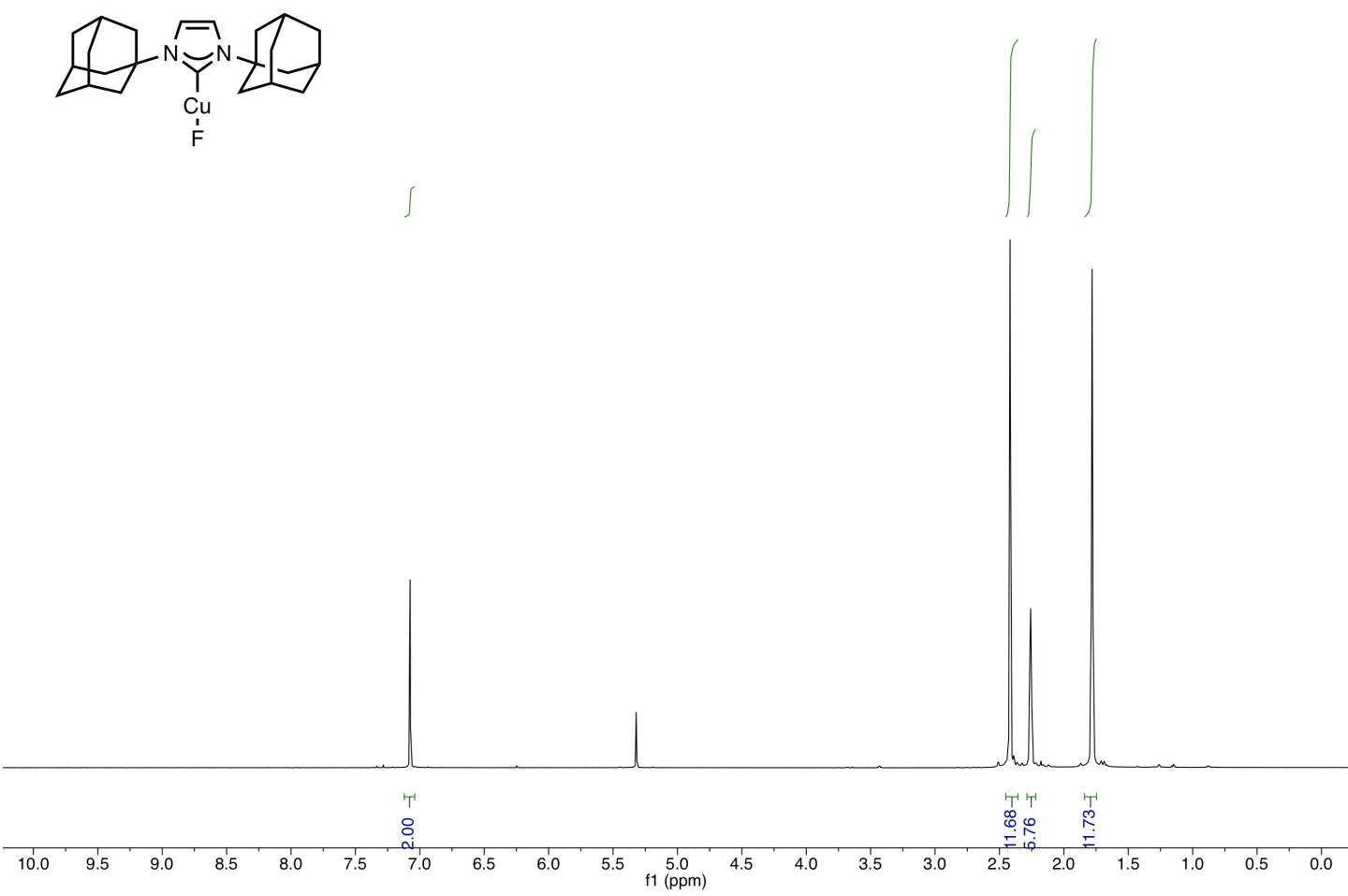


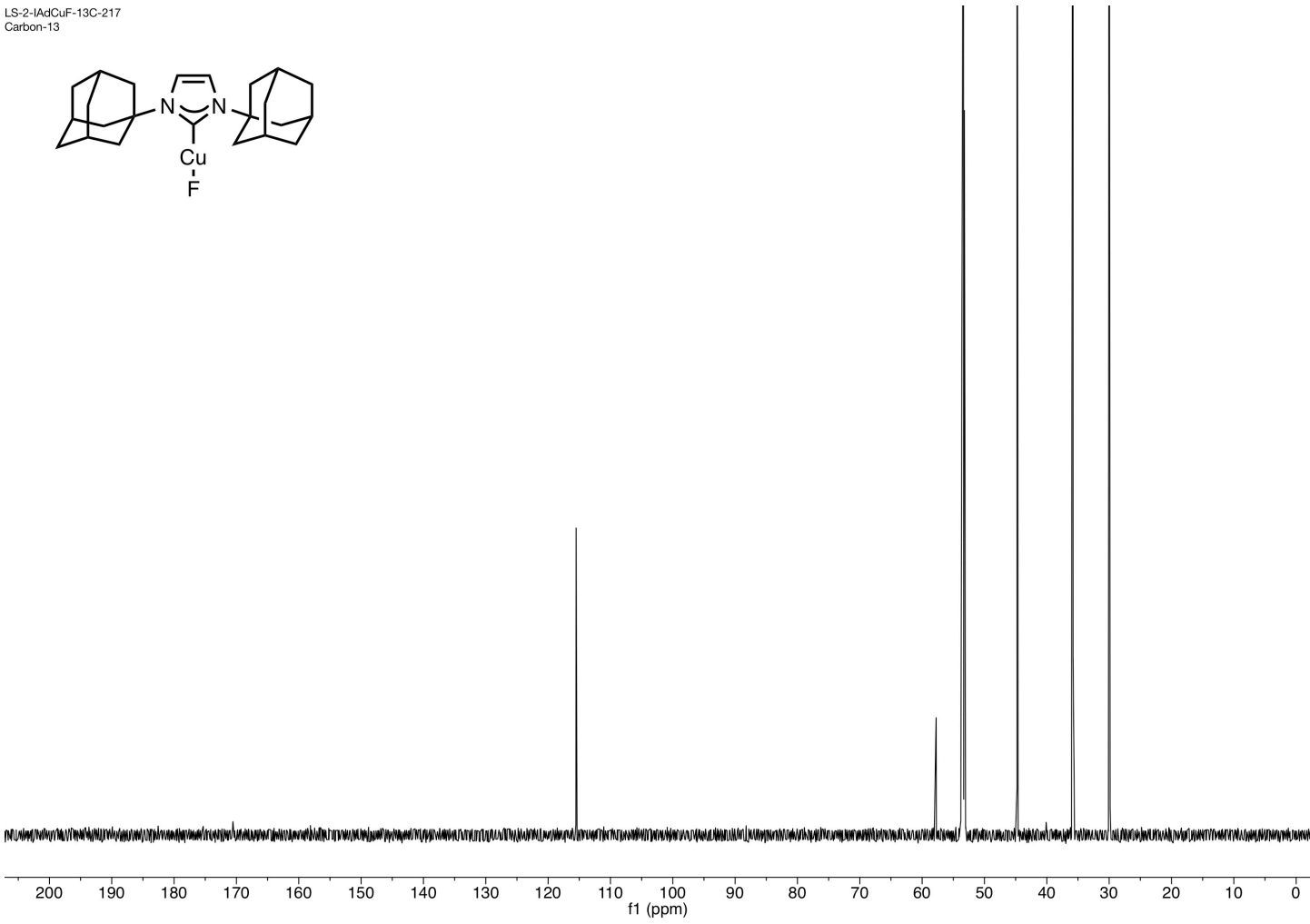



WWIV-23A_PROTON_01
WWIV-23A
Cl
HN
NH
O
N
H2O
DMF
DMF
DMSO
0.95
1.00
0.94
1.04
2.04
1.94
0.93
1.00
2.08
2.05
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1H (ppm)

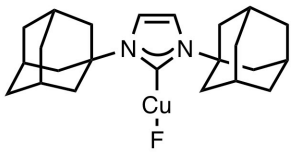

WWIV-23A_CARBON_01
WWIV-23A
Cl
HN
NH
O
N
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13C (ppm)

