Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Metal-free, oxidative decarboxylation of aryldifluoroacetic acid with formation of ArS-CF_2 bond

Contents

1. General information

^{1}H-, ^{13}C- and ^{19}F- NMR spectra were recorded in $CDCl_3$ on a Bruker AV-500. Chemical shifts for ^{l}H NMR spectra are reported in ppm relative to residual $CHCl_3$ as internal reference (δ 7.26 ppm for ^{1}H) downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in ppm relative to internal $CDCl_3$ (δ77.16 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartlet, respectively; br refers to a broad signal. The structures were solved by direct method with SHELXS-97 program and refined by full matrix least-squares on F2 with SHELXL-97 program. All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were located and included at their calculated position. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer, absorbance frequencies are given at maximum of intensity in cm^{-1}. High resolution mass spectra (HRMS) and Mass spectra (MS) were recorded using an Electron impact (EI) or Electrospray ionization (ESI) techniques. High resolution mass spectra (HRMS) was recorded on Thermo Fisher Scientific LTQ FT Ultra.

2. General synthetic procedure for the synthesis of difluoromethylated derivatives

Method A: A mixture of aryl difluoroacetic acid (0.50 mmol), aryl disulfides (0.5 mmol), and $(NH_4)_2S_2O_8$ (2.0 mmol) in 10 mL of DMSO and H_2O (v/v, 10:1) under N_2 atmosphere. The solution was stirred at 60 ^{o}C for 12 h. Then the reaction mixture was extracted with ethyl acetate and water. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by recrystallization or flash column chromatography on silica gel to give the desired aryl difluoromethylthio ether compounds. (**3aa-3ha & 3ab-3al**).

Method B: A mixture of aryl difluoroacetic acid (0.50 mmol), thiophenols (0.5

mmol), and $(NH_4)_2S_2O_8$ (2.0 mmol) in 10 mL of DMSO and H_2O (v/v, 10:1) under N_2 atmosphere. The solution was stirred at 60 °C for 12 h. Then the reaction mixture was extracted with ethyl acetate and water. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by recrystallization or flash column chromatography on silica gel to give the desired aryl difluoromethylthio ether compounds. (**3ab-3an**)

3 Single crystal X-ray analysis of 3ai (CCDC: 2080867)

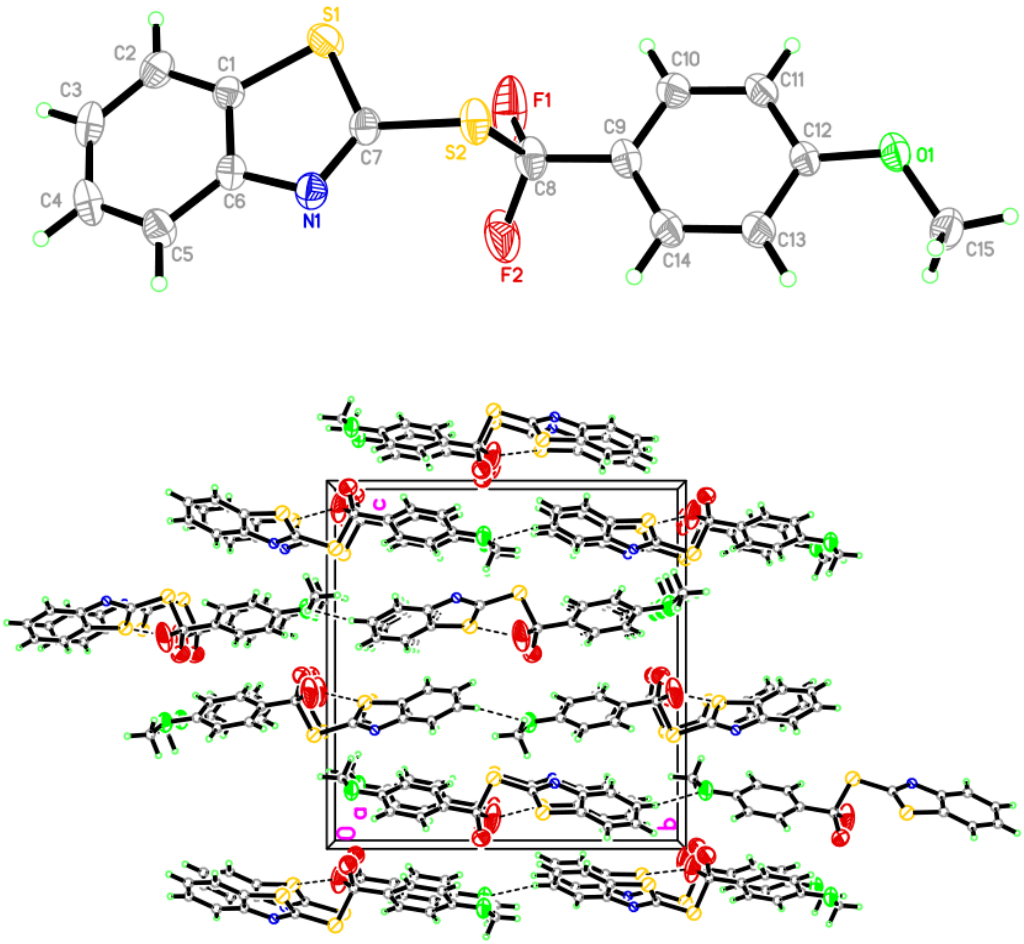


Figure S1. Crystal structure of 3ai (gray for carbon atoms, yellow for sulfur atoms, red for fluorine atom and green for oxygen atom). Thermal ellipsoids are drawn at the 50%.

The crystals suitable for X-ray crystallographic analysis were obtained by recrystallization from a solution (Hexane/Ethyl Acetate = 6/1). Crystallographic data and structural refinement results are summarized in Table S1. Bond lengths for 3ai are listed in Table S2. Bond angles for 3ai are listed in Table S3. Crystallographic data for the structure reported in the paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC 2080867 for 3ai. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S1. Crystal data and structure refinement for **3ai**

Compounds	**3ai**
Formula	$C_{15}H_{11}F_2NOS_2$
F_w	323.37 g/mol
Temperature	303(2) K
Crystal system	orthorhombic
Space group	P 21 21 21
a(Å)	5.89830(10)
b(Å)	15.4491(2)
c(Å)	15.8136(3)
α(°)	90
β(°)	90
γ(°)	90
V (Å^3)	1440.99(4)
Z	4
Dc (gcm^{-3})	1.491
F (000)	664
GOF on F^2	1.065
R_1, wR_2[I >2σ(I)]	0.0291,0.0902
R_1, wR_2 (all data)	0.0292,0.0904

R(int)	0.0250

Table S2. Bond lengths (Å) for 3ai

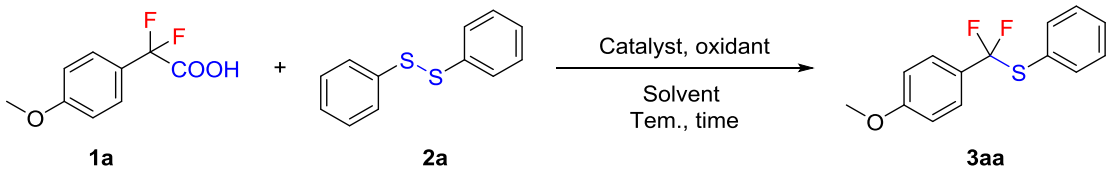
S1-C1	1.719(3)	S1-C7	1.736(3)
S2-C7	1.767(3)	S2-C8	1.808(3)
F1-C8	1.339(4)	F2-C8	1.359(5)
O1-C12	1.365(3)	O1-C15	1.433(4)
N1-C7	1.294(4)	N1-C6	1.395(3)
C1-C6	1.396(4)	C1-C2	1.400(4)
C2-C3	1.374(5)	C2-H2	0.93
C3-C4	1.385(5)	C3-H3	0.93
C4-C5	1.380(5)	C4-H4	0.93
C5-C6	1.392(4)	C5-H5	0.93
C8-C9	1.494(4)	C9-C14	1.379(5)
C9-C10	1.386(4)	C10-C11	1.375(4)
C10-H10	0.93	C11-C12	1.384(4)
C11-H11	0.93	C12-C13	1.382(4)
C13-C14	1.387(4)	C13-H13	0.93
C14-H14	0.93	C15-H15A	0.96
C15-H15B	0.96	C15-H15C	0.96

Table S3. Bond angles (°) for 3ai

C1-S1-C7	88.58(13)	C7-S2-C8	101.36(13)
C12-O1-C15	117.8(2)	C7-N1-C6	109.1(2)
C6-C1-C2	121.0(3)	C6-C1-S1	109.8(2)
C2-C1-S1	129.1(2)	C3-C2-C1	117.8(3)
C3-C2-H2	121.1	C1-C2-H2	121.1
C2-C3-C4	121.7(3)	C2-C3-H3	119.2
C4-C3-H3	119.2	C5-C4-C3	120.8(3)

C5-C4-H4	119.6	C3-C4-H4	119.6
C4-C5-C6	118.8(3)	C4-C5-H5	120.6
C6-C5-H5	120.6	C5-C6-N1	124.9(3)
C5-C6-C1	119.9(2)	N1-C6-C1	115.2(2)
N1-C7-S1	117.3(2)	N1-C7-S2	123.3(2)
S1-C7-S2	119.29(16)	F1-C8-F2	104.2(3)
F1-C8-C9	112.2(3)	F2-C8-C9	111.6(3)
F1-C8-S2	110.3(3)	F2-C8-S2	108.8(2)
C9-C8-S2	109.6(2)	C14-C9-C10	119.4(3)
C14-C9-C8	120.2(3)	C10-C9-C8	120.4(3)
C11-C10-C9	120.0(3)	C11-C10-H10	120.0
C9-C10-H10	120.0	C10-C11-C12	120.4(3)
C10-C11-H11	119.8	C12-C11-H11	119.8
O1-C12-C13	124.2(3)	O1-C12-C11	115.7(2)
C13-C12-C11	120.1(3)	C12-C13-C14	119.1(3)
C12-C13-H13	120.5	C14-C13-H13	120.5
C9-C14-C13	121.0(3)	C9-C14-H14	119.5
C13-C14-H14	119.5	O1-C15-H15A	109.5
O1-C15-H15B	109.5	H15A-C15-H15B	109.5
O1-C15-H15C	109.5	H15A-C15-H15C	109.5
H15B-C15-H15C	109.5		

4. Optimization of the reaction conditions



1a **2a** **3aa**

Table S4. Optimization varying different catalyst

Entry	Catalyst	Yield (%)
1	CuO、$AgNO_3$	56
2	CuCl、$AgNO_3$	0
3	$CuSO_4$、$AgNO_3$	50
4	None、$AgNO_3$	52
5	CH_3CO_2Ag 10%	51
6	$AgBF_4$ 10%	35
8	**none**	**48**

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a** (0.10 mmol), $(NH_4)_2S_2O_8$ (0.20 mmol), with different catalyst, 12 h, N_2 atmosphere at 80 °C temperature.

Conclusion: initially we choose metal-free catalysis.

Table S5. Optimization varying different oxidant

Entry	Oxidant	Yield (%)
1	$(NH_4)_2S_2O_8$ (2eq)	48
2	$K_2S_2O_8$ (2eq)	10
3	$Na_2S_2O_8$ (2eq)	28
4	None	0
5	$(NH_4)_2S_2O_8$ (2eq)	48
6	**$(NH_4)_2S_2O_8$ (4eq)**	**61**
7	$(NH_4)_2S_2O_8$ (6eq)	50

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a** (0.10 mmol), with different oxidant (0.2 mmol or 0.4 mmol), 12 h, N_2 atmosphere at 80 °C temperature.

Conclusion: we found that $(NH_4)_2S_2O_8$ (4eq) gave best result.

Table S6. Optimization varying different solvent

Entry	Solvent	Yield (%)
1	DMSO	61
2	DMF	0
3	NMP	0
4	Acetone	0
5	Toluene	0
6	1,4-dioxane	0
7	DMSO/H_2O (v:v, 1:1)	5
8	DMSO/H_2O (v:v, 5:1)	62
9	**DMSO/H_2O (v:v, 10:1)**	**74**

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a** (0.10 mmol), $(NH_4)_2S_2O_8$ (0.40 mmol), with different ratio of solvent, 12 h, N_2 atmosphere at 80 °C temperature.

Conclusion: we found that DMSO/H_2O (v:v, 10:1) gave best result.

Table S7. Optimization varying different temperature.

Entry	Temperature (°C)	Yield (%)
1	90	57
2	80	74
3	70	76
4	**60**	**93**
5	50	78

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a** (0.10 mmol), $(NH_4)_2S_2O_8$ (0.40 mmol), with different temperature, 12 h, N_2 atmosphere.

Conclusion: we found that 60 °C gave best result.

Table S8. Optimization varying different time.

Entry	Time (h)	Yield (%)
1	6	60
2	**12**	**93**
3	18	85
4	24	75

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a** (0.10 mmol), $(NH_4)_2S_2O_8$ (0.40 mmol), with different time, N_2 atmosphere at 60 °C temperature.

Conclusion: we found that 12 h gave best result.

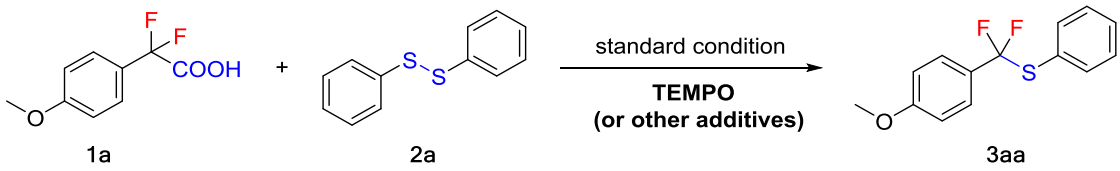
Table S9. Optimization varying different ratios of reagent.

Entry	Reagent Ratio (**1**/**2**)	Yield (%)
1	1:0.5	83
2	1:0.8	85
3	1:1	**93**
4	1:1.2	92
5	1:1.5	90
6	1:2	90

Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard, in the presence of **1a** (0.10 mmol), **2a**, $(NH_4)_2S_2O_8$ (0.40 mmol), with different ratios of reagent, N_2 atmosphere at 60 °C temperature.

Conclusion: we found that 1/2 = 1:1 gave reasonable result.

5. Preliminary mechanistic study



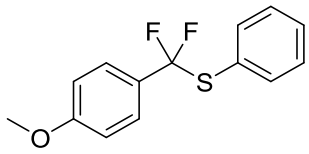
Entry	Additive (eq.)	Yield (%)
1	TEMPO (3.0)	43
2	1,4-Benzoquinone (0.50)	10
3	Hydroquinone (0.50)	0

Reaction condition:**1a** (0.10 mmol), **2a** (0.10 mmol) and $(NH_4)_2S_2O_8$ (0.40 mmol), under N_2 at 60 °C for 12 h. Yields determined by ^{19}F NMR analysis with $PhCF_3$ as the internal stander.

A mixture of aryldifluoroacetic acid (0.10 mmol) **1a**, diphenyl disulfide (0.10 mmol) **2a**, and $(NH_4)_2S_2O_8$ (0.40 mmol), in 2.0 mL of DMSO/H_2O (v/v, 10: 1) under N_2 atmosphere. The solution was stirred at 60 °C for 12 h. When 3.0 equiv TEMPO was added, the reaction yield decreased to 43%. When 0.50 equiv 1,4-Benzoquinone was added, the reaction yield decreased to 10%. When 0.50 equiv hydroquinone was added, no product was observed. The reaction was completely suppressed. But unfortunately we did not capture TEMPO-CF_2Ph, probably because this species is unstable at high temperatures.

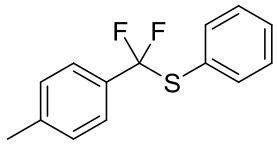
6. Characterization of the products

6.1 (difluoro(4-methoxyphenyl)methyl)(phenyl)sulfane (3aa)



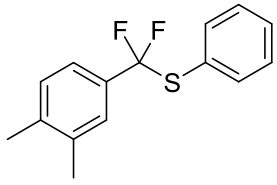
Purification by recrystallization (95% EtOH). Yield: 90%, white solid, m.p: 75-77 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.64 (d, *J* = 7.3 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.45-7.37 (m, 3H), 6.92 (d, *J* = 8.6 Hz,2H), 3.84 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.90 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.4, 136.3, 129.9, 129.1, 128.4 (t, *J* = 25.4 Hz), 128.0, 127.9 (t, *J* = 276.1 Hz), 127.2 (t, *J* = 4.5 Hz), 113.8, 55.5. **IR (**KBr, cm^{-1}**)**: ν_{max} = 3066, 2964, 2840, 1610, 1511, 1311, 1254, 1042, 826, 751, 692. **HRMS (ESI)** calcd. for $C_{14}H_{13}F_2OS$ $[M+H]^+$ 267.0650, found 267.0654.

6.2 (difluoro(p-tolyl)methyl)(phenyl)sulfane (3ba)



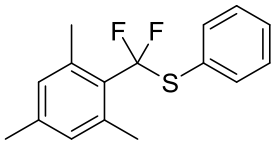
Purification by recrystallization (95% EtOH). Yield: 60%, white solid, m.p: 74-76 °C **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.67 (d, *J* = 7.8 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.46-7.39 (m, 3H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -70.91 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.8, 136.3, 133.2 (t, *J* = 25.0 Hz), 129.8, 129.0, 129.0, 127.8 (t, *J* = 278.5 Hz), 127.8, 125.4 (t, *J* = 4.6 Hz), 21.4. **IR** (KBr, cm^{-1}): ν_{max} = 2923, 2859, 1470, 1265, 1045, 919, 806, 748, 689. **HRMS (ESI)** calcd. for $C_{14}H_{13}F_2S$ $[M+H]^+$ 251.0701, found 251.0703.

6.3 ((3,4-dimethylphenyl)difluoromethyl)(phenyl)sulfane (3ca)



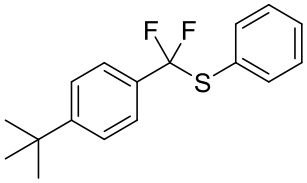
Purification by recrystallization (95% EtOH). Yield: 72%, white solid, m.p: 55-57 °C **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.72 (d, *J* = 6.9 Hz, 2H), 7.49-7.40 (m, 5H), 7.23 (d, *J* = 7.9 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -70.73 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 139.6, 136.9, 136.3, 133.5 (t, *J* = 24.7 Hz), 129.8, 129.7, 129.0, 127.9, 127.8 (t, *J* = 276.9 Hz), 126.5 (t, *J* = 4.5 Hz), 122.9 (t, *J* = 4.7 Hz), 19.9, 19.8. **IR** (KBr, cm^{-1}): ν_{max} = 2936, 1446, 1263, 1055, 955, 848, 812, 748, 690. **HRMS (ESI)** calcd. for $C_{15}H_{15}F_2S$ $[M+H]^+$ 265.0857, found 265.0853.

6.4 (difluoro(mesityl)methyl)(phenyl)sulfane (3da)



Purification by recrystallization (95% EtOH). Yield: 85%, white solid, m.p: 65-67 °C **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.74 (d, *J* = 6.9 Hz, 2H), 7.53-7.45 (m, 3H), 6.96 (s, 2H), 2.58 (s, 6H), 2.33 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -63.11 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 140.0, 137.3 (t, *J* = 2.4 Hz), 136.5, 131.0, 129.8, 129.8 (t, *J* = 20.2 Hz), 129.7 (t, *J* = 280.0 Hz), 129.0, 127.7, 22.2, 20.9. **IR** (KBr, cm^{-1}): ν_{max} = 2978, 2924, 2867, 1604, 1439, 1235, 1055, 891, 721, 686. **HRMS (ESI)** calcd. for $C_{16}H_{17}F_2S$ $[M+H]^+$ 279.1014, found 279.1015.

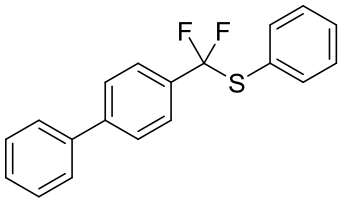
6.5 ((4-(tert-butyl)phenyl)difluoromethyl)(phenyl)sulfane (3ea)



Purification by recrystallization (95% EtOH). Yield: 55%, white solid, m.p: 41-43 °C **^{1}H NMR** (600 MHz, $CDCl_3$) δ ppm 7.65 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H),

7.45-7.42 (m, 3H), 7.40-7.37 (m, 2H), 1.34 (s, 9H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -70.96 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 153.9, 136.3, 133.1 (t, *J* = 24.6 Hz), 129.8 , 128.9, 127.8, 127.7 (t, *J* = 276.8 Hz), 125.3, 125.2 (t, *J* = 4.4 Hz), 34.9, 31.2. **IR** (KBr, cm^{-1}): ν_{max} = 3062, 2959, 2870, 1611, 1470, 1269, 1047, 920, 825, 739, 690. **HRMS (ESI)** calcd. for $C_{17}H_{19}F_2S$ $[M+H]^+$ 293.1170, found 293.1166.

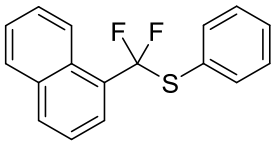
6.6 ([1,1'-biphenyl]-4-yldifluoromethyl)(phenyl)sulfane (3fa)



Purification by recrystallization (95% EtOH). Yield: 65%, white solid, m.p: 143-145 ^oC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.70-7.65 (m, 6H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.51-7.45 (m, 3H), 7.43 – 7.40 (m, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -71.30 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.5, 140.1, 136.4, 134.8 (t, *J* = 25.1 Hz) , 130.0, 129.1, 129.0, 128.0, 127.7 (t, *J* = 277.0 Hz), 127.6, 127.3, 127.1, 126.0 (t, *J* = 4.5 Hz). **IR** (KBr, cm^{-1}): ν_{max} = 3063, 2924, 1481, 1270, 1048, 922, 833, 756, 690. **HRMS (ESI)** calcd. for $C_{19}H_{15}F_2S$ $[M+H]^+$ 313.0857, found 313.0856.

6.7 (difluoro(naphthalen-1-yl)methyl)(phenyl)sulfane (3ga)

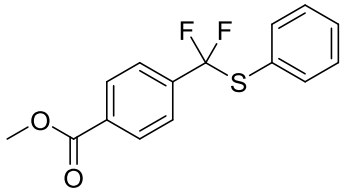


Purification by recrystallization (Hexane/Acetone). Yield: 52%, white solid, m.p: 77-79 ^oC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.65 (d, *J* = 8.6 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.72 (d, *J* = 7.4 Hz, 1H), 7.68-7.65 (m, 3H), 7.58 (t, *J* = 7.4

Hz, 1H), 7.46 – 7.43 (m, 2H), 7.41 - 7.38 (m, 2H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -68.19 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 136.4, 134.1, 131.9, 131.1 (t, *J* = 22.6 Hz) , 130.0, 129.3, 129.0, 128.7, 128.0 (t, *J* = 277.9 Hz), 127.6, 126.8, 126.2, 125.7 (t, *J* = 2.9 Hz), 124.7 (t, *J* = 7.7 Hz), 124.3. **IR** (KBr, cm^{-1}): ν_{max} = 3049, 2918, 2848, 1236, 1078, 1019, 987, 912, 797, 757, 689. **HRMS (ESI)** calcd. for $C_{17}H_{13}F_2S$ $[M+H]^+$ 287.0701, found 287.0704.

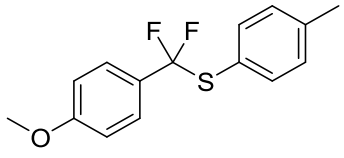
6.8 Methyl 4-(difluoro(phenylthio)methyl)benzoate (3ha)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 50/1). Yield: 15%, white solid, m.p: 61-63 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.06 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.59-7.57 (m, 2H), 7.45-7.41 (m, 1H), 7.38-7.35 (m, 2H), 3.94 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -72.81 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.3, 140.2 (t, *J* = 25.4 Hz), 136.6, 132.2, 130. 2, 129.7, 129.2, 127.3 (t, *J* = 277.1 Hz), 127.0, 125.6 (t, *J* = 4.5 Hz), 52.5. **IR** (KBr, cm^{-1}): ν_{max} = 2950, 1729, 1441, 1271, 1111, 1048, 925, 852, 756. **HRMS (ESI)** calcd. for $C_{15}H_{13}F_2O_2S$ $[M+H]^+$ 295.0599, found 295.0595.

