Electronic Supplementary Information

Catalytic regioselective construction of phenylthio- and phenoxyldifluoroalkyl tetrazoles from difluorodiazoketones

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General Information

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz at ambient temperature. Chemical shifts were reported in ppm down field from internal Me_4Si and external $CHCl_3$ or DMSO, respectively. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), sex (sextet), sep (septet), m (multiplet), dd (doublet of doublet), and br (broad signal). Coupling constants were reported in Hertz (Hz). ^{19}F NMR spectra were recorded with ^{1}H decoupling. High resolution mass spectrometry (HRMS) spectra were obtained on a Bruker miorOTOF-QII instrument. Melting points were measured in a X-6 micro melting point apparatus purchased from Beijing TECH Instrumental Company. IR data were measured on Vertex 70 Bruker.

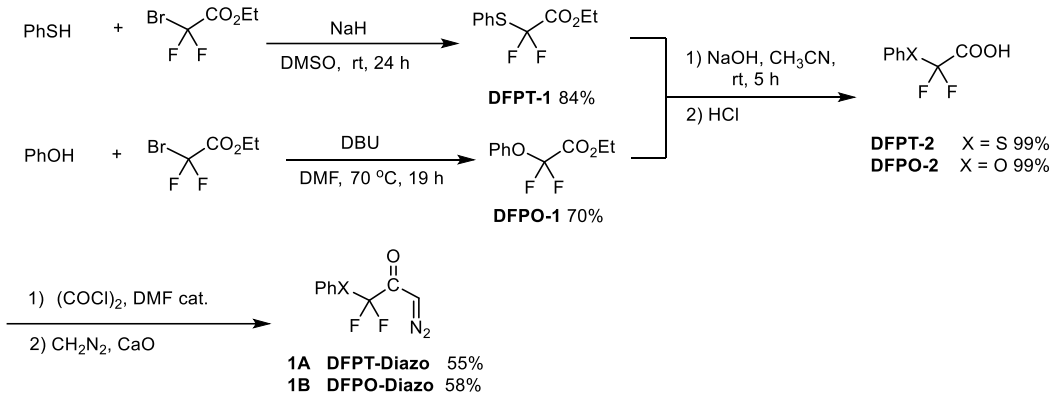
Materials: Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use; CH_3CN was distilled from P_2O_5; DMF, EtOH,and DCM were dried with 3 Å molecular sieves prior to use. All purchased reagents were used without further purification. Thin-layer chromatography (TLC) was performed on precoated GF254 silica gel plates (Qingdao Marine Chemical Inc.) and compounds were visualized with a UV light at 254 nm. Flash chromatography separations were carried out using silica gel (200–300 mesh, Qingdao Marine Chemical Inc.). The preparation of aryl diazonium salt[1] and diazomethane [2]was carried out according to the reported procedure.

Important Safety Note

The treatment of aryl diazonium salt and diazomethane should be carried out in a well-ventilated fume hood. During this study, no accidents occurred when handling these reagents, but readers should be aware of the potentially explosive nature of the aryl diazonium salt and diazomethane described in this article. When using aryl diazonium salt and diazomethane, general safety precautions should be followed. None of the reactions described in this manuscript should be carried out without a rigorous risk assessment.

Experimental Procedures

Synthesis of Difluorophenylthio- and Difluorophenoxy-diazoketone Reagents（1A DFPT-Diazo and 1B DFPO-Diazo）



DFPT-1[3] *and* ***DFPO-1***[4] *were prepared with reference to the previously reported literature.*

2,2-difluoro-2-(phenylthio)acetic acid (DFPT-2) or 2,2-difluoro-2-phenoxyacetic acid (DFPO-2)

The corresponding ester (8 mmol, 1equiv.) was diluted in 40 mL of acetonitrile, and 5.0 M NaOH(aq) solution (8 mL, 5 equiv.) was added and stirred at room temperature for 5 h (TLC monitoring). The reaction mixture was concentrated under reduced pressure, and the resulting solution was washed with methyl tert-butyl ether. Then concentrated hydrochloric acid was added dropwise to the aqueous phase to pH = 1. The aqueous phase was extracted with methyl tert-butyl ether (3 × 20 mL), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain pure acid **DFPT-2** or **PFPO-2**.

3-diazo-1,1-difluoro-1-(phenylthio)propan-2-one (1A, DFPT-Diazo) or 3-diazo-1,1-difluoro-1-phenoxypropan-2-one (1B, DFPO-Diazo)

Under an argon atmosphere, the corresponding acid **DFPT-2** or **DFPO-2** (8 mmol, 1.0 equiv.), DMF (100 μL), and dichloromethane (15 mL) were added to a dry 50 mL round bottom flask equipped with a magnetic stir bar. A mixture of oxalyl chloride (0.9 ml, 9.6 mmol, 1.2 equiv.) in dichloromethane (5 mL) was added dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then concentrated in vacuo to remove excess oxalyl chloride. The corresponding acid chloride is directly used in the next reaction without purification.

Into a dry 250 mL round bottom flask equipped with a magnetic stir bar, CaO (1 g, 18 mmol, 2.2 equiv.), diazomethane methyl tert-butyl ether solution (from 3 g nitrosated methyl urea dissolved in 40 mL methyl tert-butyl Ether prepared[2]) were carefully added. The acid chloride prepared in the previous step was dissolved in 40 mL of methyl tert-butyl ether solution and added dropwise to the diazomethane ether solution at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight, then filtered, concentrated in vacuo, and purified by column chromatography (PE: EA=100:1) to obtain **1A** or **1B**.

Diazomethane can also be replaced by $TMSCHN_2$ (1.5 equiv., 12 mmol) in hexane. Under the same operation as above (without calcium oxide), **1A** (0.69g) and **1B** (0.41) were obtained with 37% and 24% yields, respectively.

1A yellow solid, 1.0 g, 55%, mp 49.8-53.1 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.70 – 7.53 (m, 2H), 7.53 – 7.43 (m, 1H), 7.39 (dd, *J* = 8.2, 6.6 Hz, 2H), 5.65 (s, 1H).**^{19}F NMR** (376 MHz, Chloroform-*d*) δ -83.13(s). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 181.5 (t, *J* = 29.9 Hz), 136.9, 130.7, 129.4, 124.7, 122.8 (t, *J* = 290.9 Hz), 55.1; **IR** (KBr, cm^{-1}) 3226, 2967,2121, 1637,1474,1436,1370, 948, 832, 747, 688; **HRMS** (ESI) m/z calcd. for $C_9H_6N_2OSF_2Na^+$ ($[M+Na]^+$): 251.0067, found 251.0066.

1B white solid, 0.98 g, 58%, mp 30.02-33.23 ºC; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 7.46 (t, *J* = 7.7 Hz, 2H), 7.35 - 7.26 (m, 3H), 6.80 (s, 1H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -77.23 (s). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 178.5 (t, *J* = 36.5 Hz), 148.8,

130.0, 126.6, 121.4, 115.0 (t, J = 272.0 Hz), 56.8; **IR** (KBr, cm^{-1}) 3125, 2982, 2125, 1634, 1494, 1386,1264, 1133, 887, 736, 690; **HRMS** (ESI) m/z calcd. for $C_9H_7N_2F_2O_2^+$ ($[M+H]^+$): 213.1428, found 213.1429.

Thermogravimetric (TG) and differential scanning calorimetry (DSC) analysis of diazo reagents 1A and 1B

Thermogravimetric (TG) analysis was performed on a METTLER TOLEDO thermogravimetric analyzer. The masses of samples (**1A**, **1B**) are all about 20 mg, and alumina crucibles were used. After equilibrating at 25 °C, the temperature was raised to 350 °C (**1A**, **1B**) at a rate of 3 °C min^{-1}.

Differential scanning calorimetry (DSC) analysis was performed on NETZSCH DSC 214. After equilibrating at 25 °C, the sample was heated to their maximum decomposition temperature at a rate of 10 °C min^{-1} under a nitrogen atmosphere.

DSC and TG analysis suggest that the initiating decomposition temperature is 133 °C for compound **1A**, and 142 °C for compound **1B**. These results indicate that both diazo reagents **1A** and **1B** are more stable than the benchmark ethyl diazoacetate (the decomposition temperature is around 100 °C for ethyl diazoacetate).[5]

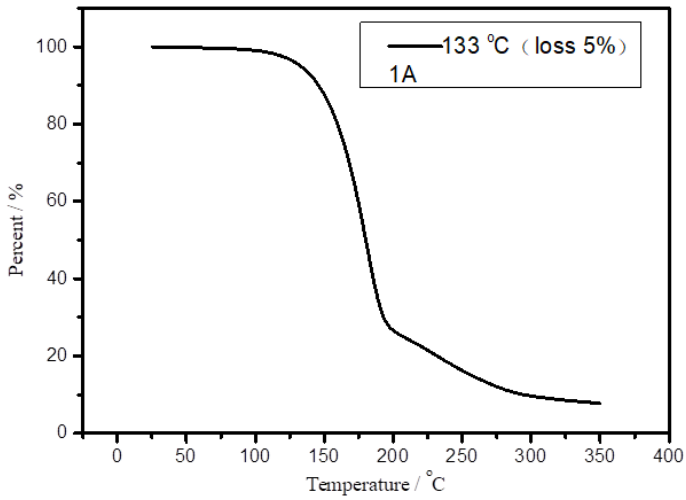


Figure S1 TG analysis curve of diazo **1A**

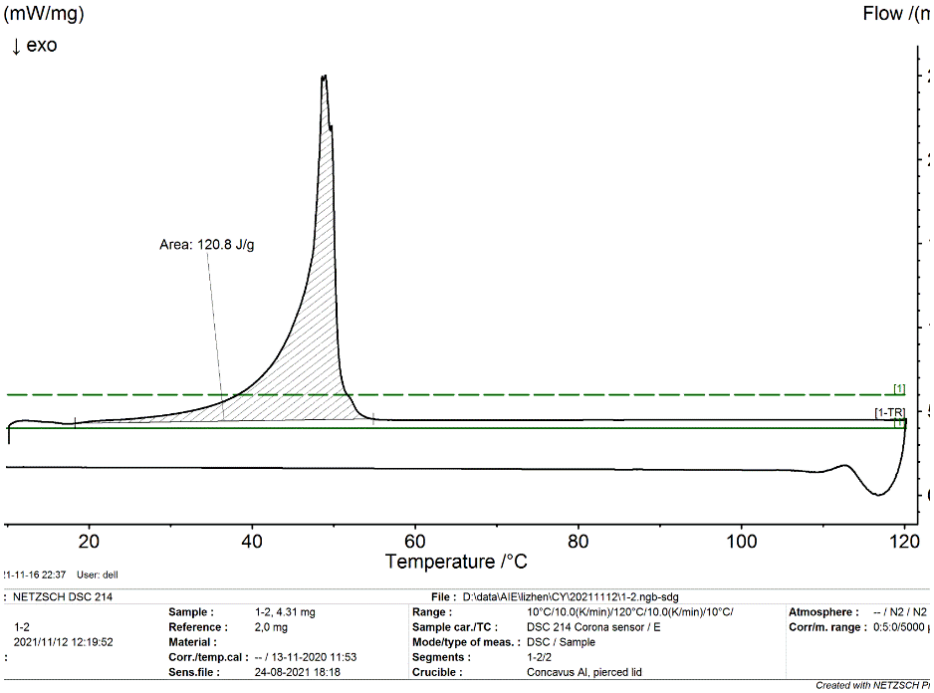


Figure S2 DSC analysis curve of diazo **1A**

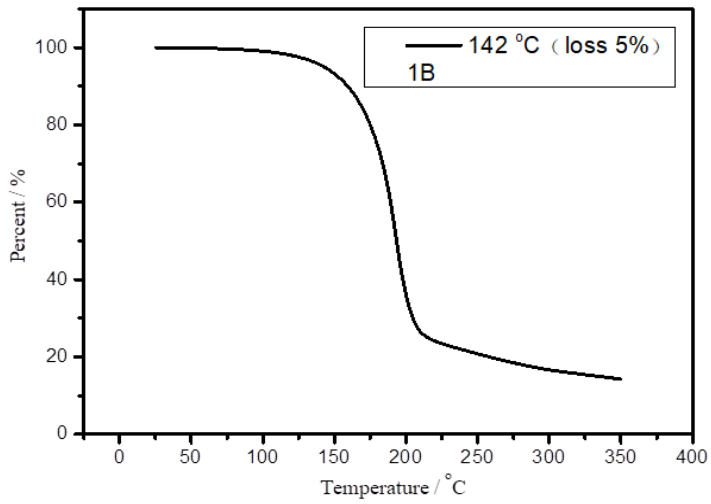


Figure S3 TG analysis curve of diazo **1B**

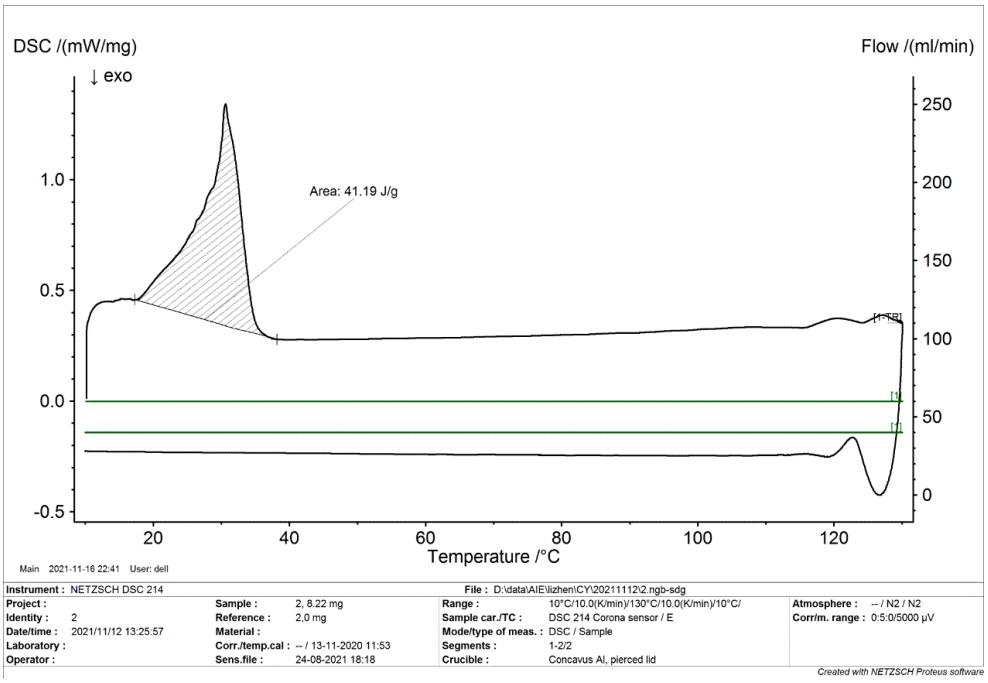
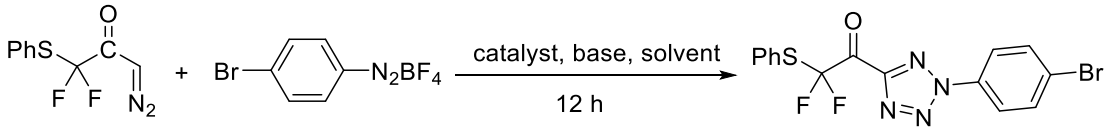


Figure S4 DSC analysis curve of diazo **1B**

Reaction Optimization



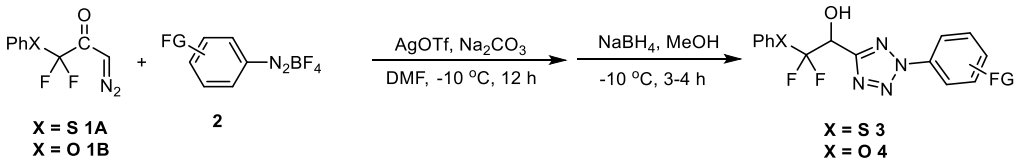
1A **2b** **3ba**

entry[a]	catalyst	base	solvent	T (°C)	yield (%)[b]
1	AgOAc	Na_2CO_3	CH_3CN	-10	72
2	AgOTf	Na_2CO_3	CH_3CN	-10	74
3	Ag_2O	Na_2CO_3	CH_3CN	-10	51
4	Ag_2CO_3	Na_2CO_3	CH_3CN	-10	56
5	AgF	Na_2CO_3	CH_3CN	-10	54
6	CF_3COOAg	Na_2CO_3	CH_3CN	-10	73
7	$AgNO_3$	Na_2CO_3	CH_3CN	-10	73
8	\	Na_2CO_3	CH_3CN	-10	nr
9	AgOAc	\	CH_3CN	-10	nr
10	AgOTf	Na_2CO_3	THF	-10	40
11	**AgOTf**	**Na_2CO_3**	**DMF**	**-10**	**81**
12[c]	AgOTf	Na_2CO_3	DMF	-10	58
13	AgOTf	Na_2CO_3	DCM	-10	15

14	AgOTf	Na_2CO_3	MeOH	-10	trace
15	AgOTf	Cs_2CO_3	DMF	-10	61
16	AgOTf	K_3PO_4	DMF	-10	44
17	AgOTf	KOAc	DMF	-10	64
18	AgOTf	DBU	CH_3CN	-10	20
19	AgOTf	Na_2CO_3	DMF	-30	58
20	AgOTf	Na_2CO_3	DMF	0	74

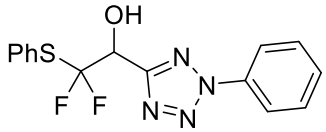
[a] General reaction conditions: **1A** (0.3 mmol), **2b** (0.2 mmol), silver catalyst (0.02 mmol), and base (0.4 mmol) in solvent (2 mL) were stirred for 12 h under air atmosphere unless otherwise labelled. [b] Isolated yields. "nr" indicates no reaction. [c] The amount of AgOTf is 0.01 mmol.

Synthesis of Phenylthiodifluoroalkyl Tetrazoles and Phenyloxydifluoroalkyl Tetrazoles



General procedure: A dry 10 mL Schlenk tube equipped with a magnetic stir bar is filled with **1A** or **1B** (0.3 mmol, 1.5 equiv.), aryl diazonium salt **2** (0.2 mmol, 1 equiv.), AgOTf (5 mg, 0.02 mmol, 0.1 equiv.) and Na_2CO_3 (42.3 mg, 0.4 mmol, 2 equiv.), and then dry DMF (2 mL) was added via a syringe. The resulting mixture was stirred at -10 °C for 12 h. After the reaction, 2 mL of methanol and $NaBH_4$ (220 mg, 0.6 mmol, 3 equiv.) were subsequently added. The reaction mixture continued to stir at -10 °C for 3 h. After the reaction was completed, it was quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic phase was washed with water and saturated brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography with eluent (EtOAc/petroleum ether) to give difluoroalkyltetrazolium **3** or **4**.

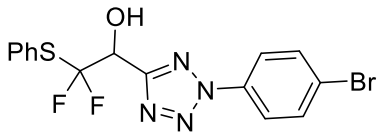
2,2-difluoro-1-(2-phenyl-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3a)



3a

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (49 mg, 74%) using EtOAc/petroleum ether (1:4) as eluent. mp 104.9-107.3 °C; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 7.6 Hz, 2H), 7.73 – 7.60 (m, 2H), 7.59 – 7.45 (m, 3H), 7.46 – 7.29 (m, 3H), 5.74 – 5.15 (m, 1H), 4.11 (d, *J* = 7.8 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.53 (d, *J* = 214.7 Hz), -85.59 (d, *J* = 215.0 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.4, 136.8, 136.7, 130.3, 129.8, 129.3, 127.6 (t, *J* = 285.8 Hz), 125.4 (t, *J* = 2.6 Hz), 120.2, 69.7 (dd, *J* = 30.3, 28.4 Hz); **IR** (KBr, cm^{-1}) 3403, 3210, 2929, 1595, 1515, 1492, 1267, 1154, 1061, 1005, 961, 817, 752, 679, 628; **HRMS** (ESI) m/z calcd. for $C_{15}H_{13}N_4OF_2S^+$ ([M+H]$^+$): 335.0778, found 335.0779.

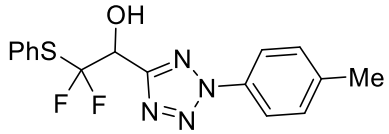
1-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3b)



3b

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (58 mg, 78%) using EtOAc/petroleum ether (1:4) as eluent. mp 117.7-118.9 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.04 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 7.66 – 7.53 (m, 2H), 7.41 – 7.50 (m, 3H), 5.51 (ddd, *J* = 11.1, 9.1, 6.5 Hz, 1H), 3.41 (s, 1H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -80.69 (d, *J* = 208.0 Hz), -82.82 (d, *J* = 208.2 Hz). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 163.4, 136.3, 135.1, 133.2, 130.3, 129.4, 128.0 (t, *J* = 285.2 Hz),125.1, 123.3, 121.8, 68.4 (t, *J* = 28.3 Hz); **IR** (KBr, cm^{-1}) 3334, 3228, 2978, 1501, 1451, 1345, 1203, 1163, 1122, 1077, 995, 819, 761, 710, 680,629, 584; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4OF_2SBr^+$ ([M+H]$^+$): 412.9883, found 412.9882.

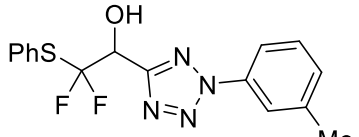
2,2-difluoro-2-(phenylthio)-1-(2-(p-tolyl)-2*H*-tetrazol-5-yl)ethan-1-ol (3c)



3c

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (55 mg, 79 %) using EtOAc/petroleum ether (1:5) as eluent. mp 101.6-103.8 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 6.8 Hz, 2H), 7.49 – 7.28 (m, 5H), 5.46 (t, *J* = 9.5 Hz, 1H), 4.09 (s, 1H), 2.43 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.50 (d, *J* = 214.6 Hz), -85.58 (d, *J* = 214.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.2, 140.7, 136.8, 134.5, 130.3, 130.3, 129.3, 127.6 (t, *J* = 285.9 Hz), 125.4, 120.1, 69.7 (dd, *J* = 30.3, 28.4 Hz), 21.3; **IR** (KBr, cm^{-1}) 3419, 3079, 2922, 1595, 1531, 1508, 1439, 1343,1209, 1154, 1063, 991, 824, 747, 690; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4OF_2S^+$ ([M+H]$^+$): 349.0935, found 349.0933.

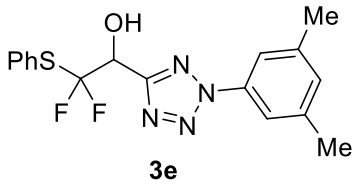
2,2-difluoro-2-(phenylthio)-1-(2-(m-tolyl)-2*H*-tetrazol-5-yl)ethan-1-ol (3d)



3d

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (54 mg, 77%) using EtOAc/petroleum ether (1:4) as eluent. mp 78.7-82.3 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 – 7.76 (m, 2H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.50 – 7.28 (m, 5H), 5.45 (t, *J* = 10.0 Hz, 1H), 3.99 (d, *J* = 8.1 Hz, 1H), 2.46 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.50 (dt, *J* = 214.7, 4.5 Hz), -85.70 (dt, *J* = 214.6, 4.0 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.2, 140.2, 136.8, 136.6, 131.1, 130.3, 129.6, 129.3, 127.6 (t, *J* = 285.8 Hz), 125.4 (t, *J* = 2.6 Hz), 120.7, 117.4, 69.7 (dd, *J* = 30.5, 28.4 Hz), 21.5; **IR** (KBr, cm^{-1}) 3419, 3226, 2980, 1602, 1494, 1439,1171, 1088, 1061, 987, 858, 792, 690, 628; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4OF_2S^+$ ([M+H]$^+$): 349.0935, found 349.0935.

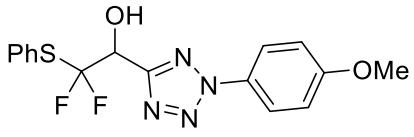
1-(2-(3,5-dimethylphenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3e)



3e

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (46 mg, 64%) using EtOAc/petroleum ether (1:4) as eluent. mp 105.2-107.6 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 (s, 2H), 7.69 – 7.61 (m, 2H), 7.49 – 7.30 (m, 3H), 7.13 (s, 1H), 5.43 (t, *J* = 9.6 Hz, 1H), 3.97 – 3.60 (m, 1H), 2.42 (s, 6H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.56 (d, *J* = 214.7 Hz), -85.89 (d, *J* = 214.9 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.1, 139.9, 136.9, 136.6, 131.9, 130.4, 129.4, 127.6 (t, *J* = 286.0 Hz), 125.4, 117.9, 69.8 (dd, *J* = 30.4, 28.3 Hz), 21.4; **IR** (KBr, cm^{-1}) 3242, 2978, 1621, 1474, 1303, 1216, 1173, 1065, 972, 860, 821, 747, 677, 580; **HRMS** (ESI) m/z calcd. for $C_{17}H_{17}N_4OF_2S^+$ ([M+H]$^+$): 363.1091, found 363.1093.

2,2-difluoro-1-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3f)

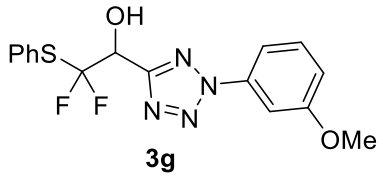


3f

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (45 mg, 62%) using EtOAc/petroleum ether (1:5) as eluent.; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 9.2 Hz, 2H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.48 – 7.29 (m, 3H), 7.12 – 6.82 (m, 2H), 5.47 (dd, *J* = 11.4, 7.5 Hz, 1H), 4.39 (s, 1H), 3.85 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.40 (d, *J* = 214.3 Hz), -85.42 (d, *J* = 214.1 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.0, 160.8, 136.7, 130.1, 130.0, 129.1, 127.5 (t, *J* = 285.8 Hz), 125.3 (t, *J* = 2.6 Hz), 121.6, 114.7, 69.6 (dd, *J* = 30.4, 28.3 Hz), 55.7; **IR** (KBr, cm^{-1}) 3425, 3226, 2916, 1604, 1513, 1439, 1324, 1256, 1165, 1063, 998, 835, 745, 686; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_2F_2S^+$

([M+H]$^+$): 365.0884, found 365.0882.

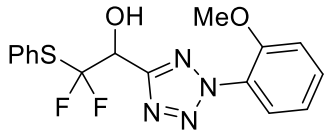
2,2-difluoro-1-(2-(3-methoxyphenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3g)



3g

Using the general procedure, the titled compound was obtained as a red solid after column chromatography (59 mg, 81%) using EtOAc/petroleum ether (1:5) as eluent. mp 94.8-95.9 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.82 – 7.52 (m, 4H), 7.53 – 7.30 (m, 4H), 7.03 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.47 (dd, *J* = 11.5, 7.5 Hz, 1H), 4.26 (s, 1H), 3.88 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.47 (d, *J* = 214.5 Hz), -85.56 (d, *J* = 214.6 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.3, 160.6, 137.5, 136.8, 130.7, 130.3, 129.3, 127.4 (t, *J* = 285.9 Hz), 125.3 (t, *J* = 2.6 Hz), 116.5, 112.3, 105.6, 69.7 (dd, *J* = 30.3, 28.4 Hz), 55.8; **IR** (KBr, cm^{-1}) 3329, 2929, 1610, 1494, 1241, 1165, 1040, 989, 851, 821, 779, 750, 679; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_2F_2S^+$ ([M+H]$^+$): 365.0884, found 365.0883.

2,2-difluoro-1-(2-(2-methoxyphenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3h)

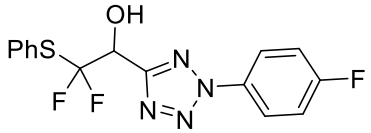


3h

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (45 mg, 62%) using EtOAc/petroleum ether (1:5) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.50 (dd, *J* = 7.6, 5.2 Hz, 2H), 7.44 – 7.28 (m, 3H), 7.16 – 6.95 (m, 2H), 5.48 (dd, *J* = 12.1, 7.1 Hz, 1H), 4.33 (s, 1H), 3.80 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.19 (d, *J* = 214.0 Hz), -85.78 (d, *J* = 213.9 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 161.9, 153.4, 136.8, 132.4, 130.2, 129.2, 127.6 (t, *J* = 285.8 Hz), 127.0, 125.9, 125.4 (t, *J* = 2.6 Hz),

120.7, 112.9, 69.6 (dd, J = 30.5, 28.1 Hz), 56.3; **IR** (KBr, cm^{-1}) 3219, 2978, 1602, 1513, 1324, 1283,1253, 1163, 1124, 1058, 998, 824,747, 686; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_2F_2S^+$ ($[M+H]^+$): 365.0884, found 365.0882.

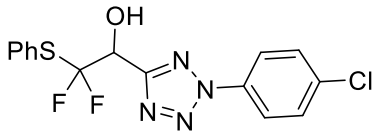
2,2-difluoro-1-(2-(4-fluorophenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3i)



3i

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (50 mg, 71%) using EtOAc/petroleum ether (1:4) as eluent. mp 87.3-90.2 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.12 – 7.92 (m, 2H), 7.66 – 7.45 (m, 2H), 7.42 – 7.22 (m, 3H), 7.22 – 7.09 (m, 2H), 5.36 (dd, J = 11.4, 7.3 Hz, 1H), 3.76 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.65 (d, J = 215.0 Hz), -85.82 (d, J = 215.3 Hz), -109.64(s). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.4 (d, J = 251.1 Hz), 162.5, 136.8, 132.9 (d, J = 3.2 Hz), 130.4, 129.4, 127.5 (t, J = 286.8 Hz), 125.3, 122.3 (d, J = 8.8 Hz), 117.0 (d, J = 23.5 Hz), 69.7 (dd, J = 30.5, 28.5 Hz). **IR** (KBr, cm^{-1}) 3230, 2924, 1593, 1506, 1230, 1169, 1080, 974, 842, 755, 690, 620; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4OF_3S^+$ ($[M+H]^+$): 353.0684, found 353.0683.

1-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3j)

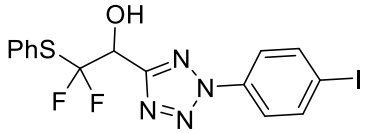


3j

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (60 mg, 82%) using EtOAc/petroleum ether (1:4) as eluent. mp 104.5-106.1 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.05 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 7.4 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.44 – 7.28 (m, 3H), 5.49 (q, J = 11.9, 10.5 Hz, 1H), 4.35 (d, J = 7.5 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.37 (d, J = 214.5 Hz), -85.52 (d, J = 214.8 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.6, 136.8, 136.2, 135.0, 130.3, 130.0, 129.3, 127.5 (t, J = 286.8 Hz), 125.2 (t, J =

2.5 Hz), 121.4, 69.6 (dd, *J* = 30.5, 28.4 Hz); **IR** (KBr, cm^{-1}) 3393, 3070,2952, 1593, 1538, 1496, 1409, 1296, 1218, 1159, 1088, 1067, 987, 821, 688; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4OF_2SCl^+$ ($[M+H]^+$): 369.0388, found 369.0388.

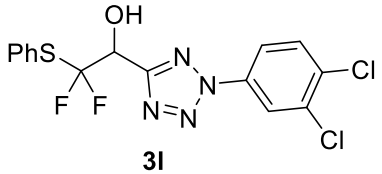
2,2-difluoro-1-(2-(4-iodophenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3k)



3k

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (71 mg, 77%) using EtOAc/petroleum ether (1:4) as eluent. mp 119.1-121.3 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.08 – 7.73 (m, 4H), 7.73 – 7.51 (m, 2H), 7.51 – 7.29 (m, 3H), 5.58 – 5.11 (m, 1H), 3.90 (d, *J* = 8.1 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.57 (d, *J* = 215.0 Hz), -85.74 (d, *J* = 215.3 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.5, 139.0, 136.8, 136.2, 130.4, 129.4, 127.5 (t, *J* = 285.9 Hz), 125.2, 121.7, 95.9, 69.7 (t, *J* = 29.3 Hz). **IR** (KBr, cm^{-1}) 3425, 3077, 2922, 1596, 1529, 1508, 1336, 1212, 1065, 989, 826, 747, 690; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4OF_2SI^+$ ($[M+H]^+$): 460.9745, found 460.9740.

1-(2-(3,4-dichlorophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3l)

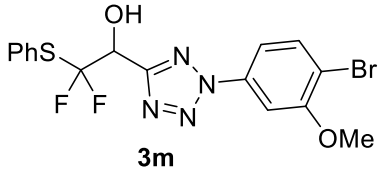


3l

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (56 mg, 70%) using EtOAc/petroleum ether (1:4) as eluent. mp 110.9-112.4 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 2.4 Hz, 1H), 7.99 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.73 – 7.50 (m, 3H), 7.50 – 7.28 (m, 3H), 5.46 (t, *J* = 9.0 Hz, 1H), 4.07 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.44 (d, *J* = 215.2 Hz), -85.76 (d, *J* = 215.3 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.8, 136.8, 135.4, 134.7, 134.3, 131.7, 130.4, 129.4, 127.4 (t, *J* = 285.8 Hz), 125.2, 122.0, 119.2,

69.6 (dd, *J* = 30.6, 28.4 Hz); **IR** (KBr, cm^{-1}) 3416, 3077, 2922, 1595, 1533, 1508, 1343, 1212, 1110, 1061, 989, 828, 783, 752, 690; **HRMS** (ESI) m/z calcd. for $C_{15}H_{11}N_4OF_2SCl_2^+$ ($[M+H]^+$): 402.9999, found 402.9997.

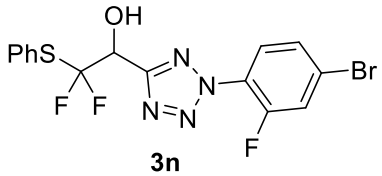
1-(2-(4-bromo-3-methoxyphenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3m)



3m

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (67 mg, 76%) using EtOAc/petroleum ether (1:4) as eluent. mp 104.9-106.9 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.75 – 7.49 (m, 5H), 7.49 – 7.29 (m, 3H), 5.46 (dd, *J* = 11.2, 6.8 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.43 (d, *J* = 214.9 Hz), -85.72 (d, *J* = 214.9 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.5, 157.0, 136.8, 136.6, 134.3, 130.4, 129.4, 127.5 (t, *J* = 286.4 Hz), 125.2 (t, *J* = 2.7 Hz), 113.8, 113.0, 103.8, 69.7 (dd, *J* = 30.5, 28.3 Hz), 56.9; **IR** (KBr, cm^{-1}) 3370, 3302, 2982, 1602, 1489, 1417, 1256, 1046, 998, 874, 844, 750, 720, 690, 580; **HRMS** (ESI) m/z calcd. for $C_{16}H_{14}N_4O_2F_2SBr^+$ ($[M+H]^+$): 442.9989, found 442.9992.

1-(2-(4-bromo-2-fluorophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-(phenylthio)ethan-1-ol (3n)

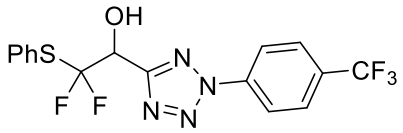


3n

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (62 mg, 72%) using EtOAc/petroleum ether (1:5) as eluent. mp 96.7-98.0 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.73 (t, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.50 (dd, *J* = 22.6, 9.2 Hz, 2H), 7.36 (dt, *J* = 14.8, 7.3 Hz, 3H), 5.81 – 5.20 (m, 1H), 4.44 (d, *J* = 7.8 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.40 (d, *J* = 214.9 Hz), -85.54 (d, *J* = 215.3 Hz), -116.96. **^{13}C NMR** (101 MHz,

Chloroform-*d*) δ 162.6, 154.2 (d, *J* = 263.3 Hz), 136.7, 130.3, 129.3, 128.5 (d, *J* = 4.0 Hz), 127.4, 126.3, 125.2 (t, *J* = 2.5 Hz), 125.0 (d, *J* = 8.3 Hz), 124.0 (d, *J* = 10.3 Hz), 121.4 (d, *J* = 22.1 Hz), 69.5 (dd, *J* = 30.4, 28.3 Hz); **IR** (KBr, cm^{-1}) 3260, 3058, 2920, 1593, 1506, 1419, 1235, 1165, 1055, 993, 879, 817, 750, 690; **HRMS** (ESI) m/z calcd. for $C_{15}H_{11}N_4OF_3SBr^+$ ($[M+H]^+$): 430.9789, found 430.9786.

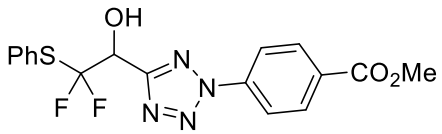
2,2-difluoro-2-(phenylthio)-1-(2-(4-(trifluoromethyl)phenyl)-2*H*-tetrazol-5-yl)ethan-1-ol (3o)



3o

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (64 mg, 79%) using EtOAc/petroleum ether (1:6) as eluent. mp 86.2-87.3 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 7.0 Hz, 2H), 7.44 – 7.29 (m, 3H), 5.55 (dt, *J* = 11.2, 7.7 Hz, 1H), 4.58 (d, *J* = 8.1 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.78, -82.32 (d, *J* = 214.7 Hz), -85.42 (d, *J* = 214.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.9, 138.8, 136.8, 132.2 (q, *J* = 33.2 Hz), 130.3, 129.3, 127.5 (t, *J* = 285.8 Hz), 127.2 (q, *J* = 3.8 Hz), 125.2 (t, *J* = 2.4 Hz), 123.5 (q, *J* = 272.4 Hz). 120.4, 69.6 (dd, *J* = 30.5, 28.4 Hz); **IR** (KBr, cm^{-1}) 3408, 3079, 2922, 1614, 1439, 1379, 1175, 1118, 1065, 991, 851, 747, 692, 626; **HRMS** (ESI) m/z calcd. for $C_{16}H_{12}N_4OF_5S^+$ ($[M+H]^+$): 403.0652, found 403.0651.

methyl 4-(5-(2,2-difluoro-1-hydroxy-2-(phenylthio)ethyl)-2*H*-tetrazol-2-yl)benzoate (3p)

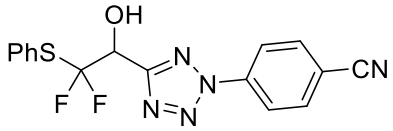


3p

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (59 mg, 75%) using EtOAc/petroleum ether (1:3) as eluent; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.24 – 8.10 (m, 4H), 7.66 – 7.53 (m, 2H),

7.44 – 7.29 (m, 3H), 5.50 (dd, *J* = 11.2, 7.8 Hz, 1H), 4.37 (s, 1H), 3.95 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.42 (d, *J* = 215.1 Hz), -85.45 (d, *J* = 215.1 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 162.8, 139.4, 136.7, 131.6, 131.3, 130.3, 129.3, 127.5 (t, *J* = 285.8 Hz), 125.2 (t, *J* = 2.5 Hz), 119.9, 69.6 (dd, *J* = 30.5, 28.4 Hz), 52.7; **IR** (KBr, cm^{-1}) 3416, 3062, 2954, 1720, 1606, 1513, 1439, 1275, 1171, 1058, 998, 860, 828, 764, 750, 690; **HRMS** (ESI) m/z calcd. for $C_{17}H_{15}N_4O_3F_2S^+$ ([M+H]$^+$): 393.0833, found 393.0836.

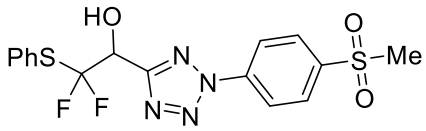
4-(5-(2,2-difluoro-1-hydroxy-2-(phenylthio)ethyl)-2*H*-tetrazol-2-yl)benzonitrile (3q)



3q

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (57 mg, 72%) using EtOAc/petroleum ether (1:3) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.28 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.50 – 7.29 (m, 3H), 5.75 – 5.15 (m, 1H), 4.18 (d, *J* = 6.6 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.35 (d, *J* = 214.8 Hz), -85.39 (d, *J* = 215.0 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.0, 139.0, 136.7, 134.0, 130.3, 129.3, 127.4 (t, *J* = 285.9 Hz)., 125.1 (t, *J* = 2.6 Hz), 120.6, 117.5, 113.9, 69.5 (dd, *J* = 30.5, 28.4 Hz); **IR** (KBr, cm^{-1}) 3315, 3056, 2922, 2231, 1606, 1508, 1413, 1306, 1186, 1154, 1085, 1065, 991, 851, 826, 792, 750, 695, 622; **HRMS** (ESI) m/z calcd. for $C_{16}H_{12}N_5OF_2S^+$ ([M+H]$^+$): 360.0731, found 360.0733.

2,2-difluoro-1-(2-(4-(methylsulfonyl)phenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3r)

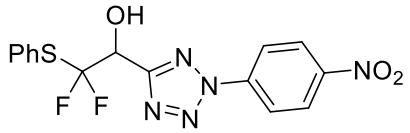


3r

Using the general procedure, the titled compound was obtained as a white solid

after column chromatography (69 mg, 84%) using EtOAc/petroleum ether (1:1) as eluent. mp 114.1-115.5 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.38 (d, J = 8.6 Hz, 2H), 8.24 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 6.7 Hz, 2H), 7.51 – 7.43 (m, 3H), 5.54 (ddd, J = 11.2, 9.0, 6.5 Hz, 1H), 3.36 (s, 1H), 3.34 (s, 3H). **^{19}F NM**R (376 MHz, DMSO-d_6) δ -80.57 (d, J = 208.3 Hz), -82.78 (d, J = 208.4 Hz). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 163.6, 142.0, 138.9, 136.2, 130.3, 129.4, 129.4, 128.0 (t, J = 285.8 Hz), 125.0, 120.7, 68.4 (t, J = 28.3 Hz), 43.3; **IR** (KBr, cm^{-1}) 3421, 3251, 2994, 1667, 1591, 1309, 1154, 1048, 815, 760, 614; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_3F_2S_2^+$ ([M+H]$^+$): 413.0554, found 413.0552.

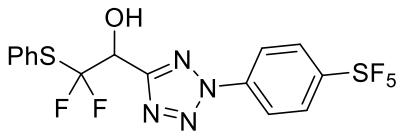
2,2-difluoro-1-(2-(4-nitrophenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3s)



3s

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (54 mg, 71%) using EtOAc/petroleum ether (1:3) as eluent. mp 127.2-129.1 °C; **^{1}H NMR** (400 MHz, Chloroform-d) δ 8.52 – 8.42 (m, 2H), 8.41 – 8.30 (m, 2H), 7.64 (dd, J = 7.0, 1.9 Hz, 2H), 7.51 – 7.32 (m, 3H), 5.46 (dt, J = 11.3, 7.3 Hz, 1H), 3.64 (d, J = 8.4 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-d) δ -82.64 (d, J = 216.0 Hz), -85.99 (d, J = 216.0 Hz). **^{13}C NMR** (101 MHz, Chloroform-d) δ 163.2, 148.4, 140.4, 136.8, 130.5, 129.5, 127.4 (t, J = 286.8 Hz), 125.7, 125.1, 120.8, 69.7 (dd, J = 30.6, 28.5 Hz); **IR** (KBr, cm^{-1}) 3313, 3118, 2927, 1610, 1531, 1510, 1413, 1343, 1311, 1061, 984, 851, 745, 622; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_5O_3F_2S^+$ ([M+H]$^+$): 380.0629, found 380.0626.

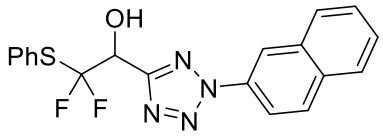
2,2-difluoro-1-(2-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3t)



3t

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (54 mg, 59%) using EtOAc/petroleum ether (1:4) as eluent. mp 87.6-92.5 °C;**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.26 (d, *J* = 8.9 Hz, 2H), 8.08 – 7.87 (m, 2H), 7.72 – 7.57 (m, 2H), 7.38 (ddd, *J* = 17.3, 8.1, 6.4 Hz, 3H), 5.48 (dd, *J* = 11.4, 7.3 Hz, 1H), 4.02 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ 82.54 (quintet, *J* = 150.4 Hz), 62.94 (d, *J* = 150.3 Hz), -82.58 (d, *J* = 215.3 Hz), -85.73 (d, *J* = 215.1 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.0, 154.5 (t, *J* = 18.9 Hz), 138.1, 136.8, 129.4, 128.7 – 127.8 (m), 127.5 (t, *J* = 285.9 Hz), 125.1 (d, *J* = 2.7 Hz), 120.3, 69.7 (dd, *J* = 30.5, 28.5 Hz); **IR** (KBr, cm^{-1}) 3421, 3075, 2952, 1579, 1508, 1407, 1101, 1063, 989, 821, 750, 713, 690, 665, 578; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4OF_7S_2^+$ ([M+H]$^+$): 461.0341, found 461.0342.

2,2-difluoro-1-(2-(naphthalen-2-yl)-2*H*-tetrazol-5-yl)-2-(phenylthio)ethan-1-ol (3u)

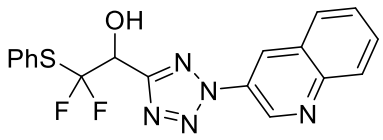


3u

Using the general procedure, the titled compound was obtained as a brown oil after column chromatography (35 mg, 45%) using EtOAc/petroleum ether (1:3) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.52 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 9.0, 2.2 Hz, 1H), 8.02 – 7.76 (m, 3H), 7.67 (d, *J* = 7.3 Hz, 2H), 7.55 (dd, *J* = 6.3, 3.3 Hz, 2H), 7.47 – 7.28 (m, 3H), 5.59 (dt, *J* = 11.5, 7.8 Hz, 1H), 4.54 (d, *J* = 8.2 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.11 (d, *J* = 214.4 Hz), -85.35 (d, *J* = 214.4 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.5, 136.8, 133.8, 133.6, 132.9, 130.2, 130.0, 129.3, 128.7, 128.0, 127.7, 127.7, 127.6 (t, *J* = 285.6 Hz), 125.4 (t, *J* = 2.5 Hz), 118.7, 117.7, 69.7 (dd, *J* = 30.4, 28.3 Hz); **IR** (KBr, cm^{-1}) 3363, 3302, 2978, 1604, 1487, 1417, 1258, 1212, 1159, 1110, 1053, 995, 876, 844, 777, 750, 722, 688, 584; **HRMS** (ESI)

m/z calcd. for $C_{19}H_{15}N_4OF_2S^+$ ([M+H]$^+$): 385.0935, found 385.0932.

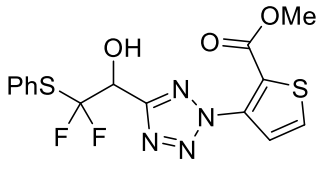
2,2-difluoro-2-(phenylthio)-1-(2-(quinolin-3-yl)-2*H*-tetrazol-5-yl)ethan-1-ol (3v)



3v

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (32 mg, 41%) using EtOAc/petroleum ether (1:3) as eluent. mp 172.4-174.6 ºC; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.57 (d, J = 2.6 Hz, 1H), 9.13 (d, J = 2.6 Hz, 1H), 8.28 (dd, J = 8.4, 1.4 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.90 (ddd, J = 8.5, 6.8, 1.5 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.68 – 7.55 (m, 2H), 7.52 – 7.45 (m, 3H), 5.56 (ddd, J = 11.5, 8.9, 6.5 Hz, 1H), 3.37 (s, 1H). **^{19}F NMR** (376 MHz, DMSO-d_6) δ -80.47 (d, J = 208.3 Hz), -82.83 (d, J = 208.4 Hz). **^{13}C NMR** (101 MHz, DMSO-d_6) δ 163.5, 147.5, 142.0, 136.2, 131.3, 130.2, 129.5, 129.4, 129.1, 128.9, 128.3, 128.0 (t, J = 285.2 Hz), 126.7, 126.6, 125.1, 68.8 – 67.9 (m); **IR** (KBr, cm^{-1}) 3368, 3060, 2943, 1680, 1612, 1494, 1434, 1303, 1165, 1055, 982, 953, 785, 745, 690; **HRMS** (ESI) m/z calcd. for $C_{18}H_{14}N_5OF_2S^+$ ([M+H]$^+$): 386.0887, found 386.0883.

Methyl 3-(5-(2,2-difluoro-1-hydroxy-2-(phenylthio)ethyl)-2*H*-tetrazol-2-yl)thiophene-2-carboxylate (3w)

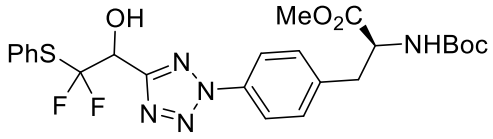


3w

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (37 mg, 46%) using EtOAc/petroleum ether (1:3) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.77 – 7.57 (m, 3H), 7.50 – 7.28 (m, 4H), 5.46 (t, J = 9.9 Hz, 1H), 4.33 (s, 1H), 3.73 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.17 (d, J = 214.5 Hz), -86.05 (d, J = 214.4 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.2, 160.0, 136.8, 135.9, 131.1, 130.3, 129.3, 128.5, 127.6 (t, J = 285.7 Hz), 126.4, 125.3 (d, J = 2.6 Hz), 69.5 (dd, J = 30.6, 28.0 Hz), 52.9; **IR** (KBr,

cm^{-1}) 3419, 3113, 2952, 1722, 1554, 1434, 1328, 1256, 1161, 1061,998, 895, 771, 750, 690; **HRMS** (ESI) m/z calcd. for $C_{15}H_{13}N_4O_3F_2S_2^+$ ([M+H]$^+$): 399.0397, found 399.0395.

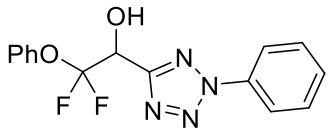
Methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-(5-(2,2-difluoro-1-hydroxy-2-(phenylthio)ethyl)-2*H*-tetrazol-2-yl)phenyl)propanoate (3x)



3x

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (44 mg, 41%) using EtOAc/petroleum ether (1:4) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.45 – 7.28 (m, 5H), 5.45 (dd, *J* = 11.2, 7.7 Hz, 1H), 5.16 (d, *J* = 8.2 Hz, 1H), 4.62 (d, *J* = 7.1 Hz, 1H), 4.47 (s, 1H), 3.71 (s, 3H), 3.16 (dd, *J* = 32.0, 16.0 Hz, 2H), 1.40 (s, 9H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -82.50 (d, *J* = 213.8 Hz), -85.34 (d, *J* = 214.2 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 172.1, 162.5, 155.2, 138.8, 136.8, 135.6, 130.7, 130.3, 129.3, 127.6 (t, *J* = 285.7 Hz), 125.4, 120.2, 80.4, 69.6 (t, *J* = 29.4 Hz), 54.4, 52.6, 38.1, 28.4; **IR** (KBr, cm^{-1}) 3425, 3079, 2925, 1733, 1697, 1595, 1533, 1508, 1338, 1212, 1156, 1061, 991, 826, 747, 692, 624; **HRMS** (ESI) m/z calcd. for $C_{24}H_{28}N_5O_5F_2S^+$ ([M+H]$^+$): 536.1779, found 536.1773.

2,2-difluoro-2-phenoxy-1-(2-phenyl-2*H*-tetrazol-5-yl)ethan-1-ol (4a)

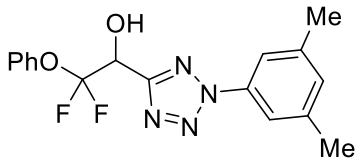


4a

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (52 mg, 82%) using EtOAc/petroleum ether (1:5) as eluent. mp 68.6-69.1 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.15 (dd, *J* = 7.4, 1.9 Hz, 2H), 7.48 - 7.57 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.11 (m, 3H), 5.62 (d, *J* = 6.3 Hz, 1H), 4.22 (d, *J* = 6.5 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.61 (d,

J = 140.6 Hz), -81.21 (d, *J* = 140.7 Hz).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.6, 149.7, 136.7, 130.3, 129.9, 129.6, 126.1, 121.9, 121.4 (t, *J* = 272.0 Hz), 120.2, 68.2 (t, *J* = 34.7 Hz); **IR** (KBr, cm^{-1}) 3221, 2973, 1593, 1253, 1165, 1069, 1003, 862, 824, 764, 739, 679; **HRMS** (ESI) m/z calcd. for $C_{15}H_{13}N_4O_2F_2^+$ ($[M+H]^+$): 319.1007, found 319.1003.

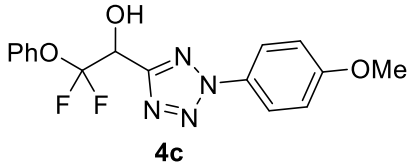
1-(2-(3,5-dimethylphenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-phenoxyethan-1-ol (4b)



4b

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (44 mg, 63%) using EtOAc/petroleum ether (1:4) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.75 (s, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.24 – 7.05 (m, 4H), 5.82 – 5.41 (m, 1H), 4.39 (s, 1H), 2.40 (s, 6H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.57 (d, *J* = 140.7 Hz), -81.17 (d, *J* = 144.0 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.3, 149.8 (d, *J* = 1.9 Hz), 139.9, 136.6, 131.9, 129.5, 126.0, 121.9, 121.4 (t, *J* = 272.0 Hz), 117.9, 68.2 (t, *J* = 34.7 Hz), 21.4; **IR** (KBr, cm^{-1}) 3428, 3205, 2925, 1618, 1593, 1494, 1251, 1159, 1063, 1016, 858, 736, 681, 546; **HRMS** (ESI) m/z calcd. for $C_{17}H_{17}N_4O_2F_2^+$ ($[M+H]^+$): 347.1320, found 347.1319.

2,2-difluoro-1-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)-2-phenoxyethan-1-ol (4c)

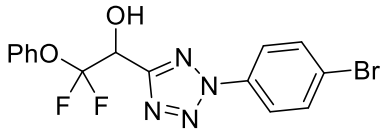


4c

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (43 mg, 61%) using EtOAc/petroleum ether (1:4) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 9.2 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.07 (t, *J* = 6.9 Hz, 3H), 6.96 – 6.82 (m, 2H), 5.54 (t, *J* = 6.3 Hz, 1H), 4.61 (s, 1H), 3.73 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.53 (d, *J* = 140.3 Hz), -

81.10 (d, J = 140.6 Hz).**^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.3, 160.9, 149.8, 130.2, 129.5, 126.0, 121.9, 121.7, 121.5 (t, J = 272.0 Hz), 114.8, 68.1 (t, J = 34.6 Hz), 55.8; **IR** (KBr, cm^{-1}) 3336, 2922, 1604, 1591, 1517, 1487, 1462, 1248, 1161, 1061, 1012, 1000, 828, 688, 620; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_3F_2^+$ ([M+H]$^+$): 349.1112, found 349.1114.

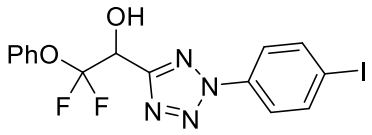
1-(2-(4-bromophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoro-2-phenoxyethan-1-ol (4d)



4d

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (50 mg, 64%) using EtOAc/petroleum ether (1:4) as eluent. mp 86.5-87.7 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.03 (d, J = 8.9 Hz, 2H), 7.68 (d, J = 8.9 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.25 – 7.11 (m, 3H), 5.61 (t, J = 6.2 Hz, 1H), 4.21 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.59 (d, J = 140.3 Hz), -81.15 (d, J = 140.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.7, 149.7 (d, J = 2.3 Hz), 135.6, 133.1, 129.6, 126.1, 124.3, 121.8, 121.6, 121.3 (t, J = 272.0 Hz), 68.2 (t, J = 34.7 Hz); **IR** (KBr, cm^{-1}) 3380, 3232, 2971, 1589, 1487, 1251, 1171, 1063, 1005, 868, 832, 757, 722, 690, 555, 516; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4O_2F_2Br^+$ ([M+H]$^+$): 397.0112, found 397.0115.

2,2-difluoro-1-(2-(4-iodophenyl)-2*H*-tetrazol-5-yl)-2-phenoxyethan-1-ol (4e)

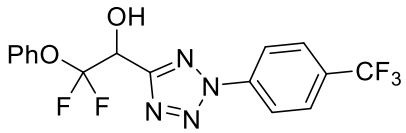


4e

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (49 mg, 55%) using EtOAc/petroleum ether (1:4) as eluent. mp 122.6-123.8 ºC; **^{1}H NMR** (400 MHz, DMSO-*d*$_6$) δ 8.05 (d, J = 8.4 Hz, 2H), 7.92 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 7.7 Hz, 2H), 7.34 – 7.24 (m, 2H), 7.18 (d, J = 8.1 Hz, 1H), 5.62 (dt, J = 9.3, 6.5 Hz, 1H), 3.36 (s, 1H). **^{19}F NMR** (376 MHz, DMSO-*d*$_6$)

δ -78.84 (d, *J* = 139.0 Hz), -80.32 (d, *J* = 139.0 Hz). **^{13}C NMR** (101 MHz, DMSO-*d*$_6$) δ 163.4, 149.2, 139.0, 135.6, 129.8, 126.1, 121.8, 121.7 (t, *J* = 272.7), 121.7, 96.7, 66.4 (t, *J* = 33.1 Hz); **IR** (KBr, cm^{-1}) 3359, 3100, 2922, 1586, 1487, 1402, 1315, 1248, 1169, 1061, 998, 865, 828, 722, 686, 553; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4O_2F_2I^+$ ([M+H]$^+$): 444.9973, found 444.9973.