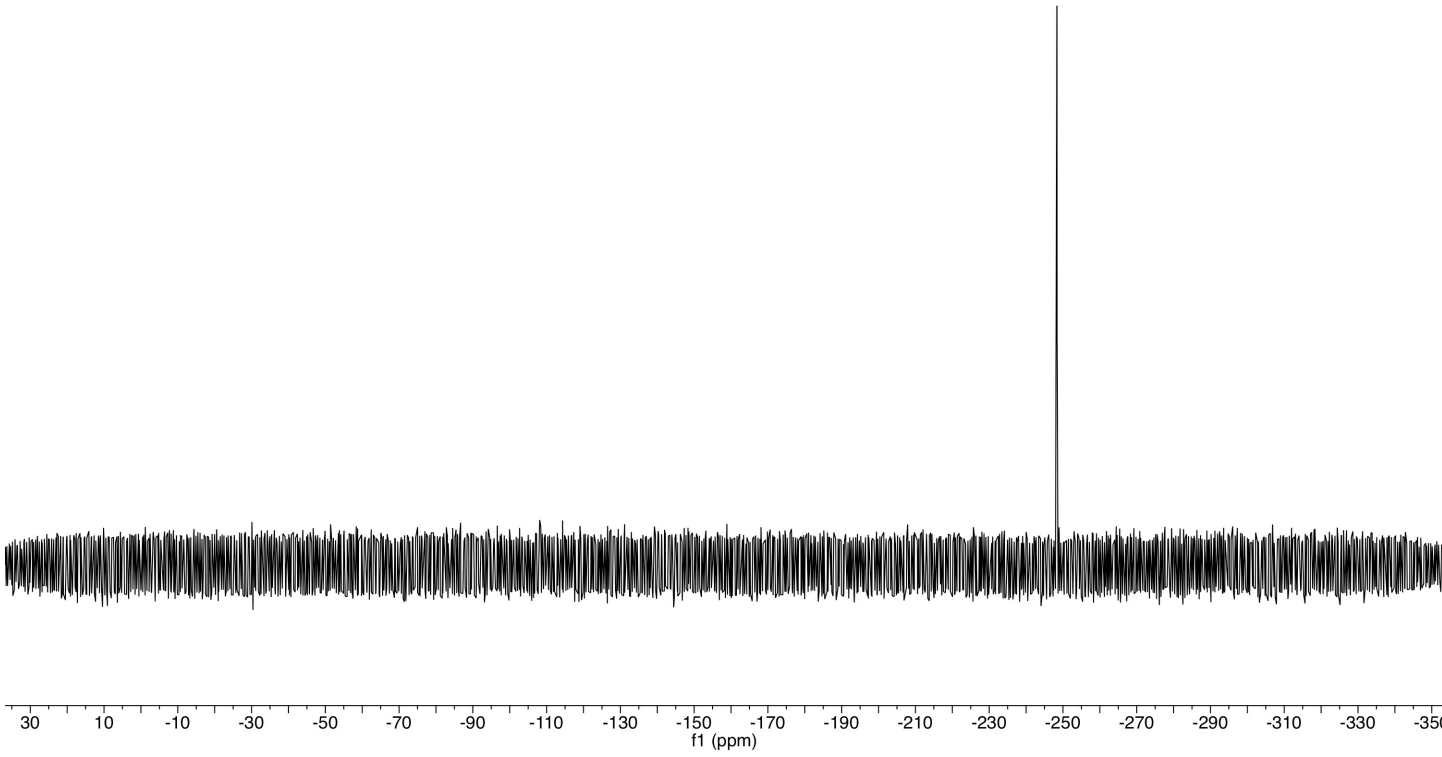
LS-2-IAdCuF-1H
Proton Spectrum



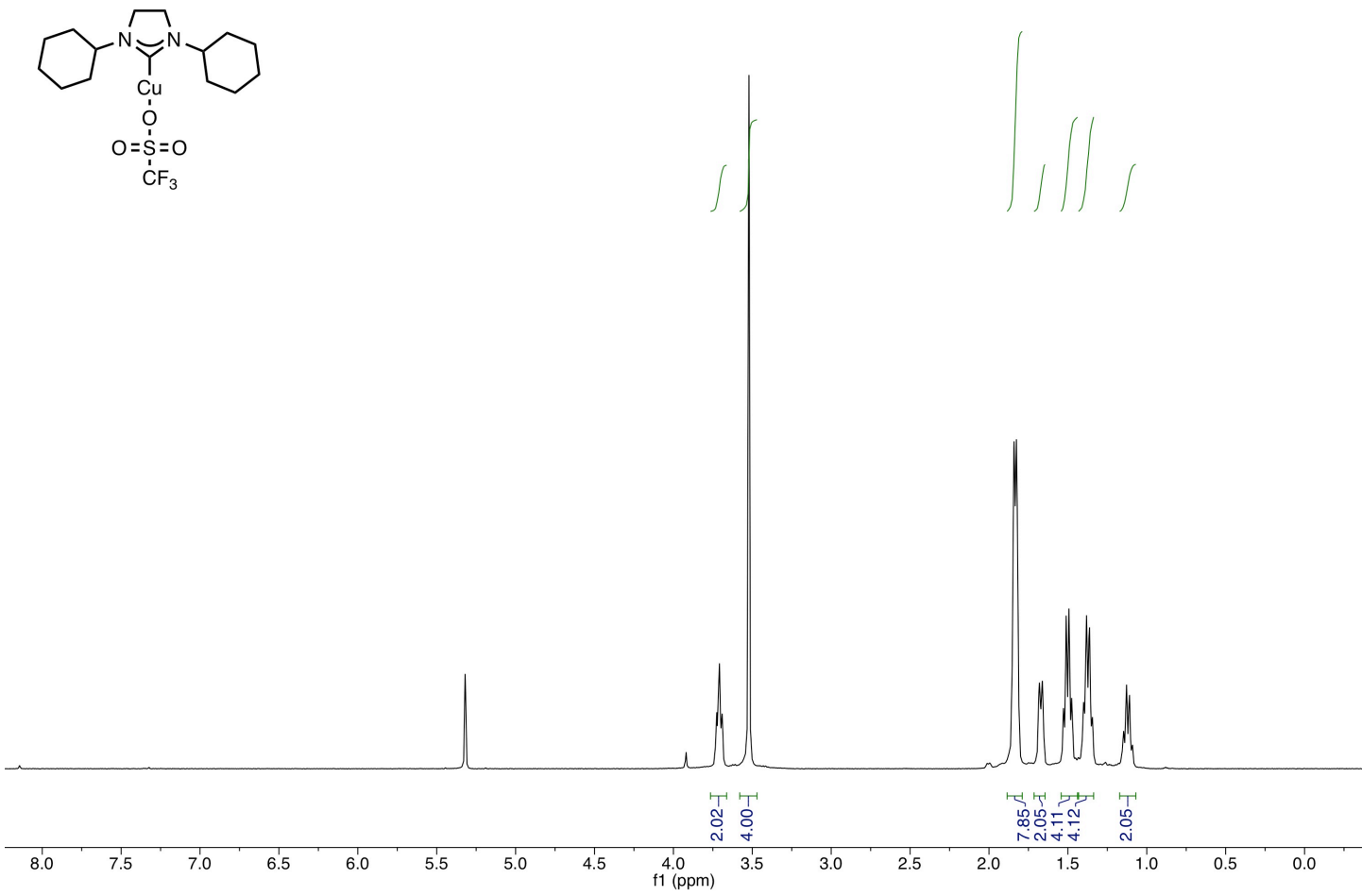

LS-2-IAdCuF-13C-217
Carbon-13
N
N
Cu
F
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

