Supporting Information

Three-component copper-catalyzed difluoroalkylamidation of alkynes: An efficient approach to difluoroalkylated enamides

Jing Ren,‡ Kaiyun Liu,‡ Jinlong Li, Xinyu Long, and Kaizhi Li*

Institute of Biopharmaceuticals, West China Hospital, Sichuan University, 37 Guoxue Alley, Chengdu 610041, China.

Email: kzli@scu.edu.cn

‡These authors contributed equally: Jing Ren and Kaiyun Liu.

Table of contents

I. General remarks

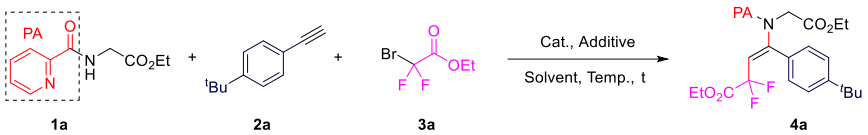
NMR spectra were obtained on a Bruker AV II-400 MHz spectrometer. The aluminum block [9-hole inner diameter 26-27 mm, H200927 (Syhtnwre)] was used as heat source. The ^{1}H NMR (400 MHz) chemical shifts were measured relative to $CDCl_3$ or TMS as the internal reference ($CDCl_3$: δ = 7.26 ppm, TMS: δ = 0.00 ppm). The ^{13}C NMR (100 MHz) chemical shifts were given using $CDCl_3$ as the internal standard ($CDCl_3$: δ = 77.16 ppm). Chemical shifts δ are reported in ppm relative to residual solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz), integration. High-resolution mass spectra (HRMS) were obtained with a high-resolution quadrupole-orbitrap tandem mass spectrometer (Q-Exactive plus; Thermo Fisher Scientific, Waltham, MA, USA) with electrospray ionization (ESI). X-Ray single-crystal diffraction data were collected on a Bruker D8 VENTURE single crystal diffraction.

Unless otherwise noted, all reagents and solvents were obtained from commercially available sources and used without further purification. Reactions were monitored by Thin Layer Chromatography (TLC) using UV light (254/365 nm) for detection. Products were purified by column chromatography, which was carried out on 200-300 mesh of silica gel purchased from Qing Dao Hai Yang Chemical Industry Co. 2-Picolinamide derivatives 1,[1-3] alkynes **2**,[4,5] and difluoroalkyl bromides **3**[6-8] were prepared according to the literature.

II. Optimization of the difluoroalkylamidation of ethyl picolinoylglycinate 1a, 4-*tert*-butylphenylacetylene 2a with ethyl bromodifluoroacetate 3a

An oven-dried Schlenk tube with a magnetic stir bar was charged with ethyl picolinoylglycinate **1a** (20.8 mg, 0.10 mmol, 1.0 equiv.), 4-*tert*-butylphenylacetylene **2a** (36.1 µl, 0.20 mmol, 2.0 equiv.), ethyl bromodifluoroacetate **3a** (25.6 µl, 0.20 mmol, 2.0 equiv.), additive, and solvent under N_2 atmosphere. The tube was sealed with a teflon-coated cap and the reaction solution was heated at indicated temperature for indicated time. After being cooled to ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10, v/v) to provide the desired product **4a**.

Table S1: Optimization of the reaction conditions[a]



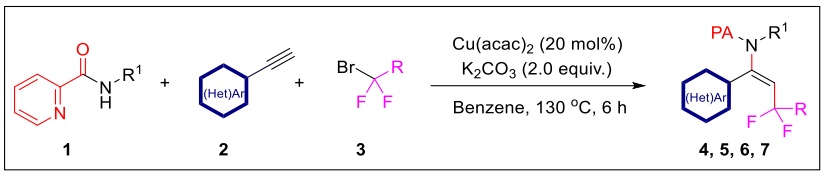
1a 2a 3a 4a

Entry	Cat. (equiv.)	Additive (equiv.)	Solvent	Temp. (°C)	t (h)	Yield (%)[b]
1	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	120	12	71
2	$Cu(acac)_2$ (0.2)	$KHCO_3$ (2.0)	Benzene	120	12	50
3	$Cu(acac)_2$ (0.2)	Na_2CO_3 (2.0)	Benzene	120	12	14
4	$Cu(acac)_2$ (0.2)	Cs_2CO_3 (2.0)	Benzene	120	12	56
5	$Cu(acac)_2$ (0.2)	Li_2CO_3 (2.0)	Benzene	120	12	n.d.
6	$Cu(acac)_2$ (0.2)	$CaCO_3$ (2.0)	Benzene	120	12	trace
7	$Cu(acac)_2$ (0.2)	NaOAc (2.0)	Benzene	120	12	n.d.
8	$Cu(acac)_2$ (0.2)	KOH (2.0)	Benzene	120	12	n.d.
9	$Cu(acac)_2$ (0.2)	K_2HPO_4(2.0)	Benzene	120	12	17
10	$Cu(acac)_2$ (0.2)	Na_2HPO_4 (2.0)	Benzene	120	12	15
11	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	120	12	57
12	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	$PhCF_3$	120	12	52
13	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	PhCl	120	12	51
14	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	CH_3CN	120	12	13
15	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	120	8	56
16	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	110	12	44
17	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	12	65
18	**$Cu(acac)_2$ (0.2)**	**K_2CO_3 (2.0)**	**Benzene**	**130**	**6**	**77**
19	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	8	71
20	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	4	65
21	$Cu(hmacac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	26
22	$Cu(tfacac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	73
23	$Cu(hfacac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	45
24	$Ni(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	n.d.
25	$Co(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	n.d.
26	$Mn(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	n.d.
27	$Fe(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	n.d.
28	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	30
29	$CuBr_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	27
30	CuCl (0.2)	K_2CO_3 (2.0)	Benzene	130	6	24
31	CuTc (0.2)	K_2CO_3 (2.0)	Benzene	130	6	25
32	$Cu(acac)_2$ (0.1)	K_2CO_3 (2.0)	Benzene	130	6	51
33	$Cu(acac)_2$ (0.2)	K_2CO_3 (1.5)	Benzene	130	6	76
34[c]	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	73
35[d]	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	69
36[e]	$Cu(acac)_2$ (0.2)	K_2CO_3 (2.0)	Benzene	130	6	46

37	--	K_2CO_3 (2.0)	Benzene	130	6	n.d.
38	$Cu(acac)_2$ (0.2)	--	Benzene	130	6	trace

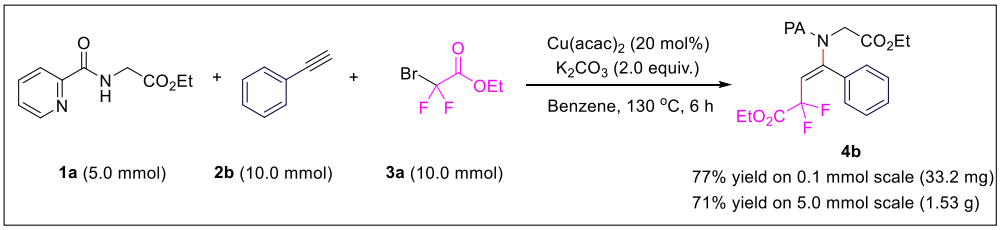
[a]Reaction conditions: **1a** (20.8 mg, 0.10 mmol, 1.0 equiv.), **2a** (34.6 μl, 0.20 mmol, 2.0 equiv.), **3a** (25.6 μl, 0.20 mmol, 2.0 equiv.), cat., additive and solvent (1.0 mL) at indicated temperature under N_2. [b]Isolated yield after chromatographic purification. [c]**2a** (1.5 equiv.) was used. [d]**3a** (1.5 equiv.) was used. [e]The reaction under an air atmosphere. $Cu(hmacac)_2$ = Copper(II) bis(2,2,6,6-tetramethyl-3,5-heptanedionate). $Cu(tfacac)_2$ = Copper(II) trifluoroacetylacetonate. $Cu(hfacac)_2$ = Copper(II) hexafluor-2,4-pentanedionate. n.d. = no product detected. PA = 2-Pyridylacyl.

III. General procedure for the synthesis of difluoroalkylated enamides



In a 25 mL Schlenk tube equipped with a stir bar was charged with 2-picolinamide substrates **1** (0.1 mmol, 1.0 equiv.), alkynes **2** (0.2 mmol, 2.0 equiv.), difluoroalkyl bromides **3** (0.2 mmol, 2.0 equiv.), $Cu(acac)_2$ (5.3 mg, 0.02 mmol, 0.2 equiv.) and K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.) in benzene (1.0 mL). The reaction was stirred at 130 °C for 6 h under N_2 atmosphere. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluents to obtain the desired products.

IV. Gram-scale synthesis of 4b

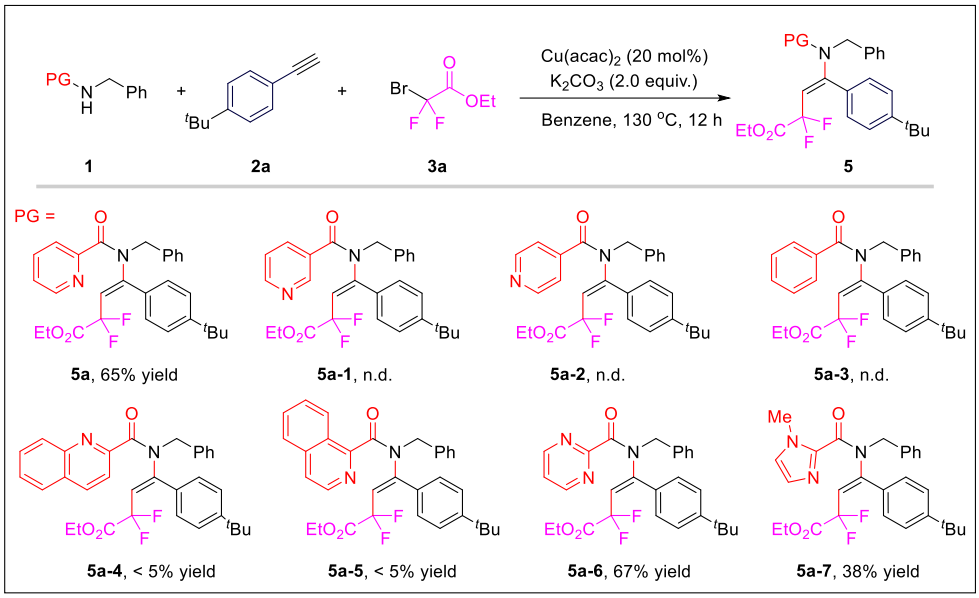


Ethyl picolinoylglycinate **1a** (5.0 mmol, 1.0 equiv., 1.04 g), ethynylbenzene **2b** (10.0 mmol, 2.0 equiv., 1.02 g/1.10 ml), ethyl 2-bromo-2,2-difluoroacetate **3a** (10.0 mmol, 2.0 equiv., 2.03 g/1.28 ml), K_2CO_3 (10.0 mmol, 2.0 equiv., 1.38 g), $Cu(acac)_2$ (1.0 mmol, 0.2 equiv., 261.8 mg) were added sequentially into a Schlenk tube under nitrogen, then the tube was capped with a rubber stopper. Benzene (25.0 mL) was then added by syringe. Then the tube was sealed with a teflon-coated cap under N_2 atmosphere and the reaction mixture was stirred at room temperature for several minutes. Then the mixture was stirred at 130 °C for 6 h. After cooled to room temperature, the solution was diluted with

20 mL of CH_2Cl_2, filtered through a celite pad, and washed with 20-30 mL of CH_2Cl_2. Then the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluents to obtain the desired product **4b** (1.53 g, 71% yield).

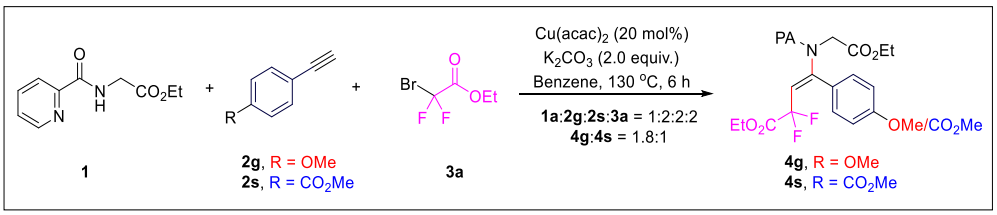
V. Investigation of the reaction mechanism

a) The effect of N-protecting groups

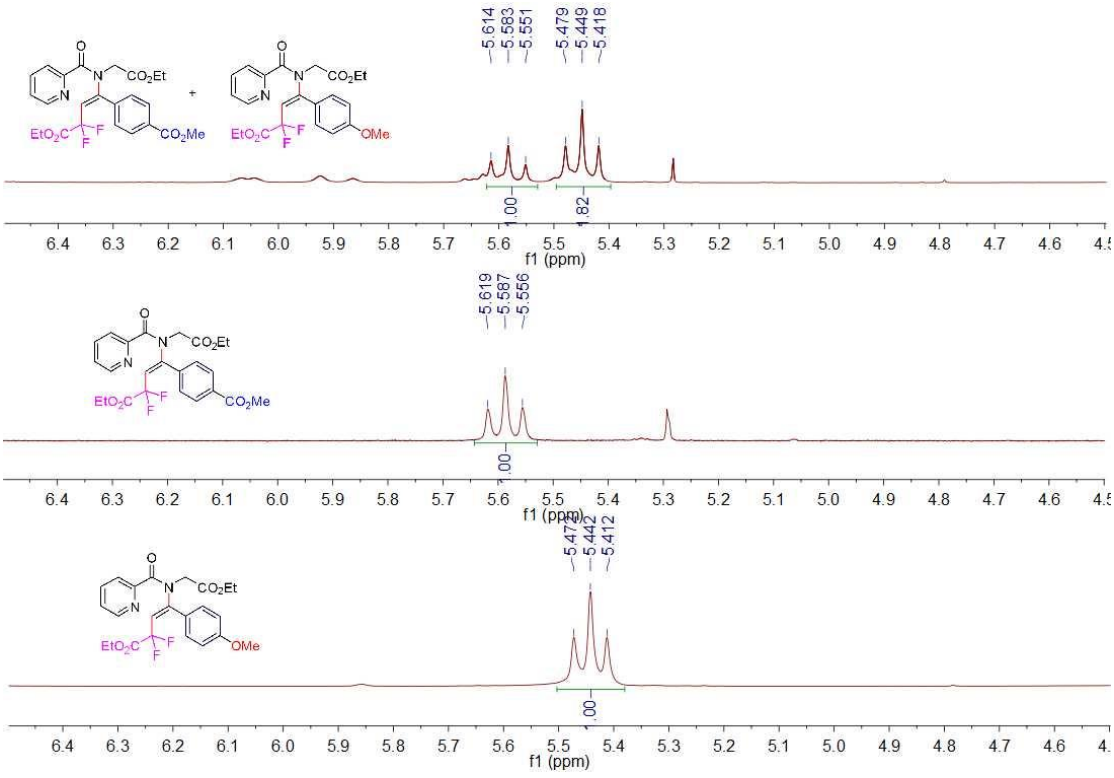


In a 25 mL Schlenk tube equipped with a stir bar was charged with **1** (0.10 mmol, 1.0 equiv.), 4-*tert*-butylphenylacetylene **2a** (36.1 µl, 0.20 mmol, 2.0 equiv.), ethyl bromodifluoroacetate **3a** (25.6 µl, 0.20 mmol, 2.0 equiv.), K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.), and $Cu(acac)_2$ (5.2 mg, 0.02 mmol, 0.2 equiv.) in benzene (1.0 mL). The reaction was stirred at 130 °C for 6 h under N_2 atmosphere. After cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluents to obtain the desired products.

b) Intermolecular competition experiments

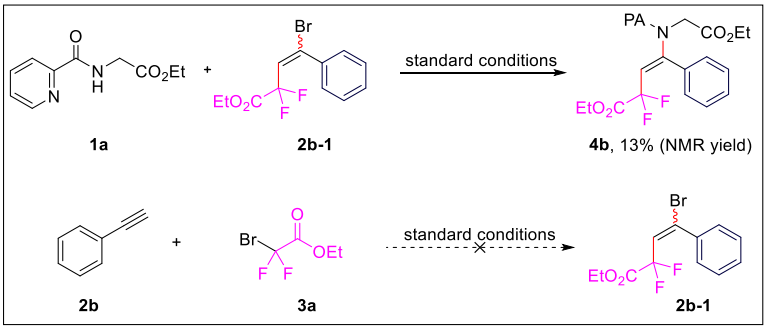


In a 25 mL Schlenk tube equipped with a stir bar was charged with **1a** (20.8 mg, 0.10 mmol, 1.0 equiv.), 1-ethynyl-4-methoxybenzene (**2g**, 26.4 mg, 0.2 mmol, 2.0 equiv.), methyl 4-ethynylbenzoate (**2s**, 32.0 mg, 0.2 mmol, 2.0 equiv.), ethyl bromodifluoroacetate **3a** (25.6 μl, 0.20 mmol, 2.0 equiv.), K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.), and $Cu(acac)_2$ (5.2 mg, 0.02 mmol, 0.2 equiv.) in benzene (1.0 mL). The reaction was stirred at 130 °C for 6 h under N_2 atmosphere. After being cooled to ambient temperature, the solvent was removed under reduced pressure, and the residue was purified by flash silica gel column chromatography using petroleum ether and ethyl acetate as eluents to obtain the products **4g** and **4s** as the mixture. Then the mixture was detected by ^1H NMR to obtain the ratio.



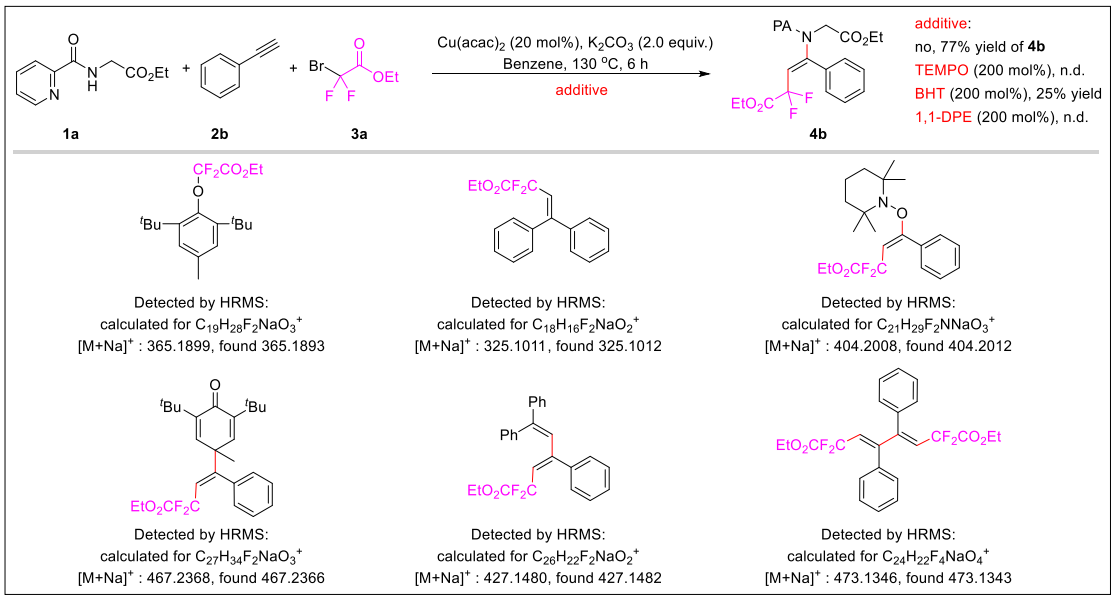
^1H–NMR spectrum comparison (400 MHz, $CDCl_3$)

c) Reactivity of difluoroalkylated vinyl bromide 2b-1

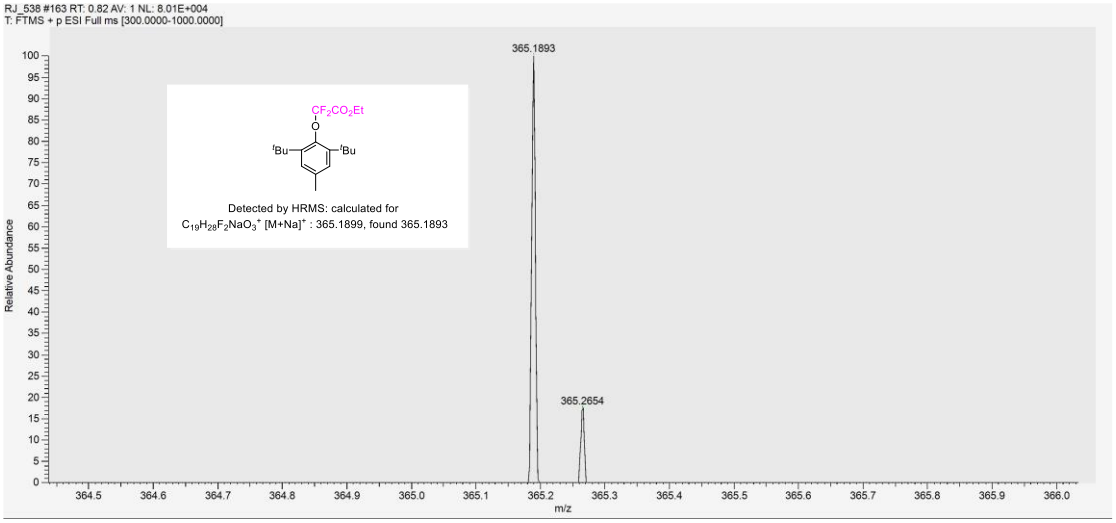


The treatment of difluoroalkylated vinyl bromide **2b-1** with **1a** under standard conditions gave target product **4b** in 13% NMR yield. Then the reaction between ethynylbenzene **2b** and bromodifluoroacetate **3a** was studied in absence of picolinamide **1a** under standard conditions; however, no difluoroalkylated vinyl bromide (**2b-1)** product was observed. This result suggested that the oxidative addition of difluoroalkylated vinyl bromide to the copper catalyst can be ruled out in current reaction mechanism.

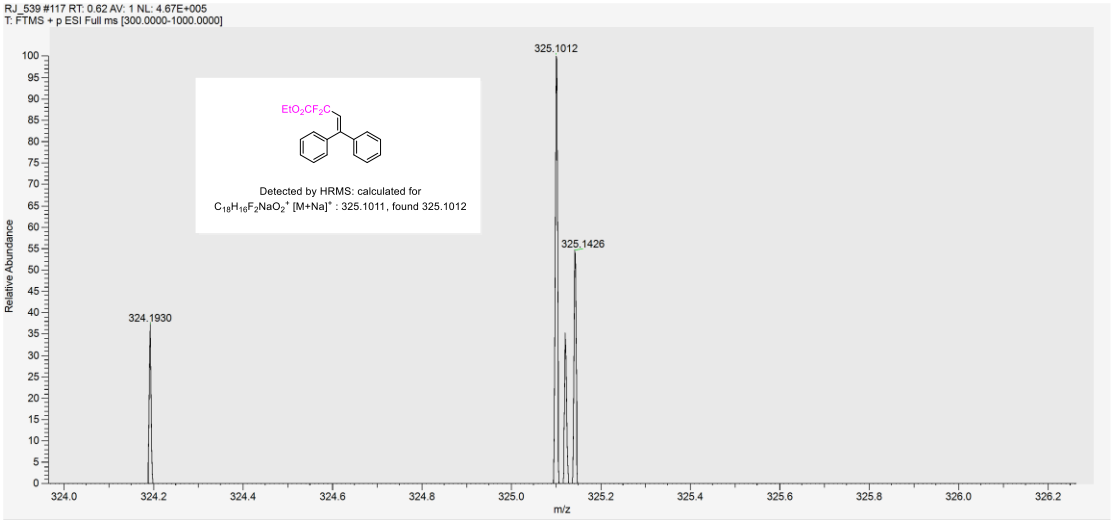
d) Radical scavenger experiments



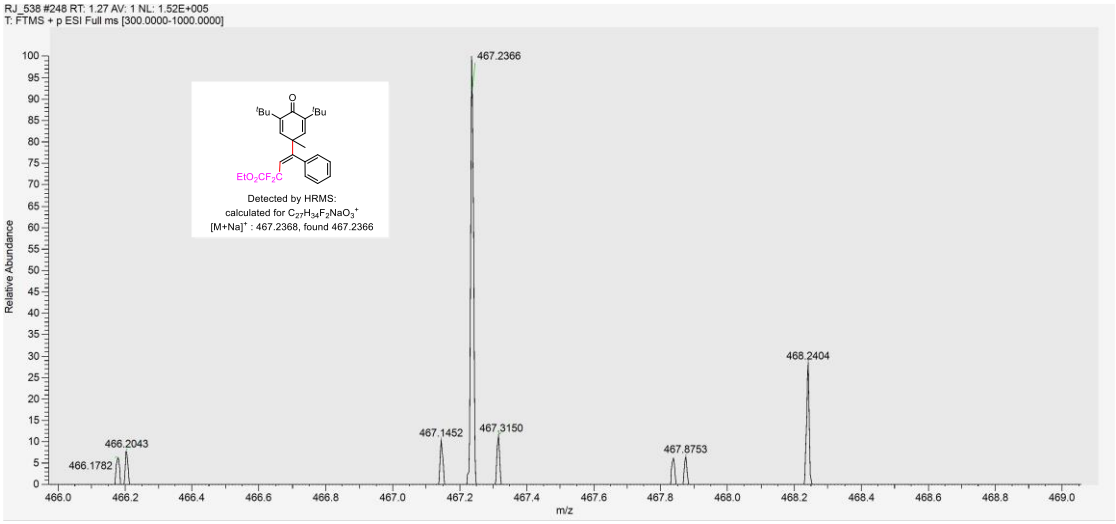
These reactions were conducted with general procedure with minor modification. In a 25 mL Schlenk tube equipped with a stir bar was charged with **1a** (20.8 mg, 0.10 mmol, 1.0 equiv.), ethynylbenzene (**2b**, 22.0 ul, 0.2 mmol, 2.0 equiv.), ethyl bromodifluoroacetate **3a** (25.6 µl, 0.20 mmol, 2.0 equiv.), K_2CO_3 (27.6 mg, 0.2 mmol, 2.0 equiv.), $Cu(acac)_2$ (5.2 mg, 0.02 mmol, 0.2 equiv.) and additive (0.2 mmol, 2.0 equiv.) in benzene (1.0 mL). The reaction was stirred at 130 °C for 6 h under N_2 atmosphere. After being cooled to ambient temperature, the solvent was removed under reduced pressure. The crude mixture was firstly analyzed by HRMS (High Resolution Mass Spectrometry). Then the solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford product **4b** to determine the yield (if necessary).



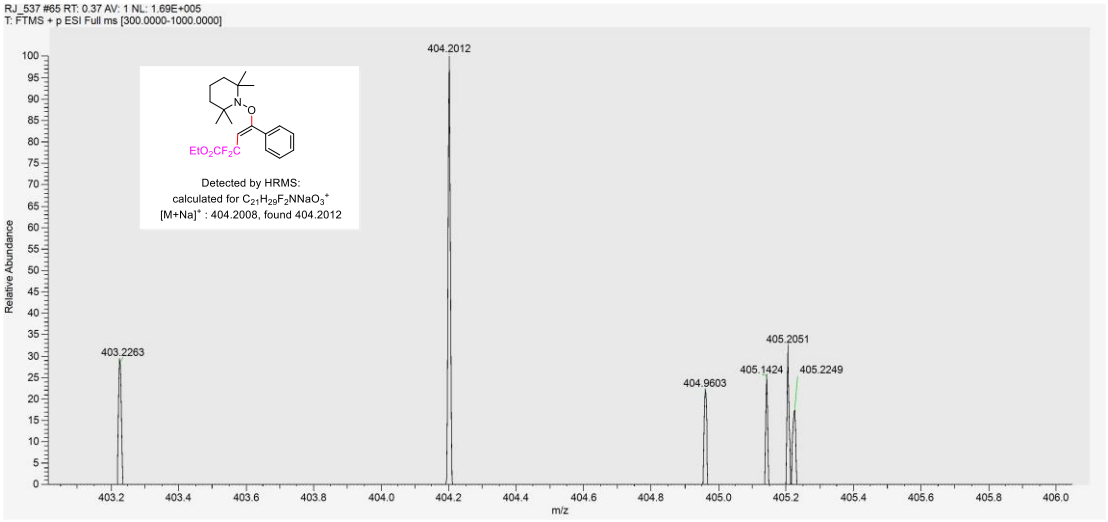
HRMS (adduct of **3a** with BHT)



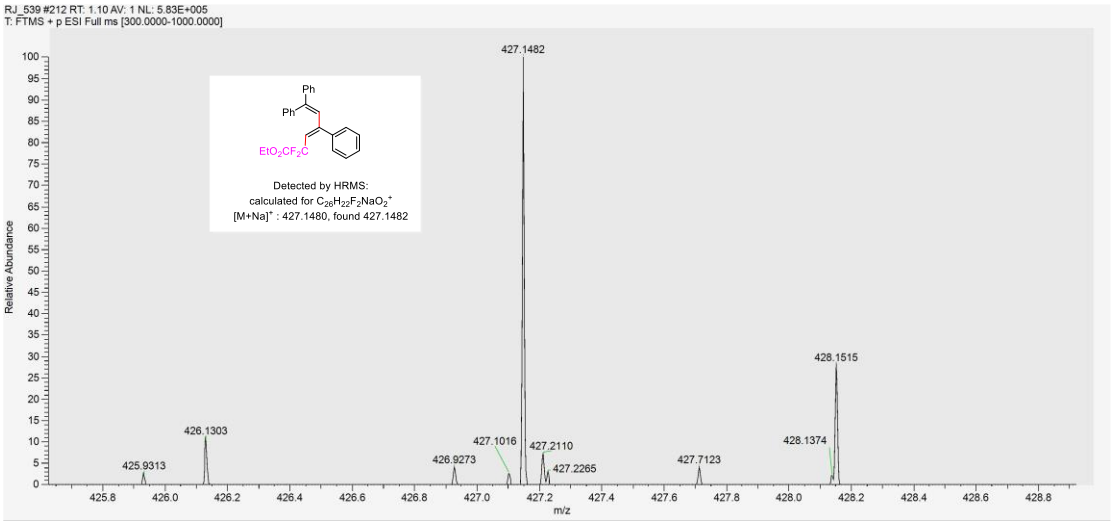
HRMS (adduct of **3a** with 1, 1-DP*E*)



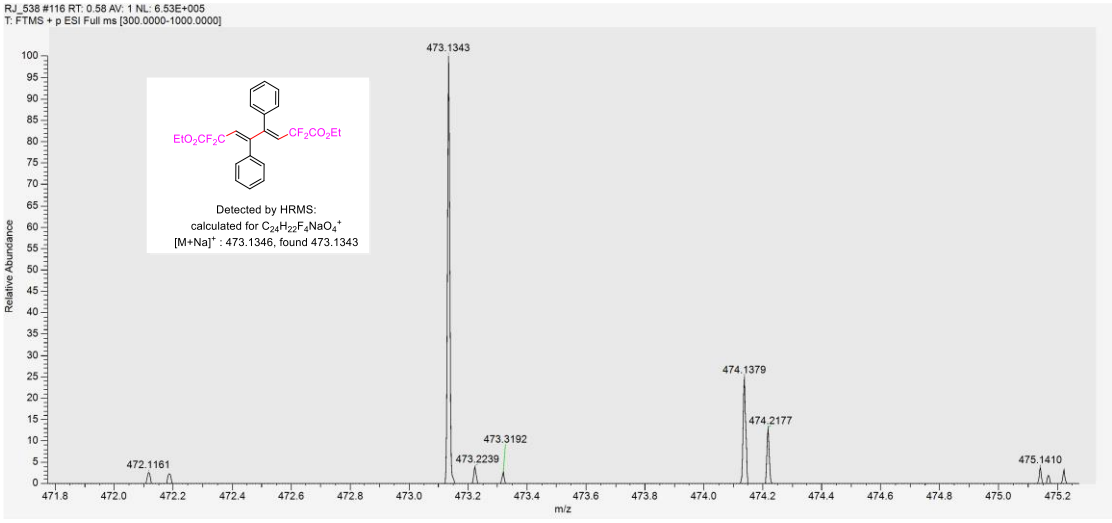
HRMS (adduct of **2b**, **3a** with BHT)



HRMS (adduct of **2b**, **3a** with TEMPO)

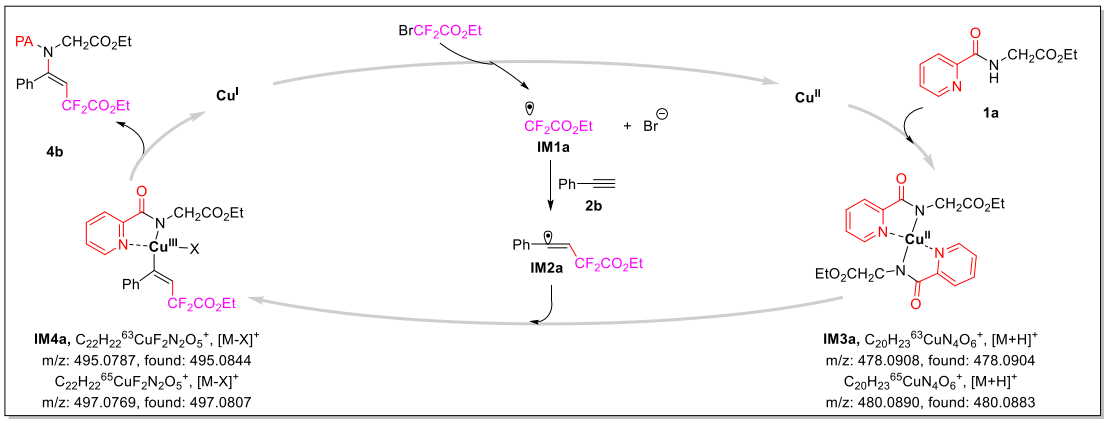


HRMS (adduct of **2b**, **3a** with 1, 1-DPE)

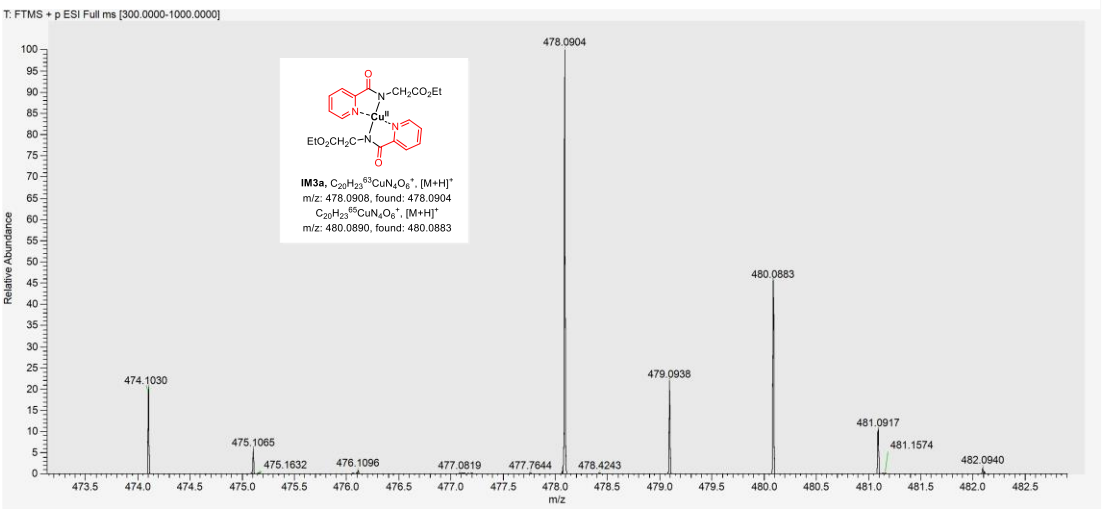


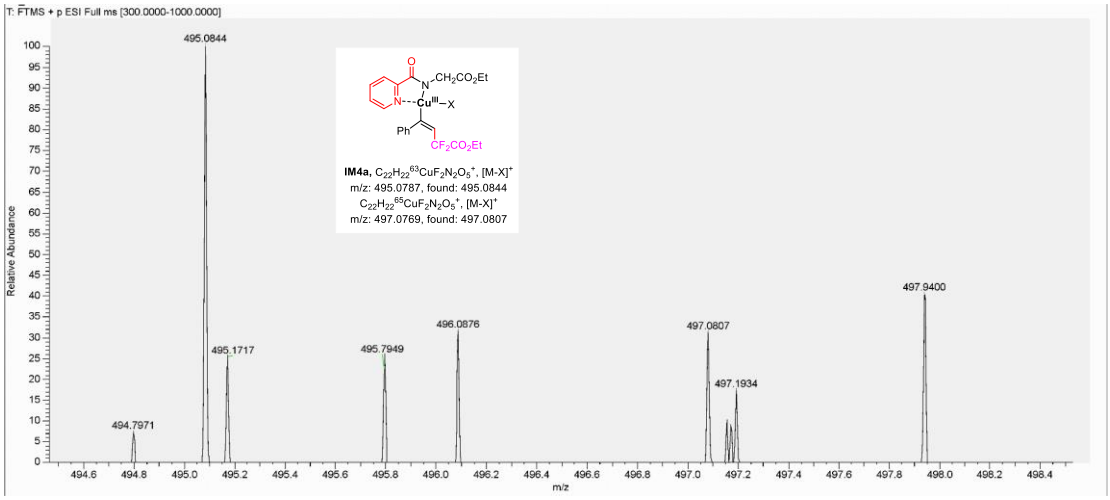
HRMS (dimerization of **2b** with **3a**)

d) Proposed catalytic cycle

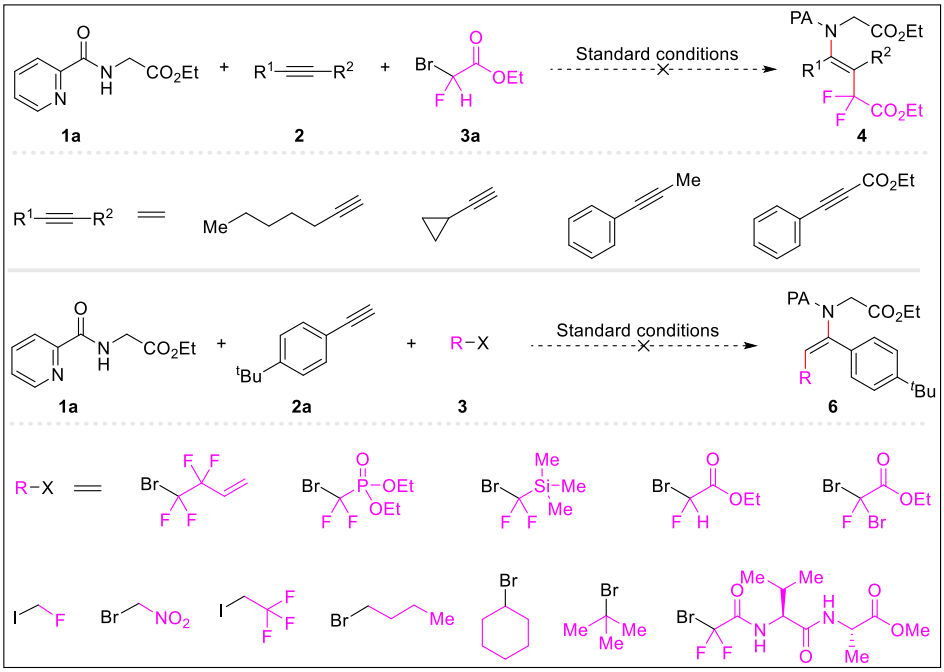


Based on the experimental outcomes and pertinent literature, we propose a plausible mechanism for this reaction. The process begins with the reduction of ethyl 2-bromo-2,2-difluoroacetate by the copper(I) catalyst via a single-electron transfer (SET) process, resulting in difluoroalkyl radical **IM1a**. This radical is then intercepted by the triple bond of the ethynylbenzene, forming difluoroalkylated vinyl radical **IM2a**. Concurrently, the ethyl picolinoylglycinate acts as a bidentate ligand, coordinating with the copper(II) catalyst to form intermediate **IM3a**. Difluoroalkylated vinyl radical **IM2a** is subsequently trapped by this complex, leading to the formation of copper(III) intermediate **IM4a**. Finally, the catalytic cycle is completed by the reductive elimination of **IM4a**, regenerating the copper(I) catalyst, which can then react with ethyl 2-bromo-2,2-difluoroacetate to regenerate the copper(II) catalyst. The presence of copper complexes **IM3a** and **IM4a** can be confirmed by HRMS analysis of the crude reaction mixture.





VI. Unsuccessful substrates



VII. The method for crystal growth

Procedure for the crystal growth of **4p** or **5t**: To a 2.5 mL sample bottle containing **4p** or **5t** (10 mg) was added ethyl acetate (about 0.5 mL), then 1.5 mL n-hexane was added slowly. The sample bottle was sealed by sealing film. Then several pinholes were made to slowly evaporate the solvents at room temperature. The desired crystals were obtained for several days (about 10-14 days).

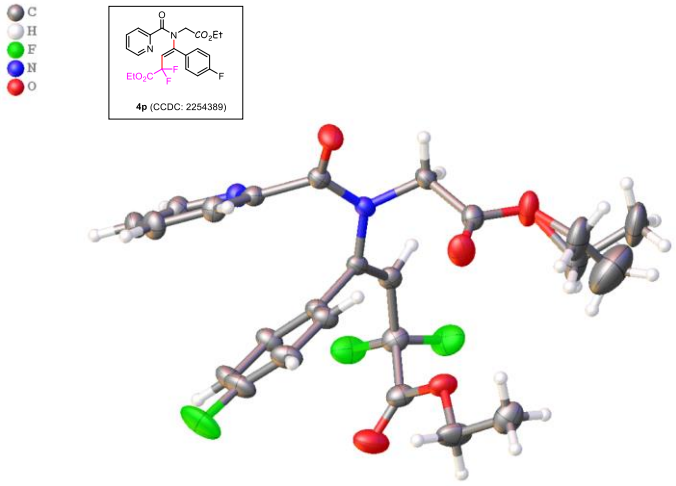


Table 2 Crystal data and structure refinement for 4p (CCDC: 2254389).

Identification code	CCDC: 2254389
Empirical formula	$C_{22}H_{21}F_3N_2O_5$
Formula weight	450.41
Temperature/K	150.0
Crystal system	triclinic
Space group	P-1
a/Å	10.0991(6)
b/Å	10.3919(7)
c/Å	10.7913(6)
α/°	98.105(2)
β/°	94.866(2)
γ/°	101.483(2)
Volume/Å^3	1091.32(12)
Z	2
ρ_{calc}g/cm^3	1.371
μ/mm^{-1}	0.114
F(000)	468.0
Crystal size/mm^3	0.5 × 0.4 × 0.2
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.838 to 55.054
Index ranges	-13 ≤ h ≤ 13, -13 ≤ k ≤ 13, -13 ≤ l ≤ 14
Reflections collected	25984
Independent reflections	4996 [R_{int} = 0.0410, R_{sigma} = 0.0295]
Data/restraints/parameters	4996/0/306
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0425, wR_2 = 0.1072
Final R indexes [all data]	R_1 = 0.0549, wR_2 = 0.1152
Largest diff. peak/hole / e Å^{-3}	0.39/-0.26

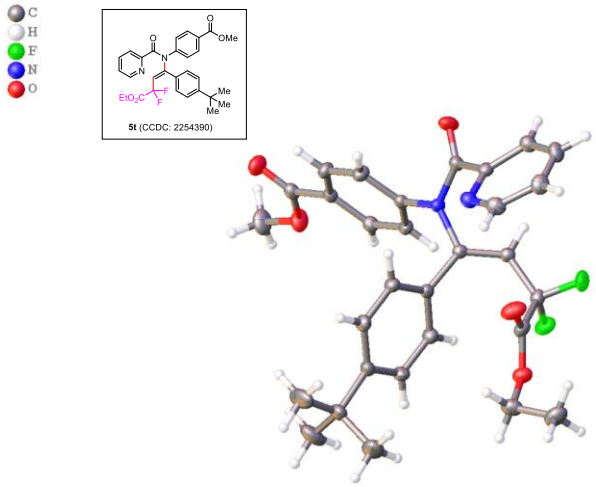
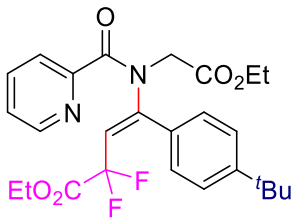


Table 3 Crystal data and structure refinement 5t (CCDC: 2254390).

Identification code	CCDC: 2254390
Empirical formula	$C_{30}H_{30}F_2N_2O_5$
Formula weight	536.56
Temperature/K	150.0
Crystal system	triclinic
Space group	P-1
a/Å	10.6872(5)
b/Å	11.2785(6)
c/Å	12.6943(7)
α/°	108.884(2)
β/°	97.089(2)
γ/°	106.591(2)
Volume/Å^3	1347.61(12)
Z	2
ρ_{calc}g/cm^3	1.322
μ/mm^{-1}	0.099
F(000)	564.0
Crystal size/mm^3	0.43 × 0.4 × 0.35
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.07 to 55.044
Index ranges	-13 ≤ h ≤ 13, -14 ≤ k ≤ 14, -16 ≤ l ≤ 16
Reflections collected	29648
Independent reflections	6189 [R_{int} = 0.0404, R_{sigma} = 0.0300]
Data/restraints/parameters	6189/0/357
Goodness-of-fit on F^2	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0401, wR_2 = 0.0980
Final R indexes [all data]	R_1 = 0.0517, wR_2 = 0.1054
Largest diff. peak/hole / e Å^{-3}	0.31/-0.30

VIII. Experimental data for the described substances



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4a)

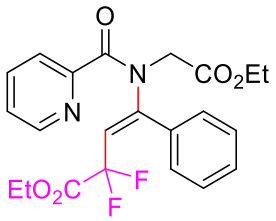
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4a** as yellow oil (37.6 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dd, J = 3.5, 1.1 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.54 (d, J = 7.3 Hz, 2H), 7.33 (d, J = 7.4 Hz, 2H), 7.29 – 7.21 (m, 1H), 5.48 (t, J = 11.8 Hz, 1H), 4.26 – 4.17 (m, 2H), 4.16 (s, 2H), 3.74 (q, J = 6.9 Hz, 2H), 1.29 (s, 9H), 1.28 – 1.22 (m, 3H), 1.02 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.71, 168.43, 162.77 (t, J = 33.8 Hz), 153.75, 152.79, 149.52 (t, J = 9.6 Hz), 148.43, 136.68, 130.36, 130.22, 125.22, 124.88, 124.16, 117.72 (t, J = 29.1 Hz), 111.76 (t, J = 244.8 Hz), 62.71, 61.45, 48.93, 34.90, 31.23, 14.21, 13.67 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.84, -91.87 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{31}F_2N_2O_5^+$ $[M + H]^+$: 489.2196, found 489.2197.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-phenylbut-3-enoate (**4b**)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4b** as pale-yellow oil (33.2 mg, 77% yield).

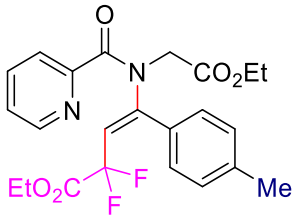
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 4.8 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.64 (d, J = 6.9 Hz, 2H), 7.35 (dt, J = 14.1, 4.7 Hz, 3H), 7.27 (m, 1H), 5.52 (t, J = 12.0 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 4.16 (s, 2H), 3.78 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.61, 168.37, 162.73 (t, J = 33.7 Hz), 152.63, 149.52 (t, J = 9.1 Hz),

148.37, 136.80, 133.36, 130.47, 130.43, 128.26, 125.01, 124.30, 118.06 (t, *J* = 28.7 Hz), 111.62 (t, *J* = 245.6 Hz), 62.80, 61.49, 48.88, 14.19, 13.70 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.50, -92.53 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{23}F_2N_2O_5^+$ $[M + H]^+$: 433.1570, found 433.1567.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(*p*-tolyl)but-3-enoate (4c)

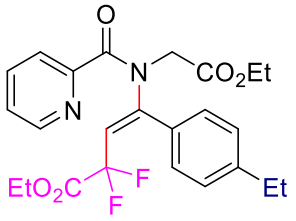
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4c** as pale-yellow oil (33.4 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.5 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.28 (m, 1H), 7.14 (d, *J* = 7.9 Hz, 2H), 5.47 (t, *J* = 12.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.15 (s, 2H), 3.81 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.67, 168.42, 162.87 (t, *J* = 33.7 Hz), 152.78, 149.61 (t, *J* = 9.1 Hz), 148.42, 140.73, 136.75, 130.44, 129.01, 124.95, 124.26, 117.73 (t, *J* = 28.5 Hz), 111.72 (t, *J* = 245.6 Hz), 62.78, 61.47, 48.87, 21.52, 14.23, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.56, -92.59 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{25}F_2N_2O_5^+$ $[M + H]^+$: 447.1726, found 447.1725.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-4-(4-ethylphenyl)-2,2-difluorobut-3-enoate (4d)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4d** as pale-yellow oil (32.5 mg, 71% yield).

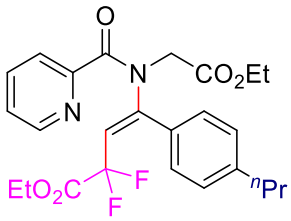
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.6 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.54 (d, *J* = 7.9 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.48 (t, *J* = 12.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 3.79

(q, *J* = 7.1 Hz, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.22 (t, *J* = 7.7 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.72, 168.45, 162.85 (t, *J* = 33.5 Hz), 152.82, 149.63 (t, *J* = 9.1 Hz), 148.44, 147.00, 136.74, 130.66, 130.54, 127.83, 124.94, 124.24, 117.71 (t, *J* = 28.7 Hz), 111.76 (t, *J* = 245.2 Hz), 62.78, 61.49, 48.92, 28.86, 15.47, 14.24, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.24, -92.27 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{27}F_2N_2O_5^+$ $[M + H]^+$: 461.1883, found 461.1883.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(4-propylphenyl)but-3-enoate (4e)

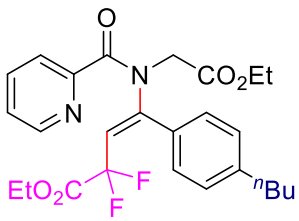
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4e** as pale-yellow oil (32.8 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.6 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 5.49 (t, *J* = 11.9 Hz, 1H), 4.24 – 4.19 (m, 2H), 4.18 (s, 2H), 3.78 (q, *J* = 7.1 Hz, 2H), 2.57 (t, *J* = 7.6 Hz, 2H), 1.65 – 1.58 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 4H), 1.06 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.74, 168.46, 162.83 (t, *J* = 33.1 Hz), 152.86, 149.69 (t, *J* = 9.5 Hz), 148.44, 145.47, 136.73, 130.74, 130.42, 128.41, 124.92, 124.22, 117.58 (t, *J* = 28.7 Hz), 111.79 (t, *J* = 245.1 Hz), 62.76, 61.50, 49.05, 37.97, 24.45, 14.24, 13.90, 13.74 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.01, -92.04 ppm.

HRMS (ESI^+): calcd for $C_{25}H_{29}F_2N_2O_5^+$ $[M + H]^+$: 475.2039, found 475.2039.



ethyl (*E*)-4-(4-butylphenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4f)

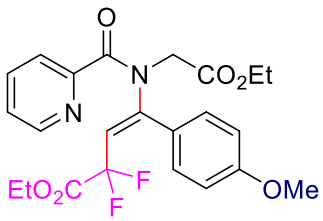
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4f** as yellow oil (34.9 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.6 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.26 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 5.49 (t, *J* = 11.9 Hz, 1H), 4.24 – 4.18 (m, 2H), 4.17 (s, 2H), 3.77 (q, *J* = 7.1 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.61 – 1.54 (m, 2H), 1.37 – 1.32 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.72, 168.44, 162.82 (t, *J* = 33.8 Hz), 152.85, 149.68 (t, *J* = 9.5 Hz), 148.43, 145.69, 136.71, 130.68, 130.43, 128.36, 124.91, 124.21, 117.58 (t, *J* = 28.9 Hz), 111.78 (t, *J* = 245.0 Hz), 62.74, 61.48, 49.03, 35.59, 33.48, 22.41, 14.23, 14.02, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.03, -92.06 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{31}F_2N_2O_5^+$ $[M + H]^+$: 489.2196, found 489.2197.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(4-methoxyphenyl)but-3-enoate (4g)

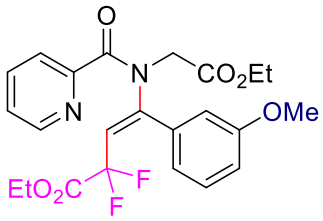
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4g** as yellow oil (27.7 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.26 (m, 1H), 6.88 – 6.79 (m, 2H), 5.44 (t, *J* = 12.0 Hz, 1H), 4.32 – 4.17 (m, 2H), 4.15 (s, 2H), 3.82 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 1.26 (td, *J* = 7.1, 1.1 Hz, 3H), 1.07 (td, *J* = 7.1, 1.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.73, 168.42, 162.87, 161.29, 152.80, 149.40 (t, *J* = 9.1 Hz), 148.39, 136.74, 132.10, 125.53, 124.93, 124.16, 117.03 (t, *J* = 28.6 Hz), 113.64, 111.79 (t, *J* = 245.0 Hz), 62.79, 61.46, 55.41, 48.95, 14.20, 13.75 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.20, -92.23 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{25}F_2N_2O_6^+$ $[M + H]^+$: 463.1675, found 463.1675.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-methoxyphenyl)but-3-enoate (4h)

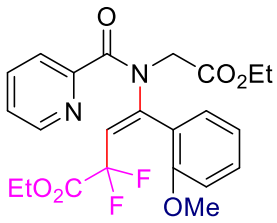
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4h** as pale-yellow oil (35.2 mg, 76% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.7 Hz, 1H), 7.76 – 7.69 (m, 2H), 7.31 – 7.27 (m, 1H), 7.26 (s, 1H), 7.24 – 7.19 (m, 2H), 6.94 – 6.89 (m, 1H), 5.50 (t, *J* = 12.0 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.18 (s, 2H), 3.83 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.63, 168.41, 162.77 (t, *J* = 33.7 Hz), 159.35, 152.70, 149.37 (t, *J* = 9.4 Hz), 148.40, 136.81, 134.70, 129.36, 125.02, 124.34, 122.82, 118.25 (t, *J* = 28.8 Hz), 116.80, 115.32, 111.68 (t, *J* = 245.3 Hz), 62.83, 61.50, 55.40, 48.91, 14.23, 13.72 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.31 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{25}F_2N_2O_6^+$ [M + H]+ : 463.1675, found 463.1675.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(2-methoxyphenyl)but-3-enoate (4i)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4i** as pale-yellow oil (25.3 mg, 55% yield).

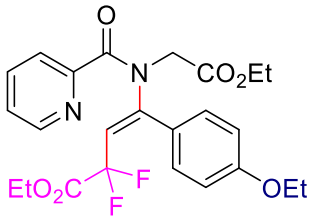
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 4.6 Hz, 1H), 7.69 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.58 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 5.68 (t, *J* = 12.3 Hz, 1H), 4.31 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.22, 168.72, 162.89 (t, *J* = 34.1 Hz), 157.40, 153.19, 148.53, 144.64, 136.62, 132.12, 131.49, 124.79, 123.95, 122.24, 120.35, 119.57 (t, *J* = 27.6 Hz), 111.77 (t, *J* = 245.8 Hz),

110.39, 62.67, 61.38, 55.37, 49.55, 14.26, 13.80 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -97.39 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{25}F_2N_2O_6^+$ $[M + H]^+$: 463.1675, found 463.1673.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-4-(4-ethoxyphenyl)-2,2-difluorobut-3-enoate (4j)

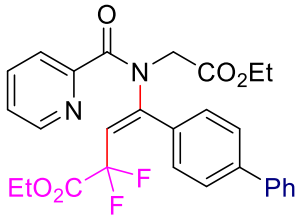
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4j** as pale-yellow oil (33.9 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.7 Hz, 1H), 7.70 (q, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.26 (m, 1H), 6.82 (d, *J* = 7.9 Hz, 2H), 5.44 (t, *J* = 11.8 Hz, 1H), 4.24 – 4.17 (m, 2H), 4.16 (s, 2H), 4.02 (q, *J* = 6.9 Hz, 2H), 3.82 (q, *J* = 7.1 Hz, 2H), 1.40 (t, *J* = 6.9 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 4H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.77, 168.44, 162.90 (t, *J* = 33.7 Hz), 160.72, 152.87, 149.48 (t, *J* = 9.3 Hz), 148.42, 136.74, 132.10, 125.36, 124.91, 124.16, 116.95 (t, *J* = 28.7 Hz), 114.14, 110.62 (t, *J* = 245.1 Hz), 63.64, 62.78, 61.47, 49.01, 14.82, 14.23, 13.77 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.04, -92.07 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{27}F_2N_2O_6^+$ $[M + H]^+$: 477.1832, found 477.1833.



ethyl (*E*)-4-([1,1'-biphenyl]-4-yl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4k)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4k** as yellow oil (41.3 mg, 81% yield).

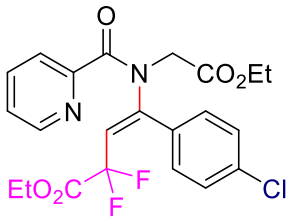
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.7 Hz, 1H), 7.75 (s, 1H), 7.73 (d, *J* = 3.8 Hz, 2H), 7.58 (t, *J* =

6.9 Hz, 4H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.33 – 7.27 (m, 1H), 5.56 (t, *J* = 12.2 Hz, 1H), 4.23 (q, *J* = 7.0 Hz, 4H), 3.84 (q, *J* = 7.1 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 169.70, 168.44, 162.85 (t, *J* = 32.0 Hz), 152.65, 149.36 (t, *J* = 9.1 Hz), 148.43, 143.18, 140.17, 136.84, 132.30, 131.03, 129.04, 128.02, 127.20, 126.91, 126.39, 125.07, 124.39, 118.04 (t, *J* = 28.7 Hz), 111.69 (t, *J* = 245.9 Hz), 62.91, 61.56, 49.01, 14.26, 13.77 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): *δ* = -92.65 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{27}F_2N_2O_5^+$ $[M + H]^+$: 509.1883, found 509.1883.



ethyl (*E*)-4-(4-chlorophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4l)

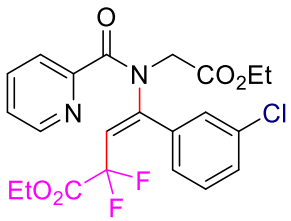
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4l** as pale-yellow oil (32.9 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 8.49 (d, *J* = 4.5 Hz, 1H), 7.73 (d, *J* = 1.0 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.29 (m, 1H), 5.52 (t, *J* = 12.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.89 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 169.49, 168.29, 162.79 (t, *J* = 33.7 Hz), 152.36, 148.59 (t, *J* = 9.0 Hz), 148.33, 136.96, 136.60, 131.98, 128.54, 128.02, 125.24, 124.54, 118.38 (t, *J* = 27.7 Hz), 111.43 (t, *J* = 247.2 Hz), 63.03, 61.60, 48.83, 14.23, 13.79 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): *δ* = -93.69, -93.71 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}{}^{35}ClF_2N_2O_5^+$ $[M + H]^+$: 467.1180, found 467.1181, $C_{22}H_{22}{}^{37}ClF_2N_2O_5^+$ $[M + H]^+$: 469.1150, found 469.1145.



ethyl (*E*)-4-(3-chlorophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4m)

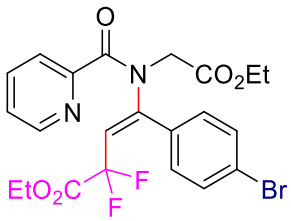
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4m** as pale-yellow oil (24.3 mg, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.76 – 7.74 (m, 1H), 7.73 (d, *J* = 1.1 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.39 – 7.34 (m, 1H), 7.33 – 7.27 (m, 2H), 5.54 (t, *J* = 12.4 Hz, 1H), 4.25 – 4.19 (m, 2H), 4.16 (s, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.42, 168.27, 162.72 (t, *J* = 33.6 Hz), 152.25, 148.36, 148.21 (t, *J* = 8.5 Hz), 136.97, 135.38, 134.25, 130.47, 130.43, 129.53, 128.90, 125.26, 124.57, 118.82 (t, *J* = 28.0 Hz), 111.38 (t, *J* = 247.1 Hz), 63.05, 61.61, 48.80, 14.22, 13.77 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.75 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}{}^{35}ClF_2N_2O_5^+$ $[M + H]^+$: 467.1180, found 467.1180, $C_{22}H_{22}{}^{37}ClF_2N_2O_5^+$ $[M + H]^+$: 469.1150, found 469.1145.



ethyl (*E*)-4-(4-bromophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4n)

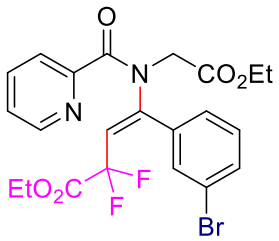
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4n** as yellow oil (43.4 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dt, *J* = 4.8, 1.3 Hz, 1H), 7.75 (dd, *J* = 2.5, 1.3 Hz, 1H), 7.74 (d, *J* = 1.3 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.30 (m, 1H), 5.52 (t, *J* = 12.5 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.45, 168.28, 162.77 (t, *J* = 33.2 Hz), 152.33, 148.64 (t, *J* = 7.9 Hz), 148.32, 136.97, 132.45, 132.20, 131.51, 125.25, 124.99, 124.56, 118.41 (t, *J* = 27.7 Hz), 111.42 (t, *J* = 247.0 Hz), 63.02, 61.58, 48.80, 14.22, 13.78 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.71 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}{}^{79}BrF_2N_2O_5^+$ $[M + H]^+$: 511.0675, found 511.0679, $C_{22}H_{22}{}^{81}BrF_2N_2O_5^+$ $[M + H]^+$: 513.0654, found 513.0656.



ethyl (*E*)-4-(3-bromophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4o)

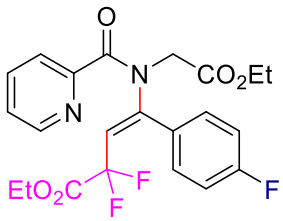
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4o** as yellow oil (41.5 mg, 81% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.53 – 8.50 (m, 1H), 7.86 (s, 1H), 7.77 – 7.71 (m, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.49 (m, 1H), 7.31 (m, 1H), 7.22 (t, *J* = 7.9 Hz, 1H), 5.54 (t, *J* = 12.4 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.17 (s, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.39, 168.26, 162.71 (t, *J* = 33.8 Hz), 152.23, 148.34, 148.11 (t, *J* = 8.3 Hz), 136.99, 135.64, 133.36, 133.29, 129.76, 129.32, 125.26, 124.55, 122.25, 118.79 (t, *J* = 28.1 Hz), 111.39 (t, *J* = 247.2 Hz), 63.07, 61.63, 48.89, 14.24, 13.80 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -93.73, -93.76 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}{}^{79}BrF_2N_2O_5^+$ $[M + H]^+$: 511.0675, found 511.0678, $C_{22}H_{22}{}^{81}BrF_2N_2O_5^+$ $[M + H]^+$: 513.0654, found 513.0657.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(4-fluorophenyl)but-3-enoate (4p)

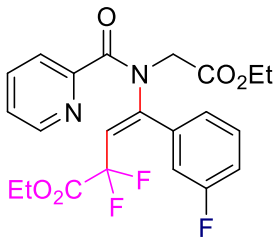
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4p** as pale-yellow oil (27.5 mg, 61% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.77 – 7.72 (m, 2H), 7.72 – 7.67 (m, 2H), 7.32 – 7.27 (m, 1H), 7.03 (t, *J* = 8.7 Hz, 2H), 5.52 (t, *J* = 12.3 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 3.88 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ =169.54, 168.33, 163.95 (d, *J* = 251.3 Hz), 162.81 (t, *J* = 33.8 Hz), 152.52, 148.73 (t, *J* = 8.5 Hz), 148.34, 136.93, 132.77 (d, *J* = 8.5 Hz), 129.57 (d, *J* = 3.3 Hz), 125.18, 124.47, 118.04 (t, *J* = 28.0 Hz), 115.37 (d, *J* = 21.8 Hz), 111.53 (t, *J* = 246.4 Hz), 62.95, 61.56, 48.86, 14.23, 13.79 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.28, -109.59 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}F_3N_2O_5^+$ $[M + H]^+$: 451.1475, found 451.1475.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-fluorophenyl)but-3-enoate (4q)

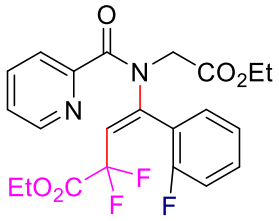
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4q** as pale-yellow oil (31.1 mg, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (dt, *J* = 4.8, 1.2 Hz, 1H), 7.74 (d, *J* = 3.5 Hz, 2H), 7.56 – 7.50 (m, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.14 – 7.05 (m, 1H), 5.54 (t, *J* = 12.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.15 (s, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.43, 168.28, 162.72 (t, *J* = 33.8 Hz), 162.38 (d, *J* = 247.0 Hz), 152.30, 148.35, 136.96, 135.69 (d, *J* = 7.9 Hz), 129.82 (d, *J* = 8.2 Hz), 126.53 (d, *J* = 2.2 Hz), 125.25, 124.56, 118.81 (t, *J* = 27.9 Hz), 117.31, 117.45 (d, *J* = 21.2 Hz), 111.38 (t, *J* = 247.0 Hz), 77.48, 77.16, 76.84, 62.99, 61.59, 48.75, 14.21, 13.76 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.74, -112.37 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}F_3N_2O_5^+$ $[M + H]^+$: 451.1475, found 451.1476.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(2-fluorophenyl)but-3-enoate (4r)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4r** as pale-yellow oil (32.0 mg, 71% yield).

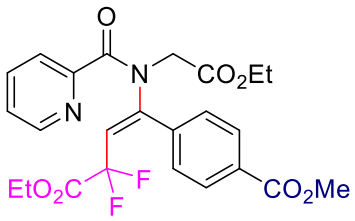
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (dt, *J* = 4.8, 1.2 Hz, 1H), 7.89 (td, *J* = 7.6, 1.5 Hz, 1H), 7.74 (d, *J* = 3.5 Hz, 2H), 7.39 – 7.33 (m, 1H), 7.31 (dd, *J* = 9.1, 4.6 Hz, 1H), 7.14 (m, 1H), 7.05 – 6.99 (m, 1H), 5.73 (t, *J* = 13.0 Hz, 1H), 4.25 (s, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.00 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.20 (t,

J = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.09, 168.37, 162.75 (t, J = 32.3 Hz), 160.44 (d, J = 250.3 Hz), 152.56, 148.40, 136.93, 132.28, 132.04 (d, J = 8.5 Hz), 125.18, 124.44, 124.22 (d, J = 3.6 Hz), 121.60, 121.47, 120.73 (t, J = 26.4 Hz), 115.43 (d, J = 21.9 Hz), 111.35 (d, J = 248.2 Hz), 63.02, 61.59, 49.04, 14.23, 13.84 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -99.52, -113.62 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}F_3N_2O_5^+$ $[M + H]^+$: 451.1475, found 451.1475.



methyl (*E*)-4-(4-ethoxy-1-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-3,3-difluoro-4-oxobut-1-en-1-yl)benzoate (4s)

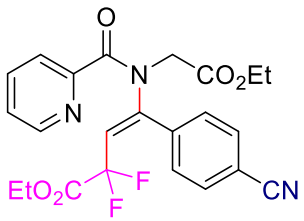
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4s** as pale-yellow oil (25.5 mg, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 4.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.76 – 7.72 (m, 2H), 7.33 – 7.27 (m, 1H), 5.59 (t, J = 12.6 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 3.93 (s, 3H), 3.88 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.44, 168.27, 166.54, 162.74 (t, J = 33.7 Hz), 152.29, 148.71 (t, J = 8.0 Hz), 148.35, 138.06, 137.00, 131.73, 130.65, 129.39, 125.31, 124.65, 118.94 (t, J = 27.7 Hz), 111.37 (t, J = 247.4 Hz), 63.04, 61.63, 52.47, 48.91, 14.24, 13.81 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.97 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{25}F_2N_2O_7^+$ $[M + H]^+$: 491.1624, found 491.1624.



ethyl (*E*)-4-(4-cyanophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4t)

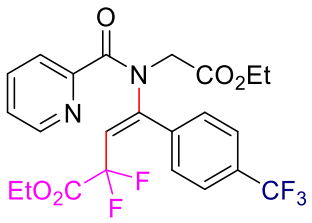
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4t** as pale-yellow oil (21.6 mg, 47% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.7 Hz, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.80 – 7.74 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.35 – 7.30 (m, 1H), 5.62 (t, *J* = 13.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 3.97 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.23, 168.16, 162.68 (t, *J* = 33.7 Hz), 151.92, 148.26, 148.00 (t, *J* = 7.4 Hz), 138.35, 137.15, 131.89, 131.36, 125.52, 124.86, 119.37 (t, *J* = 26.9 Hz), 118.34, 113.95, 111.14 (t, *J* = 248.8 Hz), 63.23, 61.72, 48.86, 14.23, 13.84 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -95.04 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{22}F_2N_3O_5^+$ $[M + H]^+$: 458.1522, found 458.1522.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(4-(trifluoromethyl)phenyl)but-3-enoate (4u)

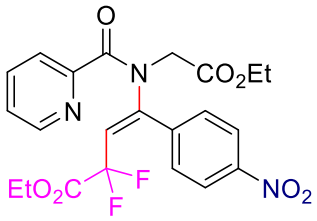
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4u** as pale-yellow oil (40.6 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (dd, *J* = 3.6, 2.4 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.76 – 7.72 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.31 (m, 1H), 5.60 (t, *J* = 12.7 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 3.90 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.36, 168.23, 162.73 (t, *J* = 33.8 Hz), 152.16, 148.32, 137.26, 137.04, 132.16 (q, *J* = 32.6 Hz), 131.09, 129.65, 125.37, 125.15 (q, *J* = 3.7 Hz), 124.72, 123.88 (q, *J* = 272.5 Hz), 119.20 (t, *J* = 27.4 Hz), 111.28 (t, *J* = 247.8 Hz), 63.09, 61.64, 48.74, 14.21, 13.74 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.96, -94.37 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{22}F_5N_2O_5^+$ $[M + H]^+$: 501.1443, found 501.1448.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(4-nitrophenyl)but-3-enoate (4v)

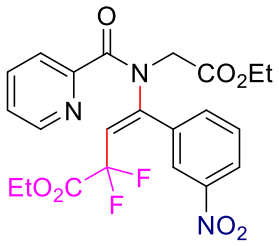
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4v** as pale-yellow oil (24.7 mg, 52% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.52 – 8.48 (m, 1H), 8.21 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 8.7 Hz, 2H), 7.82 – 7.74 (m, 2H), 7.33 (ddd, *J* = 6.9, 4.8, 2.0 Hz, 1H), 5.64 (t, *J* = 13.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.17, 168.13, 162.68 (t, *J* = 33.7 Hz), 151.82, 148.83, 148.27, 140.15, 137.19, 131.77, 125.60, 124.94, 123.26, 122.42, 119.69 (t, *J* = 26.6 Hz), 111.10 (t, *J* = 248.9 Hz), 63.29, 61.74, 41.53, 14.23, 13.86 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -95.46 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{22}F_2N_3O_7^+$ $[M + H]^+$: 478.1420, found 478.1420.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-nitrophenyl)but-3-enoate (4w)

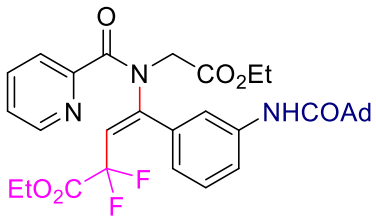
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **4w** as pale-yellow oil (34.2 mg, 72% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.52 (d, *J* = 4.7 Hz, 1H), 8.25 (ddd, *J* = 8.2, 2.1, 0.8 Hz, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.78 (m, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.32 (ddd, *J* = 6.9, 4.8, 1.9 Hz, 1H), 5.65 (t, *J* = 13.1 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ =169.16, 168.14, 162.71 (t, *J* = 33.8 Hz), 151.80, 148.30, 147.99, 147.42 (t, *J* = 6.9 Hz), 137.16, 136.57, 135.58, 129.25, 125.74, 125.57, 124.95, 124.86, 119.55 (t, *J* = 26.5 Hz), 111.14 (t, *J* = 249.1 Hz), 63.32, 61.75, 48.82, 14.21, 13.82 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -95.79 ppm.

HRMS (ESI$^+$): calcd for $C_{22}H_{22}F_2N_3O_7^+$ [M + H]$^+$: 478.1420, found 478.1420.



ethyl (*E*)-4-(3-((3s)-adamantane-1-carboxamido)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl) picolinamido)-2,2-difluorobut-3-enoate (4x)

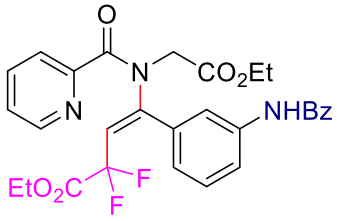
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4x** as pale-yellow oil (47.5 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dt, *J* = 4.7, 1.1 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.73 (dd, *J* = 5.1, 1.4 Hz, 2H), 7.54 (s, 1H), 7.39 – 7.34 (m, 2H), 7.32 – 7.26 (m, 2H), 5.49 (t, *J* = 12.1 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.83 (q, *J* = 7.1 Hz, 2H), 2.09 (s, 3H), 1.96 (d, *J* = 2.6 Hz, 6H), 1.82 – 1.67 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.30, 168.54, 167.40, 161.81 (t, *J* = 33.6 Hz), 151.56, 147.92 (t, *J* = 9.1 Hz), 147.46, 137.26, 135.89, 132.90, 128.06, 125.13, 124.05, 123.39, 121.34, 120.38, 117.50 (t, *J* = 28.5 Hz), 110.58 (t, *J* = 245.9 Hz), 61.96, 60.52, 47.77, 40.68, 38.34, 35.52, 27.24, 13.23, 12.76 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.92, -92.95 ppm.

HRMS (ESI$^+$): calcd for $C_{33}H_{38}F_2N_3O_6^+$ [M + H]$^+$: 610.2723, found 610.2722.



ethyl (*E*)-4-(3-benzamidophenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4y)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4y** as pale-yellow oil (26.3 mg, 48% yield).

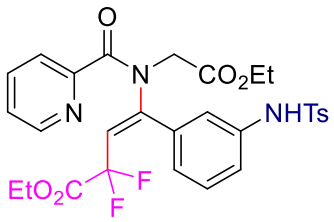
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (dt, *J* = 4.8, 1.4 Hz, 1H), 8.11 (s, 1H), 8.06 – 8.02 (m, 1H), 7.92 – 7.87

(m, 2H), 7.75 – 7.72 (m, 2H), 7.72 – 7.70 (m, 1H), 7.55 (ddd, *J* = 6.3, 3.7, 1.4 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.29 (ddd, *J* = 5.7, 4.8, 3.0 Hz, 1H), 5.53 (t, *J* = 12.1 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 4.18 (s, 2H), 3.86 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* = 169.60, 168.43, 165.93, 162.86 (t, *J* = 33.5 Hz), 152.56, 148.91 (t, *J* = 9.1 Hz), 148.49, 138.25, 136.94, 134.81, 134.11, 132.14, 129.22, 128.94, 127.27, 126.54, 125.12, 124.42, 122.50, 121.68, 118.62 (t, *J* = 28.2 Hz), 111.63 (t, *J* = 248.5 Hz), 63.05, 61.59, 48.83, 14.25, 13.79 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): *δ* = -92.79, -92.82 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{28}F_2N_3O_6^+$ $[M + H]^+$: 552.1941, found 552.1947.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-((4-methylphenyl) sulfonamido)phenyl)but-3-enoate (4z)

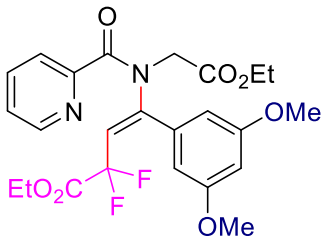
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4z** as pale-yellow oil (52.5 mg, 87% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* = 8.47 – 8.43 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 4H), 7.79 – 7.77 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.30 (s, 2H), 7.28 (s, 2H), 7.07 (m, 1H), 5.55 (t, *J* = 12.6 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* = 169.21, 168.20, 162.64 (t, *J* = 33.7 Hz), 152.01, 148.28, 147.98 (t, *J* = 8.1 Hz), 145.23, 136.94, 136.66, 134.72, 134.63, 133.62, 133.39, 132.41, 129.75, 128.81, 128.69, 125.25, 124.61, 119.28 (t, *J* = 27.6 Hz), 111.24 (t, *J* = 247.8 Hz), 63.13, 61.59, 48.45, 29.80, 21.77, 14.22, 13.85 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): *δ* = -94.22 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{30}F_2N_3O_7S^+$ $[M + H]^+$: 602.1767, found 602.1768.



ethyl (*E*)-4-(3,5-dimethoxyphenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (8aa)

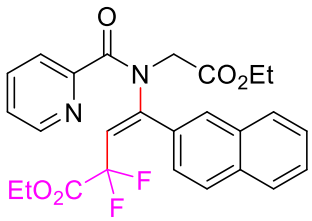
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **8aa** as yellow oil (33.4 mg, 68% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.53 – 8.50 (m, 1H), 7.76 – 7.70 (m, 2H), 7.28 (m, 1H), 6.84 (d, *J* = 2.3 Hz, 2H), 6.47 (t, *J* = 2.3 Hz, 1H), 5.48 (t, *J* = 11.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.19 (s, 2H), 3.84 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.84, 168.64, 162.95 (t, *J* = 33.6 Hz), 160.76, 152.91, 149.47 (t, *J* = 9.6 Hz), 148.61, 137.01, 135.45, 125.21, 124.53, 118.63 (t, *J* = 29.1 Hz), 111.91 (t, *J* = 245.0 Hz), 108.45, 103.32, 63.05, 61.70, 55.78, 49.11, 14.46, 13.93 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.17, -92.20 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{27}F_2N_2O_7^+$ $[M + H]^+$: 493.1781, found 493.1780.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(naphthalen-2-yl)but-3-enoate (8ab)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **8ab** as yellow oil (32.5 mg, 67% yield).

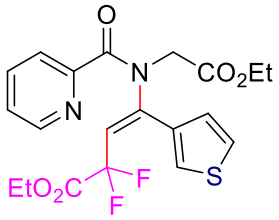
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 4.7 Hz, 1H), 8.02 (s, 1H), 7.90 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.85 (t, *J* = 9.0 Hz, 3H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.71 (td, *J* = 7.6, 1.6 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.30 – 7.26 (m, 1H), 5.60 (t, *J* = 11.9 Hz, 1H), 4.25 – 4.20 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 2H), 3.63 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.68, 168.41, 162.80 (t, *J* = 33.5 Hz), 152.66, 149.58 (t, *J* = 9.2 Hz), 148.47, 136.81, 134.11, 132.52, 131.30, 130.73, 128.79, 128.20, 127.77, 127.60, 126.78, 126.73, 125.08,

124.41, 118.68 (t, *J* = 28.7 Hz), 111.82 (t, *J* = 245.5 Hz), 77.48, 77.16, 76.84, 62.76, 61.51, 48.90, 14.24, 13.56 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.07, -92.10 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{25}F_2N_2O_5^+$ $[M + H]^+$: 483.1726, found 483.1725.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(thiophen-3-yl)but-3-enoate (8ac)

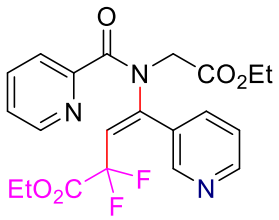
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **8ac** as yellow oil (32.0 mg, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.7 Hz, 1H), 7.70 (td, *J* = 7.7, 1.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.26 – 7.22 (m, 1H), 5.56 (t, *J* = 11.9 Hz, 1H), 4.25 (s, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 3.90 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.54, 168.43, 162.79 (t, *J* = 33.8 Hz), 152.68, 148.37, 144.86 (t, *J* = 9.5 Hz), 136.78, 134.86, 129.96, 128.97, 125.73, 125.02, 124.14, 117.84 (t, *J* = 29.2 Hz), 111.81 (t, *J* = 245.3 Hz), 62.92, 61.55, 49.41, 14.24, 13.76 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.22 ppm.

HRMS (ESI^+): calcd for $C_{20}H_{21}F_2N_2O_5S^+$ $[M + H]^+$: 439.1134, found 439.1133.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(pyridin-3-yl)but-3-enoate (8ad)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **8ad** as pale-yellow oil (23.7 mg, 55% yield).

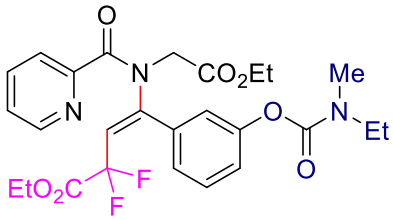
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (d, *J* = 1.4 Hz, 1H), 8.62 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.50 (d, *J* = 4.6 Hz,

1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.77 (dd, *J* = 12.2, 5.1 Hz, 2H), 7.35 – 7.28 (m, 2H), 5.63 (t, *J* = 12.9 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.23, 168.16, 162.73 (t, *J* = 33.8 Hz), 151.94, 151.03, 150.92, 148.30, 146.76 (t, *J* = 7.5 Hz), 138.29, 137.08, 129.97, 125.46, 124.80, 123.13, 119.57 (t, *J* = 26.9 Hz), 111.20 (t, *J* = 248.6 Hz), 63.19, 61.67, 48.72, 14.21, 13.80 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -94.97 ppm.

HRMS (ESI^+): calcd for $C_{21}H_{22}F_2N_3O_5^+$ $[M + H]^+$: 434.1522, found 434.1516.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-4-(3-((ethyl(methyl)carbamoyl)oxy) phenyl)-2,2-difluorobut-3-enoate (8ae)

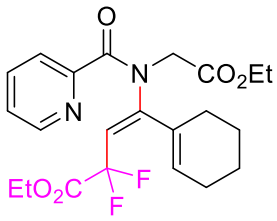
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **8ae** as pale-yellow oil (40.2 mg, 75% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.7 Hz, 1H), 7.75 (d, *J* = 1.1 Hz, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.50 (d, *J* = 1.8 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 6.7 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 1H), 5.52 (t, *J* = 12.2 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 3.86 (q, *J* = 7.1 Hz, 2H), 3.44 (m, 2H), 3.02 (d, *J* = 32.9 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 2.0 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.61, 168.40, 162.75 (t, *J* = 33.5 Hz), 154.24, 152.51, 151.50, 148.64 (t, *J* = 8.8 Hz), 148.42, 136.89, 134.52, 128.98, 127.49, 125.08, 124.45, 124.19, 123.48, 118.64 (t, *J* = 28.2 Hz), 111.51 (t, *J* = 246.2 Hz), 62.97, 61.49, 48.77, 44.25, 34.39, 29.81, 14.21, 12.57 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.96, -93.05 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{30}F_2N_3O_7^+$ $[M + H]^+$: 534.2046, found 534.2048.



ethyl (*E*)-4-(cyclohex-1-en-1-yl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (4af)

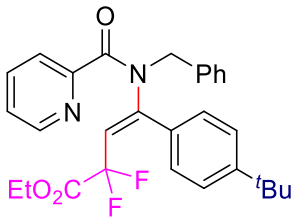
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/5, v/v) afforded **4af** as pale-yellow oil (22.0 mg, 50% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 4.8 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.32 – 7.28 (m, 1H), 5.85 (s, 1H), 5.23 (t, *J* = 10.7 Hz, 1H), 4.28 (s, 2H), 4.23 (dd, *J* = 14.3, 7.0 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.22 (d, *J* = 1.6 Hz, 2H), 1.99 (d, *J* = 3.1 Hz, 2H), 1.59 (dt, *J* = 8.1, 6.1 Hz, 2H), 1.55 – 1.49 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.76, 168.50, 163.19 (t, *J* = 33.2 Hz), 152.97, 151.88, 148.58, 137.56, 136.64, 132.09, 124.87, 124.16, 117.81 (t, *J* = 29.0 Hz), 112.24 (t, *J* = 243.0 Hz), 62.88, 61.56, 48.70, 26.05, 25.54, 22.28, 21.63, 14.29, 14.09 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -89.79, -89.81 ppm.

HRMS (ESI^+): calcd for $C_{22}H_{27}F_2N_2O_5^+$ $[M + H]^+$: 437.1883, found 437.1882.



ethyl (*E*)-4-(*N*-benzylpicolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5a)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5a** as yellow oil (32.0 mg, 65% yield).

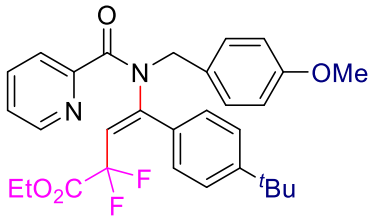
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.8 Hz, 1H), 7.65 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.30 (m, 5H), 7.30 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 5.20 (t, *J* = 12.0 Hz, 1H), 4.76 (s, 2H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.31 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.73, 162.84 (t, *J* = 33.7 Hz), 153.87, 153.50, 149.59 (t, *J* = 9.4 Hz), 148.39, 136.76, 136.58, 131.00, 130.10, 129.04, 128.58, 127.70, 125.12, 124.60, 123.97, 117.84 (t, *J* =

29.0 Hz), 111.81 (t, *J* = 244.8 Hz), 62.67, 50.89, 34.91, 31.29, 13.70 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.75 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{31}F_2N_2O_3^+$ $[M + H]^+$:493.2297, found 493.2291.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(4-methoxybenzyl)picolinamido)but-3-enoate (5b)

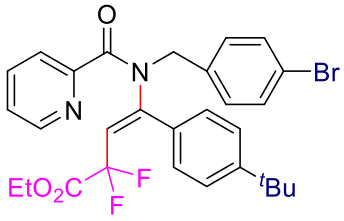
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5b** as yellow oil (31.8 mg, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.64 (td, *J* = 7.7, 1.7 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.26 – 7.23 (m, 2H), 7.23 – 7.20 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.18 (t, *J* = 12.0 Hz, 1H), 4.69 (s, 2H), 3.79 (s, 3H), 3.71 (q, *J* = 7.2 Hz, 2H), 1.31 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.63, 162.82 (t, *J* = 33.8 Hz), 159.12, 153.93, 153.46, 149.51 (t, *J* = 9.5 Hz), 148.36, 136.54, 131.06, 130.50, 130.10, 128.93, 125.10, 124.53, 123.91, 117.88 (t, *J* = 28.8 Hz), 113.88, 111.80 (d, *J* = 245.1 Hz), 62.65, 55.31, 50.25, 34.89, 31.28, 13.67 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.66 ppm.

HRMS (ESI^+): calcd for $C_{30}H_{33}F_2N_2O_4^+$ $[M + H]^+$: 523.2403, found 523.2405.



ethyl (*E*)-4-(*N*-(4-bromobenzyl)picolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5c)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5c** as yellow oil (30.9 mg, 54% yield).

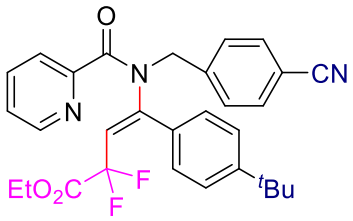
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.4 Hz, 1H), 7.67 (td, *J* = 7.7, 1.6 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.41 (m, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.22 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.15 (t, *J* = 12.0

Hz, 1H), 4.68 (s, 2H), 3.73 (q, *J* = 7.2 Hz, 2H), 1.31 (s, 9H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.73, 162.78 (t, *J* = 33.7 Hz), 153.69, 153.53, 149.47 (t, *J* = 9.4 Hz), 148.42, 136.66, 135.77, 131.68, 130.84, 130.72, 130.10, 125.20, 124.75, 124.03, 121.75, 117.91 (t, *J* = 28.9 Hz), 111.69 (t, *J* = 245.3 Hz), 62.75, 50.16, 34.93, 31.29, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.01 ppm.

HRMS (ESI$^+$): calcd for $C_{29}H_{30}{}^{79}BrF_2N_2O_3^+$ [M + H]$^+$: 571.1402, found 571.1402, $C_{29}H_{30}{}^{81}BrF_2N_2O_3^+$ [M + H]$^+$: 573.1382, found 573.1379.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(4-cyanobenzyl)picolinamido)-2,2-difluorobut-3-enoate (5d)

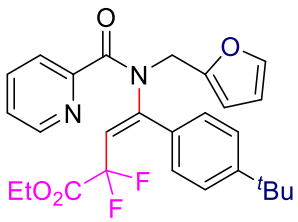
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5d** as yellow oil (39.3 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.2 Hz, 1H), 7.69 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.61 – 7.58 (m, 2H), 7.41 (dd, *J* = 8.3, 5.4 Hz, 4H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.17 (t, *J* = 11.8 Hz, 1H), 4.77 (s, 2H), 3.73 (q, *J* = 7.2 Hz, 2H), 1.31 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.83, 162.68 (t, *J* = 33.5 Hz), 153.90, 153.14, 149.63 (t, *J* = 9.4 Hz), 148.47, 142.15, 136.76, 132.39, 130.47, 130.08, 129.51, 125.28, 124.96, 124.11, 118.80, 117.81 (t, *J* = 29.1 Hz), 111.58 (d, *J* = 243.9 Hz), 62.77, 50.52, 34.94, 31.26, 13.70 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.85 ppm.

HRMS (ESI$^+$): calcd for $C_{30}H_{30}F_2N_3O_3^+$ [M + H]$^+$: 518.2250, found 518.2253.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(furan-2-ylmethyl)picolinamido)but-3-enoate (5e)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

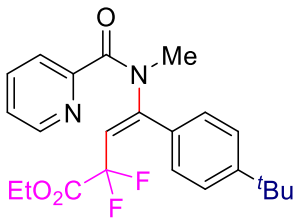
5e as yellow solid (29.6 mg, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.6 Hz, 1H), 7.64 (td, *J* = 7.6, 1.6 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 1.1 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 6.31 (m, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.30 (t, *J* = 11.9 Hz, 1H), 4.76 (s, 2H), 3.74 (q, *J* = 7.2 Hz, 2H), 1.30 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.37, 162.84 (t, *J* = 33.7 Hz), 153.54, 153.43, 150.32, 149.55 (t, *J* = 9.5 Hz), 148.32, 142.47, 136.60, 130.98, 130.03, 125.08, 124.69, 124.08, 117.64 (t, *J* = 29.0 Hz), 111.83 (d, *J* = 244.8 Hz), 110.45, 109.44, 62.68, 43.70, 34.88, 31.27, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.84 ppm.

HRMS (ESI^+): calcd for $C_{27}H_{29}F_2N_2O_4^+$ $[M + H]^+$: 483.2090, found 483.2090.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-methylpicolinamido)but-3-enoate (5f)

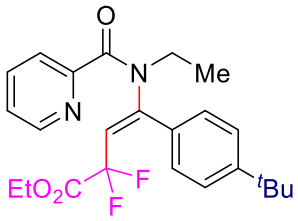
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5f** as yellow solid (20.1 mg, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.7 Hz, 1H), 7.65 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 5.35 (t, *J* = 11.9 Hz, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 3.16 (s, 3H), 1.30 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.87, 162.90 (t, *J* = 33.9 Hz), 153.81, 153.56, 151.21 (t, *J* = 9.5 Hz), 148.43, 136.61, 131.08, 129.79, 125.21, 124.55, 123.76, 116.33 (t, *J* = 29.2 Hz), 111.95 (t, *J* = 244.3 Hz), 62.76, 35.81, 34.92, 31.28, 13.72 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.33 ppm.

HRMS (ESI^+): calcd for $C_{23}H_{27}F_2N_2O_3^+$ $[M + H]^+$: 417.1984, found 417.1985.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-ethylpicolinamido)-2,2-difluorobut-3-enoate (5g)

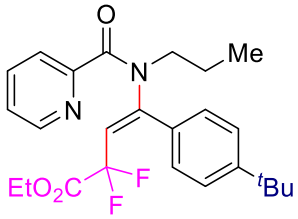
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5g** as yellow solid (21.5 mg, 50% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.7 Hz, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 5.32 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.59 (q, *J* = 7.1 Hz, 2H), 1.30 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.39, 162.86 (t, *J* = 33.8 Hz), 154.03, 153.54, 149.68 (t, *J* = 9.8 Hz), 148.42, 136.58, 131.03, 129.96, 125.14, 124.49, 123.81, 117.44 (t, *J* = 29.1 Hz), 111.86 (t, *J* = 244.7 Hz), 62.70, 42.18, 34.91, 31.28, 13.71, 12.74 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.02 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{29}F_2N_2O_3^+$ $[M + H]^+$: 431.2141, found 431.2141.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-propylpicolinamido)but-3-enoate (5h)

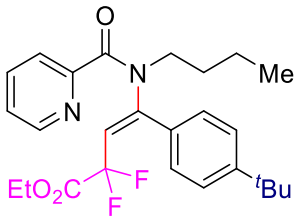
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5h** as yellow oil (18.2 mg, 41% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.23 (m, 1H), 5.32 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.48 (t, *J* = 7.6 Hz, 2H), 1.64 (m, 2H), 1.31 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.60, 162.87 (t, *J* = 33.7 Hz), 154.14, 153.53, 149.95 (t, *J* = 9.4 Hz), 148.42, 136.59, 130.92, 129.96, 125.16, 124.44, 123.81, 117.46 (t, *J* = 29.3 Hz), 111.88 (t, *J* = 244.5 Hz), 62.70, 48.65, 34.93, 31.30, 21.06, 13.73, 11.46 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.07 ppm.

HRMS (ESI$^+$): calcd for $C_{25}H_{31}F_2N_2O_3^+$ [M + H]$^+$: 445.2297, found 445.2297.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-butylpicolinamido)-2,2-difluorobut-3-enoate (5i)

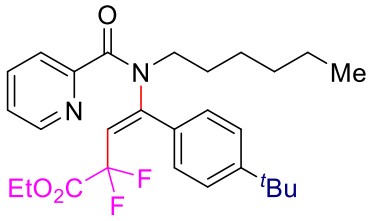
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5i** as yellow oil (23.9 mg, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.7 Hz, 1H), 7.66 (m, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 5.31 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.54 – 3.47 (m, 2H), 1.65 – 1.56 (m, 2H), 1.31 (s, 9H), 1.29 – 1.23 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.55, 162.88 (t, *J* = 33.7 Hz), 154.15, 153.52, 149.97 (t, *J* = 9.5 Hz), 148.41, 136.59, 130.98, 129.97, 125.14, 124.44, 123.81, 117.40 (t, *J* = 29.1 Hz), 111.89 (t, *J* = 244.7 Hz), 62.70, 46.91, 34.92, 31.30, 29.81, 20.18, 13.91, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.12 ppm.

HRMS (ESI$^+$): calcd for $C_{26}H_{33}F_2N_2O_3^+$ [M + H]$^+$: 459.2454, found 459.2451.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-hexylpicolinamido)but-3-enoate (5j)

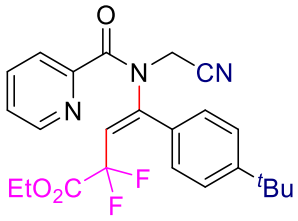
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5j** as yellow oil (29.8 mg, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.6 Hz, 1H), 7.67 (m, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 5.30 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.53 – 3.46 (m, 2H), 1.59 (m, 2H), 1.31 (s, 9H), 1.26 (m, 6H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.52, 162.88 (t, J = 33.8 Hz), 154.15, 153.51, 149.99 (t, J = 9.7 Hz), 148.41, 136.59, 130.97, 129.98, 125.13, 124.44, 123.82, 117.38 (t, J = 29.1 Hz), 111.89 (t, J = 244.7 Hz), 62.70, 47.15, 34.92, 31.52, 31.30, 27.57, 26.55, 22.58, 14.13, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.13 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{37}F_2N_2O_3^+$ $[M + H]^+$: 487.2767, found 487.2767.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(cyanomethyl)picolinamido)-2,2-difluorobut-3-enoate (5k)

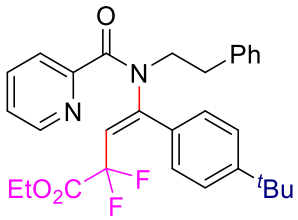
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5k** as yellow oil (33.1 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, J = 4.7 Hz, 1H), 7.78 (m, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.34 (m, 1H), 5.40 (t, J = 11.8 Hz, 1H), 4.34 (s, 2H), 3.83 (q, J = 7.2 Hz, 2H), 1.32 (s, 9H), 1.07 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.99, 162.56 (t, J = 33.5 Hz), 154.45, 151.36, 148.55, 148.31 (t, J = 8.9 Hz), 137.02, 130.07, 129.26, 125.65, 125.63, 124.65, 118.88 (t, J = 28.7 Hz), 114.56, 111.29 (t, J = 246.4 Hz), 62.97, 35.28, 35.01, 31.24, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.19 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{26}F_2N_3O_3^+$ $[M + H]^+$: 442.1937, found 442.1938.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-phenethylpicolinamido)but-3-enoate (5l)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5l** as yellow oil (17.8 mg, 35% yield).

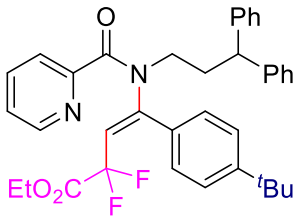
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, J = 4.6 Hz, 1H), 7.70 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.50 (d, J =

8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.24 (m, 3H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 2H), 5.20 (t, *J* = 11.8 Hz, 1H), 3.75 (q, *J* = 7.2 Hz, 2H), 3.72 – 3.68 (m, 2H), 2.99 – 2.92 (m, 2H), 1.32 (s, 9H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.51, 162.84 (t, *J* = 33.9 Hz), 153.85, 153.65, 149.82 (t, *J* = 9.6 Hz), 148.47, 138.65, 136.65, 130.83, 130.04, 129.06, 128.60, 126.59, 125.21, 124.59, 123.86, 117.62 (t, *J* = 29.0 Hz), 111.78 (t, *J* = 244.7 Hz), 62.71, 48.81, 34.94, 34.01, 31.31, 13.74 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.36 ppm.

HRMS (ESI^+): calcd for $C_{30}H_{33}F_2N_2O_3^+$ $[M + H]^+$: 507.2454, found 507.2455.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(3,3-diphenylpropyl)picolinamido)-2,2-difluorobut-3-enoate (5m)

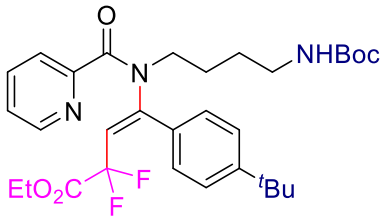
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5m** as yellow oil (33.8 mg, 57% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.5 Hz, 1H), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.20 (m, 5H), 7.17 – 7.13 (m, 5H), 7.12 (d, *J* = 1.3 Hz, 1H), 5.22 (t, *J* = 11.7 Hz, 1H), 3.90 (t, *J* = 7.9 Hz, 1H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.50 – 3.41 (m, 2H), 2.38 (dt, *J* = 11.1, 7.9 Hz, 2H), 1.33 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.47, 162.84 (t, *J* = 33.7 Hz), 153.84, 153.50, 149.99 (t, *J* = 9.6 Hz), 148.43, 144.00, 136.62, 130.82, 130.08, 128.62, 127.80, 126.41, 125.11, 124.57, 123.86, 117.23 (t, *J* = 29.1 Hz), 111.83 (d, *J* = 244.7 Hz), 62.71, 49.06, 46.52, 34.92, 33.10, 31.32, 13.73 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.22 ppm.

HRMS (ESI^+): calcd for $C_{37}H_{39}F_2N_2O_3^+$ $[M + H]^+$: 597.2923, found 597.2923.



ethyl (*E*)-4-(*N*-(4-((*tert*-butoxycarbonyl)amino)butyl)picolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5n)

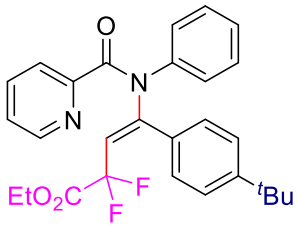
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5n** as yellow oil (35.3 mg, 62% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.67 (m, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.23 (m, 1H), 5.28 (t, *J* = 11.8 Hz, 1H), 4.61 (s, 1H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.53 – 3.45 (m, 2H), 3.09 (d, *J* = 6.4 Hz, 2H), 1.62 (m, 2H), 1.47 (m, 2H), 1.42 (s, 9H), 1.30 (s, 9H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.59, 162.79 (t, *J* = 33.7 Hz), 156.05, 153.85, 153.65, 149.81 (t, *J* = 9.5 Hz), 148.43, 136.62, 130.70, 129.95, 125.21, 124.54, 123.83, 117.56 (t, *J* = 29.2 Hz), 111.75 (t, *J* = 244.8 Hz), 79.19, 62.71, 46.55, 40.25, 34.92, 31.27, 28.52, 27.35, 24.98, 13.72 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.15 ppm.

HRMS (ESI^+): calcd for $C_{31}H_{42}F_2N_3O_5^+$ $[M + H]^+$: 574.3087, found 574.3085.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-phenylpicolinamido)but-3-enoate (5o)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5o** as yellow oil (31.3 mg, 65% yield).

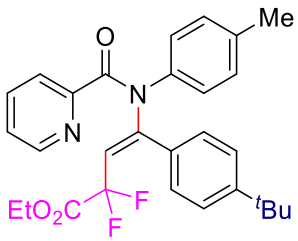
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.5 Hz, 1H), 7.62 (td, *J* = 7.7, 1.7 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 10.9, 4.4 Hz, 2H), 7.29 (t, *J* = 4.3 Hz, 2H), 7.25 – 7.22 (m, 2H), 7.22 – 7.16 (m, 2H), 5.54 (t, *J* = 11.8 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.91, 162.90 (t, *J* = 33.7 Hz), 153.92, 153.05, 151.20 (t, *J* = 10.0 Hz),

148.46, 141.92, 136.65, 131.78, 129.64, 129.30, 127.12, 127.00, 125.00, 124.92, 124.34, 118.08 (t, *J* = 29.9 Hz), 112.32 (t, *J* = 244.3 Hz), 62.78, 34.80, 31.21, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.18 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{29}F_2N_2O_3^+$ $[M + H]^+$: 479.2141, found 479.2142.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(p-tolyl)picolinamido)but-3-enoate (5p)

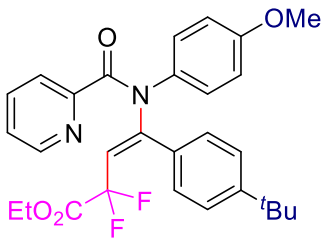
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5p** as yellow oil (39.2 mg, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.5 Hz, 1H), 7.60 (td, *J* = 7.7, 1.7 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.21 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 5.53 (t, *J* = 11.9 Hz, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.24 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.94, 162.89 (t, *J* = 33.8 Hz), 154.05, 152.94, 151.27 (t, *J* = 10.1 Hz), 148.42, 139.30, 136.85, 136.57, 131.86, 129.97, 129.59, 126.88, 124.95, 124.79, 124.23, 117.78 (t, *J* = 30.1 Hz), 112.37 (t, *J* = 243.9 Hz), 62.72, 34.76, 31.19, 21.14, 13.69 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -89.99 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{31}F_2N_2O_3^+$ $[M + H]^+$: 493.2297, found 493.2299.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(4-methoxyphenyl)picolinamido)but-3-enoate (5q)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5q** as pale-yellow oil (39.3 mg, 77% yield).

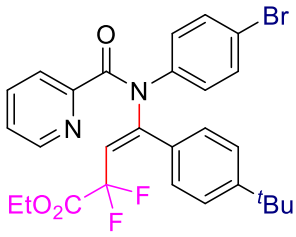
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.6 Hz, 1H), 7.62 (td, *J* = 7.7, 1.6 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.21 (m, 5H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.51 (t, *J* = 11.8 Hz, 1H), 3.76 (s, 3H),

3.74 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.94, 162.90 (t, *J* = 33.7 Hz), 158.32, 154.05, 152.94, 151.25 (t, *J* = 10.0 Hz), 148.44, 136.60, 134.50, 131.73, 129.62, 128.34, 124.95, 124.78, 124.22, 117.61 (t, *J* = 29.8 Hz), 114.57, 112.35 (t, *J* = 244.0 Hz), 62.73, 55.48, 34.78, 31.20, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.07 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{31}F_2N_2O_4^+$ $[M + H]^+$: 509.2246, found 509.2249.



ethyl (*E*)-4-(*N*-(4-bromophenyl)picolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5r)

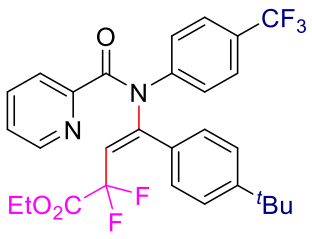
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5r** as pale-yellow solid (45.3 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.5 Hz, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 3.7 Hz, 2H), 7.43 (d, *J* = 4.1 Hz, 2H), 7.28 – 7.25 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 5.53 (t, *J* = 11.7 Hz, 1H), 3.77 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.76, 162.76 (t, *J* = 33.5 Hz), 153.45, 153.33, 150.69 (t, *J* = 10.0 Hz), 148.49, 140.76, 136.76, 132.41, 131.31, 129.68, 128.59, 125.13, 125.10, 124.40, 120.50, 118.49 (t, *J* = 29.8 Hz), 112.09 (t, *J* = 244.7 Hz), 62.82, 34.82, 31.18, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.37 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{28}{}^{79}BrF_2N_2O_3^+$ $[M + H]^+$: 557.1246, found 557.1248, $C_{28}H_{28}{}^{81}BrF_2N_2O_3^+$ $[M + H]^+$: 559.1225, found 559.1226.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(4-(trifluoromethyl)phenyl)picolinamido)but-3-enoate (5s)

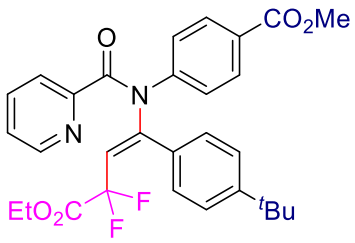
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5s** as pale-yellow oil (44.6 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.5 Hz, 1H), 7.67 (td, *J* = 7.7, 1.6 Hz, 1H), 7.59 (m, 3H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.57 (t, *J* = 11.7 Hz, 1H), 3.79 (q, *J* = 7.1 Hz, 2H), 1.24 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 162.74 (t, *J* = 33.3 Hz), 153.53, 153.24, 150.64 (t, *J* = 9.7 Hz), 148.52, 144.99, 136.84, 131.31, 129.69, 128.62 (q, *J* = 32.9 Hz), 127.01, 126.40 (q, *J* = 3.6 Hz), 125.33, 125.20, 124.52, 122.60 (q, *J* = 272.3 Hz) , 118.93 (t, *J* = 30.0 Hz), 112.06 (t, *J* = 244.7 Hz), 62.90, 34.85, 31.17, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -62.46, -90.48 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{28}F_5N_2O_3^+$ $[M + H]^+$: 547.2015, found 547.2017.



methyl (*E*)-4-(*N*-(1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)benzoate (5t)

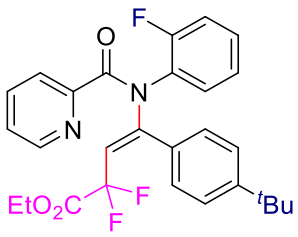
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5t** as pale-yellow oil (32.7 mg, 61% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.68 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.57 (t, *J* = 11.7 Hz, 1H), 3.89 (s, 3H), 3.79 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.80, 166.50, 162.76 (t, *J* = 33.7 Hz), 153.41, 153.32, 150.64, 148.53, 146.00, 136.81, 131.32, 130.67, 129.68, 128.20, 126.59, 125.27, 125.14, 124.52, 118.96 (t, *J* = 29.9 Hz), 112.07 (t, *J* = 245.0 Hz), 62.87, 52.30, 34.83, 31.19, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.48 ppm.

HRMS (ESI^+): calcd for $C_{30}H_{31}F_2N_2O_5^+$ $[M + H]^+$: 537.2196, found 537.2200.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(2-fluorophenyl)picolinamido)but-3-enoate (5u)

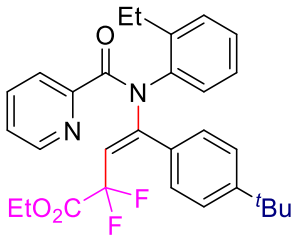
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5u** as yellow oil (37.4 mg, 75% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.0 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.49 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.19 (m, 5H), 7.09 (t, *J* = 8.5 Hz, 2H), 5.51 (t, *J* = 11.7 Hz, 1H), 3.76 (q, *J* = 7.2 Hz, 2H), 1.24 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.33, 162.85 (t, *J* = 34.1 Hz), 157.59 (d, *J* = 251.8 Hz), 153.15, 153.09, 150.68 (t, *J* = 10.6 Hz), 148.44, 136.66, 131.39, 129.62, 129.31 (d, *J* = 8.0 Hz), 129.12, 125.15, 124.97, 124.72 (d, *J* = 3.6 Hz), 124.39, 116.75 (d, *J* = 20.1 Hz), 116.61 (d, *J* = 30.2 Hz), 112.32 (t, *J* = 244.4 Hz), 62.76, 34.79, 31.19, 13.67 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -90.06, -119.18, -130.65 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{28}F_3N_2O_3^+$ $[M + H]^+$: 497.2047, found 497.2049.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethylphenyl)picolinamido)-2,2-difluorobut-3-enoate (5v)

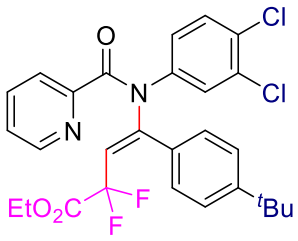
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5v** as pale-yellow oil (27.4 mg, 54% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.5 Hz, 1H), 7.58 (m, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.27 (d, *J* = 2.6 Hz, 1H), 7.22 (m, 2H), 7.21 – 7.16 (m, 3H), 5.31 (t, *J* = 11.7 Hz, 1H), 3.72 (q, *J* = 7.2 Hz, 2H), 2.77 (m, 2H), 1.23 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 170.28, 162.98 (t, *J* = 33.9 Hz), 154.02, 152.74, 151.37 (t, *J* = 10.0 Hz), 148.36, 141.57, 139.73, 136.56, 131.91, 129.54, 129.18, 128.39, 128.23, 126.97, 124.91, 124.85, 124.30, 115.40 (t, *J* = 30.1 Hz), 112.63 (t, *J* = 243.8 Hz), 62.67, 34.76, 31.21, 23.50, 13.76, 13.74 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -95.09 ppm.

HRMS (ESI$^+$): calcd for $C_{30}H_{33}F_2N_2O_3^+$ [M + H]$^+$: 507.2454, found 507.2455.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(3,4-dichlorophenyl)picolinamido)-2,2-difluorobut-3-enoate (5w)

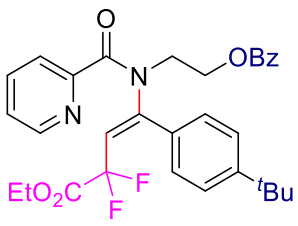
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5w** as pale-yellow solid (38.4 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.5 Hz, 1H), 7.68 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.13 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.54 (t, *J* = 11.7 Hz, 1H), 3.78 (q, *J* = 7.2 Hz, 2H), 1.25 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.71, 162.67 (t, *J* = 33.7 Hz), 153.57, 153.06, 150.38 (t, *J* = 9.8 Hz), 148.53, 141.01, 136.85, 133.05, 131.05, 130.87, 130.80, 129.70, 128.78, 126.30, 125.35, 125.22, 124.49, 118.81 (t, *J* = 29.9 Hz), 111.96 (t, *J* = 245.0 Hz), 62.89, 34.86, 31.18, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.60 ppm.

HRMS (ESI$^+$): calcd for $C_{28}H_{27}{}^{35}Cl^{35}ClF_2N_2O_3^+$ [M + H]$^+$: 547.1361, found 547.1368; $^{35}Cl^{37}ClF_2N_2O_3^+$ [M + H]$^+$: 549.1332, found 549.1342; $C_{28}H_{27}{}^{37}Cl^{37}ClF_2N_2O_3^+$ [M + H]$^+$: 551.1302, found 551.1300.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(3-oxo-3-phenylpropyl)picolinamido)but-3-enoate (5x)

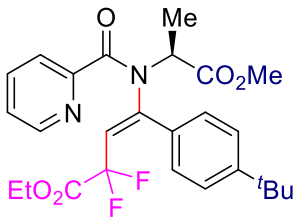
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5x** as yellow oil (40.9 mg, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.7 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.71 (td, *J* = 7.7, 1.6 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 5.37 (t, *J* = 11.8 Hz, 1H), 4.59 (t, *J* = 5.3 Hz, 2H), 3.87 (t, *J* = 5.2 Hz, 2H), 3.70 (q, *J* = 7.2 Hz, 2H), 1.30 (s, 9H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.89, 166.47, 162.69 (t, *J* = 33.5 Hz), 153.79, 153.48, 149.91 (t, *J* = 9.4 Hz), 148.51, 136.70, 133.23, 130.39, 130.08, 129.96, 129.86, 128.55, 125.34, 124.68, 123.96, 117.81 (t, *J* = 29.2 Hz), 111.65 (t, *J* = 244.9 Hz), 62.69, 62.60, 46.13, 34.92, 31.26, 13.68 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.40 ppm.

HRMS (ESI^+): calcd for $C_{31}H_{33}F_2N_2O_4^+$ $[M + H]^+$: 535.2403, found 535.2402.



(*S*,*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(1-methoxy-1-oxopropan-2-yl)picolinamido)but-3-enoate (5y)

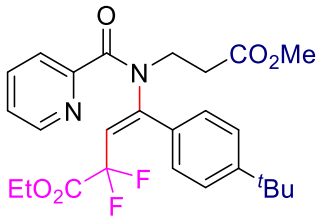
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5y** as yellow oil (27.2 mg, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 – 8.48 (m, 1H), 7.72 – 7.65 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.25 (m, 1H), 5.39 (t, *J* = 11.9 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 1H), 3.77 (d, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.31 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.19, 169.05, 162.80 (t, *J* = 33.6 Hz), 153.95, 153.20, 150.06 (t, *J* = 8.8 Hz), 148.53, 136.67, 130.60, 130.55, 125.19, 124.85, 124.02, 117.73 (t, *J* = 28.8 Hz), 111.75 (t, *J* = 245.0 Hz), 62.75, 56.87, 52.54, 34.97, 31.29, 14.50, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.42, -91.50 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{31}F_2N_2O_5^+$ $[M + H]^+$: 489.2196, found 489.2196.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(3-methoxy-3-oxopropyl)picolinamido)but-3-enoate (5z)

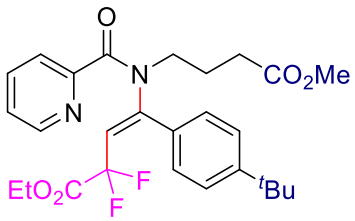
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5z** as yellow oil (37.7 mg, 77% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.7 Hz, 1H), 7.71 (td, *J* = 7.6, 1.7 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.29 – 7.26 (m, 1H), 5.28 (t, *J* = 11.7 Hz, 1H), 3.81 – 3.71 (m, 4H), 3.67 (s, 3H), 2.68 (t, *J* = 7.2 Hz, 2H), 1.32 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 171.92, 169.52, 162.71 (t, *J* = 33.1 Hz), 153.81, 153.35, 149.45 (t, *J* = 10.3 Hz), 148.45, 136.68, 130.37, 130.08, 125.29, 124.72, 123.96, 118.14 (t, *J* = 29.6 Hz), 111.64 (t, *J* = 243.7 Hz), 62.74, 51.90, 43.04, 34.94, 32.30, 31.28, 13.69 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.41 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{31}F_2N_2O_5^+$ $[M + H]^+$: 489.2196, found 489.2196.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(4-methoxy-4-oxobutyl)picolinamido)but-3-enoate (5aa)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5aa** as pale-yellow oil (30.6 mg, 61% yield).

