Supporting Information

Photo-induced difluoroalkylation/cyclization of alkyne ketones: A novel strategy to access difluoroalkyl thiofavones

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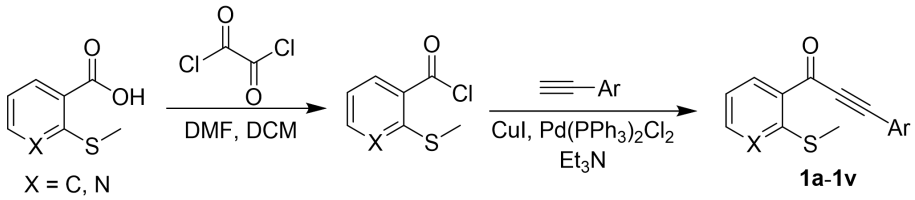
1. General Information

The reagents and solvents were purchased from commercial suppliers and used without further purification unless noted. All reactions were monitored by TLC with silica gel coated plates. ^{1}H (400 MHz) NMR, ^{1}H (600 MHz) NMR,^{13}C (100 MHz) NMR, ^{13}C (150 MHz) NMR, ^{19}F (376 MHz) NMR and ^{19}F (565 MHz) NMR spectra were recorded on Varian and Bruker spectrometers in Chloroform-*d* or DMSO-d_6 using tetramethylsilane (TMS) as the internal standards. Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q =quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets. Mass spectra were measured with a HRMS-APCI instrument using ESI ionization. UV/vis absorption spectra experiments were conducted on a HitachiF-7000 FL Spectrophotometer. Melting points were measured by WRS-1C Melting Point Apparatus (Shanghai INESA Physico-Optical Instrument Co., Ltd.). Photo-induced reactions were performed under 460-465 nm light irradiation using a 25 W LED lamp (purchased from Xuzhou Ai Jia Electronic Technology Co., Ltd. in Taobao.com). The distance from the light source to the irradiation vessel was approximate 1.5 cm, and no filter was used in our study. A fan was employed to ensure reactions remained at or near room temperature when using LED.

2. Experimental Procedures

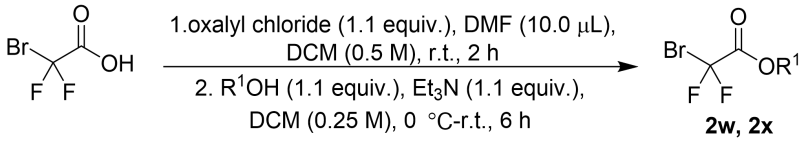
2.1 Preparation of Starting Materials

2.1.1 General Procedure A (for the synthesis of **1a-1v**)[1-3]



To a stirred solution of 2-(methylthio)benzoic acid (1.5g, 8.92 mmol) in anhydrous DCM (20 mL) was added DMF (3 drops), oxalyl dichloride (1.13 mL, 1.5 equiv.). The reaction mixture was stirred at room temperature for 4 h, before DCM was removed by rotary evaporation. To the residue was added Et_3N (25 mL), $Pd(PPh_3)_2Cl_2$ (125 mg, 0.02 equiv.) and CuI (34 mg, 0.02 equiv.). Then, the mixture was degassed and recharged with argon. Phenylacetylene (1.17 mL, 1.2 equiv.) was added by a syringe. The reaction was stirred overnight at room temperature under argon atmosphere before Et_3N was removed by rotary evaporation. The remained mixture was extracted with EtOAc (20 mL × 3), and the combined organic layers were washed with H_2O and brine, respectively, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 25/1-5/1) to provide products in 45-78% yields.

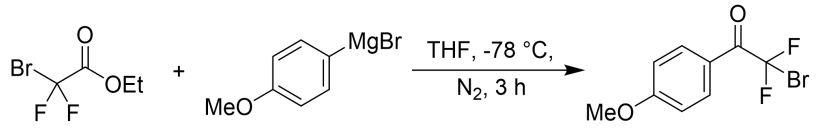
2.1.2 General Procedure B (for the synthesis of bromodifluoroacetates)[4]



The bromodifluoroacetates were synthesized according to the literature procedure. To a 2-bromo-2,2-difluoroacetic acid (875 mg, 1.0 equiv.) in DCM (10 mL, 0.50 M) solution slowly added oxalyl chloride (0.46 mL, 1.1 equiv.) and DMF (10 μL) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was cooled to 0 °C, and then a mixture of R^1OH (1.1 equiv.) and Et_3N (0.76 mL, 1.1 equiv.) dissolved in DCM (10 mL) was added dropwise. The reaction mixture stirred at room temperature for 6 h, then quenched with saturated $NaHCO_3$ solution (20 mL)

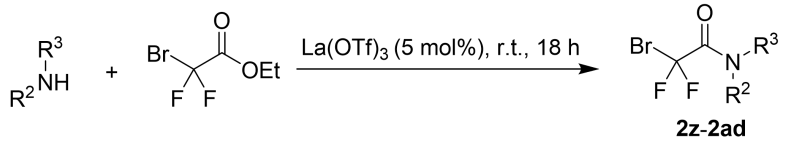
and extracted with DCM (30 mL × 3). The organic layer was collected, washed with brine, dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (30/1-10/1) to afford the title compounds.

2.1.3 General Procedure C (for the synthesis of bromodifluoroketone)[5]



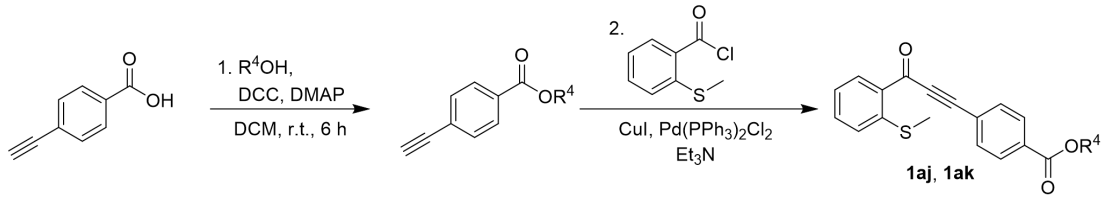
Ethyl 2-bromo-2,2-difluoroacetate (10 mmol, 1.0 equiv.) and dry THF (10 mL) were added to a Schlenk flask in a glovebox. The flask was then sealed with a screw cap before taken out from the glovebox, arylmagnesium bromide solution (1.0 M in THF, 11 mmol, 1.1 equiv.) was added slowly into the reaction system over 20 min with vigorous stirring at -78 °C. The mixture was stirred at -78 °C for further 3 h before being quenched with 3 N HCl. Water (20 mL) was then added and the organic layer was extracted with diethyl ether (15 mL × 3). The combined organic extracts were dried with anhydrous Ns_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel to give the corresponding product **2y** in 65% yield.

2.1.4 General Procedure D (for the synthesis of bromodifluoroacetamides)[4]



The bromodifluoroacetamides were synthesized according to the literature procedure. To a mixture of ethyl bromodifluoroacetate (785 μL, 1.2 equiv.) and amines (5.0 mmol, 1.0 equiv.) added $La(OTf)_3$ (146.5 mg, 5 mol%). The reaction mixture stirred at room temperature for 18 h, then quenched with H_2O (20 mL) and extracted with EtOAc (30 mL × 3). The organic layer was collected, washed with brine, dried with anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (15/1-5/1) to afford the title compounds.

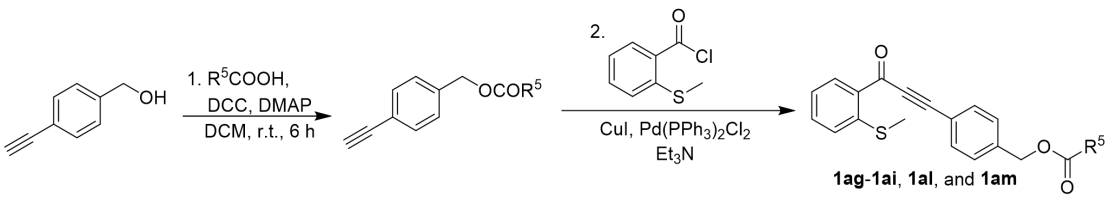
2.1.5 General procedure E (for the synthesis of **1aj** and **1ak**)



STEP 1: To a solution of 4-ethynylbenzoic acid (5.0 mmol, 1.0 equiv.), R^4OH (6.0 mmol, 1.2 equiv.) and DMAP (0.5 mmol, 0.1 equiv.) in dry DCM (25 mL) were added DCC (6.0 mmol, 1.2 equiv.). The reaction mixture was allowed to stir at room temperature for 6 h and then concentrated under reduced pressure. Cold EtOAc (10 mL) was added to the residue and dicyclohexyl urea was filtered off. The solution was concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 8/1-5/1).

STEP 2: To the **STEP 1** product was added Et_3N (25 mL), $Pd(PPh_3)_2Cl_2$ (0.02 equiv.) and CuI (0.02 equiv.). Then, the mixture was degassed and recharged with argon, 2-(methylthio)benzoyl chloride (1.5 equiv.) was added by a syringe. The reaction was stirred overnight at room temperature under argon atmosphere before Et_3N was removed by rotary evaporation. The remained mixture was extracted with EtOAc (20 mL × 3), and the combined organic layers were washed with H_2O and brine, respectively, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 20/1-10/1) to provide products in 40-58% yields.

2.1.6 General procedure F (for the synthesis of **1ag-1ai**, **1al**, and **1am**)



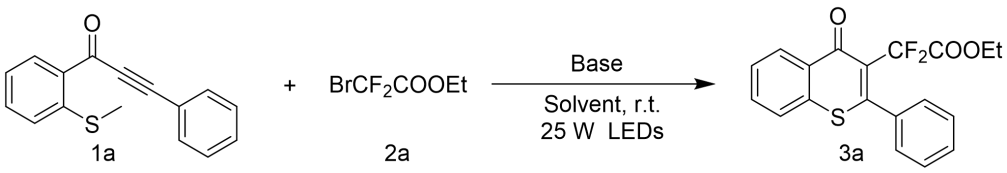
STEP 1: To a solution of (4-ethynylphenyl)methanol (6.0 mmol, 1.2 equiv.), R^5COOH (5.0 mmol, 1.0 equiv.) and DMAP (0.5 mmol, 0.1 equiv.) in dry DCM (25 mL) were added DCC (6.0 mmol, 1.2 equiv.). The reaction mixture was allowed to

stir at room temperature for 6 h and then concentrated under reduced pressure. Cold EtOAc (10 mL) was added to the residue and dicyclohexyl urea was filtered off. The solution was concentrated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 8/1-3/1).

STEP 2: To the **STEP 1** product was added Et_3N (25 mL), $Pd(PPh_3)_2Cl_2$ (0.02 equiv.) and CuI (0.02 equiv.). Then, the mixture was degassed and recharged with argon. 2-(methylthio)benzoyl chloride (1.5 equiv.) was added by a syringe. The reaction was stirred overnight at room temperature under argon atmosphere before Et_3N was removed by rotary evaporation. The remained mixture was extracted with EtOAc (20 mL × 3), and the combined organic layers were washed with H_2O and brine, respectively, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography on a silica gel (petroleum ether/EtOAc = 10/1-3/1) to provide products in 46-68% yields.

2.2 Optimization of Reaction Conditions

Table S1. Optimization of Reaction Conditions[a]

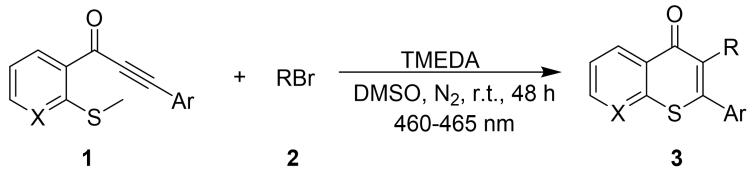


Entry	Additive	Solvent	Light source	Yield (%)[b]
1	Cs_2CO_3	DMSO	460-465 nm	24
2	K_2CO_3	DMSO	460-465 nm	27
3	DABCO	DMSO	460-465 nm	37
4	DBU	DMSO	460-465 nm	35
5	Et_3N	DMSO	460-465 nm	57
6	DIPEA	DMSO	460-465 nm	60
7	TMEDA	DMSO	460-465 nm	68
8	2,6-lutidine	DMSO	460-465 nm	34
9	-	DMSO	460-465 nm	9
10	TMEDA	CH_3CN	460-465 nm	56
11	TMEDA	THF	460-465 nm	31
12	TMEDA	DMF	460-465 nm	61
13	TMEDA	DCM	460-465 nm	42
14	TMEDA	EtOAc	460-465 nm	33
15	TMEDA	toluene	460-465 nm	49

Entry	Additive	Solvent	Light source	Yield (%)[b]
16	TMEDA	DCE	460-465 nm	47
17	TMEDA	DMSO	400-800 nm	55
18	TMEDA	DMSO	390-400 nm	53
19	TMEDA	DMSO	430-440 nm	62
20	TMEDA	DMSO	530-540 nm	NR
21	TMEDA	DMSO	In the dark	NR
22[c]	**TMEDA**	**DMSO**	**460-465 nm**	**80**
23[c,d]	TMEDA	DMSO	460-465 nm	28
24[c,e]	TMEDA	DMSO	460-465 nm	51
25[c,f]	TMEDA	DMSO	460-465 nm	71
26[c,g]	TMEDA	DMSO	460-465 nm	Trace

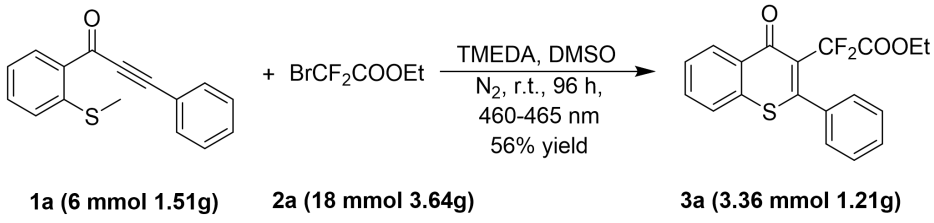
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol) and additive (0.4 mmol) in solvent (2 mL) under irradiation of 25 W 460-465 nm LEDs with N_2 protection at room temperature for 24 h unless noted otherwise. [b]Isolated yields based on **1a**. [c] Reaction time was 48 h. [d] TMEDA (0.1 mmol) was used. [e] TMEDA (0.2 mmol) was used. [f] **2a** (0.4 mmol). [g] Under an air atmosphere.

2.3 General Procedure G (for the Preparation of Compounds 3)



The reaction was conducted in an oven-dried 5-mL vial equipped with a stir bar. **1** (0.2 mmol, 1.0 equiv.), **2** (0.6 mmol, 3.0 equiv.) and TMEDA (0.4 mmol, 2.0 equiv.) were sequentially added in DMSO (2 mL) under argon atmosphere. The mixture was stirred at room temperature with a cooling fan under irradiation of a 25 W 460-465 nm LED for 48 h. Upon completion, the reaction mixture was diluted with EtOAc (10 mL), washed with brine (10 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum using a rotary evaporator. The obtained crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 30/1-4/1) to give the desired products **3**.

2.4 Scale-up Reaction



The reaction was conducted in an oven-dried 100-mL vial equipped with a stir bar. 1-(2-(methylthio)phenyl)-3-phenylprop-2-yn-1-one **1a** (6.0 mmol, 1.0 equiv.), ethyl 2-bromo-2,2-difluoroacetate **2a** (18.0 mmol, 3.0 equiv.) and TMEDA (12.0 mmol, 2.0 equiv.) were sequentially added in DMSO (30 mL) under argon atmosphere. The mixture was stirred at room temperature with a cooling fan under irradiation of a 25 W 460-465 nm LED for 48 h. Upon completion, the reaction mixture was diluted with EtOAc (40 mL), washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum using a rotary evaporator. The obtained crude product was purified by silica gel column chromatography (petroleum ether/EtOAc = 15/1) to give the desired product **3a** in 56% yield.

2.5 "On/off" LED Irradiation Experiment

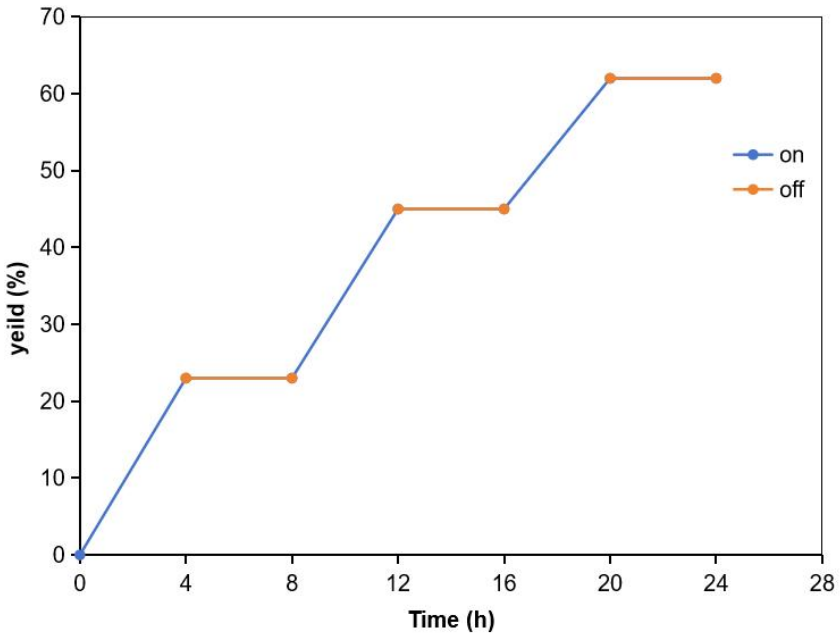


Figure S1. "On/off" LED irradiation experiment for the synthesis of **3a**

"On/off" LED irradiation experiment was used to explore the essential role of visible light in this transformation, as descripted in Figure S1. The model reaction of **1a** and **2a** was designed to be irradiated under successive on/off LED irradiation conditions at every 4 h interval for a total of 24 h. The yield of **3a** was determined by ^{19}F NMR every 4 h. As can be seen, obvious increases in yield were observed once the reaction was irradiated with blue light. In contrast, almost no increase in yield was

observed when the reaction was conducted in dark, demonstrating an essential role of the visible-light irradiation in this transformation.

2.6 UV-vis Absorbance Experiment

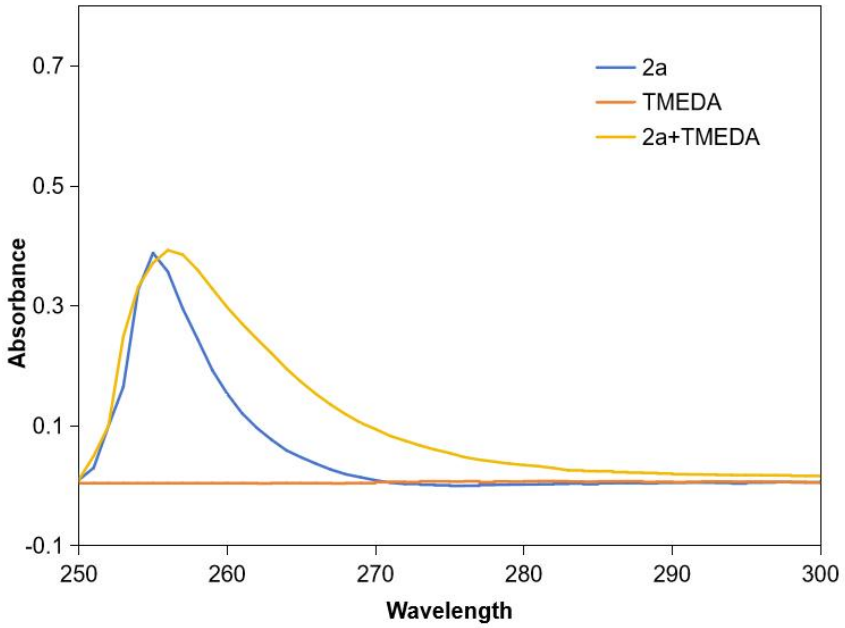


Figure S2. A variety of solutions of **2a** (0.01 M), TMEDA (0.01 M), **2a** + TMEDA (0.01 M) in DMSO were prepared. Then, the UV-vis absorption spectra of a series of solutions were recorded on a HitachiF-7000 FL Spectrophotometer, by measuring 100 μL solution into the 4 cm path quartz cuvettes with 3 mL DMSO.

UV-vis absorbance experiment has been carried out for confirming the formation of the EDA complex as illustrated above in Figure S2, the blue UV absorbance line came from $BrCF_2COOEt$ solution, orange one came from TMEDA solution, and yellow one came from the mixed solution of $BrCF_2COOEt$ and TMEDA. UV-vis spectra revealed that upon mixing $BrCF_2COOEt$ with TMEDA, an obvious bathochromic shift of the UV-vis absorbance was observed, strongly suggesting that $BrCF_2COOEt$-TMEDA EDA complex might indeed be formed in the mixed solution.

2.7 Titration Experiments of $BrCF_2COOEt$ with TMEDA

^{19}F NMR spectra of mixtures of $BrCF_2COOEt$ and TMEDA in Chloroform-*d* were recorded at 298 K. In an NMR tube, the total volume of the mixture was 0.6 mL, the concentration of $BrCF_2COOEt$ (0.03 mmol) was kept constant at 0.5 M, and that of TMEDA was varied from 0 to 2.0 M. The molar ratios of $BrCF_2COOEt$/TMEDA were 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, and 1:10. Fluorobenzene (δF_{Ph} =

-113.0660) was used as an internal standard. The ^{19}F NMR signal of -CF_2Br group in $BrCF_2COOEt$ shifted upfield along with increasing the amount of TMEDA, indicating the formation of EDA complex of $BrCF_2COOEt$ with TMEDA (Figure S3).

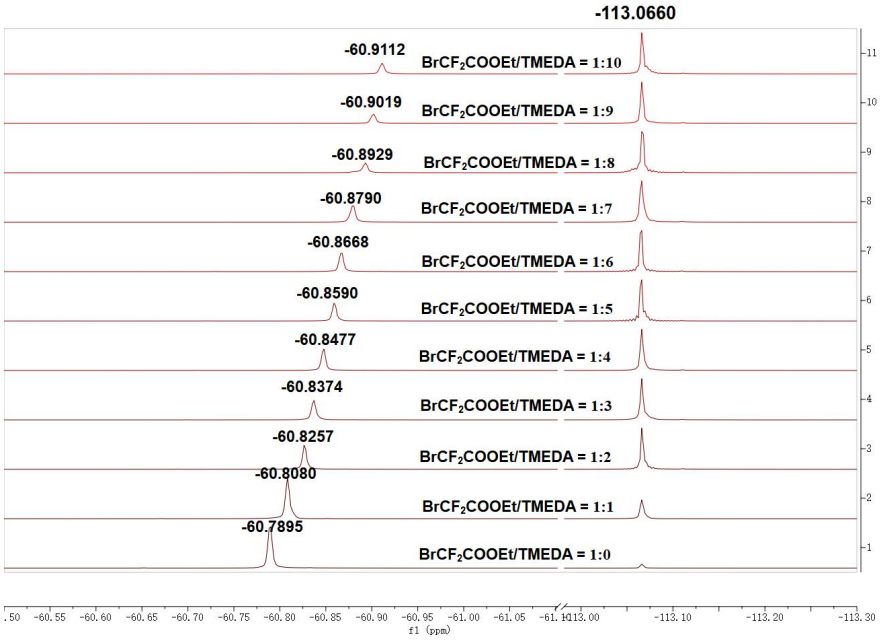


Figure S3. Titration experiments of $BrCF_2COOEt$ with TMEDA

2.8 Determination of the Association Constant (K_{TMEDA})

Entry	[$BrCF_2COOEt$](M)	1/[TMEDA](M)	δ (ppm)	Δδ (ppm)	1/Δδ (ppm)
1	0.05	-	-60.7895	-	-
2	0.05	20	-60.8080	0.0185	54.0541
3	0.05	10	-60.8257	0.0362	27.6243
4	0.05	6.67	-60.8374	0.0479	20.8768
5	0.05	5	-60.8477	0.0582	17.1821
6	0.05	4	-60.8590	0.0695	14.3885
7	0.05	3.33	-60.8668	0.0773	12.9366
8	0.05	2.86	-60.8790	0.0895	11.1732
9	0.05	2.5	-60.8929	0.1034	9.6712
10	0.05	2.22	-60.9019	0.1124	8.8968
11	0.05	2	-60.9112	0.1217	8.2169

^{19}F NMR spectra of mixtures of $BrCF_2COOEt$ and TMEDA in Chloroform-*d* were recorded at 298 K. In an NMR tube, the total volume of mixture was 0.6 mL, the concentration of $BrCF_2COOEt$ (0.03 mmol) was kept constant at 0.5 M, while that of TMEDA was varied from 0 to 2.0 M. The molar ratios of $BrCF_2COOEt$/TMEDA

were 1:0, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, and 1:10. Fluorobenzene (δF_{Ph} = -113.0660) was used as an internal standard. ^{19}F NMR for each sample was recorded and the changes of chemical shift ($\Delta\delta$) for -CF_2Br group in $BrCF_2COOEt$ were used to draw the plot. The association constant of $BrCF_2COOEt$ with TMEDA ($\mathbf{K}_{TMEDA}$) was calculated: $\mathbf{K}_{TMEDA}$ = c/a = 3.8645/2.4987 = 1.55 M^{-1}.

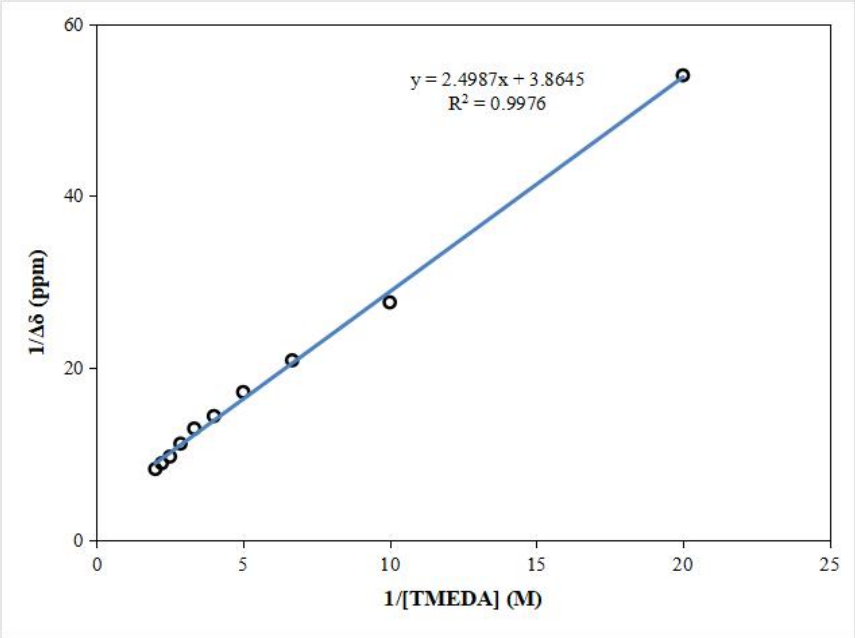


Figure S4. Plot for determination of the association constant ($\mathbf{K}_{TMEDA}$).

2.9 Determination of Binding Stoichiometry of EDA Complexes

Entry	[$BrCF_2COOEt$](M)	[BrCF2COOEt]/[BrCF2COOEt +TMEDA]	Δδ (ppm)	[$BrCF_2COOEt$]×Δδ(M.ppm)
1	0	0	0	0
2	0.05	0.1	0.0749	0.003745
3	0.10	0.2	0.0615	0.006150
4	0.15	0.3	0.0507	0.007605
5	0.20	0.4	0.0443	0.008860
6	0.25	0.5	0.0342	0.008552
7	0.30	0.6	0.0247	0.007410
8	0.35	0.7	0.0174	0.006090
9	0.4	0.8	0.0099	0.003960
10	0.45	0.9	0.0050	0.002242
11	0.5	1	0	0

The binding stoichiometry between $BrCF_2COOEt$ and TMEDA was evaluated using Job's plot analysis: ^{19}F NMR spectra mixtures of $BrCF_2COOEt$ and TMEDA in Chloroform-*d* were recorded at 298 K. Fluorobenzene (δF_{Ph} = -113.0660) was used as an internal standard. The total volume of the mixture was 0.5 mL, and the total amount of $BrCF_2COOEt$ and TMEDA was kept constant at 0.25 mmol (0.5 M), while the amount of $BrCF_2COOEt$ was varied from 0 to 0.25 mmol (0-0.5 M). The molar ratios of [$BrCF_2COOEt$]/[$BrCF_2COOEt$ + TMEDA] were 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, and 1.0. ^{19}F NMR for each sample was recorded and the changes of chemical shift ($\Delta\delta$) for $-CF_2Br$ group in $BrCF_2COOEt$ were used to draw the plot. The stoichiometry was determined by plotting ratios of [$BrCF_2COOEt$]×$\Delta\delta$ against ratios of [$BrCF_2COOEt$]/[$BrCF_2COOEt$ + TMEDA] to afford a maximum value. X_{max} = b/(-2a) = 0.0321/(-2) × (-0.0336) = 0.48. These data indicate that the formation of EDA complex of $BrCF_2COOEt$ with TMEDA in a binding stoichiometry of 1:1.

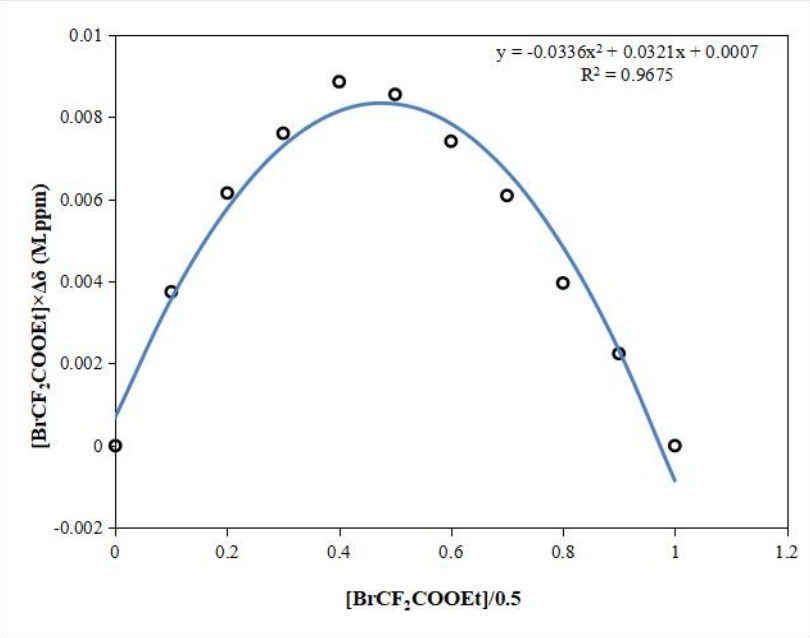
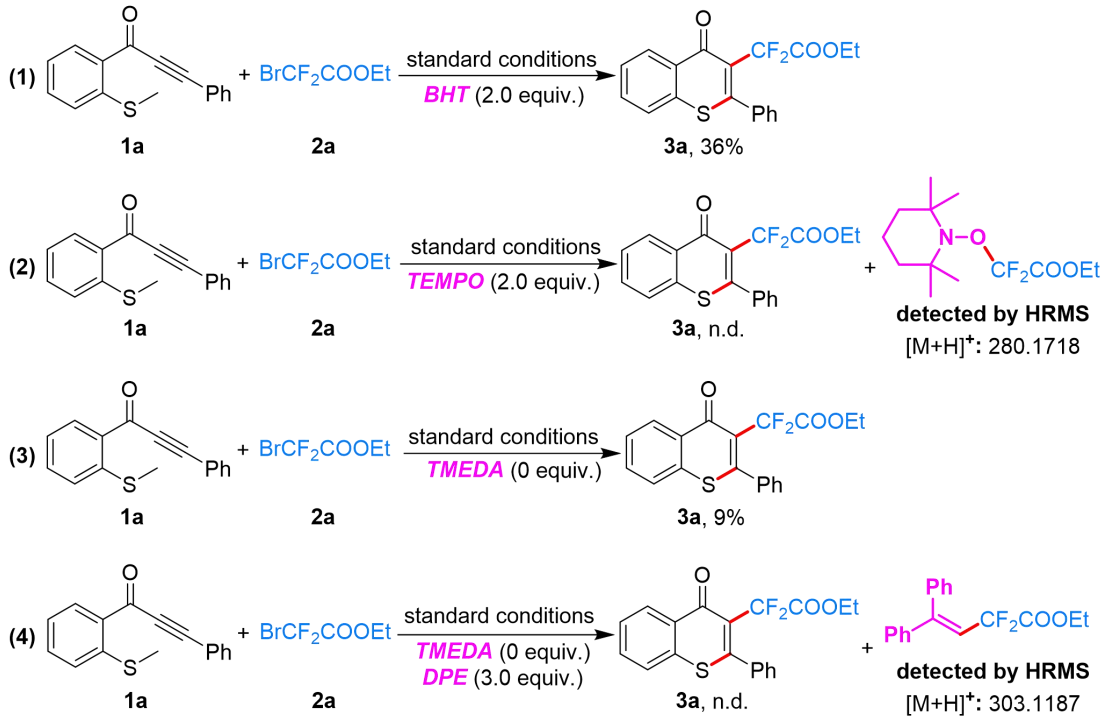


Figure S5. Job's plot.

2.10 Radical Trapping and Control Experiments



Standard conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), TMEDA (0.4 mmol), and DMSO (2 mL) were irradiated with a 460-465 nm LED (25 W) for 48 h under N_2 atmosphere at room temperature, isolated yields based on **1a**.

Radical trapping experiments between **1a** and **2a** were conducted under standard conditions with three trapping agents (TEMPO, BHT and DPE) to catch the putative radical. The desired product **3a** was obtained in 36% yield when BHT was added (**Eq. 1**). No desired product **3a** was detected when TEMPO was employed as the radical scavenger, indicating that the reaction was completely inhibited (**Eq. 2**). To our delight, the corresponding TEMPO-CF_2CO_2Et adduct was successfully detected by HRMS (Figure S6). HRMS (ESI): $C_{13}H_{24}F_2NO_3^+$, $[M+H]^+$ calcd: 280.1719, found: 280.1718. Due to a 9% yield of **3a** was obtained when the reaction was performed without TMEDA (**Eq. 3**), we further added 3.0 equiv. of DPE into this photoredox reaction system which led to no formation of **3a** (**Eq. 4**). The corresponding DPE-CF_2CO_2Et adduct was successfully detected by HRMS (Figure S7). HRMS (ESI): $C_{18}H_{17}F_2O_2^+$, $[M+H]^+$ calcd: 303.1191, found: 303.1187.

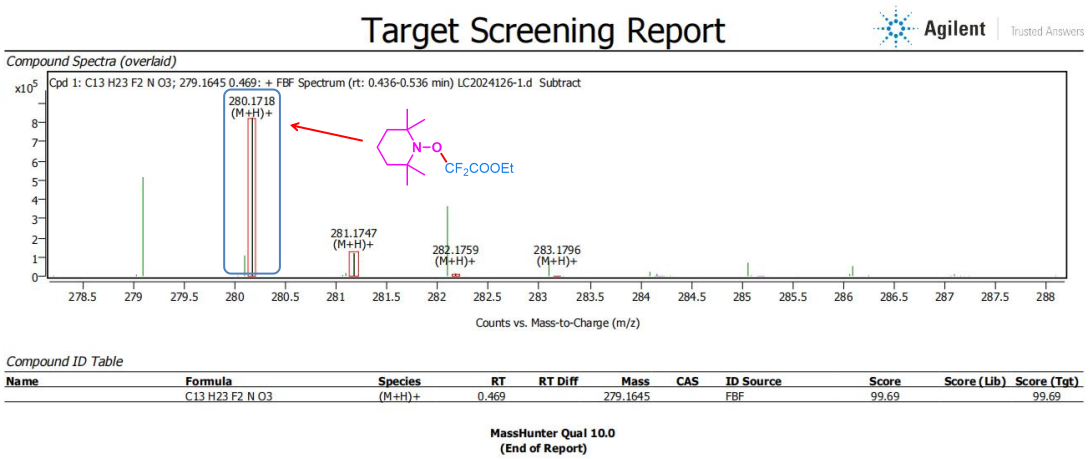


Figure S6. Crude ESI-MS of the TEMPO-trapping experiments

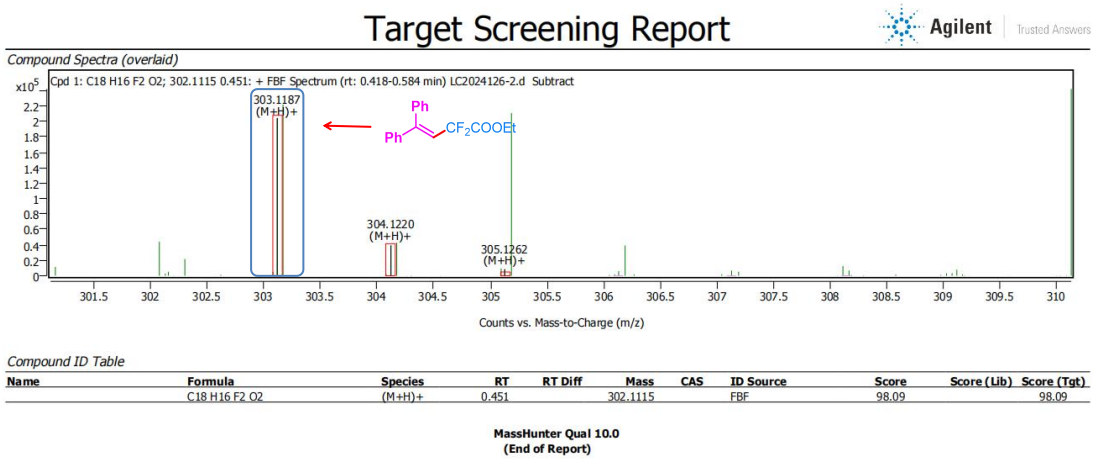
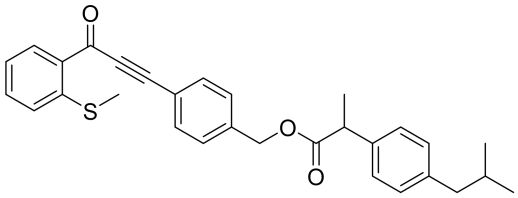


Figure S7. Crude ESI-MS of the DPE-trapping experiments

3. Characterization Data



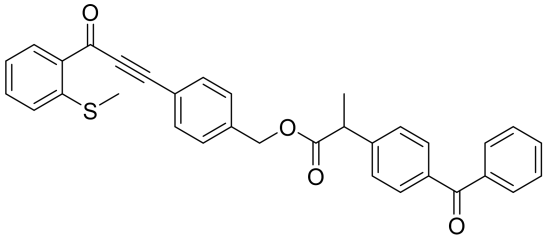
4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzyl 2-(4-isobutylphenyl)propanoate (1ag).

Prepared by general procedure F on a 5 mmol scale. Product was obtained as a yellow oil (46 % yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.45 – 8.41 (m, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.21 (m, 4H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.16 (q, *J* = 13.2 Hz, 2H), 3.80 (q, *J* = 7.1 Hz, 1H), 2.50 – 2.47 (m, 5H), 1.92 – 1.84 (m, 1H), 1.55 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 177.53, 174.29, 144.85, 140.73, 138.98, 137.43, 134.60, 133.33, 133.12, 132.98, 129.40, 127.64, 127.24, 124.32, 123.26, 119.85, 92.30, 87.41, 65.46, 45.13, 45.04, 30.20, 22.39, 18.30, 15.49.

HRMS (ESI): Calcd for $C_{30}H_{31}O_3S^+$ $[M+H]^+$: 471.1988, found: 471.1985.



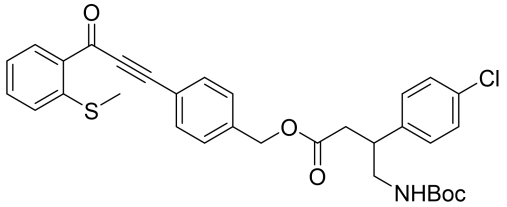
4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzyl 2-(4-benzoylphenyl)propanoate (1ah).

Prepared by general procedure F on a 5 mmol scale. Product was obtained as a yellow oil (40% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 7.8 Hz, 1H), 7.82 – 7.78 (m, 3H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.54 (m, 5H), 7.52 – 7.46 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 3H), 5.17 (s, 2H), 3.90 (q, *J* = 7.1 Hz, 1H), 2.50 (s, 3H), 1.60 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 196.42, 177.57, 173.66, 144.86, 140.52, 138.53, 138.03, 137.43, 134.66, 133.34, 133.06, 132.58, 131.47, 130.06, 129.20, 129.15, 128.60, 128.35, 127.88, 124.28, 123.28, 120.11, 92.14, 87.46, 65.85, 45.39, 18.31, 15.50.

HRMS (ESI): Calcd for $C_{33}H_{27}O_4S^+$ $[M+H]^+$: 519.1625, found: 519.1621.



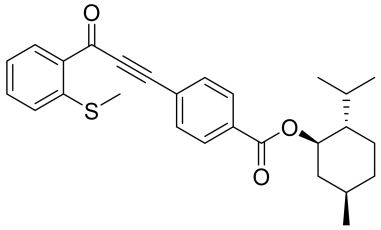
4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzyl 4-((*tert*-butoxycarbonyl) amino)-3-(4-chlorophenyl)butanoate (1ai).

Prepared by general procedure F on a 5 mmol scale. Product was obtained as a yellow solid (32% yield), m.p. 146–148 °C

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.58 – 7.54 (m, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 5.04 (q, 2H), 4.55 (s, 1H), 3.50 – 3.41 (m, 1H), 3.37 – 3.31 (m, 1H), 3.29 – 3.24 (m, 1H), 2.80 (dd, *J* = 15.6, 5.8 Hz, 1H), 2.67 (dd, *J* = 15.6, 9.2 Hz, 1H), 2.49 (s, 3H), 1.41 (s, 9H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 177.55, 171.33, 155.80, 144.84, 139.47, 138.39, 134.65, 133.34, 133.11, 133.00, 129.03, 128.90, 128.07, 124.30, 123.28, 120.09, 92.18, 87.48, 79.55, 65.59, 45.57, 42.06, 38.13, 28.34, 15.49.

HRMS (ESI): Calcd for $C_{32}H_{33}ClNO_5S^+$ $[M+H]^+$: 578.1762, found: 578.1755.



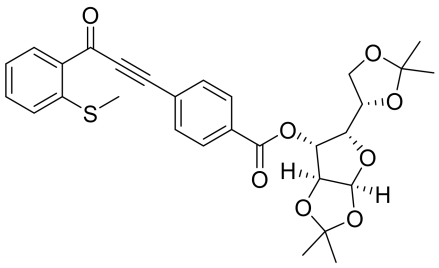
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-(3-(2-(methylthio)phenyl)-3-oxopro p-1-yn-1-yl)benzoate (1aj).

Prepared by general procedure E on a 5 mmol scale. Product was obtained as a yellow oil (41% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.45 – 8.42 (m, 1H), 8.10 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.56 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.97 (td, *J* = 10.9, 4.4 Hz, 1H), 2.50 (s, 3H), 2.15 (d, *J* = 11.9 Hz, 1H), 1.99 – 1.93 (m, 1H), 1.78 – 1.73 (m, 2H), 1.61 – 1.56 (m, 2H), 1.19 – 1.10 (m, 2H), 0.97 – 0.93 (m, 7H), 0.82 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 177.30, 165.13, 145.06, 134.68, 133.47, 132.94, 132.66, 132.37, 129.65, 124.59, 124.34, 123.31, 91.15, 88.83, 75.48, 47.27, 40.94, 34.29, 31.47, 26.59, 23.68, 22.02, 20.75, 16.55, 15.48.

HRMS (ESI): Calcd for $C_{27}H_{31}O_3S^+$ $[M+H]^+$: 435.1988, found: 435.1985.



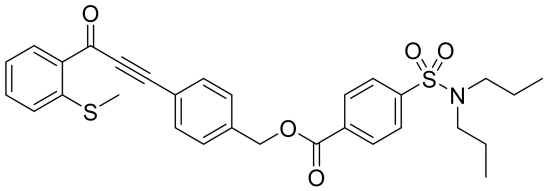
(3a*S*,5*S*,6*R*,6a*S*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl 4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzoate (1ak).

Prepared by general procedure E on a 5 mmol scale. Product was obtained as a yellow oil (35% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.43 – 8.39 (m, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.55 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.28 (m, 1H), 5.98 (d, *J* = 3.6 Hz, 1H), 5.53 (d, *J* = 2.7 Hz, 1H), 4.66 (d, *J* = 3.6 Hz, 1H), 4.38 – 4.35 (m, 1H), 4.34 – 4.32 (m, 1H), 4.16 – 4.13 (m, 1H), 4.11 – 4.08 (m, 1H), 2.49 (s, 3H), 1.58 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 177.15, 164.29, 145.15, 134.67, 133.55, 132.82, 132.79, 130.95, 129.77, 125.43, 124.37, 123.31, 112.44, 109.49, 105.16, 90.61, 89.18, 83.37, 79.99, 77.09, 72.56, 67.40, 26.86, 26.73, 26.22, 25.21, 15.46.

HRMS (ESI): Calcd for $C_{29}H_{31}O_8S^+$ $[M+H]^+$: 539.1734, found: 539.1728.



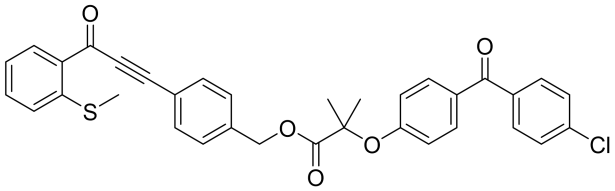
4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzyl 4-(*N*,*N*-dipropylsulfamoyl)benzoate (1al).

Prepared by general procedure F on a 5 mmol scale. Product was obtained as a yellow oil (35% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 7.8 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.50 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 4.0 Hz, 1H), 5.45 (s, 2H), 3.12 (t, *J* = 8.0 Hz, 4H), 2.50 (s, 3H), 1.61 – 1.54 (m, 4H), 0.89 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.54, 164.96, 144.92, 144.63, 138.15, 134.65, 133.39, 133.22, 133.07, 133.03, 130.37, 128.33, 127.11, 124.31, 123.27, 120.52, 91.95, 87.58, 66.57, 49.94, 21.94, 15.50, 11.16.

HRMS (ESI): Calcd for $C_{30}H_{32}NO_5S_2^+$ $[M+H]^+$: 550.1716, found: 550.1711.



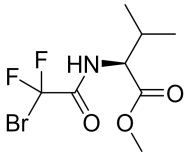
4-(3-(2-(methylthio)phenyl)-3-oxoprop-1-yn-1-yl)benzyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (1am).

Prepared by general procedure F on a 5 mmol scale. Product was obtained as a yellow oil (38% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.41 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.71 – 7.68 (m, 4H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.46 – 7.43 (m, 2H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 3H), 6.86 – 6.82 (m, 2H), 5.24 (s, 2H), 2.49 (s, 3H), 1.72 (s, 6H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 194.15, 177.49, 173.42, 159.48, 144.89, 138.47, 137.70, 136.25, 134.70, 133.41, 133.08, 132.97, 132.65, 132.02, 131.18, 130.52, 128.59, 128.39, 128.32, 124.28, 123.31, 120.42, 117.22, 91.83, 87.57, 79.42, 66.55, 25.47, 15.50.

HRMS (ESI): Calcd for $C_{34}H_{28}ClO_5S^+$ $[M+H]^+$: 583.1340, found: 583.1336.



Methyl (2-bromo-2,2-difluoroacetyl)-*L*-valinate (1an).

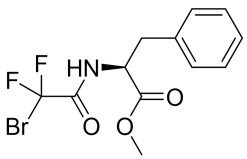
Prepared by general procedure D on a 5 mmol scale. Product was obtained as a colorless oil (41% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.83 (d, *J* = 8.4 Hz, 1H), 4.56 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.80 (s, 3H), 2.36 – 2.20 (m, 1H), 0.97 (dd, *J* = 14.2, 6.9 Hz, 6H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 171.07, 159.79 (t, *J* = 27.9 Hz), 111.31 (t, *J* = 316.0 Hz), 57.63, 52.64, 31.59, 18.76, 17.57.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -60.84 (d, *J* = 7.5 Hz).

Data are consistent with reported in the literature.[6]



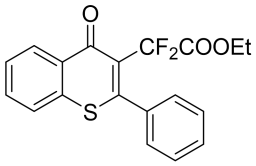
Methyl (2-bromo-2,2-difluoroacetyl)-*L*-phenylalaninate (1ao).

Prepared by general procedure D on a 5 mmol scale. Product was obtained as a white solid (64% yield), m.p. 64–65 °C.

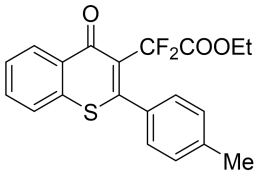
^{1}H NMR (MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 3H), 7.15 – 7.09 (m, 2H), 6.76 (d, *J* = 5.2 Hz, 1H), 4.93 – 4.86 (m, 1H), 3.81 (s, 3H), 3.34 – 3.15 (m, 2H).

^{13}C NMR (MHz, Chloroform-*d*) δ 170.49, 159.27 (t, *J* = 28.3 Hz), 134.63, 129.28, 128.83, 127.60, 111.25 (t, J = 315.8 Hz), 53.67, 52.86, 37.31.

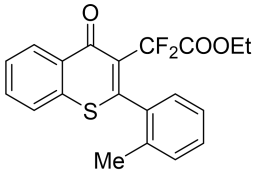
^{19}F NMR (MHz, Chloroform-*d*) δ -60.82 (d, *J* = 8.2 Hz).
HRMS (ESI): Calcd for $C_{12}H_{13}BrF_2NO_3^+$ $[M+H]^+$: 336.0041, found: 336.0037.



Ethyl 2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetate (3a).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 15/1). Product was obtained as a white solid (80% yield), m.p. 97–98 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 – 8.34 (m, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.90 – 7.84 (m, 1H), 7.76 – 7.70 (m, 1H), 7.60 – 7.51 (m, 5H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 178.80 (t, *J* = 3.0 Hz), 162.85 (t, *J* = 32.3 Hz), 158.29, 136.99, 135.11, 133.83, 130.79, 129.75, 129.59, 128.91, 128.36, 128.31, 126.86, 125.16 (t, *J* = 20.2 Hz), 112.84 (t, *J* = 251.7 Hz), 62.94, 14.12.
^{19}F NMR (376 MHz, DMSO-d_6) δ -94.80.
Data are consistent with reported in the literature.[7]



Ethyl 2,2-difluoro-2-(4-oxo-2-(*p*-tolyl)-4*H*-thiochromen-3-yl)acetate (3b).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 15/1). Product was obtained as a colorless oil (88% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.49 (m, 1H), 7.72 – 7.66 (m, 1H), 7.63 – 7.56 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.32 – 7.26 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.24 (t, *J* = 3.0 Hz), 163.46 (t, *J* = 32.2 Hz), 157.95, 140.42, 137.34, 132.46, 132.23, 130.36, 128.96, 128.91, 128.35, 128.06 (t, *J* = 3.0, 2.0 Hz), 125.92 (t, *J* = 20.2 Hz), 125.45, 112.69 (t, *J* = 253.4 Hz), 62.72, 21.45, 13.92.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.92.
Data are consistent with reported in the literature.[8]



Ethyl 2,2-difluoro-2-(4-oxo-2-(*o*-tolyl)-4*H*-thiochromen-3-yl)acetate (3c).

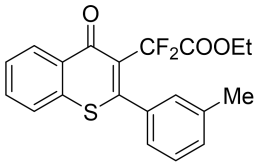
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 15/1). Product was obtained as a colorless oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 – 8.53 (m, 1H), 7.73 – 7.68 (m, 1H), 7.64 – 7.59 (m, 2H), 7.41 – 7.36 (m, 1H), 7.34 – 7.26 (m, 3H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.38 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.92 (t, *J* = 2.9 Hz), 163.24 (t, *J* = 32.2 Hz), 156.92, 137.51, 135.37 (t, *J* = 2.4 Hz), 134.20, 132.51, 130.36, 130.11, 129.73, 129.00, 128.40, 127.99 (t, *J* = 2.0 Hz), 126.74 (t, *J* = 20.3 Hz), 125.53, 125.50, 112.77 (t, *J* = 254.5 Hz), 62.74, 19.38, 13.91.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -92.03 – -108.47 (m).

HRMS: Calcd for $C_{20}H_{17}F_2O_3S^+$ $[M+H]^+$: 375.0861, found: 375.0854.



Ethyl 2,2-difluoro-2-(4-oxo-2-(*m*-tolyl)-4*H*-thiochromen-3-yl)acetate (3d).

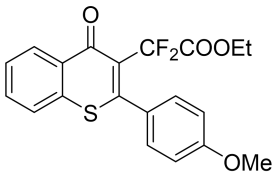
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 20/1). Product was obtained as a white solid (76% yield), m.p. 96–97 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.49 (m, 1H), 7.73 – 7.67 (m, 1H), 7.63 – 7.57 (m, 2H), 7.39 – 7.30 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.17 (t, *J* = 3.0 Hz), 163.45 (t, *J* = 32.2 Hz), 157.90, 138.07, 137.29, 134.99, 132.48, 130.86, 130.35, 128.93, 128.60 (t, *J* = 2.3 Hz), 128.37, 128.12, 125.82 (t, *J* = 20.5 Hz), 125.46, 125.28 (t, *J* = 2.5 Hz), 112.65 (t, *J* = 253.4 Hz), 62.73, 21.40, 13.92.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.06 (d, *J* = 12.9 Hz).

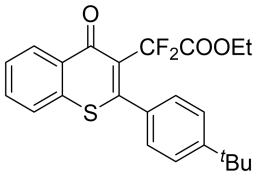
HRMS (ESI): Calcd for $C_{20}H_{17}F_2O_3S^+$ $[M+H]^+$: 375.0861, found: 375.0856.



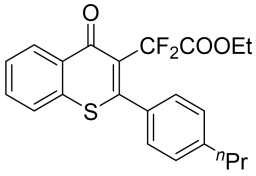
Ethyl 2,2-difluoro-2-(2-(4-methoxyphenyl)-4-oxo-4*H*-thiochromen-3-yl)acetate (3e).

Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 12/1). Product was obtained as a white solid (83% yield), m.p. 129–130 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.48 (m, 1H), 7.72 – 7.66 (m, 1H), 7.62 – 7.57 (m, 2H), 7.52 – 7.47 (m, 2H), 7.02 – 6.97 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.38 (t, *J* = 3.1 Hz), 163.51 (t, *J* = 32.3 Hz), 161.17, 157.73, 137.38, 132.42, 130.40, 129.76 (t, *J* = 2.5 Hz), 128.91, 128.31, 127.32, 125.72 (t, *J* = 20.4 Hz), 125.41, 113.73, 112.72 (t, *J* = 253.3 Hz), 62.71, 55.41, 13.92.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.76.
HRMS (ESI): Calcd for $C_{20}H_{16}F_2O_4S^+$ $[M+H]^+$: 391.0810, found: 391.0807.

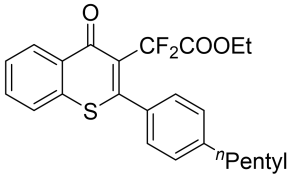


Ethyl 2-(2-(4-(*tert*-butyl)phenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3f).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 15/1). Product was obtained as a white solid (82% yield), m.p. 107–108 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.49 (m, 1H), 7.72 – 7.66 (m, 1H), 7.62 – 7.57 (m, 2H), 7.52 – 7.47 (m, 4H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.38 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.25 (t, *J* = 3.0 Hz), 163.47 (t, *J* = 32.2 Hz), 157.99, 153.47, 137.39, 132.43, 132.15, 130.37, 128.91, 128.32, 127.89 (t, *J* = 2.4 Hz), 125.79 (t, *J* = 20.5 Hz), 125.45, 125.21, 112.68 (t, *J* = 253.3 Hz), 62.69, 34.88, 31.23, 13.93.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.89.
HRMS (ESI): Calcd for $C_{23}H_{23}F_2O_3S^+$ $[M+H]^+$: 417.1330, found: 417.1325.

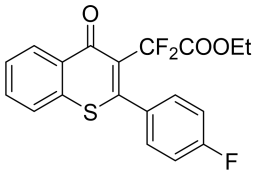


Ethyl 2,2-difluoro-2-(4-oxo-2-(4-propylphenyl)-4*H*-thiochromen-3-yl)acetate (3g).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 20/1). Product was obtained as a white solid (83% yield), m.p. 104–106 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.62 – 7.57 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H), 1.74 – 1.68 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.25 (t, *J* = 2.9 Hz), 163.47 (t, *J* = 32.2 Hz), 158.01, 145.10, 137.37, 132.45, 132.41, 130.36, 128.91, 128.33, 128.04 (t, *J* = 2.4 Hz), 125.80 (t, *J* = 20.5 Hz), 125.45, 112.68 (t, *J* = 253.3 Hz), 62.71, 37.85, 24.30, 13.92, 13.82.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.93.
HRMS (ESI): Calcd for $C_{22}H_{21}F_2O_3S^+$ $[M+H]^+$: 403.1174, found: 403.1177.

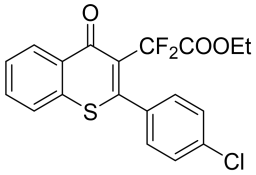


Ethyl 2,2-difluoro-2-(4-oxo-2-(4-pentylphenyl)-4*H*-thiochromen-3-yl)acetate (3h). Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =30/1). Product was obtained as a colorless oil (66% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.49 (m, 1H), 7.72 – 7.66 (m, 1H), 7.62 – 7.57 (m, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.72 – 2.66 (m, 2H), 1.71 – 1.65 (m, 2H), 1.40 – 1.31 (m, 7H), 0.93 (t, *J* = 8.0, 4.0 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.25 (t, *J* = 3.0 Hz), 163.48 (t, *J* = 32.2 Hz), 158.02, 145.39, 137.38, 132.44, 132.36, 130.37, 128.92, 128.32, 128.26, 128.06 (t, *J* = 2.4 Hz), 125.80 (t, *J* = 20.4 Hz), 125.44, 112.68 (t, *J* = 253.3 Hz), 62.70, 35.80, 31.51, 30.89, 22.54, 14.04, 13.92.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.92.
HRMS (ESI): Calcd for $C_{24}H_{25}F_2O_3S^+$ $[M+H]^+$: 431.1487, found: 431.1491.