LS-2-IAdCuF-19F
STANDARD FLUORINE PARAMETERS

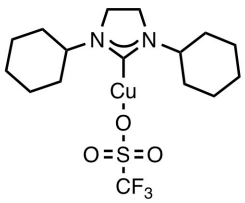




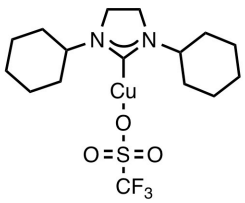
LS-2-110C-1H-conc
Proton Spectrum

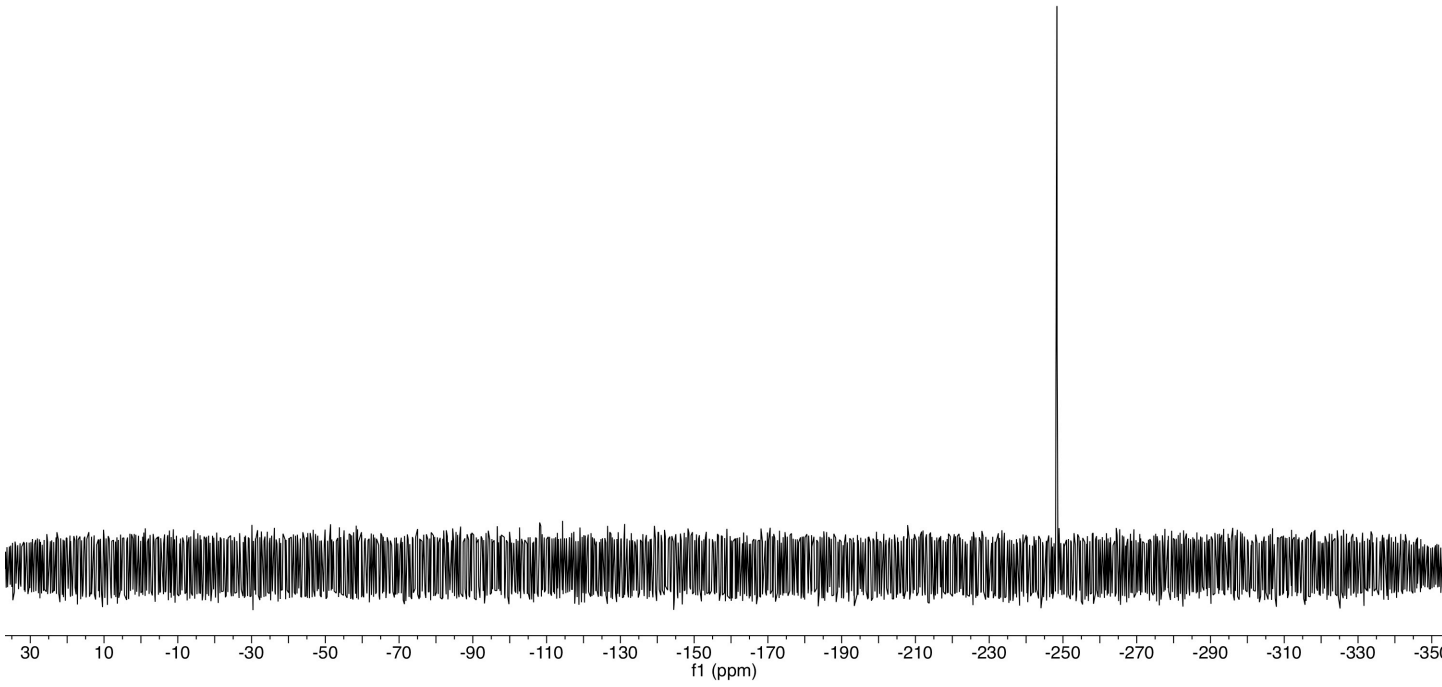


LS-2-110C-13C-conc
Carbon-13



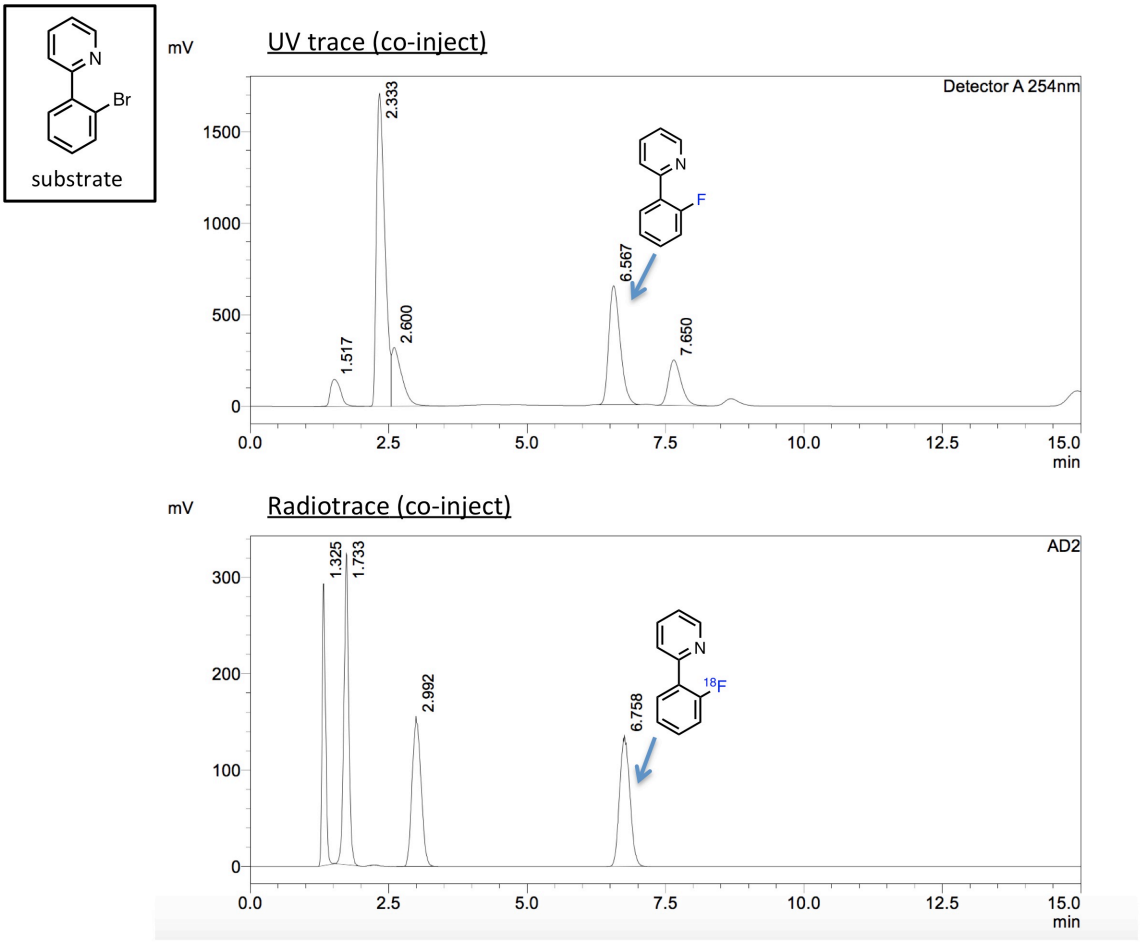
LS-2-IAdCuF-19F
STANDARD FLUORINE PARAMETERS

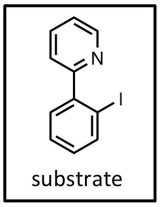




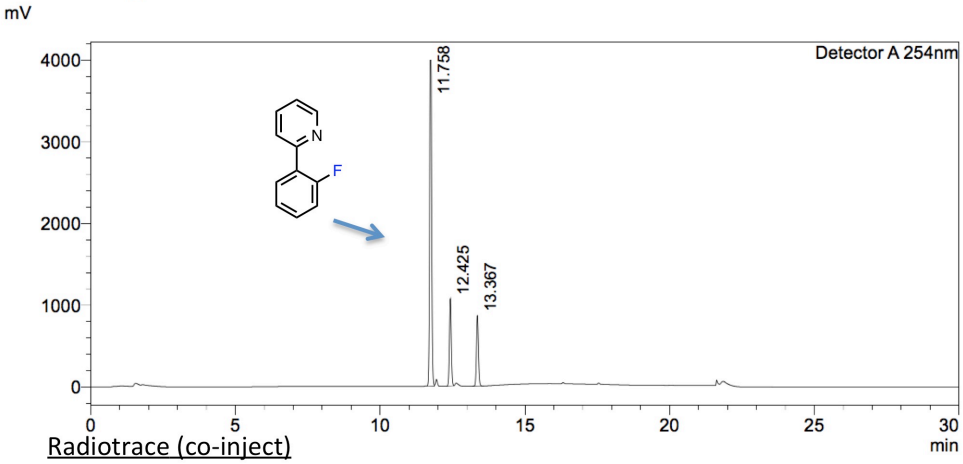
9. HPLC Traces of Radiofluorination Reactions

The identity of the radiofluorinated products was determined using HPLC analysis. For each substrate, the crude reaction mixture was spiked with a small amount of the authentic ^{19}F-containing product and injected into the HPLC unit. Both UV and RAD traces were collected, and these are shown below. The presence of the ^{18}F product was confirmed by the presence of a RAD peak with a retention time corresponding to that of the UV peak due to the co-injected authentic ^{19}F-containing product. The UV and RAD detectors are in a series, (the sample passes through the UV detector first), resulting in a ~0.2 min. delay between the corresponding UV and RAD peaks.

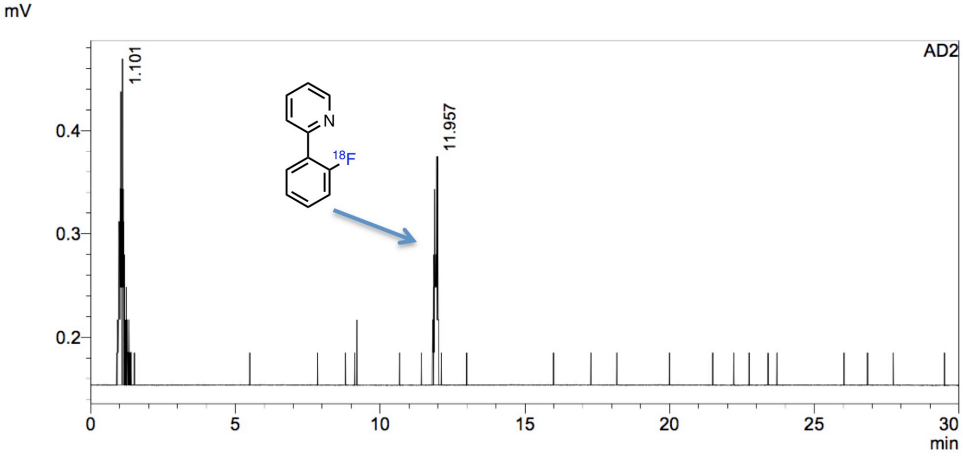


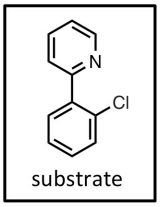


UV trace (co-inject)



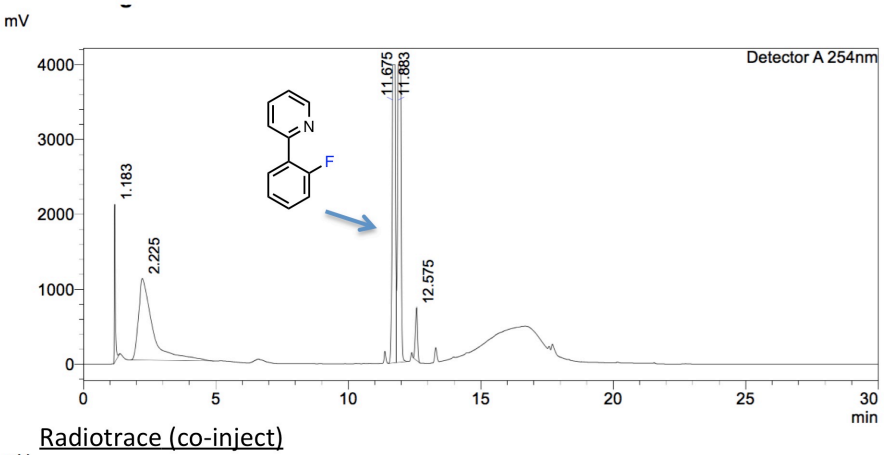
Radiotrace (co-inject)



