Supporting information

Silver-catalyzed C3 Arylthiodifluoromethylation and Aryloxydifluoromethylation of Coumarins

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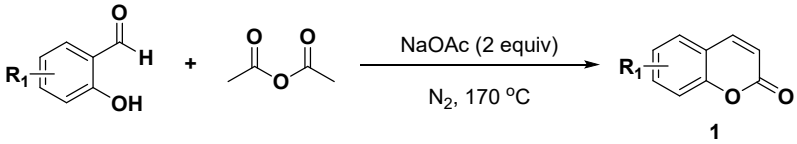
1. General information

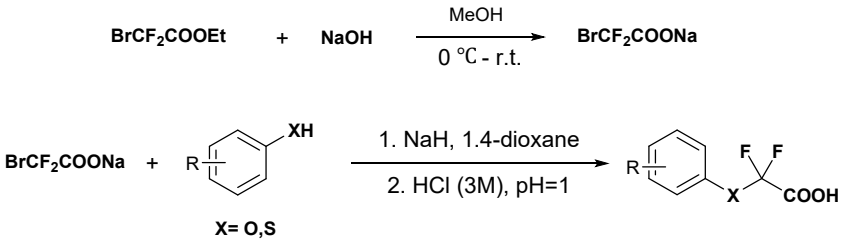
All reagents were obtained from commercial sources and used without further purification unless otherwise indicated. The starting materials and **2n** were purchased from Aladdin (https://www.aladdin-e.com/). Silica gel for column chromatography was purchased from Qingdao Haiyang Chemical Co., Ltd. Reactions were stirred using Teflon-coated magnetic stir bars. Thin-layer chromatography (TLC) was used to monitor the reaction.Melting points were determined using a Büchi B-540 capillary melting point apparatus. ^{1}H NMR (400/600 MHz), ^{13}C NMR (100/150 MHz) and ^{19}F NMR (376/565 MHz) spectra were recorded with $CDCl_3$. Chemical shifts are reported downfield from TMS (=0) for ^{1}H NMR. For $^{13}C\{^{1}H\}$ NMR, chemical shifts are reported in the scale relative to $CDCl_3$ (= 77.0). High resolution mass spectrometry (HRMS) analysis was performed on an Agilent 1290–6540 UHPLC Q-Tof HR-MS System (ESI) spectrometer.

2.1 General procedure for the synthesis of products 1[1]



Under nitrogen, add the appropriate salicylaldehyde (8.00 mmol), acetic anhydride (1.51 mL, 16 mmol) and sodium acetate (1.31 g, 16 mmol) to a 10 ml sealed tube in sequence. The resulting mixture was heated to 170 °C and then stirred for 6 h. After cooling, the reaction mixture was quenched with water (15 mL) and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography with *n*-hexane/ EtOAc (10/1 to 3/1, v/v) to afford coumarins **1**.

2.2 General procedure for the synthesis of products 2/4[2]

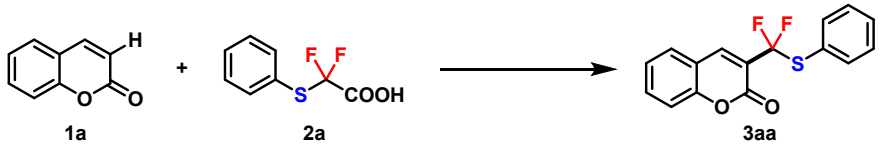


To a 250 mL oven-dried round-bottom flask equipped with a stir bar were added sodium hydroxide (4.0 g, 100.0 mmol) and MeOH (100 mL). Then, $BrCF_2CO_2Et$ (20.3 g, 100.0 mmol) was added to the resulting solution at 0 ºC. Upon addition, the mixture was warmed to room temperature and stirred for 24 h. The solvent was evaporated under vacuum and the residue was further dried under reduced pressure to give $BrCF_2CO_2Na$ as a white solid (19.0 g, 97%) ◦

To a 100 mL oven-dried Schlenk tube equipped with a stir bar was added thiophenol (or phenol) (20.0 mmol, 1.0 equiv.) under N_2 atmosphere. 1,4-Dioxane (30.0 mL) was added to dissolve the phenol or thiophenol. Then, NaH (60% purity) (880 mg, 22.0 mmol, 1.1 equiv.) and 1,4-dioxane (5.0 mL) were added under N_2 atmosphere. The solution was stirred at room temperature for 30 min. Then $BrCF_2COONa$ (4.3 g, 22.0 mmol, 1.1 equiv.) and 1,4-dioxane (5.0 mL) were added. After the mixture was heated at 60-70 ℃ in an oil bath for hours (monitor by TLC), then the mixture was cooled down to room temperature and acidified with 3M HCl (aq.) to pH = 1. The mixture was extracted with ethyl acetate for three times. The combined organic phase was washed by saturated brines and dried over Na_2SO_4. After the solution was filtered and the solvent was evaporated under vacuum, the crude product was purified by flash column chromatography (n-hexane/ethyl acetate = 5:1, v/v) to give the product **2** or **4.**

2.3 Screening condition supplement:

Table 1. Optimization of reaction conditions of coumarin and arylthiodifluoroacetic acid[a]



1a 2a 3aa

Entry	Catalyst	Oxidant	Solvents	T (℃)	Time (h)	Yield (%)[b]
1	[Fe]	$K_2S_2O_8$	H_2O	60	22	trace/n.r.
2	[Cu]	$K_2S_2O_8$	H_2O	60	22	trace/n.r.
3	$AgNO_3$	$K_2S_2O_8$	H_2O	60	22	15
4	AgOAc	$K_2S_2O_8$	H_2O	60	22	trace
5	Ag_2O	$K_2S_2O_8$	H_2O	60	22	trace
6	AgOTf	$K_2S_2O_8$	H_2O	60	22	trace

7	Ag_2CO_3	$K_2S_2O_8$	H_2O	60	22	23
8	Ag_2CO_3	$(NH_4)_2S_2O_8$	H_2O	60	22	trace
9	Ag_2CO_3	$Na_2S_2O_8$	H_2O	60	22	15
10	Ag_2CO_3	Selectfluor	H_2O	60	22	0
11	Ag_2CO_3	-	H_2O	60	22	0
12	Ag_2CO_3	$K_2S_2O_8$	DCE/H_2O (1:2)	60	22	trace
13	Ag_2CO_3	$K_2S_2O_8$	DMSO/H_2O (1:2)	60	22	n.r.
14	Ag_2CO_3	$K_2S_2O_8$	1,4-dioxane/H_2O (1:2)	60	22	n.r.
15	Ag_2CO_3	$K_2S_2O_8$	THF/H_2O (1:2)	60	22	n.r.
16	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:2)	60	22	28
17	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:2)	50	22	36
18	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	50	22	43
19	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (2:1)	50	22	28
20	**Ag_2CO_3**	**$K_2S_2O_8$**	**CH_3CN/H_2O (1:1)**	**40**	**22**	**60**
21	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	40	24	58
22	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	30	22	trace
23[c]	Ag_2CO_3	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	40	22	55
24	-	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	40	22	trace

[a]Conditions: coumarin **1a** (0.4 mmol, 58 mg), arylthiodifluoroacetic acid **2a** (0.8 mmol, 163 mg), Catalyst (0.2 equiv.), oxidant (3 equiv.) and solvent (3.0 mL) at T °C for 22 h under N_2 atmosphere, [b]Isolated yield, [c][Fe]= Fe salt, [d][Cu]= Cu salt, [e]Under air.

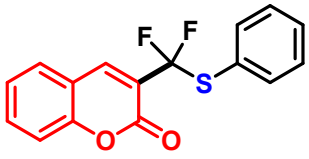
3. References

1 a) Jin, C.; Yan, Z.; Sun, B.; Yang, J. Visible-Light-Induced Regioselective Alkylation of Coumarins via Decarboxylative Coupling with *N*-Hydroxyphthalimide Esters. *Org. Lett.* **2019***, 21,* 2064−2068. (b) Wei, J.; Wang, P.; Jia, Q.; Huang J.; Du, Z.; Zhang, K.; Wang, J. Amine-Catalyzed Cascade Synthesis of 3,4-Diunsubstituted Coumarins. *Eur. J. Org. Chem.* **2013**, 2013, 4499–4502.

2 a) X.-L. Zhu, Y. Huang, X.-H. Xu and F.-L. Qing, Silver-Catalyzed C–H Aryloxydifluoromethylation and Arylthiodifluoromethylation of Heteroarenes, *Org. Lett.,* 2020, **22**, 5451-5455. b) M. Zhou, C. Ni, Z. He and J. Hu, O-Trifluoromethylation of Phenols: Access to Aryl Trifluoromethyl Ethers by O-Carboxydifluoromethylation and Decarboxylative Fluorination, *Org. Lett.,* 2016, **18**, 3754-3757.

4. Analytical data of the synthesized derivatives

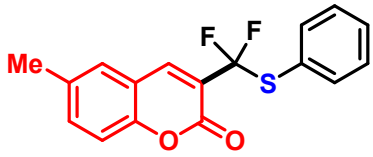
3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3aa)



Brown solid; m.p.= 120.0-121.9 ℃; 60% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 3H), 7.31 (t, J = 7.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.4, 154.3, 141.5 (t, $^{3}J_{C-F}$= 6.0 Hz), 136.7, 133.5, 130.2, 129.2, 129.1, 126.6, 124.9, 124.5 (t, $^{1}J_{C-F}$= 280.8 Hz), 122.4 (t, $^{2}J_{C-F}$= 27.2 Hz), 117.3, 116.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ -74.7 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_2NaO_2S^+$ $[M+Na]^+$ 327.0262, found 327.0261.

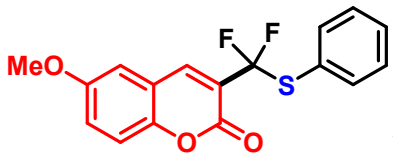
3-(difluoro(phenylthio)methyl)-6-methyl-2H-chromen-2-one (3ba)



Yellow liquid; 47% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.64 (d, J = 7.0 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.35 (t, J = 7.2 Hz, 2H), 7.26 (d, J = 1.6 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 152.5, 141.6 (t, $^{3}J_{C-F}$= 6.0 Hz), 136.8, 135.8, 134.7, 134.6, 130.2, 129.3, 129.1, 128.8, 122.2 (t, $^{2}J_{C-F}$= 27.2 Hz), 117.1, 116.4, 20.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.6 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_2S^+$ $[M+H]^+$ 319.0599, found 319.0602.

3-(difluoro(phenylthio)methyl)-6-methoxy-2H-chromen-2-one (3ca)

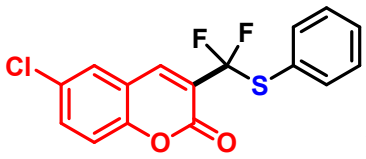


Yellow solid; m.p.= 132.0-135.0 ℃; 39% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.4 Hz, 3H), 7.31 – 7.27 (m, 2H), 7.18 (dd, J = 9.0, 3.0 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 156.3, 148.8, 141.4 (t, $^{3}J_{C-F}$= 6.0 Hz), 136.8, 135.8, 130.2, 129.3, 129.1, 121.5 (t,

$^{1}J_{C\text{-}F}$= 280.8 Hz), 120.4 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 118.4, 117.8, 110.7, 55.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ -74.7 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_3S^+$ $[M+H]^+$ 335.0548, found 335.0550.

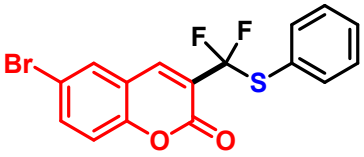
6-chloro-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3da)



White solid; m.p.= 115.4-117.6 °C; 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.55 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.48 – 7.37 (m, 2H), 7.35 (t, *J* = 7.2 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 152.6, 140.2 (t, $^{3}J_{C\text{-}F}$= 6.0 Hz), 136.8, 130.4, 130.2, 129.2, 128.2, 127.1, 126.3, 124.3 (t, $^{1}J_{C\text{-}F}$= 280.8 Hz),123.5 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 118.3, 118.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}ClF_2O_2S^+$ $[M+H]^+$ 339.0053, found 339.0050.

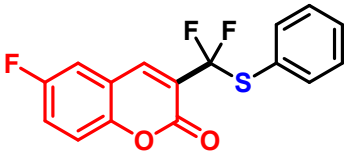
6-bromo-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3ea)



Yellow solid; m.p.= 122.7-125.2 °C; 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 2H), 7.65 – 7.57 (m, 3H), 7.45 – 7.37 (m, 1H), 7.40 – 7.30 (m, 2H), 7.26 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7 (t, $^{3}J_{C\text{-}F}$= 3.0 Hz), 153.1, 140.2, 136.8, 136.2, 131.2, 130.4, 129.2, 126.3, 124.3 (t, $^{1}J_{C\text{-}F}$= 281.8 Hz), 123.5 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 118.8, 118.5, 117.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}BrF_2O_2S^+$ $[M+H]^+$ 382.9547, found 382.9551.

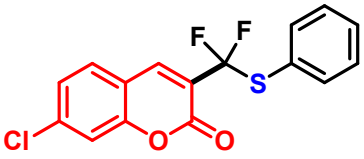
3-(difluoro(phenylthio)methyl)-6-fluoro-2H-chromen-2-one (3fa)



White solid; m.p.= 116.5-118.0 °C; 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.40

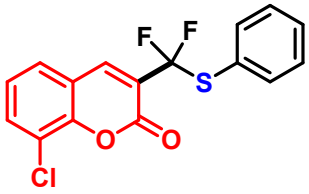
– 7.30 (m, 4H), 7.17 (dd, J = 7.6, 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 157.5, 156.0, 150.5, 140.5 (q, ^3J = 3.6 Hz), 136.8, 130.3, 129.2, 126.3, 124.3 (t, $^1J_{C\text{-}F}$= 280.8 Hz), 123.6 (t, $^2J_{C\text{-}F}$= 27.2 Hz), 121.1 (d, ^2J = 24.6 Hz), 118.4 (d, ^3J = 8.4 Hz), 114.20 (d, ^2J = 24.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.2 (s, 2F), -116.2 (s, 1F). HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_3O_2S^+$ $[M+H]^+$ 323.0348, found 323.0352.

7-chloro-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3ga)



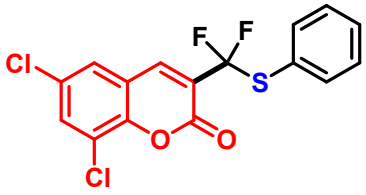
White solid; m.p.= 155.9-158.1 °C; 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.62 (d, J = 7.0 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.36 (d, J = 8.0 Hz, 3H), 7.28 (dd, J = 8.4, 2.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 154.5, 140.7 (t, $^3J_{C\text{-}F}$= 7.0 Hz), 139.7, 136.8, 130.3, 129.9, 129.2, 126.4, 125.6, 124.4, 122.3 (t, $^1J_{C\text{-}F}$= 280.8 Hz), 117.1, 115.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.9 (s, 2F). HRMS-ESI (m/z): calcd for $C_{16}H_{12}ClF_2O_2S^+$ $[M+H]^+$ 339.0053, found 339.0056.

8-chloro-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3ha)



Yellow solid; m.p.= 138.3-140.6 °C; 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.64 (dd, J = 11.2, 7.6 Hz, 3H), 7.46 – 7.31 (m, 4H), 7.26 (t, J = 4.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 150.0, 141.1 (t, $^3J_{C\text{-}F}$= 6.0 Hz), 136.8, 133.7, 130.3, 129.2, 127.5, 126.3, 125.1, 123.2 (t, $^2J_{C\text{-}F}$= 27.2 Hz), 121.7 (t, $^1J_{C\text{-}F}$= 280.8 Hz), 119.0, 118.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.0 (s, 2F).
HRMS-ESI (m/z): calcd for $C_{16}H_{12}ClF_2O_2S^+$ $[M+H]^+$ 339.0053, found 339.0058.

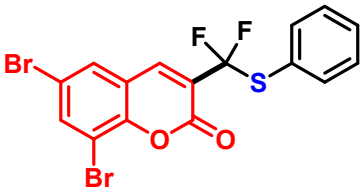
6,8-dichloro-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3ia)



White solid; m.p.= 151.1-153.2℃; 51% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.59 (m, 4H), 7.43 (t, J = 7.4 Hz, 1H), 7.39 – 7.33 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 148.6, 139.8 (t, $^{3}J_{C-F}$= 6.0 Hz), 136.8, 133.3, 130.5, 130.0, 129.2, 126.7, 126.2, 124.3 (t, $^{2}J_{C-F}$= 27.2 Hz), 124.1 (t, $^{1}J_{C-F}$= 280.8 Hz), 122.7, 119.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.4 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_9Cl_2F_2O_2S^+$ $[M+H]^+$ 372.9663, found 372.9660.

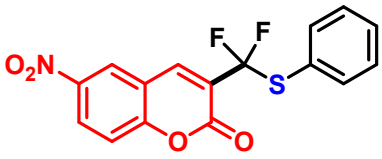
6,8-dibromo-3-(difluoro(phenylthio)methyl)-2H-chromen-2-one (3ja)



White solid; m.p.= 169.9-172.1 ℃; 48% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.61 (d, J = 5.2 Hz, 3H), 7.55 (d, J = 2.2 Hz, 1H), 7.43 (t, J = 6.8 Hz, 1H), 7.36 (t, J = 8.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 150.1, 139.7, 138.8, 136.8, 130.5, 130.4, 129.2, 126.2, 124.3 (t, $^{1}J_{C-F}$= 281.8 Hz), 124.0, 119.5, 117.3, 111.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.3 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_9Br_2F_2O_2S^+$ $[M+H]^+$ 460.8653, found 460.8655.

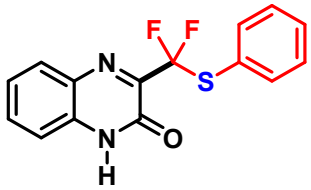
3-(difluoro(phenylthio)methyl)-6-nitro-2H-chromen-2-one (3ka)



Yellow solid; m.p.= 115.4-117.7 ℃; 37% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (dd, J = 9.0, 2.6 Hz, 1H), 8.42 (d, J = 2.6 Hz, 1H), 7.82 (s, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.37 (t, J = 7.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 157.5, 154.7 (t, $^{3}J_{C-F}$= 3.0 Hz), 144.3, 140.1 (t, $^{2}J_{C-F}$= 6.0 Hz), 136.8, 130.6, 129.3, 128.0, 126.0, 124.8, 124.7, 124.0 (t, $^{1}J_{C-F}$= 280.8 Hz), 118.0, 117.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ -75.6 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_2NO_4S^+$ $[M+H]^+$ 350.0293, found 350.0299.

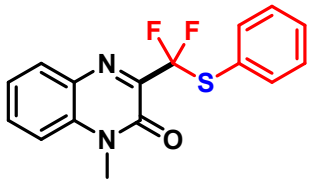
3-(difluoro(phenylthio)methyl)quinoxalin-2(1H)-one (3la)



White solid; m.p.= 183.2-186.1 ℃; 61% yield; ^{1}H NMR (600 MHz, DMSO) δ 12.92 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.31 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 151.4, 148.5 (t, $^{2}J_{C\text{-}F}$= 25.6 Hz), 136.4, 133.3, 132.8, 130.3, 129.8, 129.5, 129.3, 125.8 (t, $^{1}J_{C\text{-}F}$= 246.4 Hz), 123.9, 123.0, 115.6.^{19}F NMR (565 MHz, DMSO) δ -75.6 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{15}H_{11}F_2N_2OS^+$ $[M+H]^+$ 305.0555, found 305.0560.

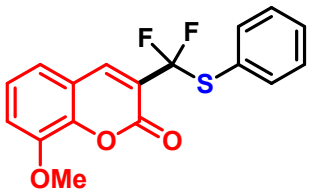
3-(difluoro(phenylthio)methyl)-1-methylquinoxalin-2(1H)-one (3ma)



Yellow solid; m.p.= 111.7-113.9 ℃; 66% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.73 – 7.62 (m, 3H), 7.45 – 7.39 (m, 2H), 7.39 – 7.34 (m, 3H), 3.74 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 151.6, 148.3 (t, $^{2}J_{C\text{-}F}$= 25.6 Hz), 136.9, 134.2, 132.7, 131.4, 130.9, 129.9, 128.9, 126.2, 124.6 (t, $^{1}J_{C\text{-}F}$= 282.4 Hz), 124.2, 113.8, 29.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ -77.2 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{12}F_2N_2OS^+$ $[M+H]^+$ 319.0711, found 319.0719.

3-(difluoro(phenylthio)methyl)-8-methoxy-2H-chromen-2-one (3na)

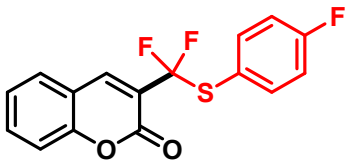


Yellow solid; m.p.= 111.5-113.7 ℃; 44% yield;^{1}H NMR (400 MHz, DMSO) δ 7.62 – 7.57 (m, 2H), 7.51 – 7.38 (m, 6H), 7.35 (d, *J* = 3.4 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 165.7, 155.4, 146.2, 143.1(t, $^{3}J_{C\text{-}F}$= 6.0 Hz),

136.2, 130.5, 129.5, 129.4, 125.9, 124.9, 124.8 (t, $^{1}J_{C\text{-}F}$= 279.8 Hz), 120.9, 117.7, 116.0, 56.1.^{19}F NMR (376 MHz, DMSO) δ -73.1(s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_2S^+$ $[M+H]^+$ 335.0548, found 335.0551.

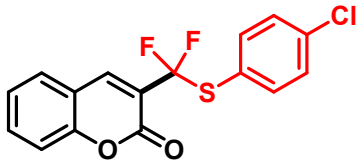
3-(difluoro((4-fluorophenyl)thio)methyl)-2H-chromen-2-one (3ab)



Yellow solid; m.p.= 98.9-100.5 ℃; 33% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.68 – 7.59 (m, 3H), 7.52 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 165.0, 163.3, 156.4, 154.4, 139.0, 129.3 (t, $^{1}J_{C\text{-}F}$= 280.8 Hz), 124.9, 122.3 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 121.8, 117.3, 116.9, 116.4, 116.2. ^{19}F NMR (565 MHz, $CDCl_3$) δ -75.0 (s, 2F), -109.7 (s, 1F).

HRMS-ESI (m/z): calcd for $C_{16}H_{12}F_3O_2S^+$ $[M+H]^+$ 323.0348, found 323.0345.

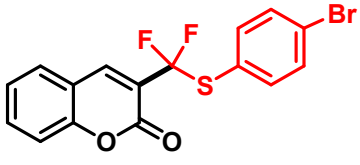
3-(((4-chlorophenyl)thio)difluoromethyl)-2H-chromen-2-one (3ac)



Yellow solid; m.p.= 102.8.3-104.6 ℃; 30% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.31 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 156.4, 154.4, 138.0, 136.9, 133.7, 129.5, 129.3, 125.1, 124.9 (t, $^{1}J_{C\text{-}F}$= 281.8 Hz), 122.3 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 117.3, 116.9, 116.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ -74.4 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}ClF_2O_2S^+$ $[M+H]^+$ 339.0353, found 339.0357.

3-(((4-bromophenyl)thio)difluoromethyl)-2H-chromen-2-one (3ad)

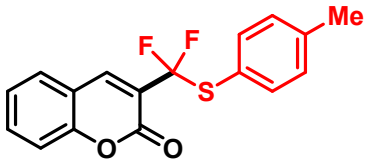


White solid; m.p.= 100.9-104.6 ℃; 40% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.56 – 7.46 (m, 5H), 7.37 (d, *J* =

8.4 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 156.4, 154.3, 138.3, 138.0, 133.7, 132.5, 132.2, 129.3, 125.2 (t, $^1J_{C\text{-}F}$= 280.8 Hz), 122.2 (t, $^2J_{C\text{-}F}$= 27.2 Hz), 117.3, 116.9, 116.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ -74.3 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}BrF_2O_2S^+$ $[M+H]^+$ 382.9547, found 382.9551.

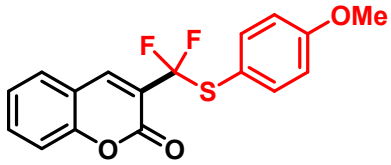
3-(difluoro(p-tolylthio)methyl)-2H-chromen-2-one (3ae)



White solid; m.p.= 127.0-129.7 ℃; 47% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 156.4, 154.3, 136.9, 136.6, 129.9, 125.0, 124.7, 124.5 (t, $^1J_{C\text{-}F}$= 281.8 Hz), 123.0, 122.5 (t, $^2J_{C\text{-}F}$= 27.2 Hz), 117.4, 116.9, 116.6, 21.7. ^{19}F NMR (565 MHz, $CDCl_3$) δ -75.0 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_2S^+$ $[M+H]^+$ 319.0599, found 319.0592.

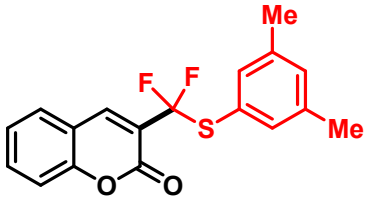
3-(difluoro((4-methoxyphenyl)thio)methyl)-2H-chromen-2-one (3af)



Yellow solid; m.p.= 102.0-104.5 ℃; 51% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.9, 161.4, 156.4, 154.3, 138.7, 138.4, 133.5, 125.0, 124.7 (t, $^1J_{C\text{-}F}$= 281.8 Hz), 122.5 (t, $^2J_{C\text{-}F}$= 27.2 Hz), 117.4, 117.0, 116.5, 114.7, 54.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -75.6 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_3S^+$ $[M+H]^+$ 335.0548, found 335.0552.

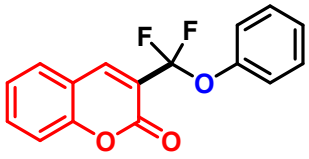
3-(((3,5-dimethylphenyl)thio)difluoromethyl)-2H-chromen-2-one (3ag)



Yellow solid; m.p.= 103.6-105.3 ℃; 55% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.60 (t, *J* = 8.6 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.25 (s, 2H), 2.26 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 165.2, 154.3, 151.9, 141.5 (t, $^{3}J_{C\text{-}F}$= 6.0 Hz), 138.7, 134.3, 133.4, 131.9, 129.1, 124.9 (t, $^{1}J_{C\text{-}F}$= 280.8 Hz), 122.5 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 117.3, 117.3, 116.6, 21.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -74.7 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{18}H_{15}F_2O_2S^+$ $[M+H]^+$ 333.0755, found 333.0759.

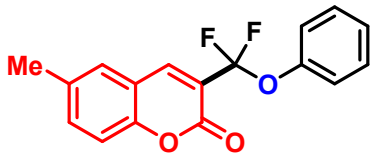
3-(difluoro(phenoxy)methyl)-2H-chromen-2-one (5aa)



Yellow solid; m.p.= 100.7-101.9 ℃; 76% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.67 – 7.54 (m, 2H), 7.40 – 7.29 (m, 6H), 7.23 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 154.5, 149.9, 142.6 (t, $^{3}J_{C\text{-}F}$= 5.0 Hz), 133.6, 129.4, 129.2, 126.0, 124.9, 122.1, 120.5 (t, $^{2}J_{C\text{-}F}$= 33.4 Hz), 119.4 (t, $^{1}J_{C\text{-}F}$= 263.6 Hz), 117.3, 116.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_2NaO_3^+$ $[M+Na]^+$ 311.0490, found 311.0492.

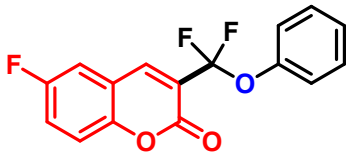
3-(difluoro(phenoxy)methyl)-6-methyl-2H-chromen-2-one (5ba)



White solid; m.p.= 100.2-102.2 ℃; 50% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.34 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.20 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.6, 152.6, 149.9, 142.6, 134.7 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 129.3, 125.9, 122.2, 122.0, 120.3 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.5 (t, $^{1}J_{C\text{-}F}$= 262.6 Hz), 117.0, 116.5, 116.4, 20.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.0 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_3^+$ $[M+H]^+$ 303.0827, found 303.0831.

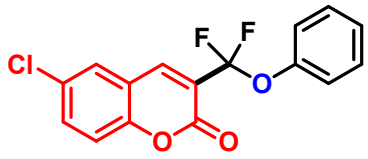
3-(difluoro(phenoxy)methyl)-6-fluoro-2H-chromen-2-one (5ca)



White solid; m.p.= 161.9-164.3 ℃; 64% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.39 – 7.34 (m, 4H), 7.33 – 7.27 (m, 3H), 7.25 (d, J = 6.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.6, 158.0, 155.9, 150.7, 149.8, 141.6 (q, ^3J = 4.8 Hz), 129.5, 126.1, 122.1, 121.7 (t, $^2J_{C\text{-}F}$= 33.2 Hz), 121.2 (d, ^2J = 24.6 Hz), 118.5 (d, ^3J = 8.4 Hz), 117.9 (t, $^1J_{C\text{-}F}$= 263.6 Hz), 114.3 (d, ^2J = 24.0 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.3 (s, 2F), -116.3 (s, 1F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_3O_3^+$ $[M+H]^+$ 307.0577, found 307.0581.

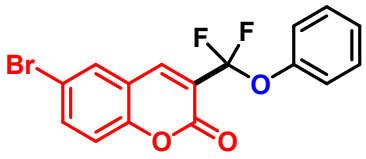
6-chloro-3-(difluoro(phenoxy)methyl)-2H-chromen-2-one (5da)



White solid; m.p.= 175.8-177.4 ℃; 78% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.58 (d, J = 10.2 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.32 (dd, J = 12.6, 8.4 Hz, 3H), 7.25 (d, J = 5.0 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.7, 152.9, 149.8, 141.4 (t, $^3J_{C\text{-}F}$= 4.6 Hz), 133.5, 130.2, 129.5, 128.3, 126.1, 122.1, 121.7 (t, $^2J_{C\text{-}F}$= 33.2 Hz), 120.9, 119.1 (t, $^1J_{C\text{-}F}$= 262.6 Hz), 118.3.^{19}F NMR (565 MHz, $CDCl_3$) δ -69.3 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}ClF_2O_3^+$ $[M+H]^+$ 323.0281, found 323.0288.

6-bromo-3-(difluoro(phenoxy)methyl)-2H-chromen-2-one (5ea)

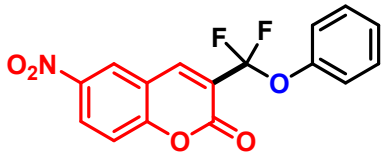


Yellow solid; m.p.= 160.4-161.6 ℃; 83% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.76 – 7.64 (m, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.26 (t, J = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.6, 153.3,

149.8, 141.3 (t, $^{3}J_{C\text{-}F}$= 6.0 Hz), 136.3, 131.4, 129.5, 126.1, 122.1, 121.7 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.1 (t, $^{1}J_{C\text{-}F}$= 263.6 Hz), 118.8, 118.5, 117.4.^{19}F NMR (565 MHz, $CDCl_3$) δ -69.2 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}BrF_2O_3^+$ $[M+H]^+$ 366.9776, found 366.9783.

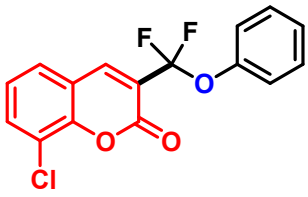
3-(difluoro(phenoxy)methyl)-6-nitro-2H-chromen-2-one (5fa)



Yellow solid; m.p.= 185.9-186.5 ℃; 40% yield; ^{1}H NMR (600 MHz, DMSO) δ 8.92 (s, 2H), 8.52 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.28 (m, 3H). ^{13}C NMR (151 MHz, DMSO) δ 157.6, 155.0, 149.2, 143.8, 143.4 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 129.9, 128.3, 128.0, 126.4, 126.0, 121.7, 120.4 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 117.9 (t, $^{1}J_{C\text{-}F}$= 263.6 Hz), 117.7. ^{19}F NMR (565 MHz, DMSO) δ -67.9 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_2NO_5^+$ $[M+H]^+$ 334.0522, found 334.0528.

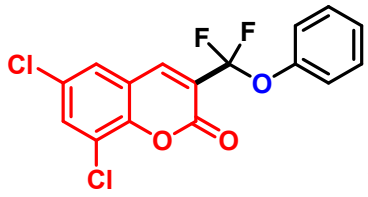
8-chloro-3-(difluoro(phenoxy)methyl)-2H-chromen-2-one (5ga)



Yellow solid; m.p.= 114.7-116.6 ℃; 63% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.28 (m, 3H), 7.24 (t, *J* = 7.4 Hz, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ 155.9, 153.1, 150.0, 141.6 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 133.7, 130.4, 129.7, 128.5, 126.3, 124.6, 122.3, 122.2 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.3 (t, $^{1}J_{C\text{-}F}$= 262.6 Hz), 118.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}ClF_2O_3^+$ $[M+H]^+$ 323.0281, found 323.0285.

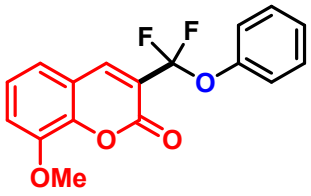
6,8-dichloro-3-(difluoro(phenoxy)methyl)-2H-chromen-2-one (5ha)



White solid; m.p.= 159.1-162.9 ℃; 56% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.37 (dd, *J* = 8.6, 7.2 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 154.5, 149.7, 148.9, 141.1 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 133.4, 130.0, 129.5, 126.9, 126.2, 122.9, 122.5 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 122.1, 119.1 (t, $^{1}J_{C\text{-}F}$= 262.6 Hz), 118.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.2 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_9Cl_2F_2O_3^+$ $[M+H]^+$ 356.9891, found 356.9895.

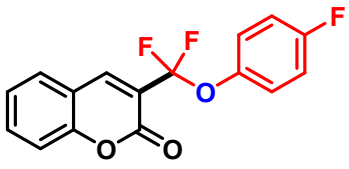
3-(difluoro(phenoxy)methyl)-8-methoxy-2H-chromen-2-one (5ia)



White solid; m.p.= 122.0-125.0 ℃; 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (d, *J* = 7.2 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 3H), 7.31 – 7.27 (m, 2H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 156.3, 148.8, 141.4 (t, $^{3}J_{C\text{-}F}$= 6.0 Hz), 136.8, 135.8, 130.2, 129.3, 129.1, 121.5 (t, $^{1}J_{C\text{-}F}$= 280.8 Hz), 120.4 (t, $^{2}J_{C\text{-}F}$= 27.2 Hz), 118.4, 117.8, 110.7, 55.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -69.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_4^+$ $[M+H]^+$ 319.0776, found 319.0779.

3-(difluoro(4-fluorophenoxy)methyl)-2H-chromen-2-one (5ab)

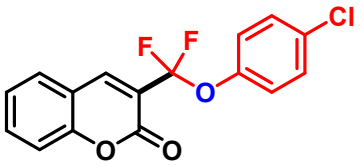


White solid; m.p.= 145.5-148.0 ℃; 70% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.29 (dd, *J* = 9.0, 4.6 Hz, 2H), 7.10 – 6.96 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 159.7, 156.3, 154.5, 142.7 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 133.7, 129.2, 124.9, 123.9

(d, ^{3}J = 8.4 Hz), 120.3 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 117.2 (t, $^{1}J_{C\text{-}F}$= 263.6 Hz), 116.8, 116.1, 116.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.6 (s, 2F), -116.4 (s, 1F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_3O_3^+$ $[M+H]^+$ 307.0577, found 307.0572.

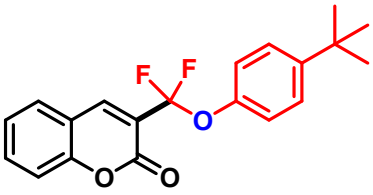
3-((4-chlorophenoxy)difluoromethyl)-2H-chromen-2-one (5ac)



White solid; m.p.= 153.1-155.2 °C; 67% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.3, 154.5, 148.4, 142.7 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 133.8, 131.6, 129.5, 129.2, 125.0, 123.6, 120.2 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.4 (t, $^{1}J_{C\text{-}F}$= 262.6 Hz), 117.2, 116.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.5 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}ClF_2O_2^+$ $[M+H]^+$ 323.0281, found 323.0286.

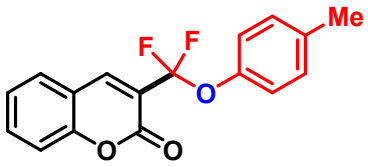
3-((4-(tert-butyl)phenoxy)difluoromethyl)-2H-chromen-2-one (5ae)



Yellow solid; m.p.= 107.6-109.7 °C; 83% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.64 – 7.54 (m, 2H), 7.38 – 7.36 (m, 2H), 7.34 (t, *J* = 3.0 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.3, 154.4, 148.8, 147.5, 142.6 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 133.5, 129.2, 126.2, 124.8, 121.5, 120.6 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.4 (t, $^{1}J_{C\text{-}F}$= 263.6 Hz), 117.3, 116.7, 34.4, 31.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{20}H_{19}F_2O_3^+$ $[M+H]^+$ 345.1297, found 345.1301.

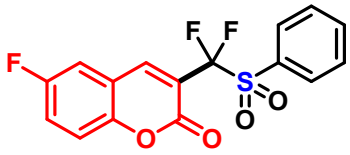
3-(difluoro(p-tolyloxy)methyl)-2H-chromen-2-one (5af)



Yellow solid; m.p.= 126.6-128.3 ℃; 71% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 2.33 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.4, 154.5, 147.6, 142.6 (t, $^{3}J_{C\text{-}F}$= 4.6 Hz), 135.7, 133.6, 129.9, 129.2, 124.9, 122.0, 120.6 (t, $^{2}J_{C\text{-}F}$= 33.2 Hz), 119.4 (t, $^{1}J_{C\text{-}F}$= 262.6 Hz), 117.3, 116.8, 20.8. ^{19}F NMR (565 MHz, $CDCl_3$) δ -69.1 (s, 2F).

HRMS-ESI (m/z): calcd for $C_{17}H_{13}F_2O_3^+$ $[M+H]^+$ 303.0827, found 303.0822.

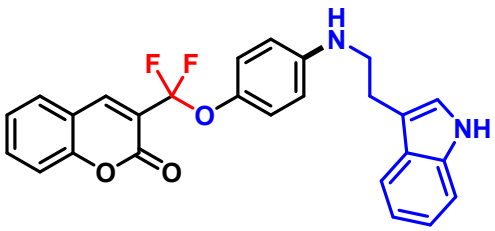
3-(difluoro(phenylsulfonyl)methyl)-6-fluoro-2H-chromen-2-one (9)



White solid; m.p.= 133.1-135.2 ℃; 89% yield; ^{1}H NMR (400 MHz, DMSO) δ 8.66 (d, *J* = 26.0 Hz, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.87 – 7.74 (m, 2H), 7.72 – 7.64 (m, 2H), 7.63 – 7.53 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ 163.7, 156.3, 154.5, 150.9, 147.2, 136.4, 131.7, 131.3 (t, $^{1}J_{C\text{-}F}$= 272.8 Hz), 130.5, 130.1, 128.9, 124.4, 122.50 (d, ^{2}J = 24.8 Hz), 114.98 (d, ^{2}J = 24.2 Hz).^{19}F NMR (376 MHz, DMSO) δ -100.6 (s, 2F), -117.7 (s, 1F).

HRMS-ESI (m/z): calcd for $C_{16}H_{10}F_3O_4S^+$ $[M+H]^+$ 354.0174, found 354.0178.

3-((4-((2-(1H-indol-3-yl)ethyl)amino)phenoxy)difluoromethyl)-2H-chromen-2-one (10)

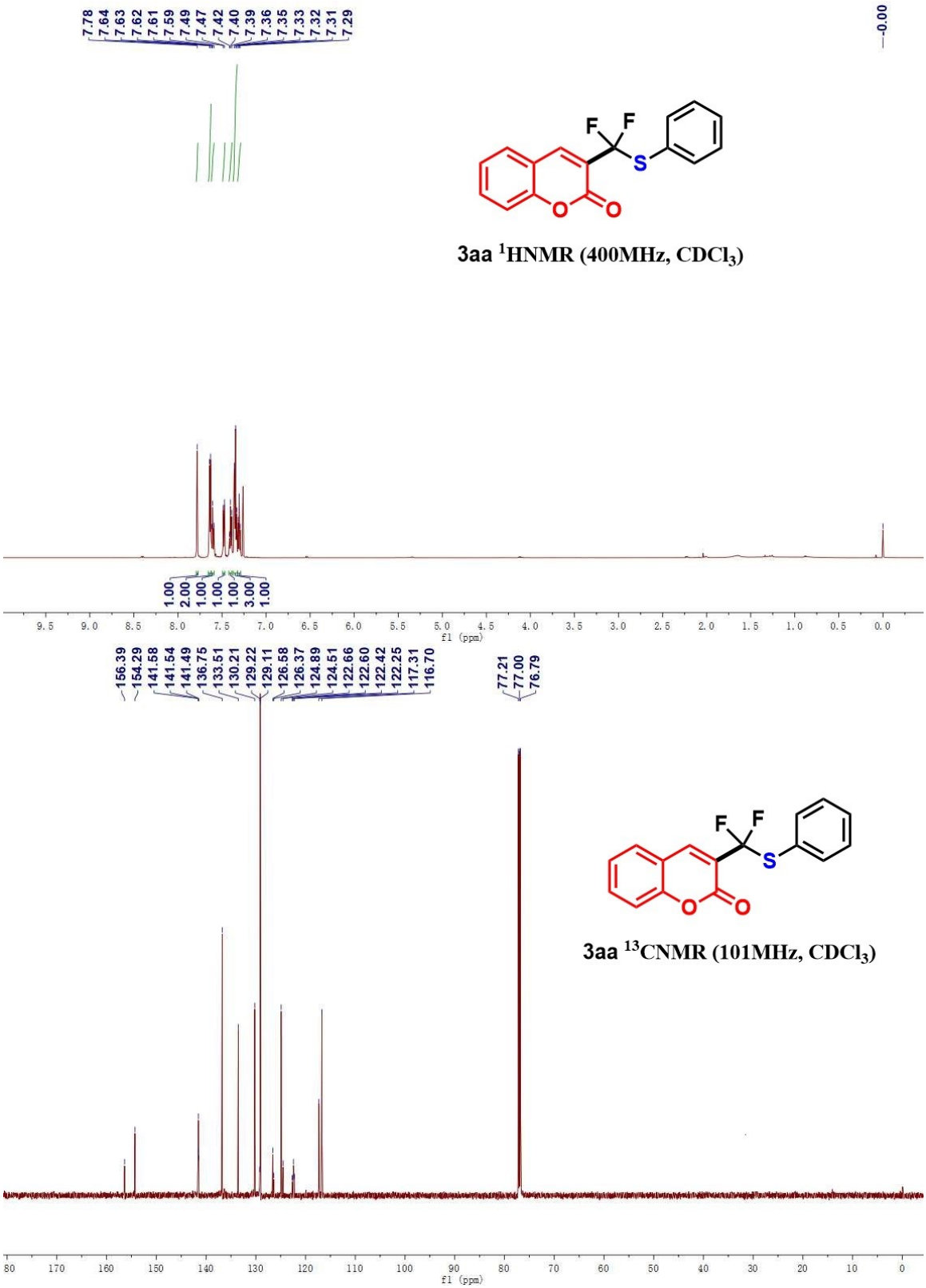


Yellow liquid; 37% yield; ^{1}H NMR (400 MHz, DMSO) δ 10.40 (t, *J* = 5.6 Hz, 1H), 8.29 (s, 1H), 7.67 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54 (dd, *J* = 8.0, 5.2 Hz, 2H), 7.52 – 7.43 (m, 1H), 7.38 – 7.28 (m, 2H), 7.20 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 – 7.11 (m, 1H), 7.09 – 7.02 (m, 3H), 7.02 – 6.92 (m, 3H), 3.71 (t, *J* = 7.2 Hz,

2H), 3.52 (q, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 161.2, 153.2, 148.8, 138.4, 136.3, 136.2, 132.4, 129.5, 127.3, 127.1, 124.0, 122.8, 122.7 (t, $^{1}J_{C\text{-}F}$= 252.4 Hz), 120.9, 120.8, 120.8, 118.3 (t, $^{3}J_{C\text{-}F}$= 4.0 Hz), 118.1, 114.8, 112.7, 111.6, 111.3, 46.3, 25.9. ^{19}F NMR (376 MHz, DMSO) δ -64.3(s, 2F).

