Supporting Information

Site-Selective *S-gem*-Difluoroallylation of Unprotected Peptides with 3,3-Difluoroallyl Sulfonium Salts

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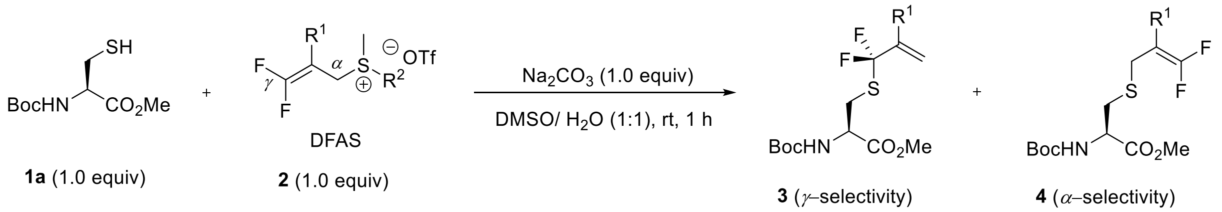
1. General Information and Materials

General information: ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AM400, AM500 or AM600 spectrometers and were calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^1H NMR, 77.00 ppm ^{13}C NMR; DMSO-d_6 at 2.50 ppm ^1H NMR, 39.52 ppm ^{13}C NMR; CH_3OD at 3.31 ppm ^1H NMR, 49.00 ppm ^{13}C NMR). ^{19}F NMR spectra were recorded on a Bruker AM400, AM500 or AM600 spectrometer ($CFCl_3$ was used as the external standard, and the low field is positive). Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. The NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before working up the reaction. High Resolution Mass spectral data were recorded on Waters Premier GC-TOF spectrometer in EI mode, JEOL AccuTOF-MS in ESI positive ion mode. IR spectra were recorded on a Bruker TENSOR 27 FTIR Spectrometer equipped with a Platinum ATR detector.

Materials: Unless otherwise noted, reagents were used as received from commercial sources and used without further purification. Peptides were customized from GenScript and TACHEM. All solvents were not superdry. DFASs were prepared according to the literature[1]. 12 W blue LED strips (GreeThink 12V-5050-60; 1 m×12.5 mm×4.4 mm) was purchased from Taobao.com.

2. Optimizations of the Reaction Conditions for the *gem*-Difluoroallylation of Protected Cysteine 1a with DFASs 2

Table S1. Optimization of the Regioselectivity[a]

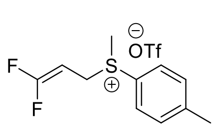


1a (1.0 equiv)

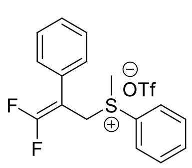
2 (1.0 equiv)

3 (γ-selectivity)

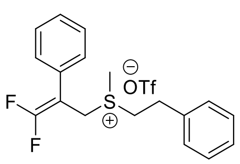
4 (α-selectivity)



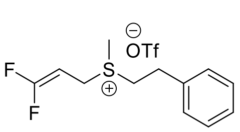
2a



2b



2c

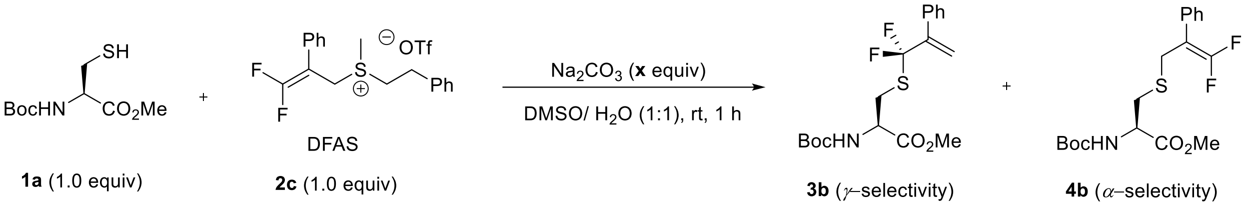


2d

Entry	DFAS	**3** and **4**	
		3 / **4**, yield (%)[b]	γ/α
1	**2a**	**3a** / **4a** = 77 / 23	3.3:1
2	**2b**	**3b** / **4b** = 79 / 8	10:1
3	**2c**	**3b** / **4b** = 92 / --	>99:1
4	**2d**	**3a** / **4a** = 93 / --	>99:1

[a] Reaction conditions (unless otherwise specified): **1a** (0.1 mmol, 1.0 equiv), **2** (0.1 mmol, 1.0 equiv), Na_2CO_3 (0.1 mmol, 1.0 equiv), H_2O (1 mL), DMSO (1 mL), rt, 1h. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard.

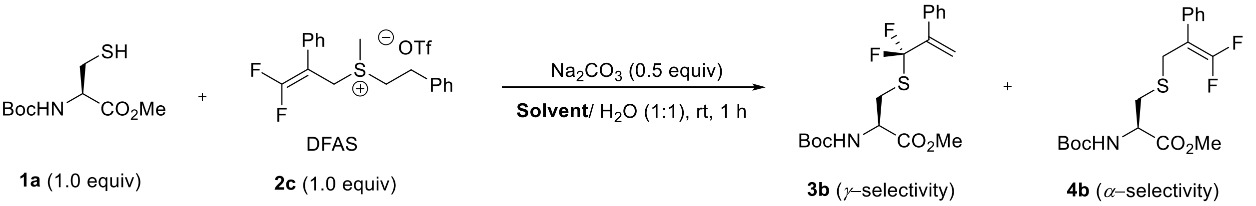
Table S2. Screening of the Loading Amount of the Base[a]



Entry	x	**3** and **4**	
		3b / **4b**, yield (%)[b]	γ/α
1	0.2	32 / --	>99:1
2	0.5	90 / --	>99:1
3	1.0	92 / --	>99:1

[a]Reaction conditions (unless otherwise specified): **1a** (0.1 mmol, 1.0 equiv), **2c** (0.1 mmol, 1.0 equiv), Na_2CO_3 (x equiv), H_2O (1 mL), DMSO (1 mL), rt, 1h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard.

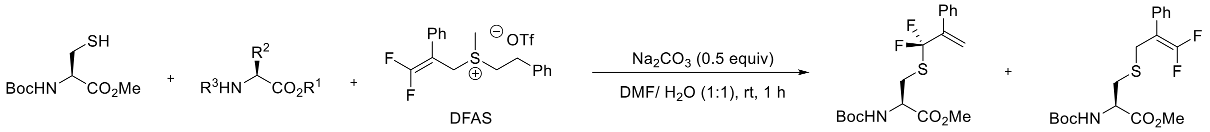
Table S3. Screening of the Solvents[a]



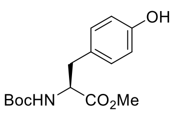
Entry	Solvent	**3** and **4**	
		3b / **4b**, yield (%)[b]	γ/α
1	H_2O	57 / --	>99:1
2	DMSO	90 / --	>99:1
3	DMF	95 / --	>99:1
4	THF	84 / --	>99:1
5	CH_3OH	92 / --	>99:1
6	CH_3CN	89 / --	>99:1

[a]Reaction conditions (unless otherwise specified): **1a** (0.1 mmol, 1.0 equiv), **2c** (0.1 mmol, 1.0 equiv), Na_2CO_3 (0.05 mmol, 0.5 equiv), Solvent (1.0 mL), H_2O (1 mL), rt, 1 h. [b]Determined by ^{19}F NMR using fluorobenzene as an internal standard.

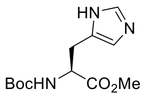
Table S4. Intermolecular Competition Experiments with Other Amino Acids[a]



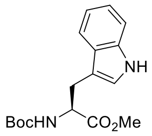
1a (1.0 equiv) + **AA** (1.0 equiv) + **2c** (1.0 equiv) → **3b** (γ–selectivity) + **4b** (α–selectivity)



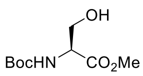
Boc-Tyr-OMe



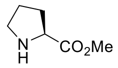
Boc-His-OMe



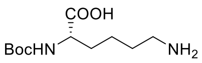
Boc-Trp-OMe



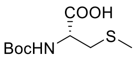
Boc-Ser-OMe



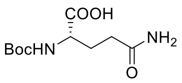
Pro-OMe



Boc-Lys



Boc-Met

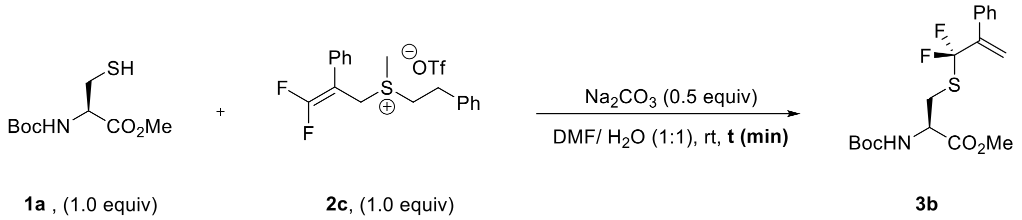


Boc-Gln

Entry	AA	**3** and **4**	
		3b / **4b**, yield (%)[b]	γ/α
1	Boc-Tyr-OMe	99 / --	>99:1
2	Boc-His-OMe	99 / --	>99:1
3	Boc-Trp-OMe	90 / --	>99:1
4	Boc-Ser-OMe	95 / --	>99:1
5	Pro-OMe	96 / --	>99:1
6[c]	Boc-Lys	95 / --	>99:1
7[c]	Boc-Met	90 / --	>99:1
8[c]	Boc-Gln	99 / --	>99:1

[a] Reaction conditions (unless otherwise specified): **1a** (0.1 mmol, 1.0 equiv), **AA** (0.1 mmol, 1.0 equiv), Na_2CO_3 (0.05 mmol, 0.5 equiv), H_2O (1 mL), DMF (1 mL), rt, 1 h. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard. nd; not detected. [c] 1.5 equiv Na_2CO_3 was used.

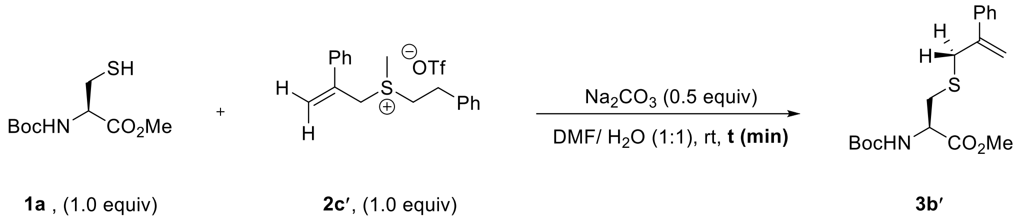
Table S5. Examination of the Reaction Time of Reaction of **1a** with DFAS **2c**[a]



Entry	**t (min)**	**3b** yield (%)[b]
1	0.5	16
2	1	50
3	2	68
4	3	85
5	4	99
6	5	99
7	10	99
8	20	99
9	30	99
10	60	99

[a] Reaction conditions (unless otherwise specified): **1a** (0.05 mmol, 1.0 equiv), **2c** (1.0 equiv), Na_2CO_3 (0.5 equiv), H_2O (1 mL), DMF (1 mL), rt, 1 h. [b] Determined by ^{19}F NMR using fluorobenzene as an internal standard.

Table S6. Examination of the Reaction Time of Reaction of **1a** with DFAS **2c′**[a]



Entry	**t (min)**	**3b'** yield (%)[b]
1	0.5	nd
2	1	nd
3	2	6
4	3	11
5	4	14
6	5	28
7	10	36
8	20	64
9	30	78
10	60	73

[a] Reaction conditions (unless otherwise specified): **1a** (0.05 mmol, 1.0 equiv), **2c′** (1.0 equiv), Na_2CO_3 (0.5 equiv), H_2O (1 mL), DMF (1 mL), rt, 1 h. [c] Determined by ^1H NMR using CH_2Br_2 as an internal standard.

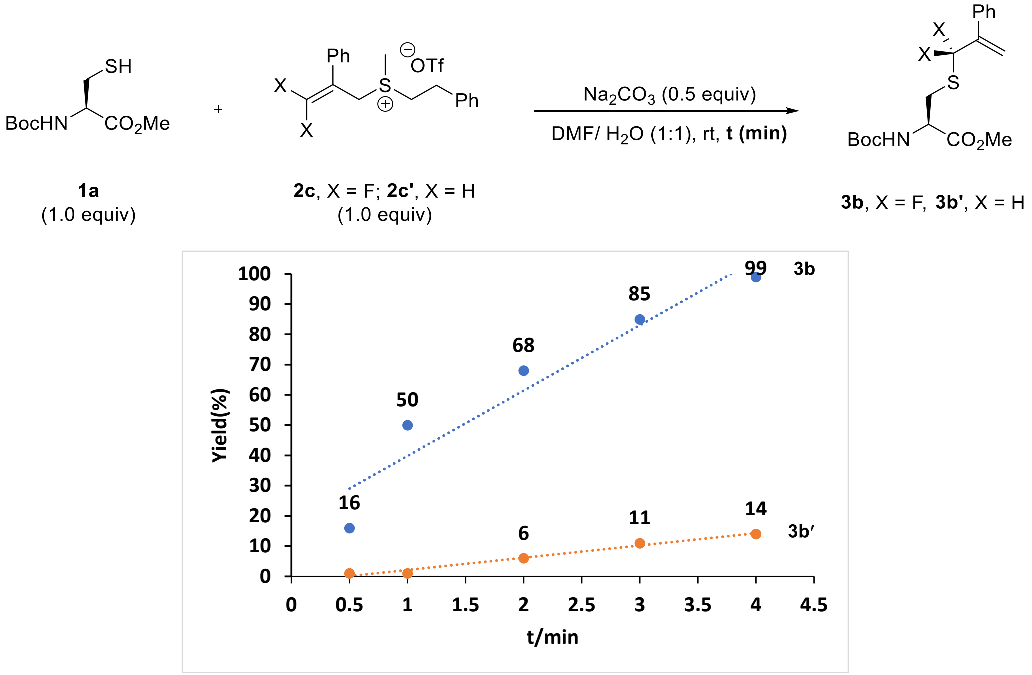
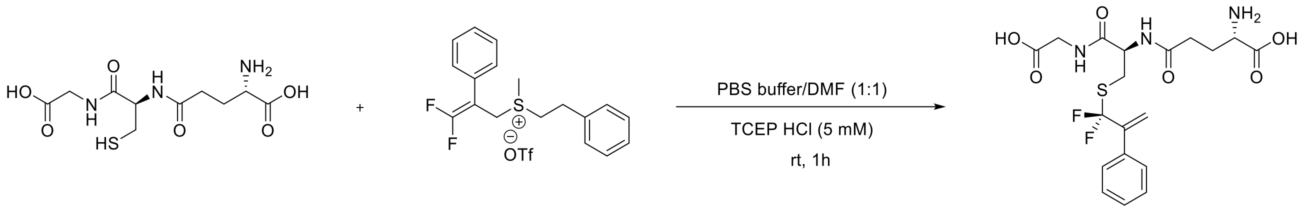


Figure S1 Kinetic studies of the reaction of **1a** with **2c** and **2c′**

Table S7. The Investigation of Concentrations of the Reaction[a]



GSH, 1.0 equiv **2c**, 5mM **3o**

Entry	Concentration	Absorption (area)	**3o**, yield (%)[b]
1	2mM	1040157.71	99
2	1mM	345263.38	90
3	0.5mM	123519.53	64
4	0.1mM	25926.08	64
5	0.05mM	13112.99	62

[a] Reaction conditions (unless otherwise specified): **GSH** (1.0 equiv), 5mM **2c** (10 mg), 5mM TCEP HCl (1.4 mg), 0.2M PBS buffer (pH = 7.9, 2 mL), DMF (2 mL), rt, 1h. [b] Determined by LC-MS.

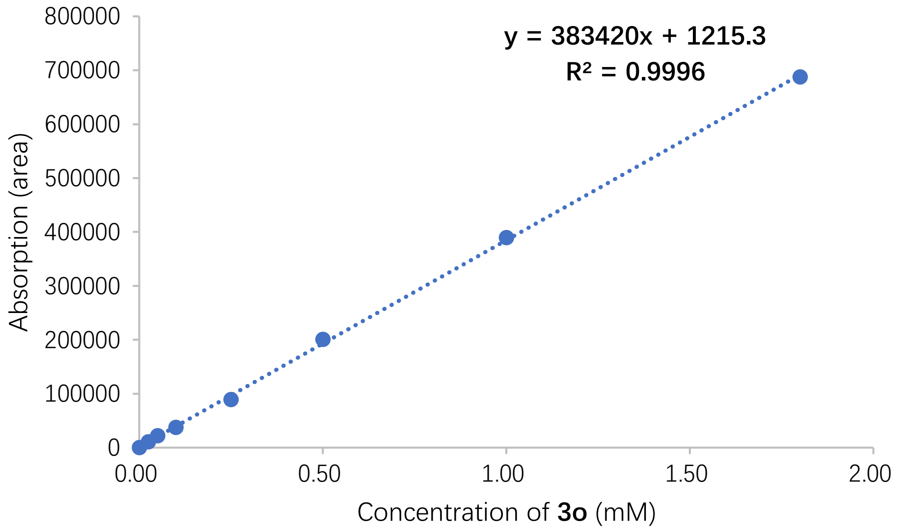
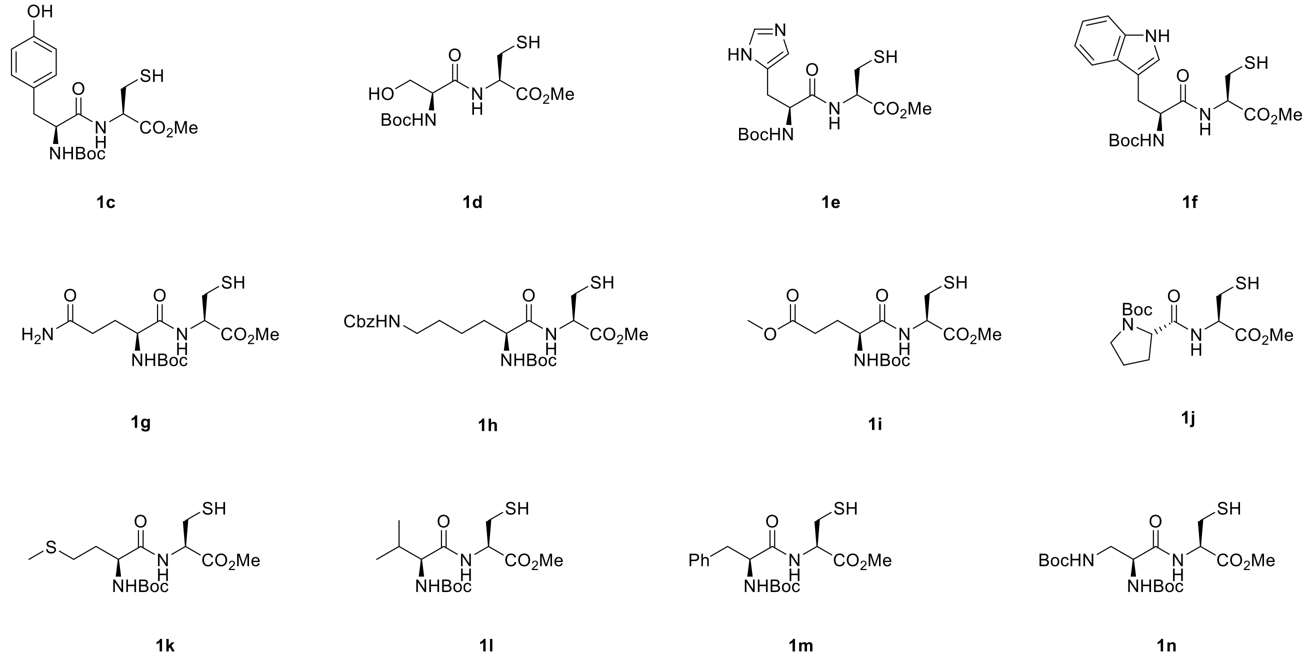


Figure S2 Calibration curve of **3o**

3. Preparation of Dipeptides 1



1c **1d** **1e** **1f**

1g **1h** **1i** **1j**

1k **1l** **1m** **1n**

Figure S3 Structures of Dipeptides **1**

Note: Dipeptides **1c-d**,[2] **1e**,[3] **and 1f-n**[2] are prepared according to the literature.

4. Preparation of 3,3-Difluoroallyl Sulfonium Salts (DFASs) 2

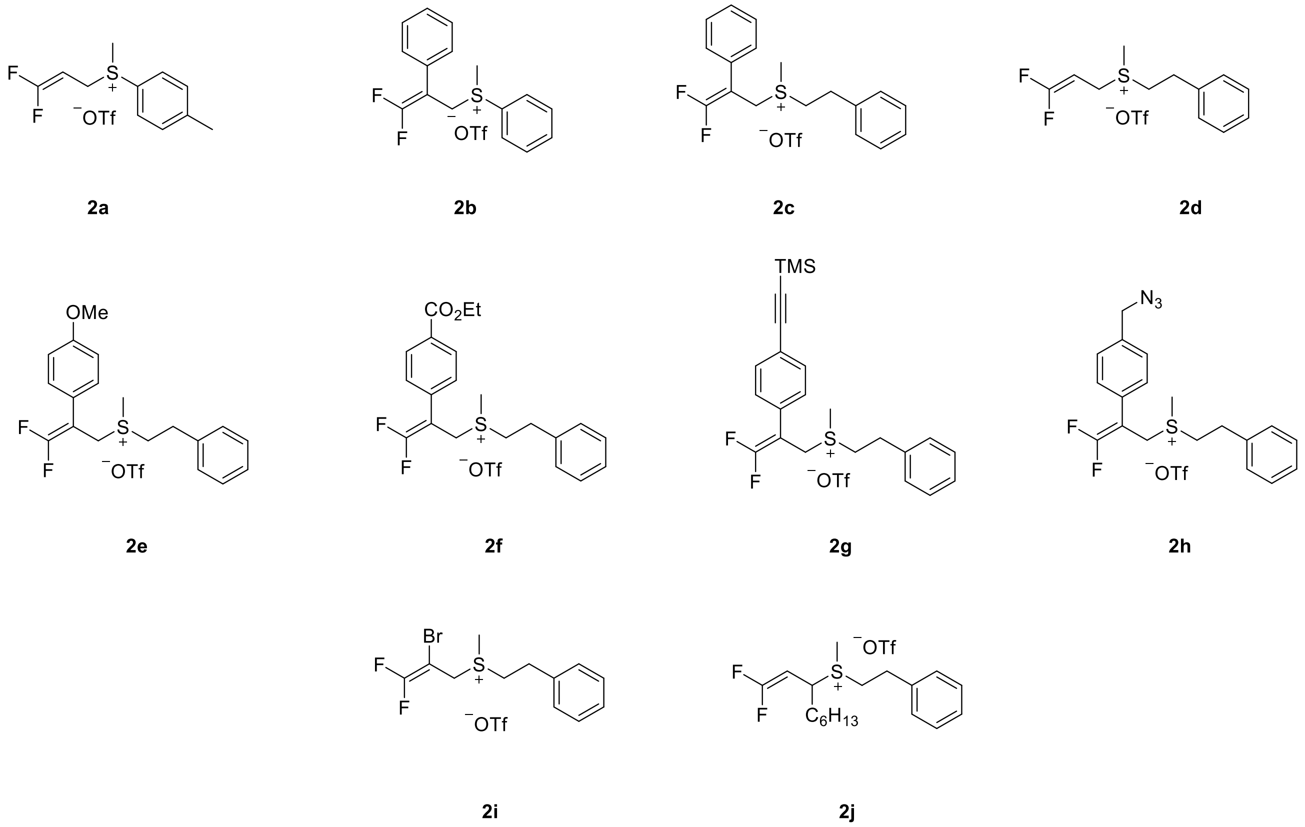
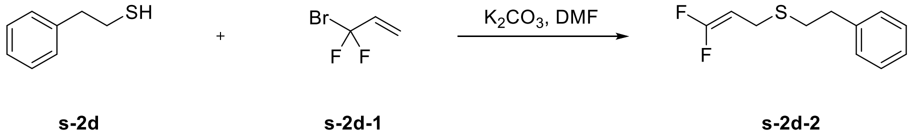


Figure S4 Structures of DFASs **2**

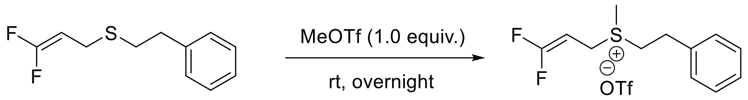
Note: DFASs **2a**,[1] **2b**,[5] **2c-f**,[4] **2i-j**[1] are prepared according to the literature.

4.1 Preparation of DFAS 2d.



Step 1: To a 250 mL round bottom bottle equipped with a magnetic stir bar were added K_2CO_3 (2.0 equiv), **s-2d-1** (20 mmol, 1.0 equiv), and DMF (50 mL). The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with ethyl acetate. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether) to afford the product **s-2d-2** (3.7g, 86% yield) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.23 (m, 2H), 7.21-7.13 (m, 3H), 4.28 (dtd, J = 24.2, 8.4, 1.6

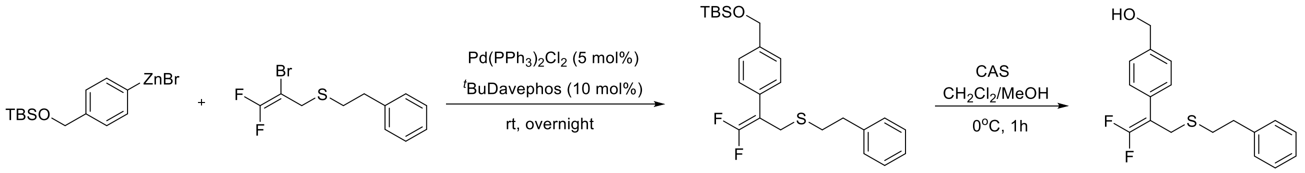
Hz, 1H), 3.12-3.06 (m, 2H), 2.88 – 2.80 (m, 2H), 2.75-2.68 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-d_6) δ -86.79 (d, *J* = 42.5 Hz), -89.82 (dd, *J* = 41.4, 24.1 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.3 (t, *J* = 290.3 Hz), 140.3, 128.5, 128.5, 126.4, 76.8 (dd, *J* = 23.6, 18.9 Hz), 36.0, 32.7, 24.6 (d, *J* = 5.8 Hz).



s-2d-2 **2d**

Step 2: To a 100 mL round bottom flask equipped with a magnetic stir bar were added **s-2d-2** (16 mmol, 1.0 equiv) and CH_2Cl_2 (10 mL). MeOTf (1.0 equiv) was then added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. Part of the solvent was removed. Ethyl ether was added to the mixture until a large amount of oil was precipitated. The oil was washed with ethyl ether three times to afford the final product **2d** as a brown oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.20 (m, 5H), 4.56 (dt, *J* = 23.2, 8.8 Hz, 1H), 3.95 (d, *J* = 8.8 Hz, 2H), 3.57 (d, *J* = 7.6 Hz, 2H), 2.73 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -75.46 (d, *J* = 15.8 Hz, 1F), -78.53 – -78.63 (m, 4F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.3 (t, *J* = 298.0 Hz), 135.9, 129.4, 128.7, 128.0, 120.5 (q, *J* = 320.9 Hz, 1F), 68.3 (dd, *J* = 31.5, 8.0 Hz), 42.7, 36.1 (d, *J* = 8.0 Hz), 36.6, 21.8. MS (ESI): m/z (%) 229 (M-OTf)$^+$. HRMS (ESI): Calcd. for $C_{12}H_{15}O_4F_2S$: 229.0857 (M-OTf)$^+$; Found: 229.0856 (M-OTf)$^+$. IR: 3026, 1740, 1604, 1499, 1457.

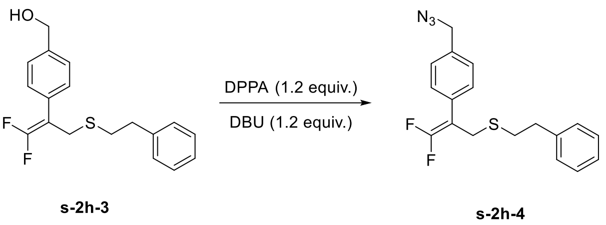
4.2 Preparation of DFAS 2h.



s-2h **s-2h-1** **s-2h-2** **s-2h-3**

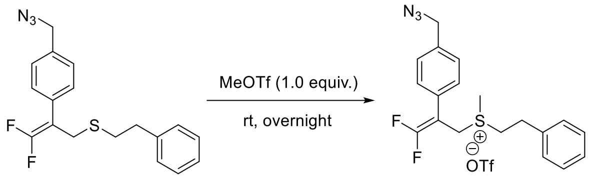
Step 1: To a 100 mL Schlenk tube equipped with a magnetic stir bar were added $Pd(PPh_3)_2Cl_2$ (5 mol%) and ^{t}BuDavephos (10 mol%). The tube was evacuated and backfilled with Ar (3 times). Aryl zinc reagent **s-2h** (1.5 equiv in THF), **s-2h-1** (11 mmol, 1.0 equiv), and CH_3CN (20 mL) were added. The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash column chromatography to afford product **s-2h-2** and used directly in the next step. ***Note:*** Aryl zinc reagent **s-2h** are prepared according to the literature.^{6}

Step 2: To a 100 mL round bottom bottle equipped with a magnetic stir bar were added the product **s-2h-2** (6 mmol, 1.0 equiv), solvent (CH_2Cl_2/MeOH = 1:1, 20 mL) and (*1S*) - (+)-Camphor-10-sulphonic acid (CAS, 0.5 equiv). The reaction was stirred under ice water bath condition for 1 hour. The reaction mixture was quenched with Et_3N, concentrated and purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1) to afford the product **s-2h-3** (1.7g, 48% yield, two step overall yield) as a yellow oil. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, 4H), 7.24 – 7.18 (m, 2H), 7.17 – 7.12 (m, 1H), 7.10 – 7.04 (m, 2H), 4.58 (s, 2H), 3.45 (s, 2H), 2.78 (m, 2H), 2.64 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -88.58 (d, *J* = 37.2 Hz, 1F), -88.81 (d, *J* = 37.2 Hz, 1F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.4 (dd, *J* = 294.8, 290.8 Hz), 140.3 (d, *J* = 17.3 Hz), 131.6 (t, *J* = 3.2 Hz), 128.5, 128.5, 128.4, 128.4, 127.0, 126.4, 90.2 (dd, *J* = 20.0, 14.6 Hz), 64.8, 35.9, 32.9, 29.8. MS (EI): m/z (%) 320 (M)$^+$, 142. HRMS (EI): Calcd. for $C_{18}H_{18}OF_2S$: 320.1041 (M)$^+$; Found: 320.1046 (M)$^+$. IR: 3346, 1726, 1605, 1583, 1513.



Step 3: To a 100 mL Schlenk tube equipped with a magnetic stir bar was evacuated and backfilled with Ar (3 times). **s-2h-3** (5 mmol, 1.0 equiv), DPPA (1.2 equiv) and DBU (1.2 equiv) were added. The resulting reaction mixture was stirred at room temperature for 0.5 hour. The reaction mixture was quenched with 1M HCl. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 50: 1) to afford the product **s-2h-4** (656 mg, 38% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 4H), 7.24-7.21 (m, 1H), 7.20-7.15 (m, 2H), 4.35 (s, 2H), 3.54 (t, *J* = 2.0 Hz, 2H), 2.89 – 2.85 (m, 2H), 2.76 – 2.72 (m, 2H). ^{19}F NMR

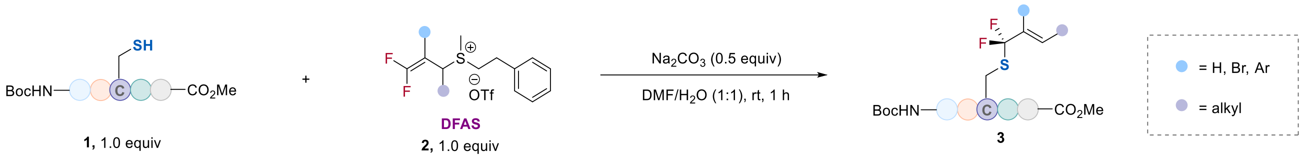
(376 MHz, $CDCl_3$) δ -88.1 (d, *J* = 35.7 Hz, 1F), -88.2 (d, *J* = 43.6 Hz, 1F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.5 (dd, *J* = 295.2, 291.7 Hz), 140.2, 135.0, 132.4 (t, *J* = 3.1 Hz), 128.7 (t, *J* = 2.7 Hz), 128.5, 128.4, 128.2, 90.1 (dd, *J* = 19.8, 14.9 Hz), 54.4, 36.0, 33.0, 30.0. MS (EI): m/z (%) 317 $(M-N_2)^+$, 180 (100). HRMS (EI): Calcd. for $C_{18}H_{17}NF_2S$: 317.1044 $(M)^+$; Found: 317.1048 $(M)^+$. IR: 2926, 2099, 1721, 1604, 1515.



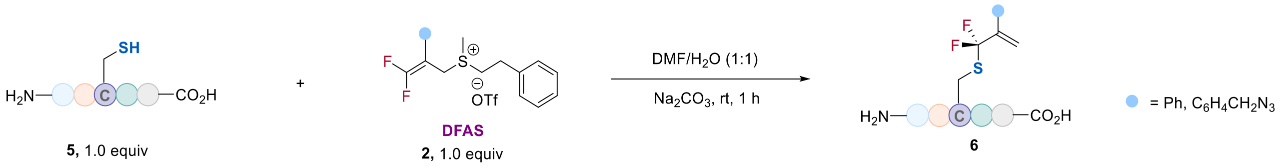
s-2h-4 **2h**

Step 4: To a 100 mL round bottom flask equipped with a magnetic stir bar were added s-2h-4 (1.9 mmol, 1.0 equiv) and CH_2Cl_2 (2 mL). MeOTf (1.0 equiv) was added dropwise at room temperature. The reaction mixture was stirred at room temperature overnight. Part of the solvent was removed. Ethyl ether was added to the mixture until a large amount of oil was precipitated. The oil was washed with ethyl ether three times to afford product **2h** (880 mg, 91% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 3H), 7.34-7.25 (m, 4H), 7.19-7.16 (m, 2H), 4.65 (d, *J* = 13.2 Hz, 1H), 4.44 (d, *J* = 14.4 Hz, 1H), 4.36 (s, 2H), 3.76 (t, *J* = 7.6 Hz, 2H), 3.15 – 3.05 (m, 2H), 2.74 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.5 (s, 3F), -78.9 (d, *J* = 16.1 Hz, 1F), -79.2 (d, *J* = 15.0 Hz, 1F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.1 (t, *J* = 300.2 Hz), 136.7, 135.7, 129.2, 128.9, 128.6, 128.6, 127.8, 120.4 (t, *J* = 321.0 Hz), 84.0 (dd, *J* = 21.0, 19.2 Hz), 54.0, 43.4, 41.0 (d, *J* = 4.1 Hz), 30.5, 22.4. MS (ESI): m/z (%) 360 $(M-OTf)^+$. HRMS (ESI): Calcd. for $C_{19}H_{20}N_3F_2S$: 360.1341 $(M-OTf)^+$; Found: 360.1431 $(M-OTf)^+$. IR: 3028, 2102, 1724, 1604, 1517.

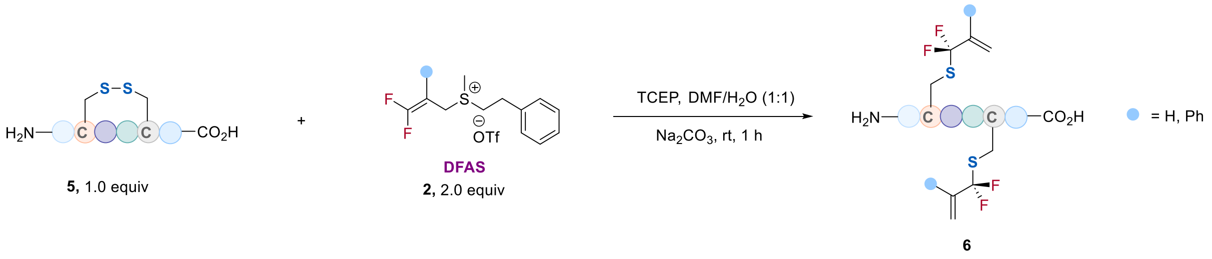
5. General Procedures for the *S-gem*-Difluoroallylation of Cysteine-Containing Peptides 1 and 5 with DFASs 2



Procedure 1: To a 25 mL of vial equipped with a stirring bar were added peptide **1** (0.2 mmol, 1.0 equiv), DFAS **2** (1.0 equiv), and Na_2CO_3 (0.5 equiv) under air. DMF (2 mL) and H_2O (2 mL) were added subsequently. After the reaction mixture stirred at room temperature for 1 h, fluorobenzene (2.0 equiv) was added. The yield was determined by ^{19}F NMR before working up. The reaction mixture was then diluted with ethyl acetate and H_2O. The resulting mixture was extracted with ethyl acetate, the combined organic layers were washed with brine, dried over Na_2SO_4, filtered through a pad of Celite®, and concentrated. The residue was purified with silica gel chromatography to provide the desired product **3**.



Procedure 2: To a 25 mL of vial equipped with a stirring bar were added oligopeptide **5** (0.02 mmol, 1.0 equiv), DFAS **2** (0.02 mmol, 1.0 equiv), and Na_2CO_3 (1.5 equiv) under air. DMF (1 mL) and H_2O (1 mL) were added subsequently. After the reaction stirred at room temperature for 1 h, the yield was determined by ^{19}F NMR before working up. The reaction was acidified with 1M HCl to pH 3-4. The reaction mixture was purified with Spherical C18, 20-45μm, 100Å directly to provide the desired product **6**.

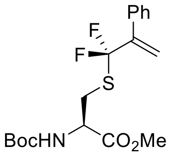


Procedure 3: To a 25 mL of vial equipped with a stirring bar were added cyclopeptide **5** (0.02 mmol, 1.0 equiv), TCEP·HCl (0.03 mmol, 1.5 equiv), and Na_2CO_3 (3.0 equiv) under air. DMF (1 mL) and H_2O (1 mL) were added subsequently. The reaction stirred at room temperature for 1 h, DFAS **2** (0.04

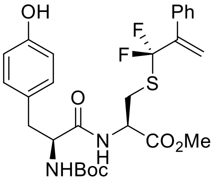
mmol, 2.0 equiv) was then added. After the reaction was stirred at room temperature for another 1 h, the yield was determined by ^{19}F NMR before working up. The reaction was acidified with 1M HCl to pH 3-4. The reaction mixture was purified with Spherical C18, 20-45μm, 100 Å directly to provide desired product **6**.

6. Characterization Data for Compounds 3, 4a, and 6.

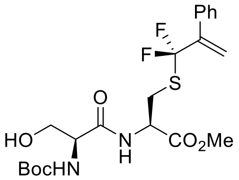
6.1 Characterization Data of Compounds 3



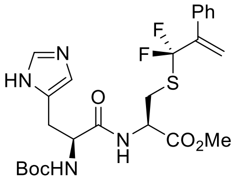
Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3b). Compound **3b** (71.5 mg, 92% yield) as a yellow oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 (s, 2H), 7.33 (s, 3H), 5.79 (s, 1H), 5.56 (s, 1H), 5.35 (s, 1H), 4.60 (s, 1H), 3.72 (s, 3H), 3.37 (dd, *J* = 37.2 Hz, 11.2 Hz, 2H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.68 (d, *J* = 206.8 Hz, 1F), -71.25 (d, *J* = 202.7 Hz, 1F). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 154.9, 143.8 (t, *J* = 22.7 Hz), 135.3, 128.5, 128.2, 128.1, 127.5 (t, *J* = 280.5 Hz), 119.6 (t, *J* = 6.9 Hz), 80.1, 53.0, 52.6, 31.3, 28.2. MS (ESI): m/z (%) 410 $(M+Na)^+$. HRMS (ESI): Calcd. for $C_{18}H_{23}O_4NF_2SNa$: 410.1208 $(M+Na)^+$; Found: 410.1208 $(M+Na)^+$. IR: 1748, 1717, 1586, 1497, 1414.



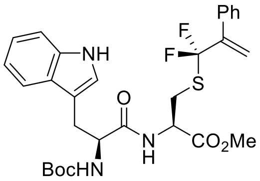
Methyl *N*-((*tert*-butoxycarbonyl)-*L*-tyrosyl)-*S*-(1,1-difluoro-2-phenylallyl)-L-cysteinate (3c). Compound **3c** (97.8 mg, 89% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1).^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44-7.42 (m, 2H), 7.37 – 7.30 (m, 3H), 7.12 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 7.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 2H), 5.79 (s, 1H), 5.57 (s, 1H), 5.17 – 5.03 (m, 1H), 4.80 (s, 1H), 4.38 – 4.26 (m, 1H), 3.70 (s, 3H), 3.36 (dd, *J* = 14.5, 5.5 Hz, 1H), 3.26 (dd, *J* = 14.0, 4.5 Hz, 1H), 3.00 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.90 (dd, *J* = 10.5, 6.0 Hz, 1H), 1.40 (s, 9H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -70.30 (d, *J* = 217.0 Hz), -71.13 (d, *J* = 217.0 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.5, 169.9, 155.5, 155.2, 143.6 (t, *J* = 22.8 Hz), 135.3, 130.3, 128.6, 128.2, 128.2, 127.5 (t, *J* = 280.1 Hz), 119.9 (t, *J* = 6.5 Hz), 115.6, 80.5, 55.8, 52.8, 52.0, 37.4, 30.7, 28.2. MS (ESI): m/z (%) 551 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{27}H_{32}O_6N_2F_2SNa$: 573.1841 $(M+Na)^+$; Found: 573.1837 $(M+Na)^+$. IR: 1748, 1666, 1615, 1596, 1417, 1440.



Methyl *N*-((*tert*-butoxycarbonyl)-*L*-seryl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3d). Compound **3d** (78.3 mg, 83% yield) as a white solid was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 2: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.40 (m, 2H), 7.39 – 7.30 (m, 3H), 5.81 (s, 1H), 5.58 (s, 1H), 5.52 (d, *J* = 6.4 Hz, 1H), 4.85 (q, *J* = 6.8 Hz, 1H), 4.22 (s, 1H), 4.03 (d, *J* = 9.2 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 1H), 3.44 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.29 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.07 (s, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.32 (d, *J* = 203.4 Hz), -71.34 (d, *J* = 203.8 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.2, 170.2, 155.9, 143.7 (t, *J* = 22.8 Hz), 135.2, 128.6, 128.2, 128.1, 127.5 (t, *J* = 280.7 Hz), 119.8 (t, *J* = 7.0 Hz),80.4, 62.7, 55.1, 52.8, 52.1, 30.5, 28.2. MS (ESI): m/z (%) 475 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{21}H_{28}O_6N_2F_2SNa$: 497.1528 (M+Na)$^+$; Found: 497.1528 (M+Na)$^+$. IR: 1762, 1692, 1666, 1522, 1498, 1448.

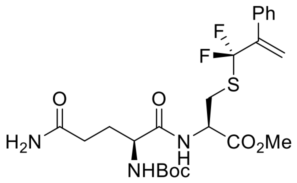


Methyl *N*-((*tert*-butoxycarbonyl)-*L*-histidyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3e). Compound **3e** (63 mg, 60% yield) as a yellow oil was purified with silica gel chromatography (Dichloromethane: Methanol = 10: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46-7.42 (m, 2H), 7.40 (s, 1H), 7.39 – 7.34 (m, 3H), 6.74 (s, 1H), 5.96 (s, 1H), 5.79 (s, 1H), 5.57 (s, 1H), 4.77 (dd, *J* = 12.4, 5.6 Hz, 1H), 4.42 (d, *J* = 5.2 Hz, 1H), 3.73 (s, 3H), 3.36 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.23 (dd, *J* = 14.0, 5.6 Hz, 1H), 3.13 (d, *J* = 14.4 Hz, 1H), 2.98 (dd, *J* = 14.8, 6.0 Hz, 1H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.46 (d, *J* = 206.4 Hz), -71.81 (dd, *J* = 203.4, 12.8 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.8, 170.1, 155.7, 143.5 (t, *J* = 22.4 Hz), 135.5, 135.1, 128.7, 128.3, 127.6 (t, *J* = 279.7 Hz), 119.8 (t, *J* = 6.8 Hz), 80.3, 54.1, 52.8, 52.1, 30.5, 28.8, 28.3. MS (ESI): m/z (%) 525 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{24}H_{31}O_5N_4F_2S$: 525.1978 (M+H)$^+$; Found: 525.1970 (M+H)$^+$. IR: 1685, 1661, 1599, 1516, 1436.

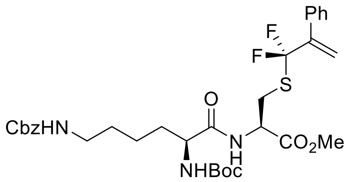


Methyl *N*-((*tert*-butoxycarbonyl)-*L*-tryptophyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3f). Compound **3f** (105.5 mg, 92% yield) as a yellow oil was purified with silica gel chromatography (Dichloromethane: Methonal = 100: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.45-7.38 (m, 2H), 7.37-7.33 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.00 (s, 1H), 5.75 (s, 1H), 5.55 (s, 1H), 5.14 (s, 1H), 4.75 (d, *J* = 4.2 Hz, 1H), 4.48 (d, *J* = 5.2 Hz, 1H), 3.66 (s, 3H), 3.36-3.25 (m, 2H), 3.25-3.14 (m, 2H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.45 (d, *J* = 203.8 Hz), -71.36 (d, *J* = 203.8 Hz). ^{13}C NMR (126

MHz, Chloroform-*d*) δ 171.6, 169.8, 155.4, 143.5 (t, *J* = 22.6 Hz), 136.1, 135.3, 128.6, 128.2, 128.2, 127.5 (t, *J* = 280.1 Hz), 123.2, 122.1, 119.8 (t, *J* = 6.8 Hz), 119.6, 118.5, 111.2, 110.0, 80.1, 55.2, 52.7, 51.9, 30.7, 28.2, 28.0. MS (ESI): m/z (%) 574 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{29}H_{33}O_5N_3F_2SNa$: 596.2001 $(M+Na)^+$; Found: 596.1995 $(M+Na)^+$. IR: 1747, 1670, 1497, 1457, 1437.

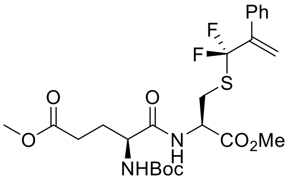


Methyl *N*-((*tert*-butoxycarbonyl)-*L*-glutaminyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3g). Compound **3g** (73.1 mg, 71% yield) as a yellow oil was purified with silica gel chromatography (Dichloromethane: Methanol = 10: 1). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.44-7.42 (m, 2H), 7.35-7.32 (m, 3H), 6.46 (s, 1H), 6.05 (s, 1H), 5.80 (s, 1H), 5.67 (d, *J* = 7.5 Hz, 1H), 5.57 (s, 1H), 4.82 (q, *J* = 6.0 Hz, 1H), 4.22 (m, 1H), 3.72 (s, 3H), 3.40 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.26 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.35-2.29 (m, 2H), 2.20-2.01 (m, 1H), 1.97-1.91 (m, 1H), 1.41 (s, 9H). ^{19}F NMR (471 MHz, Chloroform-*d*) δ -70.82 (d, *J* = 204.4 Hz), -71.38 (d, *J* = 204.4 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 175.5, 171.8, 170.6, 155.8, 143.6 (t, *J* = 22.9 Hz) 135.2, 128.6, 128.2, 128.1, 127.6 (t, *J* = 279.5 Hz), 119.8 (t, *J* = 6.8 Hz), 119.7, 80.0, 53.4, 52.7, 52.2, 31.7, 30.4, 29.0, 28.2. MS (ESI): m/z (%) 516 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{31}O_6N_3F_2SNa$: 538.1794 $(M+Na)^+$; Found: 538.1785 $(M+Na)^+$. IR: 1757, 1741, 1663, 1541, 1497, 1439.

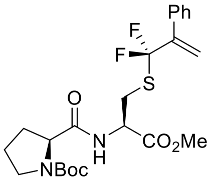


Methyl *N*-(*N6*-((benzyloxy)carbonyl)-*N2*-(*tert*-butoxycarbonyl)-*L*-lysyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3h). Compound **3h** (122.1 mg, 94% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45-7.41 (m, 2H), 7.38-7.22 (m, 8H), 7.01 (d, *J* = 6.4 Hz, 1H), 5.78 (s, 1H), 5.55 (s, 1H), 5.21 (d, *J* = 7.6 Hz, 1H), 5.06 (s, 3H), 4.82 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.18-4.04 (m, 1H), 3.68 (s, 3H), 3.39 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.28 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.19 – 3.12 (m, 2H), 1.89 – 1.72 (m, 1H), 1.66-1.55 (m, 1H), 1.54 – 1.27 (m, 13H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.23 (d, *J* = 204.2 Hz), -71.21 (d, *J* = 203.8 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.9, 170.1, 156.5, 155.5, 136.5, 135.2, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.5 (t, *J* = 280.3 Hz), 119.8 (t, *J* = 6.8

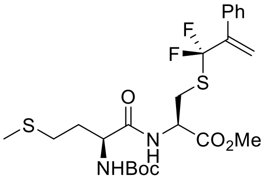
Hz), 80.0, 66.5, 54.1, 52.7, 51.8, 40.2, 31.7, 30.6, 29.3, 28.2, 22.2. MS (ESI): m/z (%) 650 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{32}H_{41}O_7N_3F_2SNa$: 672.2526 (M+Na)$^+$; Found: 672.2517 (M+Na)$^+$. IR: 1701, 1522, 1456, 1438, 1392.



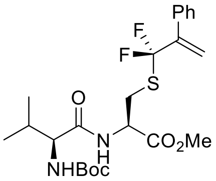
Methyl (*S*)-4-((*tert*-butoxycarbonyl)amino)-5-(((*R*)-3-((1,1-difluoro-2-phenylallyl)thio)-1-methoxy-1-oxopropan-2-yl)amino)-5-oxopentanoate (3i). Compound **3i** (93.9 mg, 89% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47-7.38 (m, 2H), 7.37-7.30 (m, 3H), 7.13 (s, 1H), 7.17-7.04 (m, 1H), 5.80 (s, 1H), 5.57 (s, 1H), 5.38-5.25 (m, 1H), 4.83 (dd, *J* = 11.6, 5.6 Hz, 1H), 4.25-4.15 (m, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.41 (dd, *J* = 14.4, 4.8 Hz, 1H), 3.29 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.52-2.34 (m, 2H), 2.25 – 2.06 (m, 1H), 1.96-1.84 (m, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.32 (d, *J* = 205.2 Hz), -71.29 (d, *J* = 203.8 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.7, 171.3, 170.0, 155.5, 143.7 (t, *J* = 22.7 Hz), 135.2, 128.5, 128.2, 128.1, 127.5 (t, *J* = 280.6 Hz), 119.8 (t, *J* = 7.0 Hz), 80.0, 53.6, 52.7, 51.9, 51.7, 30.7, 30.1, 28.2, 27.7. MS (ESI): m/z (%) 531 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{24}H_{32}O_7N_2F_2SNa$: 553.1790 (M+Na)$^+$; Found: 553.1808 (M+Na)$^+$. IR: 1740, 1521, 1438, 1392.



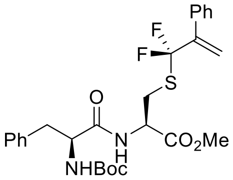
***Tert*-butyl (*R*)-2-(((*R*)-3-((1,1-difluoro-2-phenylallyl)thio)-1-methoxy-1-oxopropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3j).** Compound **3j** (89 mg, 92% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (600 MHz, DMSO-d6) δ 8.07 (d, J = 7.2 Hz, 1H), 7.47-7.42 (m, 2H), 7.40-7.35 (m, 3H), 5.80 (s, 1H), 5.70 (s, 1H), 4.57 (td, *J* = 7.8, 6.0 Hz, 1H), 4.13 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.65 (s, 3H), 3.40-3.34 (m, 1H), 3.34 – 3.27 (m, 2H), 3.19 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.16-2.01 (m, 1H), 1.91 – 1.68 (m, 3H), 1.36 (s, 9H). ^{19}F NMR (565 MHz, DMSO-*d*$_6$) δ -70.16. ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 173.0, 170.7, 154.1, 143.8 (t, *J* = 23.2 Hz), 135.4, 129.0, 128.7, 128.6 (t, *J* = 277.4 Hz), 128.4, 120.5 (t, *J* = 6.8 Hz), 79.2, 60.3, 52.6, 52.5, 47.0, 30.9, 30.5, 28.5, 23.6. MS (ESI): m/z (%) 485 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{30}O_5N_2F_2SNa$: 507.1736 $(M+Na)^+$; Found: 507.1727 $(M+Na)^+$. IR: 1748, 1698, 1519, 1479, 1437.



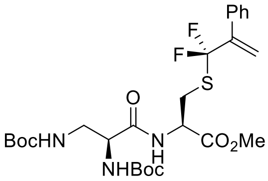
Methyl *N*-((*tert*-butoxycarbonyl)-*L*-methionyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3k). Compound **3k** (97 mg, 94% yield) as a yellow oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.40 (m, 2H), 7.42 – 7.30 (m, 3H), 7.04 (s, 1H), 5.82 (s, 1H), 5.59 (s, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.32 (s, 1H), 4.22 (s, 1H), 3.75 (s, 3H), 3.44 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.33 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 4H), 1.96-1.80 (m, 1H) 1.44 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.22 (d, *J* = 203.8 Hz), -71.18 (d, *J* = 203.4 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.3, 170.0, 155.3, 143.7 (t, *J* = 22.6 Hz), 135.2, 128.6, 128.2, 128.2, 127.5 (t, *J* = 280.8 Hz), 119.8 (t, *J* = 6.9 Hz), 80.2, 53.3, 52.8, 51.8, 31.4, 30.7, 30.0, 28.2, 15.1. MS (ESI): m/z (%) 519 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{32}O_5N_2F_2S_2Na$: 541.1613 $(M+Na)^+$; Found: 541.1608 $(M+Na)^+$. IR: 1748, 1667, 1518, 1438, 1392.



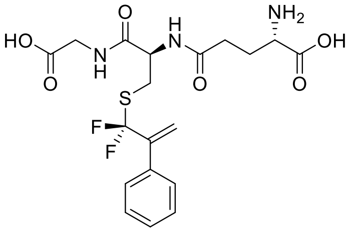
Methyl *N*-((*tert*-butoxycarbonyl)-*L*-valyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3l). Compound **3l** (84.2 mg, 87% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (s, 2H), 7.34 (s, 3H), 6.84 (d, *J* = 6.4 Hz, 1H), 5.80 (s, 1H), 5.57 (s, 1H), 5.08 (d, *J* = 8.0 Hz, 1H), 4.85 (q, *J* = 4.8 Hz, 1H), 4.00 (s, 1H), 3.72 (s, 3H), 3.36 (dd, *J* = 14.0, 4.4 Hz, 2H), 3.31 (dd, *J* = 14.1, 4.9 Hz, 1H), 2.24 – 2.06 (m, 1H), 1.42 (s, 9H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.33 (d, *J* = 203.8 Hz), -71.23 (d, *J* = 204.9 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.4, 170.1, 155.6, 143.7 (t, *J* = 22.7 Hz), 135.2, 128.5, 128.2, 128.1, 127.5 (t, *J* = 280.2 Hz), 119.7 (t, *J* = 7.1 Hz), 79.8, 59.7, 52.7, 51.7, 30.7, 28.2, 19.1, 17.4. MS (ESI): m/z (%) 487 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{23}H_{32}O_5N_2F_2SNa$: 509.1892 $(M+Na)^+$; Found: 509.1890 $(M+Na)^+$. IR: 1759, 1686, 1655, 1519, 1463, 1410.



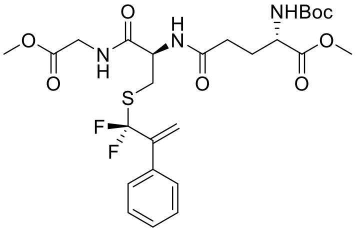
Methyl *N*-((*tert*-butoxycarbonyl)-*L*-phenylalanyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3m). Compound **3m** (92.2 mg, 86% yield) as a white solid (m.p. 114.4-115.4 °C) was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 3: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.38 (m, 2H), 7.36 – 7.28 (m, 3H), 7.27-7.08 (m, 5H), 6.81 (d, *J* = 7.2 Hz, 1H), 5.78 (s, 1H), 5.56 (s, 1H), 4.96 (s, 1H), 4.80 (d, *J* = 4.8 Hz, 1H), 4.40 (s, 1H), 3.70 (s, 3H), 3.38 (dd, *J* = 14.4, 5.2 Hz, 1H), 3.26 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.10 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.04-2.85 (m, 1H), 1.38 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.28 (d, *J* = 204.2 Hz), -71.26 (d, *J* = 203.8 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.1, 169.9, 155.2, 143.7 (t, *J* = 22.9 Hz), 136.3, 135.2, 129.2, 128.6, 128.6, 128.2, 128.1, 127.5 (t, *J* = 280.4 Hz), 126.8, 119.7 (t, *J* = 6.8 Hz), 80.2, 55.5, 52.7, 51.9, 38.1, 30.7, 28.1. MS (ESI): m/z (%) 535 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{27}H_{32}O_5N_2F_2SNa$: 557.1892 (M+Na)$^+$; Found: 557.1892 (M+Na)$^+$. IR: 1753, 1682, 1655, 1509, 1437.



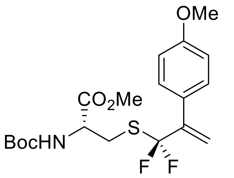
Methyl *N*-((*tert*-butoxycarbonyl)glycyl)-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinate (3n). Compound **3n** (81.3 mg, 91% yield) as a yellow oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.38 (m, 2H), 7.37 – 7.29 (m, 3H), 7.01 (d, *J* = 7.2 Hz, 1H), 5.80 (s, 1H), 5.57 (s, 1H), 5.24 (t, *J* = 4.8 Hz, 1H), 4.88 (dt, *J* = 7.6, 5.0 Hz, 1H), 3.81 (s, 2H), 3.73 (s, 3H), 3.41 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.31 (dd, *J* = 14.4, 5.2 Hz, 1H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.07 (d, *J* = 203.8 Hz), -71.22 (d, *J* = 203.8 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.1, 169.4, 155.9, 143.7 (t, *J* = 22.7 Hz), 135.2, 128.6, 128.2, 128.1, 127.5 (t, *J* = 280.2 Hz), 119.8 (t, *J* = 7.1 Hz), 52.7, 51.7, 44.1, 30.8, 28.2. MS (ESI): m/z (%) 467 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{20}H_{26}O_5N_2F_2SNa$: 467.1423 (M+Na)$^+$; Found: 467.1417 (M+Na)$^+$. IR: 1748, 1682, 1522, 1438, 1413, 1392.



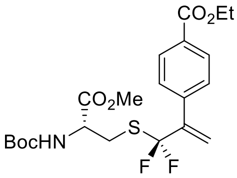
***N5*-((*R*)-1-((carboxymethyl)amino)-3-((1,1-difluoro-2-phenylallyl)thio)-1-oxopropan-2-yl)-*L*-glutamine (3o).** Compound **3o** (61.2 mg, 62% yield) as a yellow oil was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (t, *J* = 5.6 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 7.51-7.45 (m, 2H), 7.44-7.35 (m, 3H), 5.82 (s, 1H), 5.76 (s, 1H), 4.53 (td, *J* = 8.8, 4.8 Hz, 1H), 3.70 (d, *J* = 5.6 Hz, 2H), 3.36 (t, *J* = 6.4 Hz, 1H), 3.32 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.00 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.50 (t, *J* = 1.6 Hz, 3H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.04 – 1.76 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.37 (d, *J* = 206.0 Hz), -70.96 (d, *J* = 206.0 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 171.4, 171.1, 170.5, 143.3 (t, *J* = 22.9 Hz), 135.3, 129.1, 128.9, 128.7 (t, *J* = 277.7 Hz), 128.3, 120.7 (t, *J* = 7.1 Hz), 53.5, 53.0, 41.8, 31.8, 31.1, 27.1. MS (ESI): m/z (%) 460 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{19}H_{24}O_6N_3F_2S$: 460.1348 (M+H)$^+$; Found: 460.1336 (M+H)$^+$. IR: 1732, 1659, 1597, 1516, 1446.



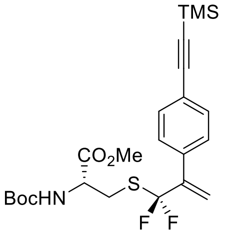
Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoro-2,5-diphenylpentyl)-*L*-cysteinate (3p). Compound **3p** (300 mg, 51% yield) as a colorless oil was purified with silica gel chromatography (Dichloromethane: Methanol = 20: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48-7.39 (m, 2H), 7.37-7.28 (m, 3H), 7.19 (t, *J* = 5.2 Hz, 1H), 6.82 (d, *J* = 7.2 Hz, 1H), 5.82 (s, 1H), 5.58 (s, 1H), 5.40 (d, *J* = 7.63 Hz, 1H), 4.87-4.68 (m, 1H), 4.39-4.27 (m, 1H), 4.05 (dd, *J* = 18.4, 6.0 Hz, 1H), 3.94 (dd, *J* = 18.0, 5.2 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.26 (d, *J* = 6.0 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.23-2.14 (m, 1H), 1.99 – 1.89 (m, 1H), 1.42 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -71.74 (d, *J* = 206.0 Hz), -71.33 (d, *J* = 206.4 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 172.3, 170.1, 169.9, 155.7, 143.7 (t, *J* = 22.8 Hz), 135.4, 128.6, 128.2, 127.9 (t, *J* = 279.8 Hz), 119.9 (t, *J* = 6.8 Hz), 80.2, 52.7, 52.4, 52.3, 41.2, 32.0, 30.1, 28.4, 28.2. MS (ESI): m/z (%) 588 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{26}H_{36}O_8N_3F_2S$: 588.2186 (M+H)$^+$; Found: 588.2189 (M+H)$^+$. IR (thin film) ν_{max} 1748, 1686, 1639, 1530, 1437.



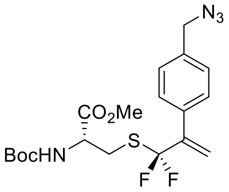
Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoro-2-(4-methoxyphenyl)allyl)-*L*-cysteinate (3q). Compound **3q** (61.1 mg, 73% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 10: 1).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.73 (s, 1H), 5.52 (s, 1H), 5.32 (d, *J* = 7.2 Hz, 1H), 4.62 (d, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.38 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.29 (dd, *J* = 14.0, 4.8 Hz, 1H), 1.44 (s, 9H).^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.69 (d, *J* = 204.2 Hz), -71.27 (d, *J* = 204.2 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 159.9, 154.9, 143.2 (t, *J* = 22.6 Hz), 129.4, 127.7 (t, *J* = 277.8 Hz), 118.2 (t, *J* = 6.9 Hz), 113.6, 80.2, 55.2, 53.0, 52.6, 31.4, 28.2. MS (ESI): m/z (%) 440 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{19}H_{25}O_5NF_2SNa$: 440.1314 (M+Na)$^+$; Found: 440.1309 (M+Na)$^+$. IR: 1748, 1717, 1609, 1574, 1514, 1457.



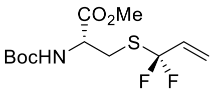
Ethyl (*R*)-4-(3-((2-((*tert*-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)thio)-3,3-difluoroprop-1-en-2-yl)benzoate (3r). Compound **3r** (89.4 mg, 97% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 5.88 (s, 1H), 5.65 (s, 1H), 5.34 (d, *J* = 7.2 Hz, 1H), 4.61 (dd, *J* = 13.2, 7.6 Hz, 1H), 4.36 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.39 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.28 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.42 (s, 9H), 1.38 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.71 (d, *J* = 204.9 Hz), -71.31 (d, *J* = 204.9 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 166.1, 154.9, 143.3 (t, *J* = 23.1 Hz), 139.6, 130.6, 129.5, 128.2, 127.3 (t, *J* = 280.5 Hz), 120.9 (t, *J* = 6.6 Hz), 80.3, 61.1, 53.0, 52.7, 31.4, 28.2, 14.3. MS (ESI): m/z (%) 460 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{21}H_{27}O_6NF_2SNa$: 482.1419 (M+Na)$^+$; Found: 482.1420 (M+Na)$^+$. IR: 1748, 1717, 1510, 1438, 1393.



Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoro-2-(4-((trimethylsilyl)ethynyl)phenyl)allyl)-*L*-cysteinate (3s). Compound **3s** (83.1 mg, 86% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 10: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 5.81 (s, 1H), 5.59 (s, 1H), 5.32 (d, *J* = 7.6 Hz, 1H), 4.60 (d, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.38 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.28 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.43 (s, 9H), 0.24 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -70.57 (d, *J* = 205.3 Hz), -71.17 (d, *J* = 204.9 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.6, 154.9, 143.3 (t, *J* = 22.8 Hz), 135.2, 131.7, 127.9, 127.3 (t, *J* = 280.4 Hz), 123.4, 119.9 (t, *J* = 6.8 Hz), 104.4, 95.5, 80.2, 53.0, 52.6, 31.4, 28.2, -0.1. MS (ESI): m/z (%) 506 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{23}H_{31}O_4NF_2SSiNa$: 506.1603(M+Na)$^+$; Found: 506.1589 (M+Na)$^+$. IR: 2158, 1749, 1718, 1506, 1456.

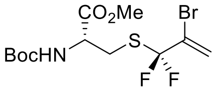


Methyl *S*-(2-(4-(azidomethyl)phenyl)-1,1-difluoroallyl)-*N*-(*tert*-butoxycarbonyl)-*L*-cysteinate (3t). Compound **3t** (78.4 mg, 88% yield) as a yellow oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.83 (s, 1H), 5.60 (s, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 4.72 – 4.52 (m, 1H), 4.35 (s, 2H), 3.74 (s, 3H), 3.40 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.30 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.43 (s, 9H).^{19}F NMR (376 MHz, Chloroform-*d*$_6$) δ -70.79 (d, *J* = 204.5 Hz), -71.38 (d, *J* = 204.5 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 154.9, 143.3 (t, *J* = 23.02 Hz), 135.9, 135.3, 128.6, 128.0, 127.4 (t, *J* = 280.0 Hz), 120.0 (t, *J* = 6.8 Hz), 80.2, 54.3, 53.0, 52.6, 31.4, 28.2. MS (ESI): m/z (%) 465 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{19}H_{24}O_4N_4F_2SNa$: 465.1378 (M+Na)$^+$; Found: 465.1379 (M+Na)$^+$. IR: 2100, 1747, 1713, 1512, 1438.

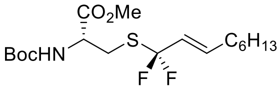


Methyl *N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoroallyl)-*L*-cysteinate (3a). Compound **3a** (58.3 mg, 94% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1).^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.08-5.90 (m, 1H), 5.71 (d, *J* = 17.2 Hz, 1H), 5.49 (d, *J* = 10.8 Hz, 1H), 5.35 (d, *J* = 6.0 Hz, 1H), 4.58 (d, *J*

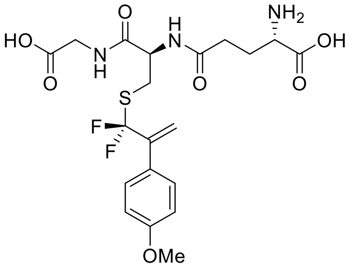
= 4.4 Hz, 1H), 3.75 (s, 3H), 3.32 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.23 (dd, *J* = 14.0, 4.8 Hz, 1H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*$_6$) δ -72.85 (dd, *J* = 204.5, 8.6 Hz, 1F), -73.47 (dd, *J* = 204.2, 8.6 Hz, 1F), -73.73 (d, *J* = 8.9 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.7, 154.9, 131.7 (t, *J* = 26.6 Hz), 126.1 (t, *J* = 275.9 Hz), 121.4 (t, *J* = 7.5 Hz), 80.2, 53.0, 52.6, 31.1, 28.2. MS (ESI): m/z (%) 334 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{12}H_{19}O_4NF_2SNa$: 334.0895 (M+Na)$^+$; Found: 334.0883 (M+Na)$^+$. IR: 1748, 1717, 1507, 1438, 1416.



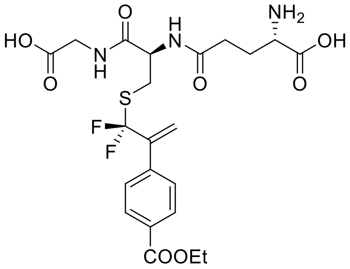
Methyl *S*-(2-bromo-1,1-difluoroallyl)-*N*-(*tert*-butoxycarbonyl)-*L*-cysteinate (3u). Compound **3u** (64.1 mg, 82% yield) as a colorless oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.34 (d, *J* = 2.4 Hz, 1H), 5.90 (d, *J* = 2.8 Hz, 1H), 5.35 (d, *J* = 6.8 Hz, 1H), 4.60 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.35 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.26 (dd, *J* = 14.0, 4.8 Hz, 1H), 1.43 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -72.20 (d, *J* = 207.2 Hz), -72.78 (d, *J* = 207.2 Hz).^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.5, 154.9, 125.4 (t, *J* = 280.4 Hz), 123.7 (t, *J* = 30.9 Hz), 123.1 (t, *J* = 5.4 Hz), 80.3, 53.0, 52.7, 31.6, 28.2. MS (ESI): m/z (%) 414 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{23}H_{30}O_5N_2F_2SNa$: 412.0000 (M+Na)$^+$; Found: 412.0002 (M+Na)$^+$. IR: 1748, 1717, 1625, 1507, 1456.



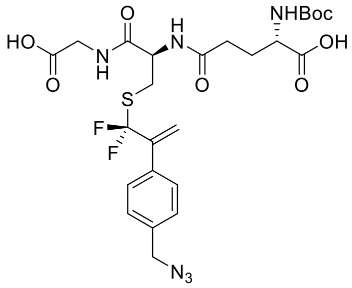
Methyl (*E*)-*N*-(*tert*-butoxycarbonyl)-*S*-(1,1-difluoronon-2-en-1-yl)-*L*-cysteinate (3v). Compound **3v** (53 mg, 67% yield) as a yellow oil was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1), *E*/*Z* =14.2:1 determined by ^{19}F NMR. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.28 – 6.11 (m, 1H), 5.74-5.52 (m, 1H), 5.34 (d, *J* = 6.8 Hz, 1H), 4.59 (s, 1H), 3.75 (s, 3H), 3.32 (dd, *J* = 13.6, 3.6 Hz, 1H), 3.23 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.09 (d, *J* = 5.2 Hz, 2H), 1.58-1.34 (m, 11H), 1.26 (s, 6H), 0.98-0.79 (m, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -69.52 (dd, *J* = 201.9, 8.3 Hz), -70.15 (dd, *J* = 200.8, 7.5 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 170.8, 155.0, 139.1 (t, *J* = 6.9 Hz), 126.4 (t, *J* = 274.9 Hz), 123.9 (t, *J* = 25.6 Hz), 53.0, 52.6, 31.6, 31.5, 31.2, 28.7, 28.2, 28.1, 22.5, 14.0. MS (ESI): m/z (%) 418 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{18}H_{31}O_4NF_2SNa$: 418.1834 (M+Na)$^+$; Found: 418.1834 (M+Na)$^+$. IR: 1749, 1717, 1670, 1506, 1457.



***N5*-((*R*)-1-((carboxymethyl)amino)-3-((1,1-difluoro-2-(4-methoxyphenyl)allyl)thio)-1-oxopropan-2-yl)-*L*-glutamine (3w).** Compound **3w** (53 mg, 54% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81-8.68 (m, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 5.71 (s, 1H), 5.68 (s, 1H), 4.63 – 4.37 (m, 1H), 3.77 (s, 3H), 3.69 (d, *J* = 5.6 Hz, 2H), 3.39 – 3.24 (m, 2H), 2.99 (dd, *J* = 14.4, 11.2 Hz, 1H), 2.39-2.26 (m, 2H), 2.01-1.76 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.39 (d, *J* = 206.4 Hz), -70.97 (d, *J* = 206.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.9, 171.0, 170.5, 170.2, 159.6, 142.3 (t, *J* = 23.2 Hz), 129.3, 128.5 (t, *J* = 276.9 Hz), 127.0, 118.6 (t, *J* = 4.9 Hz), 113.9, 55.3, 53.1, 52.7, 41.3, 31.5, 30.6, 26.8. MS (ESI): m/z (%) 490 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{20}H_{26}O_7N_3F_2S$: 490.1454 (M+H)$^+$; Found: 490.1438 (M+H)$^+$. IR: 3358, 1732, 1655, 1610, 1516, 1448.



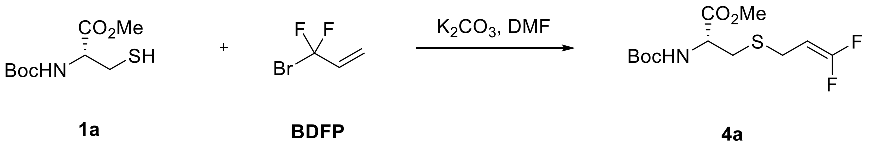
***N5*-((*R*)-1-((carboxymethyl)amino)-3-((2-(4-(ethoxycarbonyl)phenyl)-1,1-difluoroallyl)thio)-1-oxopropan-2-yl)-*L*-glutamine (3x).** Compound **3x** (39.3 mg, 74% yield) as a yellow solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (t, *J* = 6.0 Hz, 1H), 8.59 (d, *J* = 9.0 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 5.97 (s, 1H), 5.95 (s, 1H), 4.60-4.52 (m, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 3.73 (d, *J* = 6.0 Hz, 2H), 3.40-3.30 (m, 1H), 3.04 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.40-2.29 (m, 2H), 2.06 – 1.94 (m, 1H), 1.91-1.78 (m, 1H), 1.36 (t, *J* = 7.0 Hz, 3H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.39 (d, *J* = 209.4 Hz), -70.68 (d, *J* = 207.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.3, 171.3, 170.6, 170.5, 165.8, 142.4 (t, *J* = 23.7 Hz), 139.7, 130.4, 129.7, 128.7, 128.5 (t, *J* = 277.6 Hz), 122.5 (t, *J* = 5.4 Hz), 61.4, 53.4, 53.0, 41.6, 31.8, 31.0, 27.1, 14.6. HRMS (ESI): Calcd. for $C_{22}H_{28}O_8N_3F_2S$: 532.1560 (M+H)$^+$; Found: 532.1557 (M+H)$^+$. IR: 3371, 1719, 1641, 1463, 1378.



***N5*-((*R*)-3-((2-(4-(azidomethyl)phenyl)-1,1-difluoroallyl)thio)-1-((carboxymethyl)amino)-1-oxopropan-2-yl)-*N2*-(*tert*-butoxycarbonyl)-L-glutamine (3y).** Compound **3y** (34.3 mg, 52% yield) as a yellow solid was purified with Spherical C18, 20-45μm, 100Å.^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.42 (t, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 5.87 (s, 1H), 5.84 (s, 1H), 4.60 (dd, *J* = 13.6, 8.0 Hz, 1H), 4.52 (s, 2H), 3.93 (dd, *J* = 13.2, 8.4 Hz, 1H), 3.78 (t, *J* = 6.0 Hz, 2H), 3.29 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.03 (dd, *J* = 13.2, 9.2 Hz, 1H), 2.25 (t, *J* = 7.6 Hz, 2H), 2.08 – 1.90 (m, 1H), 1.86-1.71 (m, 1H), 1.41 (s, 9H). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -70.38 (d, *J* = 206.4 Hz), -70.95 (d, *J* = 207.2 Hz). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 174.4, 172.2, 171.3, 170.4, 156.0, 142.8 (t, *J* = 23.2 Hz), 136.7, 135.0, 128.8, 128.7, 128.6 (t, *J* = 278.2 Hz), 121.0 (t, *J* = 6.6 Hz), 78.5, 53.6, 53.5, 52.4, 41.3, 32.2, 31.2, 28.7, 27.2. MS (ESI): m/z (%) 637 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{25}H_{32}O_8N_6F_2SNa$: 637.1863 (M+H)$^+$; Found: 637.1848 (M+H)$^+$.

6.2 Characterization Data of Compound 4a

Note: The mixture of compounds **3a** and **4a** is difficult to separate due to their same polarity. The pure compound **4a** was prepared from the reaction of **1a** with BDFP.

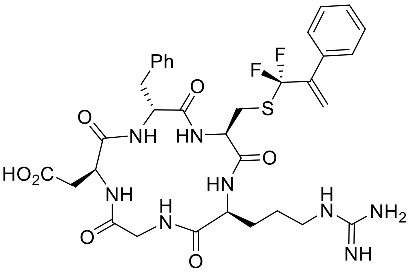


To a 100 mL round bottom bottle equipped with a magnetic stir bar were added K_2CO_3 (2.0 equiv), **1a** (2 mmol, 1.0 equiv), and DMF (10 mL). The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted with ethyl acetate. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 5: 1) to afford product **4a** (560 mg, 90% yield) as a yellow oil.

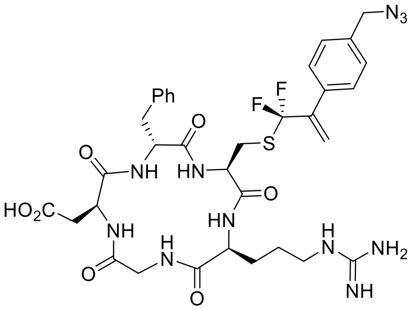
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.39 (d, *J* = 7.2 Hz, 1H), 4.49-4.38 (m, 1H), 4.23 (dt, *J* = 24.0, 8.0 Hz, 1H), 3.65 (s, 3H), 3.13-2.95 (m, 2H), 2.88 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.78 (dd, *J* = 13.6, 5.6

Hz, 1H), 1.33 (s, 9H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -86.32 (d, *J* = 39.5 Hz), -89.17 (dd, *J* = 39.5, 23.7 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 171.2, 157.1 (d, *J* = 290.6 Hz), 154.9, 79.8, 76.2 (dd, *J* = 24.4, 19.0 Hz), 52.9, 52.2, 33.5, 27.9, 24.7 (d, *J* = 5.8 Hz). MS (ESI): m/z (%) 334 (M+Na)$^+$. HRMS (ESI): Calcd. for $C_{12}H_{19}O_4NF_2SNa$: 334.0895 (M+Na)$^+$; Found: 334.0895 (M+Na)$^+$. IR: 3367, 1744, 1506, 1438, 1392.

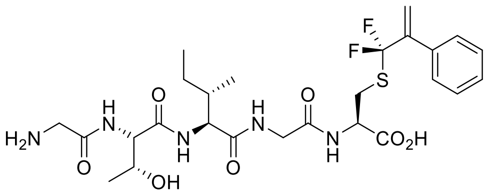
6.3 Characterization Data of Oligopeptides 6



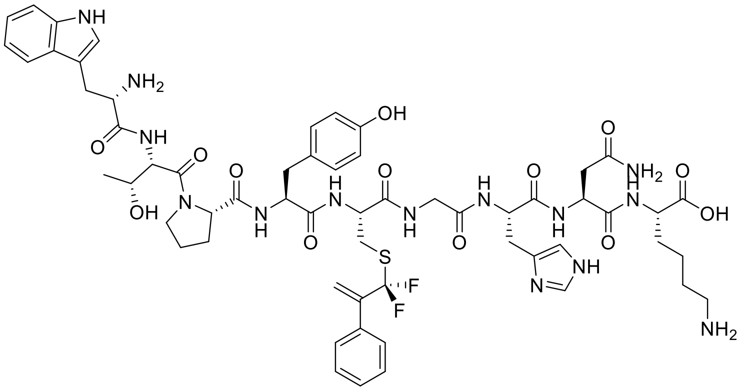
2-((*2S,5R,8R,11S*)-5-benzyl-8-(((1,1-difluoro-2-phenylallyl)thio)methyl)-11-(3-guanidinopropyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (6a). Compound **6a** (13.6 mg, 47% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (d, *J* = 8.5 Hz, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 8.23 (d, *J* = 7.0 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 5.5, 2.5 Hz, 2H), 7.46 – 7.38 (m, 3H), 7.33 – 7.11 (m, 8H), 5.85 (s, 1H), 5.82 (s, 1H), 4.74 – 4.58 (m, 2H), 4.53 (q, *J* = 7.0 Hz, 1H), 4.30 – 4.21 (m, 1H), 4.17 (q, *J* = 9.0 Hz, 1H), 3.29 (dd, *J* = 13.5, 6.0 Hz, 1H), 3.23 – 3.17 (m, 1H), 3.16 – 3.03 (m, 3H), 2.76-2.62 (m, 2H), 2.11 (dd, *J* = 16.0, 4.0 Hz, 1H), 1.88 – 1.72 (m, 1H), 1.70 – 1.57 (m, 2H), 1.55-1.46 (m, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.75 (d, *J* = 204.9 Hz), -70.75 (d, *J* = 203.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.8, 171.7, 171.0, 170.9, 170.2, 168.1, 157.4, 143.0 (t, *J* = 22.6 Hz), 138.9, 135.1, 129.4, 129.2, 128.9, 128.6 (t, *J* = 277.8 Hz), 128.5, 128.3, 126.5, 121.0 (t, *J* = 5.3 Hz), 55.7, 53.4, 51.5, 49.2, 43.4, 41.1, 36.8, 31.3, 27.8, 25.1, 14.0. MS (ESI): m/z (%) 731 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{33}H_{41}O_7N_8F_2S$: 731.2781 (M+H)$^+$; Found: 731.2776 (M+H)$^+$.



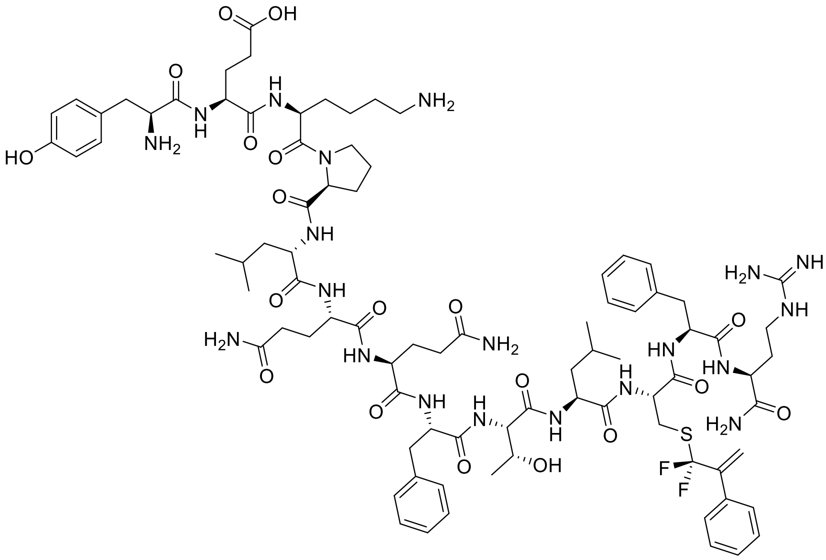
2-((*2S,5R,8R,11S*)-8-(((2-(4-(azidomethyl)phenyl)-1,1-difluoroallyl)thio)methyl)-5-benzyl-11-(3-guanidinopropyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (6b). Compound **6b** (20 mg, 51% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, *J* = 7.5 Hz, 1H), 8.53 (d, *J* = 9.0 Hz, 1H), 8.36 (d, *J* = 7.0 Hz, 1H), 8.16 (d, *J* = 9.5 Hz, 1H), 8.13 – 8.05 (m, 1H), 7.81 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.10 (m, 7H), 5.84 (s, 1H), 5.83 (s, 1H), 4.71 – 4.55 (m, 2H), 4.49 (s, 3H), 4.30 – 4.21 (m, 1H), 4.14 (dd, *J* = 16.5, 9.0 Hz, 1H), 3.26 (dd, *J* = 14.0, 6.0 Hz, 1H), 3.17 – 2.97 (m, 4H), 2.73-2.57 (m, 3H), 2.12 (d, *J* = 16.0 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.67-1.56 (m, 1H), 1.54 – 1.41 (m, 2H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -65.21 (d, *J* = 212.4 Hz), -66.09 (d, *J* = 193.6 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.9, 171.7, 171.0, 170.9, 170.2, 168.2, 157.3, 142.5 (t, *J* = 24.1 Hz), 138.8, 136.7, 134.8, 129.4, 128.8, 128.7, 128.5 (t, *J* = 277.3 Hz), 128.5, 126.5, 121.2 (t, *J* = 5.7 Hz), 55.6, 53.7, 53.6, 53.5, 51.6, 49.2, 43.4, 41.1, 36.9, 31.3, 27.8, 25.1. MS (ESI): m/z (%) 786 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{34}H_{42}O_7N_{11}F_2S$: 786.2952 (M+H)$^+$; Found: 786.2943 (M+H)$^+$.



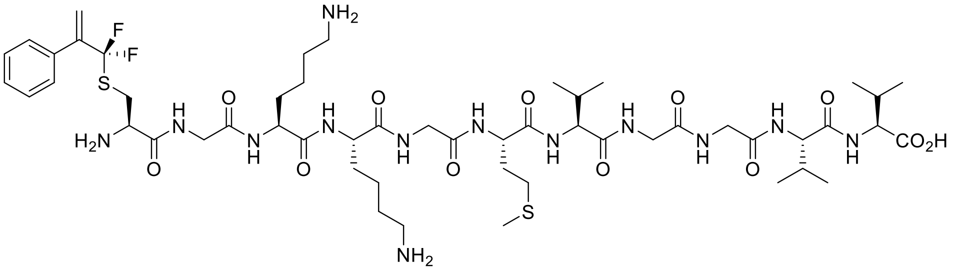
***S*-(1,1-difluoro-2-phenylallyl)-*N*-glycyl-*L*-threonyl-*L*-isoleucylglycyl-*L*-cysteine (6c)**. Compound **6c** (5.9 mg, 25% yield, ^{19}F NMR yield: 72%) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.48-7.42 (m, 2H), 7.40 – 7.26 (m, 3H), 5.80 (s, 1H), 5.63 (s, 1H), 4.68 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.41 (d, *J* = 4.4 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 1H), 4.17 – 4.10 (m, 1H), 3.98 (d, *J* = 16.8 Hz, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.77 (dd, *J* = 20.4, 16.4 Hz, 2H), 3.42 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.17 (dd, *J* = 14.0, 7.6 Hz, 1H), 1.91 – 1.79 (m, 1H), 1.64 – 1.50 (m, 1H), 1.22-1.12 (m, 4H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, Methanol-*d*4) δ -72.71. ^{13}C NMR (151 MHz, Methanol-*d*4) δ 172.6, 171.5, 171.1, 169.8, 166.3, 144.3 (t, *J* = 23.7 Hz), 135.4, 128.3, 128.0 (t, *J* = 277.4 Hz), 127.9, 118.9 (t, *J* = 6.6 Hz), 67.0, 58.8, 58.3, 52.6, 41.7, 40.2, 36.5, 30.0, 24.6, 18.7, 14.5, 10.1. MS (ESI): m/z (%) 602 (M+H) $^+$. HRMS (ESI): Calcd. for $C_{26}H_{38}O_7N_5F_2S$: 602.2455 (M+H)$^+$; Found: 602.2449 (M+H)$^+$.



