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

Supporting Information

Visible-light mediated Stereospecific C(sp^2)−H Difluoroalkylation of (*Z*)-Aldoximes

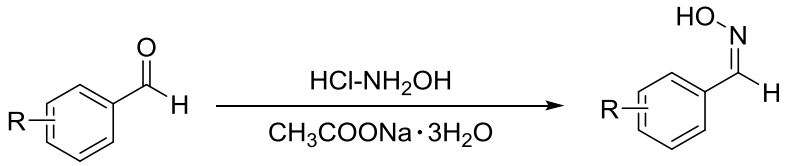
Contents

1. General information

^{1}H NMR, ^{13}C NMR spectra and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AV-500 spectrometer at room temperature. Chemical shifts for ^{1}H NMR spectra are reported in ppm relative to residual $CDCl_3$ 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 $CDCl_3$ (δ = 77.16 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.

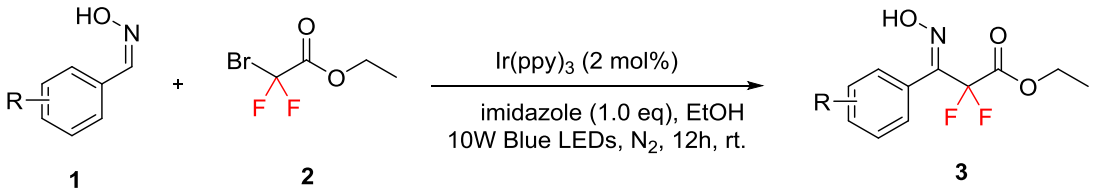
2. Preparation of compounds

2.1 General procedure for the synthesis of aldoximes 1a-1r [1]



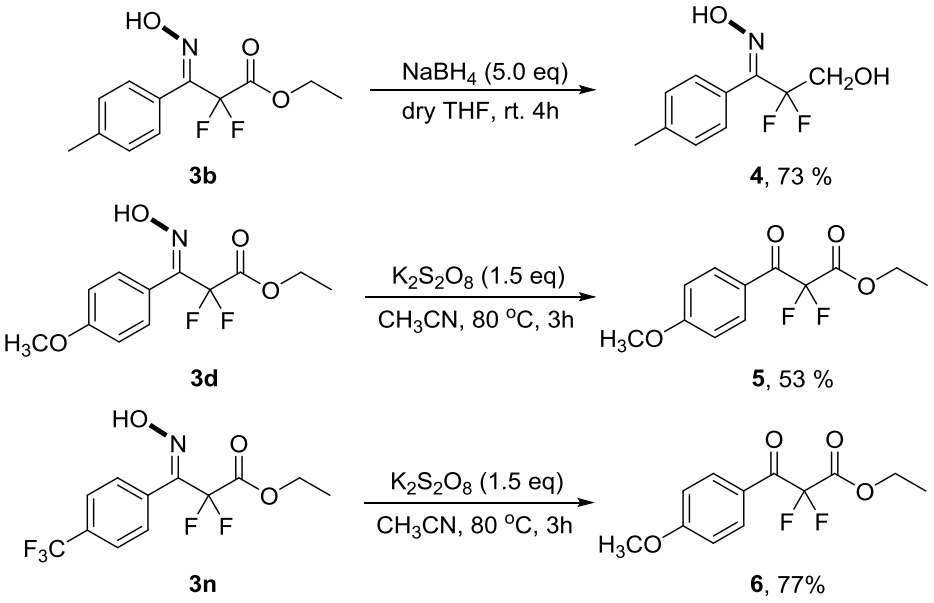
In a 250 mL round bottom flask with stir bar, benzaldehyde (10 mmol, 1 eq) was dissolved in CH_3OH (45 ml), hydroxylamine hydrochloride (20 mmol, 2 eq) was added to the solution, and then sodium acetate (20 mmol, 2 eq) and 15 ml water were added. The solution was stirred at room temperature for 12 h. The mixture was extracted with Ethyl acetate (3 × 25 ml) and saturated salt water (3 × 25 ml). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (PE/EA = 10:1) to afford pure aldoximes (**1a-1r**).

2.2 General procedure for the synthesis of difluoroalkylated oximes derivatives



A mixture of **1** (0.5 mmol, 77.79 mg) and **2** (0.1 mmol, 20.30 mg), *fac* - $[Ir(ppy)_3]$ (0.002 mmol, 1.31 mg) and imidazole (0.1 mmol, 6.81 mg) in EtOH (0.6 mL) under N_2 atmosphere was stirred under 10 W blue light at room temperature for 12 hours. Then, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 25 ml) and saturated salt water (3 × 25 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the difluoroalkylated oximes derivatives (**3a-3t**).

2.3 Application of difluoroalkylated aldehyde-derived oximes



A mixture of **3b** (0.2 mmol, 51.45 mg) and $NaBH_4$ (1.0 mmol, 37.83 mg) in CH_3CN (3.0 mL) was stirred 4 hours at room temperature. Then, the mixture was extracted with ethyl acetate (3 × 25 ml) and saturated salt water (3 × 25 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column

chromatography to afford pure reductive product **4** [2].

A mixture of **3d** (or **3n**) (0.2 mmol, 54.65 mg) and $K_2S_2O_8$ (0.3 mmol, 81.10 mg) in CH_3CN (5.0 mL) was refluxed at 80 ^oC for 3 hours. Then, the mixture was extracted with ethyl acetate (3 × 25 ml) and saturated salt water (3 × 25 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford pure product **5** (or **6**) [3].

3. Single crystal X-ray analysis of 3m

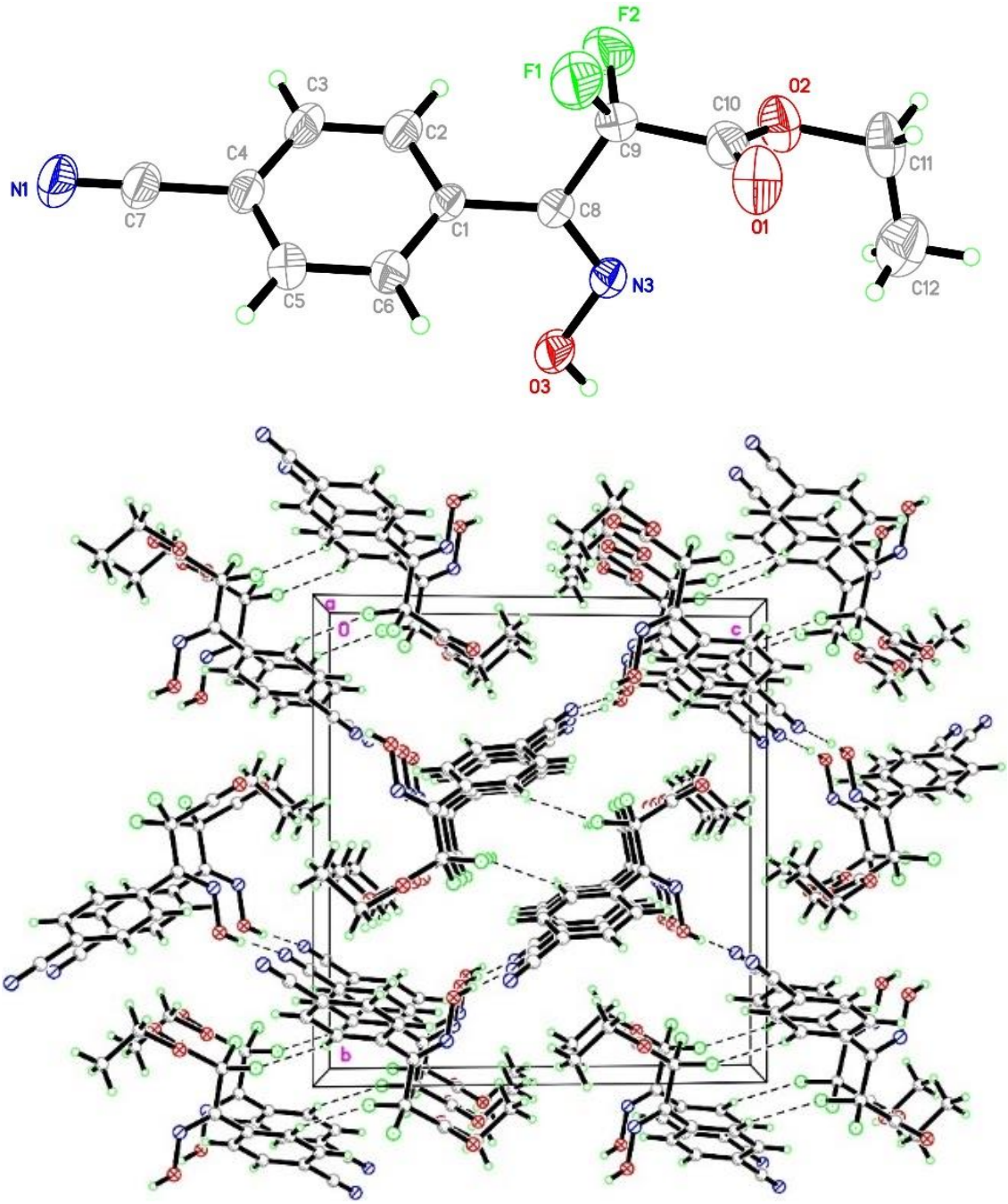


Figure 1. Crystal structure of **3m** (gray for carbon atoms, blue for nitrogen atoms, green for fluorine atom and red for oxygen atom). Thermal ellipsoids are drawn at the 50%.

Table 1 Sample and crystal data for **3m**.

Identification code	3h	
Chemical formula	$C_{12}H_{10}F_2N_2O_3$	
Formula weight	268.22 g/mol	
Temperature	303(2) K	
Wavelength	0.71073 Å	
Crystal size	0.070 x 0.070 x 0.090 mm	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 6.2592(3) Å	α = 90°
	b = 14.9217(7) Å	β = 95.929(2)°
	c = 13.9603(5) Å	γ = 90°
Volume	1296.89(10) $Å^3$	
Z	4	
Density (calculated)	1.374 g/cm^3	
Absorption coefficient	0.118 mm^{-1}	
F(000)	552	

Table 2 Data collection and structure refinement for 3m

Diffractometer	Bruker APEX-II CCD	
Theta range for data collection	2.73 to 27.47°	
Index ranges	-7<=h<=8, -19<=k<=16, -17<=l<=18	
Reflections collected	14768	
Independent reflections	2940 [R(int) = 0.0580]	
Absorption correction	none	
Max. and min. transmission	0.9920 and 0.9890	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick 2008)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014 (Sheldrick 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	2940 / 0 / 175	
Goodness-of-fit on F^2	1.041	
Final R indices	1744 data; I>2σ(I)	R1 = 0.0577, wR2 = 0.1573
	all data	R1 = 0.0963, wR2 = 0.1911
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0882P)^2+0.3503P]$ where $P=(F_o^2+2F_c^2)/3$	

Largest diff. peak and hole	0.389 and -0.330 eÅ^{-3}
R.M.S. deviation from mean	0.038 eÅ^{-3}

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å2) for 3m.

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x/a	y/b	z/c	U(eq)
F1	0.3139(4)	0.41846(12)	0.68323(16)	0.1087(7)
F2	0.0011(4)	0.46152(15)	0.62261(12)	0.1199(9)
O1	0.1632(4)	0.38717(17)	0.85097(17)	0.0941(7)
O2	0.8379(3)	0.41731(14)	0.77660(15)	0.0854(6)
O3	0.1703(3)	0.68363(12)	0.80901(13)	0.0745(6)
N1	0.8775(4)	0.76607(18)	0.43554(18)	0.0895(8)
N3	0.1182(3)	0.59486(13)	0.79316(13)	0.0556(5)
C1	0.3500(3)	0.60641(15)	0.65983(14)	0.0488(5)
C2	0.2939(4)	0.6133(2)	0.56177(15)	0.0667(7)
C3	0.4290(5)	0.6547(2)	0.50355(17)	0.0723(8)
C4	0.6208(4)	0.68957(16)	0.54336(16)	0.0579(6)
C5	0.6795(4)	0.68296(17)	0.64115(17)	0.0616(6)
C6	0.5443(4)	0.64185(17)	0.69892(16)	0.0587(6)
C7	0.7622(5)	0.73275(18)	0.48277(18)	0.0689(7)
C8	0.2042(3)	0.56167(15)	0.72222(14)	0.0501(5)
C9	0.1403(5)	0.46596(18)	0.70326(18)	0.0655(7)
C10	0.0459(5)	0.41838(18)	0.7869(2)	0.0677(7)
C11	0.7357(5)	0.3744(3)	0.8546(3)	0.0991(11)
C12	0.7063(8)	0.4396(3)	0.9307(3)	0.1272(15)

Table 4. Bond lengths (Å) for **3m**.

F1-C9	1.351(3)	F2-C9	1.352(3)
O1-C10	1.192(3)	O2-C10	1.295(3)
O2-C11	1.466(3)	O3-N3	1.377(2)
O3-H3A	0.79(4)	N1-C7	1.141(3)
N3-C8	1.275(3)	C1-C2	1.382(3)
C1-C6	1.386(3)	C1-C8	1.484(3)
C2-C3	1.379(3)	C2-H2	0.93
C3-C4	1.372(4)	C3-H3	0.93
C4-C5	1.380(3)	C4-C7	1.438(3)
C5-C6	1.373(3)	C5-H5	0.93
C6-H6	0.93	C8-C9	1.499(3)

C9-C10	1.536(4)	C11-C12	1.466(5)
C11-H11A	0.97	C11-H11B	0.97
C12-H12A	0.96	C12-H12B	0.96
C12-H12C	0.96		

Table 5. Bond angles (°) for **3m**.

C10-O2-C11	115.7(2)	N3-O3-H3A	109.5
C8-N3-O3	112.75(18)	C2-C1-C6	119.0(2)
C2-C1-C8	120.4(2)	C6-C1-C8	120.58(18)
C3-C2-C1	120.6(2)	C3-C2-H2	119.7
C1-C2-H2	119.7	C4-C3-C2	119.7(2)
C4-C3-H3	120.1	C2-C3-H3	120.1
C3-C4-C5	120.4(2)	C3-C4-C7	119.8(2)
C5-C4-C7	119.8(2)	C6-C5-C4	119.7(2)
C6-C5-H5	120.1	C4-C5-H5	120.1
C5-C6-C1	120.6(2)	C5-C6-H6	119.7
C1-C6-H6	119.7	N1-C7-C4	178.7(3)
N3-C8-C1	128.0(2)	N3-C8-C9	112.39(19)
C1-C8-C9	119.60(18)	F1-C9-F2	105.4(2)
F1-C9-C8	109.3(2)	F2-C9-C8	109.3(2)
F1-C9-C10	107.2(2)	F2-C9-C10	110.2(2)
C8-C9-C10	115.00(19)	O1-C10-O2	127.8(3)
O1-C10-C9	119.7(3)	O2-C10-C9	112.5(3)
O2-C11-C12	110.2(3)	O2-C11-H11A	109.6
C12-C11-H11A	109.6	O2-C11-H11B	109.6
C12-C11-H11B	109.6	H11A-C11-H11B	108.1
C11-C12-H12A	109.5	C11-C12-H12B	109.5
H12A-C12-H12B	109.5	C11-C12-H12C	109.5
H12A-C12-H12C	109.5	H12B-C12-H12C	109.5

Table 6. Torsion angles (°) for **3m**.

C6-C1-C2-C3	0.0(4)	C8-C1-C2-C3	-180.0(2)
C1-C2-C3-C4	-0.1(4)	C2-C3-C4-C5	0.3(4)
C2-C3-C4-C7	179.9(3)	C3-C4-C5-C6	-0.5(4)
C7-C4-C5-C6	179.9(2)	C4-C5-C6-C1	0.4(4)
C2-C1-C6-C5	-0.2(4)	C8-C1-C6-C5	179.8(2)
O3-N3-C8-C1	1.2(3)	O3-N3-C8-C9	-178.0(2)
C2-C1-C8-N3	-120.5(3)	C6-C1-C8-N3	59.6(3)
C2-C1-C8-C9	58.6(3)	C6-C1-C8-C9	-121.3(2)

N3-C8-C9-F1	-138.3(2)	C1-C8-C9-F1	42.4(3)
N3-C8-C9-F2	106.8(2)	C1-C8-C9-F2	-72.4(3)
N3-C8-C9-C10	-17.7(3)	C1-C8-C9-C10	163.0(2)
C11-O2-C10-O1	1.7(5)	C11-O2-C10-C9	-178.9(2)
F1-C9-C10-O1	39.2(3)	F2-C9-C10-O1	153.4(3)
C8-C9-C10-O1	-82.5(3)	F1-C9-C10-O2	-140.2(2)
F2-C9-C10-O2	-26.1(3)	C8-C9-C10-O2	98.0(3)
C10-O2-C11-C12	87.4(4)		

Table 7. Anisotropic atomic displacement parameters (Å^2) for 3m**.**

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	0.1324(16)	0.0681(11)	0.1397(16)	-0.0223(10)	0.0815(14)	0.0003(10)
F2	0.167(2)	0.1252(16)	0.0632(10)	-0.0018(10)	-0.0090(11)	-0.0749(15)
O1	0.0809(14)	0.0989(17)	0.1047(16)	0.0301(13)	0.0206(12)	0.0061(12)
O2	0.0688(13)	0.0913(15)	0.0977(14)	0.0124(11)	0.0160(10)	-0.0170(10)
O3	0.0963(14)	0.0582(11)	0.0765(11)	-0.0164(8)	0.0454(10)	-0.0077(9)
N1	0.109(2)	0.0856(17)	0.0820(15)	0.0010(13)	0.0500(15)	-0.0202(15)
N3	0.0605(11)	0.0551(11)	0.0541(10)	-0.0047(8)	0.0198(9)	-0.0049(9)
C1	0.0530(12)	0.0507(12)	0.0452(10)	-0.0043(9)	0.0164(9)	-0.0003(9)
C2	0.0638(15)	0.0919(19)	0.0459(12)	-0.0053(11)	0.0135(10)	-0.0143(13)
C3	0.0821(18)	0.095(2)	0.0428(11)	0.0022(12)	0.0180(12)	-0.0100(15)
C4	0.0657(15)	0.0537(13)	0.0586(13)	0.0011(10)	0.0276(11)	0.0010(11)
C5	0.0599(14)	0.0634(15)	0.0631(14)	0.0040(11)	0.0137(11)	-0.0075(11)
C6	0.0649(15)	0.0639(14)	0.0481(11)	0.0049(10)	0.0099(10)	-0.0085(11)
C7	0.0848(18)	0.0619(16)	0.0652(14)	0.0008(12)	0.0321(13)	-0.0044(13)
C8	0.0523(12)	0.0541(12)	0.0456(10)	-0.0018(9)	0.0124(9)	-0.0020(10)
C9	0.0764(17)	0.0627(15)	0.0597(13)	-0.0122(11)	0.0183(12)	-0.0128(13)
C10	0.0680(17)	0.0574(15)	0.0798(17)	-0.0020(12)	0.0176(14)	-0.0053(12)
C11	0.075(2)	0.109(3)	0.118(3)	0.028(2)	0.0321(19)	-0.0206(18)
C12	0.139(4)	0.136(4)	0.116(3)	-0.003(3)	0.055(3)	-0.012(3)

Table 8. Hydrogen atomic coordinates and isotropic atomic displacement parameters (Å^2) for **3m.**

	x/a	y/b	z/c	U(eq)
H3A	0.104(5)	0.7030(12)	0.850(2)	0.112
H2	0.1638	0.5897	0.5348	0.08
H3	0.3903	0.6591	0.4376	0.087
H5	0.8102	0.7063	0.6678	0.074

	x/a	y/b	z/c	U(eq)
H6	0.5835	0.6377	0.7649	0.07
H11A	-0.1754	0.3253	0.8810	0.119
H11B	-0.4026	0.3501	0.8294	0.119
H12A	-0.3706	0.4907	0.9033	0.191
H12B	-0.1559	0.4583	0.9606	0.191
H12C	-0.3739	0.4125	0.9781	0.191

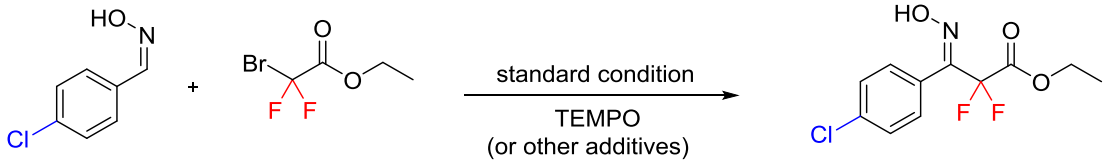
Table 9 Hydrogen bond distances (Å) and angles (°) for **3m**

	Donor-H	Acceptor-H	Donor-Acceptor	Angle
O3-H3A···N1#1	0.79	2.00	2.777(3)	165.8

Symmetry transformations used to generate equivalent atoms:
#1 x-1, -y+3/2, z+1/2

4. Preliminary mechanistic study

Table 10 Preliminary mechanistic studies



Entry	Additive (eq)	Yields [b](%)
1	TEMPO (0.5)	22
2	TEMPO (1.0)	3
3	1,4-Benzoquinone (0.5)	15
4	1,4-dinitrobenzene (0.5)	23
5	Hydroquinone (0.5)	16
6	H_2O (1.0)	25
7	Air	13
8	Without $Ir(ppy)_3$	0
9	In dark	0

[a] Reaction condition: **1** (0.50 mmol), **2** (0.10 mmol), *fac*-[$Ir(ppy)_3$] (2 mol%), imidazole (1.0 equiv.), EtOH (0.6 mL), 10 W Blue LEDs, 12h, N_2 atmosphere at room temperature. [b]Yields determined by ^{19}F NMR analysis with $PhCF_3$ as the internal stander.

(*Z*)-4-chlorobenzaldehyde oxime (0.5 mmol, 77.79 mg) and ethyl bromodifluoroacetate (0.1 mmol, 20.30 mg), *fac* - [$Ir(ppy)_3$] (0.002 mmol, 1.31 mg) and imidazole (0.1 mmol, 6.81 mg) in EtOH (0.6 mL) under N_2 atmosphere. The mixture solution was stirred under 10 W blue light at room temperature for 12 hours. When 0.5 equiv TEMPO was added, the reaction yield decreased to 22%; When the amount of TEMPO increased to 1.0 equiv, the yield was as low as 3%. At the end of the reaction, the ^{19}F NMR analysis of the mixture showed that the radical scavenger TEMPO captured the ethyl difluoroacetate radical formed by the bromination of the reactant ethyl bromodifluoroacetate, TEMPO-CF_2COOEt intermediate (**Figure 2**). In addition, when 0.5 equiv of 1,4-benzoquinone, 1,4-dinitrobenzene or p-diphenol was added to the standard reaction conditions, the yield of the reaction decreased significantly (**Table 10, entry 3-5**). We found that the yield of the reaction also decreased significantly with the addition of 1.0 equiv of water and without nitrogen protection, which may be due to the effect of oxygen on the free radical reaction (**Table 10, entry 6-7**). The experimental results also showed that the reaction did not

occur without photocatalyst or illumination (**Table 10, entry 8-9**).

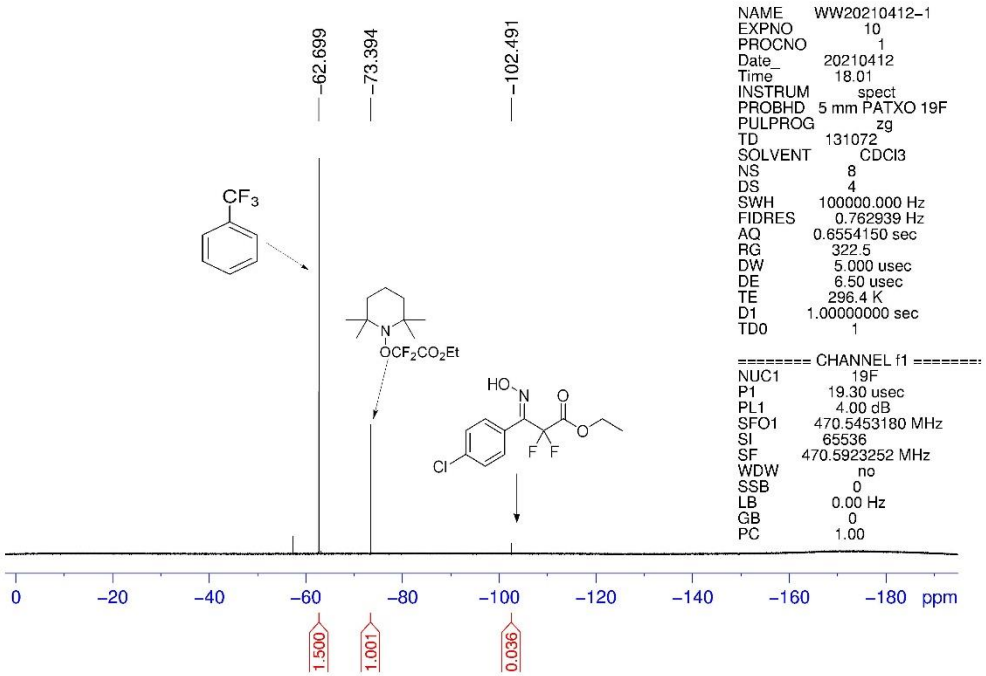
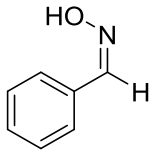


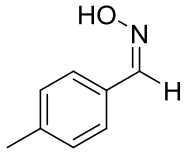
Figure 2 ^{19}F NMR of TEMPO-CF_2CO_2Et

5. Characterization of the compounds



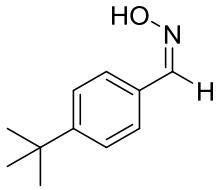
(1a)

(*Z*)-benzaldehyde oxime (1a). (Z / E = 10 : 1) Yield: 88%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.19 (s, 1H), 7.60-7.58 (m, 2H), 7.41-7.39 (m, 3H) ppm.



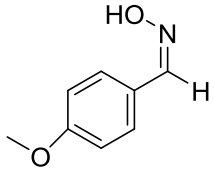
(1b)

(*Z*)-4-methylbenzaldehyde oxime (1b). Yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.66 (s, OH), 8.22 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H) ppm.



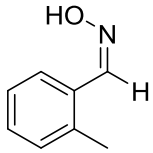
(1c)

(*Z*)-4-(tert-butyl)benzaldehyde oxime (1c) Yield: 85%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.76 (s, OH), 8.19 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 1.37 (s, 9H) ppm.



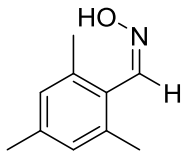
(1d)

(*Z*)-4-methoxybenzaldehyde oxime (1d) Yield: 92%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.54 (s, OH), 8.14 (s, 1H), 7.52 (d, J = 7.2 Hz, 2H), 6.90 (d, J = 7.2 Hz, 2H), 3.80 (s, 3H) ppm.



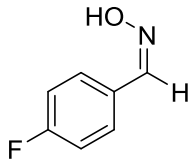
(1e)

(*Z*)-2-methylbenzaldehyde oxime (1e). Yield: 78%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.66 (d, J = 6.1 Hz, 1H), 7.29 (td, J = 6.1, 0.9 Hz, 1H), 7.23-7.19 (m, 2H), 2.44 (s, 3H) ppm.



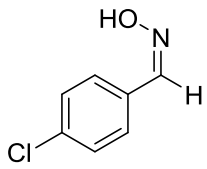
(1f)

(*Z*)-2,4,6-trimethybenzaldehyde oxime (1f) Yield: 90%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.91 (s, OH), 8.47 (s, 1H), 6.94 (s, 2H), 2.43 (s, 6H), 2.34 (s, 3H) ppm.



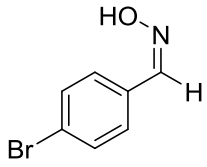
(1g)

(*Z*)-4-fluorobenzaldehyde oxime (1g) (Z / E = 6.5 : 1) Yield: 82%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.98 (s, OH), 8.15 (s, 1H), 7.58-7.56 (m, 2H), 7.11-7.07 (m, 2H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -109.84 - -109.90 (m, CF) ppm.



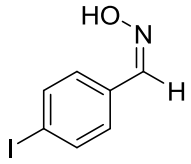
(1h)

(*Z*)-4-chlorobenzaldehyde oxime (1h) Yield: 85%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.42 (s, OH), 7.36 (d, J = 8.5 Hz, 2H) ppm.



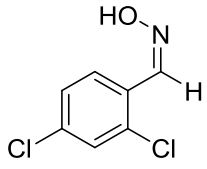
(1i)

(*Z*)-4-bromobenzaldehyde oxime (1i) Yield: 82%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.34 (s, OH) ppm.



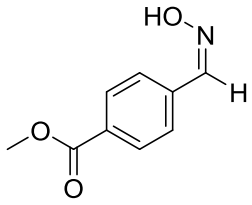
(1j)

(*Z*)-4-iodobenzaldehyde oxime (1j) Yield: 80%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.40 (s, OH), 8.08 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H) ppm.



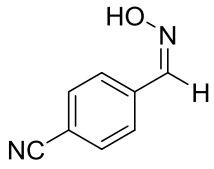
(1k)

(*Z*)-2,4-dichlorobenzaldehyde oxime (1k) Yield: 85%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.49 (s, 1H.), 7.79 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 7.41 (d, J = 8.6 Hz, 1H) ppm.



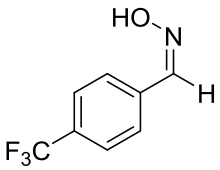
(1l)

(*Z*)-methyl-4-((hydroxyimino)methyl)benzoate (1l) Yield: 85%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.67 (s, OH), 8.18 (s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H) ppm.



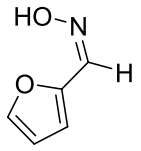
(1m)

(*Z*)-4-cyanobenzaldehyde oxime (1m) Yield: 86%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14 (s, 1H), 7.71 (s, OH), 7.69 (m, 4H) ppm.



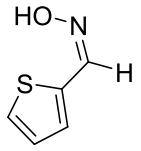
(1n)

(*Z*)-4-(trifluoromethyl)benzaldehyde oxime (1n) Yield: 82%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.17 (s, 1H), 7.70 (d, J = 6.9 Hz, 2H), 7.66 (s, OH), 7.65 (d, J = 6.9 Hz, 2H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -62.84 (s, CF_3) ppm.



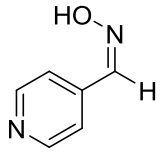
(1o)

(*Z*)-furan-2-carbaldehyde oxime (1o) Yield: 46%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.38 (s, OH), 8.03 (s, 1H), 7.48 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.45 (dd, J = 2.0, 2.8 Hz, 1H) ppm.



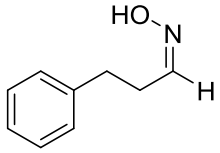
(1p)

(*Z*)-thiophene-2-carbaldehyde oxime (1p) Yield: 82%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.73 (s, OH), 7.74 (s, 1H), 7.58 (dd, J = 5.1, 1.0 Hz, 1H), 7.41 (dd, J = 3.7, 1.0 Hz, 1H), 7.11 (dd, J = 5.1, 3.7 Hz, 1H) ppm.



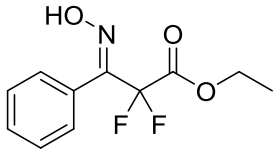
(1q)

(*Z*)-isonicotinaldehyde oxime (1q) Yield: 87%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.56 (s, OH), 8.65 (d, J = 5.2 Hz, 2H), 8.13 (s, 1H), 7.52 (d, J = 5.2 Hz, 2H) ppm.



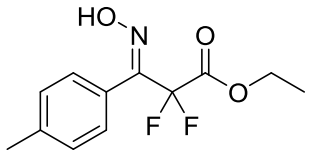
(1r)

(*Z*)-3-phenylpropanal oxime (1r) Yield: 80%, ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.49 (s, OH), 7.32-7.29 (m, 2H), 7.23-7.21 (m, 3H), 6.76 (t, J = 5.4 Hz, 1H), 2.83 (t, J = 7.7 Hz, 2H), 2.73-2.69 (m, 2H) ppm.



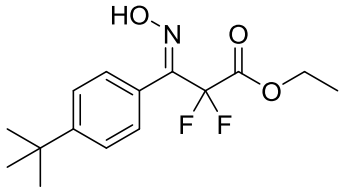
(3a)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-phenylpropanoate (3a) (E / Z = 10 : 1) Yield: 43%, white solid, m.p: 56.5 – 57.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 7.55-7.53 (m, 2H), 7.49-7.46 (m, 3H), 4.37 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -103.14 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9 (t, J = 31.3 Hz), 151.2 (t, J = 29.6 Hz), 130.4, 128.9, 128.4, 126.3, 112.3 (t, J = 249.6 Hz), 63.5, 13.8 ppm. HRMS (ESI) calcd. for $C_{11}H_{12}F_2NO_3$ $[M+H]^+$ 244.0780, found: 244.0783.



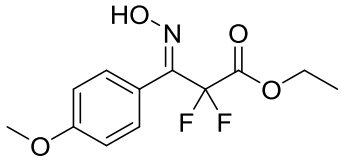
(3b)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(*p*-tolyl)propanoate (3b) (E / Z = 16 : 1) Yield: 57%, white solid, mp: 57.5 – 58.2 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -103.11 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0 (t, J = 31.5 Hz), 151.2 (t, J = 30.5 Hz), 140.7, 129.1, 128.9, 123.3, 112.4 (t, J = 249.5 Hz), 63.4, 21.5, 13.8 ppm. HRMS (ESI) calcd. for $C_{11}H_{12}F_2NO_3$ $[M+H]^+$ 258.0936, found: 258.0931.