HRMS-ESI (m/z): calcd for $C_{26}H_{21}F_2N_2O_3^+$ $[M+H]^+$ 446.1442, found 446.1440.

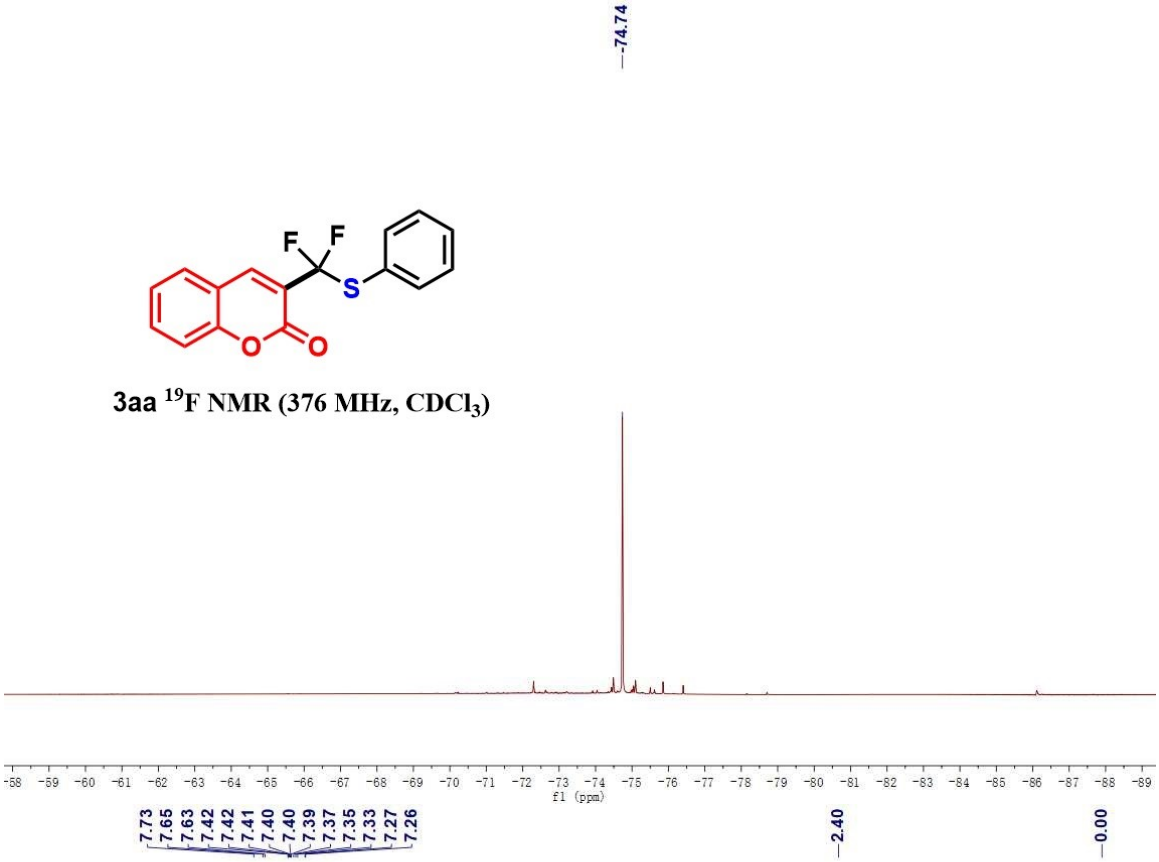
5. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR of compound



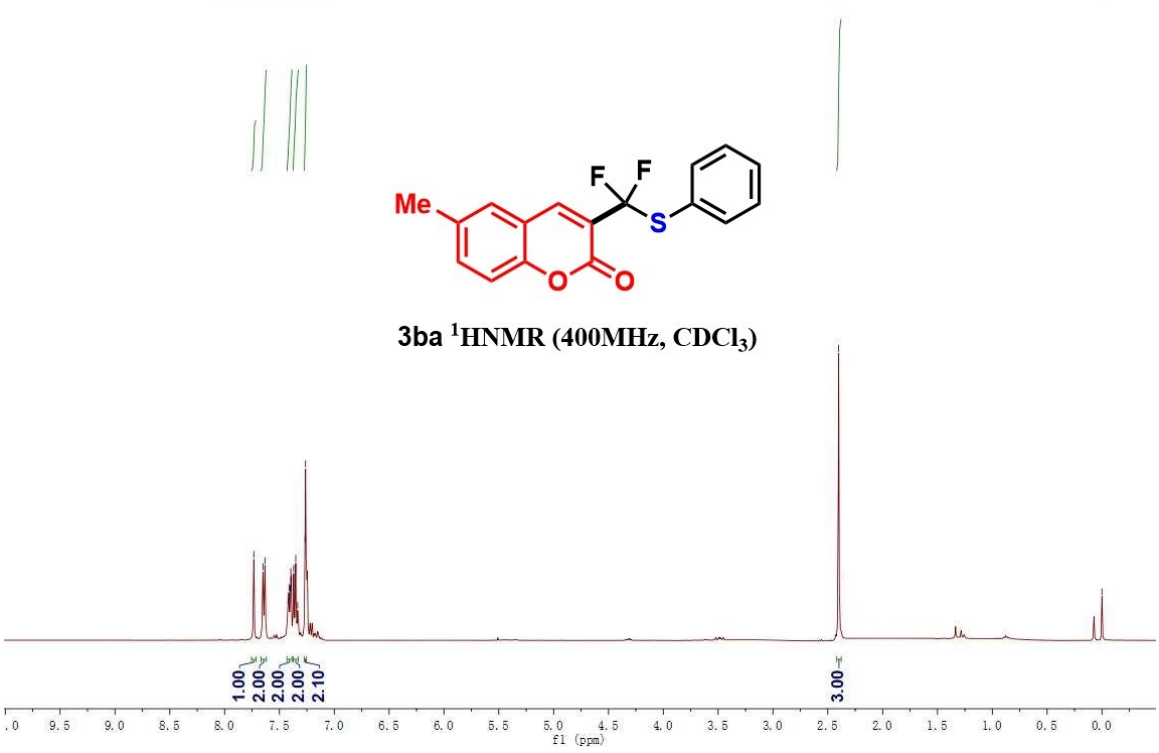
3aa ^{1}HNMR (400MHz, $CDCl_3$)

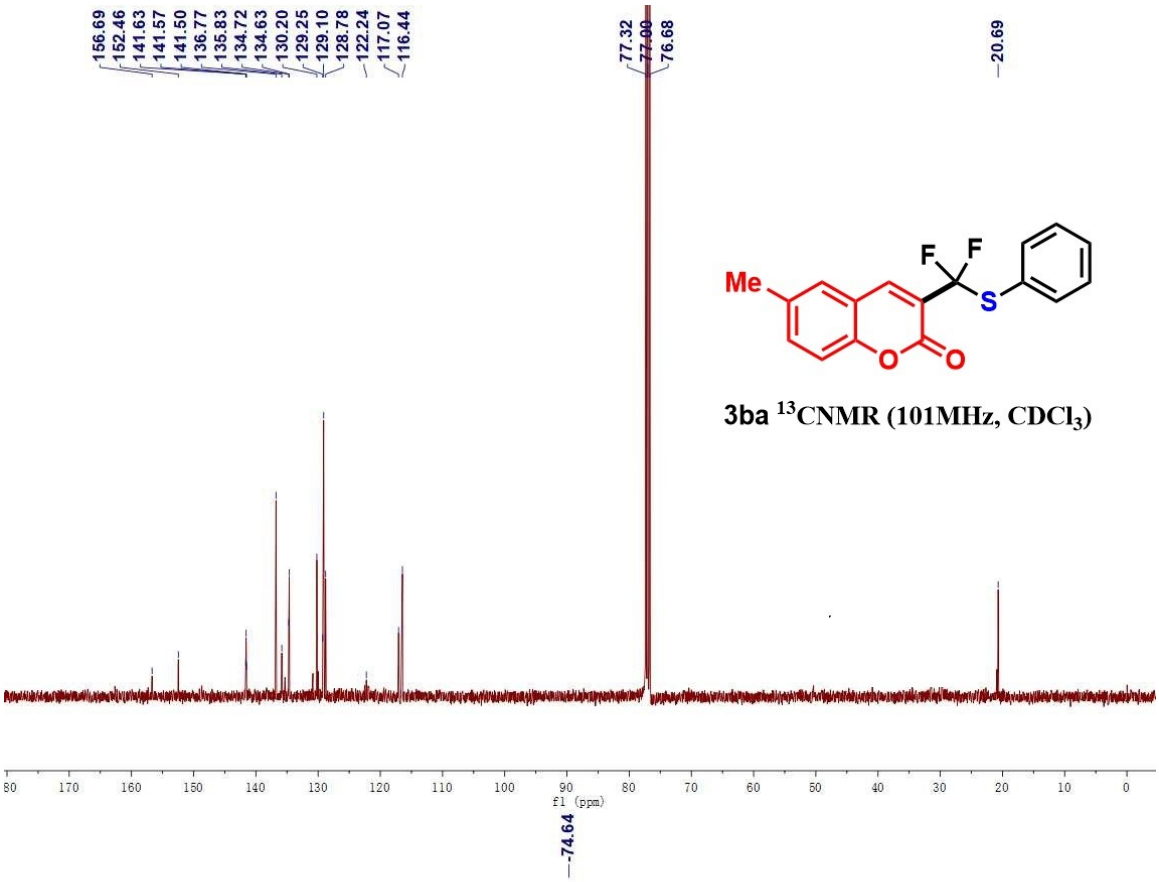
3aa ^{13}CNMR (101MHz, $CDCl_3$)

3aa ^{19}F NMR (376 MHz, $CDCl_3$)

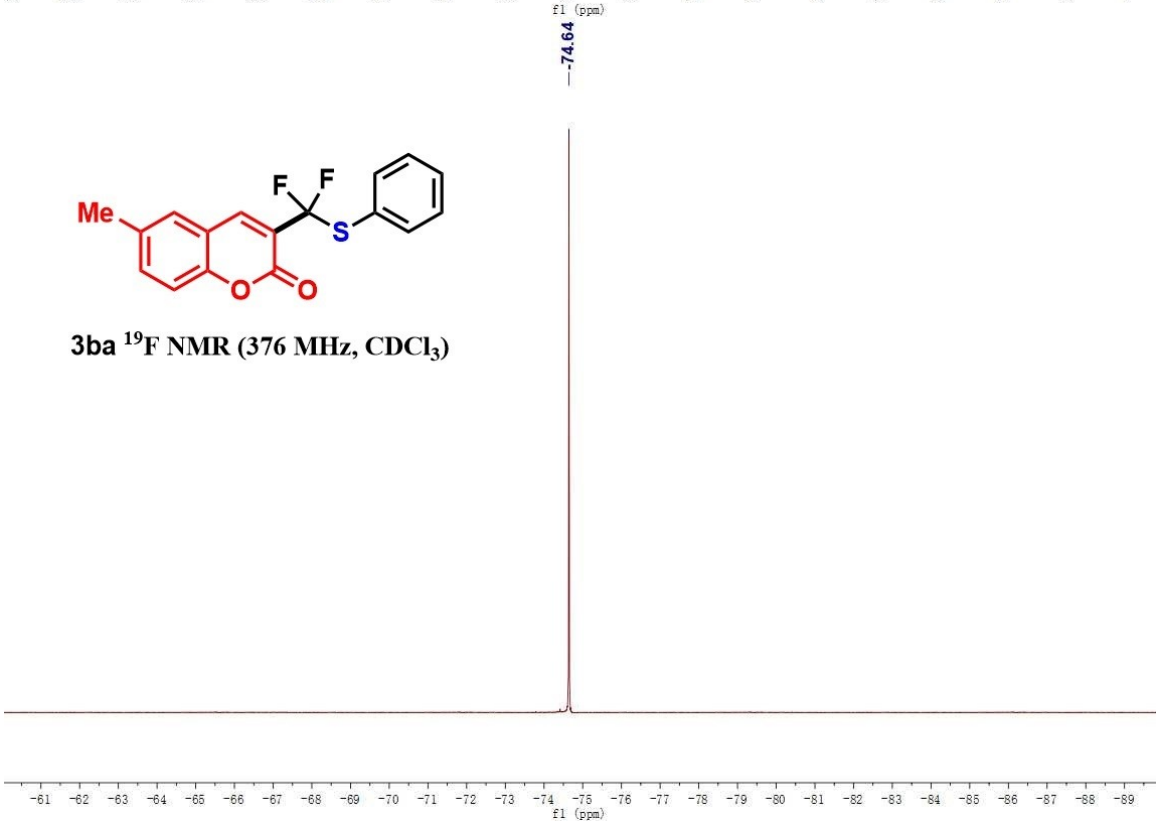


3ba ^{1}HNMR (400MHz, $CDCl_3$)

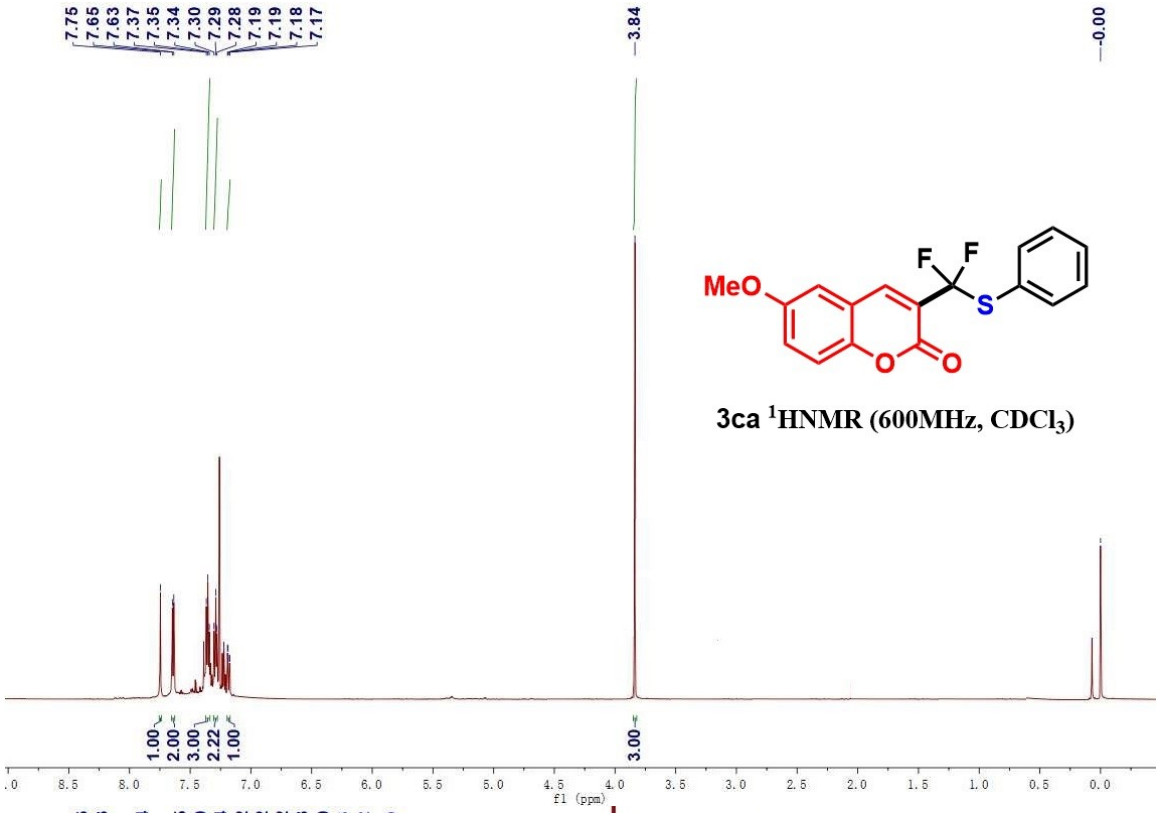




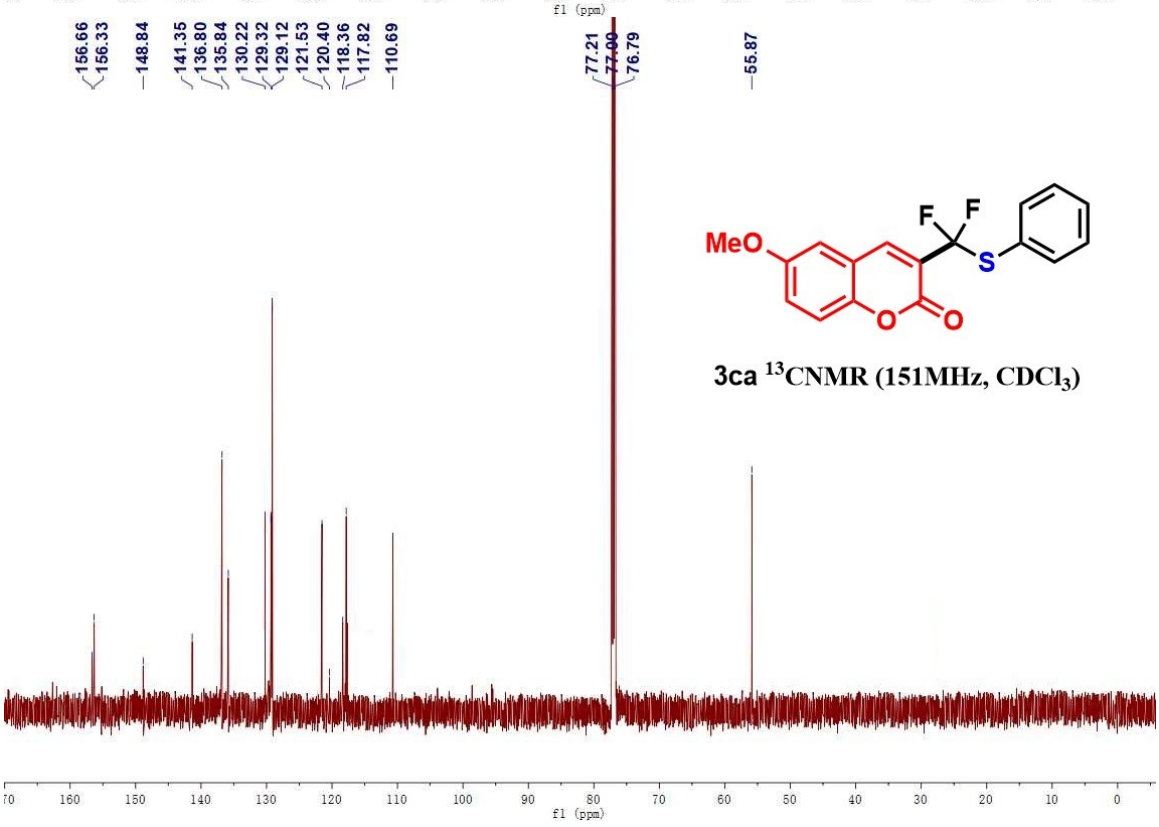
3ba ^{13}CNMR (101MHz, $CDCl_3$)



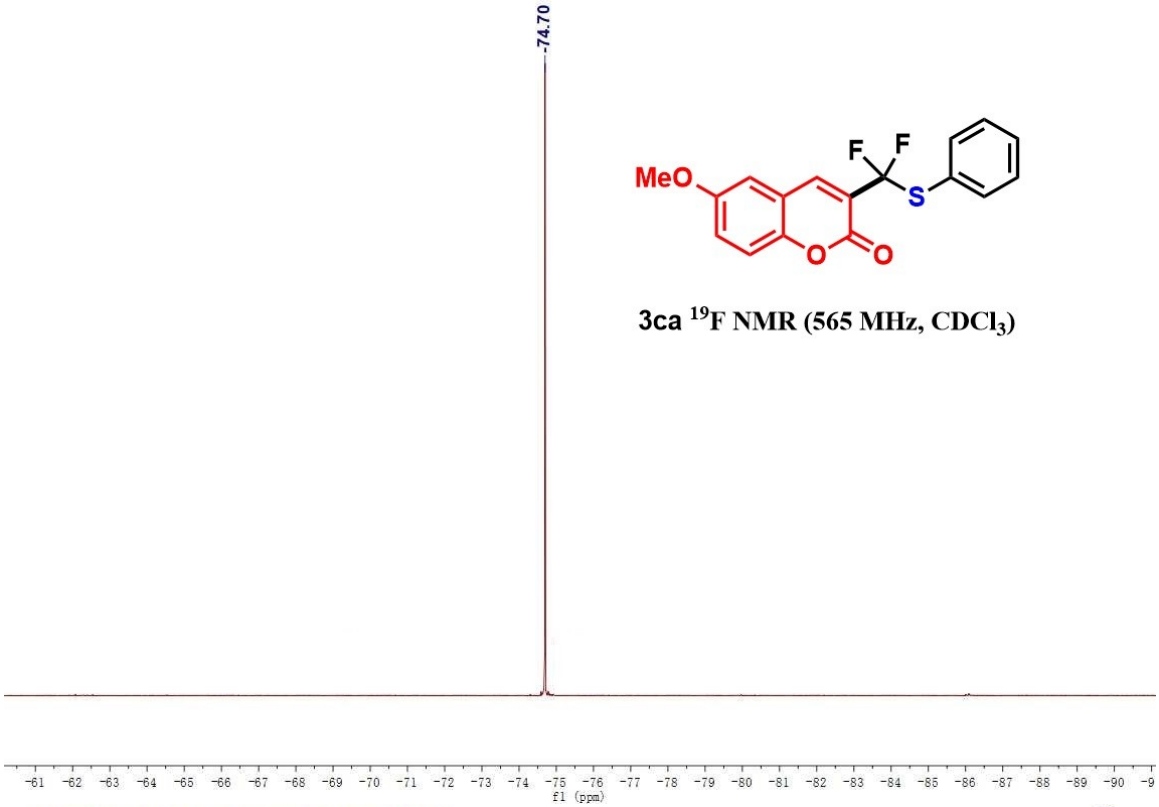
3ba ^{19}F NMR (376 MHz, $CDCl_3$)



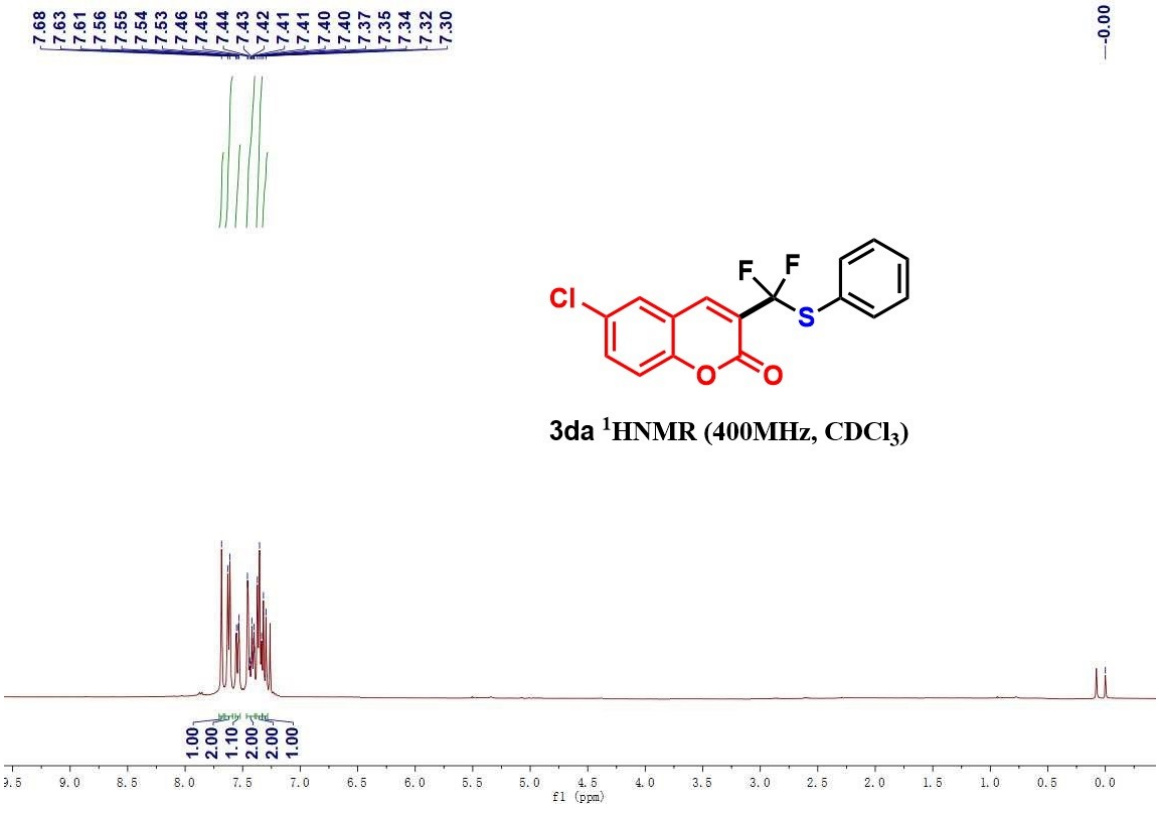
3ca ^{1}HNMR (600MHz, $CDCl_3$)



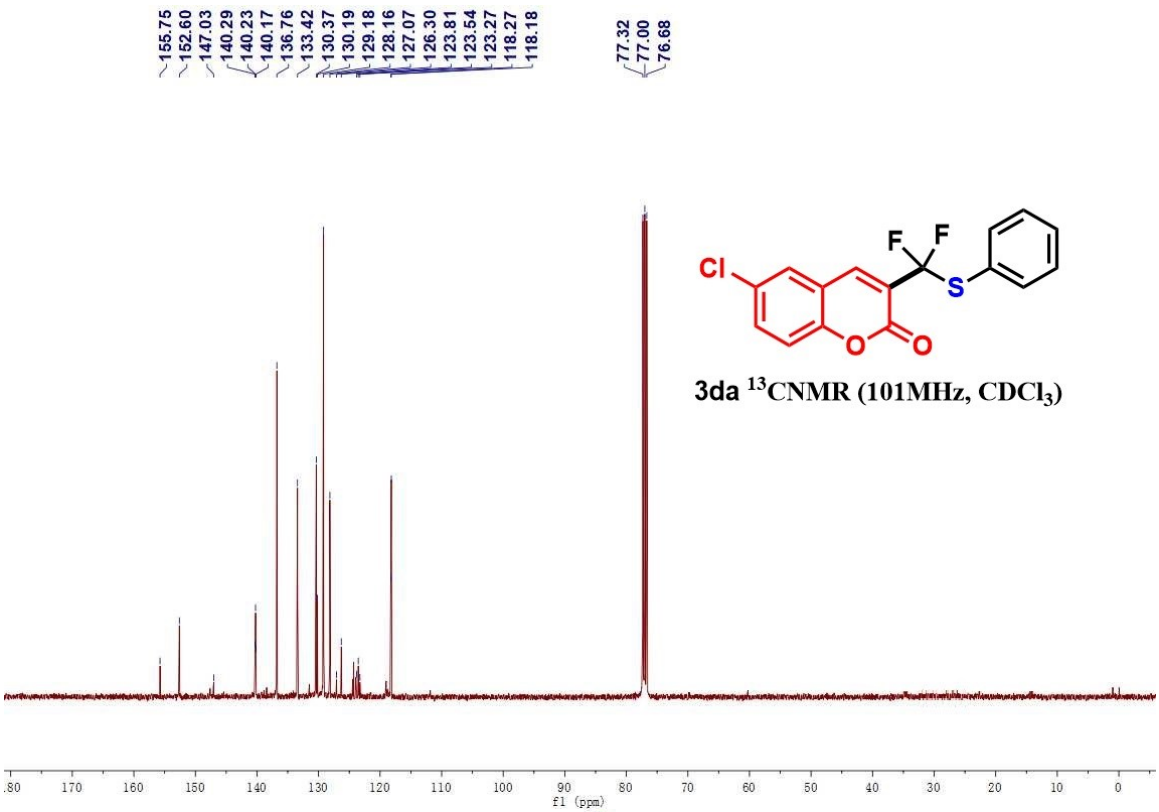
3ca ^{13}CNMR (151MHz, $CDCl_3$)



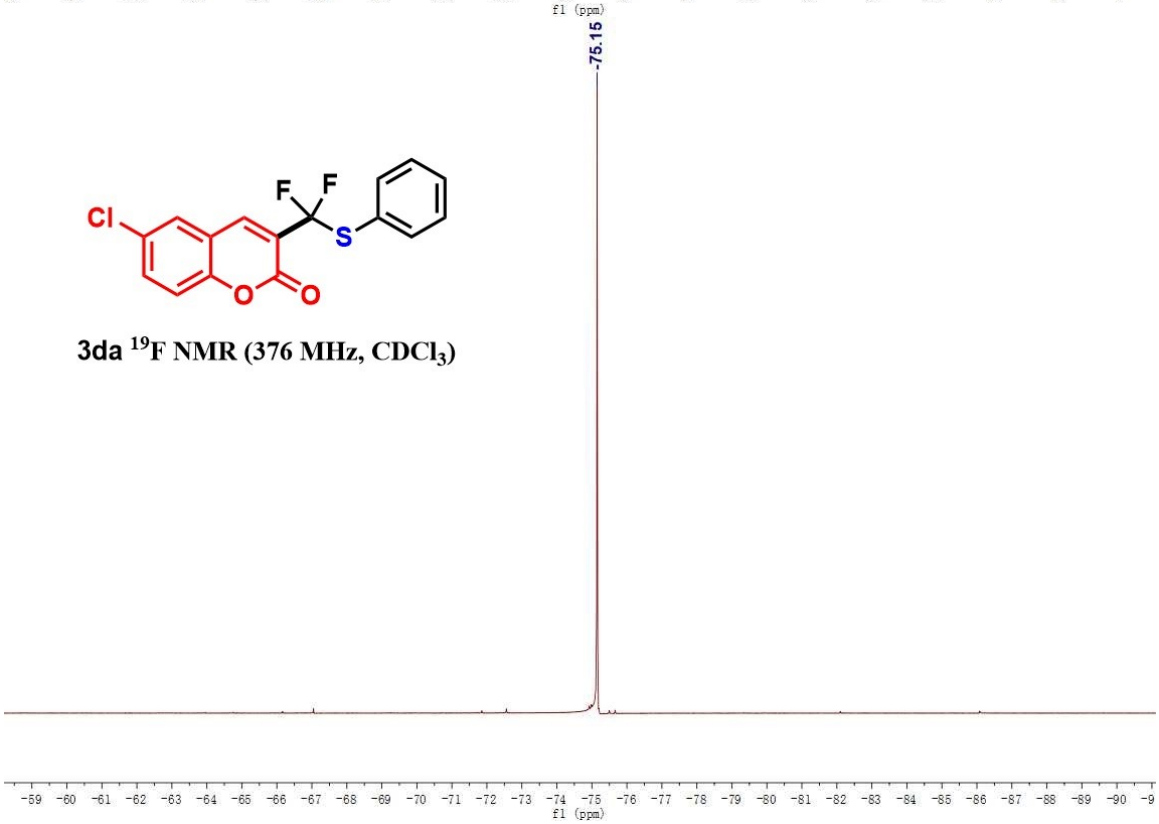
3ca ^{19}F NMR (565 MHz, $CDCl_3$)



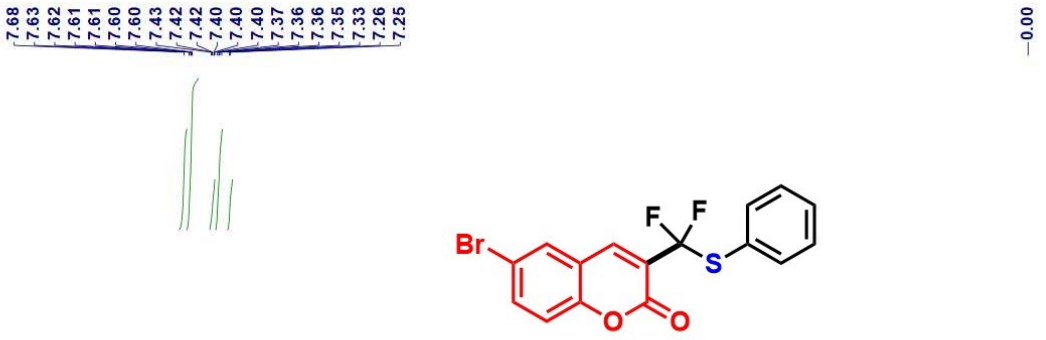
3da ^{1}HNMR (400MHz, $CDCl_3$)



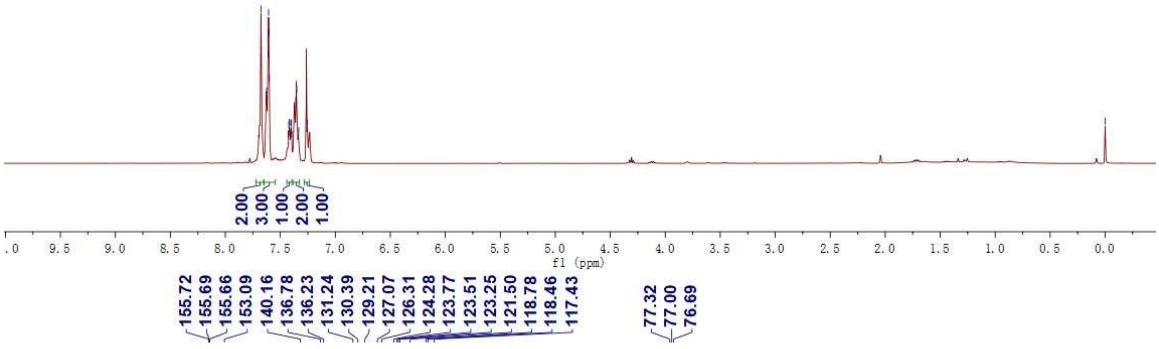
3da ^{13}CNMR (101MHz, $CDCl_3$)

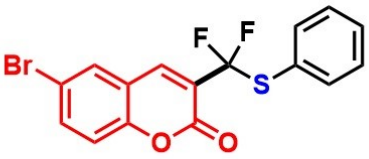


3da ^{19}F NMR (376 MHz, $CDCl_3$)

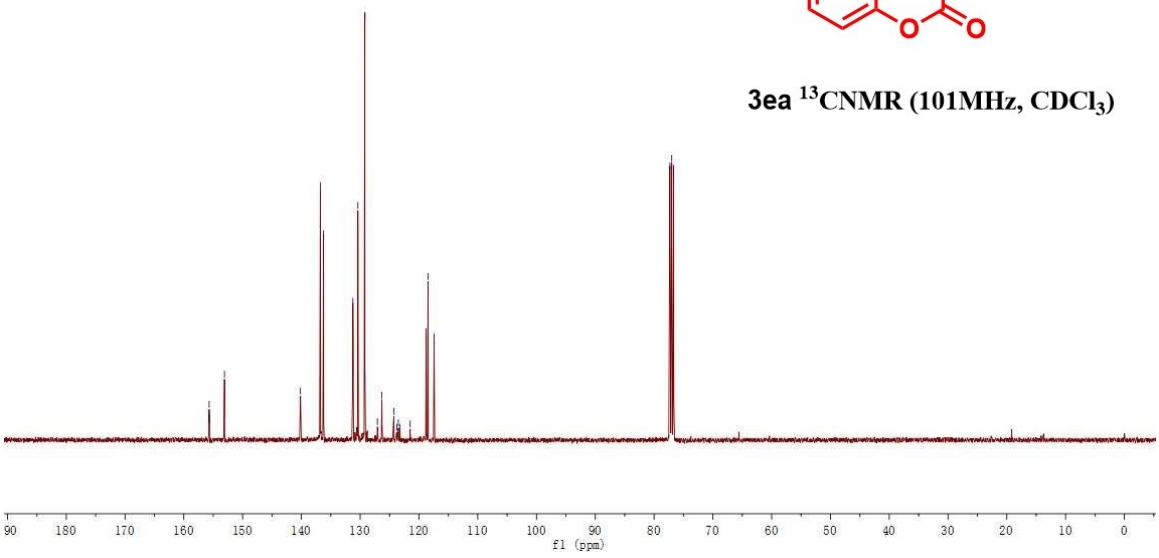


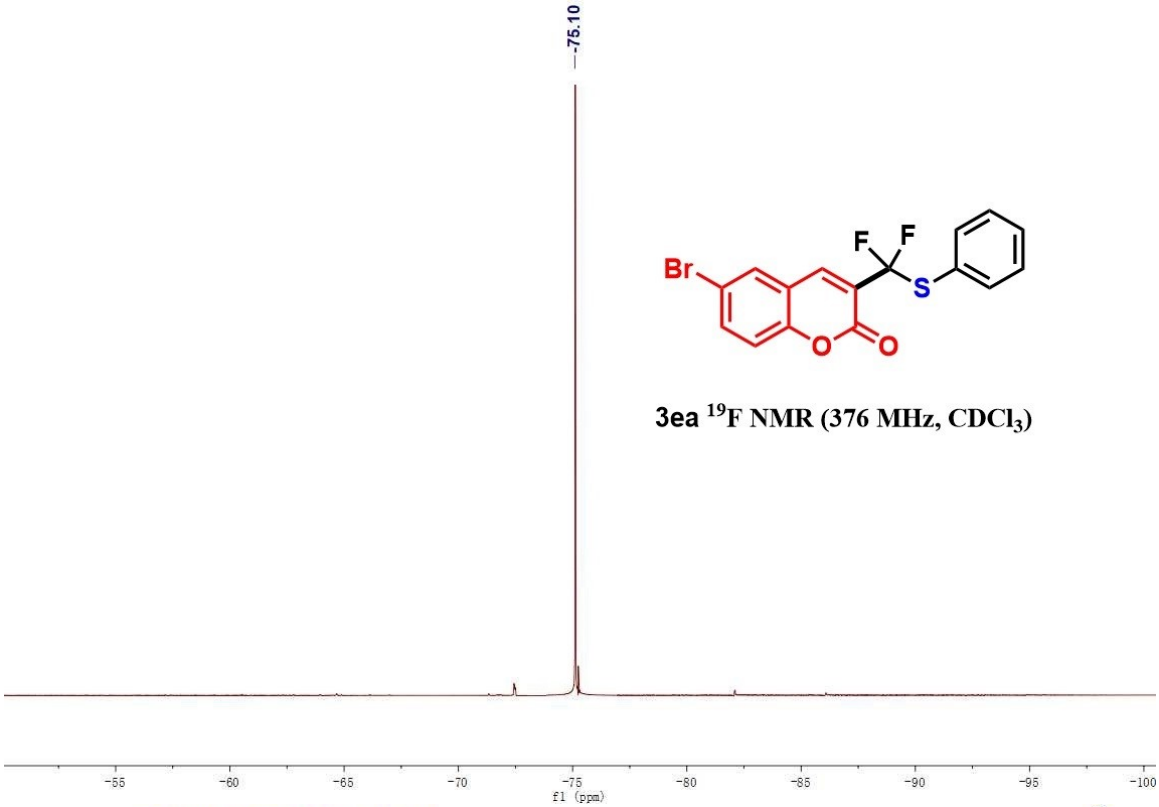
3ea ^{1}HNMR (400MHz, $CDCl_3$)



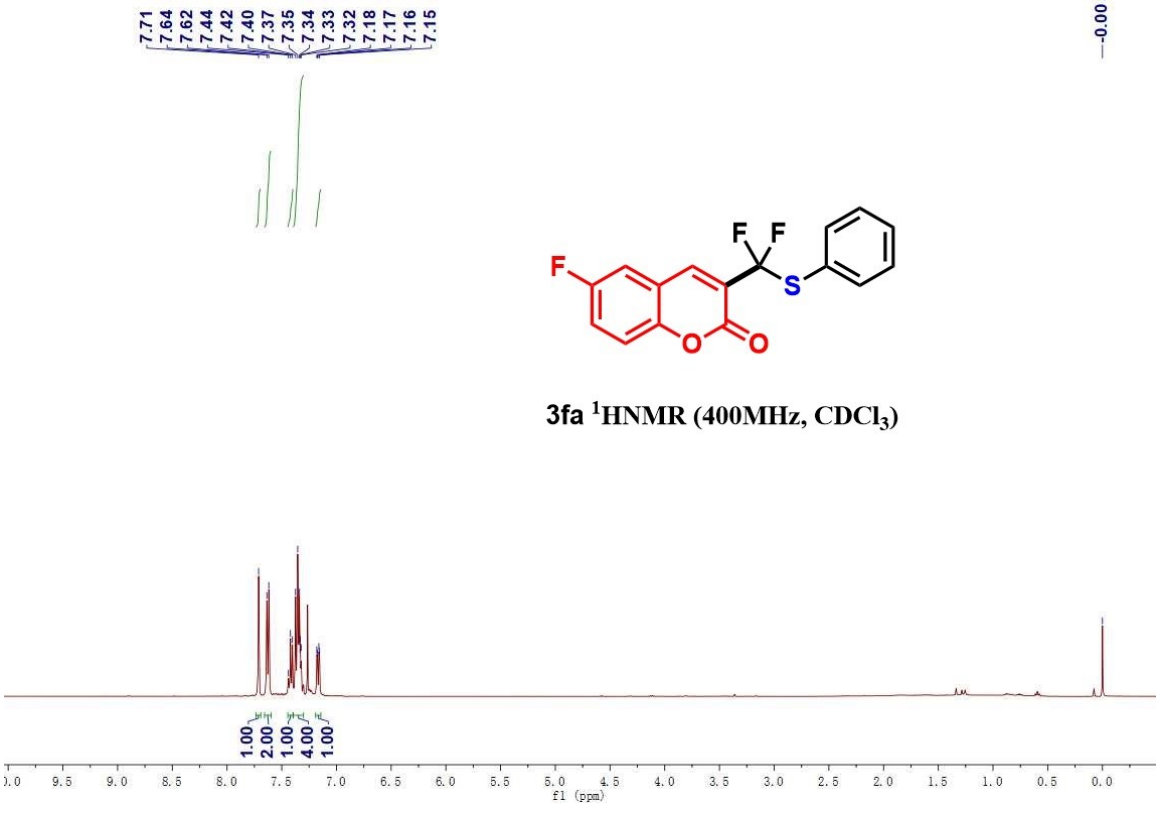


3ea ^{13}CNMR (101MHz, $CDCl_3$)