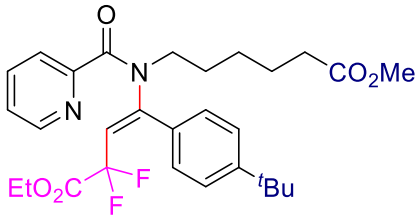
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.2 Hz, 1H), 7.69 (td, *J* = 7.7, 1.7 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.22 (m, 1H), 5.31 (t, *J* = 11.8 Hz, 1H), 3.75 (q, *J* = 7.2 Hz, 2H), 3.63 (s, 3H), 3.56 – 3.50 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.98 – 1.89 (m, 2H), 1.31 (s, 9H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 173.29, 169.66, 162.80 (t, *J* = 33.6 Hz), 153.74, 153.65, 149.72 (t, *J* = 9.5

Hz), 148.43, 136.65, 130.63, 129.99, 125.21, 124.60, 123.92, 117.70 (t, *J* = 29.1 Hz), 111.74 (t, *J* = 244.9 Hz), 62.73, 51.73, 46.15, 34.93, 31.50, 31.29, 23.07, 13.72 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.39 ppm.

HRMS (ESI^+): calcd for $C_{27}H_{33}F_2N_2O_5^+$ $[M + H]^+$: 503.2352, found 503.2353.



methyl (*E*)-6-(*N*-(1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)hexanoate (5ab)

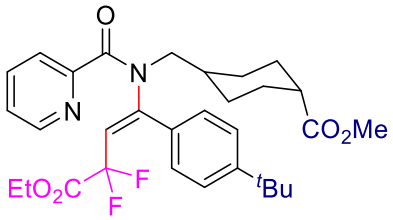
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5ab** as pale-yellow oil (30.0 mg, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.7 Hz, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.24 (m, 1H), 5.29 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 3.52 – 3.45 (m, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.60 (m, 4H), 1.36 – 1.32 (m, 2H), 1.31 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.11, 169.52, 162.82 (t, *J* = 33.9 Hz), 153.98, 153.59, 149.88 (t, *J* = 9.6 Hz), 148.41, 136.61, 130.81, 129.96, 125.18, 124.49, 123.83, 117.50 (t, *J* = 29.2 Hz), 111.81 (t, *J* = 244.6 Hz), 62.70, 51.59, 46.77, 34.92, 33.95, 31.28, 27.29, 26.38, 24.64, 13.72 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.14 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{37}F_2N_2O_5^+$ $[M + H]^+$: 531.2665, found 531.2668.



methyl (1r,4r)-4-((*N*-((*E*)-1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)methyl)cyclohexane-1-carboxylate (5ac)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

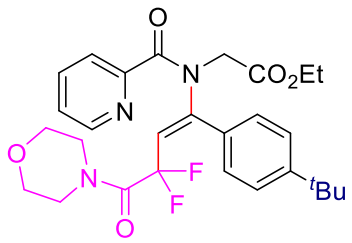
5ac as yellow oil (18.1 mg, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.7 Hz, 1H), 7.69 (td, *J* = 7.7, 1.7 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.22 (m, 1H), 5.29 (t, *J* = 11.8 Hz, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 3.35 (d, *J* = 7.1 Hz, 2H), 2.22 (m, 1H), 1.98 (dd, *J* = 13.5, 2.8 Hz, 2H), 1.78 (dd, *J* = 13.4, 2.6 Hz, 2H), 1.64 (m, 1H), 1.39 (dd, *J* = 12.7, 3.2 Hz, 2H), 1.32 (s, 9H), 1.05 (t, *J* = 7.2 Hz, 4H), 0.98 (m, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.43, 169.94, 162.81 (t, *J* = 34.0 Hz), 154.08, 153.62, 150.24 (t, *J* = 9.5 Hz), 148.47, 136.64, 130.55, 129.96, 125.23, 124.46, 123.81, 117.74 (t, *J* = 29.0 Hz), 111.76 (t, *J* = 244.9 Hz), 62.72, 52.21, 51.66, 43.18, 36.54, 34.94, 31.30, 29.96, 28.60, 13.77 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.47 ppm.

HRMS (ESI^+): calcd for $C_{31}H_{39}F_2N_2O_5^+$ $[M + H]^+$: 557.2822, found 557.2820.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3-difluoro-4-morpholino-4-oxobut-1-en-1-yl)-*N*-picolinoylglycinate (6a)

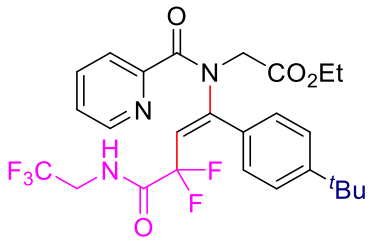
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6a** as yellow oil (43.3 mg, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 4.7 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.29 – 7.25 (m, 1H), 5.76 (s, 1H), 4.22 (s, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.53 – 3.38 (m, 4H), 3.34 – 3.10 (m, 4H), 1.29 (s, 9H), 1.25 (t, *J* = 5.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.64, 168.60, 160.95 (t, *J* = 29.6 Hz), 153.54, 153.26, 148.40, 148.20, 136.91, 130.39, 130.10, 125.11, 124.98, 124.47, 113.86 (t, *J* = 245.8 Hz), 110.15 (d, *J* = 24.6 Hz), 66.49, 61.51, 46.49, 43.06, 34.92, 31.27, 14.25 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -87.32 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{34}F_2N_3O_5^+$ $[M + H]^+$: 530.2461, found 530.2462.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3-difluoro-4-oxo-4-((2,2,2-trifluoroethyl)amino)but-1-en-1-yl)-*N*-picolinoylglycinate (6b)

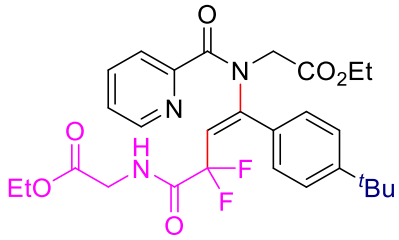
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6b** as yellow oil (18.4 mg, 34% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.47 (d, J = 4.5 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.55 (d, J = 8.3 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.33 (m, 1H), 6.53 (s, 1H), 5.57 (t, J = 11.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 4.16 (s, 2H), 3.53 – 3.41 (m, 2H), 1.32 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.08, 168.46, 163.30 (t, J = 31.1 Hz), 154.28, 152.46, 150.00 (t, J = 9.4 Hz), 148.07, 137.39, 130.32, 129.99, 125.64, 125.55, 125.38, 123.56 (t, J = 272.7 Hz), 117.38 (t, J = 30.5 Hz), 112.70 (t, J = 245.9 Hz), 61.58, 49.10, 40.73 (q, J = 35.4 Hz), 35.01, 31.24, 14.23 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -71.99, -91.12 ppm.

HRMS (ESI^+): calcd for $C_{26}H_{29}F_5N_3O_4^+$ $[M + H]^+$: 542.2073, found 542.2076.



ethyl (*E*)-*N*-(4-((2-ethoxy-2-oxoethyl)amino)-3,3-difluoro-4-oxo-1-phenylbut-1-en-1-yl)-*N*-picolinoylglycinate (6c)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6c** as yellow oil (41.8 mg, 85% yield).

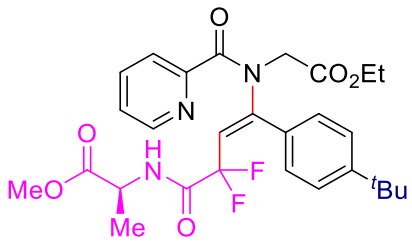
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.54 (dd, J = 3.1, 2.2 Hz, 1H), 7.77 – 7.71 (m, 2H), 7.67 (d, J = 6.4 Hz, 2H), 7.36 (s, 1H), 7.35 (d, J = 7.5 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.56 (s, 1H), 5.55 (t, J = 12.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 4H), 4.15 (s, 2H), 3.64 (d, J = 5.0 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.40, 168.65, 168.44, 162.79 (t, J = 30.6 Hz), 153.76, 152.67, 149.55 (t, J = 8.9 Hz), 148.47, 136.99, 130.56, 130.19, 125.29, 125.09, 124.78, 117.62 (t, J = 28.2 Hz), 112.85 (t,

J = 247.0 Hz), 61.88, 61.49, 48.98, 41.36, 34.93, 31.26, 29.81, 14.23, 14.21 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.84 ppm.

HRMS (ESI^+): calcd for $C_{24}H_{26}F_2N_3O_6^+$ $[M + H]^+$: 490.1784, found 490.1785.



methyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-alaninate (6d)

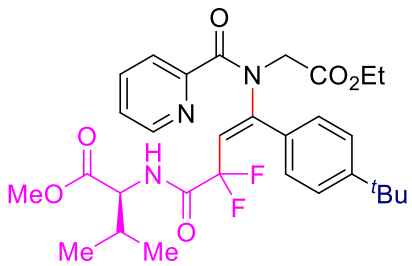
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6d** as yellow oil (45.1 mg, 83% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.7 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (m, 1H), 6.64 (d, *J* = 3.7 Hz, 1H), 5.54 (t, *J* = 12.5 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 4.13 – 4.07 (m, 1H), 3.72 (s, 3H), 1.30 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.30, 169.47, 168.48, 162.24 (t, *J* = 30.4 Hz), 153.73, 152.72, 149.62 (t, *J* = 8.9 Hz), 148.43, 136.93, 130.68, 130.17, 125.32, 125.09, 124.66, 117.52 (d, *J* = 29.4 Hz), 112.85 (t, *J* = 247.3 Hz), 61.49, 52.71, 49.10, 48.23, 34.92, 31.27, 18.02, 14.23 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.71 (dd, *J* = 274.9, 11.2 Hz), -92.76 (dd, *J* = 276.7, 9.4 Hz) ppm.

HRMS (ESI^+): calcd for $C_{28}H_{34}F_2N_3O_6^+$ $[M + H]^+$: 546.2410, found 546.2414.



methyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-valinate (6e)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

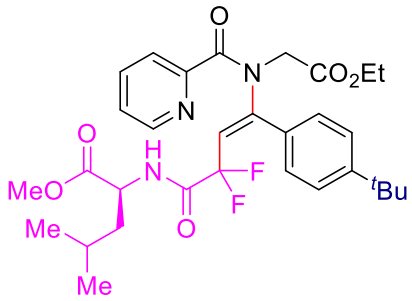
6e as yellow oil (38.7 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.5 Hz, 1H), 7.72 (d, *J* = 6.2 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 10.4 Hz, 1H), 6.55 (d, *J* = 7.0 Hz, 1H), 5.55 (t, *J* = 13.0 Hz, 1H), 4.28 – 4.22 (m, 1H), 4.22 – 4.17 (m, 2H), 4.16 (s, 2H), 3.74 (s, 3H), 1.98 (m, 1H), 1.31 (s, 9H), 1.26 (t, *J* = 6.9 Hz, 3H), 0.79 (t, *J* = 6.3 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.16, 169.61, 168.50, 162.89 (t, *J* = 30.5 Hz), 153.58, 152.75, 149.72 (t, *J* = 7.6 Hz), 148.39, 136.87, 130.70, 130.15, 125.24, 125.03, 124.56, 118.84 (t, *J* = 26.2 Hz), 112.94 (t, *J* = 247.9 Hz), 61.50, 57.23, 52.42, 34.92, 31.57, 31.30, 18.65, 17.98, 14.25 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.33 (d, *J* = 274.3 Hz), -94.11 (d, *J* = 268.2 Hz) ppm.

HRMS (ESI^+): calcd for $C_{30}H_{38}F_2N_3O_6^+$ $[M + H]^+$: 574.2723, found 574.2723.



methyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-leucinate (6f)

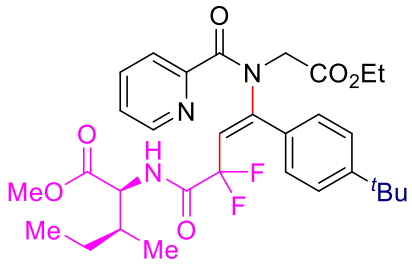
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6f** as yellow oil (41.4 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (dt, *J* = 4.7, 1.3 Hz, 1H), 7.76 – 7.67 (m, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.26 – 7.23 (m, 1H), 6.51 (s, 1H), 5.54 (t, *J* = 13.3 Hz, 1H), 4.27 (dd, *J* = 13.9, 7.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 3.72 (s, 3H), 1.59 – 1.35 (m, 4H), 1.31 (s, 9H), 1.26 (t, *J* = 5.6 Hz, 3H), 0.88 (d, *J* = 1.9 Hz, 3H), 0.86 (d, *J* = 1.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.22, 169.53, 168.52, 162.76 (t, *J* = 30.7 Hz), 153.57, 152.76, 149.66 (t, *J* = 7.4 Hz), 148.34, 136.88, 130.72, 130.12, 125.23, 125.05, 124.61, 117.02 (t, *J* = 25.9 Hz), 112.83 (t, *J* = 248.7 Hz), 61.47, 52.53, 50.97, 41.58, 34.92, 31.31, 24.80, 22.64, 22.30, 14.24 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.20 (d, *J* = 271.0 Hz), -94.50 (d, *J* = 271.0 Hz) ppm.

HRMS (ESI^+): calcd for $C_{31}H_{40}F_2N_3O_6^+$ $[M + H]^+$: 588.2880, found 588.2880.



methyl ((*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-isoleucinate (6g)

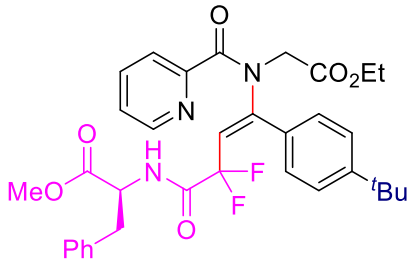
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6g** as yellow oil (33.4 mg, 57% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.1 Hz, 1H), 7.72 (d, *J* = 6.2 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24 (s, 1H), 6.58 (d, *J* = 5.6 Hz, 1H), 5.54 (t, *J* = 13.0 Hz, 1H), 4.25 (d, *J* = 9.9 Hz, 1H), 4.20 (q, *J* = 6.9 Hz, 2H), 4.15 (s, 2H), 3.73 (s, 3H), 1.70 (s, 2H), 1.31 (s, 9H), 1.28 – 1.23 (m, 3H), 1.07 (m, 1H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 171.09, 169.60, 168.50, 162.70 (t, *J* = 30.7 Hz), 153.57, 152.75, 149.66 (t, *J* = 7.4 Hz), 148.37, 136.87, 130.67, 130.14, 125.22, 125.02, 124.58, 116.91 (d, *J* = 27.8 Hz), 112.90 (t, *J* = 248.6 Hz), 61.49, 56.46, 52.36, 49.03, 38.09, 34.92, 31.30, 25.35, 15.21, 14.25, 11.71 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.66 (d, *J* = 271.4 Hz), -94.17 (d, *J* = 272.1 Hz) ppm.

HRMS (ESI^+): calcd for $C_{31}H_{40}F_2N_3O_6^+$ $[M + H]^+$: 588.2880, found 588.2880.



methyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-phenylalaninate (6h)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6h** as yellow oil (48.8 mg, 78% yield).

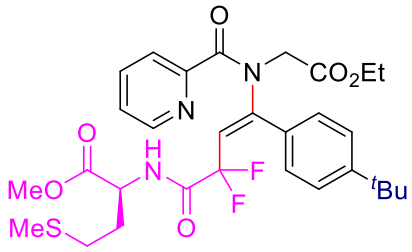
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 4.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz,

1H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 4.6 Hz, 1H), 7.24 (d, *J* = 2.7 Hz, 2H), 7.17 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 6.95 (dd, *J* = 6.5, 2.9 Hz, 2H), 6.65 (d, *J* = 6.4 Hz, 1H), 5.49 (t, *J* = 12.1 Hz, 1H), 4.32 (dd, *J* = 12.1, 5.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 2.94 (t, *J* = 5.5 Hz, 2H), 1.30 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* = 170.55, 169.37, 168.42, 162.26 (t, *J* = 30.6 Hz), 153.77, 152.55, 149.51 (t, *J* = 8.7 Hz), 148.34, 136.86, 135.24, 130.54, 130.13, 129.43, 128.68, 127.32, 125.25, 125.14, 124.75, 117.19 (t, *J* = 27.8 Hz), 112.78 (t, *J* = 246.5 Hz), 61.45, 53.55, 52.40, 49.08, 37.56, 34.91, 31.25, 14.23 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): *δ* = -91.17 (d, *J* = 277.9 Hz), -93.45 (d, *J* = 277.1 Hz) ppm.

HRMS (ESI^+): calcd for $C_{34}H_{38}F_2N_3O_6^+$ $[M + H]^+$: 622.2723, found 622.2723.



methyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-methioninate (6i)

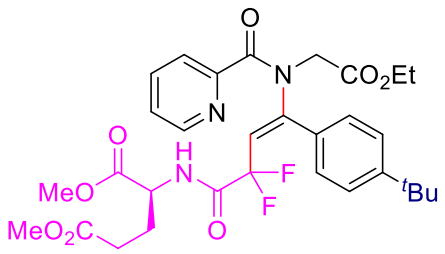
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6i** as yellow oil (41.0 mg, 68% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* = 8.53 (d, *J* = 4.8 Hz, 1H), 7.73 (dd, *J* = 6.2, 1.2 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.30 – 7.26 (m, 1H), 6.76 (s, 1H), 5.54 (t, *J* = 12.9 Hz, 1H), 4.26 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 3.74 (s, 3H), 2.33 (dd, *J* = 14.8, 6.5 Hz, 2H), 2.03 (s, 3H), 1.98 – 1.79 (m, 2H), 1.31 (s, 9H), 1.26 (t, *J* = 5.8 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* = 171.22, 169.51, 168.49, 162.74 (t, *J* = 30.7 Hz), 153.70, 152.73, 149.71 (t, *J* = 8.3 Hz), 148.38, 136.93, 130.63, 130.15, 125.28, 125.10, 124.64, 117.14 (t, *J* = 26.0 Hz), 112.85 (t, *J* = 247.9 Hz), 61.49, 52.77, 51.67, 49.08, 34.93, 31.34, 31.28, 29.68, 15.47, 14.24 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): *δ* = -92.20 (dd, *J* = 274.1, 12.1 Hz), -93.44 (d, *J* = 273.6 Hz) ppm.

HRMS (ESI^+): calcd for $C_{30}H_{38}F_2N_3O_6S^+$ $[M + H]^+$: 606.2444, found 606.2444.



dimethyl (*E*)-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoyl)-*L*-glutamate (6j)

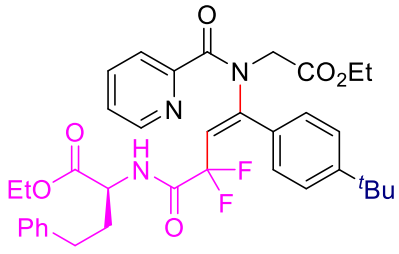
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6j** as yellow oil (49.1 mg, 79% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.53 (d, J = 4.7 Hz, 1H), 7.77 – 7.69 (m, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.29 – 7.26 (m, 1H), 6.76 (s, 1H), 5.53 (t, J = 12.7 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 2.31 – 2.14 (m, 2H), 2.07 – 1.79 (m, 2H), 1.73 (s, 1H), 1.30 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 172.88, 171.10, 169.52, 168.49, 162.83 (t, J = 30.7 Hz), 153.70, 152.69, 149.69 (t, J = 8.1 Hz), 148.41, 136.93, 130.60, 130.15, 125.27, 125.11, 124.66, 117.11 (t, J = 27.4 Hz), 112.81 (t, J = 247.9 Hz), 61.48, 52.79, 51.96, 51.73, 49.02, 34.91, 31.26, 29.71, 27.15, 14.23 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.20 (d, J = 273.9 Hz), -93.42 (d, J = 274.1 Hz) ppm.

HRMS (ESI^+): calcd for $C_{31}H_{38}F_2N_3O_8^+$ $[M + H]^+$: 618.2621, found 618.2620.



ethyl (*S*,*E*)-2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)-4-phenylbutanoate (6k)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6k** as yellow oil (42.4 mg, 65% yield).

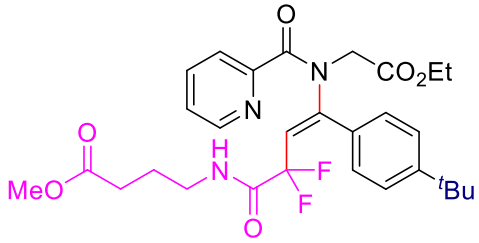
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, J = 4.8 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.68 (td, J = 7.7, 1.6 Hz, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 7.1 Hz, 1H), 7.25 (s, 1H), 7.23 – 7.16 (m,

2H), 7.11 (d, *J* = 7.0 Hz, 2H), 6.68 (s, 1H), 5.55 (t, *J* = 13.0 Hz, 1H), 4.21 (d, *J* = 7.1 Hz, 2H), 4.18 (d, *J* = 6.0 Hz, 2H), 4.16 (d, *J* = 4.6 Hz, 2H), 4.14 (s, 1H), 2.56 – 2.43 (m, 2H), 1.96 (m, 2H), 1.29 (s, 9H), 1.28 – 1.26 (t, *J* = 7.1 Hz, 3H), 1.26 – 1.24 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.09, 169.56, 168.52, 162.71 (t, *J* = 30.6 Hz), 153.64, 152.77, 149.66 (t, *J* = 7.5 Hz), 148.39, 140.38, 136.89, 130.68, 130.18, 128.63, 128.46, 126.43, 125.27, 125.06, 124.63, 112.88 (t, *J* = 26.4 Hz), 110.17 (t, *J* = 245.1 Hz), 61.91, 61.49, 52.27, 49.06, 34.91, 33.72, 31.28, 31.17, 14.27, 14.25 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.78 (d, *J* = 269.8 Hz), -93.83 (d, *J* = 272.4 Hz) ppm.

HRMS (ESI^+): calcd for $C_{36}H_{42}F_2N_3O_6^+$ $[M + H]^+$: 650.3036, found 650.3036.



methyl (*E*)-4-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)butanoate (6l)

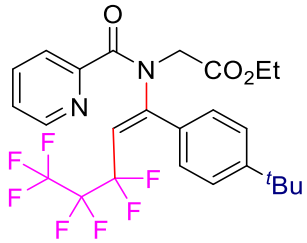
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6l** as yellow oil (32.7 mg, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.2 Hz, 1H), 7.78 (dt, *J* = 15.3, 7.7 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.29 (m, 1H), 6.30 (s, 1H), 5.57 (t, *J* = 11.7 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 3.65 (s, 3H), 2.93 (dd, *J* = 13.2, 6.6 Hz, 2H), 2.20 (t, *J* = 7.1 Hz, 2H), 1.59 – 1.50 (m, 2H), 1.30 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.49, 169.23, 168.45, 162.89 (t, *J* = 30.1 Hz), 153.86, 152.63, 149.41 (t, *J* = 9.0 Hz), 148.16, 137.23, 130.51, 130.08, 125.44, 125.34, 125.07, 117.86 (t, *J* = 31.1 Hz), 112.88 (t, *J* = 246.0 Hz), 61.53, 51.87, 49.08, 39.01, 34.96, 31.28, 31.21, 24.02, 14.24 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.56, -91.58 ppm.

HRMS (ESI^+): calcd for $C_{29}H_{36}F_2N_3O_6^+$ $[M + H]^+$: 560.2567, found 560.2565.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,4,4,5,5,5-heptafluoropent-1-en-1-yl)-*N*-picolinoylglycinate (6m)

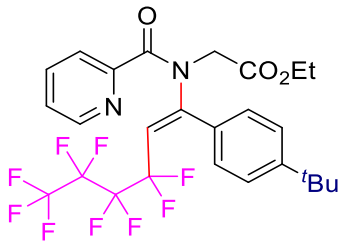
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6m** as yellow oil (29.2 mg, 55% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.7 Hz, 1H), 7.76 (dddd, *J* = 8.7, 7.9, 4.4, 3.6 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.32 – 7.27 (m, 1H), 5.38 (t, *J* = 14.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 2H), 1.34 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.65, 168.49, 153.97, 153.00, 152.32, 148.45, 136.95, 130.38, 130.26 (t, *J* = 2.6 Hz), 125.32, 125.25, 124.61, 111.47 (t, *J* = 20.2 Hz), 61.53, 48.58, 34.99, 31.34, 14.22 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -80.41 (t, *J* = 9.7 Hz, 3F), -104.15 (s, 2F), -127.66 (s, 2F) ppm.

HRMS (ESI^+): calcd for $C_{25}H_{26}F_7N_2O_3^+$ $[M + H]^+$: 535.1826, found 535.1827.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)-*N*-picolinoylglycinate (6n)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6n** as yellow oil (43.2 mg, 74% yield).

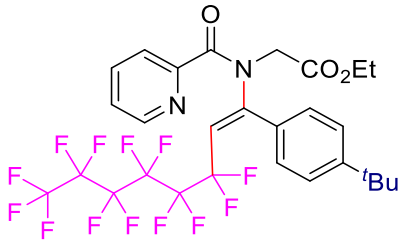
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.7 Hz, 1H), 7.78 (d, *J* = 7.3 Hz, 1H), 7.76 – 7.72 (m, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.27 (m, 1H), 5.39 (t, *J* = 14.4 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 1.34 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.67, 168.49, 153.95, 152.95, 152.36, 148.45, 136.93, 130.40, 130.26 (t, *J* = 2.6 Hz), 125.26, 125.25, 124.60, 111.61 (t, *J* = 21.0 Hz), 61.53, 48.62, 34.99, 31.34, 14.22 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -81.24 (ddd, *J* = 9.7, 6.4, 2.8 Hz, 3F), -103.59 (s, 2F), -124.18 (dd, *J* = 16.9,

8.5 Hz, 2F), -125.90 – -126.14 (m, 2F) ppm.

HRMS (ESI$^+$): calcd for $C_{26}H_{26}F_9N_2O_3^+$ [M + H]$^+$: 585.1794, found 585.1791.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooct-1-en-1-yl)-*N*-picolinoylglycinate (6o)

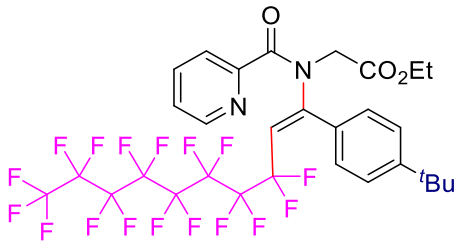
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6o** as yellow oil (51.3 mg, 75% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.7 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.74 (td, *J* = 7.6, 1.6 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.29 (ddd, *J* = 7.3, 4.8, 1.5 Hz, 1H), 5.39 (t, *J* = 14.4 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.11 (s, 2H), 1.34 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.66, 168.50, 153.95, 152.91, 152.35, 148.46, 136.92, 130.38, 130.27 (t, *J* = 2.4 Hz), 125.27, 125.25, 124.62, 111.76 (t, *J* = 21.2 Hz), 61.53, 48.60, 34.99, 31.34, 14.20 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -80.91 (t, *J* = 9.9 Hz, 3F), -103.32 (s, 2F), -121.77 – -122.15 (m, 2F), -123.02 (s, 2F), -123.21 – -123.45 (m, 2F), -126.24 (ddd, *J* = 14.7, 6.9, 3.8 Hz, 2F) ppm.

HRMS (ESI$^+$): calcd for $C_{28}H_{26}F_{13}N_2O_3^+$ [M + H]$^+$: 685.1730, found 685.1738.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodec-1-en-1-yl)-*N*-picolinoylglycinate (6p)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6p** as yellow oil (54.1 mg, 69% yield).

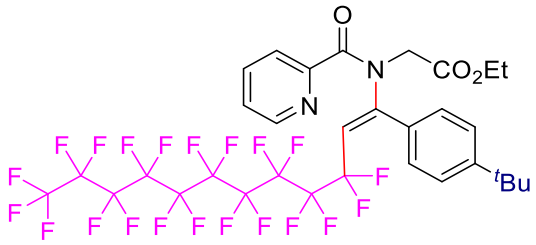
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.1 Hz, 1H), 7.77 (dd, *J* = 15.2, 7.6 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.27 (m, 1H), 5.39 (t, *J* = 14.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.11 (s,

2H), 1.34 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.68, 168.51, 153.95, 152.89, 152.34, 148.46, 136.92, 130.37, 130.27 (t, *J* = 2.3 Hz), 125.27, 125.25, 124.62, 111.77 (t, *J* = 21.4 Hz), 61.54, 48.59, 34.99, 31.34, 14.21 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.84 (t, *J* = 9.7 Hz, 3F), -103.32 (s, 2F), -121.76 (s, 2F), -122.05 (s, 4F), -122.81 (s, 2F), -123.30 (s, 2F), -126.18 (s, 2F) ppm.

HRMS (ESI^+): calcd for $C_{30}H_{26}F_{17}N_2O_3^+$ $[M + H]^+$: 785.1666, found 785.1665.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-henicosafluorododec-1-en-1-yl)-*N*-picolinoylglycinate (6q)

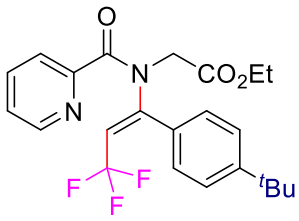
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6q** as yellow oil (59.1 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 4.1 Hz, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.31 – 7.26 (m, 1H), 5.39 (t, *J* = 14.3 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.11 (s, 2H), 1.34 (s, 9H), 1.26 (t, *J* = 6.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.69, 168.51, 153.94, 152.87, 152.30, 148.45, 136.92, 130.34, 130.27, 125.28, 125.25, 124.63, 111.76 (t, *J* = 21.4 Hz), 61.54, 48.56, 34.98, 31.32, 14.19 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -80.86 (t, *J* = 9.8 Hz, 3F), -103.37 (s, 2F), -121.95 (d, *J* = 65.9 Hz, 10F), -122.84 (s, 2F), -123.36 (s, 2F), -126.24 (s, 2F) ppm.

HRMS (ESI^+): calcd for $C_{32}H_{26}F_{21}N_2O_3^+$ $[M + H]^+$: 885.1603, found 885.1603.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-3,3,3-trifluoroprop-1-en-1-yl)-*N*-picolinoylglycinate (6r)[9]

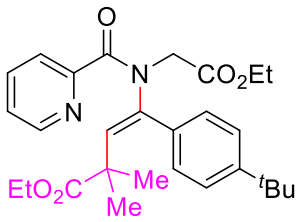
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

6r as yellow oil (35.7 mg, 82% yield, from Togni's Reagent I; 31.1 mg, 72% yield, from Togni's Reagent II).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.7 Hz, 1H), 7.74 – 7.04 (m, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.27 (m, 1H), 5.36 (q, *J* = 8.3 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.15 (s, 2H), 1.33 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.66, 168.50, 153.91, 152.45, 150.96 (q, *J* = 6.2 Hz), 148.34, 136.87, 130.11, 129.99 (q, *J* = 1.6 Hz), 125.37, 125.23, 124.42, 122.54 (q, *J* = 269.7 Hz), 114.22 (q, *J* = 35.1 Hz), 61.53, 48.70, 34.96, 31.31, 14.24 ppm.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -56.35 ppm.



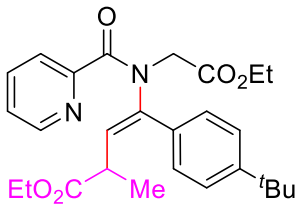
ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-dimethylbut-3-enoate (6s)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6s** as pale-yellow oil (36.5 mg, 76% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, *J* = 4.6 Hz, 1H), 7.72 (d, *J* = 3.4 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 4.8 Hz, 1H), 5.24 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.03 (s, 2H), 3.41 (q, *J* = 7.2 Hz, 2H), 1.30 (s, 9H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.81 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 175.51, 169.77, 168.70, 154.55, 152.23, 148.48, 138.84, 136.42, 135.10, 131.56, 129.94, 125.04, 124.19, 123.82, 61.13, 60.42, 47.91, 42.92, 34.81, 31.34, 26.97, 14.27, 13.98.

HRMS [ESI$^+$]: calculated for $C_{28}H_{37}N_2O_5^+$ $[M+H]^+$: 481.2697, found 481.2696.



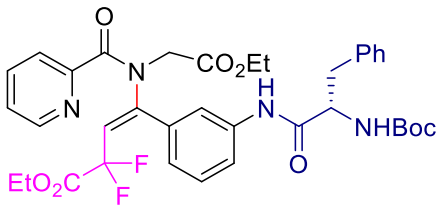
ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2-methylbut-3-enoate (6t)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **6t** as pale-yellow oil (35.0 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 4.7 Hz, 1H), 7.72 (s, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.29 – 7.20 (m, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 2H), 4.10 – 3.98 (m, 2H), 3.93 (d, *J* = 17.0 Hz, 2H), 3.16 (m, 1H), 1.33 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.62 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.06, 169.78, 168.61, 154.28, 152.17, 148.28, 141.12, 136.55, 131.14, 129.89, 128.49, 125.46, 124.38, 123.97, 61.17, 60.80, 48.39, 39.53, 34.84, 31.40, 17.53, 14.25, 14.23.

HRMS [ESI$^+$]: calculated for $C_{27}H_{35}N_2O_5^+$ [M+H]$^+$: 467.2540, found 467.2540.



ethyl (*S*,*E*)-4-(3-(2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (7a)

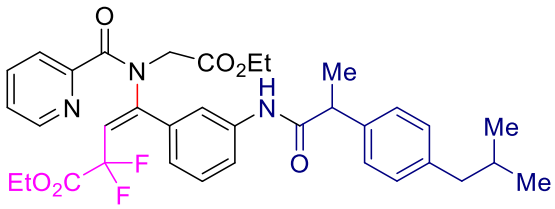
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7a** as yellow oil (33.4 mg, 48% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 4.7 Hz, 1H), 7.90 (s, 1H), 7.74 (d, *J* = 3.7 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.55 (s, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.31 (dd, *J* = 12.4, 5.1 Hz, 4H), 7.26 – 7.21 (m, 2H), 5.52 (t, *J* = 12.2 Hz, 1H), 5.14 (s, 1H), 4.47 (d, *J* = 5.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.16 (d, *J* = 6.9 Hz, 2H), 1.42 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.74, 169.53, 168.37, 162.76 (t, *J* = 34.0 Hz), 155.84, 152.49, 148.83 (t, *J* = 8.1 Hz), 148.44, 137.43, 136.89, 136.67, 134.12, 129.45, 128.97, 127.27, 126.62, 125.09, 124.41, 122.14, 121.69, 118.65 (t, *J* = 28.0 Hz), 111.50 (t, *J* = 246.1 Hz), 77.36, 62.92, 61.55, 56.76, 48.69, 38.38, 28.37, 14.25, 13.78 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.07 ppm.

HRMS (ESI$^+$): calcd for $C_{36}H_{41}F_2N_4O_8^+$ [M + H]$^+$: 695.2887, found 695.2885.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-(2-(4-isobutylphenyl)propanamido)phenyl)but-3-enoate (7b)

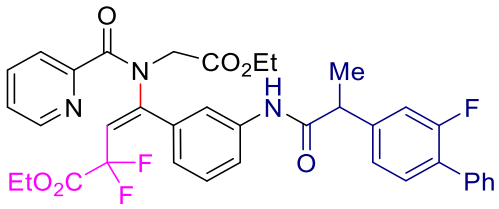
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7b** as yellow oil (50.1 mg, 79% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.7 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.65 (m, 2H), 7.46 (s, 1H), 7.33 (dd, *J* = 14.4, 6.7 Hz, 2H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.26 (s, 2H), 7.25 – 7.21 (m, 1H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.48 (t, *J* = 12.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 3.85 – 3.75 (m, 2H), 3.69 (q, *J* = 7.1 Hz, 1H), 2.46 (d, *J* = 7.2 Hz, 2H), 1.85 (m, 1H), 1.57 (d, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 172.76, 169.56, 168.37, 162.75 (t, *J* = 33.7 Hz), 152.51, 148.89 (t, *J* = 9.0 Hz), 148.39, 141.19, 138.15, 136.86, 133.93, 129.94, 129.00, 127.49, 126.11, 125.02, 124.33, 121.81, 121.08, 118.47 (t, *J* = 28.5 Hz), 111.52 (t, *J* = 246.1 Hz), 62.93, 61.51, 48.77, 47.82, 45.12, 30.29, 22.47, 18.72, 14.20, 13.71 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.88, -92.89 ppm.

HRMS (ESI^+): calcd for $C_{35}H_{40}F_2N_3O_6^+$ $[M + H]^+$: 636.2880, found 636.2878.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-(2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)phenyl)but-3-enoate (7c)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7c** as pale-yellow oil (37.7 mg, 56% yield).

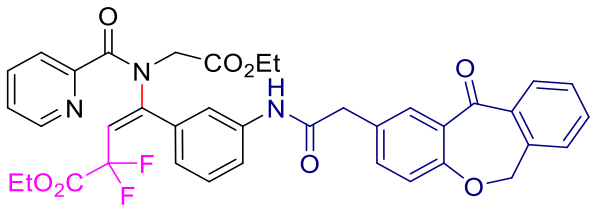
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 4.7 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.55 (dd, *J* = 13.0, 11.7 Hz, 4H), 7.44 (dd, *J* = 9.9, 4.6 Hz, 3H), 7.37 (dd, *J* = 7.6, 5.6 Hz, 2H), 7.30 (d, *J* = 7.9 Hz,

1H), 7.26 – 7.18 (m, 3H), 5.50 (t, *J* = 12.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 3.86 – 3.78 (m, 2H), 3.75 (q, *J* = 7.0 Hz, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.85, 169.60, 168.39, 162.79 (t, *J* = 33.6 Hz), 159.99 (d, *J* = 249.0 Hz), 152.46, 148.86 (t, *J* = 9.1 Hz), 148.44, 142.41 (d, *J* = 7.6 Hz), 138.08, 136.91, 135.42, 133.95, 131.32, 129.09, 129.03 (d, *J* = 2.9 Hz), 128.62, 128.27 (d, *J* = 13.6 Hz), 127.91, 126.36, 125.11, 124.36, 123.74 (d, *J* = 3.1 Hz), 122.01, 121.20, 118.58 (t, *J* = 28.3 Hz), 115.43 (d, *J* = 23.6 Hz), 111.53 (t, *J* = 245.9 Hz), 62.99, 61.56, 48.81, 47.62, 18.85, 14.19, 13.72 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.97, -116.89 ppm.

HRMS (ESI^+): calcd for $C_{37}H_{35}F_3N_3O_6^+$ $[M + H]^+$: 674.2472, found 674.2468.



ethyl (*E*)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluoro-4-(3-(2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-9-yl)acetamido)phenyl)but-3-enoate (7d)

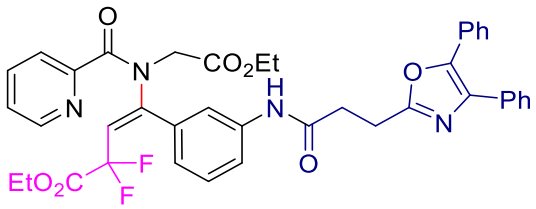
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7d** as pale-yellow oil (42.2 mg, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.7 Hz, 1H), 8.15 (d, *J* = 2.1 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.85 – 7.78 (m, 2H), 7.71 (dd, *J* = 5.1, 1.5 Hz, 2H), 7.60 (s, 1H), 7.56 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.46 (td, *J* = 7.6, 1.0 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.29 (s, 1H), 7.25 (d, *J* = 3.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 5.50 (t, *J* = 12.1 Hz, 1H), 5.18 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.81 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 2H), 1.24 (t, *J* = 5.6 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.00, 169.59, 169.13, 168.39, 162.77 (t, *J* = 33.7 Hz), 160.82, 152.46, 148.90 (t, *J* = 8.9 Hz), 148.46, 140.44, 138.05, 136.89, 136.56, 135.65, 133.96, 133.03, 132.59, 129.58, 129.43, 129.02, 128.38, 128.00, 126.37, 125.41, 125.09, 124.33, 122.03, 121.67, 121.27, 118.54 (t, *J* = 28.4 Hz), 111.53 (t, *J* = 245.9 Hz), 73.76, 62.99, 61.54, 48.83, 43.56, 14.20, 13.74 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.90 ppm.

HRMS (ESI^+): calcd for $C_{38}H_{34}F_2N_3O_8^+$ $[M + H]^+$: 698.2308, found 698.2305.



ethyl (*E*)-4-(3-(3-(4,5-diphenyloxazol-2-yl)propanamido)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (7e)

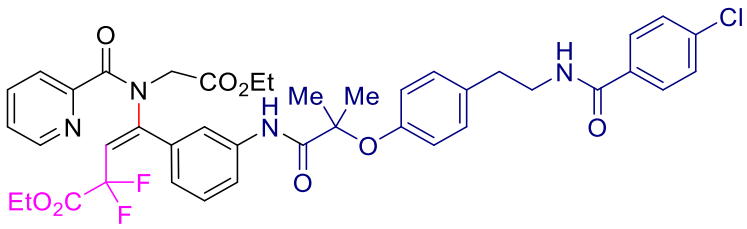
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7e** as pale-yellow oil (29.6 mg, 41% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.48 (dd, *J* = 10.2, 8.9 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.71 (td, *J* = 4.6, 2.6 Hz, 2H), 7.67 (s, 1H), 7.62 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.58 – 7.55 (m, 2H), 7.37 – 7.33 (m, 6H), 7.33 – 7.28 (m, 2H), 7.26 – 7.22 (m, 1H), 5.51 (t, *J* = 12.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 3.82 (q, *J* = 7.1 Hz, 2H), 3.29 (t, *J* = 7.0 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.96, 169.59, 168.39, 162.52 (d, *J* = 27.5 Hz), 152.52, 149.00 (d, *J* = 7.5 Hz), 148.48, 145.80, 138.25, 136.85, 135.02, 134.04, 132.31, 129.65, 129.04, 129.01, 128.81, 128.77, 128.74, 128.37, 127.98, 126.60, 126.19, 125.04, 124.33, 121.90, 121.21, 118.51 (d, *J* = 29.0 Hz), 111.53 (t, *J* = 240.3 Hz), 62.96, 61.53, 48.80, 34.10, 23.99, 14.22, 13.74 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -92.78 ppm.

HRMS (ESI^+): calcd for $C_{40}H_{37}F_2N_4O_7^+$ $[M + H]^+$: 723.2625, found 723.2625.



ethyl (*E*)-4-(3-(2-(4-(2-(4-chlorobenzamido)ethyl)phenoxy)-2-methylpropanamido)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (7f)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7f** as pale-yellow solid (61.8 mg, 78% yield).

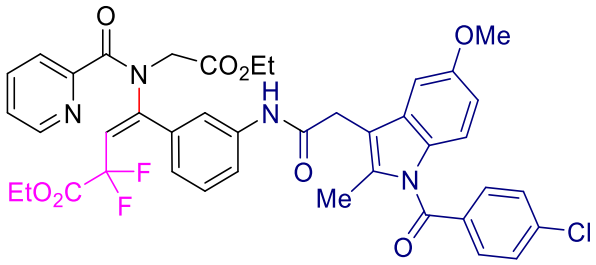
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.65 (s, 1H), 8.49 (d, *J* = 4.8 Hz, 1H), 7.84 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.72 (d, *J* = 3.5 Hz, 3H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.30 (m, 3H), 7.29 – 7.26 (m, 1H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.38 (t, *J* = 5.4 Hz, 1H), 5.50 (t, *J* = 12.2 Hz, 1H), 4.19 (q, *J*

= 7.2 Hz, 2H), 4.14 (s, 2H), 3.84 (q, *J* = 7.1 Hz, 2H), 3.64 (q, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 1.56 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 173.14, 169.50, 168.34, 166.53, 162.74 (t, *J* = 33.8 Hz), 152.51, 152.42, 148.82 (t, *J* = 8.6 Hz), 148.42, 137.68, 137.60, 136.86, 134.57, 134.15, 133.02, 129.78, 129.09, 128.84, 128.38, 126.52, 125.07, 124.35, 122.35, 121.86, 121.42, 118.58 (t, *J* = 28.2 Hz), 111.47 (t, *J* = 246.2 Hz), 82.06, 62.92, 61.50, 48.71, 41.38, 34.98, 25.02, 14.19, 13.73 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -93.21 ppm.

HRMS (ESI^+): calcd for $C_{41}H_{42}{}^{35}ClF_2N_4O_8^+$ $[M + H]^+$: 791.2654, found 791.2645, $C_{41}H_{42}{}^{37}ClF_2N_4O_8^+$ $[M + H]^+$: 793.2624, found 793.2632.



ethyl (*E*)-4-(3-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (7g)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7g** as yellow solid (47.1 mg, 60% yield).

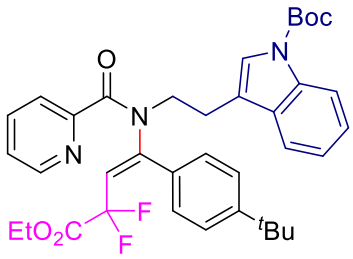
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.7 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.57 (s, 1H), 7.49 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.24 (m, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.70 (dd, *J* = 9.0, 2.4 Hz, 1H), 5.48 (t, *J* = 12.1 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.11 (s, 2H), 3.81 (d, *J* = 7.2 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 2H), 2.44 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.49, 168.50, 168.44, 168.34, 162.75 (t, *J* = 33.8 Hz), 156.46, 152.43, 151.49, 148.79, 148.36, 139.67, 137.63, 136.88, 136.76, 133.98, 133.65, 131.33, 131.10, 130.29, 129.33, 129.04, 126.39, 125.08, 124.37, 122.11, 121.64, 118.59 (t, *J* = 28.3 Hz), 115.34, 112.38, 111.49 (t, *J* = 246.0 Hz), 100.97, 62.95, 61.52, 55.84, 48.78, 33.41, 14.19, 13.71, 13.45 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -93.09 ppm.

HRMS (ESI^+): calcd for $C_{41}H_{38}{}^{35}ClF_2N_4O_8^+$ $[M + H]^+$: 787.2341, found 787.2332, $C_{41}H_{38}{}^{37}ClF_2N_4O_8^+$ [M +

H]$^+$: 789.2311, found 789.2321.



***tert*-butyl (*E*)-3-(2-(*N*-(1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)ethyl)-1*H*-indole-1-carboxylate (7h)**

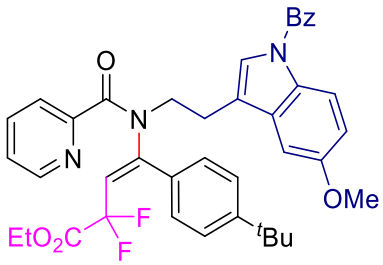
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7h** as yellow oil (35.3 mg, 55% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.52 (d, J = 4.7 Hz, 1H), 8.10 (d, J = 7.1 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.4 Hz, 3H), 7.32 – 7.25 (m, 3H), 7.14 (m, 1H), 5.22 (t, J = 11.8 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.76 – 3.70 (m, 2H), 3.09 – 3.01 (m, 2H), 1.65 (s, 9H), 1.33 (s, 9H), 1.03 (t, J = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 169.69, 162.79 (t, J = 33.6 Hz), 153.80, 153.76, 149.97 (t, J = 9.5 Hz), 149.80, 148.52, 136.69, 135.61, 130.64, 130.44, 130.17, 125.26, 124.66, 124.46, 123.92, 123.57, 122.52, 119.07, 117.48 (t, J = 29.0 Hz), 117.26, 115.36, 111.73 (t, J = 245.0 Hz), 83.59, 62.71, 47.27, 34.97, 31.33, 28.32, 23.49, 13.74 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.28 ppm.

HRMS (ESI$^+$): calcd for $C_{37}H_{42}F_2N_2O_5^+$ [M + H]$^+$: 646.3087, found 646.3084.



ethyl (*E*)-4-(*N*-(2-(1-benzoyl-5-methoxy-1*H*-indol-3-yl)ethyl)picolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (7i)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

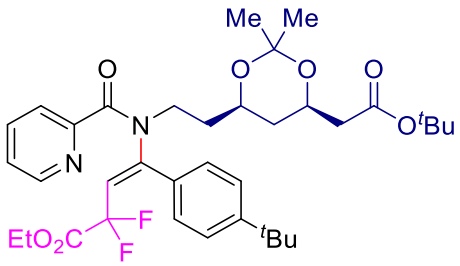
7i as yellow oil (43.4 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.4 Hz, 1H), 8.27 (d, *J* = 8.8 Hz, 1H), 7.69 (m, 3H), 7.63 – 7.56 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 1.1 Hz, 1H), 7.08 (s, 1H), 6.96 (m, 2H), 5.25 (t, *J* = 11.8 Hz, 1H), 3.85 (s, 3H), 3.78 (t, *J* = 7.7 Hz, 2H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H), 1.30 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.71, 168.18, 162.73 (t, *J* = 33.6 Hz), 156.86, 153.79, 153.64, 149.88 (t, *J* = 9.5 Hz), 148.51, 136.67, 134.82, 131.84, 131.74, 131.04, 130.60, 129.98, 129.05, 128.69, 125.80, 125.24, 124.67, 123.82, 118.65, 117.59, 117.55 (t, *J* = 29.4 Hz), 113.62, 111.71 (t, *J* = 245.0 Hz), 101.89, 62.74, 55.81, 46.97, 34.92, 31.23, 23.56, 13.71 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.06 ppm.

HRMS (ESI^+): calcd for $C_{40}H_{40}F_2N_3O_5^+$ $[M + H]^+$: 680.2931, found 680.2924.



ethyl (*E*)-4-(*N*-(2-((4*R*,6*R*)-6-(2-(*tert*-butoxy)-2-oxoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)picolinamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (7j)

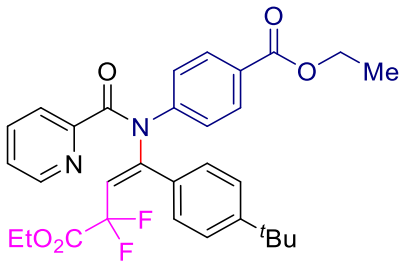
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7j** as yellow oil (28.0 mg, 43% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.8 Hz, 1H), 7.67 (m, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.23 (m, 1H), 5.34 (t, *J* = 11.8 Hz, 1H), 4.22 (m, 1H), 3.96 – 3.87 (m, 1H), 3.74 (q, *J* = 7.2 Hz, 2H), 3.70 – 3.50 (m, 2H), 2.45 – 2.25 (m, 2H), 1.82 – 1.72 (m, 2H), 1.53 (dt, *J* = 12.6, 2.4 Hz, 1H), 1.43 (s, 9H), 1.37 (d, *J* = 37.0 Hz, 6H), 1.30 (s, 9H), 1.15 (dd, *J* = 24.1, 11.6 Hz, 1H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.35, 169.55, 162.84 (d, *J* = 32.6 Hz), 153.98, 153.49, 149.85 (t, *J* = 9.4 Hz), 148.43, 136.58, 130.92, 129.98, 125.12, 124.49, 123.74, 117.65 (t, *J* = 28.8 Hz), 111.84 (d, *J* = 244.2 Hz), 98.81, 80.71, 67.01, 66.20, 62.70, 43.82, 42.82, 36.45, 34.91, 34.26, 31.30, 30.12, 28.22, 19.81, 13.74 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.18, -91.26 ppm.

HRMS (ESI$^+$): calcd for $C_{36}H_{49}F_2N_2O_7^+$ [M + H]$^+$: 659.3502, found 659.3502.



ethyl (*E*)-4-(*N*-(1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)benzoate (7k)

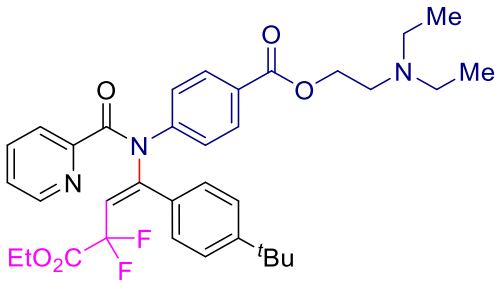
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7k** as pale-yellow oil (35.8 mg, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.6 Hz, 1H), 7.99 (d, *J* = 8.6 Hz, 2H), 7.67 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.27 (m, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.57 (t, *J* = 11.7 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.78 (q, *J* = 7.2 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 9H), 1.06 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.80, 166.01, 162.75 (t, *J* = 33.7 Hz), 153.39, 153.34, 150.67 (t, *J* = 9.7 Hz), 148.52, 145.91, 136.80, 131.34, 130.62, 129.66, 128.55, 126.55, 125.25, 125.14, 124.50, 118.93 (t, *J* = 29.9 Hz), 112.08 (t, *J* = 244.4 Hz), 62.86, 61.20, 34.83, 31.18, 14.41, 13.72 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.42 ppm.

HRMS (ESI$^+$): calcd for $C_{31}H_{33}F_2N_2O_5^+$ [M + H]$^+$: 551.2352, found 551.2358.



2-(diethylamino)ethyl (*E*)-4-(*N*-(1-(4-(*tert*-butyl)phenyl)-4-ethoxy-3,3-difluoro-4-oxobut-1-en-1-yl)picolinamido)benzoate (7l)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded

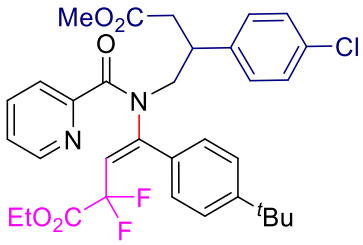
7l as yellow oil (48.7 mg, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (d, *J* = 4.4 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 2H), 7.67 (m, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.27 – 7.20 (m, 3H), 5.56 (t, *J* = 11.7 Hz, 1H), 4.38 (t, *J* = 6.1 Hz, 2H), 3.78 (q, *J* = 7.1 Hz, 2H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.66 (q, *J* = 7.1 Hz, 4H), 1.23 (s, 9H), 1.08 (d, *J* = 7.1 Hz, 6H), 1.04 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.80, 165.94, 162.75 (t, *J* = 33.6 Hz), 153.41, 153.30, 150.64 (t, *J* = 8.7 Hz), 148.53, 146.02, 136.81, 131.30, 130.69, 129.68, 128.22, 126.58, 125.27, 125.14, 124.52, 118.96 (t, *J* = 29.8 Hz), 112.07 (t, *J* = 244.6 Hz), 62.86, 50.95, 47.81, 34.83, 31.28, 31.18, 13.72, 11.81 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -90.47 ppm.

HRMS (ESI^+): calcd for $C_{35}H_{42}F_2N_3O_5^+$ $[M + H]^+$: 622.3087, found 622.3086.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-(4-chlorophenyl)-4-methoxy-4-oxobutyl)picolinamido)-2,2-difluorobut-3-enoate (7m)

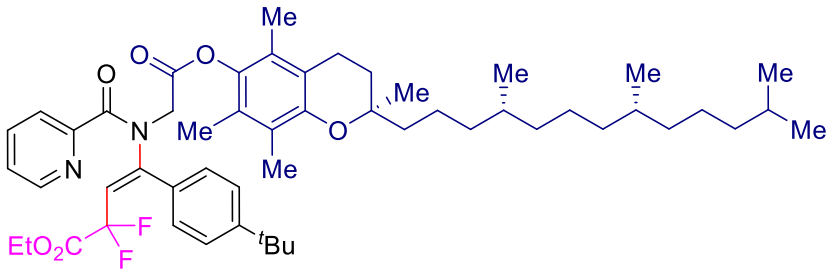
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7m** as yellow oil (38.8 mg, 63% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 4.2 Hz, 1H), 7.68 (m, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.25 – 7.22 (m, 3H), 7.11 (d, *J* = 8.5 Hz, 2H), 4.86 (t, *J* = 11.8 Hz, 1H), 3.80 (m, 1H), 3.73 (q, *J* = 7.2 Hz, 2H), 3.63 – 3.54 (m, 2H), 3.53 (s, 3H), 2.63 (m, 2H), 1.32 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.78, 169.76, 162.68 (t, *J* = 33.4 Hz), 153.79, 153.59, 149.01 (t, *J* = 9.5 Hz), 148.46, 139.42, 136.66, 133.16, 130.05, 129.50, 128.80, 125.30, 124.56, 123.78, 118.60 (t, *J* = 29.0 Hz), 111.47 (t, *J* = 245.1 Hz), 62.72, 51.76, 50.75, 40.41, 38.70, 34.97, 31.31, 13.73 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.93, -91.96 ppm.

HRMS (ESI^+): calcd for $C_{33}H_{36}{}^{35}ClF_2N_2O_5^+$ $[M + H]^+$: 613.2275, found 613.2265, $C_{33}H_{36}{}^{37}ClF_2N_2O_5^+$ $[M + H]^+$: 615.2246, found 615.2249.



ethyl (*E*)-4-(4-(*tert*-butyl)phenyl)-2,2-difluoro-4-(*N*-(2-oxo-2-((2,5,7,8-tetramethyl-2-(3,7,11-trimethyldodecyl)chroman-6-yl)oxy)ethyl)picolinamido)but-3-enoate (7n)

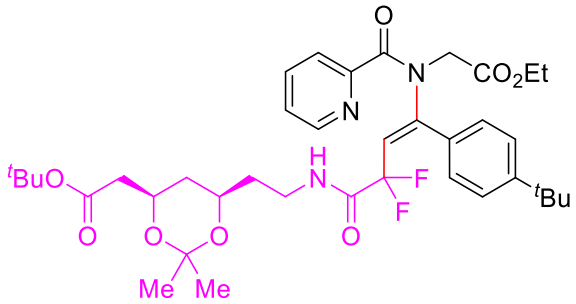
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7n** as pale-yellow oil (63.9 mg, 74% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.7 Hz, 1H), 7.73 (d, *J* = 3.7 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 8.9, 4.6 Hz, 1H), 5.51 (t, *J* = 11.7 Hz, 1H), 4.47 (s, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 2.60 (t, *J* = 6.6 Hz, 2H), 2.10 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 1.85 – 1.73 (m, 2H), 1.63 – 1.45 (m, 4H), 1.45 – 1.36 (m, 4H), 1.34 (s, 9H), 1.29 (s, 2H), 1.28 (s, 1H), 1.27 (d, *J* = 2.3 Hz, 2H), 1.24 (s, 3H), 1.18 (d, *J* = 8.1 Hz, 1H), 1.17 – 1.13 (m, 2H), 1.09 (d, *J* = 2.4 Hz, 1H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 3H), 0.87 (d, *J* = 3.3 Hz, 6H), 0.85 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.76, 167.51, 162.77 (t, *J* = 33.5 Hz), 153.93, 152.74, 150.15, 149.73, 149.40 (t, *J* = 9.5 Hz), 148.53, 140.35, 136.73, 130.32, 126.85, 125.41, 125.17, 124.97, 124.24, 123.27, 118.13 (t, *J* = 28.6 Hz), 117.59, 111.75 (t, *J* = 245.0 Hz), 75.22, 62.71, 48.52, 39.49, 37.56, 37.40, 34.96, 32.91, 32.83, 31.29, 31.18, 28.09, 24.92, 24.56, 24.13, 24.04, 22.84, 22.75, 21.15, 20.72, 19.88, 19.78, 13.69, 13.10, 12.26, 11.93 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.90 ppm.

HRMS (ESI^+): calcd for $C_{52}H_{73}F_2N_2O_6^+$ $[M + H]^+$: 859.5431, found 859.5432.



***tert*-butyl (*E*)-2-(6-(2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (7o)**

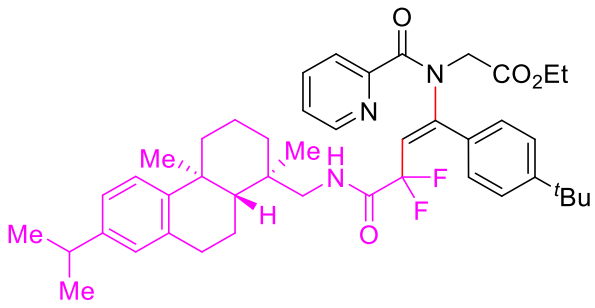
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7o** as yellow oil (45.7 mg, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, *J* = 4.7 Hz, 1H), 7.73 (d, *J* = 4.1 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.27 (m, 1H), 6.93 (s, 1H), 5.52 (t, *J* = 12.6 Hz, 1H), 4.23 (d, *J* = 6.5 Hz, 1H), 4.22 – 4.16 (m, 2H), 4.15 (s, 2H), 3.93 – 3.84 (m, 1H), 3.15 (m, 1H), 2.98 – 2.86 (m, 1H), 2.40 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.27 (dd, *J* = 15.2, 6.1 Hz, 1H), 1.78 (s, 1H), 1.61 – 1.52 (m, 1H), 1.52 – 1.45 (m, 2H), 1.43 (s, 9H), 1.38 (s, 3H), 1.31 (s, 9H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 4.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.18, 169.51, 168.47, 162.64 (t, *J* = 29.6 Hz), 153.40, 152.82, 149.04 (t, *J* = 8.2 Hz), 148.31, 136.94, 130.72, 130.16, 125.16, 124.95, 124.59, 117.93 (d, *J* = 27.4 Hz), 113.08 (t, *J* = 249.0 Hz), 98.91, 80.88, 68.96, 66.11, 61.48, 48.99, 42.60, 37.37, 36.09, 34.91, 34.06, 31.34, 29.91, 28.20, 19.77, 14.24 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.65 (d, *J* = 263.9 Hz), -94.74 (d, *J* = 269.0 Hz) ppm.

HRMS (ESI^+): calcd for $C_{38}H_{52}F_2N_3O_8^+$ $[M + H]^+$: 716.3717, found 716.3716.



ethyl *N*-((*E*)-1-(4-(*tert*-butyl)phenyl)-3,3-difluoro-4-((((1*R*,4a*S*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)amino)-4-oxobut-1-en-1-yl)-*N*-picolinoylglycinate (7p)

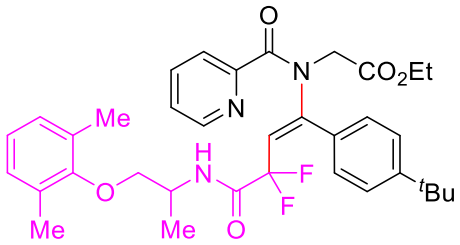
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7p** as yellow oil (28.7 mg, 39% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.7 Hz, 1H), 7.69 (d, *J* = 3.7 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 5.86 (s, 1H), 5.61 – 5.51 (m, 1H), 4.24 – 4.18 (m, 2H), 4.17 (s, 2H), 2.85 (t, *J* = 7.1 Hz, 2H), 2.82 – 2.70 (m, 2H), 2.25 (d, *J* = 12.8 Hz, 1H), 1.73 – 1.66 (m, 2H), 1.63 (s, 2H), 1.31 (s, 9H), 1.28 (d, *J* = 6.6 Hz, 4H), 1.25 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 6H), 1.17 (s, 3H), 1.05 (m, 1H), 0.82 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.63, 168.52, 163.38 (t, *J* = 29.2 Hz), 153.47, 152.85, 149.45 (d, *J* = 8.2 Hz), 148.27, 146.88, 145.83, 136.90, 134.62, 130.81, 130.18, 127.00, 125.17, 124.96, 124.55, 124.32, 124.06, 121.24 (d, *J* = 26.7 Hz), 113.26 (t, *J* = 254.2 Hz), 61.52, 50.26, 49.02, 46.00, 38.30, 37.58, 37.35, 36.16, 34.94, 33.55, 31.35, 30.28, 25.45, 24.10, 19.08, 18.60, 18.47, 14.27 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.43 ppm.

HRMS (ESI^+): calcd for $C_{44}H_{56}F_2N_3O_4^+$ $[M + H]^+$: 728.4233, found 728.4233.



ethyl (*E*)-*N*-(1-(4-(*tert*-butyl)phenyl)-4-((1-(2,6-dimethylphenoxy)propan-2-yl)amino)-3,3-difluoro-4-oxobut-1-en-1-yl)-*N*-picolinoylglycinate (7q)

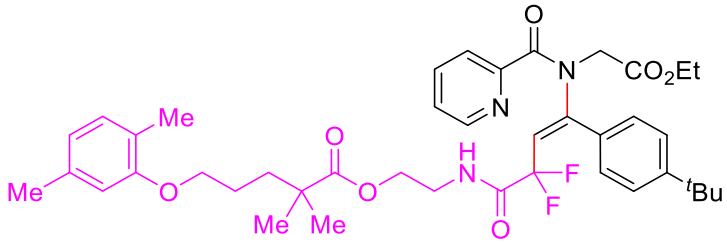
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7q** as yellow oil (28.0 mg, 45% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 4.7 Hz, 1H), 7.79 – 7.68 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.24 – 7.18 (m, 1H), 6.98 (d, *J* = 7.3 Hz, 2H), 6.95 – 6.88 (m, 1H), 6.48 (s, 1H), 5.60 (t, *J* = 12.5 Hz, 1H), 4.27 – 4.19 (m, 2H), 4.17 (d, *J* = 4.1 Hz, 2H), 3.96 (s, 1H), 3.59 (q, *J* = 9.4 Hz, 2H), 2.16 (s, 6H), 1.29 (s, 9H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.47, 168.48, 162.26 (t, *J* = 30.2 Hz), 154.62, 153.75, 152.69, 149.46 (t, *J* = 9.0 Hz), 148.49, 137.01, 130.81, 130.73, 130.16, 129.13, 125.41, 125.15, 124.77, 124.37, 117.83 (d, *J* = 25.5 Hz), 101.77 (t, *J* = 245.4 Hz), 73.10, 61.52, 49.16, 45.78, 34.93, 31.27, 17.07, 16.20, 14.26 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.20 (dd, *J* = 274.9, 11.6 Hz), -92.47 (d, *J* = 276.6 Hz) ppm.

HRMS (ESI^+): calcd for $C_{35}H_{42}F_2N_3O_5^+$ $[M + H]^+$: 622.3087, found 622.3083.



(*E*)-2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)ethyl 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoate (7r)

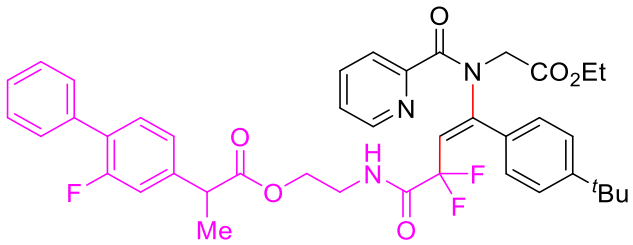
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7r** as pale-yellow oil (34.9 mg, 47% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.49 (d, *J* = 4.5 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.75 (td, *J* = 7.7, 1.4 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.30 (dd, *J* = 8.6, 3.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.66 (d, *J* = 7.5 Hz, 1H), 6.58 (s, 1H), 6.41 (s, 1H), 5.57 (t, *J* = 11.9 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.16 (s, 2H), 3.89 – 3.86 (m, 2H), 3.84 (d, *J* = 5.8 Hz, 2H), 3.15 (q, *J* = 5.7 Hz, 2H), 2.30 (s, 3H), 2.15 (s, 3H), 1.68 (d, *J* = 2.7 Hz, 4H), 1.31 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 6H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 177.76, 169.21, 168.42, 163.01 (t, *J* = 30.0 Hz), 156.96, 153.93, 152.64, 149.57 (t, *J* = 9.0 Hz), 148.14, 137.20, 136.60, 130.58, 130.43, 130.10, 125.44, 125.28, 125.06, 123.61, 120.91, 117.74 (d, *J* = 27.1 Hz), 112.90 (t, *J* = 240.5 Hz) , 112.13, 67.88, 62.14, 61.51, 49.13, 42.21, 38.64, 37.08, 34.96, 31.27, 25.23, 25.20, 21.51, 15.87, 14.24 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.71 ppm.

HRMS (ESI^+): calcd for $C_{41}H_{52}F_2N_3O_7^+$ $[M + H]^+$: 736.3768, found 736.3767.



(*E*)-2-((3-(4-(*tert*-butyl)phenyl)-3-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-1,1-difluoroallyl)(oxo-l3-methyl)-l4-azanyl)ethyl 2-(2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (7s)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7s** as yellow oil (55.7 mg, 76% yield).

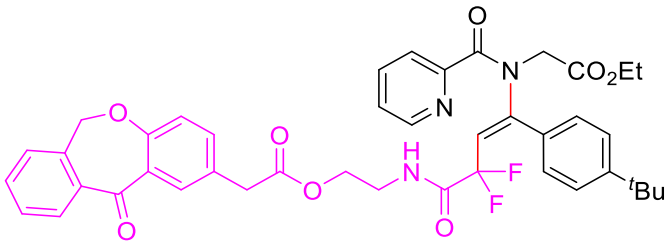
^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.75 (td, *J* = 7.7, 1.6 Hz, 1H), 7.54 – 7.48 (m, 4H), 7.47 – 7.41 (m, 2H), 7.39 – 7.36 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.32 – 7.26 (m,

3H), 7.07 (dd, *J* = 3.9, 1.4 Hz, 1H), 7.05 (s, 1H), 6.41 (s, 1H), 5.56 (t, *J* = 11.4 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 4.13 (s, 2H), 3.86 – 3.74 (m, 2H), 3.74 – 3.68 (m, 1H), 3.15 (d, *J* = 5.5 Hz, 2H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 9H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 173.80, 169.04, 168.36, 162.83 (t, *J* = 30.2 Hz), 159.77 (d, *J* = 248.9 Hz), 154.04, 152.55, 149.52 (t, *J* = 9.5 Hz), 148.01, 141.48 (d, *J* = 7.7 Hz), 137.29, 135.39, 131.06 (d, *J* = 3.8 Hz), 130.41, 129.96, 129.01 (d, *J* = 2.9 Hz), 128.58, 128.20, 128.07, 127.86, 125.49, 125.36, 125.25, 123.54 (d, *J* = 3.3 Hz), 115.22 (d, *J* = 23.8 Hz), 112.82 (d, *J* = 245.8 Hz), 62.99, 61.48, 49.15, 44.93, 38.39, 34.92, 31.20, 18.49, 14.20 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -90.64, -117.19 ppm.

HRMS (ESI^+): calcd for $C_{41}H_{43}F_3N_3O_6^+$ $[M + H]^+$: 730.3098, found 730.3098.



(*E*)-2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)ethyl 2-(11-oxo-6,11-dihydrodibenzo[*b,e*]oxepin-2-yl)acetate (7t)

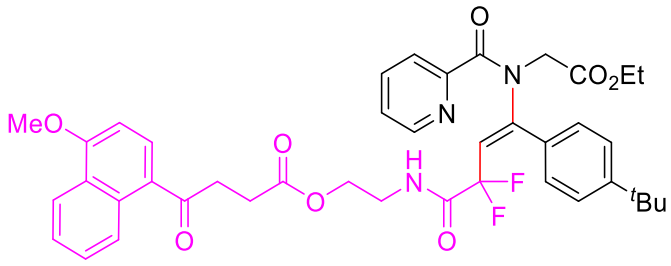
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7t** as yellow oil (56.9 mg, 75% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 4.4 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.86 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.76 (td, *J* = 7.7, 1.6 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.46 (td, *J* = 7.6, 1.1 Hz, 1H), 7.38 – 7.32 (m, 4H), 7.32 – 7.28 (m, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.54 (s, 1H), 5.56 (t, *J* = 11.3 Hz, 1H), 5.16 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 3.82 (t, *J* = 5.4 Hz, 2H), 3.61 (s, 2H), 3.17 (dd, *J* = 11.0, 5.5 Hz, 2H), 1.29 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 190.81, 171.17, 169.07, 168.40, 162.91 (t, *J* = 30.3 Hz), 160.65, 154.04, 152.56, 149.54 (t, *J* = 9.5 Hz), 148.04, 140.43, 137.29, 136.27, 135.63, 132.97, 132.41, 130.43, 129.98, 129.58, 129.39, 127.96, 127.37, 125.51, 125.41, 125.26, 125.24, 121.33, 117.83 (d, *J* = 27.8 Hz), 112.83 (t, *J* = 245.3 Hz), 73.72, 63.08, 61.49, 49.14, 40.10, 38.49, 34.95, 31.23, 14.22 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -90.75 ppm.

HRMS (ESI^+): calcd for $C_{42}H_{42}F_2N_3O_8^+$ $[M + H]^+$: 754.2934, found 754.2929.



(*E*)-2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)ethyl 4-(4-methoxynaphthalen-1-yl)-4-oxobutanoate (7u)

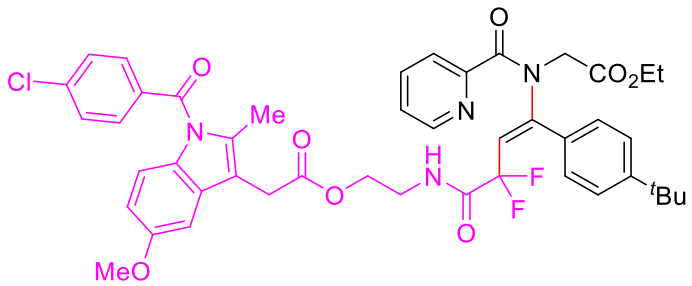
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7u** as yellow oil (47.4 mg, 64% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 8.89 (d, *J* = 8.4 Hz, 1H), 8.52 (d, *J* = 4.4 Hz, 1H), 8.31 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.73 (td, *J* = 7.7, 1.6 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.1, 2.1 Hz, 3H), 7.54 – 7.48 (m, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.29 (m, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 1H), 5.58 (t, *J* = 11.8 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.16 (s, 2H), 4.06 (s, 3H), 3.89 (t, *J* = 5.3 Hz, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 3.20 (dd, *J* = 10.8, 5.4 Hz, 2H), 2.75 (t, *J* = 6.3 Hz, 2H), 1.28 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 200.01, 173.08, 169.18, 168.41, 162.99 (t, *J* = 30.2 Hz), 159.49, 153.94, 152.60, 149.55 (t, *J* = 9.6 Hz), 148.18, 137.19, 132.08, 131.32, 130.48, 130.04, 128.88, 126.71, 126.06, 125.98, 125.87, 125.49, 125.35, 125.09, 122.24, 117.91 (d, *J* = 29.1 Hz), 112.88 (t, *J* = 245.7 Hz), 102.20, 62.85, 61.48, 55.95, 49.17, 38.54, 35.64, 34.93, 31.23, 28.89, 14.22 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -91.20 ppm.

HRMS (ESI^+): calcd for $C_{41}H_{44}F_2N_3O_8^+$ $[M + H]^+$: 744.3091, found 744.3091.



(*E*)-2-(4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enamido)ethyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetate (7v)

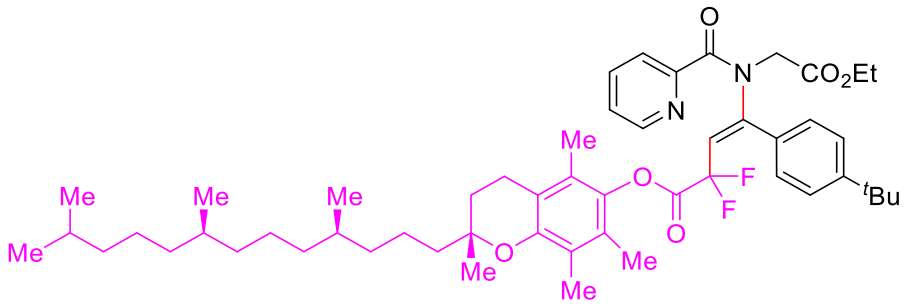
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7v** as yellow solid (56.6 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 4.6 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.74 (td, *J* = 7.7, 1.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 0.9 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.62 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.37 (s, 1H), 5.54 (t, *J* = 10.7 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.15 (s, 2H), 3.85 (t, *J* = 5.5 Hz, 2H), 3.77 (s, 3H), 3.64 (s, 2H), 3.15 (d, *J* = 5.6 Hz, 2H), 2.33 (s, 3H), 1.28 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.66, 169.13, 168.39, 168.31, 162.96 (t, *J* = 30.4 Hz), 156.15, 153.97, 152.58, 149.59 (t, *J* = 9.0 Hz), 148.03, 139.41, 137.21, 136.14, 133.88, 131.26, 130.87, 130.54, 130.50, 130.03, 129.23, 125.43, 125.28, 125.11, 115.09, 112.82 (d, *J* = 246.3 Hz), 112.08, 111.52, 101.41, 62.99, 61.48, 55.76, 49.11, 38.47, 34.92, 31.21, 30.23, 14.21, 13.35 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -91.34 ppm.

HRMS (ESI^+): calcd for $C_{45}H_{46}{}^{35}ClF_2N_4O_8^+$ $[M + H]^+$: 843.2967, found 843.2961, $C_{45}H_{46}{}^{37}ClF_2N_4O_8^+$ $[M + H]^+$: 845.2937, found 845.2947.



(*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl (*E*)-4-(4-(*tert*-butyl)phenyl)-4-(*N*-(2-ethoxy-2-oxoethyl)picolinamido)-2,2-difluorobut-3-enoate (7w)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **7w** as pale-yellow oil (58.5 mg, 68% yield).

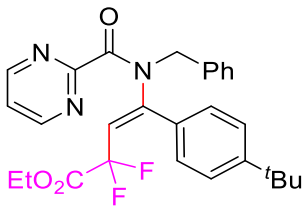
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 4.4 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.65 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.15 (m, 1H), 5.70 (t, *J* = 13.9 Hz, 1H), 4.26 – 4.21 (m, 2H), 4.20 (s, 2H), 2.55 (t, *J* = 6.6 Hz, 2H), 2.06 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H), 1.53 (dd, *J* = 7.9, 5.2 Hz, 2H), 1.45 – 1.36 (m, 4H), 1.34 (s, 9H), 1.28 (dd, *J* = 8.0, 6.3 Hz, 8H), 1.25 (d, *J* = 1.8 Hz, 1H), 1.23 (s, 3H), 1.20 (s, 1H), 1.17 (s, 1H), 1.16 – 1.04 (m, 6H), 0.88 (s, 3H), 0.87 (t, *J* = 2.4 Hz, 6H), 0.85 (d, *J* = 5.0 Hz,

3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.76, 168.44, 161.98 (t, J = 34.8 Hz), 153.73, 152.63, 150.34 (t, J = 6.8 Hz), 149.99, 148.38, 139.73, 136.68, 130.62, 130.30, 126.35, 125.37, 124.97, 124.68, 124.28, 123.37, 117.67, 116.91 (t, J = 25.5 Hz), 111.95 (t, J = 248.3 Hz), 75.35, 61.44, 48.98, 40.15, 39.49, 37.56, 37.40, 34.94, 32.91, 32.82, 31.32, 31.19, 31.11, 28.10, 24.92, 24.56, 23.99, 22.85, 22.75, 21.12, 20.65, 19.88, 19.77, 14.25, 12.64, 11.89, 11.78 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -93.29 ppm.

HRMS (ESI^+): calcd for $C_{53}H_{75}F_2N_2O_6^+$ $[M + H]^+$: 873.5588, found 873.5588.



ethyl (*E*)-4-(*N*-benzylpyrimidine-2-carboxamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5a-6)

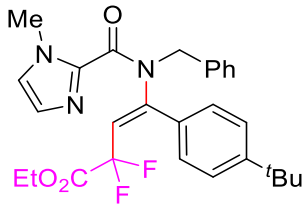
Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5a-6** as yellow oil (34.8 mg, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 2.7 Hz, 1H), 7.45 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.33 – 7.29 (m, 1H), 7.28 (s, 1H), 7.28 – 7.26 (m, 1H), 7.26 (s, 2H), 7.24 (d, J = 1.0 Hz, 1H), 5.26 (t, J = 11.7 Hz, 1H), 4.69 (s, 2H), 3.67 (q, J = 7.2 Hz, 2H), 1.33 (s, 9H), 0.98 (t, J = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.00, 162.56 (t, J = 33.3 Hz), 157.14, 153.95, 148.14 (t, J = 9.6 Hz), 136.09, 130.16, 129.71, 129.08, 128.59, 127.79, 125.34, 121.06, 119.88 (t, J = 29.3 Hz), 111.40 (t, J = 245.1 Hz), 62.66, 49.36, 34.96, 31.27, 13.67 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -92.10 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{30}F_2N_3O_3^+$ $[M + H]^+$:494.2250, found 494.2242.



ethyl (*E*)-4-(*N*-benzyl-1-methyl-1*H*-imidazole-2-carboxamido)-4-(4-(*tert*-butyl)phenyl)-2,2-difluorobut-3-enoate (5a-7)

Purification via column chromatography on silica gel (ethyl acetate/petroleum ether = 1/4, v/v) afforded **5a-7** as pale-yellow oil (19.0 mg, 38% yield).

^{1}**H NMR** (400 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 6.63 (s, 1H), 5.57 (t, *J* = 11.9 Hz, 1H), 4.96 (s, 2H), 3.75 (q, *J* = 7.2 Hz, 2H), 3.45 (s, 3H), 1.25 (s, 9H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}**C NMR** (100 MHz, $CDCl_3$): δ = 163.02, 162.71, 152.80, 150.37 (t, *J* = 9.7 Hz), 141.03, 136.85, 132.37, 129.25, 128.84, 128.78, 128.24, 127.86, 124.86, 123.40, 115.36 (t, *J* = 29.5 Hz), 112.29 (d, *J* = 244.8 Hz), 62.74, 52.58, 34.84, 33.92, 31.20, 13.68 ppm.

^{19}**F NMR** (376 MHz, $CDCl_3$): δ = -90.46 ppm.

HRMS (ESI^+): calcd for $C_{28}H_{32}F_2N_3O_3^+$ $[M + H]^+$:496.2406, found 496.2405.

IX. References

1. K. Li, G. Tan, J. Huang, F. Song and J. You, Iron-Catalyzed Oxidative C–H/C–H Cross-Coupling: An *E*fficient Route to α-Quaternary α-Amino Acid Derivatives. *Angew. Chem., Int. Ed.,* 2013, **52**, 12942−12945.

2. Q. Li, S.-Y. Zhang, G. He, W. A. Nack and G. Chen, Palladium-Catalyzed Picolinamide-Directed Acetoxylation of Unactivated γ-C(sp^3)–H Bonds of Alkylamines. *Adv. Synth. Catal.,* 2014, **356**, 1544–1548.

3. M. Tan, K. Li, J. Yin and J. You, Manganese/cobalt-catalyzed oxidative C(sp^3)–H/C(sp^3)–H coupling: a route to α-*tert*iary β-arylethylamines. *Chem. Commun.,* 2018, **54**, 1221–1224.

4. B. Thirupataiah, G. S. Reddy, G. Mounika, J. S. Kumar, K. A. Hossain, J. Mudgal, J. E. Mathew, G. G. Shenoy, M. Rajadurai, K. V. L. Parsa and M. Pal, Pd-catalysed general access to 7-membered N/O-heterocyclic compounds as potential agents against inflammation, *Chem. Commun.,* 2021, **57**, 10091–10094.

5. A. K. El-Damasy, H. Jin, S. H. Seo, E.-K. Bang and G. Keum, Design, synthesis, and biological evaluations of novel 3-amino-4-ethynyl indazole derivatives as Bcr-Abl kinase inhibitors with potent

cellular antileukemic activity. *Eur. J. Med. Chem.,* 2020, **207**, 112710–112725.

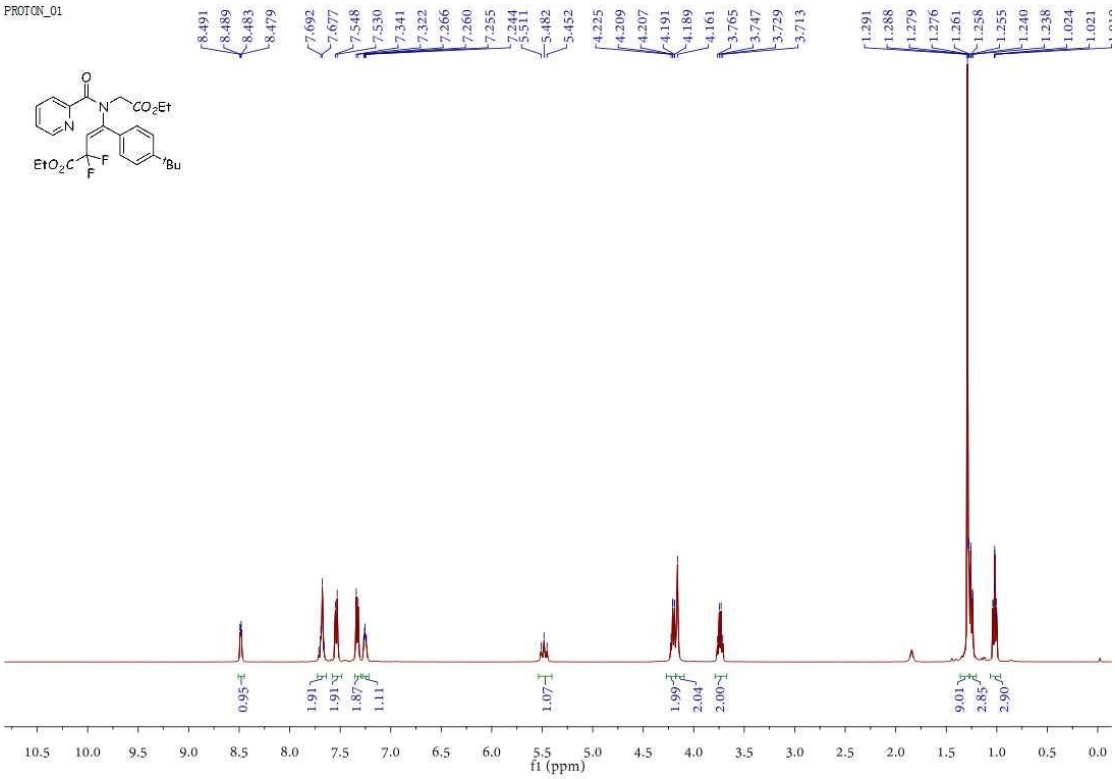
6. M. Zhang, W. Li, Y. Duan, X. Pan and C. Zhu, Cascade photoredox/iodide catalysis: access to difluoro-γ-lactams via aminodifluoroalkylation of alkenes. *Org. Lett.,* 2016, **47**, 3266–3269.

7. C. Xu, R. Cheng, Y. C. Luo, M. K. Wang and X. Zhang, *trans*-Selective Aryldifluoroalkylation of Endocyclic Enecarbamates and Enamides by Nickel Catalysis. *Angew. Chem., Int. Ed.,* 2020, **59***,* 18741–18747.

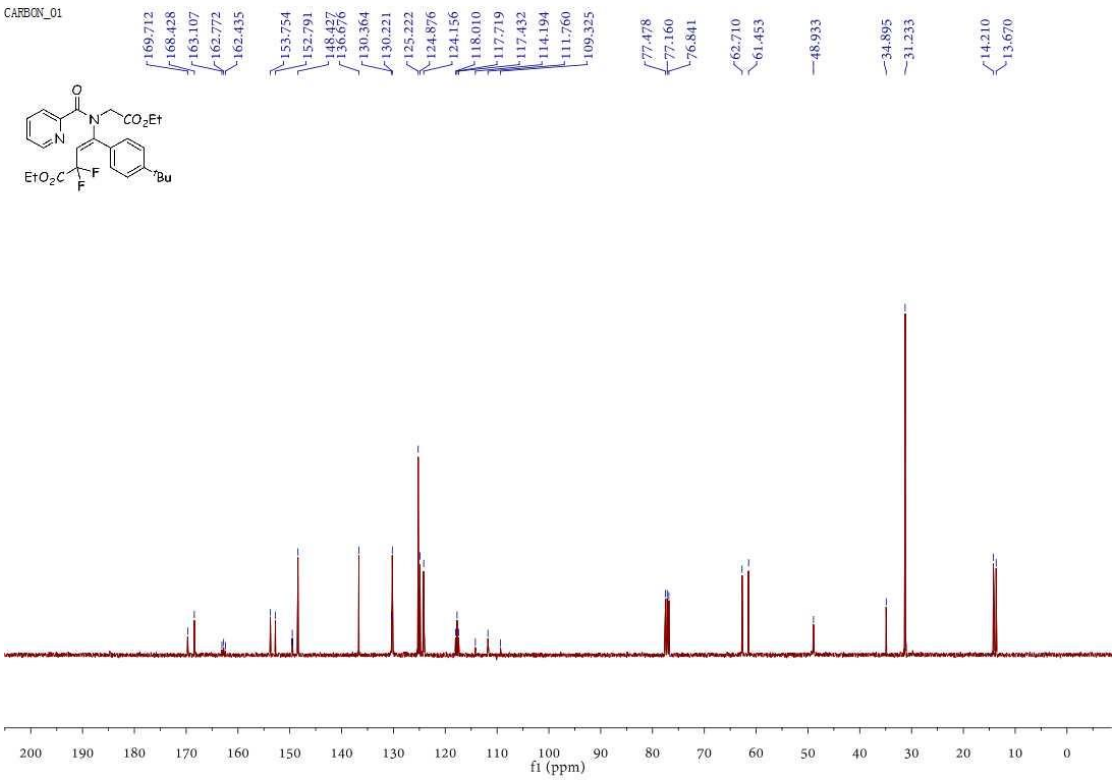
8. M. Zhou, H. Y. Zhao, S. Zhang, Y. Zhang and X. Zhang, Nickel-Catalyzed Four-Component Carbocarbonylation of Alkenes under 1 atm of CO. *J. Am. Chem. Soc.,* 2020, **142**, 18191–18199.

9. J. Ren, K. Liu, N. Wang, X. Kong, J. Li and K. Li, Copper-Catalyzed 1,2-Difunctionalization Trifluoromethylamidation of Alkynes Assisted by a Coordinating Group. *ACS Catal.*, 2023, **13**, 11001–11011.

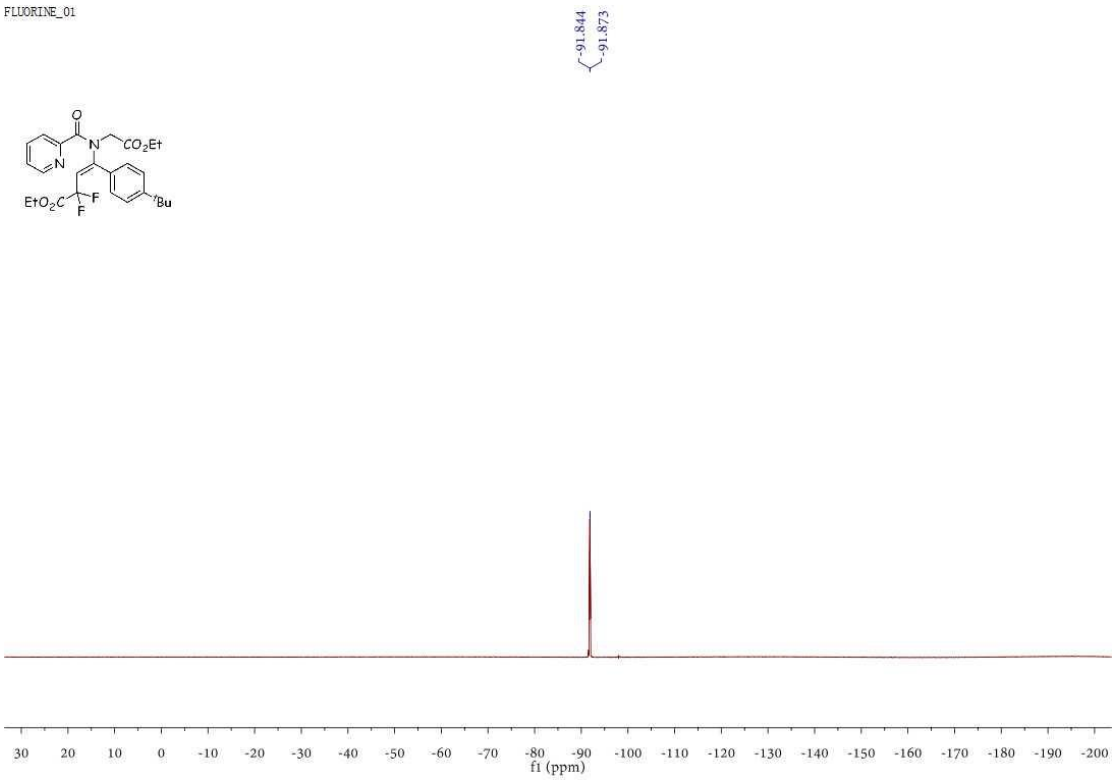
X. Copies of NMR and spectra



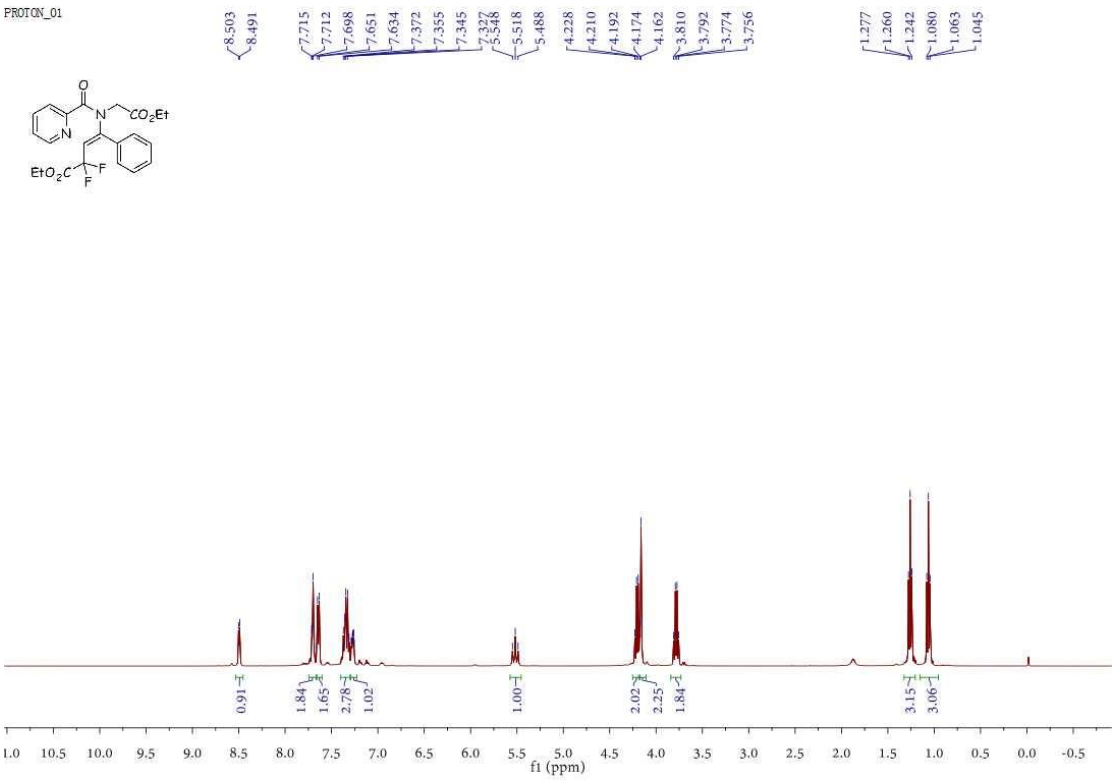
^{1}H – NMR spectrum of compound – **4a** (400 MHz, $CDCl_3$)



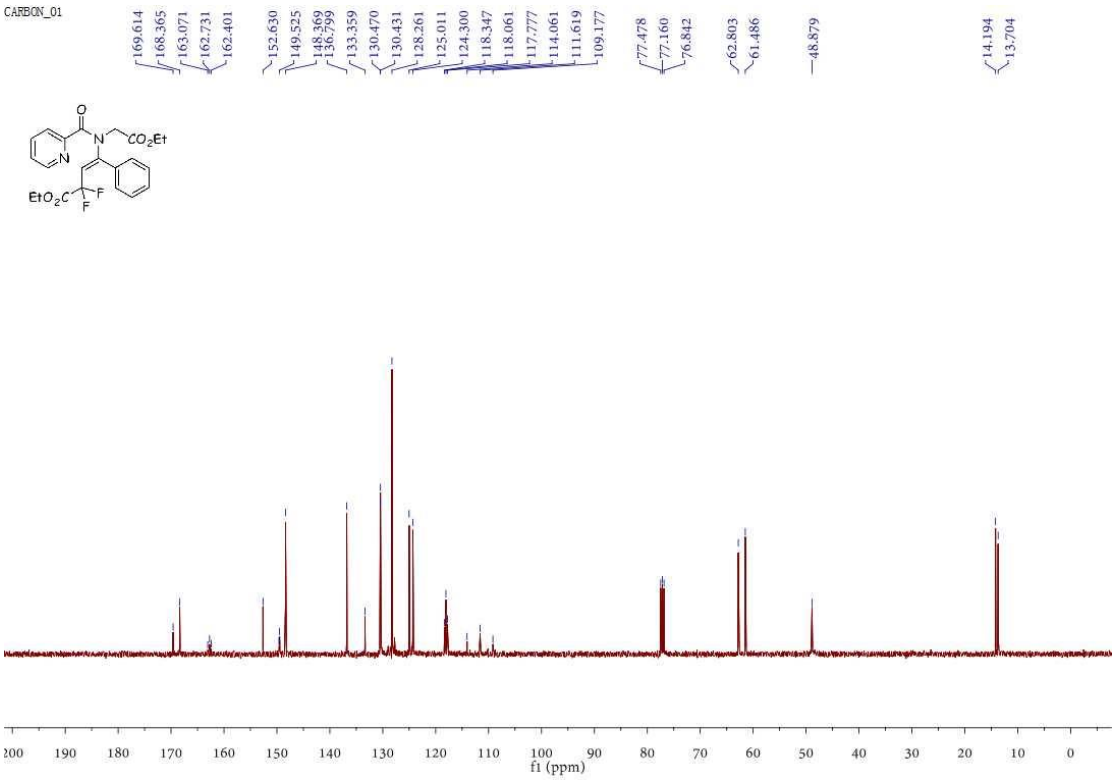
^{13}C – NMR spectrum of compound – **4a** (100 MHz, $CDCl_3$)



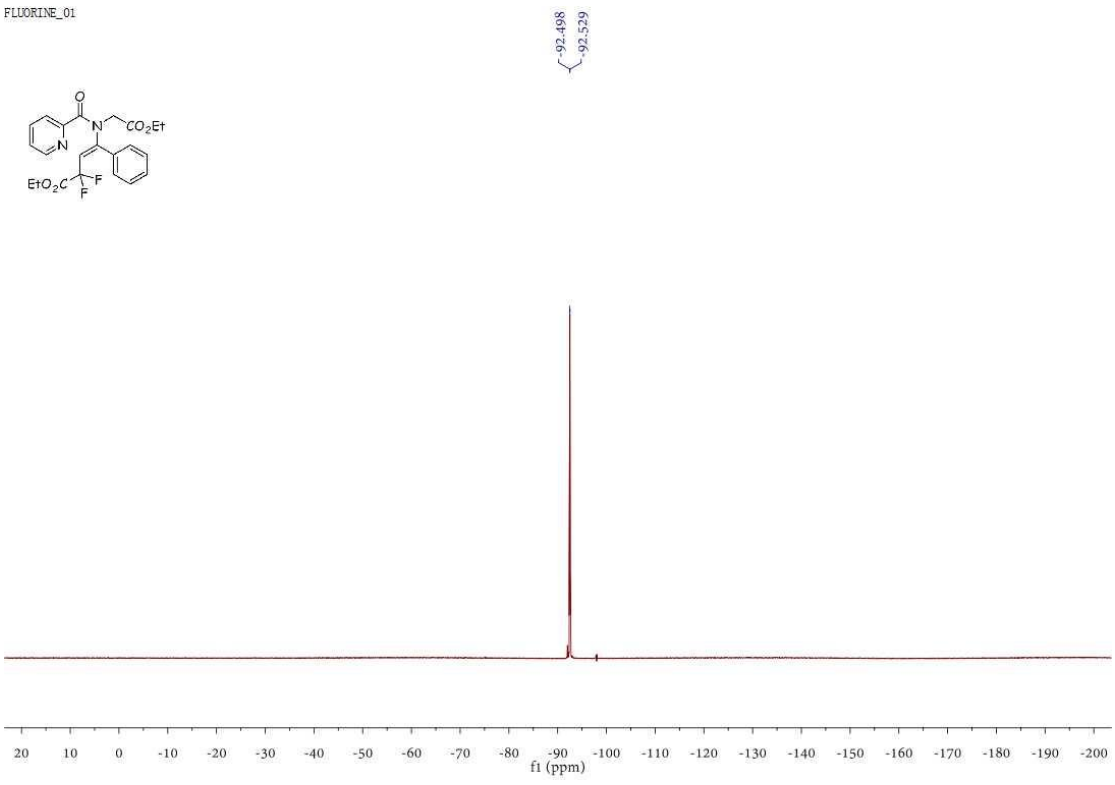
^{19}F – NMR spectrum of compound – **4a** (376 MHz, $CDCl_3$)



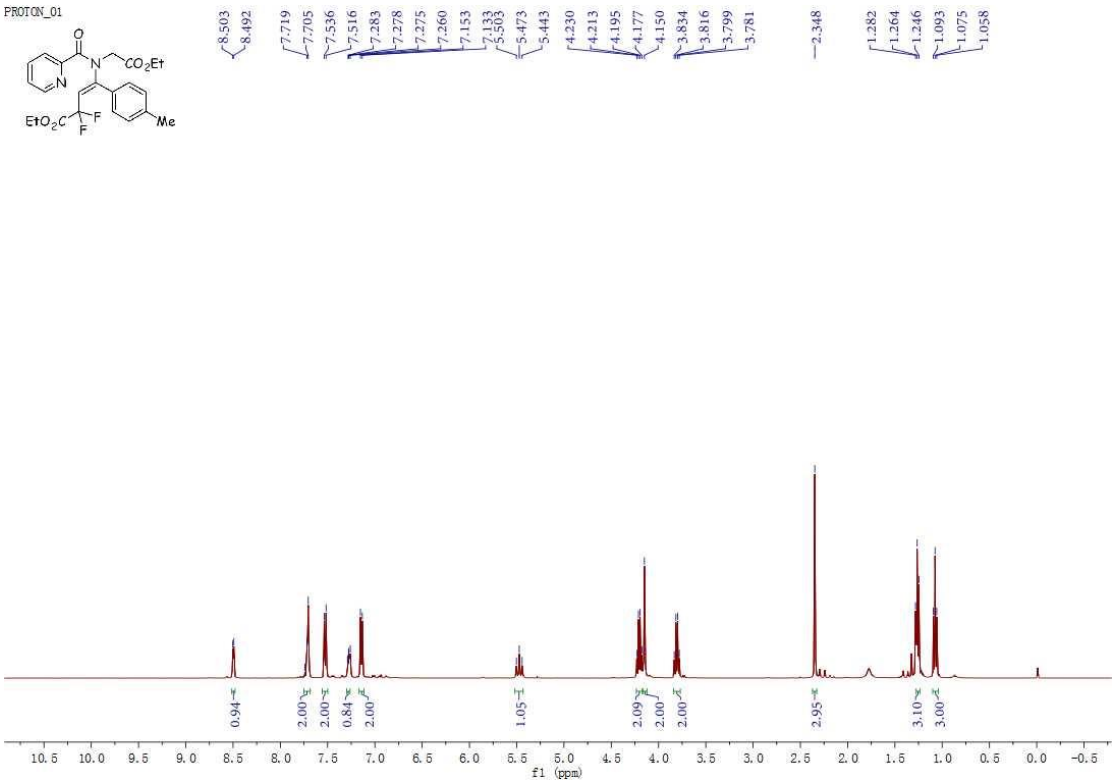
^{1}H – NMR spectrum of compound – **4b** (400 MHz, $CDCl_3$)



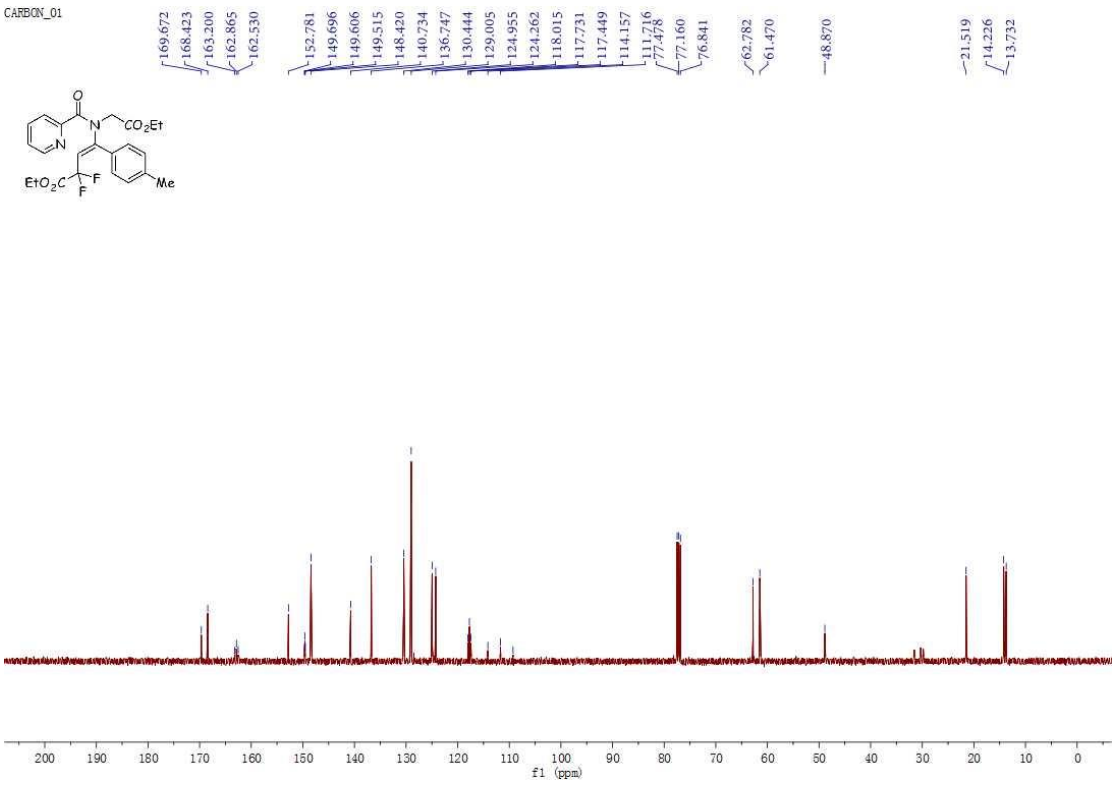
^{13}C – NMR spectrum of compound – **4b** (100 MHz, $CDCl_3$)



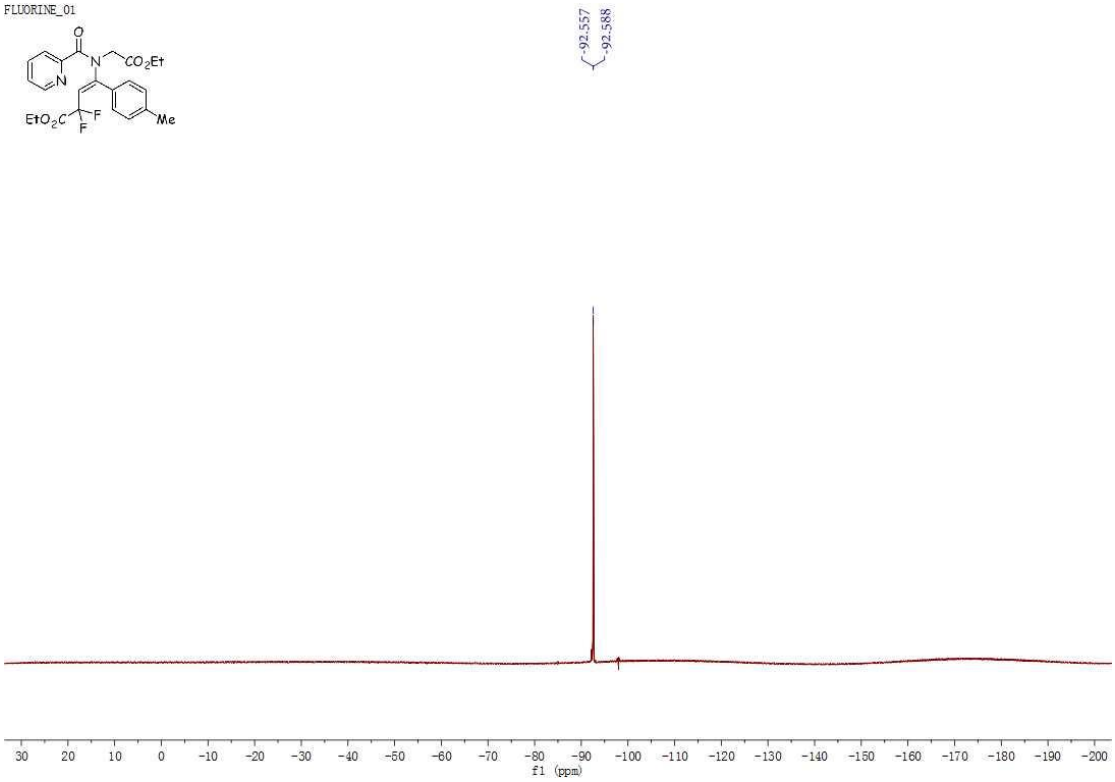
^{19}F – NMR spectrum of compound – **4b** (376 MHz, $CDCl_3$)



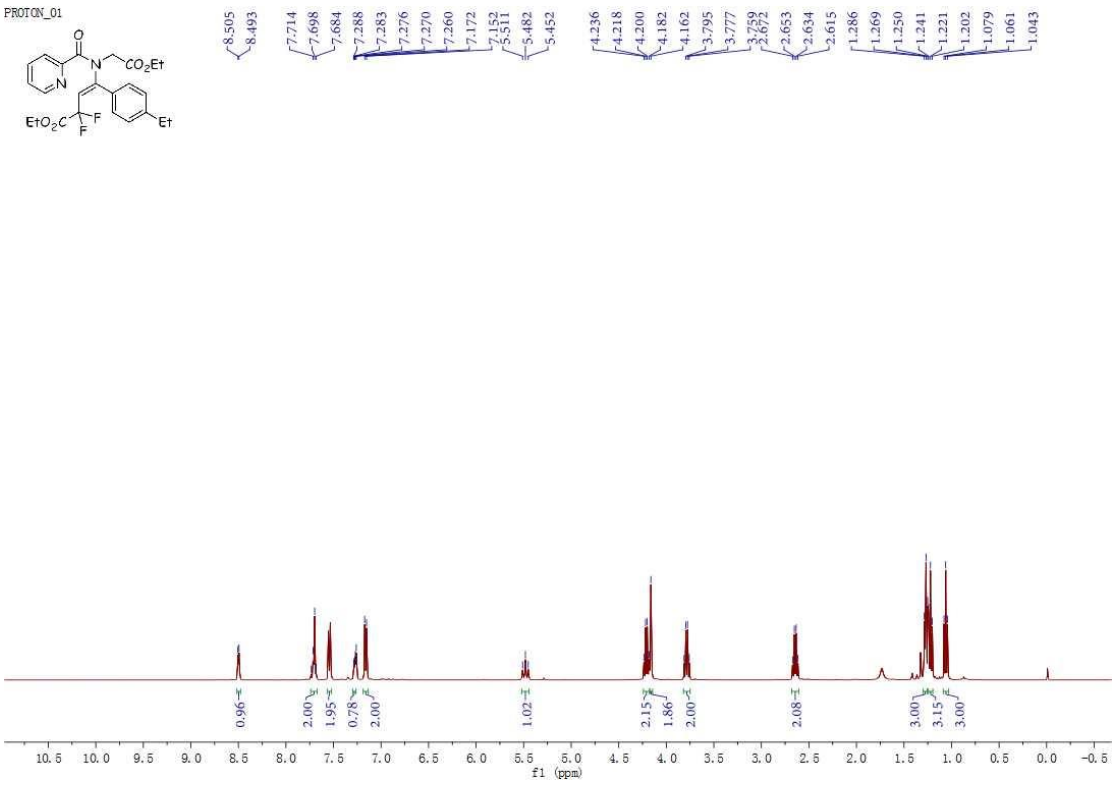
^{1}H – NMR spectrum of compound – **4c** (400 MHz, $CDCl_3$)



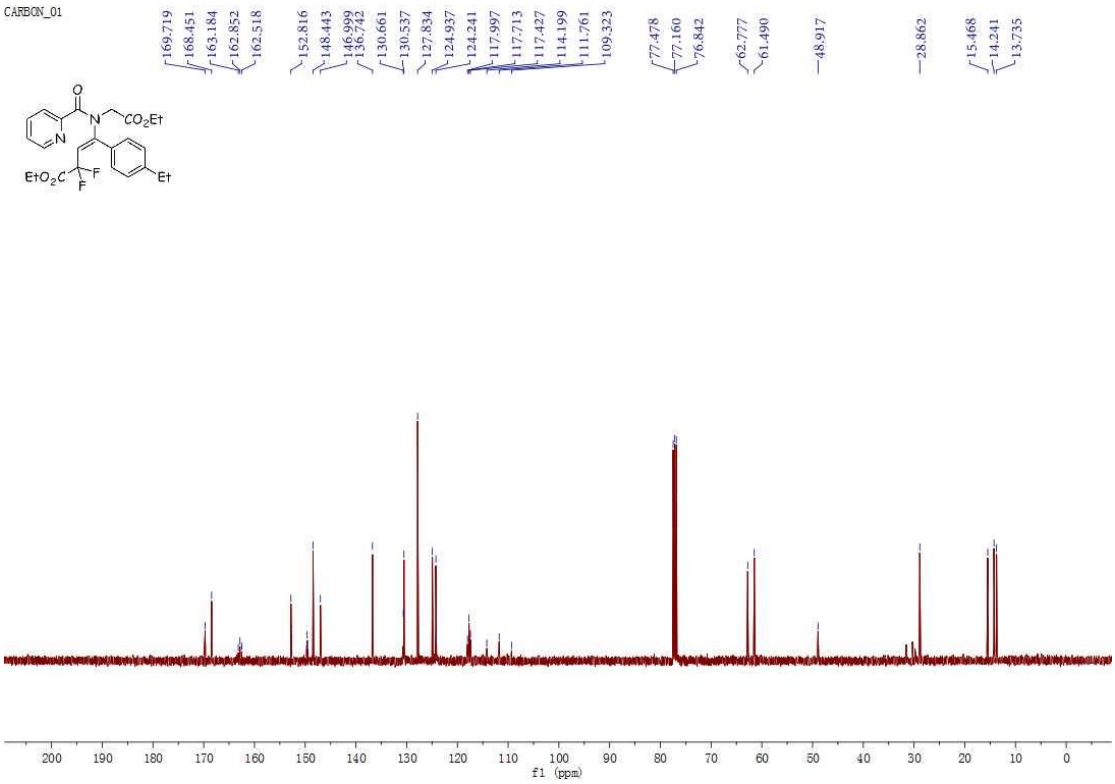
^{13}C – NMR spectrum of compound – **4c** (100 MHz, $CDCl_3$)



