Supplementary information

Electrochemistry enabled multicomponent cascade annulation and functionalization reaction to enable C(sp^3)-H trifluoromethylation

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SUPPORTING INFORMATION

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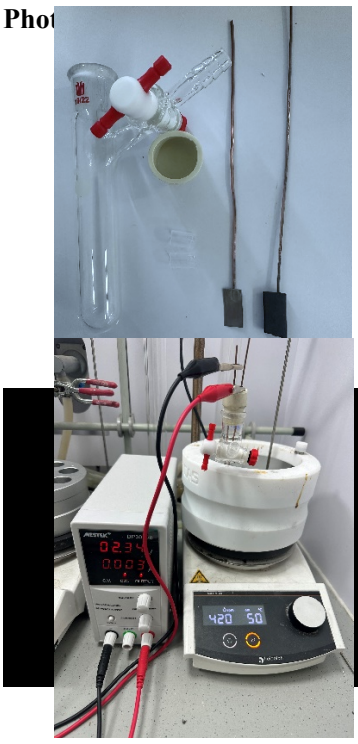
1.Experimental Section

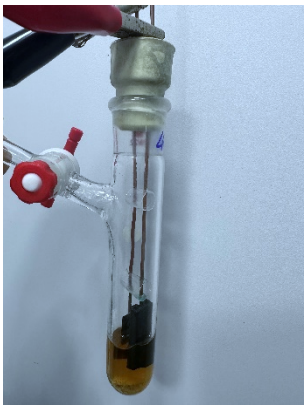
All reagents and solvents were used from commercial sources unless otherwise stated. All raw materials are obtained from commercial sources. All experiments were conducted in the air. All the reactions were monitored by thin-layer chromatography (TLC). TLC was performed on pre-coated silica gel plates (Qingdao Haiyang Chemical Co., Ltd, China). Column chromatography was performed on silica gel (240-400 mesh) with petroleum ether and ethyl acetate as eluent. ^{1}H and ^{13}C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance 400 MHz using $CDCl_3$ and DMSO-d_6 as solvent with tetramethylsilane as the internal standard. Melting points are determined using an WRS-1B apparatus and are uncorrected. High resolution mass spectra were obtained with the Q-TOF-Premier mass spectrometer. Reactions were monitored by TLC and visualized with ultraviolet light.

General Procedure (4a as an example)

2-Aminoacetophenone (40.5 mg, 0.3 mmol), *p*-Tolyl isocyanate (43.9 mg, 0.33 mmol), Togni II reagent (114 mg, 0.36 mmol) and Bu_4NBF_4 (237 mg, 0.3 mmol) were added to a solution of THF/H_2O (5 mL/1 mL) , the reaction mixture was proceeded under a constant current of 3 mA in an undivided cell equipped with a graphite felt anode and a Ni plate cathode at 50 °C for 3 h. The reaction was monitored by TLC. Once the reaction was completed, the reaction mixture was treated with H_2O (15.0 mL) and DCM (8.0 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with DCM (3 x 8 mL). The combined organic extracts were dried (Na_2SO_4), then the solvent was removed under reduced pressure and the remaining residue was purified by column chromatography. Compound **4aa** (234 mg, 71% yield) was obtained as a white solid.

Phot setup





Cyclic voltammetry studies

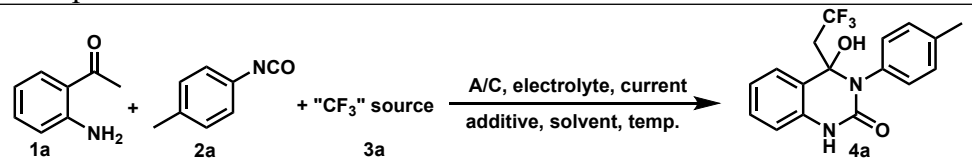
The cyclic voltammograms experiments were conducted in a Schlenk tube that contained the

substance dissolved in a 0.1 M solution of tetrabutylammonium tetrafluoroborate in acetonitrile. A glassy carbon electrode working electrode, a platinum wire counter electrode and an Ag/Ag^{+} reference electrode were used. The reference electrode was stored in silver nitrate solution for activation before use. The relevant parameters were controlled by an electrochemical workstation CHI600E.

2.Optimization of reaction conditions.

2-Aminoacetophenone (**1a**, 40.5 mg, 0.3 mmol), *p*-Tolyl isocyanate (**2a**, 43.9 mg, 0.33 mmol), trifluoromethylation reagent (0.36 mmol), electrolyte and additive dissolved in the solvent were added to an undivided cell equipped with electrode. The samples were reacted with the respective current for the mentioned time. The reaction was monitored by TLC. Once the reaction was completed, the reaction mixture was treated with H_2O (15.0 mL) and DCM (8.0 mL). The organic and aqueous layers were then separated, and the aqueous layer was extracted with DCM (3 x 8 mL). The combined organic extracts were dried (Na_2SO_4), then the solvent was removed under reduced pressure and the remaining residue was purified by column chromatography. The yield of **4a** was the isolated yield.

Table 1. Optimization of reaction conditions[a]



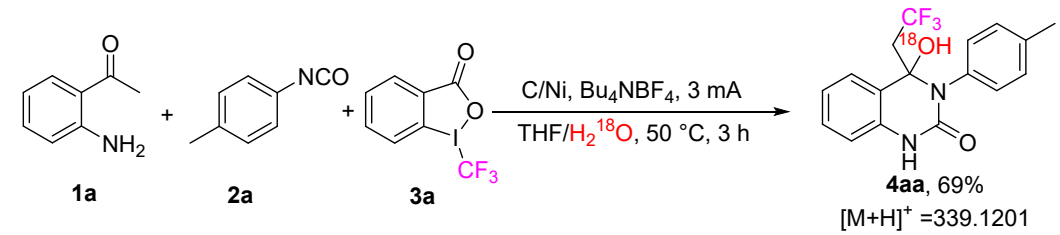
Entry	"CF_3" source	A/C	electrolyte	current	solvent	additive	Time (h)	temp. (℃)	Yield (%)[a]
1	CF_3SO_2Na	C/Pt	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	<5
2	Togni	C/Pt	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	13
3	$TMSCF_3$	C/Pt	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	N.D.
4	Togni	C/Ni	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	32
5	Togni	C/C	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	<5
6	Togni	Pt/Pt	Bu_4NPF_6	5 mA	MeCN/H_2O(1:1)	-	3.5	50	<5
7	Togni	C/Ni	Bu_4NPF_6	5 mA	Dioxane/H_2O(1:1)	-	3.5	50	N.D.
8	Togni	C/Ni	Bu_4NPF_6	5 mA	THF/H_2O(1:1)	-	3.5	50	45
9	Togni	C/Ni	Bu_4NPF_6	5 mA	Acetone/H_2O(1:1)	-	3.5	50	25
10	Togni	C/Ni	Bu_4NPF_6	5 mA	EtOH/H_2O(1:1)	-	3.5	50	<10
11	Togni	C/Ni	Bu_4NPF_6	5 mA	DMF/H_2O(1:1)	-	3.5	50	<10
12	Togni	C/Ni	Bu_4NPF_6	5 mA	MeCN	-	3.5	50	N.D.
13	Togni	C/Ni	Bu_4NBF_4	5 mA	THF/H_2O(1:1)	-	3.5	50	67
14	Togni	C/Ni	TBAB	5 mA	THF/H_2O(1:1)	-	3.5	50	36
15	Togni	C/Ni	$LiClO_4$	5 mA	THF/H_2O(1:1)	-	3.5	50	57
16	Togni	C/Ni	Et_4NClO_4	5 mA	THF/H_2O(1:1)	-	3.5	50	64
17	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	-	3.5	50	69
18	Togni	C/Ni	Bu_4NBF_4	7 mA	THF/H_2O(1:1)	-	3.5	50	62

19	Togni	C/Ni	Bu_4NBF_4	10 mA	THF/H_2O(1:1)	-	3.5	50	58
20	Togni	C/Ni	Bu_4NBF_4	15 mA	THF/H_2O(1:1)	-	3.5	50	43
21	Togni	C/Ni	Bu_4NBF_4	5 mA	THF/H_2O(1:1)	-	3.5	30	64
22	Togni	C/Ni	Bu_4NBF_4	5 mA	THF/H_2O(1:1)	-	3.5	70	67
23	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	-	1.5	50	43
24	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	-	2.5	50	62
25	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	-	3.5	50	69[b]
26	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	-	4.5	50	46
27	Togni	C/Ni	Bu_4NBF_4	3 mA	THF/H_2O(1:1)	NaOH	3.5	50	Trace
28	Togni	C/Ni	Bu_4NBF_4	5 mA	THF/H_2O(2:1)	-	3.5	70	69
29	Togni	C/Ni	Bu_4NBF_4(0.1 eq.)	5 mA	THF/H_2O(5:1)	-	3.5	70	32
30	Togni	C/Ni	Bu_4NBF_4(0.5 eq.)	5 mA	THF/H_2O(5:1)	-	3.5	70	44
31	Togni	C/Ni	Bu_4NBF_4(1.5 eq.)	5 mA	THF/H_2O(5:1)	-	3.5	70	68
32	Togni	C/Ni	Bu_4NBF_4(2 eq.)	5 mA	THF/H_2O(5:1)	-	3.5	70	71
33	Togni	C/Ni	-	5 mA	THF/H_2O(5:1)	-	3.5	70	<5

Reaction conditions: **1a** (0.3 mmol), **2a** (0.33 mmol), **3a** (0.36 mmol), elecrtrolyte (0.6 mmol) and solvent (6 mL) in an undivided cell at the indicated reaction conditions.

[a]Isolated yield [b]N_2 atmosphere

3. HRMS for O^{18} labeling experiments



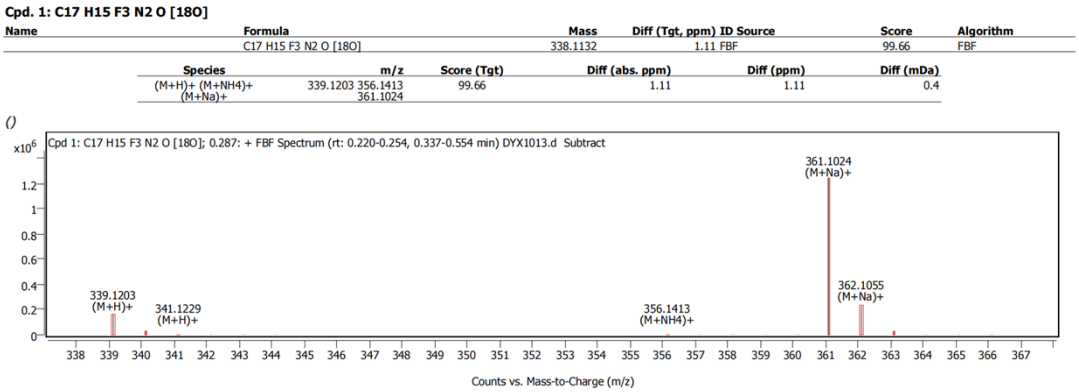
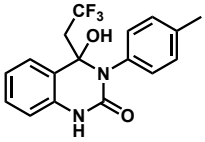
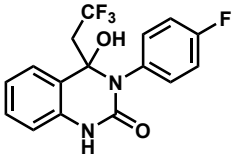


Fig. S1. HRMS for O^{18} labeling experiments.

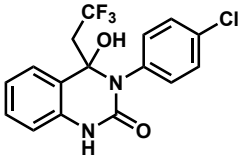
4.Data of compounds



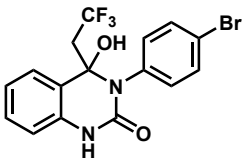
4-hydroxy-3-(*p*-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4aa): White solid; mp 211.7-218.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.66 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.05 (t, *J* = 7.9 Hz, 1H), 6.74 (s, 1H), 3.84 (q, *J* = 9.8 Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.89, 152.65, 143.38, 138.96, 136.28, 135.08, 131.48(q, *J* = 285 Hz), 130.64, 129.69, 121.09, 120.93, 120.60, 114.41, 43.02(q, *J* = 28 Hz), 20.86. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.05. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 337.1158; found 337.1155.



3-(4-fluorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ab): White solid; mp 225.6-232.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.94 (s, 1H), 8.46 – 8.40 (m, 1H), 8.01 – 7.98 (m, 1H), 7.65 – 7.59 (m, 1H), 7.56 – 7.50 (m, 2H), 7.17 – 7.09 (m, 3H), 4.49 (q, *J* = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.22, 158.02 (d, *J* = 238 Hz), 152.76, 142.09, 136.37 (d, *J* = 3.0 Hz), 135.50, 132.12, 129.73, 125.51 (q, *J* = 275 Hz), 121.47, 120.83 (d, *J* = 8.0 Hz), 120.63, 115.74 (d, *J* = 22 Hz), 43.06 (q, *J* = 27 Hz).^{19}F NMR (376 MHz, DMSO-d_6) δ -60.88, -120.91. HRMS (ESI): calcd. for $C_{16}H_{13}F_4N_2O_2$ $[M+H]^+$ 341.0908; found 341.0905.

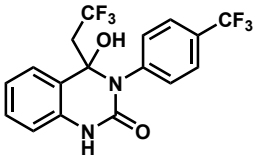


3-(4-chlorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1*H*)-one (4ac): White solid; mp 196.2-198.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.05 (s, 1H), 8.41 (dd, *J* = 8.6, 1.2 Hz, 1H), 8.01 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.63 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.39 – 7.31 (m, 2H), 7.14 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 4.50 (q, *J* = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.41, 152.62, 141.88, 139.08, 135.50, 132.12, 129.08, 126.25, 125.51 (q, *J* = 275 Hz), 121.63, 120.70, 120.57, 115.65, 43.07 (q, *J* = 25 Hz).^{19}F NMR (376 MHz, DMSO-d_6) δ -60.87. HRMS (ESI): calcd. for $C_{16}H_{13}ClF_3N_2O_2$ $[M+H]^+$ 357.0612; found 357.0617.

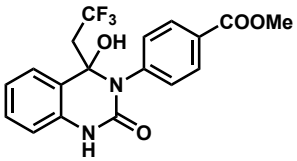


3-(4-bromophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ad): White solid; mp 215.8-220.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 10.05 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.53 – 7.43 (m, 4H), 7.13 (t, *J* = 7.7

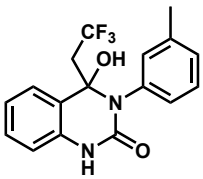
Hz, 1H), 4.49 (q, J = 10.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.21, 152.59, 141.86, 139.51, 135.50, 132.11, 131.97, 128.29 (q, J = 287 Hz), 121.64, 121.59, 120.98, 120.71, 114.18, 43.07 (q, J = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.89. HRMS (ESI): calcd. for $C_{16}H_{13}BrF_3N_2O_2$ $[M+H]^+$ 401.0107; found 401.0110.



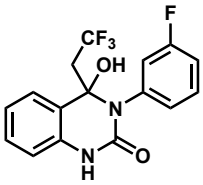
4-hydroxy-4-(2,2,2-trifluoroethyl)-3-(4-(trifluoromethyl)phenyl)-3,4-dihydroquinazolin-2(1H)-one (4ae): White solid; mp 212.9-222.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H), 10.32 (s, 1H), 8.43 (d, J = 8.6 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.73 (t, J = 9.0 Hz, 2H), 7.66 (d, J = 8.6 Hz, 2H), 7.51 – 7.21 (m, 1H), 7.19 – 7.07 (m, 1H), 4.51 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.27, 152.59, 142.73 (q, J = 226 Hz), 135.51, 132.13, 126.86, 126.50 (q, J = 3 Hz), 125.23 (q, J = 222 Hz), 123.65, 122.62 (q, J = 31 Hz), 121.89, 121.80, 120.82, 43.08 (q, J = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.17, -60.91. HRMS (ESI): calcd. for $C_{17}H_{13}F_6N_2O_2$ $[M+H]^+$ 391.0876; found 391.0870.



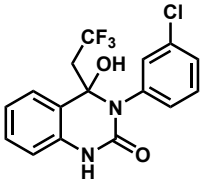
methyl 4-(4-hydroxy-2-oxo-4-(2,2,2-trifluoroethyl)-1,4-dihydroquinazolin-3(2H)-yl)benzoate (4af): White solid; mp 191.2-192.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 10.34 (s, 1H), 8.42 (dd, J = 8.6, 1.2 Hz, 1H), 8.02 (dd, J = 8.2, 1.6 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.72 – 7.59 (m, 3H), 7.20 – 7.13 (m, 1H), 4.52 (q, J = 10.7 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.26, 166.38, 152.49, 144.78, 141.57, 135.50, 132.13, 130.81, 125.51 (q, J = 274 Hz), 123.27, 121.89, 121.78, 120.85, 118.21, 52.28, 43.08 (q, J = 26 Hz).^{19}F NMR (376 MHz, DMSO-d_6) δ -60.90. HRMS (ESI): calcd. for $C_{18}H_{16}F_3N_2O_4$ $[M+H]^+$ 381.1057; found 381.1061.



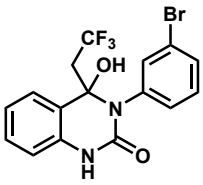
4-hydroxy-3-(m-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ah): White solid; mp 196.2-198.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.84 (s, 1H), 8.43 – 8.36 (m, 1H), 7.99 (dd, J = 8.1, 1.7 Hz, 1H), 7.61 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.37 (d, J = 2.1 Hz, 1H), 7.30 (d, J = 8.1 Hz, 1H), 7.20 – 7.08 (m, 2H), 6.81 (d, J = 7.4 Hz, 1H), 4.48 (q, J = 10.7 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.08, 152.71, 142.06, 139.98, 138.32, 135.40, 132.05, 129.04, 125.52 (q, J = 276 Hz), 123.43, 121.6, 121.44, 120.75, 119.70, 116.32, 43.07 (q, J = 28 Hz), 21.72.^{19}F NMR (376 MHz, DMSO-d_6) δ -60.87. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 337.1158; found 337.1162.



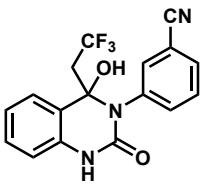
3-(3-fluorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ai): White solid; mp 187.1-192.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.13 (s, 1H), 8.48 – 8.36 (m, 1H), 8.03 – 7.95 (m, 1H), 7.72 – 7.59 (m, 1H), 7.57 – 7.44 (m, 1H), 7.36 – 7.27 (m, 1H), 7.25 – 7.20 (m, 1H), 7.17 – 7.10 (m, 1H), 6.84 – 6.76 (m, 1H), 4.50 (q, J = 10.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.24, 162.78 (d, J = 240 Hz), 152.61, 141.96 (d, J = 11 Hz), 141.76, 135.50, 132.11, 130.76 (d, J = 10 Hz), 125.50 (q, J = 275 Hz), 121.73, 121.68, 120.77, 114.75 (d, J = 3 Hz), 109.02 (d, J = 21 Hz), 105.73 (d, J = 26 Hz), 43.08 (q, J = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.90, -112.18. HRMS (ESI): calcd. for $C_{16}H_{13}F_4N_2O_2$ $[M+H]^+$ 341.0908; found 341.0912.



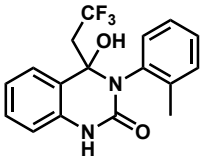
3-(3-chlorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4aj): White solid; mp 224.3-227.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.13 (s, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.00 (dd, J = 8.2, 1.5 Hz, 1H), 7.75 (t, J = 2.0 Hz, 1H), 7.63 (ddd, J = 8.6, 7.2, 1.5 Hz, 1H), 7.47 – 7.29 (m, 2H), 7.16 – 7.10 (m, 1H), 7.04 (dt, J = 7.8, 1.5 Hz, 1H), 4.50 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.25, 152.61, 141.69, 141.65, 141.53, 135.49, 133.60, 132.10, 130.86, 125.50 (q, J = 275 Hz), 122.31, 121.77, 120.76, 118.42, 117.40, 43.08 (q, J = 26 Hz).^{19}F NMR (376 MHz, DMSO-d_6) δ -60.89. HRMS (ESI): calcd. for $C_{16}H_{13}ClF_3N_2O_2$ $[M+H]^+$ 357.0612; found 357.0615.



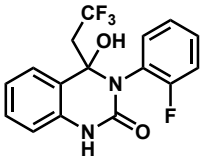
3-(3-bromophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ak): White solid; mp 222.0-225.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.10 (s, 1H), 8.45 – 8.36 (m, 1H), 8.01 (dd, J = 8.1, 1.6 Hz, 1H), 7.94 – 7.84 (m, 1H), 7.67 – 7.58 (m, 1H), 7.41 (dd, J = 8.2, 1.9 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.21 – 7.05 (m, 2H), 4.50 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.28, 152.58, 141.79, 141.74, 135.52, 132.13, 131.17, 125.50 (q, J = 275 Hz), 125.21, 122.12, 121.76, 121.66, 121.28, 120.73, 117.78, 43.08 (q, J = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.89. HRMS (ESI): calcd. for $C_{16}H_{13}BrF_3N_2O_2$ $[M+H]^+$ 401.0107; found 401.0103.



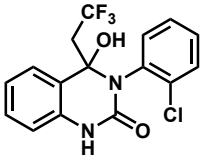
3-(4-hydroxy-2-oxo-4-(2,2,2-trifluoroethyl)-1,4-dihydroquinazolin-3(2H)-yl)benzonitrile (4al): White solid; mp 218.0-218.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 10.29 (s, 1H), 8.42 (dd, J = 8.6, 1.1 Hz, 1H), 8.05 – 7.98 (m, 2H), 7.73 (dt, J = 8.4, 1.6 Hz, 1H), 7.65 (ddd, J = 8.7, 7.2, 1.5 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.46 (dt, J = 7.7, 1.5 Hz, 1H), 7.19 – 7.14 (m, 1H), 4.52 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.37, 152.65, 141.59, 141.00, 135.57, 132.16, 130.68, 126.17, 125.50 (q, J = 275 Hz), 123.61, 121.90, 121.69, 121.57, 120.72, 119.34, 112.04, 43.08 (q, J = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.90. HRMS (ESI): calcd. for $C_{17}H_{13}F_3N_3O_2$ $[M+H]^+$ 348.0954; found 348.0959.



4-hydroxy-3-(o-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4am): White solid; mp 212.7-215.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 9.11 (s, 1H), 8.30 (dd, J = 8.6, 1.2 Hz, 1H), 7.96 (dd, J = 8.3, 1.5 Hz, 1H), 7.58 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.44 (dd, J = 8.2, 1.5 Hz, 1H), 7.20 (dd, J = 8.0, 1.7 Hz, 1H), 7.17 – 7.08 (m, 2H), 7.04 (td, J = 7.4, 1.3 Hz, 1H), 4.44 (q, J = 10.7 Hz, 2H), 2.24 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 194.71, 153.43, 141.88, 137.11, 135.16, 131.80, 131.67, 130.78, 125.50 (q, J = 275 Hz), 125.04, 124.89, 122.33, 121.48, 121.11, 43.10 (q, J = 27 Hz), 17.61.^{19}F NMR (376 MHz, DMSO-d_6) δ -60.86. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 337.1158; found 337.1166.

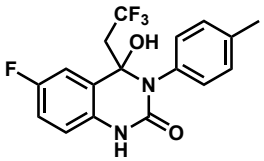


3-(2-fluorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4an): White solid; mp 221.4-226.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H), 9.72 (s, 1H), 8.26 – 8.17 (m, 1H), 7.97 (dd, J = 8.1, 1.6 Hz, 1H), 7.94 – 7.81 (m, 1H), 7.68 – 7.56 (m, 1H), 7.29 – 7.19 (m, 1H), 7.18 – 7.11 (m, 2H), 7.11 – 6.98 (m, 1H), 4.45 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.51, 153.87 (d, J = 242 Hz), 152.97, 141.00, 135.00, 131.67, 127.28 (d, J = 11 Hz), 125.50 (q, J = 274 Hz), 124.83 (d, J = 4 Hz), 124.41 (d, J = 7 Hz), 123.62, 123.12, 122.00, 121.68, 115.81 (d, J = 19 Hz), 43.17 (q, J = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.90, -126.28. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 341.0908; found 341.0905.

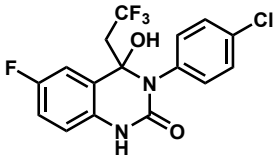


3-(2-chlorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4ao): White solid; mp 220.9-223.8 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 9.43 (s, 1H), 8.17 (dd, J = 8.5, 1.2 Hz, 1H), 7.95 (dd, J = 8.0, 1.6 Hz, 1H), 7.79 (dt, J = 8.2, 1.3 Hz, 1H), 7.60 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.31 (td, J = 7.7, 1.5 Hz, 1H), 7.14 (dtd, J = 9.6, 7.8, 1.4 Hz, 2H), 4.44 (q, J = 10.8 Hz, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 194.39, 153.17, 140.74, 135.99, 134.86, 131.47,

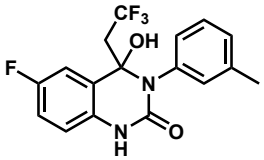
129.91, 129.61, 128.62, 127.86, 125.99, 125.56, 125.48 (q, J = 274Hz), 123.71, 122.15, 121.86, 43.15 (q, J = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.89. HRMS (ESI): calcd. for $C_{16}H_{13}ClF_3N_2O_2$ $[M+H]^+$ 357.0612; found 357.0617.



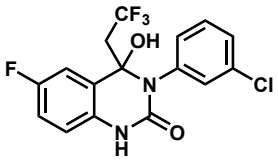
6-fluoro-4-hydroxy-3-(p-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4at): White solid; mp 217.5-218.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.77 (s, 1H), 8.36 (dd, J = 9.4, 5.2 Hz, 1H), 7.85 (dd, J = 9.9, 3.0 Hz, 1H), 7.54 – 7.45 (m, 1H), 7.42 – 7.37 (m, 2H), 7.13 – 7.05 (m, 2H), 4.49 (q, J = 10.6 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.17, 162.39, 156.24 (d, J = 238 Hz), 152.81, 138.26, 137.40, 131.59, 129.61, 125.45 (q, J = 303 Hz), 123.17 (d, J = 7.5 Hz), 122.37 (d, J = 22.5 Hz), 119.22, 117.42 (d, J = 24 Hz), 43.24 (q, J = 36 Hz), 20.82. ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.02, -121.29. HRMS (ESI): calcd. for $C_{17}H_{15}F_4N_2O_2$ $[M+H]^+$ 355.1064; found 355.1061.



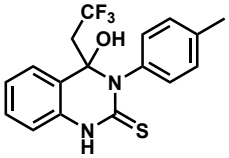
3-(4-chlorophenyl)-6-fluoro-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4au): White solid; mp 206.3-206.7 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 10.02 (s, 1H), 8.36 (dd, J = 9.4, 5.2 Hz, 1H), 7.87 (dd, J = 9.9, 3.0 Hz, 1H), 7.57 – 7.51 (m, 3H), 7.36 – 7.33 (m, 2H), 4.50 (q, J = 10.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.32, 156.38 (d, J = 238 Hz), 152.70, 139.01, 137.93 (d, J = 2 Hz), 129.10, 128.79, 126.27, 125.75 (q, J = 193 Hz), 123.16 (d, J = 7 Hz), 122.43 (d, J = 23 Hz), 120.54, 117.53 (d, J = 23 Hz), 43.28 (q, J = 17 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.03, -120.89. HRMS (ESI): calcd. for $C_{16}H_{12}ClF_4N_2O_2$ $[M+H]^+$ 375.0518 found 375.0521.



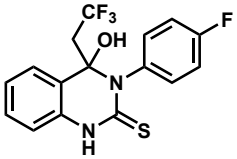
6-fluoro-4-hydroxy-3-(m-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4av): White solid; mp 214.5-216.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 9.81 (s, 1H), 8.36 (dd, J = 9.4, 5.2 Hz, 1H), 7.85 (dd, J = 9.9, 3.0 Hz, 1H), 7.52 (ddd, J = 9.3, 7.8, 3.1 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 7.4 Hz, 1H), 4.49 (q, J = 10.7 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 194.16, 156.28 (d, J = 238 Hz), 152.79, 139.92, 138.35, 138.14, 129.05, 125.36 (q, J = 275 Hz), 123.46, 123.21 (d, J = 7.5 Hz), 122.35 (d, J = 21 Hz), 119.69, 117.43 (d, J = 24 Hz), 116.31, 43.28 (q, J = 27 Hz), 20.77. ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.02, -121.18. HRMS (ESI): calcd. for $C_{17}H_{15}F_4N_2O_2$ $[M+H]^+$ 355.1064 found 355.1069.



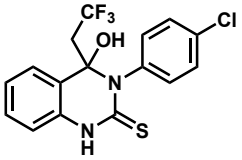
3-(3-chlorophenyl)-6-fluoro-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazolin-2(1H)-one (4aw): White solid; mp 204.2-204.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 10.09 (s, 1H), 8.36 (dd, J = 9.4, 5.2 Hz, 1H), 7.87 (dd, J = 9.9, 3.0 Hz, 1H), 7.74 (t, J = 2.0 Hz, 1H), 7.58 – 7.50 (m, 1H), 7.38 – 7.28 (m, 2H), 7.05 (dt, J = 7.4, 1.8 Hz, 1H), 4.50 (q, J = 10.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.35, 156.46 (d, J = 238 Hz), 152.68, 141.58, 137.76 (d, J = 2 Hz), 133.61, 130.88, 125.34 (q, J = 275 Hz), 123.22 (d, J = 8 Hz), 122.53, 122.32, 118.39, 117.55 (d, J = 24 Hz), 117.37, 43.29 (q, J = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -61.04, -120.72. HRMS (ESI): calcd. for $C_{16}H_{12}ClF_4N_2O_2$ $[M+H]^+$ 375.0518 found 375.0515.



4-hydroxy-3-(p-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6aa): White solid; mp 211.3-214.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H), 9.78 (s, 1H), 8.41 (dd, J = 8.6, 1.2 Hz, 1H), 7.99 (dd, J = 8.2, 1.6 Hz, 1H), 7.61 (ddd, J = 8.6, 7.1, 1.6 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.15 – 7.06 (m, 3H), 4.47 (q, J = 10.7 Hz, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.00, 152.75, 142.18, 137.45, 135.39, 132.03, 131.59, 129.58, 125.56 (q, J = 275 Hz), 121.60, 121.35, 120.73, 119.30, 43.07 (q, J = 26 Hz), 20.82. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.86. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2OS$ $[M+H]^+$ 353.0930; found 353.0935.

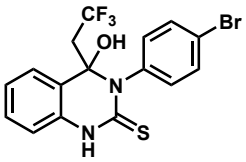


3-(4-fluorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6ab): White solid; mp 219.1-222.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 9.95 (s, 1H), 8.45 – 8.39 (m, 1H), 8.02 – 7.94 (m, 2H), 7.77 – 7.70 (m, 1H), 7.65 – 7.60 (m, 1H), 7.53 – 7.50 (m, 1H), 7.28 – 7.18 (m, 1H), 7.11 (dd, J = 6.0, 1.9 Hz, 1H), 4.50 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.20, 158.03 (d, J = 237 Hz), 152.76, 142.11, 136.37 (d, J = 3 Hz), 135.50, 129.73, 129.03, 125.51 (q, J = 274 Hz), 121.46, 120.83 (d, J = 8 Hz), 120.63, 115.74 (d, J = 22 Hz), 43.06 (q, J = 25 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.87, -120.89. HRMS (ESI): calcd. for $C_{16}H_{13}F_4N_2OS$ $[M+H]^+$ 357.0679; found 357.0677.

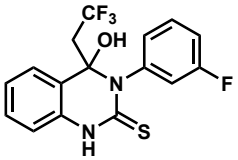


3-(4-chlorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6ac): White solid; mp 212.6-215.0 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.05 (s, 1H), 8.42

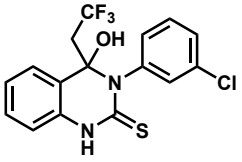
(dd, J = 8.6, 1.8 Hz, 1H), 8.02 (d, J = 1.5 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.58 – 7.52 (m, 2H), 7.38 – 7.33 (m, 2H), 7.16 – 7.10 (m, 1H), 4.50 (q, J = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.24, 152.62, 141.88, 139.08, 137.36, 135.51, 132.12, 129.73, 129.09, 125.51 (q, *J* = 274 Hz), 121.63, 121.04, 120.58, 43.07 (q, *J* = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.87. HRMS (ESI): calcd. for $C_{16}H_{13}ClF_3N_2OS$ $[M+H]^+$ 373.0384; found 373.0387.



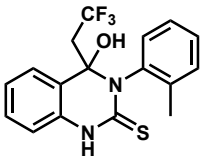
3-(4-bromophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6ad): White solid; mp 215.4-220.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 10.04 (s, 1H), 8.41 (dd, *J* = 8.5, 1.3 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.67 – 7.58 (m, 2H), 7.48 (d, *J* = 2.1 Hz, 3H), 7.17 – 7.09 (m, 1H), 4.49 (q, *J* = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.24, 152.59, 141.87, 139.51, 135.51, 132.12, 129.73, 129.04, 125.50 (q, *J* = 273 Hz), 121.64, 120.98, 120.71, 114.19, 43.09 (q, *J* = 27 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.88. HRMS (ESI): calcd. for $C_{16}H_{13}BrF_3N_2OS$ $[M+H]^+$ 416.9879; found 416.9875.