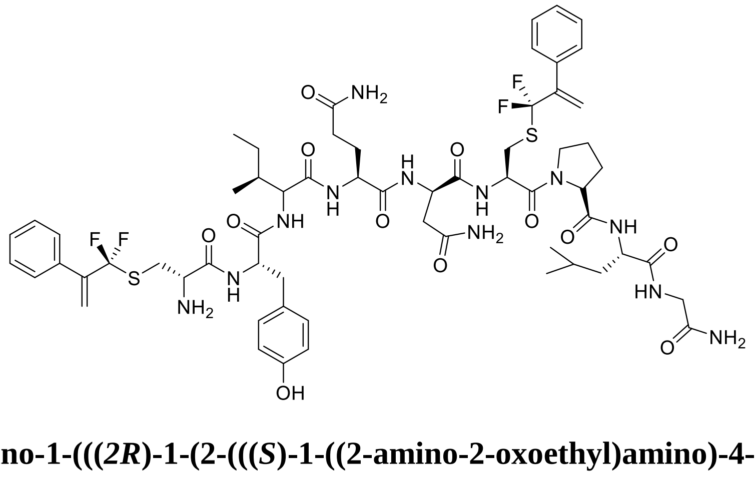
***N*-*L*-Tryptophyl-*L*-threonyl-*L*-prolyl-*L*-tyrosyl-*S*-(1,1-difluoro-2-phenylallyl)-*L*-cysteinylglycyl-*L*-histidyl-*L*-asparaginyl-*L*-lysine (6d).** Compound **6d** (9.9 mg, 39% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, Methanol-*d*4) δ 8.71 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.39 (m, 2H), 7.36-7.27 (m, 5H), 7.16 (s, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.77 (s, 1H), 5.60 (s, 1H), 4.68 (dd, *J* = 13.2, 6.0 Hz, 2H), 4.60 (d, *J* = 4.8 Hz, 1H), 4.41 – 4.32 (m, 3H), 4.26 – 4.21 (m, 1H), 4.19 (d, *J* = 7.2 Hz, 1H), 4.16-4.08 (m, 1H), 3.86 (d, *J* = 16.4 Hz, 1H), 3.72 (d, *J* = 16.4 Hz, 1H), 3.66-3.56 (m, 1H), 3.55-3.46 (m, 1H), 3.43 – 3.36 (m, 1H), 3.25 – 2.98 (m, 6H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.85 – 2.77 (m, 1H), 2.73 (d, *J* = 6.0 Hz, 2H), 2.15-2.03 (m, 1H), 1.95 – 1.67 (m, 5H), 1.66-1.55 (m, 2H), 1.49-1.38 (m, 2H), 1.19 (d, *J* = 6.4 Hz, 3H). ^{19}F NMR (376 MHz, Methanol-*d*4) δ -72.53. ^{13}C NMR (151 MHz, Methanol-*d*4) δ 173.6, 173.0, 172.5, 171.7, 171.2, 170.6, 170.4, 169.2, 168.7, 156.1, 144.2 (t, *J* = 23.2 Hz), 136.8, 135.4, 133.5, 129.9, 129.5, 128.3, 128.2 (t, *J* = 277.5 Hz), 128.0, 127.9, 127.5, 127.2, 124.3, 121.3, 119.1 (t, *J* = 6.3 Hz), 118.7, 117.7, 117.4, 115.0, 111.3, 106.5, 67.2, 60.6, 56.1, 55.7, 54.3, 53.7, 52.4, 52.0, 50.5, 48.5, 42.6, 39.1, 36.0, 35.7, 30.5, 29.3, 29.0, 27.2, 26.5, 26.2, 24.3, 22.2, 18.4. MS (ESI): m/z (%) 1255 (M-H)$^-$. HRMS (ESI): Calcd. for $C_{59}H_{73}O_{13}N_{14}F_2S$: 1255.5176 (M-H)$^-$; Found: 1255.5197 (M-H)$^-$.



(*S*)-5-(((*S*)-6-amino-1-((*S*)-2-(((*5S,8S,11R,14S,17S,20S,23S,26S,29S*)-1-amino-23,26-bis(3-amino-3-oxopropyl)-8,20-dibenzyl-5-carbamoyl-11-(((1,1-difluoro-2-phenylallyl)thio)methyl)-17-((*R*)-1-hydroxyethyl)-1-imino-14-isobutyl-31-methyl-7,10,13,16,19,22,25,28-octaoxo-2,6,9,12,15,18,21,24,27-nonaazadotriacontan-29-yl)carbamoyl)pyrrolidin-1-yl)-1-oxohexan-2-yl)amino)-4-((*S*)-2-amino-3-(4-hydroxyphenyl)propanamido)-5-oxopentanoic acid (6e). Compound **6e** (20.6 mg, 57% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.44-7.37 (m, 2H), 7.35 – 7.27 (m, 3H), 7.23 – 7.11 (m, 10H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.75 (s, 1H), 5.59 (s, 1H), 4.60 – 4.44 (m, 4H), 4.44-4.37 (m, 3H), 4.36-4.26 (m, 3H), 4.25-4.20 (m, 3H), 4.17 – 4.11 (m, 2H), 4.10 – 3.98 (m, 3H), 3.88-3.78 (m, 1H), 3.74-3.63 (m, 1H), 3.22 – 3.08 (m, 5H), 2.98-2.86 (m, 5H), 2.69 (d, *J* = 6.8 Hz, 2H), 2.40 (t, *J* = 8.8 Hz, 2H), 2.33-2.20 (m, 2H), 2.14-2.04 (m, 2H), 1.96 – 1.82 (m, 4H), 1.81 – 1.57 (m, 12H), 1.55-1.43 (m, 2H), 1.29-1.17 (m, 4H), 0.94 (d, *J* = 5.6 Hz, 6H), 0.88 (t, *J* = 5.6 Hz, 6H). ^{19}F NMR (376 MHz, Methanol-d_4) δ -72.24 (d, *J* = 207.9 Hz, 1F), -73.25 (d, *J* = 207.6 Hz, 1F). ^{13}C NMR (151 MHz, Methanol-d_4) δ 176.3, 175.0, 174.9, 174.9, 174.6, 174.1, 173.8, 173.2, 173.2, 173.1, 172.7, 172.1, 171.8, 171.4, 171.1, 168.6, 157.2, 156.9, 144.1 (t, *J* = 22.3 Hz), 137.2, 136.7, 135.4, 130.3, 129.0, 128.8, 128.4, 128.3, 128.2, 128.1 (t, *J* = 276.0 Hz), 128.0, 127.9, 126.6, 126.4, 124.5, 119.1, 115.5, 66.4, 62.3, 61.3, 57.0, 55.6, 55.2, 54.5, 54.4, 53.9, 53.6, 52.8, 52.6, 51.8, 48.5, 40.5, 39.4, 39.3, 39.1, 36.5, 36.4, 36.3, 35.4, 31.2, 29.9, 29.6, 29.6, 29.1, 28.4, 27.2, 26.7, 24.9, 24.7, 24.5, 24.5, 22.1, 21.9, 20.7, 20.4, 19.0. MS (ESI): m/z (%) 1808 (M-H)$^-$. HRMS (ESI): Calcd. for $C_{86}H_{121}O_{19}N_{20}F_2S$: 1807.8811 (M-H)$^-$; Found: 1807.8833 (M-H)$^-$.

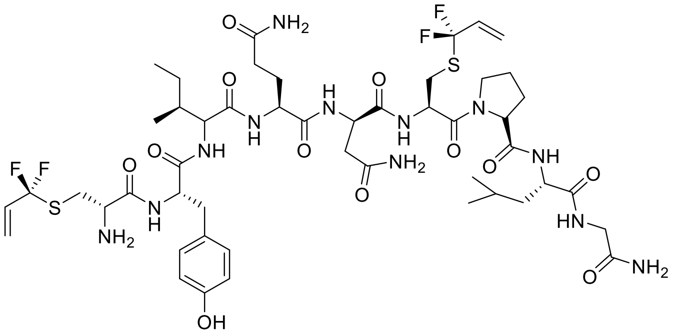


S-(1,1-Difluoro-2-phenylallyl)-L-cysteinylglycyl-L-lysyl-L-lysylglycyl-L-methionyl-L-valylglycylglycyl-L-valyl-L-valine (6f). Compound **6f** (9.8 mg, 41% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.01 (d, J = 203.8 Hz, 1F), -70.26 (d, J = 204.5 Hz, 1F). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28-7.99 (m, 5H), 7.93-7.69 (m, 4H), 7.52-7.45 (m, 2H), 7.44-7.36 (m, 3H), 5.87 (s, 1H), 5.82 (s, 1H), 4.48-4.38 (m, 1H), 4.37-4.27 (m, 2H), 4.25 – 4.02 (m, 7H), 3.90 – 3.61 (m, 7H), 3.51-3.22 (m, 2H), 2.82-2.67 (m, 4H), 2.45-2.32 (m, 2H), 2.02 (s, 3H), 2.00-1.91 (m, 2H), 1.82-1.73 (m, 1H), 1.71-1.60 (m, 2H), 1.57-1.44 (m, 6H), 1.37-1.26 (m, 2H), 0.92-0.78 (m, 18H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.2, 172.3, 171.9, 171.5, 171.4, 169.3, 169.1, 168.9, 168.2, 167.3, 143.0 (t, J = 22.3 Hz), 135.0, 129.3, 128.9, 128.4, 128.2 (t, J = 279.4 Hz), 58.3, 58.2, 57.8, 57.7, 57.5, 57.5, 52.9, 52.7, 52.3, 52.2, 51.8, 42.1, 39.0, 32.5, 32.0, 31.7, 31.3, 30.9, 30.0, 29.9, 29.8, 27.0, 22.7, 19.7, 19.6, 19.5, 18.6, 18.6, 18.4, 15.1. MS (ESI): m/z (%) 1184 (M-H)$^-$. HRMS (ESI): Calcd. for $C_{52}H_{84}O_{12}N_{13}F_2S_2$: 1184.5777 (M-H)$^-$; Found: 1184.5792 (M-H)$^-$.

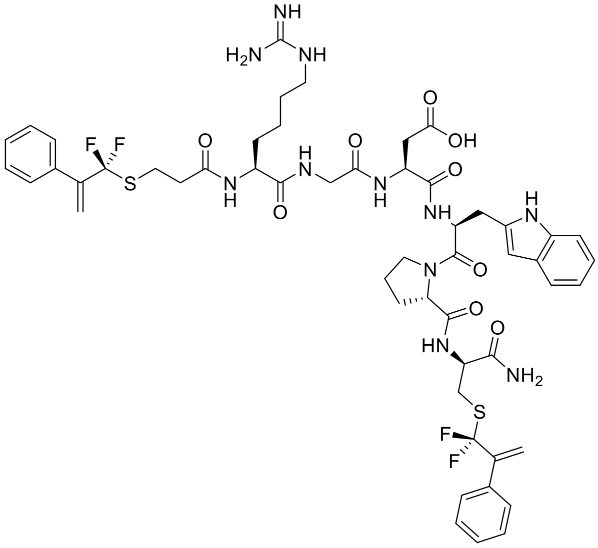


(2S)-$N1$-((2R)-4-amino-1-(((2R)-1-(2-(((S)-1-((2-amino-2-oxoethyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-((1,1-difluoro-2-phenylallyl)thio)-1-oxopropan-2-yl)amino)-1,4-dioxobutan-2-yl)-2-((3S)-2-((S)-2-((S)-2-amino-3-((1,1-difluoro-2-phenylallyl)thio)propanamido)-3-(4-hydroxyphenyl)propanamido)-3-

methylpentanamido)pentanediamide (6g). Compound **6g** (21.2 mg, 80% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.39 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 8.15-8.03 (m, 4H), 8.02-8.00 (m, 1H), 7.56 – 7.48 (m, 4H), 7.47-7.40 (m, 6H), 7.39 – 7.36 (m, 1H), 7.34 – 7.21 (m, 4H), 7.13 (s, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.98 – 6.93 (m, 1H), 6.89 – 6.81 (m, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 5.84 (d, *J* = 8.0 Hz, 2H), 5.79 (d, *J* = 6.5 Hz, 2H), 4.80 (q, *J* = 7.5 Hz, 1H), 4.60-4.50 (m, 2H), 4.35 – 4.25 (m, 2H), 4.24-4.17 (m, 2H), 3.70-3.53 (m, 4H), 3.17 (q, *J* = 7.5 Hz, 1H), 3.10 (dd, *J* = 12.5, 4.5 Hz, 1H), 2.98 (q, *J* = 7.0 Hz, 1H), 2.91-2.82 (m, 3H), 2.75-2.72 (m, 1H), 2.46 (q, *J* = 8.5 Hz, 1H), 2.17 – 2.12 (m, 2H), 2.07-2.00 (m, 1H), 1.95 – 1.84 (m, 5H), 1.83 – 1.70 (m, 3H), 1.68-1.59 (m, 1H), 1.57 – 1.48 (m, 2H), 1.47 – 1.40 (m, 1H), 1.14 – 1.02 (m, 1H), 0.90 (d, J = 6.5 Hz, 3H), 0.87 – 0.79 (m, 9H). ^{19}F NMR (376 MHz, DMSO-*d*$_6$) δ -70.48 (m). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 174.4, 172.9, 172.6, 172.1, 171.6, 171.4, 171.3, 171.2, 162.8, 156.2, 143.6 (t, *J* = 23.3 Hz), 143.3 (t, *J* = 23.2 Hz), 141.0, 135.4, 135.3, 130.8, 129.1, 129.1, 129.0, 128.9, 128.8 (t, *J* = 277.3 Hz), 128.7, 128.3, 127.9, 126.6, 120.9 (t, *J* = 6.7 Hz), 120.5 (t, *J* = 5.9 Hz), 115.2, 60.4, 57.3, 54.8, 53.8, 52.7, 51.9, 51.6, 50.2, 47.2, 42.4, 37.4, 37.0, 36.3, 35.5, 35.2, 34.5, 32.0, 31.2, 29.3, 28.4, 24.8 (t, *J* = 8.3 Hz), 24.6, 23.5, 22.0, 15.8, 11.4. MS (ESI): m/z (%) 1313 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{61}H_{81}O_{12}N_{12}F_4S_2$: 1313.5469 (M+H)$^+$; Found: 1313.5477 (M+H)$^+$.



(2*S*)-*N1*-((2*R*)-4-amino-1-(((2*R*)-1-(2-(((*S*)-1-((2-amino-2-oxoethyl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-((1,1-difluoroallyl)thio)-1-oxopropan-2-yl)amino)-1,4-dioxobutan-2-yl)-2-((3*S*)-2-((*S*)-2-((*S*)-2-amino-3-((1,1-difluoroallyl)thio)propanamido)-3-(4-hydroxyphenyl)propanamido)-3-methylpentanamido)pentanediamide (6h). Compound **6h** (12.8 mg, 55% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.22 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.40-8.28 (m, 3H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.09 (dd, *J* = 10.4, 8.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.95 (t, *J* = 5.6 Hz, 1H), 7.34 (s, 1H), 7.20 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.91 (s, 1H), 6.82 (s, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.28-6.11 (m, 2H), 5.79 – 5.55 (m, 4H), 4.73 (q, *J* = 7.6 Hz, 1H), 4.65-4.56 (m, 1H), 4.52 (q, *J* = 6.8 Hz, 1H), 4.28 – 4.10 (m, 4H), 4.06-3.96 (m, 1H), 3.63 (dd, *J* = 16.8, 6.0 Hz, 1H), 3.27 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.16 – 3.01 (m, 3H), 2.94-2.82 (m, 3H), 2.68 (dd, *J* = 14.4, 9.6 Hz, 2H), 2.16-1.95 (m, 3H), 1.92-1.66 (m, 7H), 1.65-1.56 (m, 1H), 1.53-1.34 (m, 3H), 1.12-1.00 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.85-0.72 (m, 9H). ^{19}F NMR (376 MHz, DMSO-d_6) δ -72.06 (dd, *J* = 47.0, 9.8 Hz), -72.60 (dd, *J* = 16.5, 10.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.5, 172.6, 172.1, 171.6, 171.3, 171.3, 171.3, 170.9, 168.5, 166.8, 156.3, 132.2 (t, *J* = 26.5 Hz), 131.8 (t, *J* = 26.1 Hz), 130.6, 127.9, 127.6 (t, *J* = 272.4 Hz), 127.0 (t, *J* = 274.2 Hz), 123.2 (t, *J* = 6.8 Hz), 122.4 (t, *J* = 7.2 Hz), 115.4, 60.4, 57.3, 54.8, 52.6, 51.9, 51.6, 50.1, 47.2, 42.4, 37.4, 37.0, 36.9, 32.0, 29.9, 29.7, 29.4, 28.6, 24.8, 24.6, 23.5, 22.0, 15.8, 11.3. MS (ESI): m/z (%) 1161 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{49}H_{73}O_{12}N_{12}F_4S_2$: 1161.4843 $(M+H)^+$; Found: 1161.4830 $(M+H)^+$.

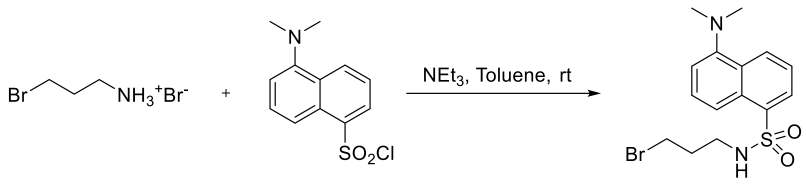


(*3S,9S*)-3-(((*S*)-1-((*S*)-2-(((*S*)-1-amino-3-((1,1-difluoro-2-phenylallyl)thio)-1-oxopropan-2-yl)carbamoyl)pyrrolidin-1-yl)-3-(1H-indol-2-yl)-1-oxopropan-2-yl)carbamoyl)-15,15-difluoro-9-(4-guanidinobutyl)-5,8,11-trioxo-16-phenyl-14-thia-4,7,10-triazaheptadec-16-enoic acid (6i). Compound **6i** (17.3 mg, 76% yield) as a white solid was purified with Spherical C18, 20-45μm, 100Å. ^{19}F NMR (376 MHz, DMSO-d_6) δ -70.64 (m). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.38-8.25 (m, 1H), 8.24-8.12 (m, 2H), 8.06 (dd, *J* = 8.0, 3.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.52-7.44 (m, 5H), 7.43-7.33 (m, 10H), 7.27 (s, 1H), 7.22 (s, 1H), 7.06 (t, *J* = 6.4 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 2H), 5.80 (s, 2H), 5.74 (s, 2H), 4.73-4.63 (m, 1H), 4.61-4.52 (m, 1H), 4.46-4.36 (m, 1H), 4.30 – 4.19 (m, 2H), 3.76-3.72 (m, 1H), 3.34 (dd, *J* = 12.8, 5.2, 1H), 3.31-3.08 (m, 1H), 3.07 – 2.98 (m, 5H), 2.93 (dd, *J* = 14.8, 9.2 Hz, 1H), 2.68 – 2.54 (m, 4H), 2.43 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.86-1.74 (m, 3H), 1.72-1.61 (m, 1H), 1.58-1.39 (m, 3H), 1.37-1.25 (m, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 176.1, 173.4, 172.1, 171.8, 171.8, 171.1, 170.1, 168.6, 157.9, 143.5 (t, *J* = 23.2 Hz), 143.3 (t, *J* = 23.2 Hz), 136.5, 135.4, 135.2, 129.1, 129.1, 128.9 (t, *J* = 275.9 Hz), 128.8, 128.7 (t, *J* = 277.2 Hz), 128.3, 127.7, 124.4, 121.3, 120.7 (t, *J* = 6.0 Hz), 120.5 (t, *J* = 6.7 Hz), 118.7, 118.5, 111.8, 110.2, 61.0, 56.5, 53.5, 52.8, 52.4, 49.9, 47.2, 43.7, 28.5, 35.5, 32.1, 30.6, 29.3, 28.0, 27.5, 25.0, 24.8, 23.1. MS (ESI): m/z (%) 1136 (M-H)$^-$. HRMS (ESI): Calcd. for $C_{53}H_{62}O_9N_{11}F_4S_2$: 1136.4115 (M-H)$^-$; Found: 1136.4126 (M-H)$^-$.

7. Synthetic Applications of the *gem*-Difloroallylated Peptides

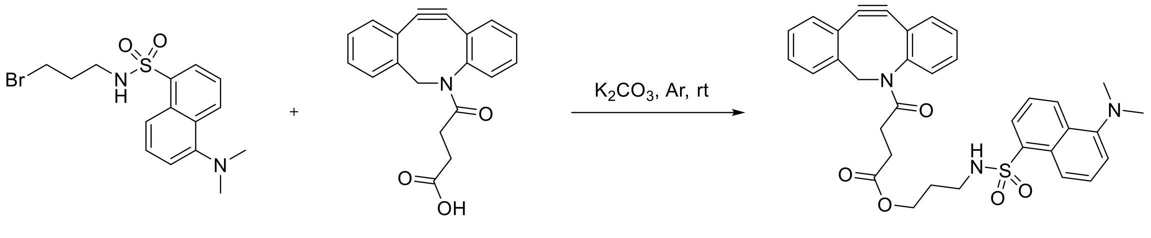
7.1 Click Reaction of Oligopeptide 6b with Compounds 7a and 7b

A. Preparation of compounds 7a and 7b:



s-7a **s-7a-1** **s-7a-2**

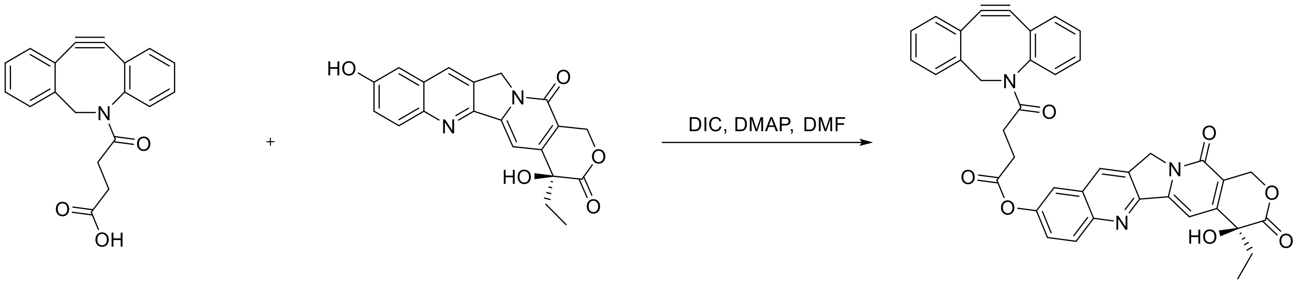
Procedure: To a 25 mL Schlenk tube equipped with a magnetic stir bar were added **s-7a** (2 mmol, 1.0 equiv) and **s-7a-1** (1.2 equiv). The tube was evacuated and backfilled with Ar (3 times). Et_3N (3.0 equiv) and toluene (10 mL) were added. The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1) to afford the product **s-7a-2** (0.34g, 47% yield) as a green oil. ***Note:*** **s-7a-2** is prepared according to the literature[7].



s-7a-2 **s-7a-3** **7a**

Procedure: To a 25 mL Schlenk tube equipped with a magnetic stir bar was added **s-7a-3** (0.32 mmol, 1.0 equiv). The tube was evacuated and backfilled with Ar (3 times). **s-7a-2** (2.0 equiv) and DMF (5 mL) were added. The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with silica gel chromatography (Petroleum ether: Ethyl acetate = 1: 1) to afford the product **7a** (0.23 g, 99% yield) as a yellow oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.43 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 8.8

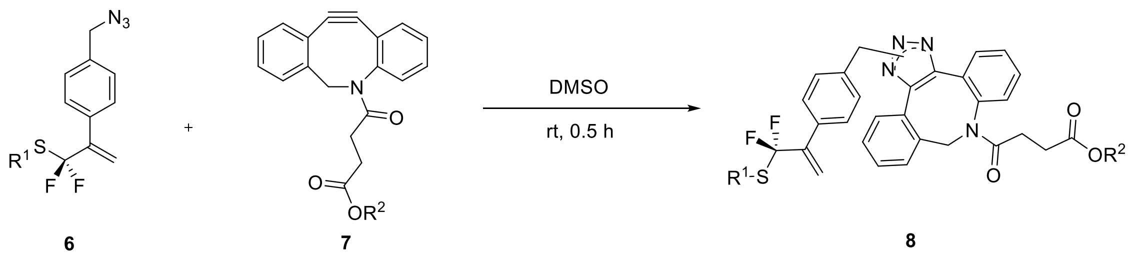
Hz, 1H), 8.13 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.54 – 7.36 (m, 4H), 7.34-7.29 (m, 3H), 7.20 – 7.11 (m, 3H), 7.08 (dt, *J* = 7.6 Hz, 1H), 5.01 (d, *J* = 14.0 Hz, 1H), 3.94 – 3.72 (m, 2H), 3.55 (d, *J* = 13.6 Hz, 1H), 2.83-2.74 (m, 8H), 2.67-2.53 (m, 1H), 2.43 – 2.27 (m, 1H), 2.16 (dt, *J* = 17.2, 5.6 Hz, 1H), 1.83 (dt, *J* = 16.8, 5.6 Hz, 1H), 1.67 – 1.37 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.8, 171.7, 151.8, 151.1, 147.8, 135.0, 132.2, 130.2, 129.8, 129.5, 129.2, 129.2, 128.5, 128.2, 128.1, 127.6, 127.0, 125.3, 123.1, 122.9, 122.5, 115.1, 114.8, 107.5, 61.4, 55.4, 45.3, 39.7, 29.6, 29.0, 28.5. MS (ESI): m/z (%) 596 $(M+H)^+$. MS (ESI): m/z (%) 596 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{34}H_{34}O_5NF_3S$: 596.2227 $(M+H)^+$; Found: 596.2215 $(M+H)^+$. IR: 2927, 1733, 1660, 1612, 1588.



s-7a-3 **s-7b** **7b**

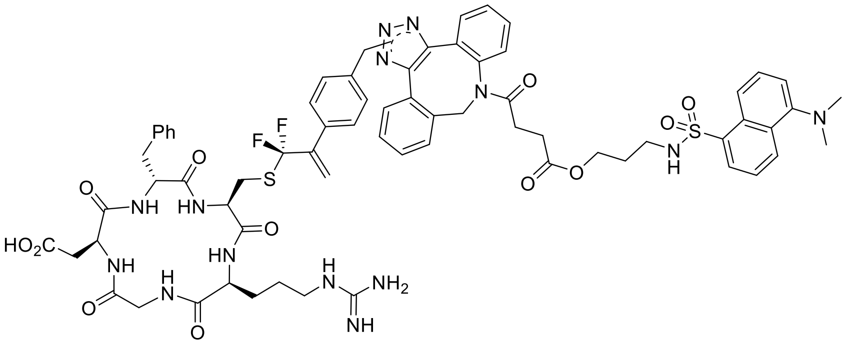
Procedure: To a 25 mL Schlenk tube equipped with a magnetic stir bar were added **s-7a-3** (0.32 mmol, 1.0 equiv), **s-7b** (1.0 equiv) and DMAP (0.1 equiv). The tube was evacuated and backfilled with Ar (3 times). DIC (1.1 equiv) and DMF (3 mL) were added. The resulting reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate and water. The organic layer was separated. The aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with Spherical C18, 20-45μm, 100Å to afford the product **7b** (0.16g, 72% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.82 – 7.01 (m, 10H), 6.52 (s, 1H), 5.39 (s, 2H), 5.23 (s, 2H), 5.06 (d, *J* = 14.0 Hz, 1H), 3.64 (d, *J* = 13.6 Hz, 1H), 2.86-2.56 (m, 2H), 2.09 – 1.72 (m, 3H), 1.22 – 1.06 (m, 2H), 0.92-0.76 (m, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.9, 171.4, 171.3, 157.6, 152.3, 151.2, 150.2, 149.6, 148.0, 146.8, 146.2, 132.3, 131.1, 130.6, 129.3, 129.0, 128.6, 128.3, 128.3, 127.8, 127.2, 126.0, 125.6, 123.1, 122.8, 118.8, 118.6, 115.0, 107.6, 98.1, 72.8, 66.3, 55.6, 50.0, 31.7, 29.7, 29.5, 24.6, 7.8. MS (ESI): m/z (%) 652 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{39}H_{30}O_7N_3$: 652.2078 $(M+H)^+$; Found: 652.2077 $(M+H)^+$.

B. Click Reaction between 6b and Compounds 7a and 7b:



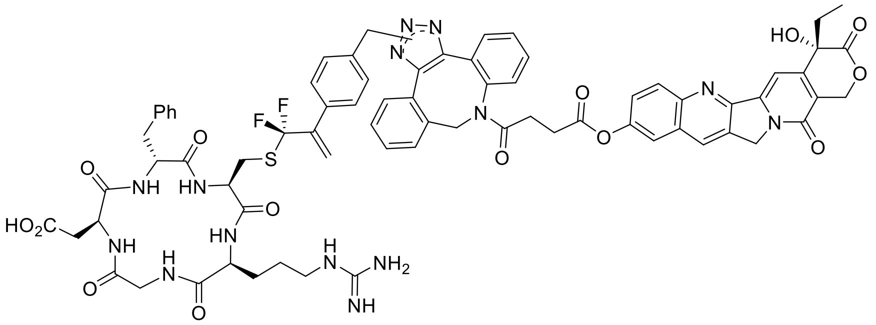
Procedure: To a 25 mL of vial equipped with a stirring bar were added alkyne compound **7** (0.05 mmol, 1.0 equiv) and peptide **6** (0.05 mmol, 1.0 equiv) under air. DMSO (2 mL) was added subsequently. After the mixture was stirred at rt for 0.5 h, the corresponding compound was purified with Spherical C18, 20-45μm, 100Å directly.

Characterization Data for Compounds 8a and 8b:



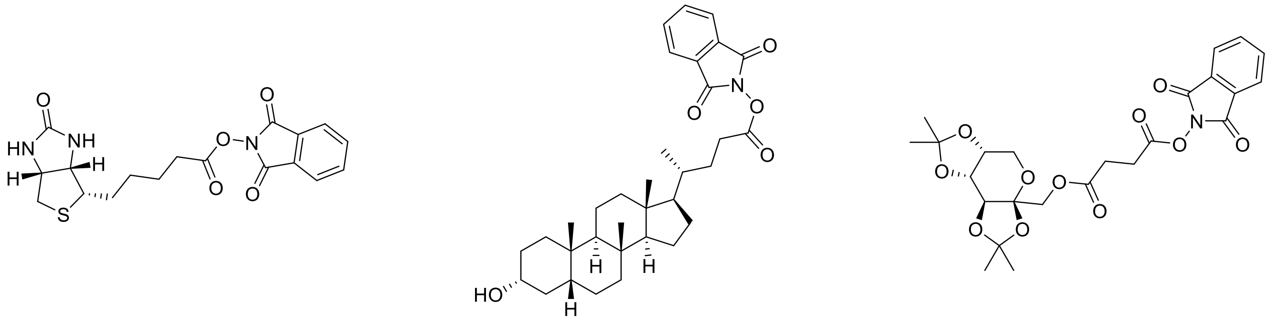
2-((*2S,5R,8R,11S*)-5-benzyl-8-(((2-(4-((8-(4-(3-((5-(dimethylamino)naphthalene)-1-sulfonamido)propoxy)-4-oxobutanoyl)-8,9-dihydro-1H-dibenzo[b,f][1,2,3]triazolo[4,5-d]azocin-1-yl)methyl)phenyl)-1,1-difluoroallyl)thio)methyl)-11-(3-guanidinopropyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (8a). Compound **8a** (11.8 mg, 85% yield, as a mixture of two isomers (1:1), determined by ^{19}F NMR) as a yellow solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.63 (t, J = 9.6 Hz, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.38 (t, J = 9.0 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.21-8.12 (m, 2H), 8.10 (d, J = 6.6, 4.8 Hz, 1H), 7.96-7.89 (m, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.64 – 7.53 (m, 4H), 7.52-7.44 (m, 4H), 7.35 (d, J = 7.2 Hz, 1H), 7.33 – 7.25 (m, 4H), 7.24 (d, J = 7.2 Hz, 2H), 7.21-7.16 (m, 5H), 7.14-7.09 (m, 1H), 7.01 (d, J = 7.8 Hz, 4H), 5.85-5.62 (m, 2H), 4.66-4.56 (m, 2H), 4.48-4.40 (m, 1H), 4.39 – 4.32 (m, 1H), 4.16 (dd, J = 14.4, 7.2 Hz, 1H), 3.86 (dd, J = 19.2, 6.6 Hz, 2H), 3.39 – 3.17 (m, 9H), 2.87 (t, J = 6.0 Hz, 4H), 2.84 (s, 6H), 2.74-2.65 (m, 2H), 1.84 – 1.67 (m, 2H), 1.62 (q, J = 6.0 Hz, 2H), 1.59 –

1.51 (m, 2H), 1.26 (s, 2H), 1.18 (t, *J* = 6.6 Hz, 2H). ^{19}F NMR (565 MHz, DMSO-*d*$_6$) δ -69.49 (d, *J* = 207.9 Hz), -69.56 (d, *J* = 217.0 Hz), -70.04 (d, *J* = 206.8 Hz), -70.10 (d, *J* = 210.2 Hz). ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 172.0, 171.3, 171.2, 171.0, 170.6, 170.2, 168.5, 157.7, 152.0, 143.2, 140.6, 138.8, 136.9, 136.5, 136.0, 135.2, 134.8, 134.3, 132.2, 131.6, 131.0, 130.3, 130.0, 129.9, 129.8, 129.8, 129.7, 129.6, 129.4, 128.8, 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.2, 127.7, 127.5, 127.3, 126.4, 123.8, 119.7, 115.6, 61.8, 61.7, 55.6, 54.0, 52.1, 51.6, 49.5, 45.5, 43.7, 42.1, 41.3, 37.2, 31.5, 29.3, 29.2, 29.1, 29.1, 27.8, 25.2. MS (ESI): m/z (%) 1381 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{68}H_{75}O_{12}N_{14}F_2S_2$: 1381.5093 (M+H)$^+$; Found: 1381.5073 (M+H)$^+$.



2-((*2S,5R,8R,11S*)-5-benzyl-8-(((2-(4-((8-(4-((4-ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-4-oxobutanoyl)-8,9-dihydro-1H-dibenzo[b,f][1,2,3]triazolo[4,5-d]azocin-1-yl)methyl)phenyl)-1,1-difluoroallyl)thio)methyl)-11-(3-guanidinopropyl)-3,6,9,12,15-pentaoxo-1,4,7,10,13-pentaazacyclopentadecan-2-yl)acetic acid (8b). Compound **8b** (20 mg, 56% yield, a mixture of two isomers (1:1), determined by ^{19}F NMR) as a yellow solid was purified with Spherical C18, 20-45μm, 100Å. ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.64 – 8.47 (m, 1H), 8.44-8.28 (m, 1H), 8.21 – 8.08 (m, 2H), 8.05-7.82 (m, 1H), 7.77 (d, *J* = 25.8 Hz, 1H), 7.69 – 7.47 (m, 6H), 7.46-7.26 (m, 7H), 7.25 – 7.07 (m, 7H), 7.04 – 6.90 (m, 2H), 5.88-5.56 (m, 2H), 5.55-5.20 (m, 4H), 4.69 – 4.56 (m, 2H), 4.51-4.42 (m, 1H), 4.31-4.23 (m, 1H), 4.19-4.10 (m, 1H), 3.53-2.97 (m, 14H), 2.79-2.61 (m, 3H), 2.20 (d, *J* = 18.0 Hz, 1H), 1.98-1.84 (m, 2H), 1.20-1.05 (m, 1H), 0.91 (t, *J* = 6.6 Hz, 3H). ^{19}F NMR (565 MHz, DMSO-*d*$_6$) δ -68.97 – -70.81 (m). ^{13}C NMR (151 MHz, DMSO-*d*$_6$) δ 172.8, 172.7, 171.3, 171.1, 171.0, 170.3, 157.6, 157.5, 157.2, 150.6, 150.0, 146.5, 145.9, 144.0, 131.7, 131.6, 131.1, 130.2, 129.7, 129.4, 129.4, 128.8, 128.7, 128.5, 128.4, 127.5, 127.3, 126.5, 126.2, 123.6, 119.7, 119.4, 118.7, 109.5, 97.3, 96.4, 72.9, 72.9, 65.9, 55.6, 52.2, 50.6, 50.5, 49.5, 49.1, 43.6, 41.3, 41.2, 37.1, 31.4, 29.3, 28.8, 27.7, 25.2, 8.1. MS (ESI): m/z (%) 1437 $(M+H)^+$. HRMS (ESI): Calcd. for $C_{73}H_{71}O_{14}N_{14}F_2S$: 1437.4958 $(M+H)^+$; Found: 1437.4940 $(M+H)^+$.

7.2 Radical Addition Reactions

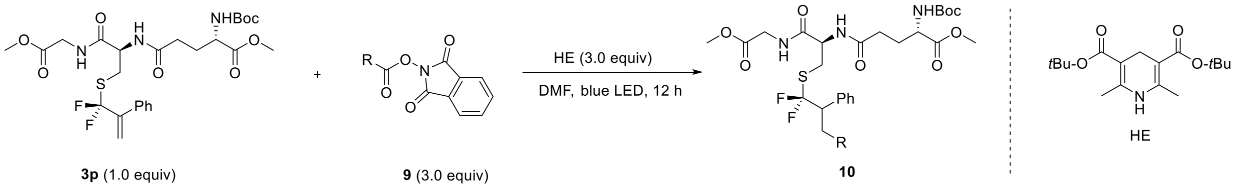


9a **9b** **9c**

Figure S5 Structures of redox esters **9**

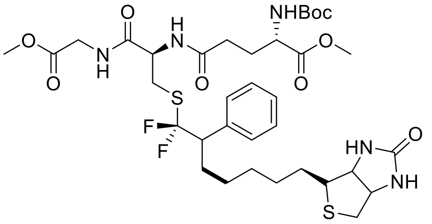
Note: Redox ester **9a**[8], **9b**[9], **and 9c**[10] were prepared according to the literature.

A. Reaction of 3p with Redox Esters 9:

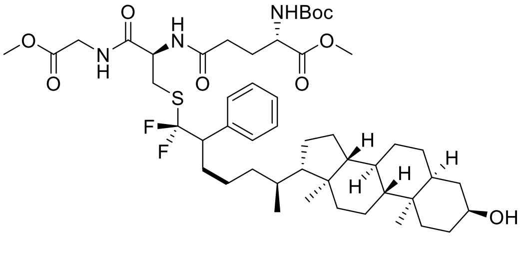


Procedure: To a 25 mL of Schlenk tube were added Hantzsch ester (0.3 mmol, 3.0 equiv), redox ester **9** (0.3 mmol, 3.0 equiv), and compound **3p** (0.1 mmol, 1.0 equiv) under air. The reaction mixture was then evacuated and backfilled with Ar (3 times). DMF (2 mL) was then added. The reaction mixture was stirred for 12 h under irradiation of blue LED (12W, 460-465 nm). The reaction mixture was diluted with ethyl acetate and H_2O. The organic layers were washed with brine three times, dried over Na_2SO_4, filtered and concentrated. The residue was purified with silica gel chromatography to give product **10**.

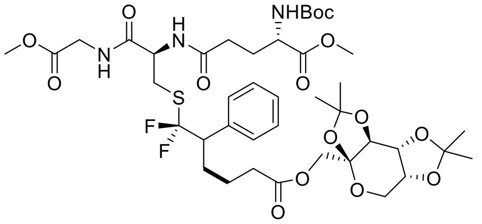
Characterization Data for Compounds 10a-c:



Methyl *N2*-(*tert*-butoxycarbonyl)-*N5*-(3-((1,1-difluoro-7-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-2-phenylheptyl)thio)-1-((2-methoxy-2-oxoethyl)amino)-1-oxopropan-2-yl)-*L*-glutaminate (10a). Compound **10a** (44 mg, 28% yield) as a yellow oil was purified with silica gel chromatography (Dichloromethane: Methanol = 20: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 (d, *J* = 20.4 Hz, 1H), 7.33-7.16 (m, 5H), 7.10 (d, *J* = 7.6 Hz, 1H), 5.89 (d, *J* = 12.8 Hz, 1H), 5.73 (s, 1H), 5.58 (d, *J* = 8.8 Hz, 1H), 4.76-4.60 (m, 1H), 4.43 (t, *J* = 6.4 Hz, 2H), 4.66 (d, *J* = 7.9 Hz, 1H), 4.32-4.14 (m, 2H), 4.03 – 3.82 (m, 3H), 3.67 (s, 6H), 3.23 – 3.01 (m, 4H), 2.84 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.68 (d, *J* = 12.8 Hz, 1H), 2.26 (t, *J* = 6.8 Hz, 2H), 2.20 (s, 1H), 2.17-2.03 (m, 1H), 1.99 – 1.89 (m, 2H), 1.85 – 1.70 (m, 1H), 1.64-1.49 (m, 2H), 1.38 (s, 9H), 1.32-1.21 (m, 3H), 1.14-1.03 (m, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -74.85 (ddd, *J* = 201.5, 129.0, 9.4 Hz), -74.46 (ddd, *J* = 202.7, 162.0, 17.3 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.9, 172.4, 170.5, 170.1, 163.8, 155.7, 136.4, 131.8 (t, *J* = 282.9 Hz), 129.4, 128.4, 127.8, 80.0, 62.0, 60.1, 55.6, 54.5, 54.3, 54.2, 52.8, 52.6, 52.6, 52.4, 52.3, 41.1, 40.5, 32.0, 29.1, 29.0, 28.6, 28.5, 28.3, 26.7, 26.6. MS (ESI): m/z (%) 787 $(M+H)^{+}$. HRMS (ESI): Calcd. for $C_{35}H_{52}O_{9}N_{5}F_{2}S_{2}$: 788.3169 $(M+H)^{+}$; Found: 788.3176 $(M+H)^{+}$. IR: 1744, 1701, 1526, 1455, 1392.

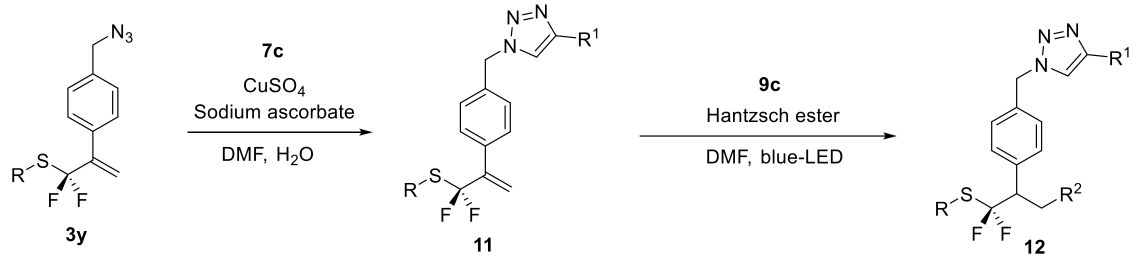


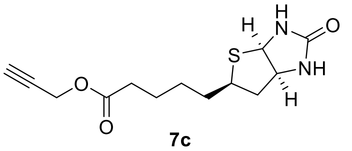
Methyl *N2*-(*tert*-butoxycarbonyl)-*N5*-(3-(((*6R*)-1,1-difluoro-6-((*3R,10S,13R*)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)-2-phenylheptyl)thio)-1-((2-methoxy-2-oxoethyl)amino)-1-oxopropan-2-yl)-*L*-glutaminate (10b). Compound **10b** (70 mg, 38% yield) as a yellow oil was purified with silica gel chromatography (Dichloromethane: Methanol = 20: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.06 (m, 6H), 6.83 (s, 1H), 5.45 (d, *J* = 7.6 Hz, 1H), 4.67 (d, *J* = 5.6 Hz, 1H), 4.26 (s, 1H), 3.99 (dd, *J* = 18.0, 5.6 Hz, 1H), 3.92-3.80 (m, 1H), 3.68 (s, 5H), 3.65-3.52 (m, 1H), 3.24-3.00 (m, 4H), 2.26 (t, *J* = 6.4 Hz, 2H), 2.08 (s, 1H), 1.97-1.56 (m, 9H), 1.56 – 0.88 (m, 32H), 0.87 (s, 3H), 0.73 (t, *J* = 7.6 Hz, 3H), 0.56 (s, 3H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -74.21 (dd, *J* = 201.2, 9.0 Hz), -74.97 (dd, *J* = 201.2, 9.8 Hz), -76.51 (dd, *J* = 201.5, 15.0 Hz), -76.99 (dd, *J* = 201.2, 15.0 Hz). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 172.8, 172.3, 170.2, 169.9, 136.4, 131.8 (t, *J* = 286.8 Hz), 129.4, 128.3, 127.8, 80.1, 71.8, 56.4, 56.2, 54.5 (t, *J* = 22.2 Hz), 53.4, 52.7, 52.4, 52.3, 42.6, 42.0, 40.4, 40.1, 36.3, 35.8, 35.6, 35.4, 35.4, 35.3, 34.5, 31.9, 30.4, 29.6, 29.3, 28.9, 28.2, 27.1, 26.4, 24.1, 23.6, 23.5, 23.3, 20.7, 18.5, 18.3. MS (ESI): m/z (%) 920 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{49}H_{76}O_9N_3F_2S$: 920.5265 (M+H)$^+$; Found: 920.5272 (M+H)$^+$. IR: 1747, 1659, 1529, 1454, 1367.



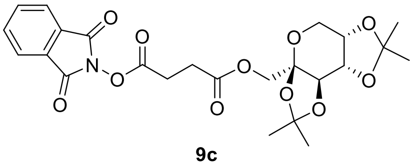
Methyl *N2*-(*tert*-butoxycarbonyl)-*N5*-(3-((1,1-difluoro-6-oxo-2-phenyl-7-(((*3aS,5aR,8aR,8bS*)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)oxy)heptyl)thio)-1-((2-methoxy-2-oxoethyl)amino)-1-oxopropan-2-yl)-L-glutaminate (10c). Compound **10c** (87.6 mg, 49% yield) as a white solid (m.p.91.0-92.2°C) was purified with silica gel chromatography (Dichloromethane: Methanol = 20: 1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.12 (m, 5H), 6.98 (dd, *J* = 10.8, 5.6 Hz, 1H), 6.56 (t, *J* = 6.0 Hz, 1H), 5.28 (d, *J* = 8.0 Hz, 1H), 4.67-4.55 (m, 1H), 4.52 (dd, *J* = 7.6, 2.0 Hz, 1H), 4.29 (d, *J* = 11.6 Hz, 1H), 4.26 – 4.10 (m, 1H), 4.19 – 4.13 (m, 2H), 4.02 – 3.78 (m, 4H), 3.69 (s, 1H), 3.66 (s, 6H), 3.25 – 2.99 (m, 3H), 2.35 – 2.14 (m, 4H), 2.14-1.99 (m, 2H), 1.94-1.71 (m, 3H), 1.45 (s, 3H), 1.39 (s, 4H), 1.36 (s, 9H), 1.26 (s, 6H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -74.50 (td, *J* = 201.5, 10.2 Hz), -76.94 (ddd, *J* = 202.7, 119.6, 15.8 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 172.8, 172.3, 172.3, 170.1, 169.9, 155.6, 135.7, 131.6 (t, *J* = 282.5 Hz), 129.4, 128.5, 128.0, 109.1, 108.7, 101.4, 80.2, 70.7, 70.4, 69.9, 65.2, 65.1, 61.1, 60.4, 54.4 (t, *J* = 21.8 Hz), 52.6, 52.5, 52.3, 41.1, 33.6, 33.6, 31.9, 28.2, 26.4, 25.8, 25.1, 24.0, 22.3, 22.3, 21.0, 14.1. MS (ESI): m/z (%) 904 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{41}H_{60}O_{15}N_3F_2S$: 904.3708 (M+H)$^+$; Found: 904.3707 (M+H)$^+$. IR: 2938, 1745, 1530, 1455, 1382.

7.3 Cascade Modification of 3y





7c

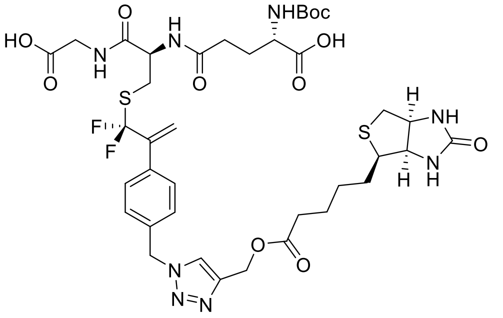


9c

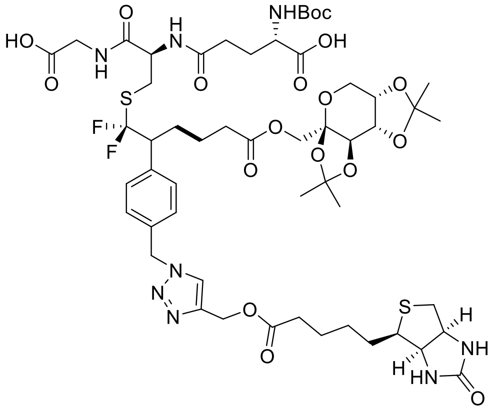
Procedure: To a 25 mL of vial equipped with a stirring bar were added $CuSO_4$ (0.05 mmol, 1.0 equiv), sodium ascorbate (0.05 mmol, 1.0 equiv), alkyne compound **7c** (0.05 mmol, 1.0 equiv), *gem*-difluoroallylated thiol **3y** (0.05 mmol, 1.0 equiv) under air. DMF (2 mL) and H_2O (2 mL) were added subsequently. After the mixture was stirred for 0.5 h, the corresponding compounds was purified with Spherical C18, 20-45μm, 100Å to give product **11** (53 mg, 50% yield) as a colorless solid. ***Note***: Compound **7c** is prepared according to the literature[11].

To a 25 mL of Schlenk tube were added Hantzsch ester (0.3 mmol, 3.0 equiv), redox ester **9c** (0.3 mmol, 3.0 equiv), and compounds **11** (0.1 mmol, 1.0 equiv) under air. The reaction mixture was then evacuated and backfilled with Ar (3 times). DMF (2 mL) was then added. The reaction mixture was stirred for 12 h under irradiation of blue LED (12W, 460-465 nm). The corresponding compounds was purified with Spherical C18, 20-45μm, 100Å to give product **12** (20 mg, 33% yield) as a colorless oil.

Characterization Data for Compounds 11 and 12:



***N2*-(*tert*-butoxycarbonyl)-*N5*-((*R*)-1-((carboxymethyl)amino)-3-((1,1-difluoro-2-(4-((4-(((5-((*3aR*,*4R*,*6aS*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)phenyl)allyl)thio)-1-oxopropan-2-yl)-*L*-glutamine (11).** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (s, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.81 (s, 1H), 5.65 (s, 1H), 5.60 (s, 2H), 5.16 (s, 2H), 4.75 – 4.64 (m, 1H), 4.45 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.24 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.10 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.89 (s, 2H), 3.37 (dd, *J* = 13.6, 5.2 Hz, 1H), 3.30-3.28 (m, 1H), 3.20 – 2.99 (m, 2H), 2.89 (dd, *J* = 13.2, 5.2 Hz, 1H), 2.66 (d, *J* = 12.8 Hz, 1H), 2.43-2.27 (m, 4H), 2.19-2.08 (m, 1H), 1.98-1.81 (m, 1H), 1.75 – 1.48 (m, 4H), 1.46-1.30 (m, 12H). ^{19}F NMR (376 MHz, Methanol-d_4) δ -72.68. ^{13}C NMR (101 MHz, Methanol-d_4) δ 174.4, 173.6, 173.5, 171.4, 171.0, 168.1, 164.7, 156.7, 143.5 (t, *J* = 23.2 Hz), 143.1, 137.1, 135.7, 135.7, 128.6, 128.0 (t, *J* = 275.5 Hz), 127.7, 124.6, 119.6 (t, *J* = 6.7 Hz), 117.5, 79.2, 62.0, 60.2, 56.8, 55.5, 53.1, 52.8, 40.6, 39.7, 33.2, 31.7, 30.2, 28.2, 28.0, 27.4, 27.3, 24.4. MS (ESI): m/z (%) 897 (M+H)$^+$. HRMS (ESI): Calcd. for $C_{38}H_{51}O_{11}N_8F_2S_2$: 897.3081 (M+H)$^+$; Found: 897.3078 (M+H)$^+$.



***N2*-(*tert*-butoxycarbonyl)-*N5*-((*2R*)-1-((carboxymethyl)amino)-3-((1,1-difluoro-6-oxo-2-(4-((4-(((5-((*3aR,4R,6aS*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)oxy)methyl)-1H-1,2,3-triazol-1-yl)methyl)phenyl)-6-(((3aR,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-3aH-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-3a-yl)methoxy)hexyl)thio)-1-oxopropan-2-yl)-*L*-glutamine (12).** ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 (s, 1H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 5.57 (s, 2H), 5.15 (s, 2H), 4.61 – 4.52 (m, 2H), 4.45 (dd, *J* = 7.2, 4.8 Hz, 1H), 4.29 – 4.18 (m, 4H), 4.11-4.01 (m, 1H), 3.94-3.79 (m, 4H), 3.64-3.54 (m, 1H), 3.29-3.23 (m, 3H), 3.19 – 3.08 (m, 1H), 3.01-2.91 (m, 1H), 2.87 (dd, *J* = 12.8, 4.8 Hz, 1H), 2.66 (d, *J* = 12.4 Hz, 1H), 2.40-2.20 (m, 6H), 2.16 – 1.96 (m, 2H), 1.95-1.78 (m, 2H), 1.72 – 1.48 (m, 4H), 1.45 (s, 3H), 1.41 (s, 10H), 1.37 (s, 4H), 1.29 (s, 3H), 1.25 (d, *J* = 8.8 Hz, 4H). ^{19}F NMR (376 MHz, Methanol-d_4) δ -76.48 (dd, *J* = 53.3, 11.2 Hz), -76.76 (ddd, *J* = 204.9, 53.8, 11.6 Hz), -78.43 (ddd, *J* = 203.8, 36.8, 14.7 Hz). ^{13}C NMR (126 MHz, Methanol-d_4) δ 174.6, 173.7, 173.5, 172.6, 171.9, 171.0, 164.7, 156.7, 143.1, 136.6, 135.1, 131.7 (t, *J* = 281.7 Hz), 131.0, 130.1, 128.5, 127.8, 124.6, 108.8, 108.6, 101.4, 79.2, 70.8, 70.4, 70.0, 64.6, 61.9, 60.9, 60.2, 56.8, 55.5, 53.2, 48.5, 39.7, 33.2, 33.2, 33.1, 31.8, 28.9, 28.3, 28.2, 28.0, 27.4, 25.3, 24.9, 24.4, 24.3, 24.3, 22.9, 22.2, 22.1. MS (ESI): m/z (%) 1211 (M-H)$^-$. HRMS (ESI): Calcd. for $C_{53}H_{73}O_{18}N_8F_2S_2$: 1211.4458 (M-H)$^-$; Found: 1211.4464 (M-H)$^-$.

8. References

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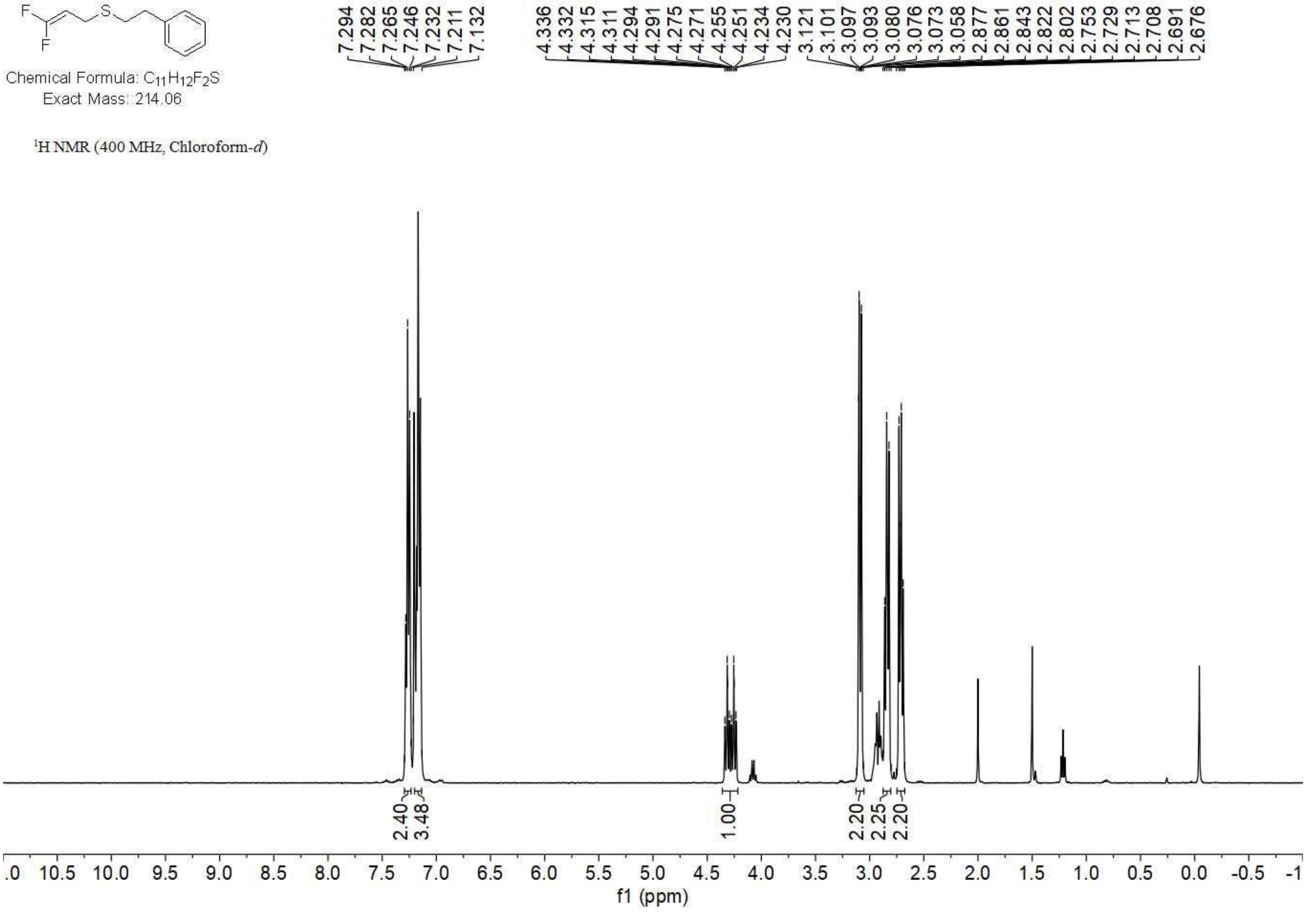
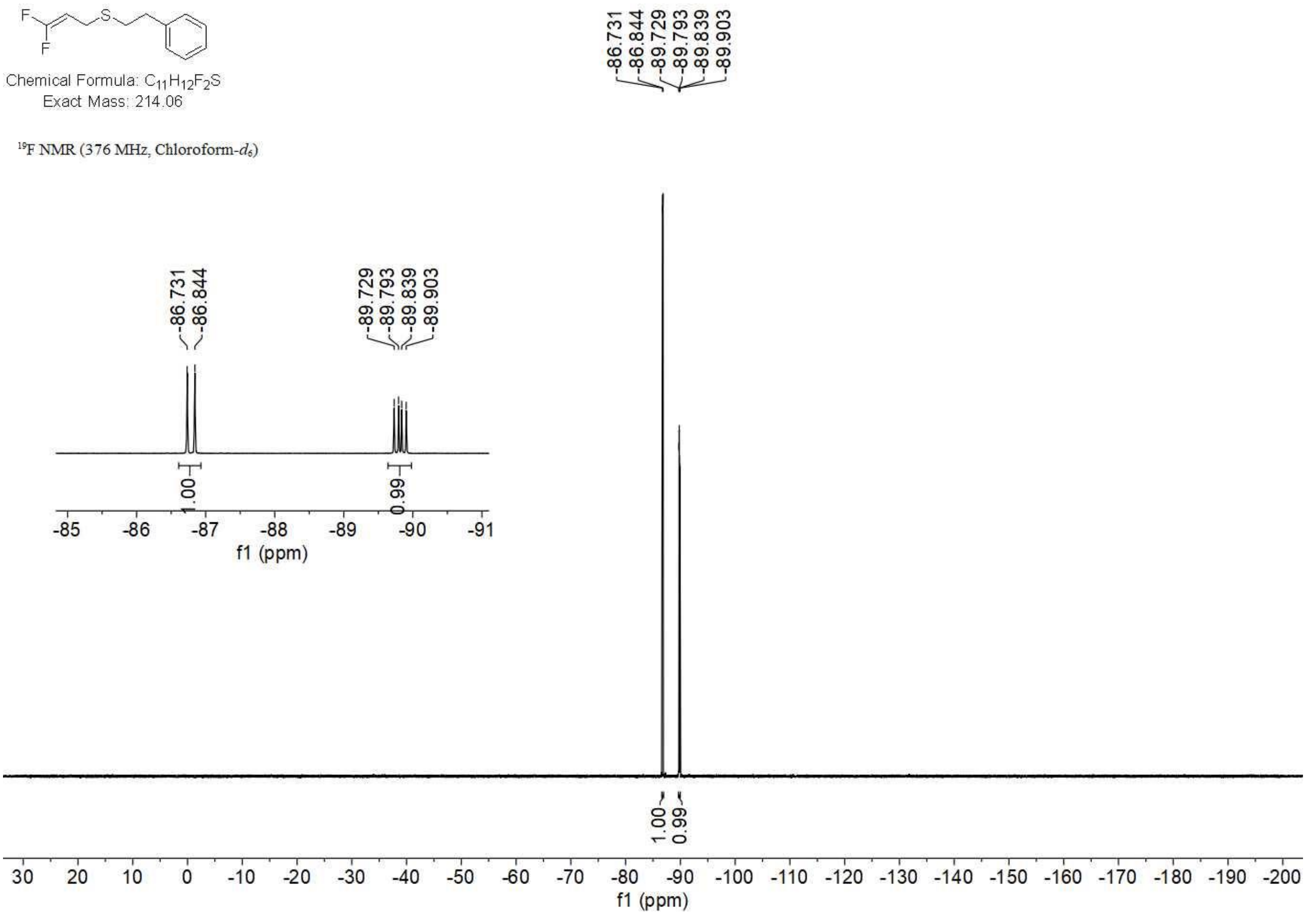
9. Copies of ^{1}H, ^{19}F, ^{13}C Spectra

9.1 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for DFAS 2d and 2h

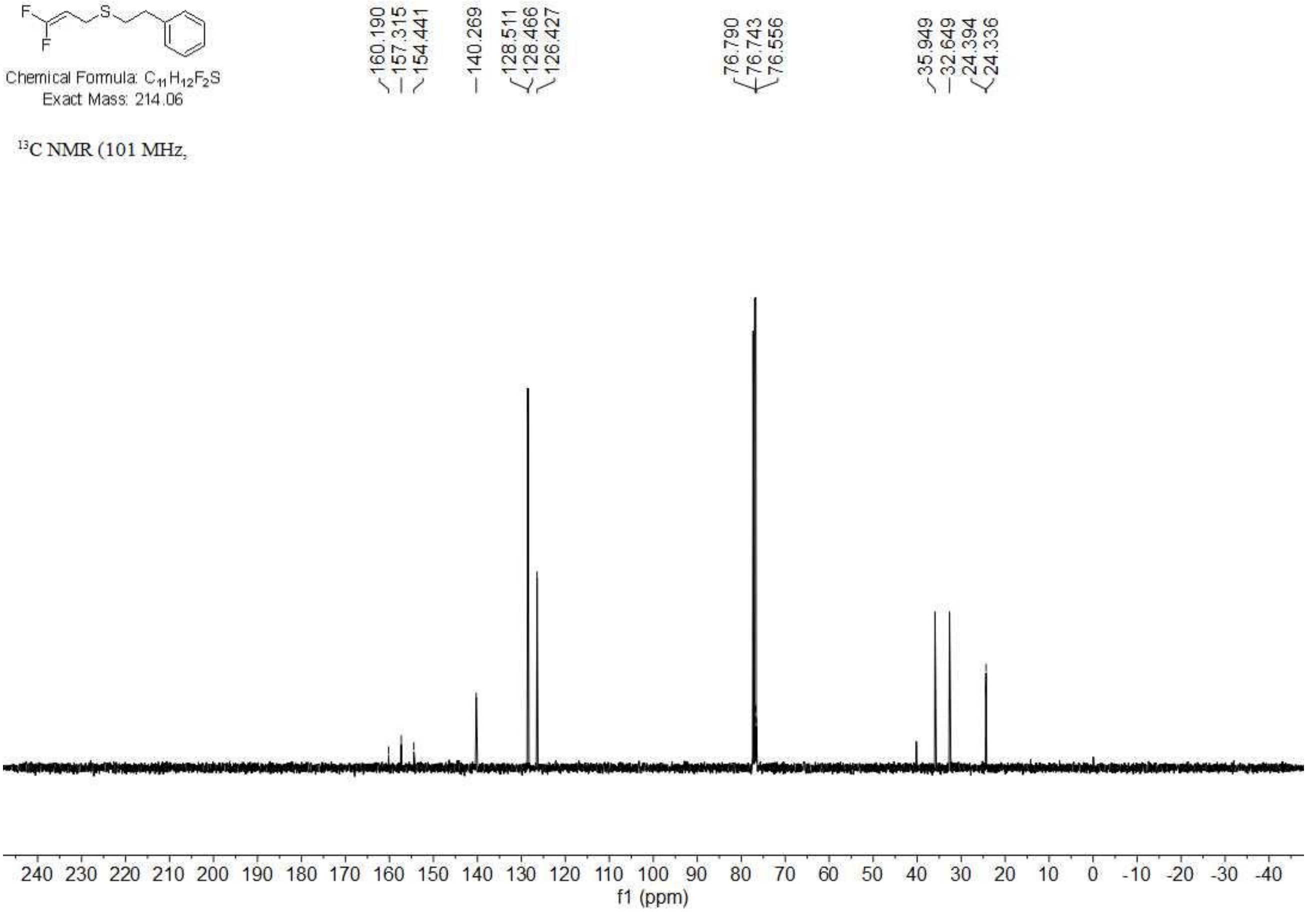
Spectra of s-2d-2





Chemical Formula: $C_{11}H_{12}F_2S$
Exact Mass: 214.06

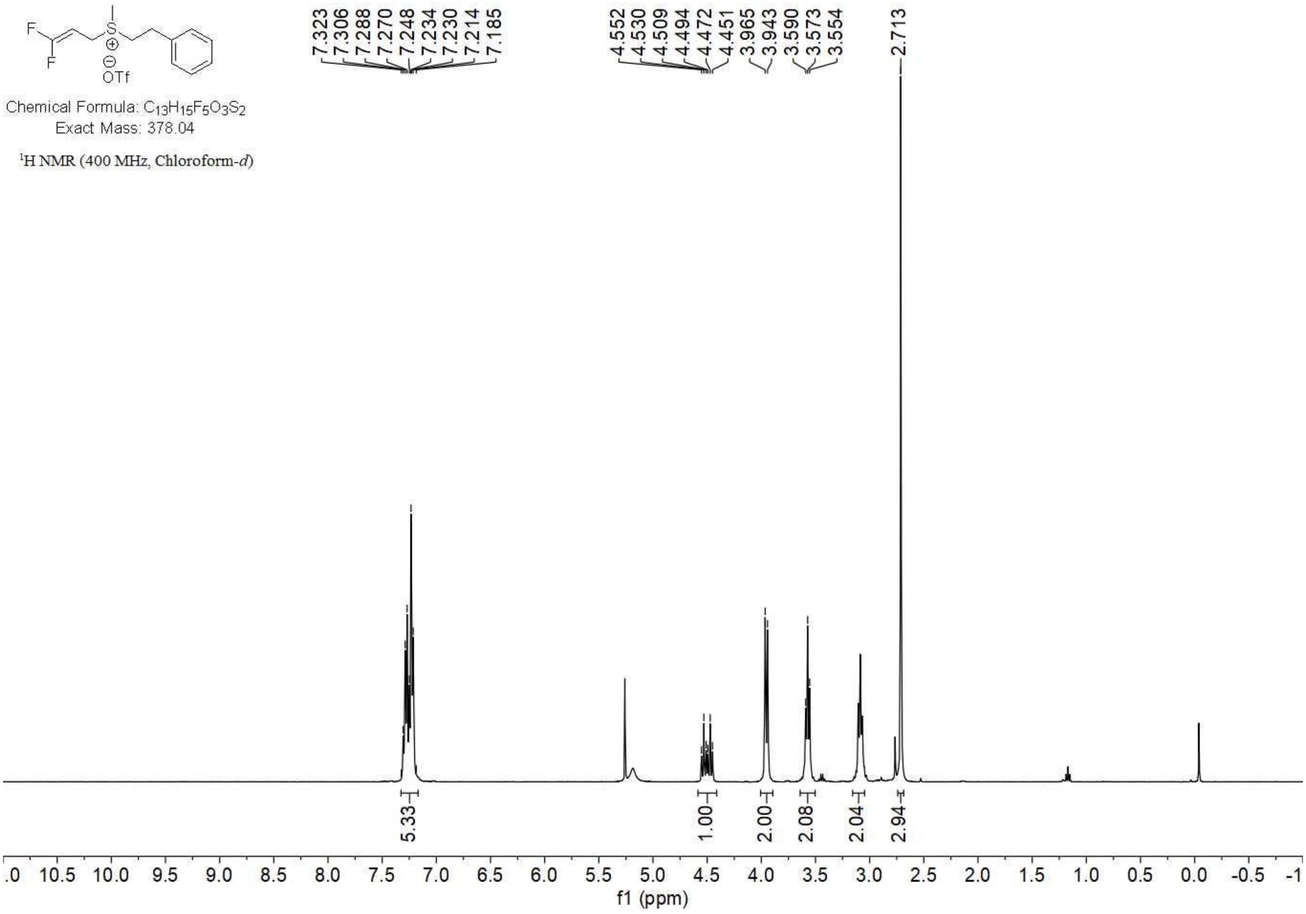
^{19}F NMR (376 MHz, Chloroform-*d*$_6$)



Chemical Formula: $C_{11}H_{12}F_2S$
Exact Mass: 214.06

^{13}C NMR (101 MHz,

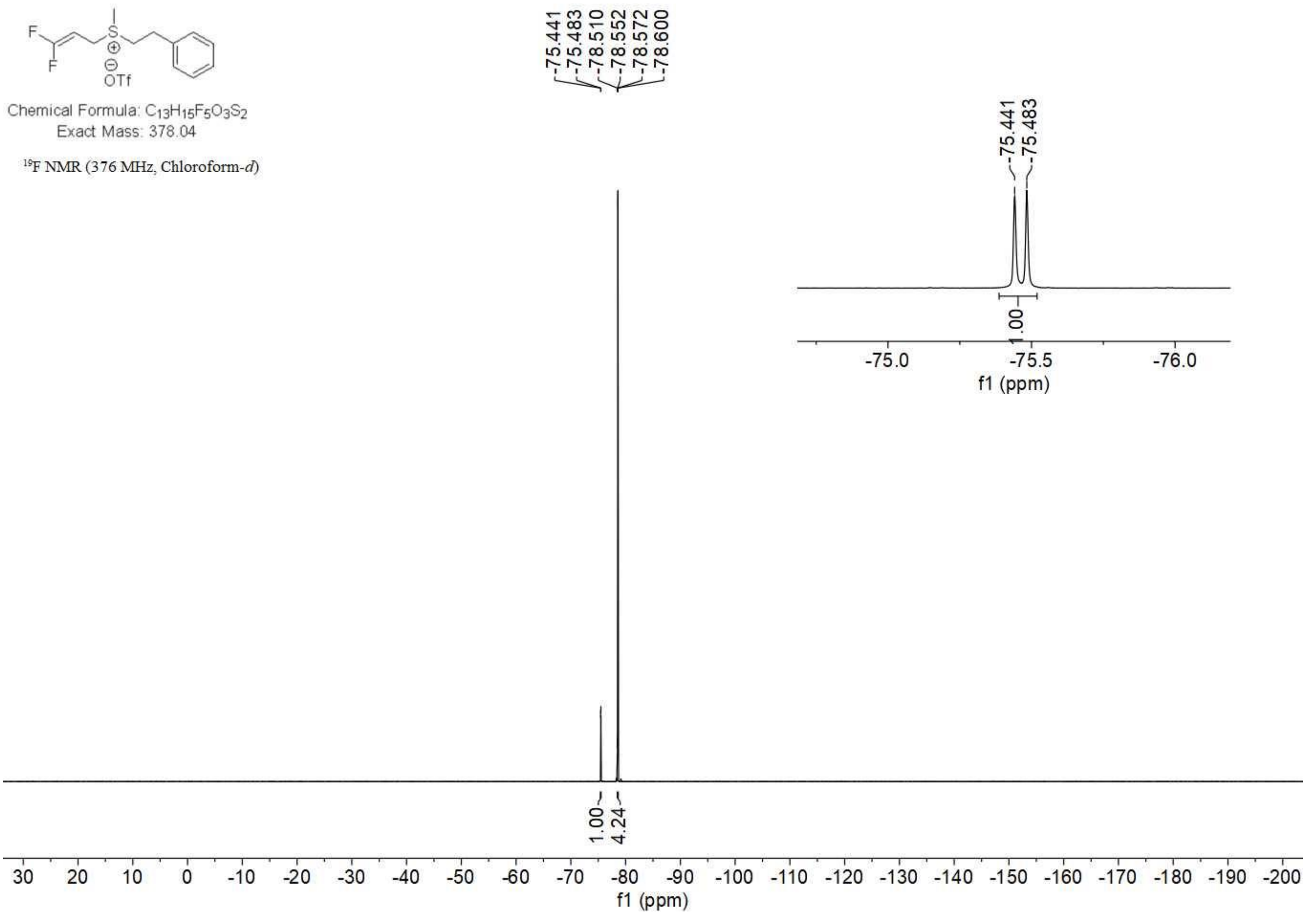
Spectra of 2d



Chemical Formula: $C_{13}H_{15}F_5O_3S_2$

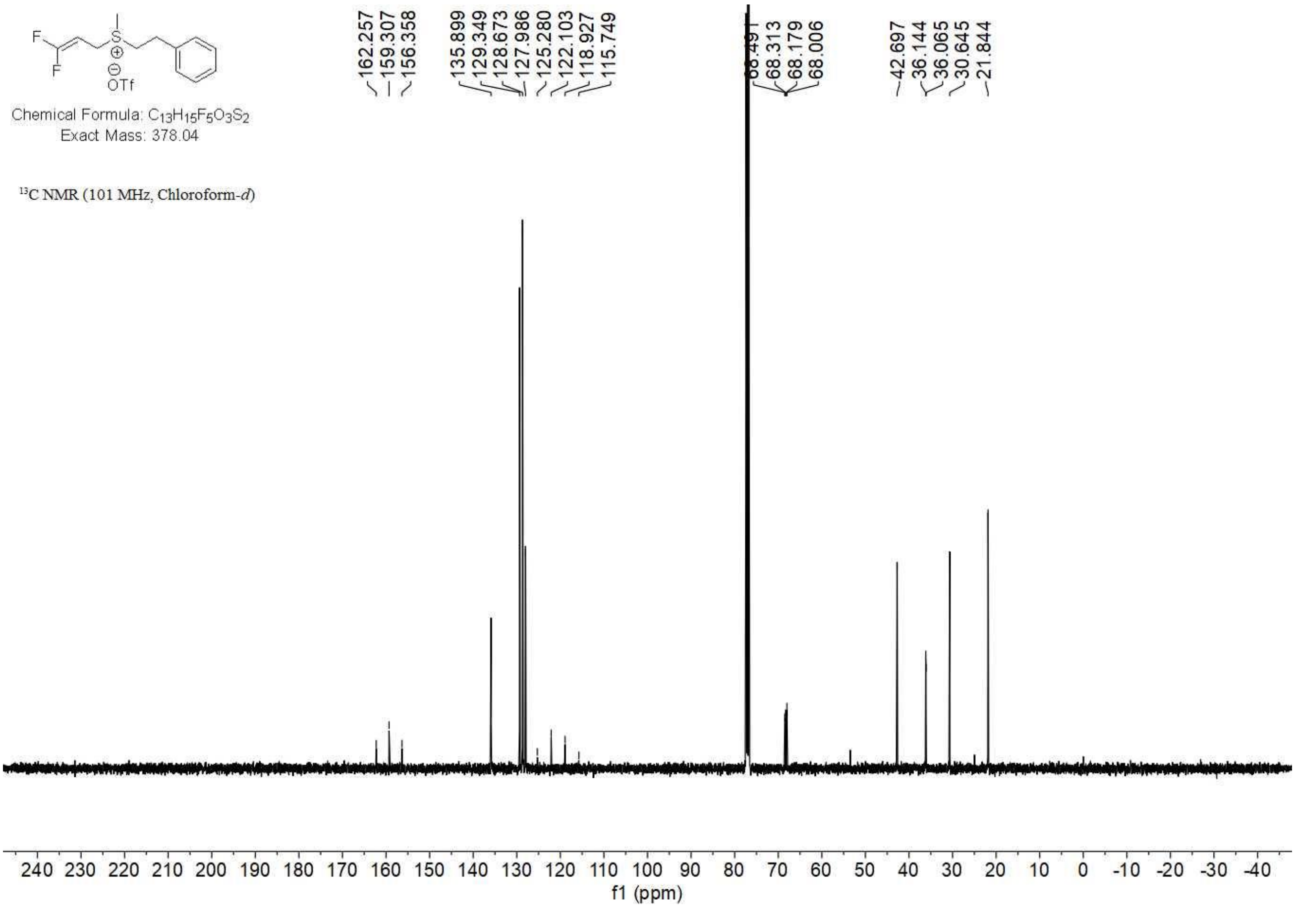
Exact Mass: 378.04

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



Chemical Formula: $C_{13}H_{15}F_5O_3S_2$
Exact Mass: 378.04

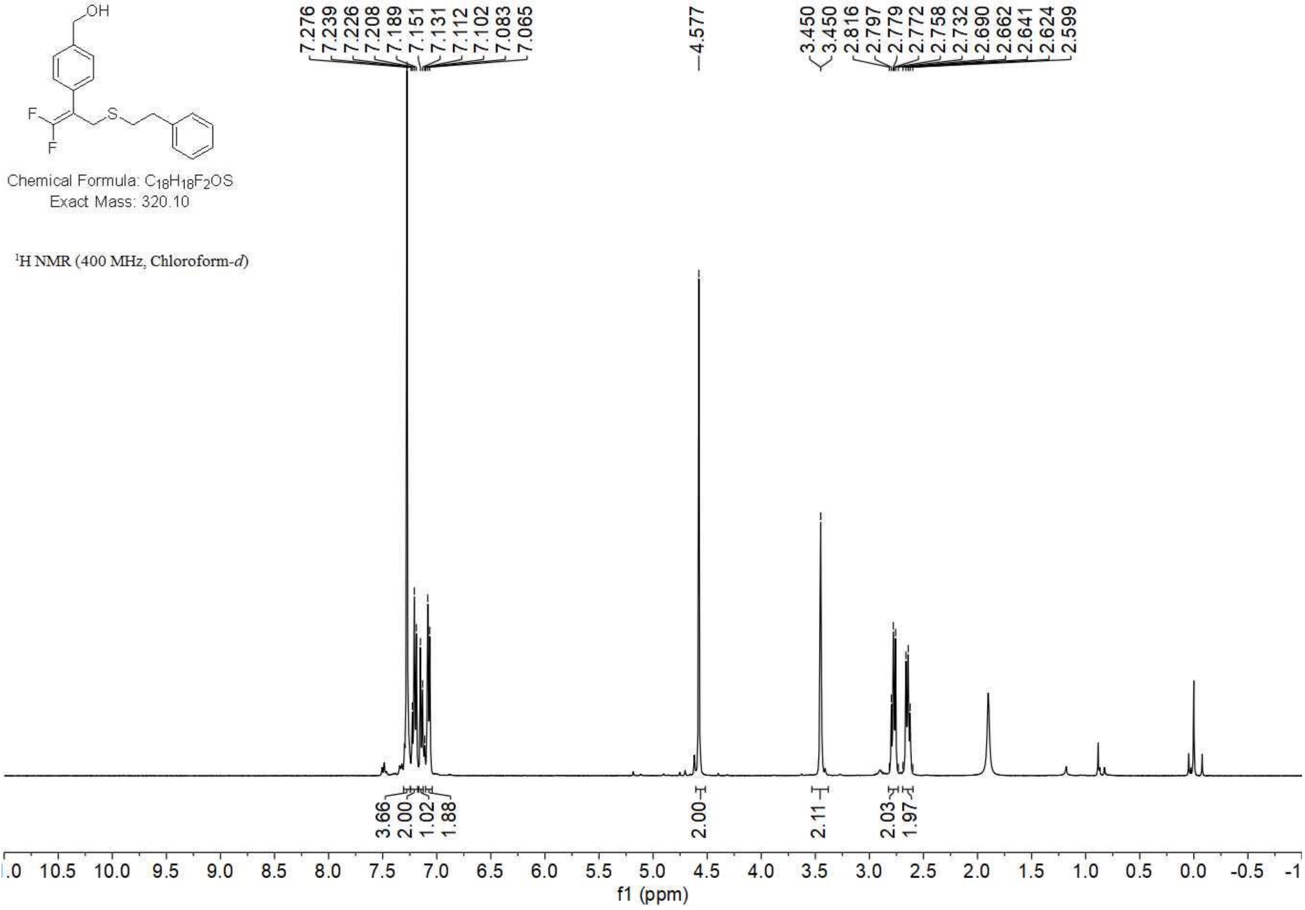
^{19}F NMR (376 MHz, Chloroform-*d*)

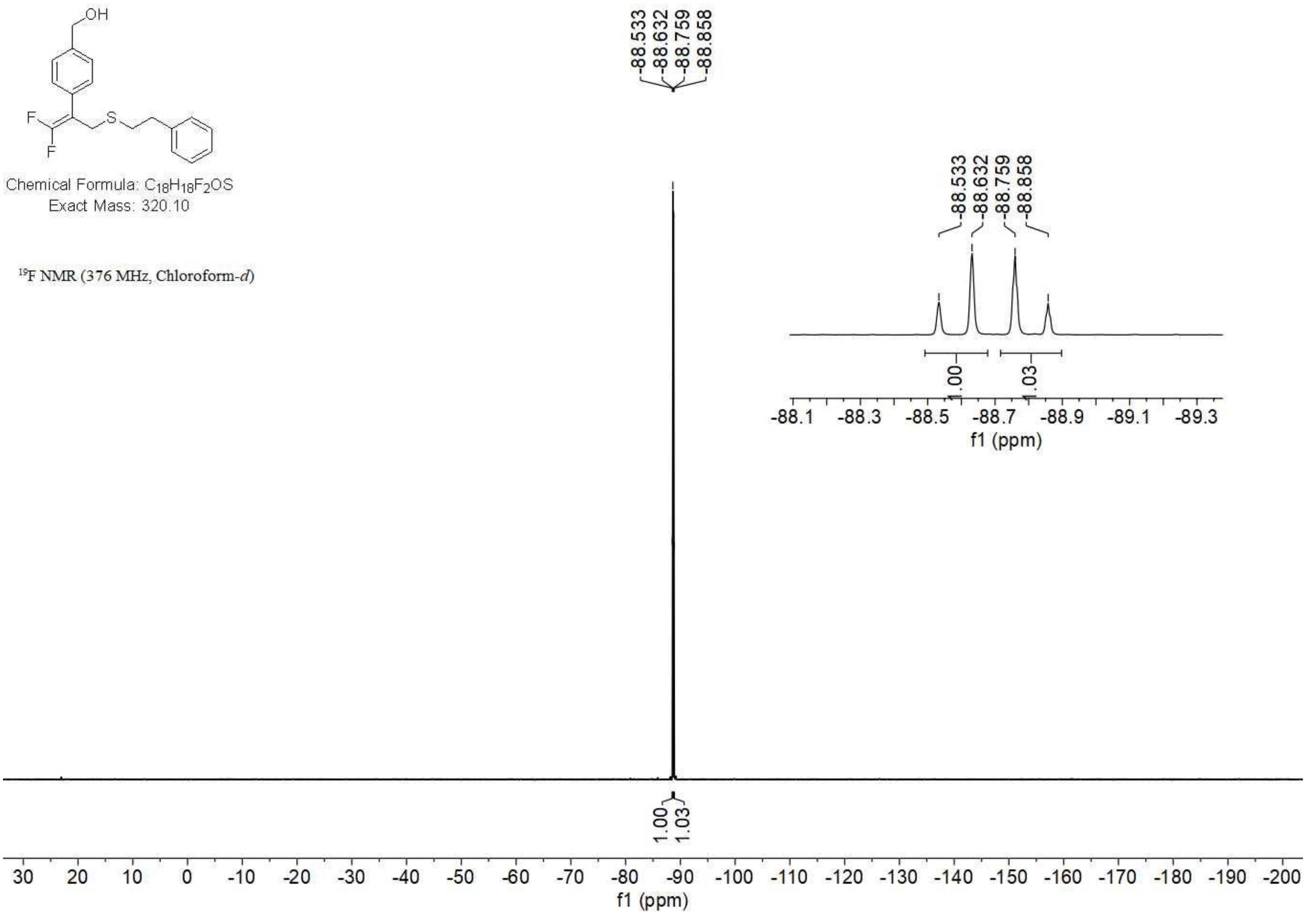


Chemical Formula: $C_{13}H_{15}F_5O_3S_2$
Exact Mass: 378.04

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

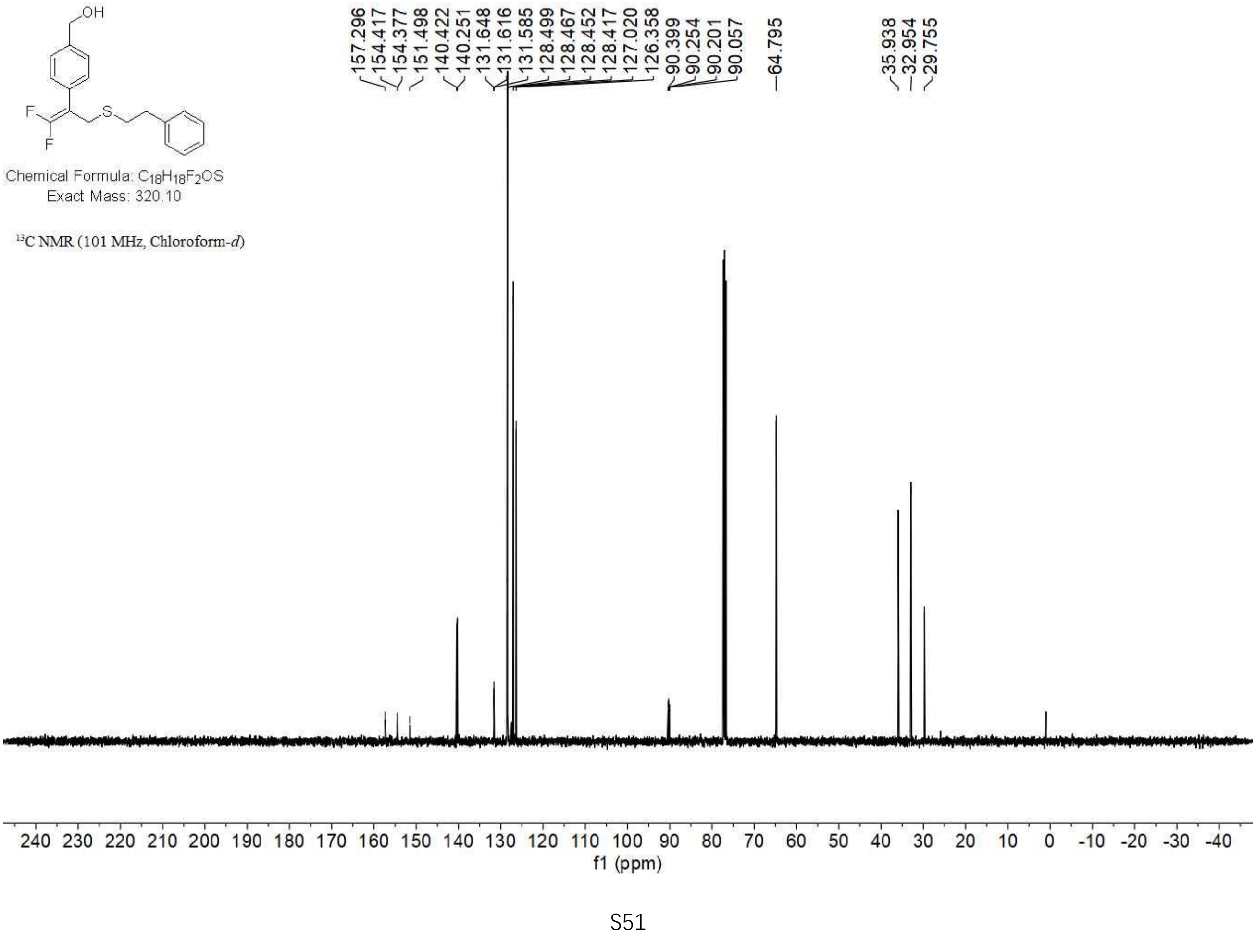
Spectra of s-2h-3





Chemical Formula: $C_{18}H_{18}F_2OS$
Exact Mass: 320.10

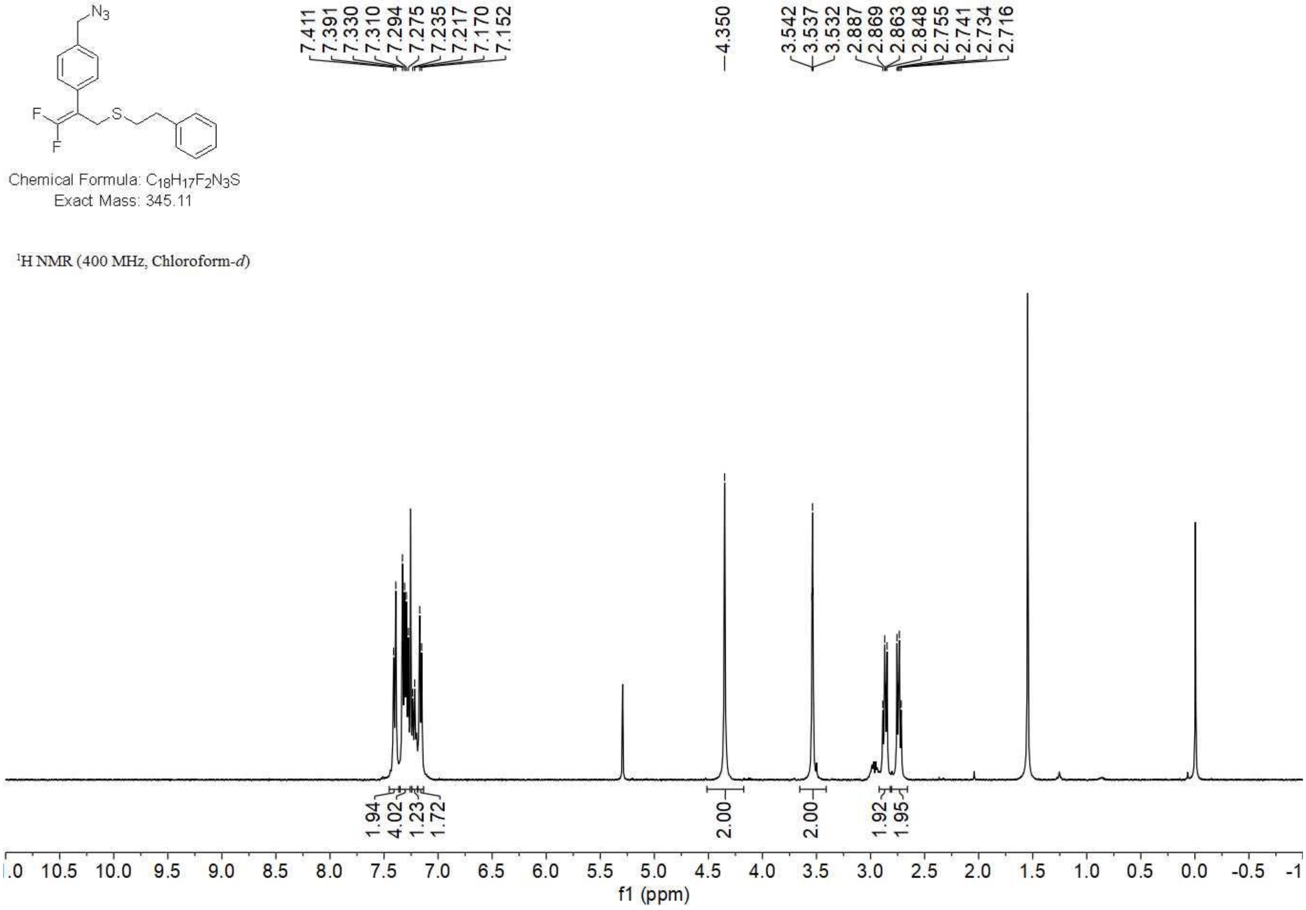
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{18}H_{18}F_2OS$
Exact Mass: 320.10