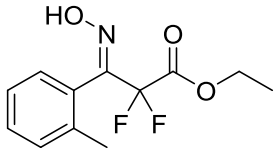
(3c)

(*E*)-ethyl-3-(4-(tert-butyl)phenyl)-2,2-difluoro-3-(hydroxyimino)propanoate (3c) (E / Z = 6 : 1). Yield: 52% (the isolated yield given for the inseparable E- and Z-isomers of **3c**). white solid, mp: 68.1 – 70.3 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 7.52 -7.48 (q, J = 8.0 Hz, 4H), 4.37 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 12H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.91 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.0 (t, J = 31.3 Hz), 153.6, 151.1 (t, J = 29.6 Hz), 128.7, 125.4, 123.3, 112.5 (t, J = 249.6 Hz), 63.4, 34.9, 31.1, 13.8 ppm. HRMS (ESI) calcd. for $C_{15}H_{20}F_2NO_3$ $[M+H]^+$ 300.1406, found: 300.1409.



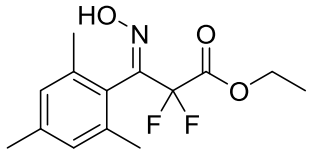
(3d)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(4-methoxyphenyl)propanoate (3d) (E / Z = 23 : 1) Yield: 41%, white solid, mp: 84.6 – 85.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.67 (s, 1H), 7.56 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.76 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9 (t, J = 31.6 Hz), 161.0, 150.8 (t, J = 29.9 Hz), 130.7, 118.3, 113.9, 112.6 (t, J = 249.6 Hz), 63.3, 55.3, 13.9 ppm. HRMS (ESI) calcd. for $C_{12}H_{14}F_2NO_4$ $[M+H]^+$ 274.0885, found: 274.0880.



(3e)

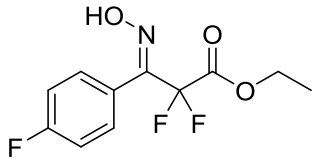
(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(*o*-tolyl)propanoate (3e) (E / Z = 2.6 : 1) Yield: 50%, white solid, mp: 104.8 – 105.9 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (s, 1H), 7.38 (dt, J = 1.5, 7.5 Hz, 1H), 7.31-7.26 (m, 2H), 7.22 (d, J = 7.5 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 2.30 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -104.42 (dd, J = 276.9, 276.5 Hz, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9 (t, J = 31.1 Hz), 152.5 (t, J = 30.8 Hz), 137.5, 130.2, 130.1, 128.0, 126.6, 125.7, 112.0 (t, J = 248.3 Hz), 63.5, 19.5, 13.9 ppm. HRMS (ESI) calcd. for $C_{12}H_{14}F_2NO_4$ $[M+H]^+$ 258.0936, found: 258.0937.



(3f)

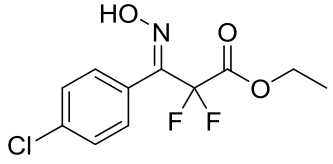
(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-mesitylpropanoate (3f) (E / Z = 7 : 10) Yield: 48%, white solid, mp: 116.2 – 117.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 6.95 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.31 (s, 3H), 2.23 (s, 6H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -103.66 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.9 (t, J = 31.4 Hz), 153.7 (t, J = 32.2 Hz), 139.8, 136.9, 128.4, 123.6, 112.3 (t, J = 248.3 Hz), 63.2, 21.2, 19.6, 14.0 ppm. HRMS (ESI) calcd. for

$C_{14}H_{18}F_2NO_3$ $[M+H]^+$ 286.1249, found: 286.1245.



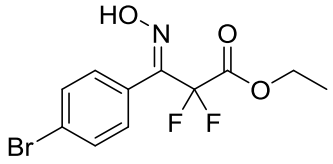
(3g)

(*E*)-ethyl-2,2-difluoro-3-(4-fluorophenyl)-3-(hydroxyimino)propanoate (3g) (E / Z = 32 : 1) Yield: 58%, white solid, mp: 59.1 – 61.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.58-7.55 (m, 2H), 7.15 (t, J = 9.0 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.95 (s, CF_2), -109.05 - -109.11 (m, CF) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 163.7 (d, J = 249.8 Hz), 162.8 (t, J = 31.1 Hz), 150.3 (t, J = 29.8 Hz), 131.3 (d, J = 8.6 Hz), 122.1 (d, J = 3.5 Hz), 115.7 (d, J = 21.8 Hz), 112.3 (t, J = 249.8 Hz), 63.5, 13.8 ppm. HRMS (ESI) calcd. for $C_{11}H_{11}F_3NO_3$ $[M+H]^+$ 262.0686, found: 262.0682.



(3h)

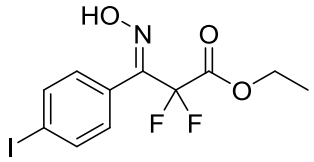
(*E*)-ethyl-3-(4-chlorophenyl)-2,2-difluoro-3-(hydroxyimino)propanoate (3h) (E / Z = 32 : 1) Yield: 70 %, white solid, mp: 77.5 – 78.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.62 (s, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.95 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.8 (t, J = 31.1 Hz), 150.4 (t, J = 29.8 Hz), 136.8, 130.6, 128.9, 124.6, 112.4 (t, J = 249.8 Hz), 63.7, 14.0 ppm. HRMS (ESI) calcd. for $C_{11}H_{11}ClF_2NO_3$ $[M+H]^+$ 278.0390, found: 278.0388.



(3i)

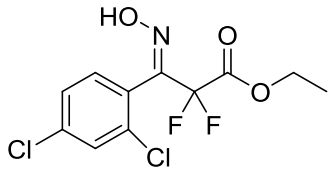
(*E*)-ethyl-3-(4-bromophenyl)-2,2-difluoro-3-(hydroxyimino)propanoate (3i) (E / Z = 20 : 1) Yield: 76%, white solid, mp: 89.8 – 90.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.26 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.98 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.5 (t, J = 31.3 Hz), 150.5 (t, J = 30.0 Hz),

131.8, 130.6, 125.0, 125.0, 112.2 (t, J = 249.4 Hz), 63.5, 13.9 ppm. HRMS (ESI) calcd. for $C_{11}H_{11}BrF_2NO_3$ $[M+H]^+$ 321.9885, found: 321.9889.



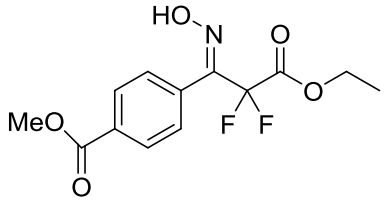
(3j)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(4-iodophenyl)propanoate (3j) (E / Z = 23 : 1) Yield: 48%, white solid, mp: 104.5 – 105.5 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.45 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -102.99 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.6 (t, J = 31.0 Hz), 150.5 (t, J = 30.1 Hz), 137.7, 130.5, 125.6, 112.2 (t, J = 249.6 Hz), 97.1, 63.5, 13.9 ppm. HRMS (ESI) calcd. for $C_{11}H_{11}F_2INO_3$ $[M+H]^+$ 369.9746, found: 369.9748.



(3k)

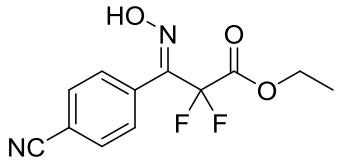
(*E*)-ethyl-3-(2,4-dichlorophenyl)-2,2-difluoro-3-(hydroxyimino)propanoate (3k) (E / Z = 24 : 1) Yield: 50%, white solid, mp: 55.8 – 56.2 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.56 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.35 (dd, J = 2.0, 8.5 Hz, 1H), 7.23 (d, J = 8.5 Hz 1H), 4.39 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -104.46 (dd, J = 277.4, 275.5 Hz, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.4 (t, J = 31.0 Hz), 148.8 (t, J = 30.9 Hz), 137.0, 134.5, 130.7, 129.8, 127.3, 125.1, 111.4 (t, J = 249.2 Hz), 63.7, 13.9 ppm. HRMS (ESI) calcd. for $C_{11}H_{10}Cl_2F_2NO_3$ $[M+H]^+$ 312.0000, found: 312.0004.



(3l)

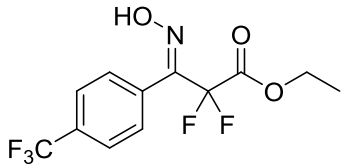
(*E*)-methyl-4-(3-ethoxy-2,2-difluoro-1-(hydroxyimino)-3-oxopropyl)benzoate (3l) (E / Z = 17 : 1) Yield: 41%, white solid, mp: 97.6 – 98.6 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.99 (s, 1H), 8.14 (d, J = 8.5 Hz, 2H), 7.63(d, J = 8.5 Hz, 2H), 4.39 (q, J =

7.2 Hz, 2H), 3.97 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -102.94 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 166.6, 162.6 (t, *J* = 30.9 Hz), 150.4 (t, *J* = 30.1 Hz), 131.5, 130.9, 129.6, 129.1, 112.2 (t, *J* = 249.4 Hz), 63.5, 52.5, 13.9 ppm. HRMS (ESI) calcd. for $C_{13}H_{14}F_2NO_5$ $[M+H]^+$ 302.0835, found: 302.0833.



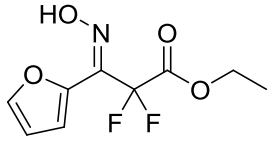
(3m)

(*E*)-ethyl-3-(4-cyanophenyl)-2,2-difluoro-3-(hydroxyimino)propanoate (3m) (E / Z = 7 : 1) Yield: 28%, white solid, mp: 119.6 – 120.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.76 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -102.77 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 162.4 (t, *J* = 30.7 Hz), 149.7 (t, *J* = 30.3 Hz), 132.3, 131.0, 130.0, 118.2, 114.2, 112.2 (t, *J* = 249.5 Hz), 63.8, 14.0 ppm. HRMS (ESI) calcd. for $C_{12}H_{11}F_2N_2O_3$ $[M+H]^+$ 269.0732, found: 269.0729.



(3n)

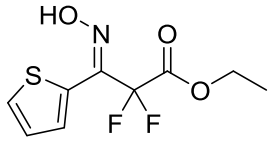
(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-[4(trifluoromethyl)phenyl]propanoate (3n) (E / Z = 62 : 1) Yield: 15%, white solid, mp: 87.5 – 88.7 °C. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.96 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -103.04 (s, CF_2), -63.17 (s, CF_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 162.8 (t, *J* = 30.8 Hz), 150.2 (t, *J* = 30.1 Hz), 132.4 (q, *J* = 32.7 Hz), 130.0, 129.6, 125.5 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 270.8 Hz), 112.2 (t, *J* = 249.8 Hz), 63.9, 13.9 ppm. HRMS (ESI) calcd. for $C_{12}H_{11}F_5NO_3$ $[M+H]^+$ 312.0654, found: 312.0650.



(3o)

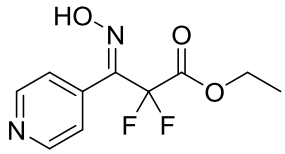
(*E*)-ethyl-2,2-difluoro-3-(furan-2-yl)-3-(hydroxyimino)propanoate (3o) (E / Z = 3 : 2) Yield: 77%, clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.65 (s, 1H), {Z : 8.01, E :

7.52, (m, 1H)}, {Z : 6.82-6.81, E : 7.36-7.35, (m, 1H)}, {Z : 6.69 - 6.68, E : 6.88 - 6.87, (m, 1H)}, 4.39 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -102.91 (s, CF_2), -103.26 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 162.0 (td, *J* = 33.4, 2.8 Hz), 149.4, 146.7, 145.6 (t, *J* = 33.8 Hz), 144.7 (t, *J* = 33.8 Hz), 139.7, 136.6, 118.4, 113.7 (t, *J* = 3.2 Hz), 113.2 (t, *J* = 3.5 Hz), 112.0, 108.4 (td, *J* = 247.5, 13.8 Hz), 63.8, 63.8, 13.9, 13.9 ppm. HRMS (ESI) calcd. for $C_9H_{10}F_2NO_4$ $[M+H]^+$ 234.0572, found: 234.0568.



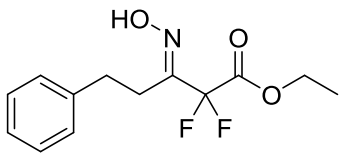
(3p)

(*Z*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(thiophen-2-yl)propanoate (3p) (E / Z = 1 : 4) Yield: 82%, white solid, mp: 78.6– 80.2 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 8.24 (s, 1H), 7.67 (s,1H), 7.32-7.31 (m, 1H), 7.13-7.12 (m, 1H), 4.37 (q, *J* = 7.2 Hz, 2H) 1.36 (t, *J* = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -94.18 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 163.1 (t, *J* = 34.7 Hz), 144.4, 139.3, 135.4 (t, *J* = 30.1 Hz), 128.9, 128.6 (t, *J* = 5.9 Hz), 111.4 (t, *J* = 249.8 Hz), 63.8, 14.0 ppm. HRMS (ESI) calcd. for $C_9H_{10}F_2NO_3S$ $[M+H]^+$ 250.0344, found: 250.0348.



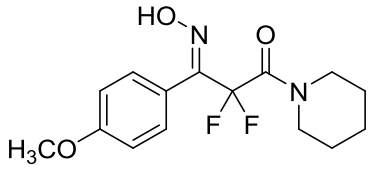
(3q)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-3-(pyridin-4-yl)propanoate (3q) (E / Z > 98 : 2) Yield: 40%, white solid, mp: 136.1 – 137.5 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 12.85 (s, 1H), 8.68 (d, *J* = 5.0 Hz, 2H), 7.60 (d, *J* = 5.0 Hz, 2H), 4.37 (q, *J* = 7.0 Hz, 2H), 1.32 (t, *J* = 7.0 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) *δ*: -102.56 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 162.3 (t, *J* = 30.9 Hz), 149.0, 147.0 (t, *J* = 30.0 Hz), 136.1, 124.1, 112.8 (t, *J* = 248.5 Hz), 63.3, 13.9 ppm. HRMS (ESI) calcd. for $C_{10}H_{11}F_2N_2O_3$ $[M+H]^+$ 245.0732, found: 245.0727.



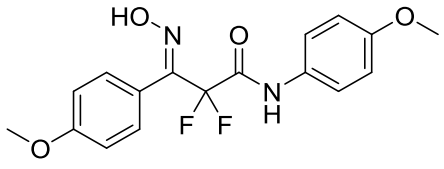
(3r)

(*E*)-ethyl-2,2-difluoro-3-(hydroxyimino)-5-phenylpentanoate (3r) (E / Z = 4 : 1) Yield: 38%, white solid, mp: 56.5 – 57.5°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.27 (s, 1H), 7.33-7.28 (m, 2H), 7.26-7.21 (m, 3H), 4.36 (q, J = 7.2 Hz, 2H), 2.94-2.91 (m, 2H), 2.81-2.77 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -106.19 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 162.6 (t, J = 31.1 Hz), 154.0 (t, J = 30.1 Hz), 140.7, 128.5, 128.3, 126.4, 112.5 (t, J = 247.9 Hz), 63.3, 31.6, 25.7, 13.9 ppm. HRMS (ESI) calcd. for $C_{13}H_{16}F_2NO_3$ $[M+H]^+$ 272.1093, found: 272.1097.



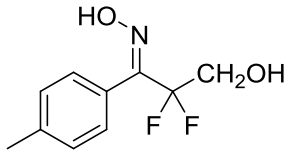
(3s)

(*E*)-2,2-difluoro-3-(hydroxyimino)-3-(4-methoxyphenyl)-1-(piperidin-1-yl)propan-1-one (3s) (E / Z = 15 : 1) Yield: 55%, white solid, mp: 149.5 – 150.4 °C. ^{1}H NMR (500 MHz, $CDCl_3$)δ: 9.24 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.60 (t, J = 5.3 Hz, 2H), 3.41 (t, J = 5.3 Hz, 2H), 1.65 – 1.59 (m, 6H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -96.21 (s, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 161.9 (t, J = 27.3 Hz), 160.9, 150.1 (t, J = 29.7 Hz), 130.9, 118.8, 114.7 (t, J = 246.7 Hz), 113.9, 55.4, 47.8, 44.6, 25.8, 25.4, 24.4 ppm. HRMS (ESI) calcd. for $C_{15}H_{19}F_2N_2O_3$ $[M+H]^+$ 313.1358, found: 313.1353.



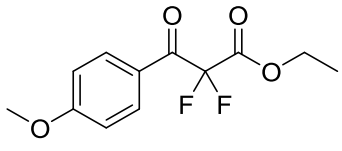
(3t)

(*E*)-2,2-difluoro-3-(hydroxyimino)-N,3-bis(4-methoxyphenyl)propenamide (3t) (E / Z > 99%) Yield: 61%, white solid, mp: 183.5 – 184.6 °C. ^{1}H NMR (500 MHz, Acetone)δ: 11.38 (s, NH), 9.68 (s, OH), 7.68 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 9.0 Hz, 2H), 7.05 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H) ppm; ^{19}F NMR (471 MHz, Acetone) δ: -101.91 (s, CF_2) ppm; ^{13}C NMR (125 MHz, Acetone) 160.7, 160.3 (t, J = 27.9 Hz), 156.8, 149.7 (t, J = 29.5 Hz), 130.9, 130.6, 121.8, 119.9, 114.3 (t, J = 248.7 Hz), 113.8, 113.5, 54.8, 54.8 ppm. HRMS (ESI) calcd. for $C_{17}H_{17}F_2N_2O_4$ $[M+H]^+$ 351.1151, found: 351.1156.



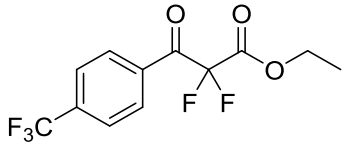
(4)

(*E*)-2,2-difluoro-3-hydroxy-1-(p-tolyl)propan-1-one oxime (4) Yield: 73%, faint yellow solid, mp: 95.2 – 96.1 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.71 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.15 – 4.09 (m, 2H), 2.45 (t, J = 7.5 Hz, 1H), 2.40 (s, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -105.35 (t, J = 12.0 Hz, CF_2) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.1 (t, J = 31.2 Hz), 140.3, 129.1, 128.7, 124.2, 117.9 (t, J = 240.9 Hz), 63.4 (t, J = 30.5 Hz), 21.5 ppm. HRMS (ESI) calcd. for $C_{10}H_{12}F_2NO_2$ $[M+H]^+$ 216.0831, found: 216.0827.



(5)

Ethyl 2,2-difluoro-3-(4-methoxyphenyl)-3-oxopropanoate (5) Yield: 53%,^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -107.25 (s, CF_2) ppm.



(6)

Ethyl 2,2-difluoro-3-oxo-3-(4-(trifluoromethyl)phenyl) propanoate (6) Yield: 77%, ^{1}H NMR (**500** MHz, $CDCl_3$) δ: 7.81 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 4.45 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H) ppm; ^{19}F NMR (471 MHz, $CDCl_3$) δ: -107.82 (s, CF_2) ppm.

6. References

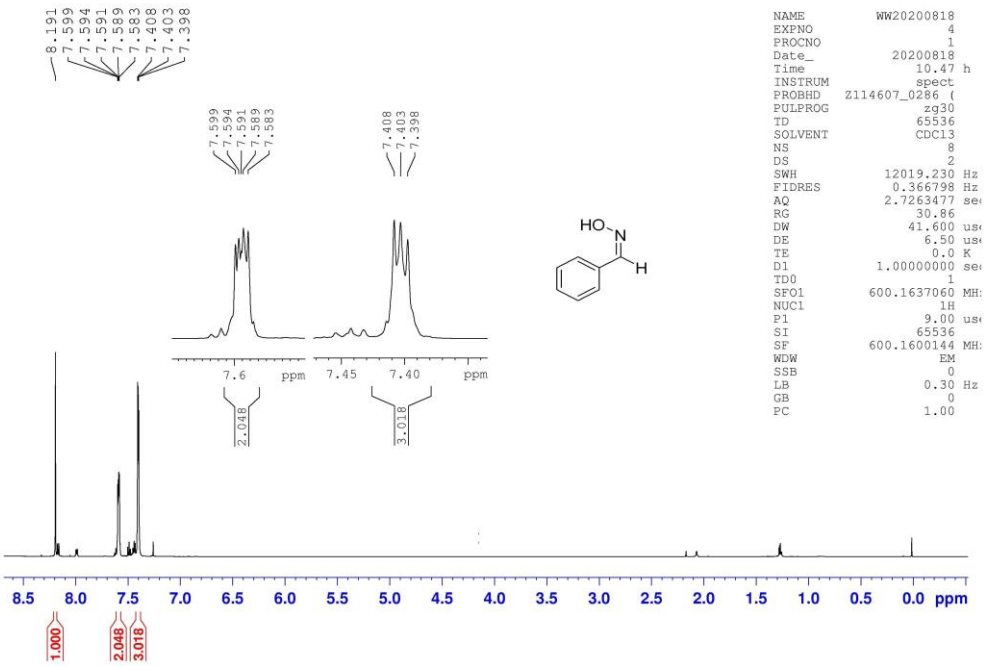
[1] (a) Kim, B. R.; Sung, G. H.; Kim, J. J.; Yoon, Y. J. *J. Korean Chem. Soc.***2013**, *57*, 295; (b) *Synlett* **2001**, *1*, 99. (c) *J. Chin. Chem. Soc.* **2012**, *59*, 1119. (d) Wertz, S.; Studer, A.; Helv. Chim. Acta., **2012**, *95*, 1758

[2] Ke, M. L.; Song, Q. L. *J. Org. Chem*. **2016**, *81*, 3654.

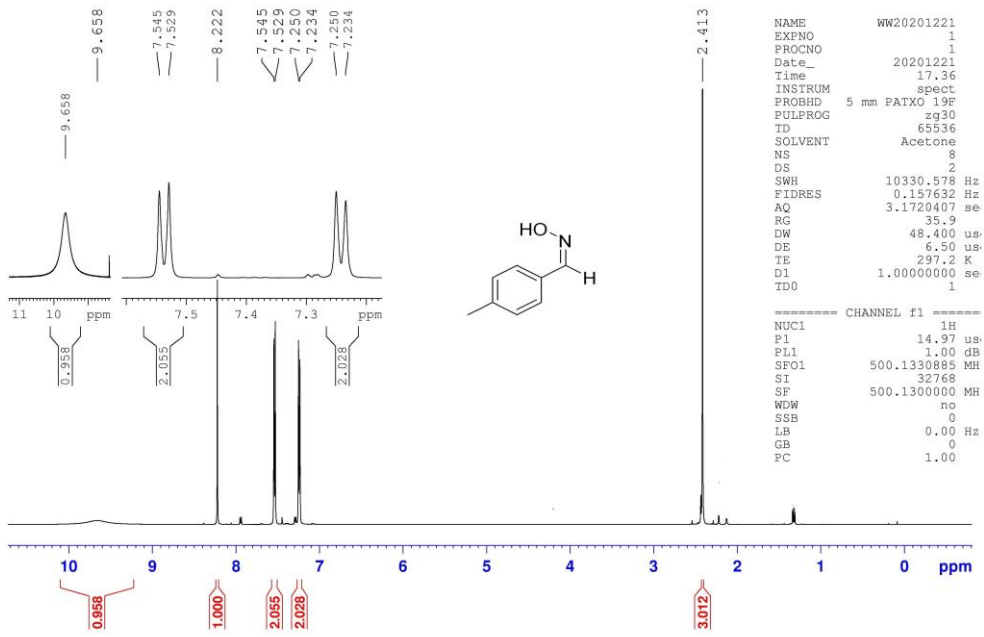
[3] (a) Waheed, M.; Ahmed, N.; Alsharif, M. A.; Alahmdi, M. I.; Mukhtar, S.; *ChemistrySelect* **2019**, *4*, 7572. (b) Fan, P.; Zhang, C.; Zhang, L. C.; Wang, C. *Org. Lett.* **2020**, *22*, 3875. (c) Zhao, H. Y.; Feng, Z.; Luo, Z. J.; Zhang, X. G. *Angew. Chem. Int. Ed*. **2016**, *55*, 10401.