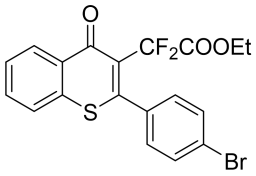


Ethyl 2,2-difluoro-2-(2-(4-fluorophenyl)-4-oxo-4*H*-thiochromen-3-yl)acetate (3i). Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 12/1). Product was obtained as a white solid (75% yield), m.p. 108–109 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.48 (m, 1H), 7.74 – 7.68 (m, 1H), 7.64 – 7.58 (m, 2H), 7.54 (dd, *J* = 8.5, 5.2 Hz, 2H), 7.17 (t, *J* = 8.6 Hz, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.10 (t, *J* = 3.0 Hz), 163.76 (d, *J* = 250.9 Hz), 163.32 (t, *J* = 32.1 Hz), 156.38, 137.00, 132.62, 131.00 (d, *J* = 3.5 Hz), 130.33, 130.21 (dt, *J* = 8.7, 2.6 Hz), 128.95, 128.54, 126.26 (t, *J* = 20.5 Hz), 125.47, 115.55 (d, *J* = 22.1 Hz), 112.65 (t, *J* = 253.4 Hz), 62.83, 13.91.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.90, -104.36 – -117.28 (m).

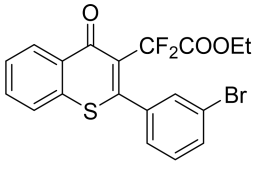
HRMS (ESI): Calcd for $C_{19}H_{14}F_3O_3S^+$ $[M+H]^+$: 379.0610, found: 379.0606.



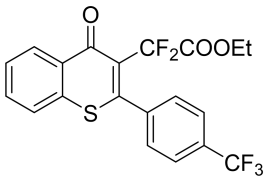
Ethyl 2-(2-(4-chlorophenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3j).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 12/1). Product was obtained as a white solid (65% yield), m.p. 127–129 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.36 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 7.6 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.65 – 7.58 (m, 4H), 4.25 (q, J = 7.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 178.71 (t, J = 2.8 Hz), 162.72 (t, J = 32.2 Hz), 156.93, 136.84, 135.77, 133.93, 133.86, 130.26 (t, J = 3.0, 2.0 Hz), 129.74, 129.72, 129.09, 128.38, 126.92, 125.39 (t, J = 20.2 Hz), 112.82 (t, J = 251.6 Hz), 63.03, 14.12.
^{19}F NMR (376 MHz, DMSO-d_6) δ -94.78.
Data are consistent with reported in the literature.[8]



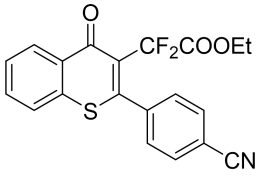
Ethyl 2-(2-(4-bromophenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3 k).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 12/1). Product was obtained as a white solid (76% yield), m.p. 133–134 °C.
^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 – 8.49 (m, 1H), 7.74 – 7.69 (m, 1H), 7.65 – 7.59 (m, 4H), 7.44 – 7.39 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-d) δ 179.00 (t, J = 3.0 Hz), 163.25 (t, J = 32.0 Hz), 156.07, 136.89, 133.89, 132.66, 131.58, 130.30, 129.68 (t, J = 2.5 Hz), 128.98, 128.60, 126.18 (t, J = 20.6 Hz), 125.50, 124.70, 112.62 (t, J = 253.6 Hz), 62.88, 13.91.
^{19}F NMR (376 MHz, Chloroform-d) δ -95.91.
Data are consistent with reported in the literature.[8]



Ethyl 2-(2-(3-bromophenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3l).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 20/1). Product was obtained as a white solid (58% yield), m.p. 110–112 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.34 (m, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.82 (t, J = 1.6 Hz, 1H), 7.81 – 7.72 (m, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 178.67 (t, J = 2.5 Hz), 162.67 (t, J = 32.3 Hz), 156.30, 137.08, 136.82, 133.97, 133.63, 131.10, 130.78, 129.76, 128.39, 127.58, 126.95, 125.39 (t, J = 20.2 Hz), 121.90, 112.81 (t, J = 251.7 Hz), 63.07, 14.13.
^{19}F NMR (376 MHz, DMSO-d_6) δ -94.88 (d, J = 15.8 Hz).
HRMS (ESI): Calcd for $C_{19}H_{14}BrF_2O_3S^+$ $[M+H]^+$: 438.9810, found: 438.9809.

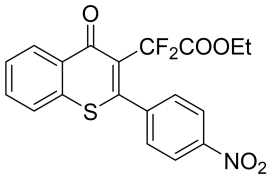


Ethyl 2,2-difluoro-2-(4-oxo-2-(4-(trifluoromethyl)phenyl)-4*H*-thiochromen-3-yl) acetae (3m).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 15/1). Product was obtained as a white solid (68% yield), m.p. 116–117 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.50 (m, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.74 – 7.70 (m, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.65 – 7.61 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.84 (t, J = 3.0 Hz), 163.13 (t, J = 31.9 Hz), 155.44, 138.50, 136.70, 132.78, 132.03 (q, J = 32.9 Hz), 130.27, 129.00, 128.74, 128.60 (t, J = 2.5 Hz), 126.42 (t, J = 20.6 Hz), 125.57, 125.32 (q, J = 3.7 Hz), 123.70 (q, J = 272.5 Hz), 112.60 (t, J = 253.5 Hz), 62.94, 13.89.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.87, -95.98.
Data are consistent with reported in the literature.[8]

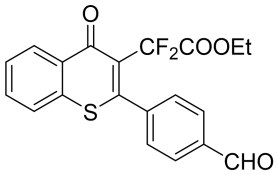


Ethyl 2-(2-(4-cyanophenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3n).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 8/1). Product was obtained as a white solid (65% yield), m.p. 177–178 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.36 (m, 1H), 8.06 – 8.03 (m, 2H), 8.03 – 8.00 (m, 1H), 7.93 – 7.88 (m, 1H), 7.82 – 7.78 (m, 2H), 7.78 – 7.73 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 178.52 (t, J = 2.8 Hz), 162.58 (t, J = 32.3 Hz), 156.18, 139.50, 136.65, 134.04, 132.93, 129.86, 129.71, 129.42, 128.41, 127.02, 125.44 (t, J = 20.3 Hz), 118.60, 113.50, 112.78 (t, J = 251.8 Hz), 63.14, 14.12.
^{19}F NMR (376 MHz, DMSO-d_6) δ -94.88.
HRMS (ESI): Calcd for $C_{20}H_{14}F_2NO_3S^+$ $[M+H]^+$: 386.0657, found: 386.0651.

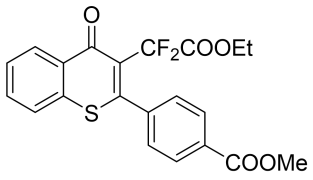


Ethyl 2,2-difluoro-2-(2-(4-nitrophenyl)-4-oxo-4*H*-thiochromen-3-yl)acetate (3o).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 8/1). Product was obtained as a white solid (50% yield), m.p. 239–240 °C.
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.36 (m, 3H), 8.04 (d, J = 7.9 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.89 (d, J = 8.7 Hz, 2H), 7.80 – 7.74 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 178.50 (t, J = 3.0 Hz), 162.55 (t, J = 32.2 Hz), 155.78, 148.95, 141.15, 136.60, 134.09, 130.03, 129.92, 129.73, 128.43, 127.06, 125.54 (t, J = 20.6 Hz), 124.12, 112.79 (t, J = 246.4 Hz), 63.17, 14.12.
^{19}F NMR (376 MHz, DMSO-d_6) δ -94.87.
HRMS (ESI): Calcd for $C_{19}H_{14}F_2NO_5S^+$ $[M+H]^+$: 406.0555, found: 406.0551.

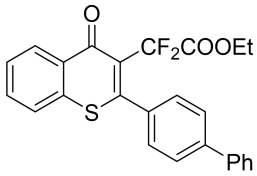


Ethyl 2,2-difluoro-2-(2-(4-formylphenyl)-4-oxo-4*H*-thiochromen-3-yl)acetate (3p).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 10/1). Product was obtained as a colorless oil (52% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.12 (s, 1H), 8.55 – 8.51 (m, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.76 – 7.70 (m, 3H), 7.66 – 7.61 (m, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 191.41, 178.81 (t, J = 3.1 Hz), 163.13 (t, J = 31.9 Hz), 155.56 (t, J = 1.7 Hz), 140.64, 137.12, 136.68, 132.78, 130.28, 129.47, 129.04, 128.91 (t, J = 2.5 Hz), 128.75, 126.30 (t, J = 20.7 Hz), 125.57, 112.59 (t, J = 253.6 Hz), 62.96, 13.91.

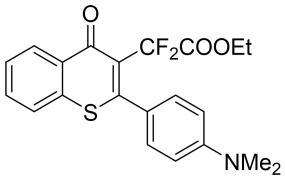
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.03.
HRMS (ESI): Calcd for $C_{20}H_{14}F_2O_4S^+$ $[M+H]^+$: 389.0654, found: 389.0659.



Methyl 4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzoate (3q).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 7/1). Product was obtained as a colorless oil (60% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.49 (m, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 7.74 – 7.69 (m, 1H), 7.65 – 7.59 (m, 4H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.88 (t, *J* = 3.0 Hz), 166.27, 163.19 (t, *J* = 31.9 Hz), 156.09, 139.28, 136.82, 132.70, 131.57, 130.28, 129.47, 128.99, 128.65, 128.24 (t, *J* = 2.5 Hz), 126.21 (t, *J* = 20.7 Hz), 125.54, 112.58 (t, *J* = 253.5 Hz), 62.89, 52.45, 13.90.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.07.
HRMS (ESI): Calcd for $C_{21}H_{17}F_2O_5S^+$ $[M+H]^+$: 419.0759, found: 419.0755.



Ethyl 2-(2-([1,1'-biphenyl]-4-yl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3r).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 25/1). Product was obtained as a white solid (69% yield), m.p. 117–119 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (d, *J* = 8.3 Hz, 1H), 7.74 – 7.69 (m, 3H), 7.69 – 7.65 (m, 2H), 7.65 – 7.59 (m, 4H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.45 – 7.40 (m, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.20 (t, *J* = 3.0 Hz), 163.44 (t, *J* = 32.2 Hz), 157.41, 143.01, 139.96, 137.26, 133.92, 132.53, 130.39, 128.98, 128.96, 128.65 (t, *J* = 2.4 Hz), 128.44, 127.99, 127.21, 126.93, 125.98 (t, *J* = 20.3 Hz), 125.50, 112.71 (t, *J* = 254.5 Hz), 62.80, 13.93.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.83.
HRMS (ESI): Calcd for $C_{25}H_{19}F_2O_3S^+$ $[M+H]^+$: 437.1017, found: 437.1014.



Ethyl 2-(2-(4-(dimethylamino)phenyl)-4-oxo-4*H*-thiochromen-3-yl)-2,2-difluoroacetate (3s).

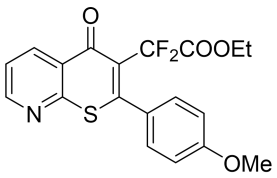
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 10/1). Product was obtained as a yellow solid (46% yield), m.p. 171–173 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.46 (m, 1H), 7.70 – 7.64 (m, 1H), 7.61 – 7.54 (m, 2H), 7.48 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.06 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.70 (t, *J* = 2.9 Hz), 163.73 (t, *J* = 32.5 Hz), 158.82, 151.53, 137.69, 132.20, 130.49, 129.71 (t, *J* = 2.5 Hz), 128.84, 128.04, 125.35, 124.69 (t, *J* = 20.2 Hz), 112.86 (t, *J* = 253.0 Hz), 111.24, 62.57, 40.24, 13.93.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.35.

HRMS (ESI): Calcd for $C_{21}H_{20}F_2NO_3S^+$ $[M+H]^+$: 404.1126, found: 404.1130.



Ethyl 2,2-difluoro-2-(2-(4-methoxyphenyl)-4-oxo-4*H*-thiopyrano[2,3-*b*]pyridin-3-yl)acetate (3t).

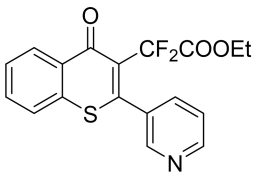
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =4/1). Product was obtained as a white solid (75% yield), m.p. 151–153 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.85 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.72 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.55 (dd, *J* = 8.1, 4.6 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 180.07 (t, *J* = 3.0 Hz), 163.35 (t, *J* = 32.1 Hz), 161.37, 159.62, 158.10, 153.60, 137.05, 129.69 (t, *J* = 2.4 Hz), 127.59, 126.98, 126.11 (t, *J* = 20.6 Hz), 123.41, 113.88, 112.52 (t, *J* = 254.0 Hz), 62.85, 55.44, 13.91.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.97.

HRMS (ESI): Calcd for $C_{19}H_{16}F_2NO_3S^+$ $[M+H]^+$: 392.0763, found: 392.0759.



Ethyl 2,2-difluoro-2-(4-oxo-2-(pyridin-3-yl)-4*H*-thiochromen-3-yl)acetate (3u).

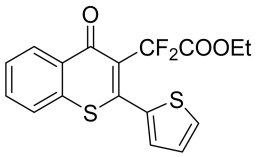
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA = 5/1). Product was obtained as a colorless oil (61% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.83 – 8.72 (m, 2H), 8.54 – 8.49 (m, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.67 – 7.61 (m, 2H), 7.47 – 7.42 (m, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.78 (t, *J* = 3.0 Hz), 163.04 (t, *J* = 31.9 Hz), 153.29, 151.01, 147.86 (t, *J* = 2.3 Hz), 136.69, 135.72 (t, *J* = 2.6 Hz), 132.79, 131.38, 130.31, 129.05, 128.81, 126.97 (t, *J* = 20.6 Hz), 125.55, 123.03, 112.63 (t, *J* = 253.4 Hz), 62.98, 13.90.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.63 (d, *J* = 103.6 Hz).

HRMS (ESI): Calcd for $C_{18}H_{14}F_2NO_3S^+$ $[M+H]^+$: 362.0657, found: 362.0654.



Ethyl 2,2-difluoro-2-(4-oxo-2-(thiophen-2-yl)-4*H*-thiochromen-3-yl)acetate (3v).

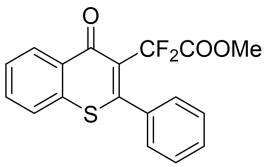
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =10/1). Product was obtained as a yellow solid (55% yield), m.p. 92–94 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 – 8.45 (m, 1H), 7.73 – 7.67 (m, 1H), 7.63 – 7.56 (m, 3H), 7.46 (d, *J* = 3.5 Hz, 1H), 7.18 – 7.14 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.37 (t, *J* = 3.0 Hz), 163.34 (t, *J* = 32.2 Hz), 150.30, 137.08, 134.46, 132.62, 130.66 (t, *J* = 3.4 Hz), 130.43, 129.78, 128.92, 128.53, 127.69, 126.39 (t, *J* = 20.5 Hz), 125.39, 112.32 (t, *J* = 253.3 Hz), 62.77, 13.92.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.58.

HRMS (ESI): Calcd for $C_{17}H_{13}F_2O_3S_2^+$ $[M+H]^+$: 367.0269, found: 367.0272.

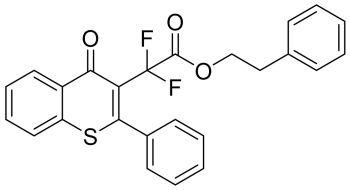


Methyl 2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetate (3w).

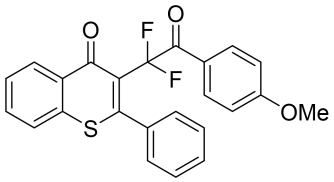
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =15/1). Product was obtained as a white solid (65% yield), m.p. 95–97 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 – 8.50 (m, 1H), 7.73 – 7.68 (m, 1H), 7.64 – 7.59 (m, 2H), 7.56 – 7.46 (m, 5H), 3.90 (s, 3H).

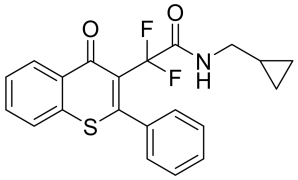
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.16 (t, *J* = 3.0 Hz), 163.97 (t, *J* = 32.3 Hz), 157.87, 137.23, 134.97, 132.58, 130.27, 130.11, 129.00, 128.47, 128.27, 128.05 (t, *J* = 2.5 Hz), 125.84 (t, *J* = 20.5 Hz), 125.49, 112.60 (t, *J* = 253.3 Hz), 53.42.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.01.
HRMS (ESI): Calcd for $C_{18}H_{13}F_2O_3S^+$ $[M+H]^+$: 347.0548, found: 347.0547.



Phenethyl 2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetate (3x).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =25/1). Product was obtained as a colorless oil (67% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.45 (m, 1H), 7.74 – 7.69 (m, 1H), 7.64 – 7.58 (m, 2H), 7.53 – 7.45 (m, 5H), 7.22 – 7.15 (m, 4H), 7.15 – 7.10 (m, 1H), 4.49 (t, *J* = 7.1 Hz, 2H), 3.01 (t, *J* = 7.1 Hz, 2H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.08 (t, *J* = 2.9 Hz), 163.17 (t, *J* = 32.6 Hz), 157.52, 137.25, 137.22, 135.00, 132.53, 130.26, 130.05, 129.02, 128.88, 128.42, 128.38, 128.25, 128.04 (t, *J* = 2.4 Hz), 126.49, 125.89 (t, *J* = 20.5 Hz), 125.43, 112.59 (t, *J* = 253.0 Hz), 66.91, 34.64.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.40.
HRMS (ESI): Calcd for $C_{25}H_{19}F_2O_3S^+$ $[M+H]^+$: 437.1017, found: 437.1015.



3-(1,1-difluoro-2-(4-methoxyphenyl)-2-oxoethyl)-2-phenyl-4*H*-thiochromen-4-one (3y).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =25/1). Product was obtained as a white solid (72% yield), m.p. 109–111 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 2H), 7.70 – 7.66 (m, 1H), 7.63 – 7.59 (m, 3H), 7.58 – 7.53 (m, 1H), 7.52 – 7.47 (m, 3H), 6.96 – 6.92 (m, 2H), 3.88 (s, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 187.08, 179.06 (t, *J* = 3.0 Hz), 163.68, 156.99, 137.34, 135.24, 132.42, 132.11 (t, *J* = 3.2 Hz), 130.51, 129.95, 129.06, 128.27, 128.23, 128.14 (t, *J* = 2.4 Hz), 127.74 (t, *J* = 21.2, 20.2 Hz), 126.19 (t, *J* = 1.9 Hz), 125.40, 116.82 (t, *J* = 258.6 Hz), 113.75, 55.48.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.68.
HRMS (ESI): Calcd for $C_{24}H_{17}F_2O_3S^+$ $[M+H]^+$: 423.0861, found: 423.0856.



***N*-(cyclopropylmethyl)-2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetamide (3z).**

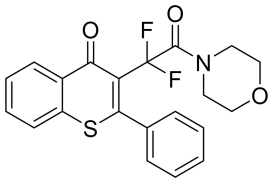
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =5/1). Product was obtained as a white solid (62% yield), m.p. 166–168 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.47 (m, 1H), 7.69 – 7.65 (m, 1H), 7.62 – 7.55 (m, 4H), 7.51 – 7.43 (m, 3H), 6.76 (s, 1H), 3.34 – 3.24 (m, 2H), 1.13 – 1.05 (m, 1H), 0.62 – 0.56 (m, 2H), 0.33 – 0.28 (m, 2H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.29 (t, *J* = 2.7 Hz), 164.05 (t, *J* = 27.8 Hz), 157.76 (t, *J* = 2.0 Hz), 137.11, 135.49, 132.32, 130.67, 129.84, 128.92, 128.21, 128.17 (t, *J* = 3.0 Hz), 128.07, 125.59 (t, *J* = 20.2 Hz), 125.33, 114.94 (t, *J* = 257.3 Hz), 44.52, 10.35, 3.51.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -91.73 – -103.61 (m).

HRMS (ESI): Calcd for $C_{21}H_{18}F_2NO_2S^+$ $[M+H]^+$: 386.1021, found: 386.1024.



3-(1,1-difluoro-2-morpholino-2-oxoethyl)-2-phenyl-4*H*-thiochromen-4-one (3aa).

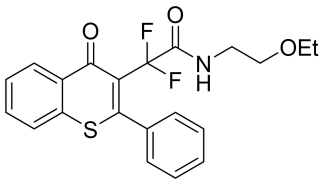
Prepared by general procedure E on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =5/1). Product was obtained as a white solid (42% yield), m.p. 152–154 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.75 – 7.70 (m, 1H), 7.58 – 7.50 (m, 5H), 3.62 – 3.53 (m, 2H), 3.51 – 3.44 (m, 6H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 178.13, 161.27 (t, *J* = 28.1 Hz), 156.63, 136.76, 135.57, 133.60, 130.52, 130.23, 129.42, 128.81, 128.54, 128.29, 126.82 (t, *J* = 20.6 Hz), 126.70, 115.67 (t, *J* = 255.2 Hz), 66.39, 66.15, 46.44, 43.55.

^{19}F NMR (376 MHz, DMSO-d_6) δ -88.30.

HRMS (ESI): Calcd for $C_{21}H_{18}F_2NO_3S^+$ $[M+H]^+$: 402.0970, found: 402.0967.



***N*-(2-ethoxyethyl)-2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetamid e (3ab).**

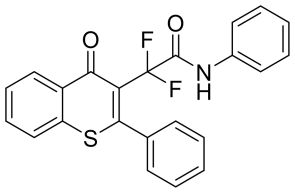
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =4/1). Product was obtained as a white solid (65% yield), m.p. 139–140 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.45 (m, 1H), 7.69 – 7.64 (m, 1H), 7.62 – 7.55 (m, 4H), 7.50 – 7.43 (m, 3H), 7.03 (s, 1H), 3.63 – 3.54 (m, 6H), 1.24 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.25 (t, *J* = 2.6 Hz), 164.27 (t, *J* = 28.0 Hz), 157.75 (t, *J* = 1.7 Hz), 137.10, 135.48, 132.32, 130.66, 129.84, 128.93, 128.20, 128.16 (t, *J* = 2.6 Hz), 128.08, 125.60 (t, *J* = 20.3 Hz), 125.33, 114.84 (t, *J* = 257.4 Hz), 68.54, 66.56, 39.54, 15.13.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.92 – -103.61 (m).

HRMS (ESI): Calcd for $C_{21}H_{20}F_2NO_3S^+$ $[M+H]^+$: 404.1126, found: 404.1123.



2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)-*N*-phenylacetamide (3ac).

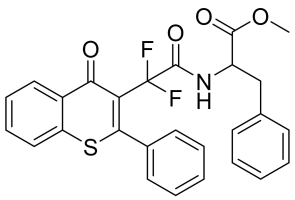
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =5/1). Product was obtained as a white solid (58% yield), m.p. 114–116 °C.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.59 (s, 1H), 8.50 (d, *J* = 7.9 Hz, 1H), 7.70 – 7.65 (m, 3H), 7.63 – 7.57 (m, 4H), 7.53 – 7.47 (m, 3H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H).

^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.41 (t, *J* = 2.6 Hz), 162.04 (t, *J* = 28.0 Hz), 158.53, 137.12, 136.75, 135.29, 132.50, 130.58, 130.01, 129.10, 128.98, 128.38, 128.20, 128.16, 125.38, 125.33 (t, *J* = 20.5 Hz), 125.06, 120.24, 114.91 (t, *J* = 258.7 Hz).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.96.

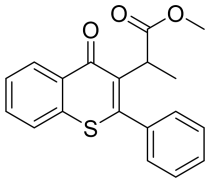
HRMS (ESI): Calcd for $C_{23}H_{16}F_2NO_2S^+$ $[M+H]^+$: 408.0864, found: 408.0859.



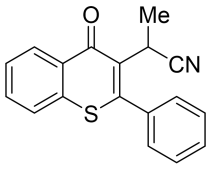
Methyl (2,2-difluoro-2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)acetyl)phenylalani nate (3ad).

Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =3/1). Product was obtained as a white solid (50% yield), m.p. 132–133 °C.

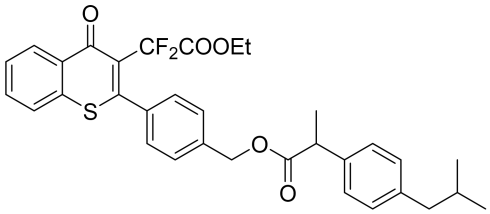
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 – 8.49 (m, 1H), 7.71 – 7.66 (m, 1H), 7.62 – 7.55 (m, 4H), 7.51 – 7.45 (m, 3H), 7.31 – 7.26 (m, 5H), 7.24 – 7.20 (m, 1H), 5.01 – 4.94 (m, 1H), 3.74 (s, 3H), 3.27 (d, *J* = 5.5 Hz, 2H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.16 (t, *J* = 2.8 Hz), 170.94, 163.57 (t, *J* = 28.6 Hz), 157.97, 137.05, 135.61, 135.36, 132.36, 130.67, 129.92, 129.57, 129.03, 128.55, 128.24, 128.17 (t, *J* = 3.0 Hz), 128.13, 127.14, 125.36 (t, *J* = 20.3 Hz), 125.33, 114.60 (t, *J* = 257.2 Hz), 53.51, 52.39, 37.90.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.19 (d, *J* = 23.7 Hz).
HRMS (ESI): Calcd for $C_{27}H_{22}F_2NO_4S^+$ $[M+H]^+$: 494.1232, found: 494.1228.



Methyl 2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)propanoate (3ae).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =15/1). Product was obtained as a white solid (45% yield), m.p. 139–141 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 – 8.53 (m, 1H), 7.66 – 7.61 (m, 1H), 7.60 – 7.54 (m, 2H), 7.54 – 7.49 (m, 5H), 3.69 (s, 3H), 3.62 (q, *J* = 7.0 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.87, 174.15, 149.83, 137.39, 136.22, 135.15, 131.49, 130.80, 129.78, 129.22, 128.98, 128.44, 127.55, 125.54, 52.07, 40.32, 15.28.
HRMS (ESI): Calcd for $C_{19}H_{17}O_3S^+$ $[M+H]^+$: 325.0893, found: 325.0895.



2-(4-oxo-2-phenyl-4*H*-thiochromen-3-yl)propanenitrile (3af).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =10/1). Product was obtained as a white solid (41% yield), m.p. 126–127 °C.
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 – 8.60 (m, 1H), 7.70 – 7.65 (m, 1H), 7.64 – 7.54 (m, 5H), 7.47 – 7.41 (m, 2H), 3.98 (q, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 177.96, 152.27, 136.74, 135.08, 131.99, 130.63, 130.46, 129.37, 129.35, 129.32, 128.20, 128.12, 125.56, 120.65, 26.15, 17.77.
HRMS (ESI): Calcd for $C_{18}H_{14}NOS^+$ $[M+H]^+$: 292.0791, found: 292.0788.



4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzyl-2-(4-isobutylphenyl)propanoate (3ag).

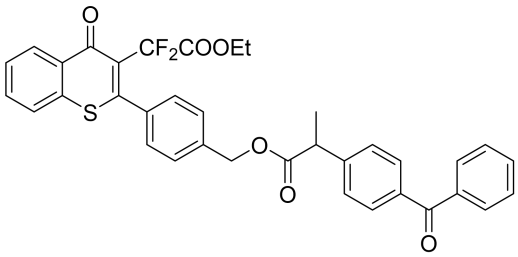
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =20/1). Product was obtained as a yellow oil (65% yield).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.52 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.3 Hz, 1H), 7.61 (d, *J* = 5.7 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.20 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.82 (q, *J* = 7.1 Hz, 1H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 6H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 179.08, 174.41, 163.33 (t, *J* = 32.1 Hz), 157.08, 140.71, 138.30, 137.49, 137.14, 134.62, 132.55, 130.35, 129.41, 128.95, 128.47, 128.24, 127.30, 127.24, 126.07 (t, *J* = 20.5 Hz), 125.48, 112.64 (t, *J* = 253.5 Hz), 65.52, 62.76, 45.14, 45.04, 30.21, 22.39, 18.38, 13.92.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -95.92.

HRMS (ESI): Calcd for $C_{33}H_{33}F_2O_5S^+$ $[M+H]^+$: 579.2011, found: 579.2006.



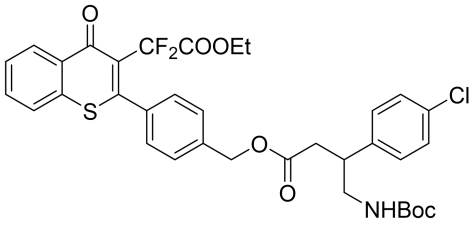
4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzyl 2-(4-benzoylphenyl)propanoate (3ah).

Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =20/1). Product was obtained as a yellow oil (60% yield).

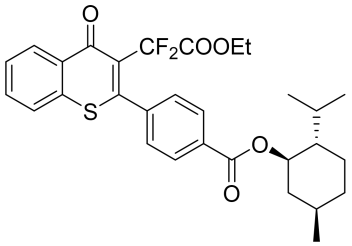
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 6.7 Hz, 3H), 7.71 (t, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 8.2 Hz, 3H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.45 (m, 5H), 7.34 (d, *J* = 7.9 Hz, 2H), 5.21 (s, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.92 (q, *J* = 7.1 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 196.43, 179.06 (t, *J* = 2.7 Hz), 173.74, 163.31 (t, *J* = 32.1 Hz), 156.96, 140.57, 137.99, 137.93, 137.47, 137.10, 134.81, 132.54, 131.51, 130.34, 130.07, 129.28, 129.15, 128.96, 128.64, 128.47, 128.34, 127.48, 126.06 (t, *J* = 20.3 Hz), 125.48, 112.63 (t, *J* = 253.5 Hz), 65.87, 62.78, 45.41, 18.35, 13.91.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -95.93.
HRMS (ESI): Calcd for $C_{36}H_{29}F_2O_6S^+$ $[M+H]^+$: 627.1647, found: 627.1639.

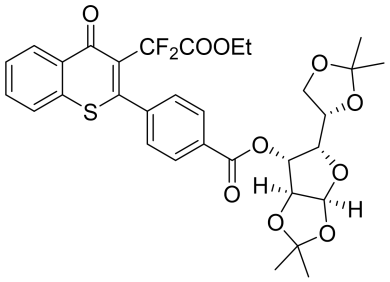


4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzyl 4-((*tert*-butoxycarbonyl)amino)-3-(4-chlorophenyl)butanoate (3ai).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =4/1). Product was obtained as a yellow oil (45% yield).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.62 – 7.58 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.25 (m, 4H), 7.15 (d, *J* = 8.1 Hz, 2H), 5.09 (s, 2H), 4.58 (s, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.50 – 3.41 (m, 1H), 3.38 – 3.33 (m, 1H), 3.31 – 3.26 (m, 1H), 2.81 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.69 (dd, *J* = 15.6, 9.1 Hz, 1H), 1.42 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 179.07 (t, *J* = 3.0 Hz), 171.45, 163.31 (t, *J* = 32.1 Hz), 157.04, 155.85, 139.52, 137.77, 137.12, 134.82, 132.93, 132.59, 130.30, 129.08, 128.93, 128.50, 128.29, 127.75, 126.02 (t, *J* = 20.5 Hz), 125.52, 112.63 (t, *J* = 253.3 Hz), 79.56, 65.65, 62.79, 45.59, 42.02, 38.14, 28.35, 13.93.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.91.
HRMS (ESI): Calcd for $C_{35}H_{35}ClF_2NO_7S^+$ $[M+H]^+$: 686.1785, found: 686.1782.

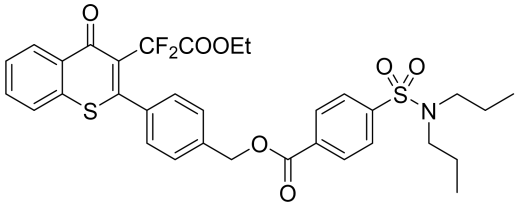


(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzoate (3aj).
Prepared by general procedure E on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =25/1). Product was obtained as a yellow oil (50% yield).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.53 – 8.50 (m, 1H), 8.15 (d, *J* = 8.3 Hz, 2H), 7.73 – 7.69 (m, 1H), 7.63 – 7.59 (m, 4H), 4.99 (td, *J* = 10.9, 4.4 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.16 (d, *J* = 11.8 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.79 – 1.74 (m, 2H), 1.62 – 1.56 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.20 – 1.11 (m, 2H), 0.98 – 0.93 (m, 7H), 0.83 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 178.89, 165.25, 163.19 (t, *J* = 32.0 Hz), 156.22, 139.09, 136.85, 132.69, 132.27, 130.28, 129.45, 128.98, 128.64, 128.19,

126.17 (t, *J* = 20.7 Hz), 125.56, 112.61 (t, *J* = 253.5 Hz), 75.36, 62.88, 47.24, 40.94, 34.27, 31.47, 26.47, 23.54, 22.07, 20.83, 16.47, 13.92.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -96.01.
HRMS (ESI): Calcd for $C_{30}H_{33}F_2O_5S^+$ $[M+H]^+$: 543.2011, found: 543.2017.

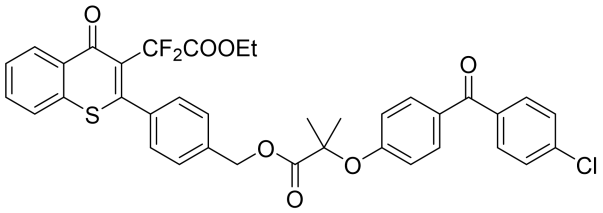


(3a*S*,5*S*,6*R*,6a*S*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl 4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzoate (3ak).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =6/1). Product was obtained as a yellow oil (49% yield).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 2H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 4H), 5.98 (d, *J* = 3.4 Hz, 1H), 5.54 (d, *J* = 2.3 Hz, 1H), 4.67 (d, *J* = 3.4 Hz, 1H), 4.42 – 4.33 (m, 4H), 4.18 – 4.14 (m, 1H), 4.14 – 4.11 (m, 1H), 1.58 (s, 3H), 1.44 (s, 3H), 1.36 – 1.33 (m, 6H), 1.30 (s, 3H).
^{13}C NMR (150 MHz, Chloroform-*d*) δ 178.80, 164.40, 163.11 (t, *J* = 31.9 Hz), 155.69, 139.85, 136.70, 132.73, 130.95, 130.29, 129.58, 129.07, 129.01, 128.70, 128.41, 126.29 (t, *J* = 20.6 Hz), 125.54, 112.59 (t, *J* = 253.6 Hz), 112.44, 109.52, 105.14, 83.36, 79.93, 72.55, 67.36, 62.90, 26.90, 26.73, 26.21, 25.24, 13.89.
^{19}F NMR (565 MHz, Chloroform-*d*) δ -96.02 (d, *J* = 8.0 Hz).
HRMS (ESI): Calcd for $C_{32}H_{33}F_2O_{10}S^+$ $[M+H]^+$: 647.1757, found: 647.1749.

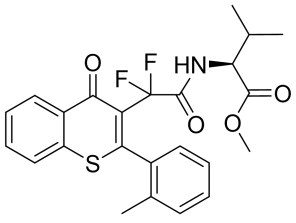


4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzyl 4-(*N*,*N*-dipropylsulfamoyl)benzoate (3al).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =6/1). Product was obtained as a yellow solid (42% yield), m.p. 131–133 °C.
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.52 – 8.49 (m, 1H), 8.23 (d, *J* = 8.5 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.72 – 7.69 (m, 1H), 7.62 – 7.55 (m, 6H), 5.47 (s, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.13 – 3.10 (m, 4H), 1.59 – 1.53 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 179.03, 165.00, 163.28 (t, *J* = 32.1 Hz), 156.84, 144.55, 137.61, 137.04, 135.16, 133.15, 132.61, 130.40, 130.32, 128.93, 128.52, 128.51, 127.94, 127.09, 126.10 (t, *J* = 19.1 Hz), 125.51, 112.66 (t, *J* = 253.3 Hz), 66.56, 62.79, 49.96, 21.95, 13.90, 11.16.
^{19}F NMR (565 MHz, Chloroform-*d*) δ -95.86.
HRMS (ESI): Calcd for $C_{33}H_{34}F_2NO_7S_2^+$ [M+H]$^+$: 658.1739, found: 658.1731.



4-(3-(2-ethoxy-1,1-difluoro-2-oxoethyl)-4-oxo-4*H*-thiochromen-2-yl)benzyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate (3am).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =8/1). Product was obtained as a yellow oil (61% yield).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.47 (m, 1H), 7.71 – 7.67 (m, 5H), 7.62 – 7.57 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.84 – 6.80 (m, 2H), 5.28 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.73 (s, 6H), 1.32 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, Chloroform-*d*) δ 194.13, 179.00 (t, *J* = 3.0 Hz), 173.44, 163.26 (t, *J* = 32.0 Hz), 159.46, 156.75, 138.44, 137.12, 136.99, 136.29, 135.17, 132.60, 132.01, 131.18, 130.49, 130.27, 128.90, 128.56, 128.51, 128.34, 128.07, 126.02 (t, *J* = 20.5 Hz), 125.56, 117.26, 112.63 (t, *J* = 253.4 Hz), 79.41, 66.61, 62.81, 25.45, 13.91.
^{19}F NMR (376 MHz, Chloroform-*d*) δ -95.95.
HRMS (ESI): Calcd for $C_{37}H_{30}ClF_2O_7S^+$ [M+H]$^+$: 691.1363, found: 691.1355.



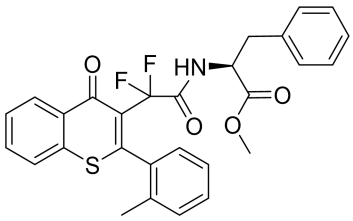
Methyl (2,2-difluoro-2-(4-oxo-2-(*o*-tolyl)-4*H*-thiochromen-3-yl)acetyl)-*L*-valinate (3an).
Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =8/1). Product was obtained as a yellow oil (46% yield).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 8.2 Hz, 1H), 7.66 (td, *J* = 7.6, 1.5 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.38 – 7.33 (m, 2H), 7.29 – 7.25 (m, 2H), 7.11 (t, *J* =

8.7 Hz, 1H), 4.61 – 4.55 (m, 1H), 3.79 (s, 3H), 2.40 (d, *J* = 6.6 Hz, 3H), 2.33 – 2.25 (m, 1H), 1.07 – 1.02 (m, 6H).

^{13}C NMR (150 MHz, Chloroform-*d*) δ 178.71, 171.51, 163.78 (td, *J* = 28.2, 9.5 Hz), 157.25 (d, *J* = 9.8 Hz), 137.30, 135.44 (d, *J* = 8.5 Hz), 134.64 (d, *J* = 6.1 Hz), 132.28, 130.64 (d, *J* = 3.1 Hz), 129.99 (d, *J* = 6.7 Hz), 129.55, 129.04 (d, *J* = 2.7 Hz), 128.15, 128.03, 126.26 (td, *J* = 19.6, 6.5 Hz), 125.43 (d, *J* = 3.3 Hz), 125.34, 114.74 (td, *J* = 257.6, 6.0 Hz), 57.43 (d, *J* = 2.1 Hz), 52.27, 31.73, 19.43 (d, *J* = 3.3 Hz), 18.80, 17.86.

^{19}F NMR (565 MHz, Chloroform-*d*) δ -97.13 – -101.92 (m).

HRMS (ESI): Calcd for $C_{24}H_{24}F_2NO_4S^+$ $[M+H]^+$: 460.1389, found: 460.1396.



Methyl (2,2-difluoro-2-(4-oxo-2-(*o*-tolyl)-4*H*-thiochromen-3-yl)acetyl)-*L*-phenylalaninate (3ao).

Prepared by general procedure G on a 0.2 mmol scale and purified by flash chromatography on silica gel (PE/EA =8/1). Product was obtained as a white solid (51% yield), m.p. 68–69 °C.

^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.54 (d, *J* = 7.4 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.61 – 7.56 (m, 2H), 7.40 – 7.36 (m, 1H), 7.36 – 7.33 (m, 1H), 7.32 – 7.25 (m, 7H), 7.15 – 7.10 (m, 1H), 4.98 – 4.92 (m, 1H), 3.73 (d, *J* = 1.3 Hz, 3H), 3.32 – 3.21 (m, 2H), 2.40 (s, 3H).

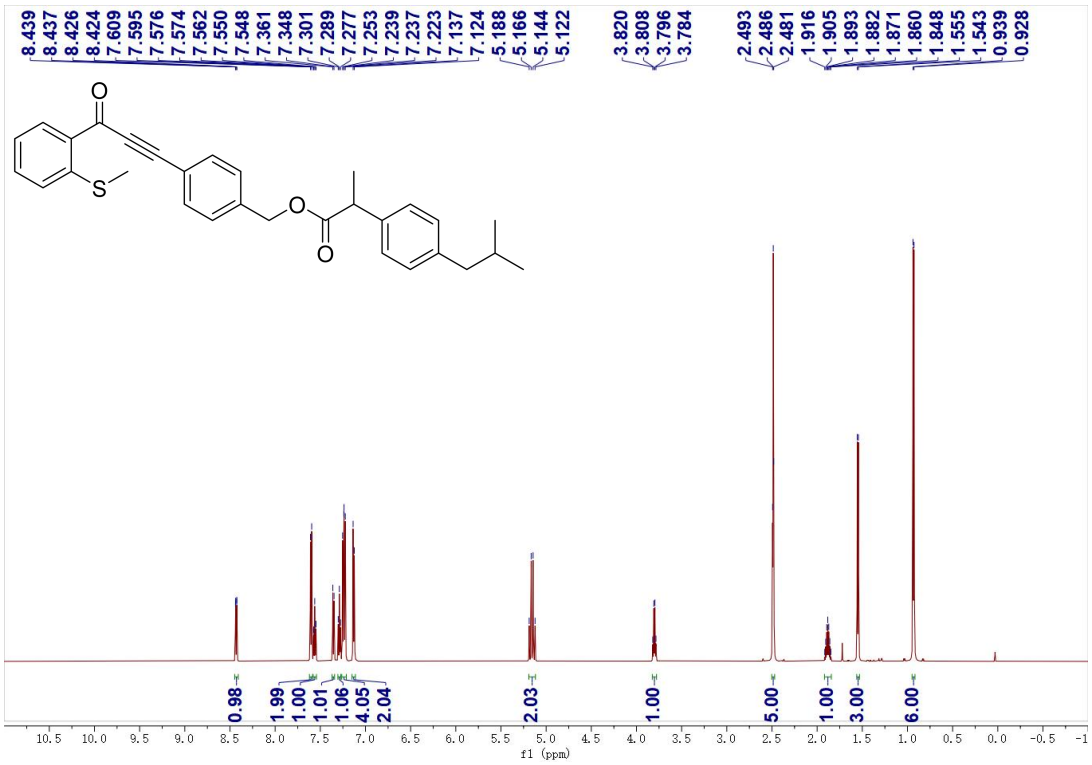
^{13}C NMR (150 MHz, Chloroform-*d*) δ 178.79, 170.92, 163.43 (t, *J* = 28.4 Hz), 157.41, 137.33, 135.62, 135.44 (t, *J* = 2.4 Hz), 134.59, 132.33, 130.65, 130.03 (d, *J* = 2.7 Hz), 129.59, 129.56, 129.07, 128.54, 128.21, 128.02, 127.12, 126.27 (t, *J* = 20.0 Hz), 125.46, 125.36, 114.58 (t, *J* = 257.3 Hz), 53.46 (d, *J* = 4.4 Hz), 52.34, 37.91 (d, *J* = 12.4 Hz), 19.44 (d, *J* = 2.0 Hz).

^{19}F NMR (565 MHz, Chloroform-*d*) δ -95.08 – -106.87 (m).

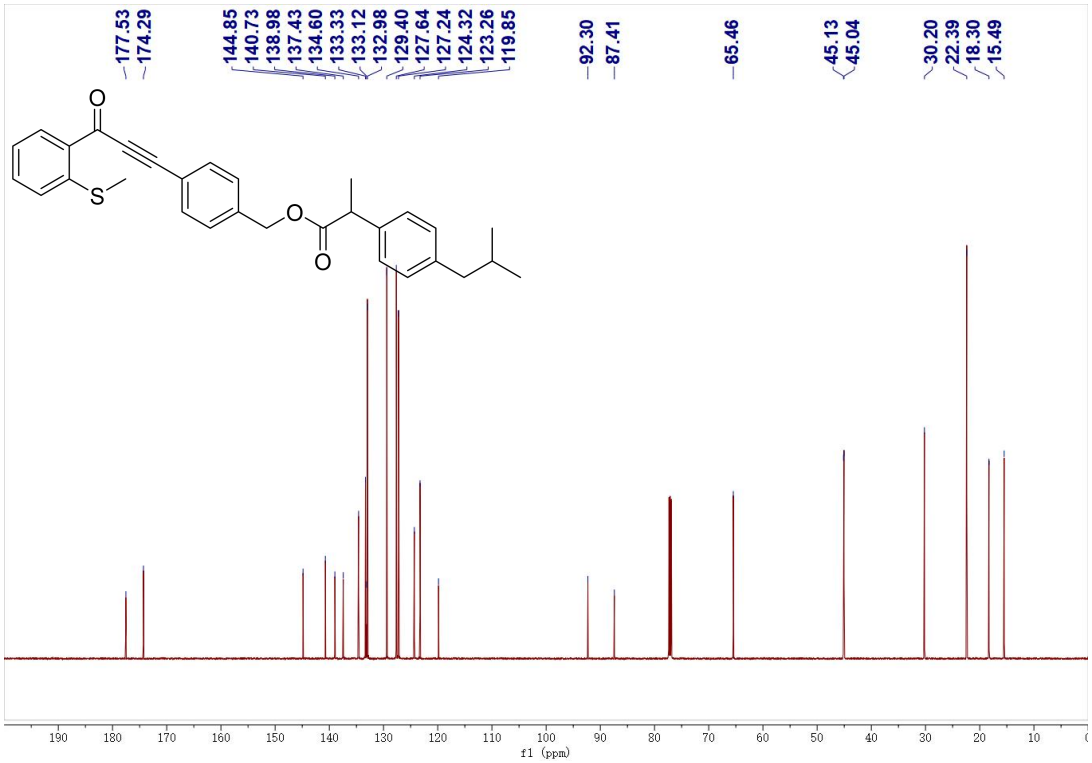
HRMS (ESI): Calcd for $C_{28}H_{24}F_2NO_4S^+$ $[M+H]^+$: 508.1389, found: 508.1381.

4. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR Spectra

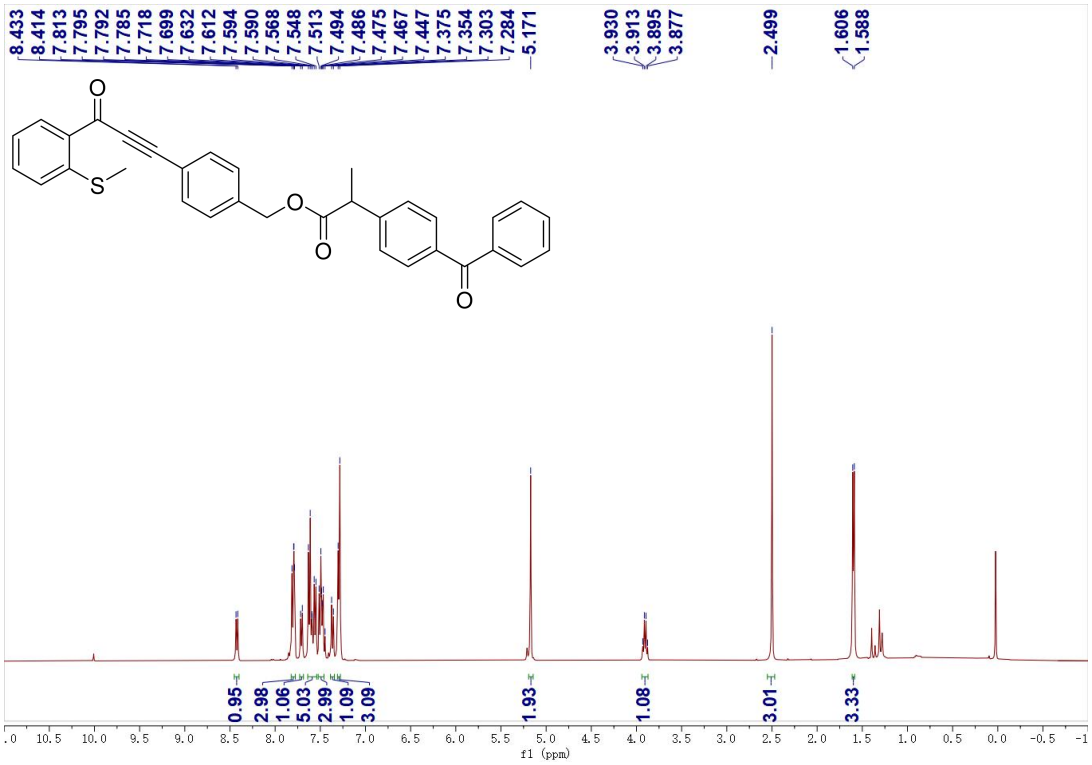
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **1ag**



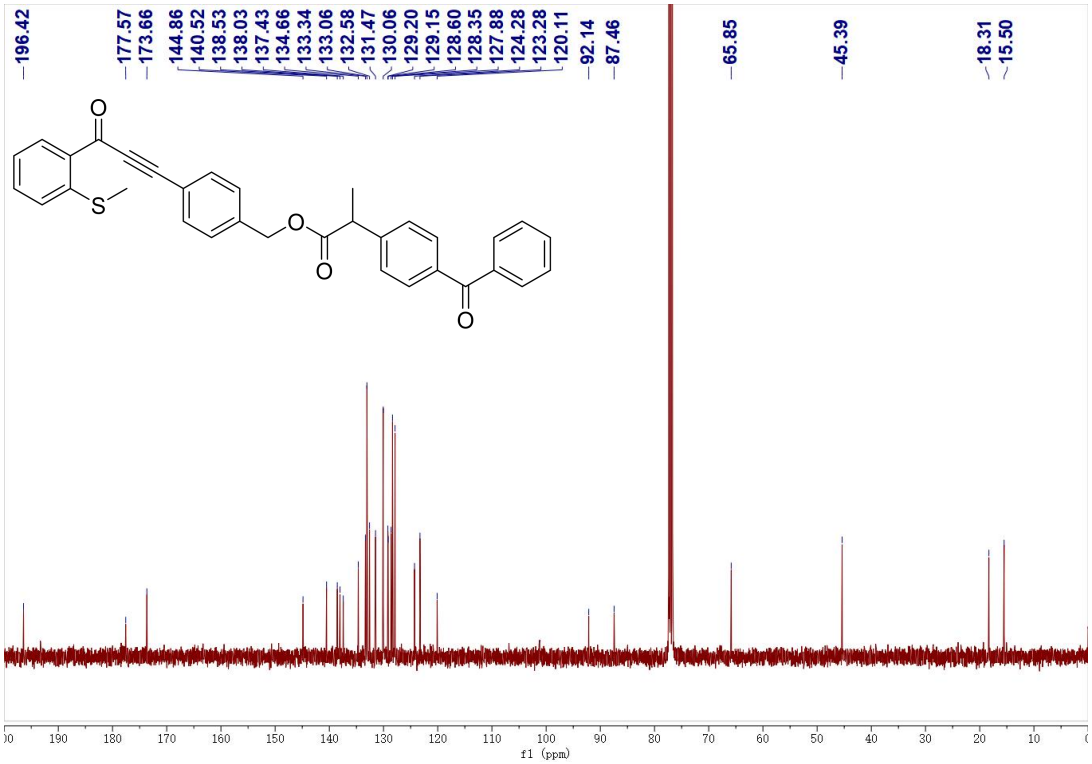
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **1ag**



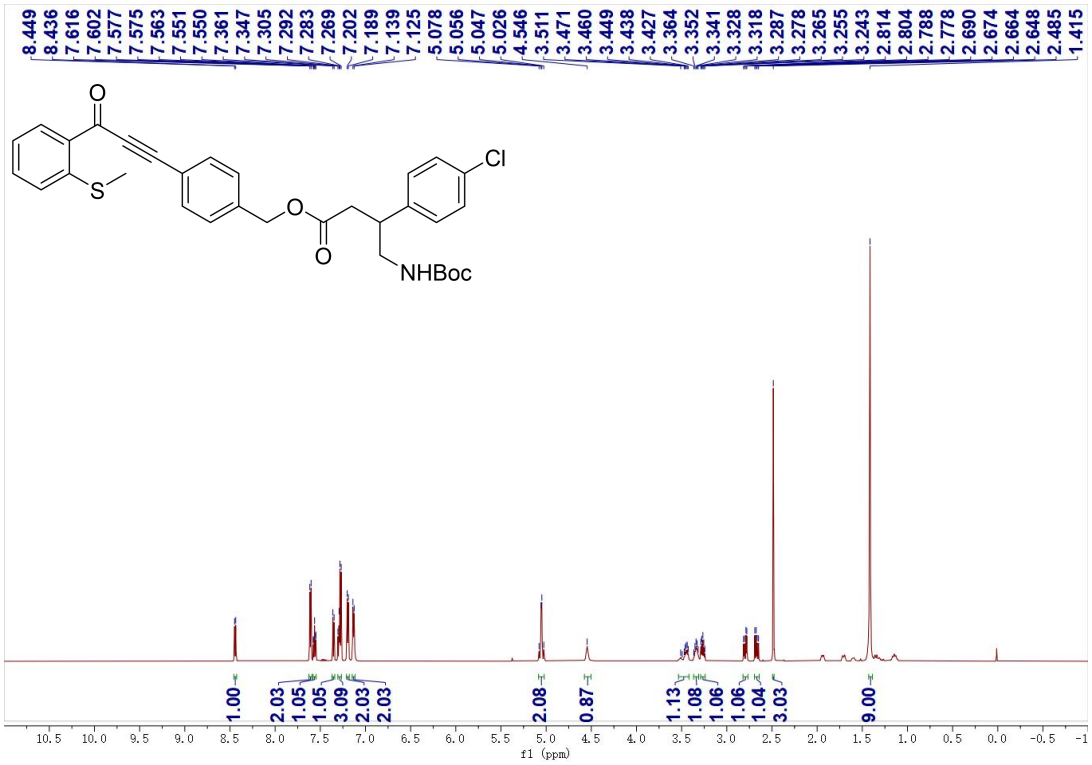
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **1ah**



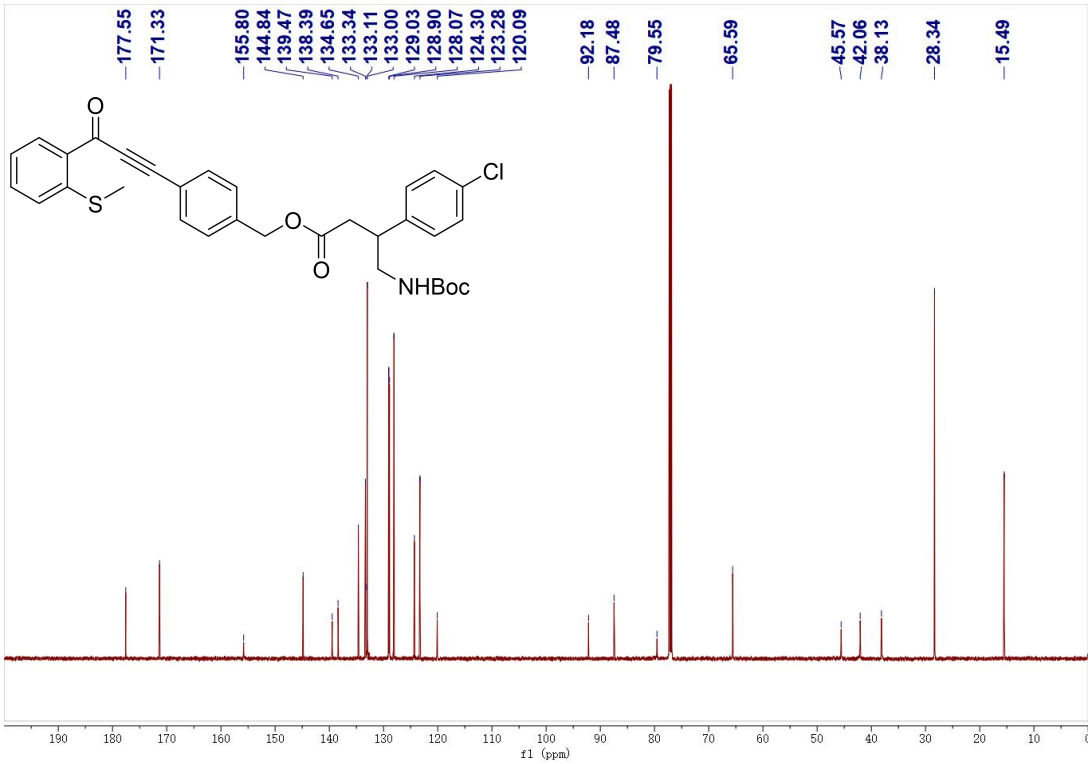
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **1ah**



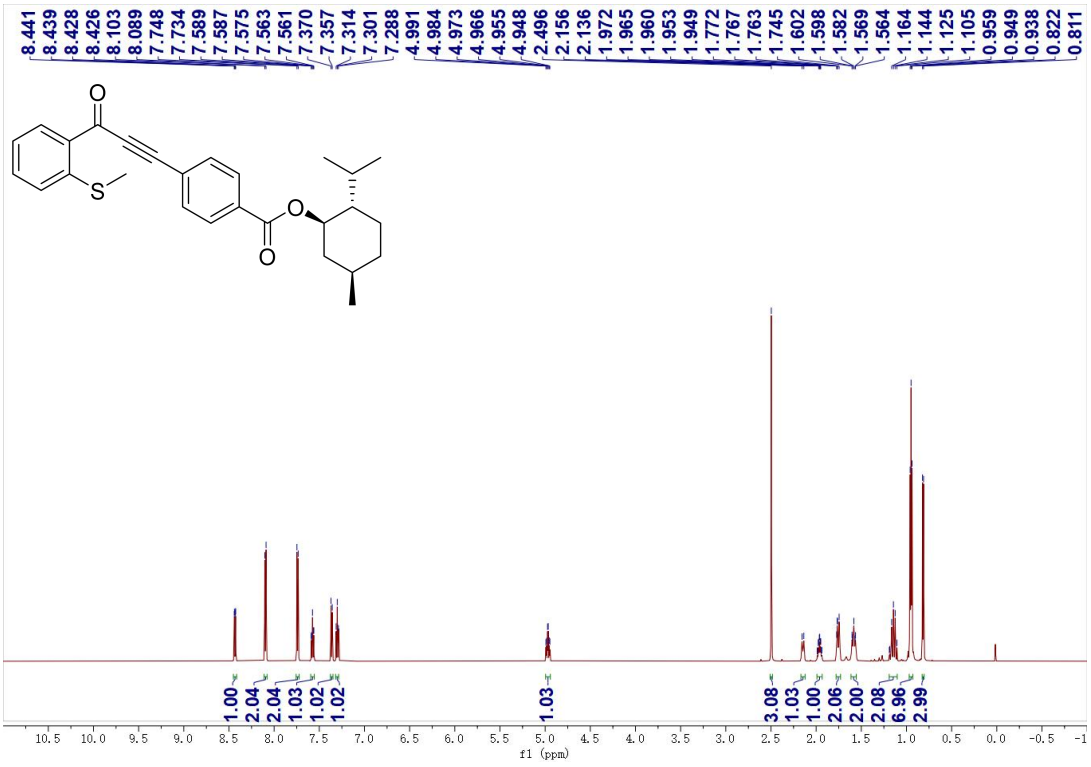
[1]H NMR (600 MHz, Chloroform-*d*) spectrum of **1ai**