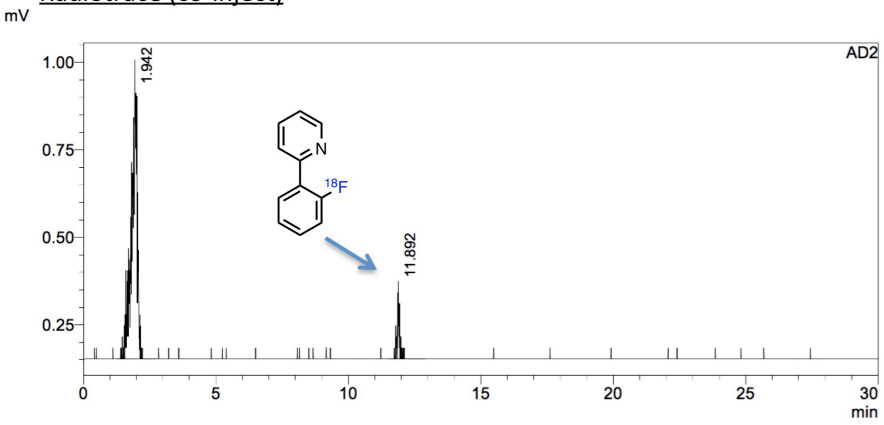


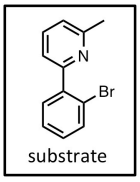
substrate

UV trace (co-inject)

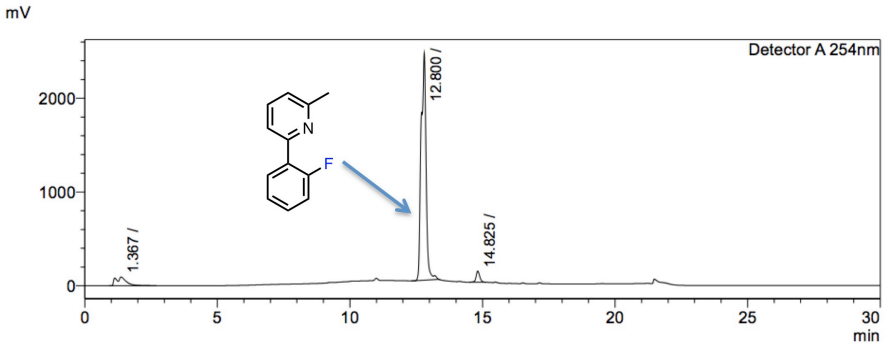


Radiotrace (co-inject)

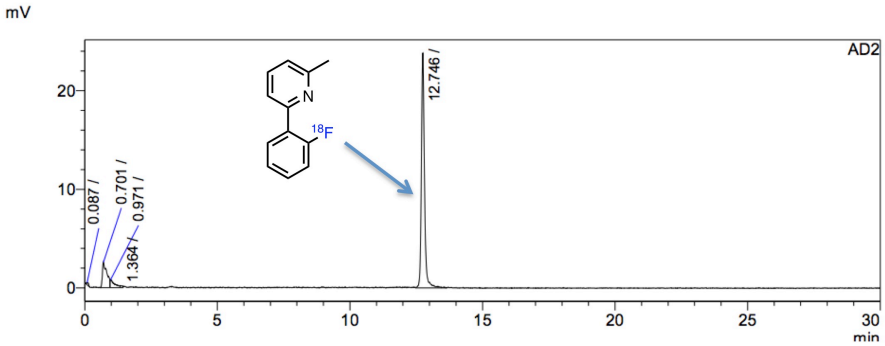


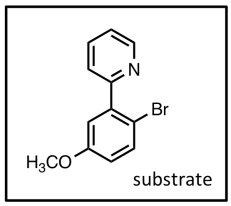


UV trace (co-inject)

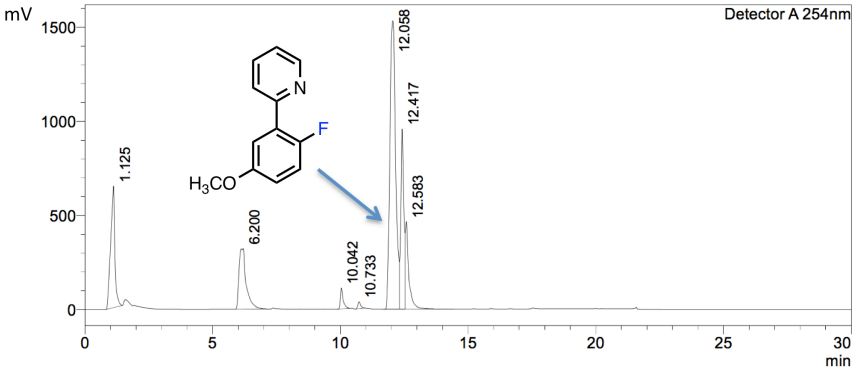


Radiotrace (co-inject)

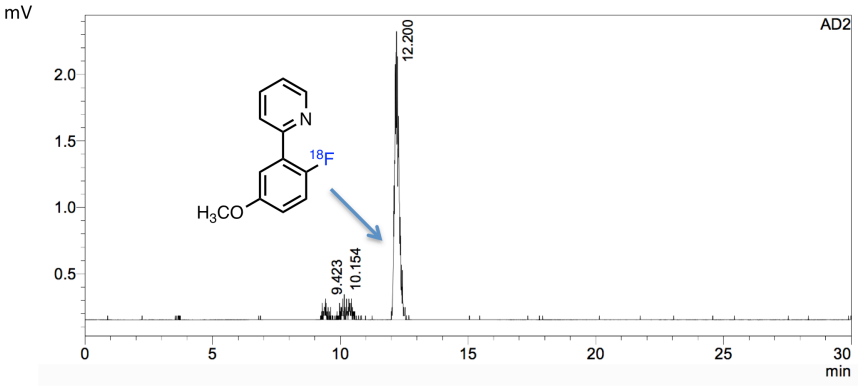


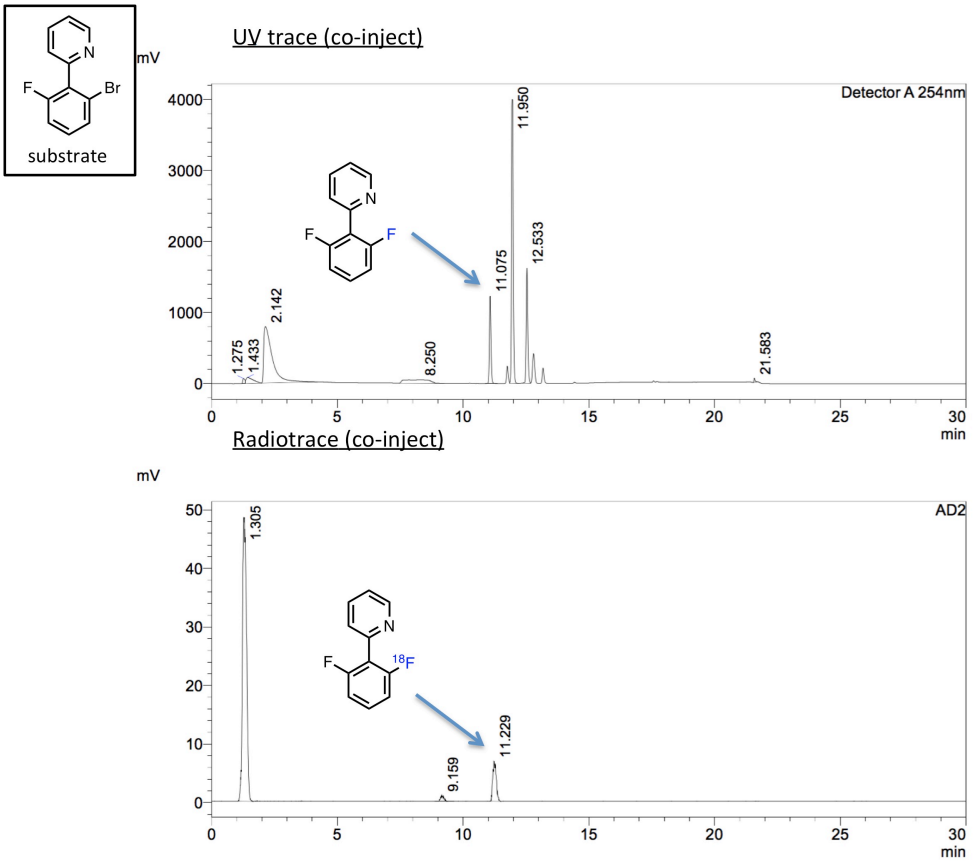


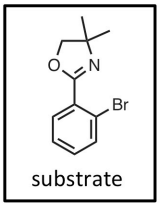
UV trace (co-inject)



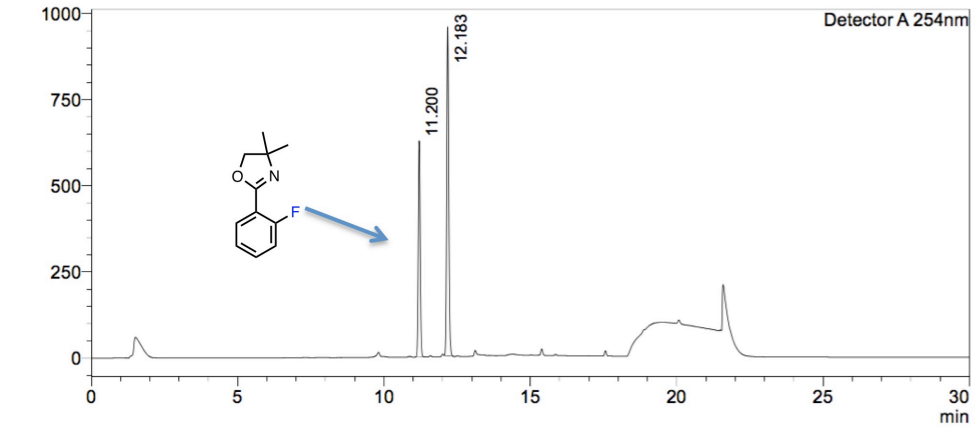
Radiotrace (co-inject)