7. Copies of ^{1}H NMR spectra of 1a-1r

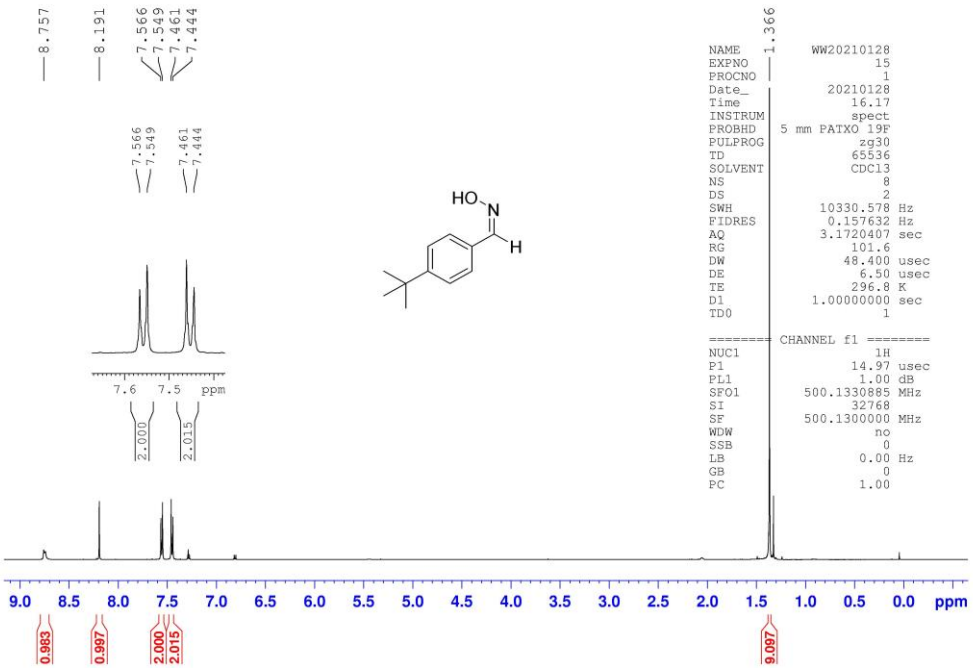
^{1}H NMR Spectra of **1a**



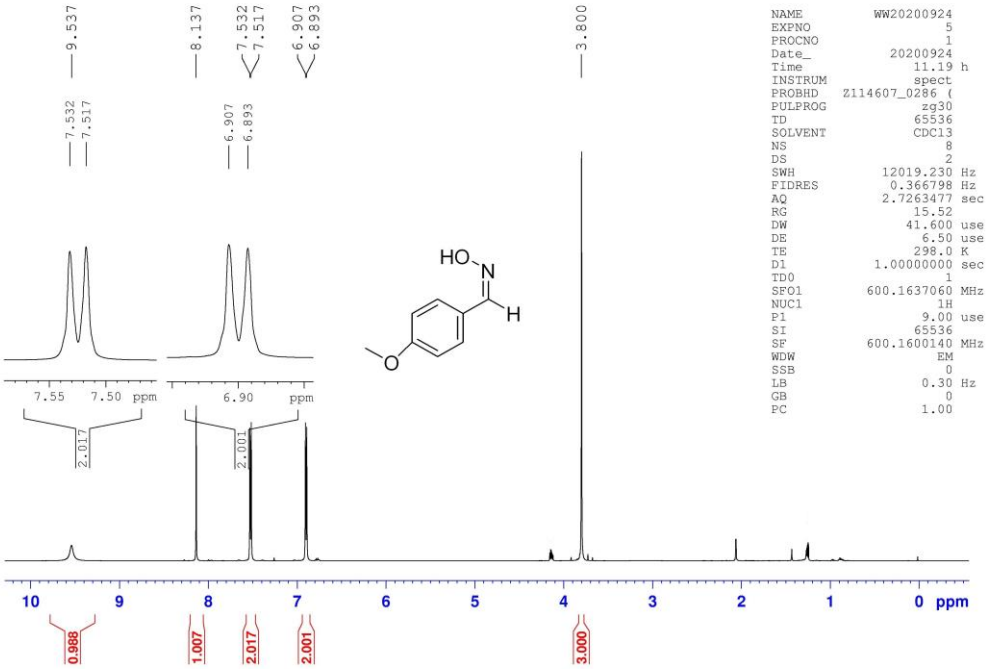
^{1}H NMR Spectra of **1b**



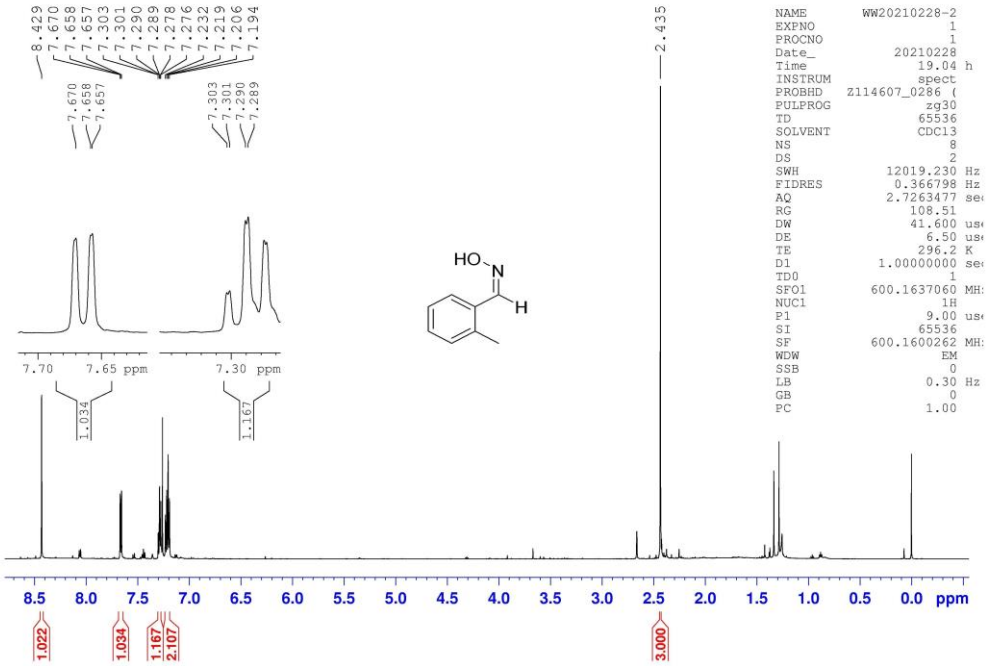
^{1}H NMR Spectra of **1c**



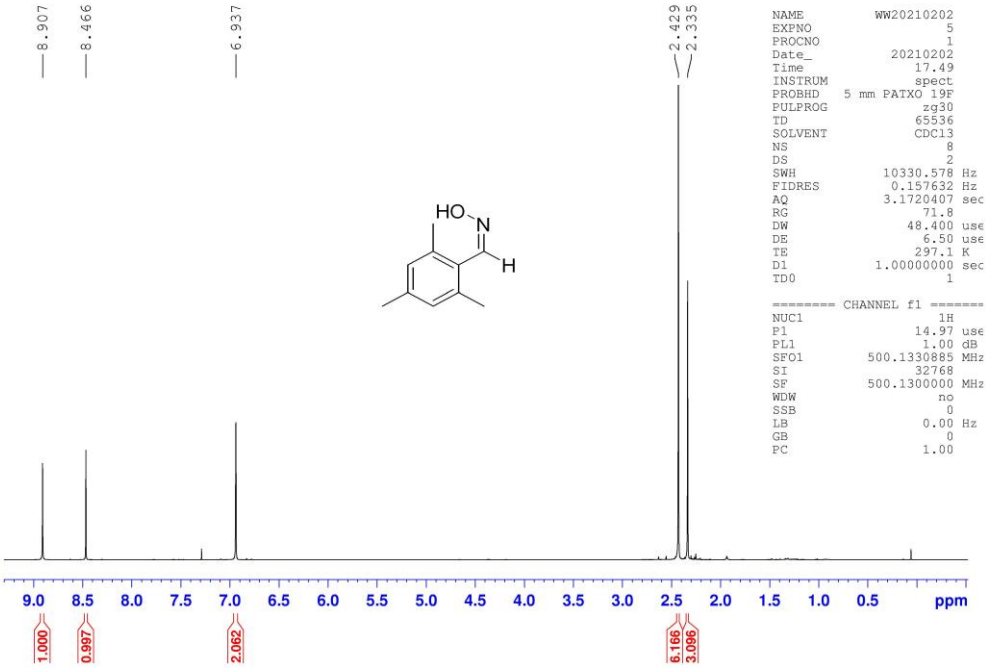
^{1}H NMR Spectra of **1d**



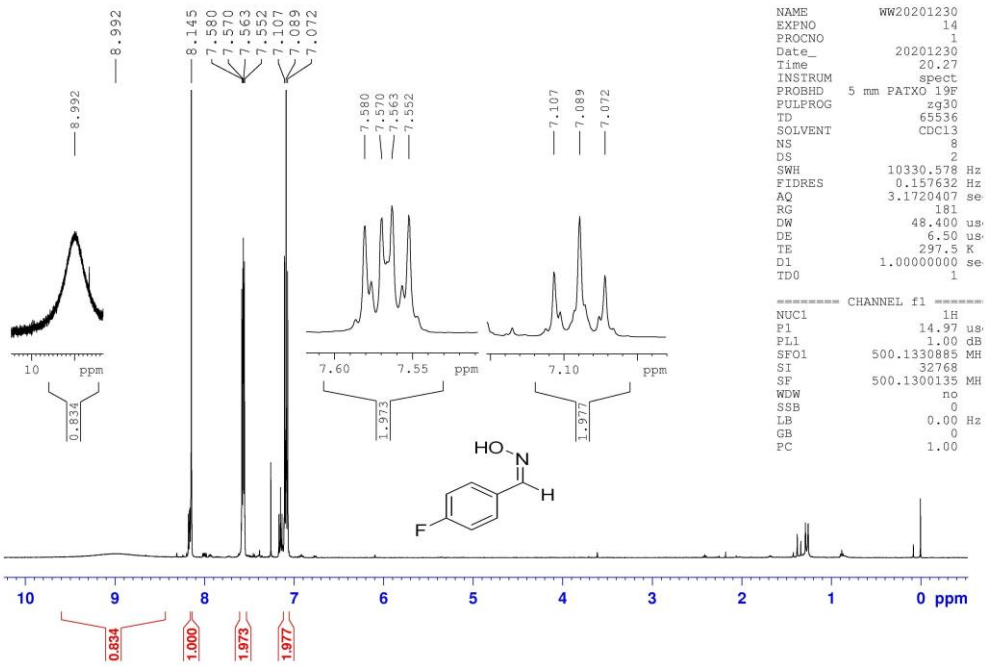
^{1}H NMR Spectra of **1e**



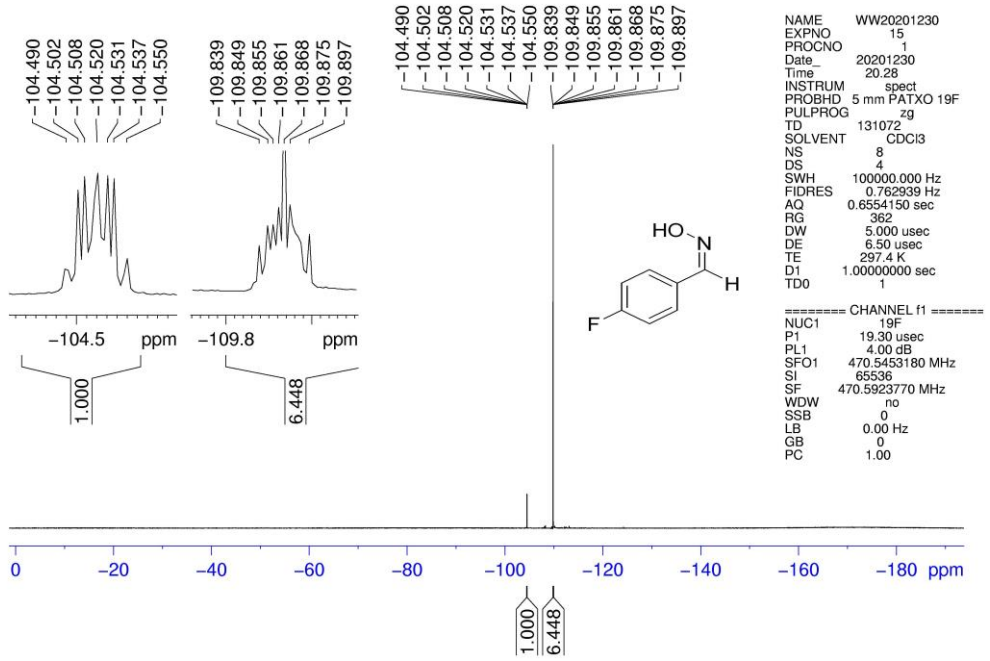
^{1}H NMR Spectra of **1f**



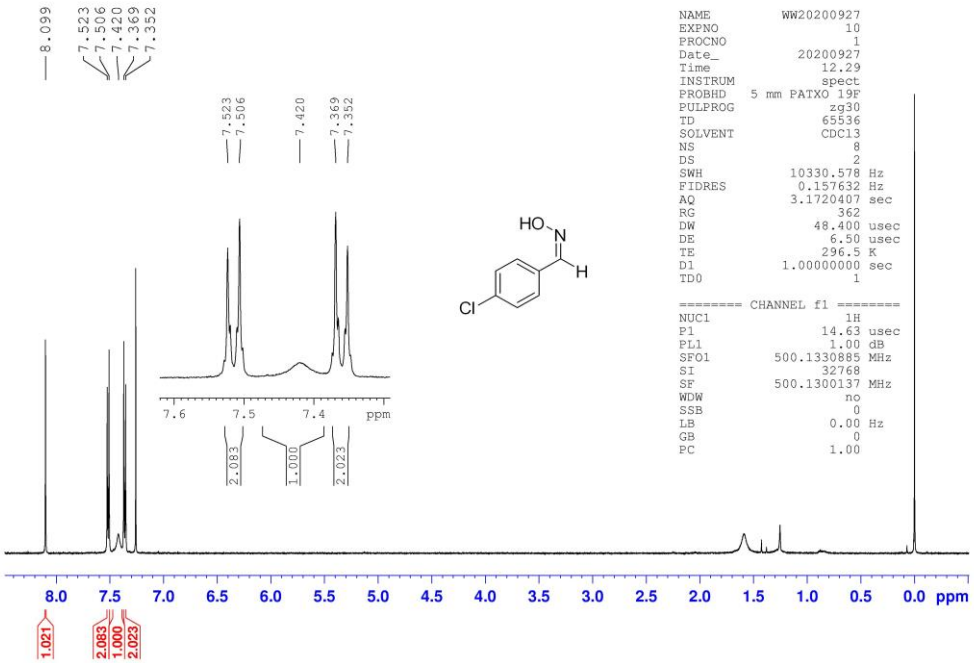
^{1}H NMR Spectra of **1g**



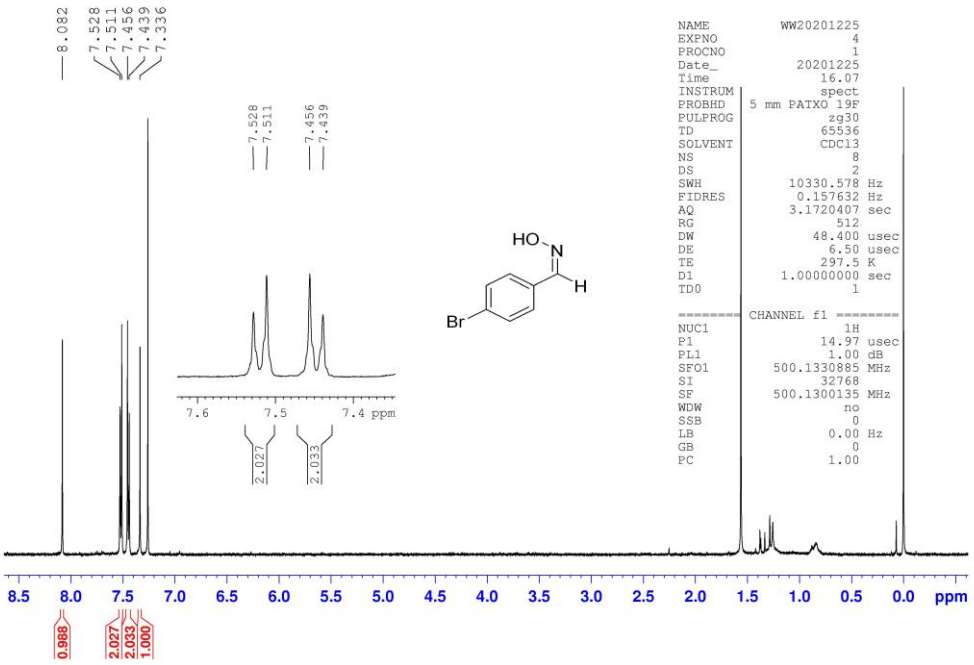
^{19}F NMR Spectra of **1g**



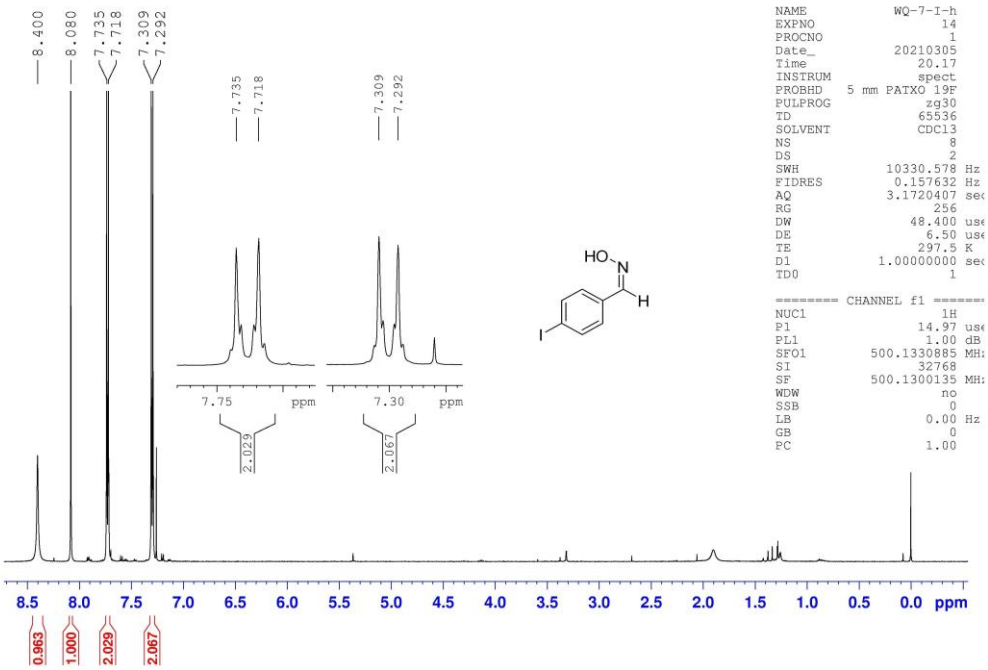
^{1}H NMR Spectra of **1h**



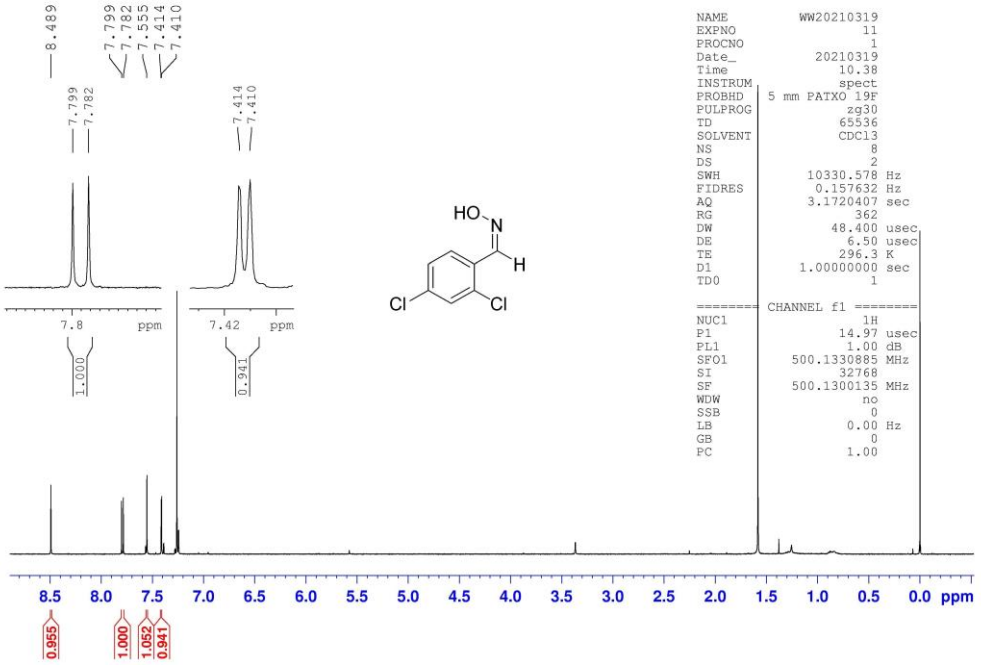
^{1}H NMR Spectra of **1i**



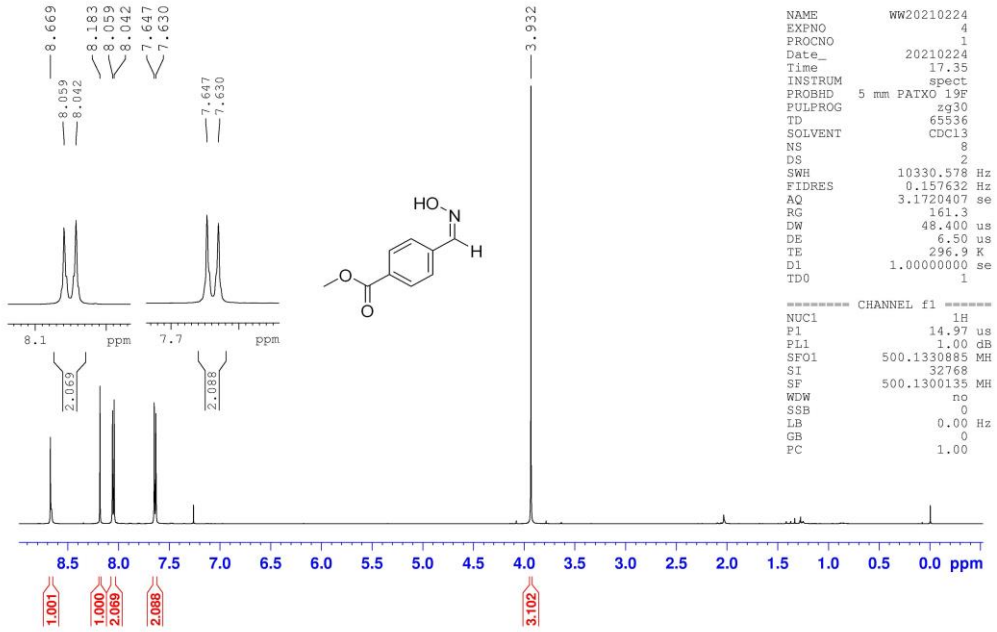
^{1}H NMR Spectra of **1j**



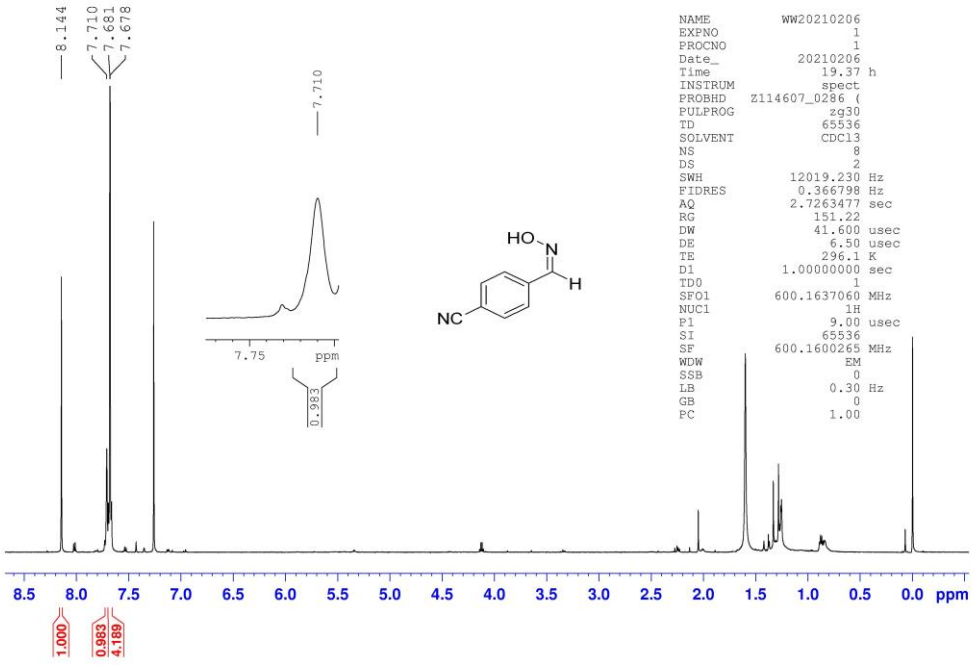
^{1}H NMR Spectra of **1k**



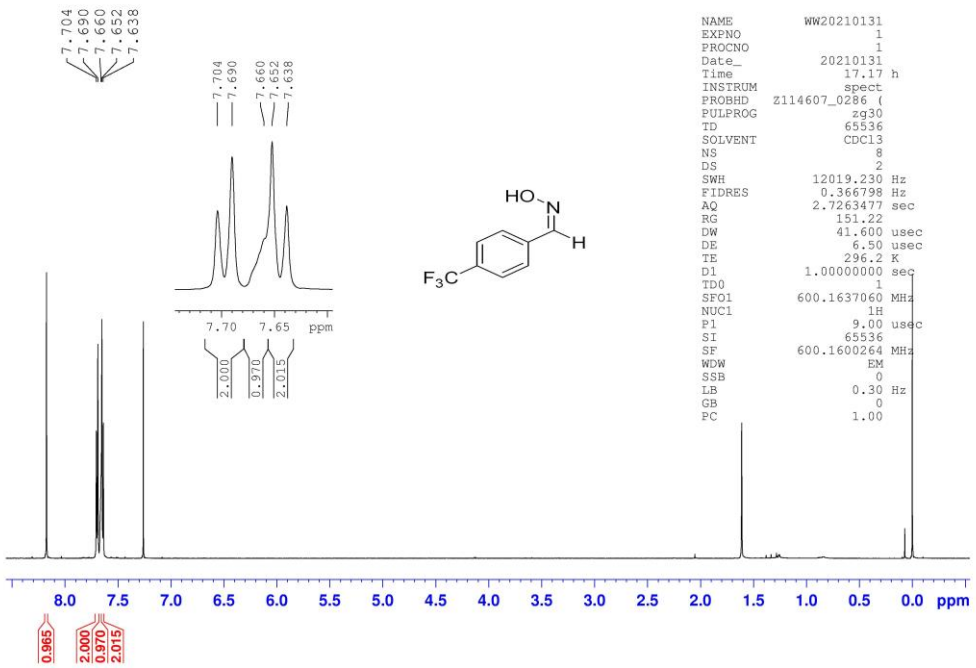
^{1}H NMR Spectra of **1l**



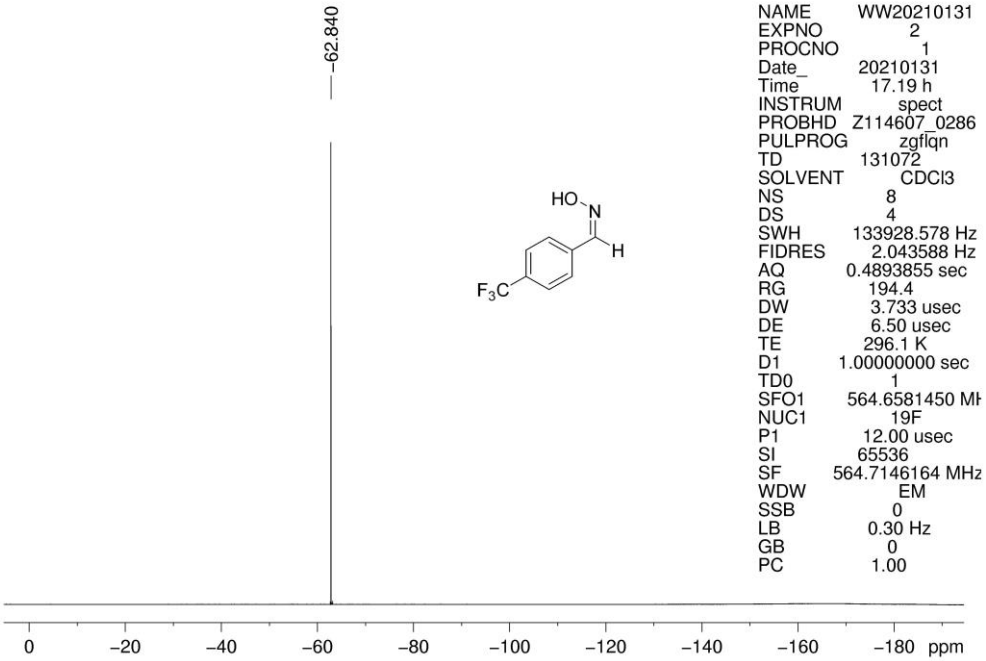
^{1}H NMR Spectra of 1**m**



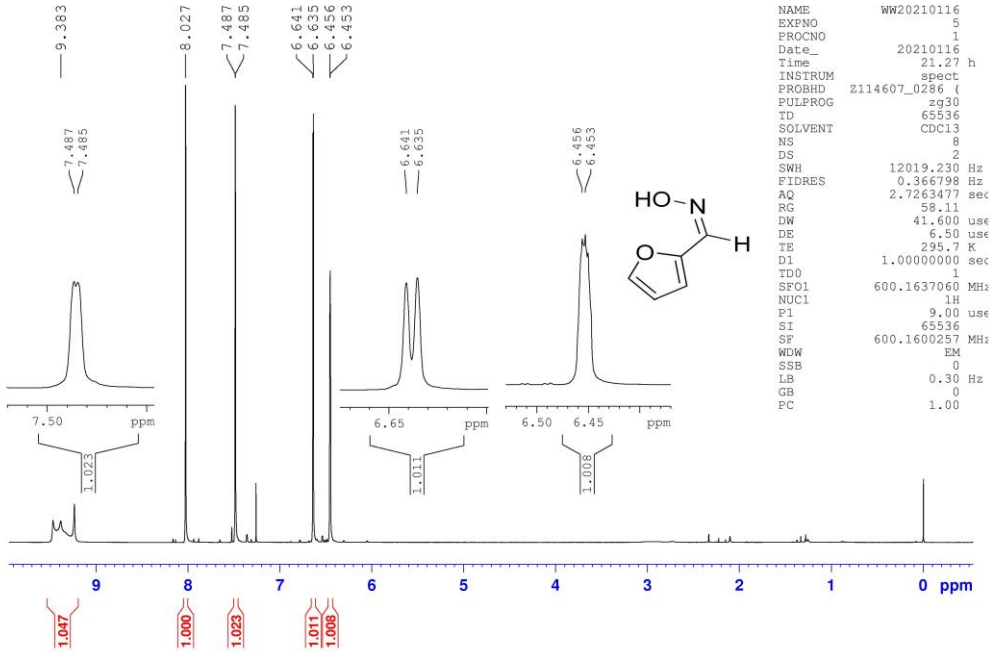
^{1}H NMR Spectra of **1n**



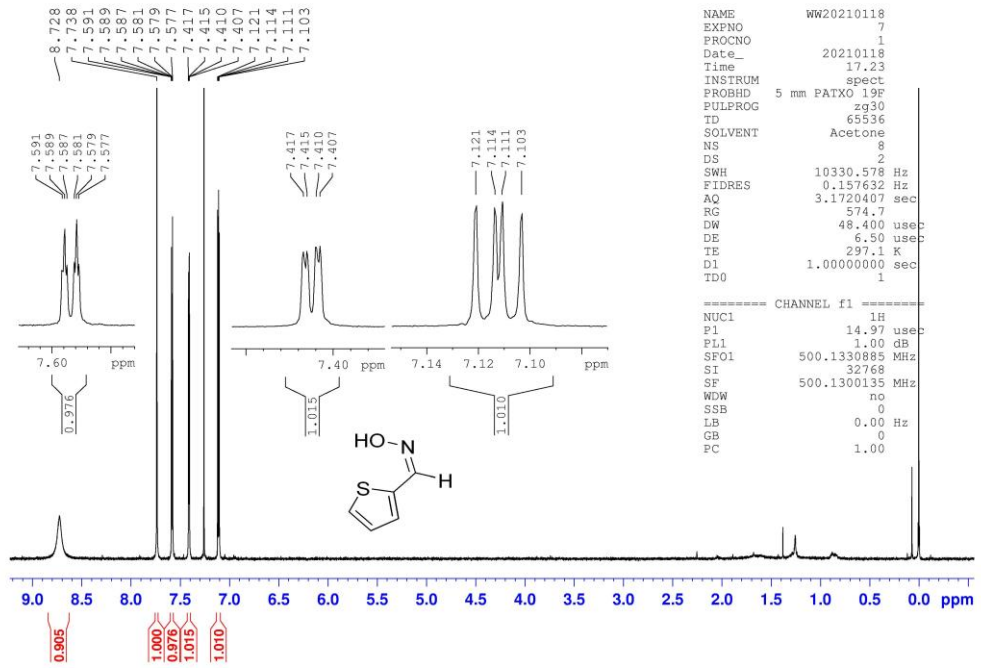
^{19}F NMR Spectra of **1n**



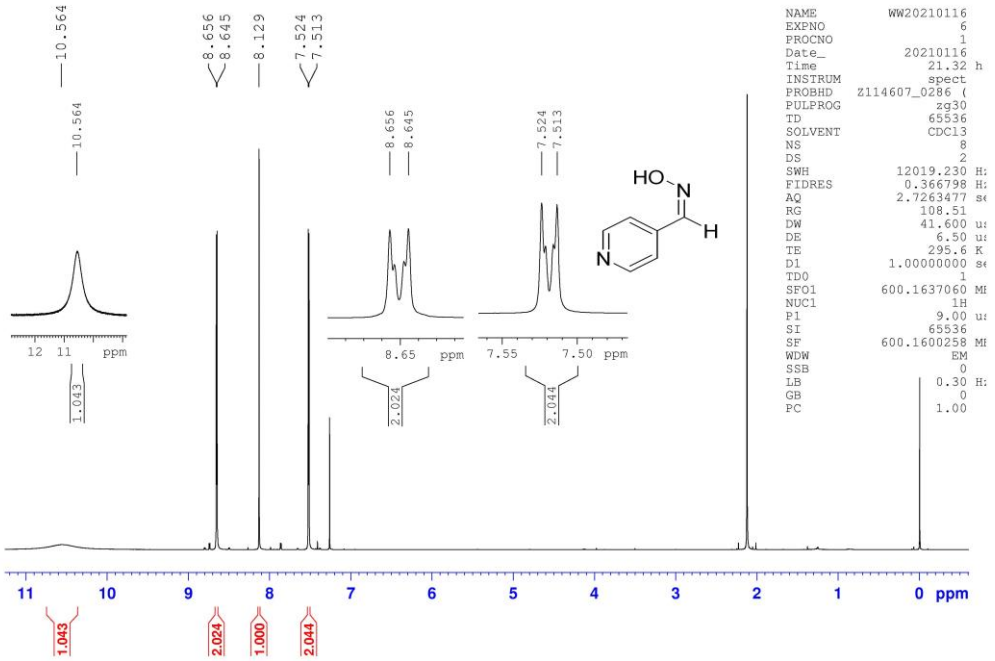
^{1}H NMR Spectra of **1o**



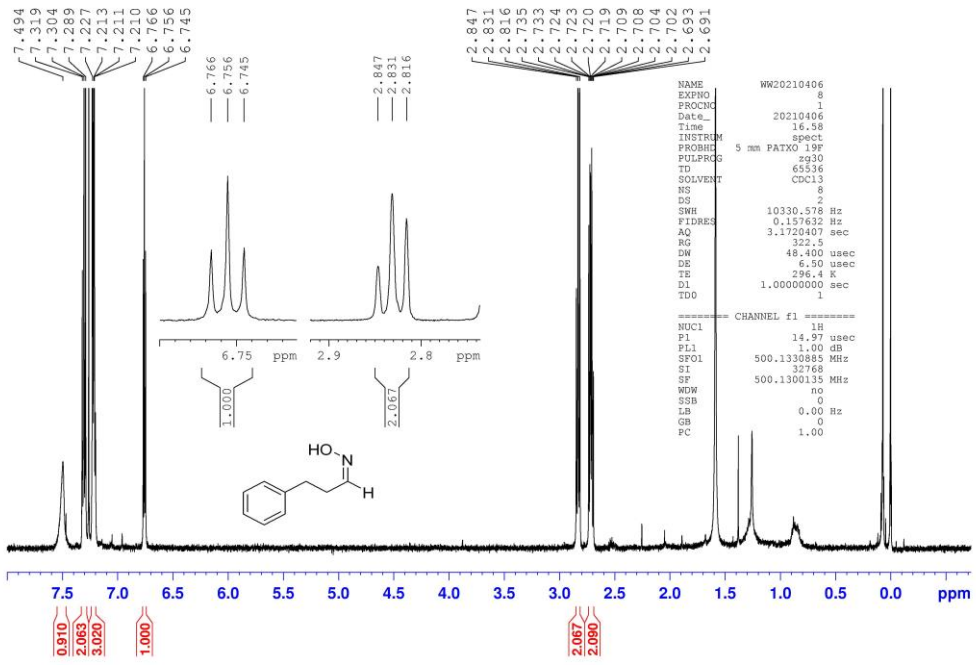
^{1}H NMR Spectra of **1p**



^{1}H NMR Spectra of **1q**

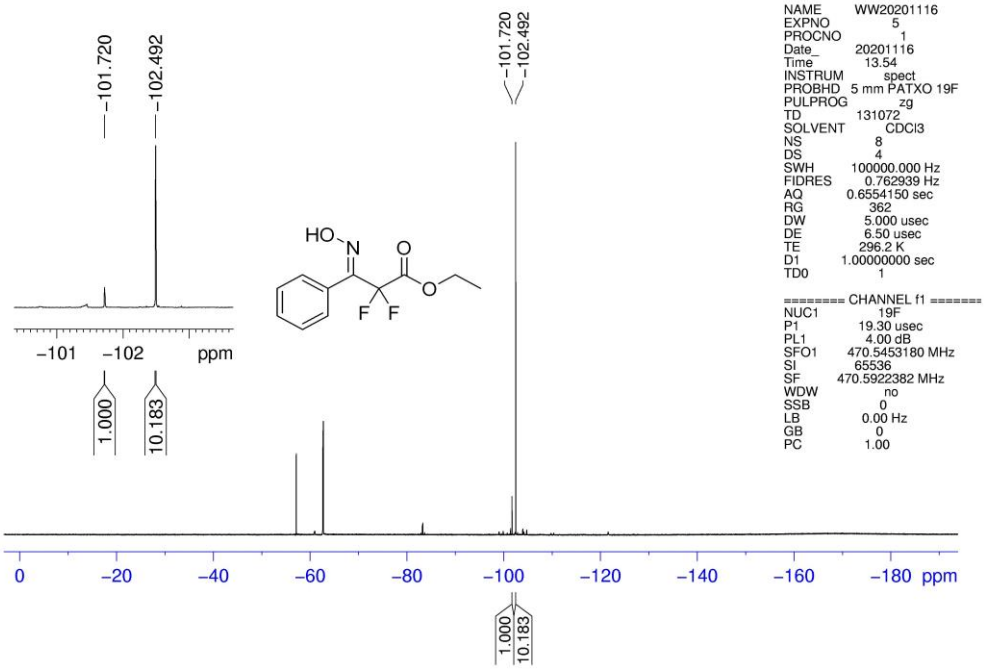


^{1}H NMR Spectra of **1r**

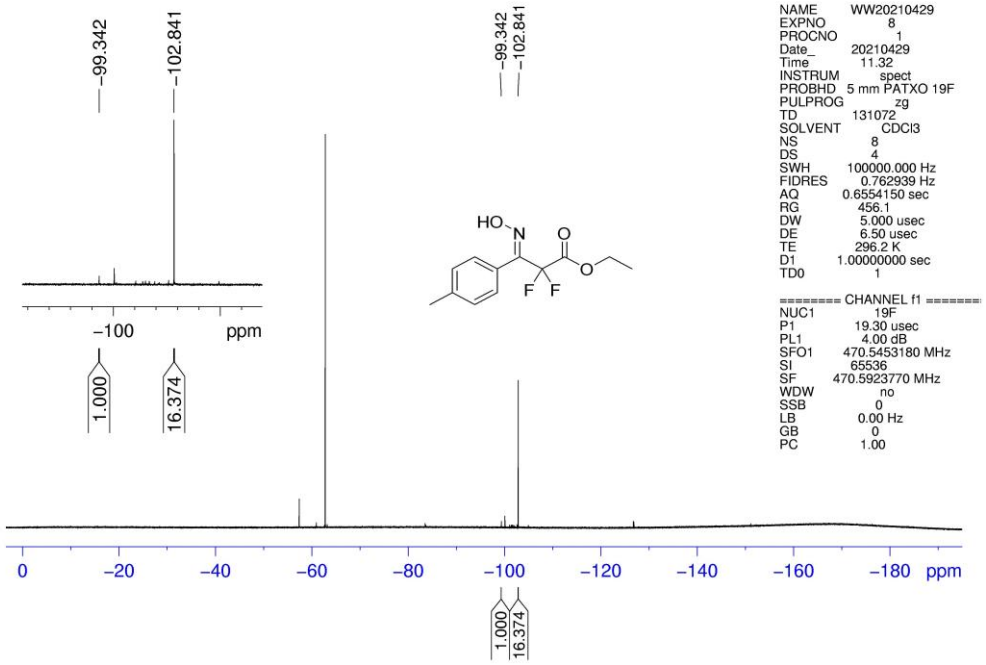


8. ^{19}F NMR spectra of the reaction mixture

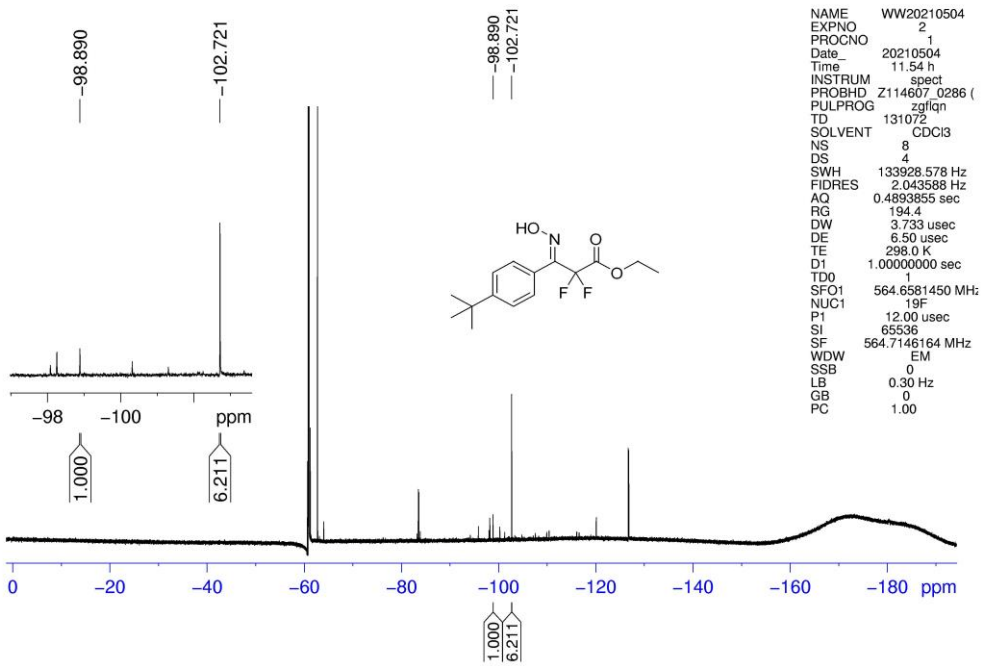
^{19}F NMR of 3a reaction mixture (E / Z = 10 : 1)