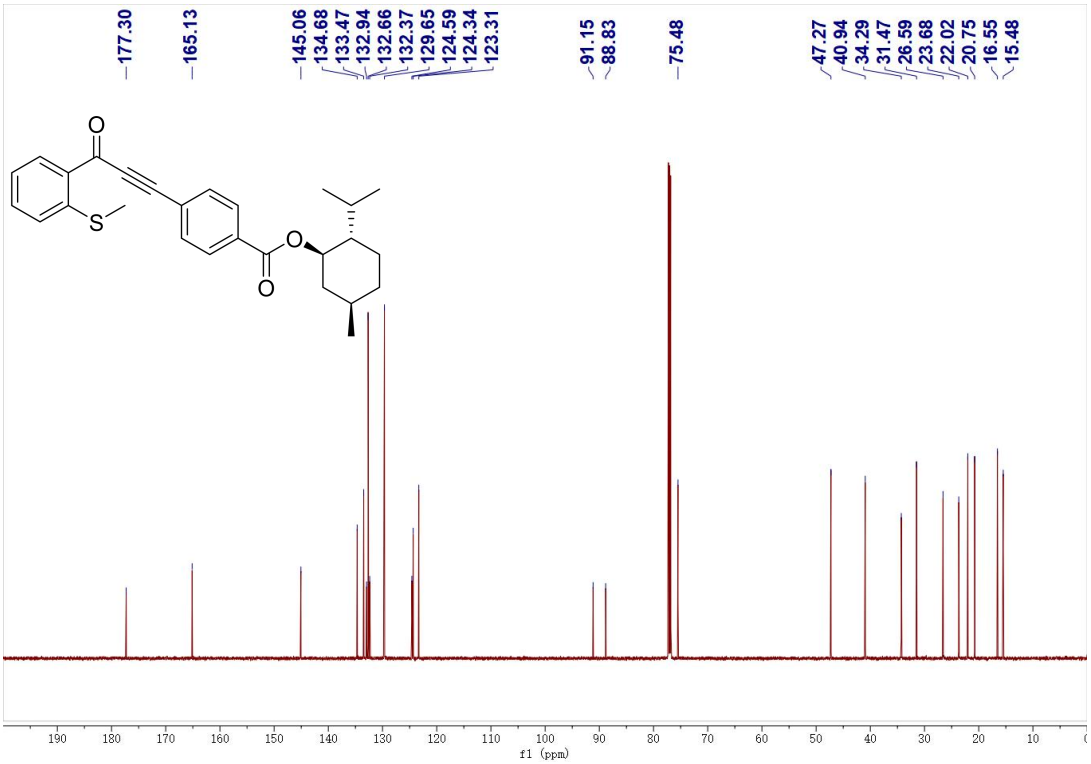
[13]C NMR (150 MHz, Chloroform-*d*) spectrum of **1ai**



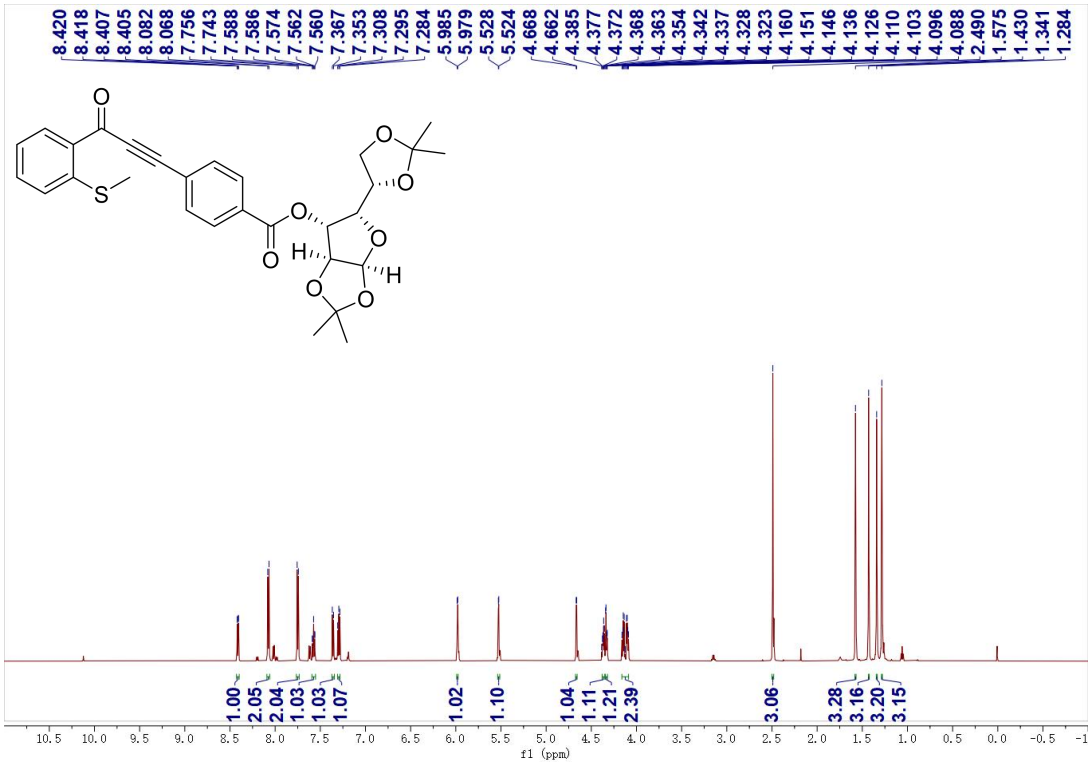
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **1aj**



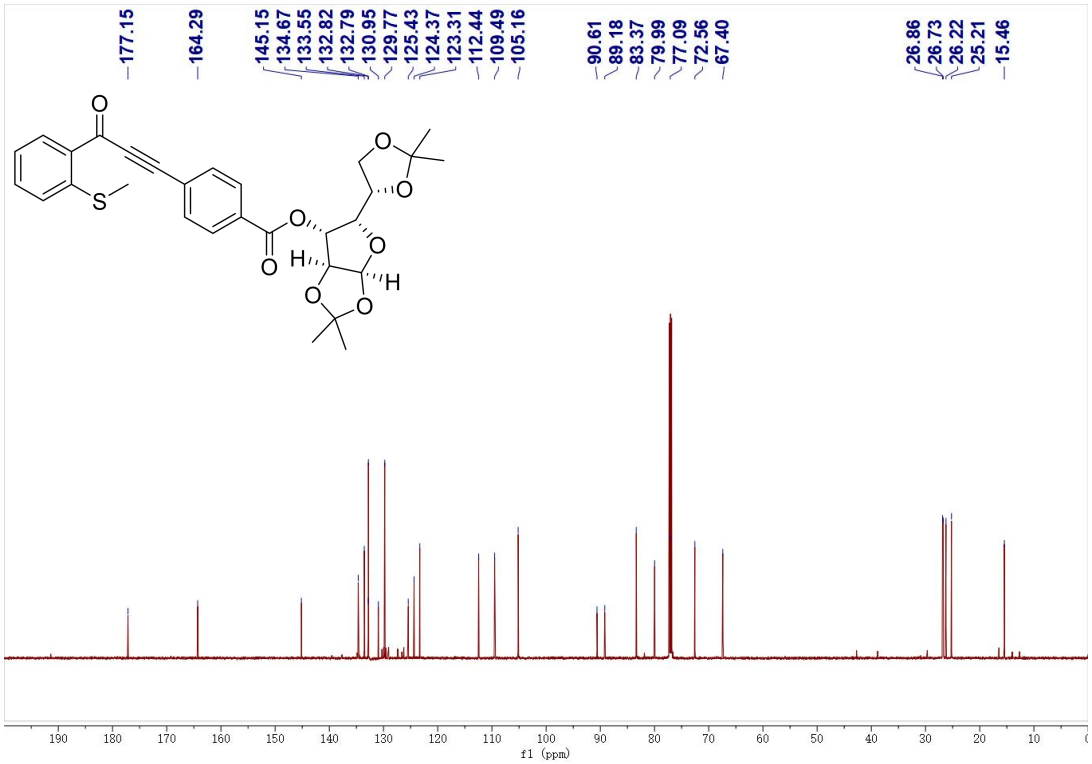
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **1aj**



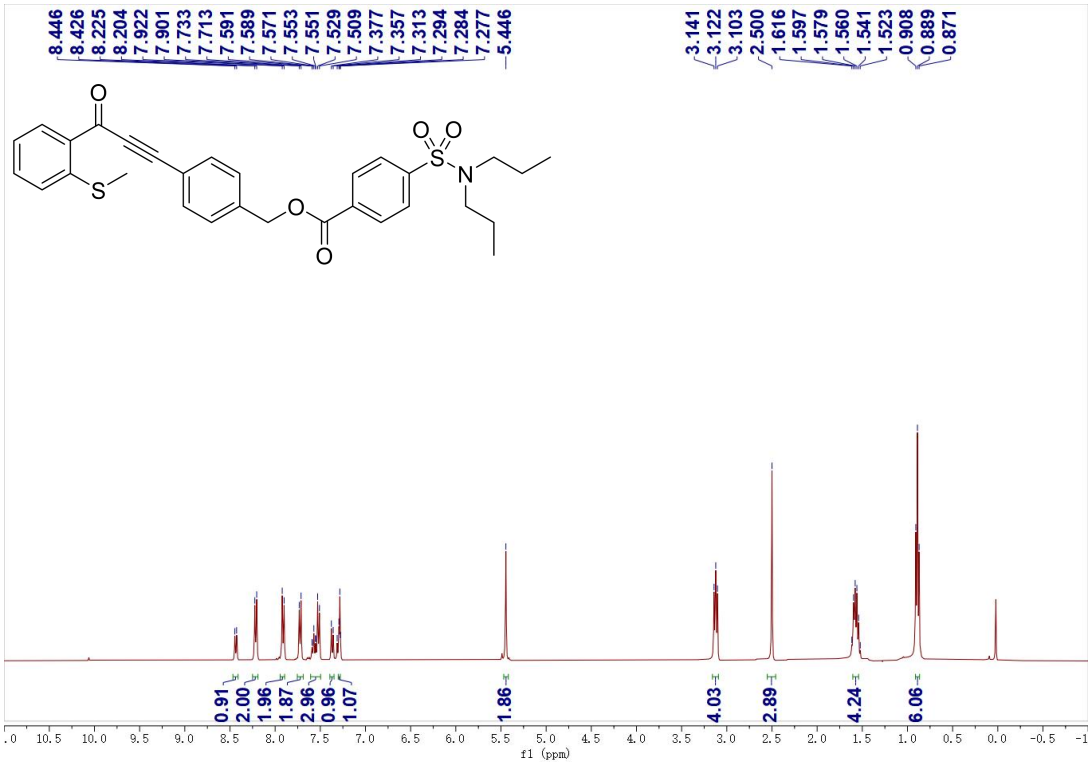
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **1ak**



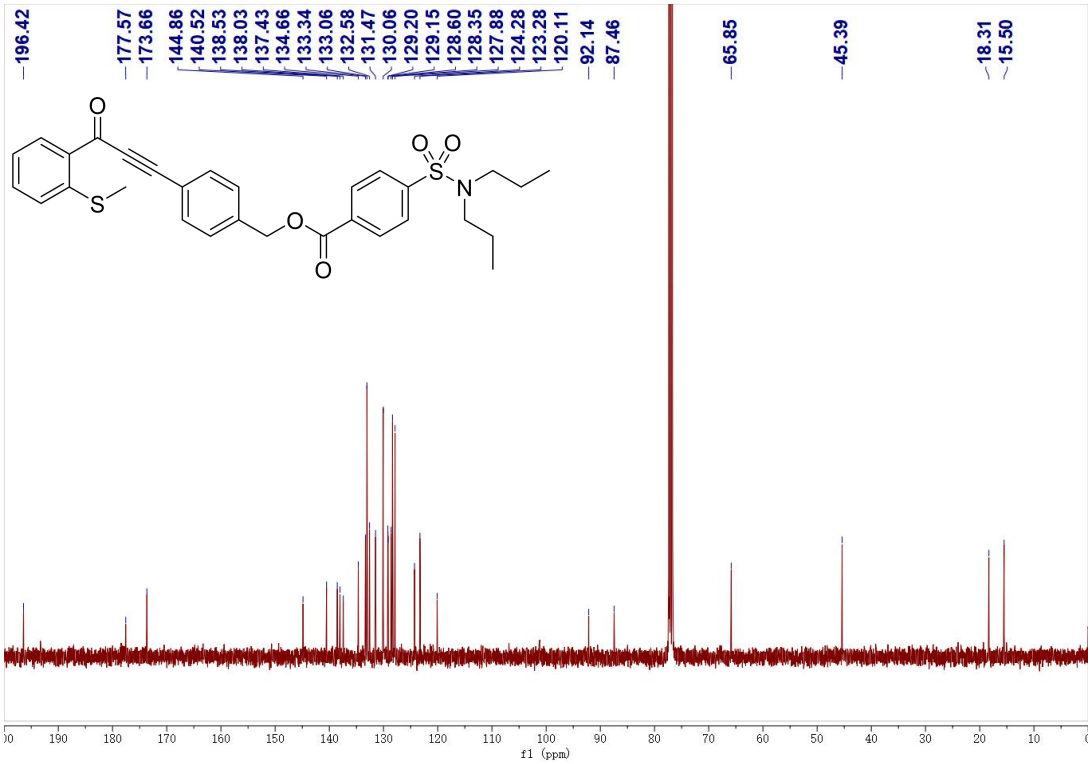
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **1ak**



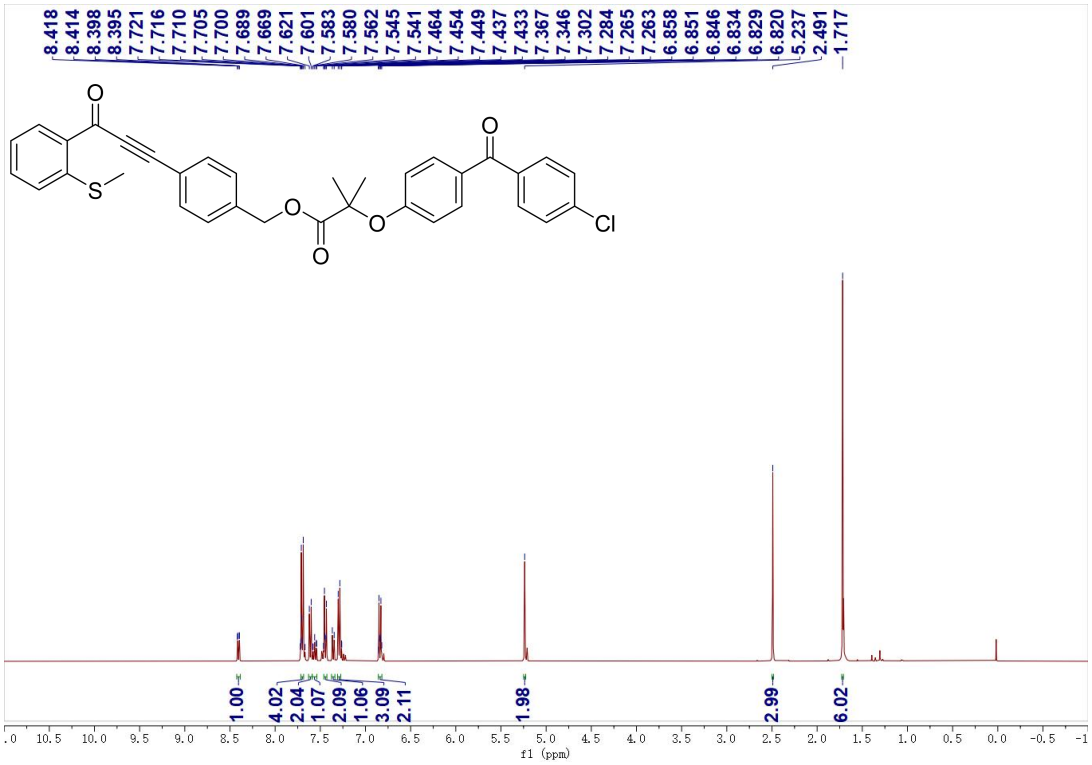
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **1al**



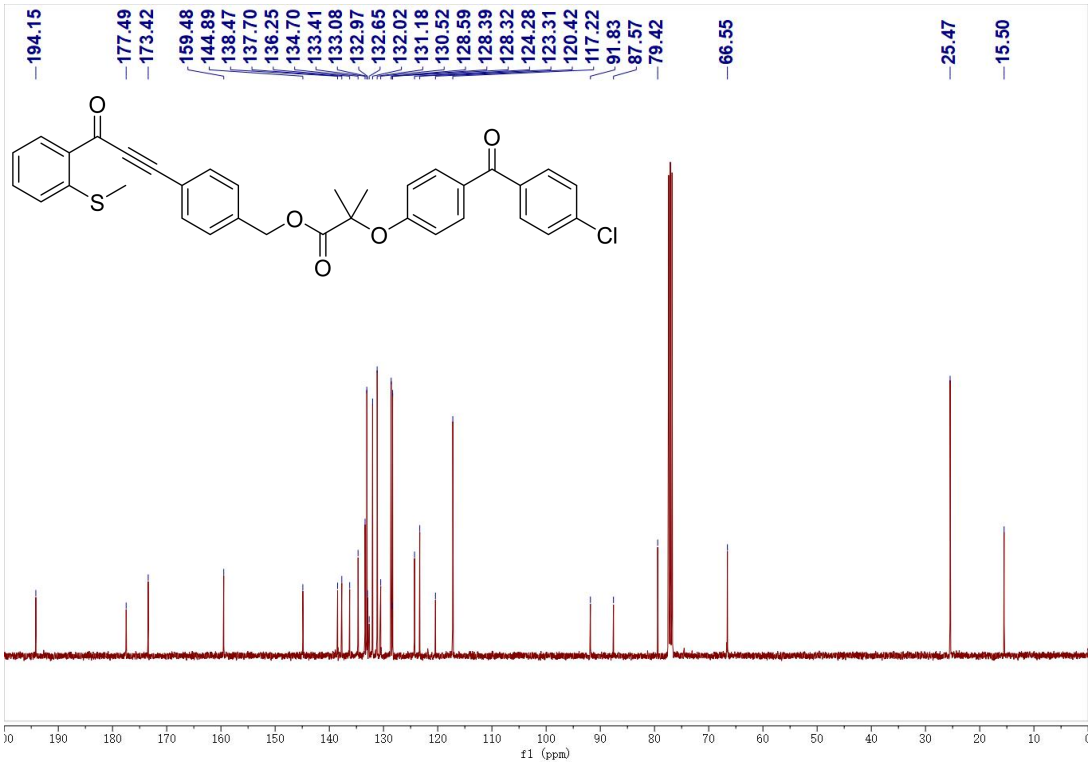
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **1al**



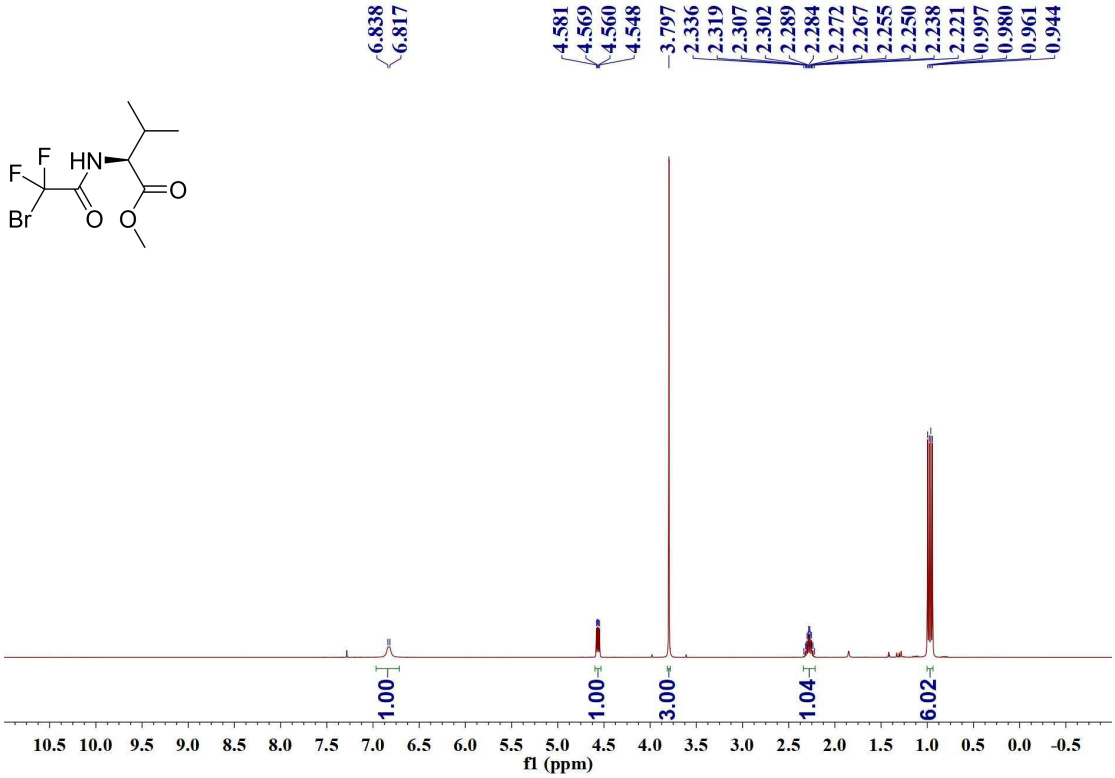
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **1am**



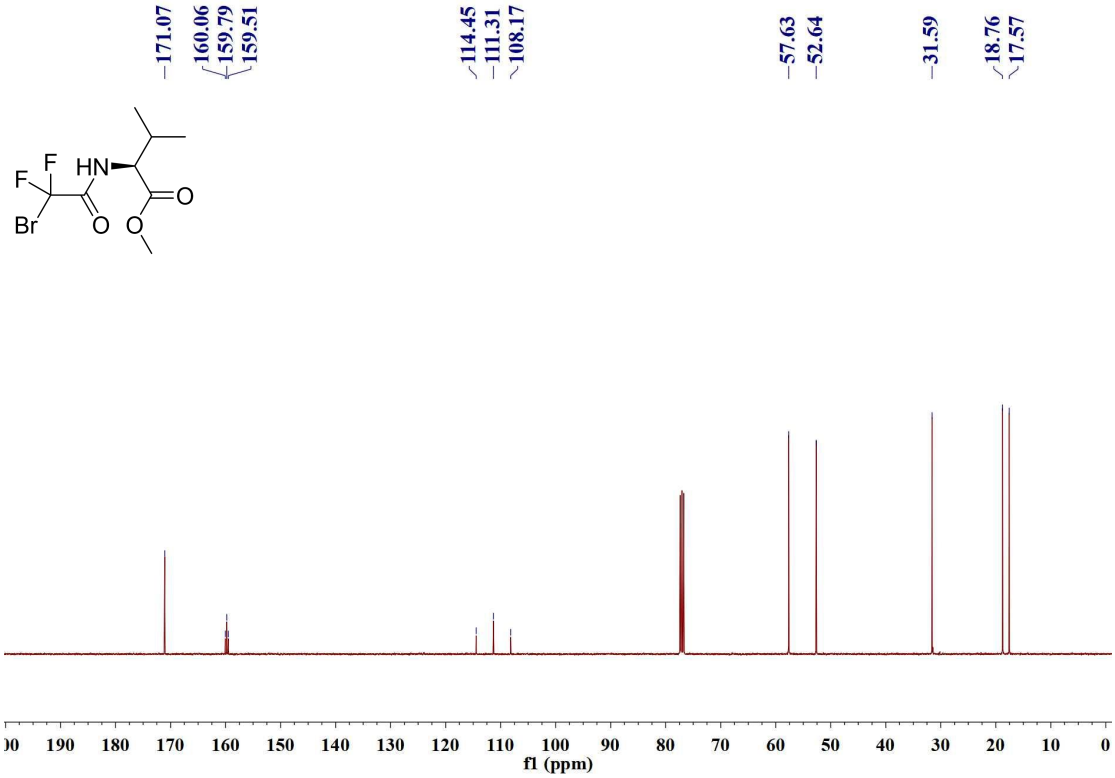
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **1am**



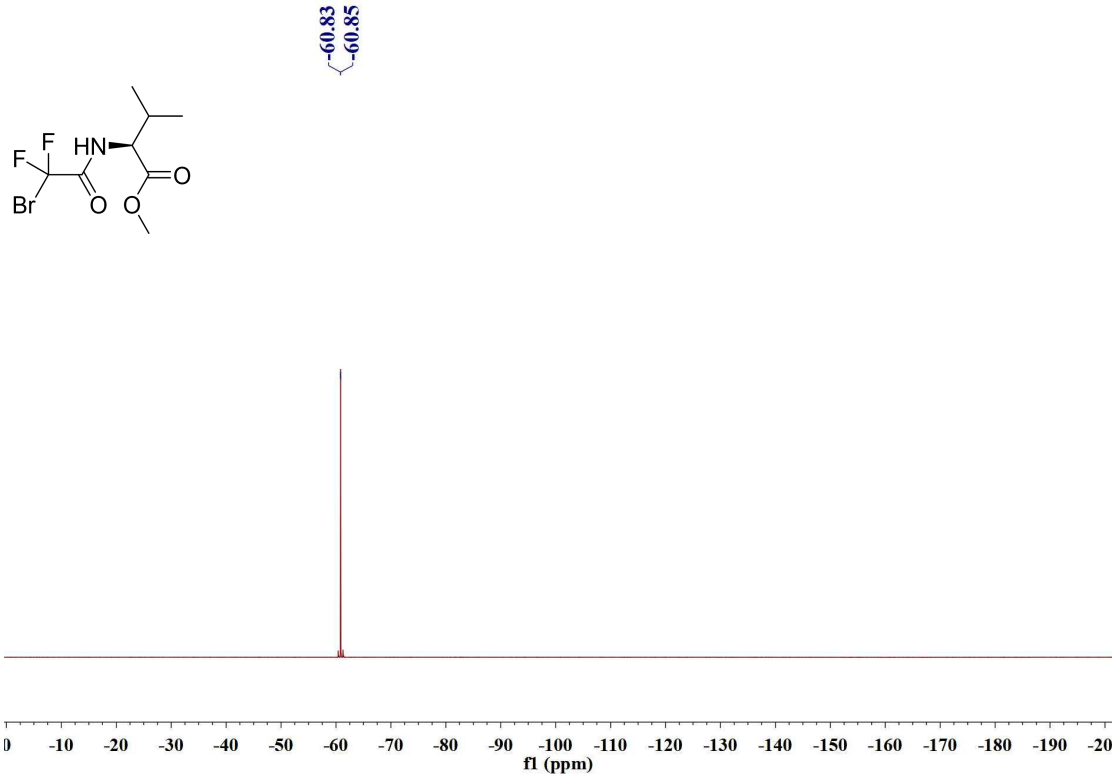
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **1an**



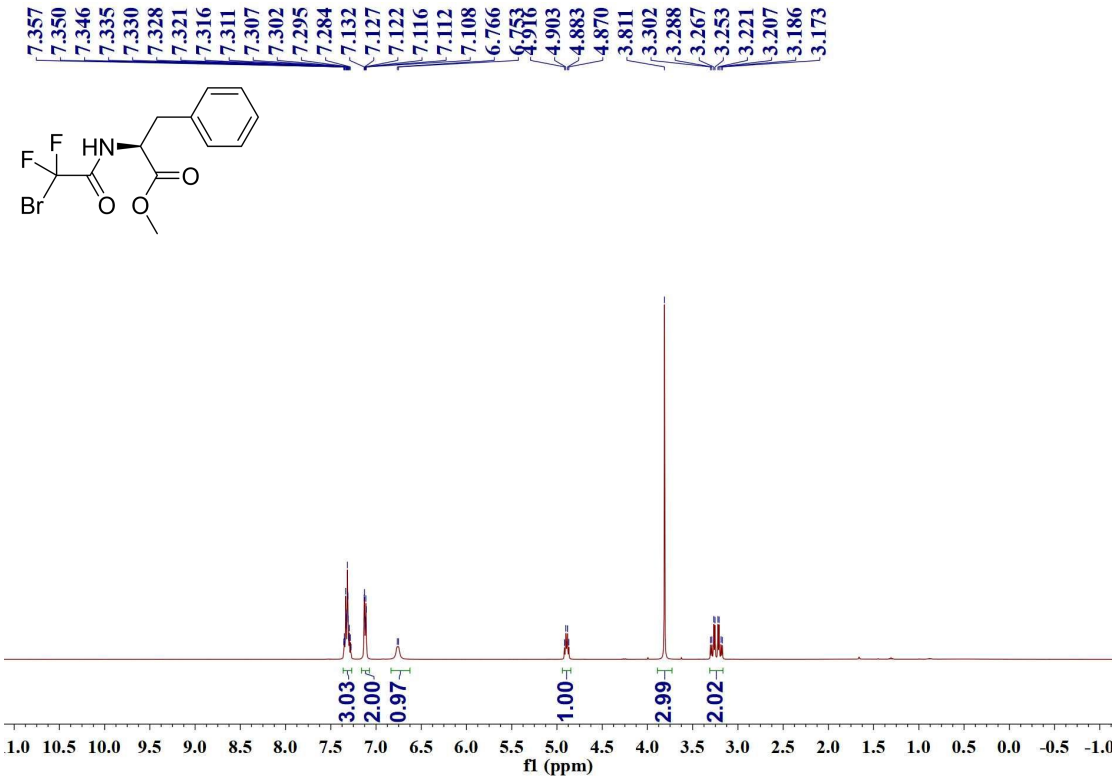
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **1an**



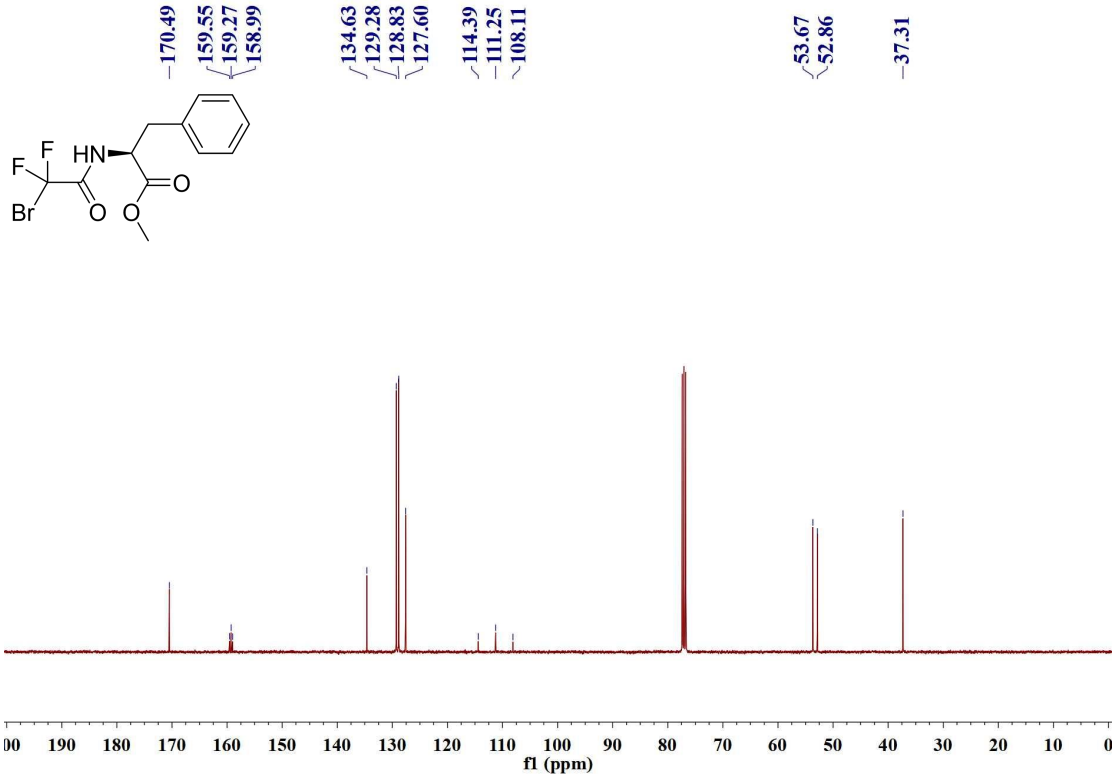
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **1an**



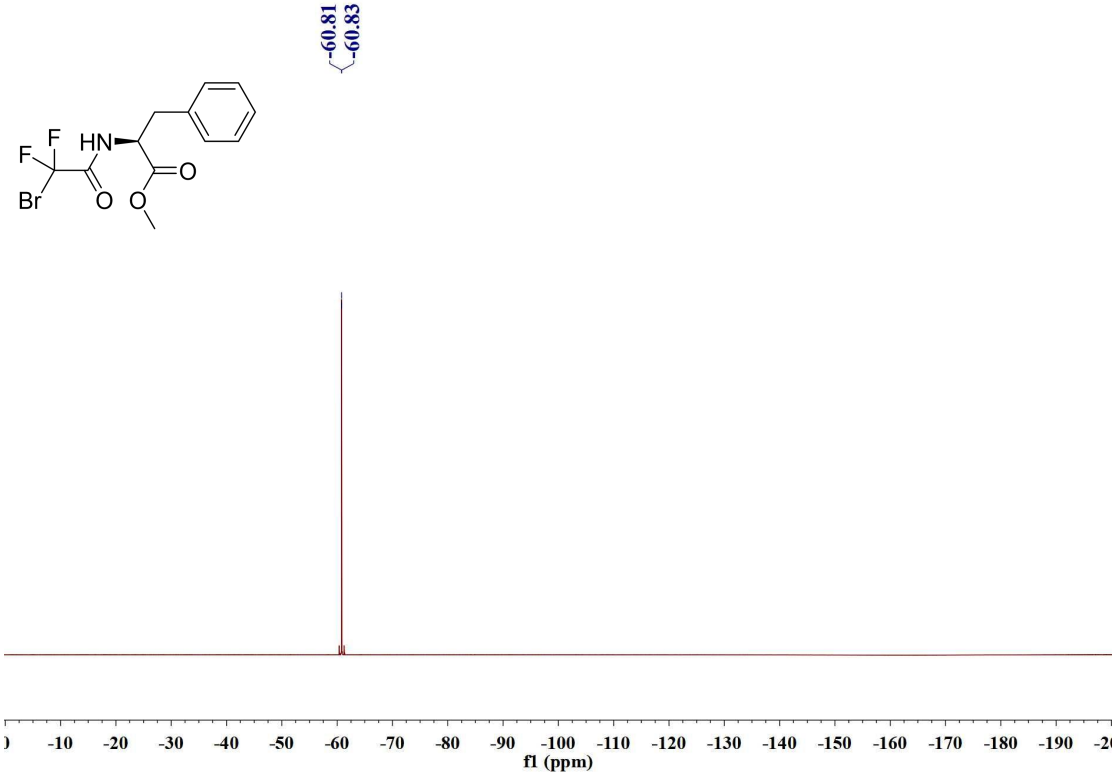
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **1ao**



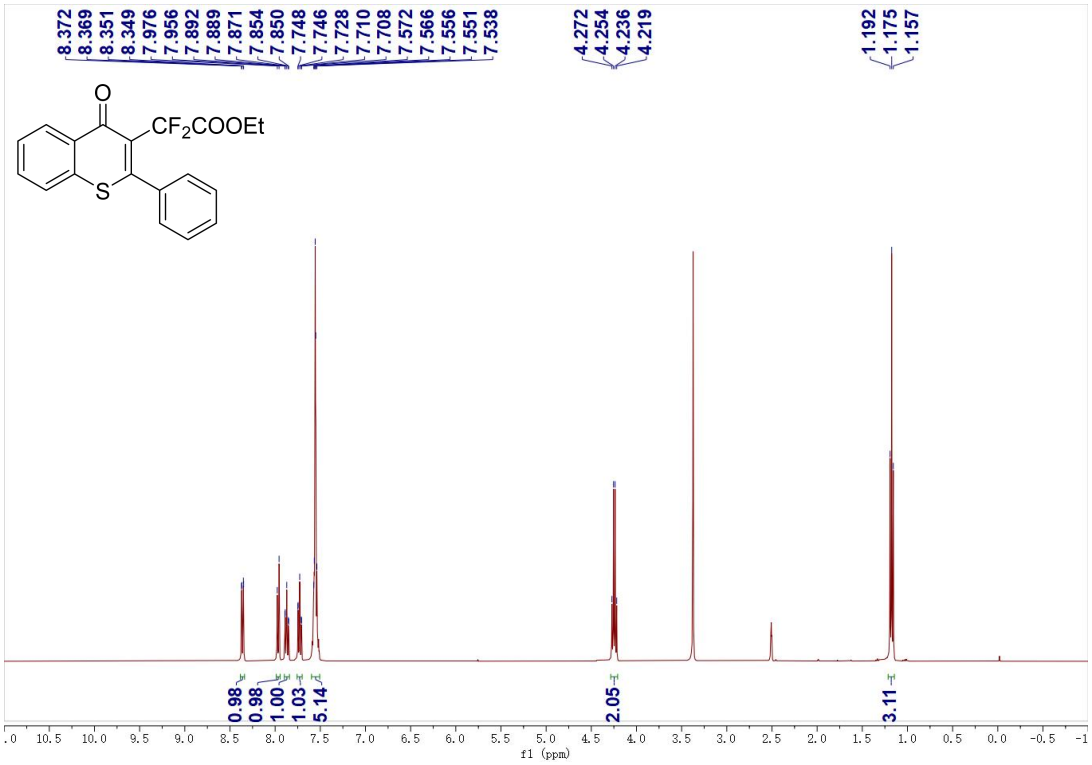
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **1ao**



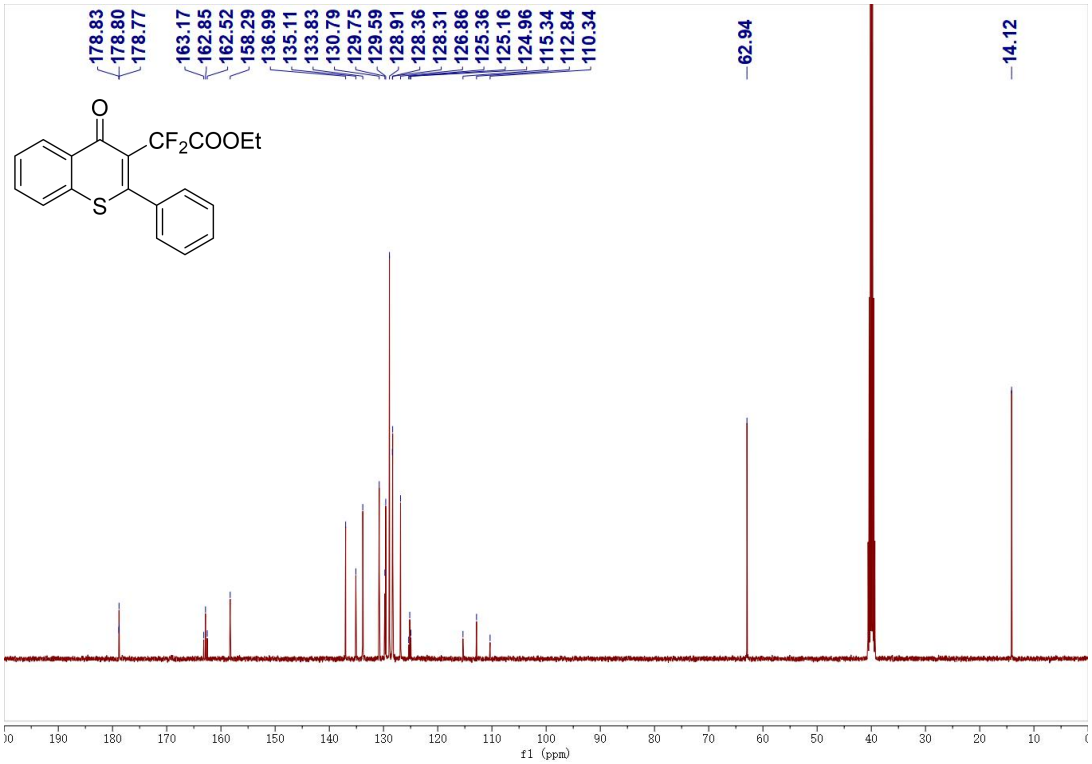
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **1ao**



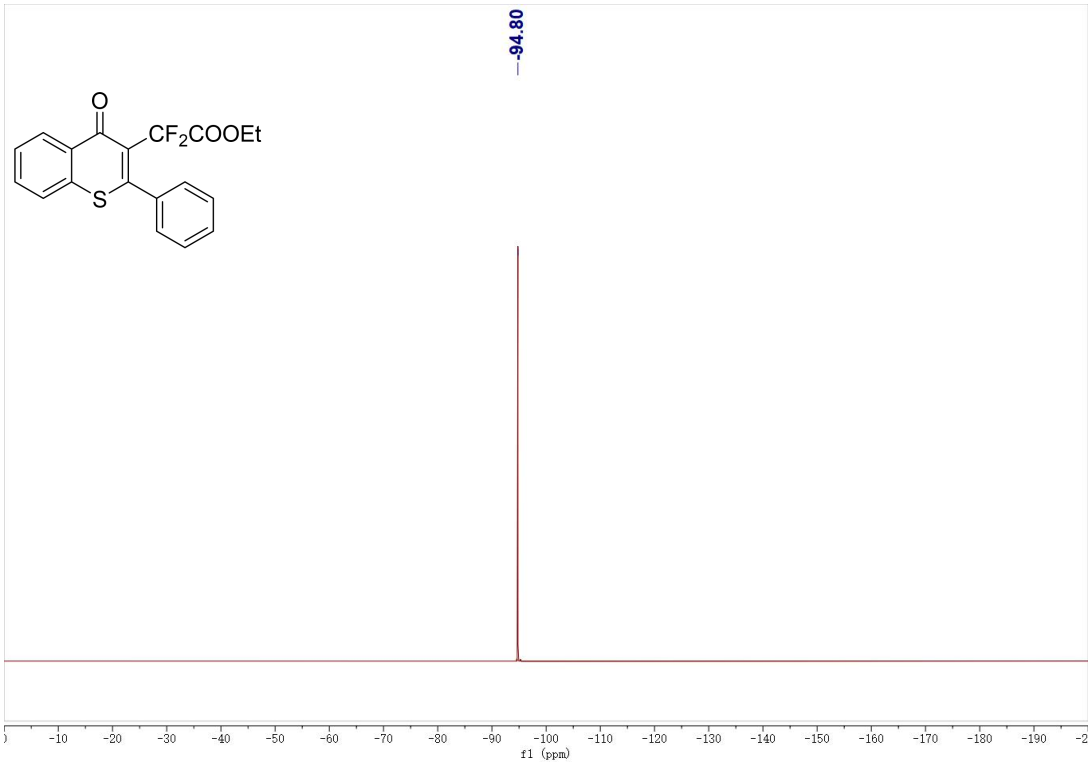
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3a**



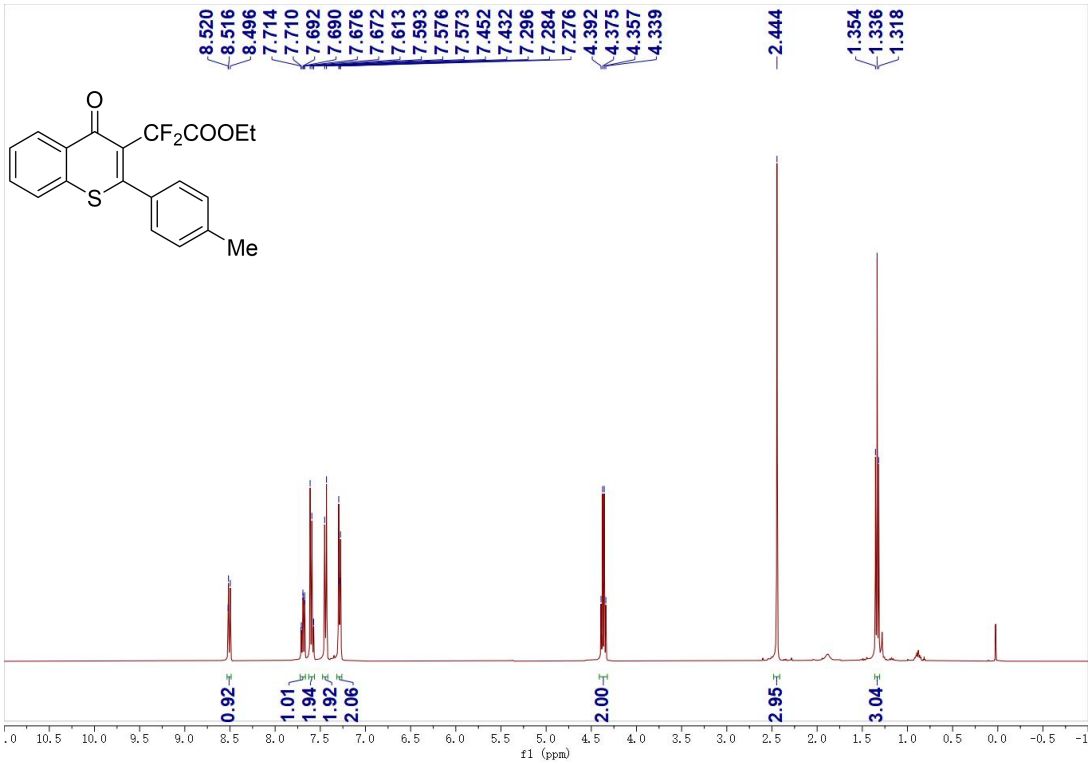
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3a**



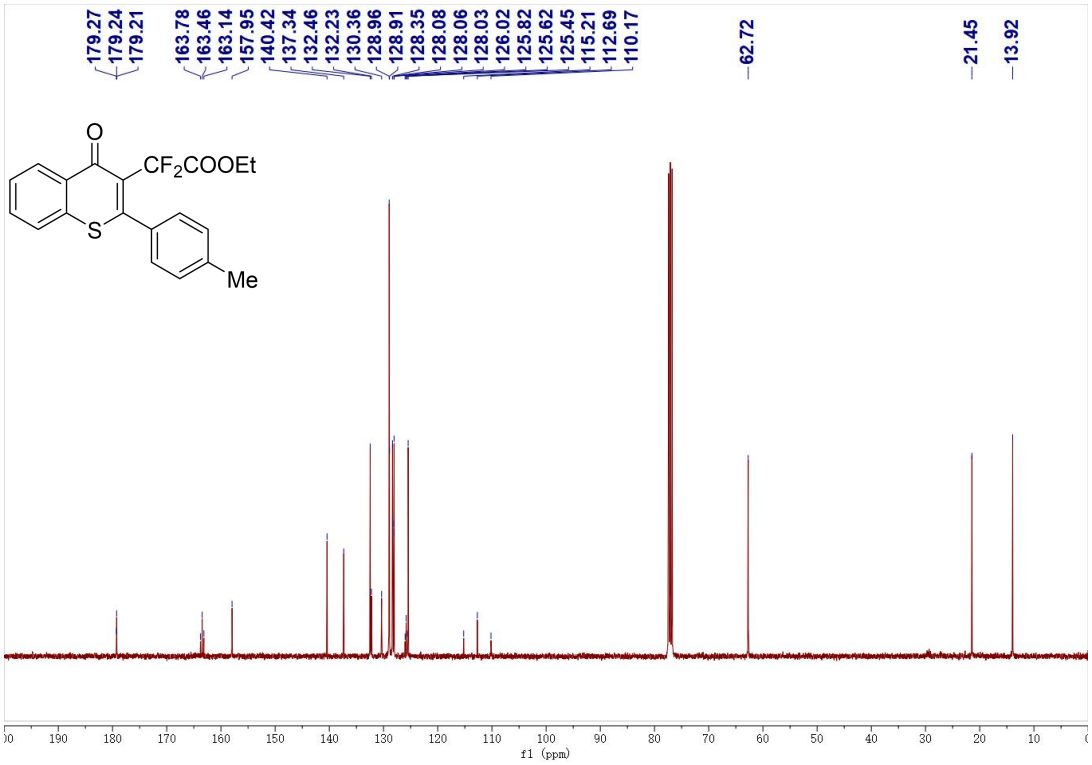
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3a**



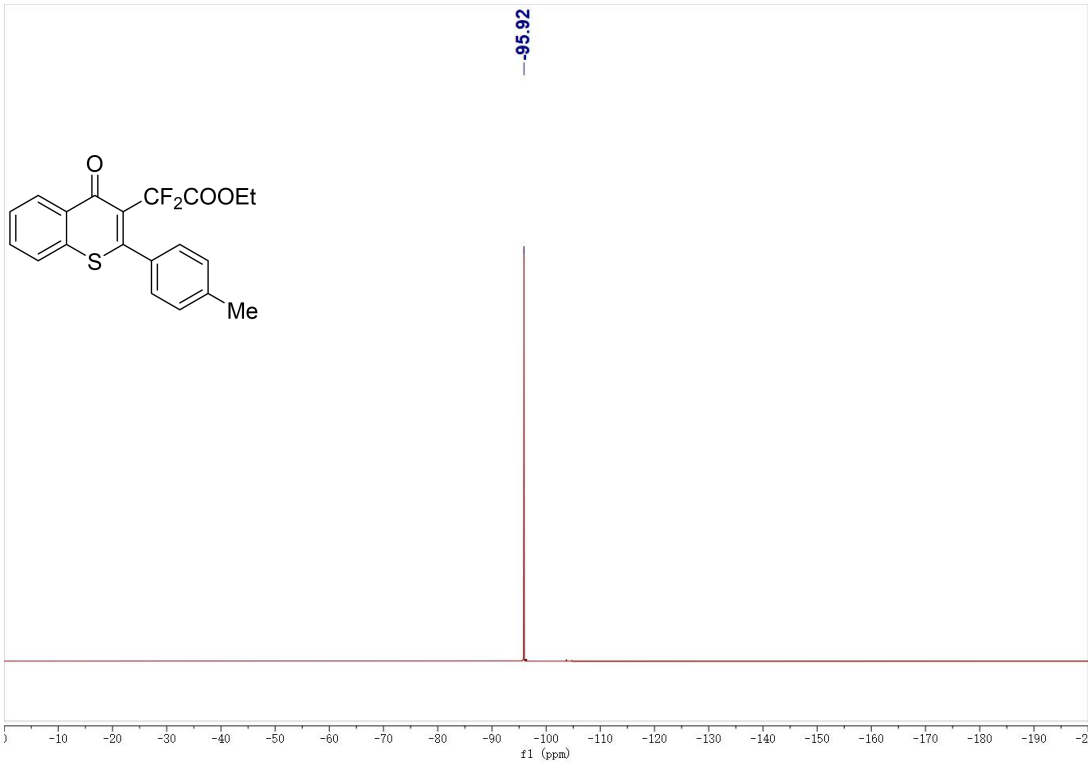
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3b**



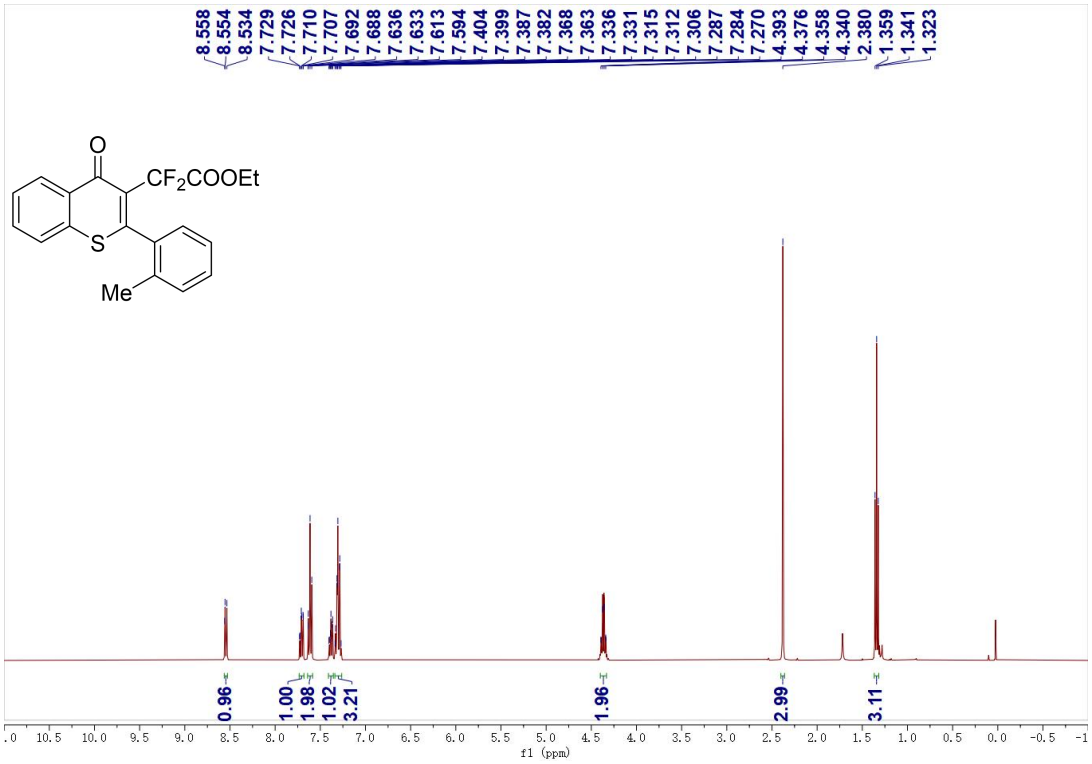
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3b**



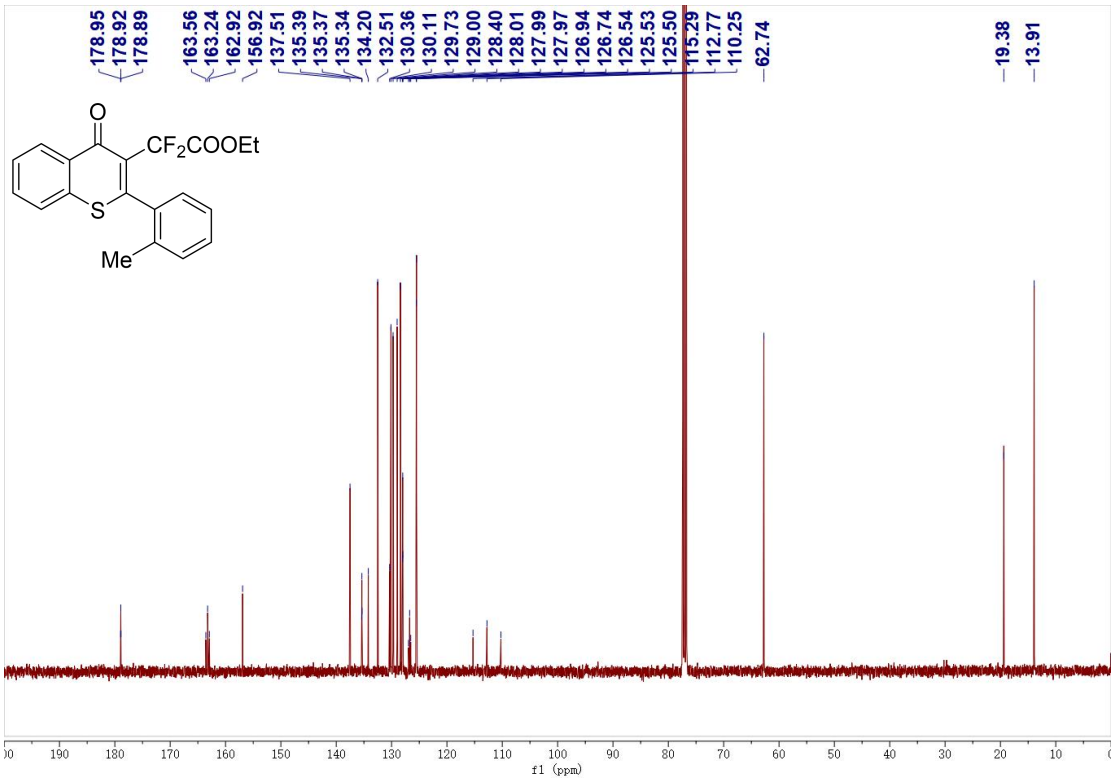
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3b**



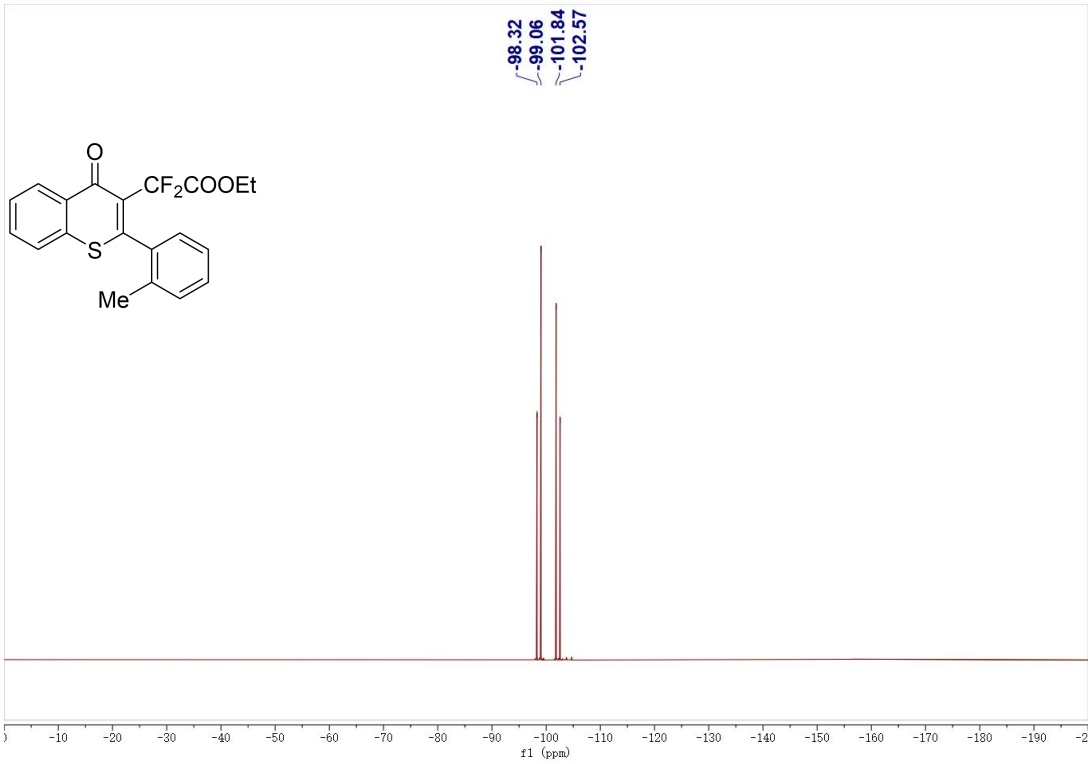
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3c**