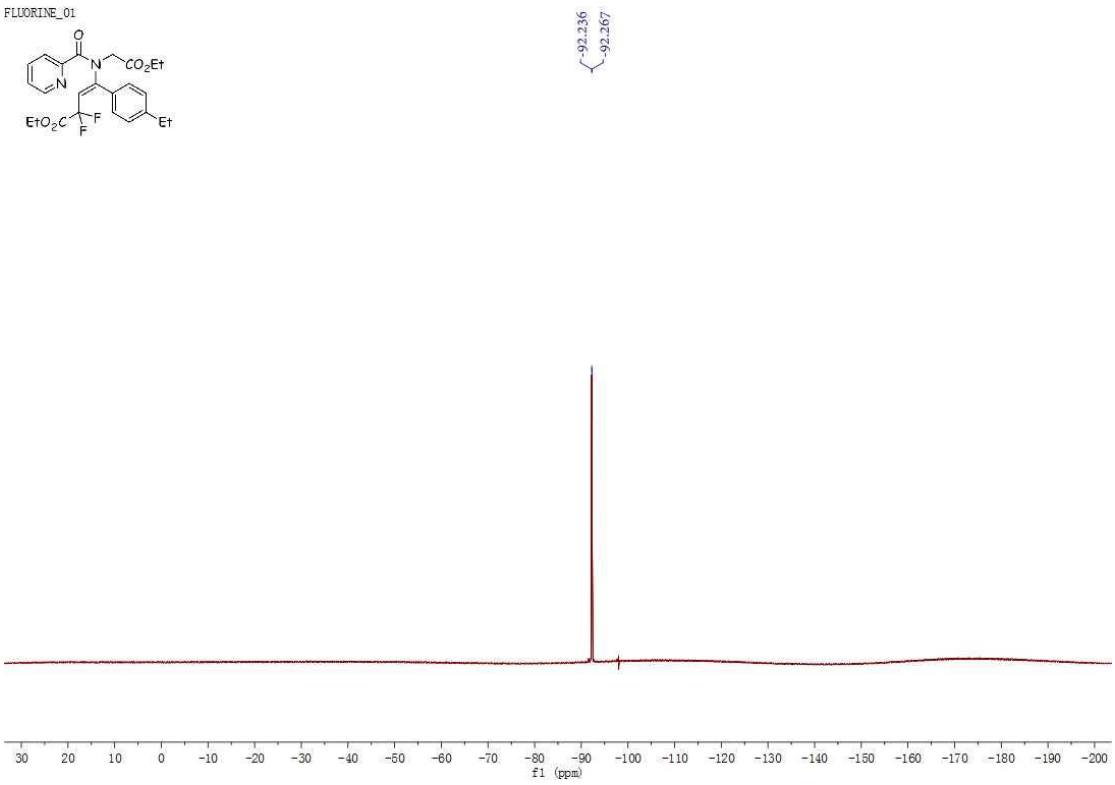
^{19}F – NMR spectrum of compound – **4c** (376 MHz, $CDCl_3$)



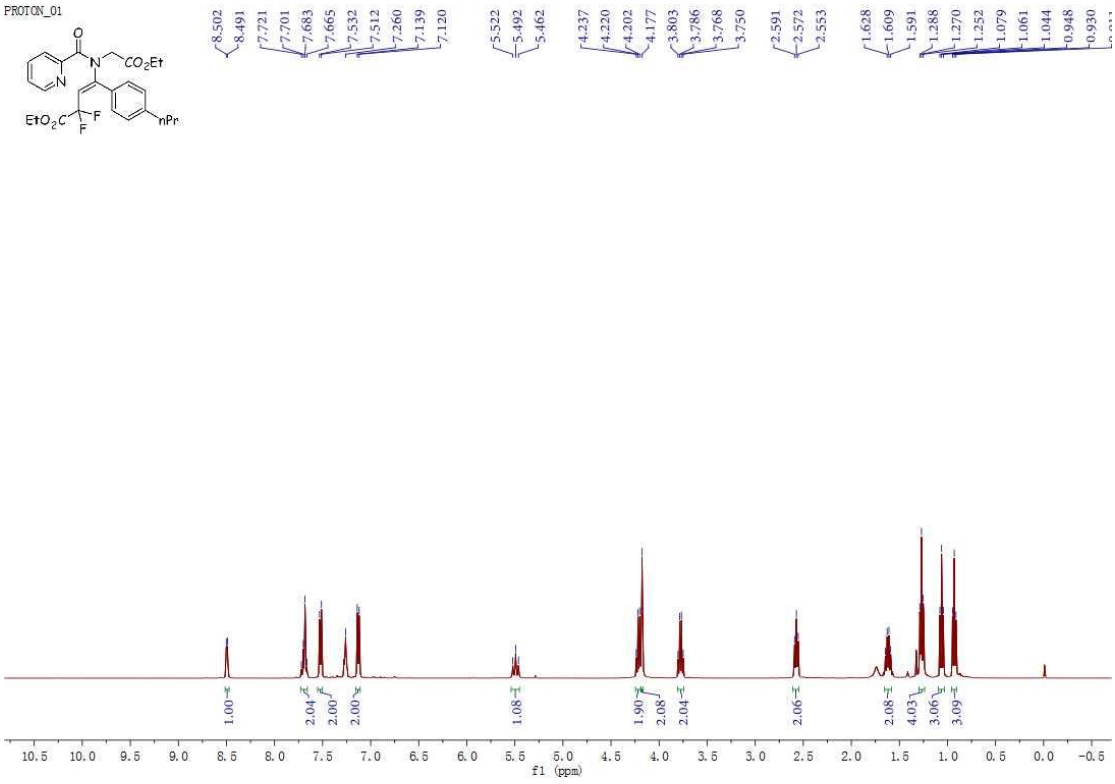
^{1}H – NMR spectrum of compound – **4d** (400 MHz, $CDCl_3$)



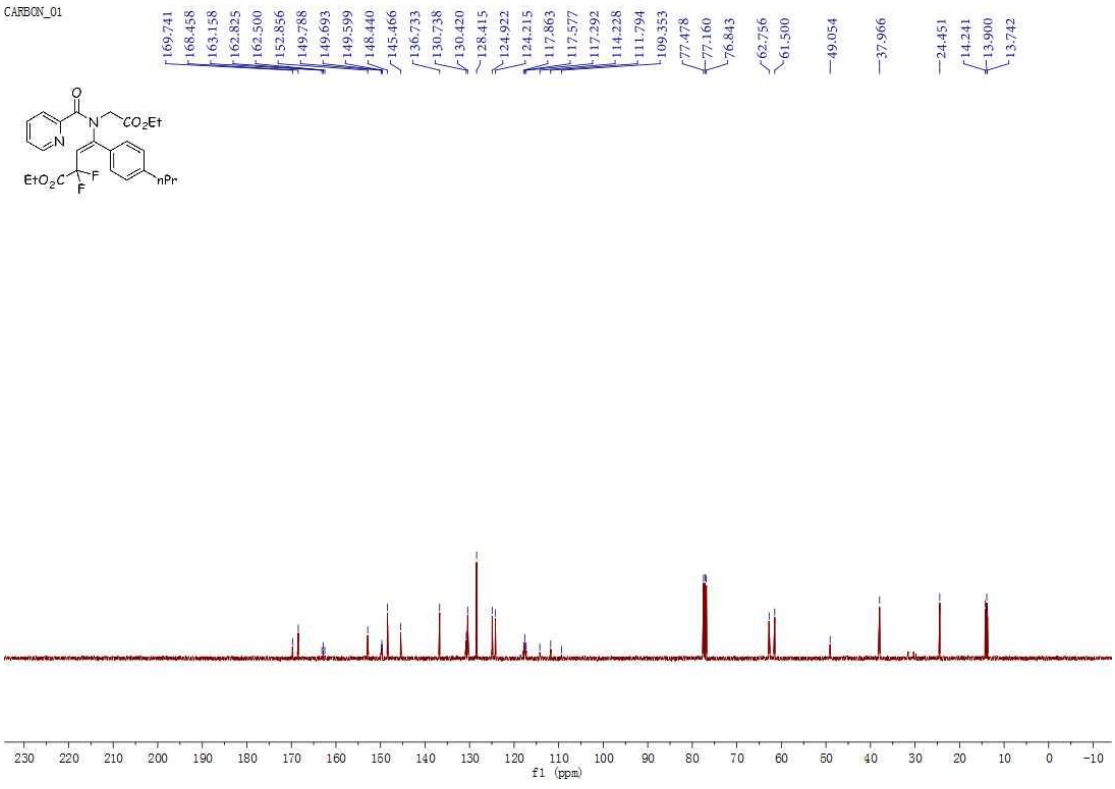
^{13}C – NMR spectrum of compound – **4d** (100 MHz, $CDCl_3$)



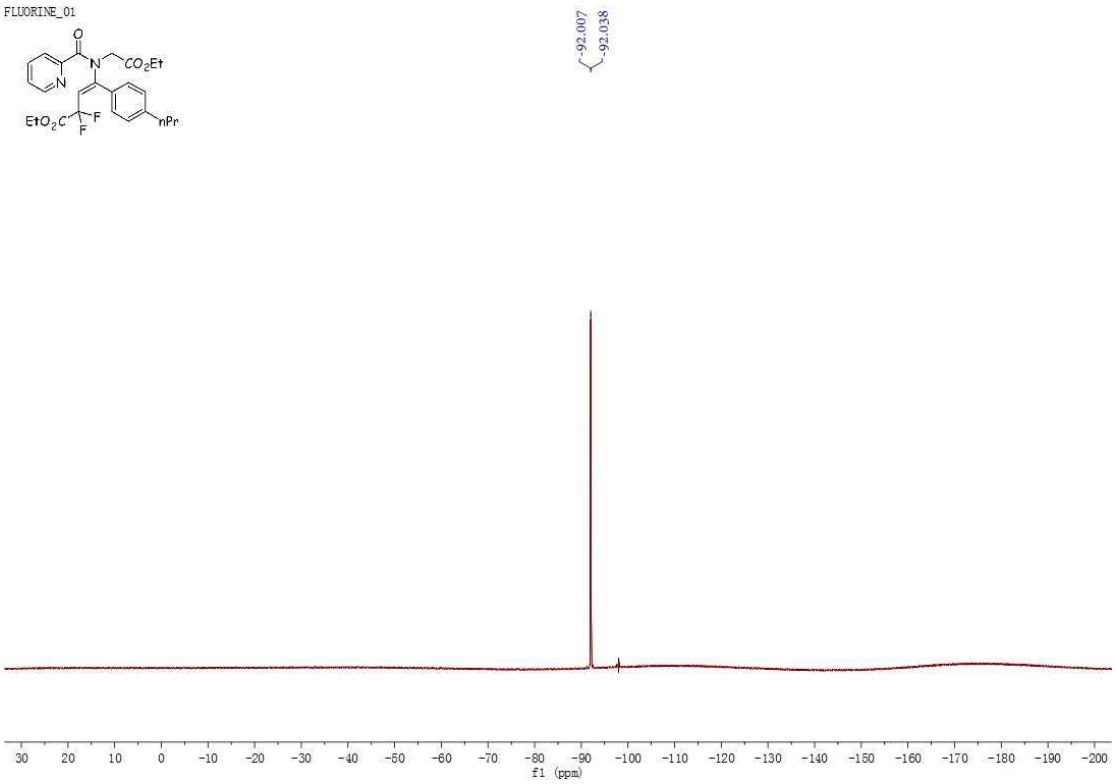
^{19}F – NMR spectrum of compound – **4d** (376 MHz, $CDCl_3$)



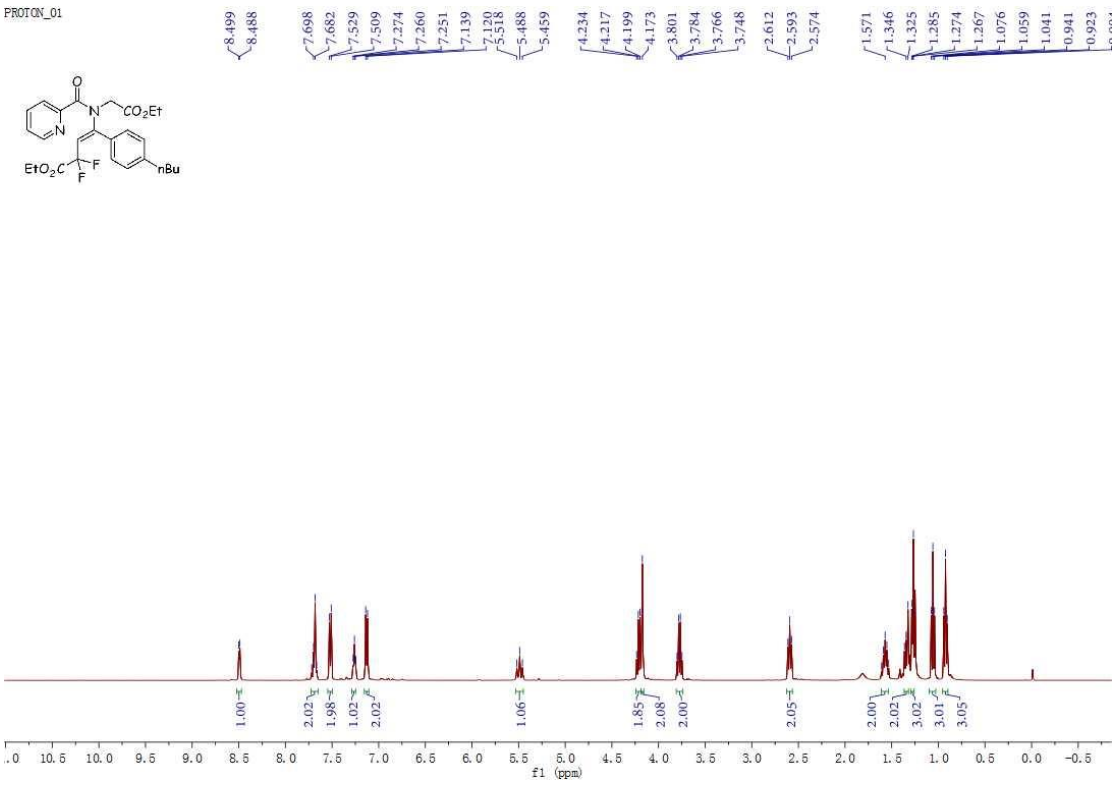
^{1}H – NMR spectrum of compound – **4e** (400 MHz, $CDCl_3$)



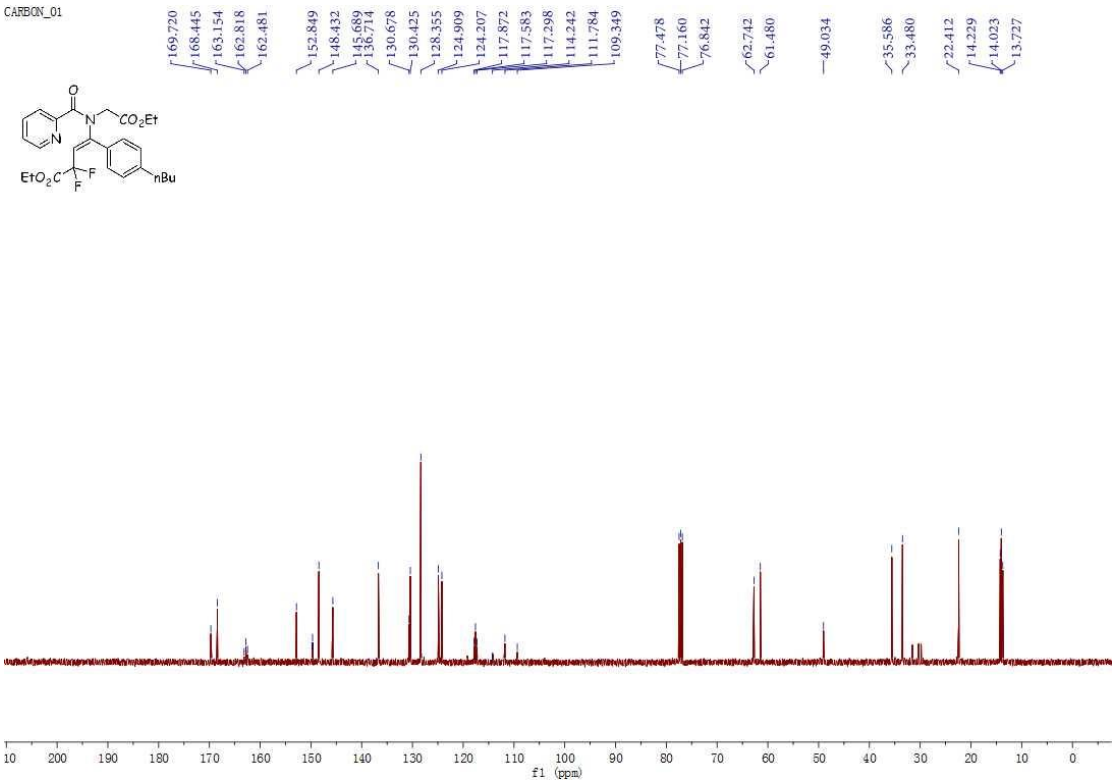
^{13}C – NMR spectrum of compound – **4e** (100 MHz, $CDCl_3$)



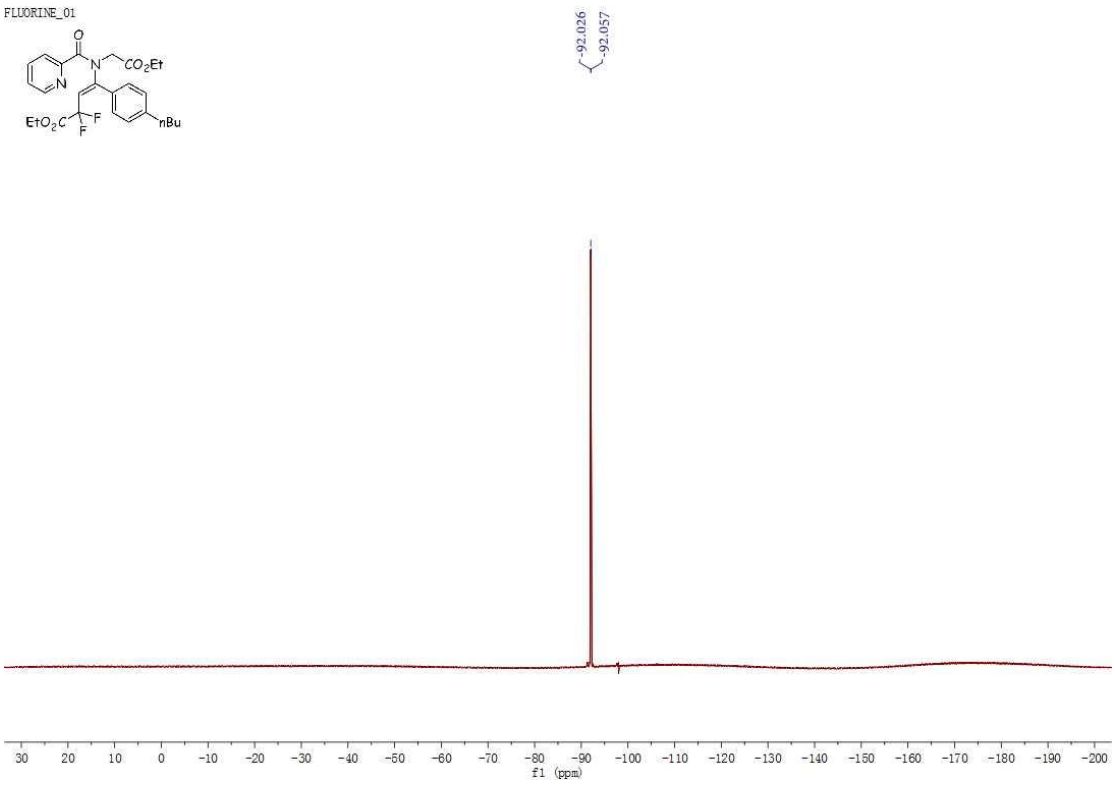
^{19}F – NMR spectrum of compound – **4e** (376 MHz, $CDCl_3$)



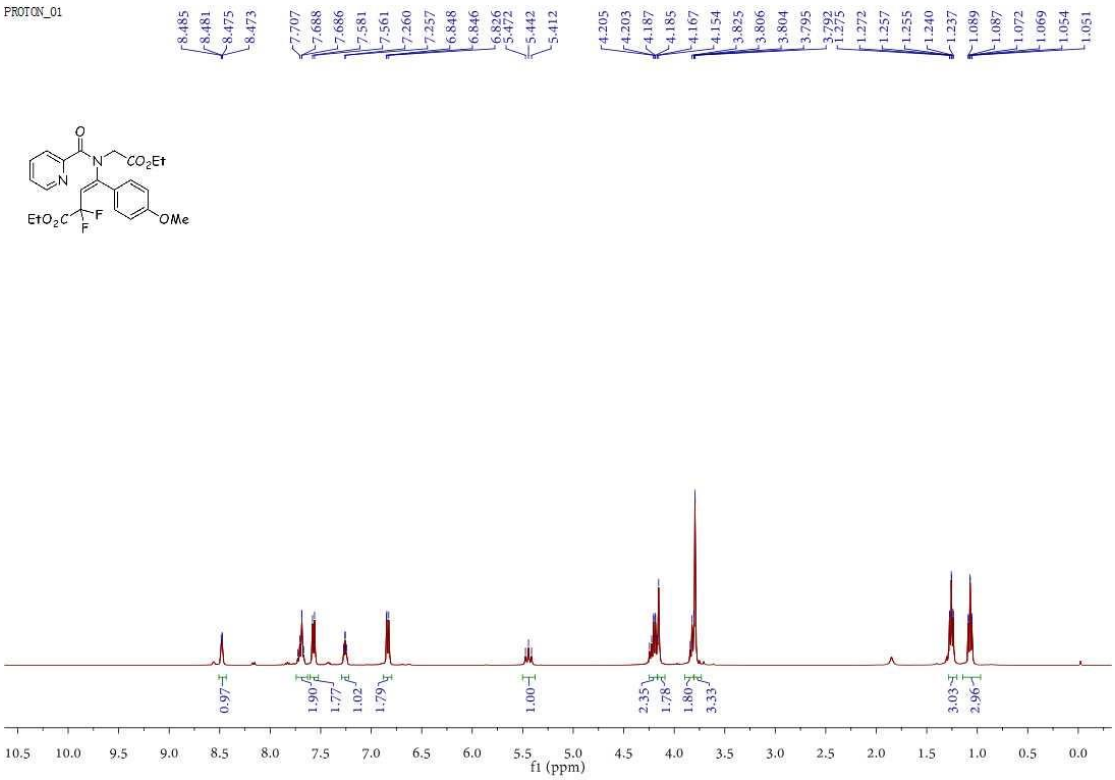
^{1}H – NMR spectrum of compound – **4f** (400 MHz, $CDCl_3$)



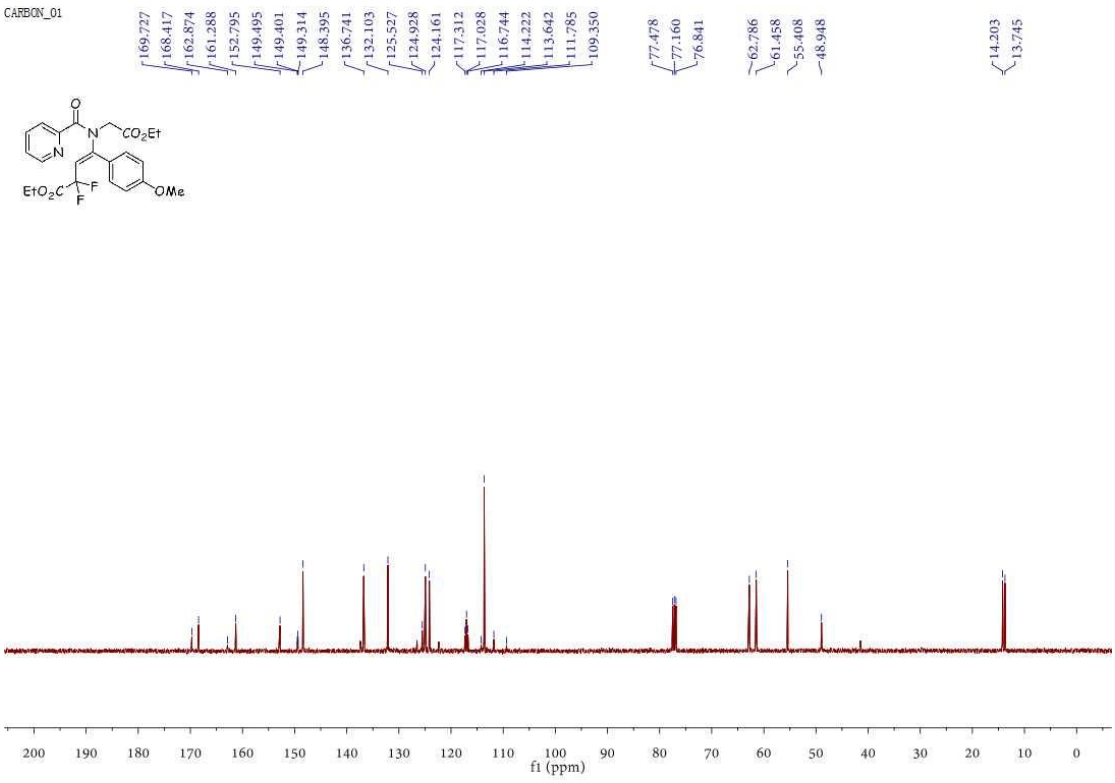
^{13}C – NMR spectrum of compound – **4f** (100 MHz, $CDCl_3$)



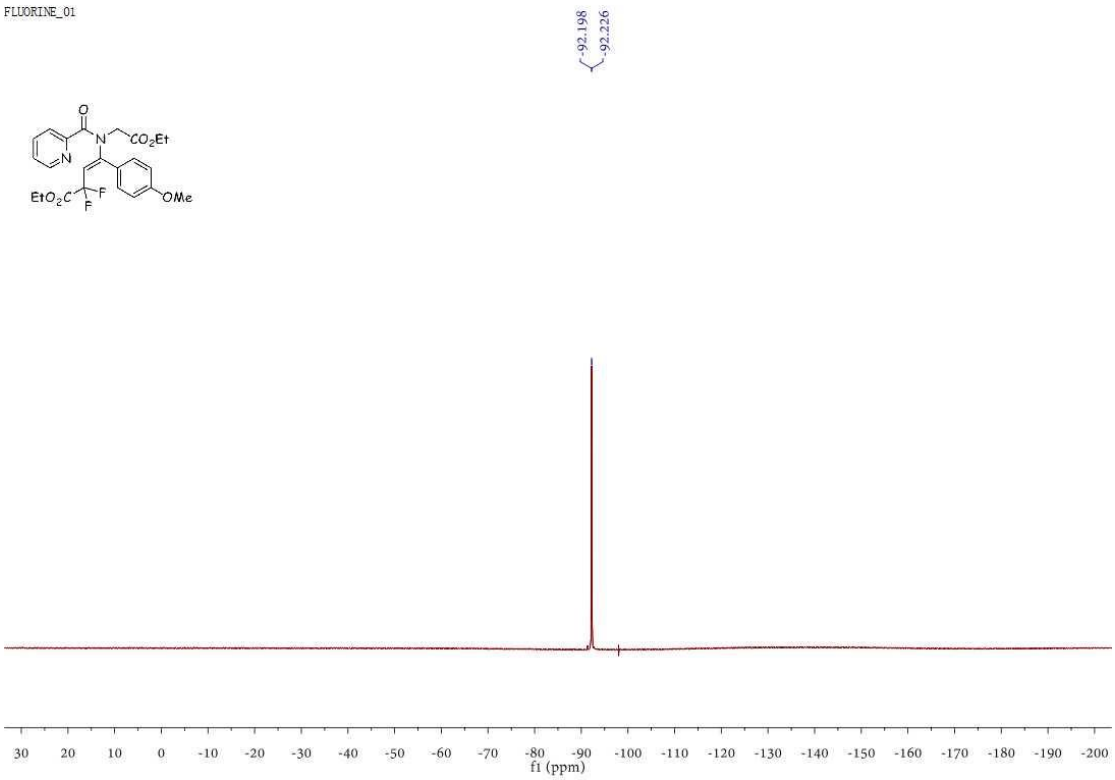
^{19}F – NMR spectrum of compound – **4f** (376 MHz, $CDCl_3$)



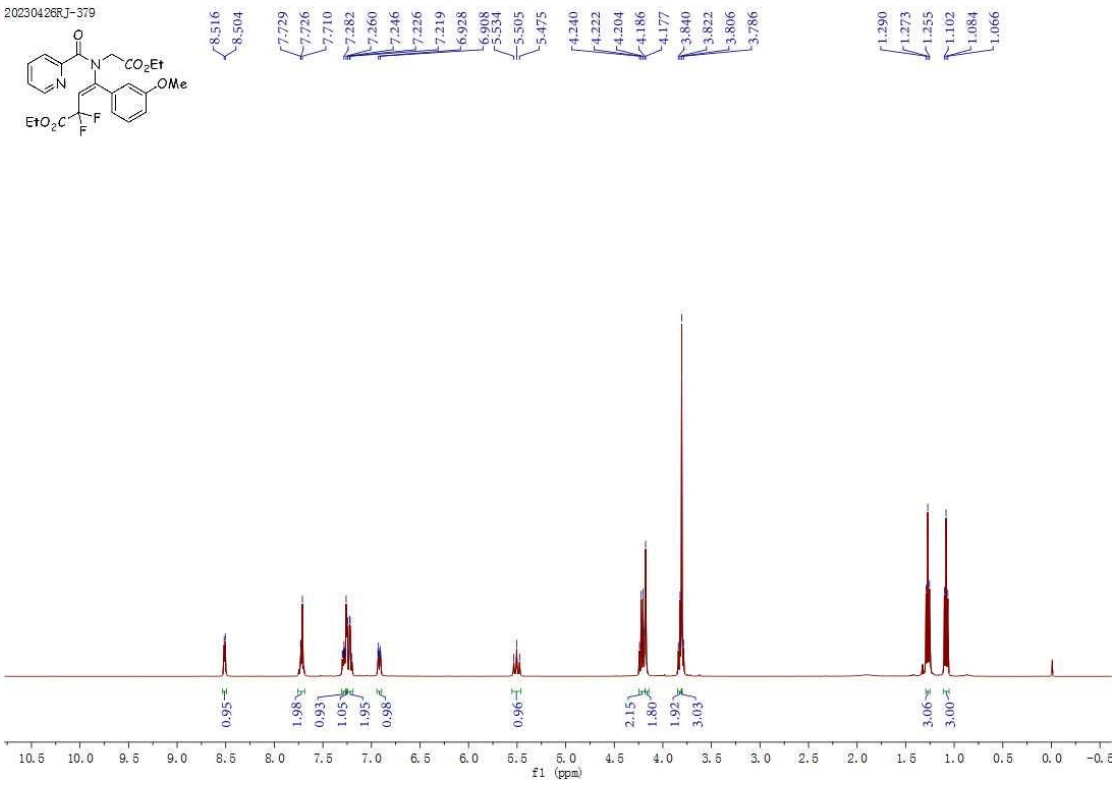
^{1}H – NMR spectrum of compound – **4g** (400 MHz, $CDCl_3$)



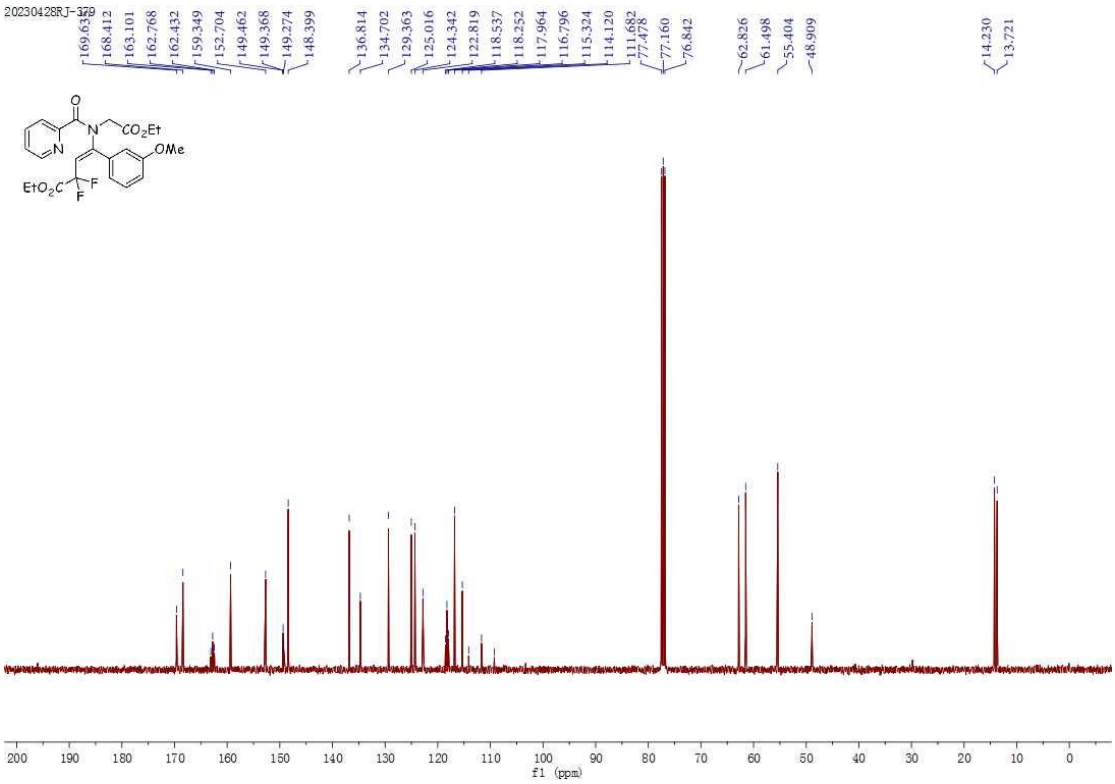
^{13}C – NMR spectrum of compound – **4g** (100 MHz, $CDCl_3$)



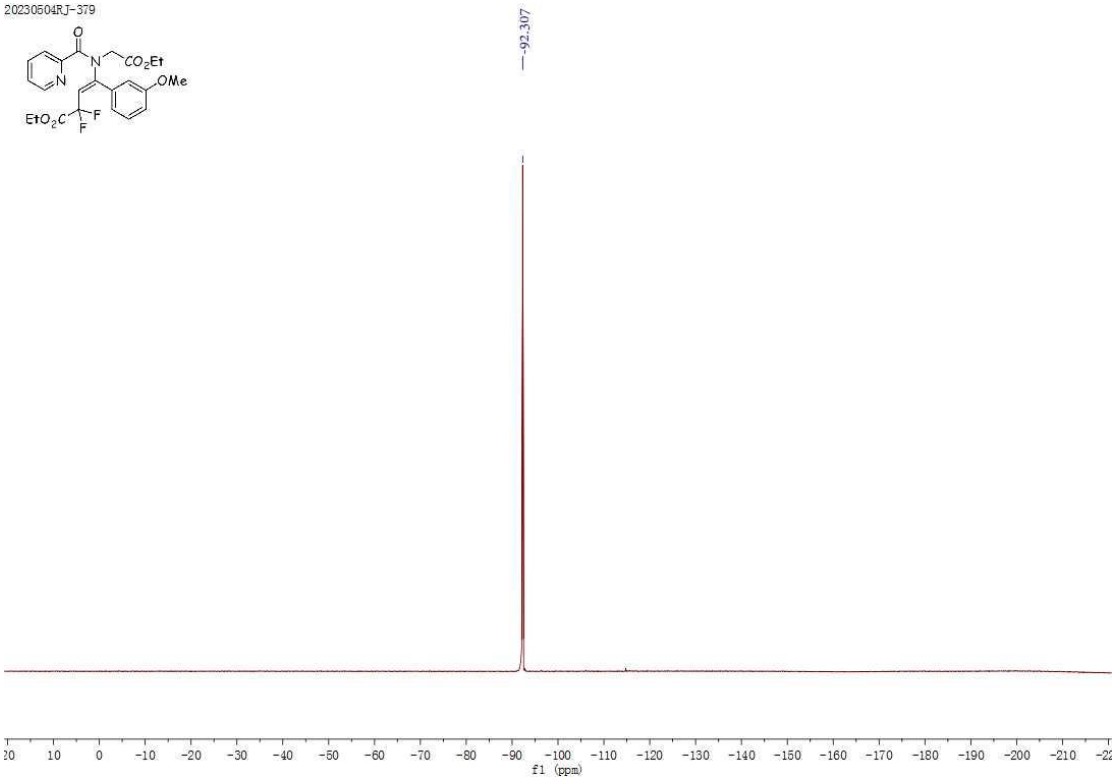
^{19}F – NMR spectrum of compound – **4g** (376 MHz, $CDCl_3$)



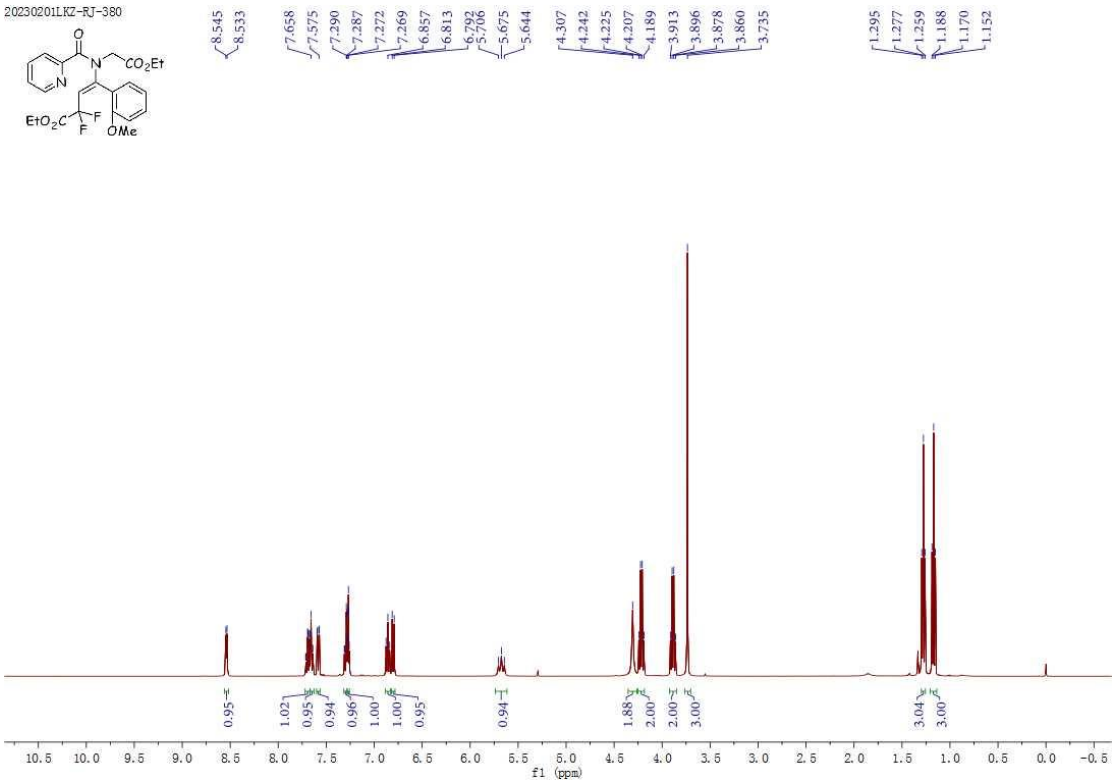
^{1}H – NMR spectrum of compound – **4h** (400 MHz, $CDCl_3$)



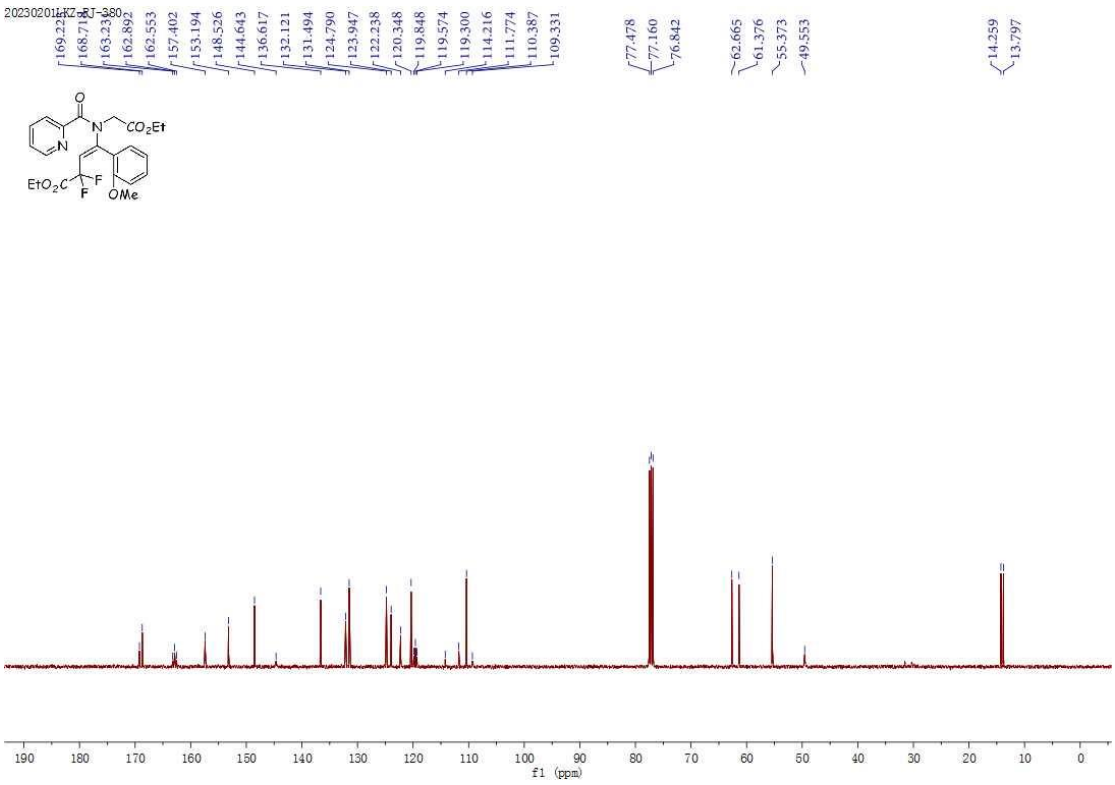
^{13}C – NMR spectrum of compound – **4h** (100 MHz, $CDCl_3$)



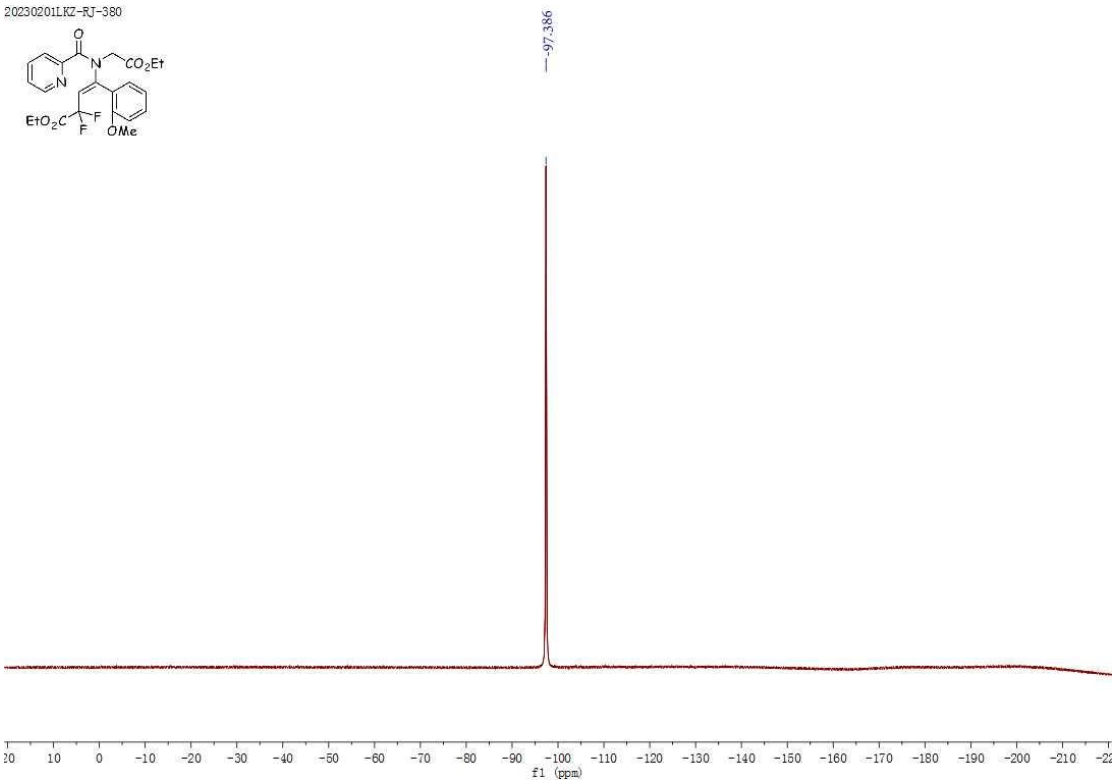
^{19}F – NMR spectrum of compound – **4h** (376 MHz, $CDCl_3$)



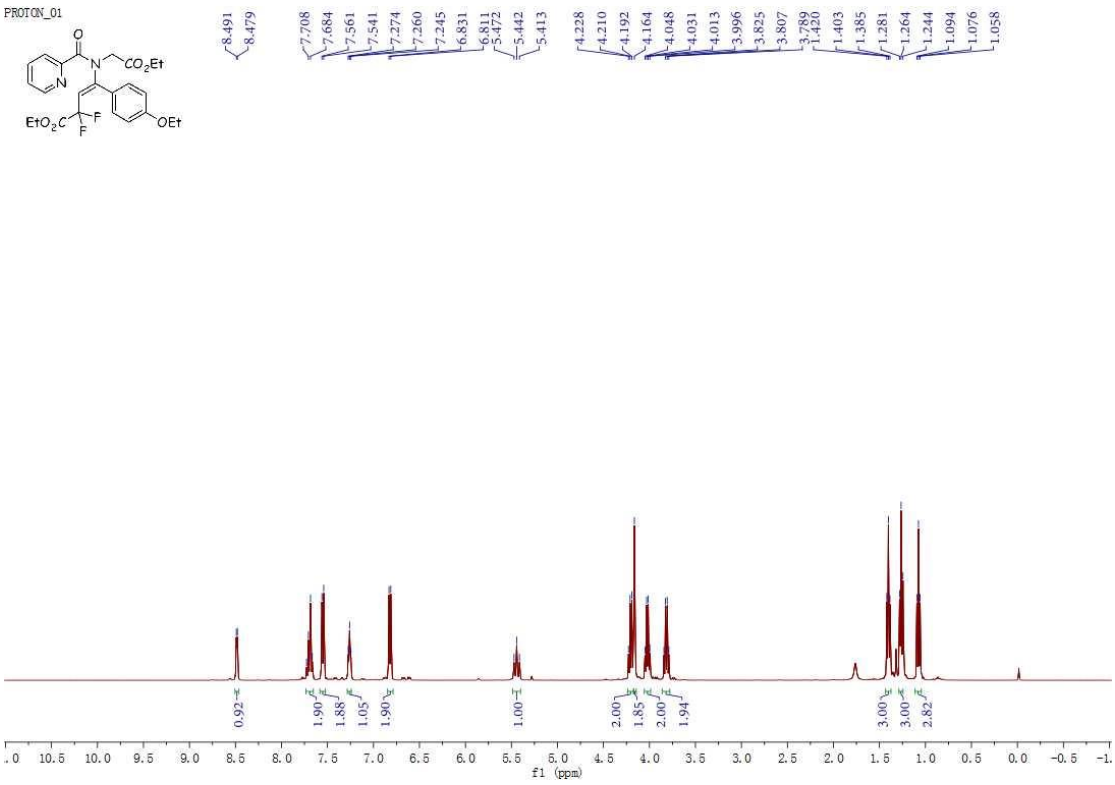
^{1}H – NMR spectrum of compound – **4i** (400 MHz, $CDCl_3$)



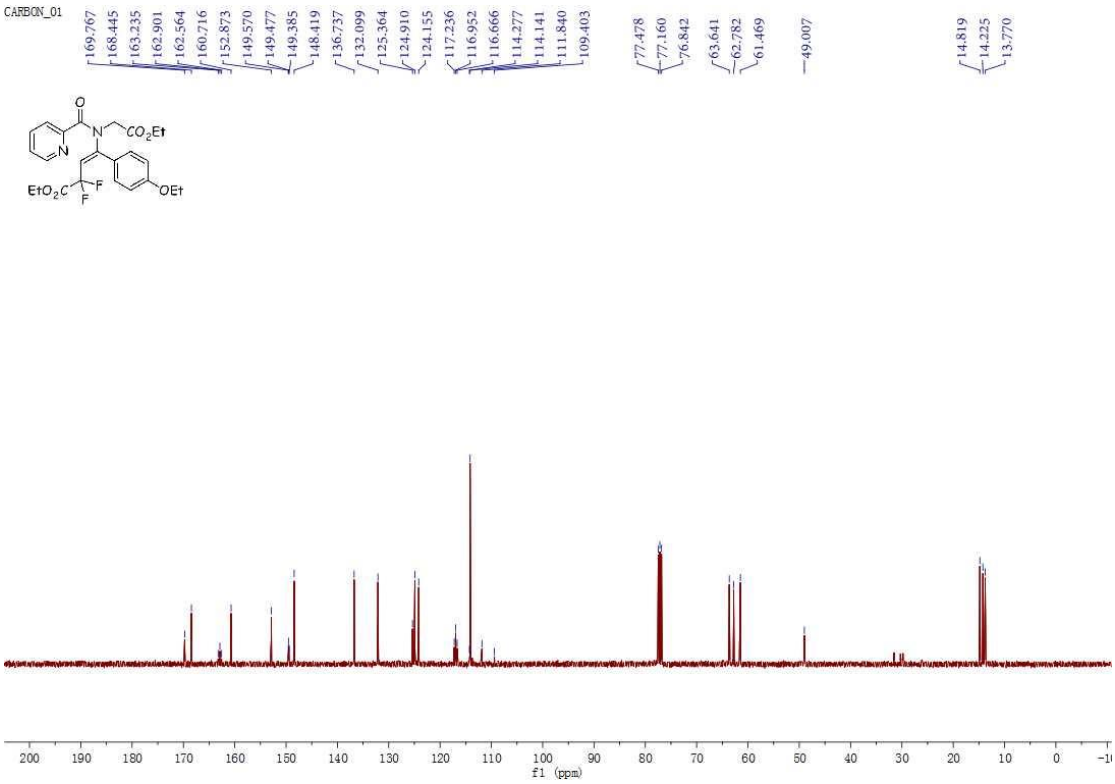
^{13}C – NMR spectrum of compound – **4i** (100 MHz, $CDCl_3$)



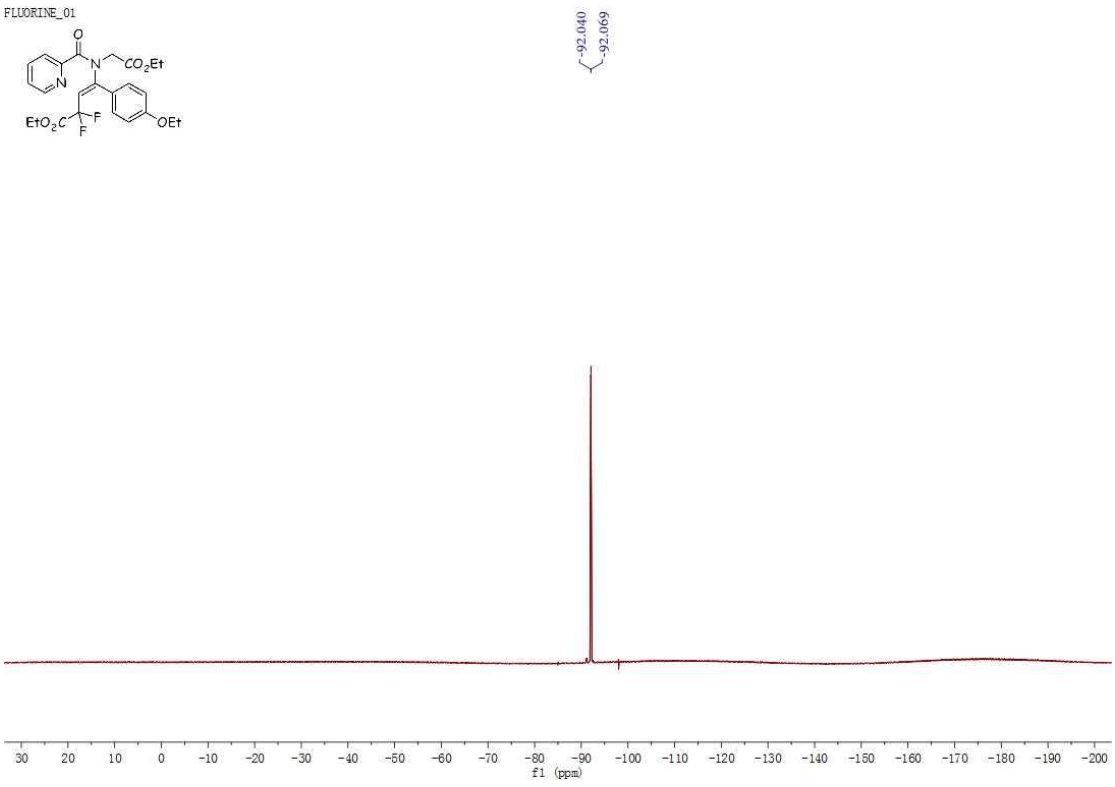
^{19}F – NMR spectrum of compound – **4i** (376 MHz, $CDCl_3$)



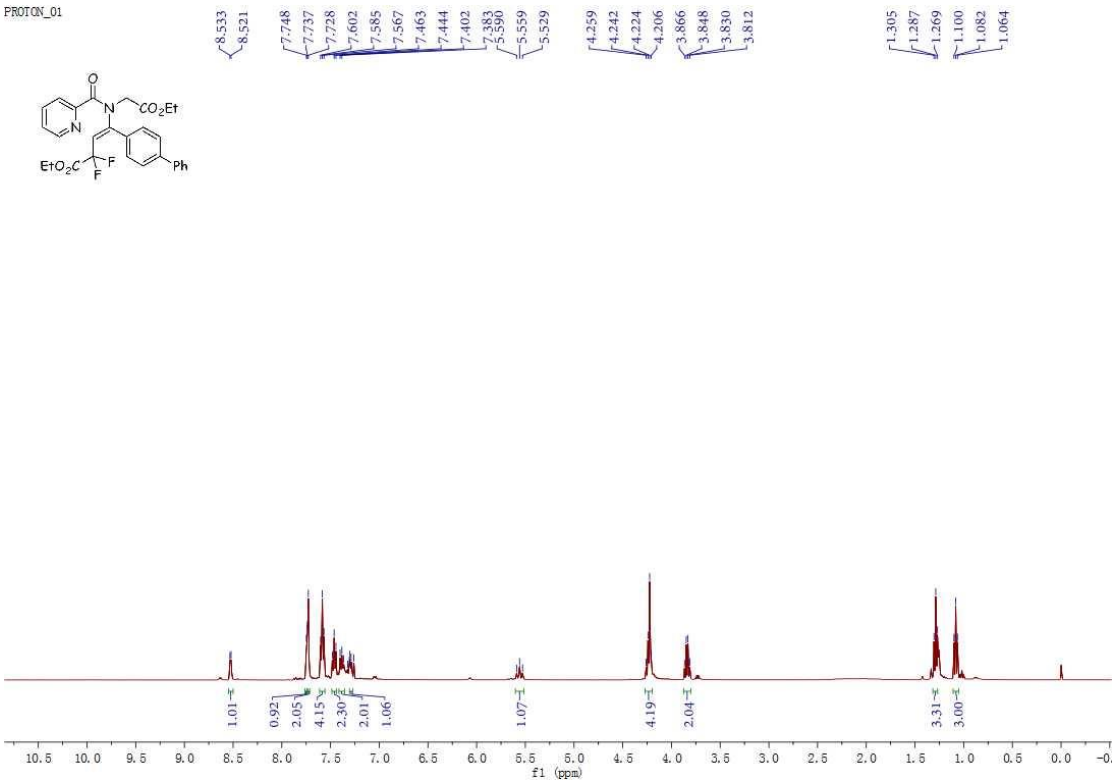
^{1}H – NMR spectrum of compound – **4j** (400 MHz, $CDCl_3$)



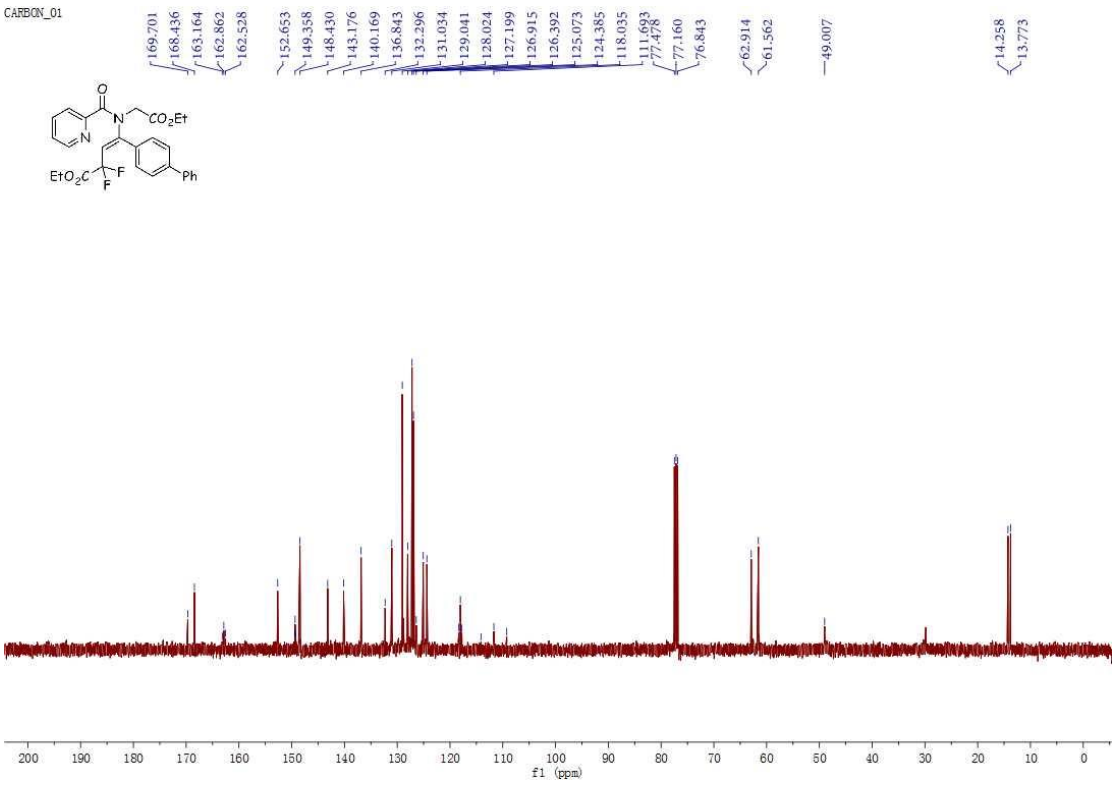
^{13}C – NMR spectrum of compound – **4j** (100 MHz, $CDCl_3$)



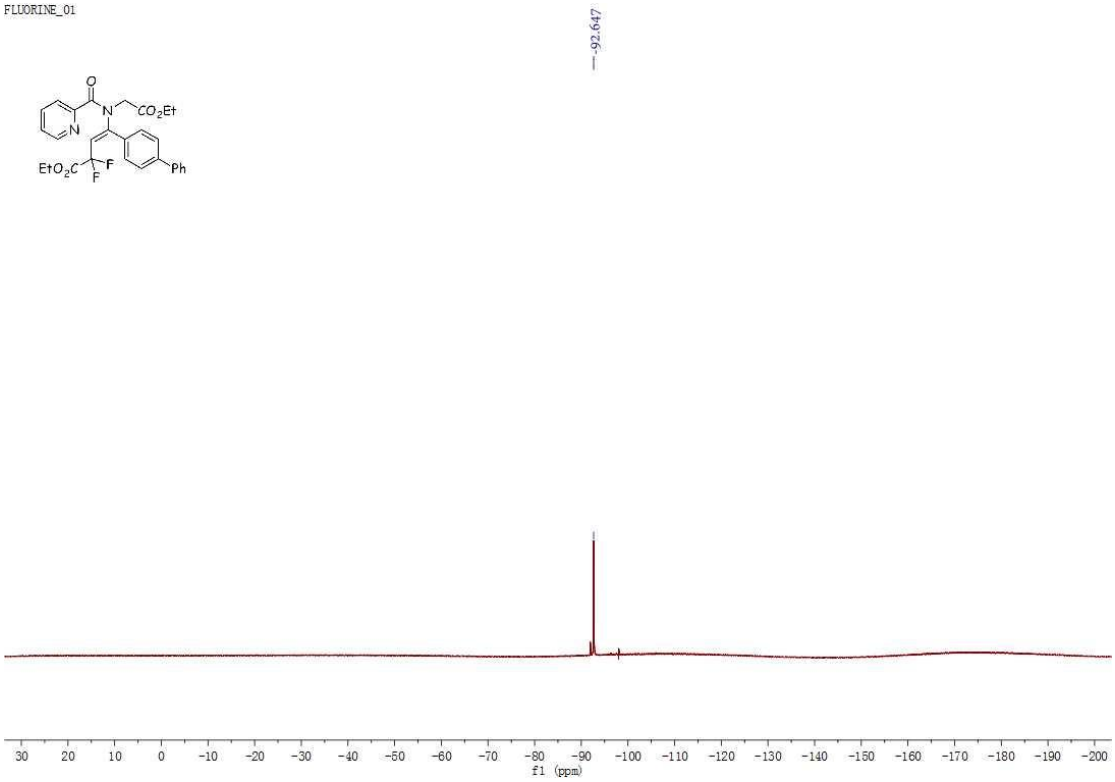
^{19}F – NMR spectrum of compound – **4j** (376 MHz, $CDCl_3$)



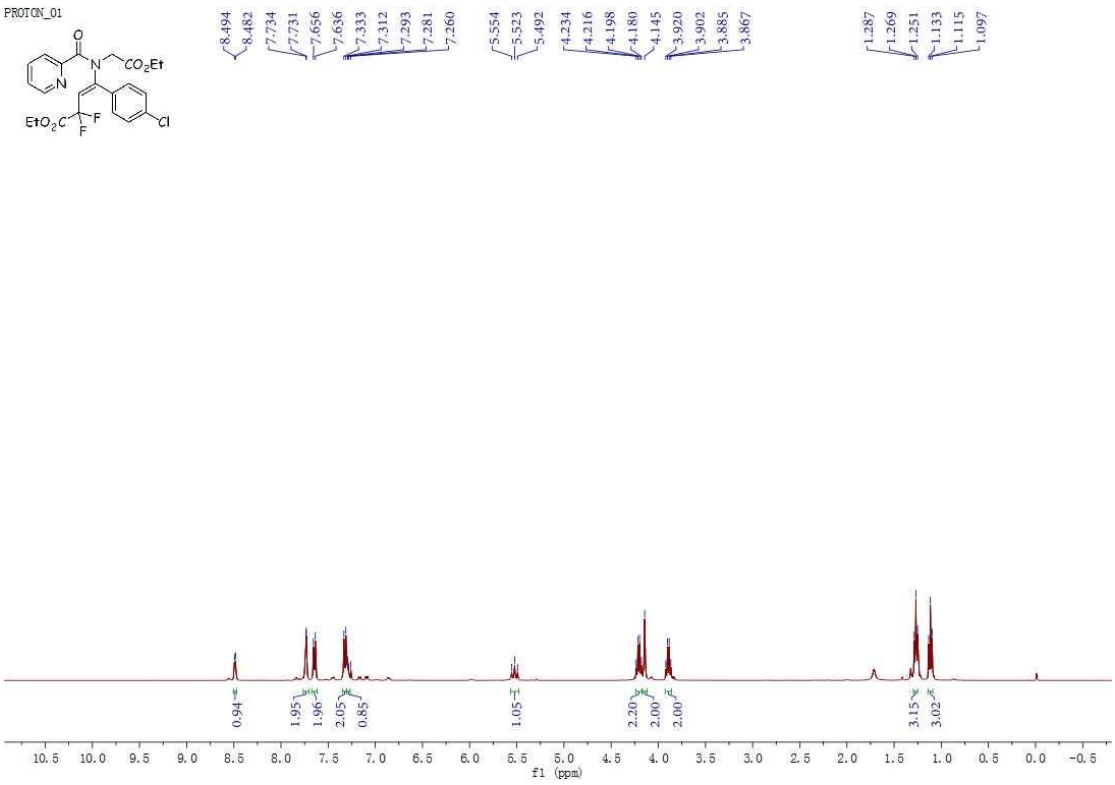
^{1}H – NMR spectrum of compound – **4k** (400 MHz, $CDCl_3$)



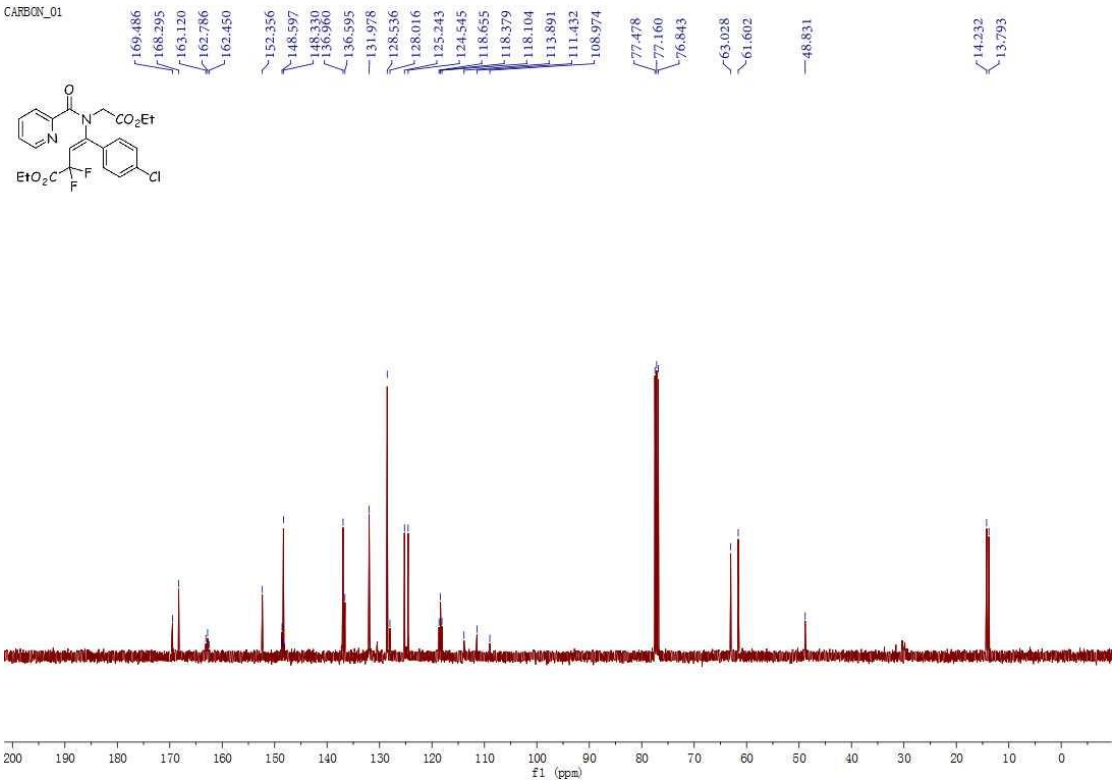
^{13}C – NMR spectrum of compound – **4k** (100 MHz, $CDCl_3$)



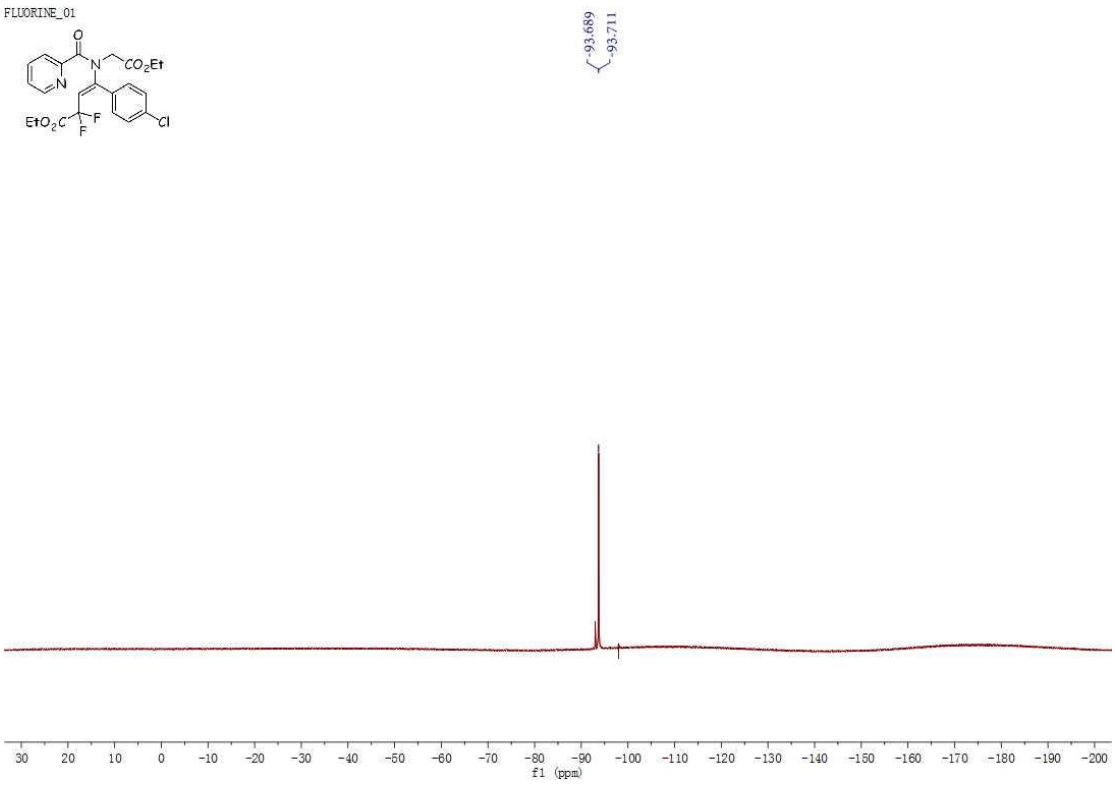
^{19}F – NMR spectrum of compound – **4k** (376 MHz, $CDCl_3$)



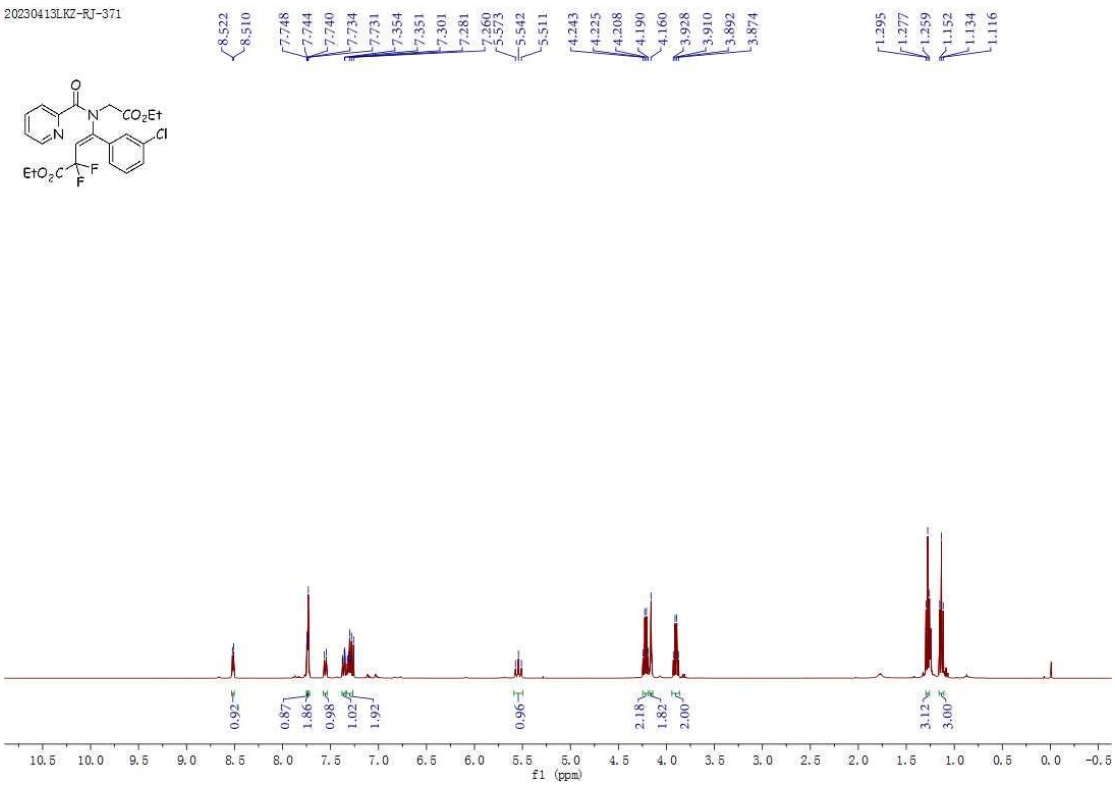
^{1}H – NMR spectrum of compound – **4l** (400 MHz, $CDCl_3$)



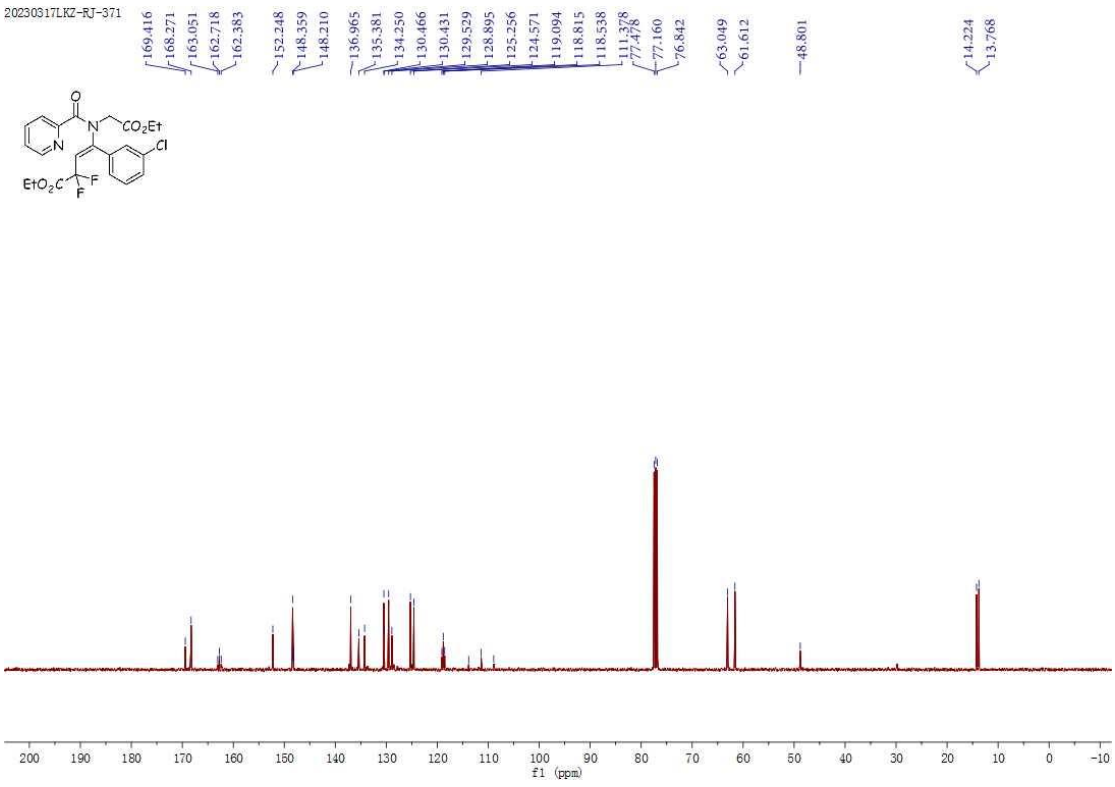
^{13}C – NMR spectrum of compound – **4l** (100 MHz, $CDCl_3$)



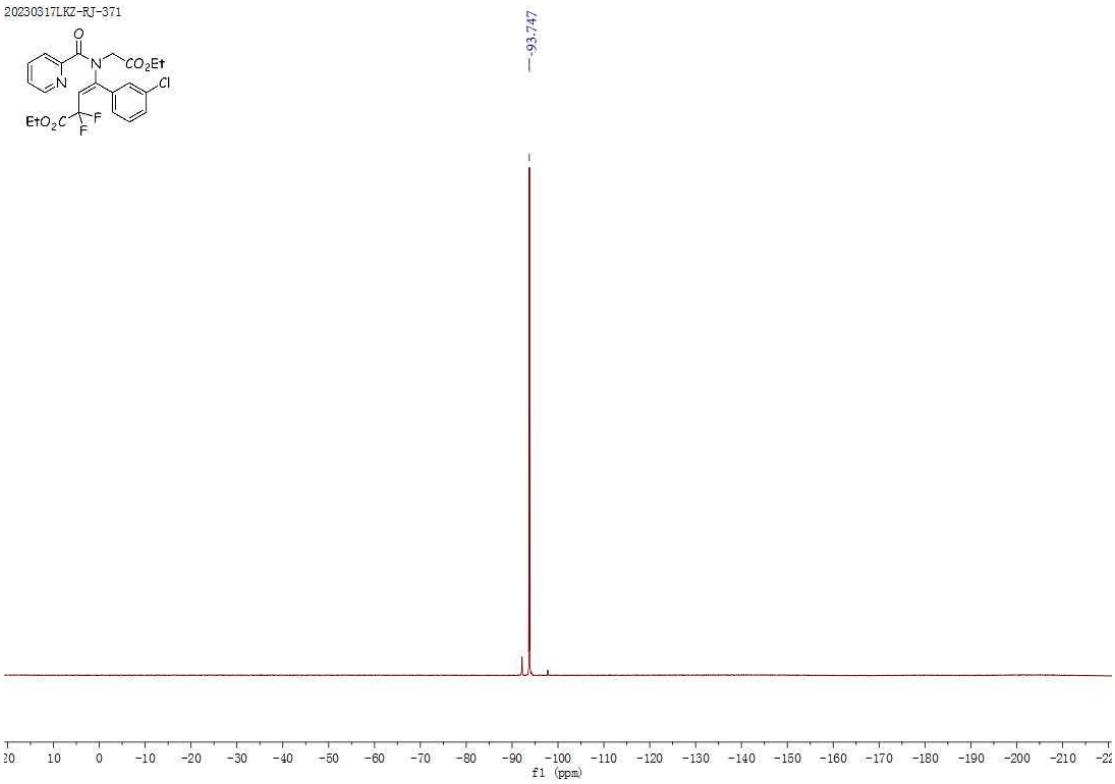
^{19}F – NMR spectrum of compound – **4l** (376 MHz, $CDCl_3$)



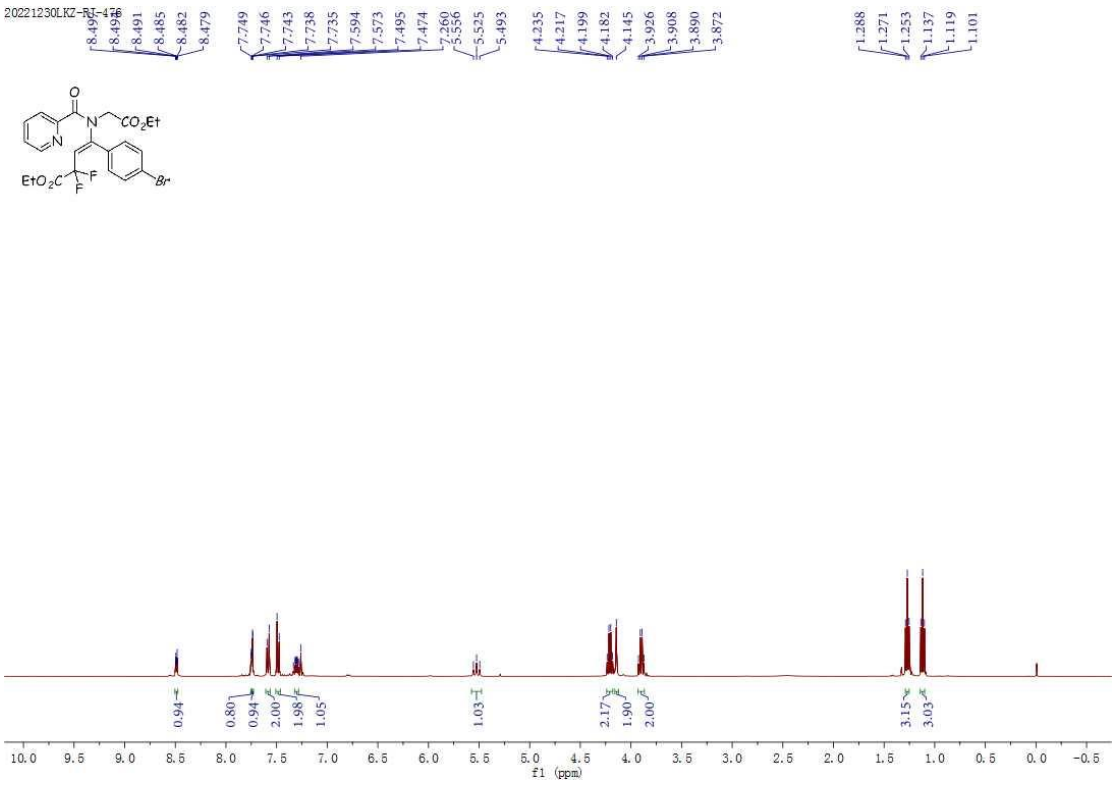
^{1}H – NMR spectrum of compound – **4m** (400 MHz, $CDCl_3$)



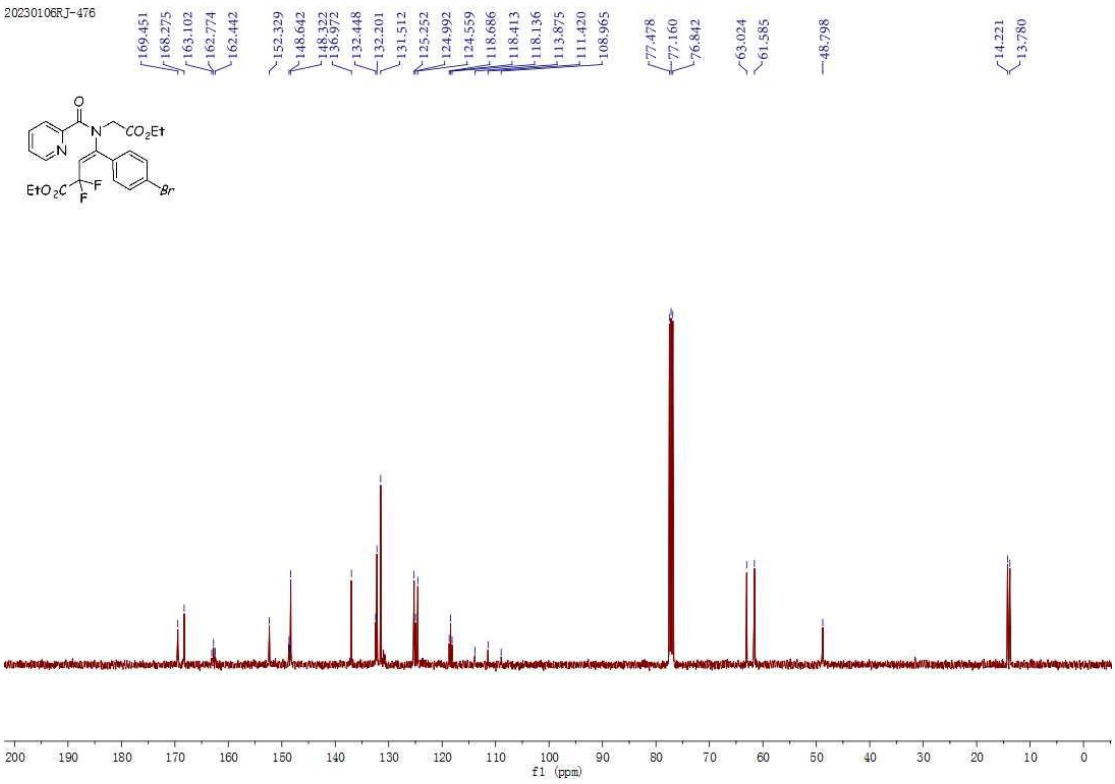
^{13}C – NMR spectrum of compound – **4m** (100 MHz, $CDCl_3$)



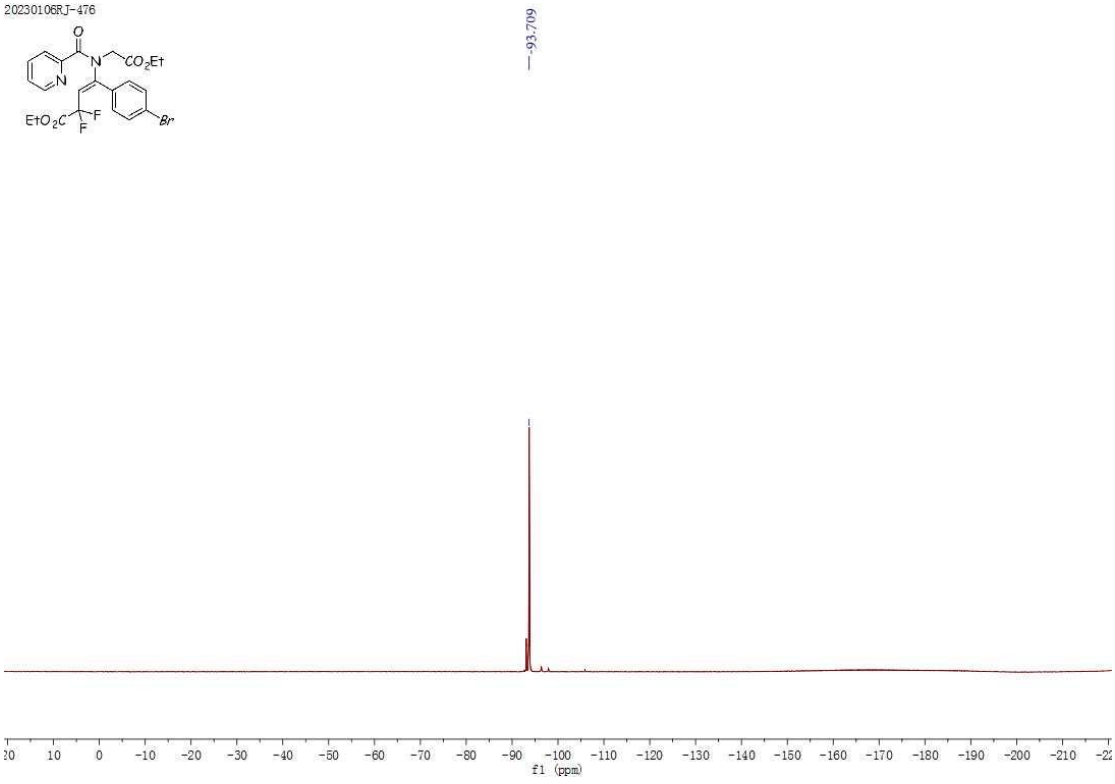
^{19}F – NMR spectrum of compound – **4m** (376 MHz, $CDCl_3$)



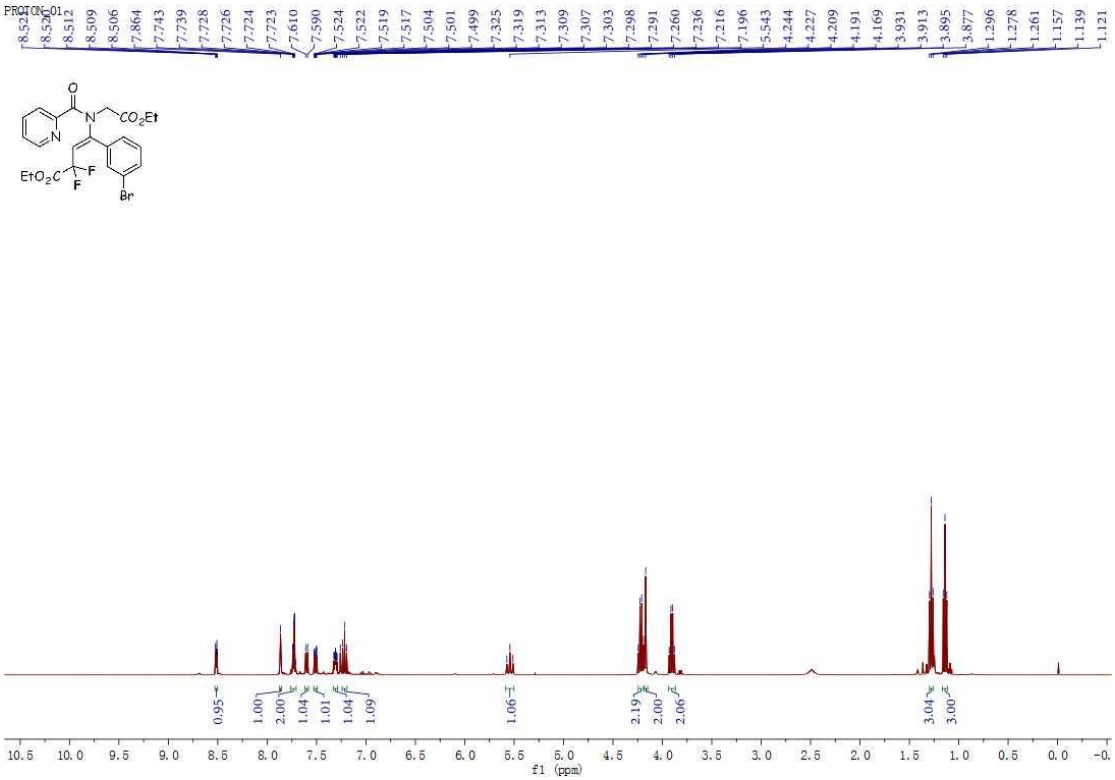
^{1}H – NMR spectrum of compound – **4n** (400 MHz, $CDCl_3$)



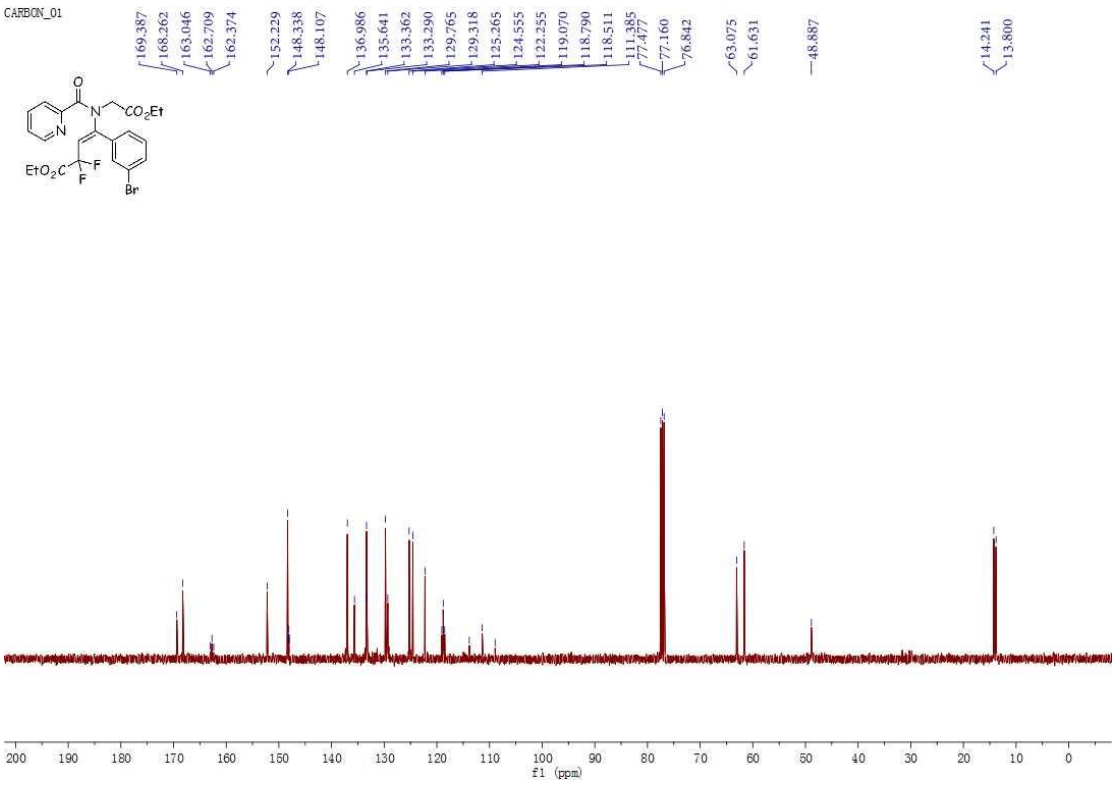
^{13}C – NMR spectrum of compound – **4n** (100 MHz, $CDCl_3$)



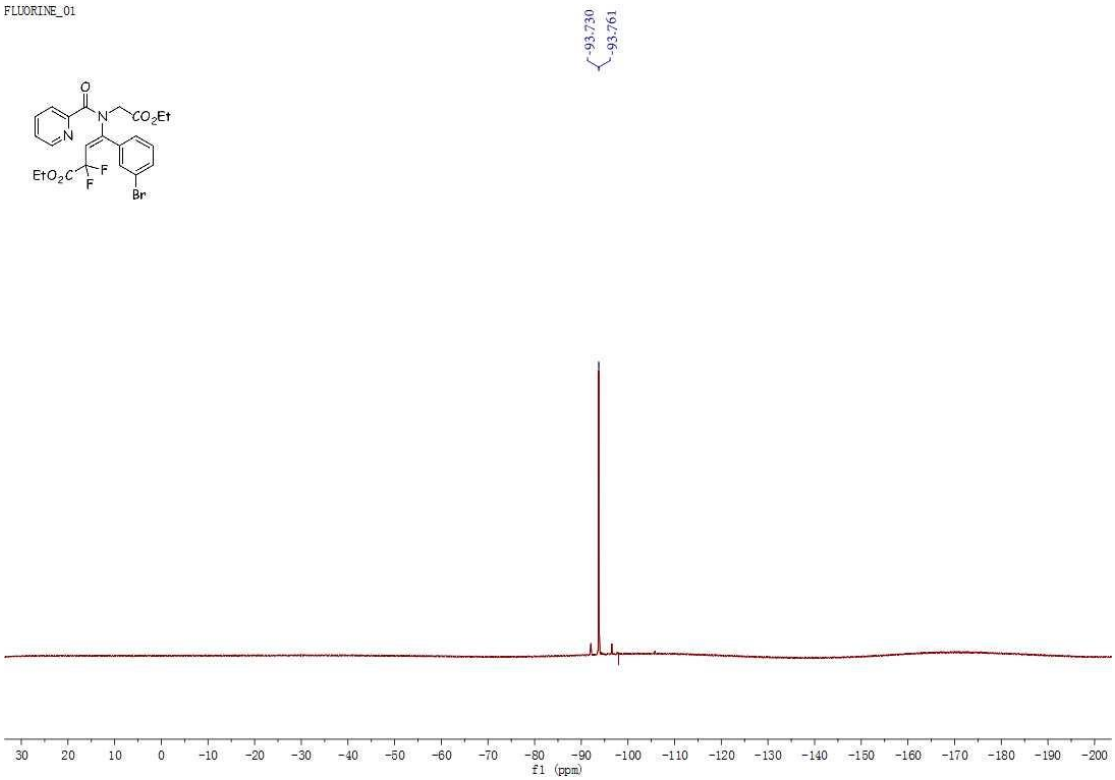
^{19}F – NMR spectrum of compound – **4n** (376 MHz, $CDCl_3$)



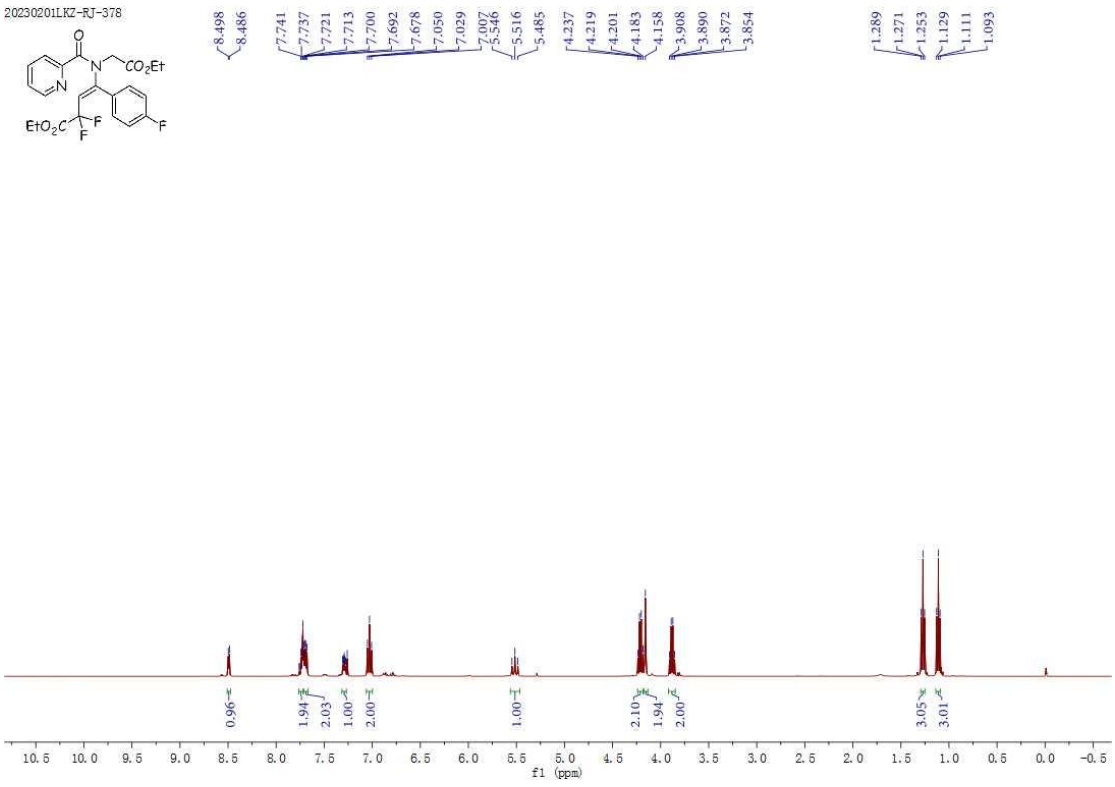
^{1}H – NMR spectrum of compound – **4o** (400 MHz, $CDCl_3$)



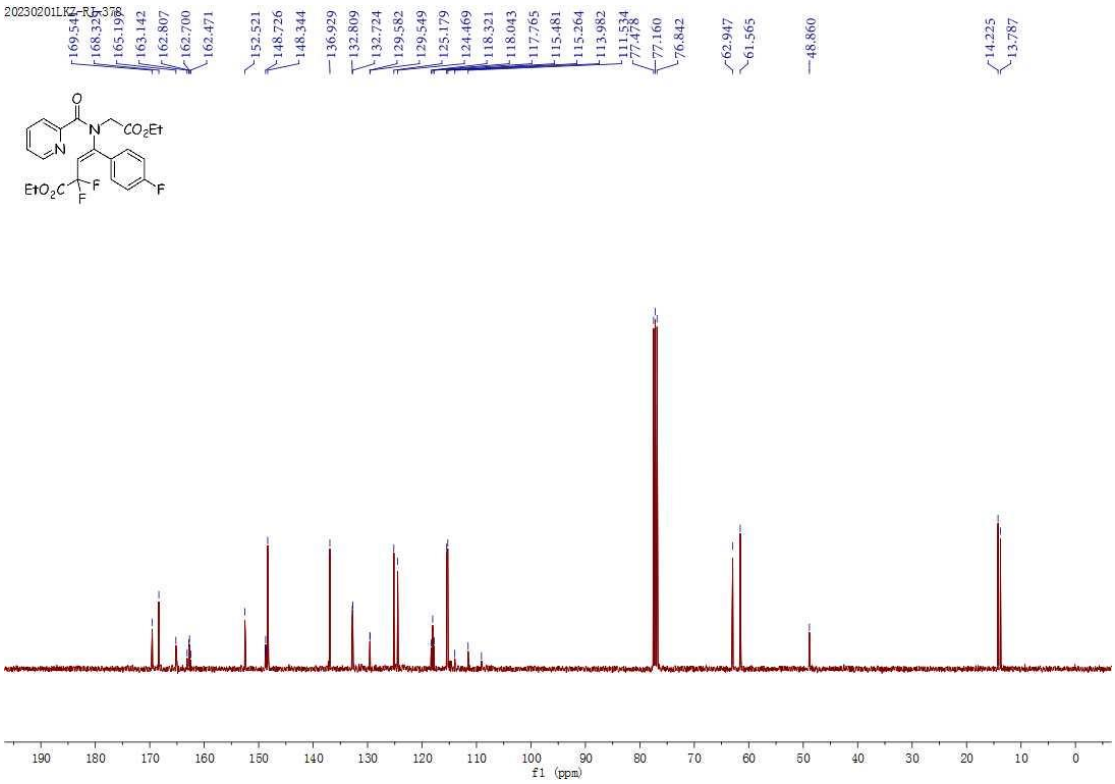
^{13}C – NMR spectrum of compound – **4o** (100 MHz, $CDCl_3$)



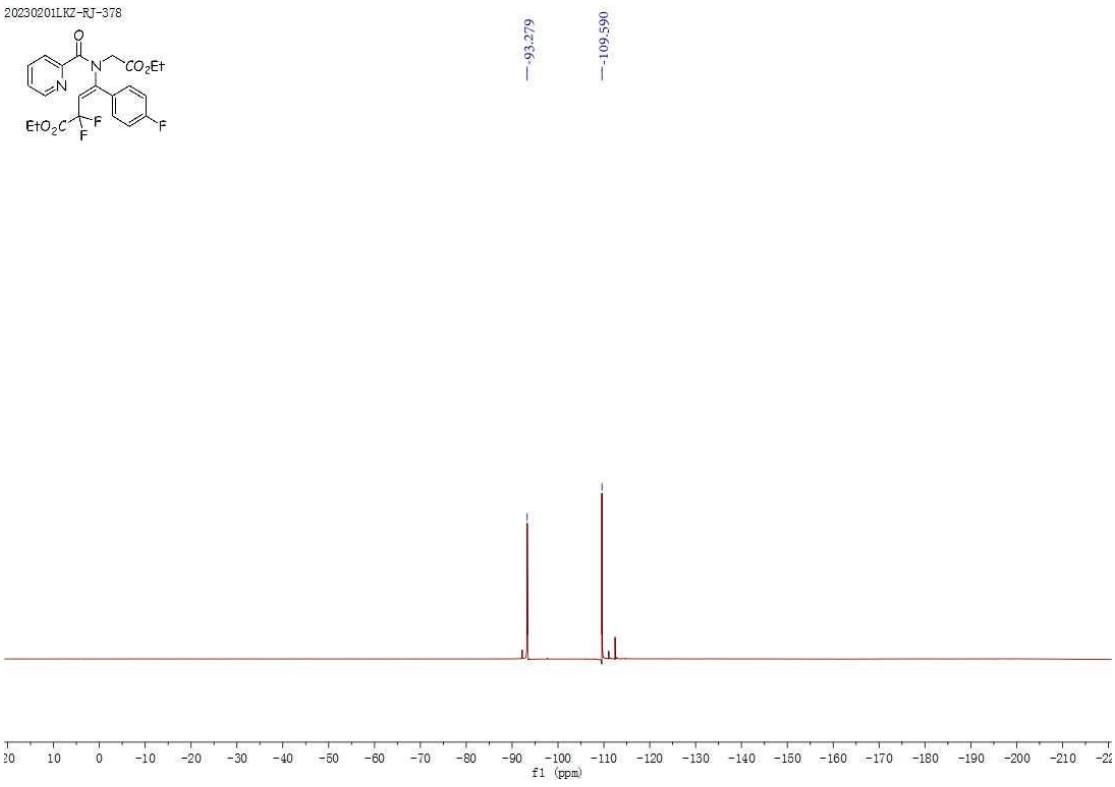
^{19}F – NMR spectrum of compound – **4o** (376 MHz, $CDCl_3$)



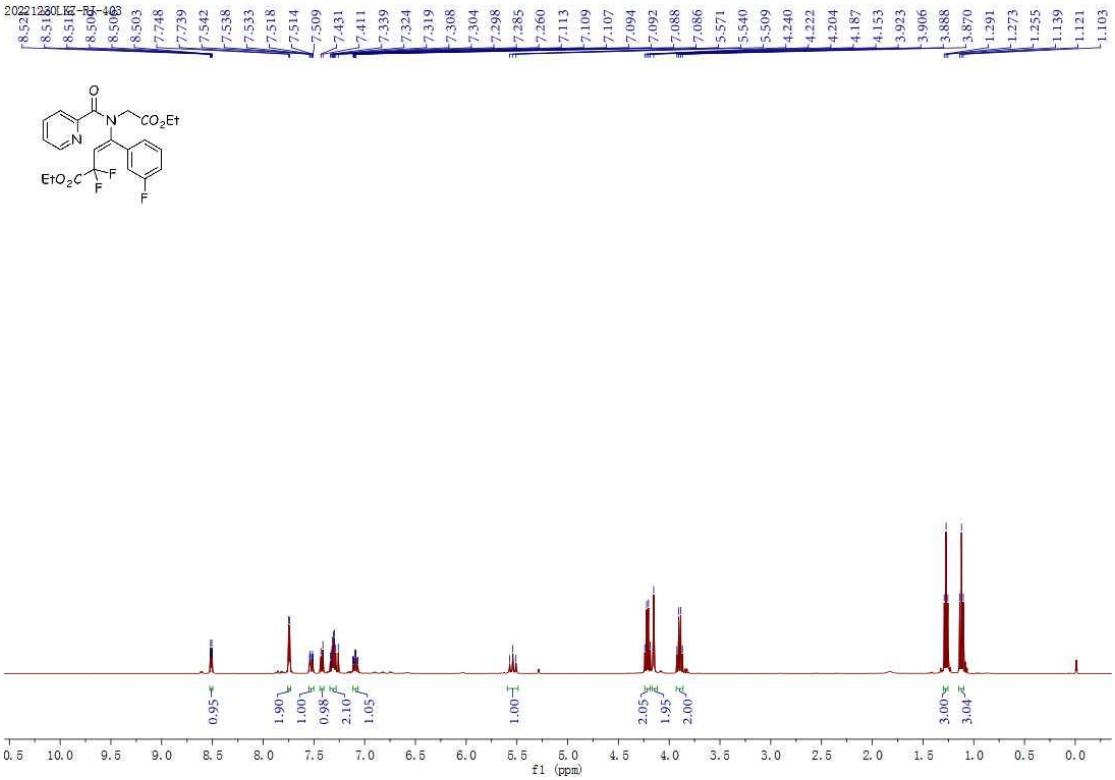
^{1}H – NMR spectrum of compound – **4p** (400 MHz, $CDCl_3$)



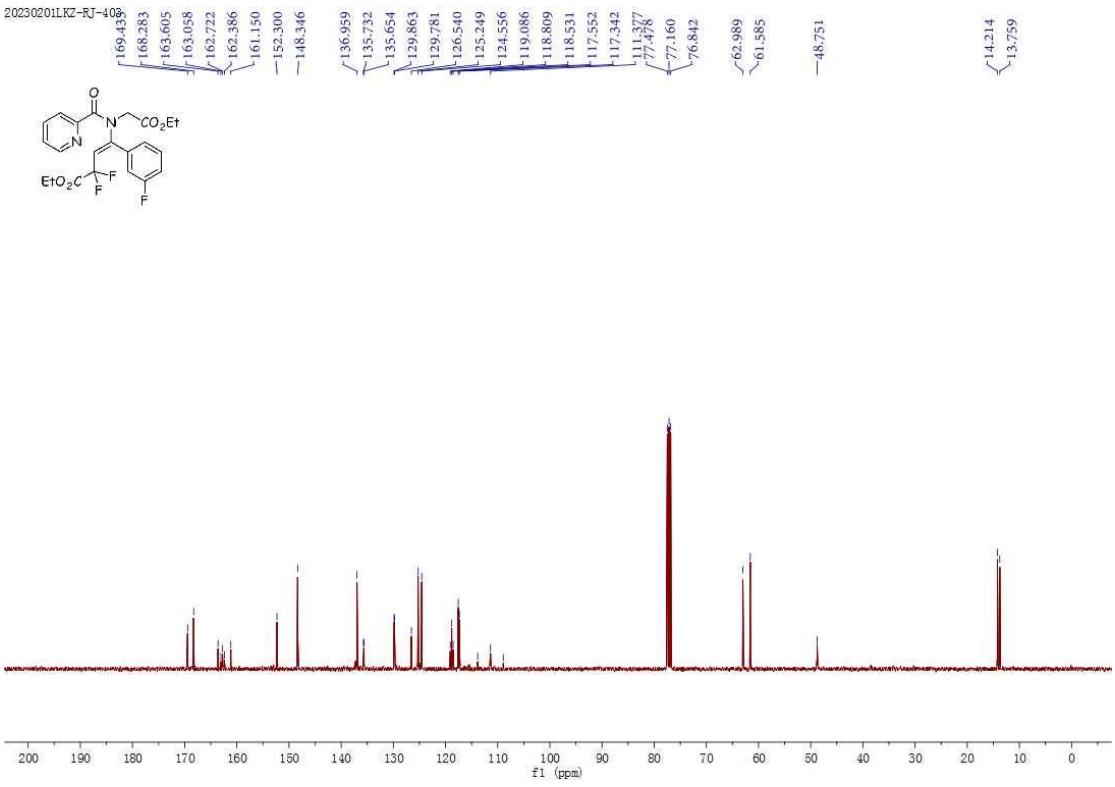
^{13}C – NMR spectrum of compound – **4p** (100 MHz, $CDCl_3$)



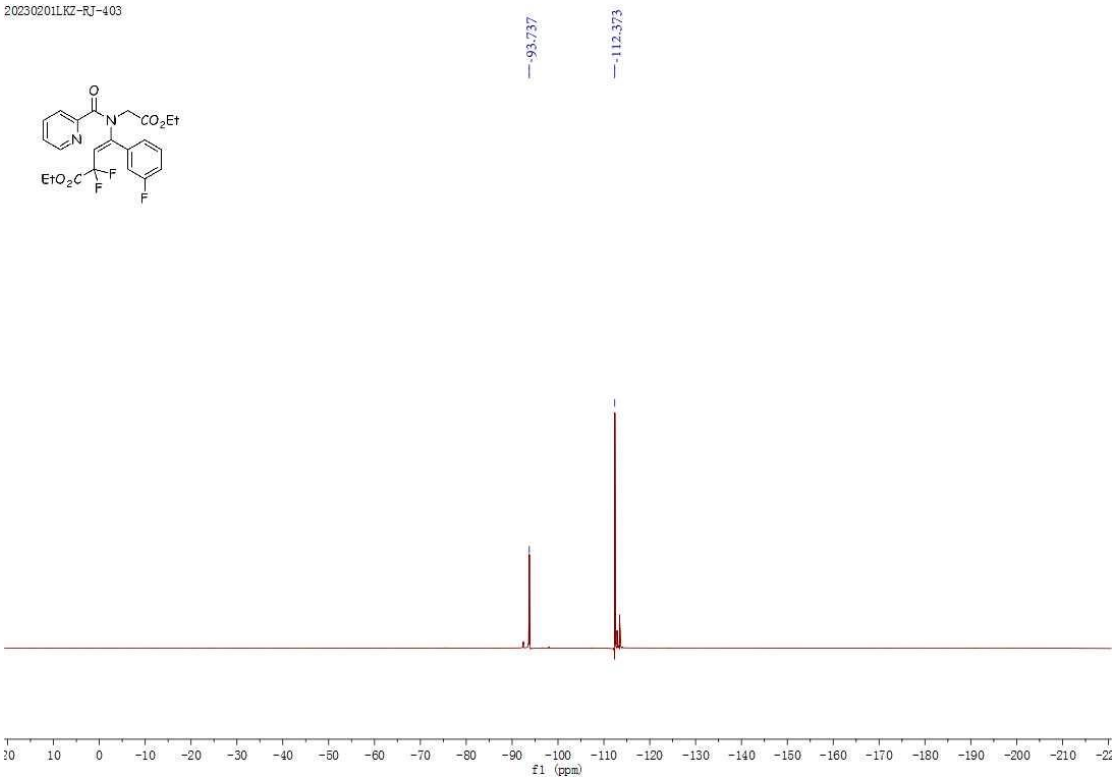
^{19}F – NMR spectrum of compound – **4p** (376 MHz, $CDCl_3$)



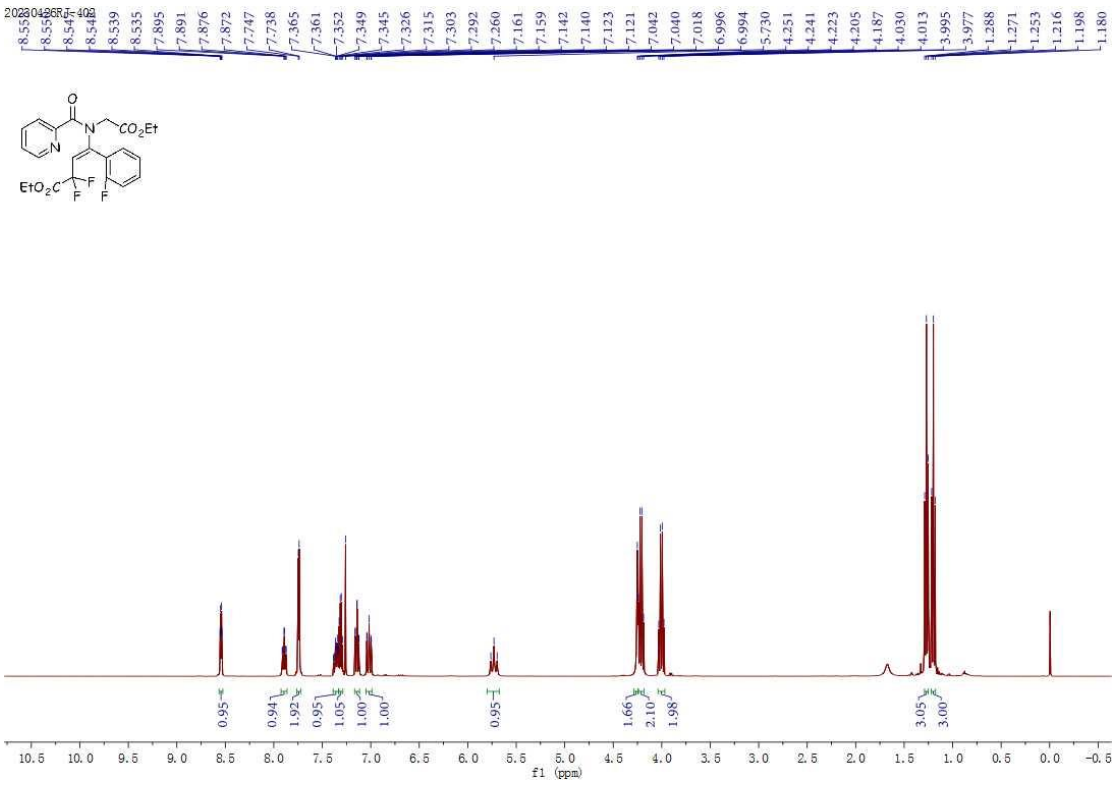
^{1}H – NMR spectrum of compound – **4q** (400 MHz, $CDCl_3$)