6.9 (difluoro(4-methoxyphenyl)methyl)(p-tolyl)sulfane (3ab)

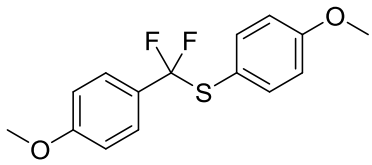


Purification by recrystallization (95% EtOH). Yield: 85%, white solid, m.p: 90-93 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (d, J = 8.9 Hz, 2H), 7.52 (d, J = 7.9 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 2.38 (s, 3H); **^{19}F NMR**

(471 MHz, $CDCl_3$) δ ppm -70.25 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.2, 140.2, 136.3, 129.8, 128.4 (t, *J* = 25.2 Hz), 127.7 (t, *J* = 276.1 Hz), 127.1 (t, *J* = 4.5 Hz), 124.3, 113.6, 55.4, 21.3. **IR** (KBr, cm^{-1}): ν_{max} = 2971, 2847, 1608, 1508, 1254, 1174, 1027, 912, 822, 655. **HRMS (ESI)** calcd. for $C_{15}H_{15}F_2OS$ $[M+H]^+$ 281.0806, found 281.0802.

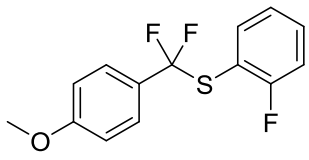
6.10 (difluoro(4-methoxyphenyl)methyl)(4-methoxyphenyl)sulfane (3ac)



Purification by recrystallization (95% EtOH). Yield: 62%, white solid, m.p: 133-135 ^oC

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.54 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.91 (t, *J* = 8.0 Hz, 4H), 3.83 (s, 3H), 3.82 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -70.90 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.3, 161.2, 138.3, 128.4 (t, *J* = 25.4 Hz), 127.8 (t, *J* = 276.0 Hz), 127.1 (t, *J* = 4.5 Hz), 118.5, 114.6, 113.7, 55.5, 55.5. **IR** (KBr, cm^{-1}): ν_{max} = 2968, 2840, 2039, 1914, 1601, 1505, 1304, 1248, 1170, 1038, 914, 828, 643. **HRMS (ESI)** calcd. for $C_{15}H_{15}F_2O_2S$ $[M+H]^+$ 297.0755, found 297.0751.

6.11 (difluoro(4-methoxyphenyl)methyl)(2-fluorophenyl)sulfane (3ad)

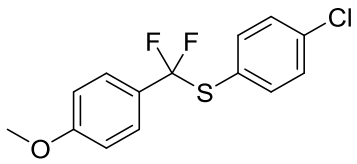


Purification by recrystallization (Hexane). Yield: 55%, white solid, m.p: 53-55 ^oC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.66 (t, *J* = 7.3 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H),

7.46-7.41 (m, 1H), 7.19-7.17 (m, 1H), 7.16-7.13 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.30 (s, CF_2), -105.65- -105.71 (m, F); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 163.5 (d, *J* = 248.8 Hz), 161.5, 139.1, 132.7 (d, *J* = 8.1 Hz), 127.9 (t, *J* = 25.0 Hz), 127.7 (t, *J* = 277.8 Hz), 127.2 (t, *J* = 4.6 Hz), 124.6 (d, *J* = 3.8 Hz), 116.4, 115.0 (d, *J* = 18.2 Hz), 113.8, 55.5. **IR** (KBr, cm^{-1}): ν_{max} = 2927, 1608, 1511, 1472, 1257, 1041, 910, 824, 760, 650. **HRMS (ESI)** calcd. for $C_{14}H_{12}F_3OS$ $[M+H]^+$ 285.0555, found 285.0558.

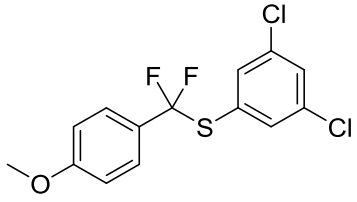
6.12 (4-chlorophenyl)(difluoro(4-methoxyphenyl)methyl)sulfane (3ae)



Purification by recrystallization (EtOH). Yield: 50%, white solid, m.p: 73-75 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.87 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.5, 137.6, 136.5, 129.33, 128.0 (t, *J* = 25.1 Hz), 127.7 (t, *J* = 277.2 Hz), 127.2 (t, *J* = 4.5 Hz), 126.4, 113.8, 55.5. **IR** (KBr, cm^{-1}): ν_{max} = 2968, 1610, 1509, 1465, 1254, 1043, 912, 825, 735, 651. **HRMS (ESI)** calcd. for $C_{14}H_{12}ClF_2OS$ $[M+H]^+$ 301.0260, found 301.0261.

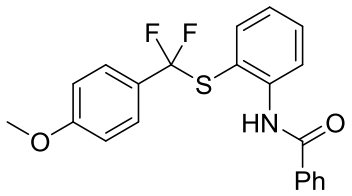
6.13 (3,5-dichlorophenyl)(difluoro(4-methoxyphenyl)methyl)sulfane (3af)



Purification by recrystallization (EtOH/ Hexane). Yield: 52%, white solid, m.p: 62-64 ^{o}C

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (d, *J* = 1.9 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.42 (t, *J* = 1.9 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.17 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.7, 135.2, 133.8, 131.1, 130.1, 127.6 (t, *J* = 278.0 Hz), 127.5 (t, *J* = 25.0 Hz), 127.2 (t, *J* = 4.7 Hz), 114.0, 55.6. **IR** (KBr, cm^{-1}): ν_{max} = 2932, 2843, 1607, 1558, 1510, 1255, 1049, 910, 821, 794, 659. **HRMS (ESI)** calcd. for $C_{14}H_{11}Cl_2F_2OS$ $[M+H]^+$ 334.9870, found 334.9865.

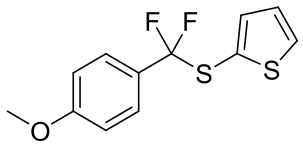
6.14 N-(2((difluoro(4methoxyphenyl)methyl)thio)phenyl)benzamide (3ag)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 10/1). Yield: 45%, white solid, m.p: 86-88 ^{o}C

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 9.22 (s, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.61-7.58 (m, 2H), 7.55-7.50 (m, 3H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.84(d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.63 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 165.1, 161.5, 141.5, 139.1, 135.0, 132.5, 132.2, 129.0, 127.8 (t, *J* = 278.7 Hz), 127.6 (t, *J* = 25.2 Hz), 127.2, 126.73 (t, *J* = 4.8 Hz), 124.2, 120.6, 115.6, 113.9, 55.5. **IR** (KBr, cm^{-1}): ν_{max} = 3401, 2922, 2846, 1690, 1584, 1522, 1434, 1307, 1257, 1047, 903, 824, 752, 698. **HRMS (ESI)** calcd. for $C_{21}H_{18}F_2NO_2S$ $[M+H]^+$ 386.1021, found 386.1017.

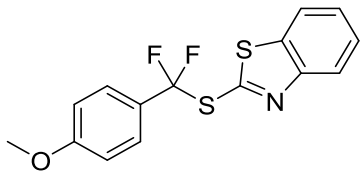
6.15 2-((difluoro(4-methoxyphenyl)methyl)thio)thiophene (3ah)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 100/1). Yield: 50%, white solid, m.p: 56-58 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.53 (d, *J* = 5.3 Hz, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 3.6 Hz, 1H), 7.07 (dd, *J* = 5.3, 3.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -71.85 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.4, 138.2, 132.8, 127.8, 127.4 (t, *J* = 5.0 Hz), 127.1 (t, *J* = 2.9 Hz), 126.9 (t, *J* = 278.4 Hz), 125.0, 113.7, 55.4. **IR** (KBr, cm^{-1}): ν_{max} = 2962, 2924, 2849, 1610, 1510, 1258, 1093, 1042, 910, 804, 720. **HRMS (ESI)** calcd. for $C_{12}H_{11}F_2OS_2$ $[M+H]^+$ 273.0214, found 273.0211.

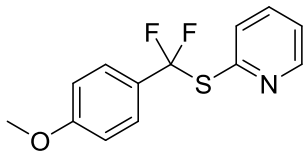
6.16 2-((difluoro(4-methoxyphenyl)methyl)thio)benzo[d]thiazole (3ai)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 15/1). Yield: 75%, white solid, m.p: 87-89 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.10 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.52-7.49 (m, 1H), 7.45-7.41 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -67.11 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.9, 156.3, 153.0, 137.8, 127.4 (t, *J* = 280.5 Hz), 127.4 (t, *J* = 4.4 Hz), 126.6 (t, *J* = 24.0 Hz), 126.5, 126.0, 123.7, 121.2, 114.0, 55.5. **IR** (KBr, cm^{-1}): ν_{max} = 3061, 2924, 2853, 1601, 1504, 1451, 1310, 1251, 1042, 899, 823, 757, 657, 568. **HRMS (ESI)** calcd. for $C_{15}H_{12}F_2NOS_2$ $[M+H]^+$ 324.0323, found 324.0325.

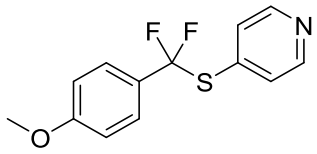
6.17 2-((difluoro(4-methoxyphenyl)methyl)thio)pyridine (3aj)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 10/1). Yield: 47%, white solid, m.p: 53-55 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.57 (d, *J* = 4.8 Hz, 1H), 7.71-7.65 (m, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.24-7.22 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -68.68 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.6, 152.9, 150.3, 137.2, 128.5, 128.3 (t, *J* = 277.7 Hz), 127.9 (t, *J* = 24.8 Hz), 127.3 (t, *J* = 4.8 Hz), 123.1, 113.9, 55.5; **IR** (KBr, cm^{-1}): ν_{max} = 3049, 2972, 2927, 2847, 1610, 1570, 1514, 1258, 1181, 1037, 914, 829, 768, 656; **HRMS (ESI)** calcd. for $C_{13}H_{11}F_2NOS$ $[M+H]^+$ 268.0602, found 268.0603. **HRMS (ESI)** calcd. for $C_{13}H_{12}F_2NOS$ $[M+H]^+$ 268.0602, found 268.0605.

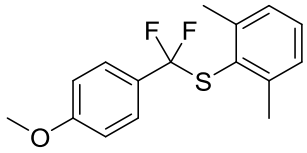
6.18 4-((difluoro(4-methoxyphenyl)methyl)thio)pyridine (3ak)



Purification by column chromatography on silica gel (petroleum ether/EtOAc = 3/1). Yield: 73%, white solid, m.p: 38-40 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.55 (d, *J* = 5.5 Hz, 2H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 5.8 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -68.27 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.6, 150.0, 139.8, 127.8 (t, *J* = 278.7 Hz), 127.3 (t, *J* = 24.9 Hz), 127.3, 127.1 (t, *J* = 4.6 Hz), 113.8, 55.4. **IR** (KBr, cm^{-1}): ν_{max} = 3041, 2954, 2837, 1611, 1572, 1511, 1254, 1173, 1050, 915, 829, 801, 695, 657. **HRMS (ESI)** calcd. for $C_{13}H_{12}F_2NOS$ $[M+H]^+$ 268.0602, found 268.0603.

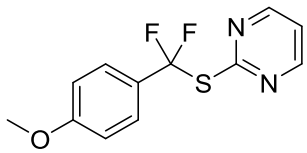
6.19 (difluoro(4-methoxyphenyl)methyl)(2,6-dimethylphenyl)sulfane (3am)



Purification by recrystallization (95% EtOH). Yield: 80%, white solid, m.p: 64-67 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.56 (d, *J* = 8.8 Hz, 2H), 7.25-7.23 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 2.61 (s, 6H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -69.0 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 161.3, 145.6, 130.2, 128.8 (t, *J* = 277.7 Hz), 128.7 (t, *J* = 25.0 Hz), 128.3, 126.8 (t, *J* = 4.6 Hz), 126.7, 113.7, 55.4, 22.5. **IR** (KBr, cm^{-1}): ν_{max} = 2924, 2841, 1609, 1509, 1456, 1307, 1257, 1171, 1018, 909, 822, 775, 647. **HRMS (ESI)** calcd. for $C_{16}H_{17}F_2OS$ $[M+H]^+$ 295.0963, found 295.0967.

6.20 2-((difluoro(4-methoxyphenyl)methyl)thio)pyrimidine (3an)

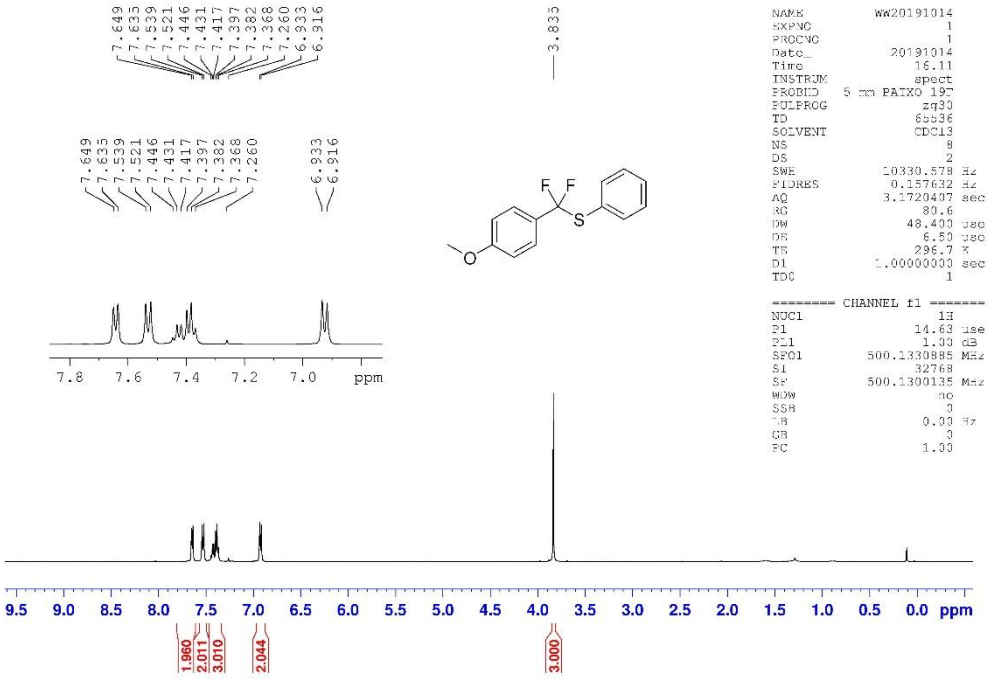


Purification by column chromatography on silica gel (petroleum ether/EtOAc = 5/1). Yield: 16%, white solid, m.p: 38-41 ºC

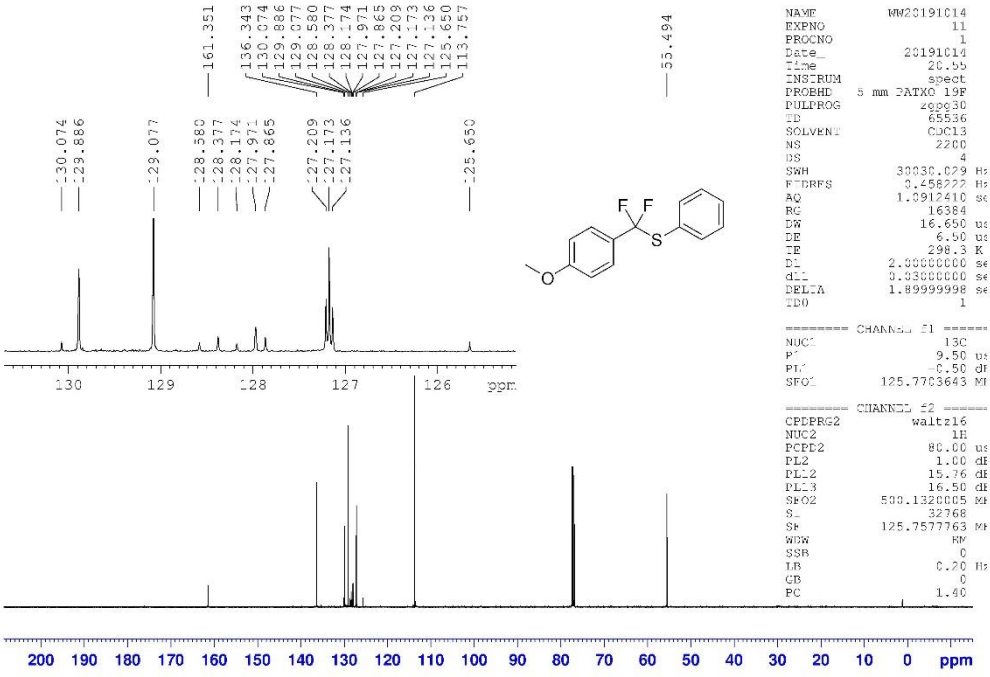
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.60 (d, *J* = 5.0 Hz, 2H), 7.65 (d, *J* = 8.9 Hz, 2H), 7.09 (t, *J* = 5.0 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H); **^{19}F NMR** (471 MHz, $CDCl_3$) δ ppm -71.03 (s, CF_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 168.2, 161.5, 157.7, 128.0 (t, *J* = 24.6 Hz), 127.6 (t, *J* = 5.0 Hz), 127.3 (t, *J* = 277.9 Hz), 118.4, 113.7, 55.4. **IR** (KBr, cm^{-1}): ν_{max} = 2964, 1614, 1557, 1512, 1386, 1314, 1257, 1177, 1054, 914, 830. **HRMS (ESI)** calcd. for $C_{12}H_{11}F_2N_2OS$ $[M+H]^+$ 269.0555, found 269.0557.