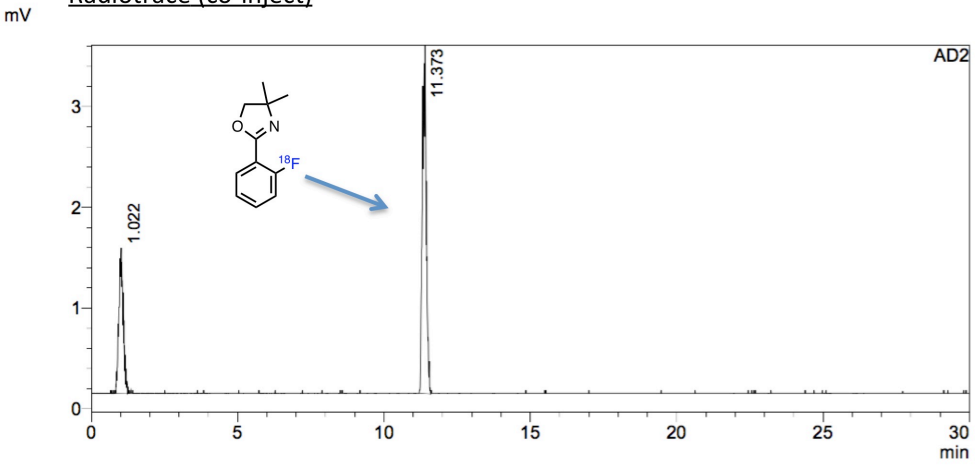

substrate
UV trace (co-inject)
mV
Detector A 254nm
11.950
11.075
12.533
2.142
1.275
1.433
8.250
21.583
min
Radiotrace (co-inject)
mV
AD2
1.305
11.229
9.159
min

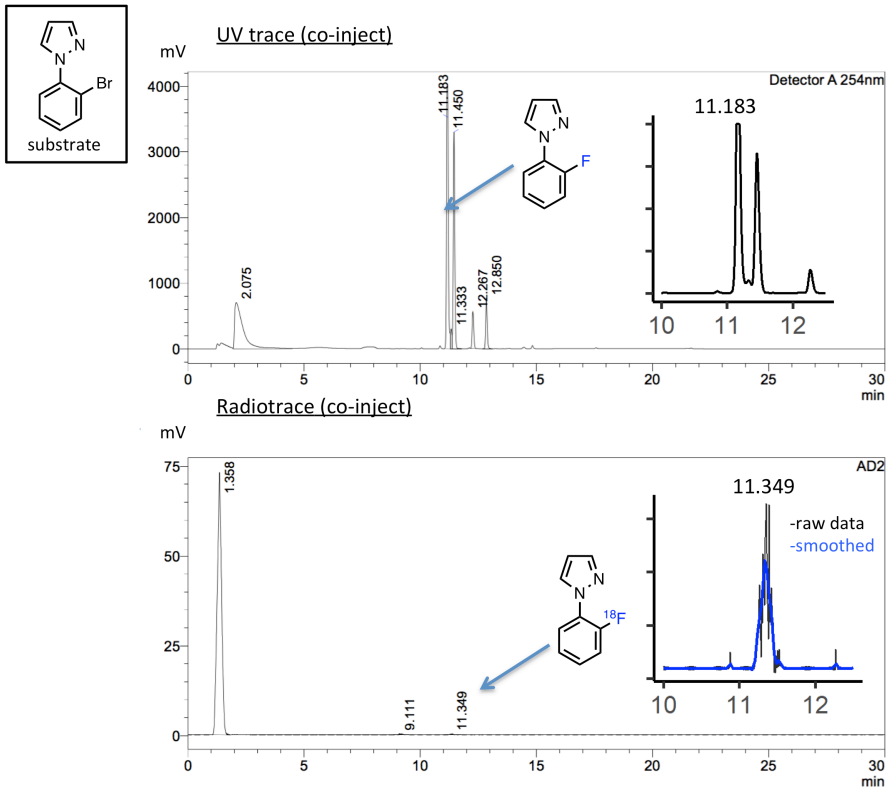


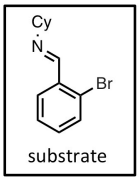
UV trace (co-inject)

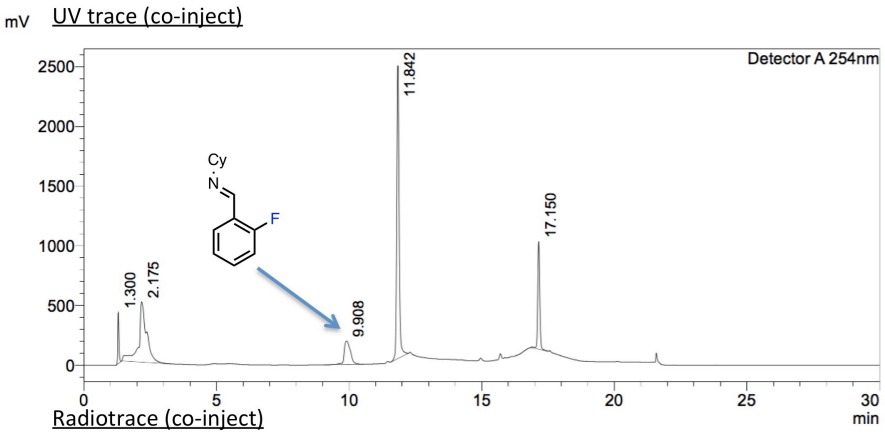


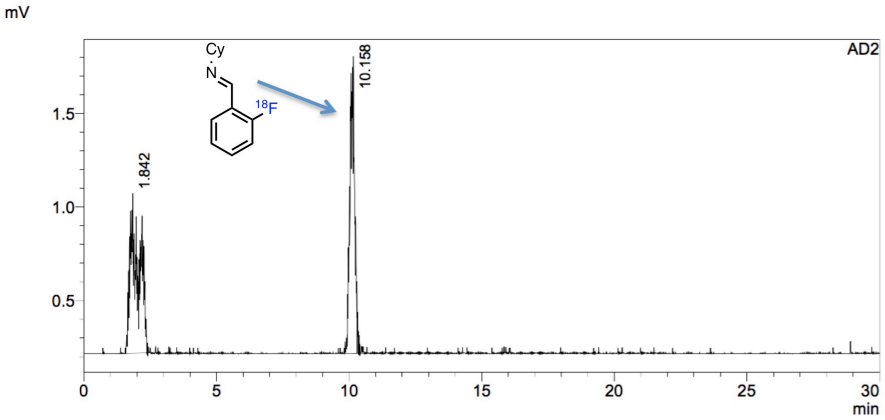
Radiotrace (co-inject)

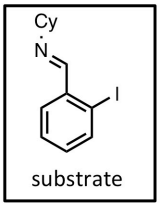



substrate
Br
UV trace (co-inject)
mV
Detector A 254nm
11.183
11.450
2.075
11.333
12.267
12.850
F
11.183
10
11
12
min
Radiotrace (co-inject)
mV
AD2
1.358
9.111
11.349
11.349
-raw data
-smoothed
18F
10
11
12
min

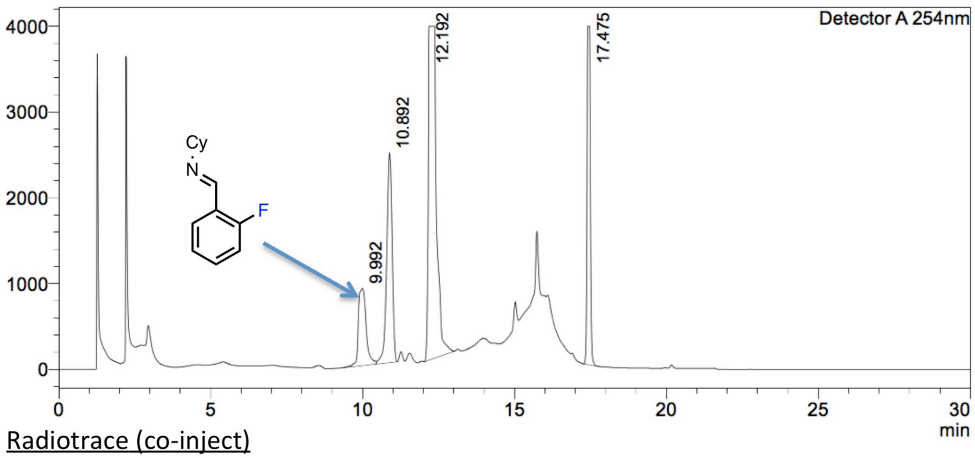

Cy
N
Br
substrate


mV
UV trace (co-inject)
Detector A 254nm
2500
2000
1500
1000
500
0
1.300
2.175
9.908
11.842
17.150
Cy
N
F
0
5
10
15
20
25
30
min


mV
Radiotrace (co-inject)
AD2
1.5
1.0
0.5
1.842
10.158
Cy
N
18F
0
5
10
15
20
25
30
min