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

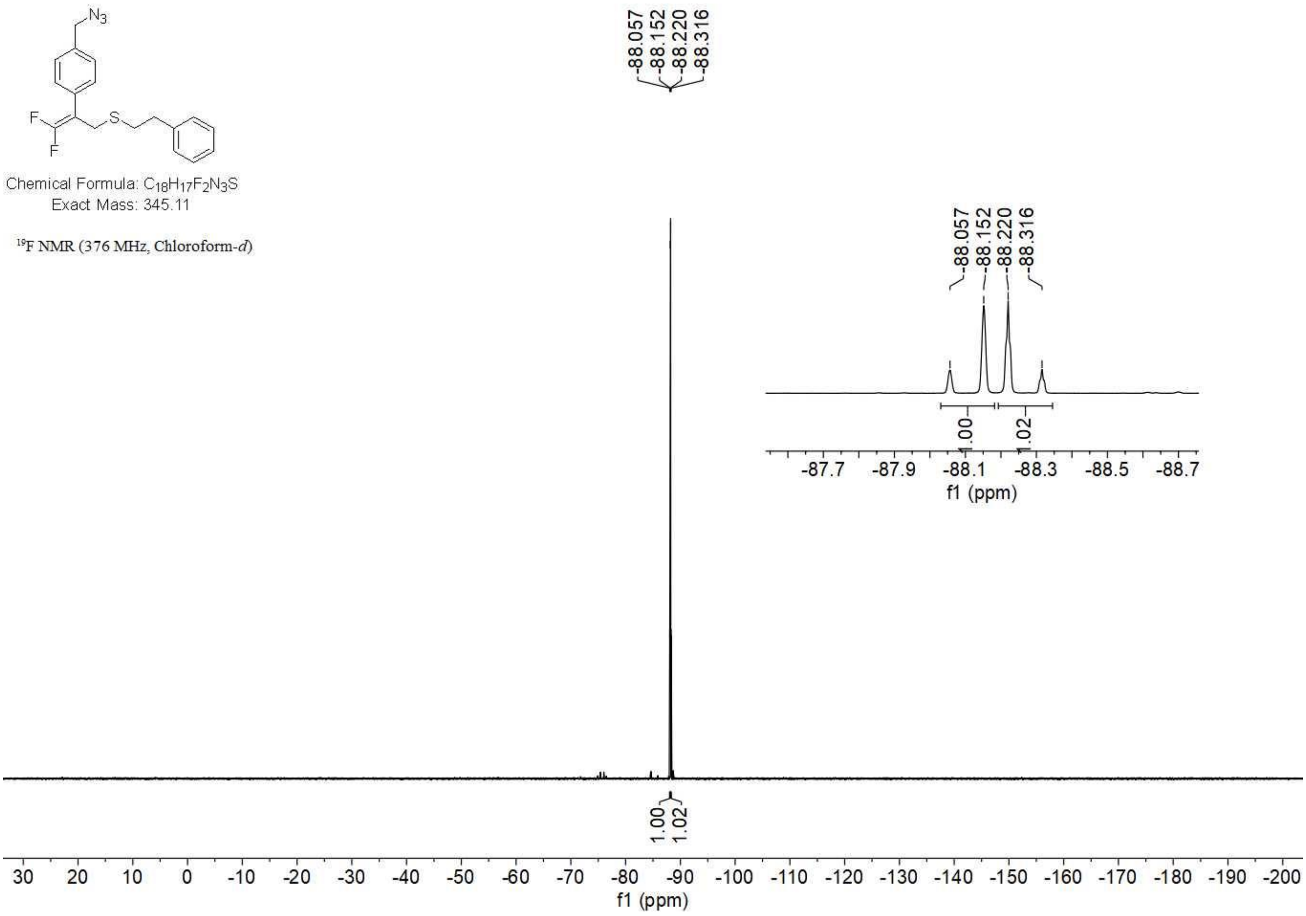
Spectra of s-2h-4



Chemical Formula: $C_{18}H_{17}F_2N_3S$

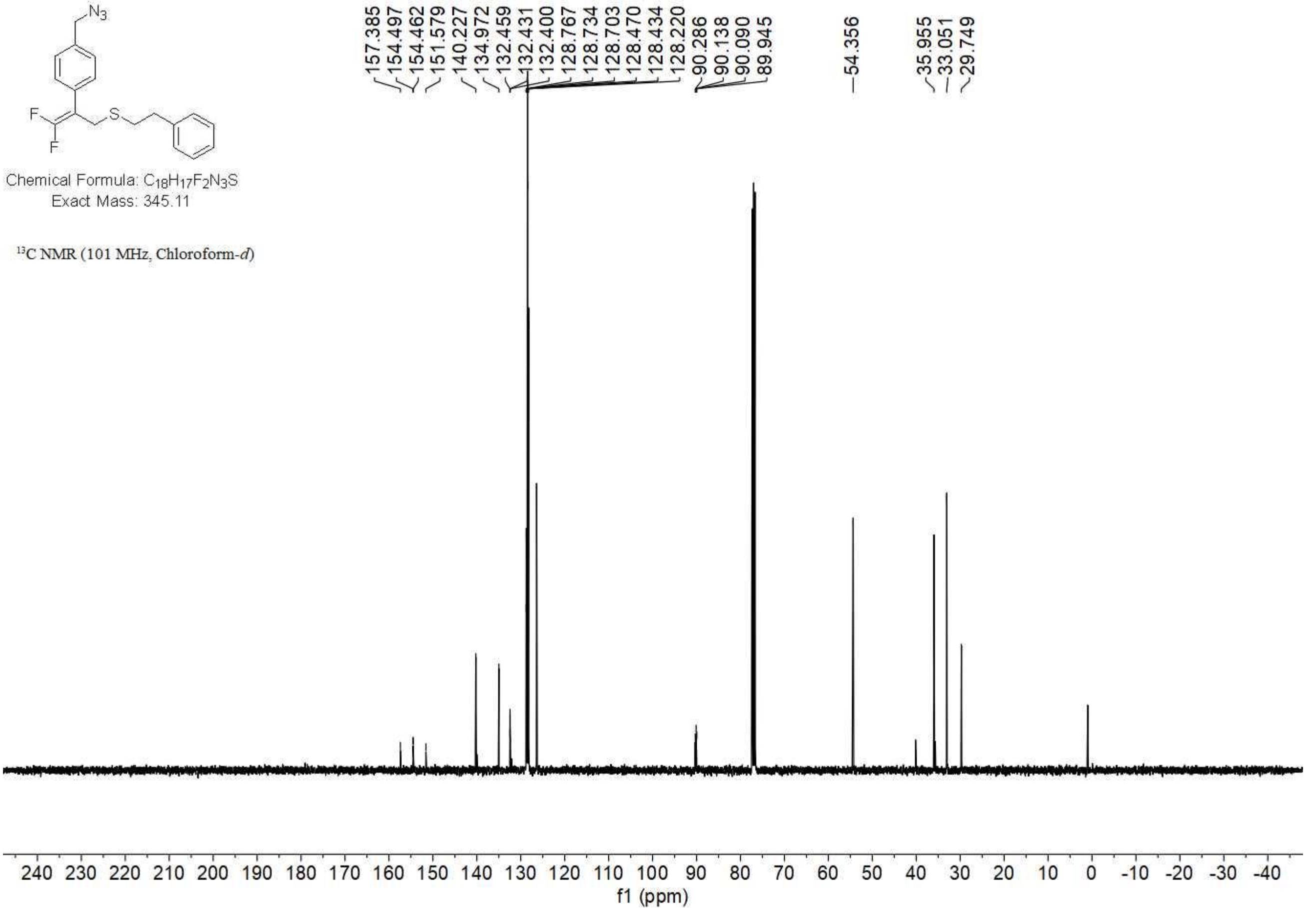
Exact Mass: 345.11

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



Chemical Formula: $C_{18}H_{17}F_2N_3S$
Exact Mass: 345.11

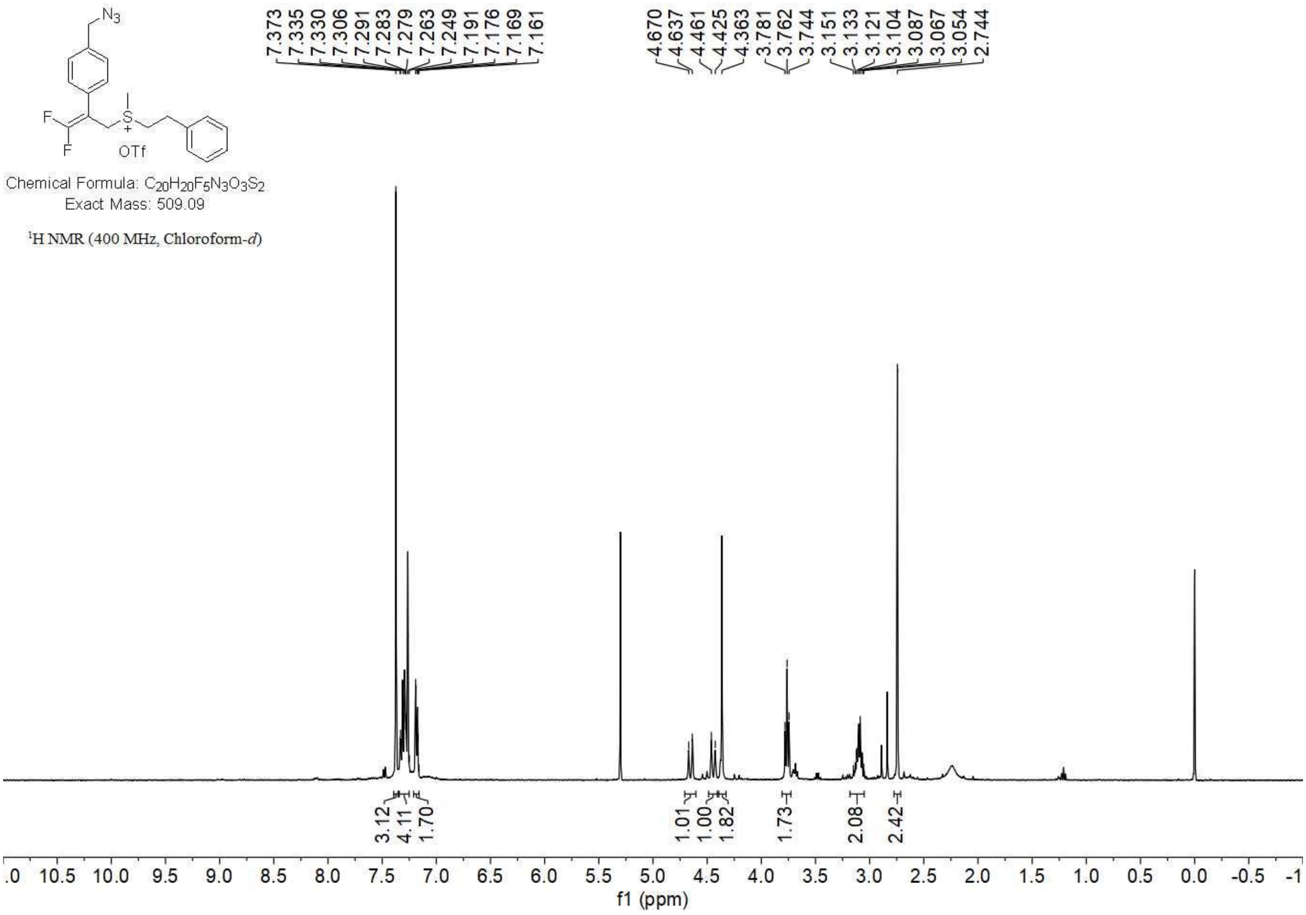
^{19}F NMR (376 MHz, Chloroform-*d*)

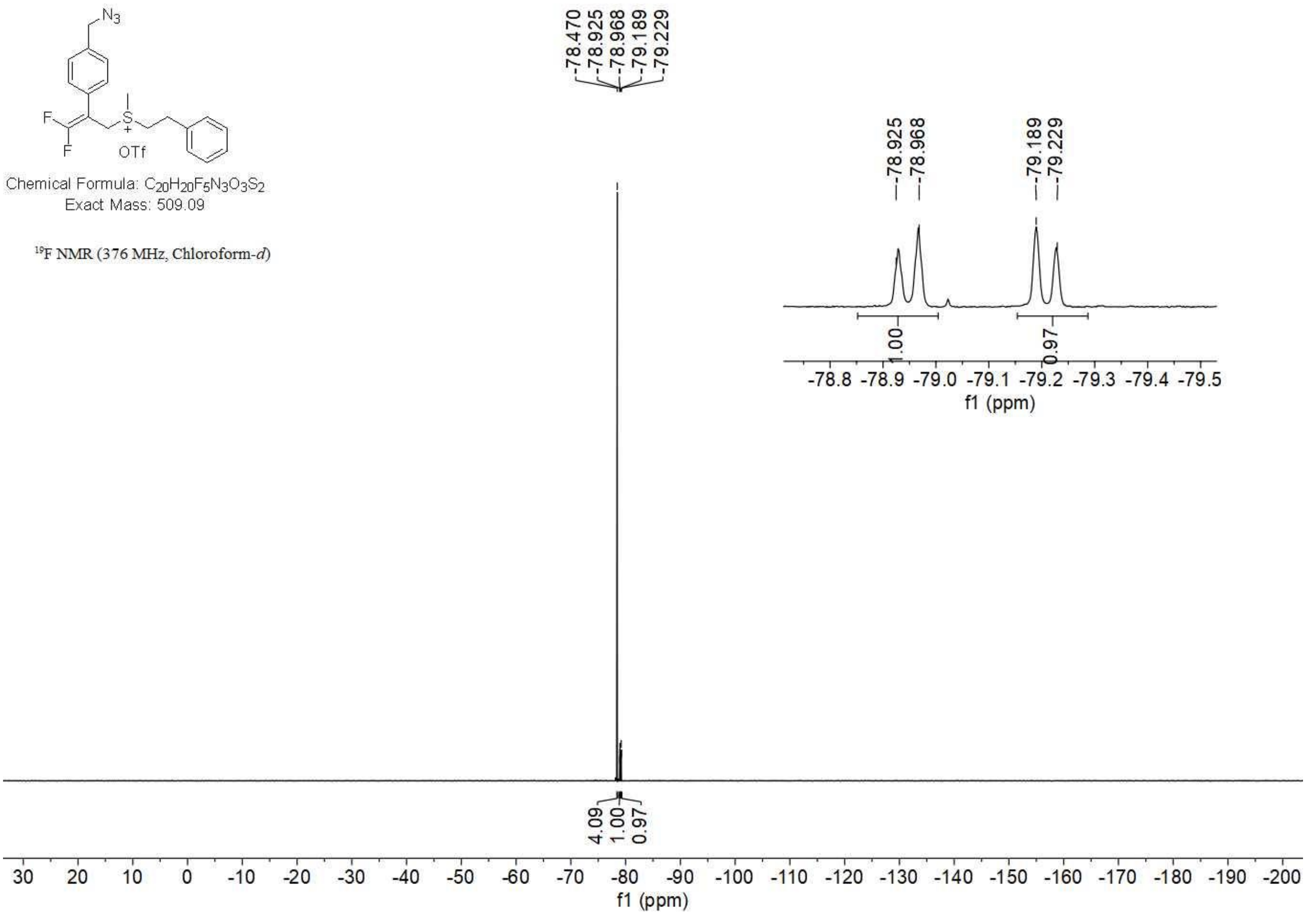


Chemical Formula: $C_{18}H_{17}F_2N_3S$
Exact Mass: 345.11

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

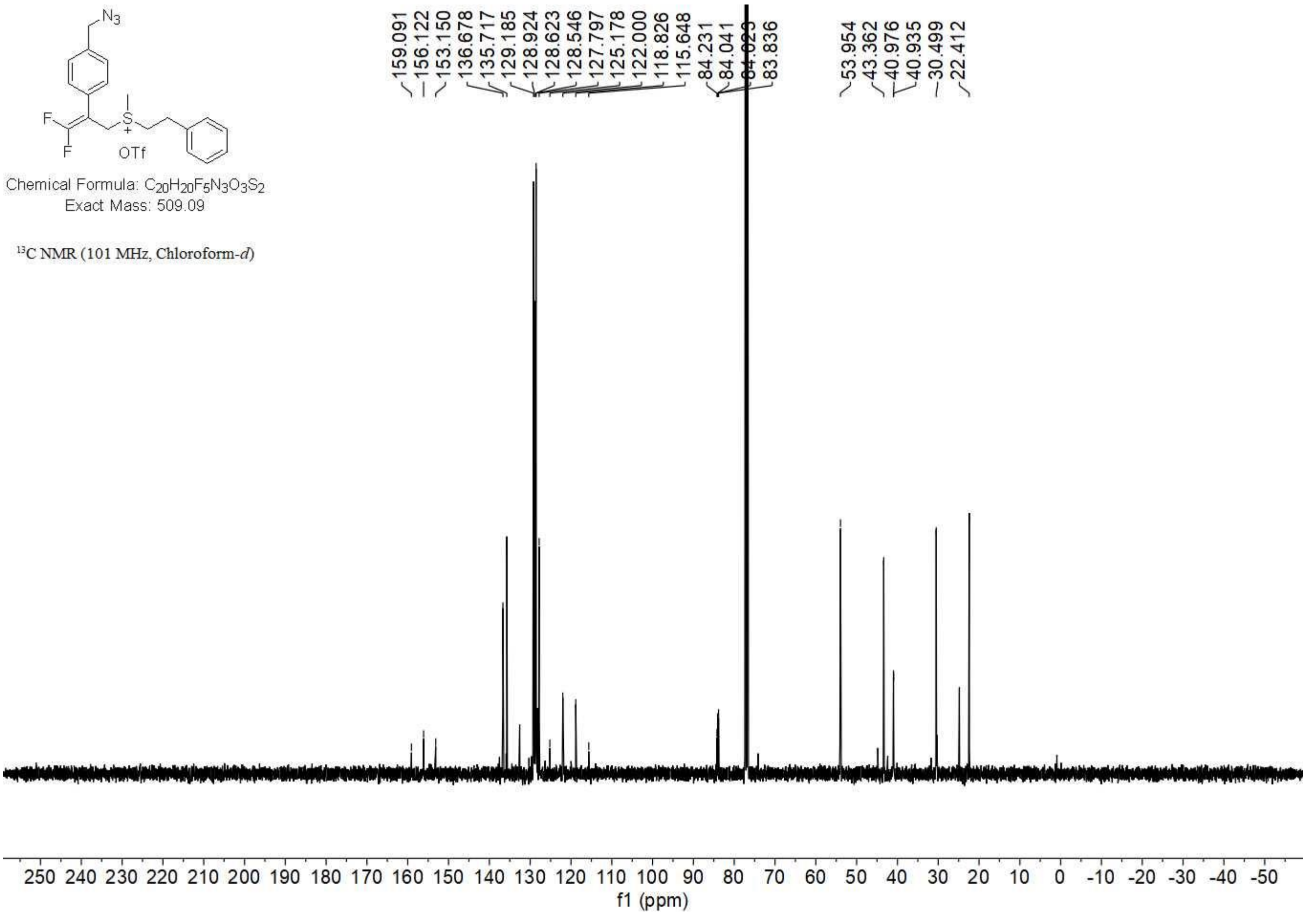
Spectra of 2h





Chemical Formula: $C_{20}H_{20}F_5N_3O_3S_2$
Exact Mass: 509.09

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

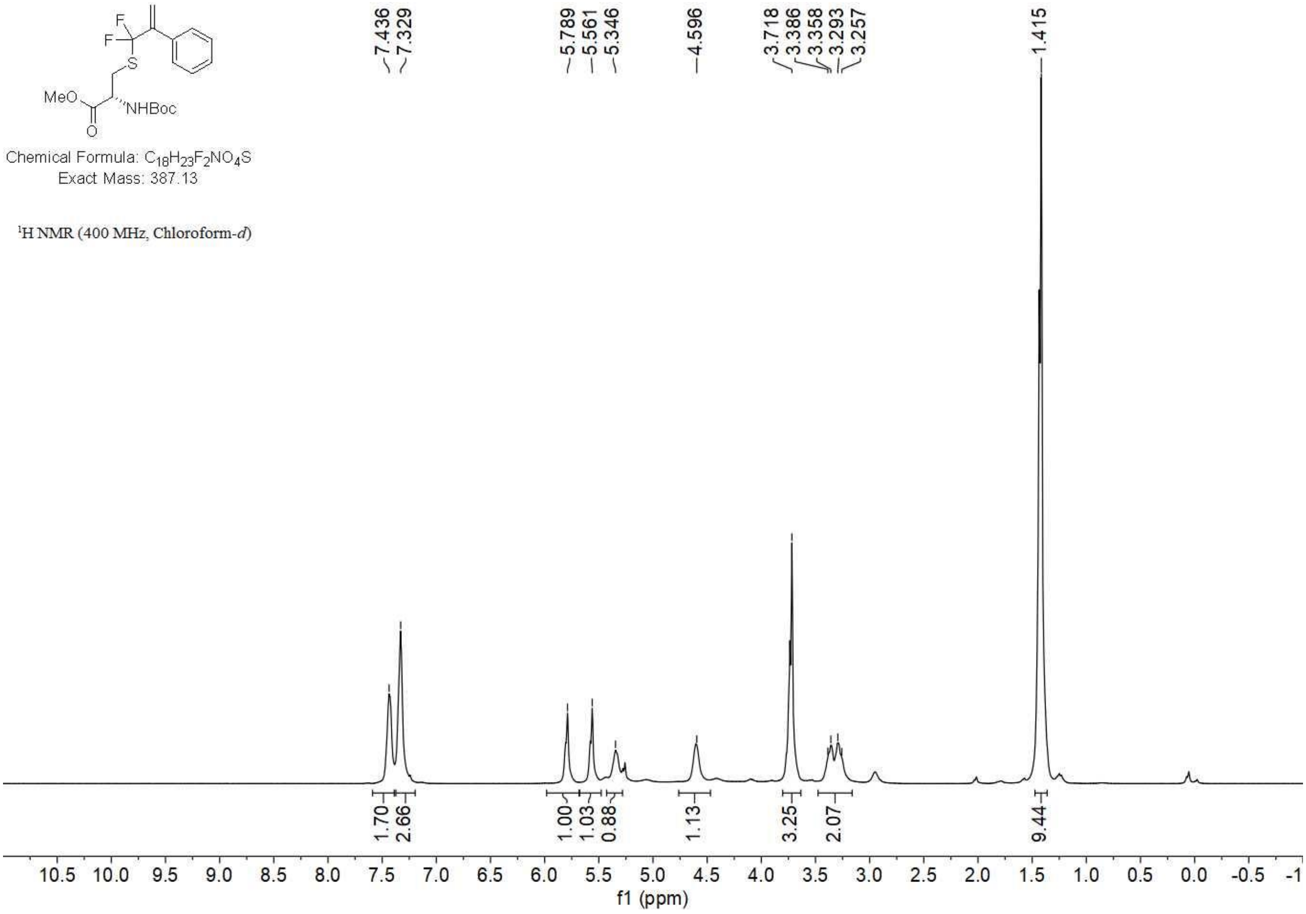


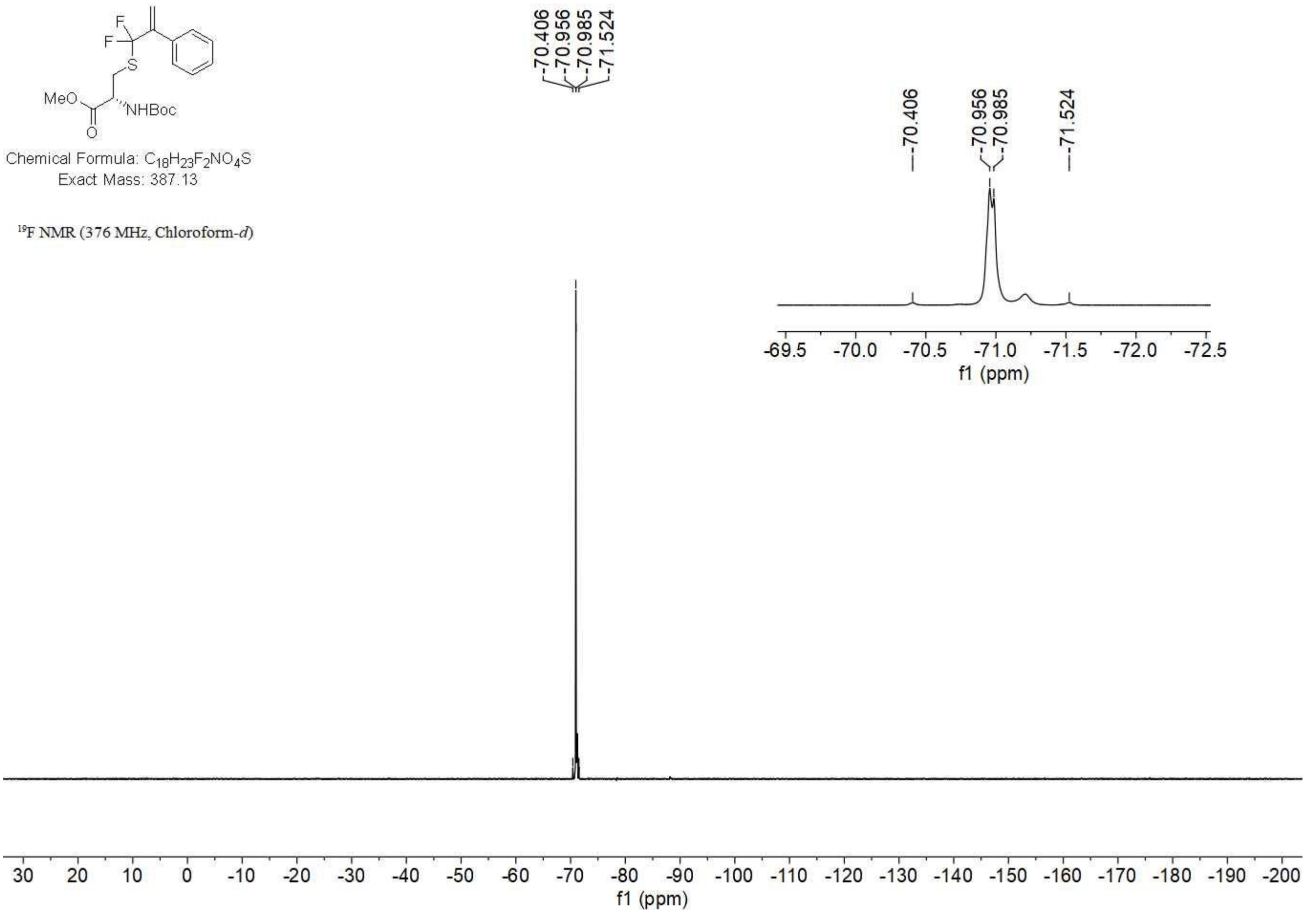
Chemical Formula: $C_{20}H_{20}F_5N_3O_3S_2$
Exact Mass: 509.09

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

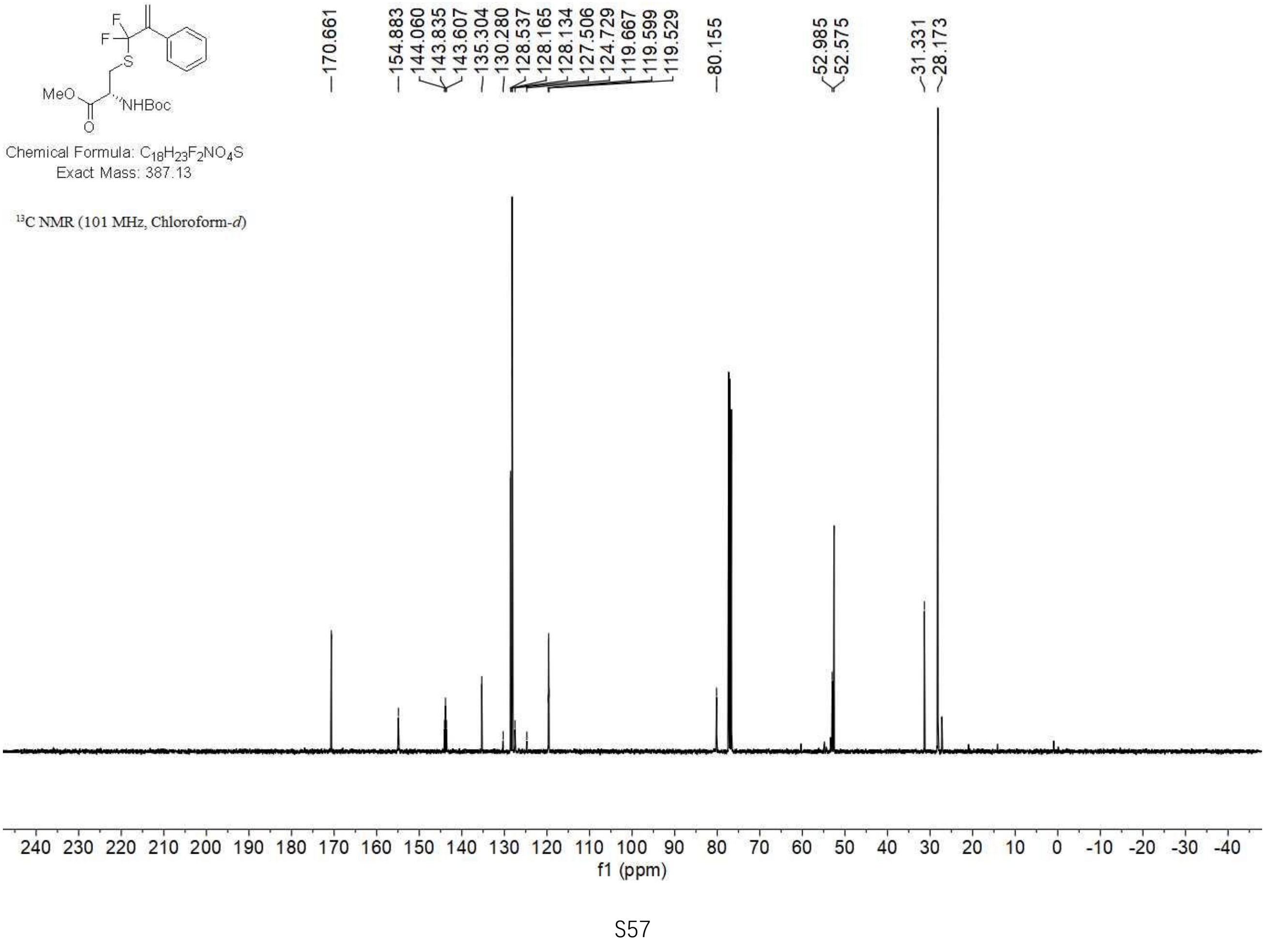
9.2 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for Compounds 3b-p

Spectra of 3b



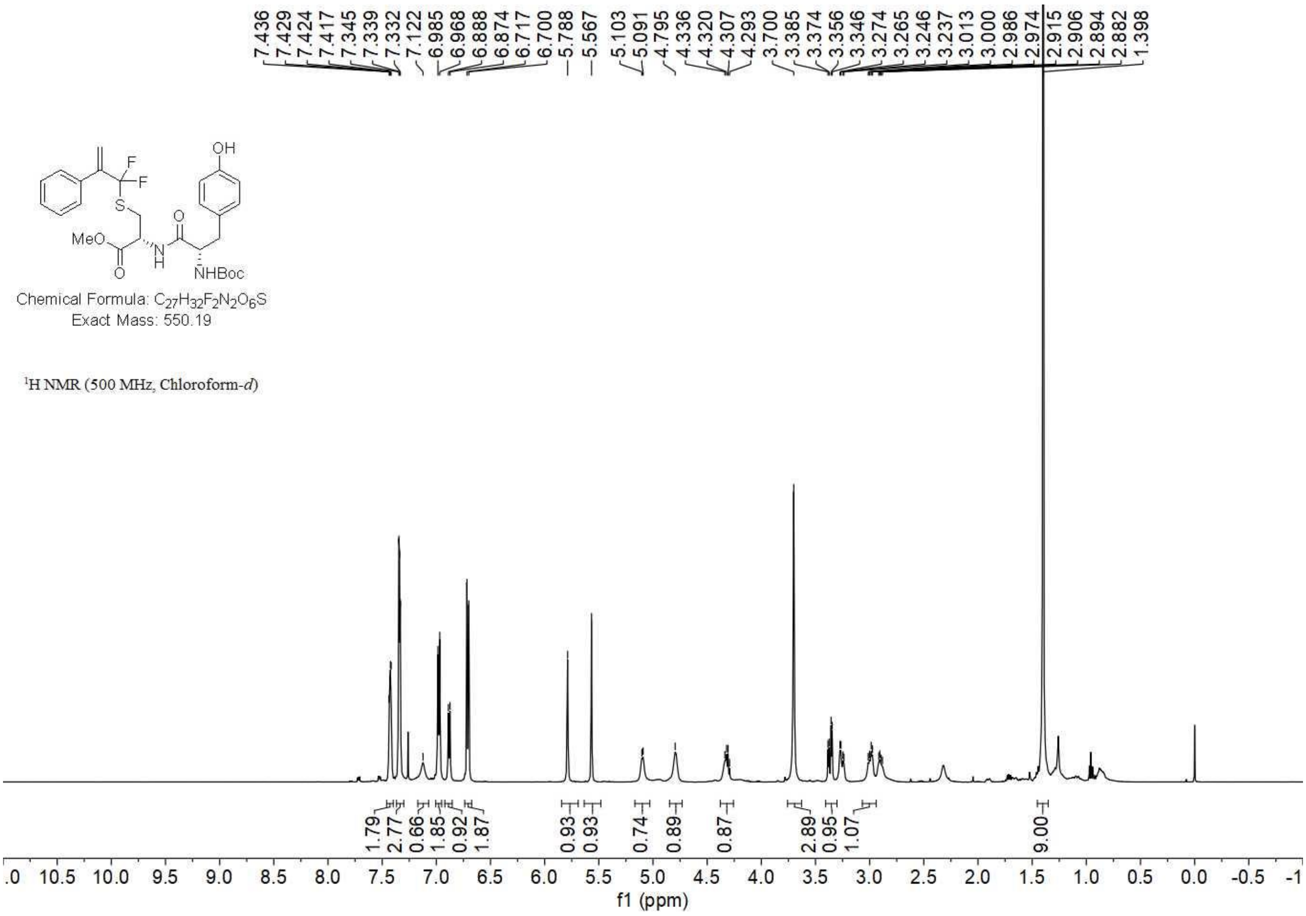

Chemical Formula: $C_{18}H_{23}F_2NO_4S$
Exact Mass: 387.13

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


Chemical Formula: $C_{18}H_{23}F_2NO_4S$
Exact Mass: 387.13

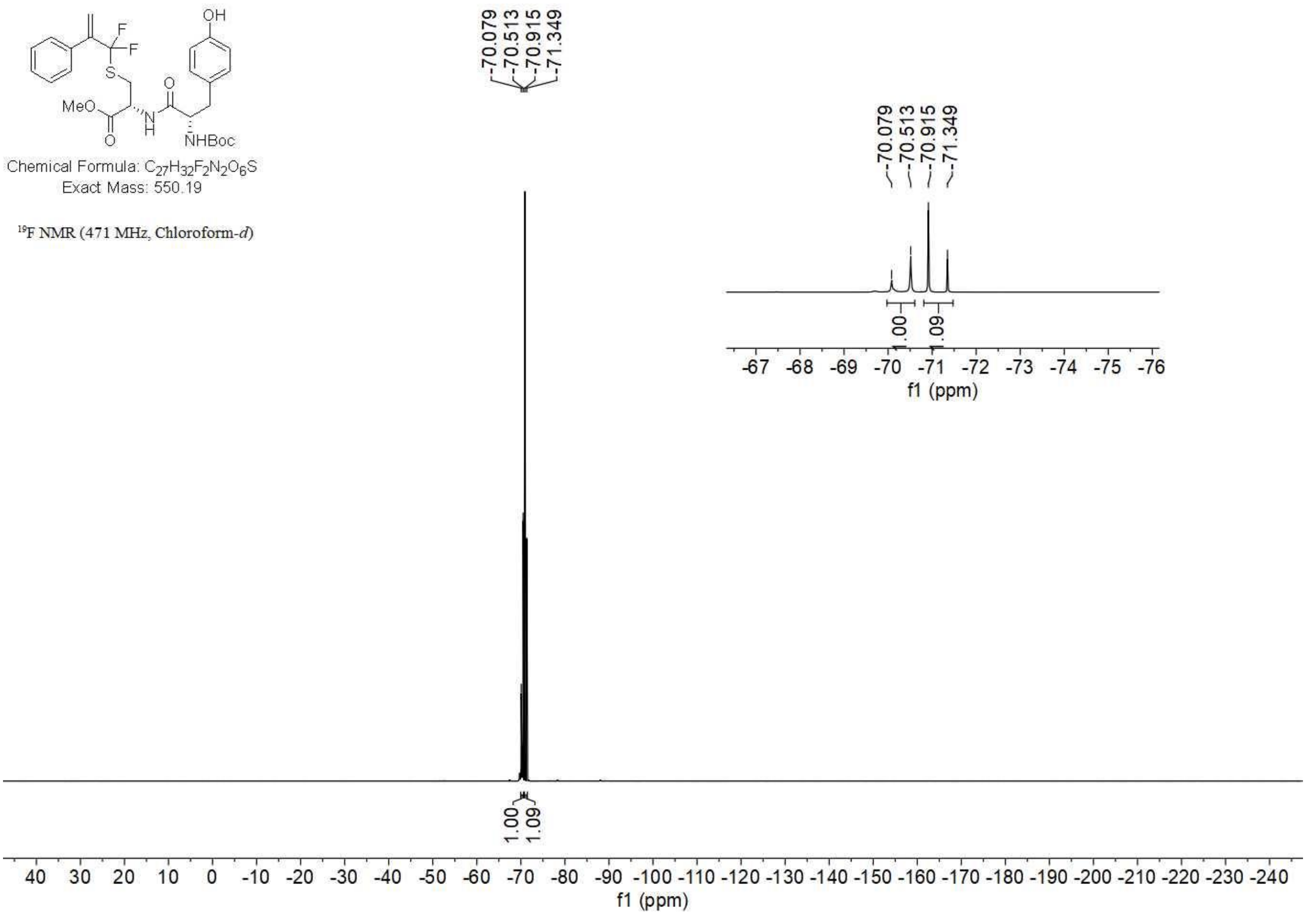
^{13}C NMR (101 MHz, Chloroform-*d*)

Spectra of 3c



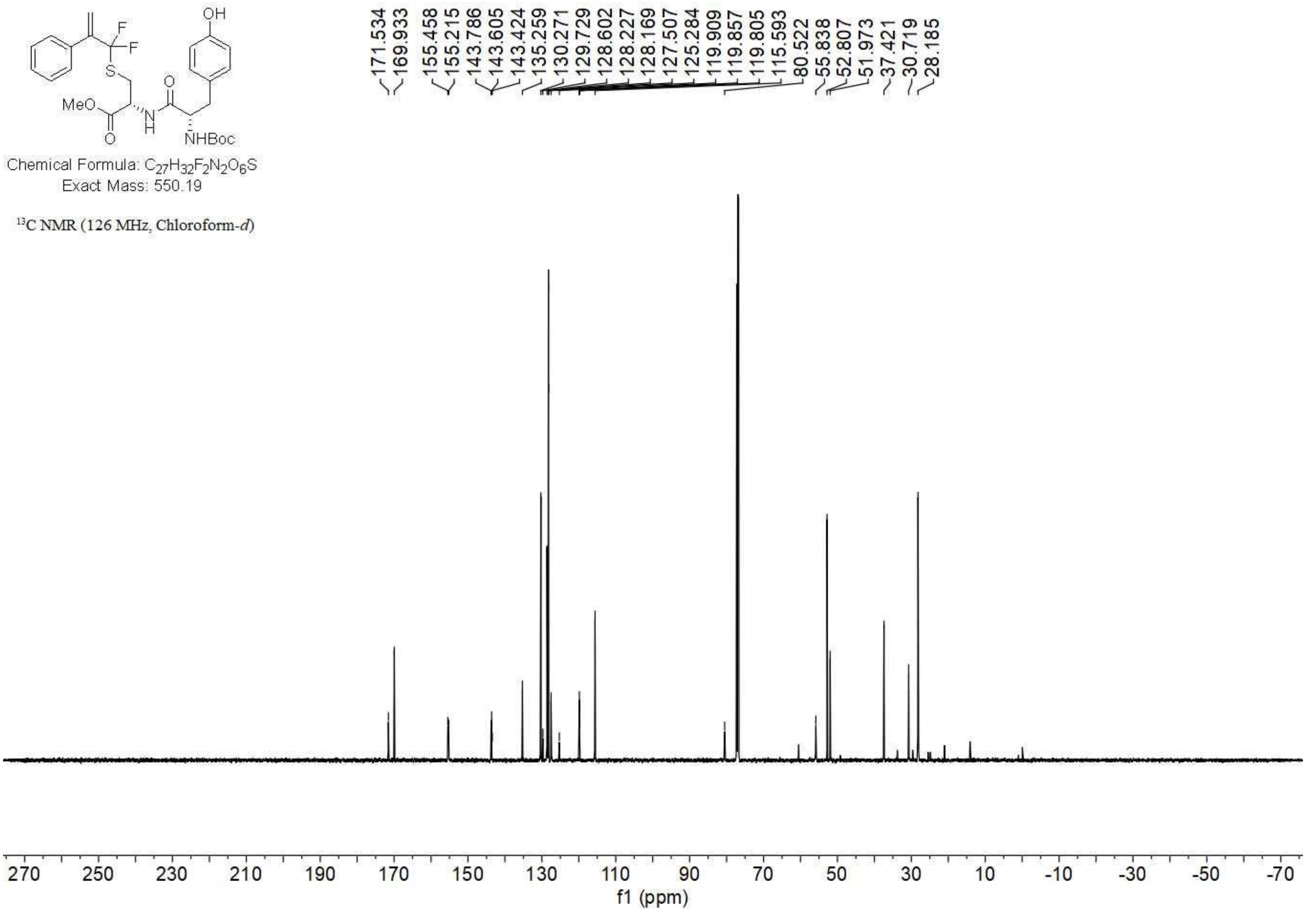
Chemical Formula: $C_{27}H_{32}F_2N_2O_6S$
Exact Mass: 550.19

^{1}H NMR (500 MHz, Chloroform-*d*)



Chemical Formula: $C_{27}H_{32}F_2N_2O_6S$
Exact Mass: 550.19

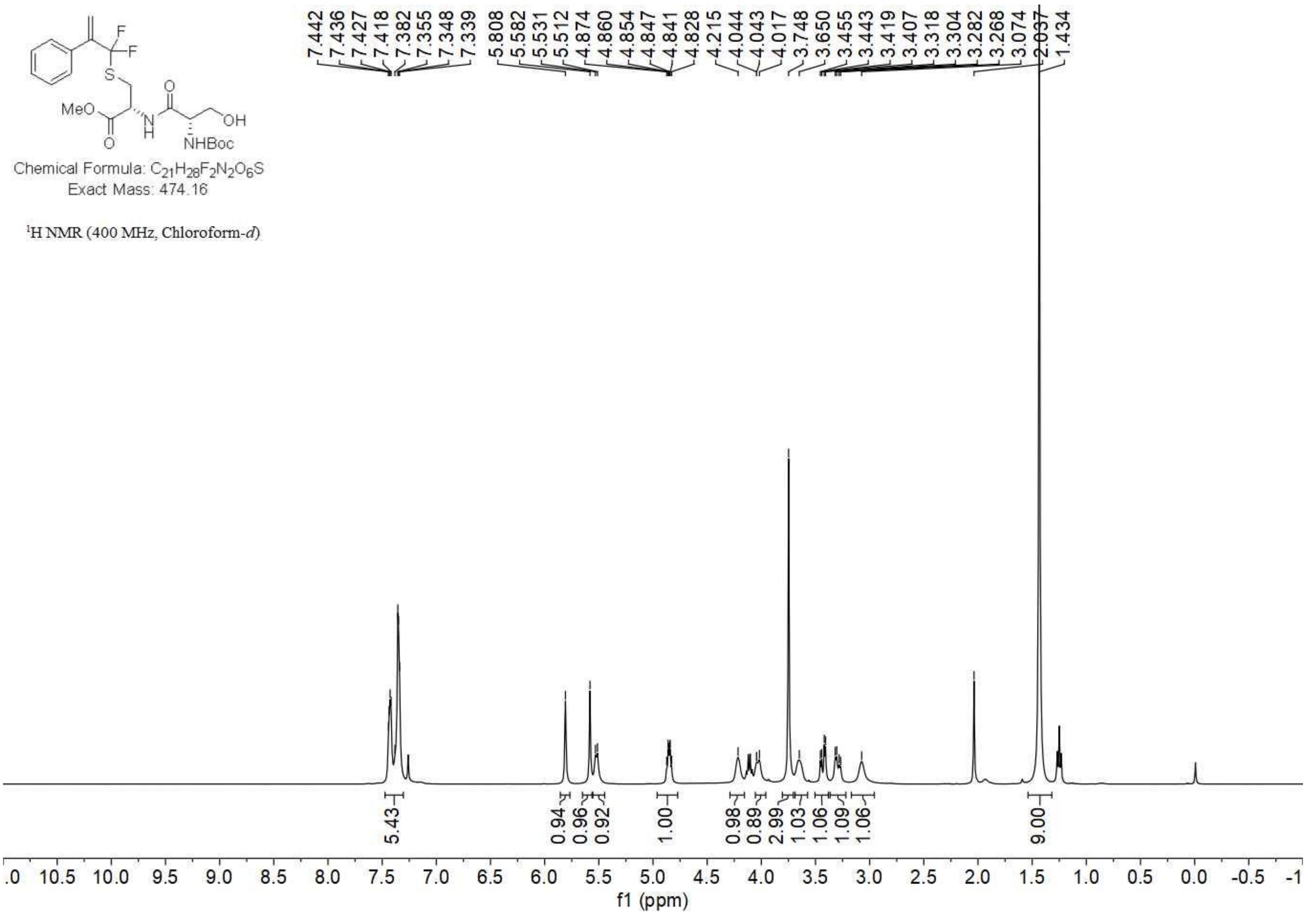
^{19}F NMR (471 MHz, Chloroform-*d*)

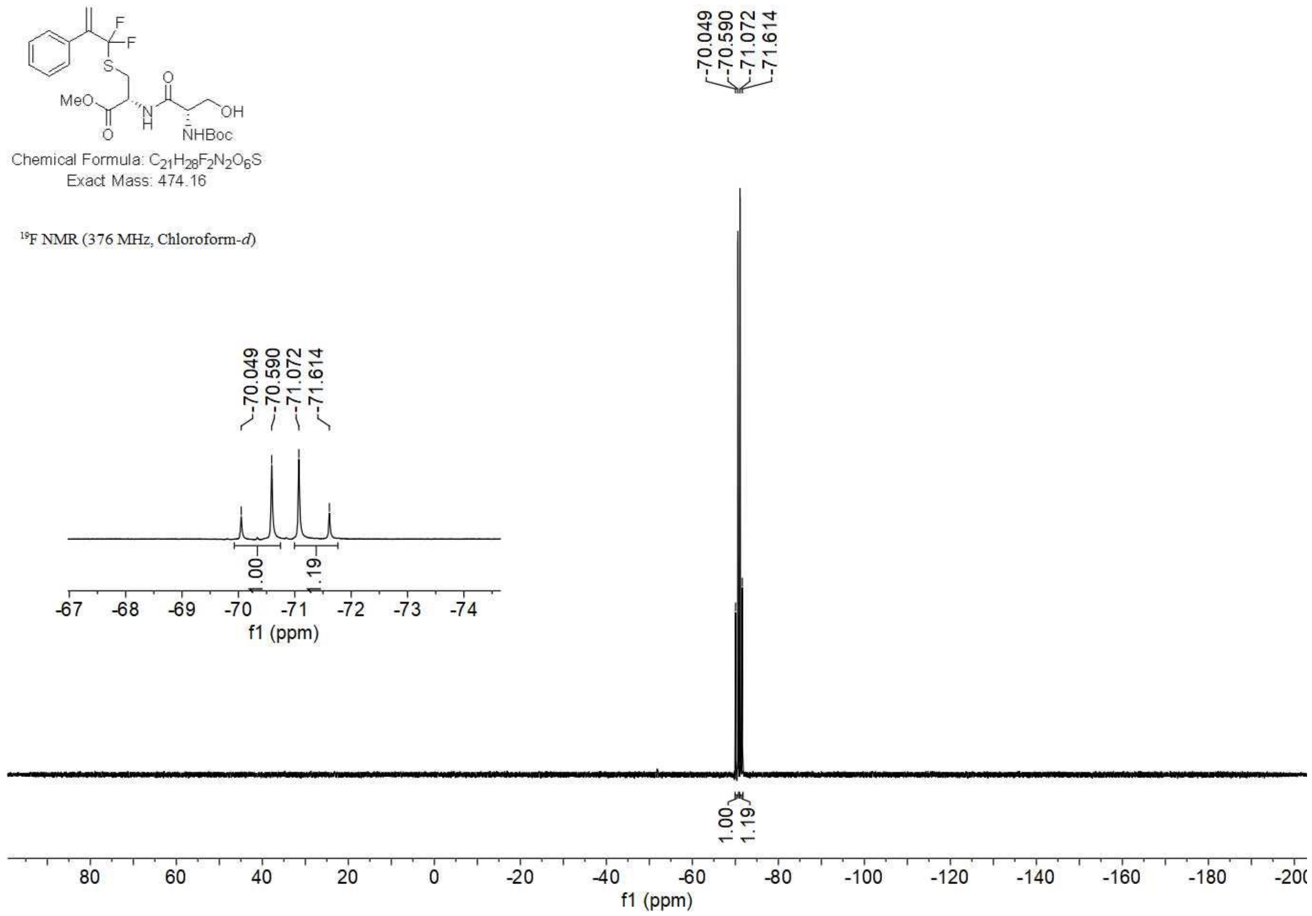


Chemical Formula: $C_{27}H_{32}F_2N_2O_6S$
Exact Mass: 550.19

^{13}C NMR (126 MHz, Chloroform-*d*)

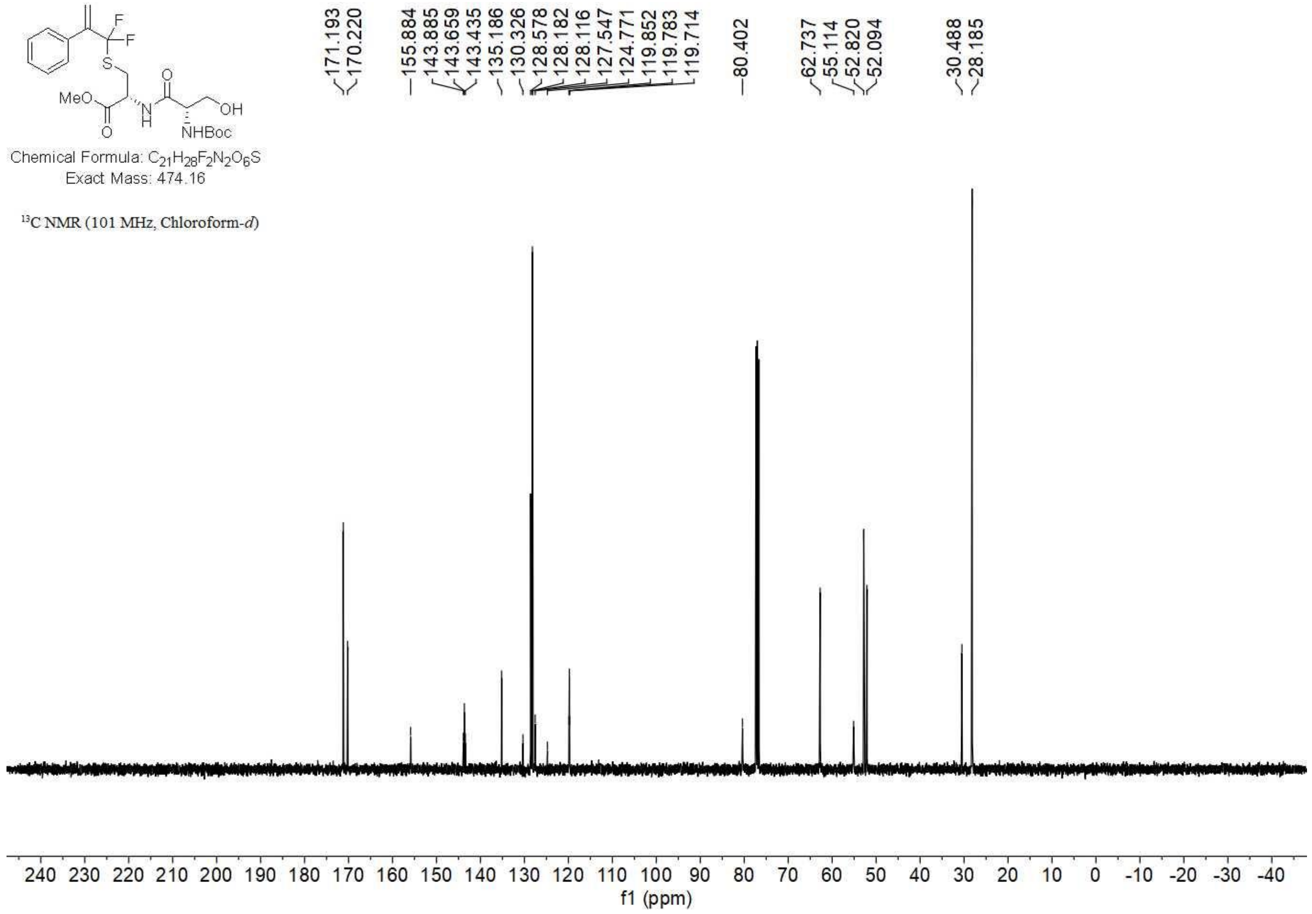
Spectra of 3d





Chemical Formula: $C_{21}H_{28}F_2N_2O_6S$
Exact Mass: 474.16

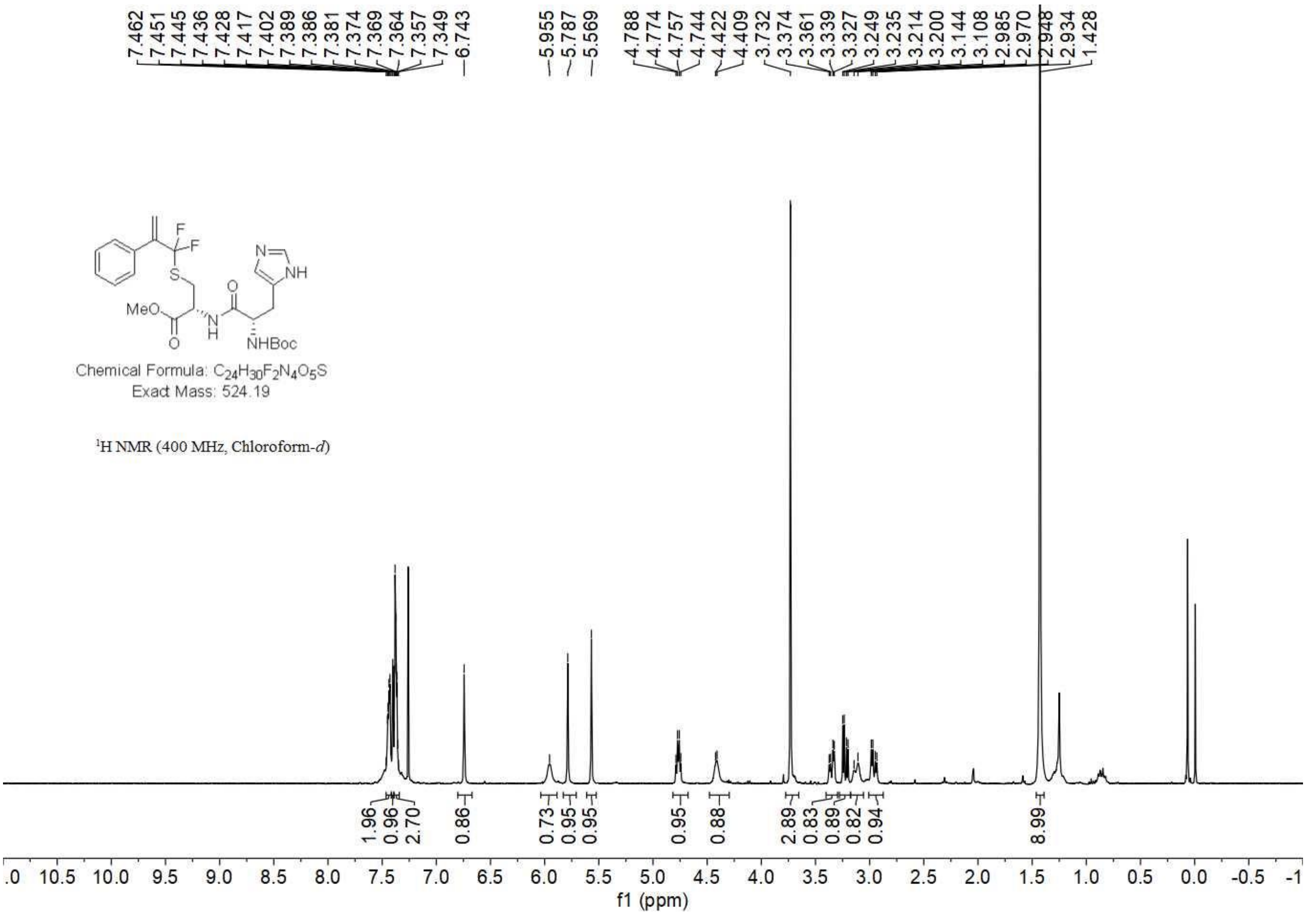
^{19}F NMR (376 MHz, Chloroform-*d*)

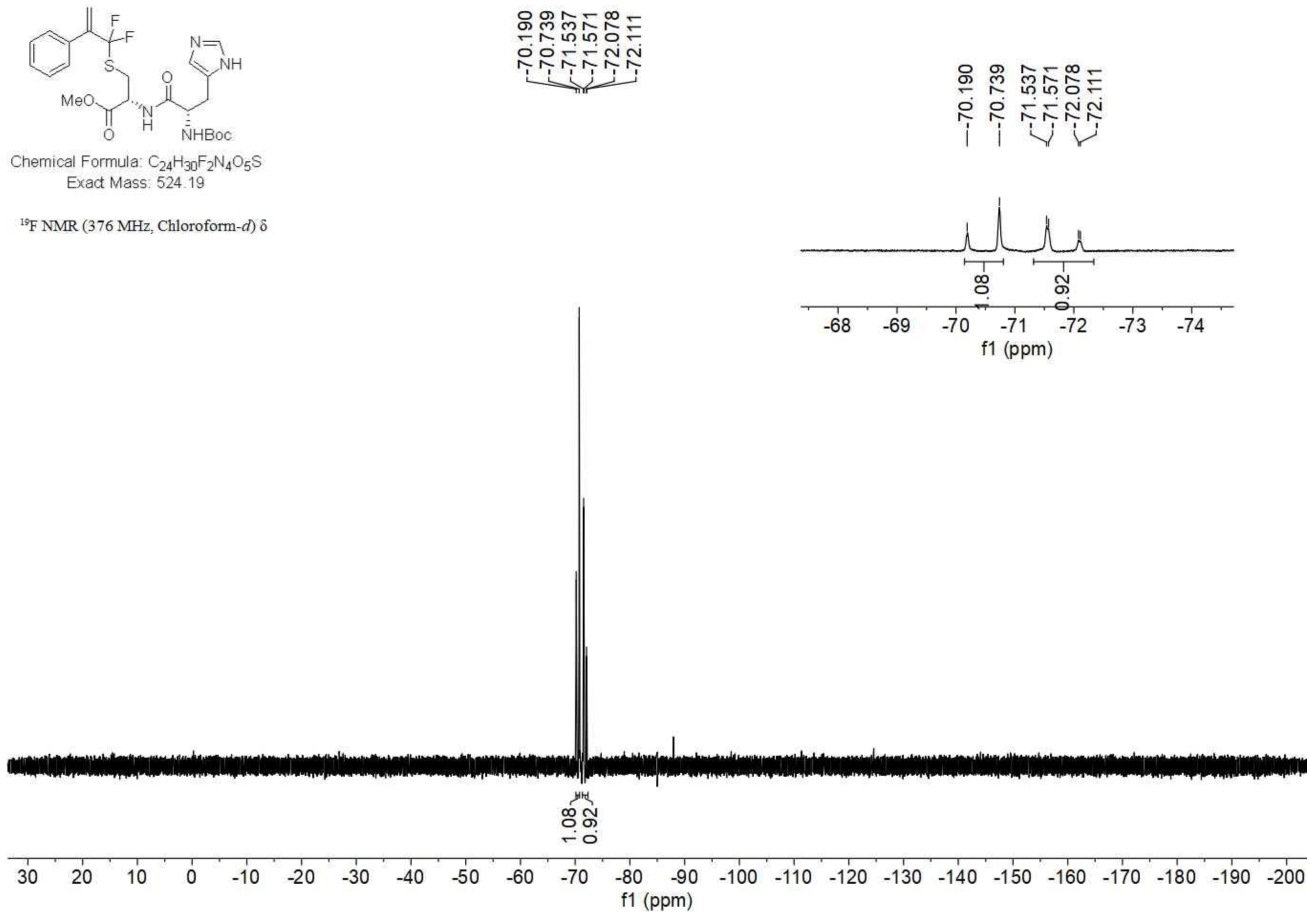


Chemical Formula: $C_{21}H_{28}F_2N_2O_6S$
Exact Mass: 474.16

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

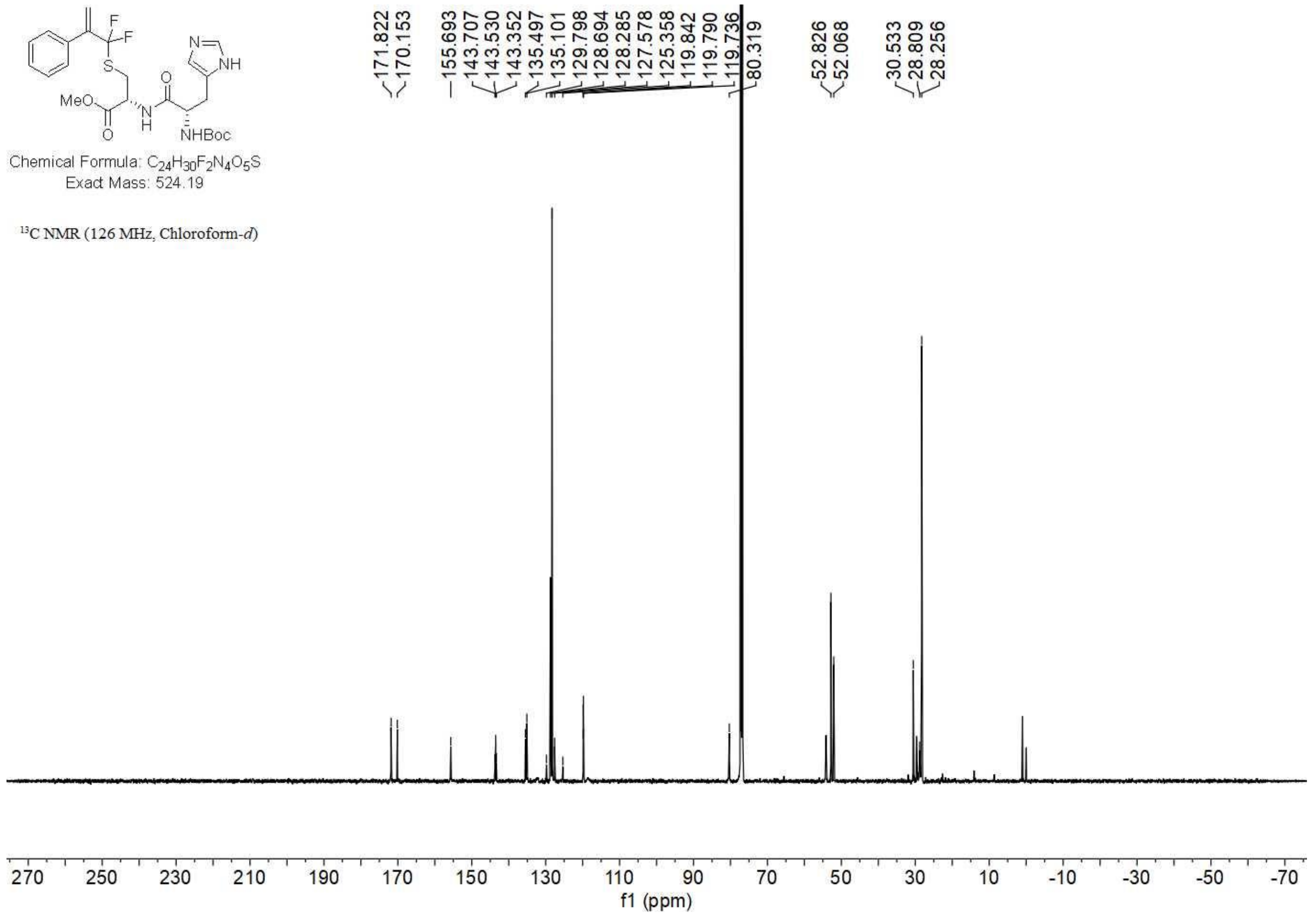
Spectra of 3e





Chemical Formula: $C_{24}H_{30}F_2N_4O_5S$
Exact Mass: 524.19

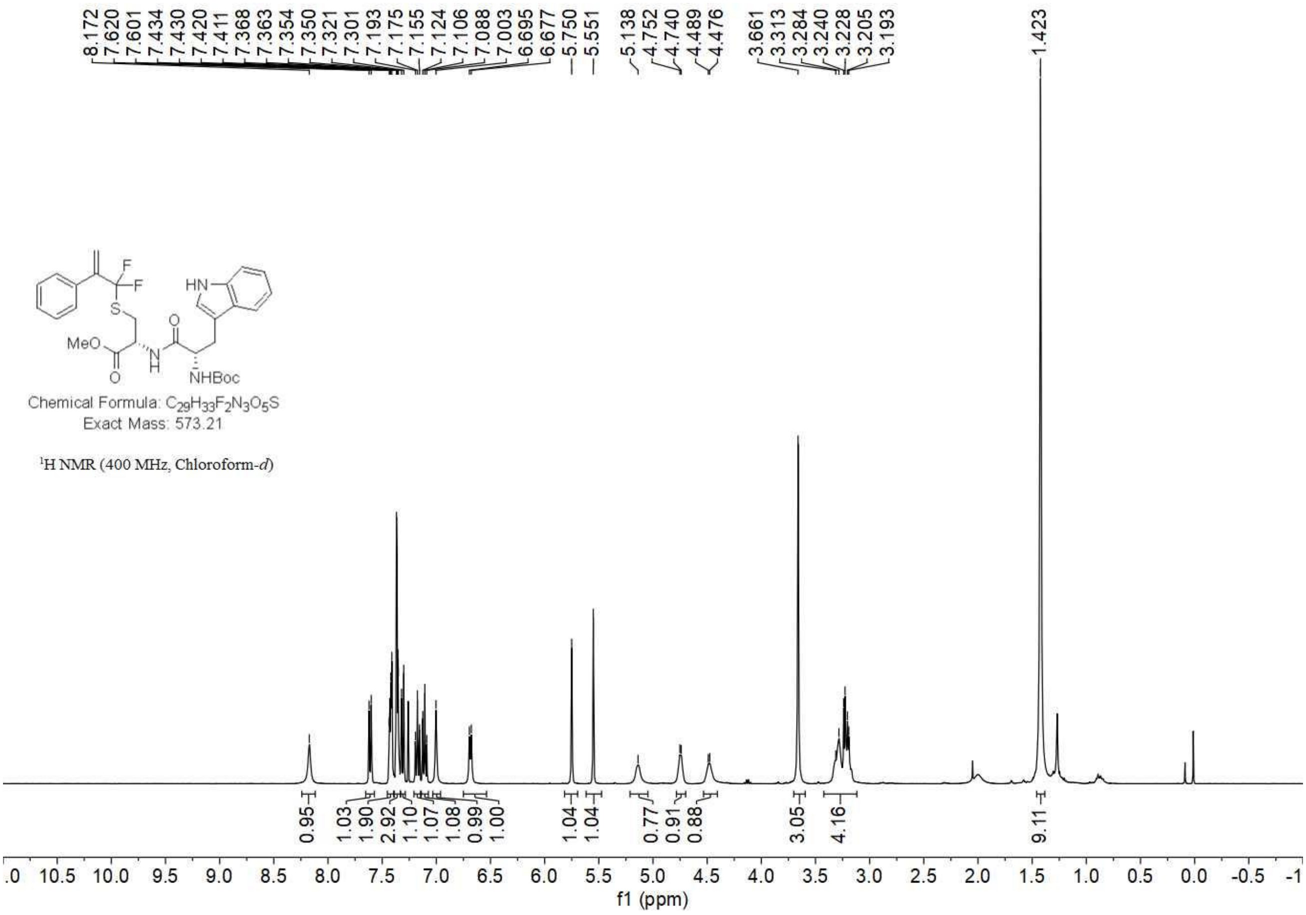
^{19}F NMR (376 MHz, Chloroform-*d*) δ

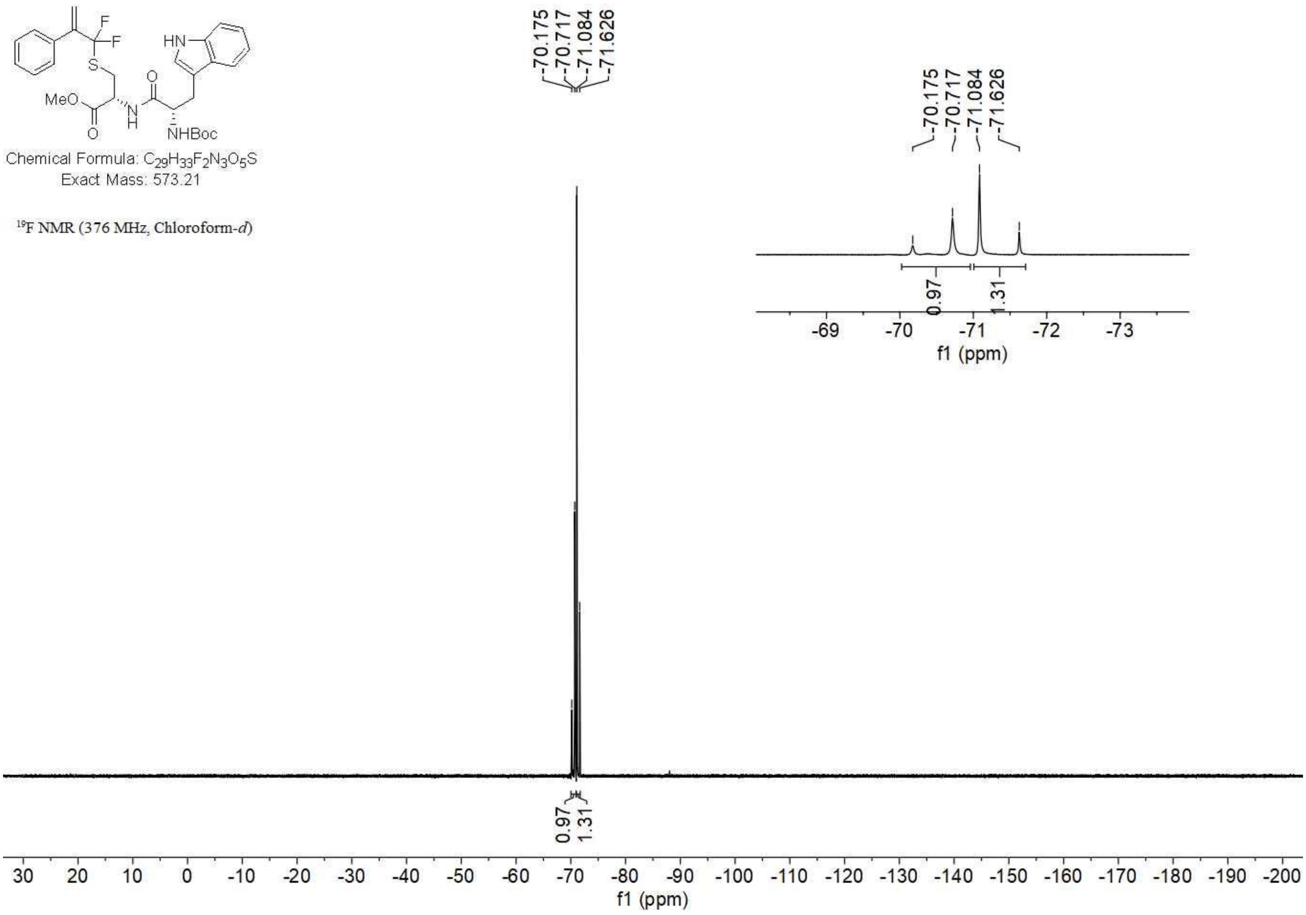


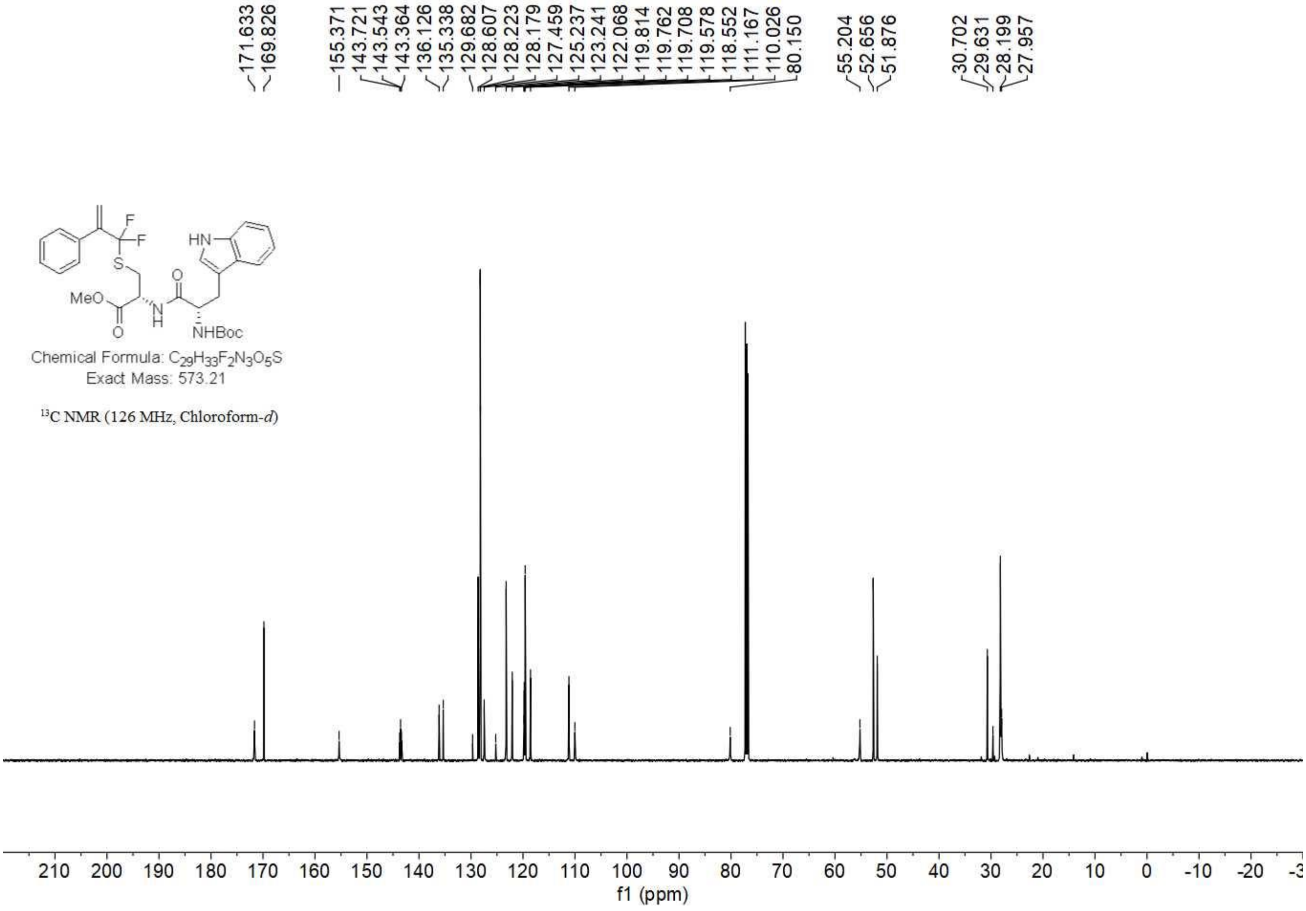
Chemical Formula: $C_{24}H_{30}F_2N_4O_5S$
Exact Mass: 524.19

^{13}C NMR (126 MHz, Chloroform-*d*)

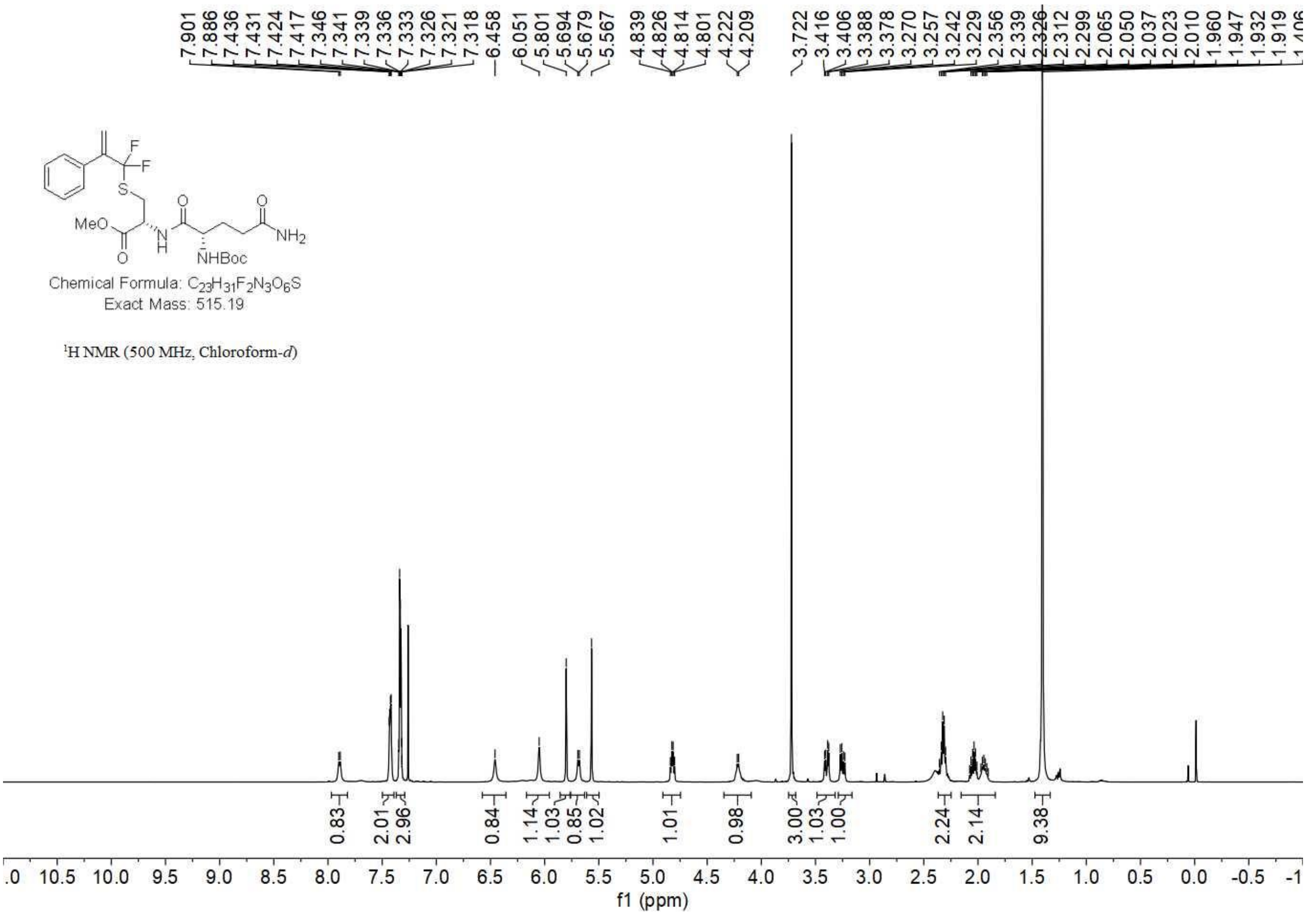
Spectra of 3f

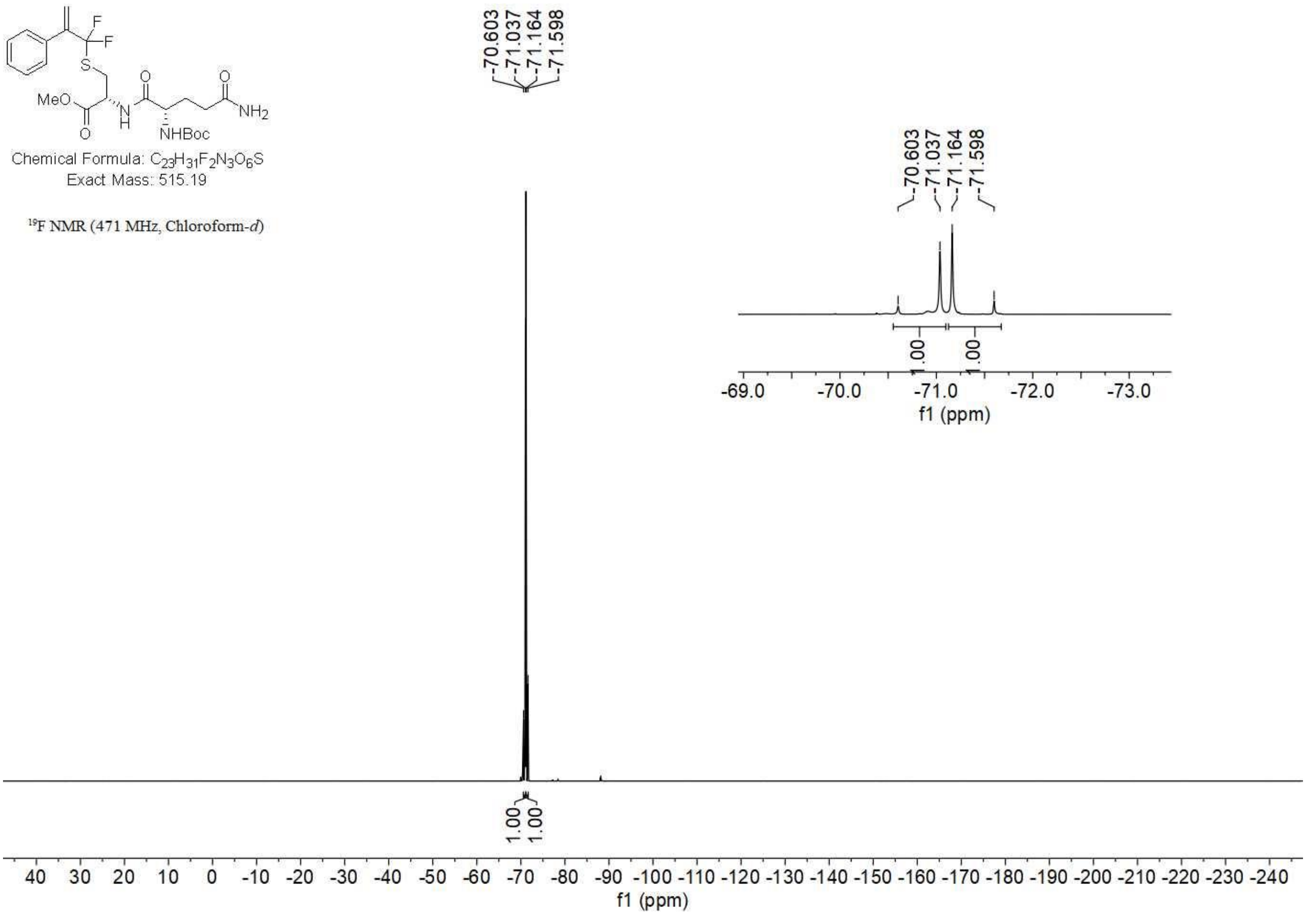



Chemical Formula: $C_{29}H_{33}F_2N_3O_5S$
Exact Mass: 573.21
^{19}F NMR (376 MHz, Chloroform-*d*)
-70.175
-70.717
-71.084
-71.626
0.97
1.31
-69
-70
-71
-72
-73
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