7. Copies of ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectra of the products

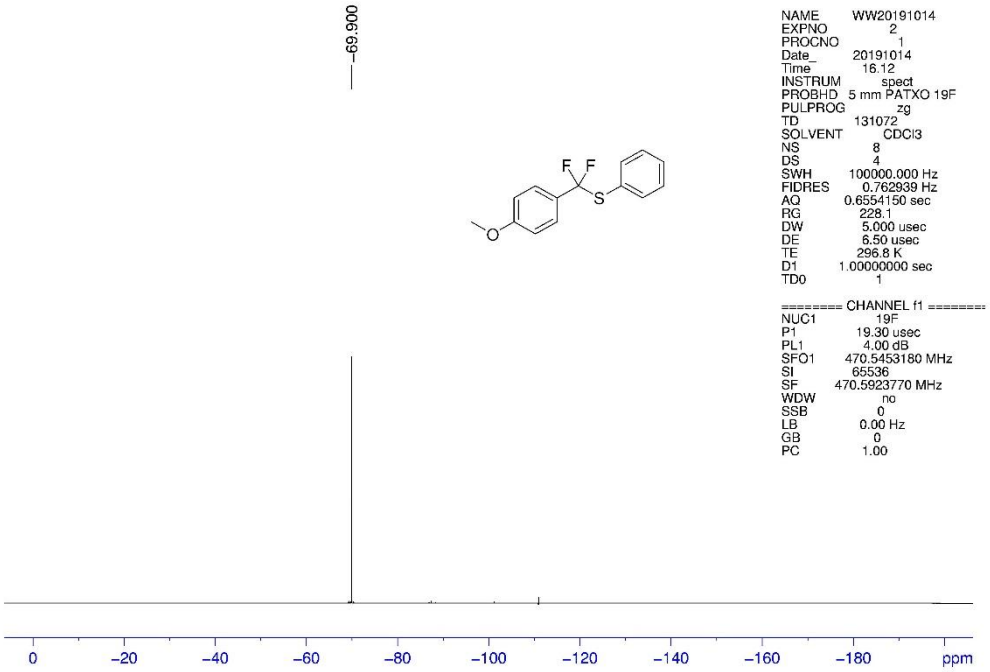
^{1}H NMR Spectra of **3aa**



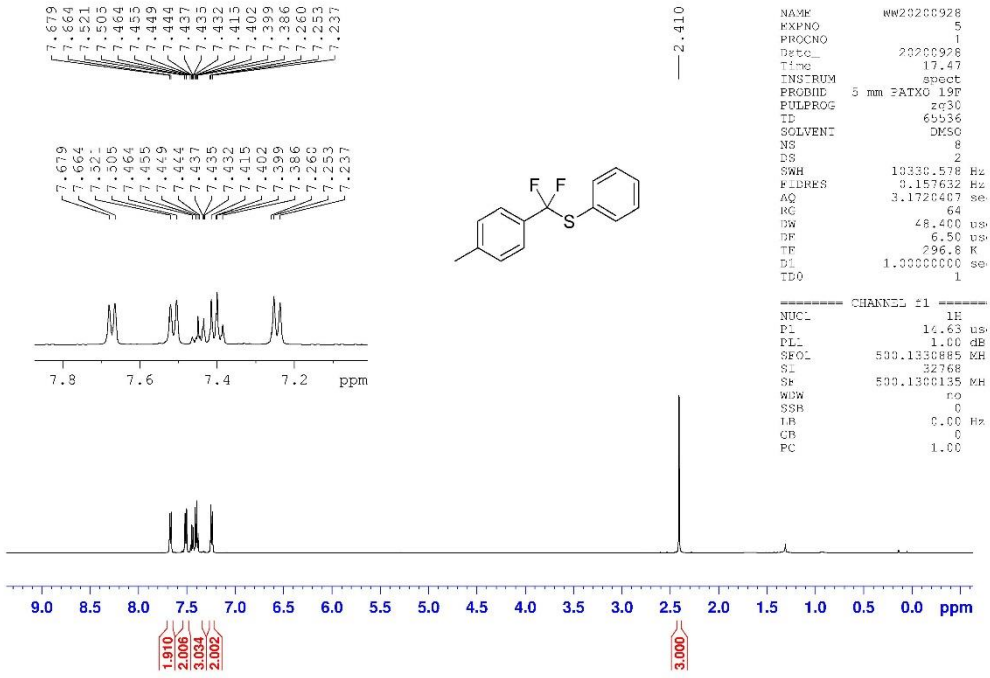
^{13}C NMR Spectra of **3aa**



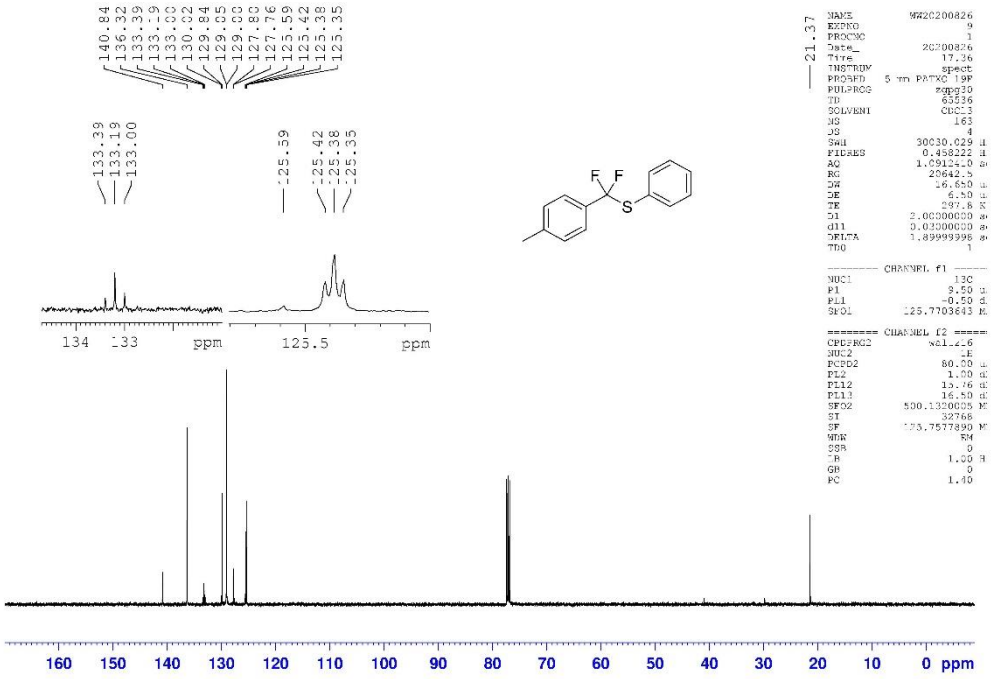
^{19}F NMR Spectra of **3aa**



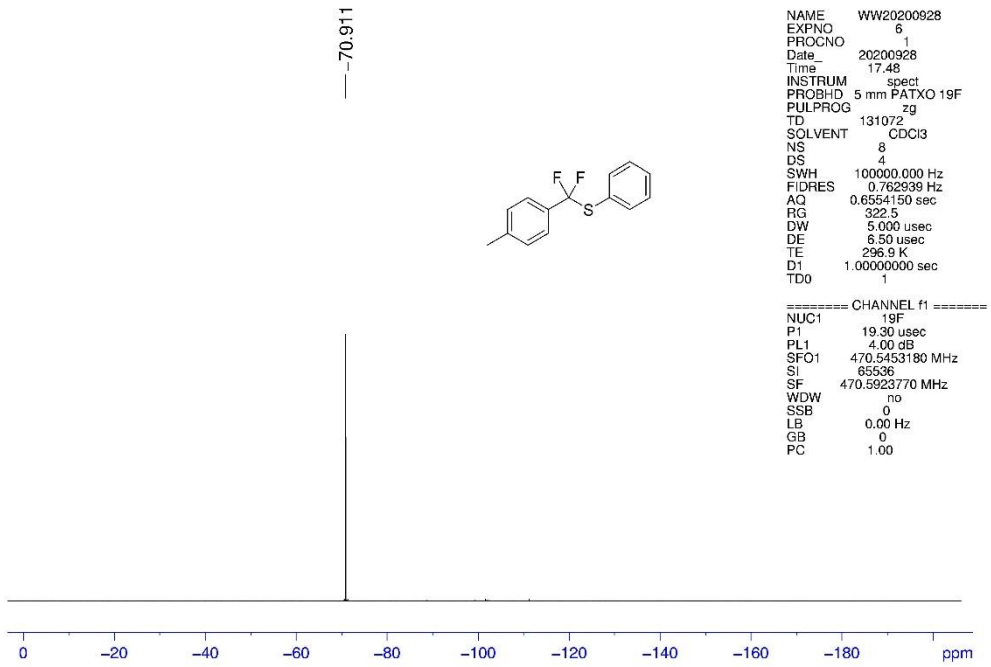
^{1}H NMR Spectra of **3ba**



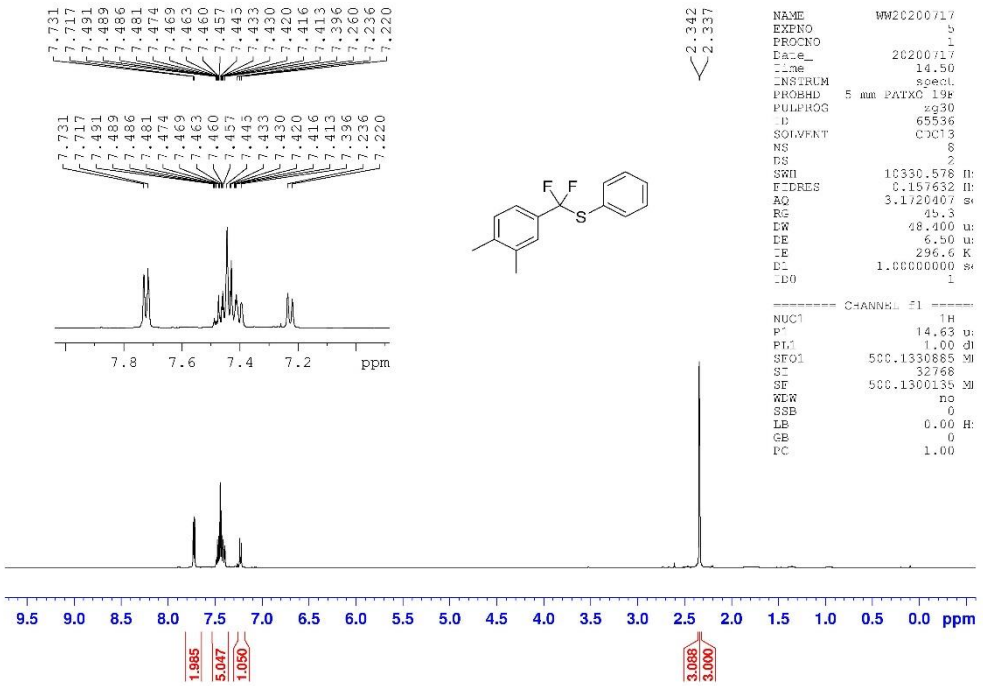
^{13}C NMR Spectra of **3ba**



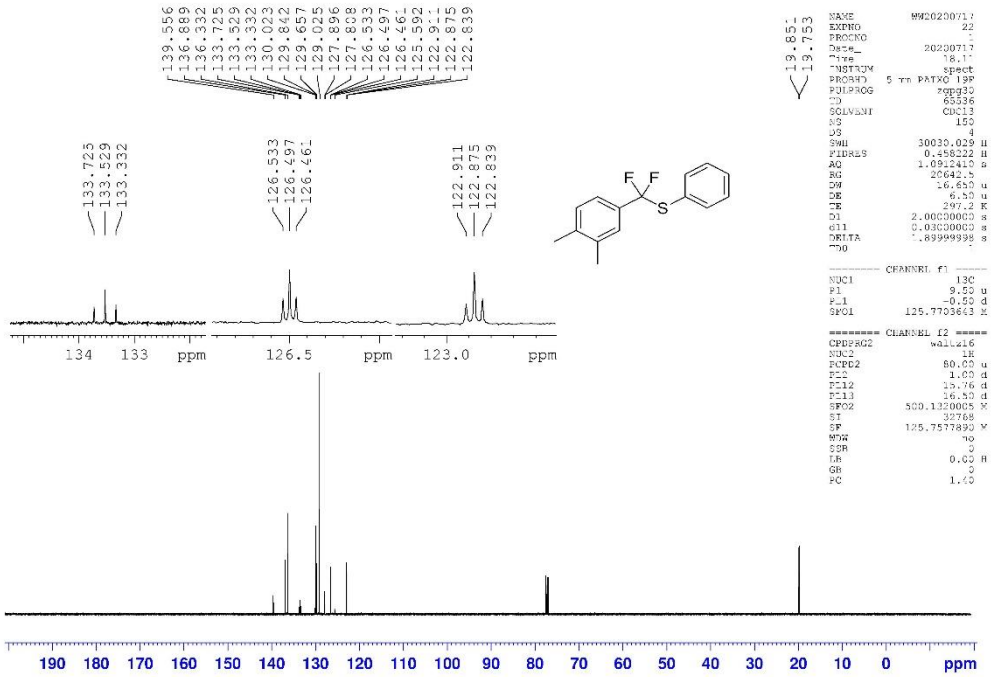
^{19}F NMR Spectra of **3ba**



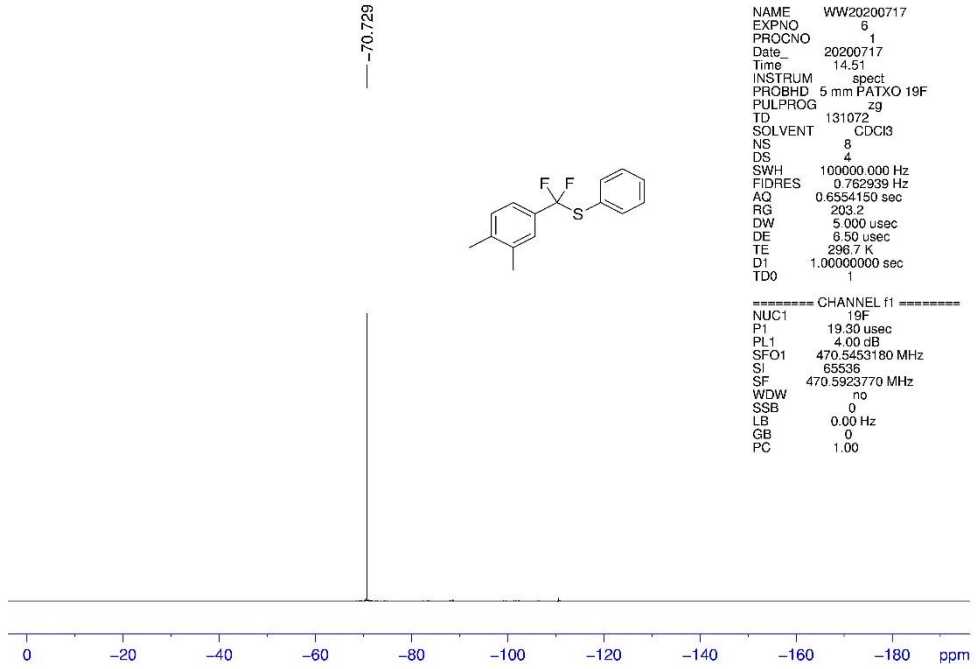
^{1}H NMR Spectra of **3ca**



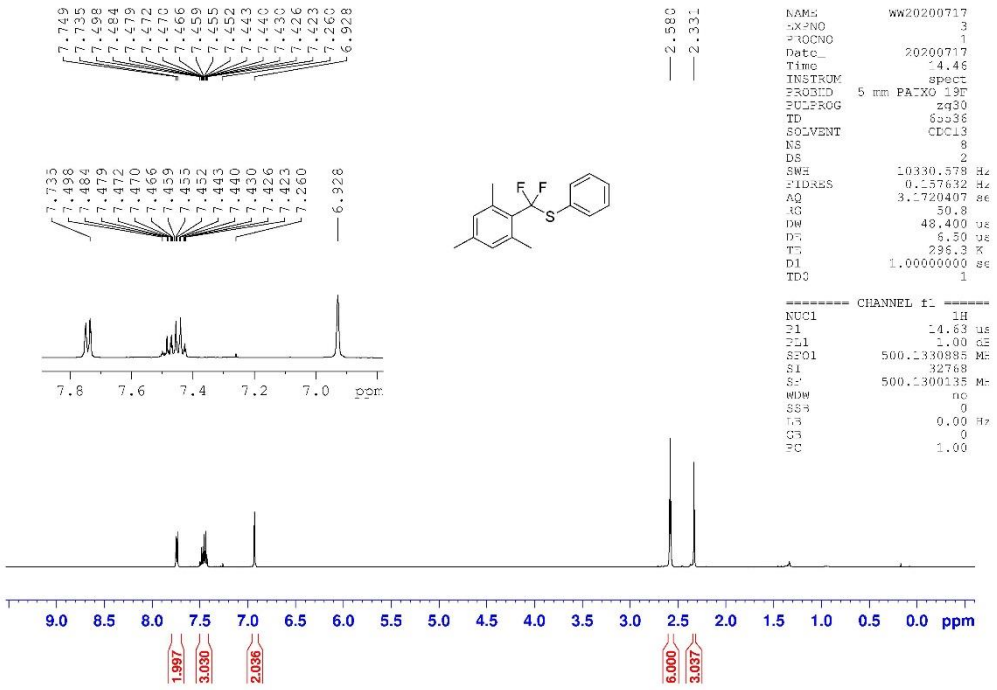
^{13}C NMR Spectra of **3ca**



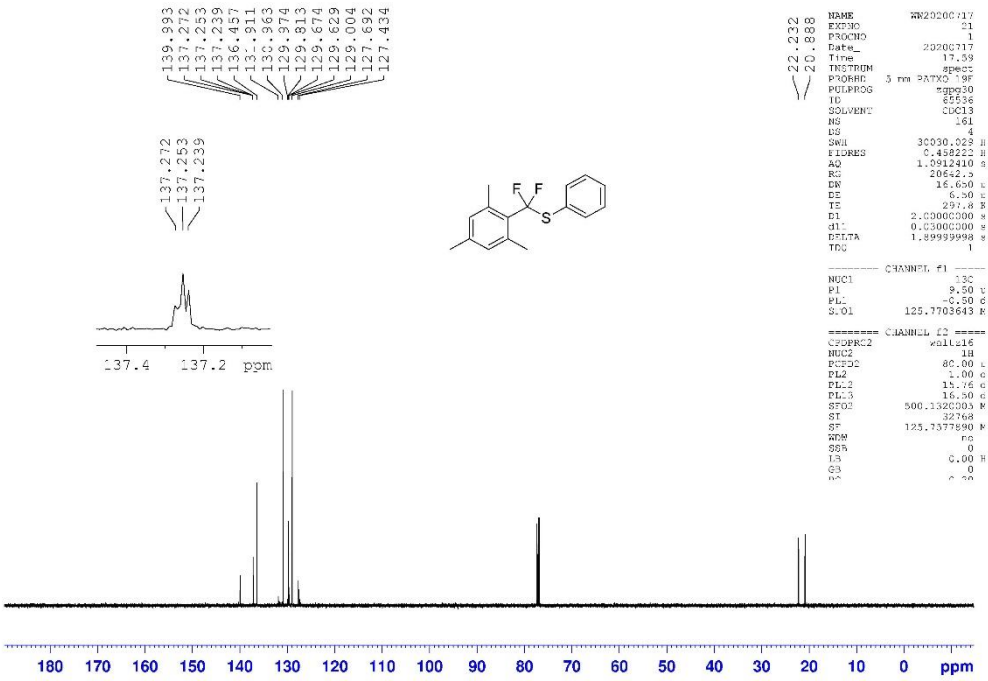
^{19}F NMR Spectra of **3ca**



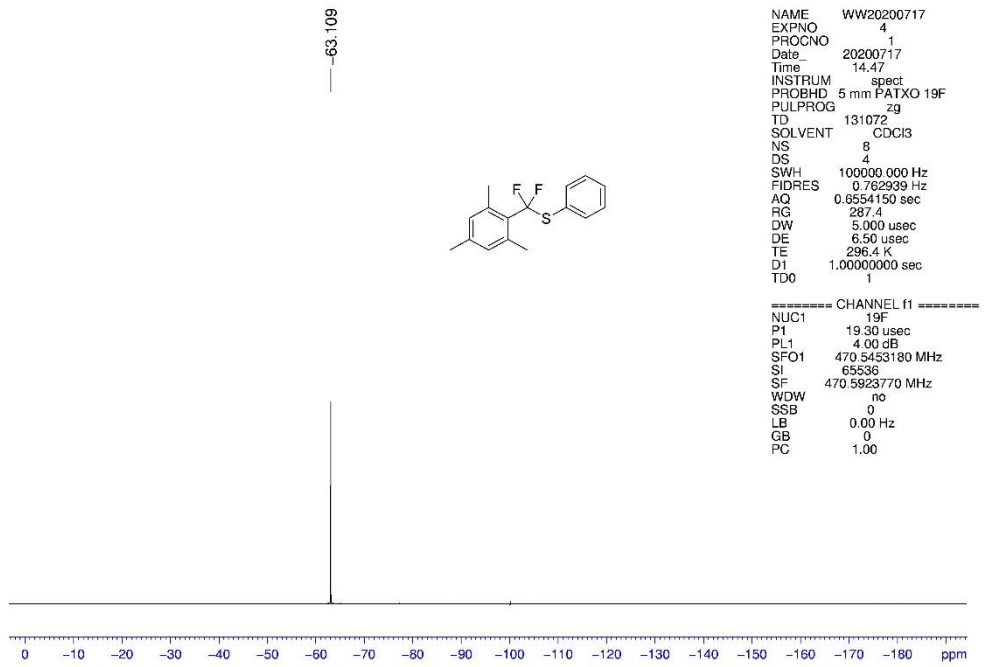
^{1}H NMR Spectra of **3da**



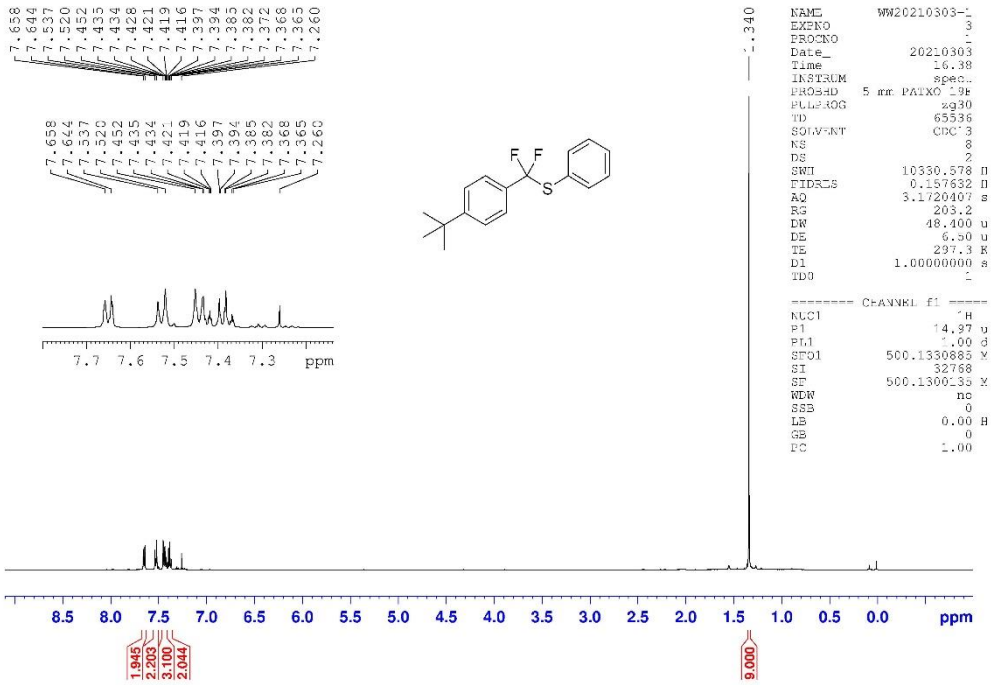
^{13}C NMR Spectra of **3da**



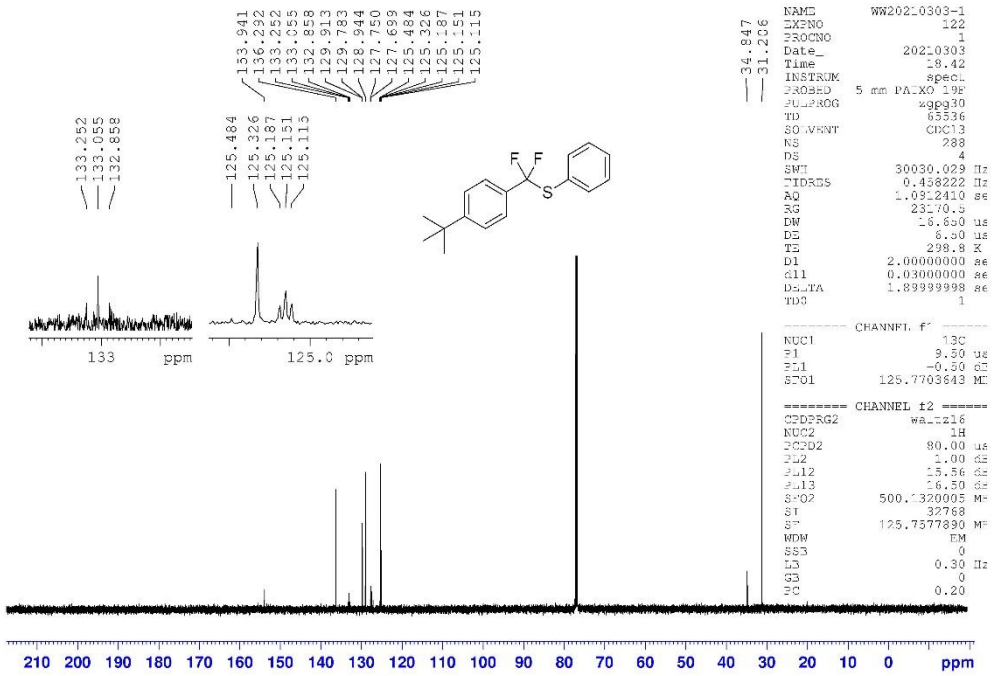
^{19}F NMR Spectra of **3da**