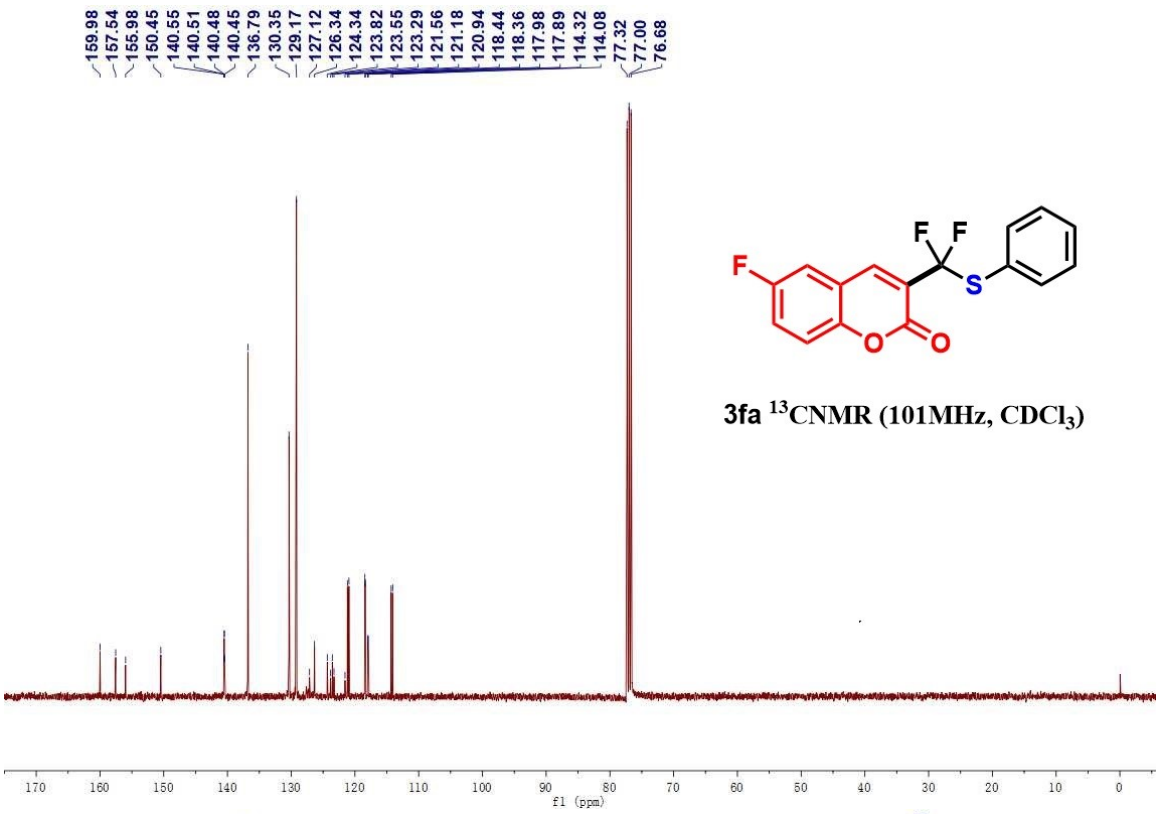




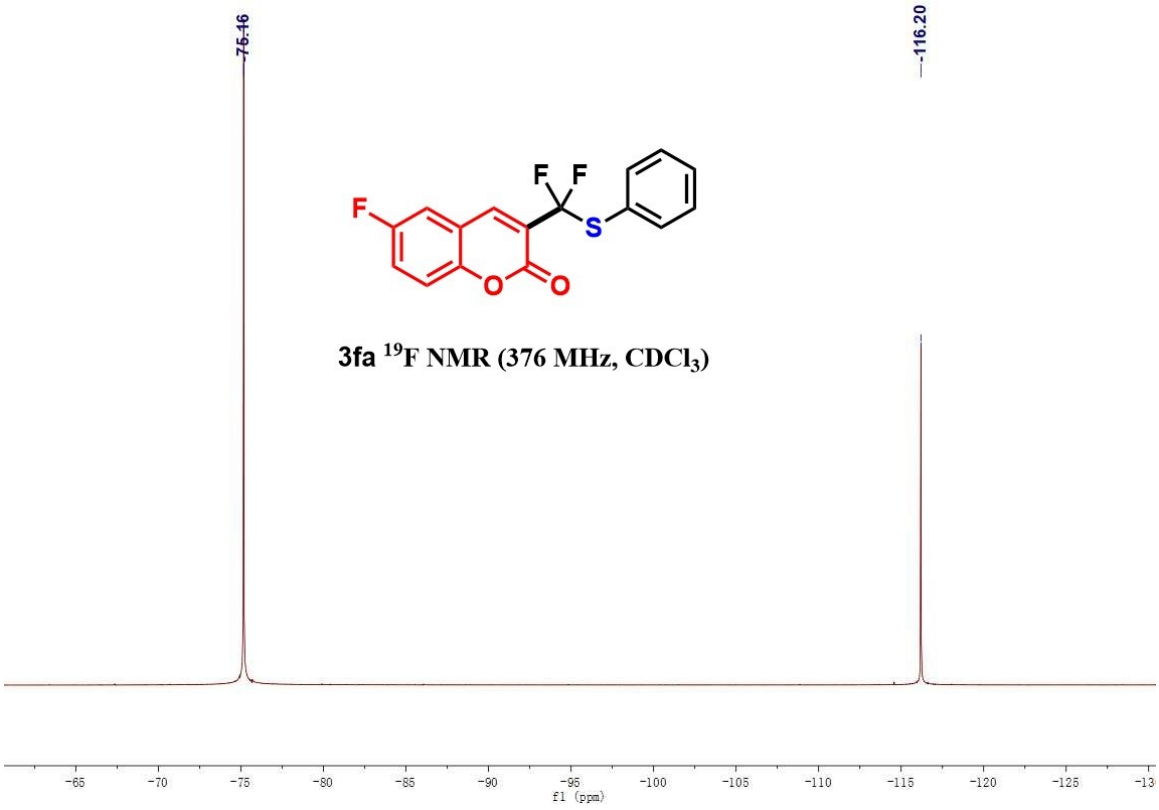
3ea ^{19}F NMR (376 MHz, $CDCl_3$)



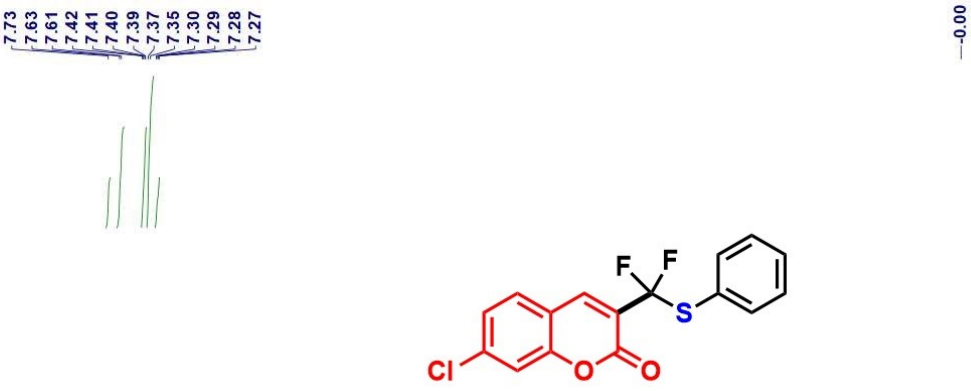
3fa ^{1}HNMR (400MHz, $CDCl_3$)



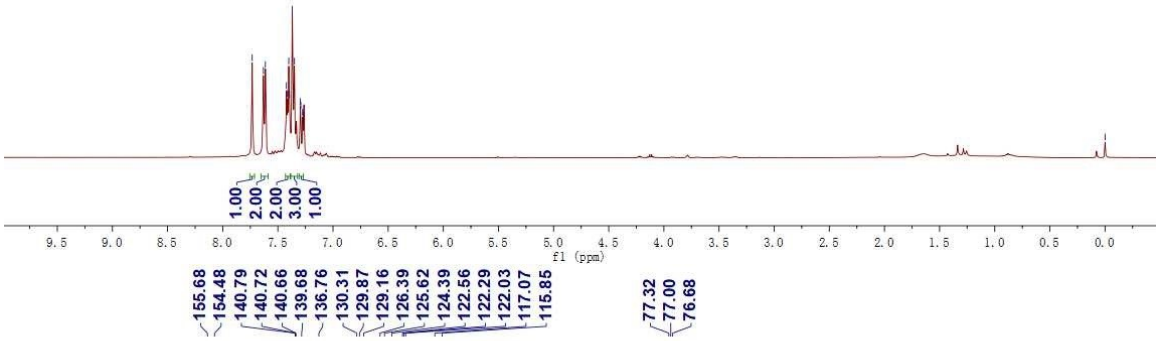
3fa ^{13}CNMR (101MHz, $CDCl_3$)

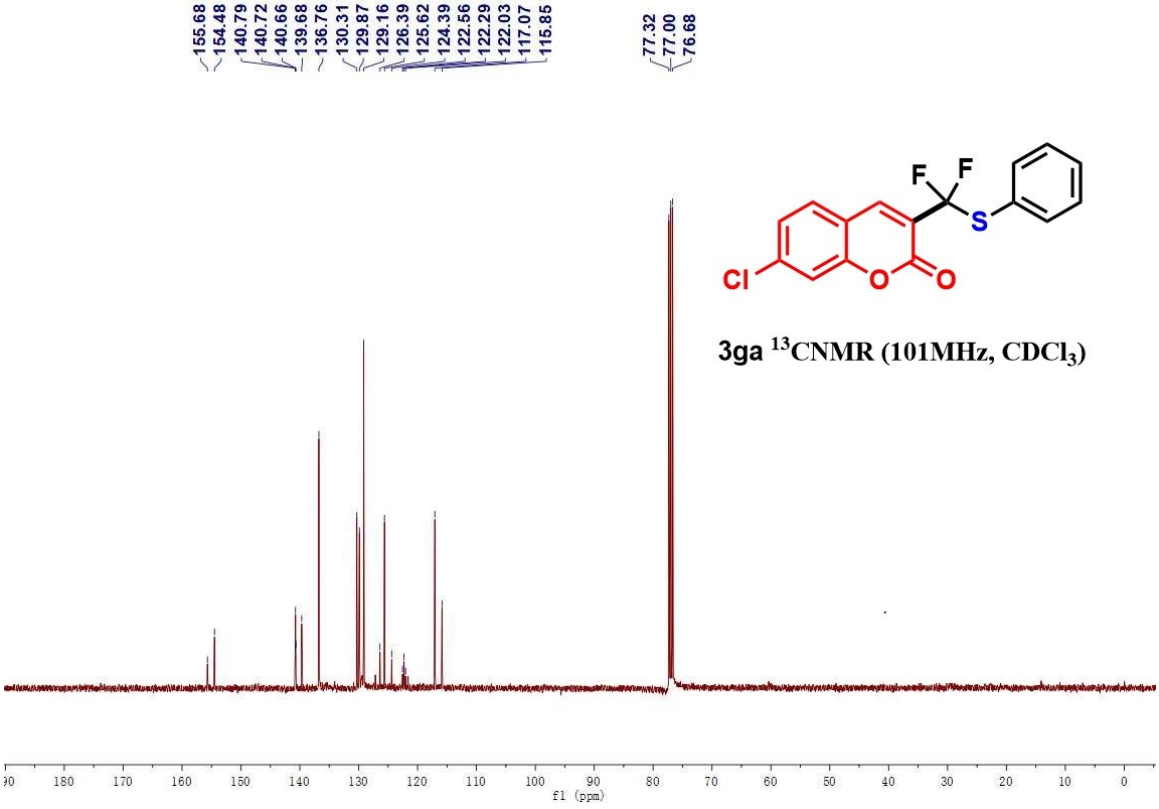


3fa ^{19}F NMR (376 MHz, $CDCl_3$)

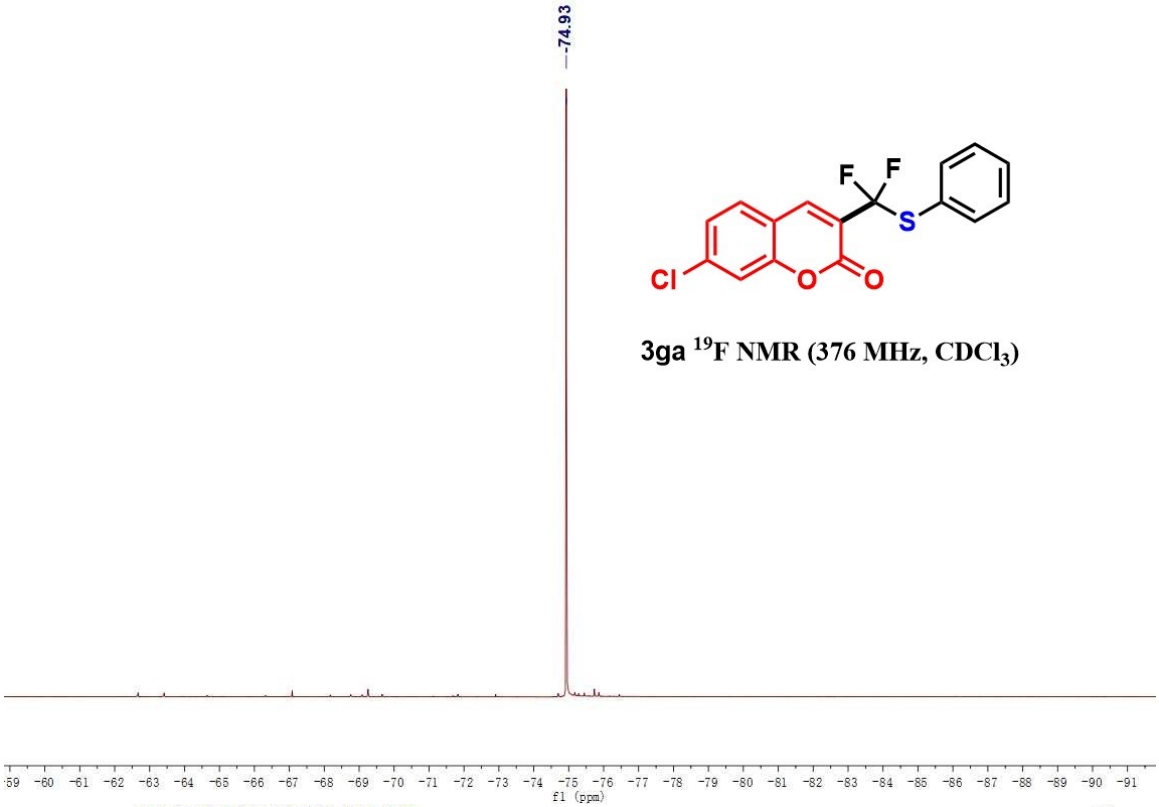


3ga ^{1}HNMR (400MHz, $CDCl_3$)

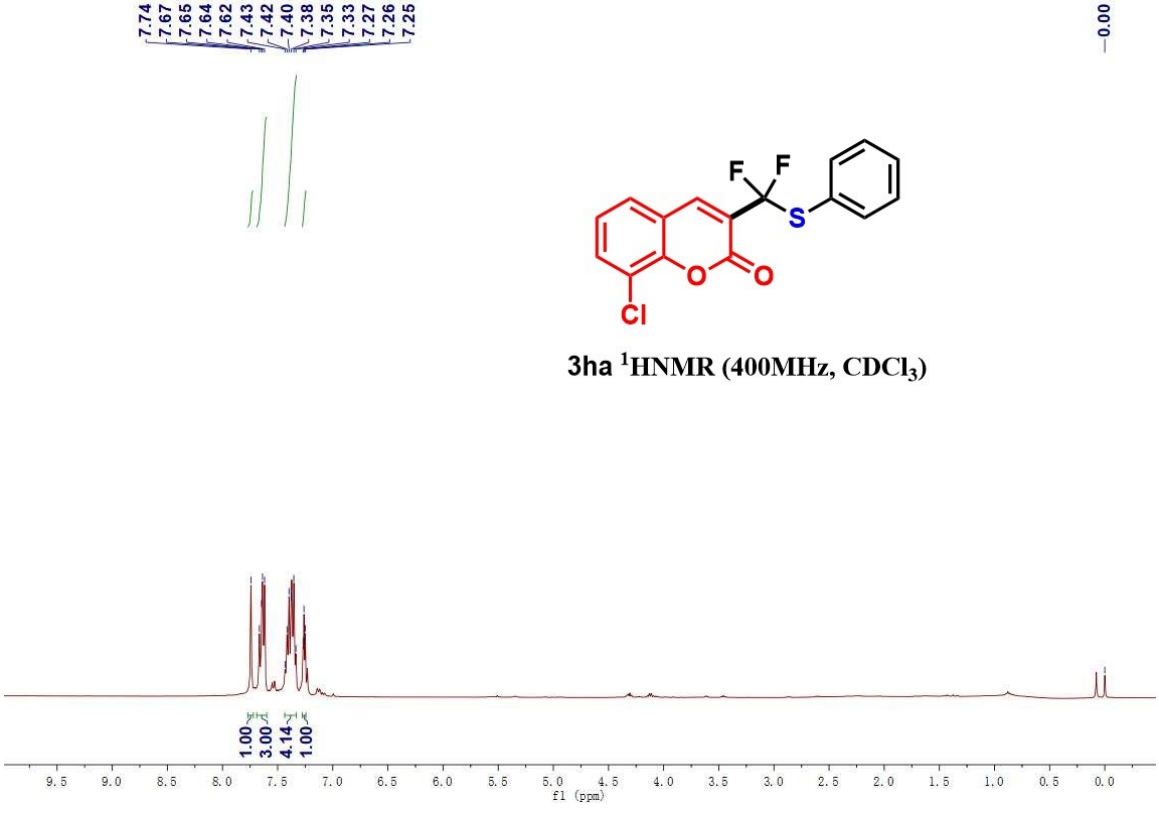




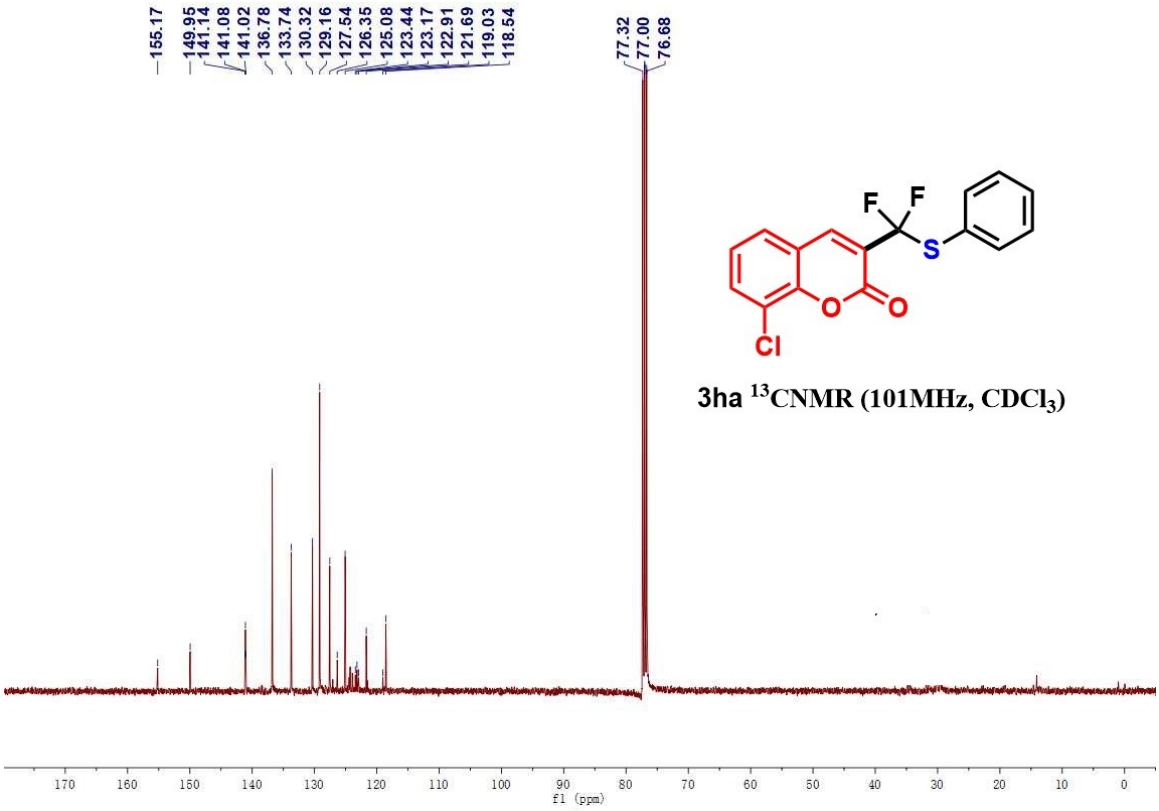
3ga ^{13}CNMR (101MHz, $CDCl_3$)



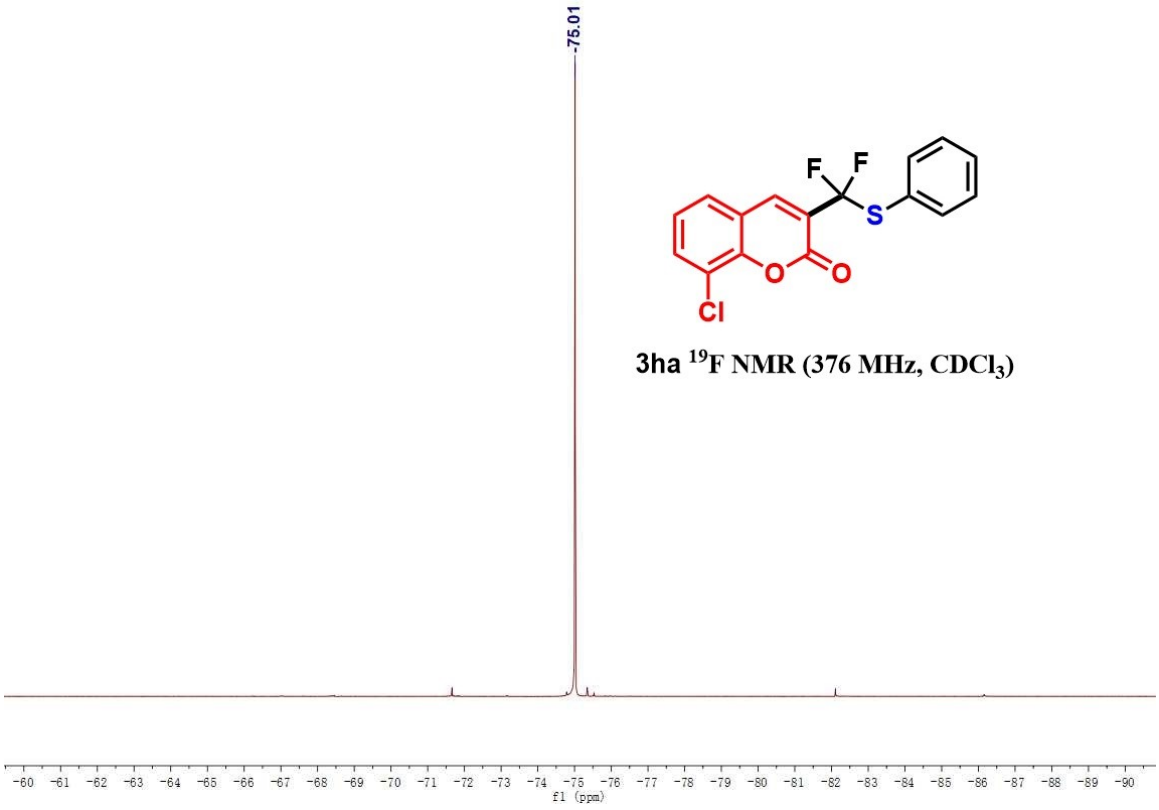
3ga ^{19}F NMR (376 MHz, $CDCl_3$)



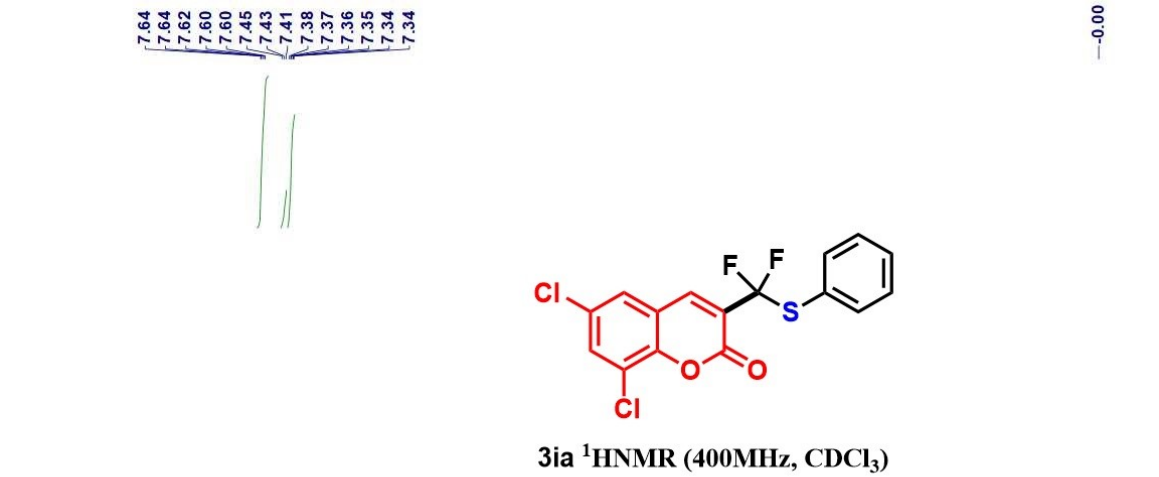
3ha ^{1}HNMR (400MHz, $CDCl_3$)



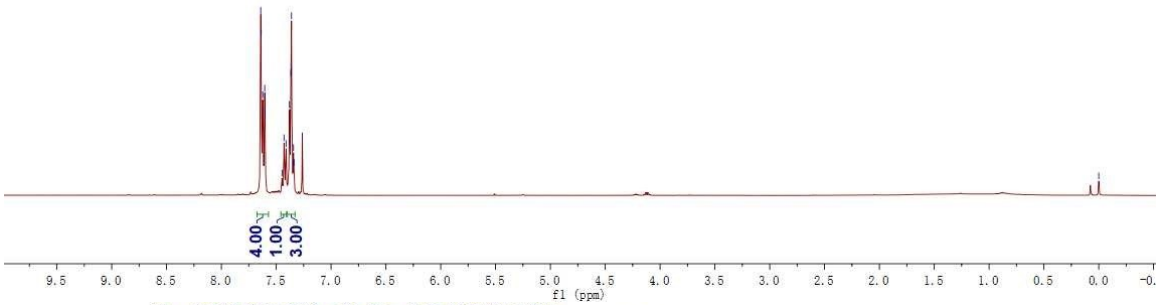
3ha ^{13}CNMR (101MHz, $CDCl_3$)

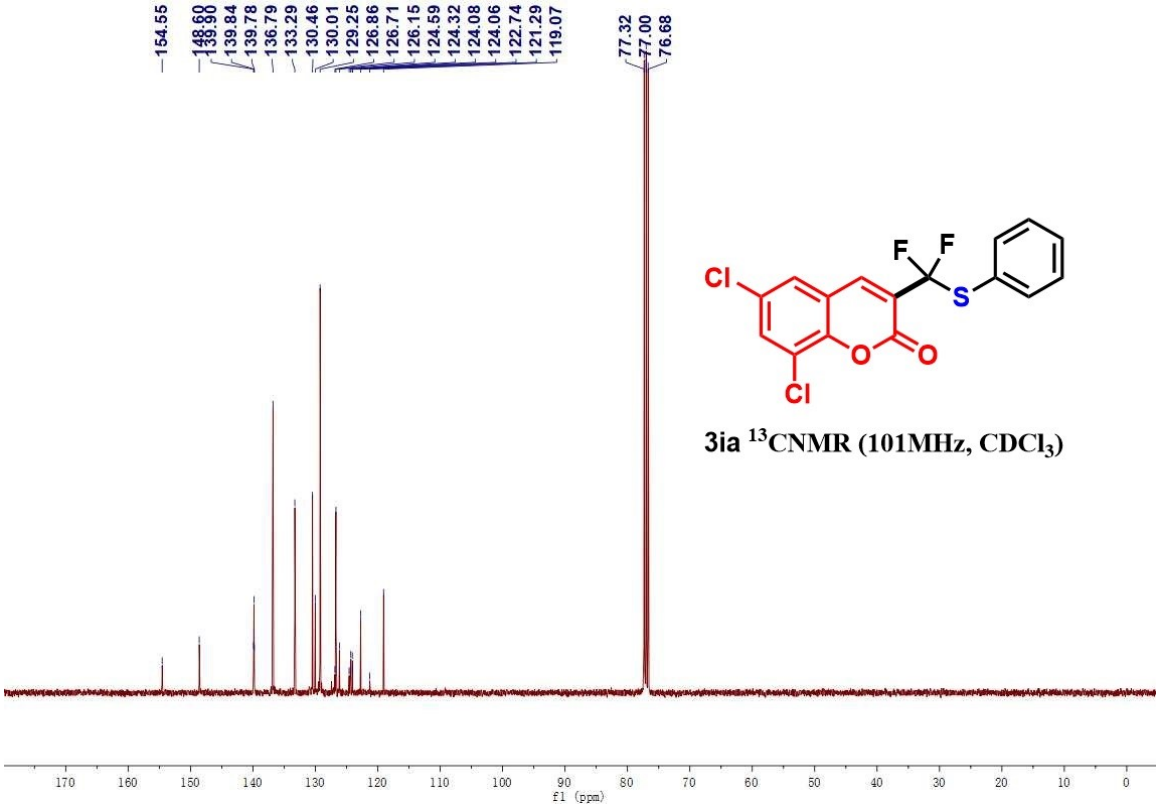


3ha ^{19}F NMR (376 MHz, $CDCl_3$)

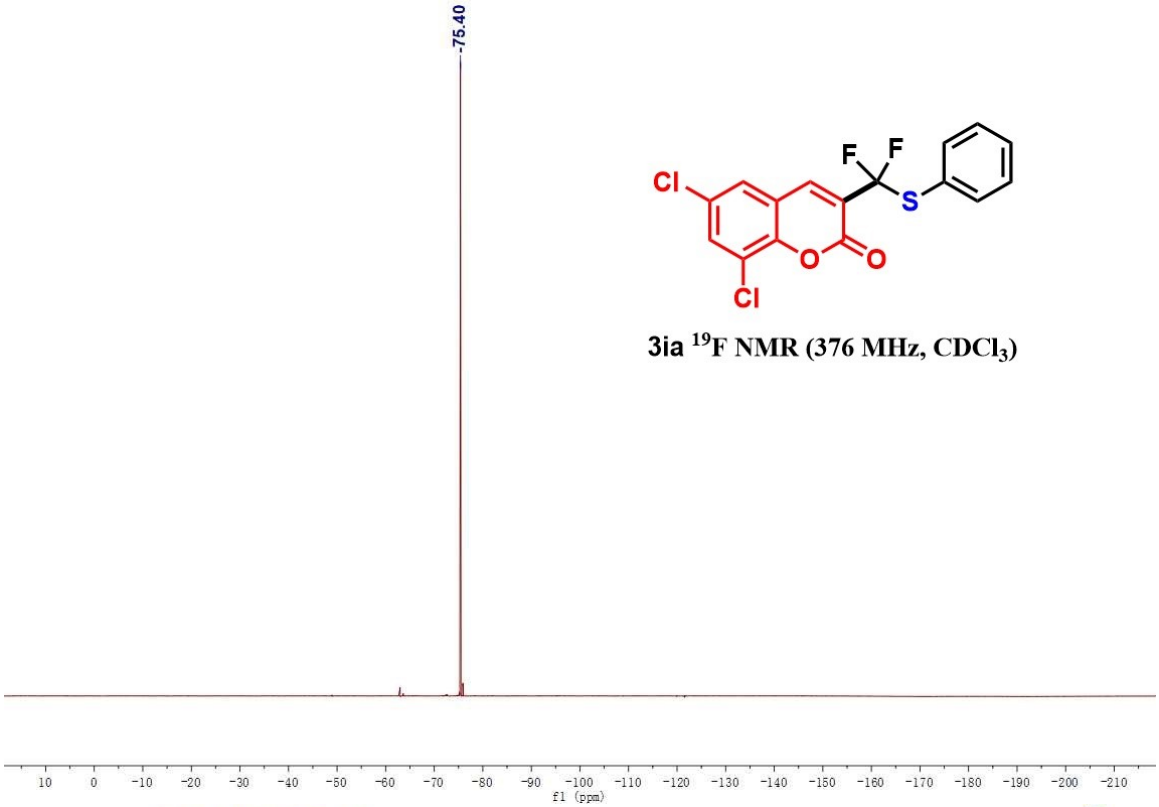


3ia ^{1}HNMR (400MHz, $CDCl_3$)

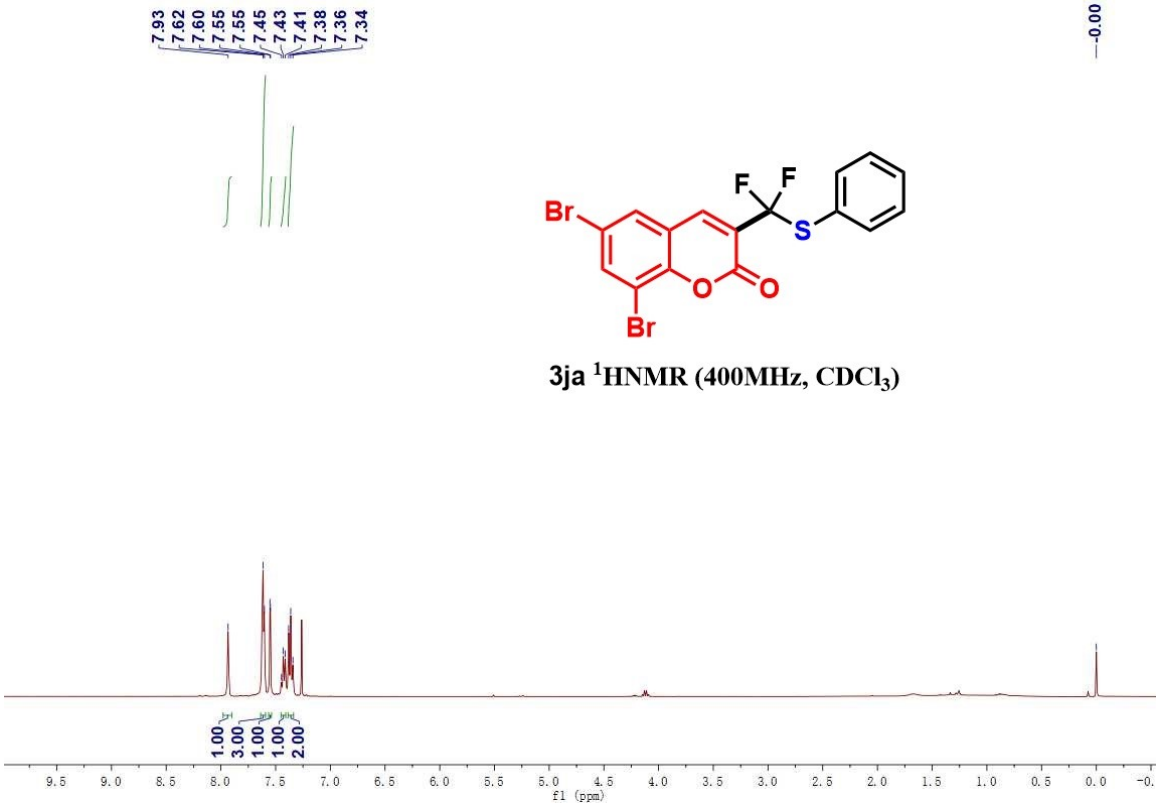




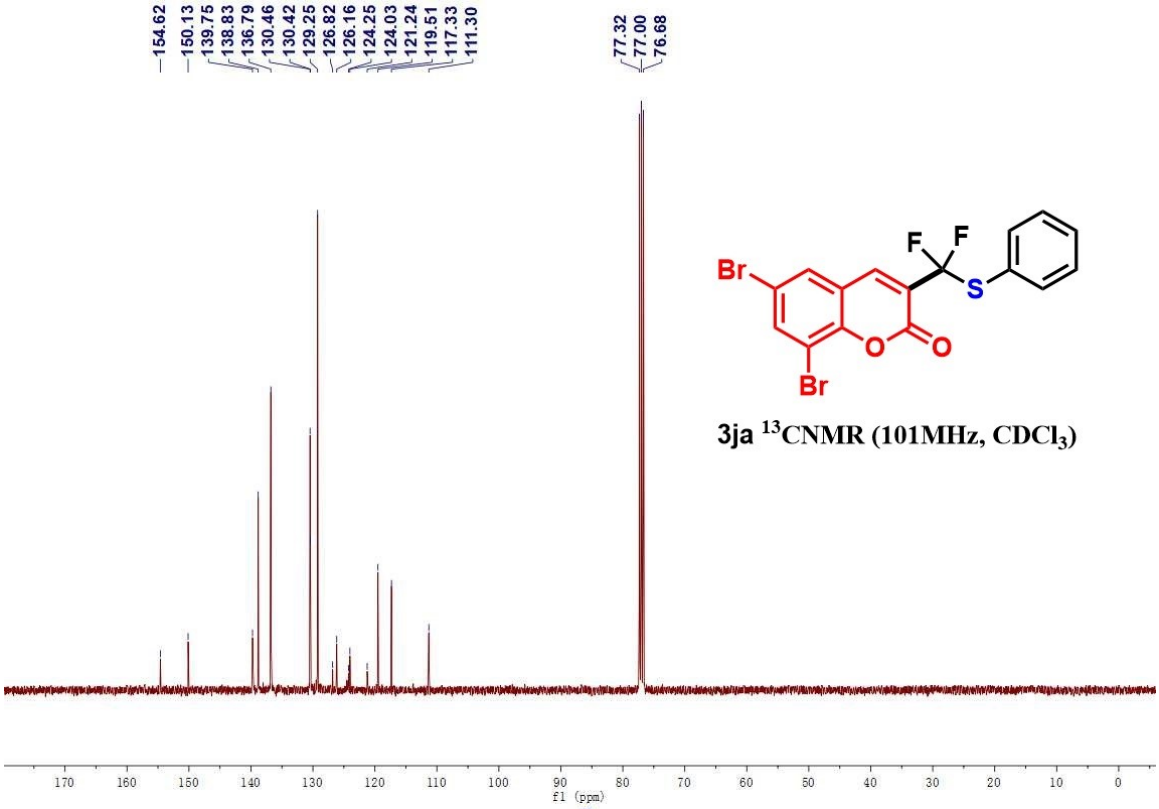
3ia ^{13}CNMR (101MHz, $CDCl_3$)



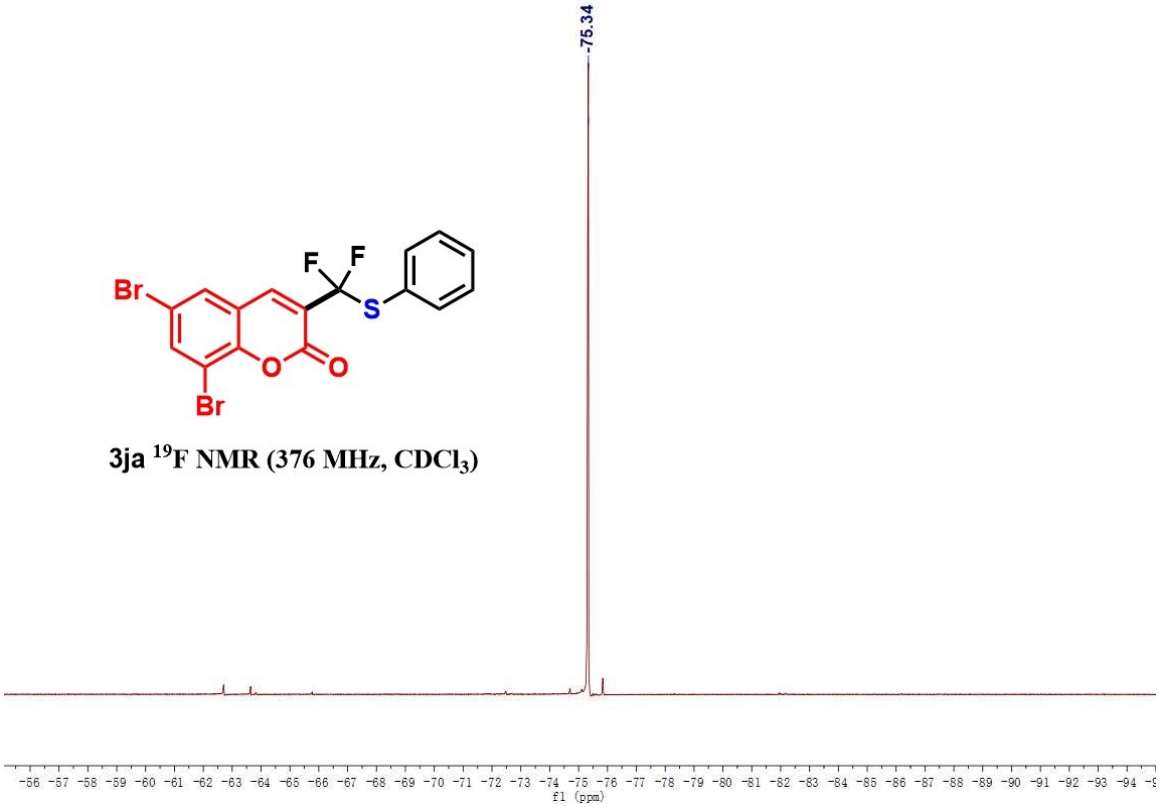
3ia ^{19}F NMR (376 MHz, $CDCl_3$)



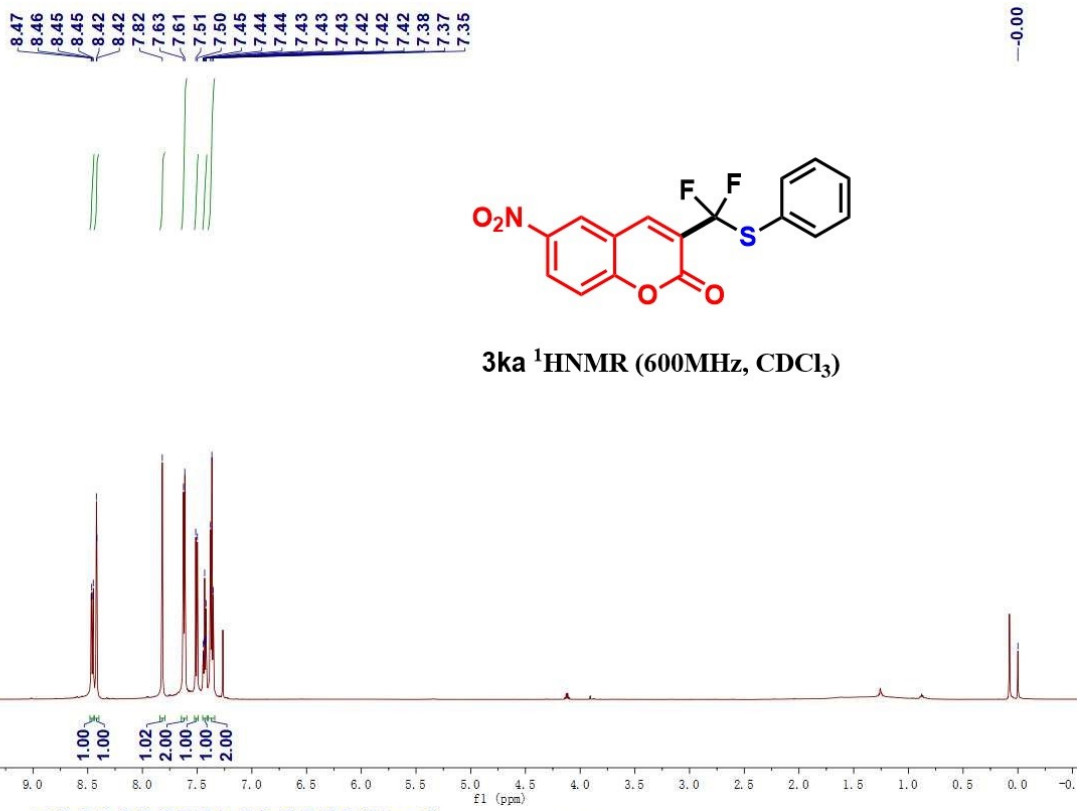
3ja ^{1}HNMR (400MHz, $CDCl_3$)



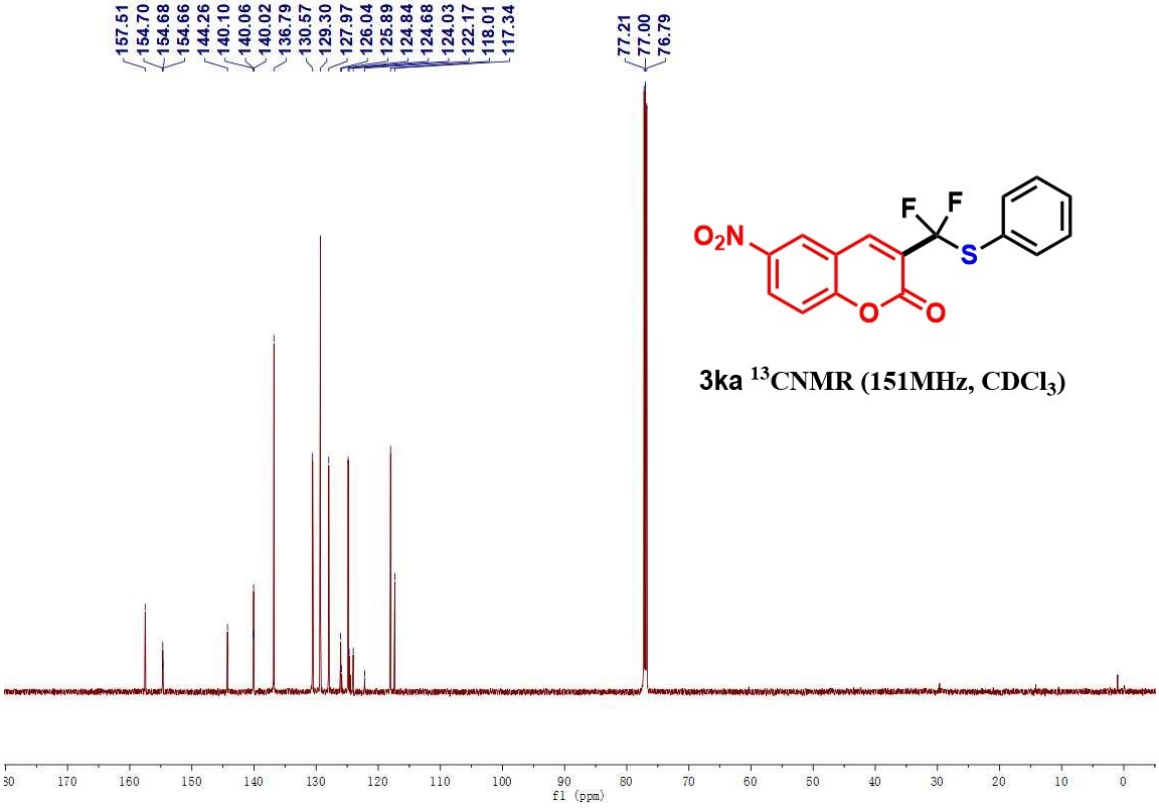
3ja ^{13}CNMR (101MHz, $CDCl_3$)