3-(3-fluorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6ae): White solid; mp 189.9-192.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.14 (s, 1H), 8.44 – 8.38 (m, 1H), 7.97 – 7.93 (m, 1H), 7.67 – 7.59 (m, 2H), 7.56 – 7.52 (m, 1H), 7.36 – 7.28 (m, 1H), 7.18 – 7.11 (m, 1H), 6.85 – 6.77 (m, 1H), 4.50 (q, *J* = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.25, 162.77 (d, *J* = 239 Hz), 152.61, 141.95 (d, *J* = 12 Hz), 141.73, 135.51, 133.34, 132.10, 131.20, 130.77 (d, *J* = 9 Hz), 125.50 (q, *J* = 275 Hz), 121.76, 120.78, 114.76 (d, *J* = 2 Hz), 109.04 (d, *J* = 21 Hz), 105.73 (d, *J* = 23 Hz), 43.08 (q, *J* = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.88, -112.16. HRMS (ESI): calcd. for $C_{16}H_{13}F_4N_2OS$ $[M+H]^+$ 357.0679; found 353.0677.



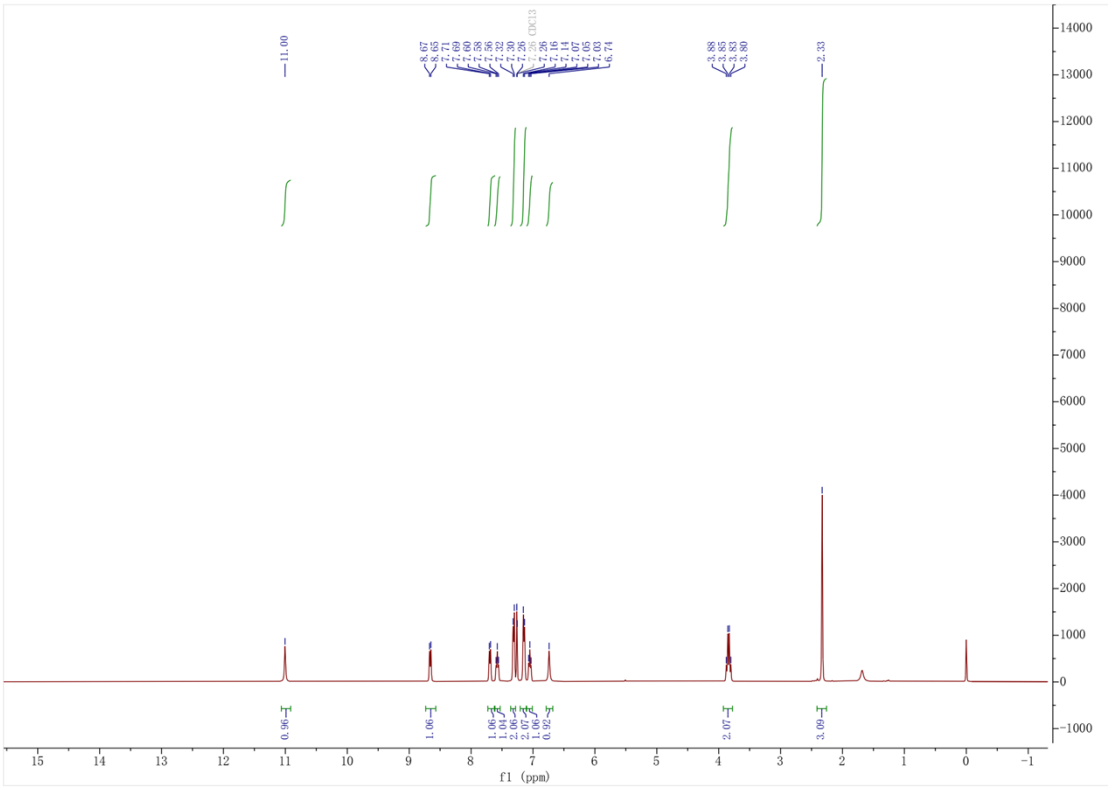
3-(3-chlorophenyl)-4-hydroxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6af): White solid; mp 224.1-227.4 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H), 10.10 (s, 1H), 8.40 (d, *J* = 8.5 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.38 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.05 (dd, *J* = 7.7, 2.1 Hz, 1H), 4.49 (q, *J* = 10.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.22, 152.60, 141.76, 141.65, 137.34, 135.51, 133.62, 132.89, 132.10, 125.48 (q, *J* = 275 Hz), 122.31, 121.74, 120.74, 118.45, 117.40, 43.08 (q, *J* = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.86. HRMS (ESI): calcd. for $C_{16}H_{13}ClF_3N_2OS$ $[M+H]^+$ 373.0384; found 373.0388.



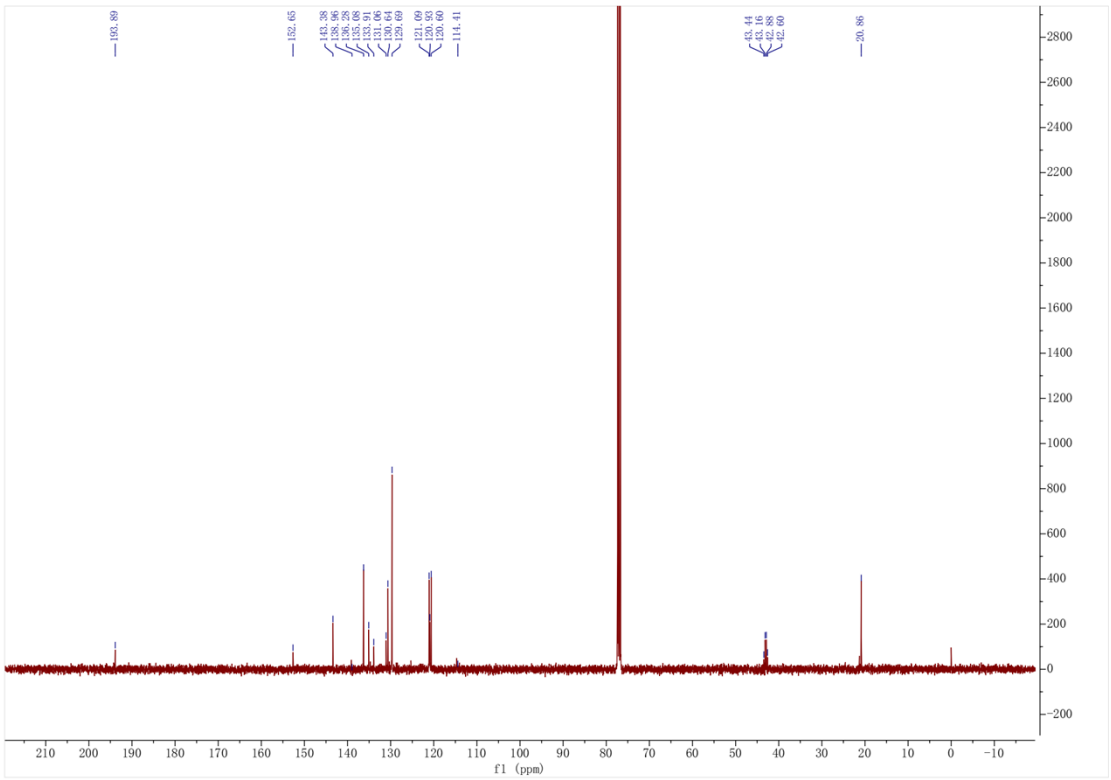
4-hydroxy-3-(o-tolyl)-4-(2,2,2-trifluoroethyl)-3,4-dihydroquinazoline-2(1H)-thione (6ag): White solid; mp 221.5-224.1 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.13 (s, 1H), 8.35 – 8.29 (m, 1H), 7.98 (dd, J = 8.1, 1.6 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.46 (dd, J = 8.0, 1.5 Hz, 1H), 7.22 (dd, J = 7.5, 1.6 Hz, 1H), 7.19 – 7.02 (m, 3H), 4.46 (q, J = 10.7 Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.74 (q, J = 2 Hz), 153.42, 141.94, 137.10, 135.19, 131.83, 131.70, 130.78, 126.48, 125.74 (q, J = 275 Hz), 125.07, 124.90, 122.22 (q, J = 2 Hz), 121.44, 121.09, 43.59, 42.83 (q, J = 26 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.87. HRMS (ESI): calcd. for $C_{17}H_{16}F_3N_2OS$ $[M+H]^+$ 353.0930; found 353.0933.

5.Copies of all NMR spectra

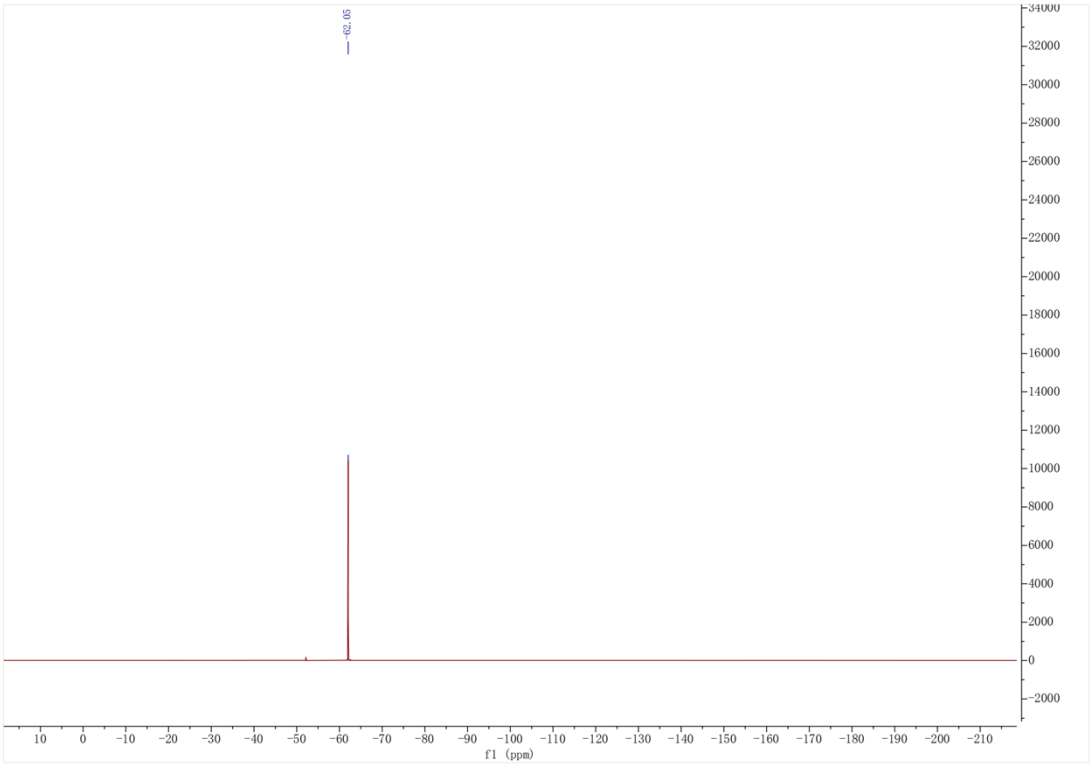
^{1}H NMR (400 MHz, $CDCl_3$) of **4aa**



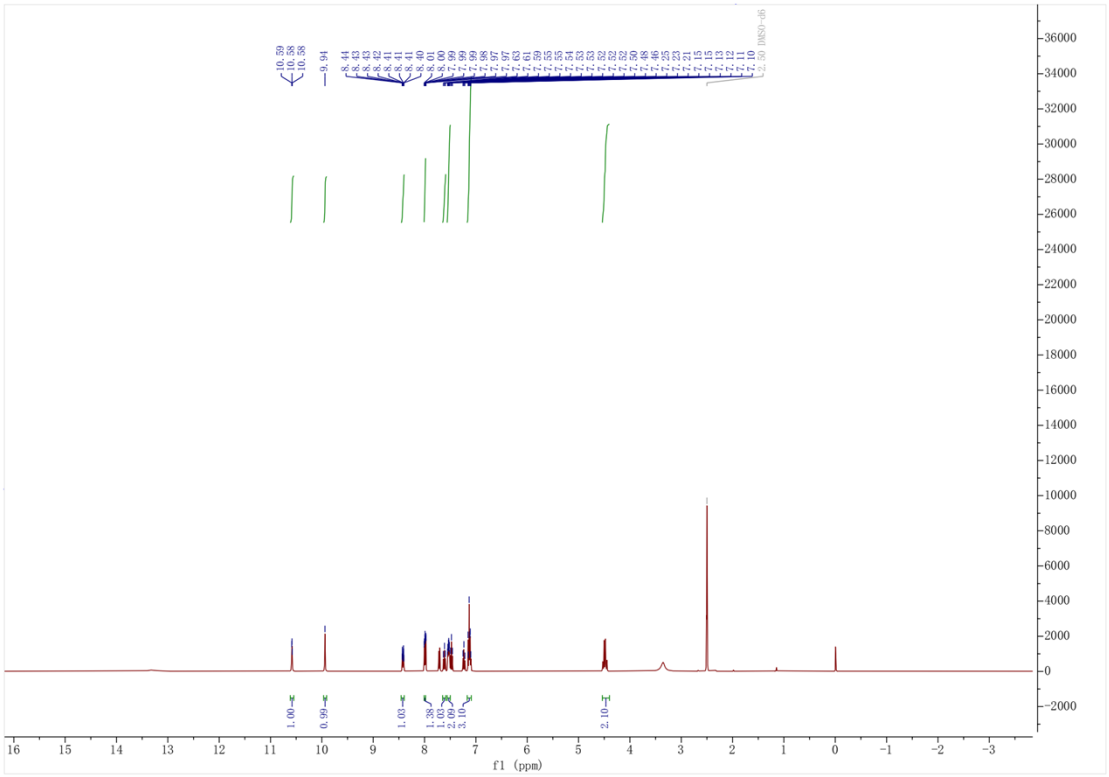
^{13}C NMR (100 MHz, $CDCl_3$) of **4aa**



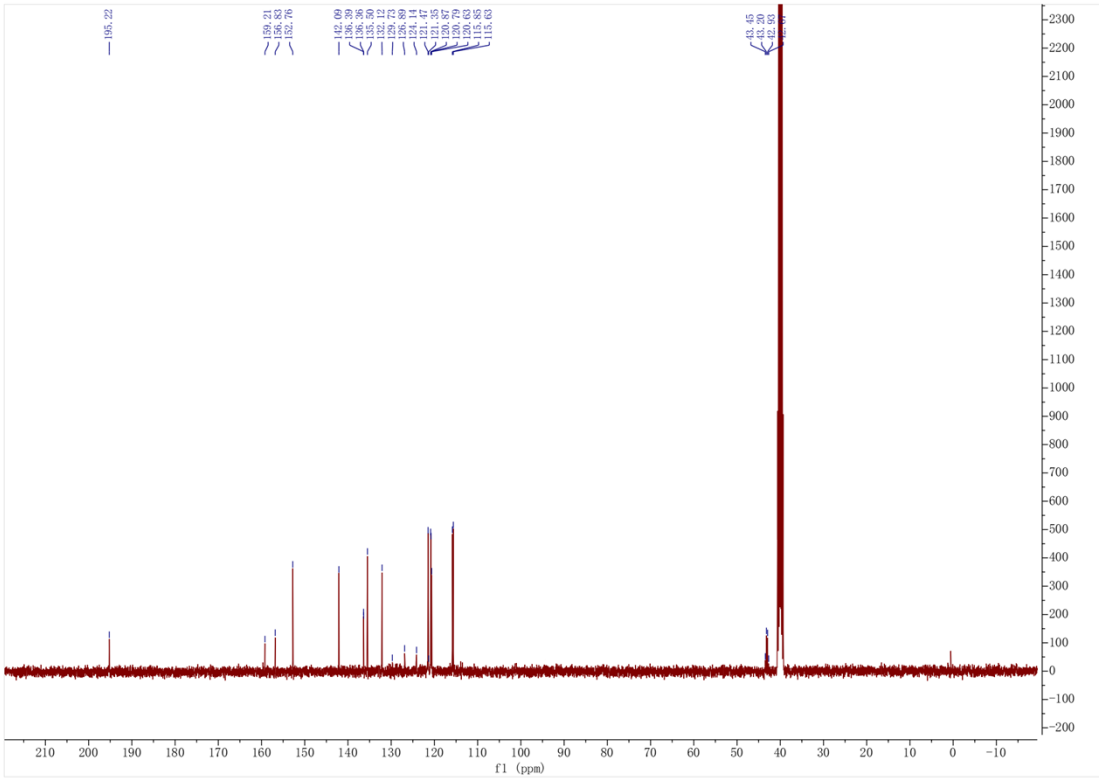
^{19}F NMR (376 MHz, $CDCl_3$) of **4aa**



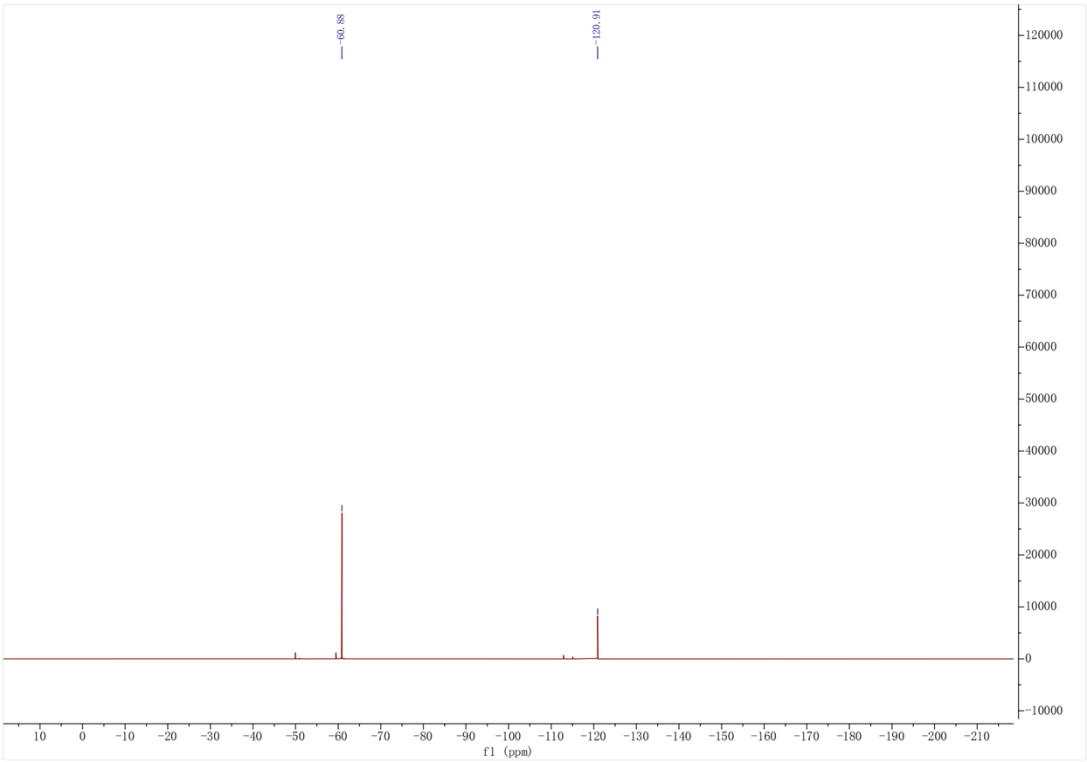
^{1}H NMR (400 MHz, DMSO-d_6) of **4ab**



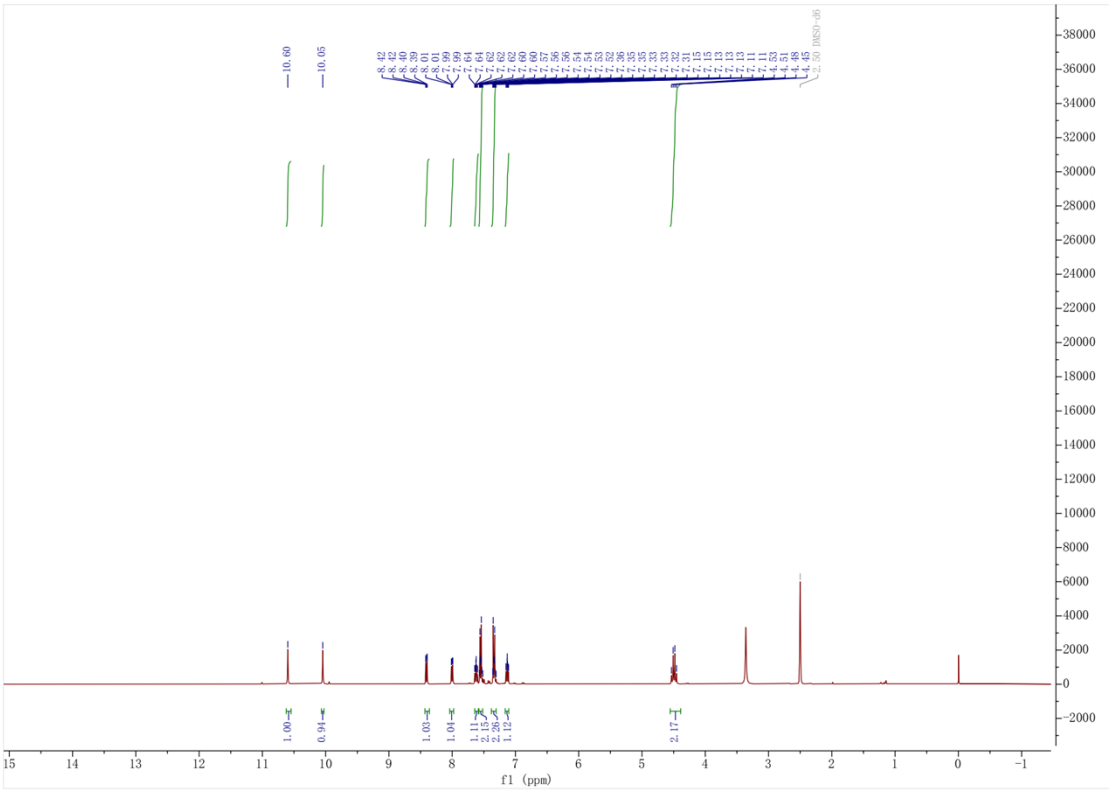
^{13}C NMR (100 MHz, DMSO-d_6) of **4ab**



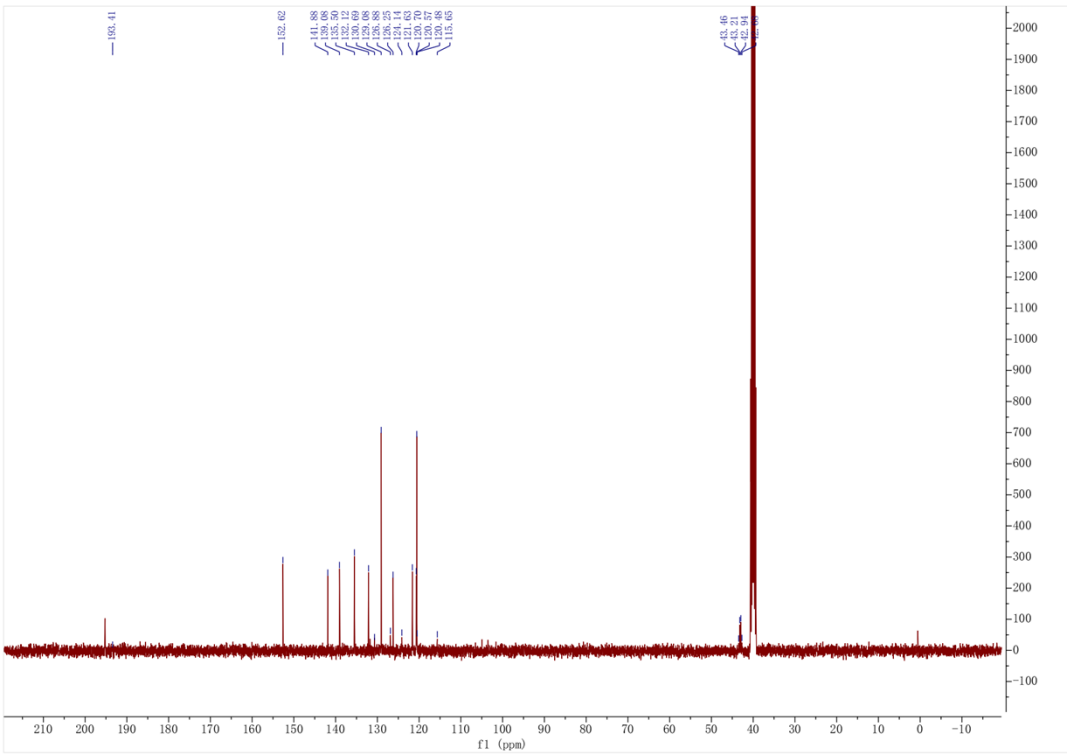
^{19}F NMR (376 MHz, DMSO-d_6) of **4ab**



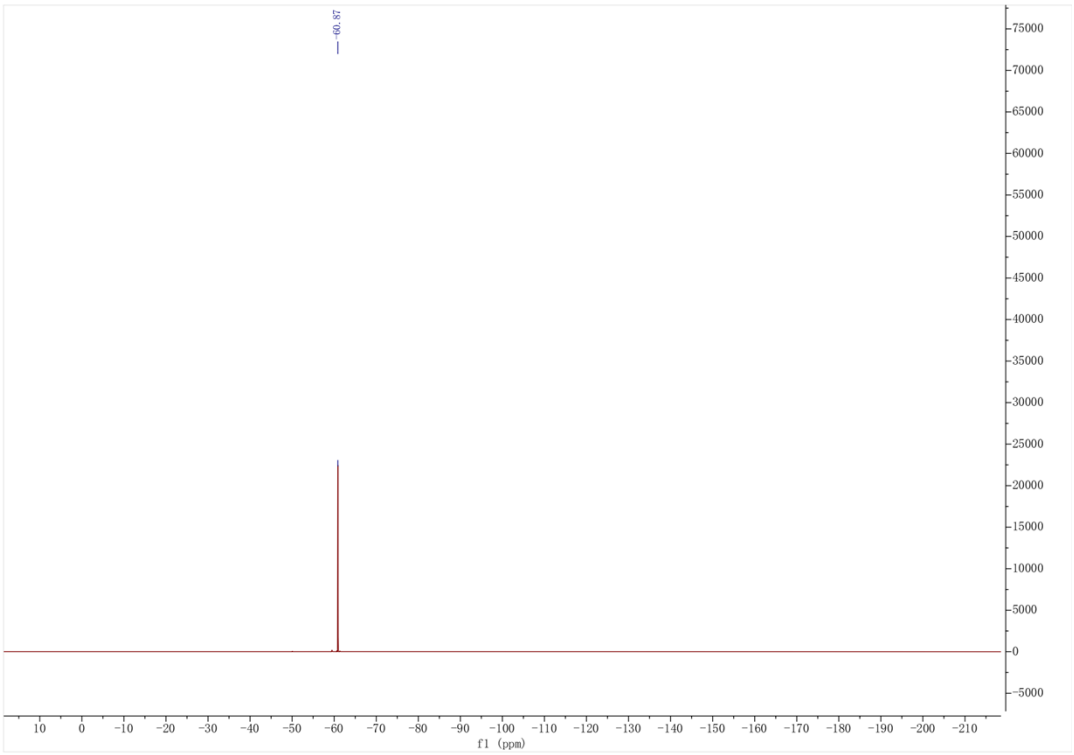
^{1}H NMR (400 MHz, DMSO-d_6) of **4ac**



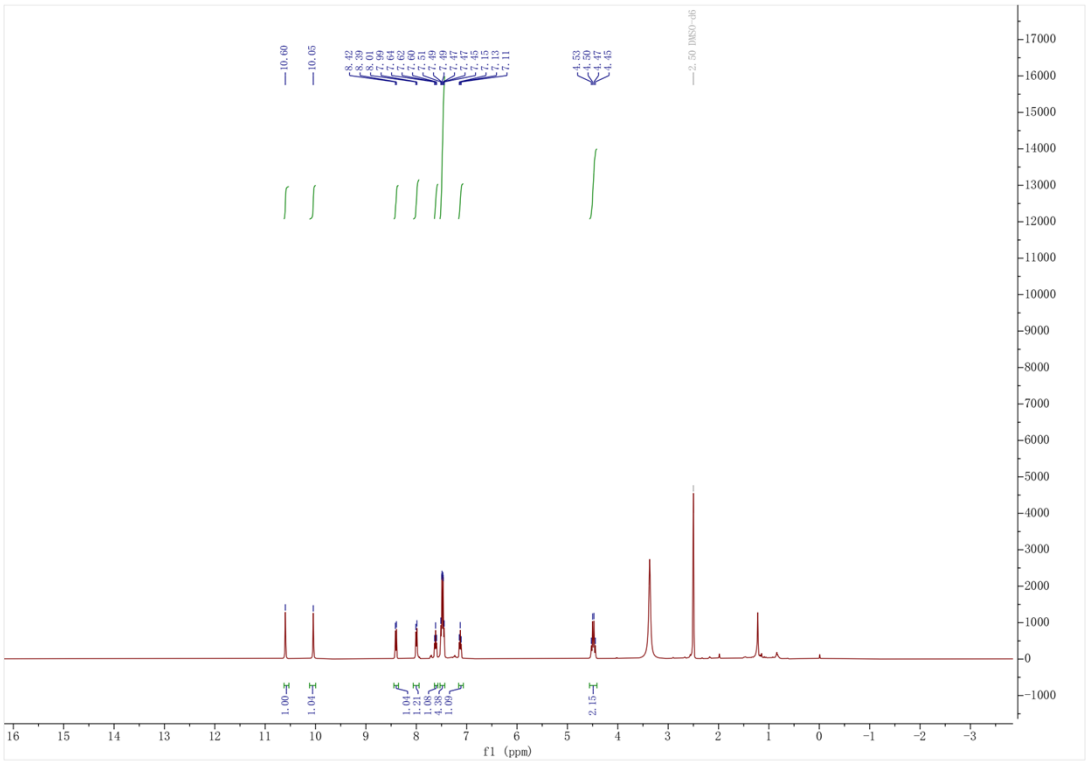
^{13}C NMR (100 MHz, DMSO-d_6) of **4ac**



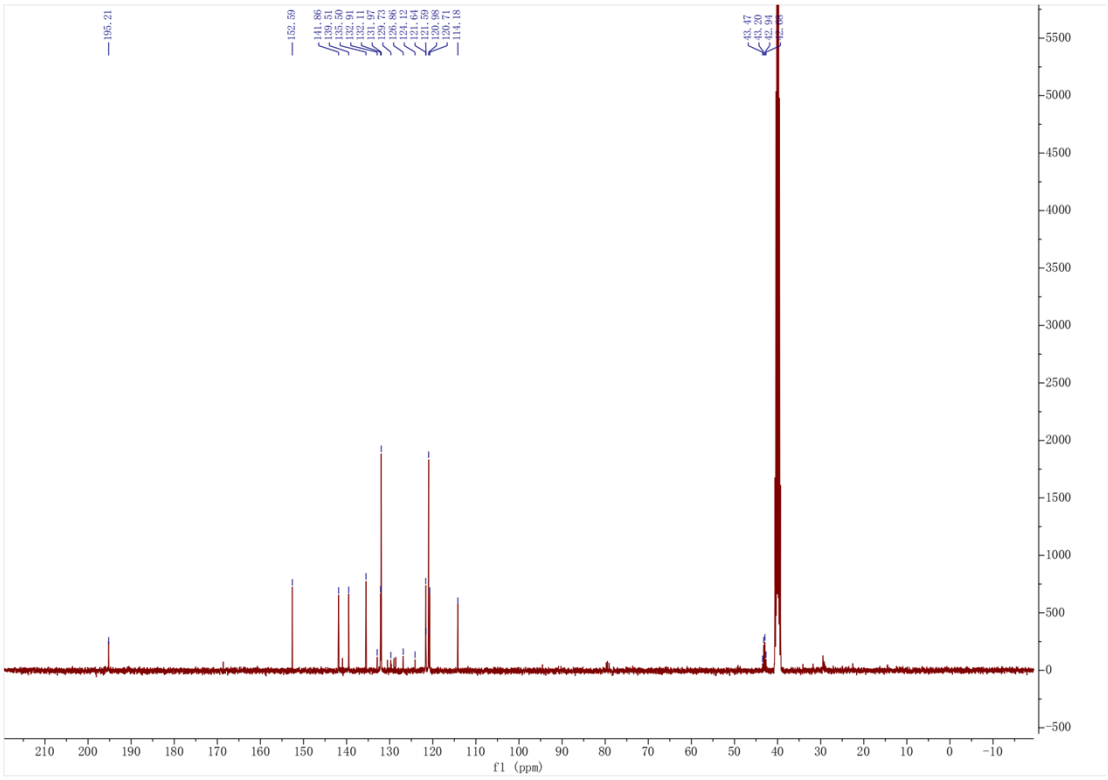
^{19}F NMR (376 MHz, DMSO-d_6) of **4ac**