171.633
169.826
155.371
143.721
143.543
143.364
136.126
135.338
129.682
128.607
128.223
128.179
127.459
125.237
123.241
122.068
119.814
119.762
119.708
119.578
118.552
111.167
110.026
80.150
55.204
52.656
51.876
30.702
29.631
28.199
27.957
Chemical Formula: $C_{29}H_{33}F_2N_3O_5S$
Exact Mass: 573.21
^{13}C NMR (126 MHz, Chloroform-*d*)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -3
f1 (ppm)

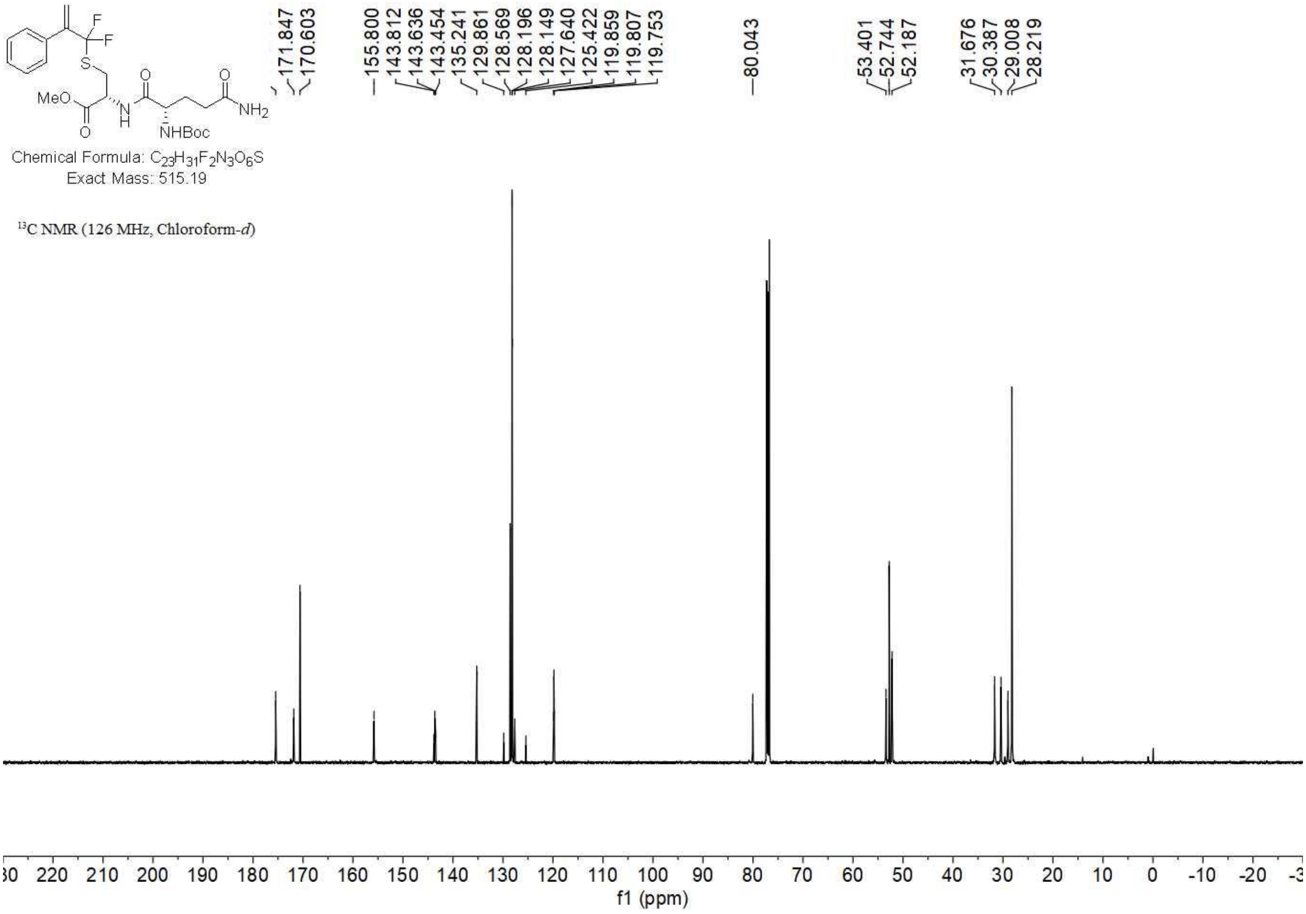
Spectra of 3g





Chemical Formula: $C_{23}H_{31}F_2N_3O_6S$
Exact Mass: 515.19

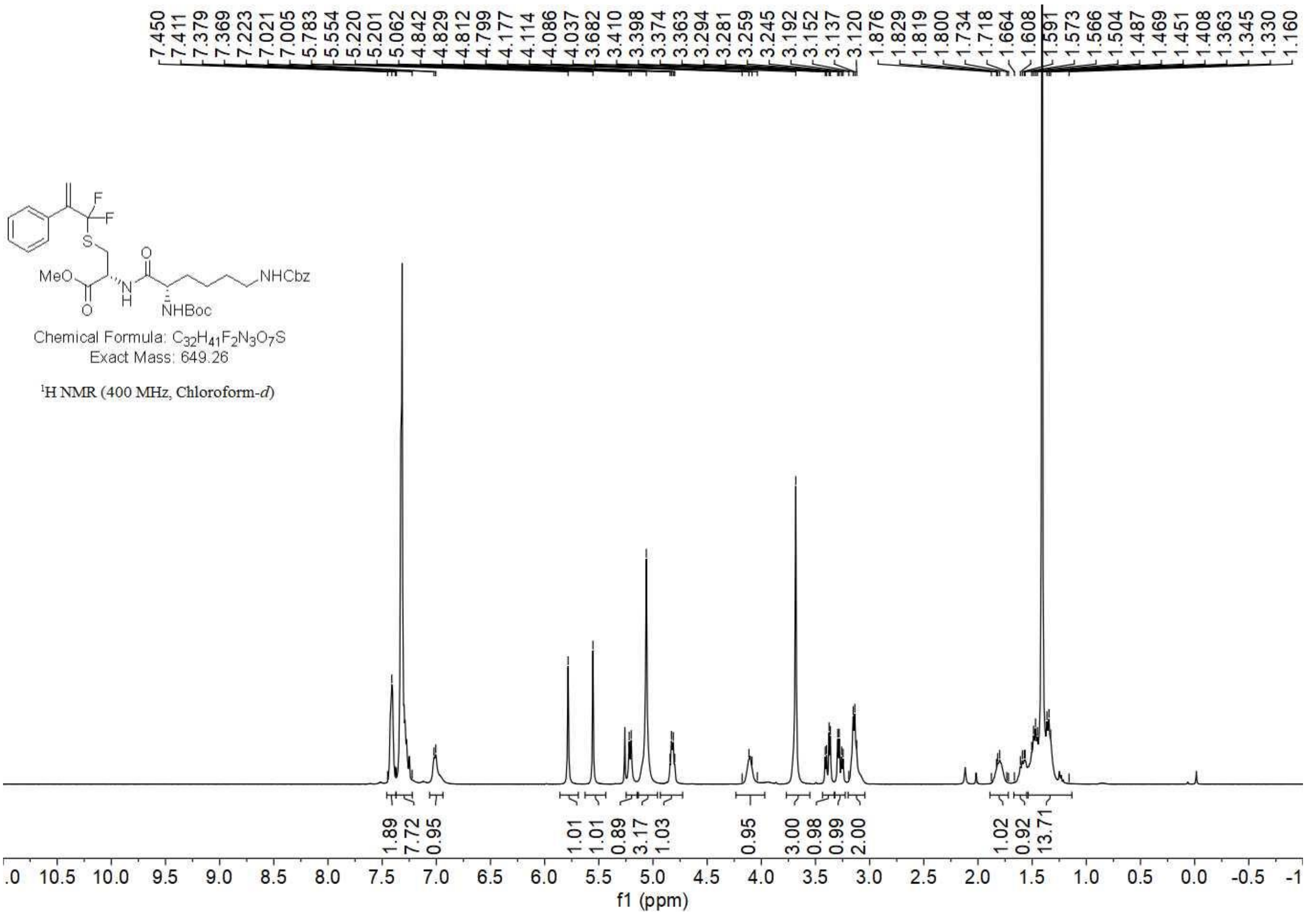
^{19}F NMR (471 MHz, Chloroform-*d*)

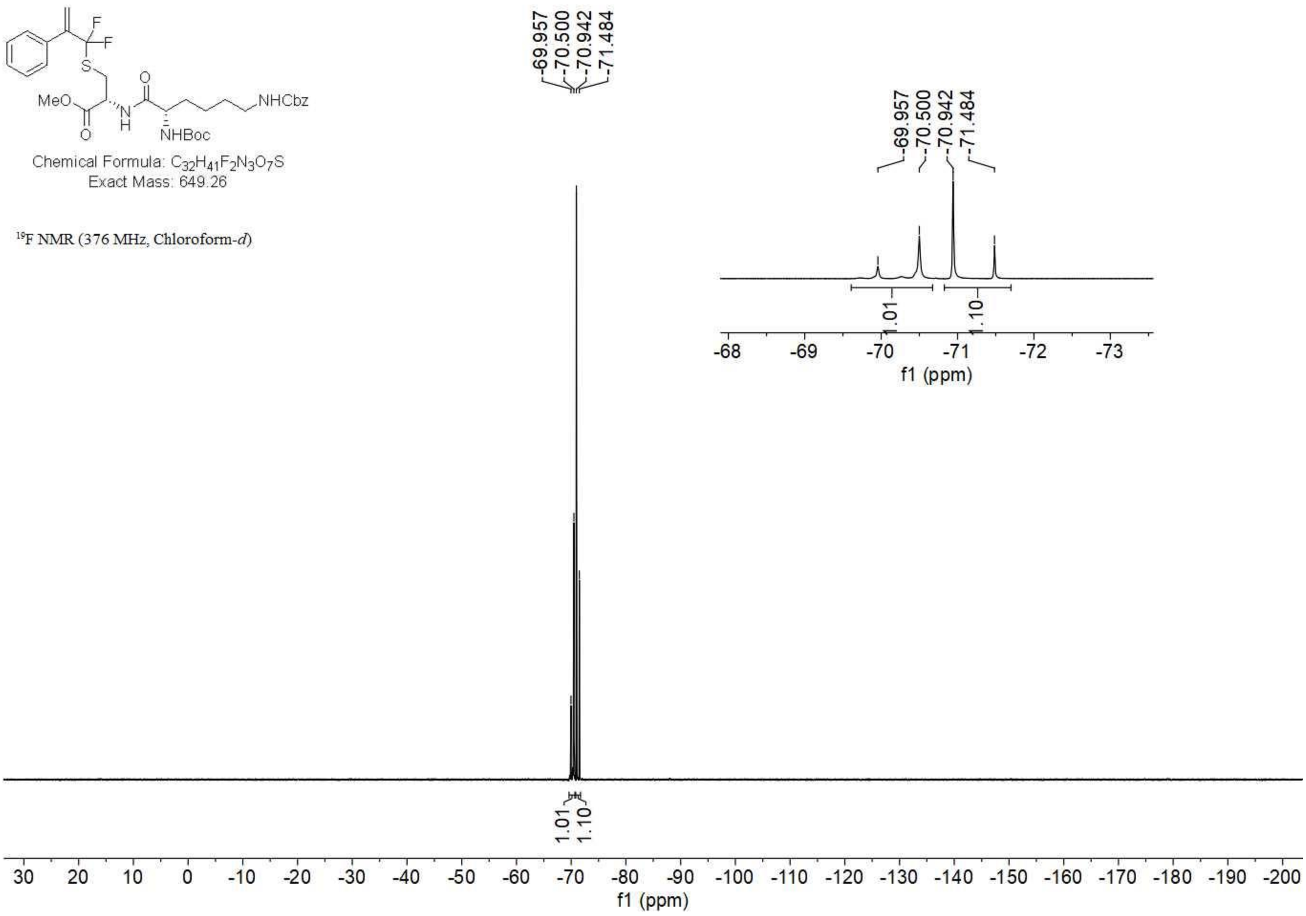


Chemical Formula: $C_{23}H_{31}F_2N_3O_6S$
Exact Mass: 515.19

^{13}C NMR (126 MHz, Chloroform-*d*)

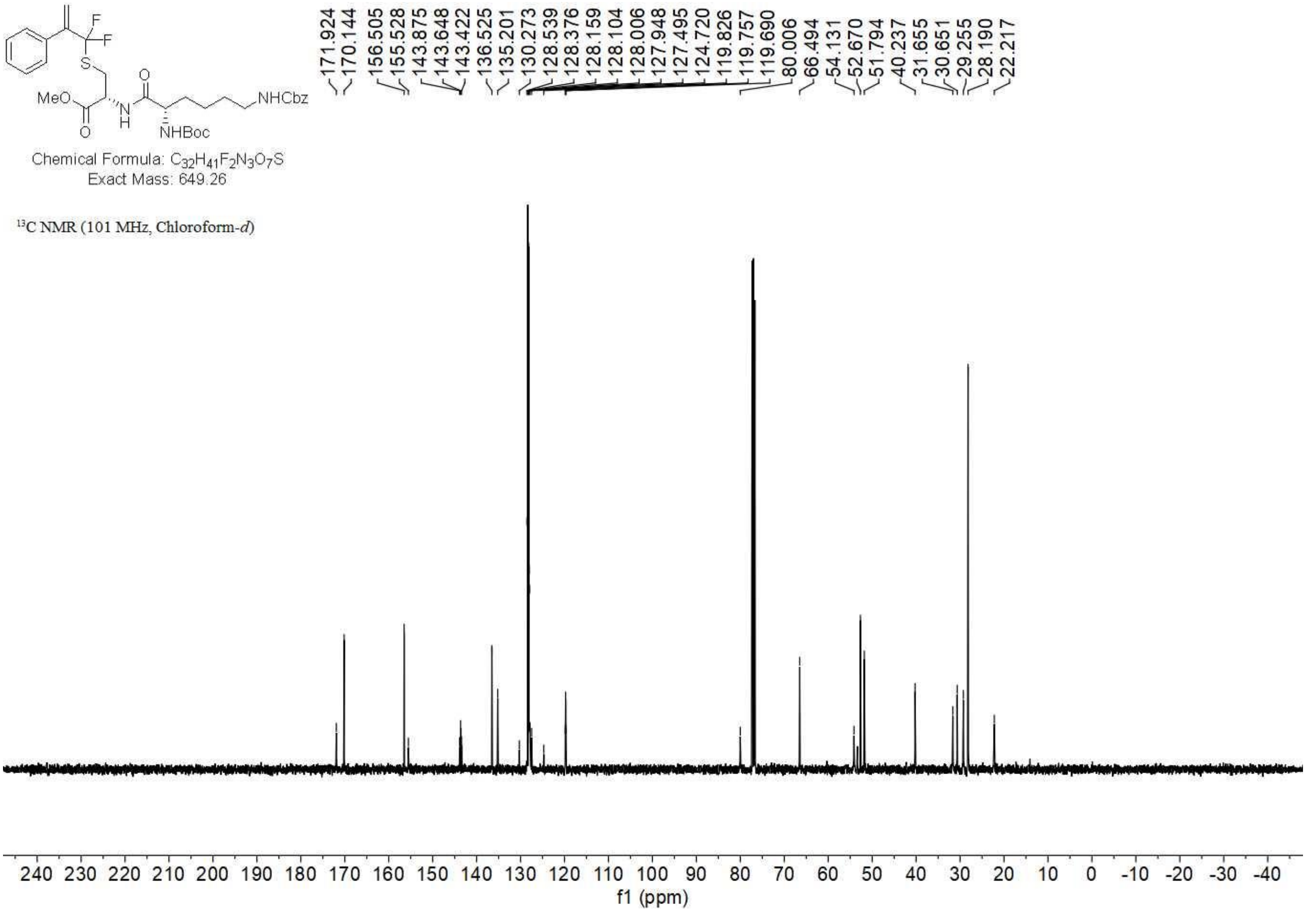
Spectra of 3h





Chemical Formula: $C_{32}H_{41}F_2N_3O_7S$
Exact Mass: 649.26

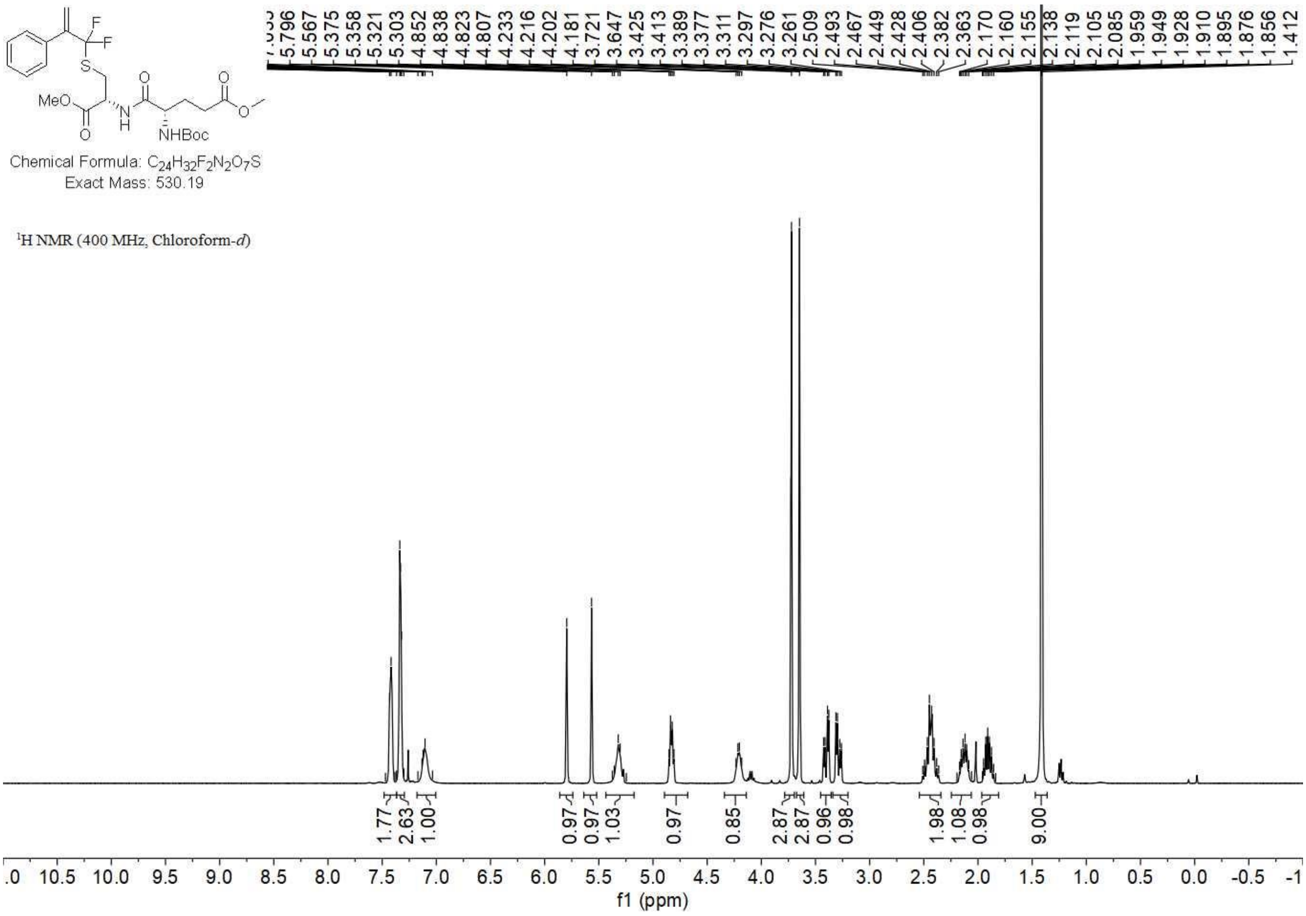
^{19}F NMR (376 MHz, Chloroform-*d*)



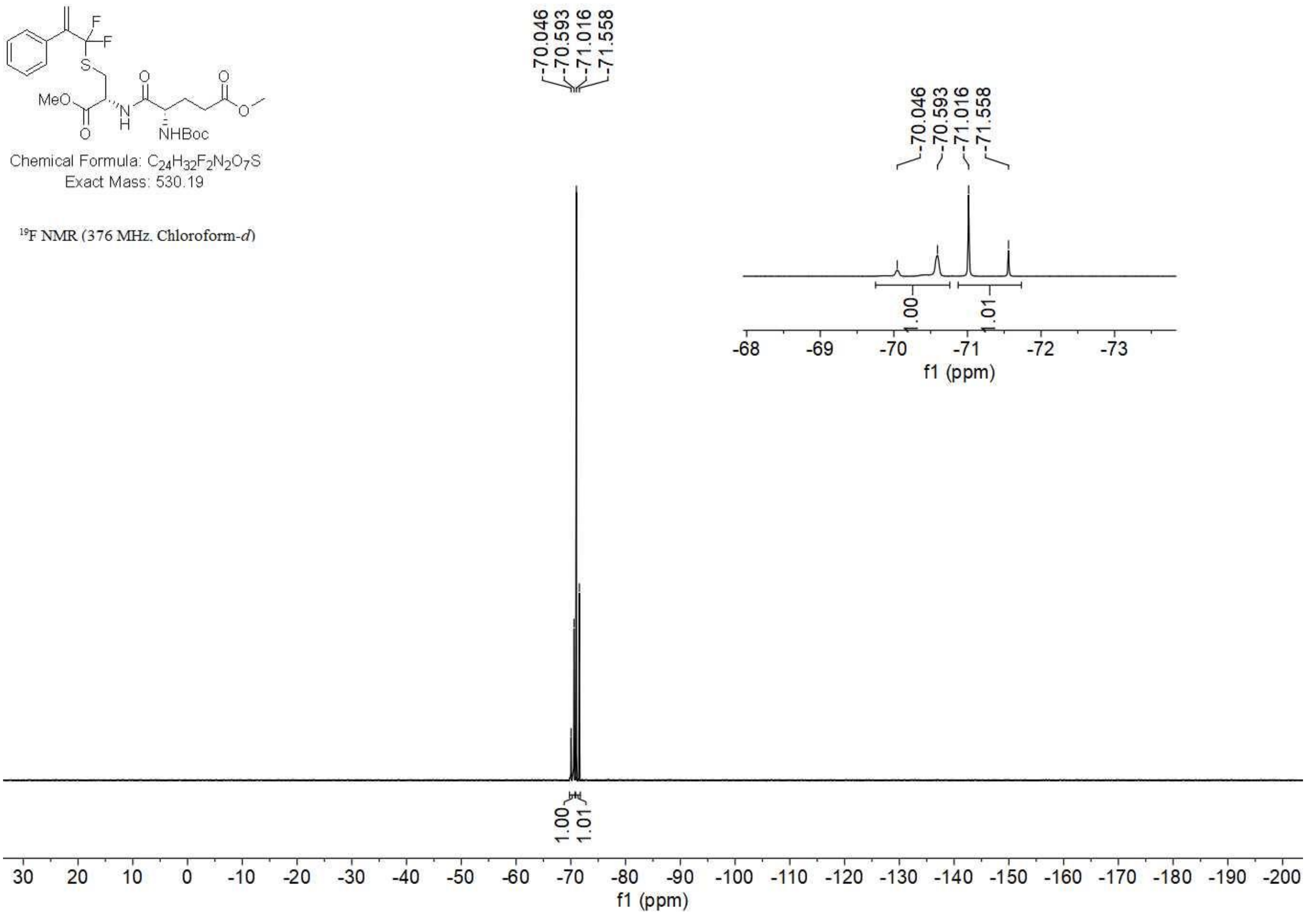
Chemical Formula: $C_{32}H_{41}F_2N_3O_7S$
Exact Mass: 649.26

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

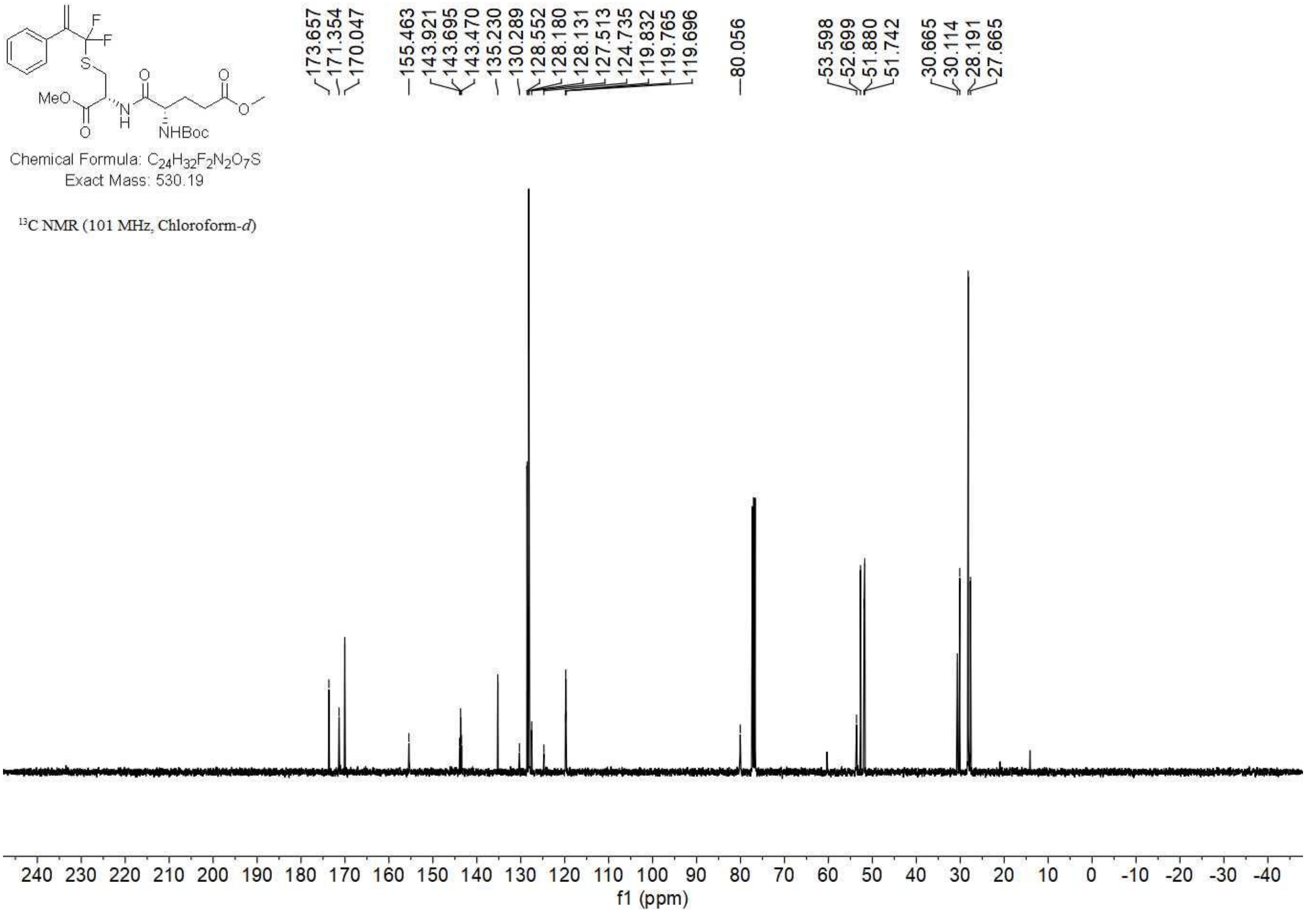
Spectra of 3i


Chemical Formula: $C_{24}H_{32}F_2N_2O_7S$
Exact Mass: 530.19

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

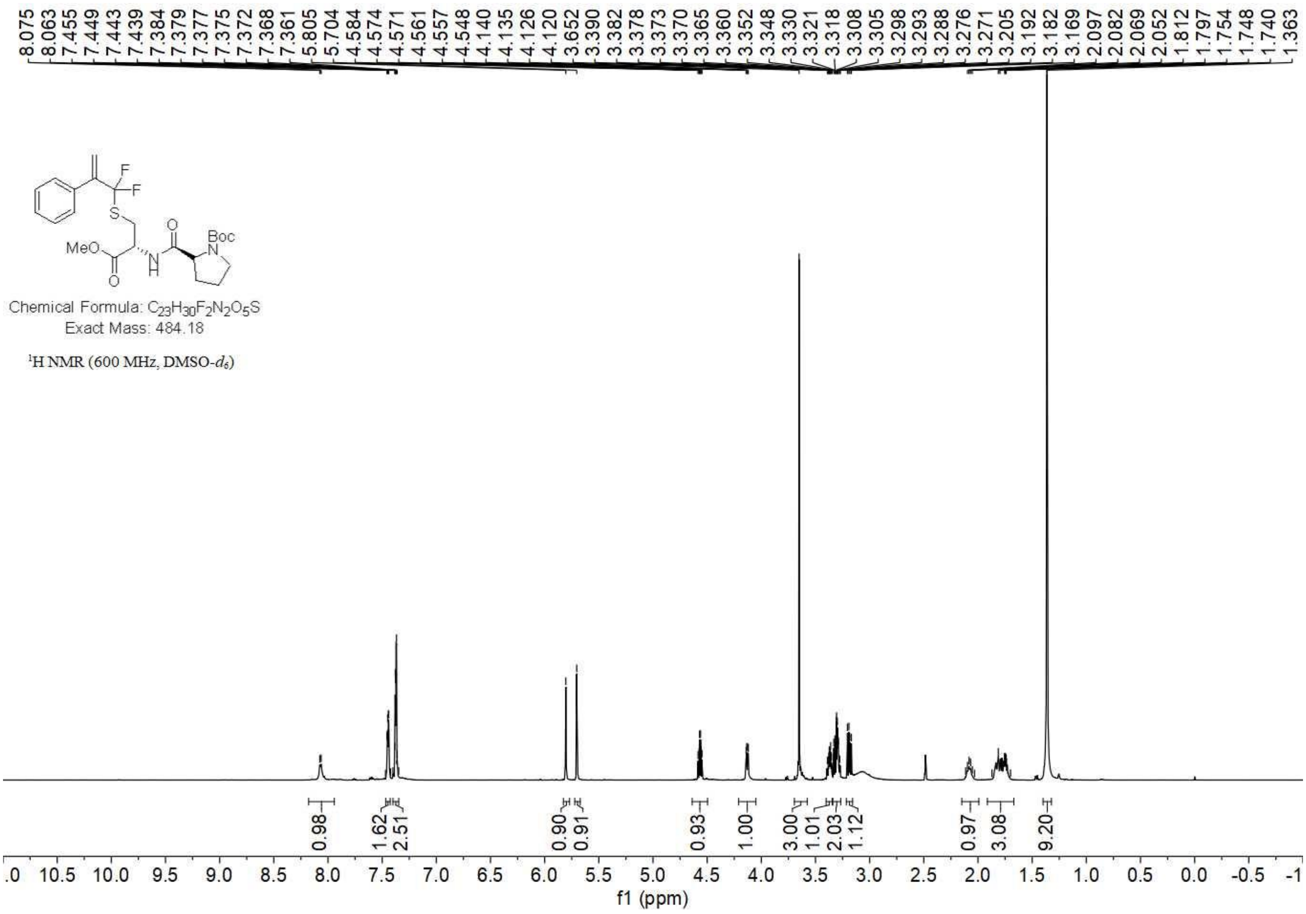


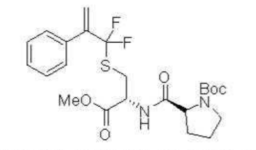
MeO
NHBoc
Chemical Formula: $C_{24}H_{32}F_2N_2O_7S$
Exact Mass: 530.19
^{19}F NMR (376 MHz, Chloroform-*d*)
-70.046
-70.593
-71.016
-71.558
1.00
1.01
-68
-69
-70
-71
-72
-73
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)



MeO
NHBoc
Chemical Formula: $C_{24}H_{32}F_2N_2O_7S$
Exact Mass: 530.19
^{13}C NMR (101 MHz, Chloroform-*d*)
173.657
171.354
170.047
155.463
143.921
143.695
143.470
135.230
130.289
128.552
128.180
128.131
127.513
124.735
119.832
119.765
119.696
80.056
53.598
52.699
51.880
51.742
30.665
30.114
28.191
27.665
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

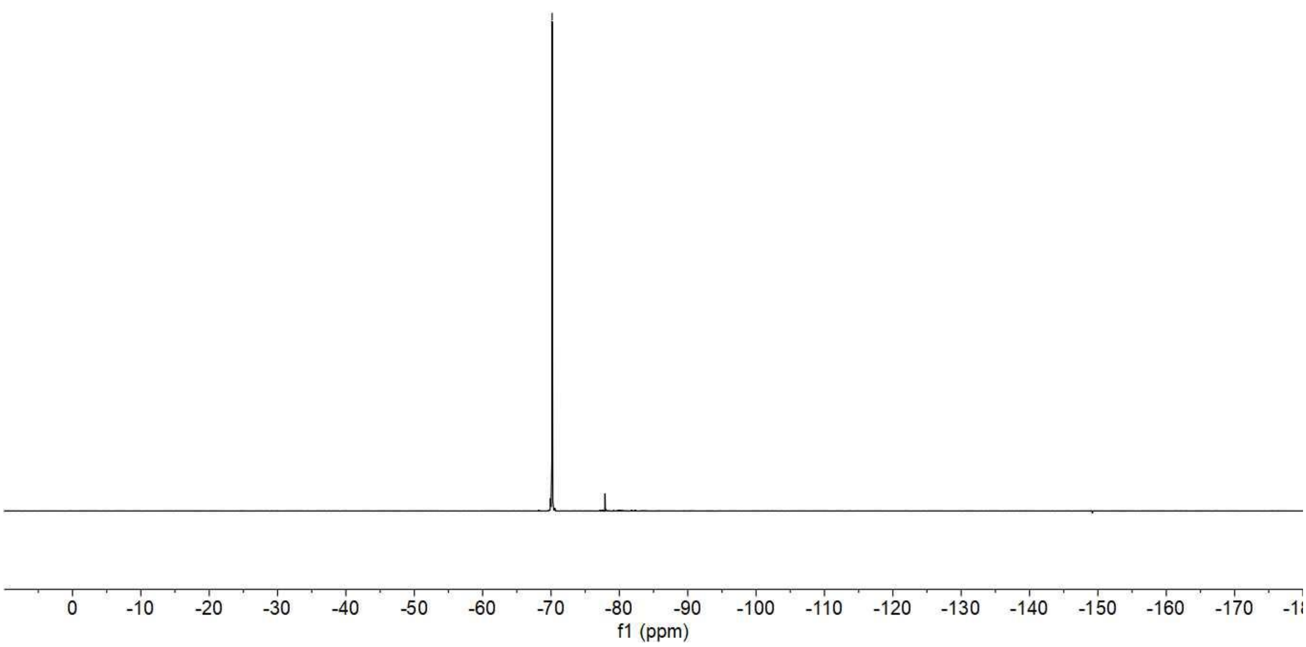
Spectra of 3j

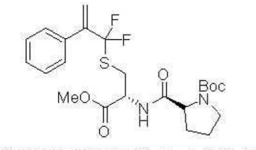




Chemical Formula: $C_{23}H_{30}F_2N_2O_5S$
Exact Mass: 484.18

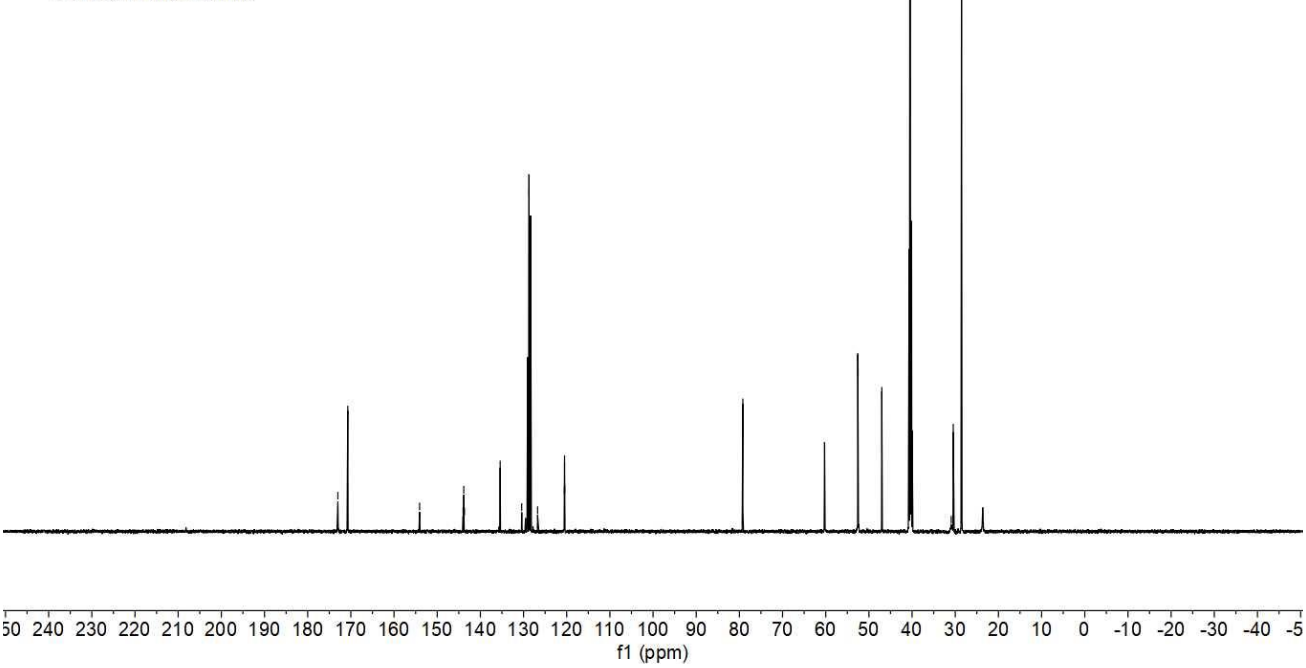
^{19}F NMR (565 MHz, DMSO-d_6)



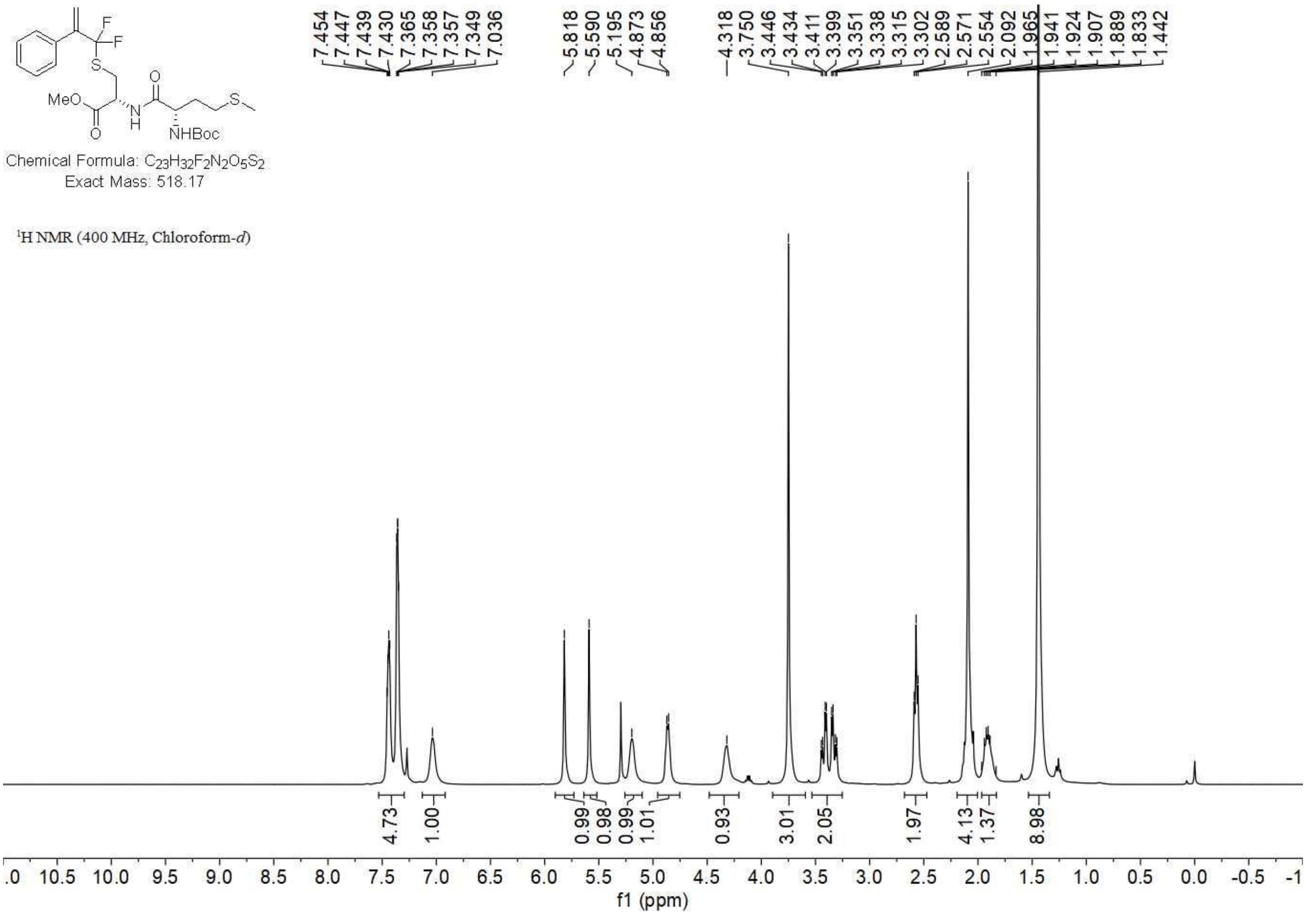


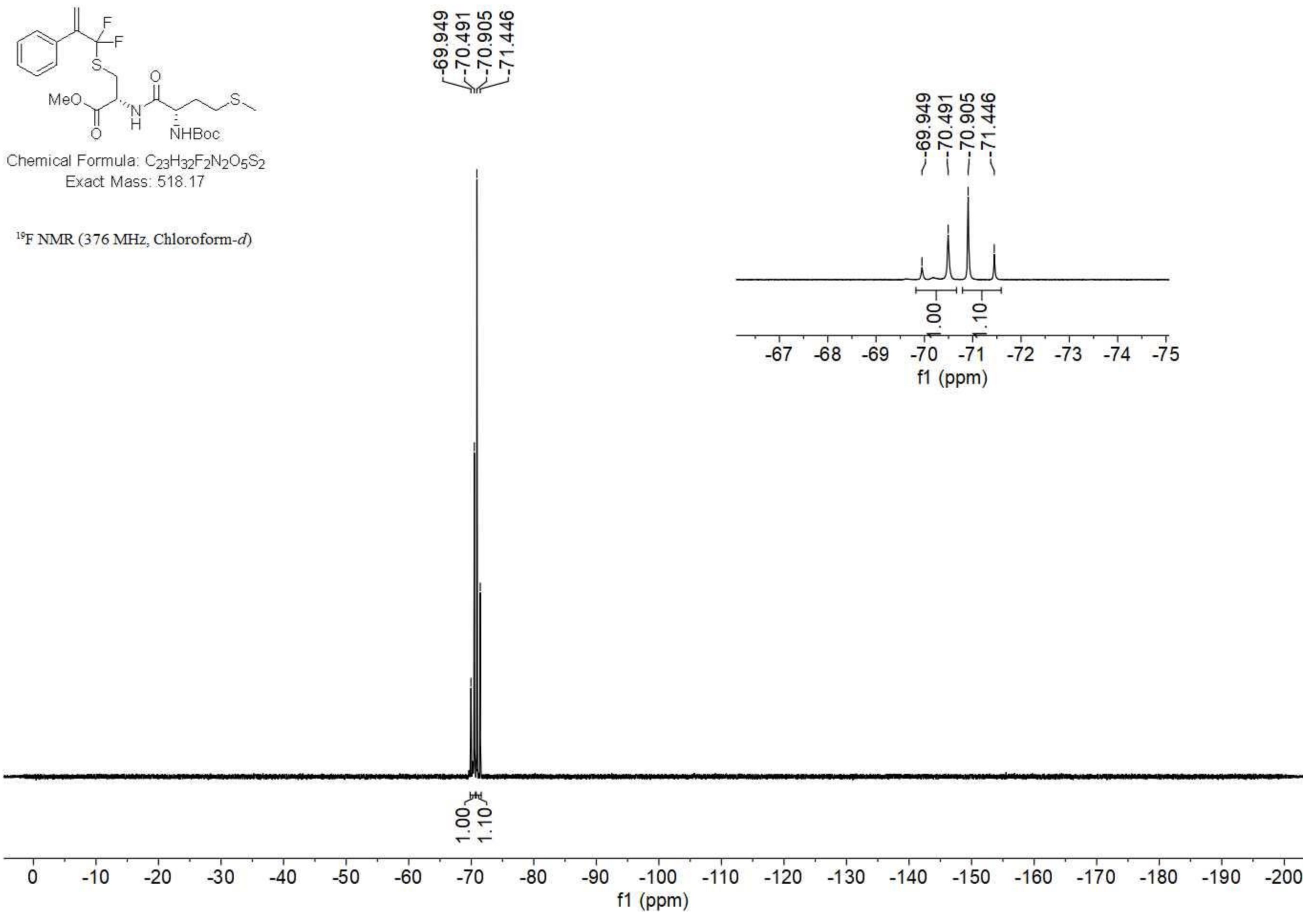
Chemical Formula: $C_{23}H_{30}F_2N_2O_5S$
Exact Mass: 484.18

^{13}C NMR (151 MHz, DMSO-d_6)



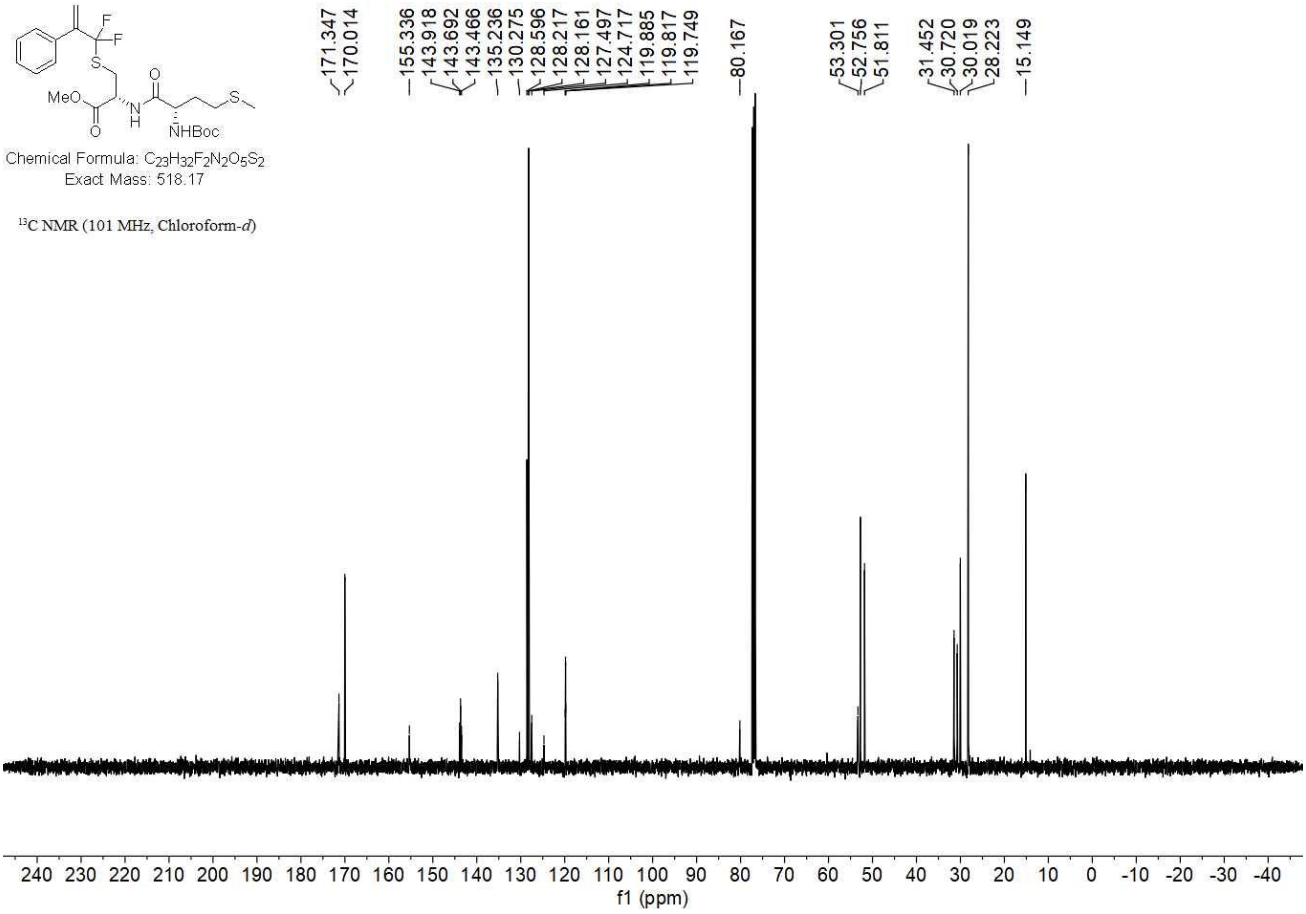
Spectra of 3k





Chemical Formula: $C_{23}H_{32}F_2N_2O_5S_2$
Exact Mass: 518.17

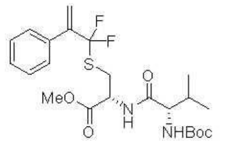
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{23}H_{32}F_2N_2O_5S_2$
Exact Mass: 518.17

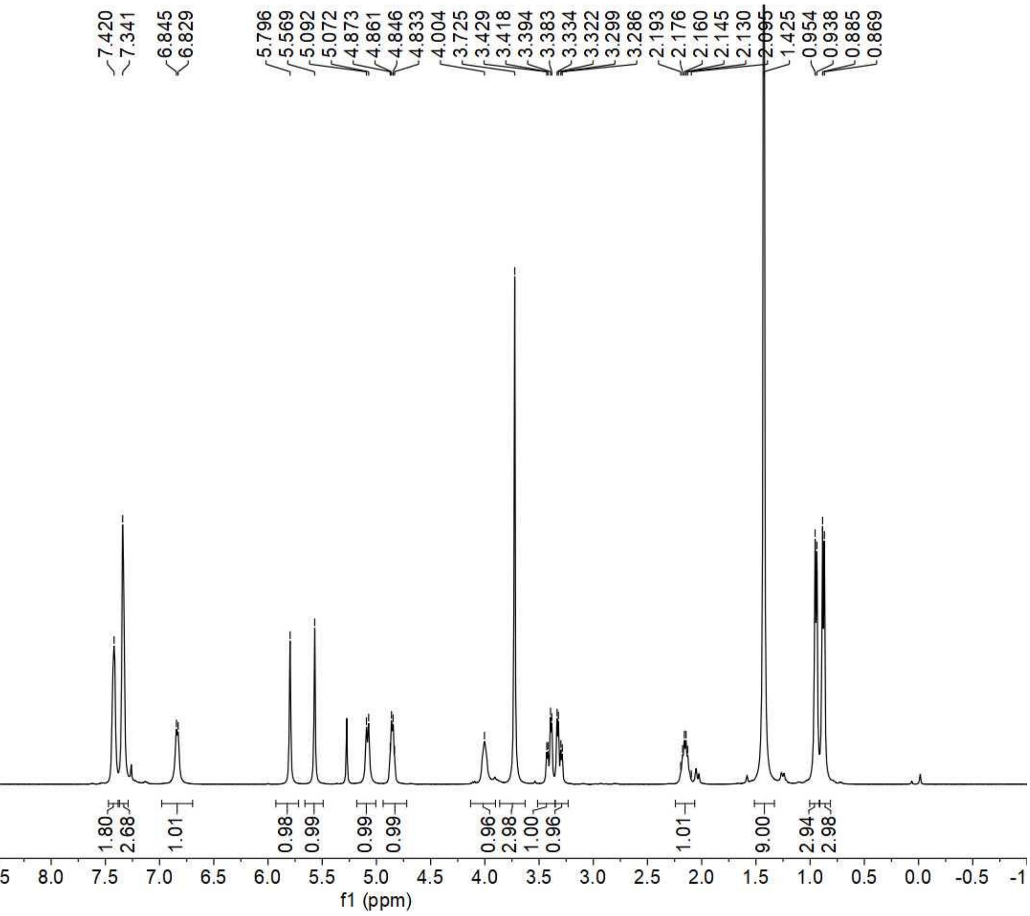
^{13}C NMR (101 MHz, Chloroform-*d*)

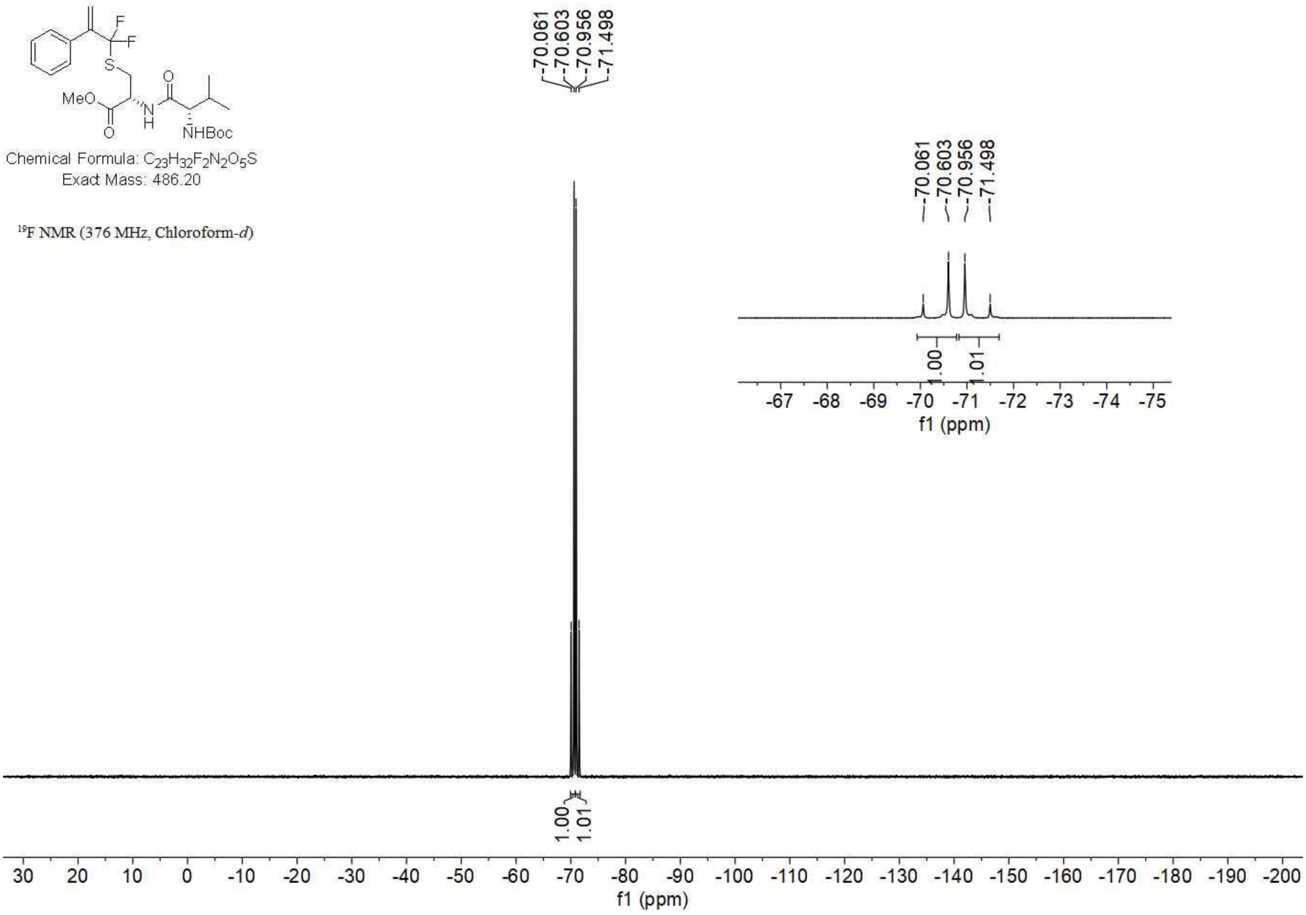
Spectra of 3l



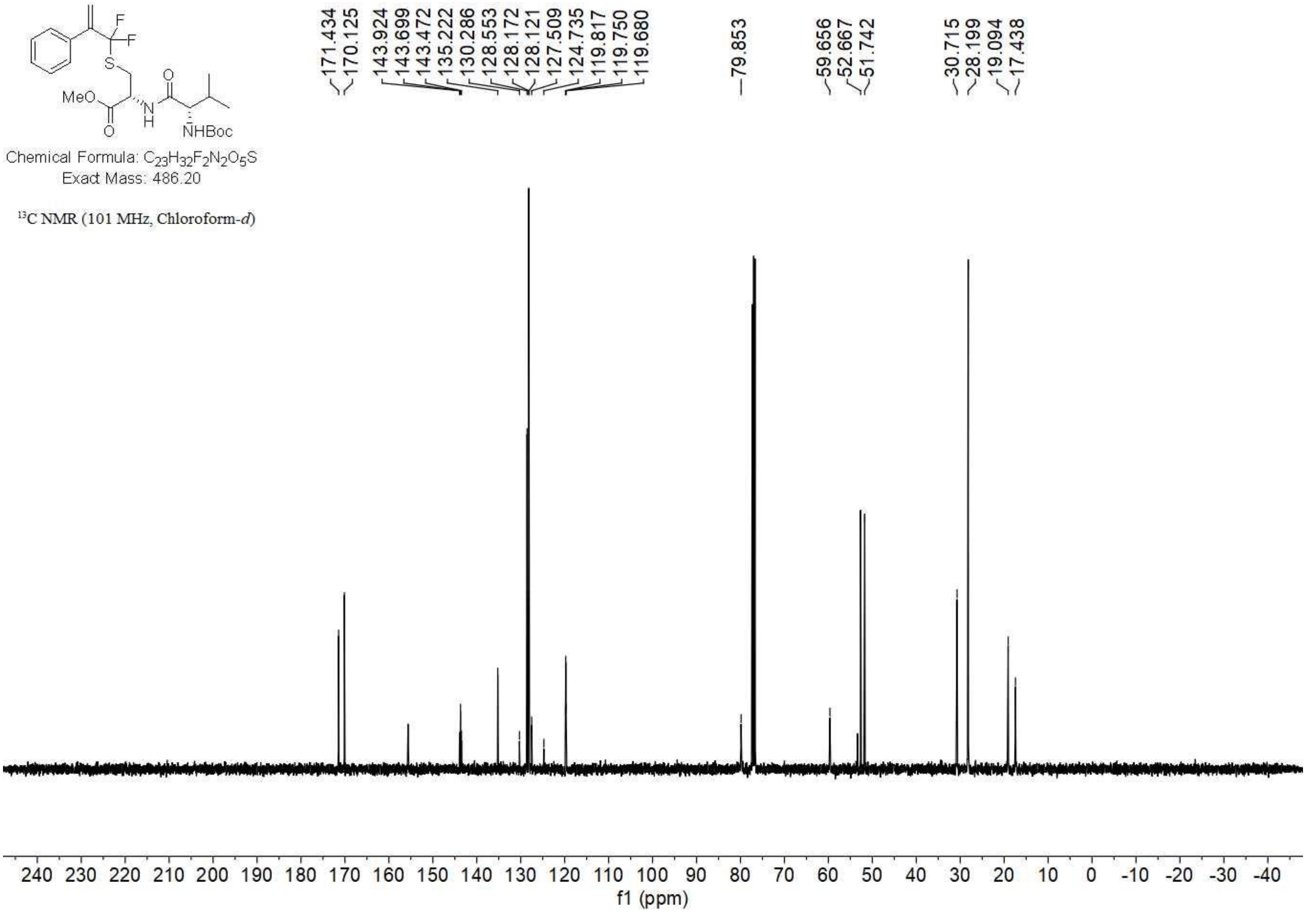
Chemical Formula: $C_{23}H_{32}F_2N_2O_5S$
Exact Mass: 486.20

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



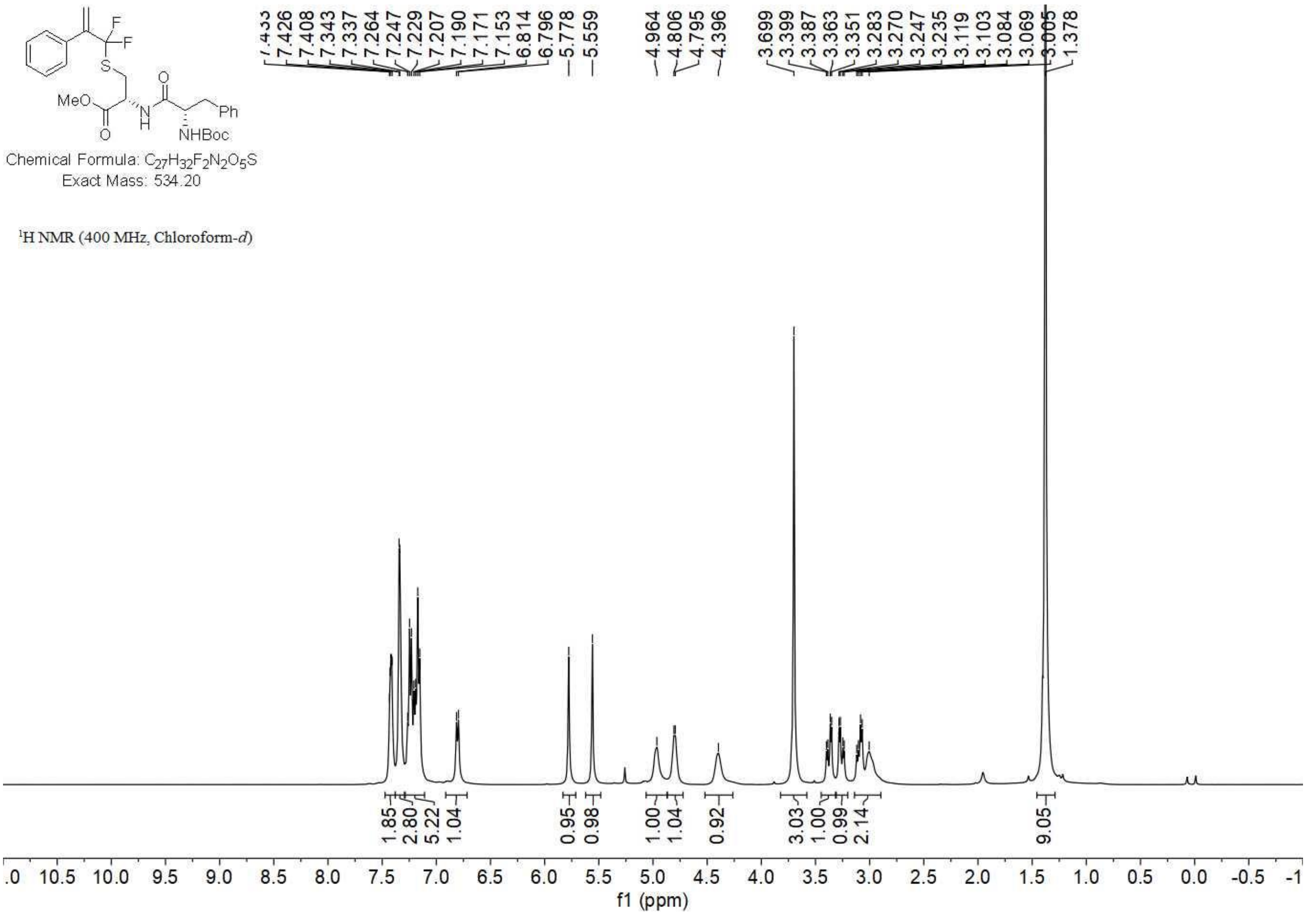

Chemical Formula: $C_{23}H_{32}F_2N_2O_5S$
Exact Mass: 486.20

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

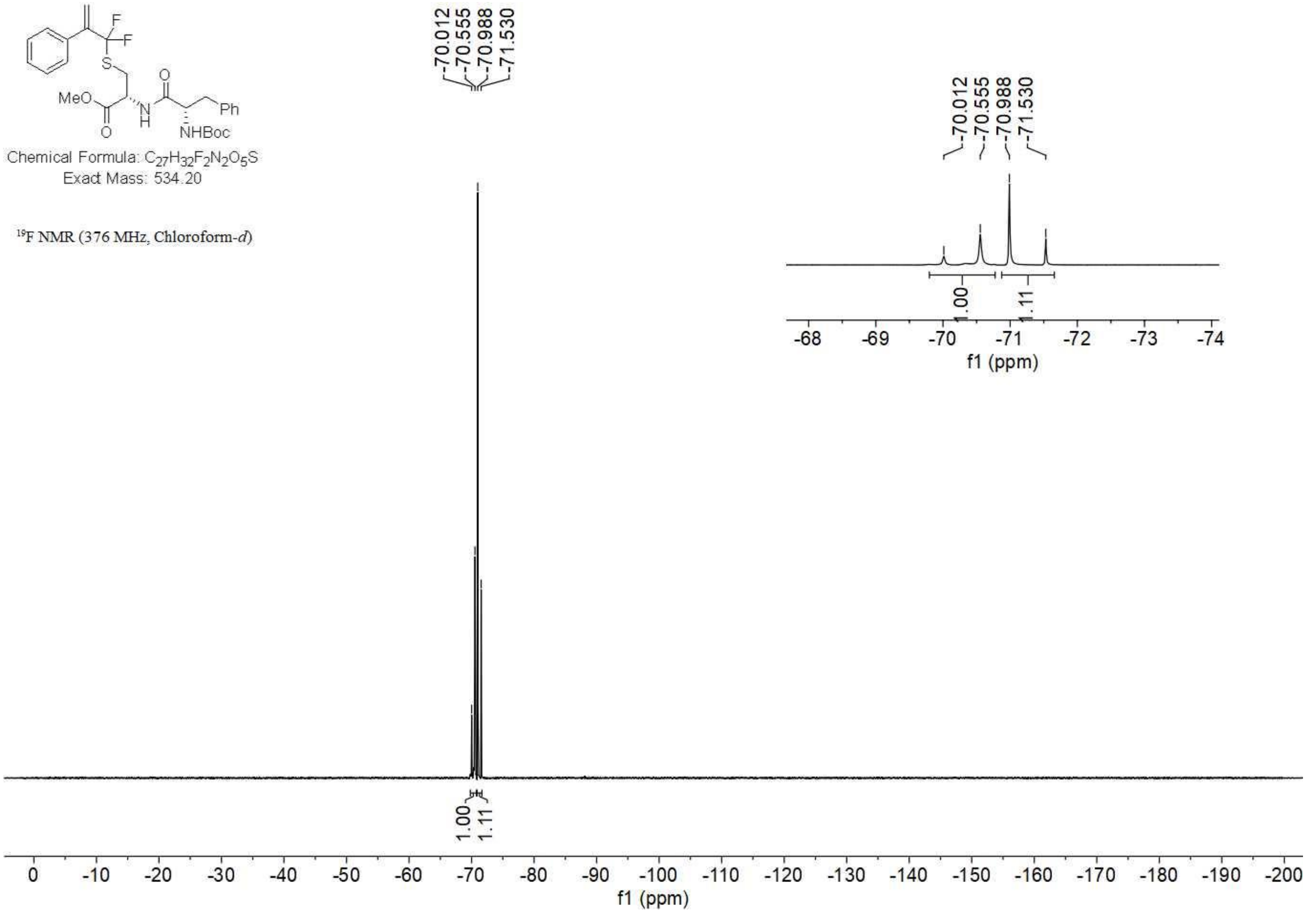

Chemical Formula: $C_{23}H_{32}F_2N_2O_5S$
Exact Mass: 486.20

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

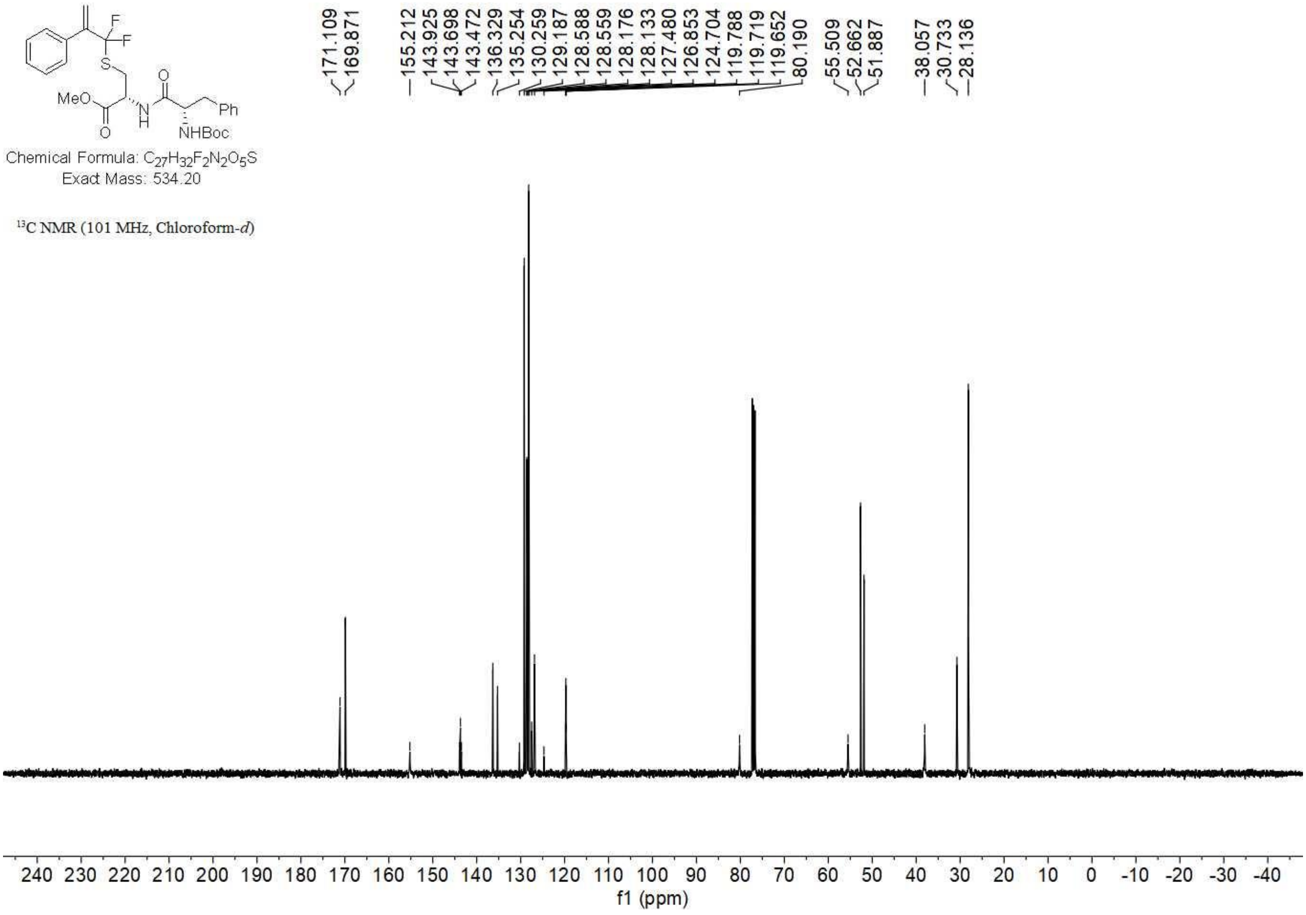
Spectra of 3m



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

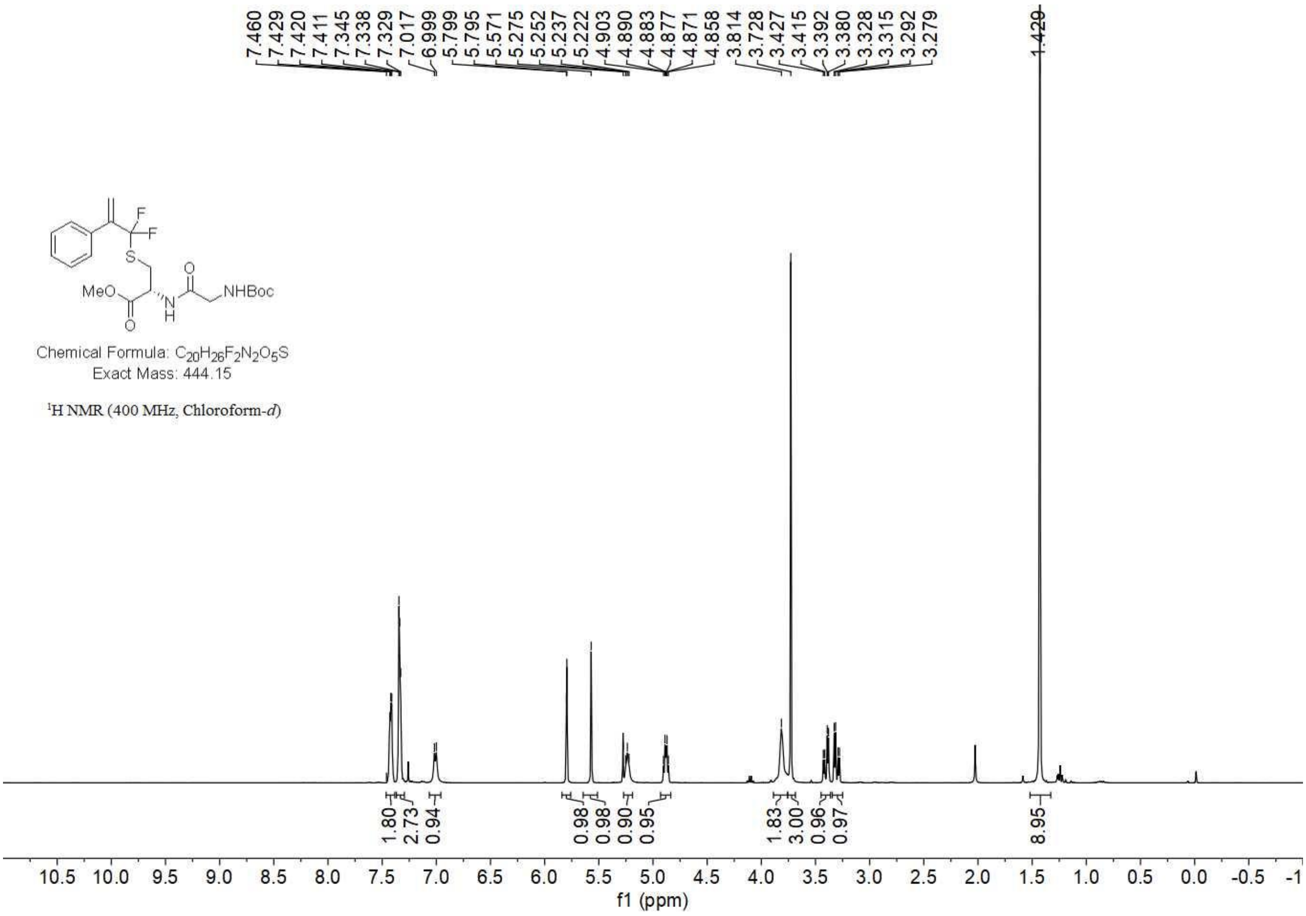

Chemical Formula: $C_{27}H_{32}F_2N_2O_5S$
Exact Mass: 534.20

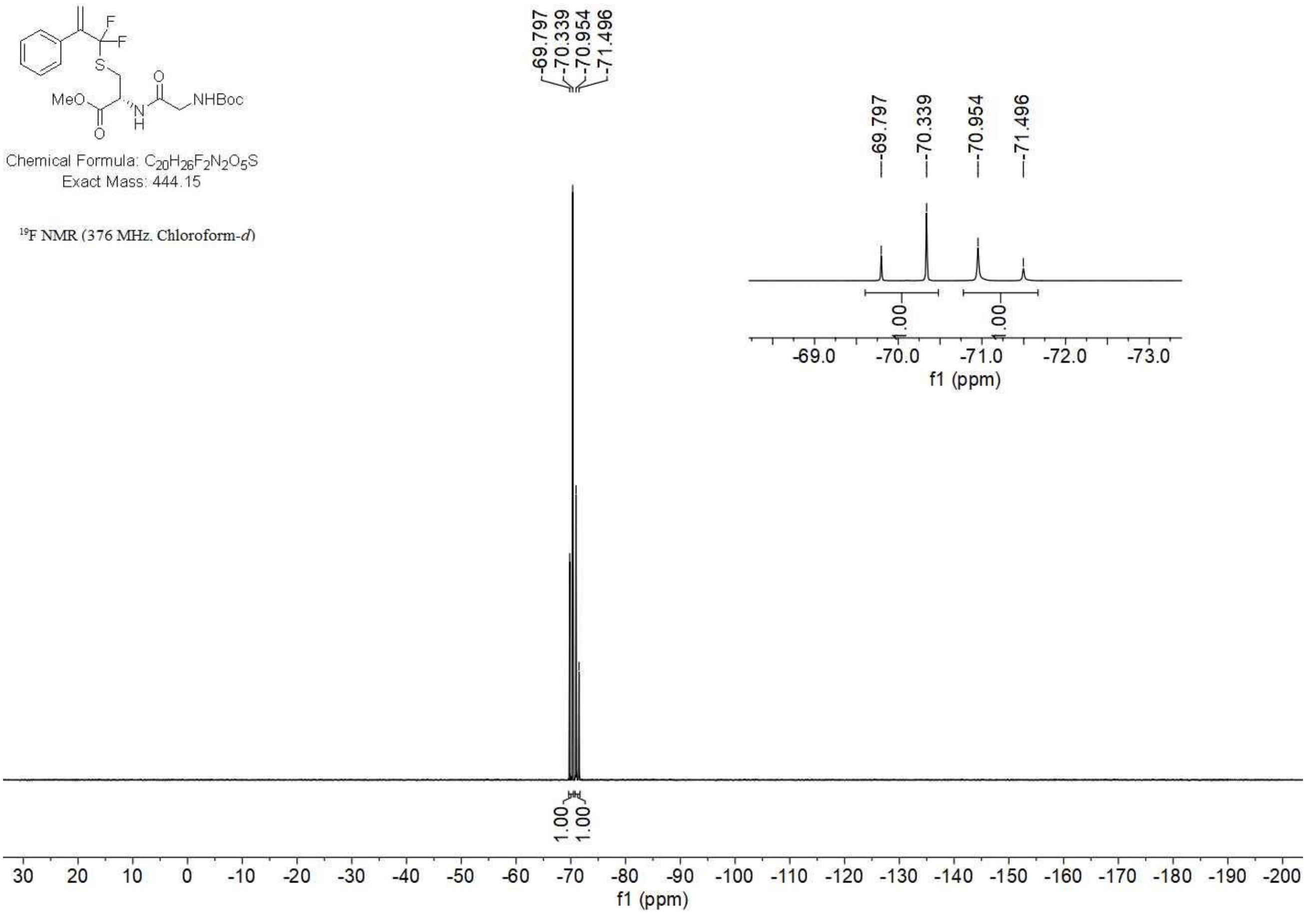
^{19}F NMR (376 MHz, Chloroform-*d*)


Chemical Formula: $C_{27}H_{32}F_2N_2O_5S$
Exact Mass: 534.20

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

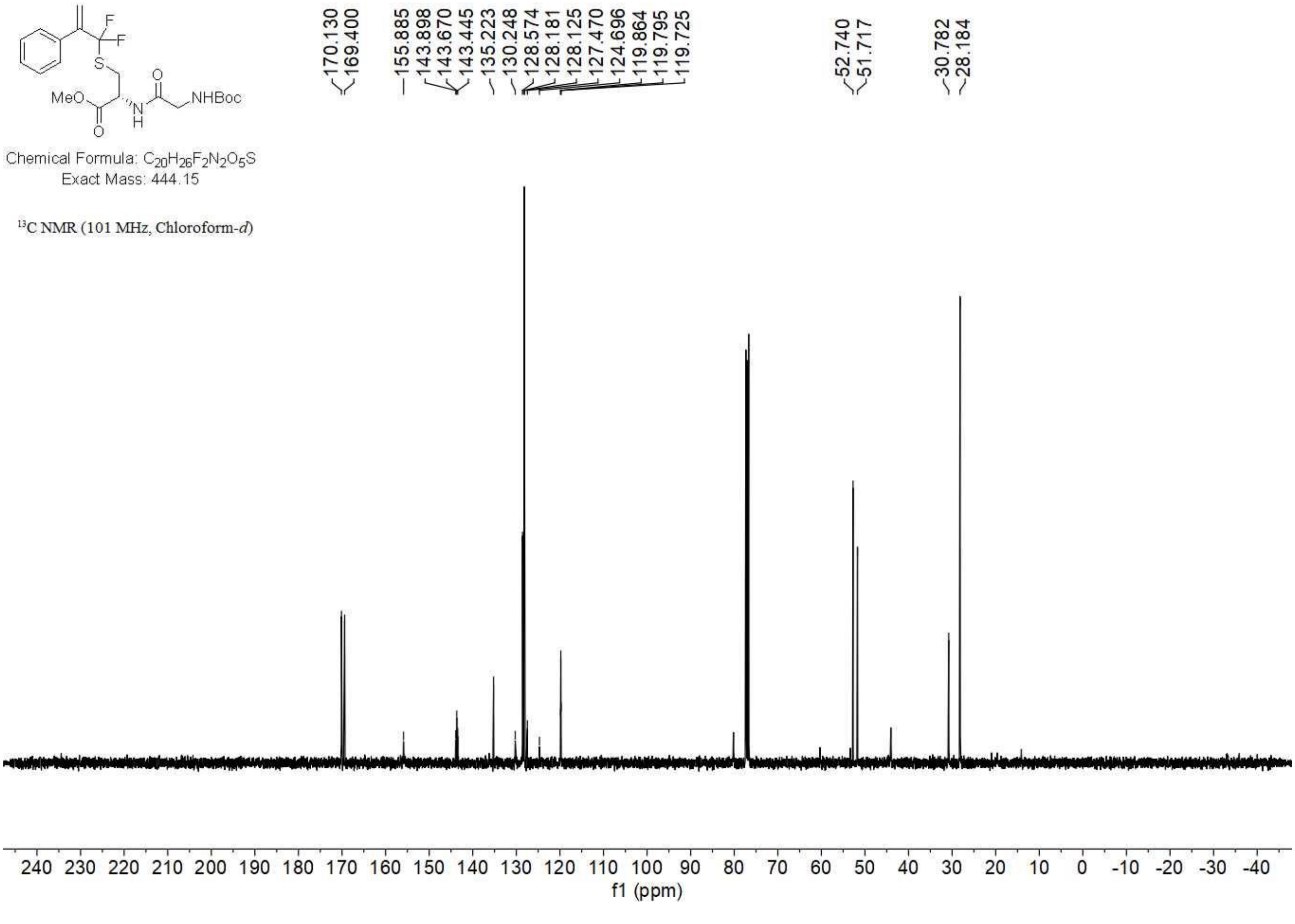
Spectra of 3n





Chemical Formula: $C_{20}H_{26}F_{2}N_{2}O_{5}S$
Exact Mass: 444.15

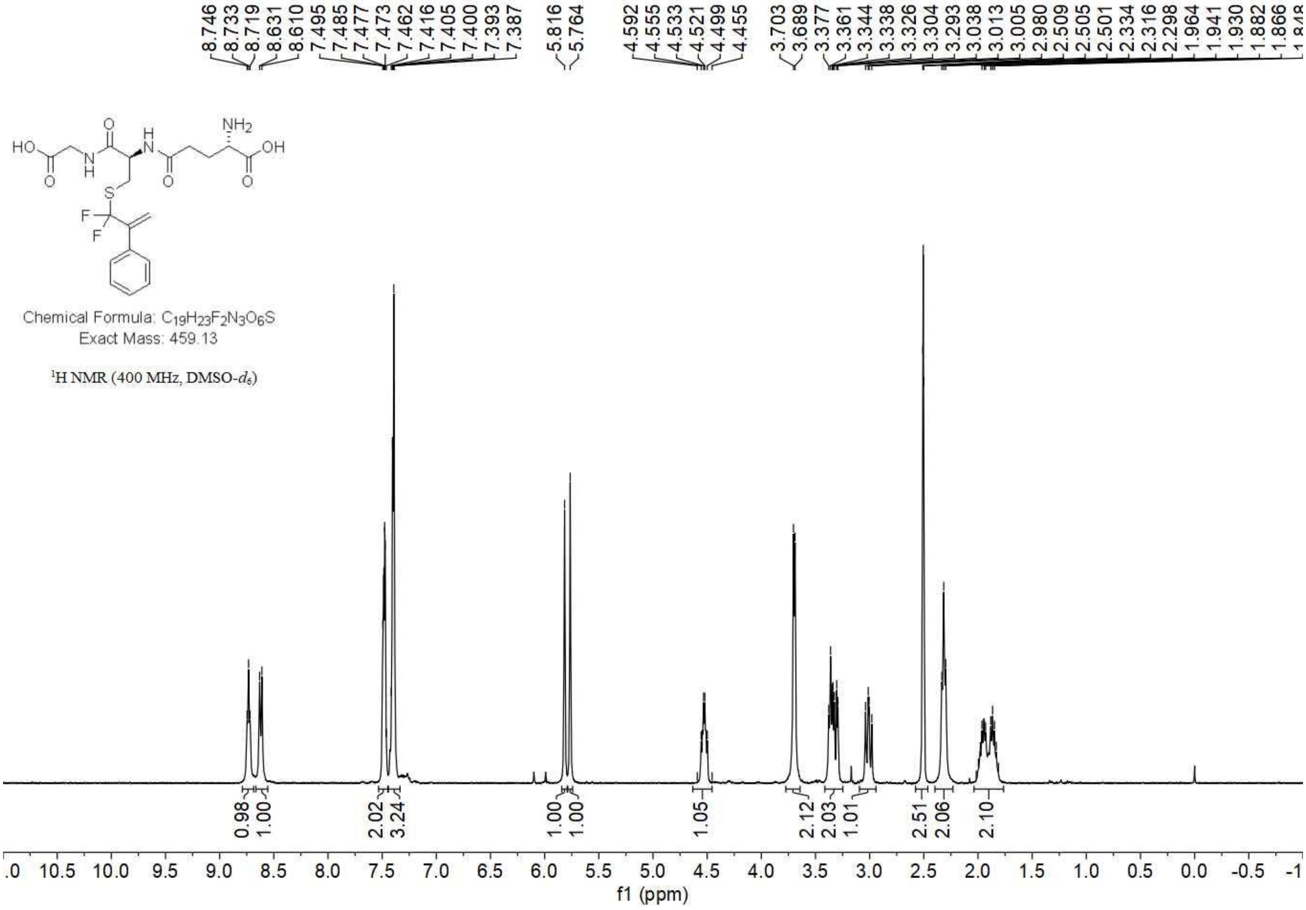
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{20}H_{26}F_{2}N_{2}O_{5}S$
Exact Mass: 444.15