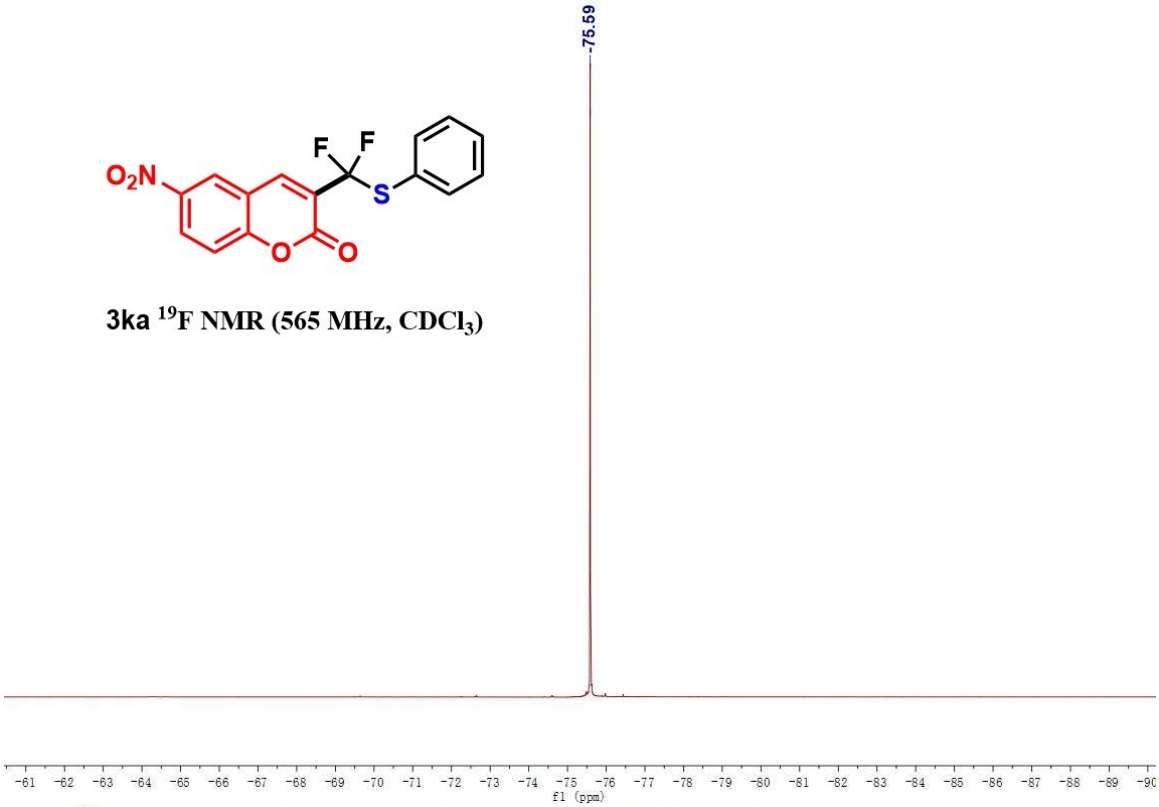
3ja ^{19}F NMR (376 MHz, $CDCl_3$)



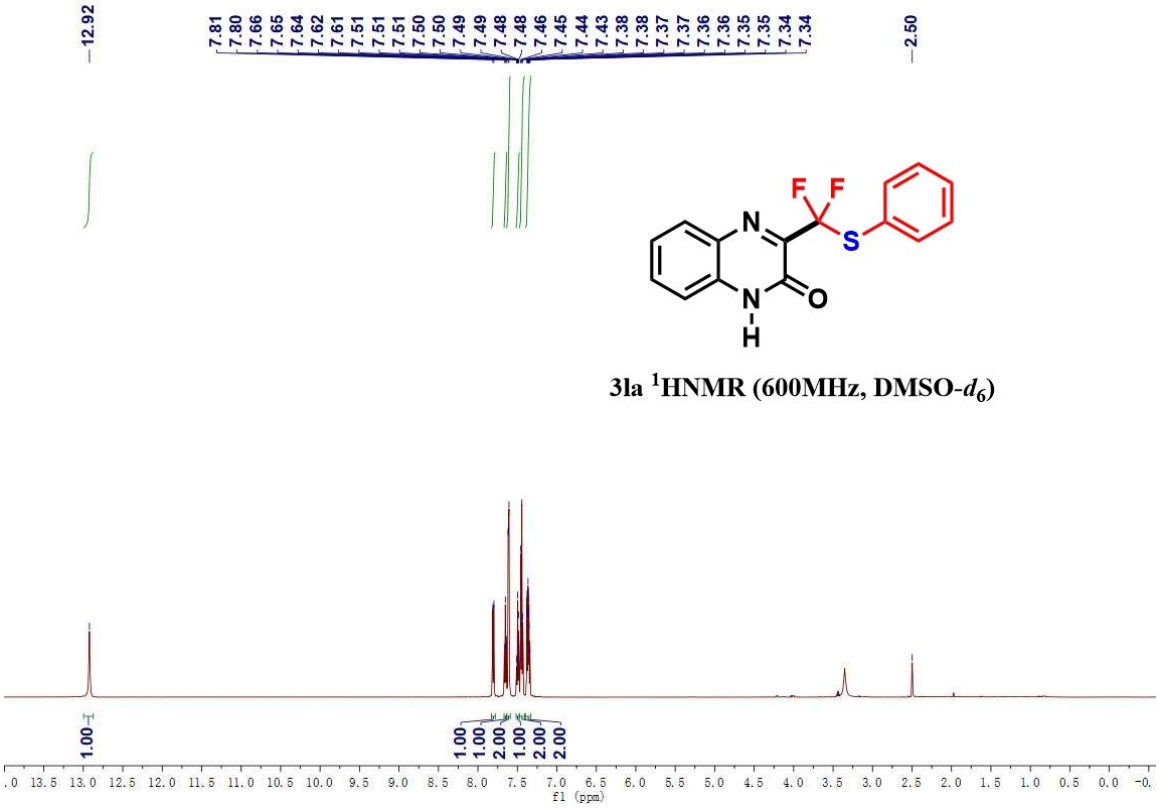
3ka ^{1}HNMR (600MHz, $CDCl_3$)



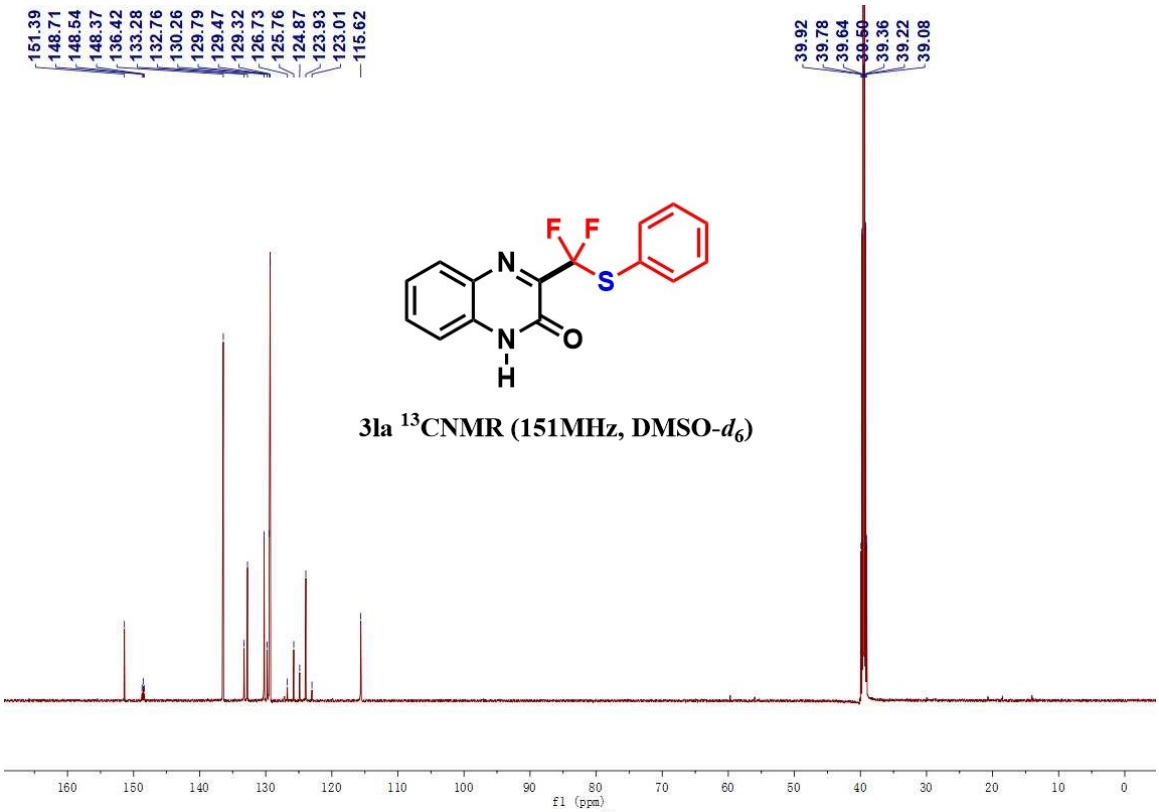
3ka ^{13}CNMR (151MHz, $CDCl_3$)



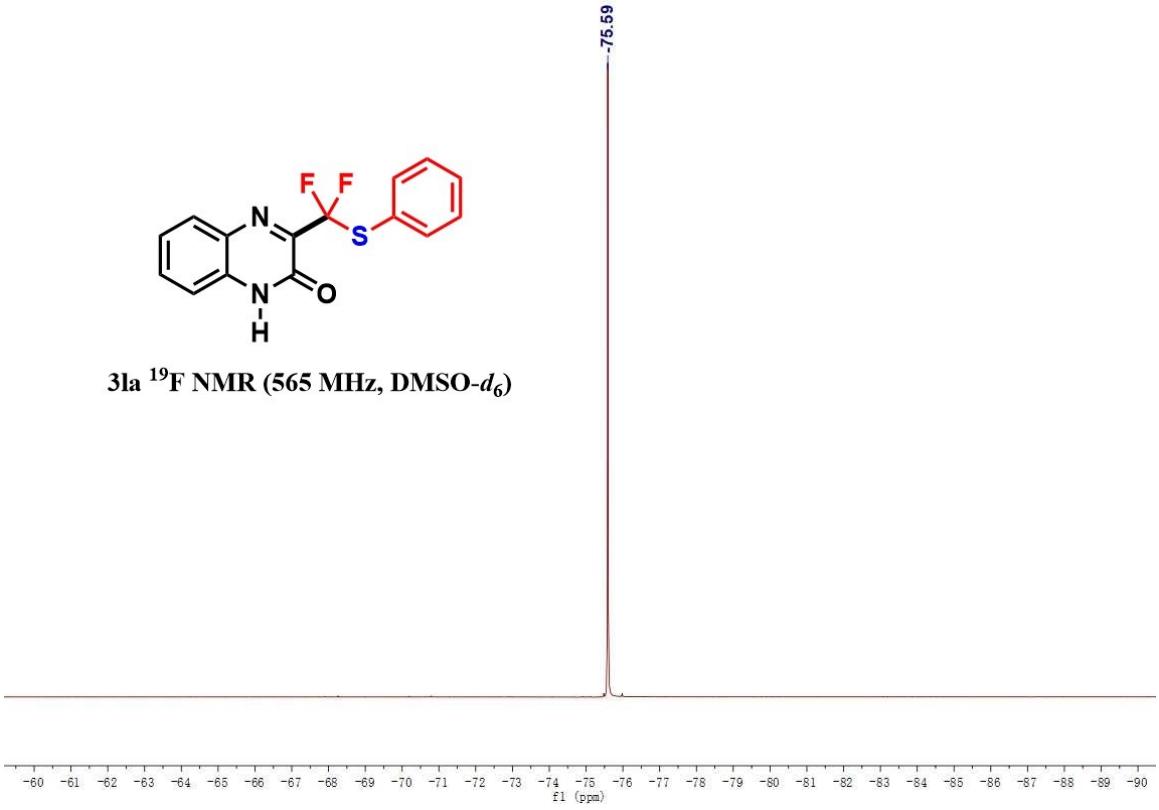
3ka ^{19}F NMR (565 MHz, $CDCl_3$)



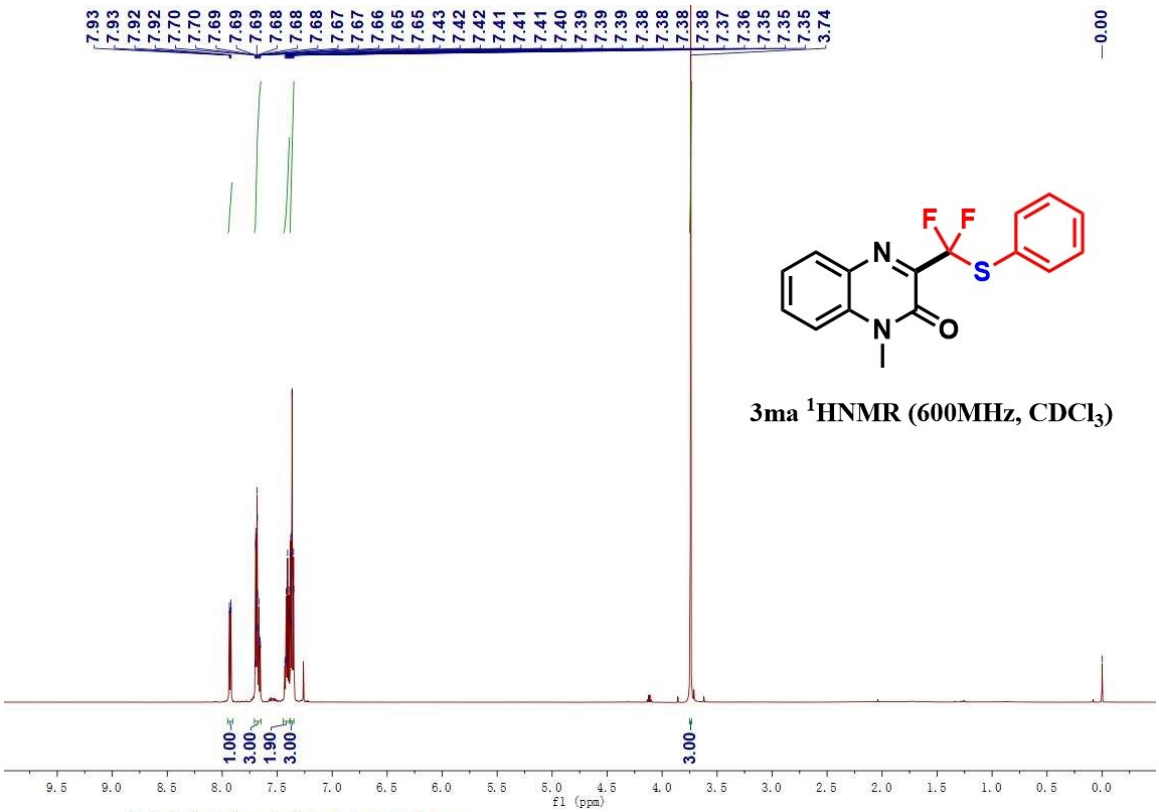
3la ^{1}HNMR (600MHz, DMSO-d_6)



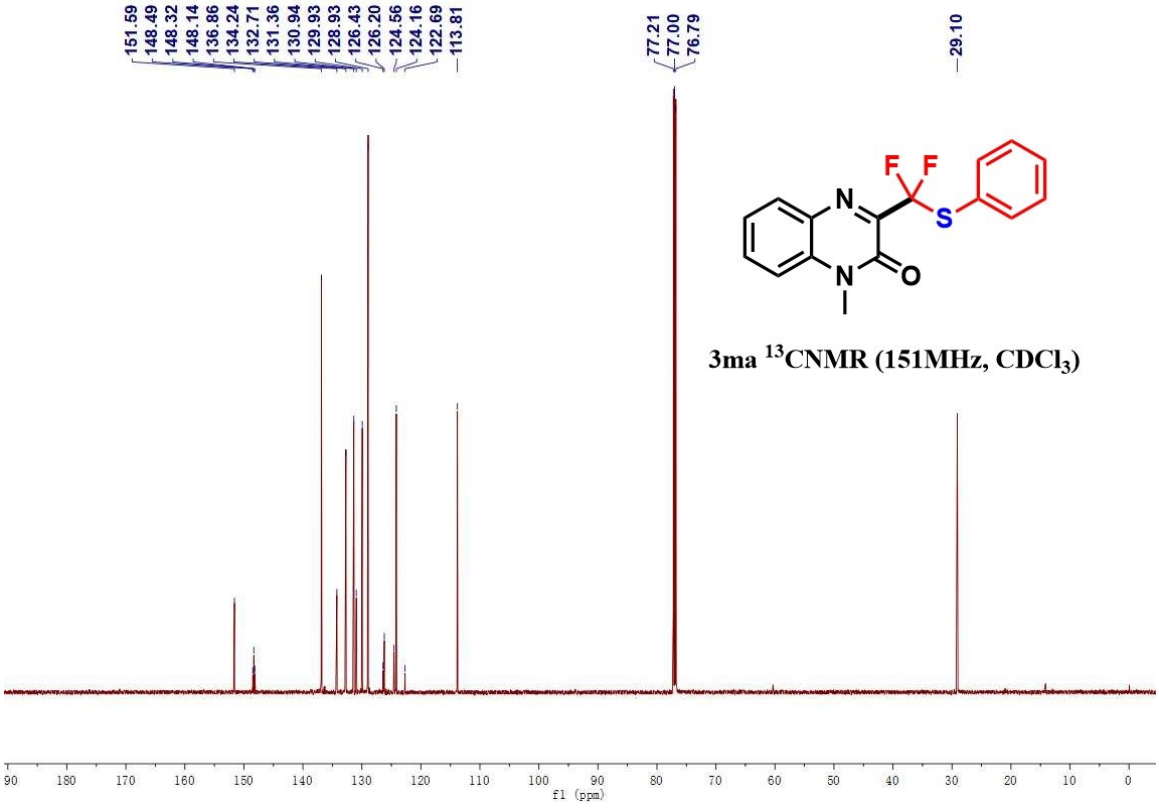
3la ^{13}CNMR (151MHz, DMSO-d_6)



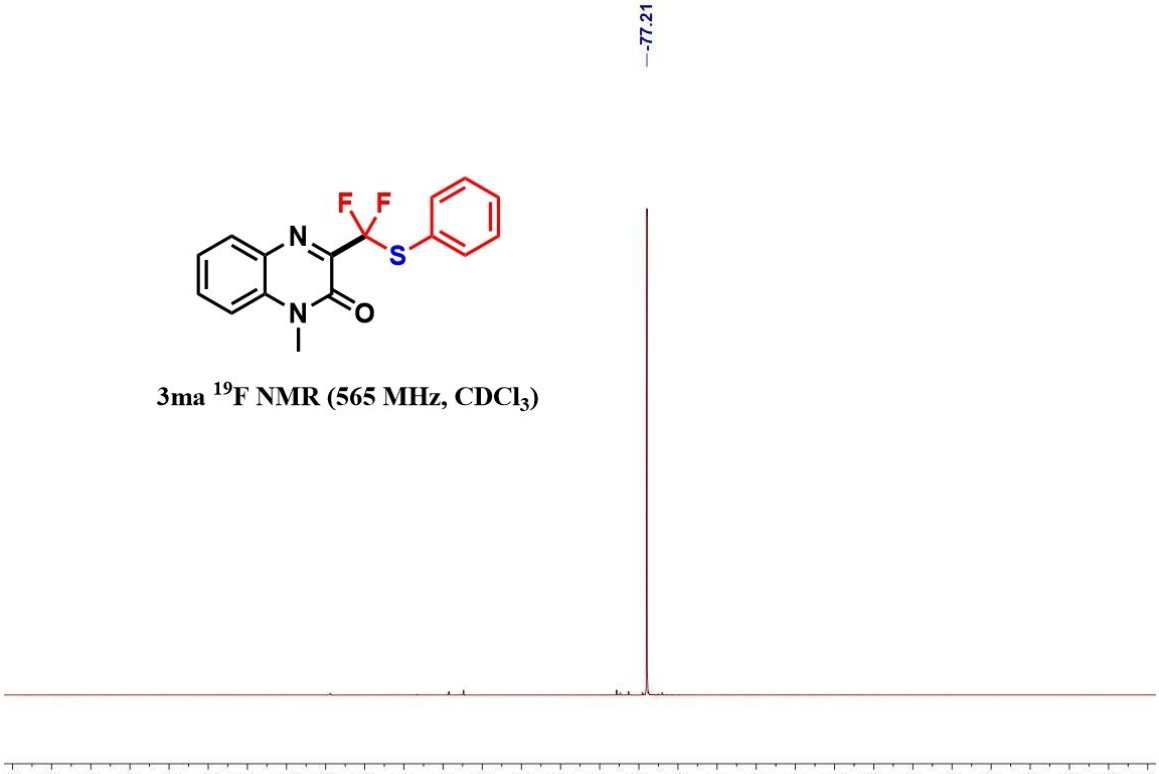
3la ^{19}F NMR (565 MHz, DMSO-d_6)



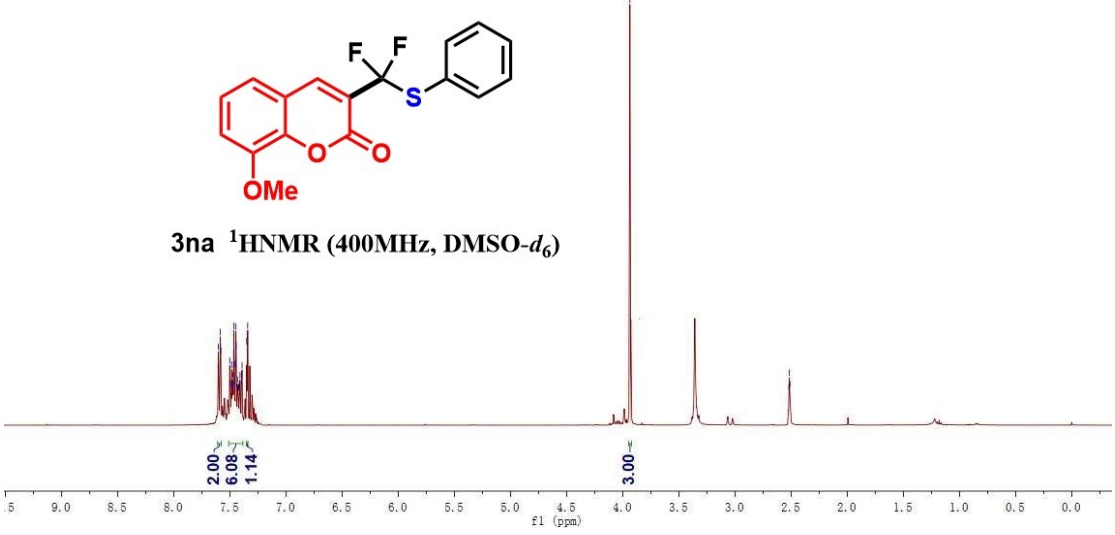
3ma ^{1}HNMR (600MHz, $CDCl_3$)



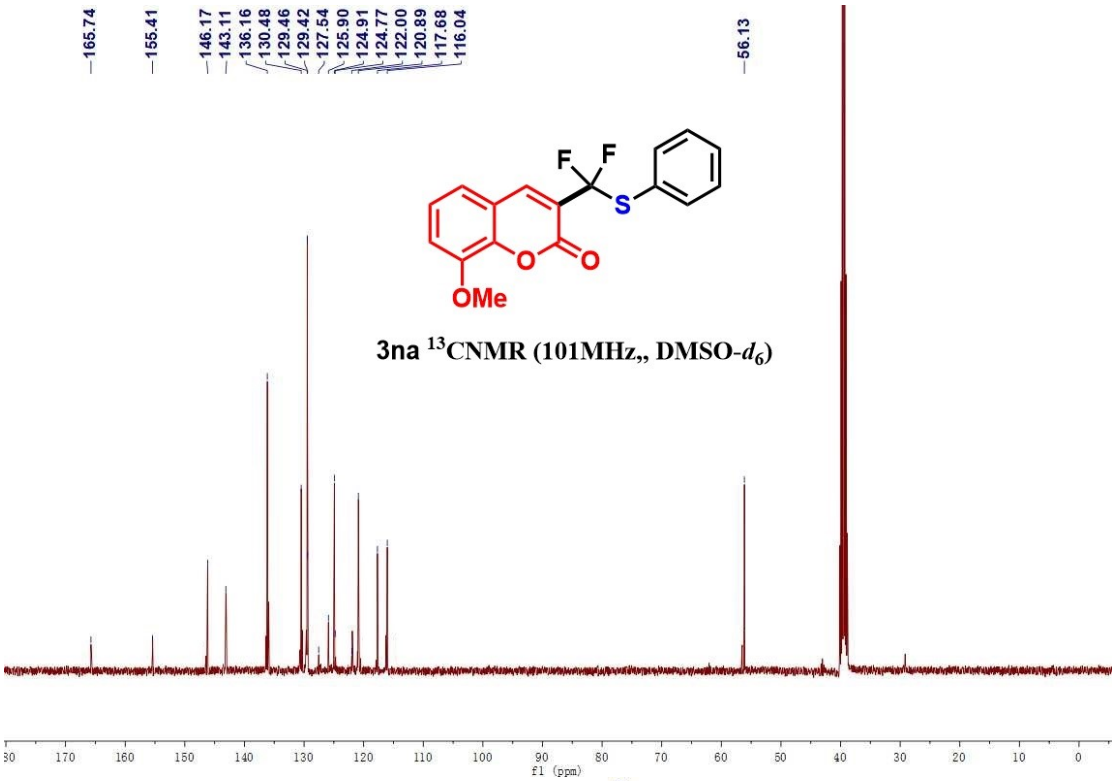
3ma ^{13}CNMR (151MHz, $CDCl_3$)



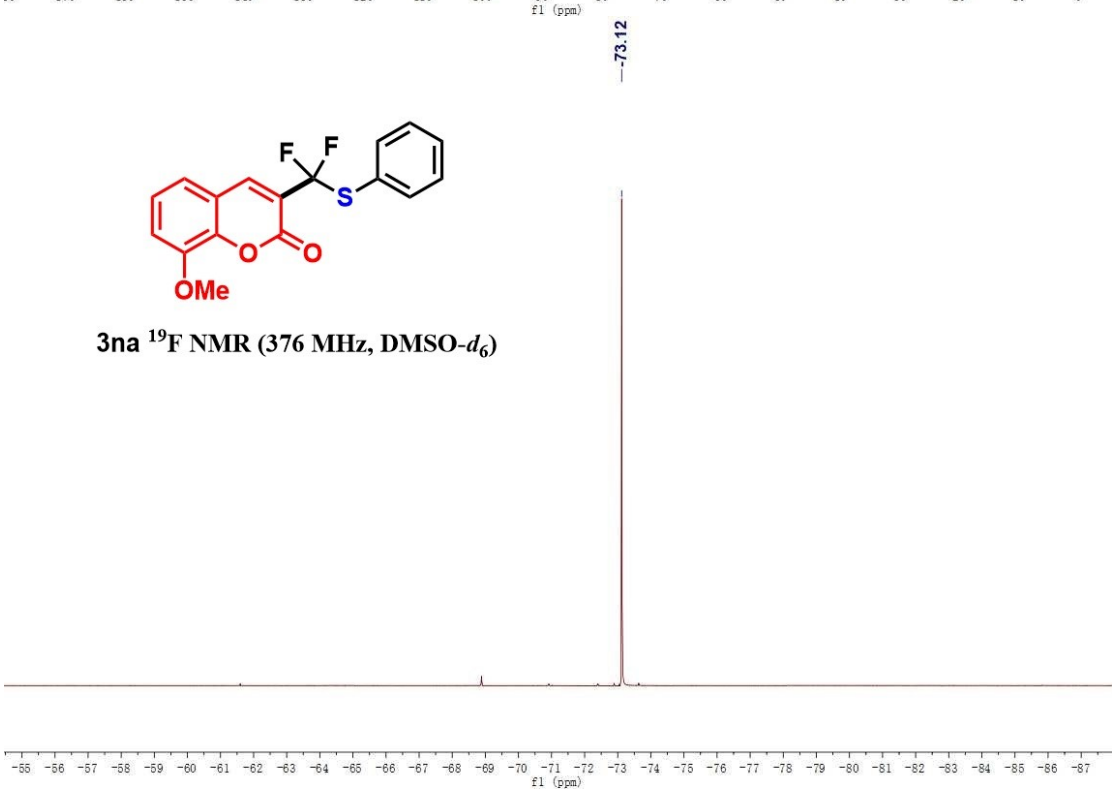
3ma ^{19}F NMR (565 MHz, $CDCl_3$)



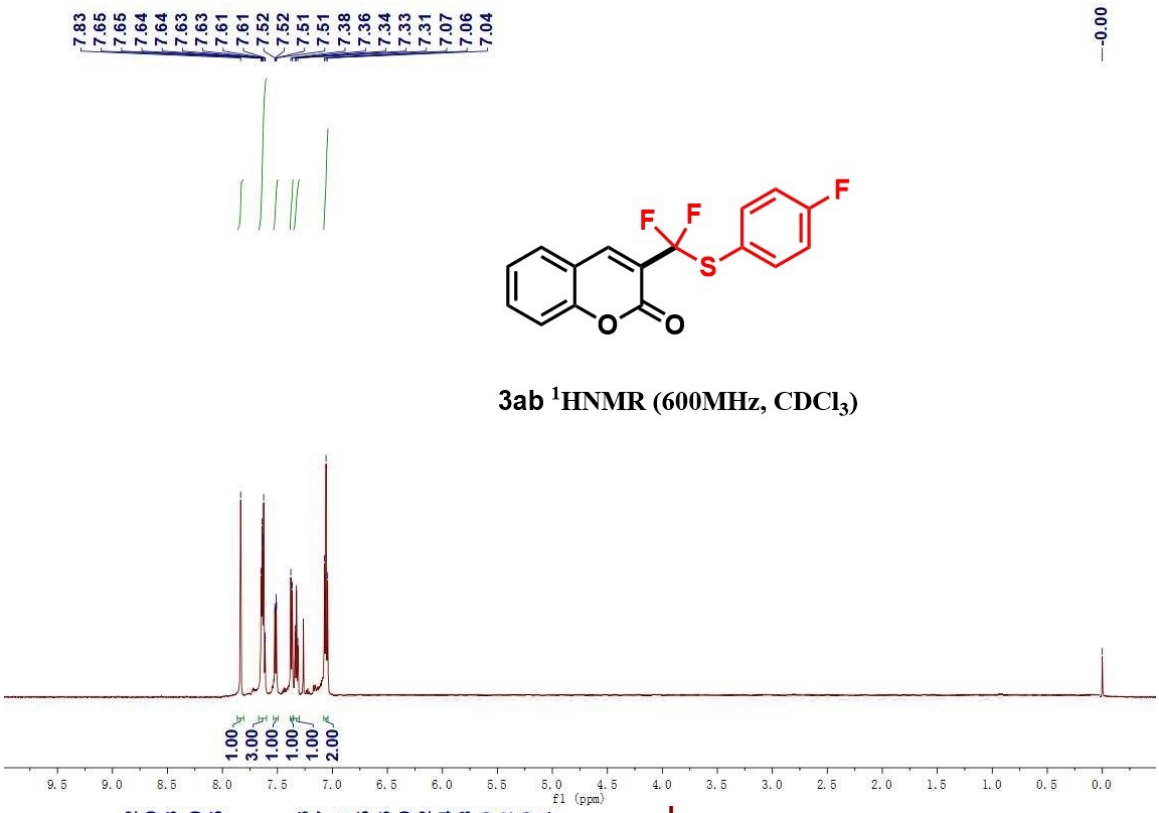
3na ^{1}HNMR (400MHz, DMSO-d_6)



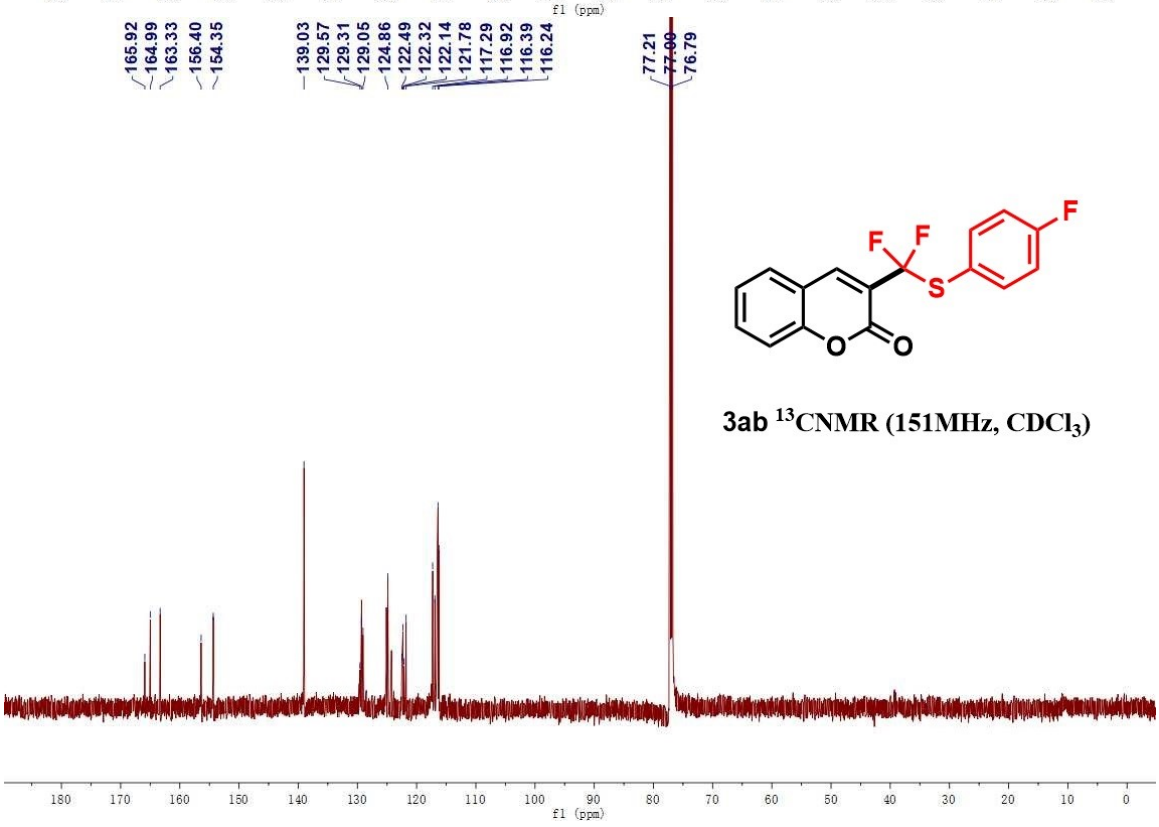
3na ^{13}CNMR (101MHz,, DMSO-d_6)



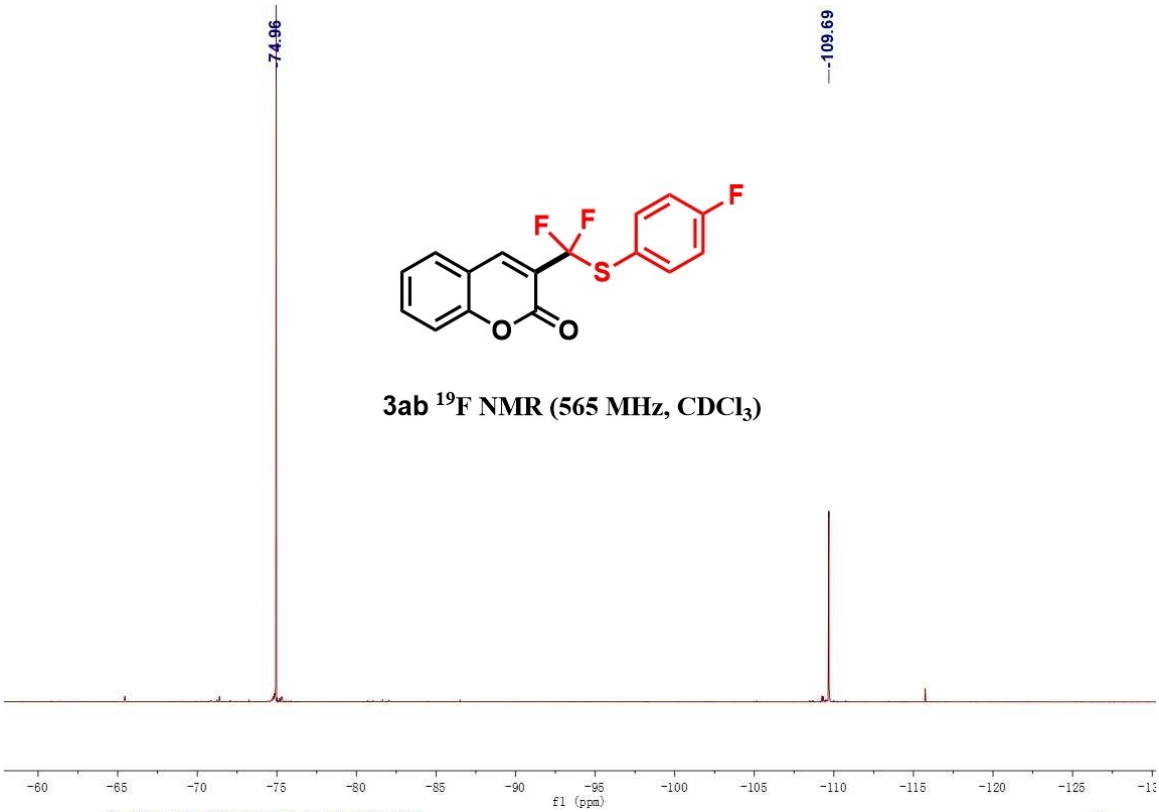
3na ^{19}F NMR (376 MHz, DMSO-d_6)



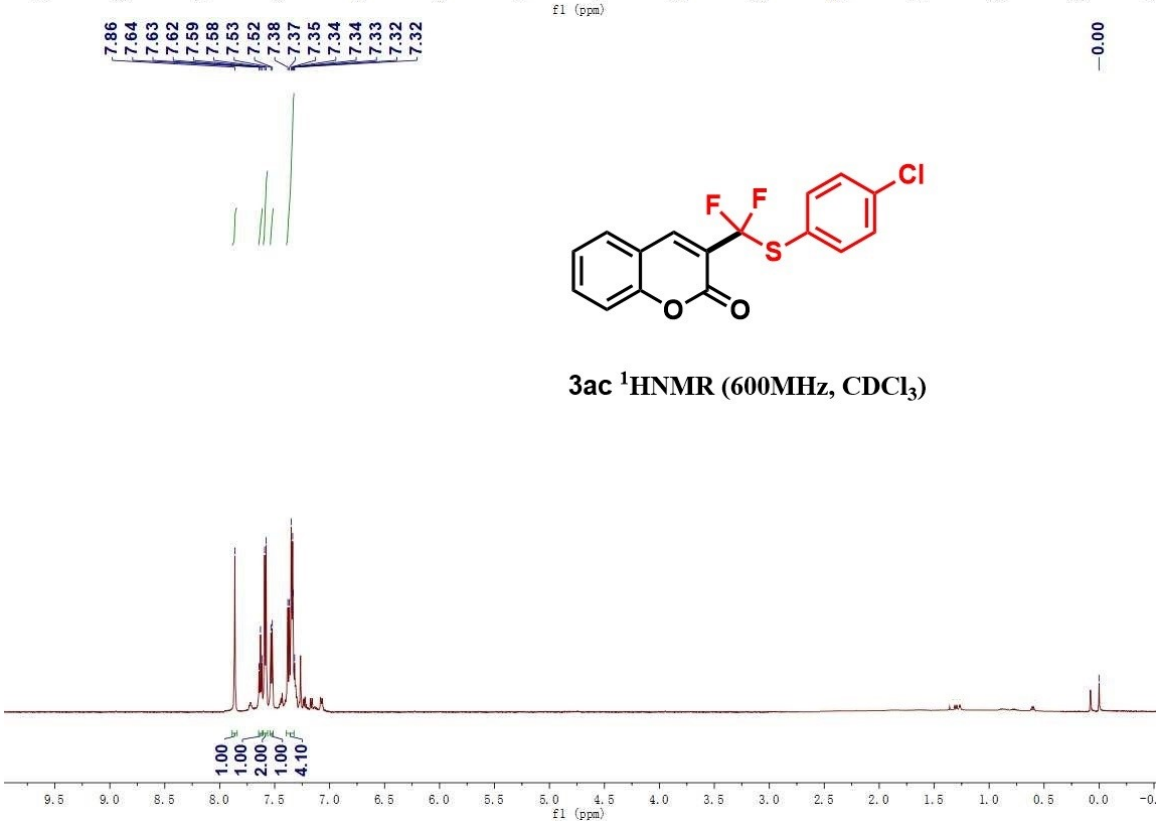
3ab ^{1}HNMR (600MHz, $CDCl_3$)



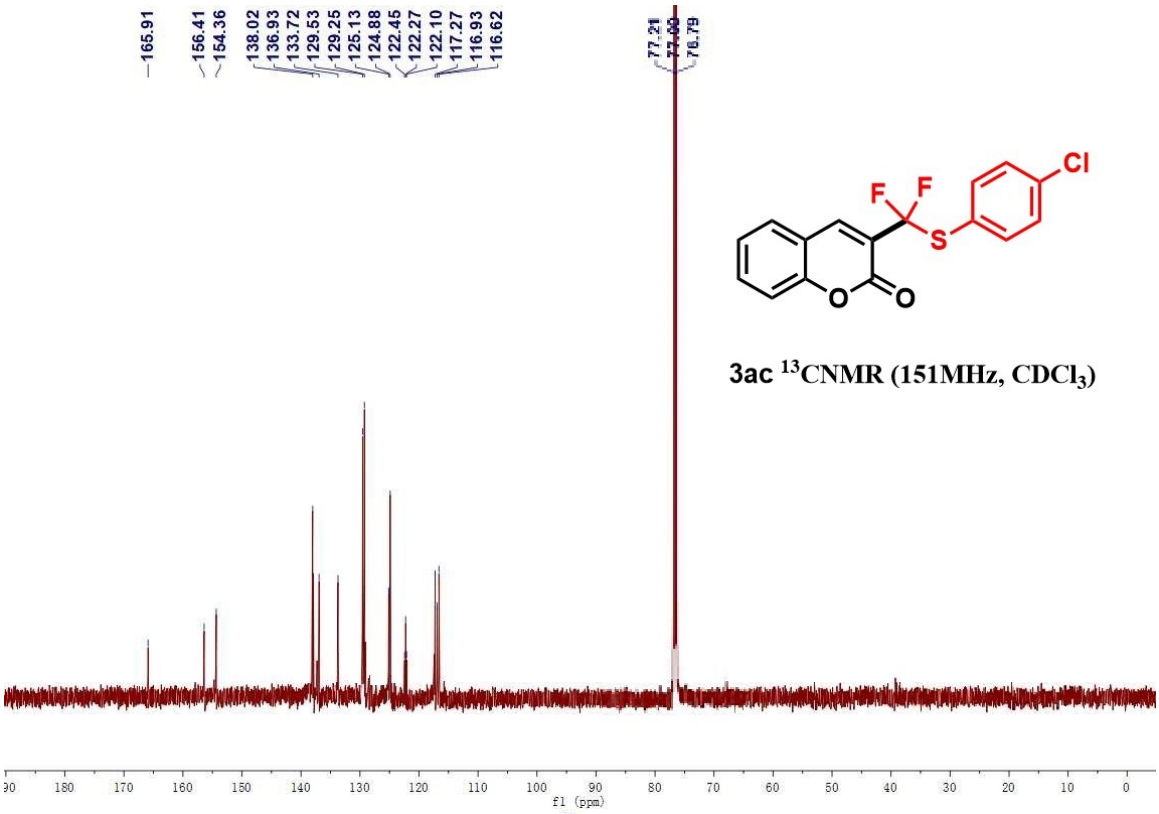
3ab ^{13}CNMR (151MHz, $CDCl_3$)