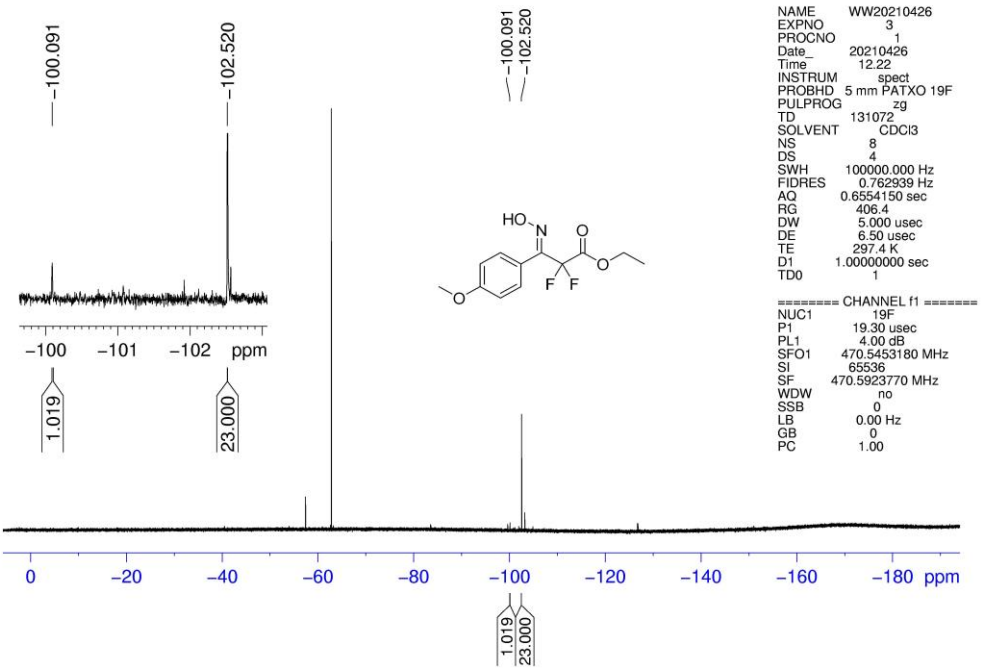
^{19}F NMR of 3b reaction mixture (E / Z = 16 : 1)



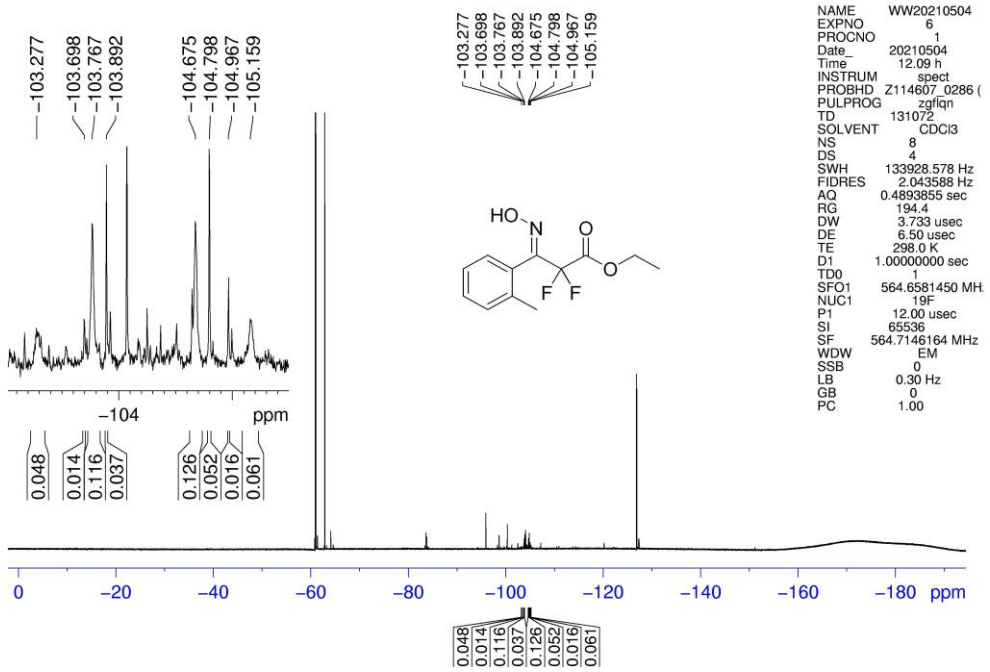
^{19}F NMR of 3c reaction mixture (E / Z = 6 : 1)



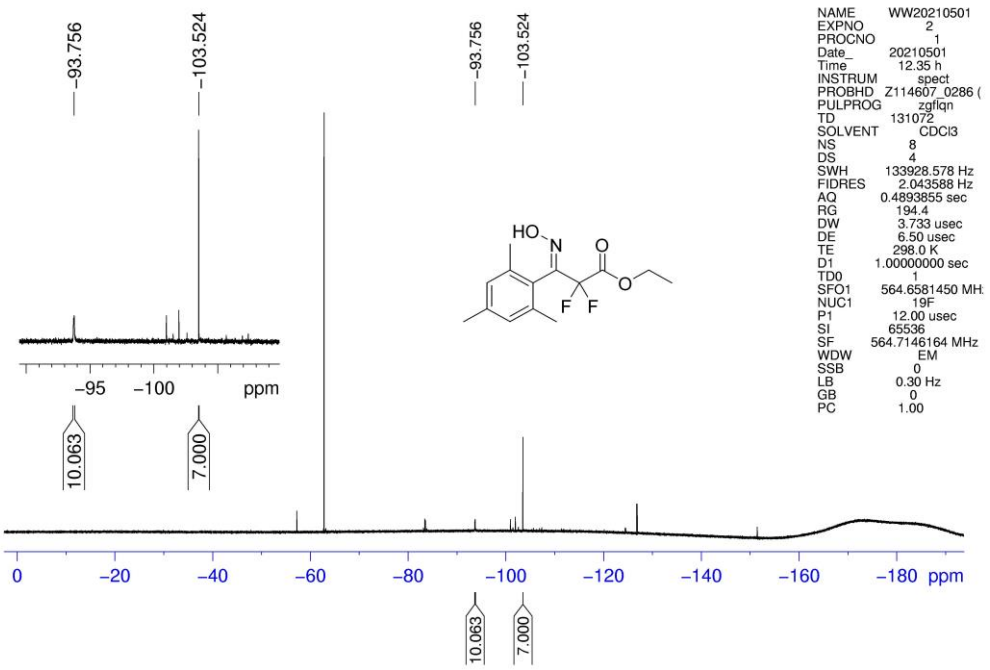
^{19}F NMR of 3d reaction mixture (E / Z = 23 : 1)



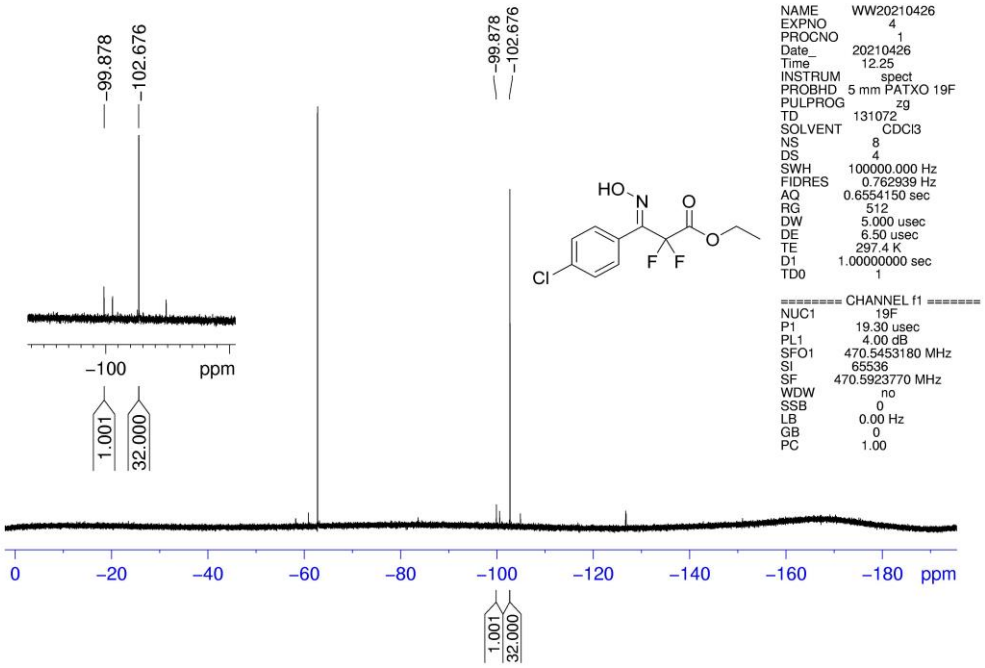
^{19}F NMR of 3e reaction mixture (E / Z = 2.6 : 1)



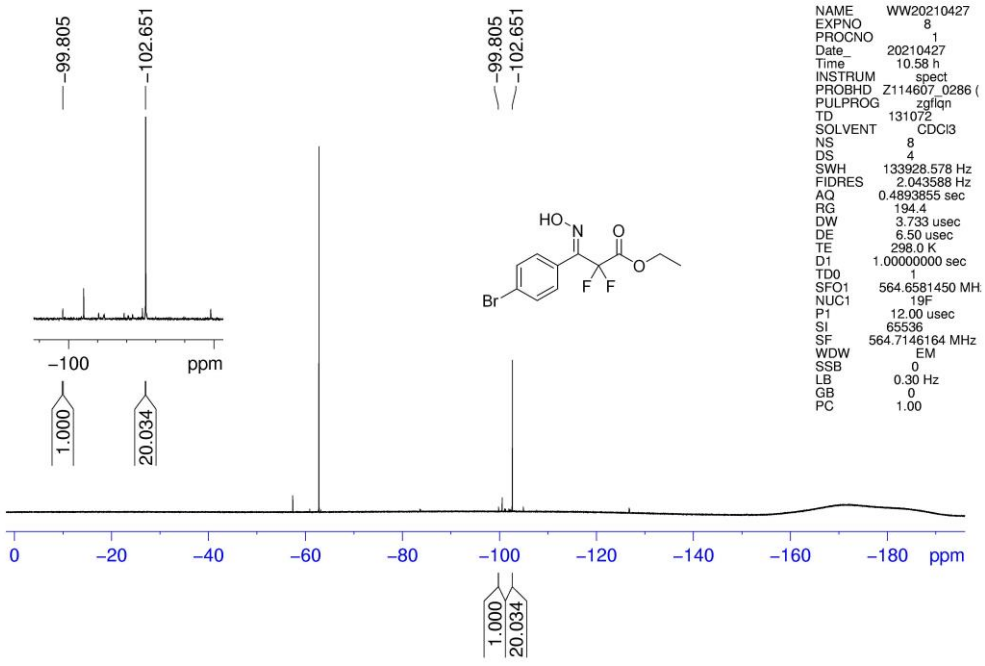
^{19}F NMR of 3f reaction mixture (E / Z = 7 : 10)



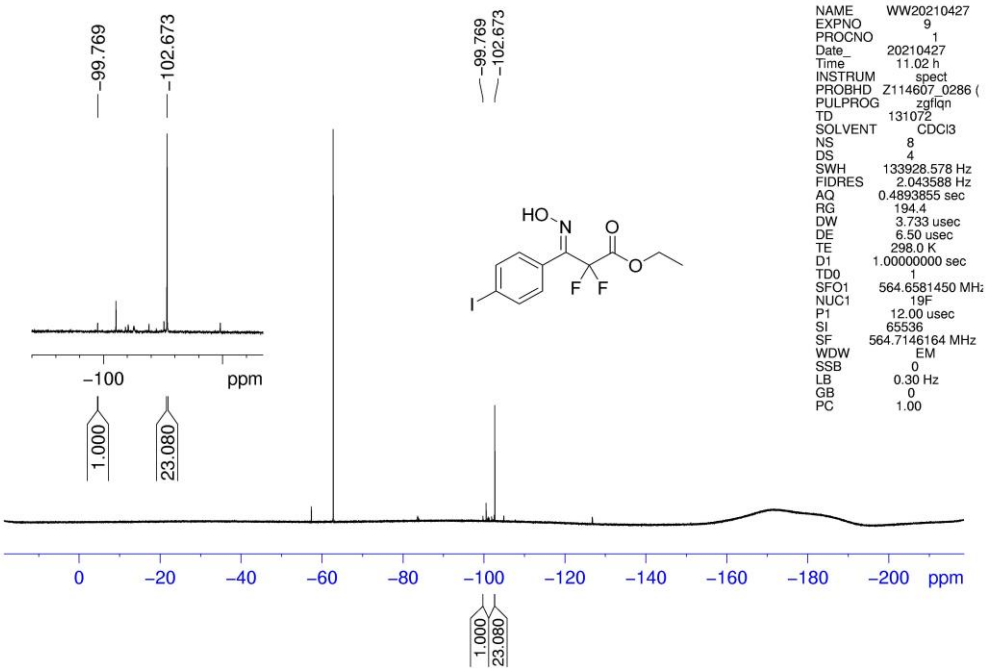
^{19}F NMR of 3g reaction mixture (E / Z = 32 : 1)



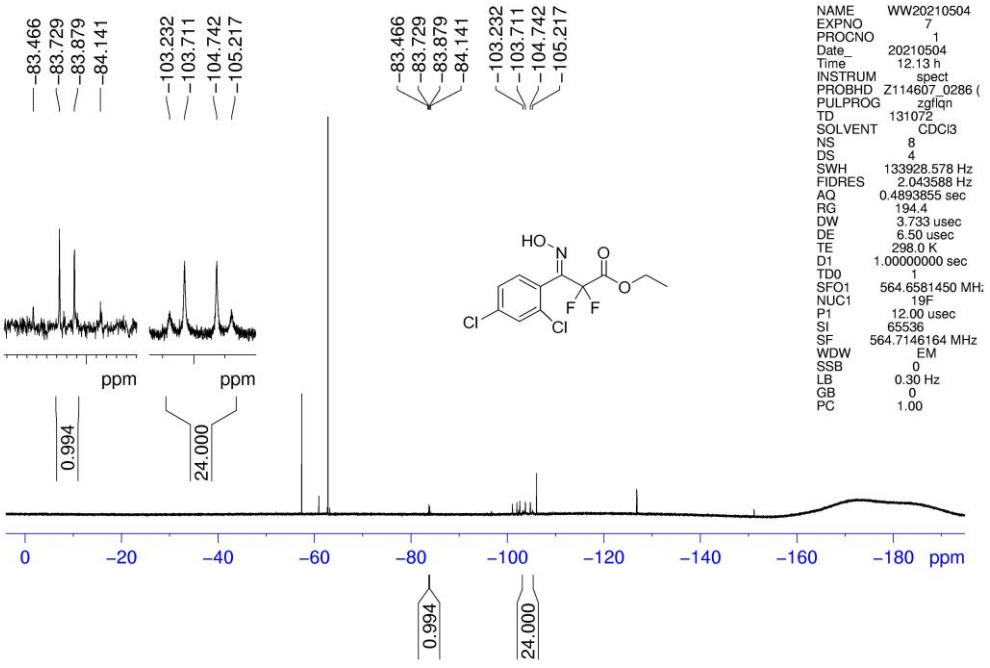
^{19}F NMR of 3i reaction mixture (E / Z = 20 : 1)



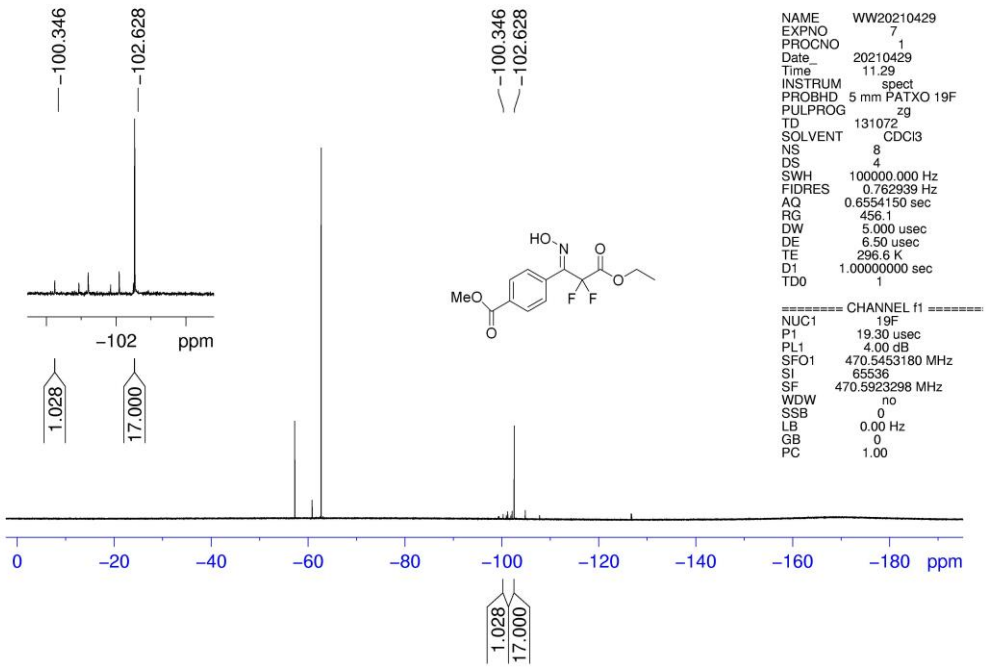
^{19}F NMR of 3j reaction mixture (E / Z = 23 : 1)



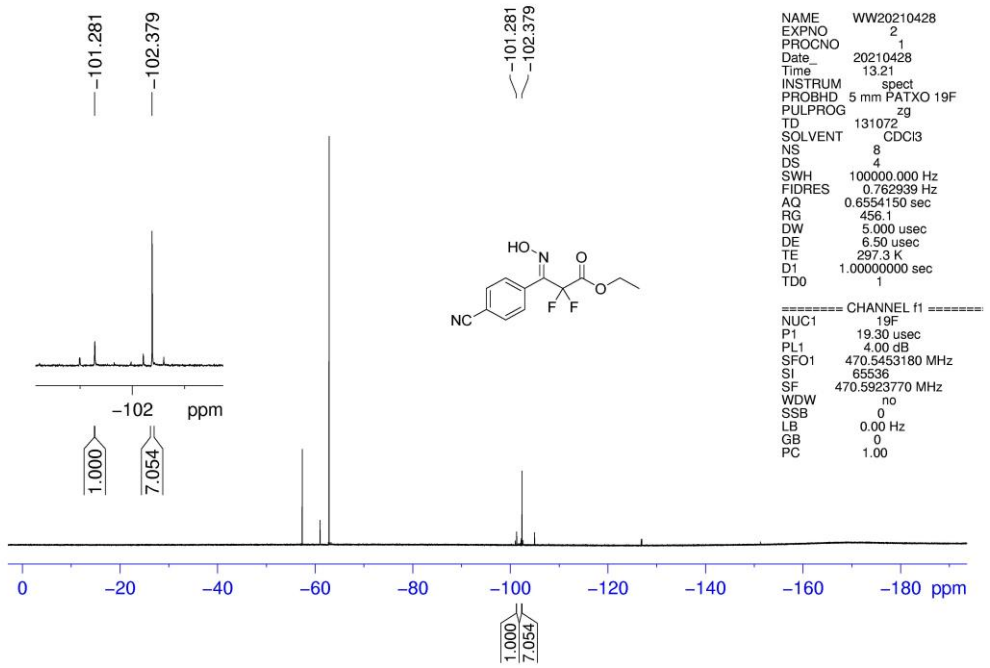
^{19}F NMR of 3k reaction mixture (E / Z = 24 : 1)



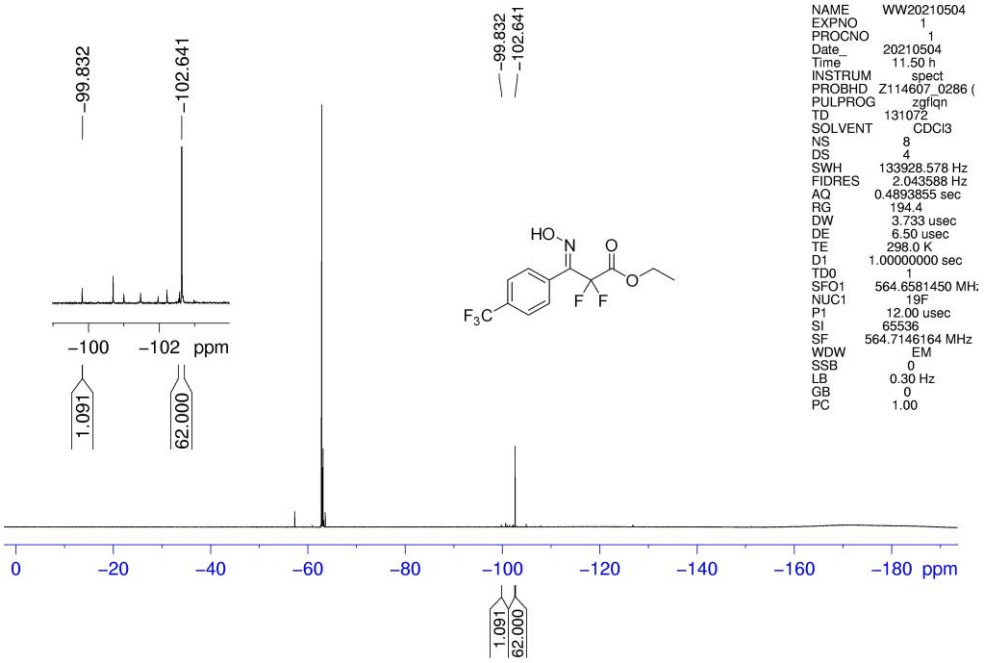
^{19}F NMR of 3l reaction mixture (E / Z = 17 : 1)



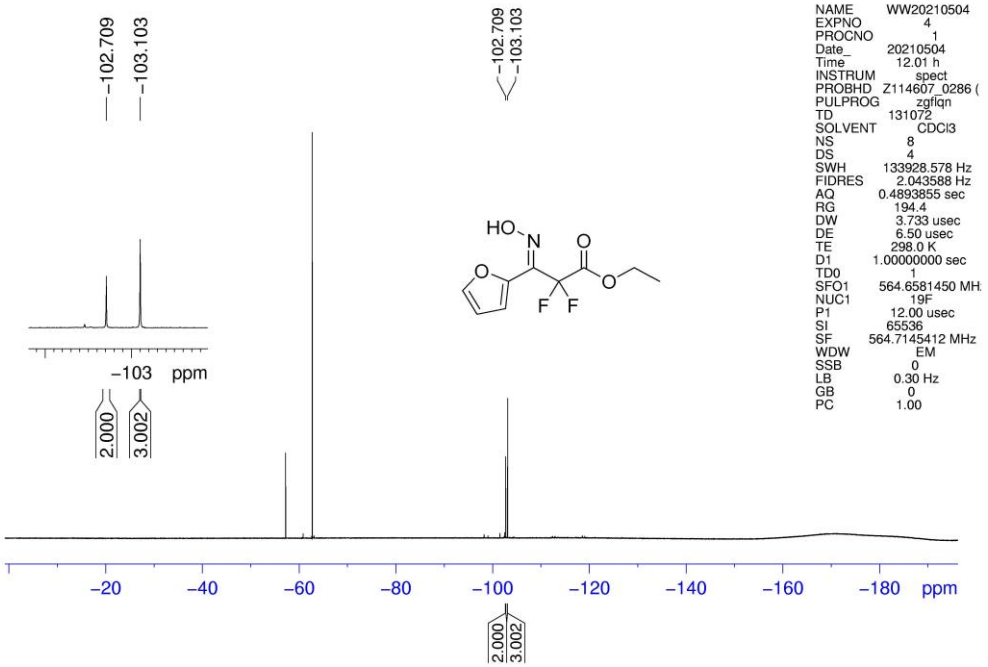
^{19}F NMR of 3m reaction mixture (E / Z = 7 : 1)



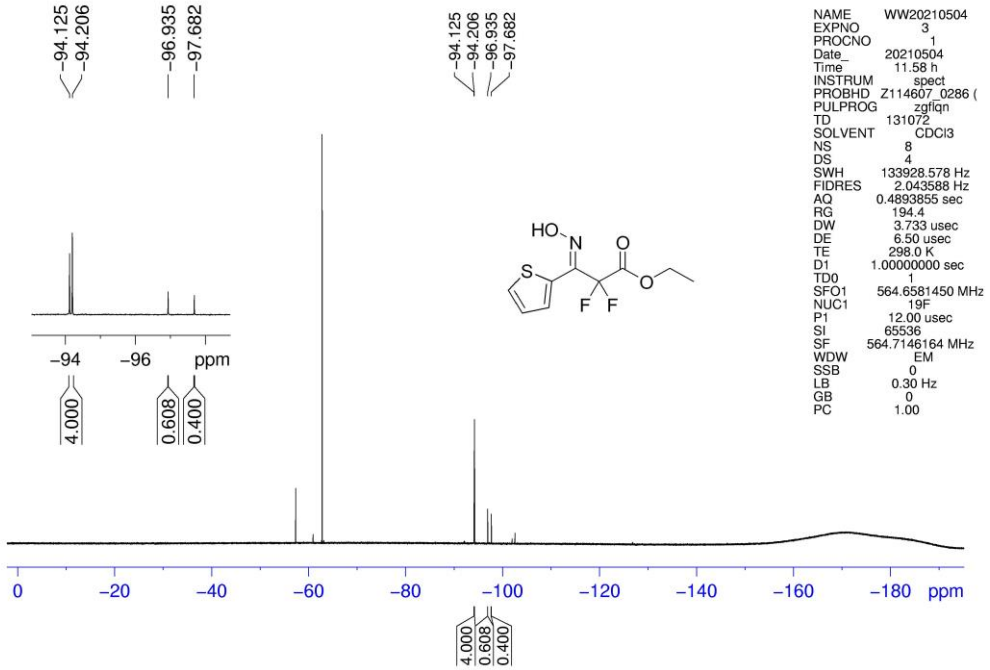
^{19}F NMR of 3n reaction mixture (E / Z = 62 : 1)



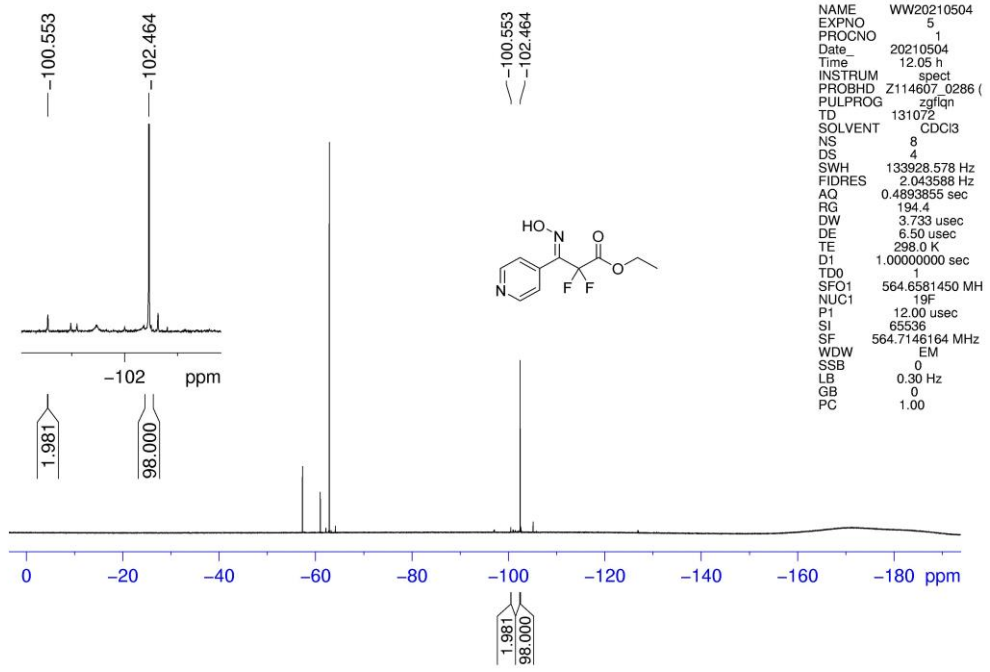
^{19}F NMR of 3o reaction mixture (E / Z = 3 : 2)



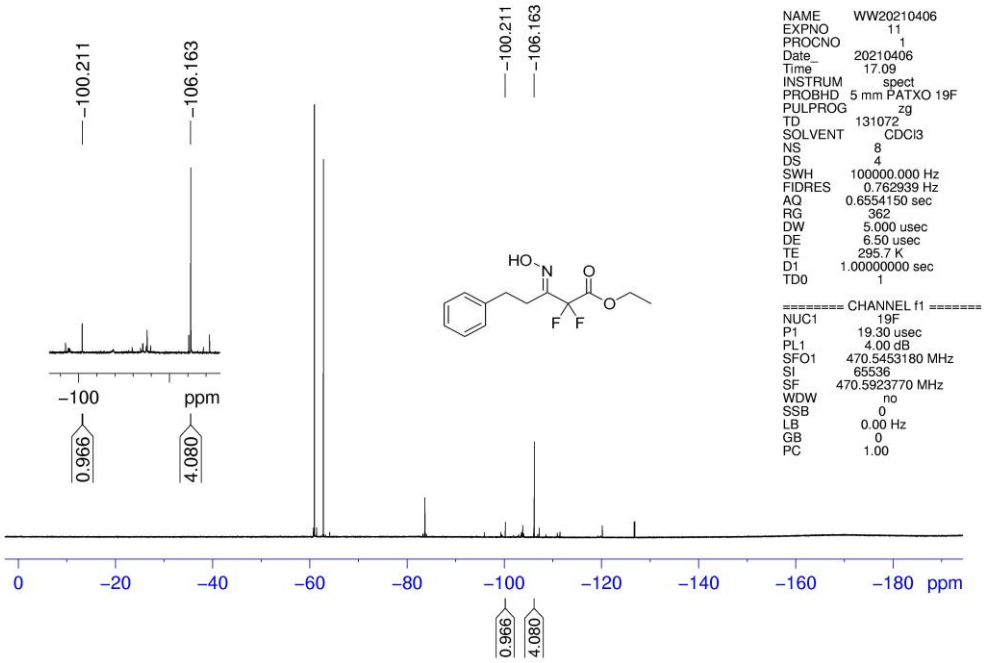
^{19}F NMR of 3p reaction mixture (E / Z = 1 : 4)



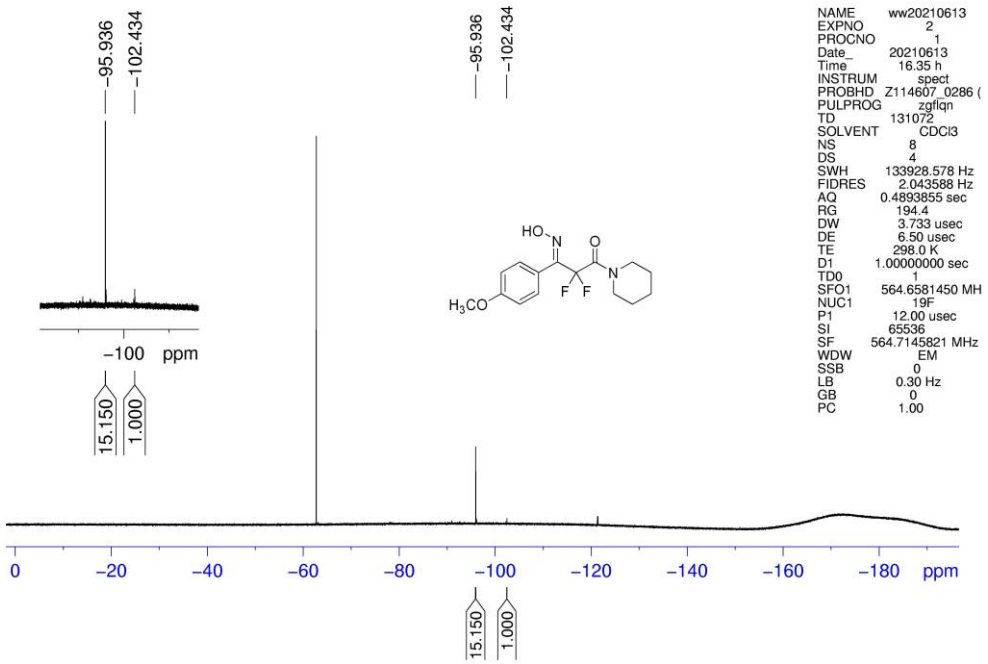
^{19}F NMR of 3q reaction mixture (E / Z > 99 : 1)



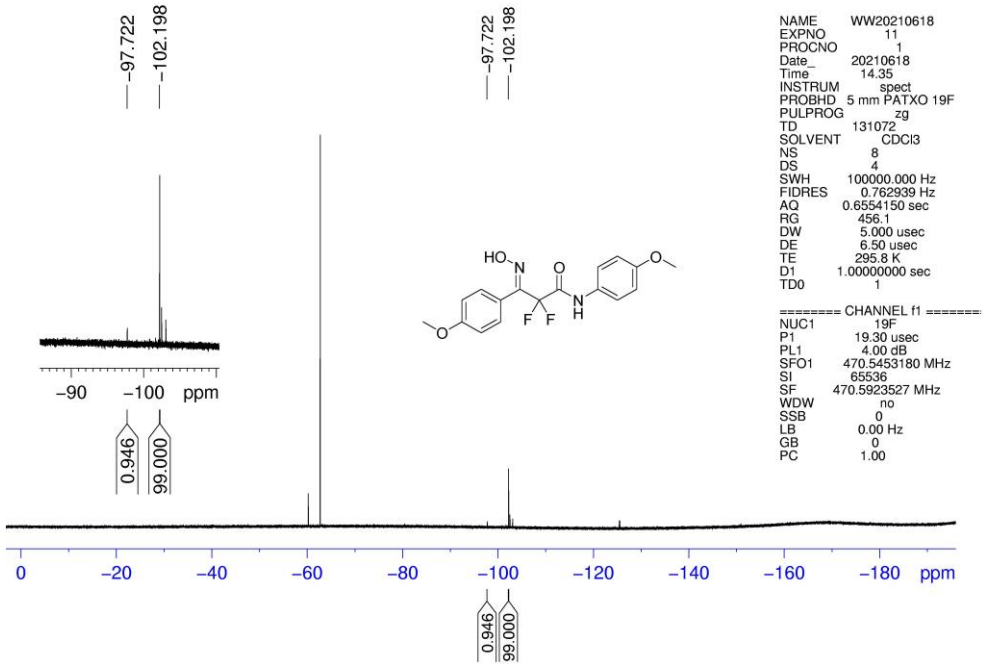
^{19}F NMR of 3r reaction mixture (E / Z = 4 : 1)