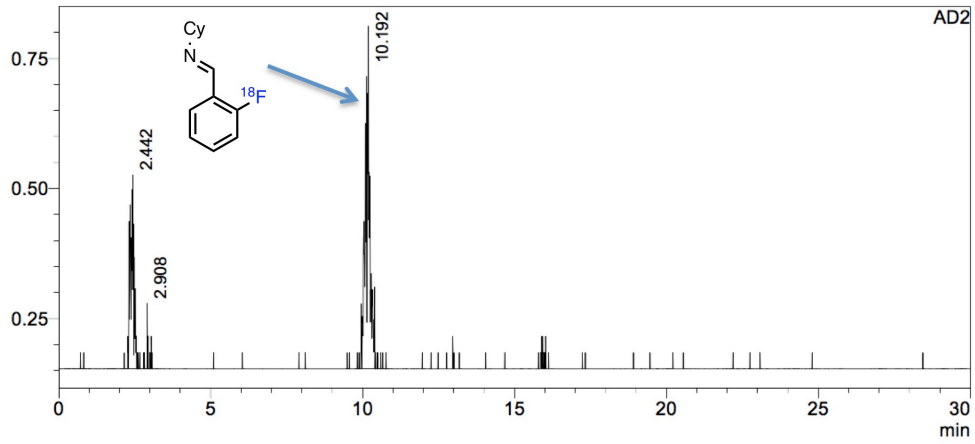


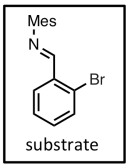
mV UV trace (co-inject)

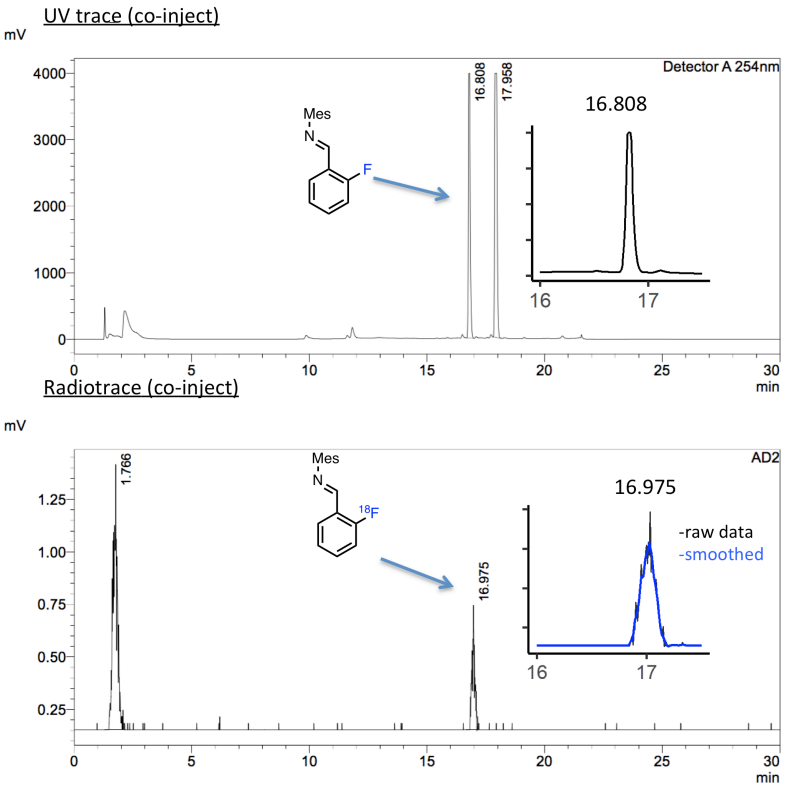


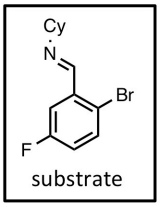
Radiotrace (co-inject)

mV

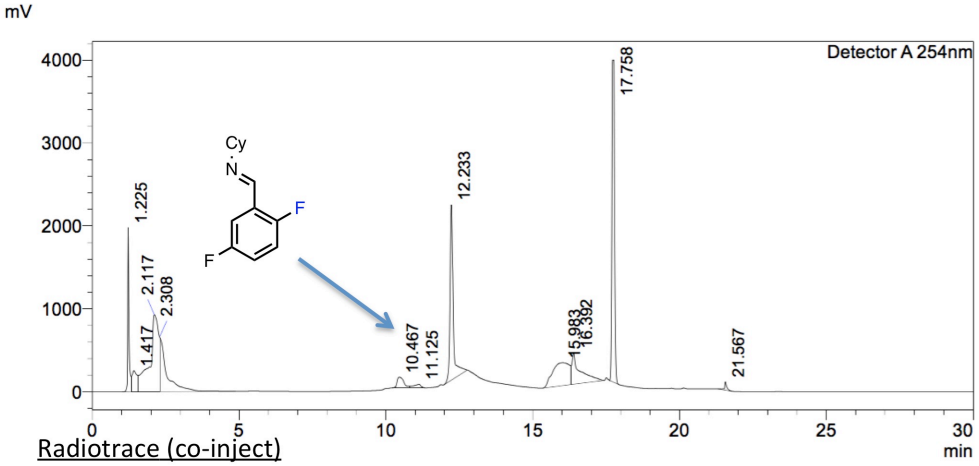



Mes
N
Br
substrate

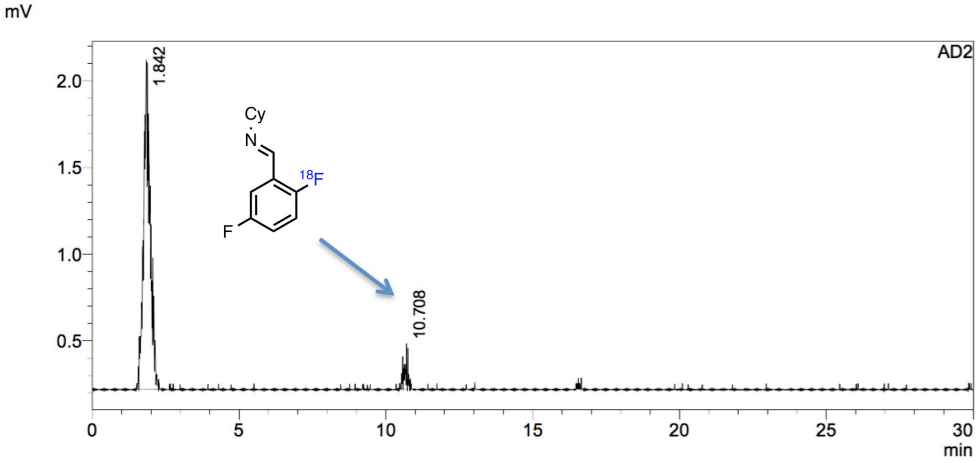

UV trace (co-inject)
mV
Detector A 254nm
16.808
17.958
Mes
N
F
16.808
16
17
4000
3000
2000
1000
0
0
5
10
15
20
25
30
min
Radiotrace (co-inject)
mV
AD2
1.766
16.975
Mes
N
18F
16.975
-raw data
-smoothed
16
17
1.25
1.00
0.75
0.50
0.25
0
5
10
15
20
25
30
min

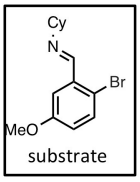


UV trace (co-inject)

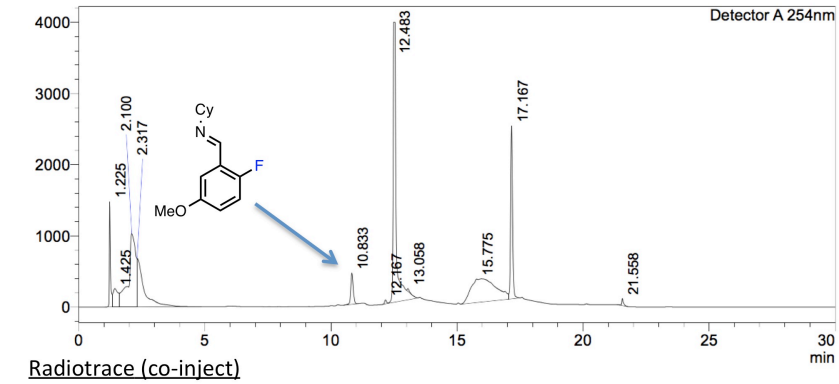


Radiotrace (co-inject)

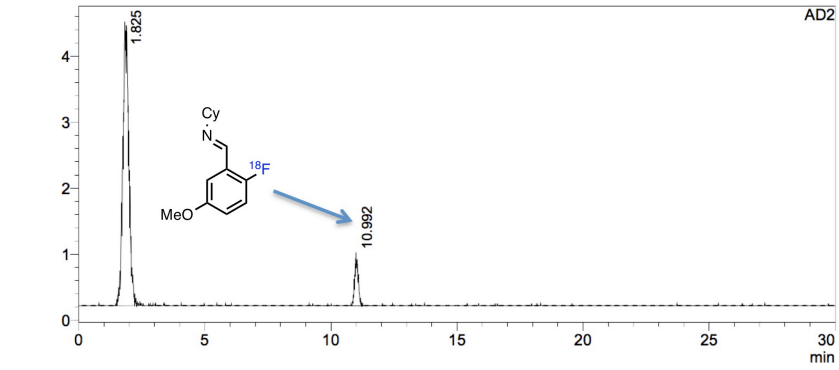


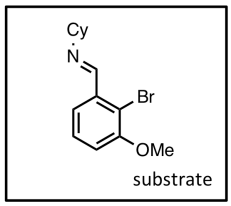


UV trace (co-inject)