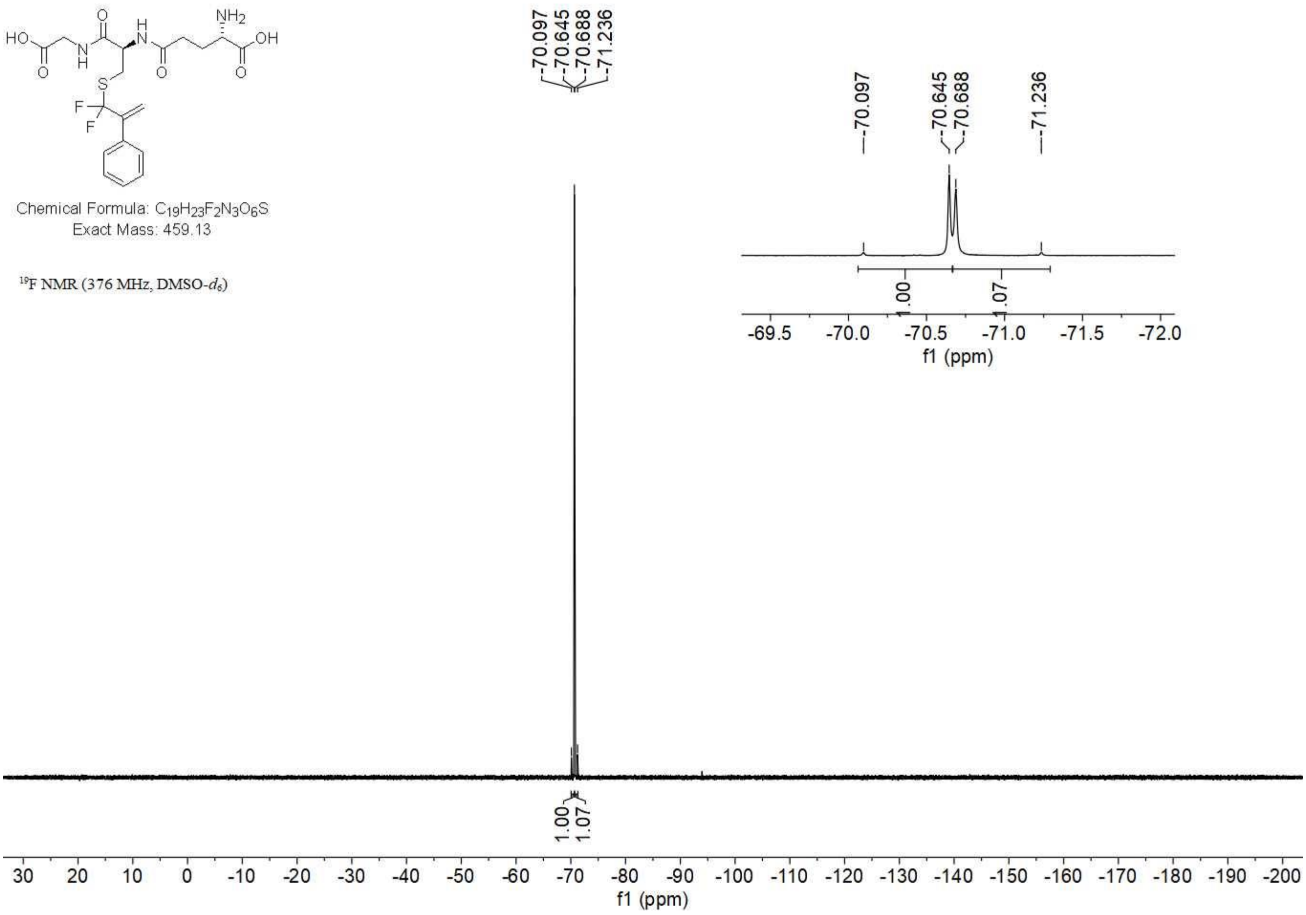
^{13}C NMR (101 MHz, Chloroform-*d*)

Spectra of 3o



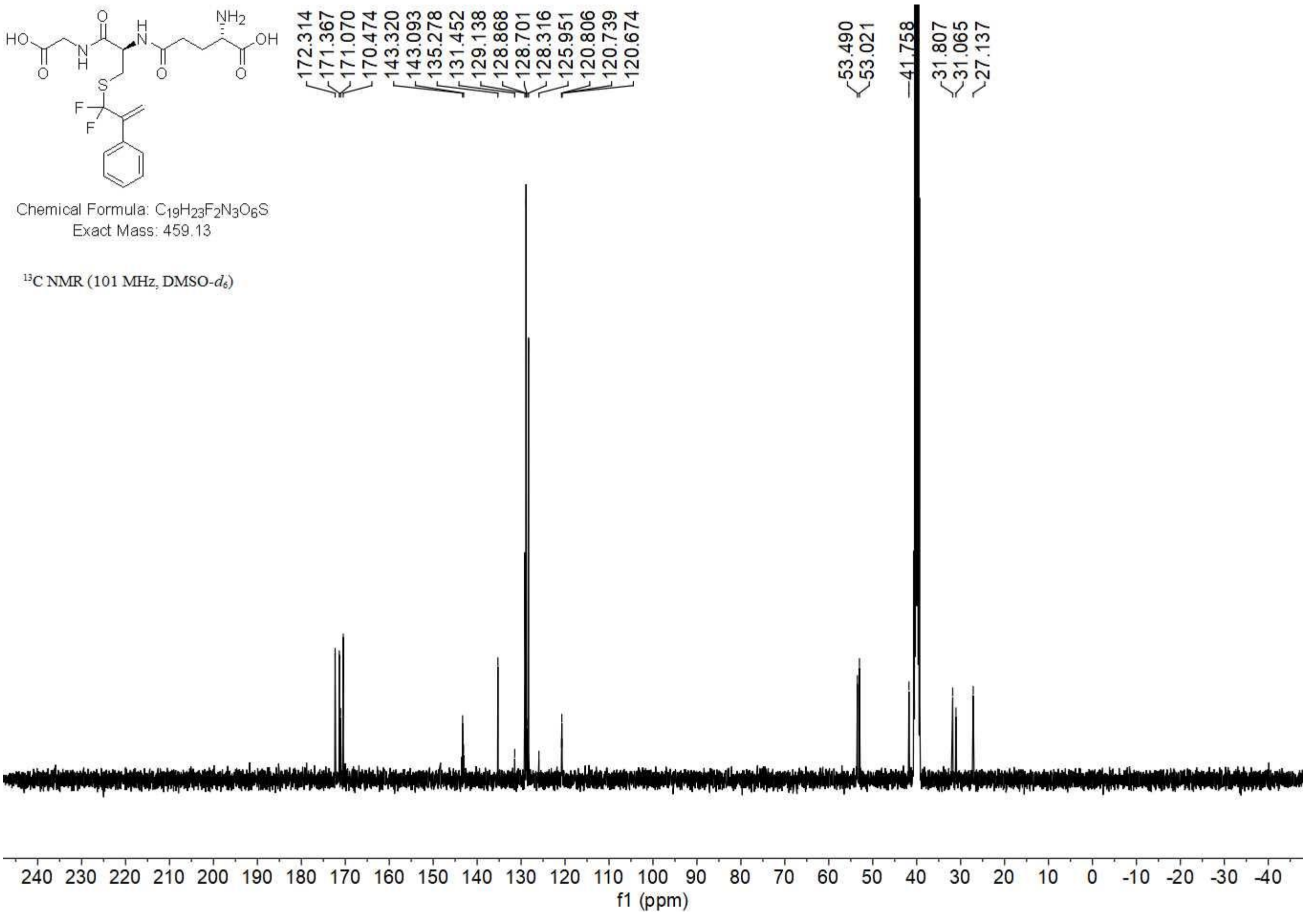
Chemical Formula: $C_{19}H_{23}F_2N_3O_6S$
Exact Mass: 459.13

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



Chemical Formula: $C_{19}H_{23}F_2N_3O_6S$
Exact Mass: 459.13

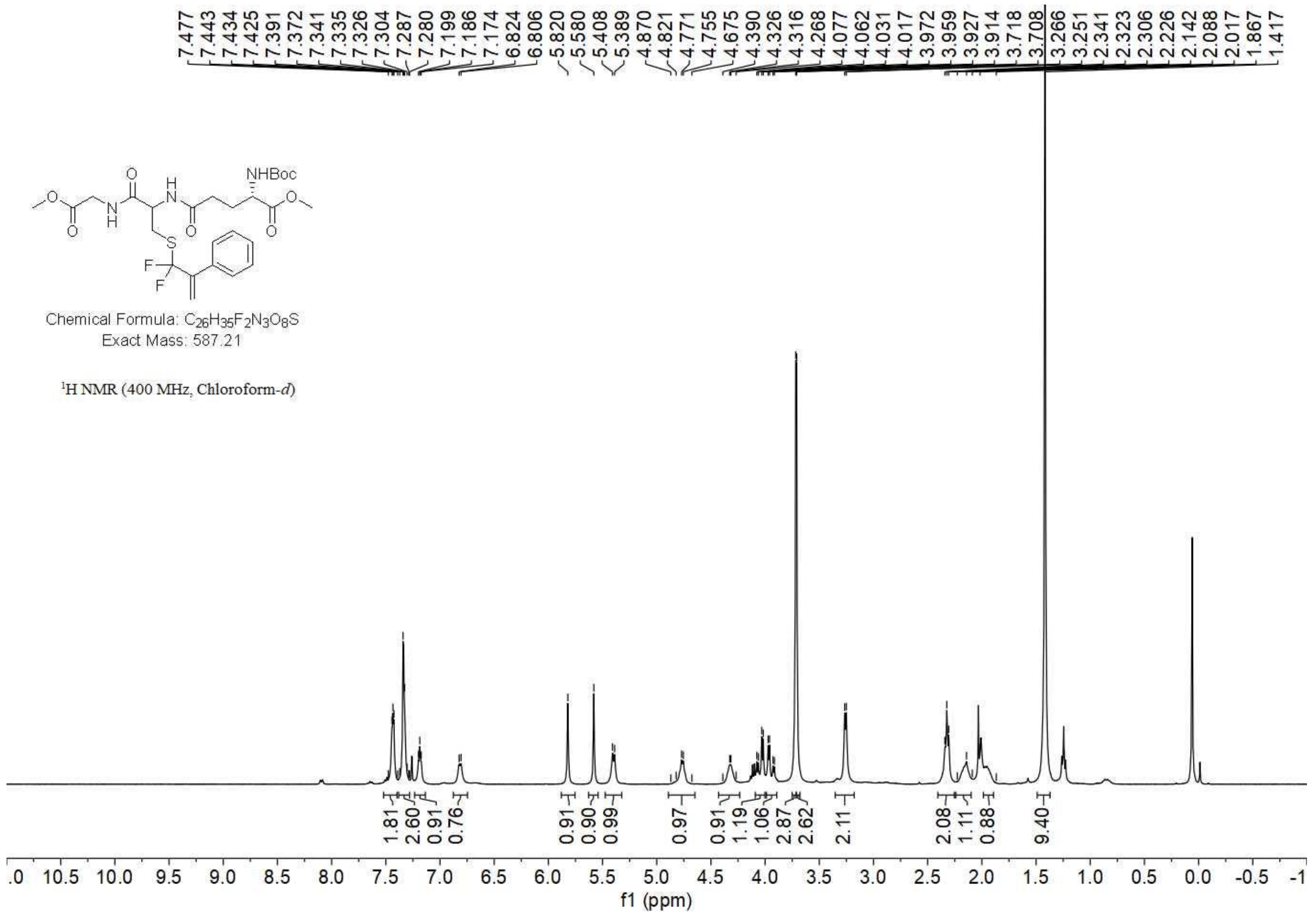
^{19}F NMR (376 MHz, DMSO-d_6)



Chemical Formula: $C_{19}H_{23}F_2N_3O_6S$
Exact Mass: 459.13

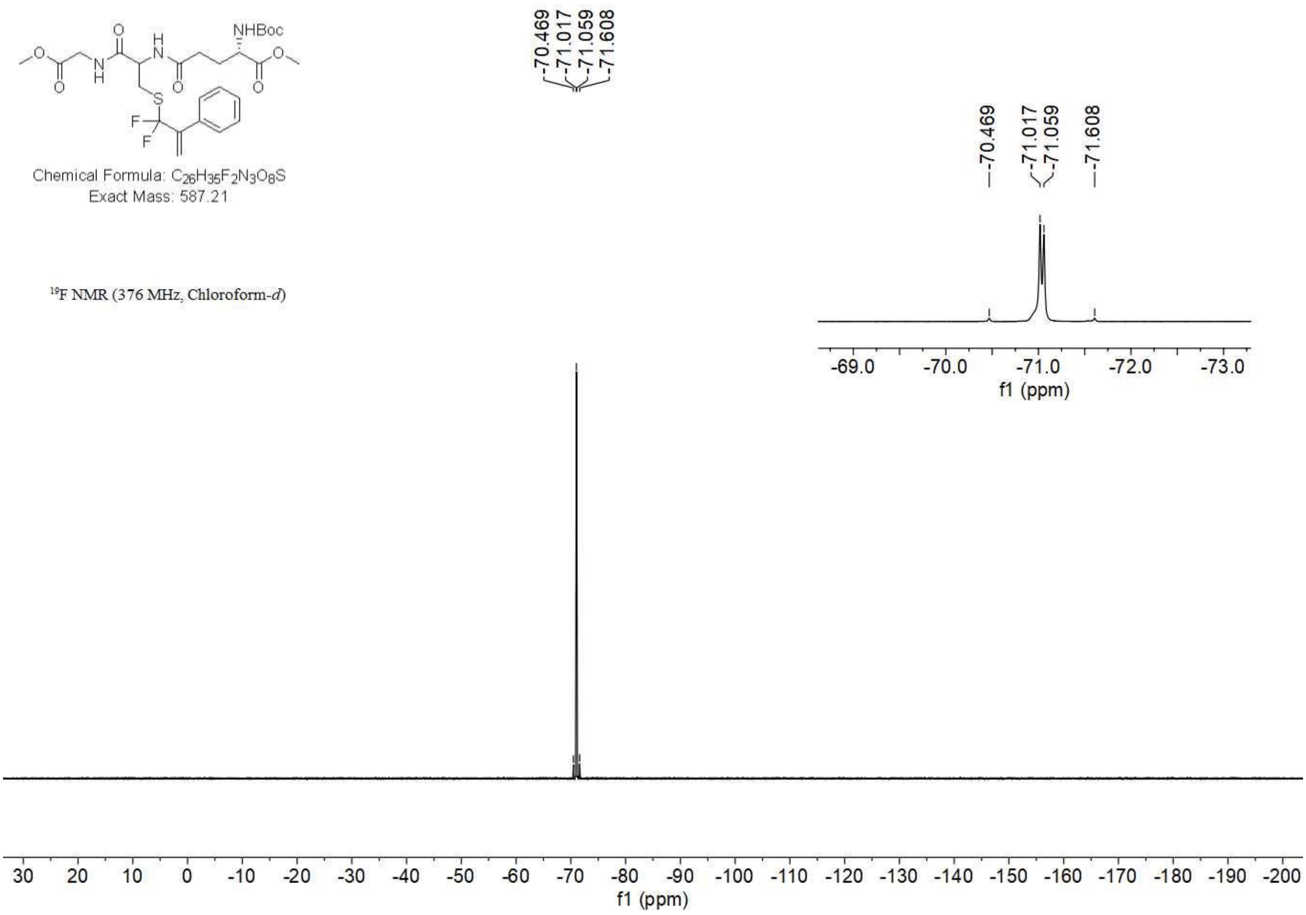
^{13}C NMR (101 MHz, DMSO-d_6)

Spectra of 3p



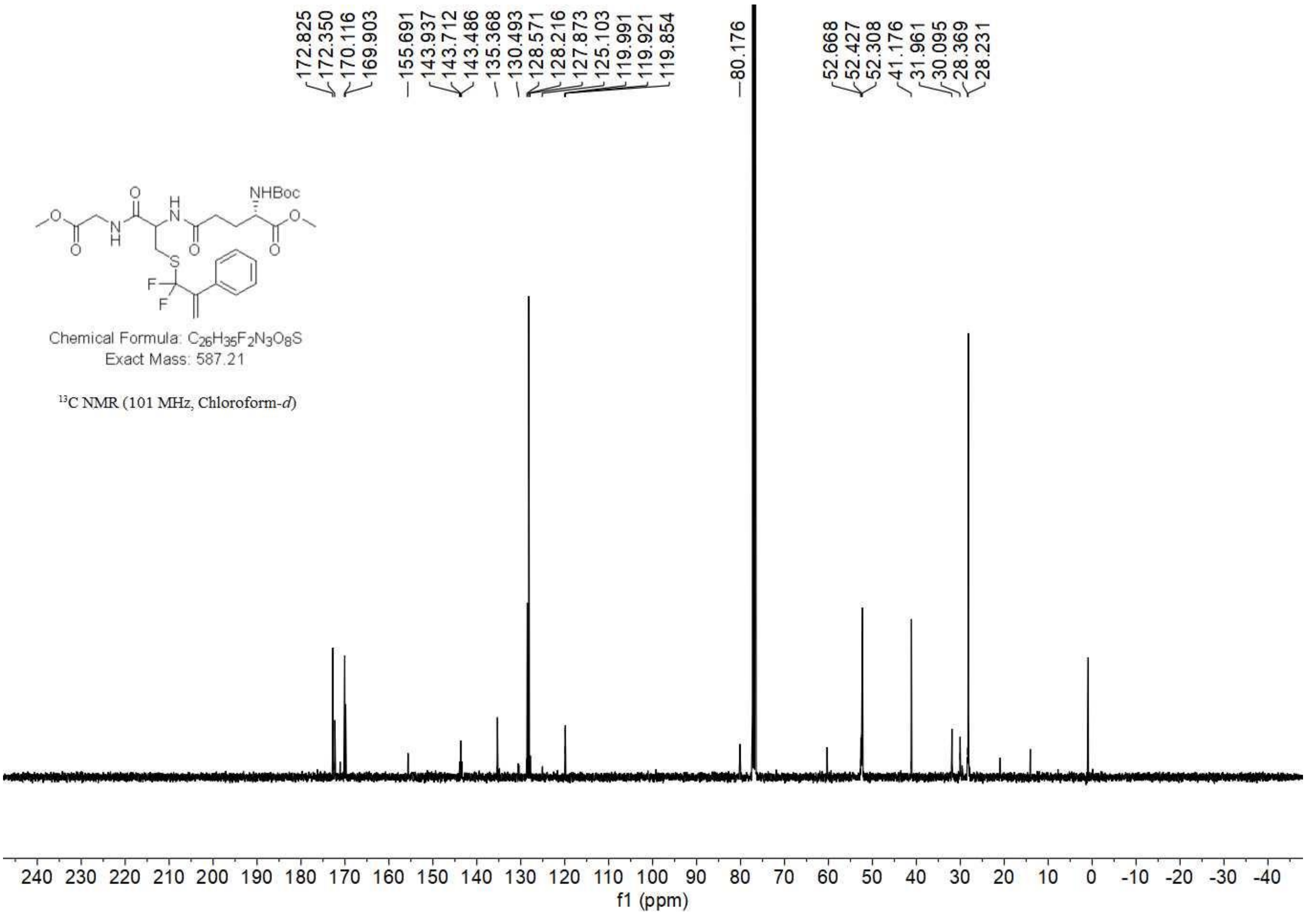
Chemical Formula: $C_{26}H_{35}F_2N_3O_8S$
Exact Mass: 587.21

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



Chemical Formula: $C_{26}H_{35}F_2N_3O_8S$
Exact Mass: 587.21

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

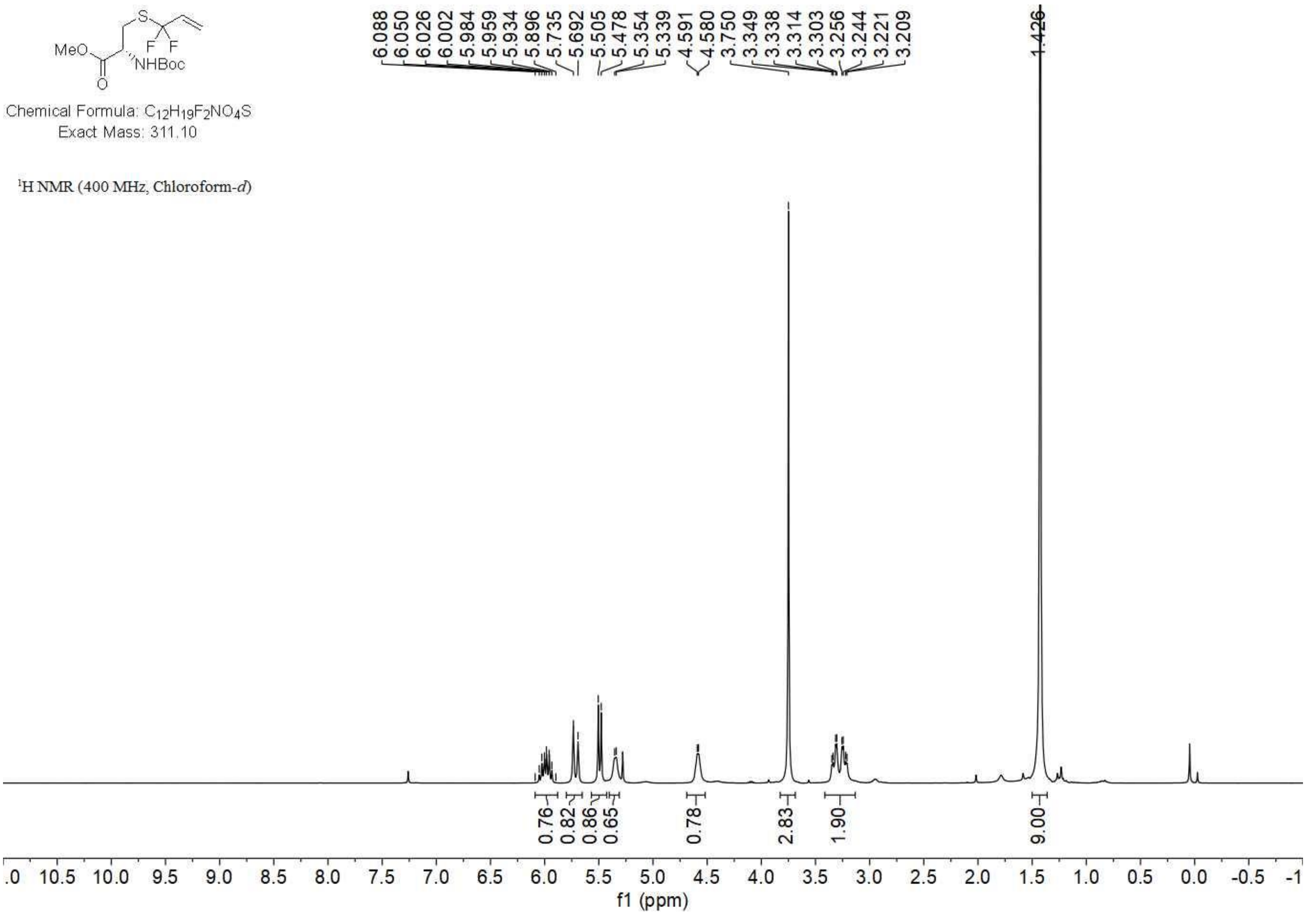


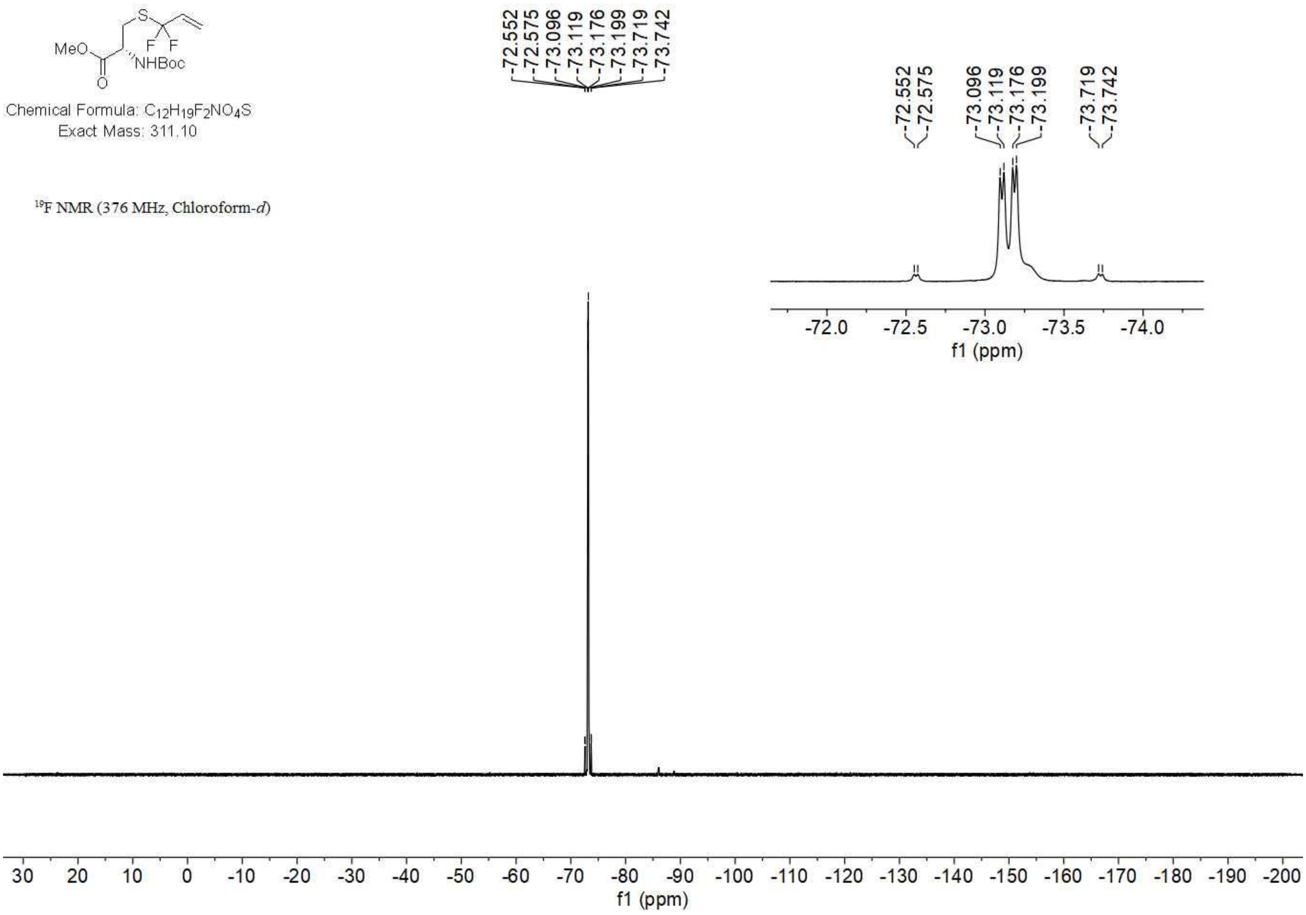
Chemical Formula: $C_{26}H_{35}F_2N_3O_8S$
Exact Mass: 587.21

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

9.3 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for Compounds 3a and 3q-y

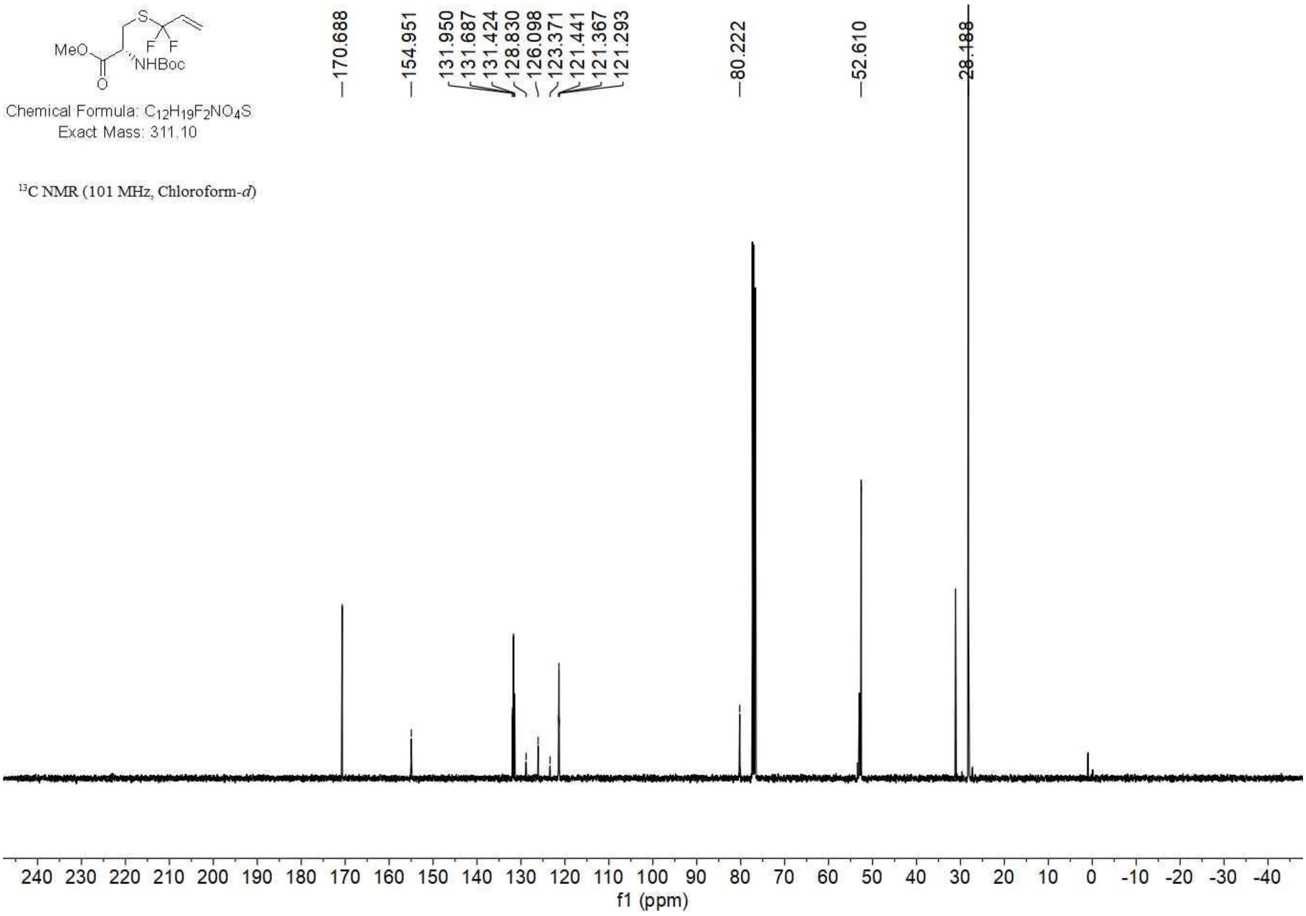
Spectra of 3a





Chemical Formula: $C_{12}H_{19}F_2NO_4S$
Exact Mass: 311.10

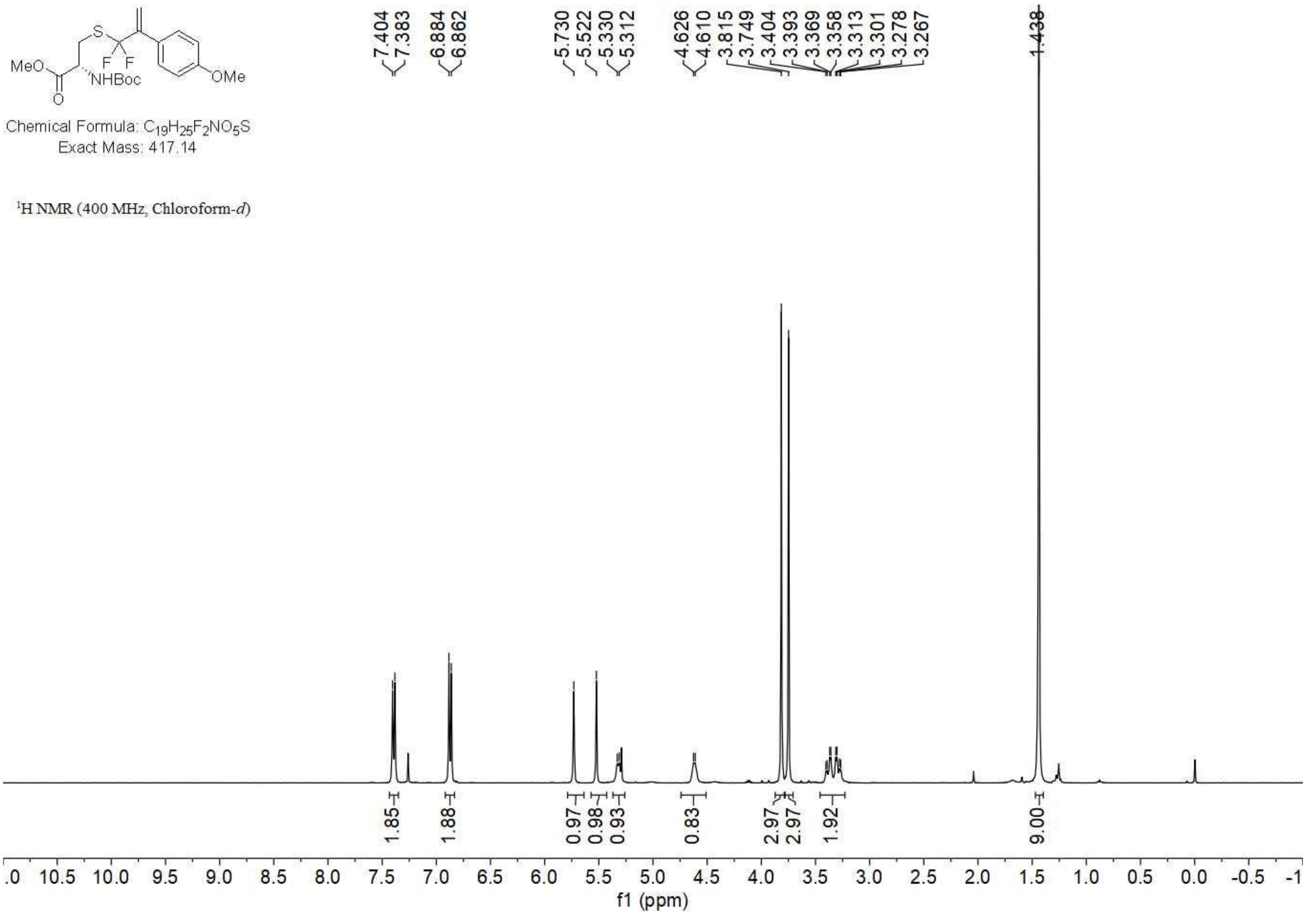
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{12}H_{19}F_2NO_4S$
Exact Mass: 311.10

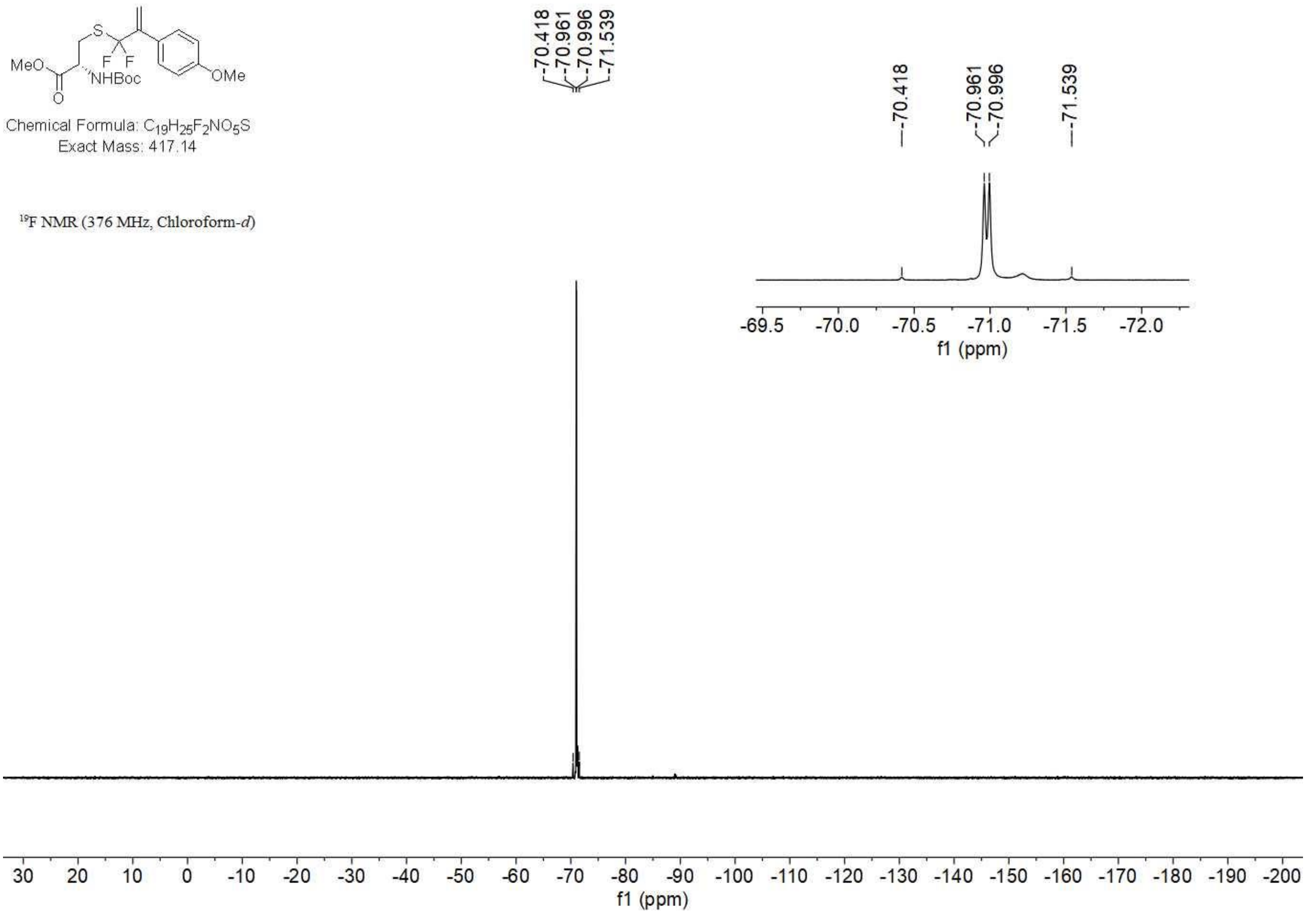
^{13}C NMR (101 MHz, Chloroform-*d*)

Spectra of 3q



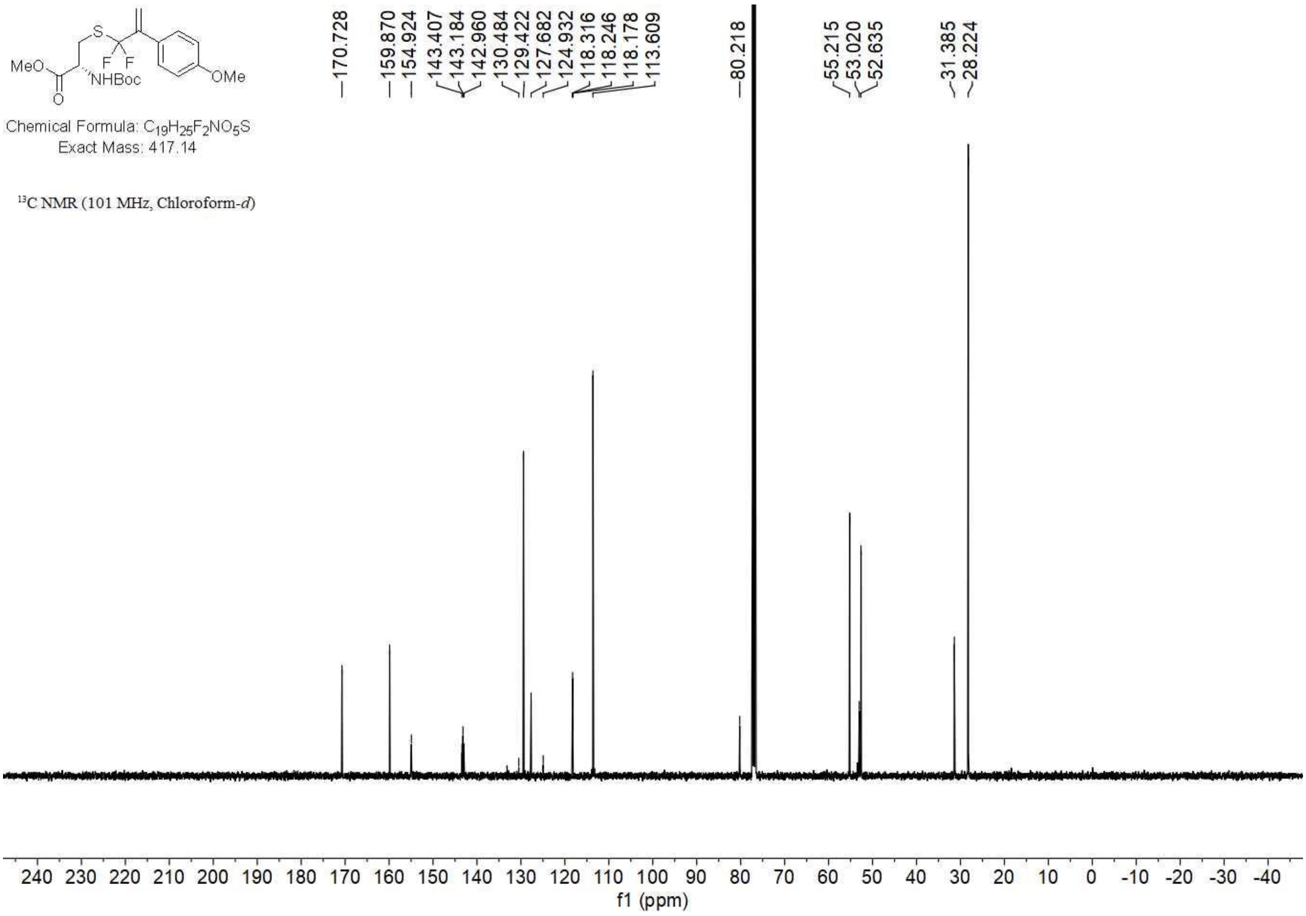
Chemical Formula: $C_{19}H_{25}F_2NO_5S$
Exact Mass: 417.14

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



Chemical Formula: $C_{19}H_{25}F_2NO_5S$
Exact Mass: 417.14

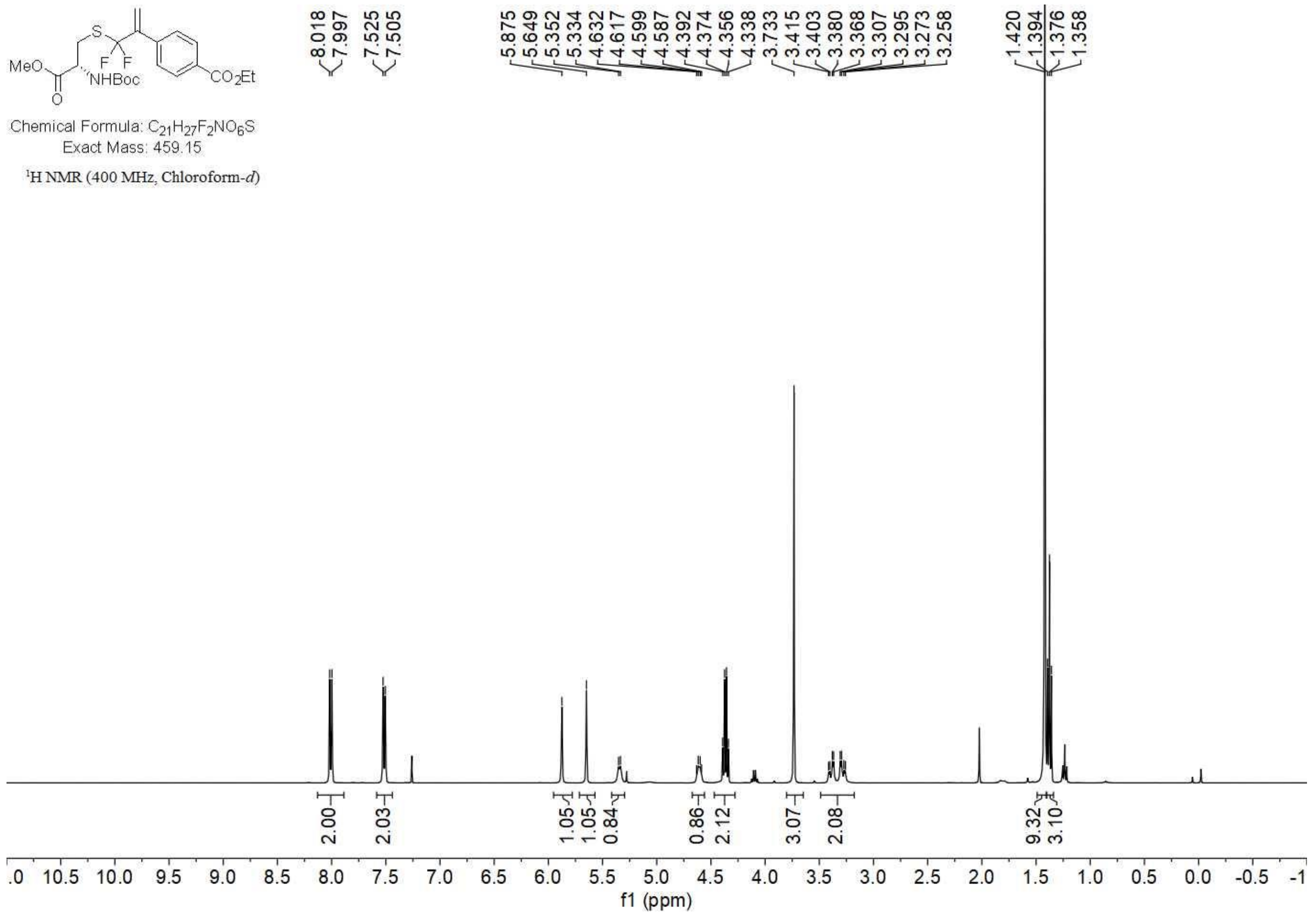
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{19}H_{25}F_2NO_5S$
Exact Mass: 417.14

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

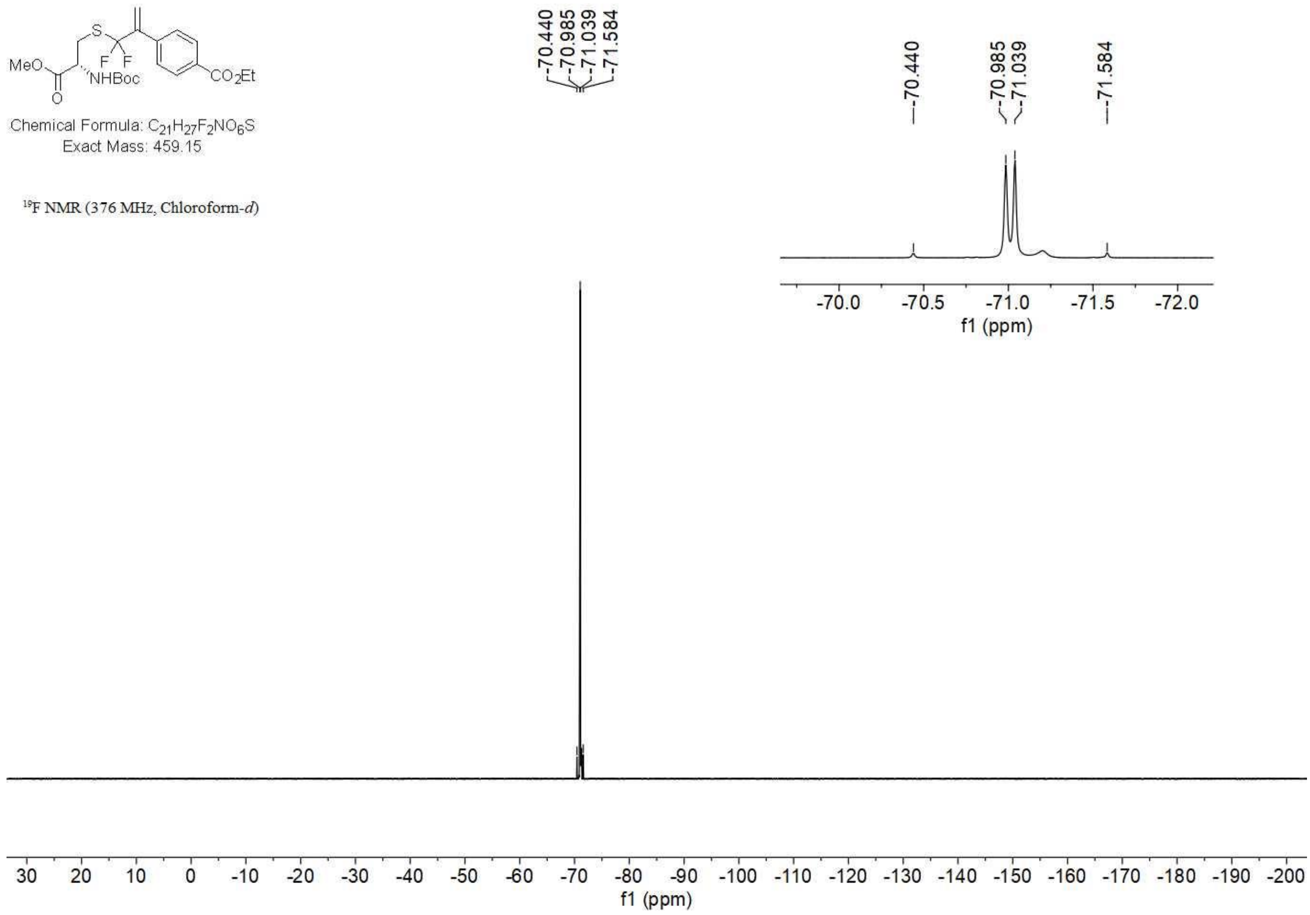
Spectra of 3r



Chemical Formula: $C_{21}H_{27}F_2NO_6S$

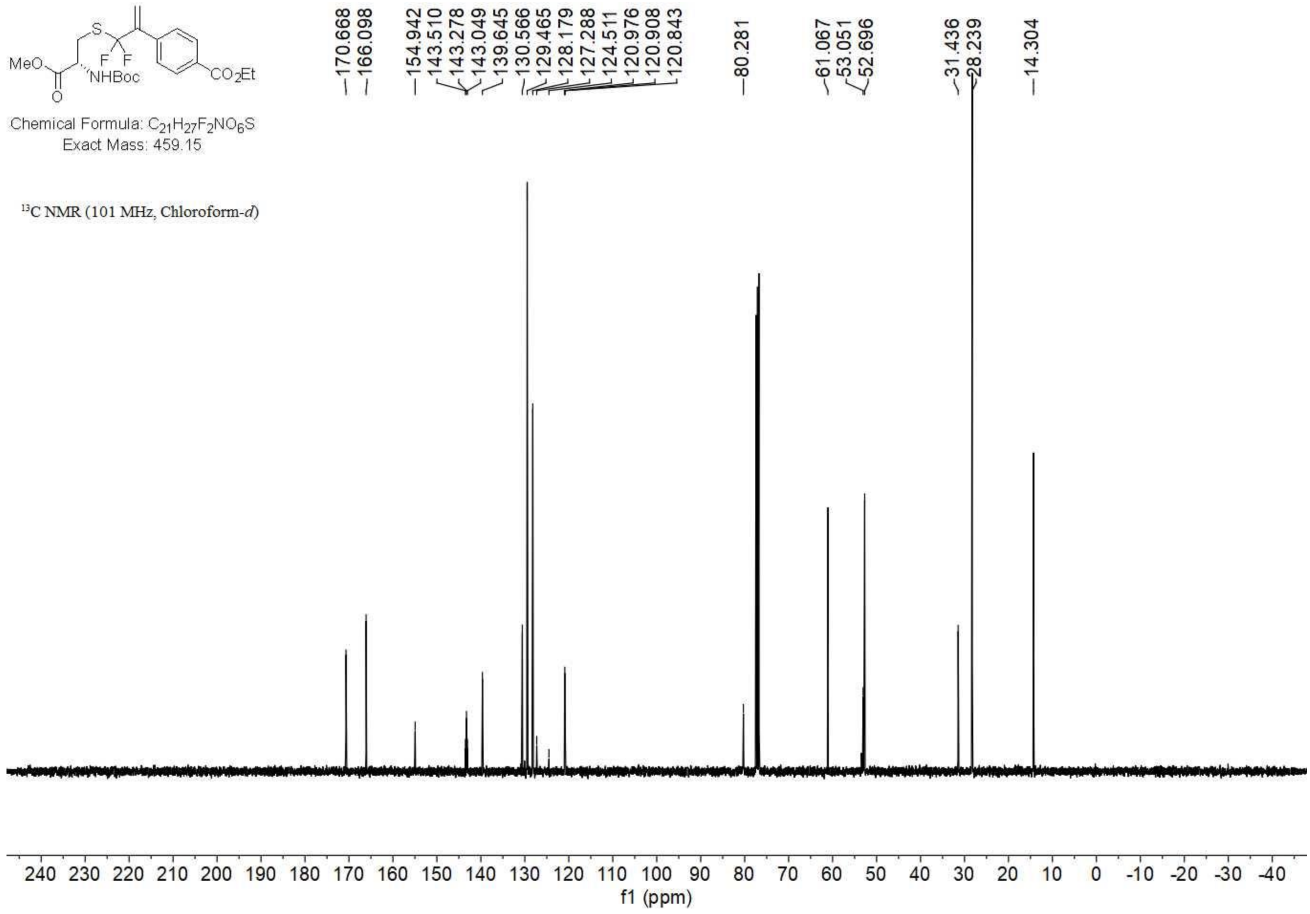
Exact Mass: 459.15

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



Chemical Formula: $C_{21}H_{27}F_2NO_6S$
Exact Mass: 459.15

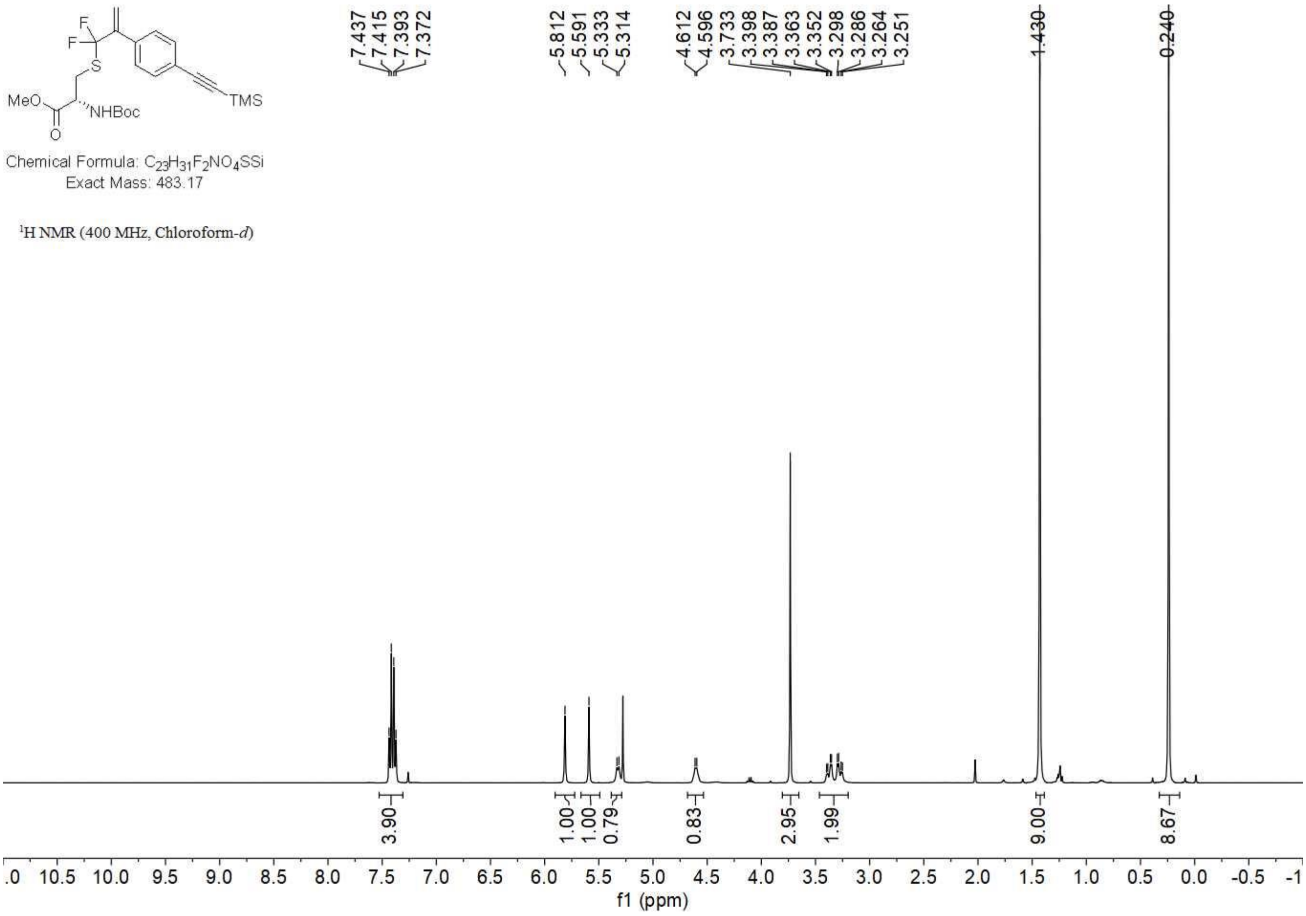
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{21}H_{27}F_2NO_6S$
Exact Mass: 459.15

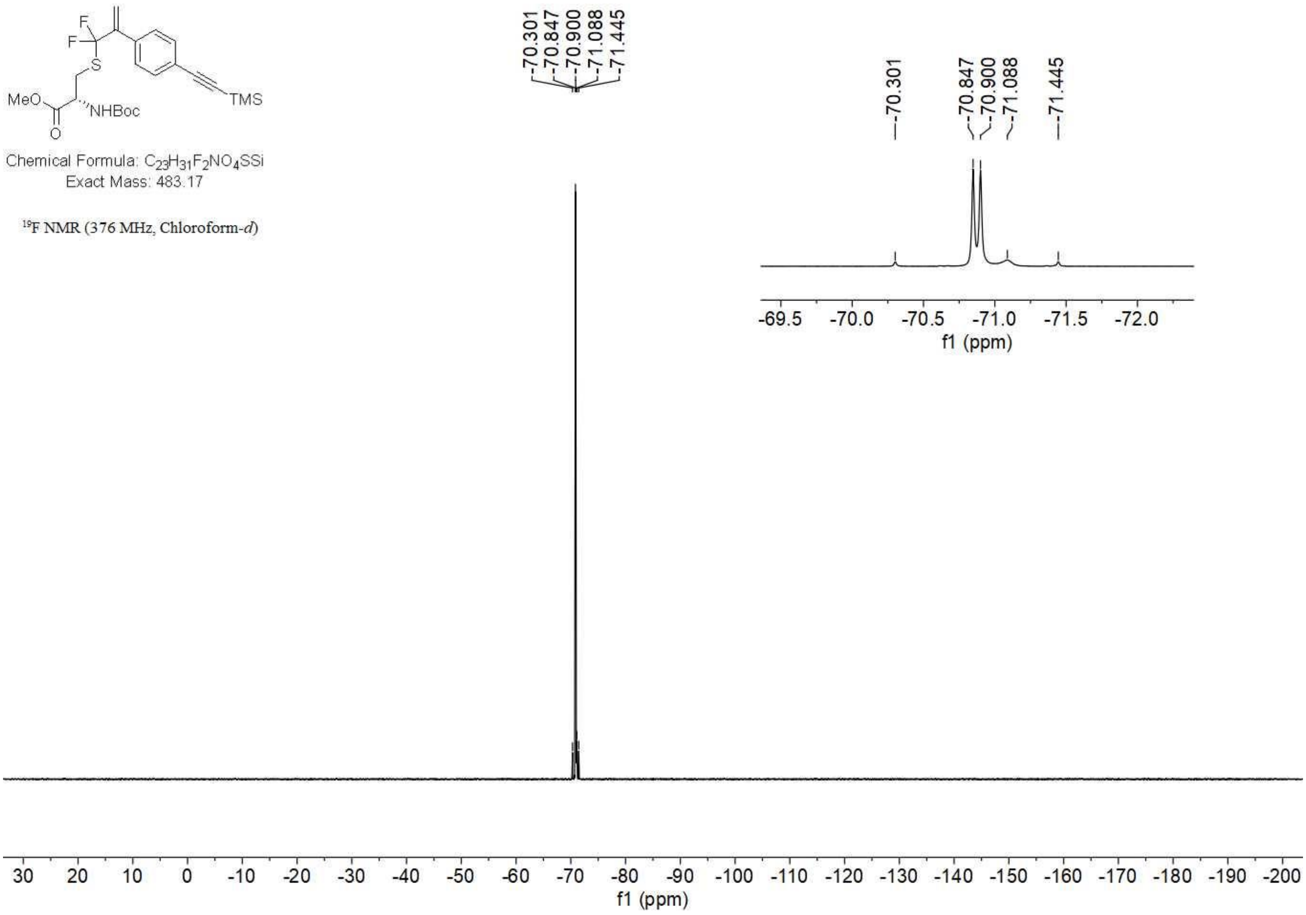
^{13}C NMR (101 MHz, Chloroform-*d*)

Spectra of 3s



Chemical Formula: $C_{23}H_{31}F_2NO_4SSi$
Exact Mass: 483.17

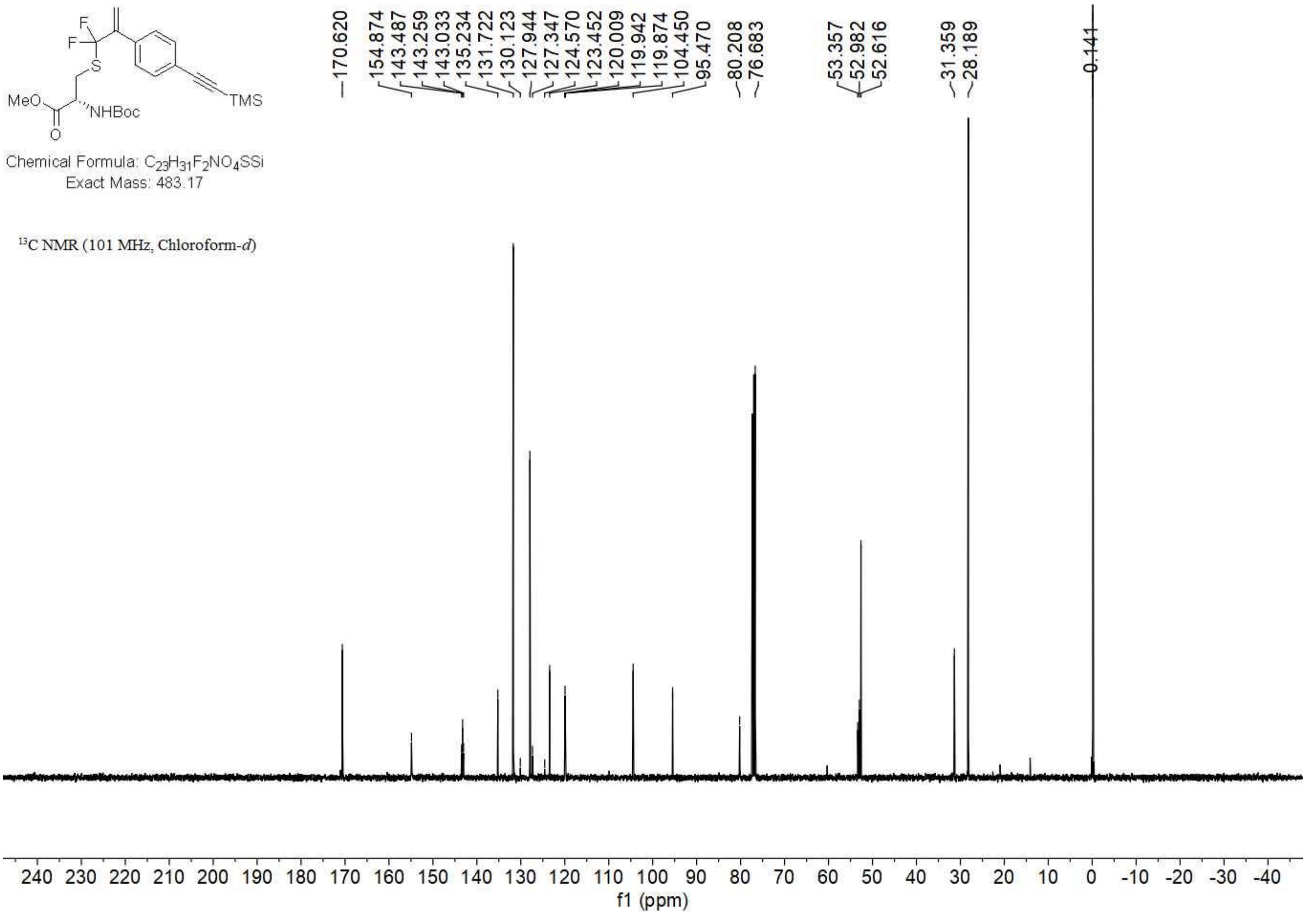
^{1}H NMR (400 MHz, Chloroform-*d*)



Chemical Formula: $C_{23}H_{31}F_2NO_4SSi$

Exact Mass: 483.17

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

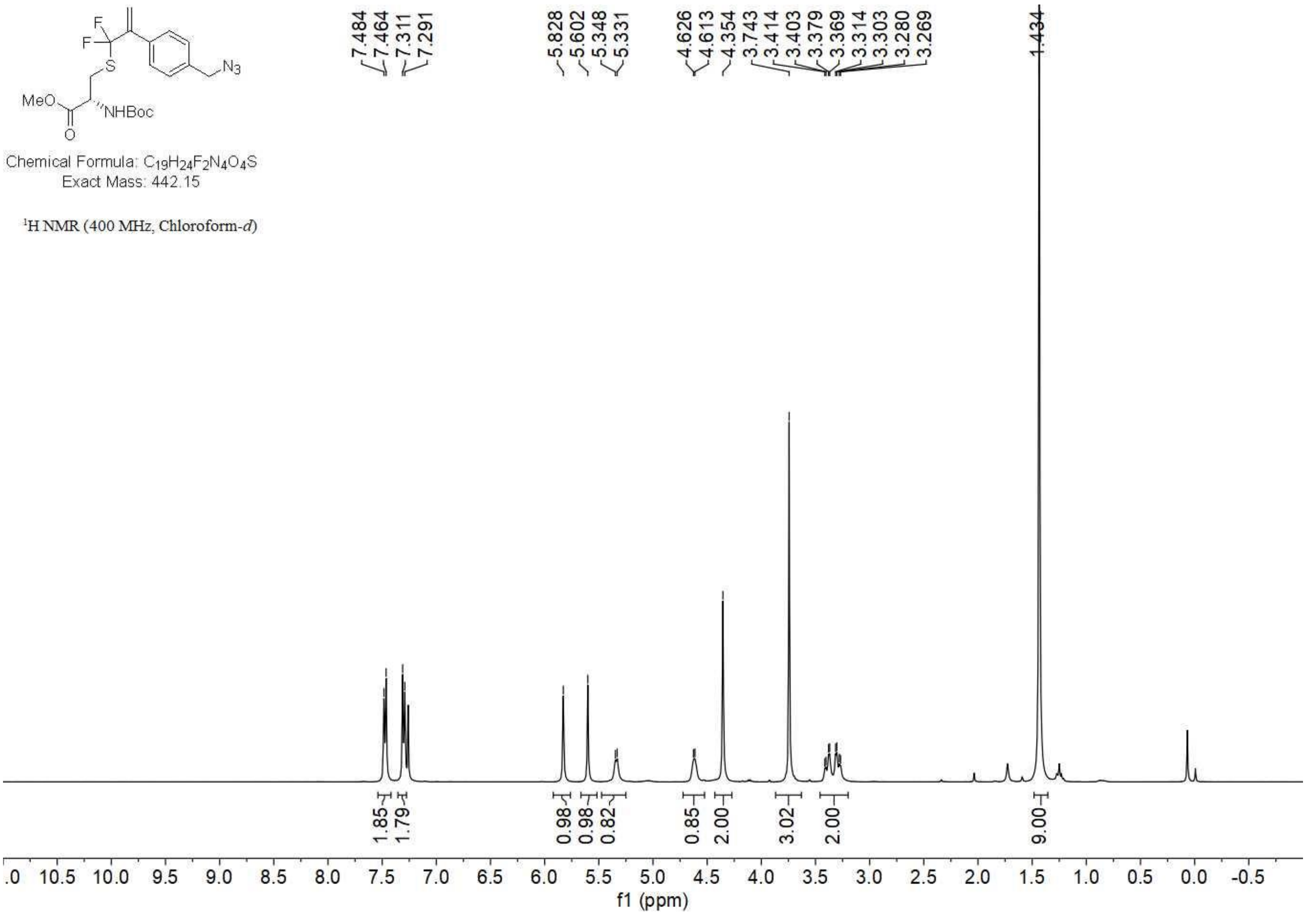


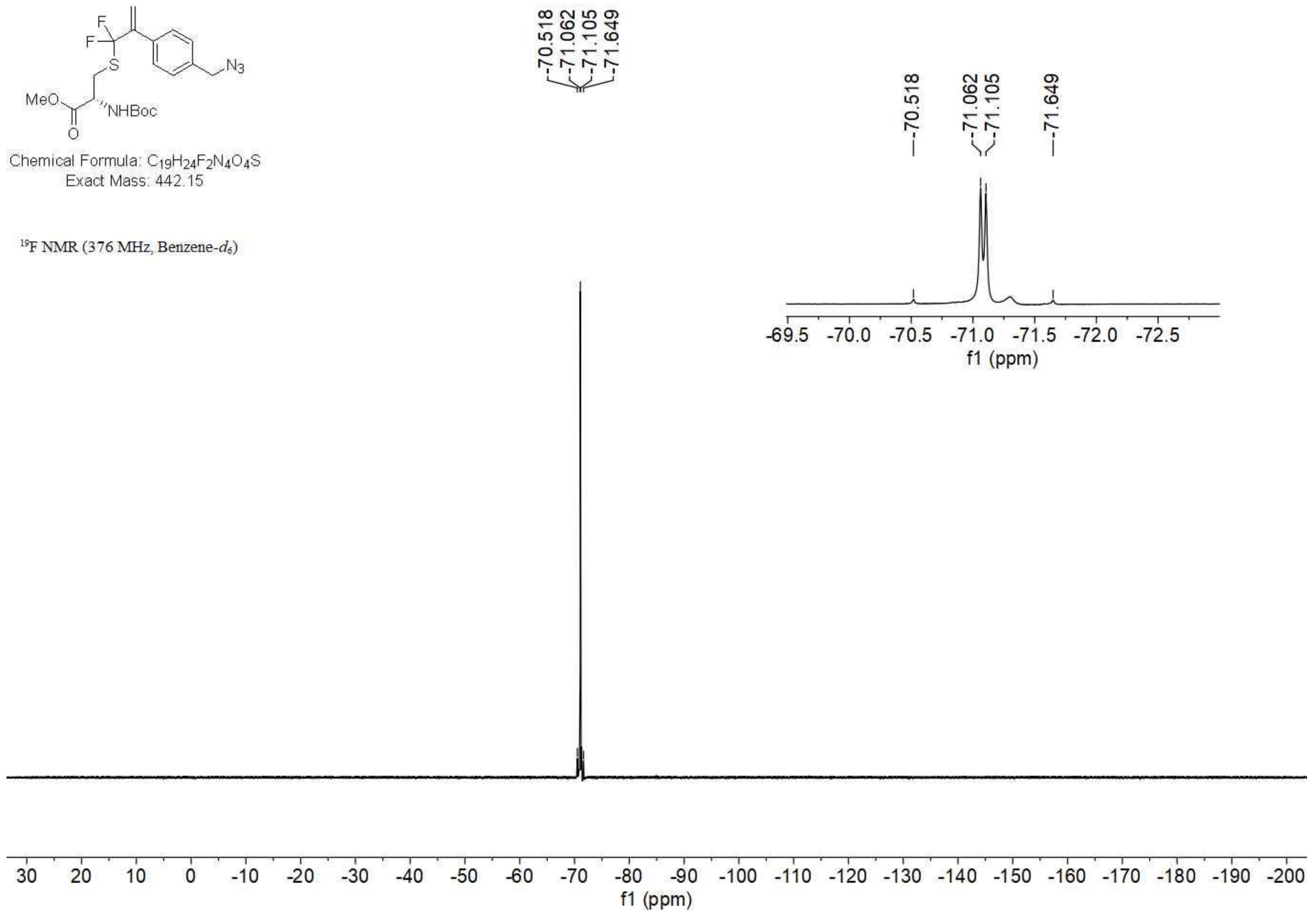
Chemical Formula: $C_{23}H_{31}F_2NO_4SSi$

Exact Mass: 483.17

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

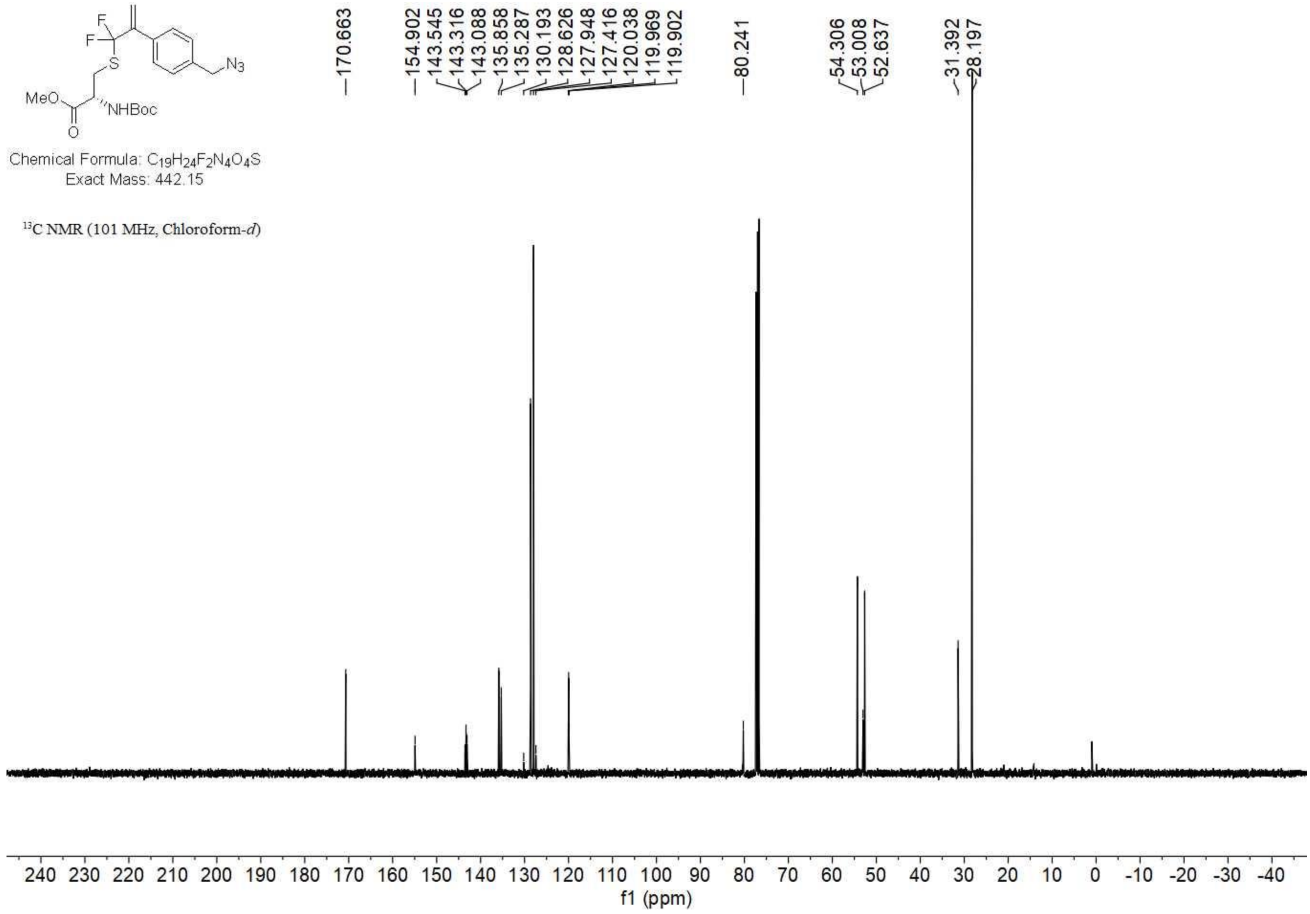
Spectra of 3t





Chemical Formula: $C_{19}H_{24}F_2N_4O_4S$
Exact Mass: 442.15

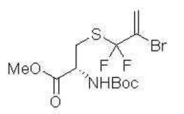
^{19}F NMR (376 MHz, Benzene-d_6)



Chemical Formula: $C_{19}H_{24}F_2N_4O_4S$
Exact Mass: 442.15

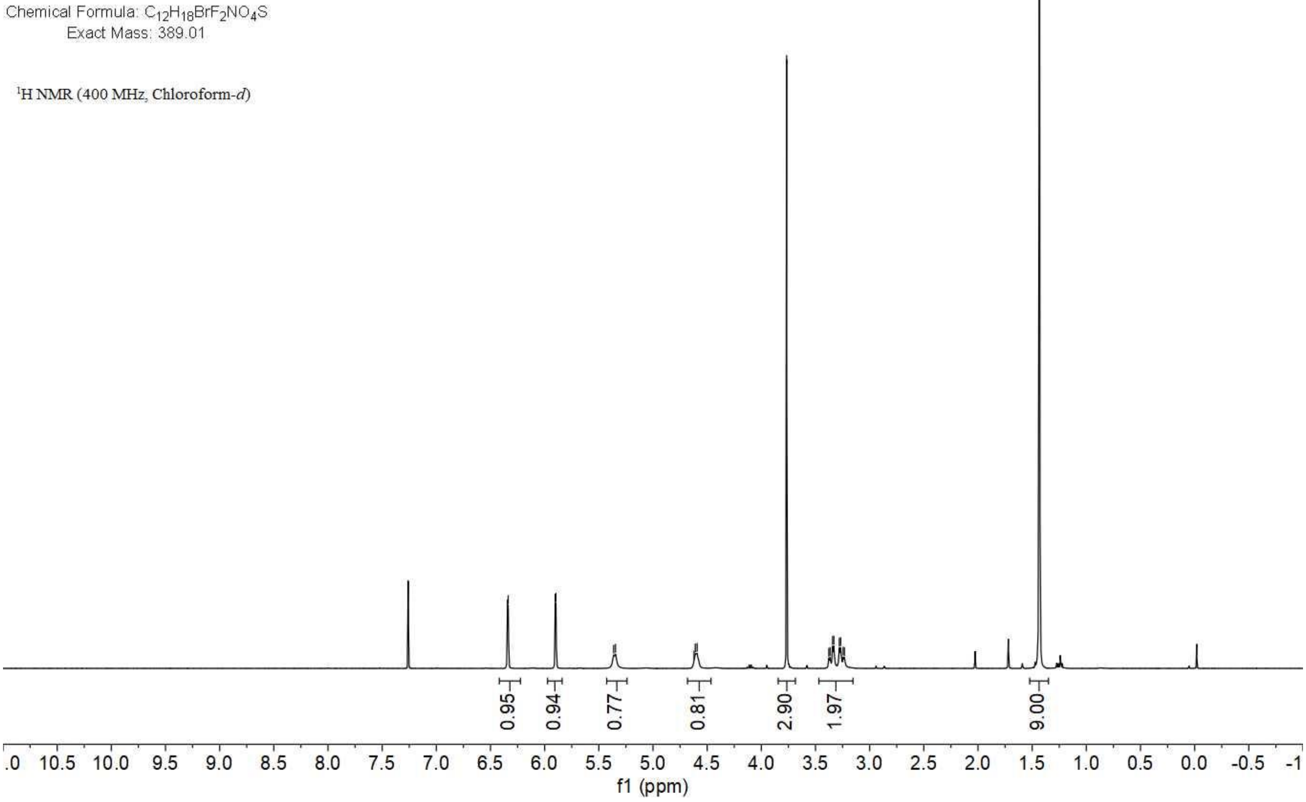
^{13}C NMR (101 MHz, Chloroform-d)

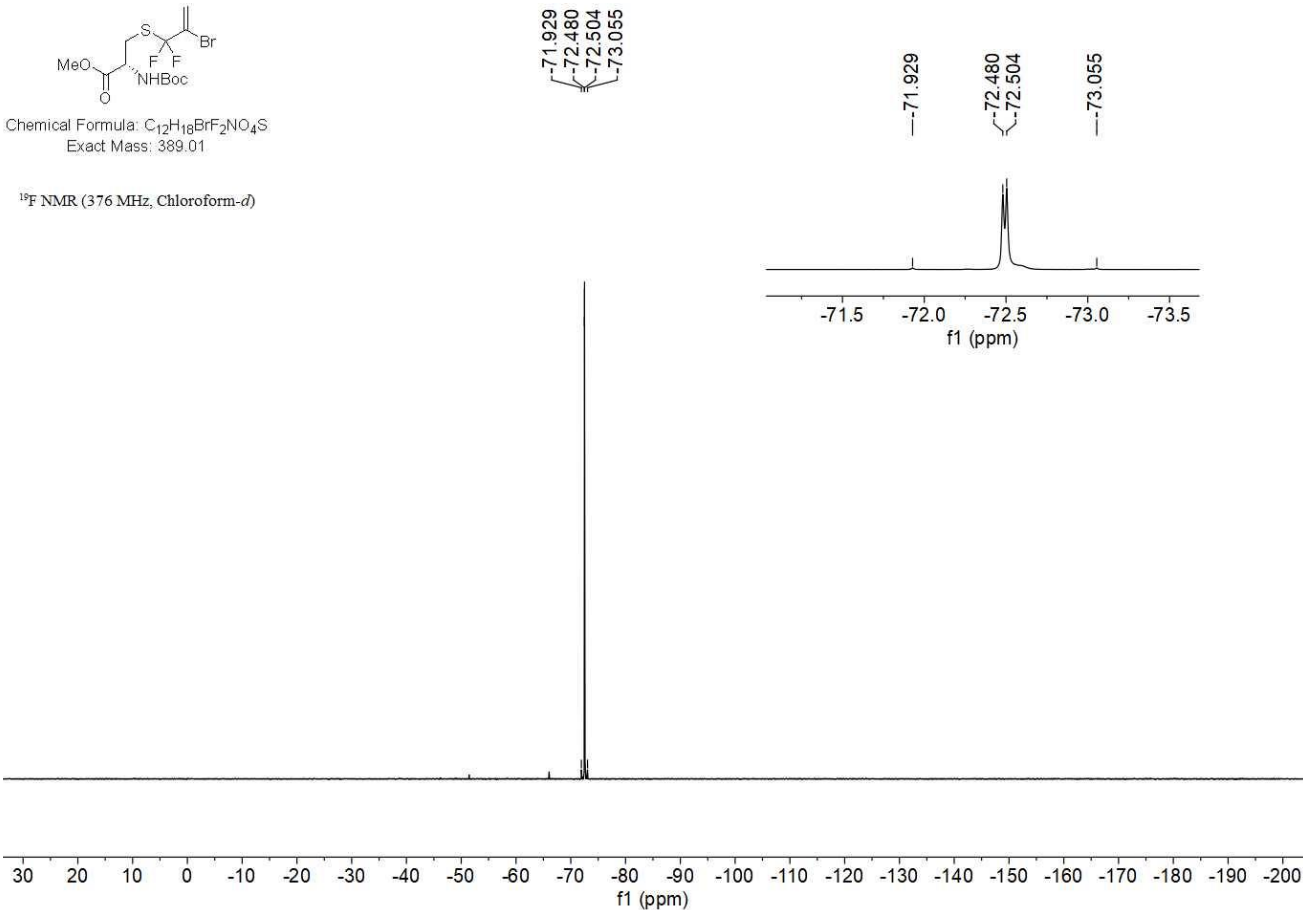
Spectra of 3u



Chemical Formula: $C_{12}H_{18}BrF_2NO_4S$
Exact Mass: 389.01

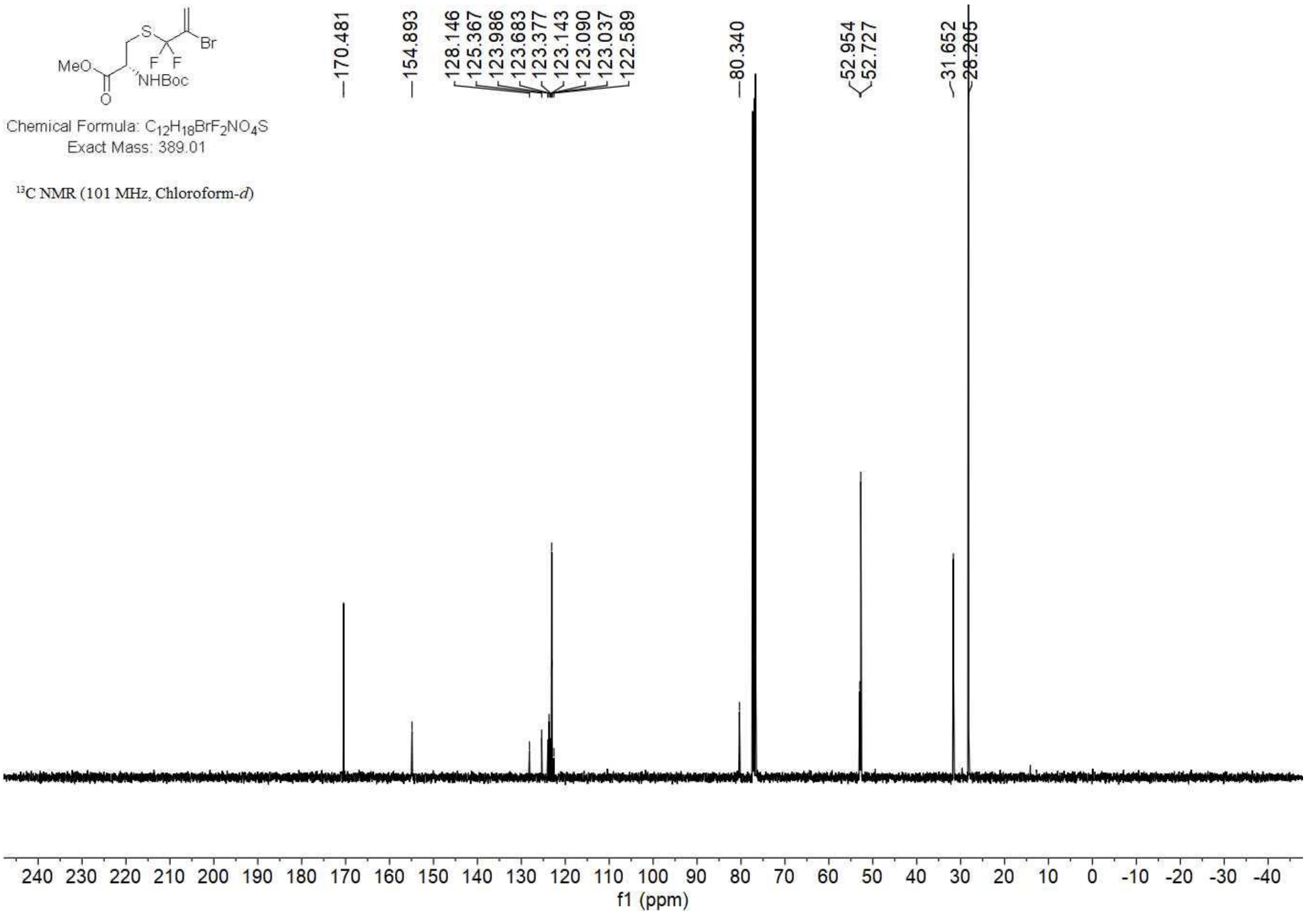
^{1}H NMR (400 MHz, Chloroform-*d*)