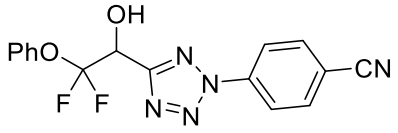
2,2-difluoro-2-phenoxy-1-(2-(4-(trifluoromethyl)phenyl)-2*H*-tetrazol-5-yl)ethan-1-ol (4f)



4f

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (59 mg, 76%) using EtOAc/petroleum ether (1:5) as eluent; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.25 – 7.09 (m, 2H), 7.08 – 6.89 (m, 3H), 5.60 (t, *J* = 6.4 Hz, 1H), 4.76 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.83, -80.47 (d, *J* = 140.5 Hz), -81.03 (d, *J* = 140.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.1, 148.7 (d, *J* = 1.9 Hz), 137.8 (d, *J* = 1.6 Hz), 131.1 (q, *J* = 33.2 Hz), 128.5, 126.2 (q, *J* = 3.7 Hz), 125.1, 122.5 (q, *J* = 272.4 Hz) 120.8, 120.4 (t, *J* = 272.0 Hz), 119.4, 67.1 (t, *J* = 34.7 Hz); **IR** (KBr, cm^{-1}) 3442, 3242, 2973, 1616, 1489, 1322, 1258, 1159, 1124, 1067, 995, 887, 849, 805, 745, 686, 592; **HRMS** (ESI) m/z calcd. for $C_{16}H_{12}N_4O_2F_5^+$ ([M+H]$^+$): 387.0880, found 387.0884.

4-(5-(2,2-difluoro-1-hydroxy-2-phenoxyethyl)-2*H*-tetrazol-2-yl)benzonitrile (4g)

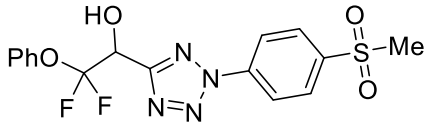


4g

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (35 mg, 51%) using EtOAc/petroleum ether (1:3) as eluent. mp 116.5-121.1 ºC ;**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.30 (d, *J* = 8.5 Hz,

2H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.13 – 7.21 (m, 3H), 5.65 (t, *J* = 6.3 Hz, 1H), 4.39 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.47 (d, *J* = 140.5 Hz), -81.04 (d, *J* = 140.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.24, 149.63, 139.15, 134.06, 129.62, 126.22, 121.78, 121.31 (t, *J* = 272.1 Hz), 120.68, 117.60, 114.00, 68.14 (t, *J* = 34.8 Hz); **IR** (KBr, cm^{-1}) 3350, 3107, 2922, 2229, 1300, 1515, 1492, 1417, 1273, 1207, 1173, 1120, 1083, 998, 900, 844, 800, 739, 704, 550; **HRMS** (ESI) m/z calcd. for $C_{16}H_{12}N_5O_2F_2^+$ ($[M+H]^+$): 344.0959, found 344.0948.

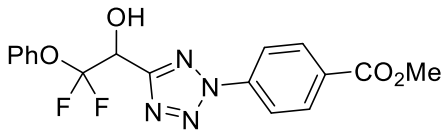
2,2-difluoro-1-(2-(4-(methylsulfonyl)phenyl)-2*H*-tetrazol-5-yl)-2-phenoxyethan-1-ol (4h)



4h

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (42 mg, 53%) using EtOAc/petroleum ether (1:1) as eluent. mp 90.2-92.1 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.23 – 7.00 (m, 3H), 5.69 (q, *J* = 6.9 Hz, 1H), 4.70 (d, *J* = 8.1 Hz, 1H), 3.14 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.39 (d, *J* = 140.3 Hz), -80.99 (d, *J* = 140.3 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.2 (d, *J* = 2.0 Hz), 149.5 (d, *J* = 1.9 Hz), 141.7, 139.9, 129.5, 129.5, 126.1, 121.7, 121.3 (t, *J* = 272.0 Hz)., 120.8, 68.0 (t, *J* = 34.6 Hz), 44.4; **IR** (KBr, cm^{-1}) 3340, 3107, 2922, 1591, 1489, 1294, 1256, 1148, 1083, 1005, 966, 779, 684, 541; **HRMS** (ESI) m/z calcd. for $C_{16}H_{15}N_4O_4F_2S^+$ ($[M+H]^+$): 397.0782, found 397.0778.

methyl 4-(5-(2,2-difluoro-1-hydroxy-2-phenoxyethyl)-2*H*-tetrazol-2-yl)benzoate (4i)

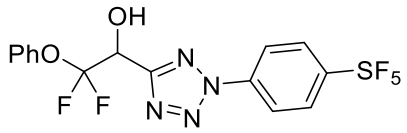


4i

Using the general procedure, the titled compound was obtained as a white solid

after column chromatography (42 mg, 56%) using EtOAc/petroleum ether (1:3) as eluent. mp 92.8-96.4 ºC;**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.21 (s, 4H), 7.35 – 7.24 (m, 2H), 7.23 – 7.09 (m, 3H), 5.67 (t, *J* = 6.3 Hz, 1H), 4.55 (s, 1H), 3.96 (s, 3H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -80.49 (d, *J* = 140.5 Hz), -81.07 (d, *J* = 140.6 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 165.9, 163.0, 149.7 (d, *J* = 1.9 Hz), 139.4, 131.6, 131.4, 129.5, 126.1, 121.8, 121.4 (t, *J* = 272.0 Hz), 119.9, 68.1 (t, *J* = 34.8 Hz), 52.7; **IR** (KBr, cm^{-1}) 3476, 3217, 2920, 1726, 1610, 1487, 1441, 1273, 1244, 1165, 1086, 1000, 764, 684; **HRMS** (ESI) m/z calcd. for $C_{17}H_{15}N_4O_4F_2^+$ ([M+H]$^+$): 377.1061, found 377.1058.

2,2-difluoro-1-(2-(4-(pentafluoro-λ^6-sulfaneyl)phenyl)-2*H*-tetrazol-5-yl)-2-phenoxyethan-1-ol (4j)

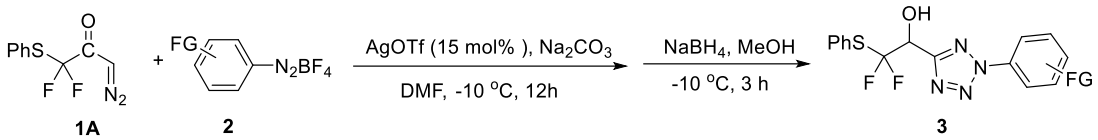


4j

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (45 mg, 51%) using EtOAc/petroleum ether (1:3) as eluent.**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 9.1 Hz, 2H), 7.27 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.21 – 7.08 (m, 3H), 5.72 (t, *J* = 6.3 Hz, 1H), 4.69 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ 82.55 (quintet, *J* = 150.4 Hz), 62.90 (d, *J* = 149.8 Hz), -80.14 – -81.70 (m). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.29, 155.34 – 153.21 (m), 149.69 (d, *J* = 1.9 Hz), 138.17, 129.63, 128.02 (q, *J* = 4.9 Hz), 126.21, 121.82, 121.40 (t, *J* = 272.0 Hz), 120.27, 68.19 (t, *J* = 34.8 Hz). **IR** (KBr, cm^{-1}) 3329, 2920, 1597, 1492, 1428, 1343, 1253, 1165, 1083, 1003, 824, 736, 665, 580; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4O_2F_7S^+$ ([M+H]$^+$): 445.0569, found 445.0568.

Gram-experiment and Synthesis Transformation

Gram-level synthesis



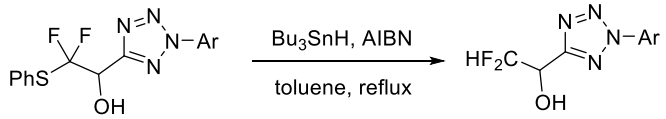
Difluoro-diazoketone **1A** (1.2 equiv.), aryl diazonium salt **2** (1 equiv.), Na_2CO_3 (2 equiv.), and AgOTf (15 mol%) were added to a dry 100 mL round bottom flask equipped with magnets in sequence, and then 30 mL DMF was added with a syringe under argon atmosphere at –10 °C. The reaction mixture was stirred at –10 °C for 12 h. After the reaction, 30 mL of anhydrous methanol and $NaBH_4$ (3 equiv.) was subsequently added in batches. The reaction mixture was stirred at –10°C for 4 h. After the reaction was completed, the reaction solution was quenched with saturated ammonium chloride solution and extracted with 40 mL of ethyl acetate. The organic phase was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was further purified by silica gel column chromatography using EtOAc/petroleum ether as an eluent to obtain **3**.

Following the general procedure, the compound **3a** was prepared using aryl diazonium salt **2a** (1 equiv., 6 mmol) and **1A** (1.2 equiv., 7.2 mmol) using PE/EA (5:1) as an eluent (1.18 g, 58% yield).

Following the general procedure, the compound **3b** was prepared using aryl diazonium salt **2b** (1 equiv., 5 mmol) and **1A** (1.2 equiv., 6 mmol) using PE/EA (4:1) as an eluent (1.37 g, 66% yield).

Following the general procedure, the compound **3e** was prepared using aryl diazonium salt **2e** (1 equiv., 5 mmol) and **1A** (1.2 equiv., 6 mmol) using PE/EA (5:1) as an eluent (1.30 g, 71% yield).

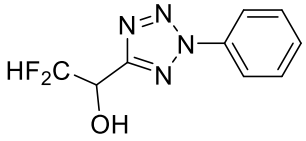
Desulfurization Reduction Reaction



3 **5**

General procedure: Argon was bubbled through a solution of **3** (0.5 mmol, 1 equiv.) in dry toluene (5 mL) for 30 minutes, then Bu_3SnH (0.25 mL, 0.875 mmol, 1.75 equiv.) was added. The reaction mixture was subjected to deoxygenate by bubbling argon for 5 minutes via an argon balloon. AIBN (12.5 mg, 0.075 mmol, 0.15 equiv.) was added and the solution was refluxed for 15 hours.[6] The volatiles were evaporated and the residue was dissolved in EtOAc (5 mL). The solution was stirred with KF/H_2O (30 mg/0.3 mL) overnight and extracted with EtOAc (3×10 mL). The organic phase was washed successively with water and brine, and dried over anhydrous sodium sulfate. After removing the solvent, the crude product was purified by silica gel column chromatography to obtain **5**.

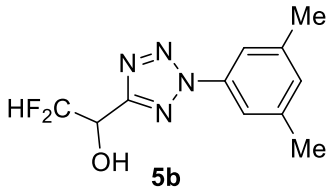
2,2-difluoro-1-(2-phenyl-2*H*-tetrazol-5-yl)ethan-1-ol (5a)



5a

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (107 mg, 95%) using EtOAc/petroleum ether (1:5) as eluent. mp. 82.3-83.6 ºC. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.10 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.71 – 7.41 (m, 3H), 6.23 (t, *J* = 55.1 Hz, 1H), 5.37 (td, *J* = 10.4, 4.1 Hz, 1H), 4.14 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -128.26 (d, *J* = 289.5 Hz), -129.15 (d, *J* = 289.5 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.7, 136.6, 130.4, 129.9, 120.2, 114.3 (t, *J* = 246.0 Hz), 66.8 (t, *J* = 26.8 Hz); **IR** (KBr, cm^{-1}) 3285, 2922, 1600, 1468, 1182, 1055, 1010, 915, 851, 757, 681, 527; **HRMS** (ESI) m/z calcd. for $C_9H_9N_4OF_2^+$ ($[M+H]^+$): 227.0744, found 227.0745.

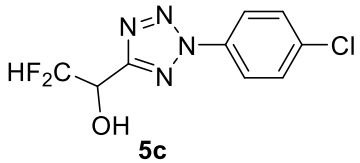
1-(2-(3,5-dimethylphenyl)-2*H*-tetrazol-5-yl)-2,2-difluoroethan-1-ol (5b)



5b

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (129 mg, 98%) using EtOAc/petroleum ether (1:5) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.68 (s, 2H), 7.10 (s, 1H), 6.23 (td, *J* = 55.1, 4.2 Hz, 1H), 5.38 (tt, *J* = 10.0, 3.9 Hz, 1H), 4.49 (s, 1H), 2.38 (s, 6H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -128.13 (d, *J* = 289.5 Hz), -129.10 (d, *J* = 285.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.4, 139.8, 136.4, 131.9, 117.8, 114.2 (t, *J* = 246.1 Hz), 66.8 (t, *J* = 26.7 Hz), 21.3; **IR** (KBr, cm^{-1}) 3373, 3304, 2922, 1621, 1597, 1476, 1182, 1074, 849, 677, 628; **HRMS** (ESI) m/z calcd. for $C_{11}H_{13}N_4OF_2^+$ ([M+H]$^+$): 255.1057, found 255.1059.

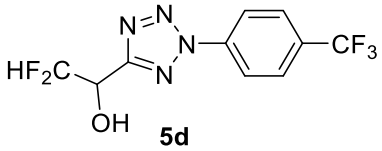
1-(2-(4-chlorophenyl)-2*H*-tetrazol-5-yl)-2,2-difluoroethan-1-ol (5c)



5c

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (119 mg, 91%) using EtOAc/petroleum ether (1:5) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 9.0 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 2H), 6.22 (td, *J* = 55.0, 4.1 Hz, 1H), 5.37 (s, 1H), 4.37 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -128.21 (d, *J* = 289.5 Hz), -129.01 (d, *J* = 285.7 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 162.8, 136.3, 134.9, 130.0, 121.3, 114.1 (t, *J* = 246.1 Hz), 66.7 (t, *J* = 27.3 Hz); **IR** (KBr, cm^{-1}) 3403, 3079, 2920, 1597, 1492, 1065, 1000, 830, 752, 692; **HRMS** (ESI) m/z calcd. for $C_9H_8N_4OF_2Cl^+$ ([M+H]$^+$): 261.0355, found 261.0353.

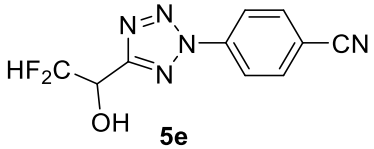
2,2-difluoro-1-(2-(4-(trifluoromethyl)phenyl)-2*H*-tetrazol-5-yl)ethan-1-ol (5d)



5d

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (117 mg, 80 %) using EtOAc/petroleum ether (1:5) as eluent. mp. 85.2-88.9 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.5 Hz, 2H), 6.23 (td, *J* = 55.0, 4.1 Hz, 1H), 5.40 (td, *J* = 10.3, 4.1 Hz, 1H), 4.34 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -62.90, -128.73 (d, *J* = 7.8 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.2, 138.8, 132.4 (q, *J* = 33.3 Hz), 127.3 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.5 Hz), 120.4, 114.2 (t, *J* = 246.2 Hz), 66.9 (t, *J* = 26.8 Hz). **IR** (KBr, cm^{-1}) 3247, 2922, 1621, 1428, 1322, 1143, 1058, 1005, 847, 624; **HRMS** (ESI) m/z calcd. for $C_{10}H_8N_4OF_5^+$ ($[M+H]^+$): 295.0618, found 295.0620.

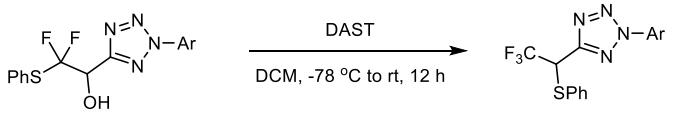
4-(5-(2,2-difluoro-1-hydroxyethyl)-2*H*-tetrazol-2-yl)benzonitrile (5e)



5e

Using the general procedure, the titled compound was obtained as a yellow solid after column chromatography (61 mg, 49 %) using EtOAc/petroleum ether (1:3) as eluent. mp. 118.7-122.3 °C. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.31 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 6.22 (td, *J* = 55.0, 4.1 Hz, 1H), 5.37 (td, *J* = 10.3, 4.1 Hz, 1H), 3.74 (s, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -128.74 (d, *J* = 2.8 Hz). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 163.3, 139.1, 134.1, 120.7, 117.5, 114.2, 114.0 (t, *J* = 246.5 Hz), 66.9 (t, *J* = 26.8 Hz); **IR** (KBr, cm^{-1}) 3395, 3113, 2925, 2246, 1602, 1501, 1373, 1248, 1124, 1061,849, 557; **HRMS** (ESI) m/z calcd. for $C_{10}H_8N_5OF_2^+$ ($[M+H]^+$): 252.0697, found 252.0694.

Phenylthiol Migration / Fluorination Reaction

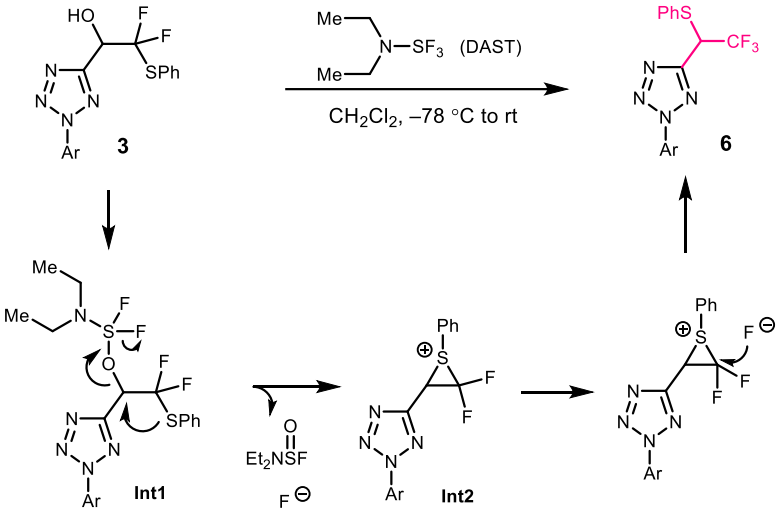


3 **6**

General procedure: compound **3** (0.5 mmol, 1 equiv.) was dissolved in 5 mL DCM and cooled to -78 °C, then DAST (201 mg, 1.25 mmol, 2.5 equiv.) was added dropwise.

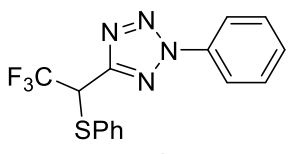
After the addition, the temperature was raised to room temperature and reacted for 12 hours (TLC monitoring). After the reaction, it was quenched with saturated $NaHCO_3$ solution, extracted with DCM (5 mL × 2), the combined organic phase was washed with saturated brine, and dried with anhydrous sodium sulfate. Finally, the residue was purified by silica gel column chromatography to obtain **6**.

A reasonable mechanism for the migration reaction of phenylthio group



We have proposed a plausible mechanism for the rearrangement of difluoromethyl carbinols **3** to trifluoromethyl thioethers **6** based on the previous studies and experimental results.[7] The reaction might start with the activation of the alcohol group of **3** by DAST to give an alkoxyaminosulfur difluoride intermediate **Int1**. Then an intramolecular substitution process (S_Ni reaction) could proceed fast to produce a difluorinated three-membered sulfonium species **Int2**. In situ generated fluoride anion then attacked at the difluorinated carbon atom and led to the formation of trifluoromethyl thioether product **6**.

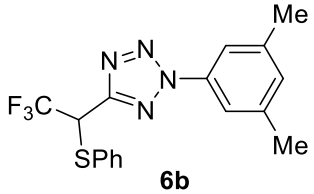
2-phenyl-5-(2,2,2-trifluoro-1-(phenylthio)ethyl)-2*H*-tetrazole (6a)



6a

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (101 mg, 60%) using EtOAc/petroleum ether (1:70) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 8.18 – 7.97 (m, 2H), 7.62 – 7.46 (m, 5H), 7.40 – 7.28 (m, 3H), 5.13 (q, *J* = 8.0 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -67.73. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.5 (d, *J* = 1.9 Hz), 136.5, 134.5, 131.4, 130.2, 129.8, 129.5, 129.5, 124.5 (q, *J* = 280.78 Hz), 120.0, 48.5 (q, *J* = 32.4 Hz); **IR** (KBr, cm^{-1}) 3226, 2927, 1597, 1494, 1260, 1154, 1063, 1005, 966, 819, 752, 686, 626; **HRMS** (ESI) m/z calcd. for $C_{15}H_{12}N_4F_3S^+$ ($[M+H]^+$): 337.0735, found 337.0736.

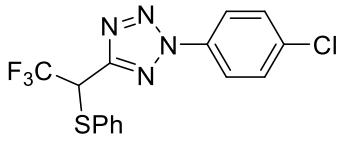
2-(3,5-dimethylphenyl)-5-(2,2,2-trifluoro-1-(phenylthio)ethyl)-2*H*-tetrazole (6b)



6b

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (115 mg, 63%) using EtOAc/petroleum ether (1:80) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.69 (s, 2H), 7.55 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.33 (d, *J* = 6.7 Hz, 3H), 7.11 (s, 1H), 5.13 (q, *J* = 8.0 Hz, 1H), 2.40 (s, 6H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -67.75. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.3 (d, *J* = 2.0 Hz), 139.8, 136.4, 134.4, 131.8, 131.5, 129.5, 129.4, 124.5 (q, *J* = 279.7 Hz), 117.7, 48.5 (q, *J* = 32.3 Hz), 21.3; **IR** (KBr, cm^{-1}) 3226, 2980, 1596, 1494, 1251, 1161, 1065, 847, 743, 658; **HRMS** (ESI) m/z calcd. for $C_{17}H_{16}N_4F_3S^+$ ($[M+H]^+$): 365.1048, found 365.1044.

2-(4-chlorophenyl)-5-(2,2,2-trifluoro-1-(phenylthio)ethyl)-2*H*-tetrazole (6c)

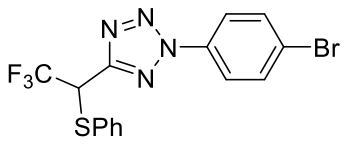


6c

Using the general procedure, the titled compound was obtained as a yellow oil after column chromatography (118 mg, 64%) using EtOAc/petroleum ether (1:80) as eluent. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.49 – 7.34 (m,

4H), 7.29 – 7.16 (m, 3H), 5.01 (q, *J* = 8.0 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -67.73. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.8 (d, *J* = 1.8 Hz), 136.2, 134.9, 134.5, 131.3, 130.0, 129.6, 129.5, 124.4 (q, *J* = 280.7 Hz), 121.3, 48.4 (q, *J* = 32.3 Hz); **IR** (KBr, cm^{-1}) 3104, 2954, 1589, 1489, 1290, 1251, 1150, 1093, 1005, 832, 747, 686; **HRMS** (ESI) m/z calcd. for $C_{15}H_{11}N_4F_3SCl^+$ ($[M+H]^+$): 371.0345, found 371.0345.

2-(4-bromophenyl)-5-(2,2,2-trifluoro-1-(phenylthio)ethyl)-2*H*-tetrazole (6d)



6d

Using the general procedure, the titled compound was obtained as a white solid after column chromatography (115 mg, 56%) using EtOAc/petroleum ether (1:80) as eluent. mp 63.2-65.9 ºC; **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.97 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 7.53 (dd, *J* = 7.7, 1.9 Hz, 2H), 7.38 - 7.28 (m, 3H), 5.11 (q, *J* = 8.0 Hz, 1H). **^{19}F NMR** (376 MHz, Chloroform-*d*) δ -67.70. **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 160.8 (d, *J* = 1.8 Hz), 135.5, 134.6, 133.0, 131.4, 129.6, 129.5, 124.3 (q, *J* = 279.7 Hz), 124.3, 121.5, 48.5 (q, *J* = 32.4 Hz); **IR** (KBr, cm^{-1}) 3107, 2952, 1492, 1419, 1251, 1090, 1000, 835, 750, 684; **HRMS** (ESI) m/z calcd. for $C_{15}H_{11}N_4F_3SBr^+$ ($[M+H]^+$): 414.9840, found 414.9844.

References

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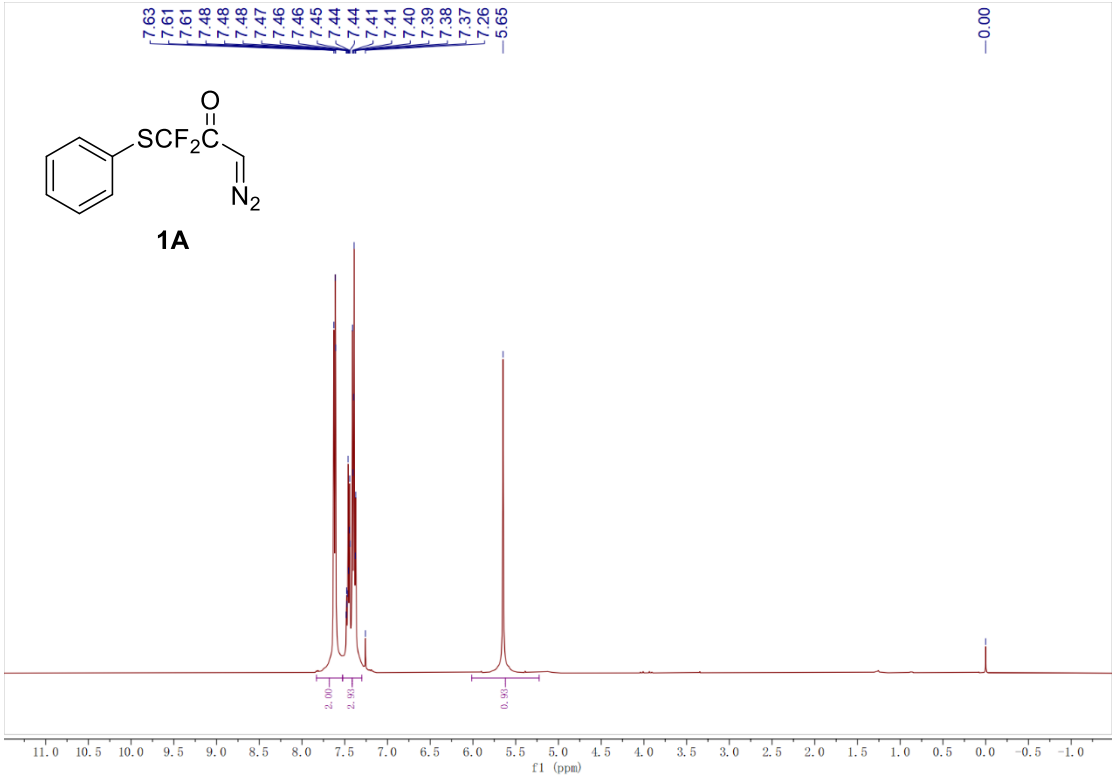
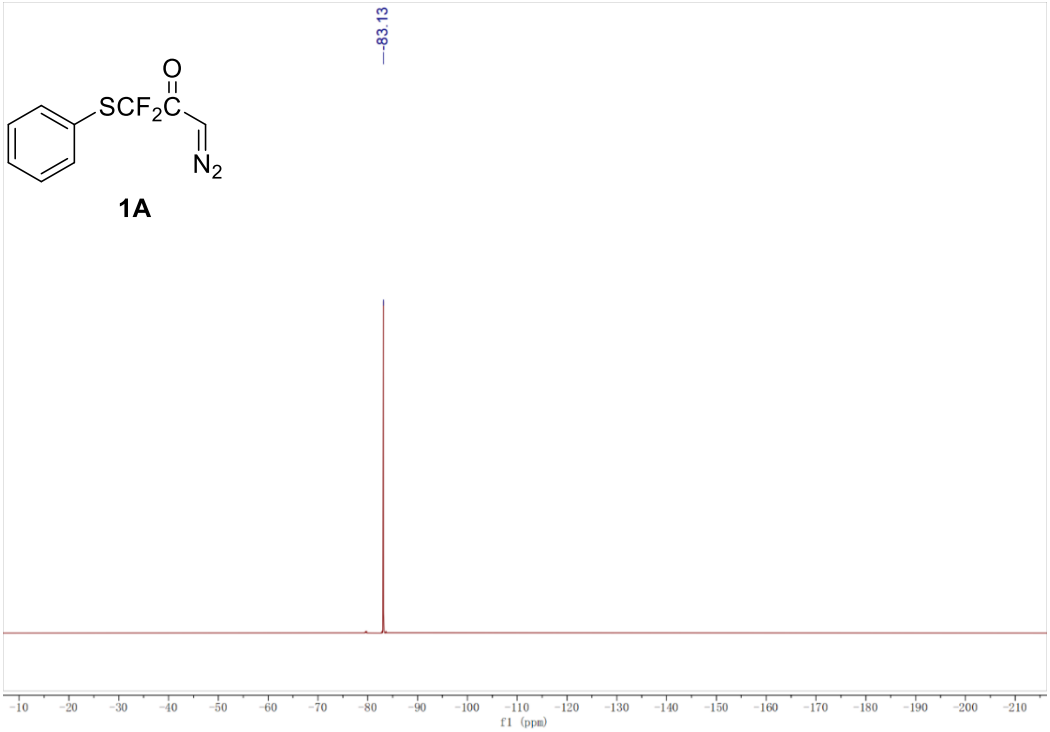
Copies of NMR Spectra for New Compounds

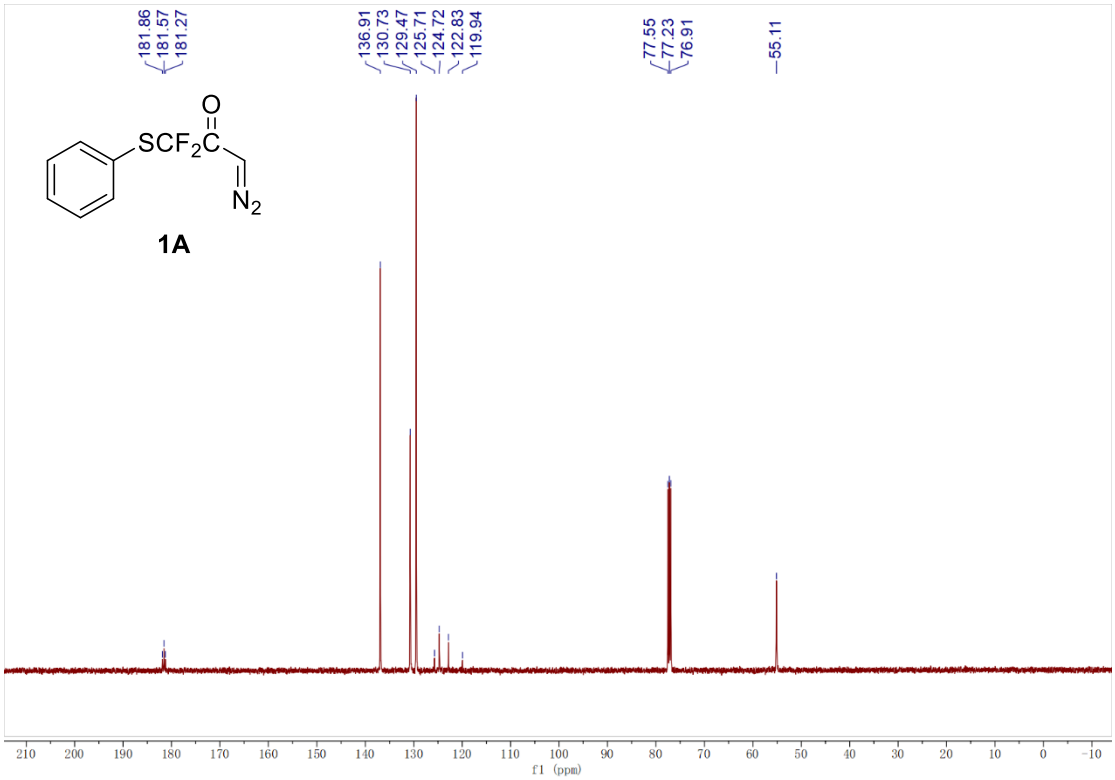
^{1}H, ^{13}C, and ^{19}F NMR spectra of **1A**



^{1}H NMR (400 MHz, Chloroform-*d*) of **1A**

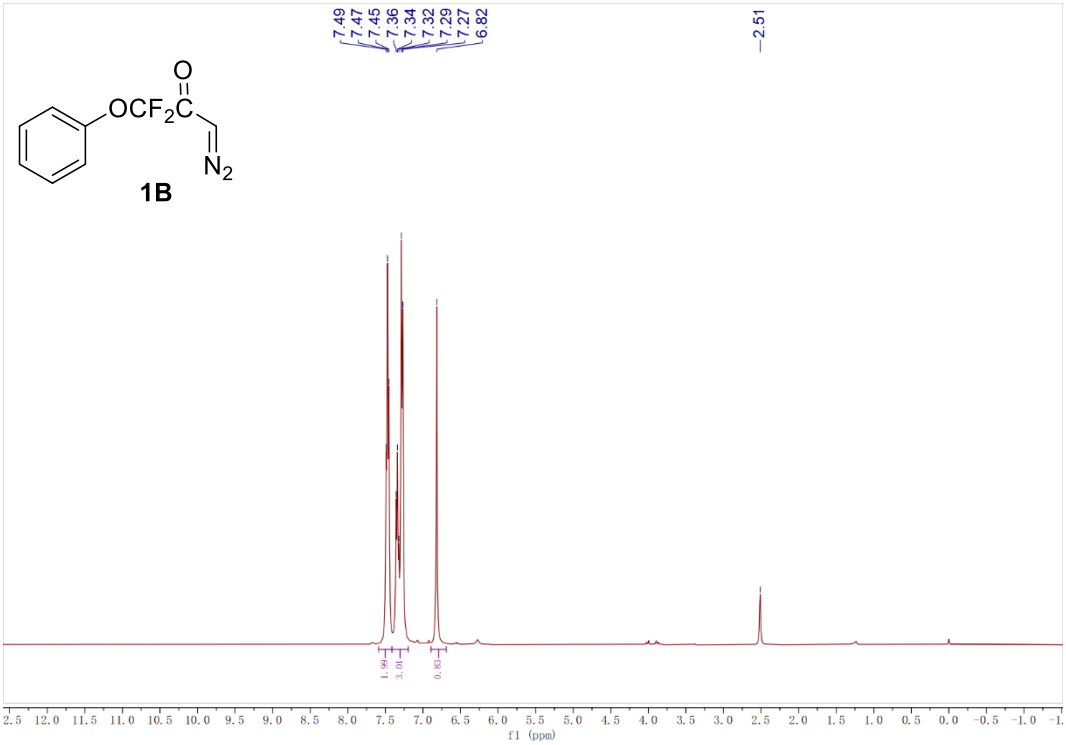


^{19}F NMR (376 MHz, Chloroform-*d*) of **1A**

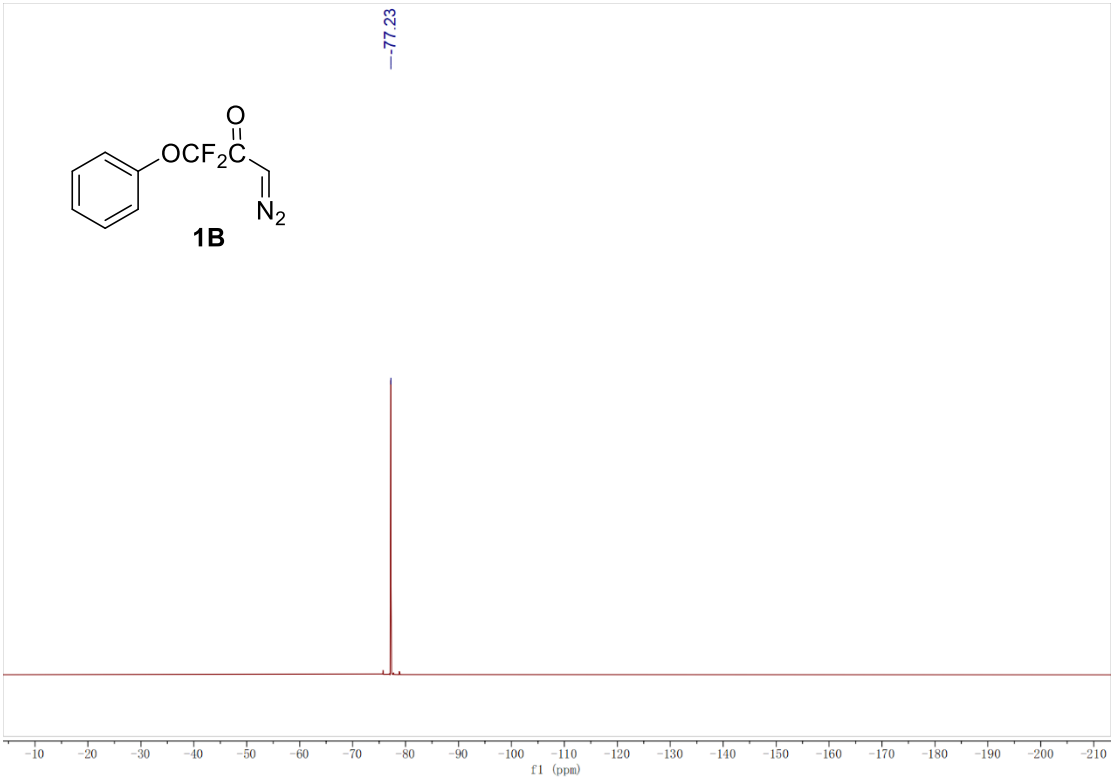


^{13}C NMR (101 MHz, Chloroform-*d*) of **1A**

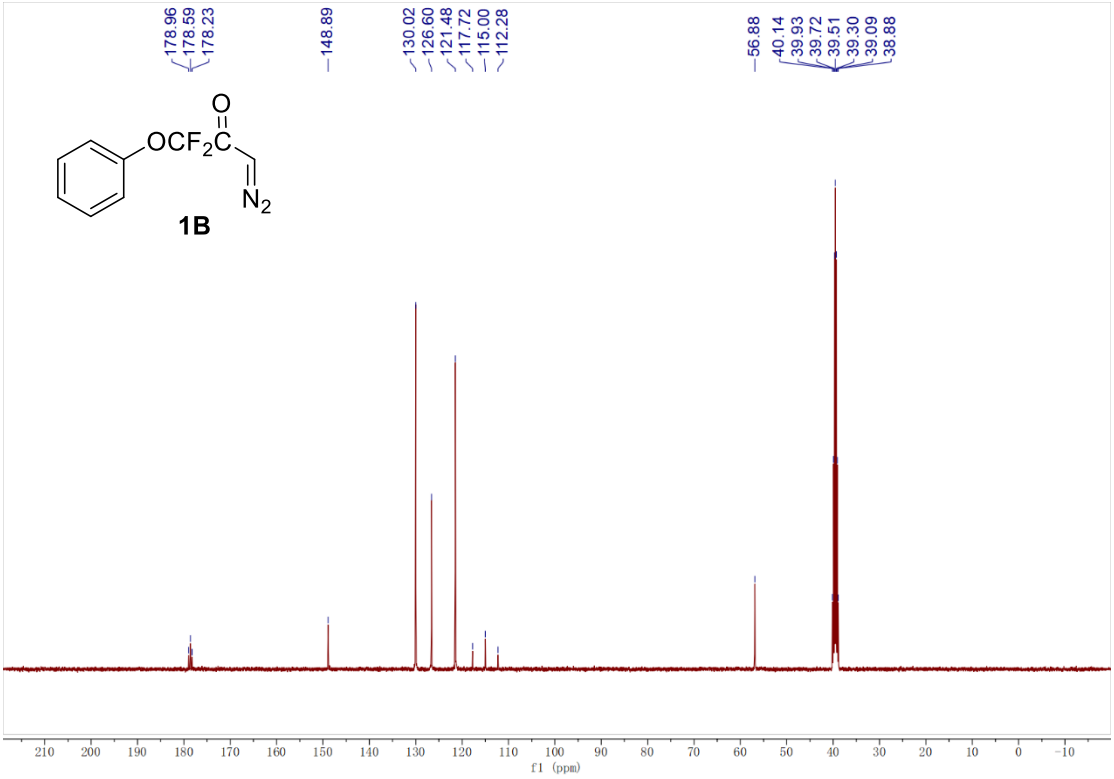
^{1}H, ^{13}C, and ^{19}F NMR spectra of **1B**



^{1}H NMR (400 MHz, DMSO-d_6) of **1B**

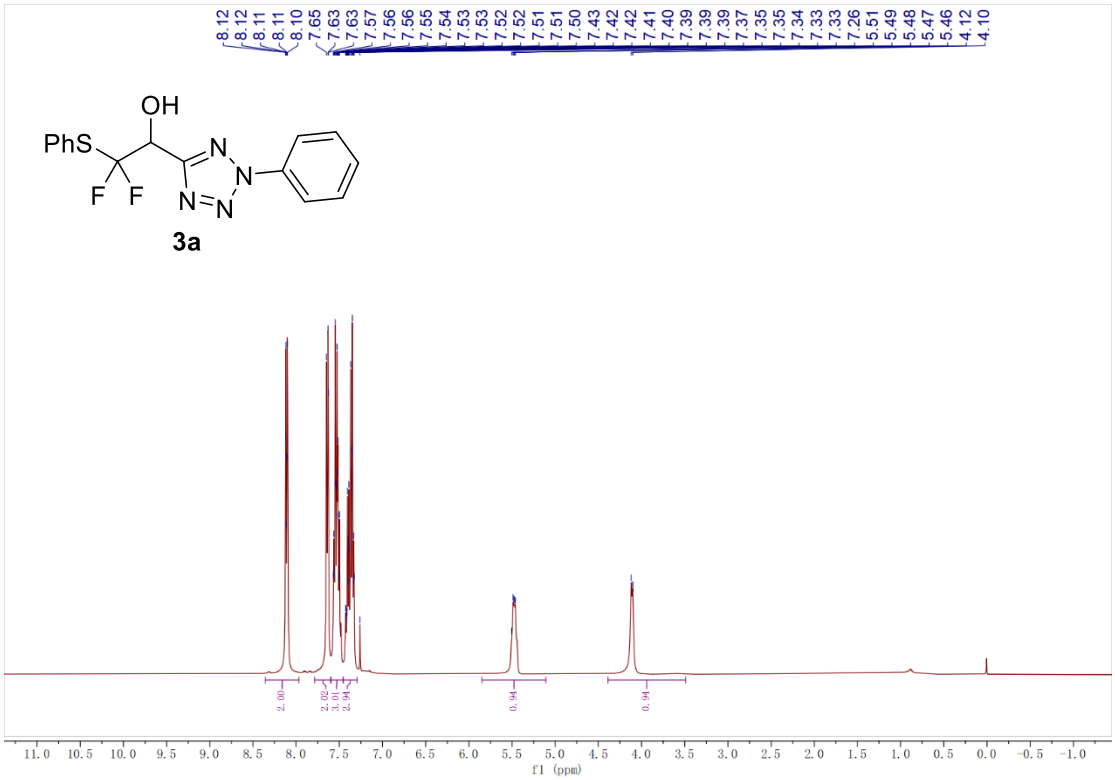


^{19}F NMR (376 MHz, DMSO-d_6) of **1B**

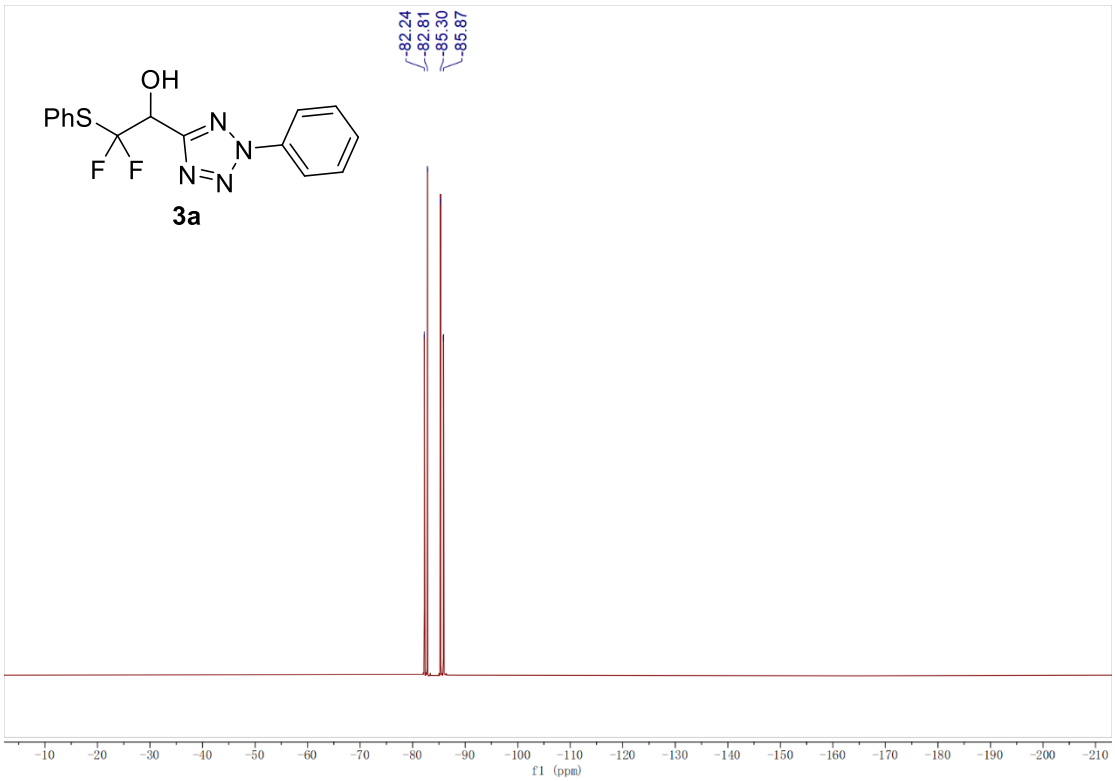


^{13}C NMR (101 MHz, DMSO-d_6) of **1B**

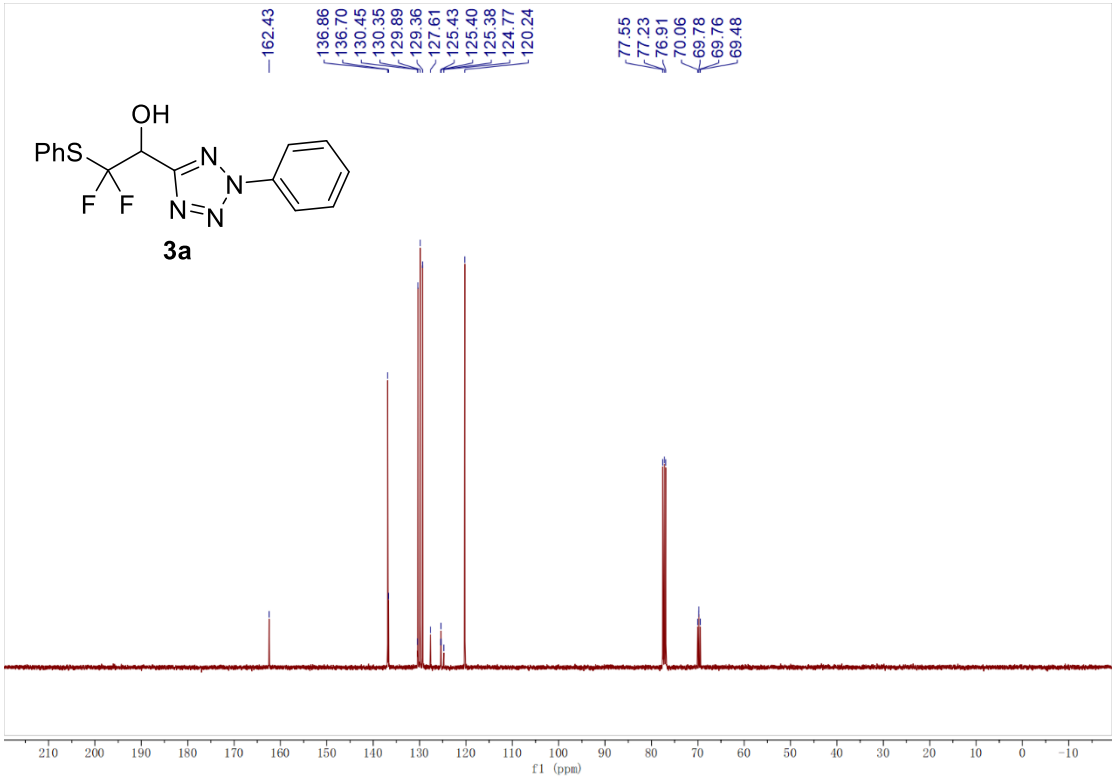
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3a**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3a**

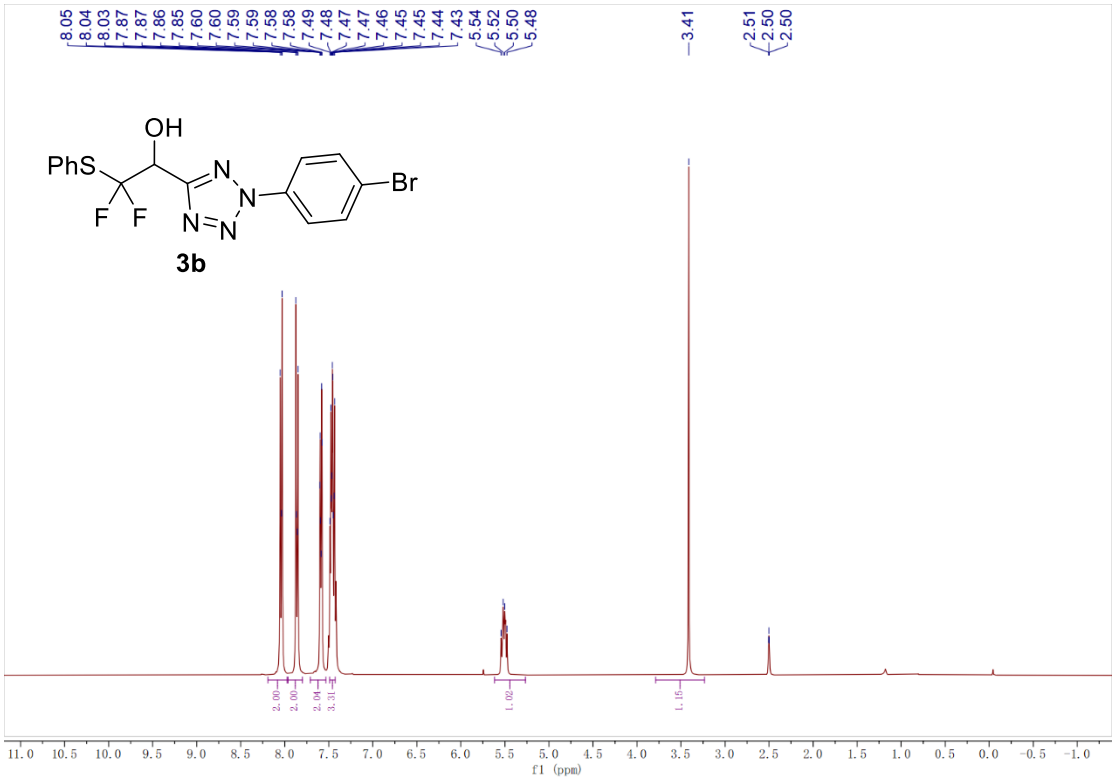


^{19}F NMR (376 MHz, Chloroform-*d*) of **3a**

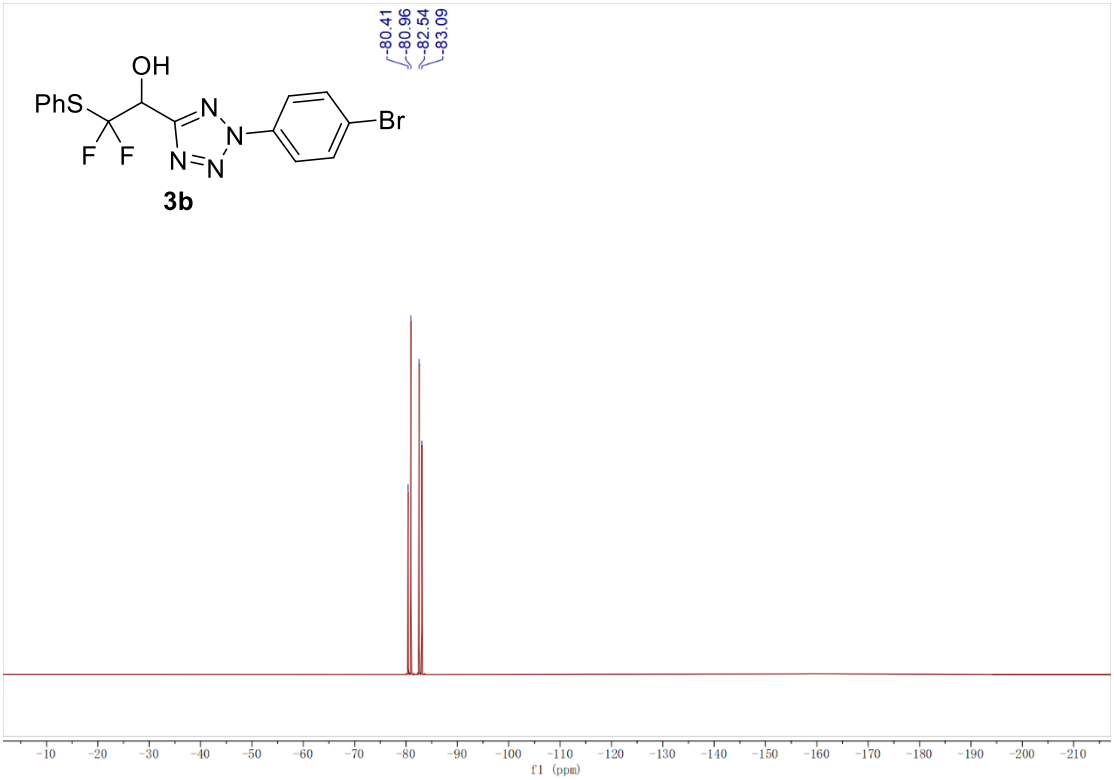


^{13}C NMR (101 MHz, Chloroform-*d*) of **3a**

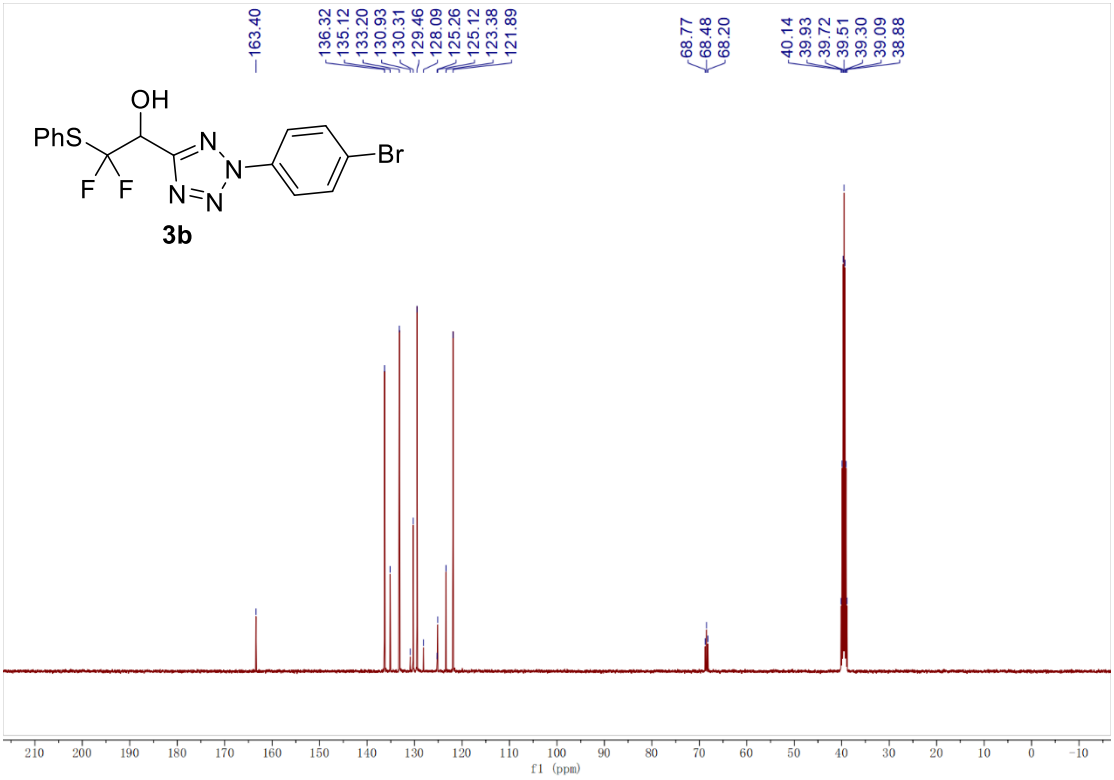
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3b**