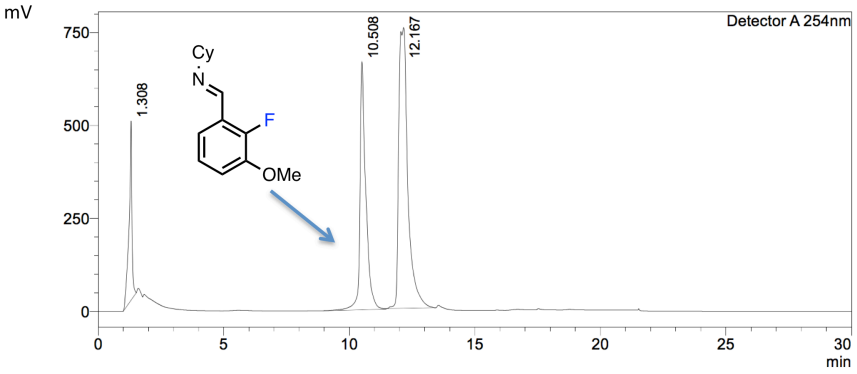


Radiotrace (co-inject)

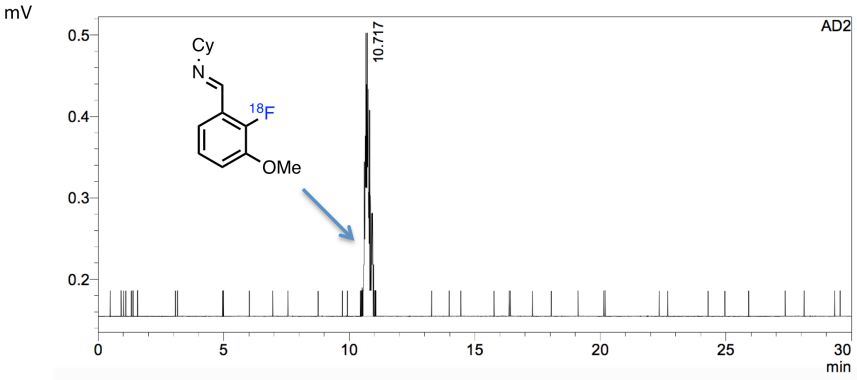


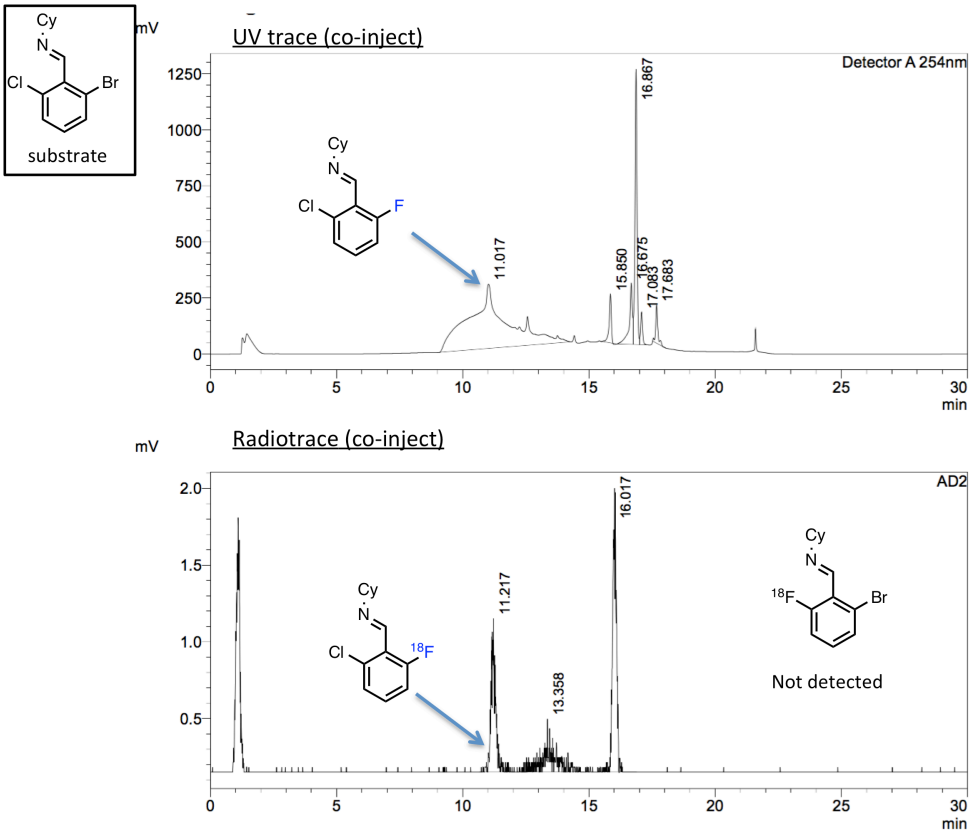


UV trace (co-inject)

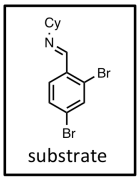


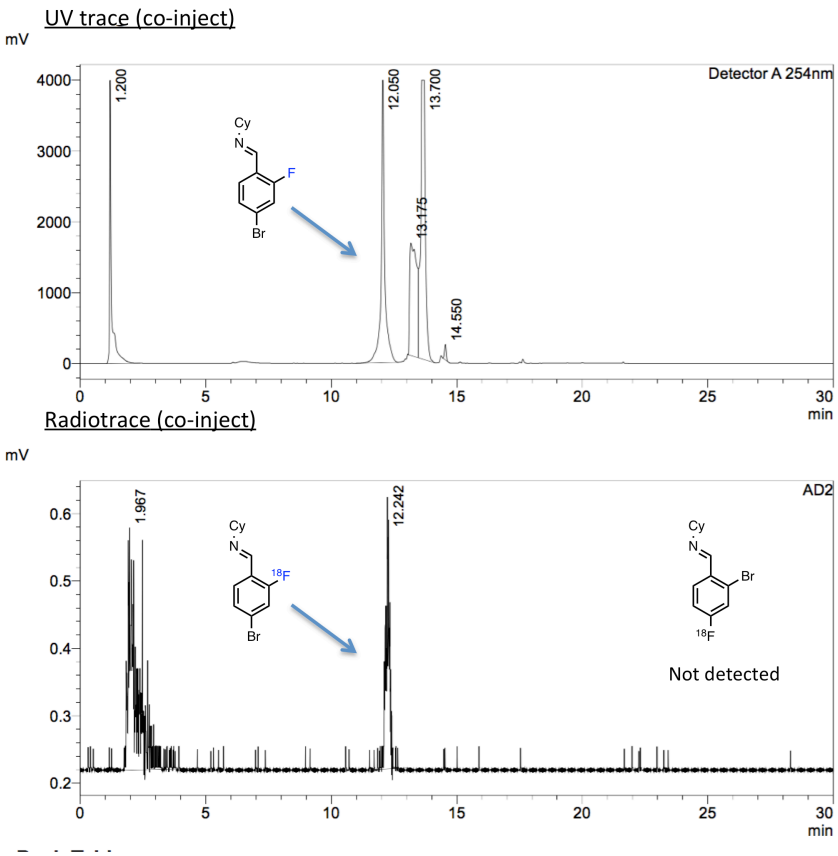
Radiotrace (co-inject)