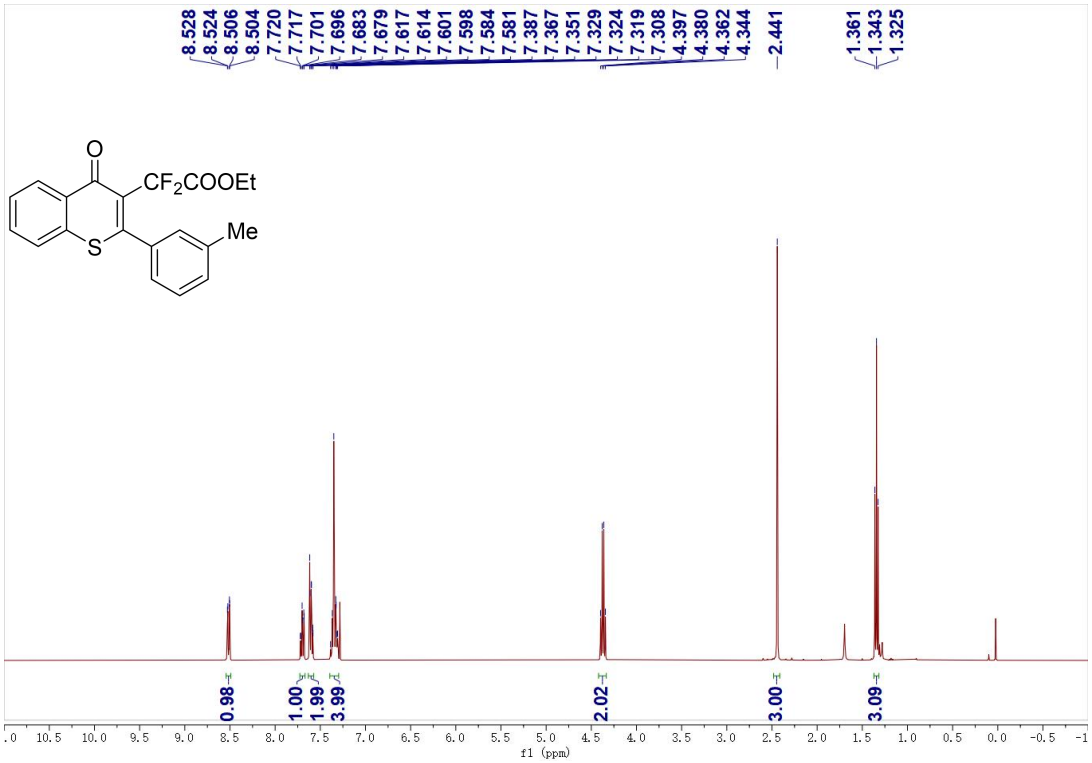
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3c**



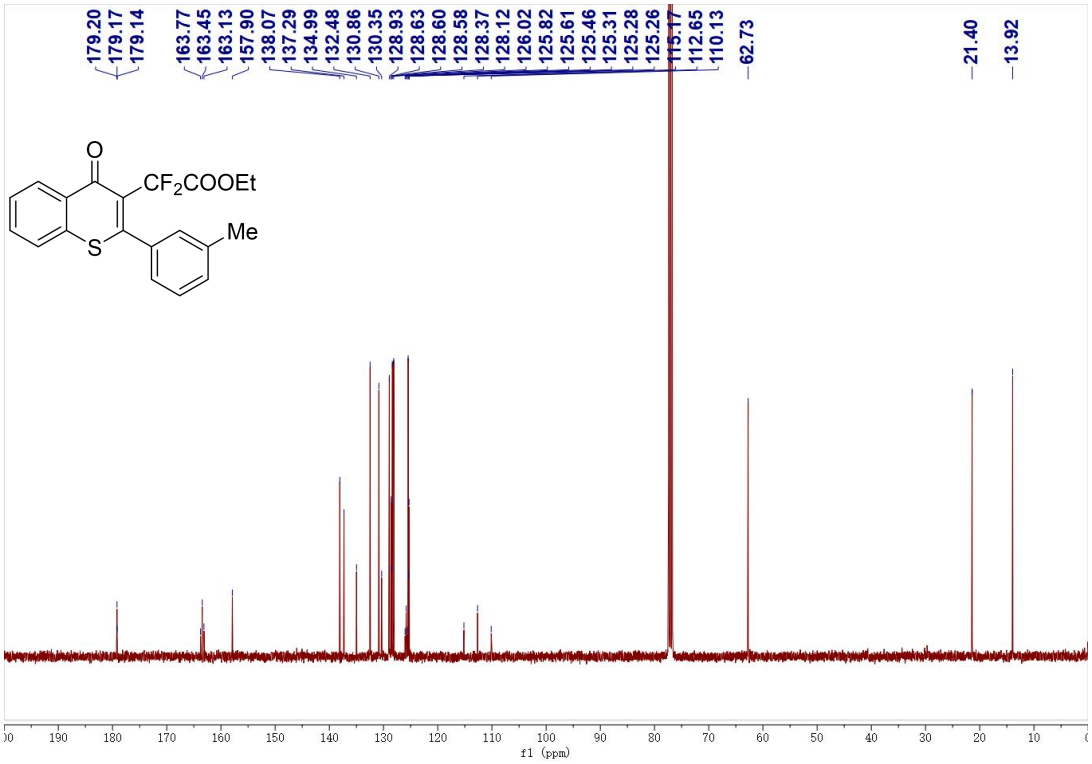
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3c**



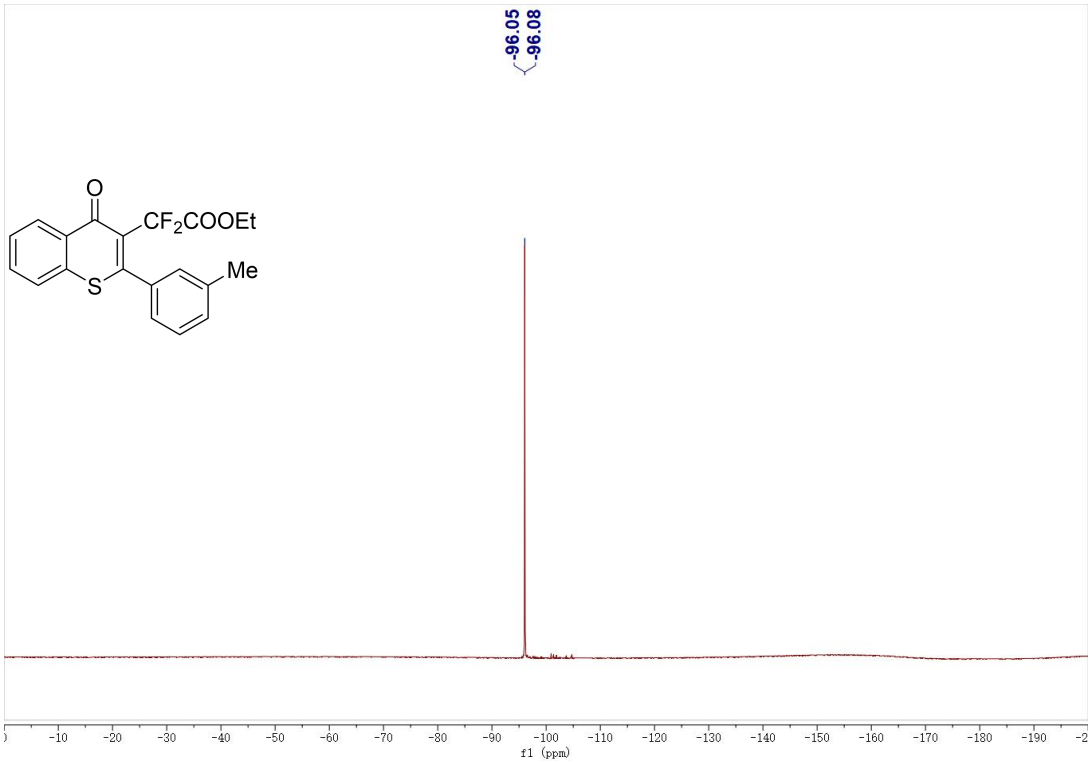
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3d**



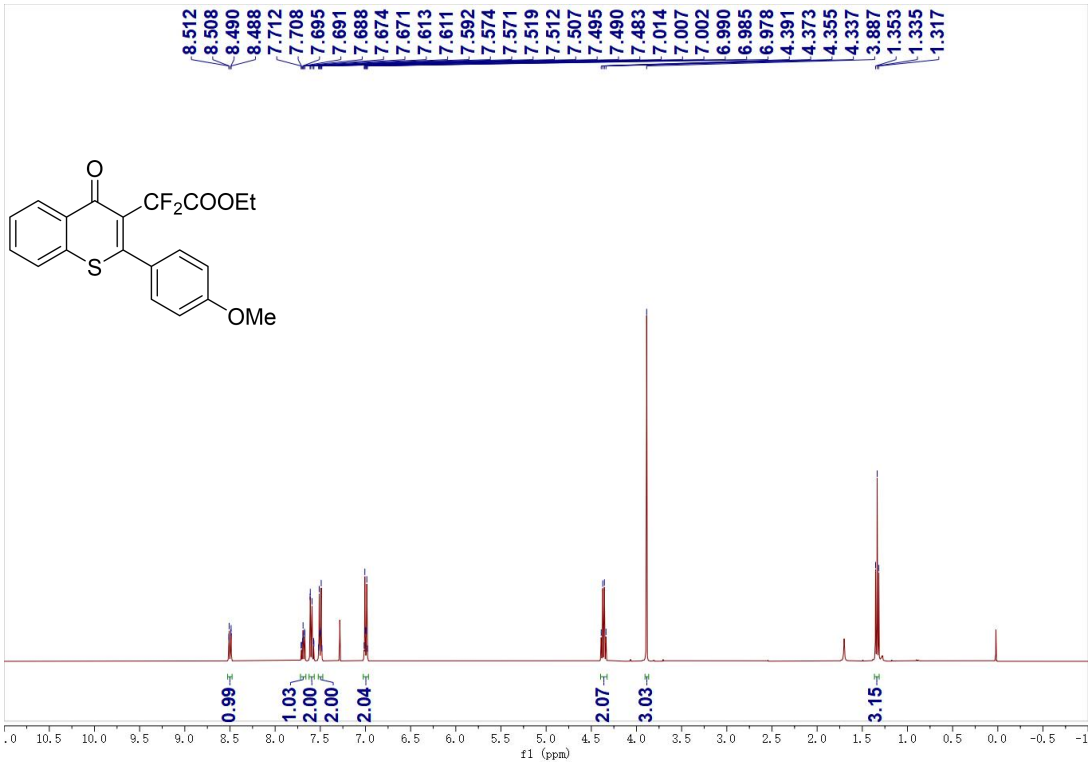
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3d**



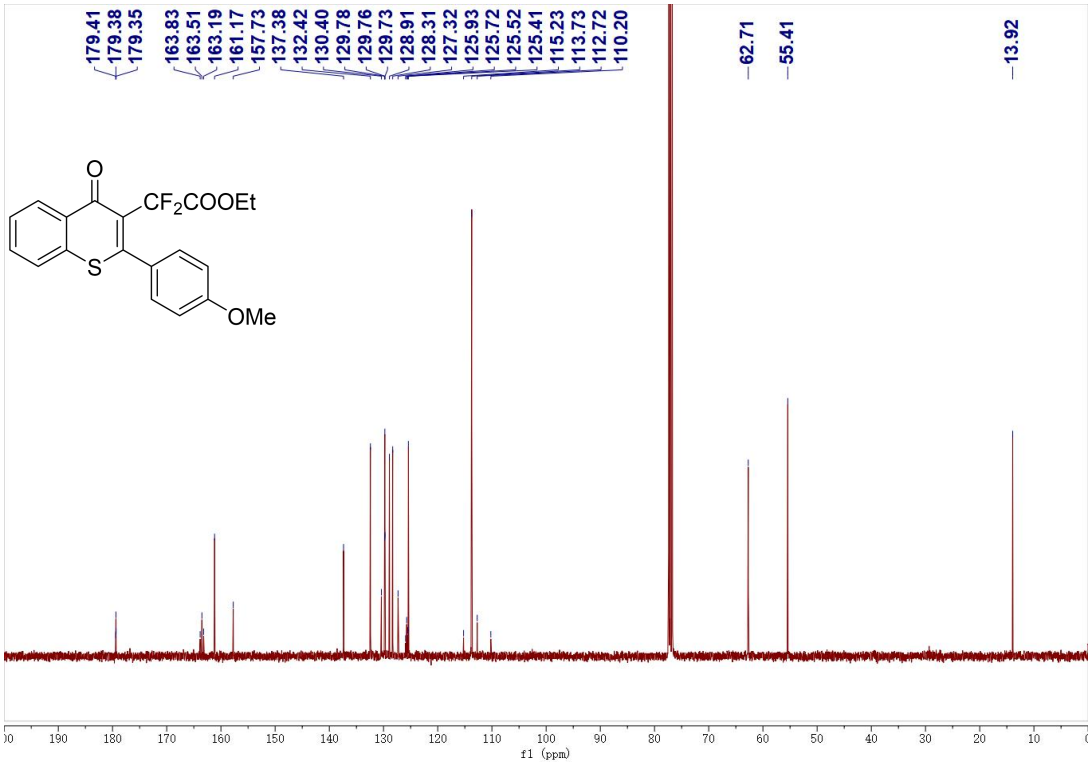
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3d**



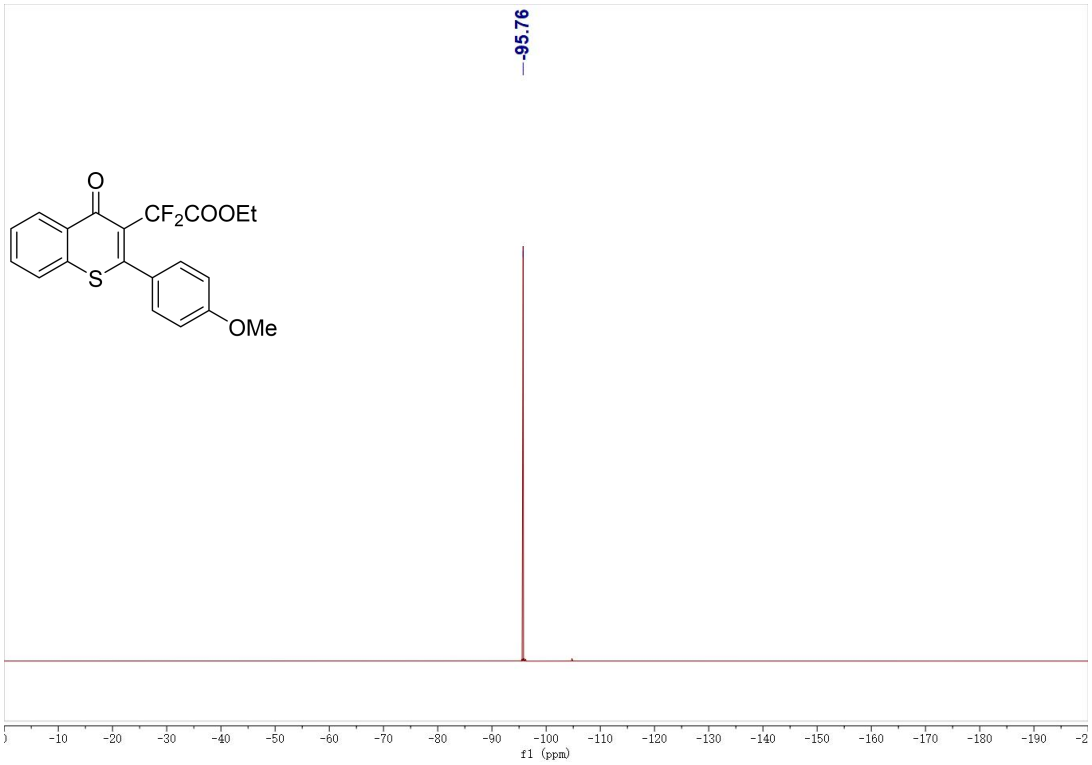
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3e**



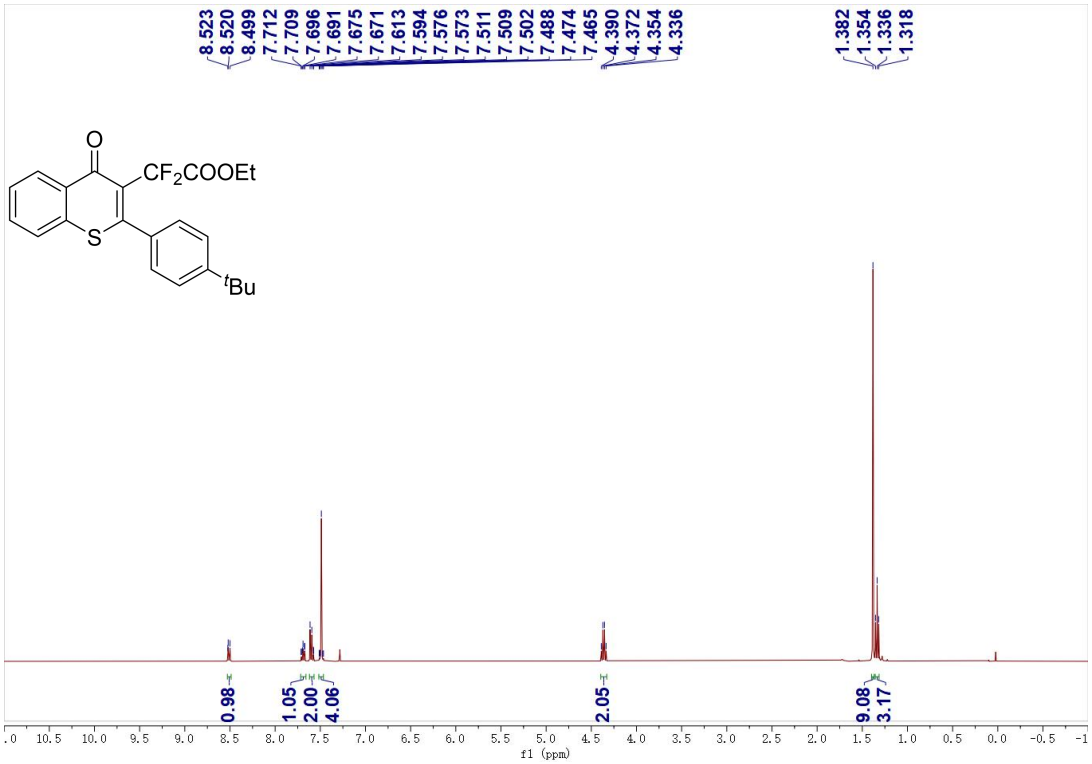
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3e**



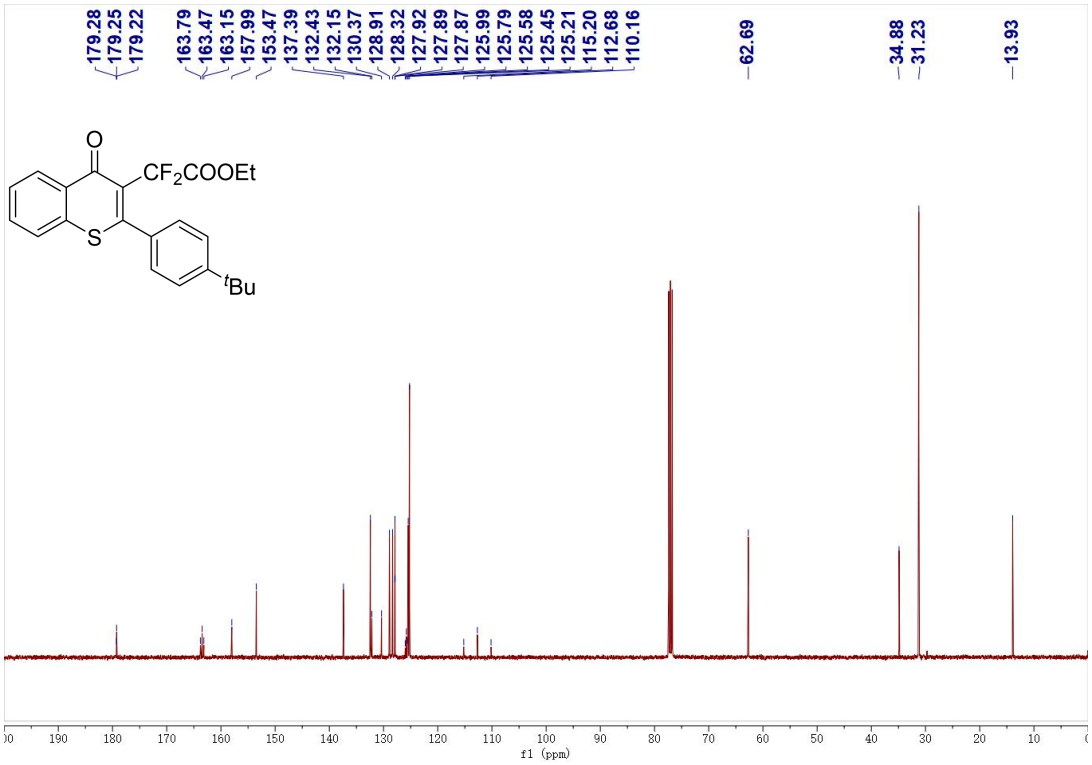
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3e**



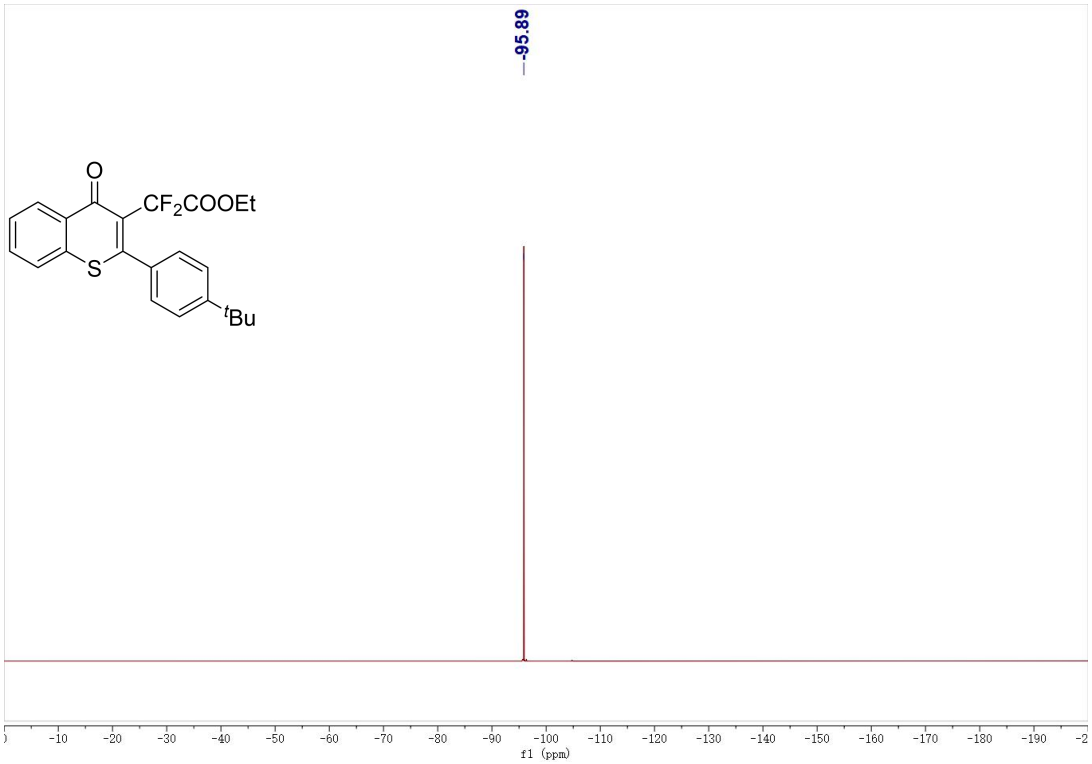
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3f**



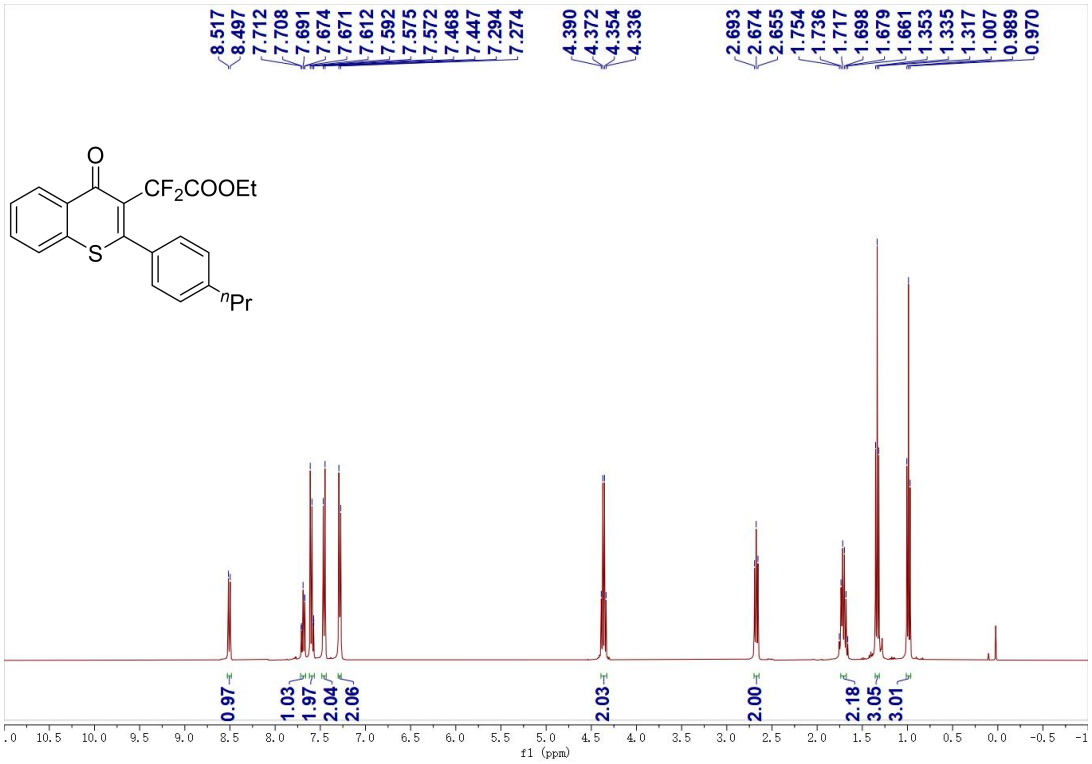
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3f**



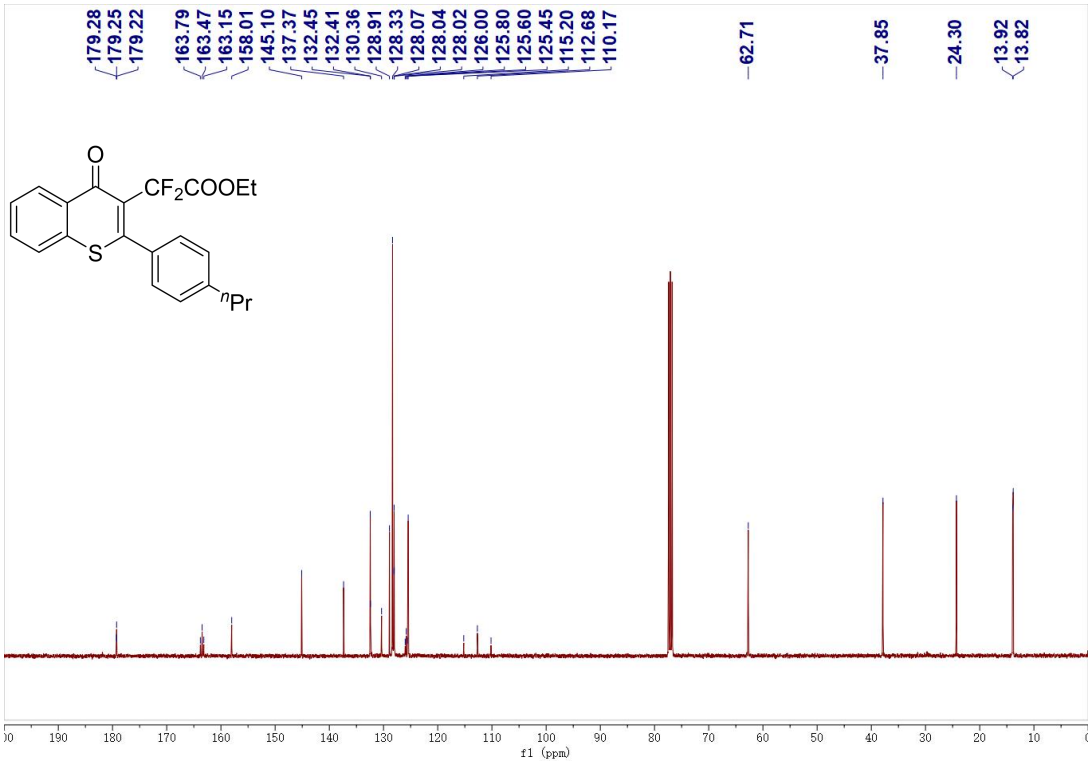
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3f**



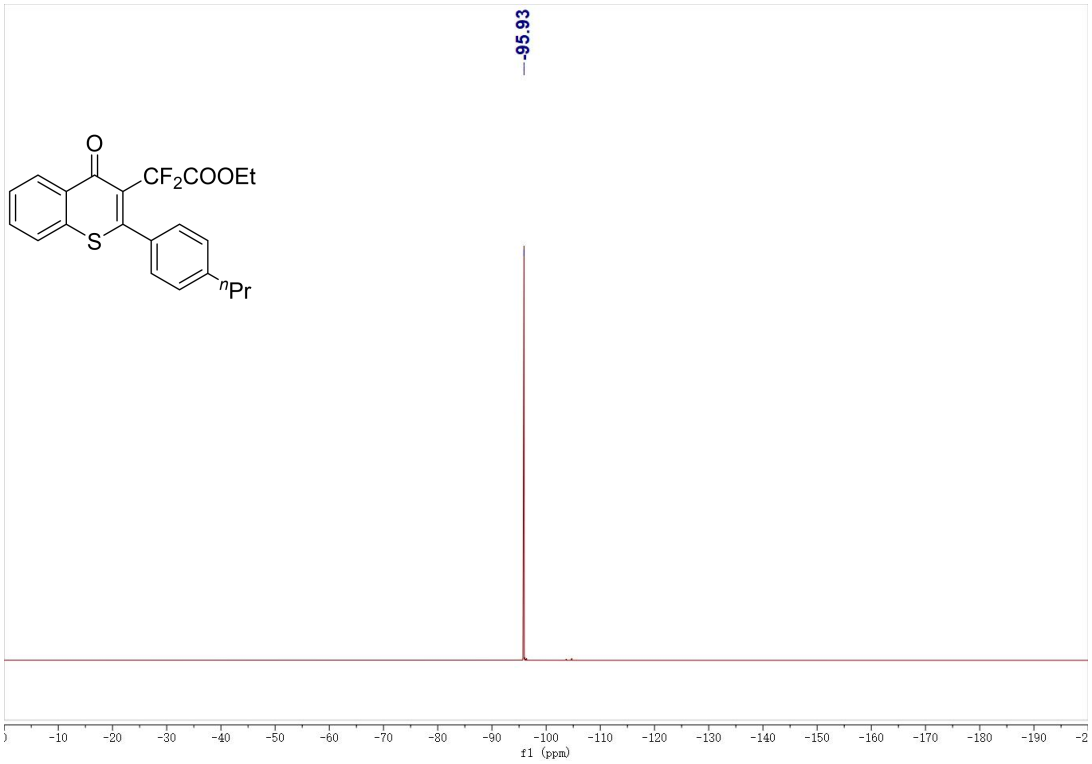
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3g**



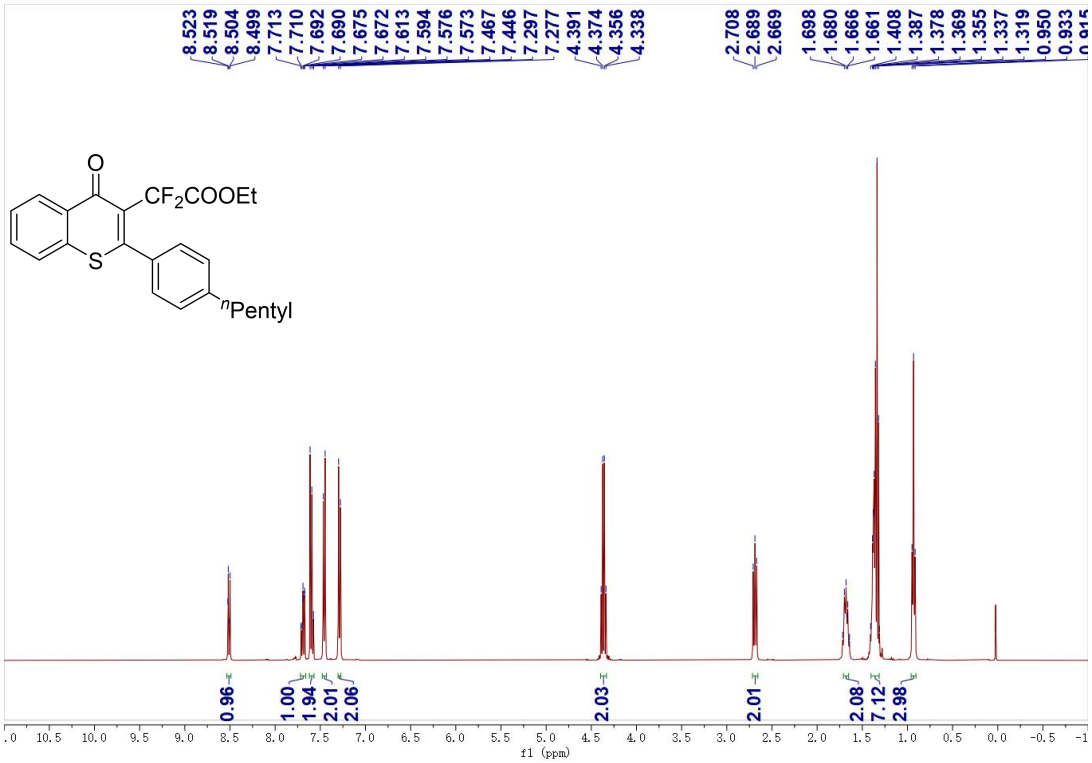
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3g**



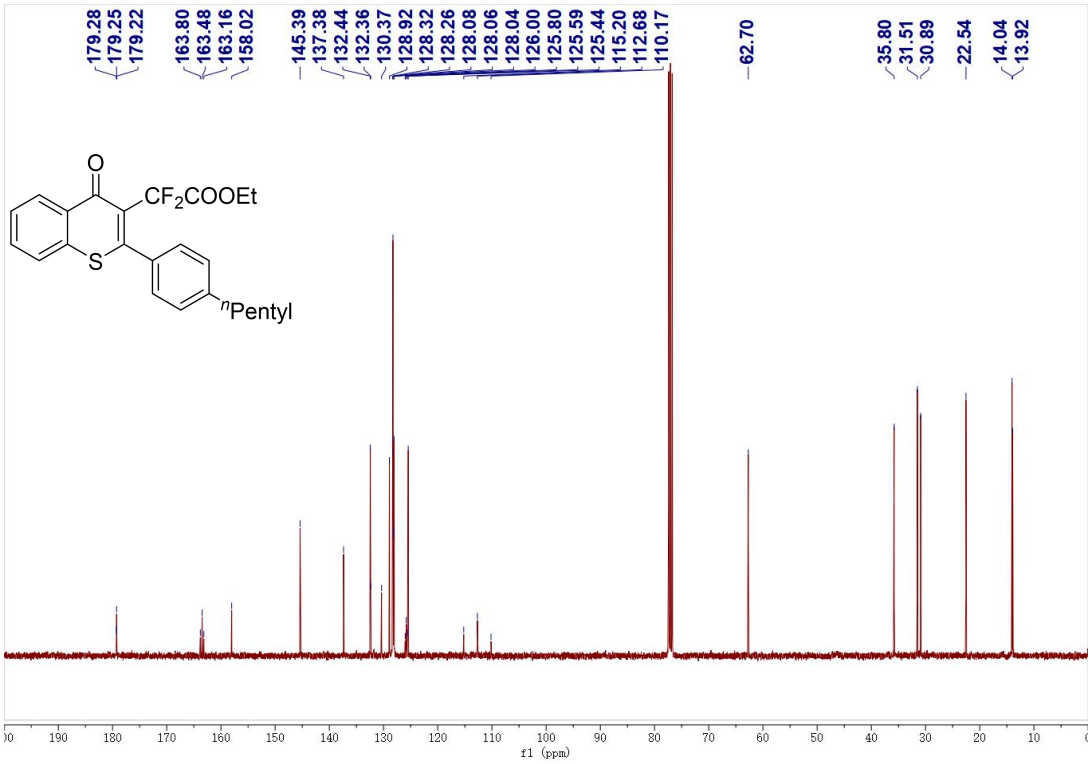
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3g**



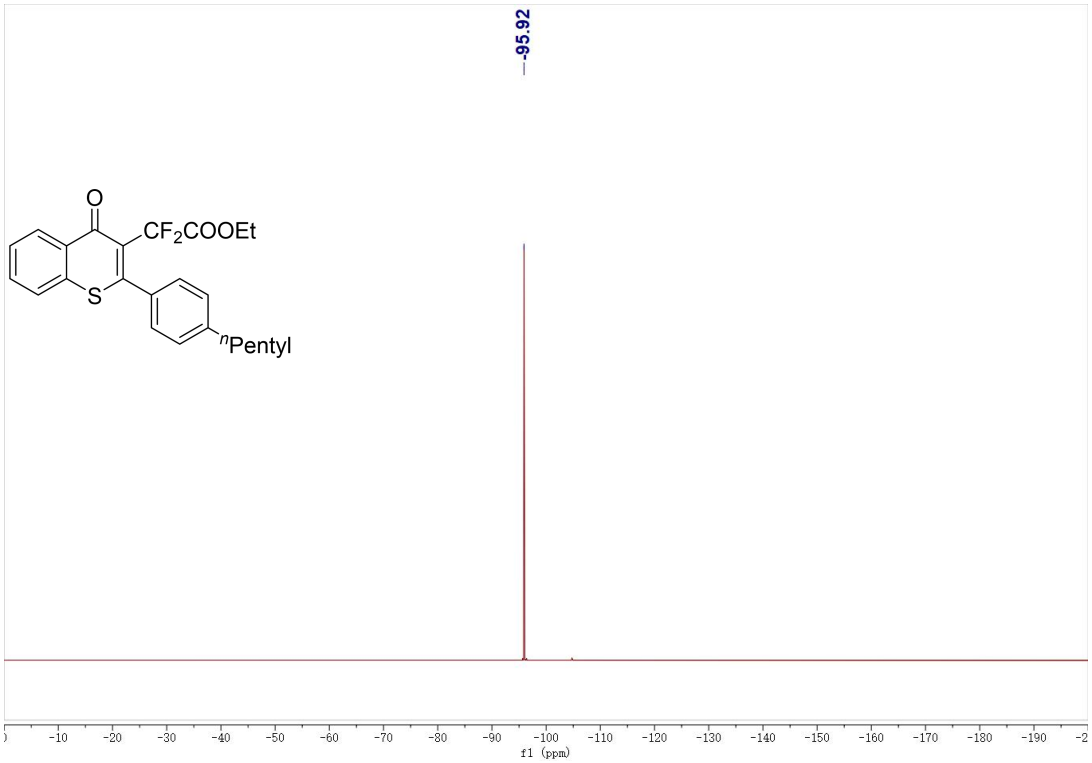
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3h**



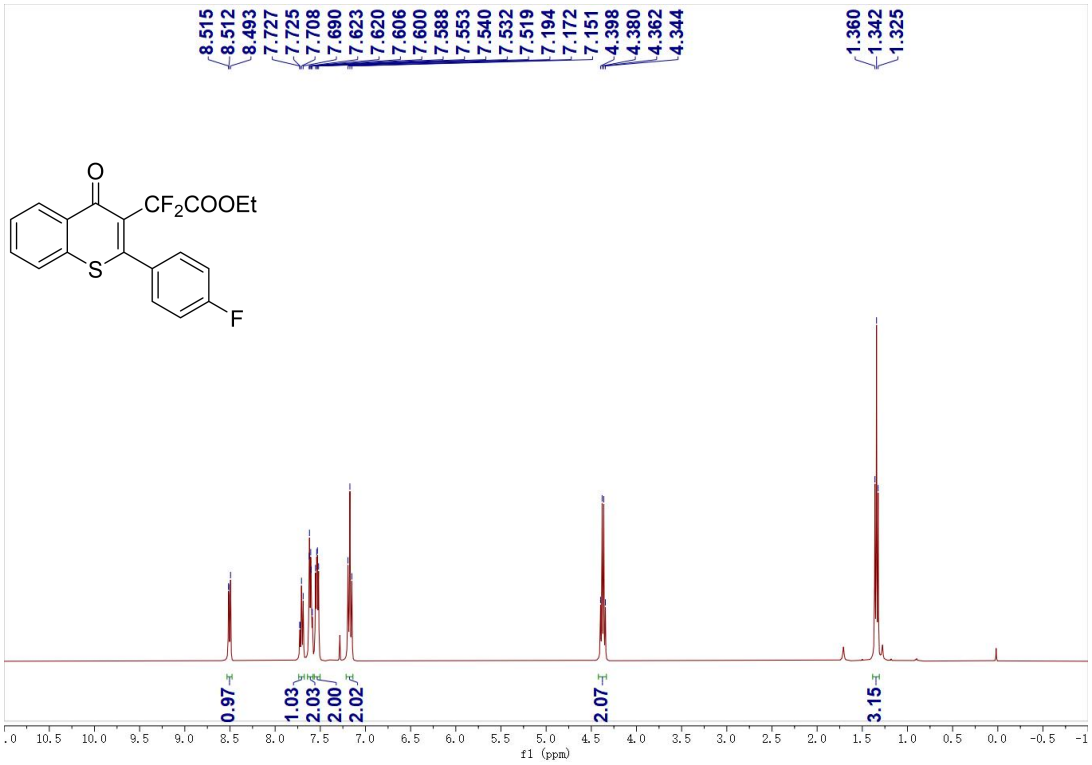
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3h**



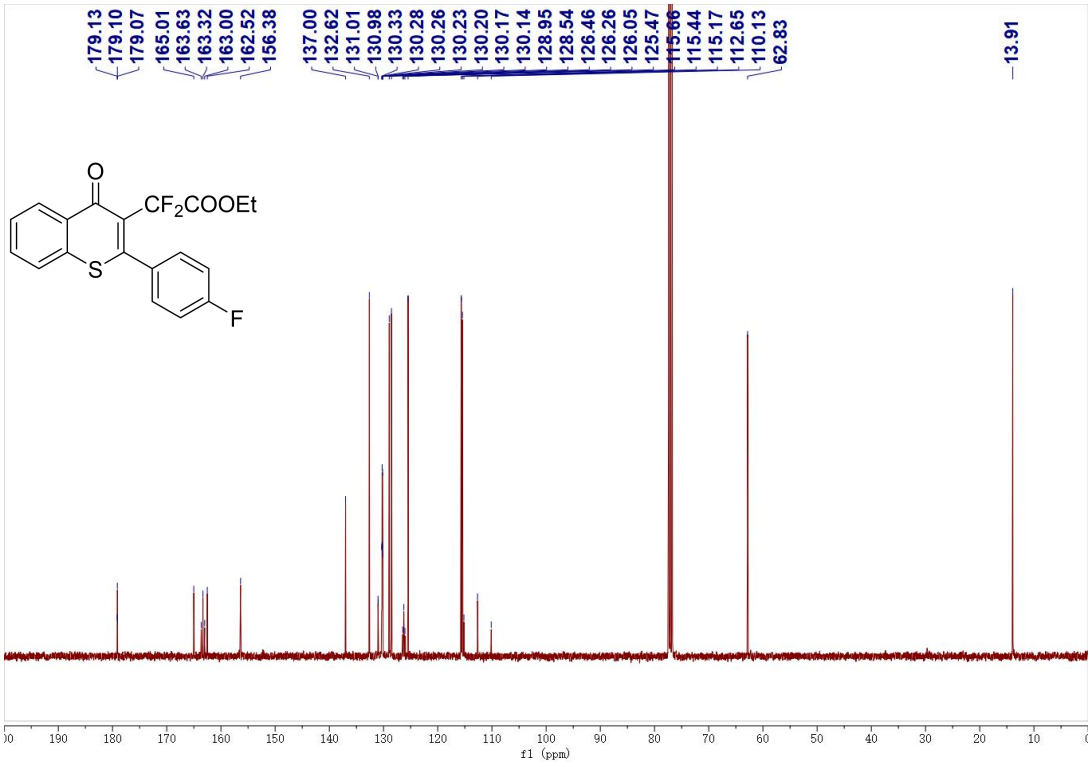
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3h**



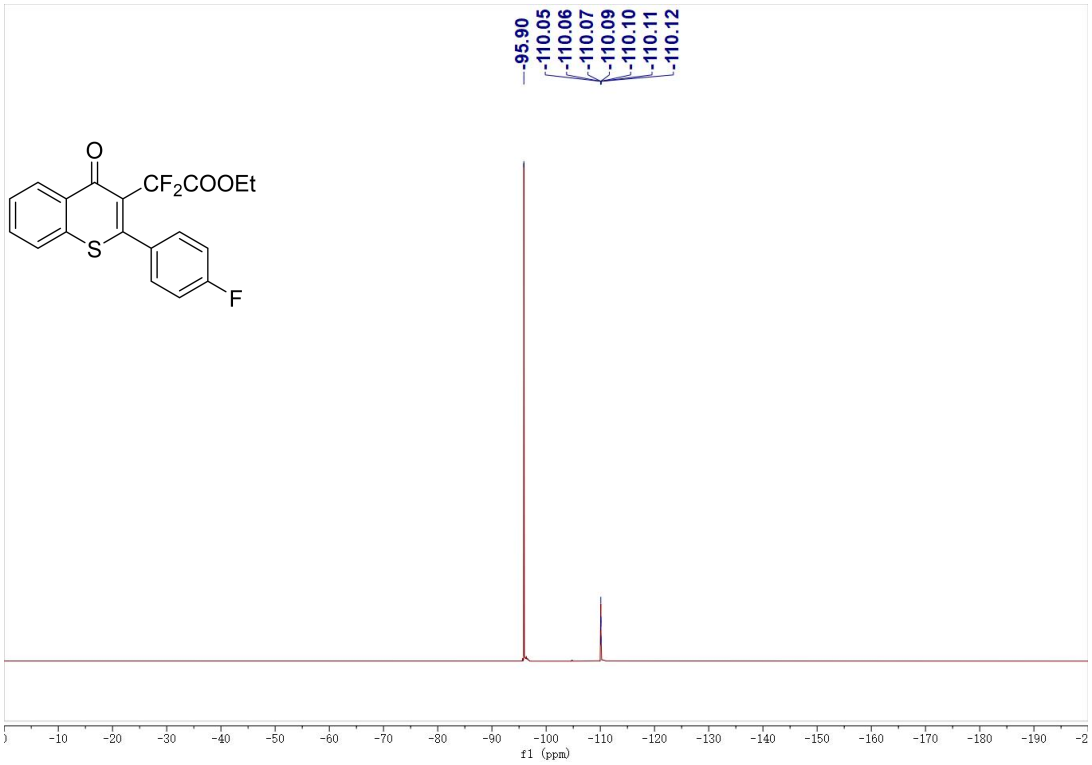
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3i**



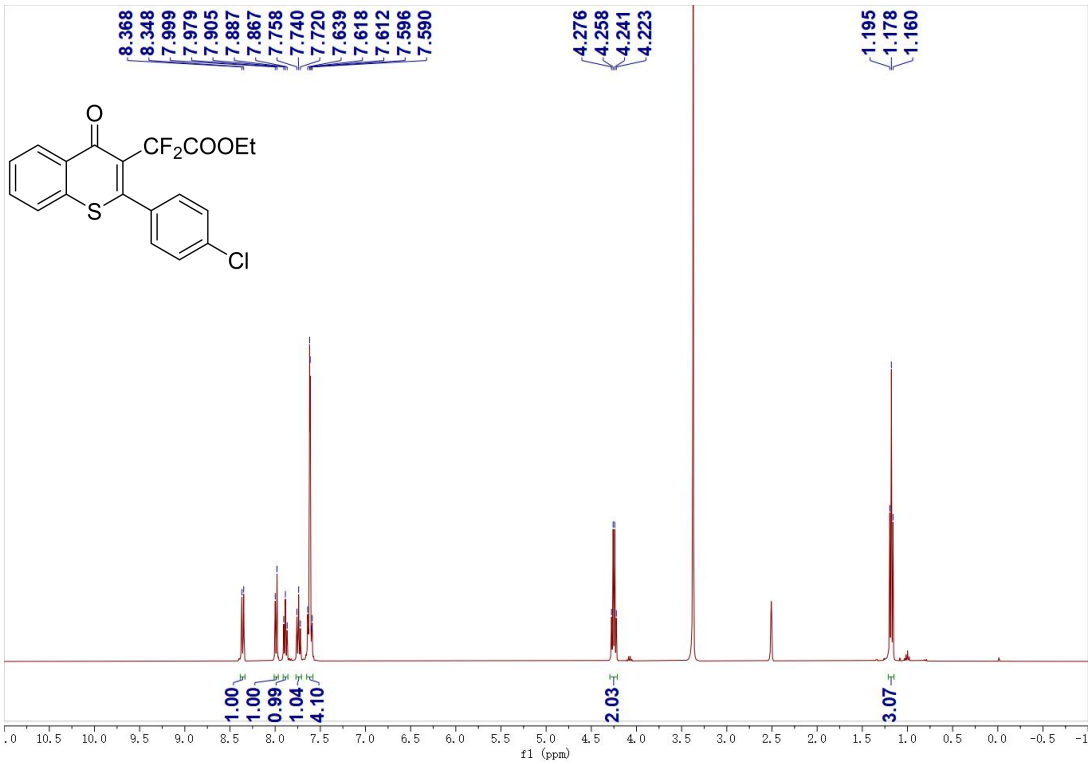
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3i**



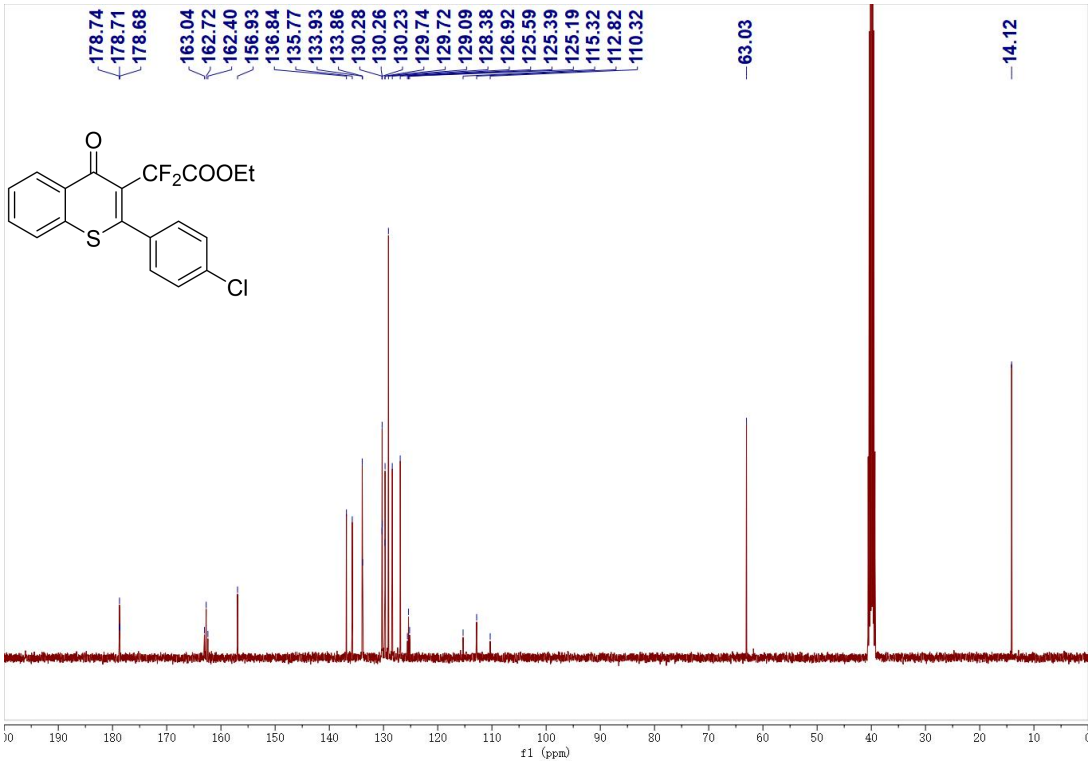
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3i**



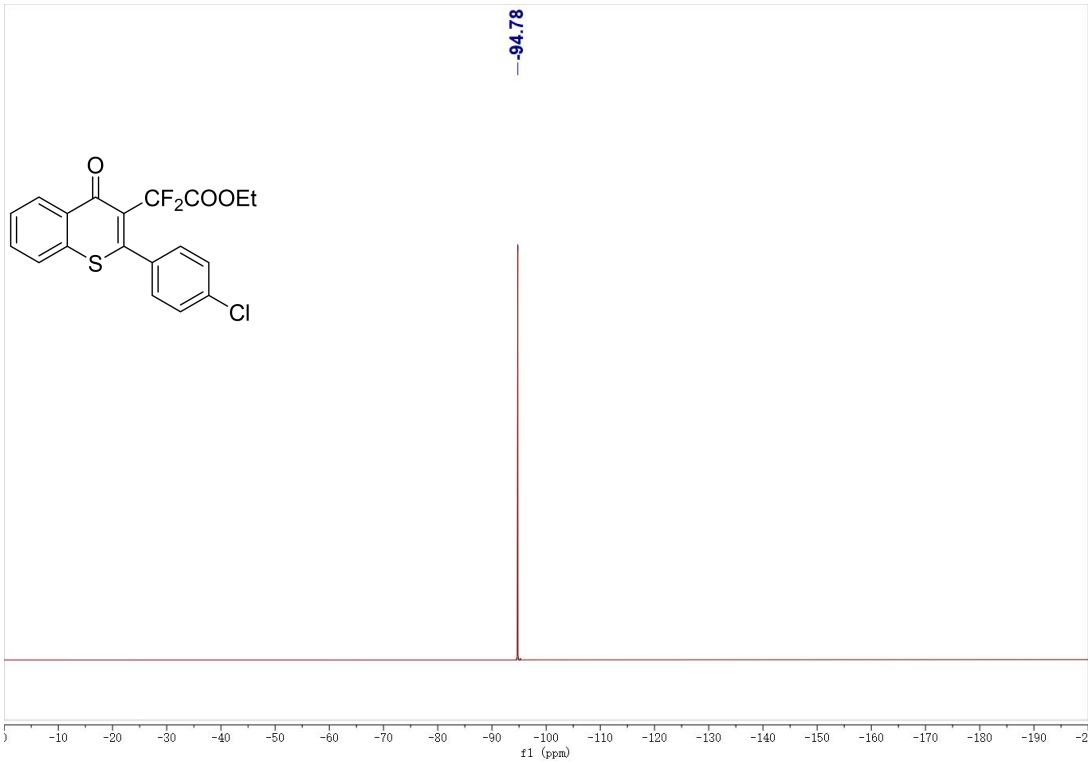
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3j**



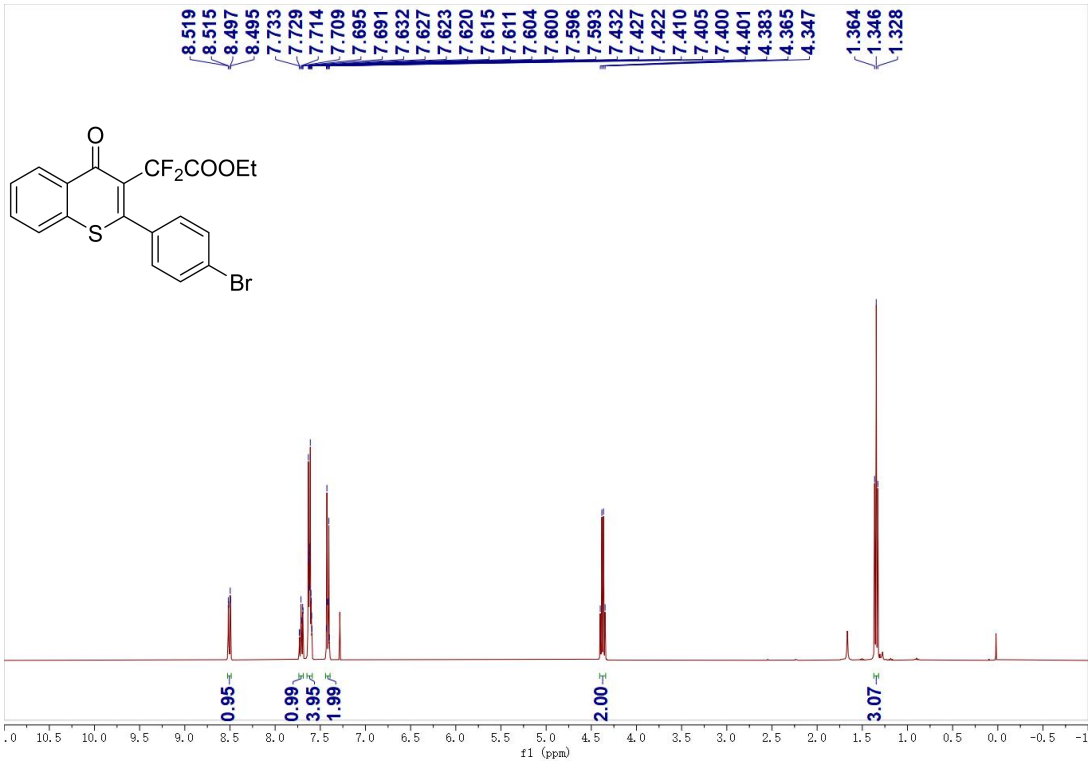
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3j**