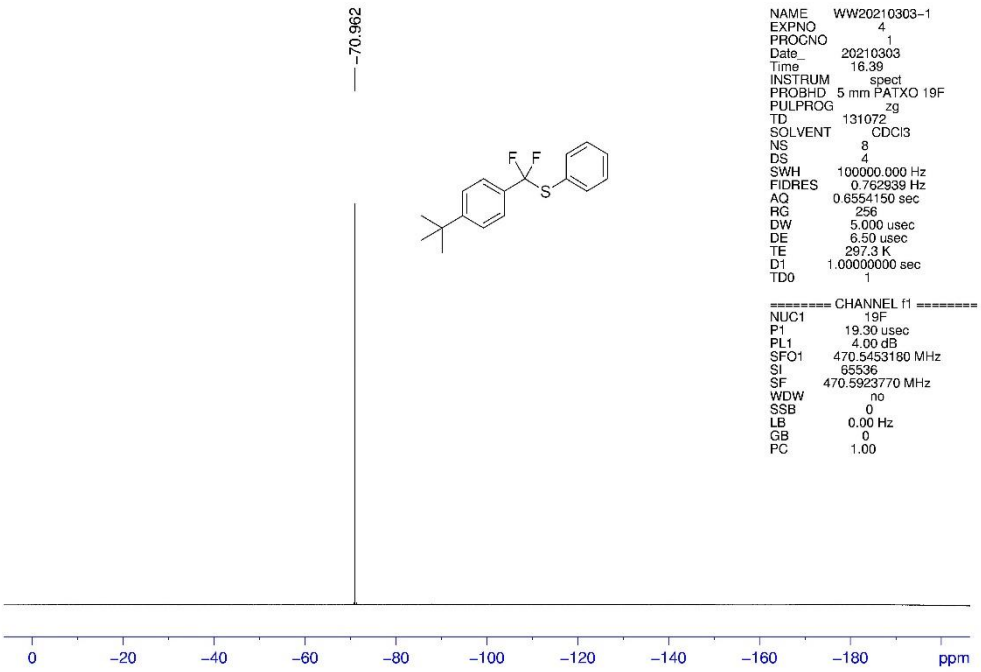
^{1}H NMR Spectra of **3ea**



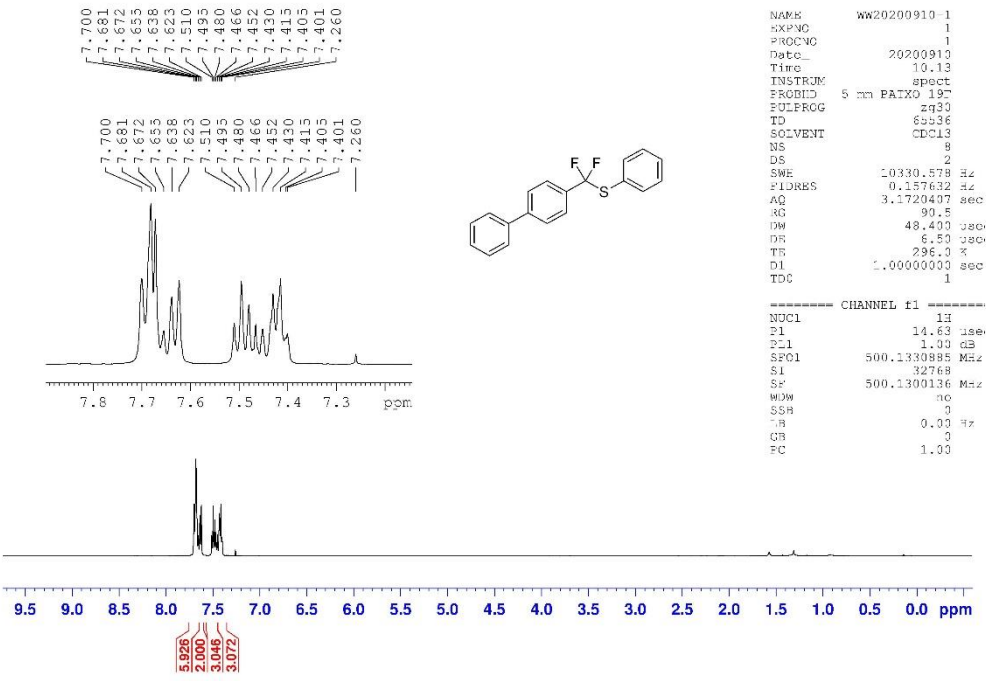
^{13}C NMR Spectra of **3ea**



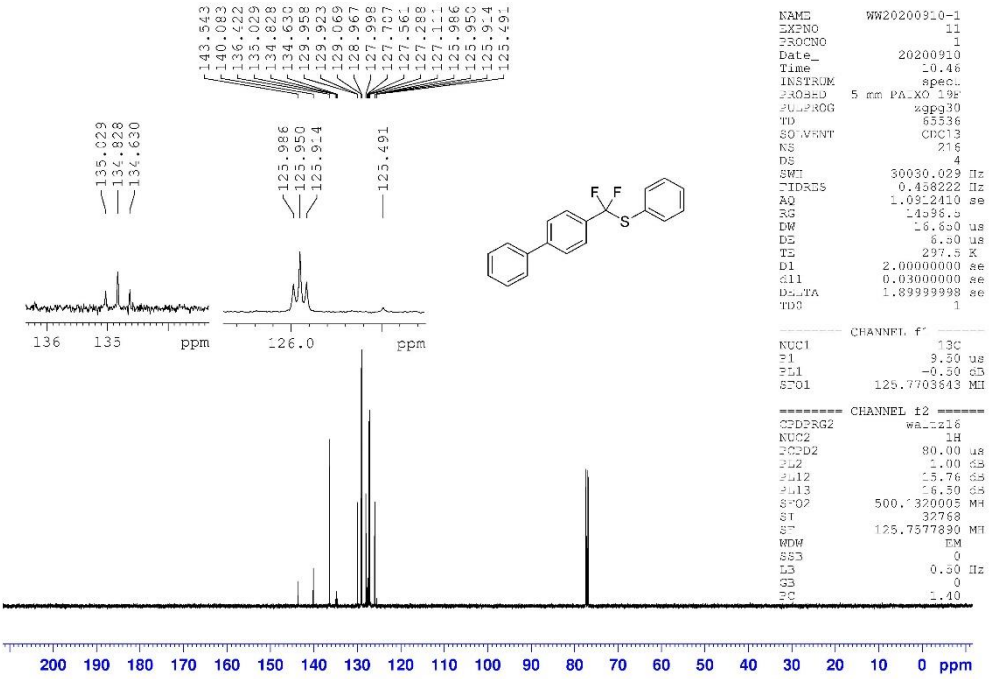
^{19}F NMR Spectra of **3ea**



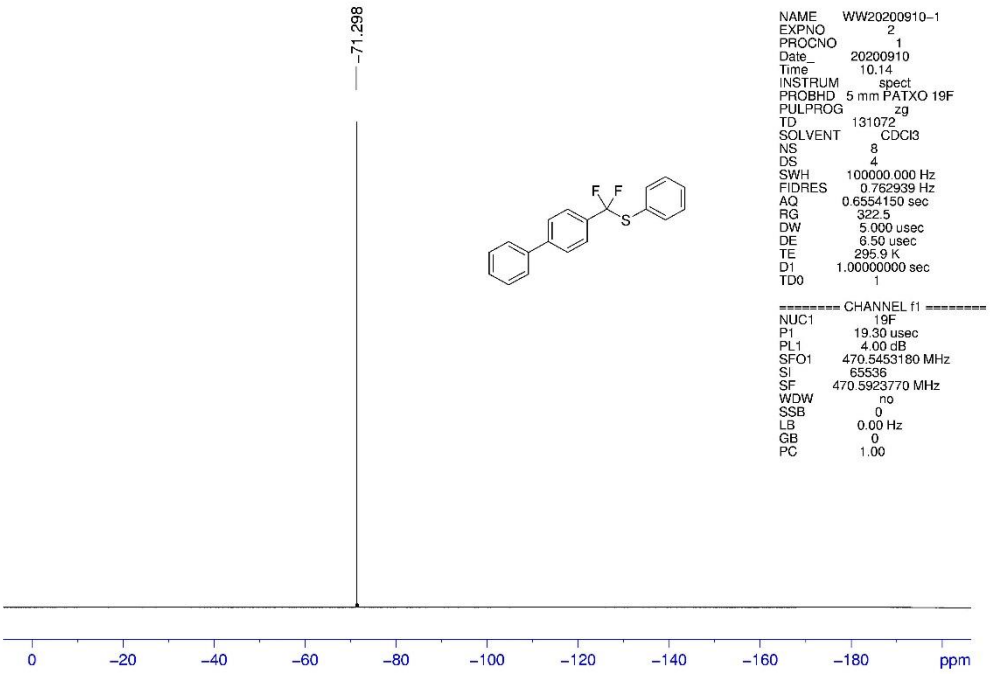
^{1}H NMR Spectra of **3fa**



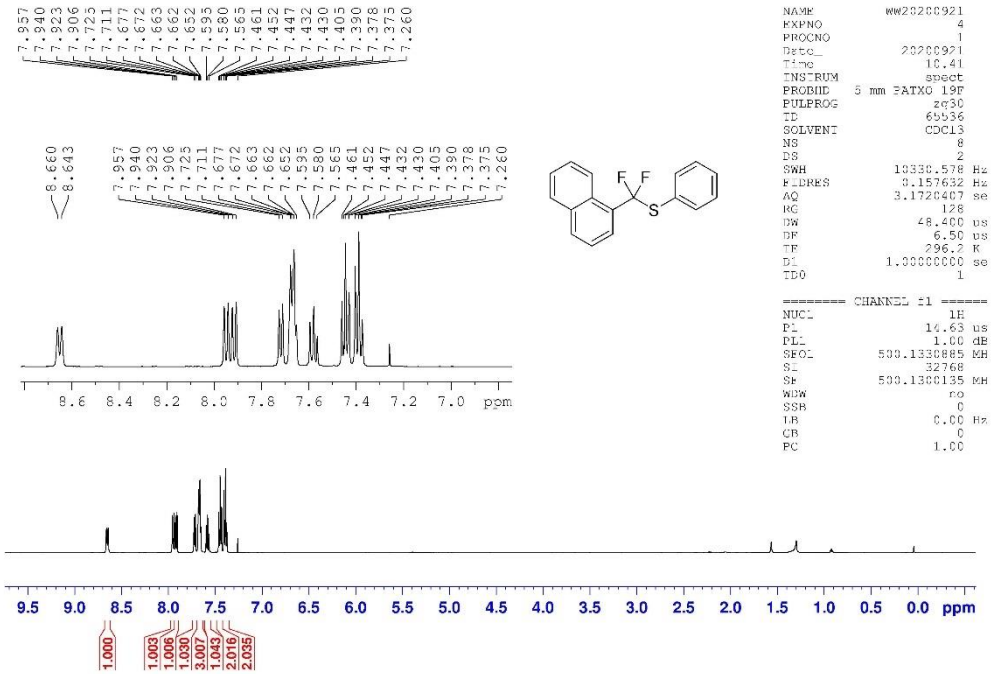
^{13}C NMR Spectra of **3fa**



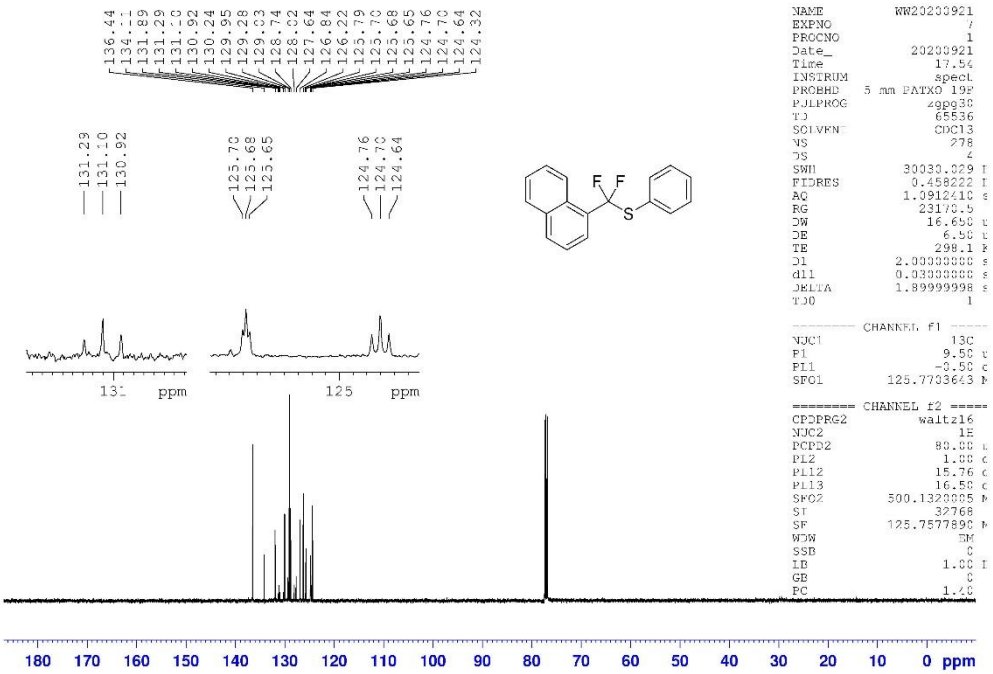
^{19}F NMR Spectra of **3fa**



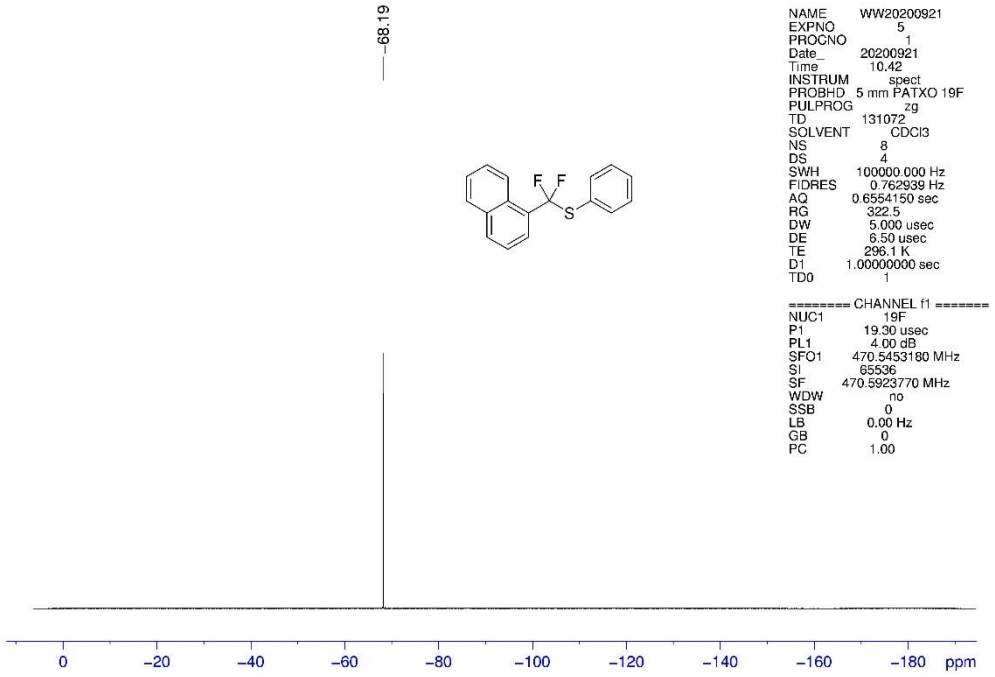
^{1}H NMR Spectra of **3ga**



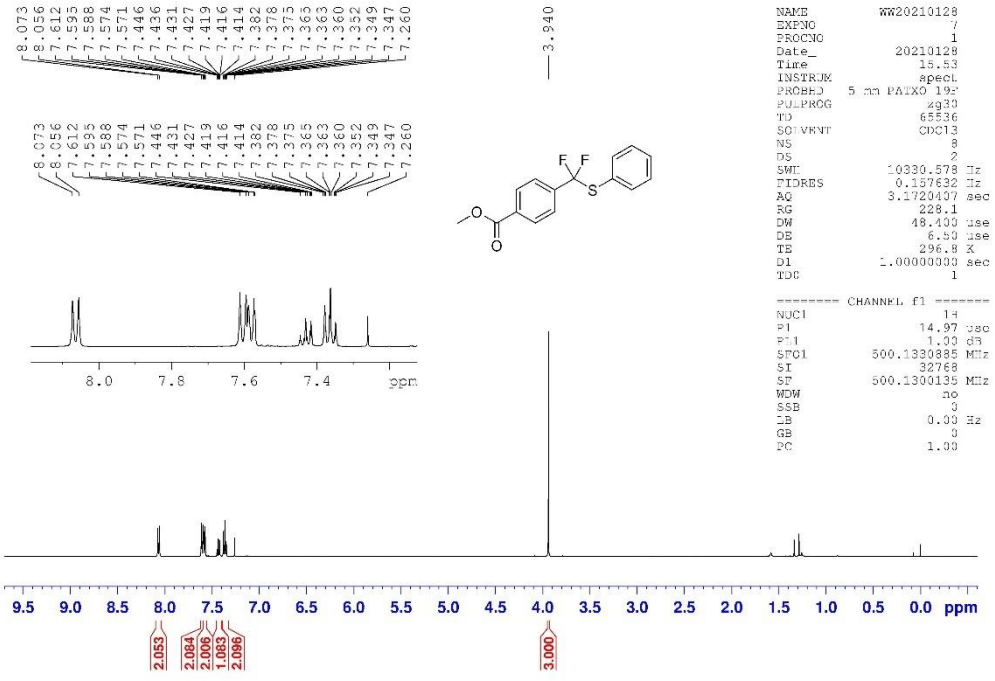
^{13}C NMR Spectra of **3ga**



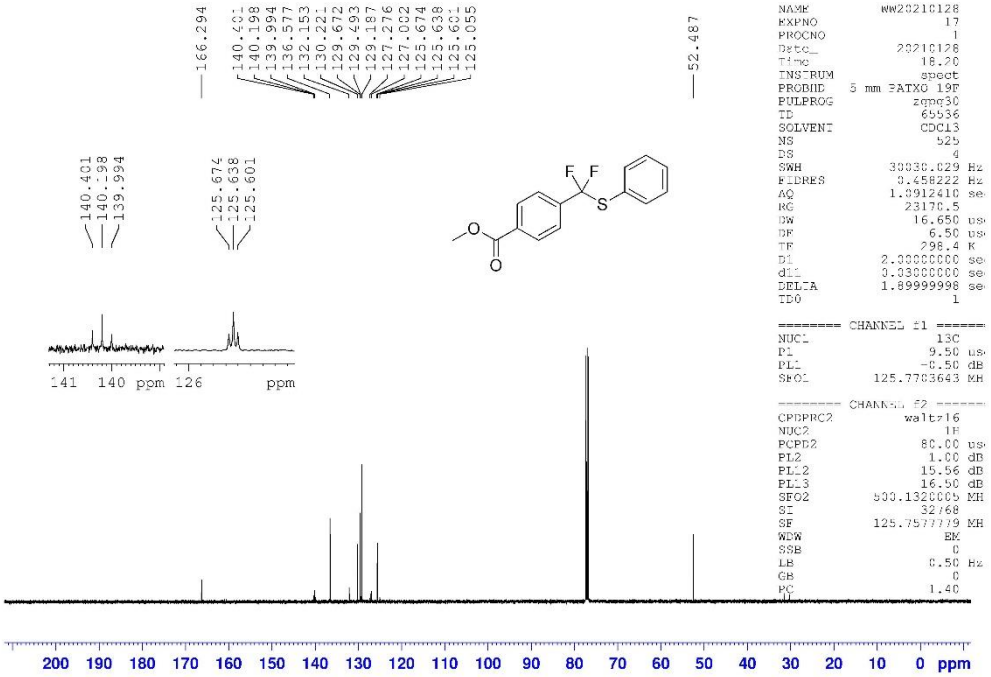
^{19}F NMR Spectra of **3ga**



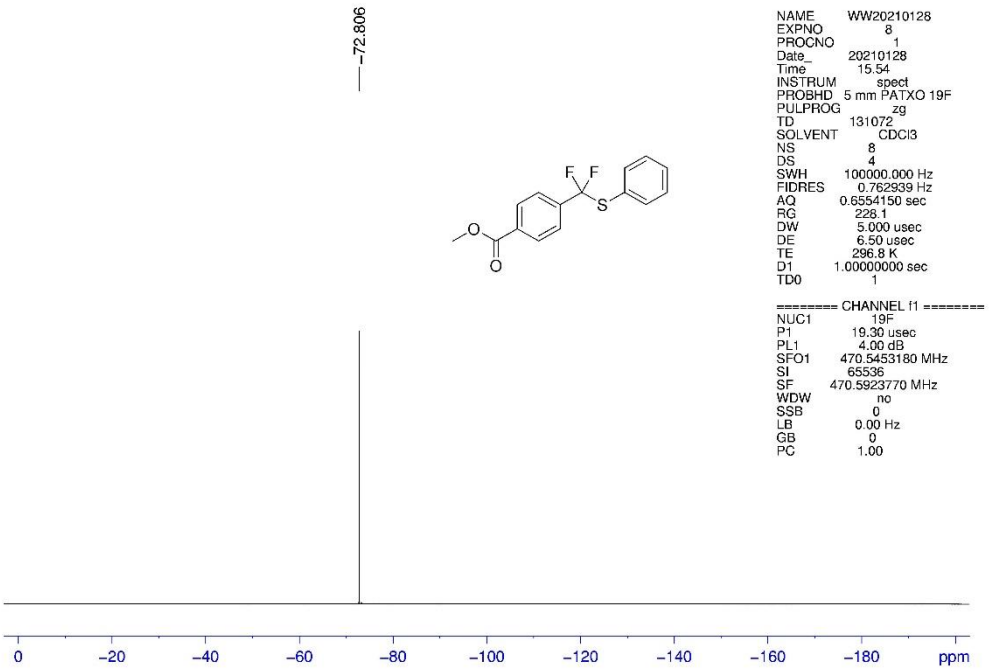
^{1}H NMR Spectra of **3ha**



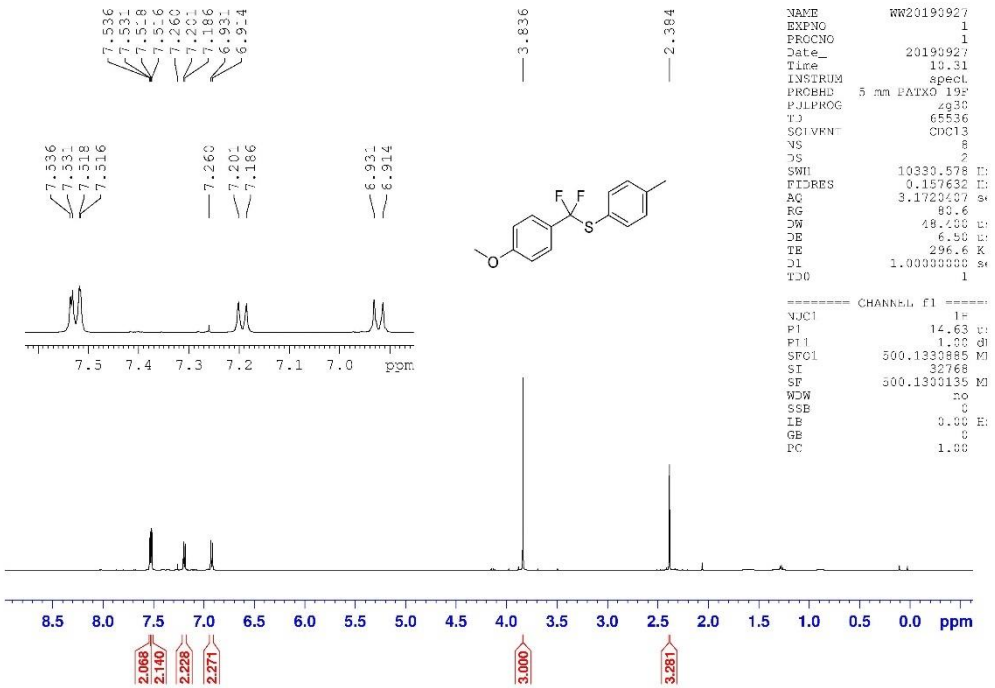
^{13}C NMR Spectra of **3ha**



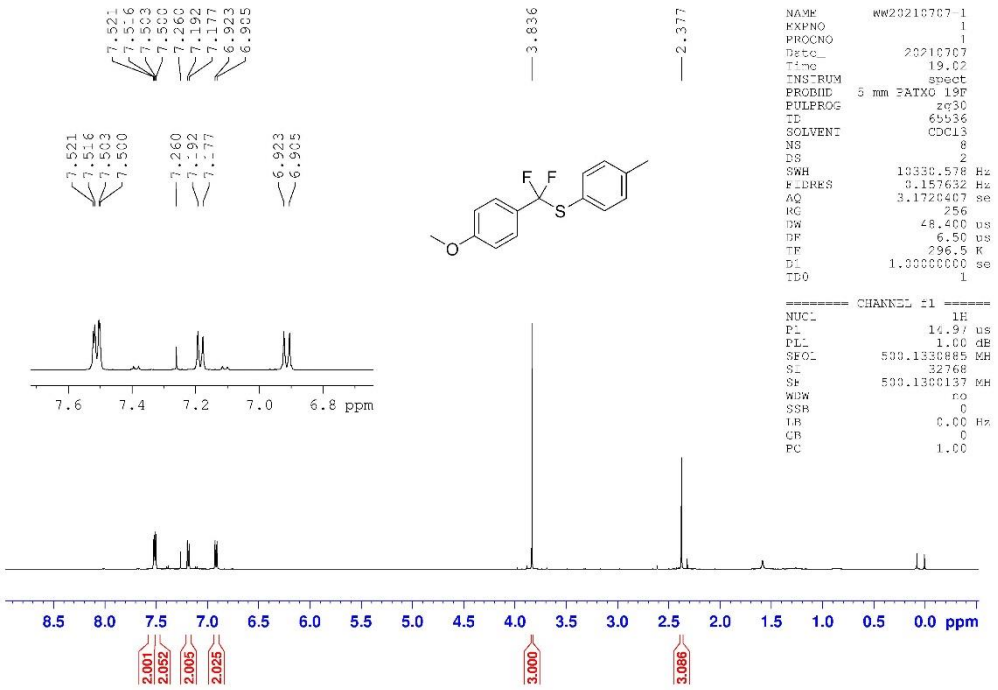
^{19}F NMR Spectra of **3ha**



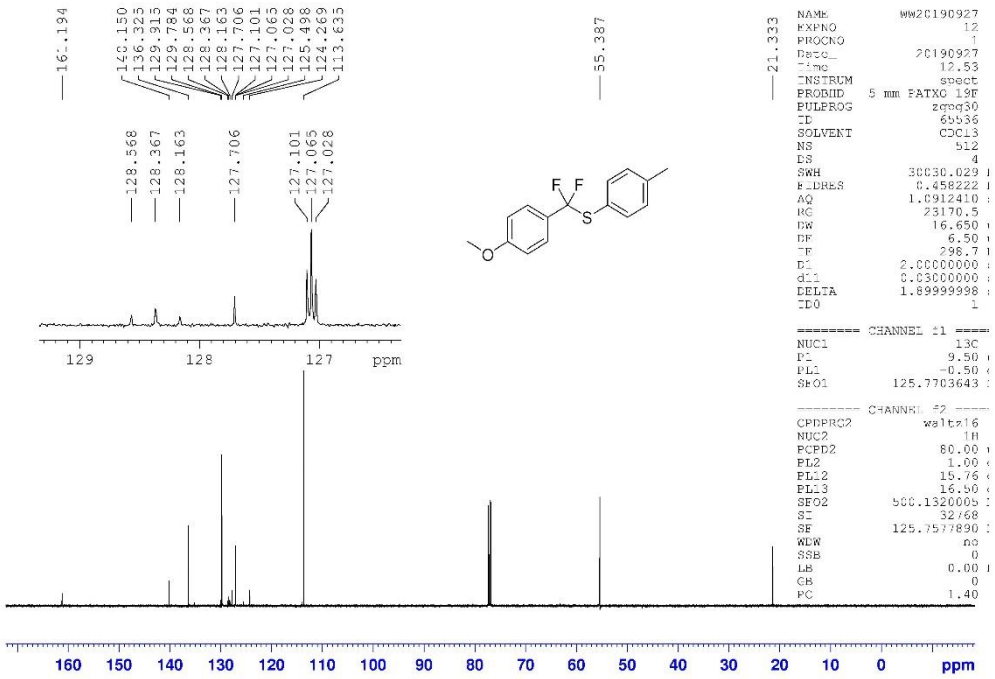
^{1}H NMR Spectra of **3ab** From Method A