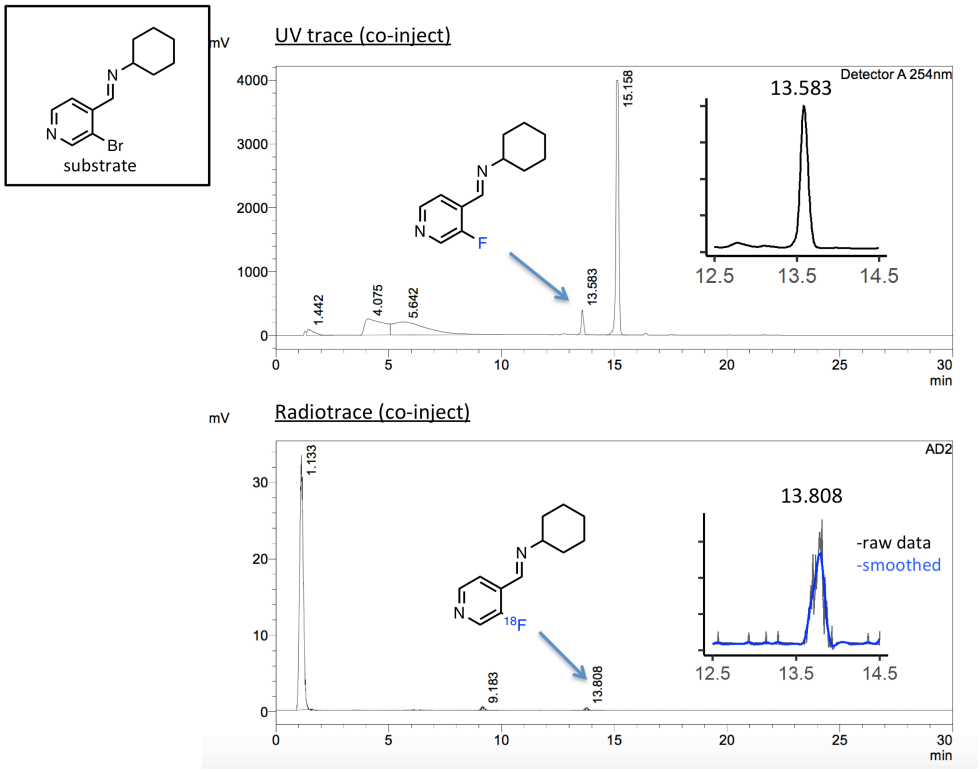


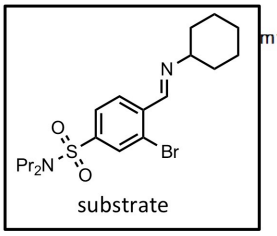


*Partial cleavage of imine observed during HPLC analysis

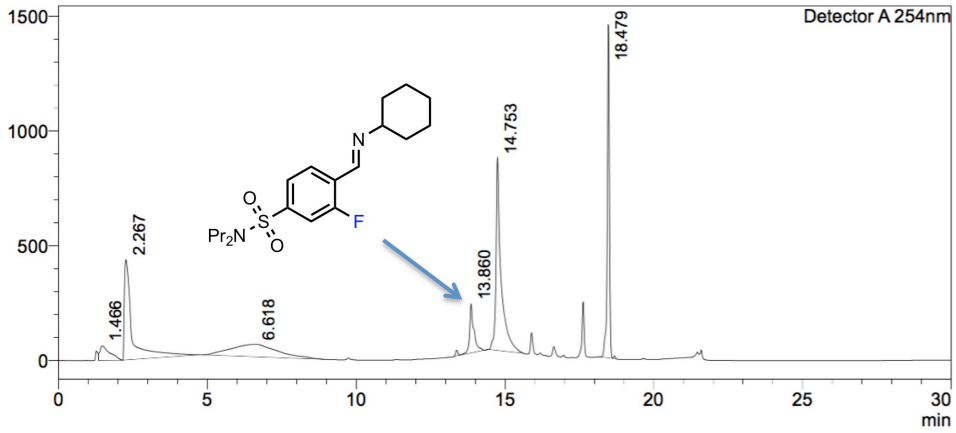

Cy
N
Br
Br
substrate


UV trace (co-inject)
mV
Detector A 254nm
1.200
12.050
13.700
13.175
14.550
Cy
N
F
Br
4000
3000
2000
1000
0
0
5
10
15
20
25
30
min
Radiotrace (co-inject)
mV
AD2
1.967
12.242
Cy
N
18F
Br
Cy
N
Br
18F
Not detected
0.6
0.5
0.4
0.3
0.2
0
5
10
15
20
25
30
min

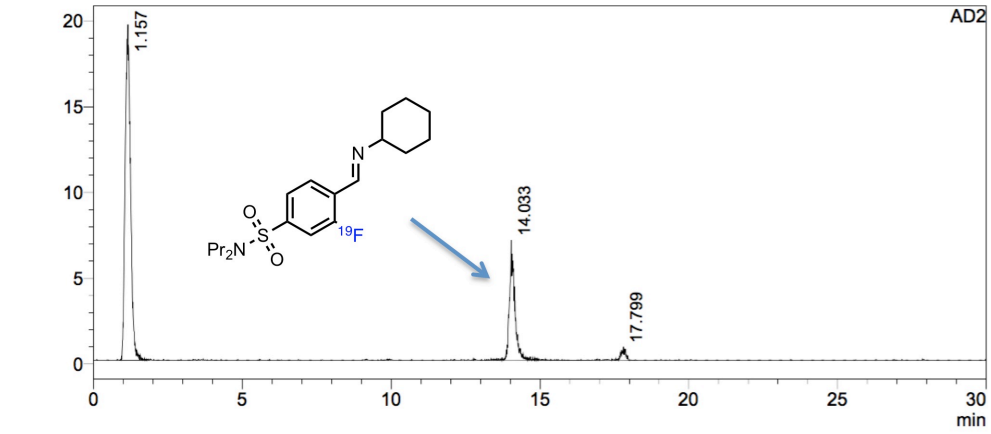

substrate
Br
N
mV
UV trace (co-inject)
Detector A 254nm
13.583
15.158
1.442
4.075
5.642
13.583
F
min
mV
Radiotrace (co-inject)
AD2
13.808
-raw data
-smoothed
1.133
9.183
13.808
18F
min

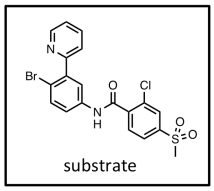


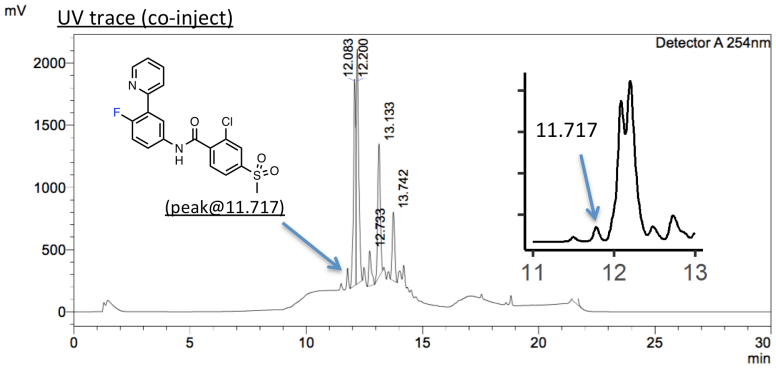
UV trace (co-inject)

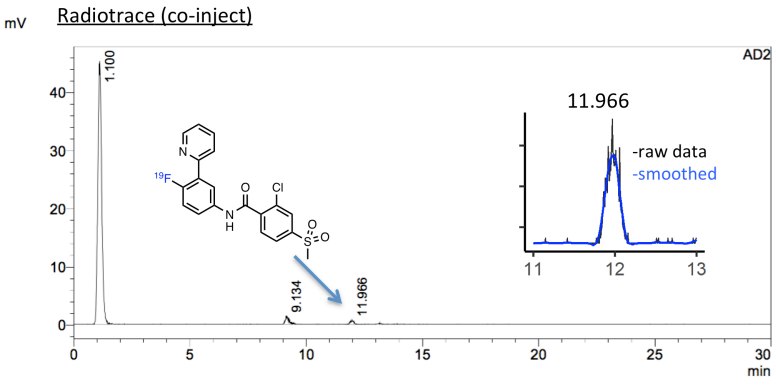


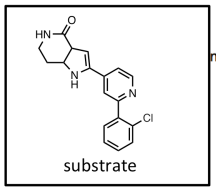
Radiotrace (co-inject)



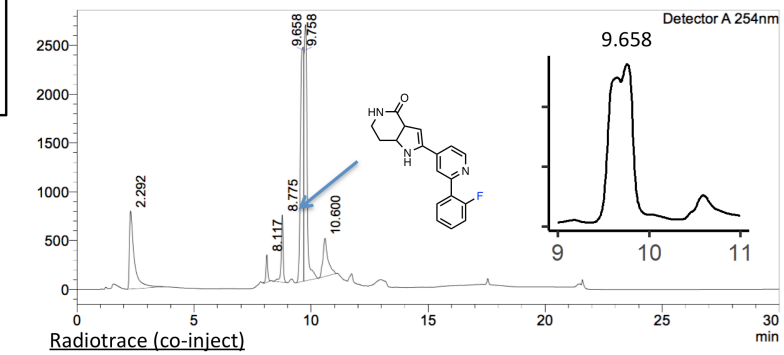

substrate


mV
UV trace (co-inject)
Detector A 254nm
12.083
12.200
13.133
13.742
12.733
(peak@11.717)
11.717
min

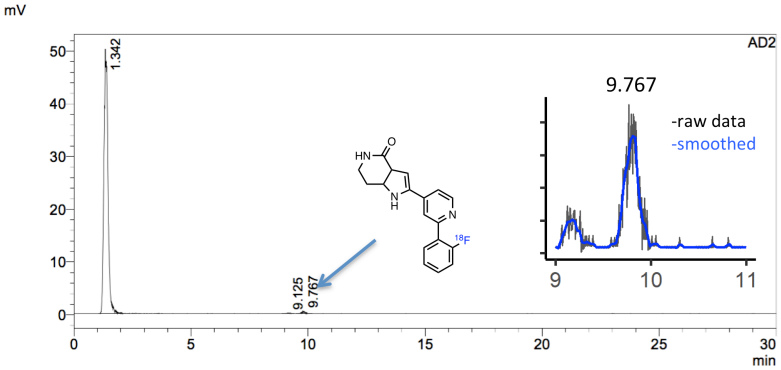

mV
Radiotrace (co-inject)
AD2
1.100
9.134
11.966
11.966
-raw data
-smoothed
min



UV trace (co-inject)



Radiotrace (co-inject)



10. References

[1] Xie, W.; Chang, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 1876–1880.
[2] Uehling, M. R.; Suess, A. M.; Lalic, G. *J. Am. Chem. Soc.* **2015**, 137, 1424–1427.
[3] Diez-Gonzalez, S.; Escudero-Adan, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans*., **2010**, *39*, 7595–7606. *Note: the following modification was made to the reported procedure: after following the reported work-up, the product was taken up in DCM and passed through a 1-inch silica plug to remove impurities.*
[4] Laitar, D. S. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 2006.
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[8] The chlorination procedure from the following reference was used to synthesize **1-Cl**: Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526.
Spectra of **1-Cl** matched those reported in the following reference: Botla, V.; Akudari, A.; Malapaka, C. *Tetrahedron Lett*. **2019**, *60*, 115–119.
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