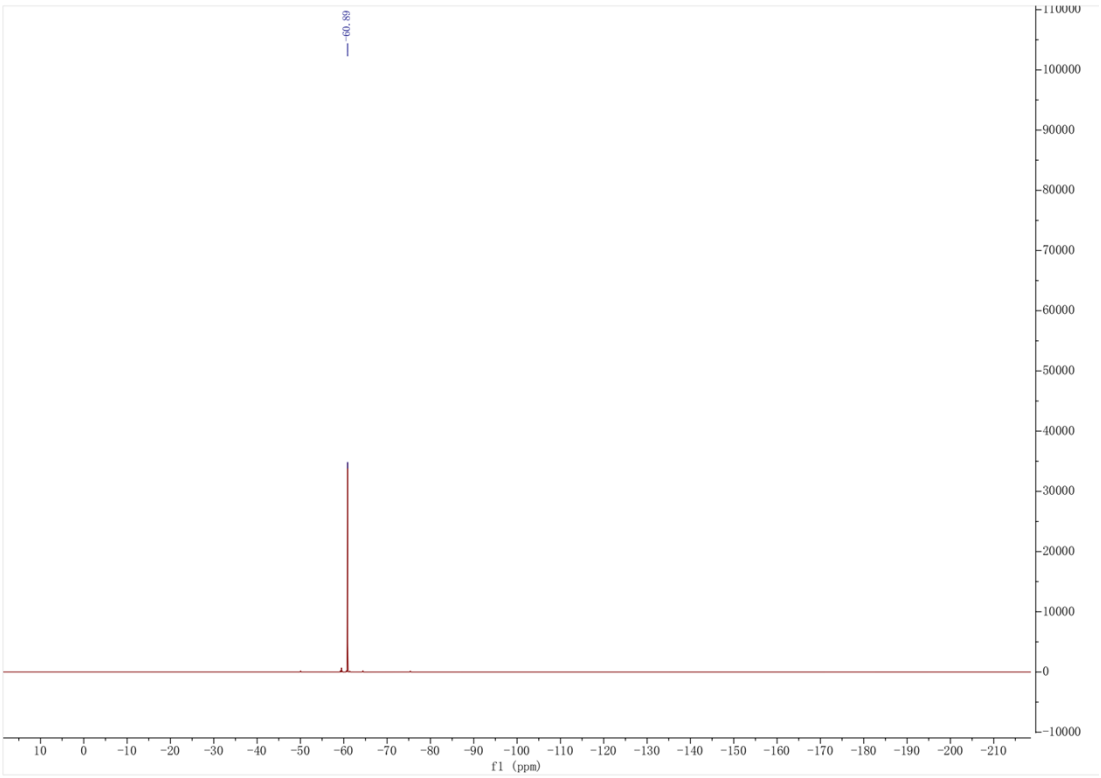
^{1}H NMR (400 MHz, DMSO-d_6) of **4ad**



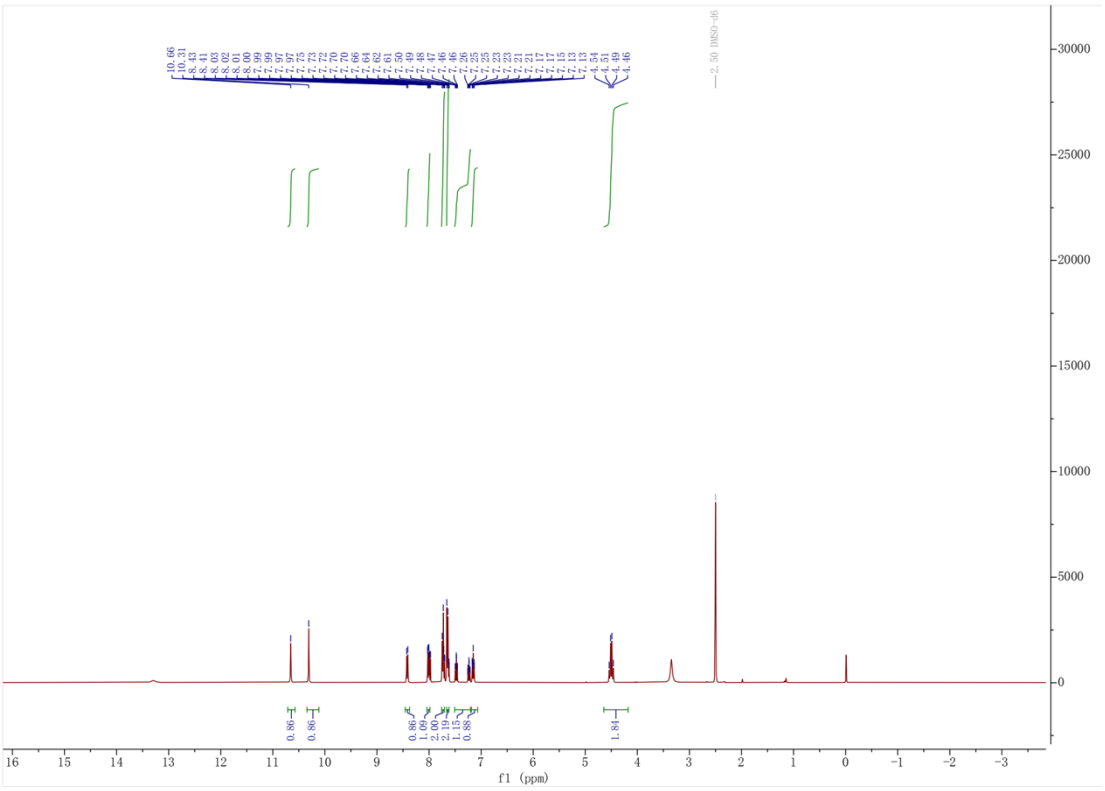
^{13}C NMR (100 MHz, DMSO-d_6) of **4ad**



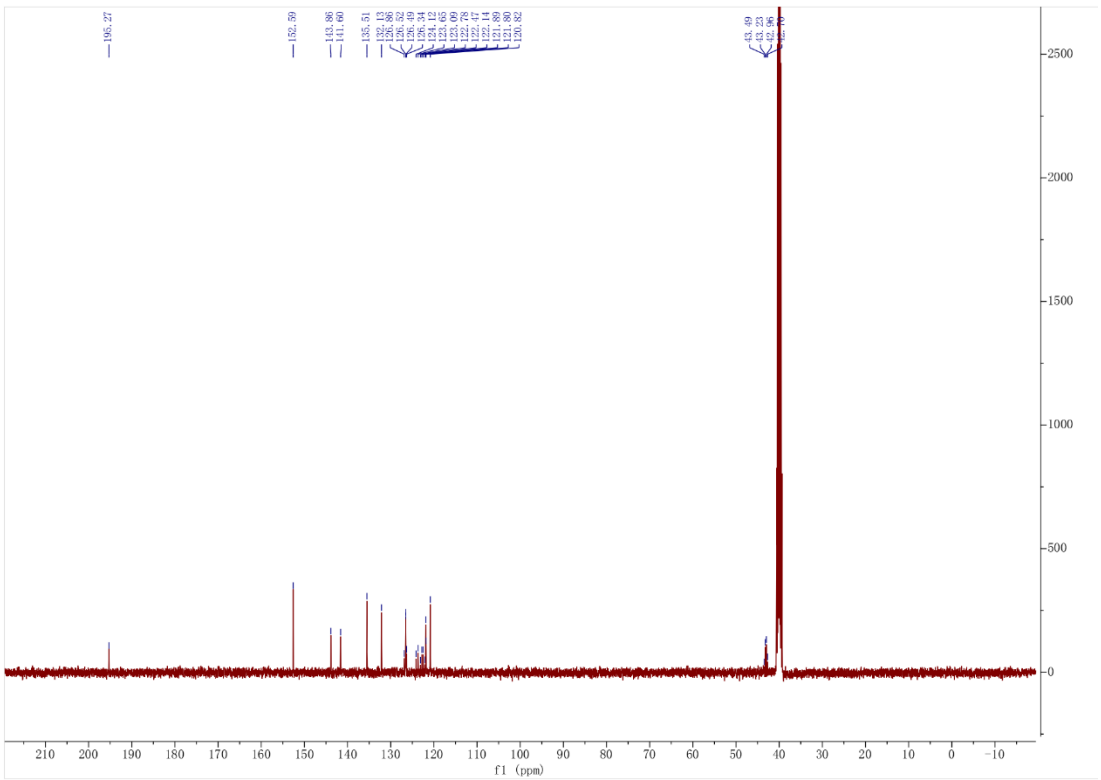
^{19}F NMR (376 MHz, DMSO-d_6) of **4ad**



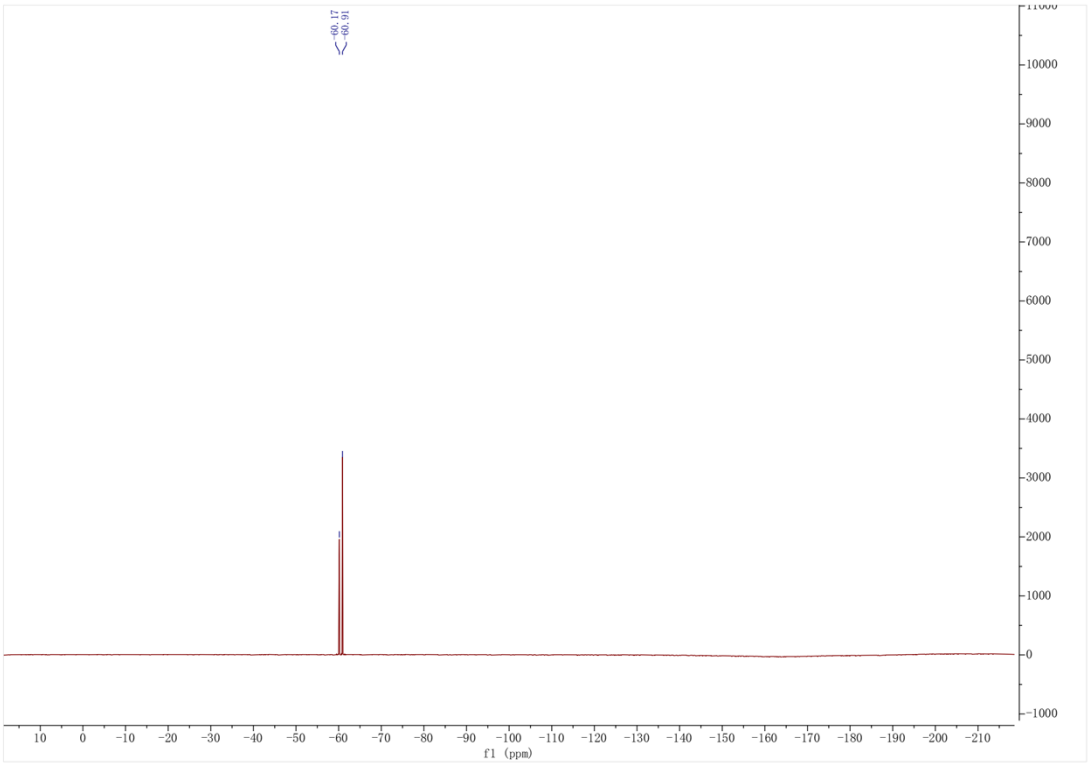
^{1}H NMR (400 MHz, DMSO-d_6) of **4ae**



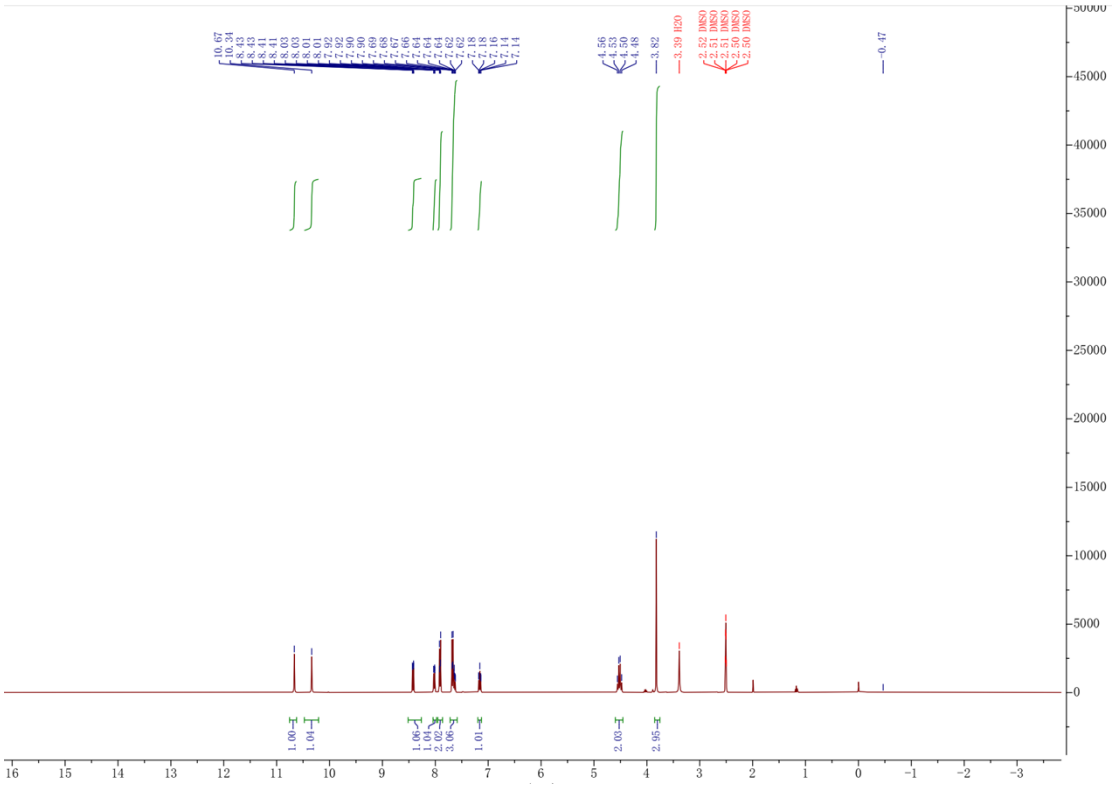
^{13}C NMR (100 MHz, DMSO-d_6) of **4ae**



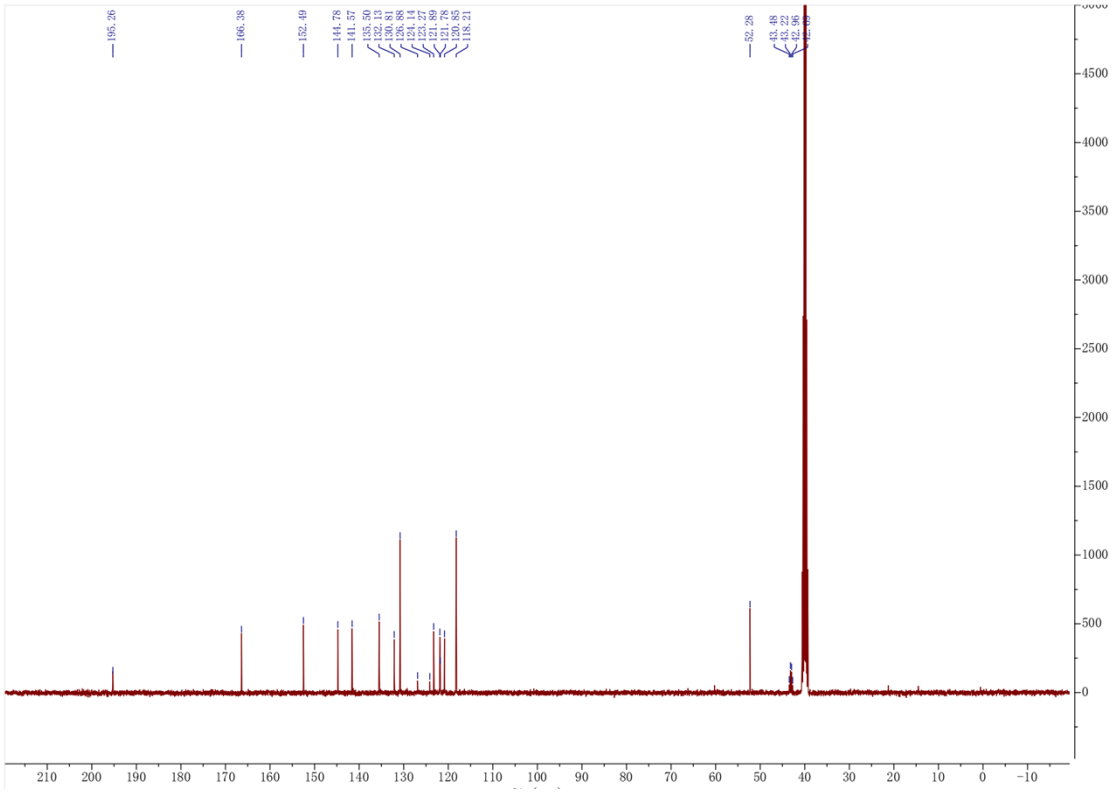
^{19}F NMR (376 MHz, DMSO-d_6) of **4ae**



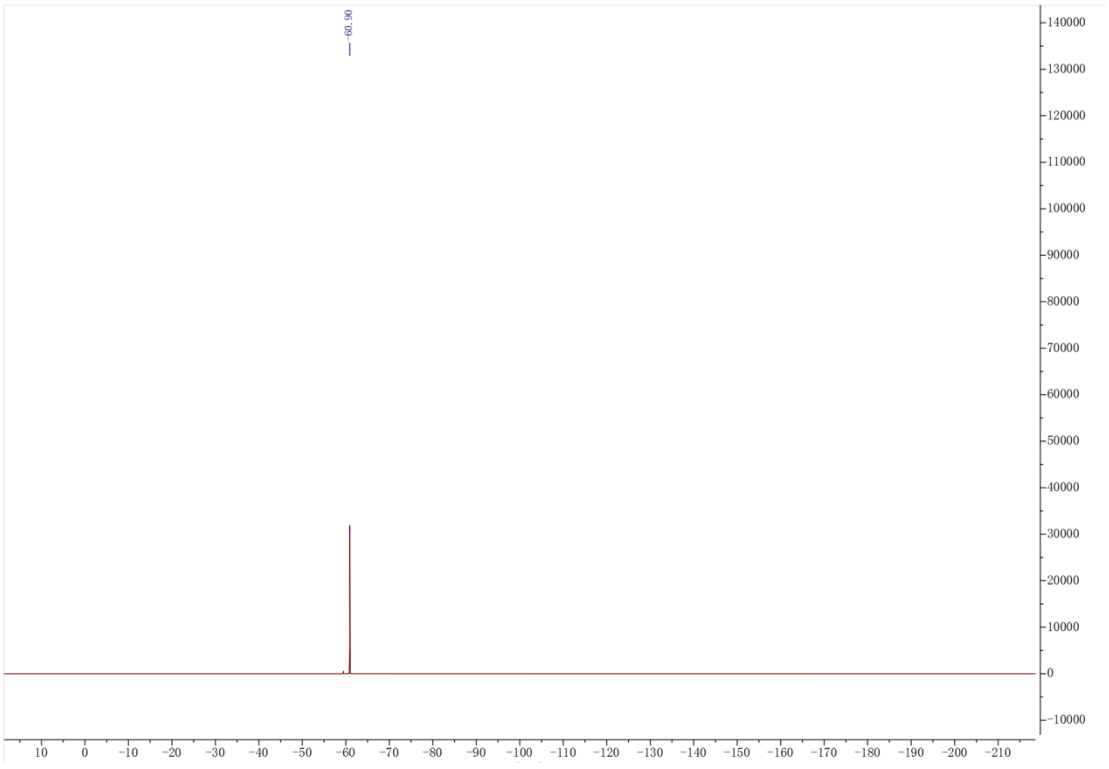
^{1}H NMR (400 MHz, DMSO-d_6) of **4af**



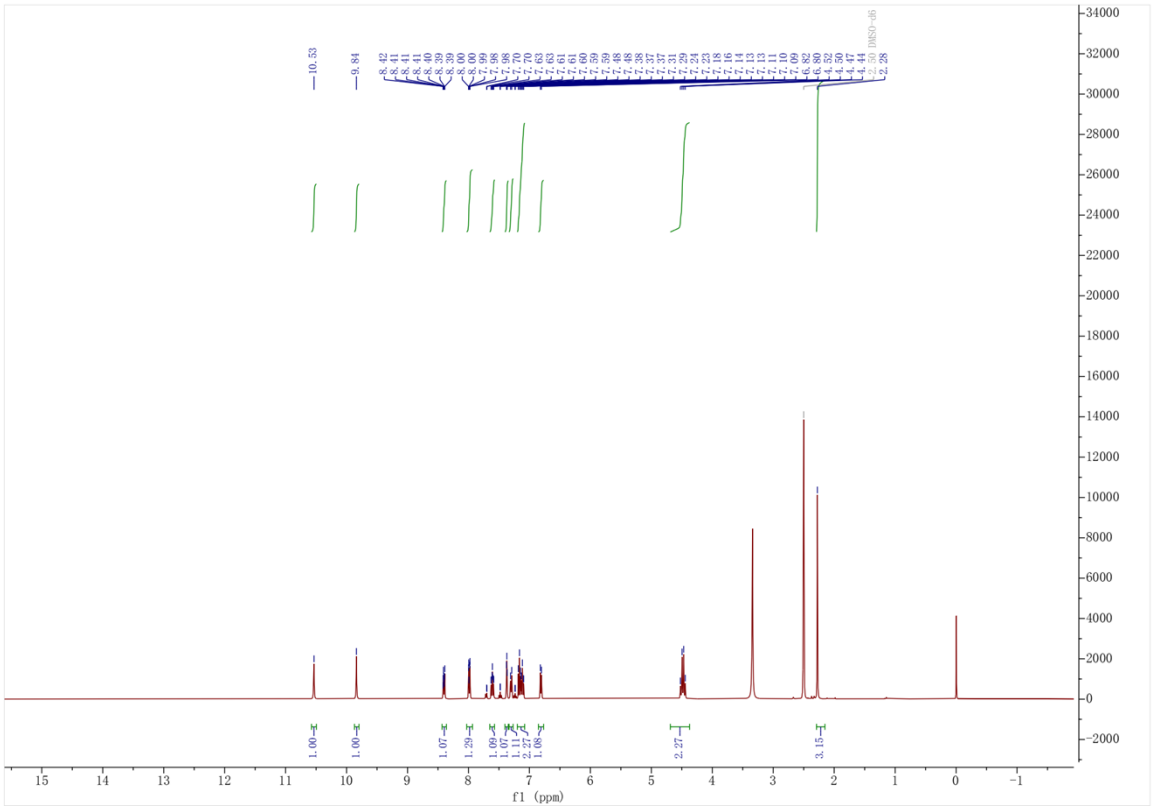
^{13}C NMR (100 MHz, DMSO-d_6) of **4af**



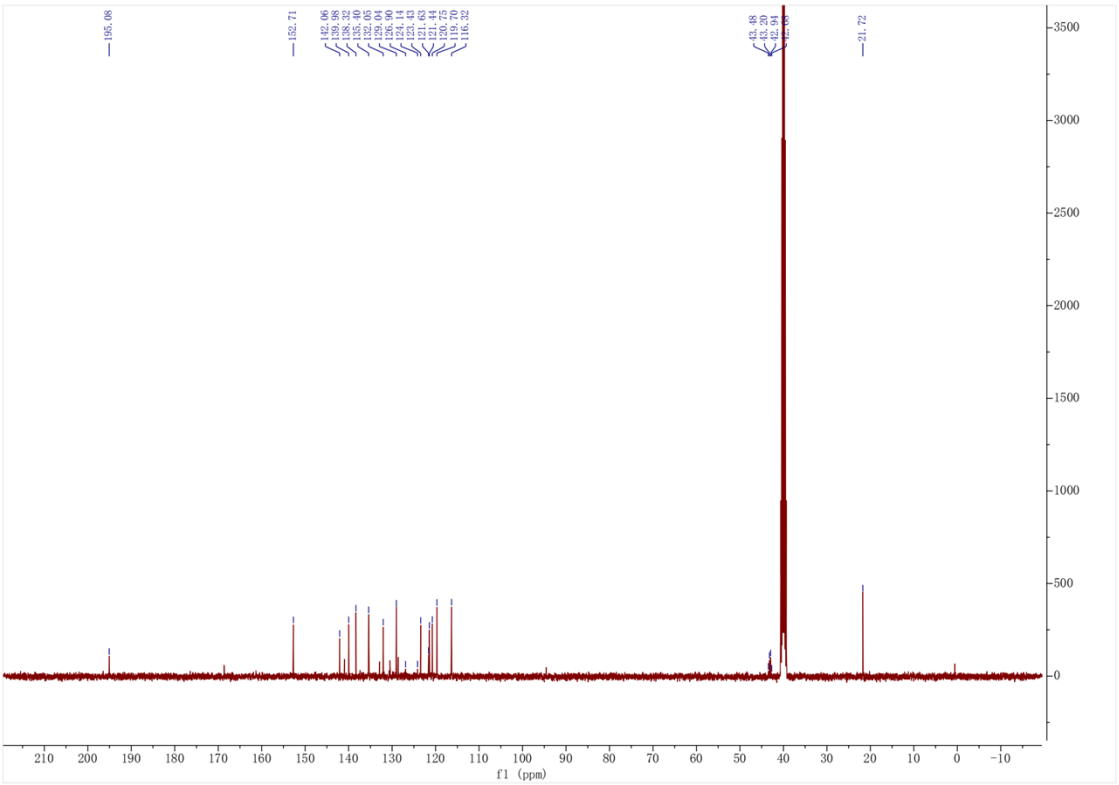
^{19}F NMR (400 MHz, DMSO-d_6) of **4af**



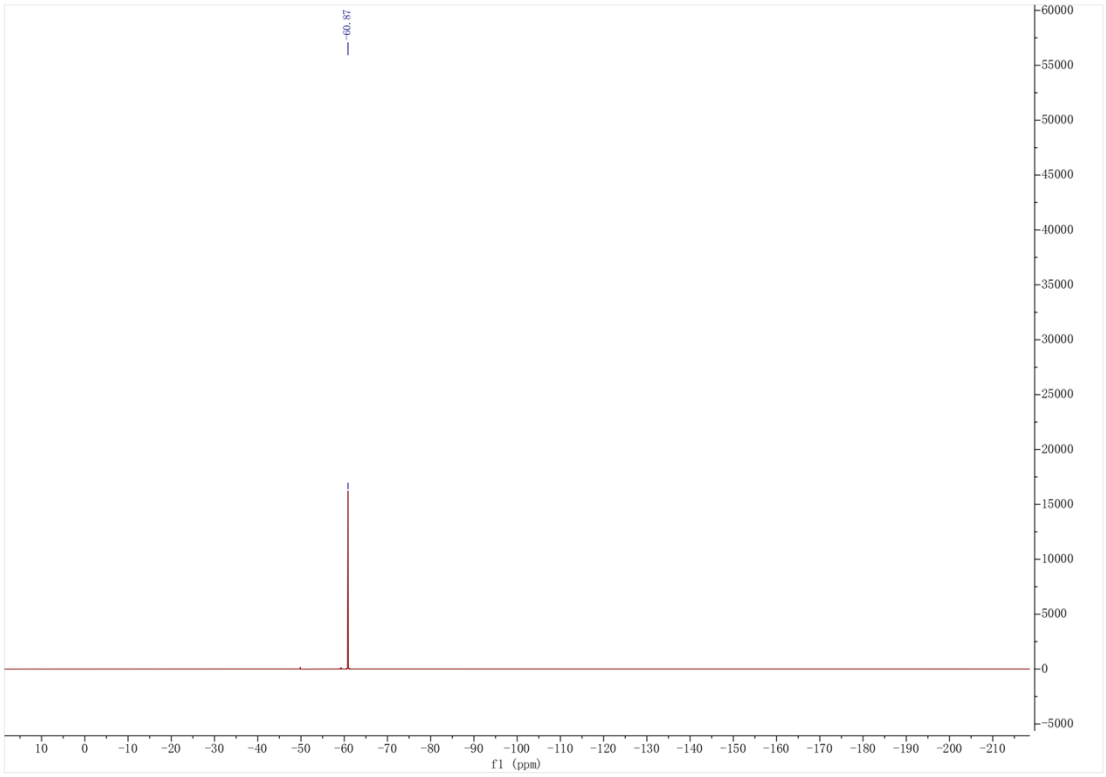
^{1}H NMR (400 MHz, DMSO-d_6) of **4ah**



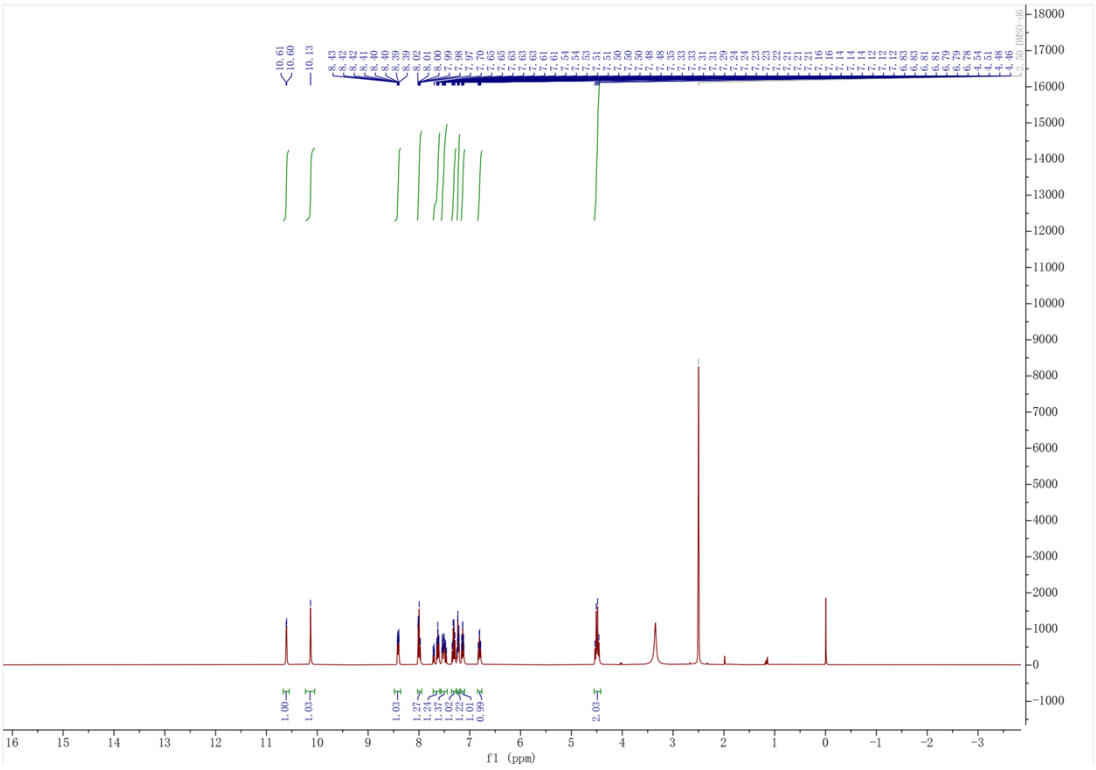
^{19}F NMR (400 MHz, DMSO-d_6) of **4ah**



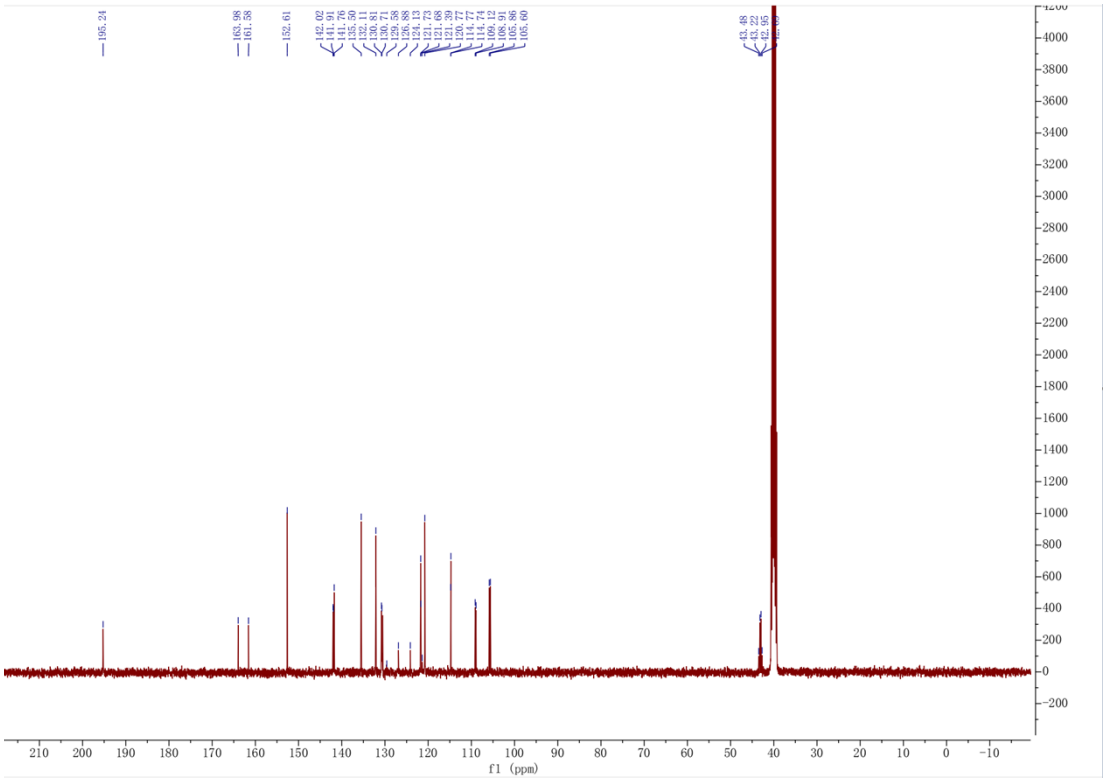
^{19}F NMR (376 MHz, DMSO-d_6) of **4ah**