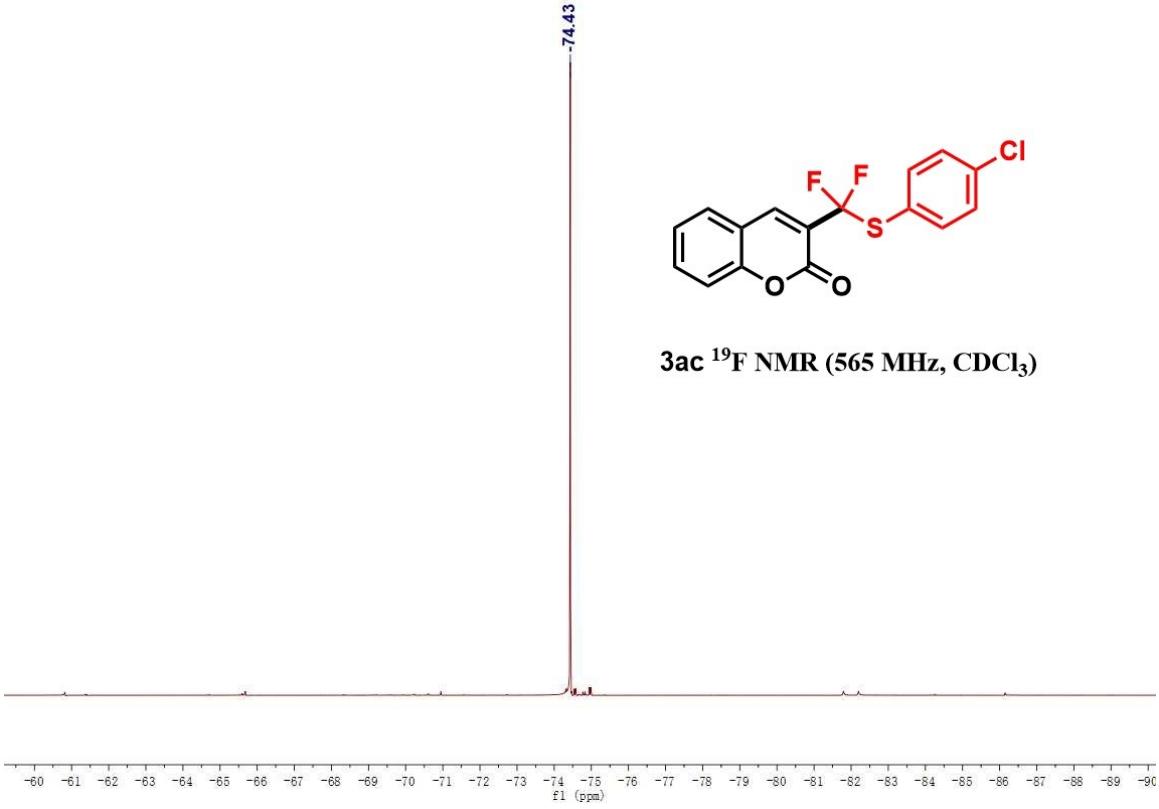
3ab ^{19}F NMR (565 MHz, $CDCl_3$)



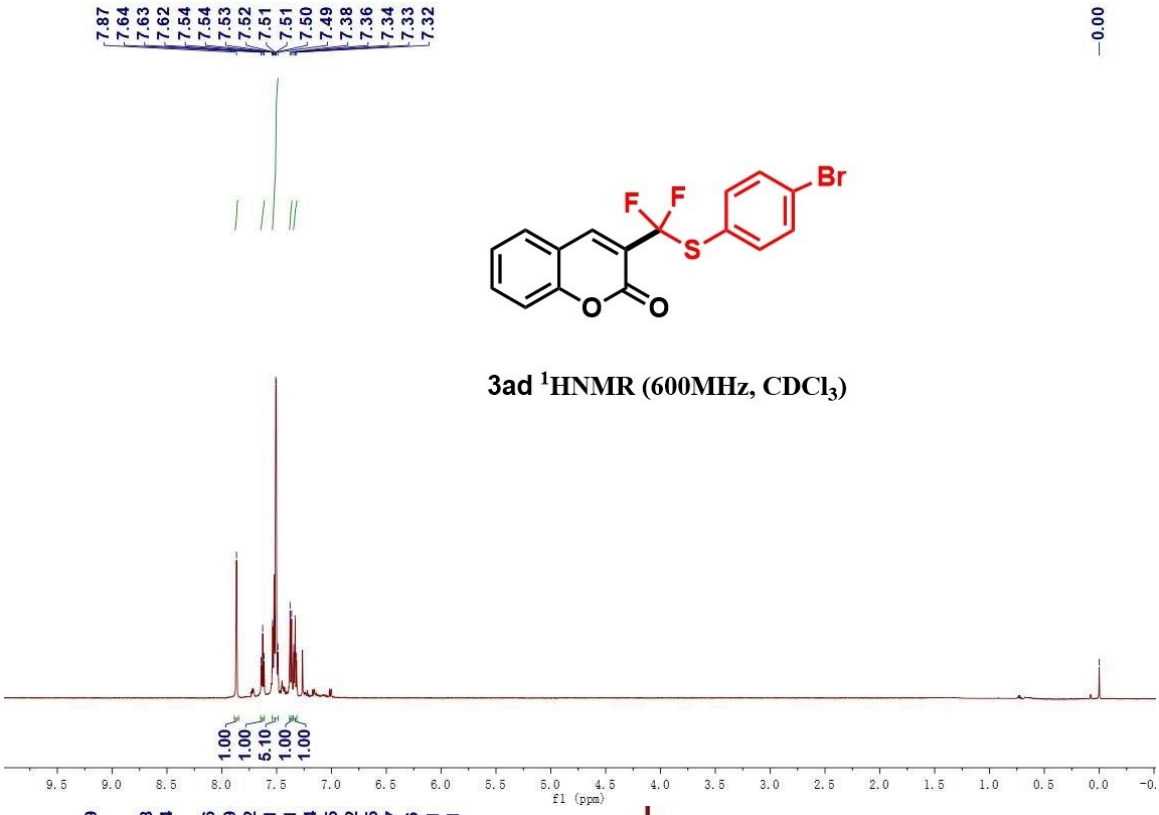
3ac ^{1}HNMR (600MHz, $CDCl_3$)



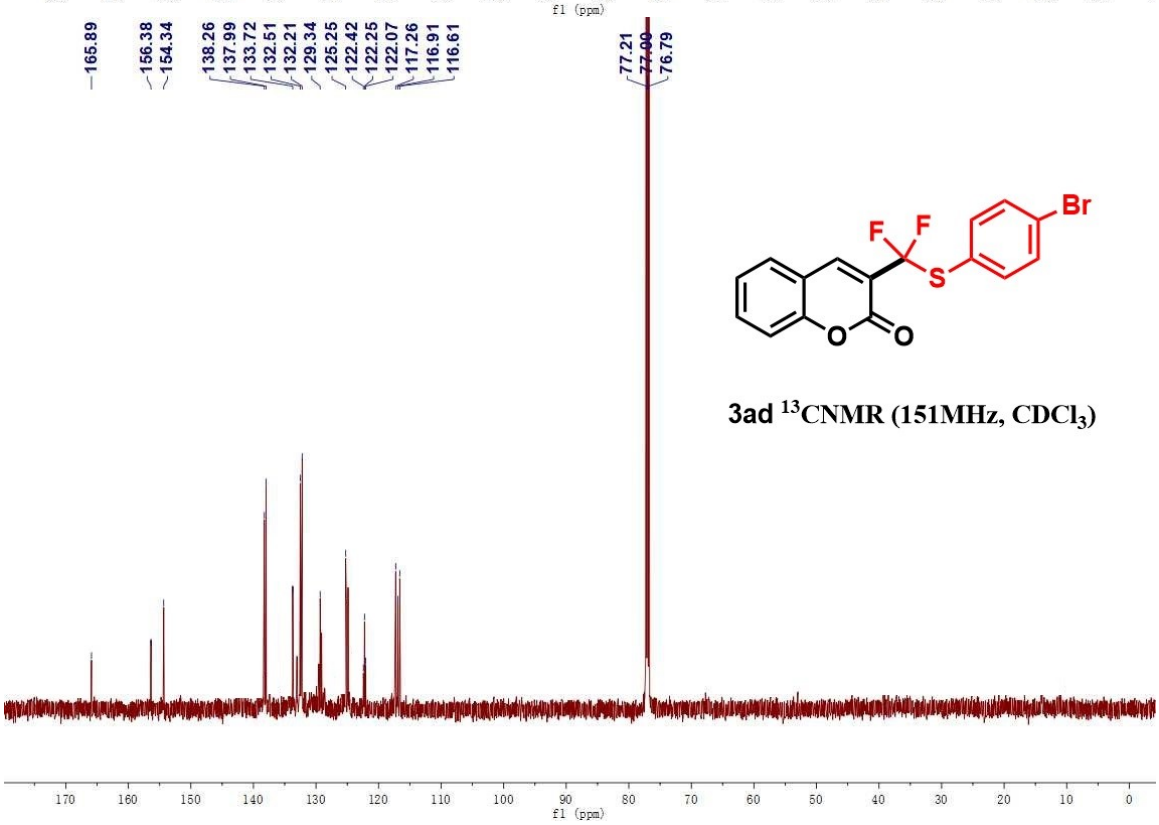
3ac ^{13}CNMR (151MHz, $CDCl_3$)



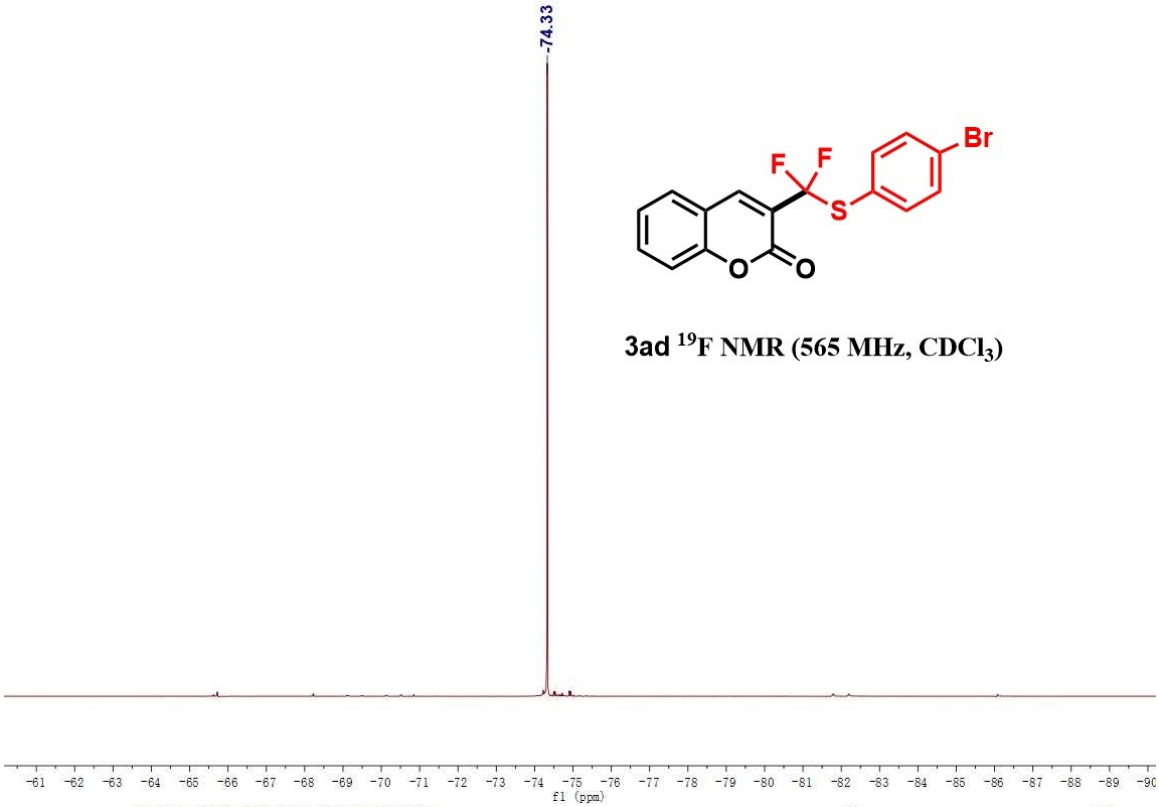
3ac ^{19}F NMR (565 MHz, $CDCl_3$)



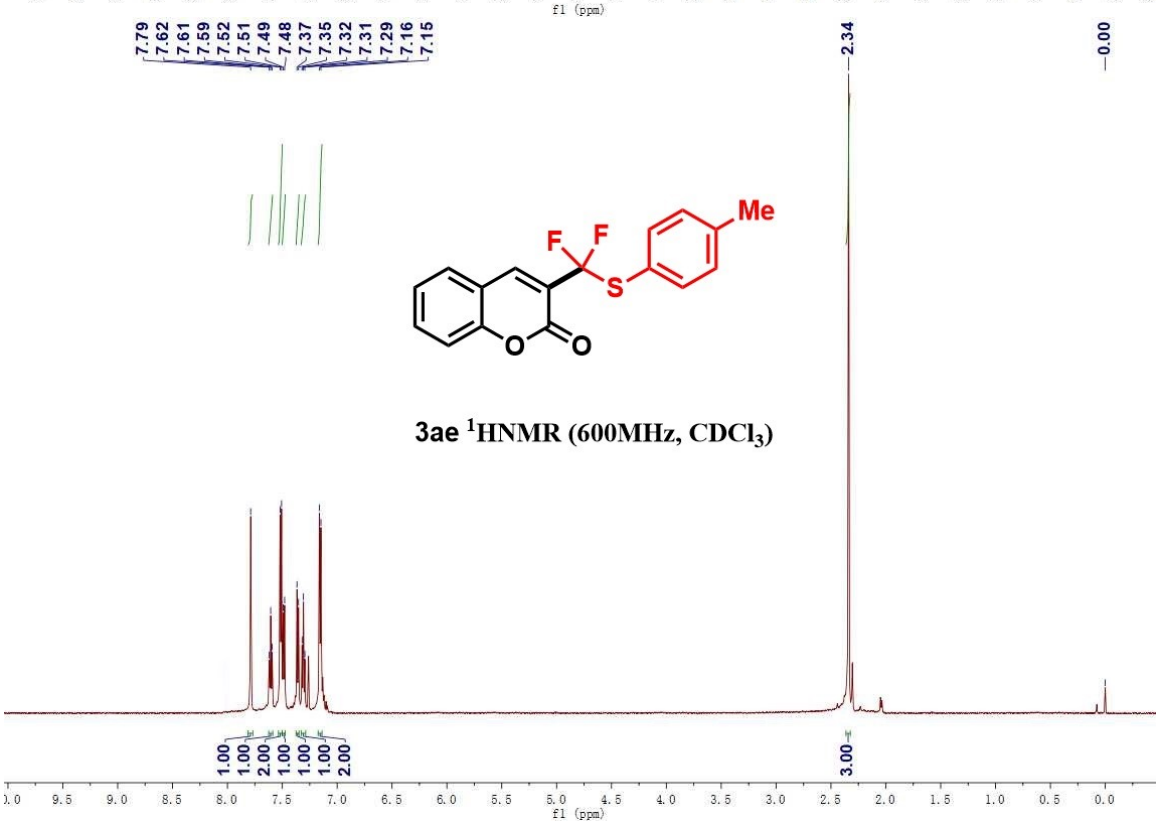
3ad ^{1}HNMR (600MHz, $CDCl_3$)



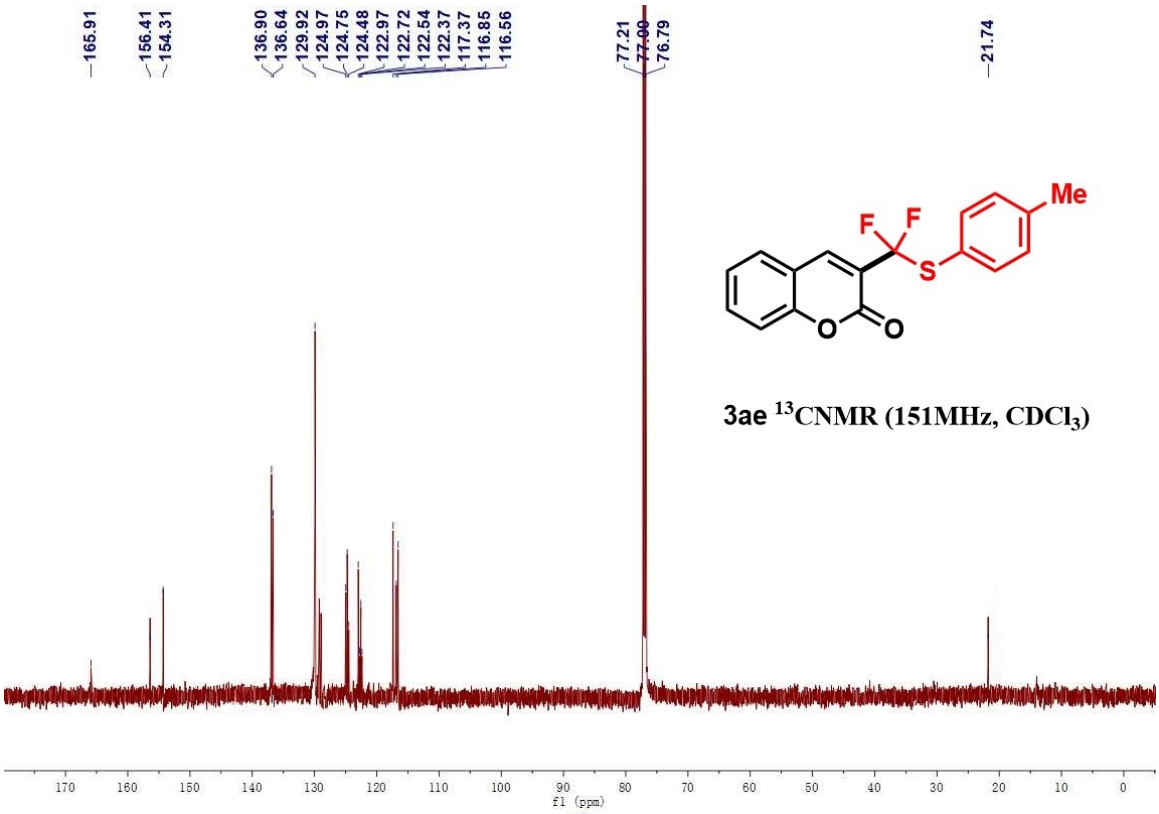
3ad ^{13}CNMR (151MHz, $CDCl_3$)



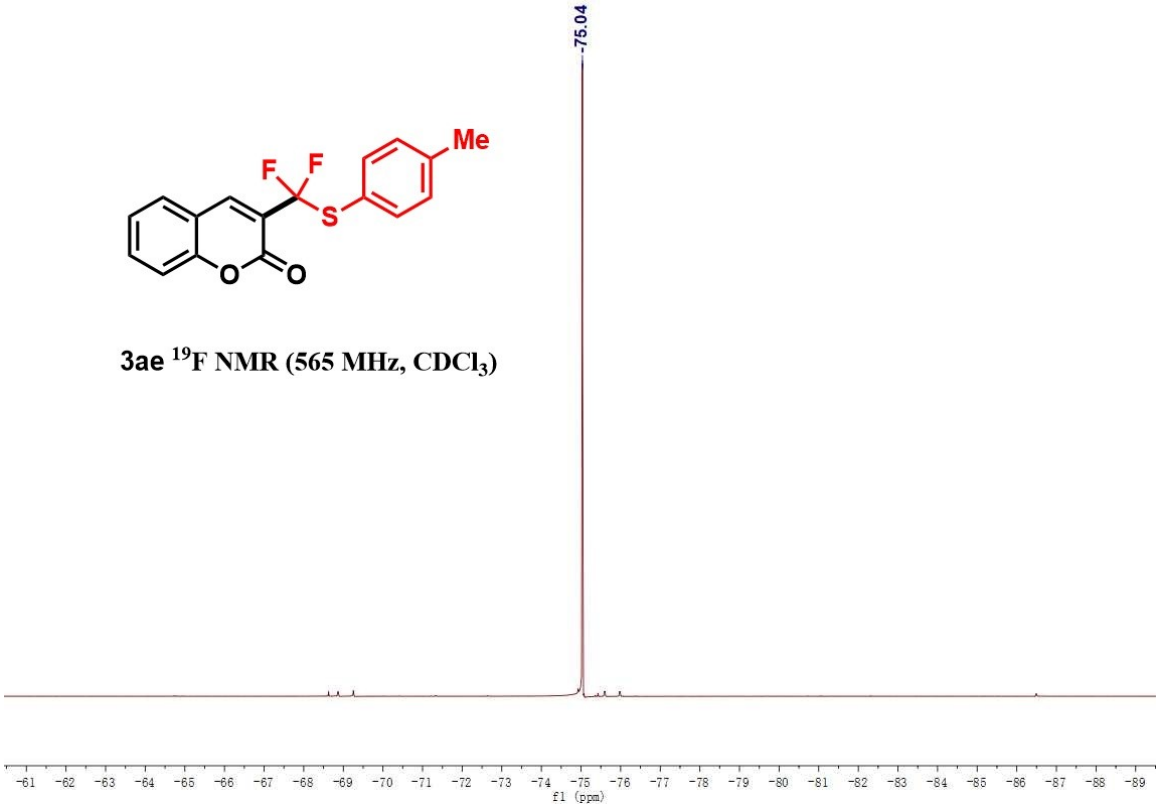
3ad ^{19}F NMR (565 MHz, $CDCl_3$)



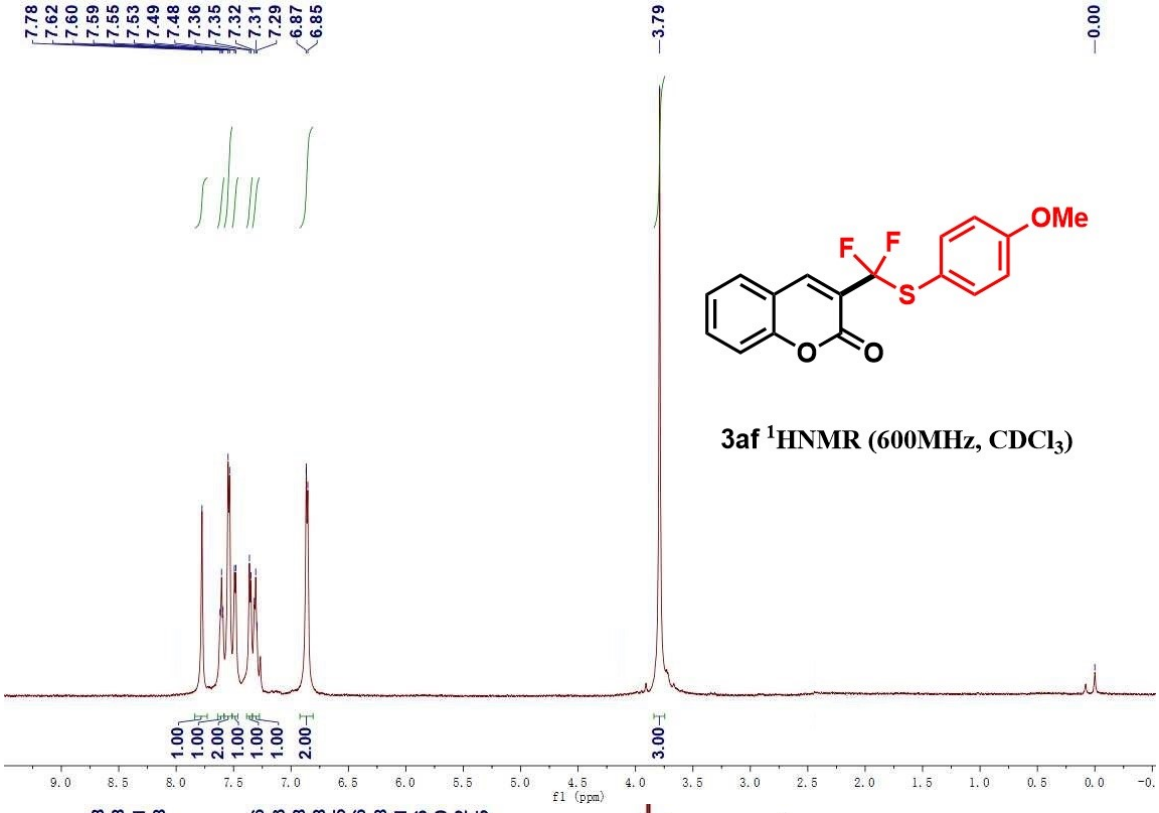
3ae ^{1}HNMR (600MHz, $CDCl_3$)



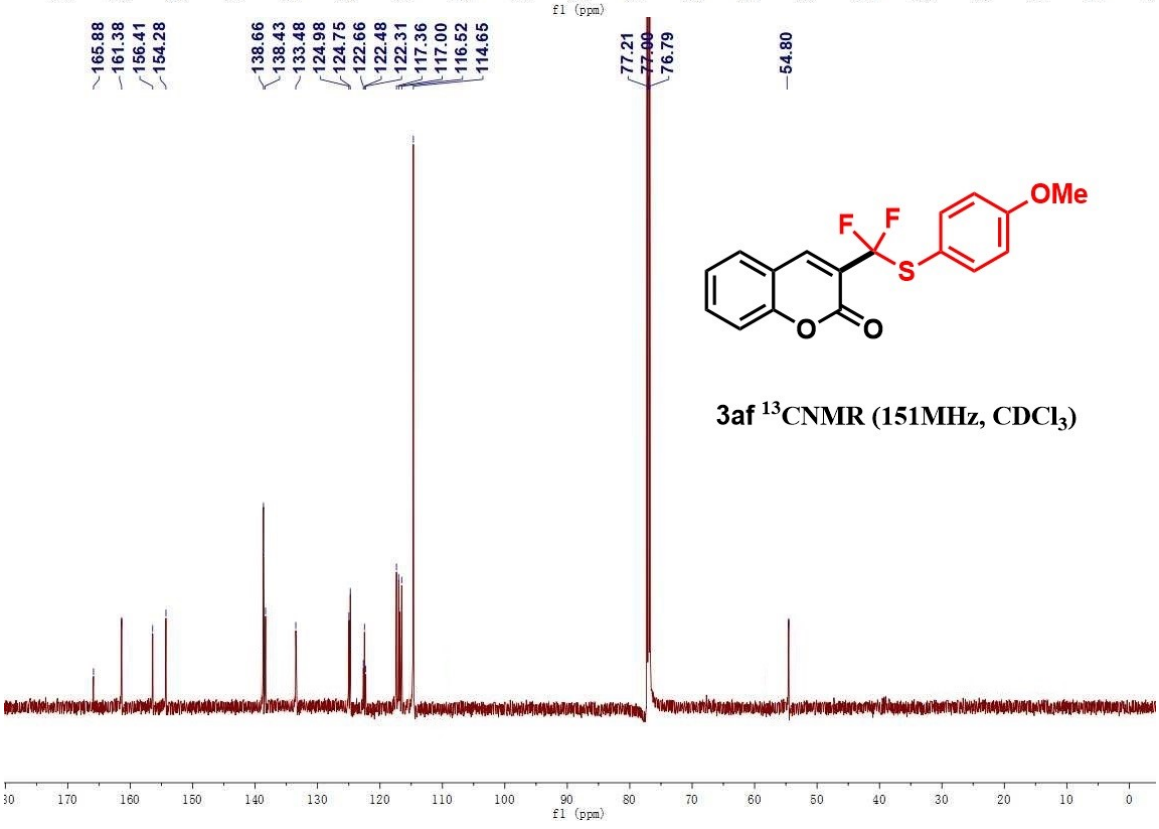
3ae ^{13}CNMR (151MHz, $CDCl_3$)



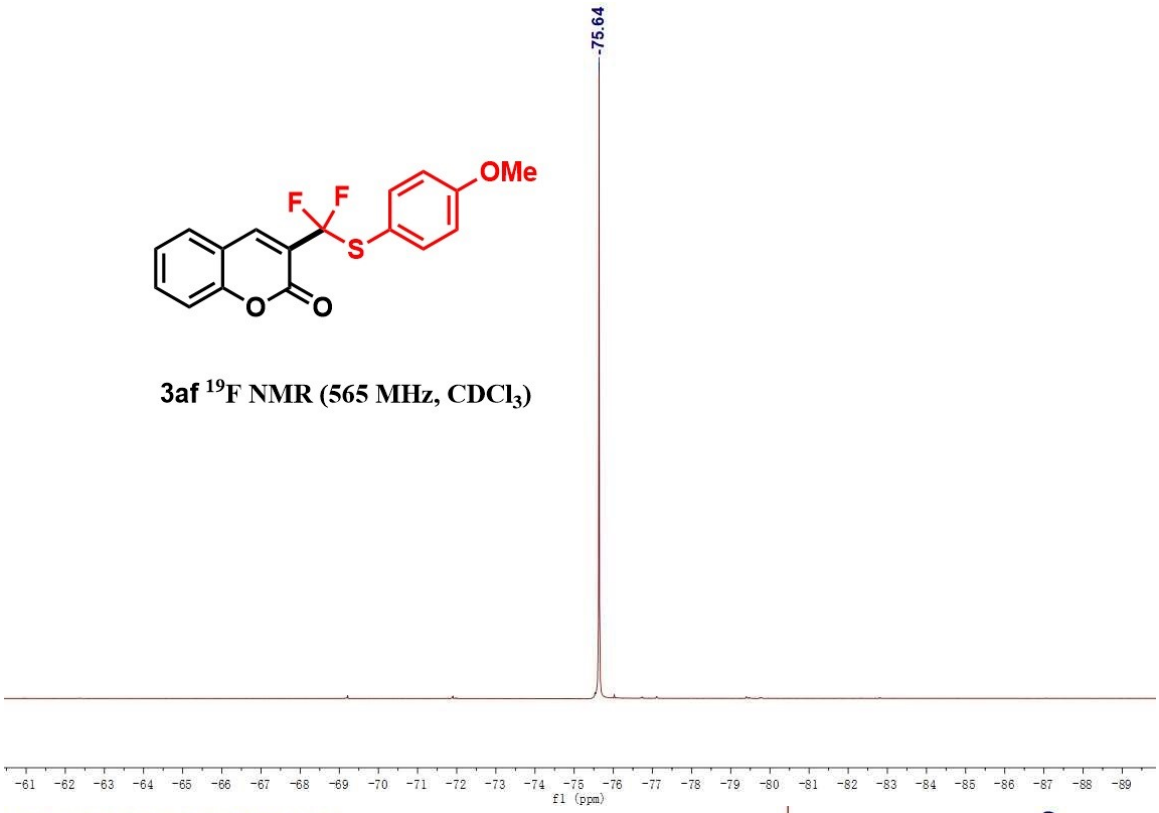
3ae ^{19}F NMR (565 MHz, $CDCl_3$)



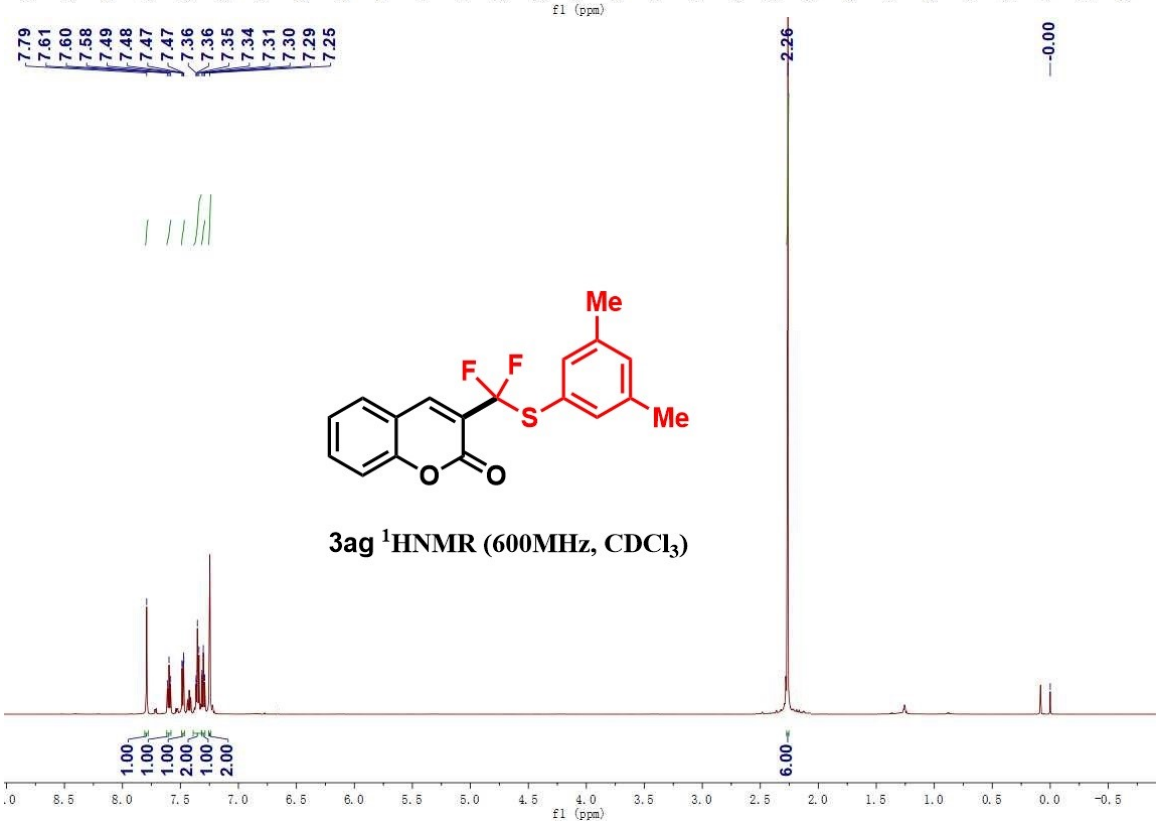
3af ^{1}HNMR (600MHz, $CDCl_3$)



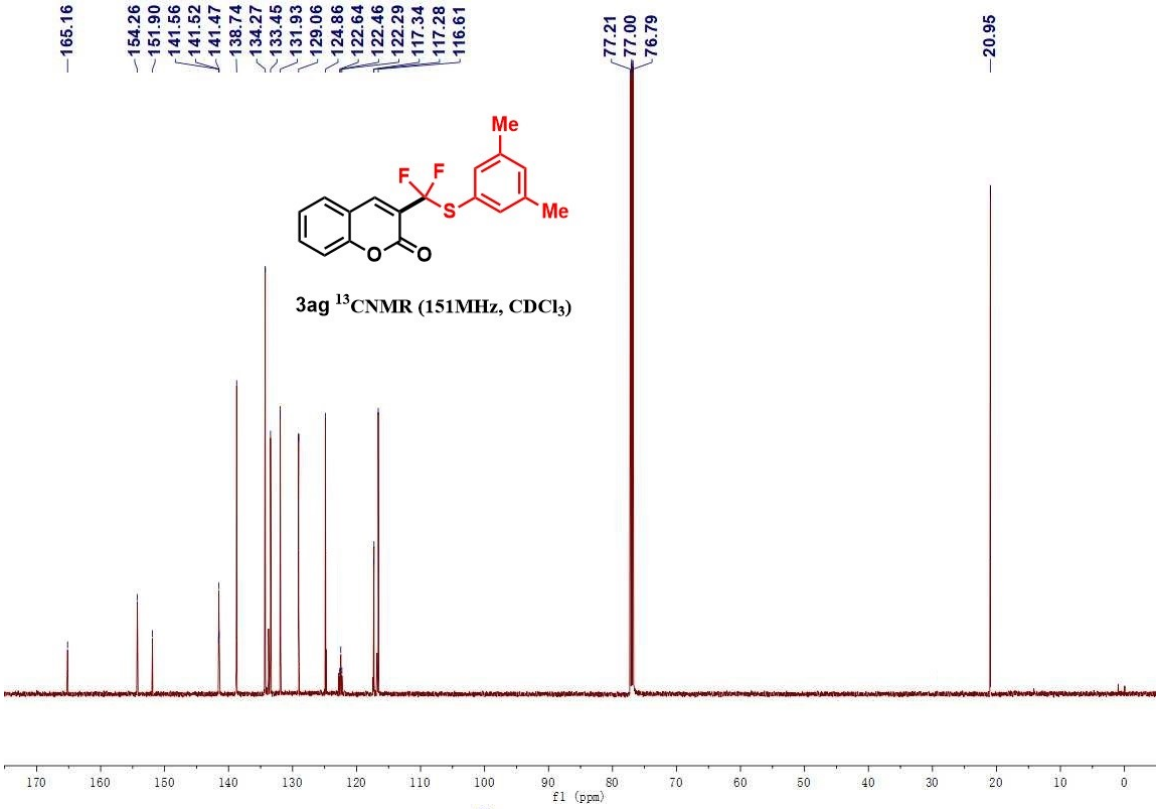
3af ^{13}CNMR (151MHz, $CDCl_3$)



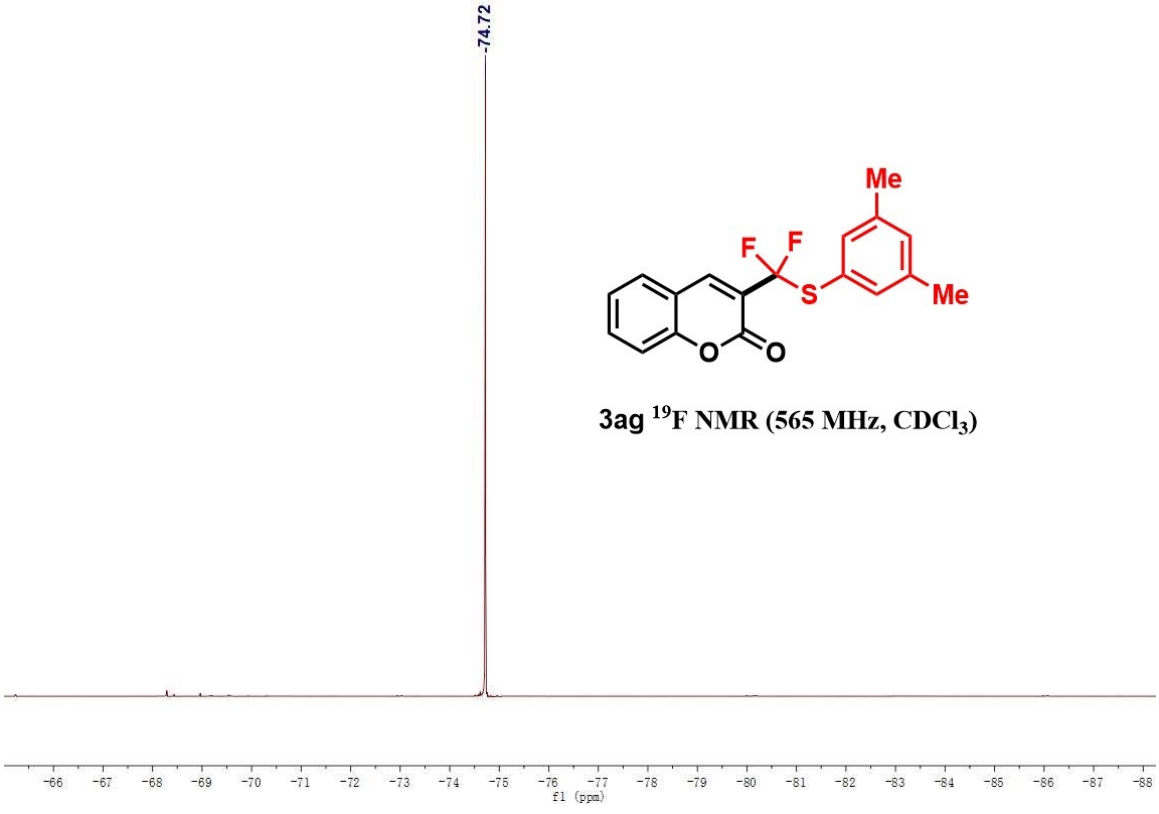
3af ^{19}F NMR (565 MHz, $CDCl_3$)



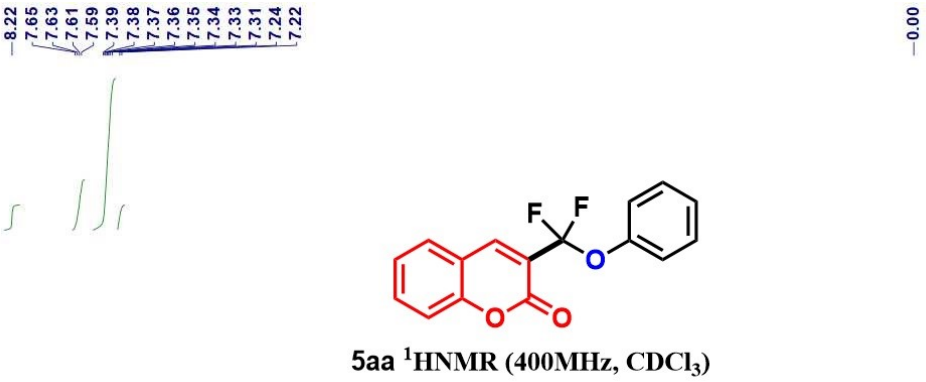
3ag ^{1}HNMR (600MHz, $CDCl_3$)



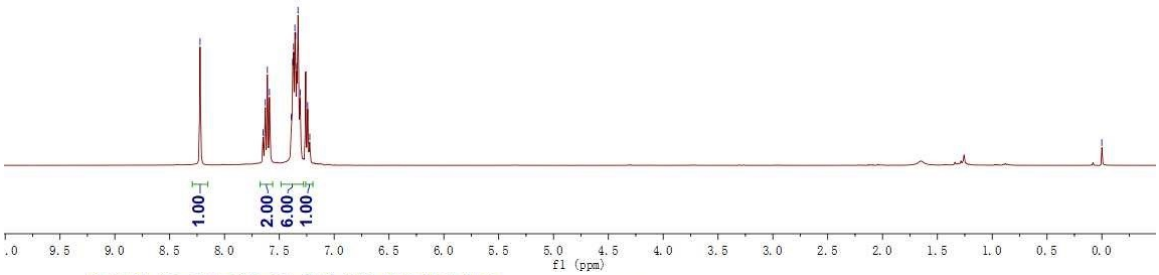
3ag ^{13}CNMR (151MHz, $CDCl_3$)