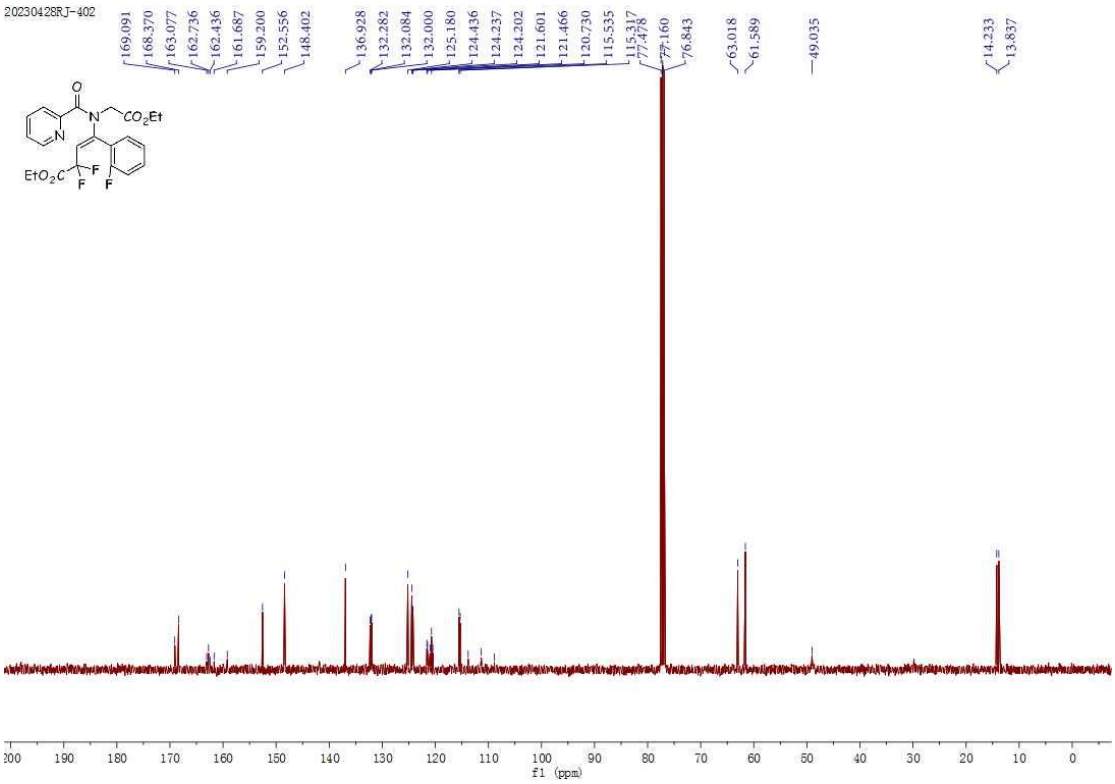
^{13}C – NMR spectrum of compound – **4q** (100 MHz, $CDCl_3$)



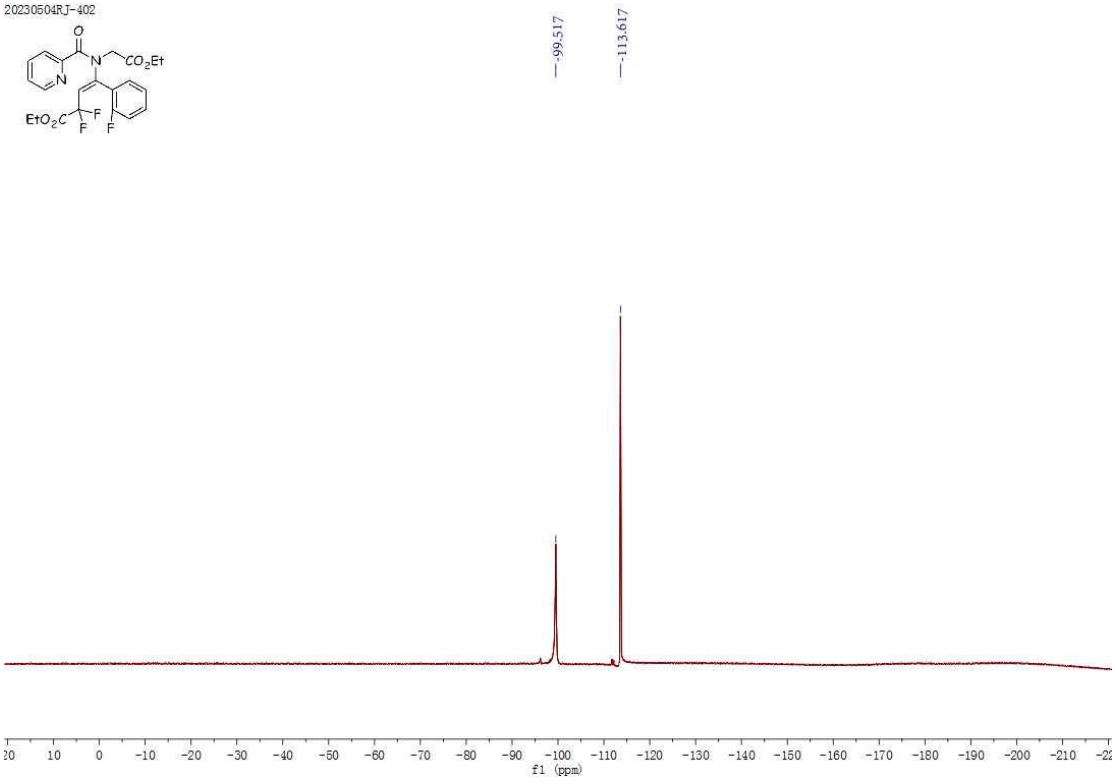
^{19}F – NMR spectrum of compound – **4q** (376 MHz, $CDCl_3$)



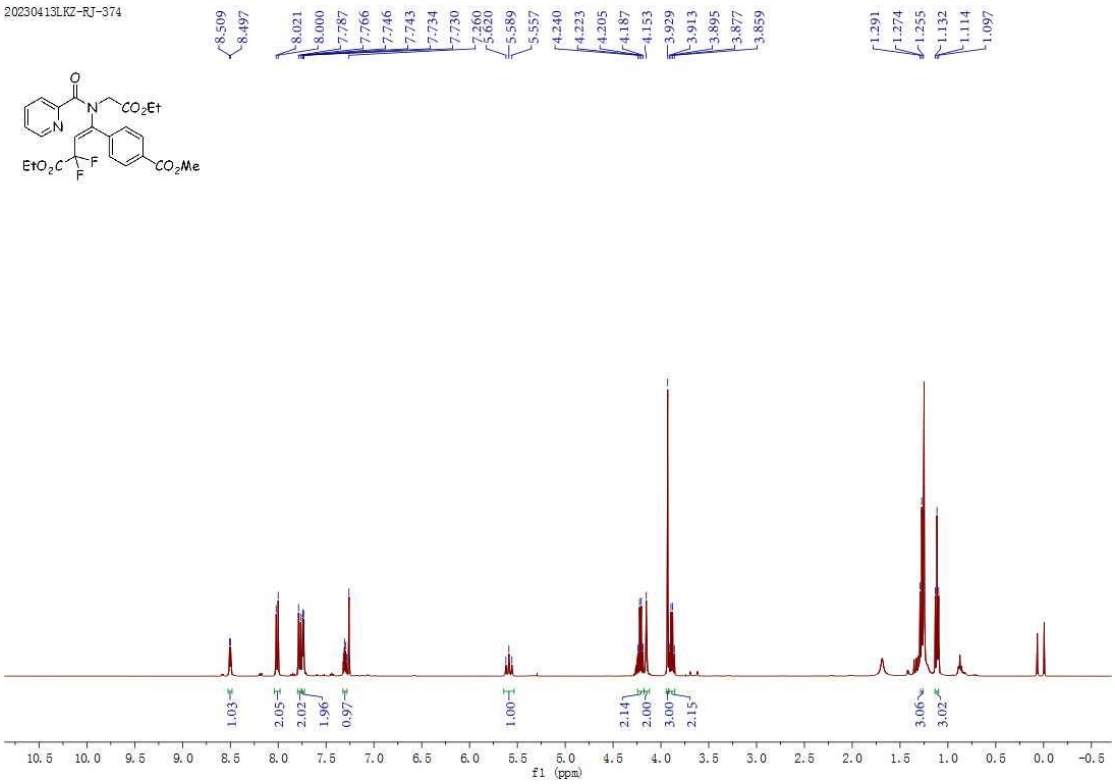
^{1}H – NMR spectrum of compound – **4r** (400 MHz, $CDCl_3$)



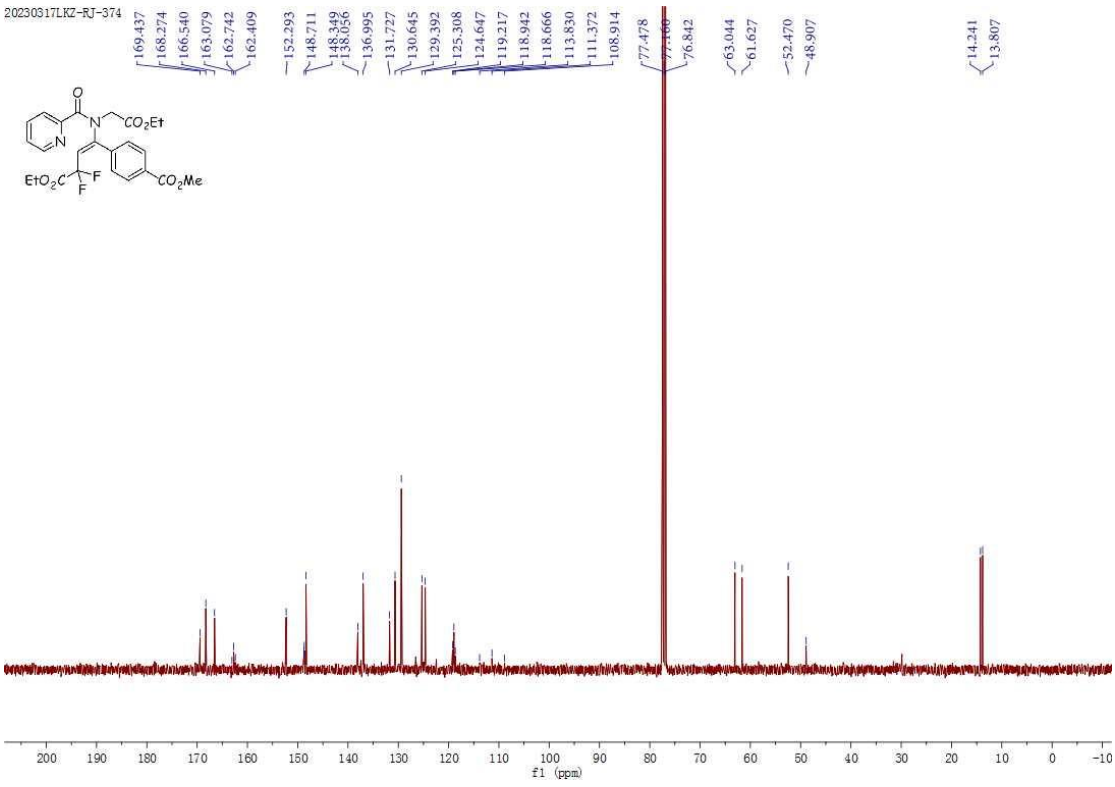
^{13}C – NMR spectrum of compound – **4r** (100 MHz, $CDCl_3$)



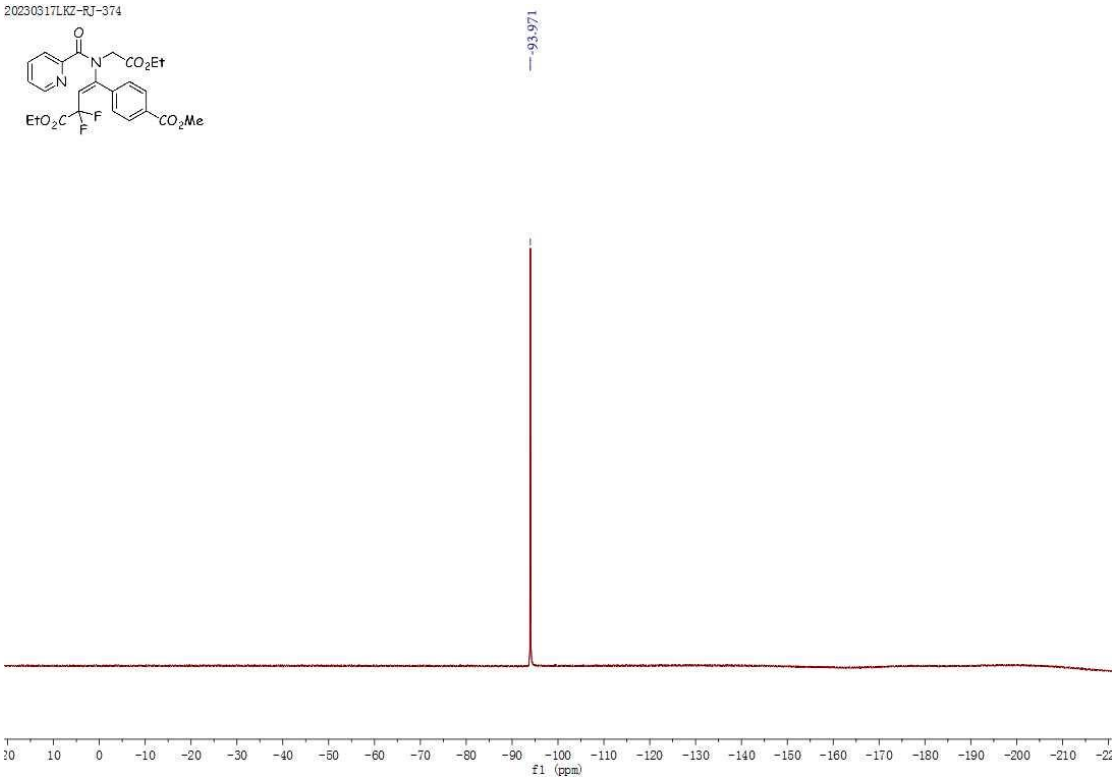
^{19}F – NMR spectrum of compound – **4r** (376 MHz, $CDCl_3$)



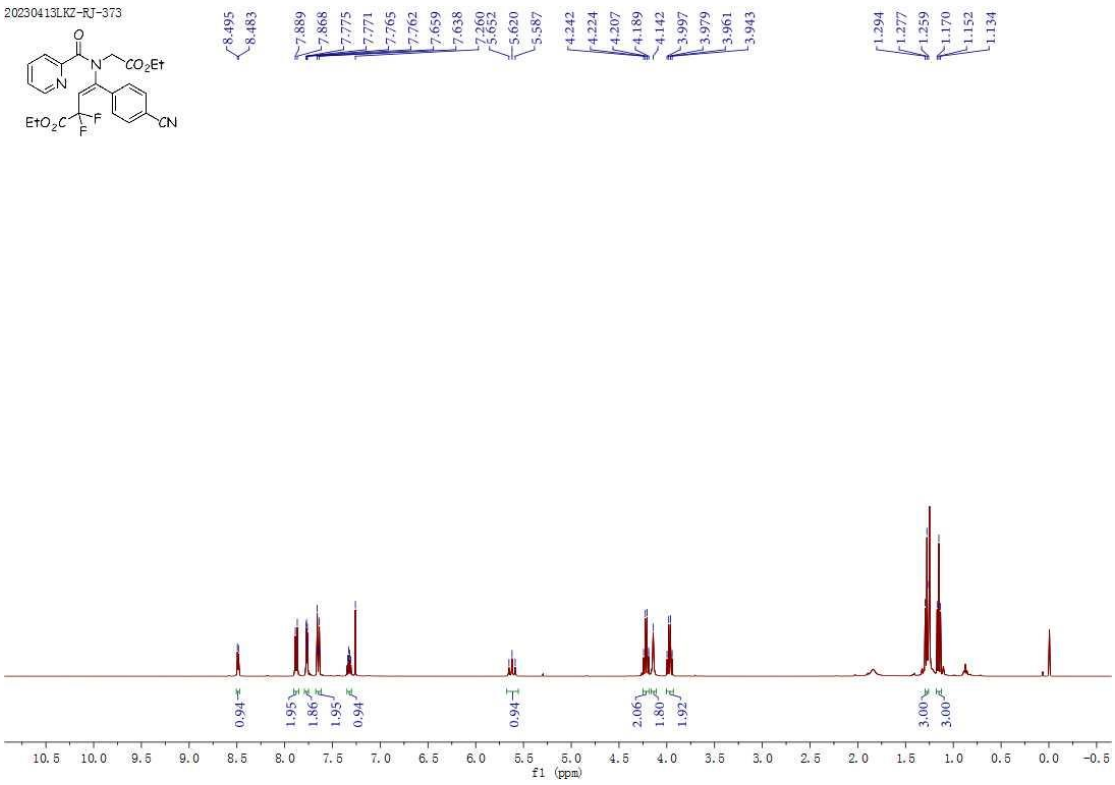
^{1}H – NMR spectrum of compound – **4s** (400 MHz, $CDCl_3$)



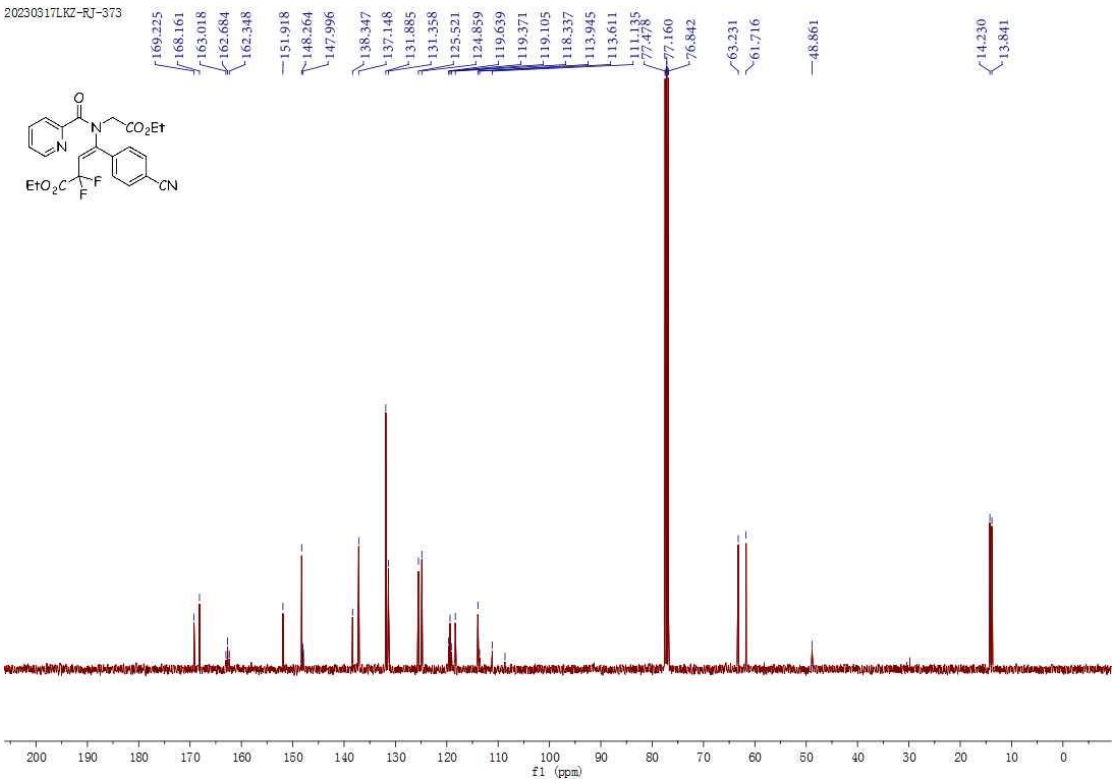
^{13}C – NMR spectrum of compound – **4s** (100 MHz, $CDCl_3$)



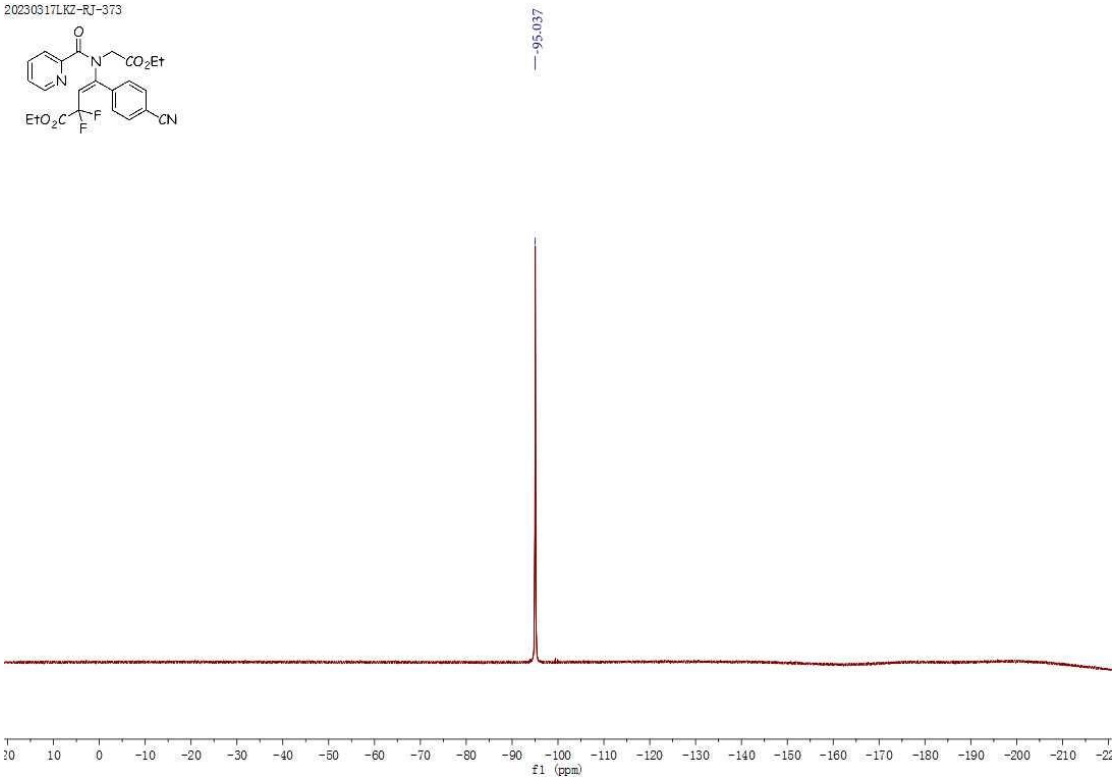
^{19}F – NMR spectrum of compound – **4s** (376 MHz, $CDCl_3$)



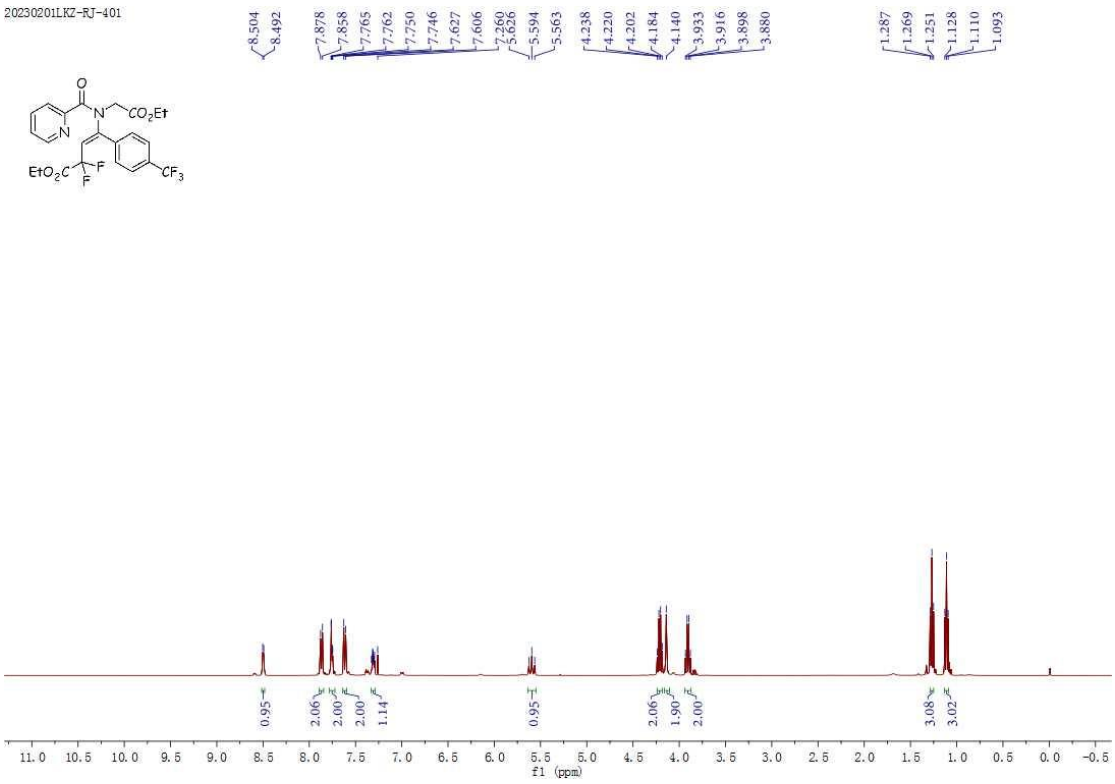
^{1}H – NMR spectrum of compound – **4t** (400 MHz, $CDCl_3$)



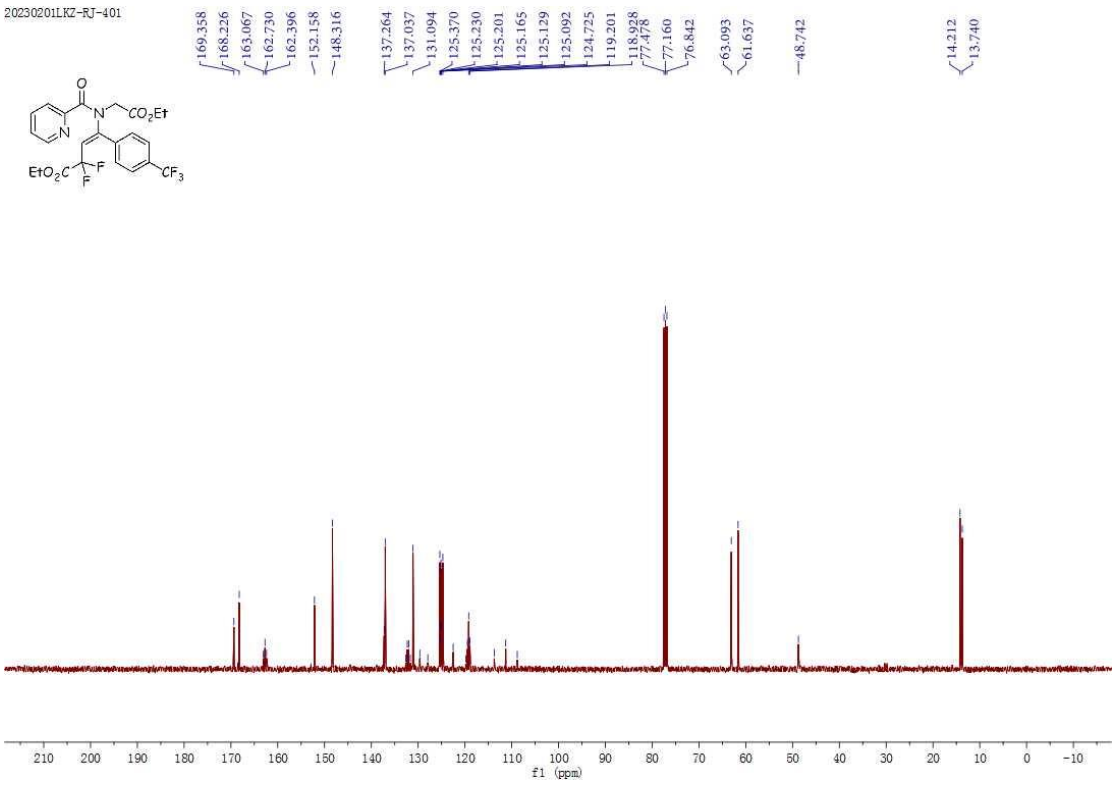
^{13}C – NMR spectrum of compound – **4t** (100 MHz, $CDCl_3$)



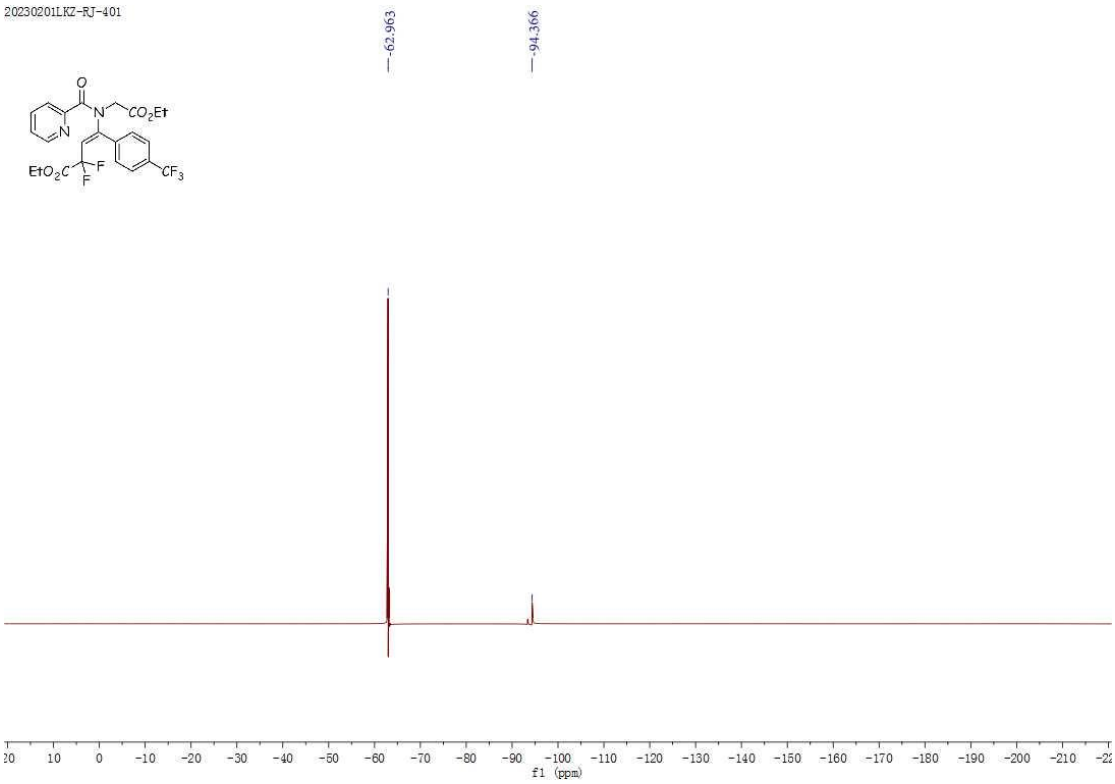
^{19}F – NMR spectrum of compound – **4t** (376 MHz, $CDCl_3$)



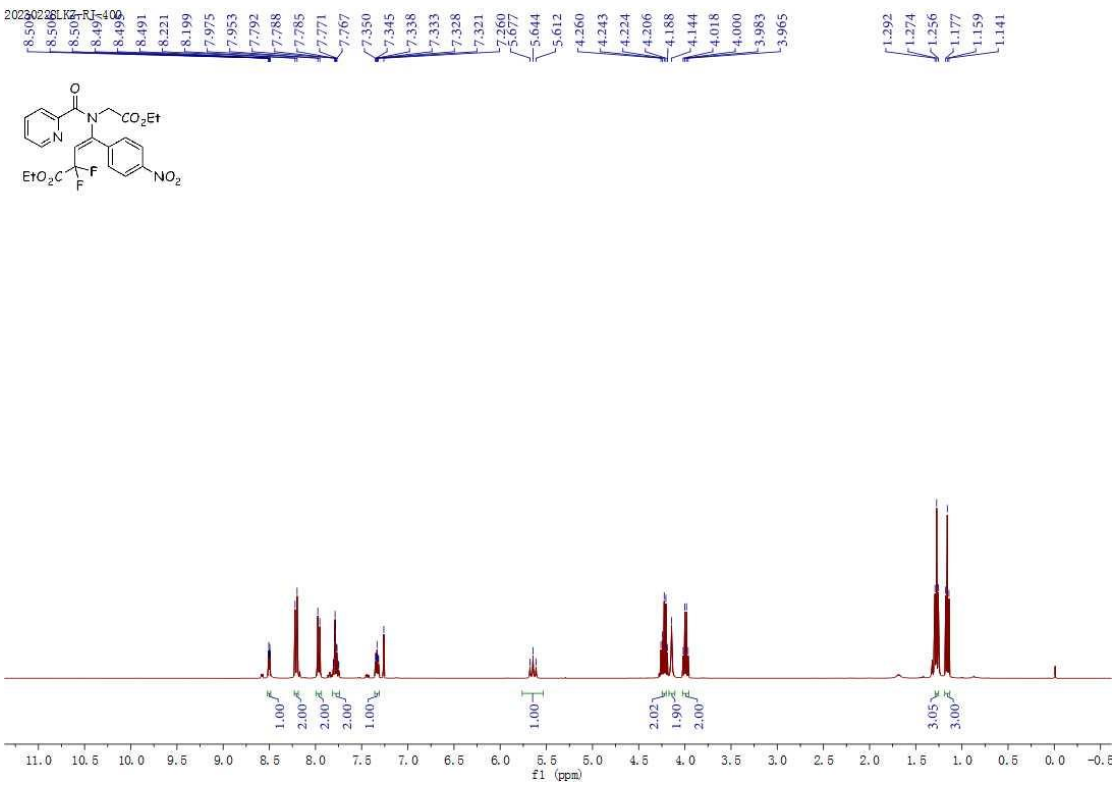
^{1}H – NMR spectrum of compound – **4u** (400 MHz, $CDCl_3$)



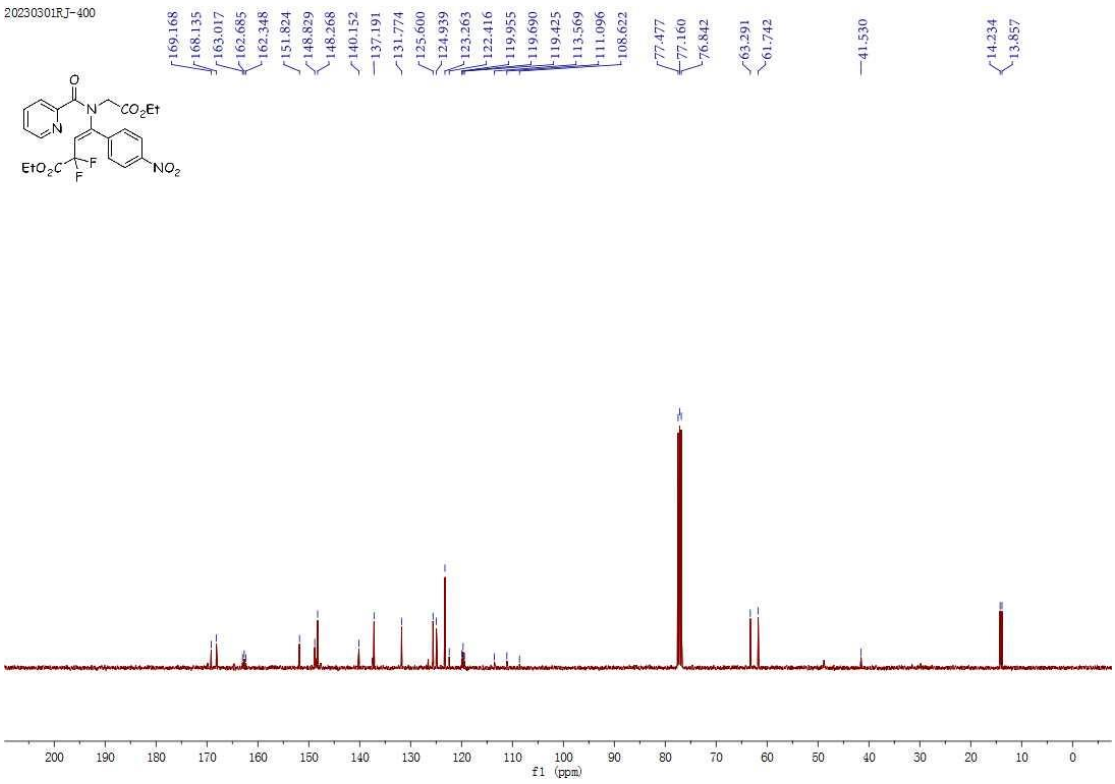
^{13}C – NMR spectrum of compound – **4u** (100 MHz, $CDCl_3$)



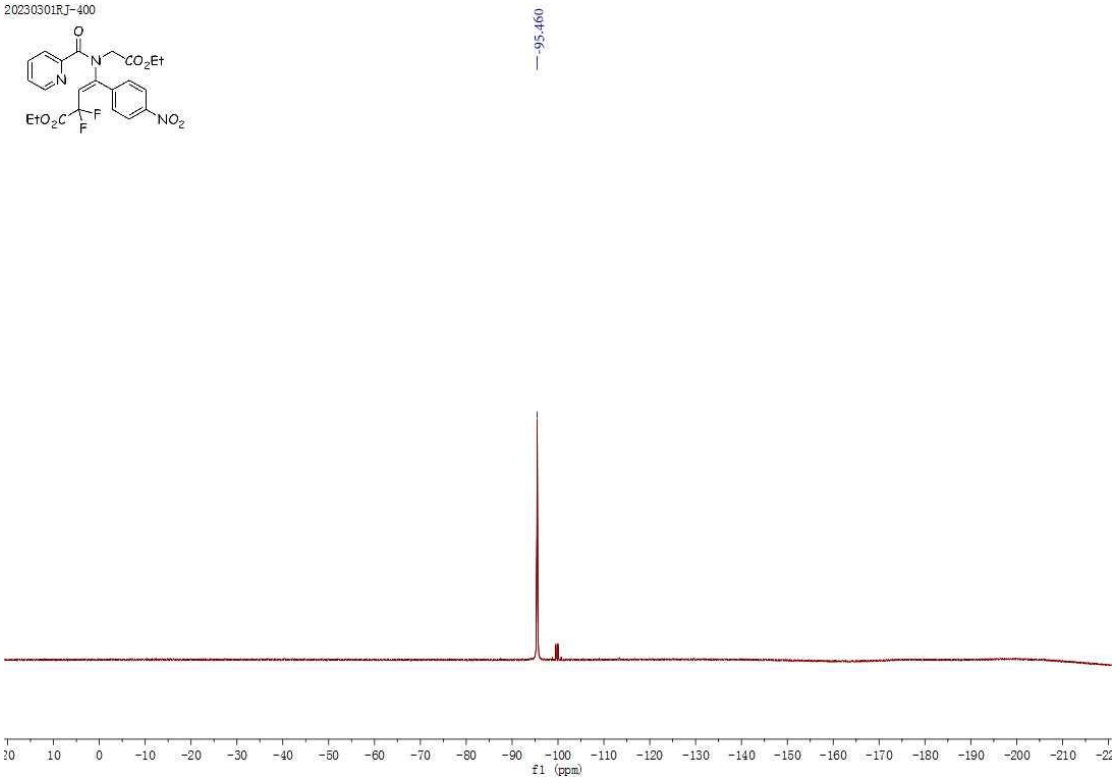
^{19}F – NMR spectrum of compound – **4u** (376 MHz, $CDCl_3$)



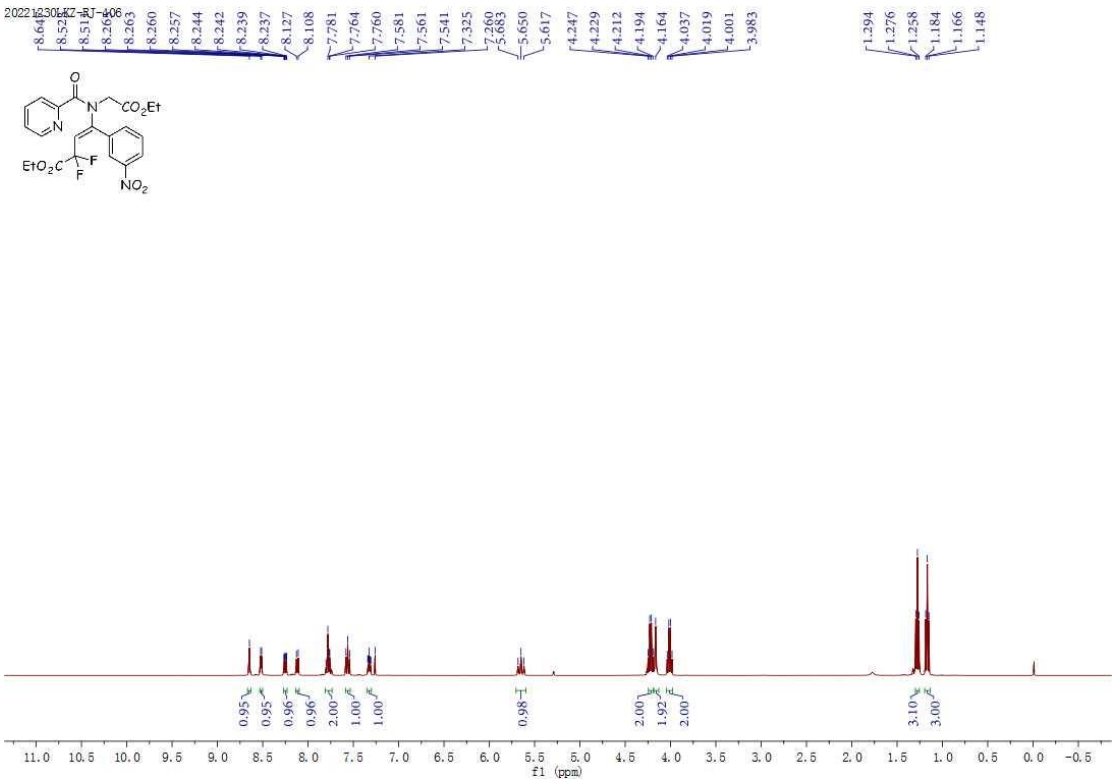
^{1}H – NMR spectrum of compound – **4v** (400 MHz, $CDCl_3$)



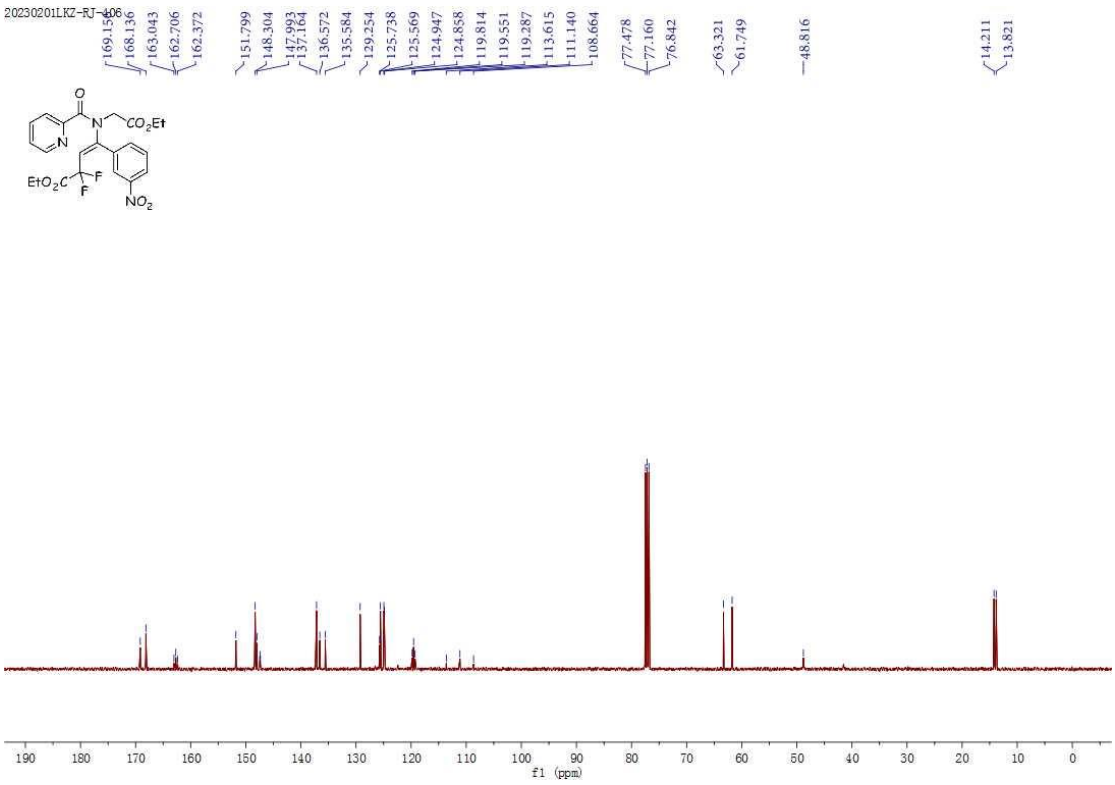
^{13}C – NMR spectrum of compound – **4v** (100 MHz, $CDCl_3$)



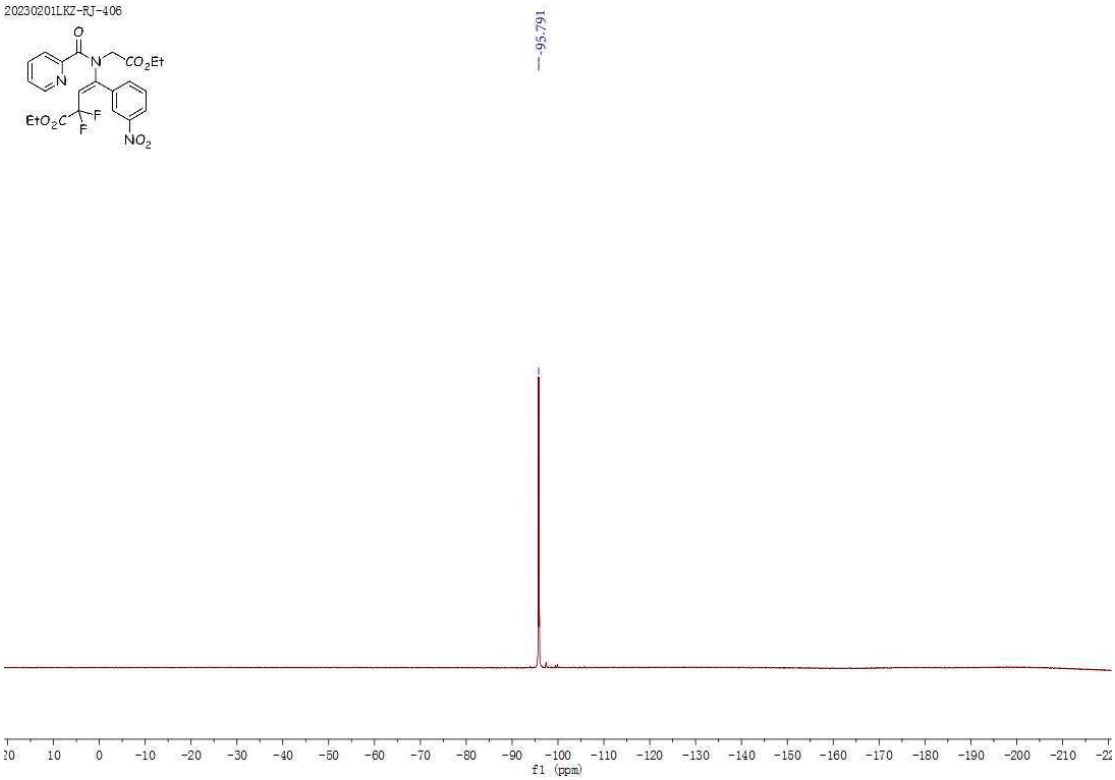
^{19}F – NMR spectrum of compound – **4v** (376 MHz, $CDCl_3$)



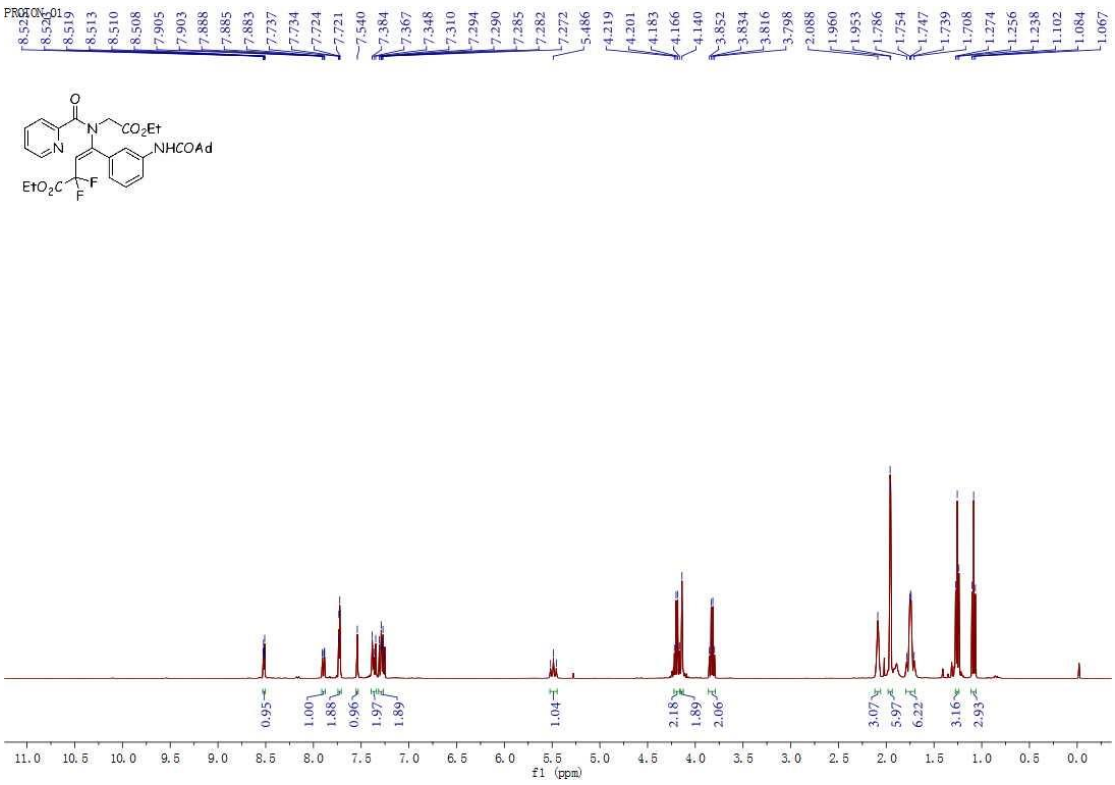
^{1}H – NMR spectrum of compound – **4w** (400 MHz, $CDCl_3$)



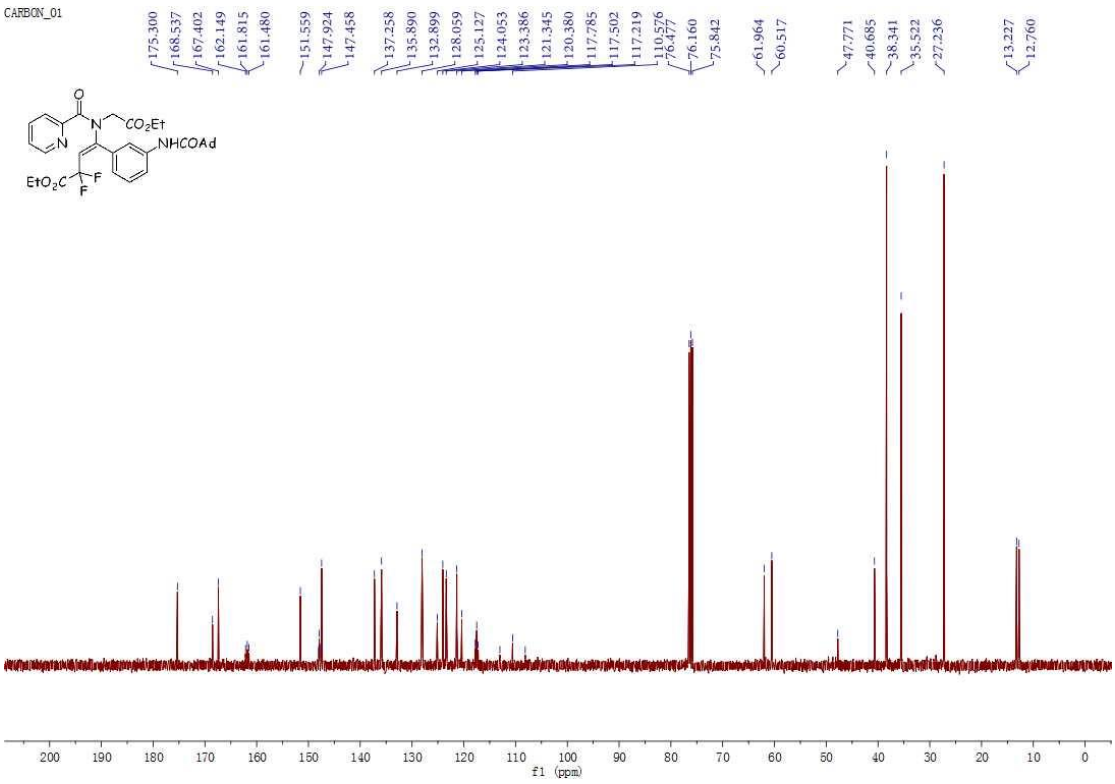
^{13}C – NMR spectrum of compound – **4w** (100 MHz, $CDCl_3$)



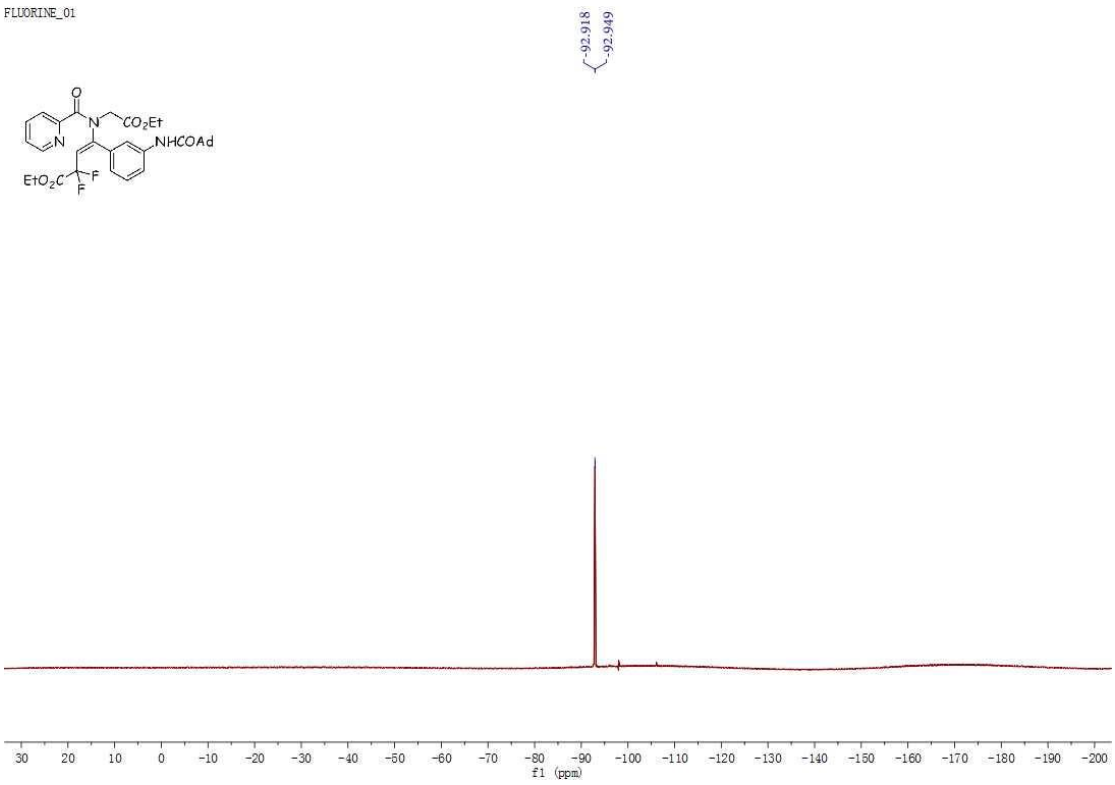
^{19}F – NMR spectrum of compound – **4w** (376 MHz, $CDCl_3$)



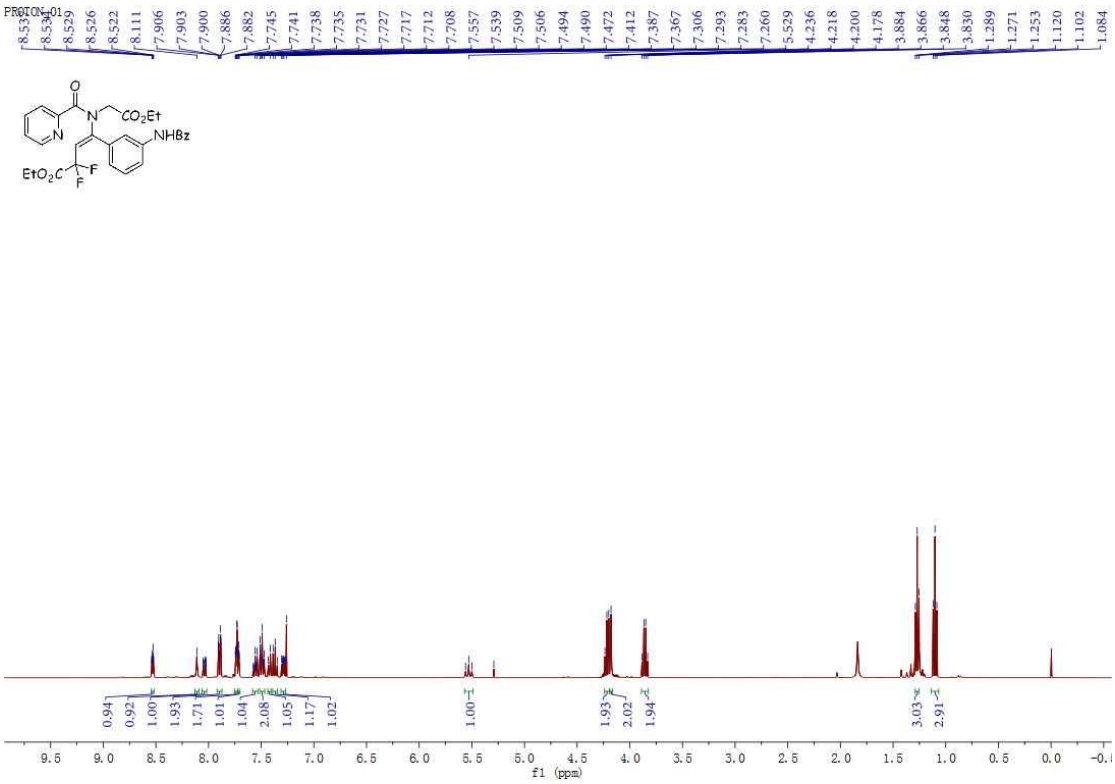
^{1}H – NMR spectrum of compound – **4x** (400 MHz, $CDCl_3$)



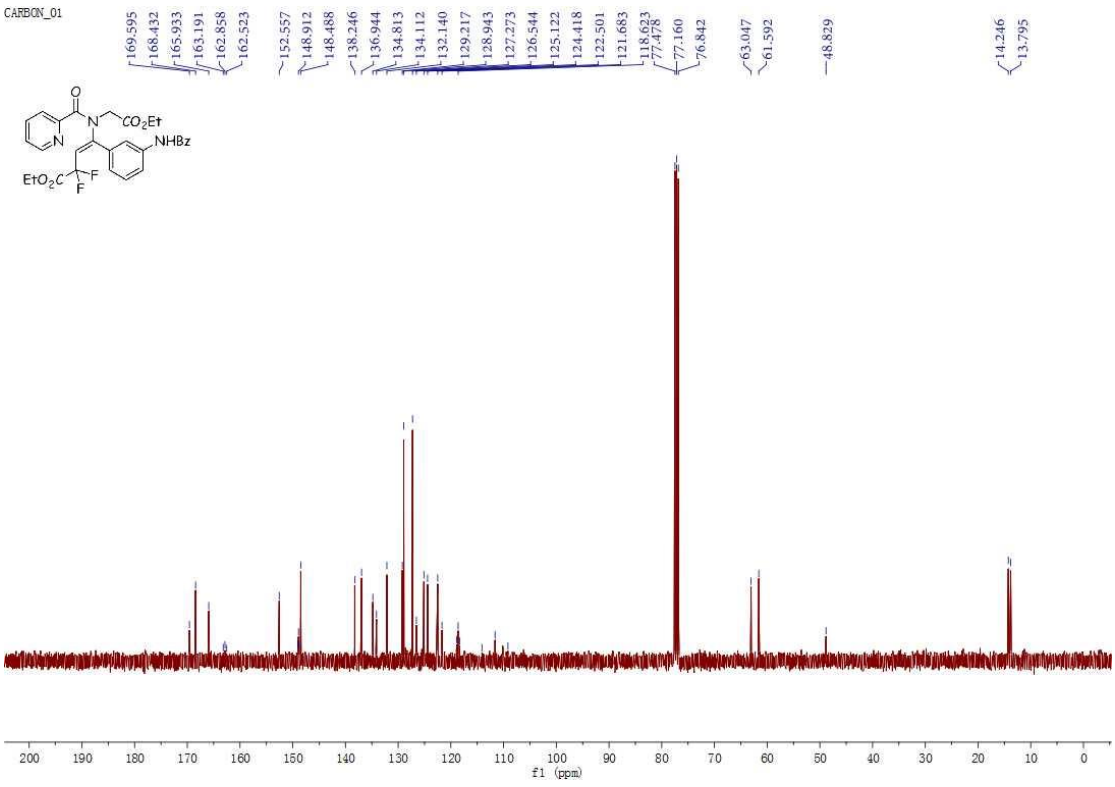
^{13}C – NMR spectrum of compound – **4x** (100 MHz, $CDCl_3$)



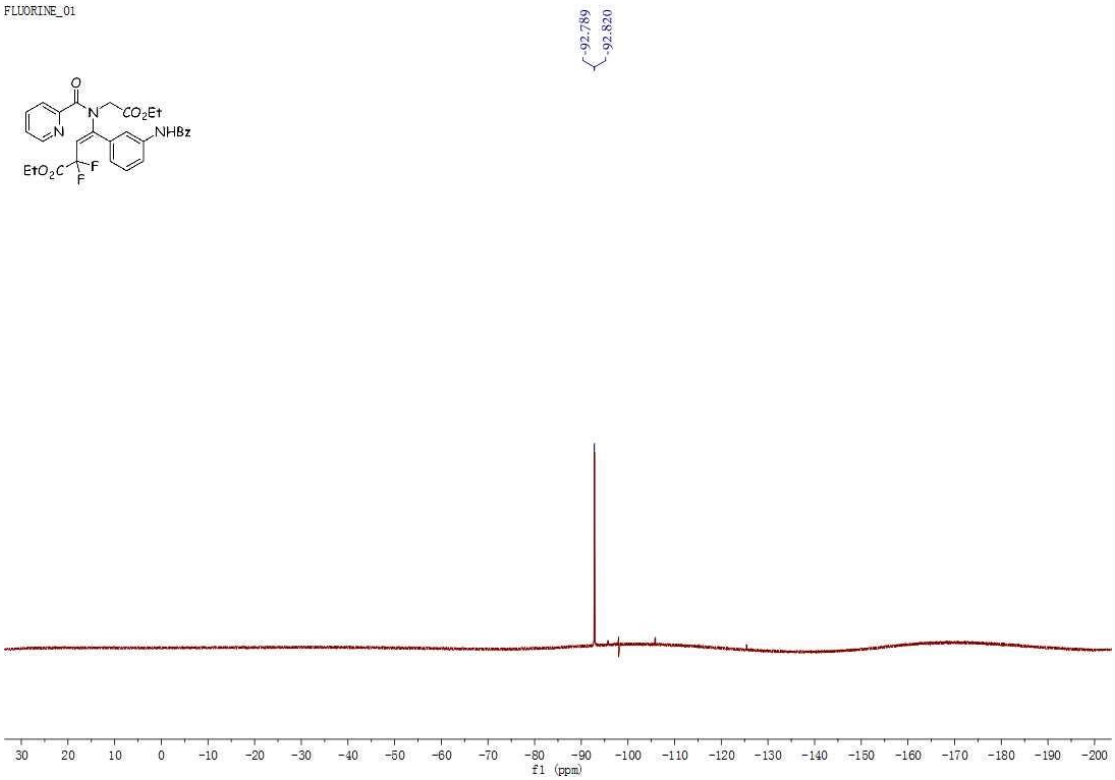
^{19}F – NMR spectrum of compound – **4x** (376 MHz, $CDCl_3$)



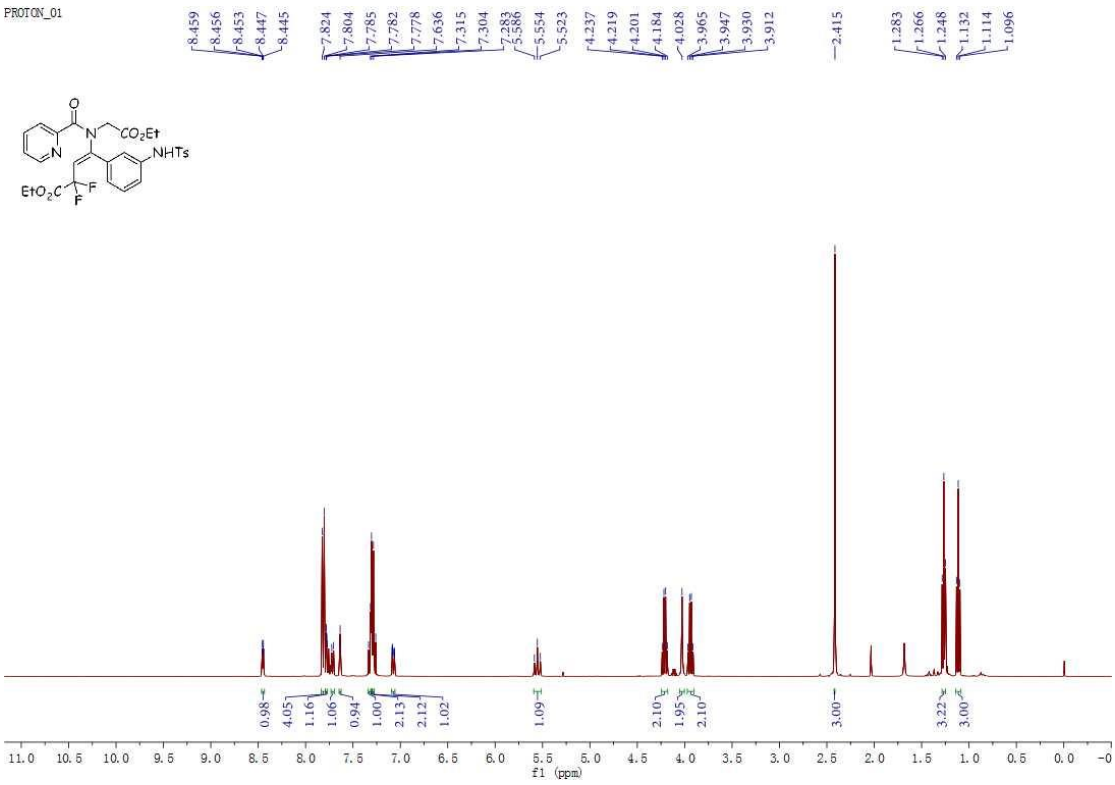
^{1}H – NMR spectrum of compound – **4y** (400 MHz, $CDCl_3$)



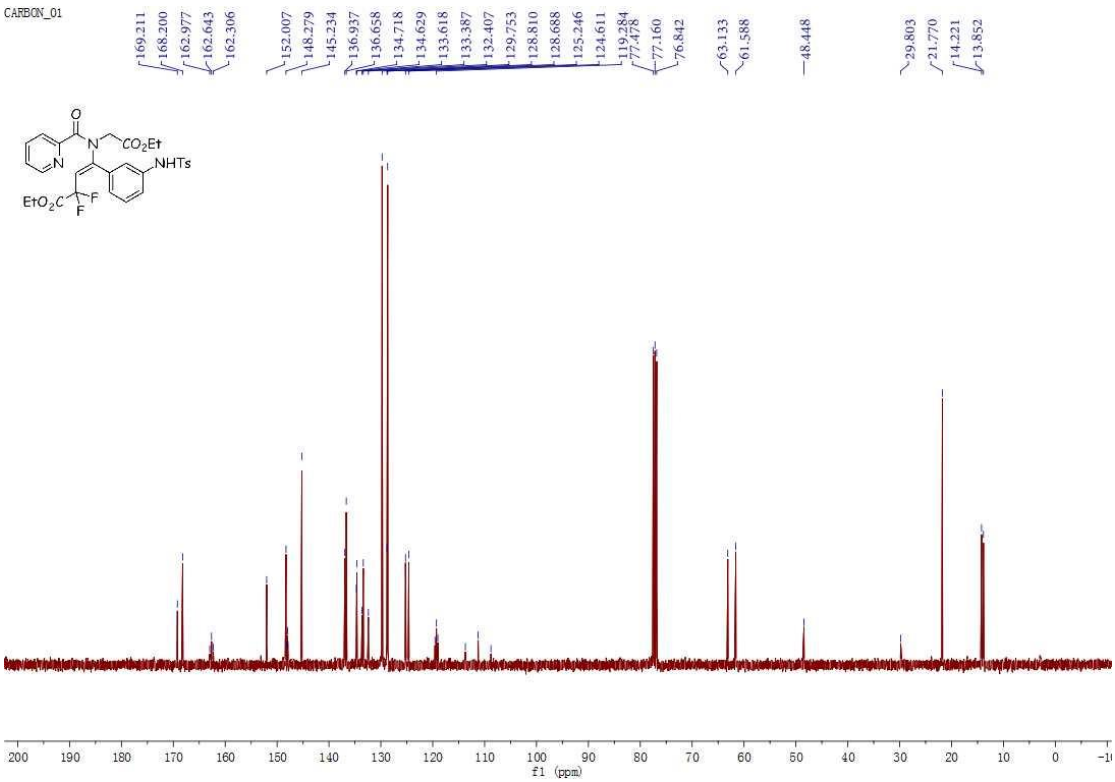
^{13}C – NMR spectrum of compound – **4y** (100 MHz, $CDCl_3$)



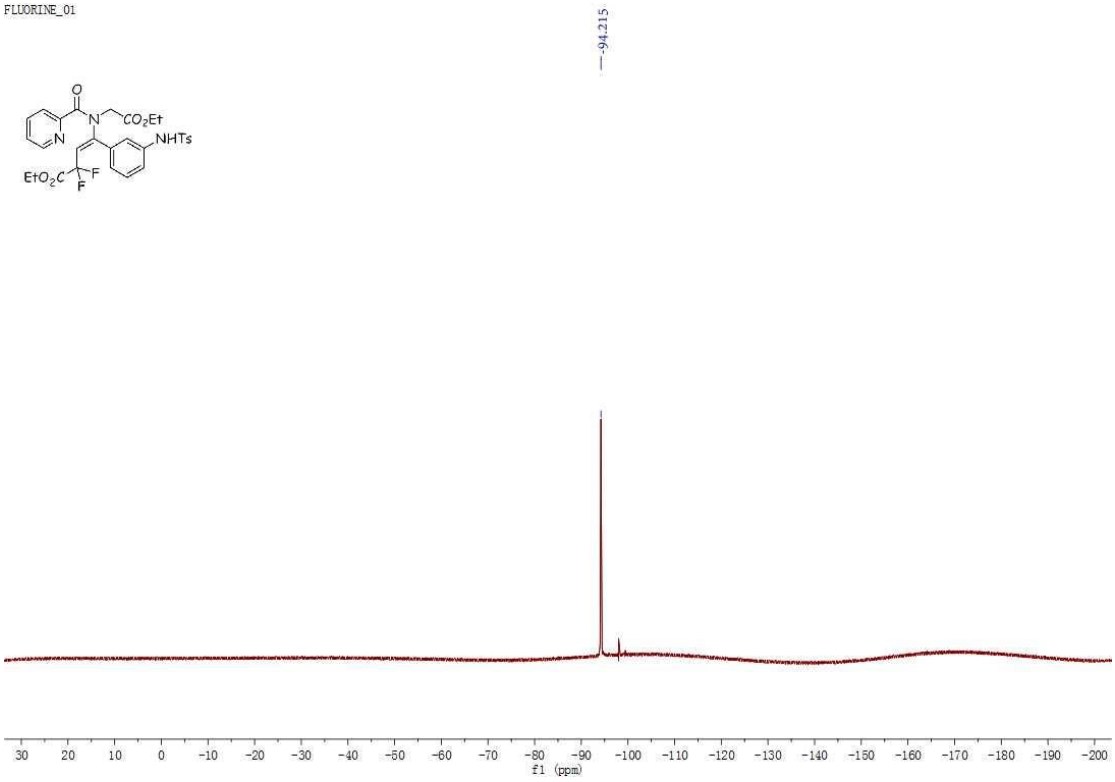
^{19}F – NMR spectrum of compound – **4y** (376 MHz, $CDCl_3$)



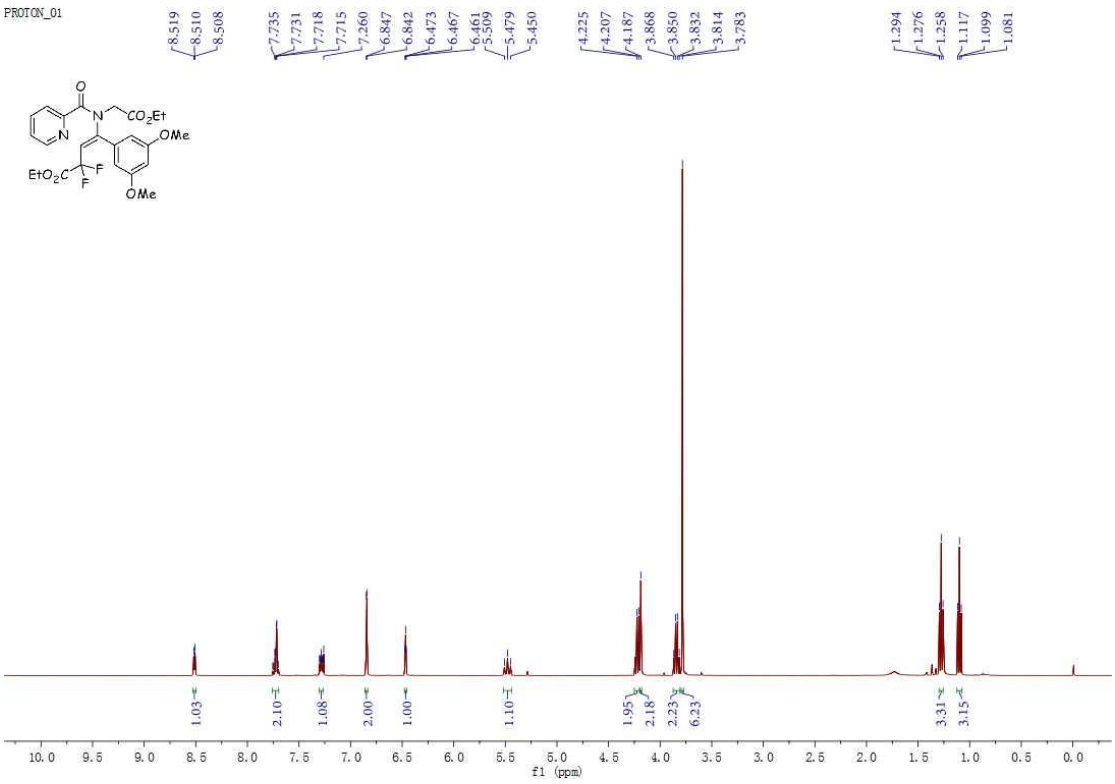
^{1}H – NMR spectrum of compound – **4z** (400 MHz, $CDCl_3$)



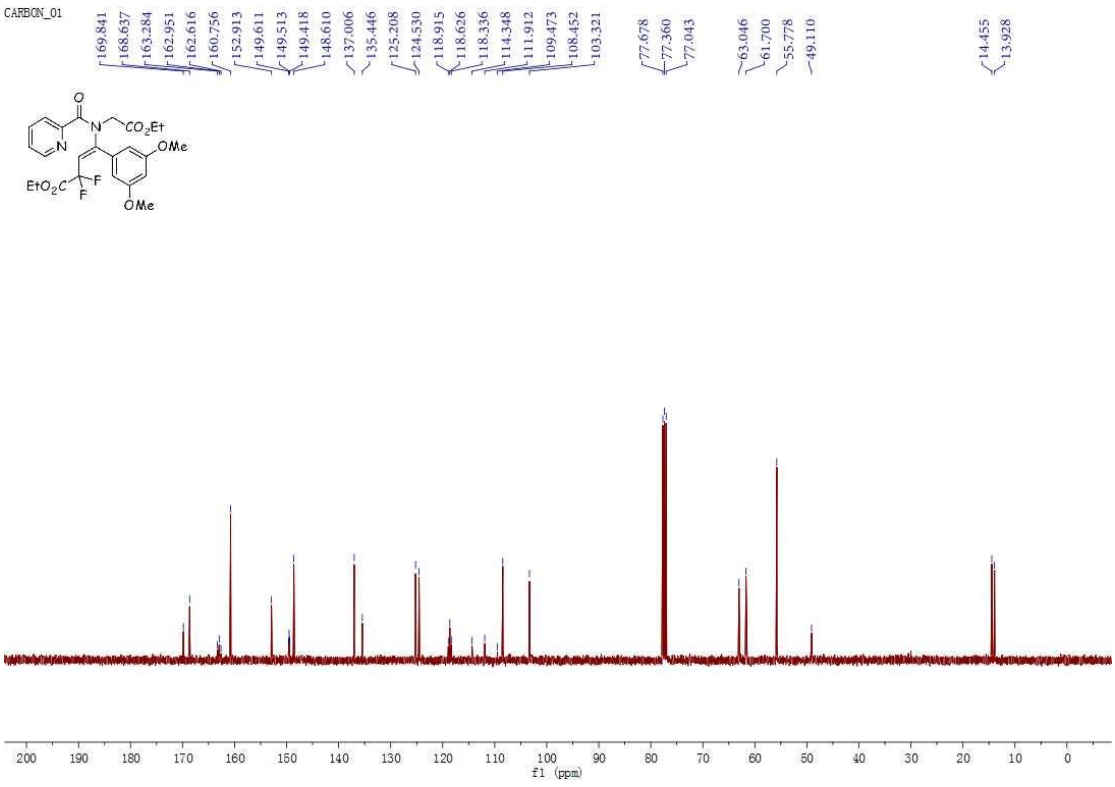
^{13}C – NMR spectrum of compound – **4z** (100 MHz, $CDCl_3$)



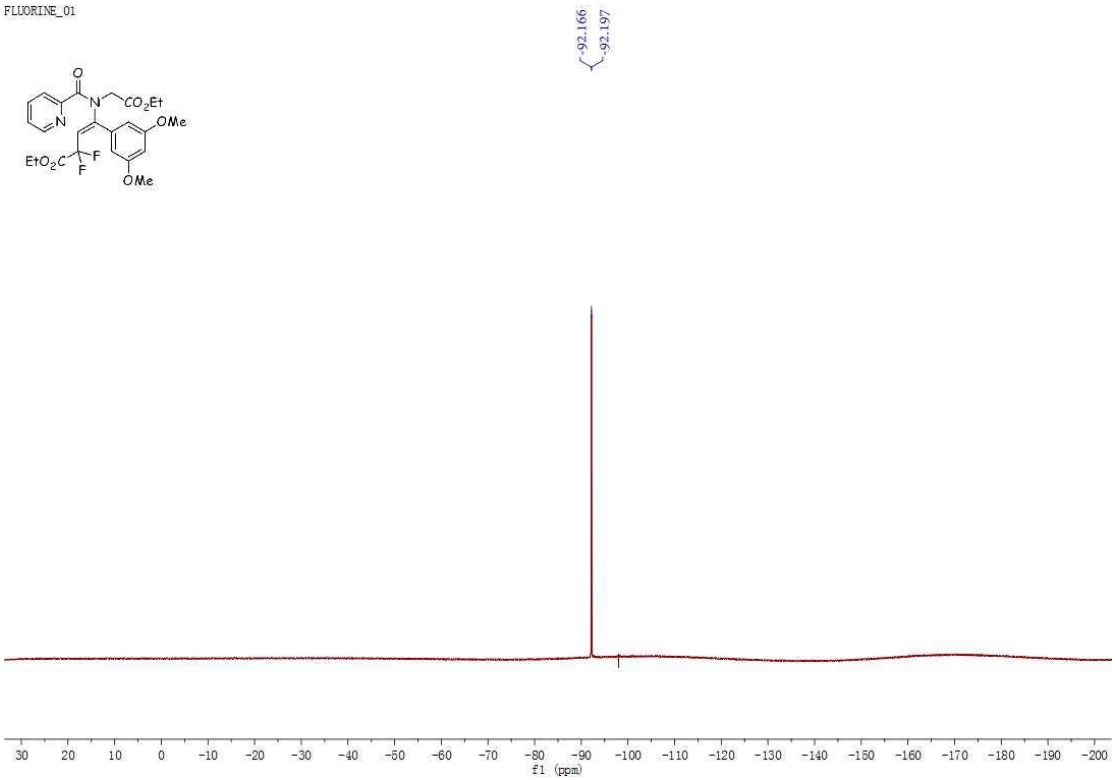
^{19}F – NMR spectrum of compound – **4z** (376 MHz, $CDCl_3$)



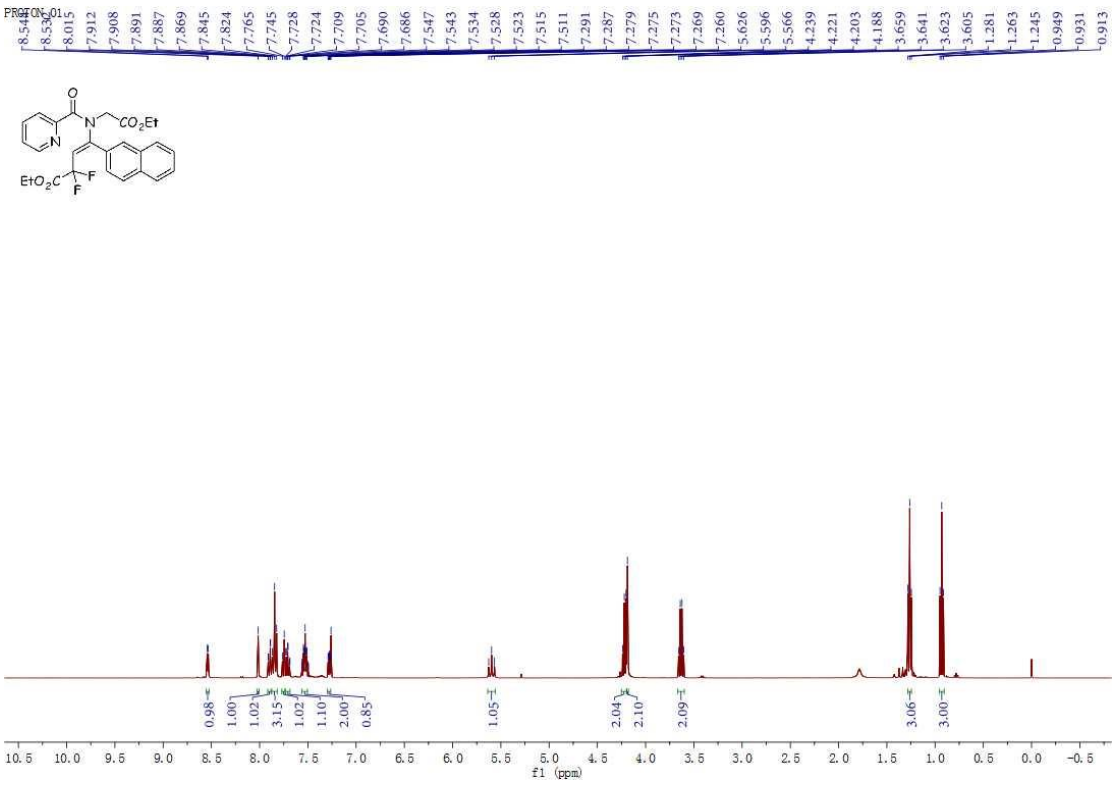
^{1}H – NMR spectrum of compound – **4aa** (400 MHz, $CDCl_3$)



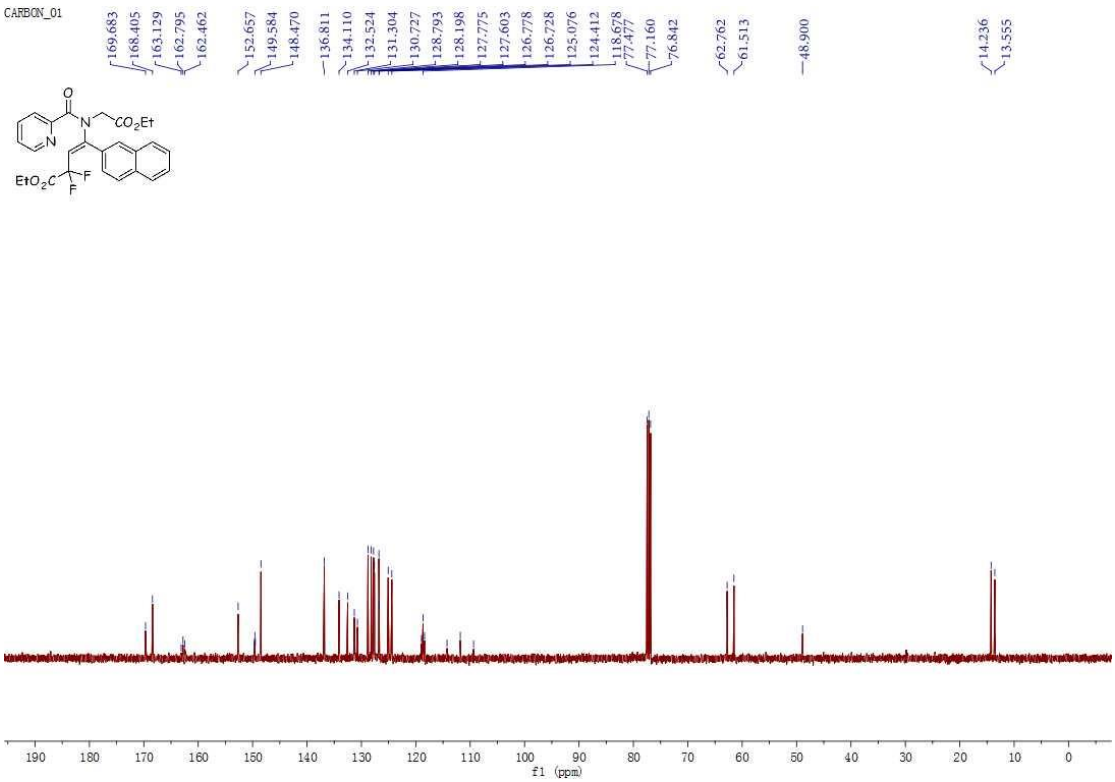
^{13}C – NMR spectrum of compound – **4aa** (100 MHz, $CDCl_3$)



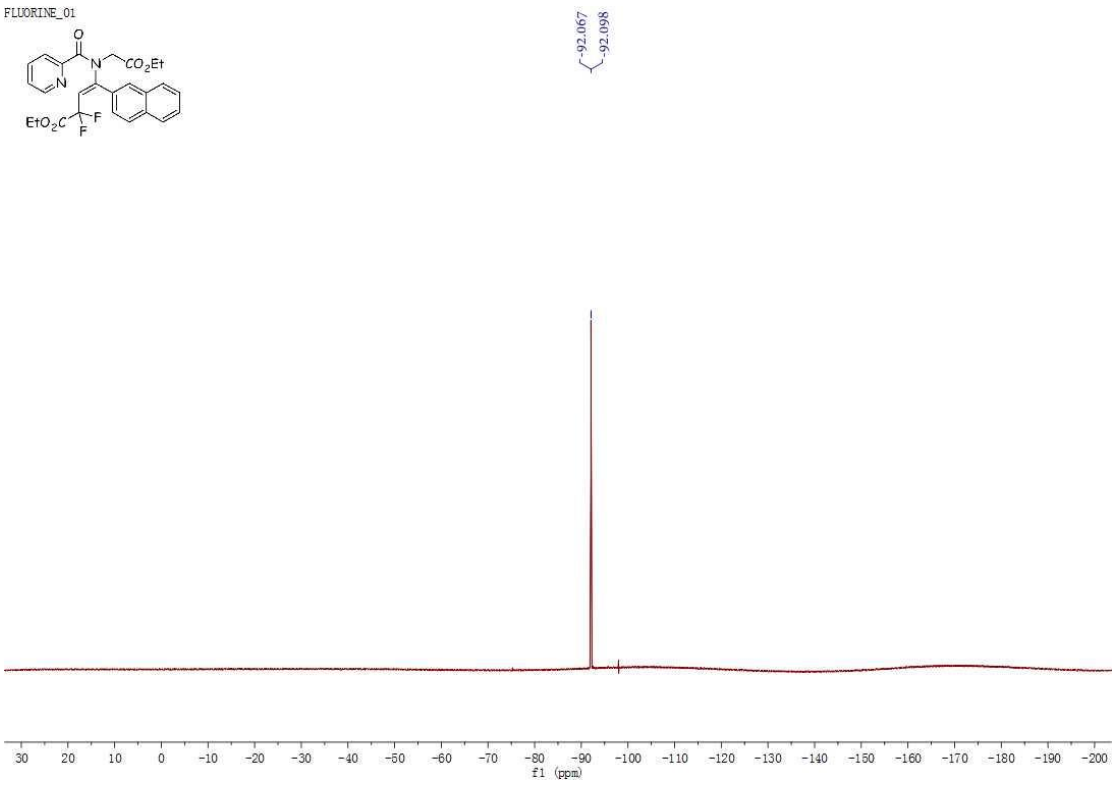
^{19}F – NMR spectrum of compound – **4aa** (376 MHz, $CDCl_3$)



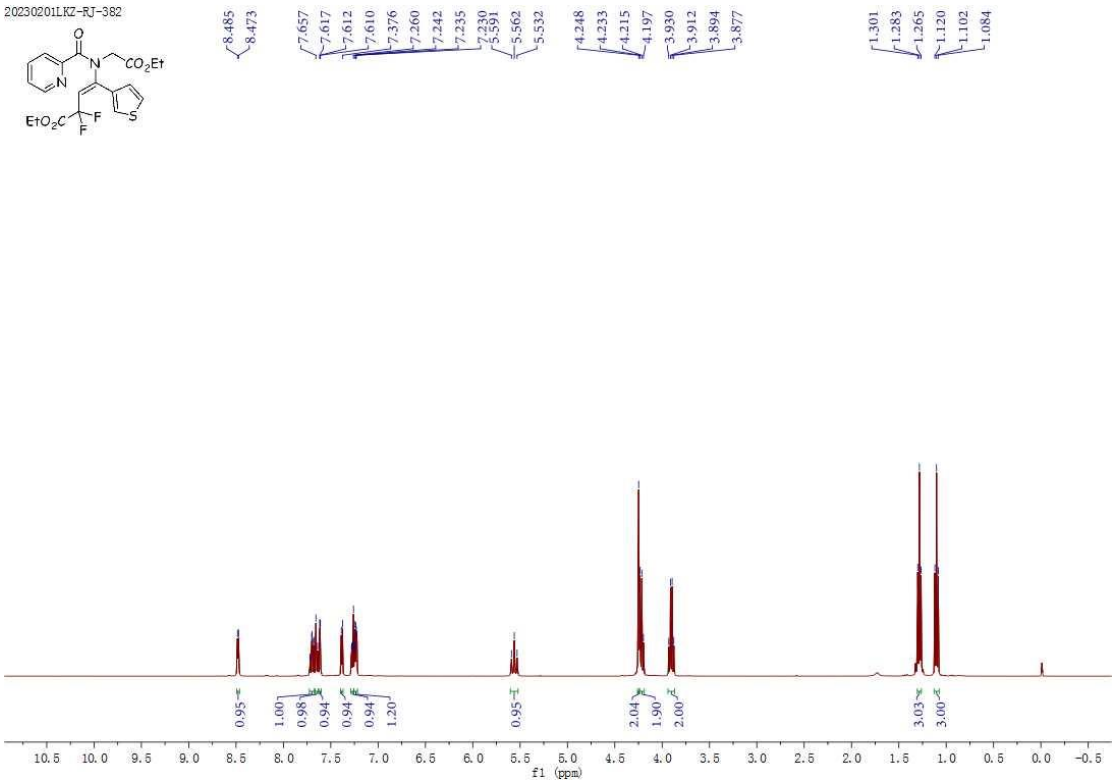
^{1}H – NMR spectrum of compound – **4ab** (400 MHz, $CDCl_3$)



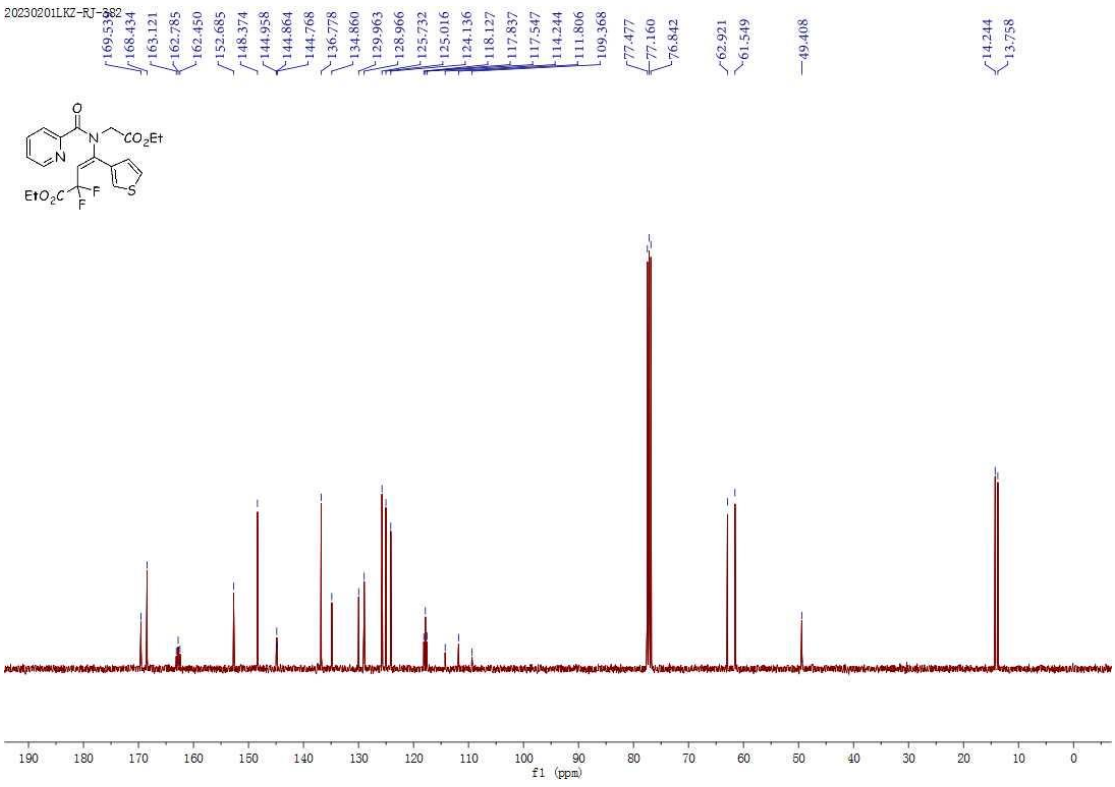
^{13}C – NMR spectrum of compound – **4ab** (100 MHz, $CDCl_3$)



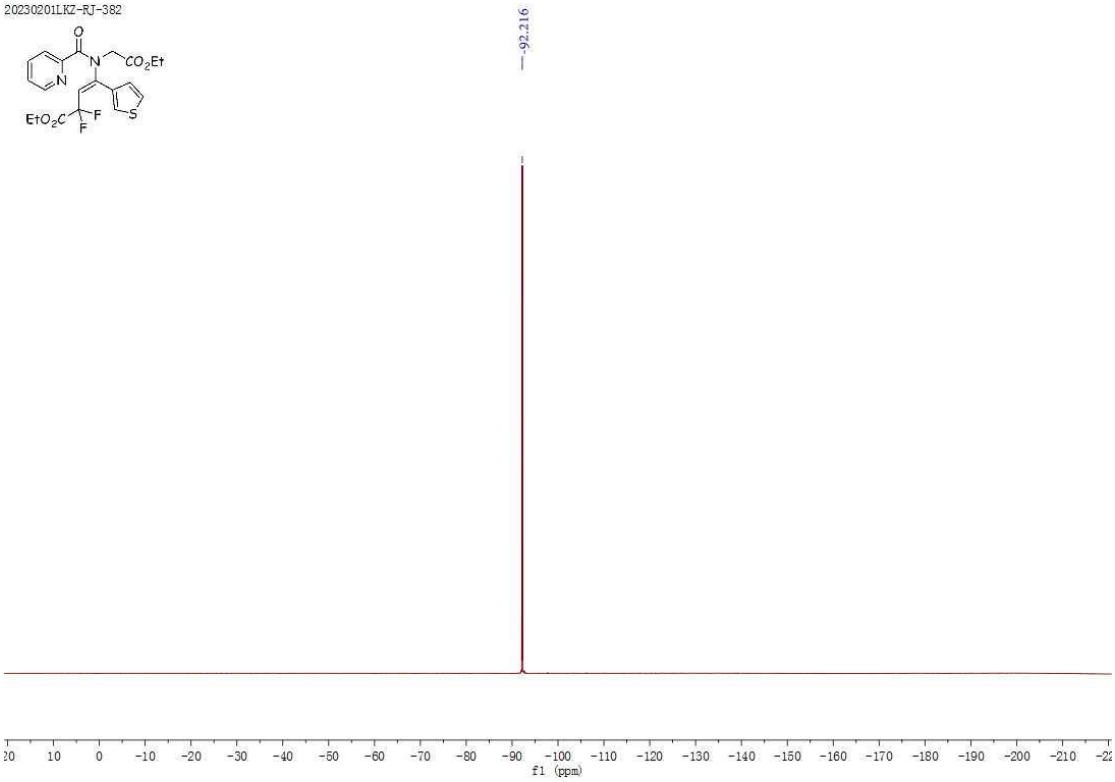
^{19}F – NMR spectrum of compound – **4ab** (376 MHz, $CDCl_3$)



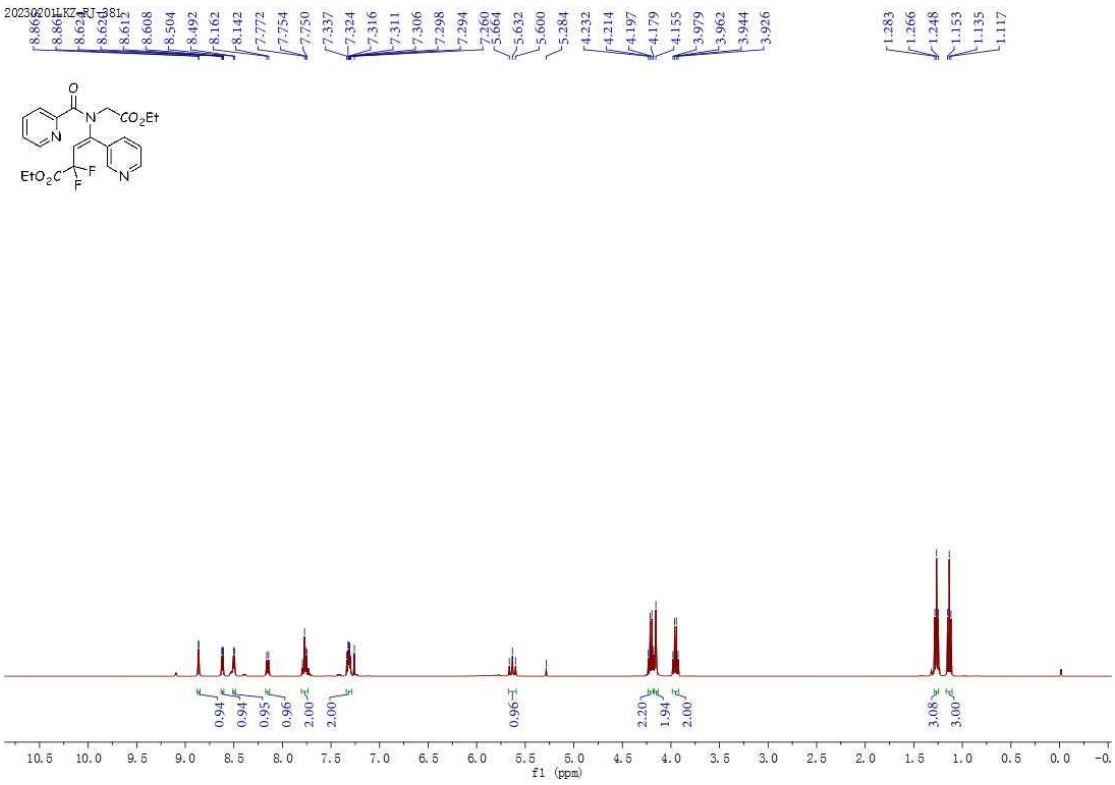
^{1}H – NMR spectrum of compound – **4ac** (400 MHz, $CDCl_3$)



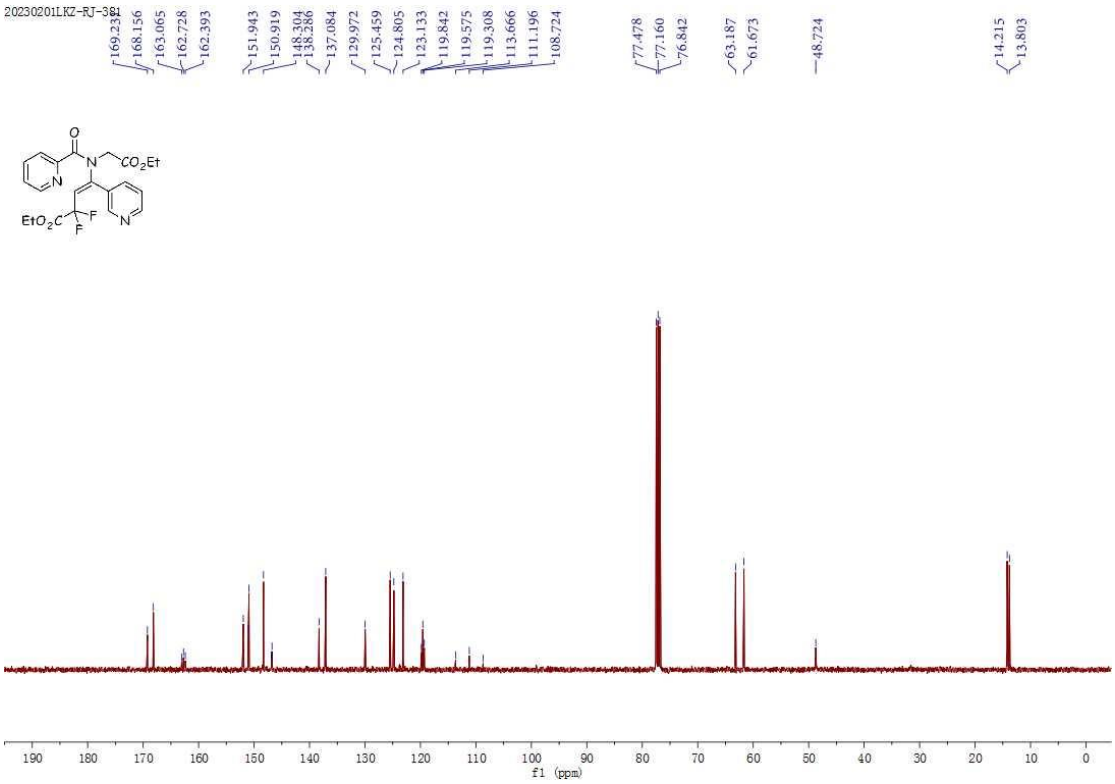
^{13}C – NMR spectrum of compound – **4ac** (100 MHz, $CDCl_3$)



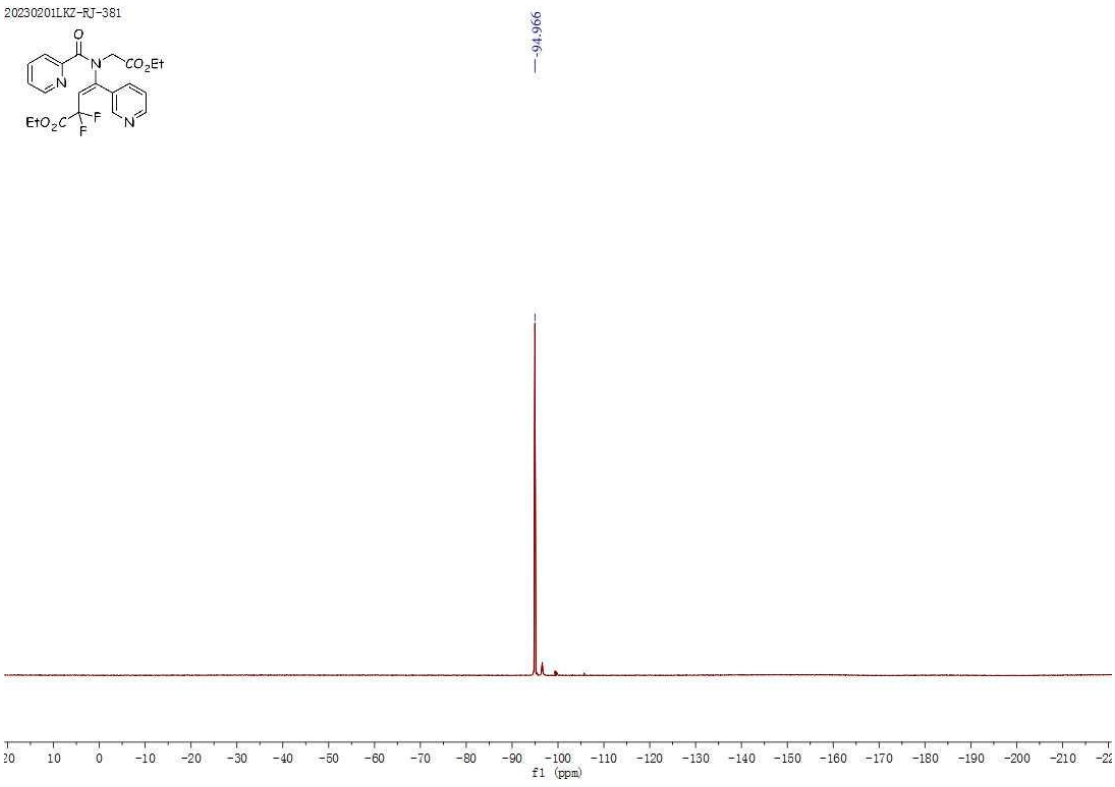
^{19}F – NMR spectrum of compound – **4ac** (376 MHz, $CDCl_3$)



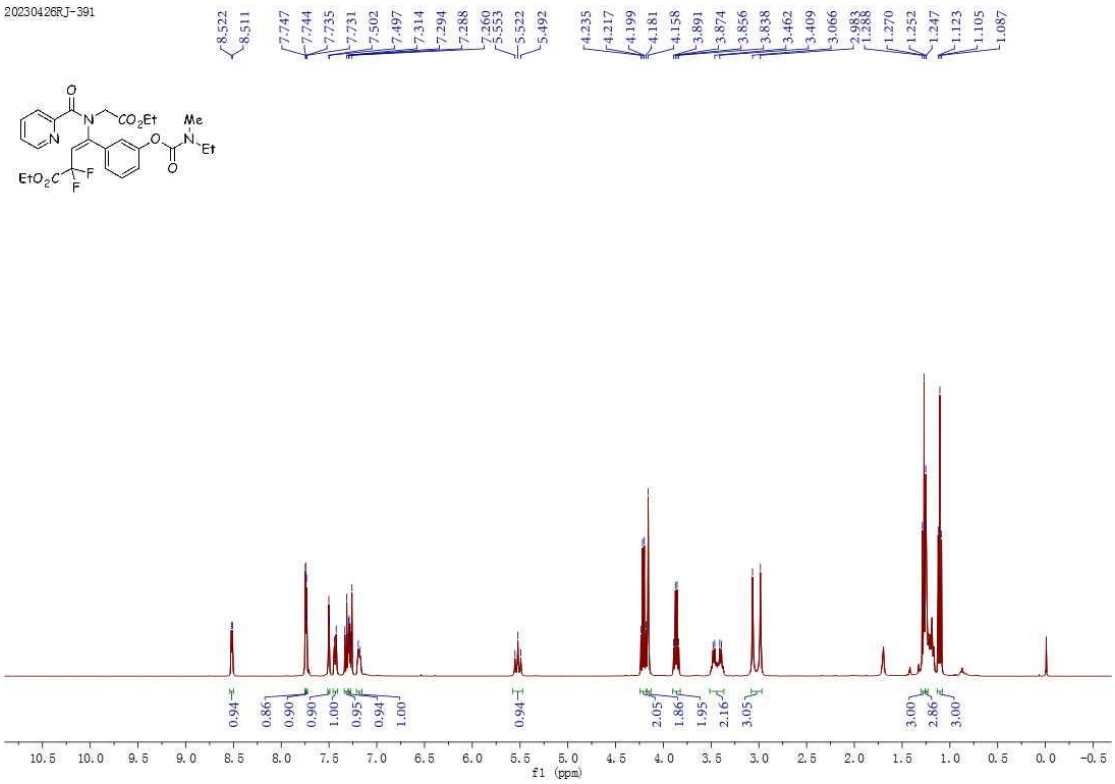
^{1}H – NMR spectrum of compound – **4ad** (400 MHz, $CDCl_3$)



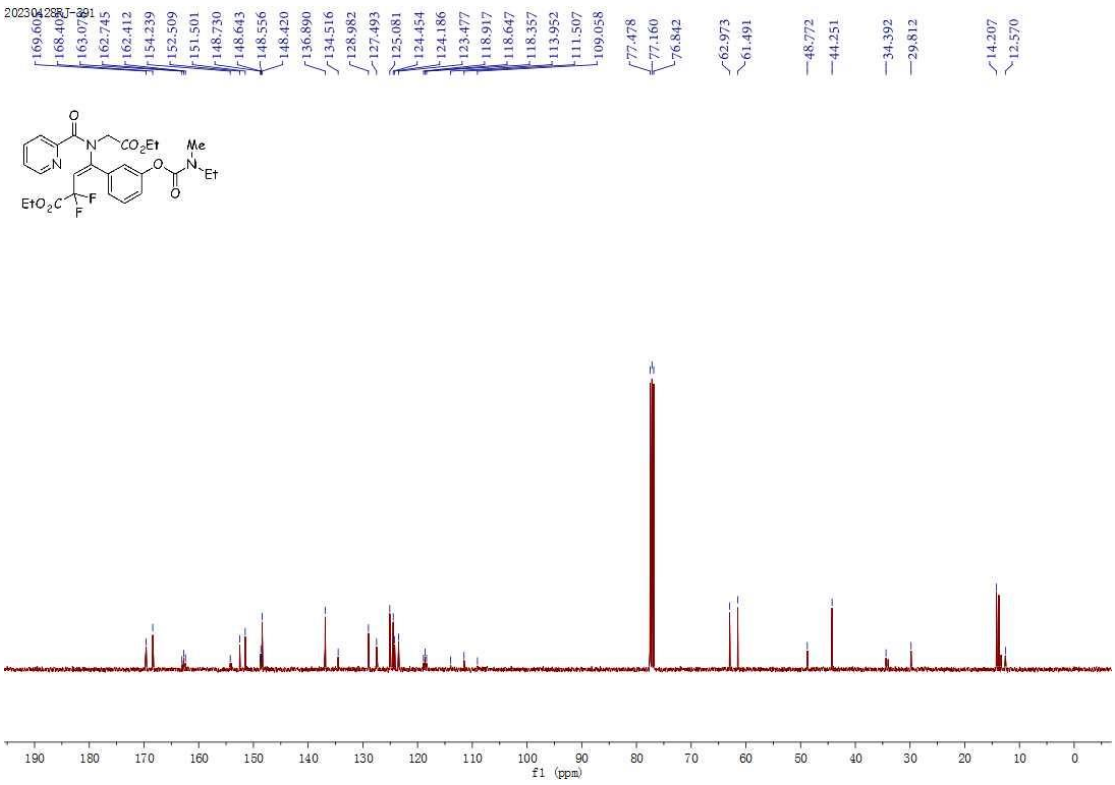
^{13}C – NMR spectrum of compound – **4ad** (100 MHz, $CDCl_3$)



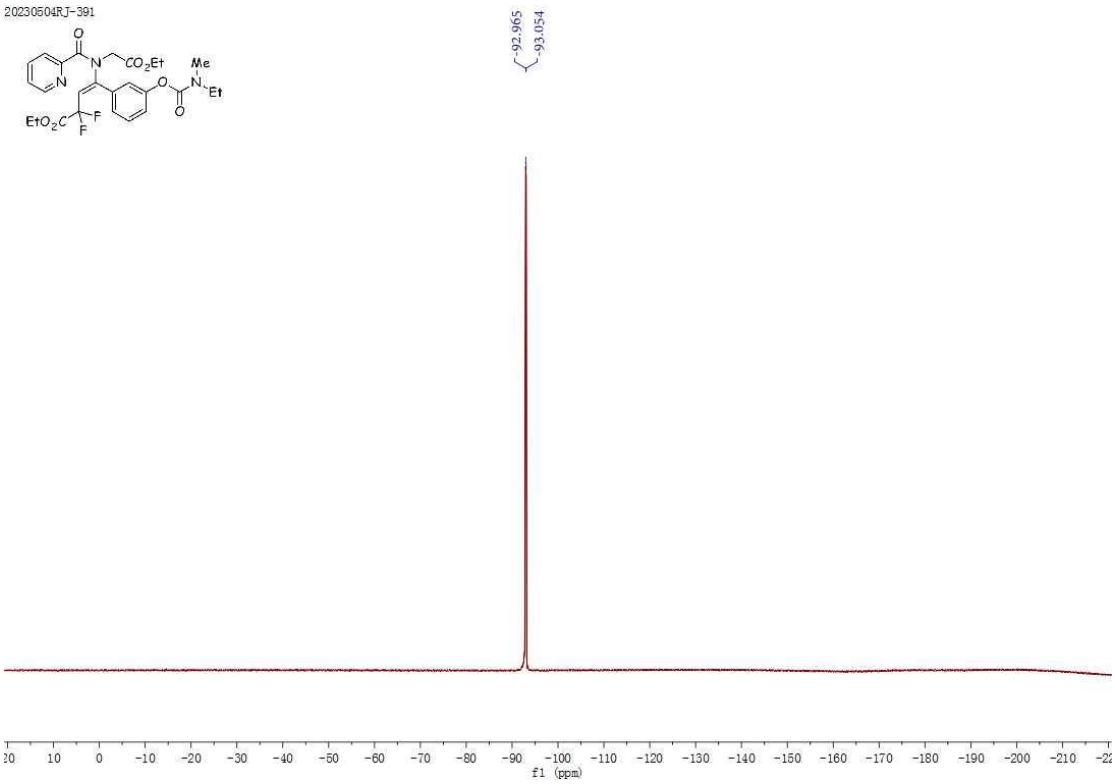
^{19}F – NMR spectrum of compound – **4ad** (376 MHz, $CDCl_3$)



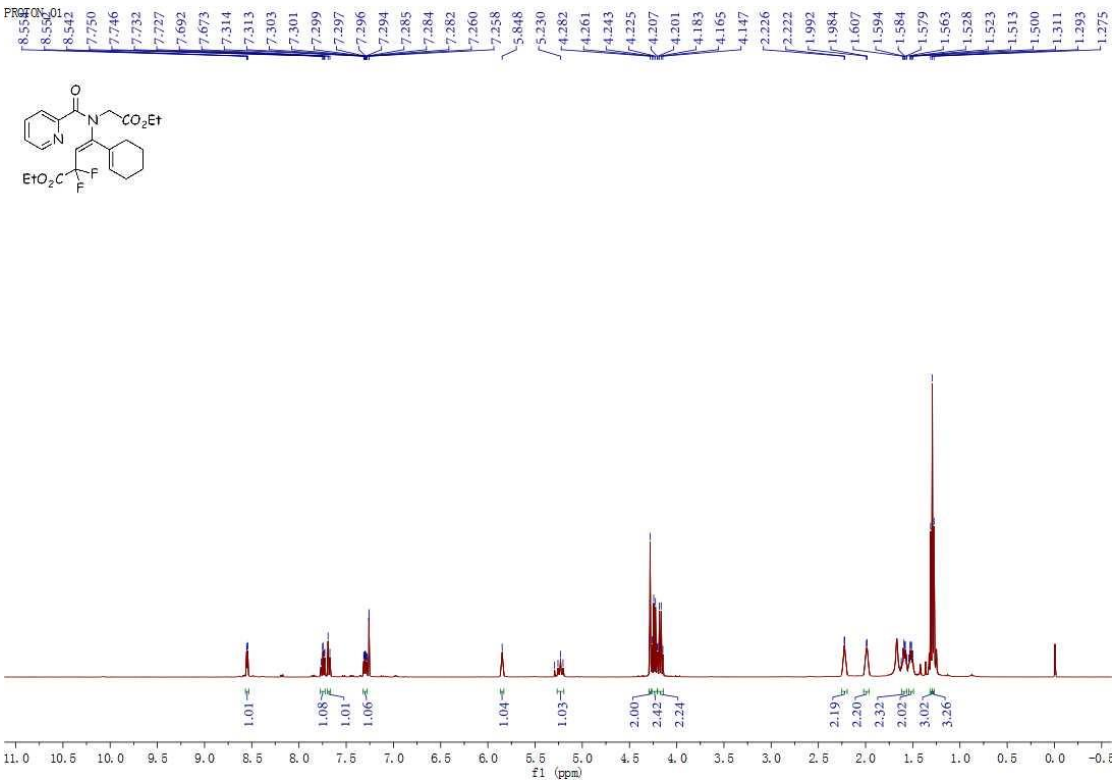
^{1}H – NMR spectrum of compound – **4ae** (400 MHz, $CDCl_3$)