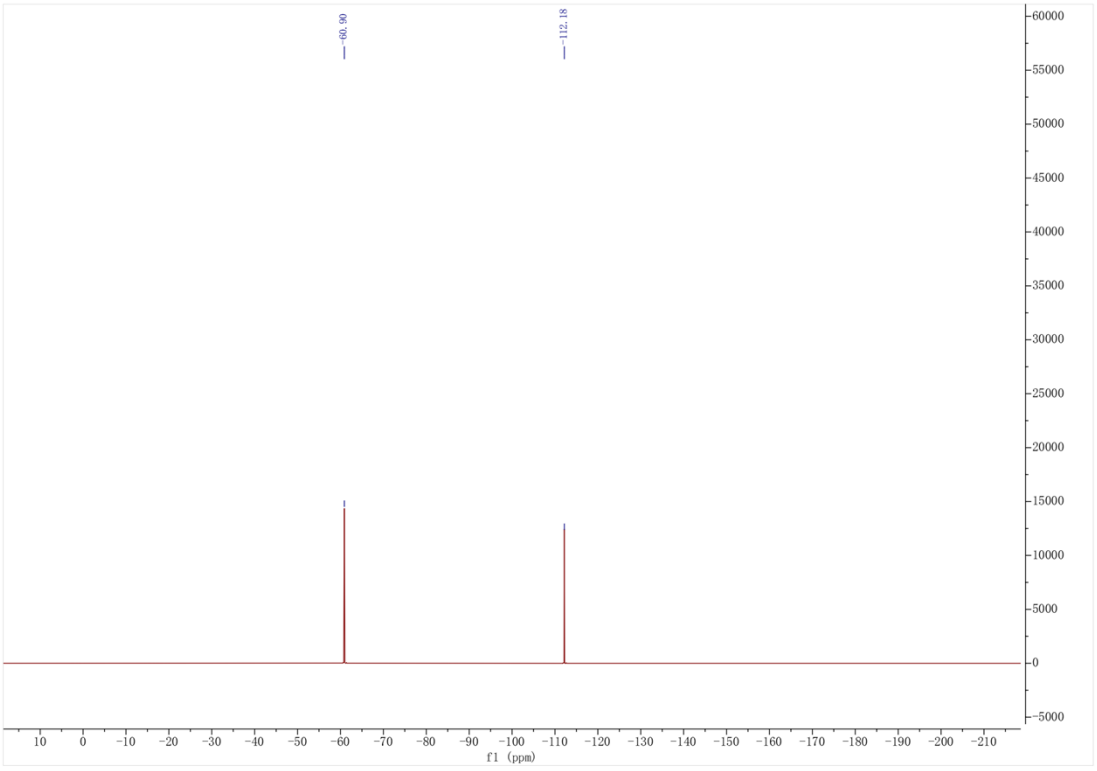
^{1}H NMR (400 MHz, DMSO-d_6) of **4ai**



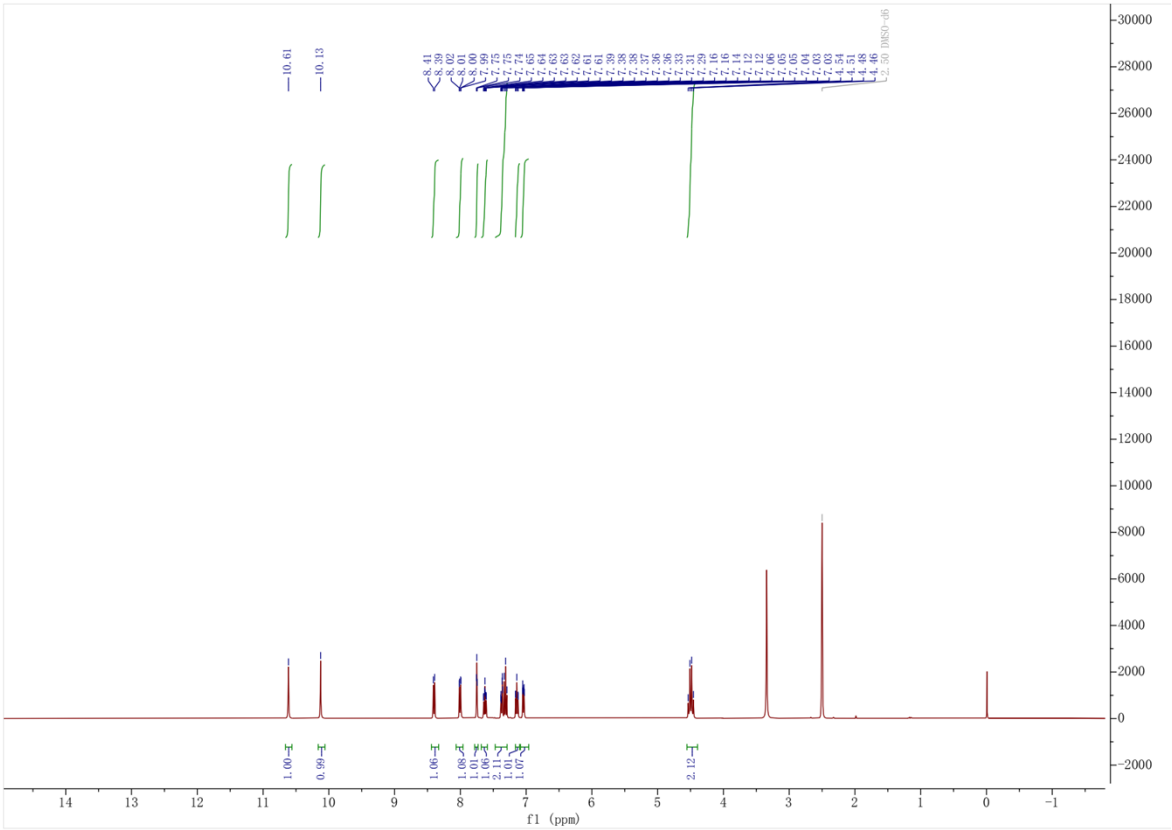
^{13}C NMR (100 MHz, DMSO-d_6) of **4ai**



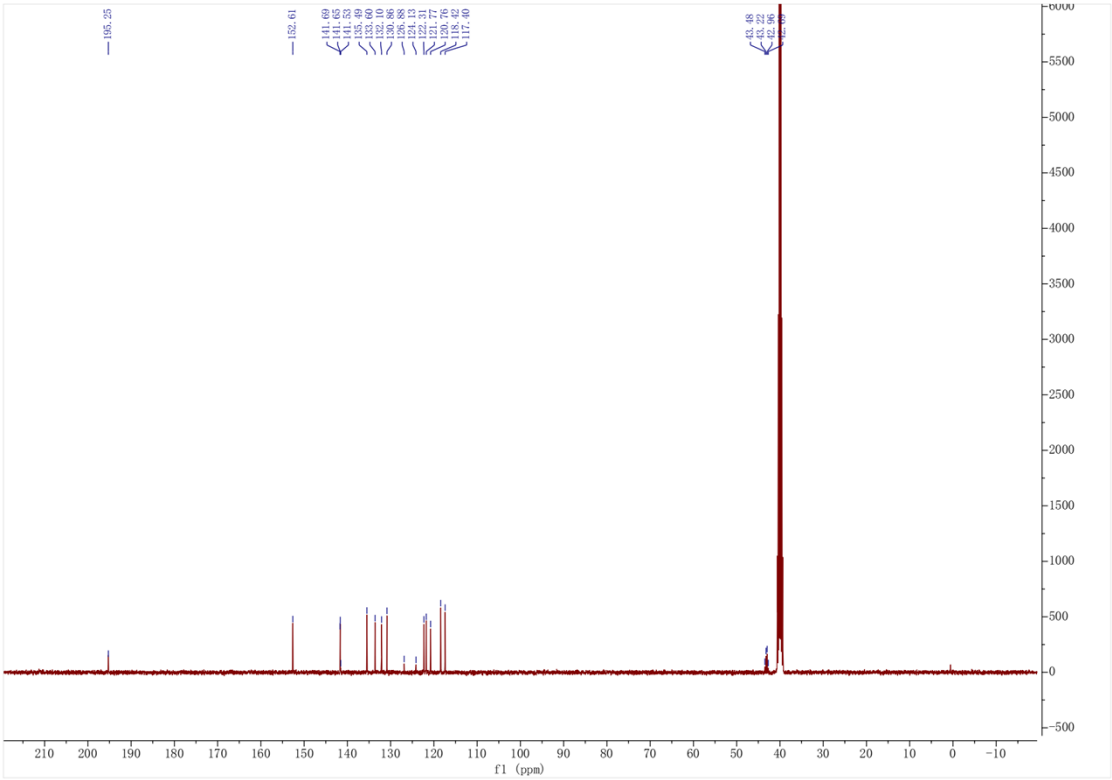
^{19}F NMR (376 MHz, DMSO-d_6) of **4ai**



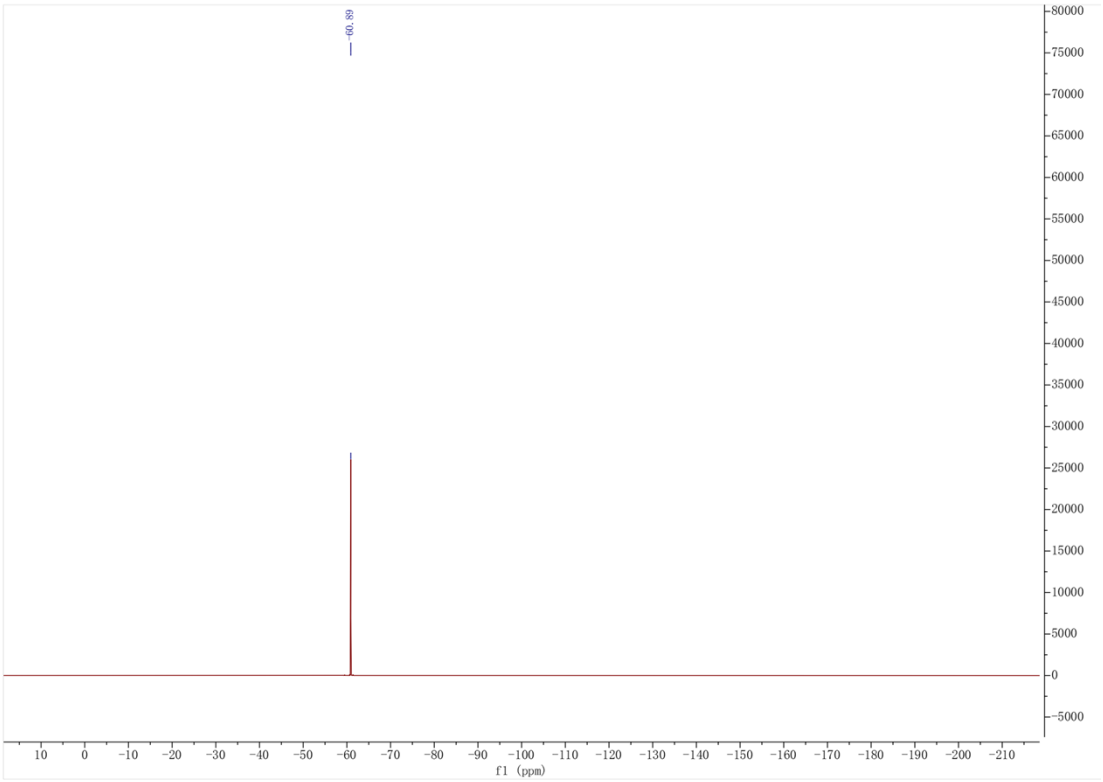
^{1}H NMR (400 MHz, DMSO-d_6) of **4aj**



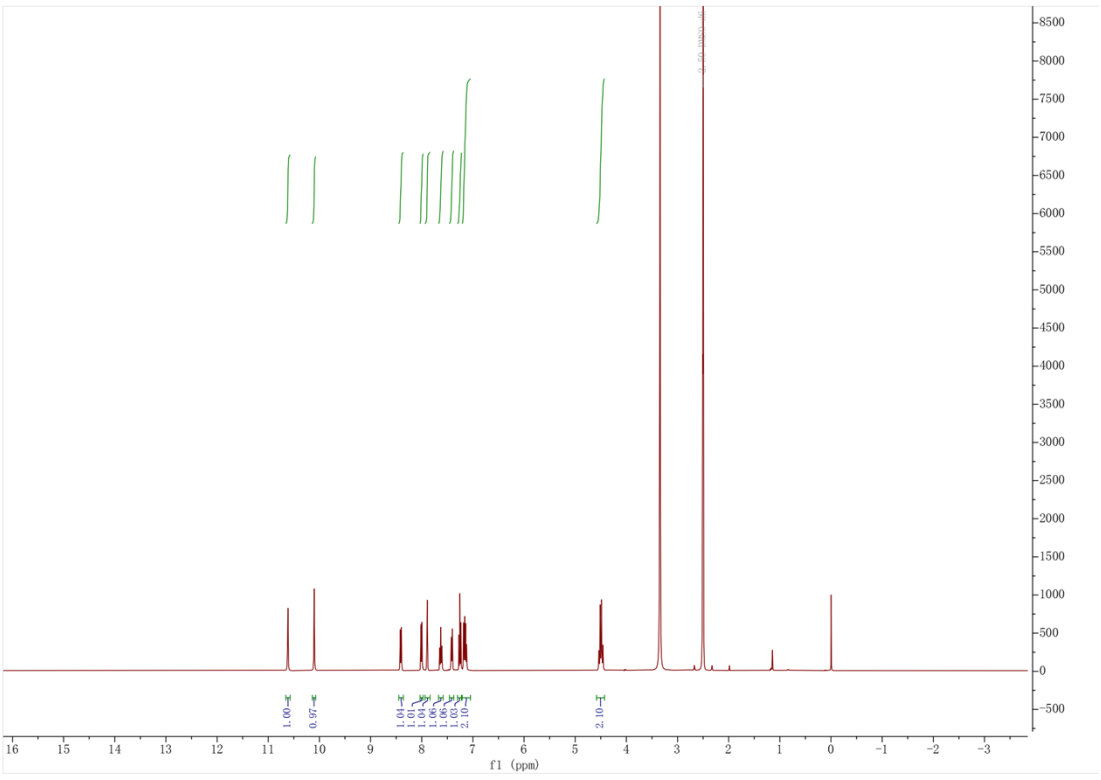
^{13}C NMR (100 MHz, DMSO-d_6) of **4aj**



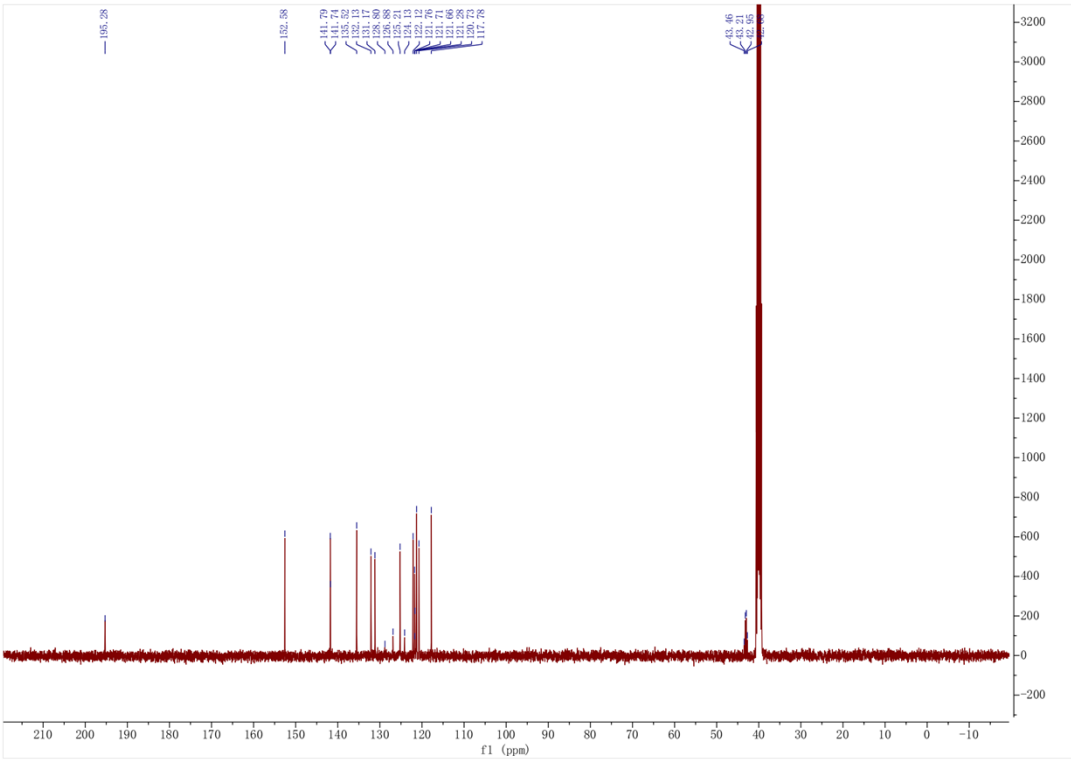
^{19}F NMR (376 MHz, DMSO-d_6) of **4aj**



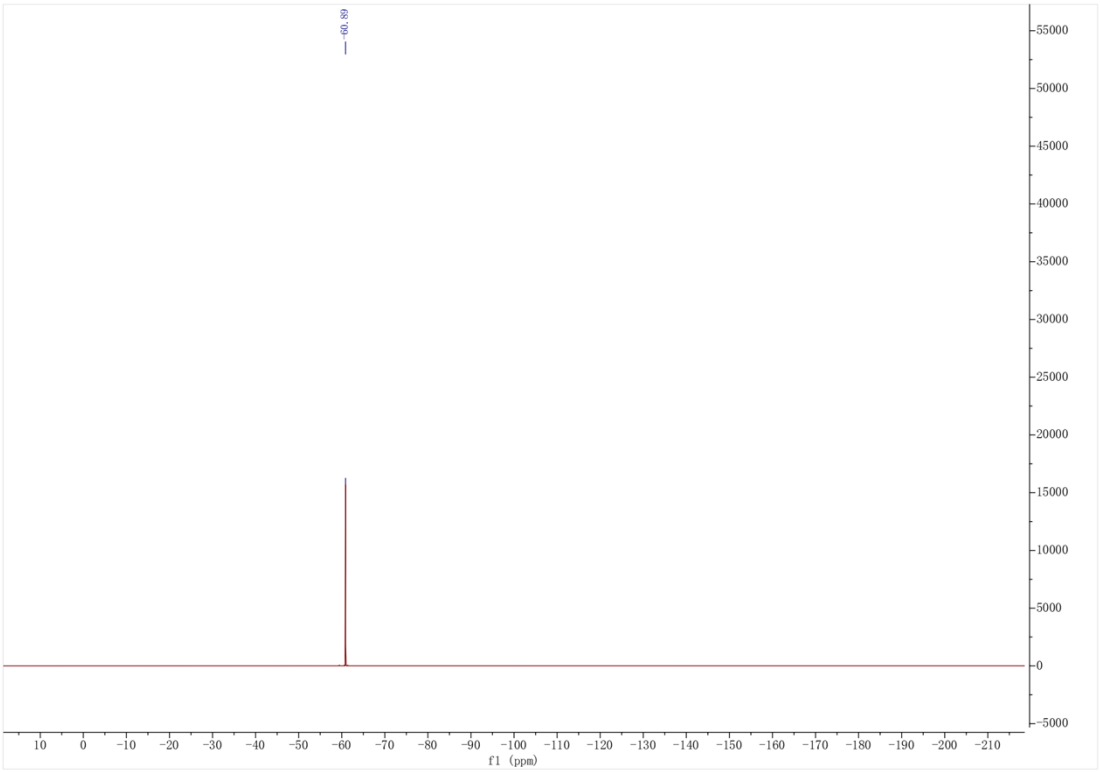
^{1}H NMR (400 MHz, DMSO-d_6) of **4ak**



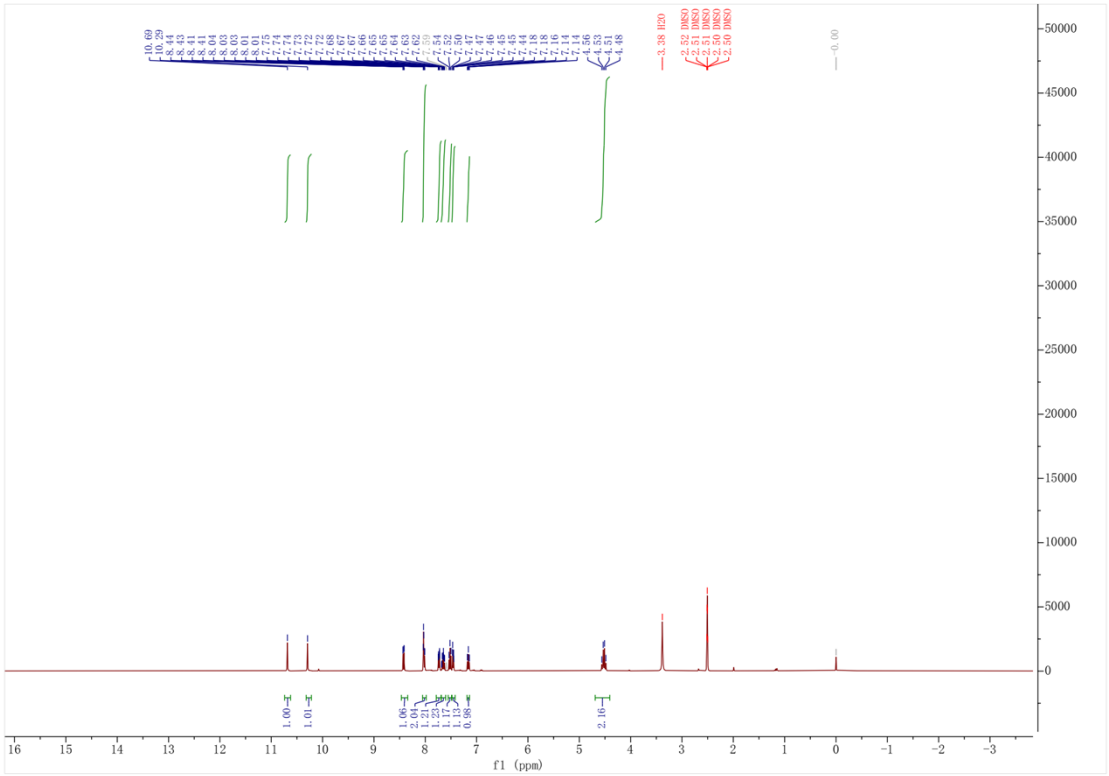
^{13}C NMR (100 MHz, DMSO-d_6) of **4ak**



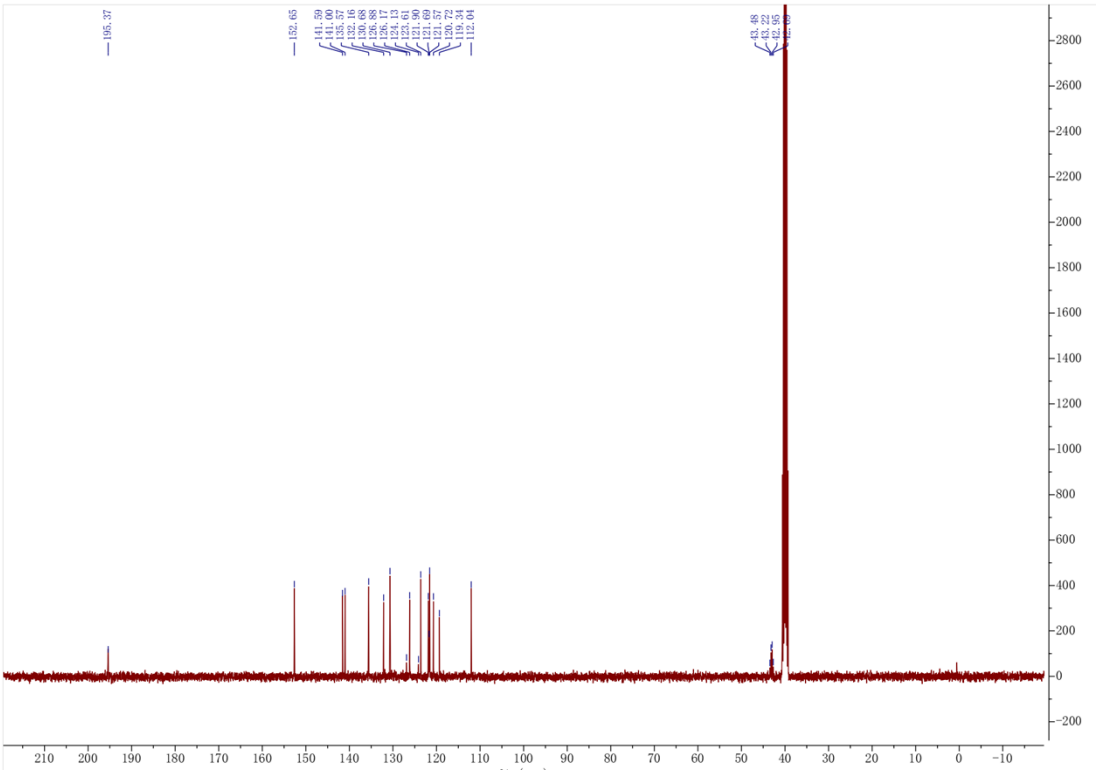
^{19}F NMR (376 MHz, DMSO-d_6) of **4ak**



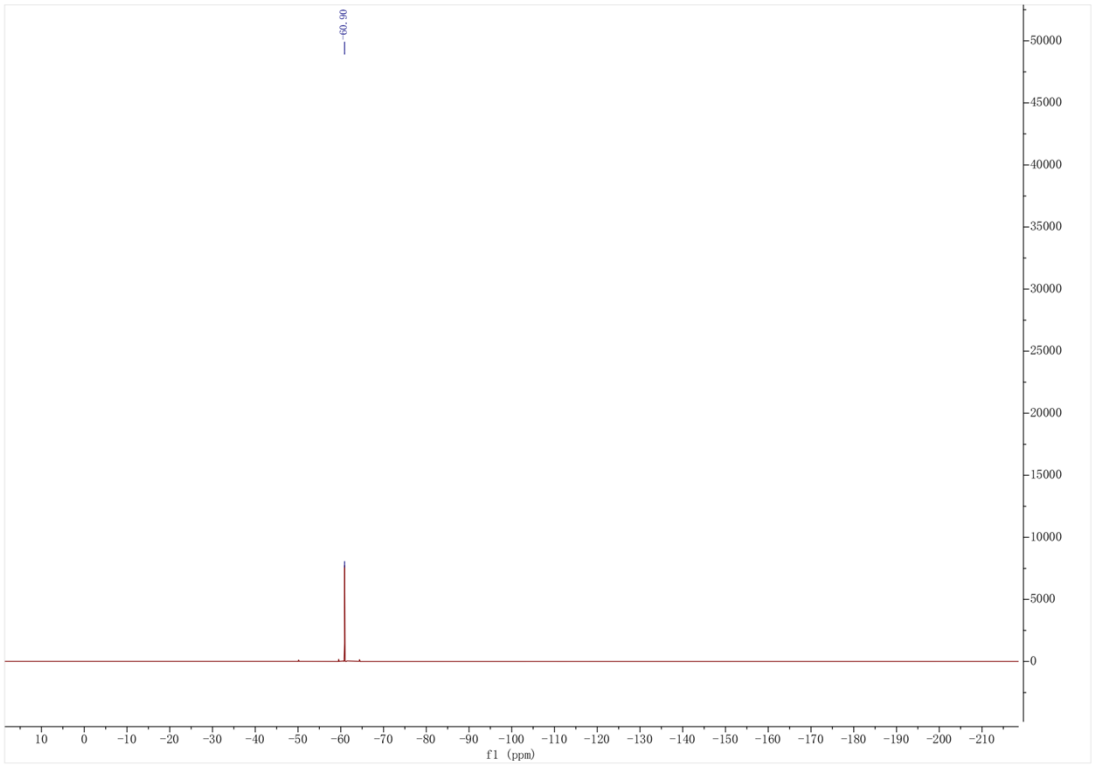
^{1}H NMR (400 MHz, DMSO-d_6) of **4al**



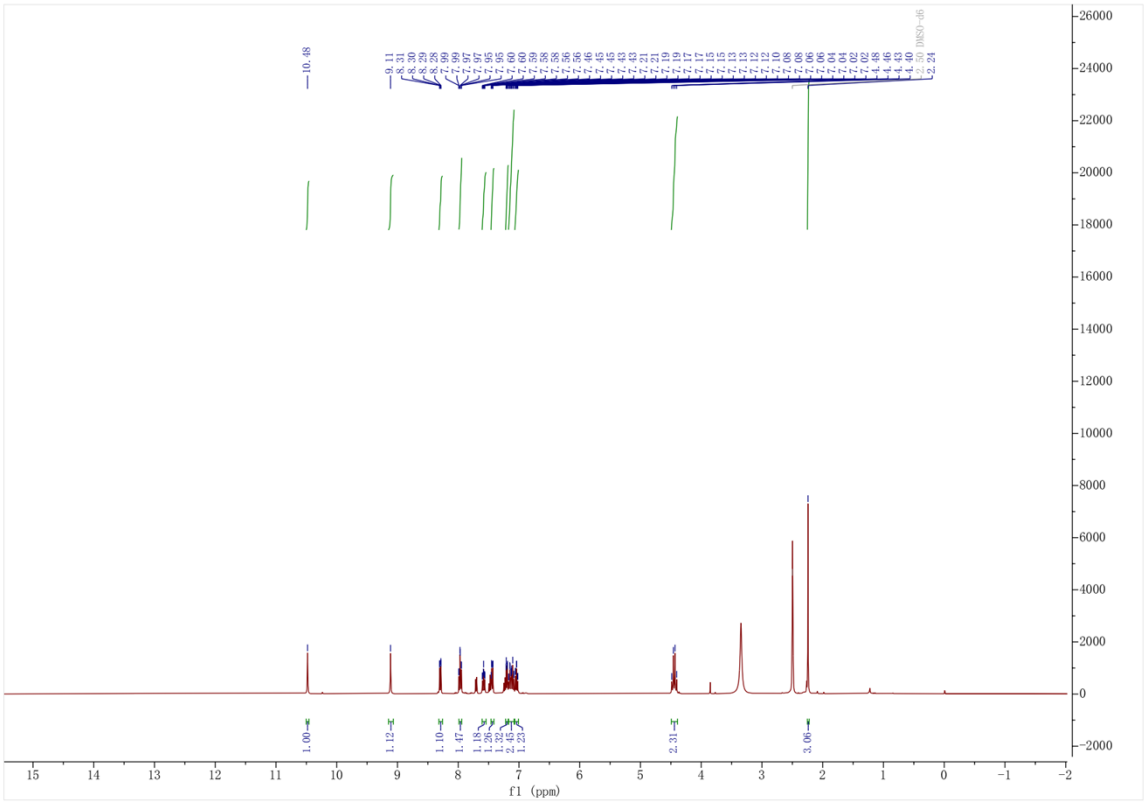
^{13}C NMR (100 MHz, DMSO-d_6) of **4al**