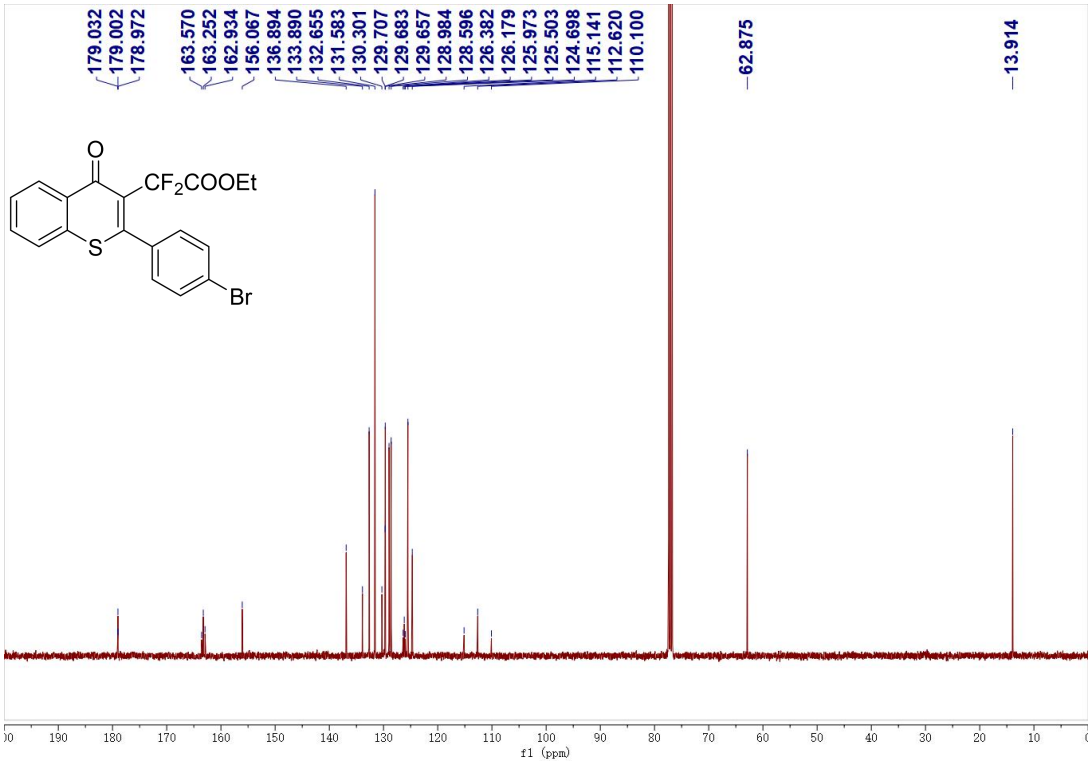
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3j**



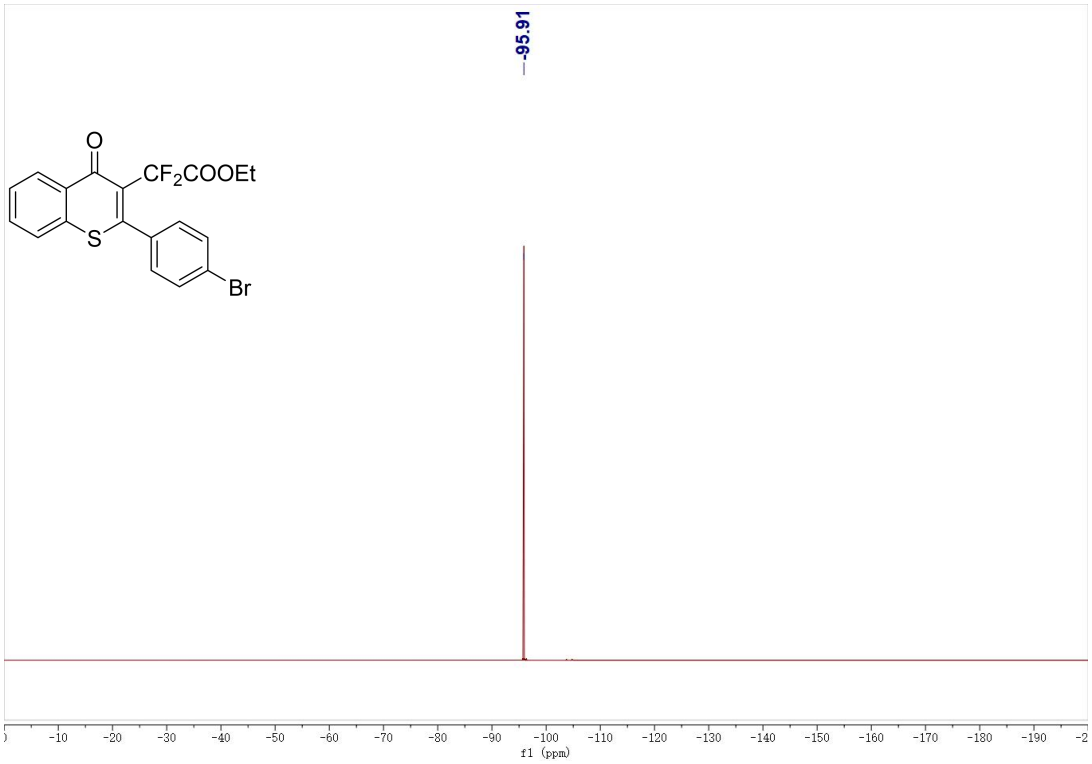
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3k**



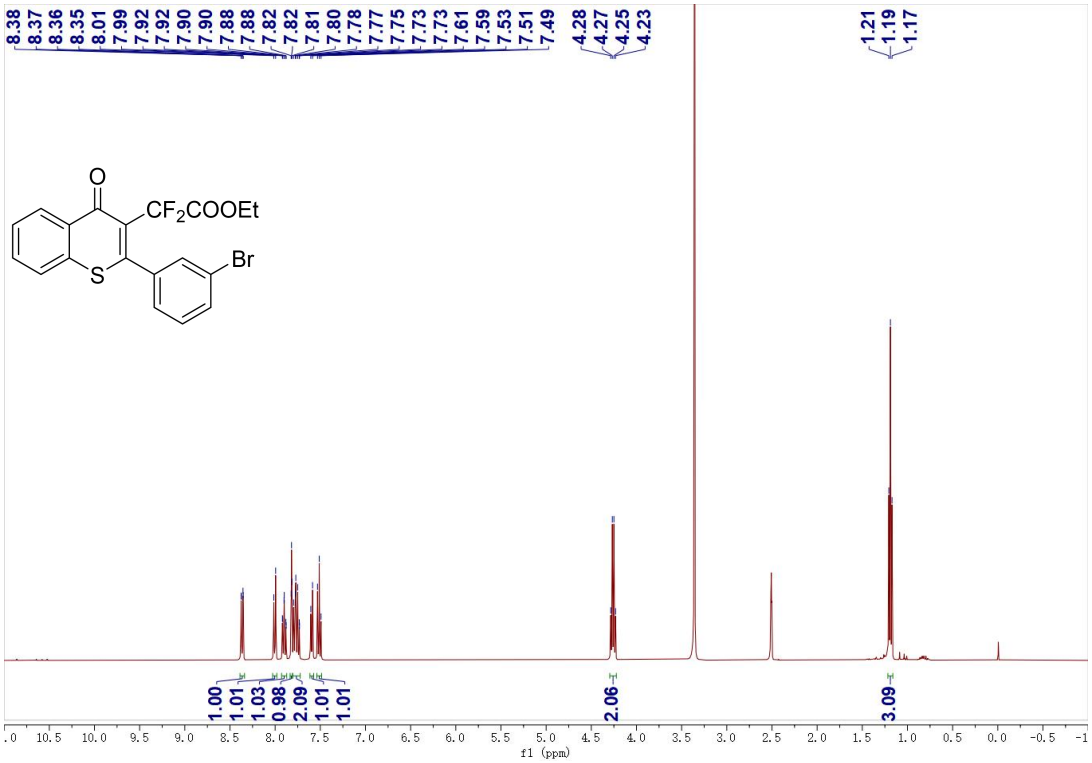
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3k**



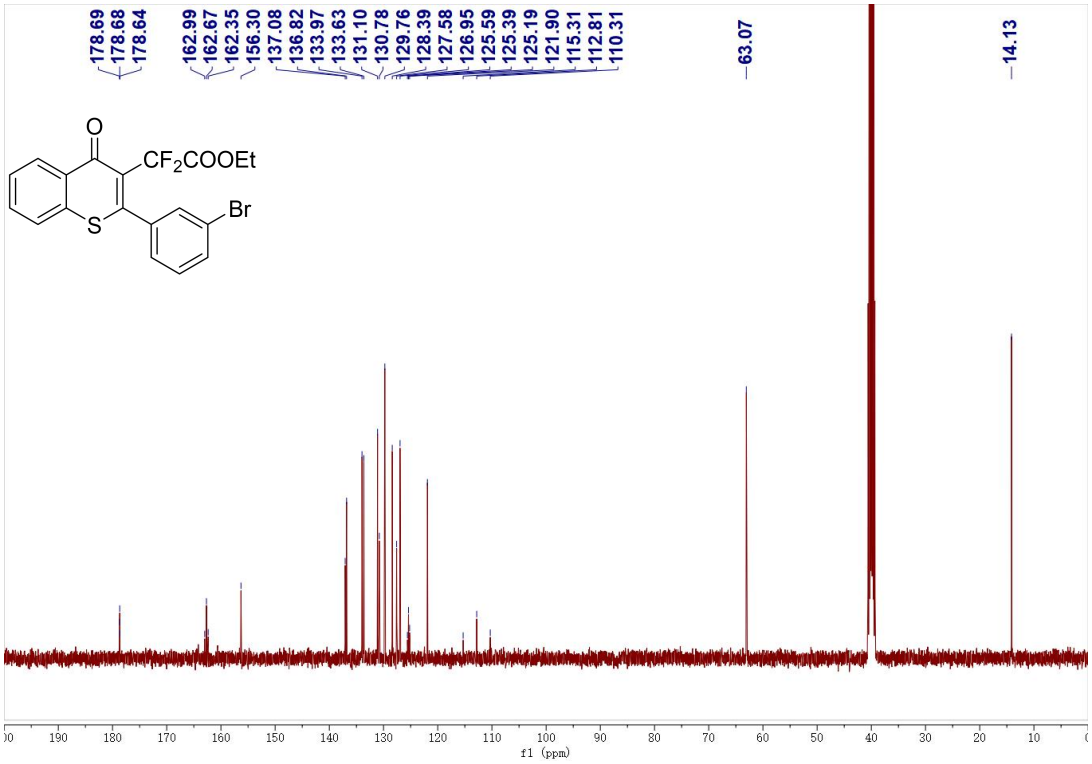
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3k**



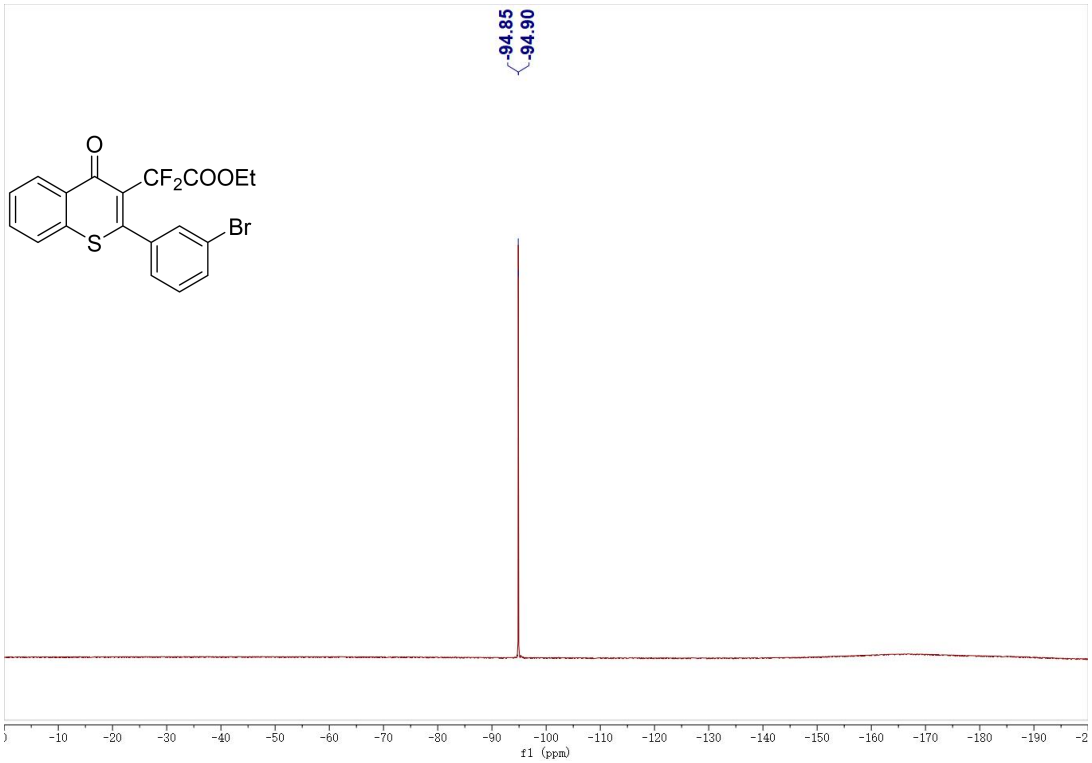
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3l**



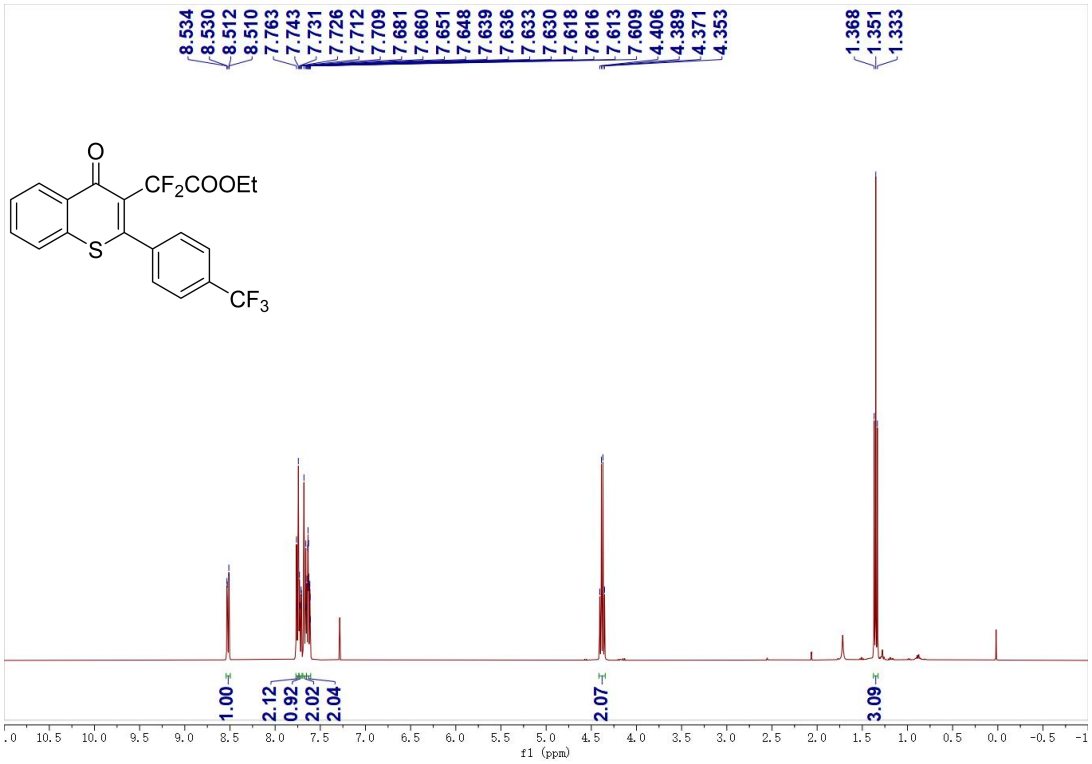
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3l**



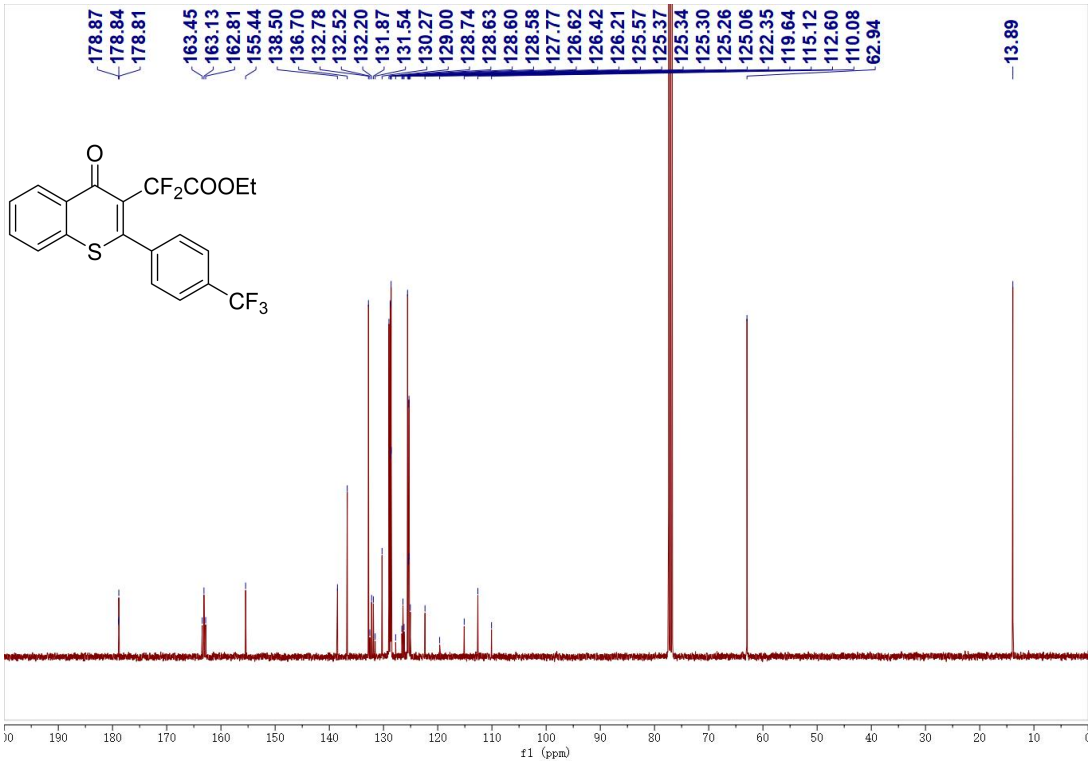
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3l**



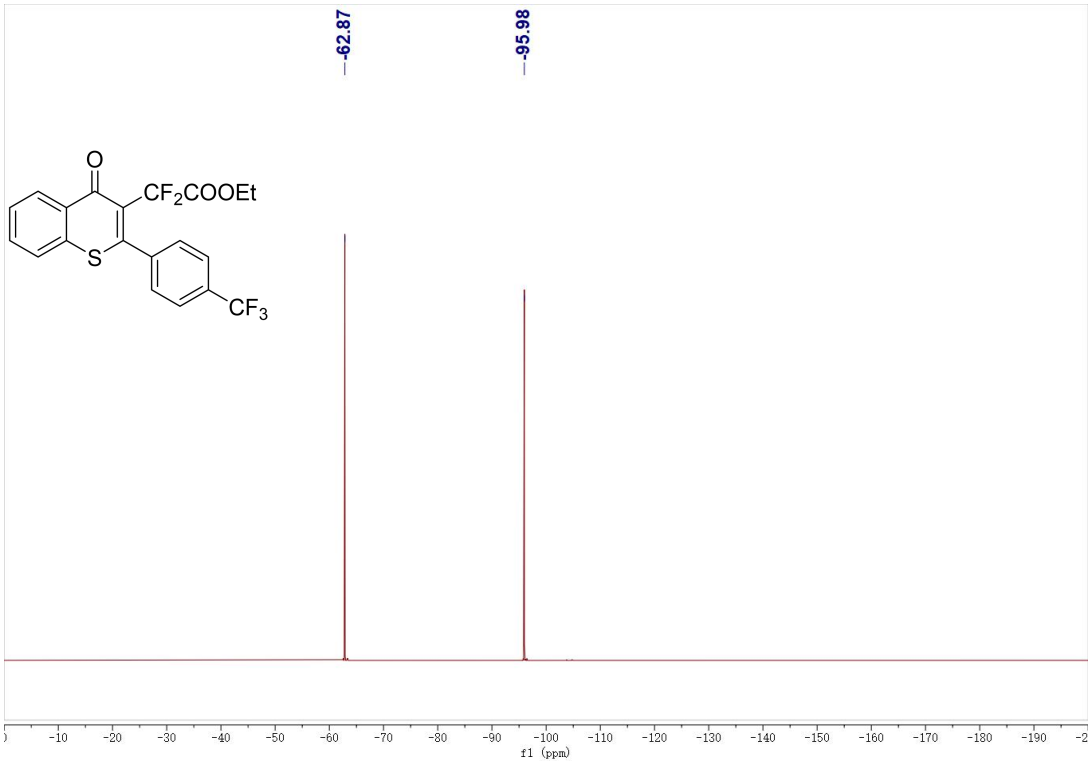
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3m**



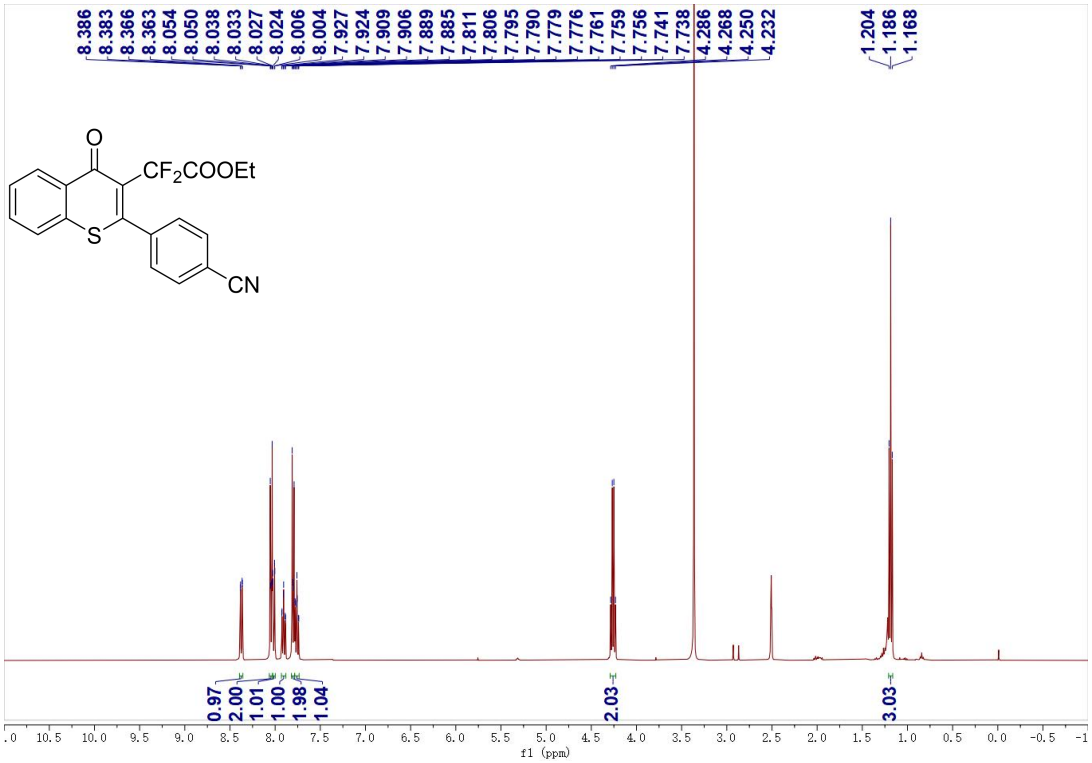
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3m**



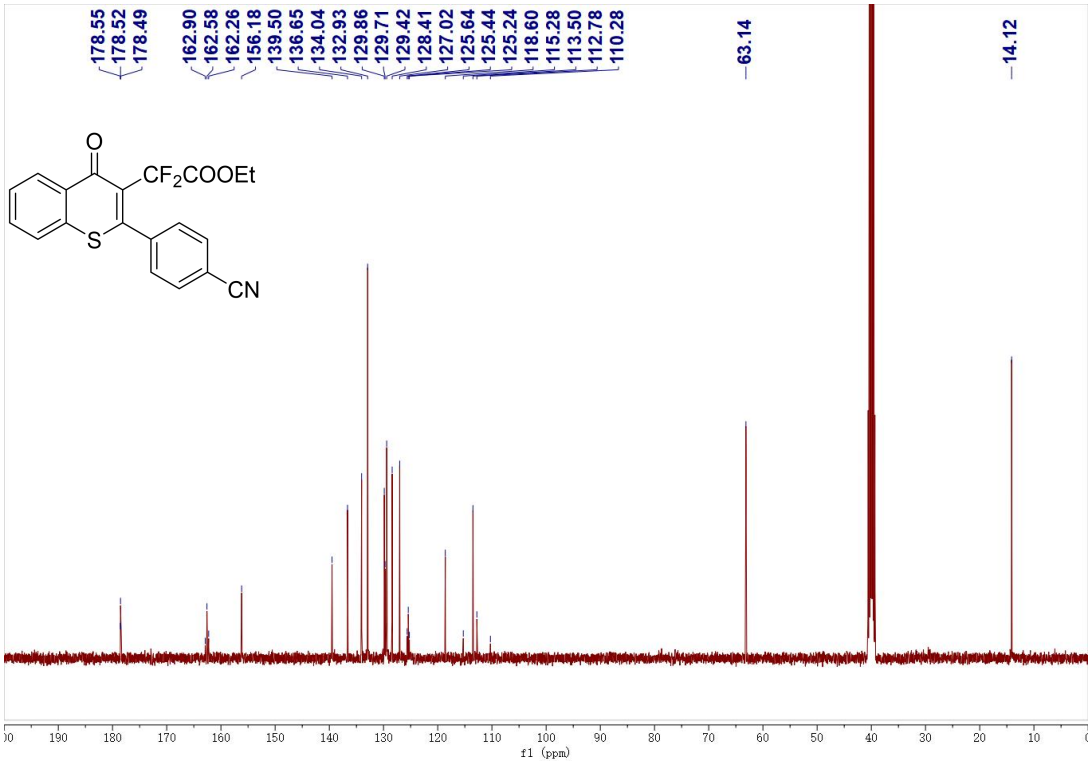
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3m**



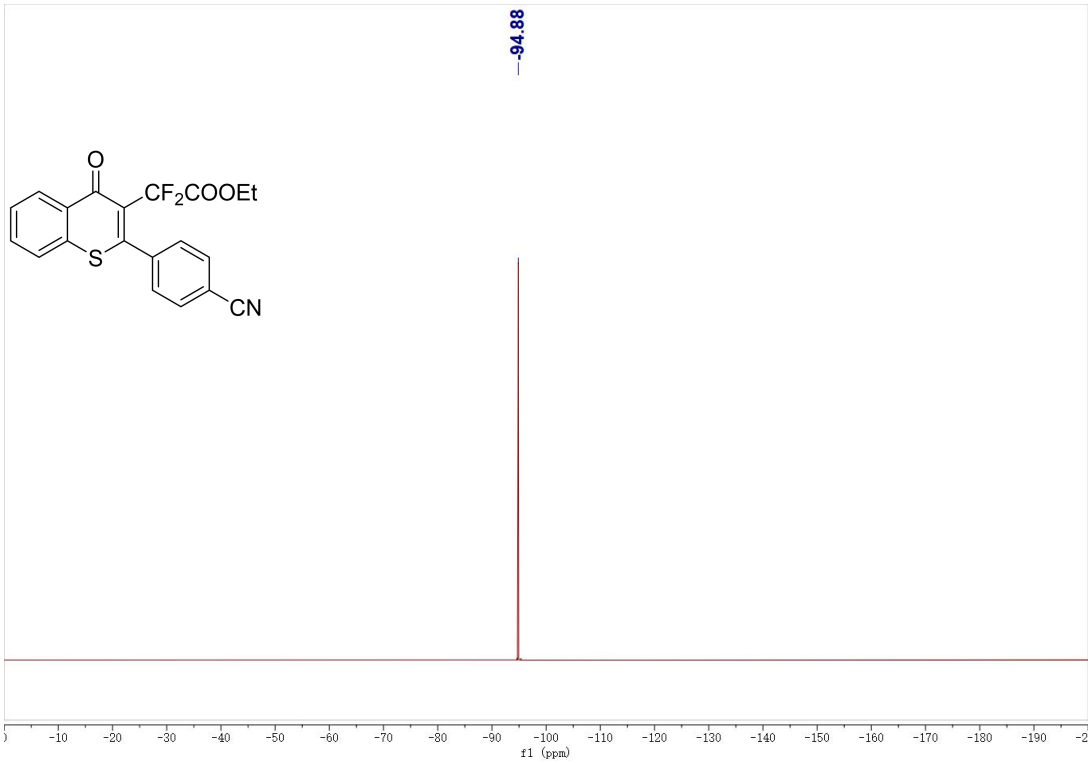
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3n**



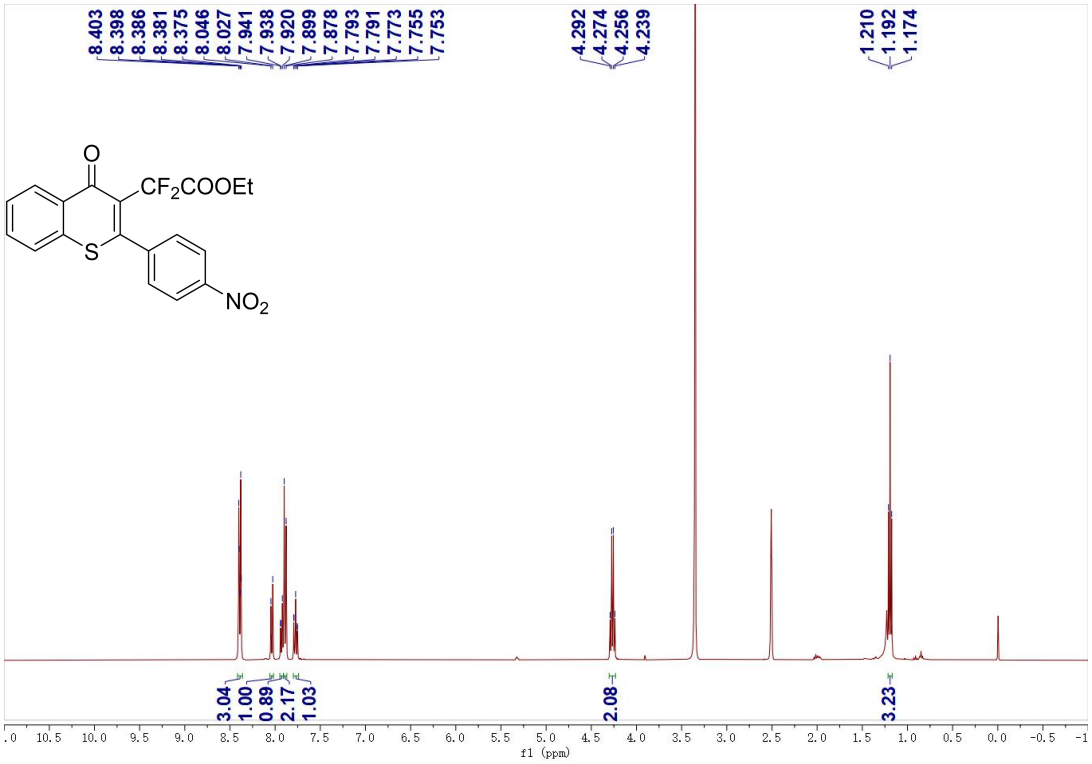
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3n**



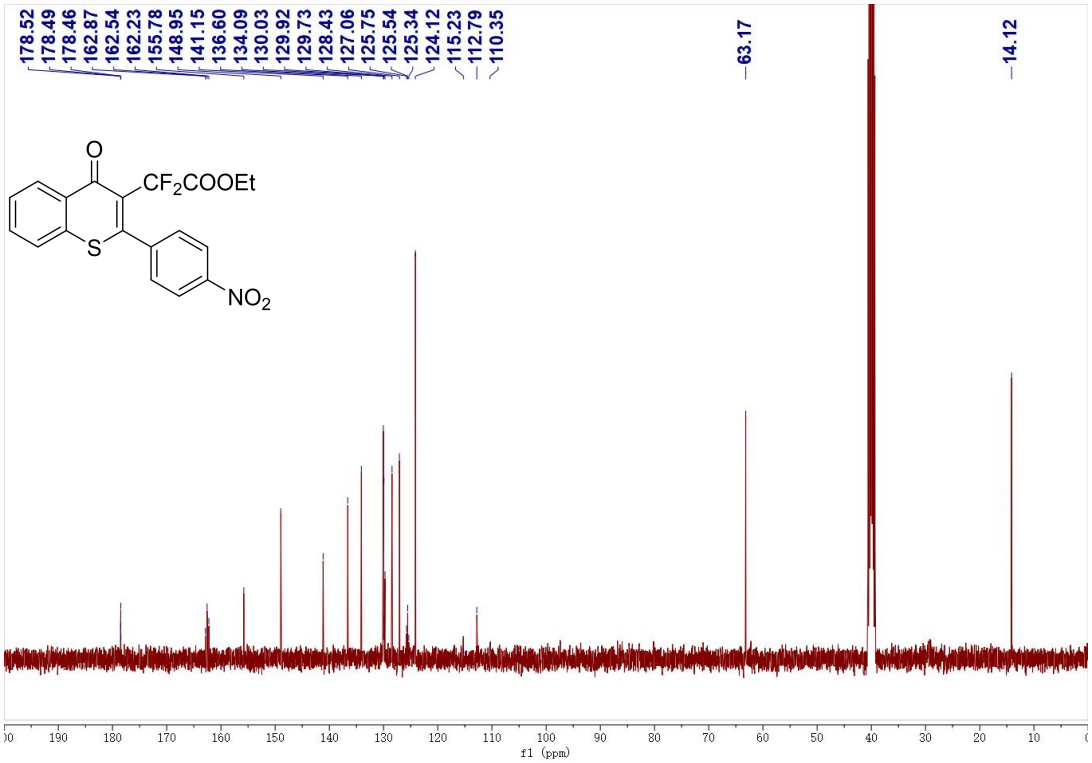
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3n**



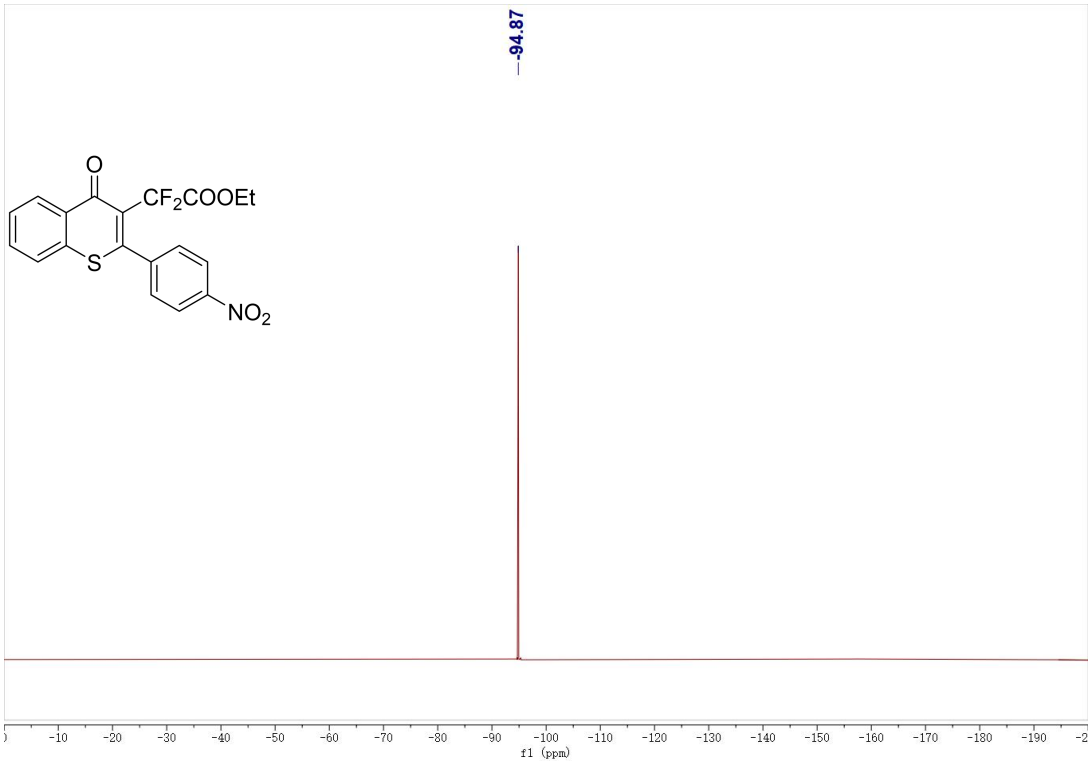
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3o**



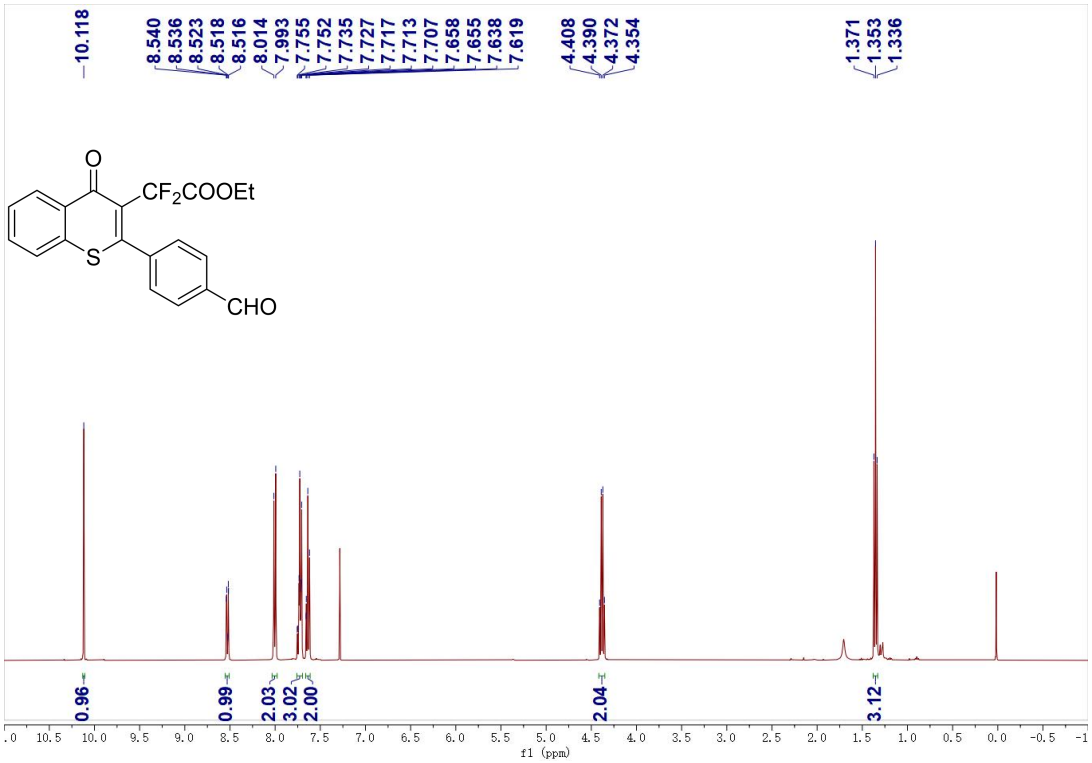
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3o**



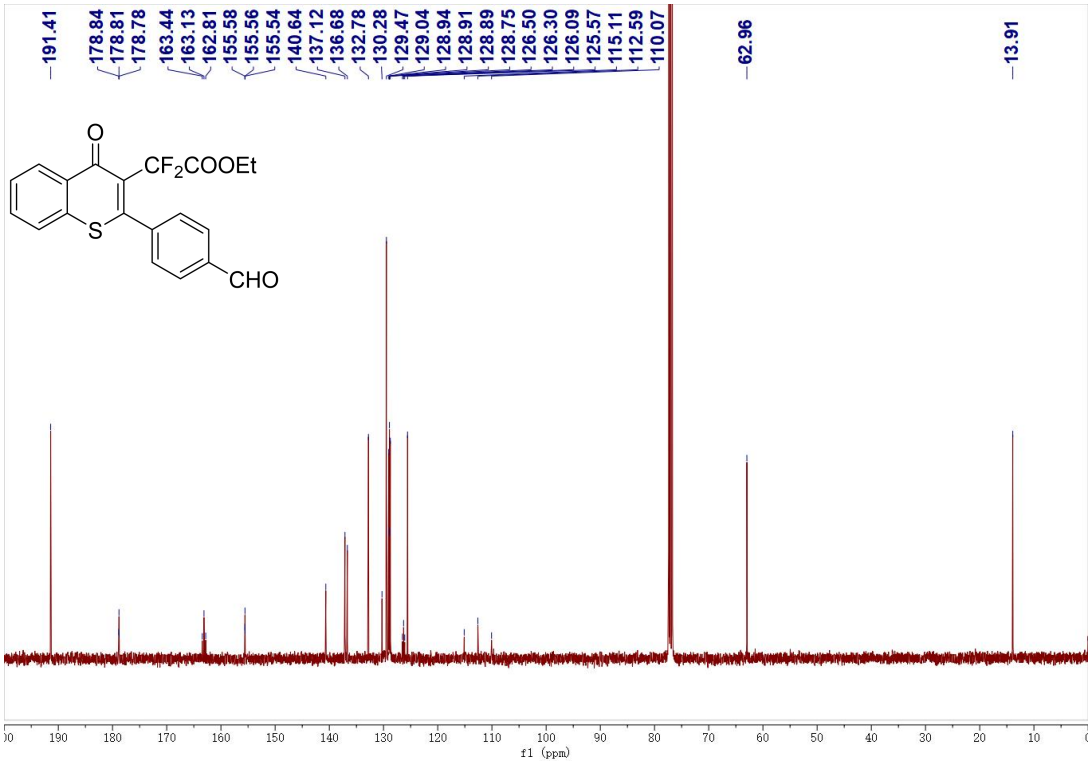
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3o**



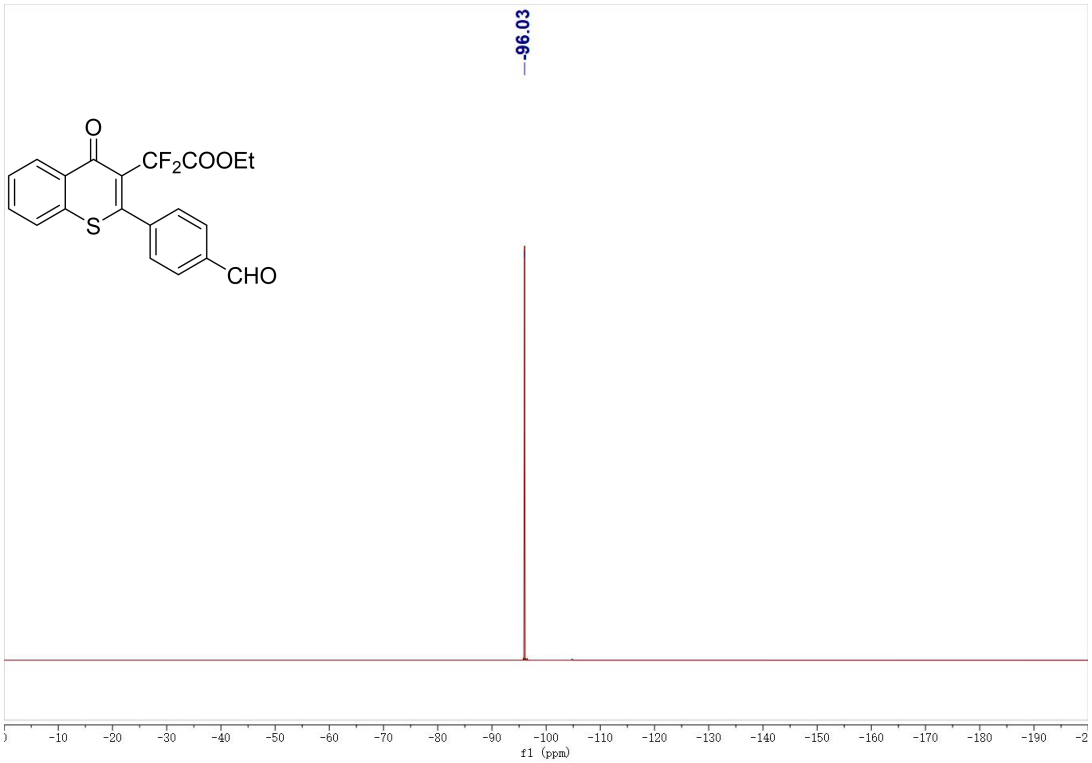
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3p**



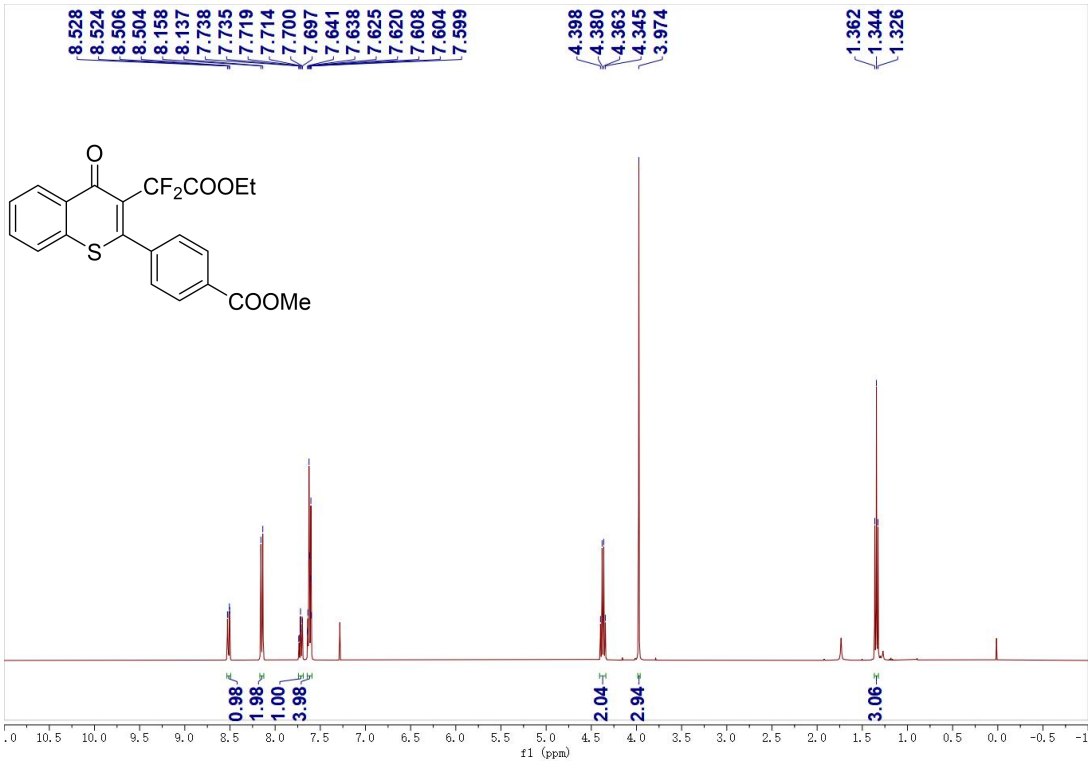
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3p**



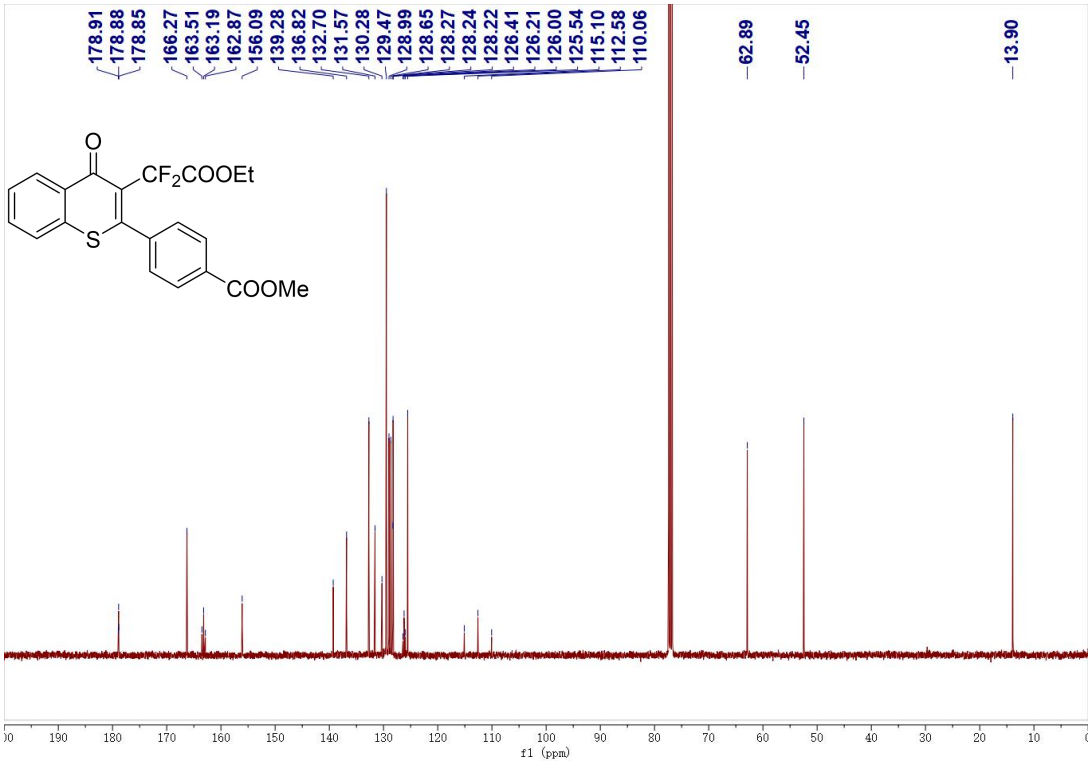
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3p**



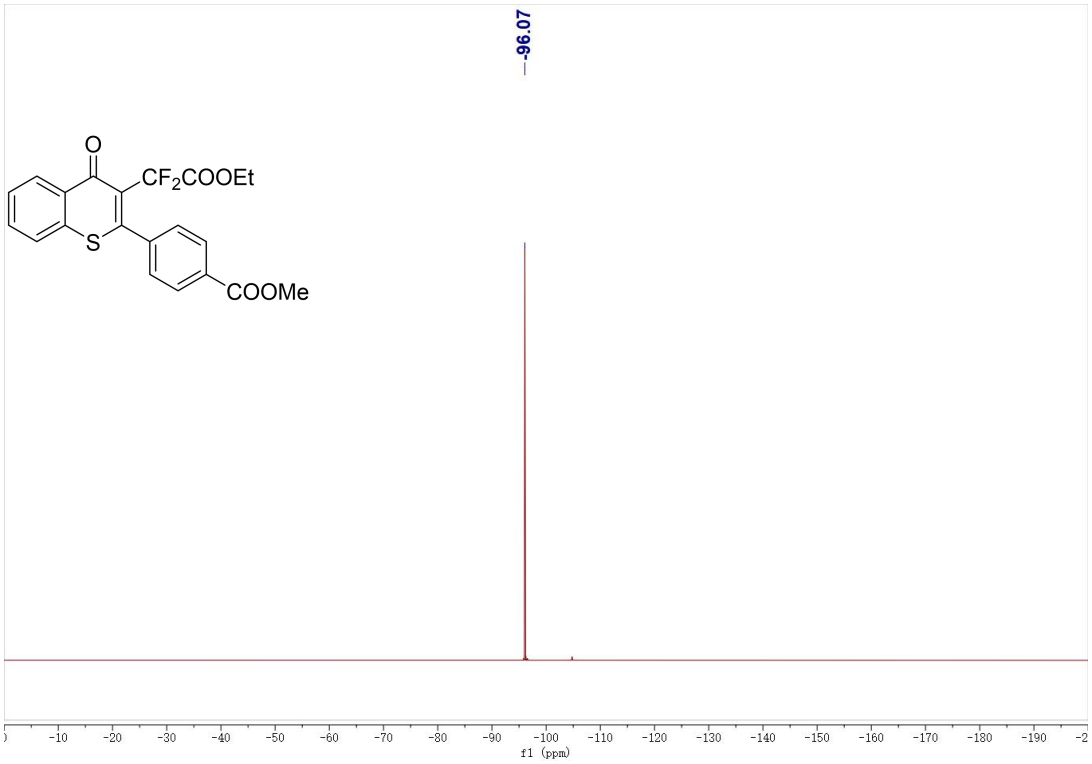
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3q**



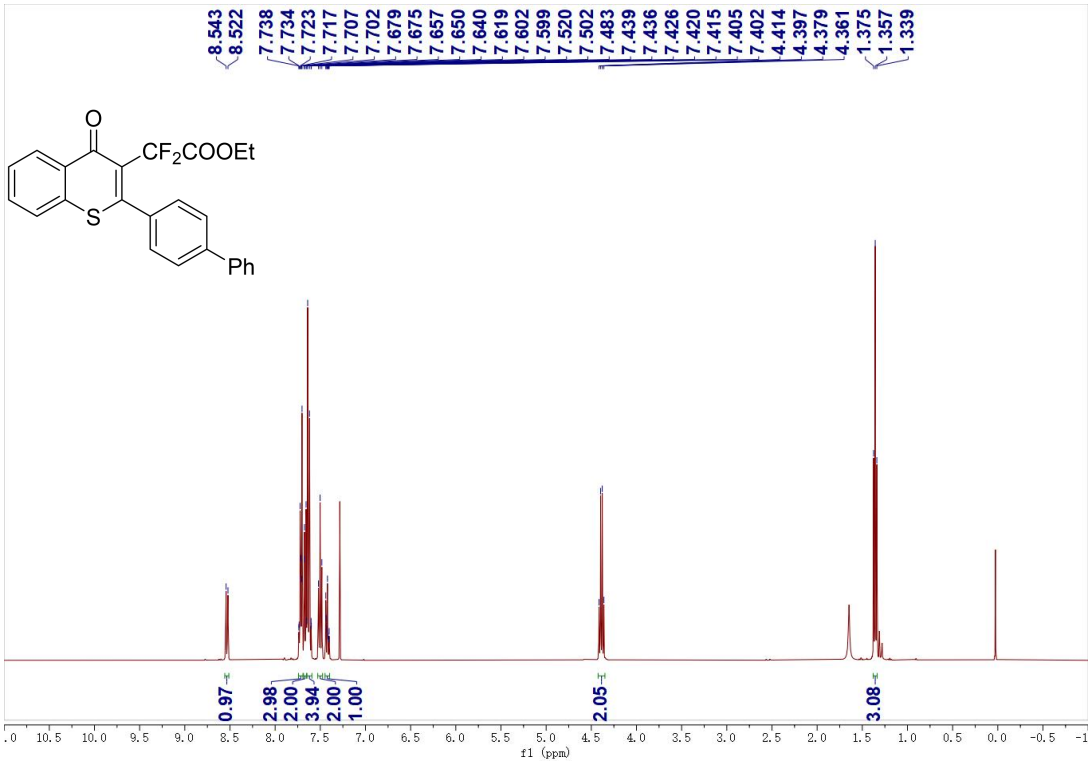
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3q**



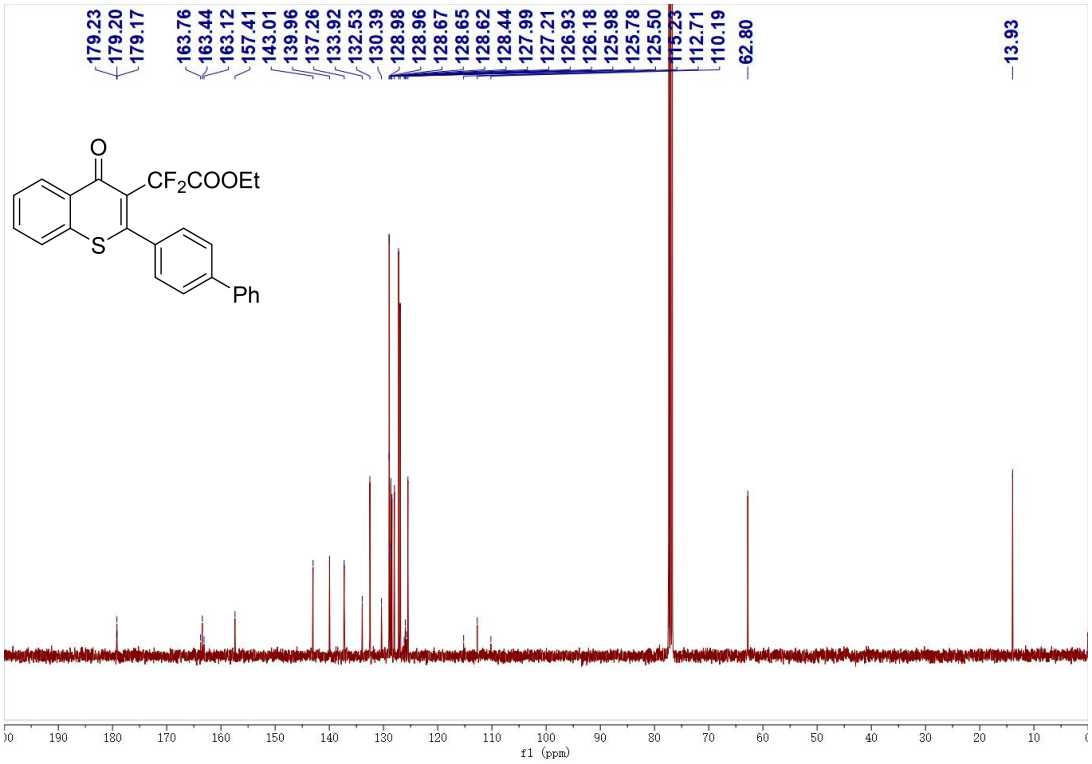
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3q**