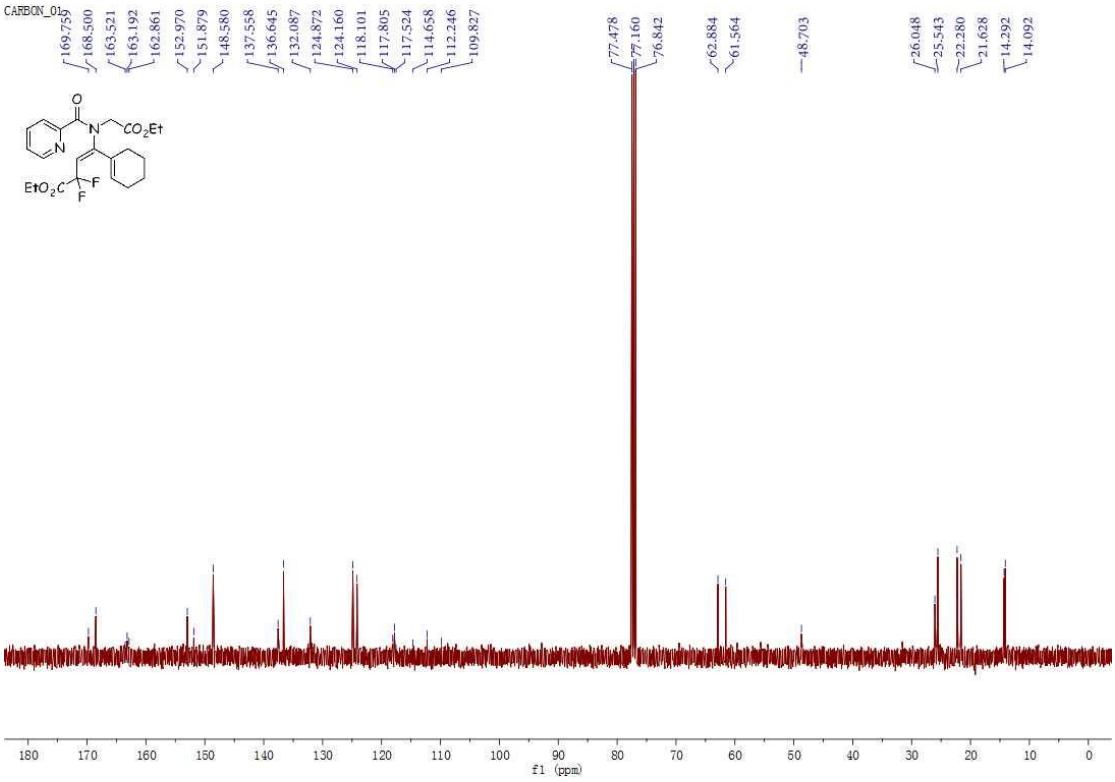
^{13}C – NMR spectrum of compound – **4ae** (100 MHz, $CDCl_3$)



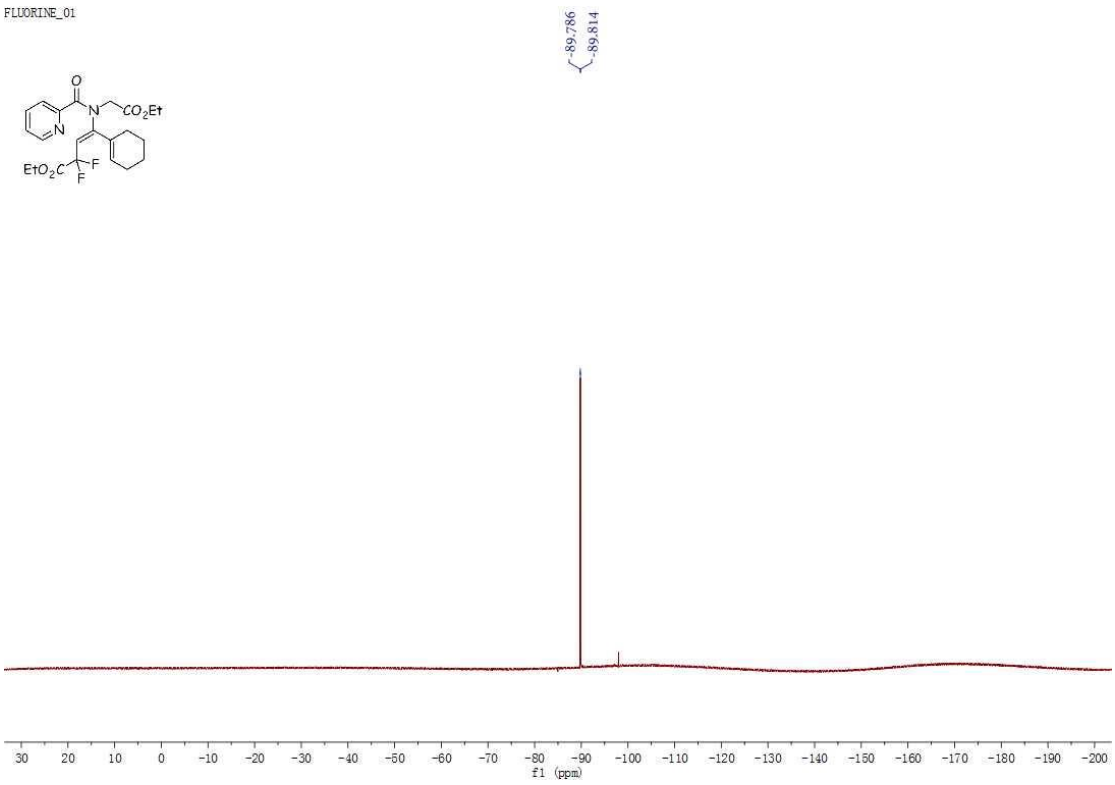
^{19}F – NMR spectrum of compound – **4ae** (376 MHz, $CDCl_3$)



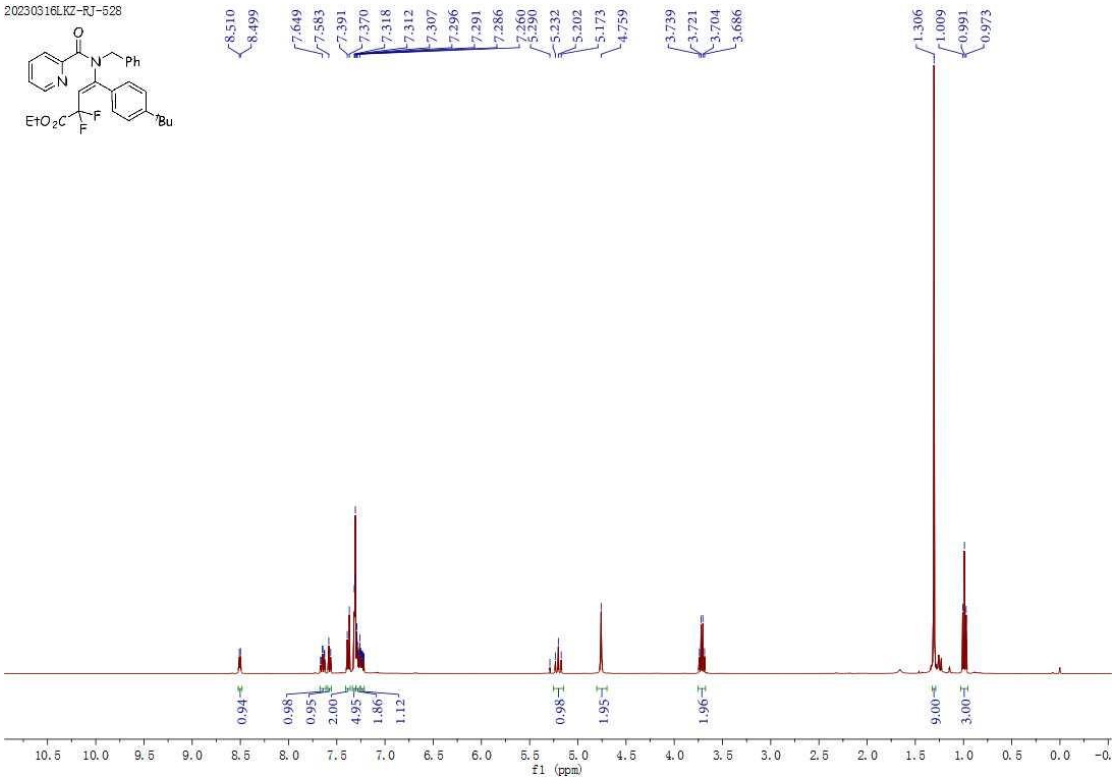
^{1}H – NMR spectrum of compound – **4af** (400 MHz, $CDCl_3$)



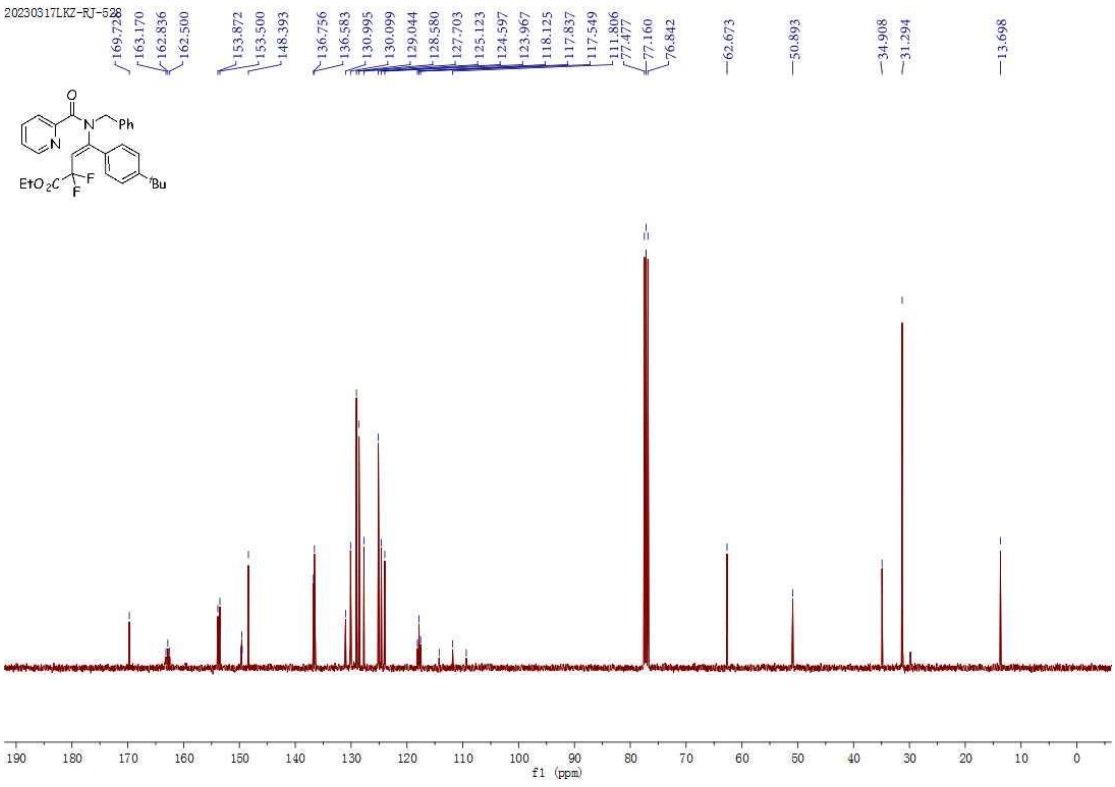
^{13}C – NMR spectrum of compound – **4af** (100 MHz, $CDCl_3$)



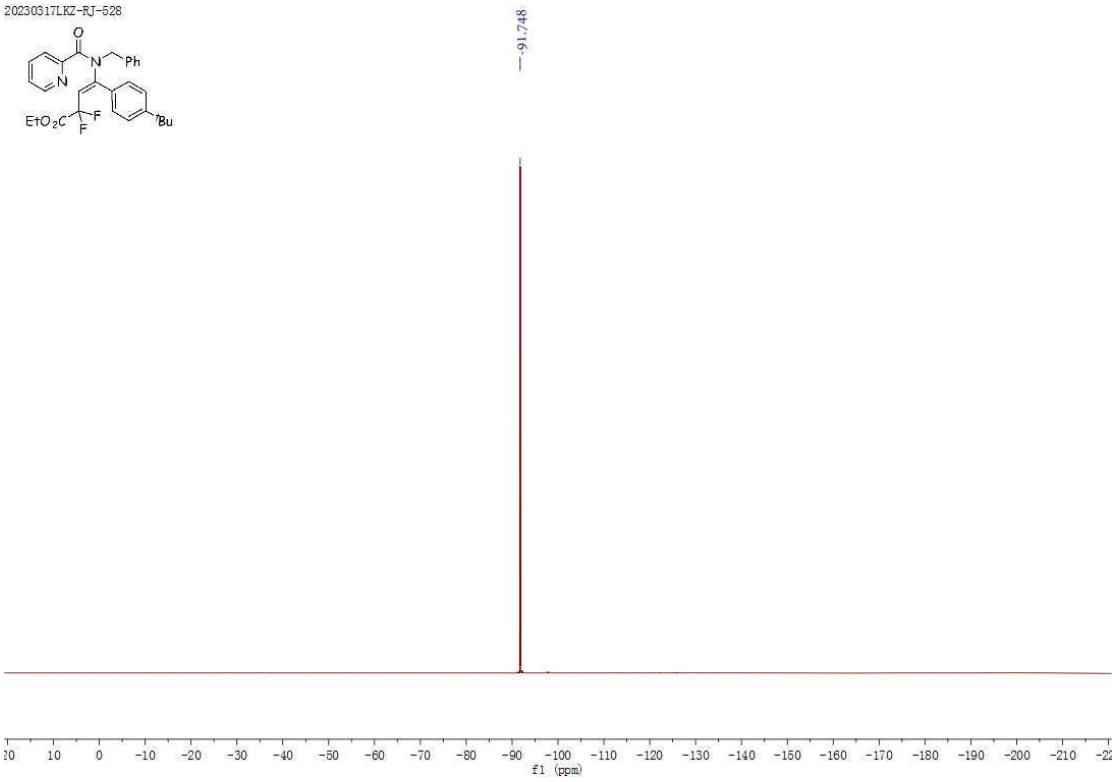
^{19}F – NMR spectrum of compound – **4af** (376 MHz, $CDCl_3$)



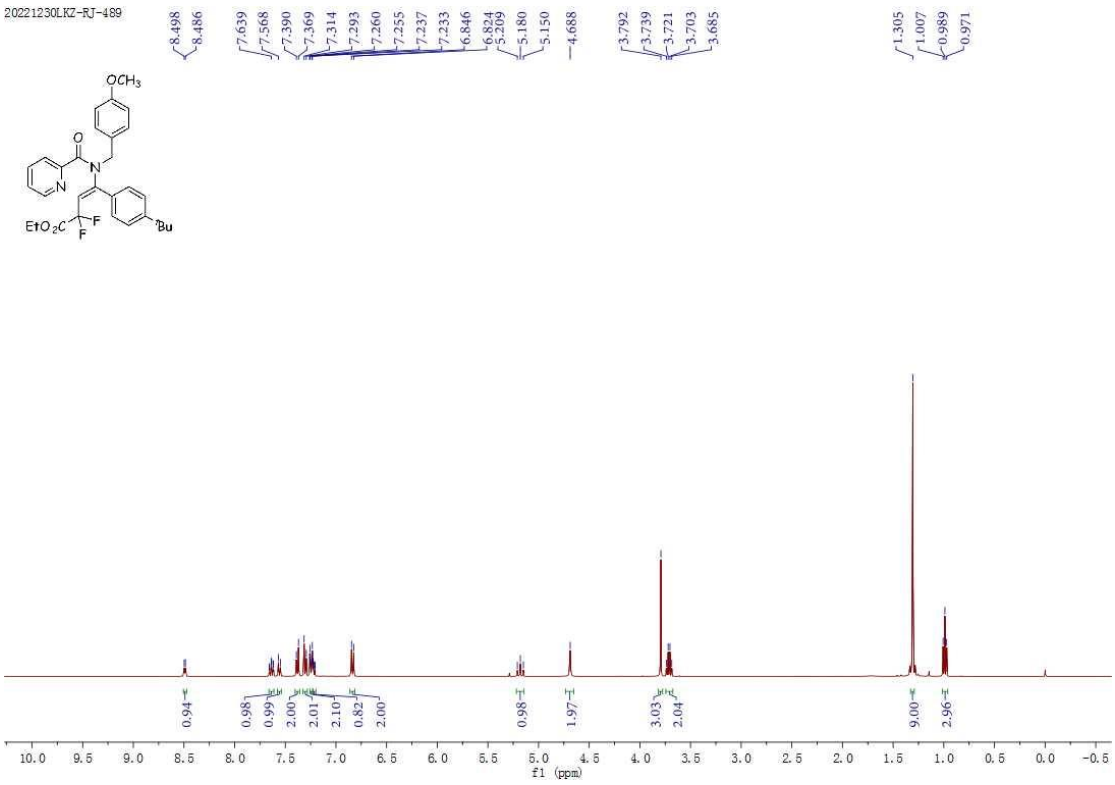
^{1}H – NMR spectrum of compound – **5a** (400 MHz, $CDCl_3$)



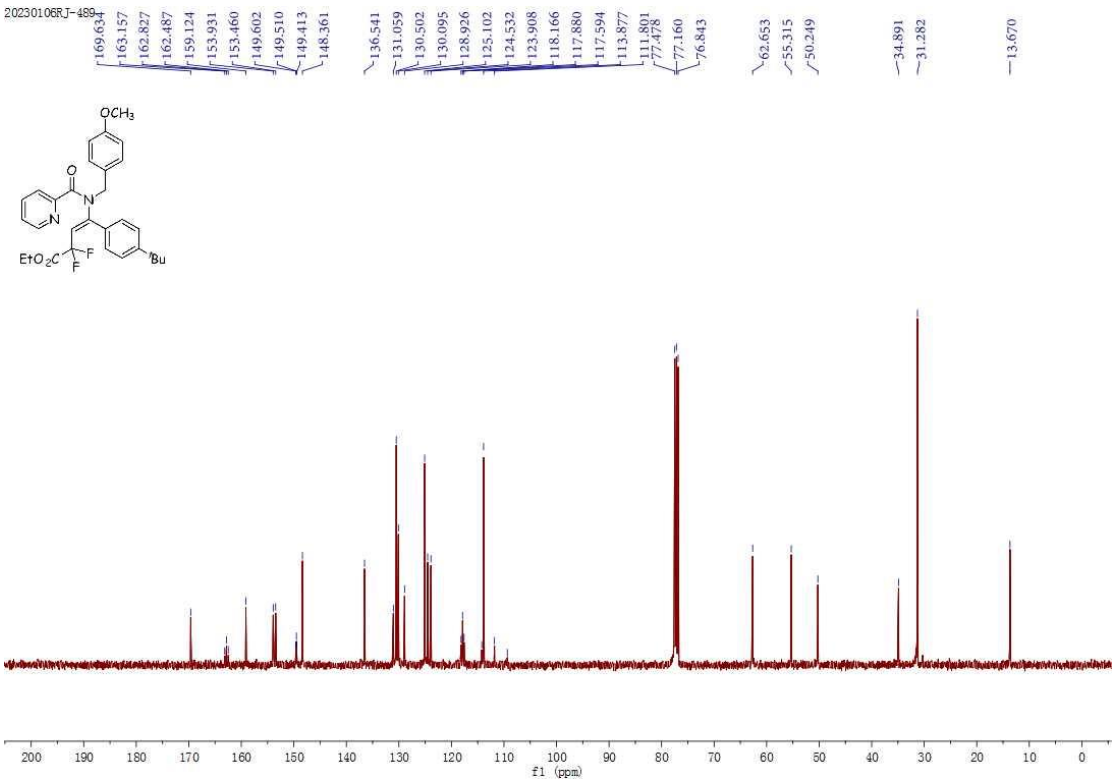
^{13}C – NMR spectrum of compound – **5a** (100 MHz, $CDCl_3$)



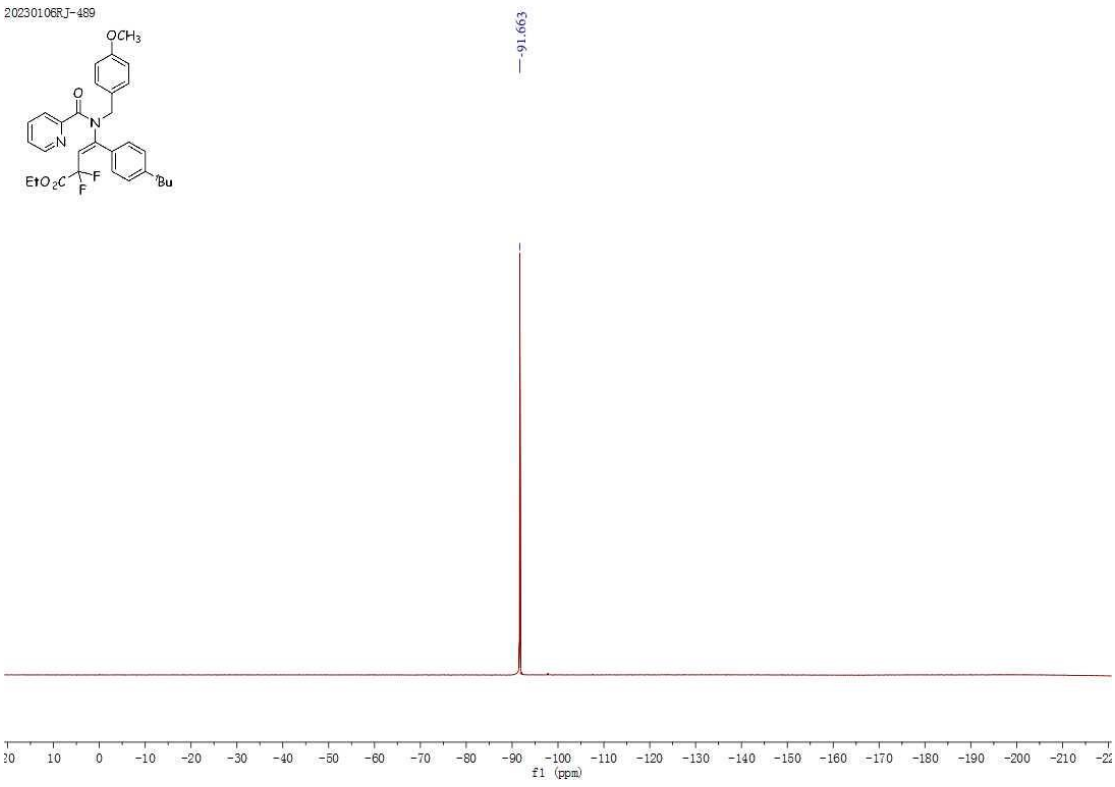
^{19}F – NMR spectrum of compound – **5a** (376 MHz, $CDCl_3$)



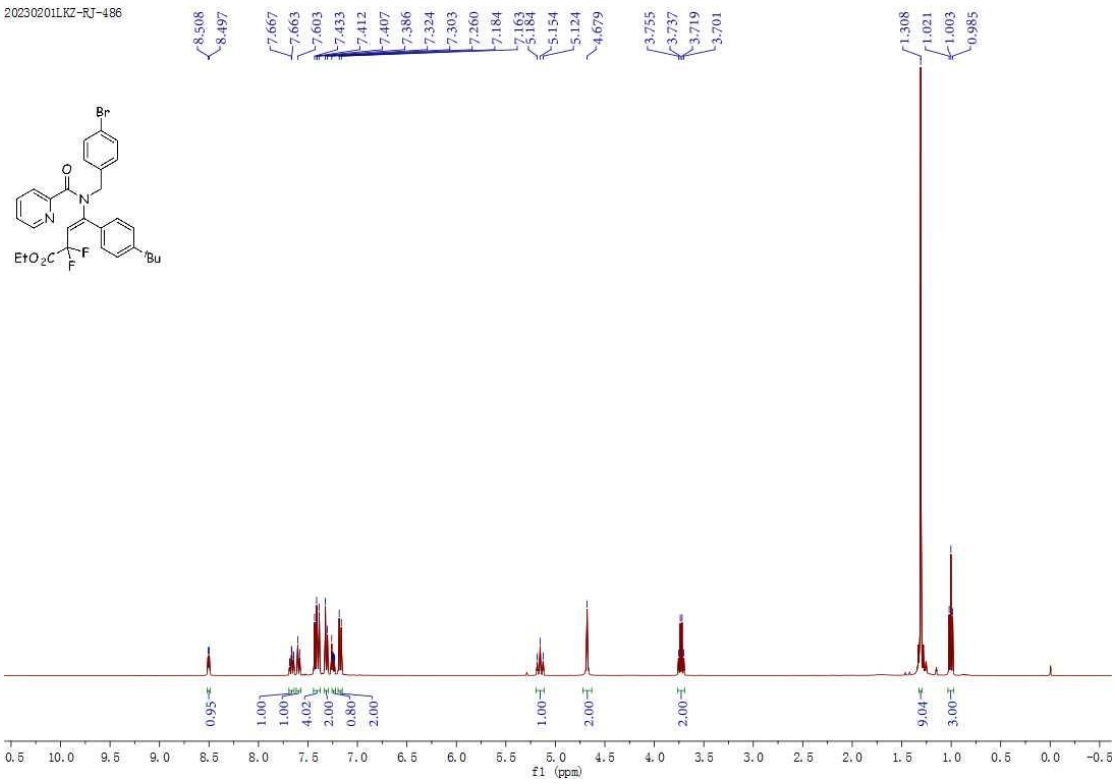
^{1}H – NMR spectrum of compound – **5b** (400 MHz, $CDCl_3$)



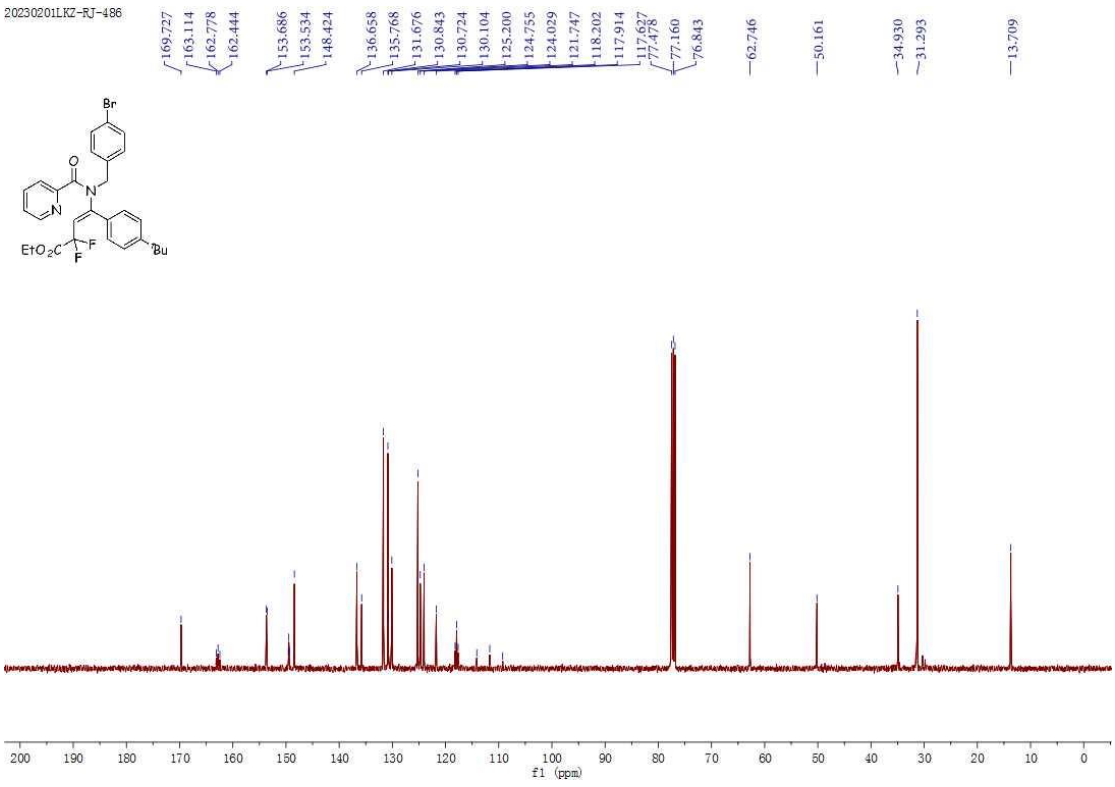
^{13}C – NMR spectrum of compound – **5b** (100 MHz, $CDCl_3$)



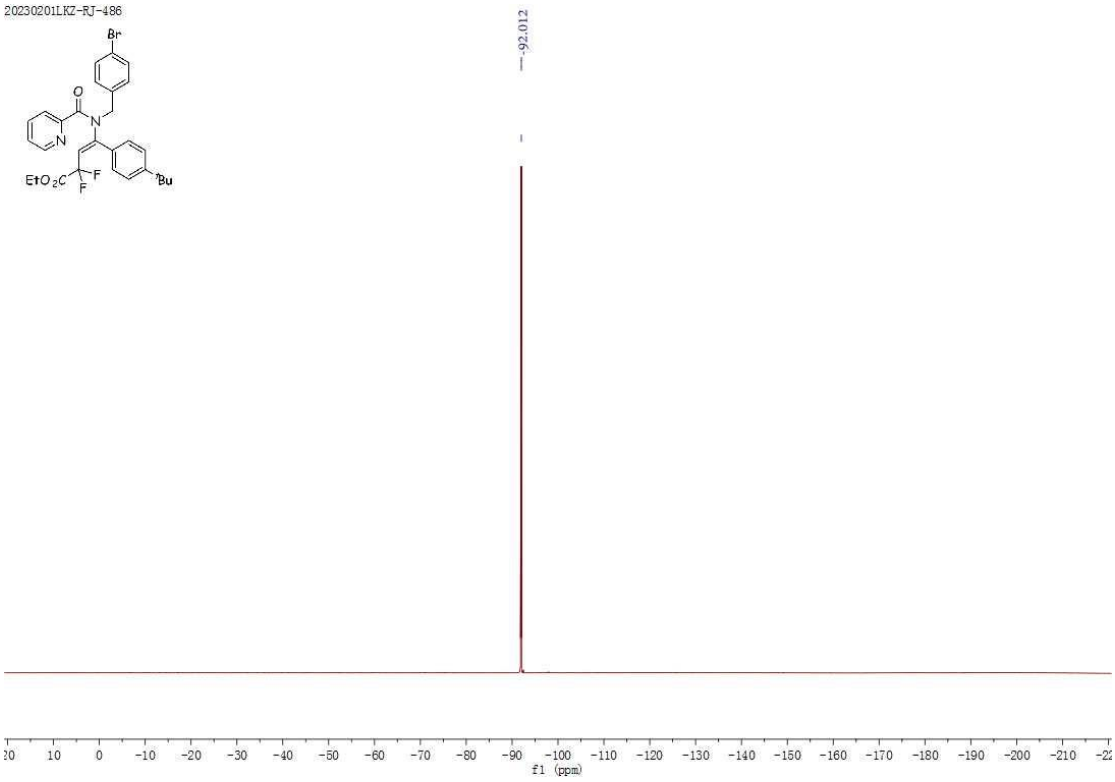
^{19}F – NMR spectrum of compound – **5b** (376 MHz, $CDCl_3$)



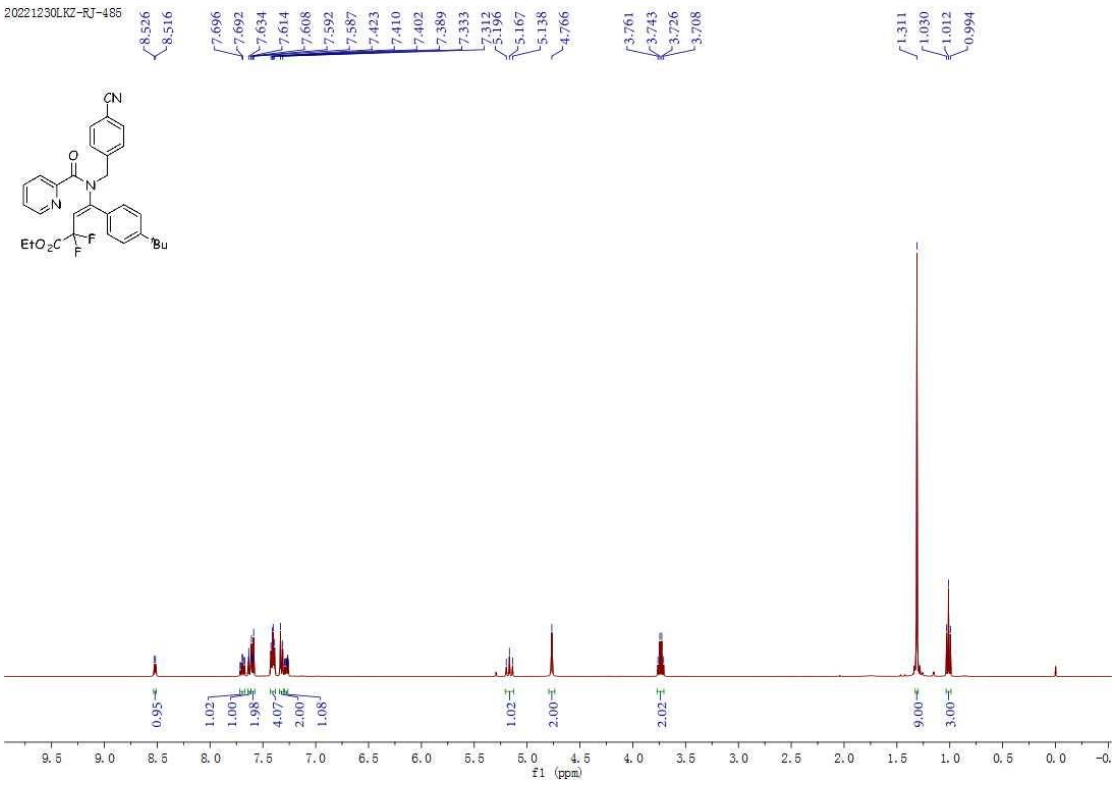
^{1}H – NMR spectrum of compound – **5c** (400 MHz, $CDCl_3$)



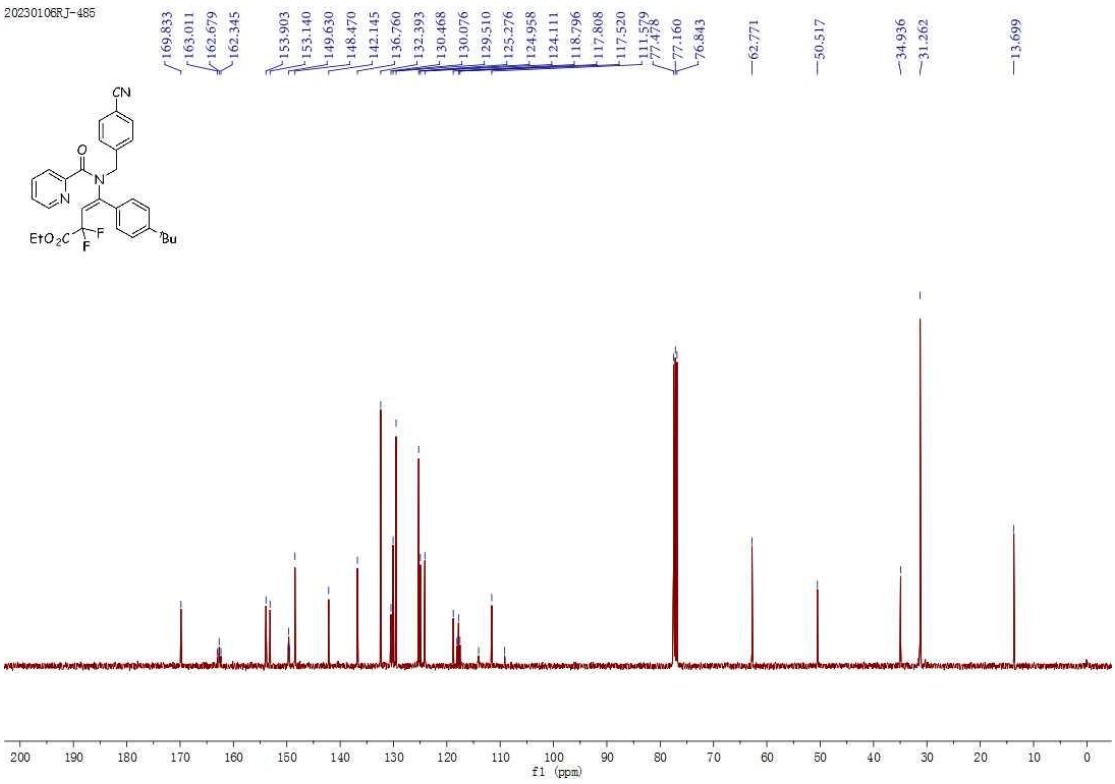
^{13}C – NMR spectrum of compound – **5c** (100 MHz, $CDCl_3$)



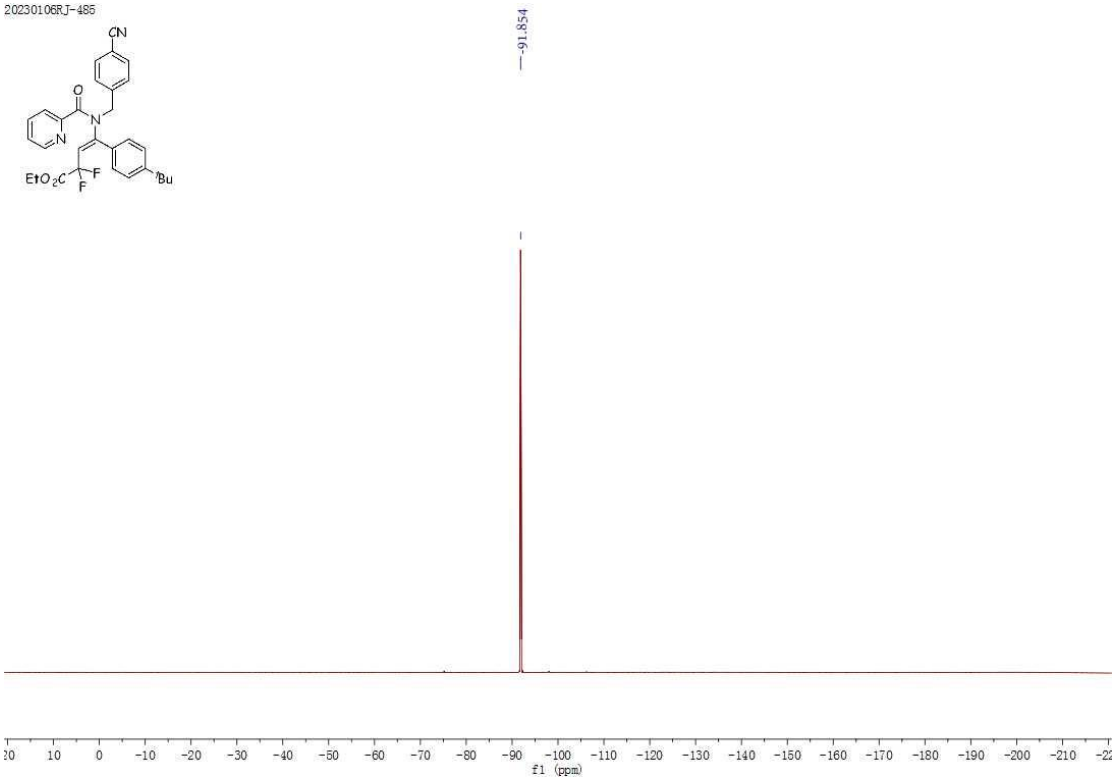
^{19}F – NMR spectrum of compound – **5c** (376 MHz, $CDCl_3$)



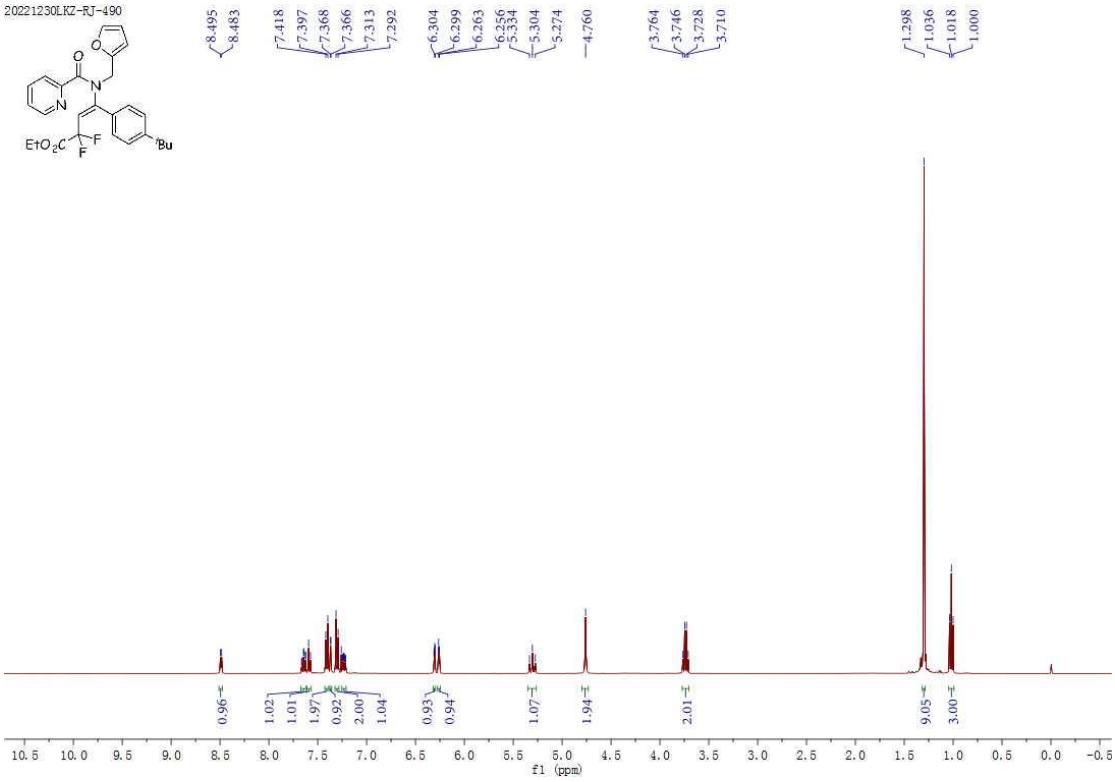
^{1}H – NMR spectrum of compound – **5d** (400 MHz, $CDCl_3$)



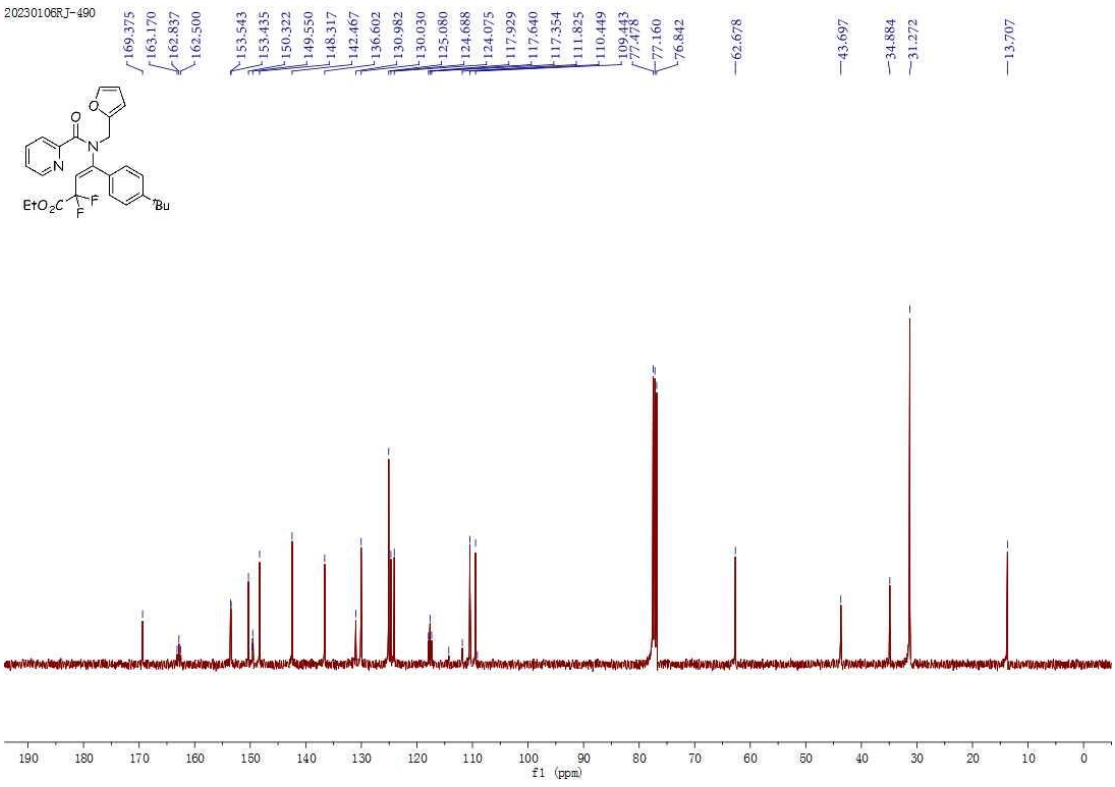
^{13}C – NMR spectrum of compound – **5d** (100 MHz, $CDCl_3$)



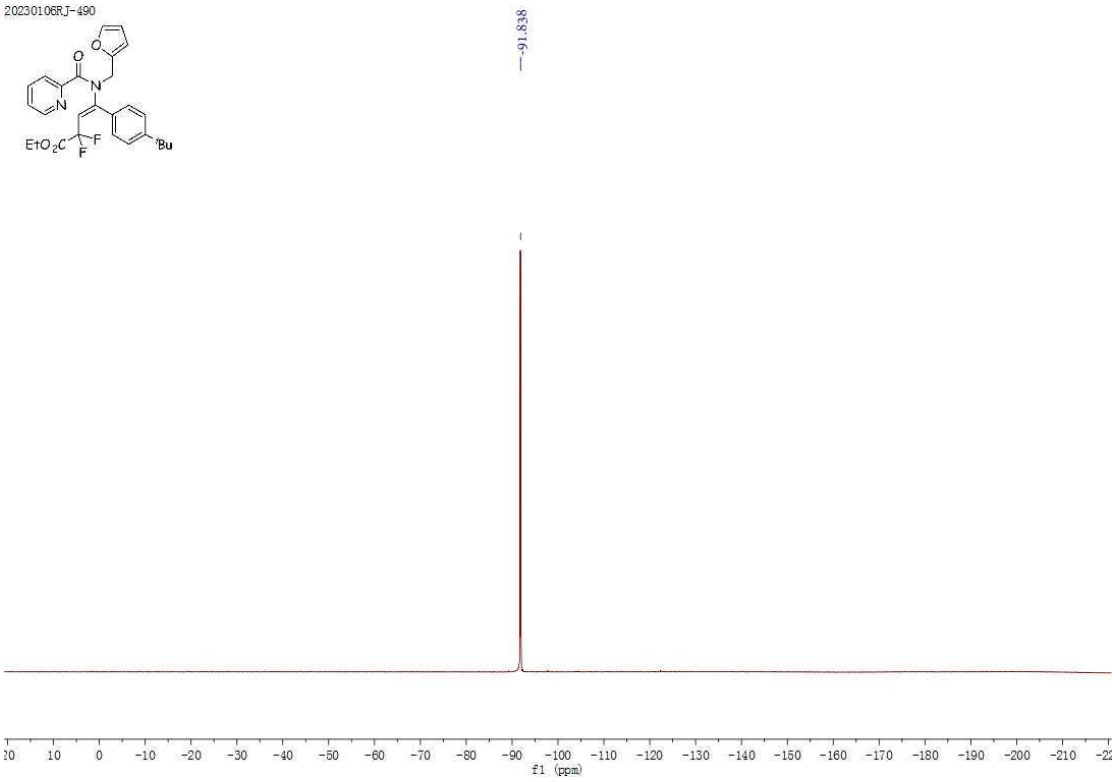
^{19}F – NMR spectrum of compound – **5d** (376 MHz, $CDCl_3$)



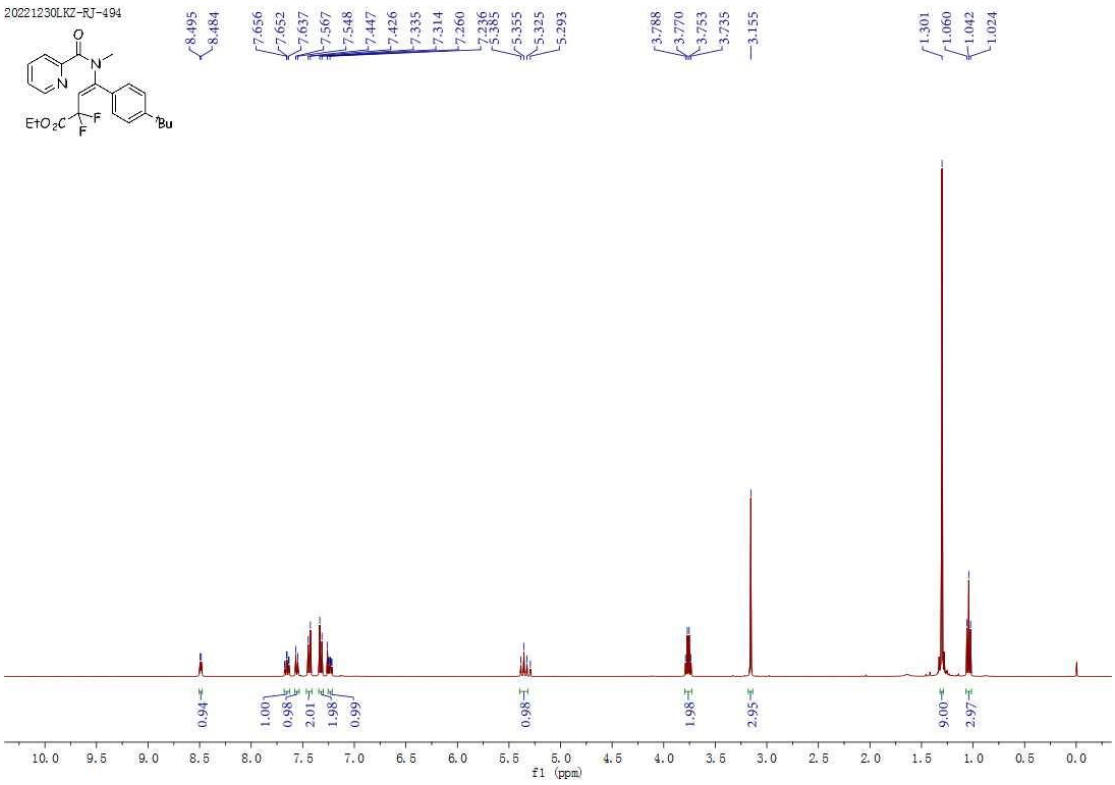
^{1}H – NMR spectrum of compound – **5e** (400 MHz, $CDCl_3$)



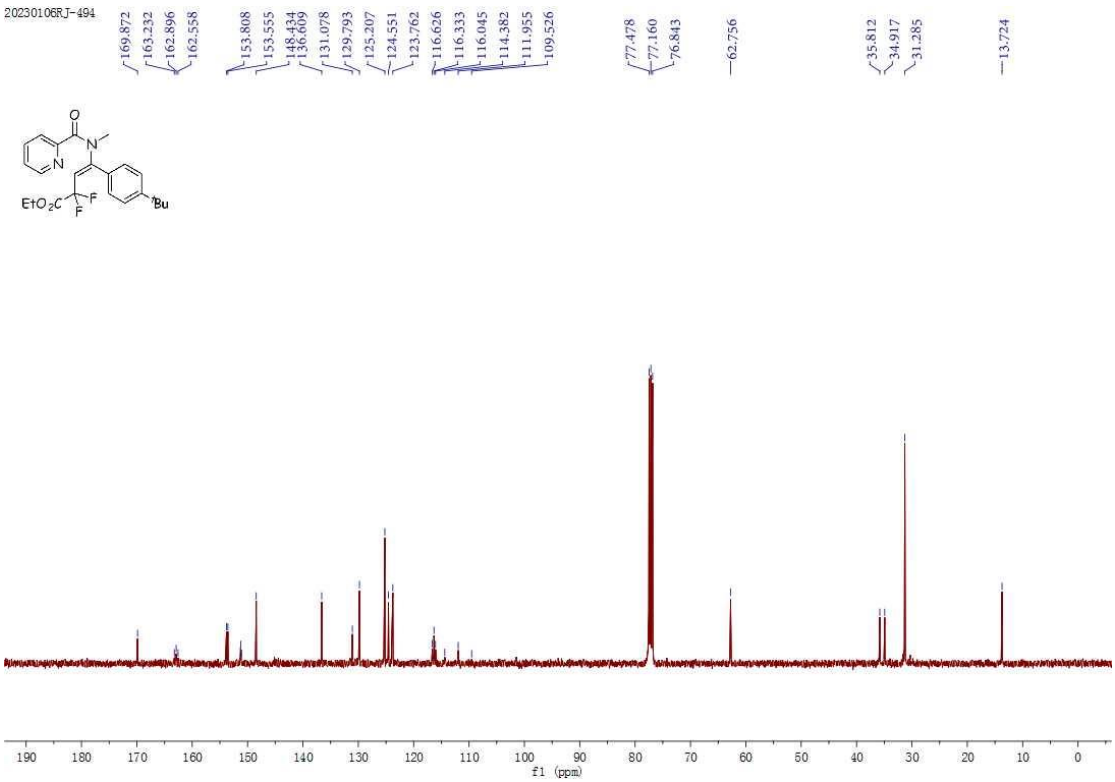
^{13}C – NMR spectrum of compound – **5e** (100 MHz, $CDCl_3$)



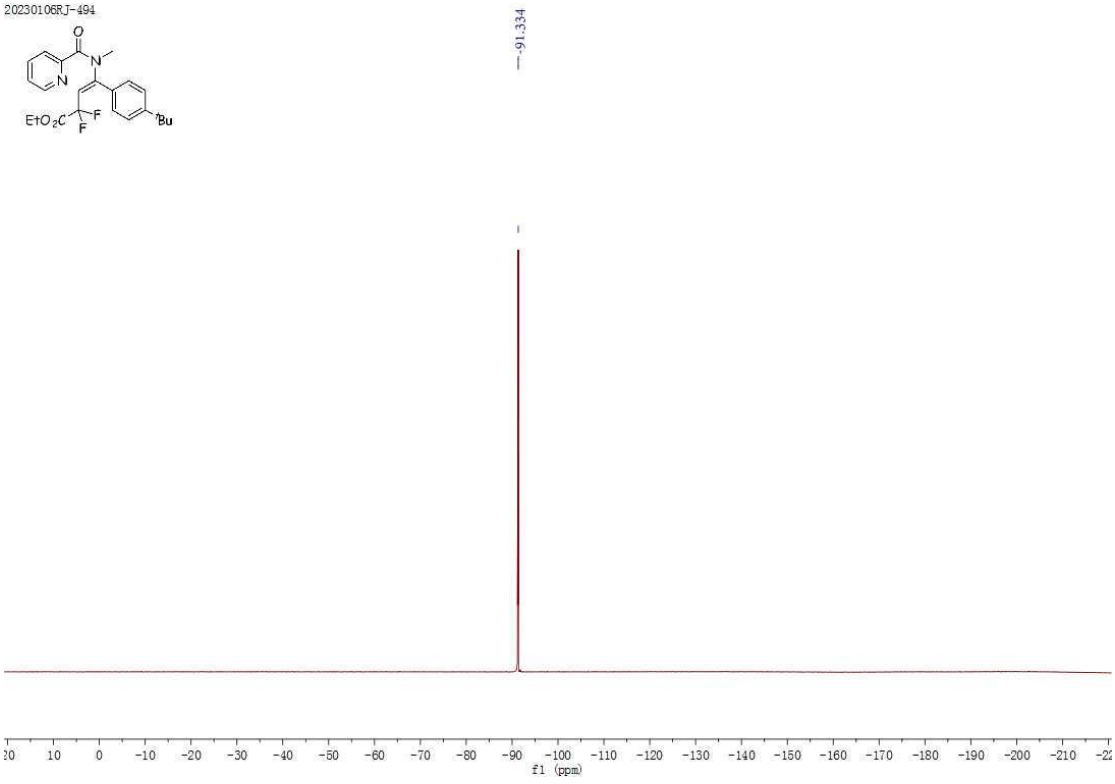
^{19}F – NMR spectrum of compound – **5e** (376 MHz, $CDCl_3$)



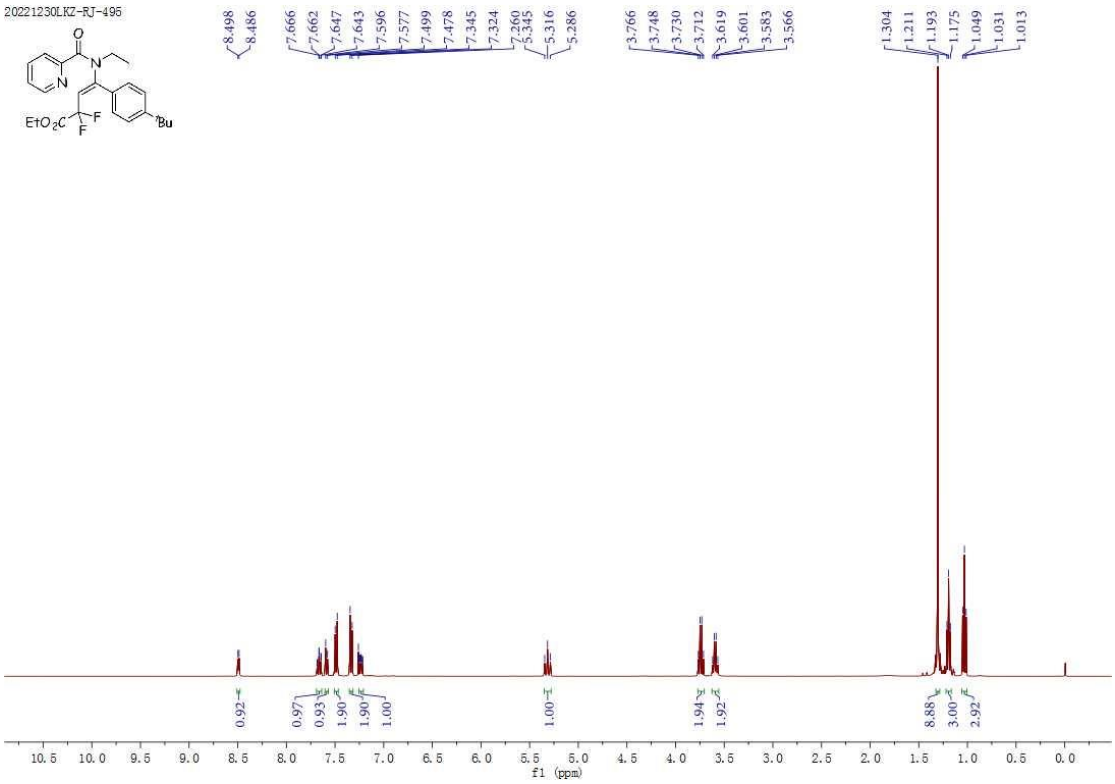
^{1}H – NMR spectrum of compound – **5f** (400 MHz, $CDCl_3$)



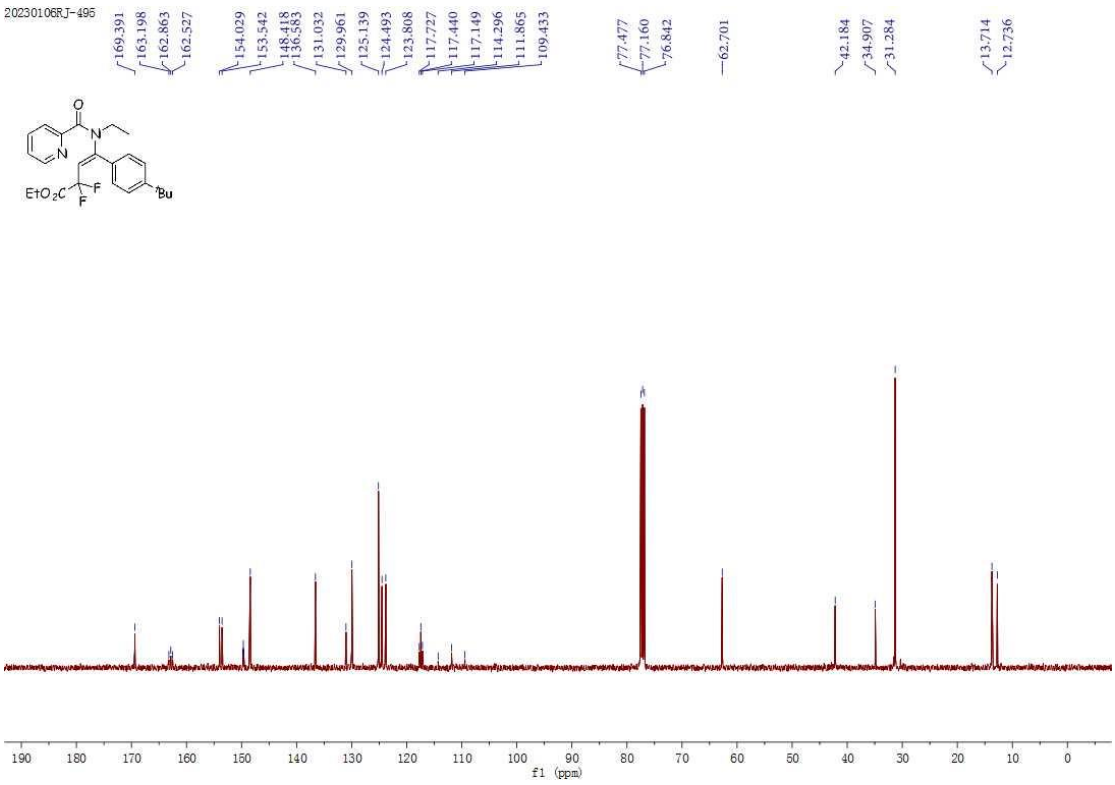
^{13}C – NMR spectrum of compound – **5f** (100 MHz, $CDCl_3$)



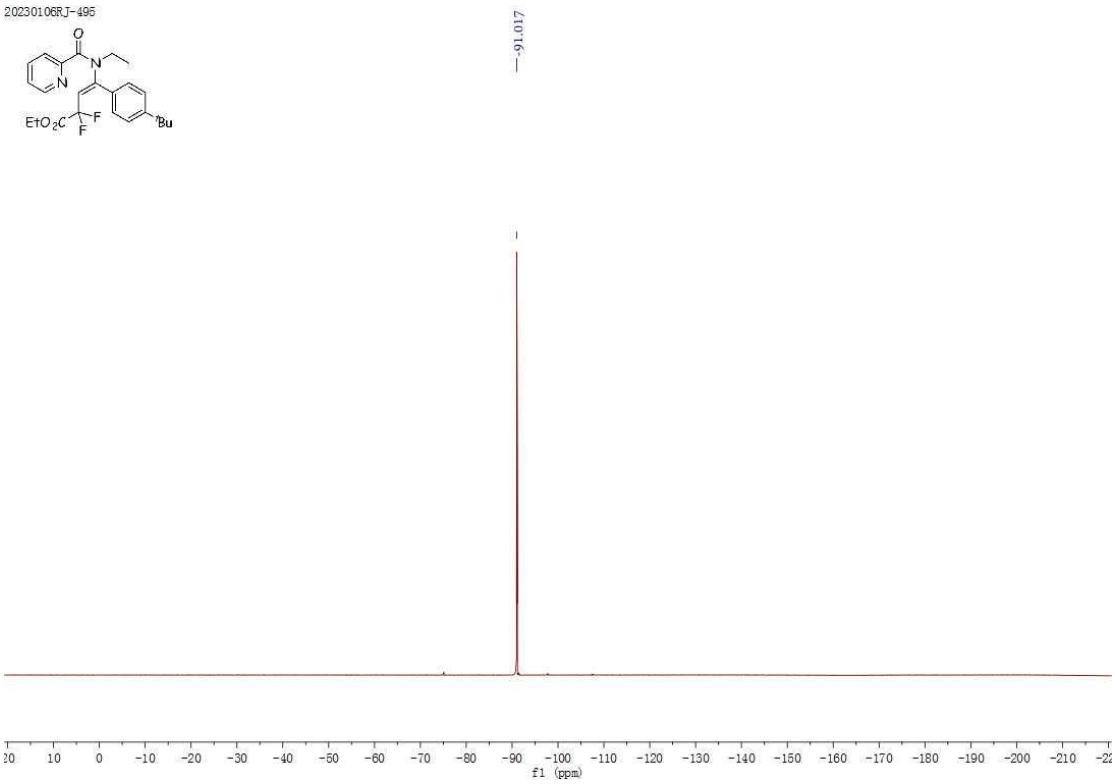
^{19}F – NMR spectrum of compound – **5f** (376 MHz, $CDCl_3$)



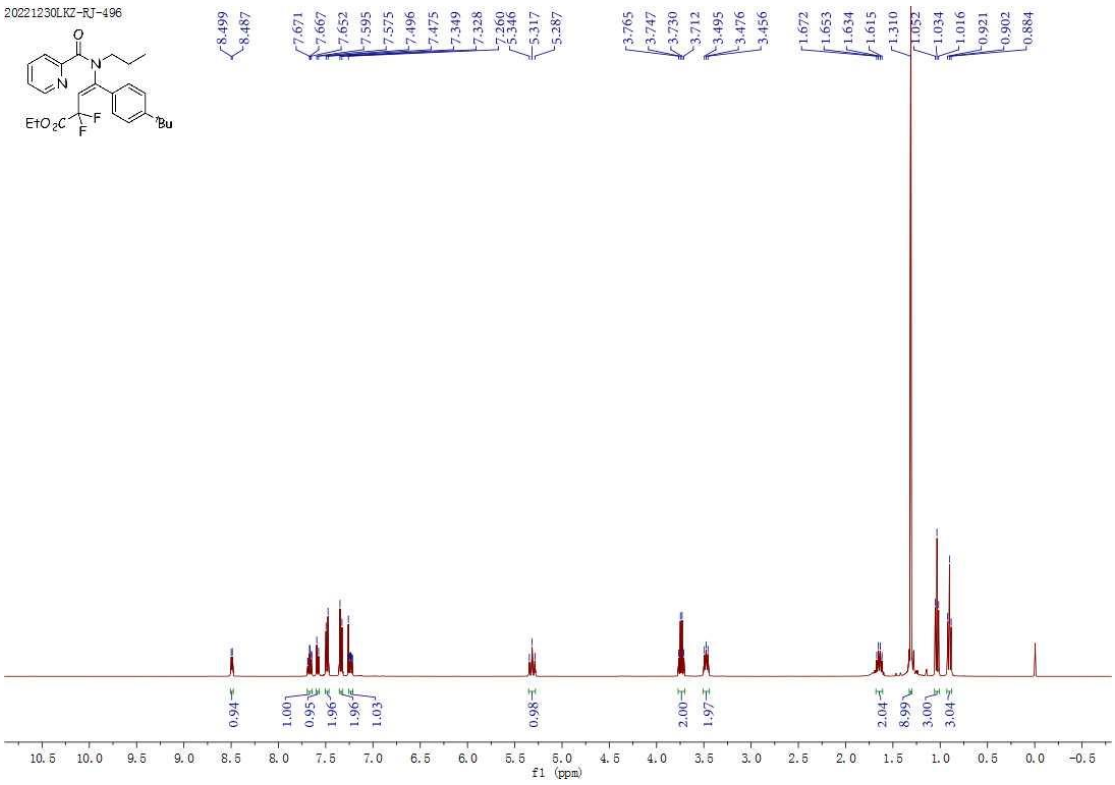
^{1}H – NMR spectrum of compound – **5g** (400 MHz, $CDCl_3$)



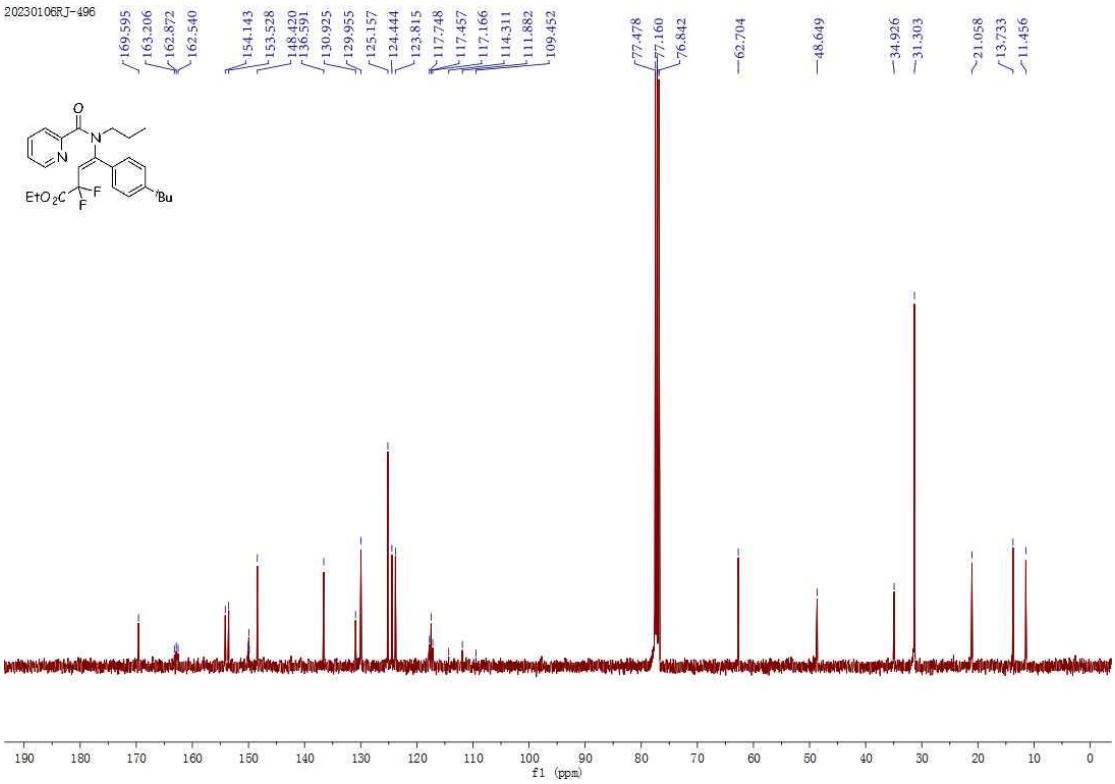
^{13}C – NMR spectrum of compound – **5g** (100 MHz, $CDCl_3$)



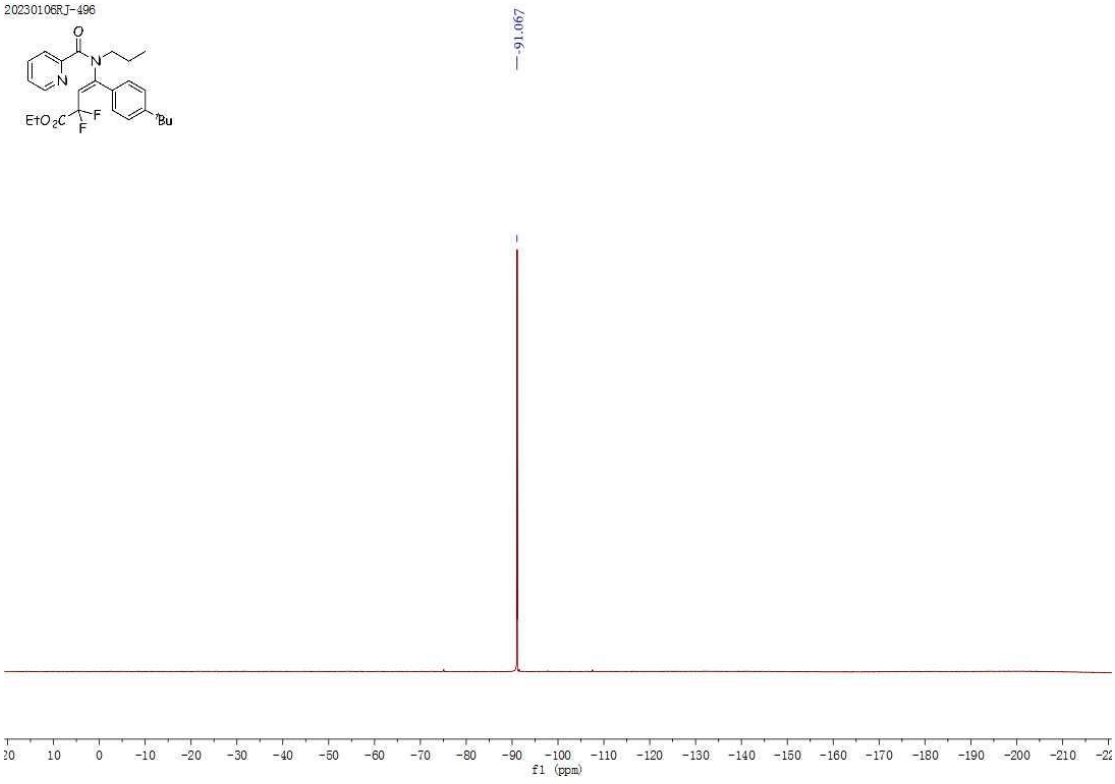
^{19}F – NMR spectrum of compound – **5g** (376 MHz, $CDCl_3$)



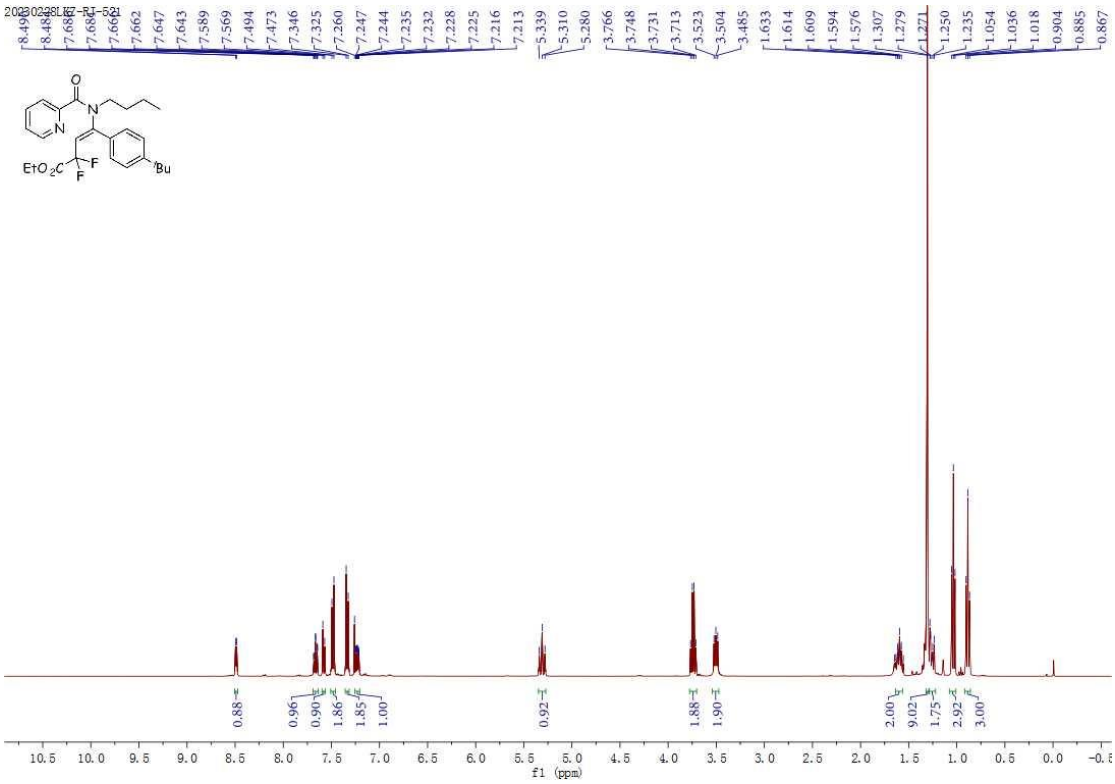
^{1}H – NMR spectrum of compound – **5h** (400 MHz, $CDCl_3$)



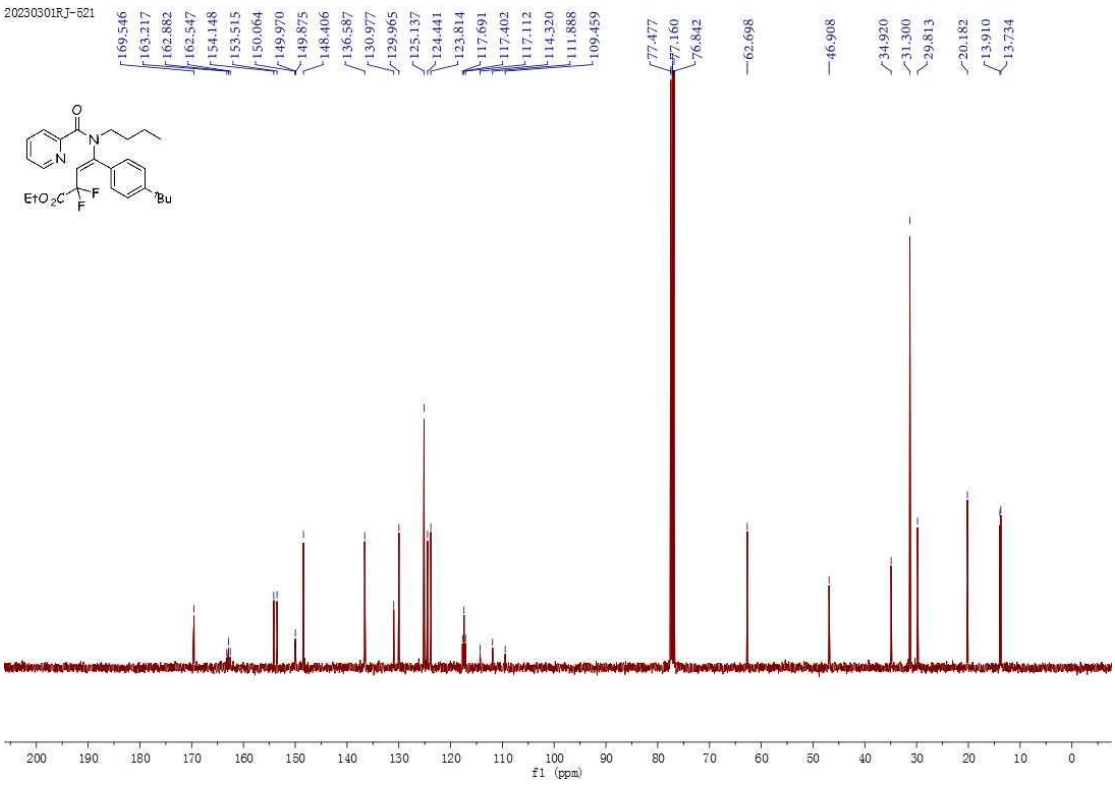
^{13}C – NMR spectrum of compound – **5h** (100 MHz, $CDCl_3$)



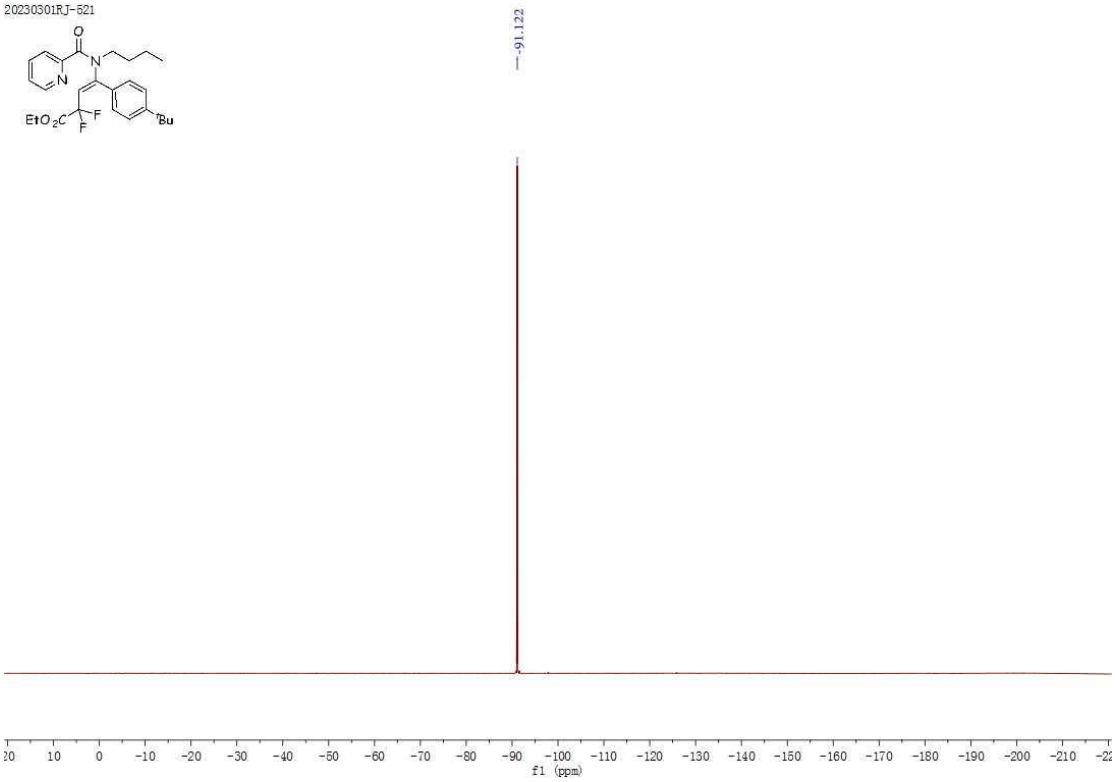
^{19}F – NMR spectrum of compound – **5h** (376 MHz, $CDCl_3$)



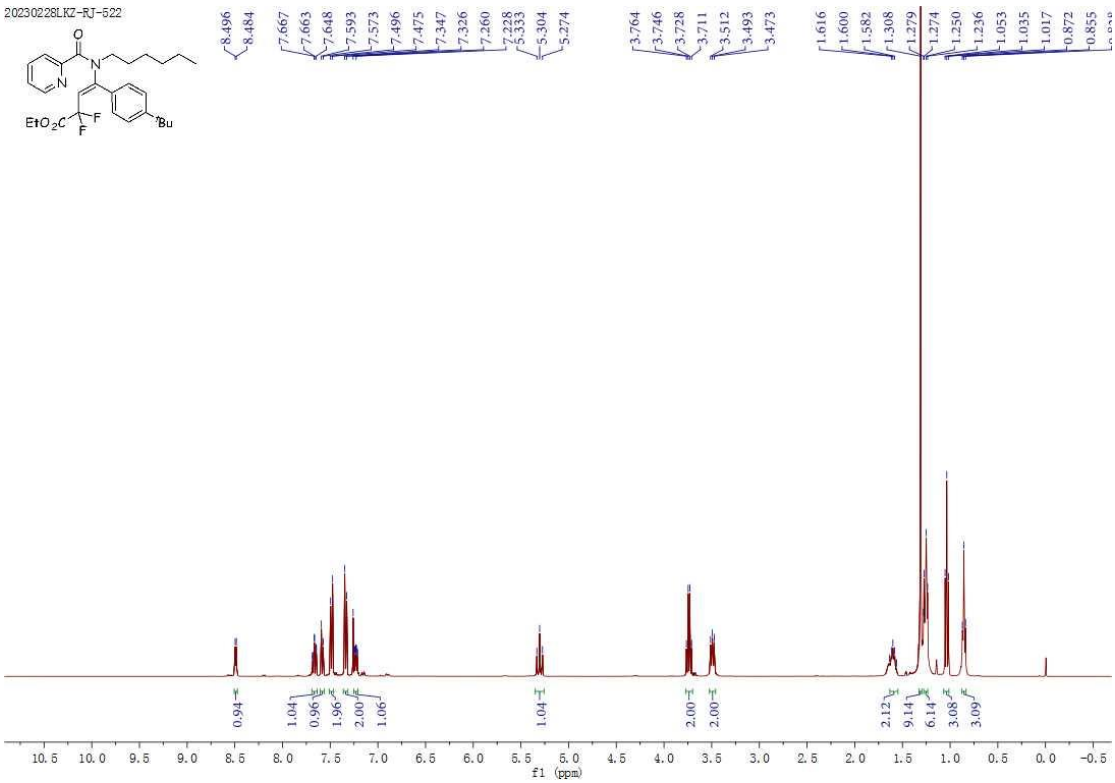
^{1}H – NMR spectrum of compound – **5i** (400 MHz, $CDCl_3$)



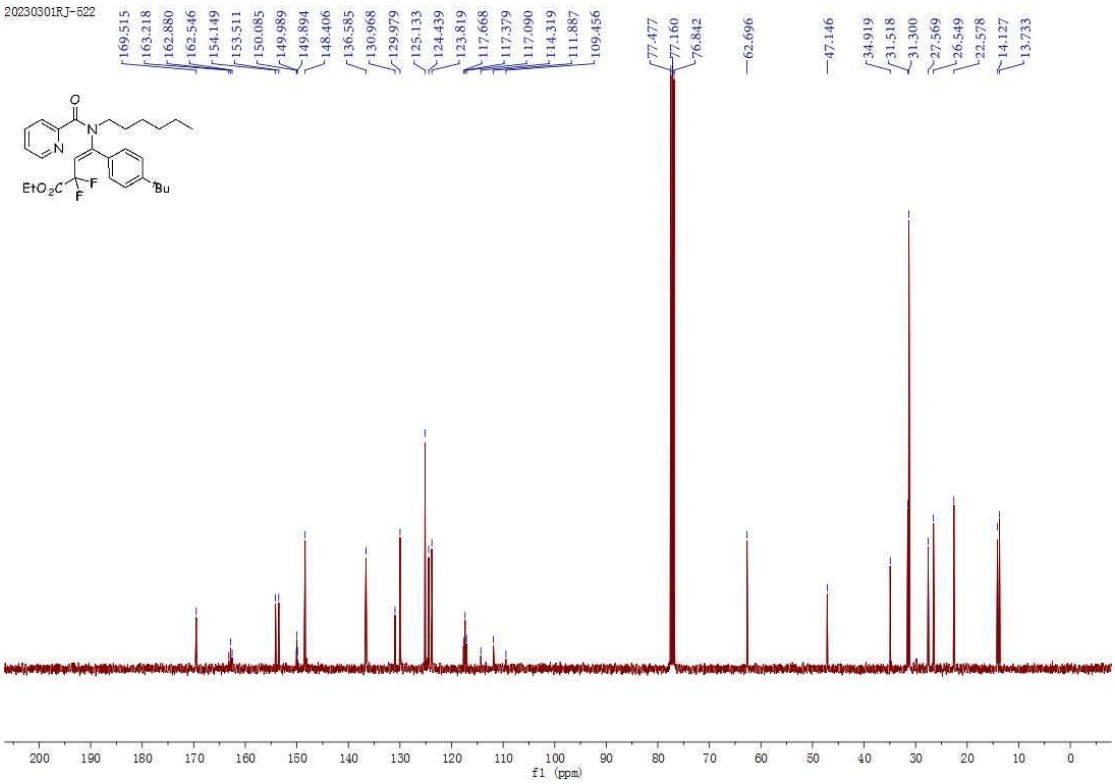
^{13}C – NMR spectrum of compound – **5i** (100 MHz, $CDCl_3$)



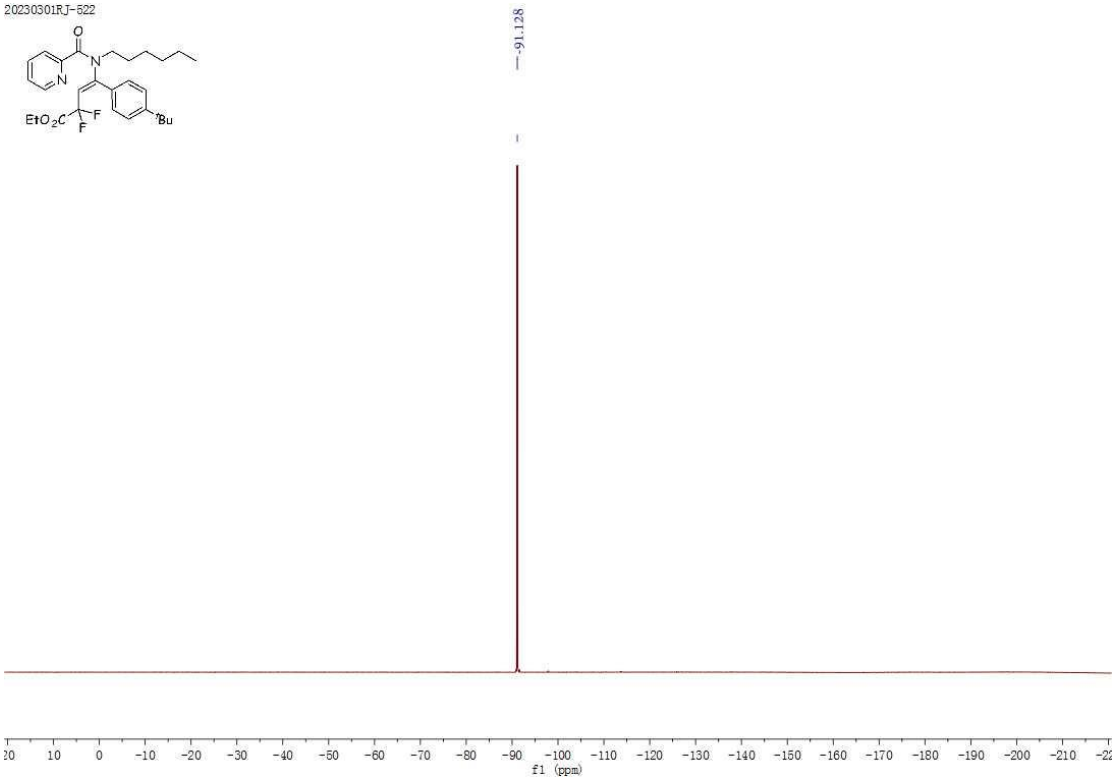
^{19}F – NMR spectrum of compound – **5i** (376 MHz, $CDCl_3$)



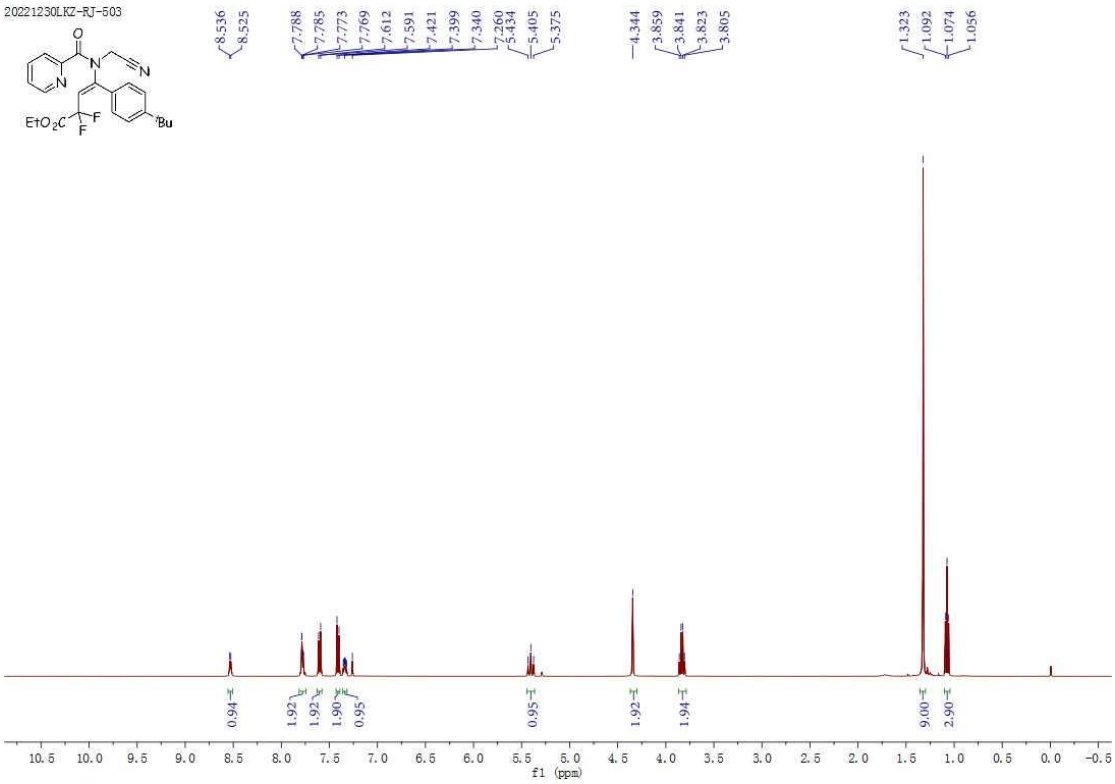
^{1}H – NMR spectrum of compound – **5j** (400 MHz, $CDCl_3$)



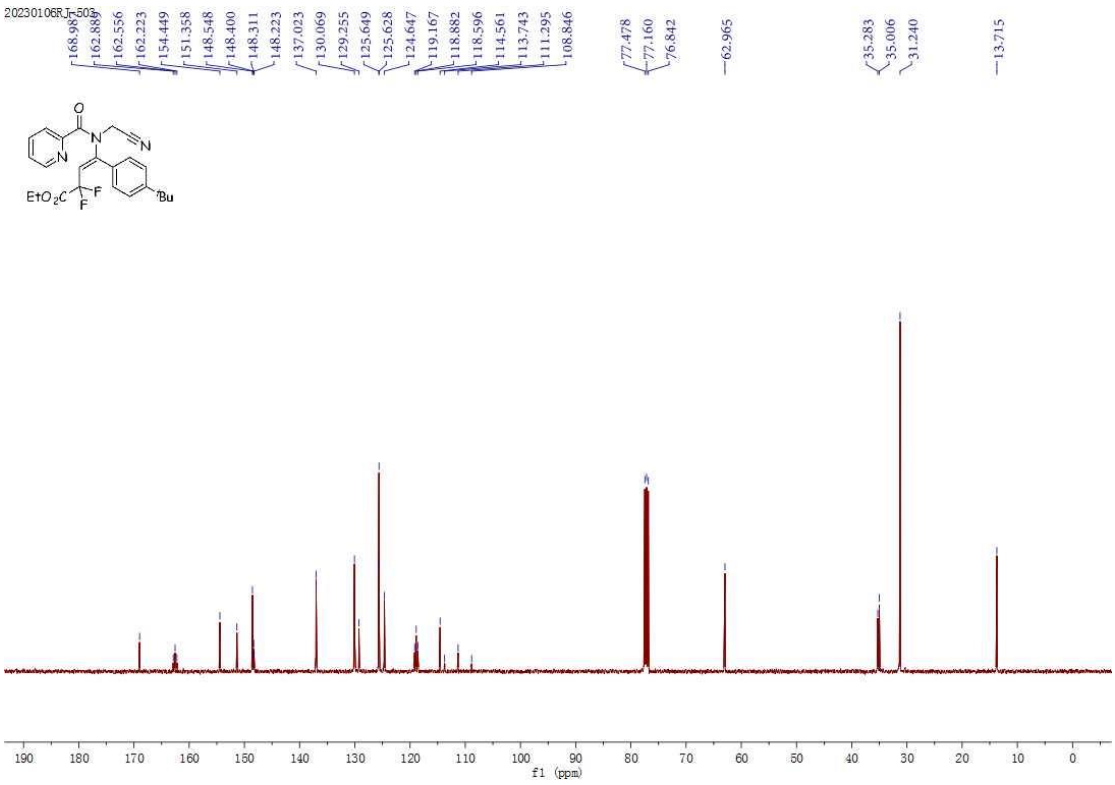
^{13}C – NMR spectrum of compound – **5j** (100 MHz, $CDCl_3$)



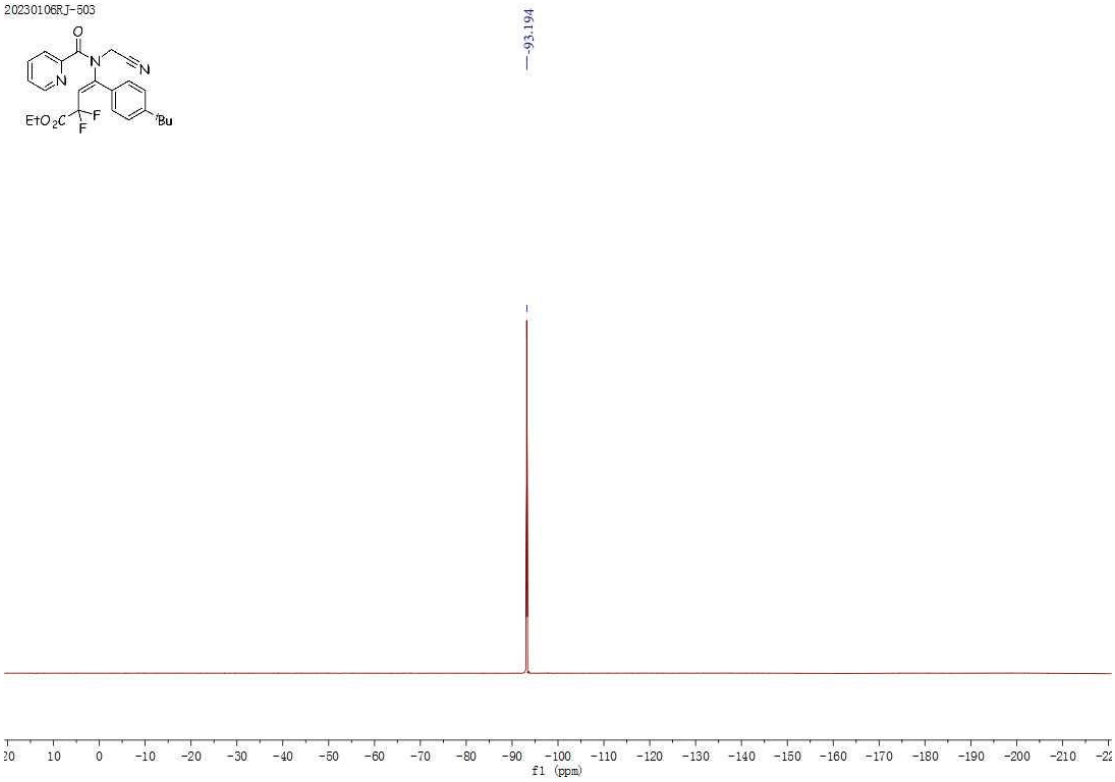
^{19}F – NMR spectrum of compound – **5j** (376 MHz, $CDCl_3$)



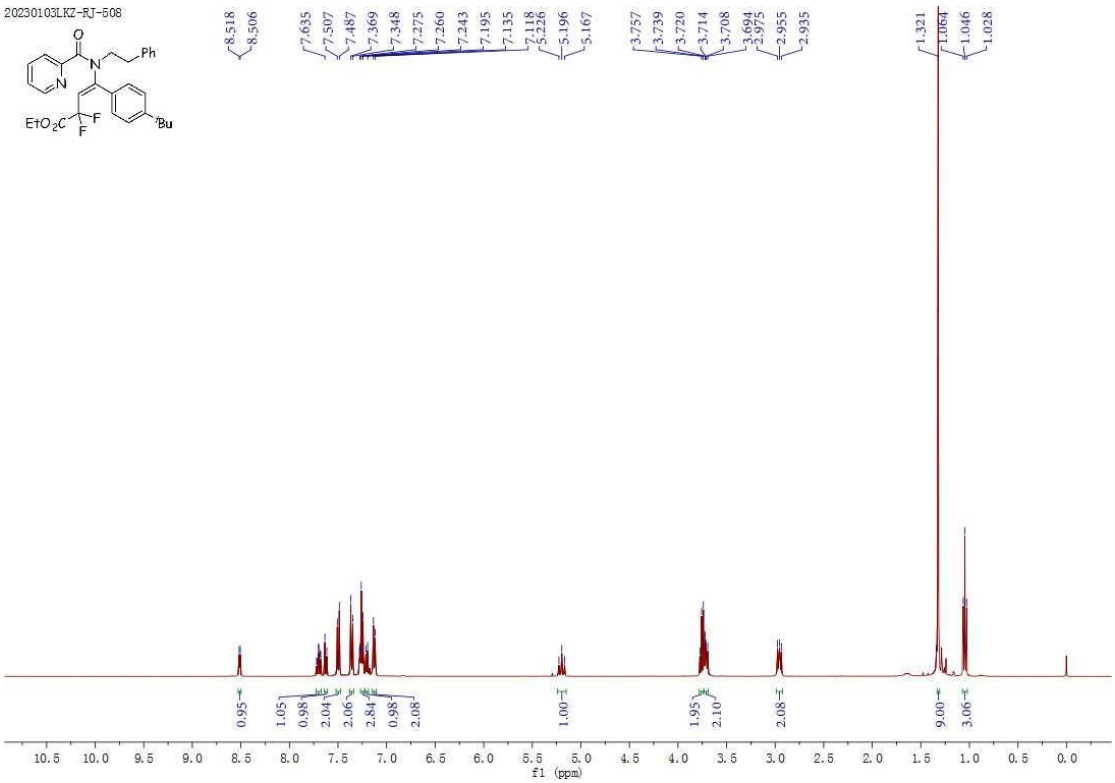
^{1}H – NMR spectrum of compound – **5k** (400 MHz, $CDCl_3$)



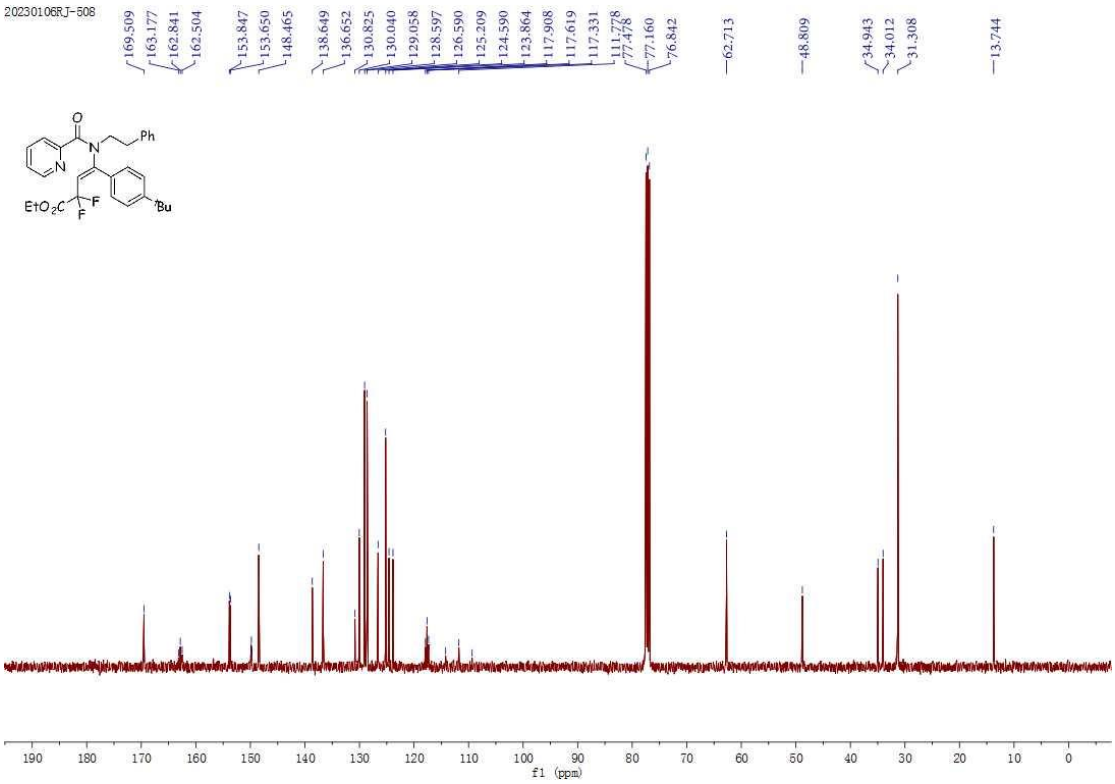
^{13}C – NMR spectrum of compound – **5k** (100 MHz, $CDCl_3$)



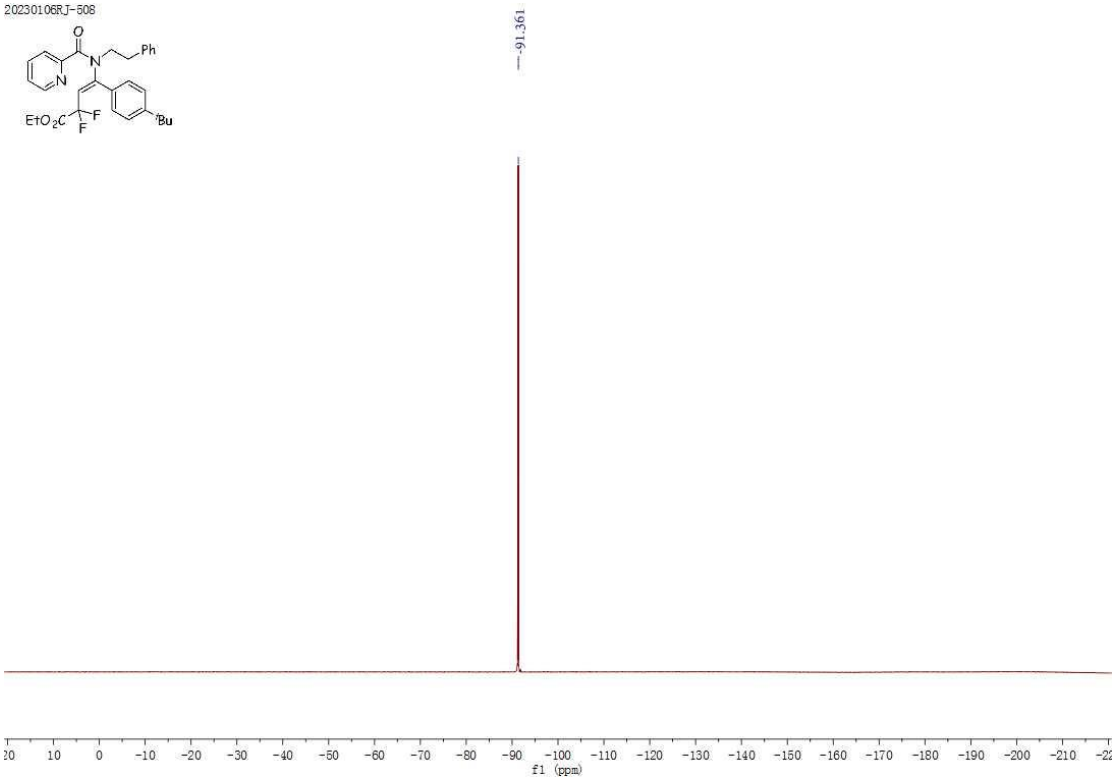
^{19}F – NMR spectrum of compound – **5k** (376 MHz, $CDCl_3$)



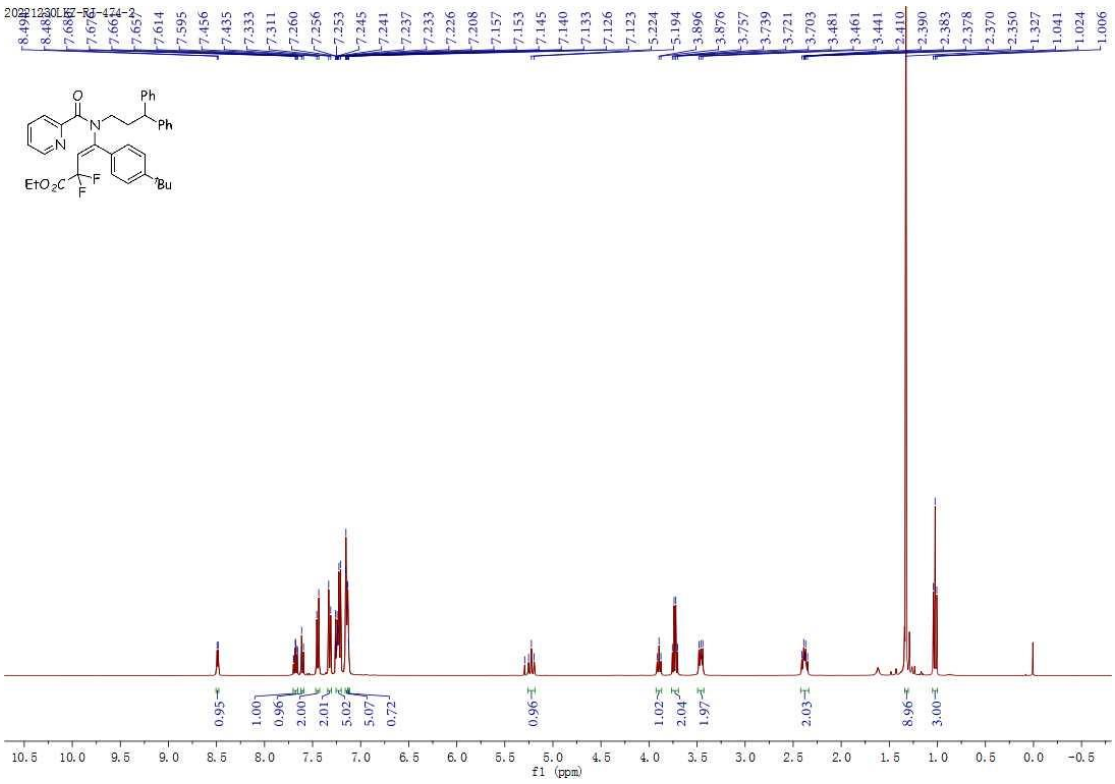
^{1}H – NMR spectrum of compound – **5l** (400 MHz, $CDCl_3$)



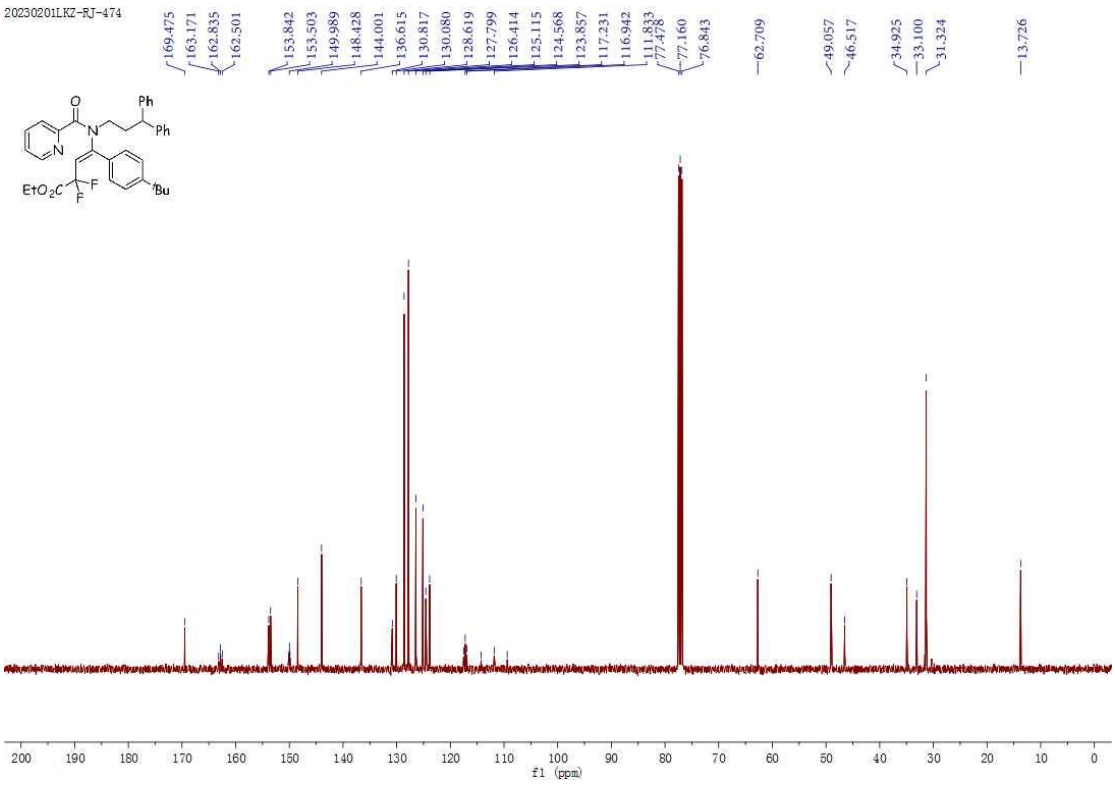
^{13}C – NMR spectrum of compound – **5l** (100 MHz, $CDCl_3$)



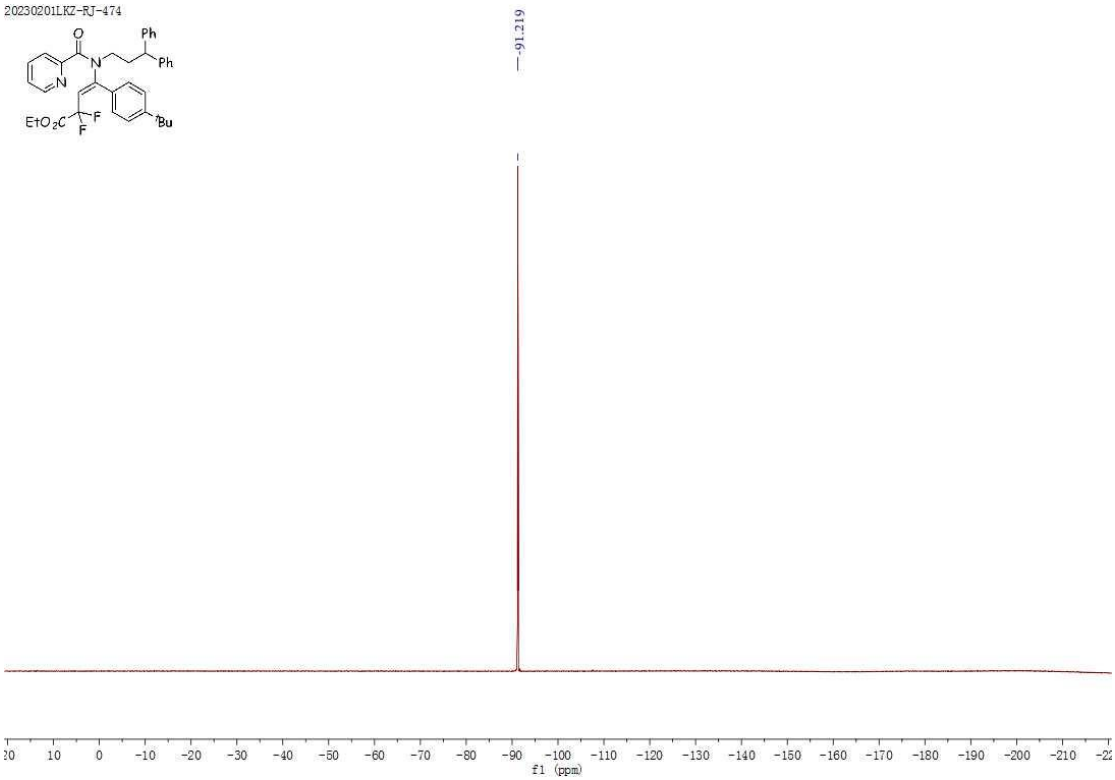
^{19}F – NMR spectrum of compound – **5l** (376 MHz, $CDCl_3$)