Chemical Formula: $C_{12}H_{18}BrF_2NO_4S$
Exact Mass: 389.01

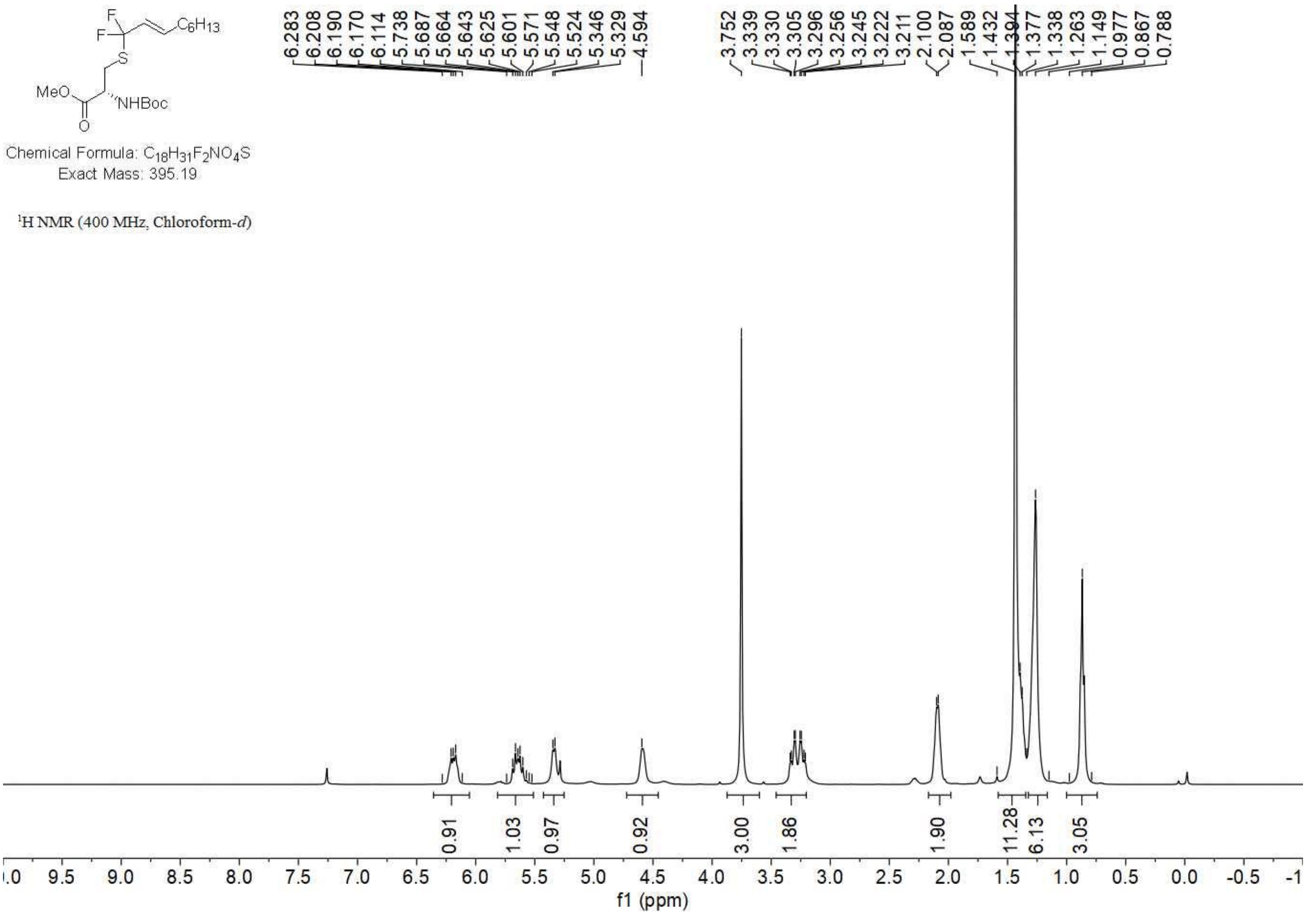
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{12}H_{18}BrF_2NO_4S$
Exact Mass: 389.01

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

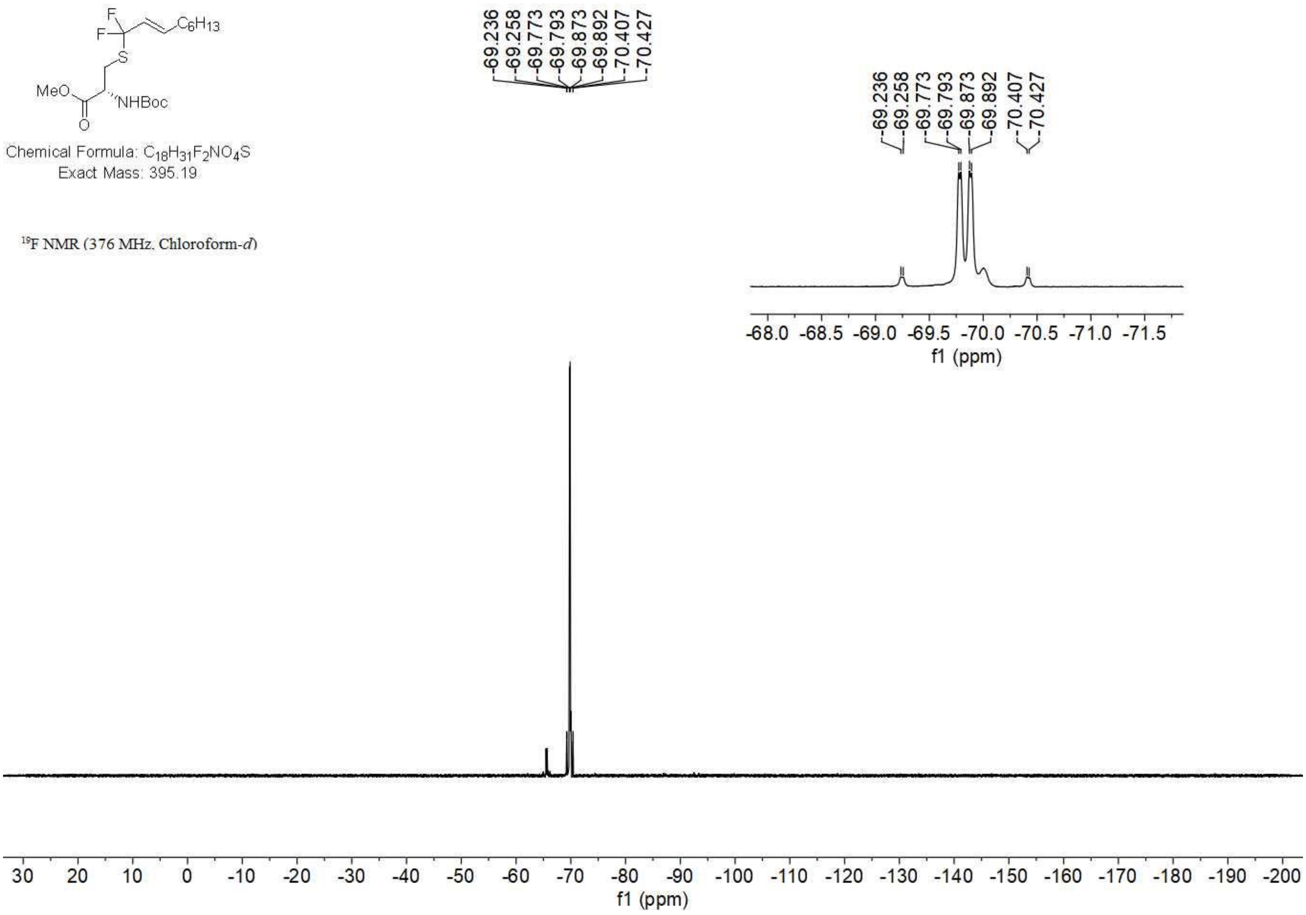
Spectra of 3v



Chemical Formula: $C_{18}H_{31}F_2NO_4S$

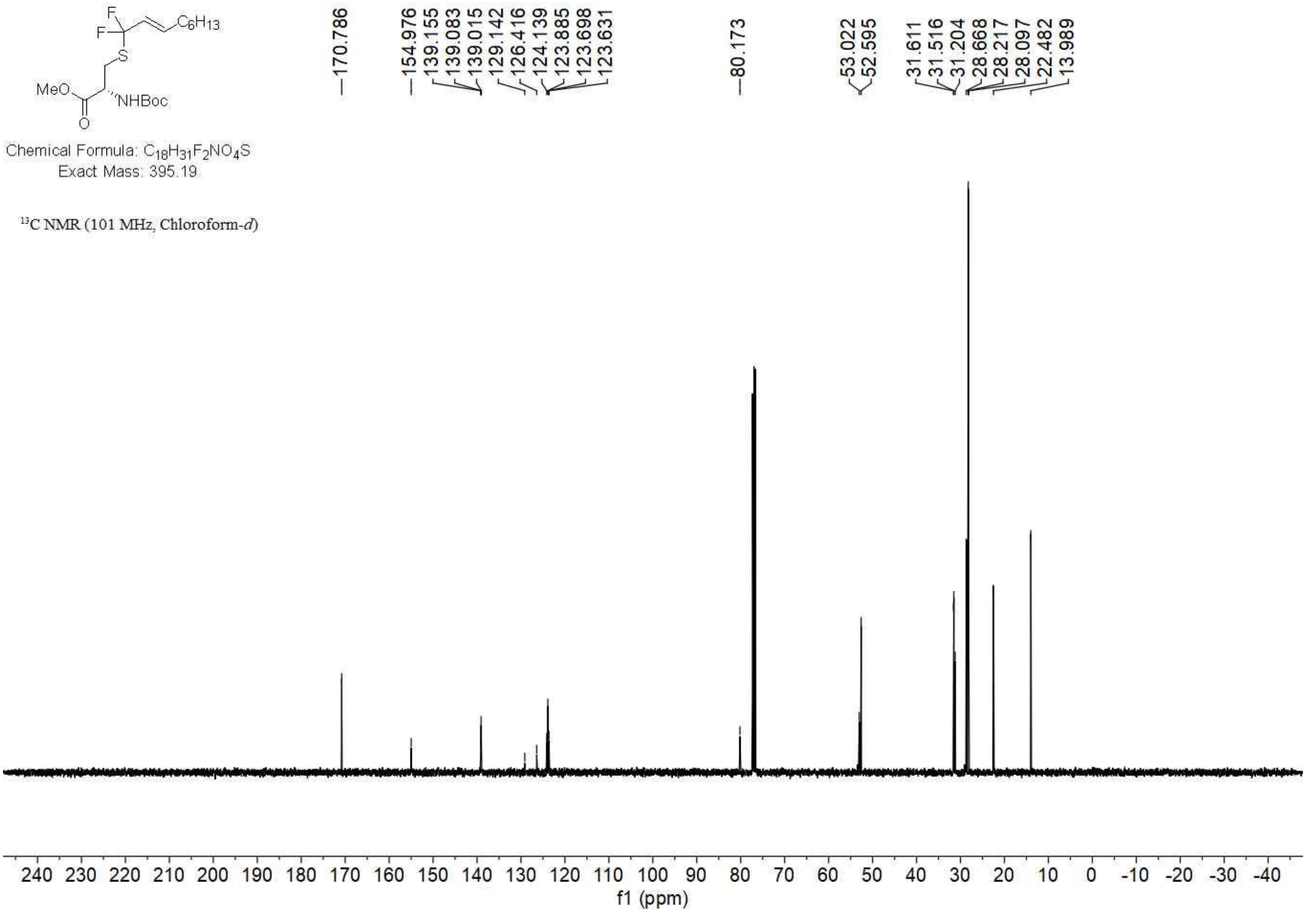
Exact Mass: 395.19

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



Chemical Formula: $C_{18}H_{31}F_2NO_4S$
Exact Mass: 395.19

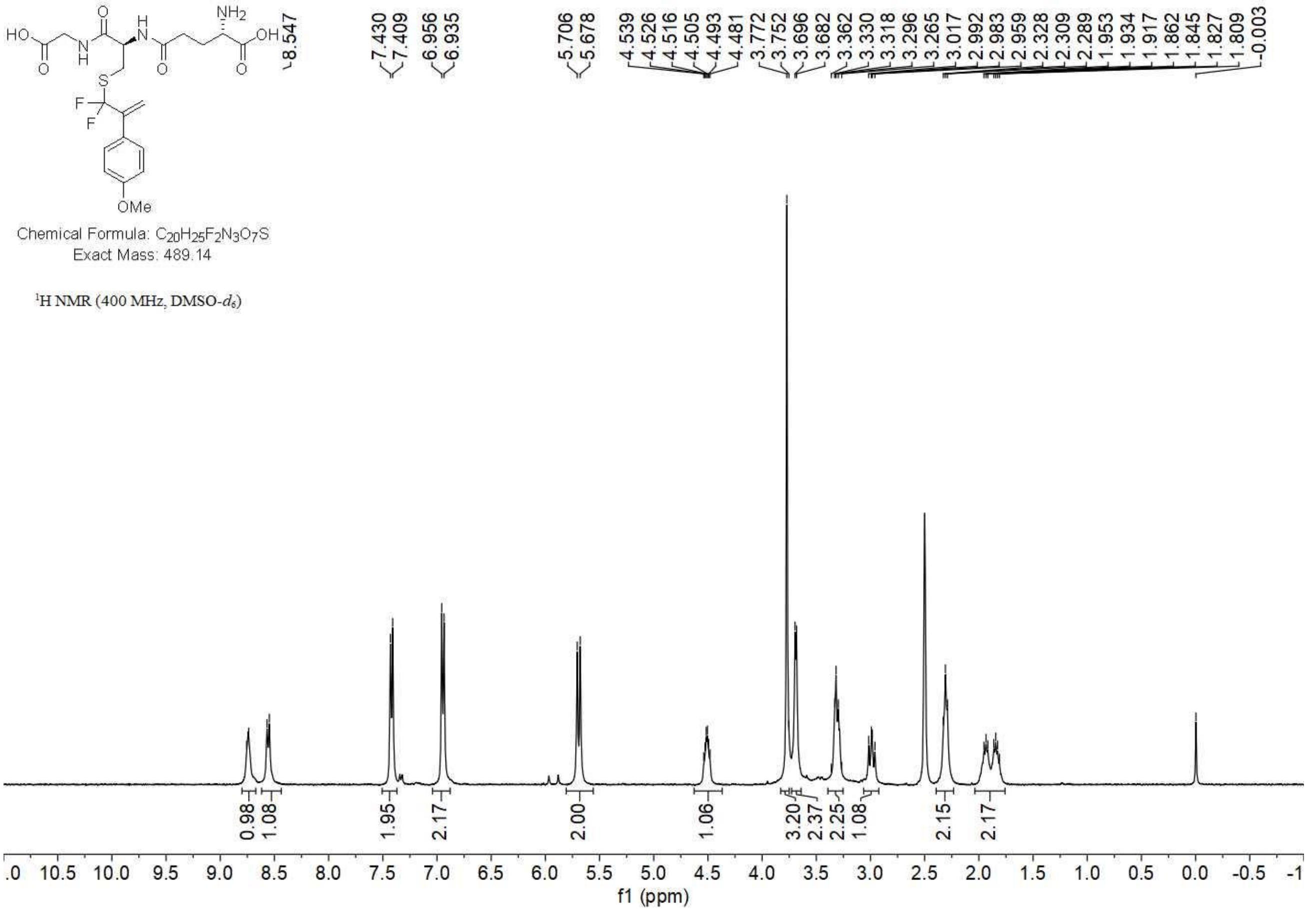
^{19}F NMR (376 MHz, Chloroform-*d*)

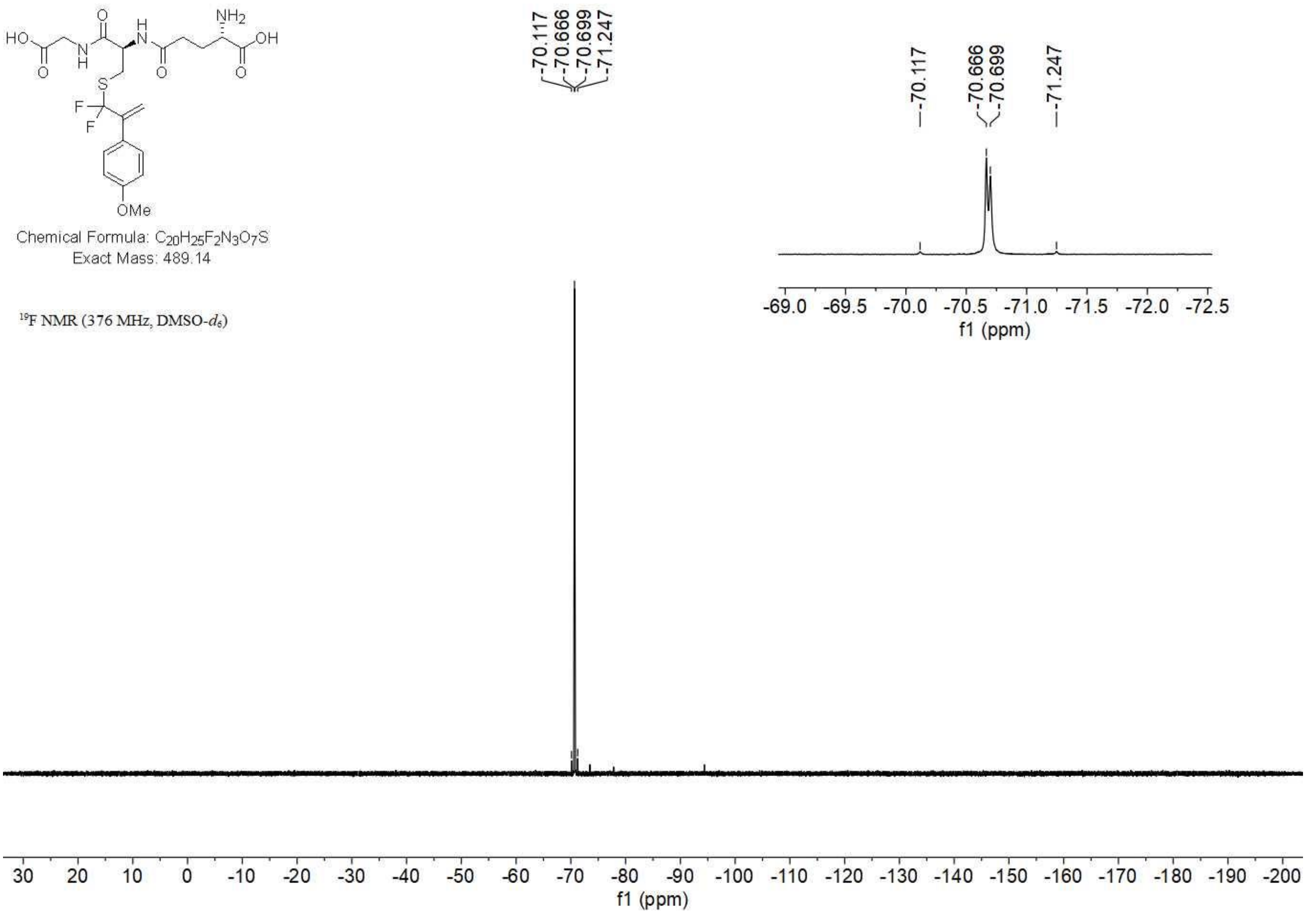


Chemical Formula: $C_{18}H_{31}F_2NO_4S$
Exact Mass: 395.19

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

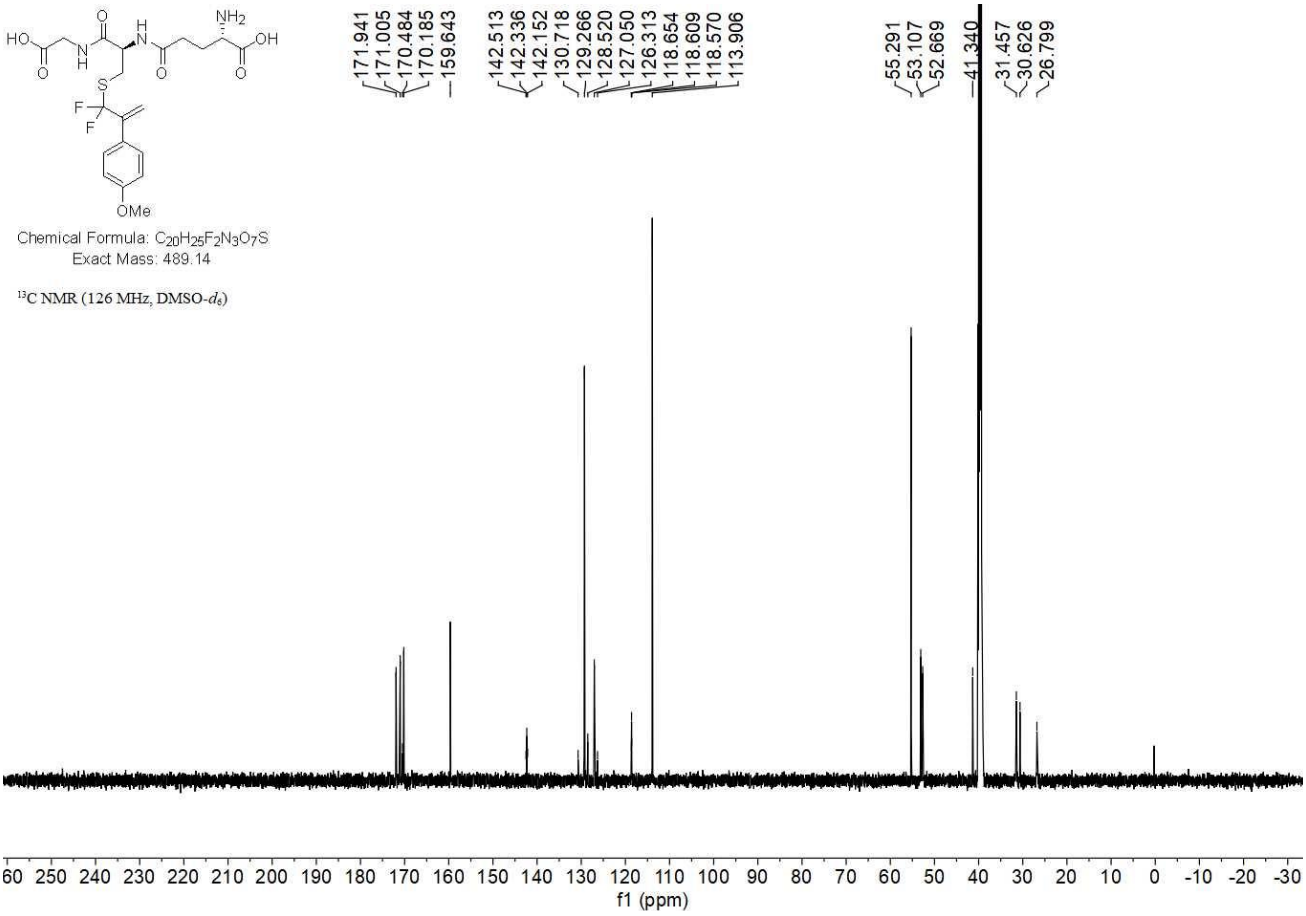
Spectra of 3w





Chemical Formula: $C_{20}H_{25}F_2N_3O_7S$
Exact Mass: 489.14

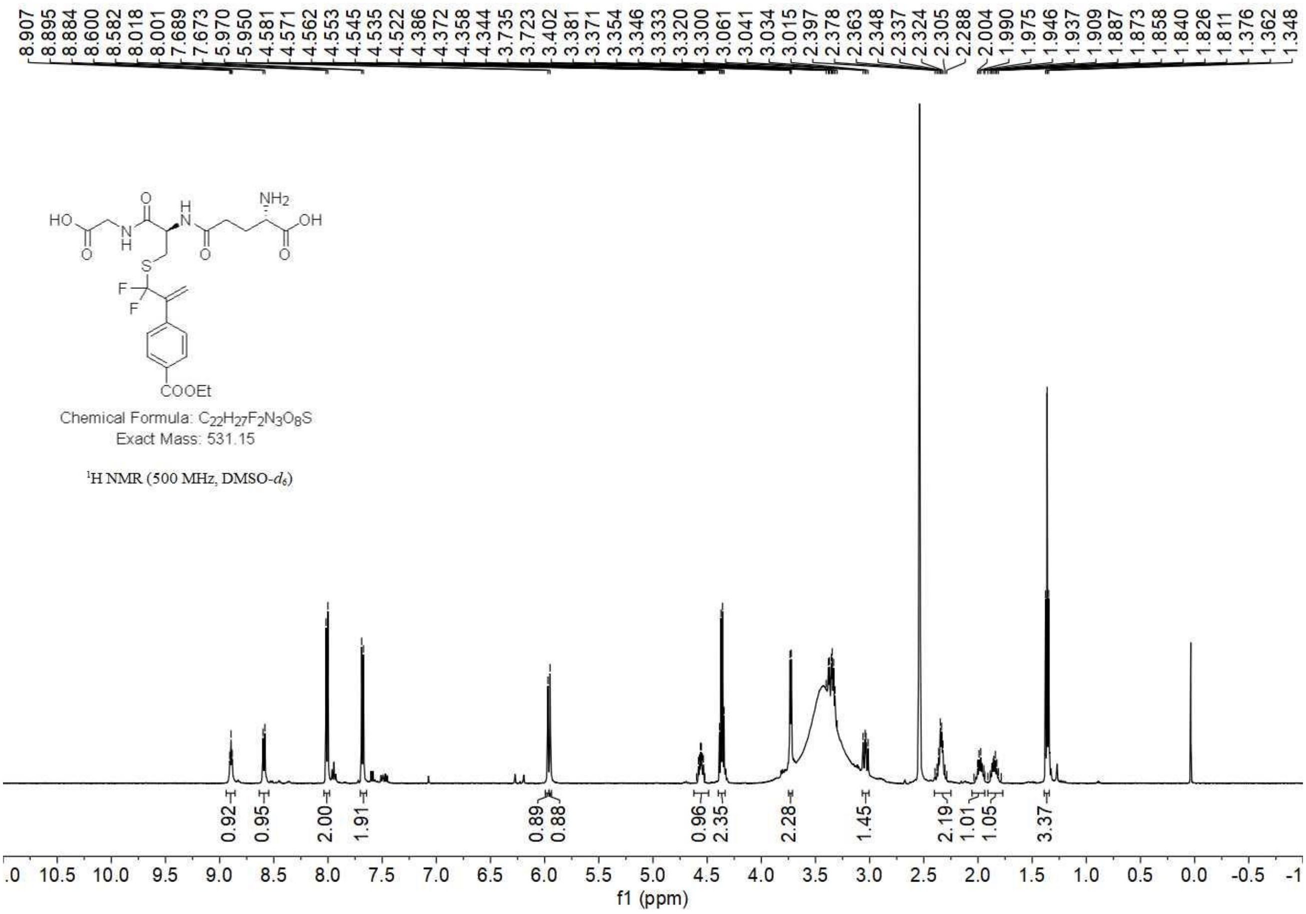
^{19}F NMR (376 MHz, DMSO-d_6)

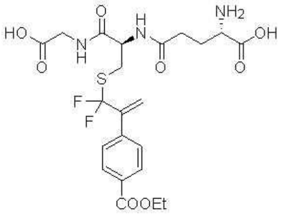


Chemical Formula: $C_{20}H_{25}F_2N_3O_7S$
Exact Mass: 489.14

^{13}C NMR (126 MHz, DMSO-d_6)

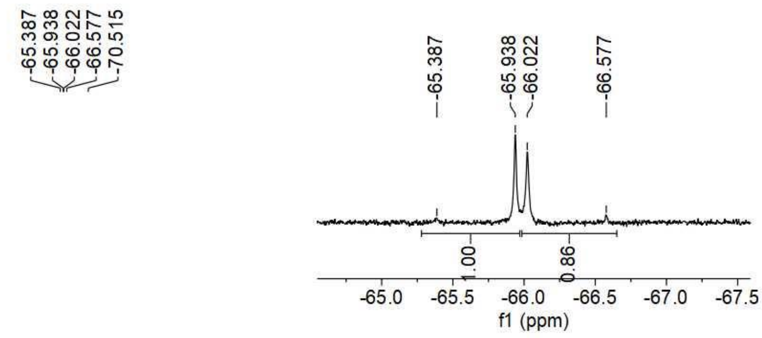
Spectra of 3x

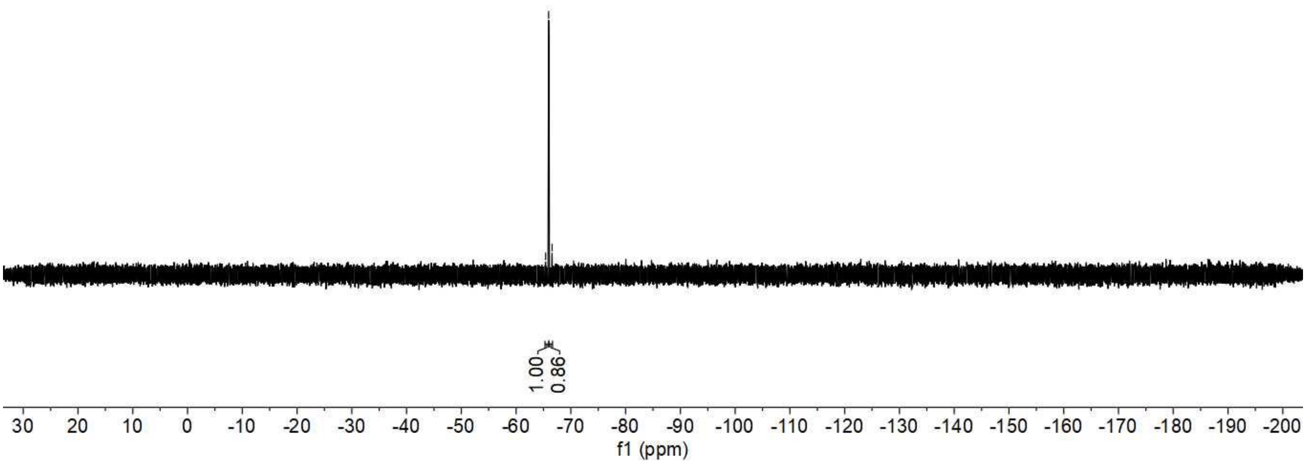


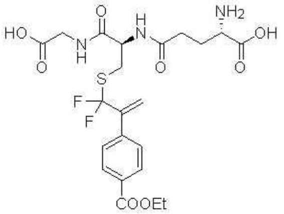


Chemical Formula: $C_{22}H_{27}F_2N_3O_8S$
Exact Mass: 531.15

^{19}F NMR (376 MHz, DMSO-d_6)

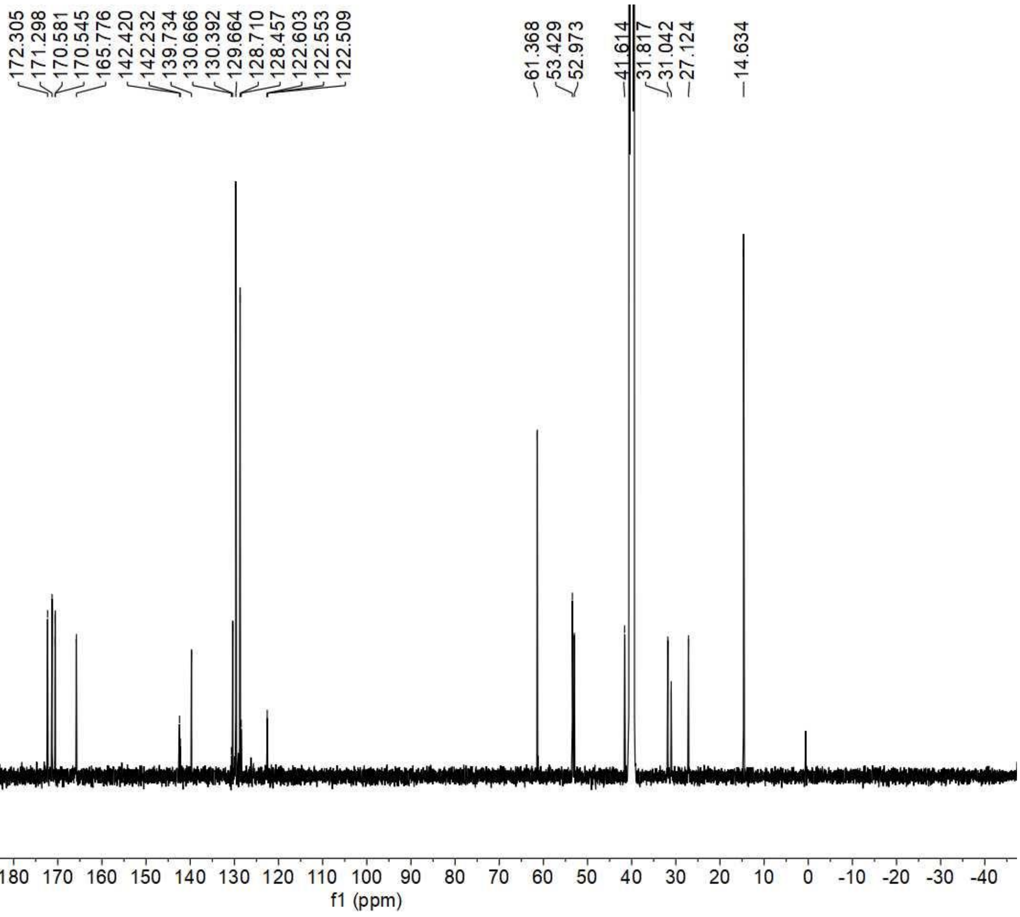




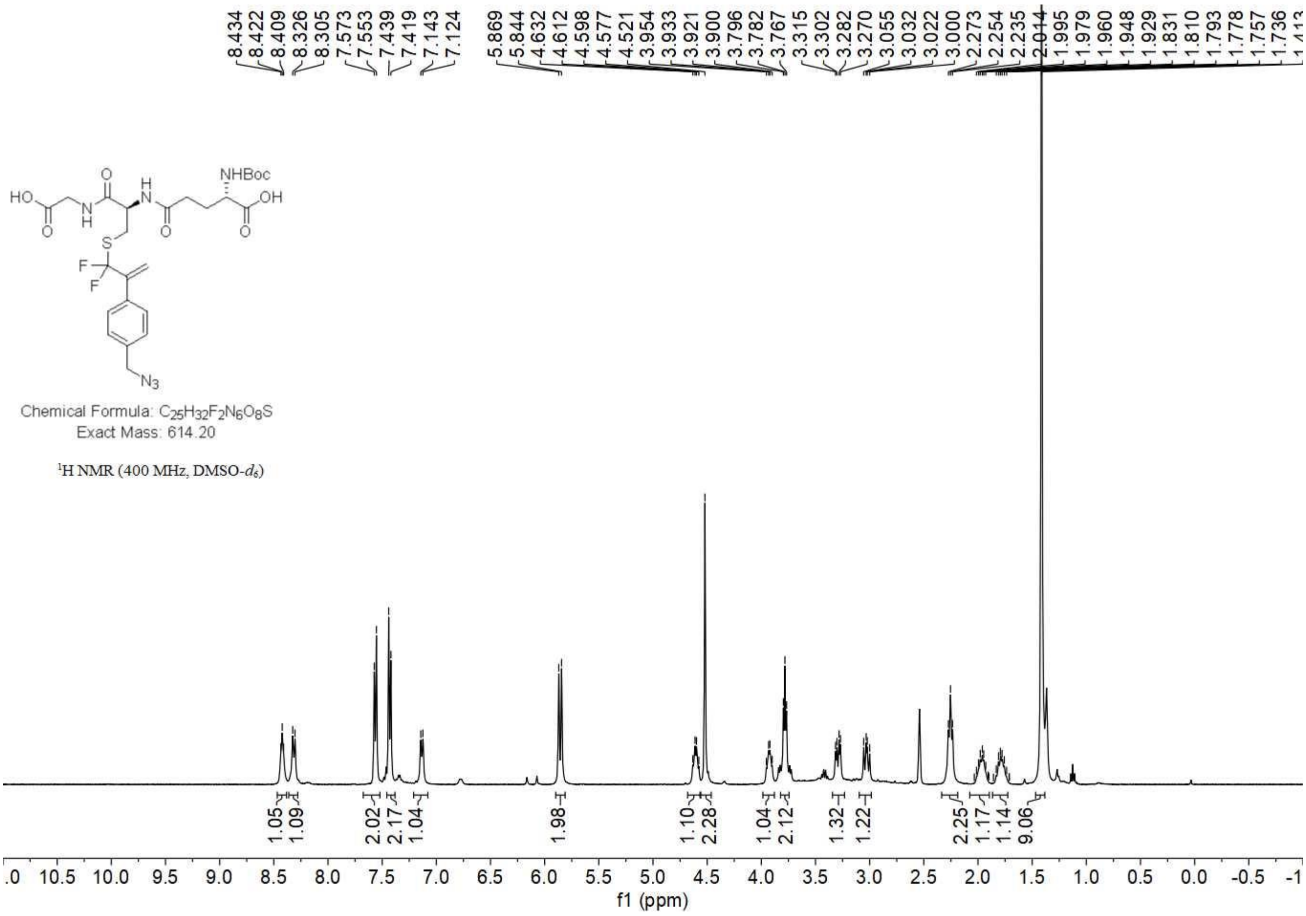


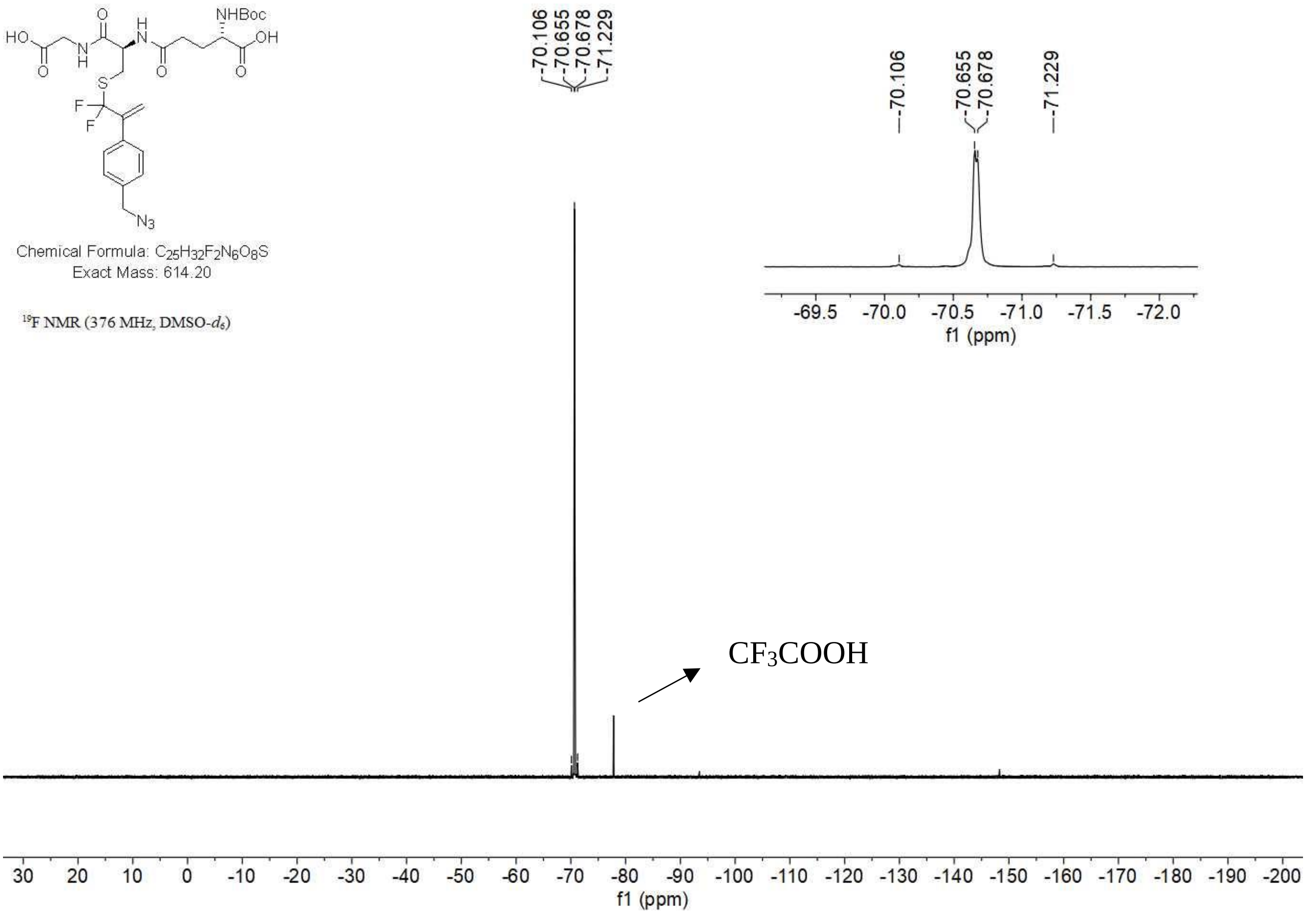
Chemical Formula: $C_{22}H_{27}F_2N_3O_8S$
Exact Mass: 531.15

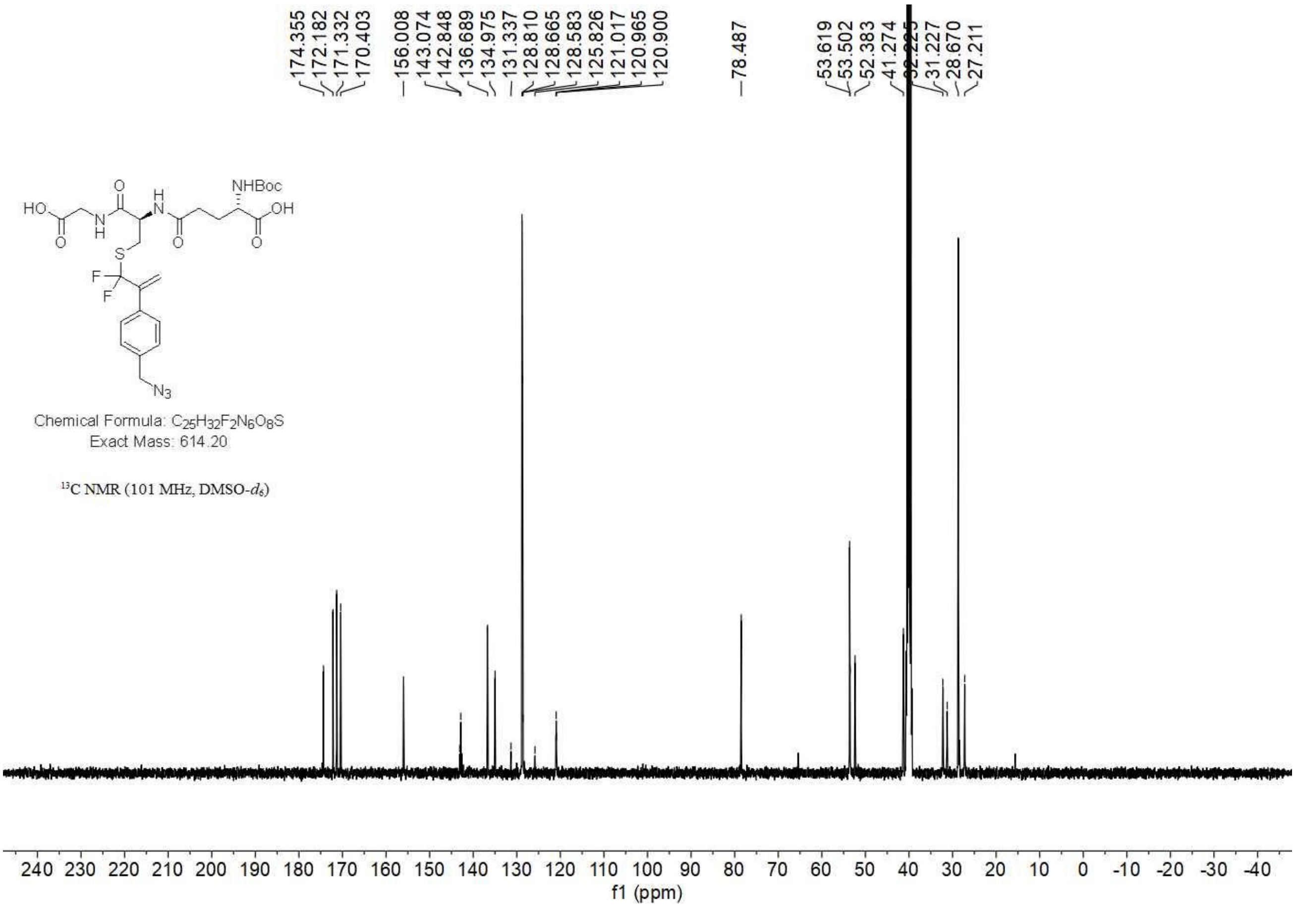
^{13}C NMR (126 MHz, DMSO-d_6)



Spectra of 3y

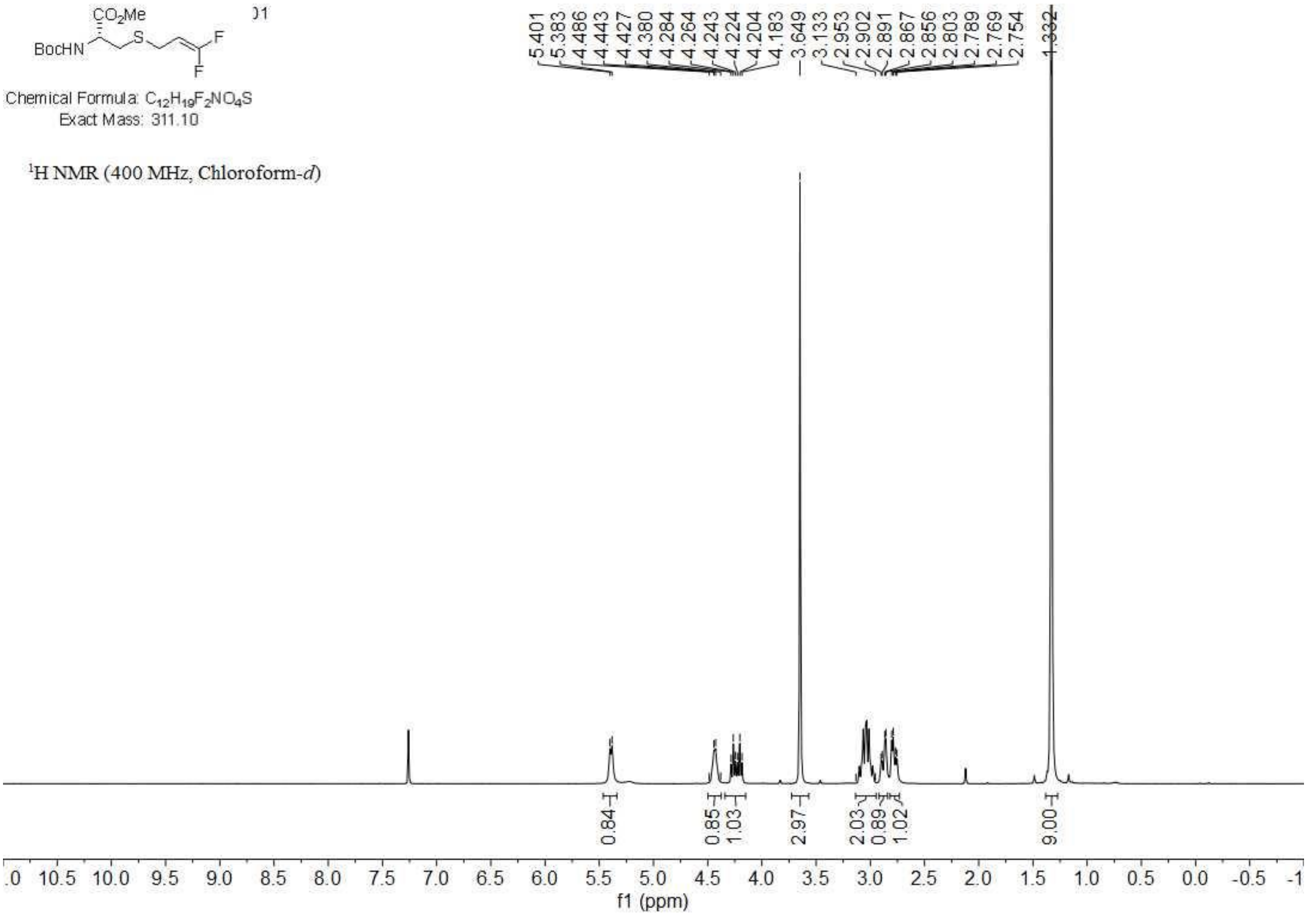


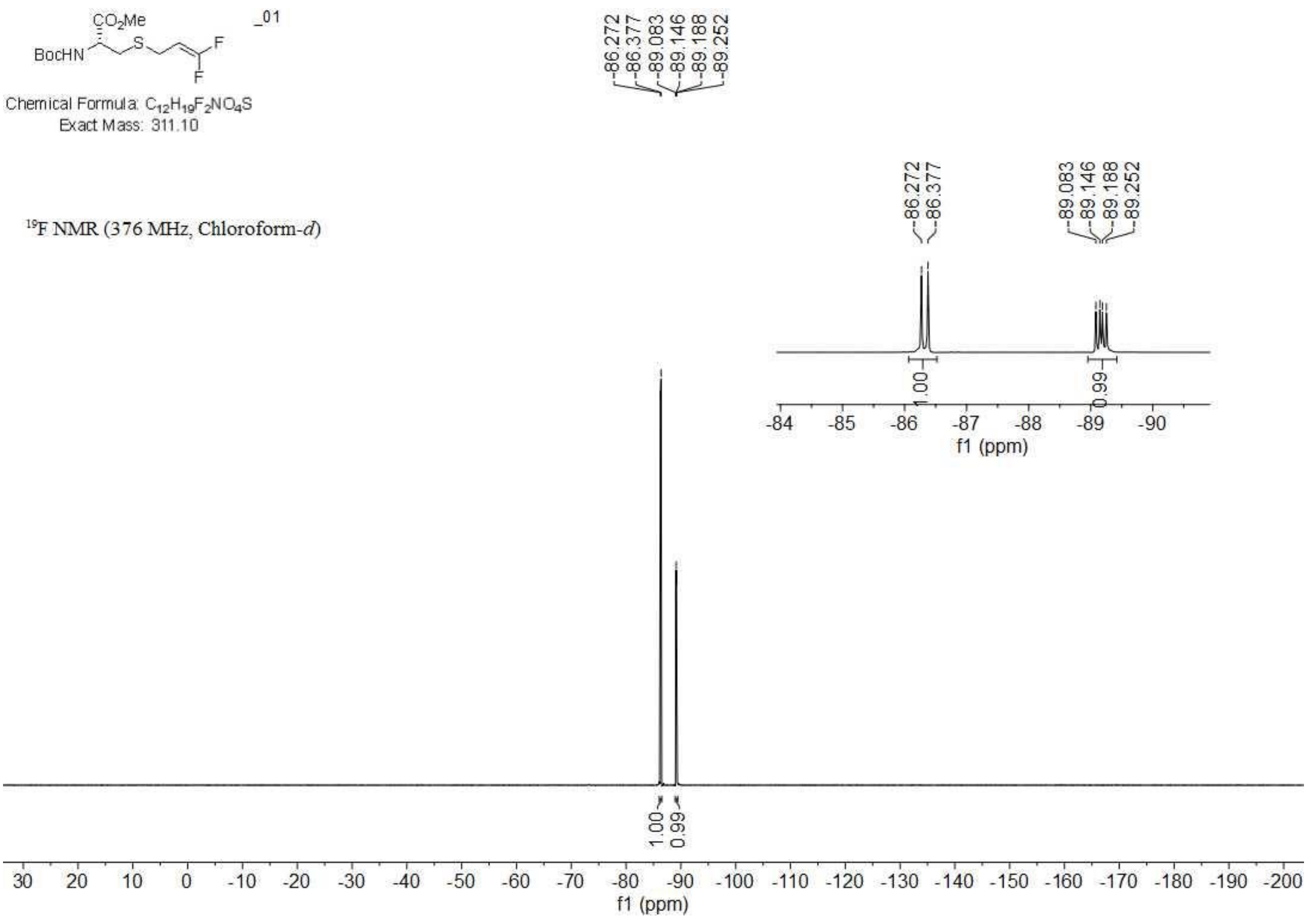

Chemical Formula: C25H32F2N6O8S
Exact Mass: 614.20
19F NMR (376 MHz, DMSO-d6)
NHBoc
HO
OH
N
H
F
F
S
N3
-70.106
-70.655
-70.678
-71.229
CF3COOH
-69.5
-70.0
-70.5
-71.0
-71.5
-72.0
f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)


174.355
172.182
171.332
170.403
156.008
143.074
142.848
136.689
134.975
131.337
128.810
128.665
128.583
125.826
121.017
120.965
120.900
78.487
53.619
53.502
52.383
41.274
32.225
31.227
28.670
27.211
Chemical Formula: C25H32F2N6O8S
Exact Mass: 614.20
13C NMR (101 MHz, DMSO-d6)
NHBoc
HO
OH
N
H
F
F
S
N3
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

9.4 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for Compound 4a

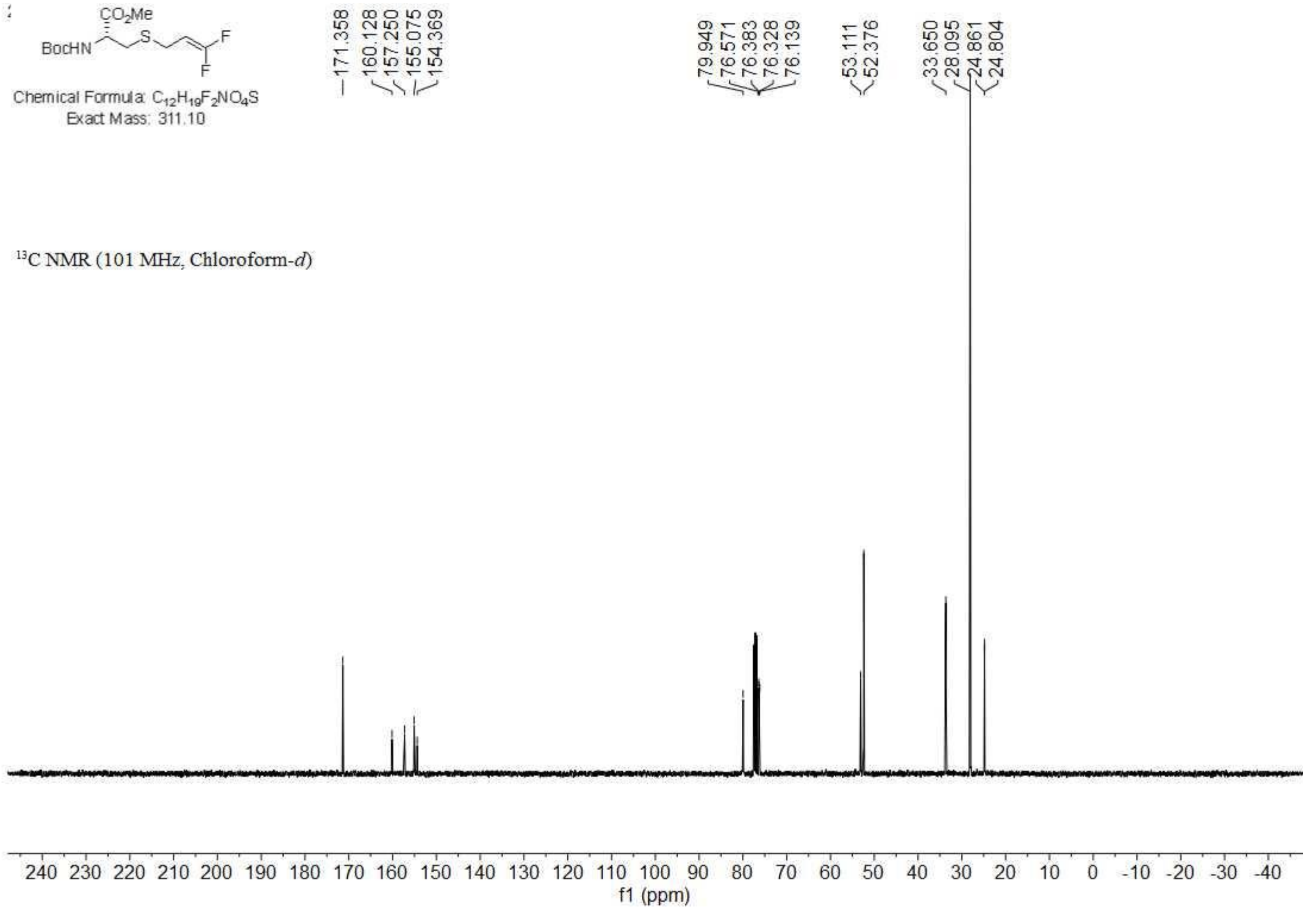
Spectra of 4a





Chemical Formula: $C_{12}H_{19}F_2NO_4S$
Exact Mass: 311.10

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

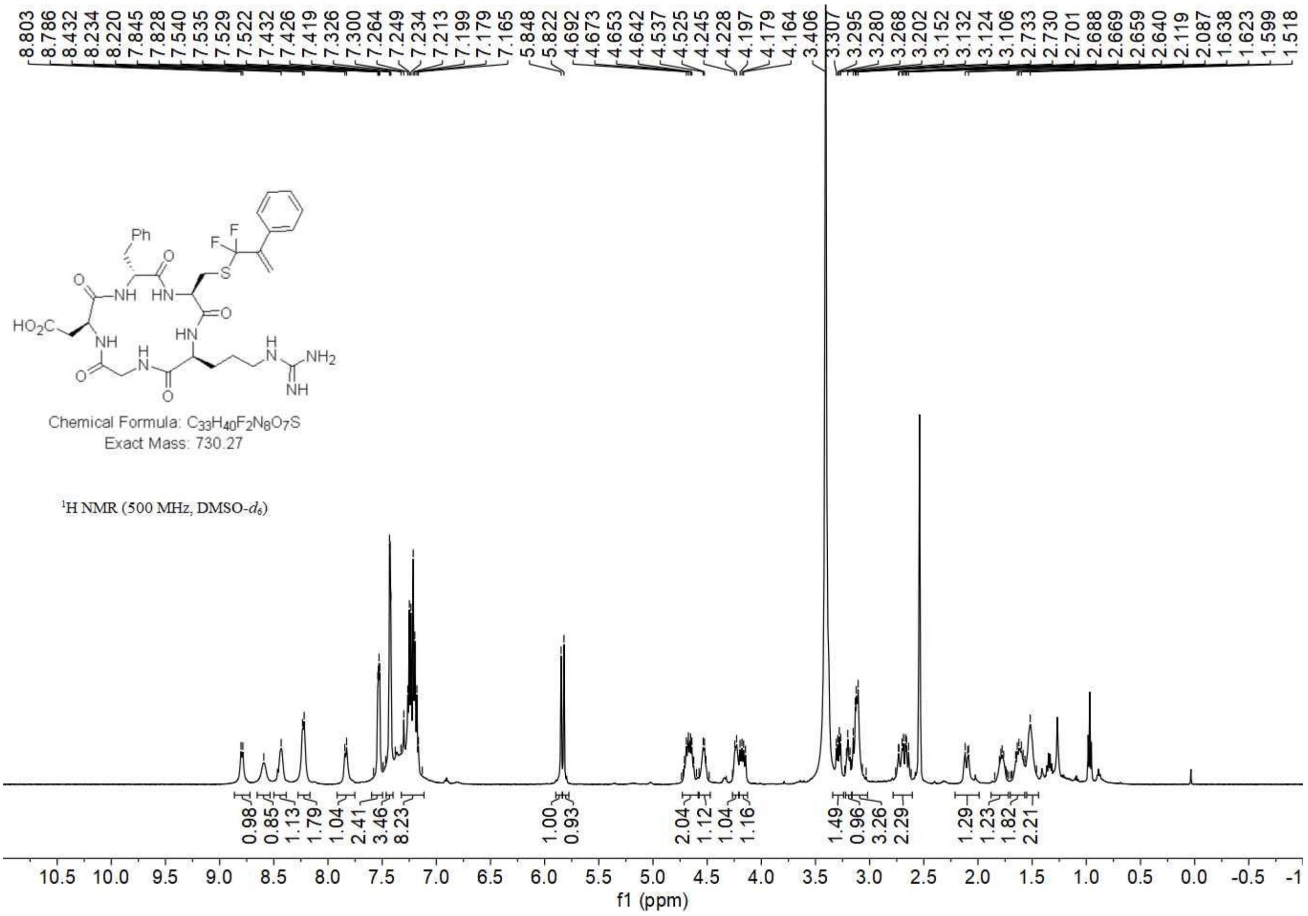


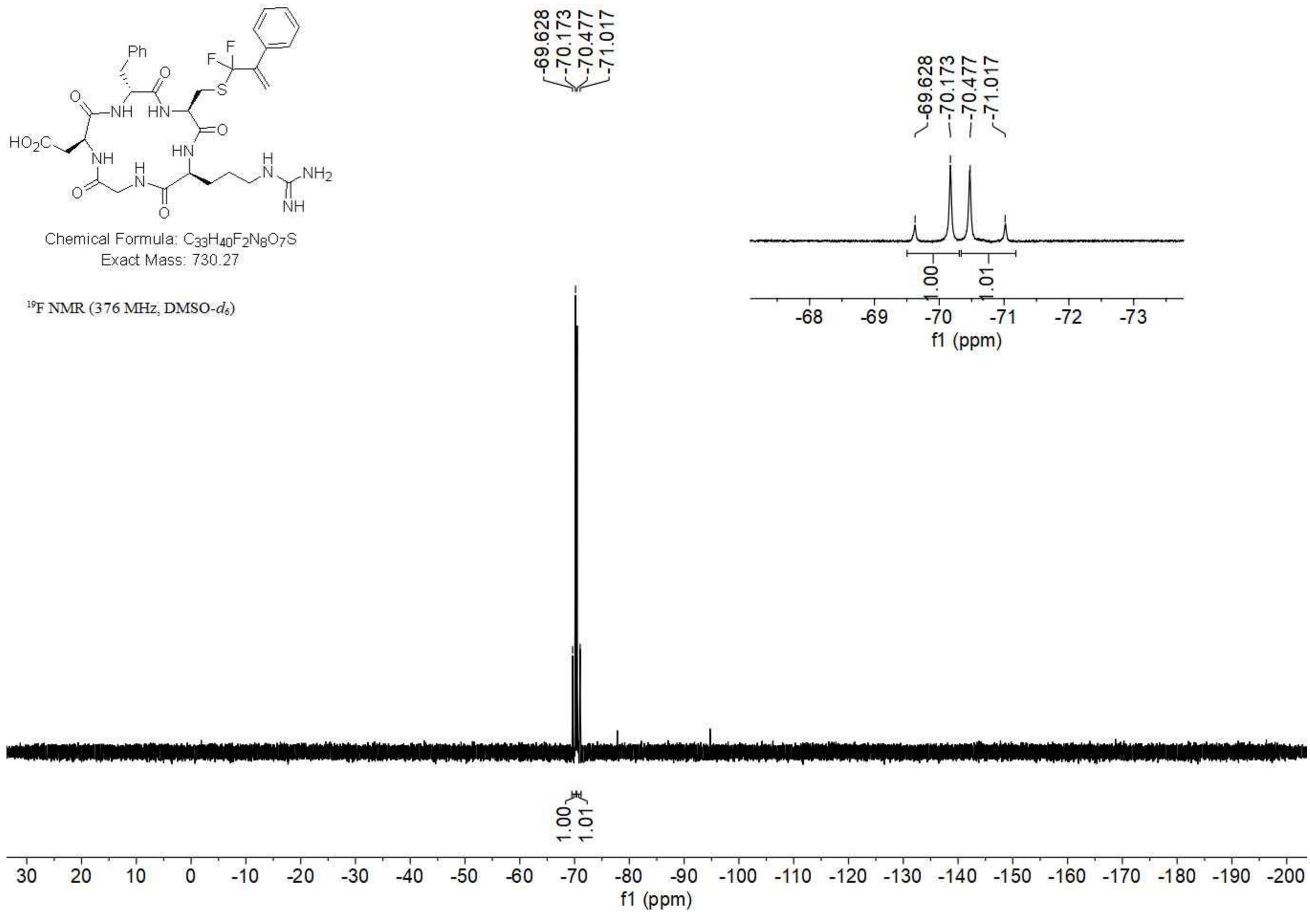
Chemical Formula: $C_{12}H_{19}F_2NO_4S$
Exact Mass: 311.10

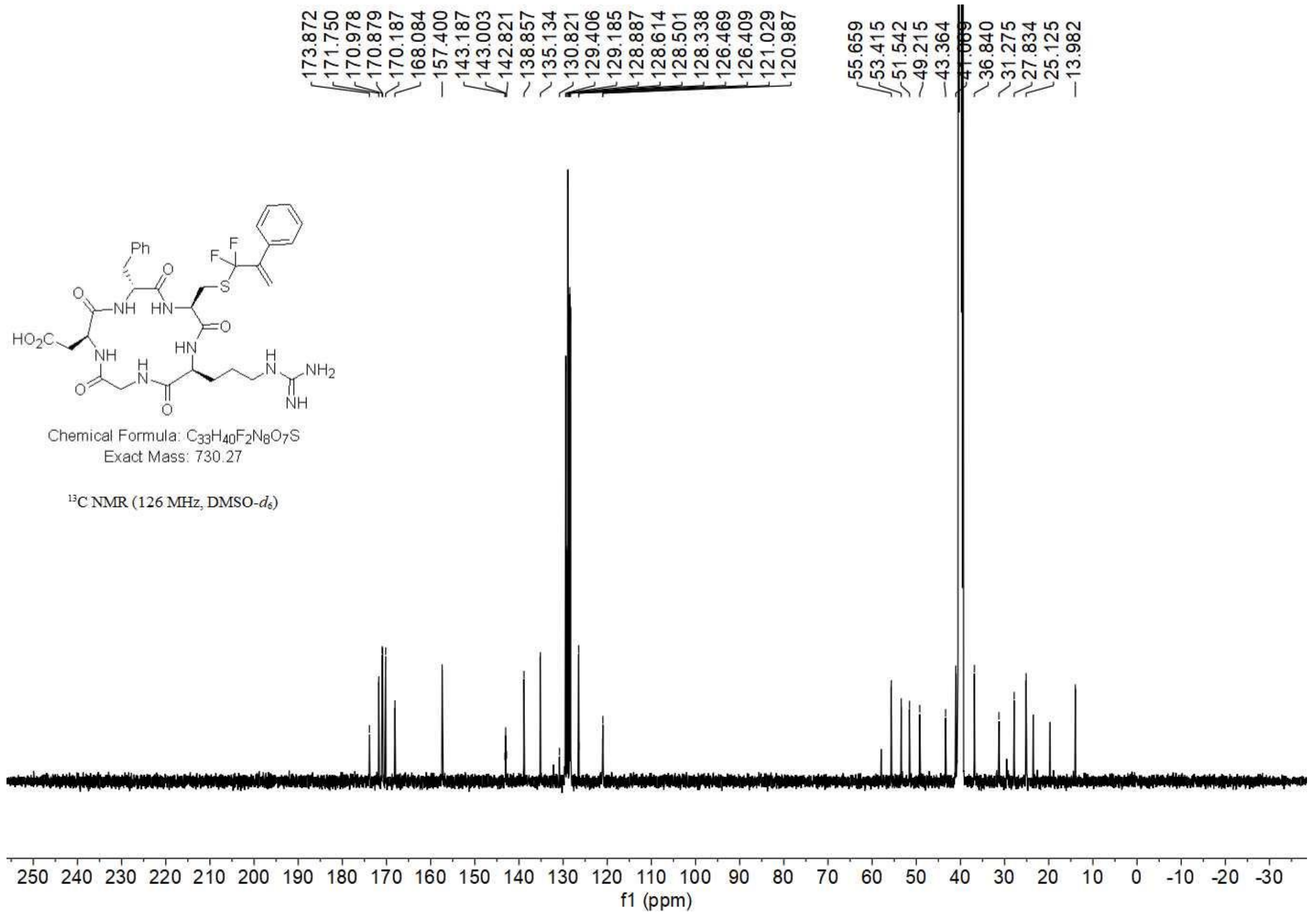
^{13}C NMR (101 MHz, Chloroform-*d*)

9.5 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for Compounds 6a-i

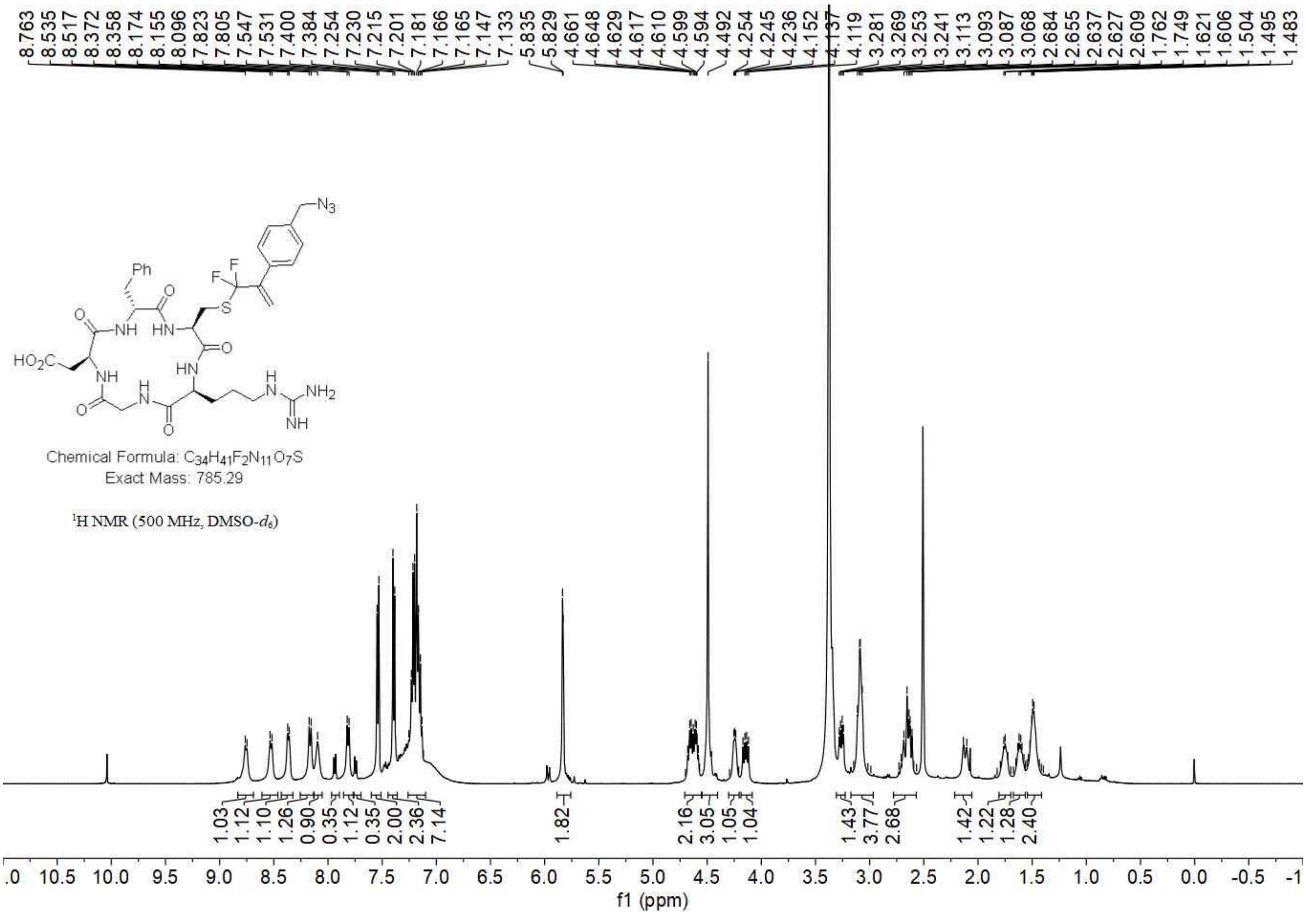
Spectra of 6a

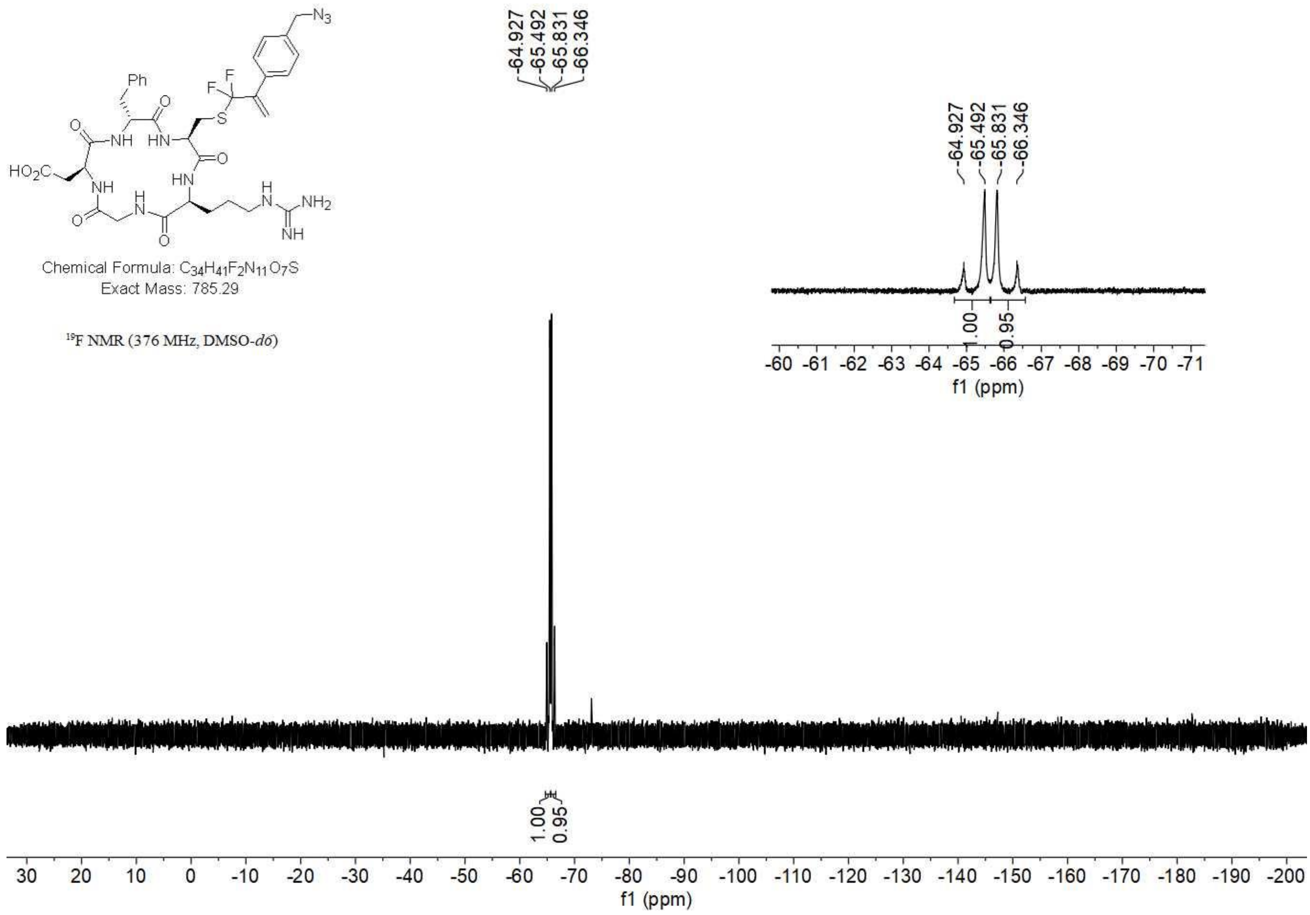



Ph
F
F
S
O
NH
HN
O
HO2C
NH
HN
H
N
NH2
NH
O
N
H
O
O
Chemical Formula: C33H40F2N8O7S
Exact Mass: 730.27
19F NMR (376 MHz, DMSO-d6)
-69.628
-70.173
-70.477
-71.017
1.00
1.01
-68
-69
-70
-71
-72
-73
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

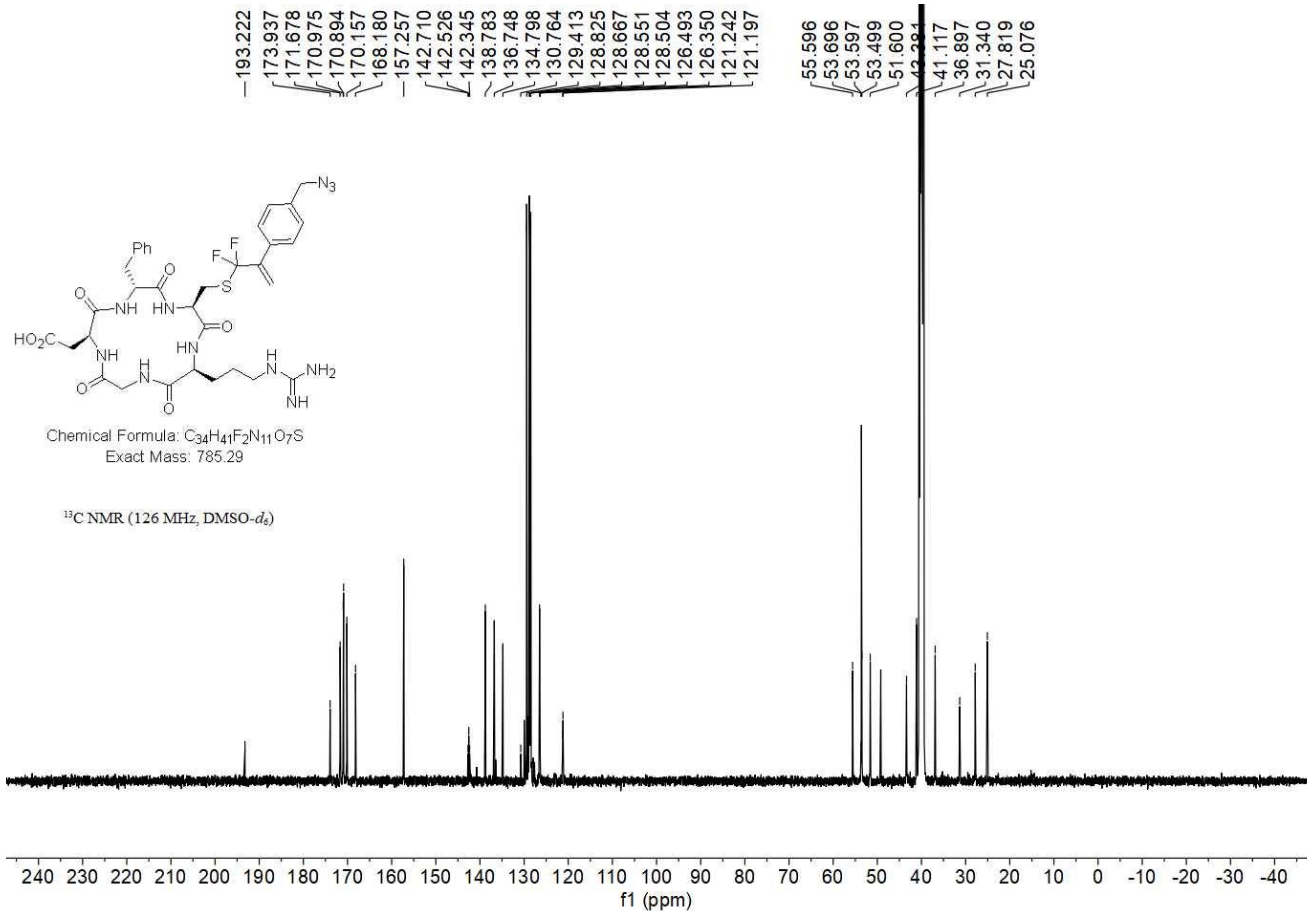

173.872
171.750
170.978
170.879
170.187
168.084
157.400
143.187
143.003
142.821
138.857
135.134
130.821
129.406
129.185
128.887
128.614
128.501
128.338
126.469
126.409
121.029
120.987
55.659
53.415
51.542
49.215
43.364
41.069
36.840
31.275
27.834
25.125
13.982
Ph
F
F
S
O
NH
HN
O
HO2C
NH
HN
H
N
NH2
NH
O
N
H
O
O
Chemical Formula: C33H40F2N8O7S
Exact Mass: 730.27
13C NMR (126 MHz, DMSO-d6)
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

Spectra of 6b



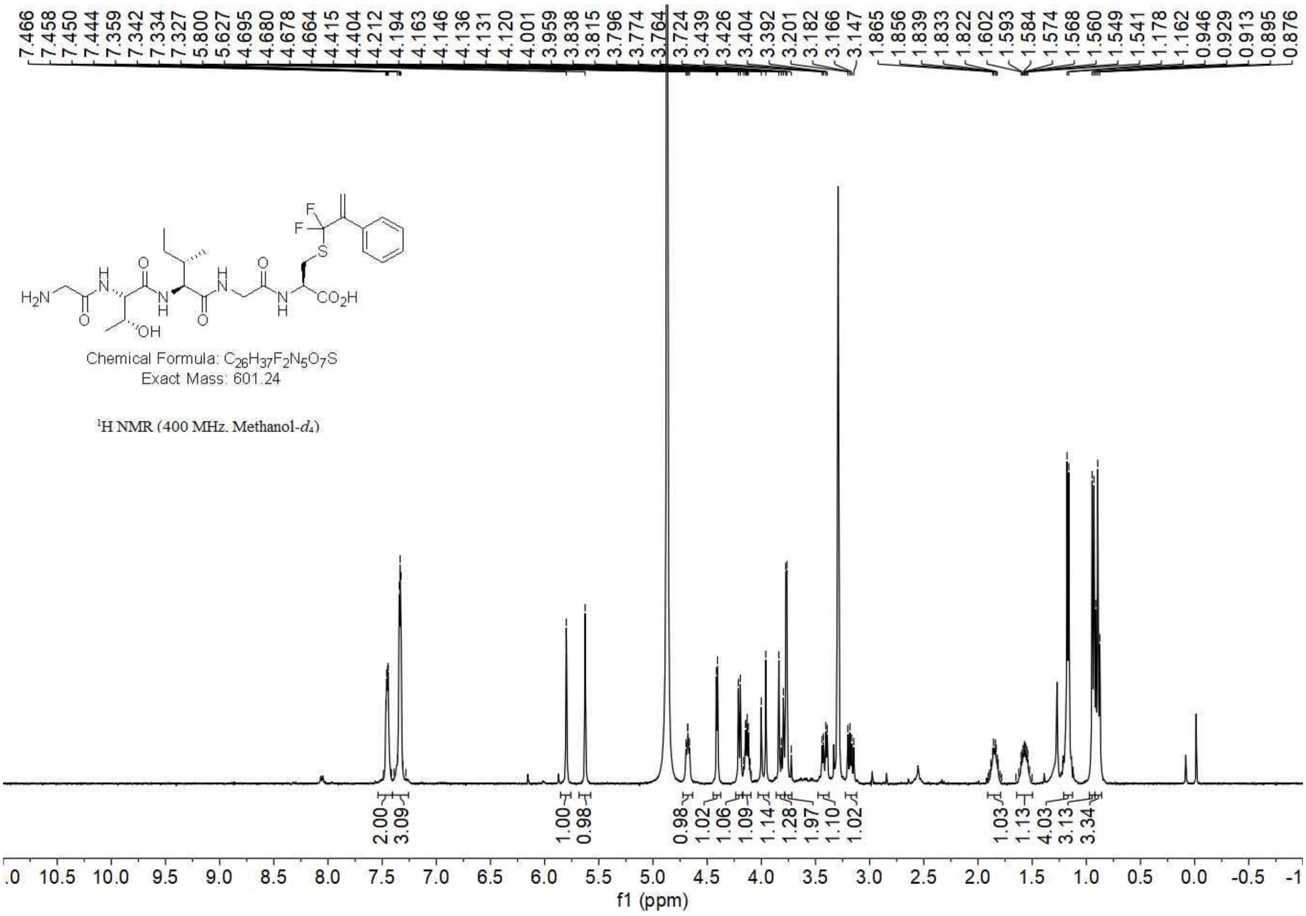

Chemical Formula: $C_{34}H_{41}F_2N_{11}O_7S$
Exact Mass: 785.29

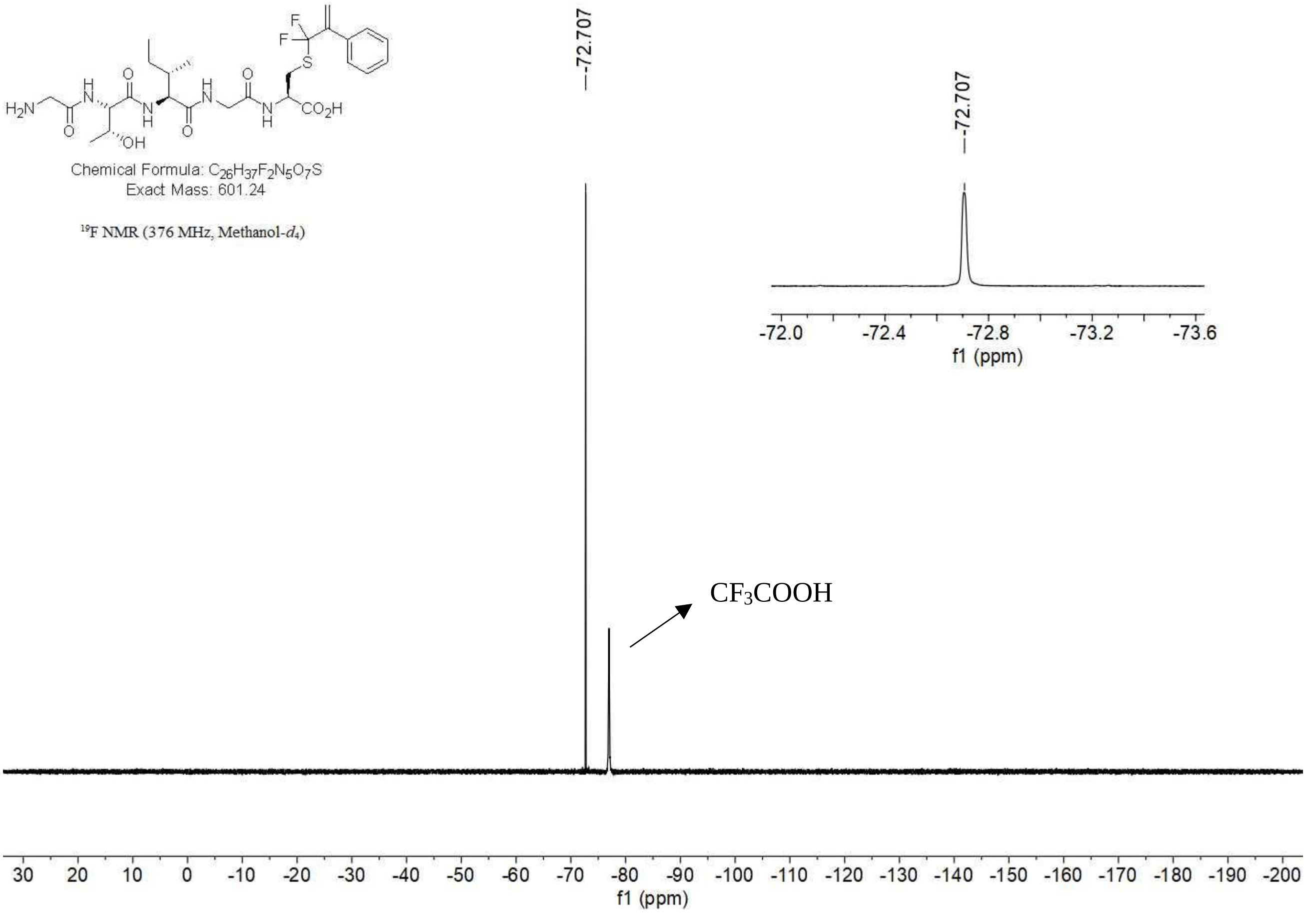
^{19}F NMR (376 MHz, DMSO-*d6*)