^{1}H NMR (400 MHz, DMSO-d_6) of **3b**

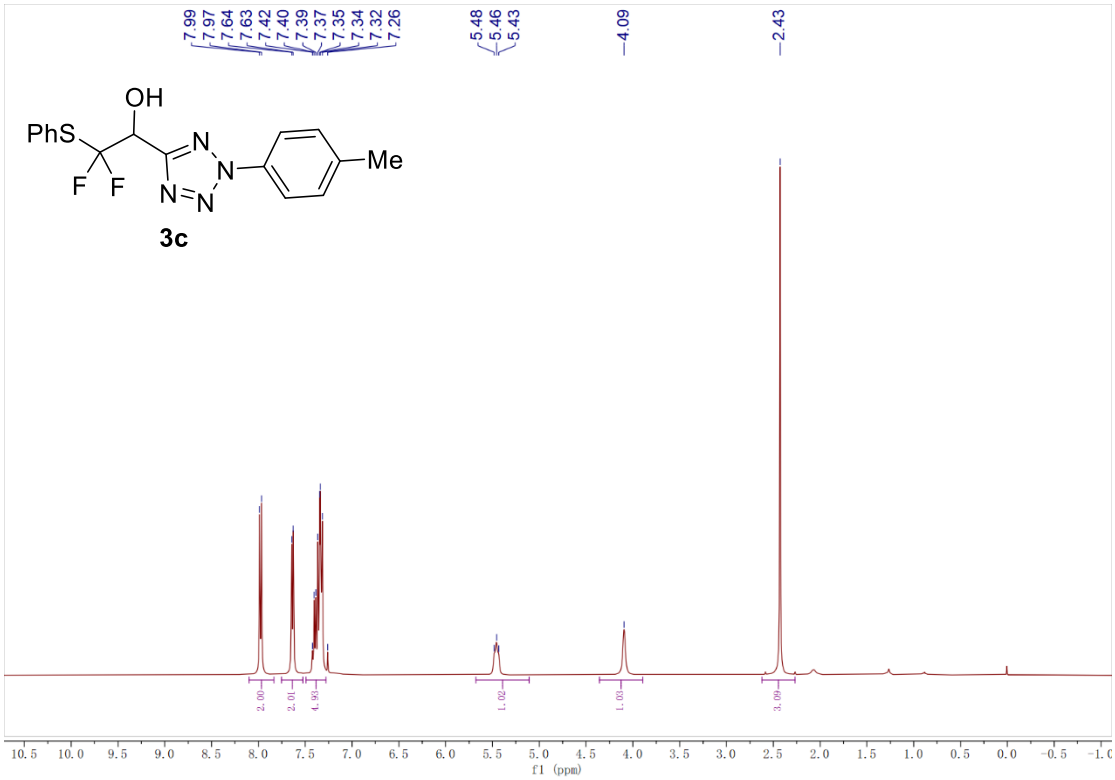


^{19}F NMR (376 MHz, DMSO-d_6) of **3b**

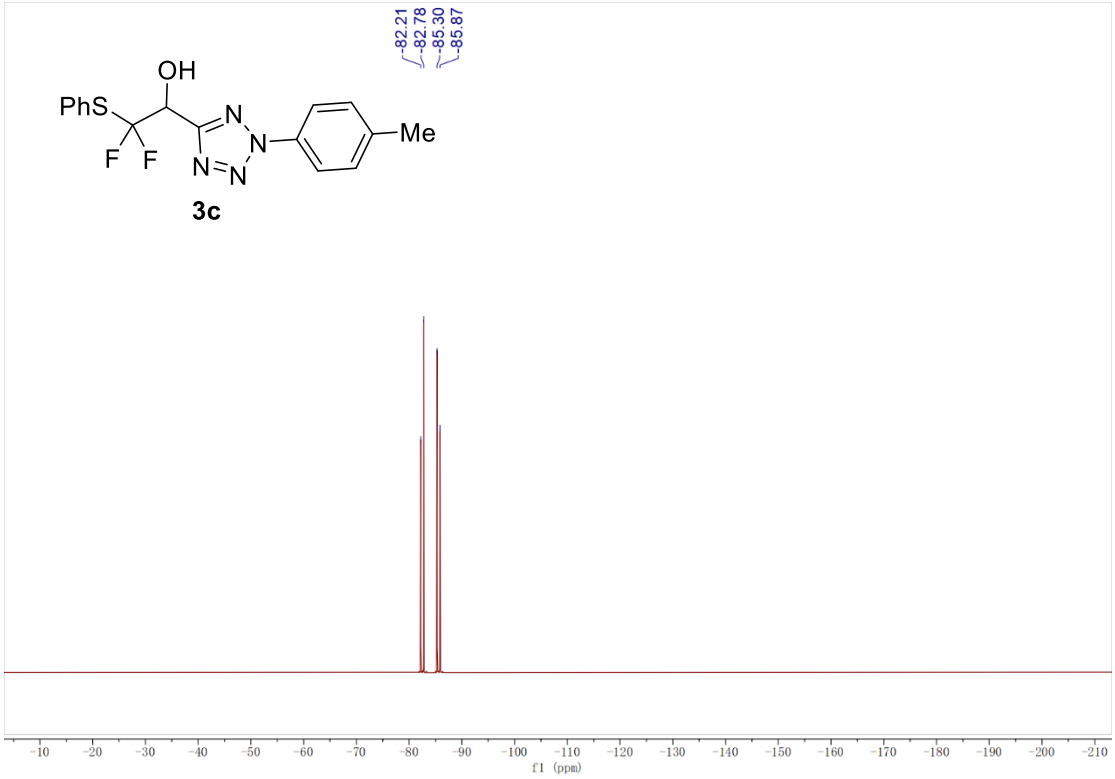


^{13}C NMR (101 MHz, DMSO-d_6) of **3b**

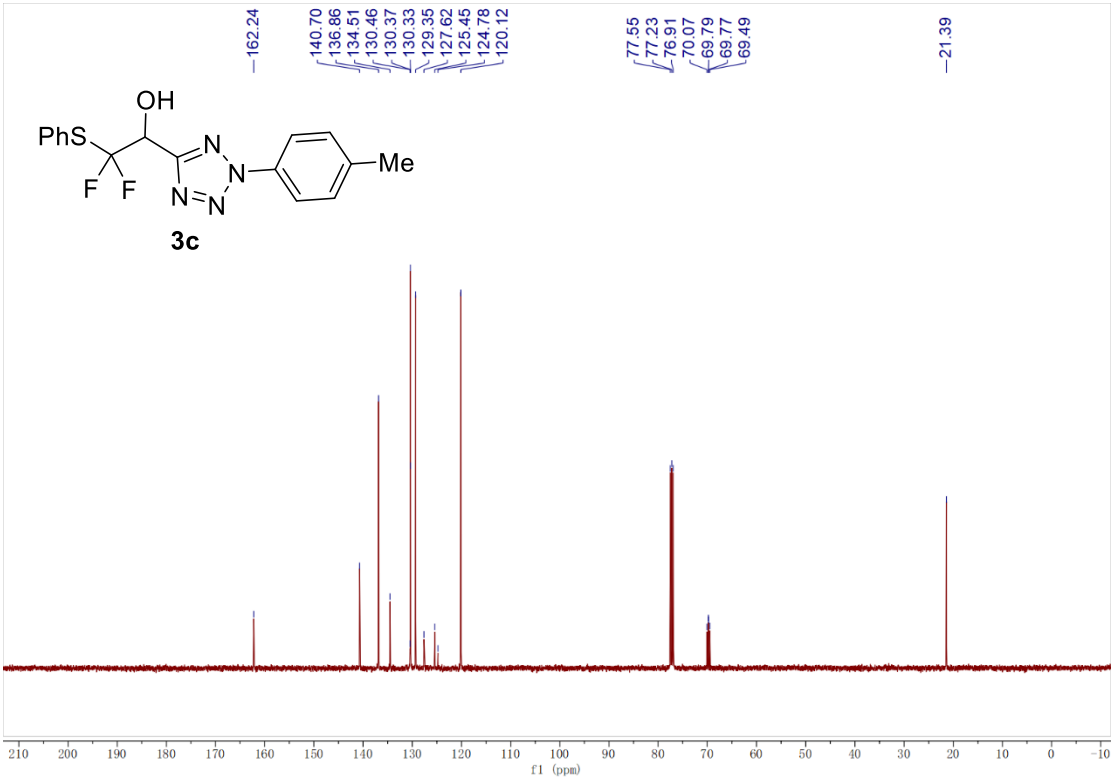
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3c**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3c**

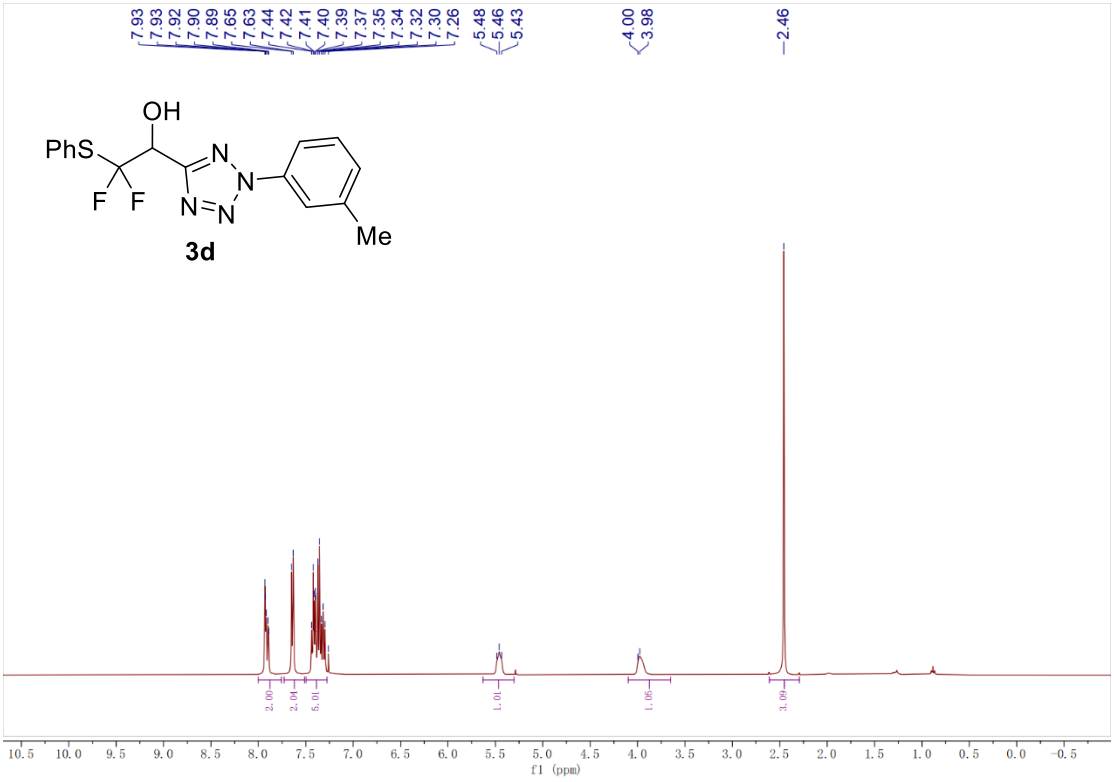


^{19}F NMR (376 MHz, Chloroform-*d*) of **3c**

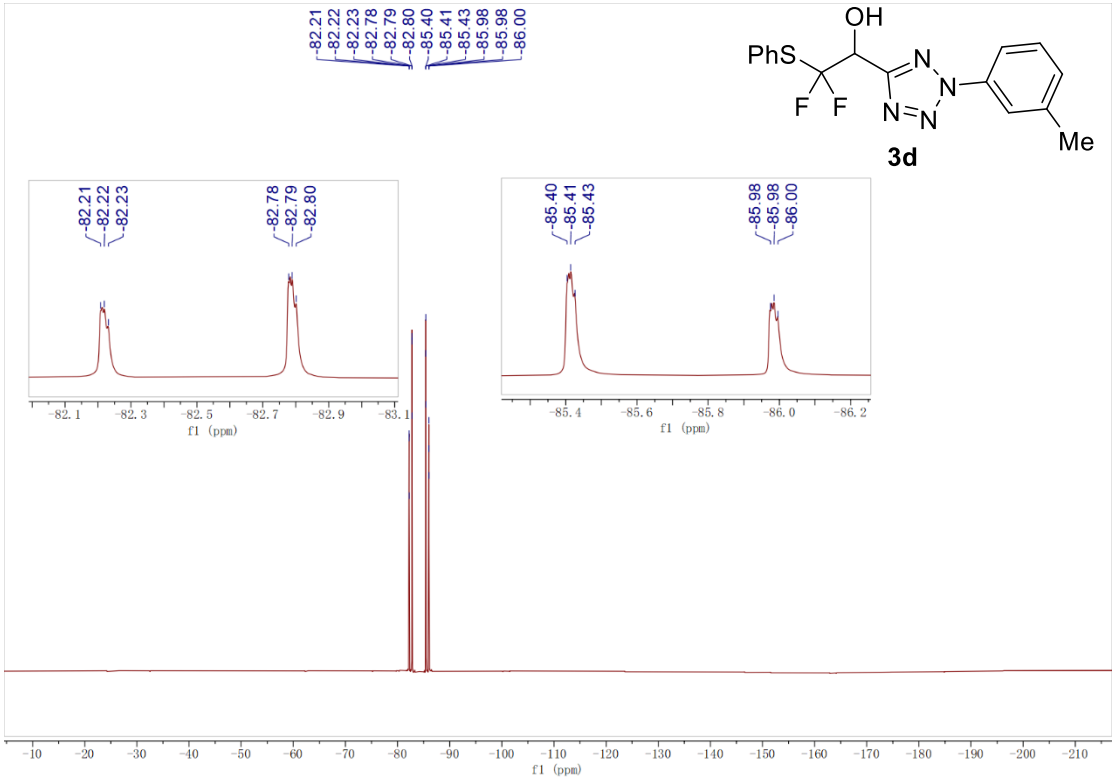


^{13}C NMR (101 MHz, Chloroform-*d*) of **3c**

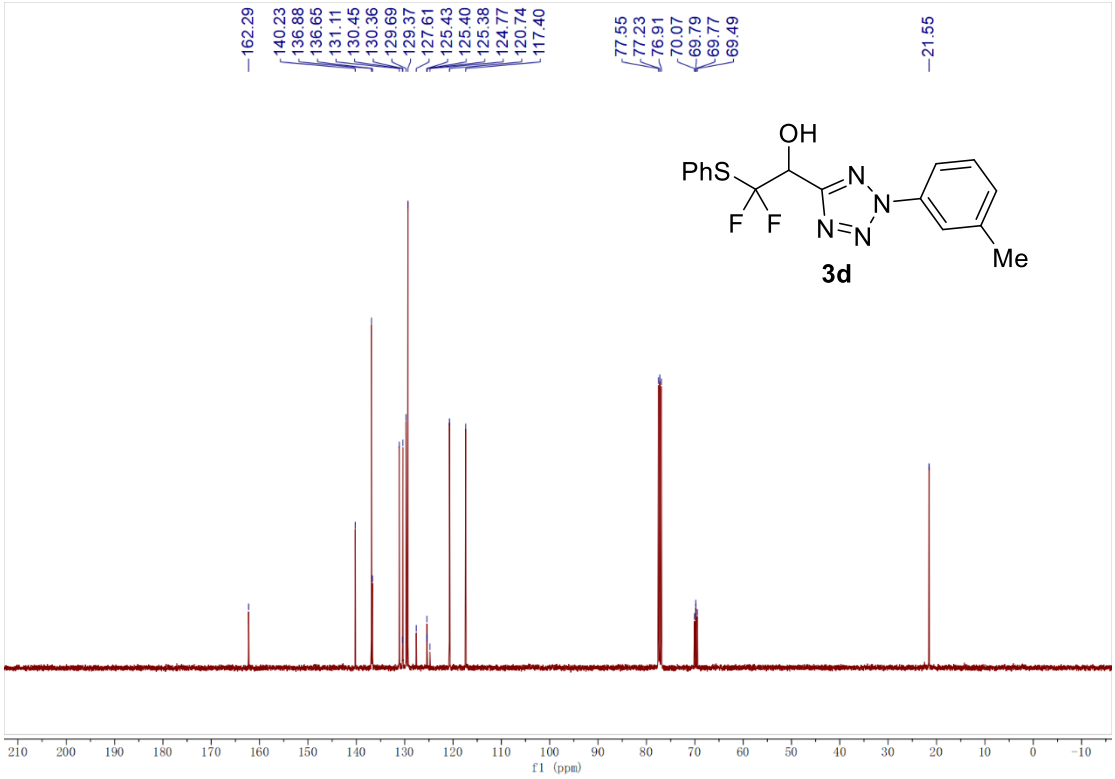
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3d**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3d**

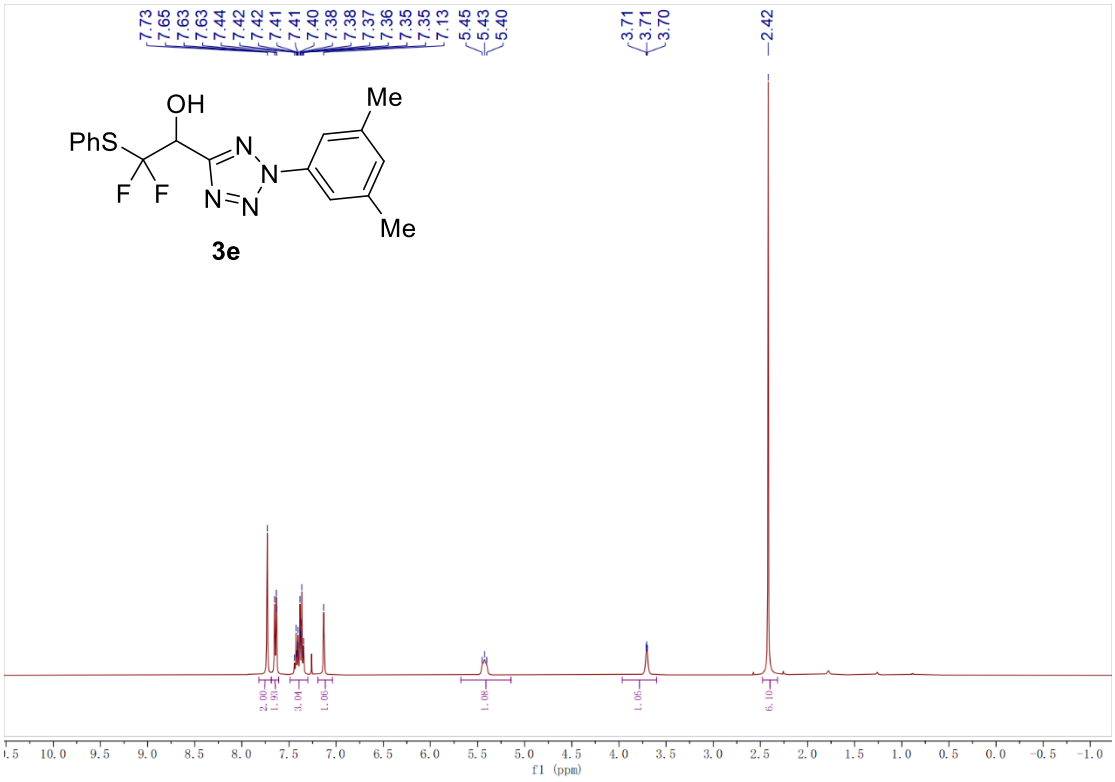


^{19}F NMR (376 MHz, Chloroform-*d*) of **3d**

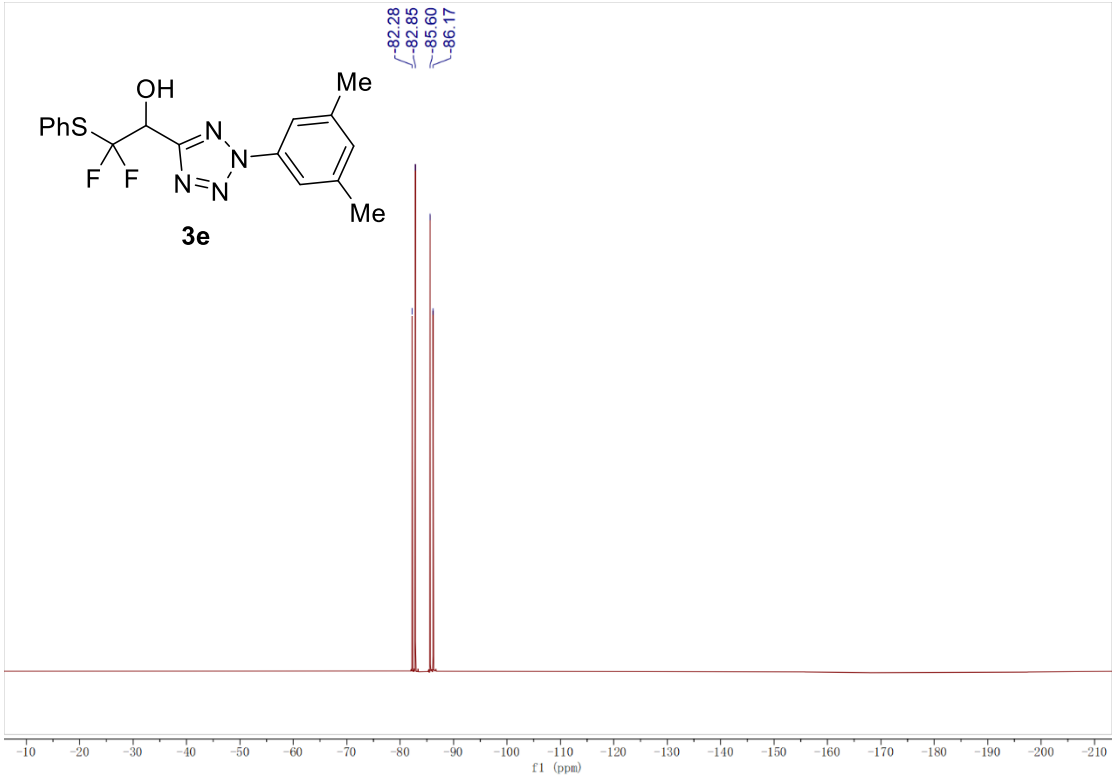


^{13}C NMR (101 MHz, Chloroform-*d*) of **3d**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3e**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3e**



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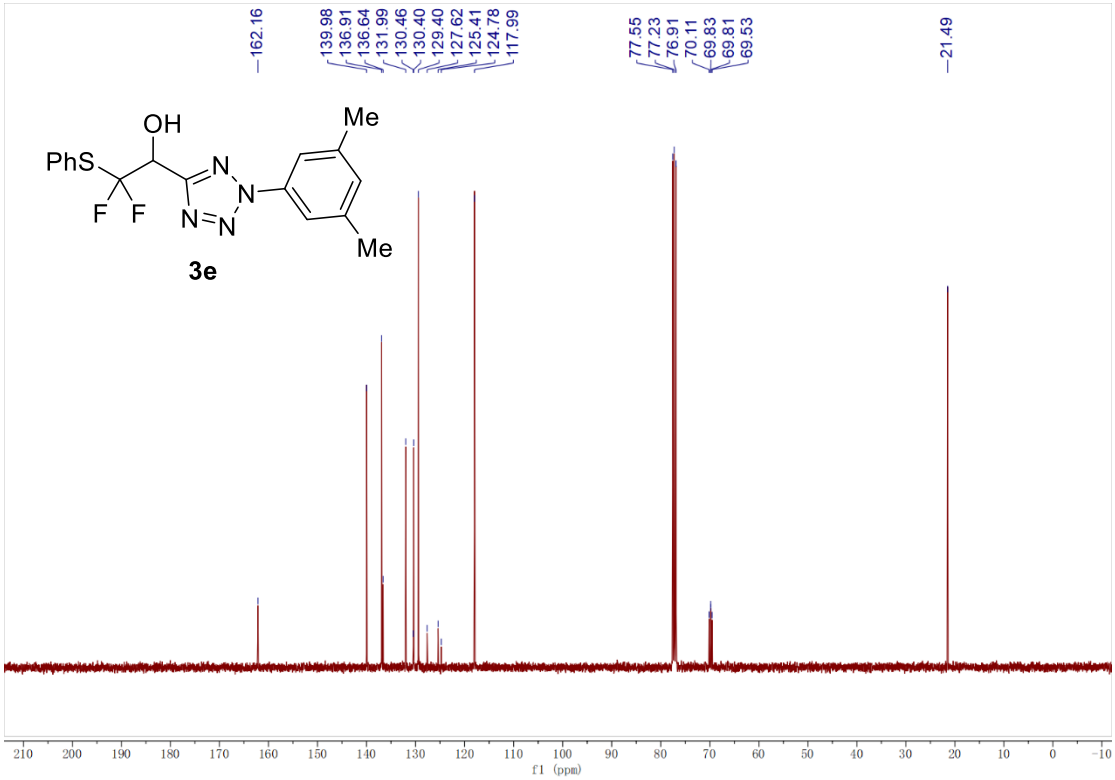
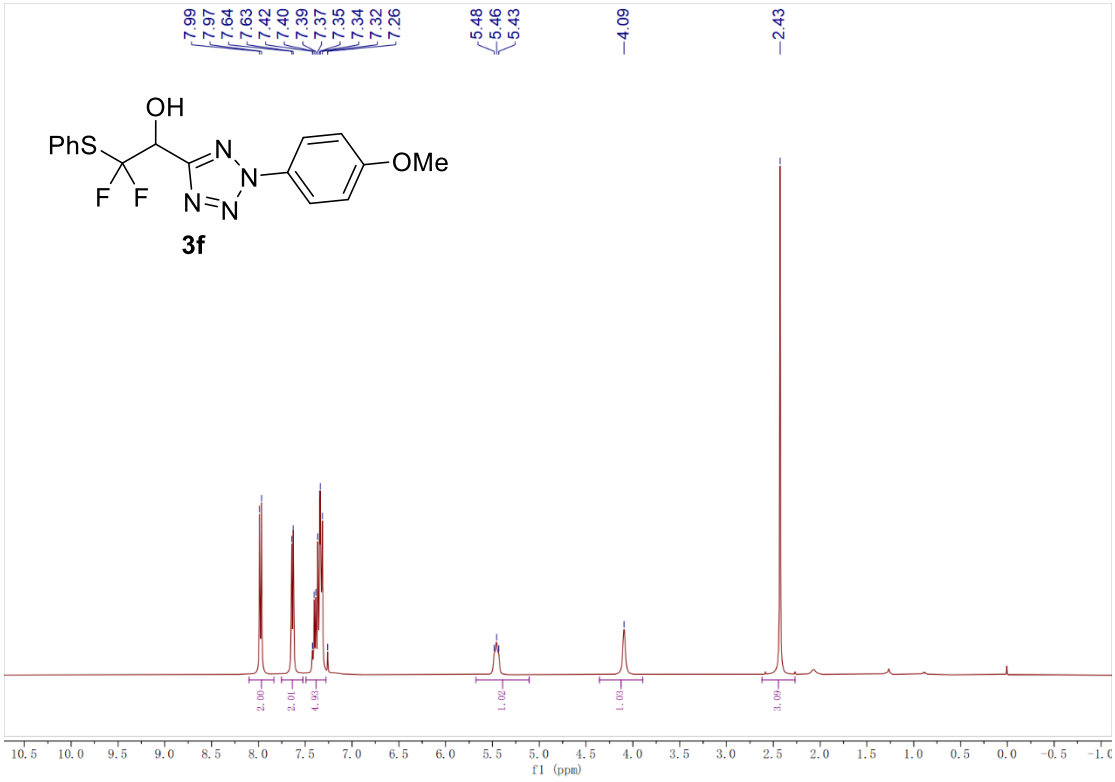


^{13}C NMR (101 MHz, Chloroform-*d*) of **3e**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3f**



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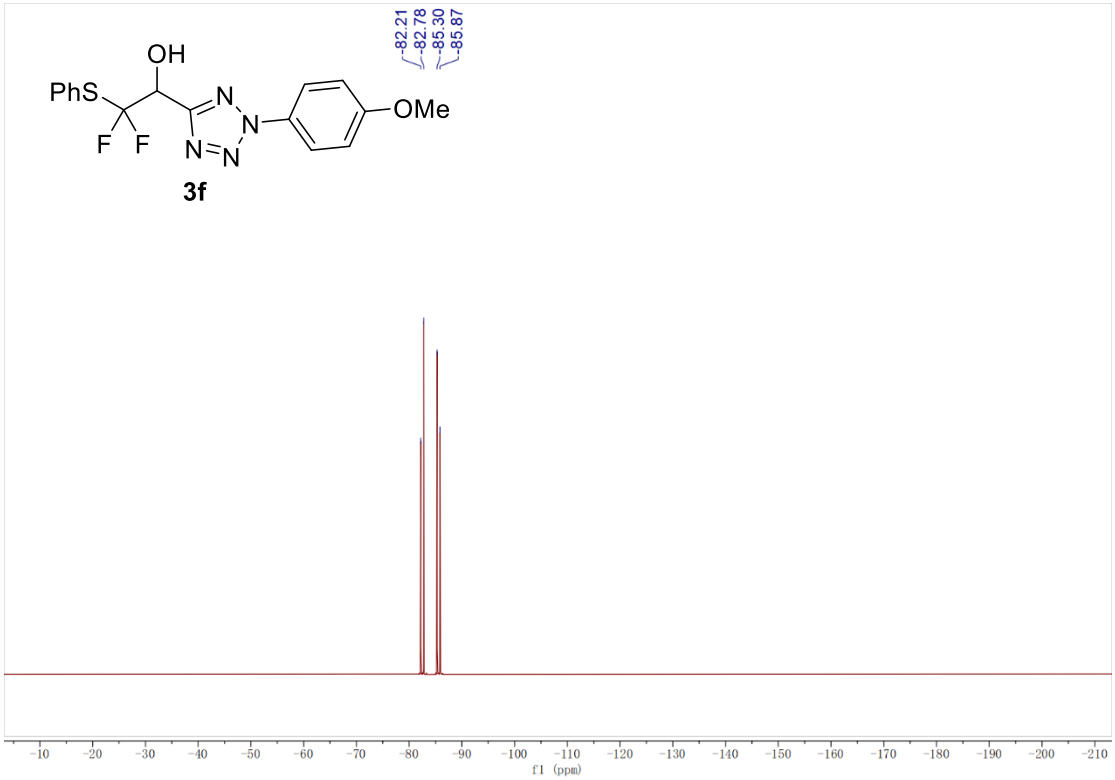
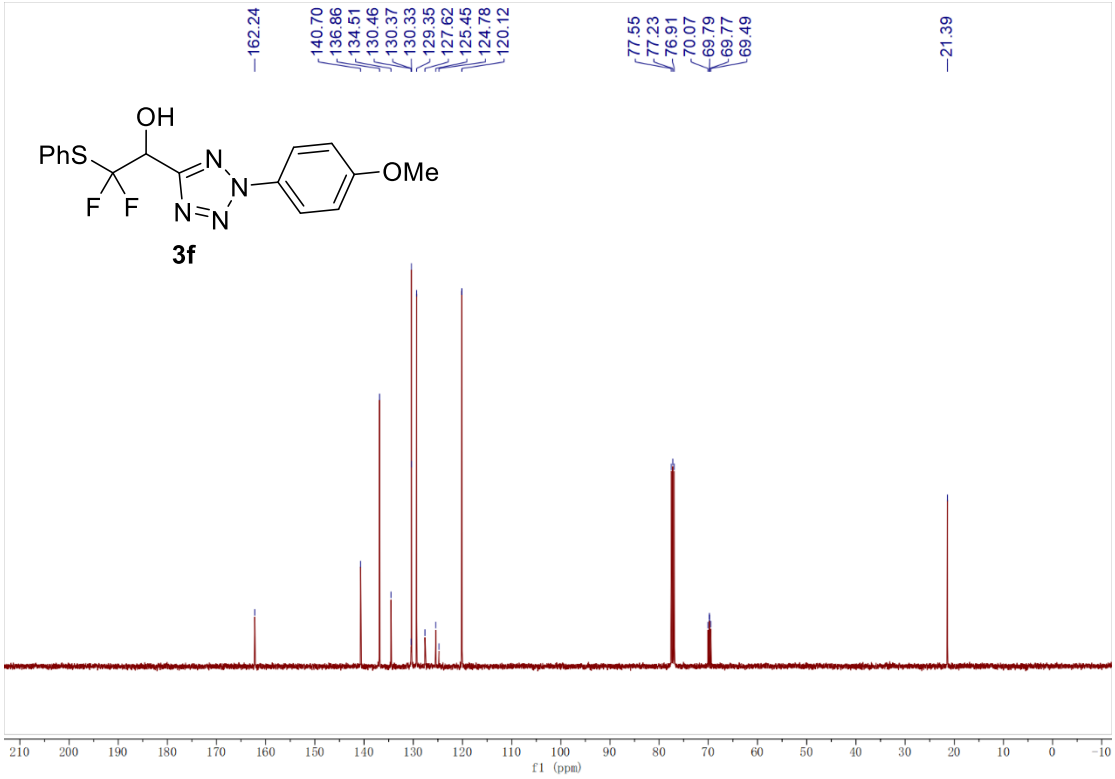
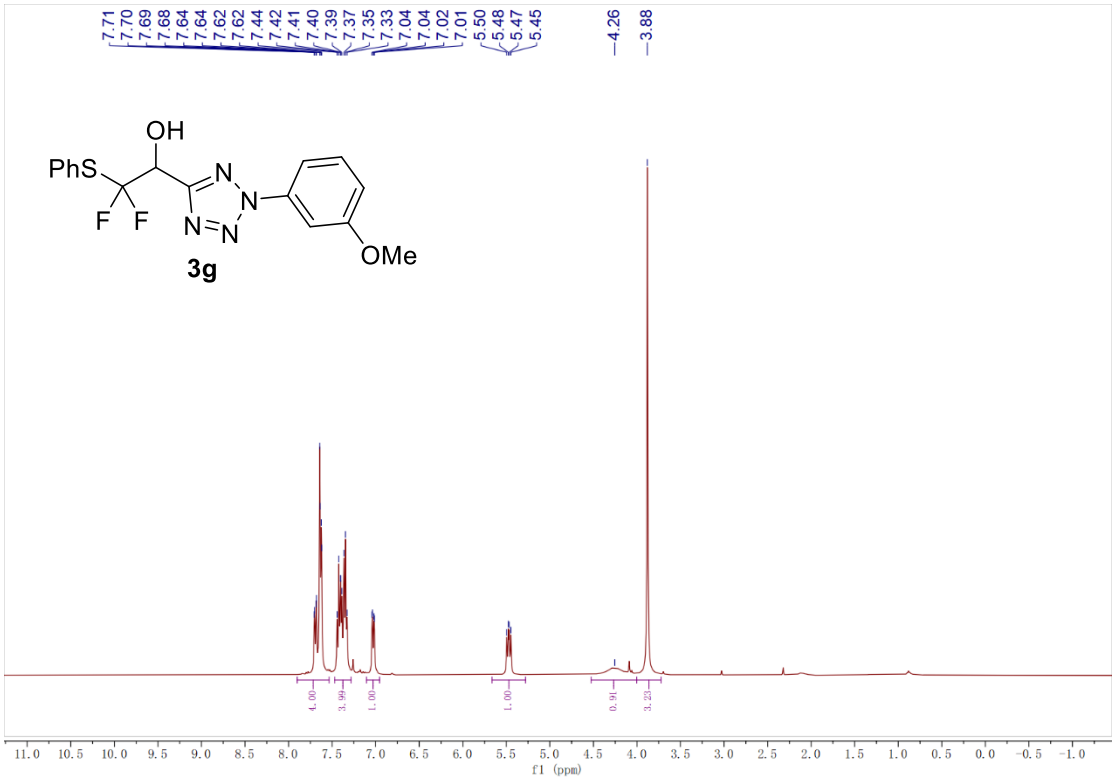


^{19}F NMR (376 MHz, Chloroform-*d*) of **3f**

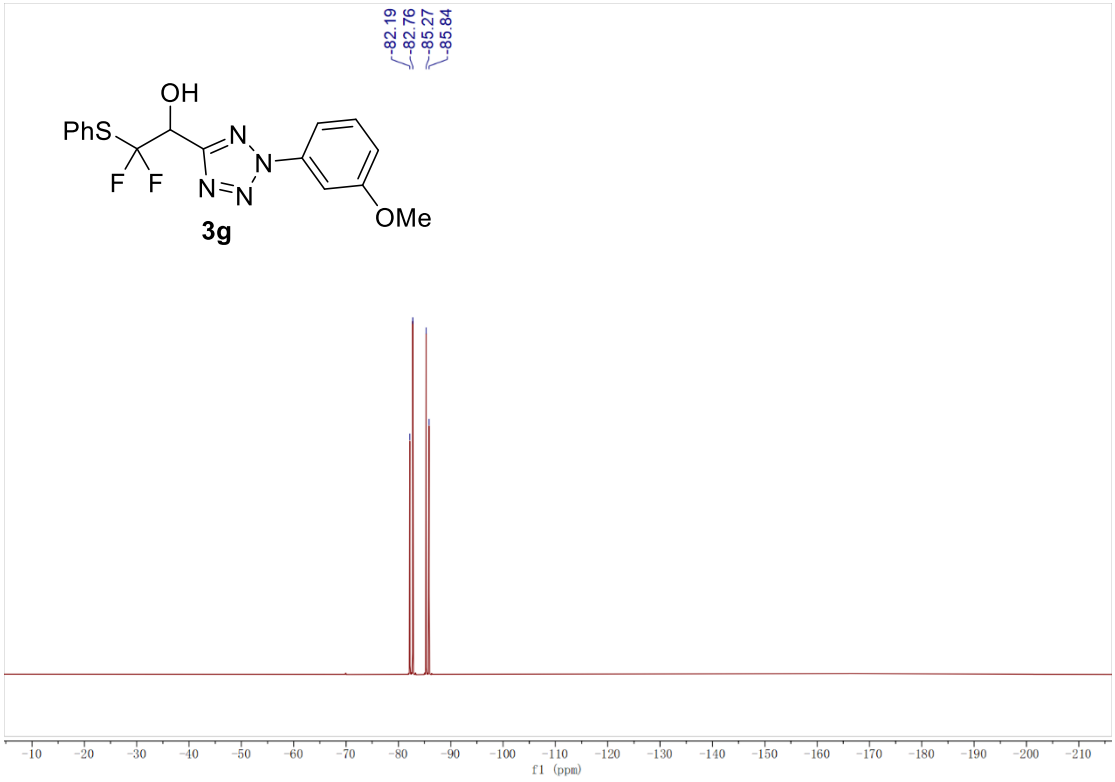


^{13}C NMR (101 MHz, Chloroform-*d*) of **3f**

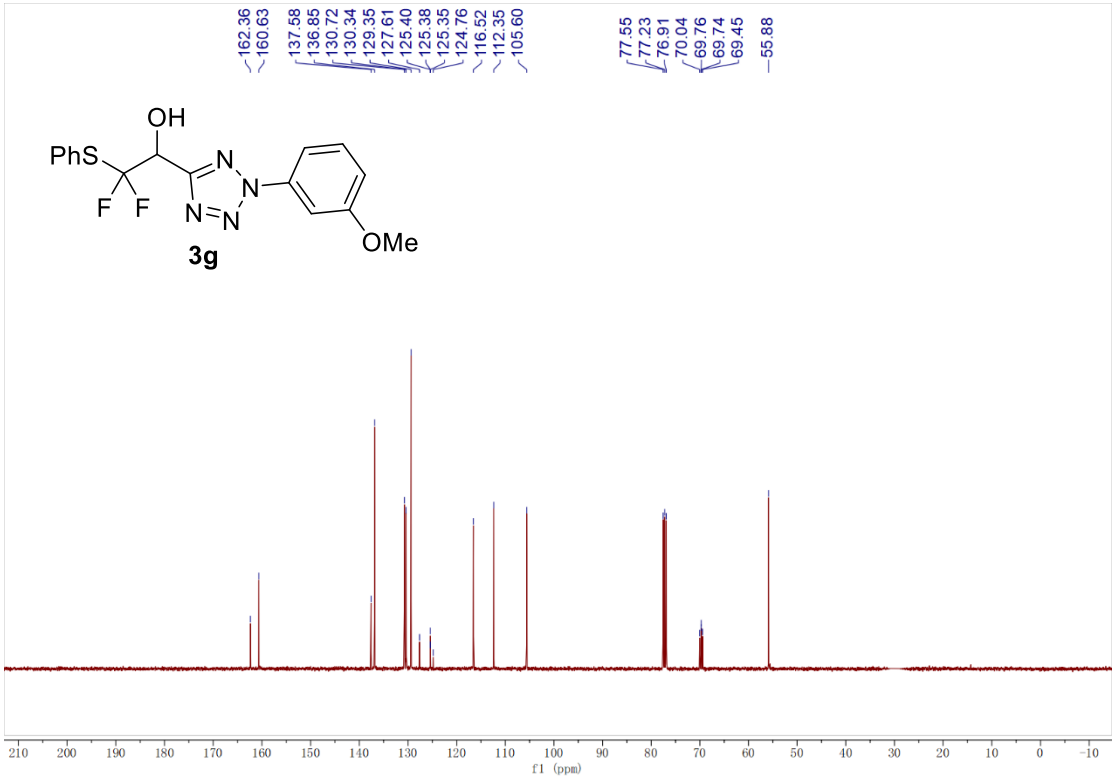
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3g**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3g**

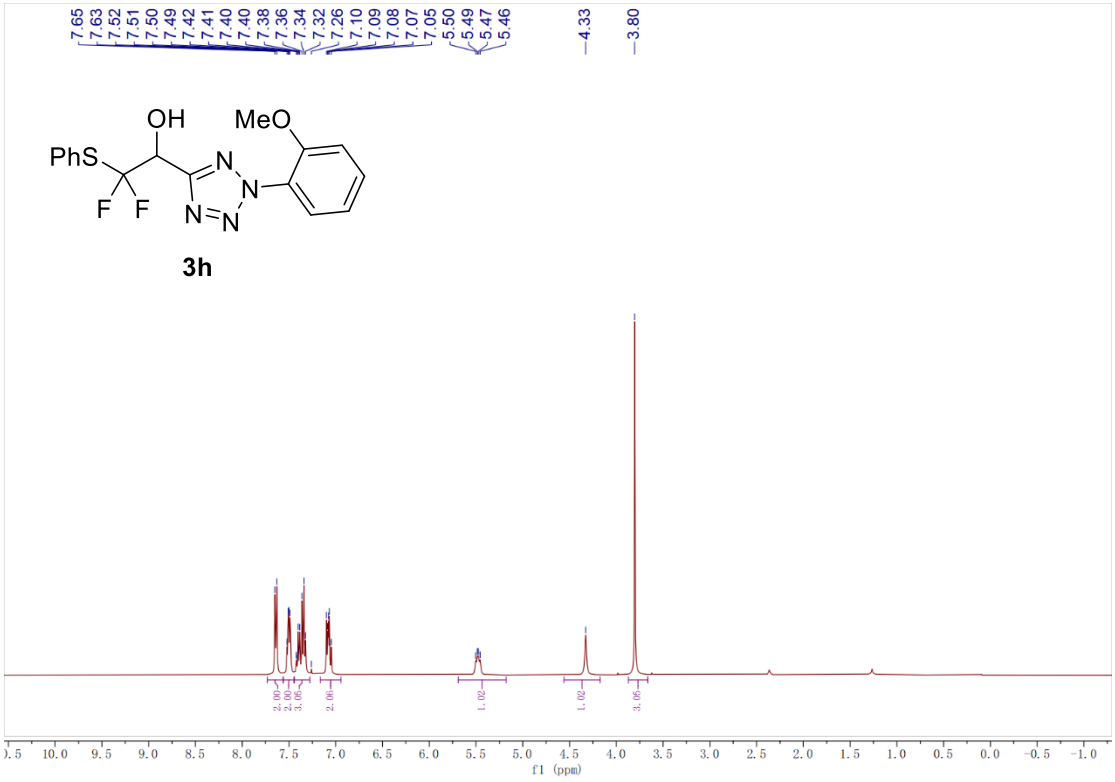


^{19}F NMR (376 MHz, Chloroform-*d*) of **3g**



^{13}C NMR (101 MHz, Chloroform-*d*) of **3g**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3h**



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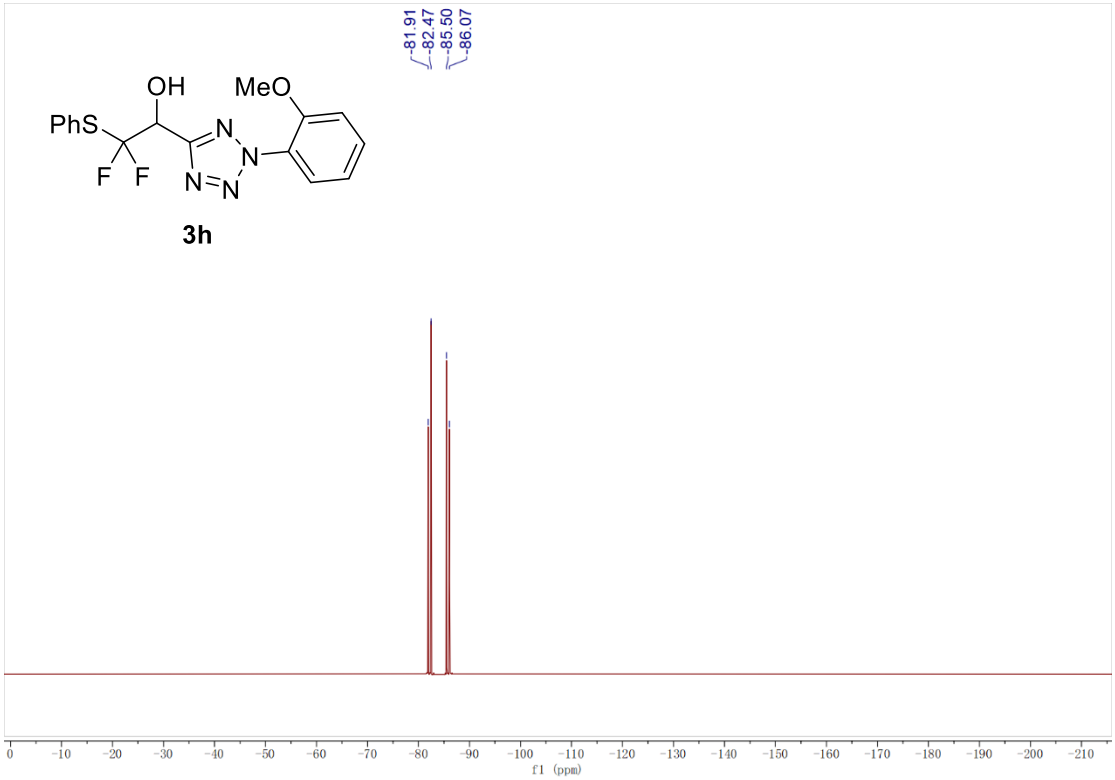

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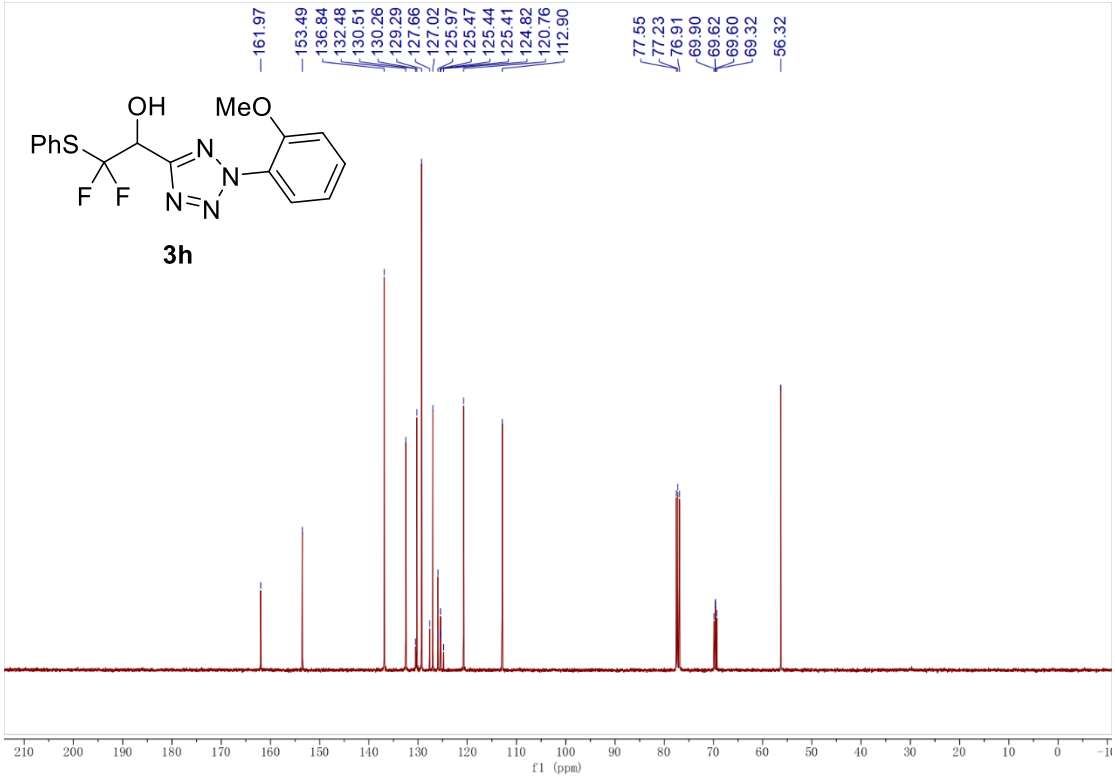
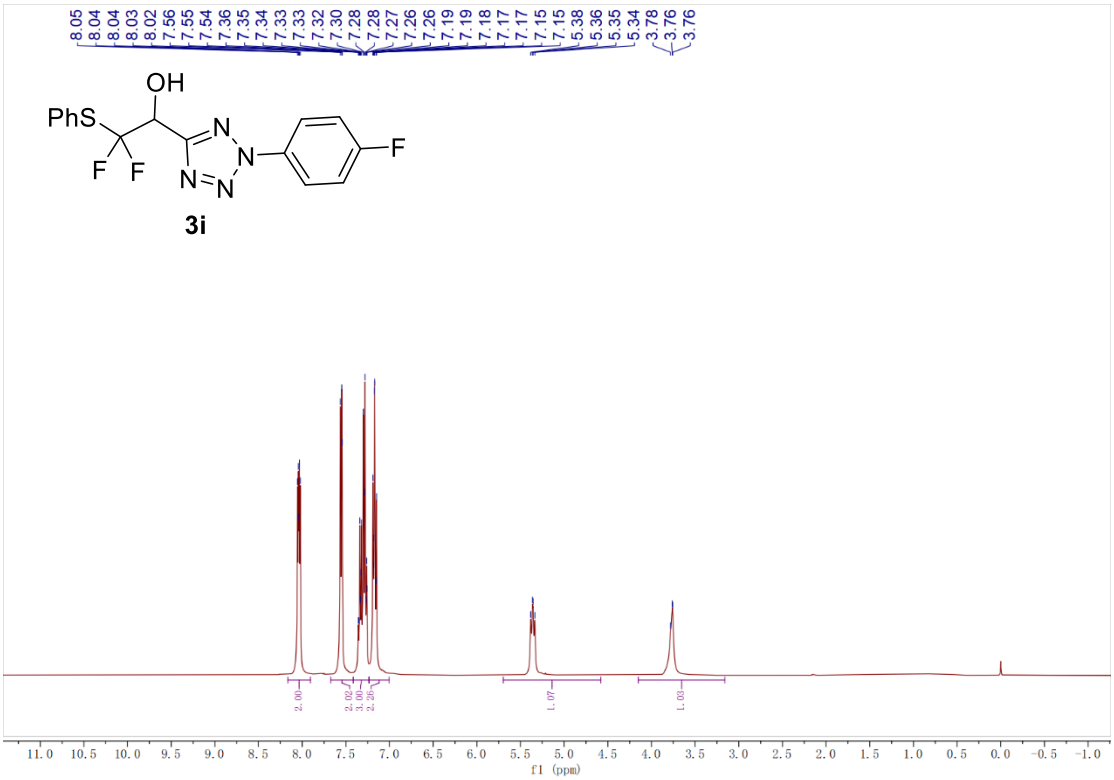
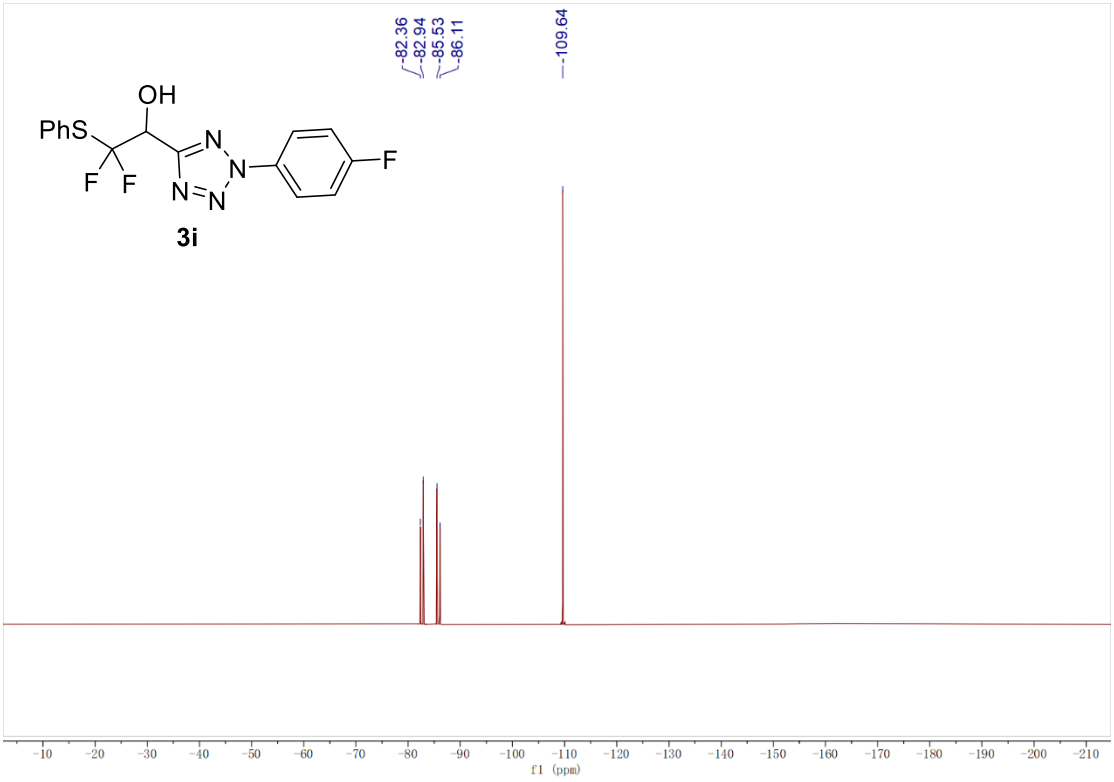


^{13}C NMR (101 MHz, Chloroform-*d*) of **3h**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3i**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3i**



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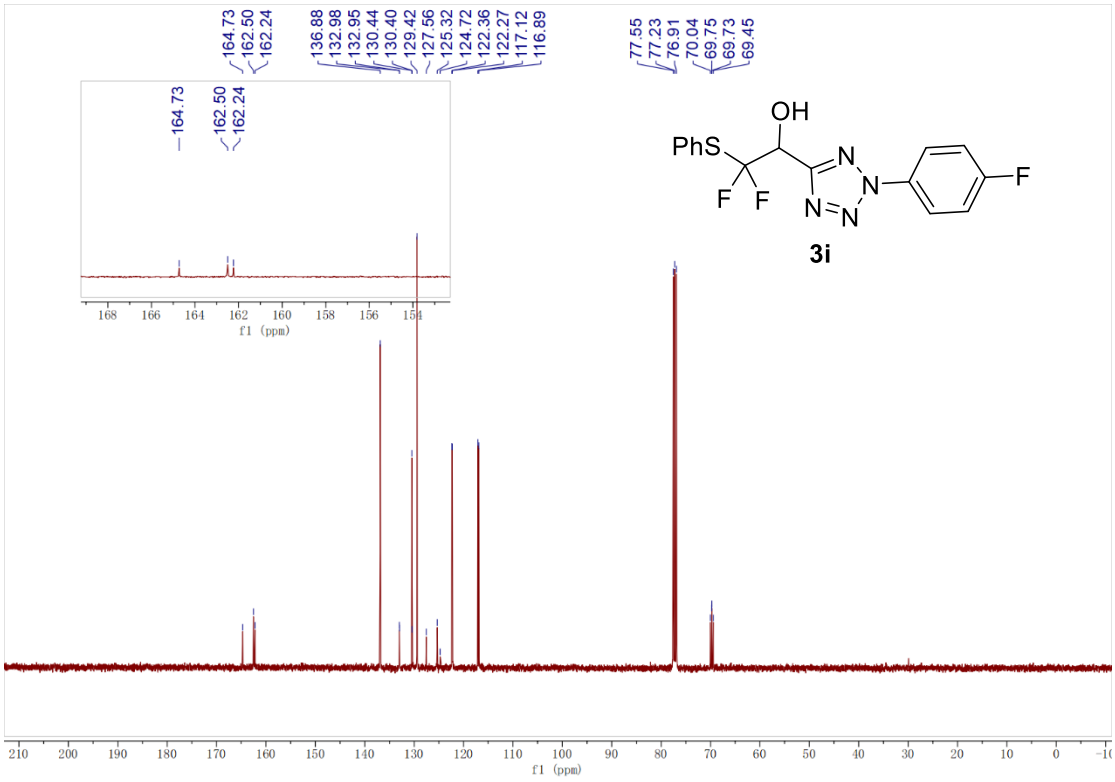