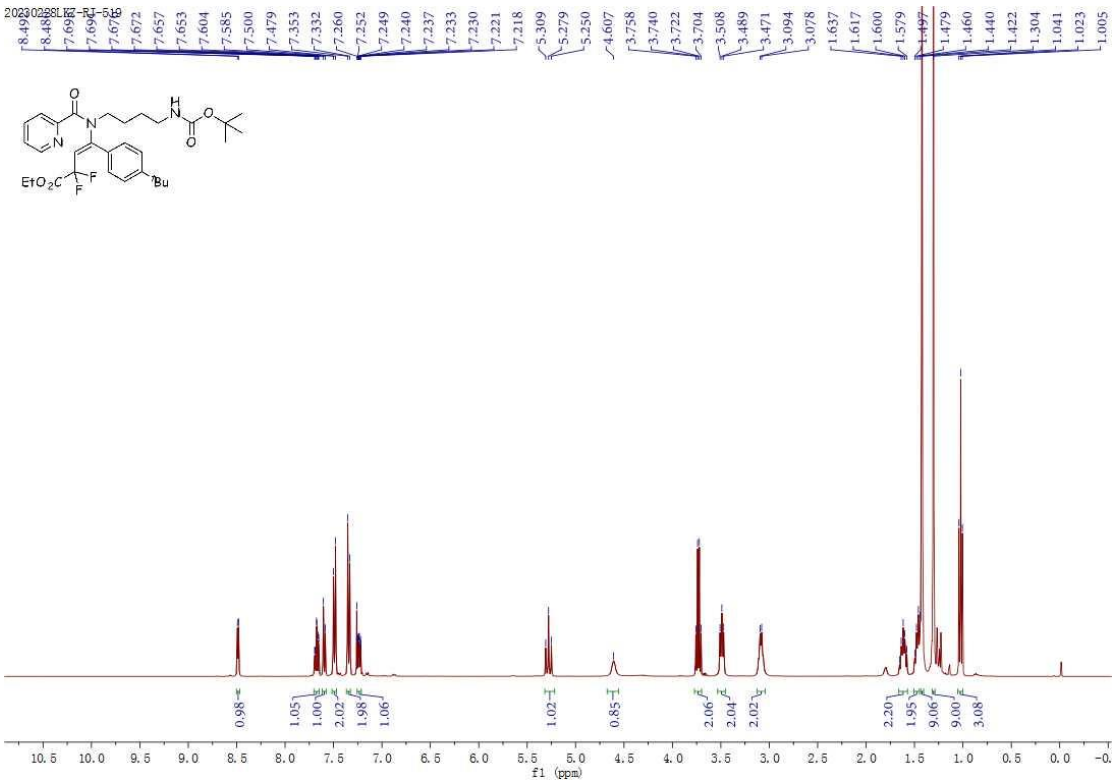
^{1}H – NMR spectrum of compound – **5m** (400 MHz, $CDCl_3$)



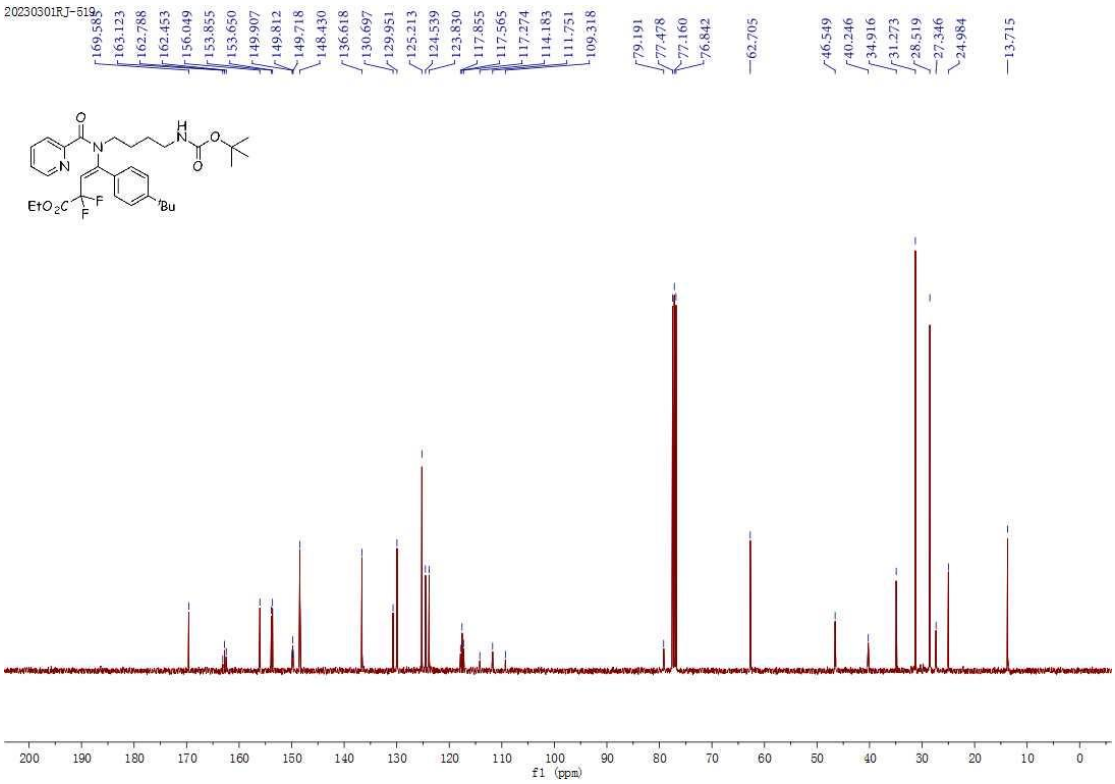
^{13}C – NMR spectrum of compound – **5m** (100 MHz, $CDCl_3$)



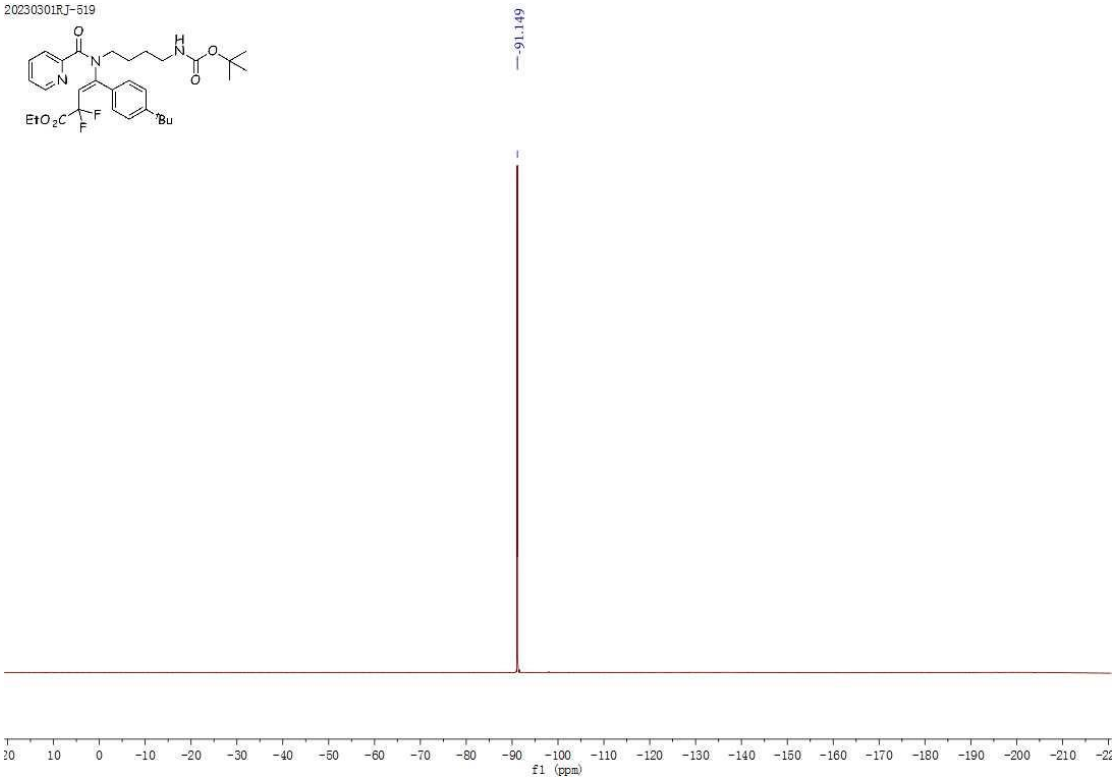
^{19}F – NMR spectrum of compound – **5m** (376 MHz, $CDCl_3$)



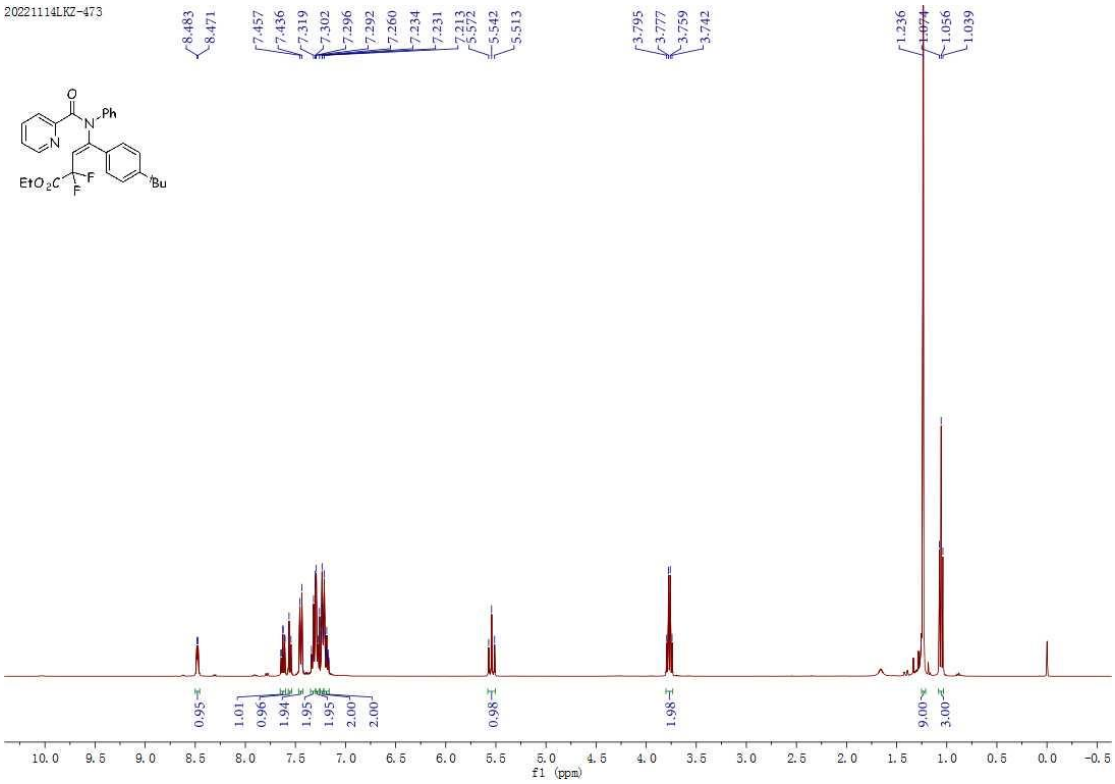
^{1}H – NMR spectrum of compound – **5n** (400 MHz, $CDCl_3$)



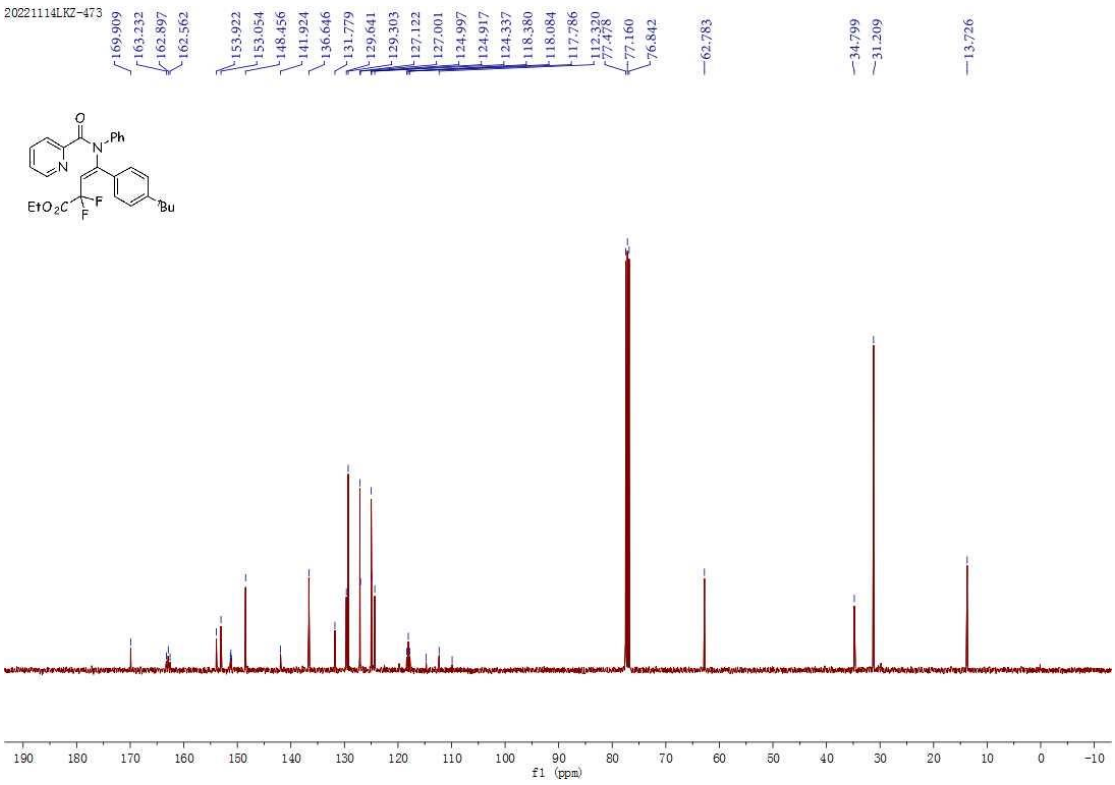
^{13}C – NMR spectrum of compound – **5n** (100 MHz, $CDCl_3$)



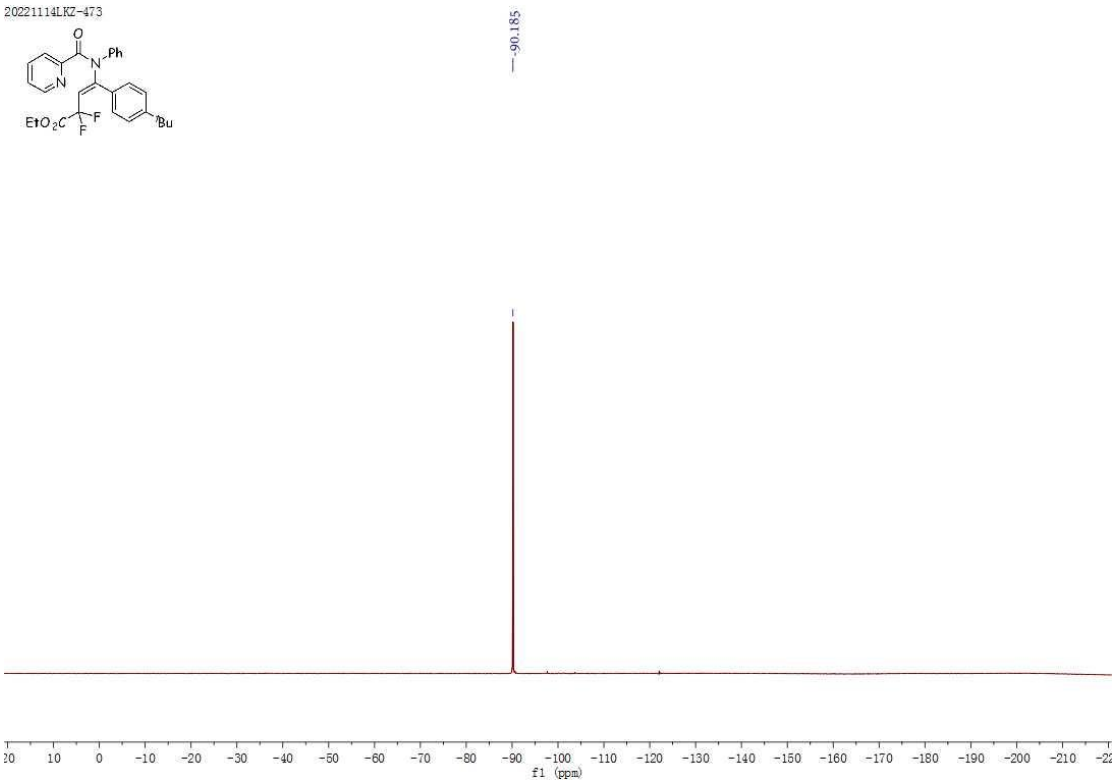
^{19}F – NMR spectrum of compound – **5n** (376 MHz, $CDCl_3$)



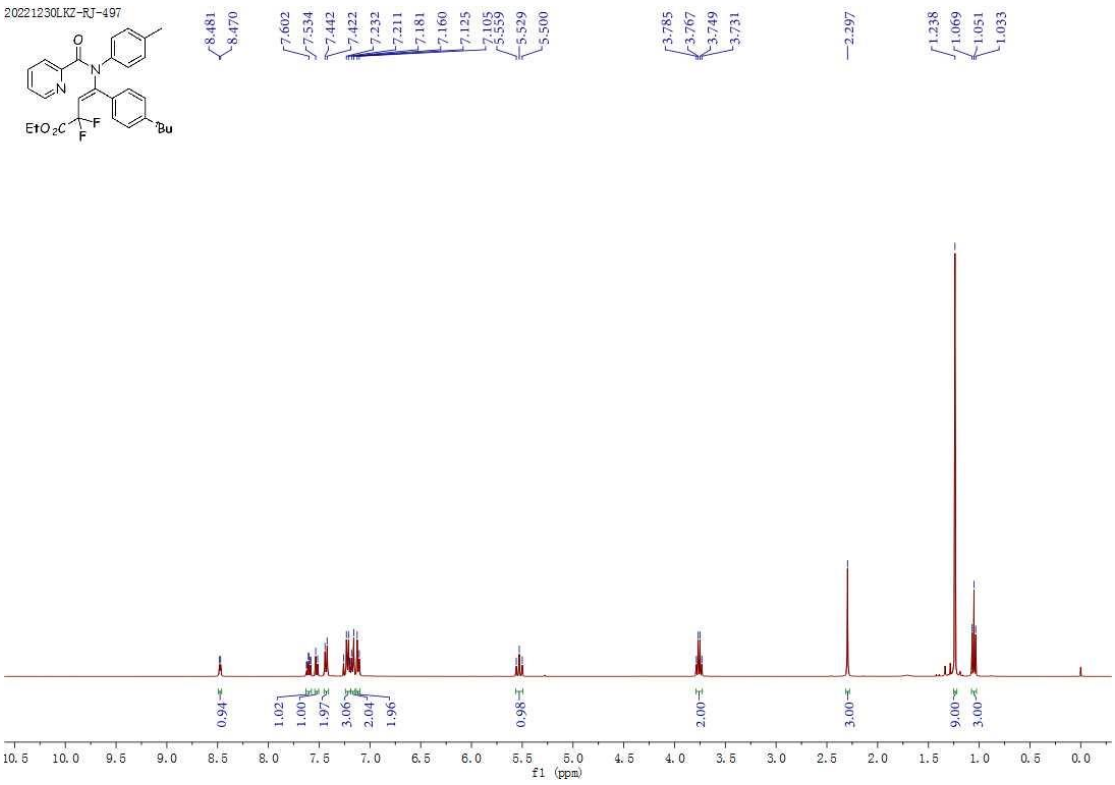
^{1}H – NMR spectrum of compound – **5o** (400 MHz, $CDCl_3$)



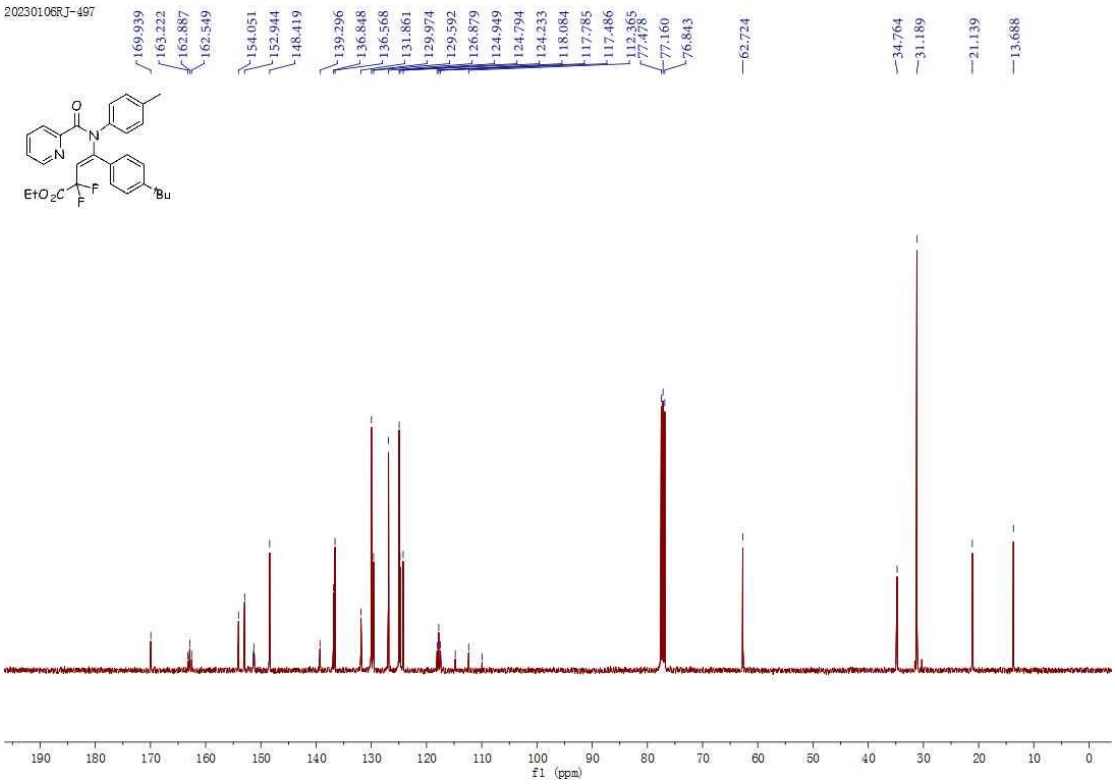
^{13}C – NMR spectrum of compound – **5o** (100 MHz, $CDCl_3$)



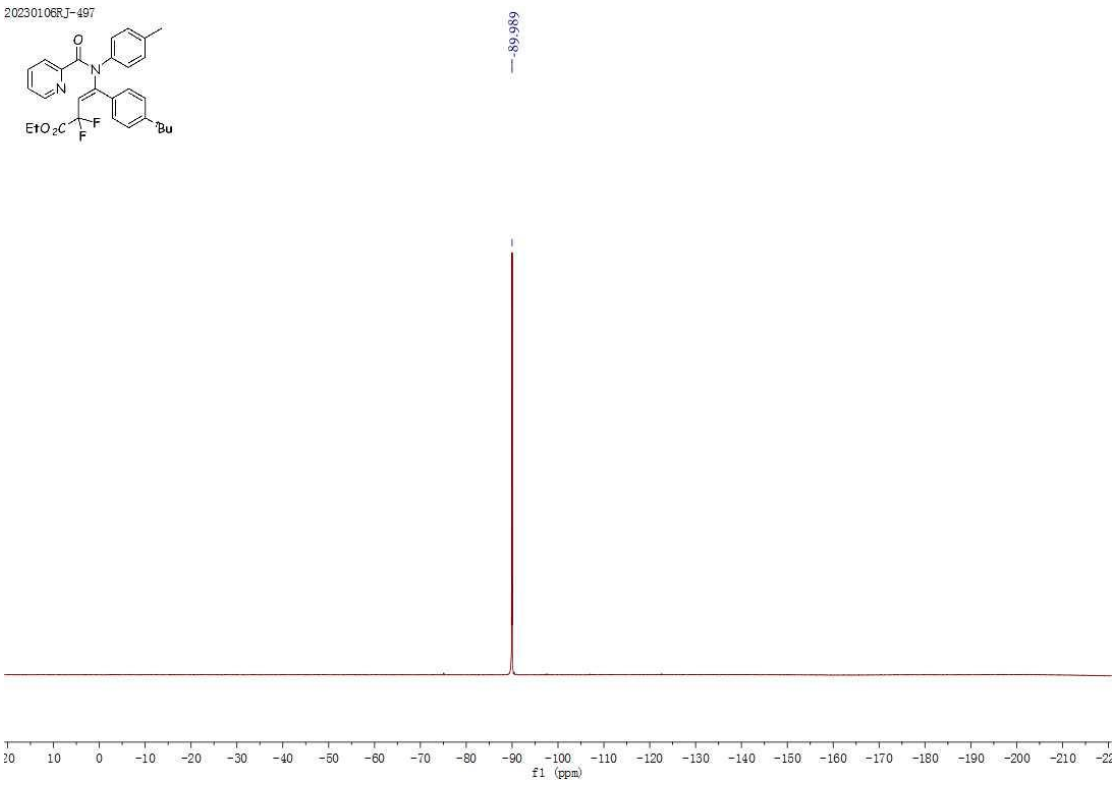
^{19}F – NMR spectrum of compound – **5o** (376 MHz, $CDCl_3$)



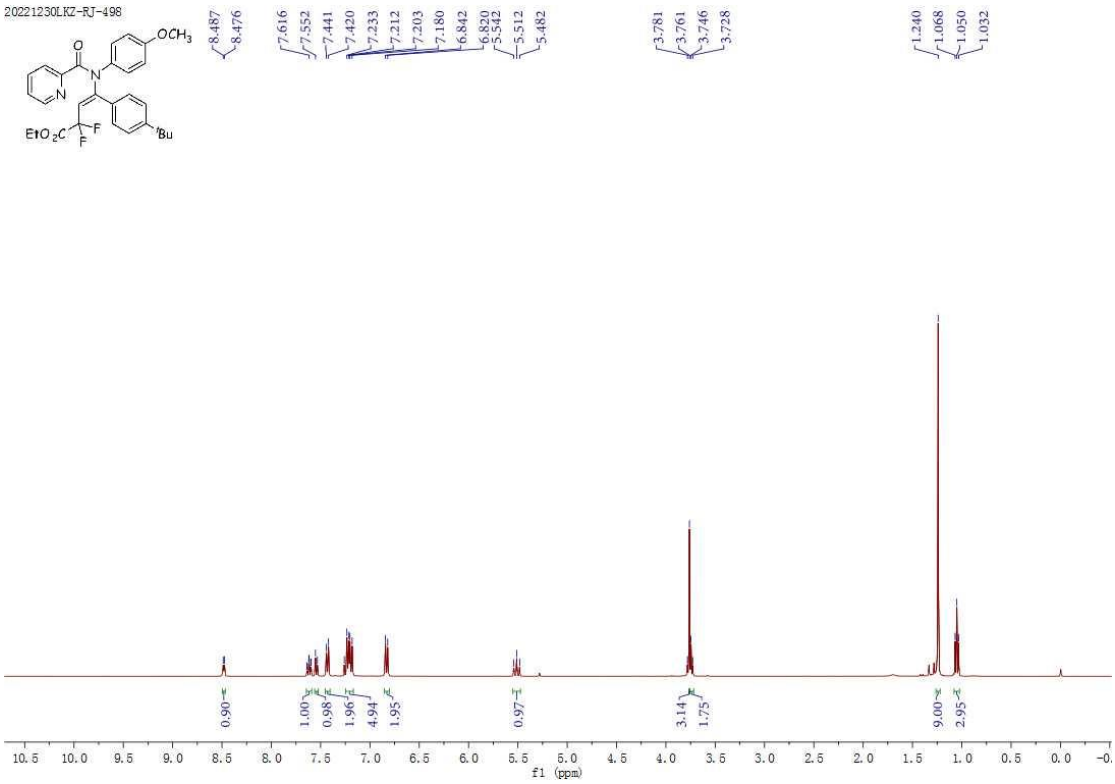
^{1}H – NMR spectrum of compound – **5p** (400 MHz, $CDCl_3$)



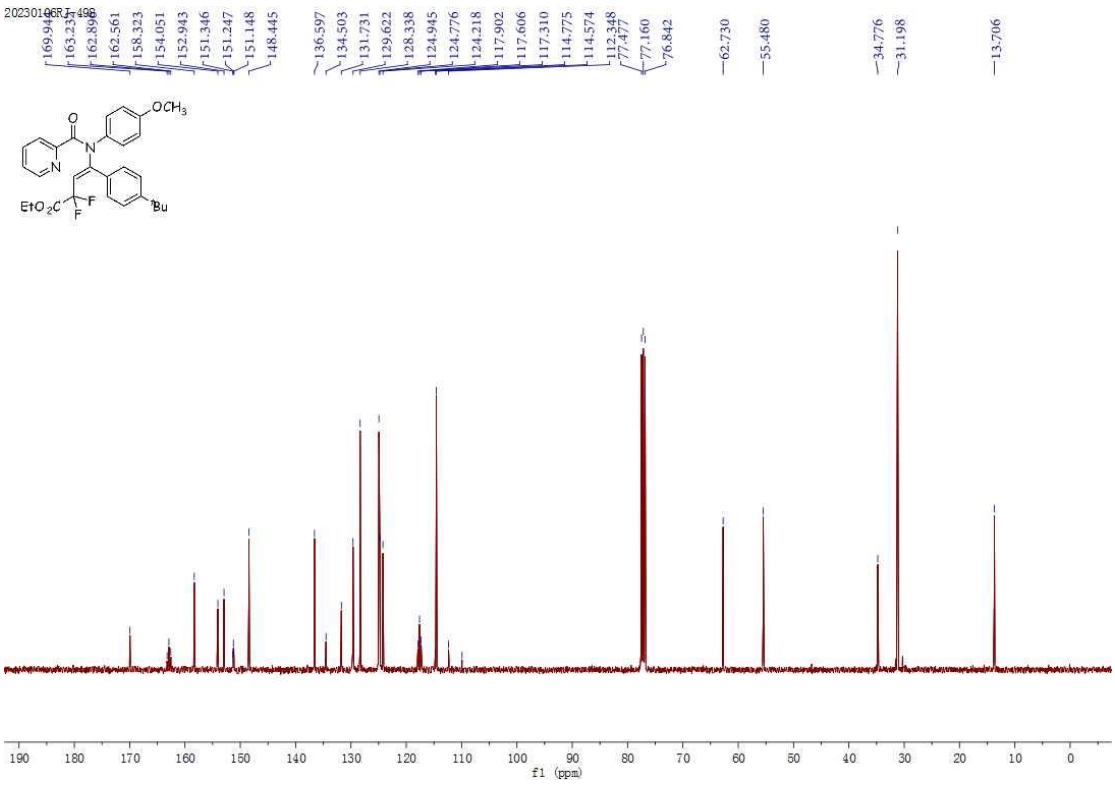
^{13}C – NMR spectrum of compound – **5p** (100 MHz, $CDCl_3$)



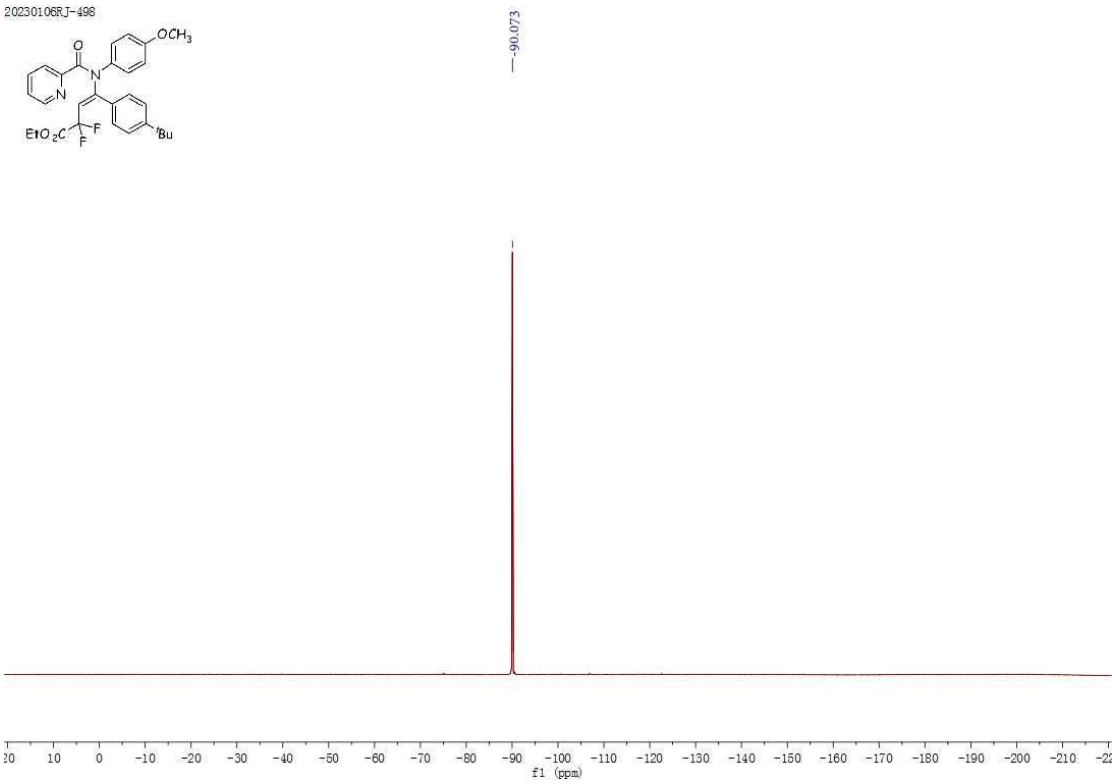
^{19}F – NMR spectrum of compound – **5p** (376 MHz, $CDCl_3$)



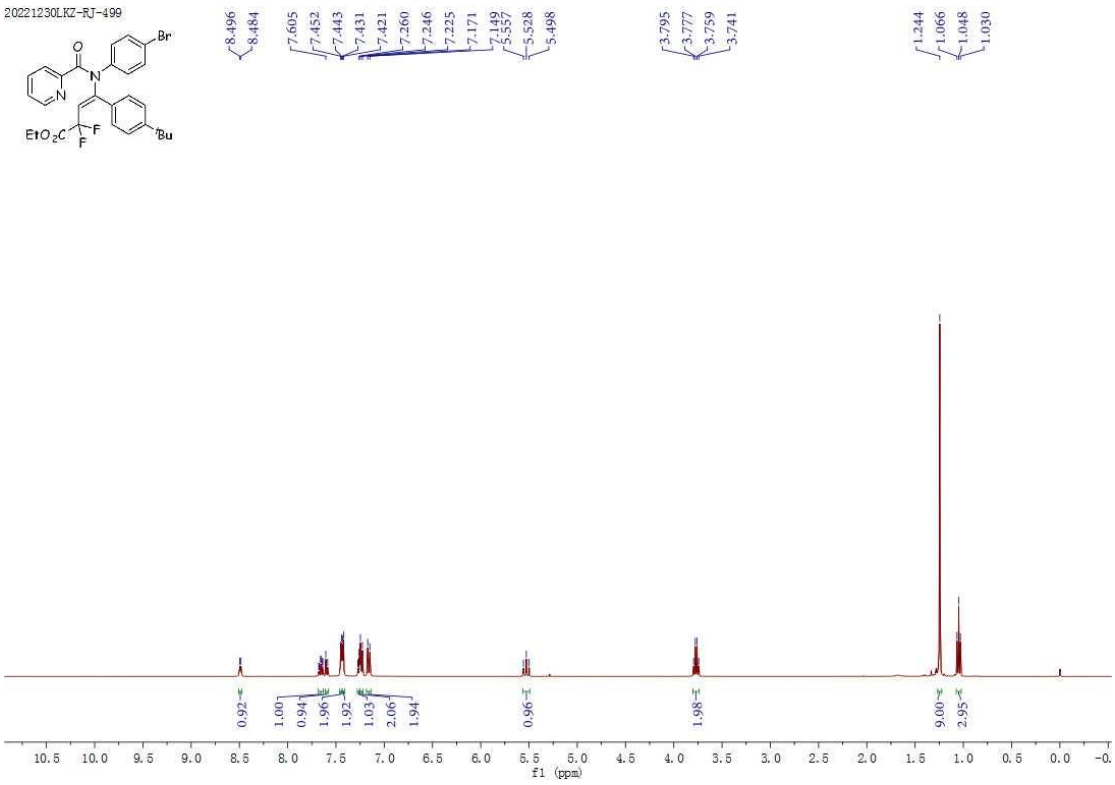
^{1}H – NMR spectrum of compound – **5q** (400 MHz, $CDCl_3$)



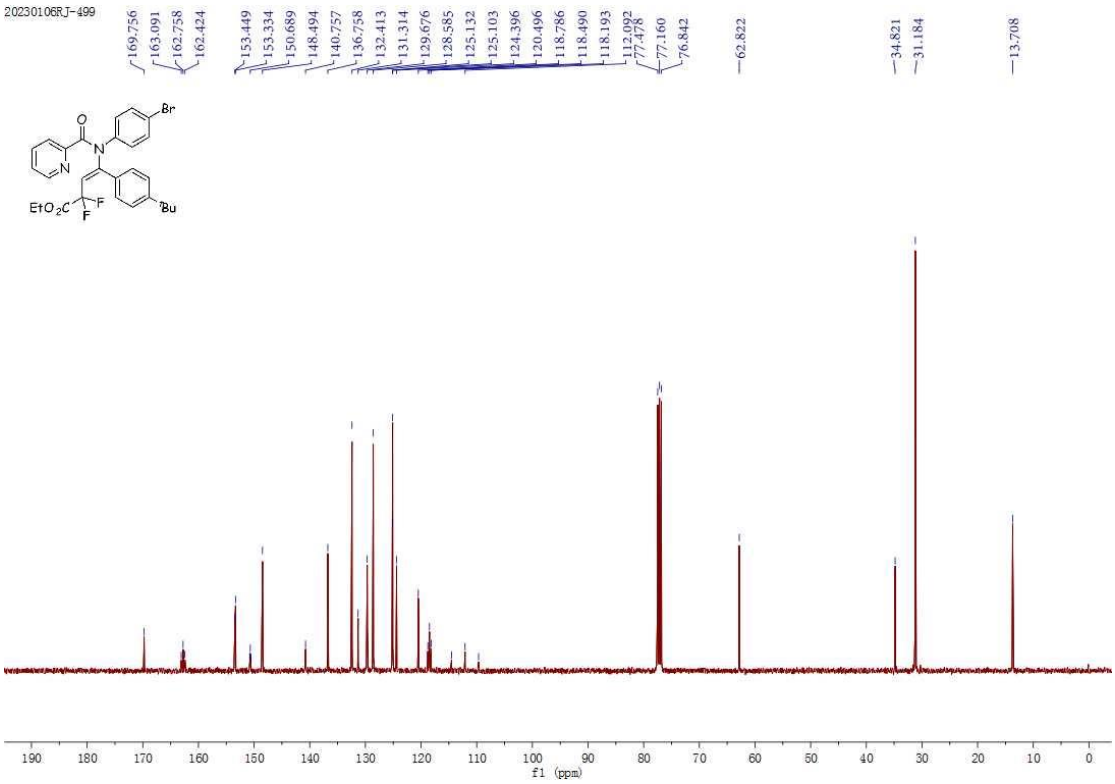
^{13}C – NMR spectrum of compound – **5q** (100 MHz, $CDCl_3$)



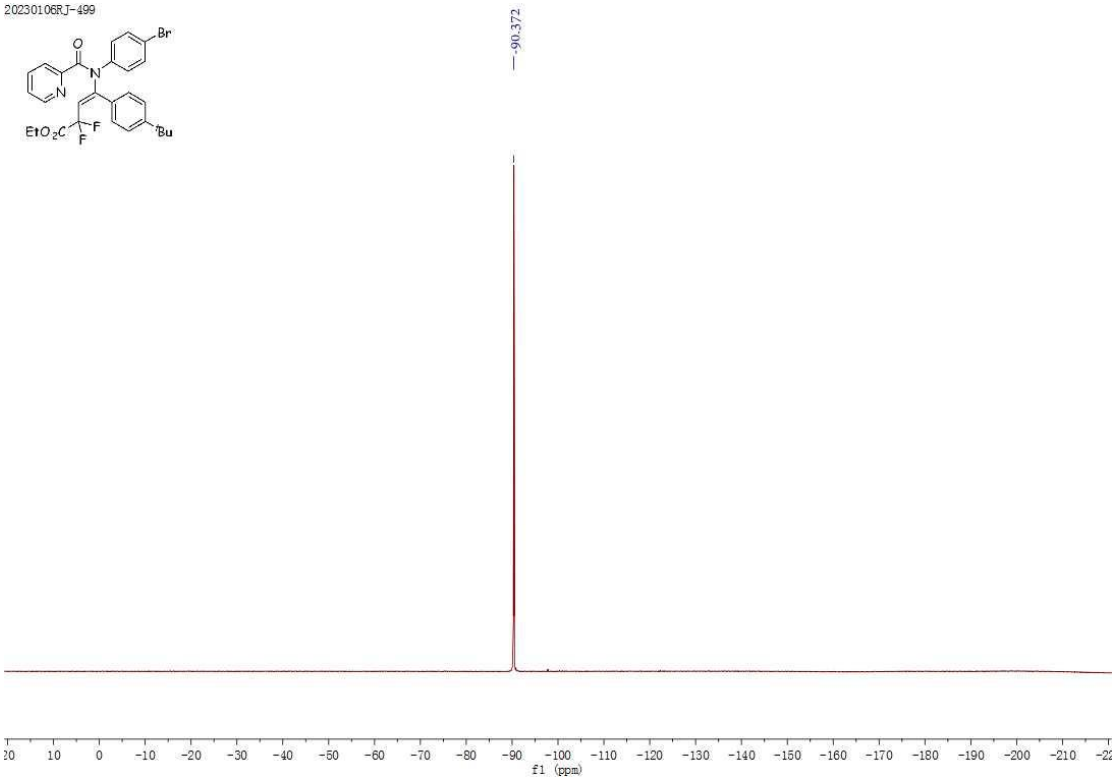
^{19}F – NMR spectrum of compound – **5q** (376 MHz, $CDCl_3$)



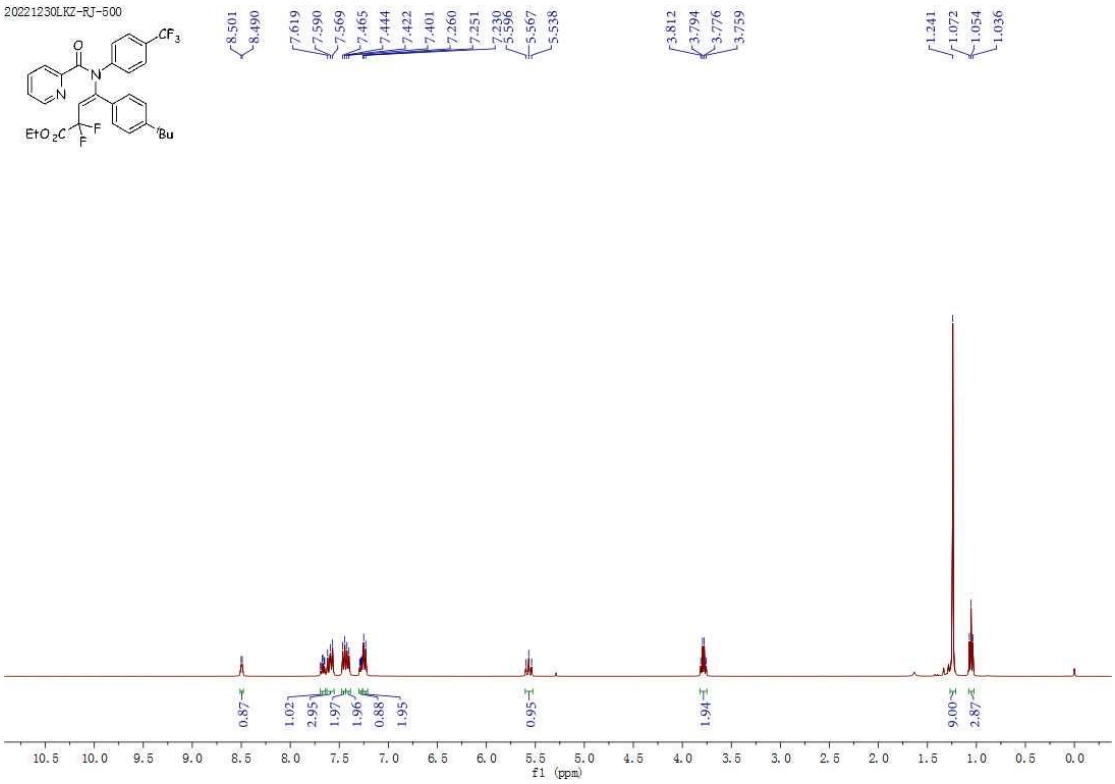
^{1}H – NMR spectrum of compound – **5r** (400 MHz, $CDCl_3$)



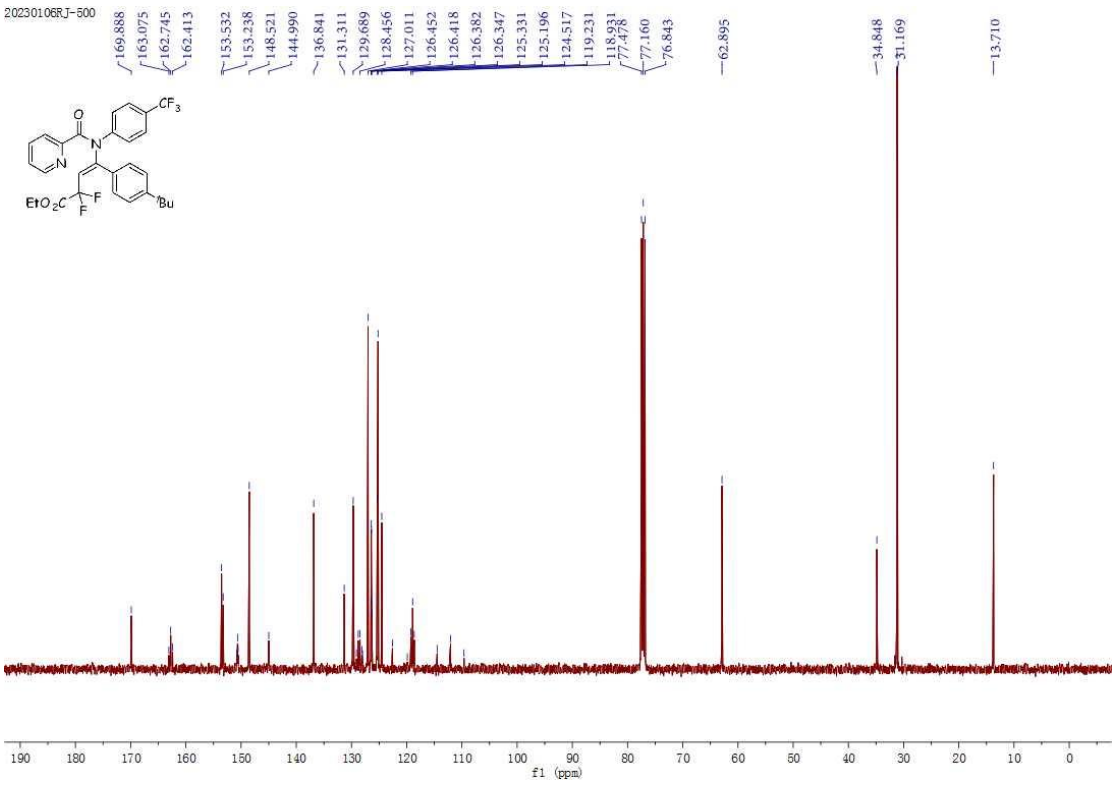
^{13}C – NMR spectrum of compound – **5r** (100 MHz, $CDCl_3$)



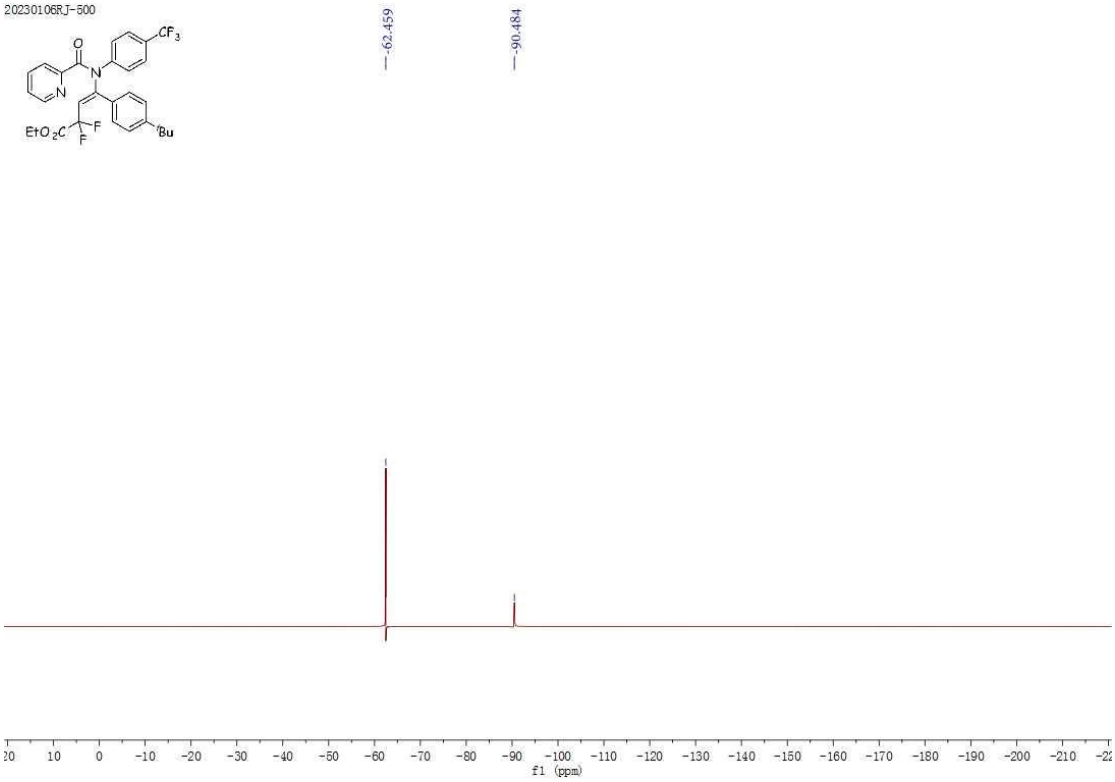
^{19}F – NMR spectrum of compound – **5r** (376 MHz, $CDCl_3$)



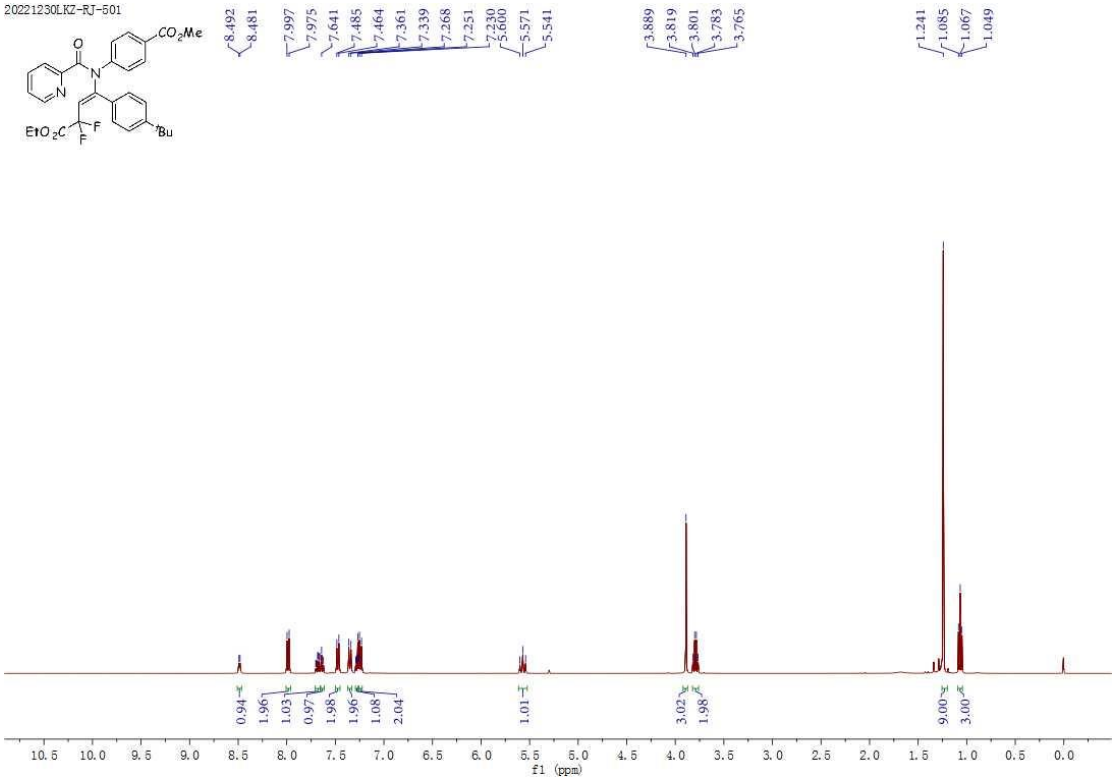
^{1}H – NMR spectrum of compound – **5s** (400 MHz, $CDCl_3$)



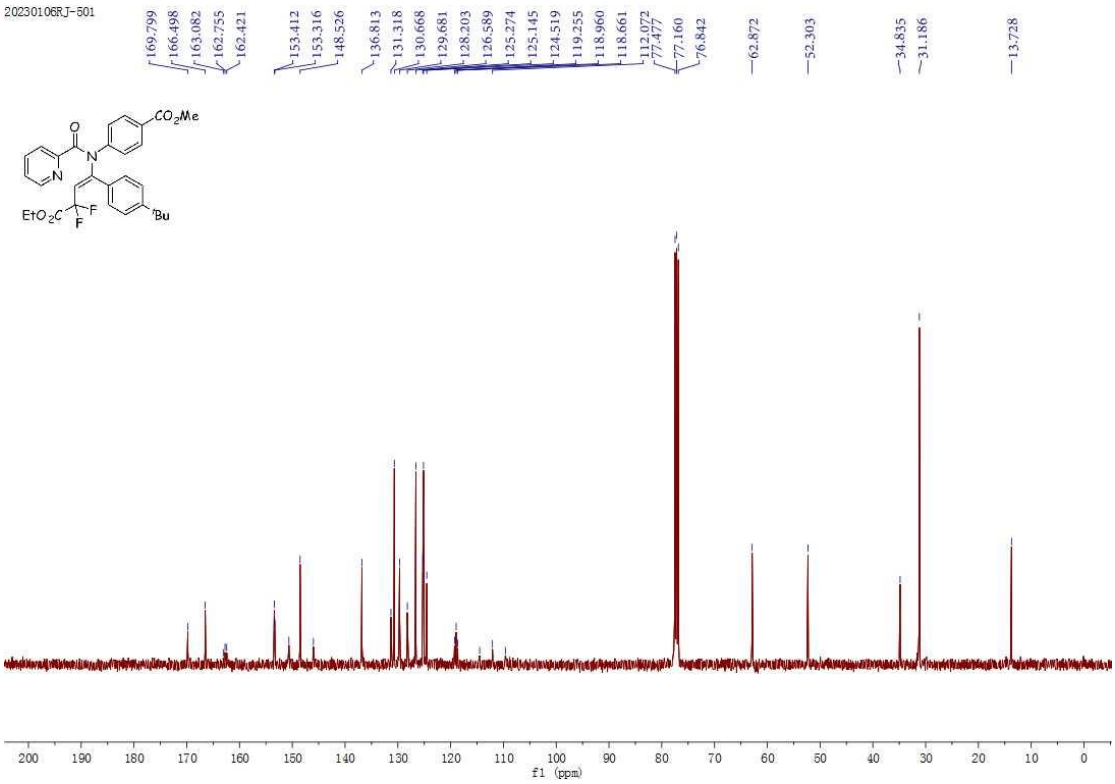
^{13}C – NMR spectrum of compound – **5s** (100 MHz, $CDCl_3$)



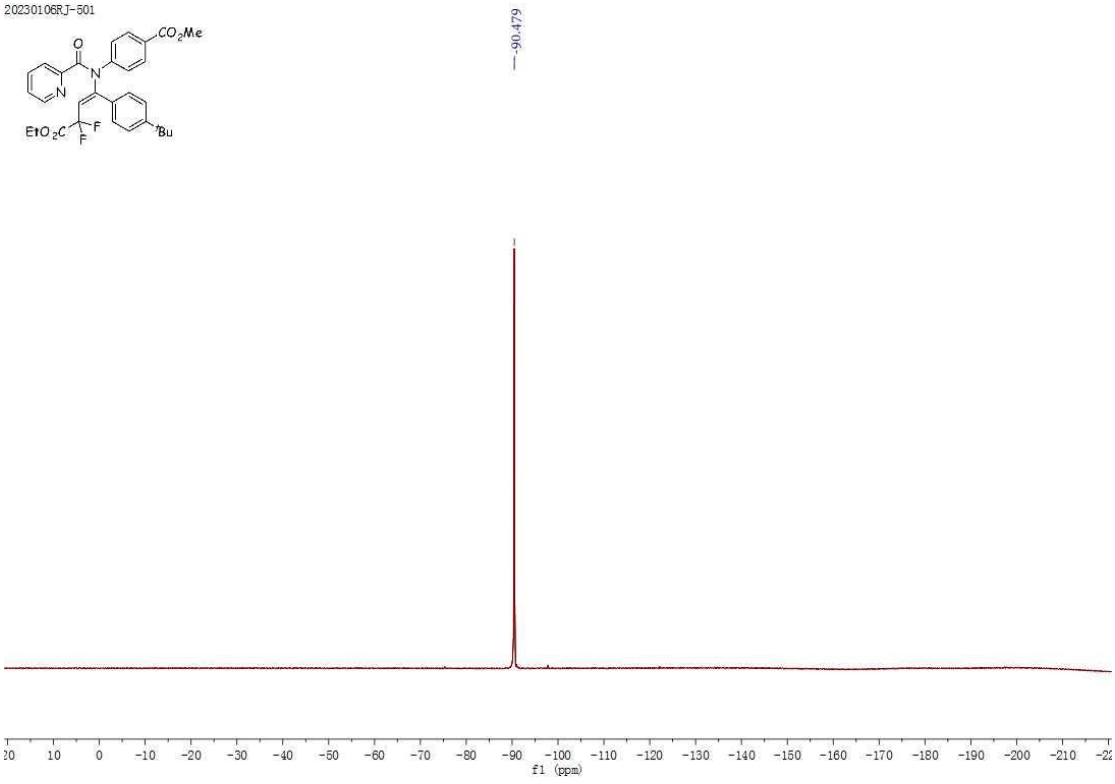
^{19}F – NMR spectrum of compound – **5s** (376 MHz, $CDCl_3$)



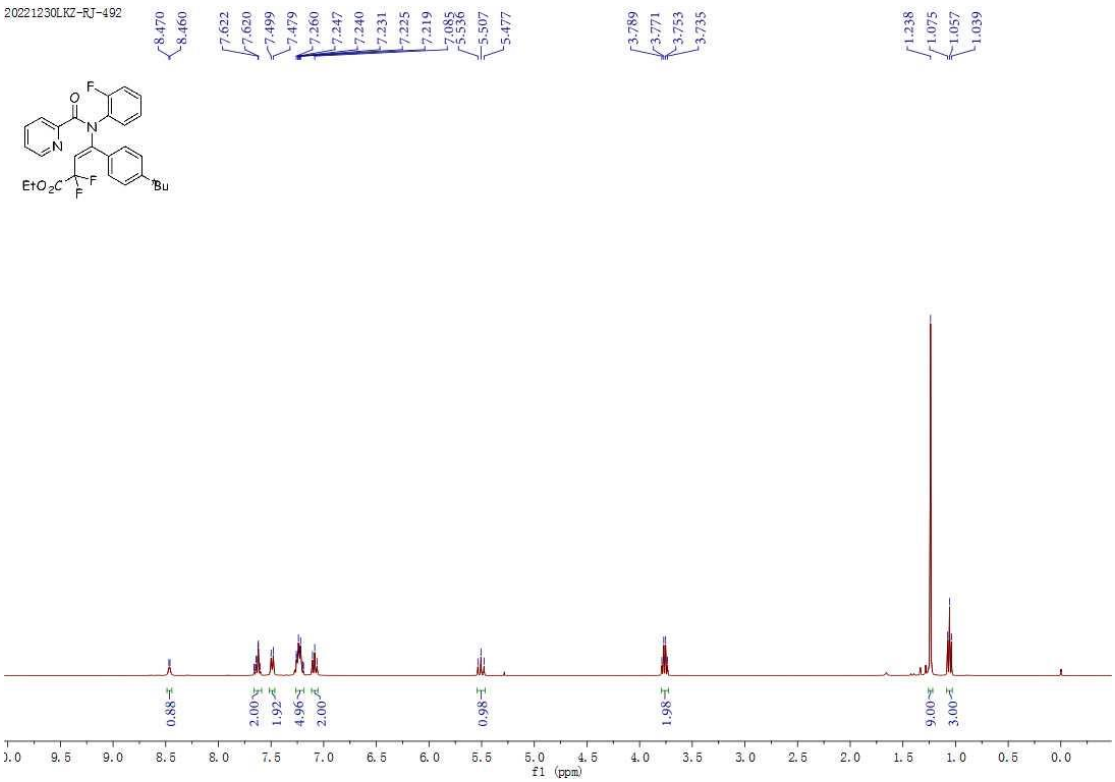
^{1}H – NMR spectrum of compound – **5t** (400 MHz, $CDCl_3$)



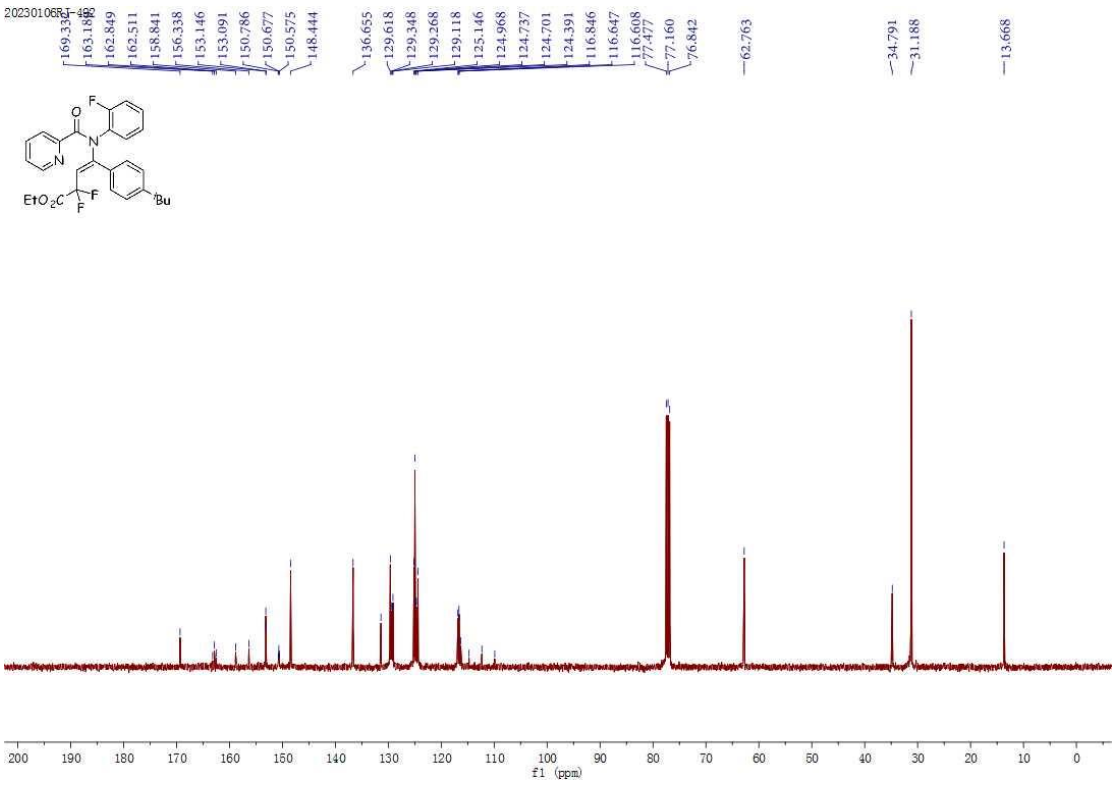
^{13}C – NMR spectrum of compound – **5t** (100 MHz, $CDCl_3$)



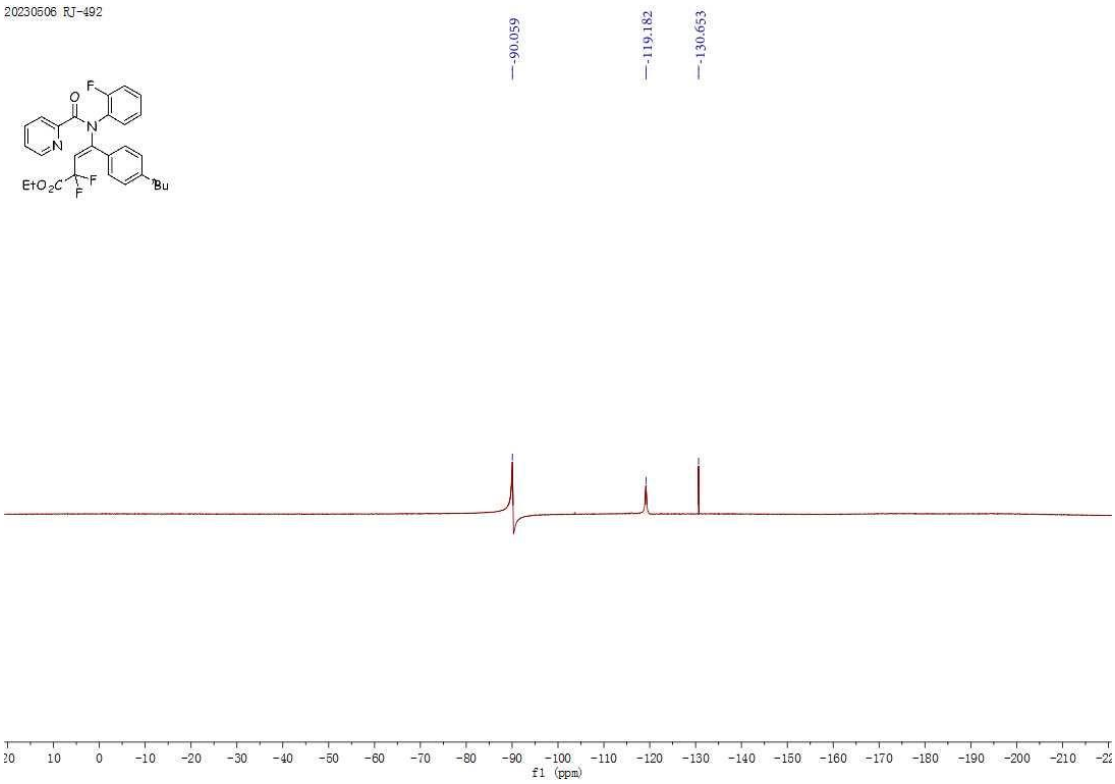
^{19}F – NMR spectrum of compound – **5t** (376 MHz, $CDCl_3$)



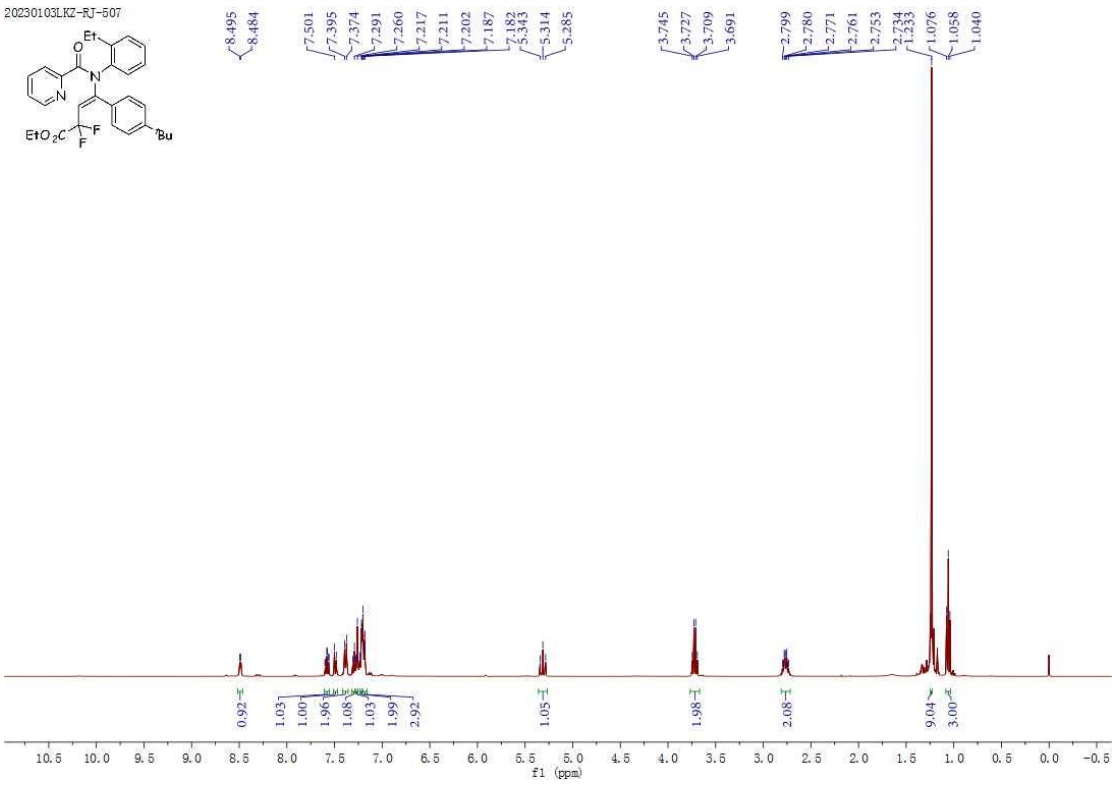
^{1}H – NMR spectrum of compound – **5u** (400 MHz, $CDCl_3$)



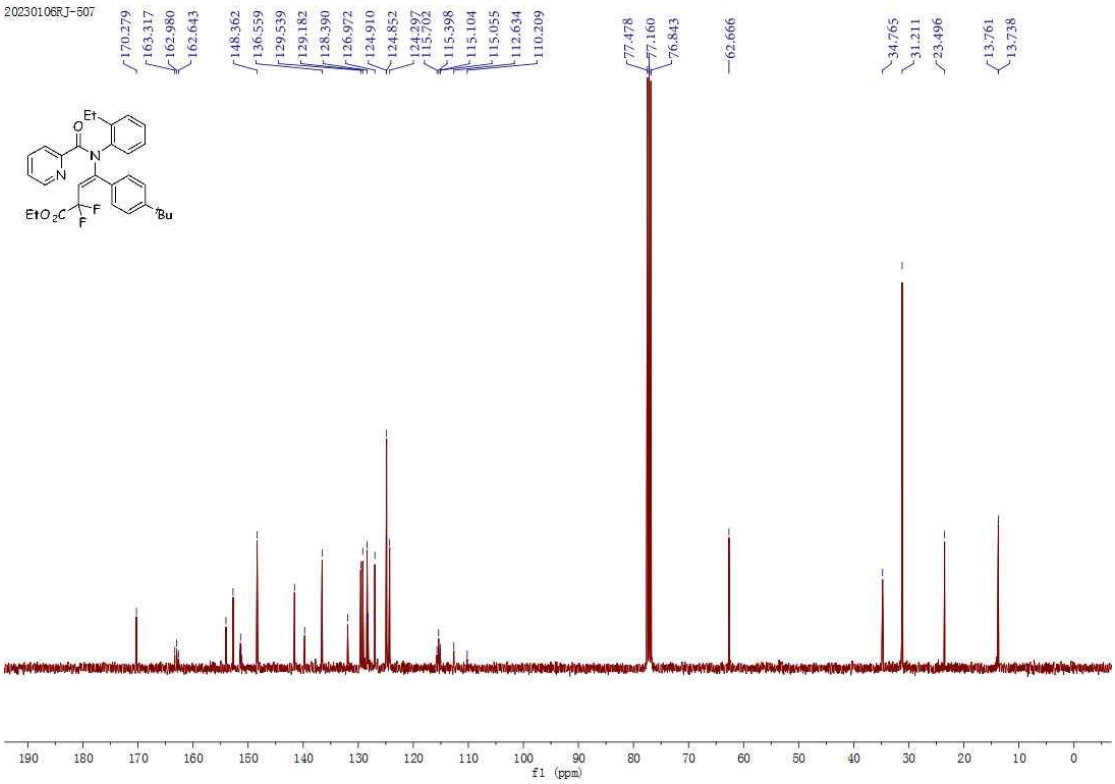
^{13}C – NMR spectrum of compound – **5u** (100 MHz, $CDCl_3$)



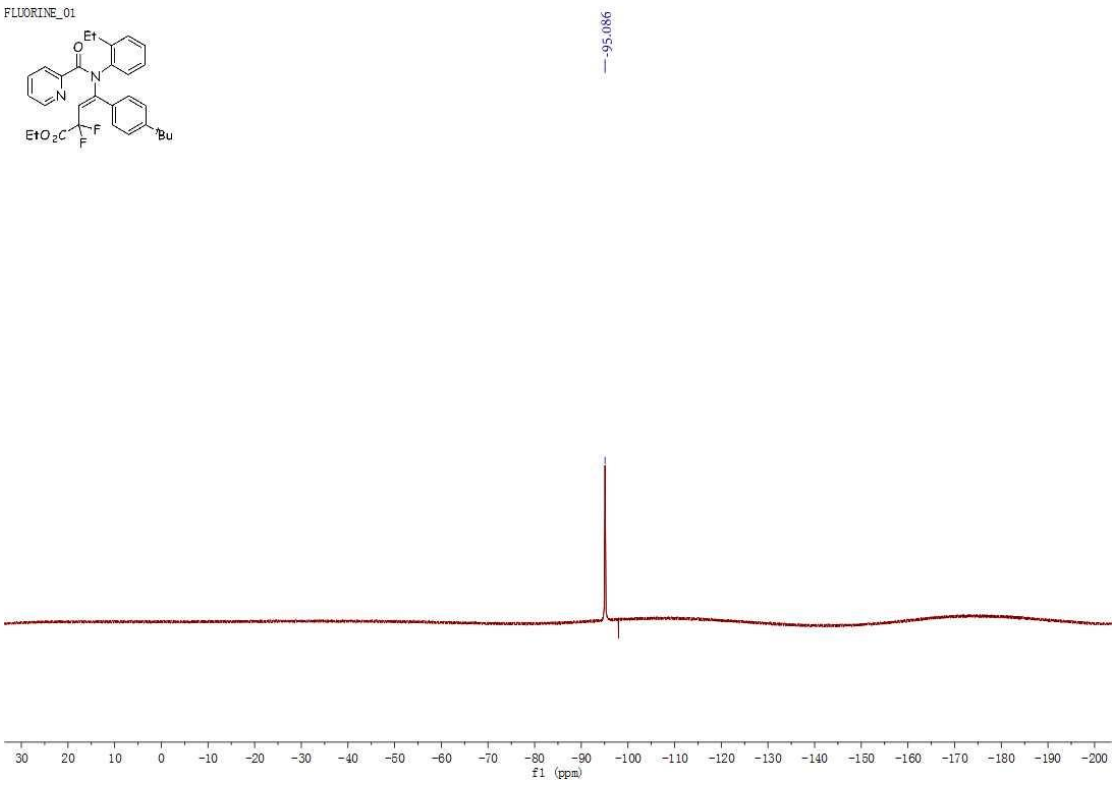
^{19}F – NMR spectrum of compound – **5u** (376 MHz, $CDCl_3$)



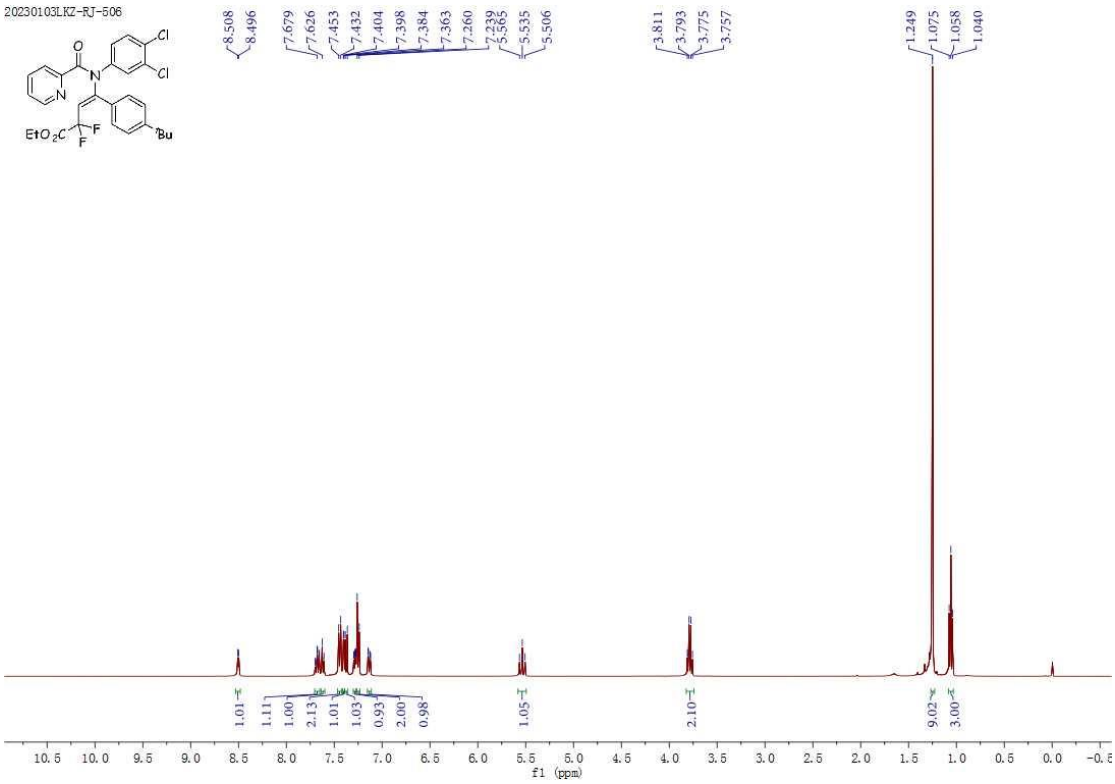
^{1}H – NMR spectrum of compound – **5v** (400 MHz, $CDCl_3$)



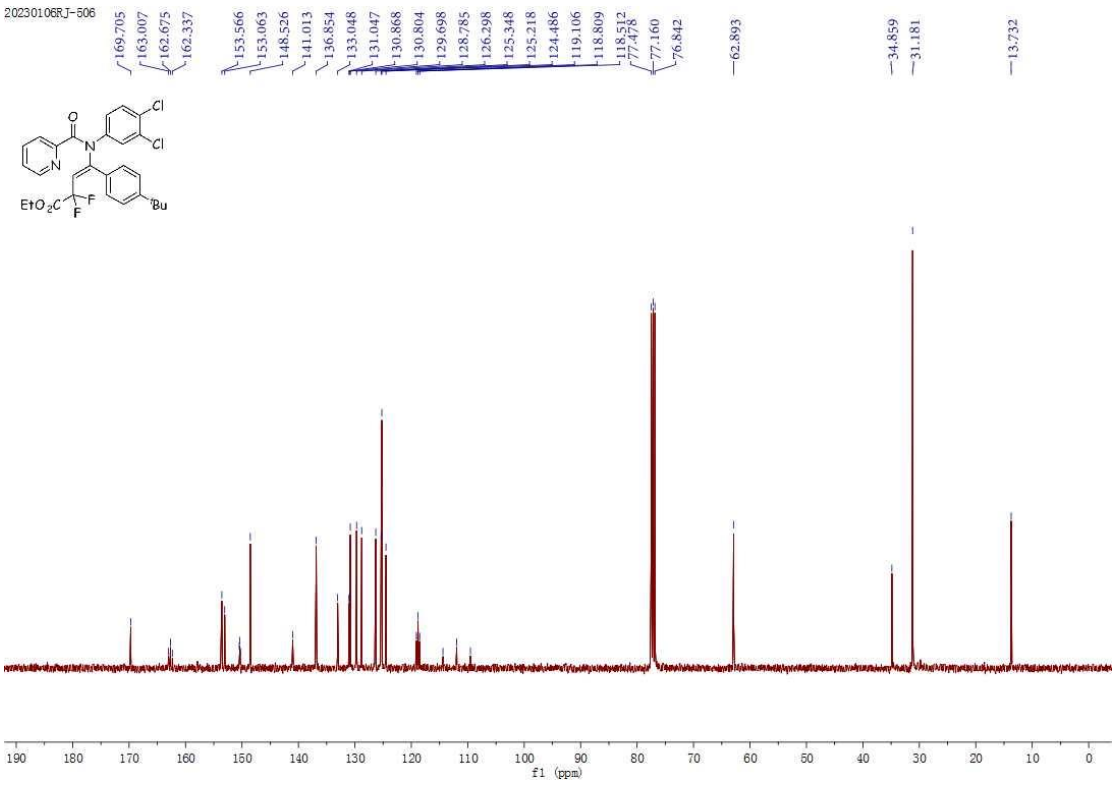
^{13}C – NMR spectrum of compound – **5v** (100 MHz, $CDCl_3$)



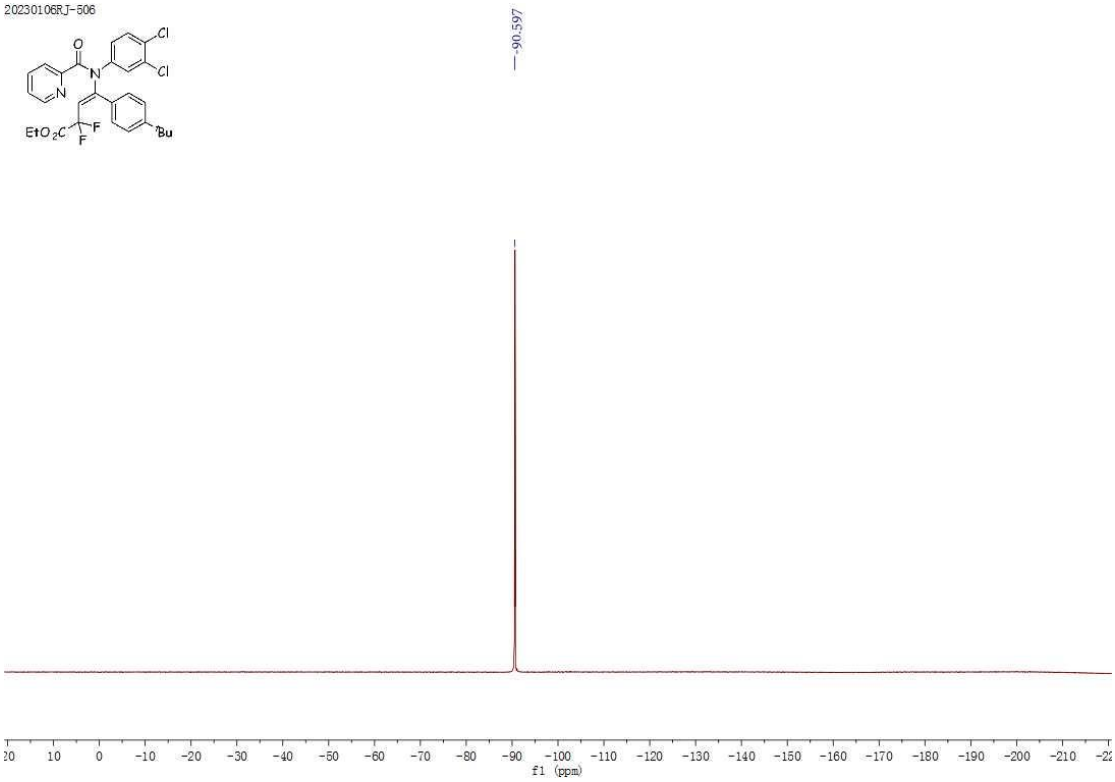
^{19}F – NMR spectrum of compound – **5v** (376 MHz, $CDCl_3$)



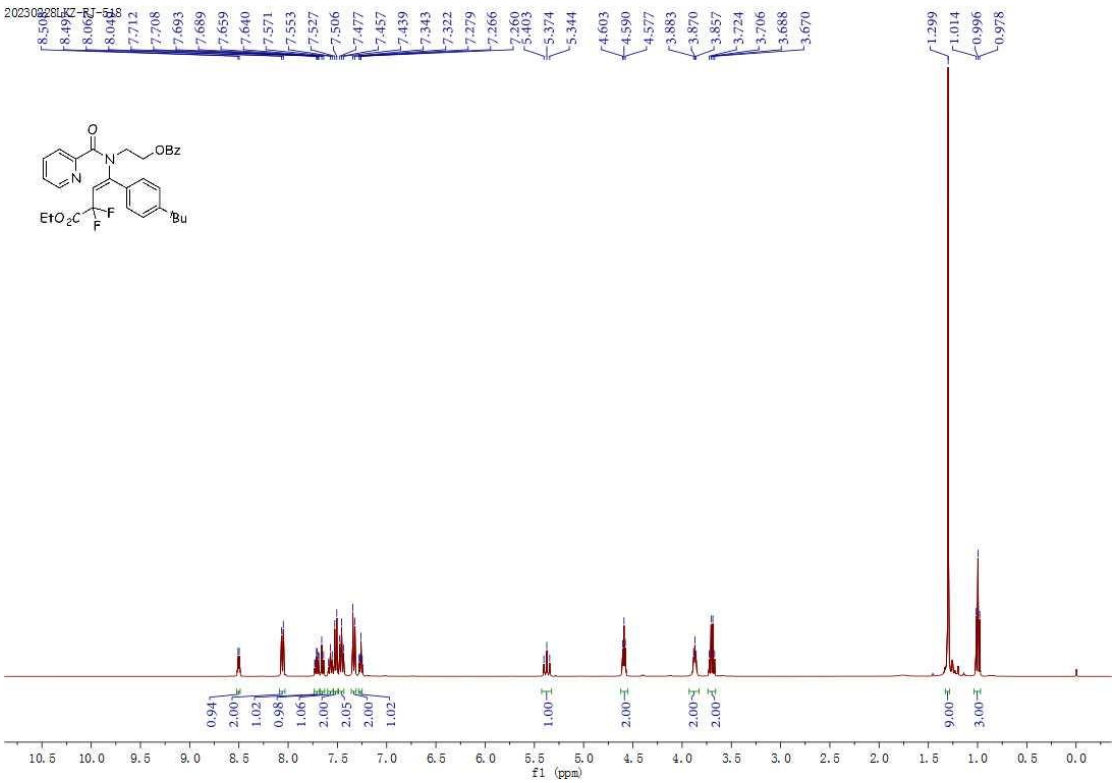
^{1}H – NMR spectrum of compound – **5w** (400 MHz, $CDCl_3$)



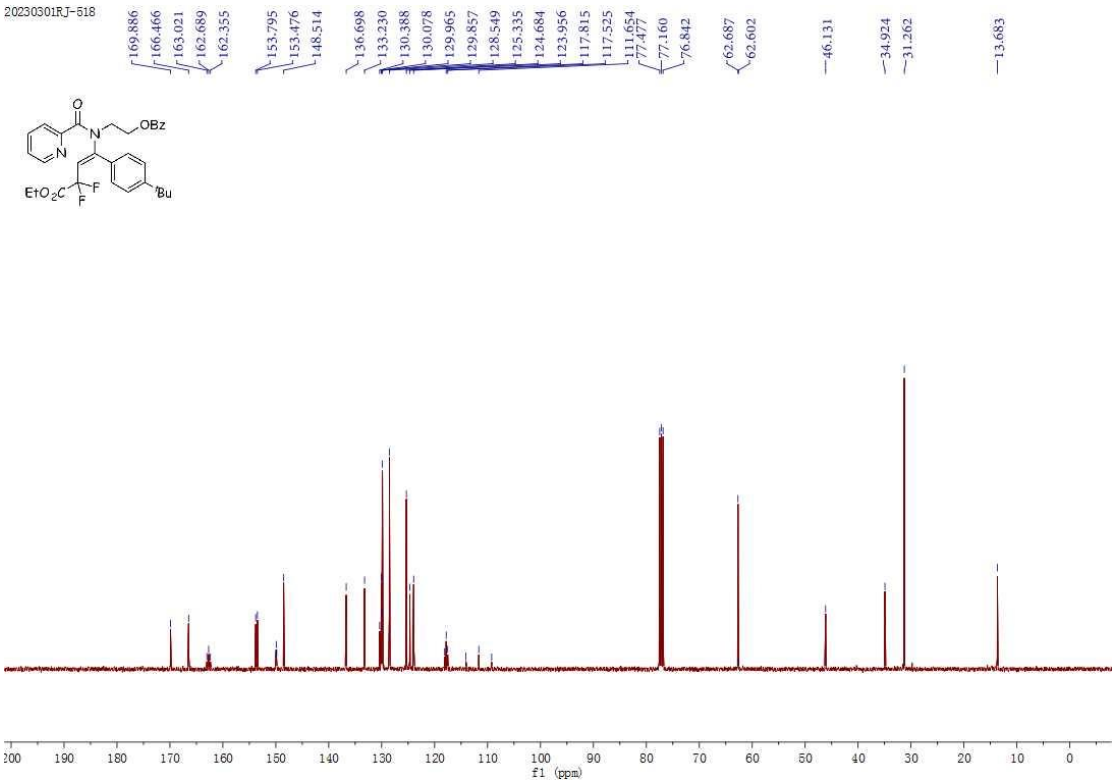
^{13}C – NMR spectrum of compound – **5w** (100 MHz, $CDCl_3$)



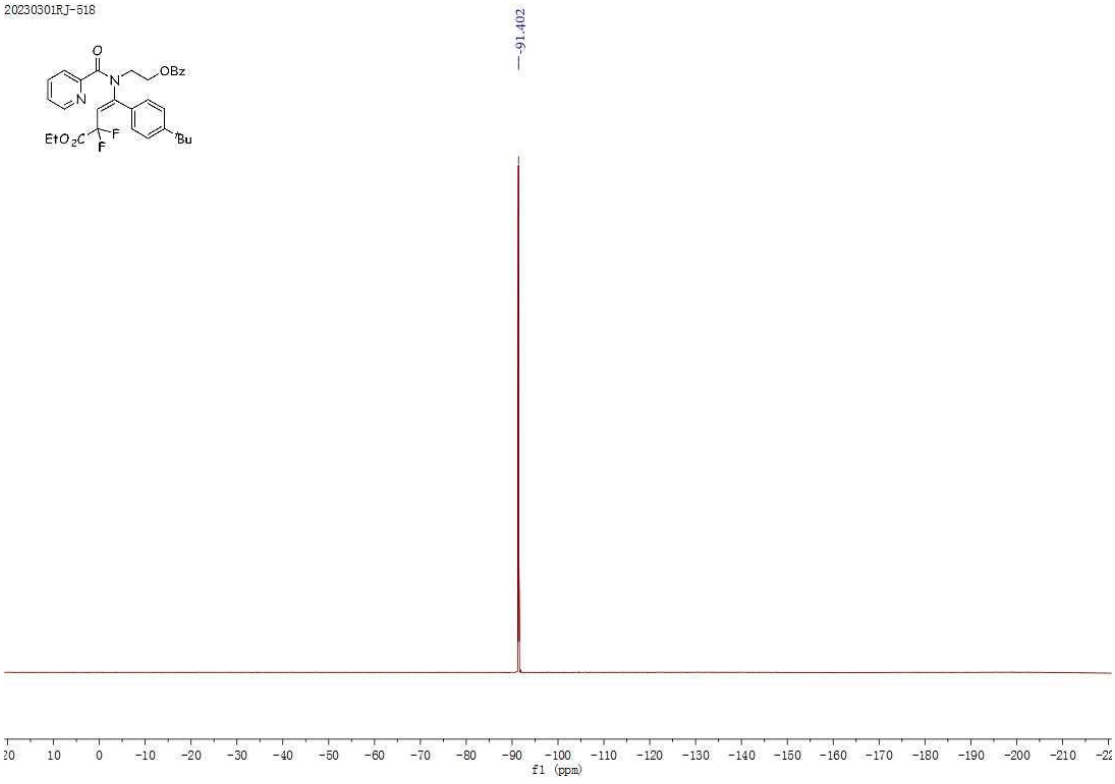
^{19}F – NMR spectrum of compound – **5w** (376 MHz, $CDCl_3$)



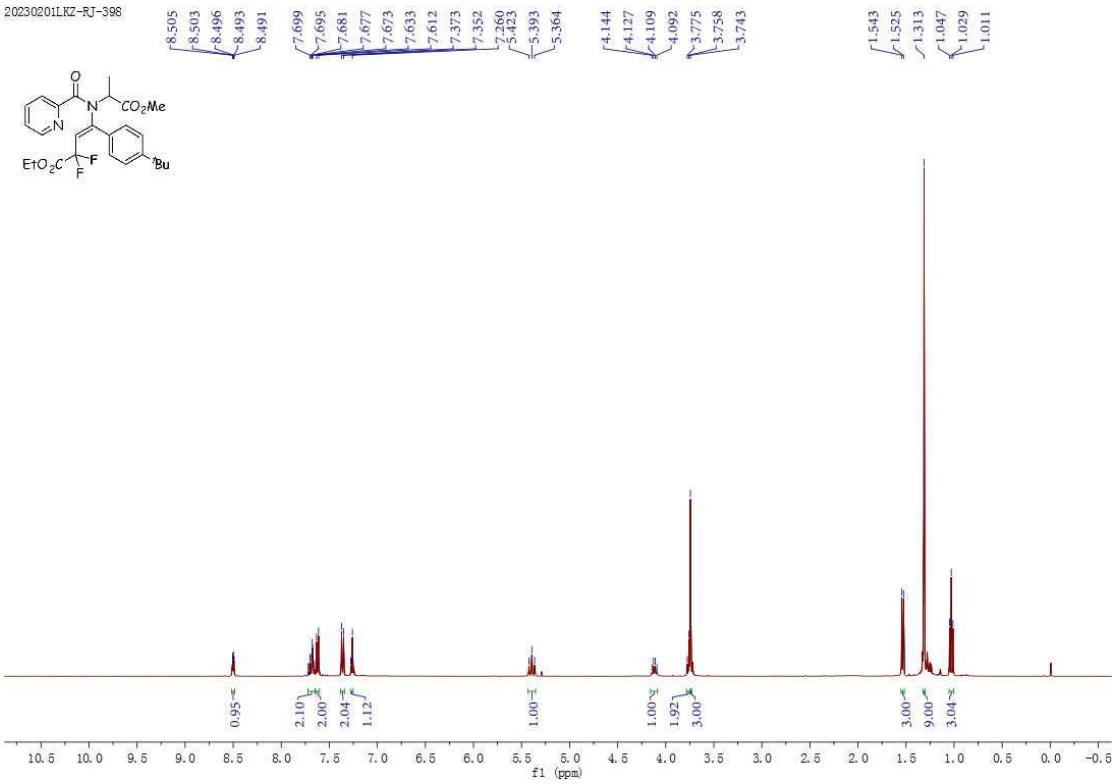
^{1}H – NMR spectrum of compound – **5x** (400 MHz, $CDCl_3$)



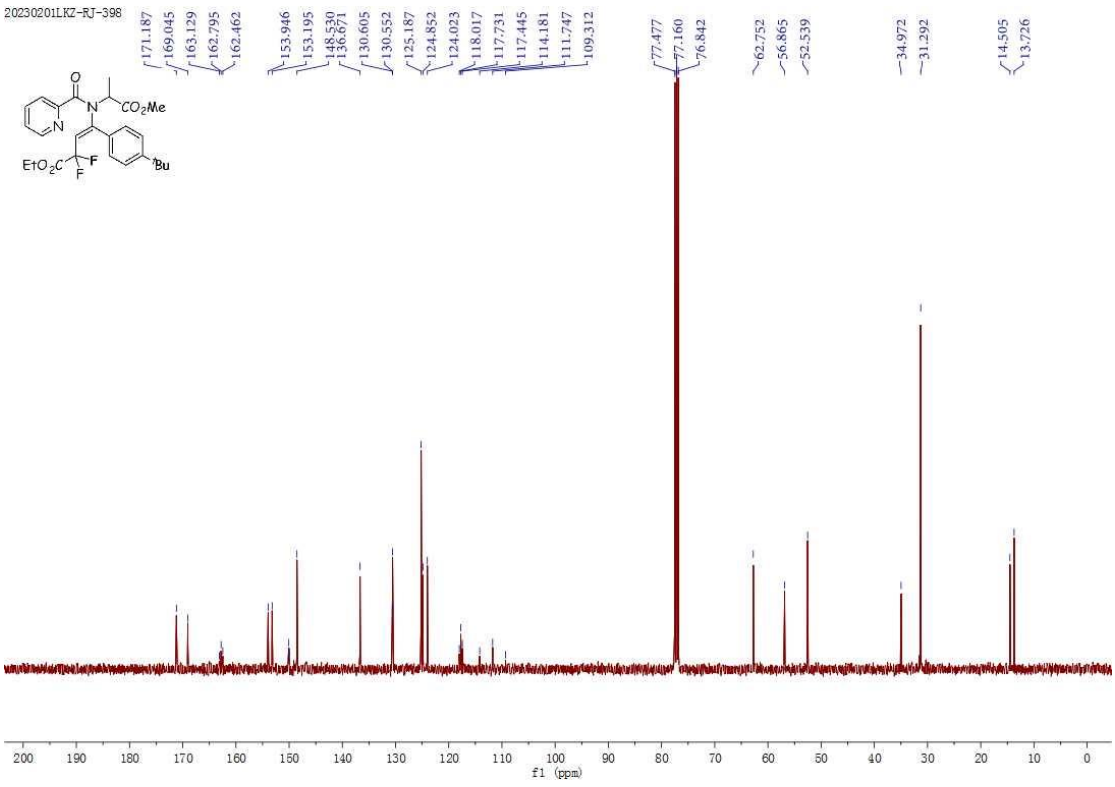
^{13}C – NMR spectrum of compound – **5x** (100 MHz, $CDCl_3$)



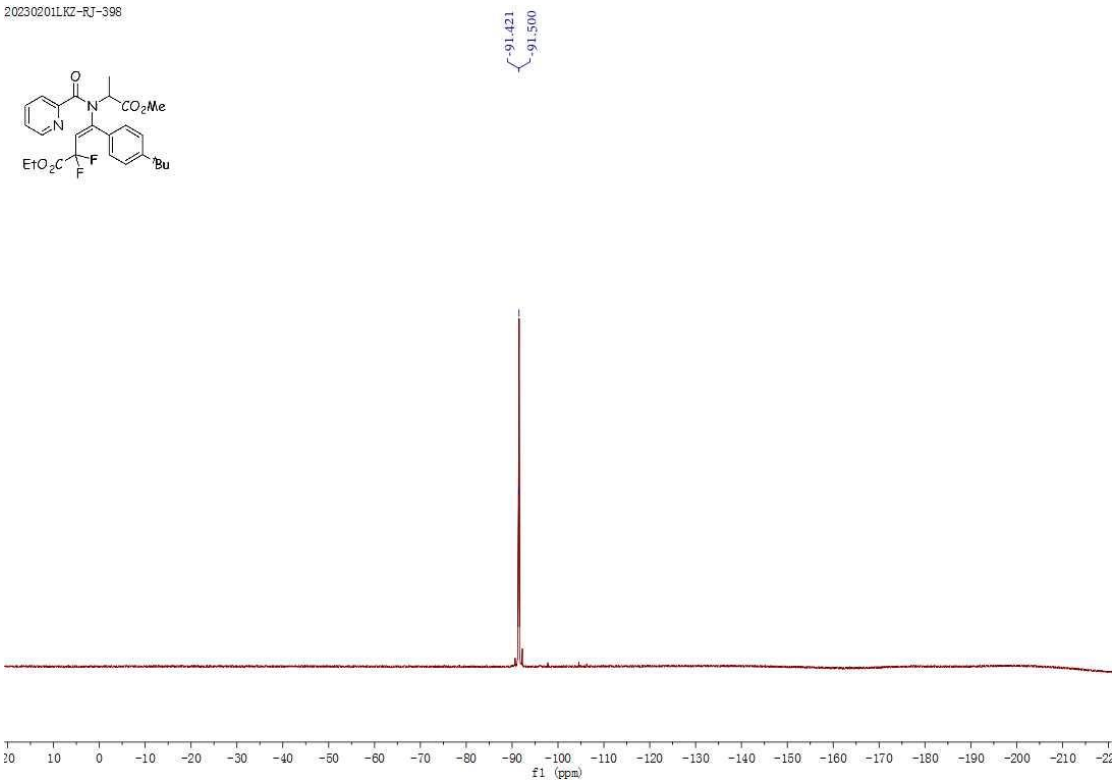
^{19}F – NMR spectrum of compound – **5x** (376 MHz, $CDCl_3$)



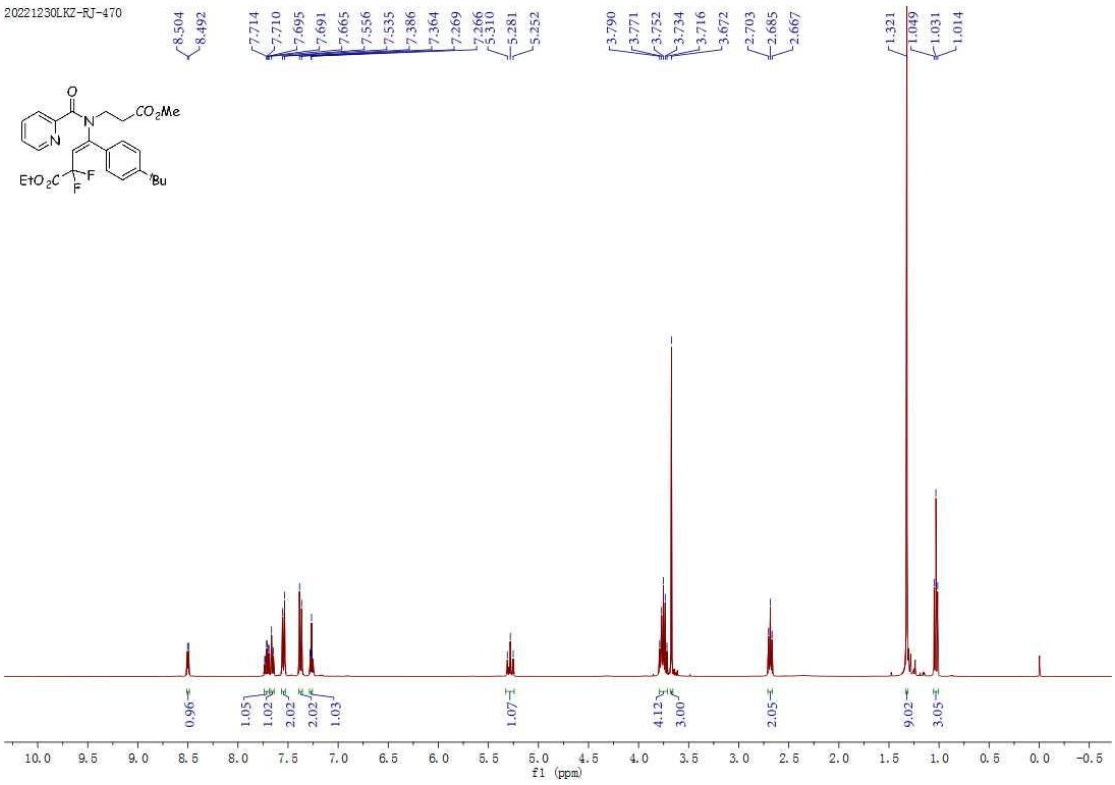
^{1}H – NMR spectrum of compound – **5y** (400 MHz, $CDCl_3$)



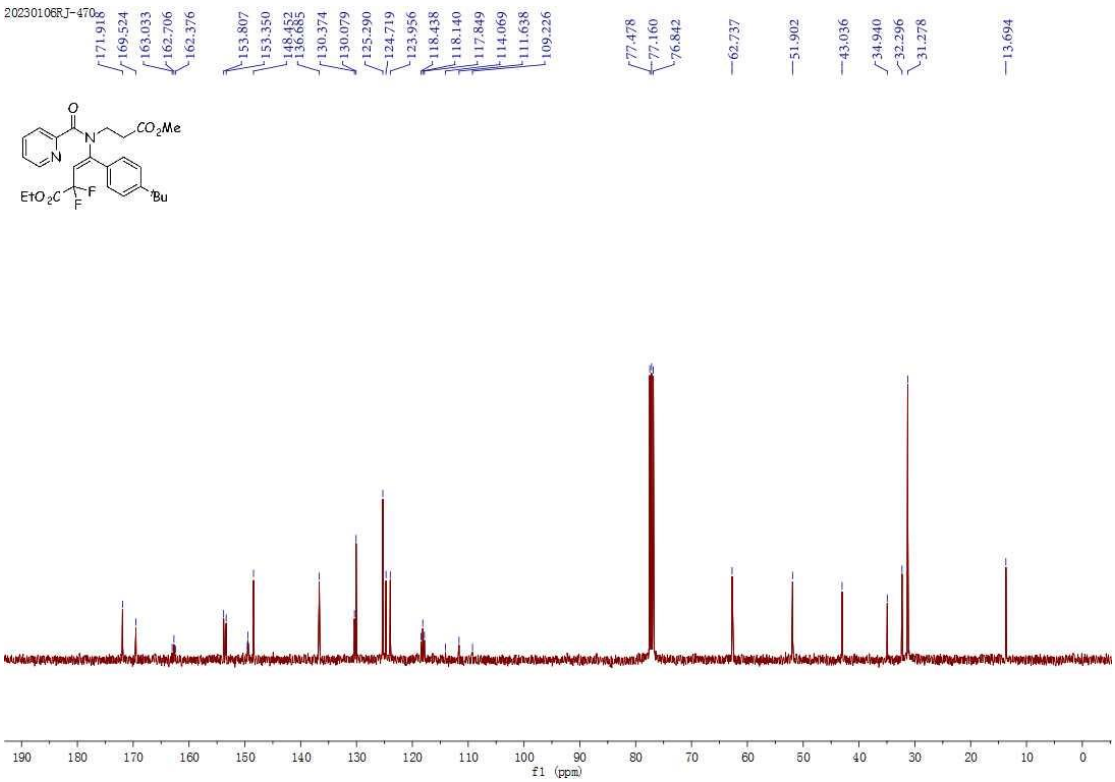
^{13}C – NMR spectrum of compound – **5y** (100 MHz, $CDCl_3$)



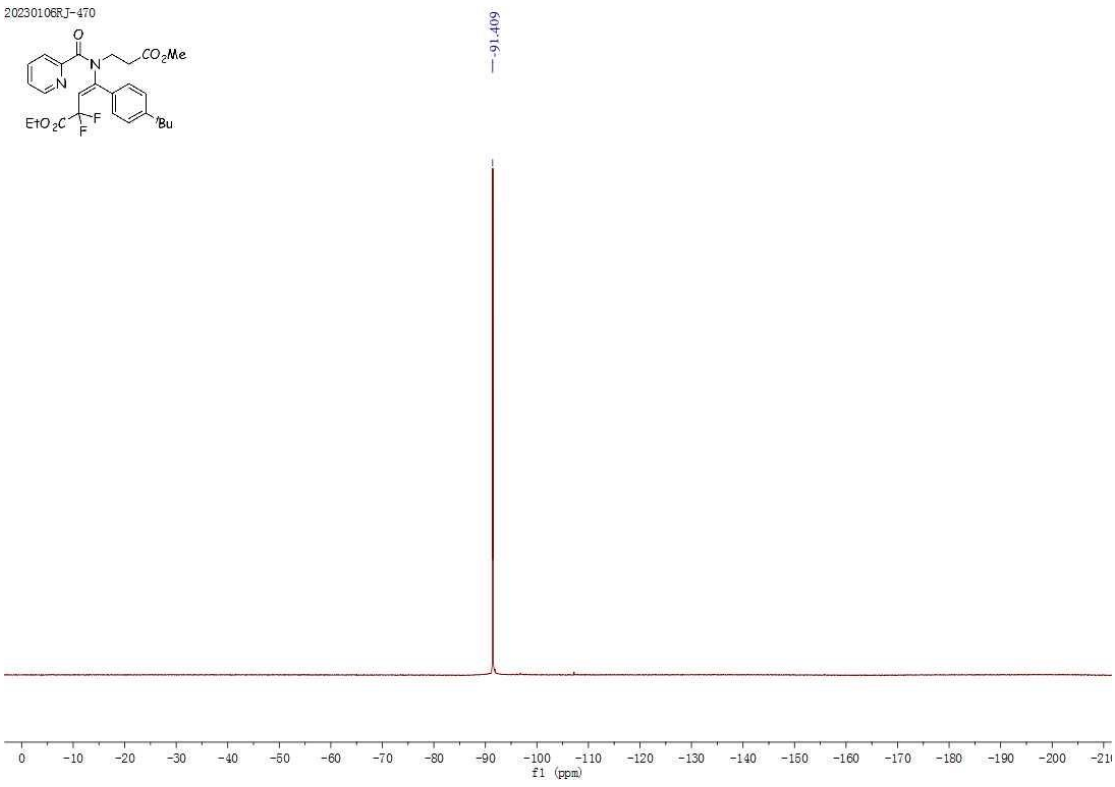
^{19}F – NMR spectrum of compound – **5y** (376 MHz, $CDCl_3$)



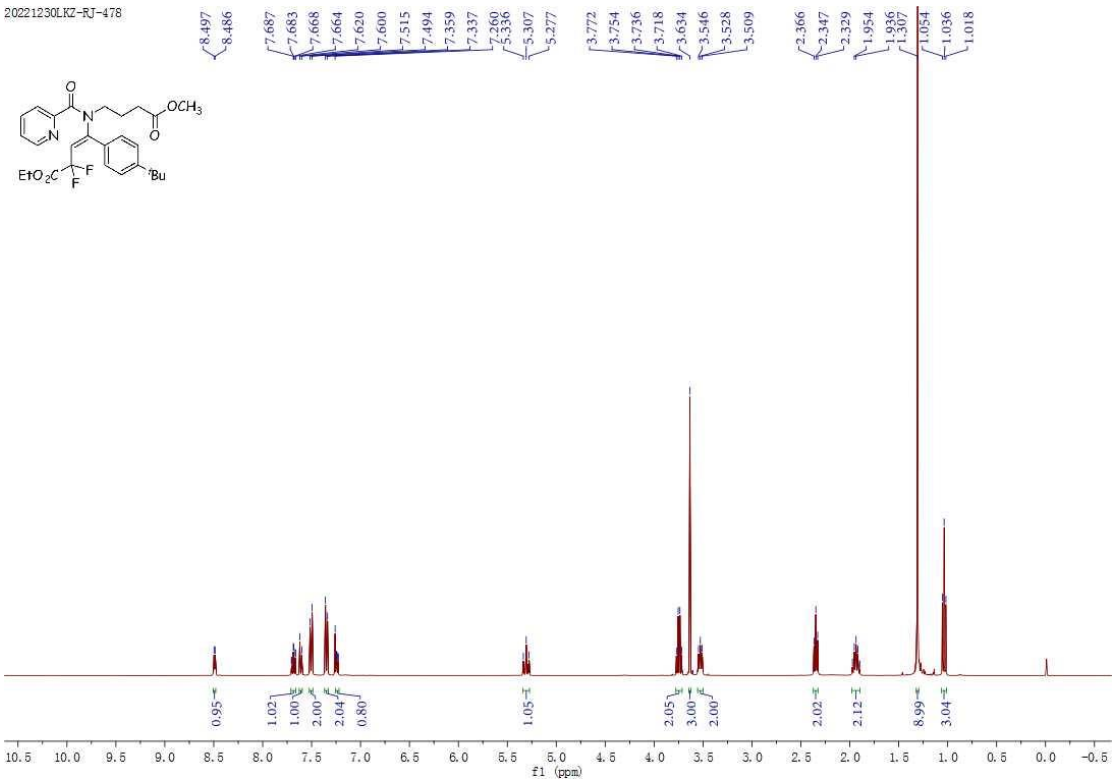
^{1}H – NMR spectrum of compound – **5z** (400 MHz, $CDCl_3$)



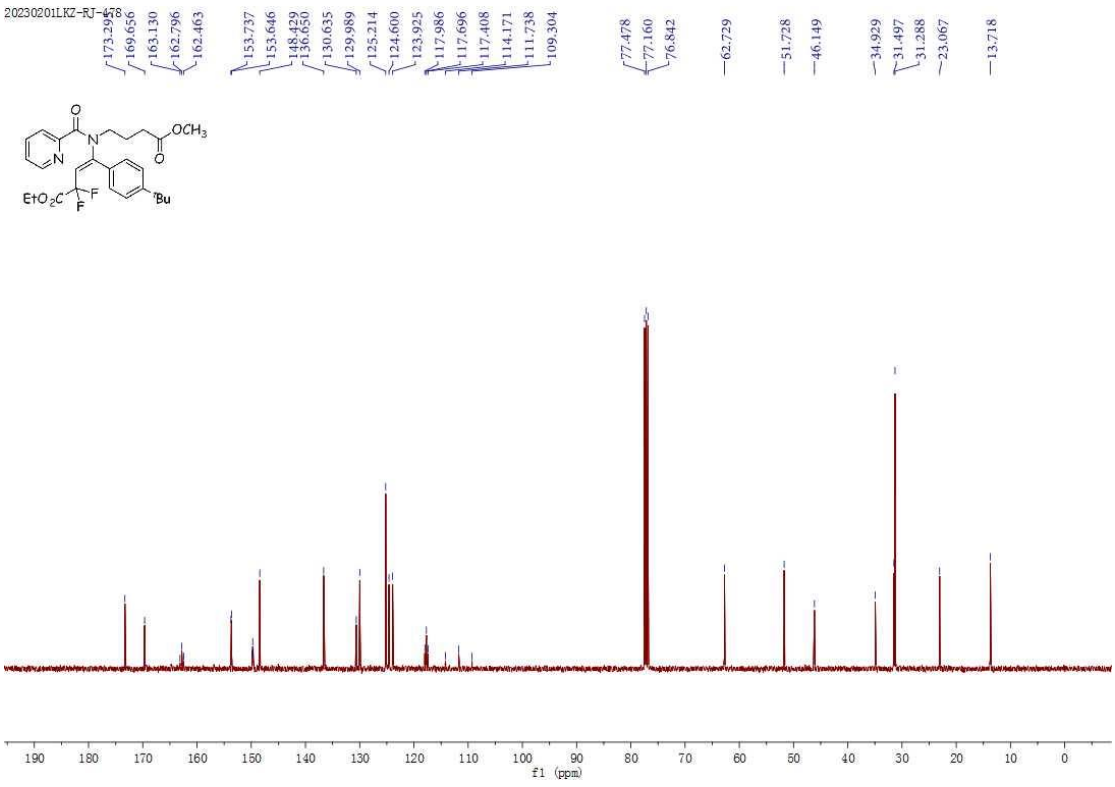
^{13}C – NMR spectrum of compound – **5z** (100 MHz, $CDCl_3$)