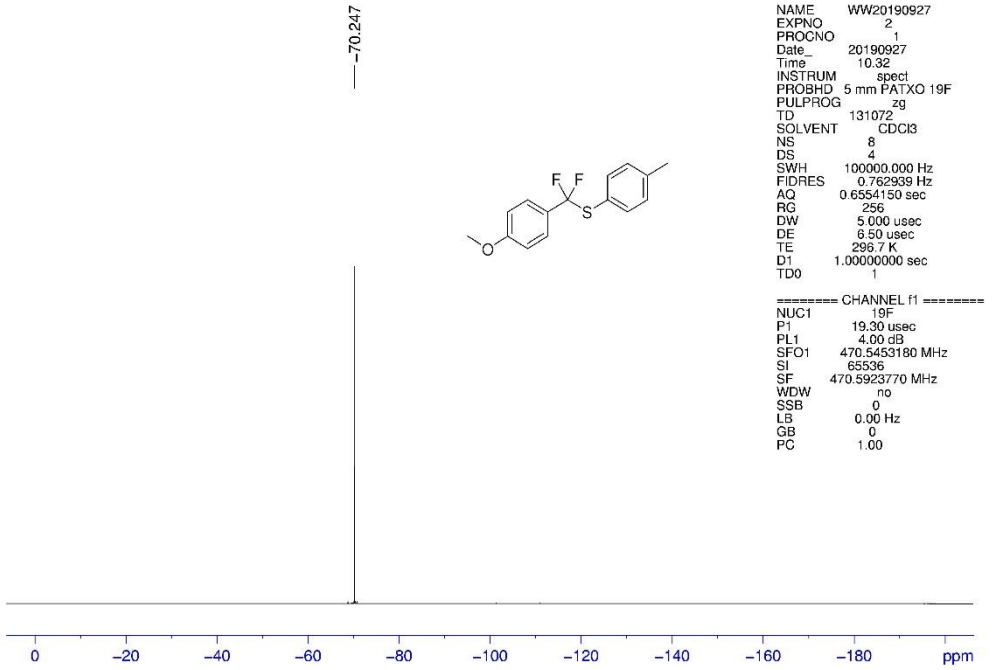
^{1}H NMR Spectra of **3ab** From Method B



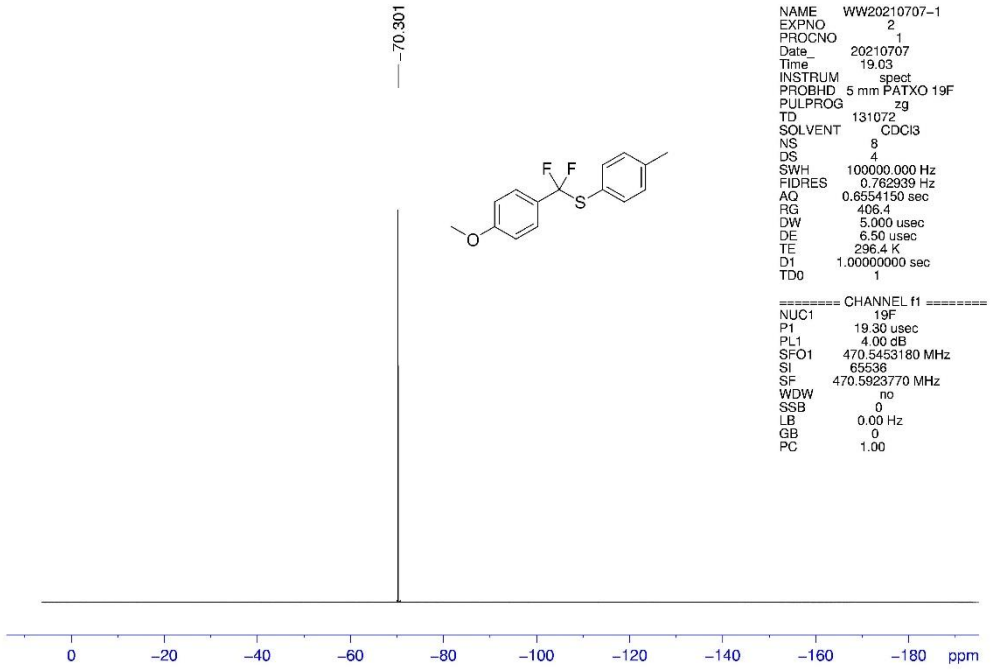
^{13}C NMR Spectra of **3ab** From Method A



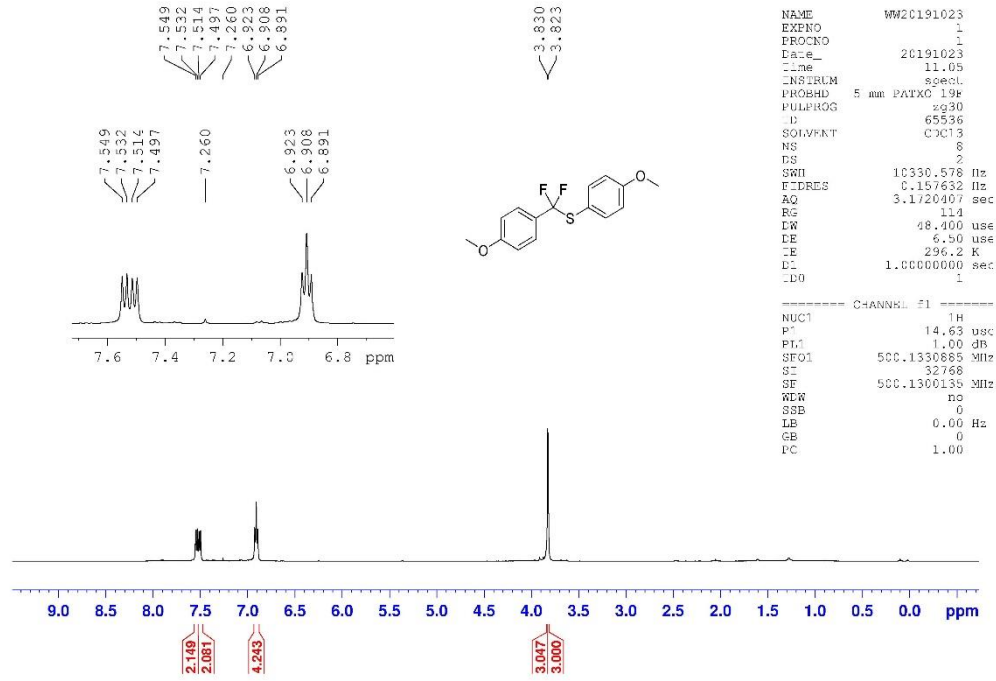
^{19}F NMR Spectra of **3ab** From Method A



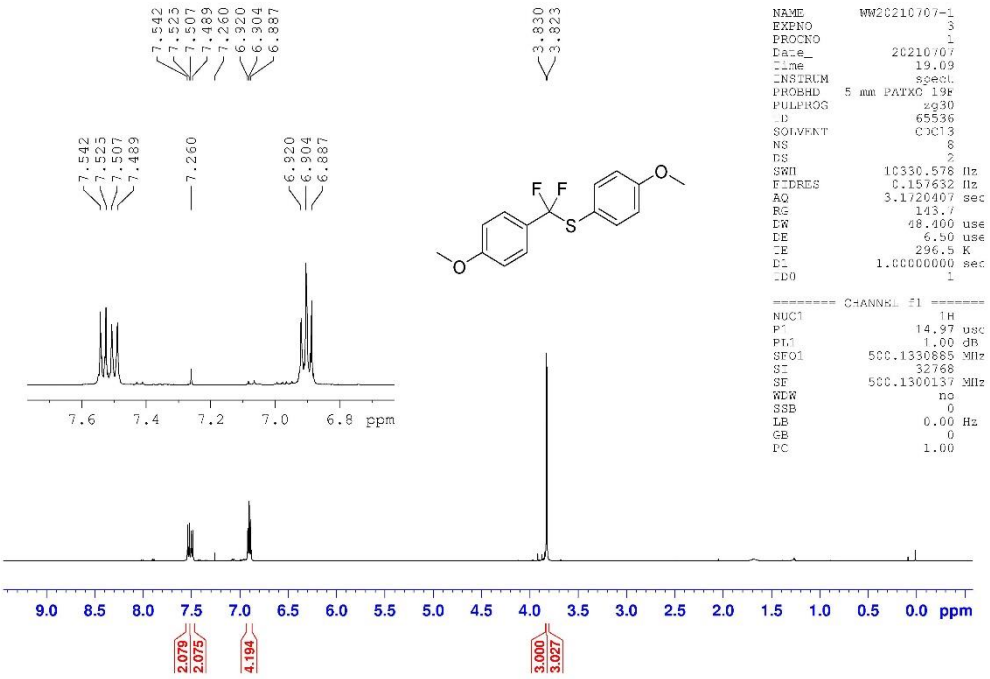
^{19}F NMR Spectra of **3ab** From Method B



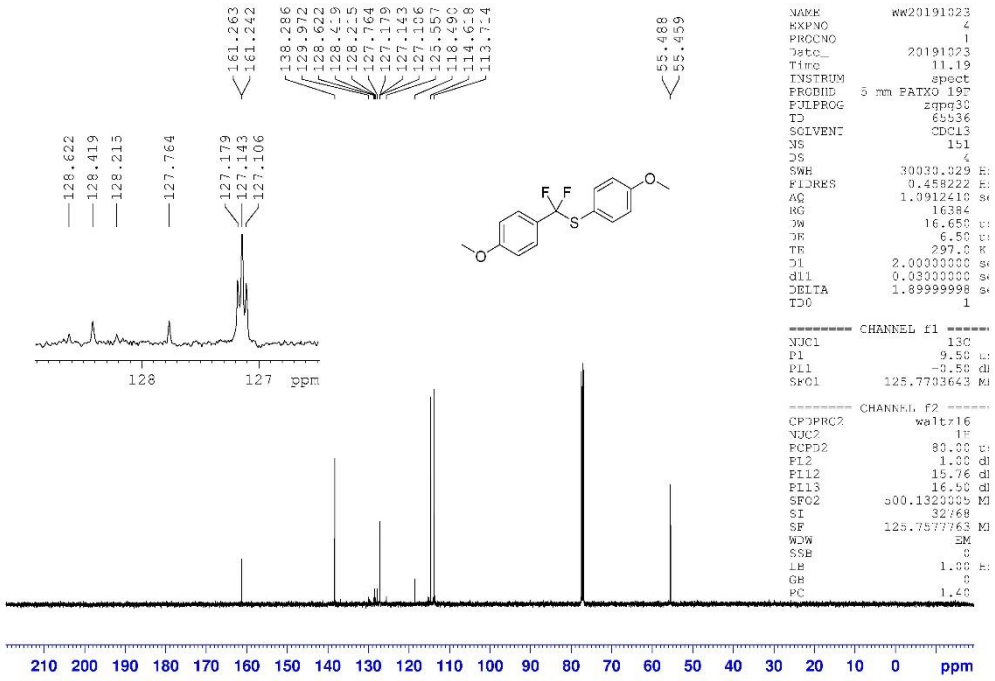
^{1}H NMR Spectra of **3ac** From Method A



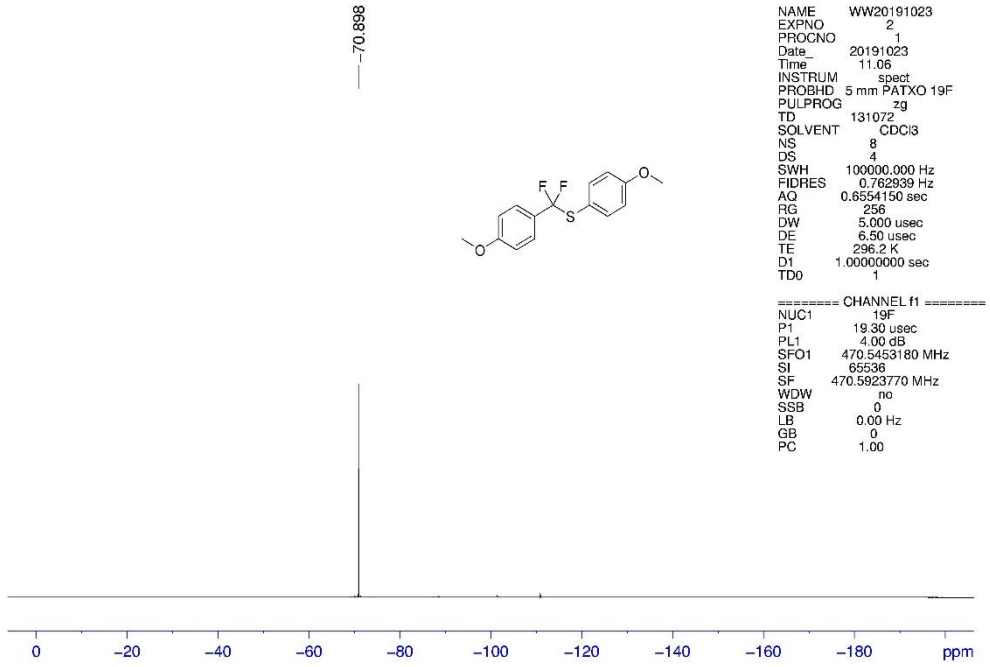
^{1}H NMR Spectra of **3ac** From Method B



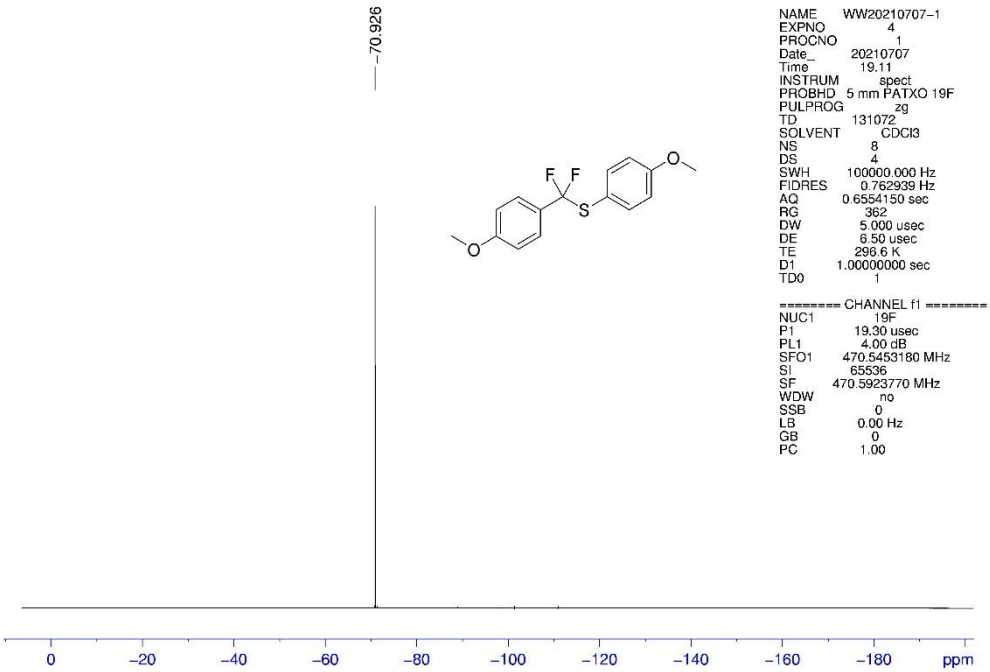
^{13}C NMR Spectra of **3ac** From Method A



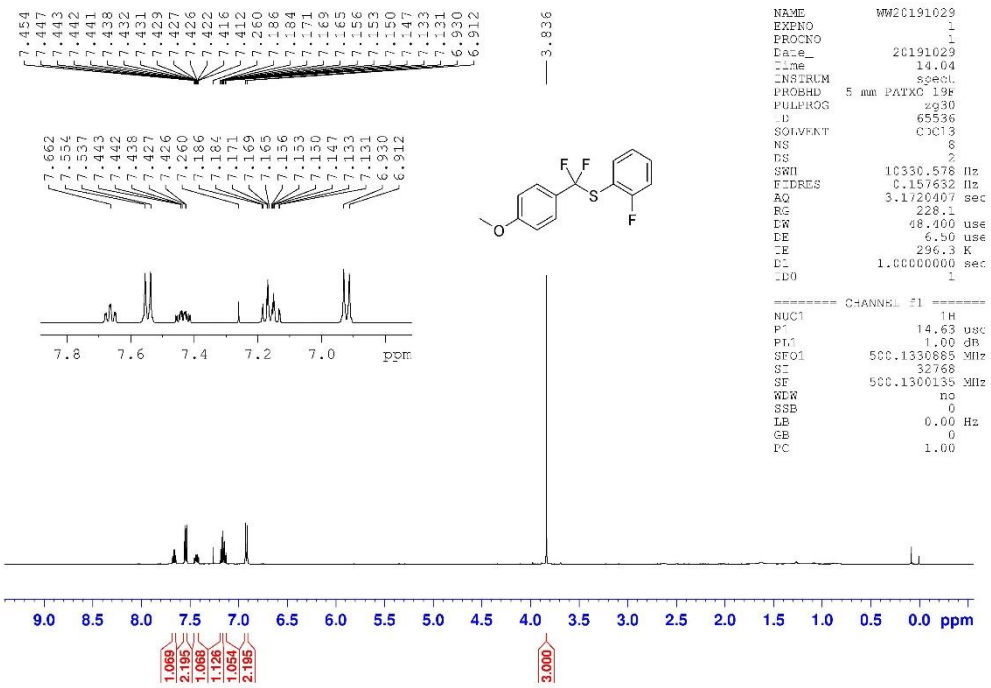
^{19}F NMR Spectra of **3ac** From Method A



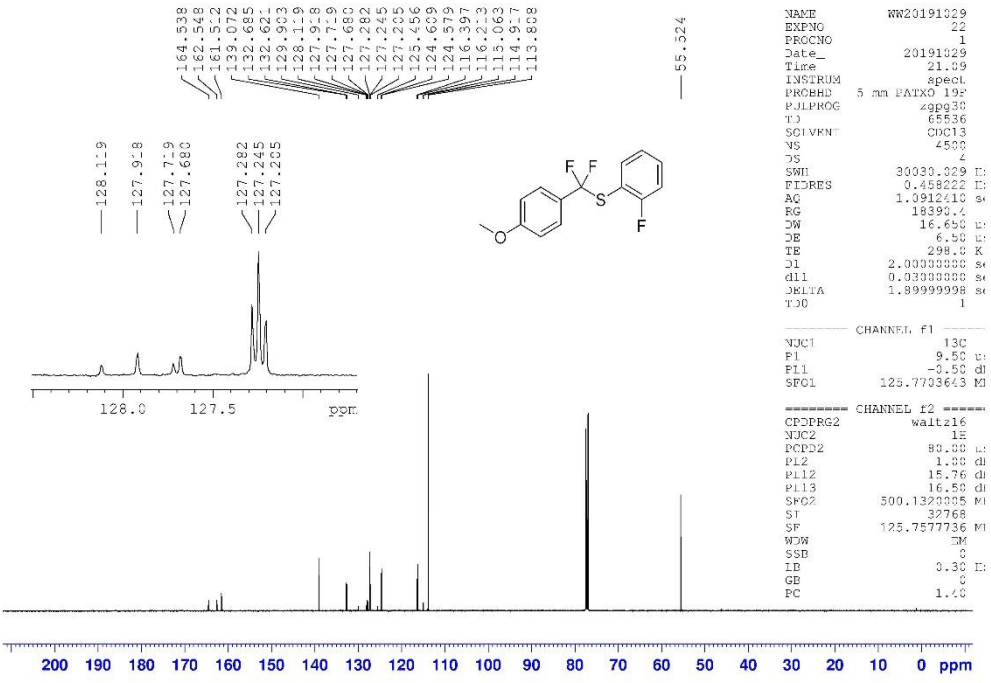
^{19}F NMR Spectra of **3ac** From Method B