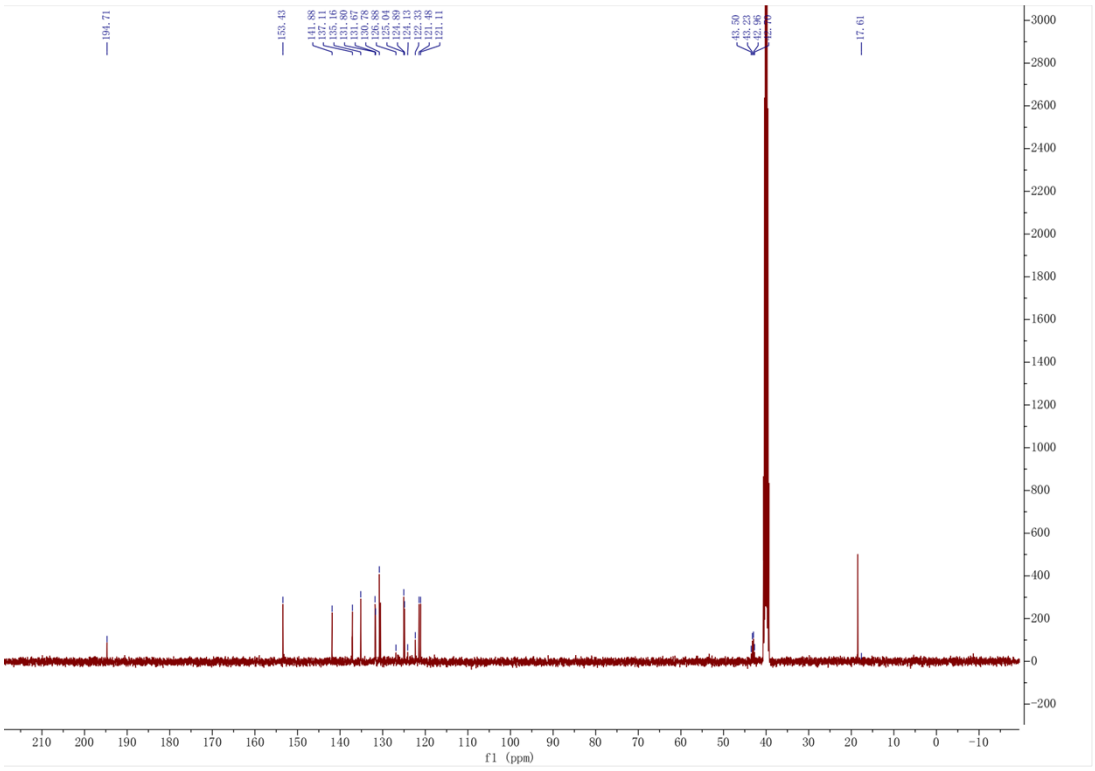
^{19}F NMR (376 MHz, DMSO-d_6) of **4al**



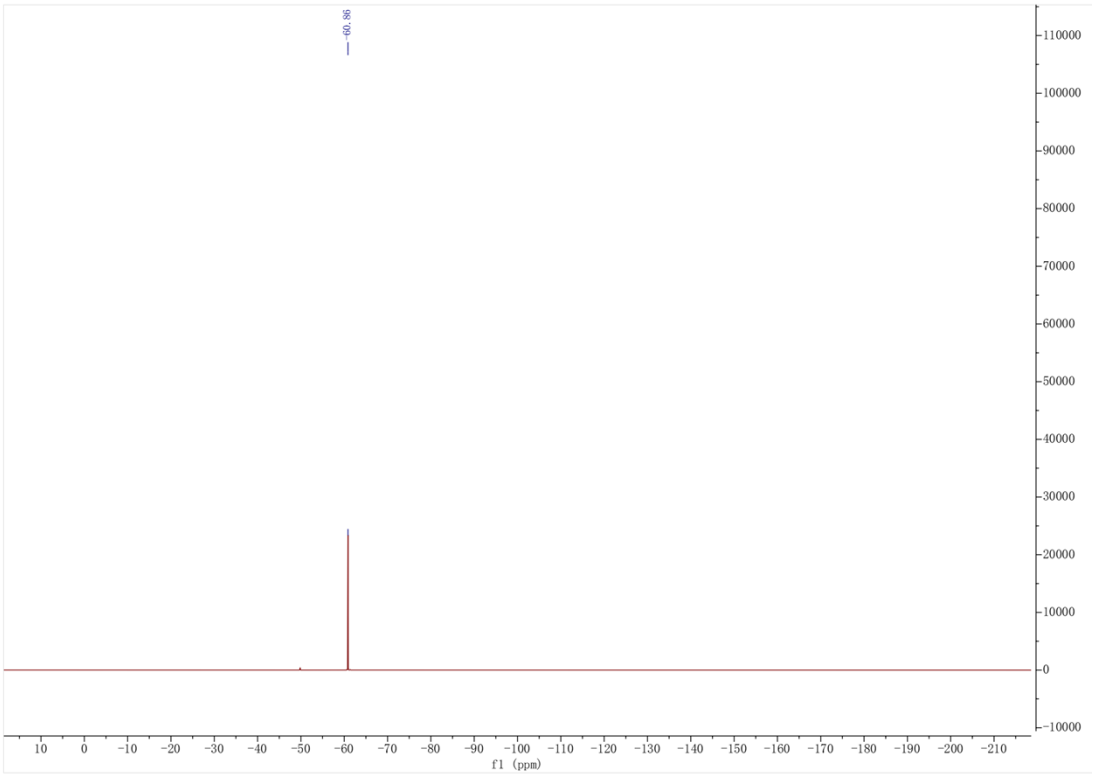
^{1}H NMR (400 MHz, DMSO-d_6) of **4am**



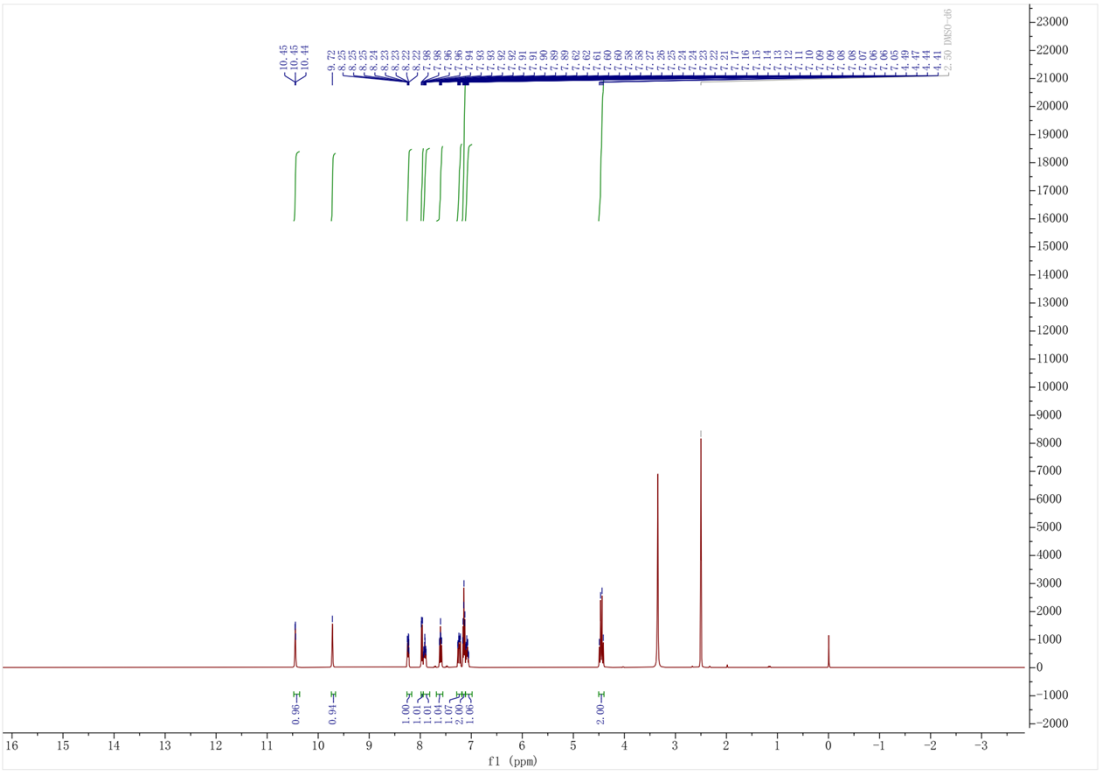
^{13}C NMR (100 MHz, DMSO-d_6) of **4am**



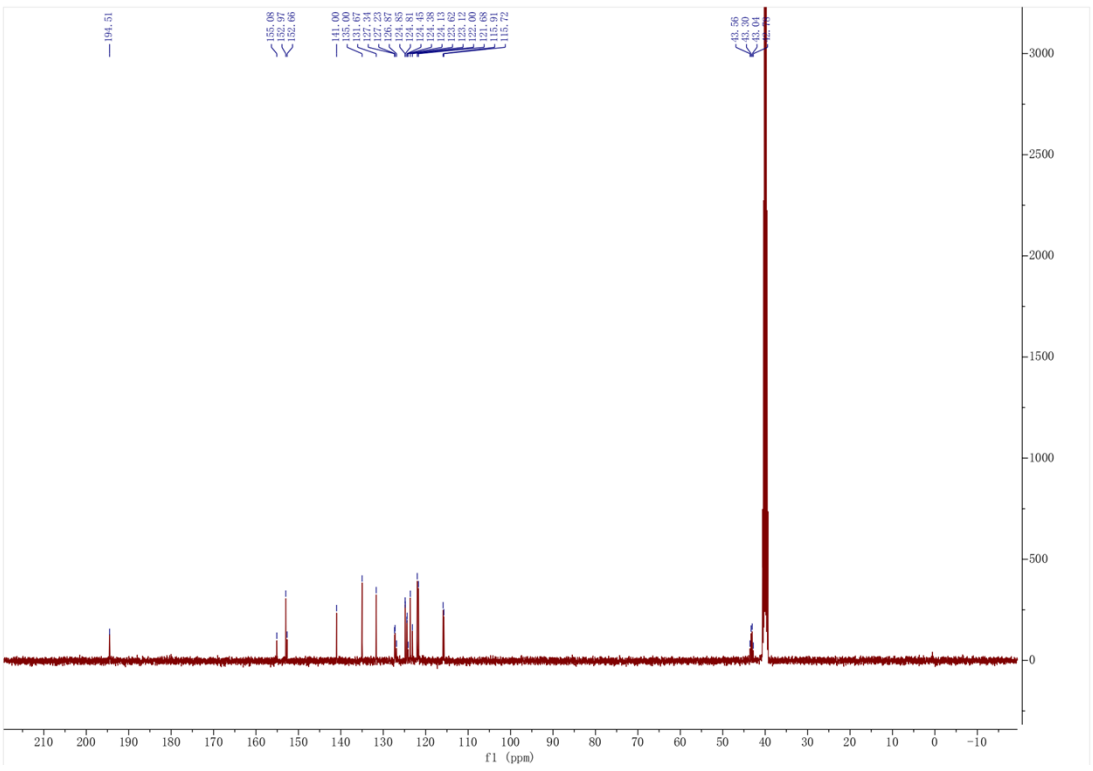
^{19}F NMR (376 MHz, DMSO-d_6) of **4am**



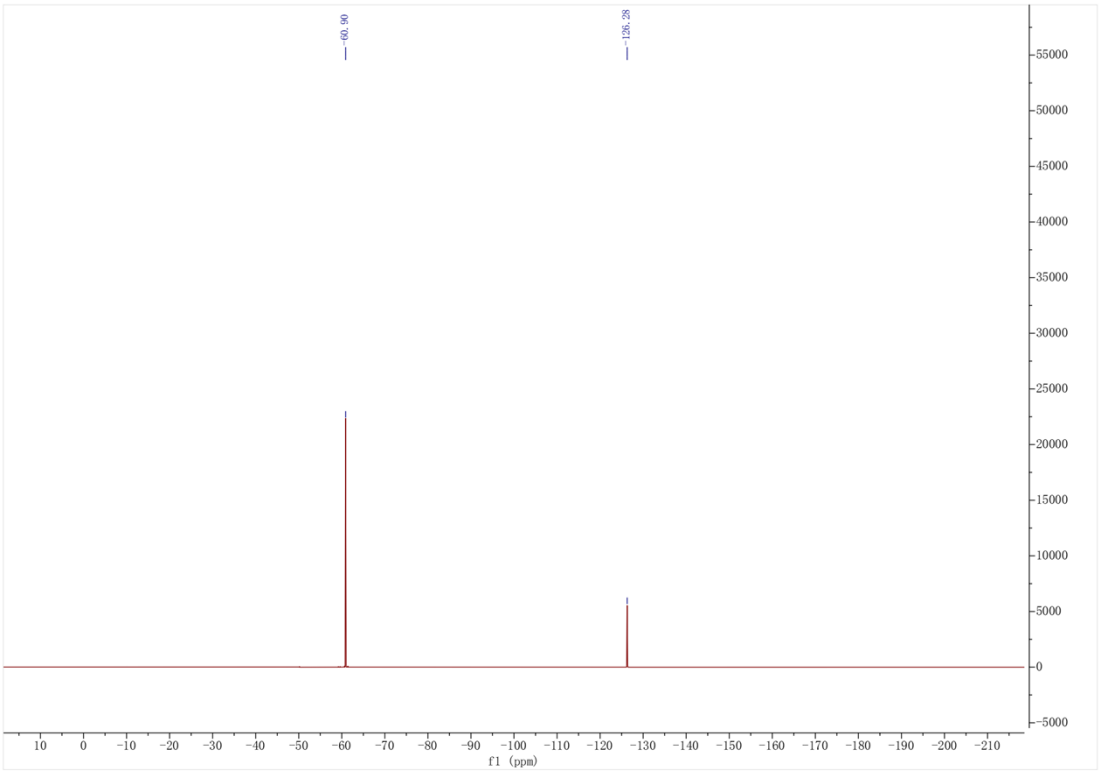
^{1}H NMR (400 MHz, DMSO-d_6) of **4an**



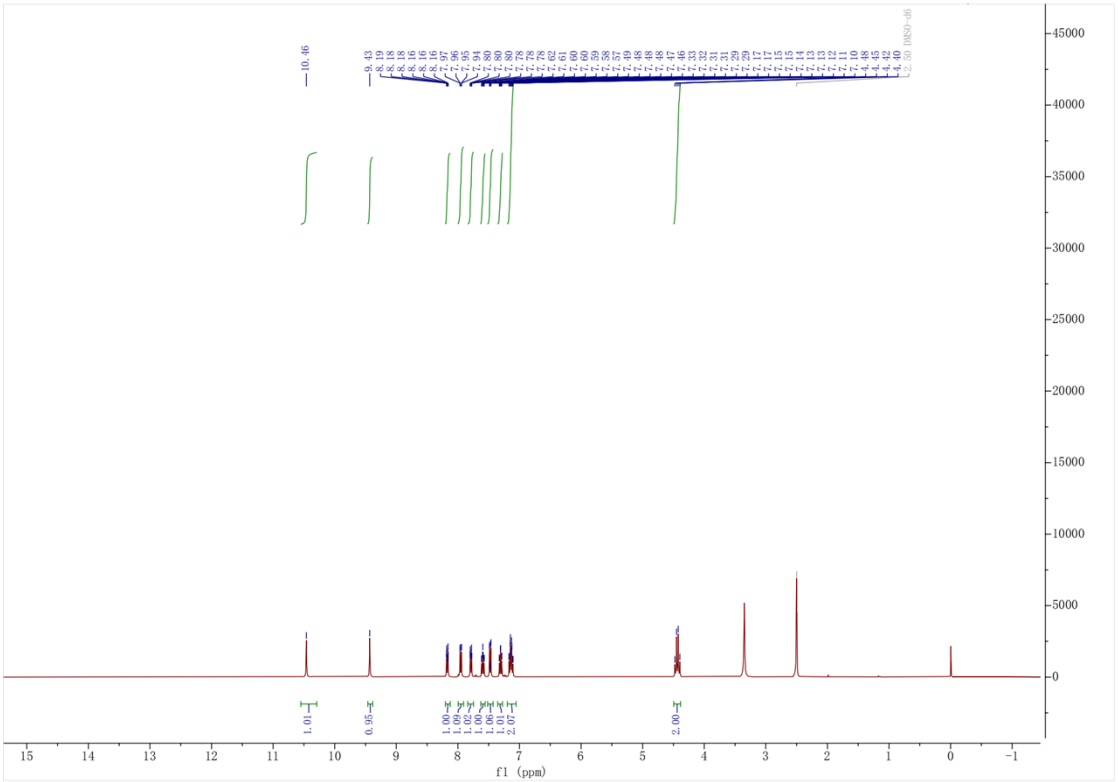
^{13}C NMR (100 MHz, DMSO-d_6) of **4an**



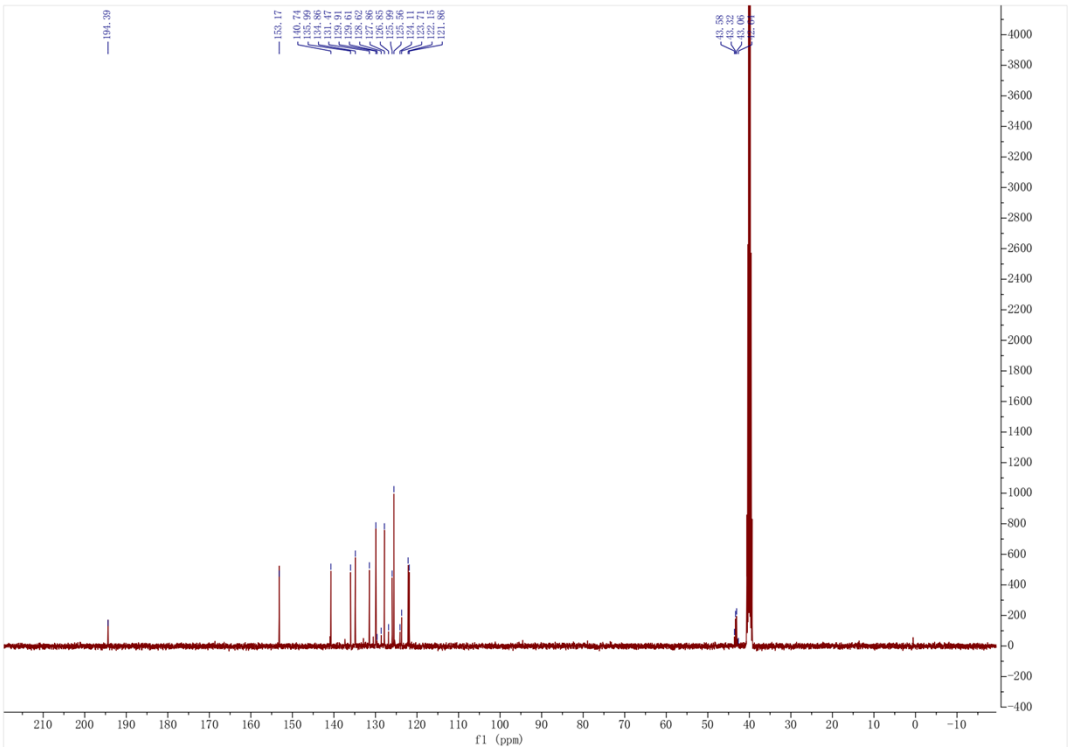
^{19}F NMR (376 MHz, DMSO-d_6) of **4an**



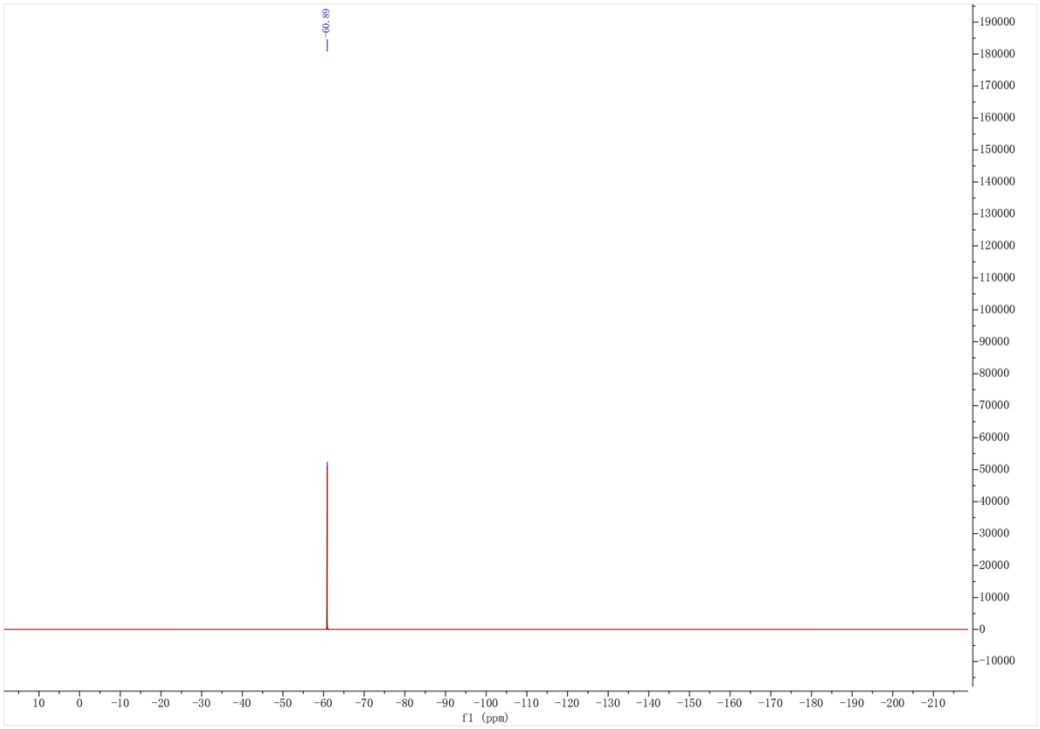
^{1}H NMR (400 MHz, DMSO-d_6) of **4ao**



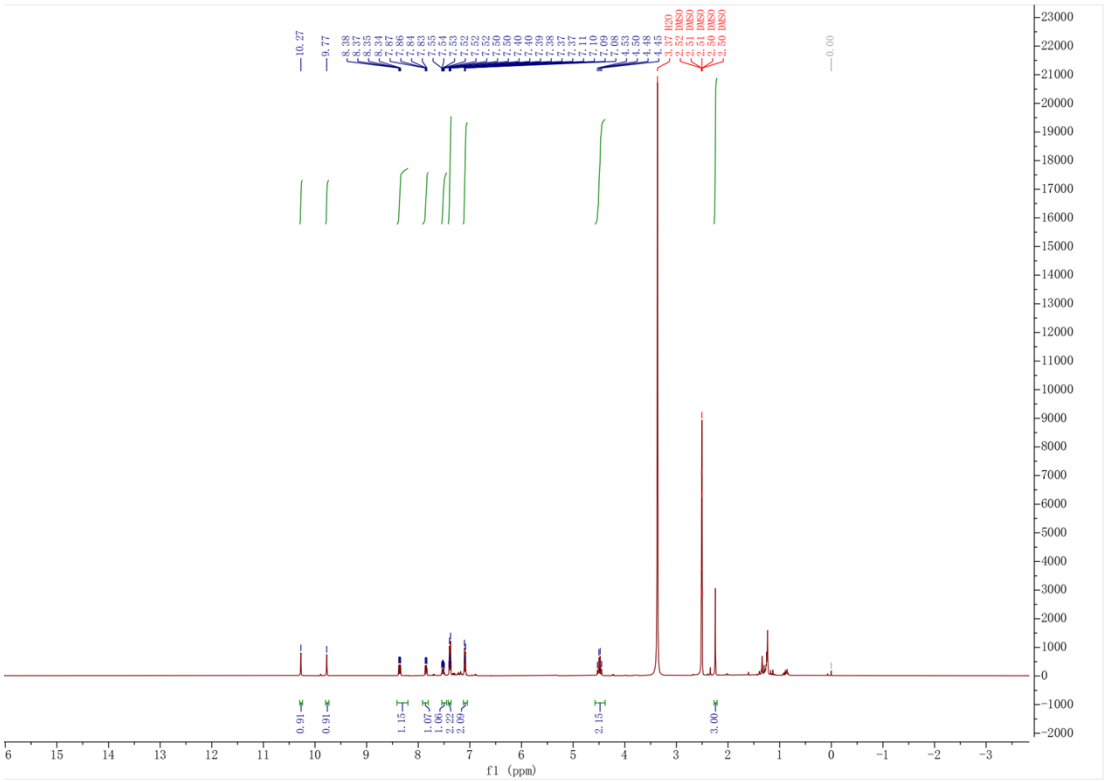
^{13}C NMR (100 MHz, DMSO-d_6) of **4ao**



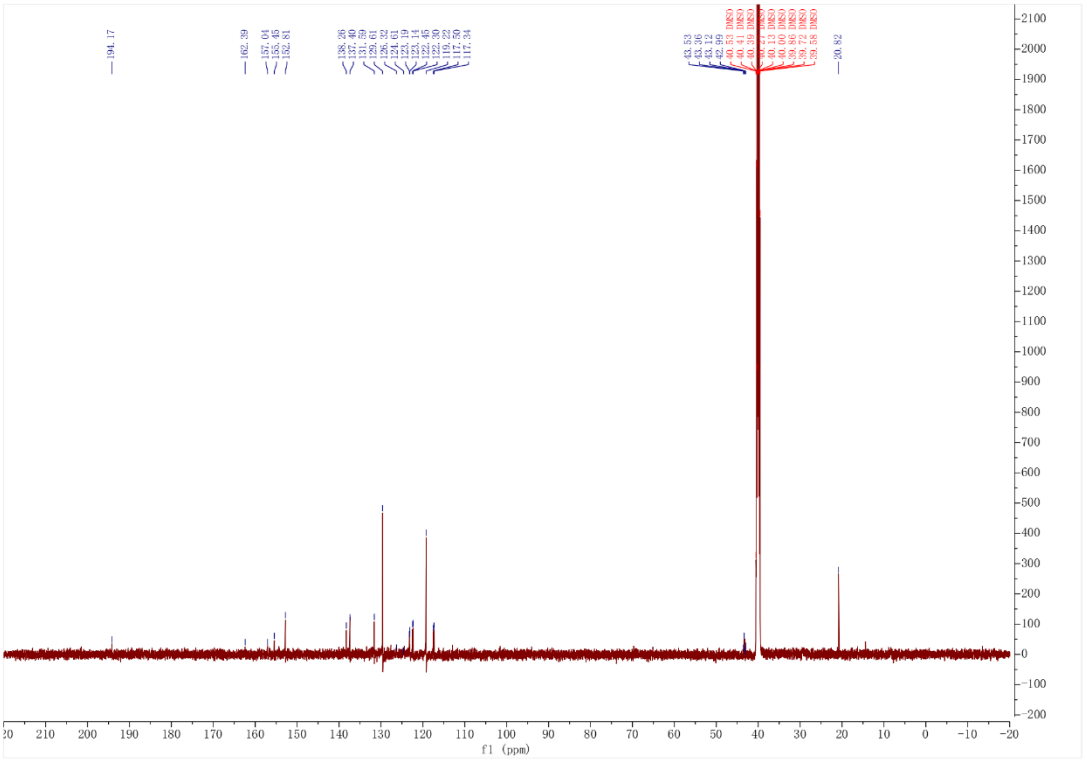
^{19}F NMR (376 MHz, DMSO-d_6) of **4ao**



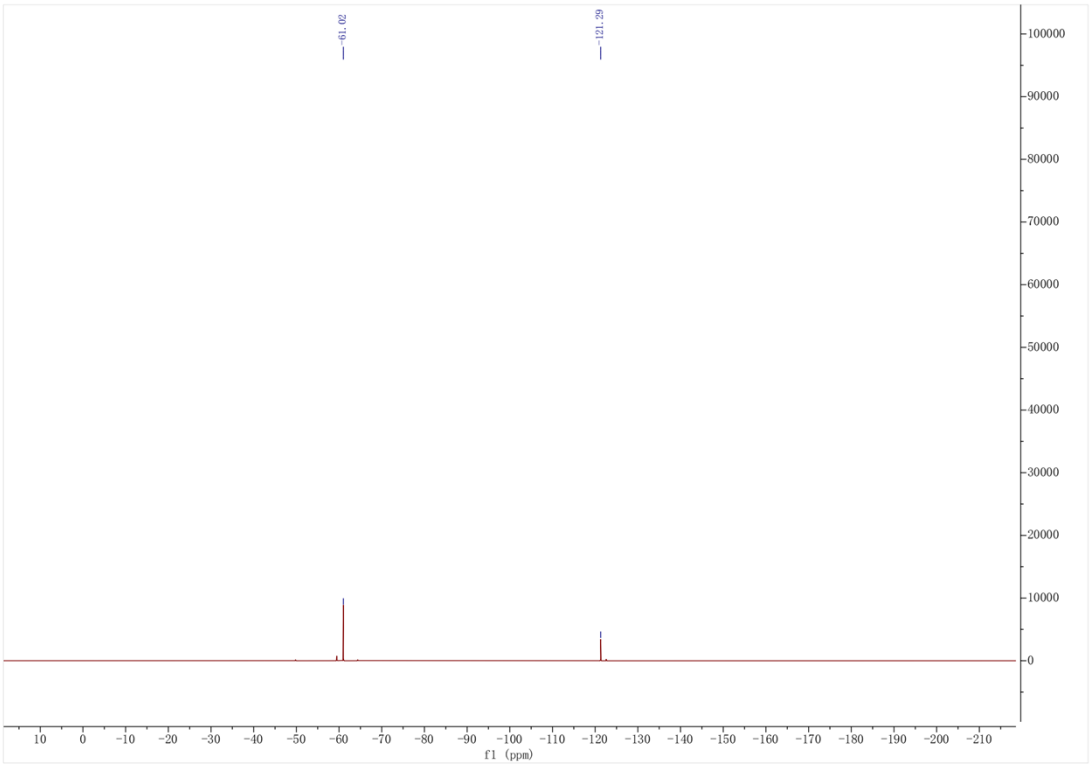
^{1}H NMR (400 MHz, DMSO-d_6) of **4at**



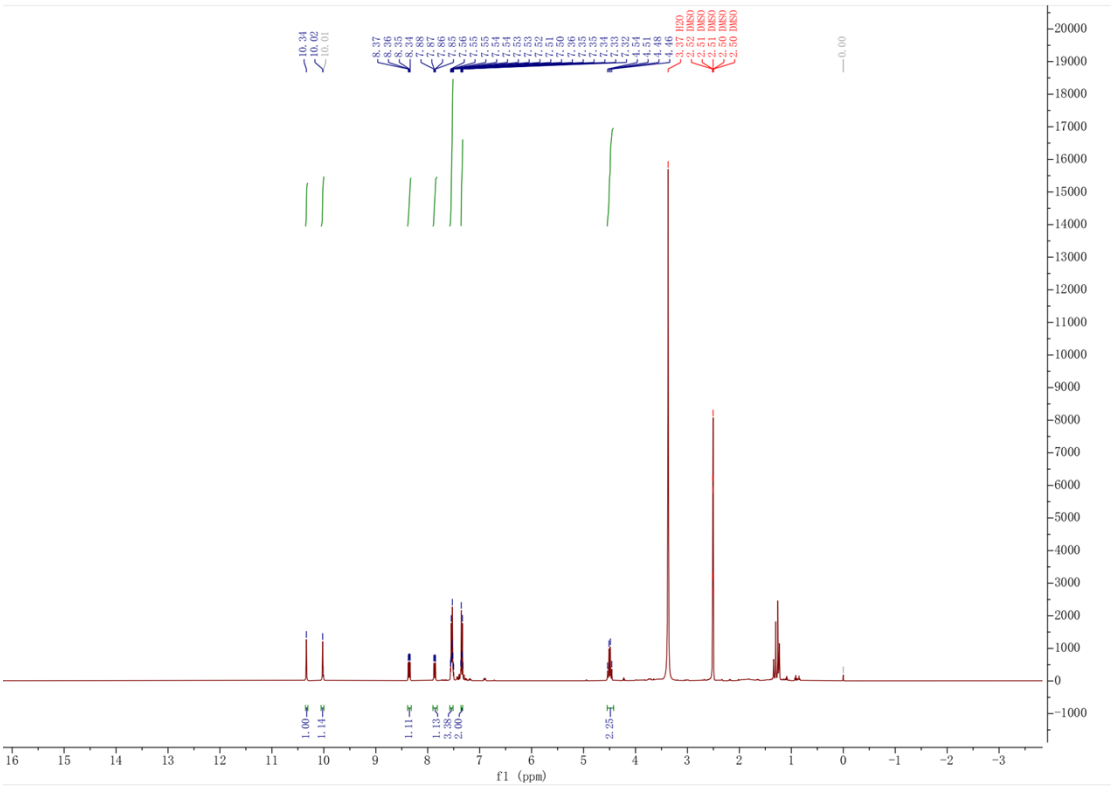
^{13}C NMR (150 MHz, DMSO-d_6) of **4at**