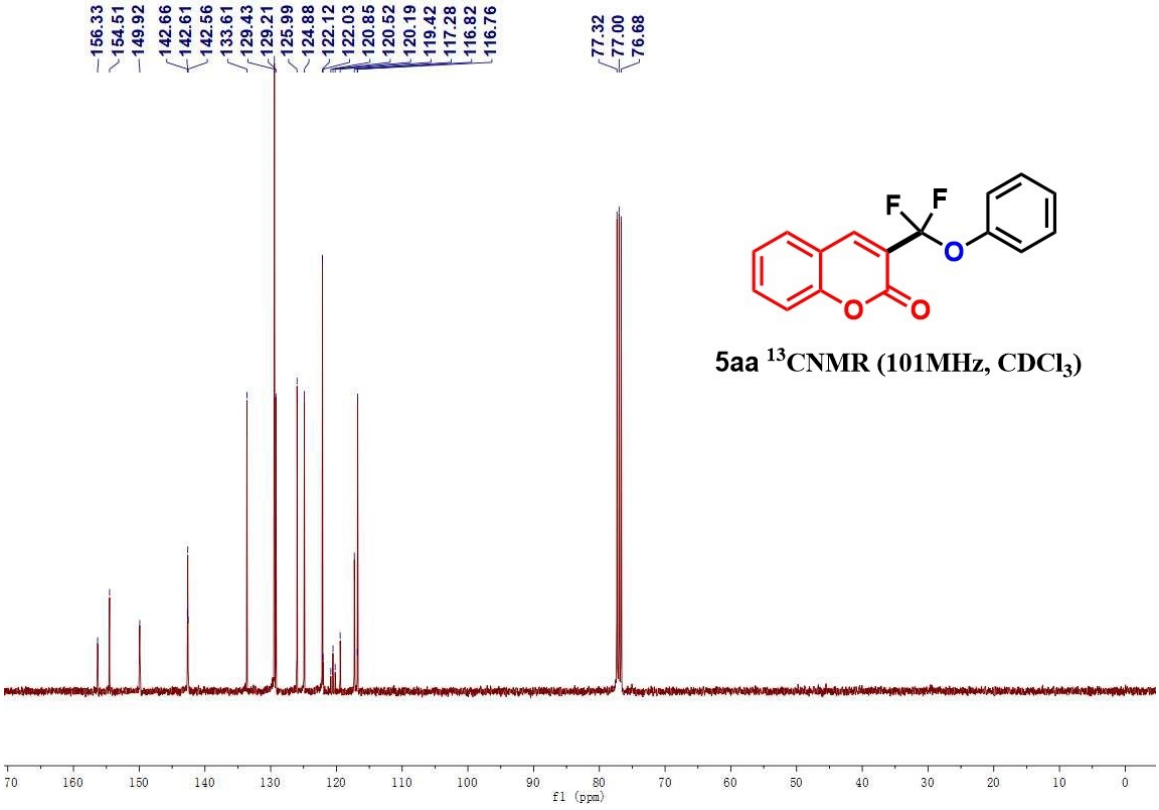


3ag ^{19}F NMR (565 MHz, $CDCl_3$)

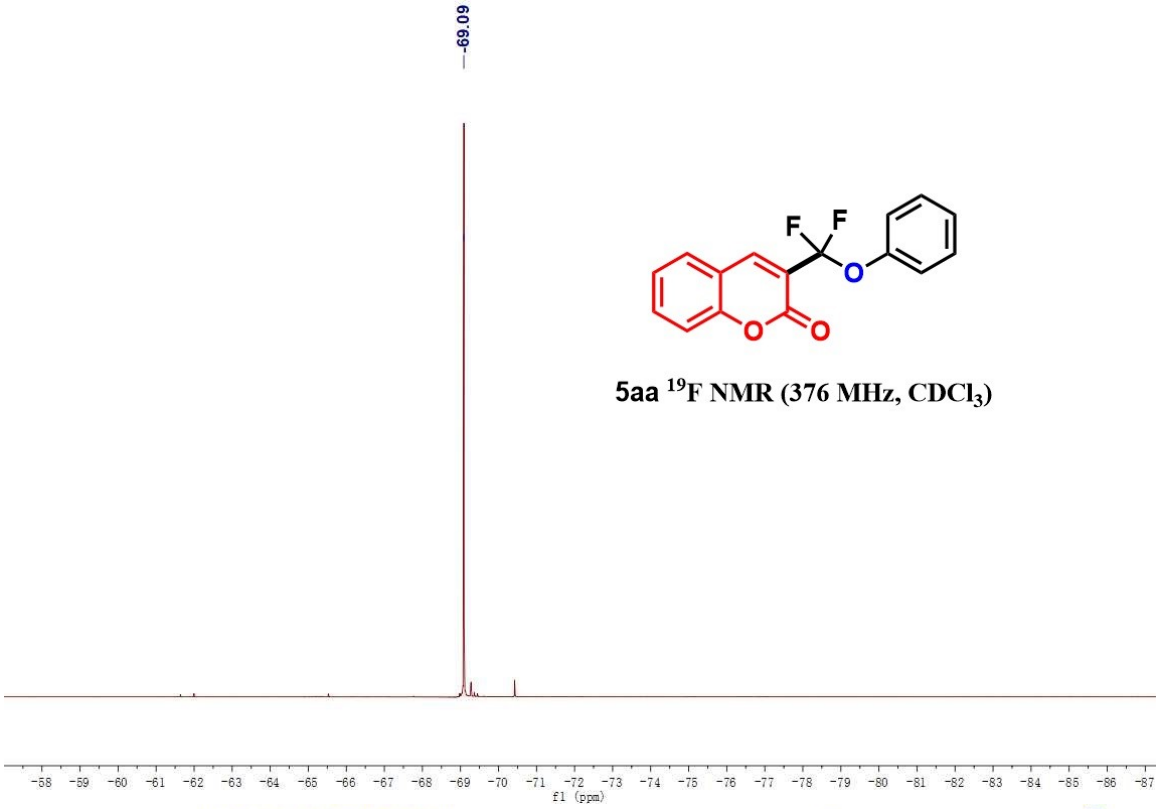


5aa ^{1}HNMR (400MHz, $CDCl_3$)

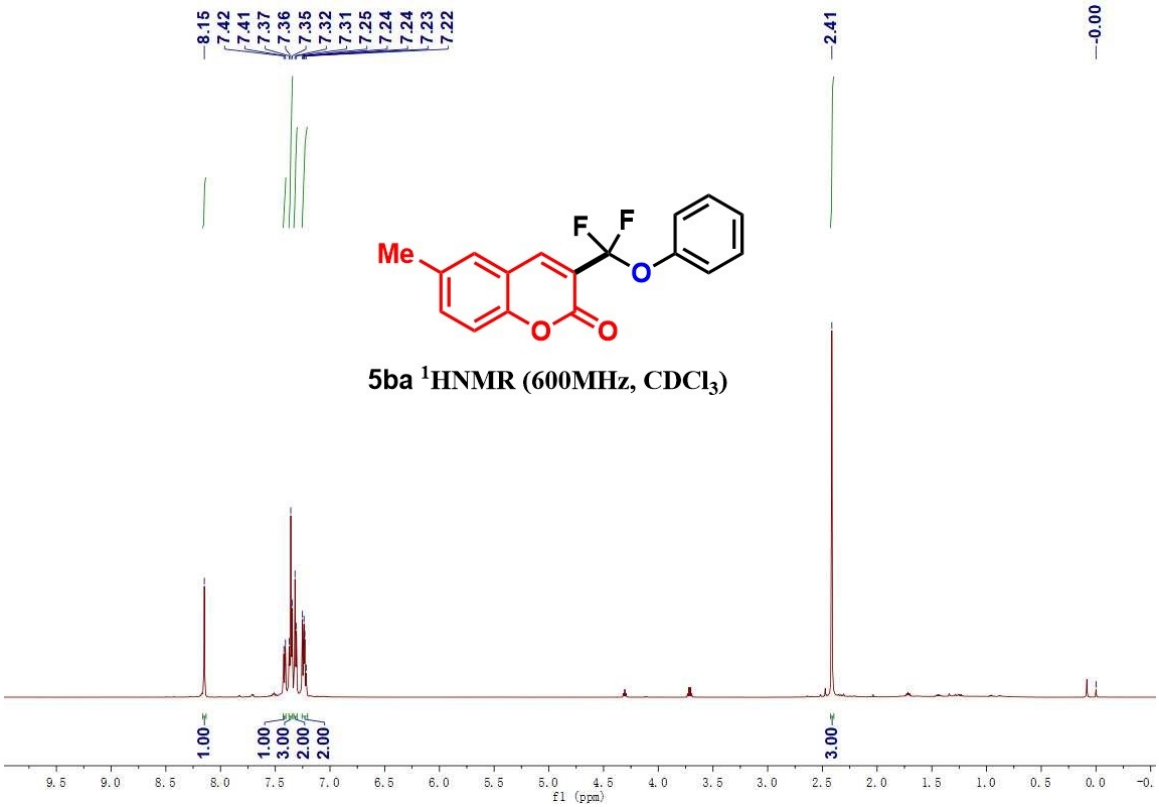




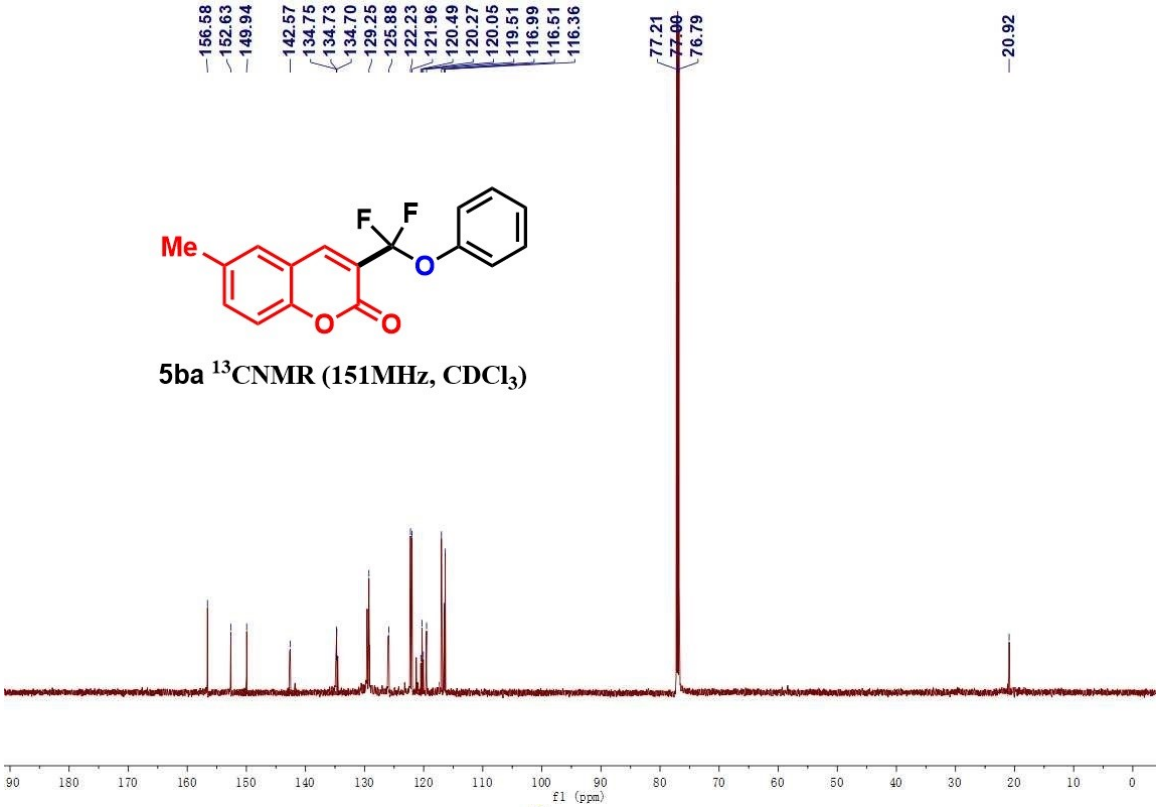
5aa ^{13}CNMR (101MHz, $CDCl_3$)



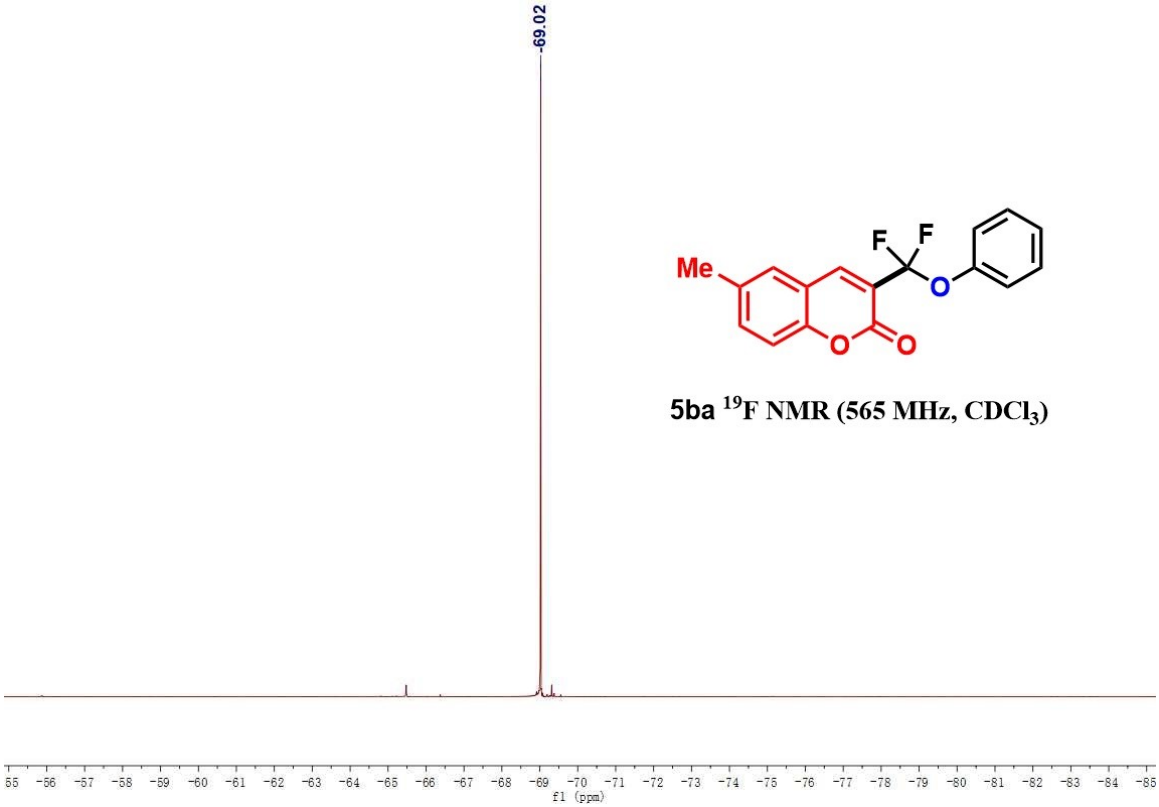
5aa ^{19}F NMR (376 MHz, $CDCl_3$)



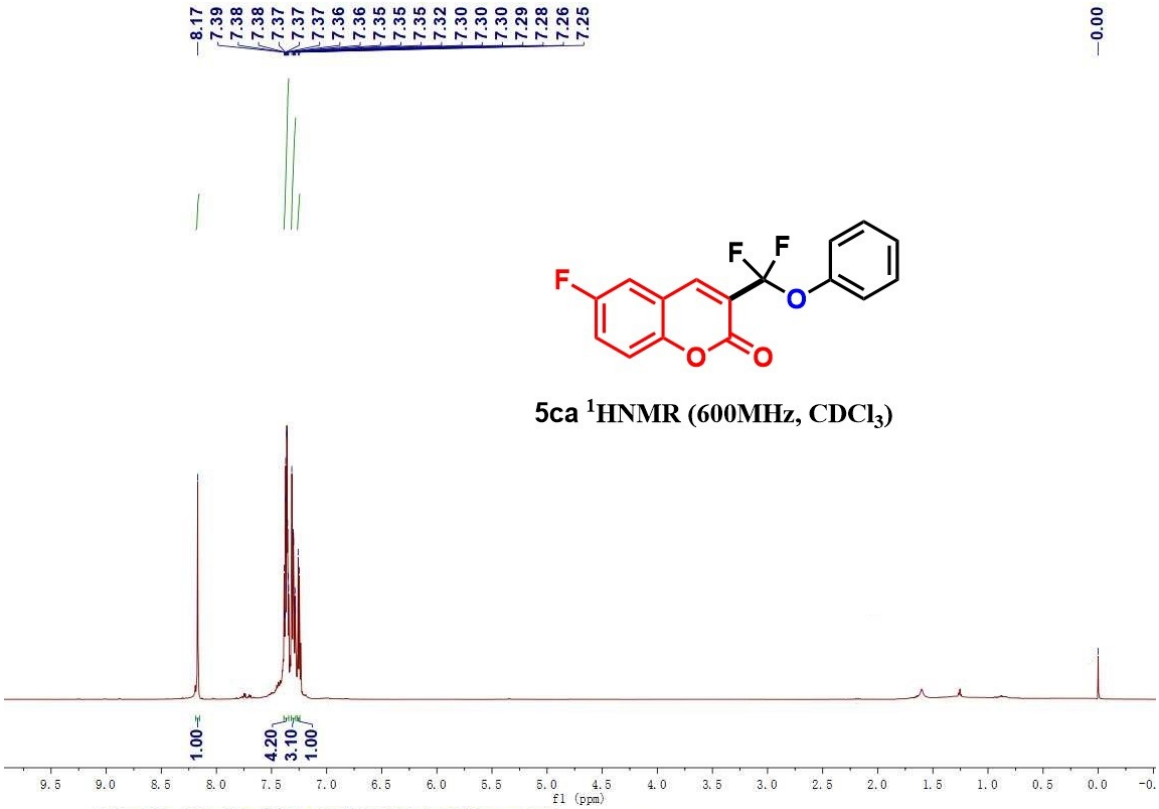
5ba ^{1}HNMR (600MHz, $CDCl_3$)



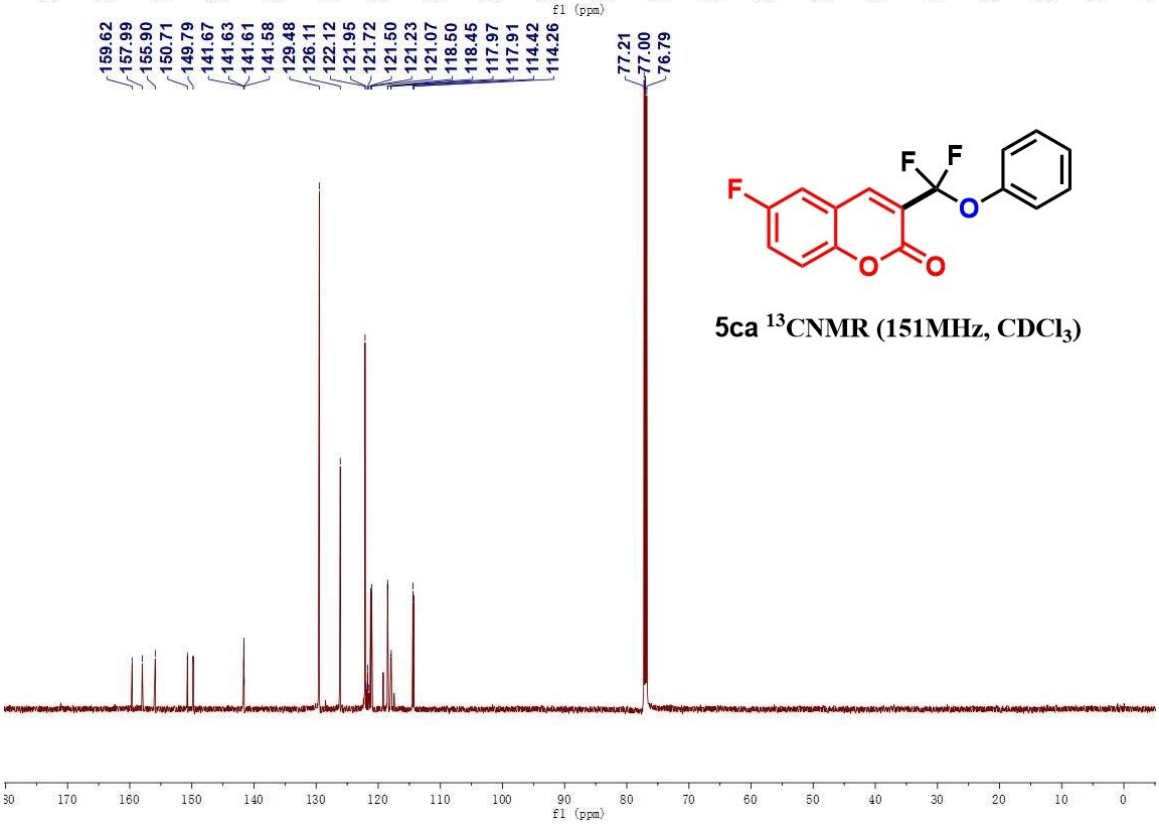
5ba ^{13}CNMR (151MHz, $CDCl_3$)



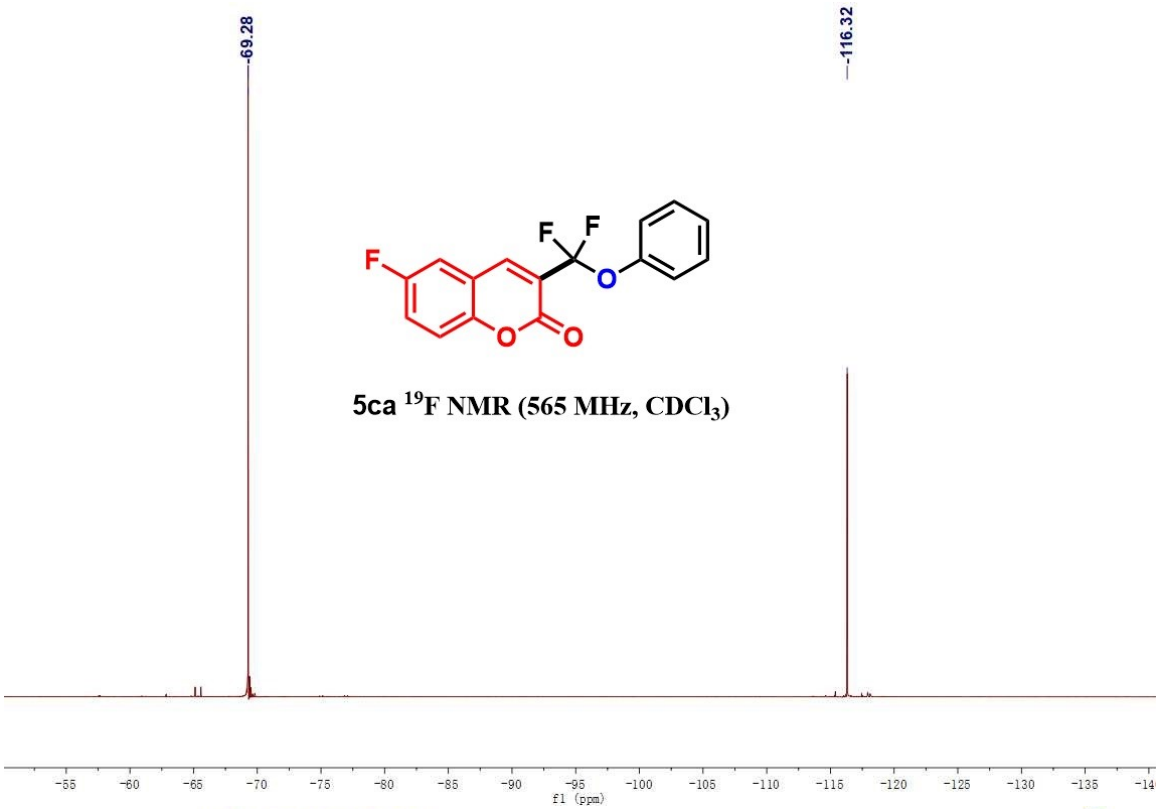
5ba ^{19}F NMR (565 MHz, $CDCl_3$)



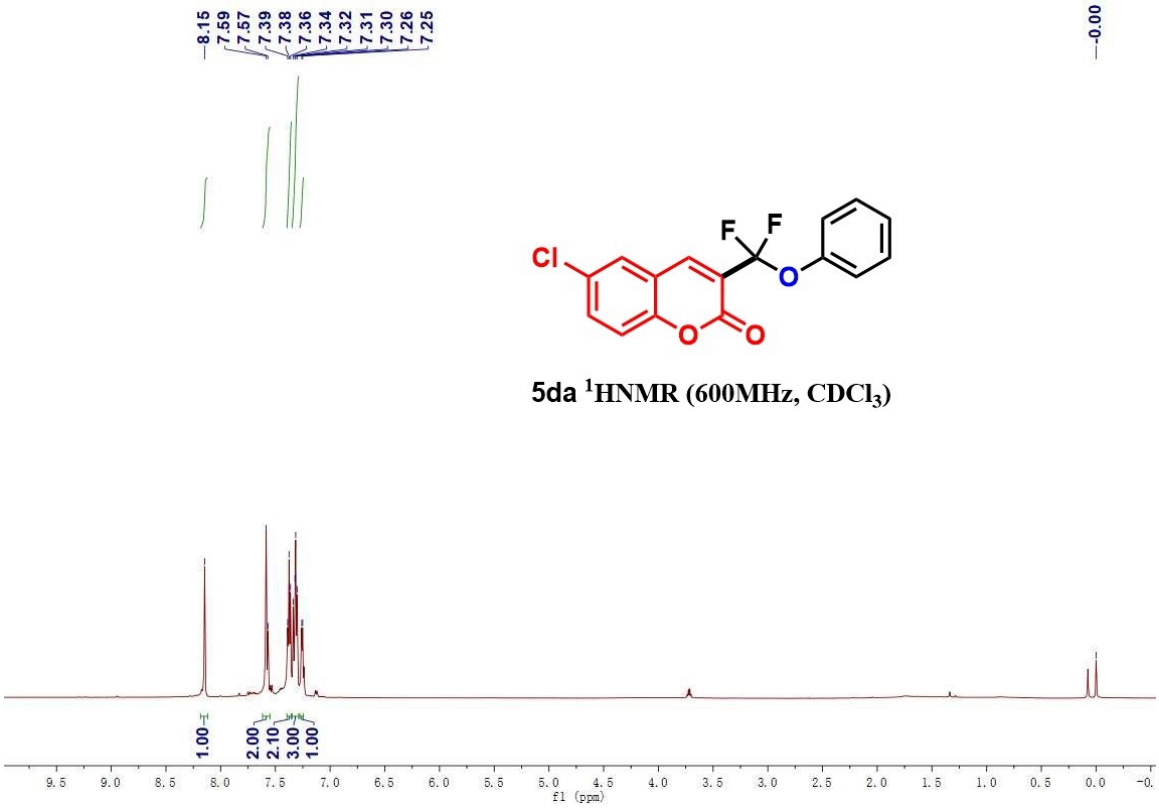
5ca ^{1}HNMR (600MHz, $CDCl_3$)



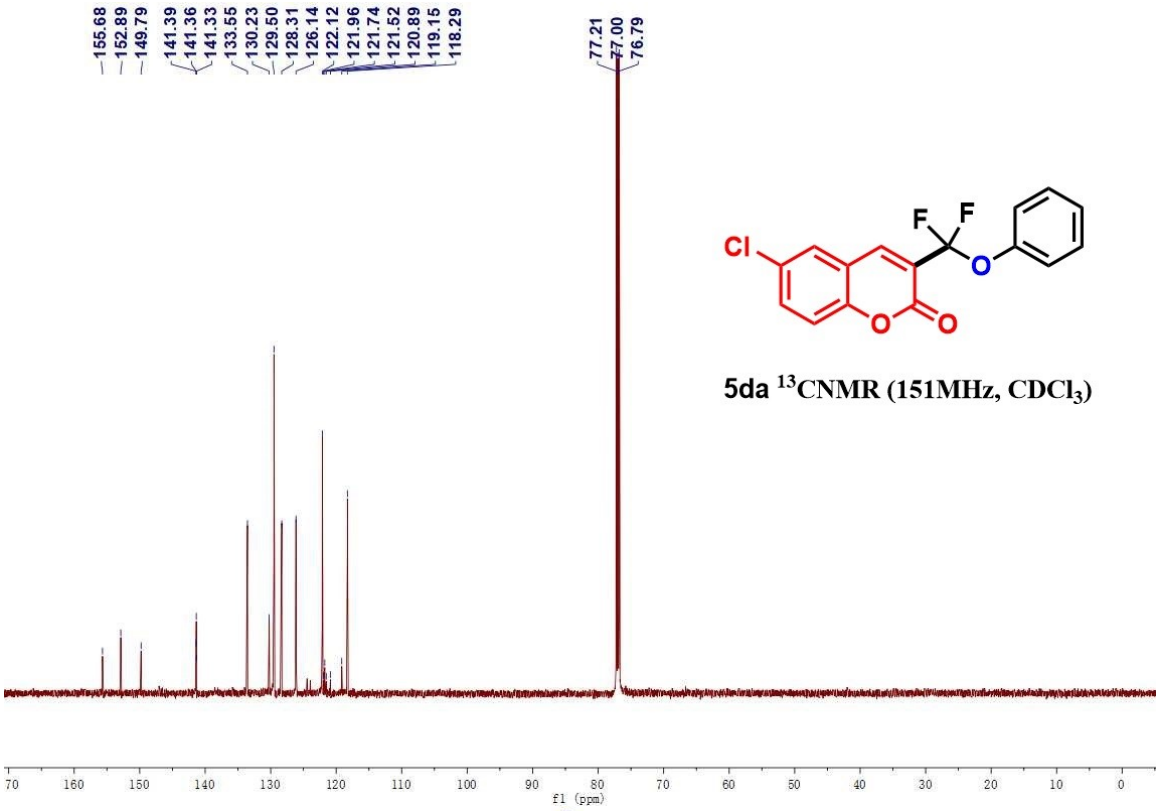
5ca ^{13}CNMR (151MHz, $CDCl_3$)



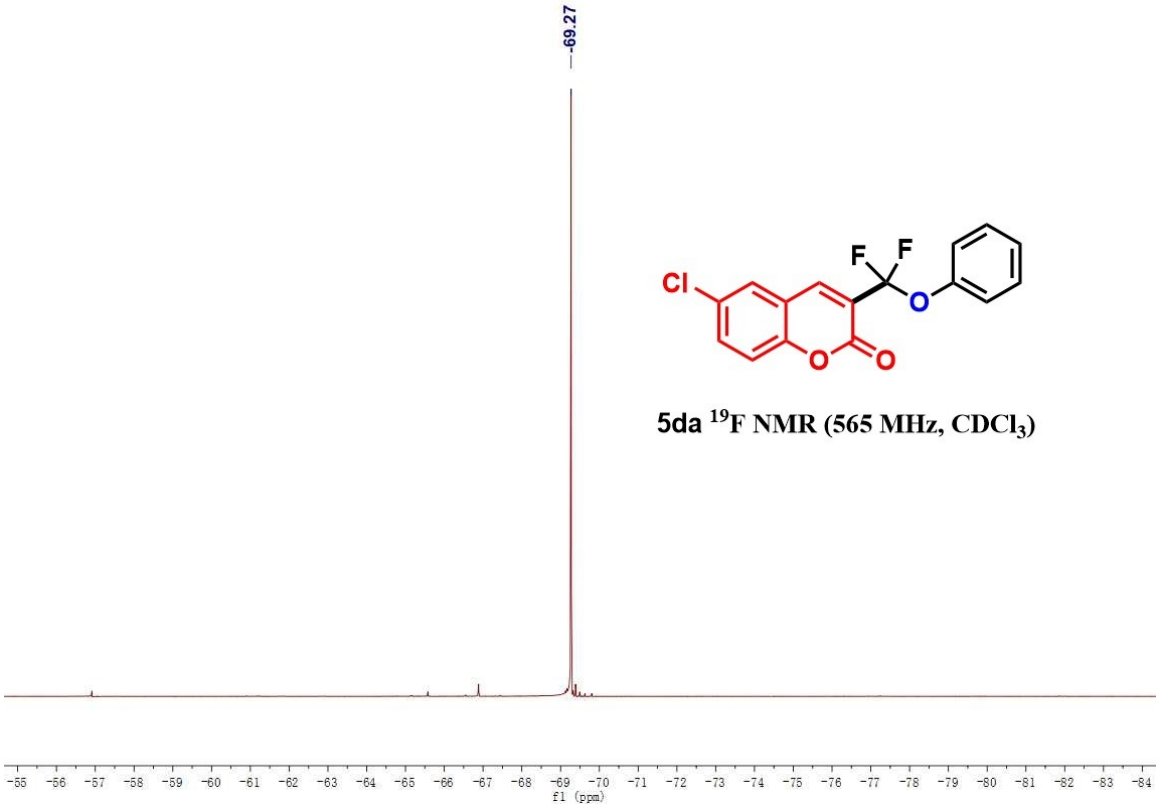
5ca ^{19}F NMR (565 MHz, $CDCl_3$)



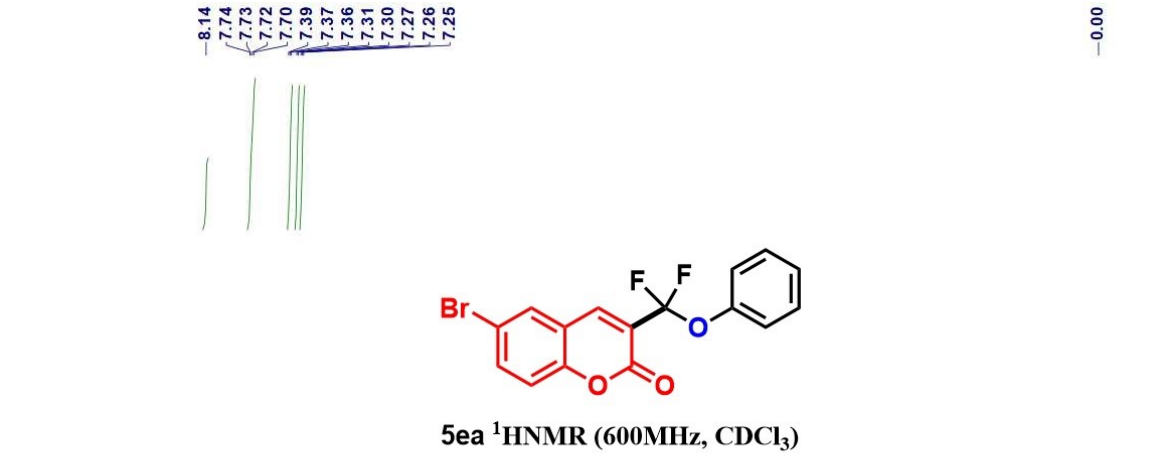
5da ^{1}HNMR (600MHz, $CDCl_3$)



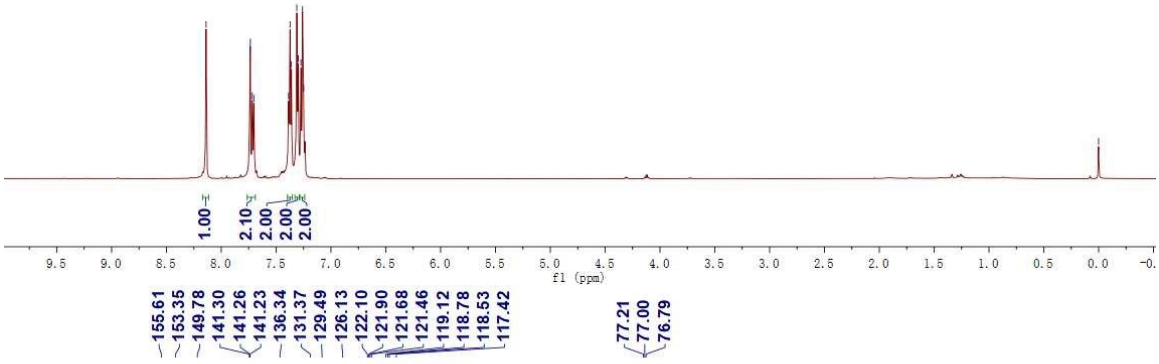
5da ^{13}CNMR (151MHz, $CDCl_3$)

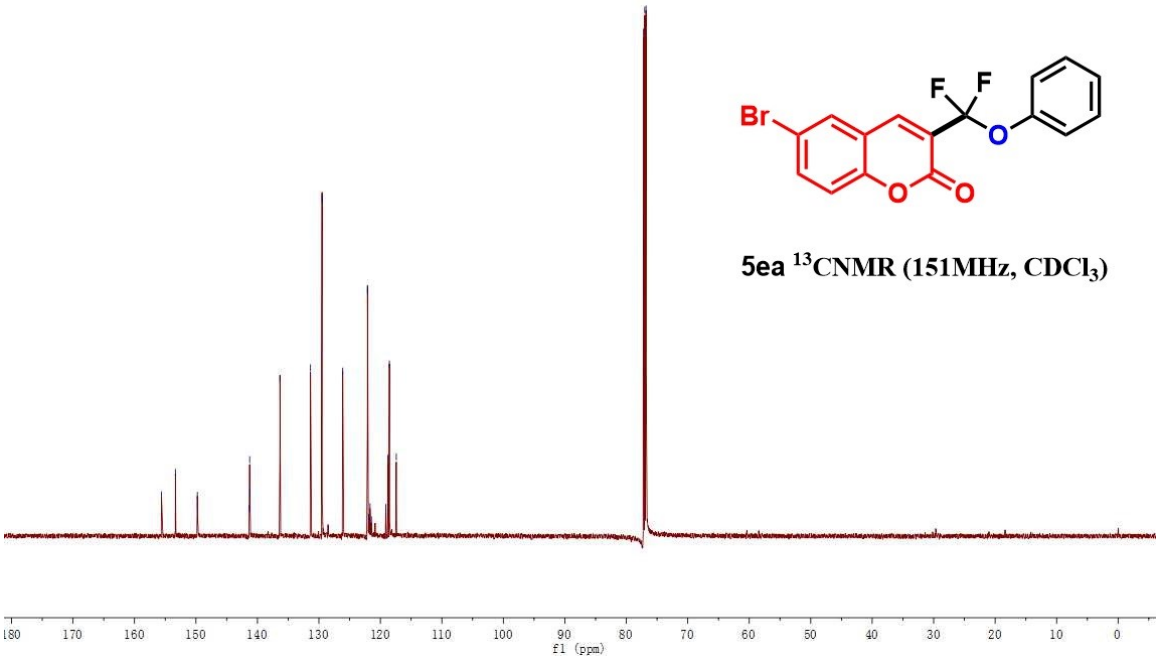


5da ^{19}F NMR (565 MHz, $CDCl_3$)

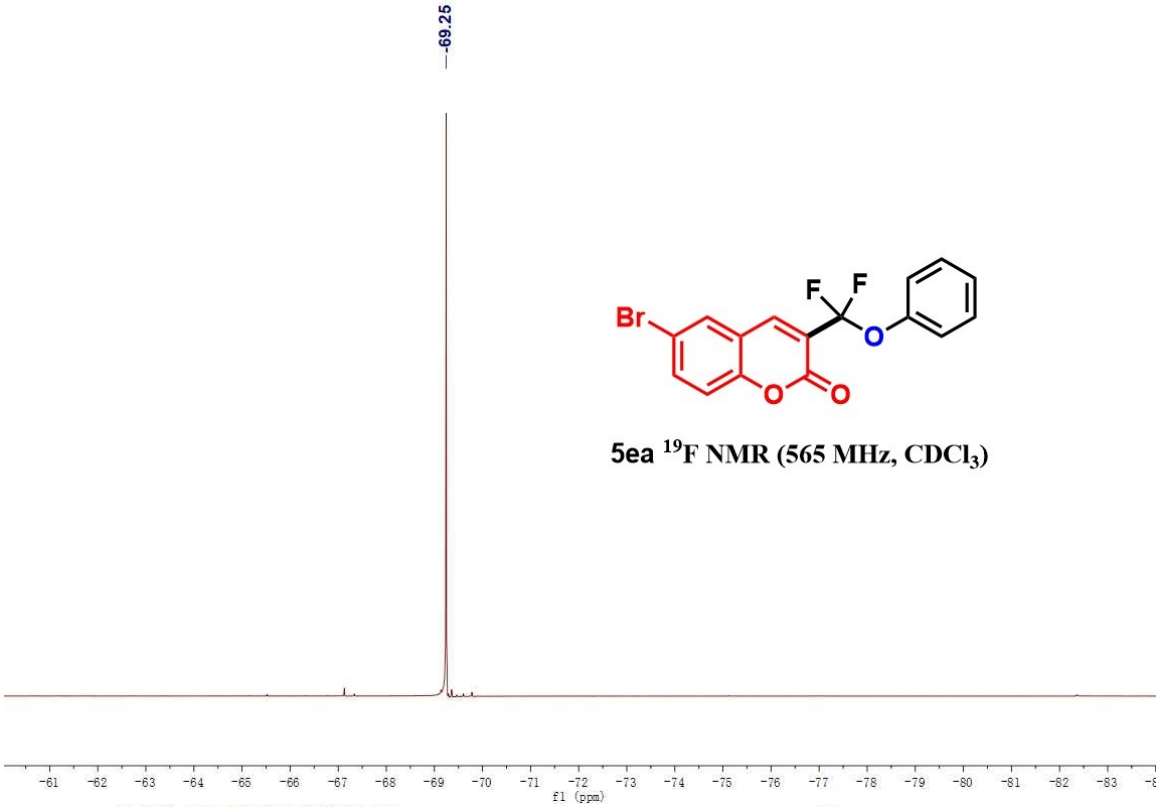


5ea ^{1}HNMR (600MHz, $CDCl_3$)

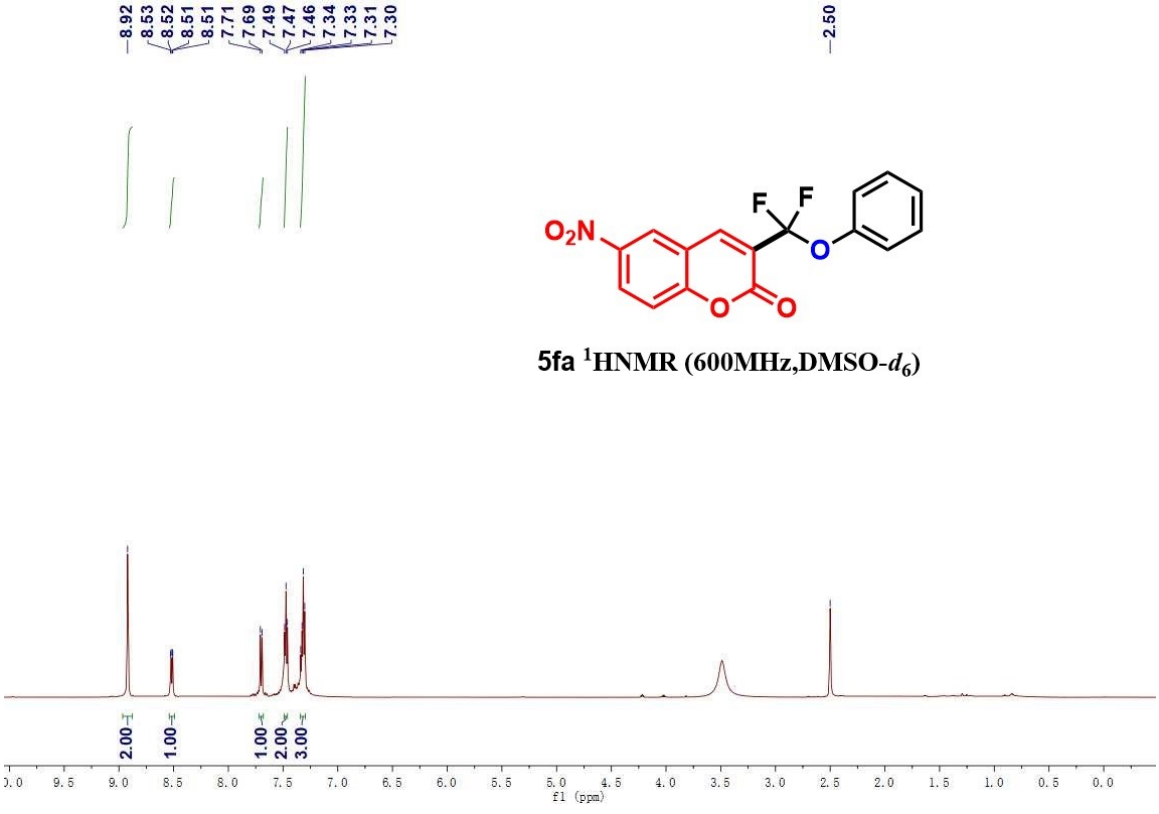




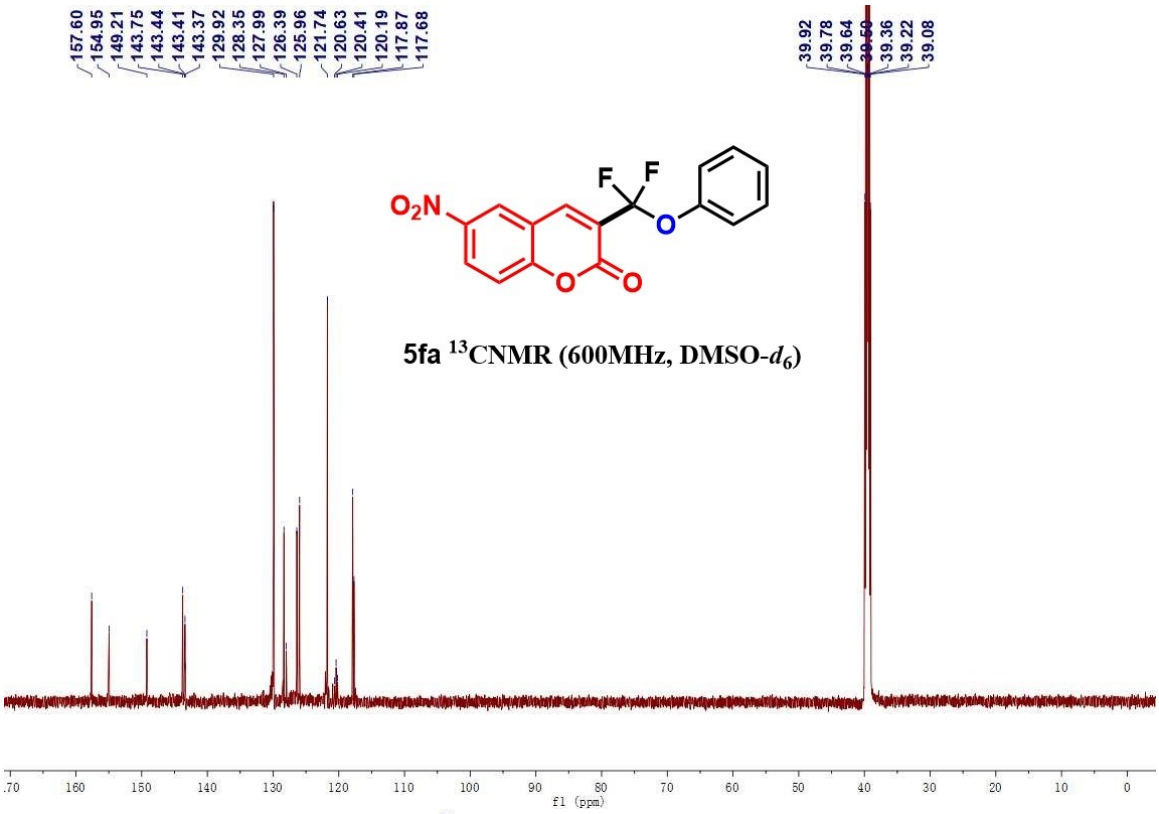
5ea ^{13}CNMR (151MHz, $CDCl_3$)