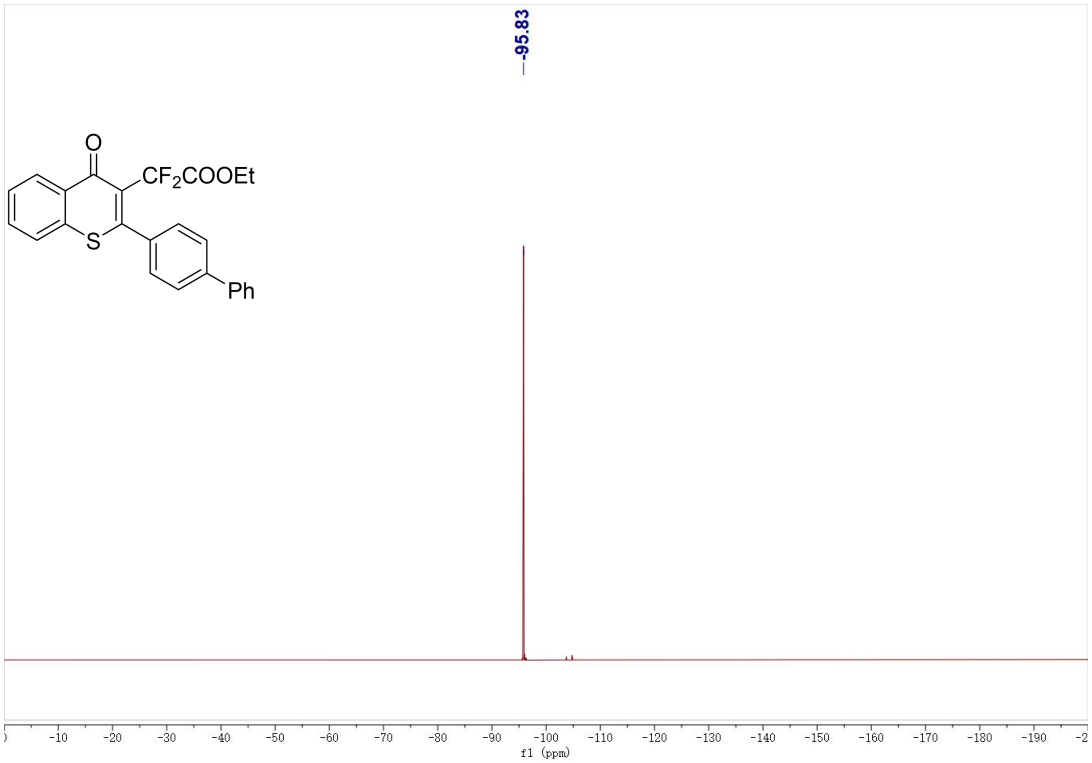
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3r**



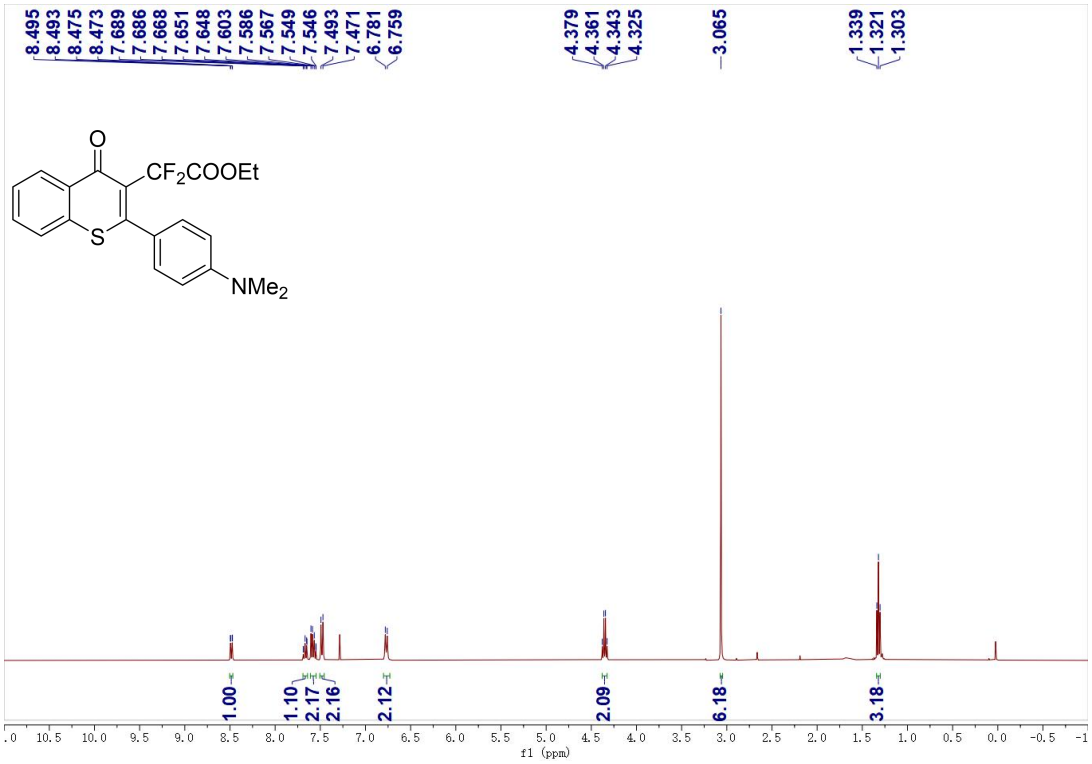
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3r**



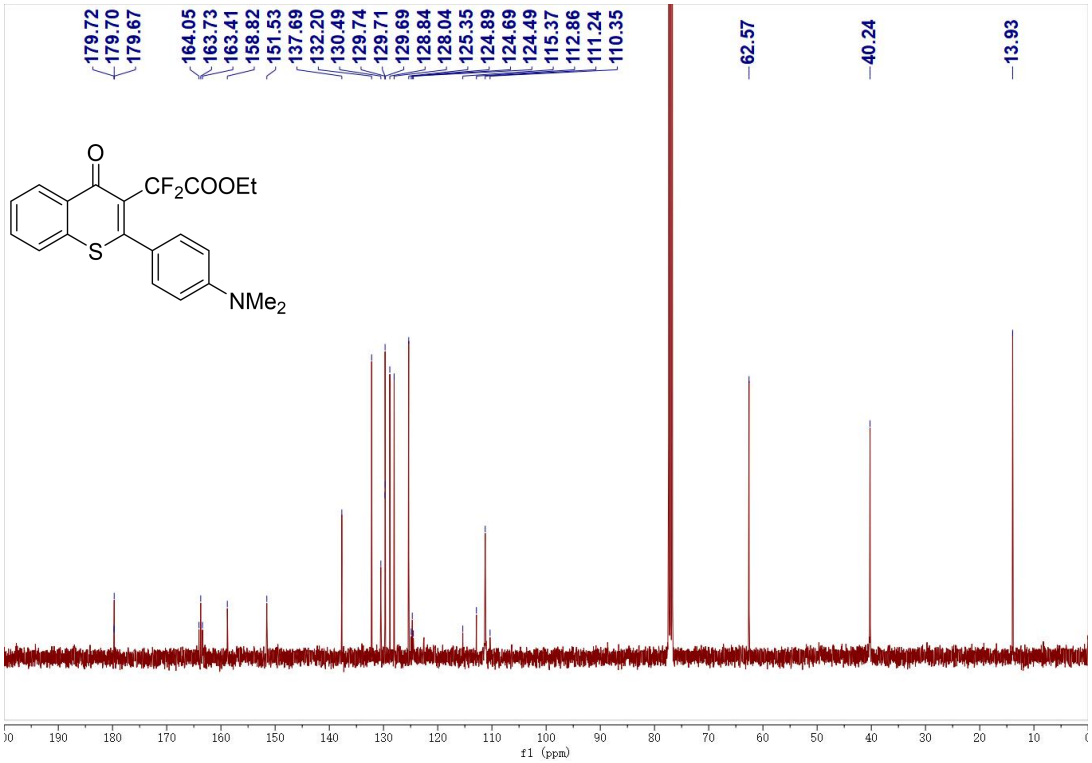
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3r**



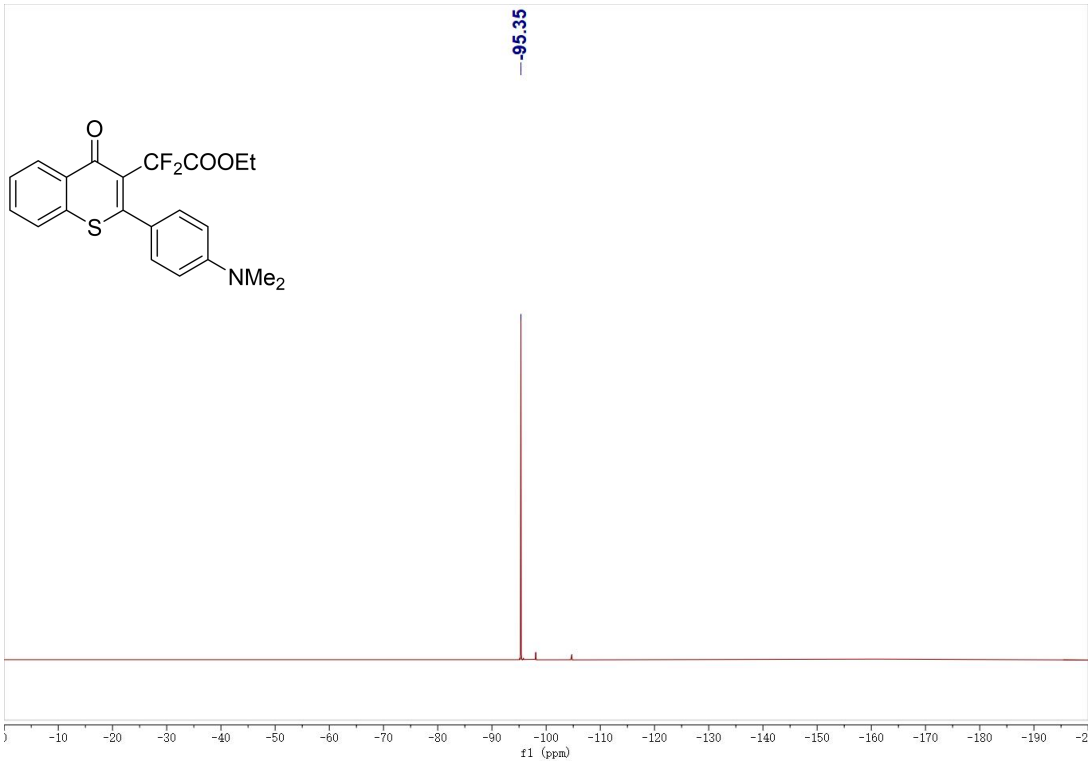
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3s**



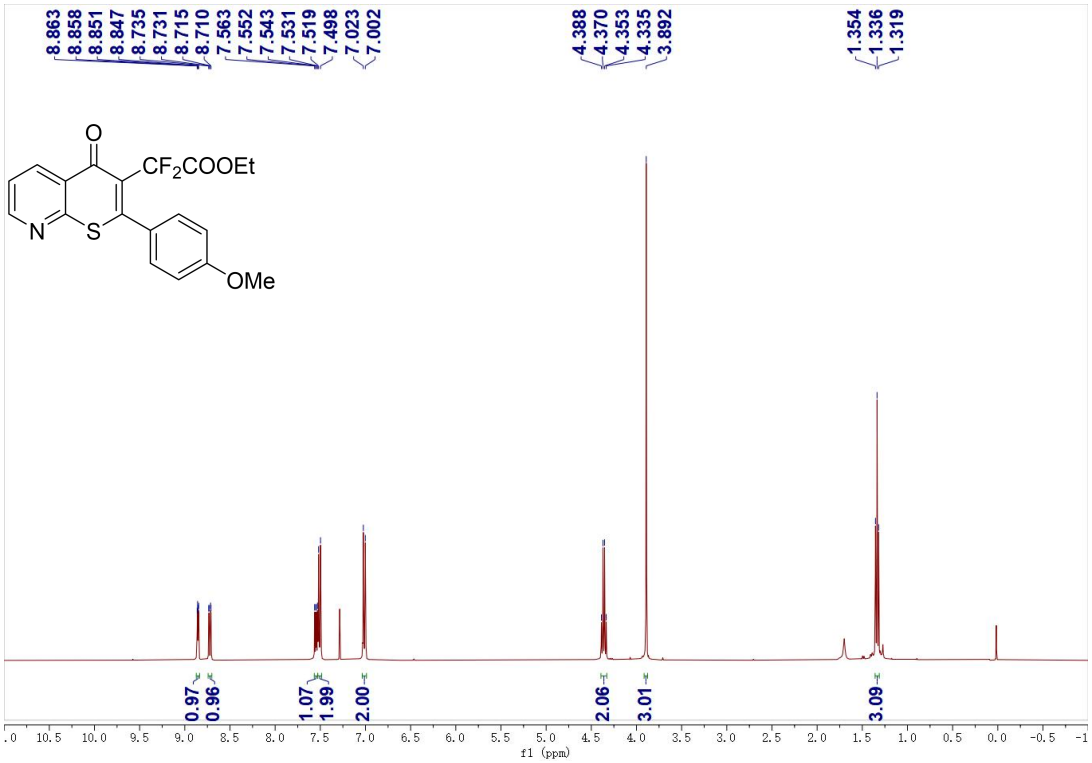
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3s**



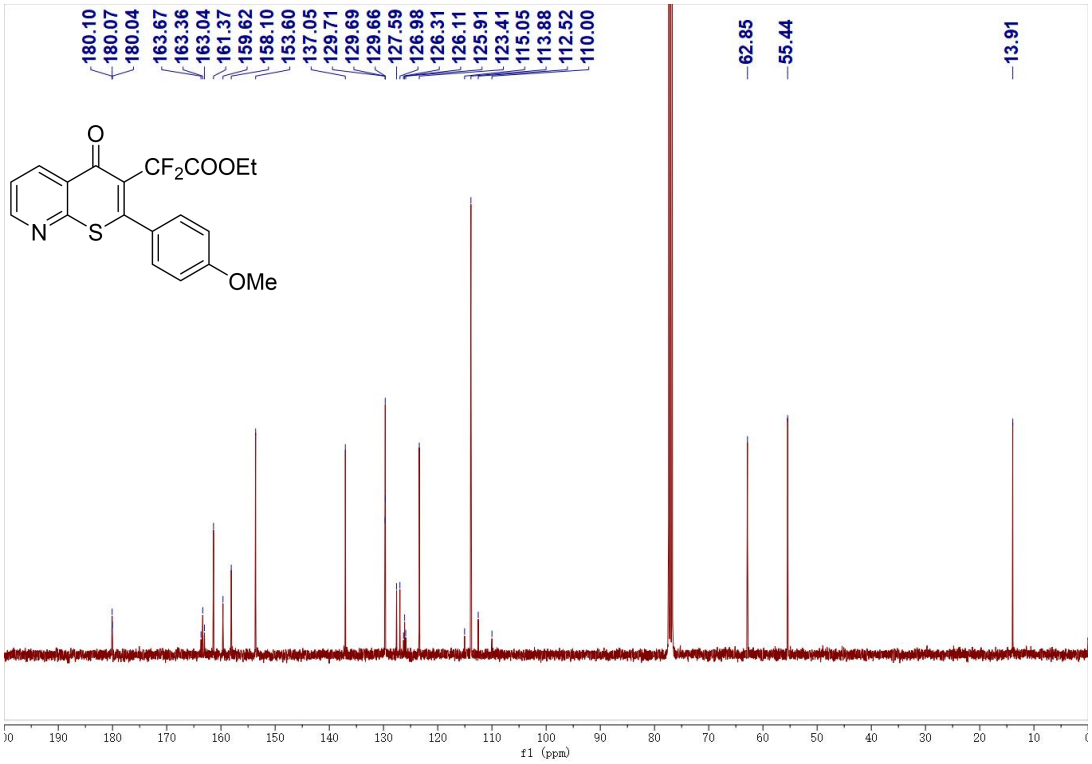
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3s**



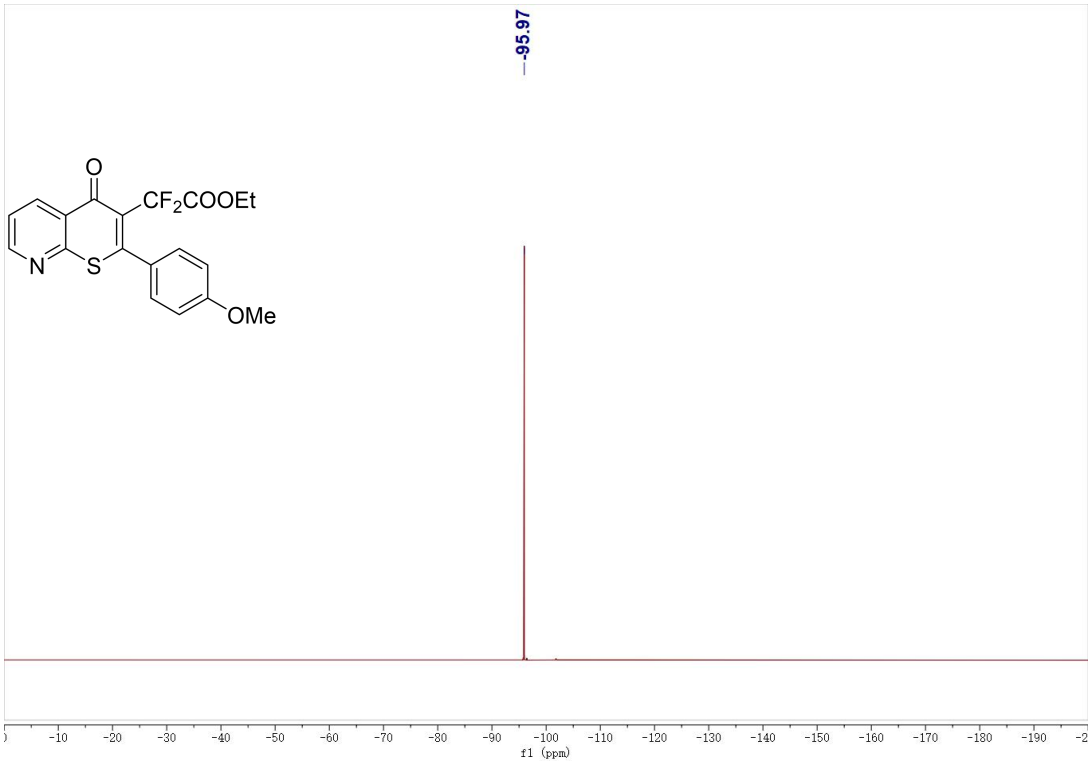
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3t**



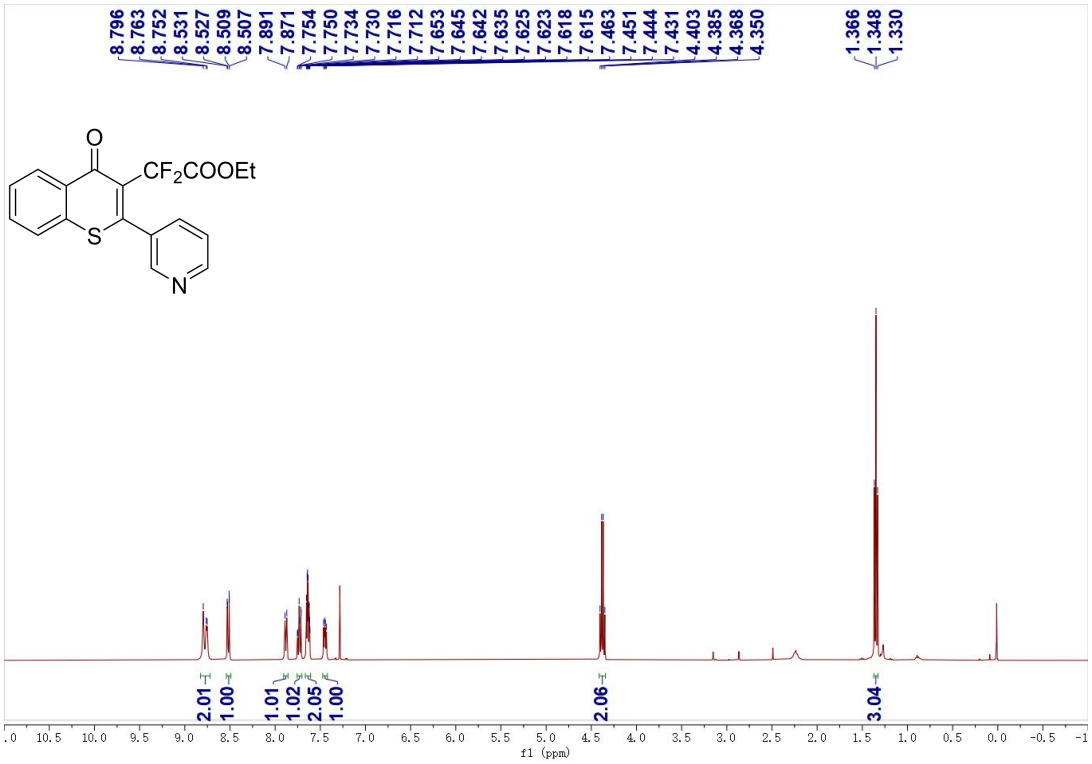
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3t**



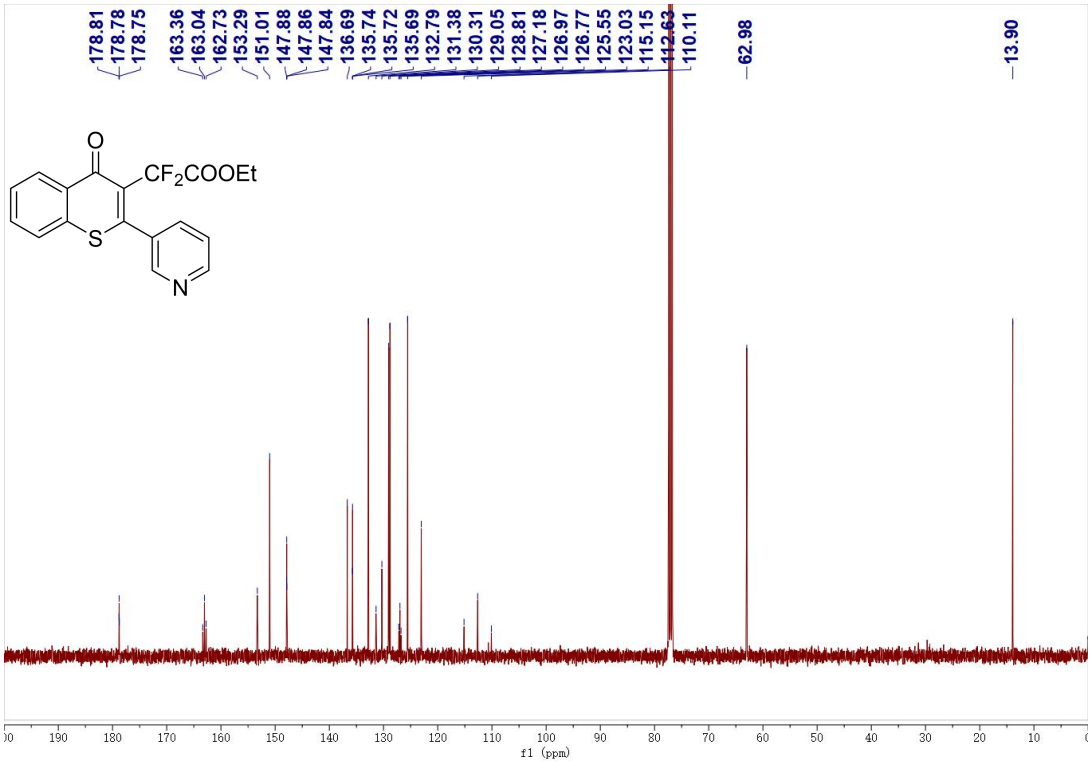
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3t**



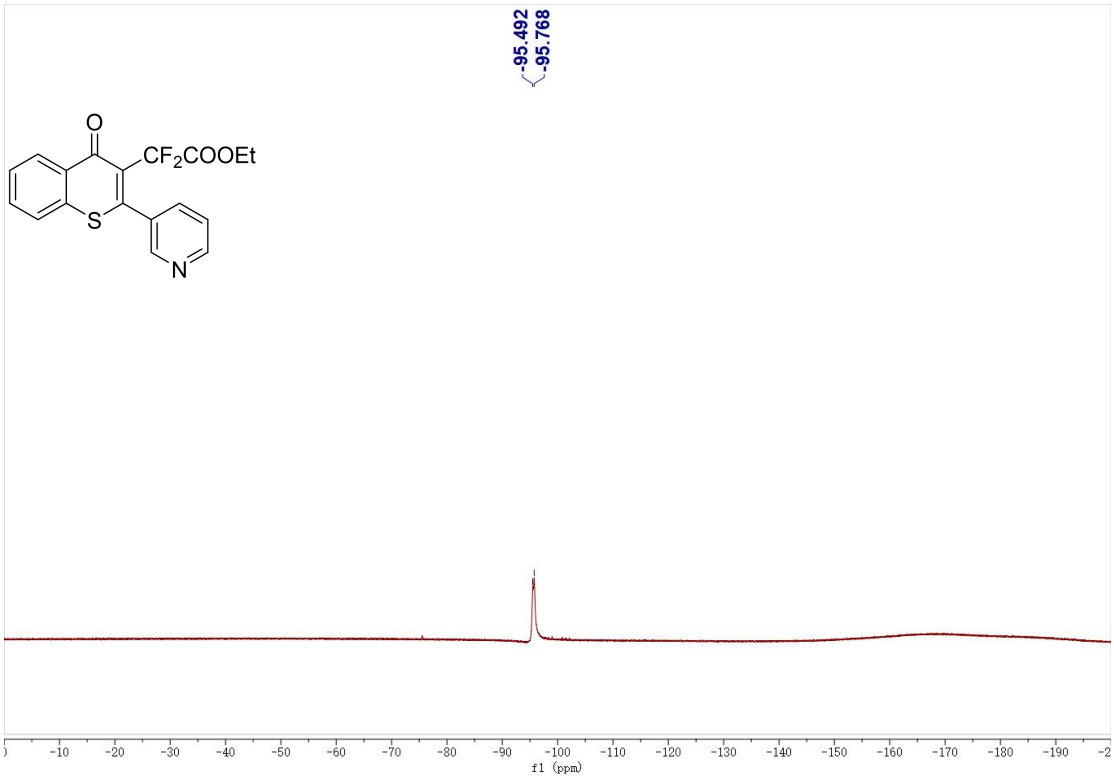
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3u**



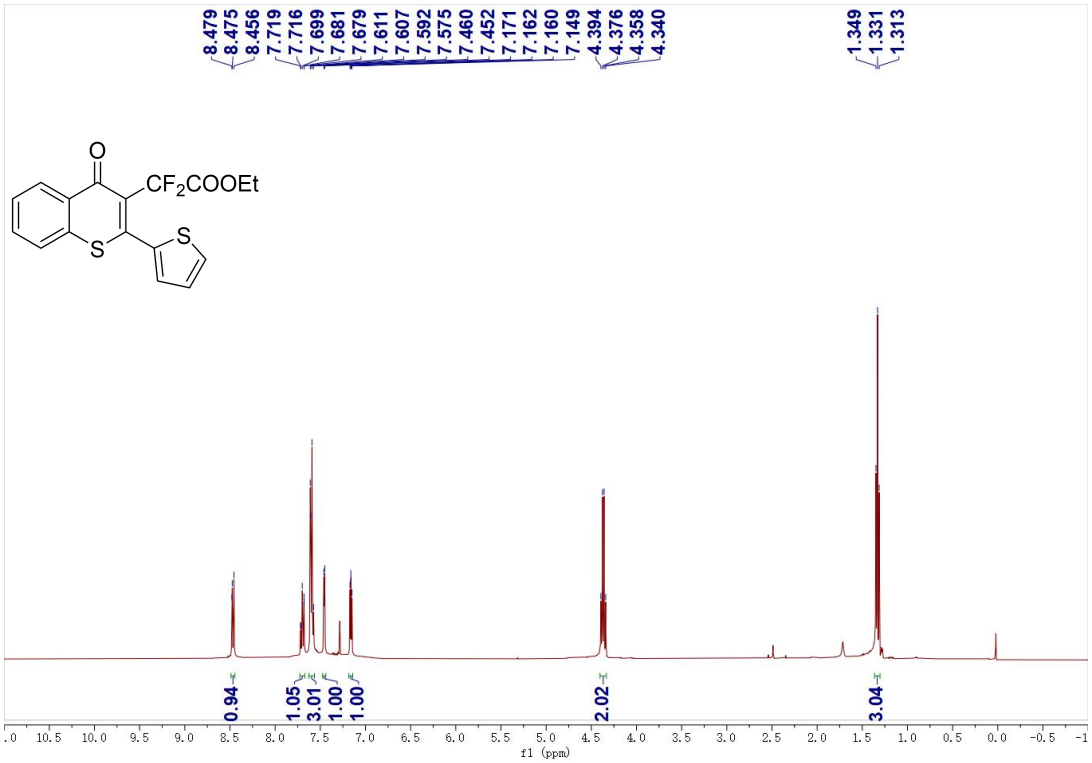
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3u**



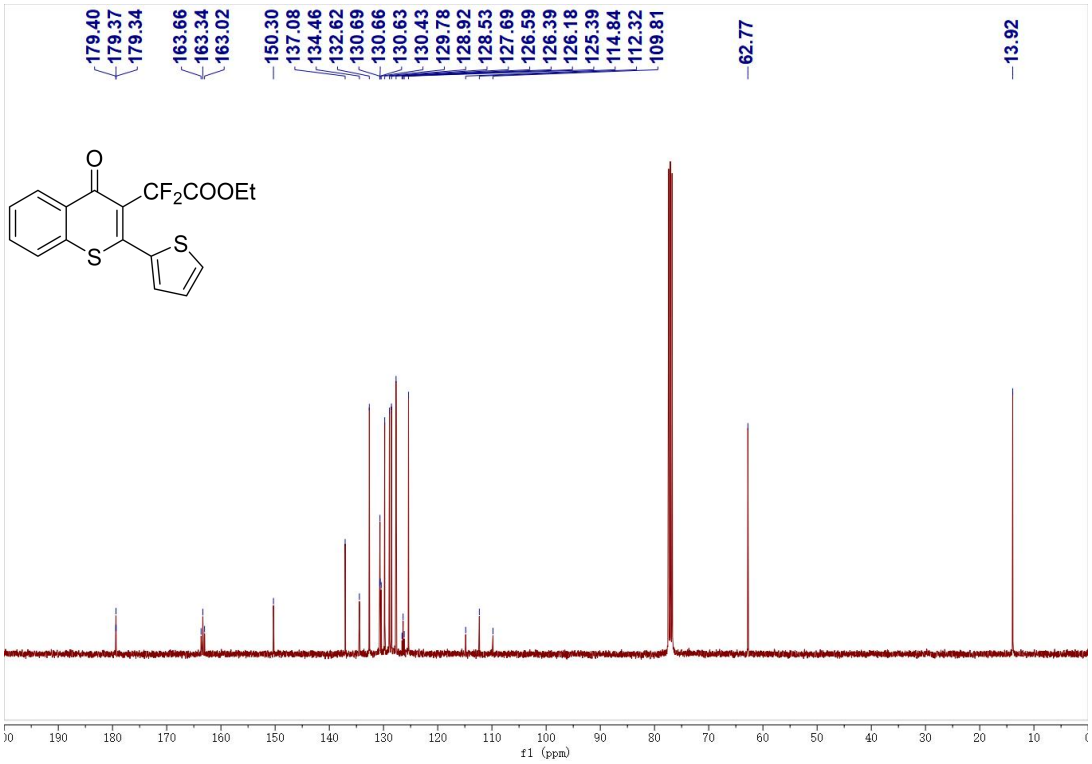
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3u**



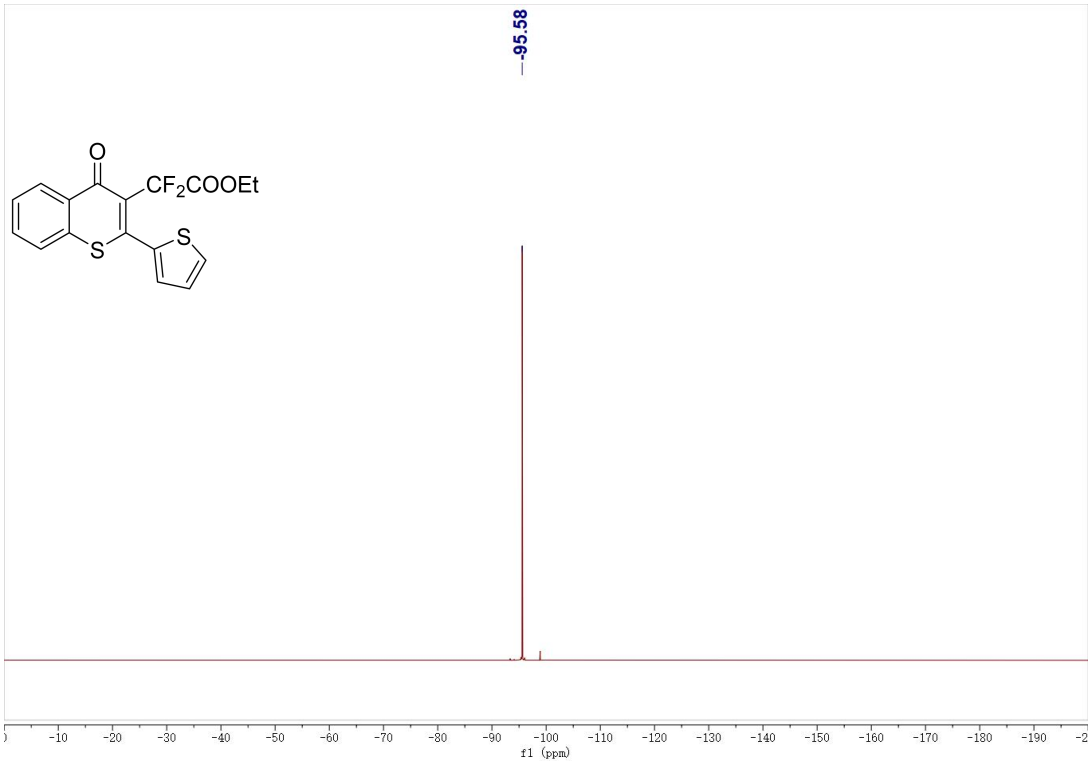
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3v**



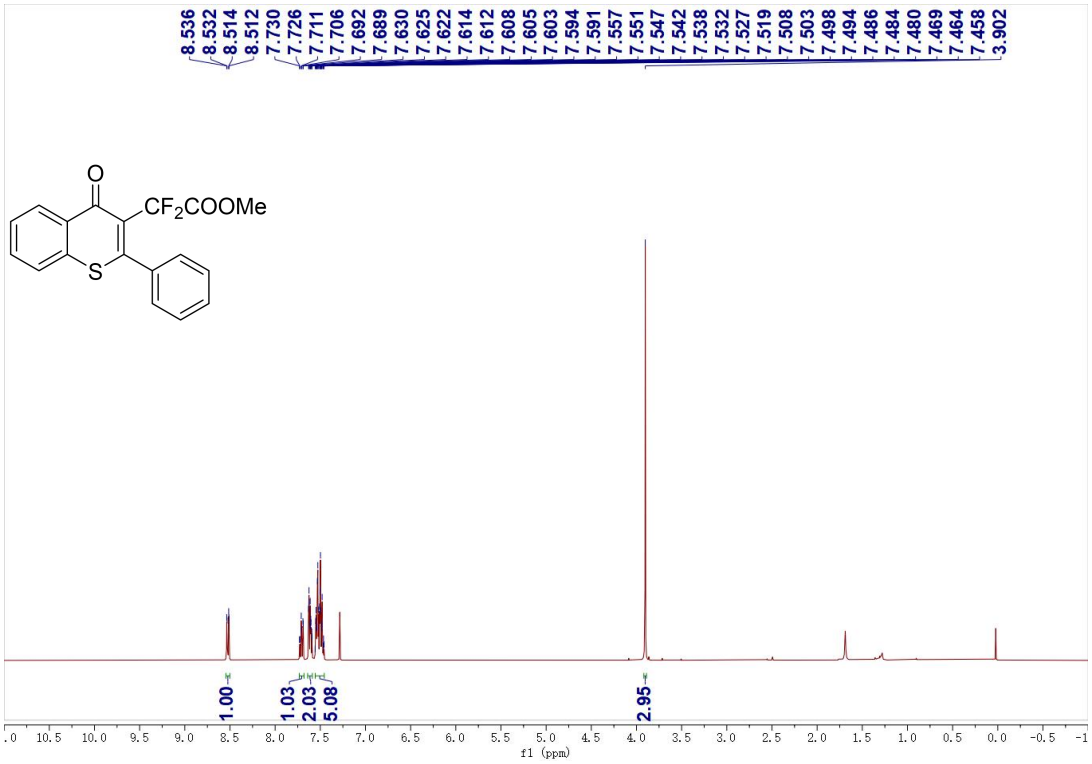
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3v**



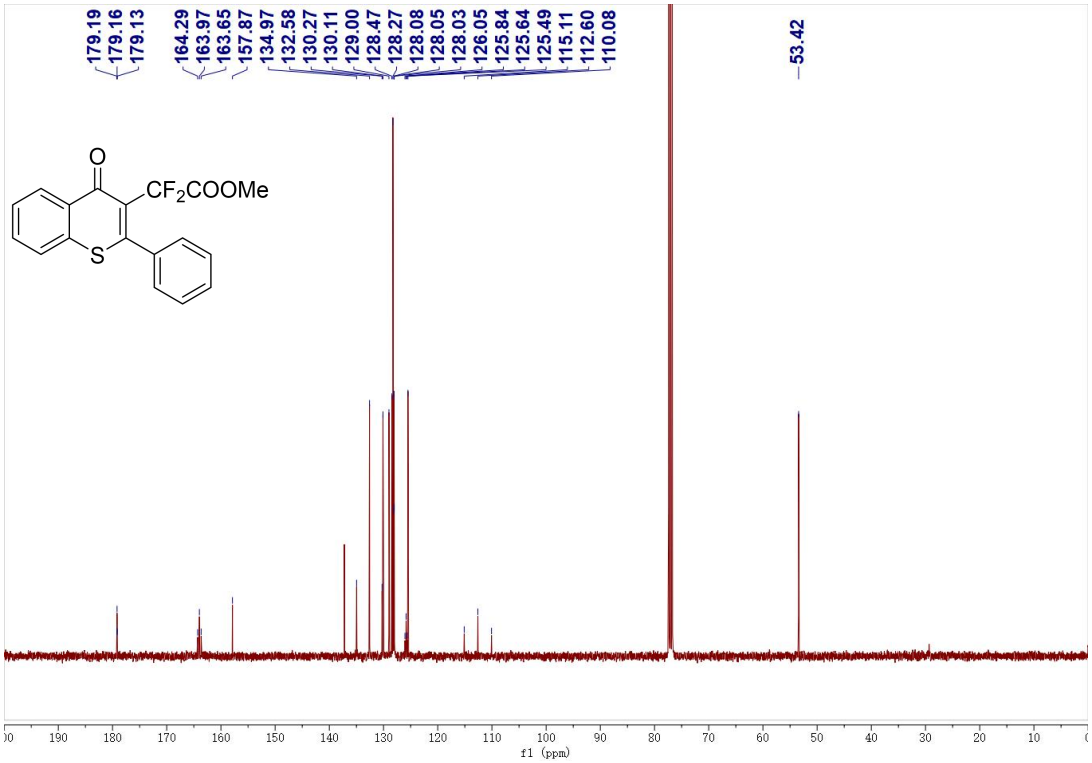
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3v**



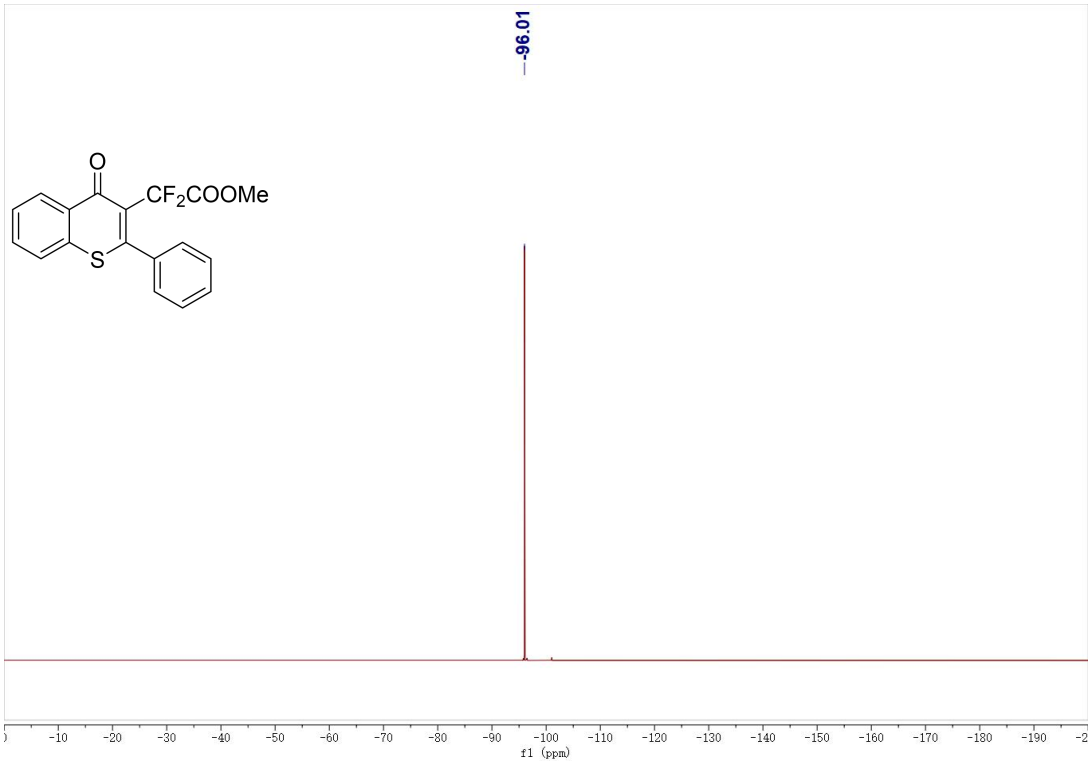
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3w**



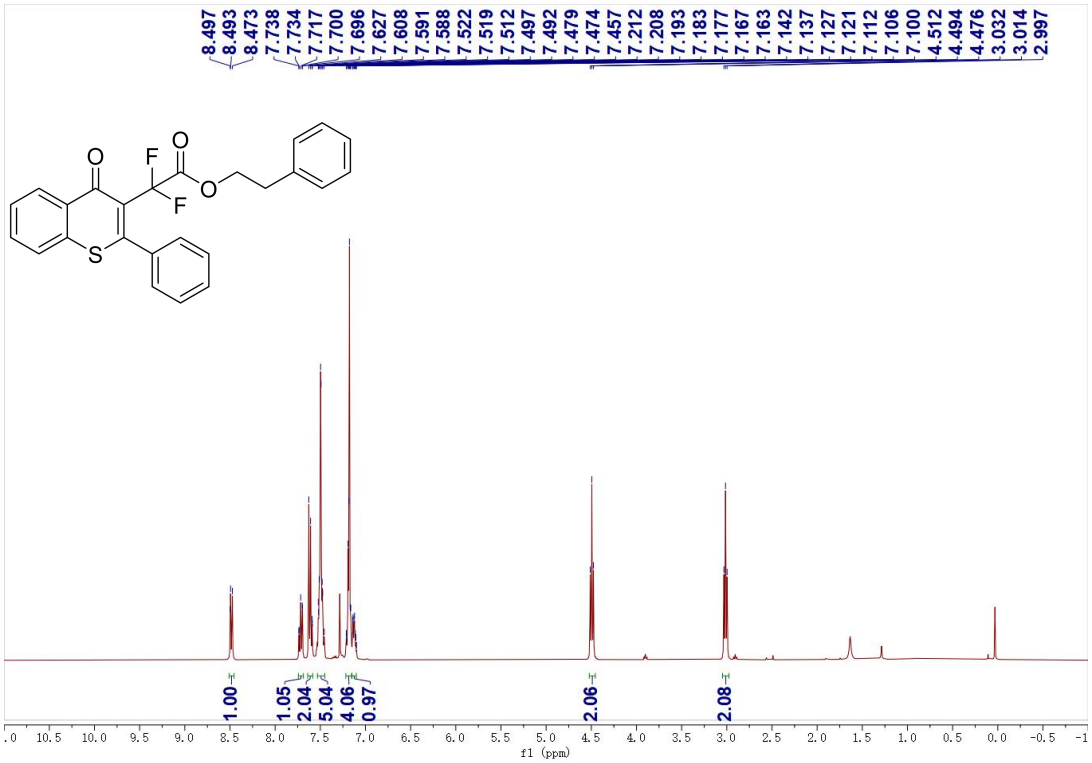
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3w**



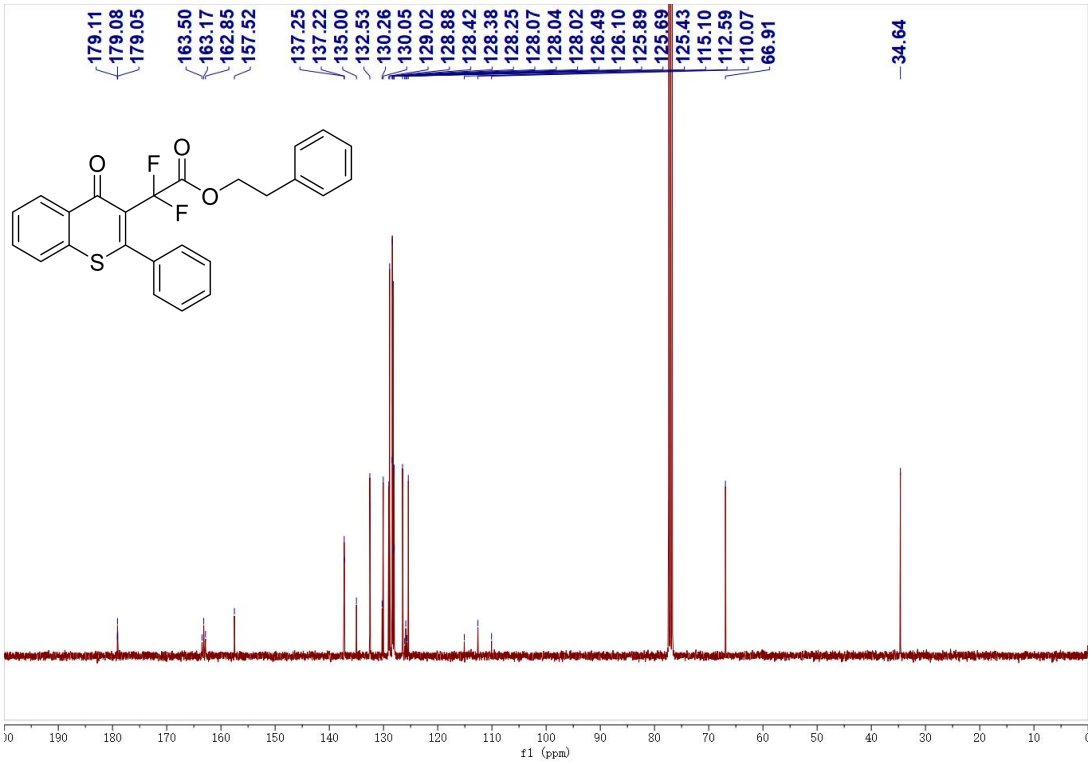
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3w**



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

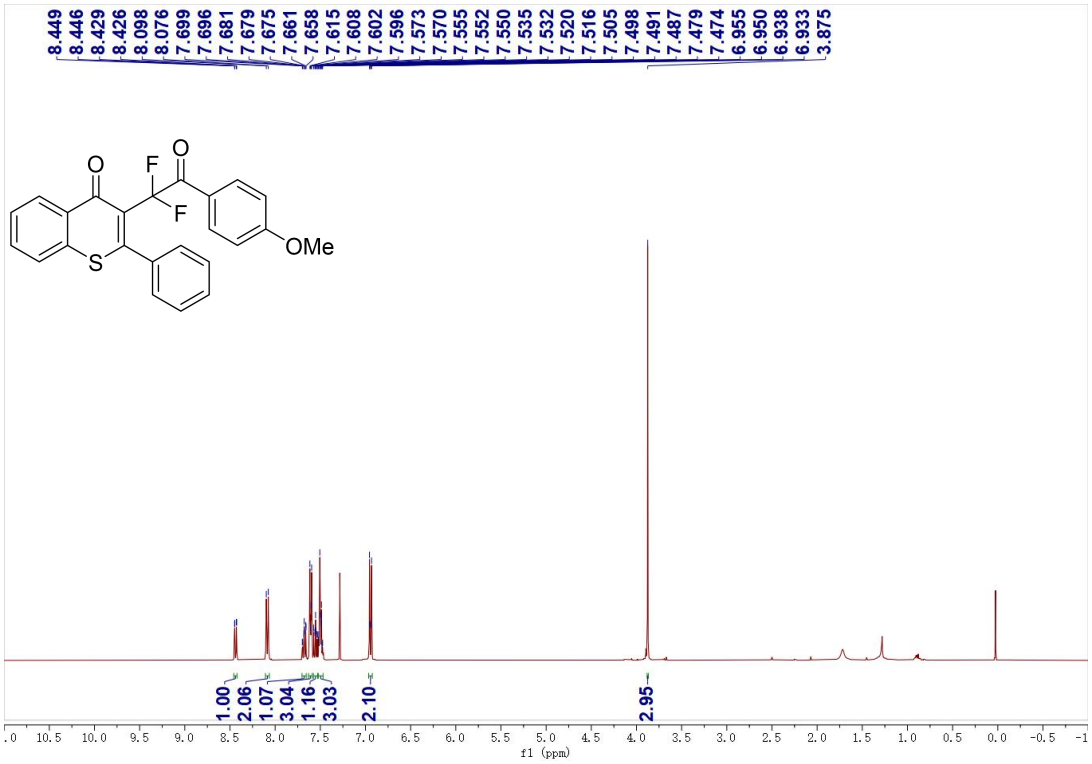


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3x**

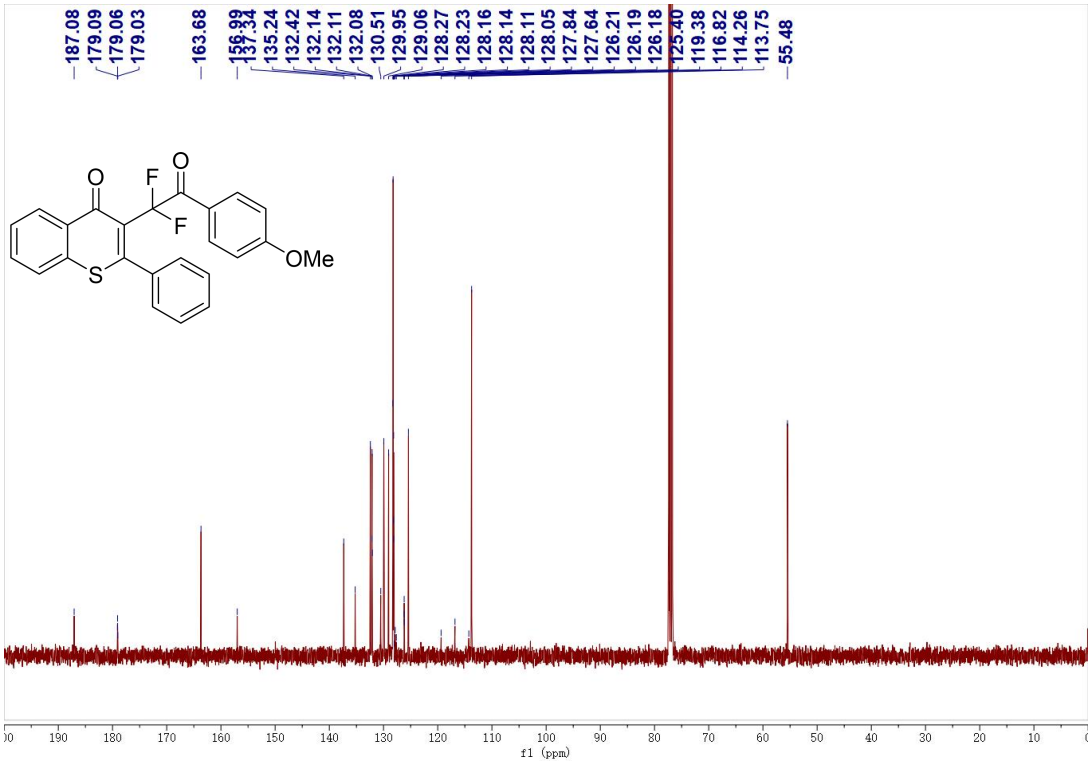


^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3x**

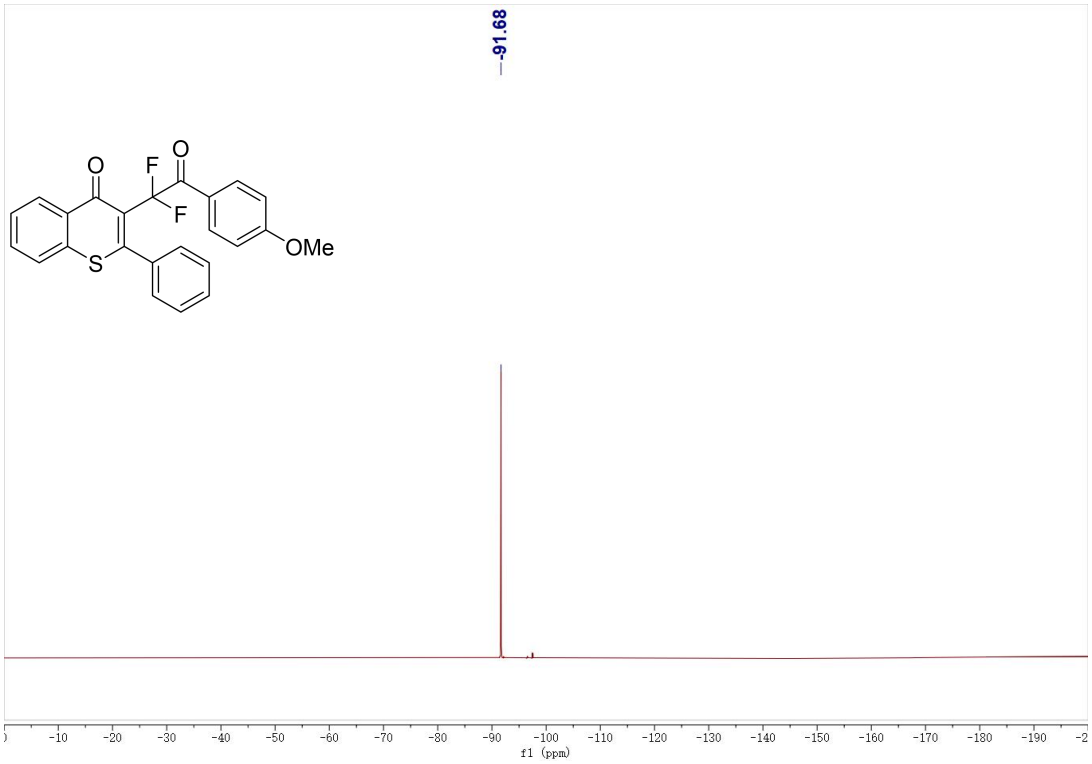
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3y**



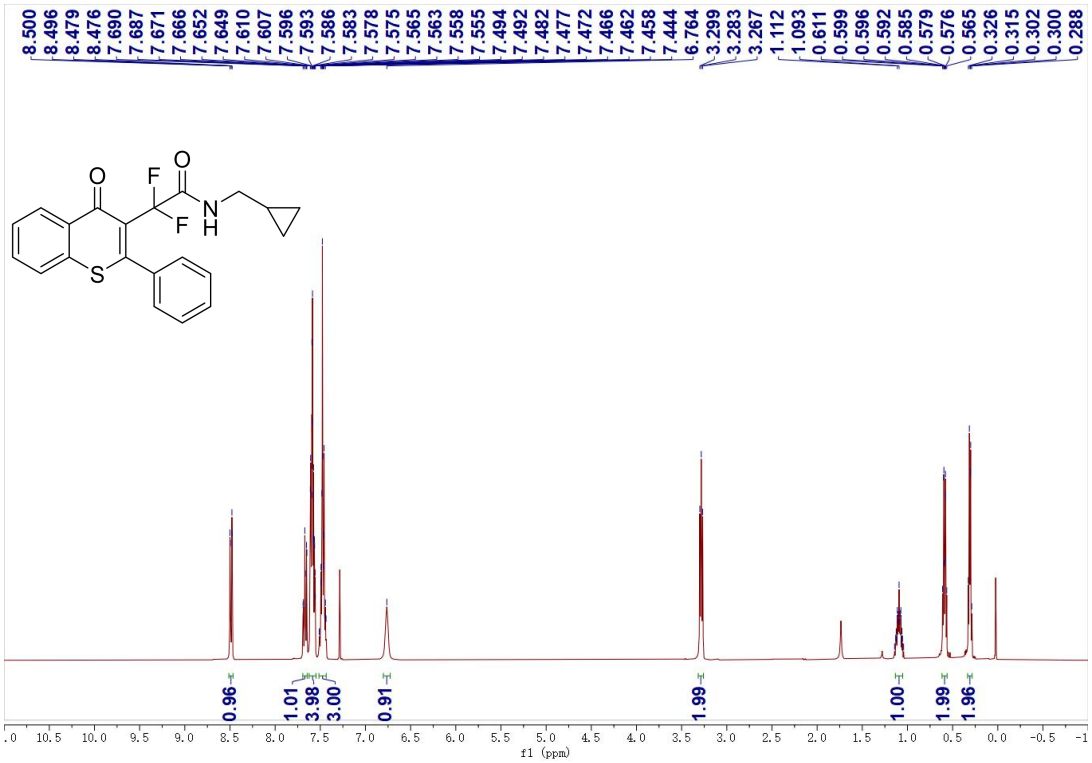
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3y**