^{19}F NMR of 3s reaction mixture (E / Z = 15 : 1)

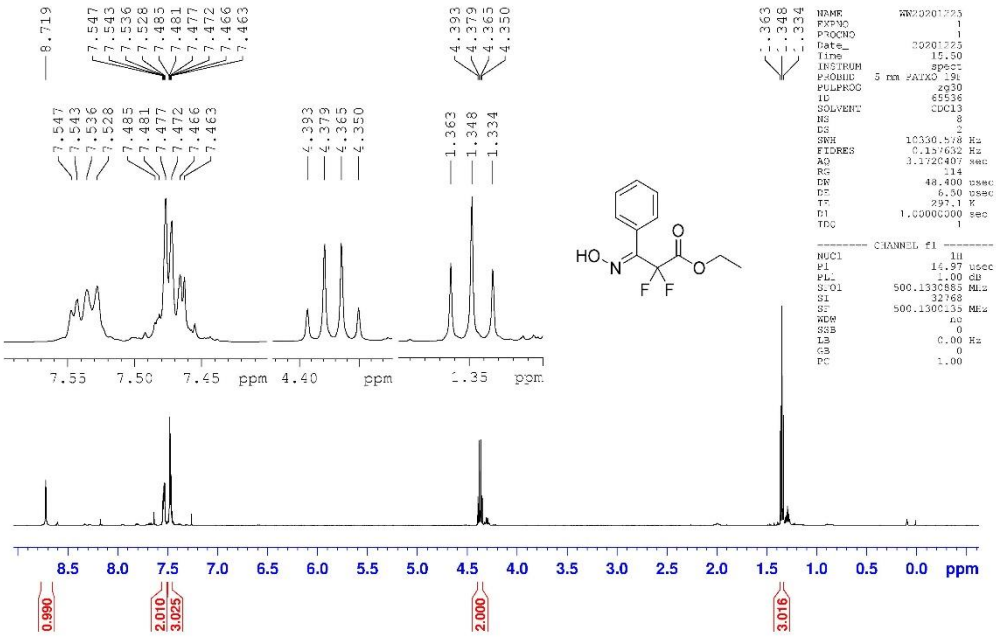


^{19}F NMR of 3t reaction mixture (E / Z > 99 : 1)