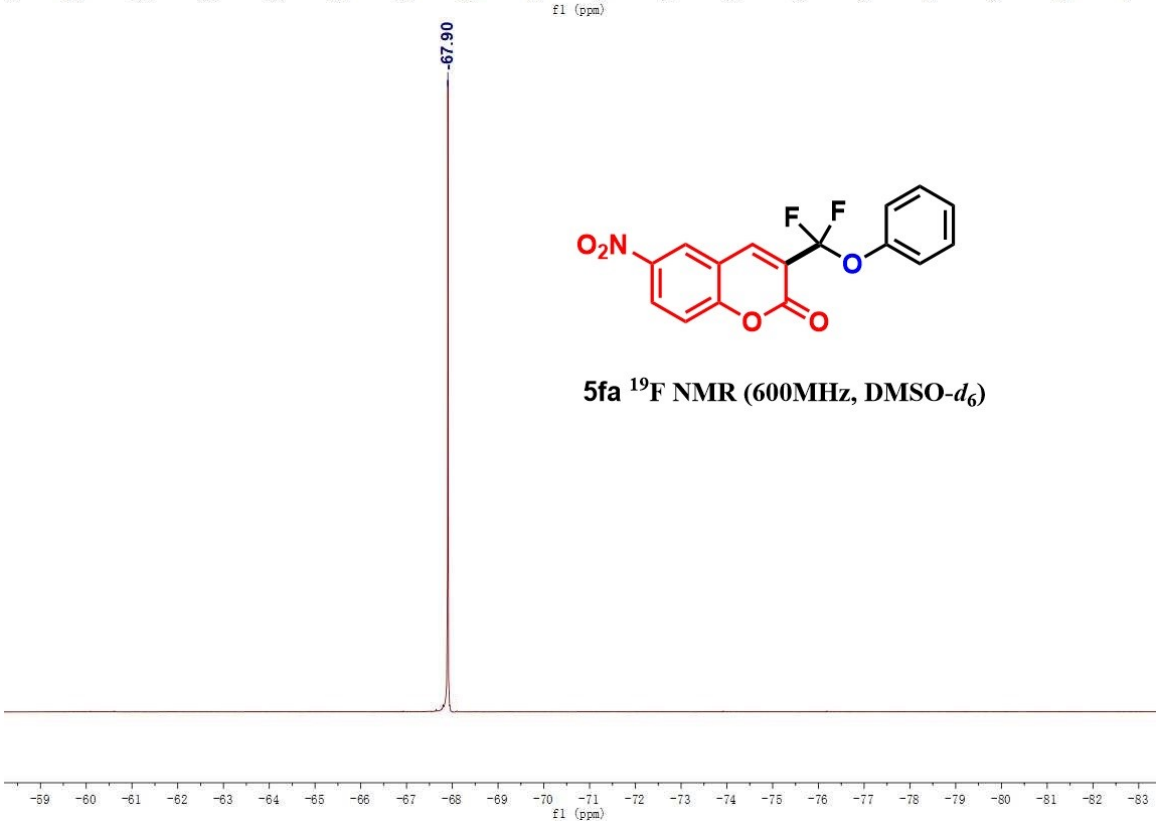
5ea ^{19}F NMR (565 MHz, $CDCl_3$)



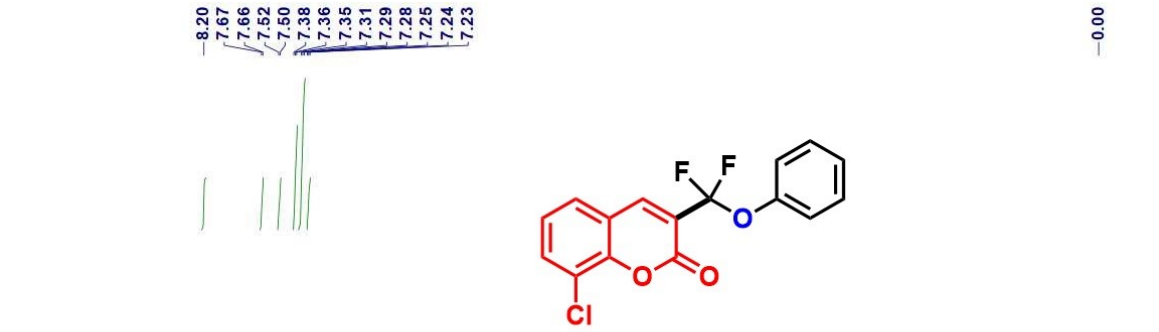
5fa ^{1}HNMR (600MHz,DMSO-d_6)



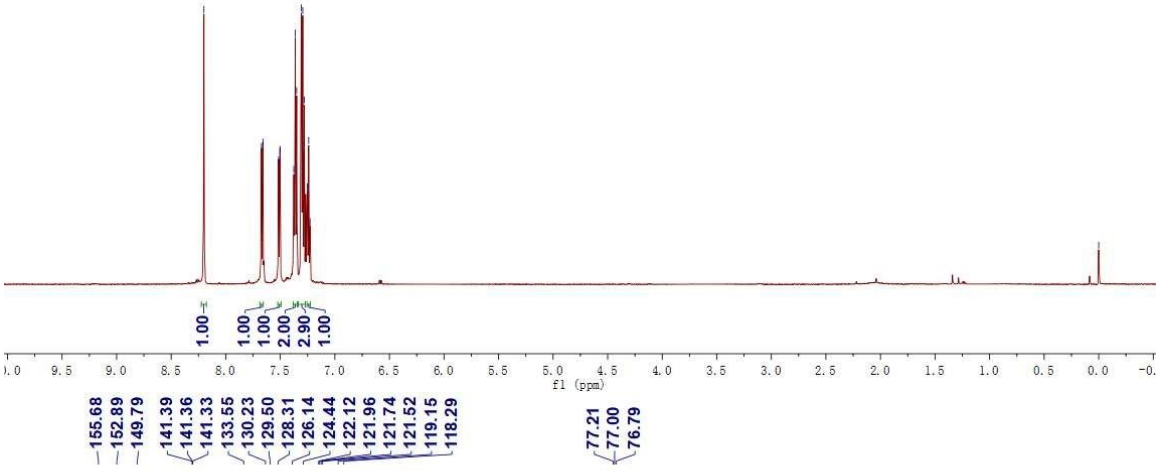
5fa ^{13}CNMR (600MHz, DMSO-d_6)

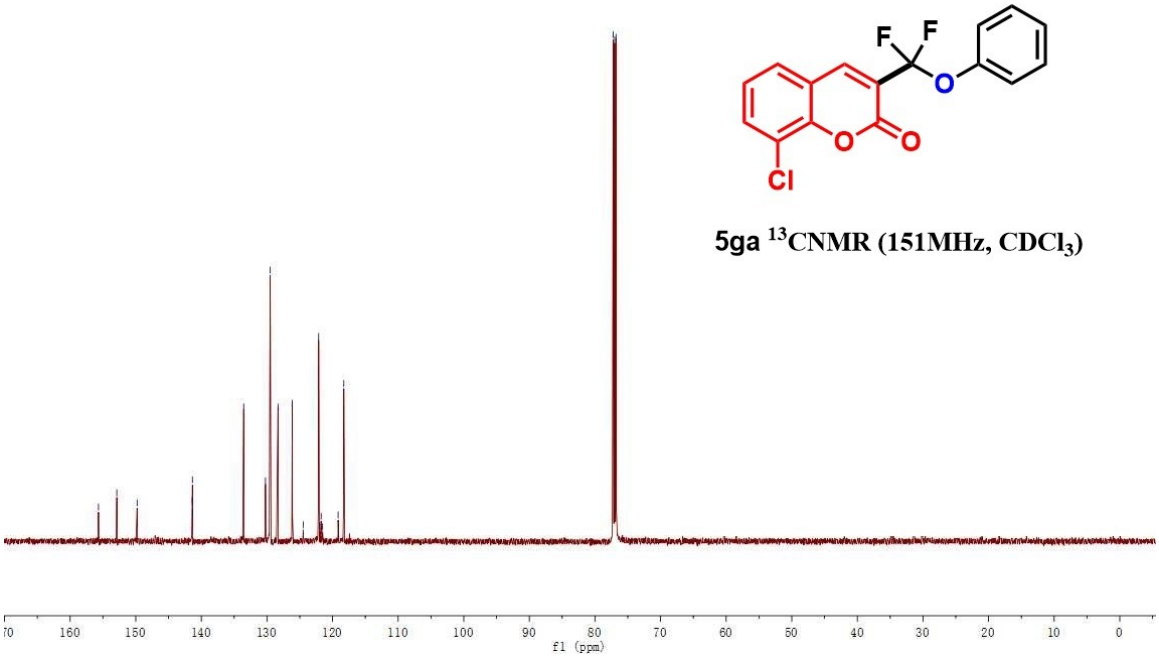


5fa ^{19}F NMR (600MHz, DMSO-d_6)

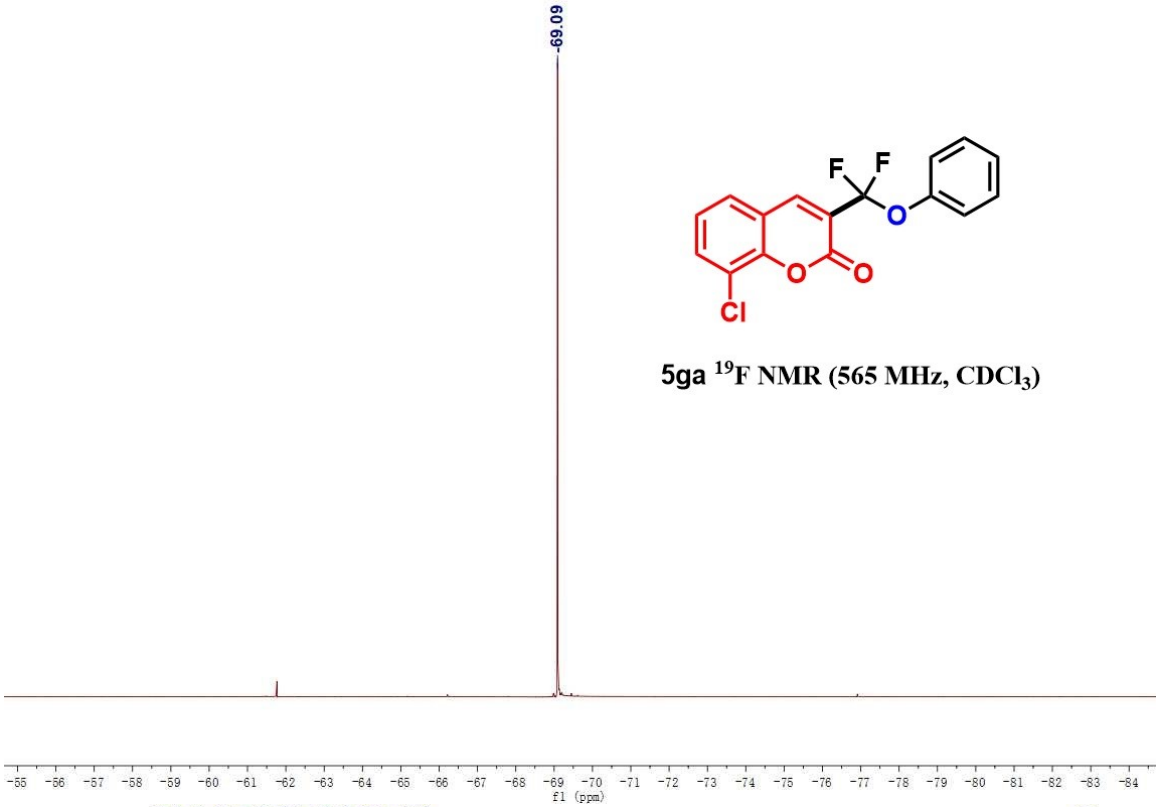


5ga ^{1}HNMR (600MHz, $CDCl_3$)

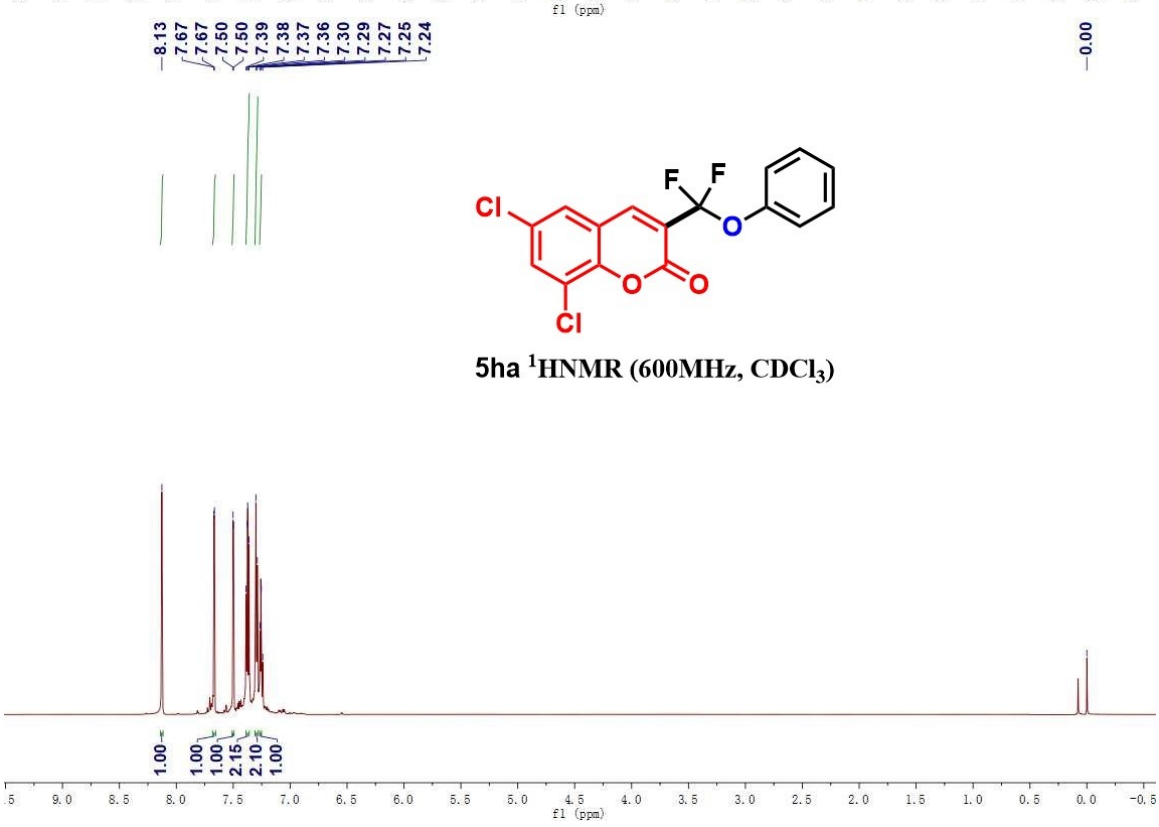




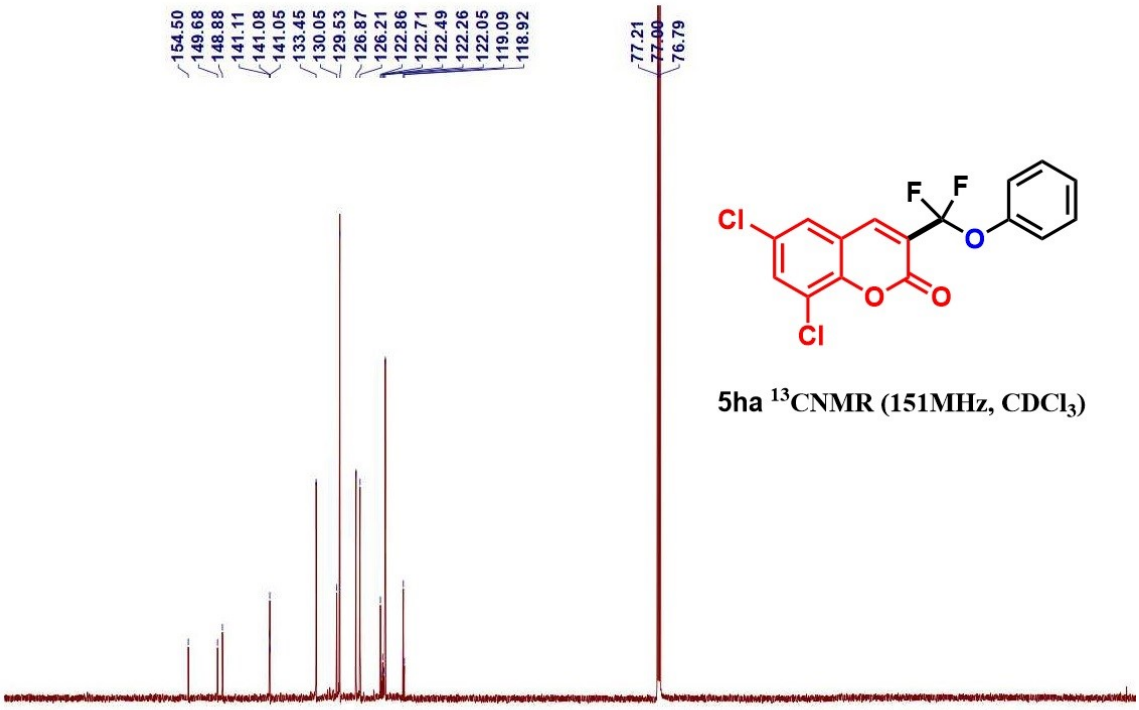
5ga ^{13}CNMR (151MHz, $CDCl_3$)



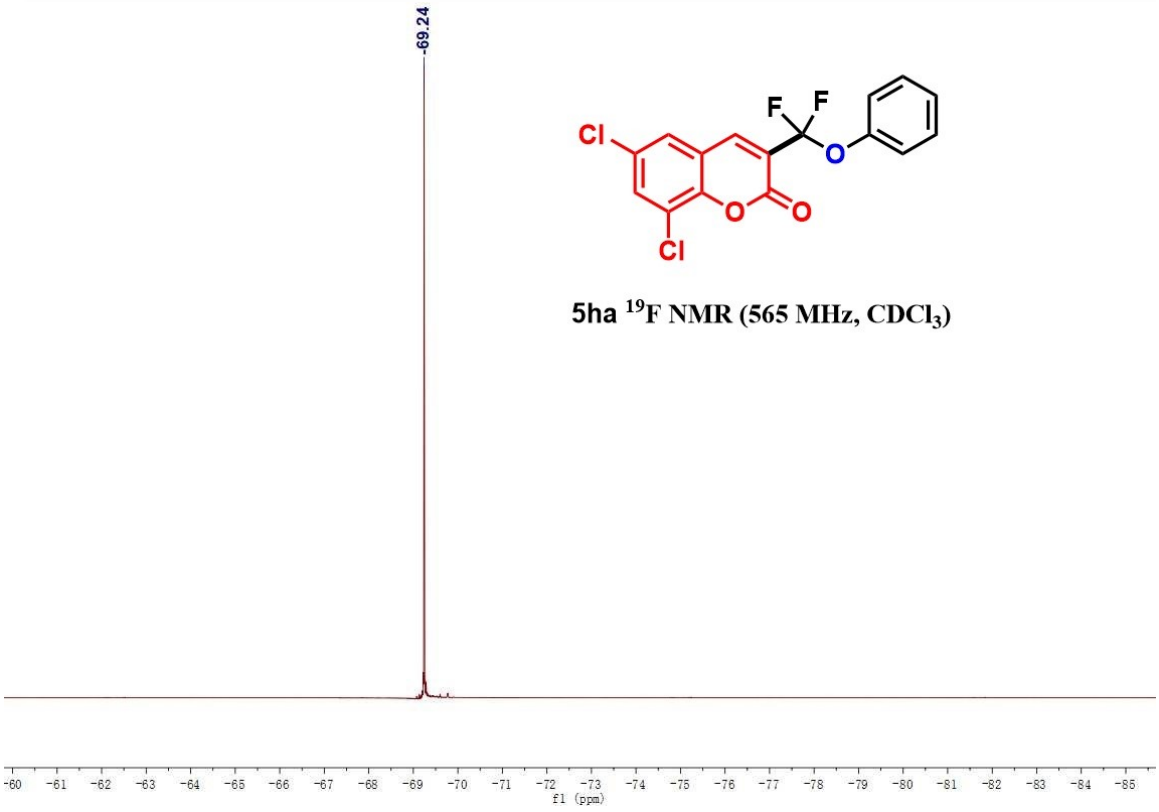
5ga ^{19}F NMR (565 MHz, $CDCl_3$)



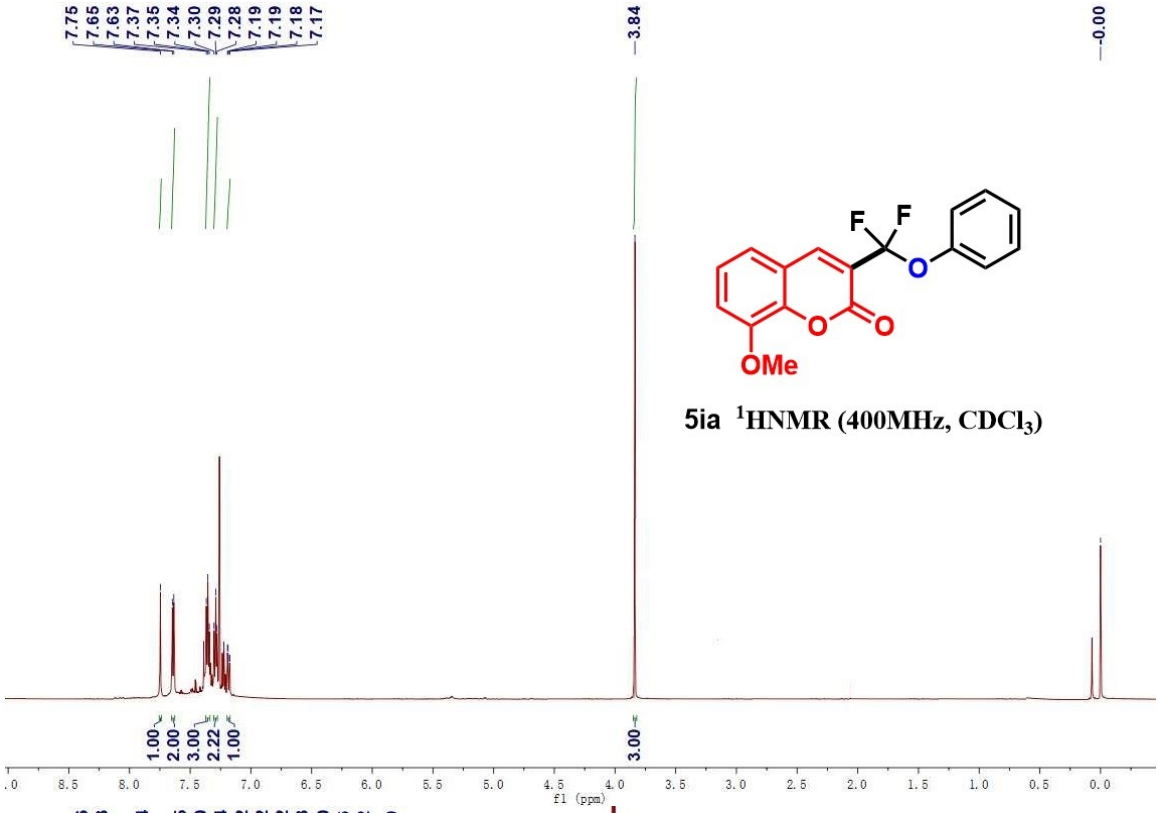
5ha ^{1}HNMR (600MHz, $CDCl_3$)



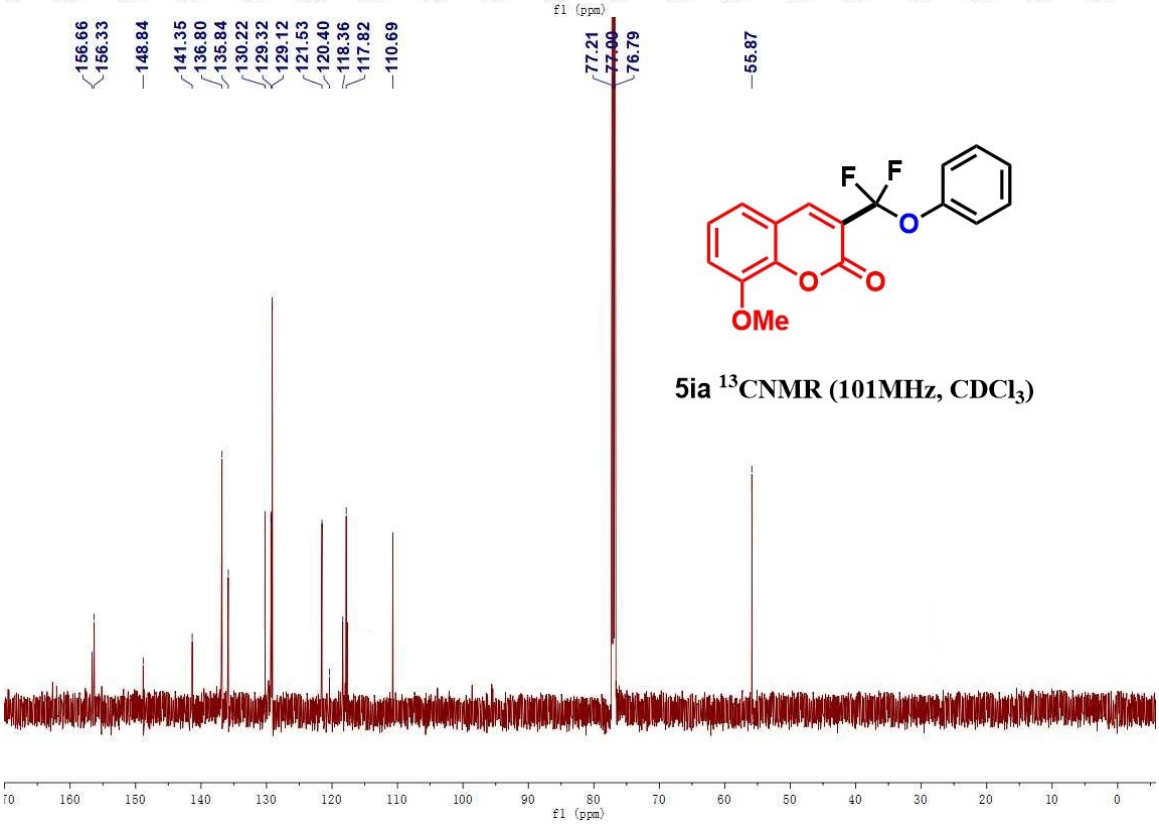
5ha ^{13}CNMR (151MHz, $CDCl_3$)



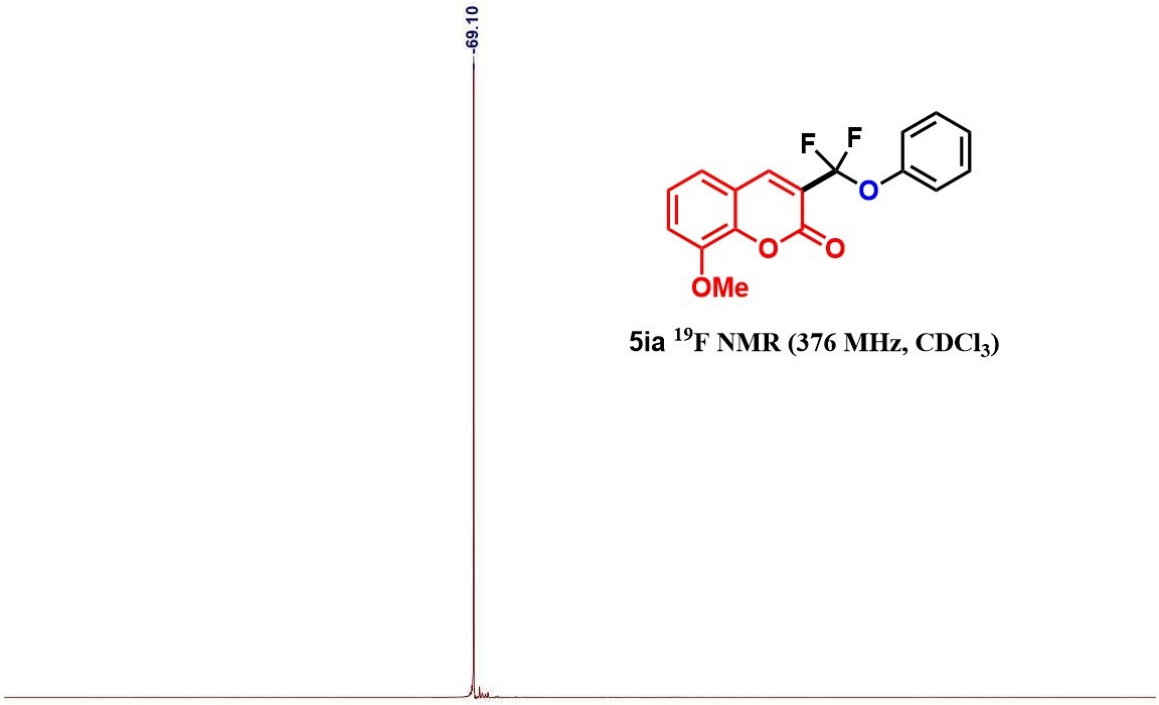
5ha ^{19}F NMR (565 MHz, $CDCl_3$)



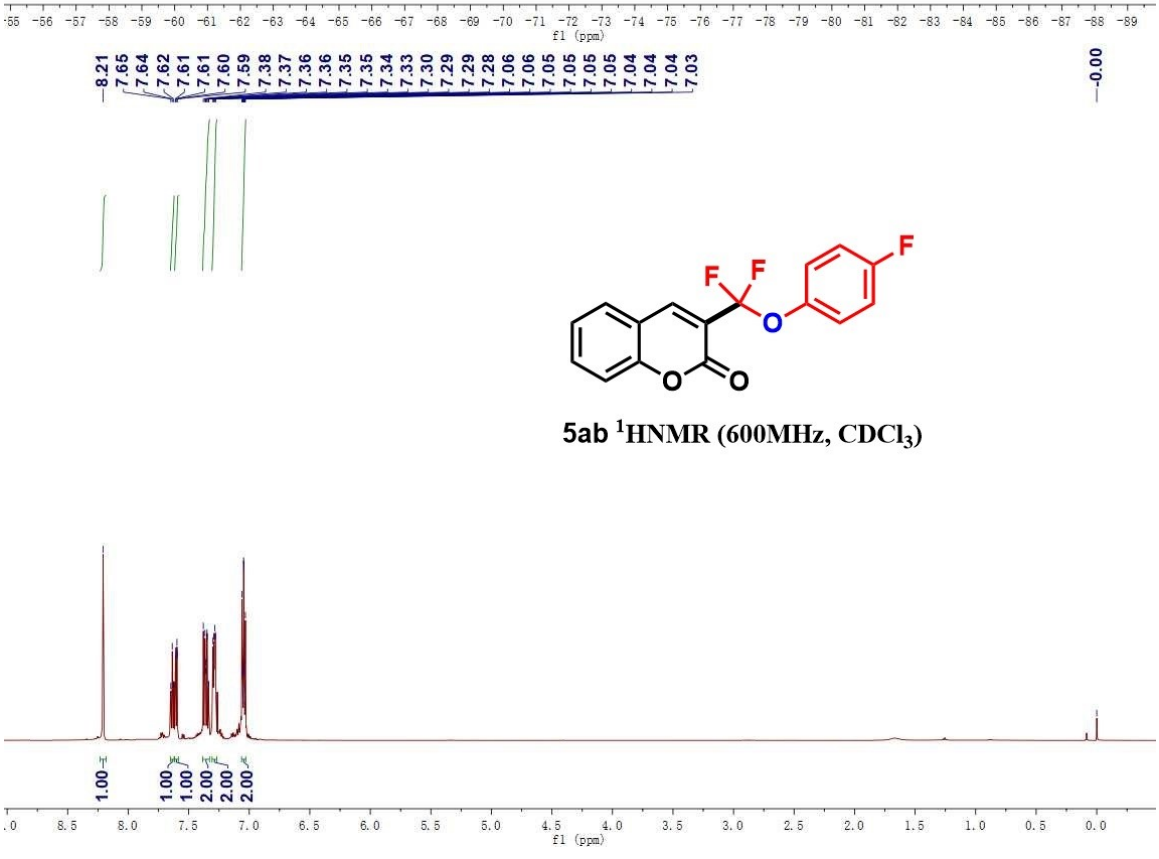
5ia ^{1}HNMR (400MHz, $CDCl_3$)



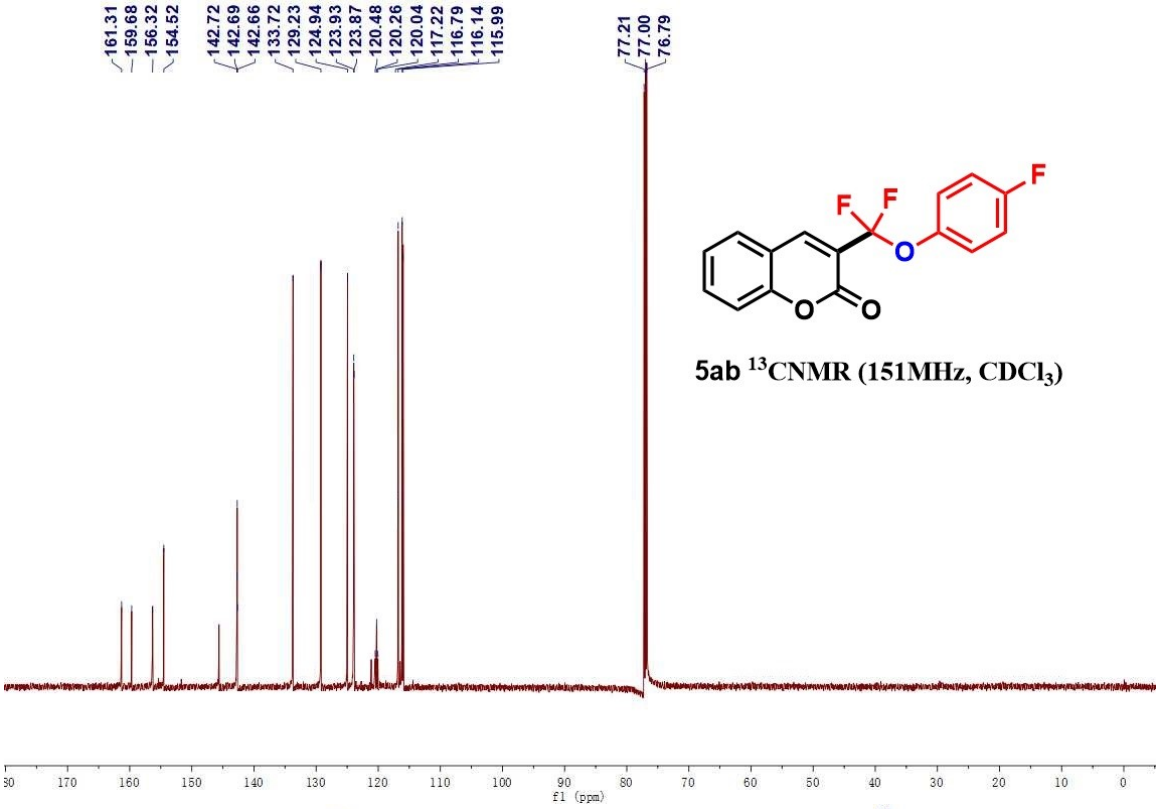
5ia ^{13}CNMR (101MHz, $CDCl_3$)



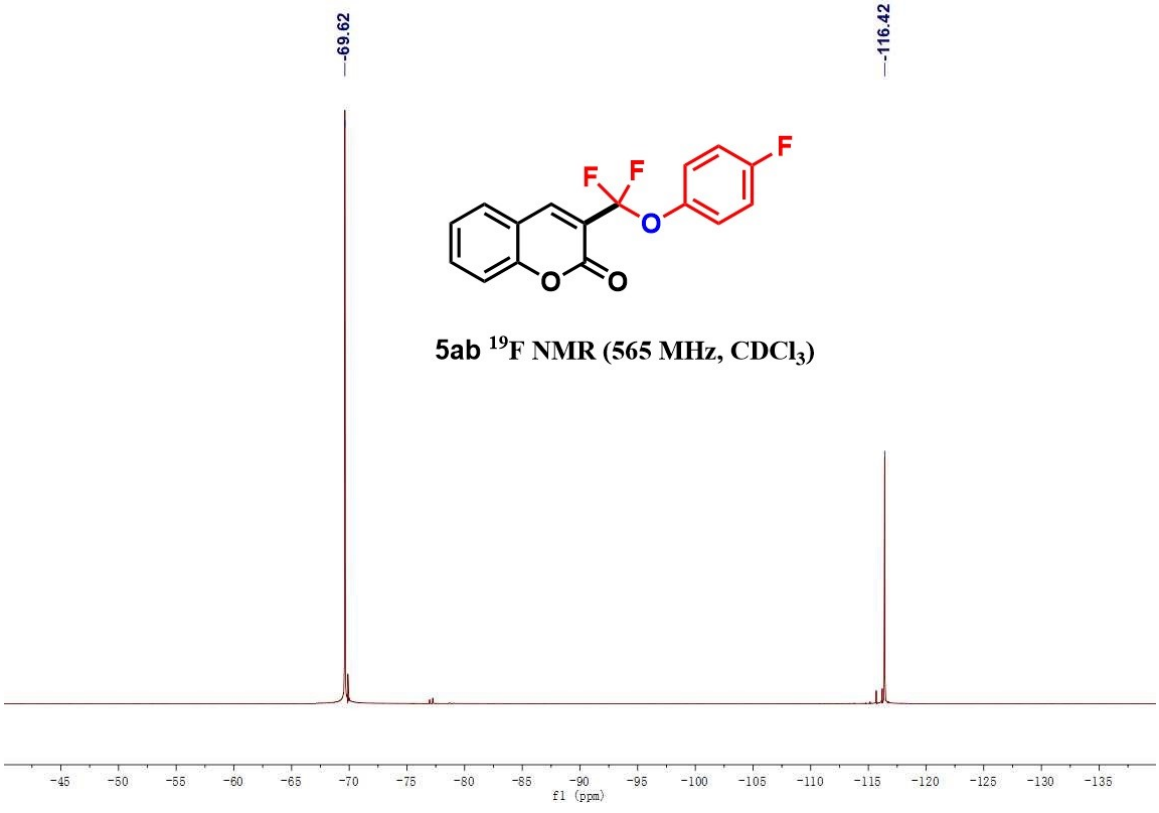
5ia ^{19}F NMR (376 MHz, $CDCl_3$)



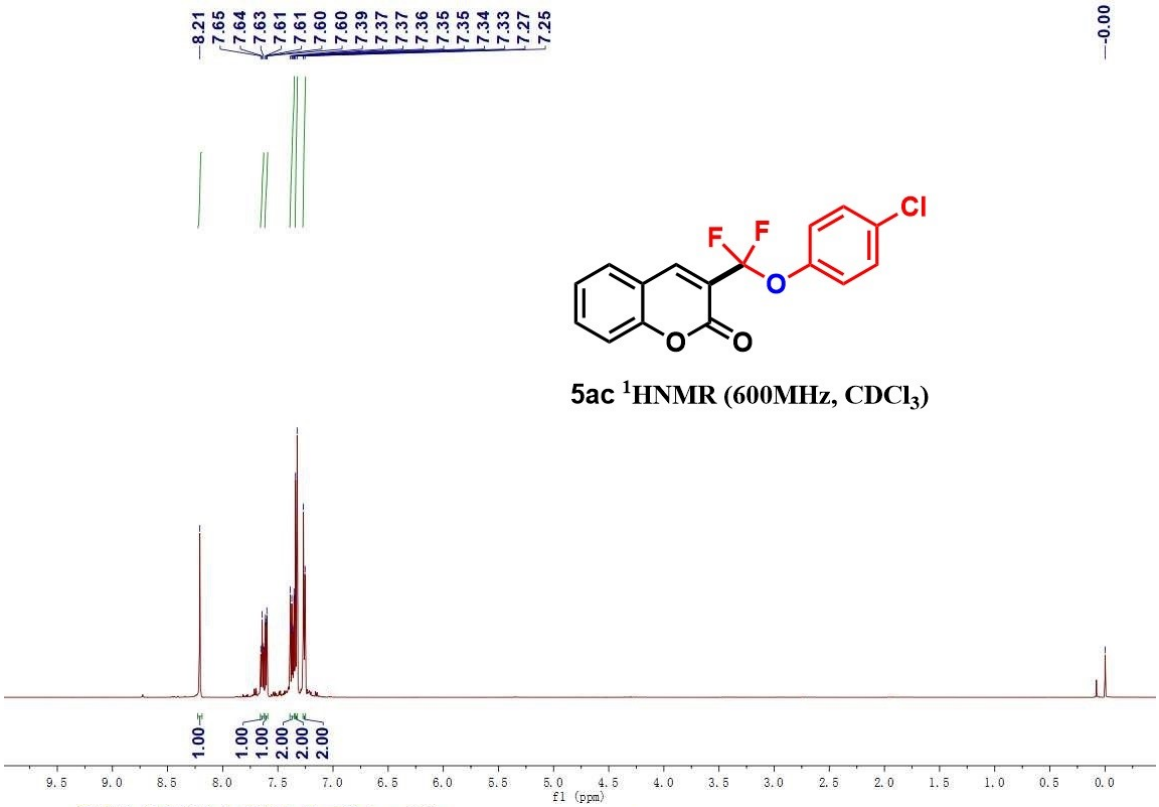
5ab ^{1}HNMR (600MHz, $CDCl_3$)