Chemical Formula: $C_{34}H_{41}F_2N_{11}O_7S$
Exact Mass: 785.29

^{13}C NMR (126 MHz, DMSO-*d*$_6$)

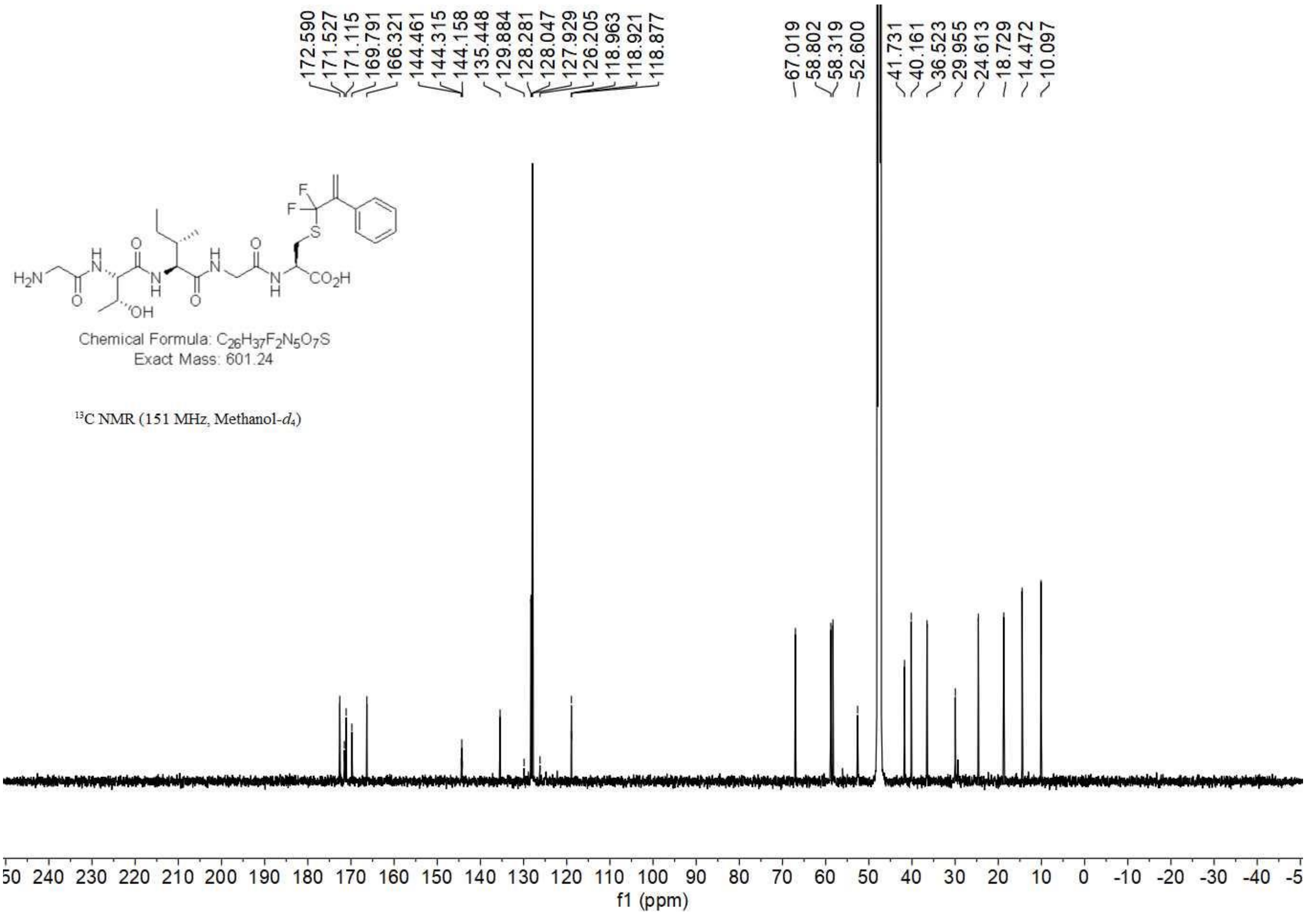
Spectra of 6c





Chemical Formula: $C_{26}H_{37}F_2N_5O_7S$
Exact Mass: 601.24

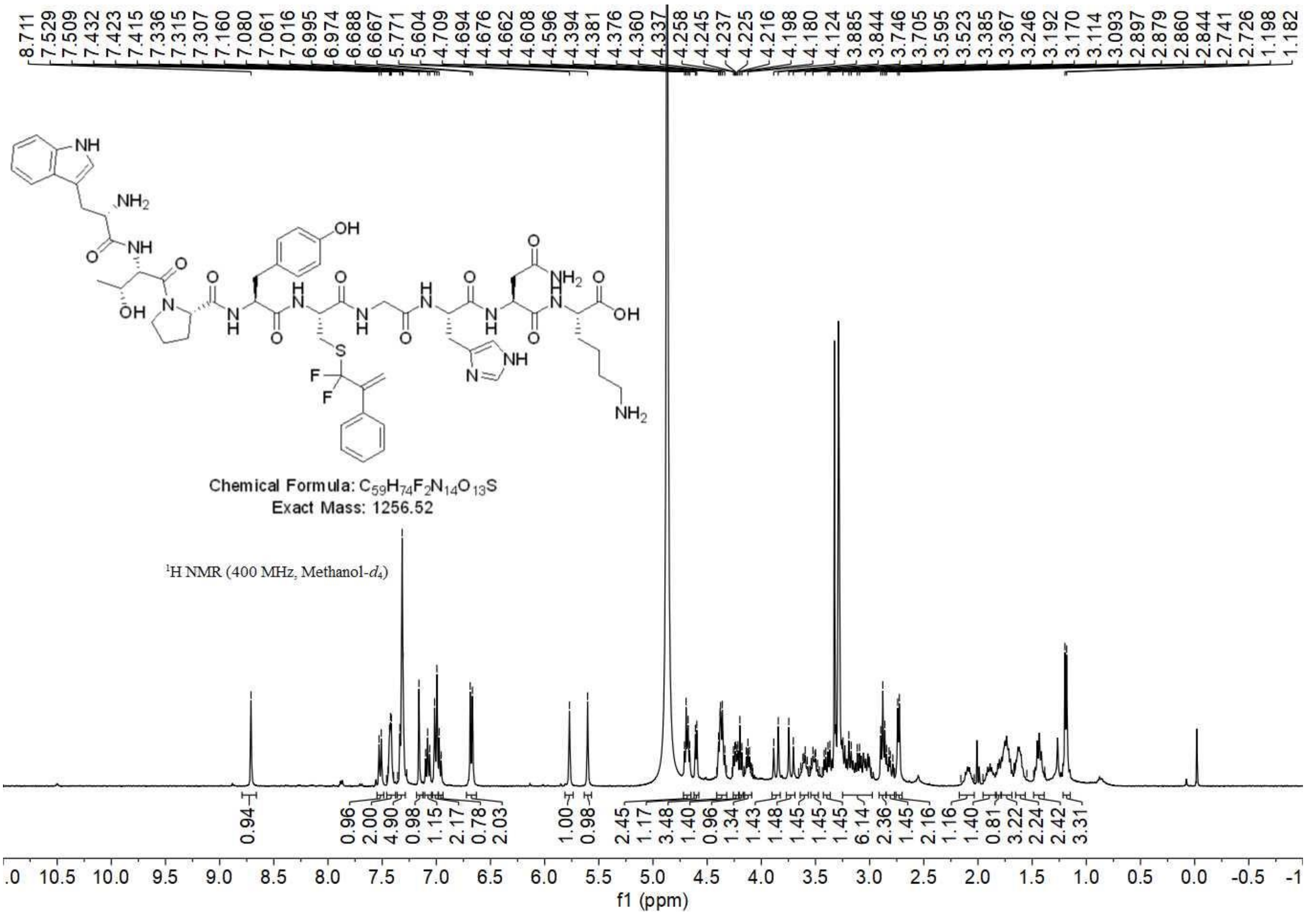
^{19}F NMR (376 MHz, Methanol-d_4)

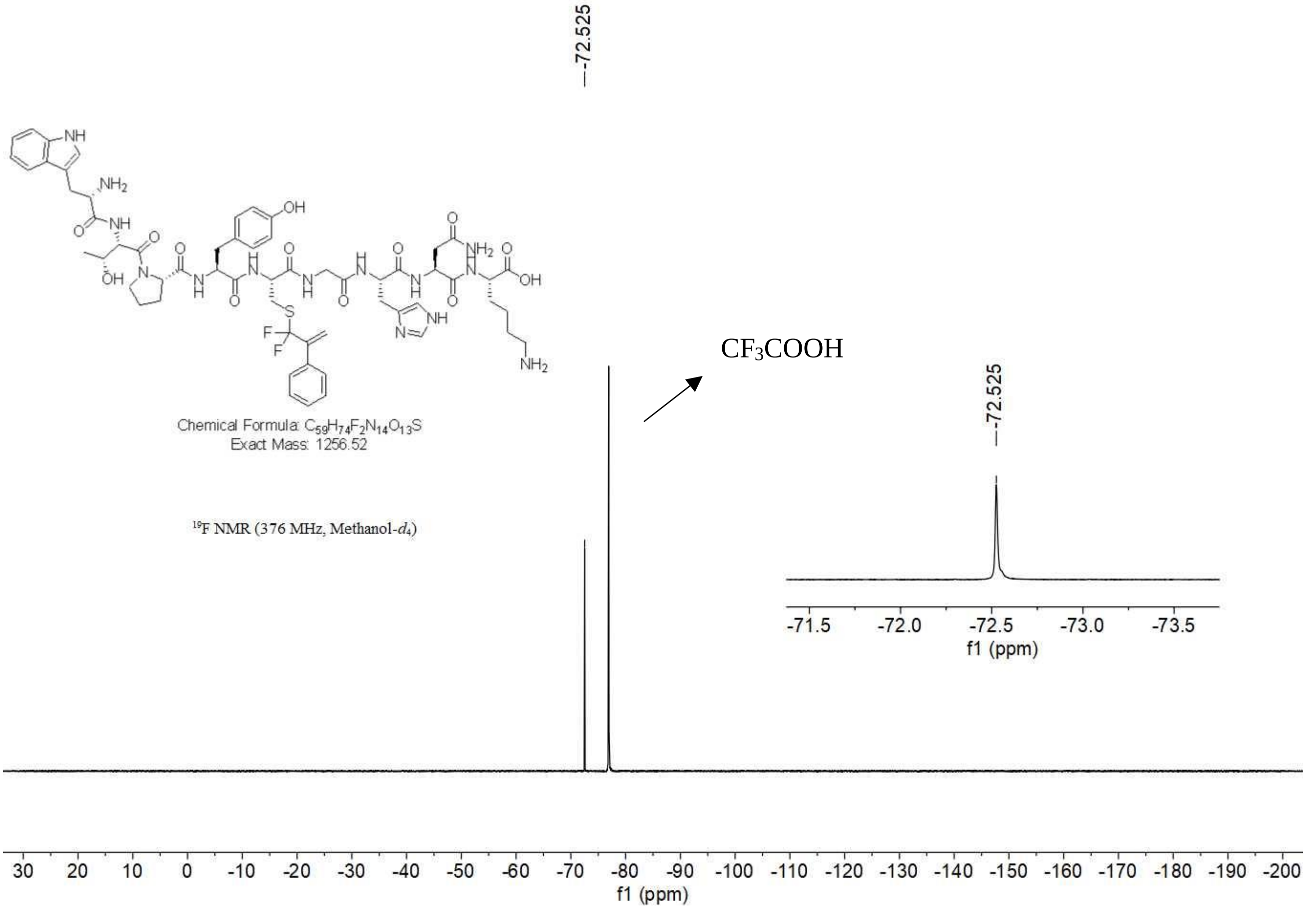


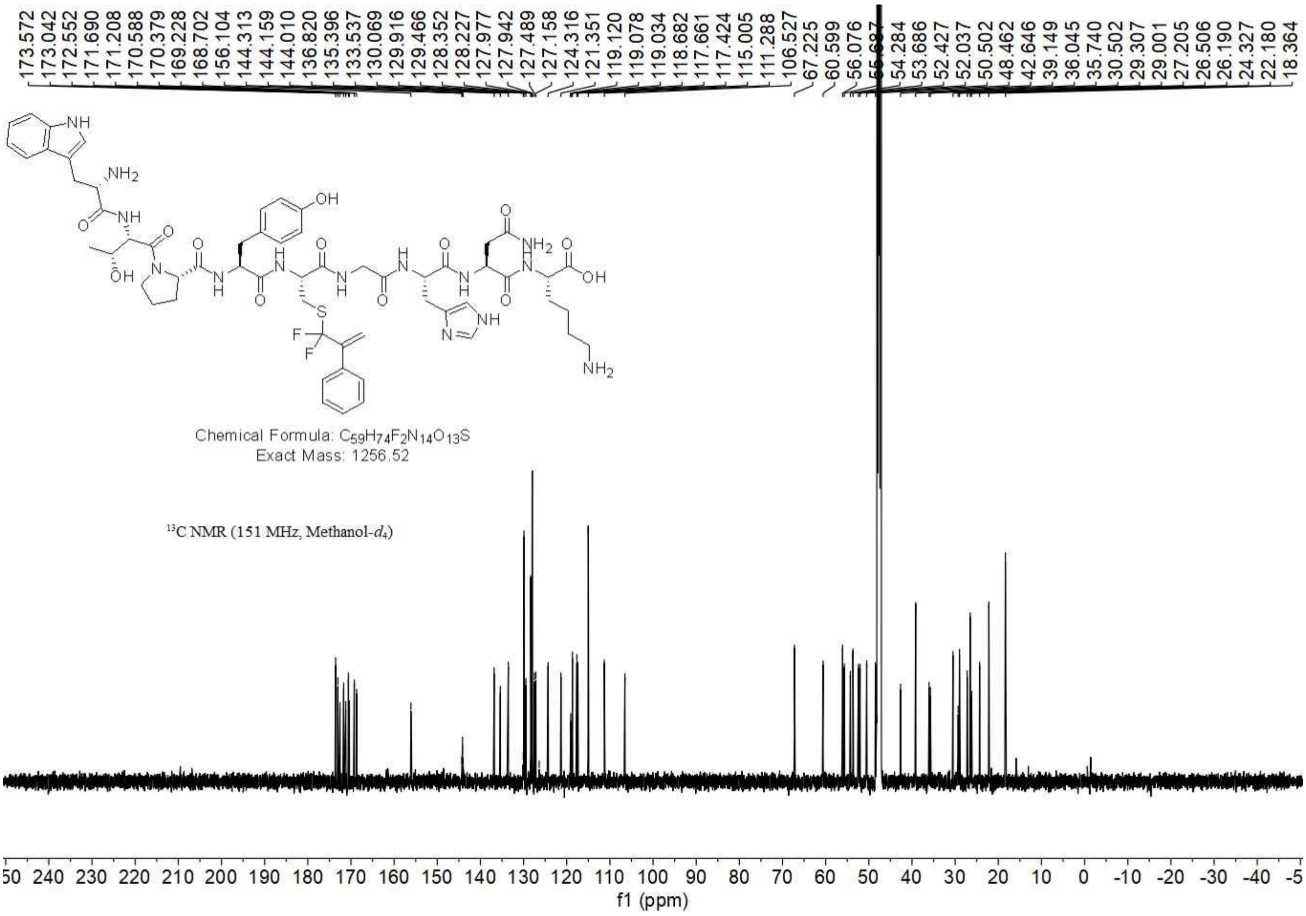
Chemical Formula: $C_{26}H_{37}F_2N_5O_7S$
Exact Mass: 601.24

^{13}C NMR (151 MHz, Methanol-d_4)

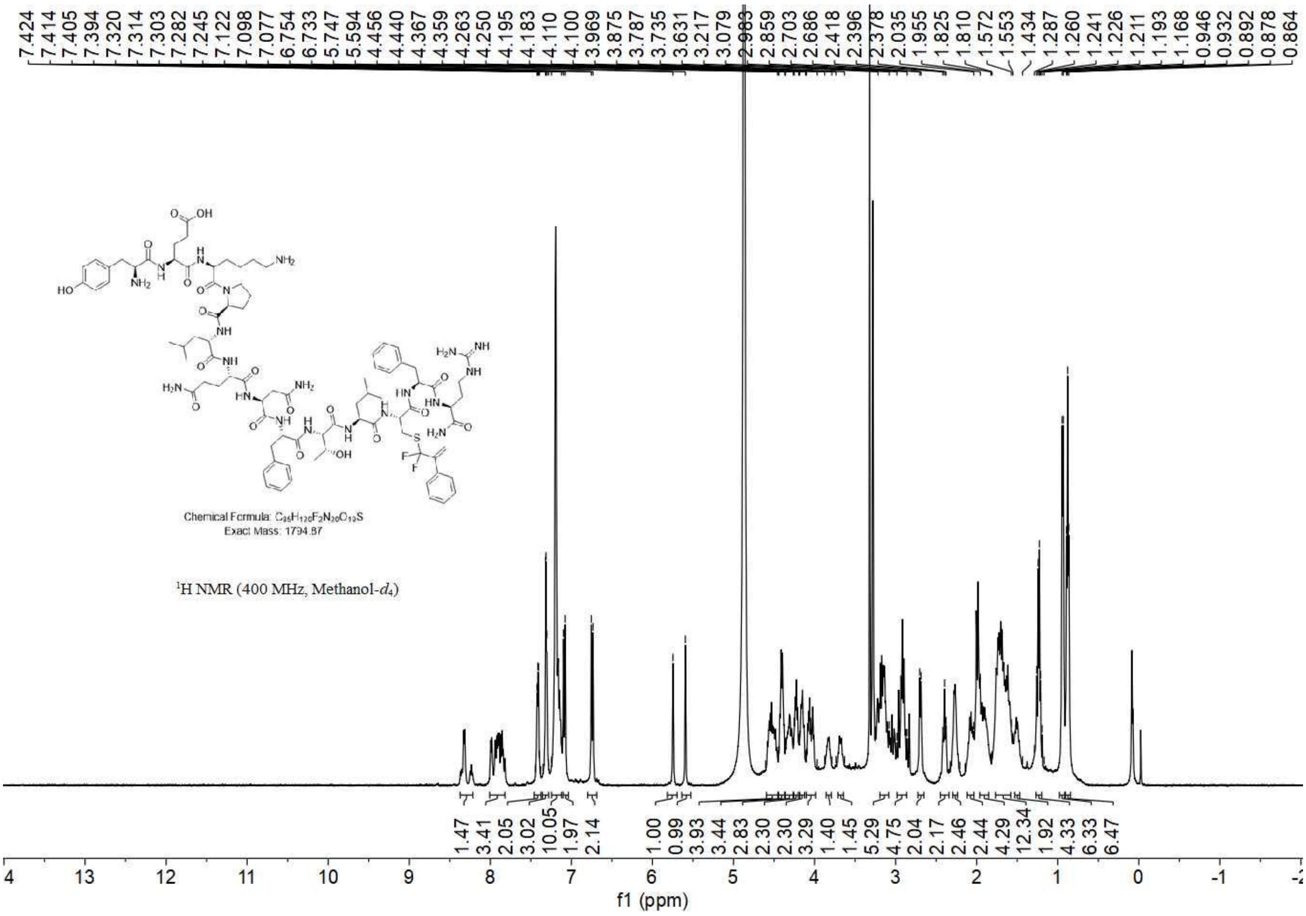
Spectra of 6d

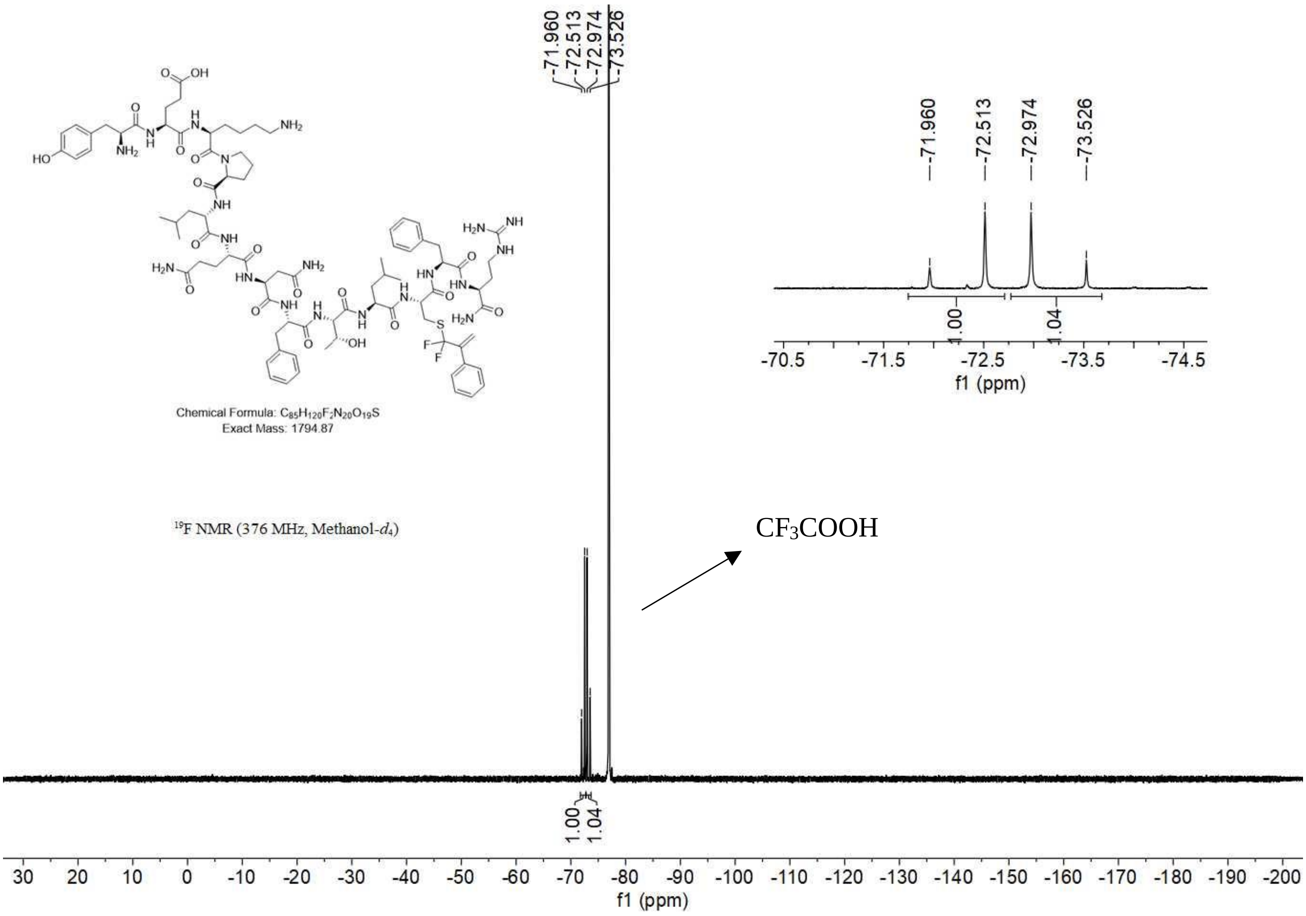


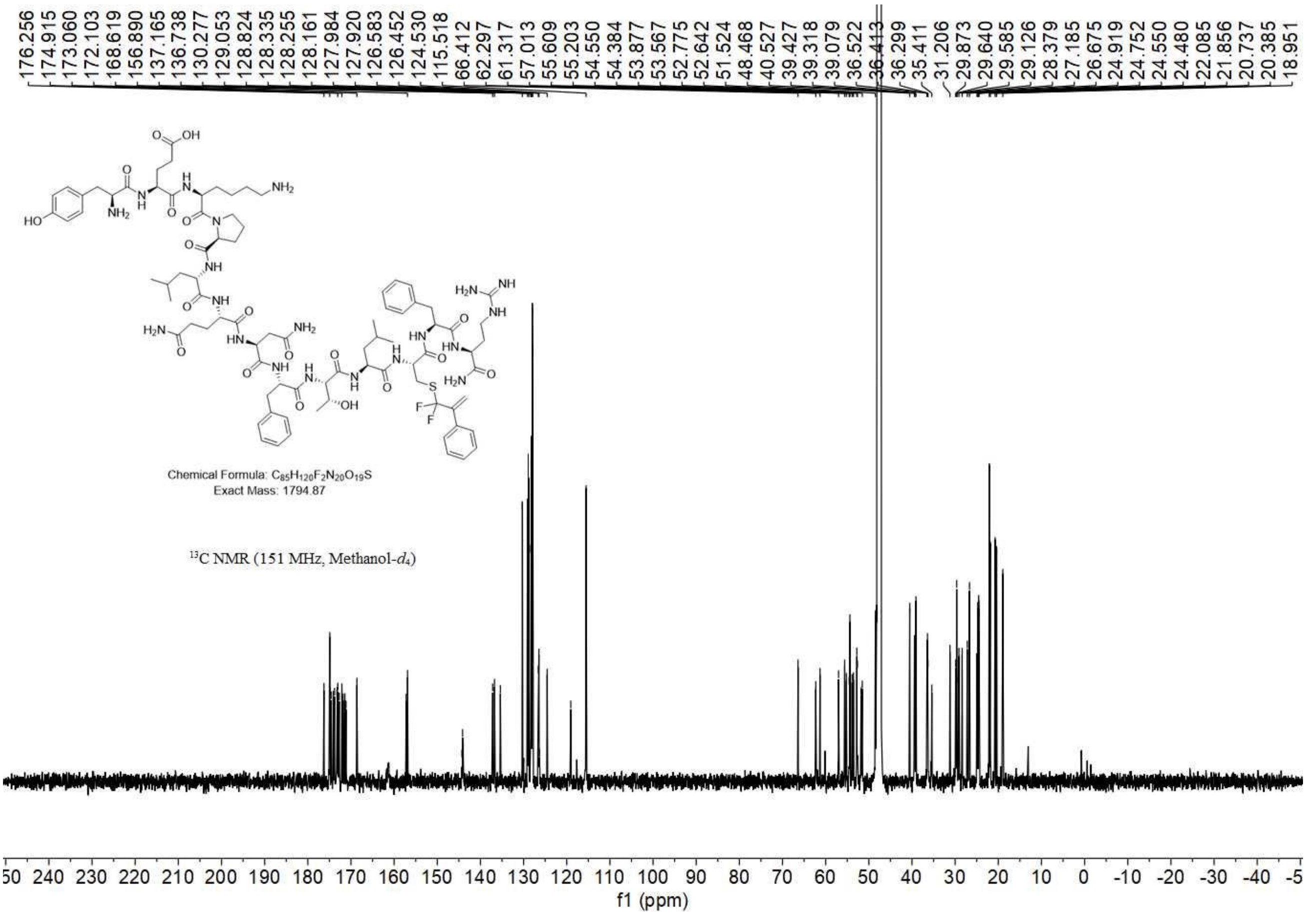

-72.525
NH
NH2
OH
NH2
OH
F
F
NH
NH2
CF3COOH
Chemical Formula: C59H74F2N14O13S
Exact Mass: 1256.52
19F NMR (376 MHz, Methanol-d4)
-72.525
-71.5
-72.0
-72.5
-73.0
-73.5
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


173.572
173.042
172.552
171.690
171.208
170.588
170.379
169.228
168.702
156.104
144.313
144.159
144.010
136.820
135.396
133.537
130.069
129.916
129.466
128.352
128.227
127.977
127.942
127.489
127.158
124.316
121.351
119.120
119.078
119.034
118.682
117.661
117.424
115.005
111.288
106.527
67.225
60.599
56.076
55.687
54.284
53.686
52.427
52.037
50.502
48.462
42.646
39.149
36.045
35.740
30.502
29.307
29.001
27.205
26.506
26.190
24.327
22.180
18.364
NH
NH2
OH
NH2
OH
F
F
NH
NH2
Chemical Formula: C59H74F2N14O13S
Exact Mass: 1256.52
13C NMR (151 MHz, Methanol-d4)
50
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-5
f1 (ppm)

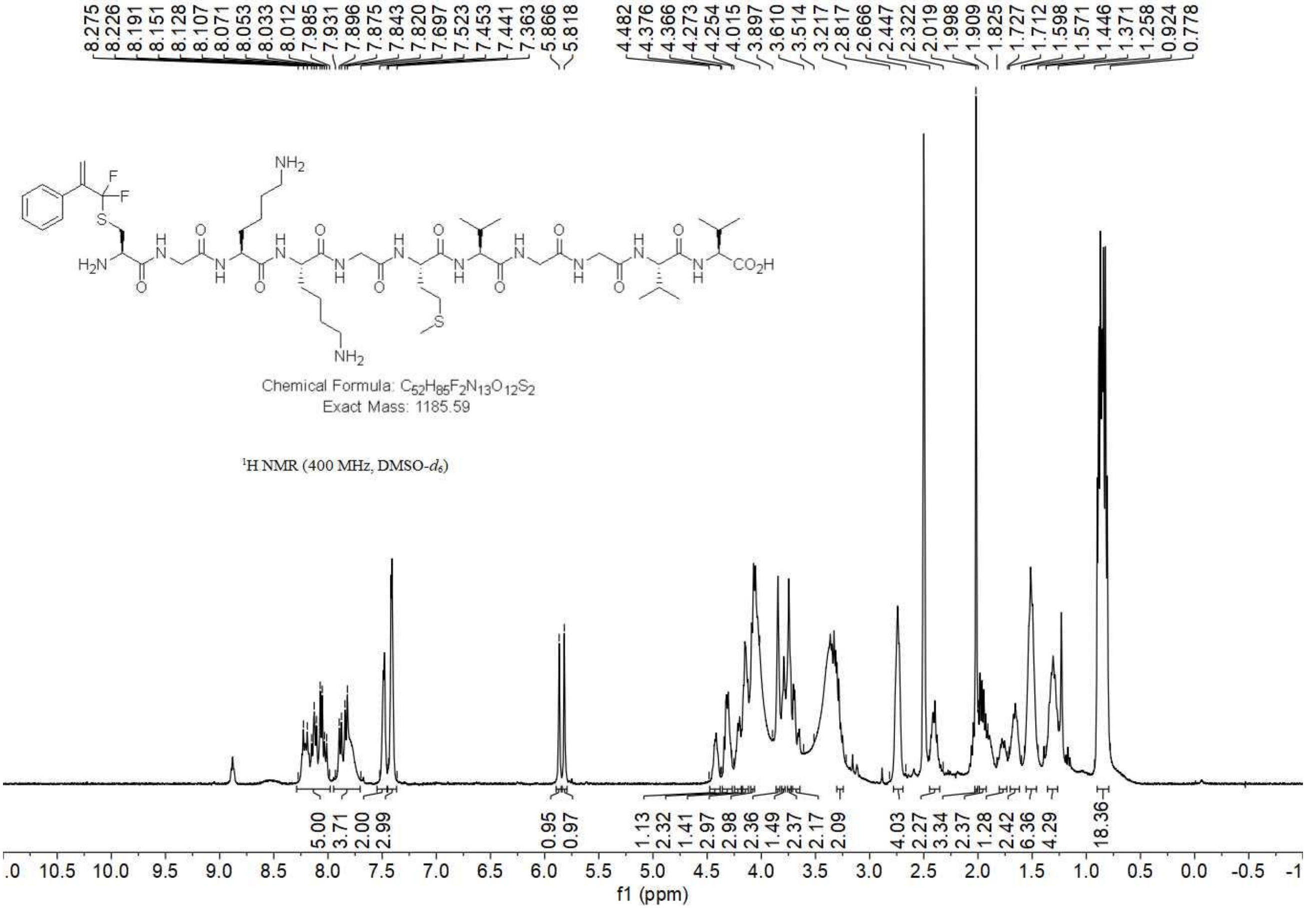
Spectra of 6e

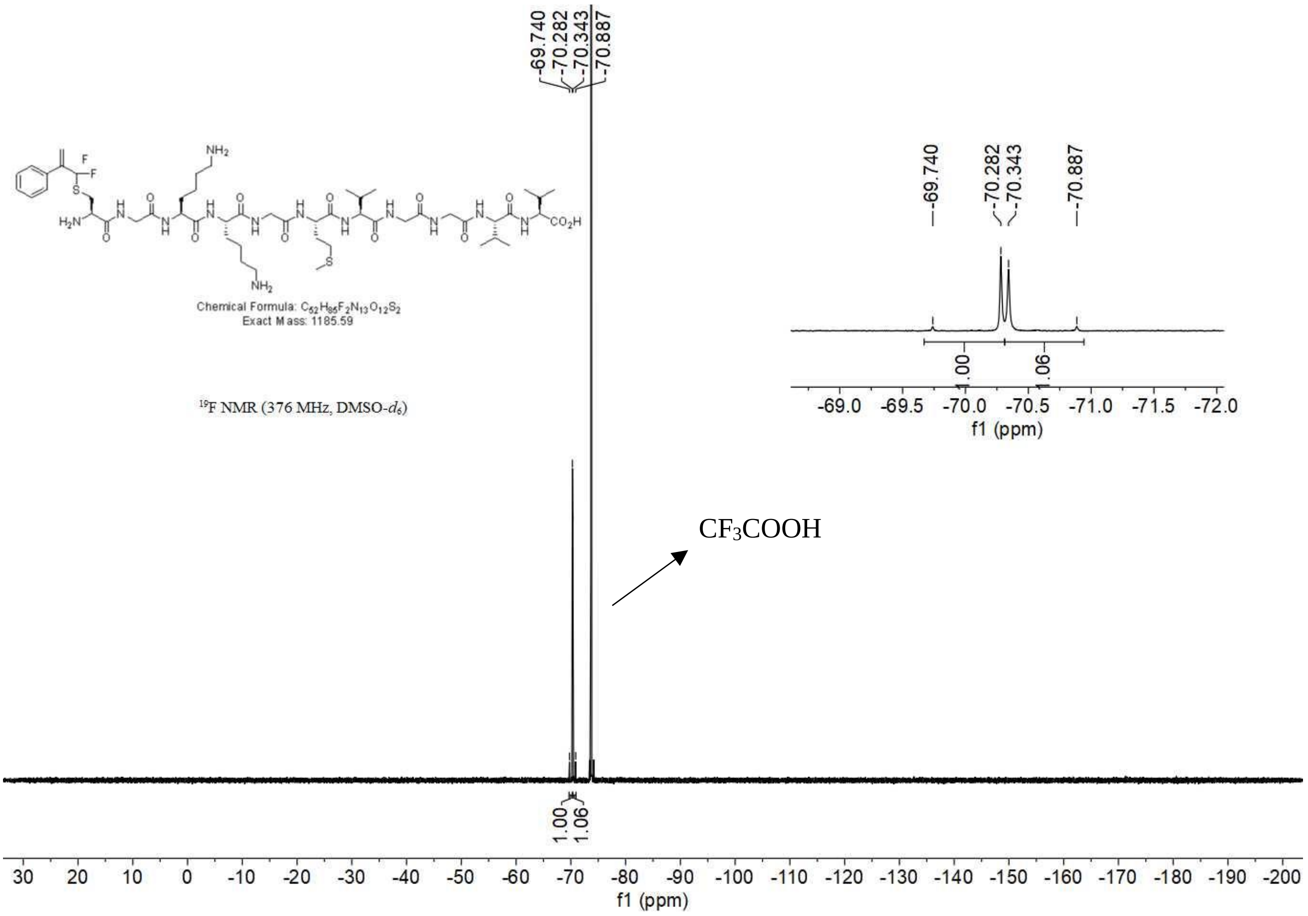



-71.960
-72.513
-72.974
-73.526
Chemical Formula: $C_{85}H_{120}F_2N_{20}O_{19}S$
Exact Mass: 1794.87
^{19}F NMR (376 MHz, Methanol-d_4)
CF$_3$COOH
1.00
1.04
-70.5
-71.5
-72.5
-73.5
-74.5
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


176.256
174.915
173.060
172.103
168.619
156.890
137.165
136.738
130.277
129.053
128.824
128.335
128.255
128.161
127.984
127.920
126.583
126.452
124.530
115.518
66.412
62.297
61.317
57.013
55.609
55.203
54.550
54.384
53.877
53.567
52.775
52.642
51.524
48.468
40.527
39.427
39.318
39.079
36.522
36.413
36.299
35.411
31.206
29.873
29.640
29.585
29.126
28.379
27.185
26.675
24.919
24.752
24.550
24.480
22.085
21.856
20.737
20.385
18.951
Chemical Formula: $C_{85}H_{120}F_2N_{20}O_{19}S$
Exact Mass: 1794.87
^{13}C NMR (151 MHz, Methanol-d_4)
50
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-5
f1 (ppm)

Spectra of 6f

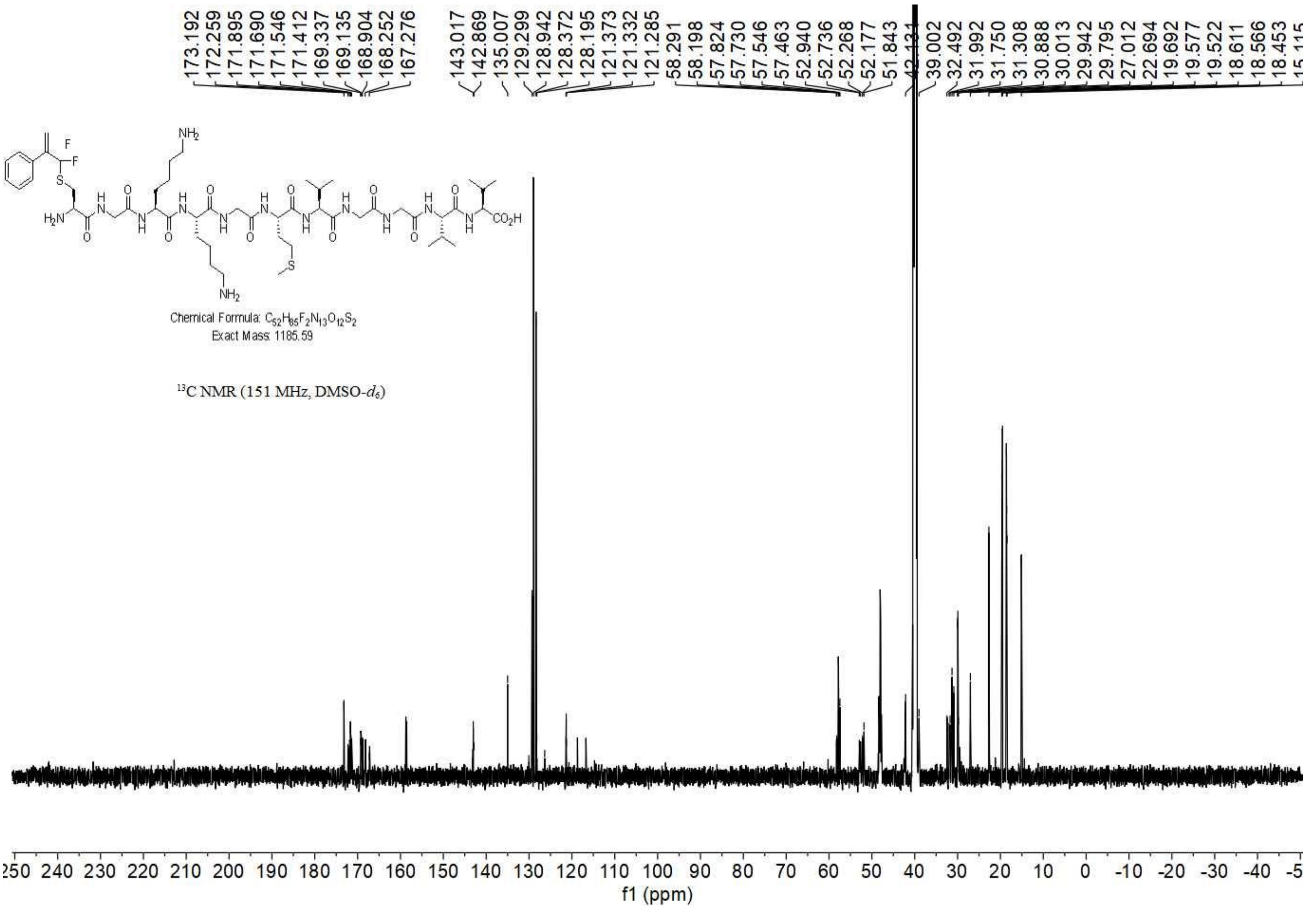




Chemical Formula: $C_{52}H_{85}F_2N_{13}O_{12}S_2$
Exact Mass: 1185.59

^{19}F NMR (376 MHz, DMSO-d_6)

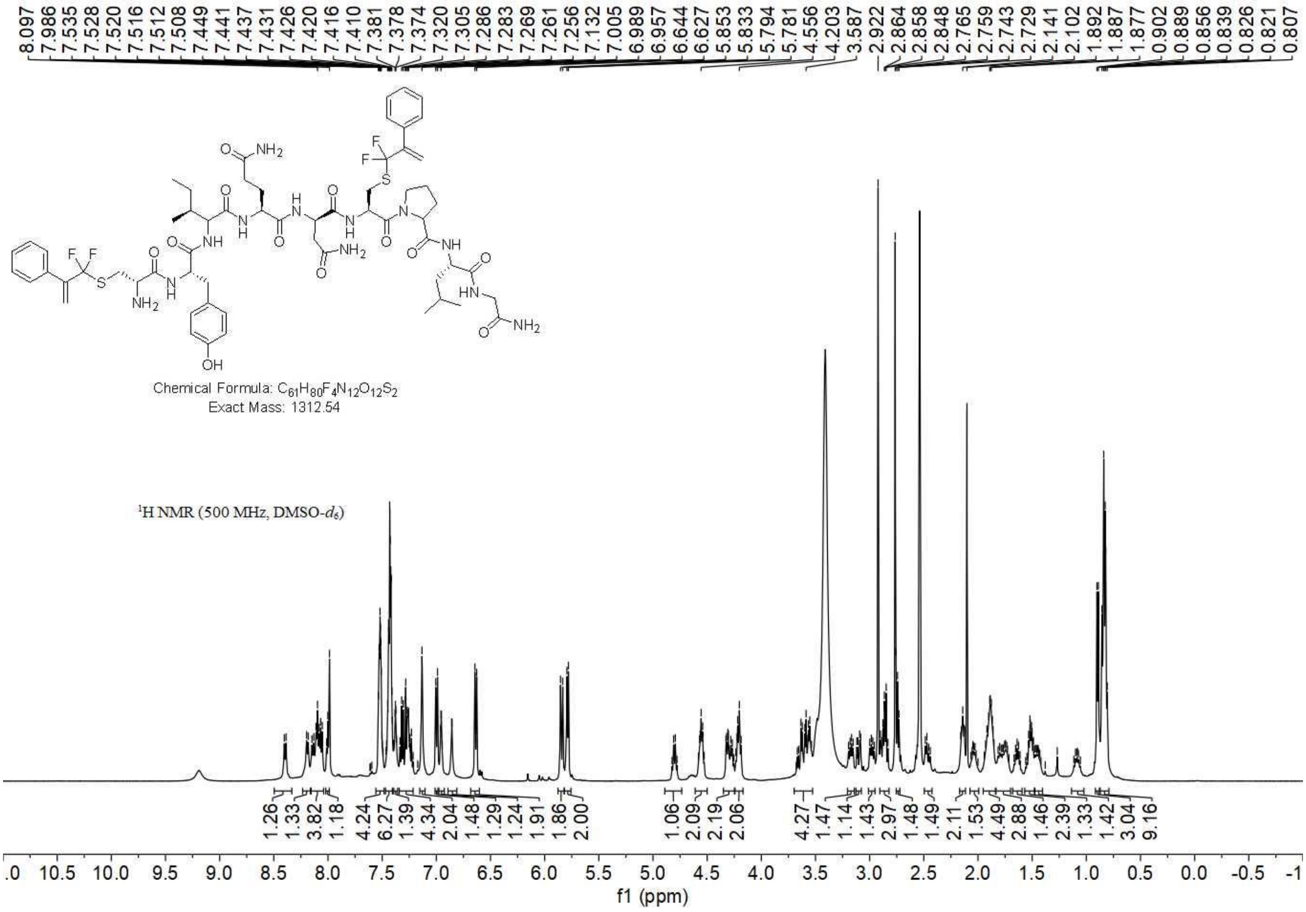
CF_3COOH

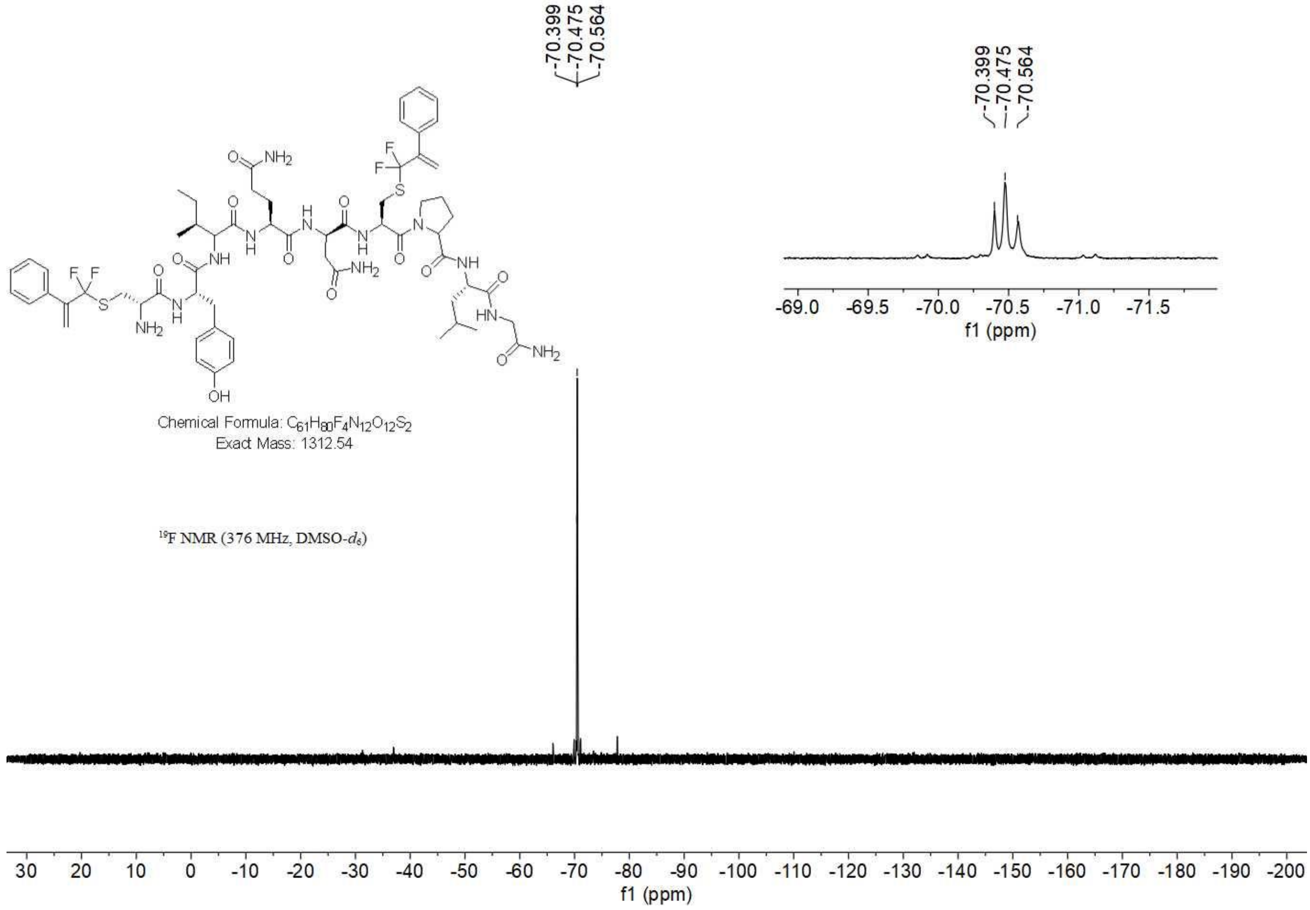


Chemical Formula: $C_{52}H_{85}F_2N_{13}O_{12}S_2$
Exact Mass: 1185.59

^{13}C NMR (151 MHz, DMSO-d_6)

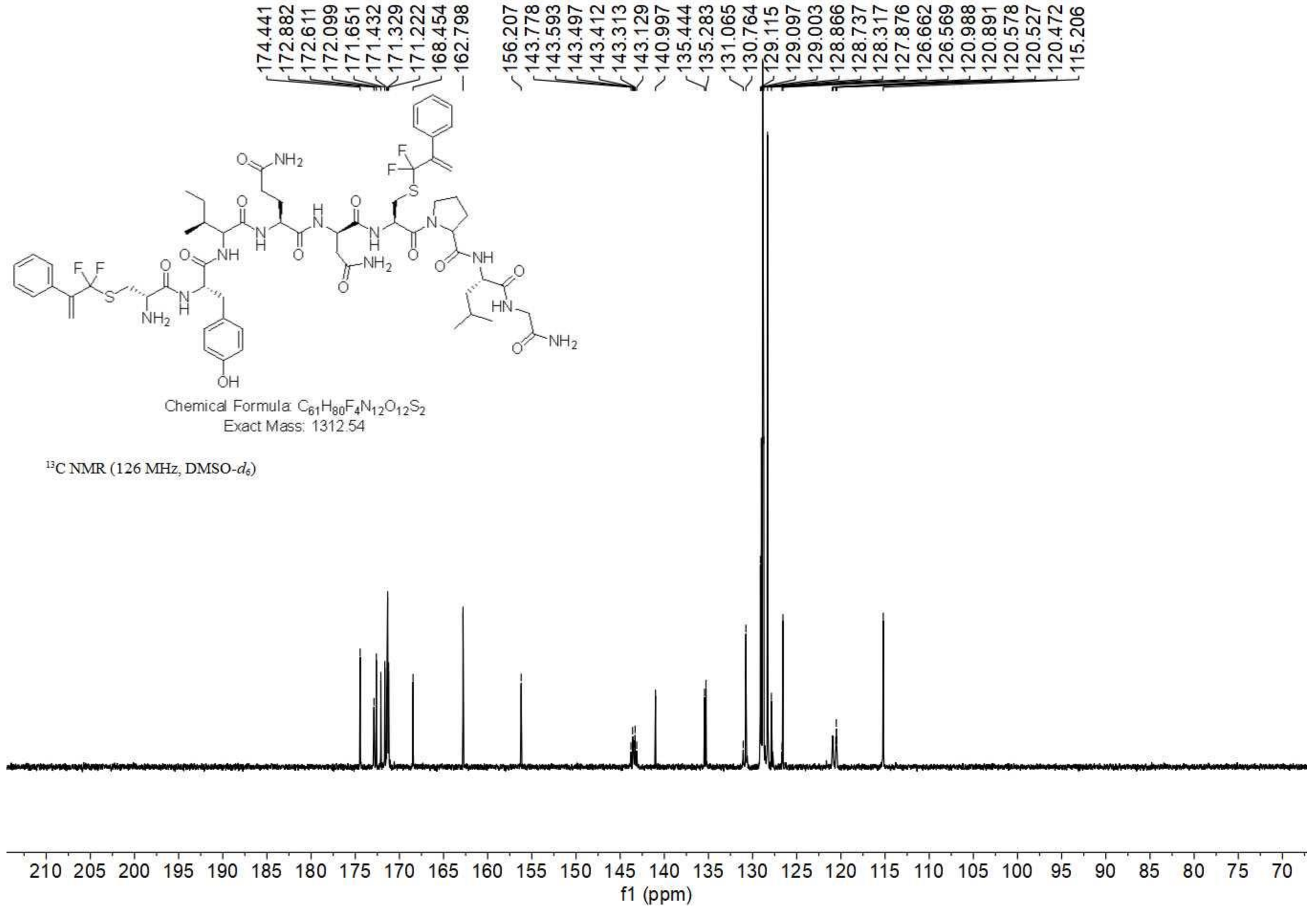
Spectra of 6g





Chemical Formula: $C_{61}H_{80}F_4N_{12}O_{12}S_2$
Exact Mass: 1312.54

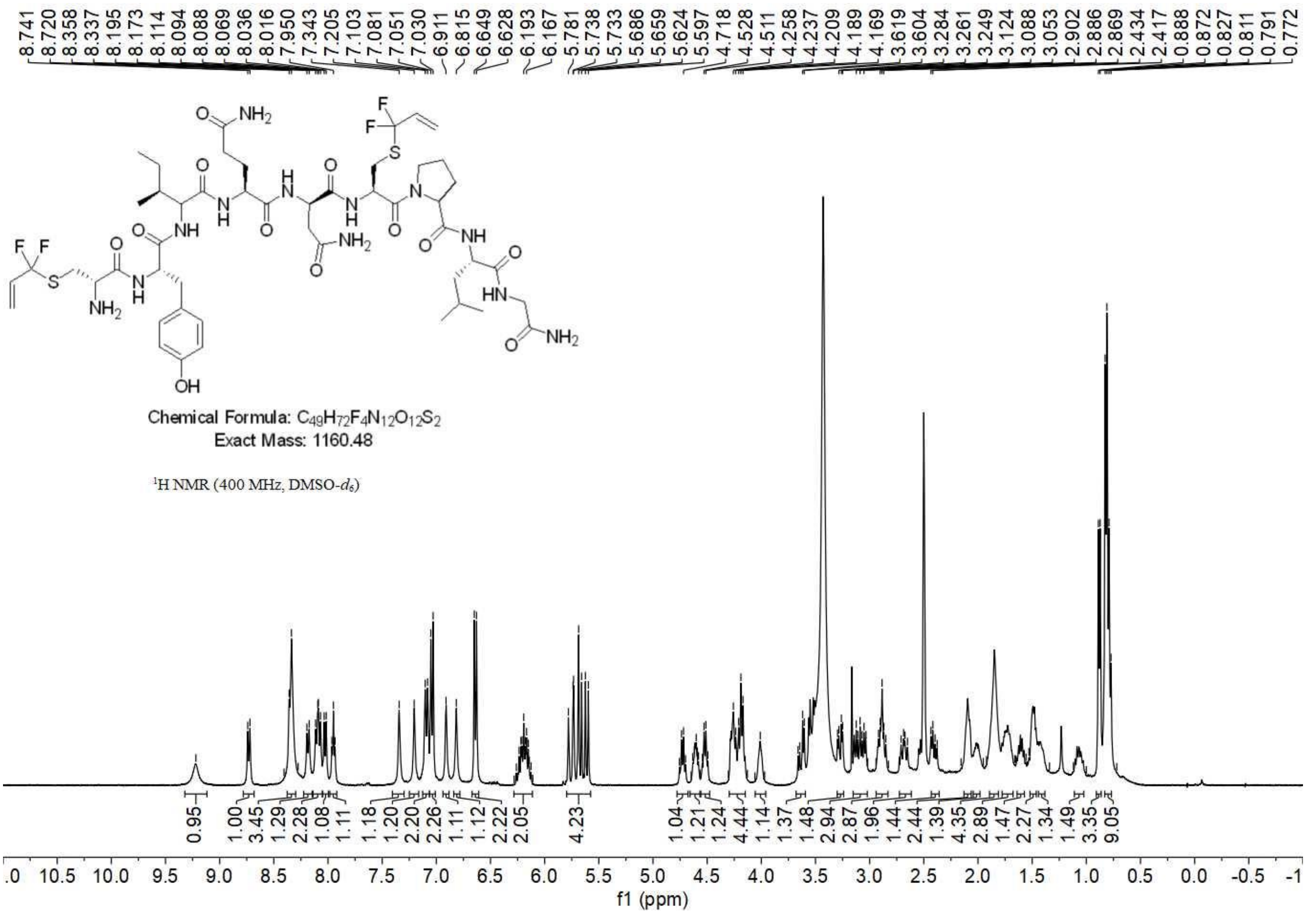
^{19}F NMR (376 MHz, DMSO-d_6)



Chemical Formula: $C_{61}H_{80}F_4N_{12}O_{12}S_2$
Exact Mass: 1312.54

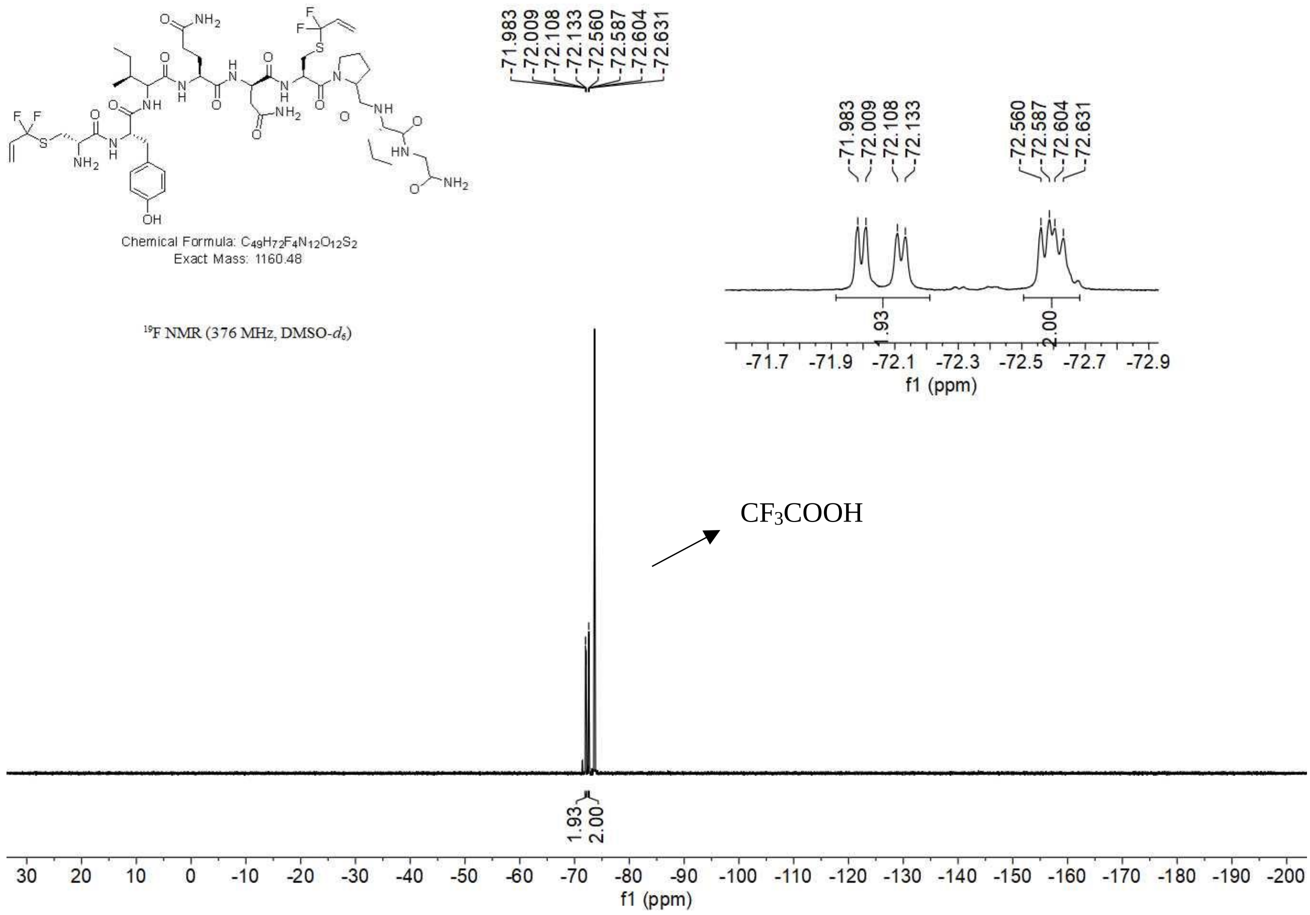
^{13}C NMR (126 MHz, DMSO-d_6)

Spectra of 6h



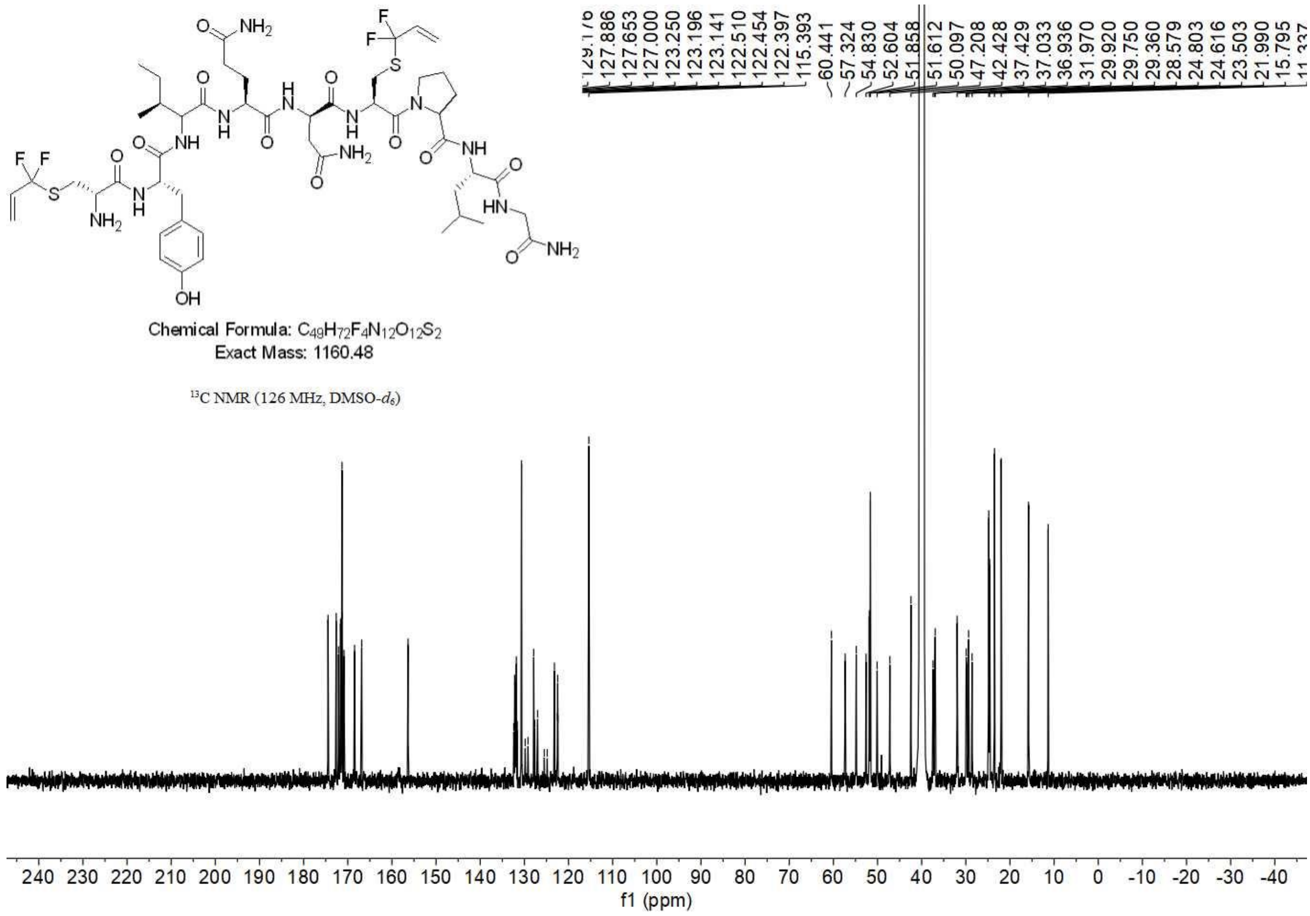
Chemical Formula: $C_{49}H_{72}F_4N_{12}O_{12}S_2$
Exact Mass: 1160.48

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



Chemical Formula: $C_{49}H_{72}F_4N_{12}O_{12}S_2$
Exact Mass: 1160.48

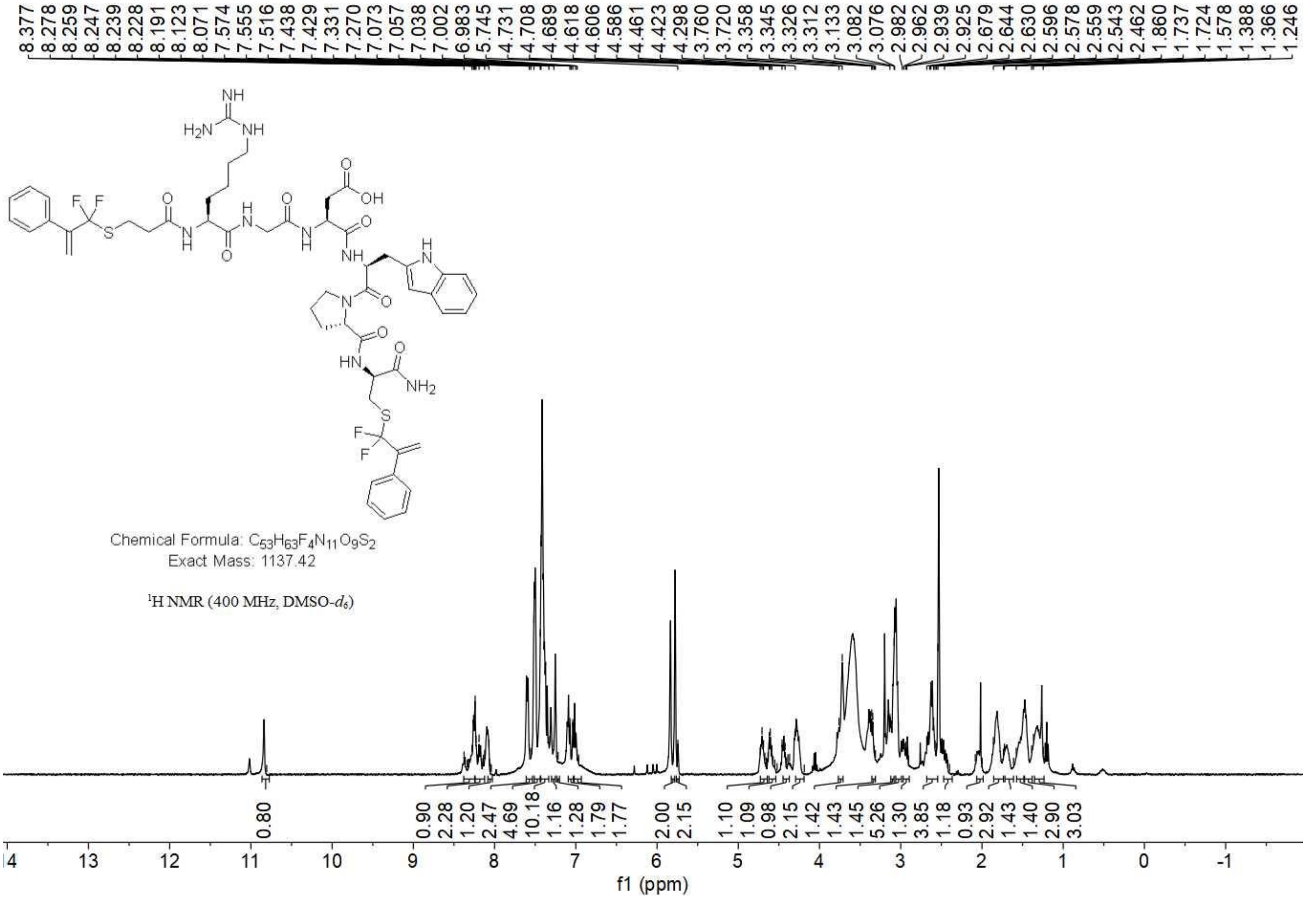
^{19}F NMR (376 MHz, DMSO-d_6)

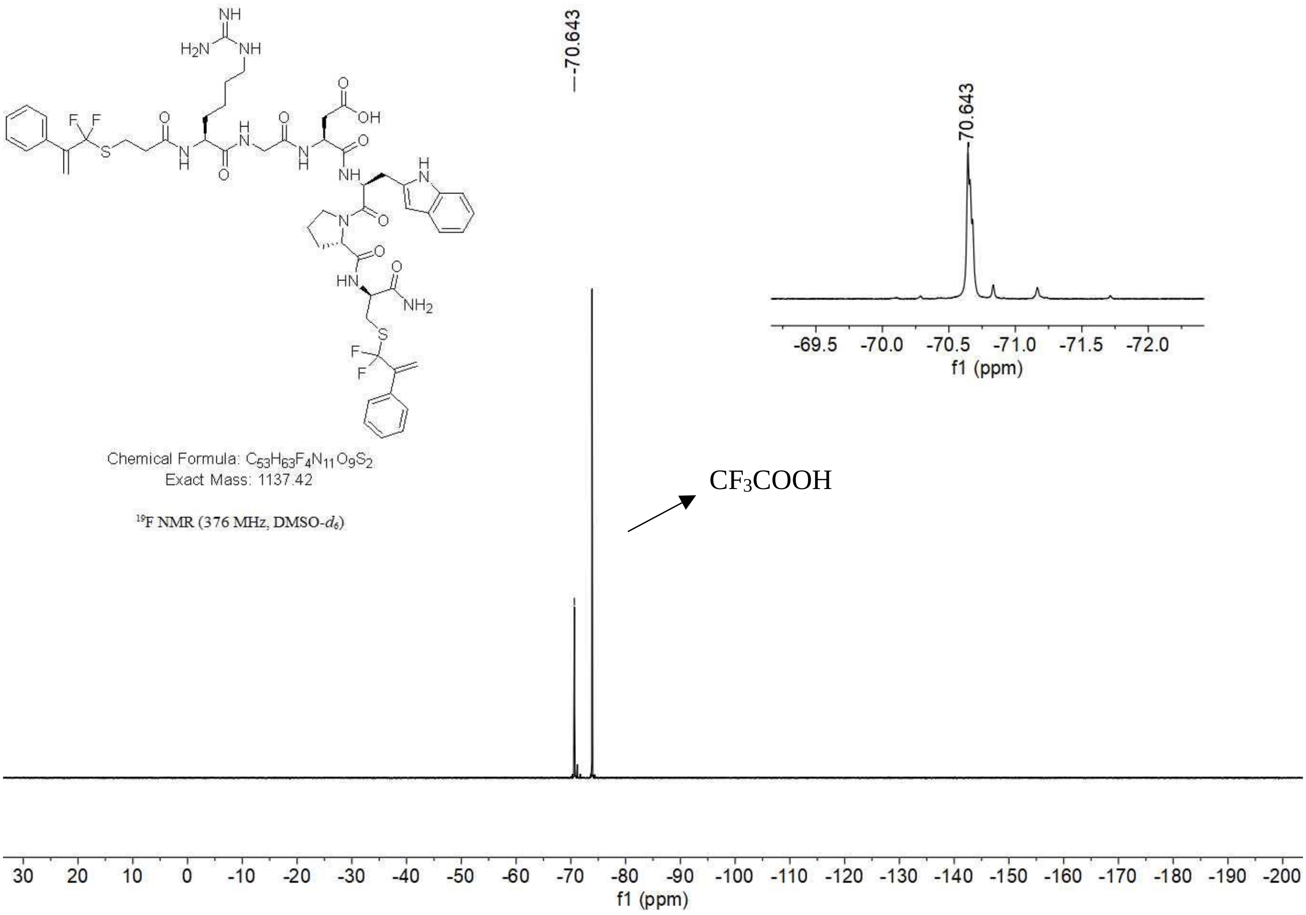


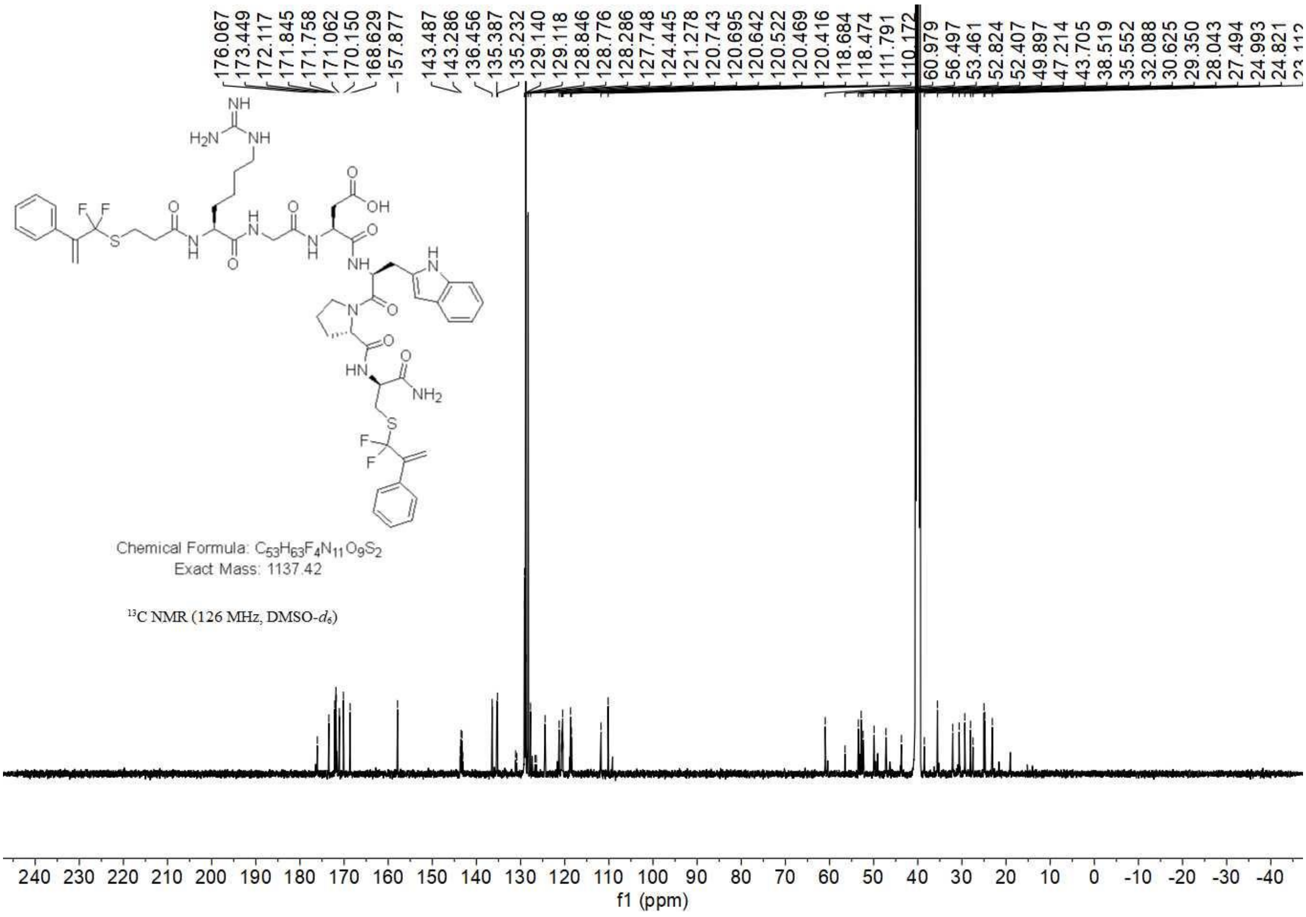
Chemical Formula: $C_{49}H_{72}F_4N_{12}O_{12}S_2$
Exact Mass: 1160.48

^{13}C NMR (126 MHz, DMSO-d_6)

Spectra of 6i

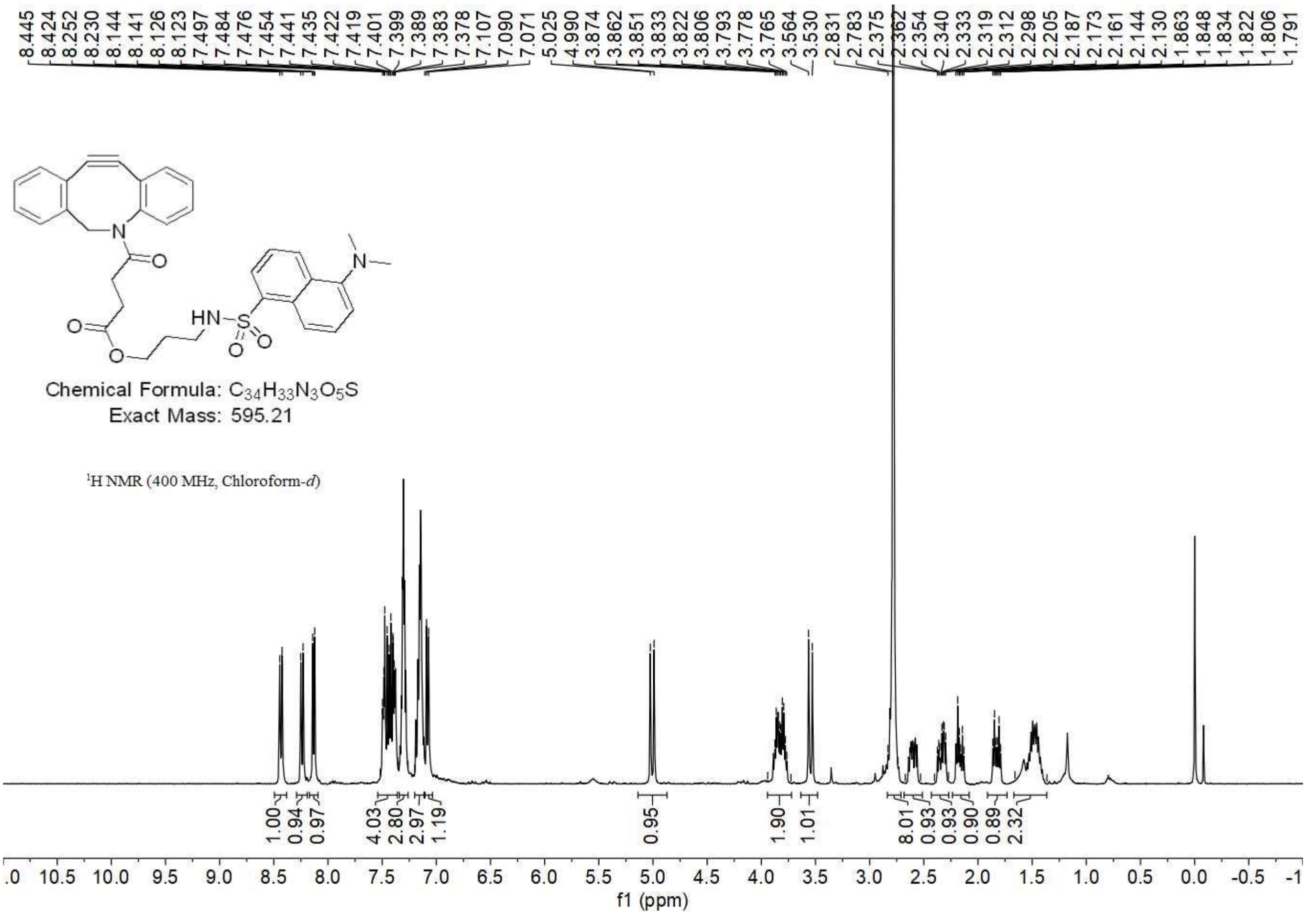


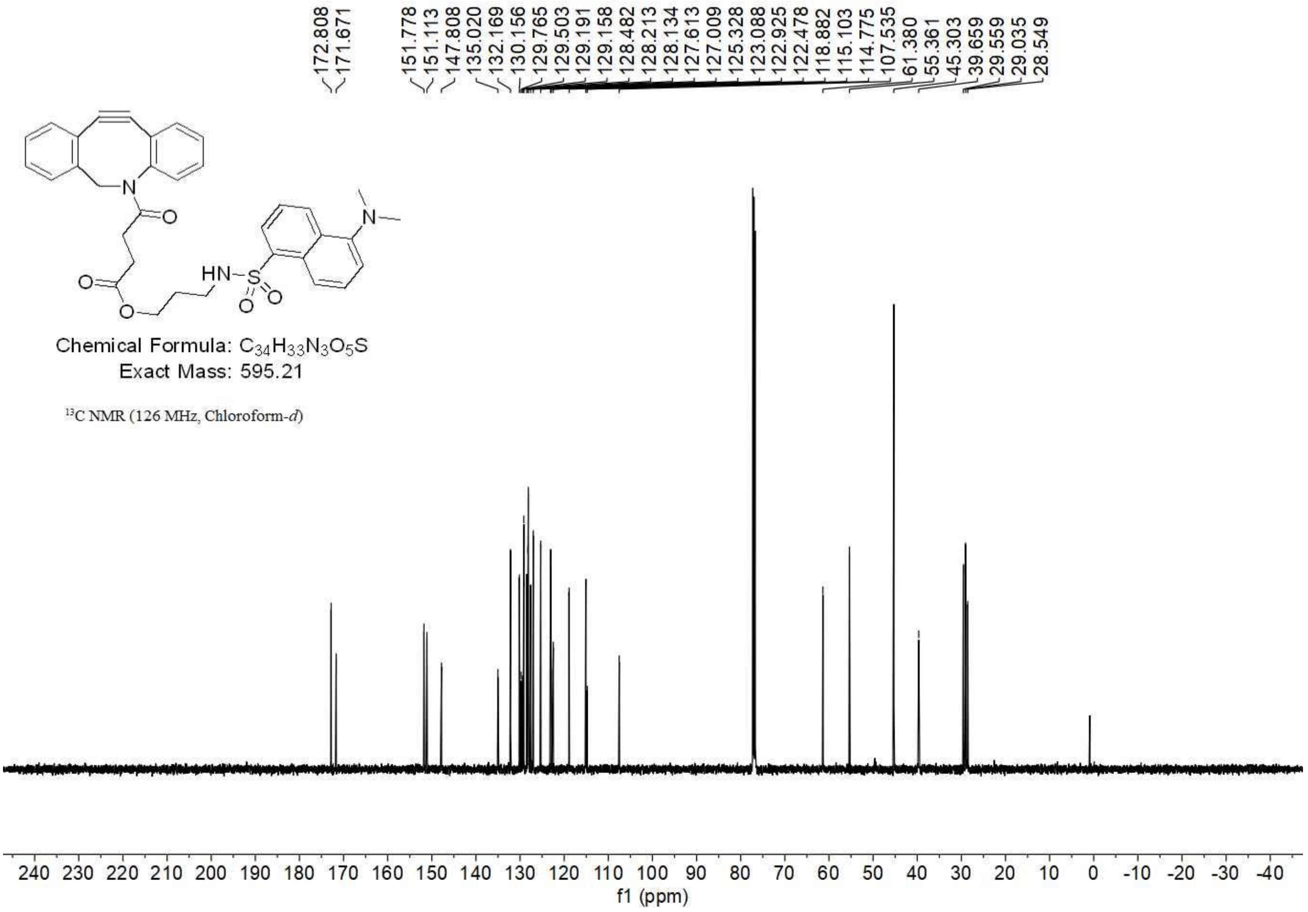

Chemical Formula: C53H63F4N11O9S2
Exact Mass: 1137.42
19F NMR (376 MHz, DMSO-d6)
--70.643
-70.643
-69.5
-70.0
-70.5
-71.0
-71.5
-72.0
f1 (ppm)
CF3COOH
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


176.067
173.449
172.117
171.845
171.758
171.062
170.150
168.629
157.877
143.487
143.286
136.456
135.387
135.232
129.140
129.118
128.846
128.776
128.286
127.748
124.445
121.278
120.743
120.695
120.642
120.522
120.469
120.416
118.684
118.474
111.791
110.172
60.979
56.497
53.461
52.824
52.407
49.897
47.214
43.705
38.519
35.552
32.088
30.625
29.350
28.043
27.494
24.993
24.821
Chemical Formula: C53H63F4N11O9S2
Exact Mass: 1137.42
13C NMR (126 MHz, DMSO-d6)
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
f1 (ppm)