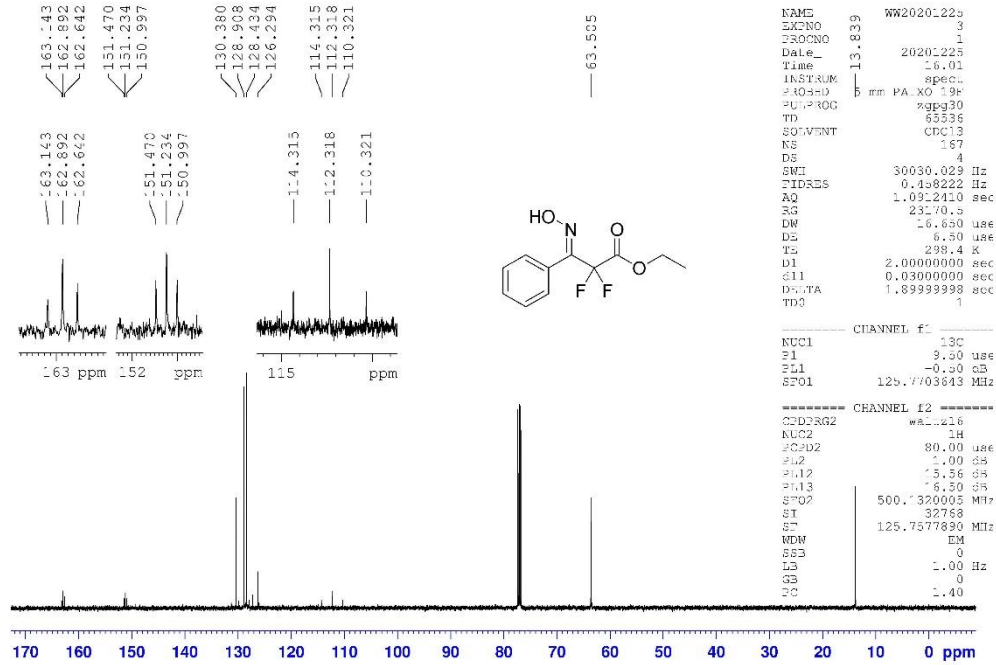


9. Copies of ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectra of the products

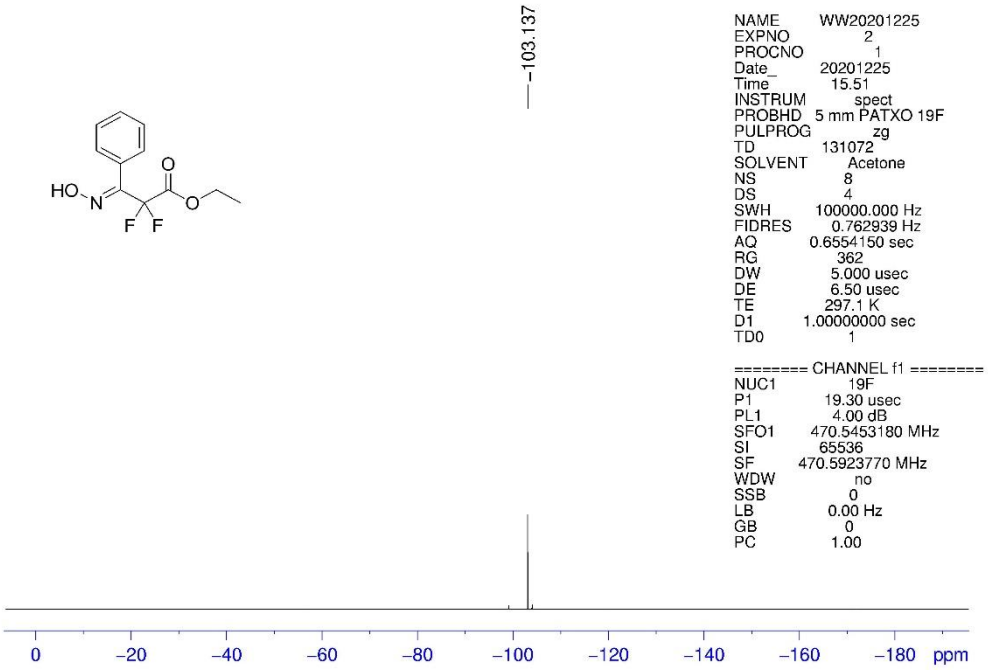
^{1}H NMR Spectra of **3a**



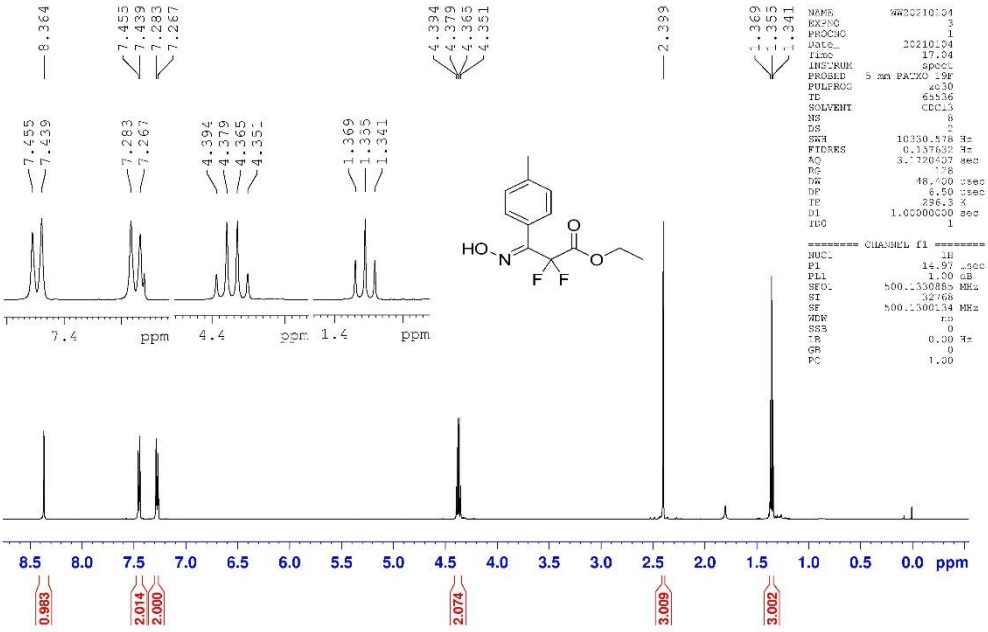
^{13}C NMR Spectra of **3a**



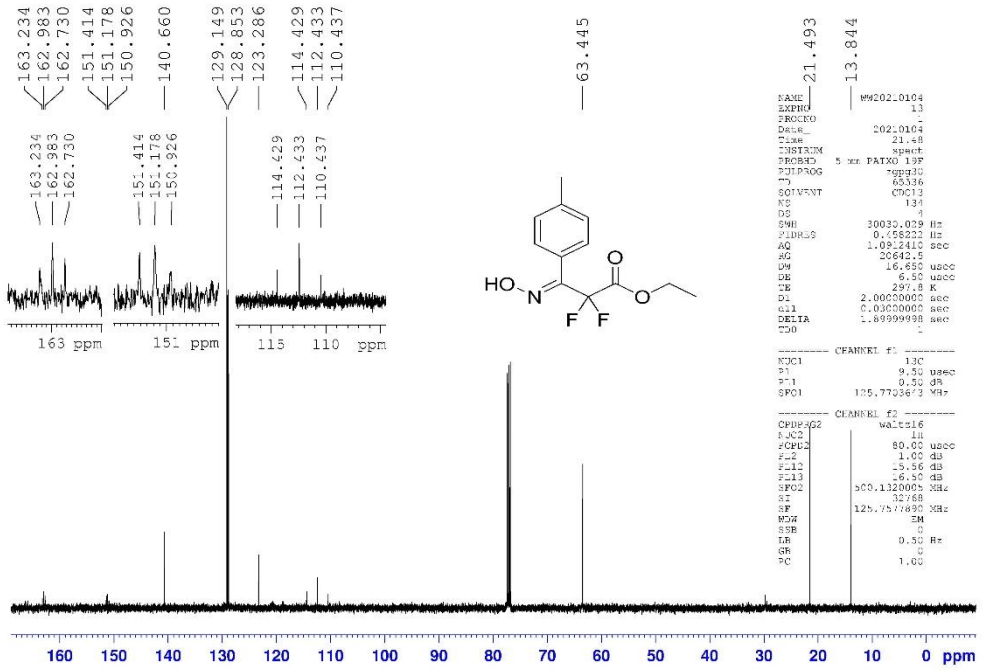
^{19}F NMR Spectra of **3a**



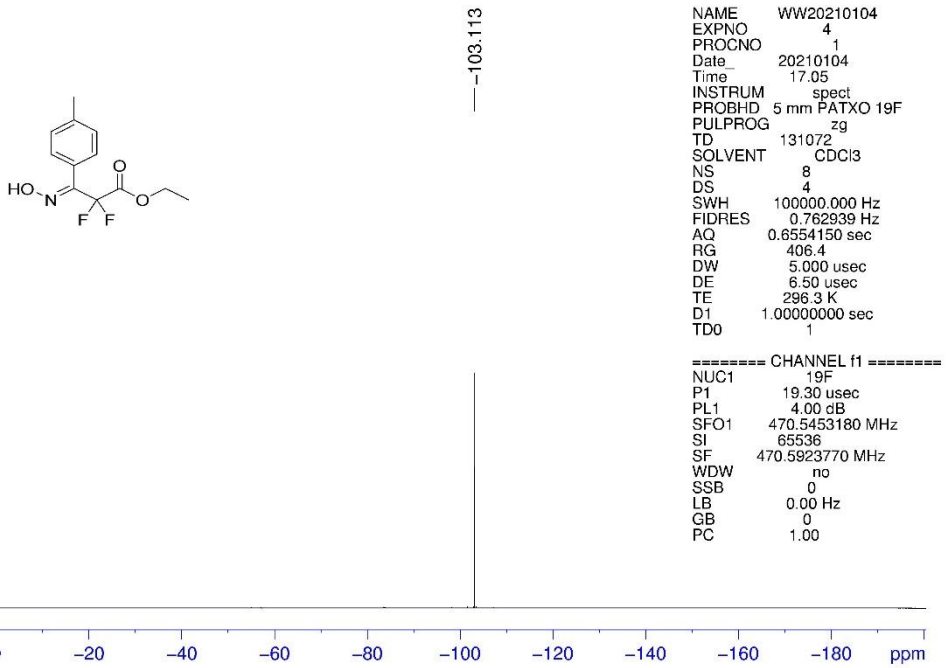
^{1}H NMR Spectra of **3b**



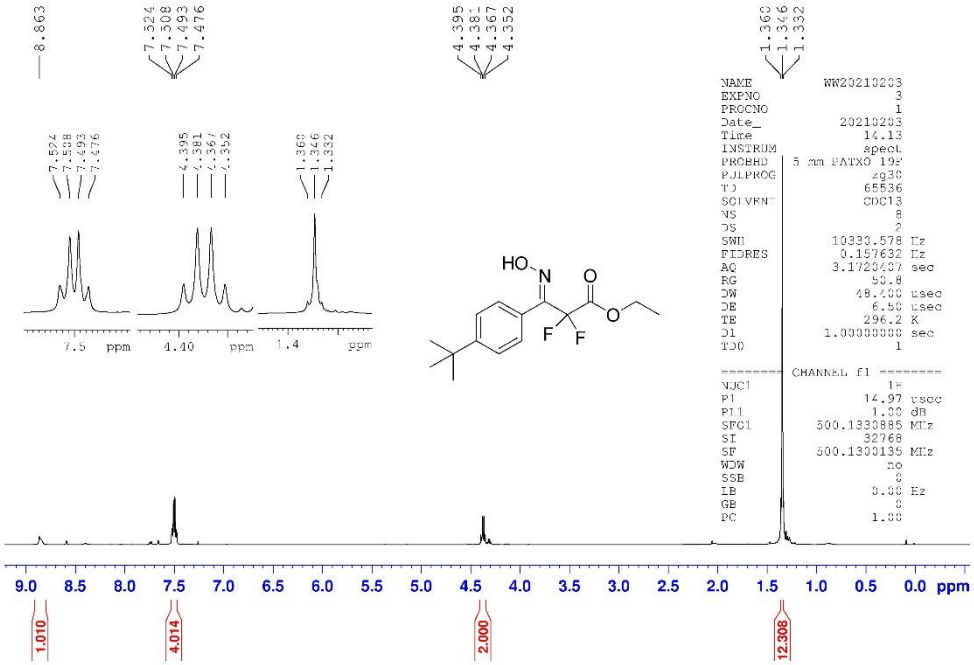
^{13}C NMR Spectra of **3b**



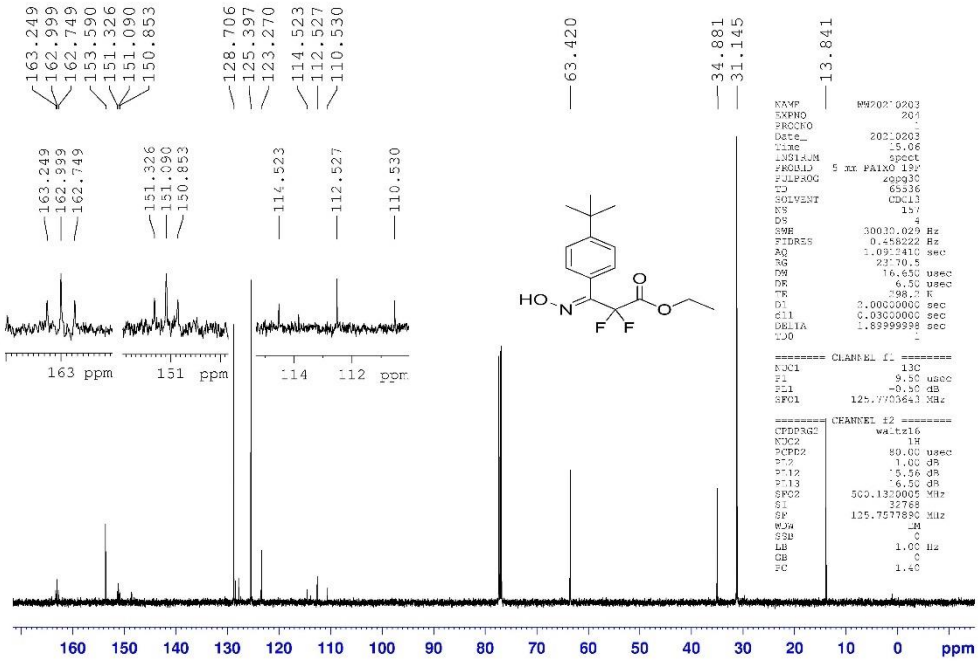
^{19}F NMR Spectra of **3b**



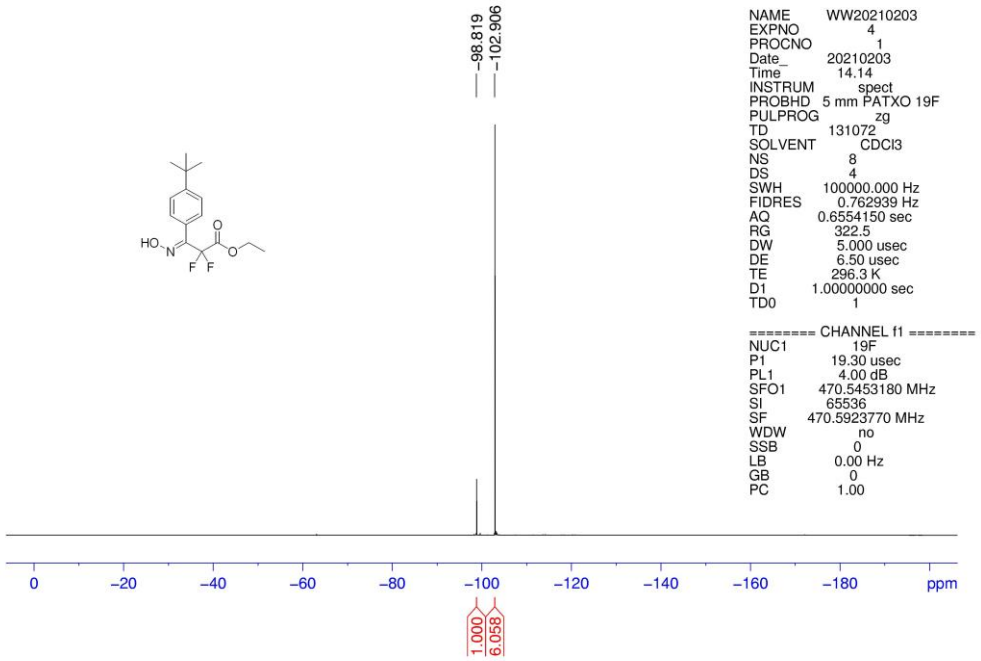
^{1}H NMR Spectra of **3c**



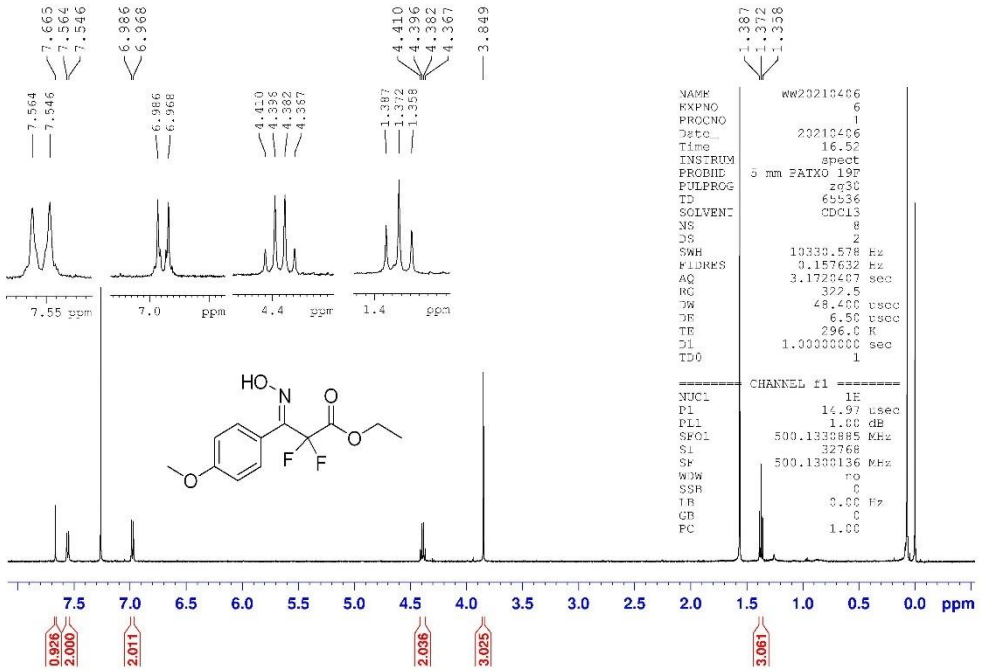
^{13}C NMR Spectra of **3c**



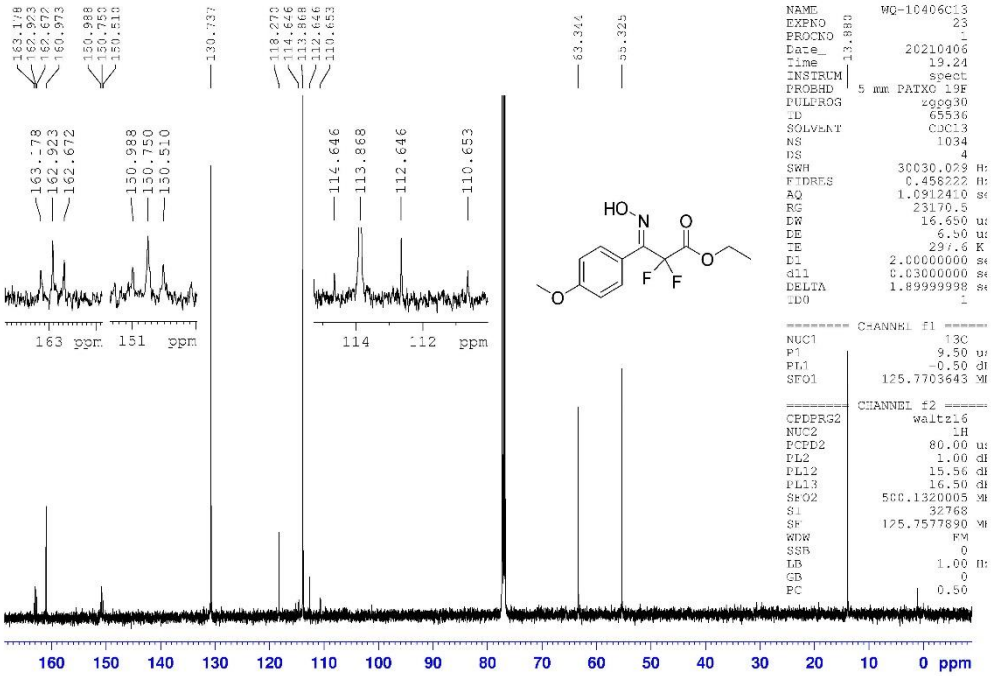
^{19}F NMR Spectra of **3c**



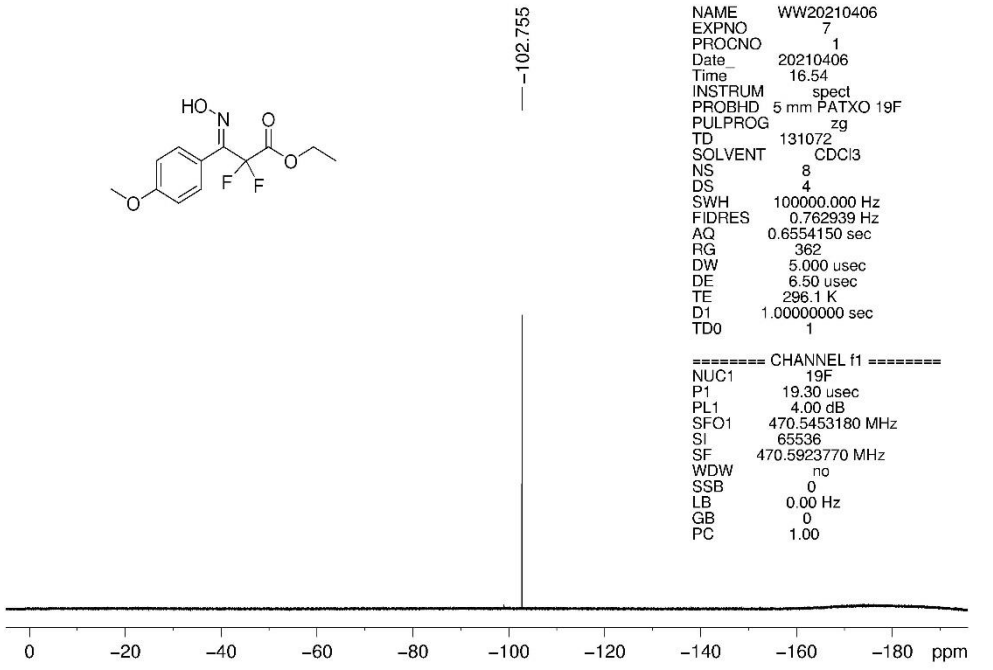
^{1}H NMR Spectra of **3d**



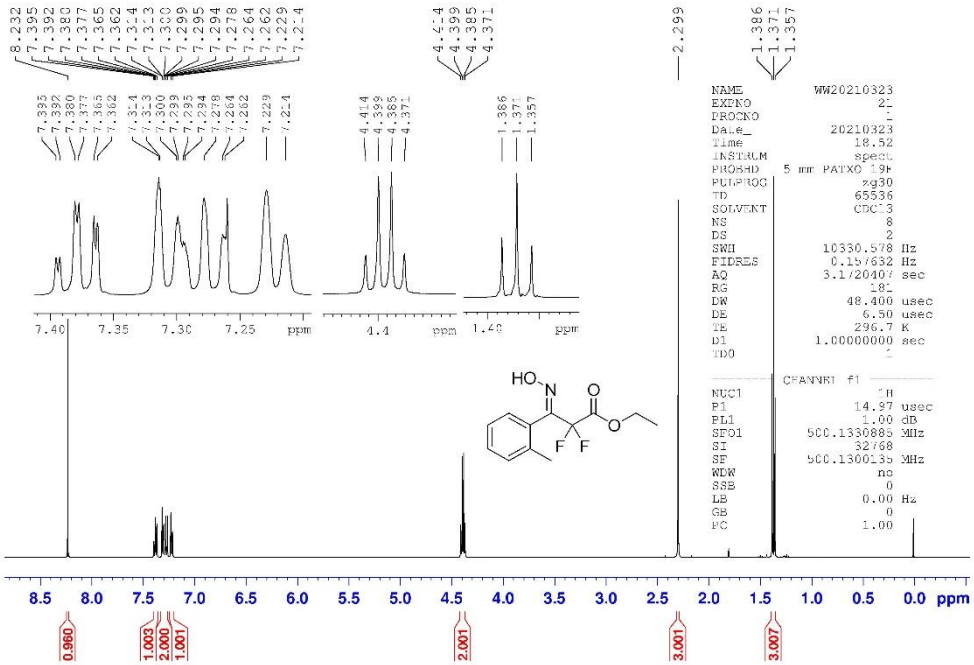
^{13}C NMR Spectra of **3d**



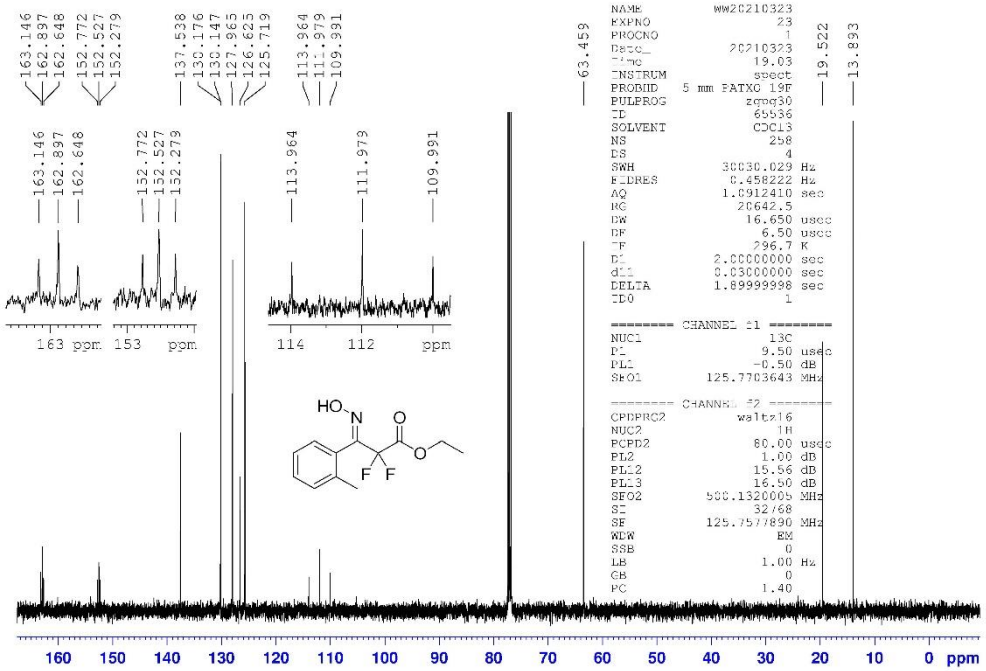
^{19}F NMR Spectra of **3d**



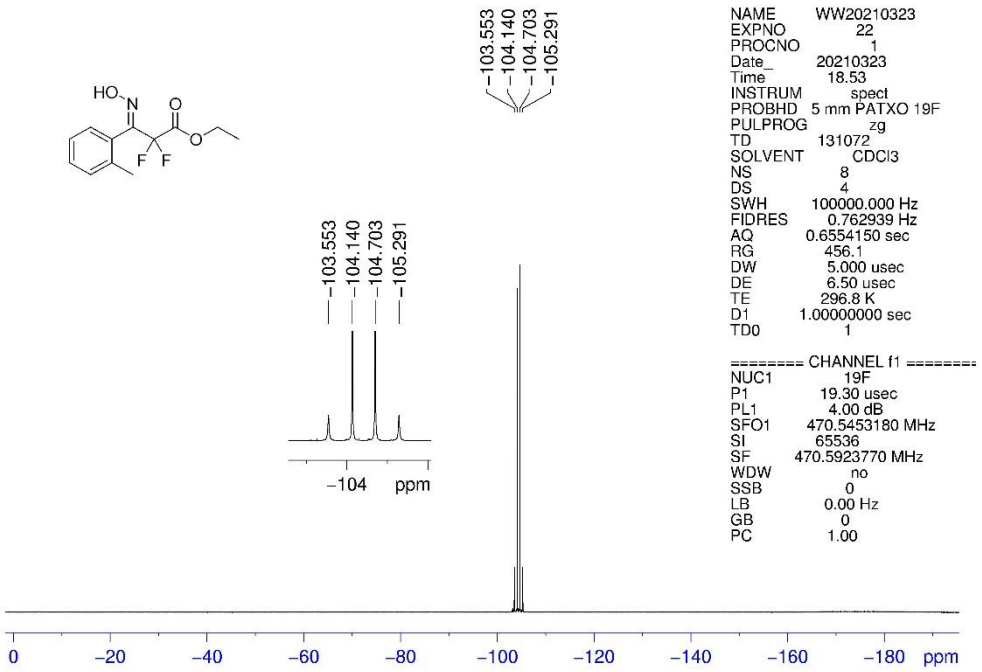
^{1}H NMR Spectra of **3e**



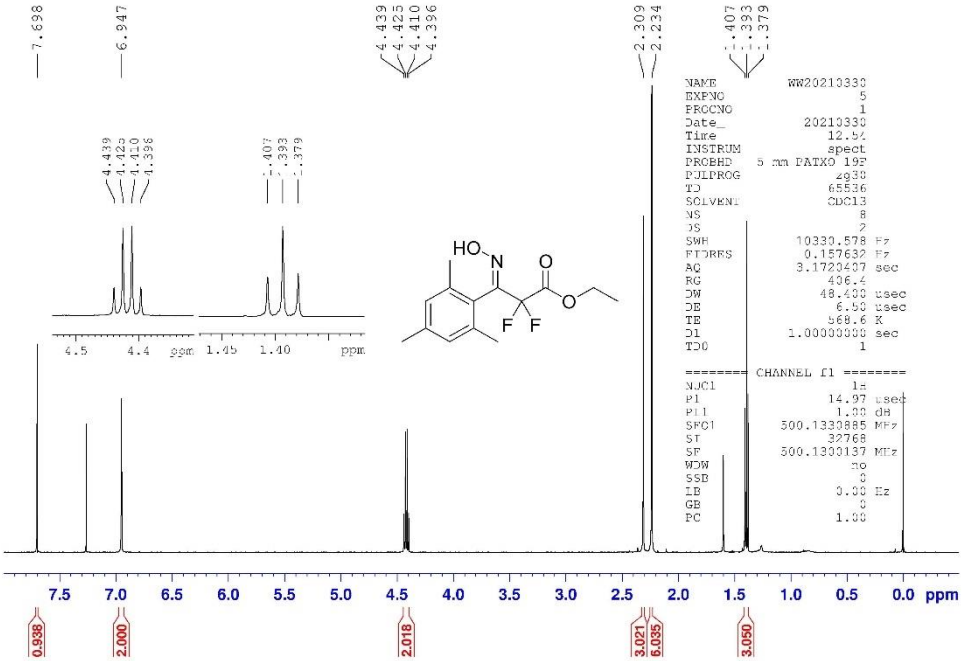
^{13}C NMR Spectra of **3e**



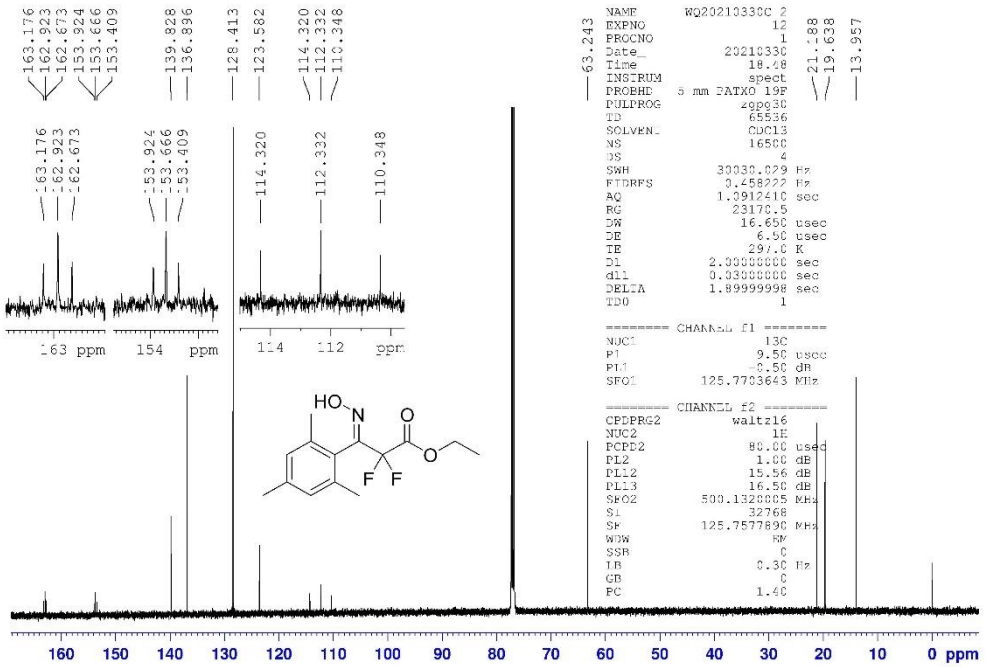
^{19}F NMR Spectra of **3e**



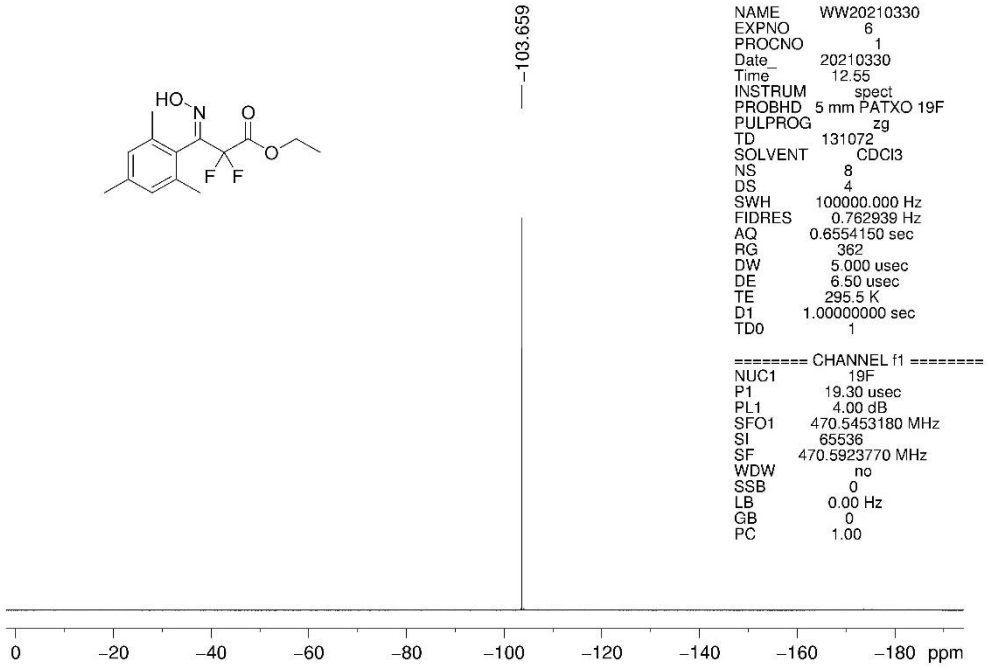
^{1}H NMR Spectra of **3f**



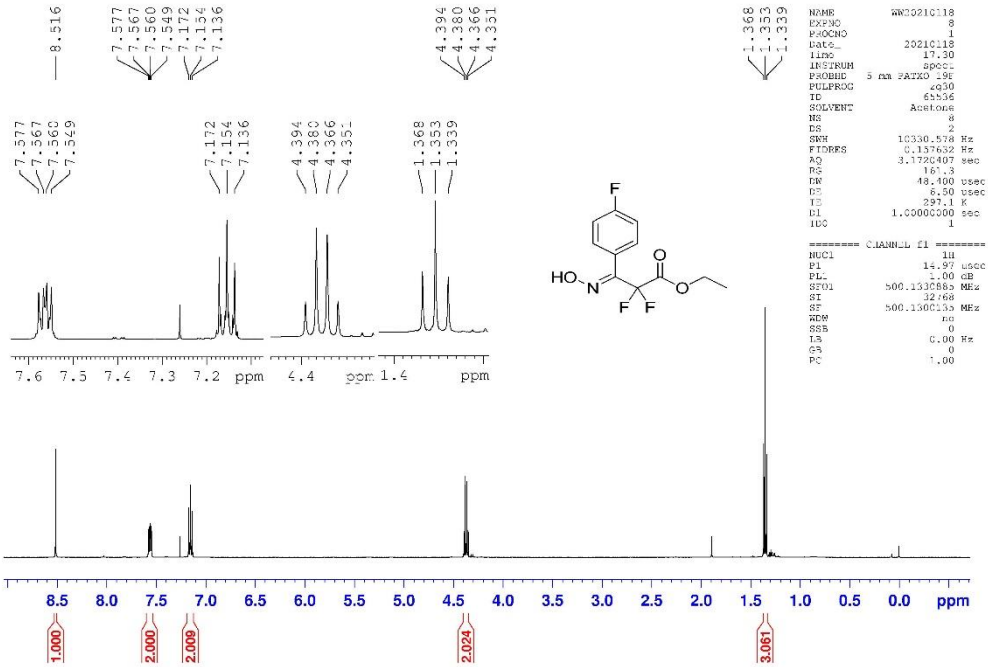
^{13}C NMR Spectra of **3f**



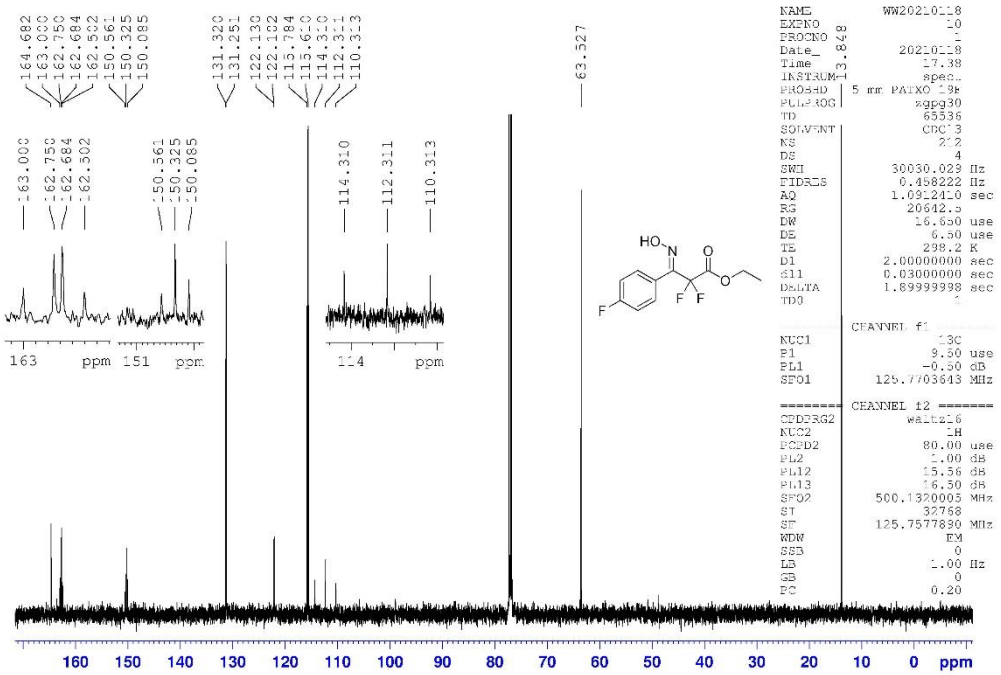
^{19}F NMR Spectra of **3f**



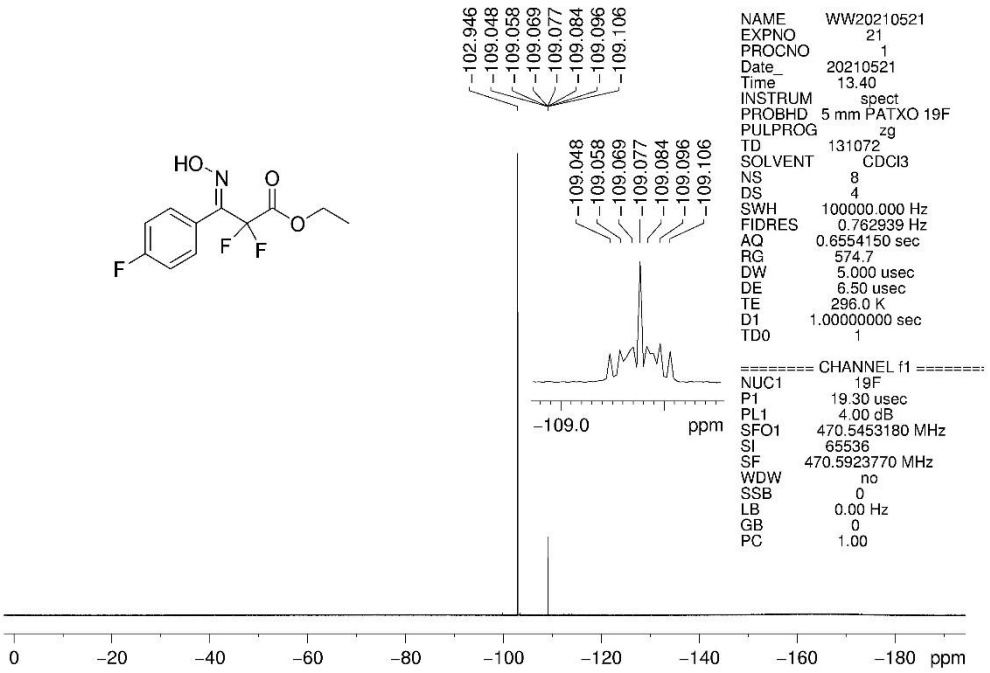
^{1}H NMR Spectra of **3g**



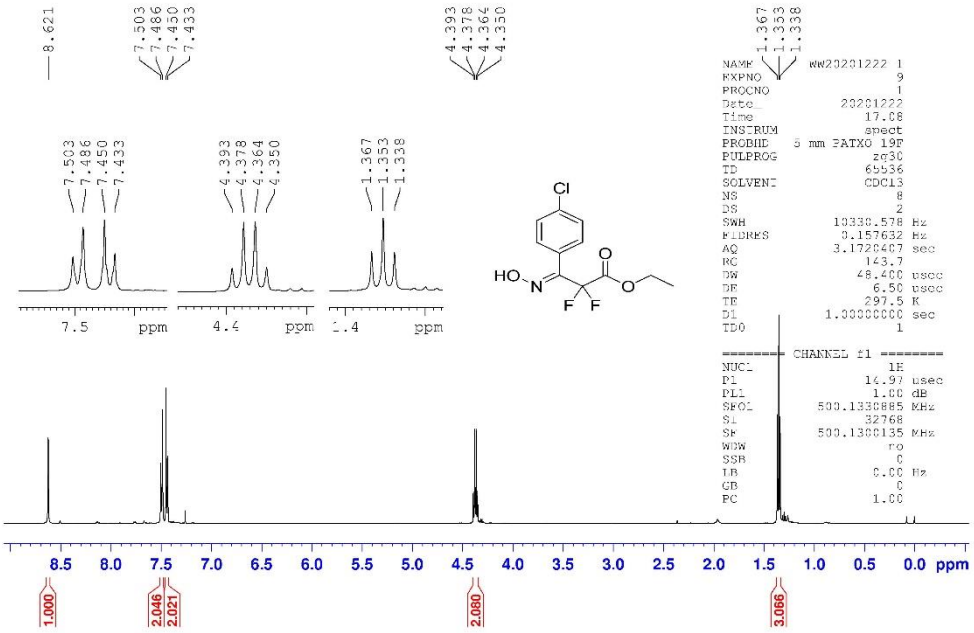
^{13}C NMR Spectra of **3g**



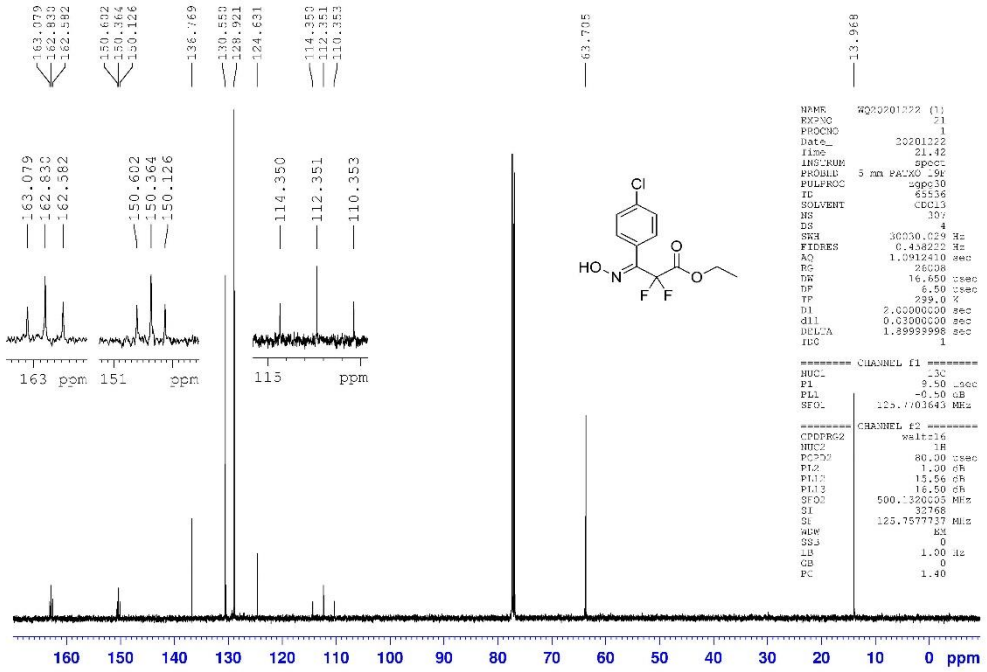
^{19}F NMR Spectra of **3g**



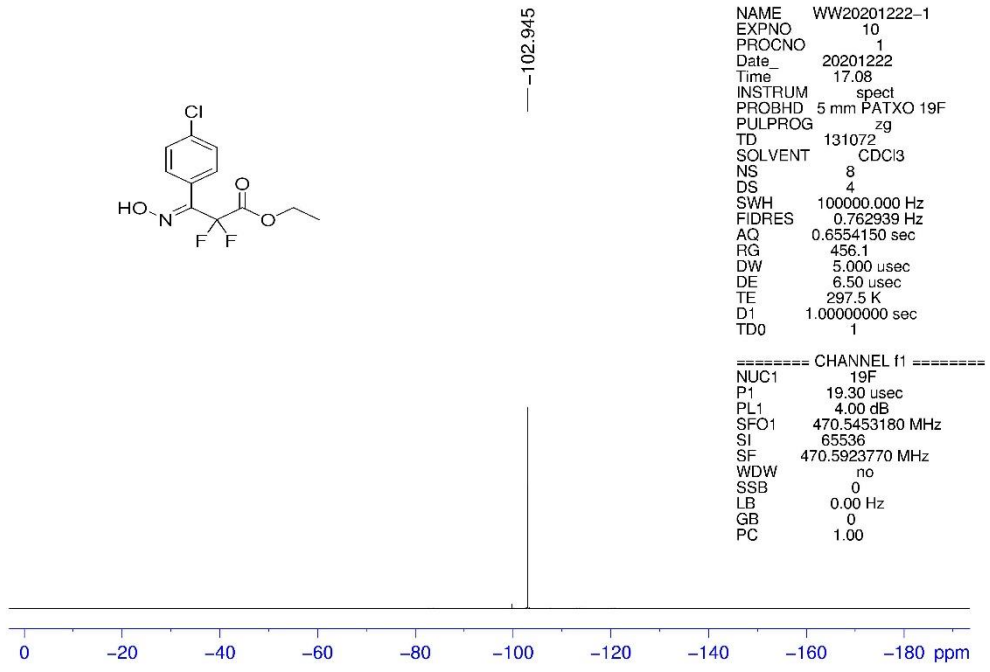