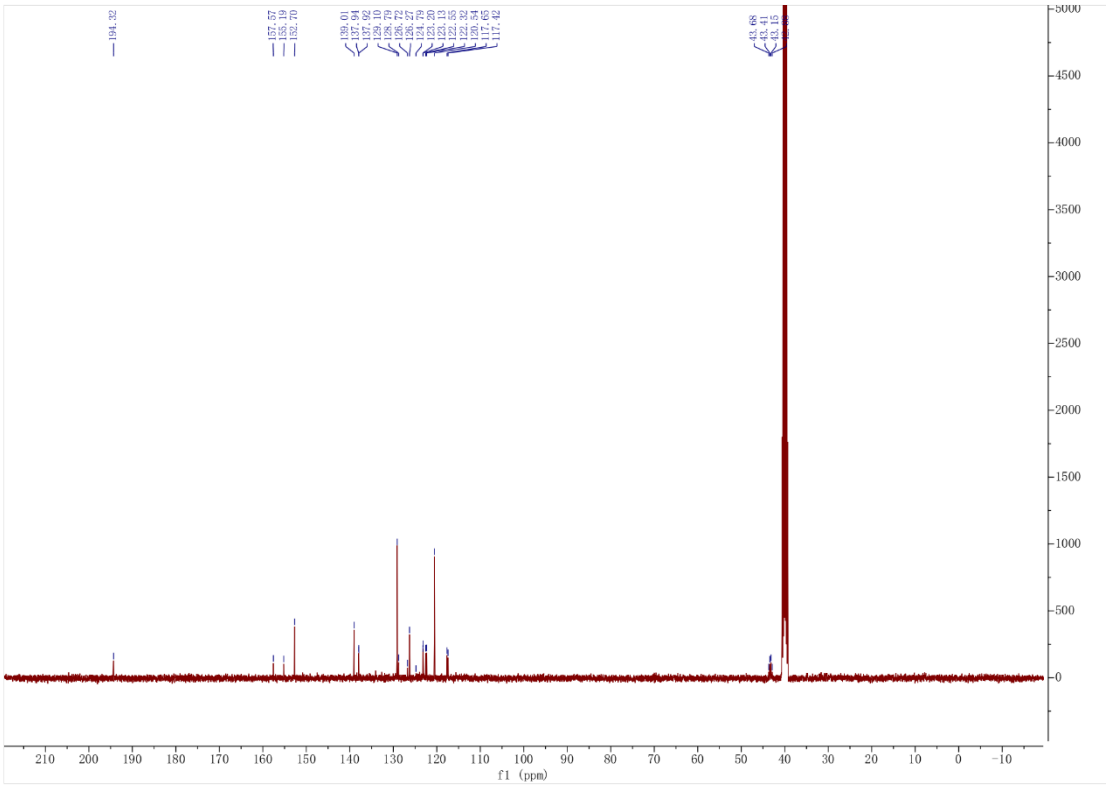
^{19}F NMR (378 MHz, DMSO-d_6) of **4at**



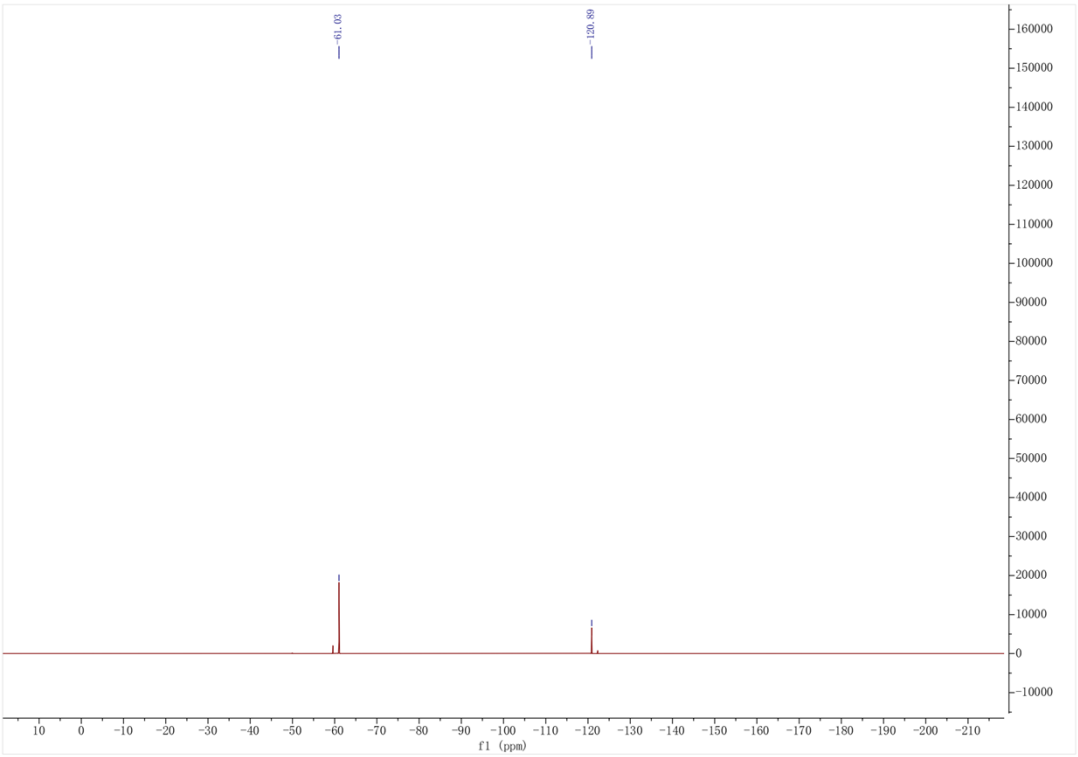
^{1}H NMR (400 MHz, DMSO-d_6) of **4au**



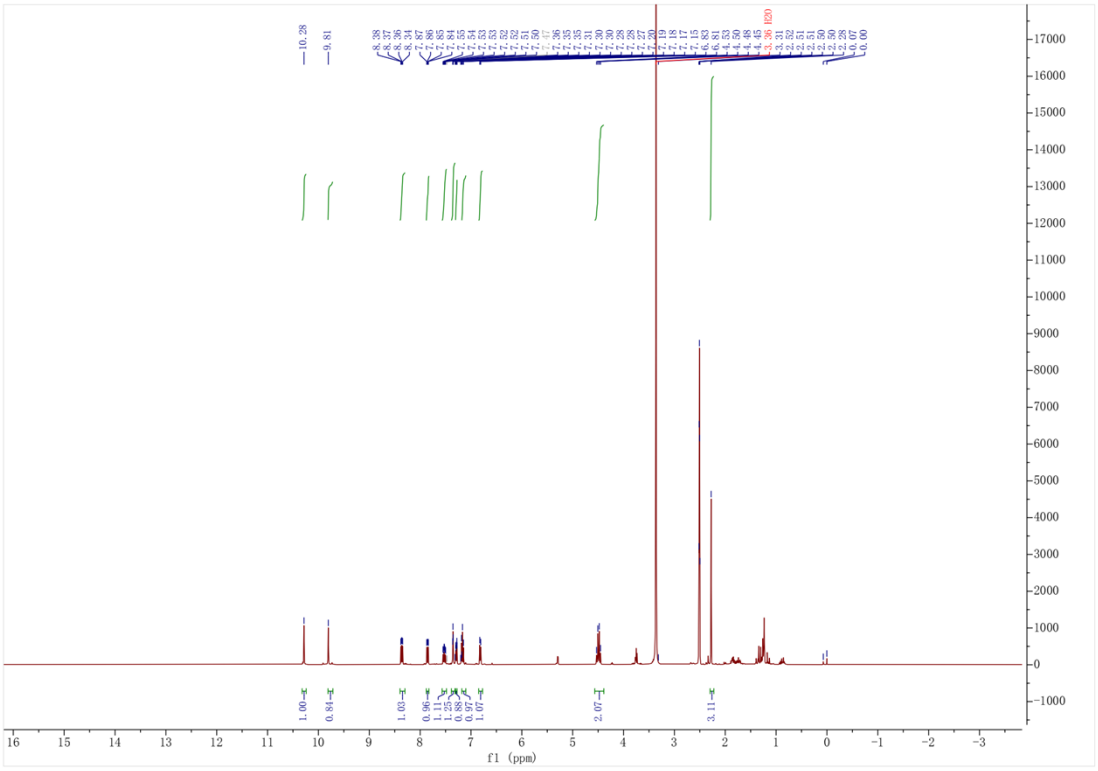
^{13}C NMR (100 MHz, DMSO-d_6) of **4au**



^{19}F NMR (378 MHz, DMSO-d_6) of **4au**



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



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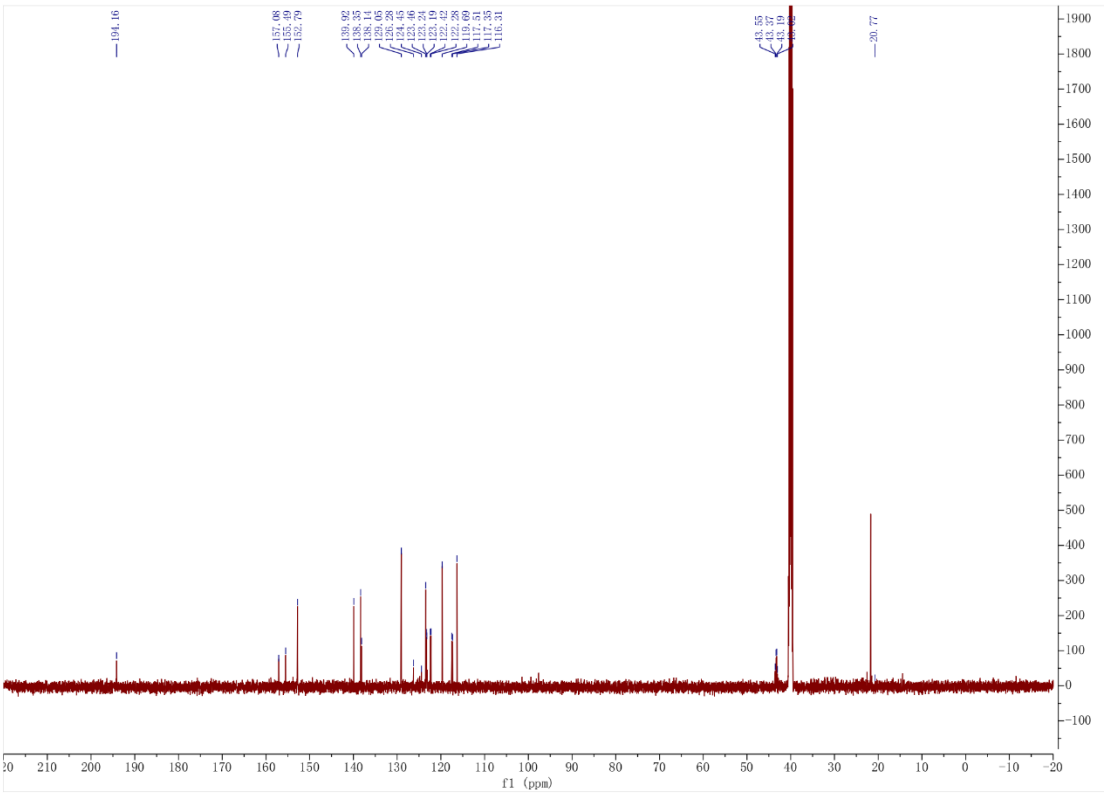
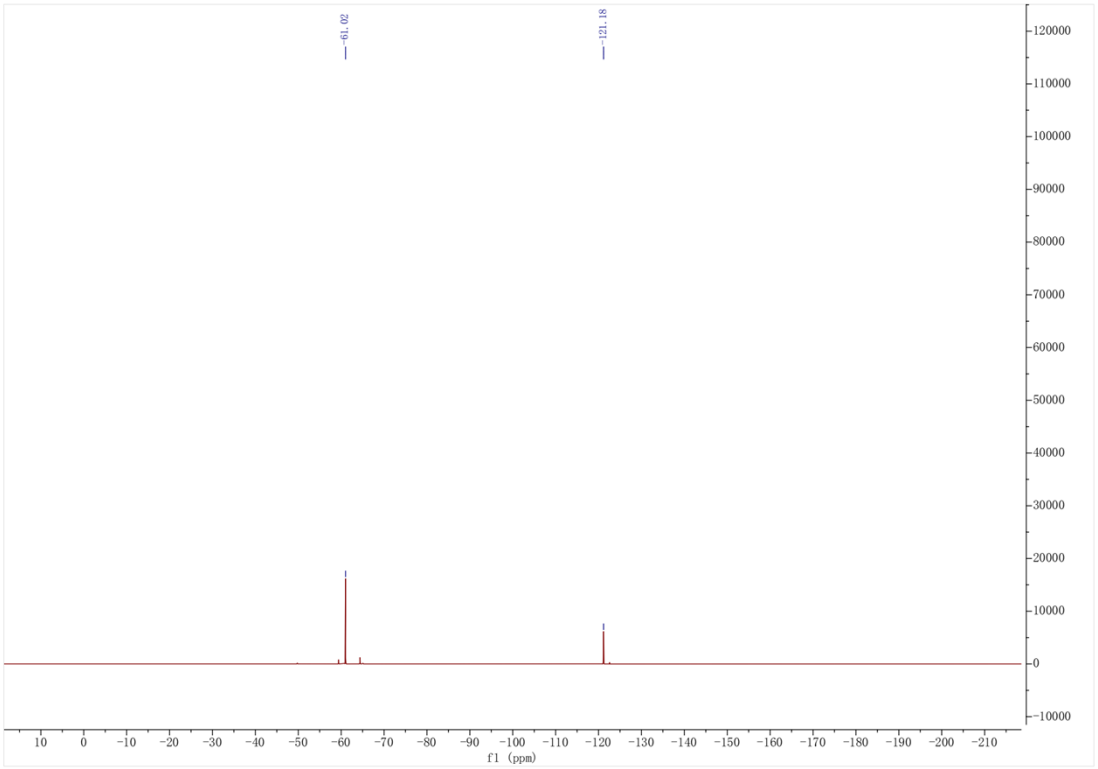
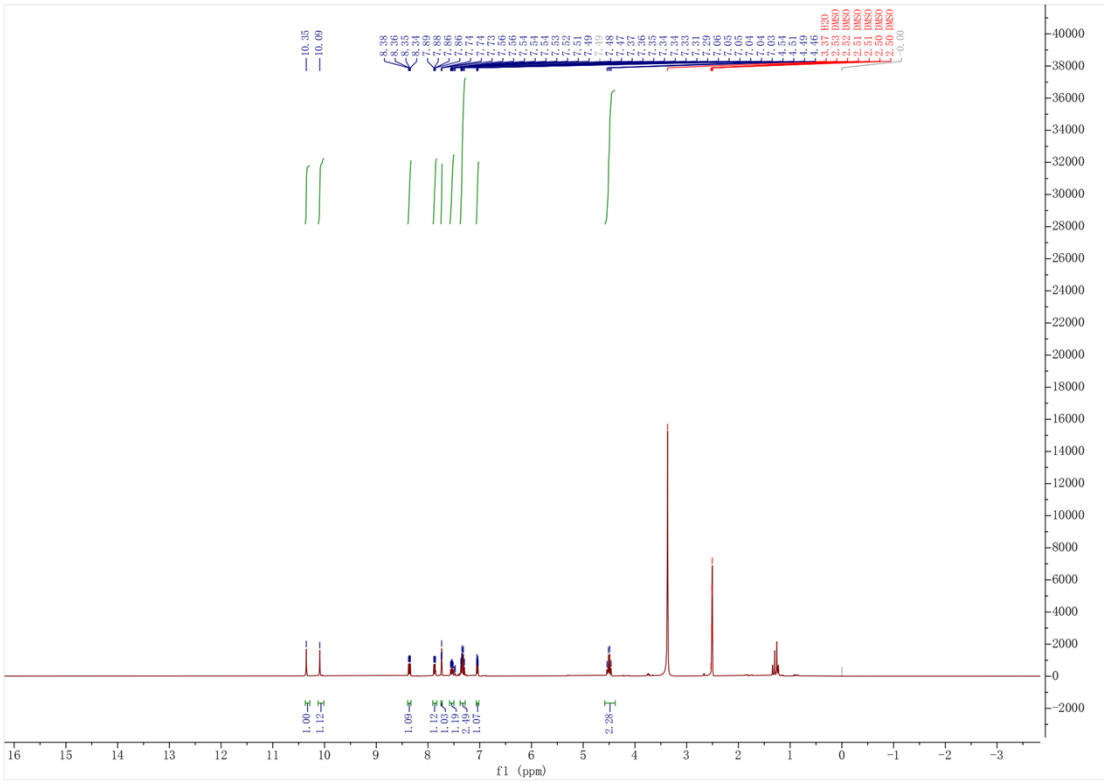


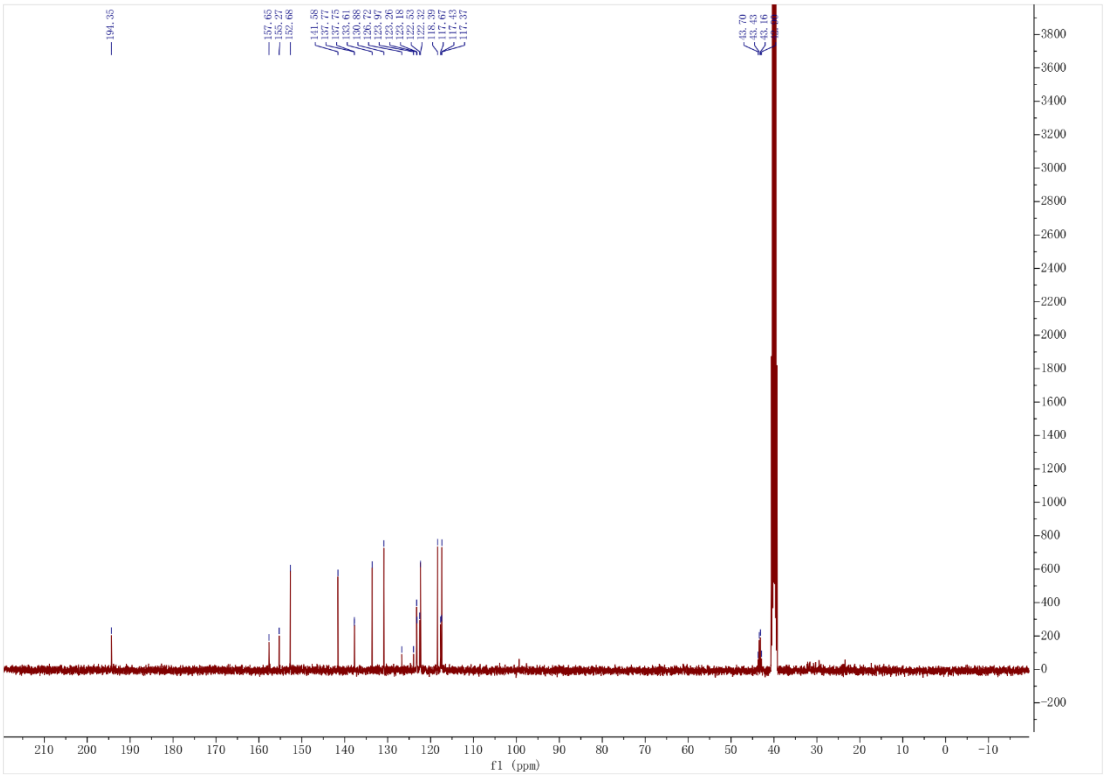
^{19}F NMR (378 MHz, DMSO-d_6) of **4av**



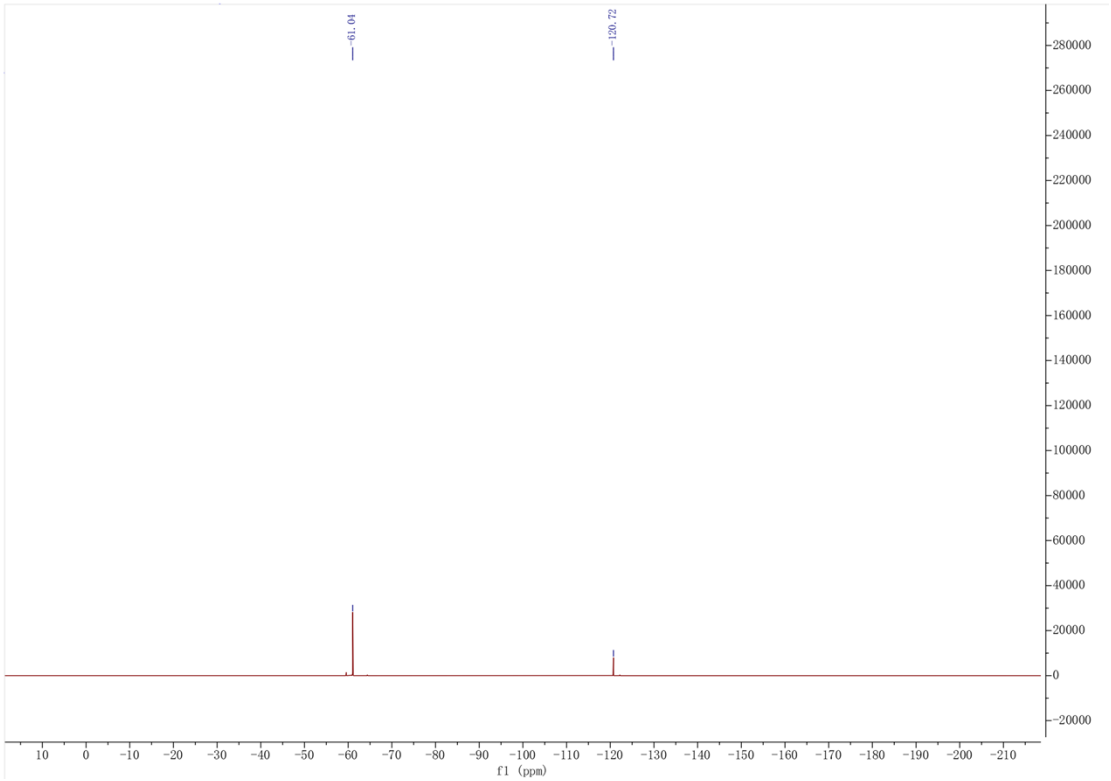
^{1}H NMR (400 MHz, DMSO-d_6) of **4aw**



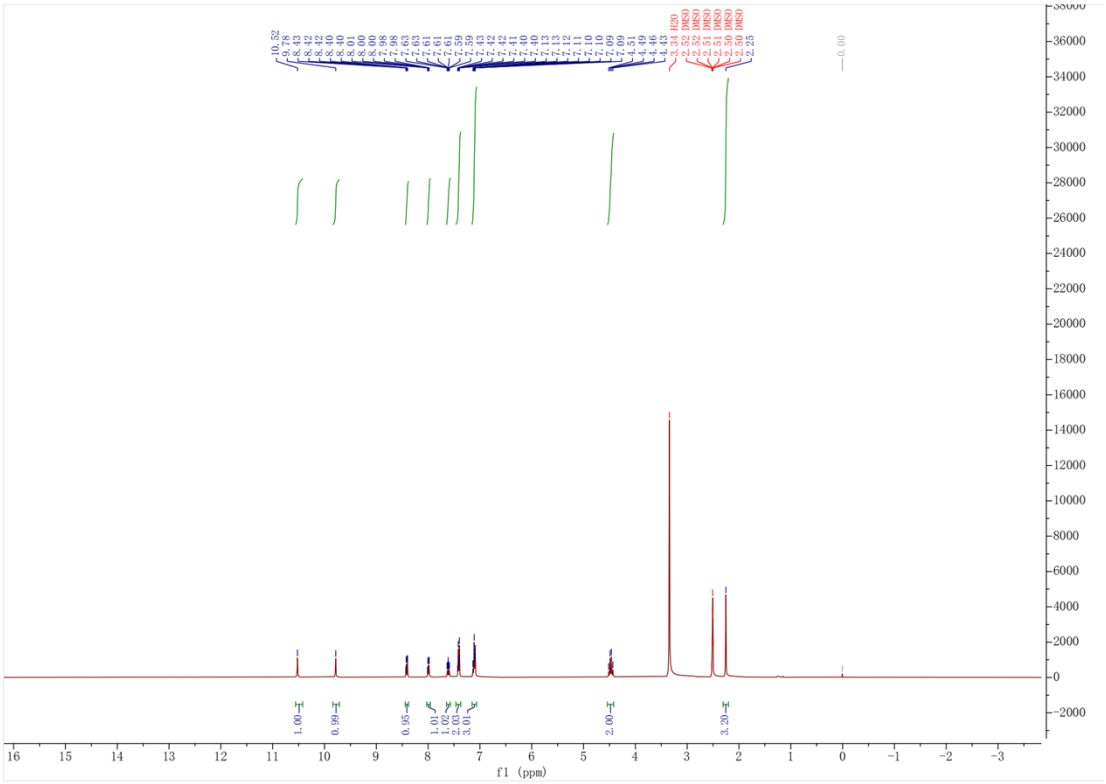
^{13}C NMR (100 MHz, DMSO-d_6) of **4aw**



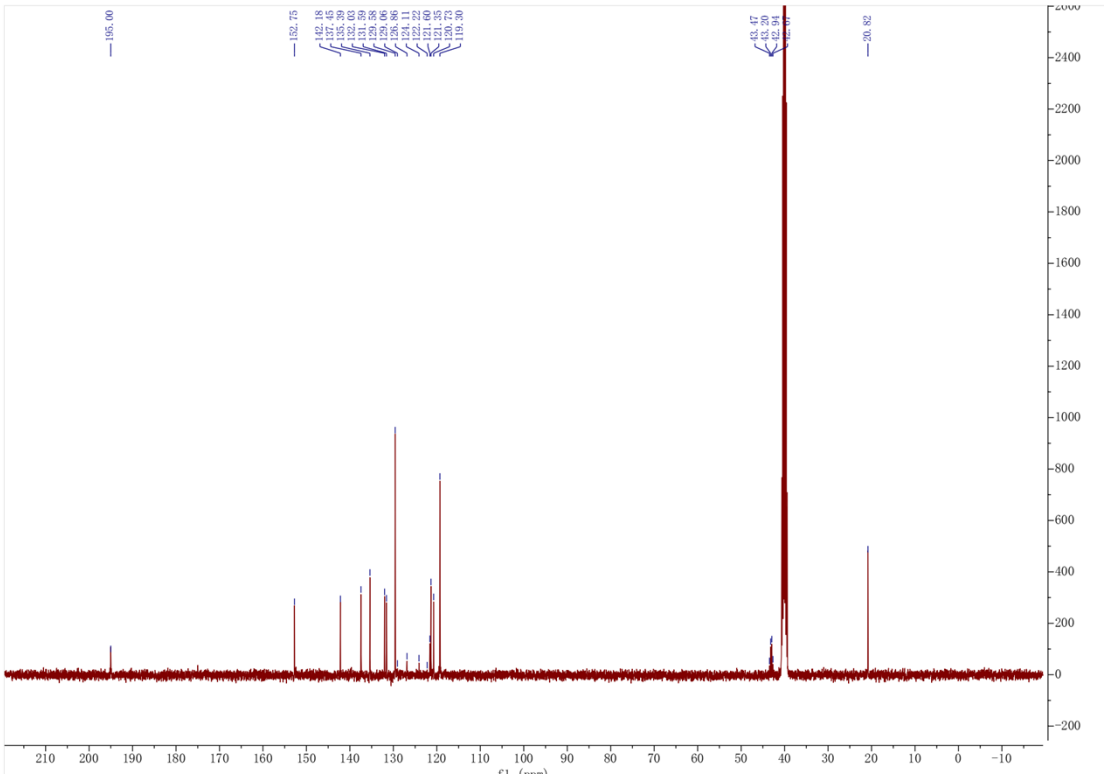
^{19}F NMR (378 MHz, DMSO-d_6) of **4aw**



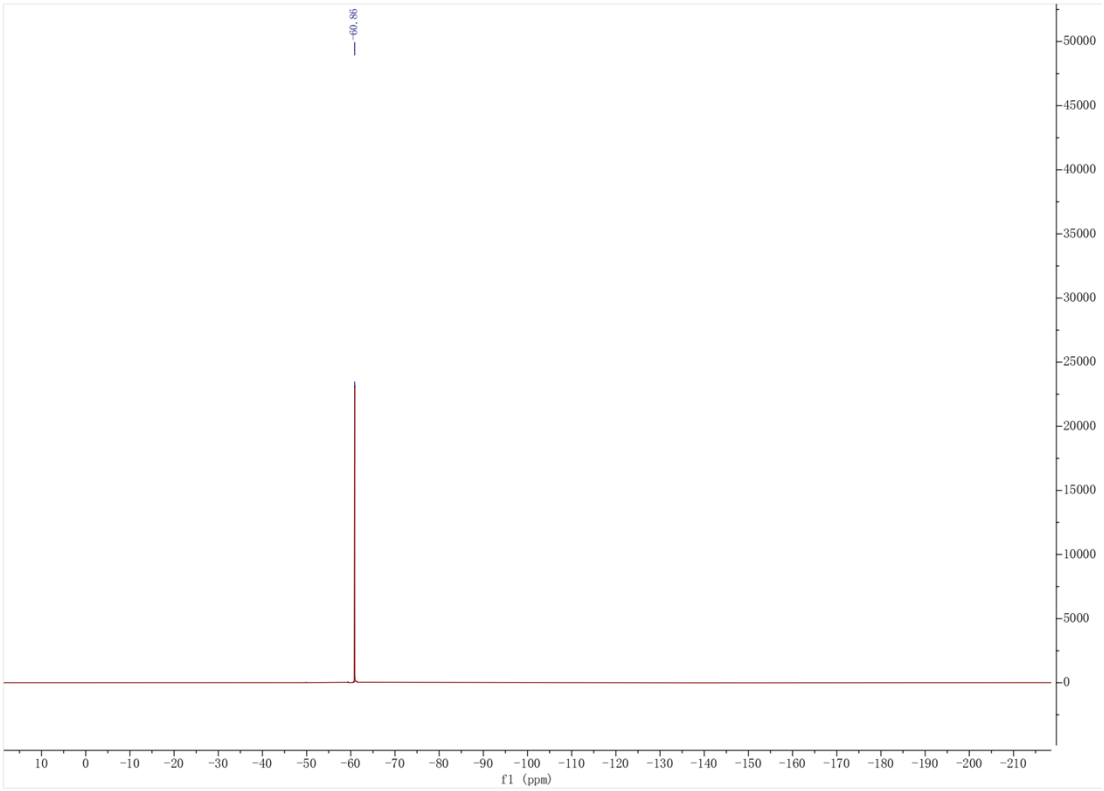
^{1}H NMR (400 MHz, DMSO-d_6) of **6aa**



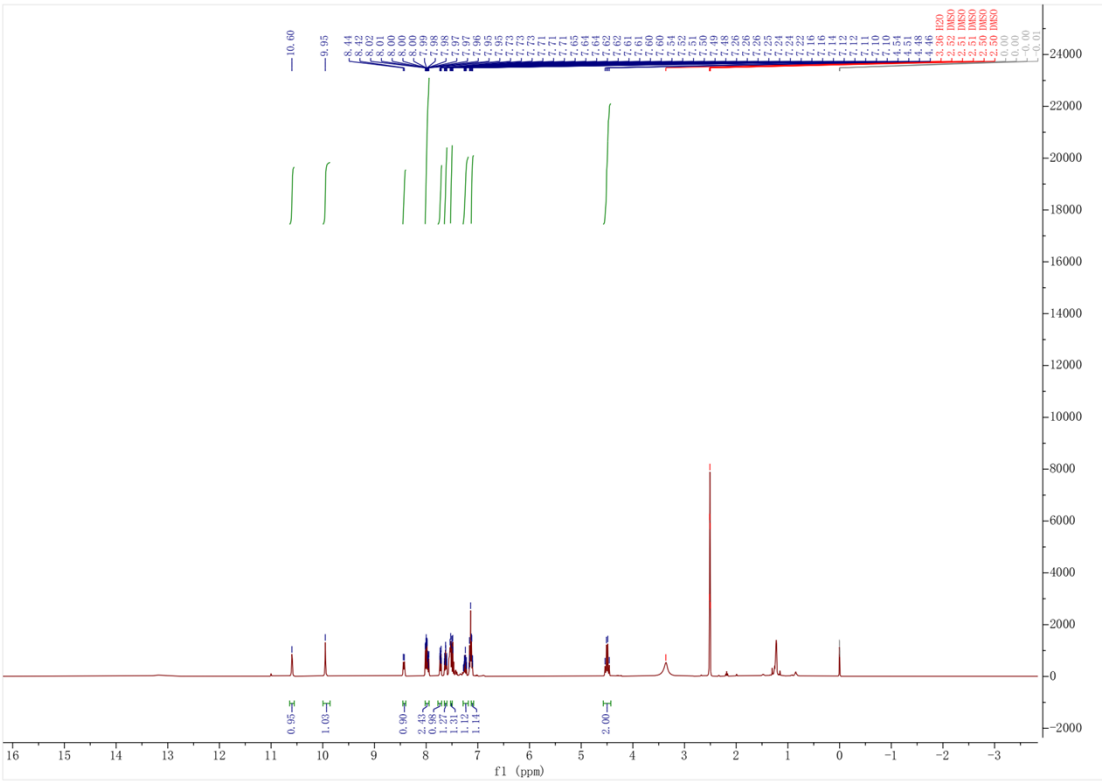
^{13}C NMR (100 MHz, DMSO-d_6) of **6aa**