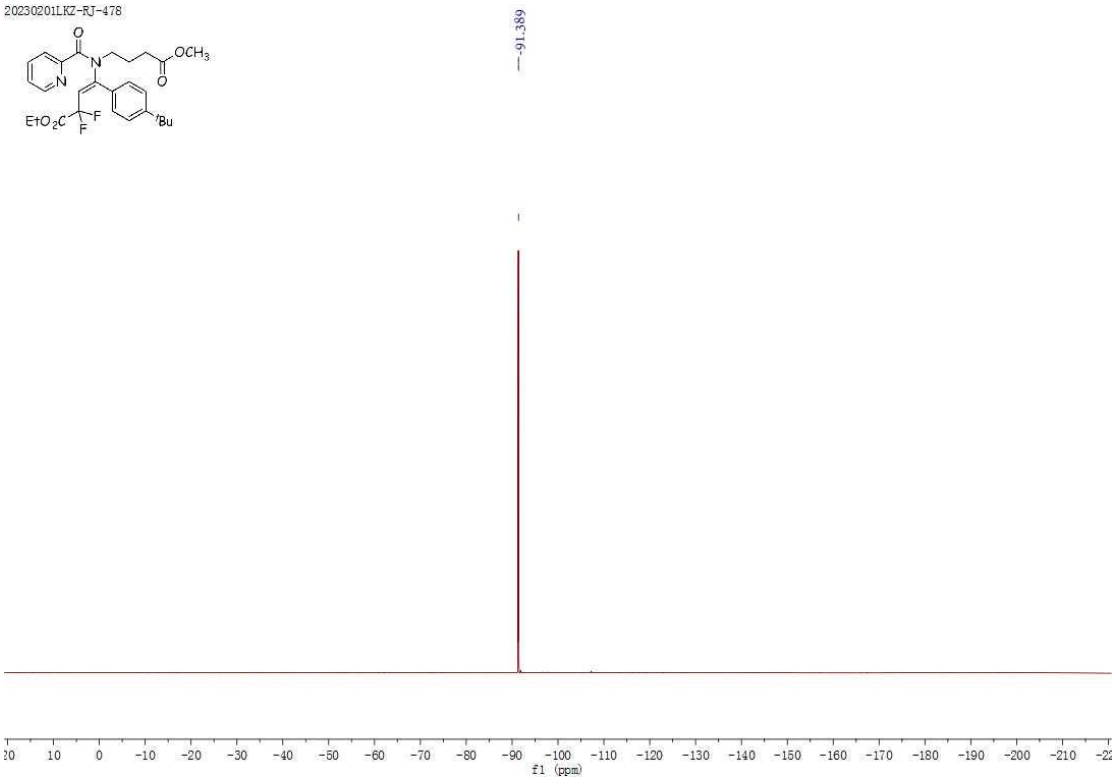
^{19}F – NMR spectrum of compound – **5z** (376 MHz, $CDCl_3$)



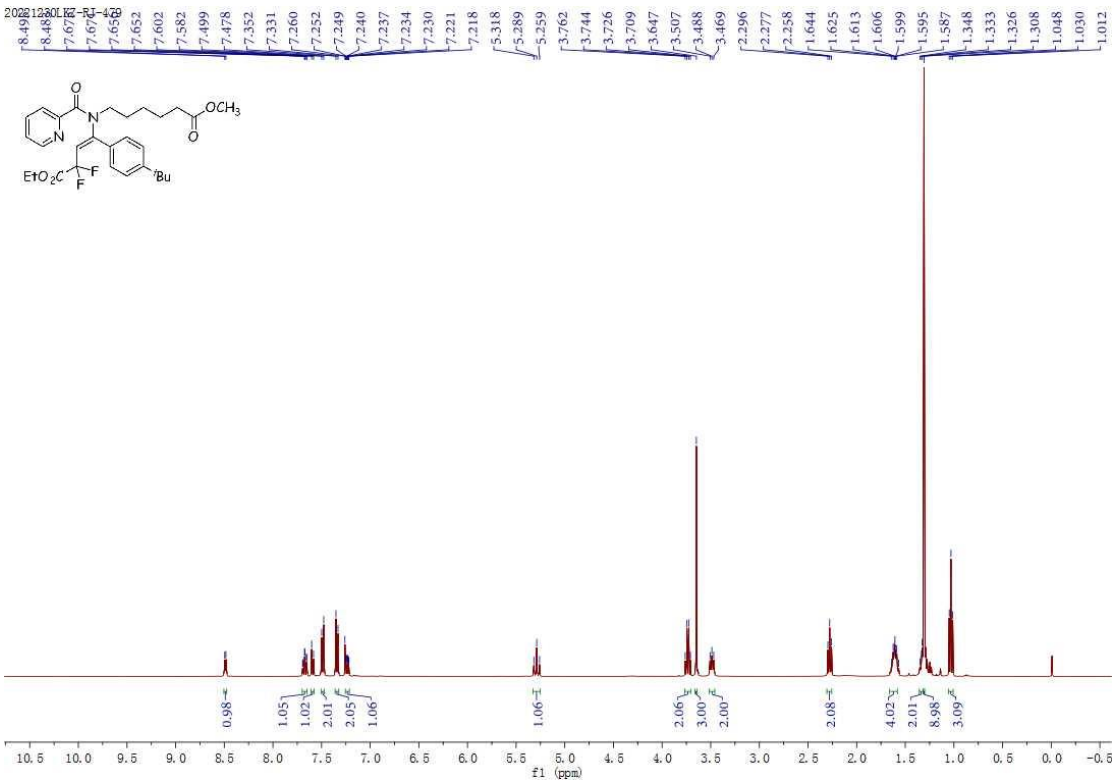
^{1}H – NMR spectrum of compound – **5aa** (400 MHz, $CDCl_3$)



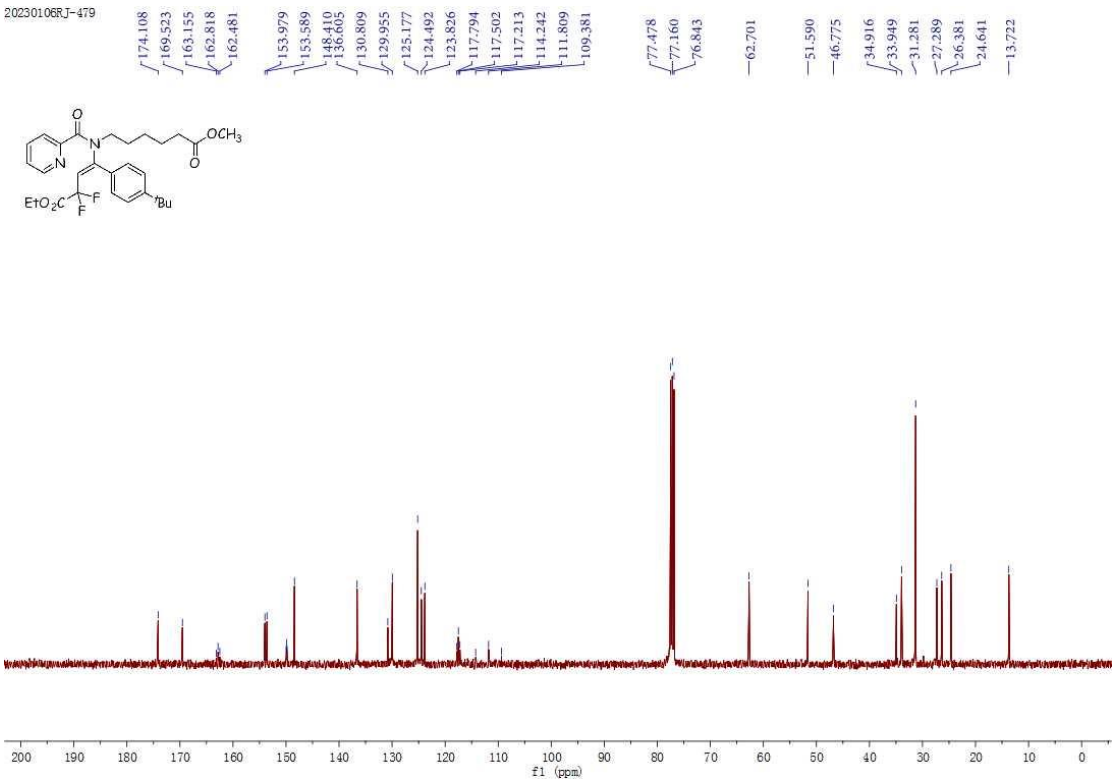
^{13}C – NMR spectrum of compound –**5aa** (100 MHz, $CDCl_3$)



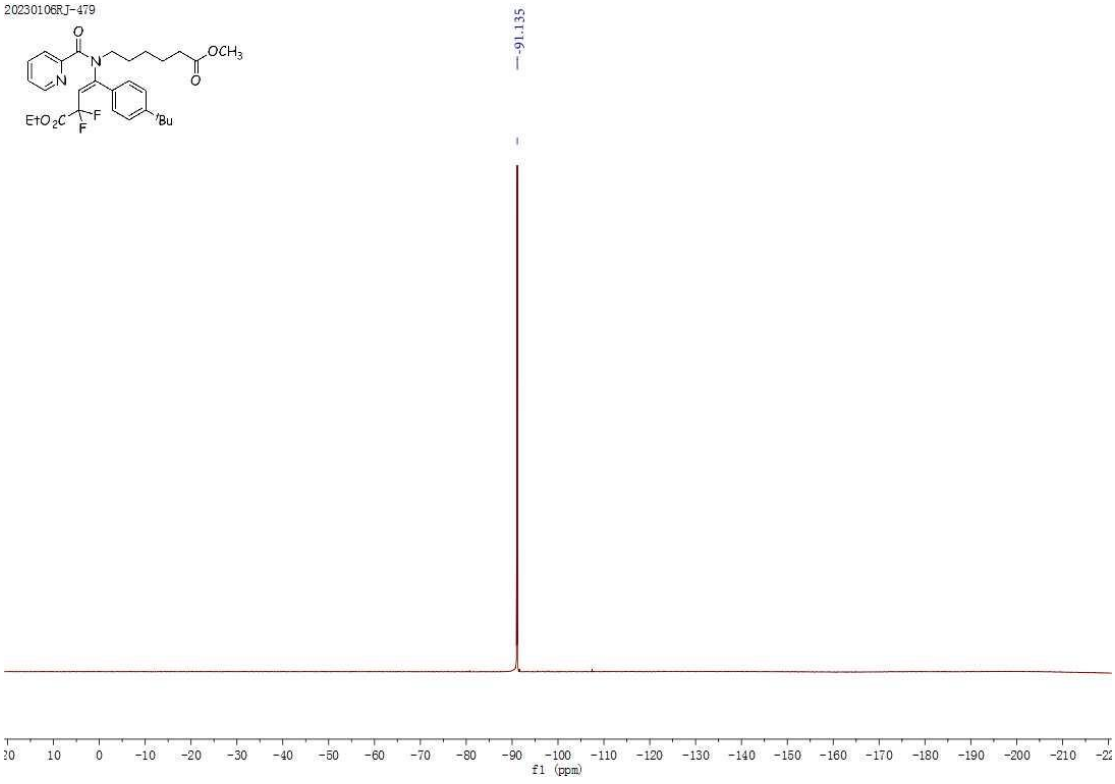
^{19}F – NMR spectrum of compound – **5aa** (376 MHz, $CDCl_3$)



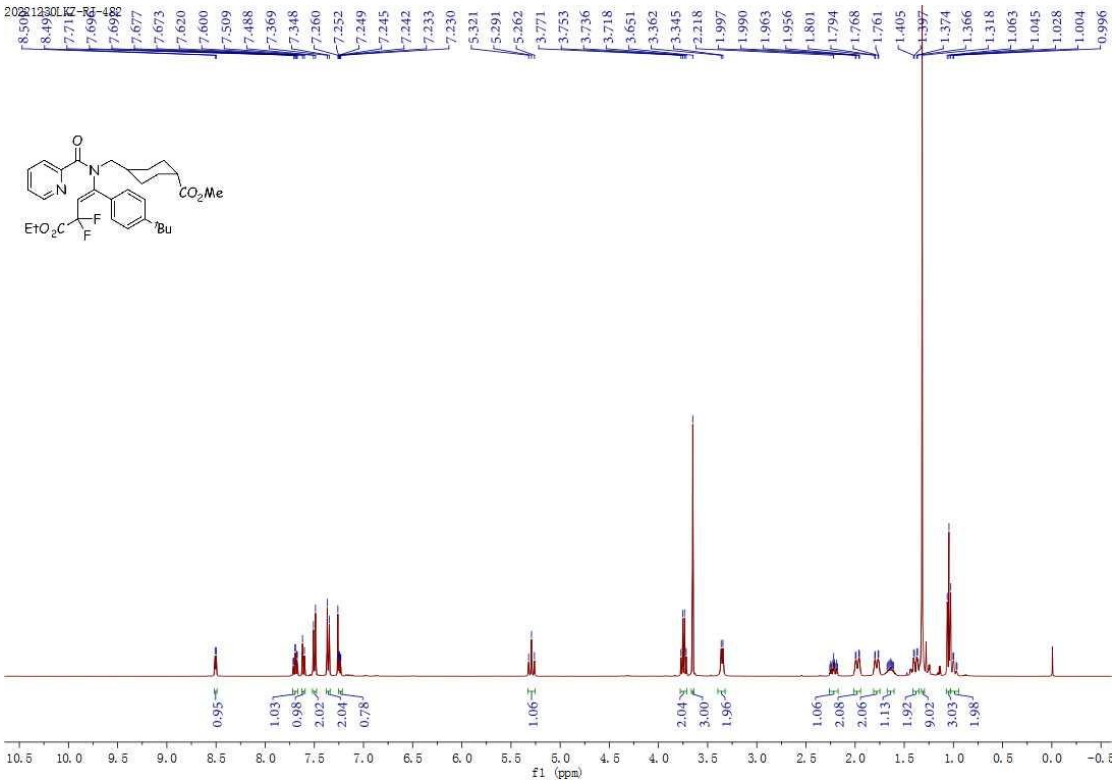
^{1}H – NMR spectrum of compound – **5ab** (400 MHz, $CDCl_3$)



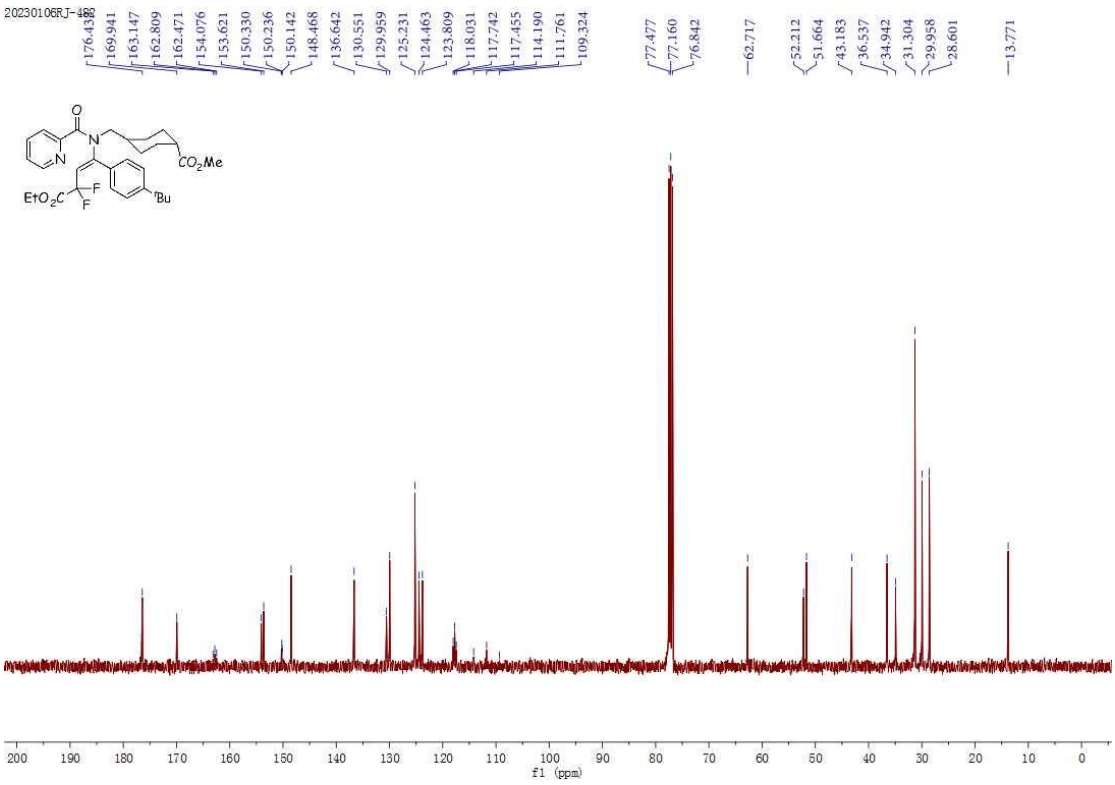
^{13}C – NMR spectrum of compound – **5ab** (100 MHz, $CDCl_3$)



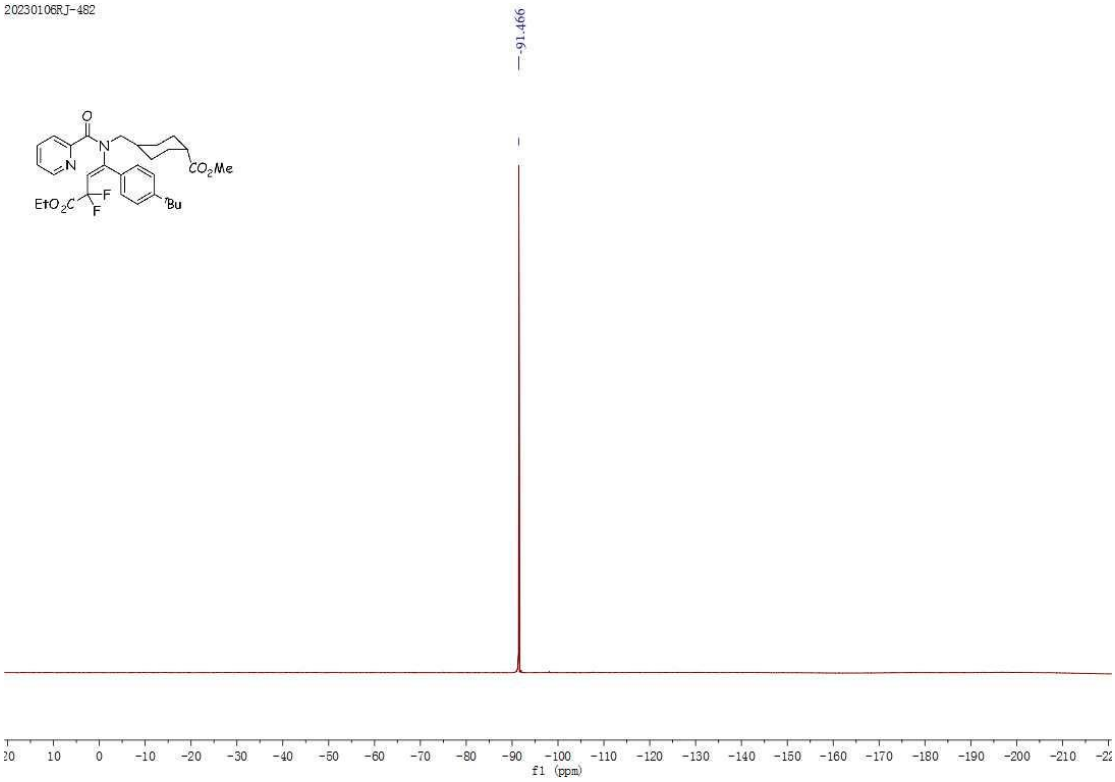
^{19}F – NMR spectrum of compound – **5ab** (376 MHz, $CDCl_3$)



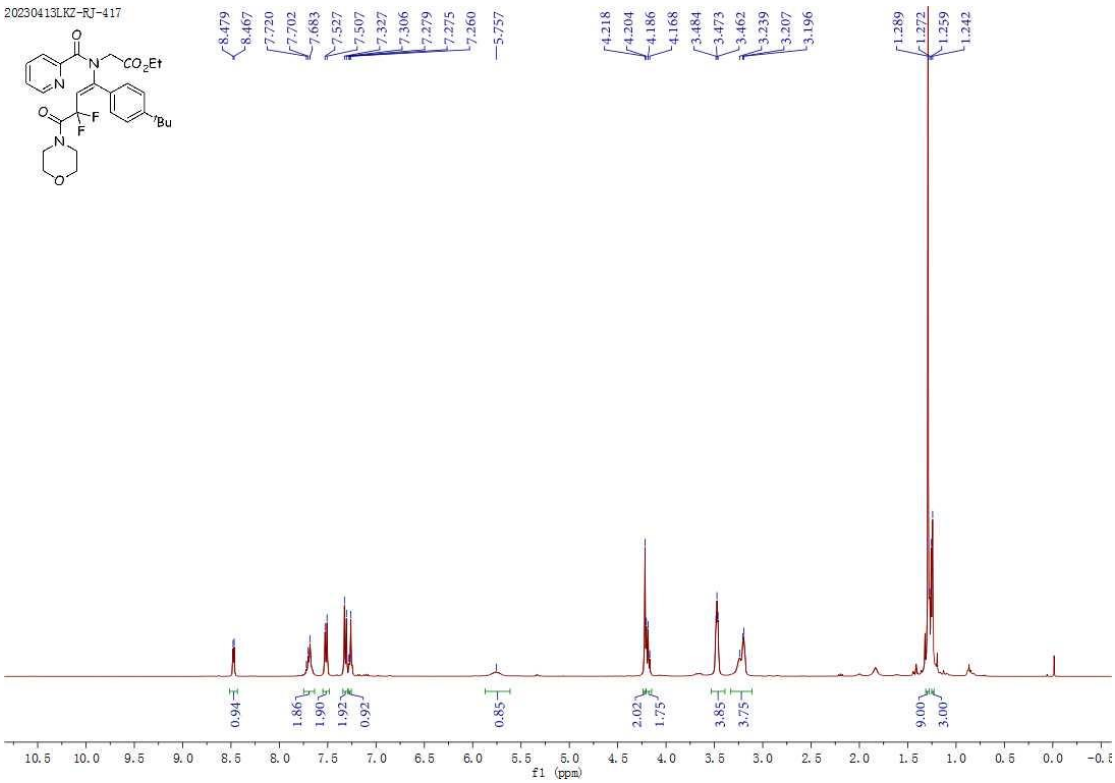
^{1}H – NMR spectrum of compound – **5ac** (400 MHz, $CDCl_3$)



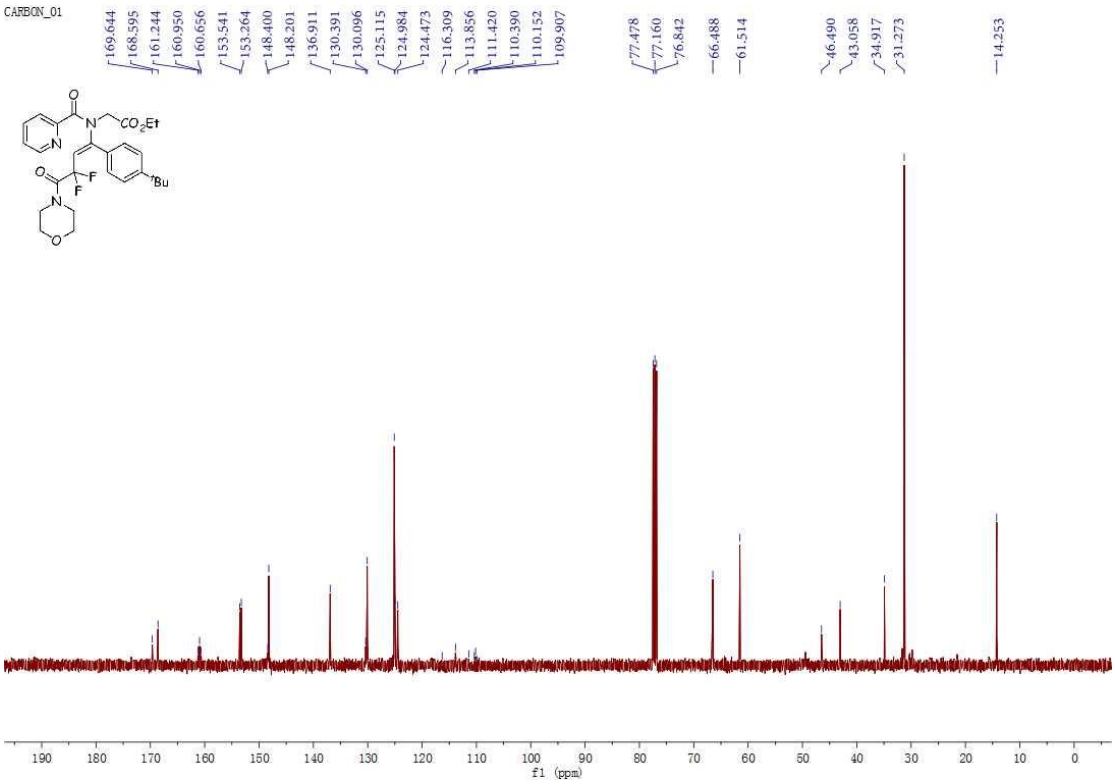
^{13}C – NMR spectrum of compound – **5ac** (100 MHz, $CDCl_3$)



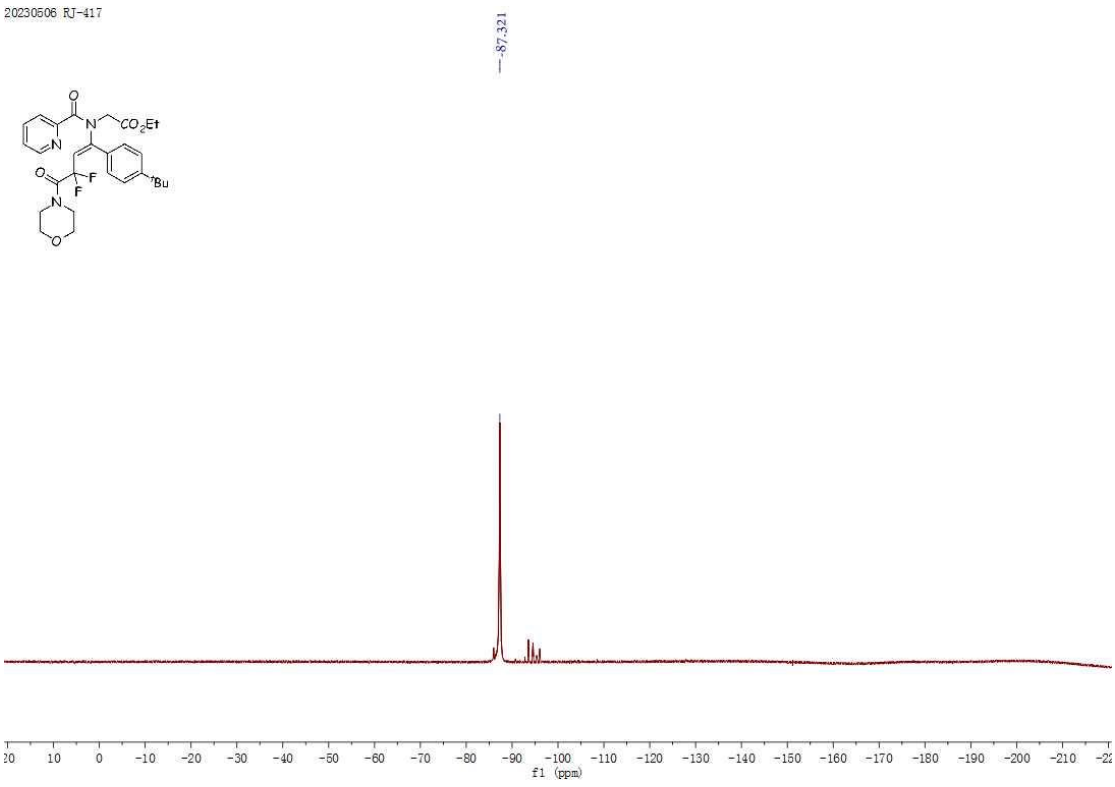
^{19}F – NMR spectrum of compound – **5ac** (376 MHz, $CDCl_3$)



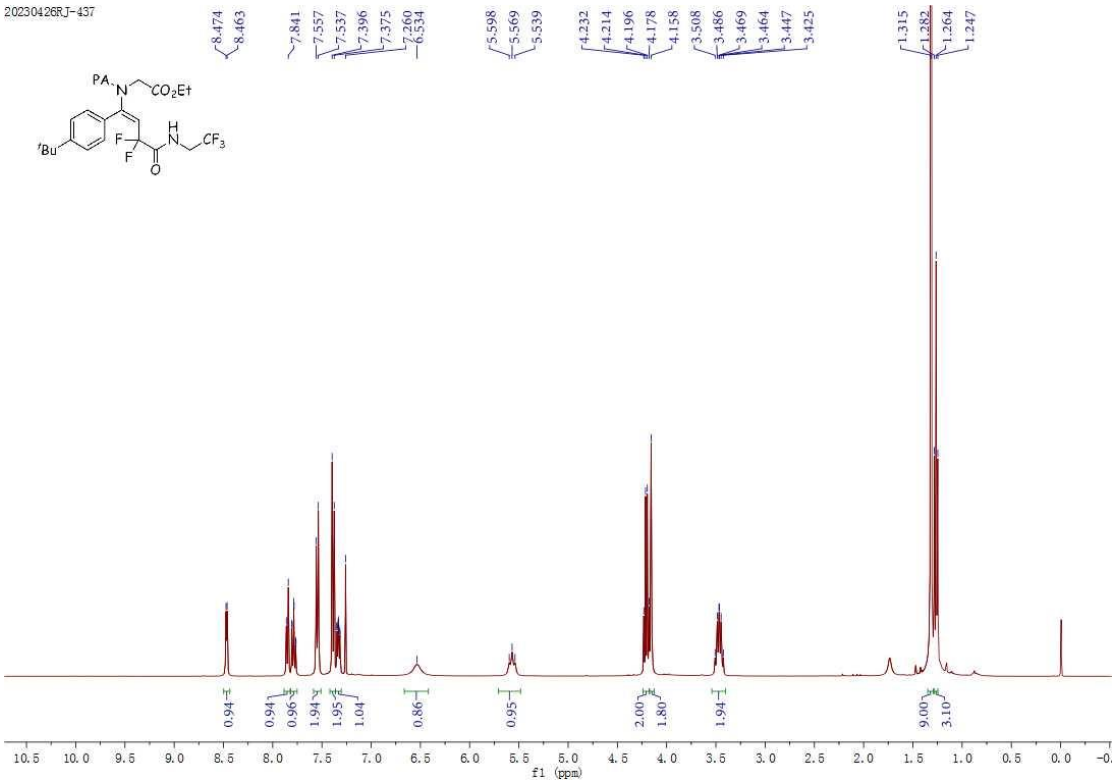
^{1}H – NMR spectrum of compound – **6a** (400 MHz, $CDCl_3$)



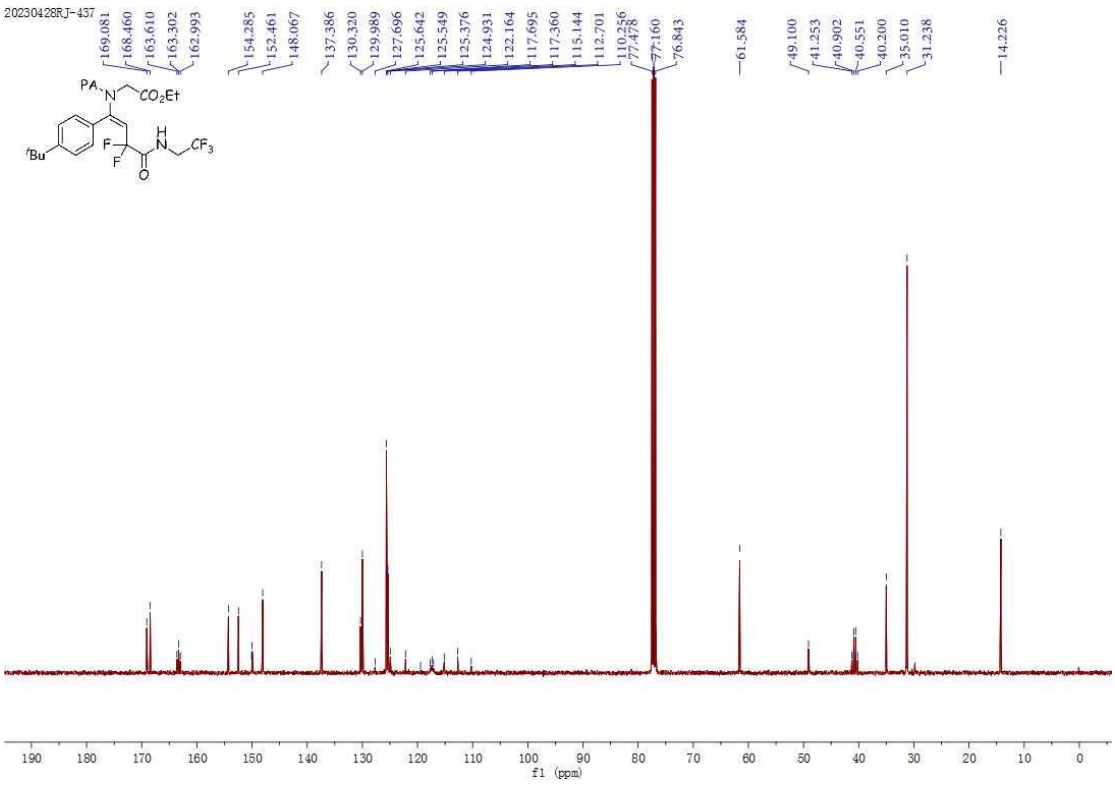
^{13}C – NMR spectrum of compound – **6a** (100 MHz, $CDCl_3$)



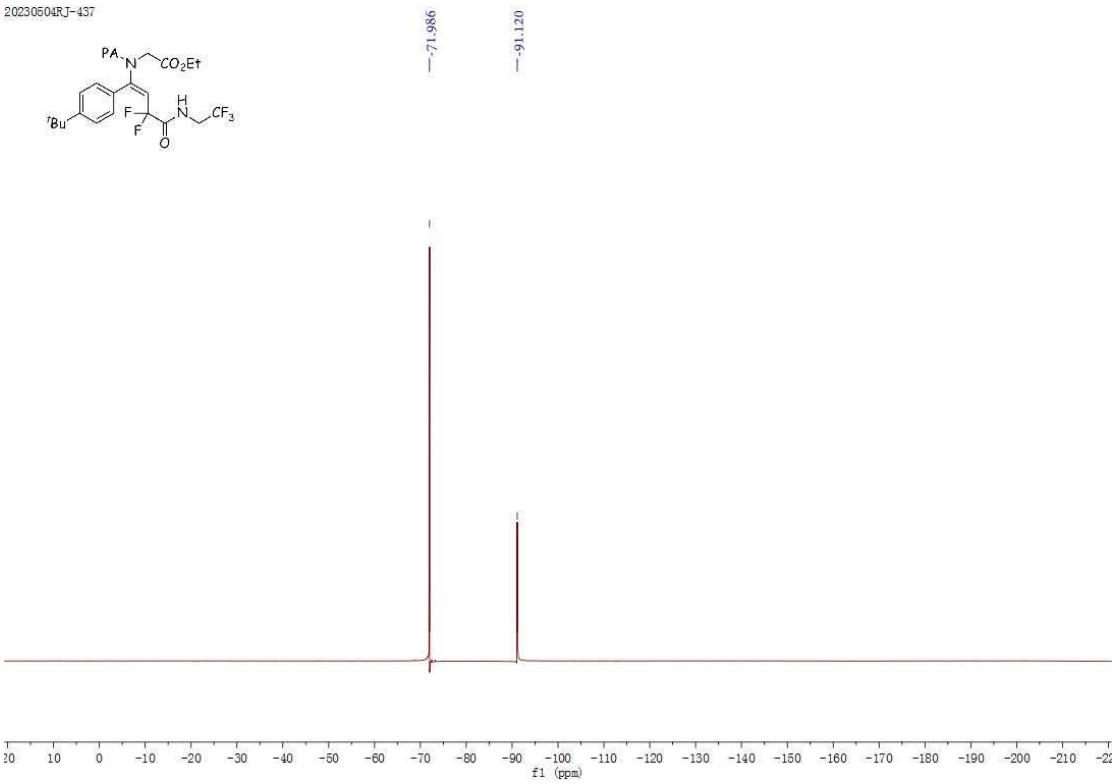
^{19}F – NMR spectrum of compound – **6a** (376 MHz, $CDCl_3$)



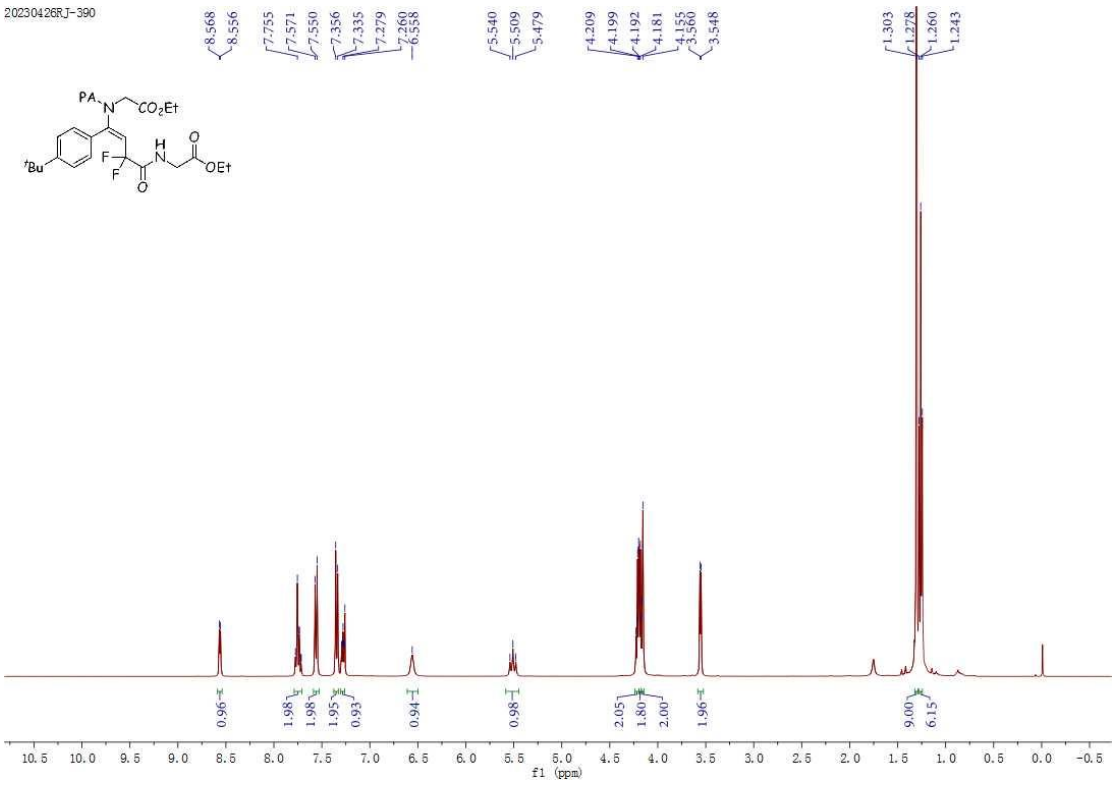
^{1}H – NMR spectrum of compound – **6b** (400 MHz, $CDCl_3$)



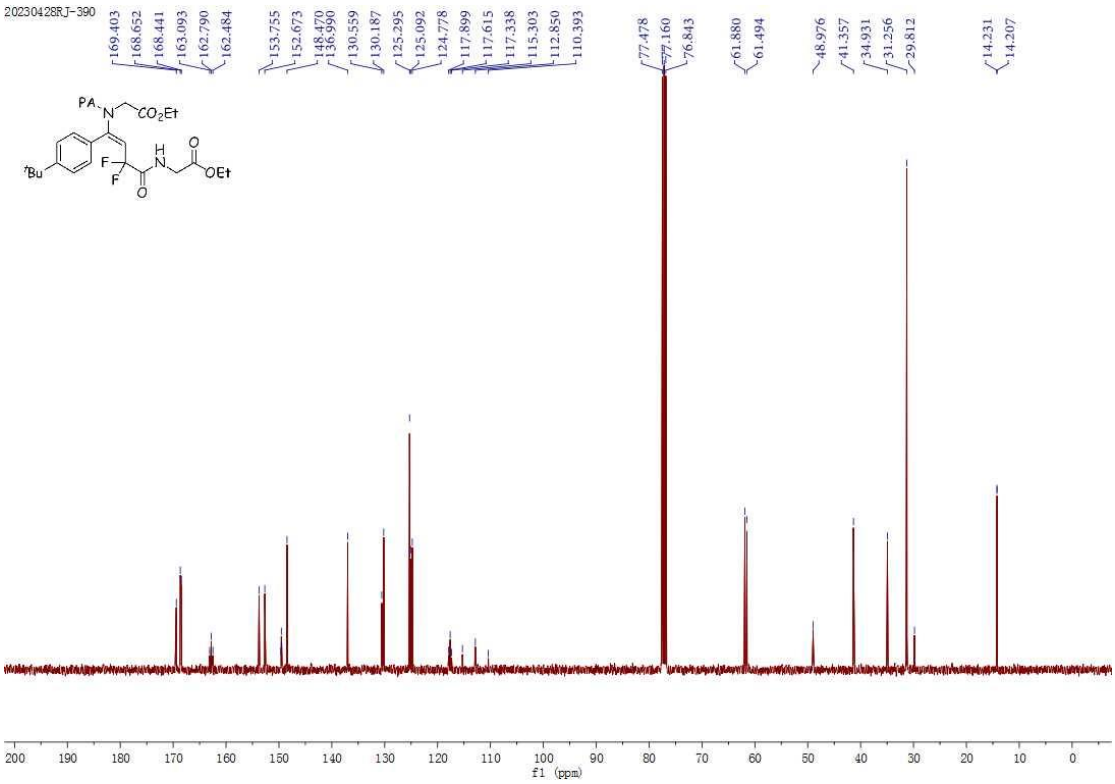
^{13}C – NMR spectrum of compound – **6b** (100 MHz, $CDCl_3$)



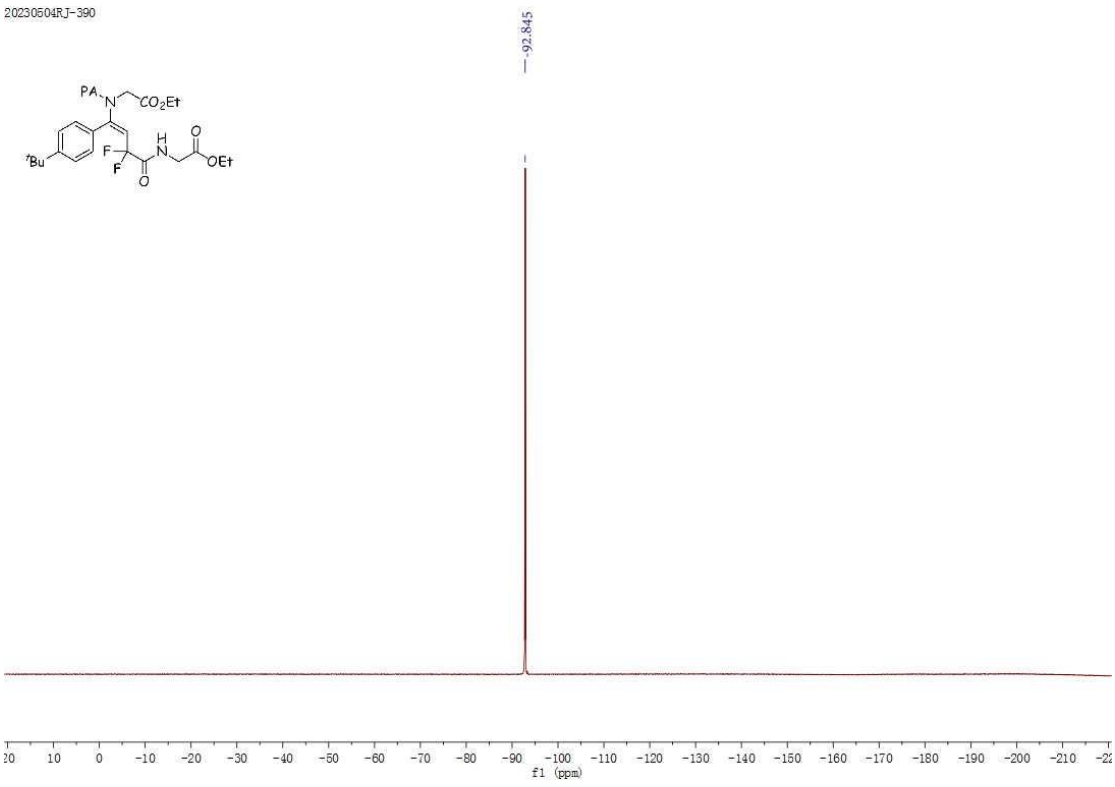
^{19}F – NMR spectrum of compound – **6b** (376 MHz, $CDCl_3$)



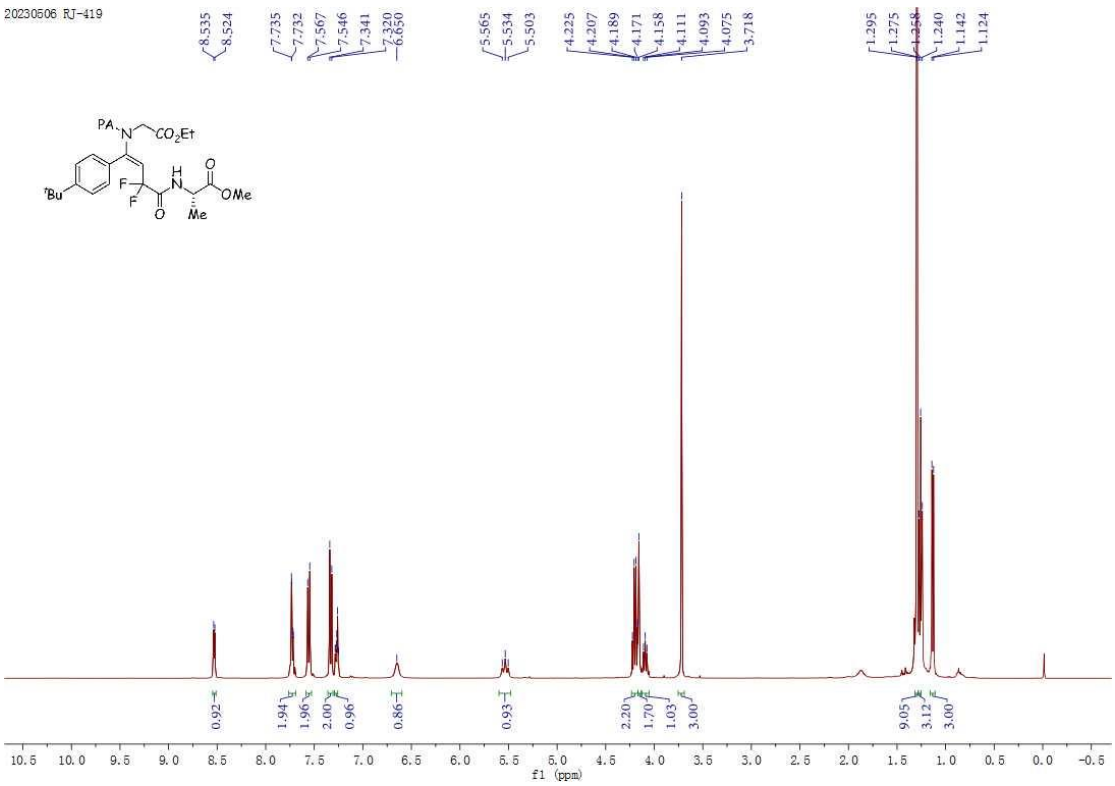
^{1}H – NMR spectrum of compound – **6c** (400 MHz, $CDCl_3$)



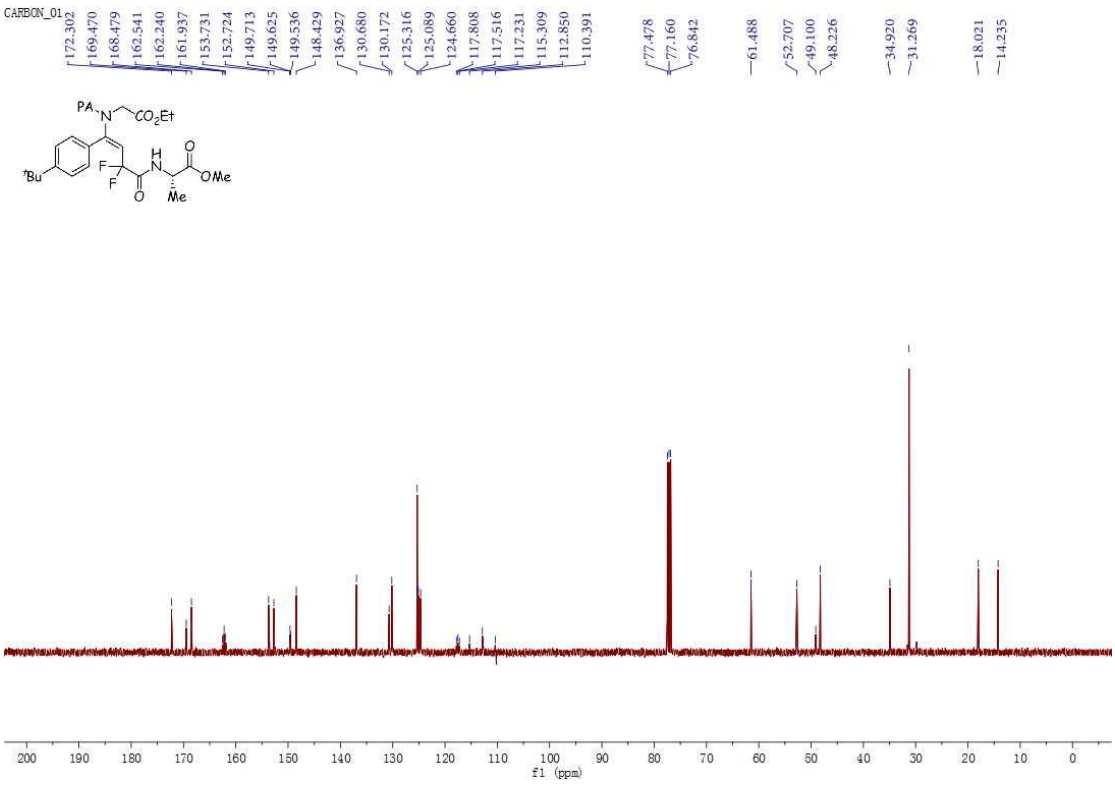
^{13}C – NMR spectrum of compound – **6c** (100 MHz, $CDCl_3$)



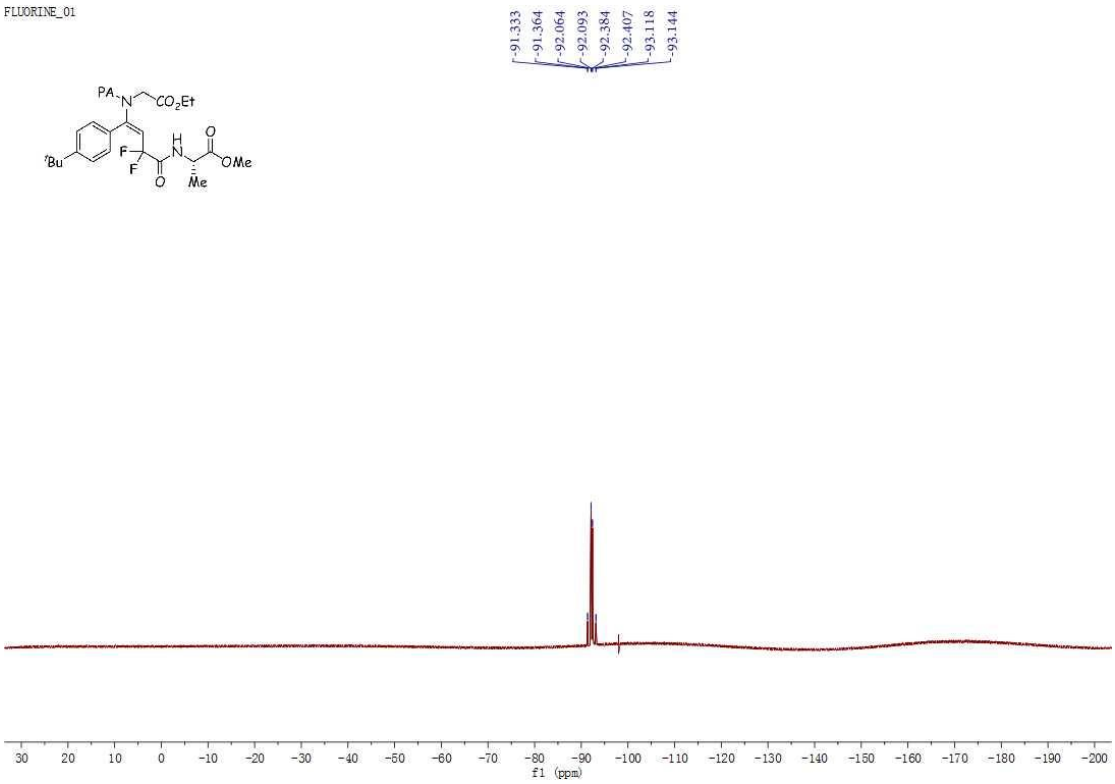
^{19}F – NMR spectrum of compound – **6c** (376 MHz, $CDCl_3$)



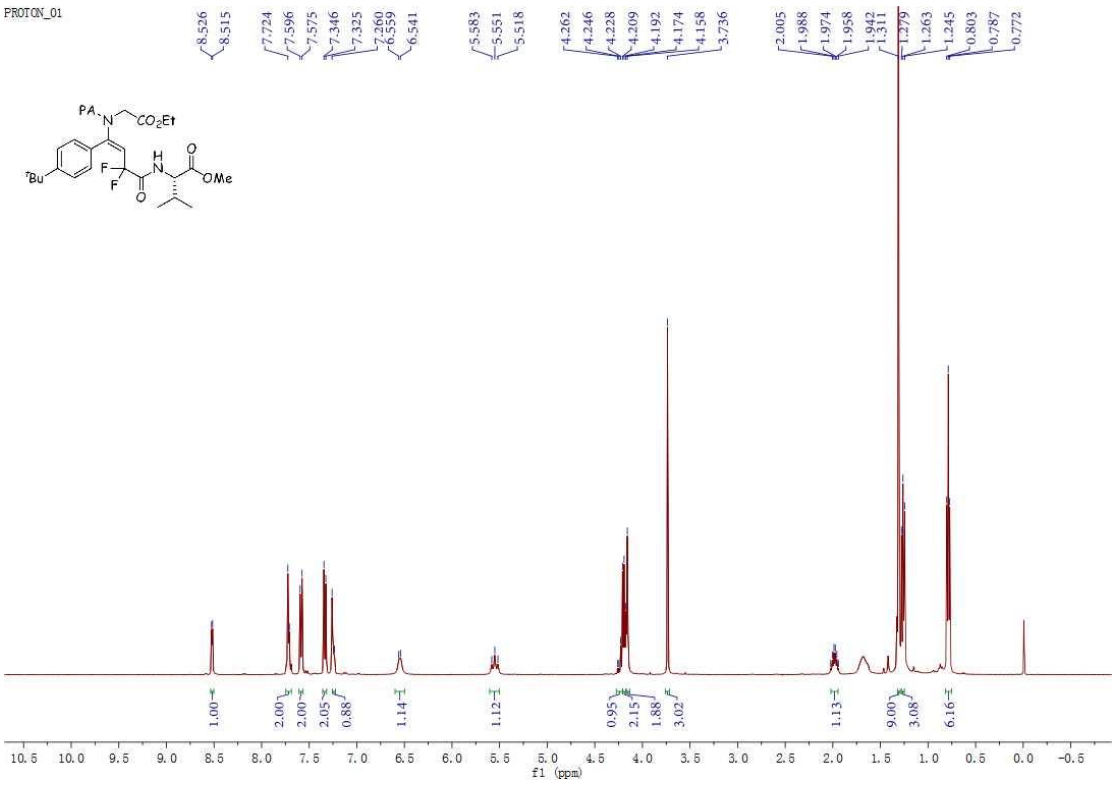
^{1}H – NMR spectrum of compound – **6d** (400 MHz, $CDCl_3$)



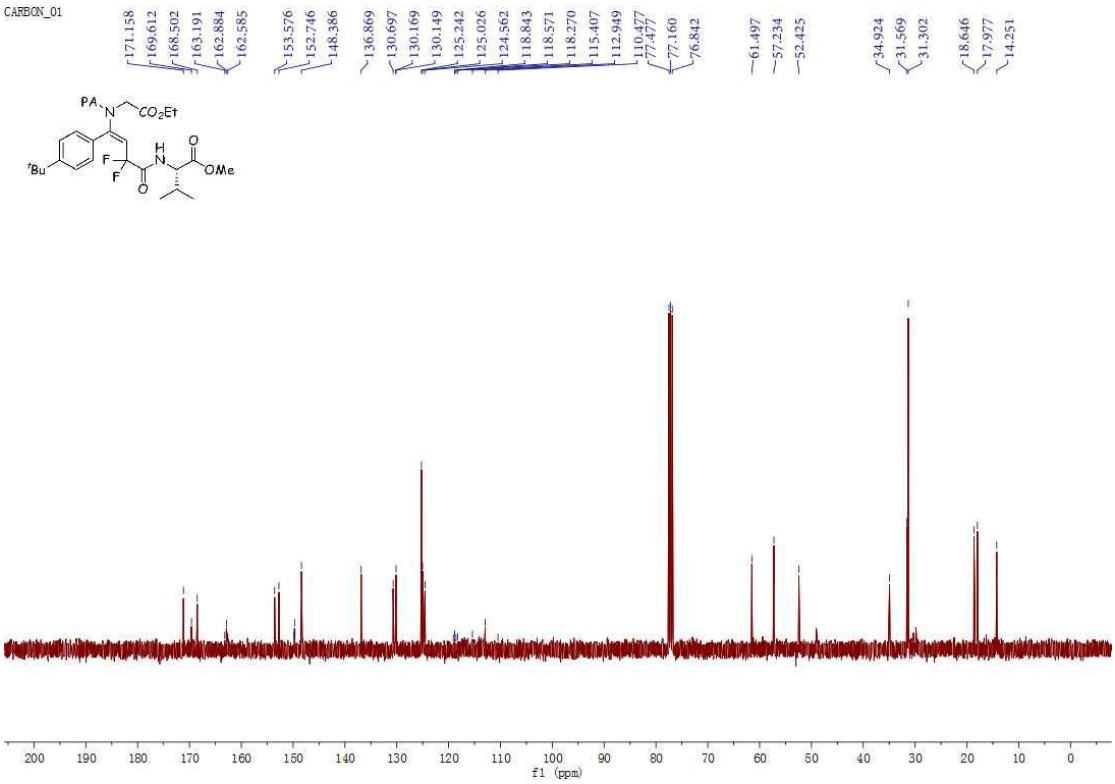
^{13}C – NMR spectrum of compound – **6d** (100 MHz, $CDCl_3$)



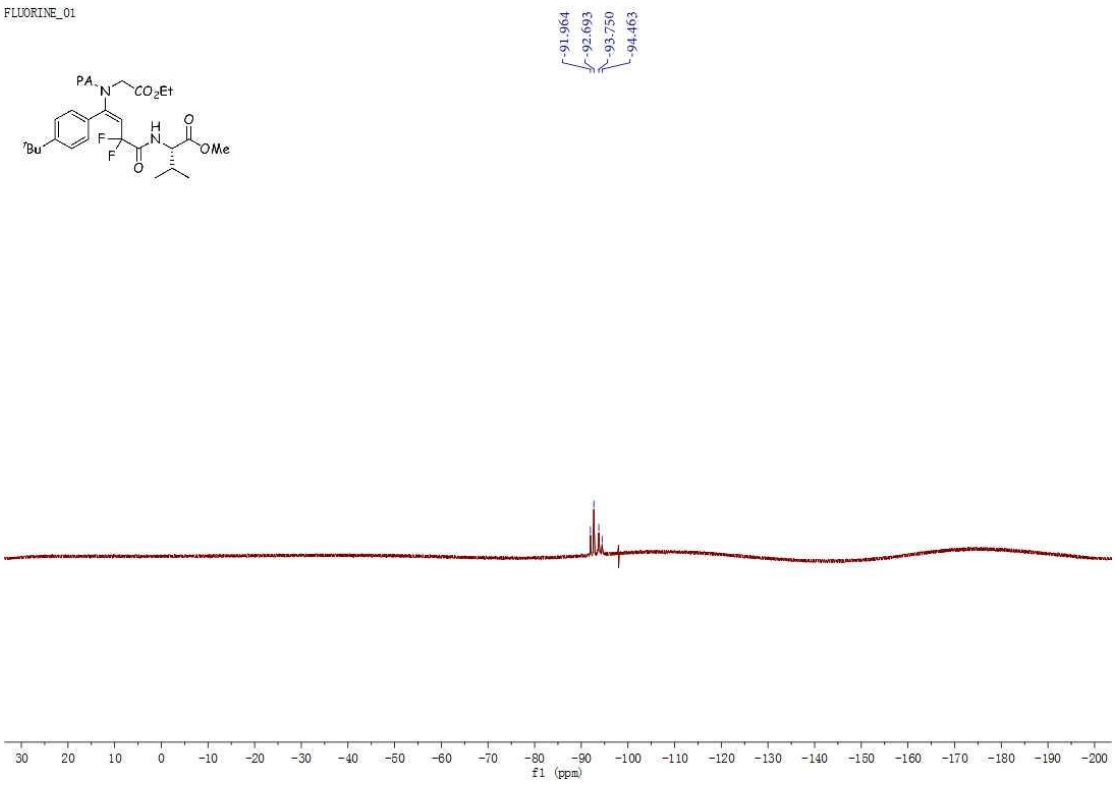
^{19}F – NMR spectrum of compound – **6d** (376 MHz, $CDCl_3$)



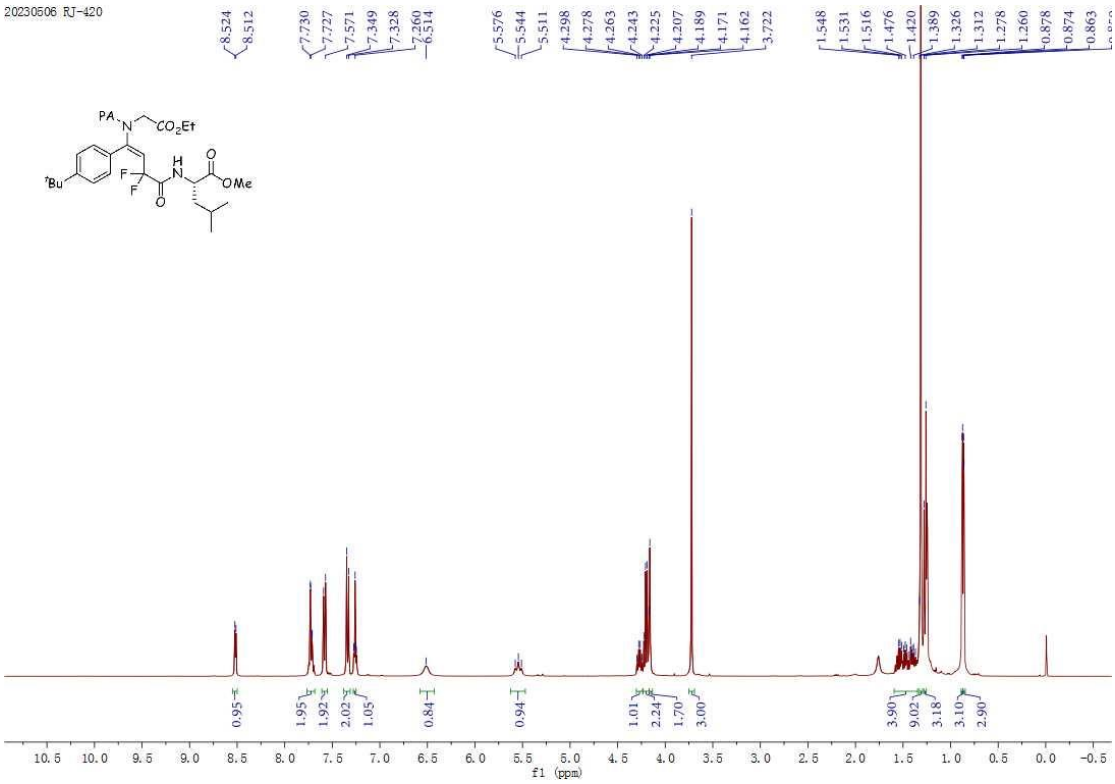
^{1}H – NMR spectrum of compound – **6e** (400 MHz, $CDCl_3$)



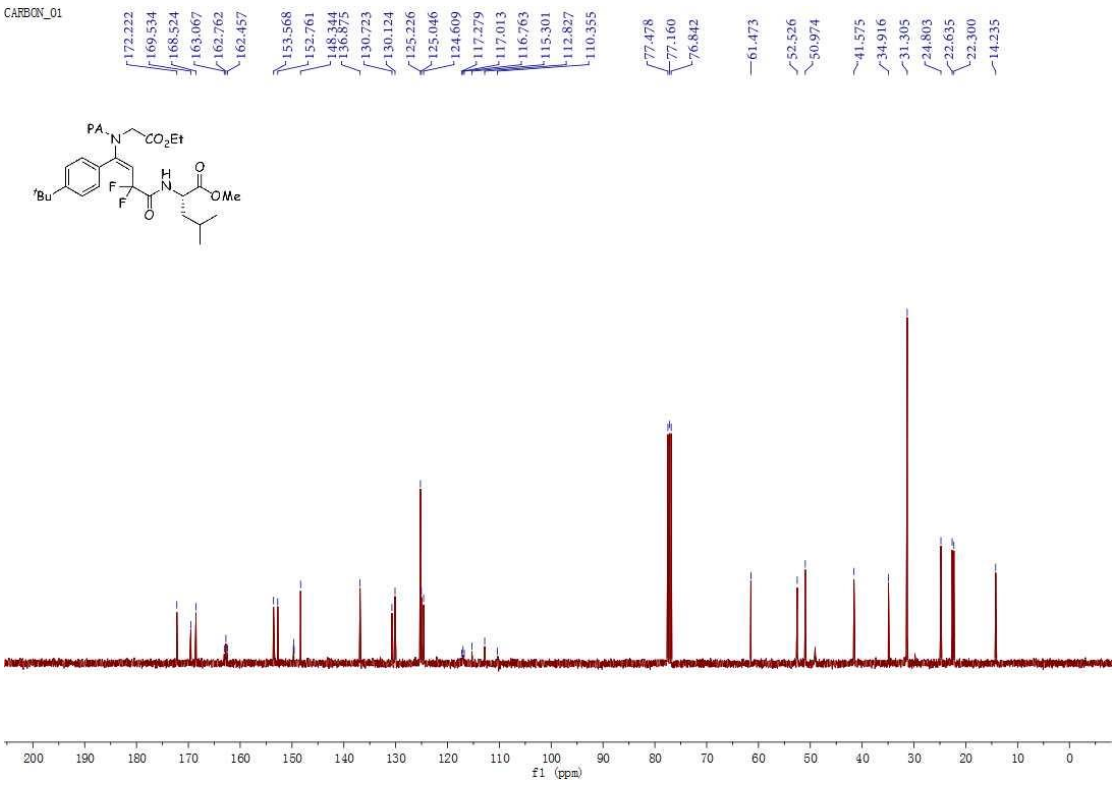
^{13}C – NMR spectrum of compound – **6e** (100 MHz, $CDCl_3$)



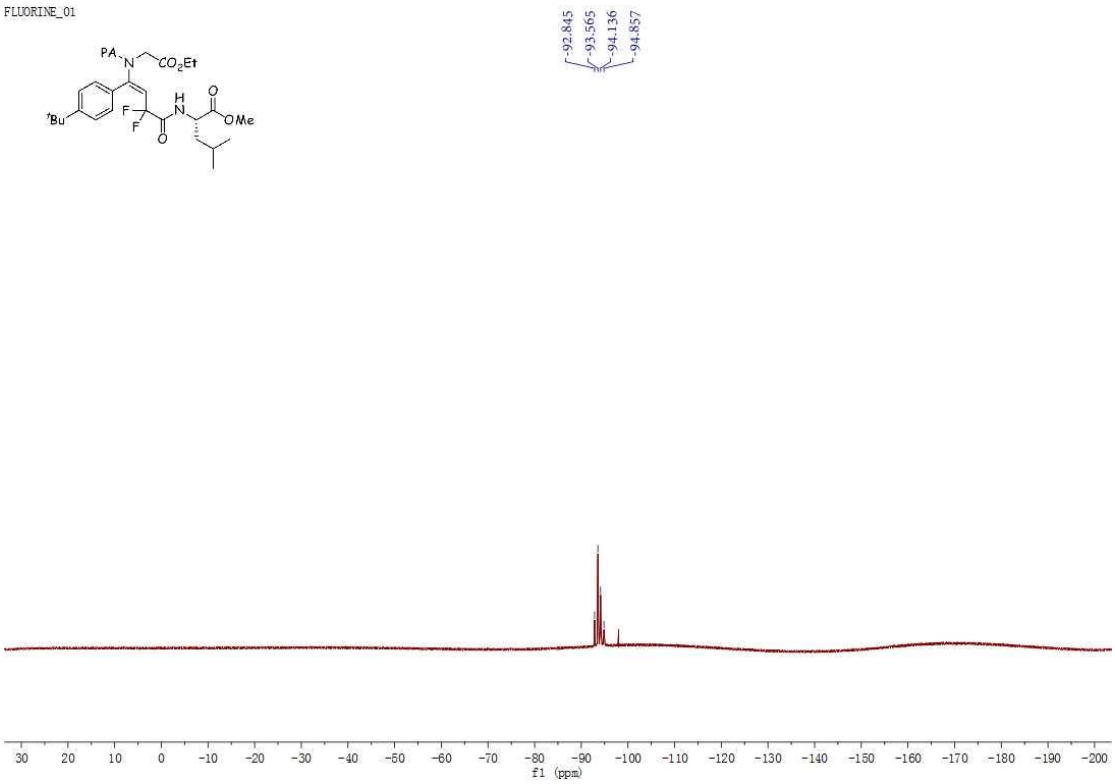
^{19}F – NMR spectrum of compound – **6e** (376 MHz, $CDCl_3$)



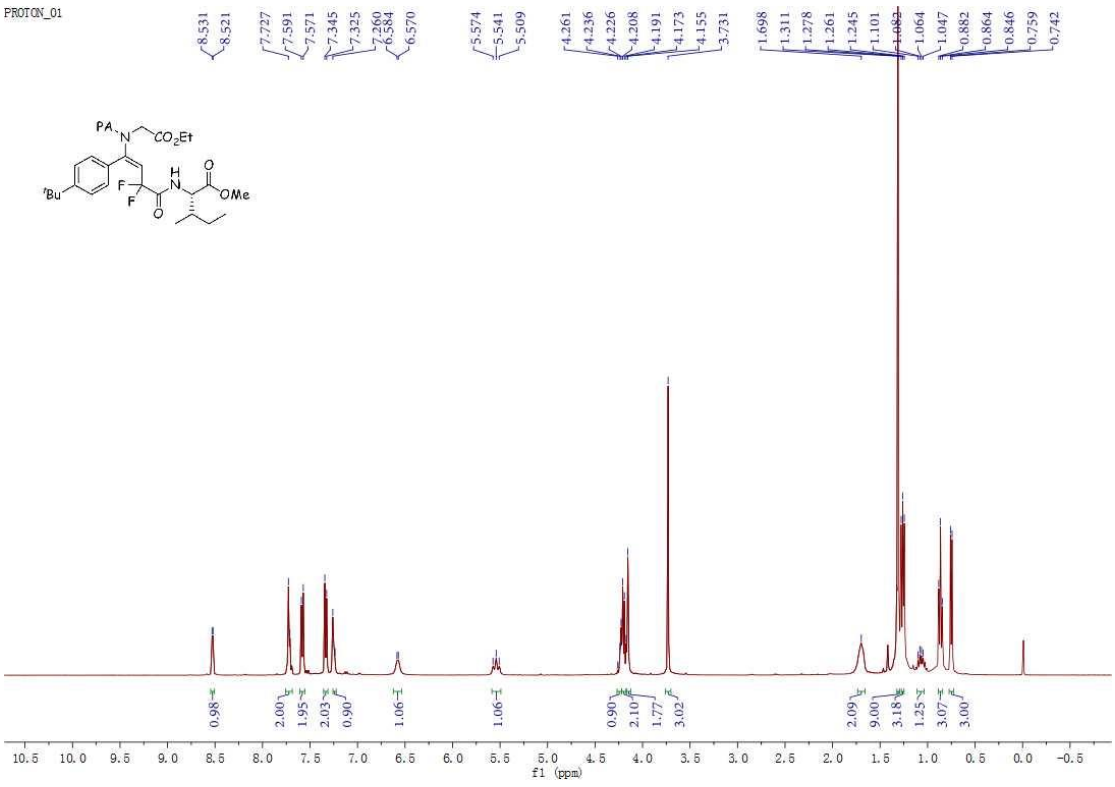
^{1}H – NMR spectrum of compound – **6f** (400 MHz, $CDCl_3$)



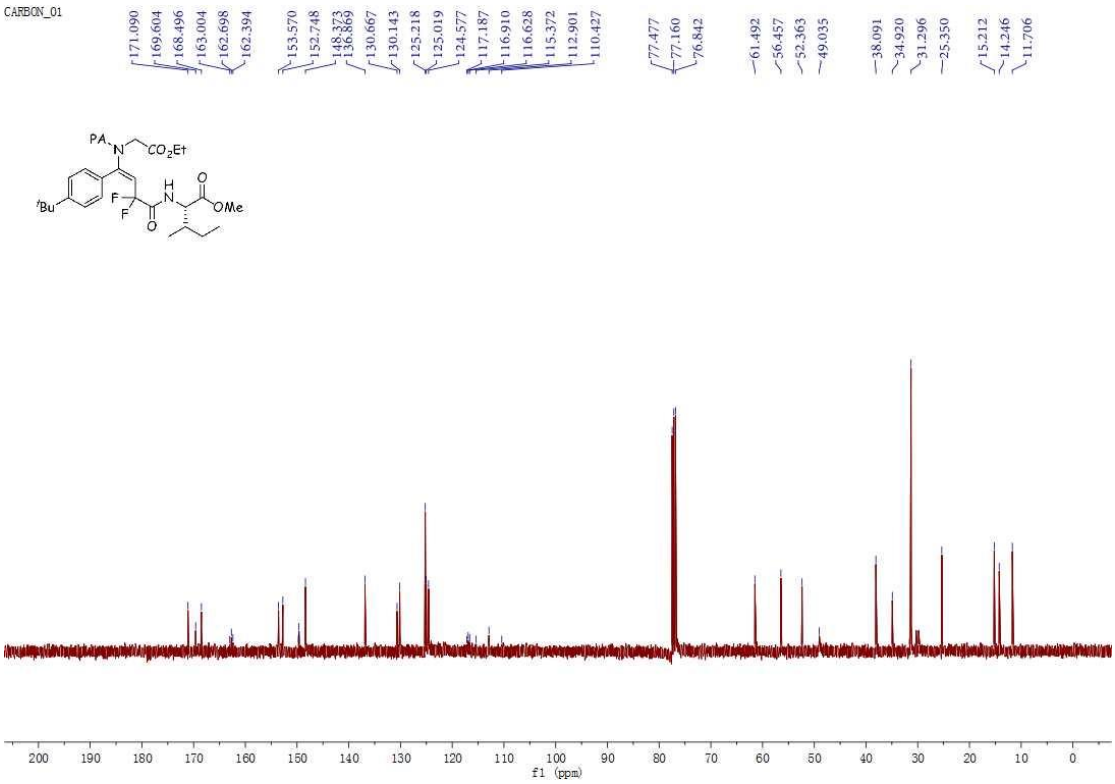
^{13}C – NMR spectrum of compound – **6f** (100 MHz, $CDCl_3$)



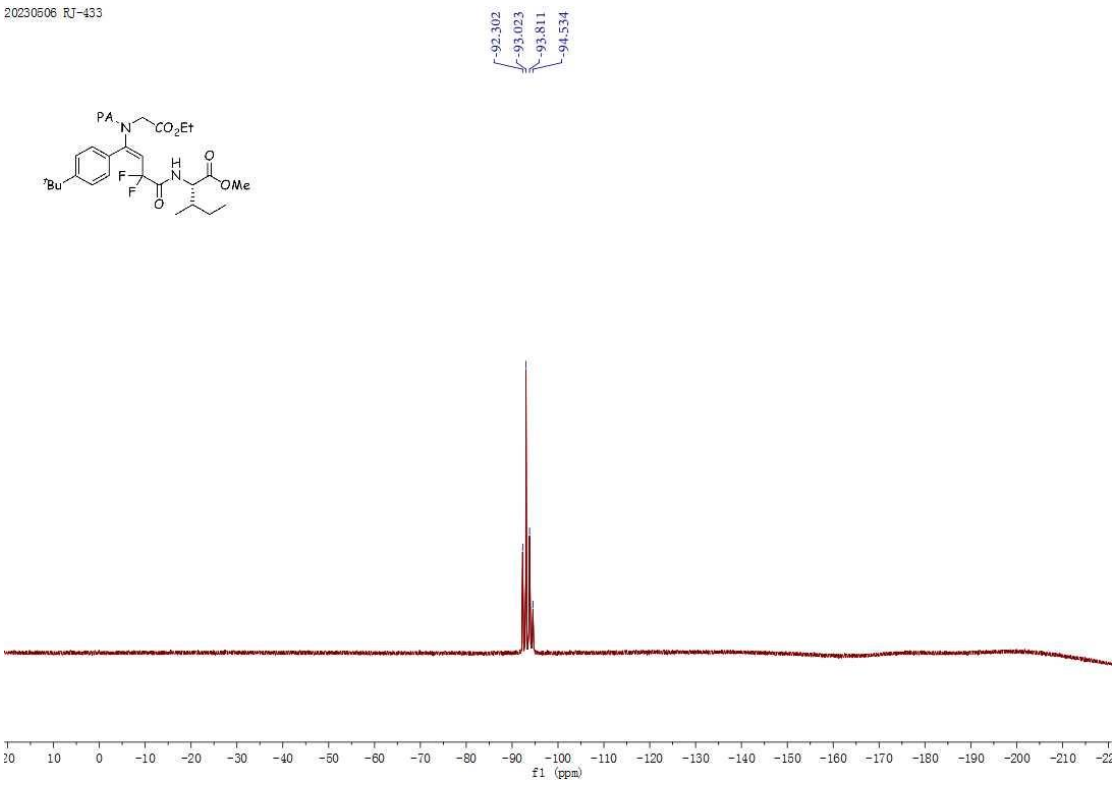
^{19}F – NMR spectrum of compound – **6f** (376 MHz, $CDCl_3$)



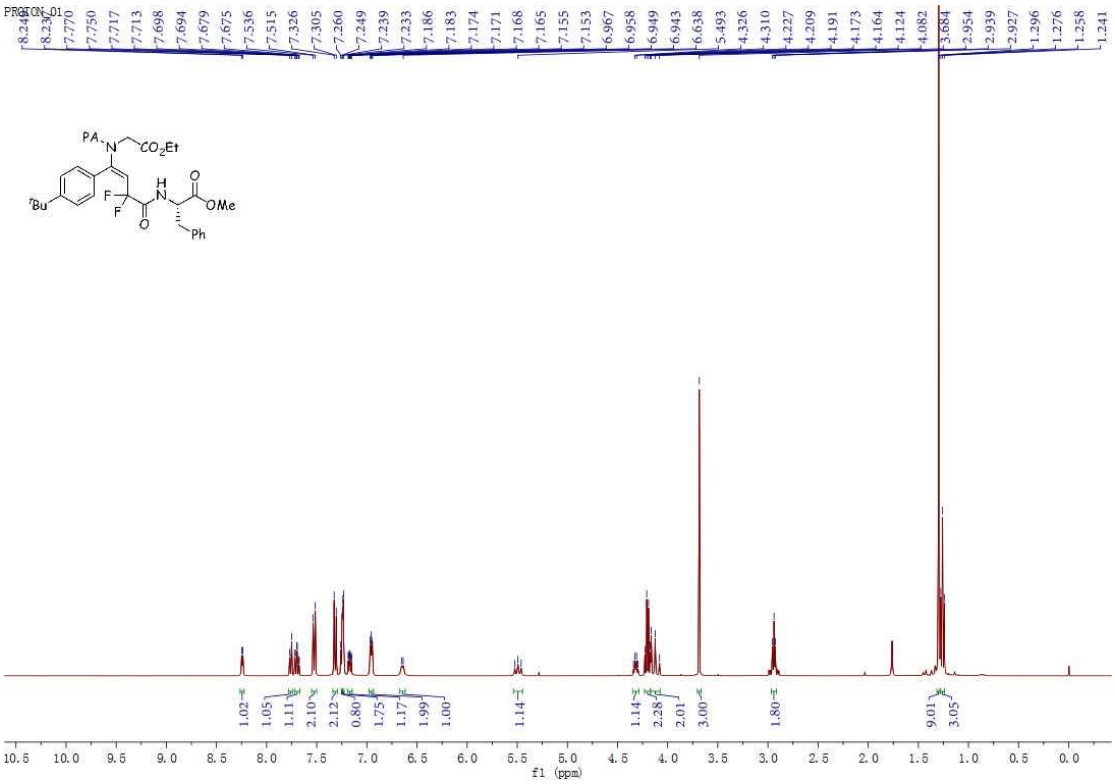
^{1}H – NMR spectrum of compound – **6g** (400 MHz, $CDCl_3$)



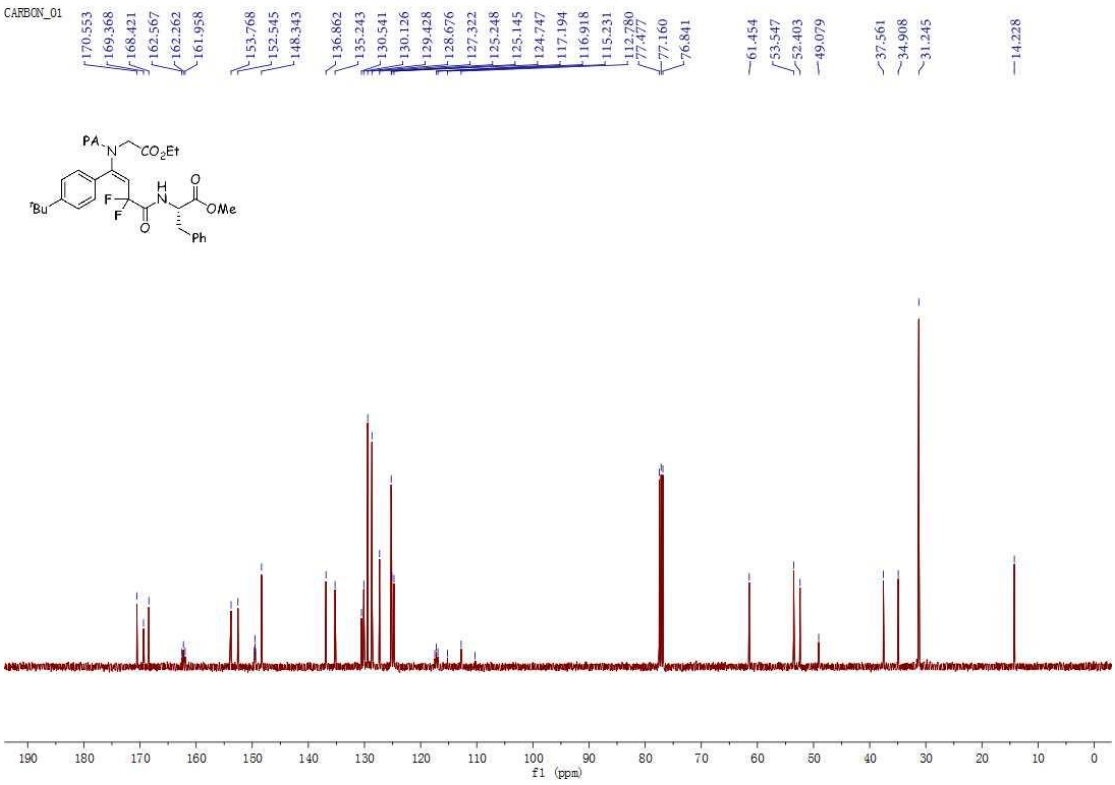
^{13}C – NMR spectrum of compound – **6g** (100 MHz, $CDCl_3$)



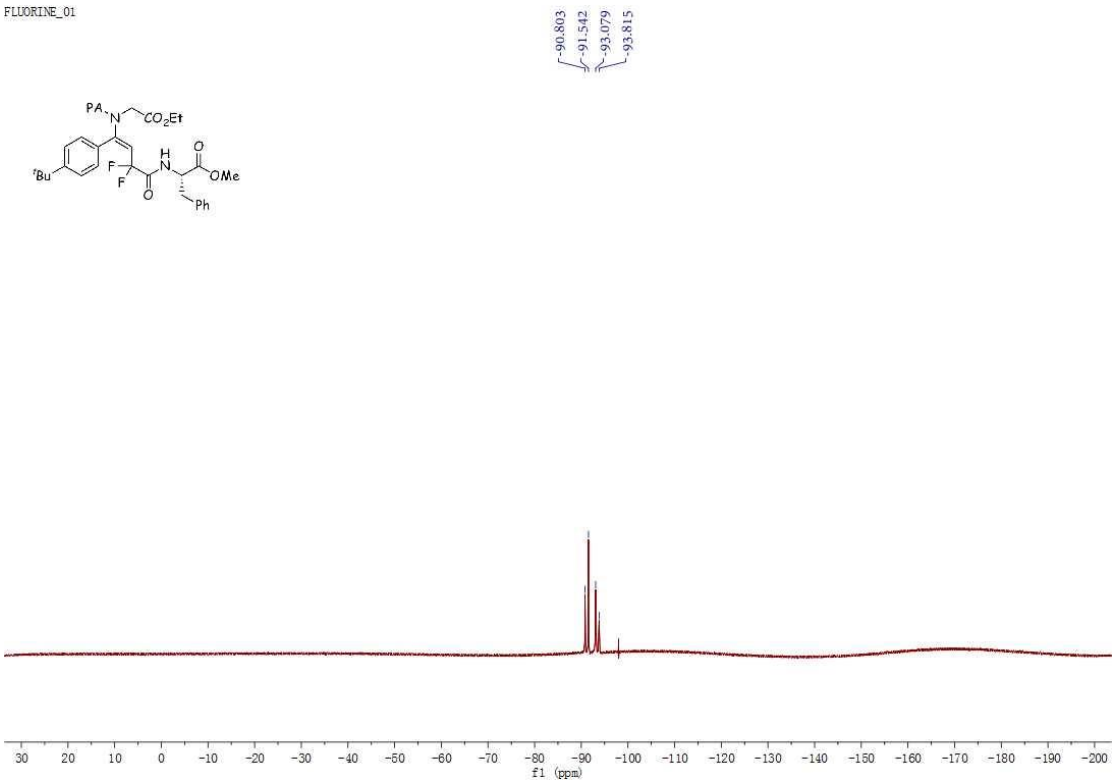
^{19}F – NMR spectrum of compound – **6g** (376 MHz, $CDCl_3$)



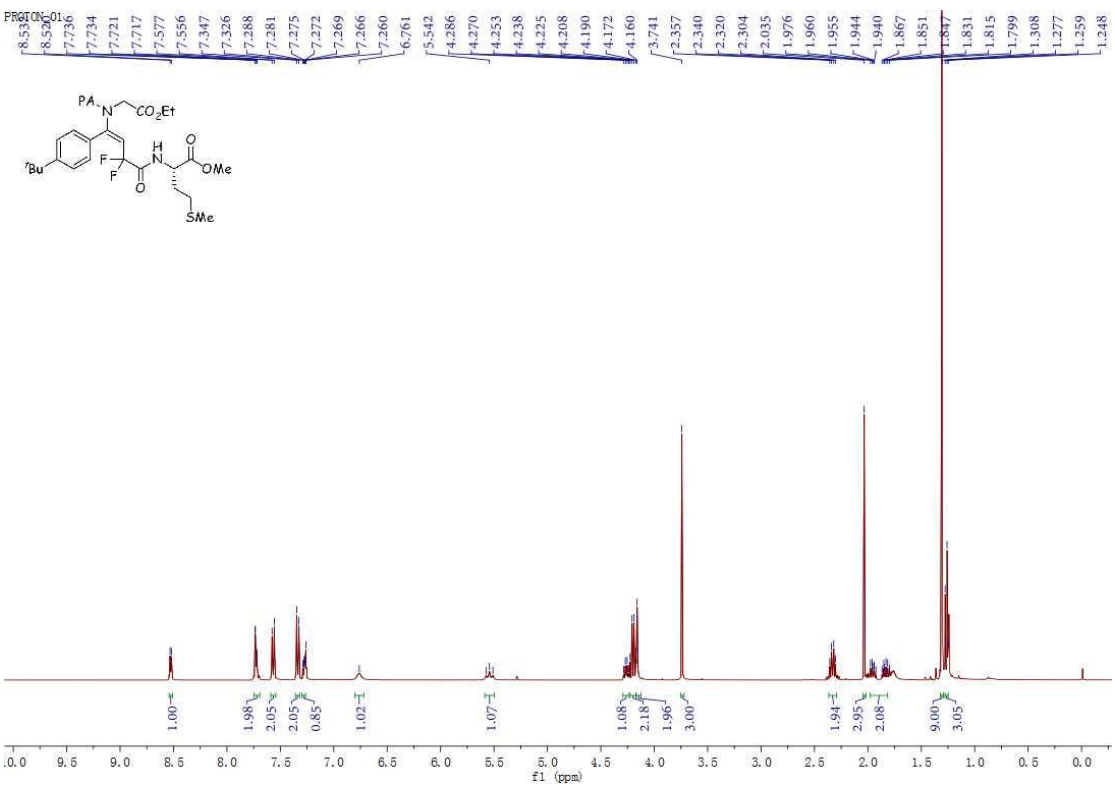
^{1}H – NMR spectrum of compound – **6h** (400 MHz, $CDCl_3$)



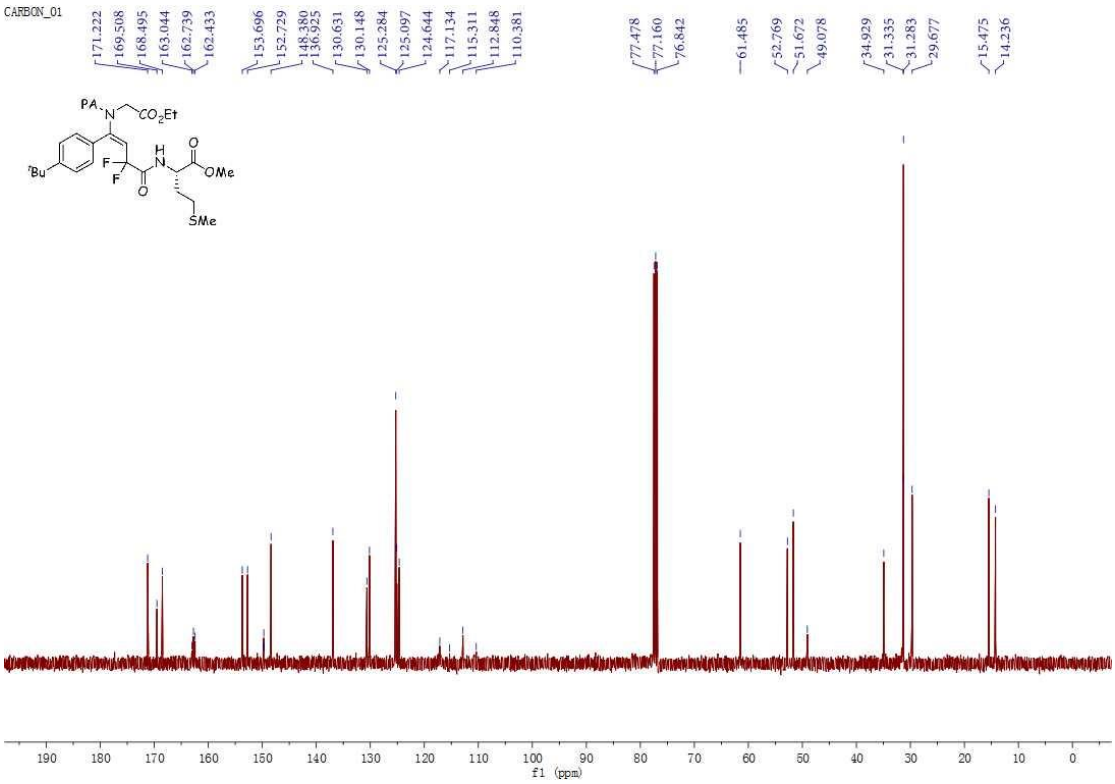
^{13}C – NMR spectrum of compound – **6h** (100 MHz, $CDCl_3$)



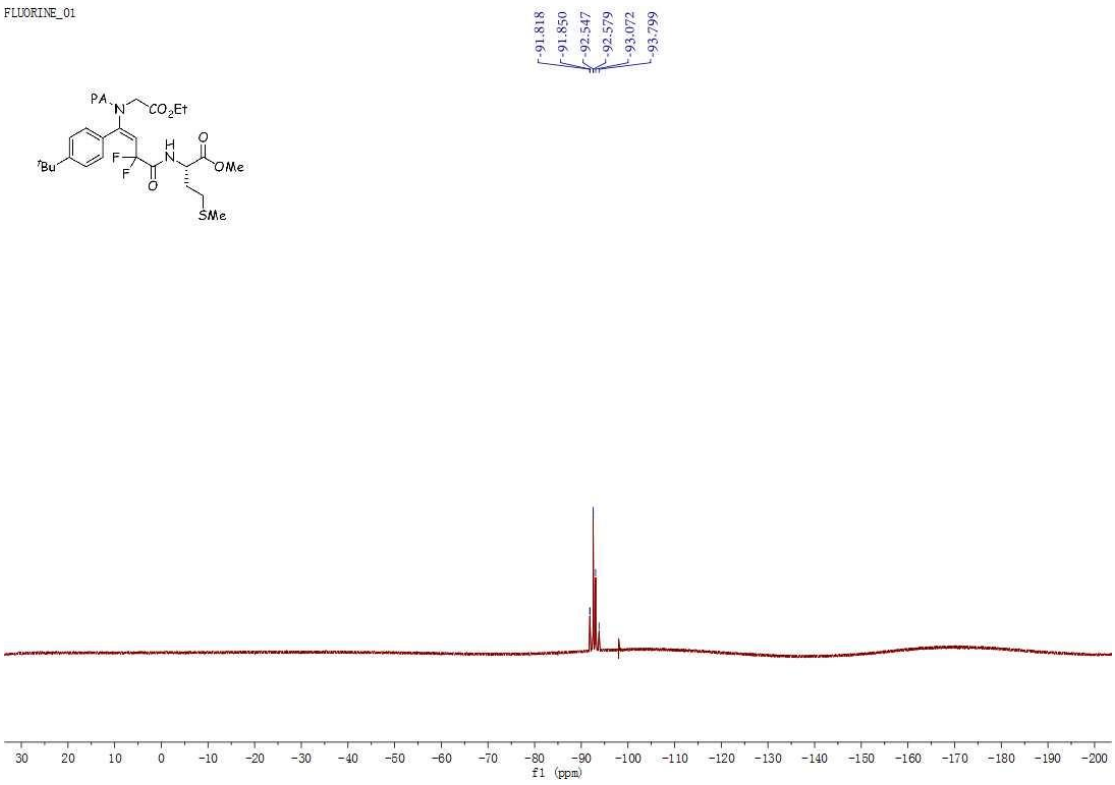
^{19}F – NMR spectrum of compound – **6h** (376 MHz, $CDCl_3$)



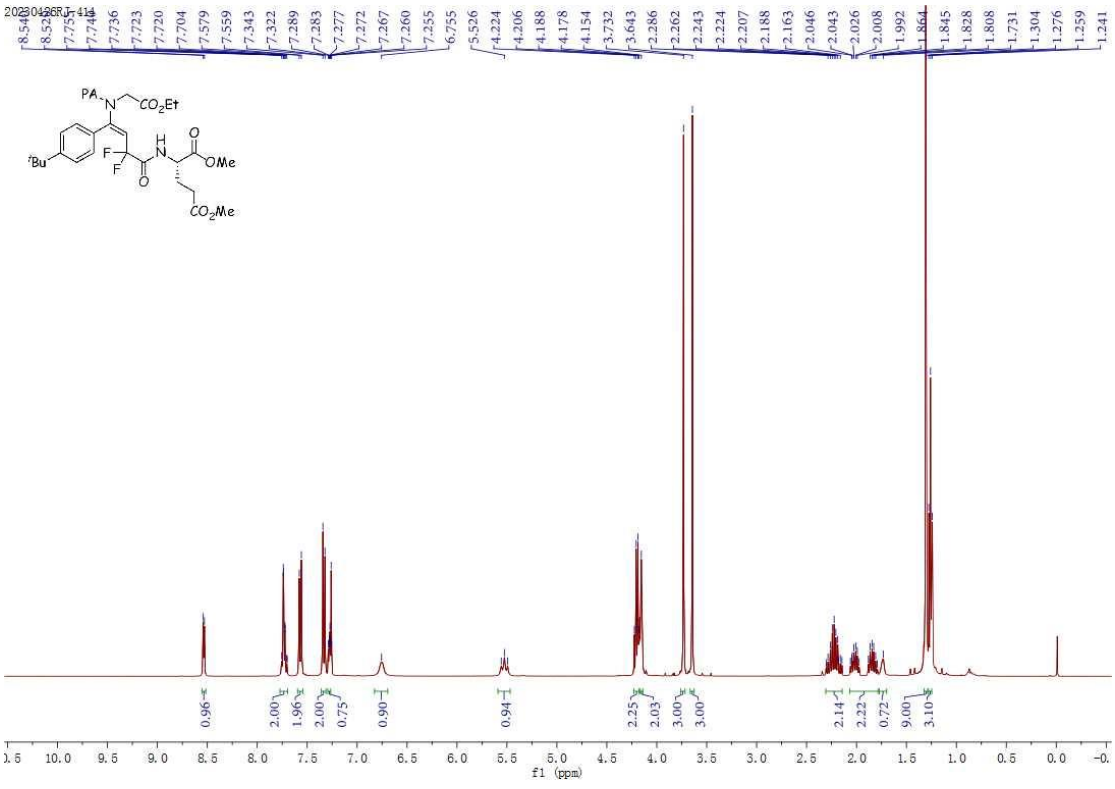
^{1}H – NMR spectrum of compound – **6i** (400 MHz, $CDCl_3$)



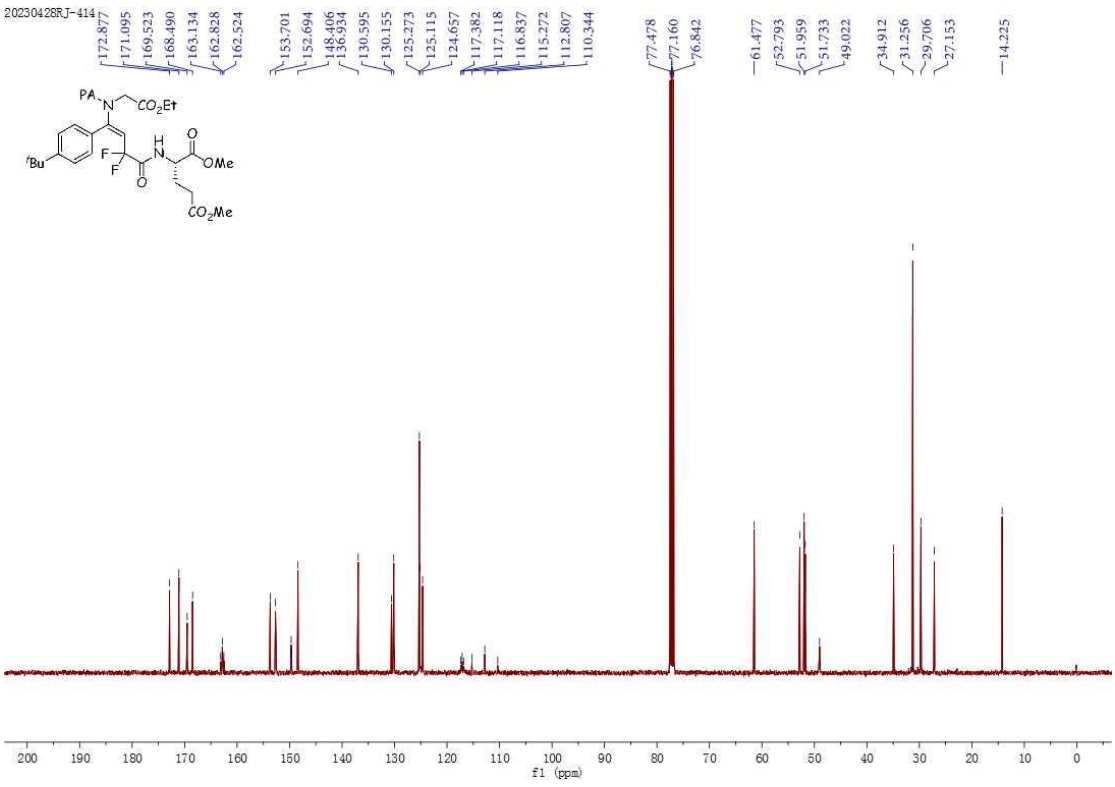
^{13}C – NMR spectrum of compound – **6i** (100 MHz, $CDCl_3$)



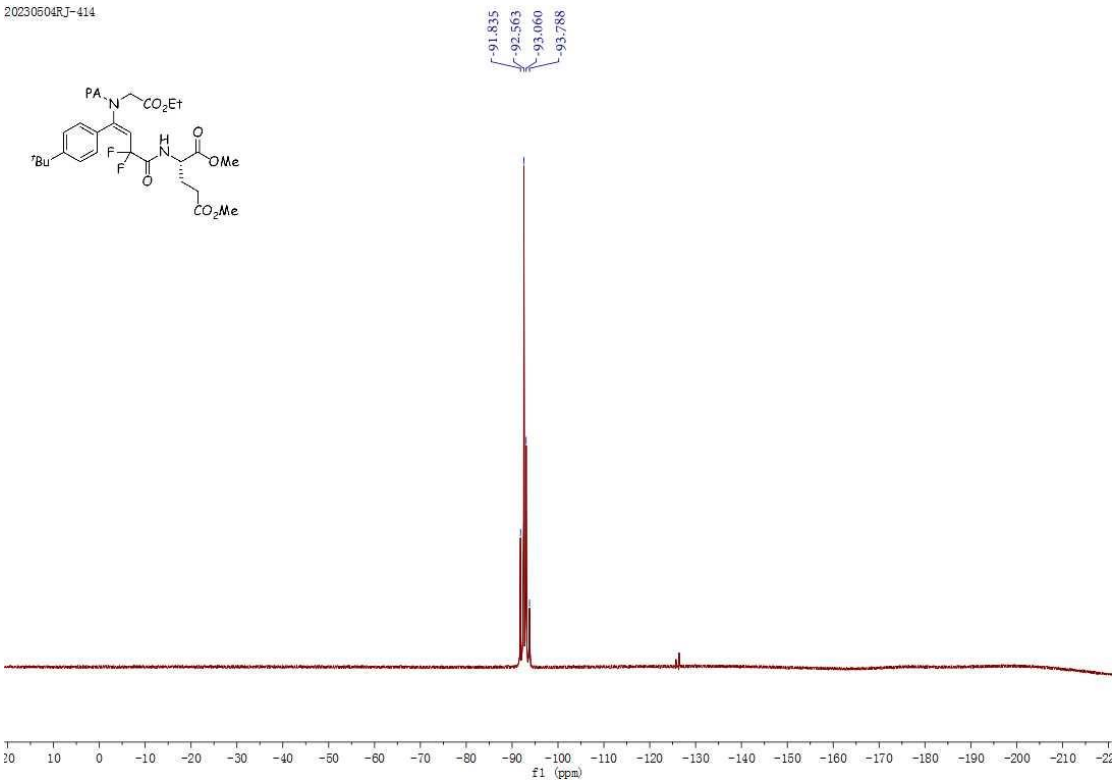
^{19}F – NMR spectrum of compound – **6i** (376 MHz, $CDCl_3$)



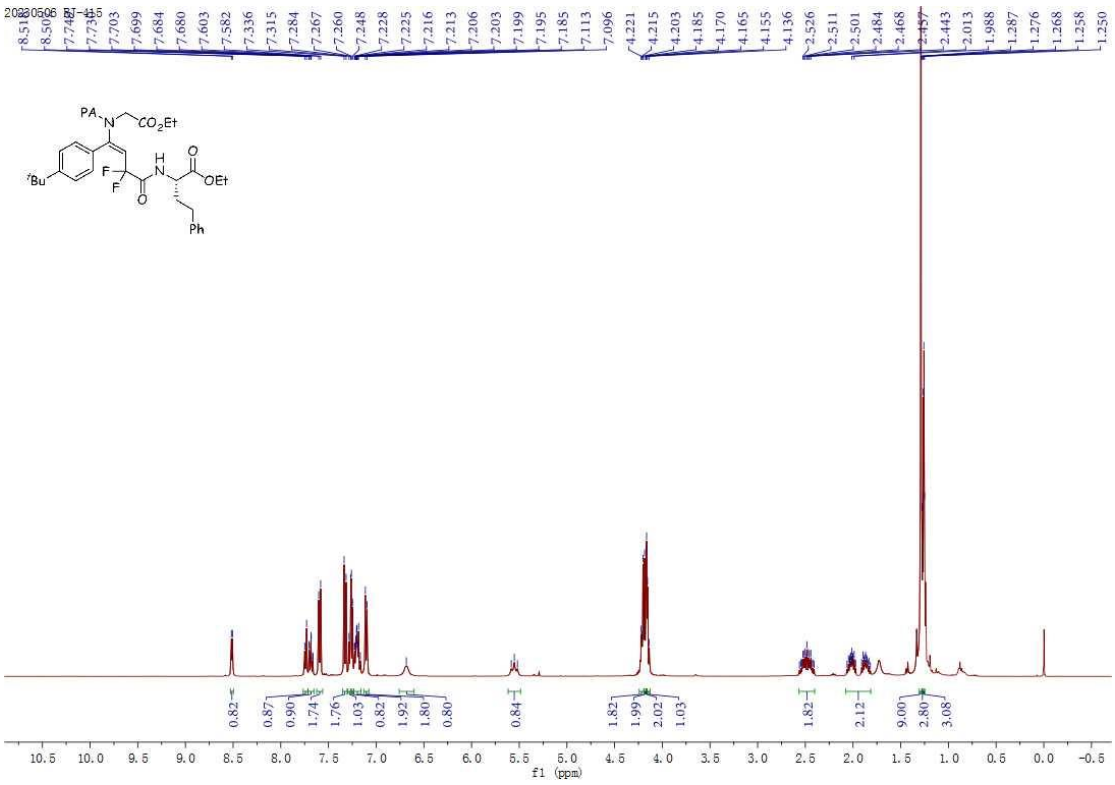
^{1}H – NMR spectrum of compound – **6j** (400 MHz, $CDCl_3$)



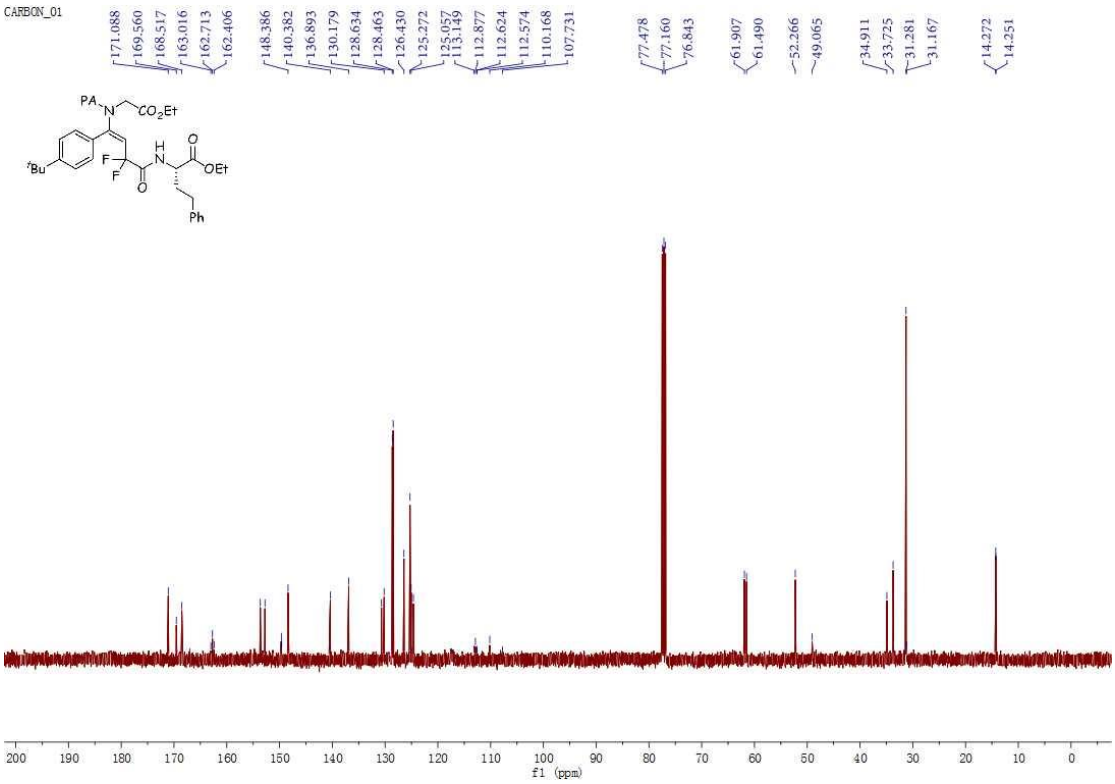
^{13}C – NMR spectrum of compound – **6j** (100 MHz, $CDCl_3$)



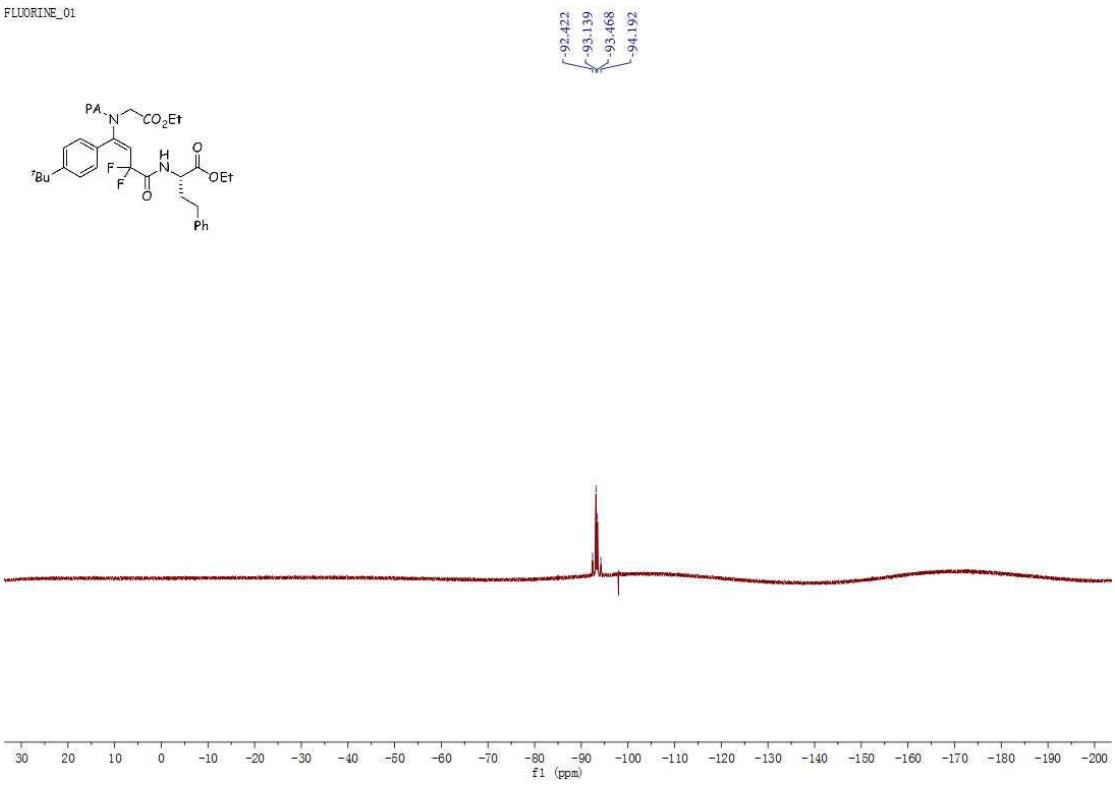
^{19}F – NMR spectrum of compound – **6j** (376 MHz, $CDCl_3$)



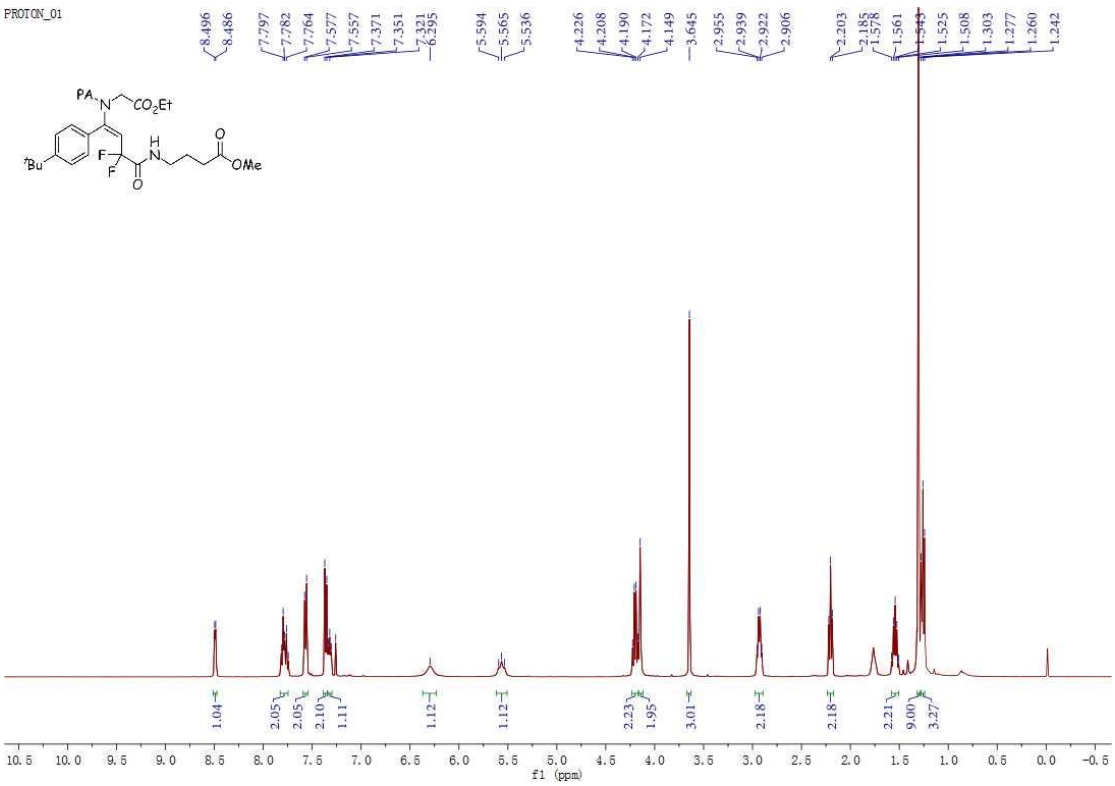
^{1}H – NMR spectrum of compound – **6k** (400 MHz, $CDCl_3$)