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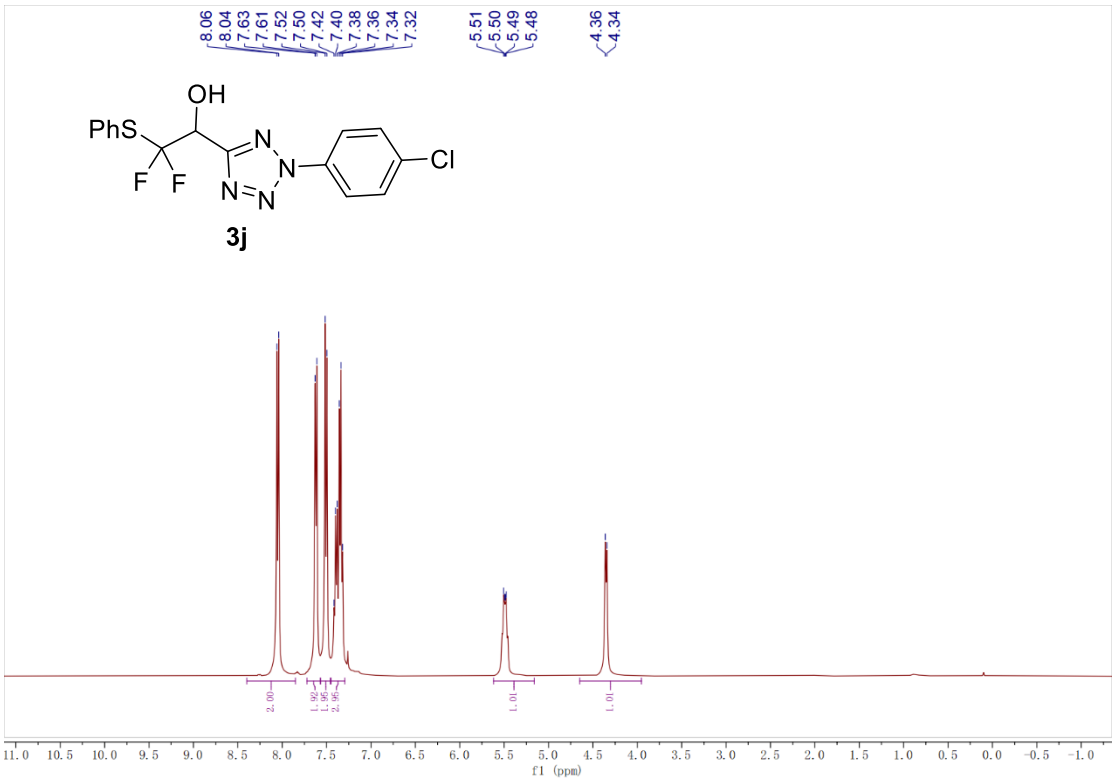

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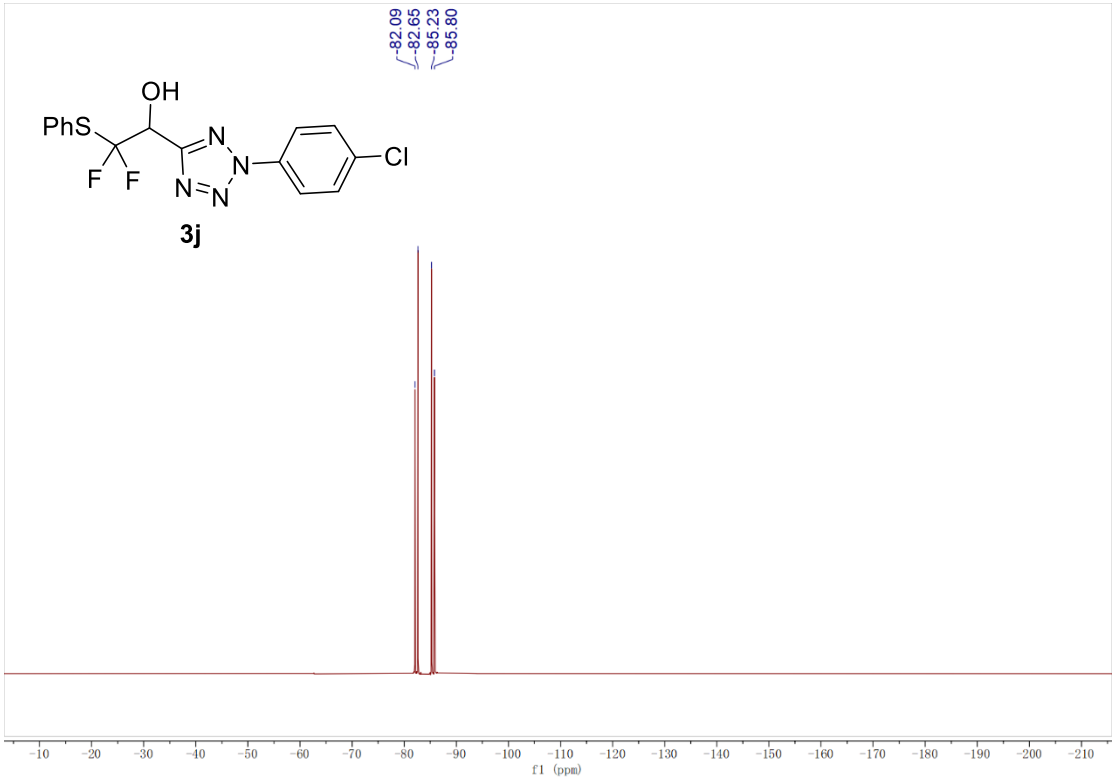
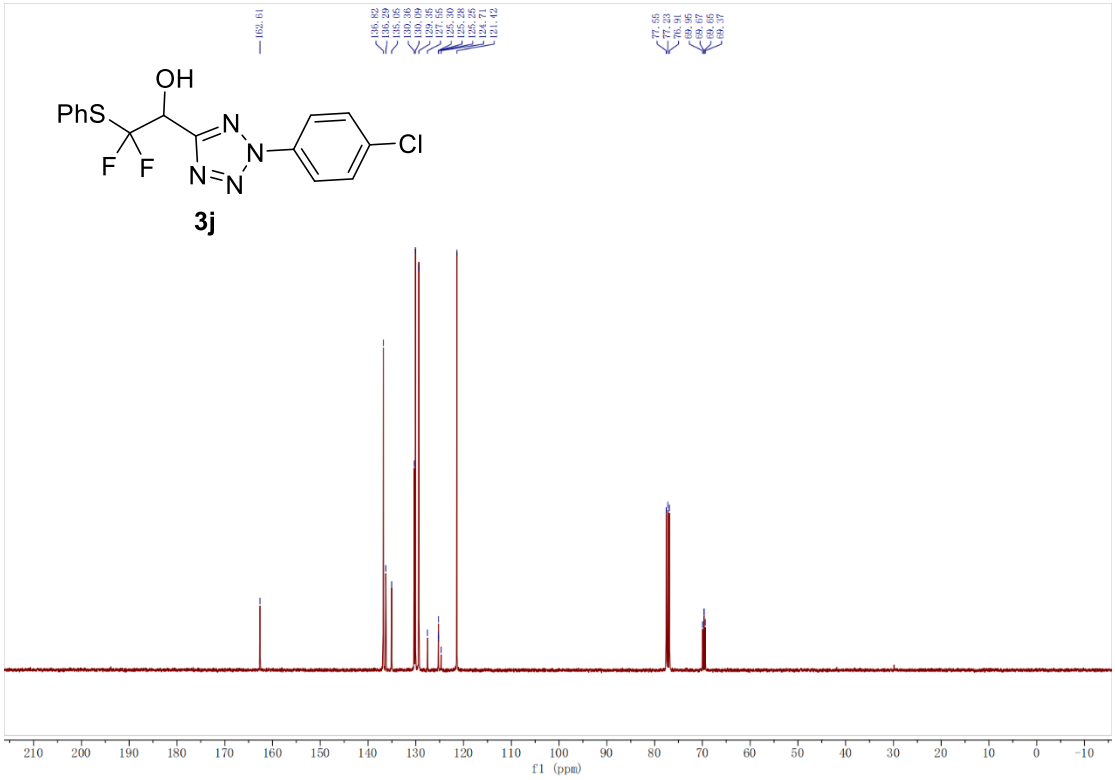
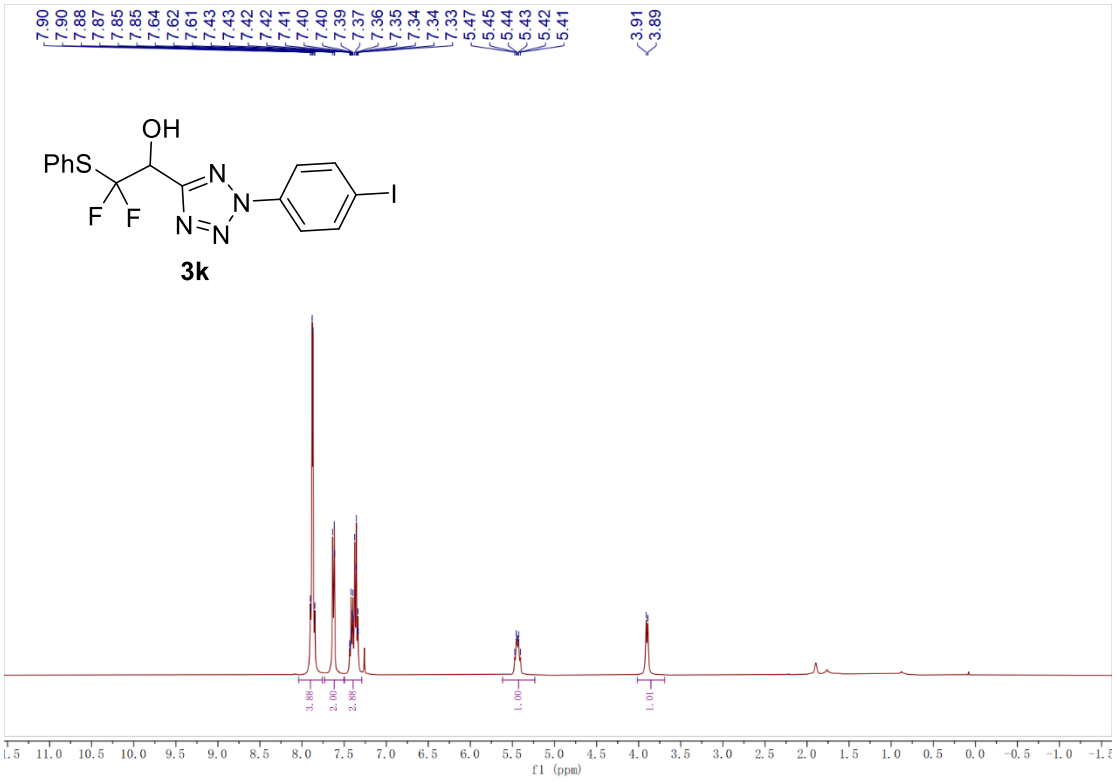


^{19}F NMR (376 MHz, Chloroform-*d*) of **3j**

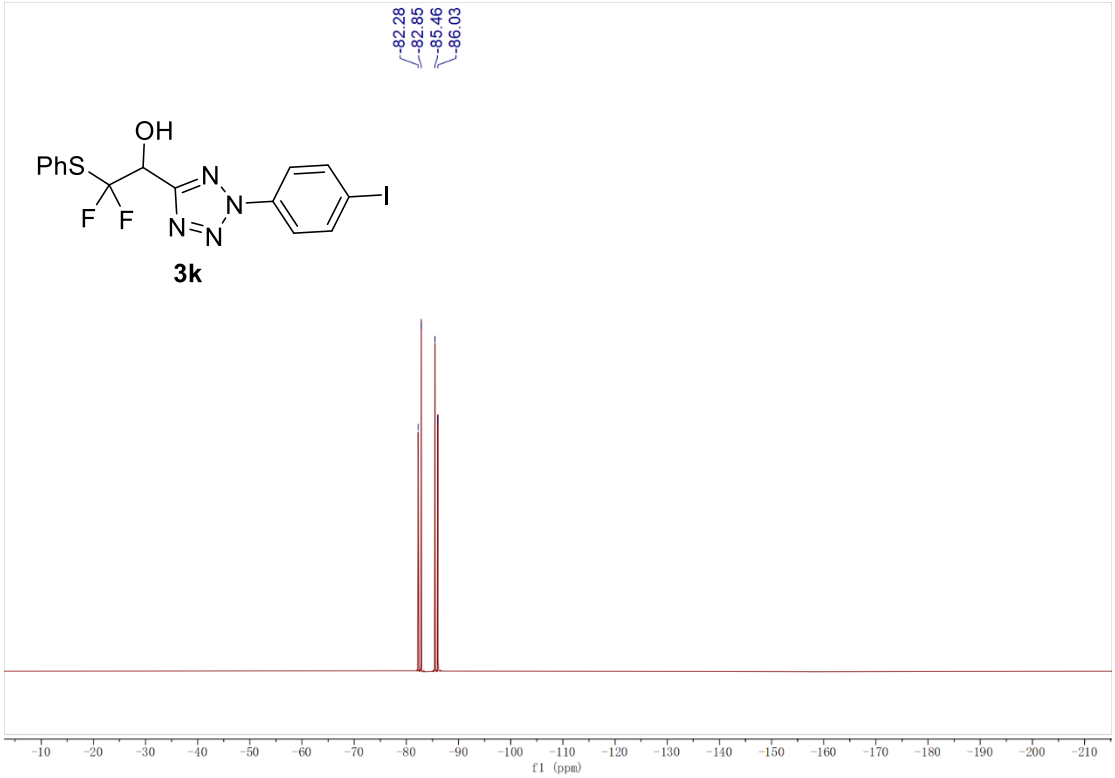


^{13}C NMR (101 MHz, Chloroform-*d*) of **3j**

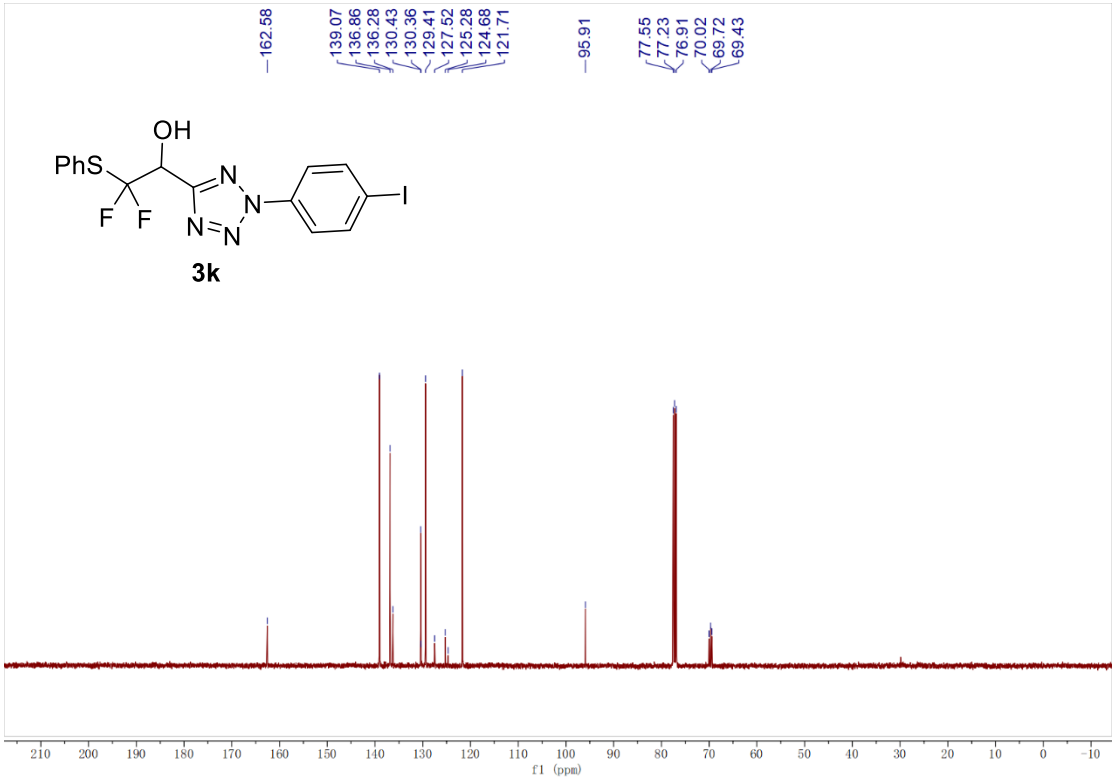
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3k**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3k**

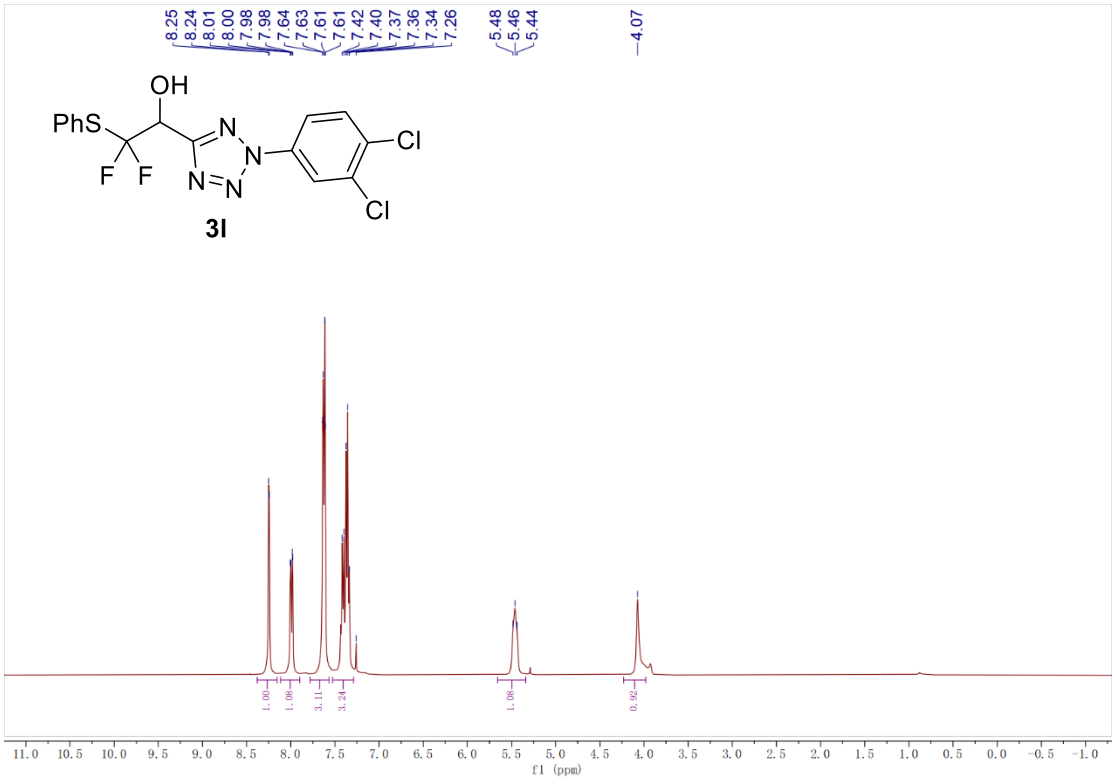


^{19}F NMR (376 MHz, Chloroform-*d*) of **3k**



^{13}C NMR (101 MHz, Chloroform-*d*) of **3k**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3l**



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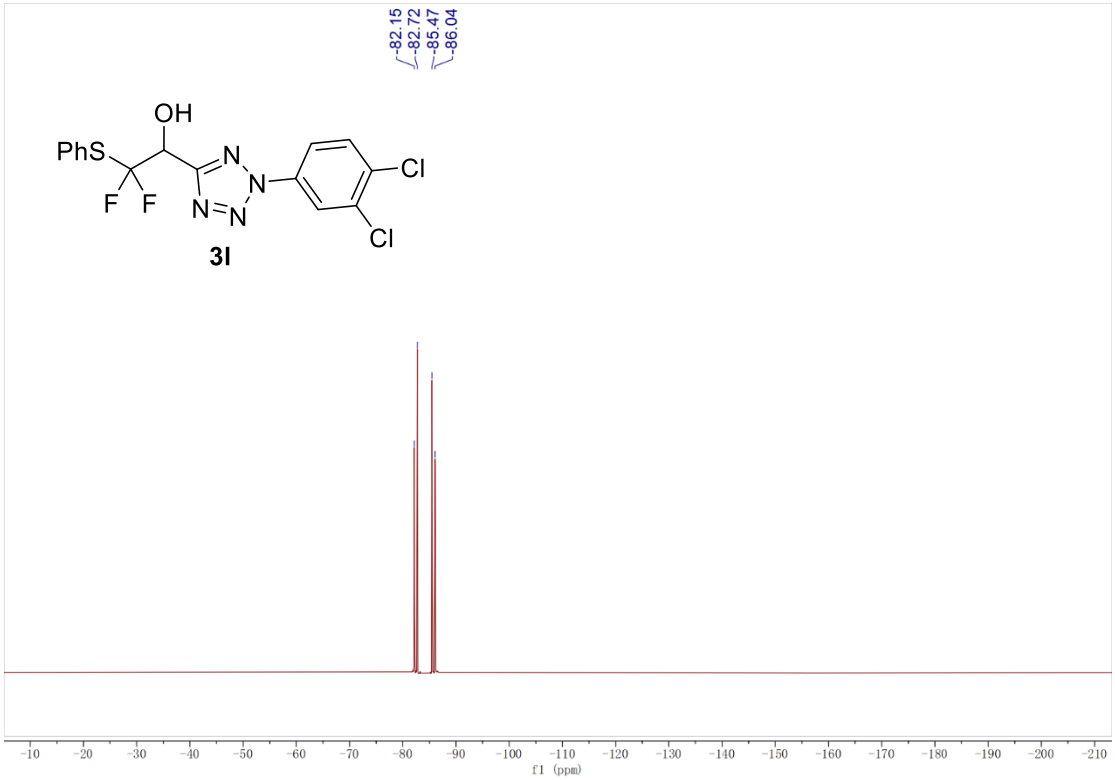

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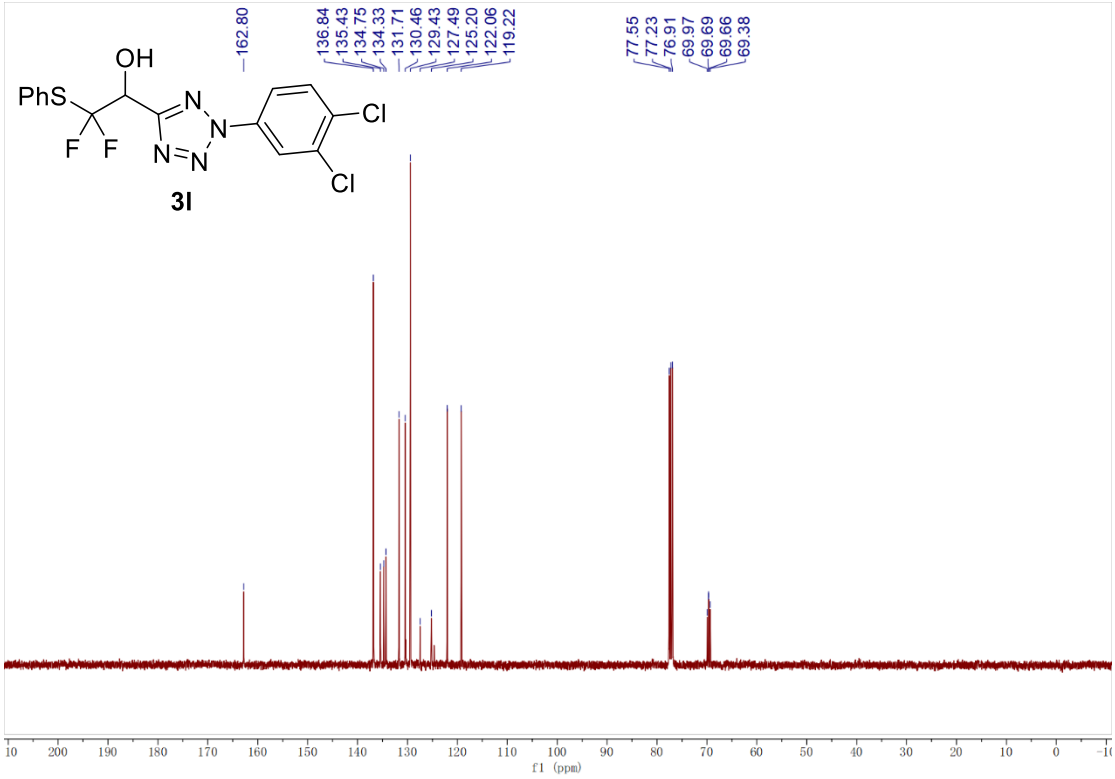
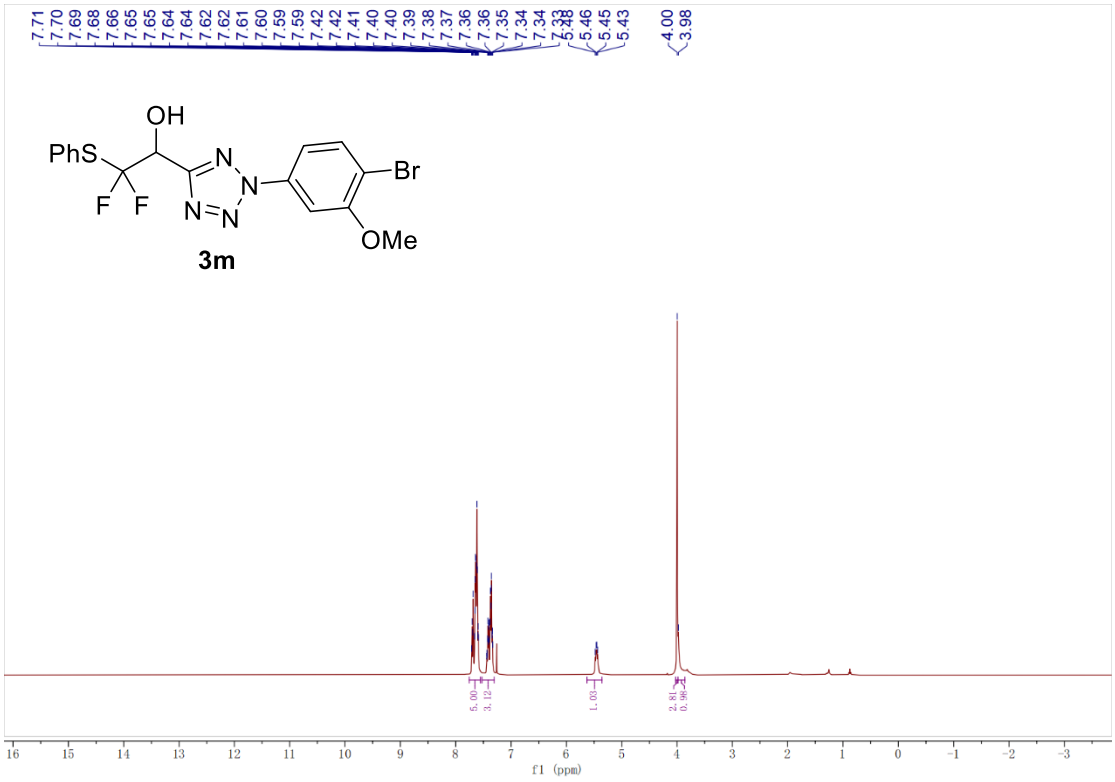


^{13}C NMR (101 MHz, Chloroform-*d*) of **3l**

^{1}H, ^{13}C, and ^{19}F NMR spectra of **3m**



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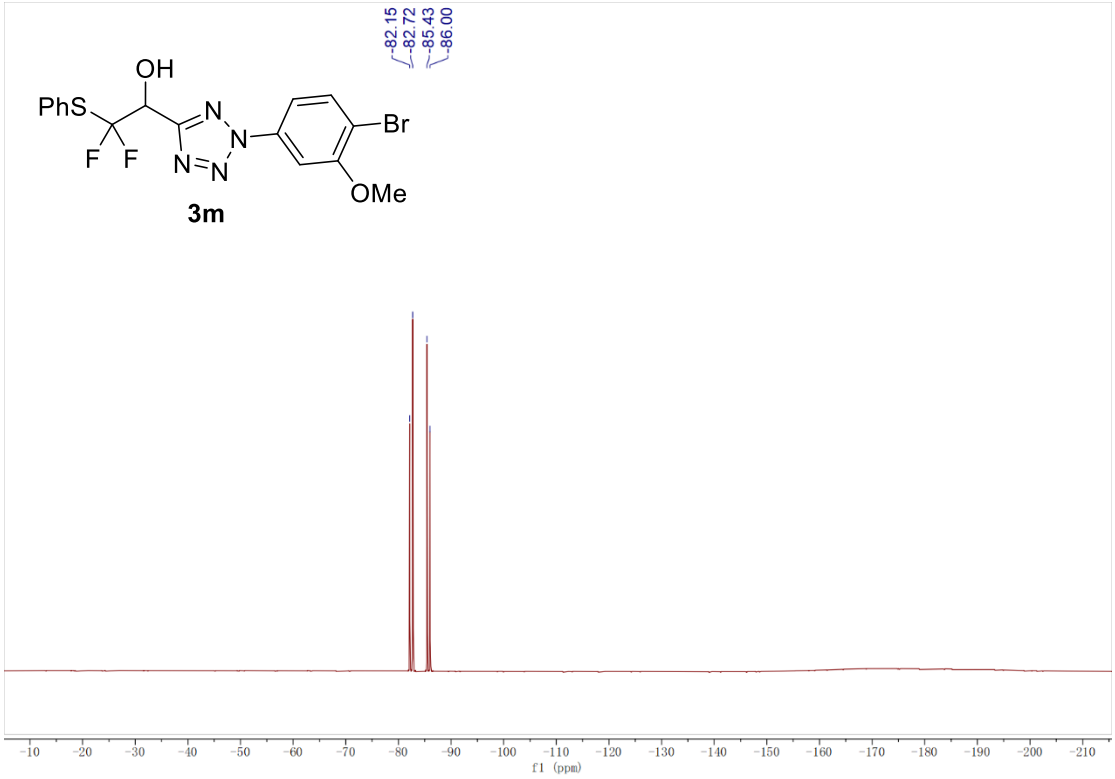

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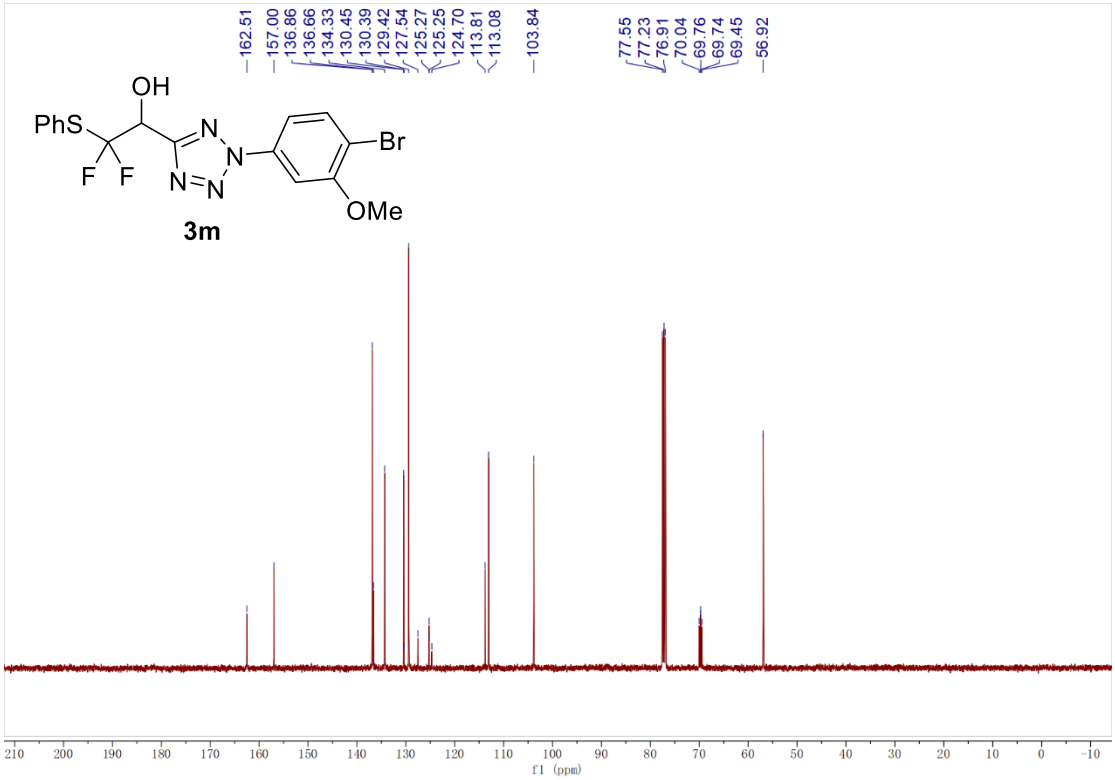
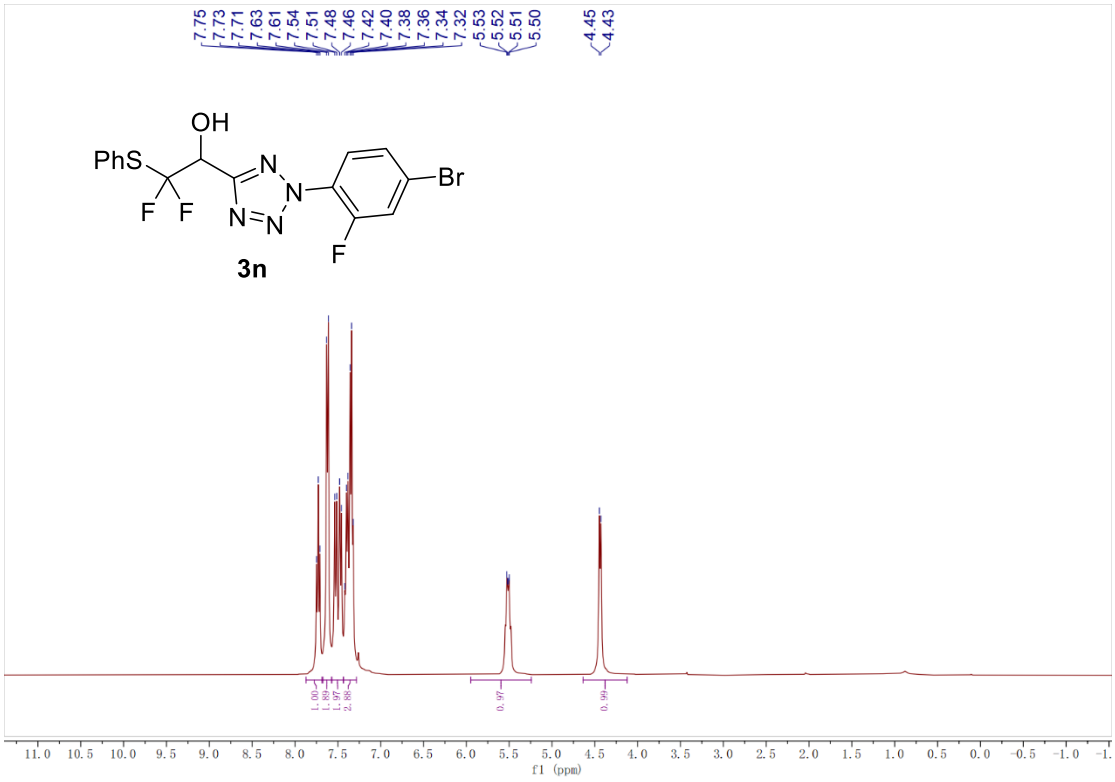
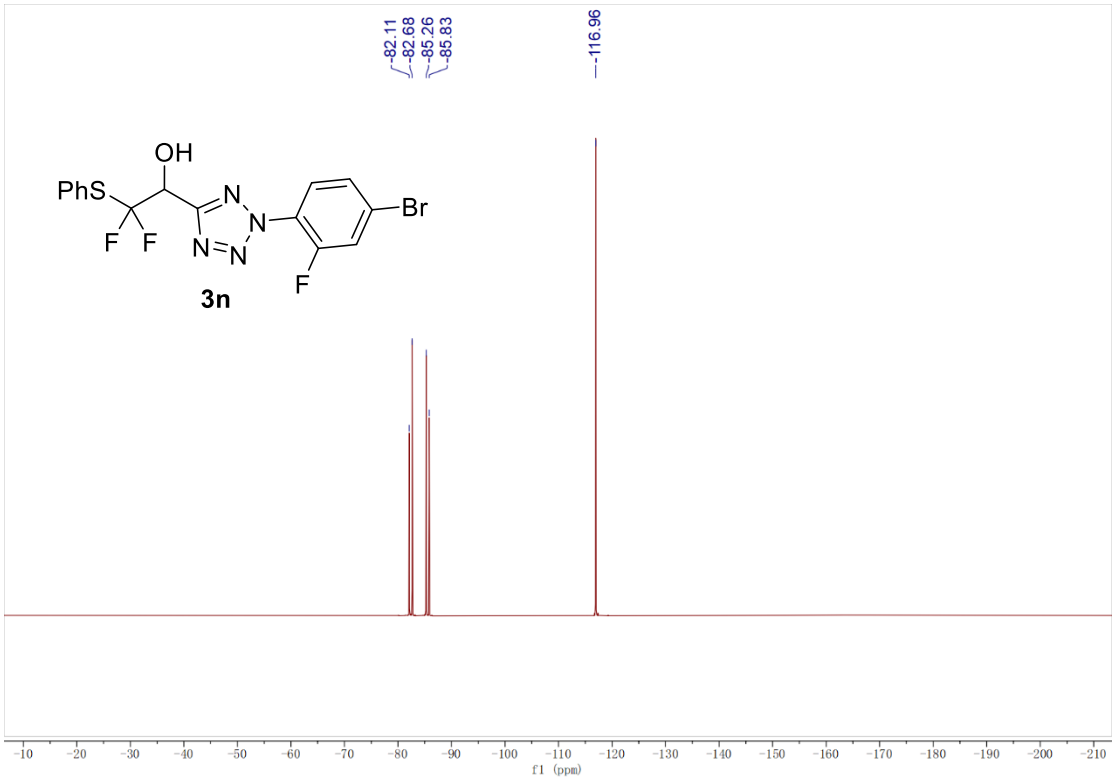


^{13}C NMR (101 MHz, Chloroform-*d*) of **3m**

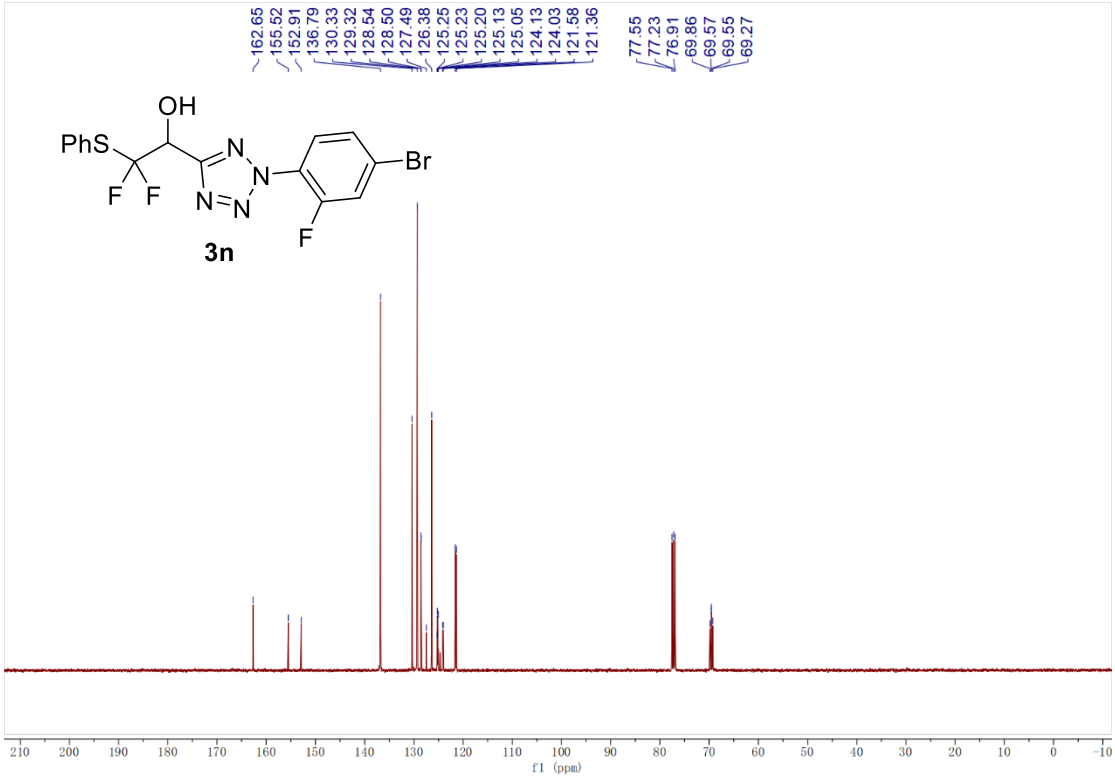
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3n**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3n**

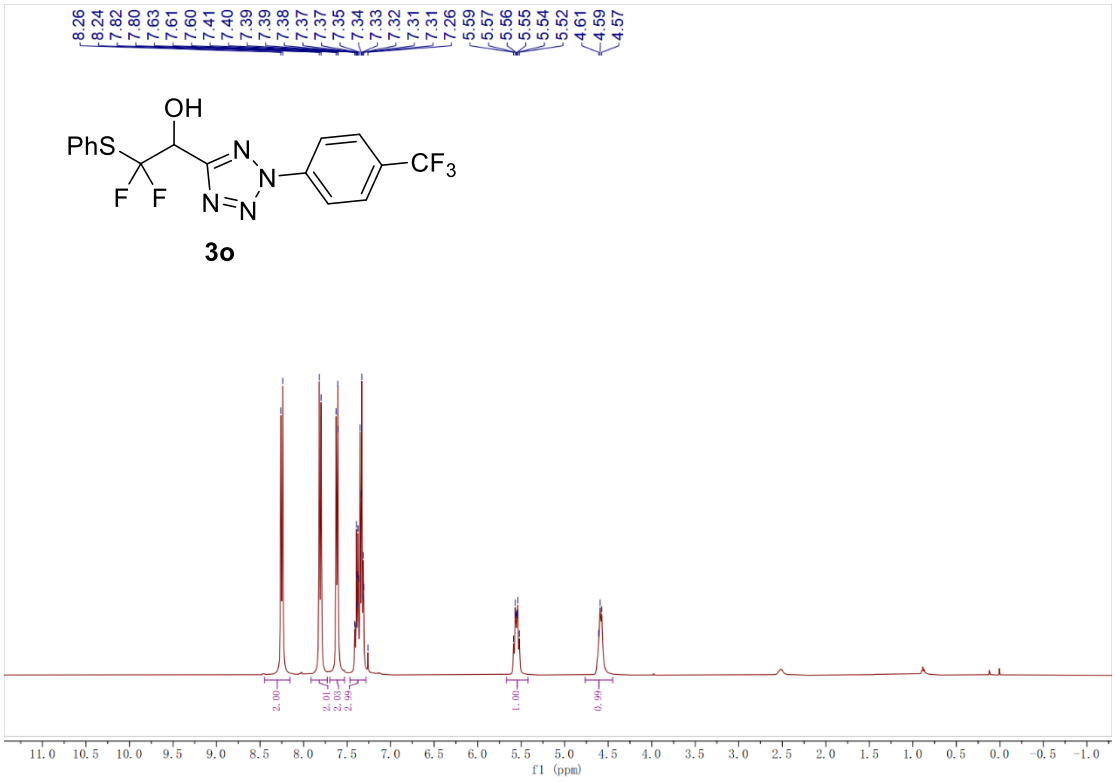


^{19}F NMR (376 MHz, Chloroform-*d*) of **3n**

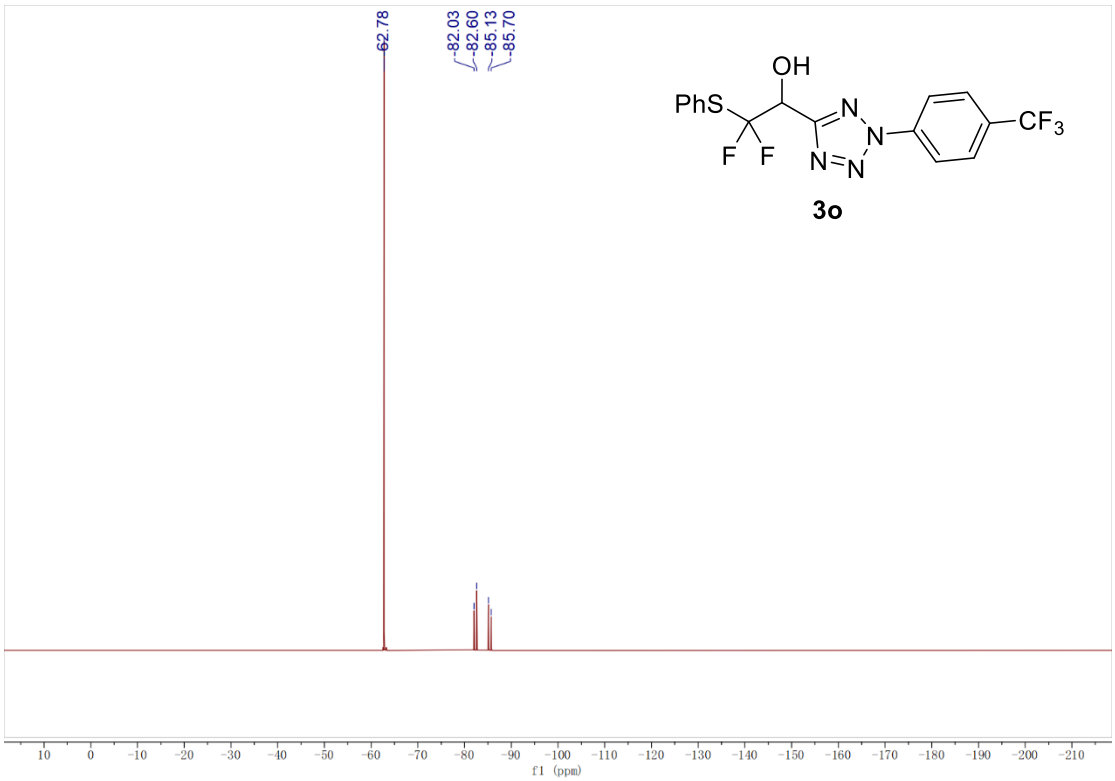


^{13}C NMR (101 MHz, Chloroform-*d*) of **3n**

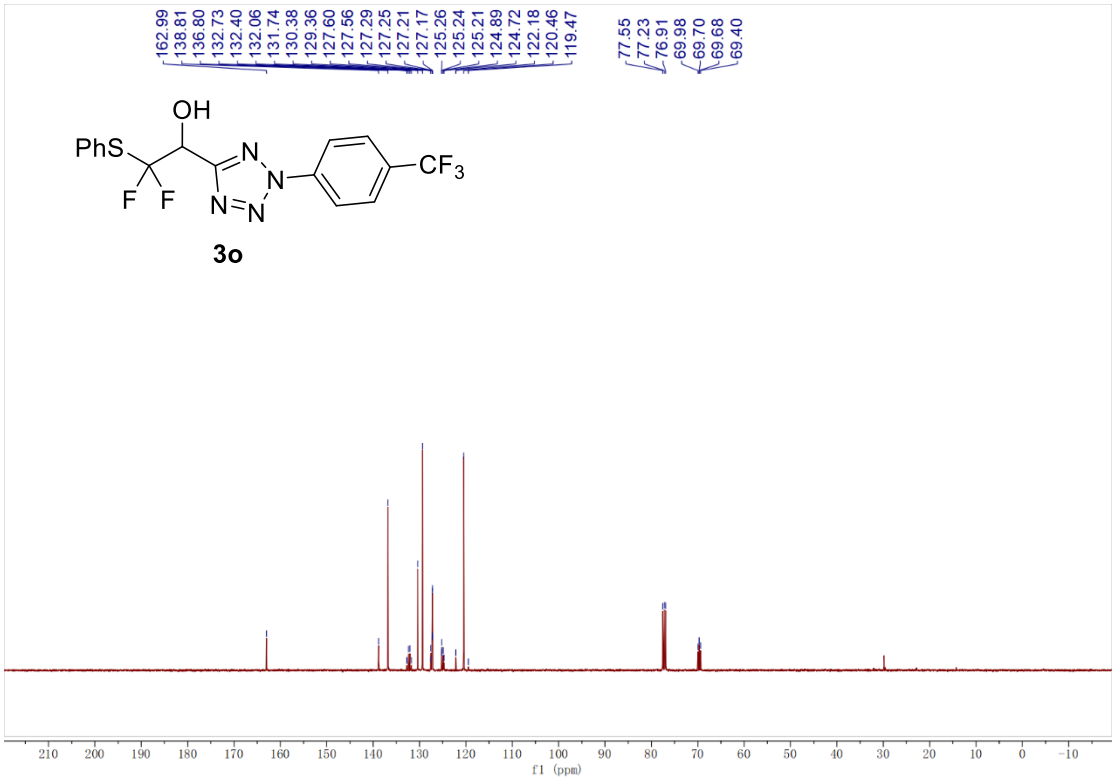
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3o**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3o**

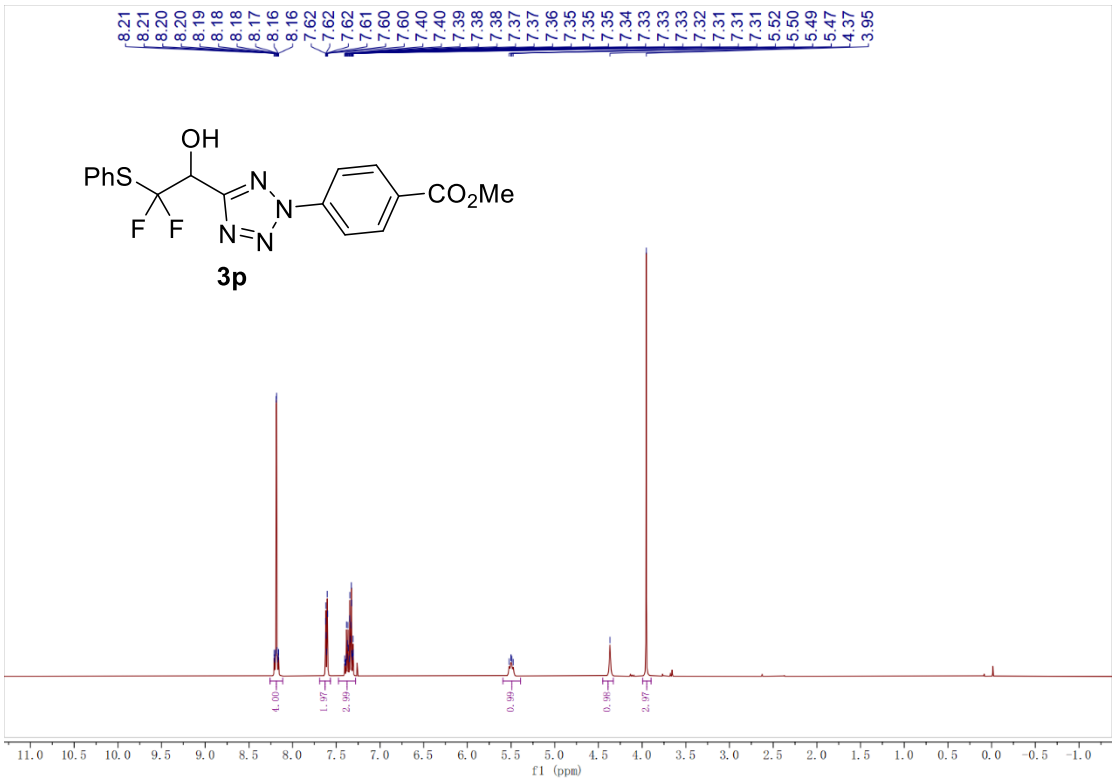


^{19}F NMR (376 MHz, Chloroform-*d*) of **3o**

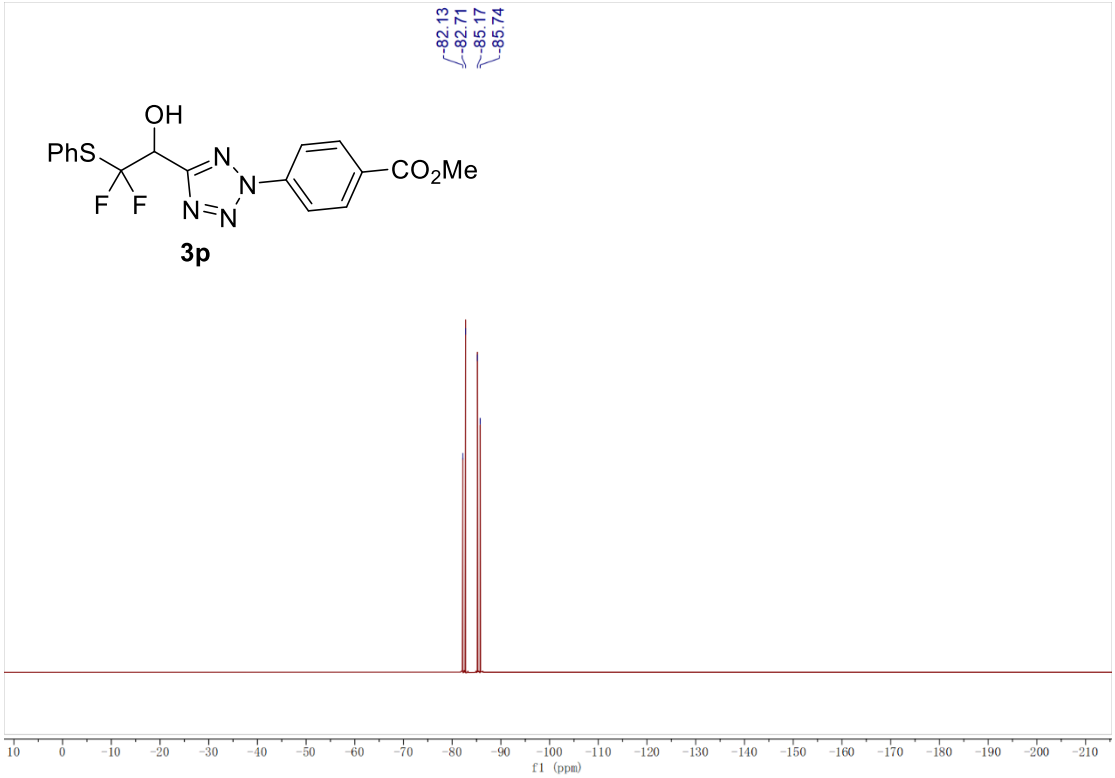


^{13}C NMR (101 MHz, Chloroform-*d*) of **3o**

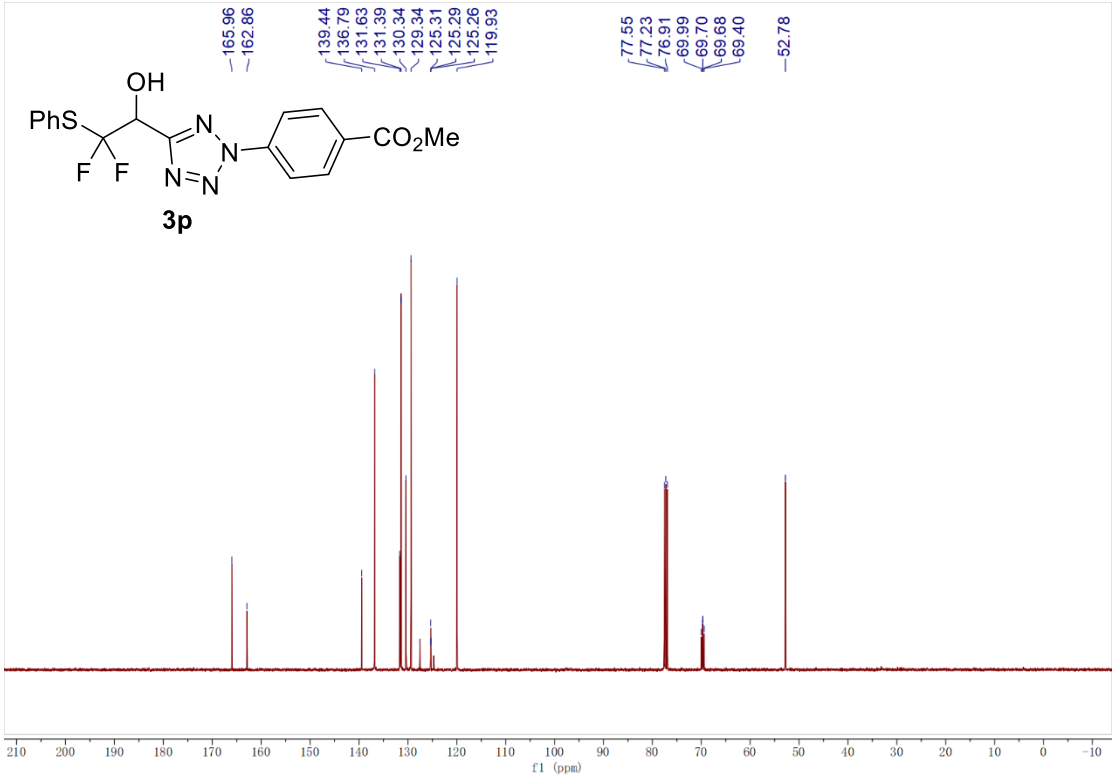
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3p**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3p**