^{1}H NMR Spectra of **3h**



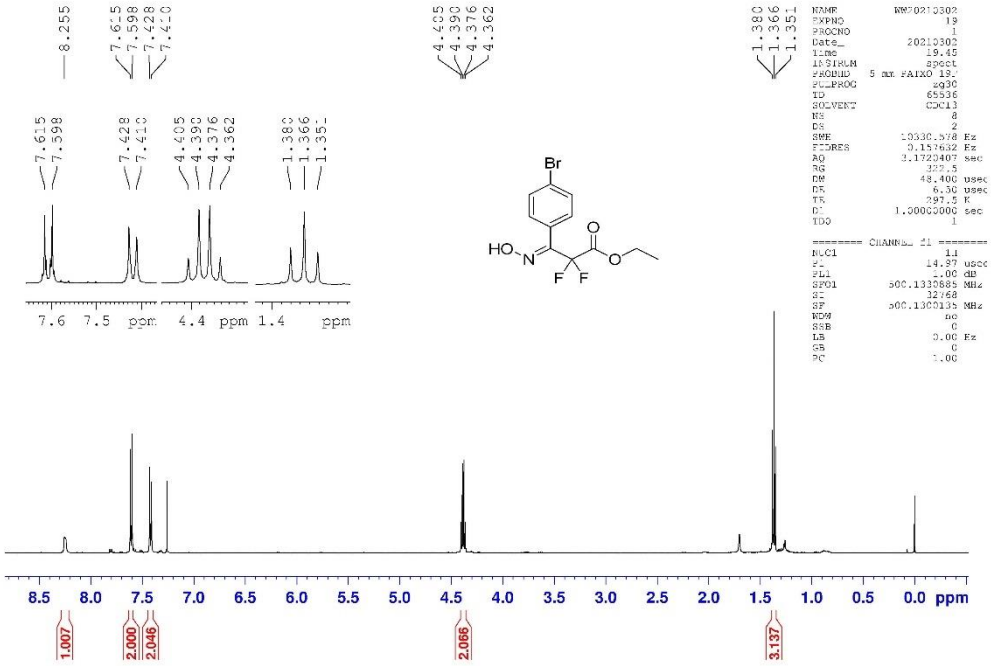
^{13}C NMR Spectra of **3h**



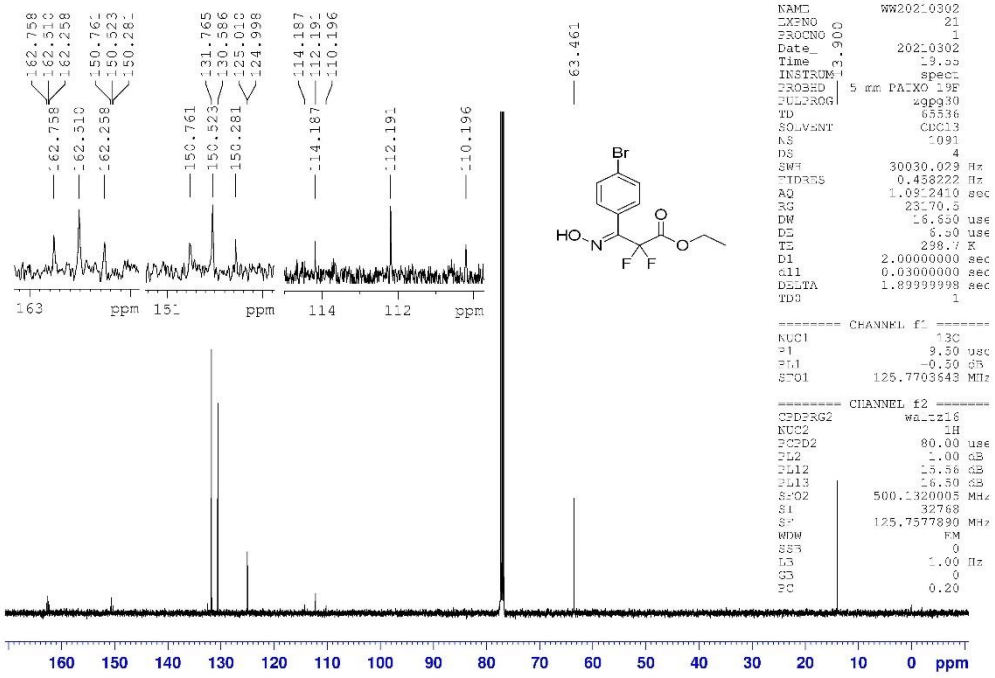
^{19}F NMR Spectra of **3h**



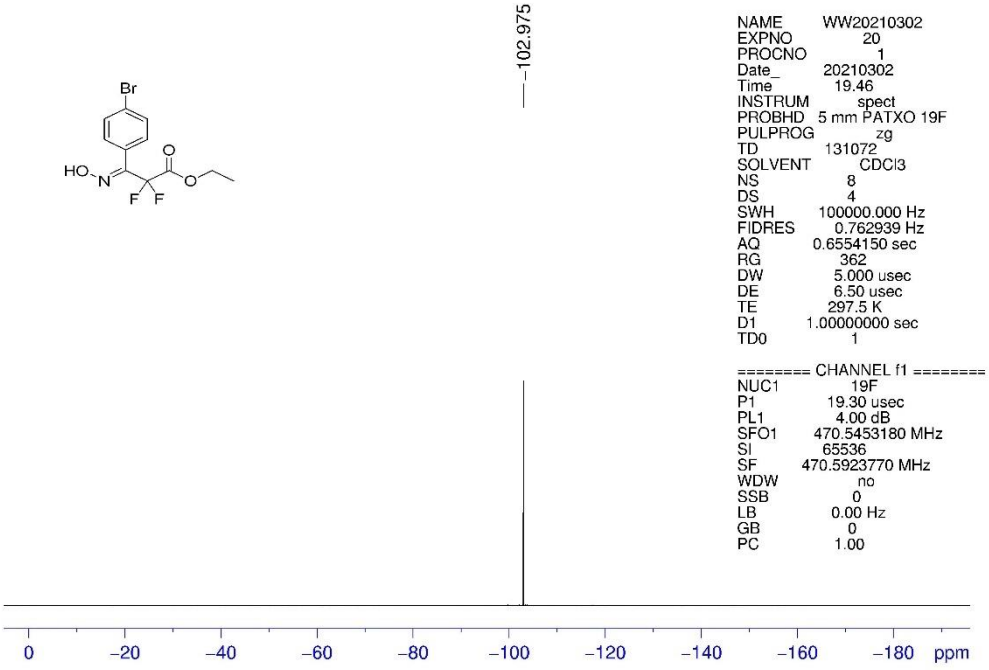
^{1}H NMR Spectra of **3i**



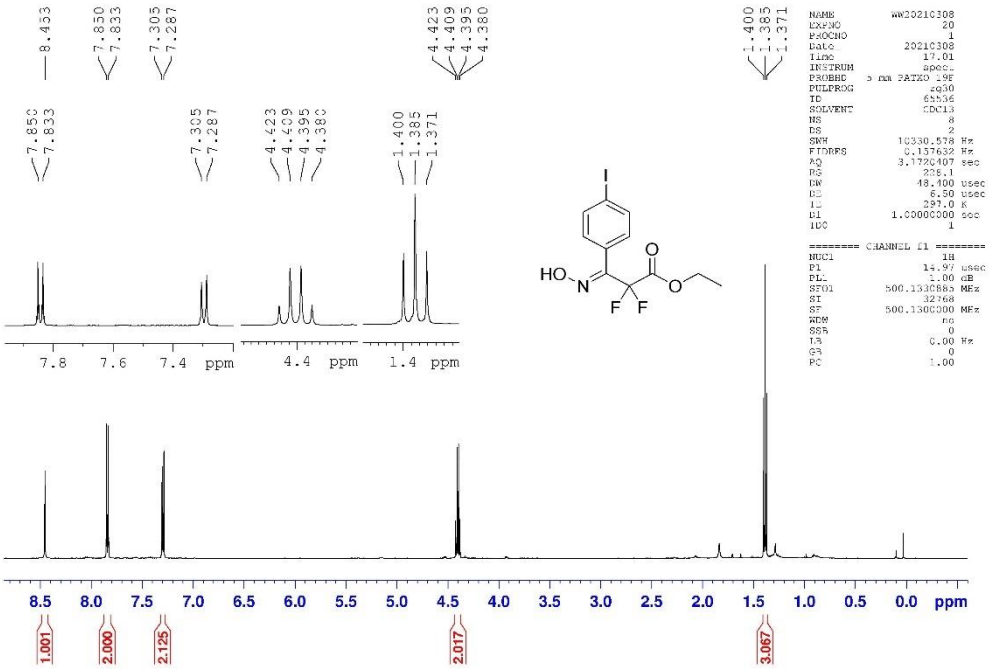
^{13}C NMR Spectra of **3i**



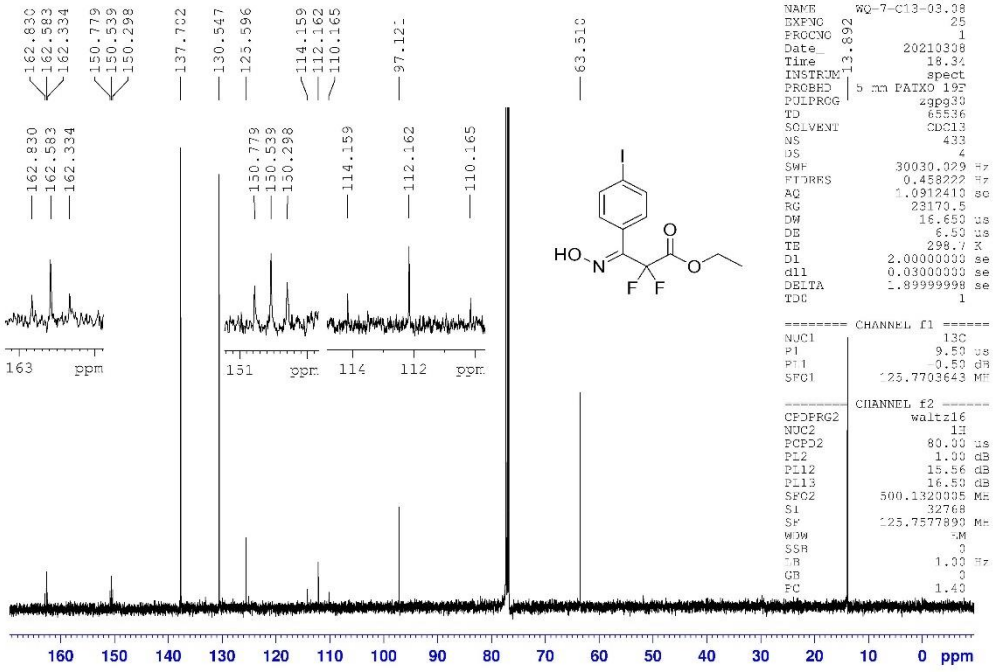
^{19}F NMR Spectra of **3i**



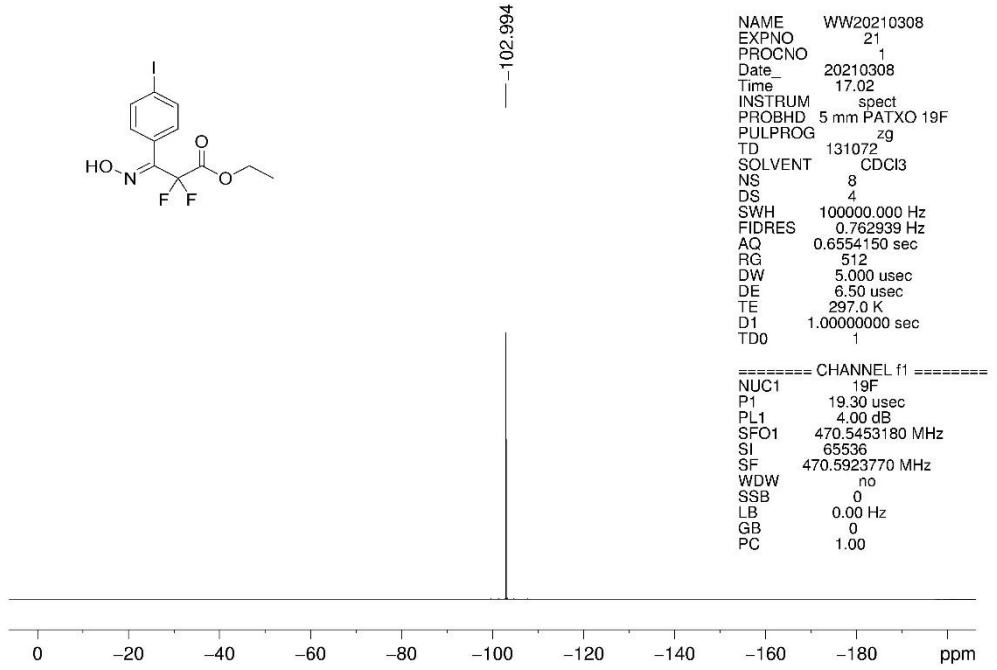
^{1}H NMR Spectra of **3j**



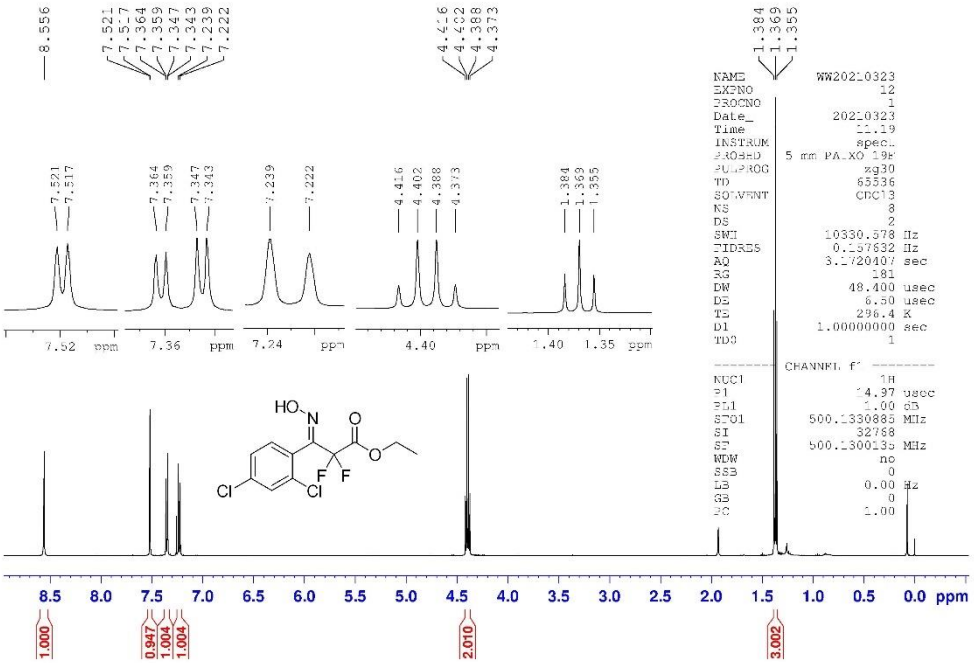
^{13}C NMR Spectra of **3j**



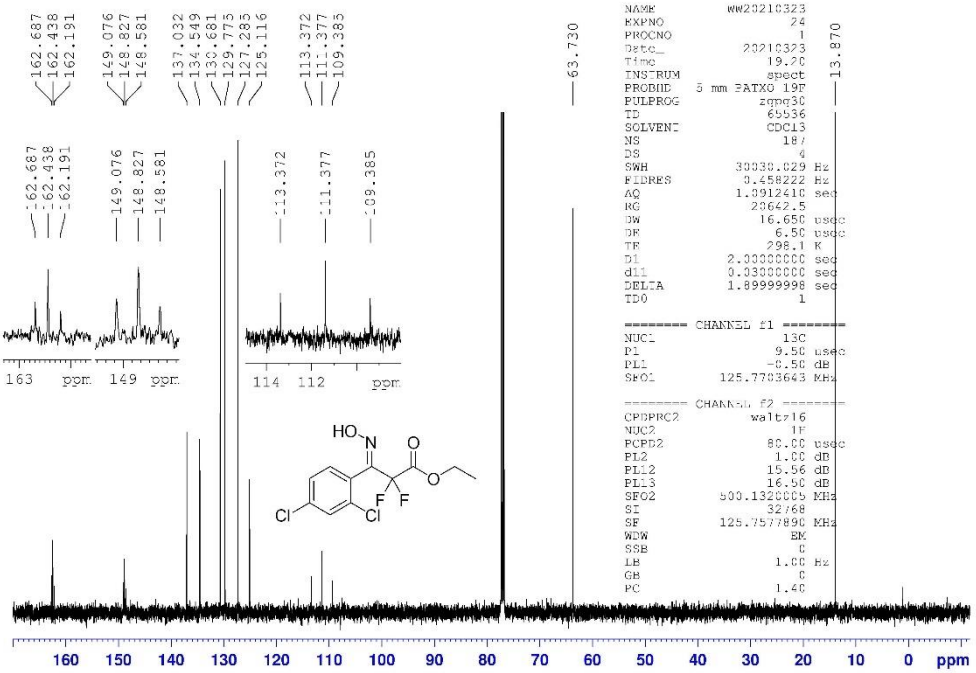
^{19}F NMR Spectra of **3j**



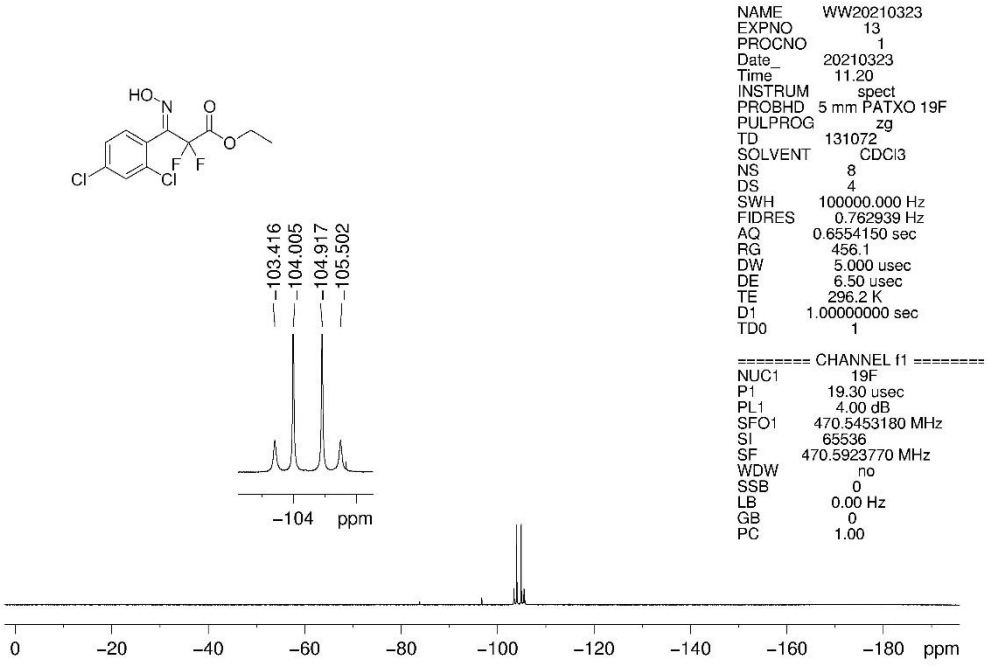
^{1}H NMR Spectra of **3k**



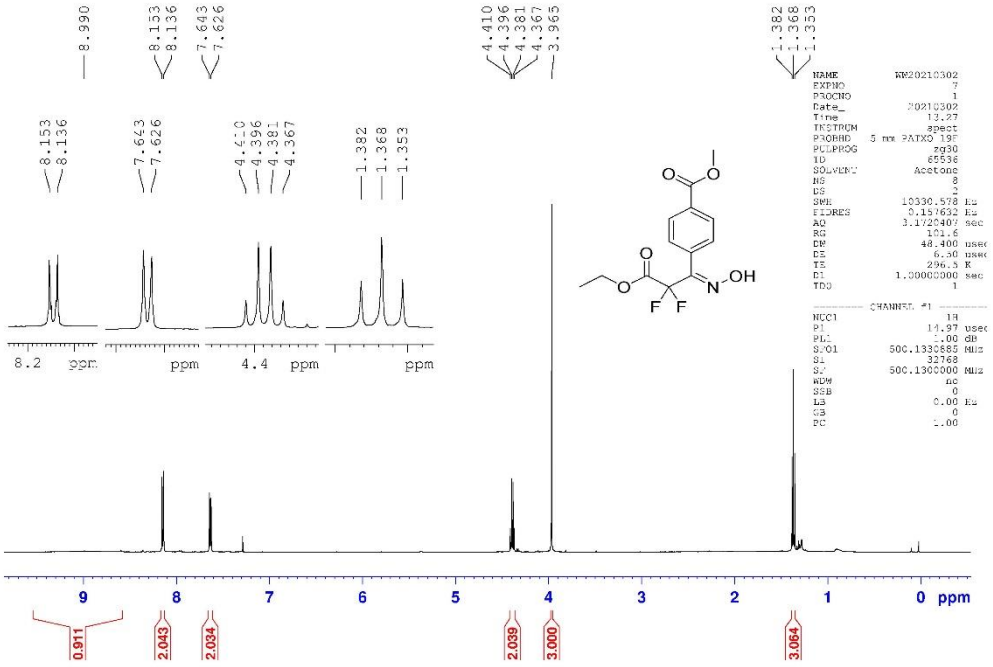
^{13}C NMR Spectra of **3k**



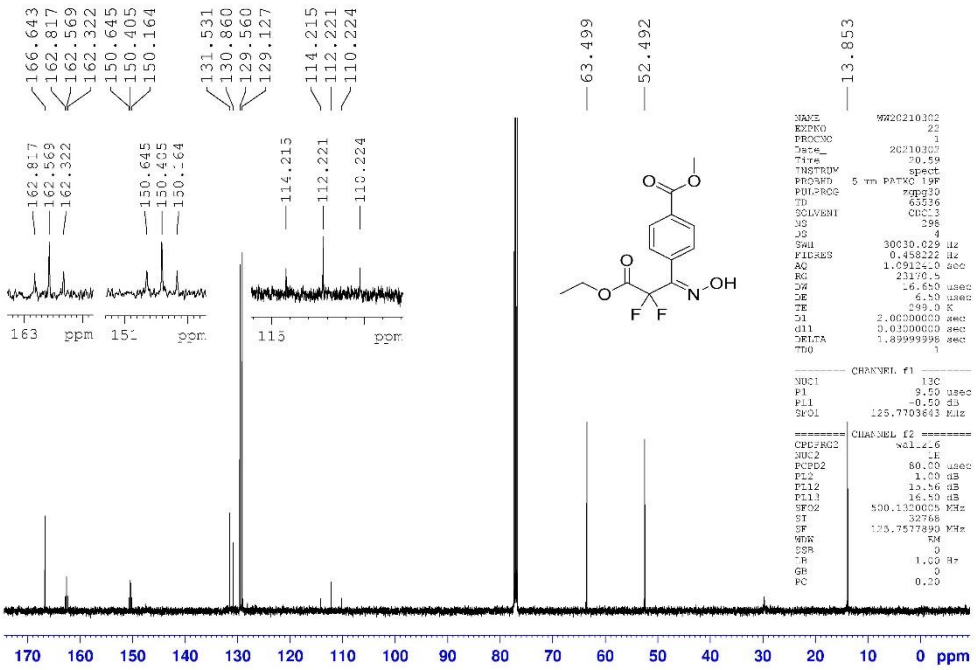
^{19}F NMR Spectra of **3k**



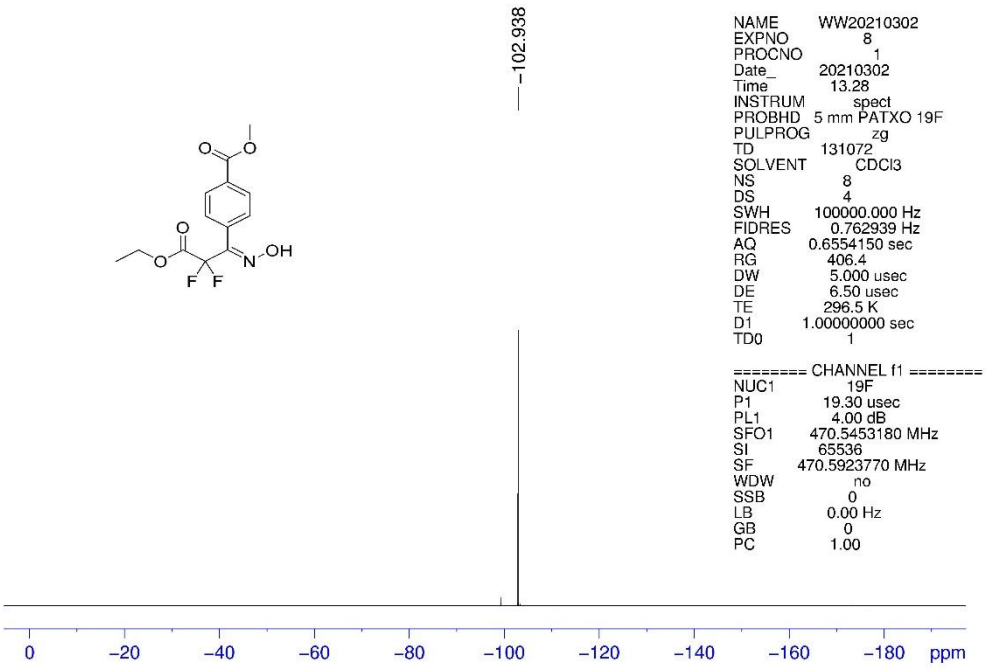
^{1}H NMR Spectra of **3l**



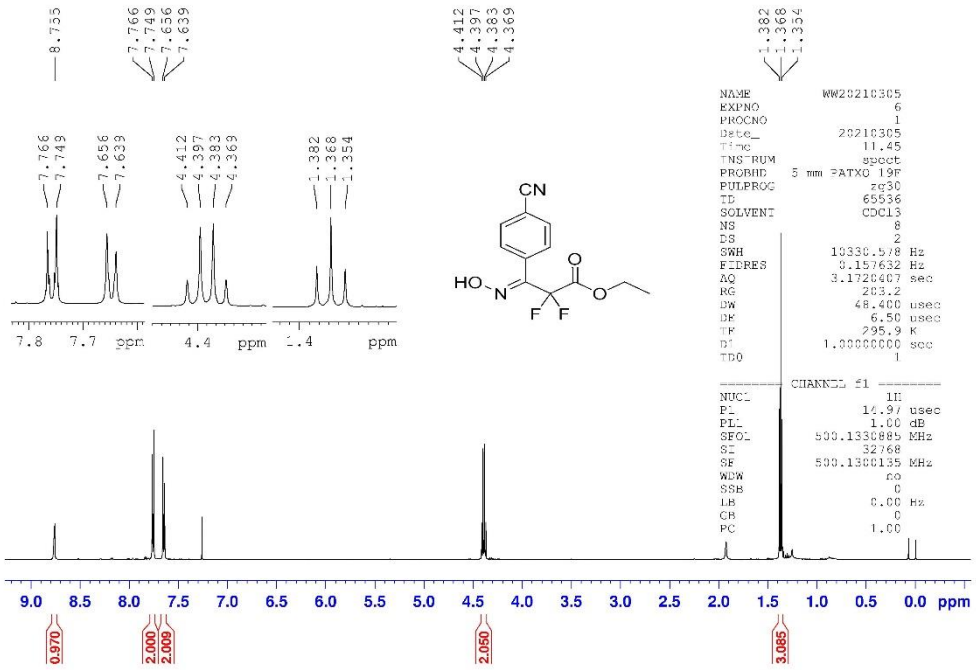
^{13}C NMR Spectra of **3l**



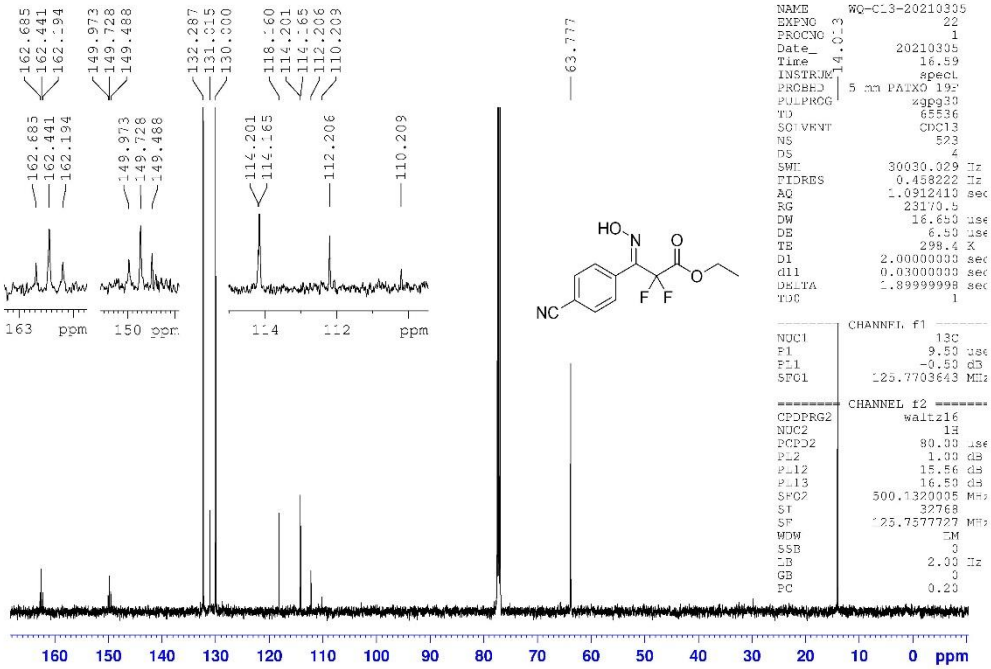
^{19}F NMR Spectra of **3l**



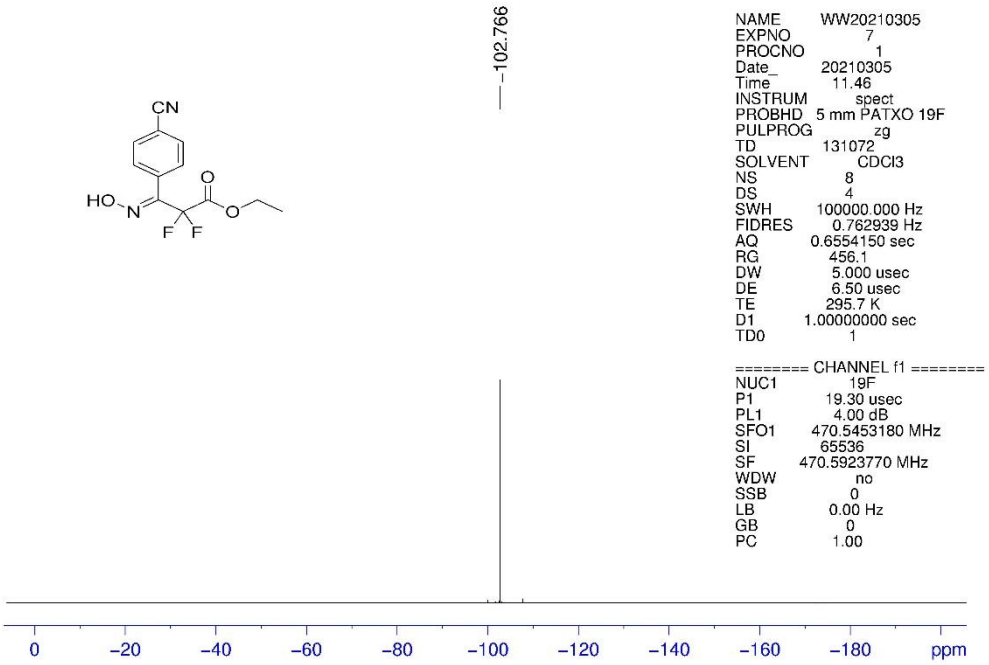
^{1}H NMR Spectra of **3m**



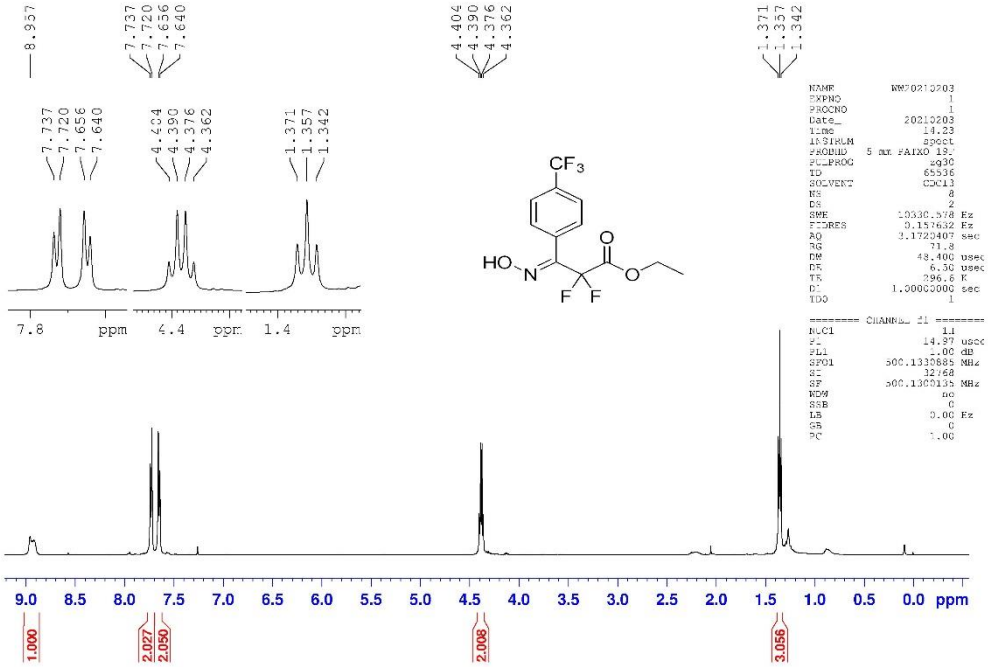
^{13}C NMR Spectra of **3m**



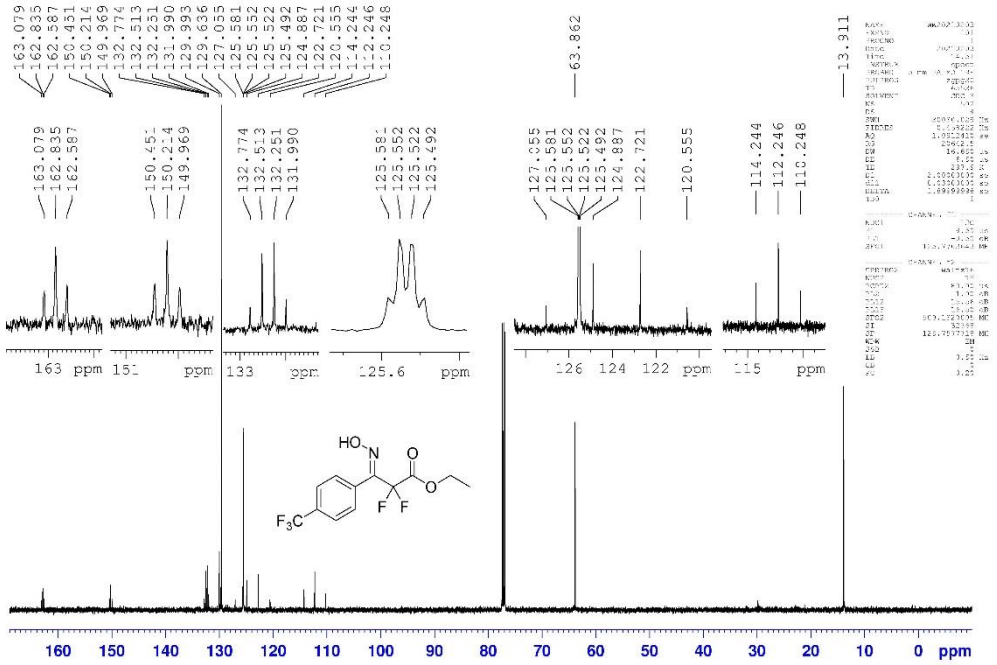
^{19}F NMR Spectra of **3m**



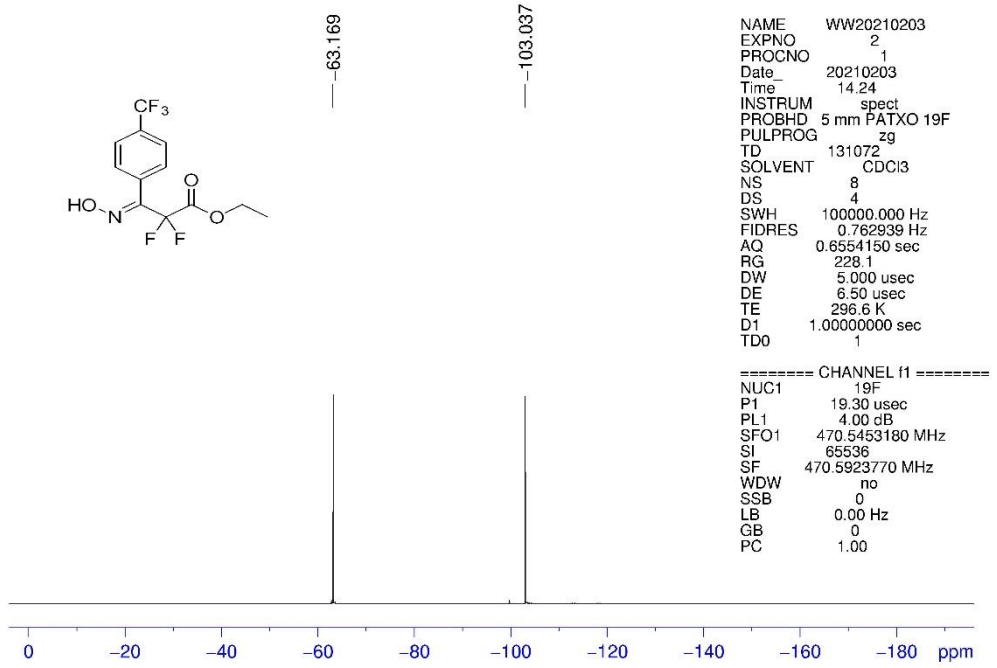
^{1}H NMR Spectra of **3n**



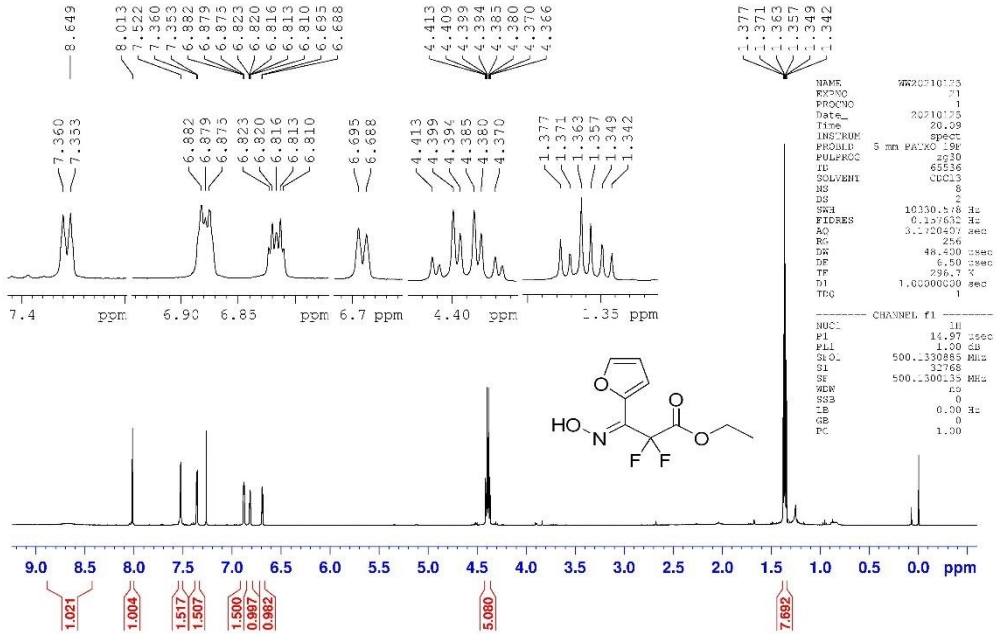
^{13}C NMR Spectra of **3n**



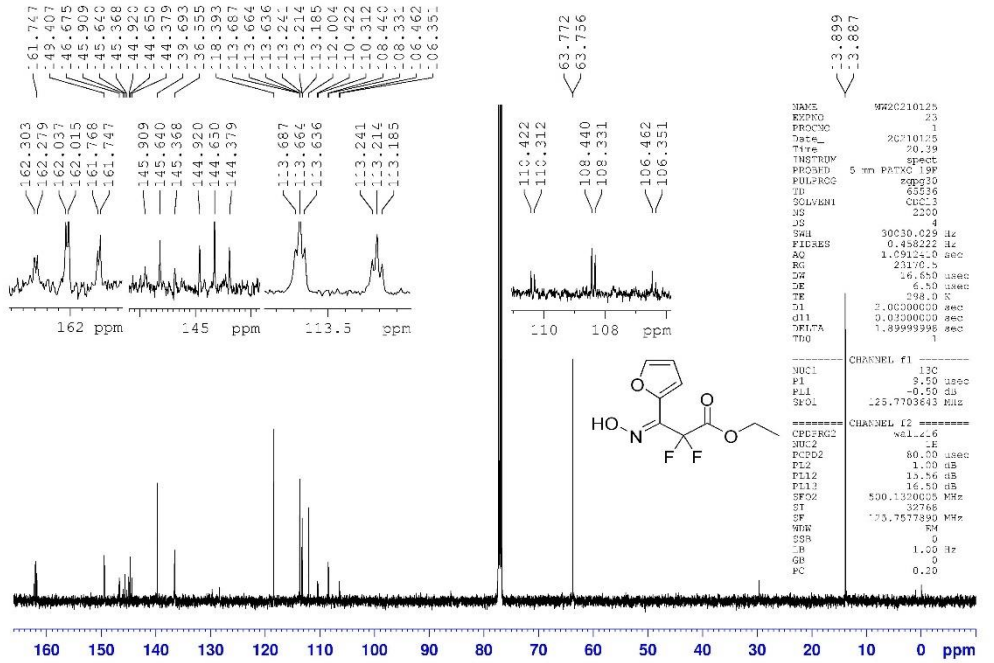
^{19}F NMR Spectra of **3n**



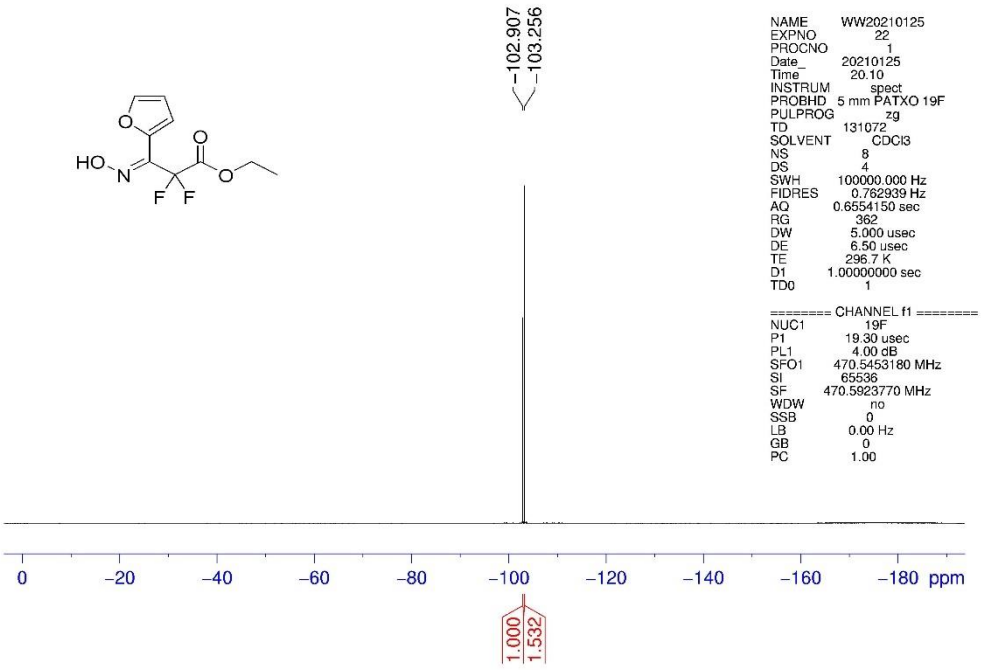
^{1}H NMR Spectra of **3o**



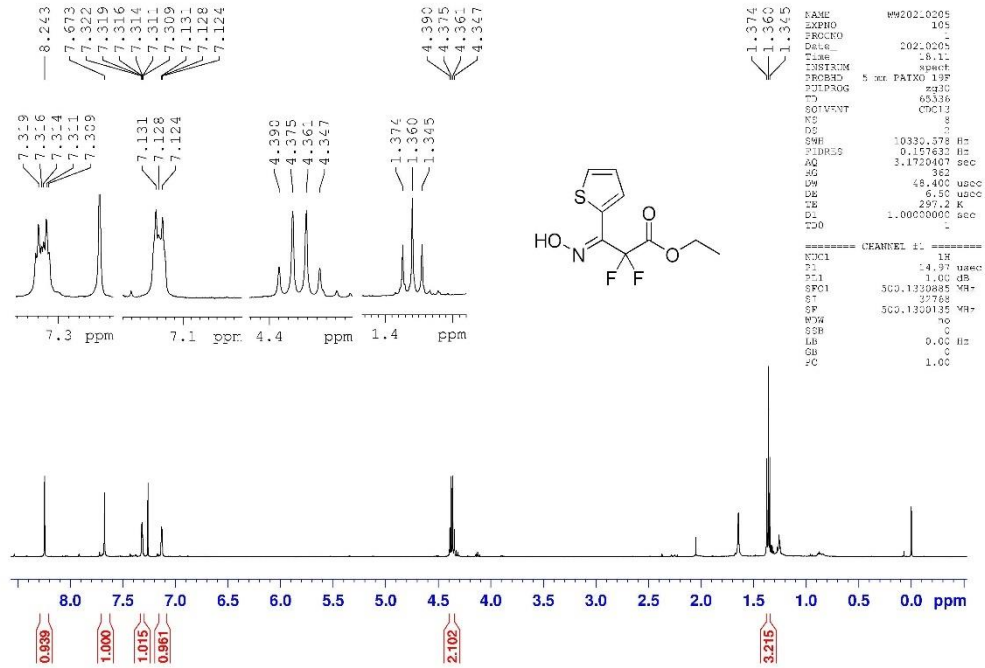
^{13}C NMR Spectra of **3o**



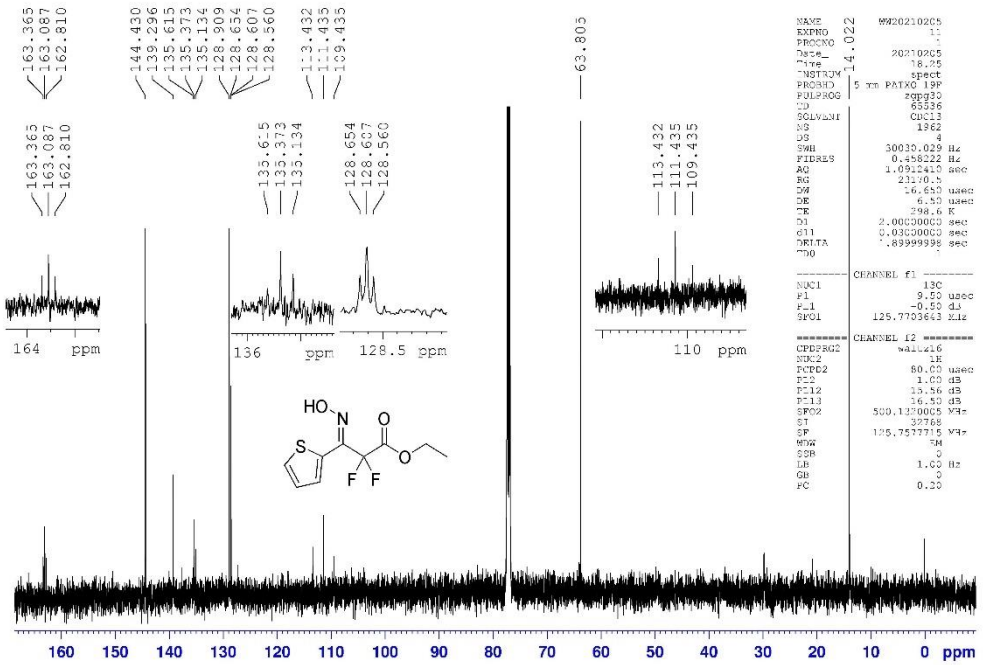
^{19}F NMR Spectra of **3o**