9.6 Copies of ^{1}H, ^{19}F, ^{13}C Spectra for Compounds 7, 8, 10, 11, 12

Spectra of 7a

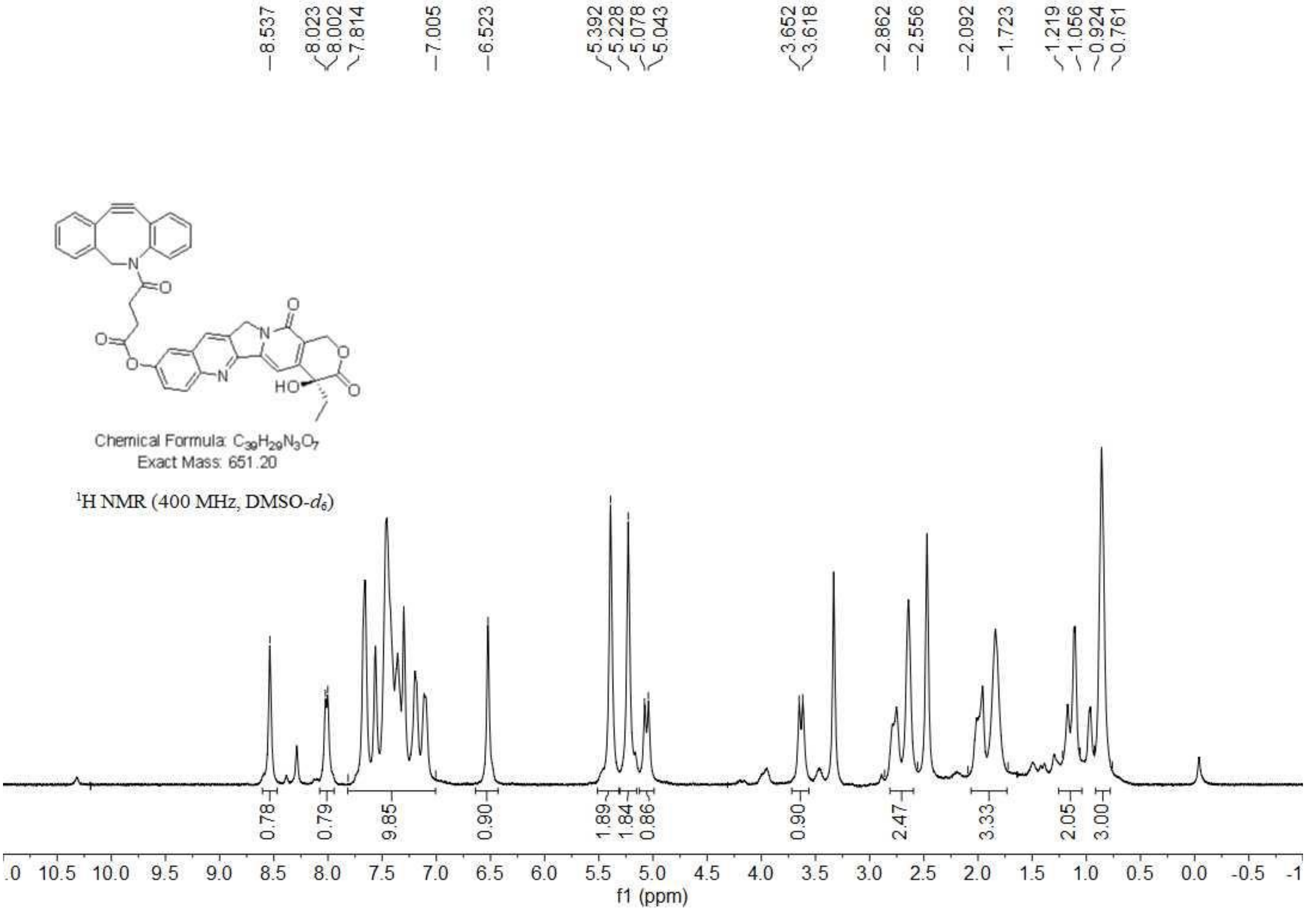


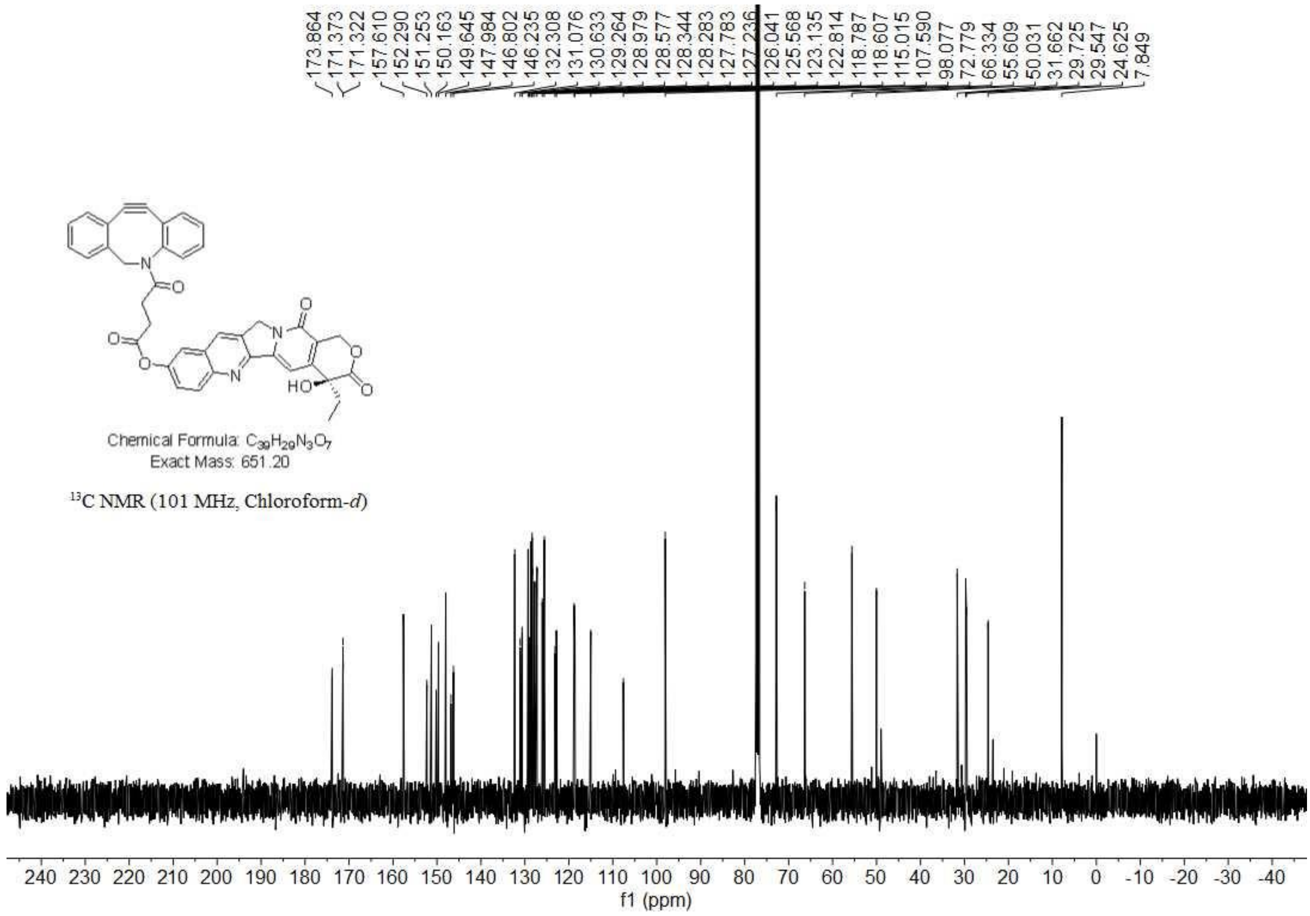


Chemical Formula: $C_{34}H_{33}N_3O_5S$
Exact Mass: 595.21

^{13}C NMR (126 MHz, Chloroform-*d*)

Spectra of 7b



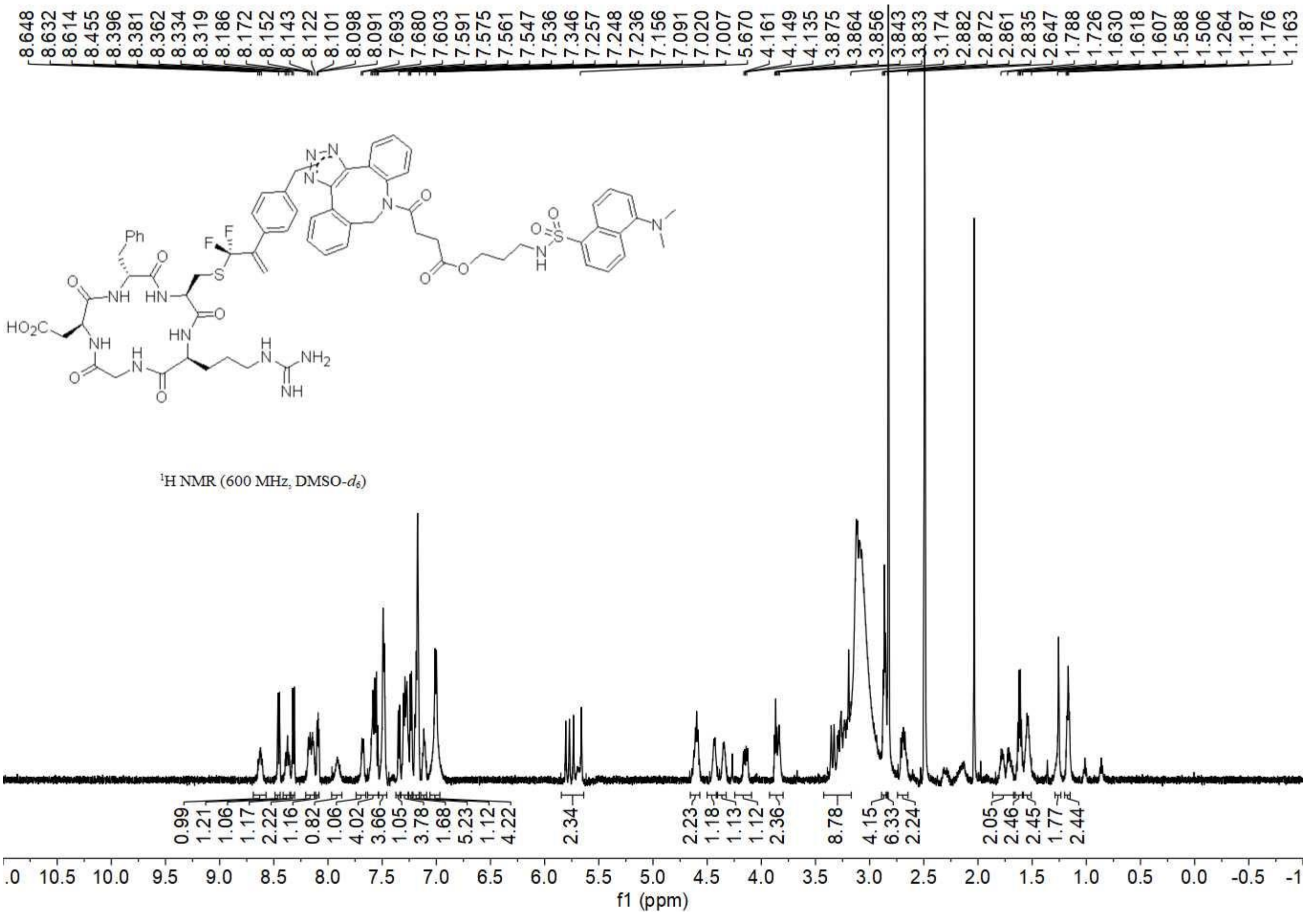


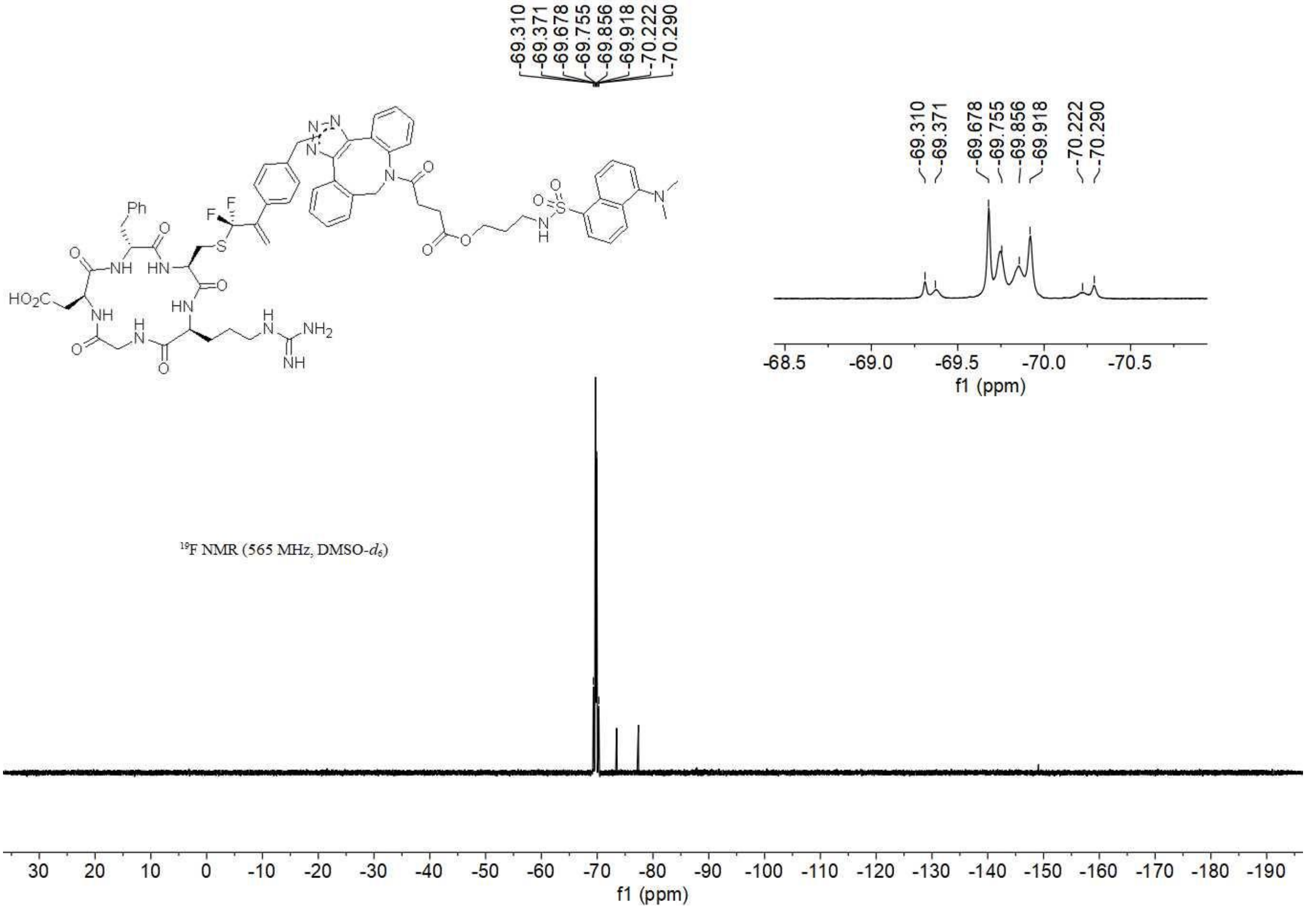
Chemical Formula: $C_{39}H_{29}N_3O_7$

Exact Mass: 651.20

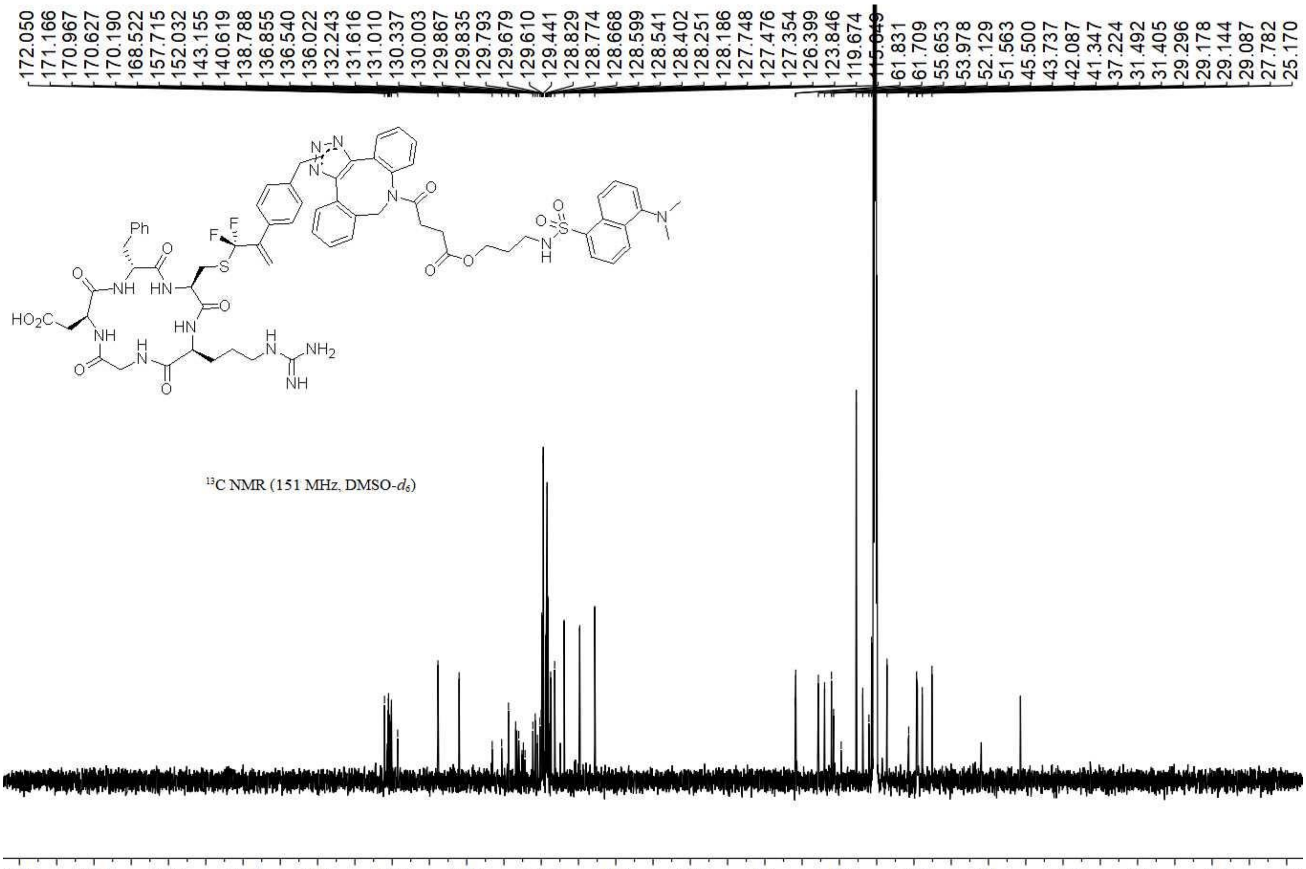
^{13}C NMR (101 MHz, Chloroform-*d*)

Spectra of 8a



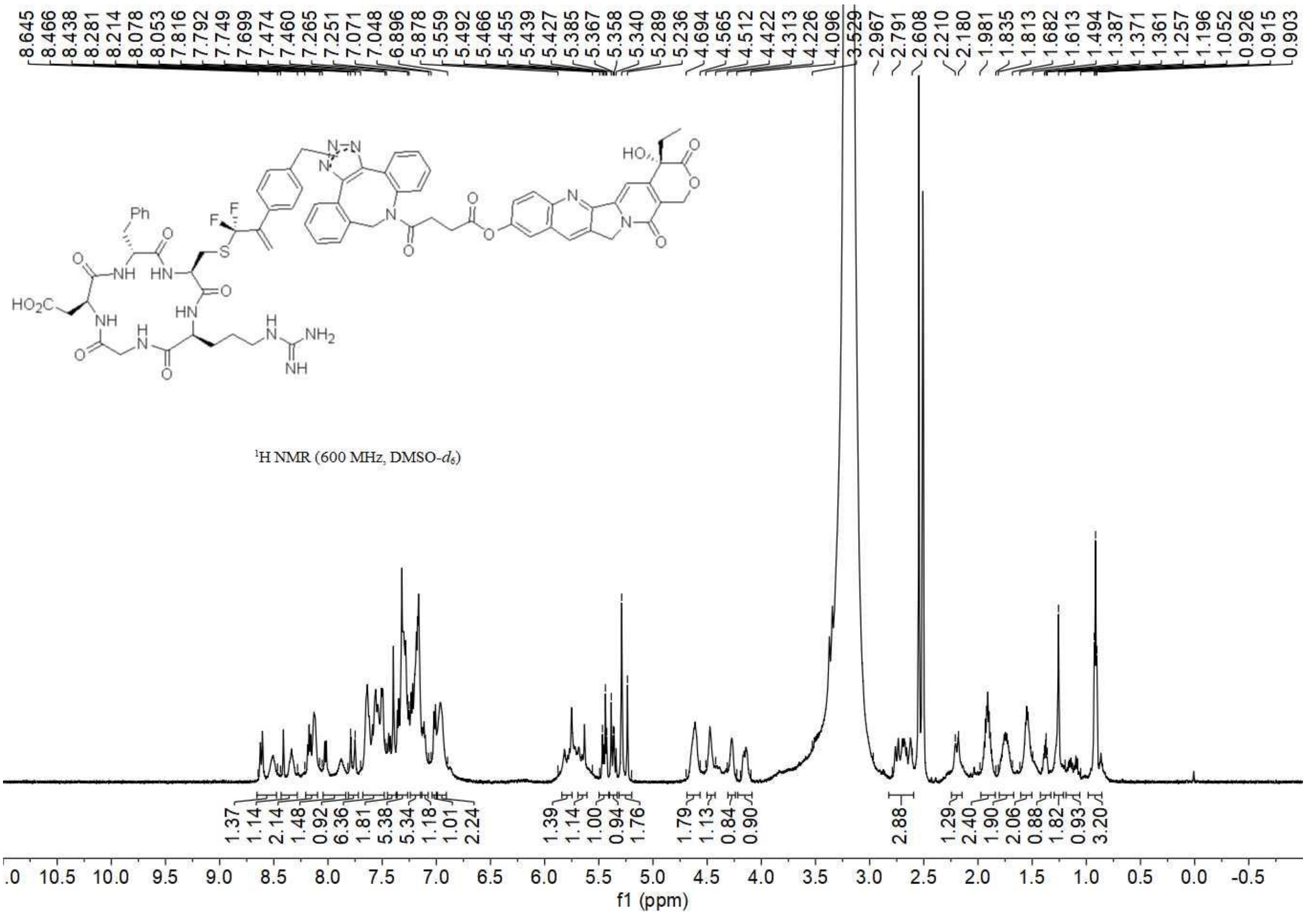


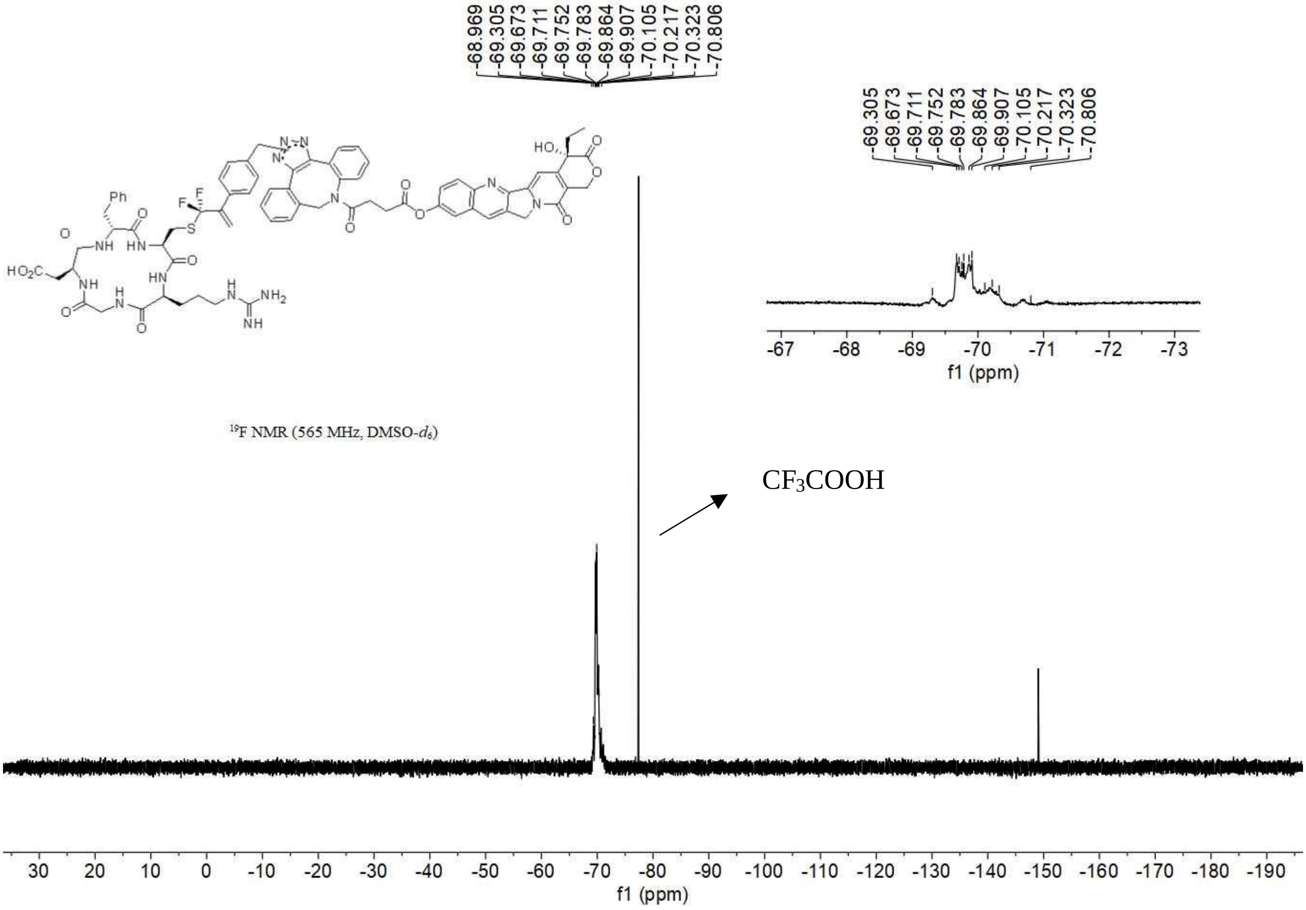
^{19}F NMR (565 MHz, DMSO-d_6)



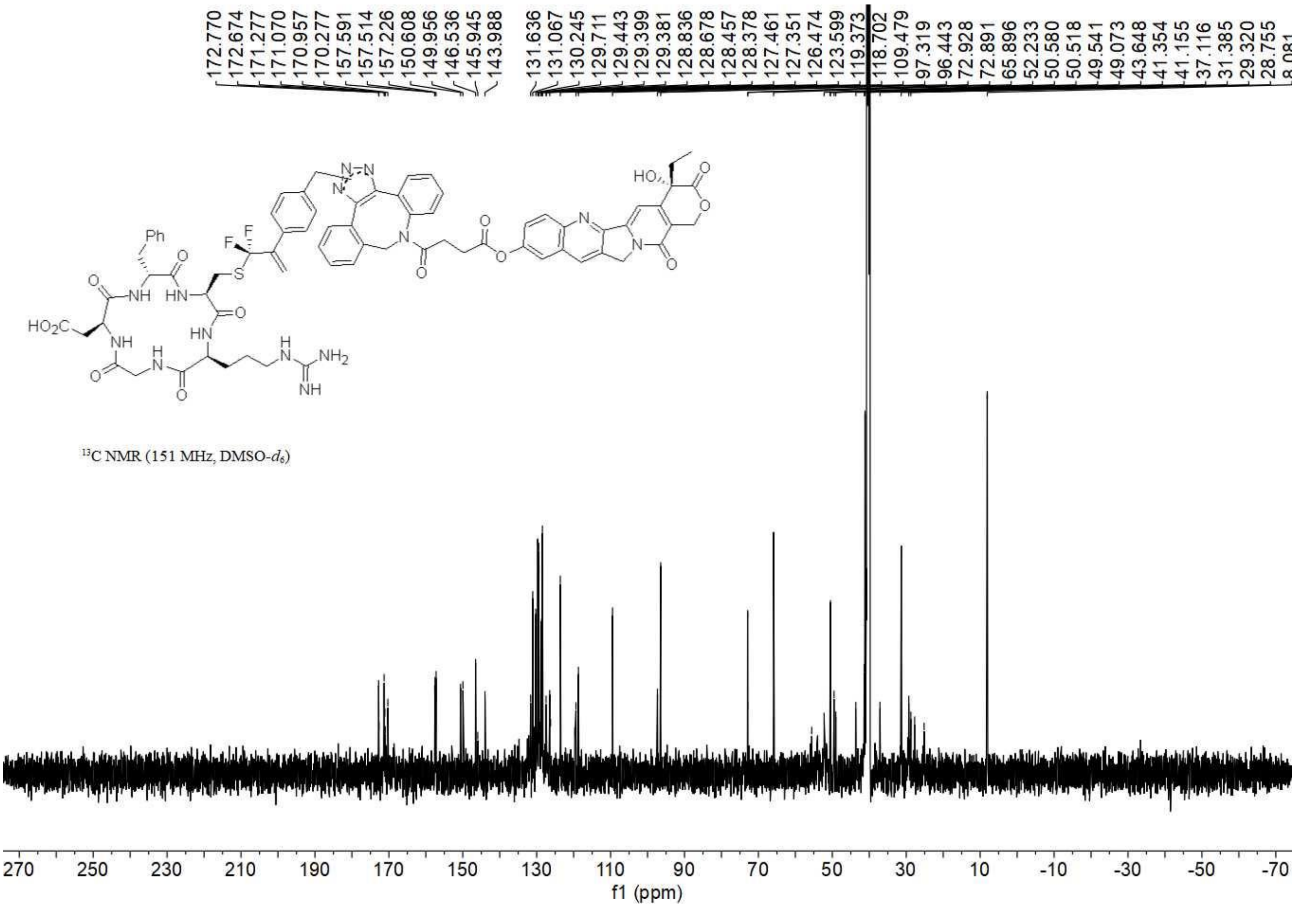
^{13}C NMR (151 MHz, DMSO-d_6)

Spectra of 8b



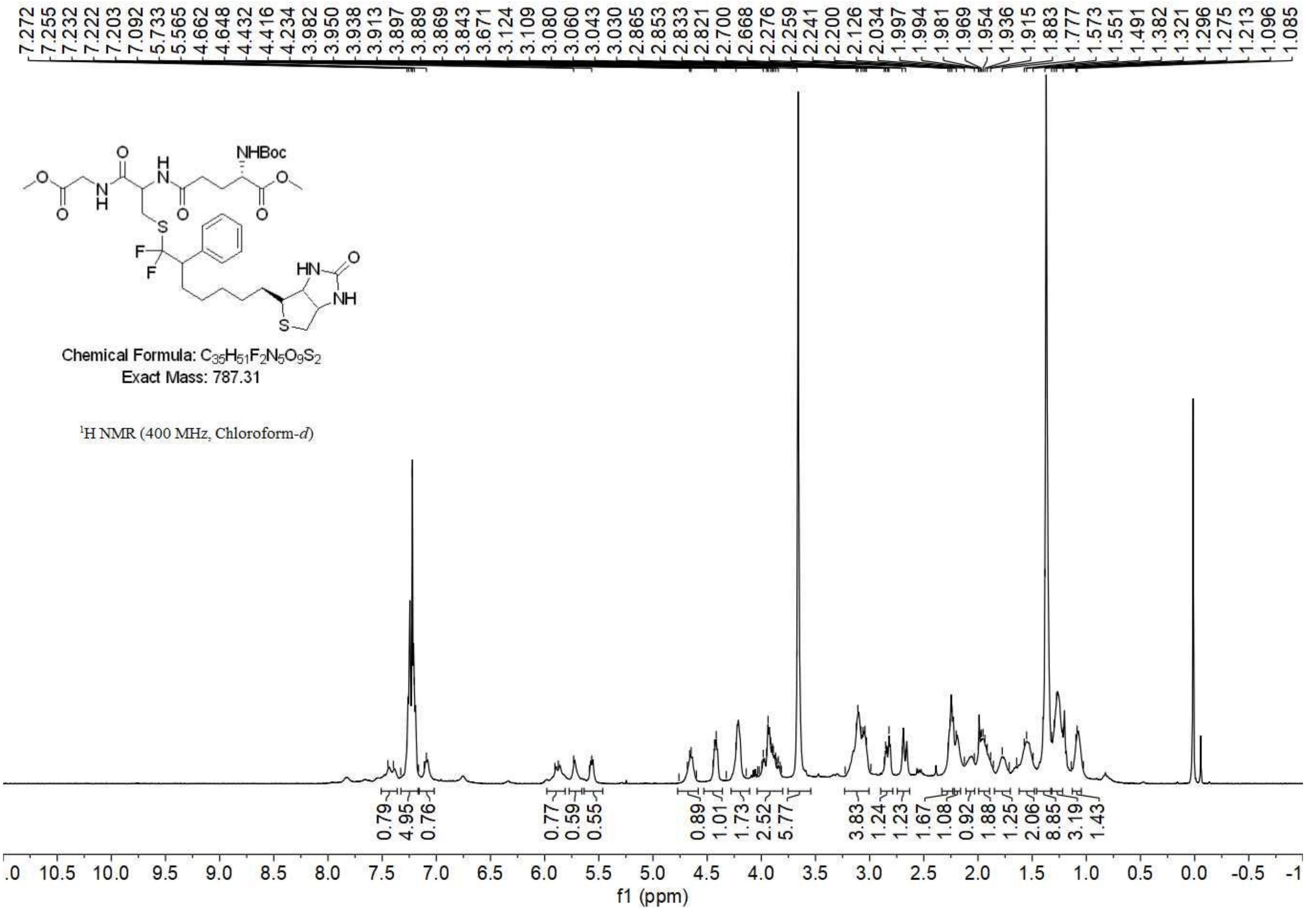


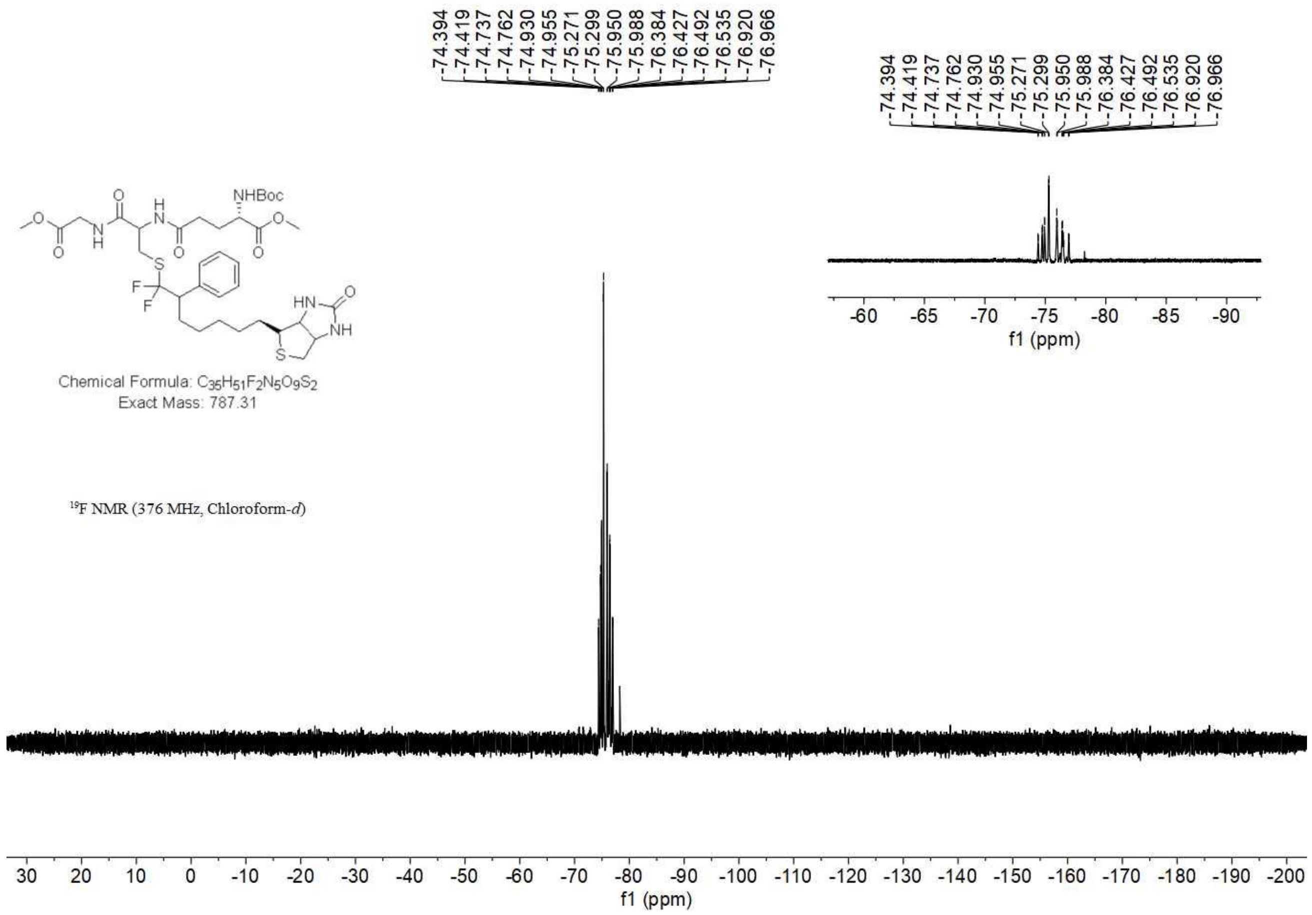
^{19}F NMR (565 MHz, DMSO-d_6)

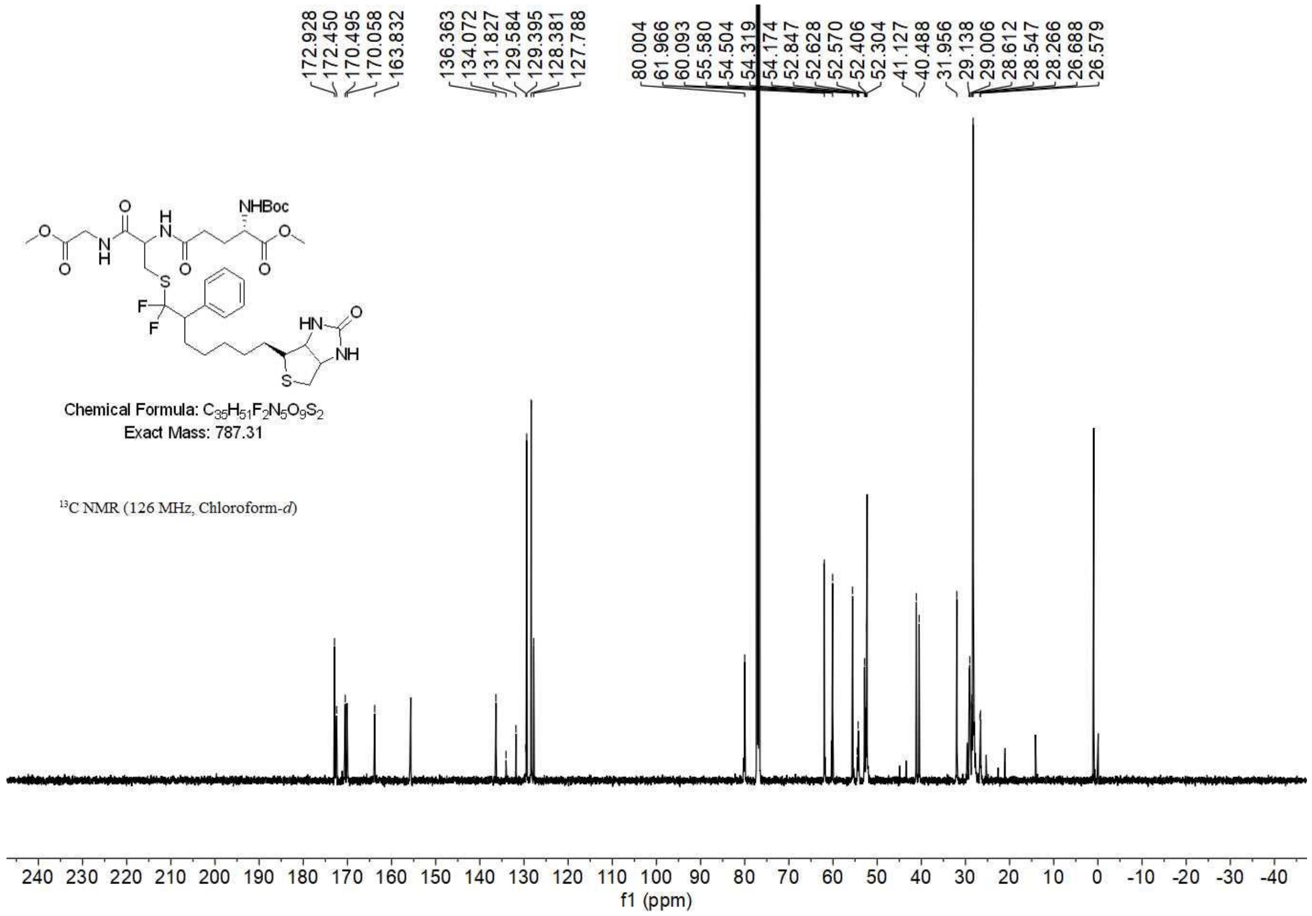


^{13}C NMR (151 MHz, DMSO-d_6)

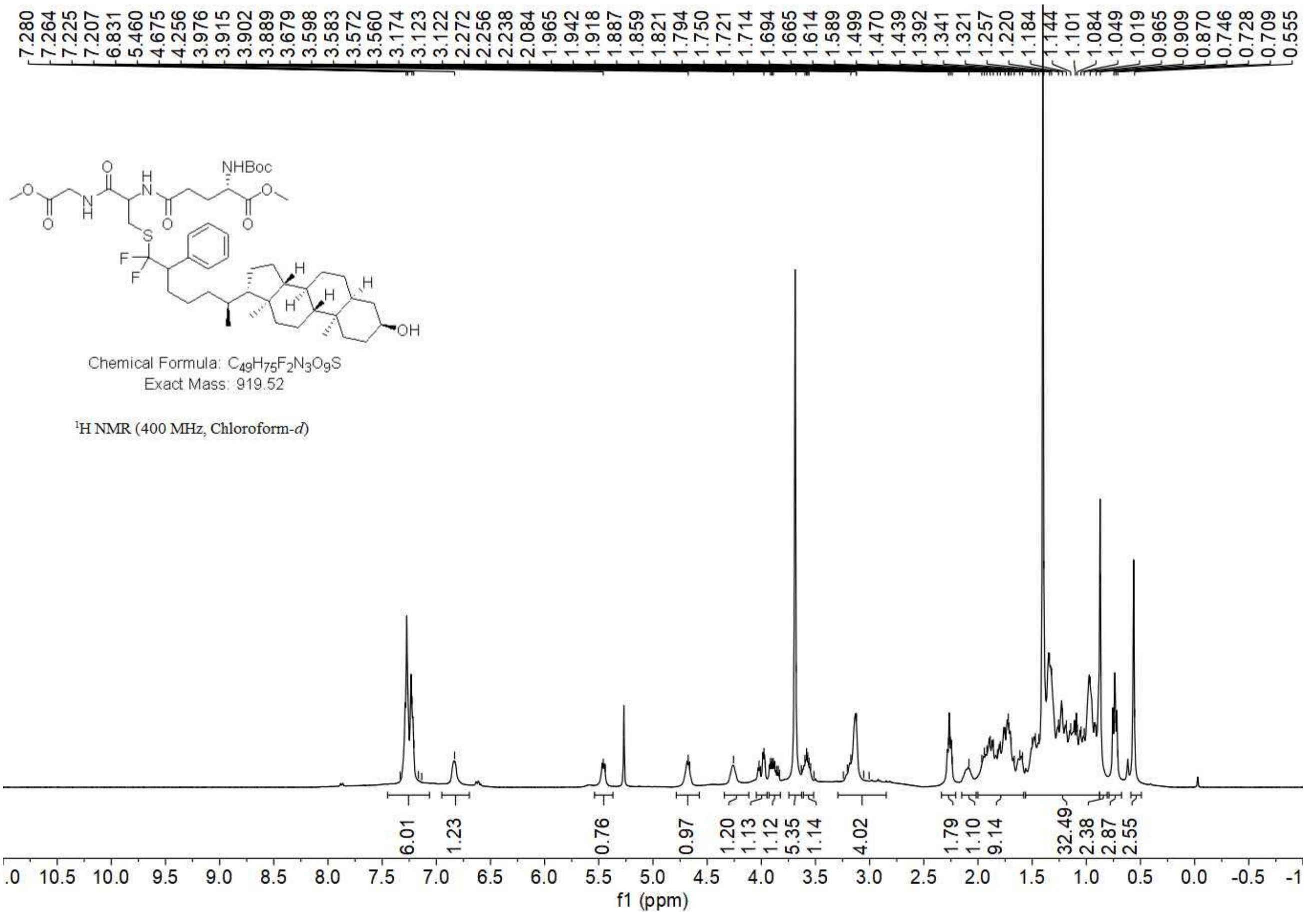
Spectra of 10a

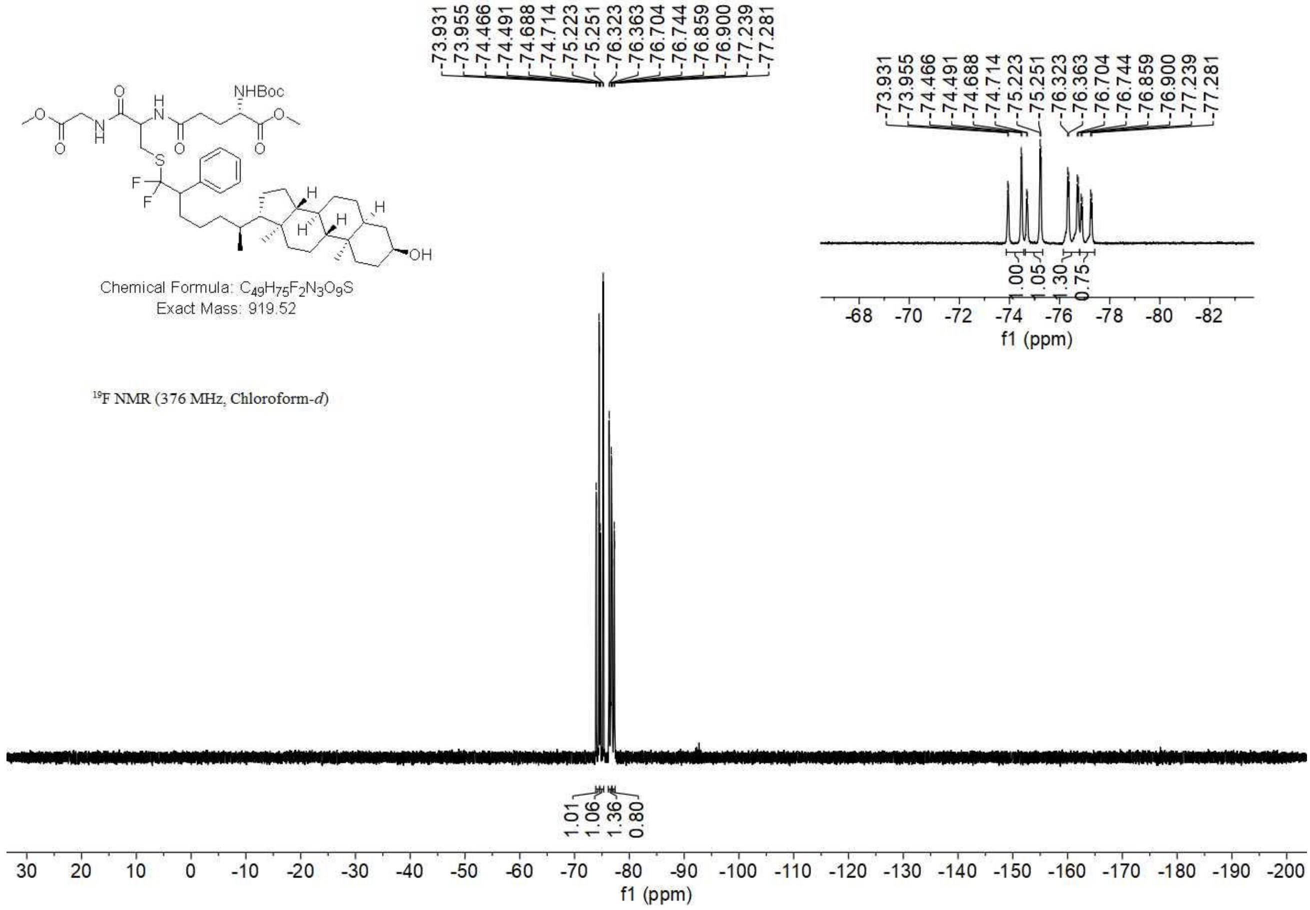



-74.394
-74.419
-74.737
-74.762
-74.930
-74.955
-75.271
-75.299
-75.950
-75.988
-76.384
-76.427
-76.492
-76.535
-76.920
-76.966
NHBoc
O
H
N
S
F
F
HN
NH
Chemical Formula: $C_{35}H_{51}F_2N_5O_9S_2$
Exact Mass: 787.31
^{19}F NMR (376 MHz, Chloroform-*d*)
-60
-65
-70
-75
-80
-85
-90
f1 (ppm)
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)


172.928
172.450
170.495
170.058
163.832
136.363
134.072
131.827
129.584
129.395
128.381
127.788
80.004
61.966
60.093
55.580
54.504
54.319
54.174
52.847
52.628
52.570
52.406
52.304
41.127
40.488
31.956
29.138
29.006
28.612
28.547
28.266
26.688
26.579
NHBoc
O
H
N
S
F
F
HN
NH
Chemical Formula: $C_{35}H_{51}F_2N_5O_9S_2$
Exact Mass: 787.31
^{13}C NMR (126 MHz, Chloroform-*d*)
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
f1 (ppm)

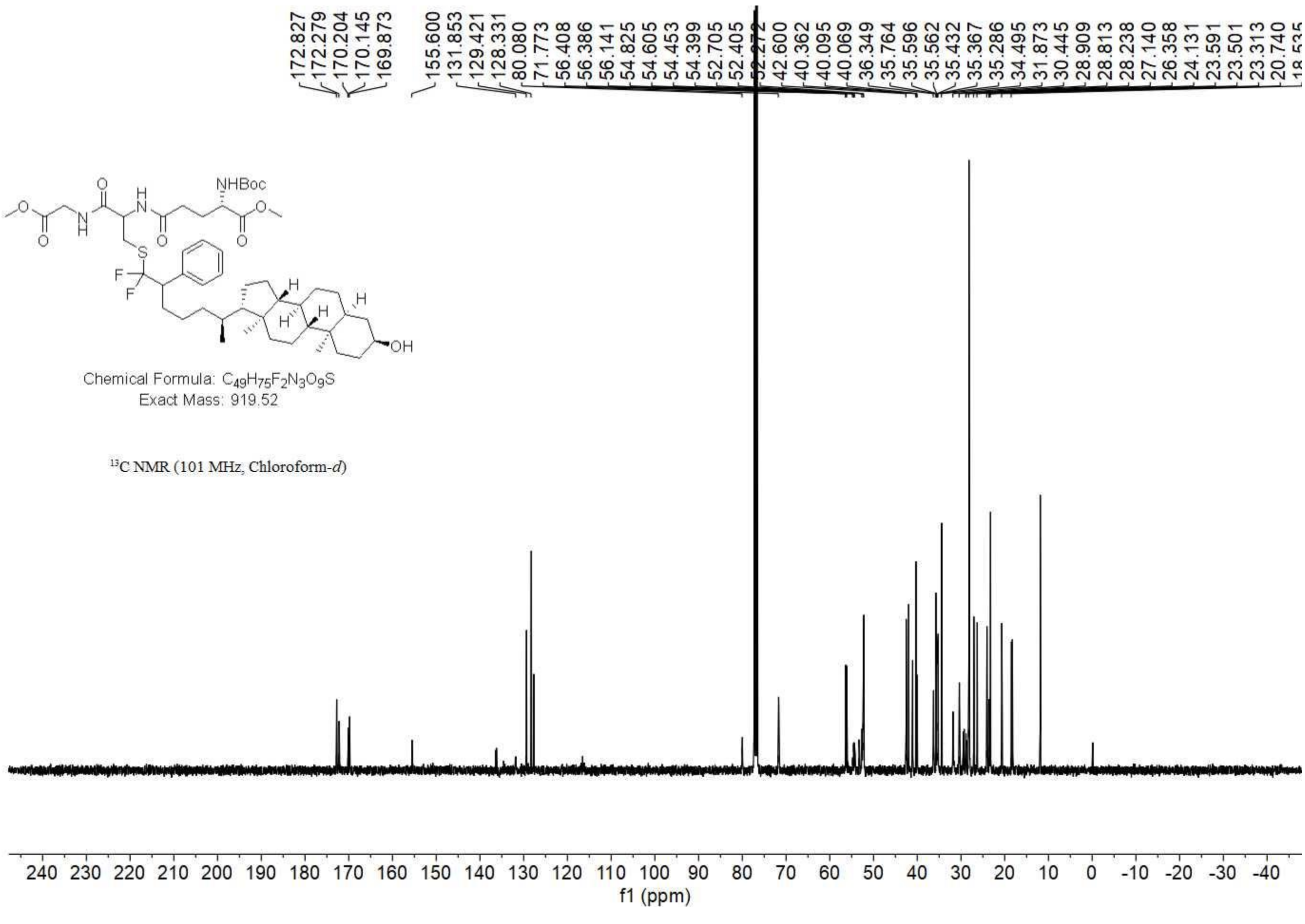
Spectra of 10b





Chemical Formula: $C_{49}H_{75}F_2N_3O_9S$
Exact Mass: 919.52

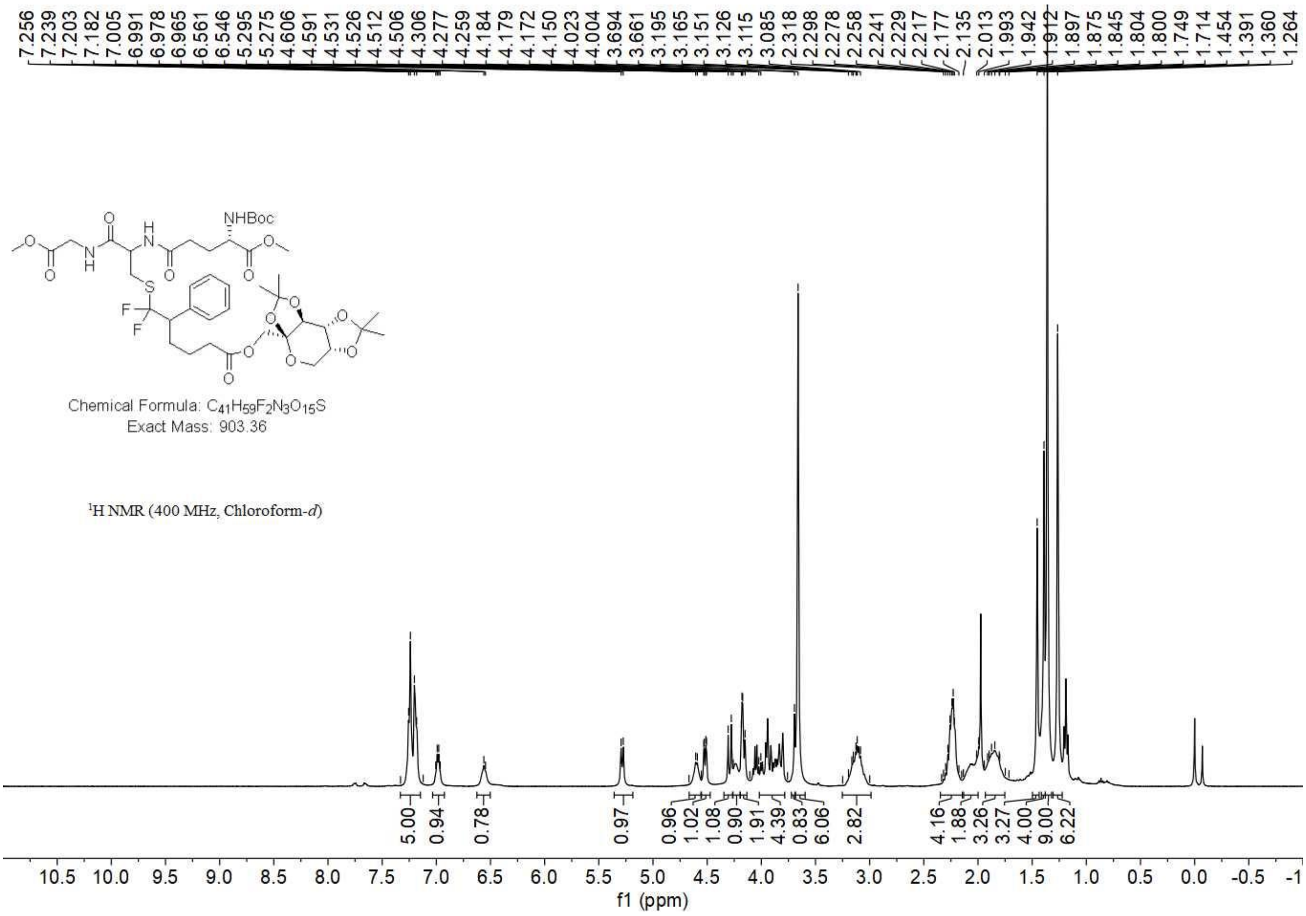
^{19}F NMR (376 MHz, Chloroform-*d*)

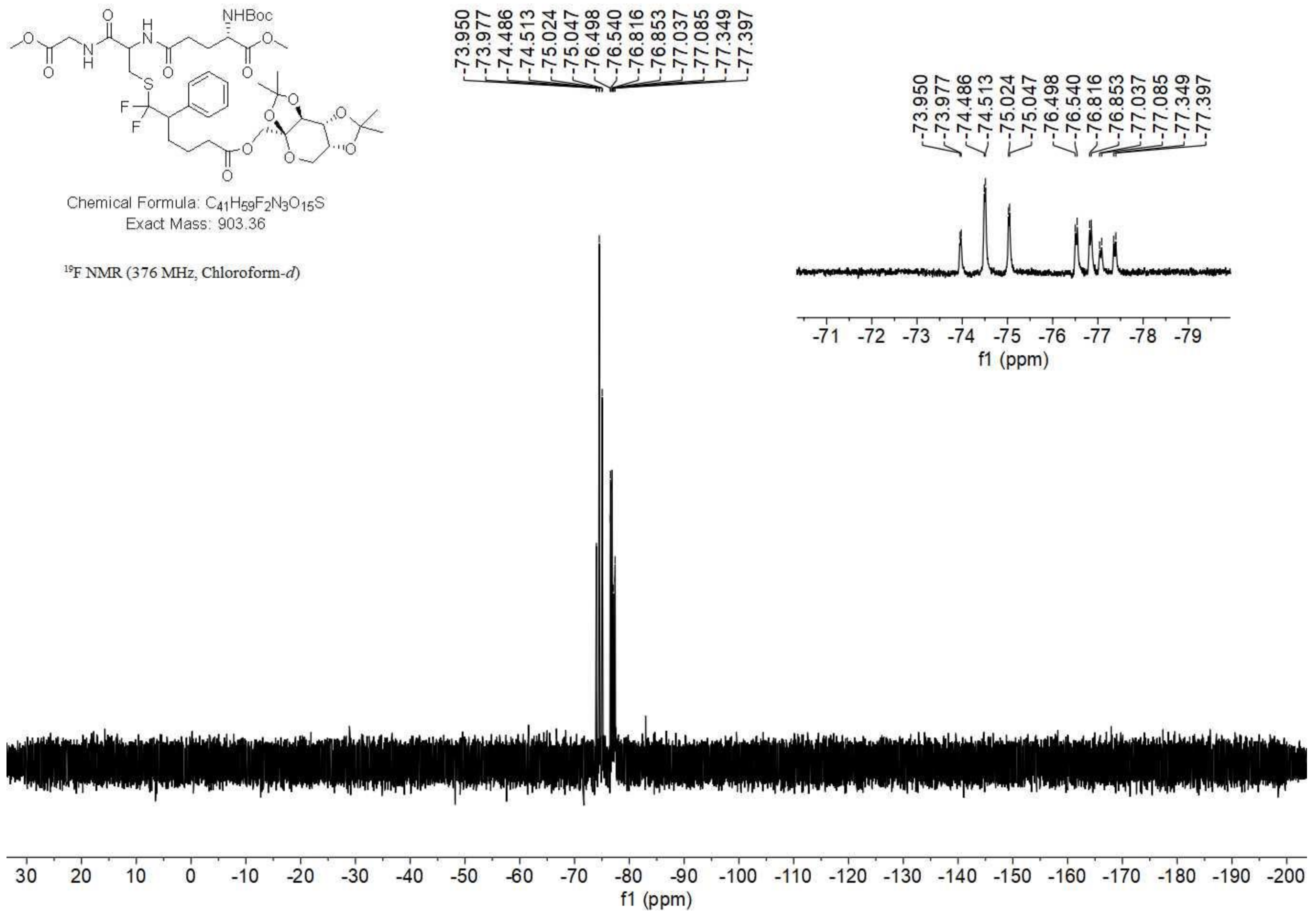


Chemical Formula: $C_{49}H_{75}F_2N_3O_9S$
Exact Mass: 919.52

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

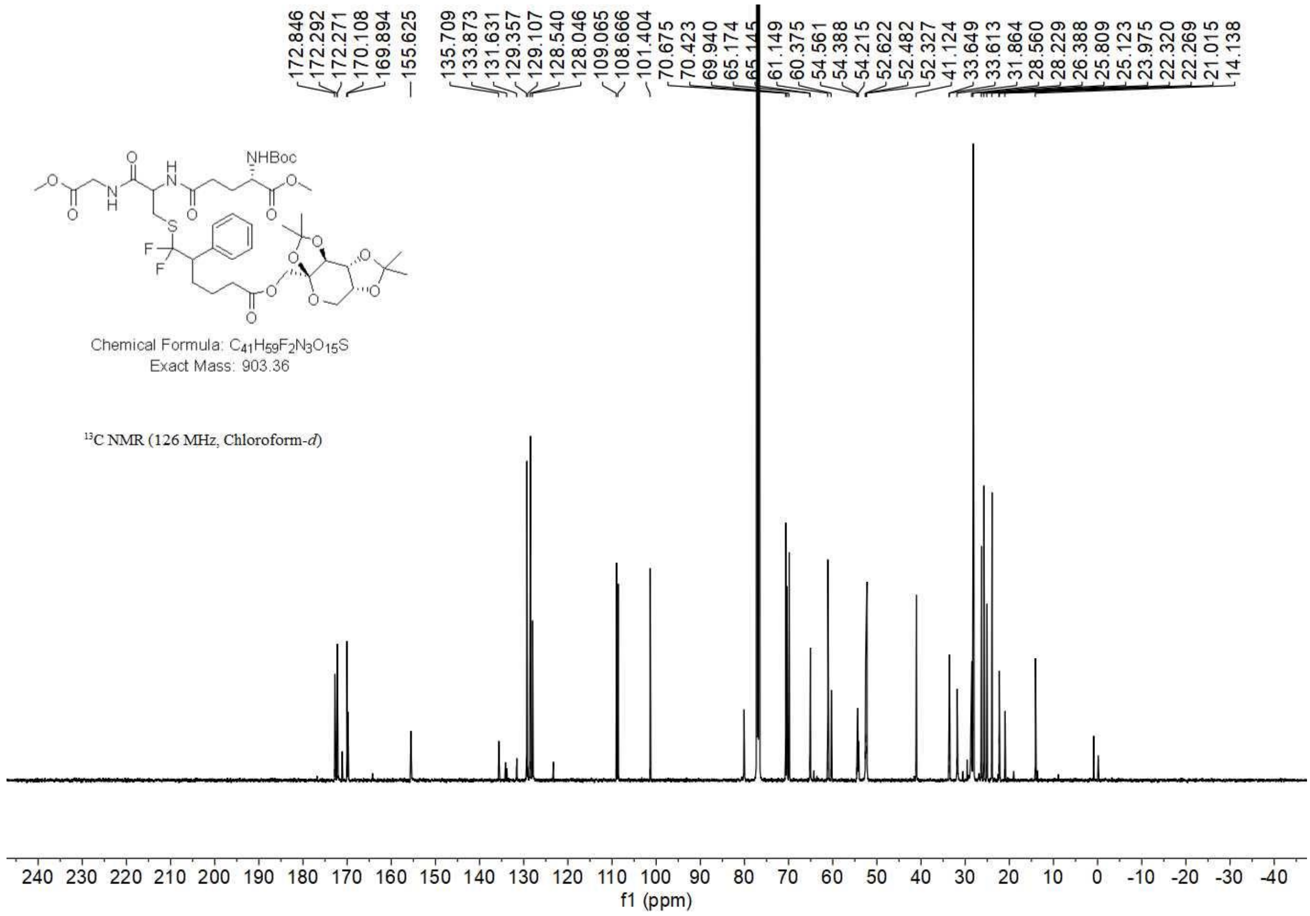
Spectra of 10c





Chemical Formula: $C_{41}H_{59}F_2N_3O_{15}S$
Exact Mass: 903.36

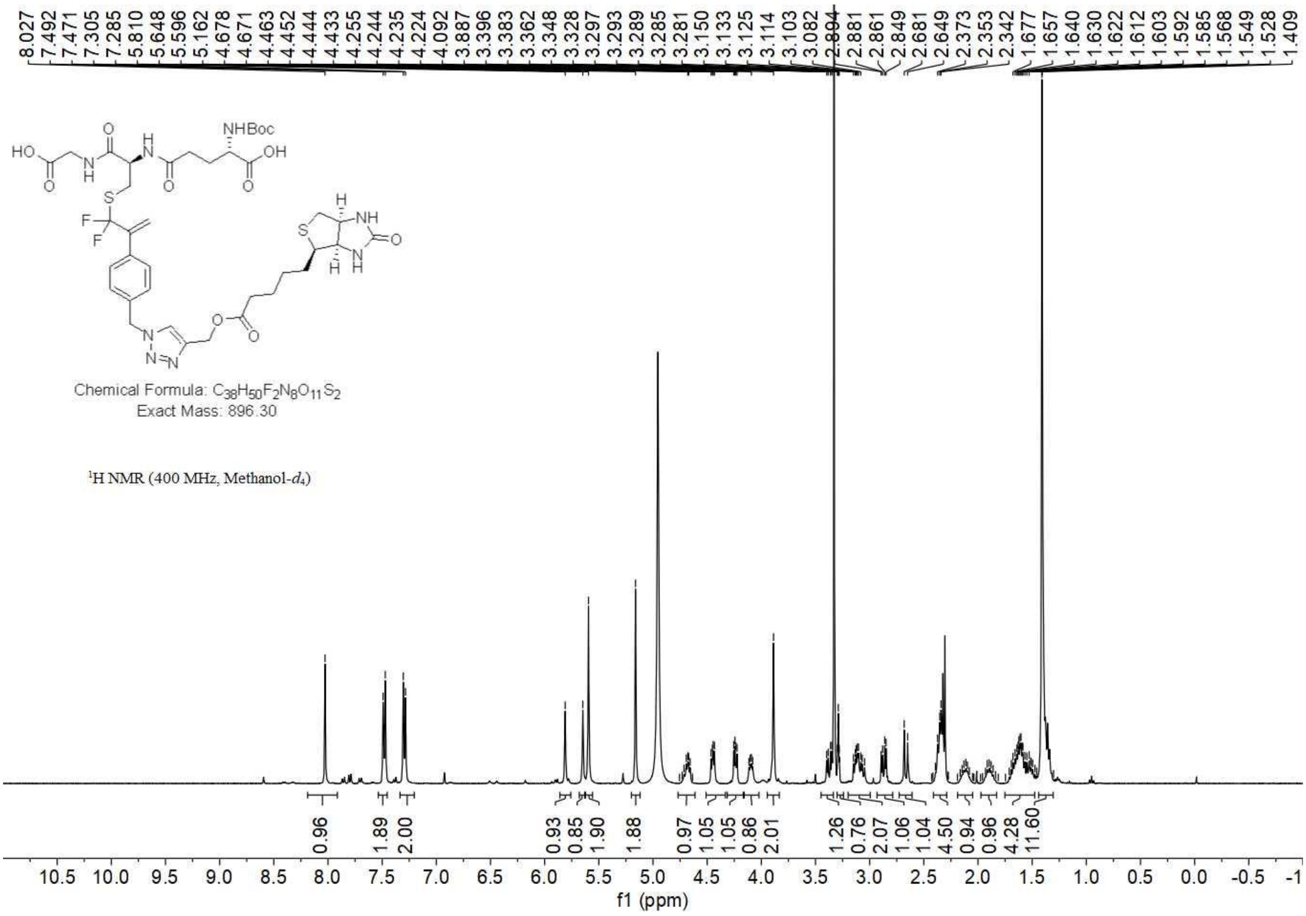
^{19}F NMR (376 MHz, Chloroform-*d*)



Chemical Formula: $C_{41}H_{59}F_2N_3O_{15}S$
Exact Mass: 903.36

^{13}C NMR (126 MHz, Chloroform-*d*)

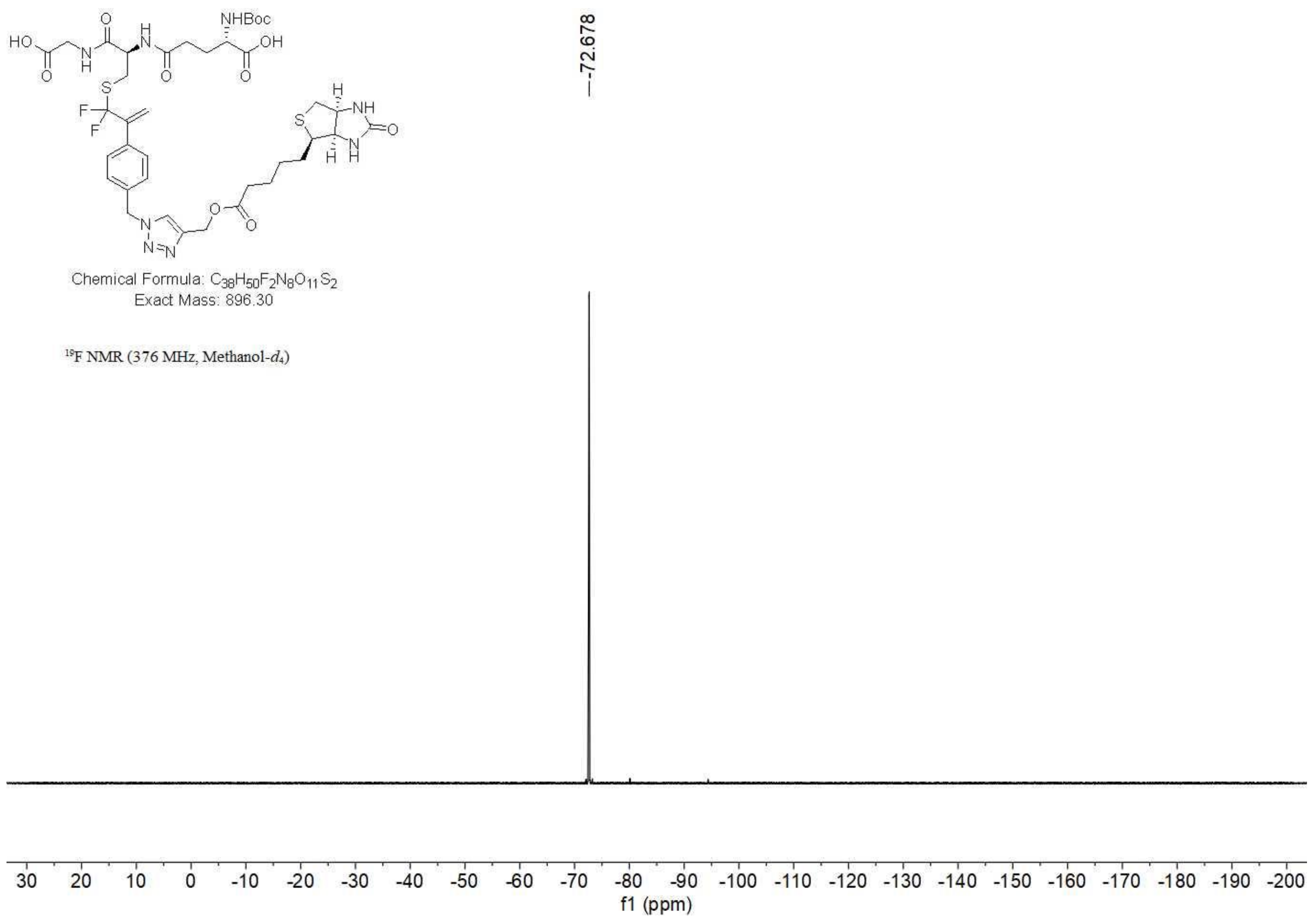
Spectra of 11



Chemical Formula: $C_{38}H_{50}F_2N_8O_{11}S_2$

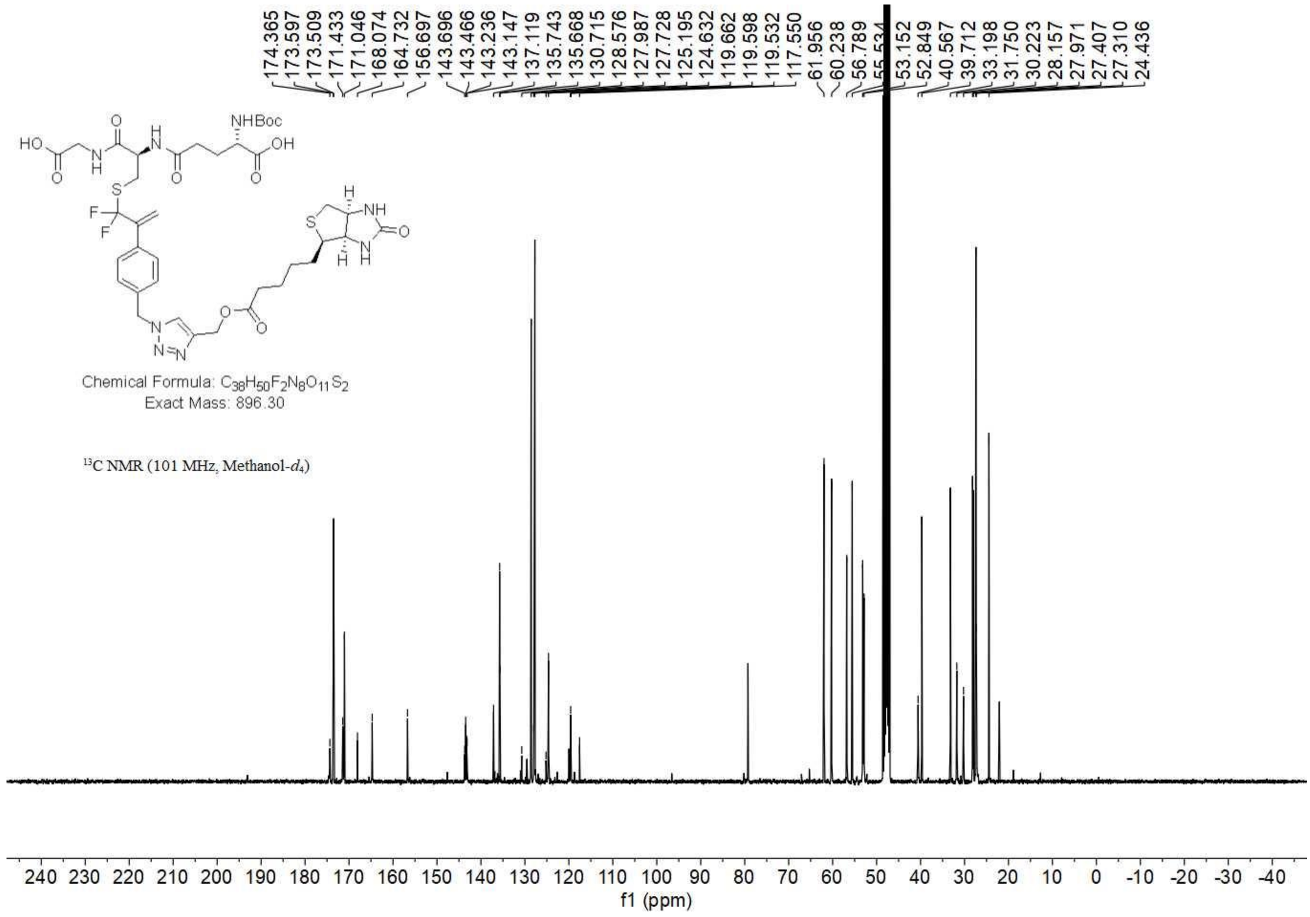
Exact Mass: 896.30

^{1}H NMR (400 MHz, Methanol-d_4)



Chemical Formula: $C_{38}H_{50}F_2N_8O_{11}S_2$
Exact Mass: 896.30

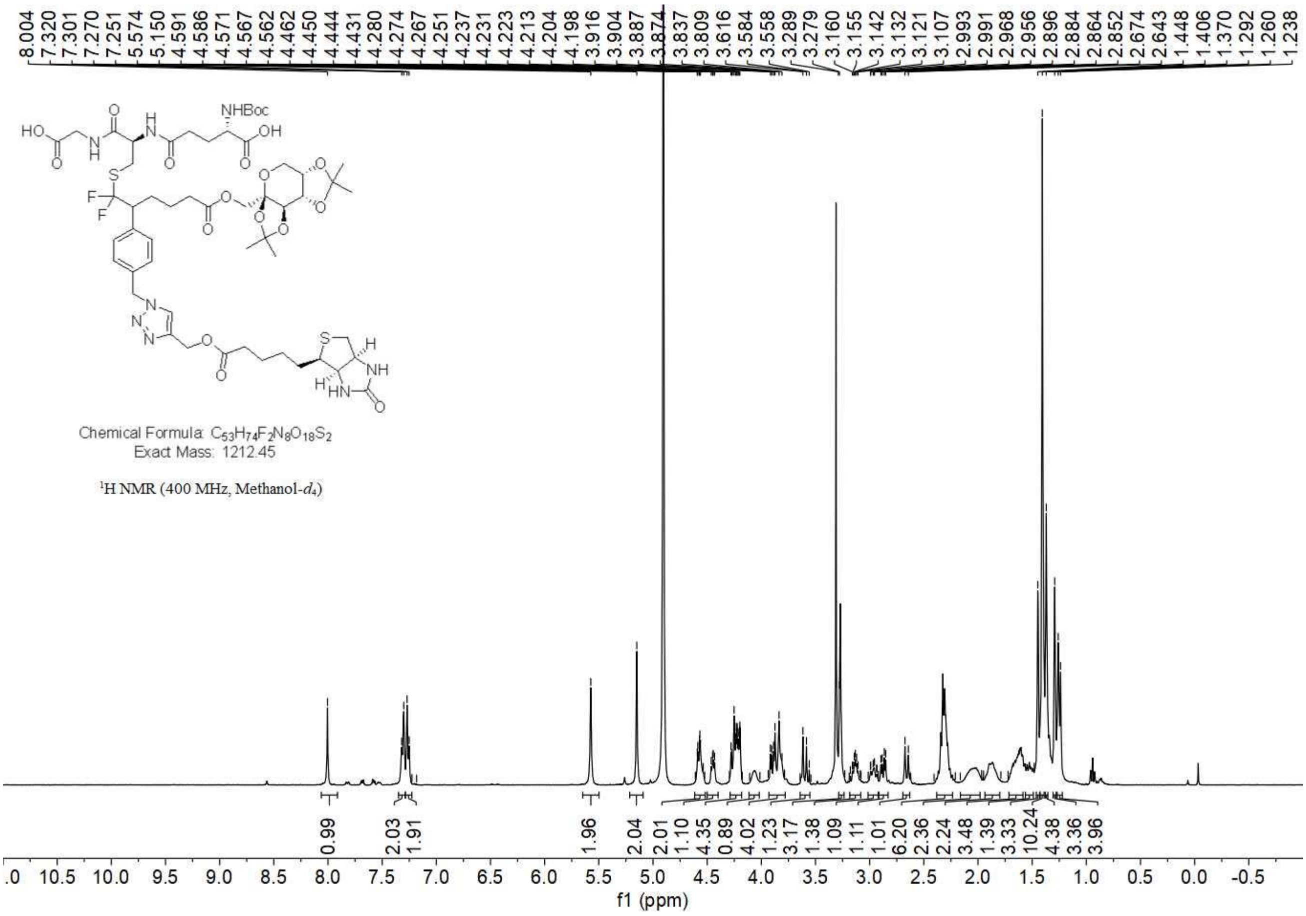
^{19}F NMR (376 MHz, Methanol-*d*$_4$)

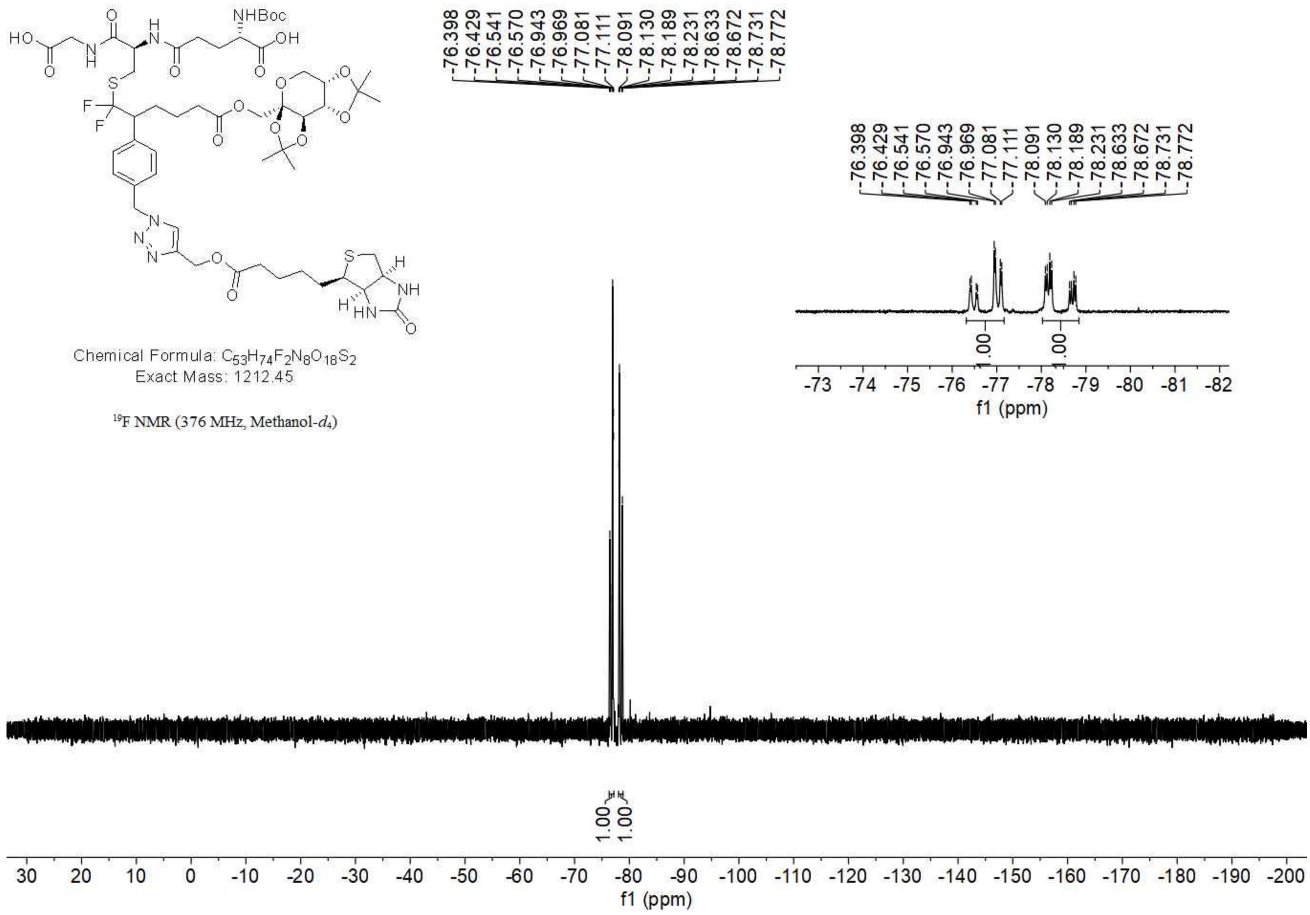


Chemical Formula: $C_{38}H_{50}F_2N_8O_{11}S_2$
Exact Mass: 896.30

^{13}C NMR (101 MHz, Methanol-*d*$_4$)

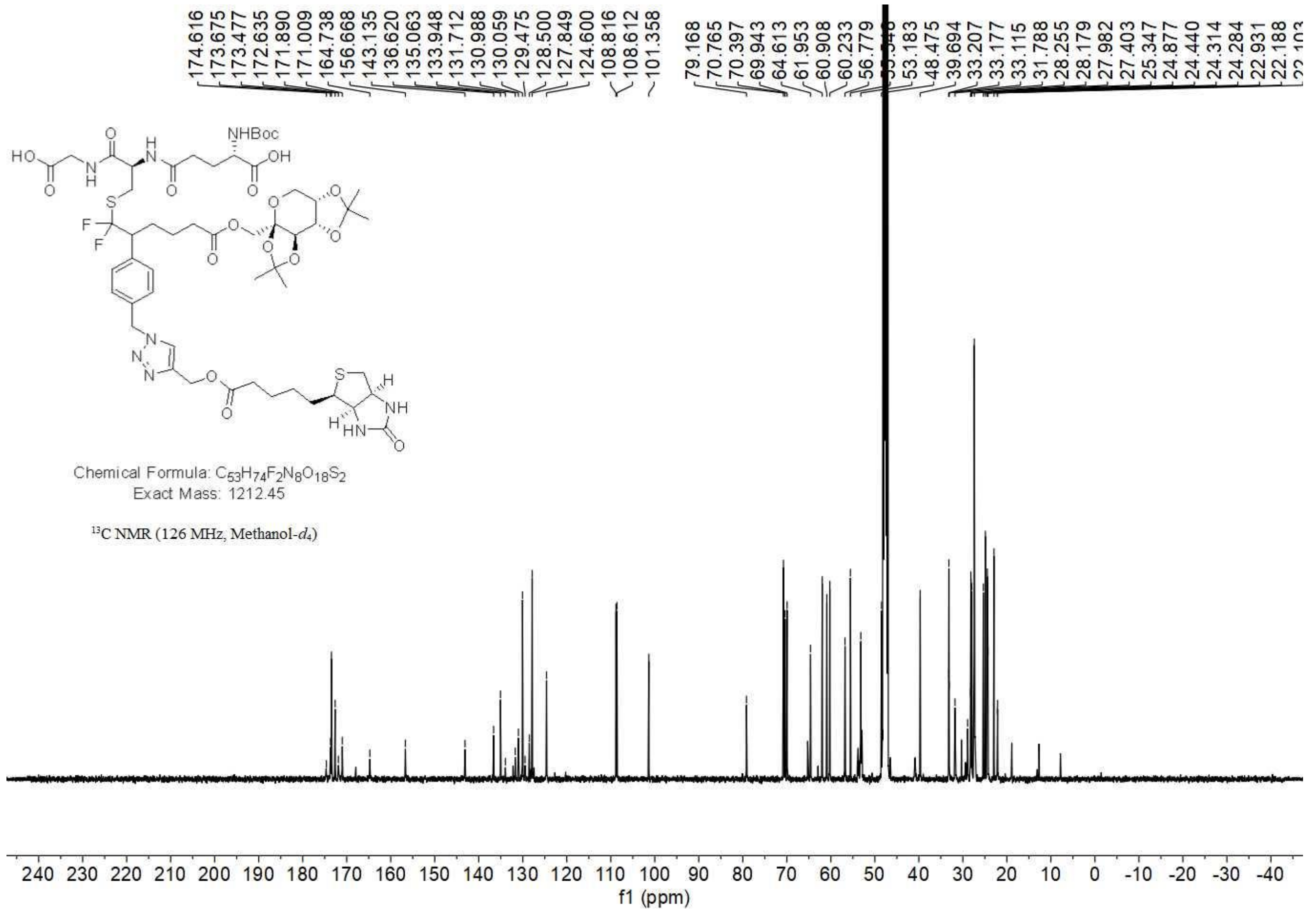
Spectra of 12





Chemical Formula: $C_{53}H_{74}F_2N_8O_{18}S_2$
Exact Mass: 1212.45

^{19}F NMR (376 MHz, Methanol-d_4)



Chemical Formula: $C_{53}H_{74}F_2N_8O_{18}S_2$
Exact Mass: 1212.45

^{13}C NMR (126 MHz, Methanol-d_4)