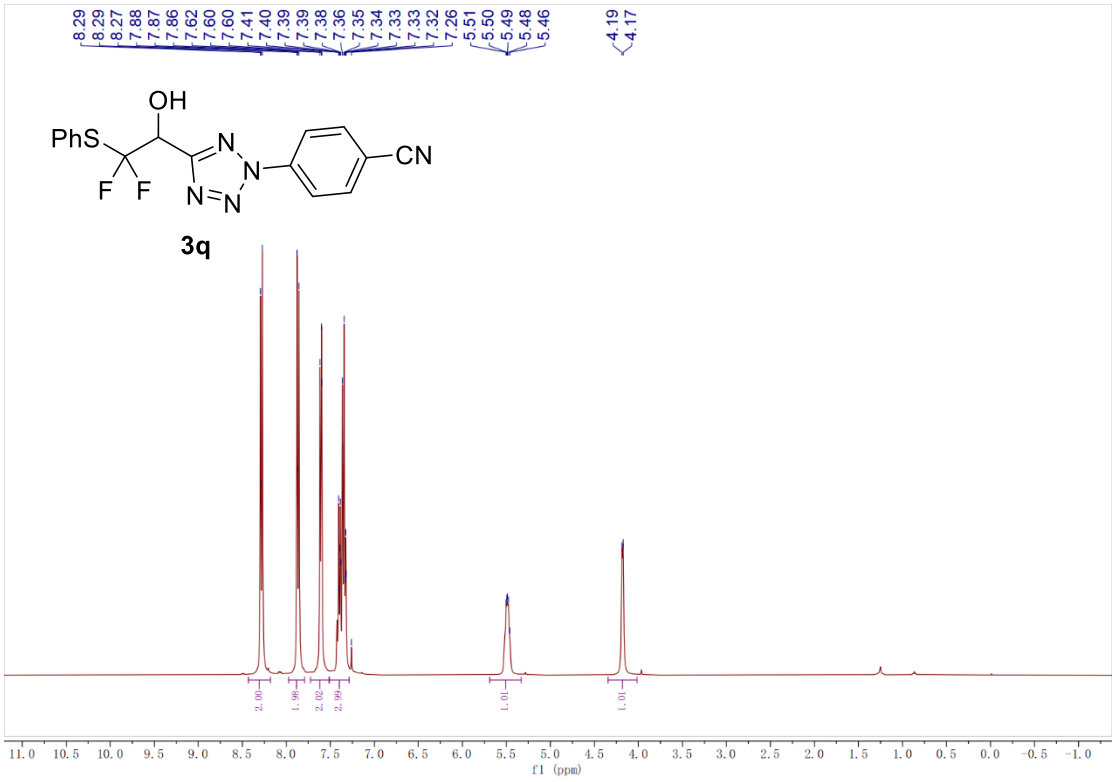


^{19}F NMR (376 MHz, Chloroform-*d*) of **3p**

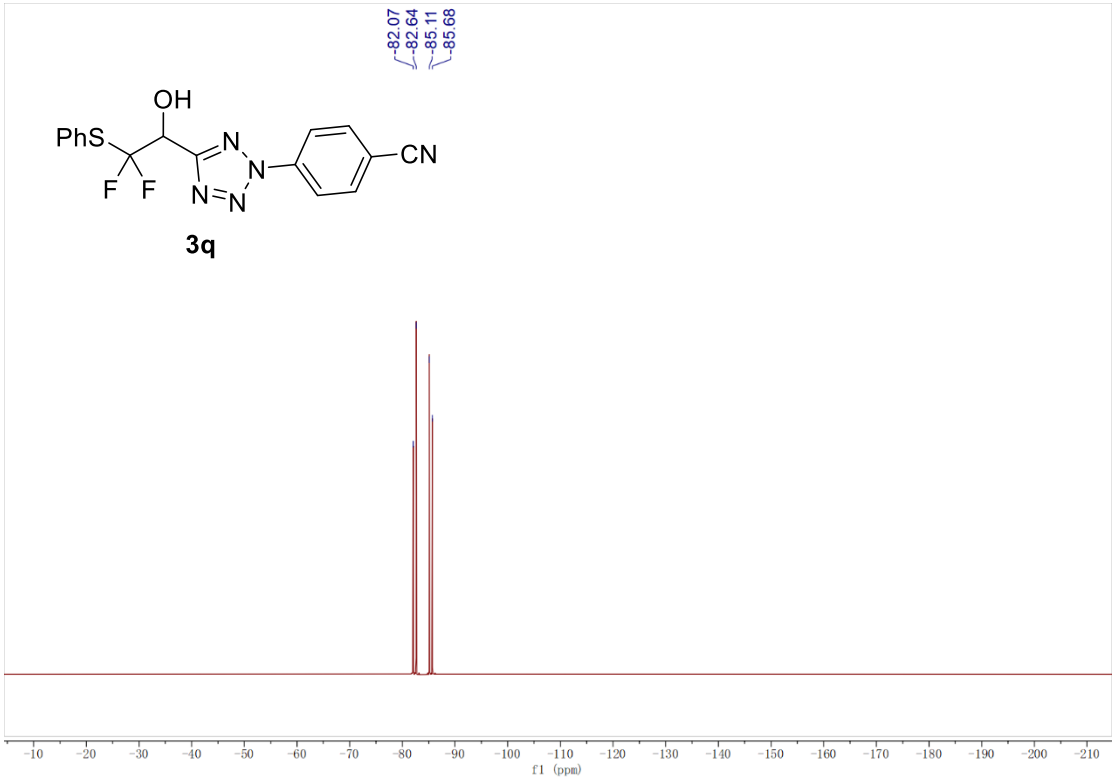


^{13}C NMR (101 MHz, Chloroform-*d*) of **3p**

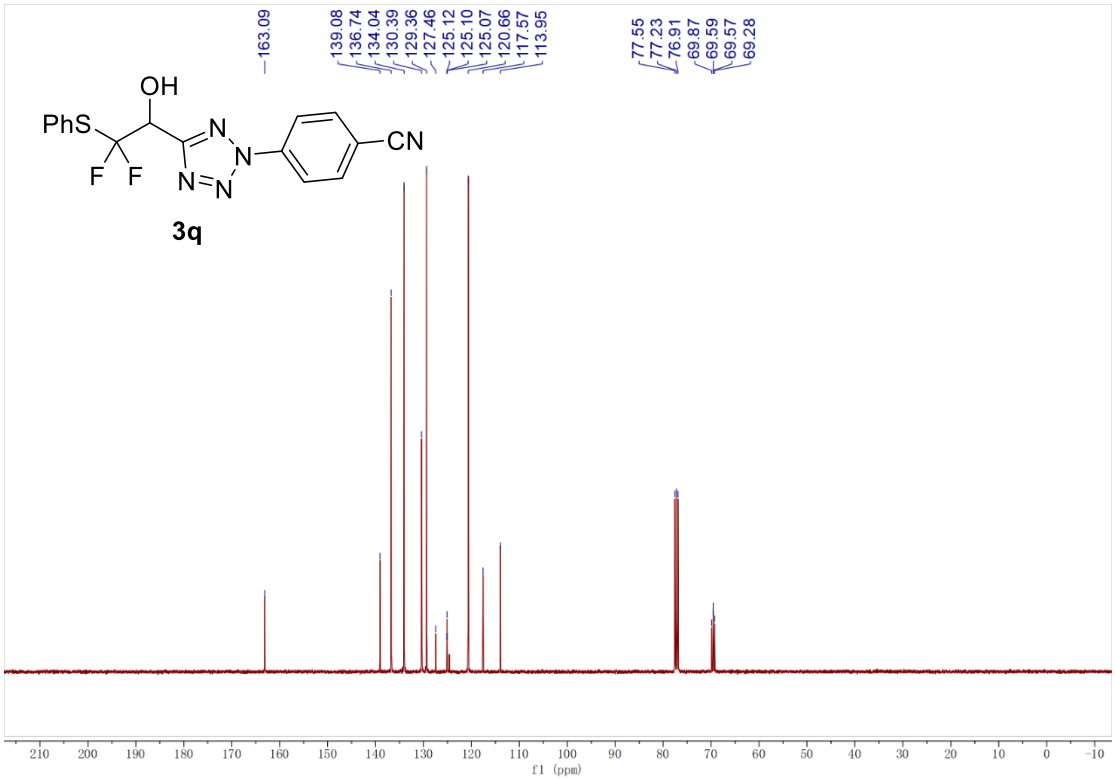
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3q**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3q**

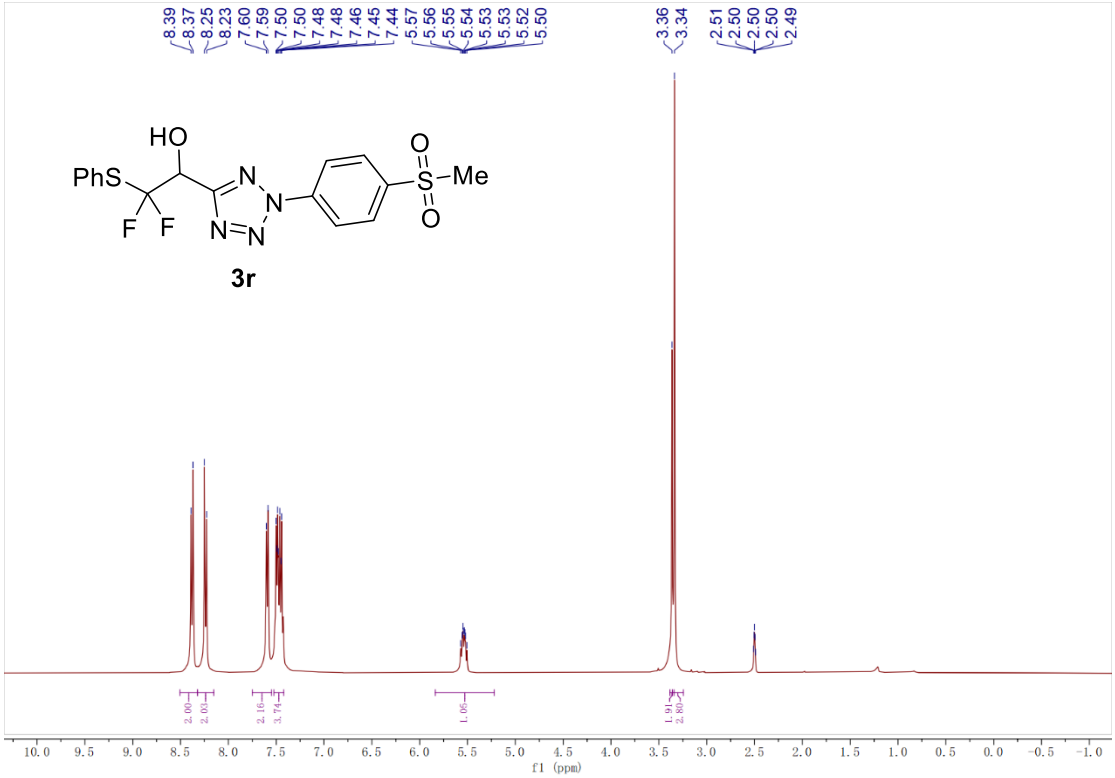


^{19}F NMR (376 MHz, Chloroform-*d*) of **3q**

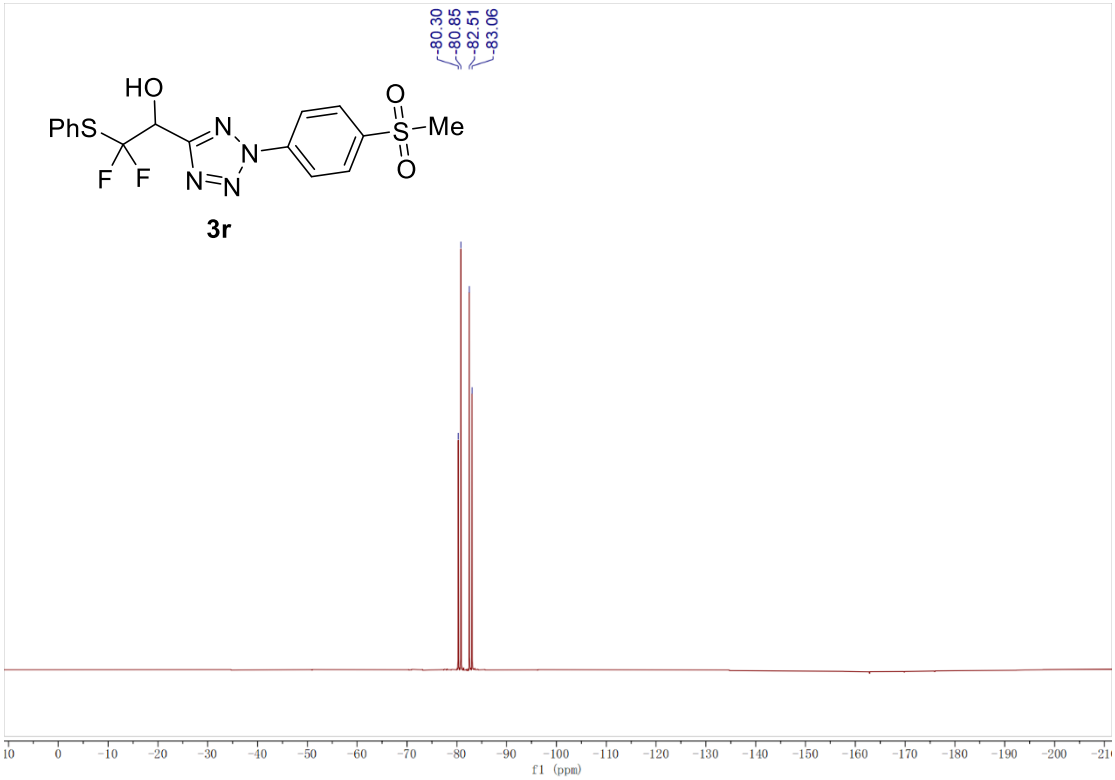


^{13}C NMR (101 MHz, Chloroform-*d*) of **3q**

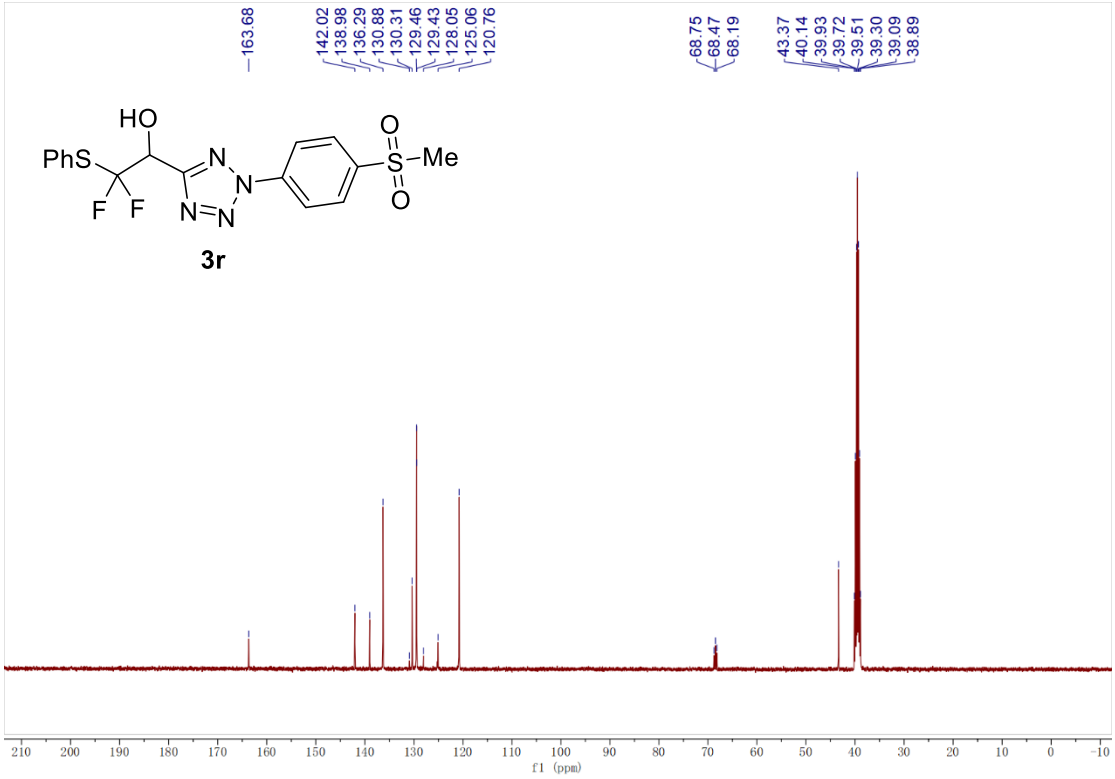
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3r**



^{1}H NMR (400 MHz, DMSO-d_6) of **3r**

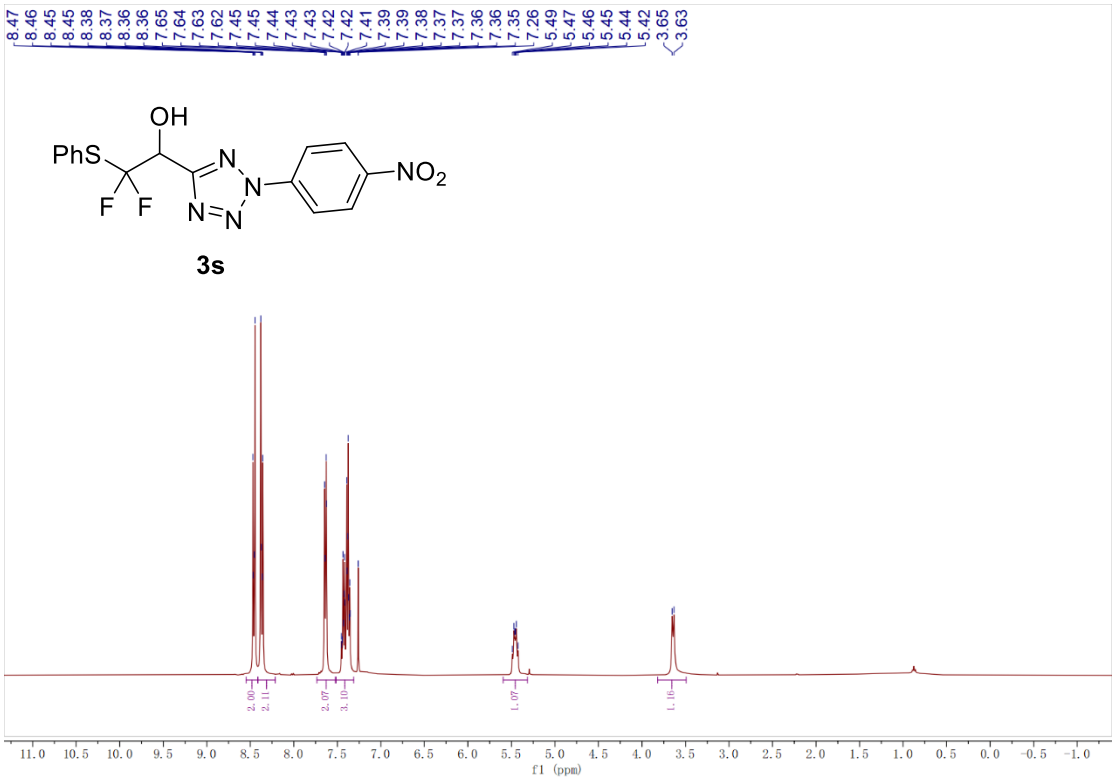


^{19}F NMR (376 MHz, DMSO-d_6) of **3r**

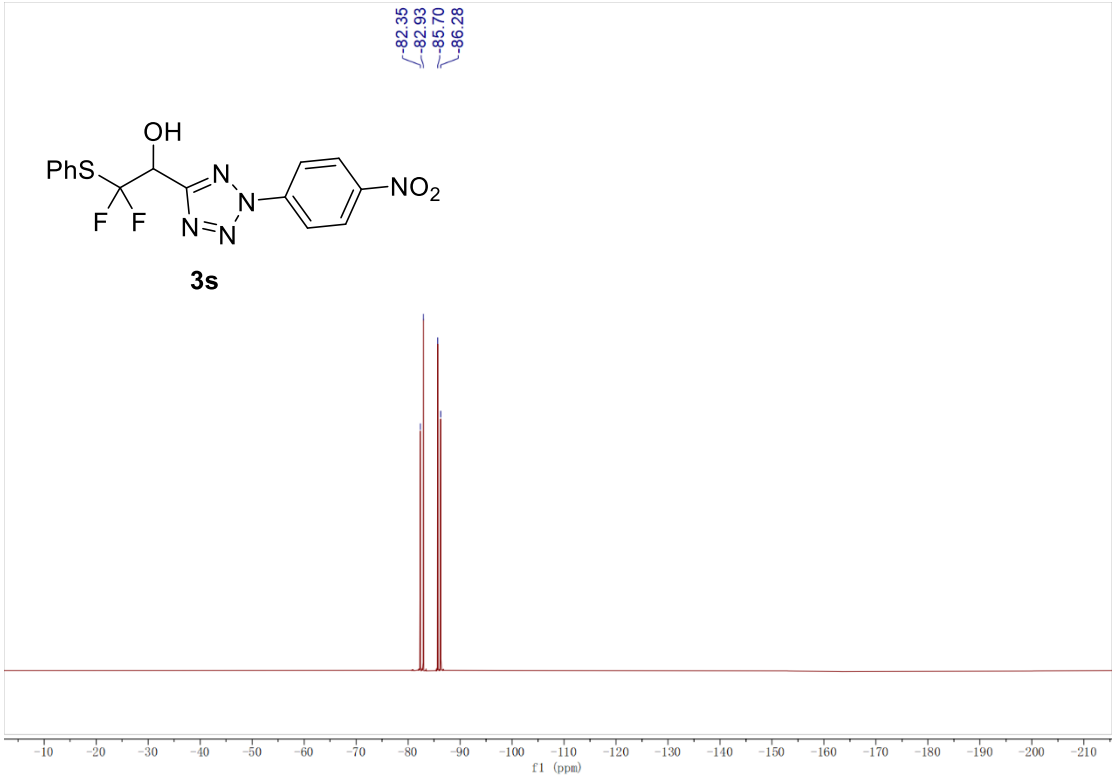


^{13}C NMR (101 MHz, DMSO-d_6) of **3r**

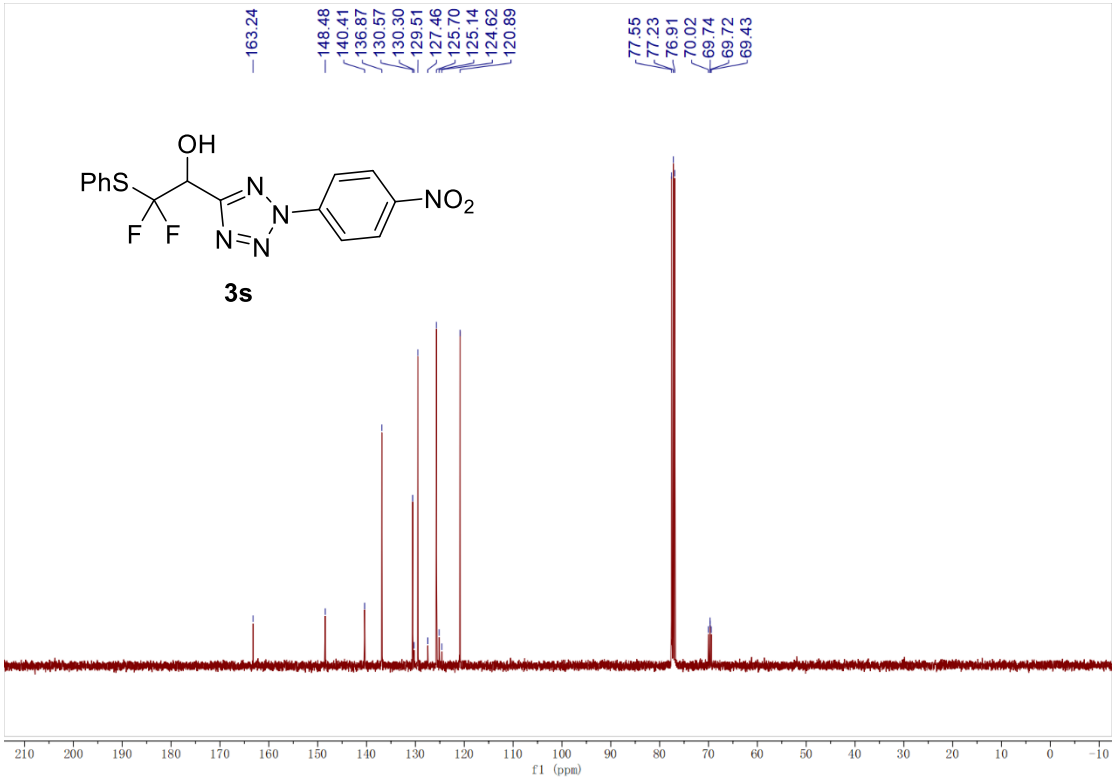
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3s**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3s**

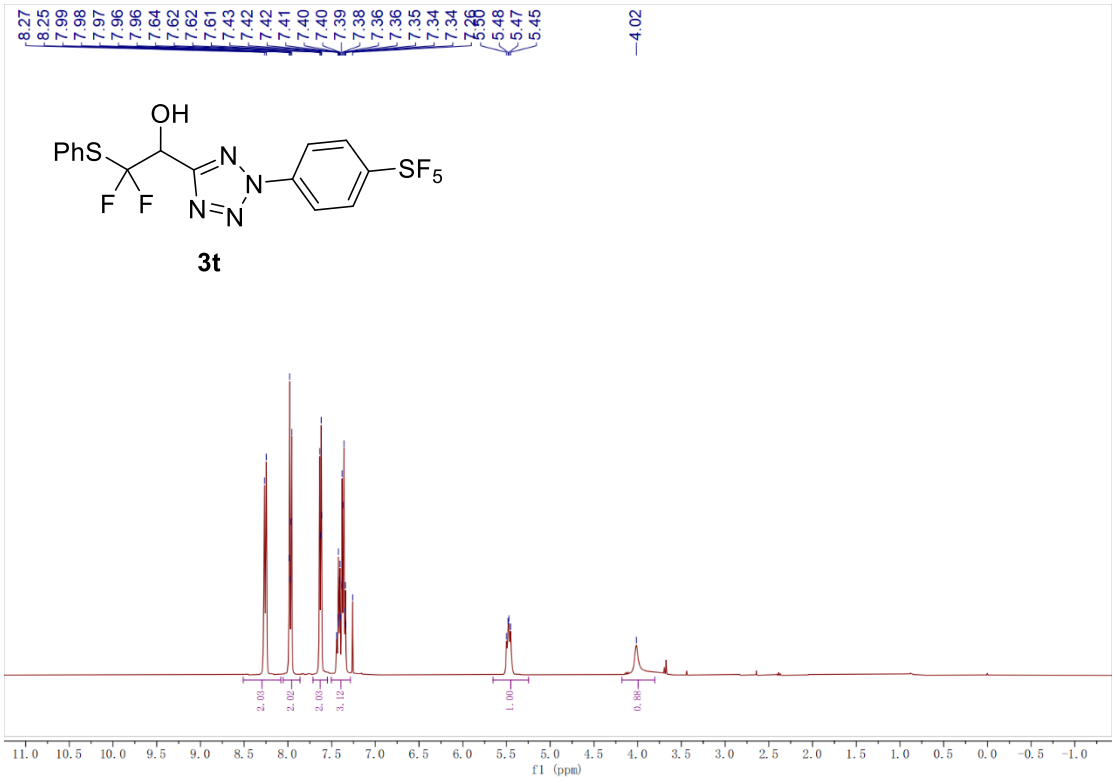


^{19}F NMR (376 MHz, Chloroform-*d*) of **3s**

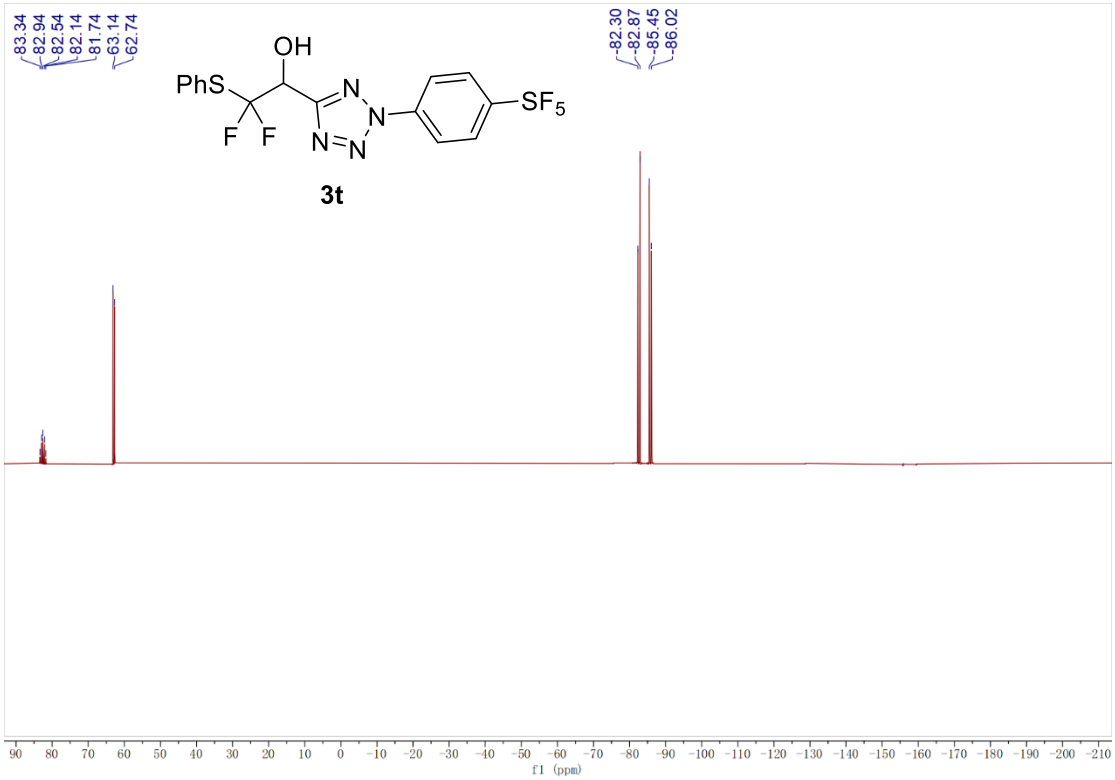


^{13}C NMR (101 MHz, Chloroform-*d*) of **3s**

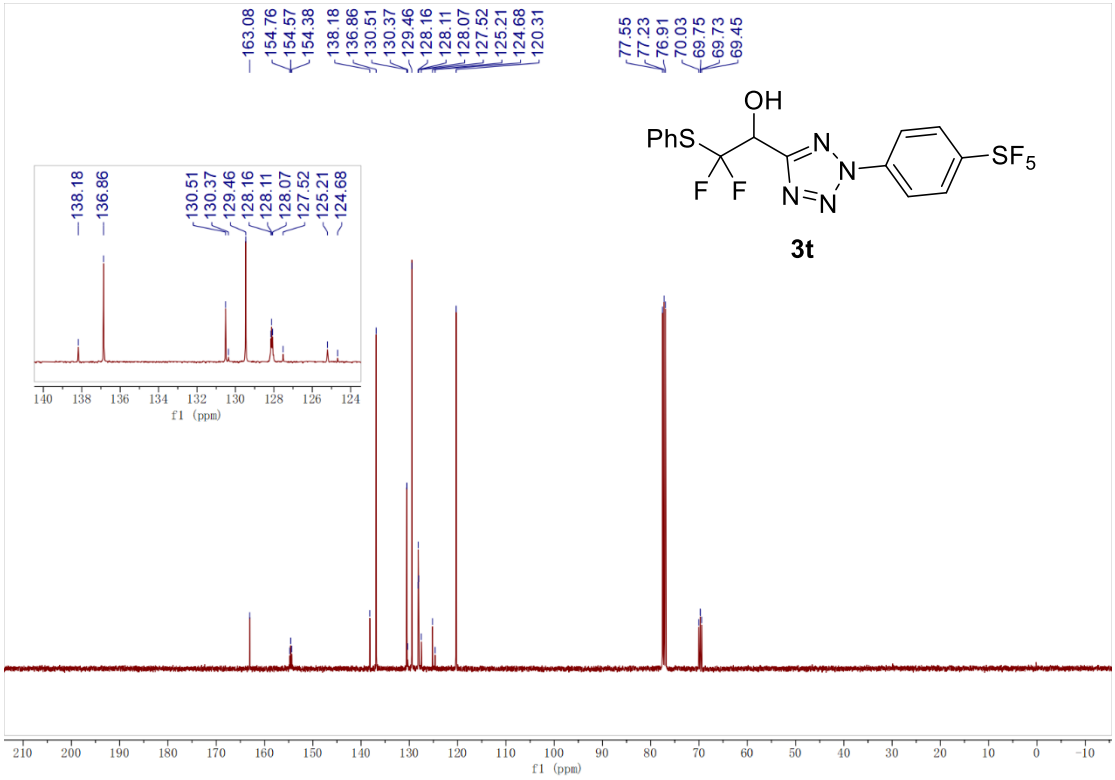
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3t**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3t**

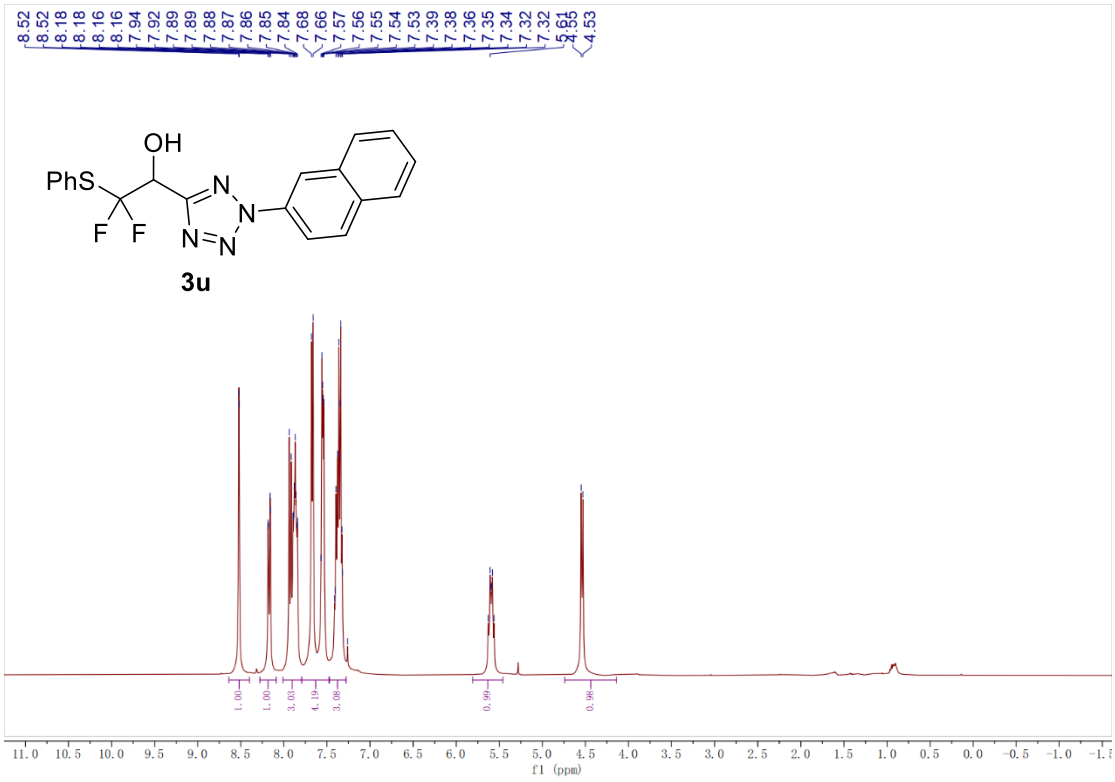


^{19}F NMR (376 MHz, Chloroform-*d*) of **3t**

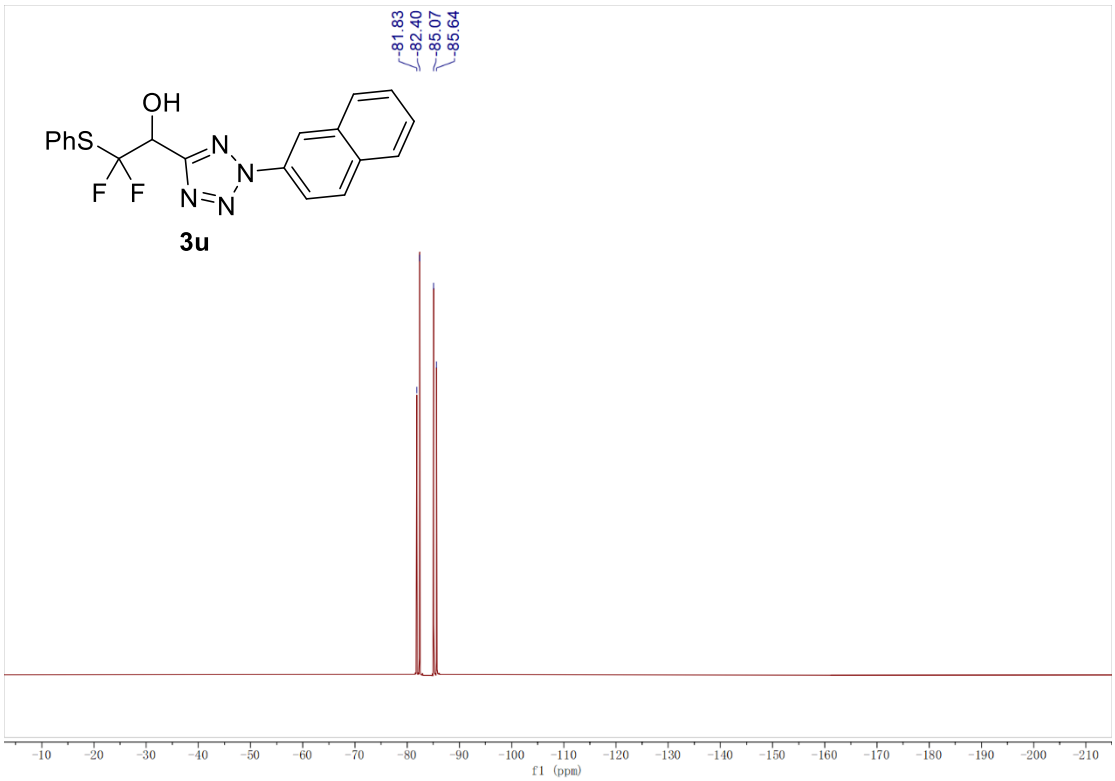


^{13}C NMR (101 MHz, Chloroform-*d*) of **3t**

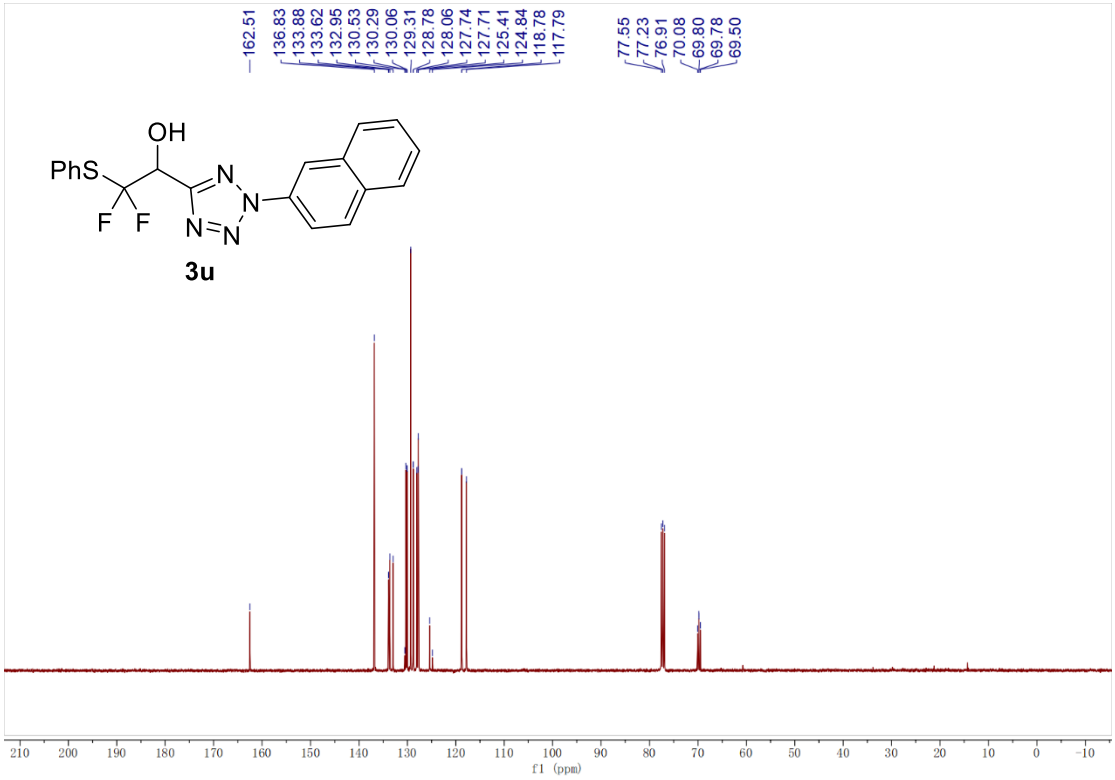
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3u**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3u**

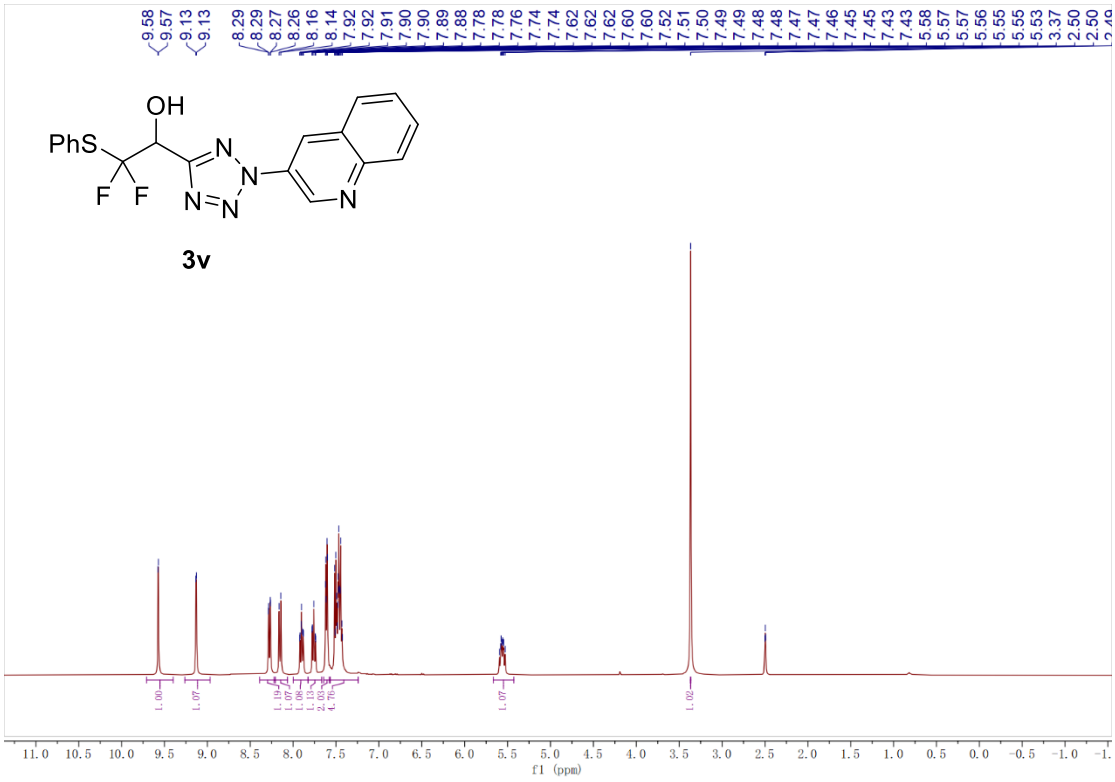


^{19}F NMR (376 MHz, Chloroform-*d*) of **3u**

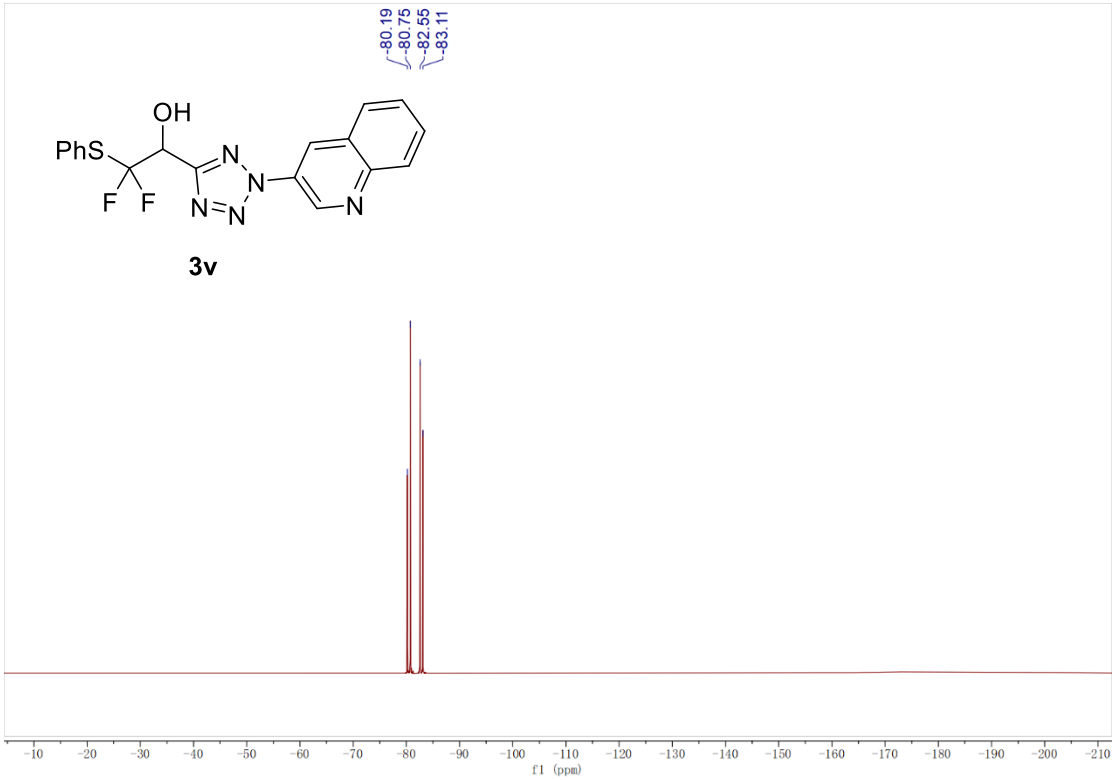


^{13}C NMR (101 MHz, Chloroform-*d*) of **3u**

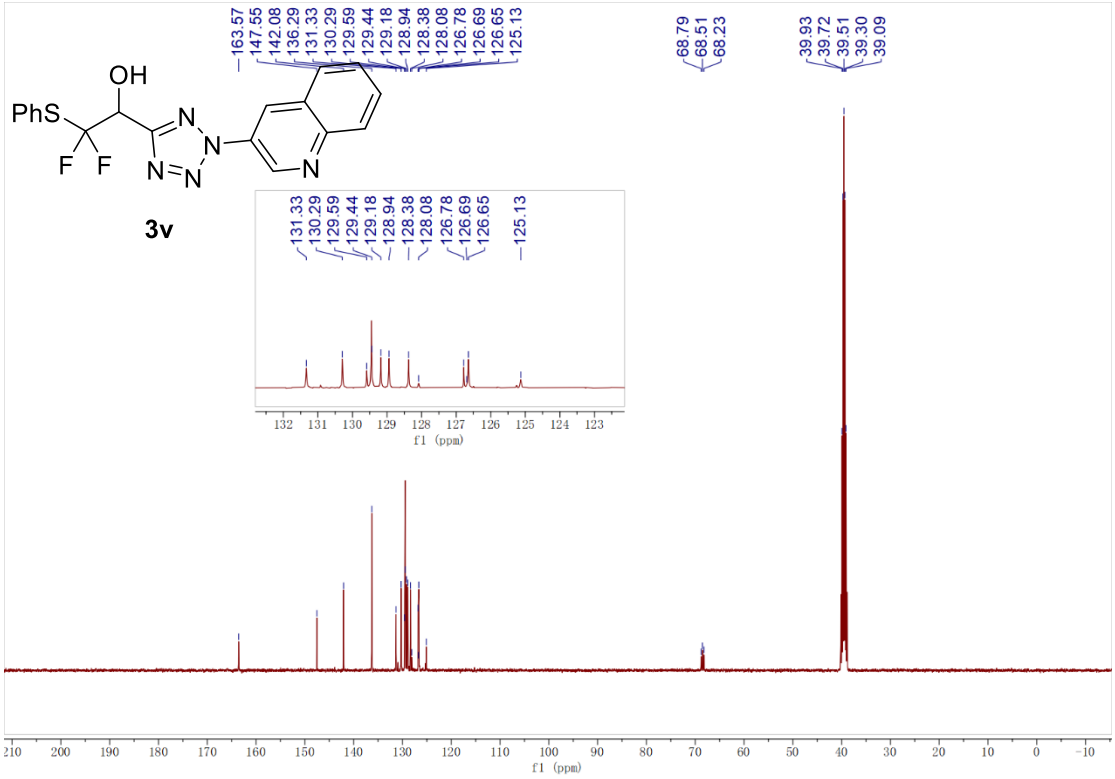
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3v**



^{1}H NMR (400 MHz, DMSO-d_6) of **3v**

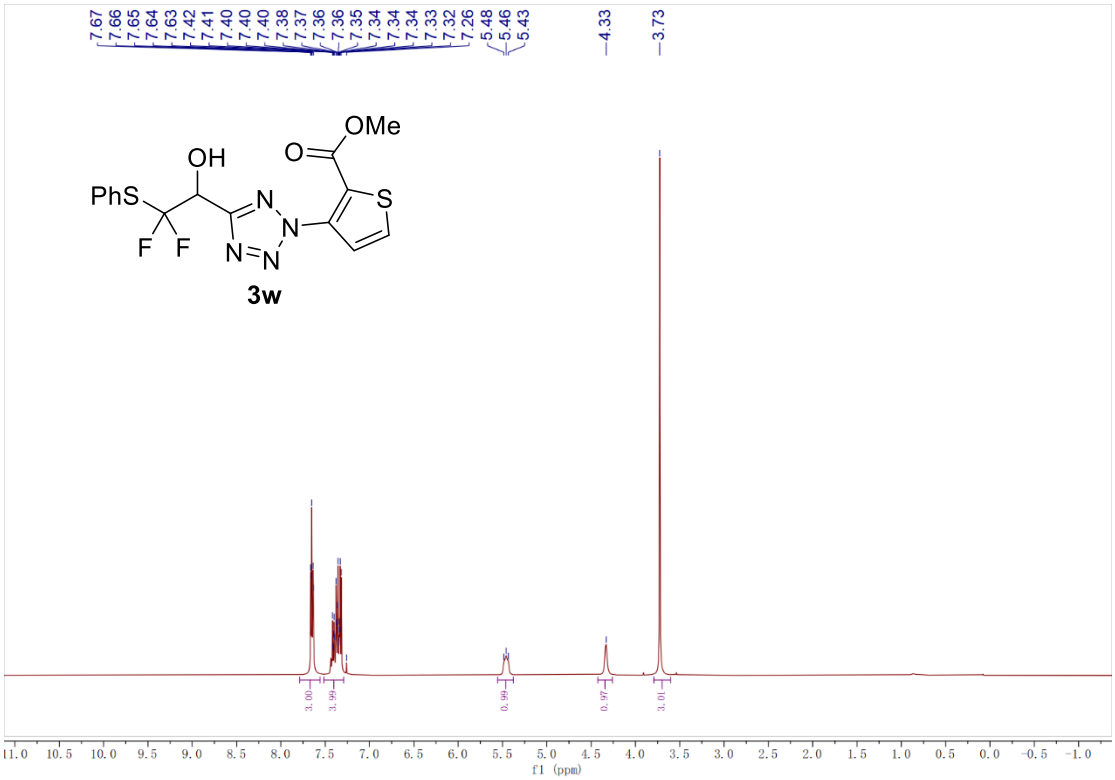


^{19}F NMR (376 MHz, DMSO-d_6) of **3v**

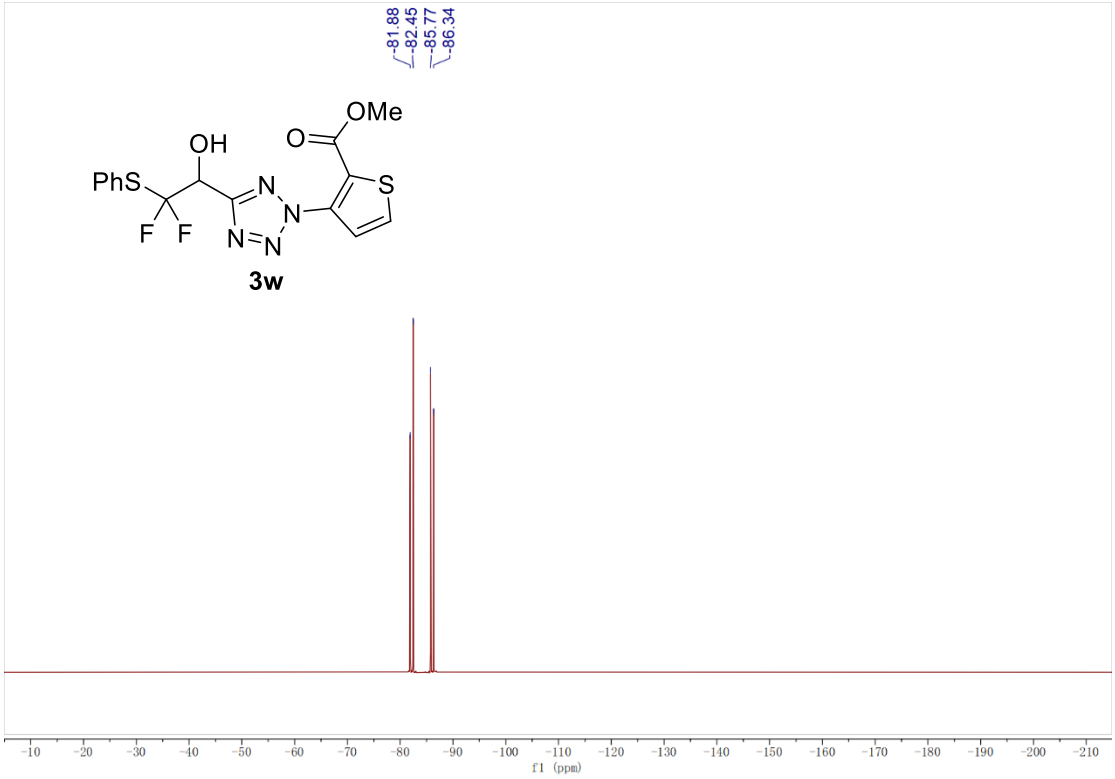


^{13}C NMR (101 MHz, DMSO-d_6) of **3v**

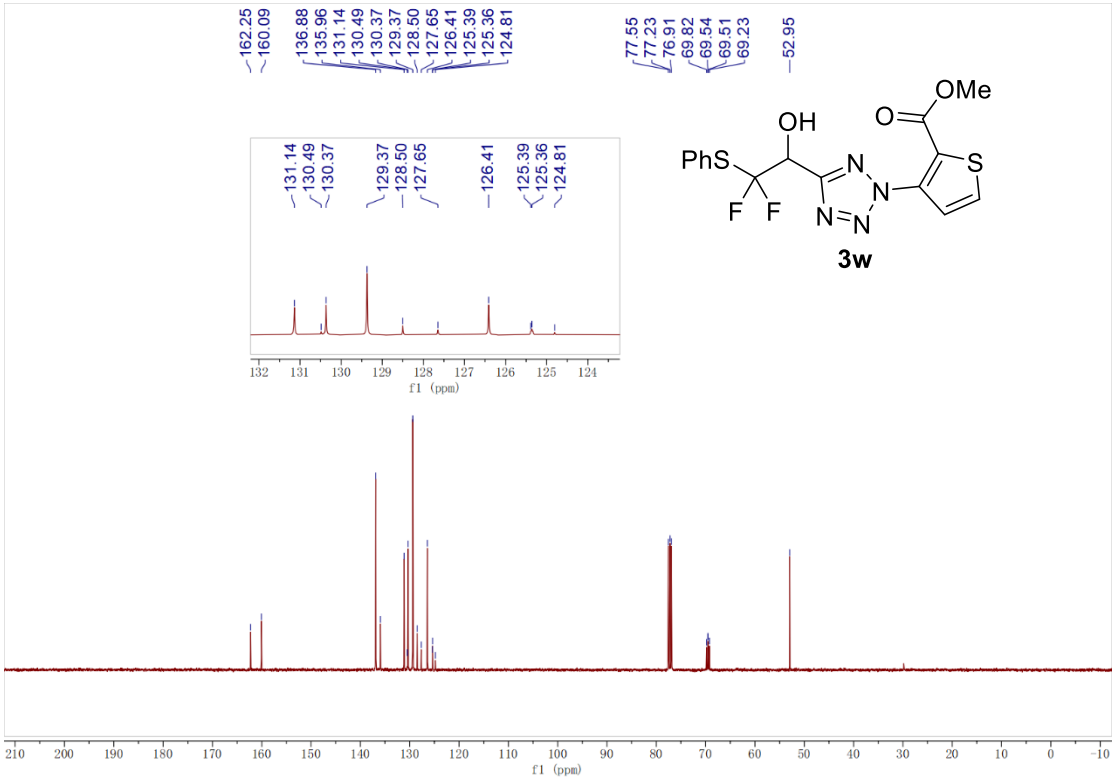
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3w**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3w**