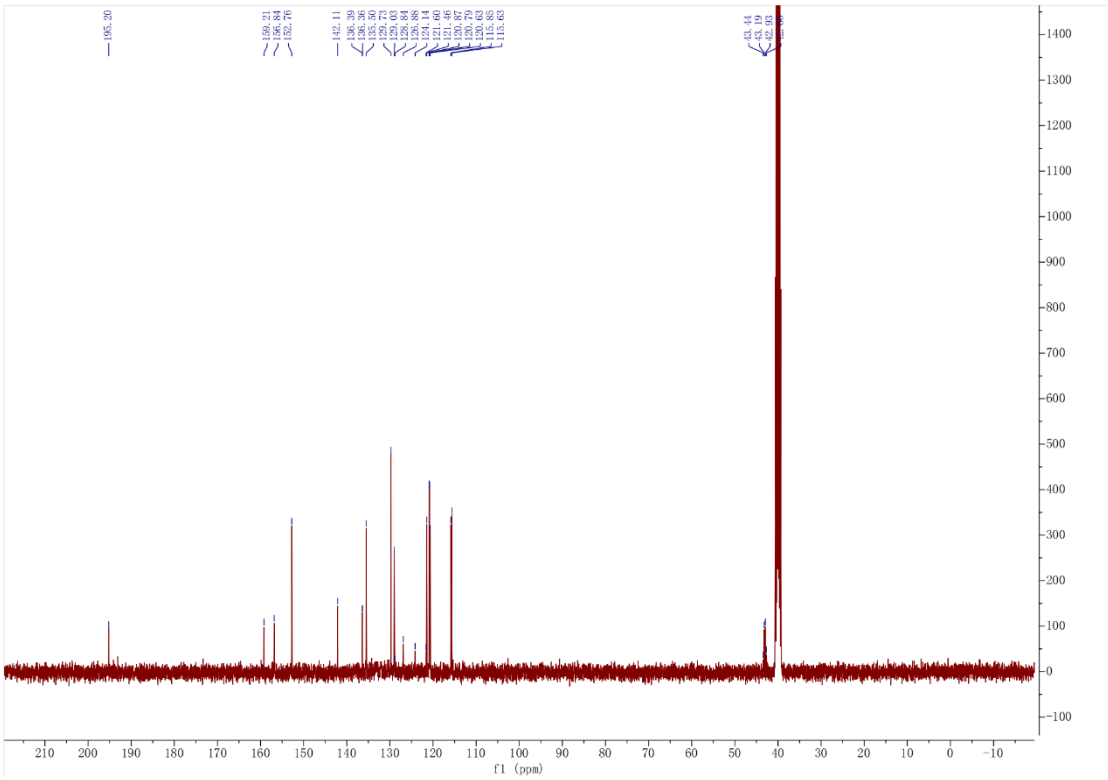
^{19}F NMR (376 MHz, DMSO-d_6) of **6aa**



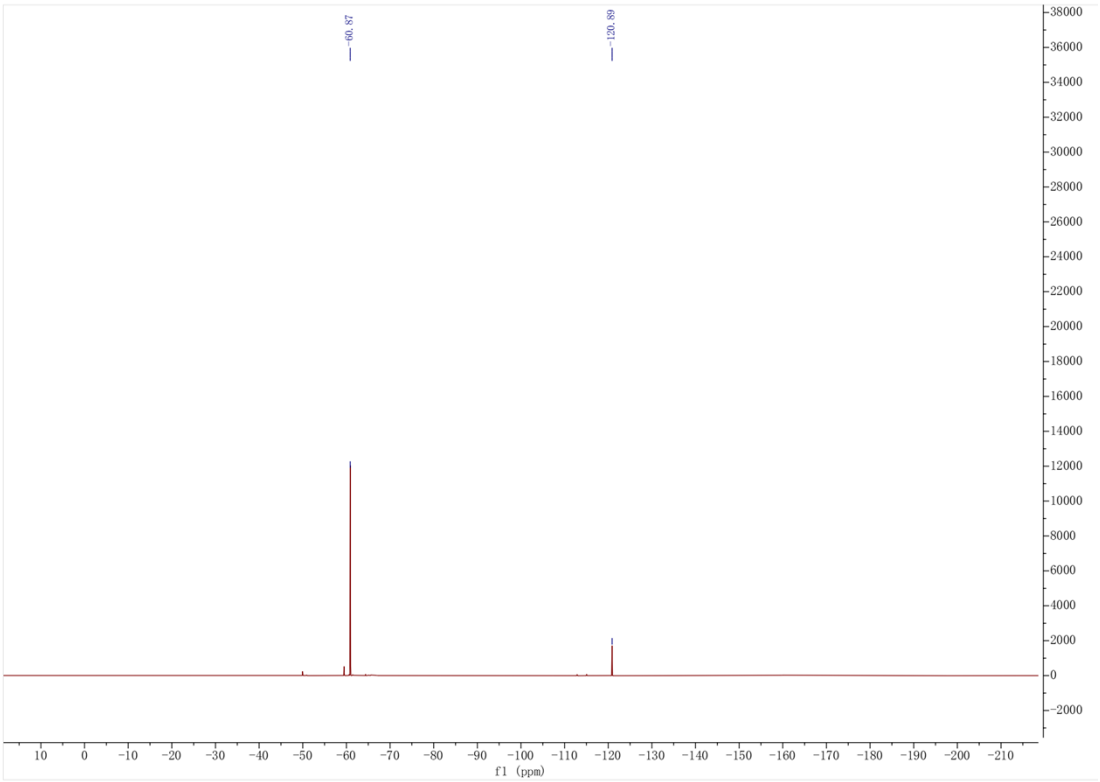
^{1}H NMR (400 MHz, DMSO-d_6) of **6ab**



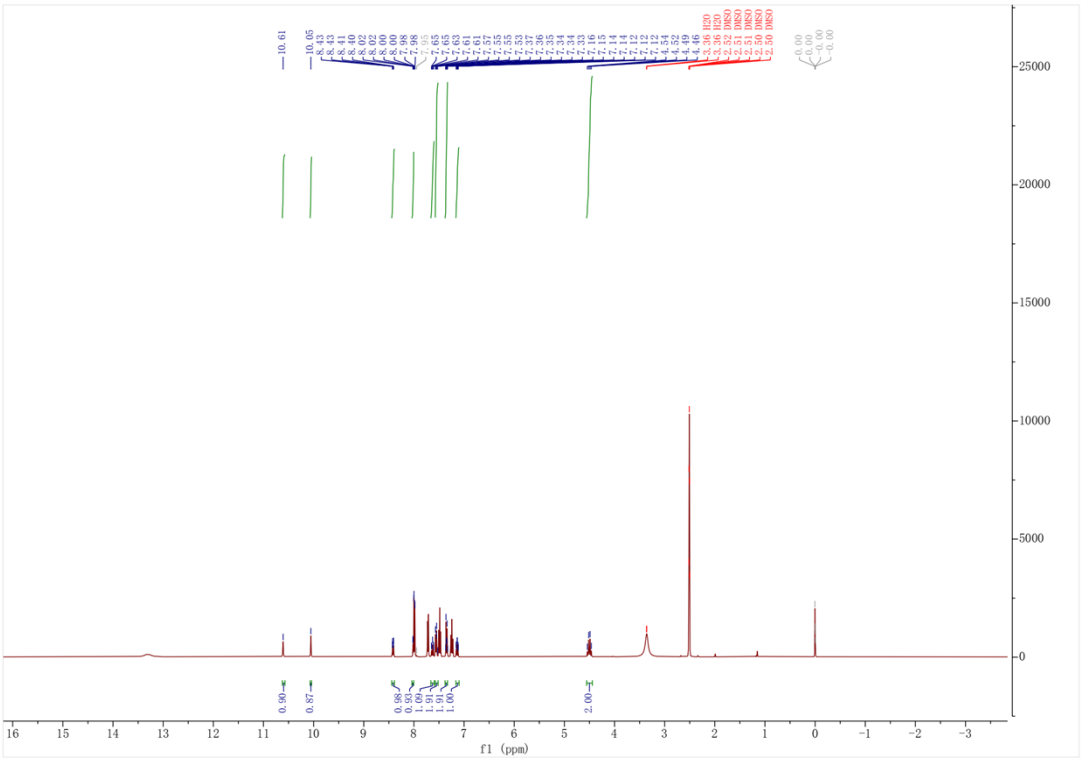
^{13}C NMR (100 MHz, DMSO-d_6) of **6ab**



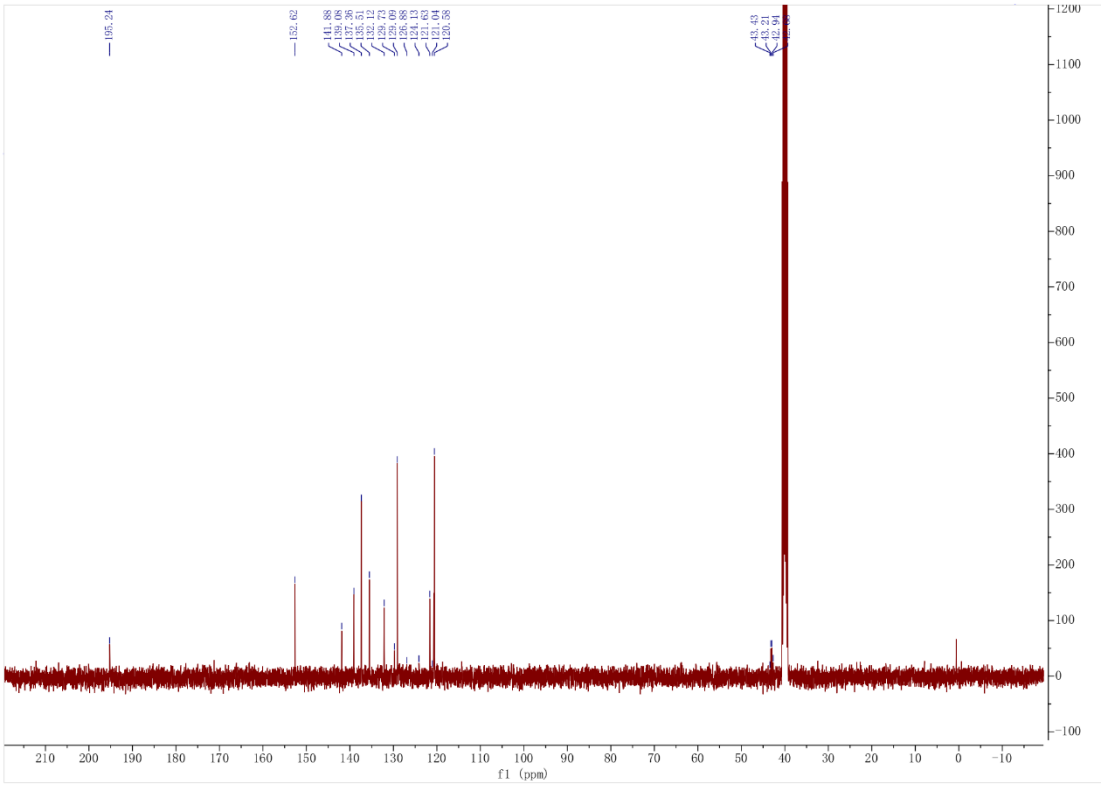
^{19}F NMR (376 MHz, DMSO-d_6) of **6ab**



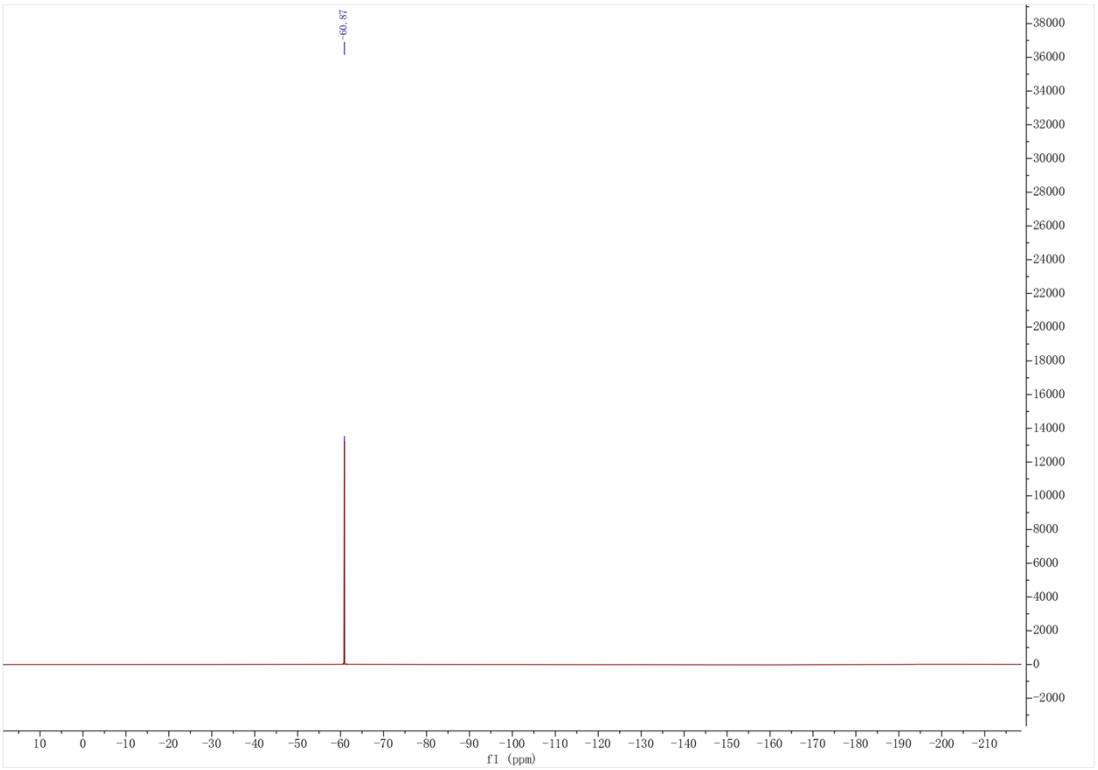
^{1}H NMR (400 MHz, DMSO-d_6) of **6ac**



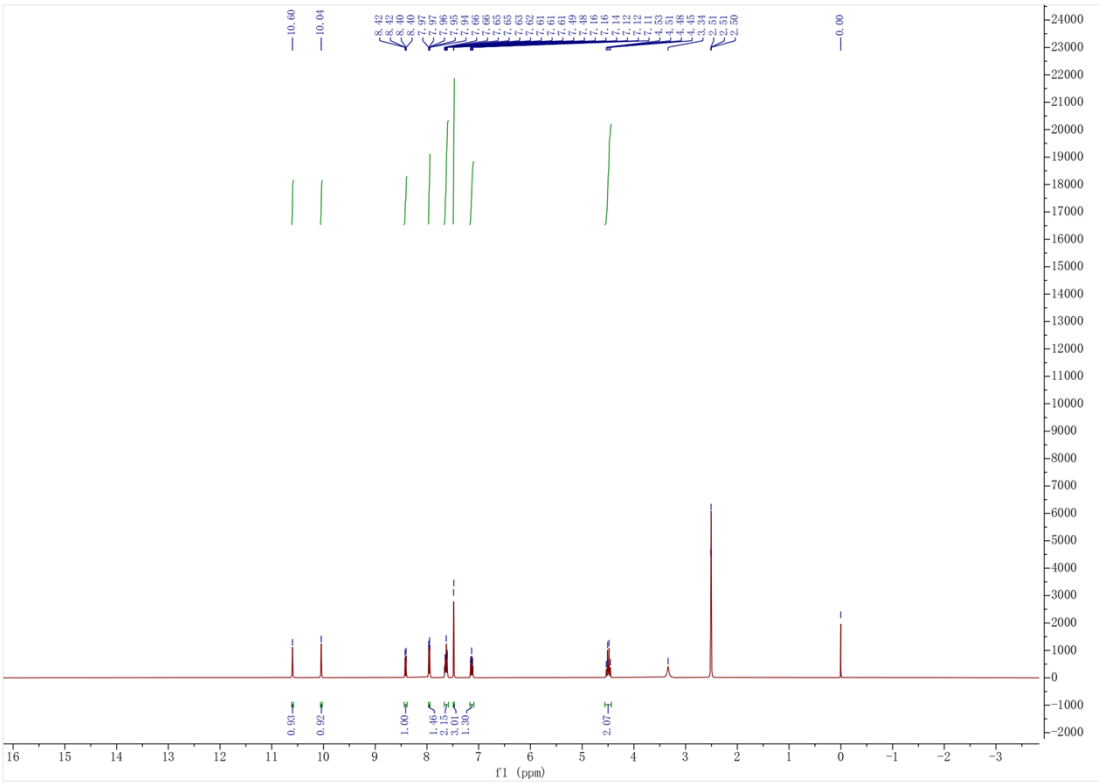
^{13}C NMR (100 MHz, DMSO-d_6) of **6ac**



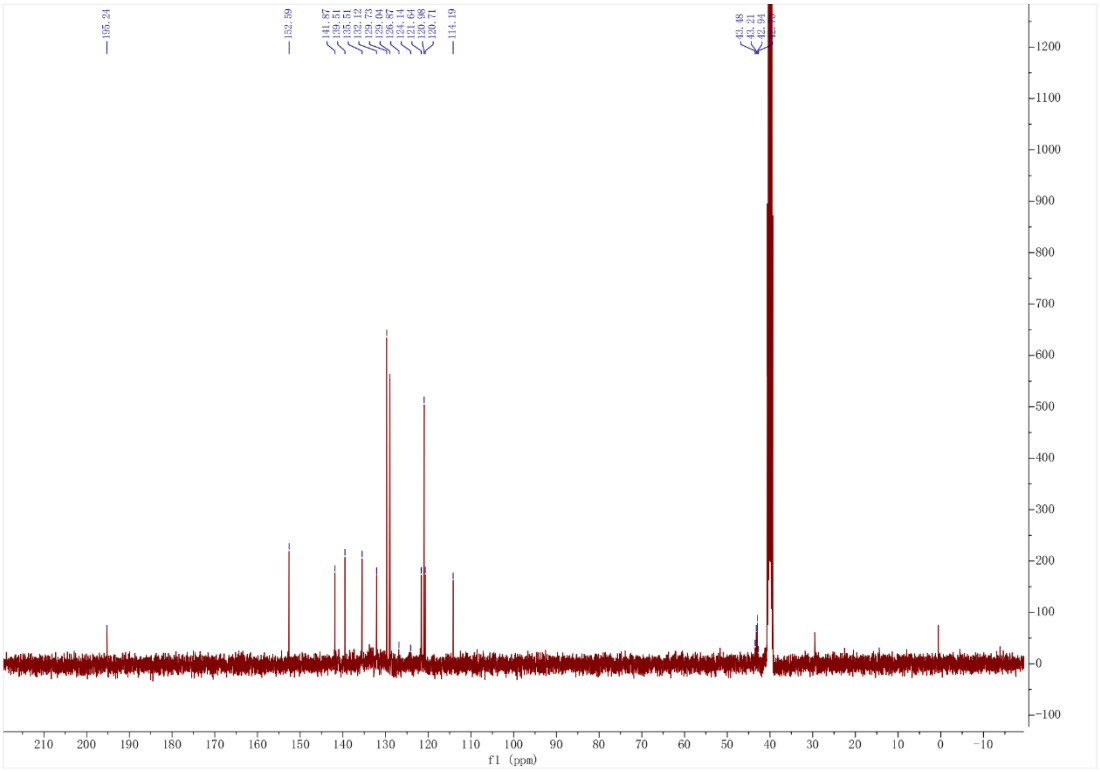
^{19}F NMR (376 MHz, DMSO-d_6) of **6ac**



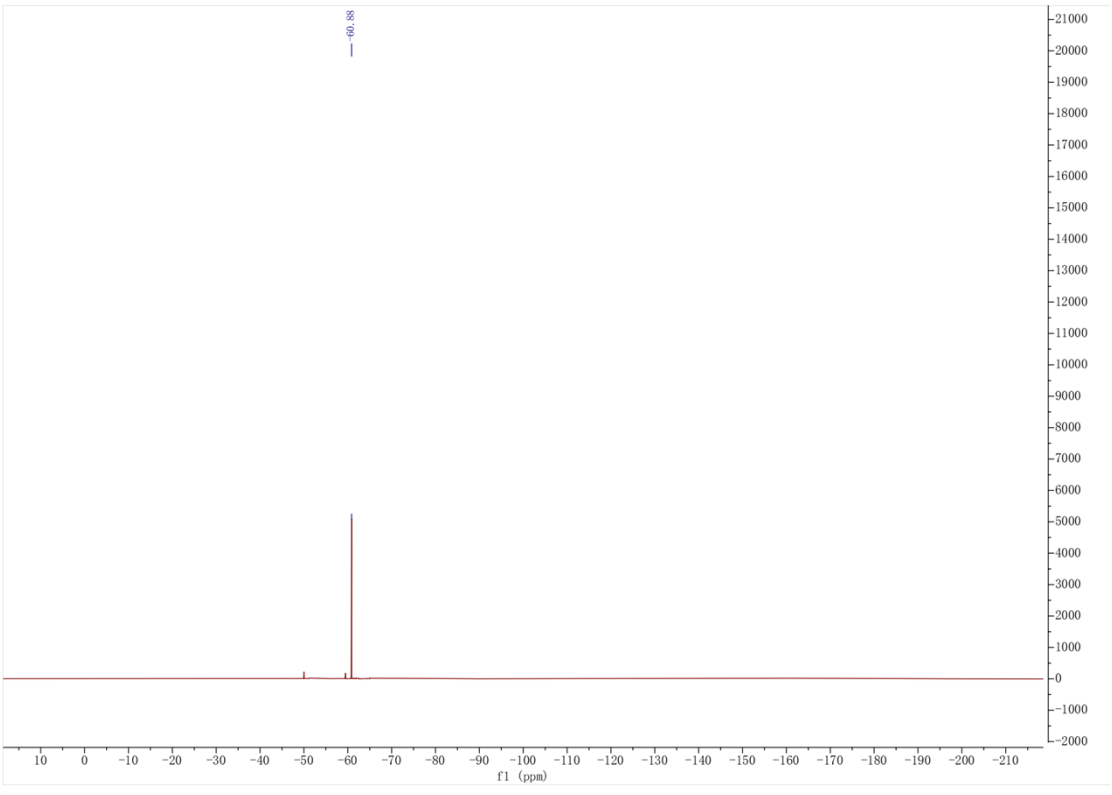
^{1}H NMR (400 MHz, DMSO-d_6) of **6ad**



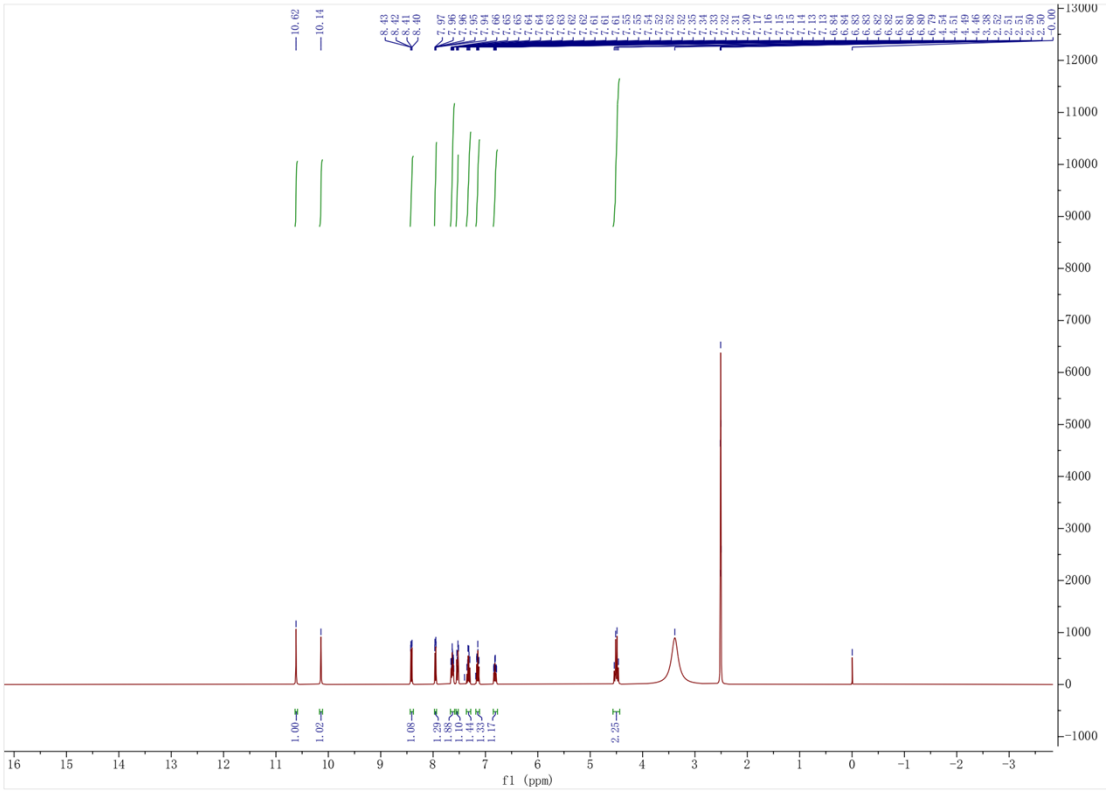
^{13}C NMR (100 MHz, DMSO-d_6) of **6ad**



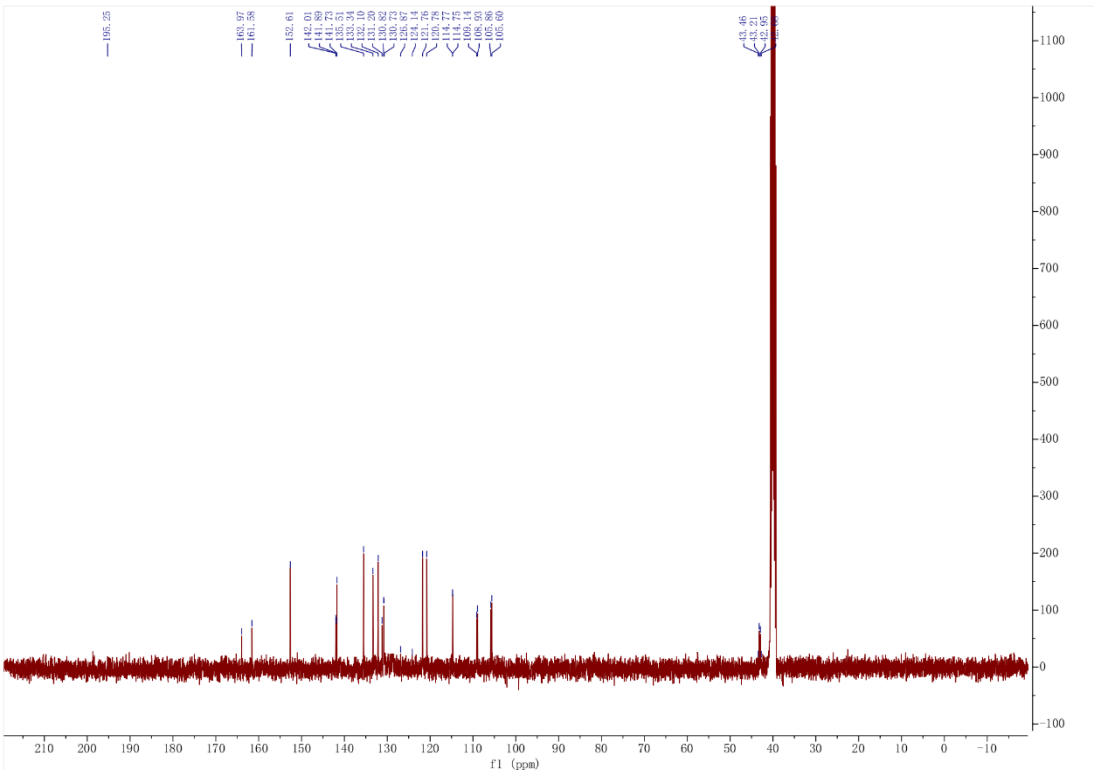
^{19}F NMR (376 MHz, DMSO-d_6) of **6ad**



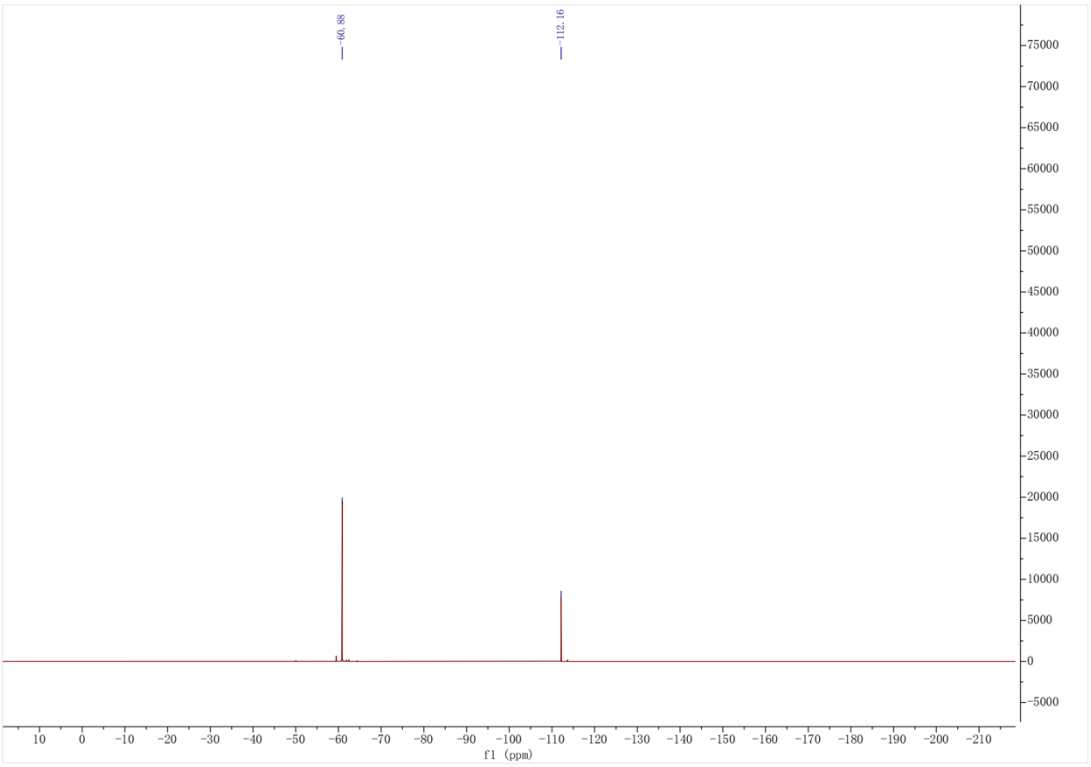
^{1}H NMR (400 MHz, DMSO-d_6) of **6ae**



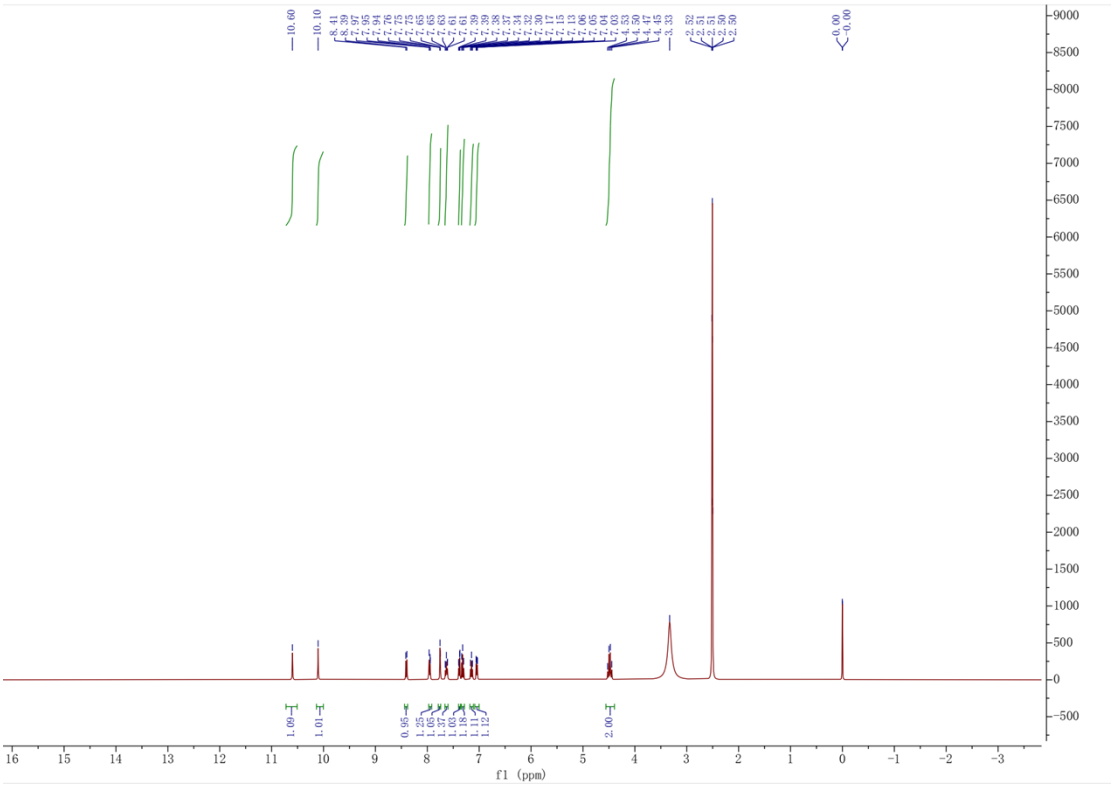
^{13}C NMR (100 MHz, DMSO-d_6) of **6ae**