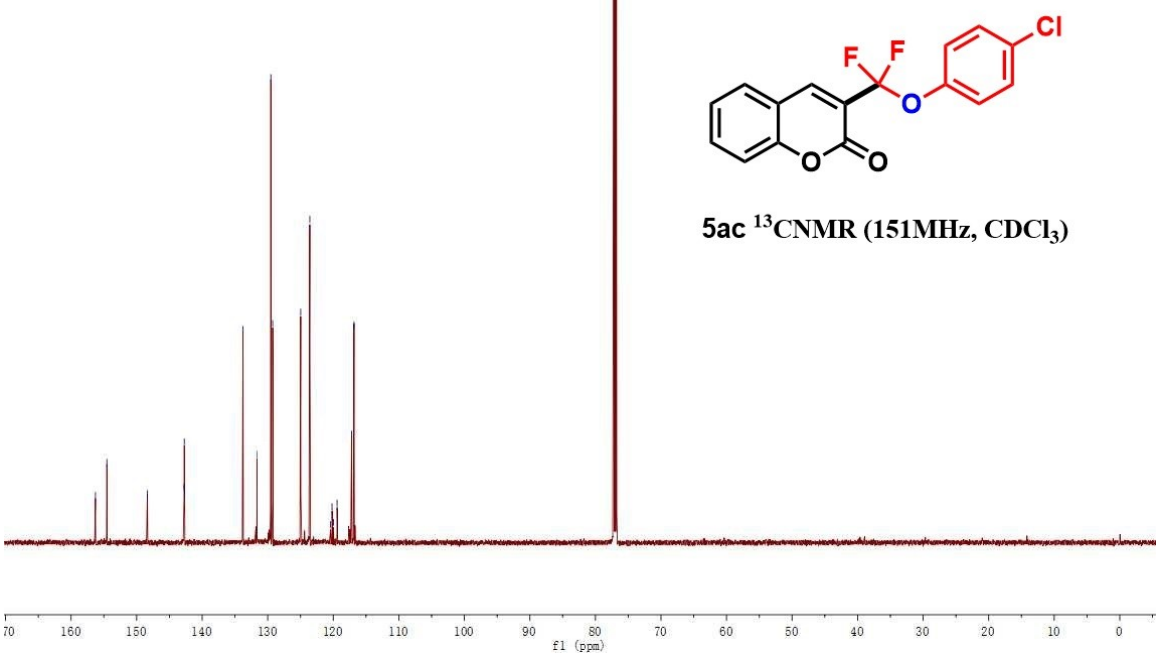
5ab ^{13}CNMR (151MHz, $CDCl_3$)



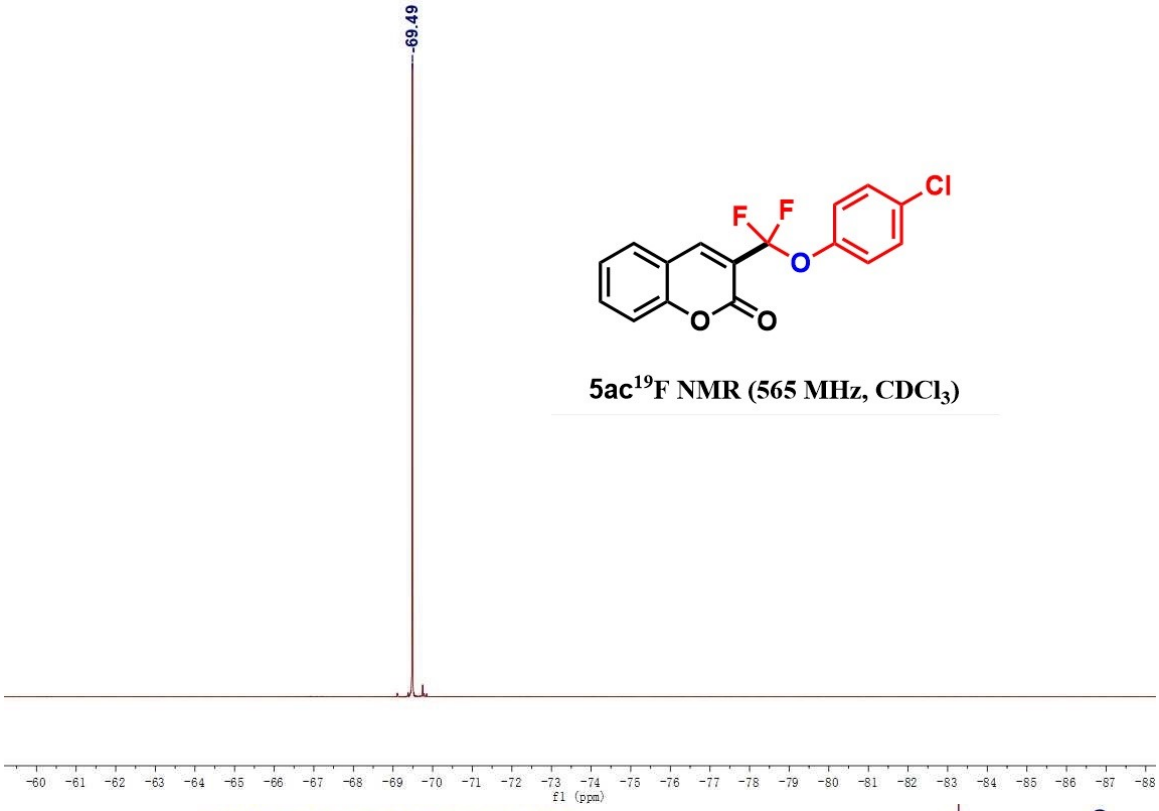
5ab ^{19}F NMR (565 MHz, $CDCl_3$)



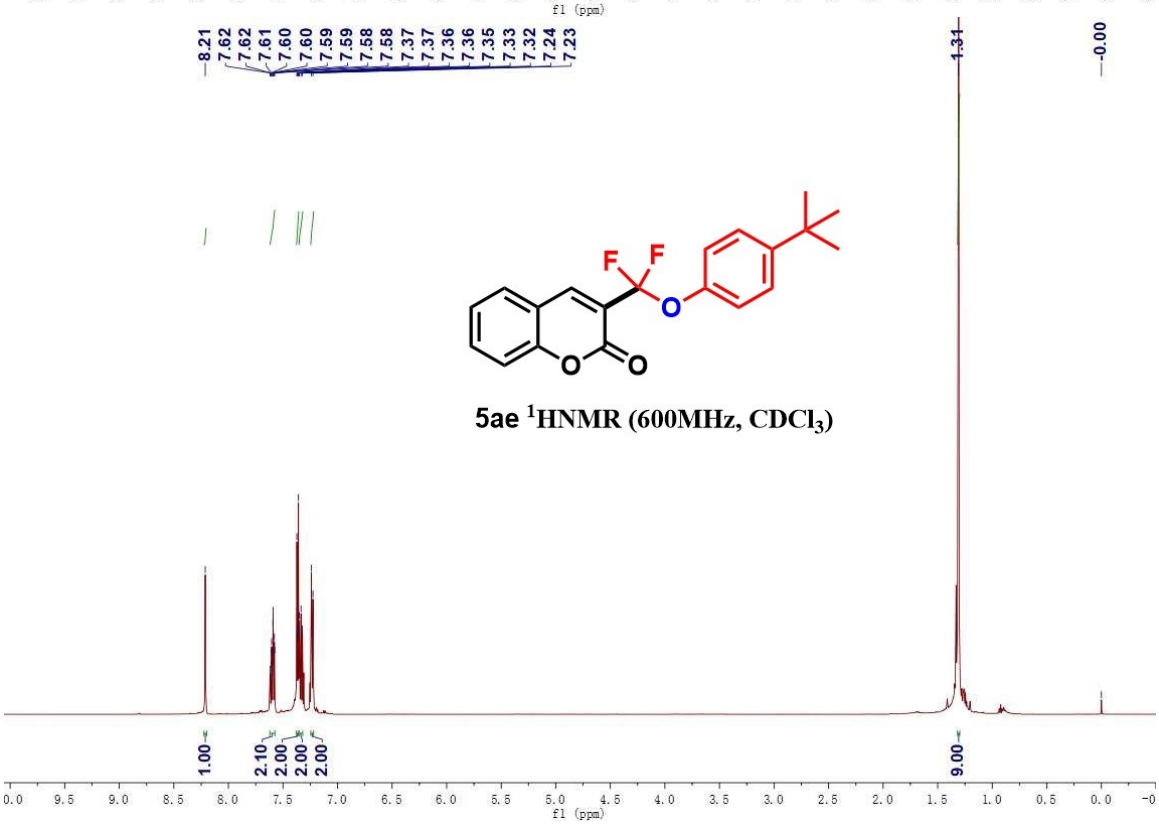
5ac ^{1}HNMR (600MHz, $CDCl_3$)



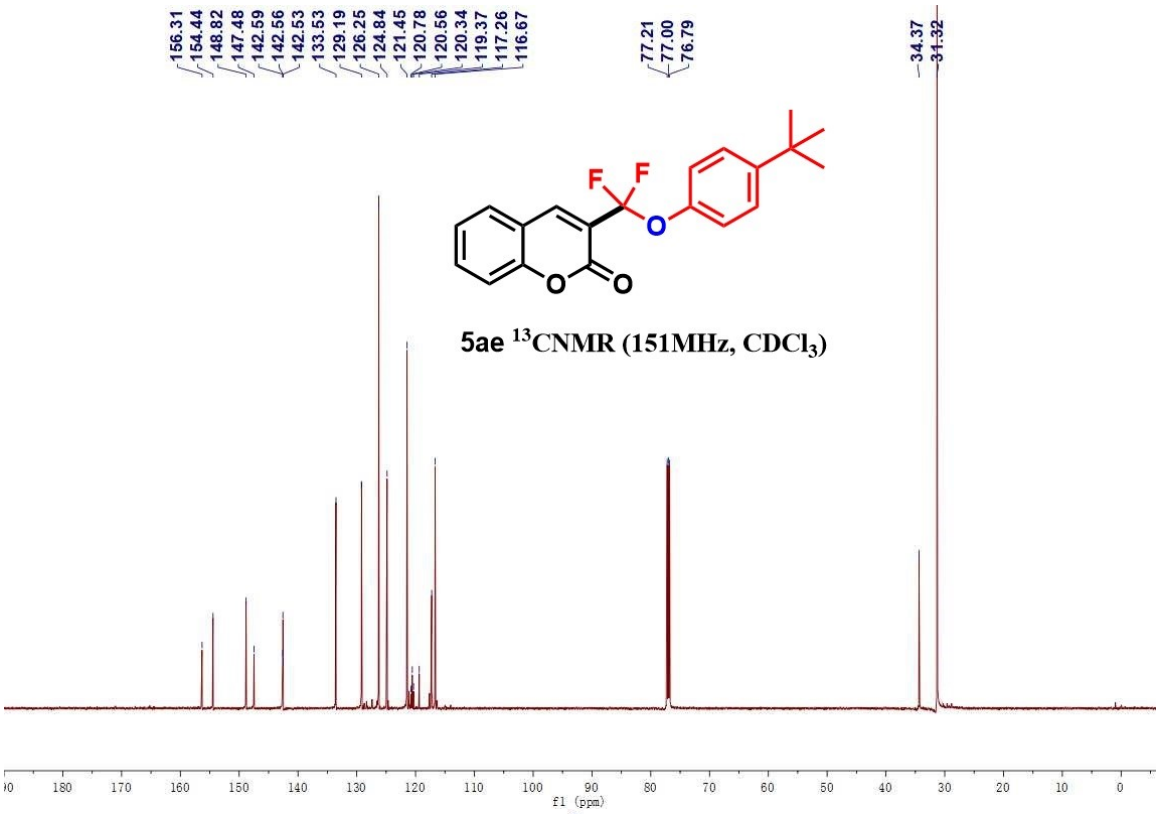
5ac ^{13}CNMR (151MHz, $CDCl_3$)



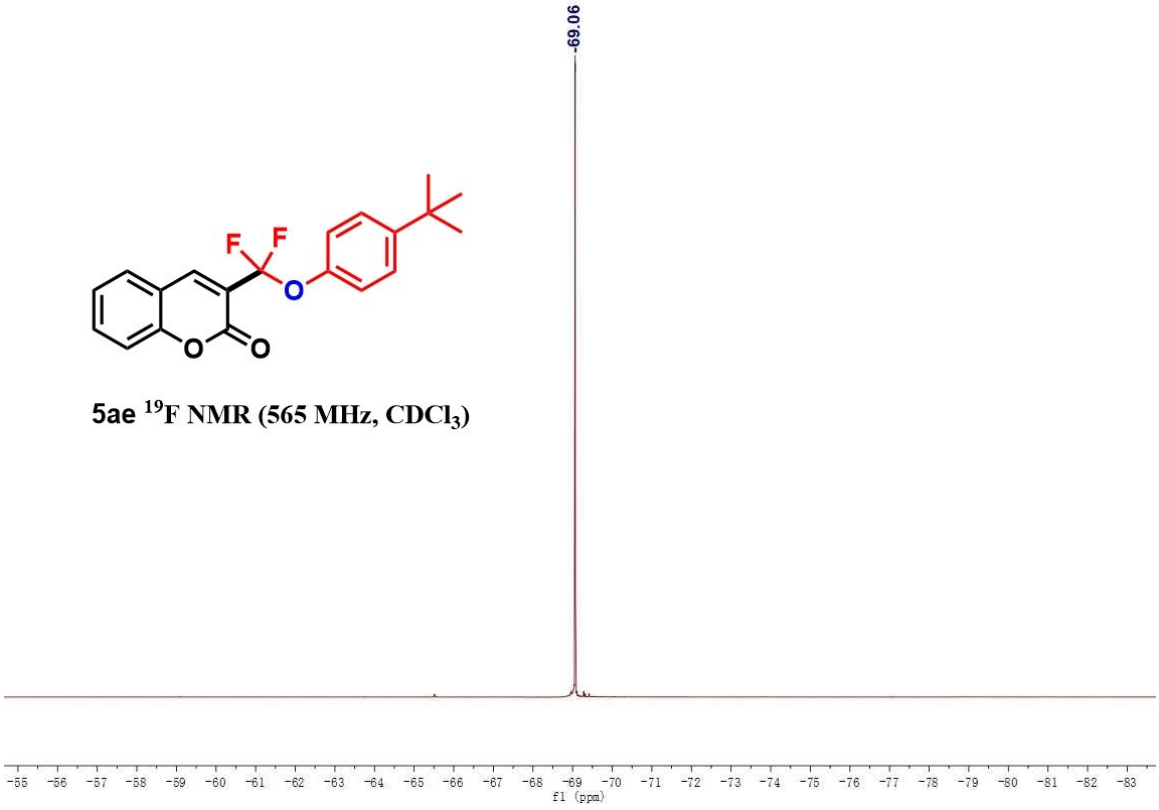
5ac ^{19}F NMR (565 MHz, $CDCl_3$)



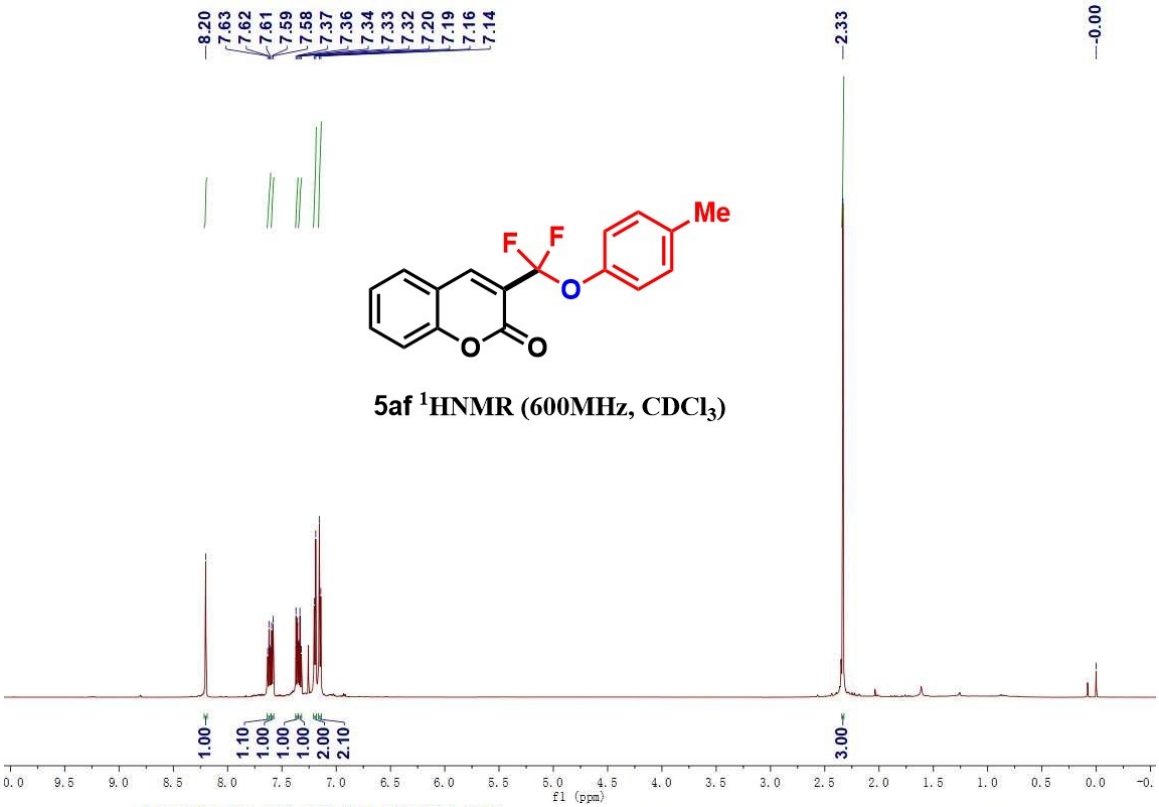
5ae ^{1}HNMR (600MHz, $CDCl_3$)



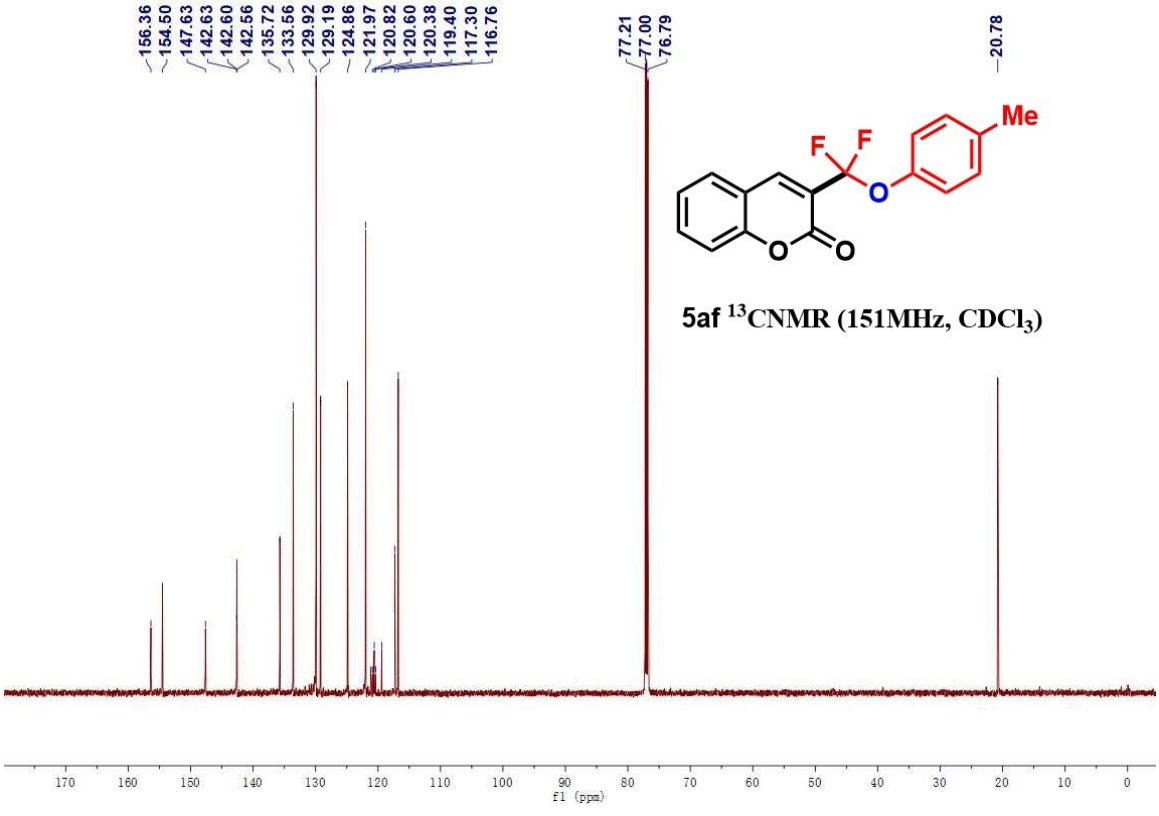
5ae ^{13}CNMR (151MHz, $CDCl_3$)



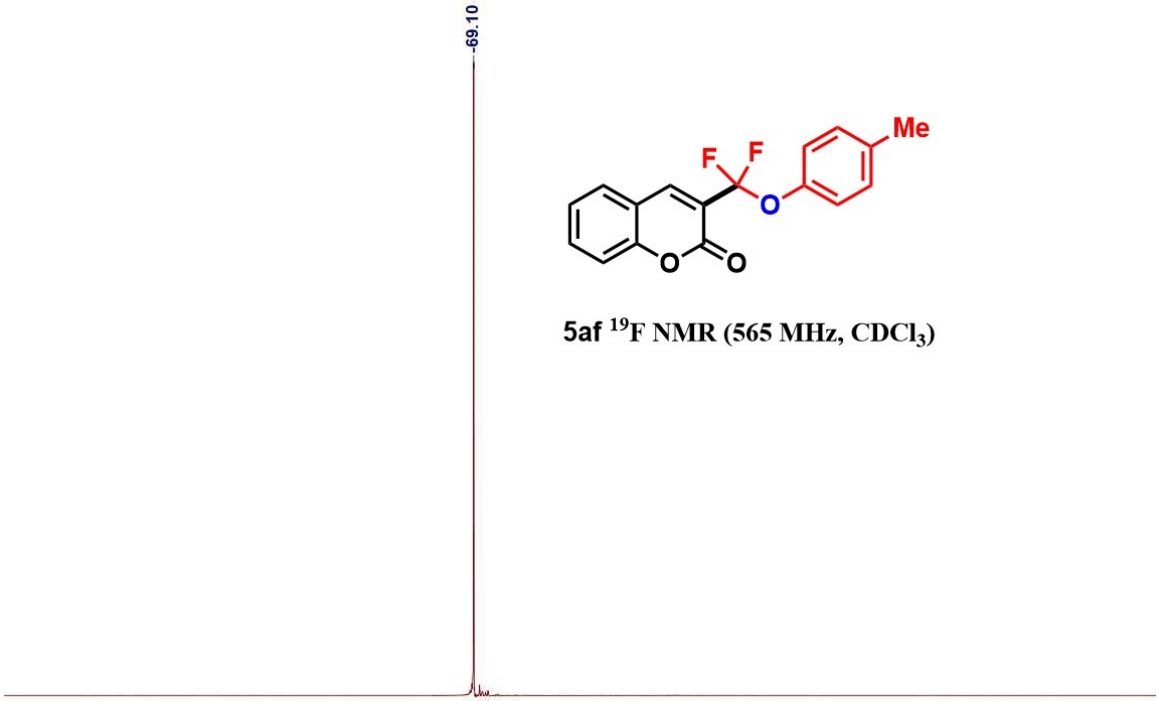
5ae ^{19}F NMR (565 MHz, $CDCl_3$)



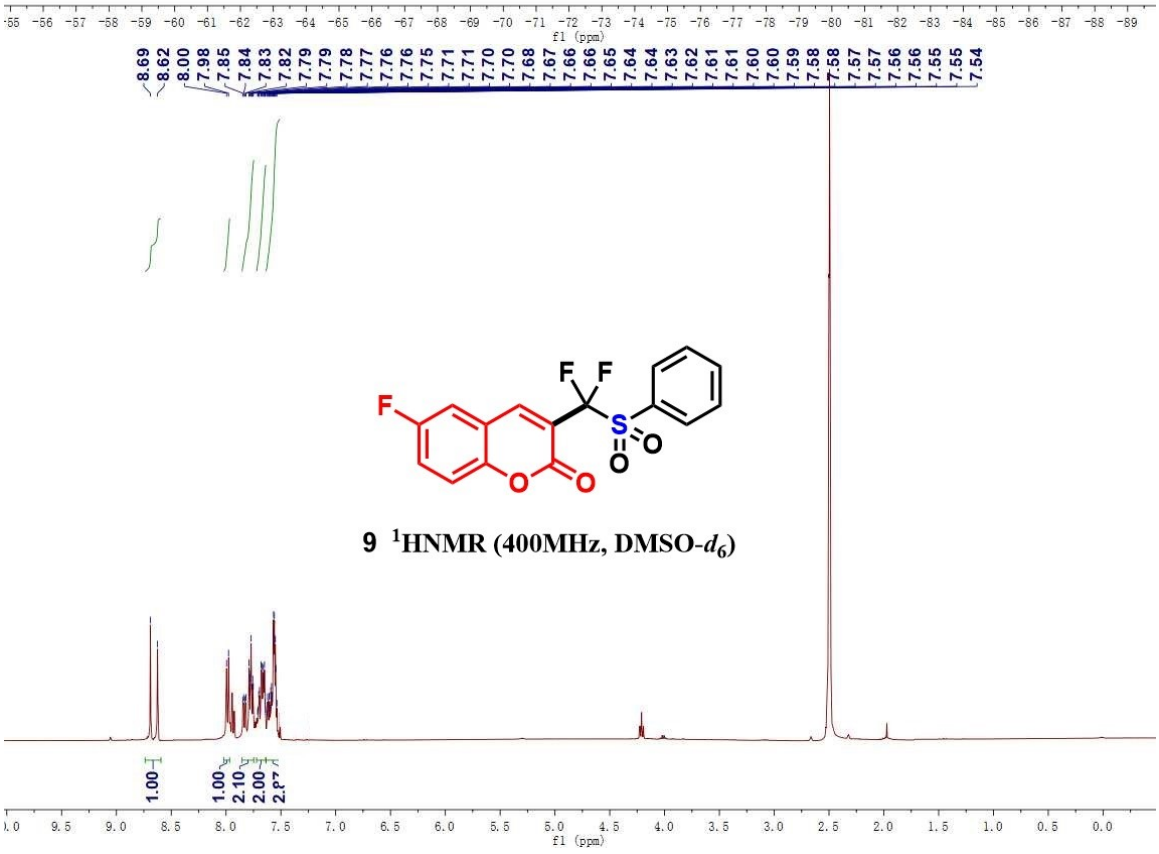
5af ^{1}HNMR (600MHz, $CDCl_3$)



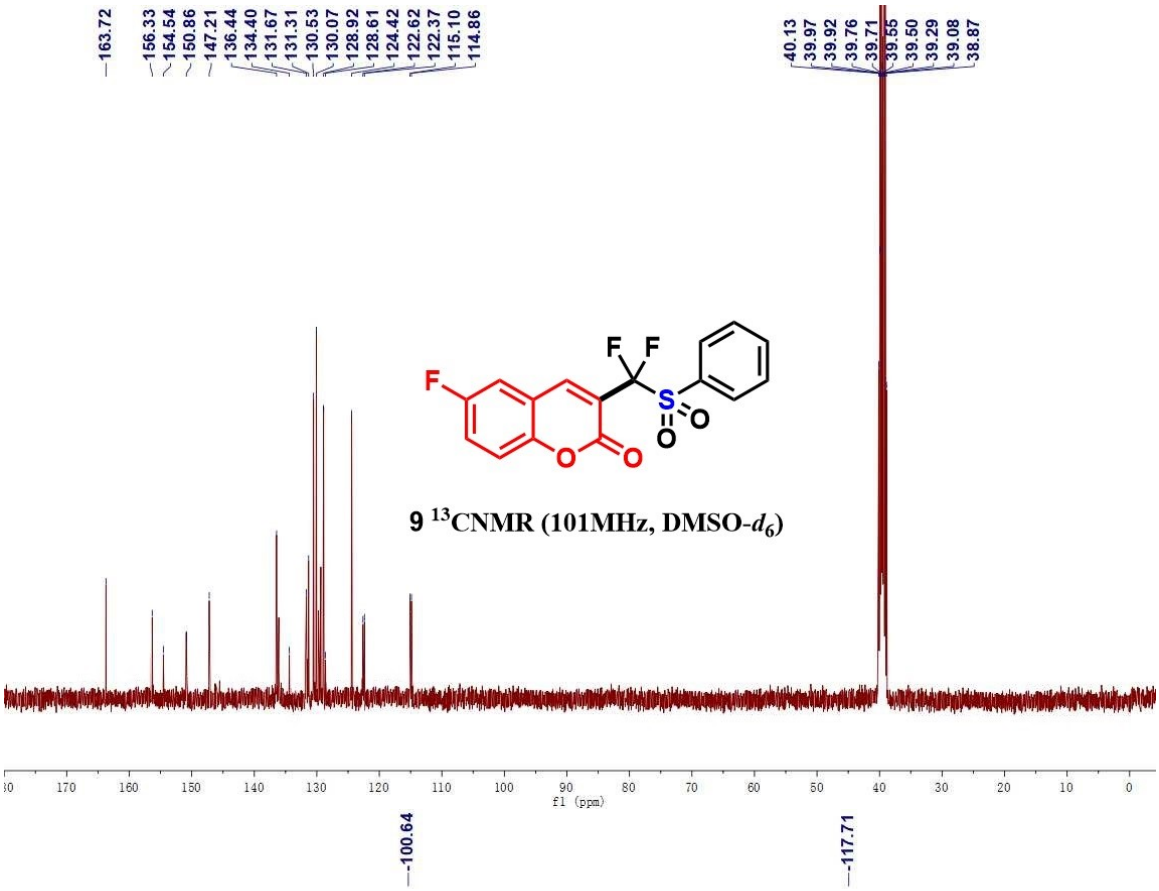
5af ^{13}CNMR (151MHz, $CDCl_3$)



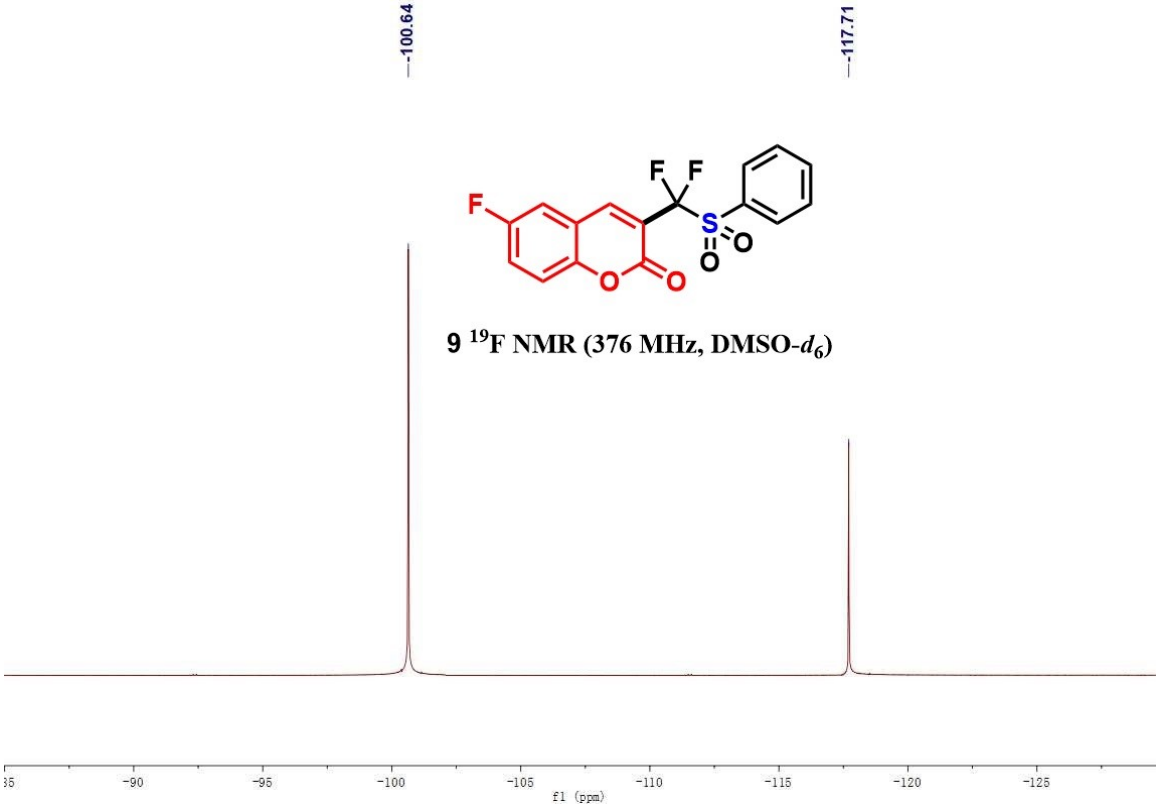
5af ^{19}F NMR (565 MHz, $CDCl_3$)



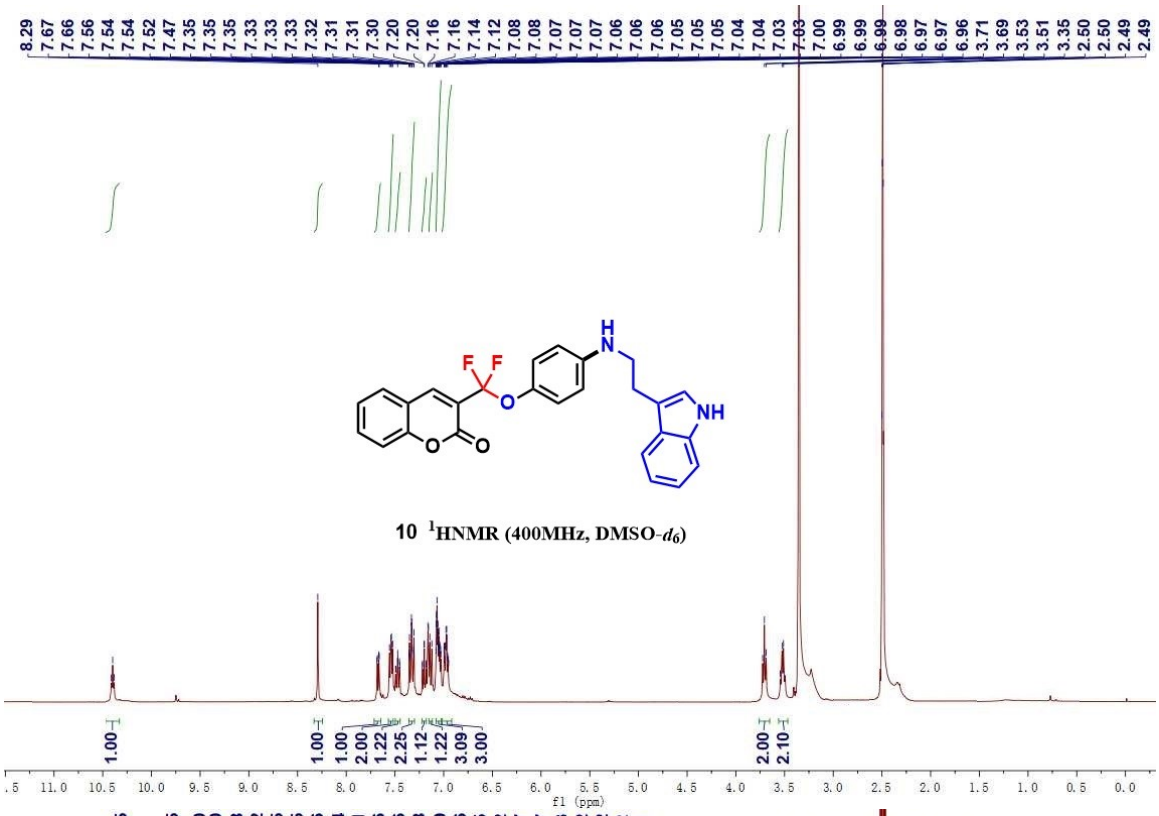
9 ^{1}HNMR (400MHz, DMSO-d_6)



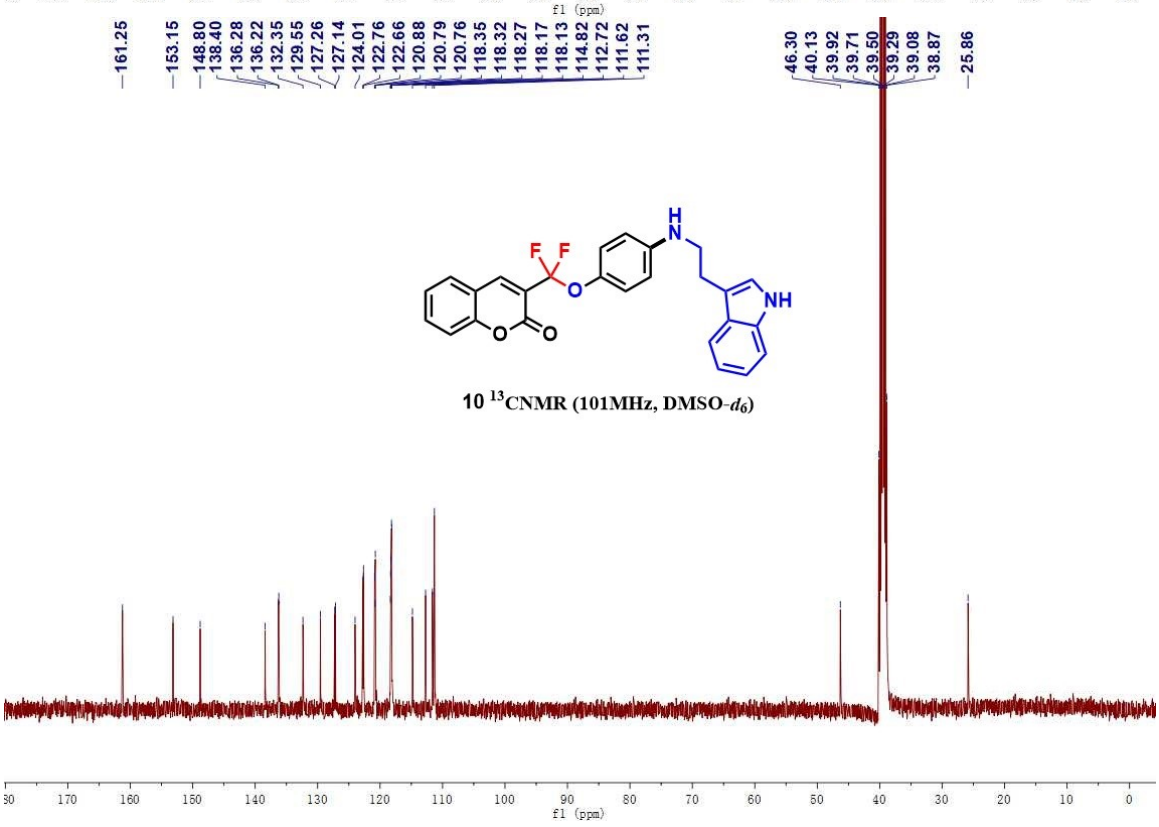
9 ^{13}CNMR (101MHz, DMSO-d_6)



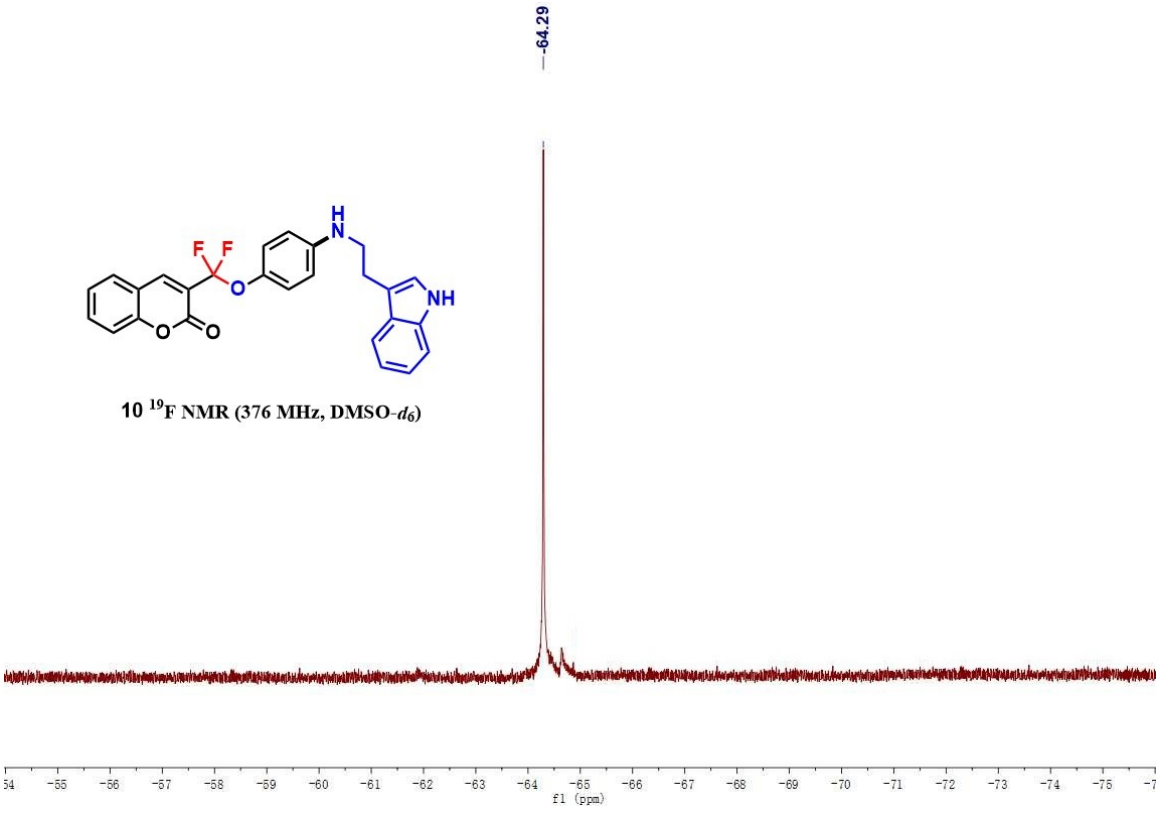
9 ^{19}F NMR (376 MHz, DMSO-d_6)



10 ^{1}**HNMR (400MHz, DMSO-d_6)**



10 ^{13}**CNMR (101MHz, DMSO-d_6)**



10 ^{19}**F NMR (376 MHz, DMSO-*d*$_6$)**

6.The HRMS spectra for Compound 8

HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{23}F_2NNaOS$ + 338.1361; found 338.1365.

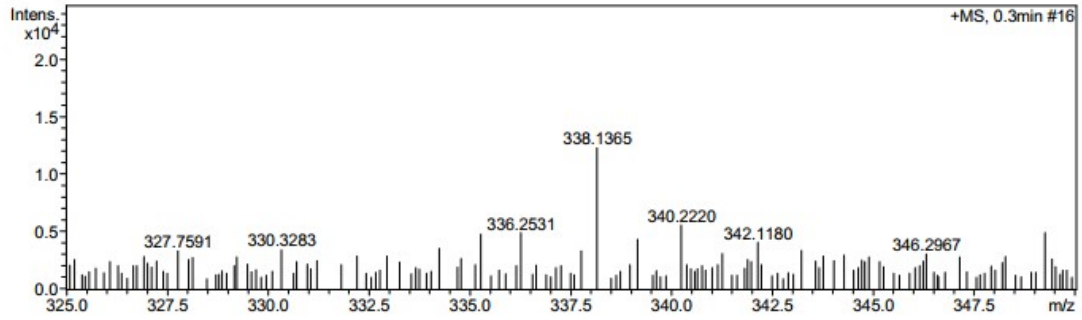
Mass Spectrum SmartFormula Report

Analysis Info

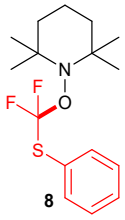
Analysis Name	D:\Data\2021\0609\SJ-20210608-375-TEMPO_1-D,8_01_15343.d	Acquisition Date	6/10/2021 11:21:30 AM
Method	lcms_pos_2min.m	Operator	BDAL@DE
Sample Name	SJ-20210608-375-TEMPO	Instrument / Ser#	micrOTOF-Q II 10366
Comment			

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.8 Bar
Focus	Not active	Set Capillary	5500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	2.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	150.0 Vpp	Set Divert Valve	Waste



Meas. m/z	Formula	m/z	err [ppm]	mSigma
338.1365	C 16 H 23 F 2 N Na O S	338.1361	-1.4	121.3



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