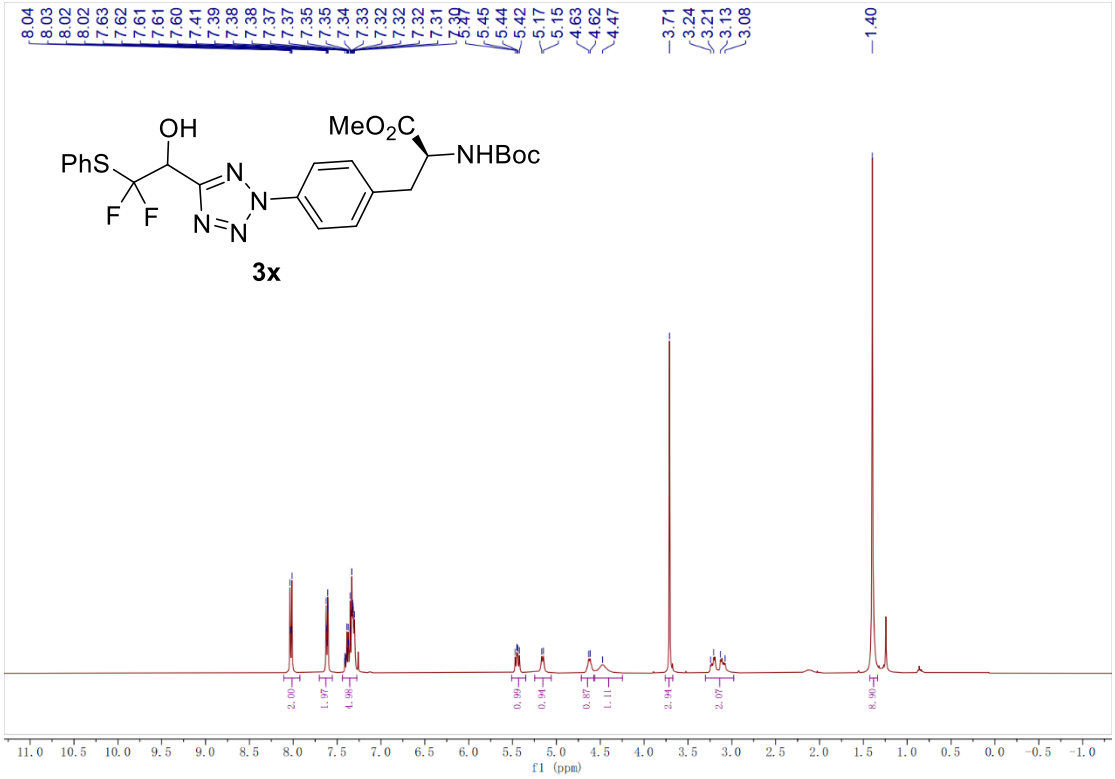


^{19}F NMR (376 MHz, Chloroform-*d*) of **3w**

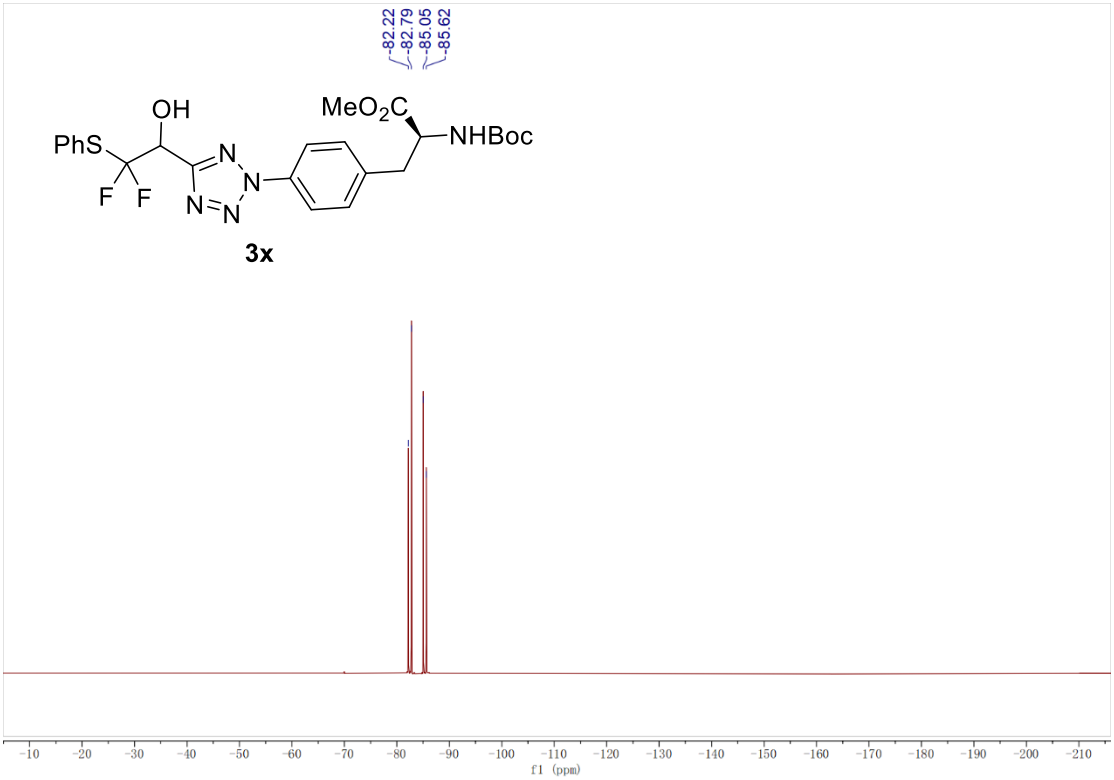


^{13}C NMR (101 MHz, Chloroform-*d*) of **3w**

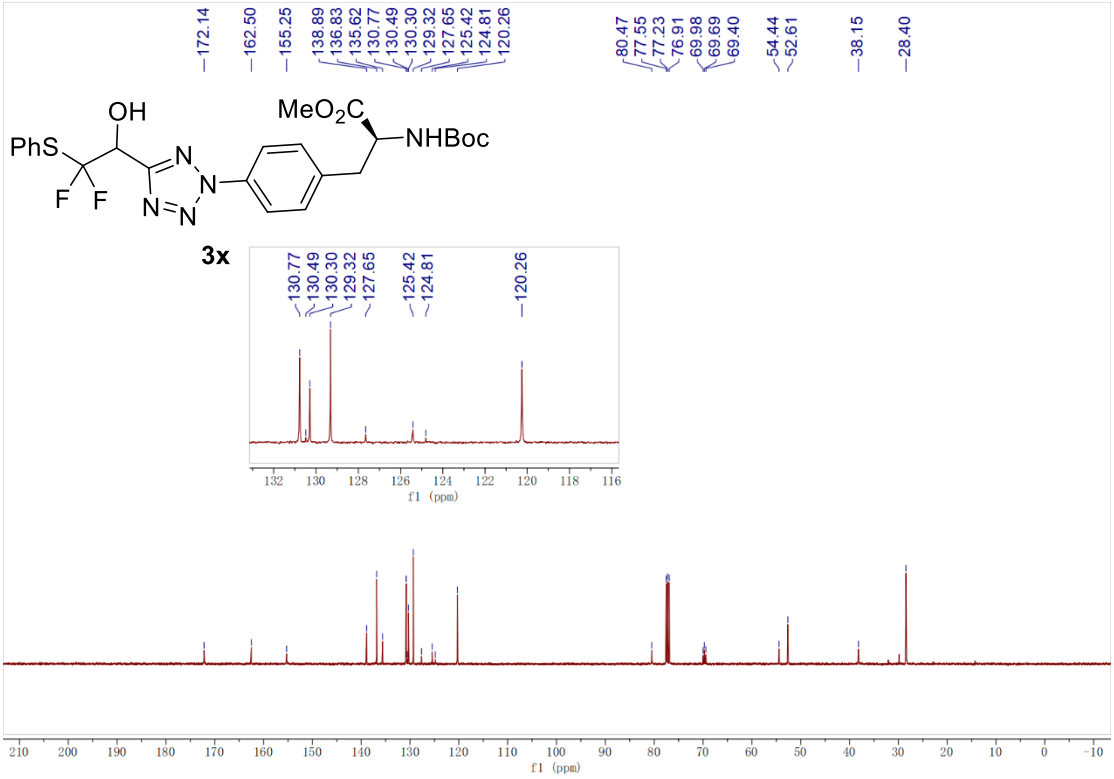
^{1}H, ^{13}C, and ^{19}F NMR spectra of **3x**



^{1}H NMR (400 MHz, Chloroform-*d*) of **3x**

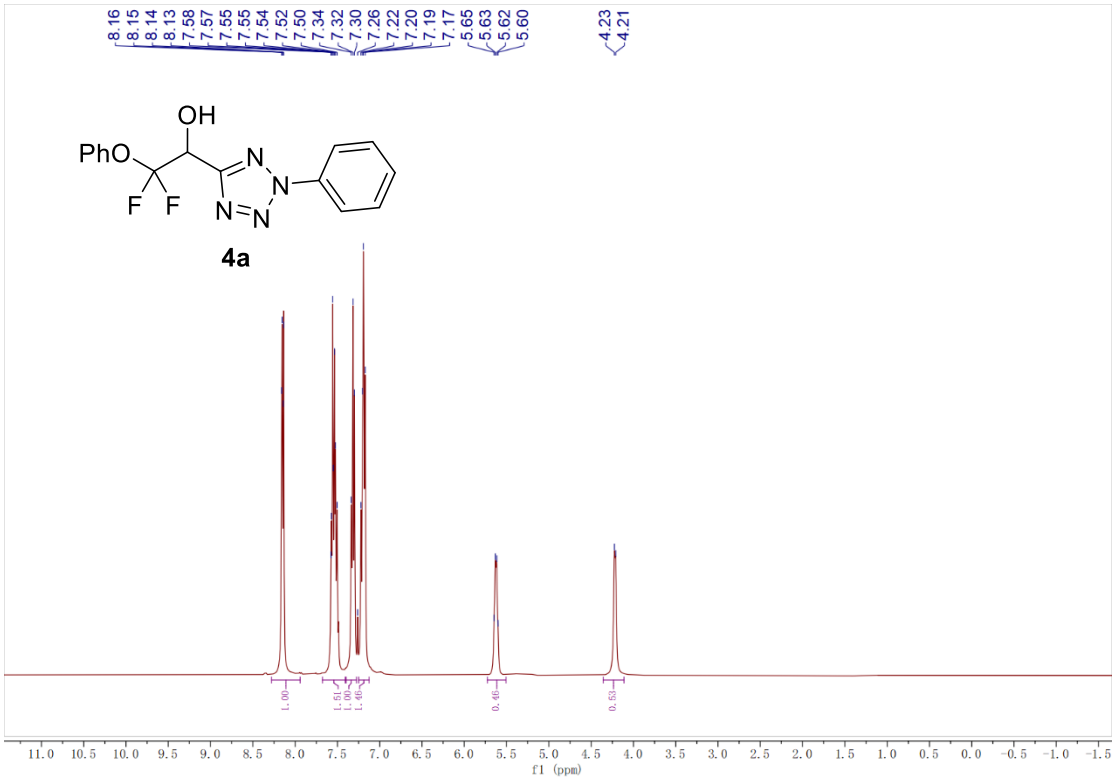


^{19}F NMR (376 MHz, Chloroform-*d*) of **3x**

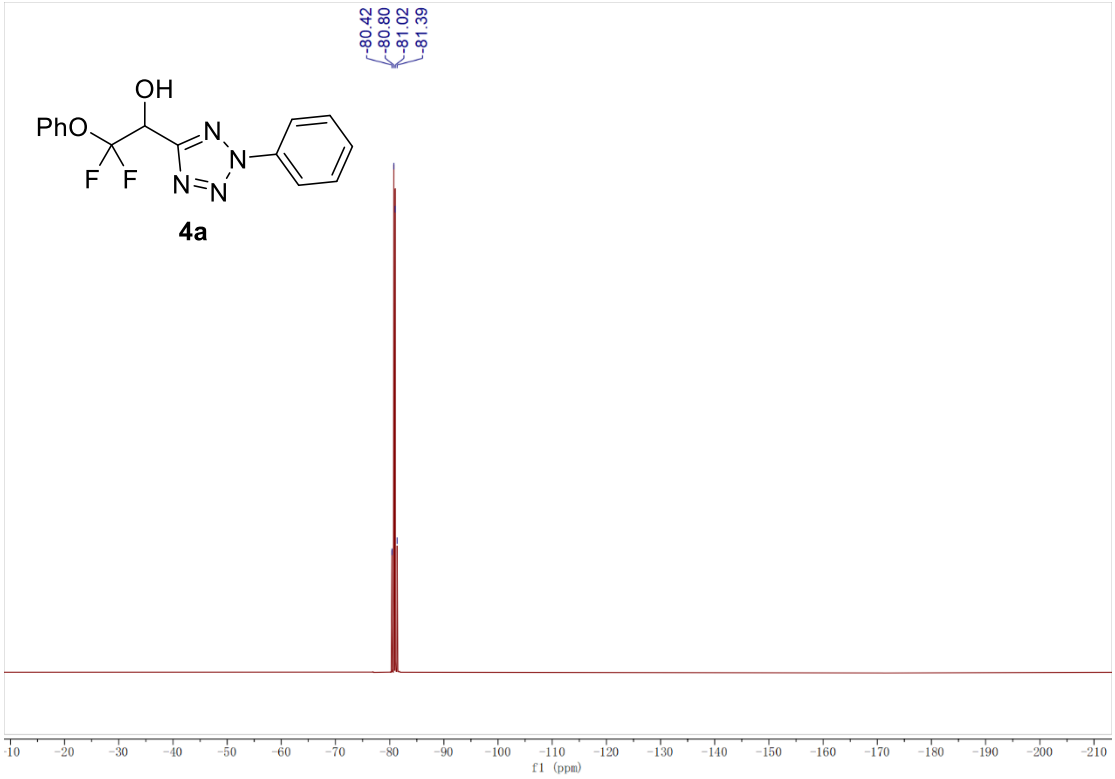


^{13}C NMR (101 MHz, Chloroform-*d*) of **3x**

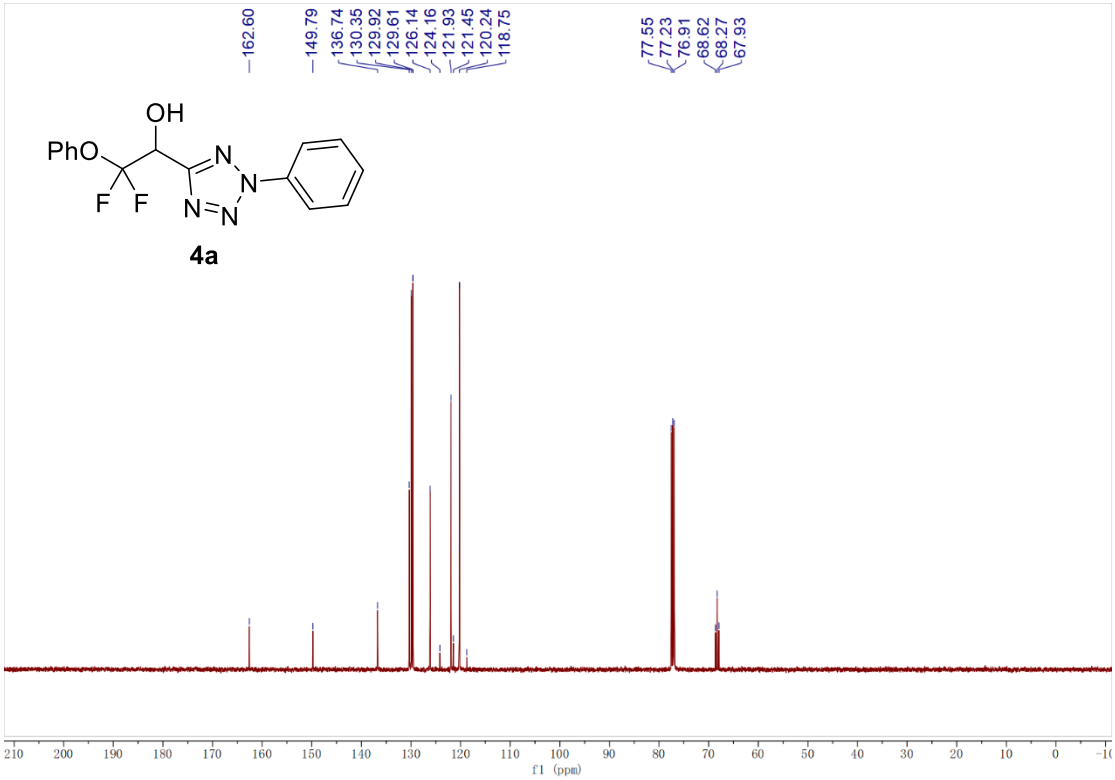
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4a**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4a**

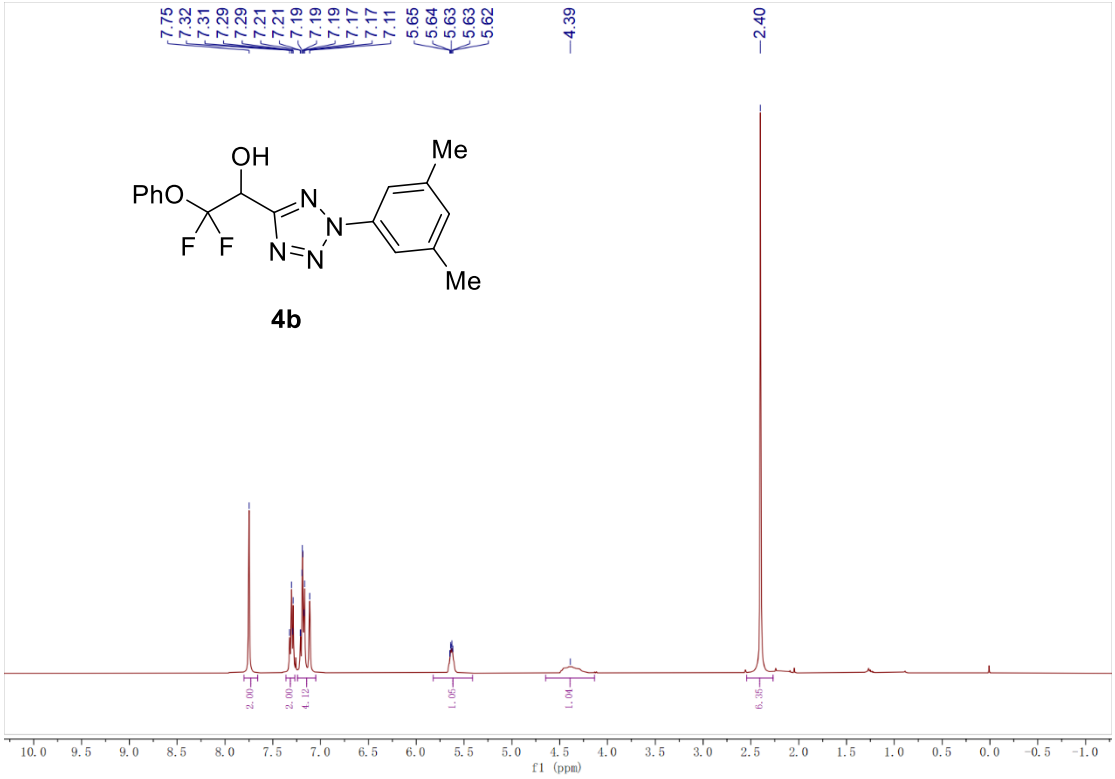


^{19}F NMR (376 MHz, Chloroform-*d*) of **4a**

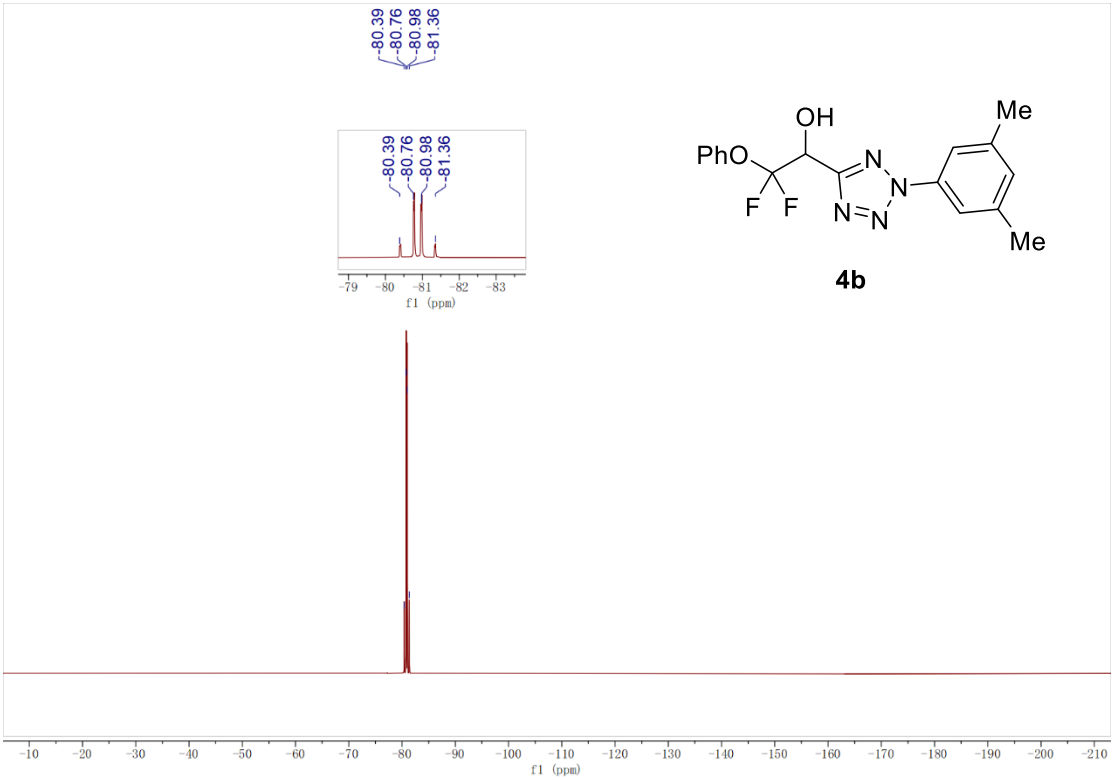


^{13}C NMR (101 MHz, Chloroform-*d*) of **4a**

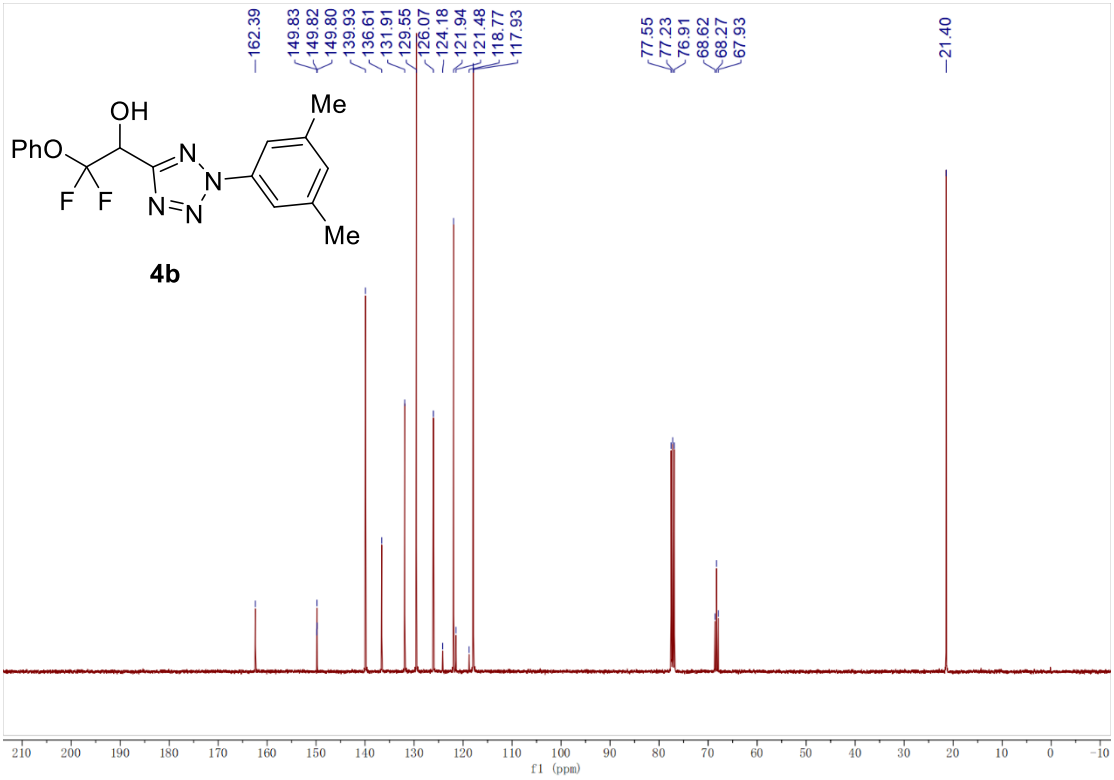
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4b**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4b**

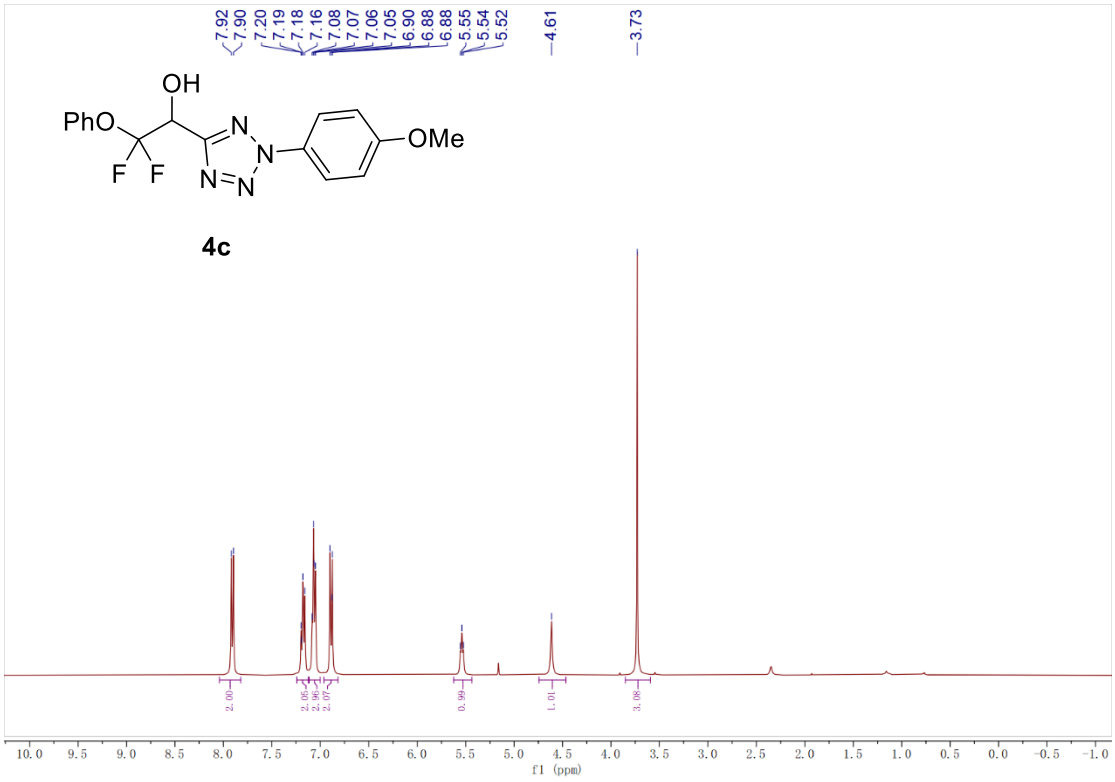


^{19}F NMR (376 MHz, Chloroform-*d*) of **4b**

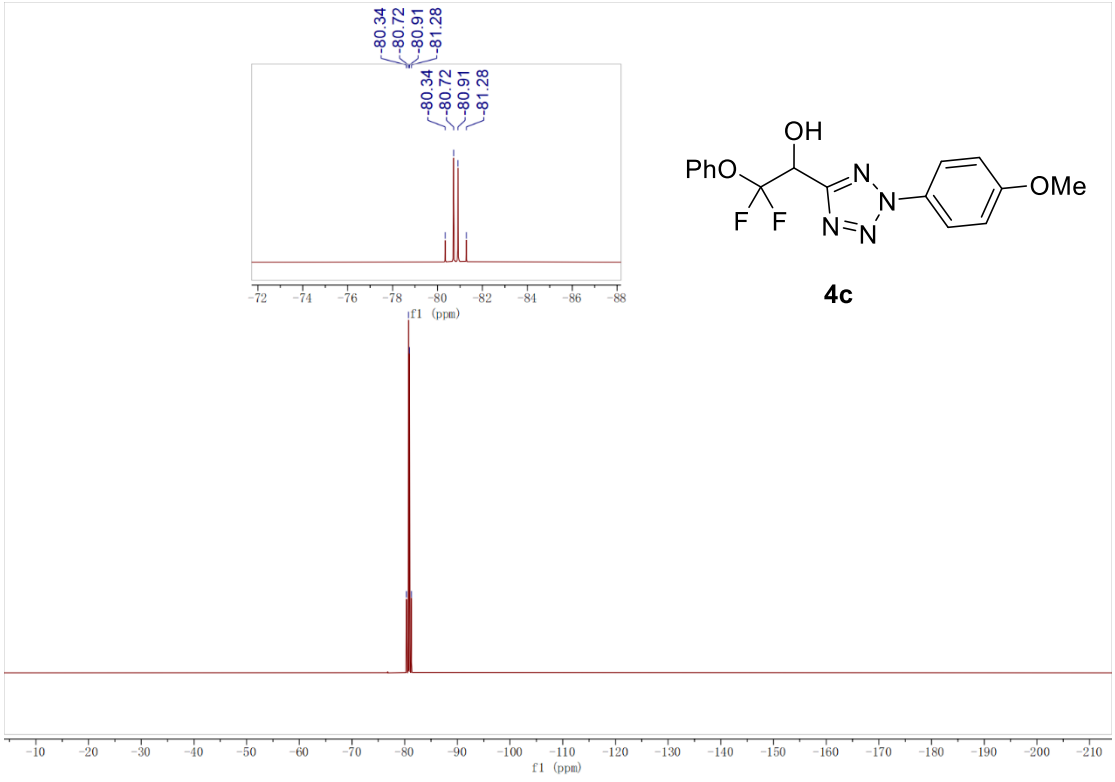


^{13}C NMR (101 MHz, Chloroform-*d*) of **4b**

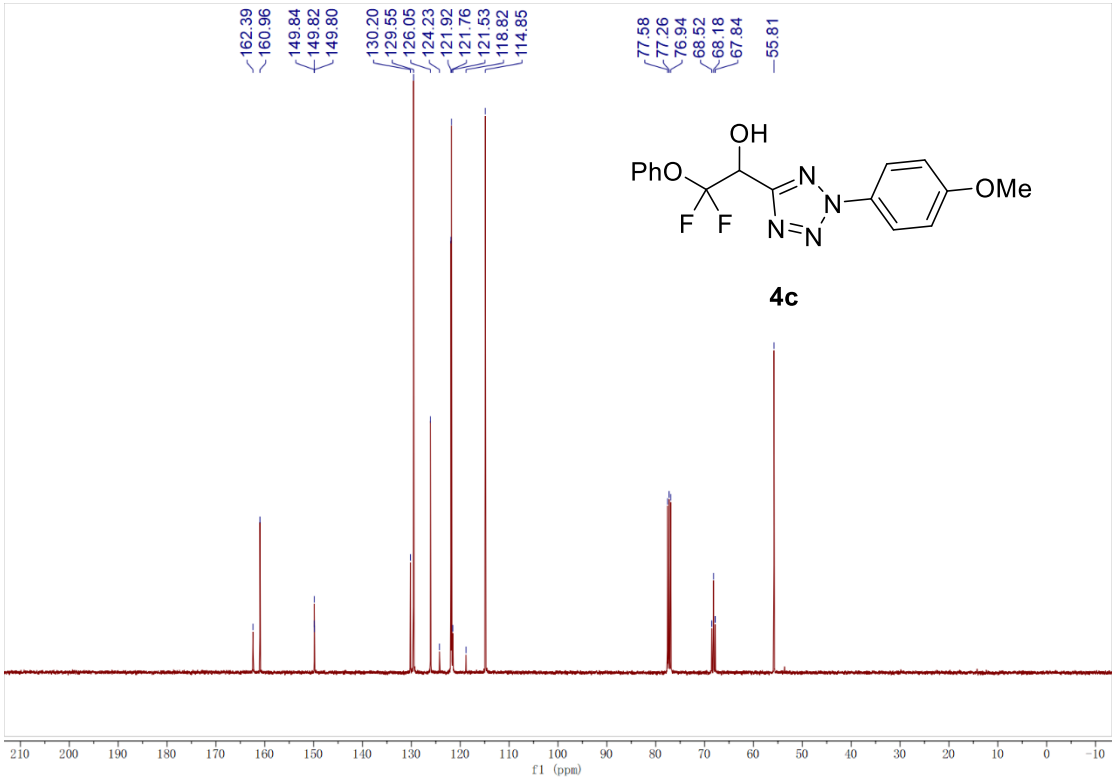
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4c**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4c**

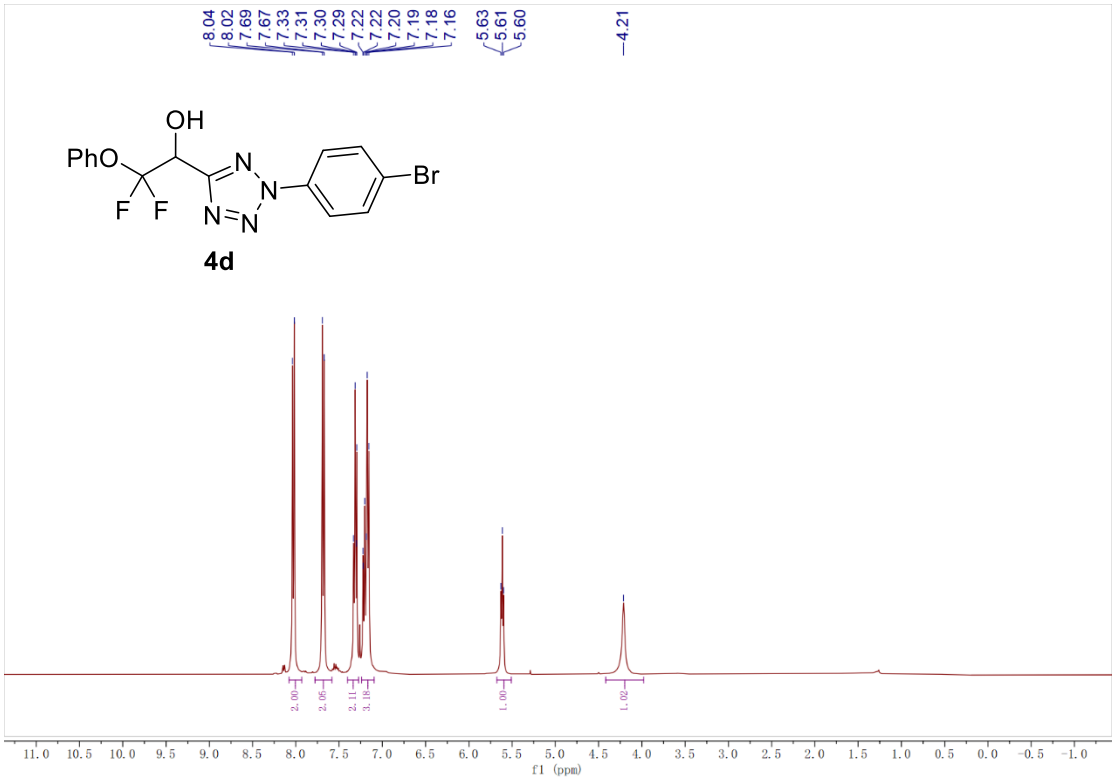


^{19}F NMR (376 MHz, Chloroform-*d*) of **4c**

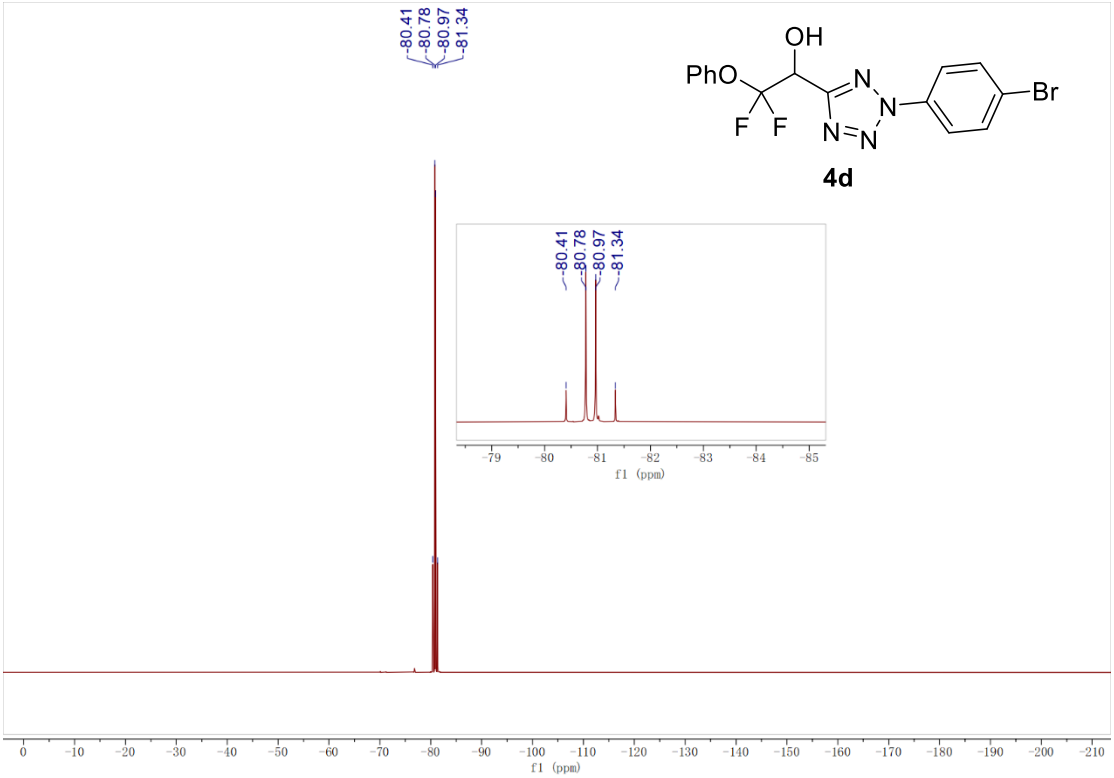


^{13}C NMR (101 MHz, Chloroform-*d*) of **4c**

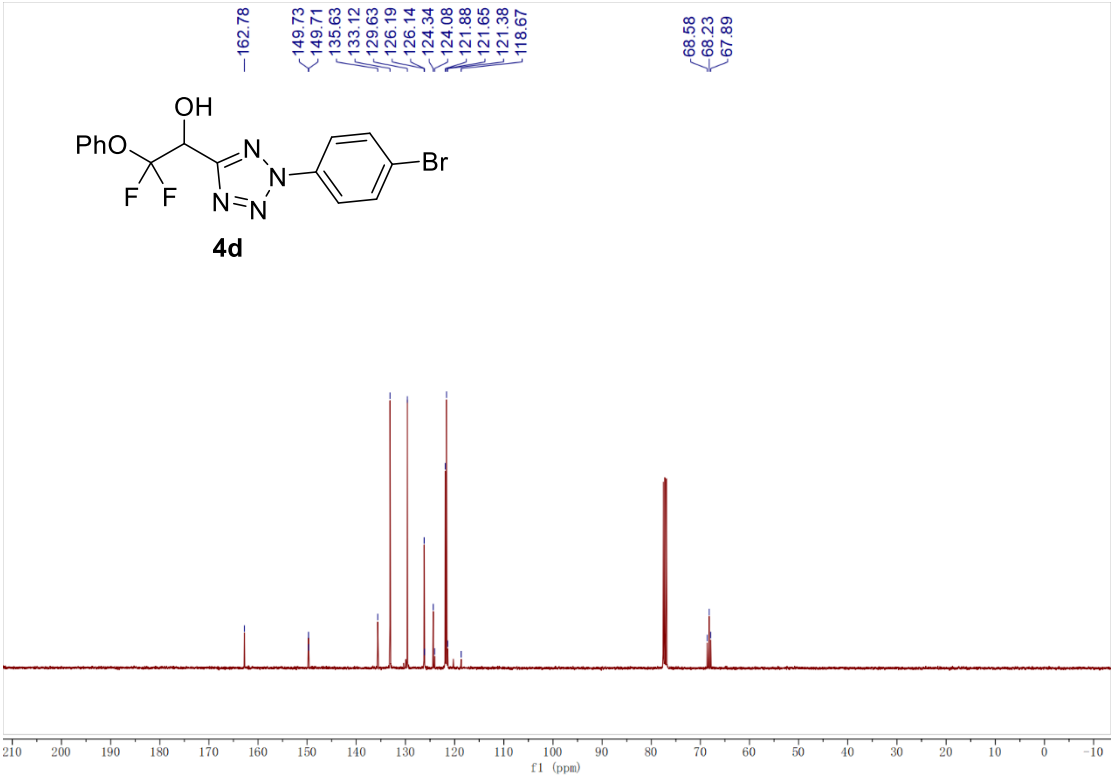
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4d**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4d**

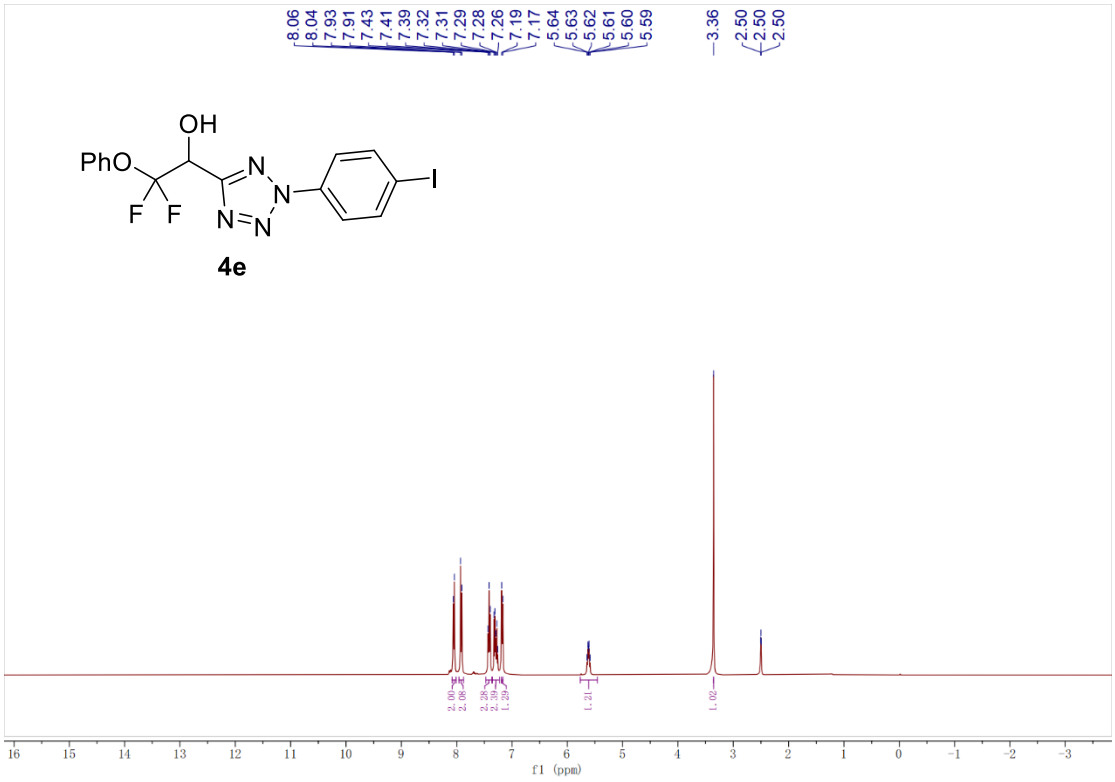


^{19}F NMR (376 MHz, Chloroform-*d*) of **4d**

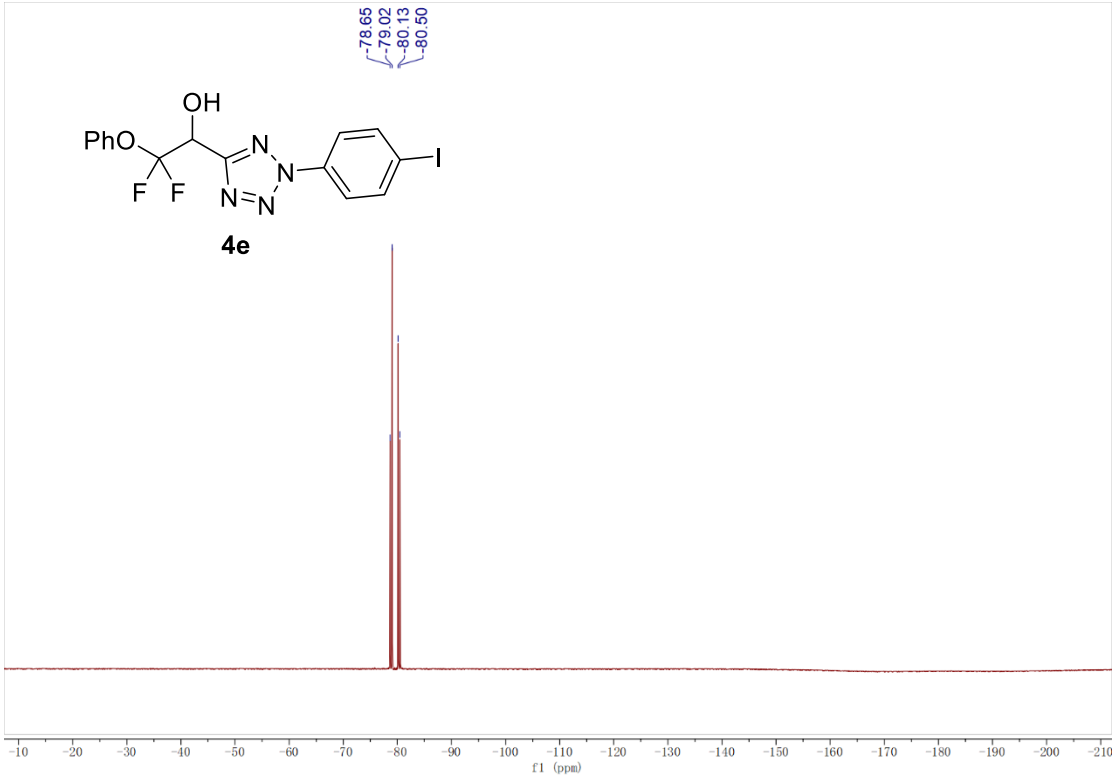


^{13}C NMR (101 MHz, Chloroform-*d*) of **4d**

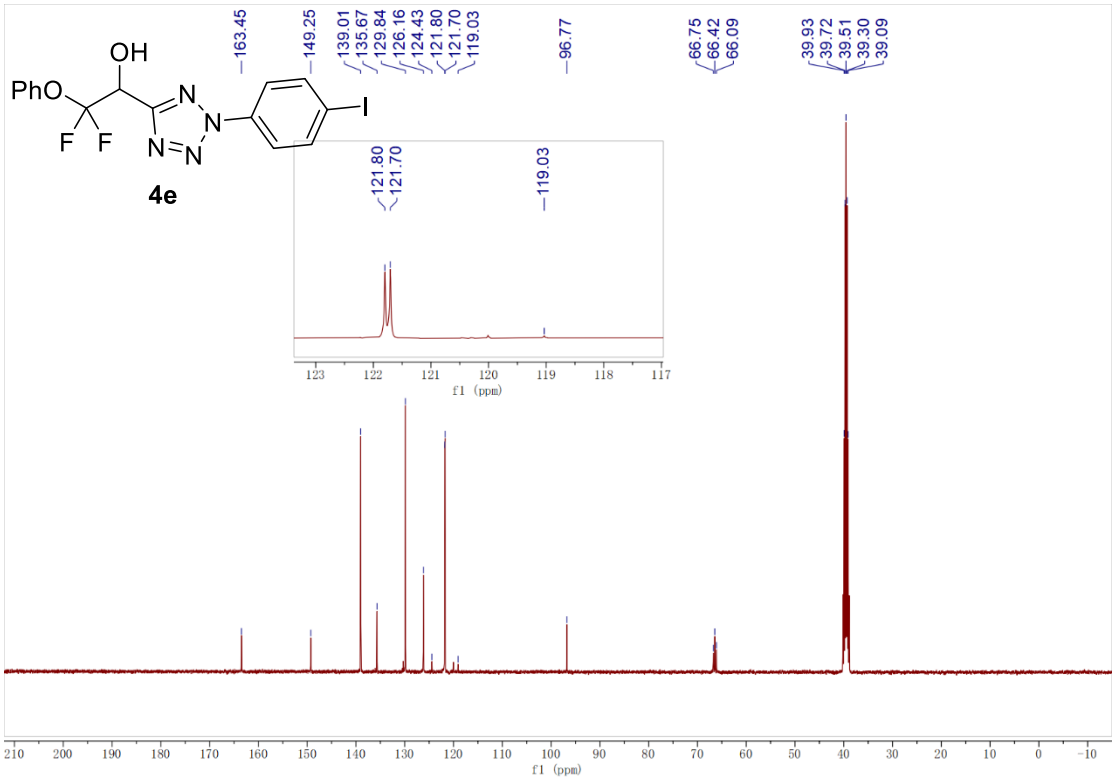
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4e**



^{1}H NMR (400 MHz, DMSO-d_6) of **4e**

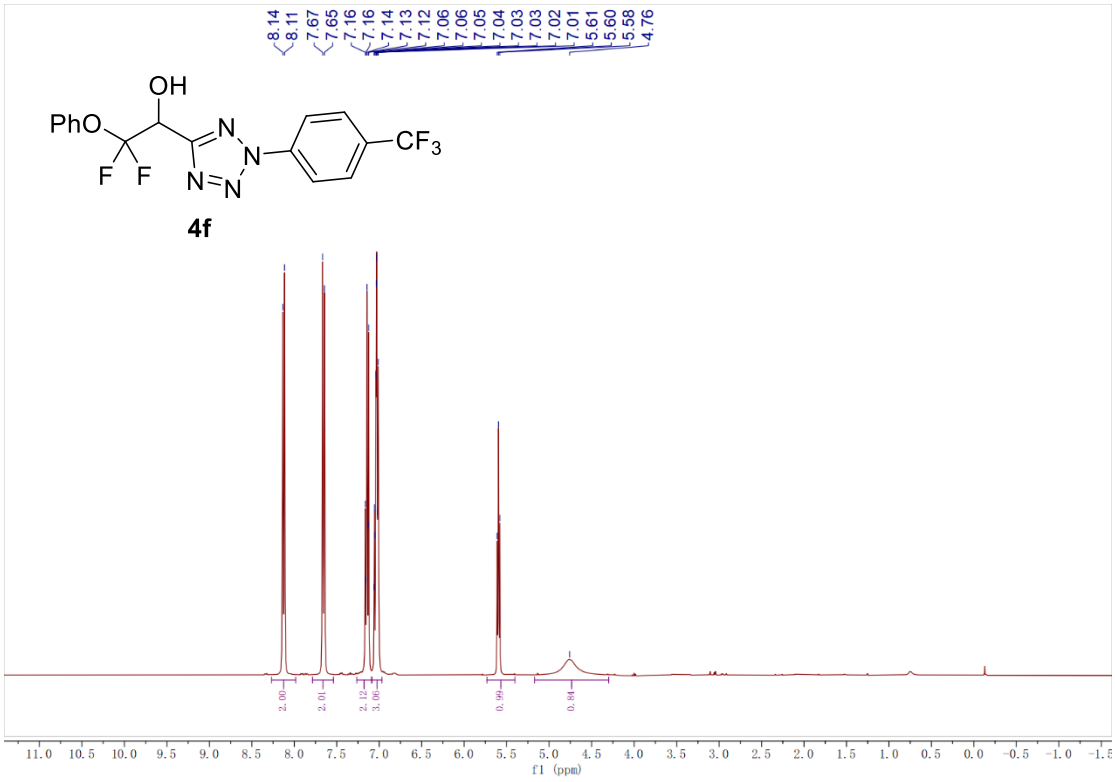


^{19}F NMR (376 MHz, DMSO-d_6) of **4e**

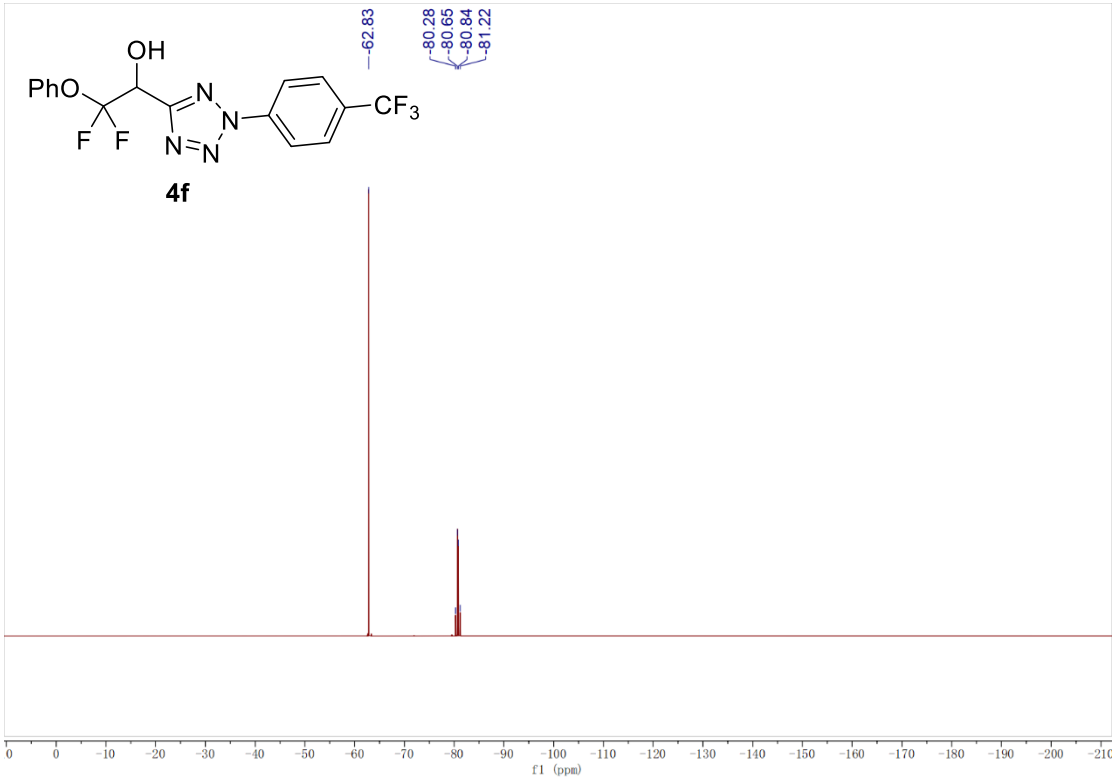


^{13}C NMR (101 MHz, DMSO-d_6) of **4e**

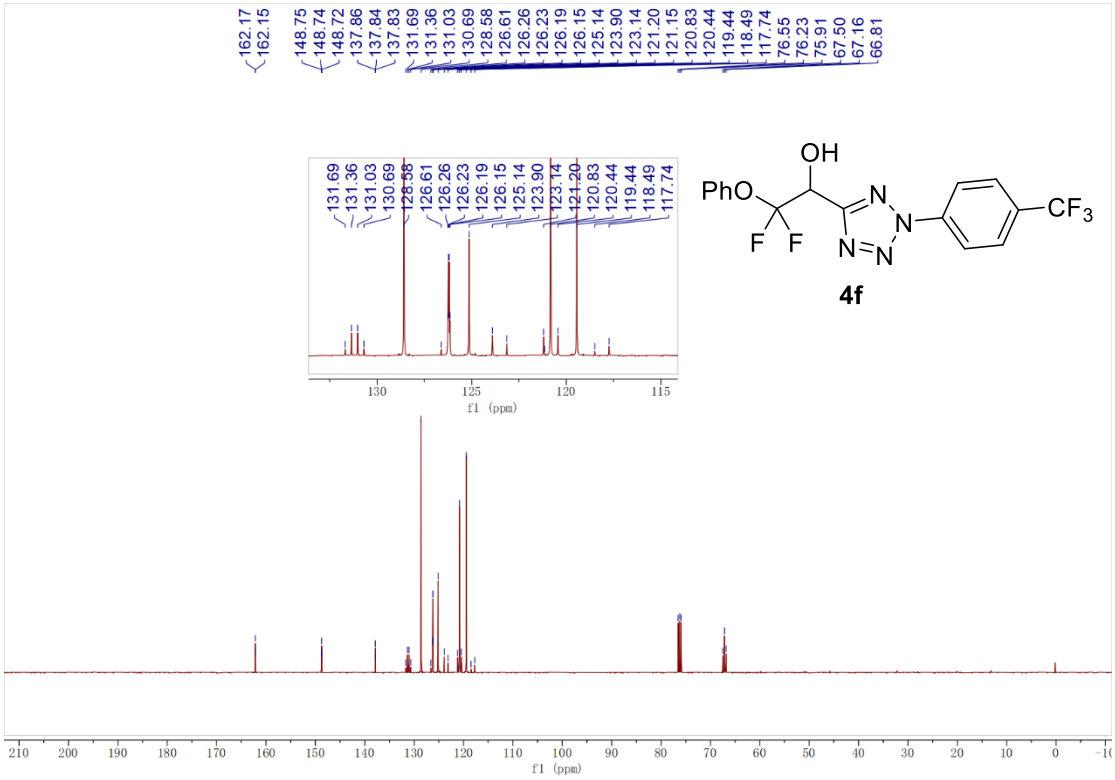
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4f**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4f**