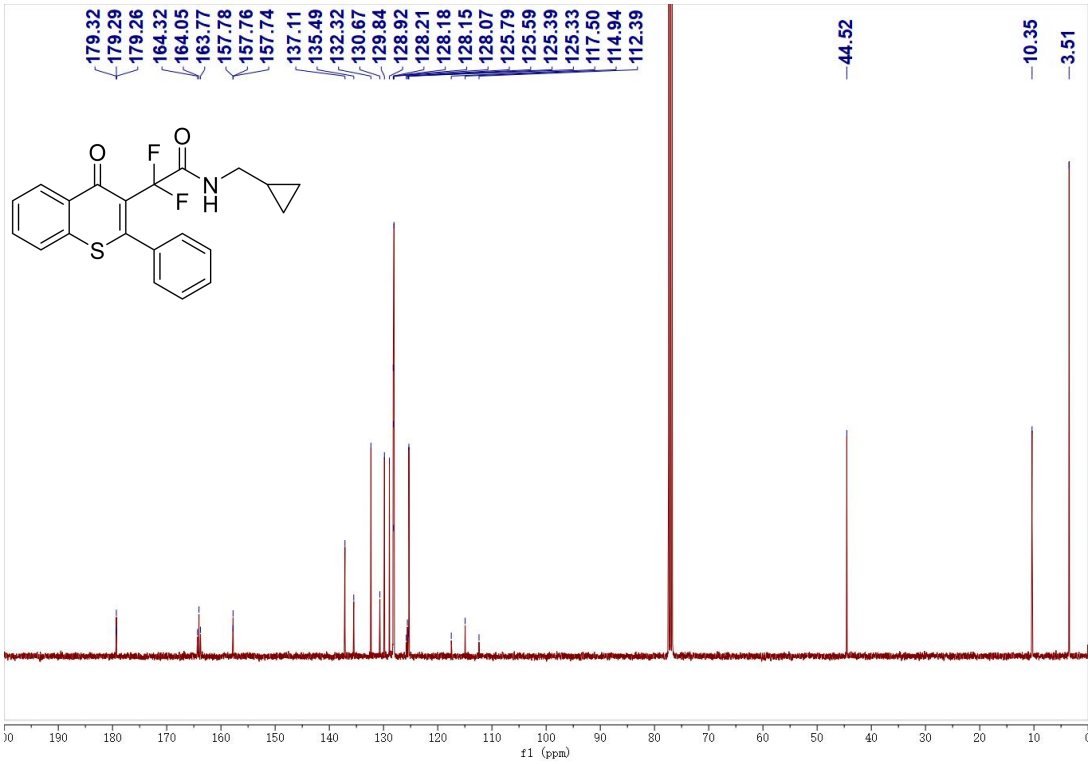
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3y**



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

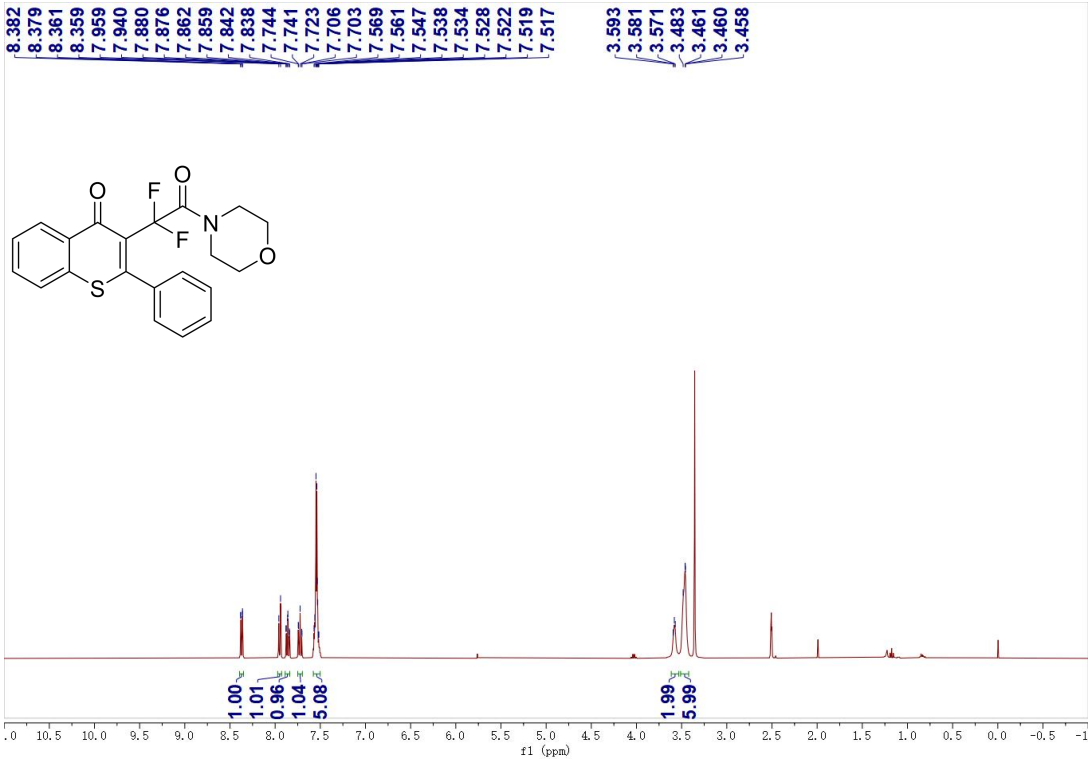


^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3z**

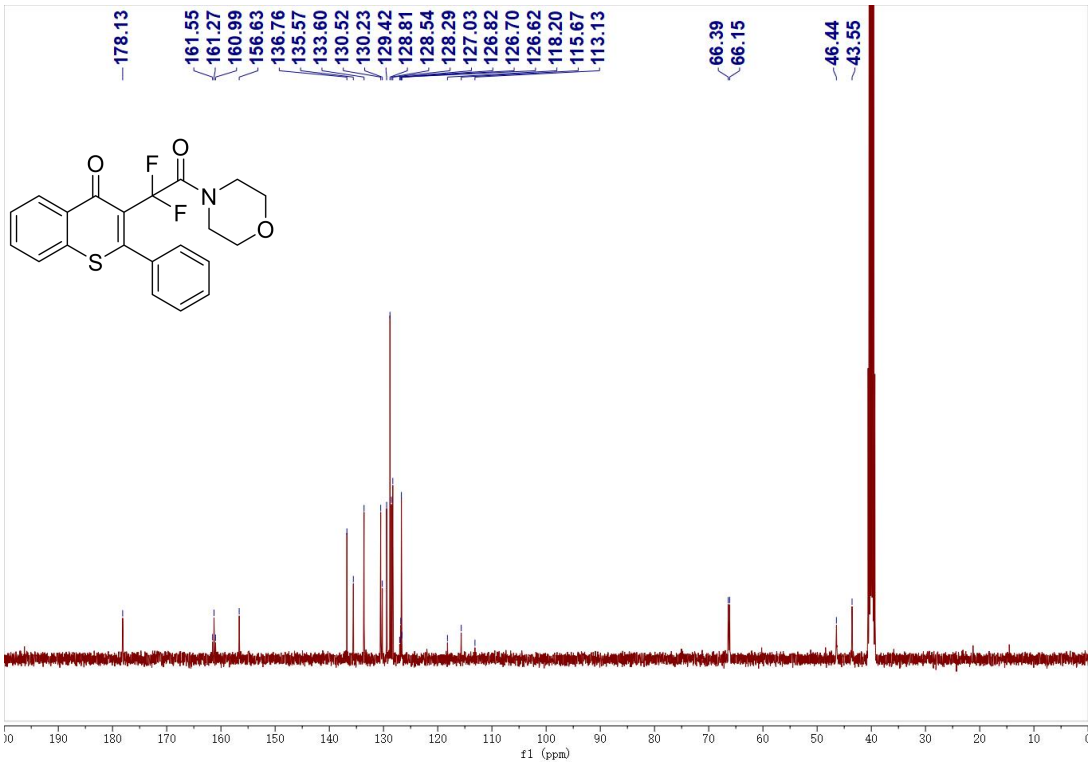


^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3z**

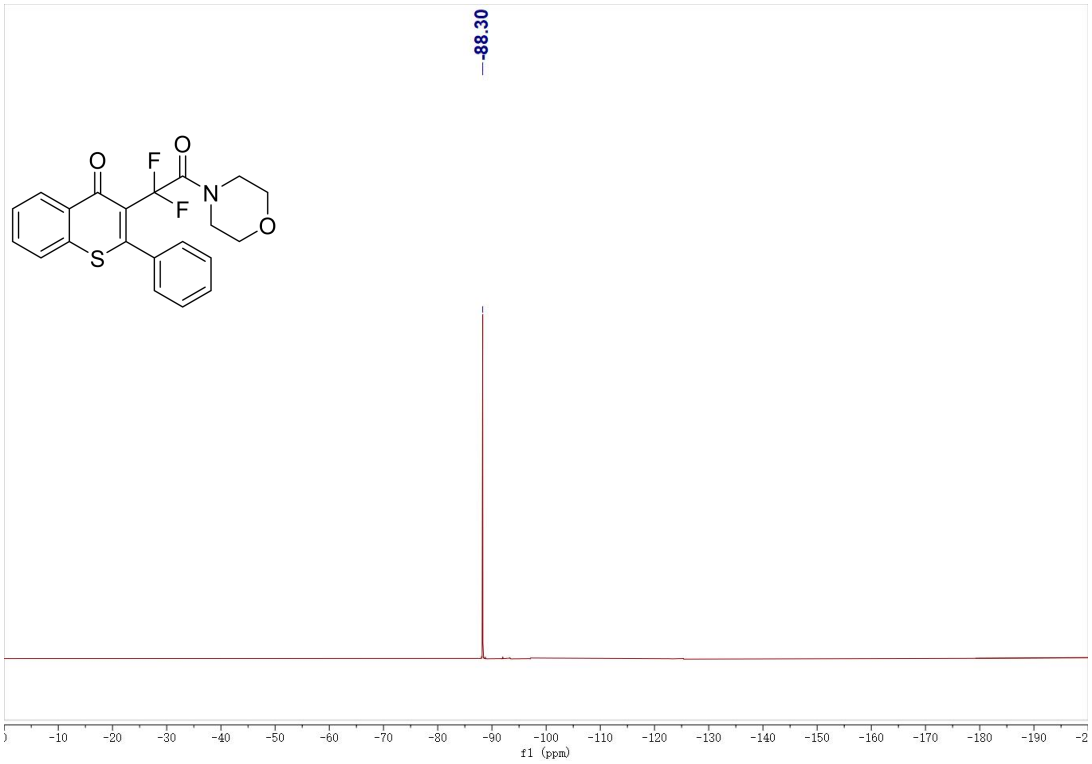
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **3aa**



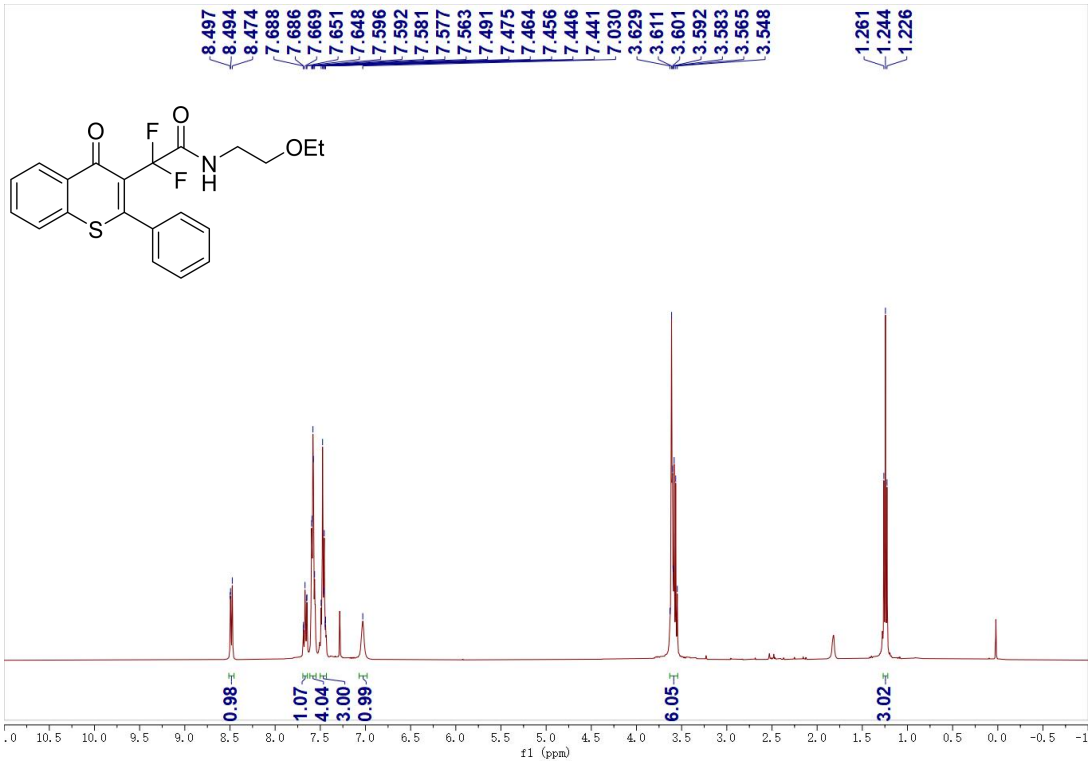
^{13}C NMR (100 MHz, DMSO-d_6) spectrum of **3aa**



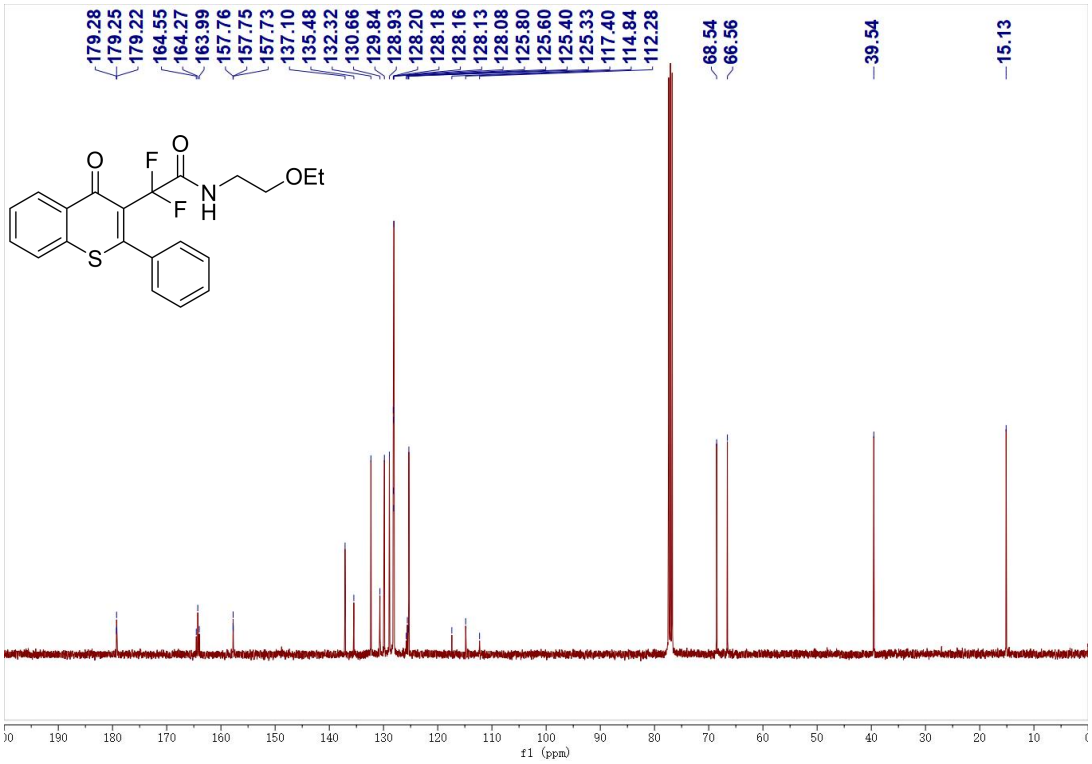
^{19}F NMR (376 MHz, DMSO-d_6) spectrum of **3aa**



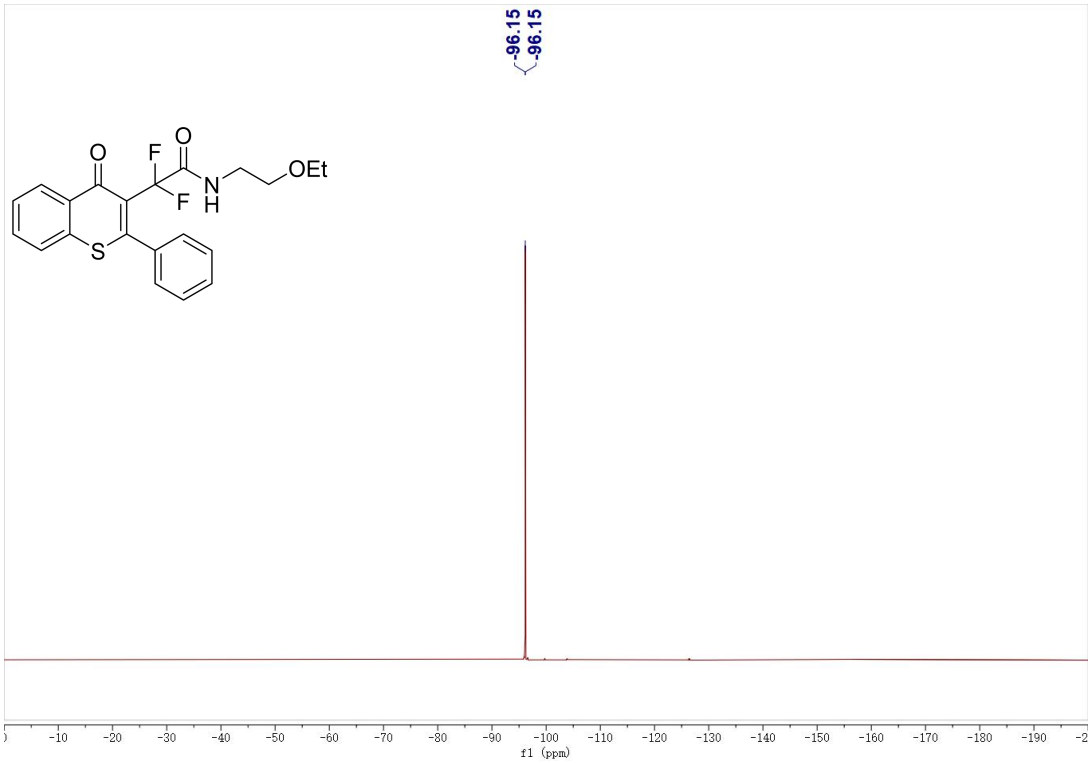
^{1}H NMR (400 MHz, Chloroform-d) spectrum of **3ab**



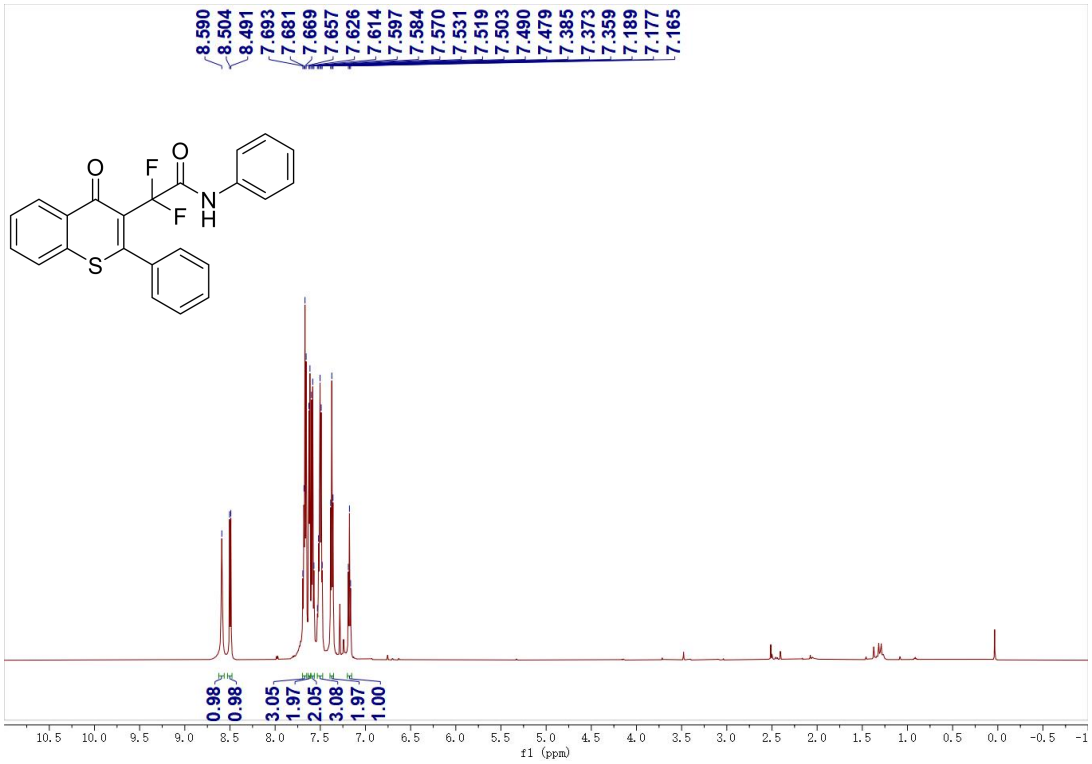
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3ab**



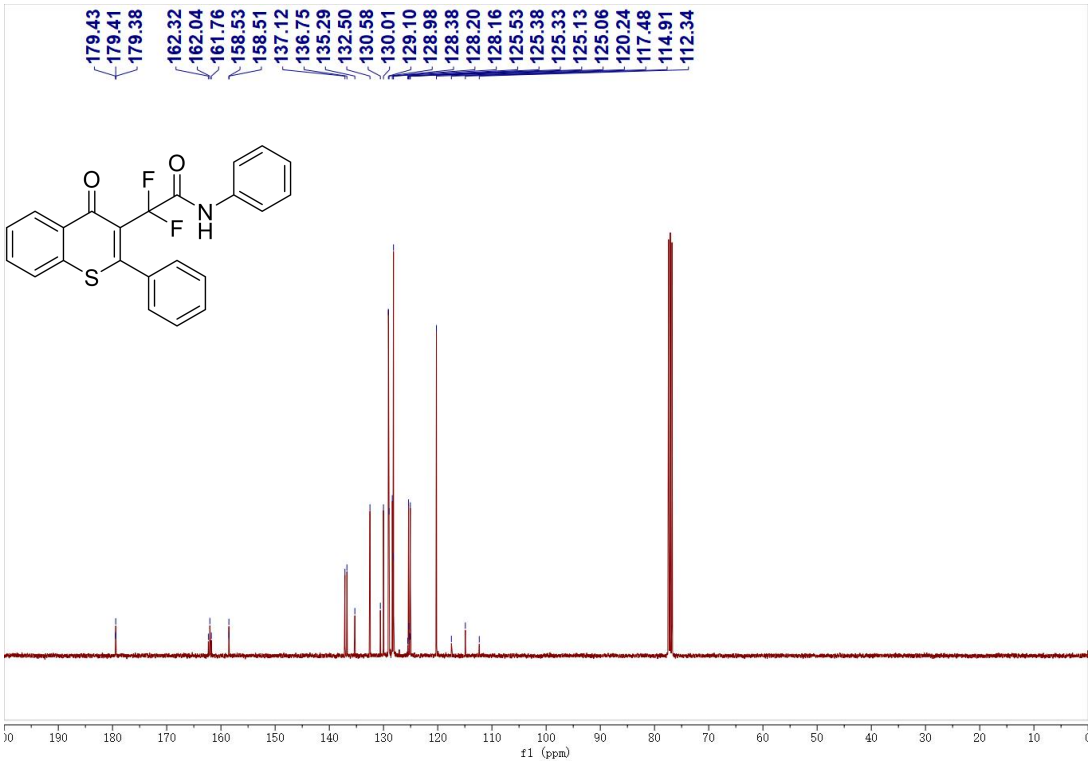
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3ab**



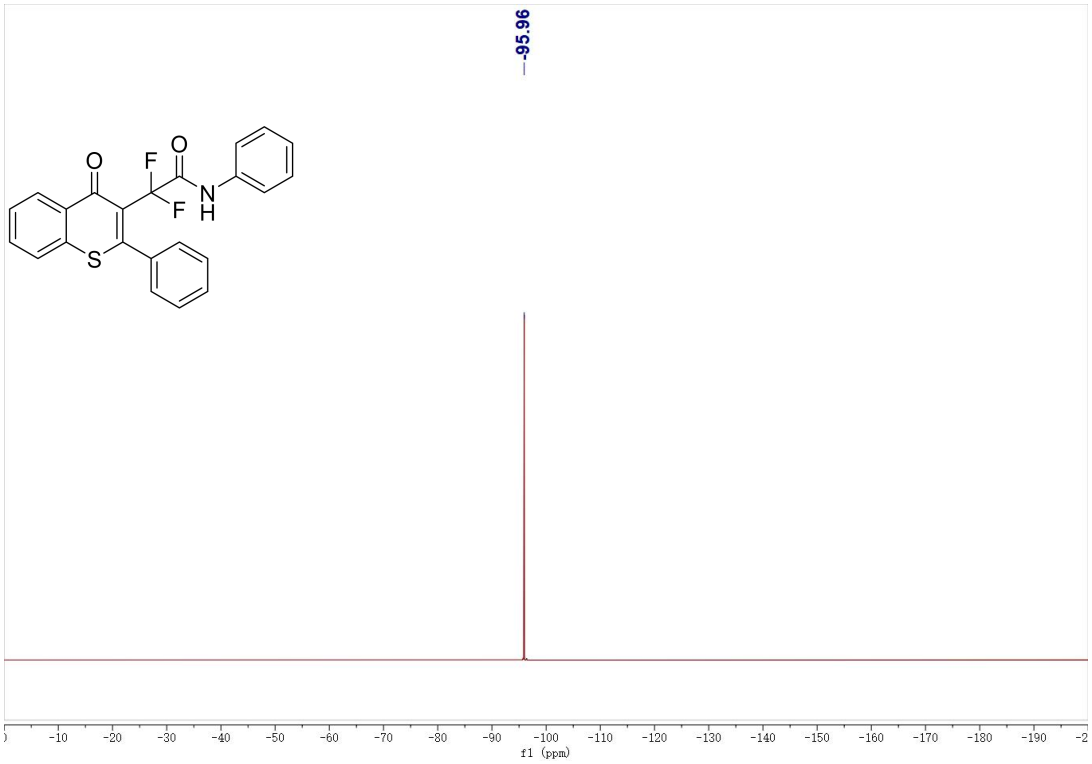
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ac**



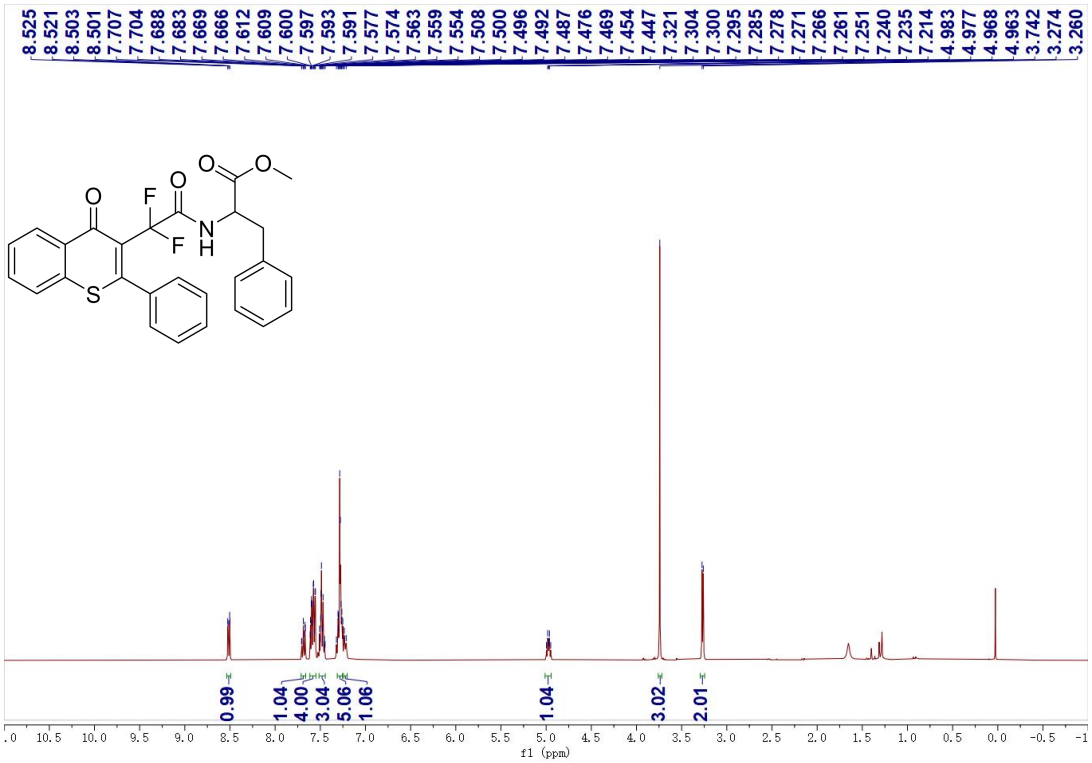
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3ac**



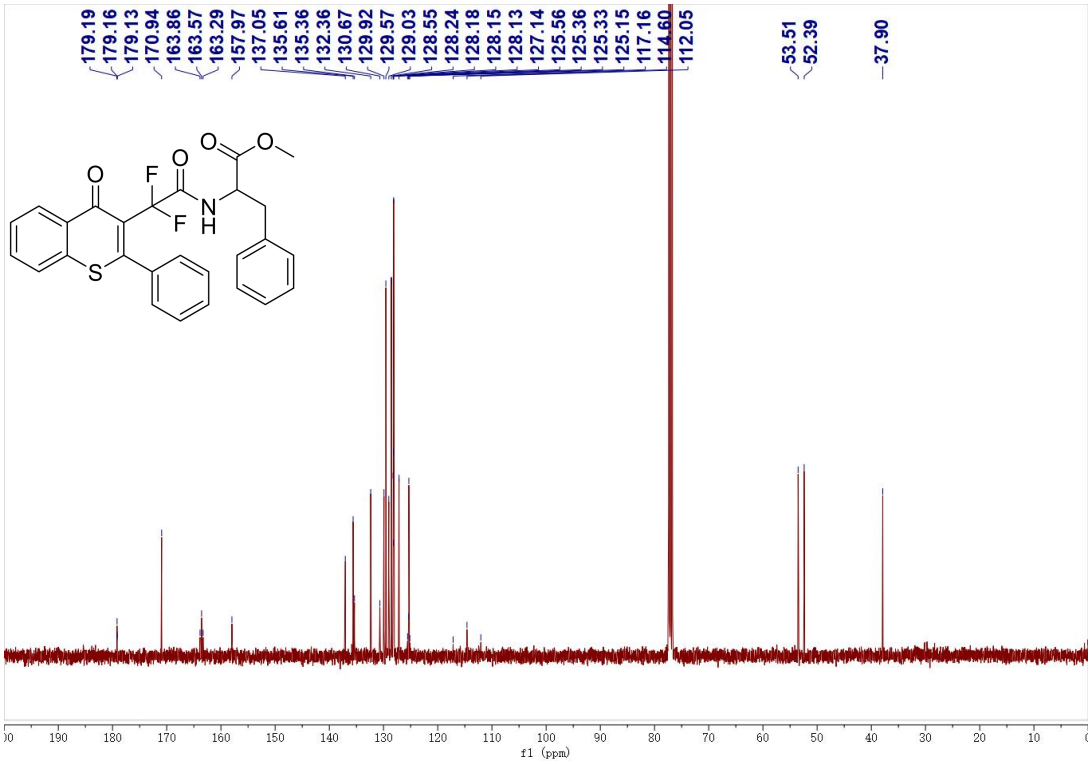
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3ac**



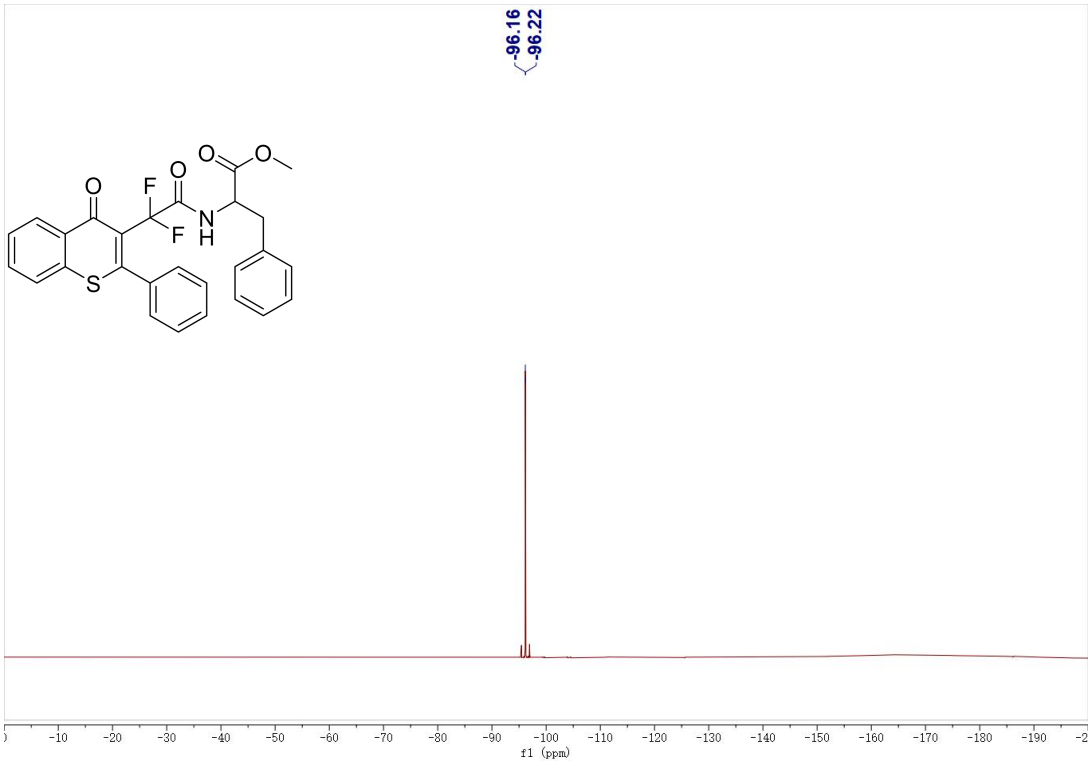
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3ad**



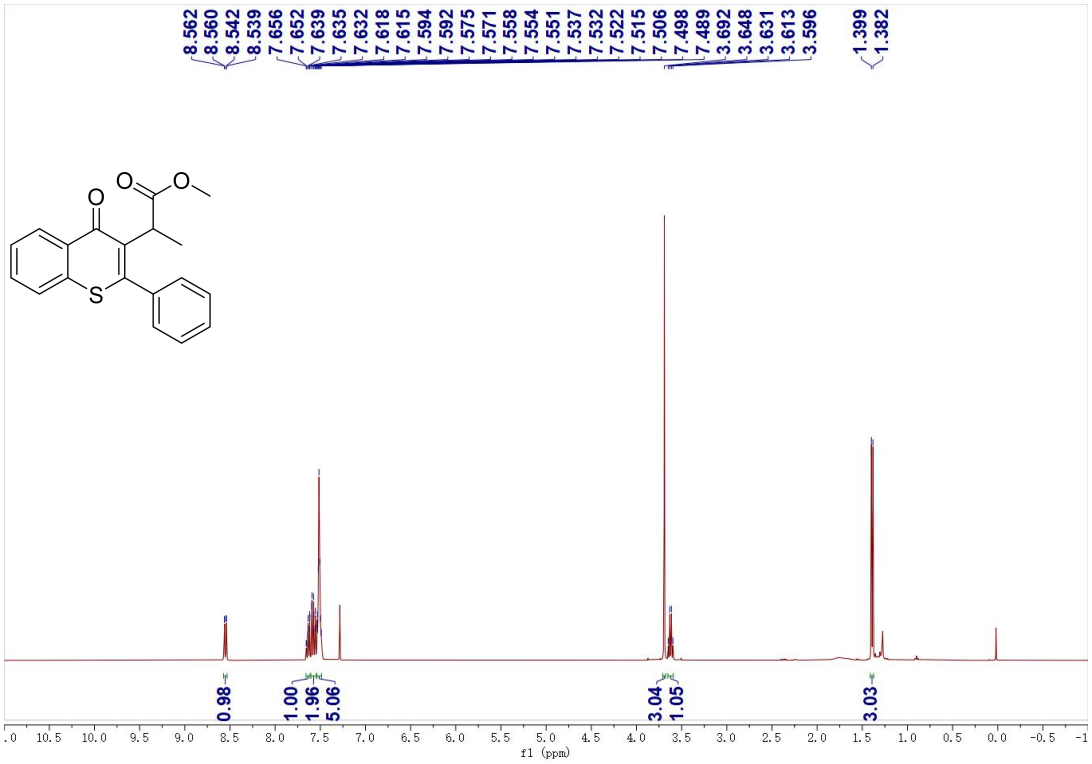
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3ad**



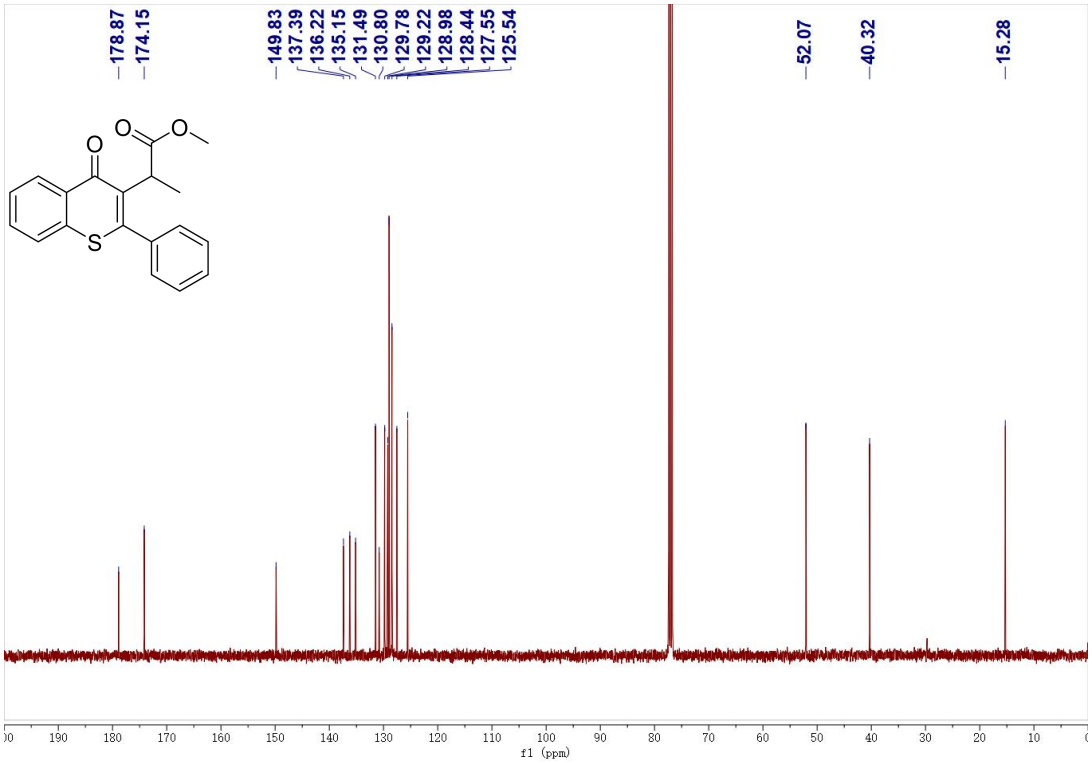
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3ad**



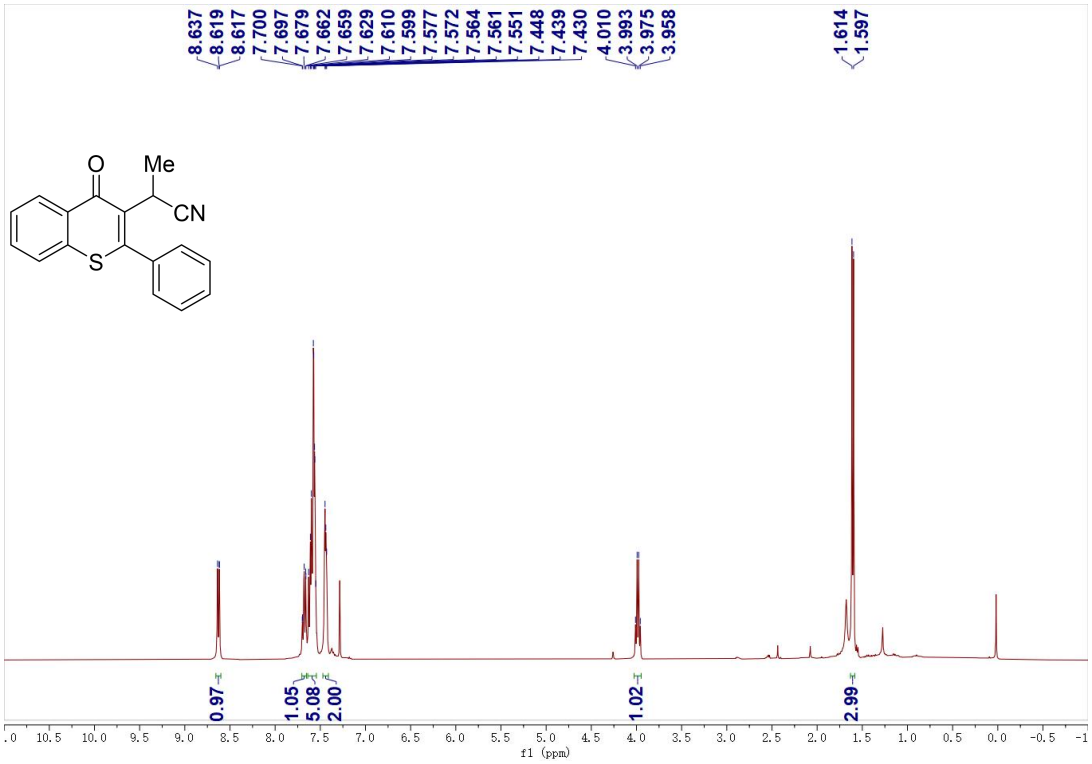
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3ae**



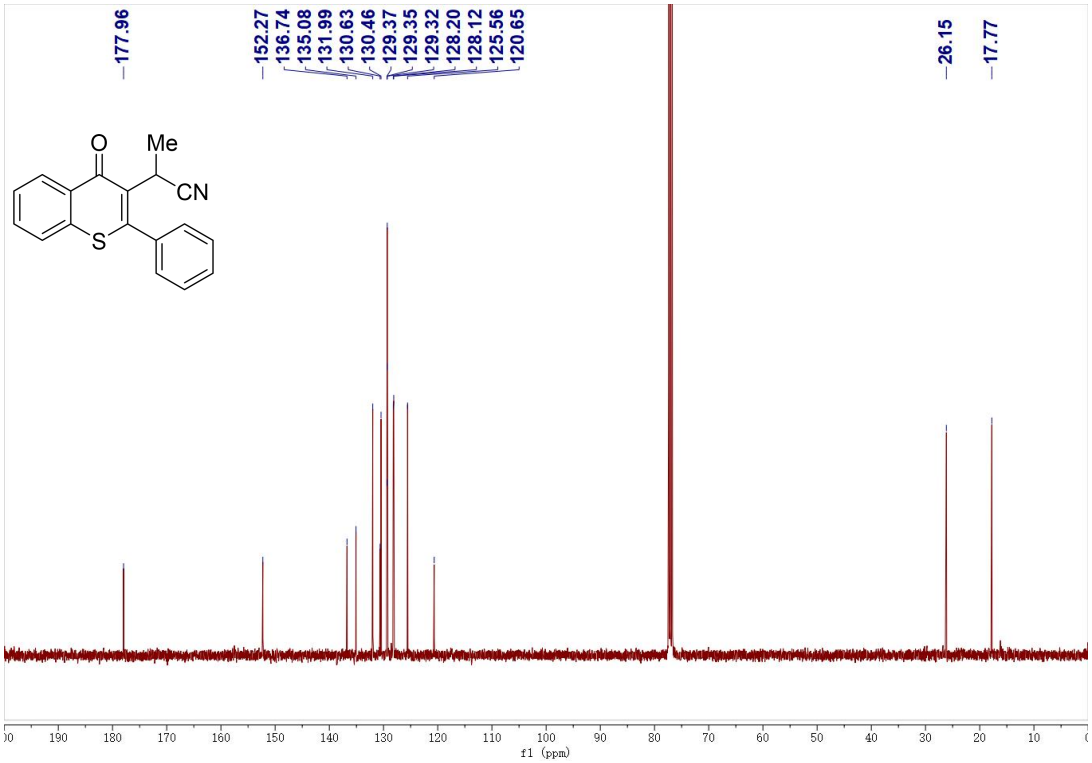
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3ae**



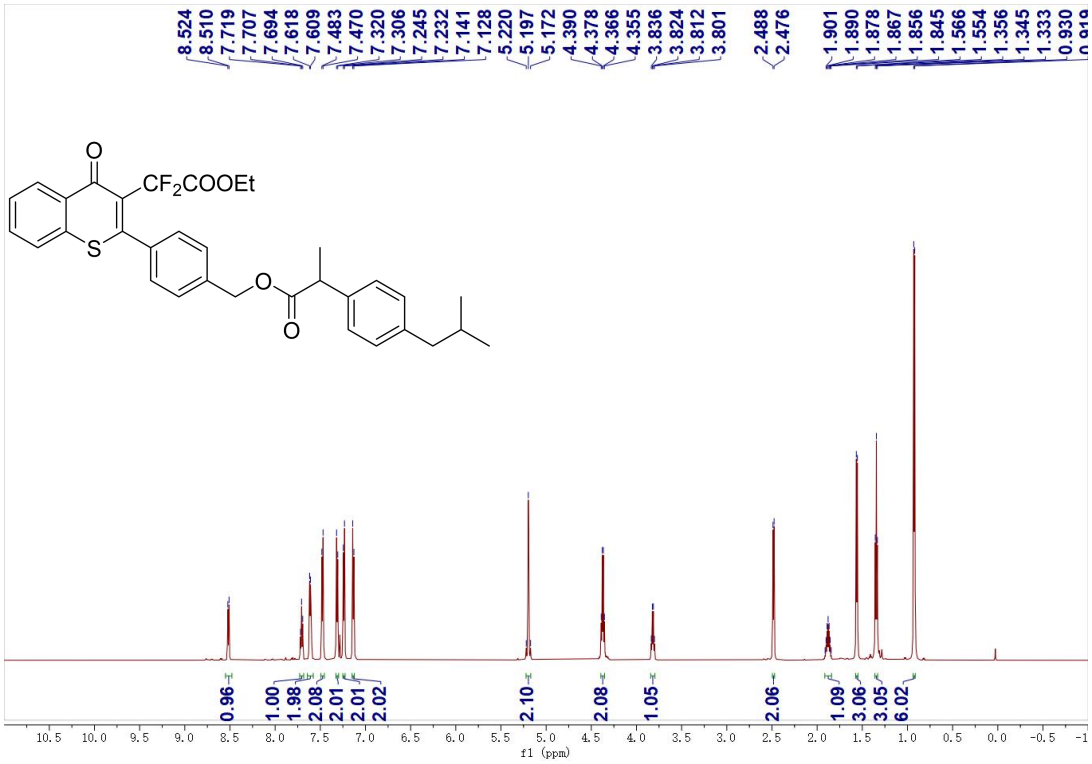
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3af**



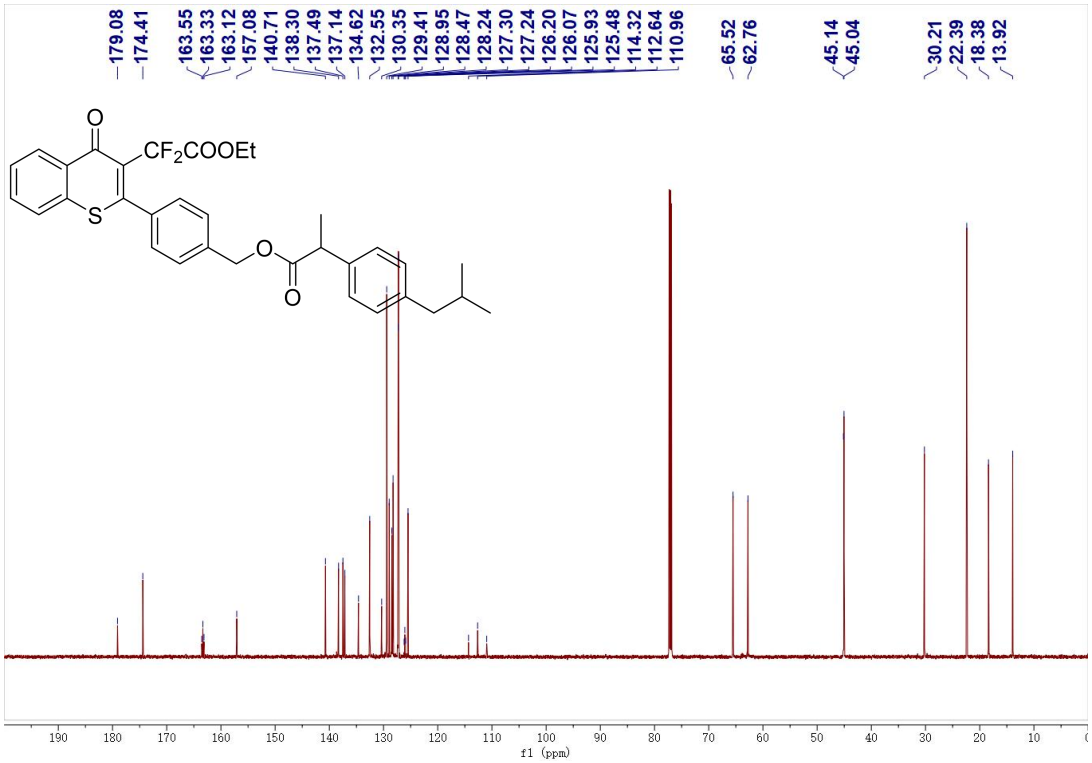
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3af**



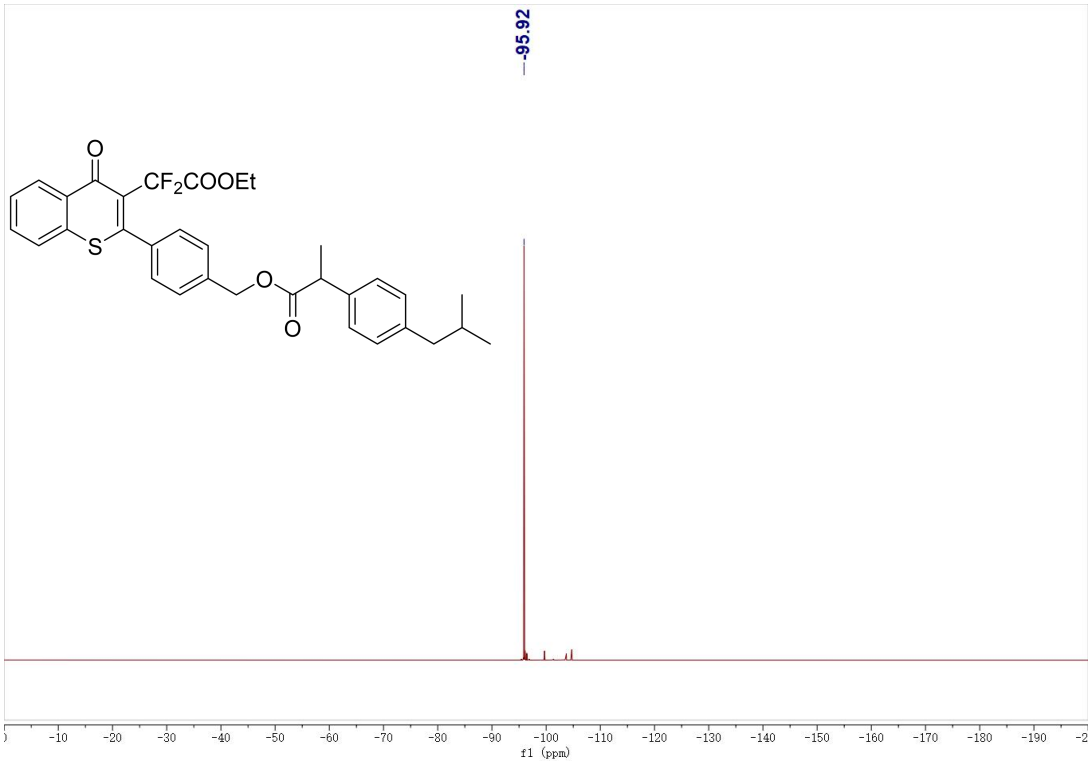
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ag**



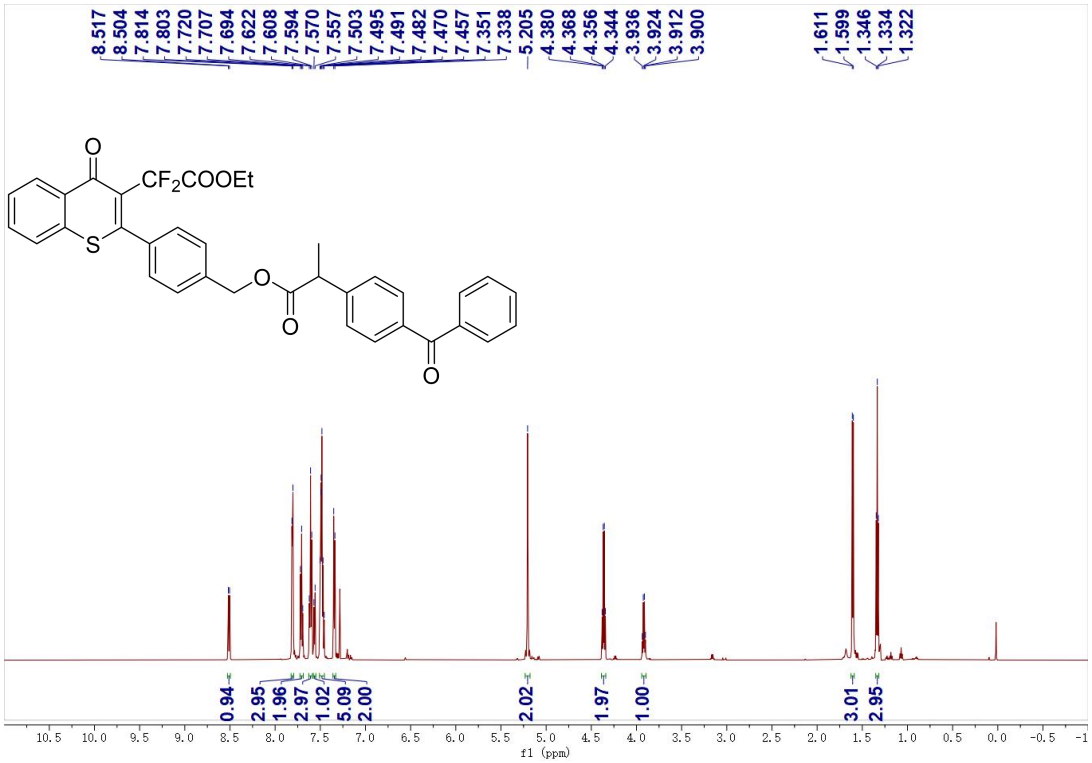
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3ag**



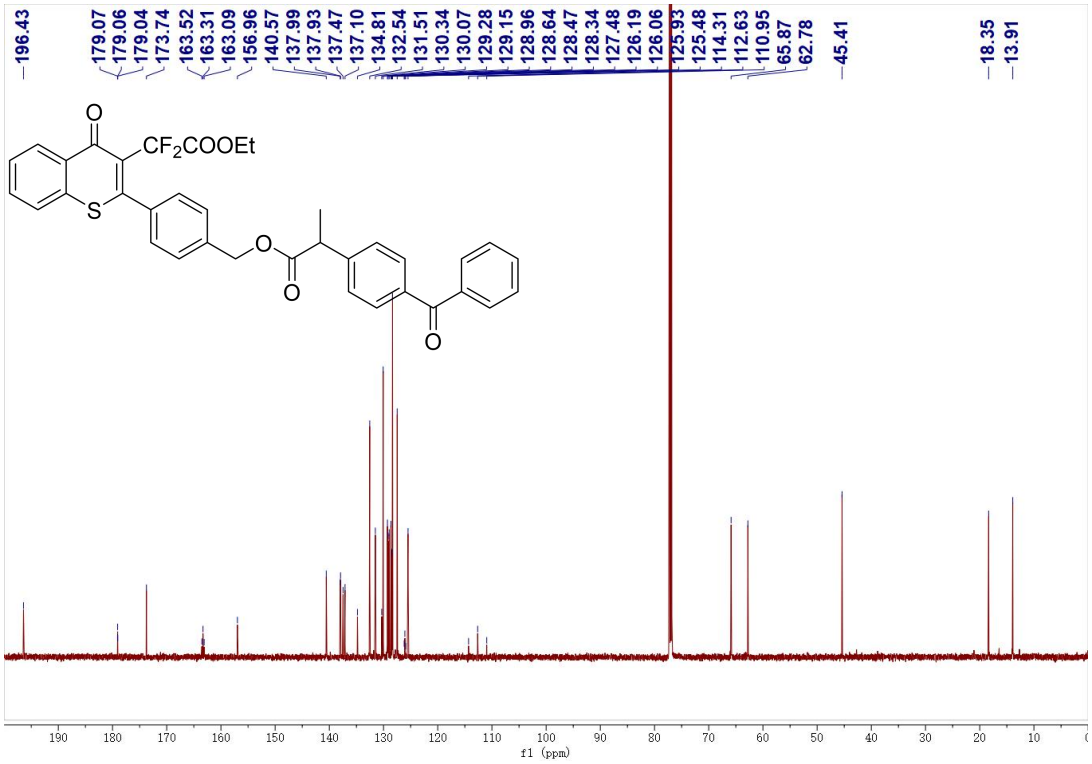
^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3ag**