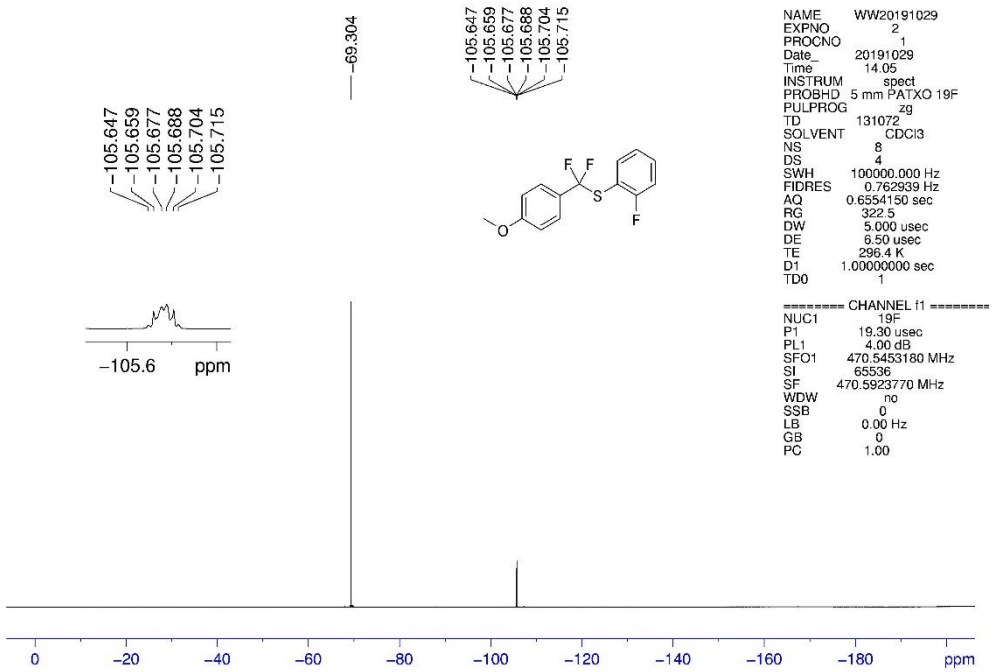
^{1}H NMR Spectra of **3ad**



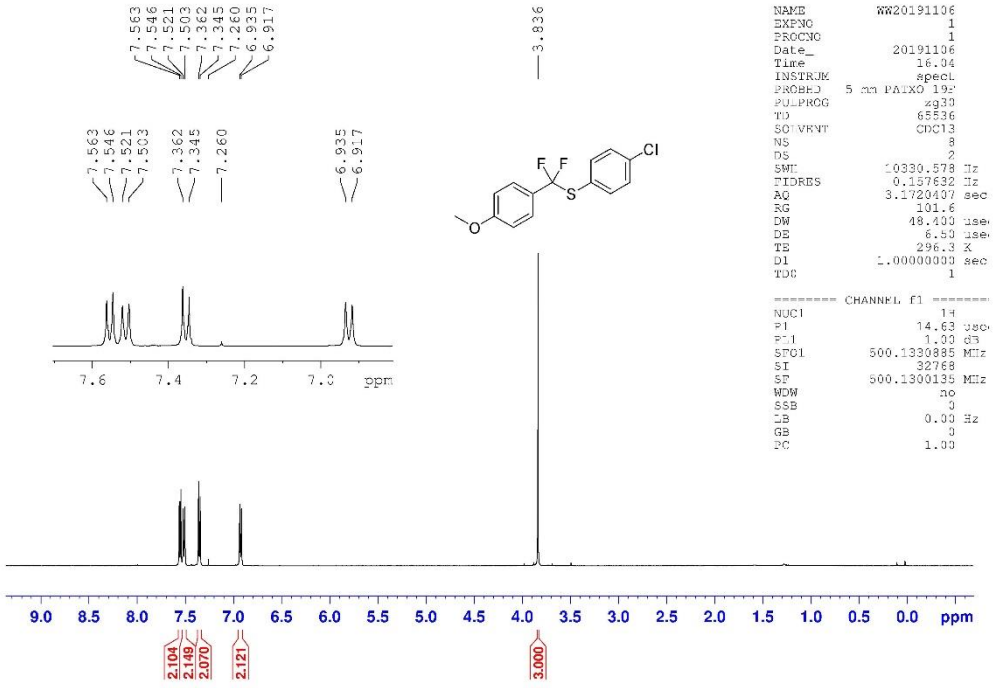
^{13}C NMR Spectra of **3ad**



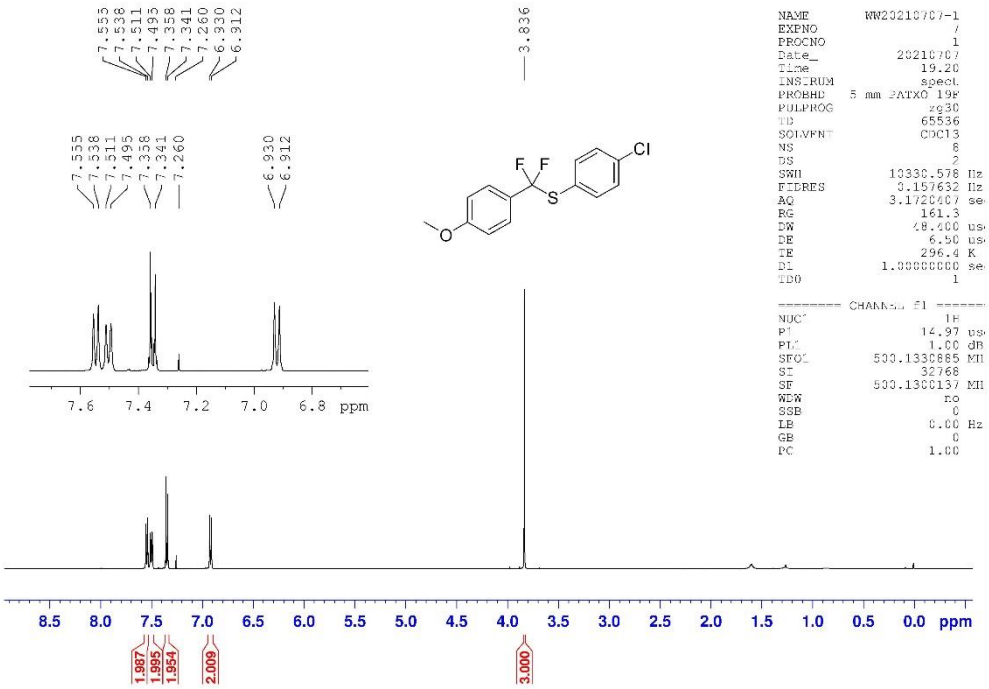
^{19}F NMR Spectra of **3ad**



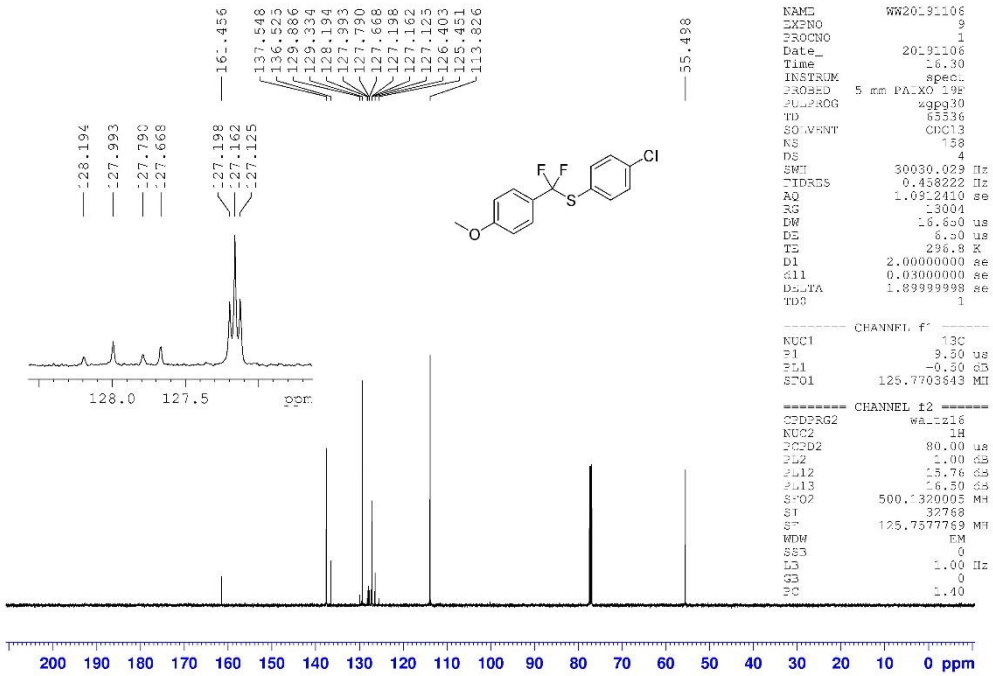
^{1}H NMR Spectra of **3ae** From Method A



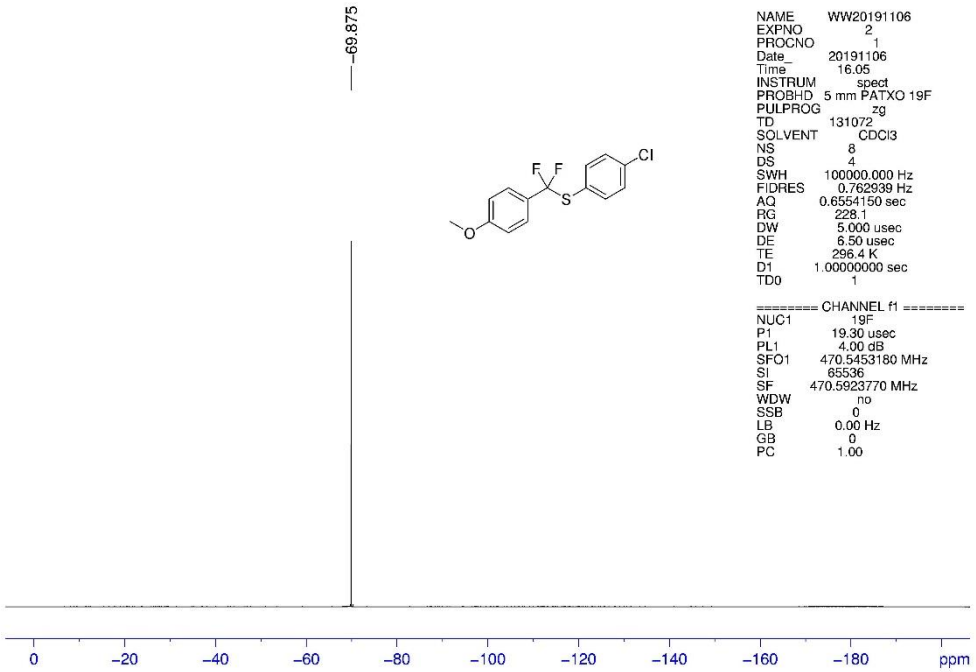
^{1}H NMR Spectra of **3ae** From Method B



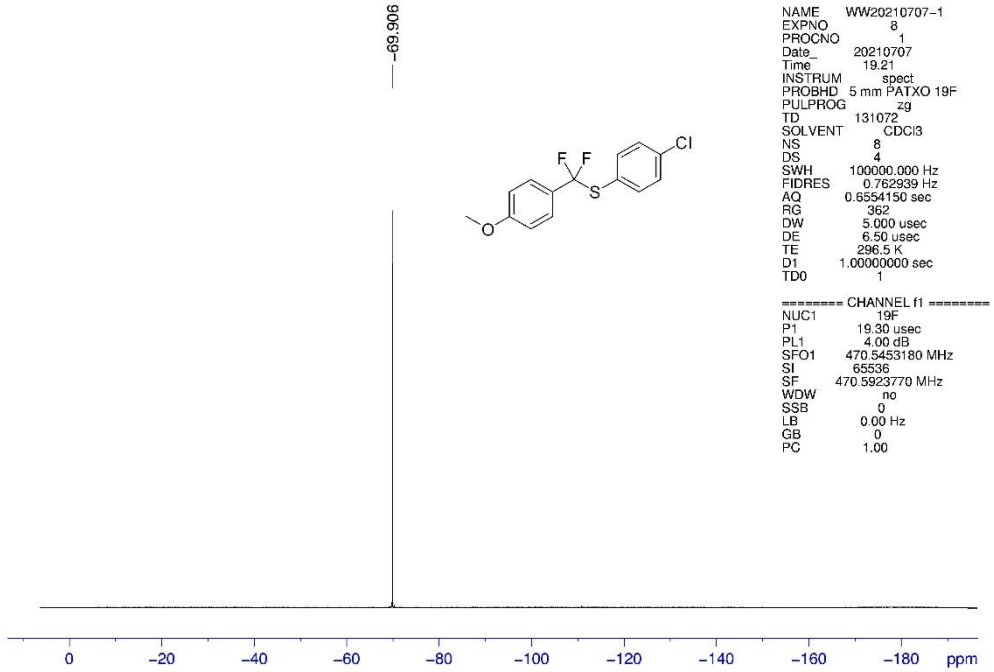
^{13}C NMR Spectra of **3ae** From Method A



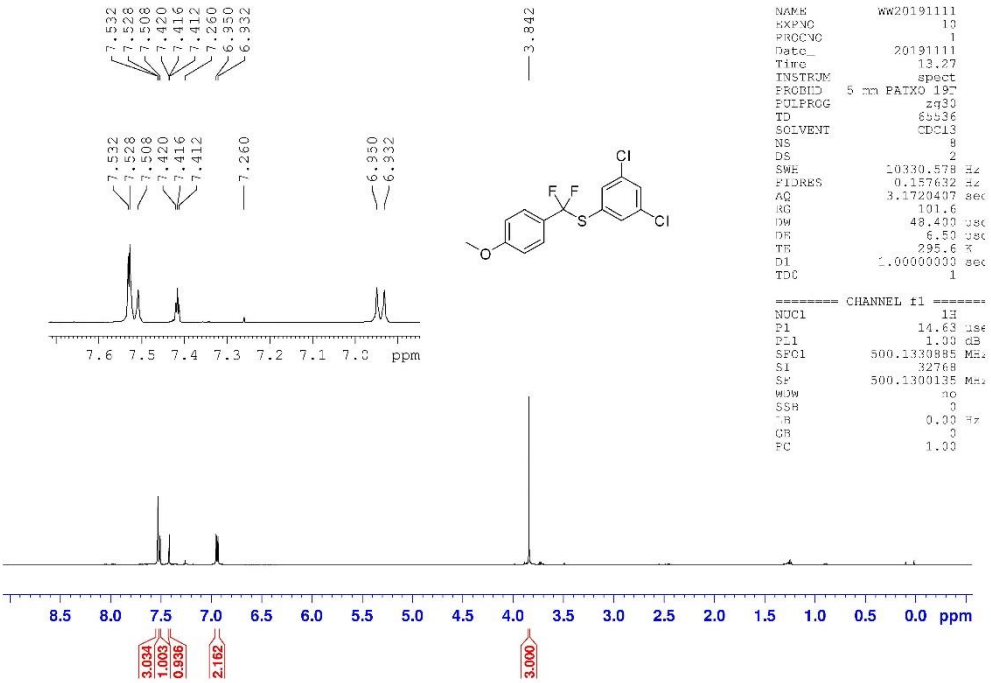
^{19}F NMR Spectra of **3ae** From Method A



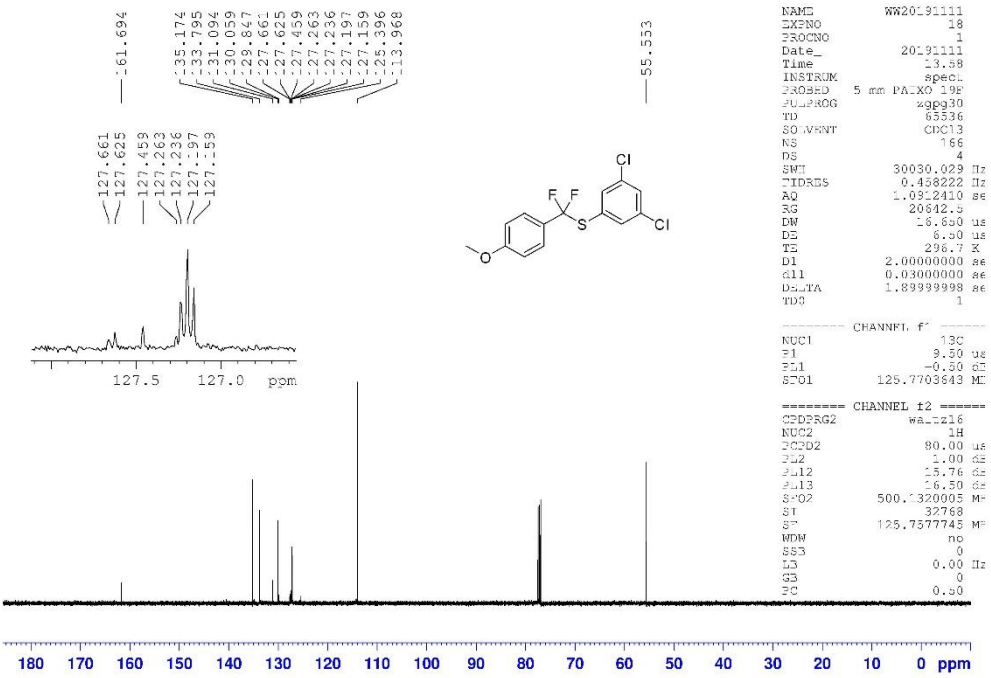
^{19}F NMR Spectra of **3ae** From Method B