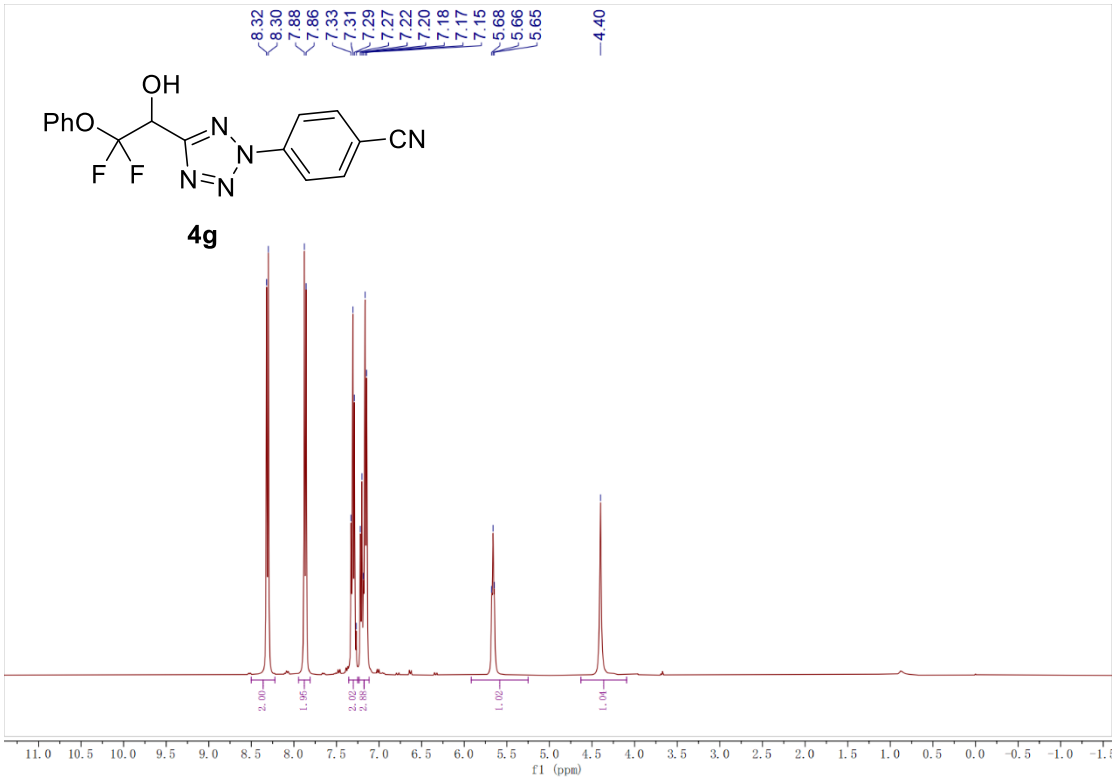


^{19}F NMR (376 MHz, Chloroform-*d*) of **4f**

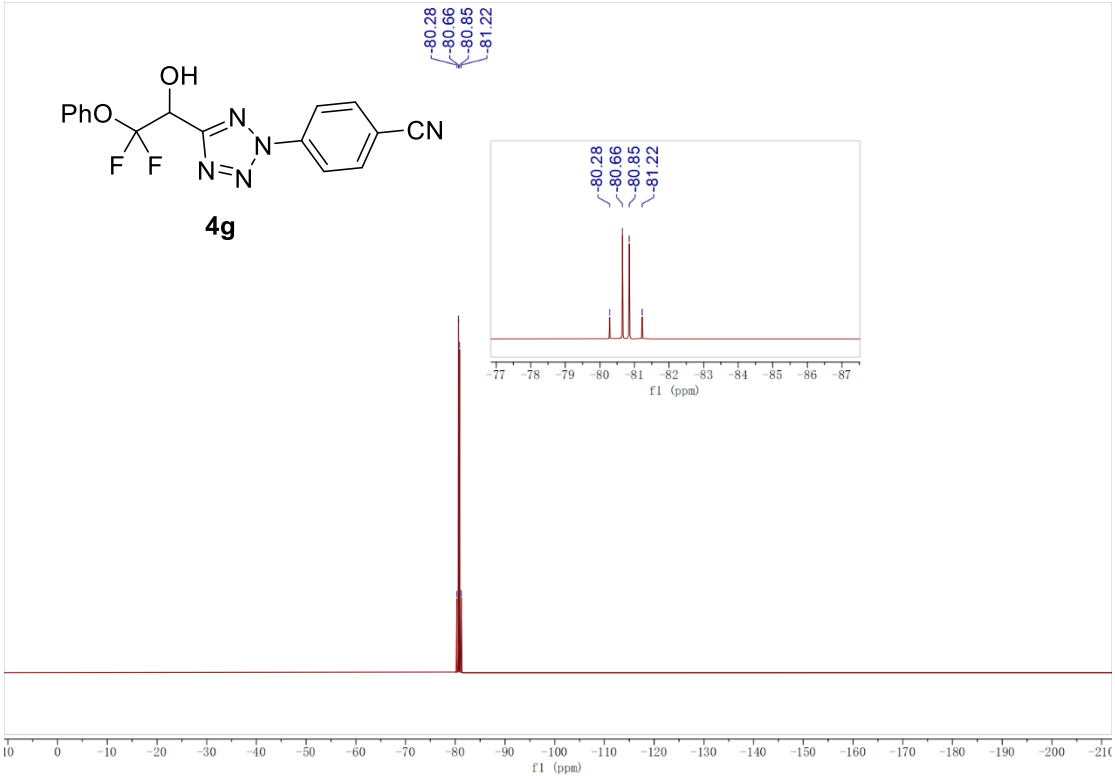


^{13}C NMR (101 MHz, Chloroform-*d*) of **4f**

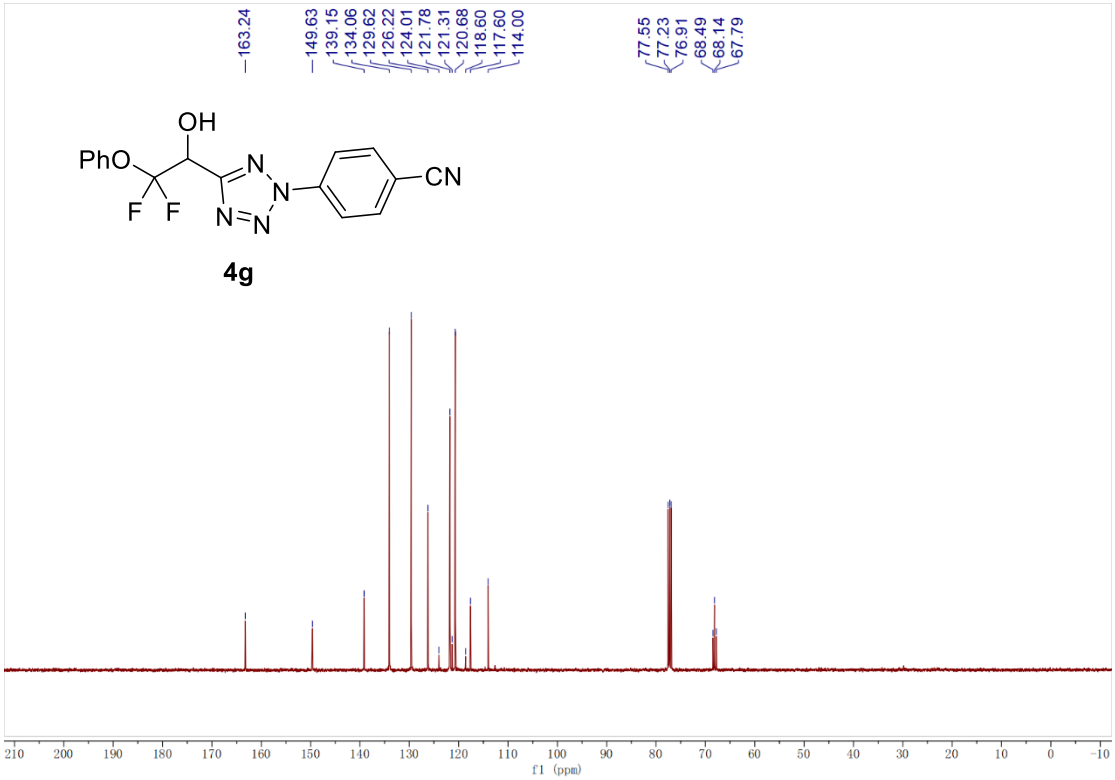
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4g**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4g**

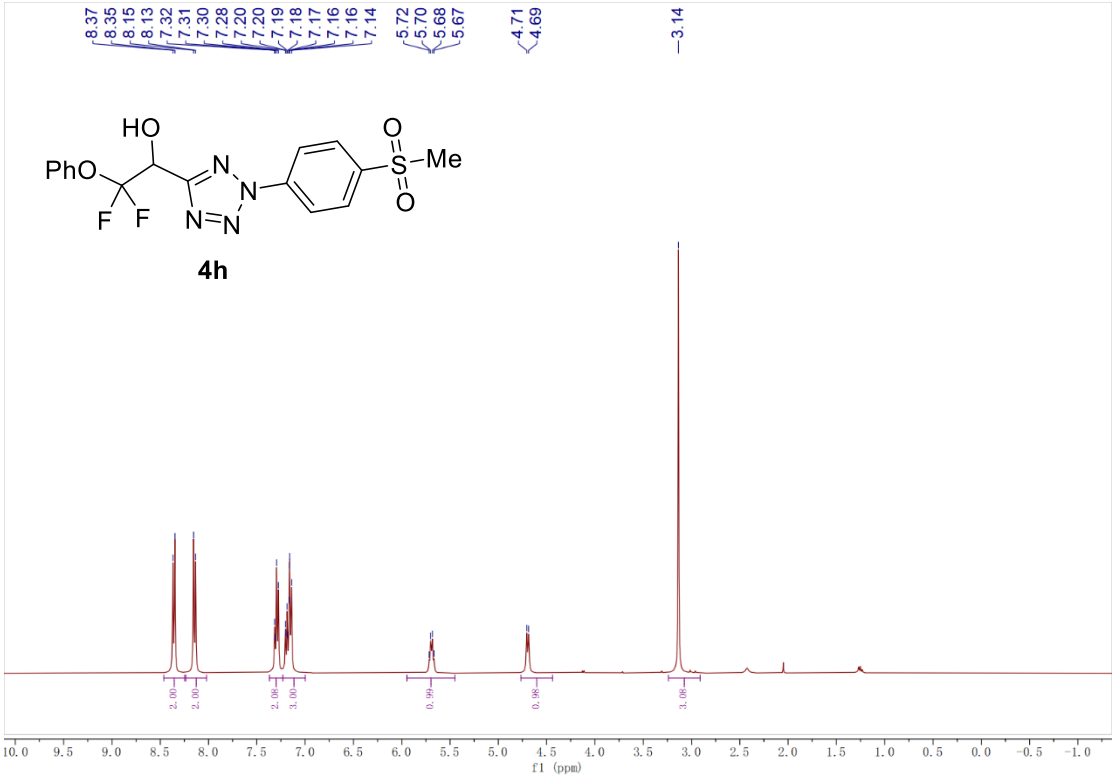


^{19}F NMR (376 MHz, Chloroform-*d*) of **4g**

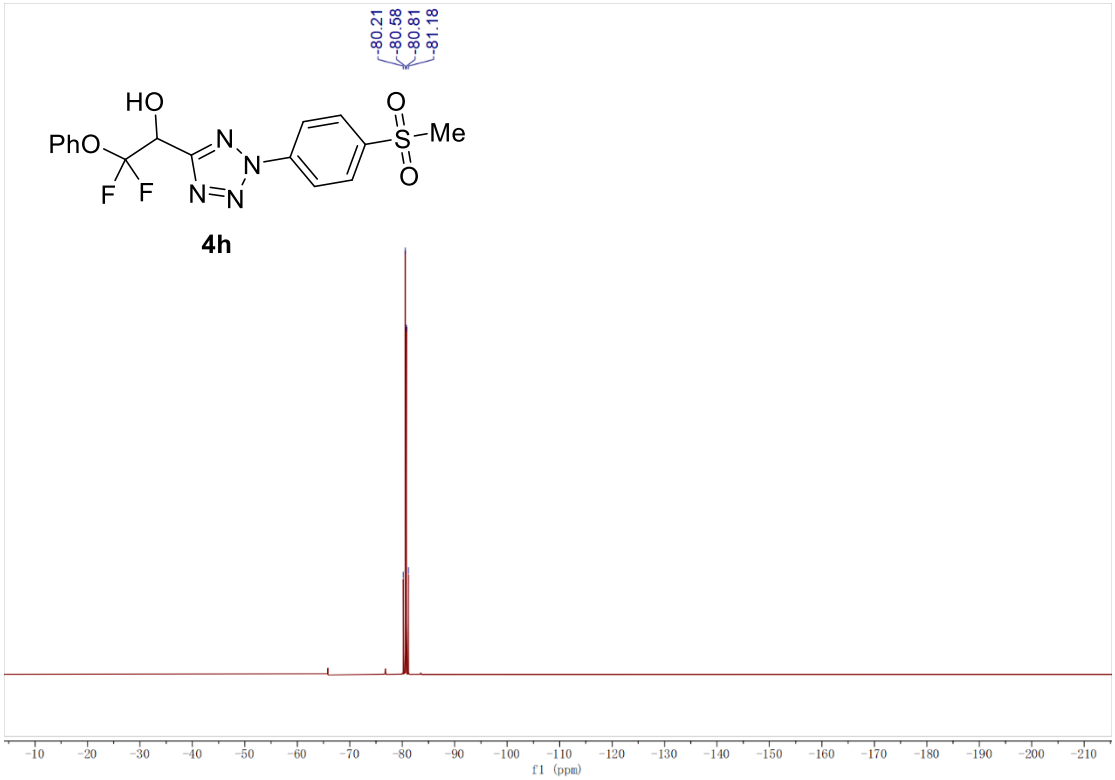


^{13}C NMR (101 MHz, Chloroform-*d*) of **4g**

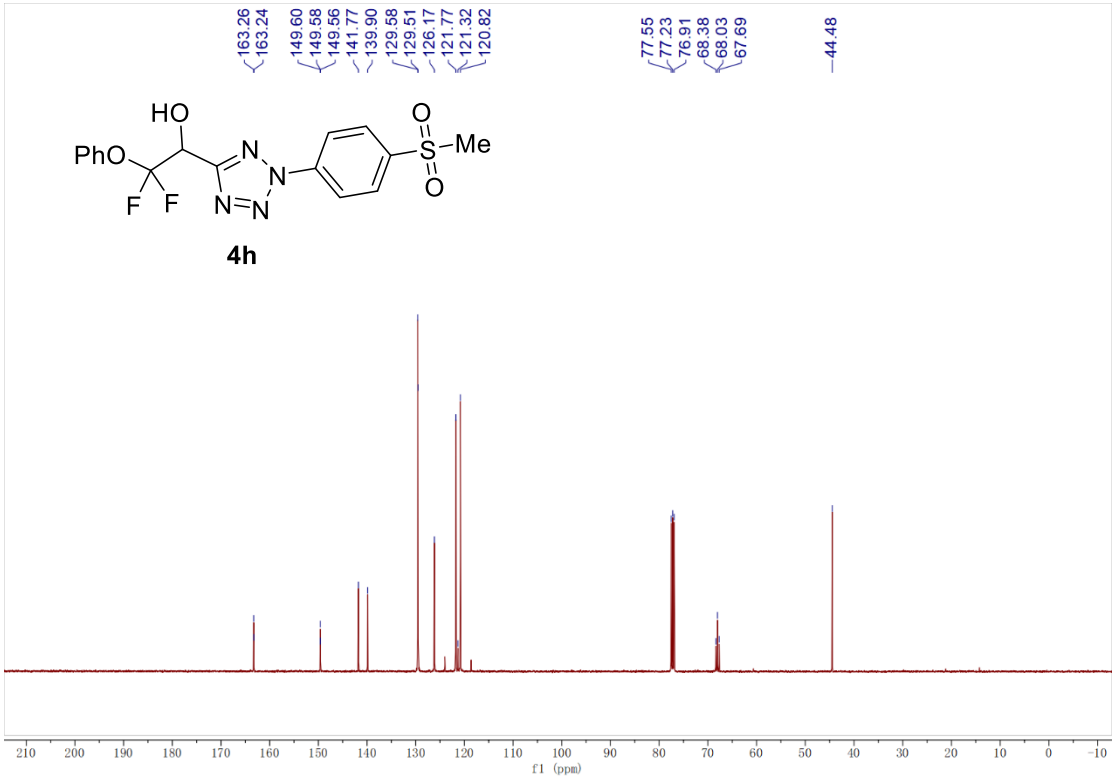
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4h**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4h**

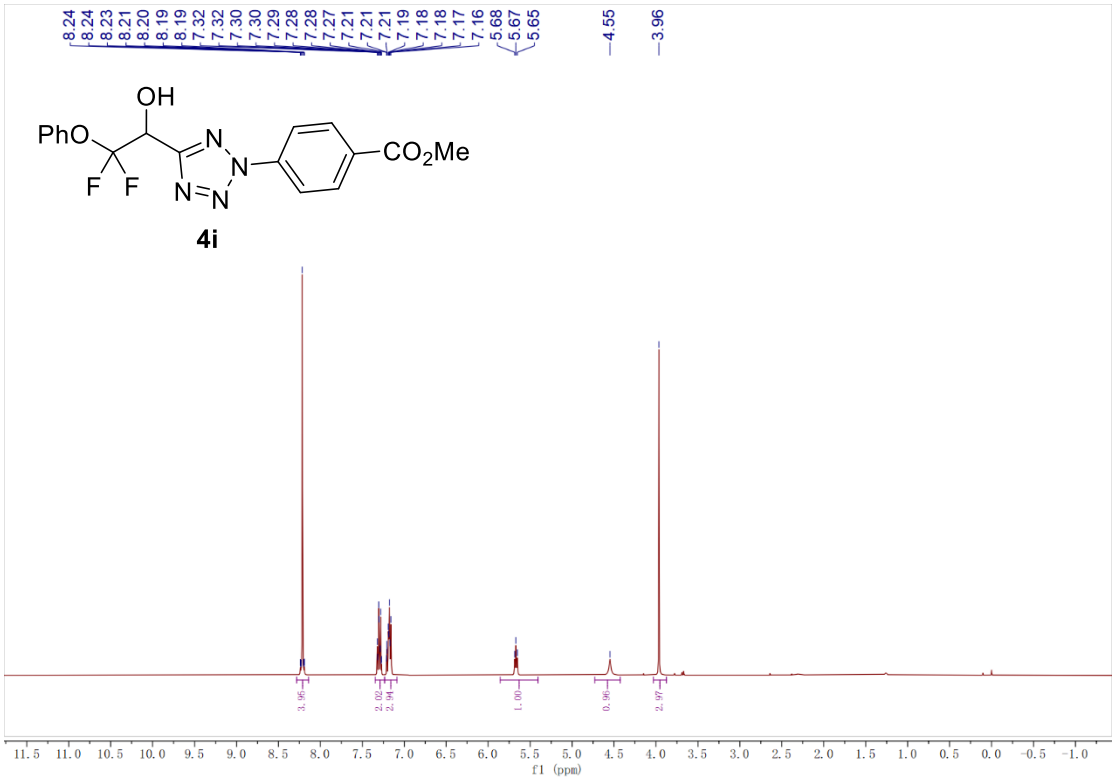


^{19}F NMR (376 MHz, Chloroform-*d*) of **4h**

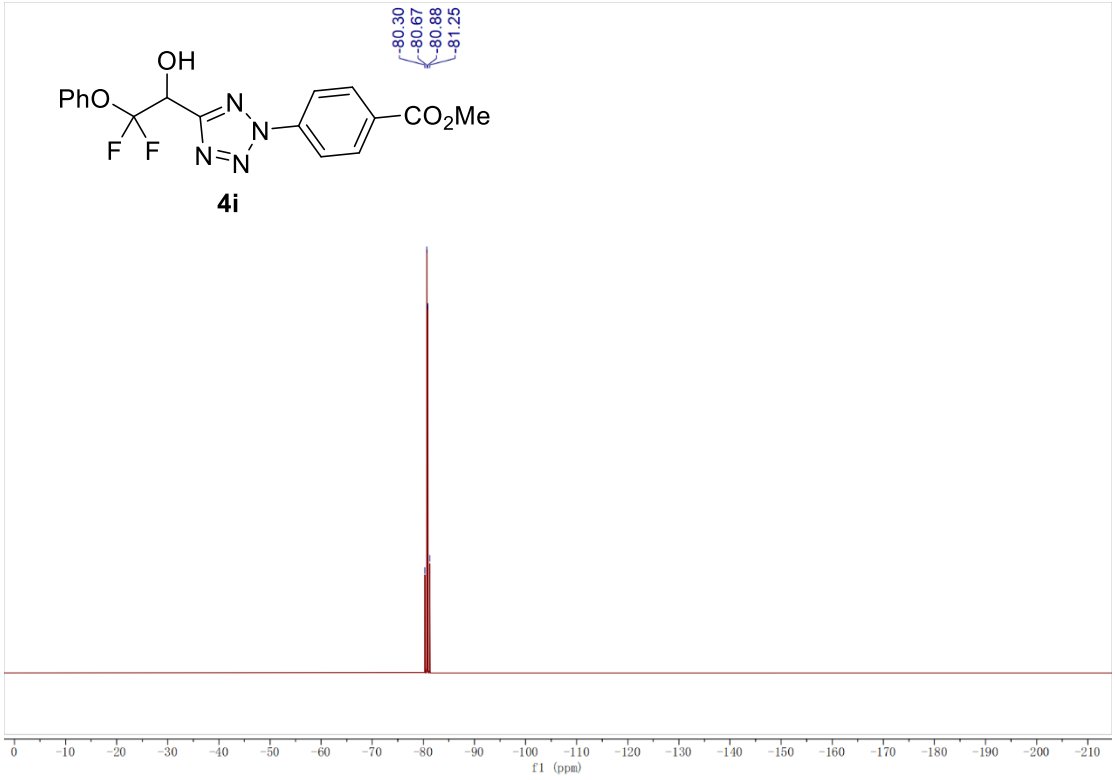


^{13}C NMR (101 MHz, Chloroform-*d*) of **4h**

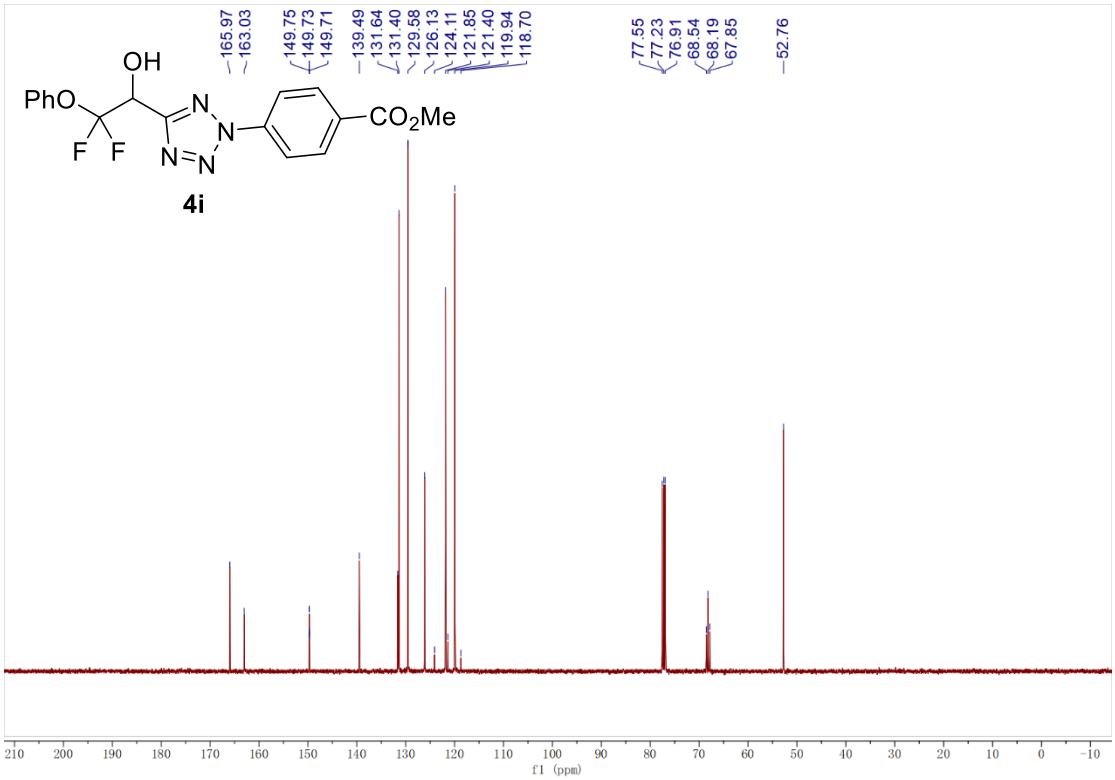
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4i**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4i**

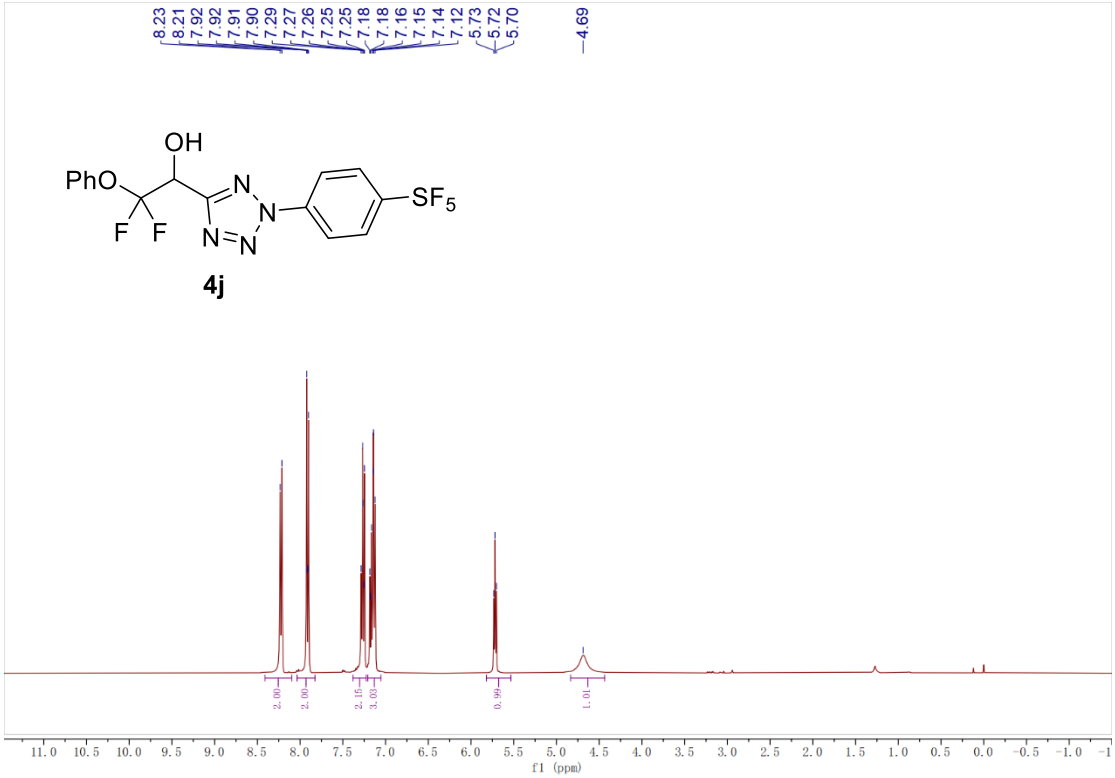


^{19}F NMR (376 MHz, Chloroform-*d*) of **4i**

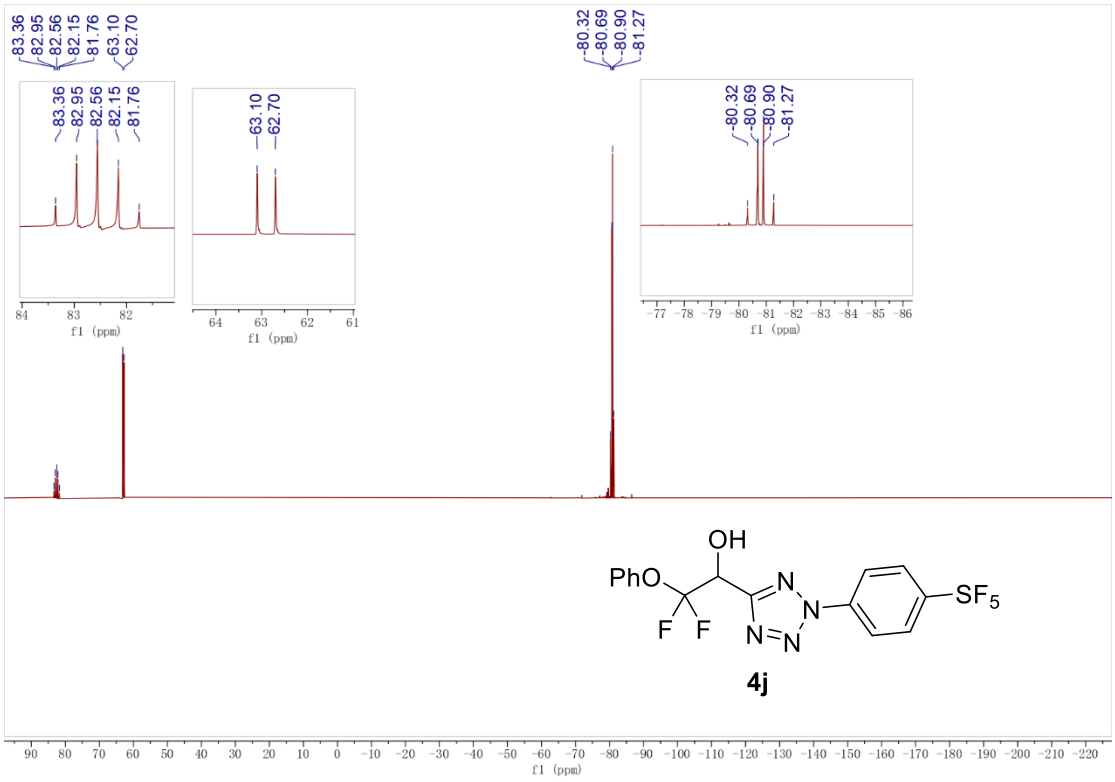


^{13}C NMR (101 MHz, Chloroform-*d*) of **4i**

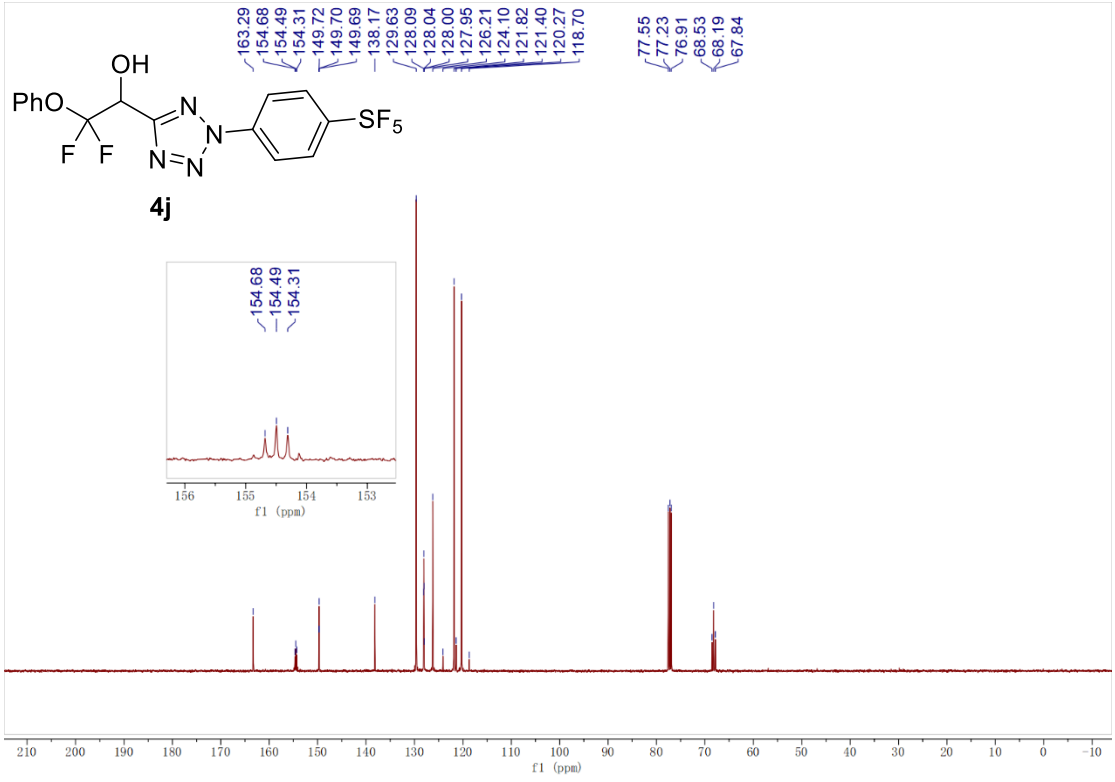
^{1}H, ^{13}C, and ^{19}F NMR spectra of **4j**



^{1}H NMR (400 MHz, Chloroform-*d*) of **4j**

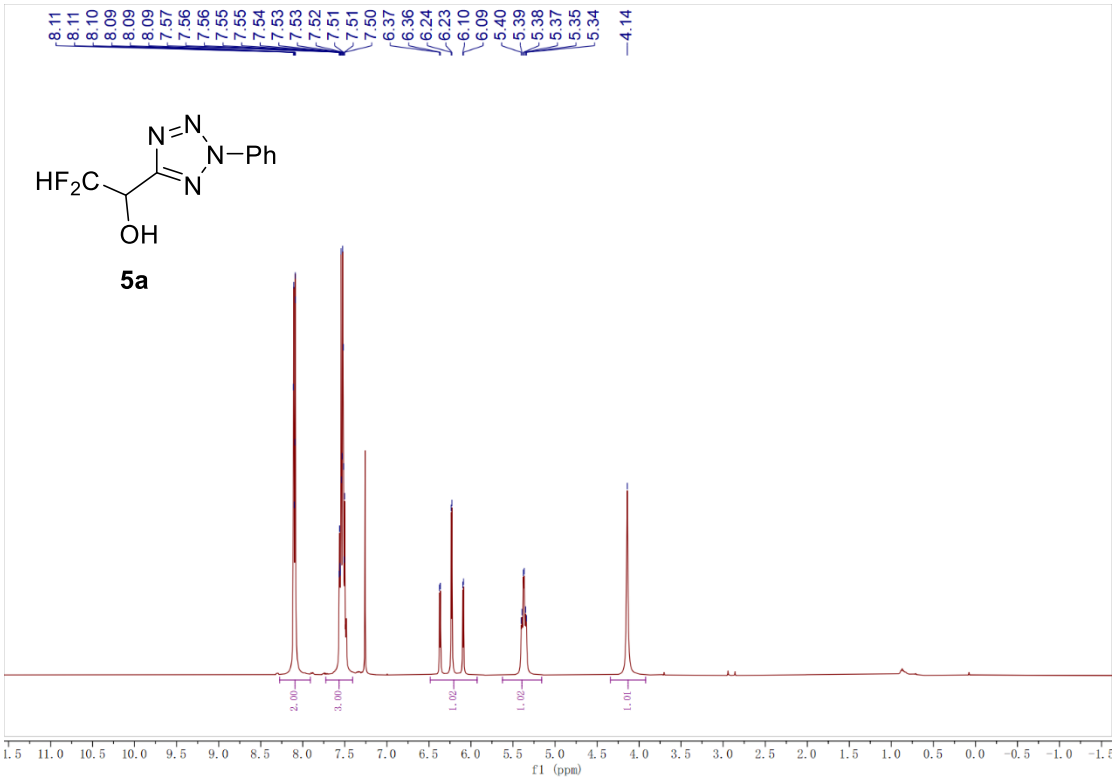


^{19}F NMR (376 MHz, Chloroform-*d*) of **4j**

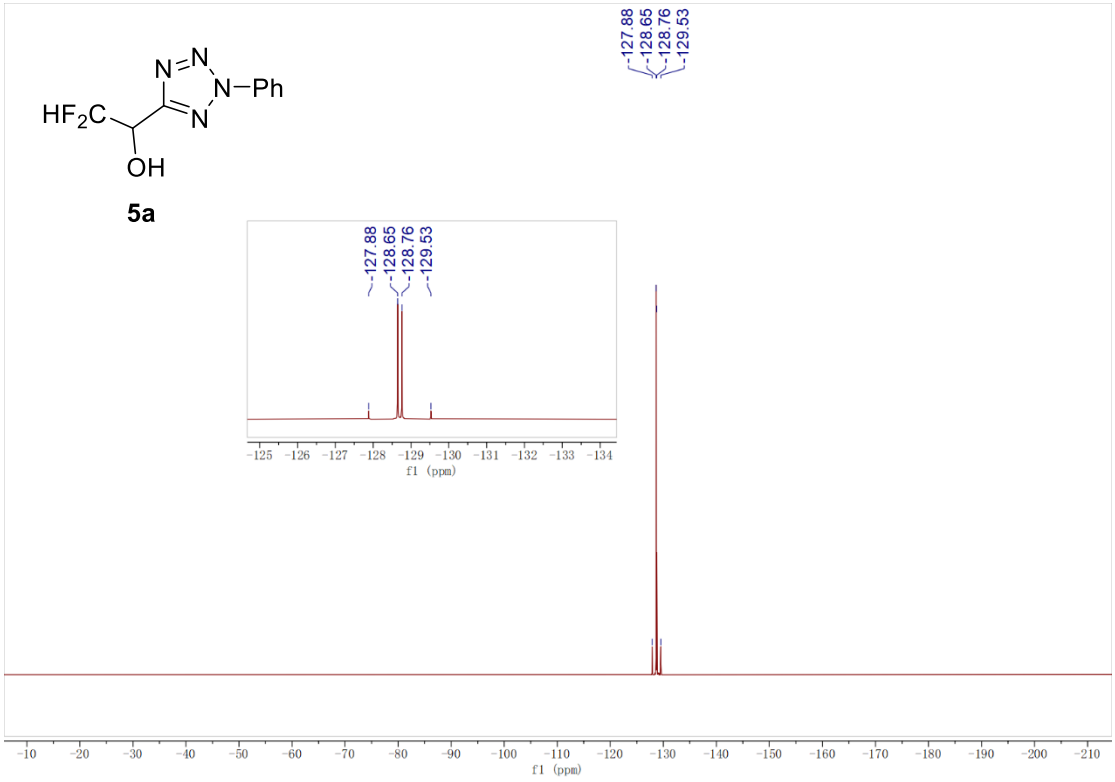


^{13}C NMR (101 MHz, Chloroform-*d*) of **4j**

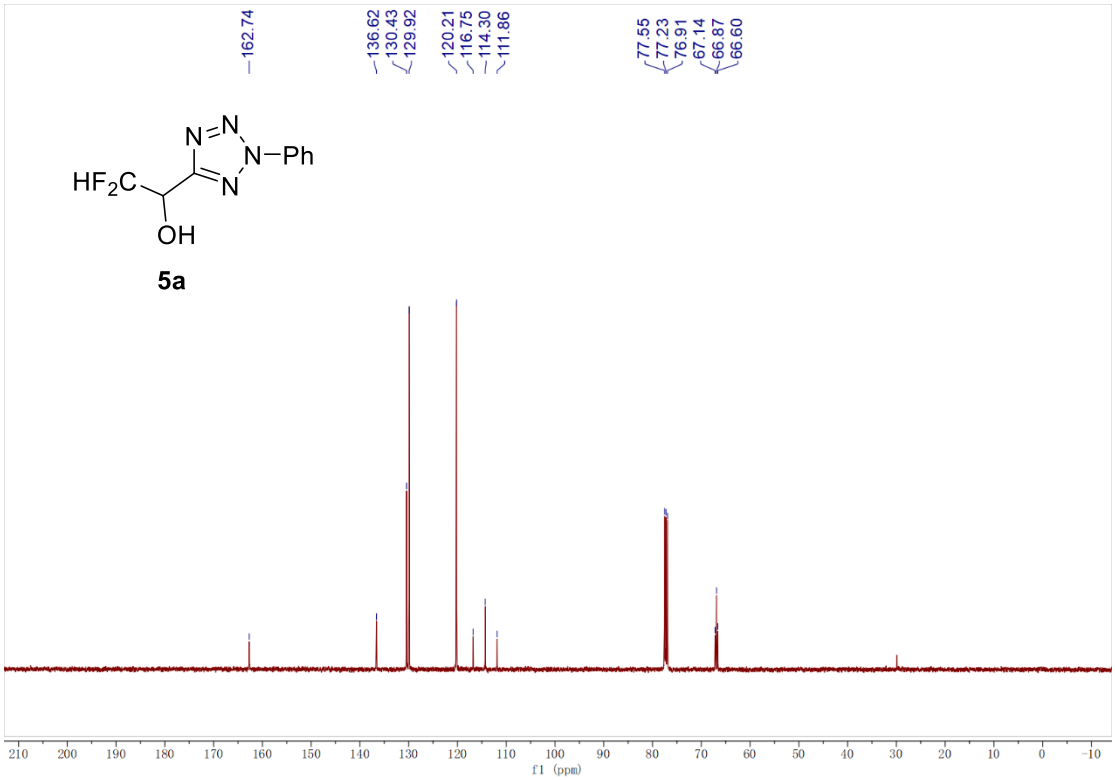
^{1}H, ^{13}C, and ^{19}F NMR spectra of **5a**



^{1}H NMR (400 MHz, Chloroform-*d*) of **5a**

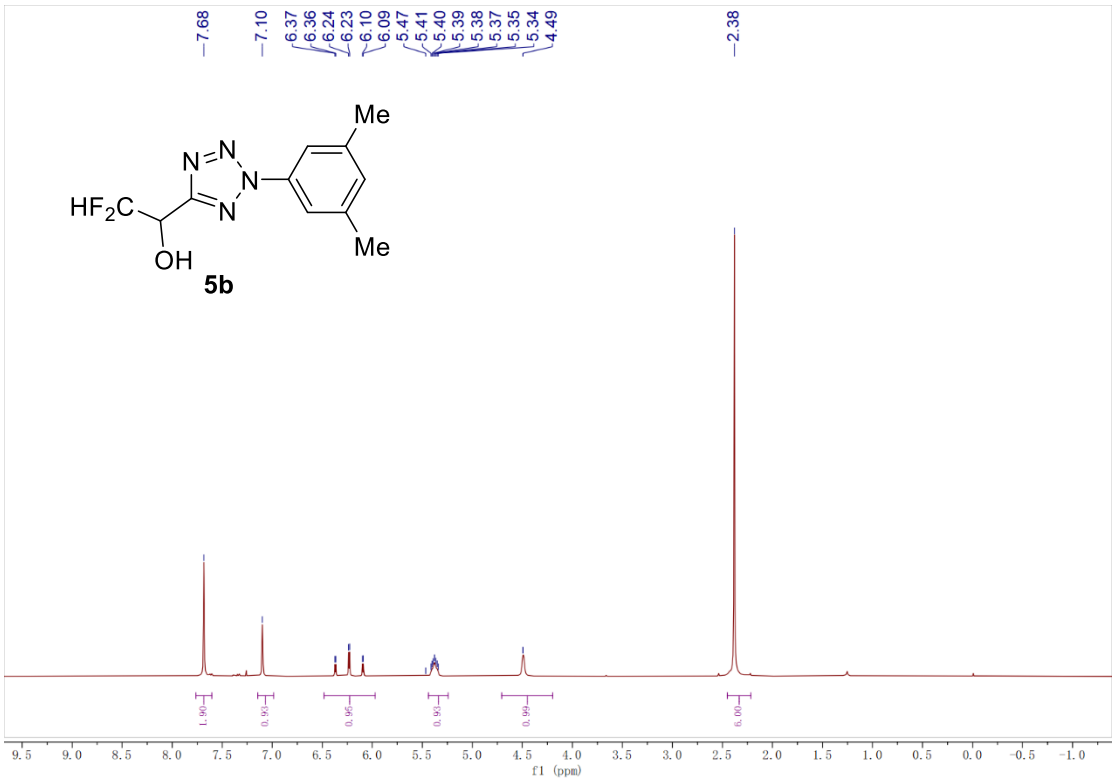


^{19}F NMR (376 MHz, Chloroform-*d*) of **5a**

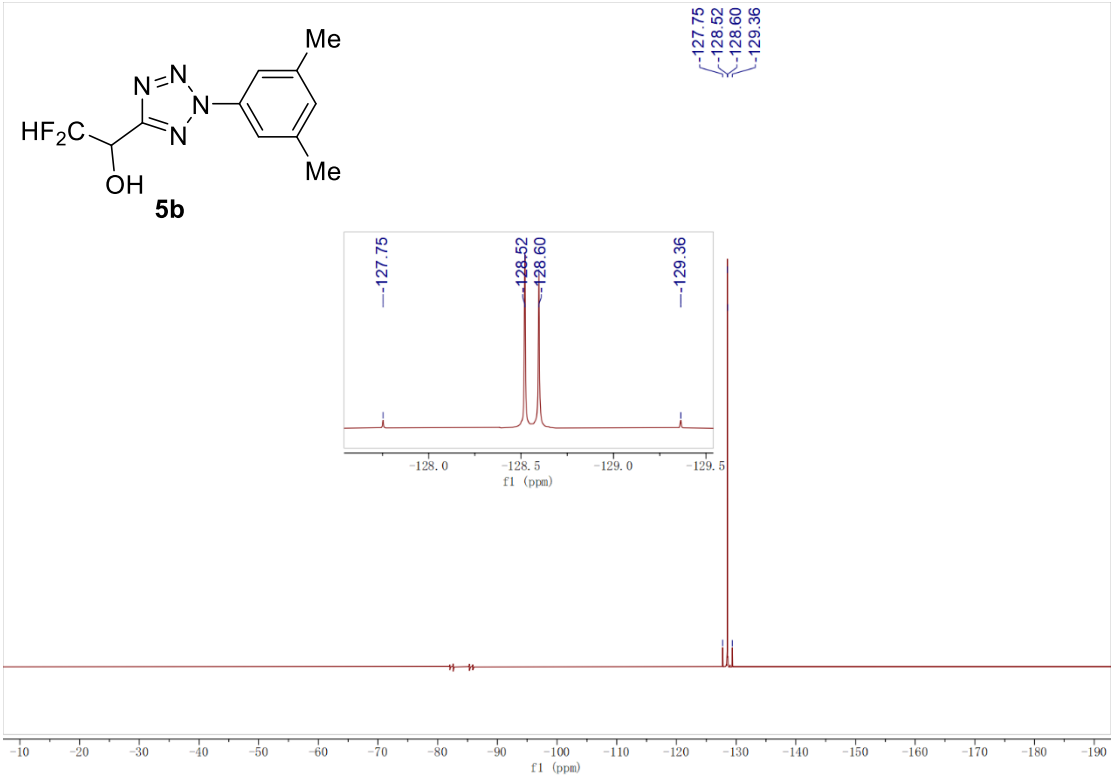


^{13}C NMR (101 MHz, Chloroform-*d*) of **5a**

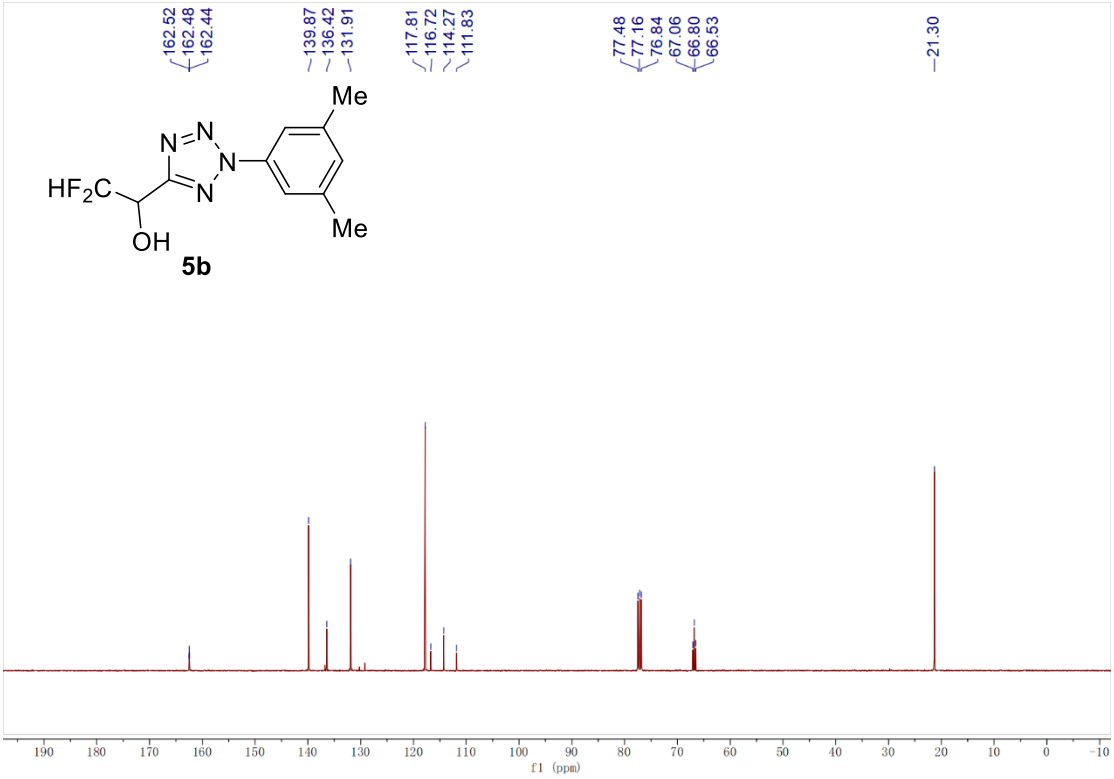
^{1}H, ^{13}C, and ^{19}F NMR spectra of **5b**



^{1}H NMR (400 MHz, Chloroform-*d*) of **5b**

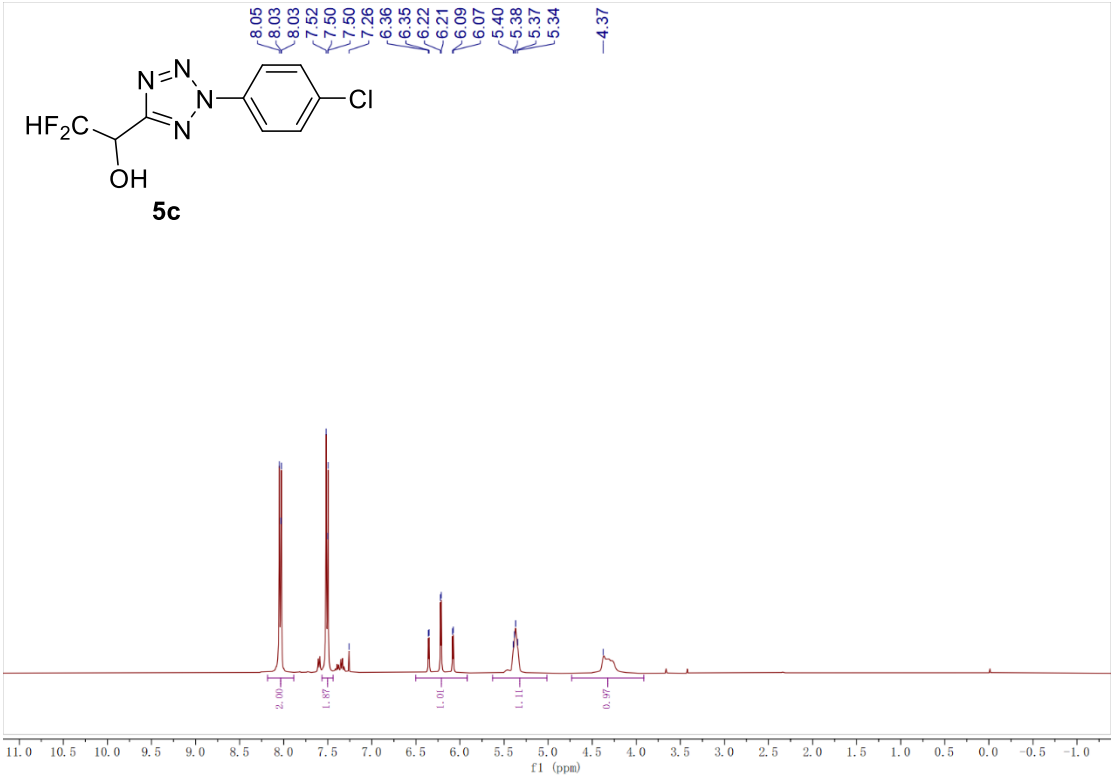


^{19}F NMR (376 MHz, Chloroform-*d*) of **5b**

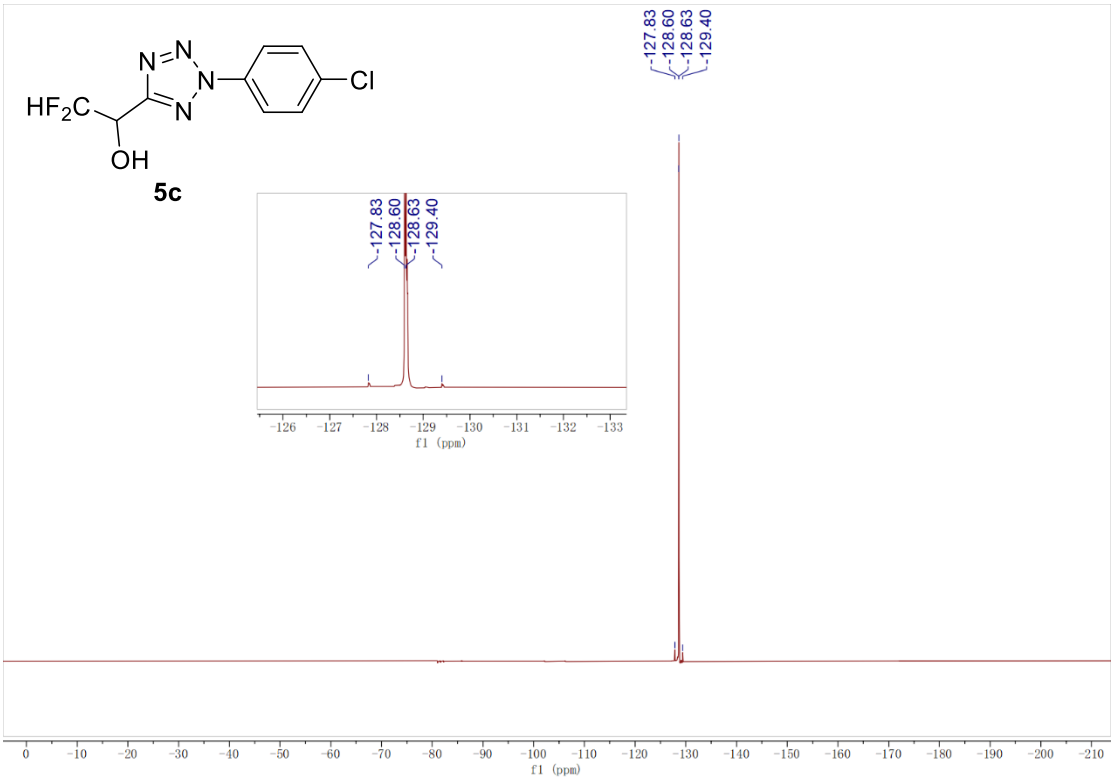


^{13}C NMR (101 MHz, Chloroform-*d*) of **5b**

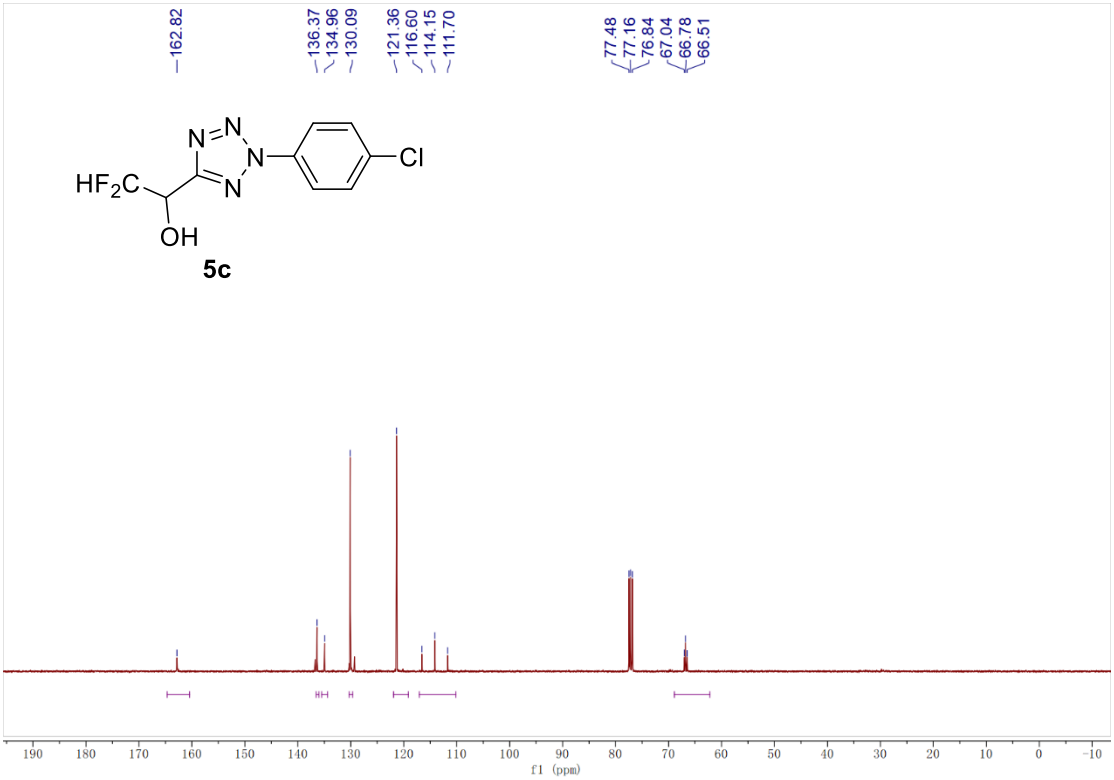
^{1}H, ^{13}C, and ^{19}F NMR spectra of **5c**