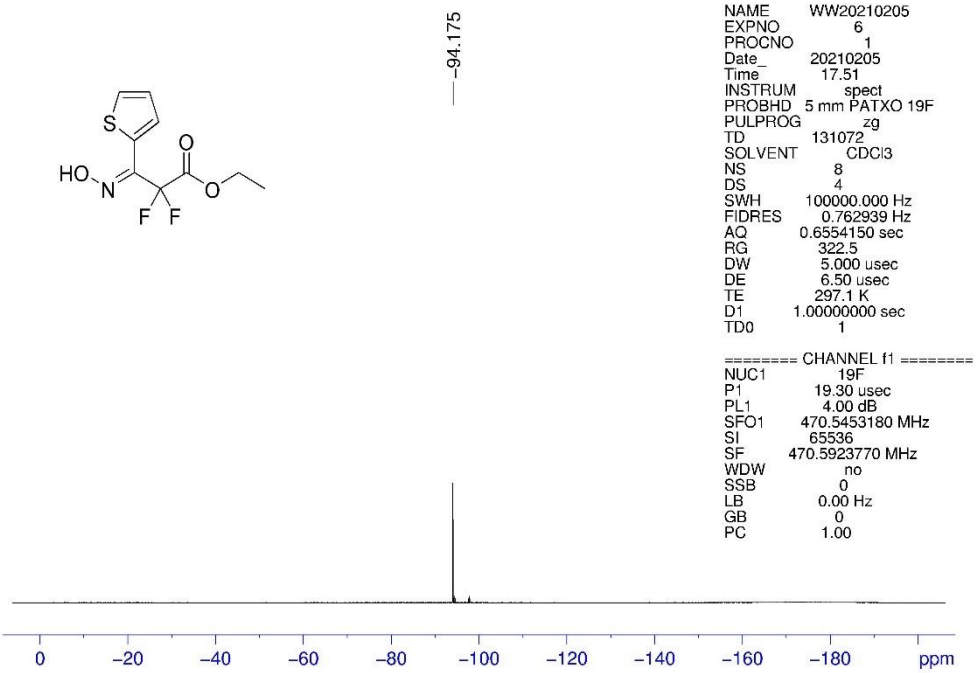
^{1}H NMR Spectra of **3p**



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



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



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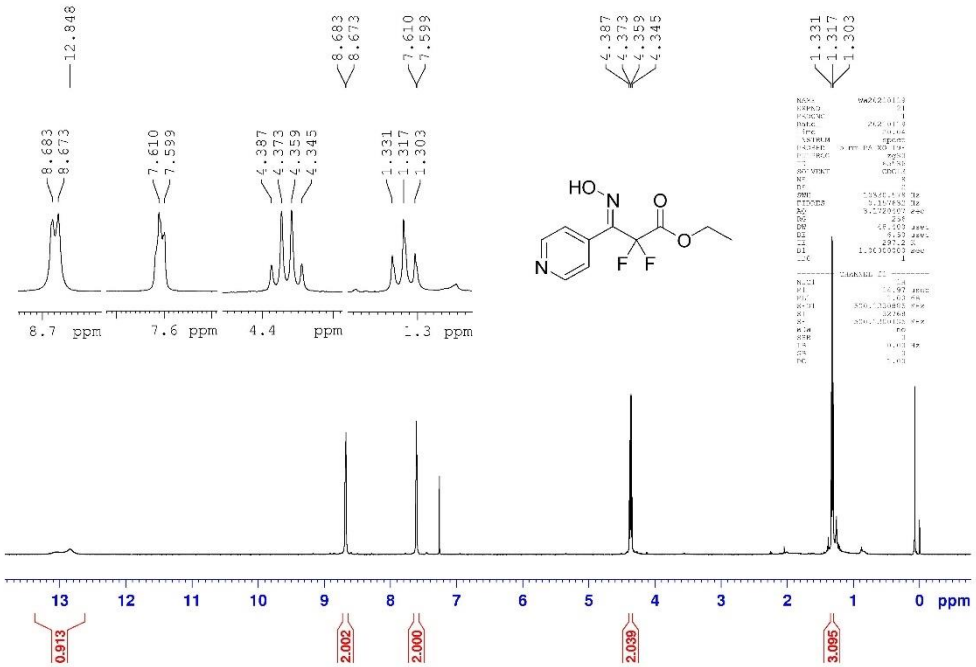
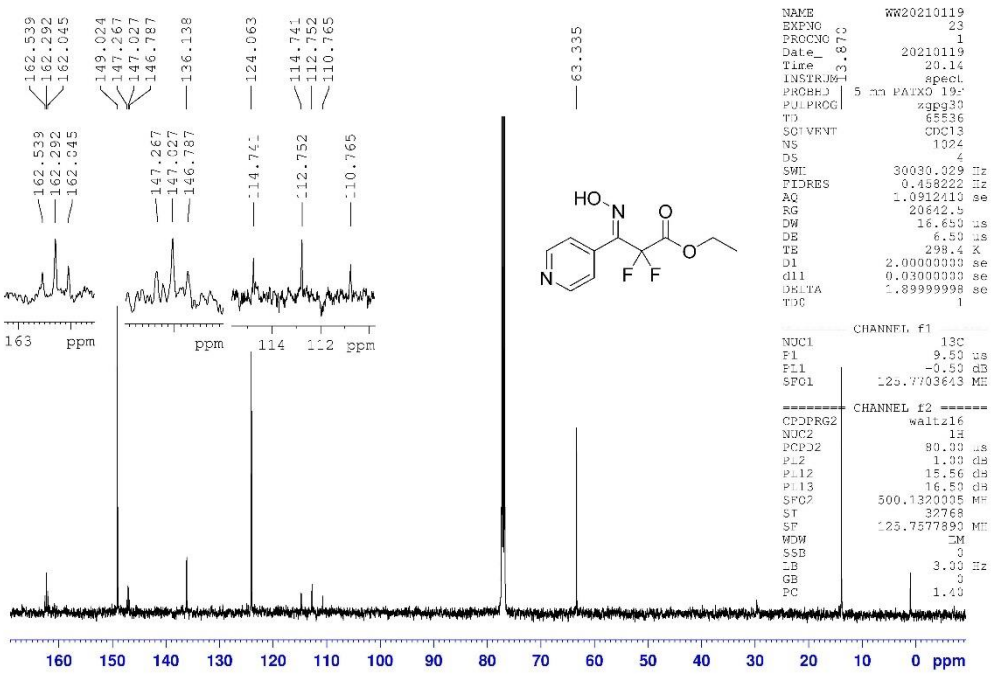
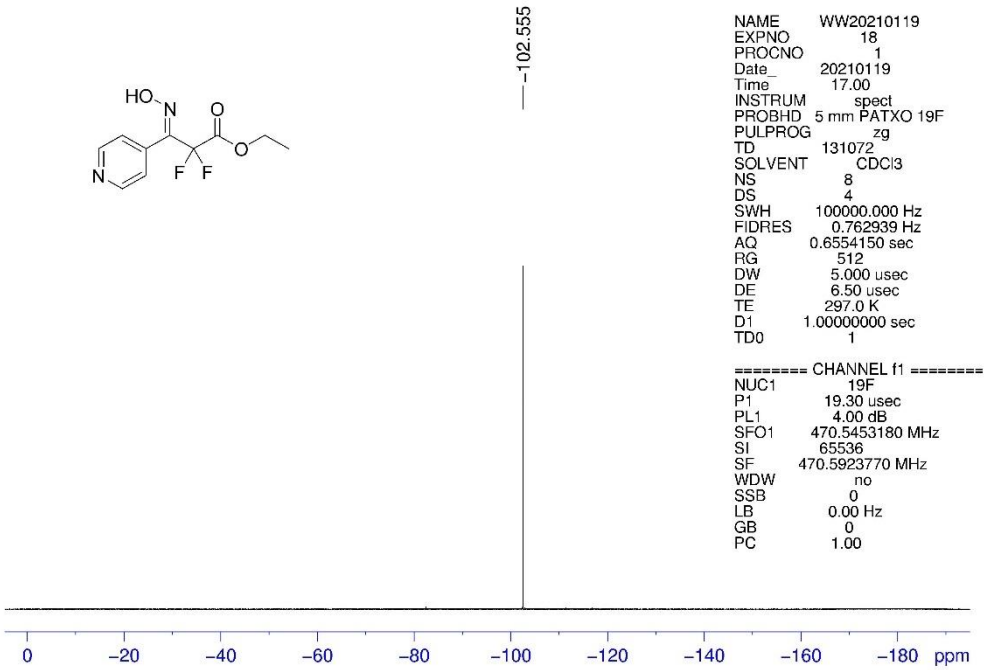


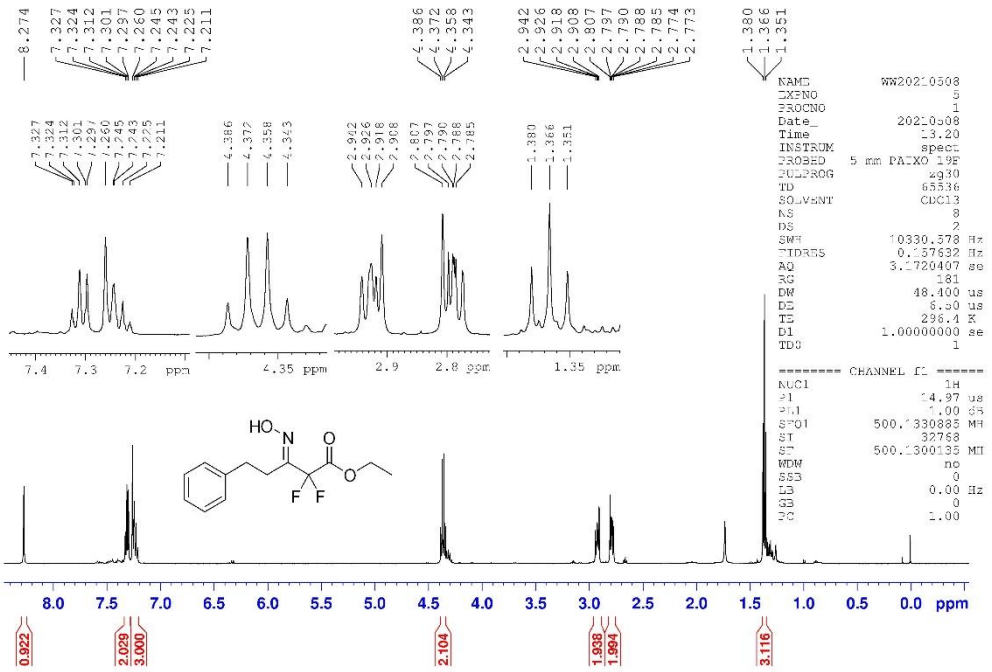
^{13}C NMR Spectra of **3q**



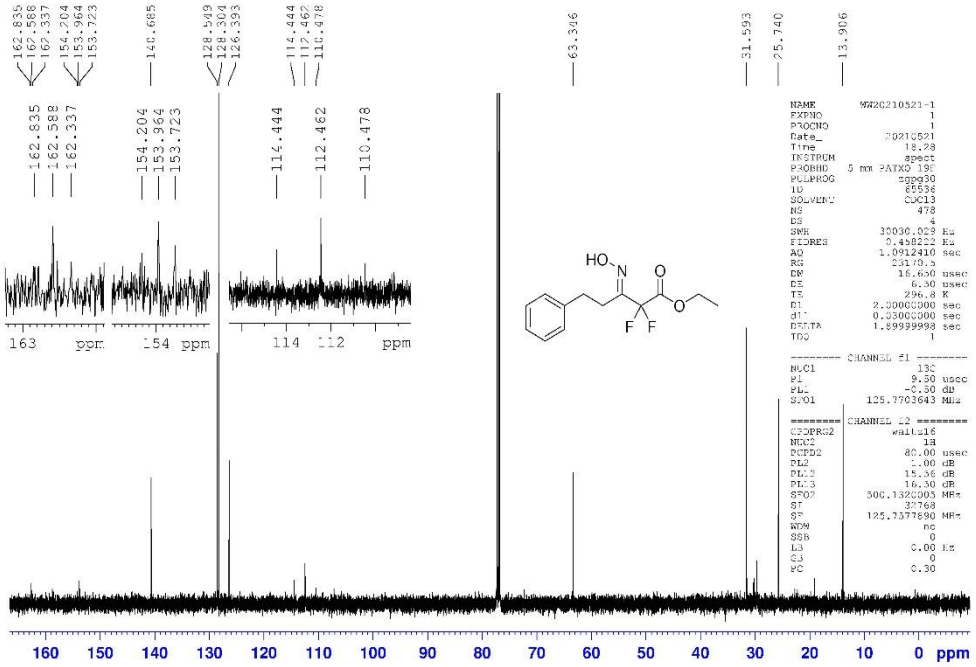
^{19}F NMR Spectra of **3q**



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



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



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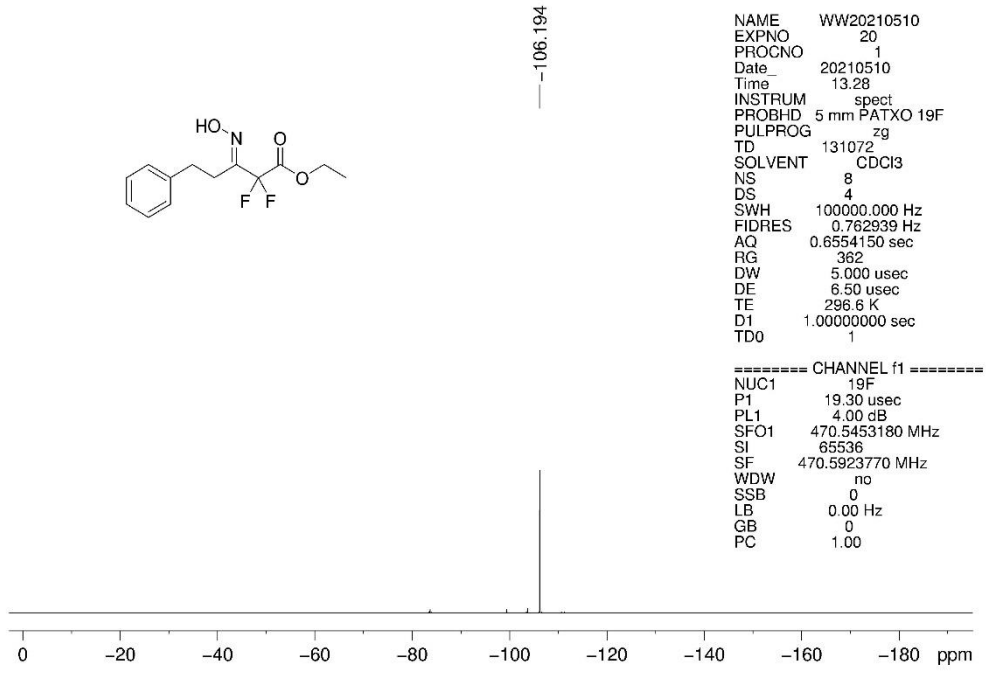

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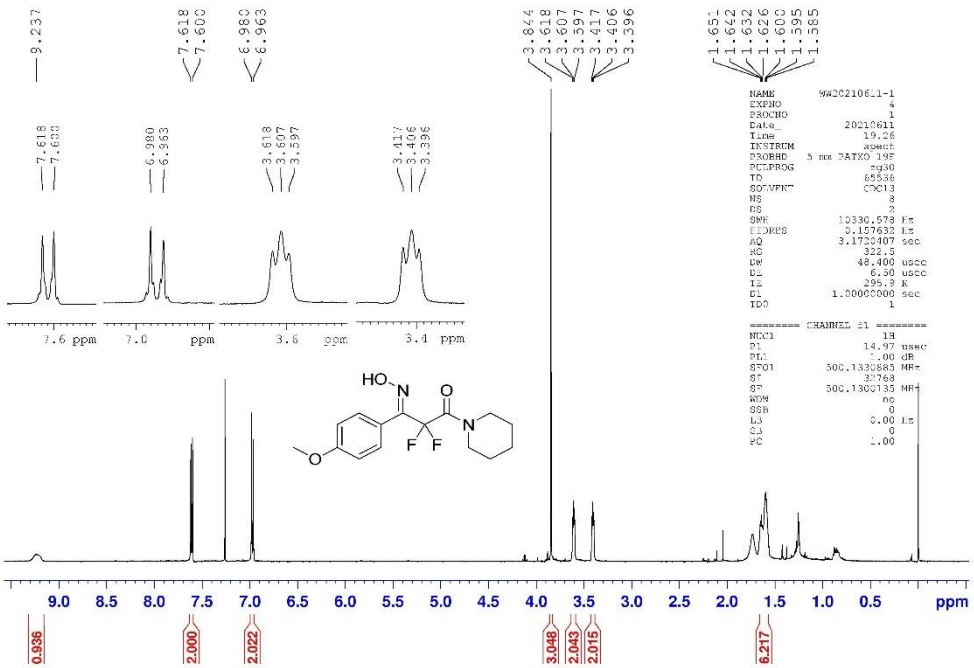

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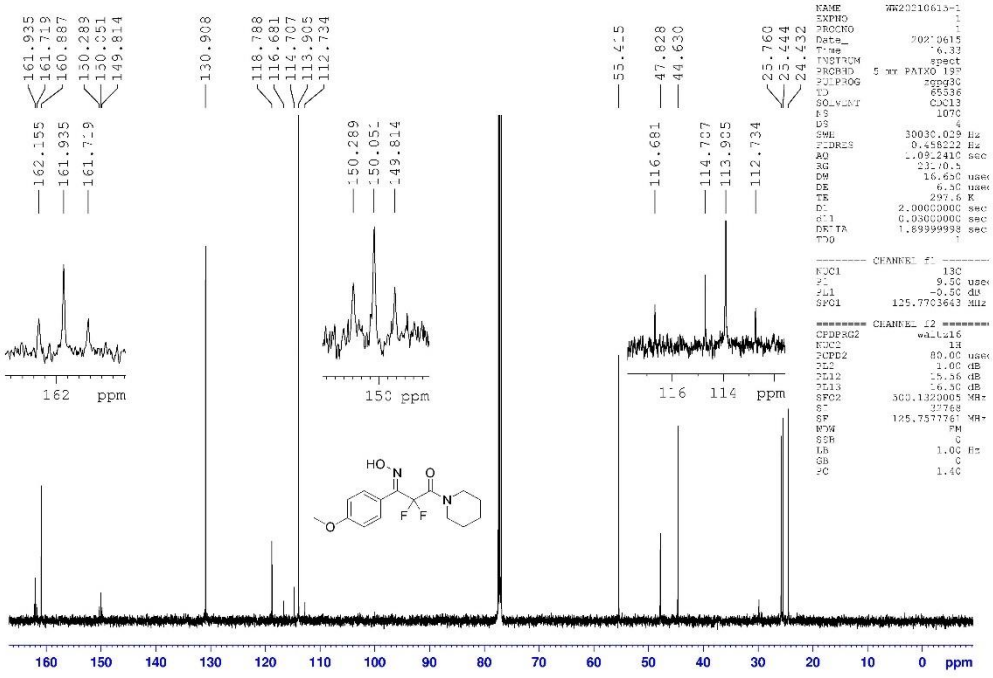

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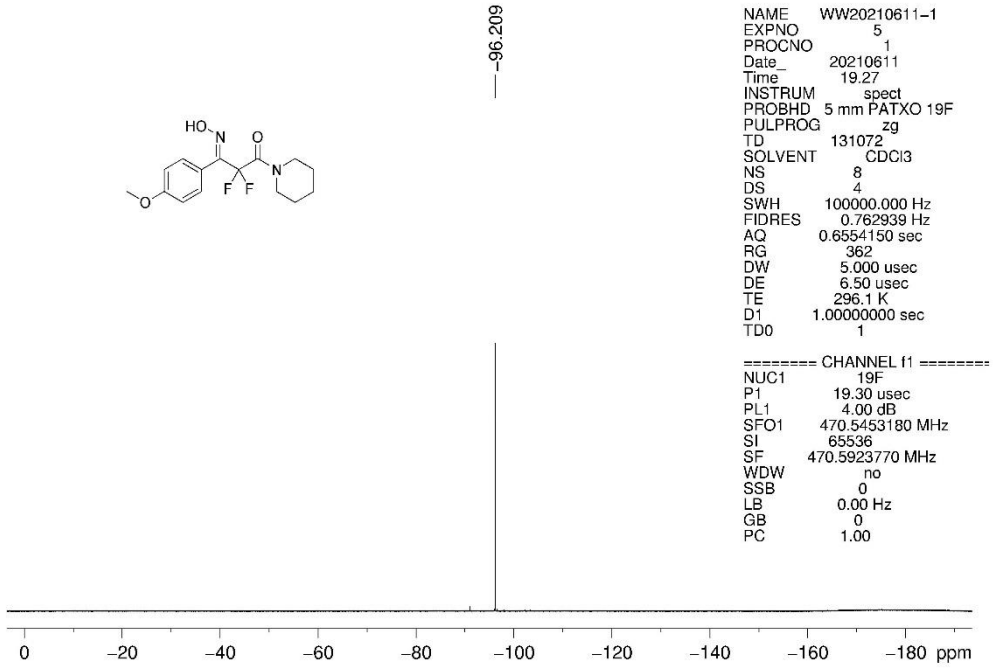
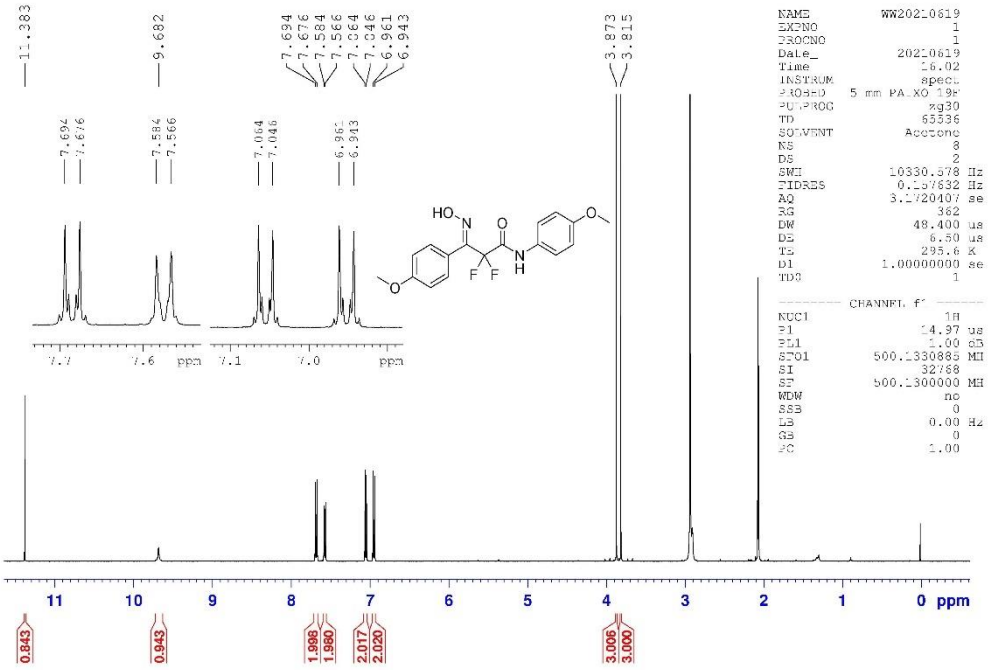
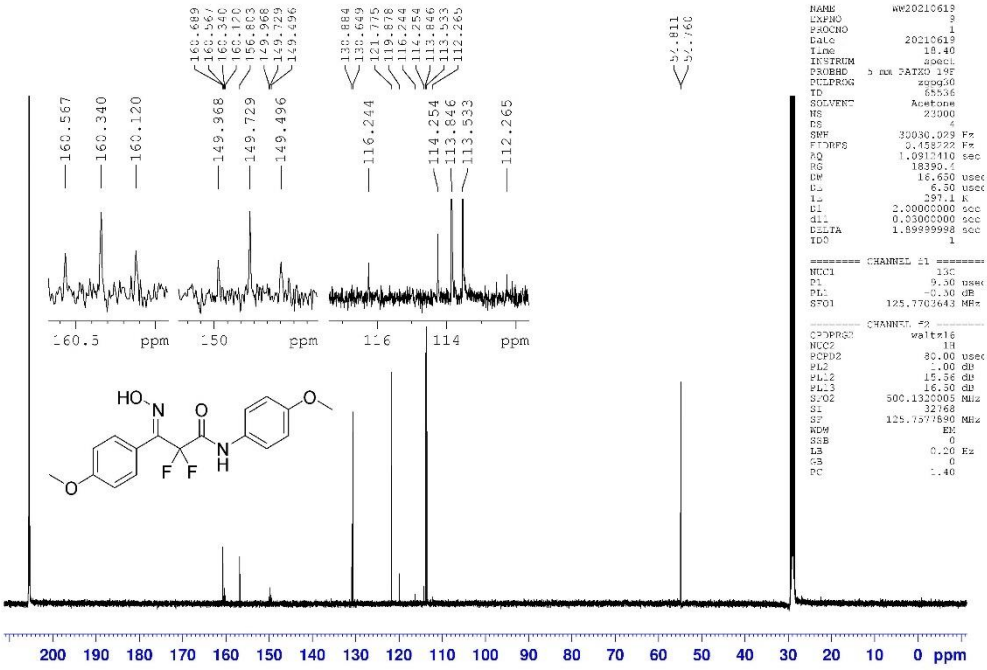


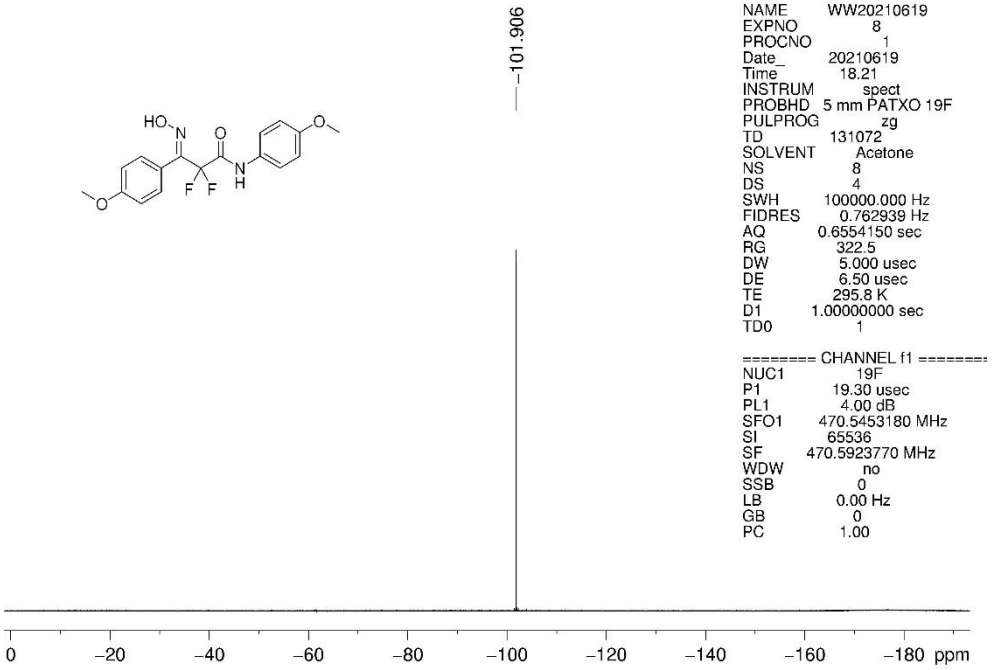
^{1}H NMR Spectra of **3t**



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



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



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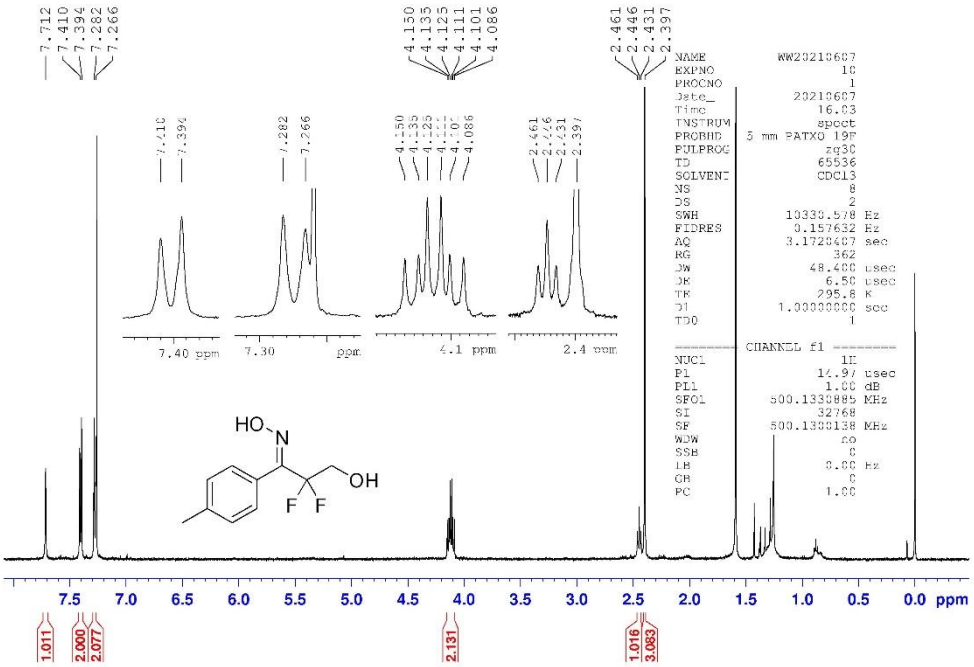
GB	0
PC	1.00

^{1}H NMR Spectra of **4**



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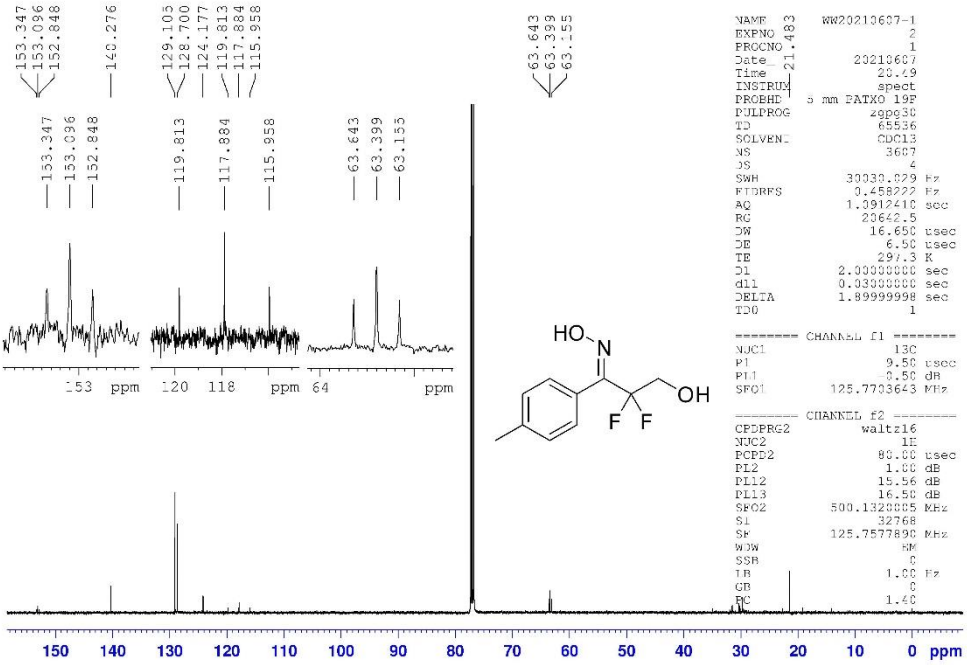

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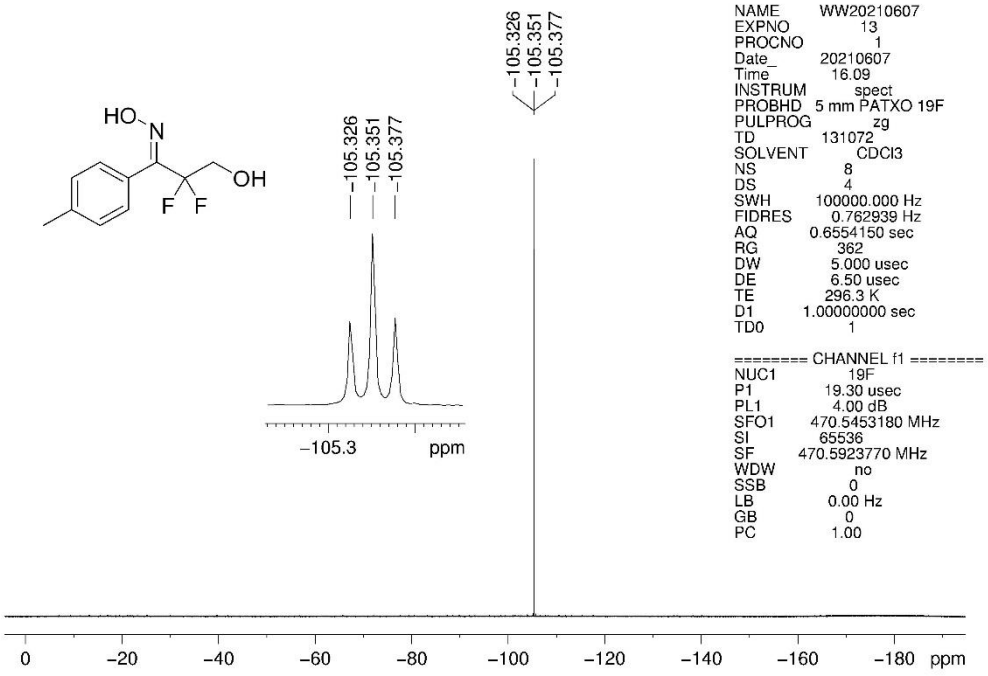
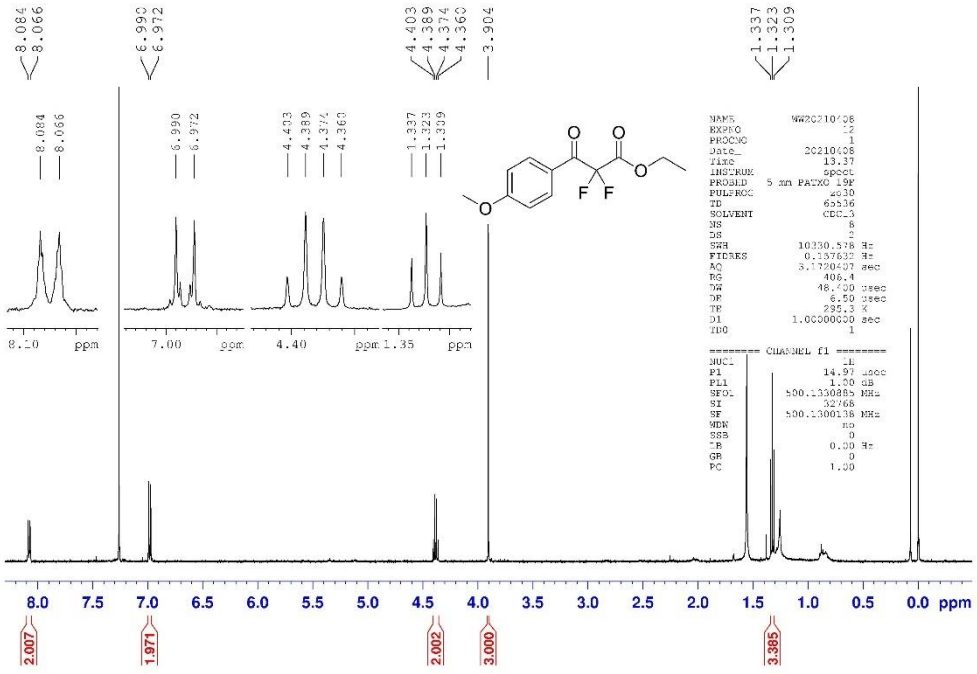


^{1}H NMR Spectra of **5**



^{19}F NMR Spectra of **5**