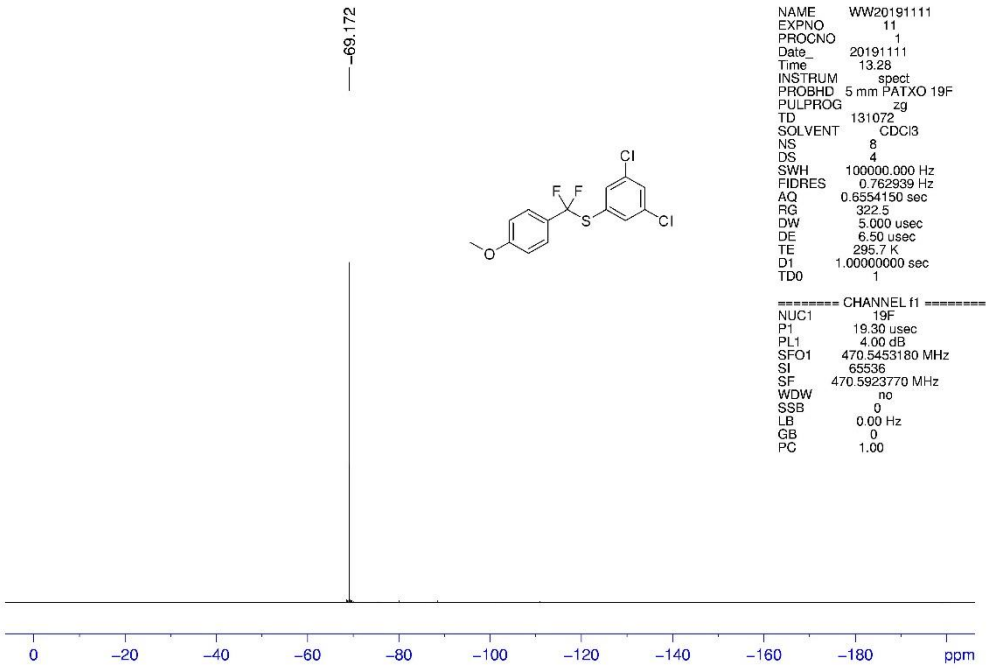
^{1}H NMR Spectra of **3af**



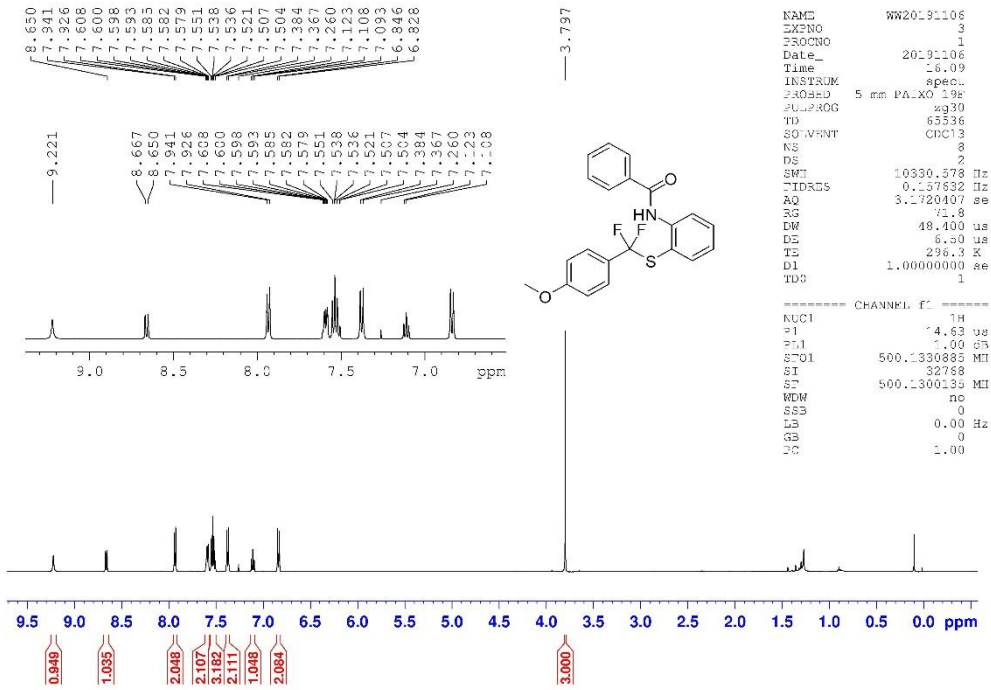
^{13}C NMR Spectra of **3af**



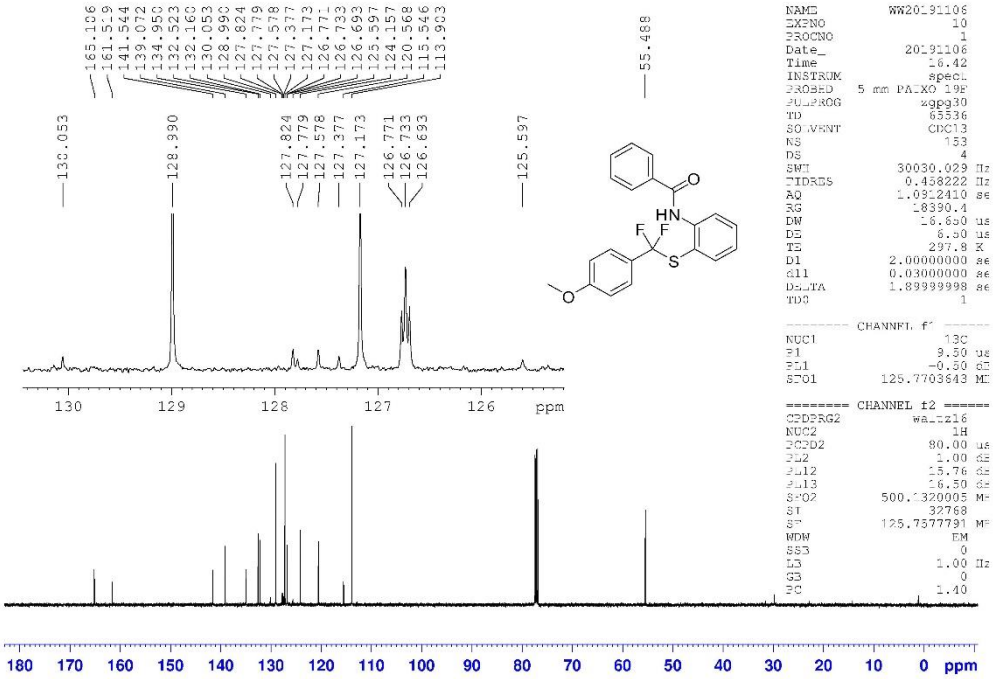
^{19}F NMR Spectra of **3af**



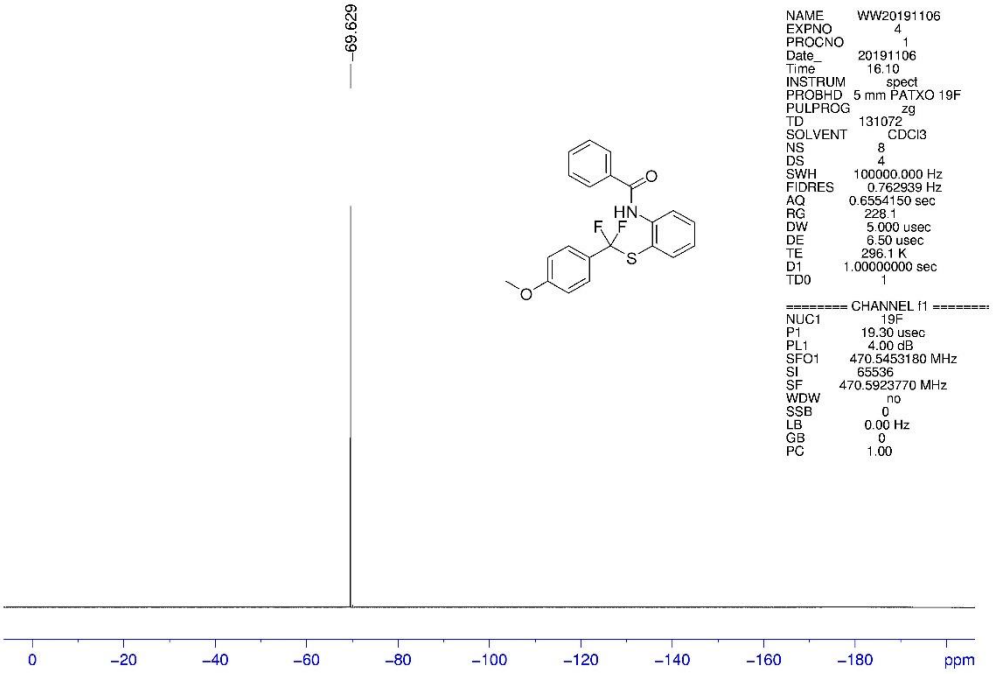
^{1}H NMR Spectra of **3ag**



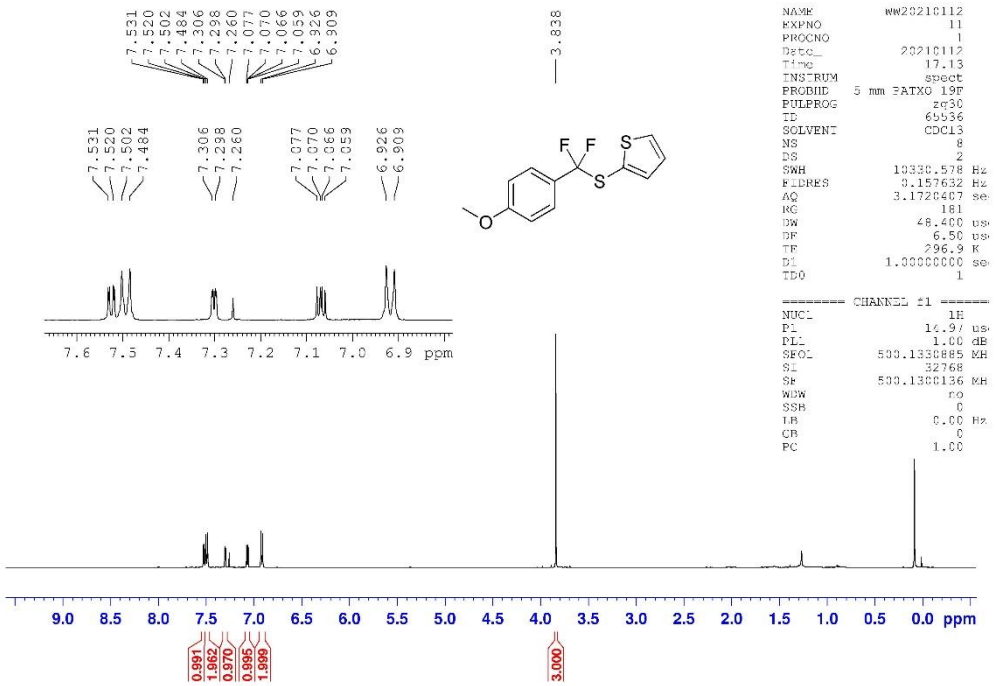
^{13}C NMR Spectra of **3ag**



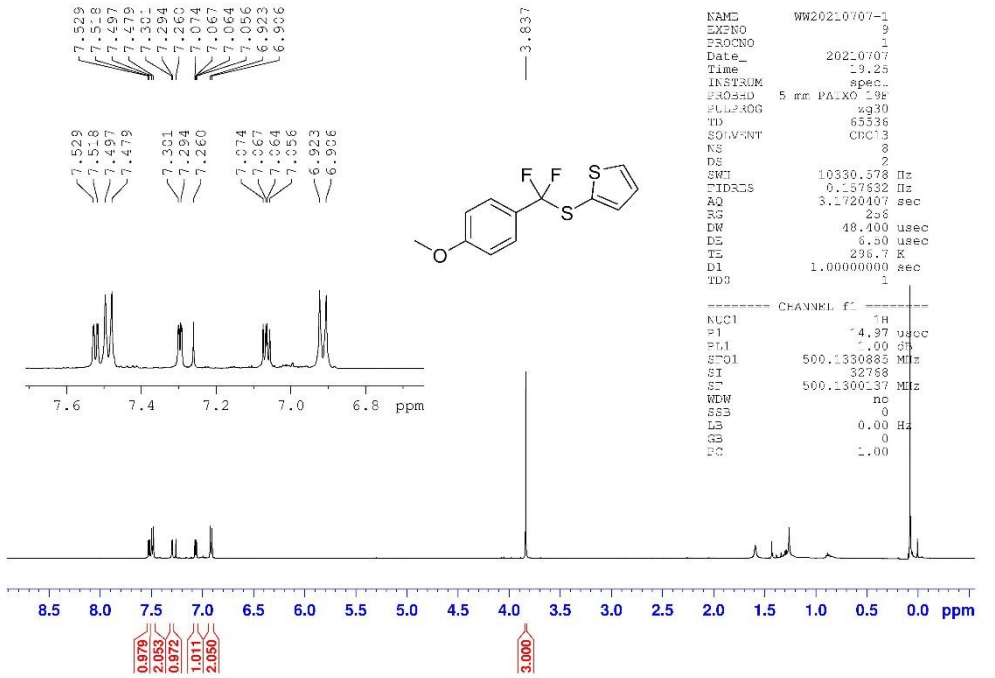
^{19}F NMR Spectra of **3ag**



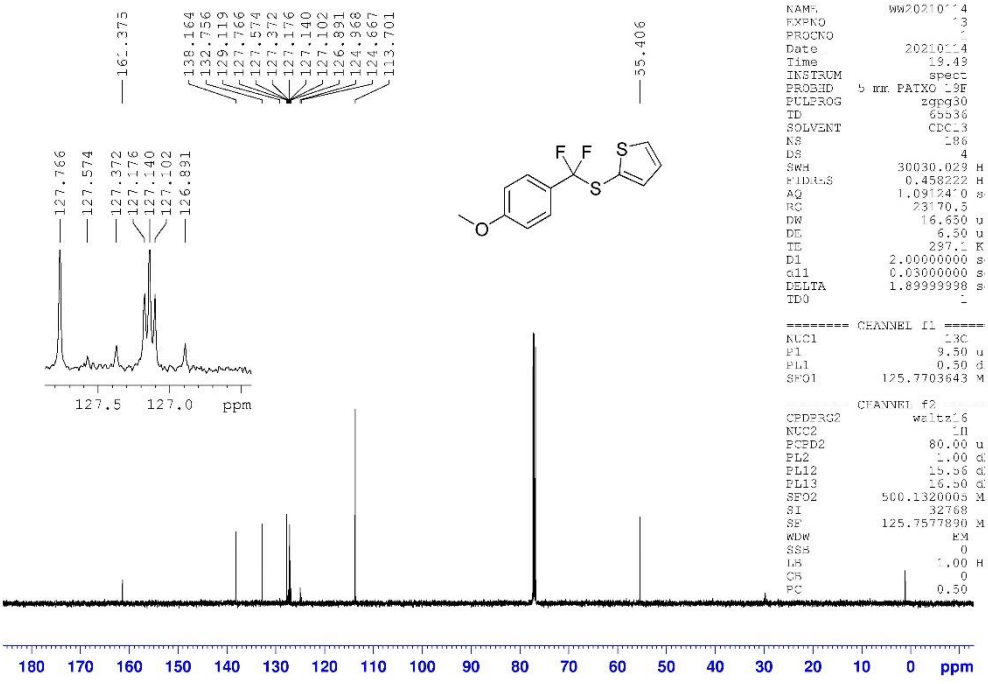
^{1}H NMR Spectra of **3ah** From Method A



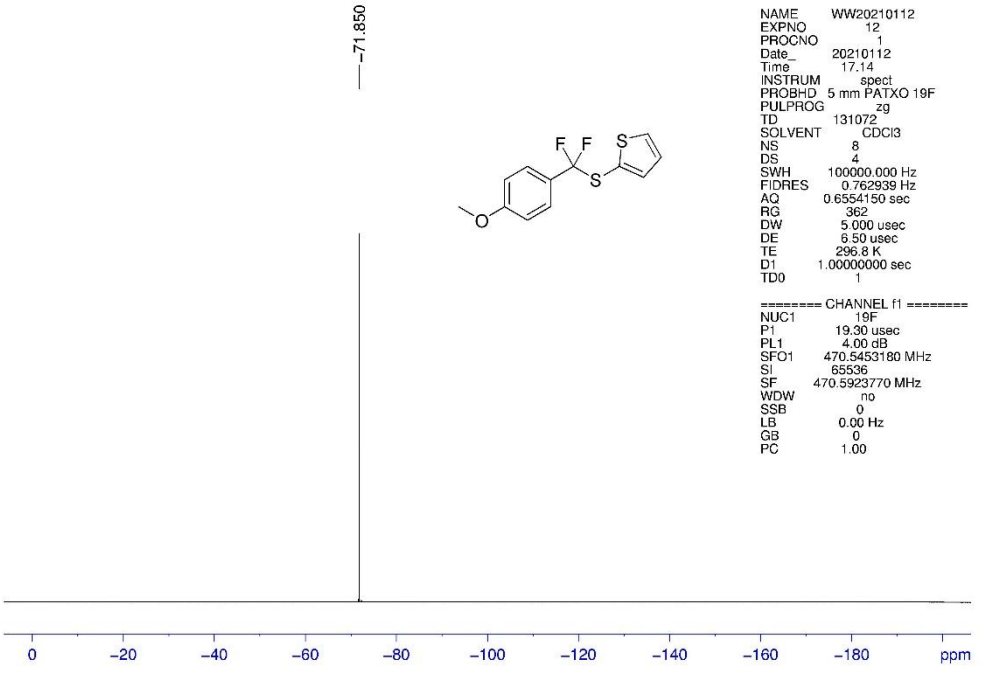
^{1}H NMR Spectra of **3ah** From Method B



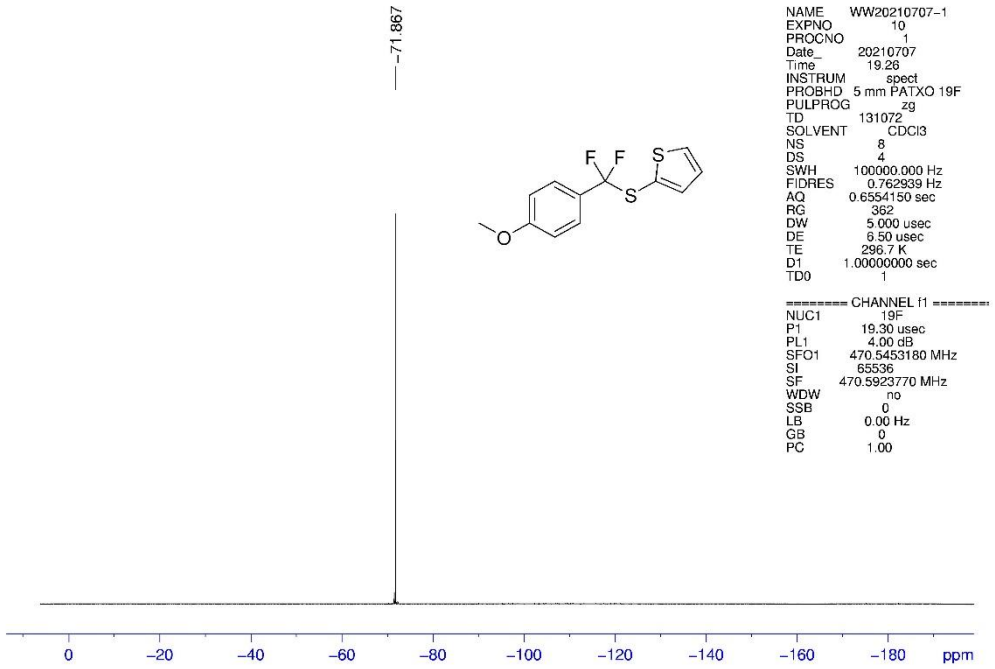
^{13}C NMR Spectra of **3ah** From Method A



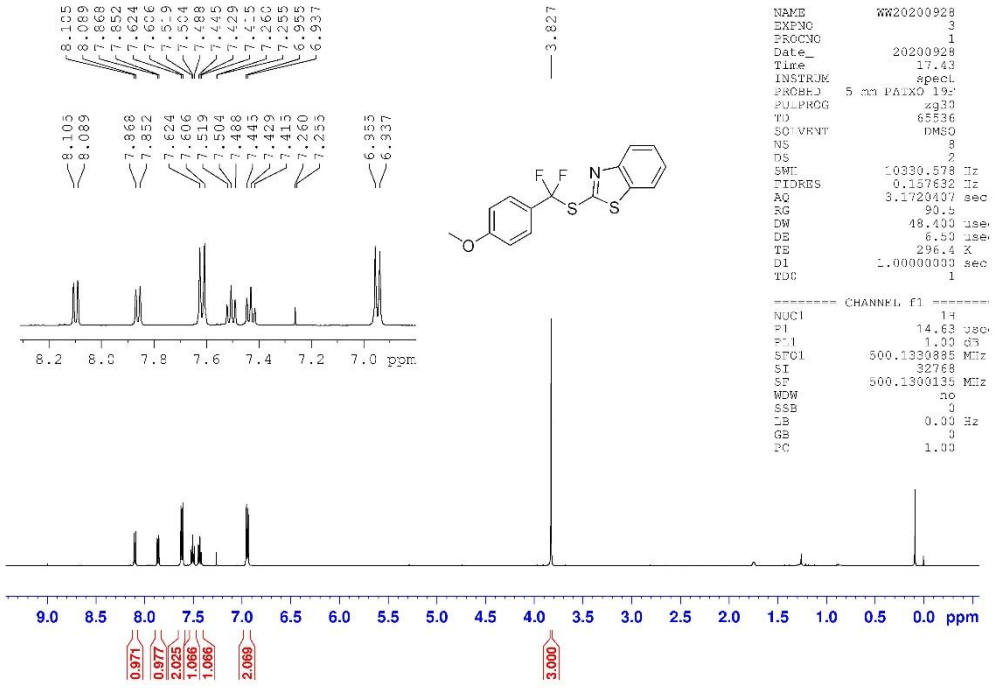
^{19}F NMR Spectra of **3ah** From Method A



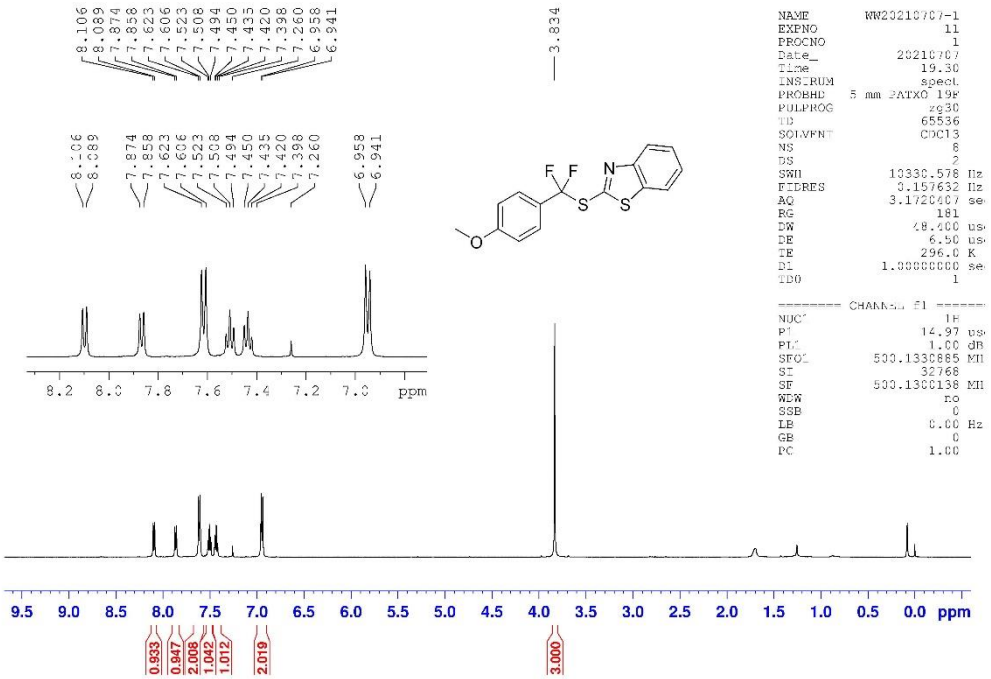
^{19}F NMR Spectra of **3ah** From Method B



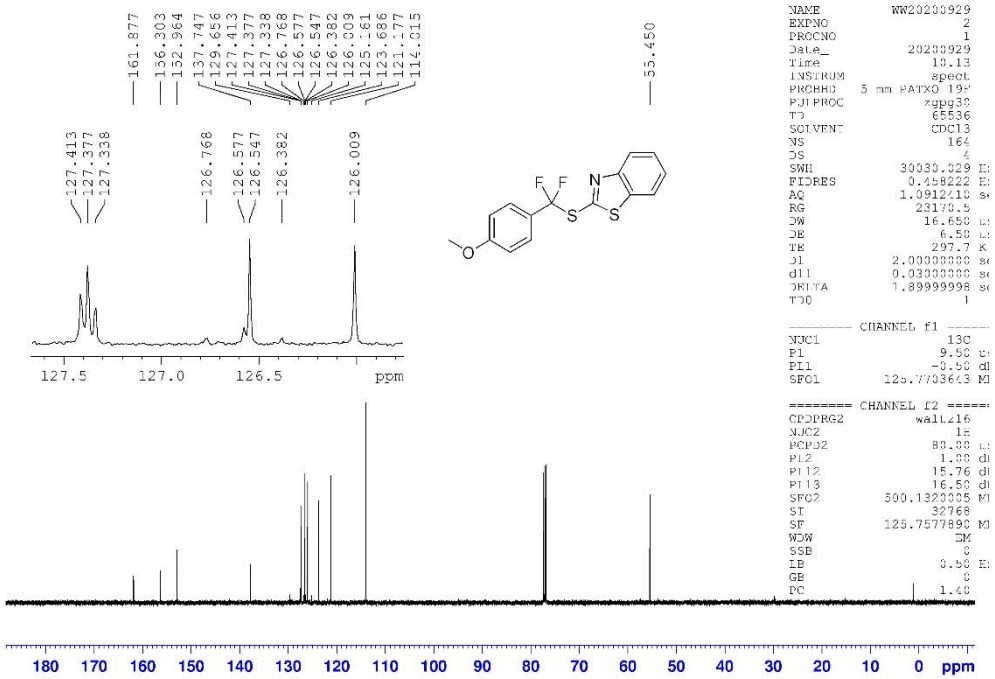
^{1}H NMR Spectra of **3ai** From Method A



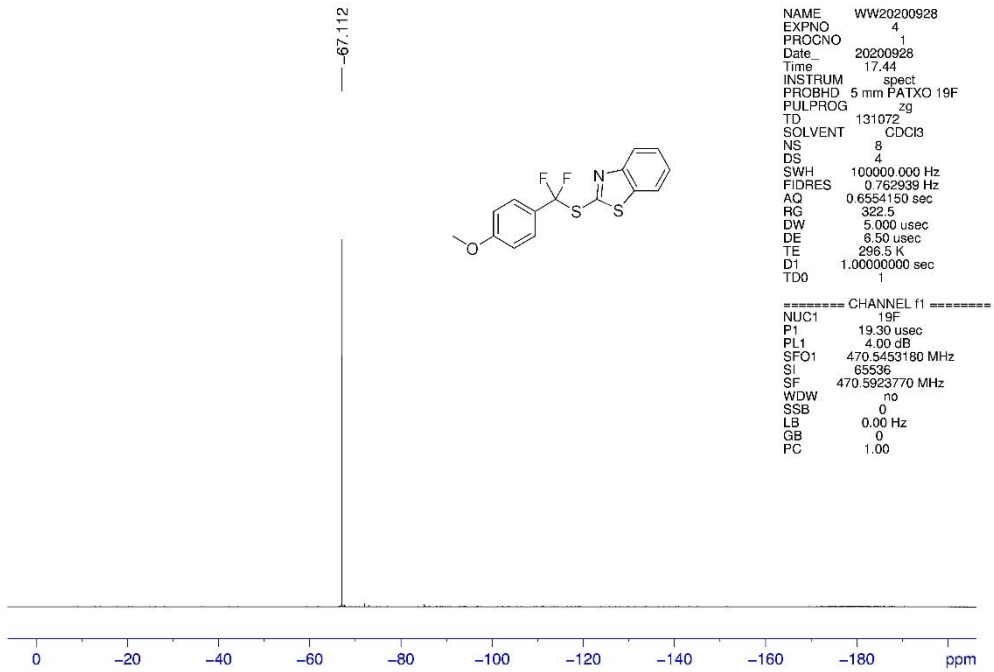
^{1}H NMR Spectra of **3ai** From Method B



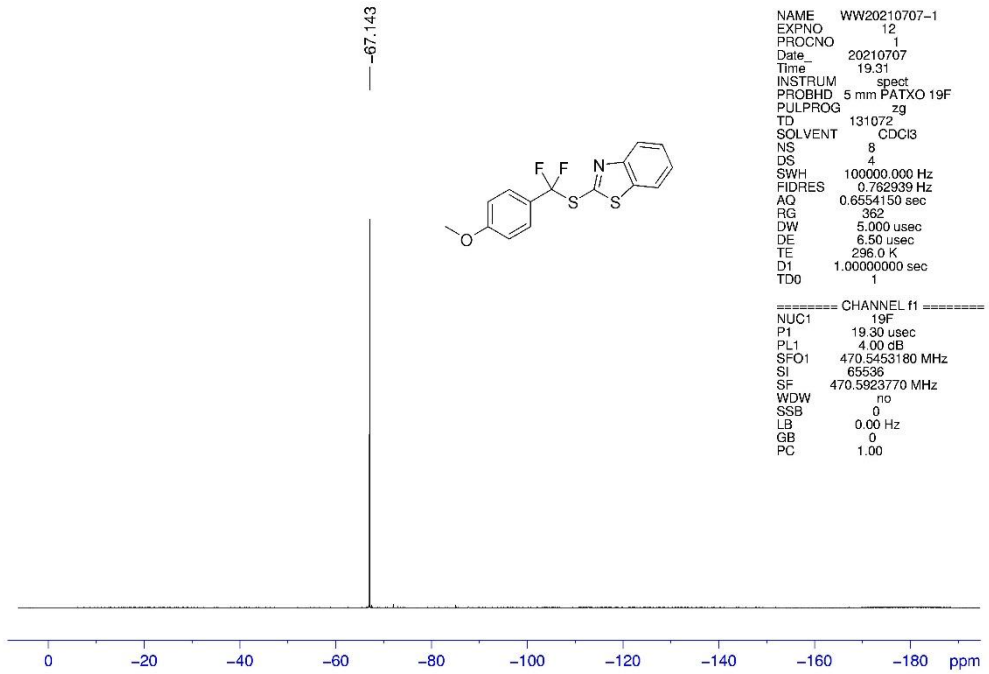
^{13}C NMR Spectra of **3ai** From Method A



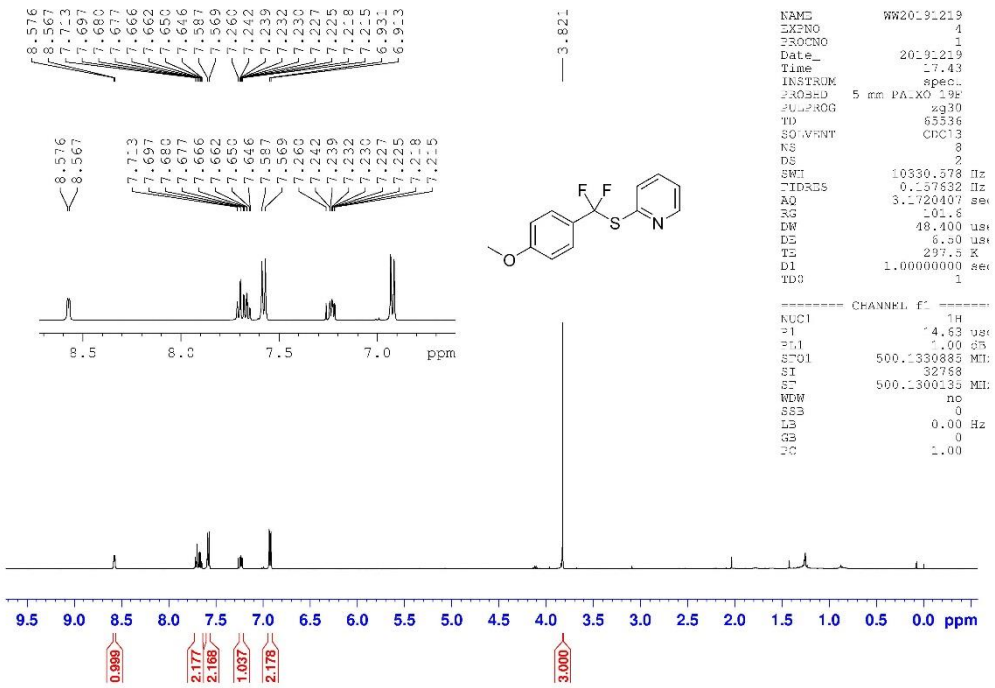
^{19}F NMR Spectra of **3ai** From Method A



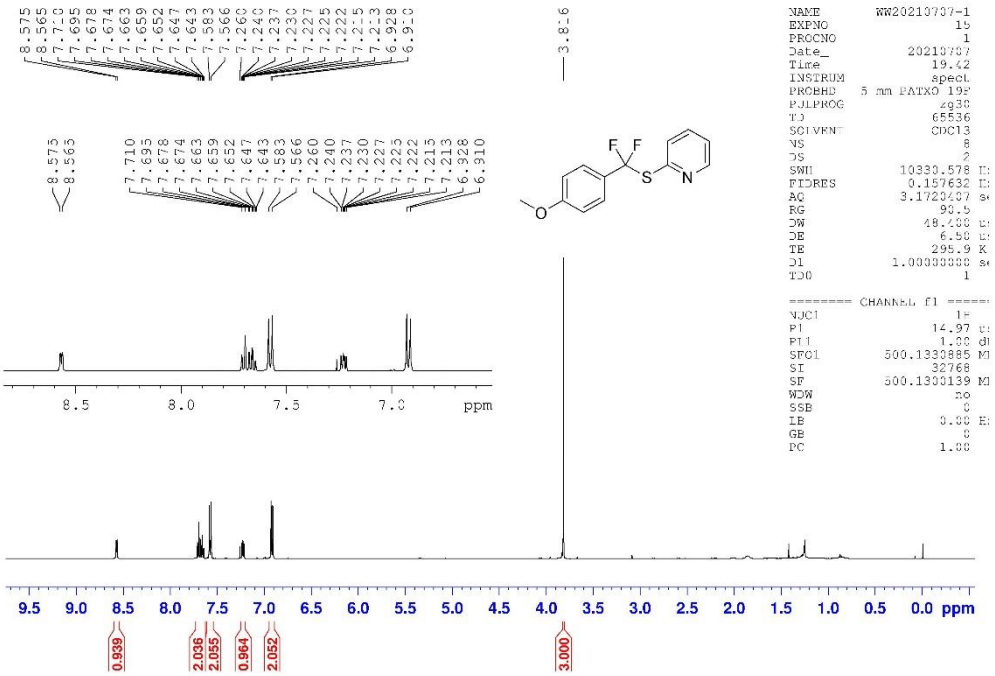
^{19}F NMR Spectra of **3ai** From Method B