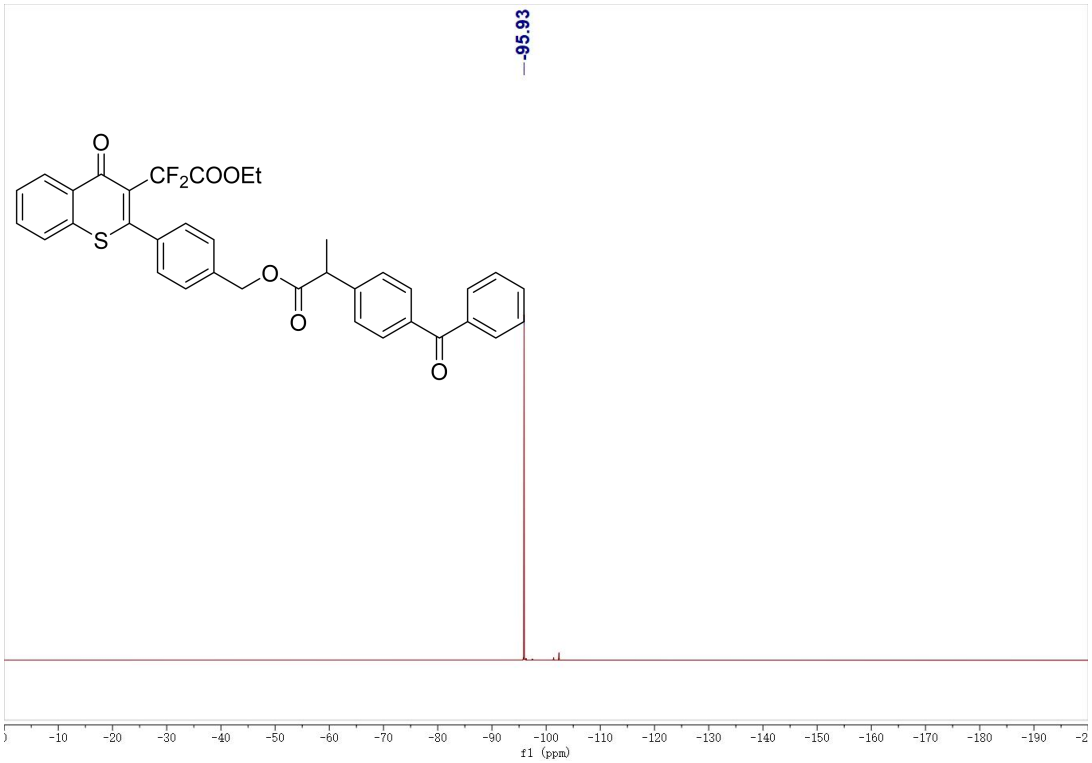
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ah**



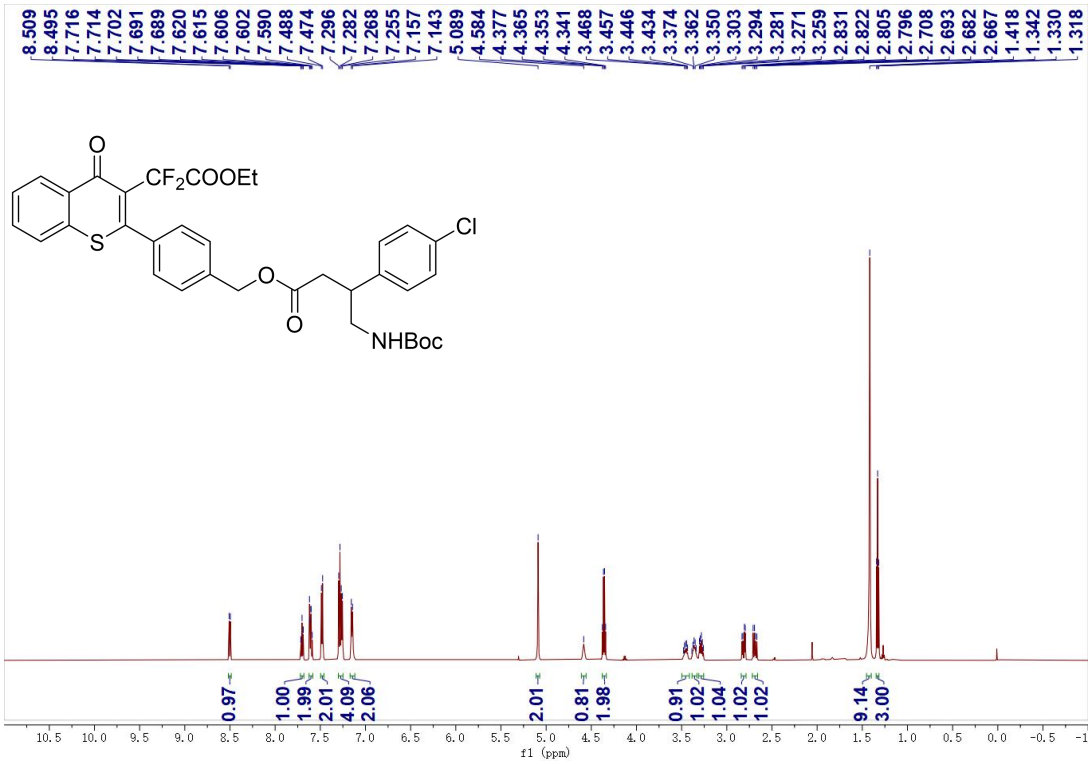
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3ah**



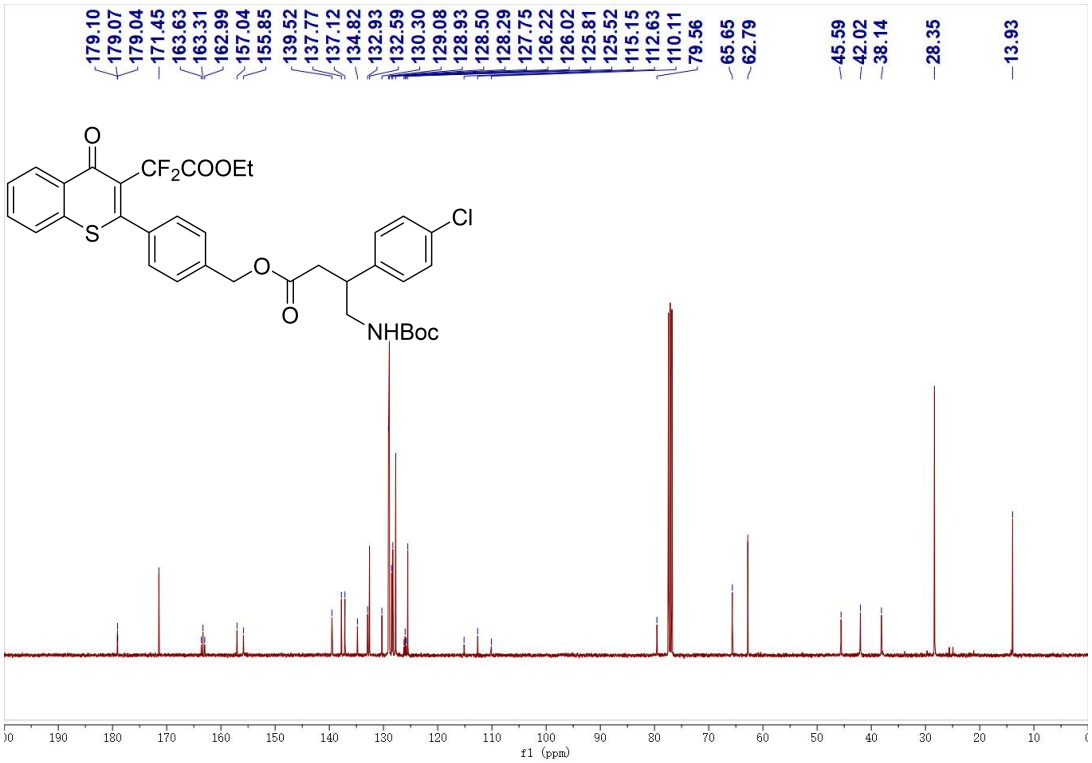
^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3ah**



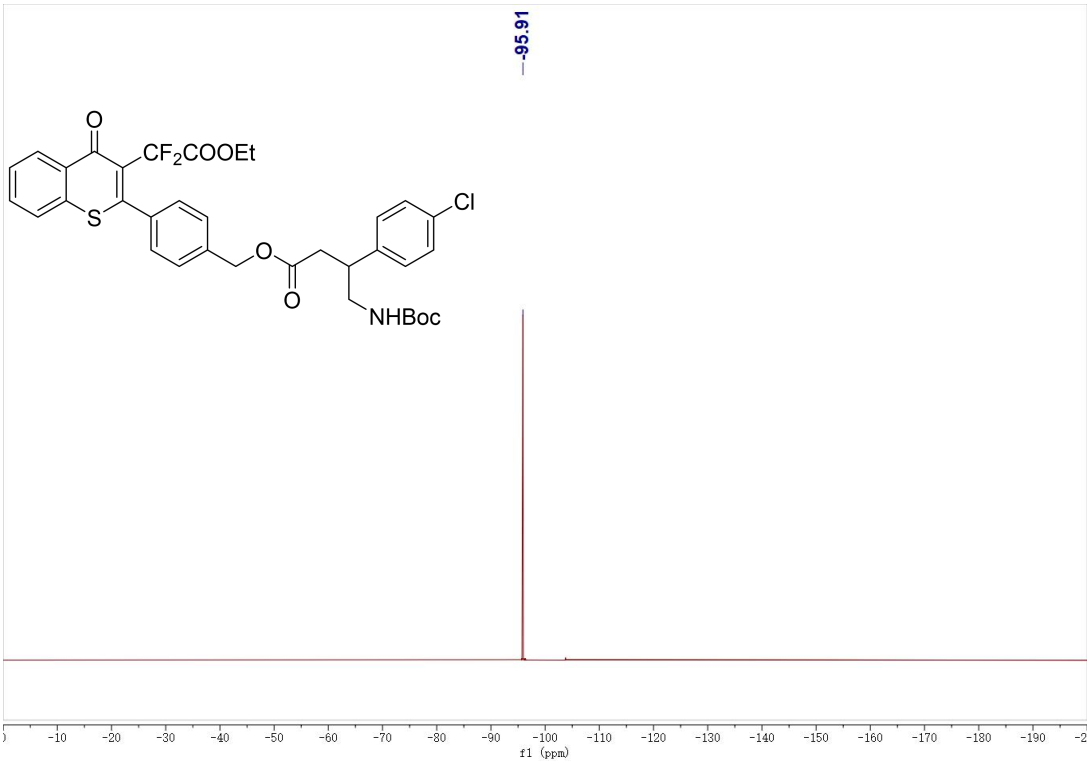
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ai**



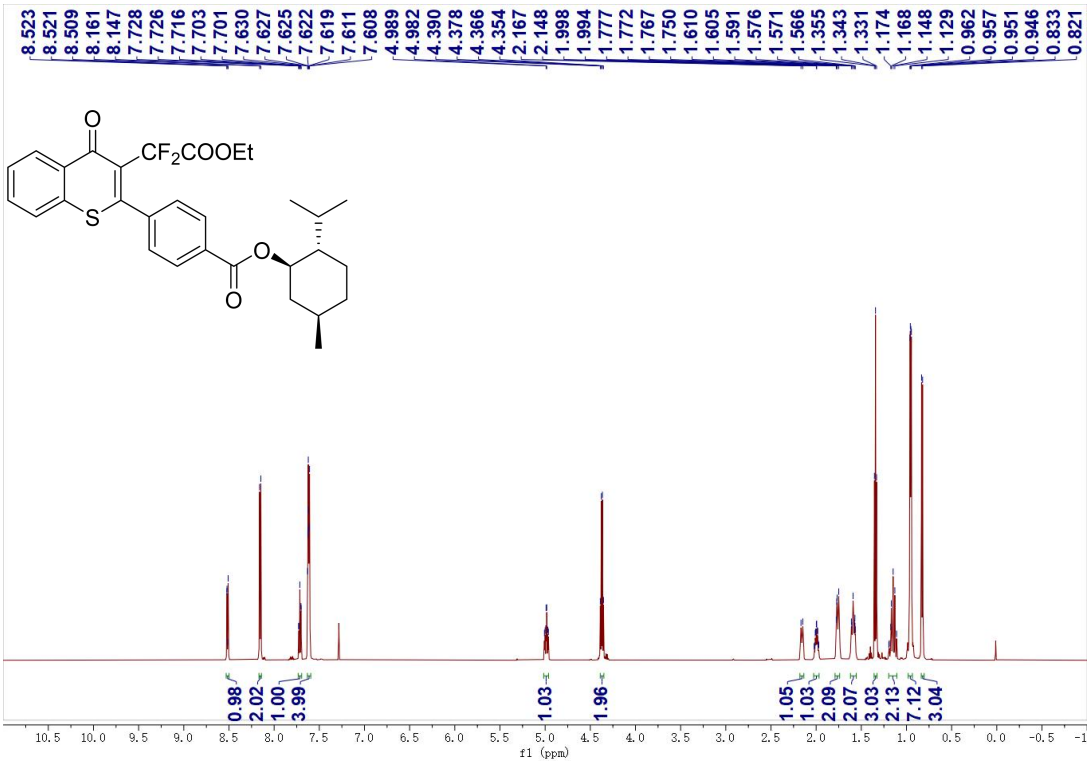
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3ai**



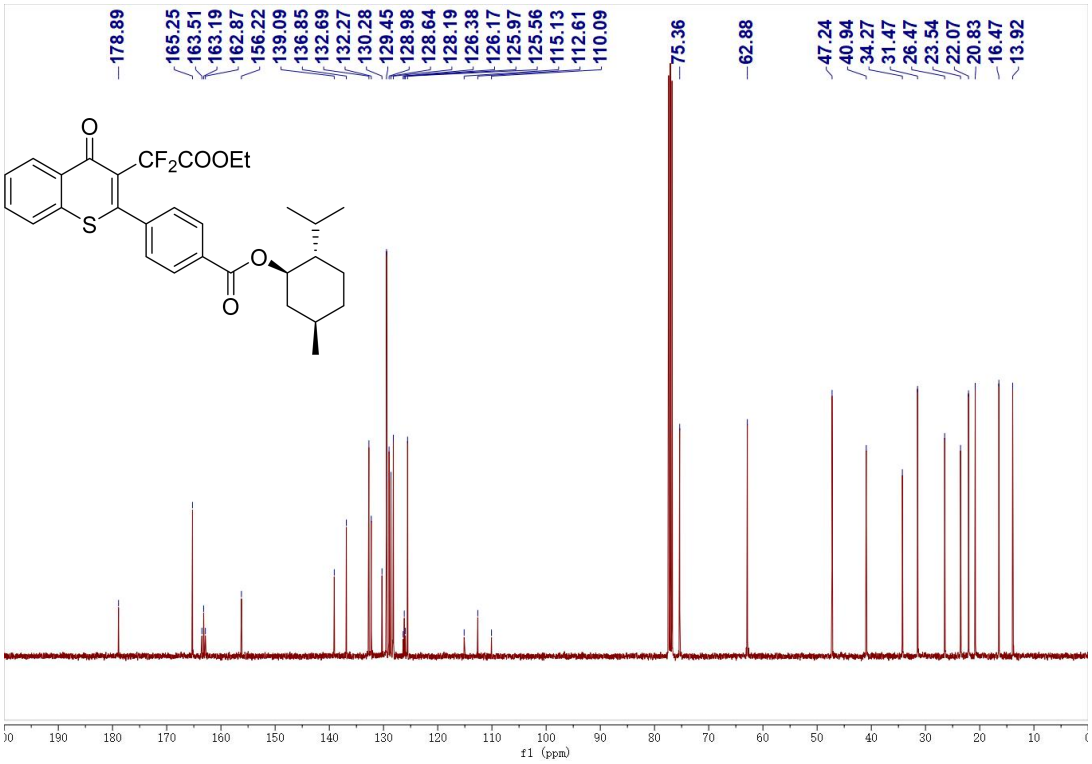
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3ai**



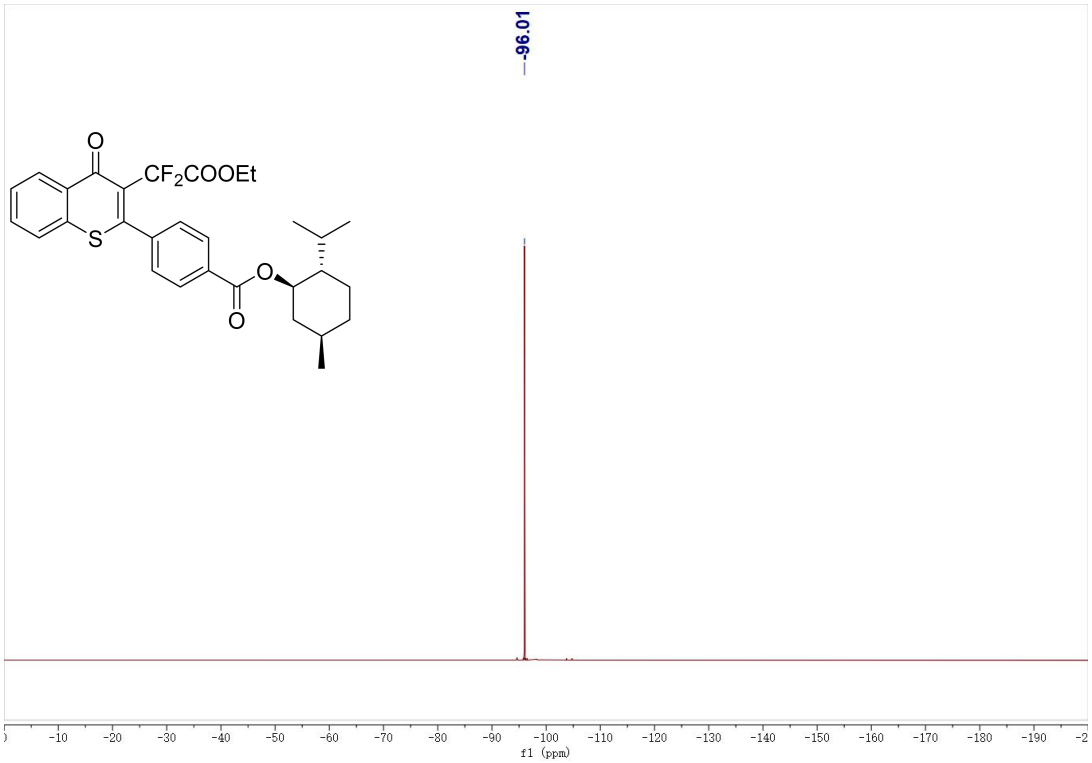
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3aj**



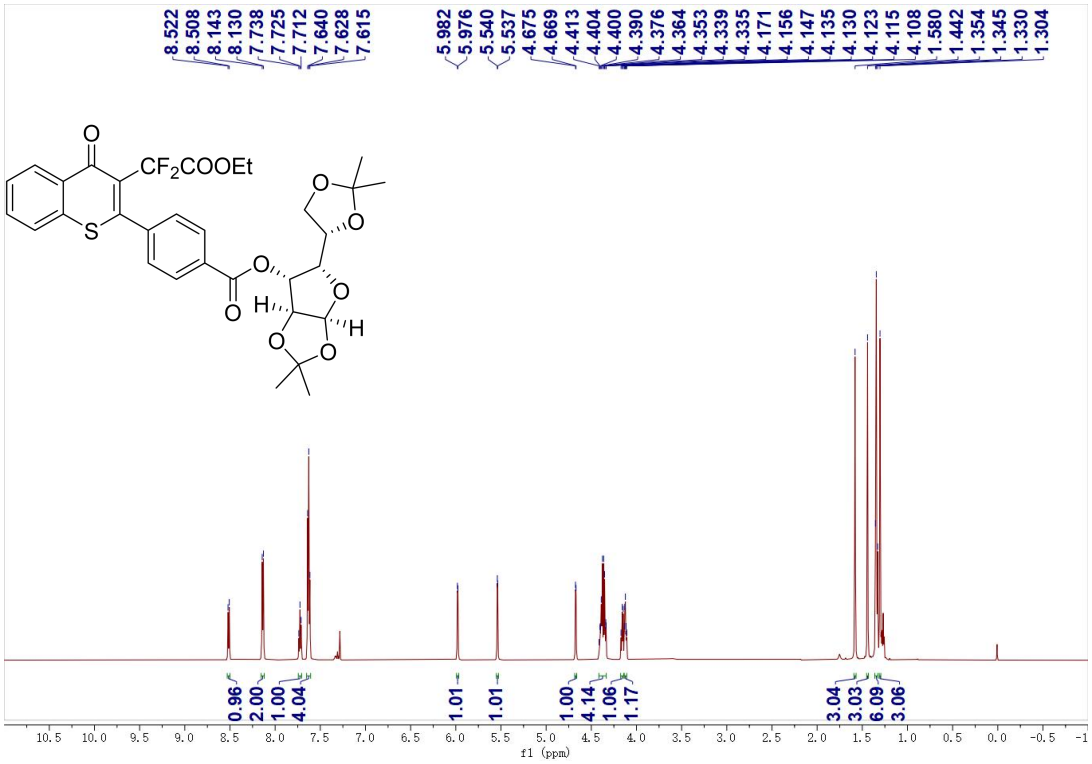
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3aj**



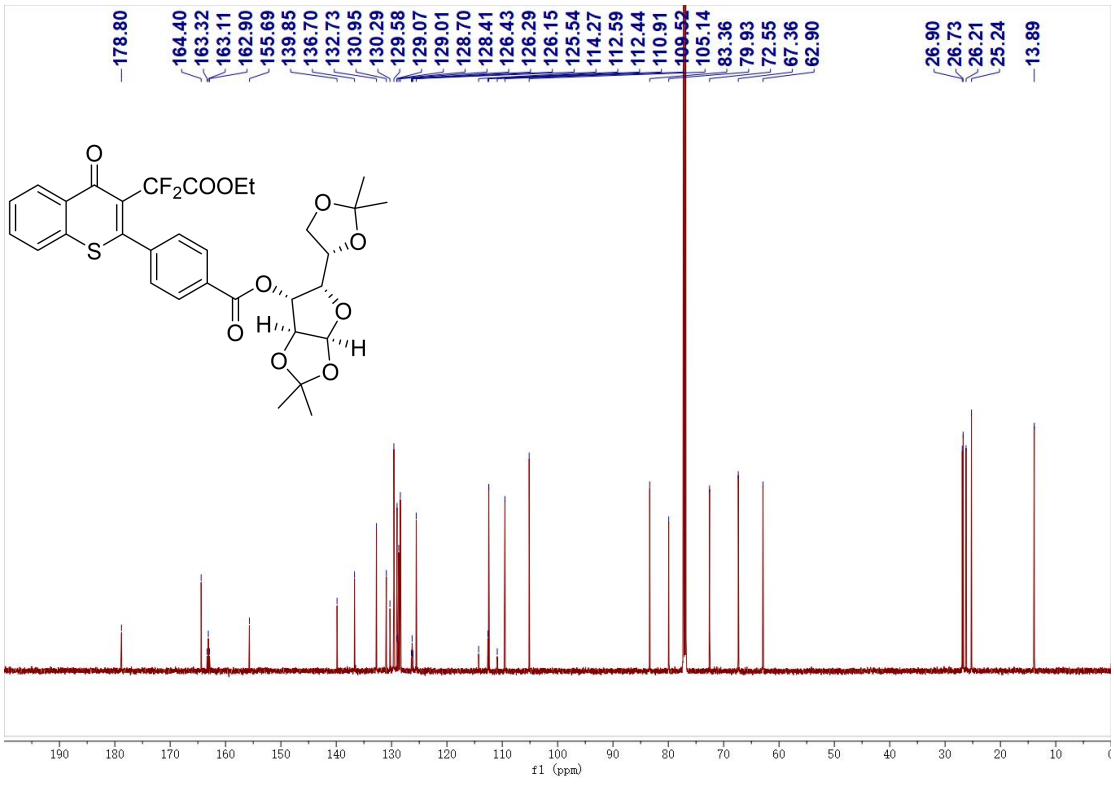
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3aj**



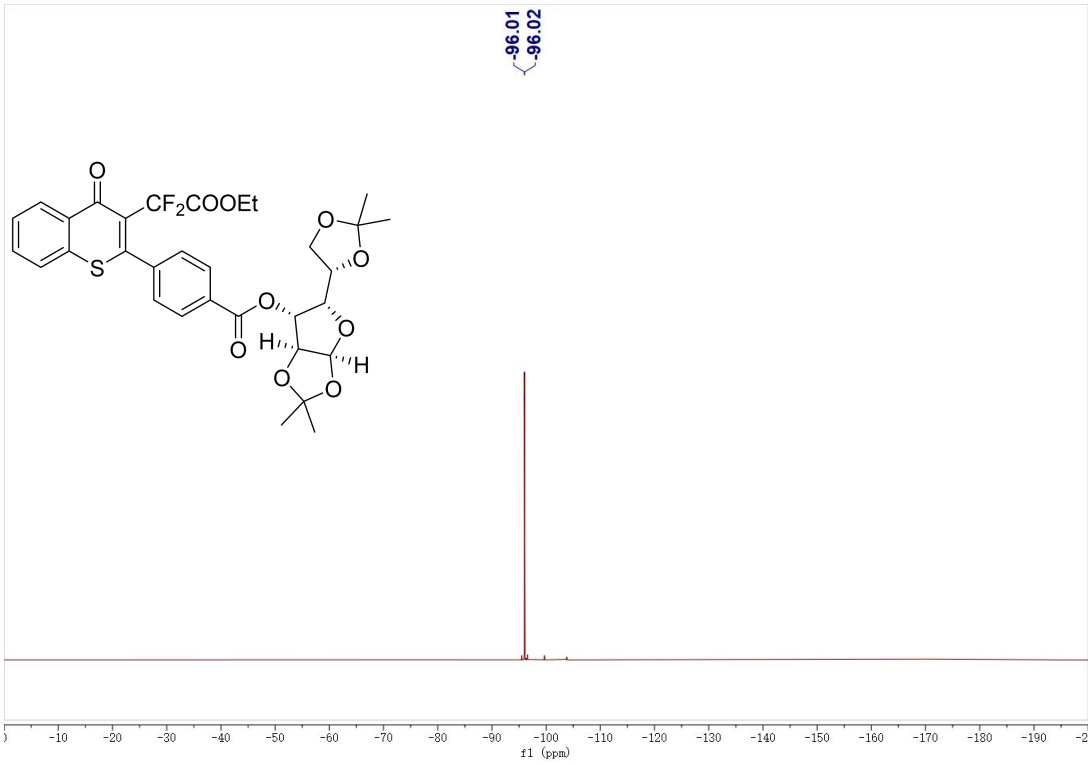
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ak**



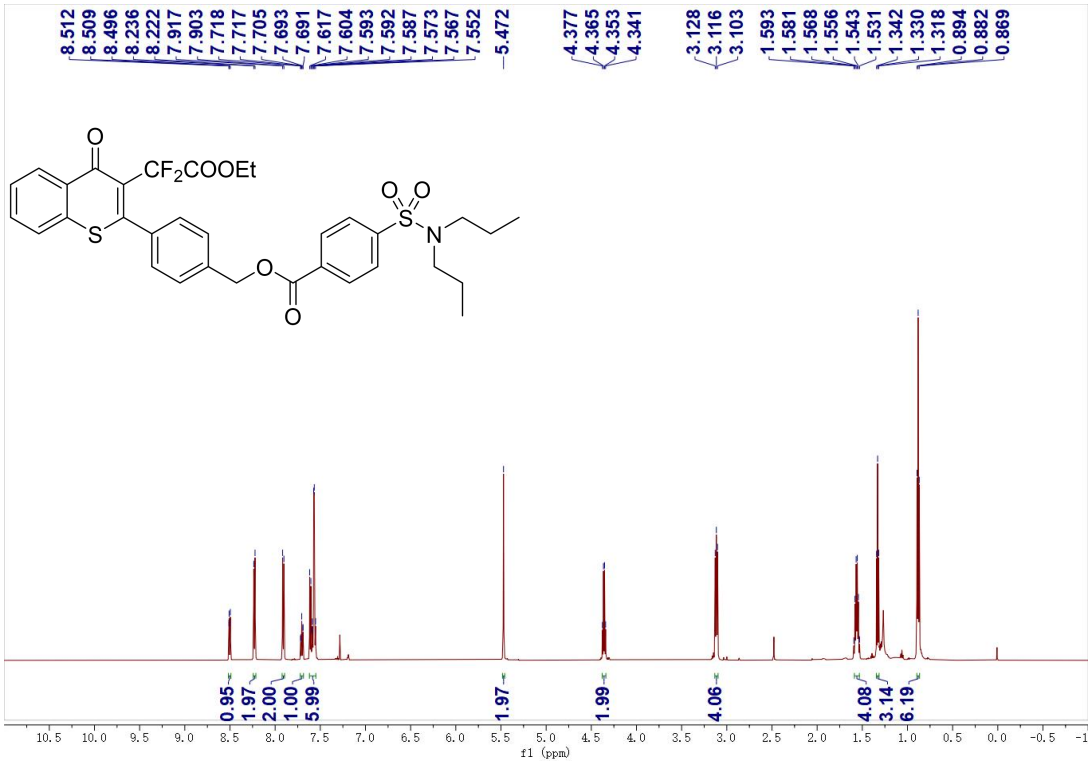
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3ak**



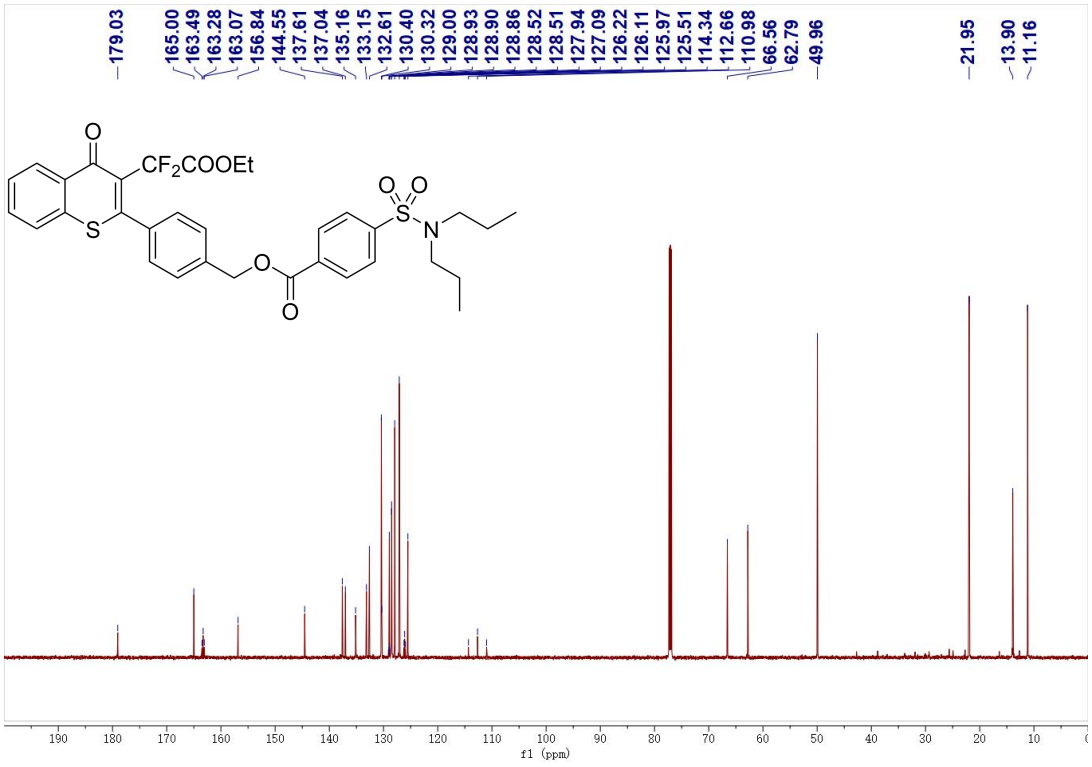
^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3ak**



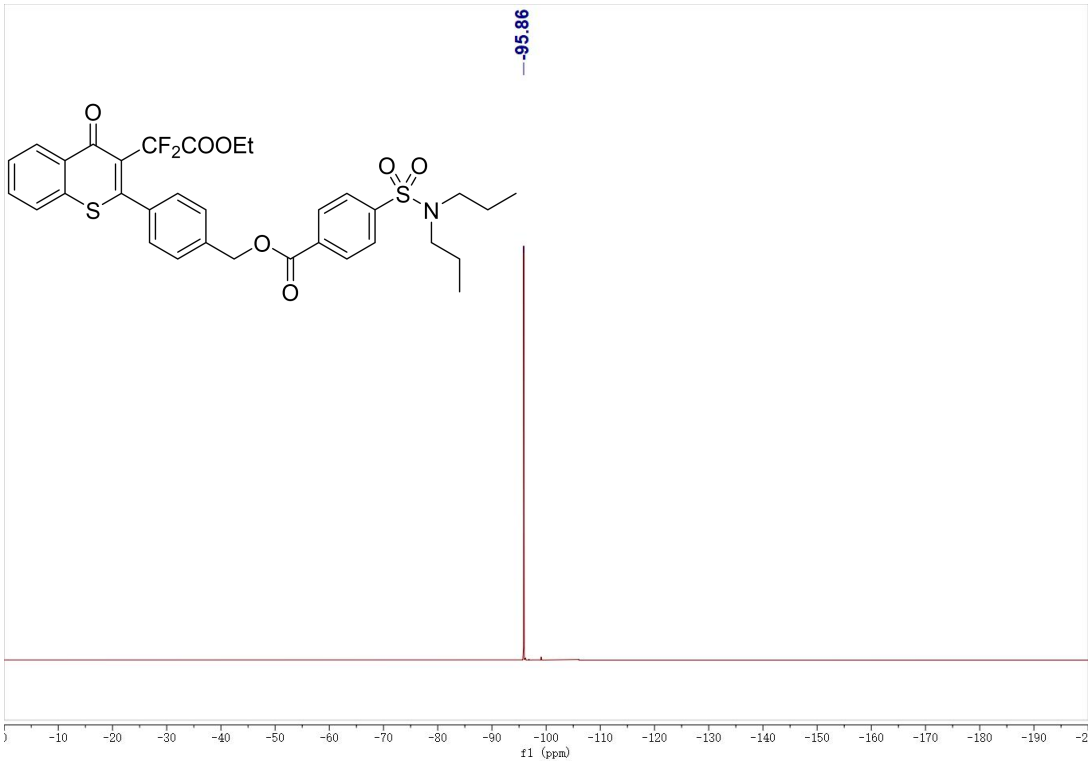
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3al**



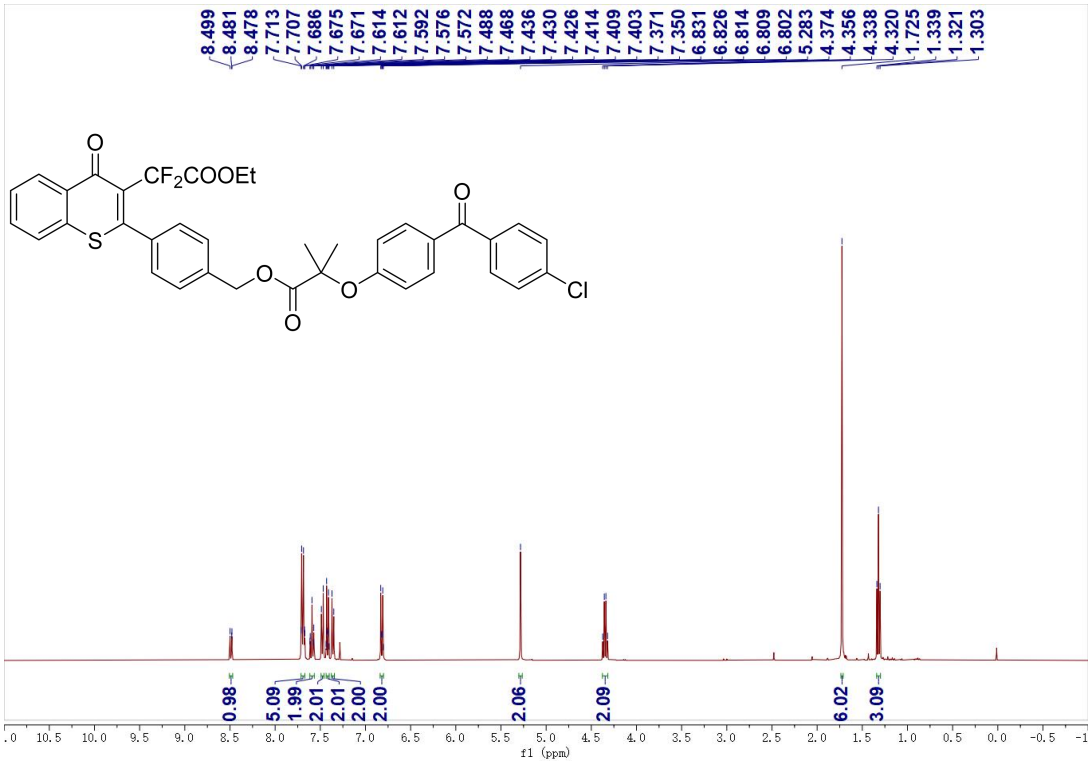
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3al**



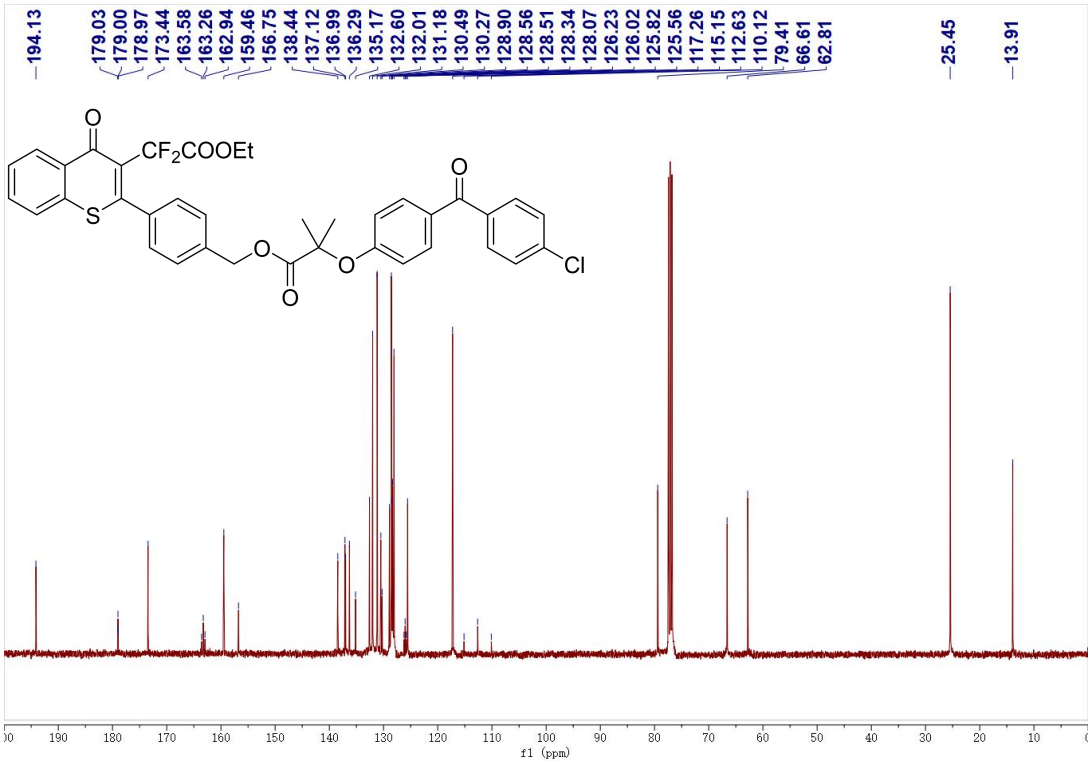
^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3al**



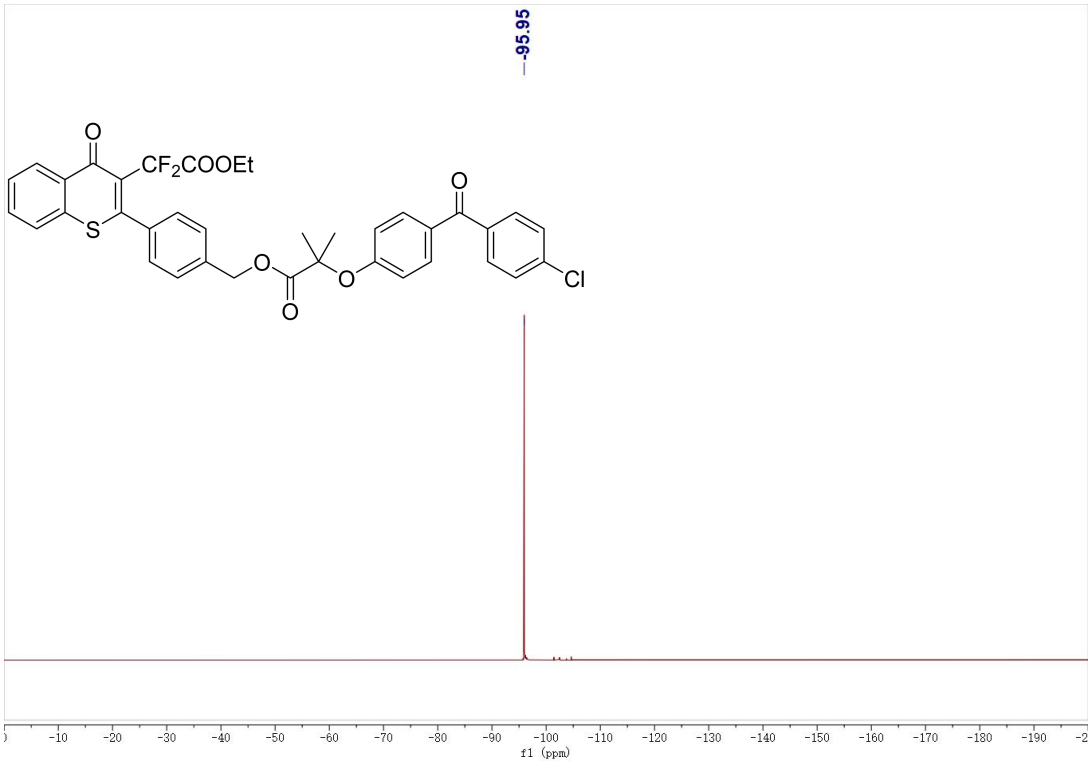
^{1}H NMR (400 MHz, Chloroform-*d*) spectrum of **3am**



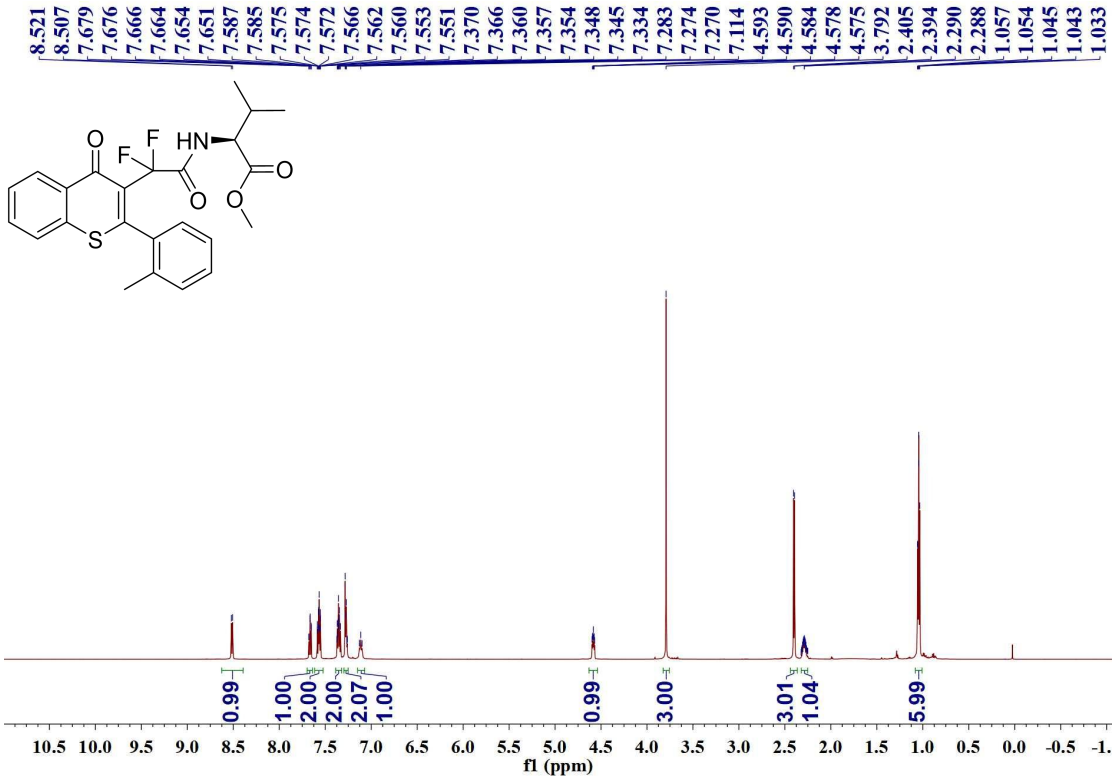
^{13}C NMR (100 MHz, Chloroform-*d*) spectrum of **3am**



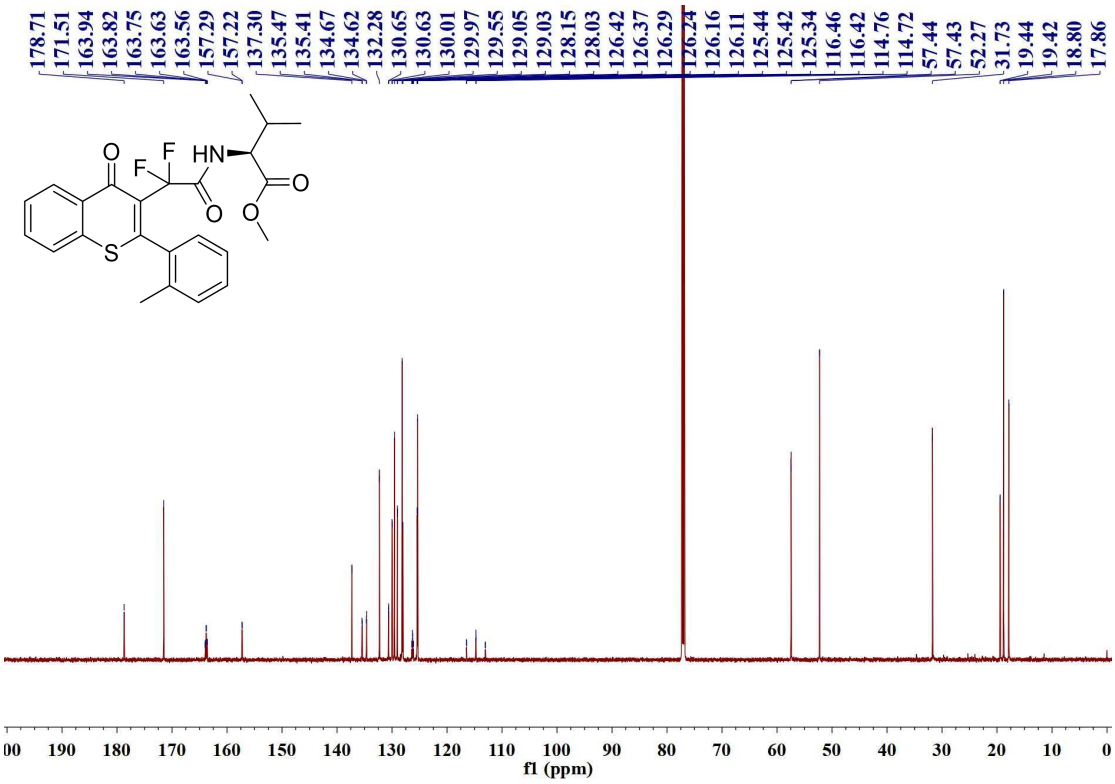
^{19}F NMR (376 MHz, Chloroform-*d*) spectrum of **3am**



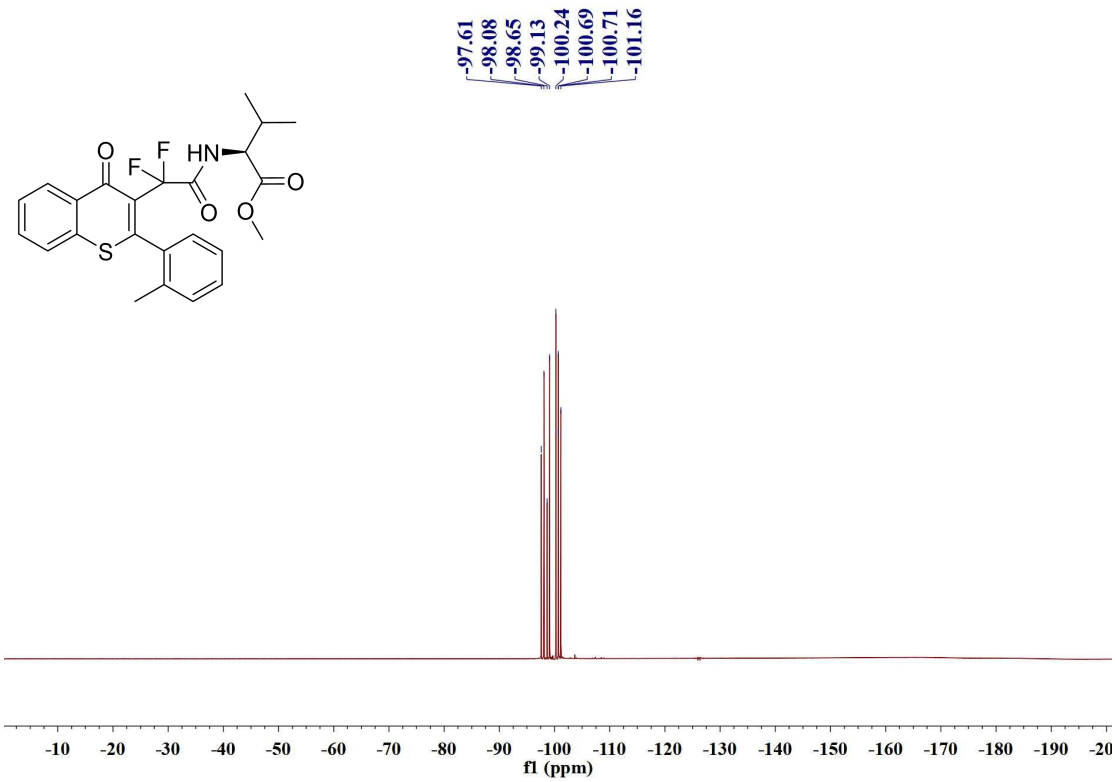
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3an**



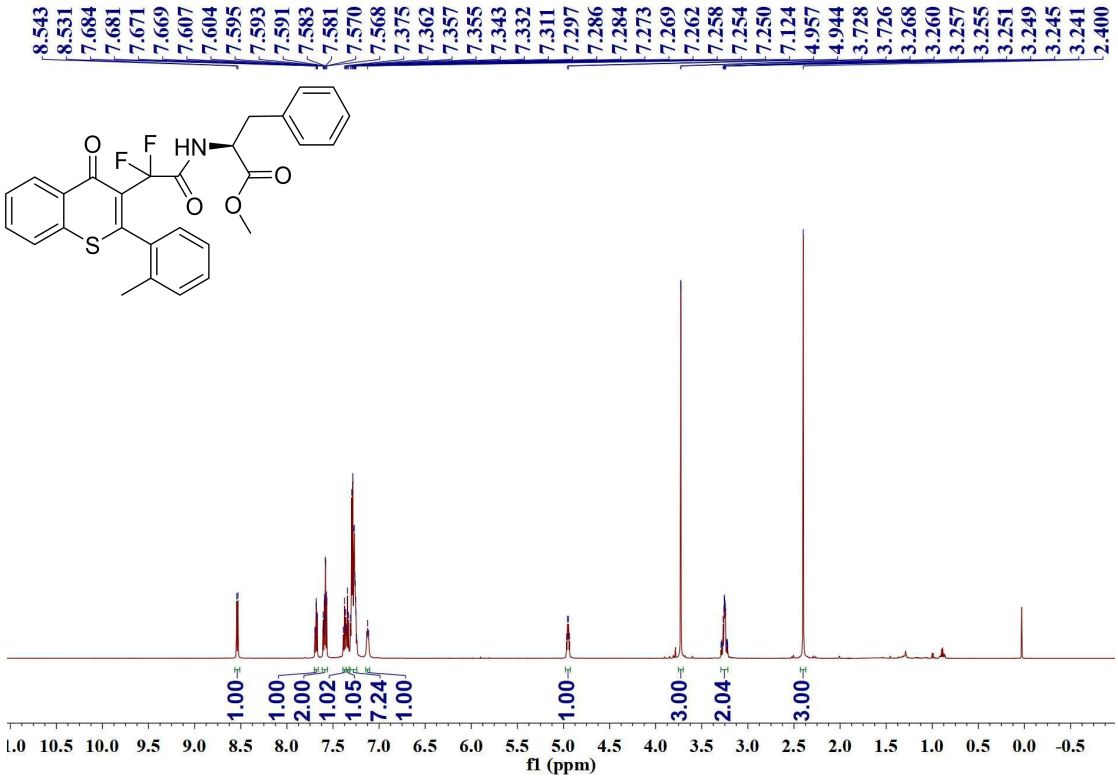
^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3an**



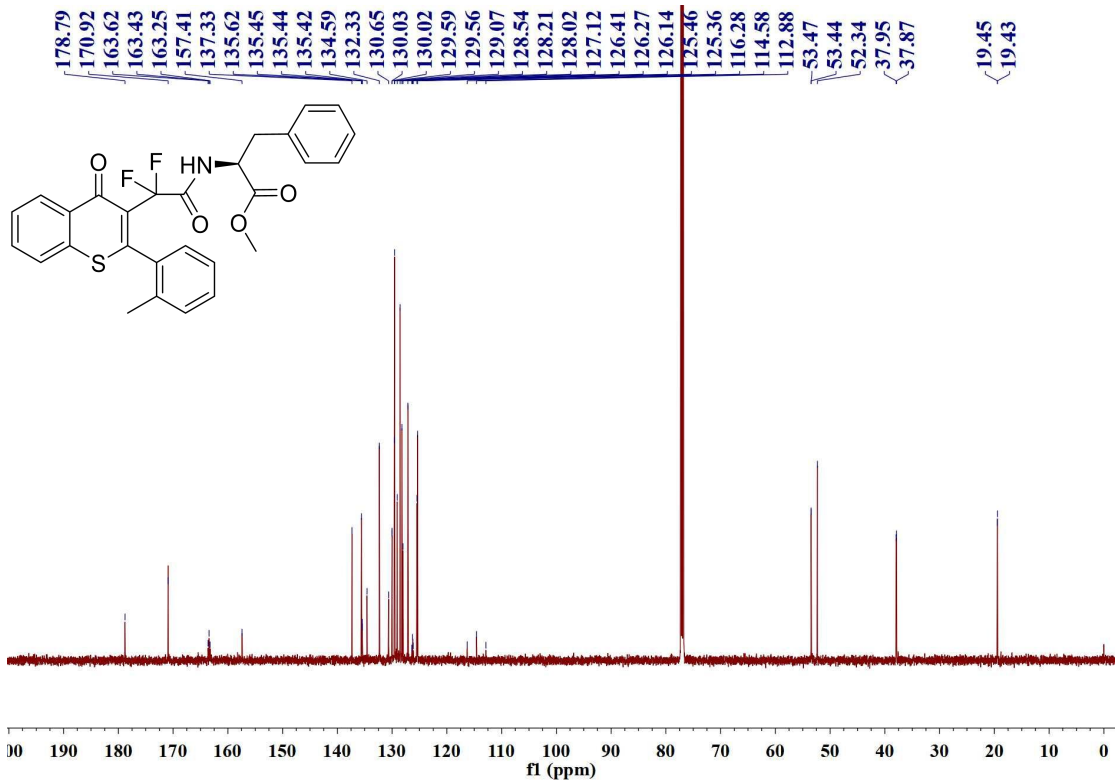
^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3an**



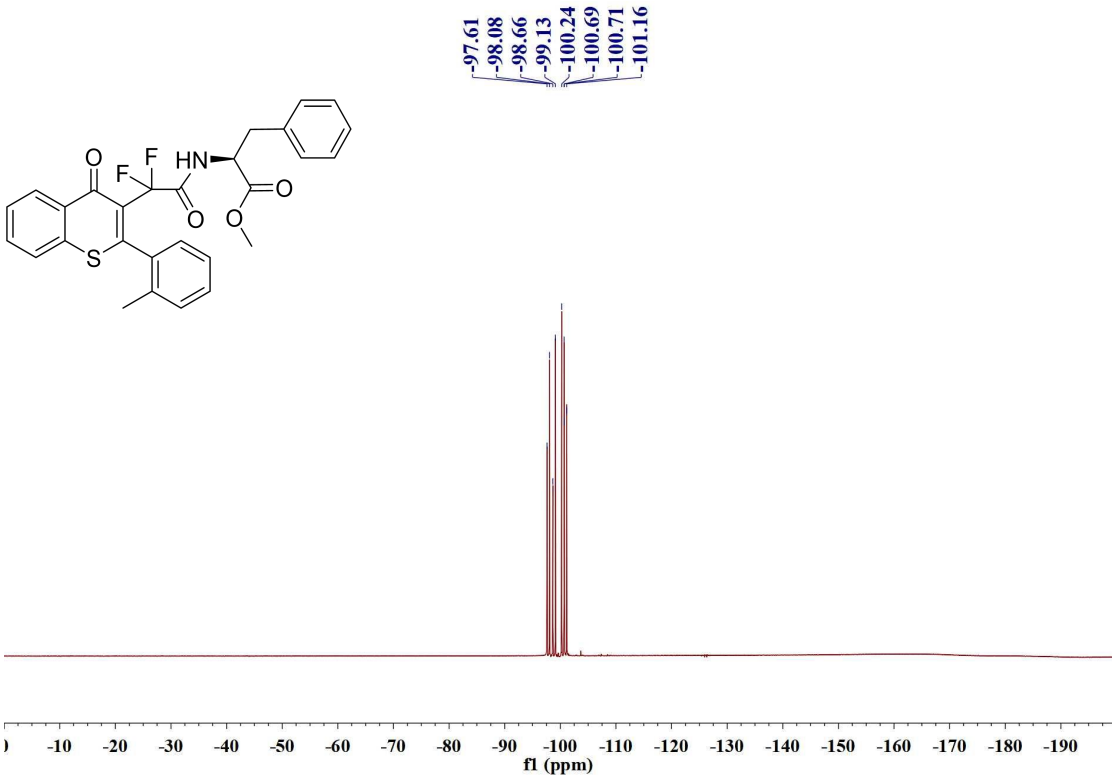
^{1}H NMR (600 MHz, Chloroform-*d*) spectrum of **3ao**



^{13}C NMR (150 MHz, Chloroform-*d*) spectrum of **3ao**



^{19}F NMR (565 MHz, Chloroform-*d*) spectrum of **3ao**



5. References

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