^{1}H NMR (400 MHz, Chloroform-*d*) of **5c**

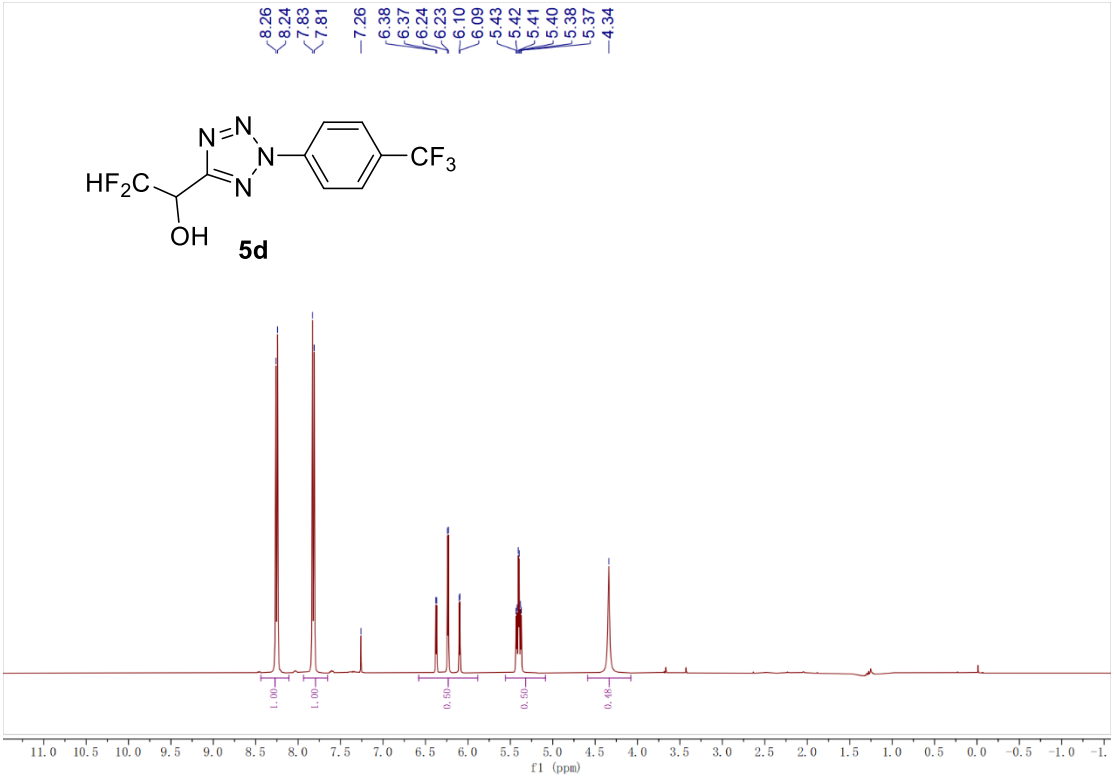


^{19}F NMR (376 MHz, Chloroform-*d*) of **5c**

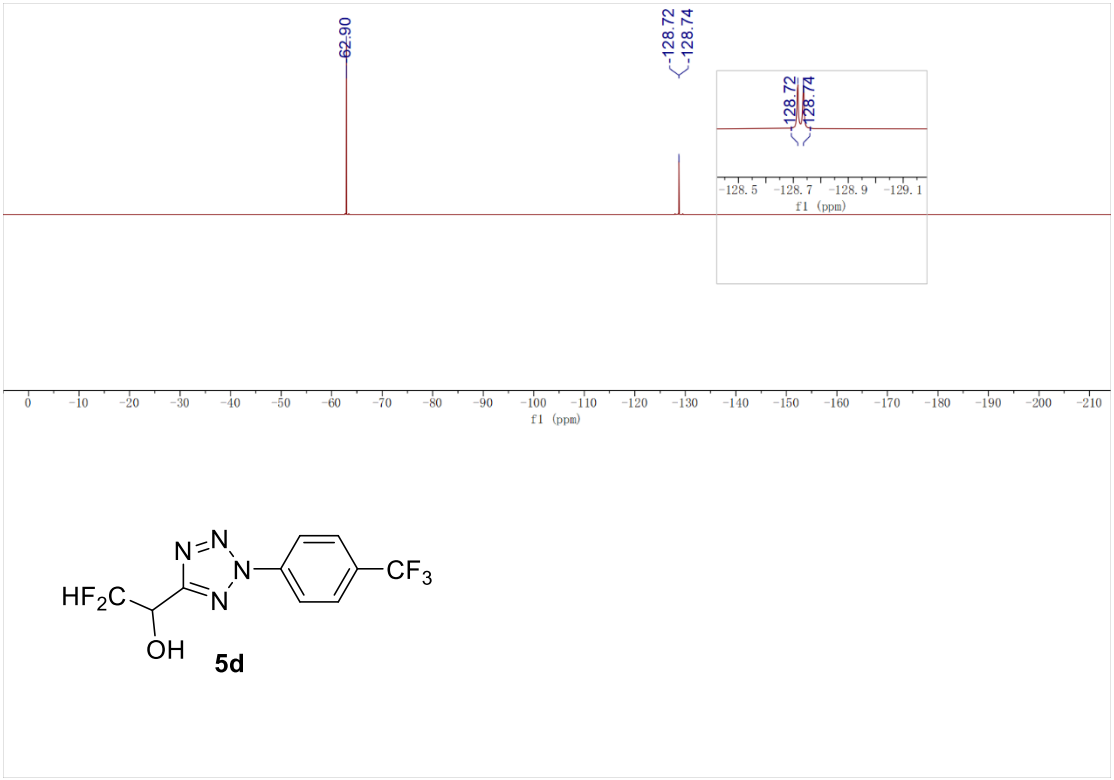


^{13}C NMR (101 MHz, Chloroform-*d*) of **5c**

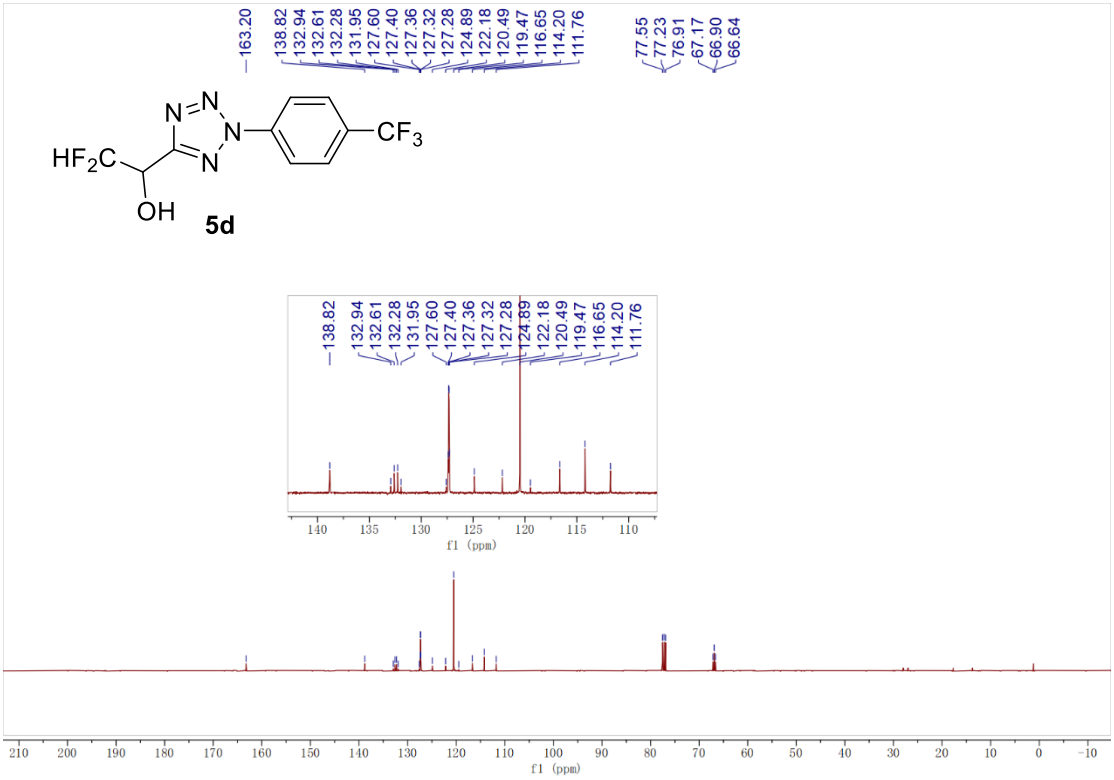
^{1}H, ^{13}C, and ^{19}F NMR spectra of **5d**



^{1}H NMR (400 MHz, Chloroform-*d*) of **5d**

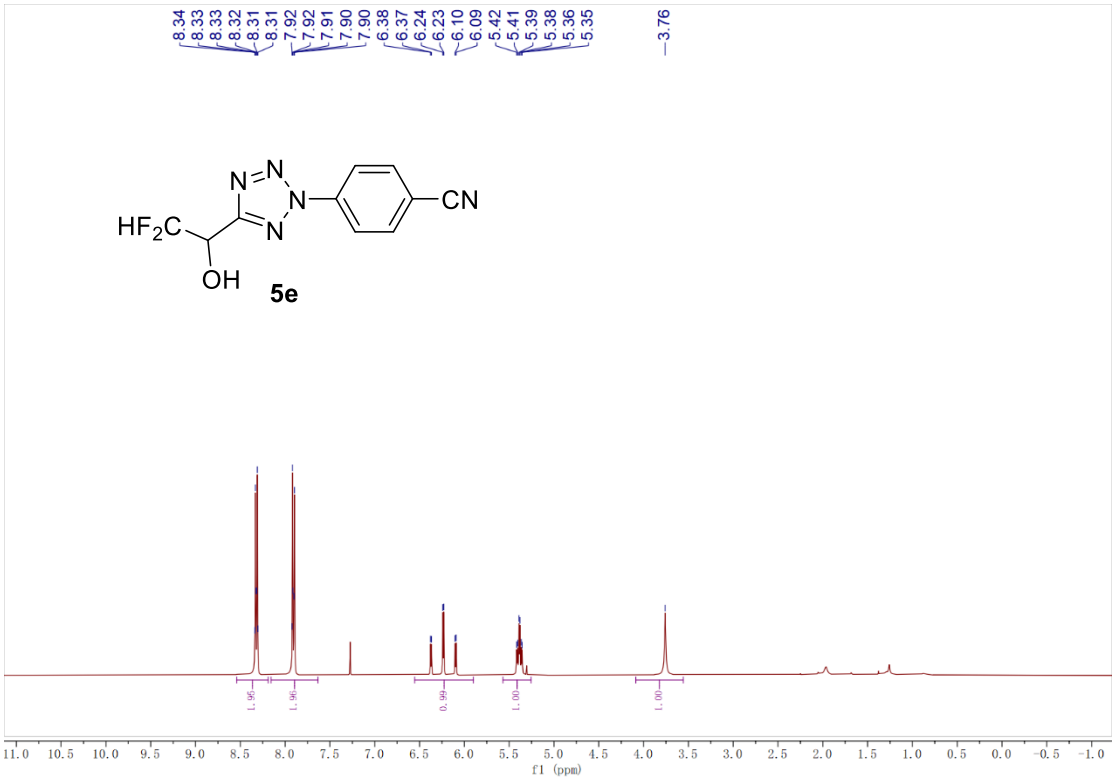


^{19}F NMR (376 MHz, Chloroform-*d*) of **5d**

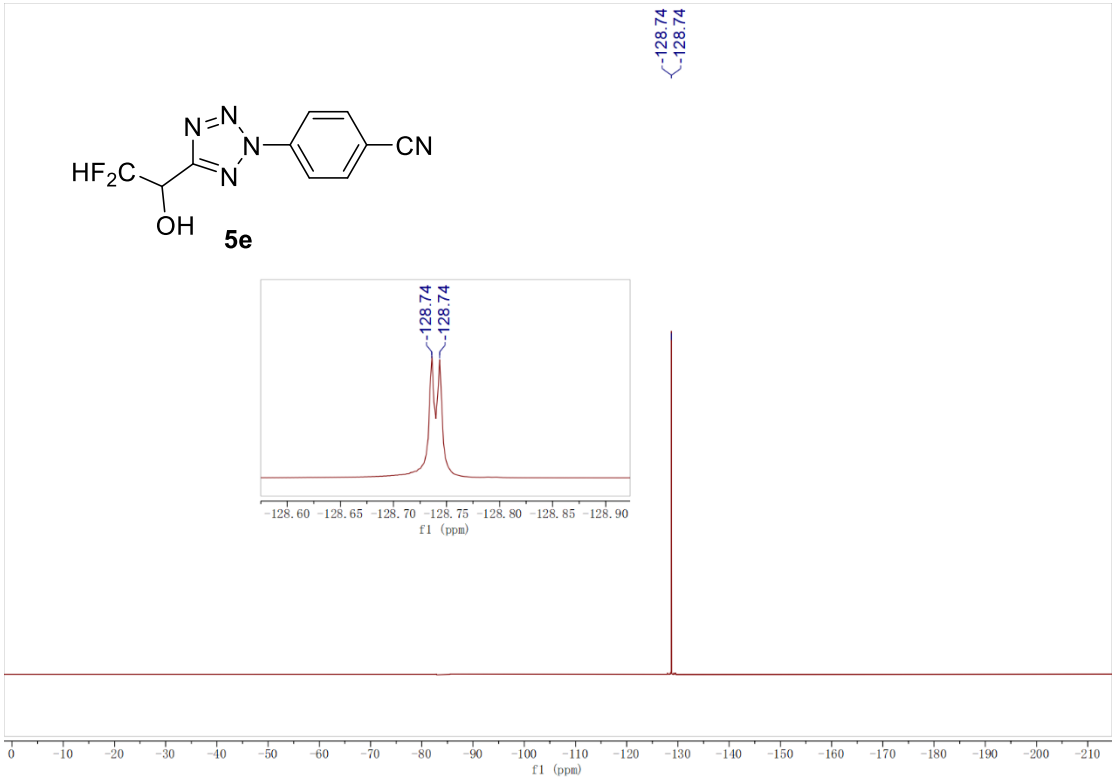


^{13}C NMR (101 MHz, Chloroform-*d*) of **5d**

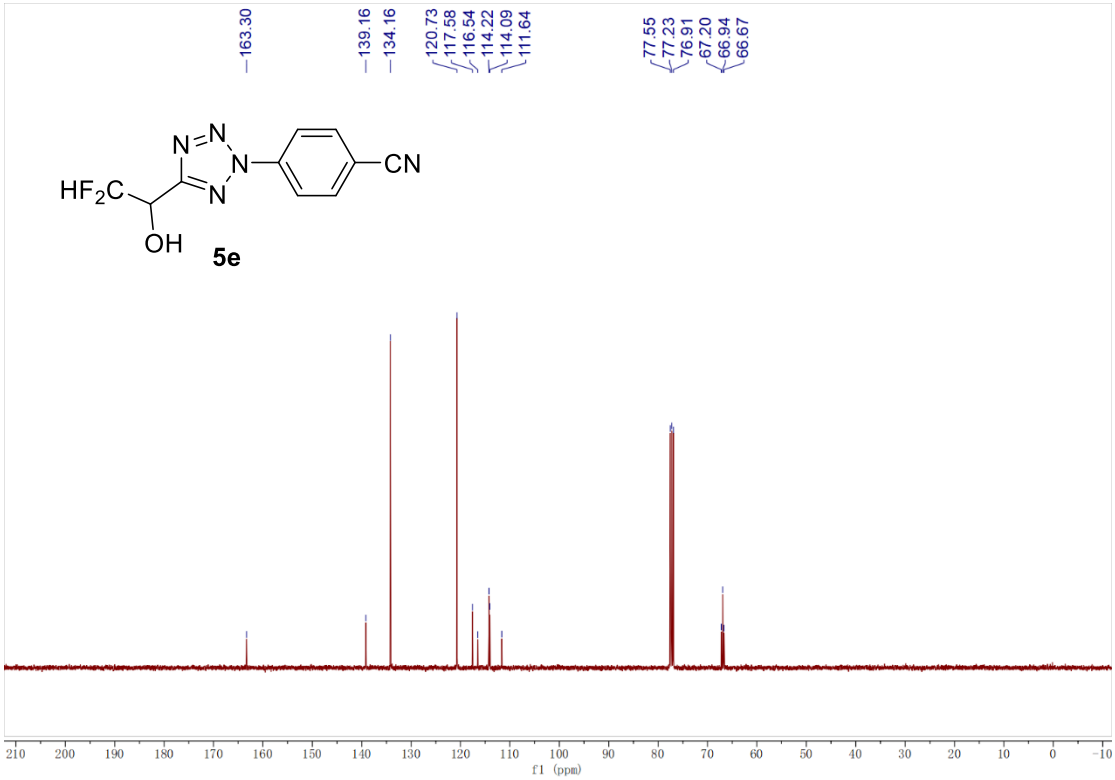
^{1}H, ^{13}C, and ^{19}F NMR spectra of **5e**



^{1}H NMR (400 MHz, Chloroform-*d*) of **5e**

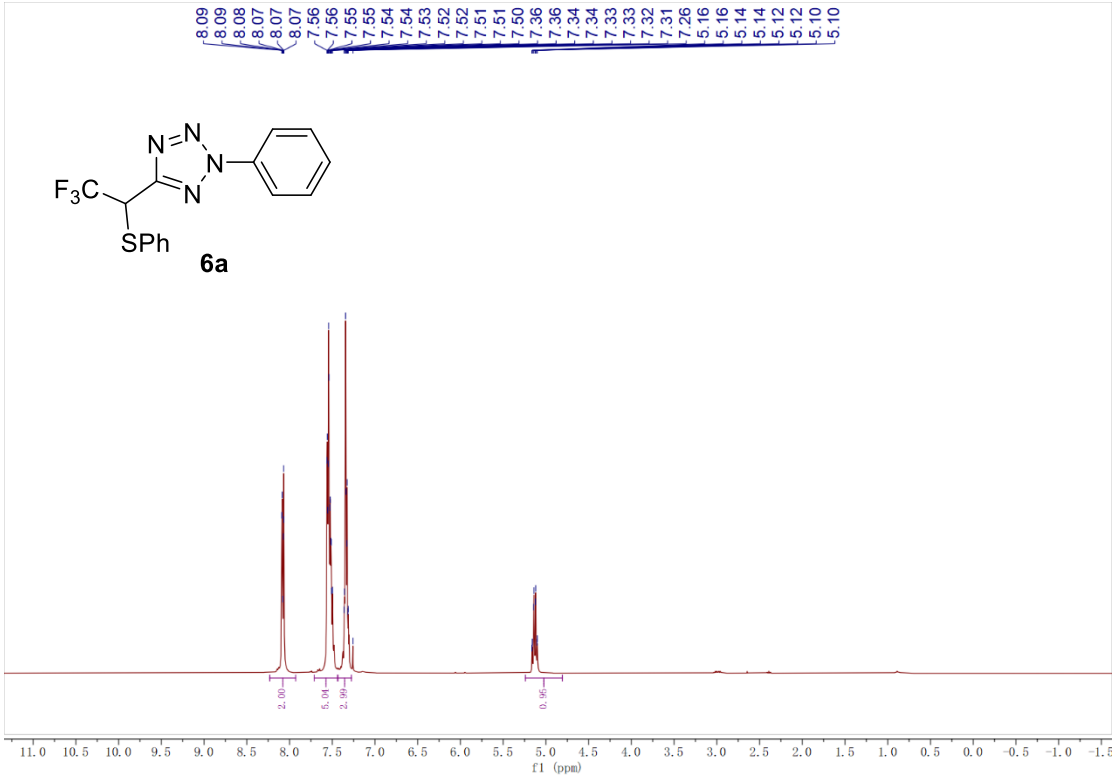


^{19}F NMR (376 MHz, Chloroform-*d*) of **5e**

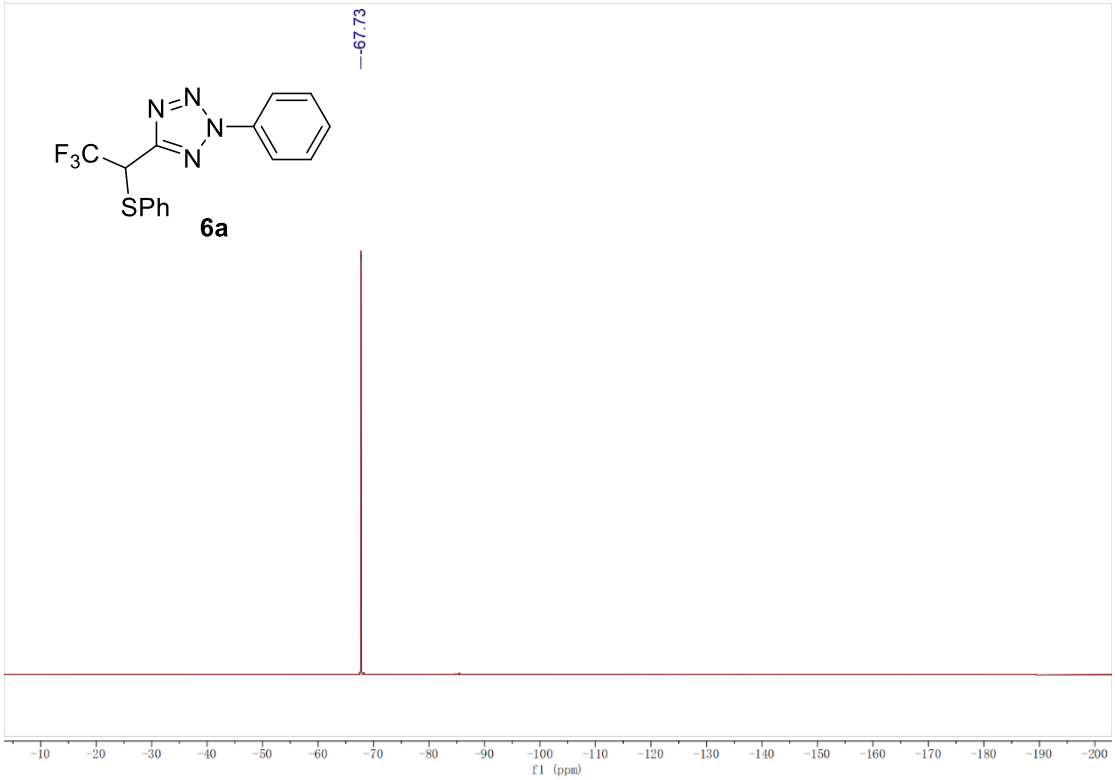


^{13}C NMR (101 MHz, Chloroform-*d*) of **5e**

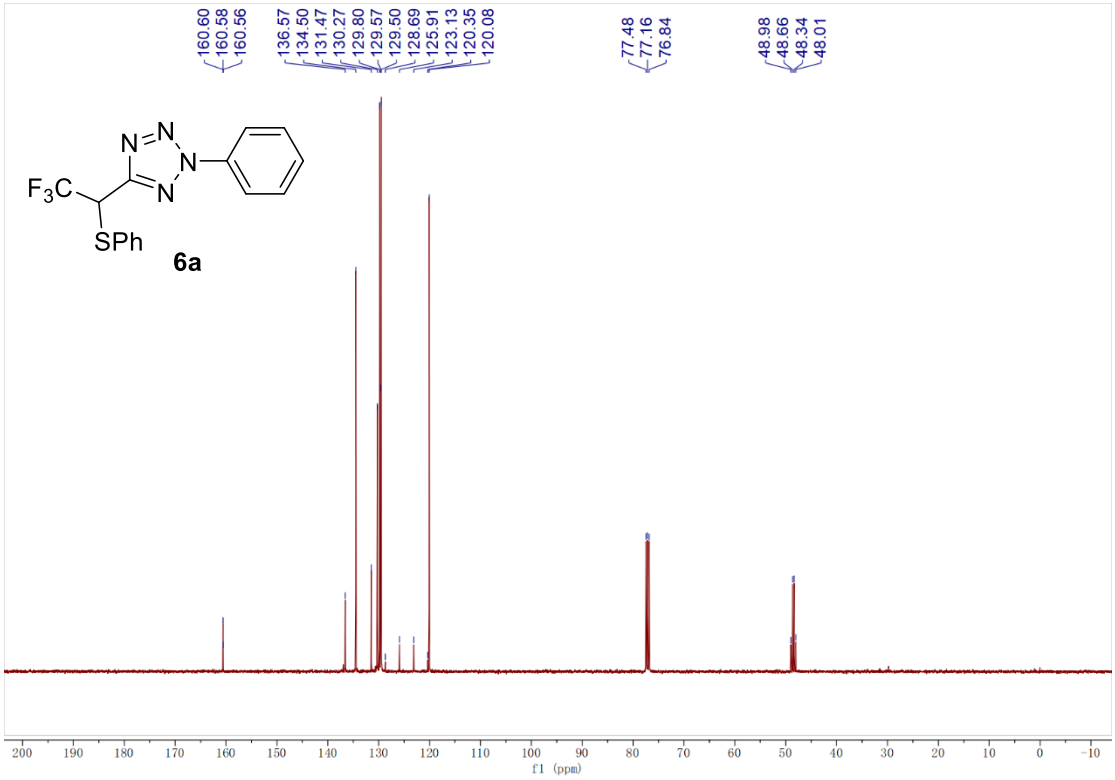
^{1}H, ^{13}C, and ^{19}F NMR spectra of **6a**



^{1}H NMR (400 MHz, Chloroform-*d*) of **6a**

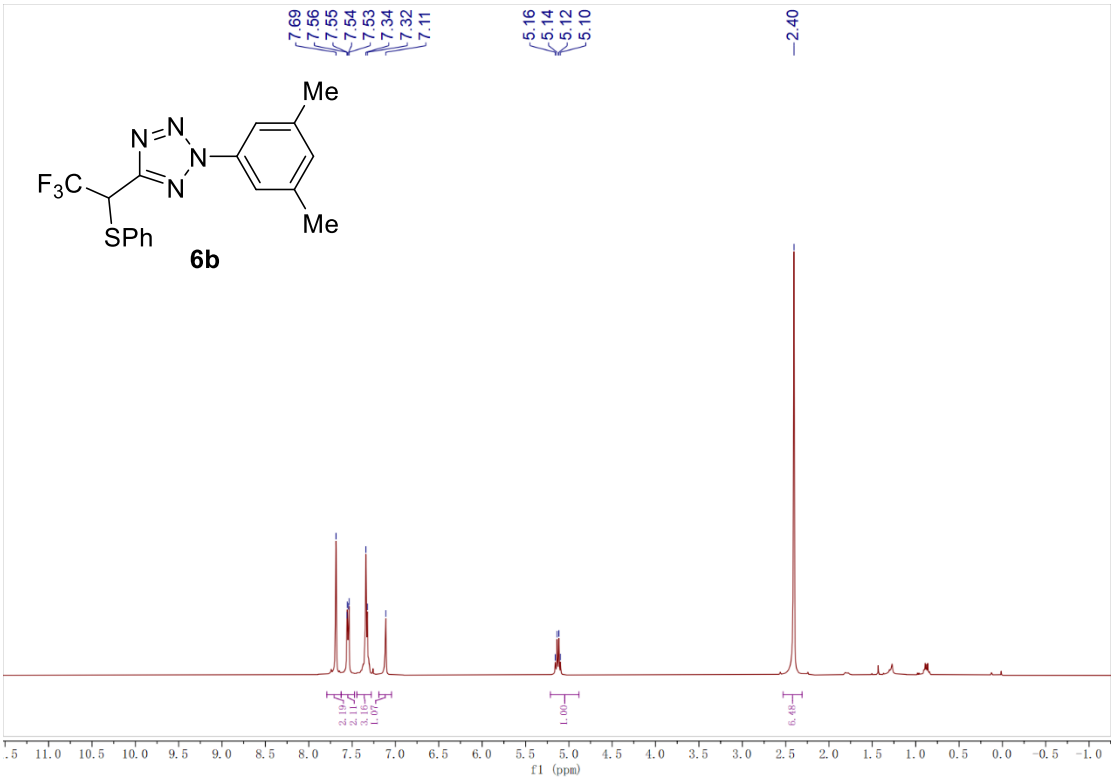


^{19}F NMR (376 MHz, Chloroform-*d*) of **6a**

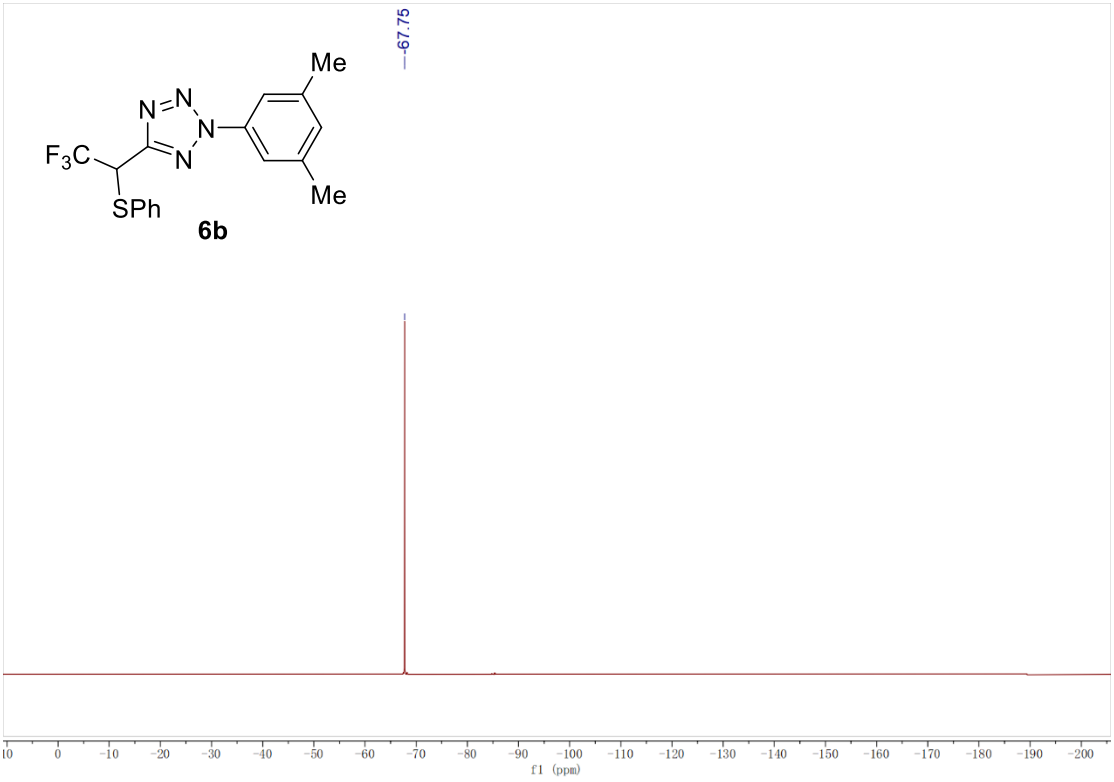


^{13}C NMR (101 MHz, Chloroform-*d*) of **6a**

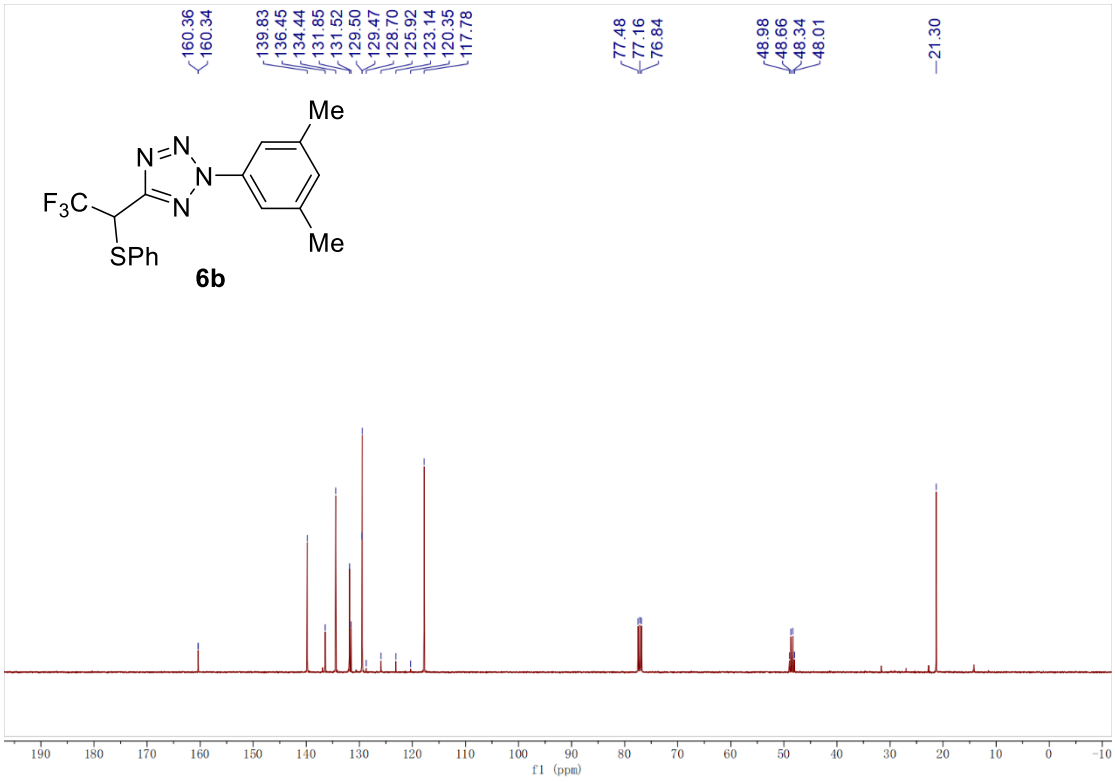
^{1}H, ^{13}C, and ^{19}F NMR spectra of **6b**



^{1}H NMR (400 MHz, Chloroform-*d*) of **6b**

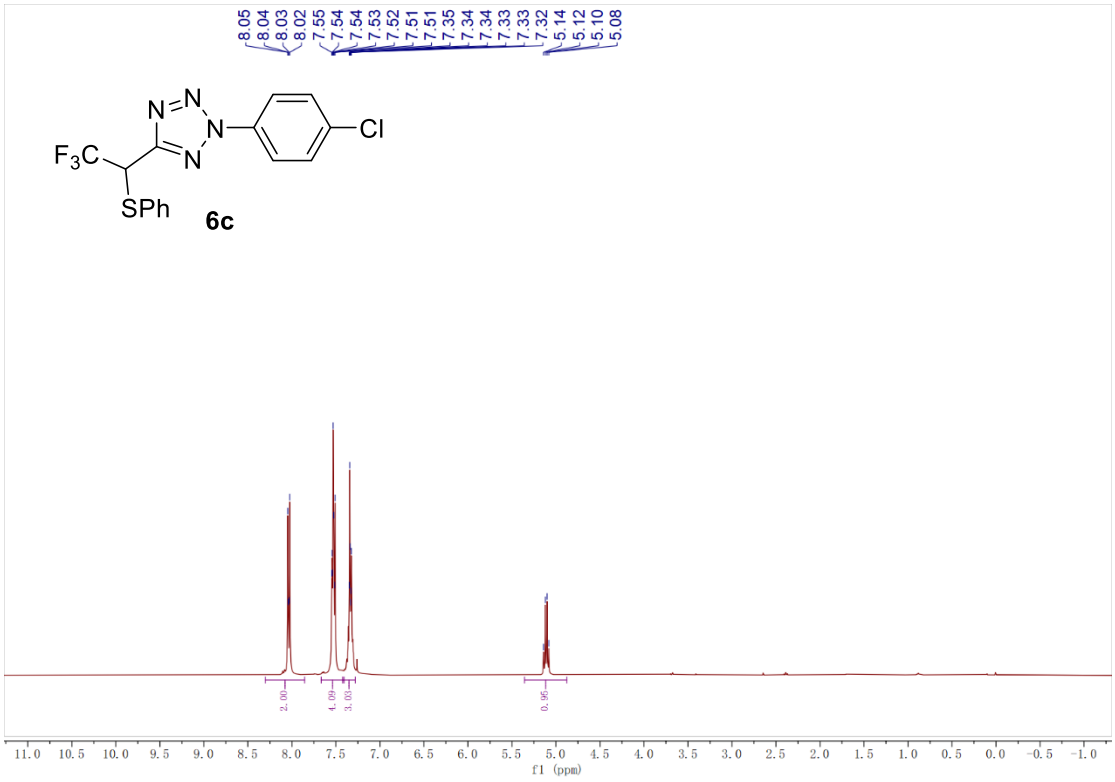


^{19}F NMR (376 MHz, Chloroform-*d*) of **6b**

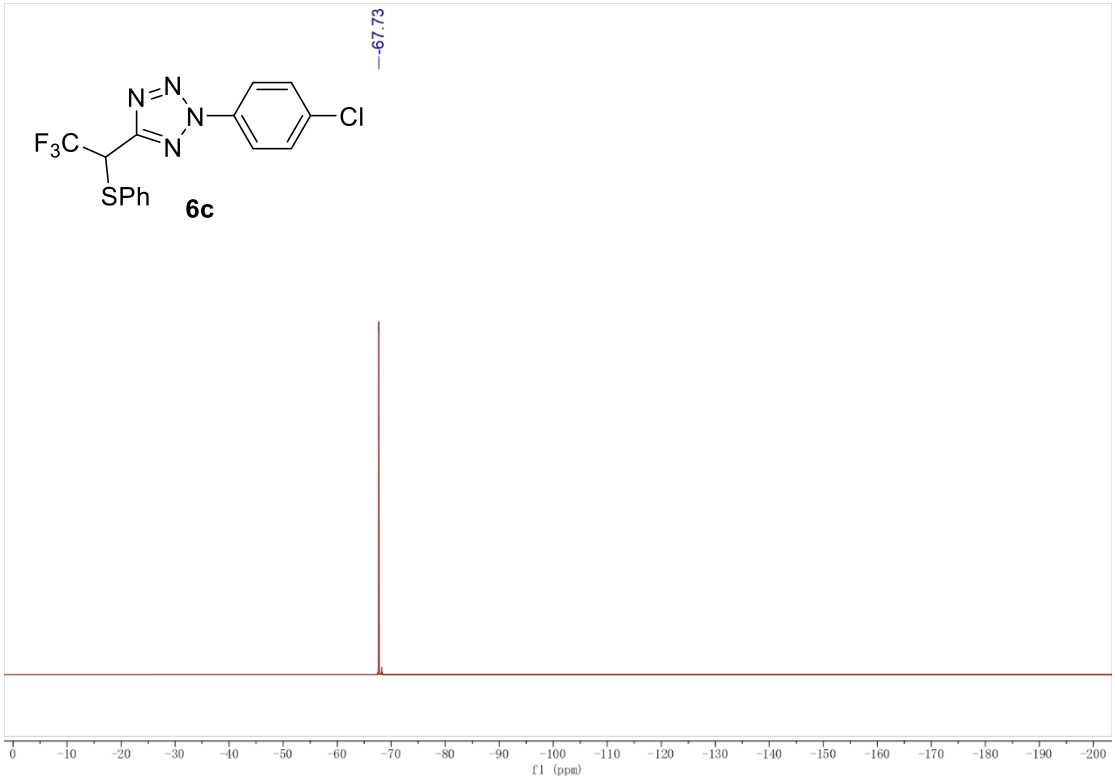


^{13}C NMR (101 MHz, Chloroform-*d*) of **6b**

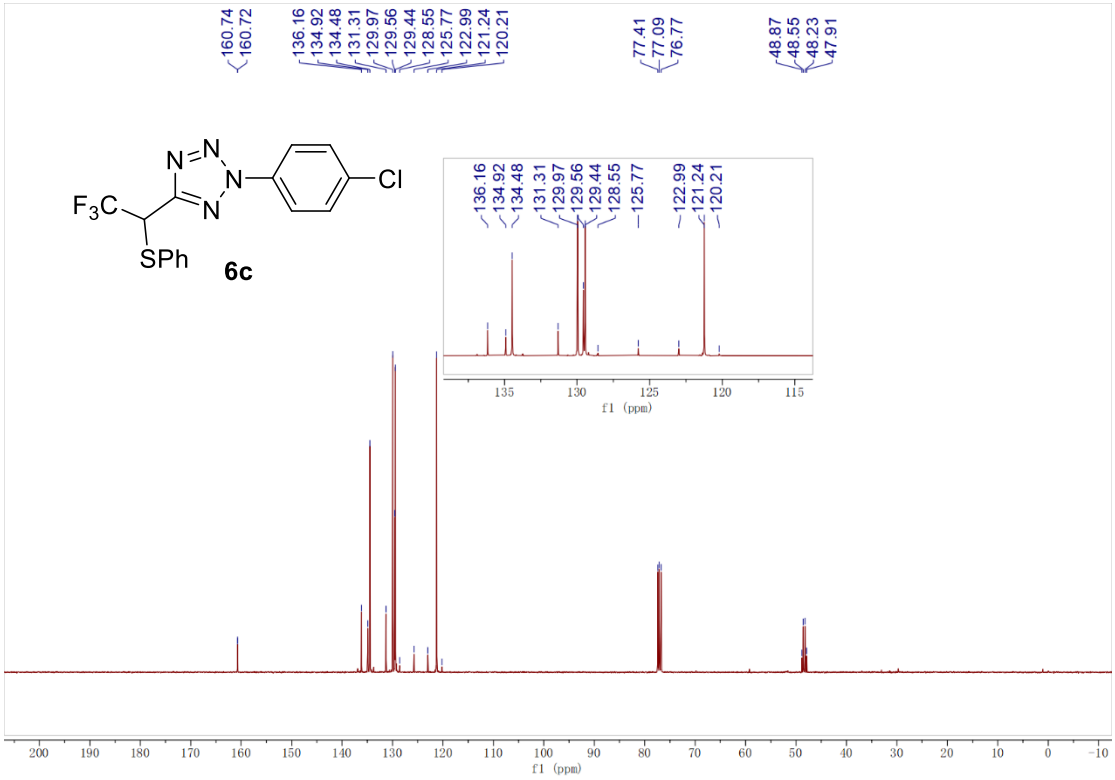
^{1}H, ^{13}C, and ^{19}F NMR spectra of **6c**



^{1}H NMR (400 MHz, Chloroform-*d*) of **6c**

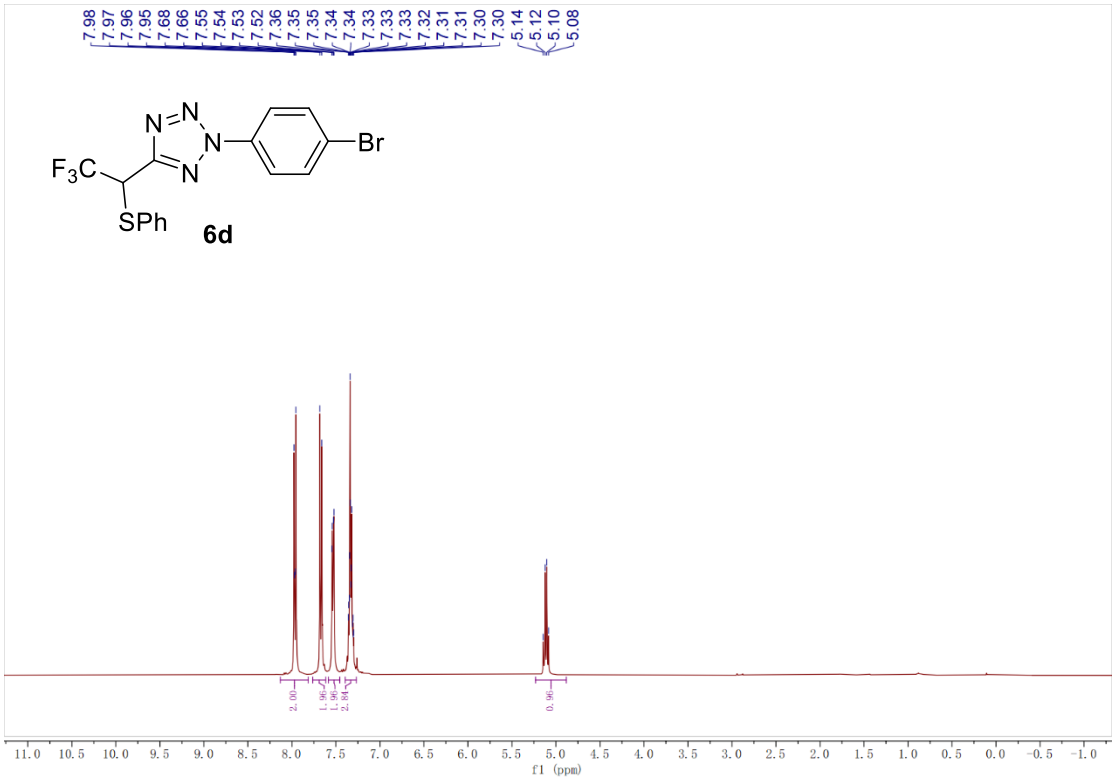


^{19}F NMR (376 MHz, Chloroform-*d*) of **6c**

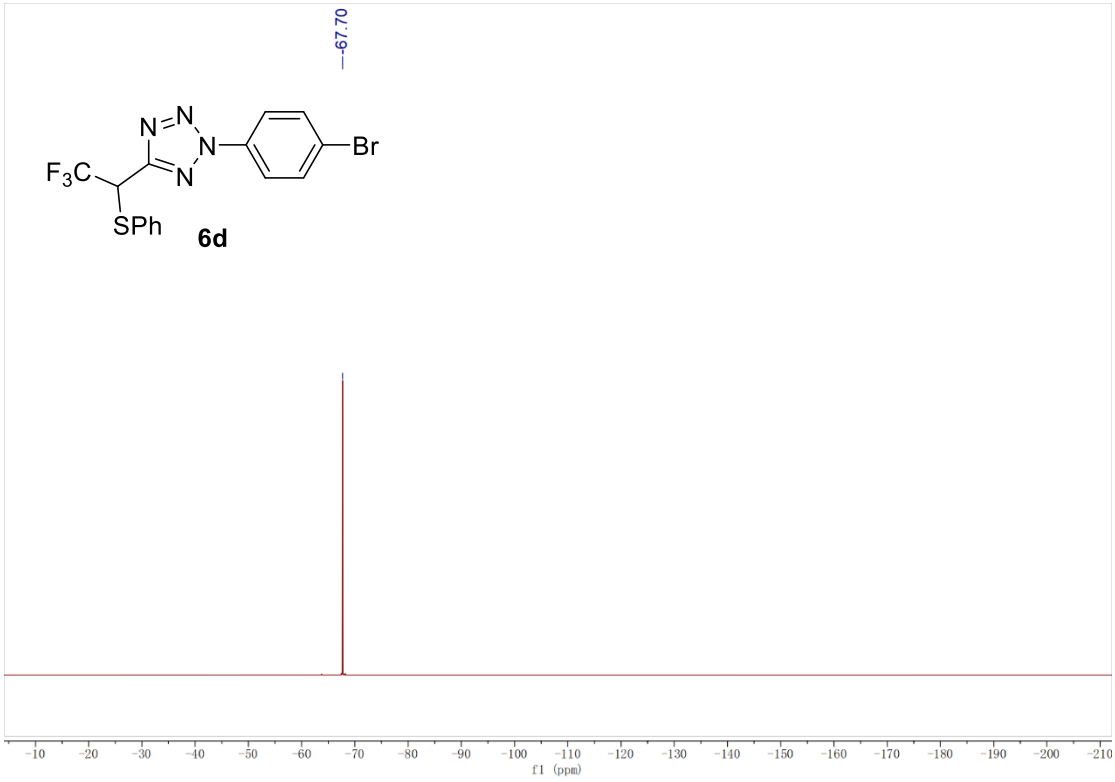


^{13}C NMR (101 MHz, Chloroform-*d*) of **6c**

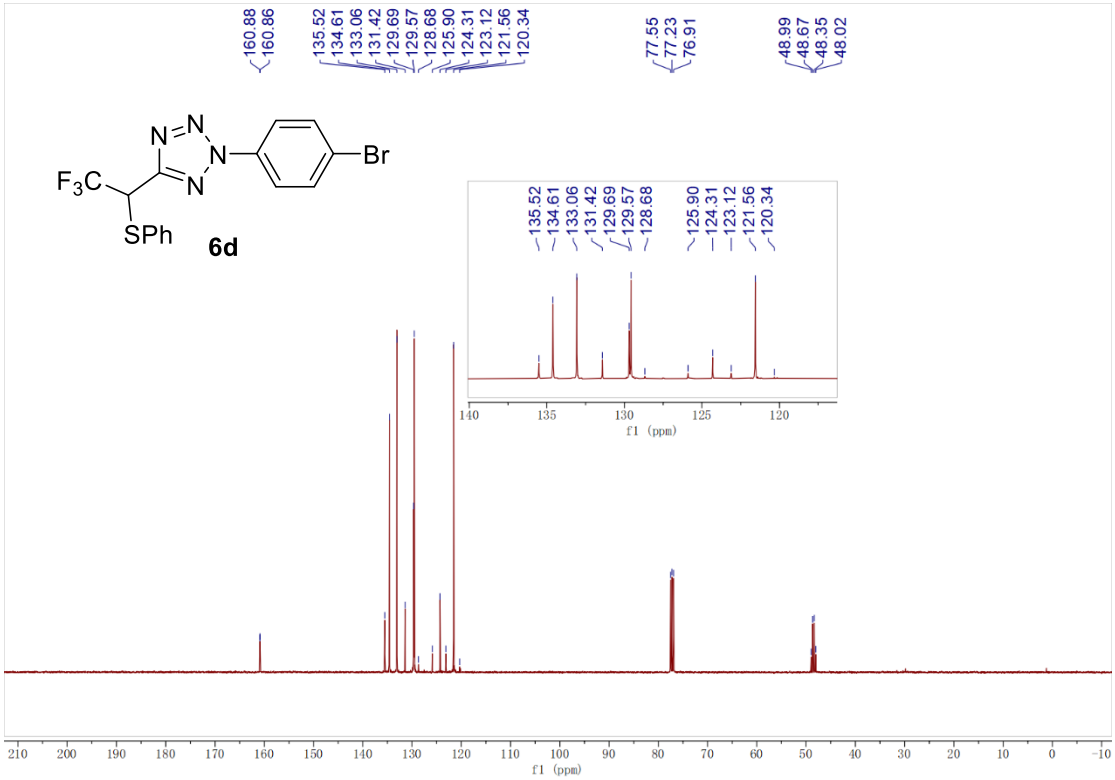
^{1}H, ^{13}C, and ^{19}F NMR spectra of **6d**



^{1}H NMR (400 MHz, Chloroform-*d*) of **6d**



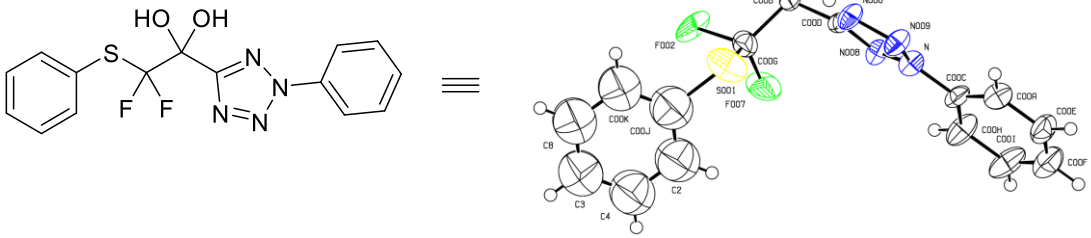
^{19}F NMR (376 MHz, Chloroform-*d*) of **6d**



^{13}C NMR (101 MHz, Chloroform-*d*) of **6d**

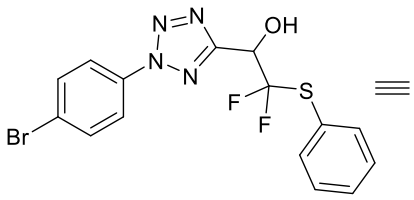
X-Ray Crystallographic Data

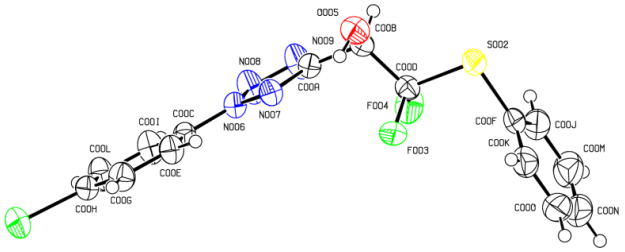
The X-ray crystallographic structure for ketal compound (**3ab**). Crystal data has been deposited to CCDC, number 2116297.



Empirical formula	$C_{15}H_{12}F_2N_4O_2S$
Formula weight	350.35
Temperature/K	293.15
Crystal system	monoclinic
Space group	Ia
a/Å	5.4470(4)
b/Å	26.496(4)
c/Å	11.3845(12)
α/°	90
β/°	102.428(7)
γ/°	90
Volume/Å^3	1604.6(3)
Z	4
ρ_{calc}g/cm^3	1.450
μ/mm^{-1}	0.239
F(000)	720.0
Crystal size/mm^3	0.26 × 0.18 × 0.12
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	3.972 to 50.05
Index ranges	$-5 \le h \le 6$, $-31 \le k \le 31$, $-13 \le l \le 13$
Reflections collected	10241
Independent reflections	2544 [R_{int} = 0.0328, R_{sigma} = 0.0371]
Data/restraints/parameters	2544/98/195
Goodness-of-fit on F^2	1.059
Final R indexes [I>=2σ (I)]	R_1 = 0.0879, wR_2 = 0.2488
Final R indexes [all data]	R_1 = 0.0969, wR_2 = 0.2626
Largest diff. peak/hole / e Å^{-3}	0.88/-0.59
Flack parameter	0.13(6)

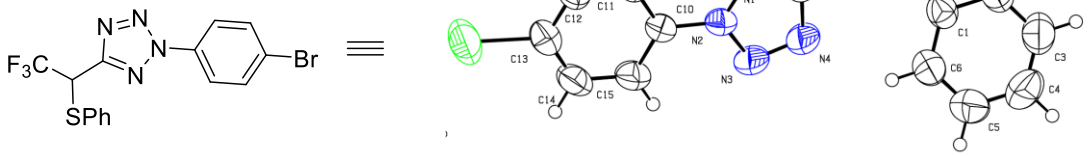
The X-ray crystallographic structure for **3b**. Crystal data has been deposited to CCDC, number 2116301.





Empirical formula	$C_{15}H_{11}BrF_2N_4OS$
Formula weight	413.25
Temperature/K	293(2)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	15.5290(10)
b/Å	10.7691(7)
c/Å	9.7943(6)
α/°	90
β/°	94.839(5)
γ/°	90
Volume/Å^3	1632.10(18)
Z	4
ρ_{calc}g/cm^3	1.682
μ/mm^{-1}	2.678
F(000)	824.0
Crystal size/mm^3	0.38 × 0.32 × 0.29
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.634 to 58.926
Index ranges	-20 ≤ h ≤ 16, -11 ≤ k ≤ 14, -12 ≤ l ≤ 13
Reflections collected	12938
Independent reflections	3856 [R_{int} = 0.0290, R_{sigma} = 0.0401]
Data/restraints/parameters	3856/0/218
Goodness-of-fit on F^2	1.013
Final R indexes [I>=2σ (I)]	R_1 = 0.0456, wR_2 = 0.0923
Final R indexes [all data]	R_1 = 0.0830, wR_2 = 0.1042
Largest diff. peak/hole / e Å^{-3}	0.91/-0.45

The X-ray crystallographic structure for **6d**. Crystal data has been deposited to CCDC, number 2116304.



Empirical formula	$C_{15}H_{10}BrF_3N_4S$
Formula weight	415.24
Temperature/K	296.15
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	10.1584(16)
b/Å	4.7541(7)
c/Å	34.462(5)
α/°	90
β/°	96.312(7)
γ/°	90
Volume/Å^3	1654.2(4)
Z	4
ρ_{calc}g/cm^3	1.667
μ/mm^{-1}	2.646
F(000)	824.0
Crystal size/mm^3	0.32× 0.12 × 0.11
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.078 to 50.05
Index ranges	$-12 \le h \le 12$, $-5 \le k \le 5$, $-41 \le l \le 41$
Reflections collected	30213
Independent reflections	2932 [R_{int} = 0.0776, R_{sigma} = 0.0366]
Data/restraints/parameters	2932/0/217
Goodness-of-fit on F^2	1.003
Final R indexes [I>=2σ (I)]	R_1 = 0.0338, wR_2 = 0.0677
Final R indexes [all data]	R_1 = 0.0762, wR_2 = 0.0783
Largest diff. peak/hole / e Å^{-3}	0.14/-0.28