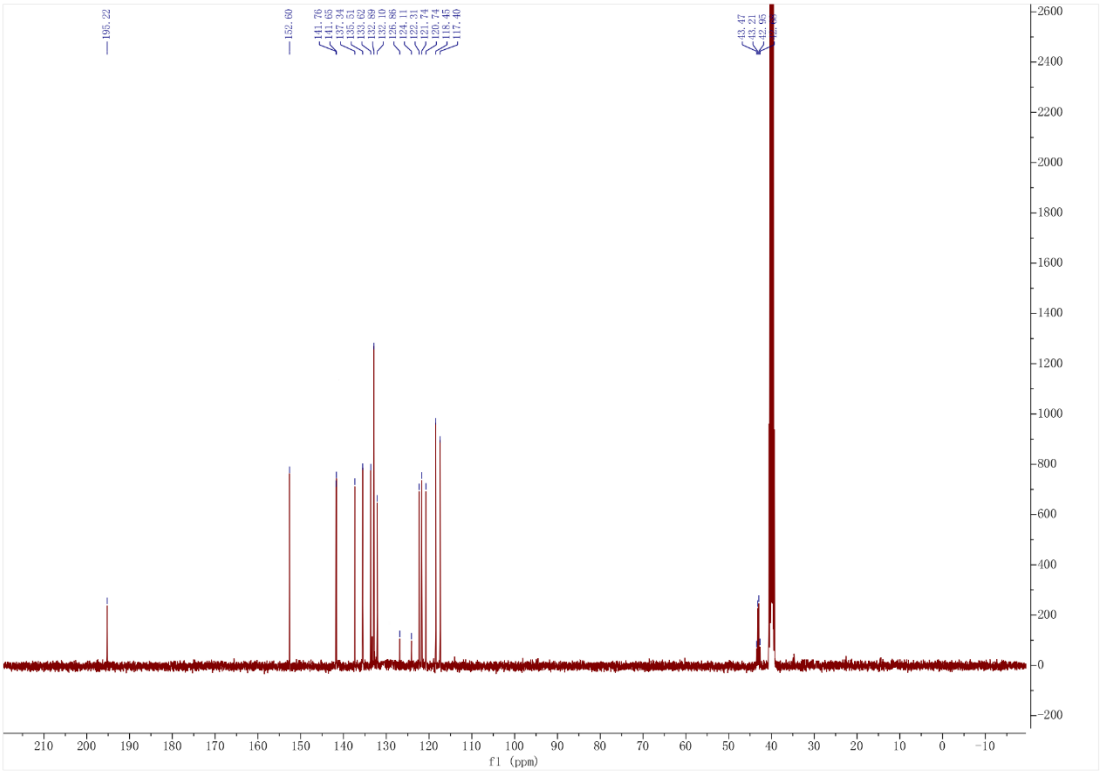
^{19}F NMR (376 MHz, DMSO-d_6) of **6ae**



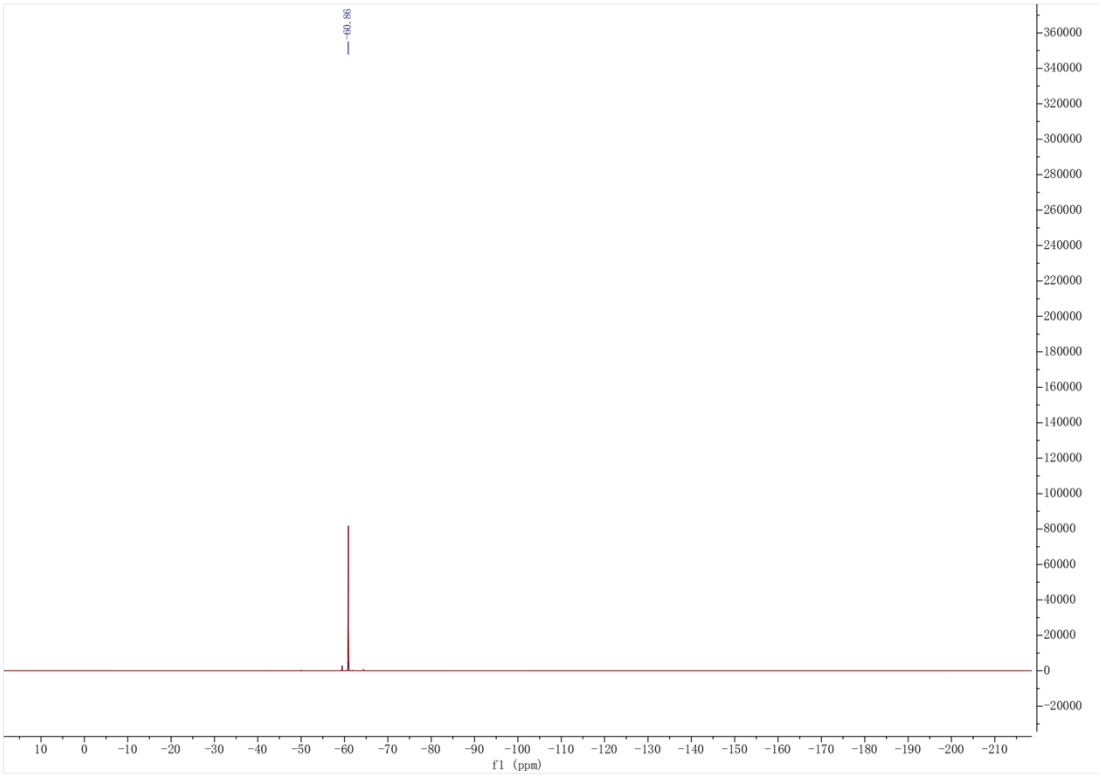
^{1}H NMR (400 MHz, DMSO-d_6) of **6af**



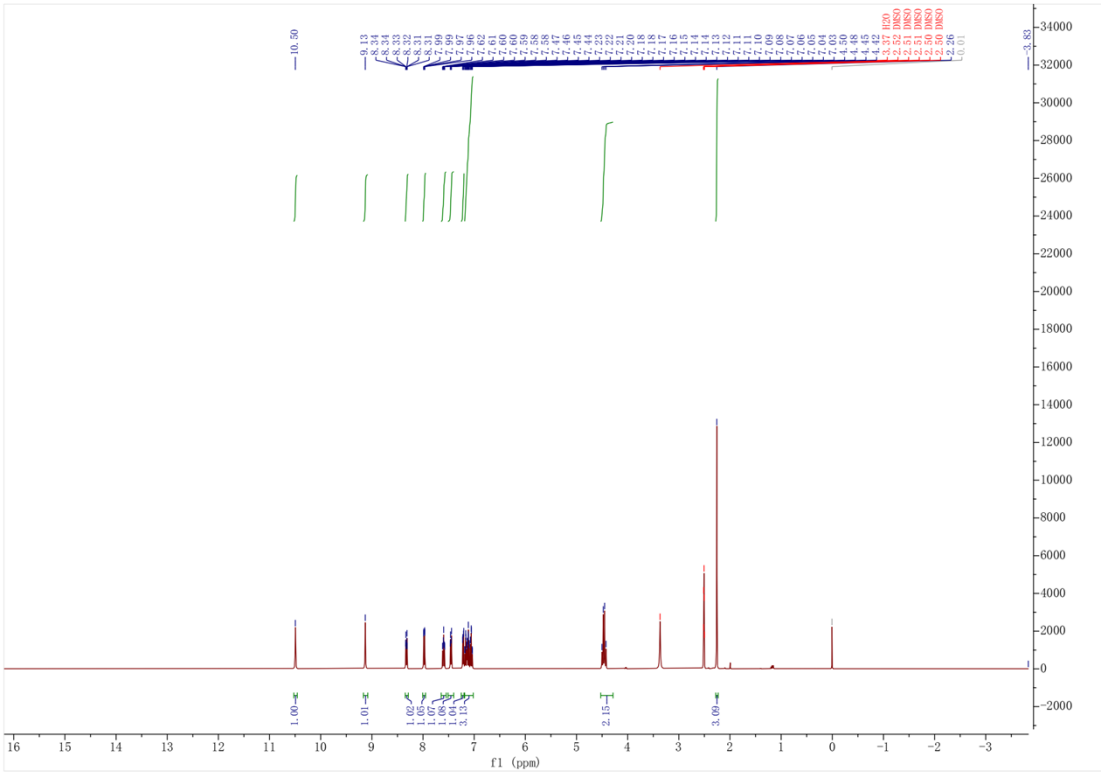
^{13}C NMR (100 MHz, DMSO-d_6) of **6af**



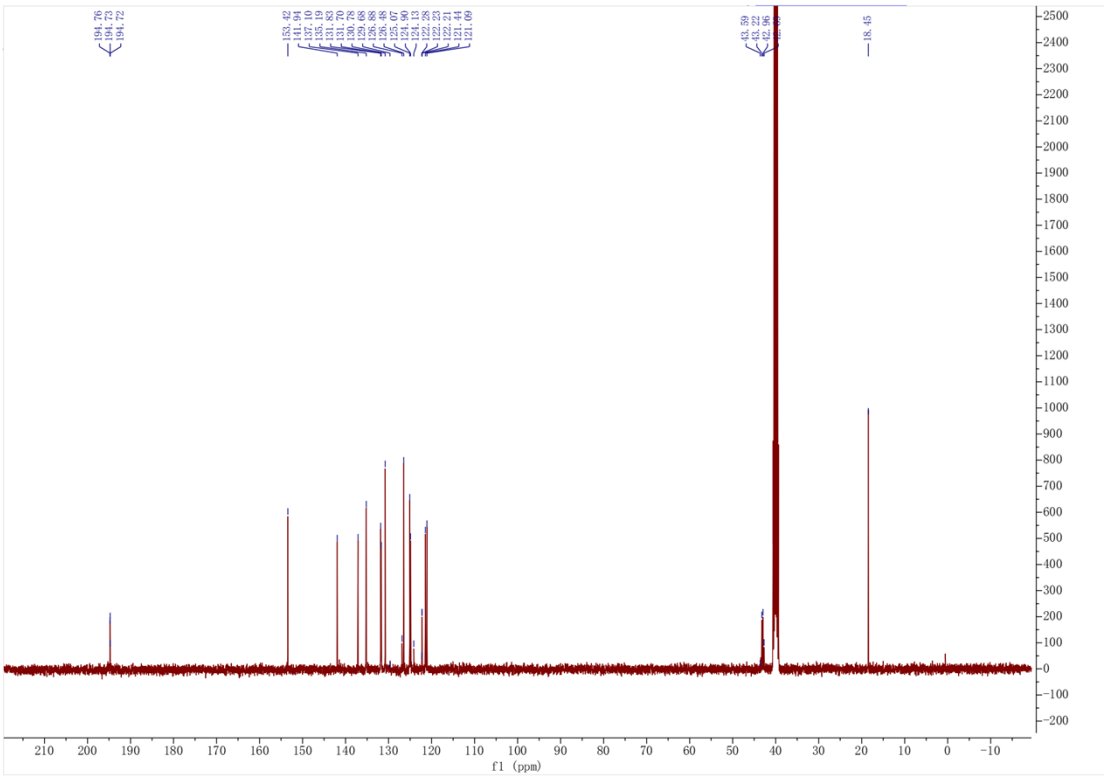
^{19}F NMR (376 MHz, DMSO-d_6) of **6af**



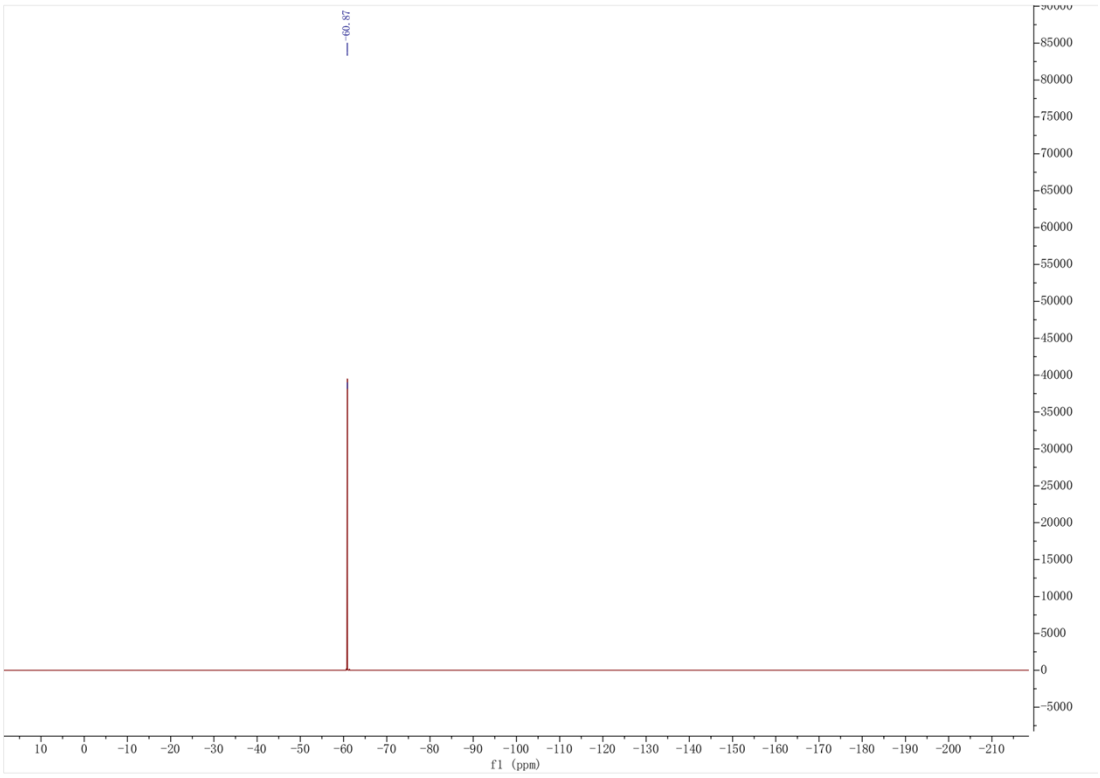
^{1}H NMR (400 MHz, DMSO-d_6) of **6ag**



^{13}C NMR (100 MHz, DMSO-d_6) of **6ag**



^{19}F NMR (376 MHz, DMSO-d_6) of **6ag**



6. The Computational Calculations

6.1. Computational Details

Density functional theory (DFT) calculations were performed with Gaussian 16. [1] The geometry of each species was optimized using the B3LYP functional[2] and the 6-311G(d,p) basis set with the SMD[3] solvation model for THF. Frequency calculations were also conducted at the same level of theory to obtain vibrational frequencies to determine the identity of stationary points as intermediates or transition states, as well as obtaining the thermal corrections to enthalpy ($H_{correction}$) and free energy ($G_{correction}$) at the temperature of 298 K. All DFT calculations were with an ultrafine integration grid. All structural figures were generated with CYLview[4]. Distances in structural figures are shown in Å and energies are in kcal/mol.

6.2. DFT-computed Gibbs free-energy profiles for benzyl isocyanate[a].

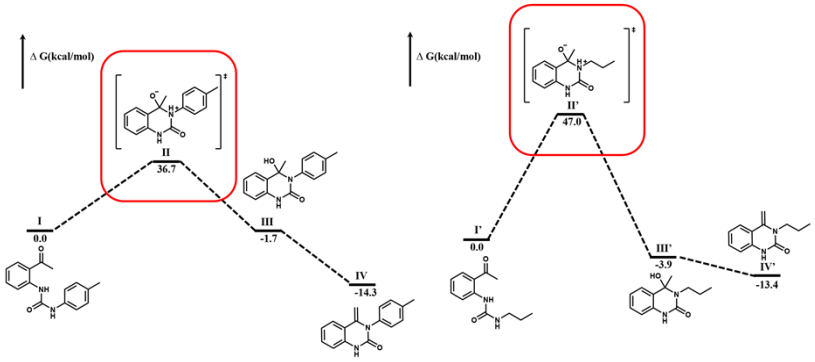


Fig. S2. DFT-computed Gibbs free-energy profiles for benzyl isocyanate[a].

[a]Values are in kcal mol^{-1}, obtained at the B3LYP/6-311G (d, p), SMD (THF) level of theory for the

intramolecular cyclization reaction sequence.

6.3. Cartesian Coordinates and Energies of Calculated Structures

1a			
C	−1.7478080	0.6324750	−0.9503300
C	−0.3747320	0.7232540	−0.8524250
C	0.2446500	1.7972170	−0.1659040
C	−0.5912570	2.8003440	0.4233040
C	−1.9908150	2.6644890	0.2992370
C	−2.5759000	1.6066510	−0.3704940
H	−2.1876130	−0.2043460	−1.4828670
H	0.2598250	−0.0343390	−1.3015730
H	−2.6294370	3.4175070	0.7431200
H	−3.6537810	1.5318110	−0.4478440
C	−0.0122280	3.9557270	1.1352970
O	1.2053300	4.1125760	1.2513750
C	−0.9380460	4.9918080	1.7451090
H	−1.5993170	4.5432090	2.4916820
H	−0.3271690	5.7574940	2.2219600
H	−1.5683180	5.4586970	0.9831110
N	1.5967530	1.8365030	−0.0750900
H	2.1524490	1.1600230	−0.5733190
H	2.0264540	2.6416240	0.3586640

2a			
C	−1.4830410	0.2484440	0.0204360
C	−0.1032330	0.3026080	0.2369890
C	0.6118370	1.4866130	0.0722000
C	−0.0521240	2.6497960	−0.3170080
C	−1.4345380	2.6178440	−0.5392930
C	−2.1317510	1.4287290	−0.3702810
H	0.4258090	−0.5948410	0.5401140
H	1.6813950	1.5174830	0.2427740
H	−1.9513740	3.5219320	−0.8418910
H	−3.2029050	1.4171880	−0.5456350
C	−2.2584370	−1.0330350	0.1981380
H	−1.6066700	−1.8525120	0.5075360
H	−3.0409670	−0.9201350	0.9554260
H	−2.7527080	−1.3285810	−0.7330020
N	0.6922260	3.8265250	−0.4751240
C	0.5479770	4.9801810	−0.7758600
O	0.5401720	6.1196050	−1.0503910

I			
C	−0.2292600	0.5643620	−1.6018530
C	−0.9702690	−0.1568460	−0.6501360
C	−2.1498310	0.4359960	−0.1045240
C	−2.5035880	1.7322580	−0.5239570

C	-1.7533230	2.4371790	-1.4496780
C	-0.6147120	1.8374160	-1.9909390
H	0.6443770	0.1128690	-2.0489900
H	-3.3956550	2.1906000	-0.1185410
H	-2.0527010	3.4325240	-1.7548710
H	-0.0220720	2.3632860	-2.7314630
C	-3.0261500	-0.2816930	0.8586420
O	-2.8637870	-1.4706340	1.1293410
C	-4.1617660	0.4668440	1.5240050
H	-4.6302140	-0.1974010	2.2491270
H	-3.8063310	1.3683510	2.0293830
H	-4.9106740	0.7732920	0.7878940
N	-0.6054110	-1.4386790	-0.2487180
H	-1.3675630	-1.9594230	0.1808060
C	0.5046390	-2.2221110	-0.5577670
N	1.7377320	-1.6078690	-0.6487550
H	2.4328810	-2.2312530	-1.0396330
C	2.2654100	-0.5048590	0.0721850
C	3.4134830	0.1162990	-0.4349500
C	1.7266010	-0.0450780	1.2764870
C	4.0047750	1.1720830	0.2483960
H	3.8414060	-0.2374180	-1.3672400
C	2.3200940	1.0269770	1.9401450
H	0.8541110	-0.5229580	1.7025080
C	3.4654520	1.6574870	1.4462640
H	4.8985220	1.6316420	-0.1620980
H	1.8850080	1.3678610	2.8742160
O	0.3828180	-3.4255530	-0.7290730
C	4.0925110	2.8270270	2.1638800
H	5.1817990	2.7355150	2.2004000
H	3.8648330	3.7709170	1.6556470
H	3.7240300	2.9077490	3.1889150

II			
C	-0.3020180	-0.5436080	0.4122790
C	0.9780930	-0.0900890	0.8209960
C	1.1581040	1.1814290	1.3217180
C	0.0577270	2.0515820	1.3979490
C	-1.1821940	1.6676680	0.9258170
C	-1.3812680	0.3843480	0.3767870
H	1.8087230	-0.7845040	0.8084400
H	2.1328640	1.4980340	1.6718780
H	0.1852690	3.0495760	1.8021840
H	-2.0096370	2.3692440	0.9264240
C	-0.5056220	-1.9447510	0.1810010
N	-2.1177760	-1.7797510	-1.5598970
C	-2.8521880	-0.6469000	-1.4333500
N	-2.5768940	0.1260310	-0.2587370
H	-3.2236830	0.9060780	-0.2278090
O	-3.7549650	-0.2274420	-2.1547340
O	-1.5681180	-2.5470840	0.7250410

H	-2.1851930	-2.5780030	-0.0767480
C	0.5722310	-2.8407270	-0.3072530
H	0.9980720	-3.3796010	0.5490750
H	0.1265820	-3.5994300	-0.9567690
H	1.3627240	-2.3169680	-0.8410750
C	-2.0554930	-2.4205800	-2.8045660
C	-1.9701710	-3.8232140	-2.8327410
C	-1.9897110	-1.7398690	-4.0373590
C	-1.8246020	-4.5137350	-4.0338430
H	-2.0394150	-4.3714470	-1.8992820
C	-1.8411110	-2.4389260	-5.2271220
H	-2.0607130	-0.6602490	-4.0544340
C	-1.7565800	-3.8393070	-5.2557500
H	-1.7687500	-5.5979230	-4.0177970
H	-1.7904440	-1.8850380	-6.1602570
C	-1.6135200	-4.5799520	-6.5620650
H	-0.7740880	-4.1946750	-7.1497700
H	-1.4483110	-5.6471320	-6.3981100
H	-2.5121860	-4.4732270	-7.1797870

III			
C	-2.6583300	0.3219700	1.4634160
C	-1.3354500	0.2795450	1.0467470
C	-0.7866850	1.3670240	0.3538460
C	-1.5569810	2.5034950	0.0805200
C	-2.8873500	2.5216890	0.5070970
C	-3.4404610	1.4465740	1.1964360
H	-3.0787290	-0.5223590	1.9983900
H	-0.7154770	-0.5873310	1.2497500
H	-3.5099120	3.3803090	0.2914990
H	-4.4751130	1.4840350	1.5164540
N	0.5338310	1.3298280	-0.0724500
H	1.0858520	0.5024620	0.1071470
C	1.2516300	2.4182220	-0.5156090
O	2.4521470	2.3368540	-0.7325350
N	0.5268140	3.5919130	-0.6546380
C	1.2761860	4.7164080	-1.1652660
C	1.8052380	5.6545930	-0.2807890
C	1.4759420	4.8820050	-2.5367120
C	2.5122550	6.7526140	-0.7636020
H	1.6589330	5.5215080	0.7849990
C	2.1802150	5.9856070	-3.0123370
H	1.0943500	4.1409600	-3.2289840
C	2.7108060	6.9395200	-2.1365490
H	2.9155730	7.4759200	-0.0621290
H	2.3260670	6.1018710	-4.0815630
C	3.5031460	8.1139130	-2.6546070
H	3.1528930	8.4279130	-3.6409060
H	3.4367230	8.9691810	-1.9779780
H	4.5637900	7.8556200	-2.7521450
C	-0.9587860	3.6288340	-0.7544060

C	-1.4660640	5.0089620	-0.3252620
H	-1.0393040	5.7893290	-0.9572040
H	-2.5491700	5.0528820	-0.4333730
H	-1.2029750	5.2211640	0.7123340
O	-1.3752000	3.3641420	-2.1048550
H	-1.2305690	4.1679730	-2.6214570

IV			
C	-2.0326350	-0.2184310	-0.0135940
C	-0.6852040	-0.2654030	-0.3932770
C	0.0658890	0.8997910	-0.4194290
C	-0.5195770	2.1172210	-0.0608620
C	-1.8560290	2.1575990	0.3116390
C	-2.6441930	0.9970890	0.3338830
H	-0.2430840	-1.2190230	-0.6610400
H	1.1087680	0.8596040	-0.7127980
H	0.0657330	3.0290970	-0.0688650
H	-2.2930760	3.1055430	0.5972490
N	-2.7853960	-1.3843300	0.0226540
H	-2.3483560	-2.2636780	-0.2175870
C	-4.0811820	-1.4816920	0.4705520
N	-4.6825600	-0.2780480	0.8263360
C	-6.0469080	-0.3675250	1.2905400
C	-7.0992310	-0.3775900	0.3766780
C	-6.3111890	-0.4272530	2.6546300
C	-8.4108180	-0.4556250	0.8328210
H	-6.8878880	-0.3278230	-0.6853930
C	-7.6289240	-0.5038220	3.1028140
H	-5.4891580	-0.4173600	3.3613390
C	-8.6989840	-0.5200670	2.2028560
H	-9.2242220	-0.4687370	0.1142040
H	-7.8260980	-0.5556740	4.1685210
C	-10.1259690	-0.6103970	2.6837230
H	-10.7184550	0.2374460	2.3255930
H	-10.6091940	-1.5200800	2.3127130
H	-10.1782960	-0.6227360	3.7742080
O	-4.6541920	-2.5561230	0.5446430
C	-4.0771570	1.0056730	0.7015030
C	-4.7833450	2.1311400	0.9144880
H	-5.8270360	2.1126670	1.1897130
H	-4.3179800	3.1001300	0.8118560

2a'			
C	-1.1885880	-0.1381950	0.2802190
H	-0.9672320	-1.1898790	0.4877520
H	-1.0050180	0.0392130	-0.7842130
H	-2.2548060	0.0188320	0.4637330
C	-0.3451250	0.7907230	1.1545360
H	-0.5998050	1.8359250	0.9480630
H	-0.5605570	0.6113510	2.2127540

C	1.1534630	0.5918190	0.9167480
H	1.4068710	0.7979750	-0.1279040
H	1.4337390	-0.4431150	1.1231090
N	1.9749900	1.4377610	1.7687340
C	2.1202620	2.5910540	2.0515480
O	2.3630060	3.6847440	2.4126400

I'			
C	-0.2775780	0.5888170	-1.6949930
C	-0.9160450	-0.1271560	-0.6643430
C	-2.0795430	0.4417390	-0.0565550
C	-2.5095290	1.7109190	-0.4887930
C	-1.8569100	2.4112160	-1.4885950
C	-0.7404490	1.8315520	-2.0957640
H	0.5778270	0.1521380	-2.1906650
H	-3.3858310	2.1508070	-0.0317890
H	-2.2146200	3.3847870	-1.8010170
H	-0.2265000	2.3505390	-2.8976790
C	-2.8635690	-0.2770660	0.9804200
O	-2.6214080	-1.4417960	1.2947140
C	-4.0101590	0.4356940	1.6678500
H	-4.4056750	-0.2220350	2.4408000
H	-3.6863840	1.3766780	2.1199970
H	-4.8084400	0.6672040	0.9564940
N	-0.4634960	-1.3699930	-0.2426670
H	-1.1668150	-1.8973490	0.2703220
C	0.5971640	-2.1638130	-0.7139170
N	1.8005580	-1.5491720	-0.9194220
H	2.4914530	-2.1956070	-1.2798820
O	0.4248180	-3.3603390	-0.9027930
C	2.3498060	-0.4102640	-0.1759300
H	2.6918520	0.3551000	-0.8813850
H	1.5522770	0.0326330	0.4197460
C	3.5090530	-0.8268980	0.7348230
H	4.2764270	-1.3251860	0.1303700
H	3.1467840	-1.5656090	1.4577170
C	4.1252670	0.3668000	1.4664630
H	4.9530670	0.0490070	2.1061470
H	4.5158130	1.1076020	0.7613540
H	3.3876630	0.8674490	2.1017820

II'			
C	-0.5293690	-0.6781030	0.0808170
C	0.6126030	-0.8538080	0.8695310
C	1.3406890	0.2332390	1.3445810
C	0.9335560	1.5286850	1.0275030
C	-0.1850600	1.7274950	0.2290650
C	-0.9117800	0.6287890	-0.2433000
H	0.9272380	-1.8551230	1.1361000
H	2.2146990	0.0693290	1.9641790

H	1.4895620	2.3842780	1.3936560
H	-0.5017900	2.7300460	-0.0397110
C	-1.4202750	-1.8500220	-0.2817770
N	-2.3998160	-1.4076610	-1.6299660
C	-2.6694590	-0.0156850	-1.8820910
N	-2.0094030	0.8646260	-1.0829240
H	-2.2528210	1.8322320	-1.2577240
O	-3.4746410	0.3353720	-2.7239970
O	-2.4852580	-2.0092220	0.5209510
H	-3.0635050	-1.7415310	-0.6819590
C	-0.6657570	-3.1202050	-0.6420450
H	-0.2006160	-3.4932670	0.2738130
H	-1.3586500	-3.8912790	-0.9791690
H	0.1160710	-2.9655860	-1.3894970
C	-2.4995630	-2.2643240	-2.8513970
H	-1.5479850	-2.7821510	-2.9754880
H	-2.6412690	-1.6095930	-3.7104980
C	-3.6564070	-3.2603270	-2.7685140
H	-4.5893690	-2.7003940	-2.6462350
H	-3.5431690	-3.8843690	-1.8763410
C	-3.7356370	-4.1423600	-4.0152070
H	-4.5750160	-4.8393460	-3.9461350
H	-3.8758140	-3.5413130	-4.9192680
H	-2.8229180	-4.7329930	-4.1445740

III'			
C	-5.0149090	0.1060340	0.0752620
C	-4.0839660	1.1286420	-0.0304990
C	-2.7135110	0.8287190	-0.0598490
C	-2.2779780	-0.4977970	0.0014300
C	-3.2323210	-1.5111770	0.1264110
C	-4.5920930	-1.2227900	0.1601330
H	-6.0721850	0.3457980	0.0998610
H	-4.3997750	2.1654110	-0.0810400
H	-2.9012550	-2.5392190	0.2112340
H	-5.3153370	-2.0240220	0.2565240
N	-1.7751140	1.8456360	-0.1347240
H	-2.0807930	2.8080870	-0.1123430
C	-0.4081550	1.6669620	-0.0874150
O	0.3424460	2.6381850	-0.0487410
N	0.0432810	0.3711130	-0.1151810
C	-0.7971080	-0.8485910	-0.0378960
C	-0.4827380	-1.7689270	-1.2281340
H	0.5705560	-2.0617780	-1.2294010
H	-1.0878740	-2.6753400	-1.1743030
H	-0.6995490	-1.2597390	-2.1686870
O	-0.5261280	-1.5392390	1.1900460
H	0.1830270	-2.1742930	1.0335610
C	1.5055760	0.2062550	-0.0379910
H	1.8827860	0.8939420	0.7215490
H	1.7109010	-0.8030450	0.3206790

C	2.2462910	0.4543670	−1.3569120
H	2.0277770	1.4708340	−1.6928250
H	1.8698100	−0.2283120	−2.1250640
C	3.7574690	0.2744910	−1.1963010
H	4.2779010	0.4566230	−2.1407150
H	4.1634300	0.9706820	−0.4551890
H	4.0080990	−0.7408230	−0.8702440

IV'			
C	2.5319070	0.7426740	−0.2209540
C	3.8908400	1.0700590	−0.1392440
C	4.8061770	0.1120560	0.2708560
C	4.3707680	−1.1715480	0.6117610
C	3.0218670	−1.4897900	0.5250450
C	2.0775560	−0.5475260	0.0919050
H	4.2112390	2.0742580	−0.3954120
H	5.8577730	0.3676790	0.3354180
H	5.0804270	−1.9176540	0.9492250
H	2.6951300	−2.4822210	0.8081400
N	1.6024410	1.6921540	−0.6203180
H	1.9143950	2.6282660	−0.8397900
C	0.2364020	1.5398110	−0.5569110
N	−0.2169200	0.2747320	−0.2010260
O	−0.5079480	2.4789270	−0.8038670
C	0.6367170	−0.8518050	−0.0568630
C	0.1607370	−2.1118810	−0.0441860
H	−0.8881010	−2.3498830	−0.1261160
H	0.8397190	−2.9466440	0.0485730
C	−1.6786230	0.0851650	−0.1725600
H	−1.9326330	−0.7375530	−0.8456680
H	−2.1084900	0.9933200	−0.5882270
C	−2.2522080	−0.1660470	1.2280730
H	−3.3219850	−0.3647450	1.0973030
H	−1.8198340	−1.0747310	1.6562610
C	−2.0613250	1.0011480	2.1985480
H	−2.5209850	0.7778960	3.1658760
H	−1.0015860	1.2028170	2.3787330
H	−2.5167960	1.9191400	1.8151490

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