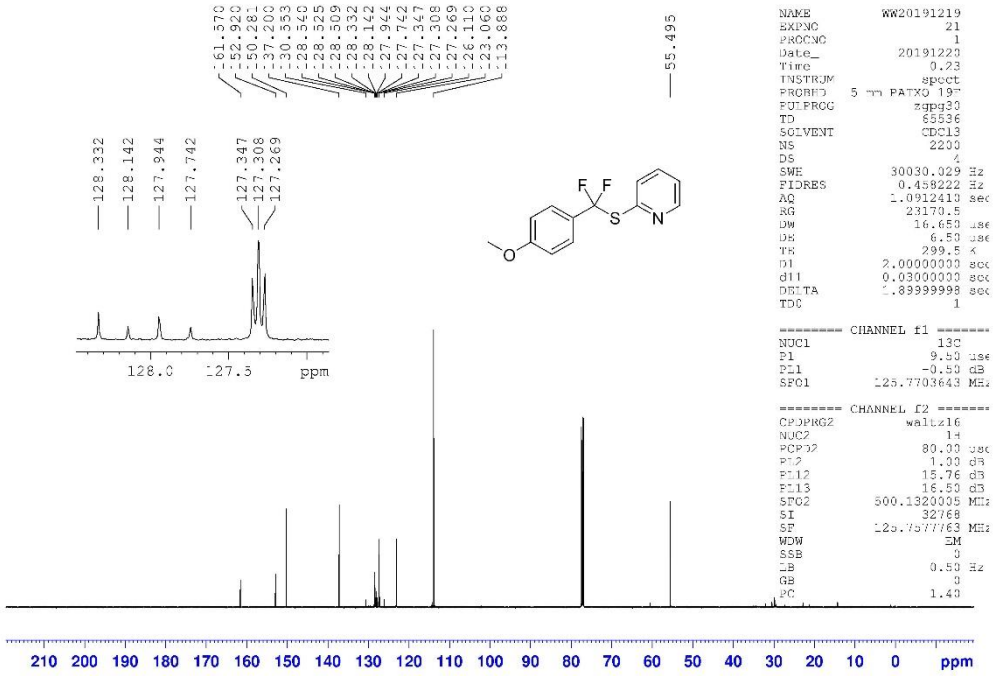
^{1}H NMR Spectra of **3aj** From Method A



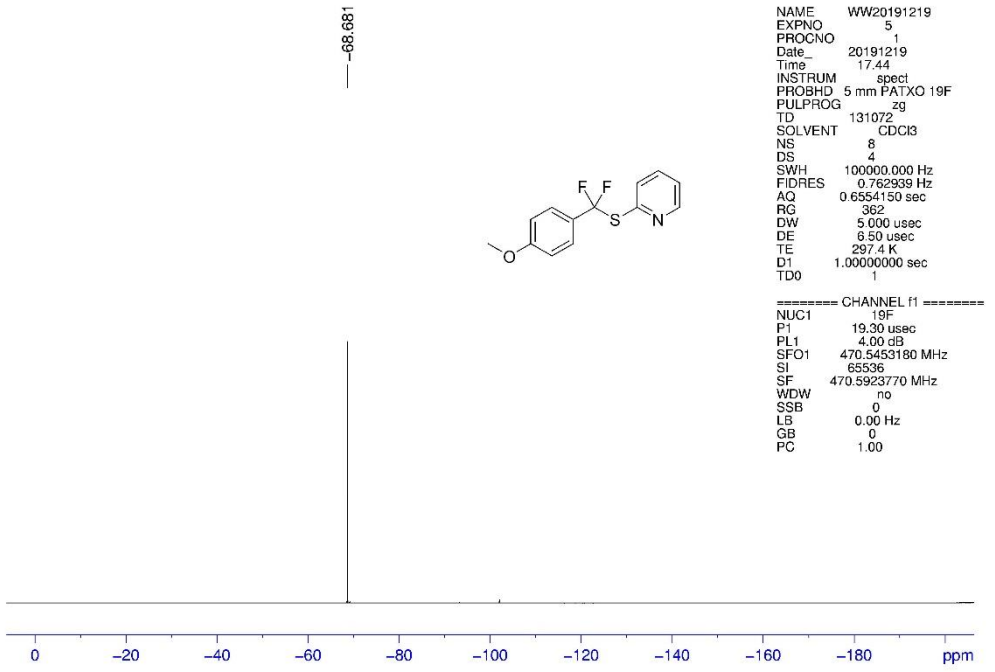
^{1}H NMR Spectra of **3aj** From Method B



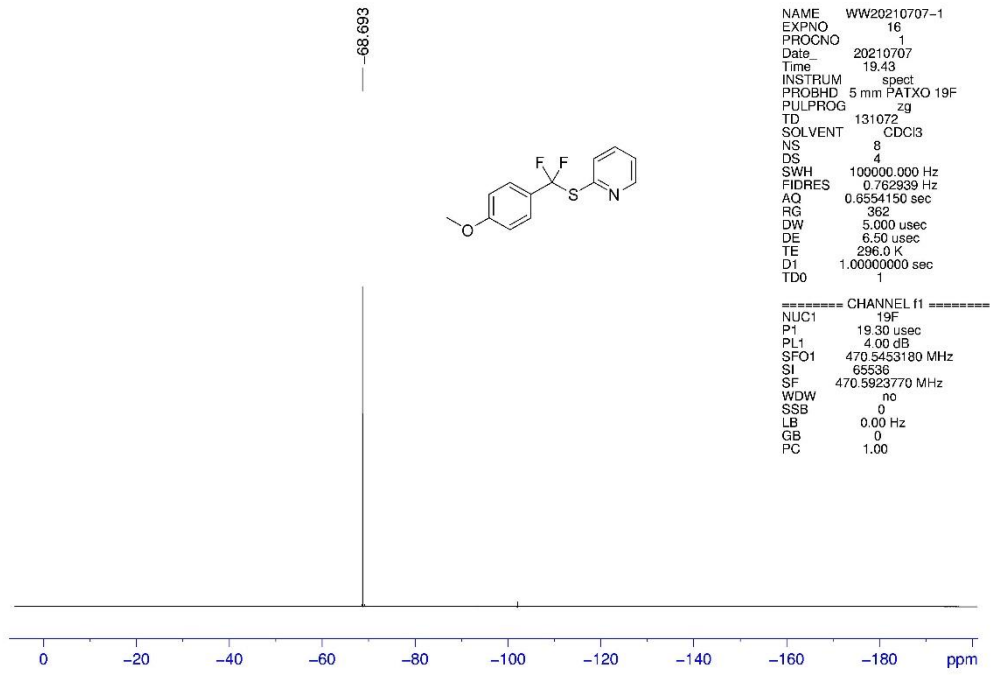
^{13}C NMR Spectra of **3aj** From Method A



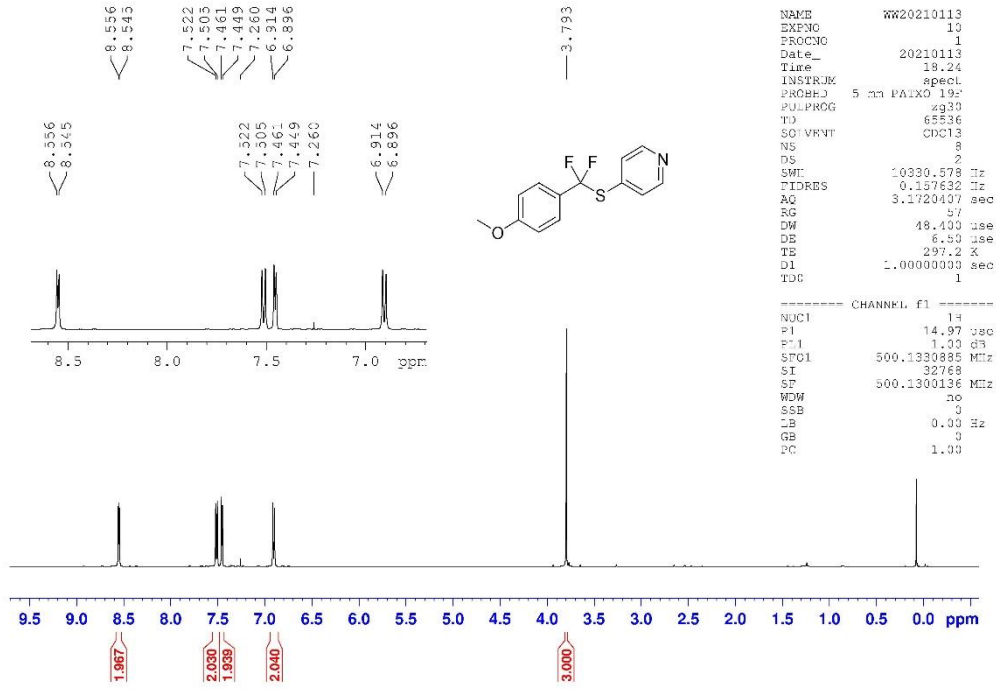
^{19}F NMR Spectra of **3aj** From Method A



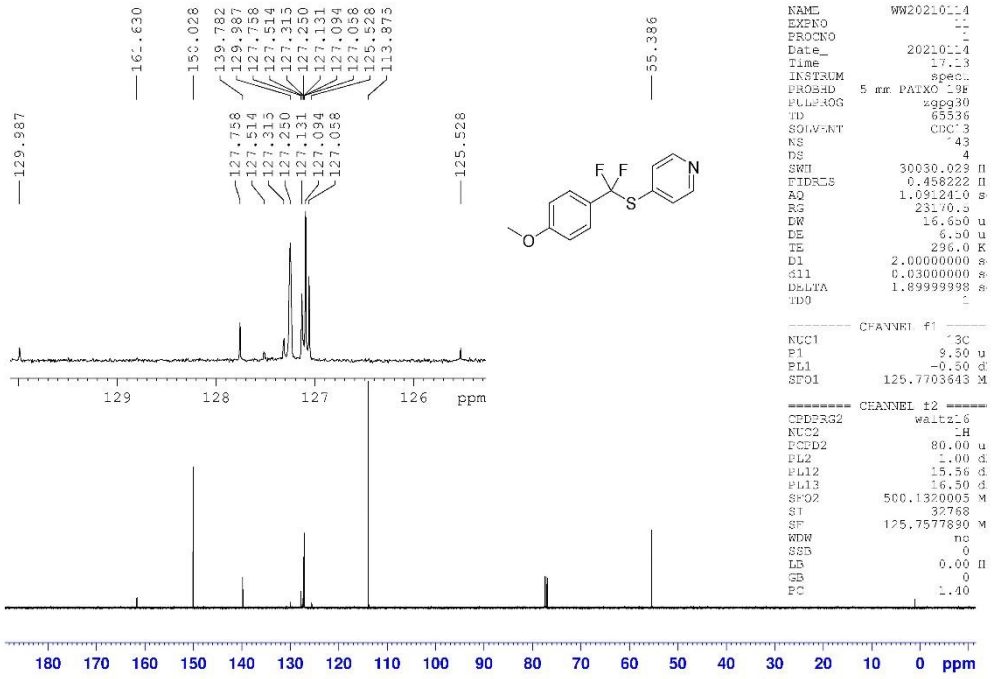
^{19}F NMR Spectra of **3aj** From Method B



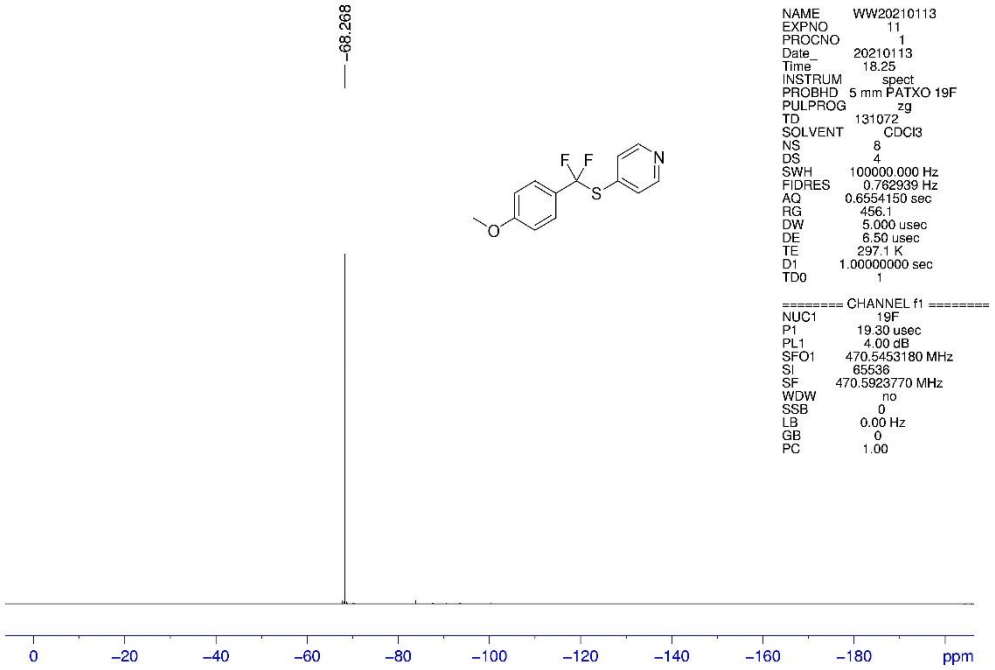
^{1}H NMR Spectra of **3ak**



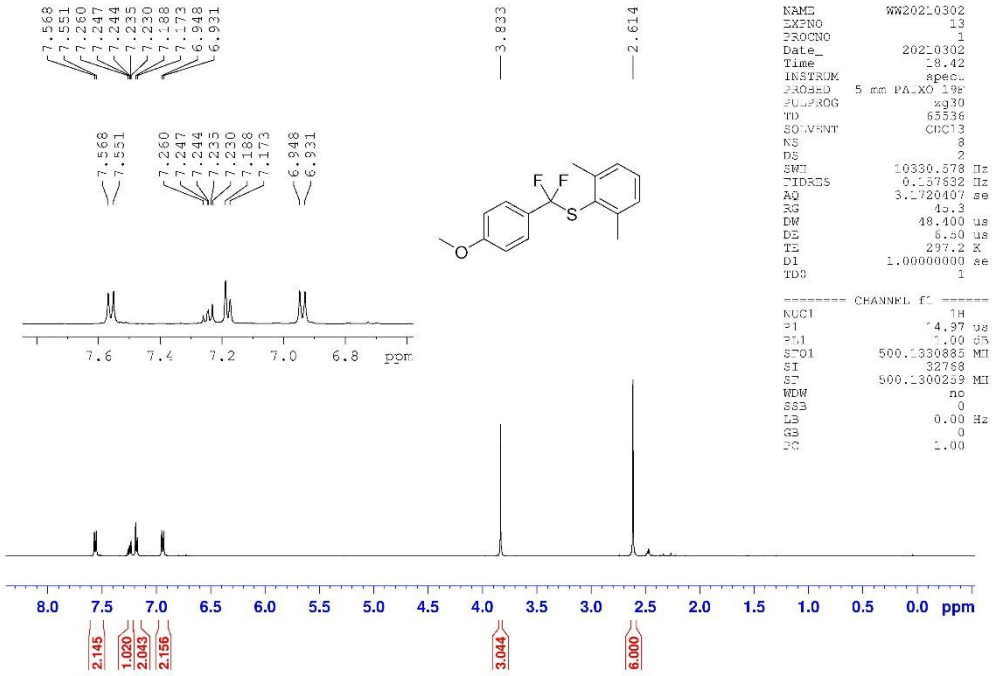
^{13}C NMR Spectra of **3ak**



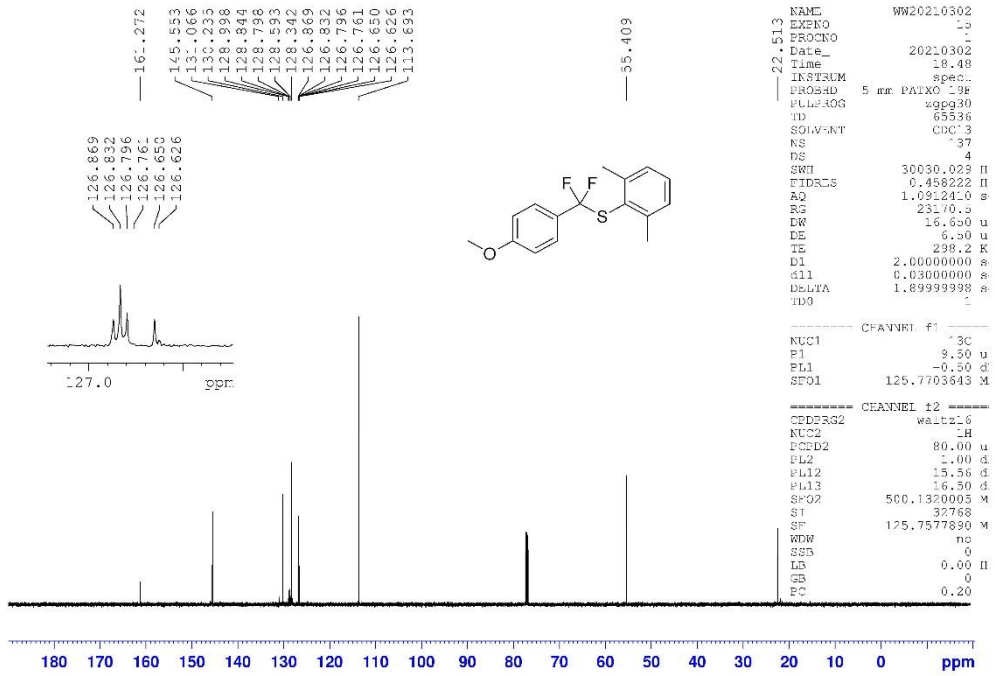
^{19}F NMR Spectra of **3ak**



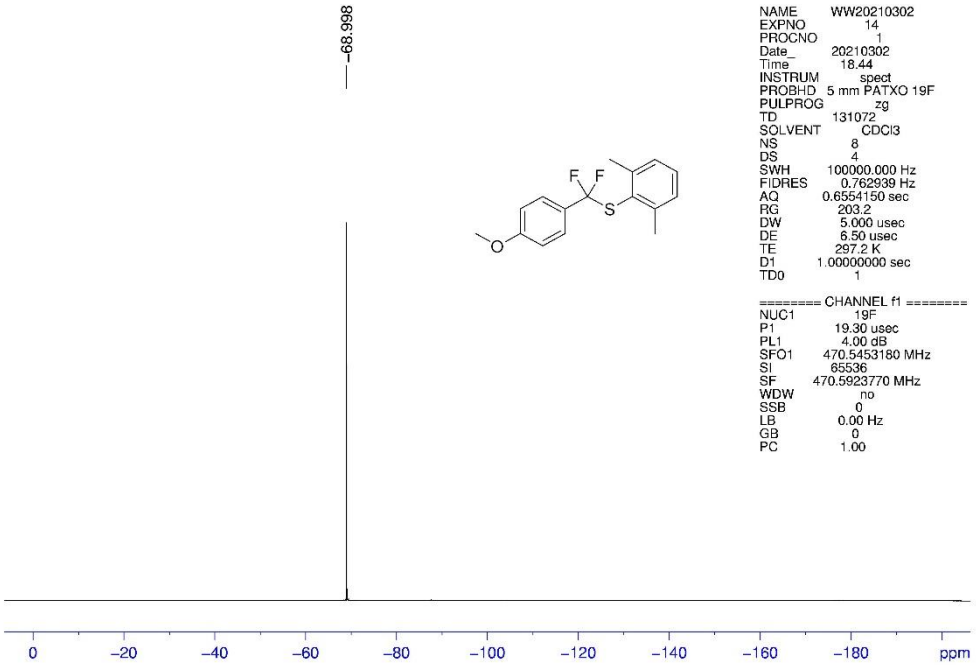
^{1}H NMR Spectra of **3am**



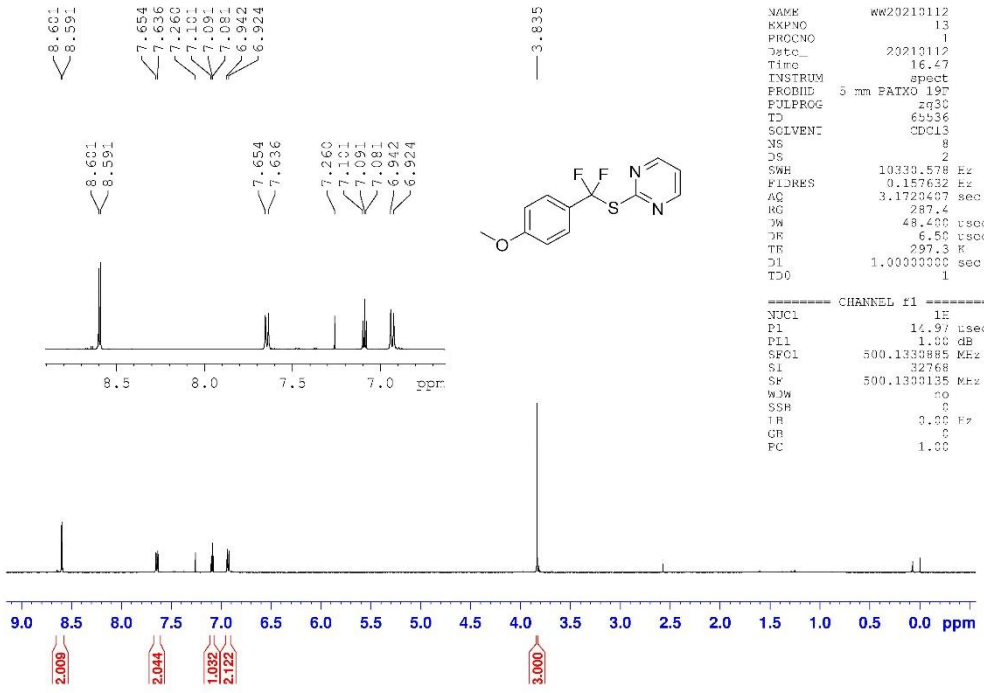
^{13}C NMR Spectra of **3am**



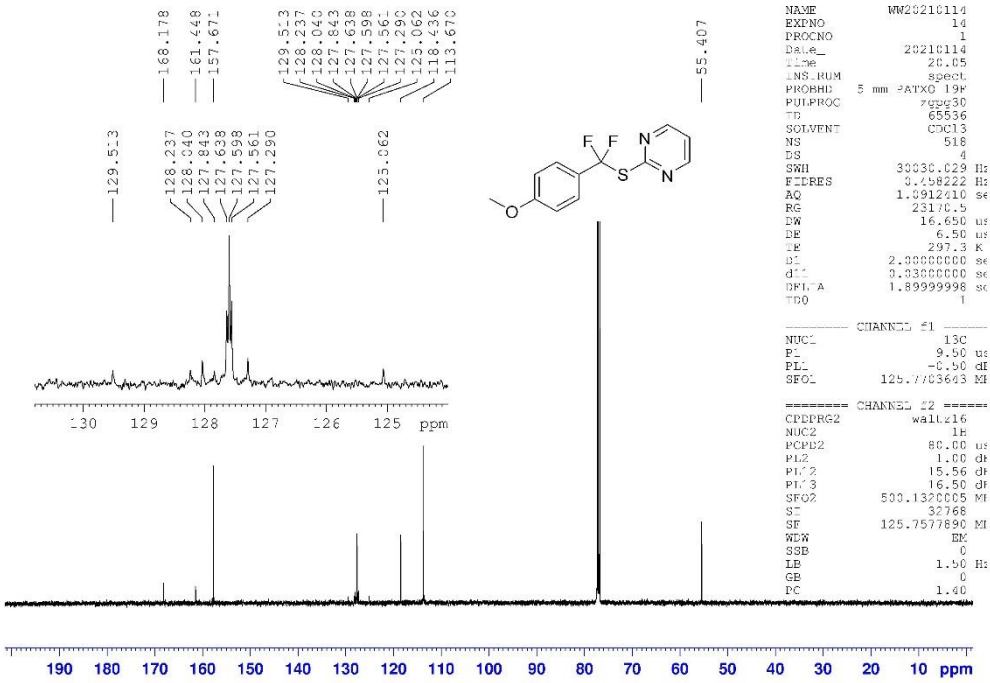
^{19}F NMR Spectra of **3am**



^{1}H NMR Spectra of **3an**



^{13}C NMR Spectra of **3an**



^{19}F NMR Spectra of **3an**