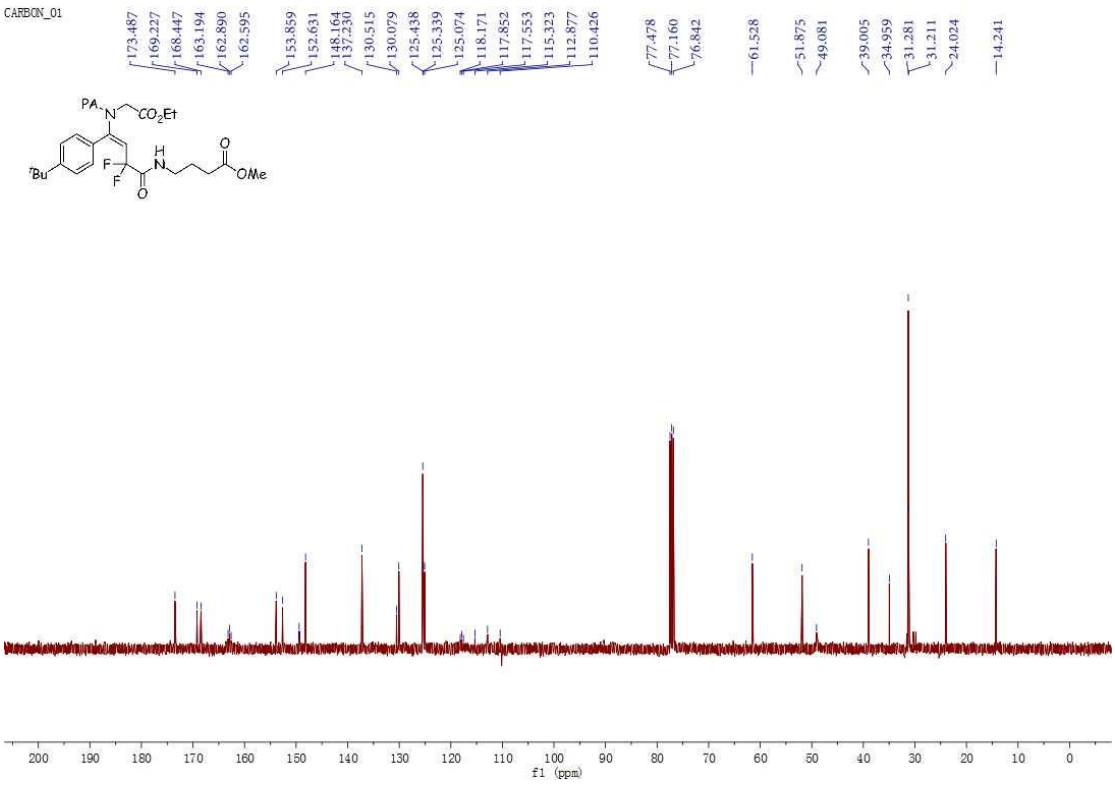
^{13}C – NMR spectrum of compound – **6k** (100 MHz, $CDCl_3$)



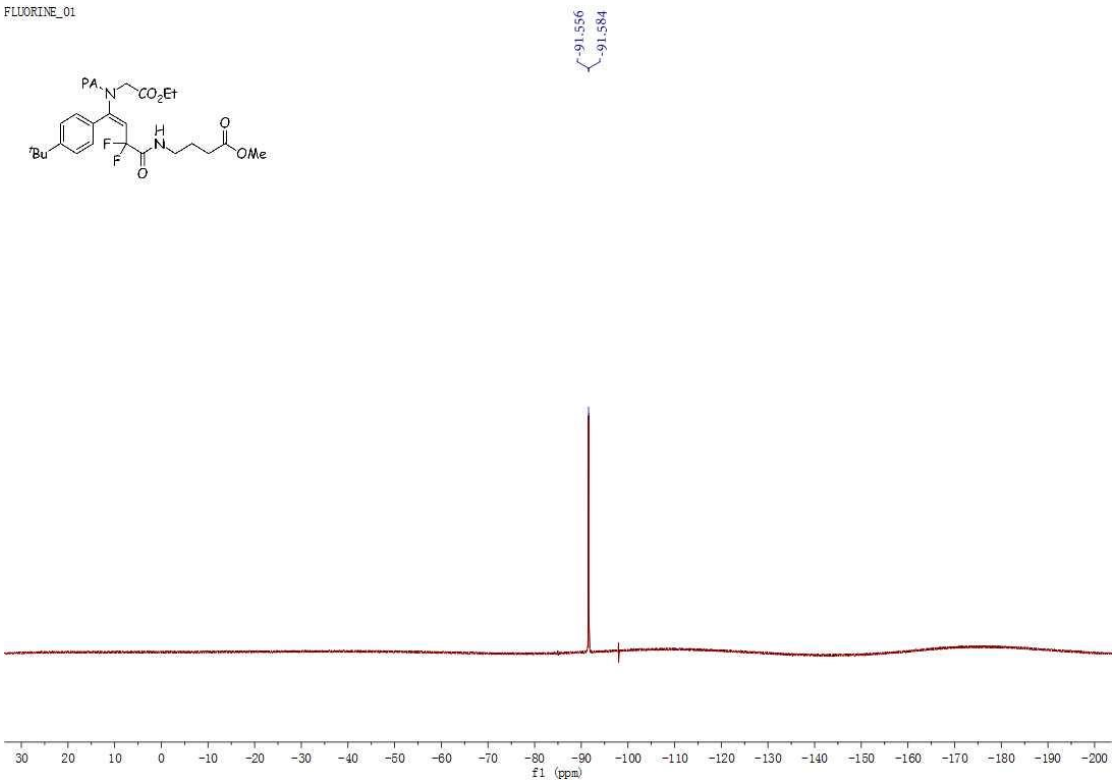
^{19}F – NMR spectrum of compound – **6k** (376 MHz, $CDCl_3$)



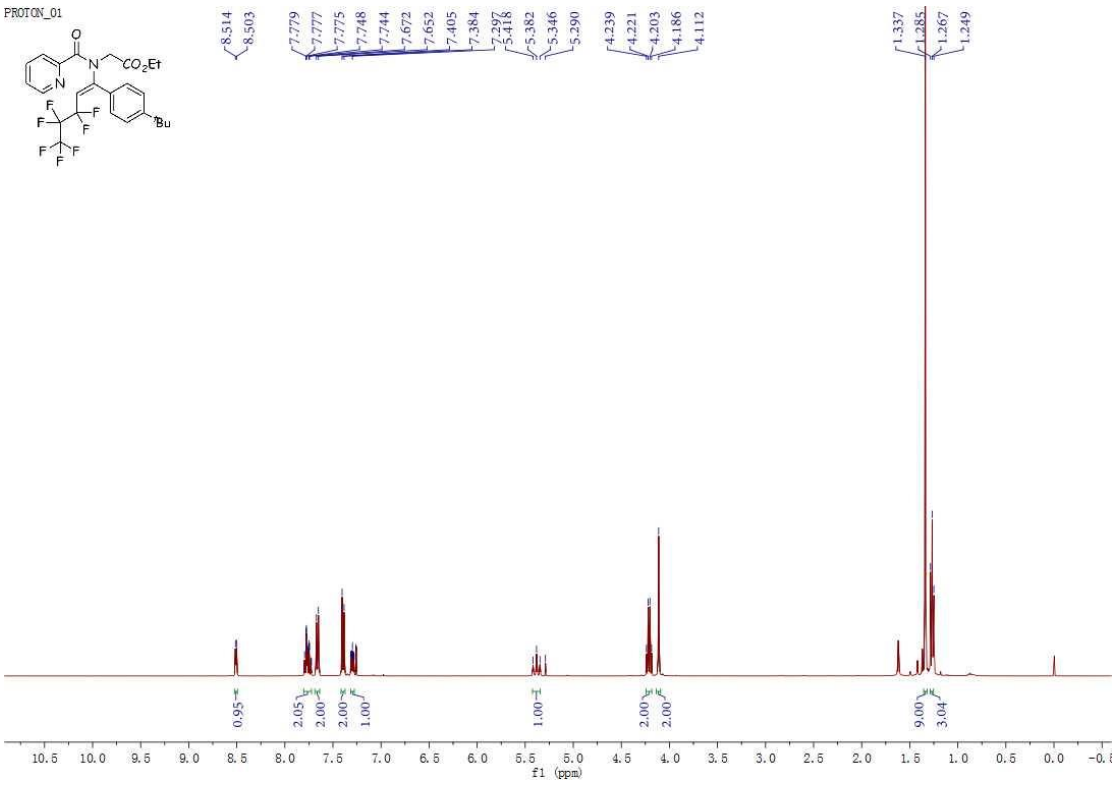
^{1}H – NMR spectrum of compound – **6l** (400 MHz, $CDCl_3$)



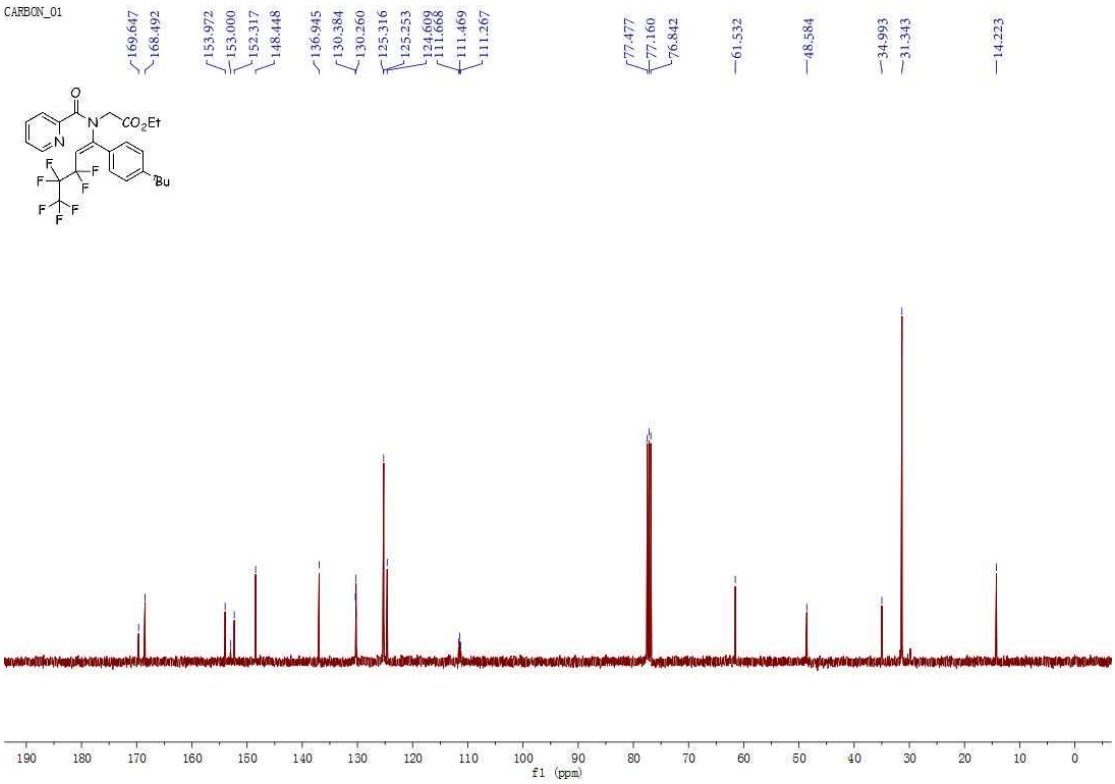
^{13}C – NMR spectrum of compound – **6l** (100 MHz, $CDCl_3$)



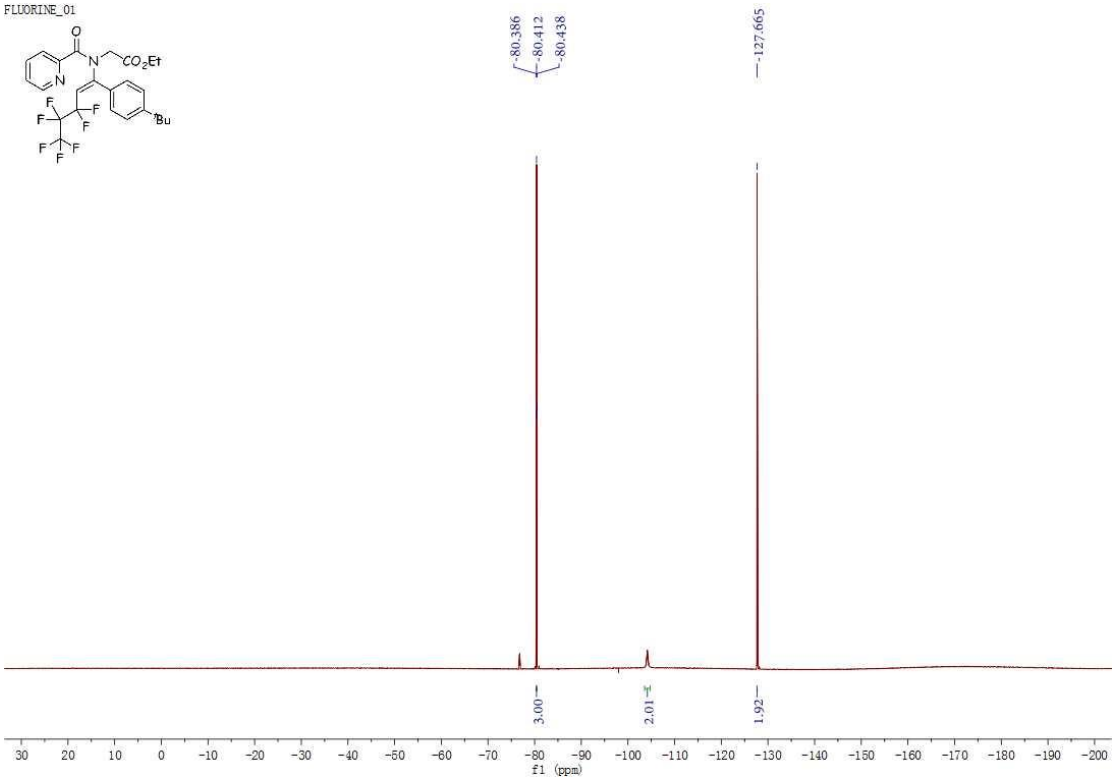
^{19}F – NMR spectrum of compound – **6l** (376 MHz, $CDCl_3$)



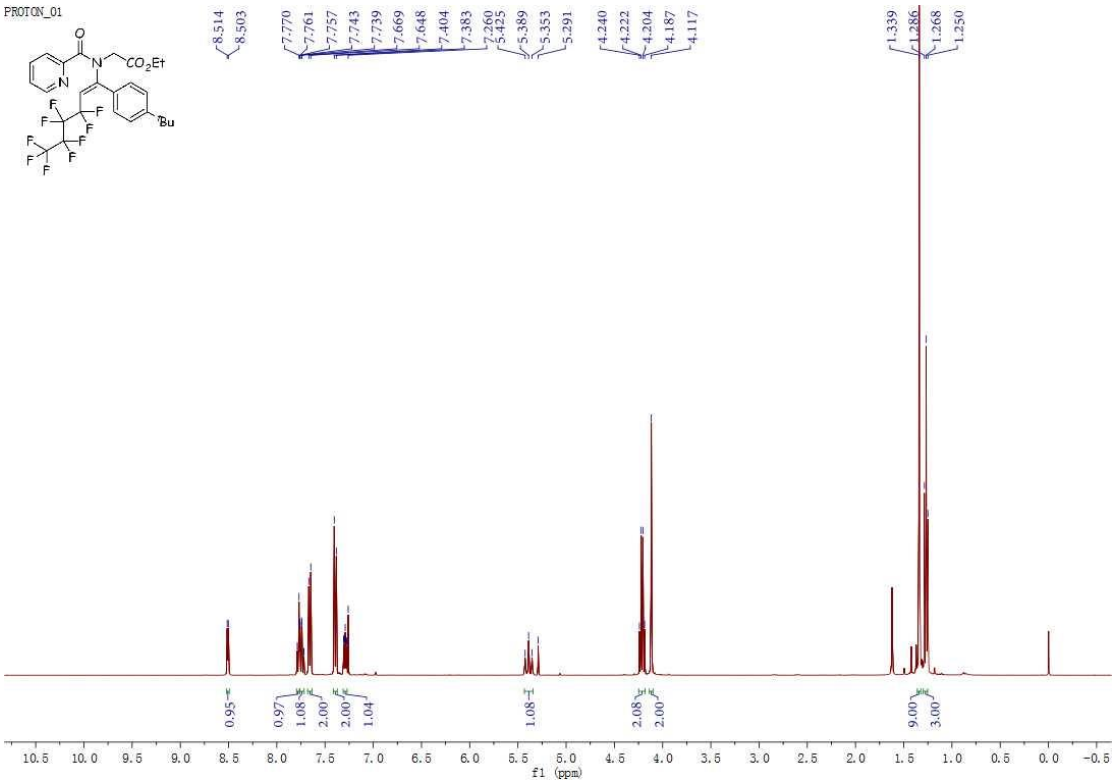
^{1}H – NMR spectrum of compound – **6m** (400 MHz, $CDCl_3$)



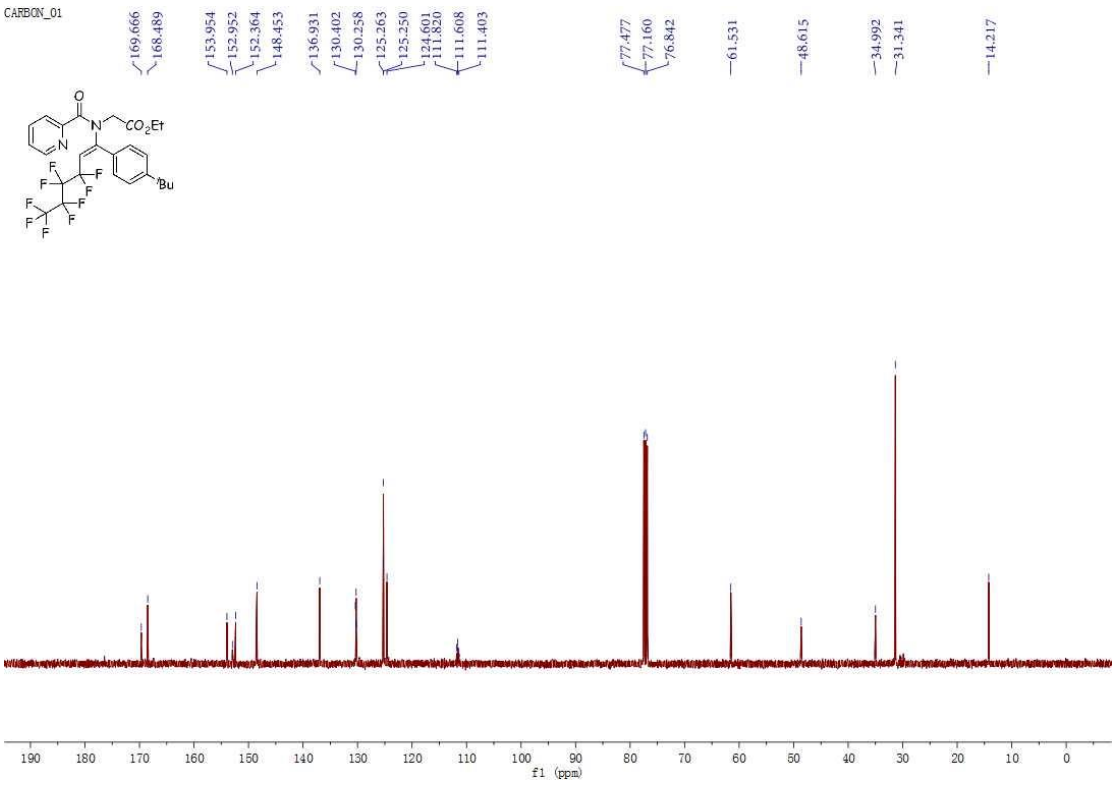
^{13}C – NMR spectrum of compound – **6m** (100 MHz, $CDCl_3$)



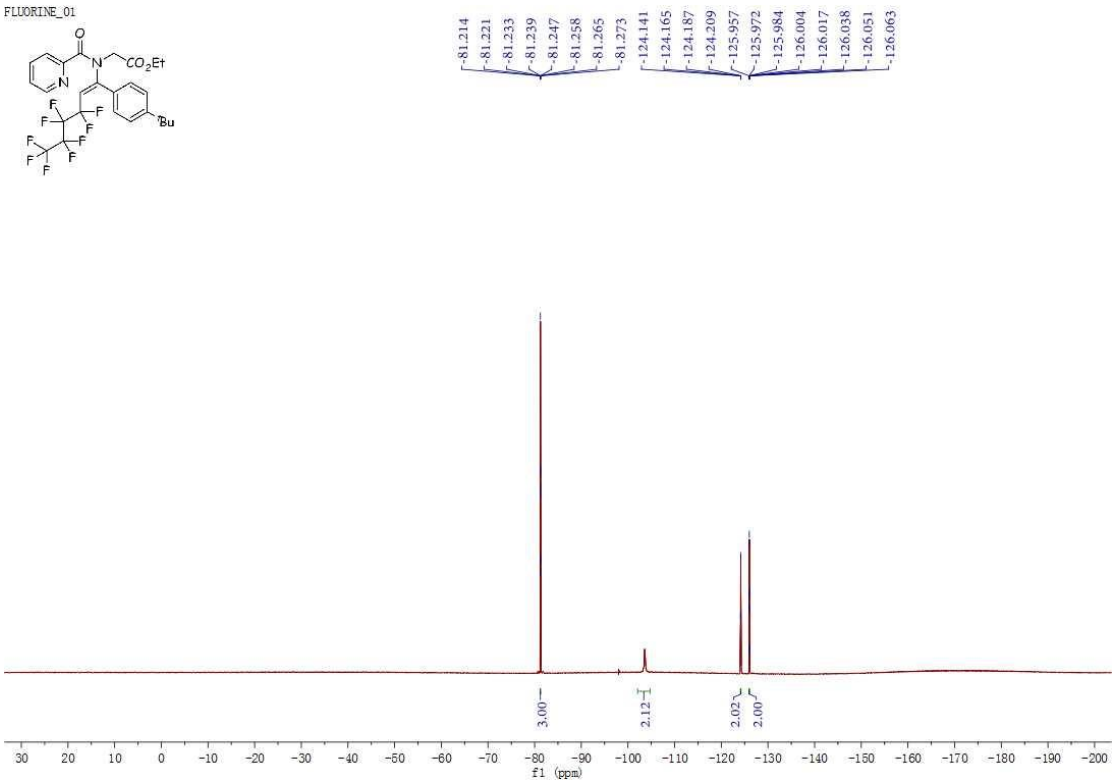
^{19}F – NMR spectrum of compound – **6m** (376 MHz, $CDCl_3$)



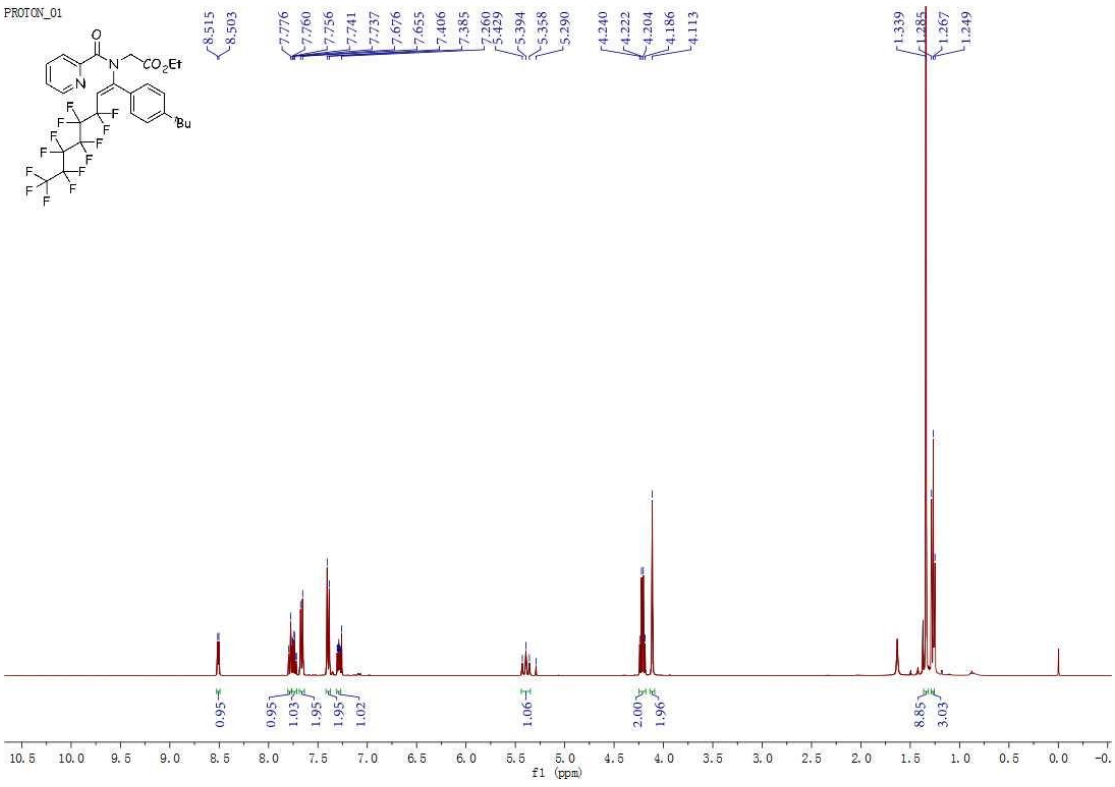
^{1}H – NMR spectrum of compound – **6n** (400 MHz, $CDCl_3$)



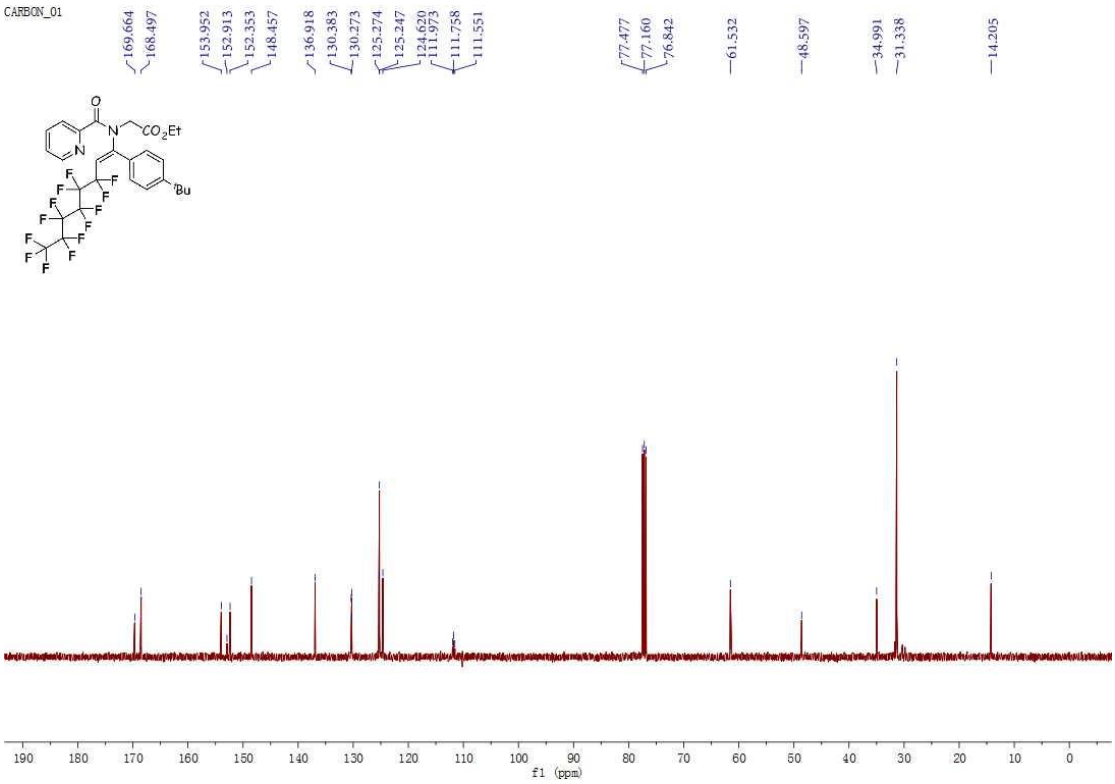
^{13}C – NMR spectrum of compound – **6n** (100 MHz, $CDCl_3$)



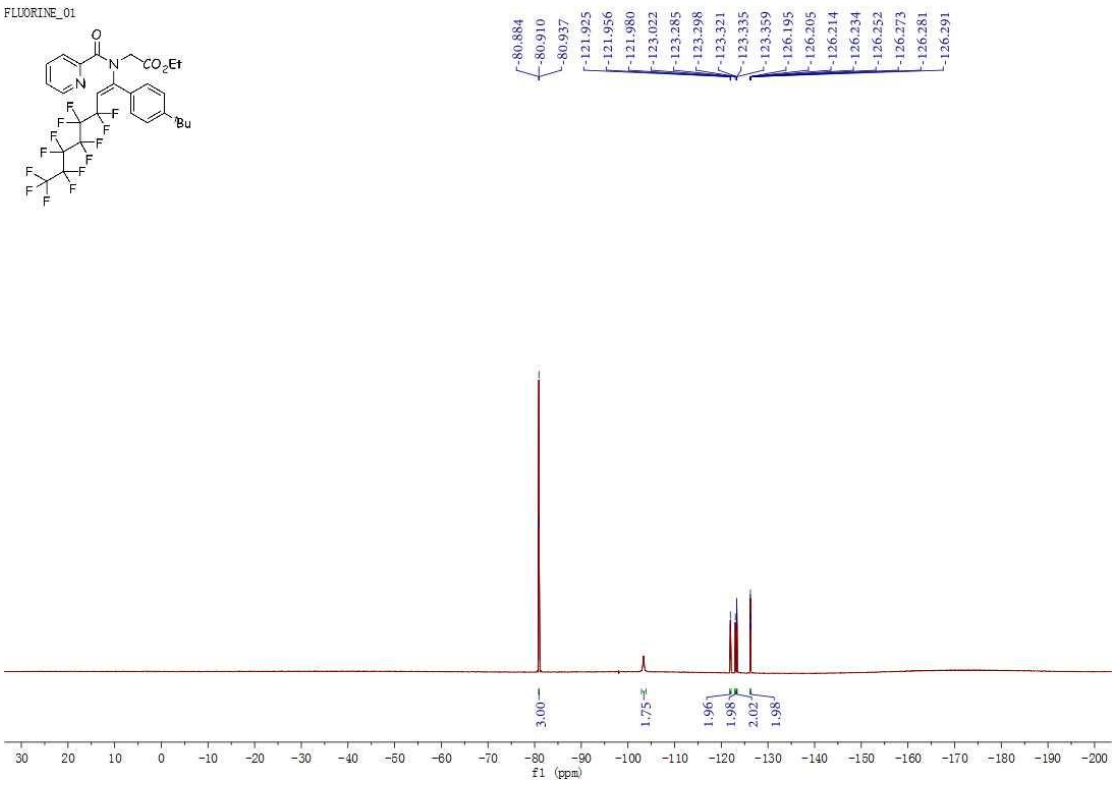
^{19}F – NMR spectrum of compound – **6n** (376 MHz, $CDCl_3$)



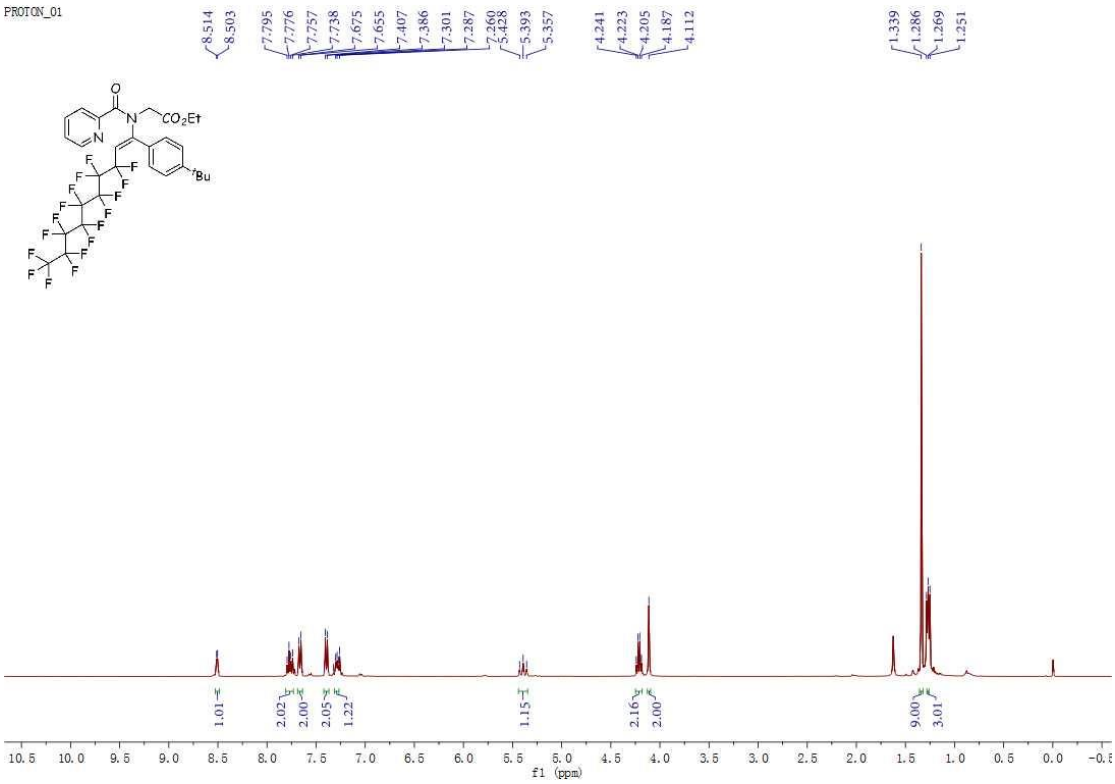
^{1}H – NMR spectrum of compound – **6o** (400 MHz, $CDCl_3$)



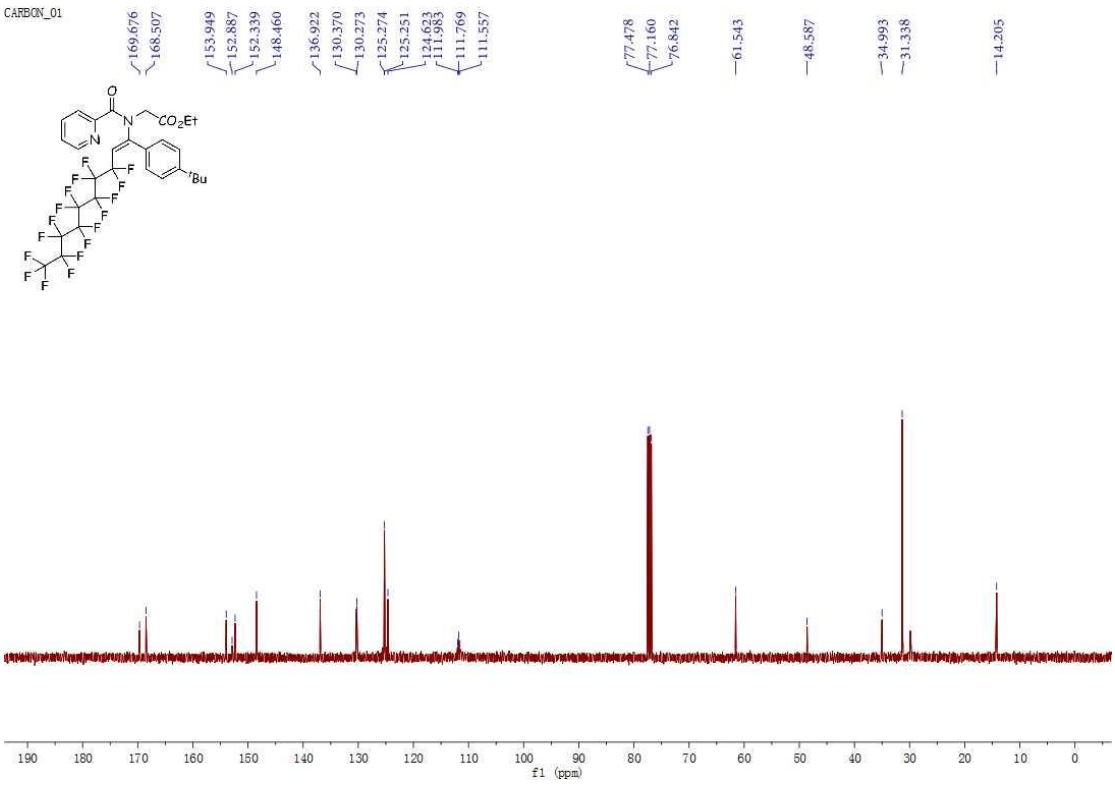
^{13}C – NMR spectrum of compound – **6o** (100 MHz, $CDCl_3$)



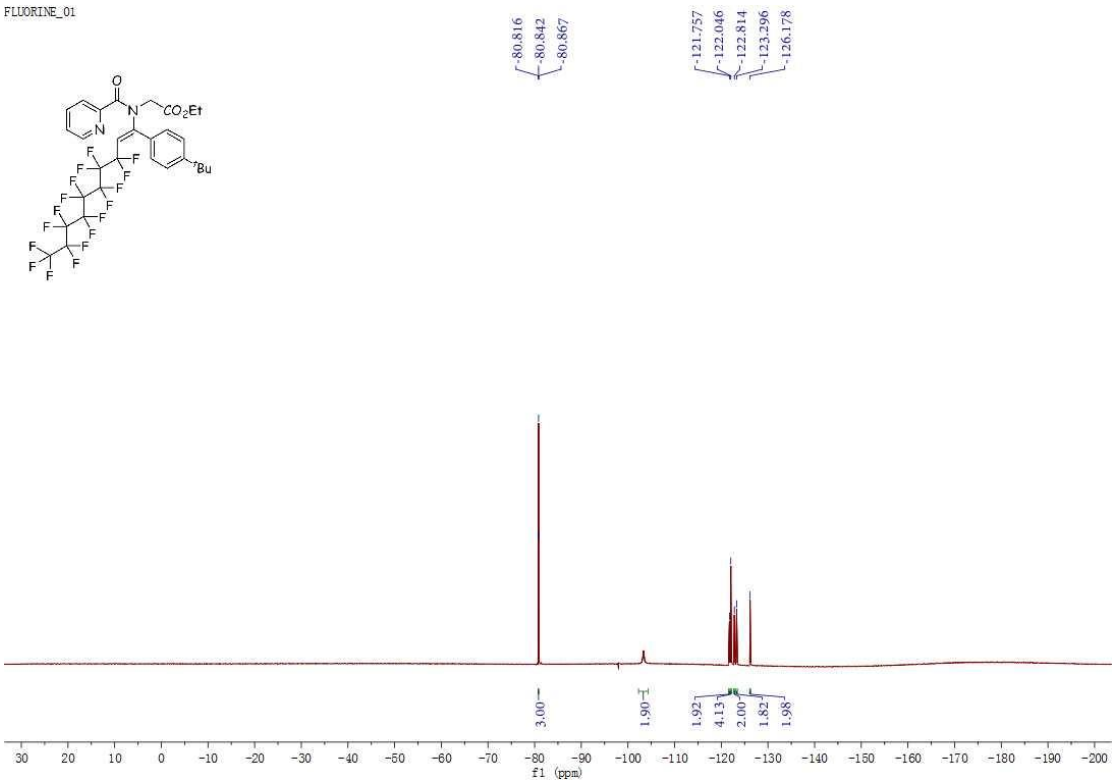
^{19}F – NMR spectrum of compound – **6o** (376 MHz, $CDCl_3$)



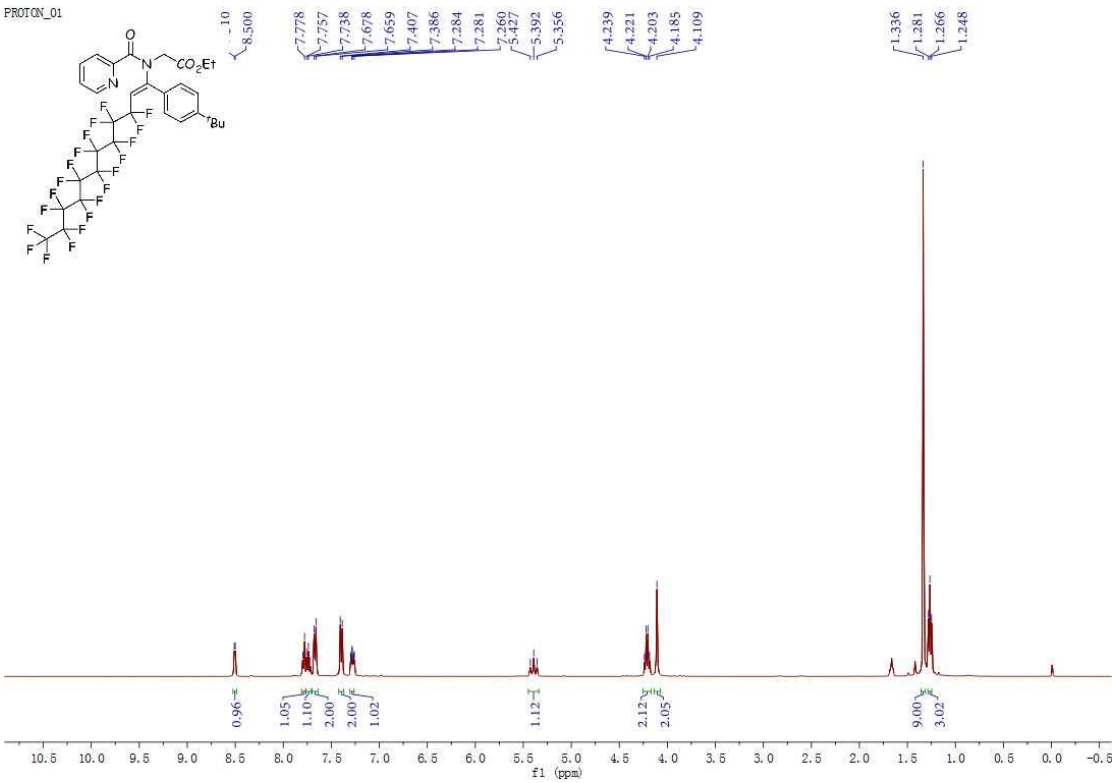
^{1}H – NMR spectrum of compound – **6p** (400 MHz, $CDCl_3$)



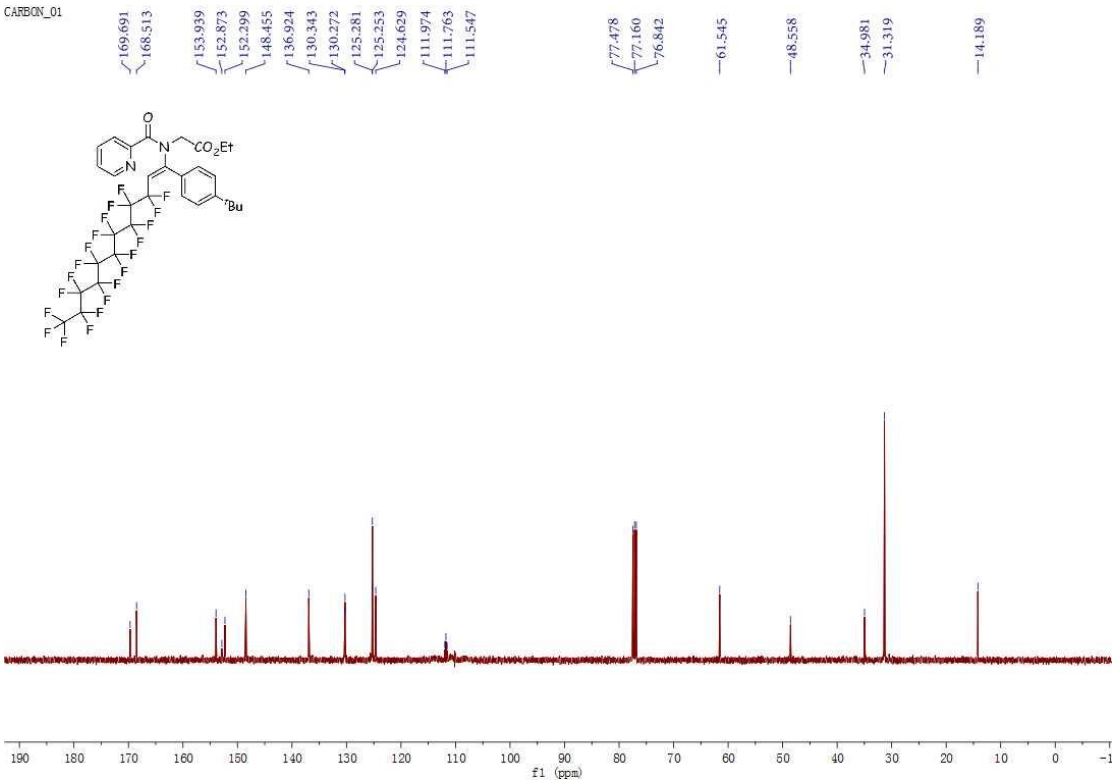
^{13}C – NMR spectrum of compound – **6p** (100 MHz, $CDCl_3$)



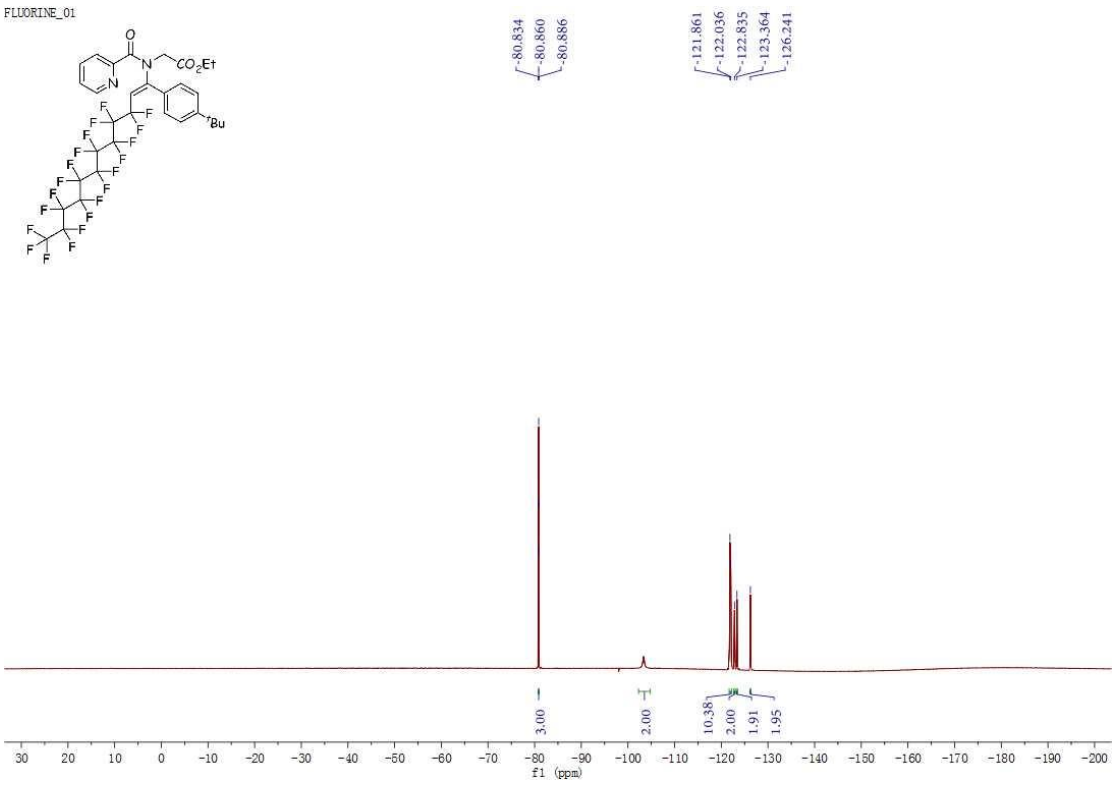
^{19}F – NMR spectrum of compound – **6p** (376 MHz, $CDCl_3$)



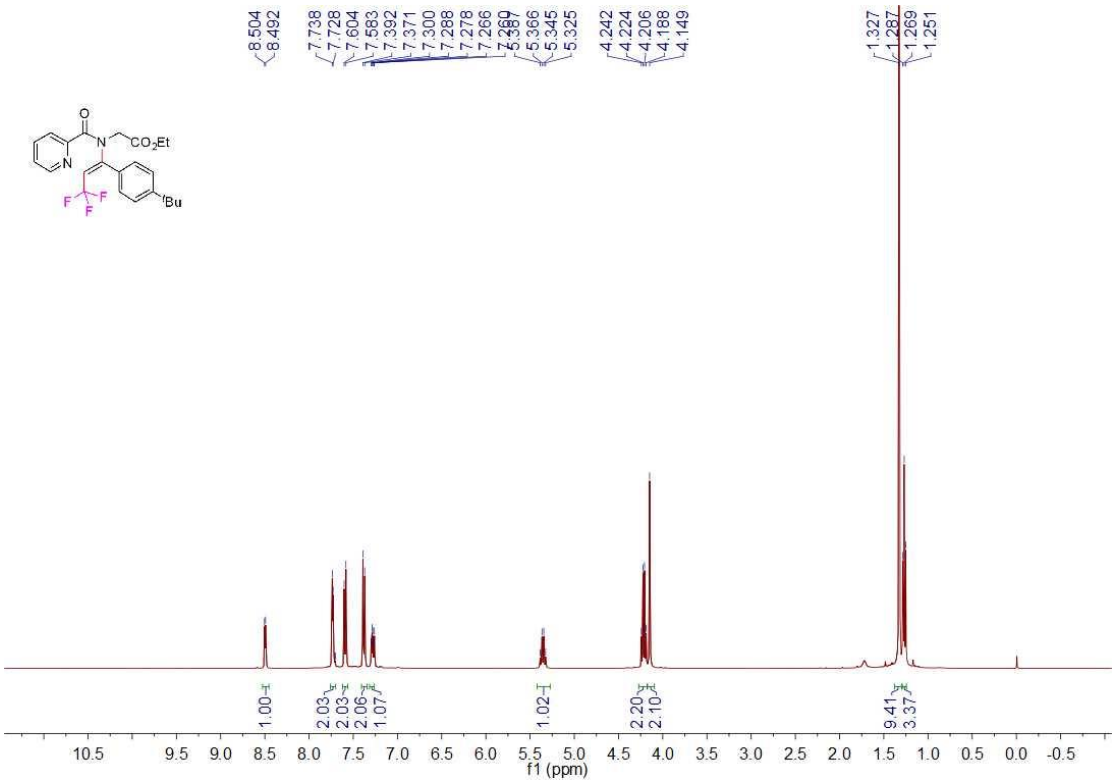
^{1}H – NMR spectrum of compound – **6q** (400 MHz, $CDCl_3$)



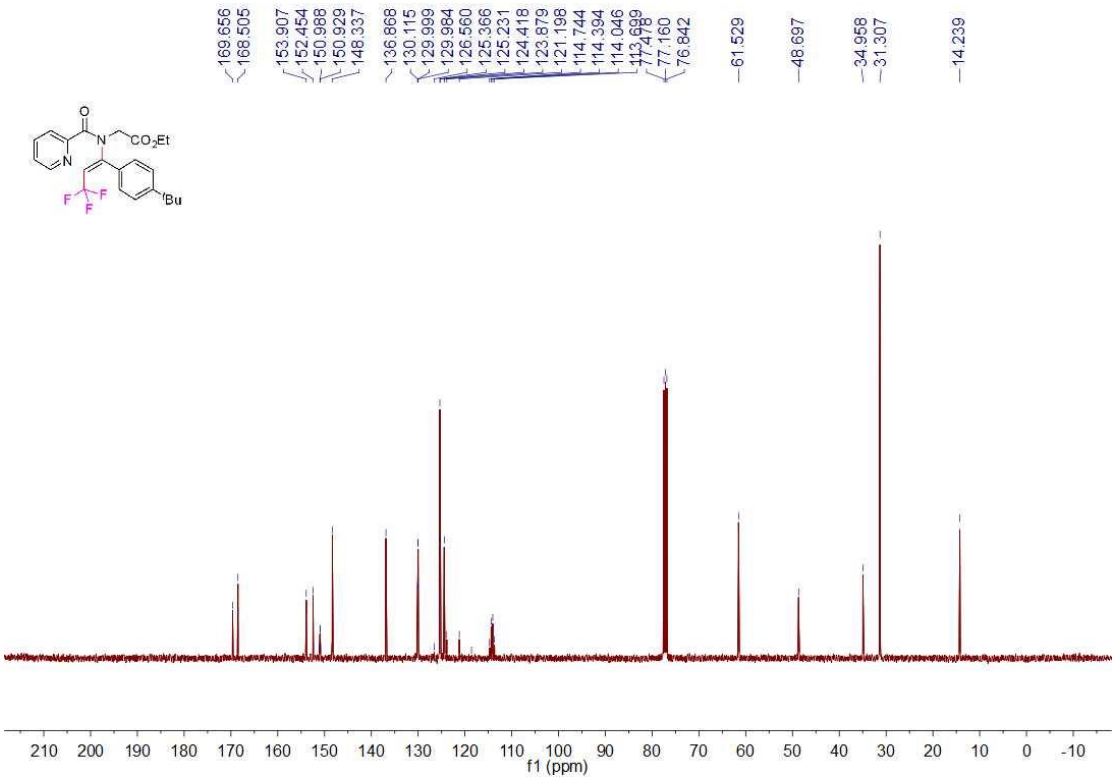
^{13}C – NMR spectrum of compound – **6q** (100 MHz, $CDCl_3$)



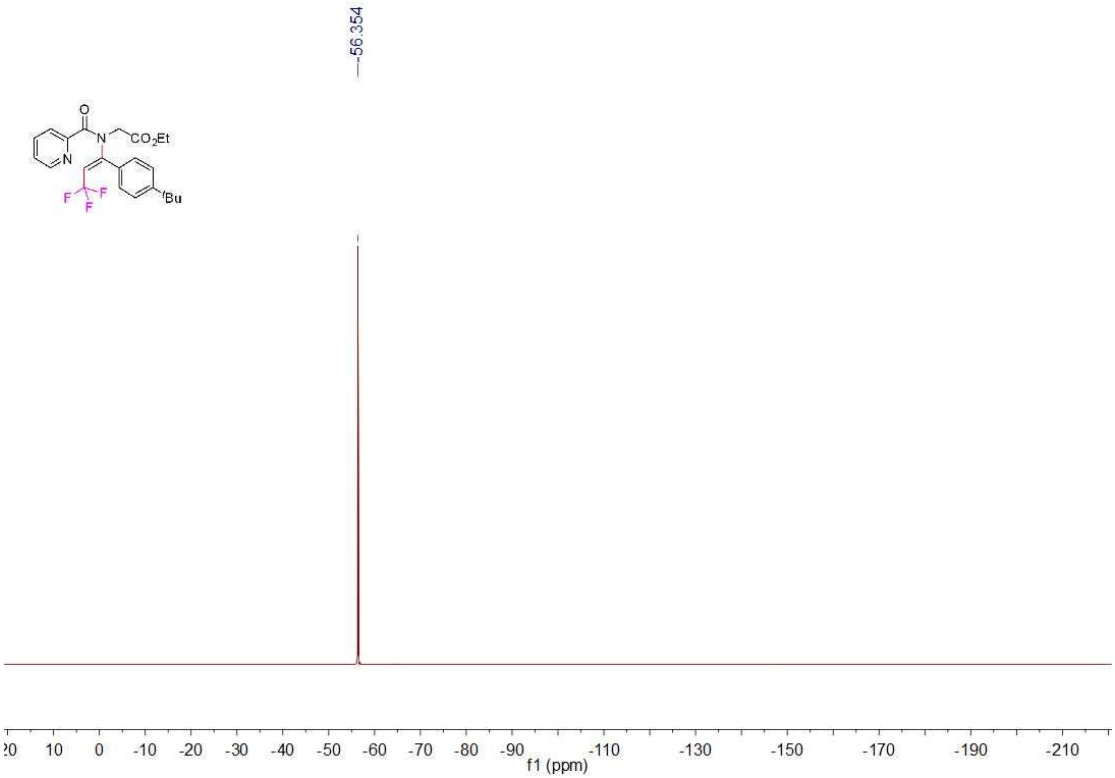
^{19}F – NMR spectrum of compound – **6q** (376 MHz, $CDCl_3$)



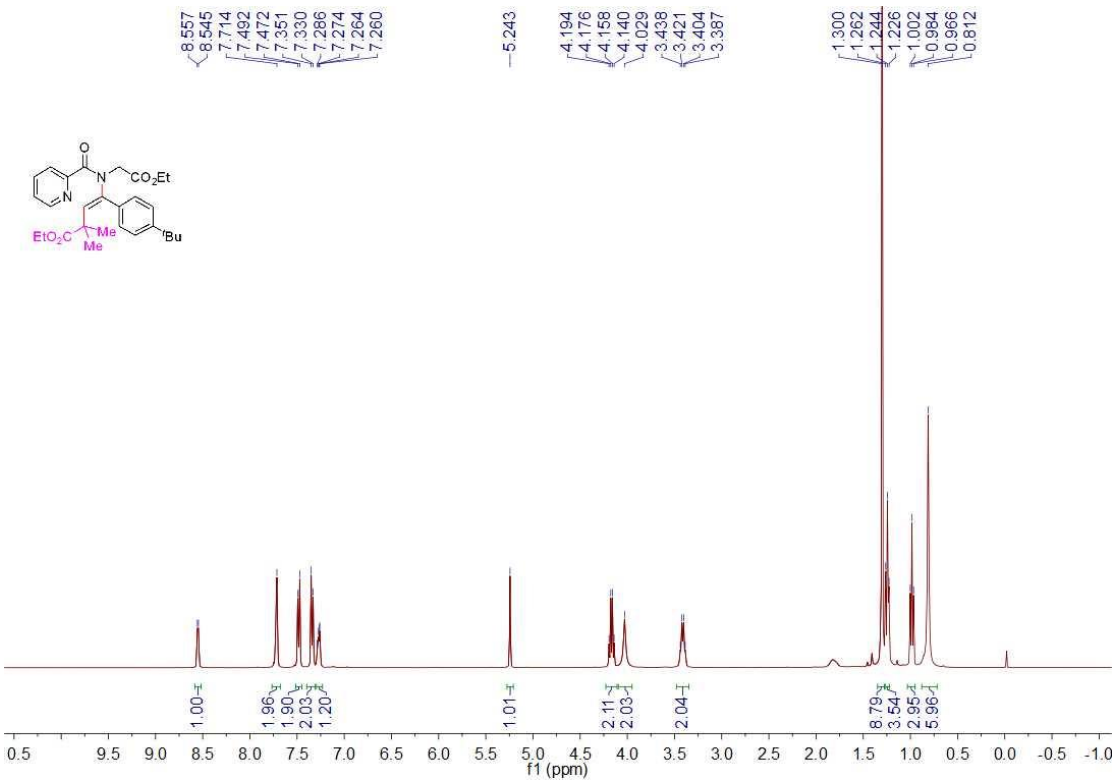
^{1}H – NMR spectrum of compound – **6r** (400 MHz, $CDCl_3$)



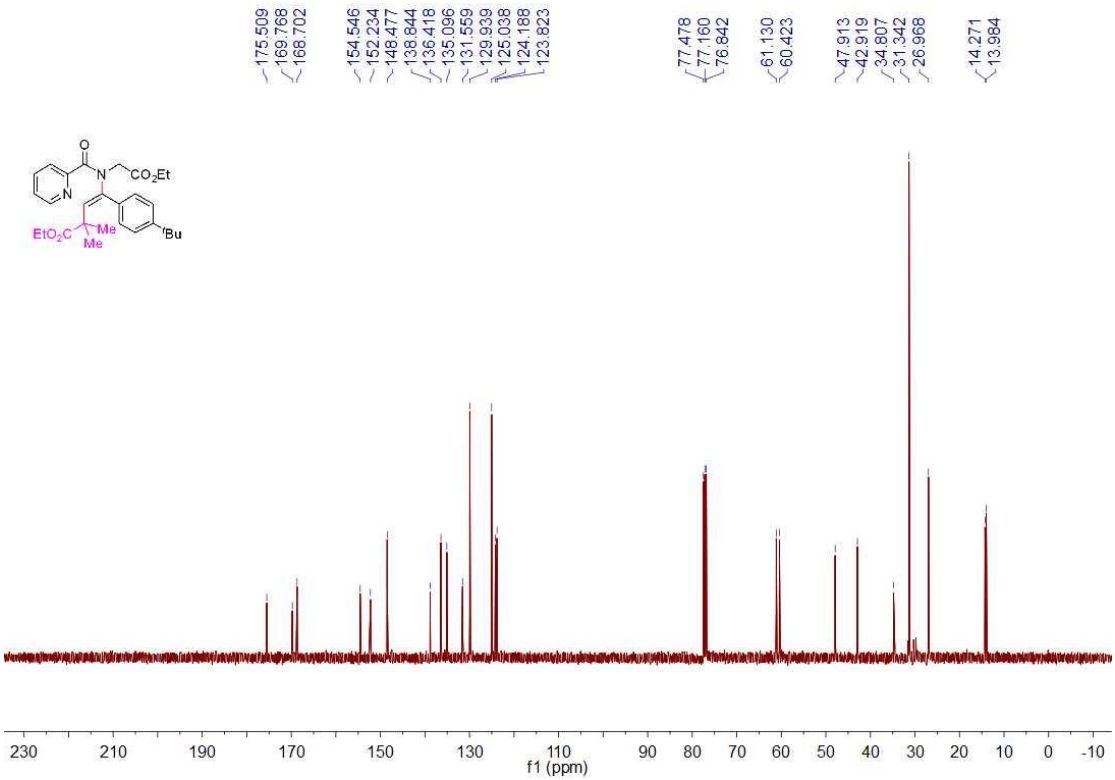
^{13}C – NMR spectrum of compound – **6r** (100 MHz, $CDCl_3$)



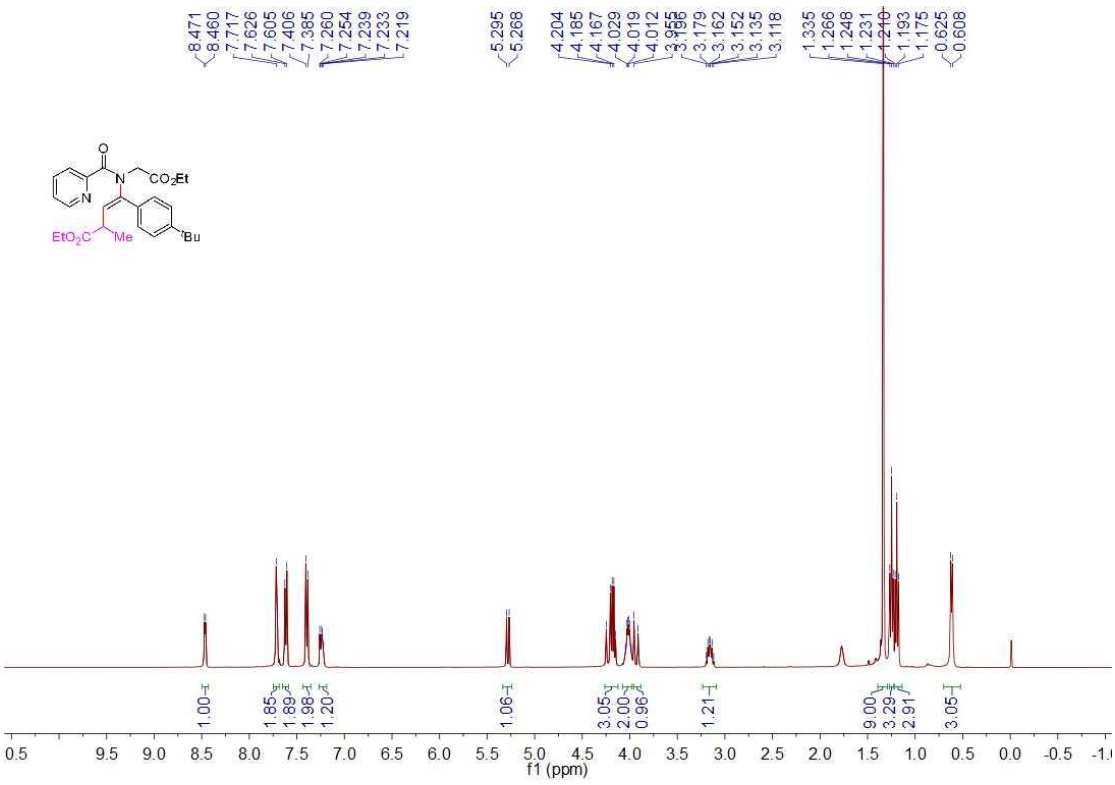
^{19}F – NMR spectrum of compound – **6r** (376 MHz, $CDCl_3$)



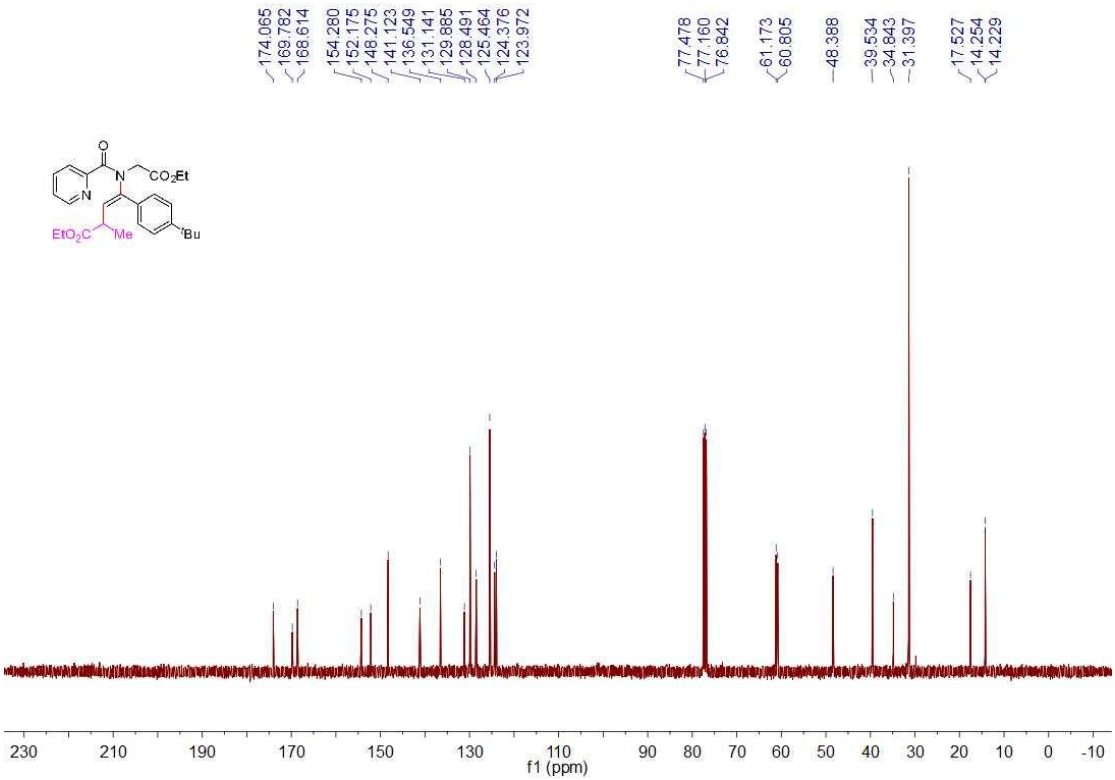
^{1}H – NMR spectrum of compound – **6s** (400 MHz, $CDCl_3$)



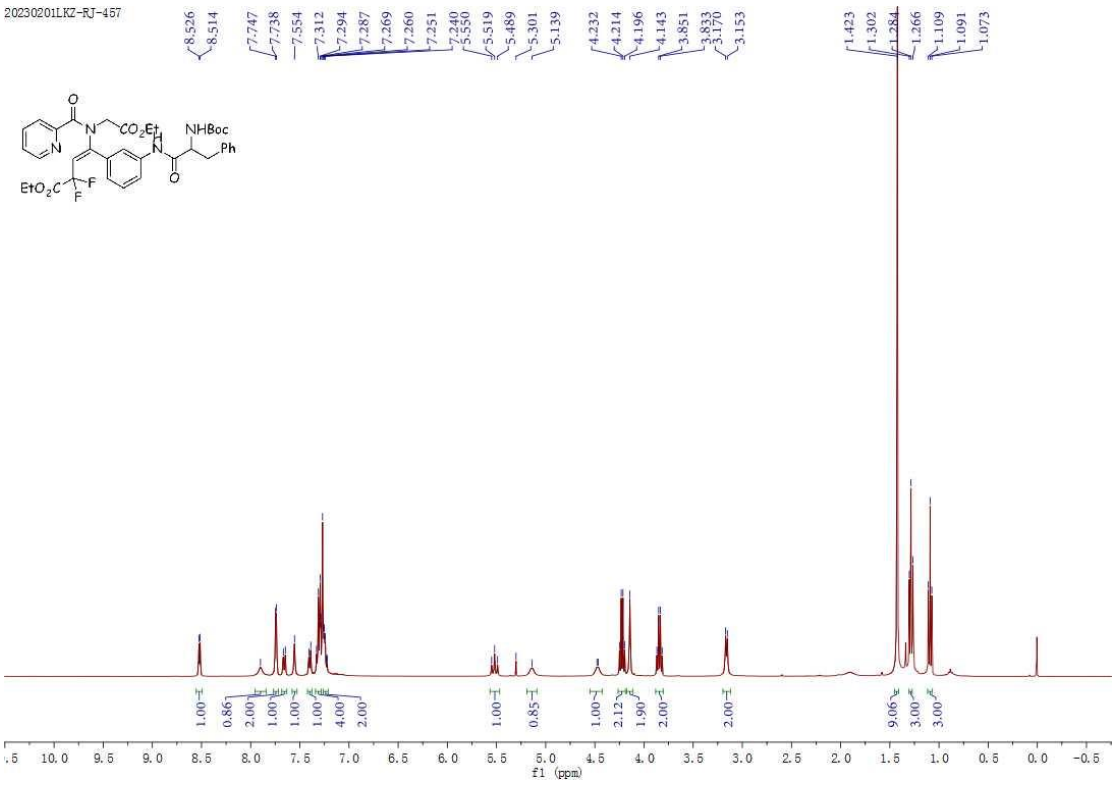
^{13}C – NMR spectrum of compound – **6s** (100 MHz, $CDCl_3$)



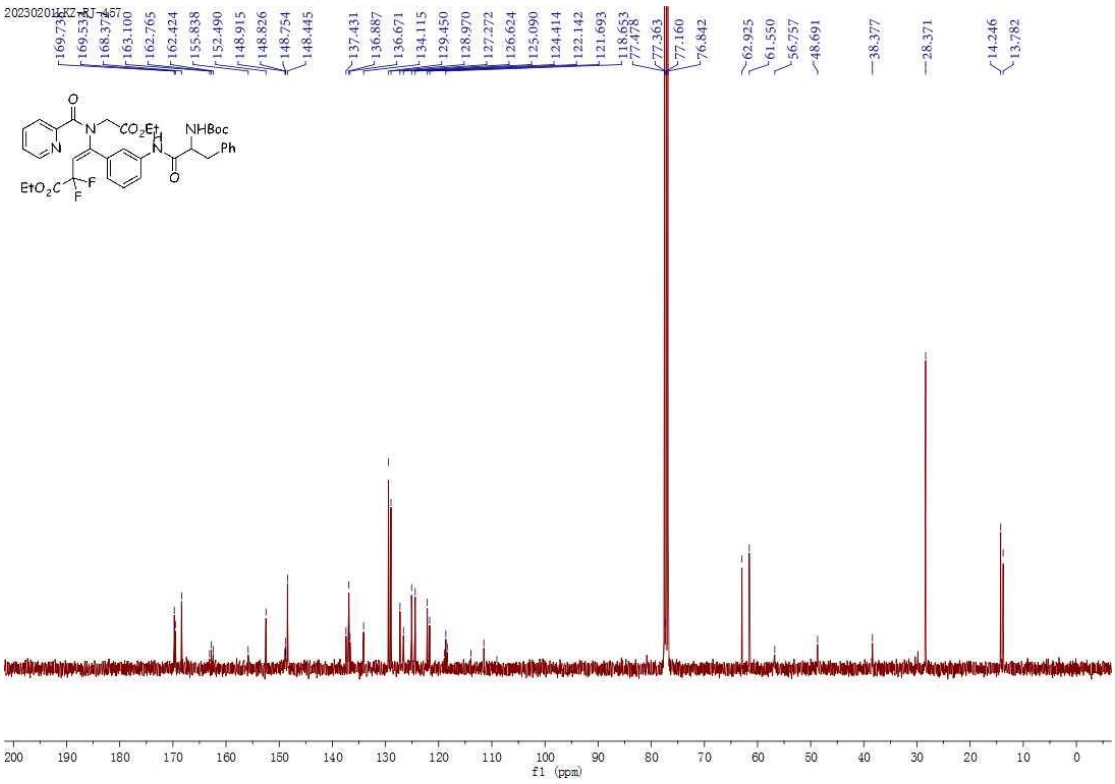
^{1}H – NMR spectrum of compound – **6t** (400 MHz, $CDCl_3$)



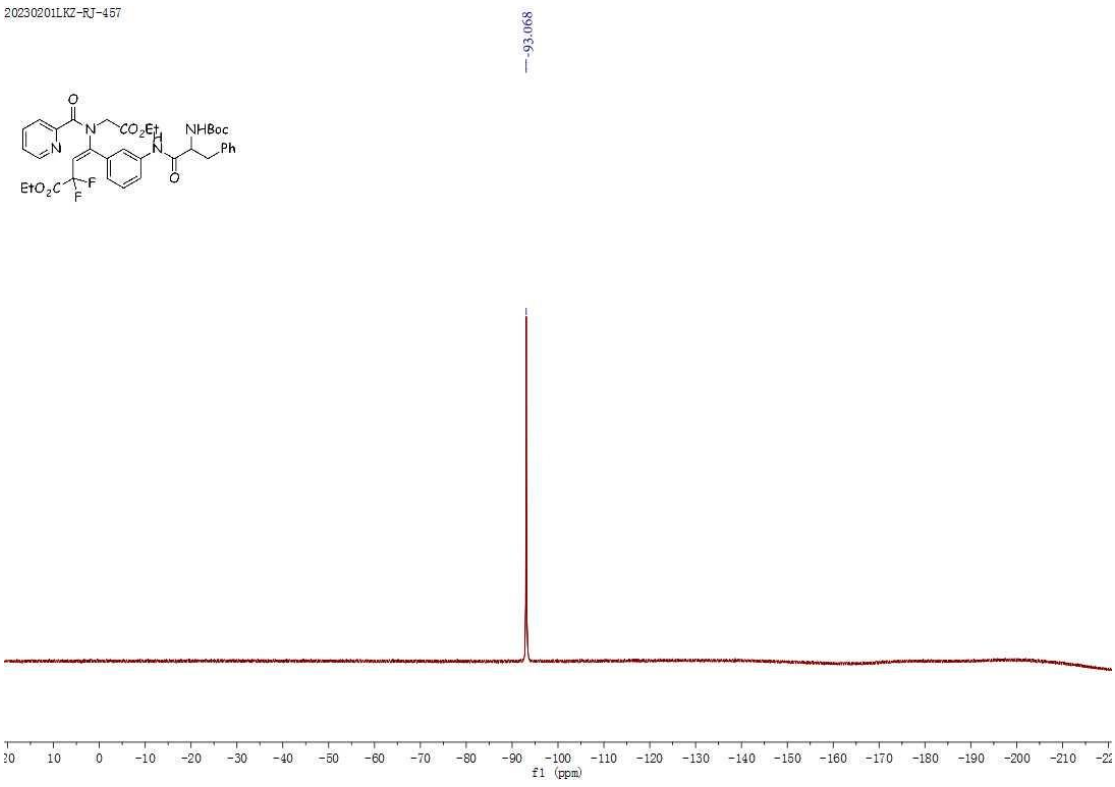
^{13}C – NMR spectrum of compound – **6t** (100 MHz, $CDCl_3$)



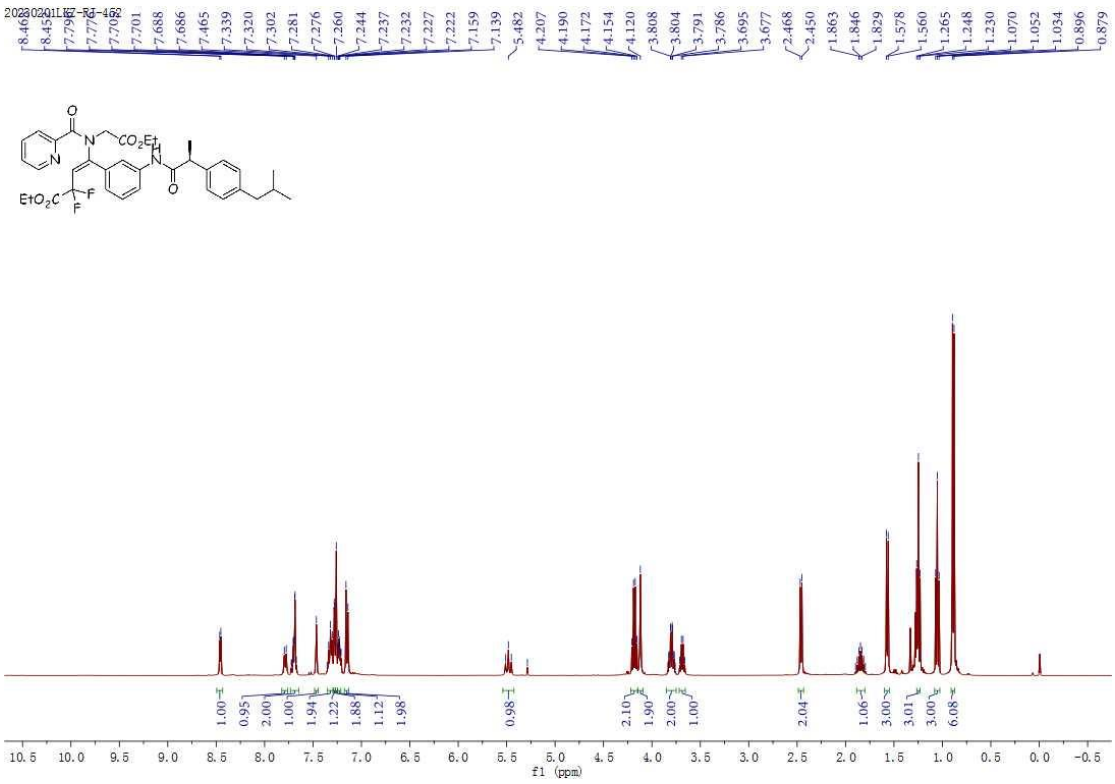
^{1}H – NMR spectrum of compound – **7a** (400 MHz, $CDCl_3$)



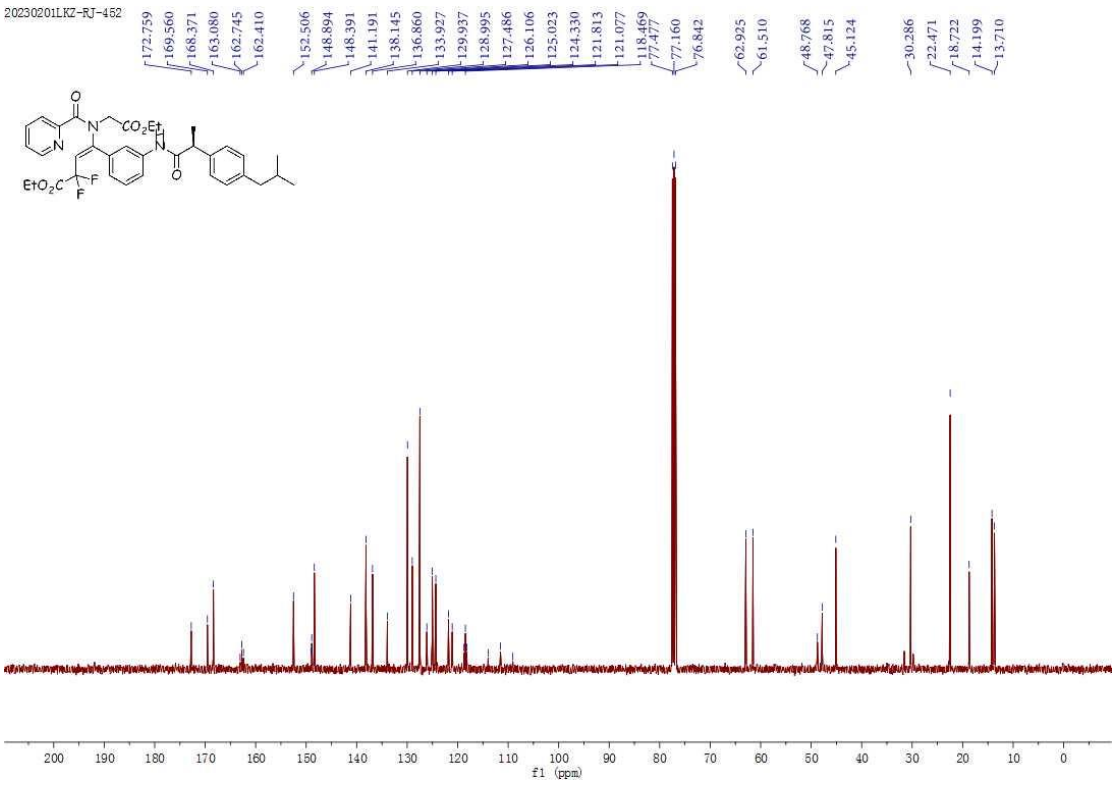
^{13}C – NMR spectrum of compound – **7a** (100 MHz, $CDCl_3$)



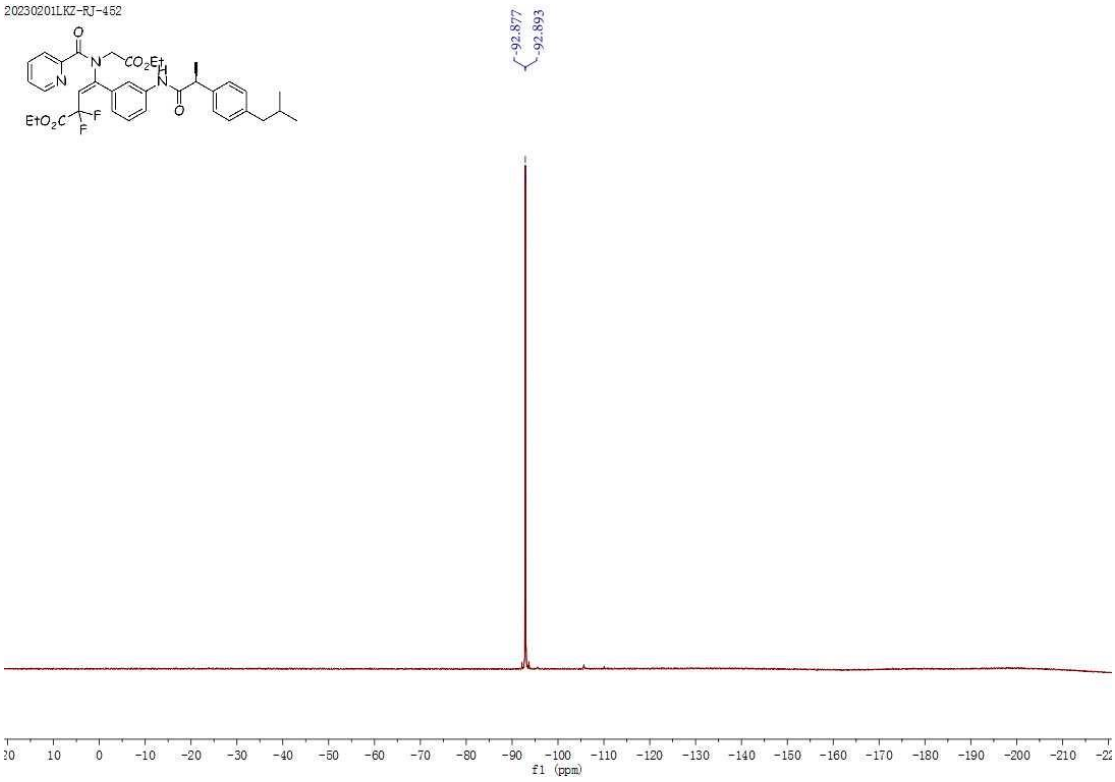
^{19}F – NMR spectrum of compound – **7a** (376 MHz, $CDCl_3$)



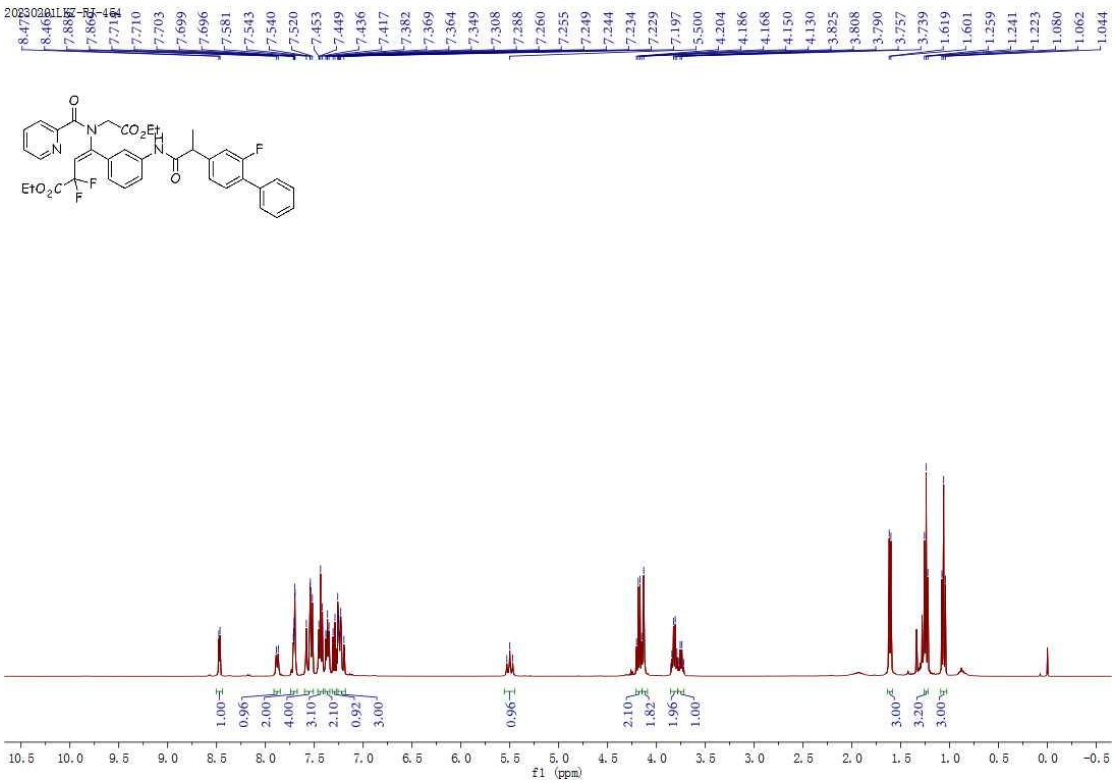
^{1}H – NMR spectrum of compound – **7b** (400 MHz, $CDCl_3$)



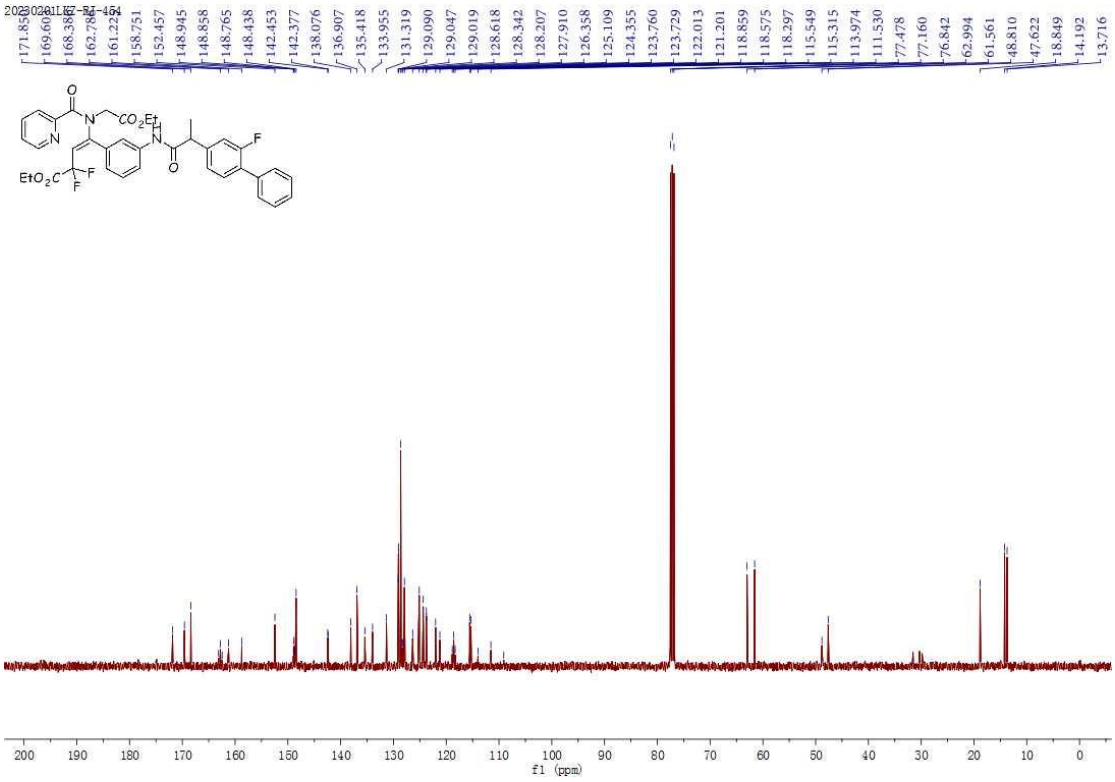
^{13}C – NMR spectrum of compound – **7b** (100 MHz, $CDCl_3$)



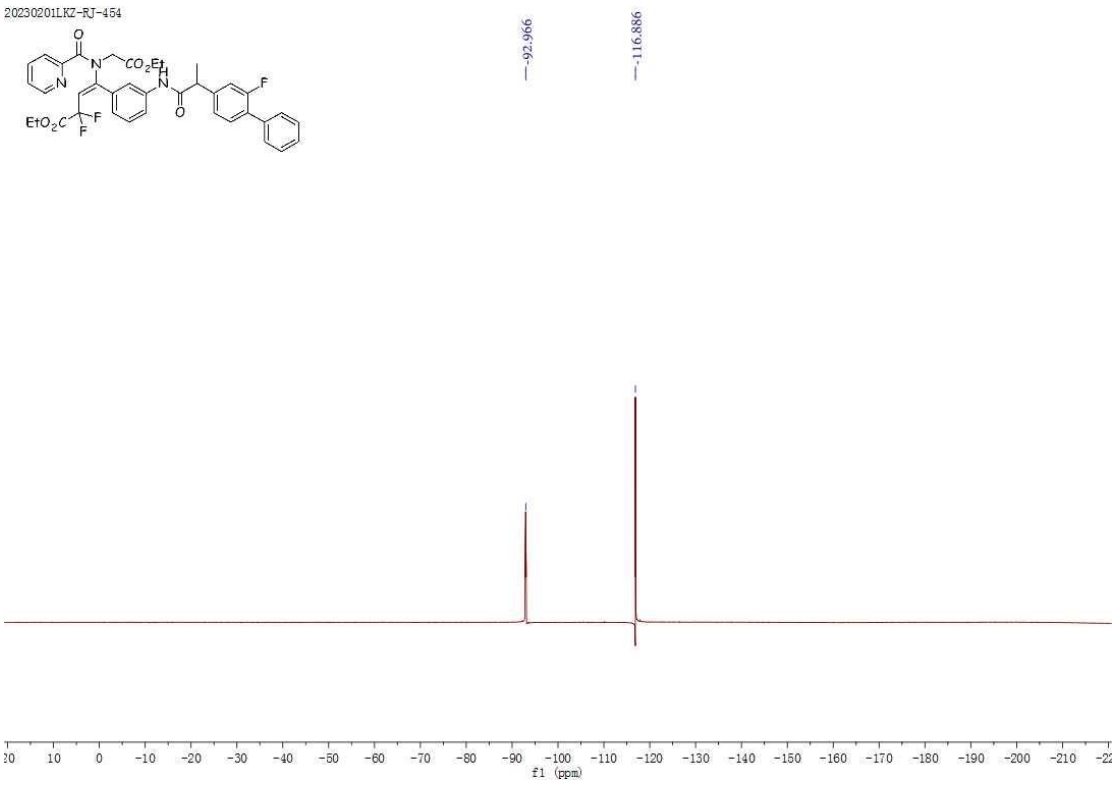
^{19}F – NMR spectrum of compound – **7b** (376 MHz, $CDCl_3$)



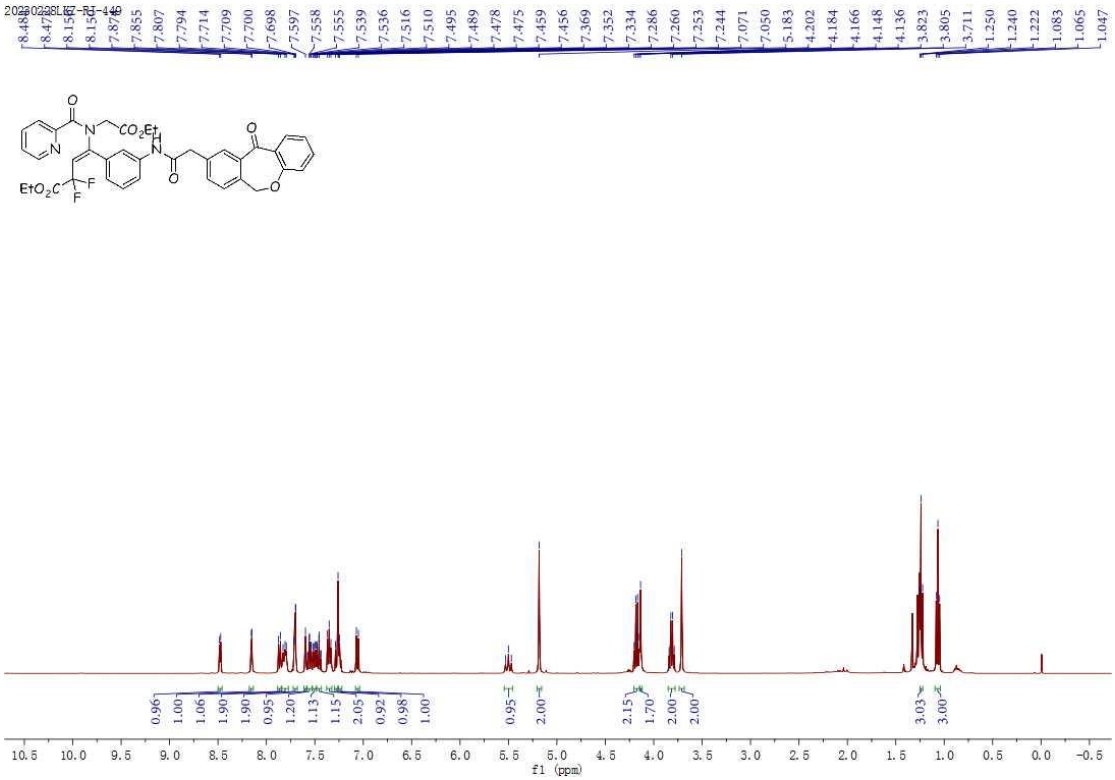
^{1}H – NMR spectrum of compound – **7c** (400 MHz, $CDCl_3$)



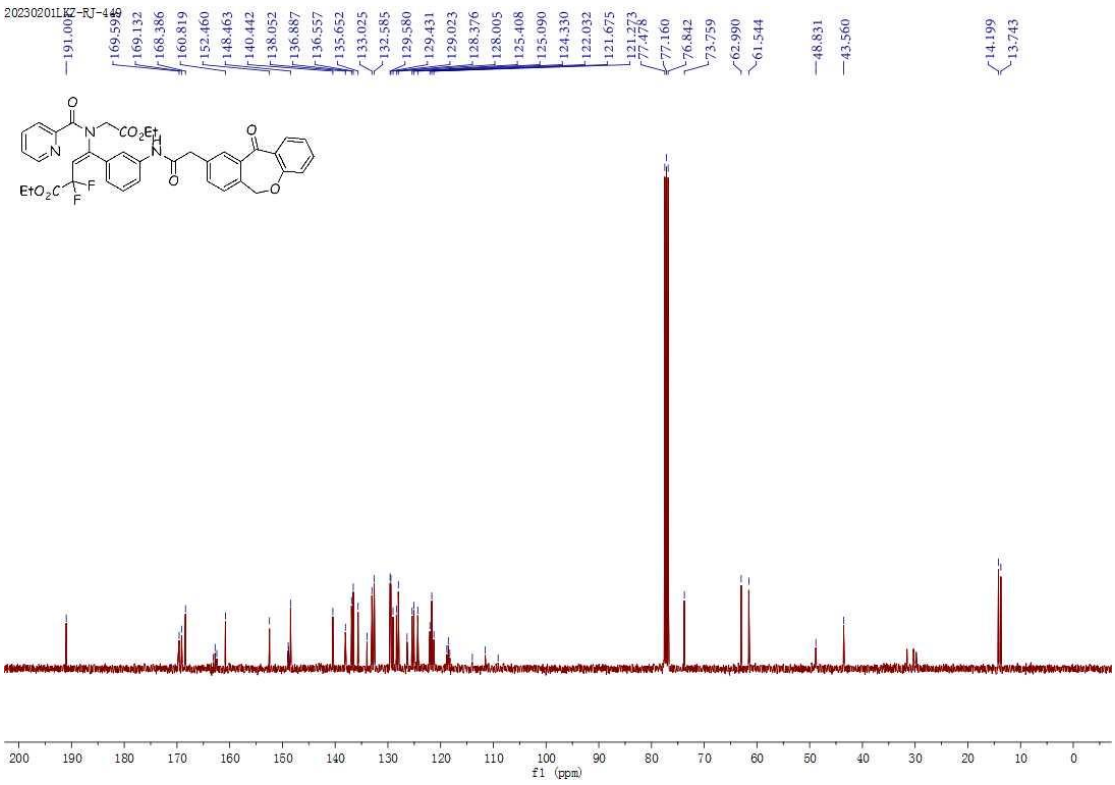
^{13}C – NMR spectrum of compound – **7c** (100 MHz, $CDCl_3$)



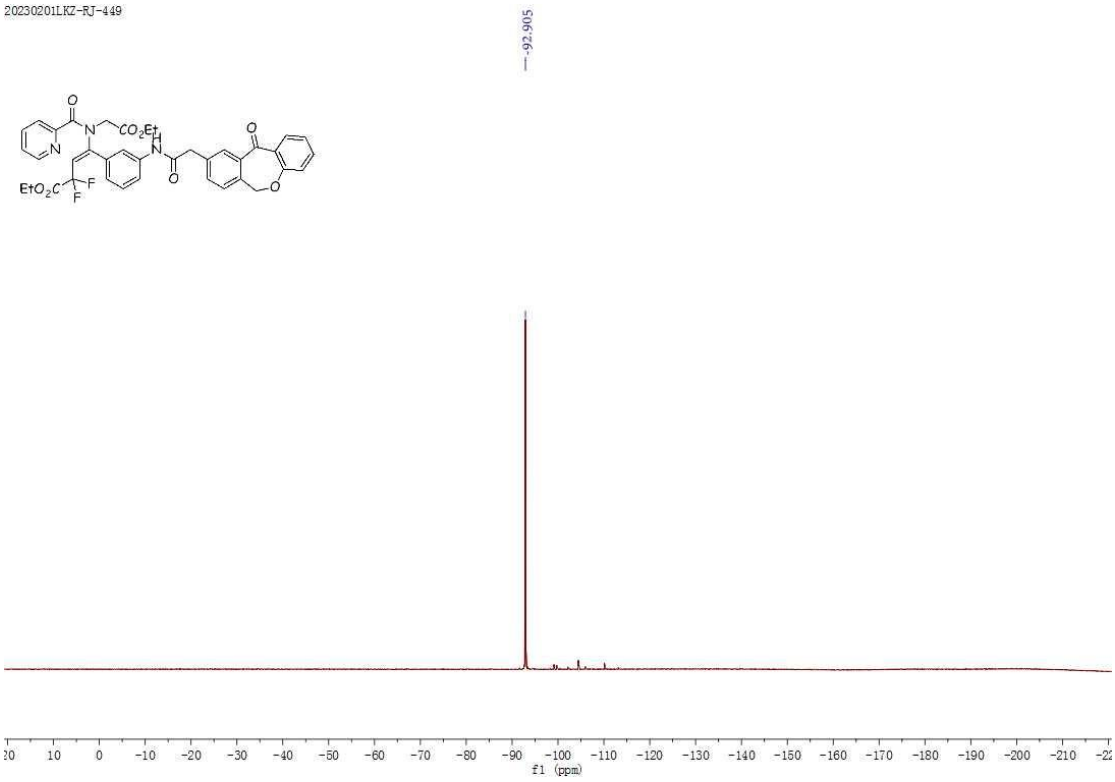
^{19}F – NMR spectrum of compound – **7c** (376 MHz, $CDCl_3$)



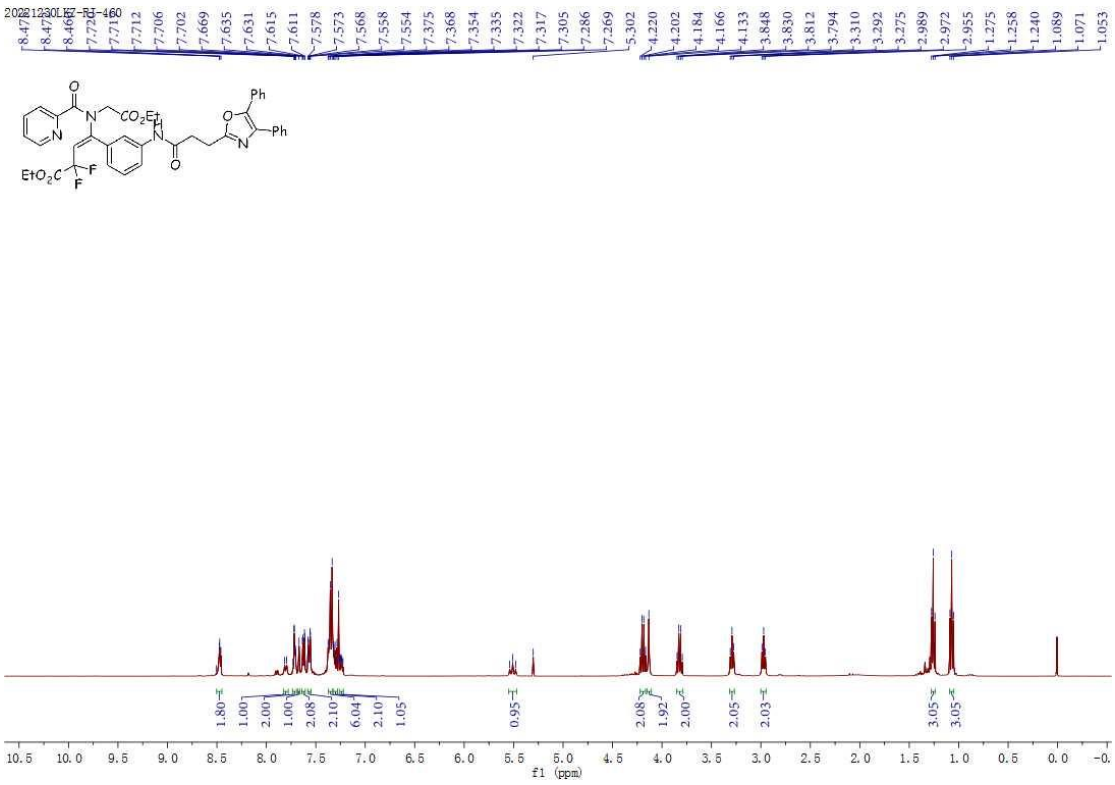
^{1}H – NMR spectrum of compound – **7d** (400 MHz, $CDCl_3$)



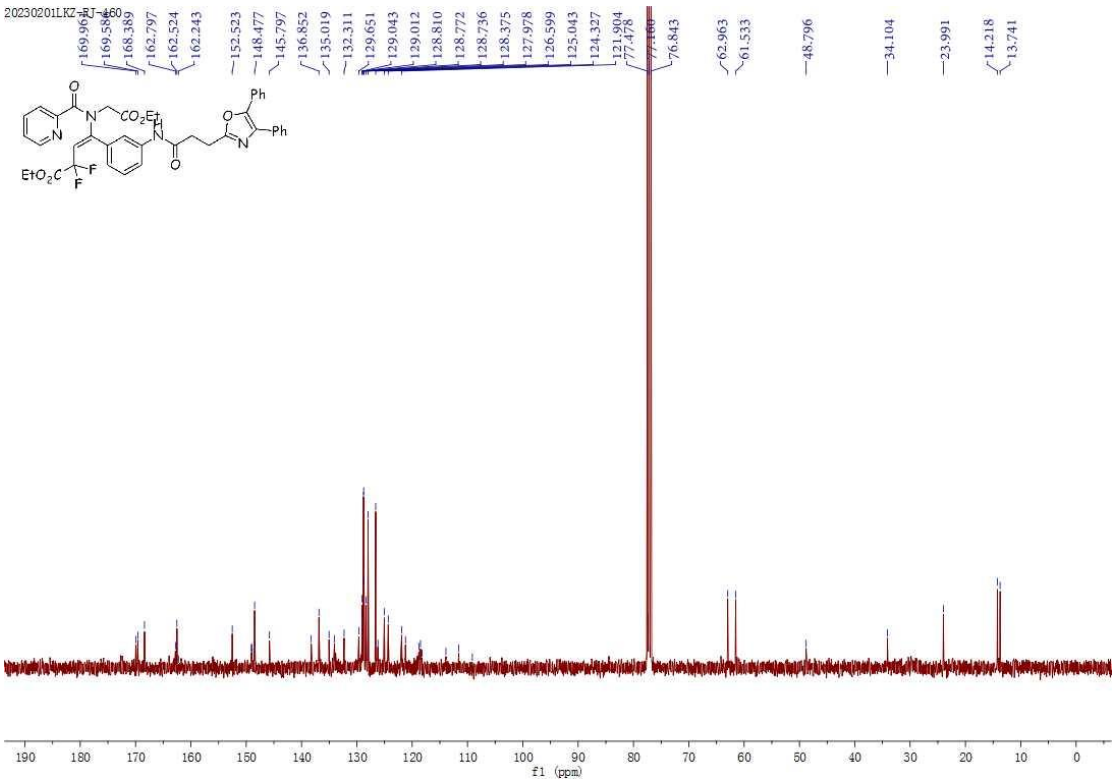
^{13}C – NMR spectrum of compound – **7d** (100 MHz, $CDCl_3$)



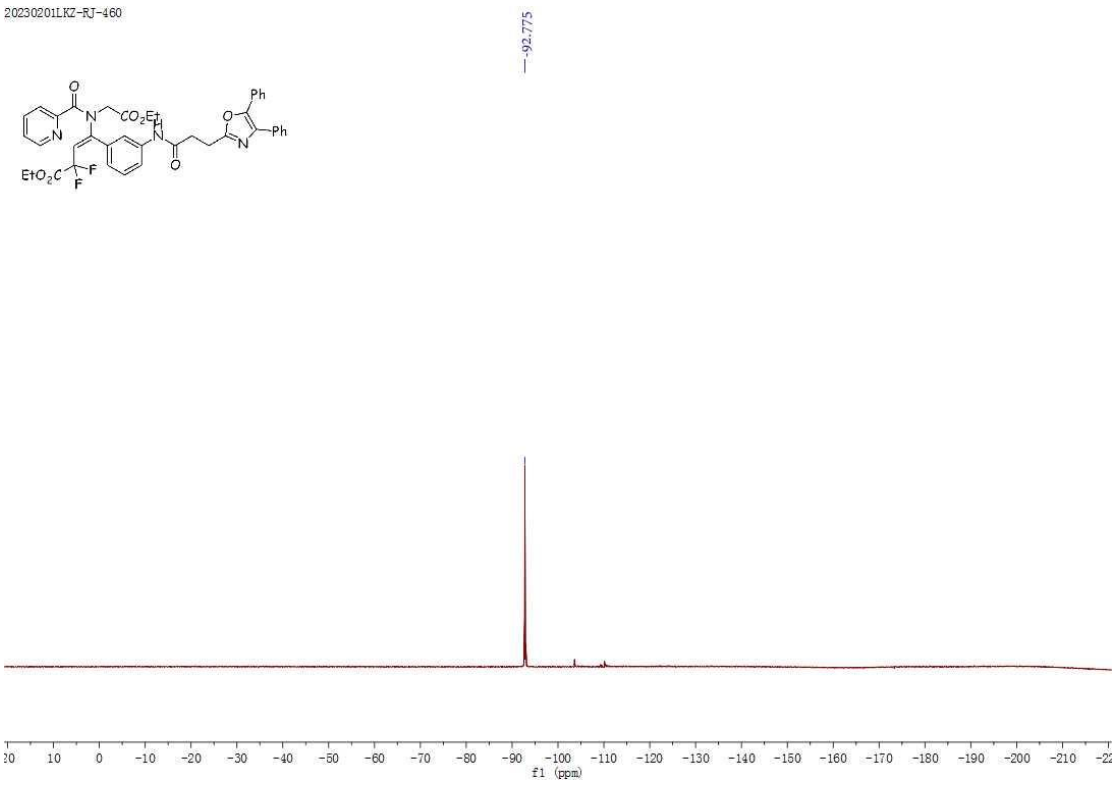
^{19}F – NMR spectrum of compound – **7d** (376 MHz, $CDCl_3$)



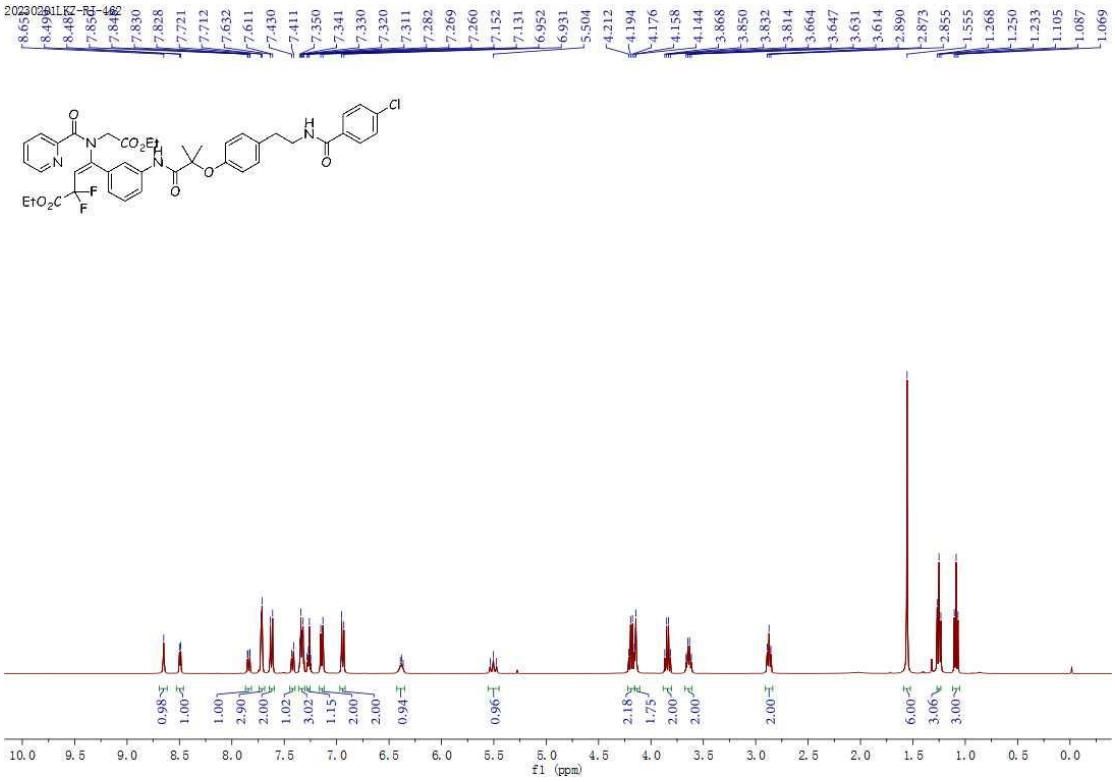
^{1}H – NMR spectrum of compound – **7e** (400 MHz, $CDCl_3$)



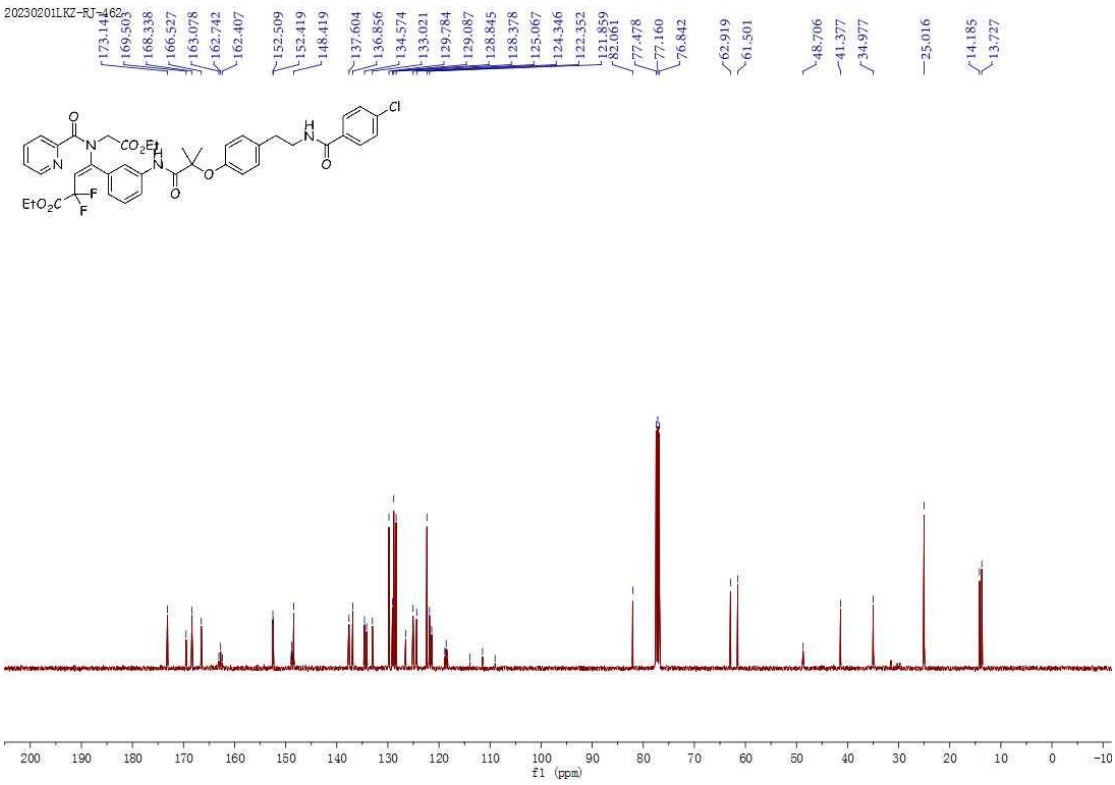
^{13}C – NMR spectrum of compound – **7e** (100 MHz, $CDCl_3$)



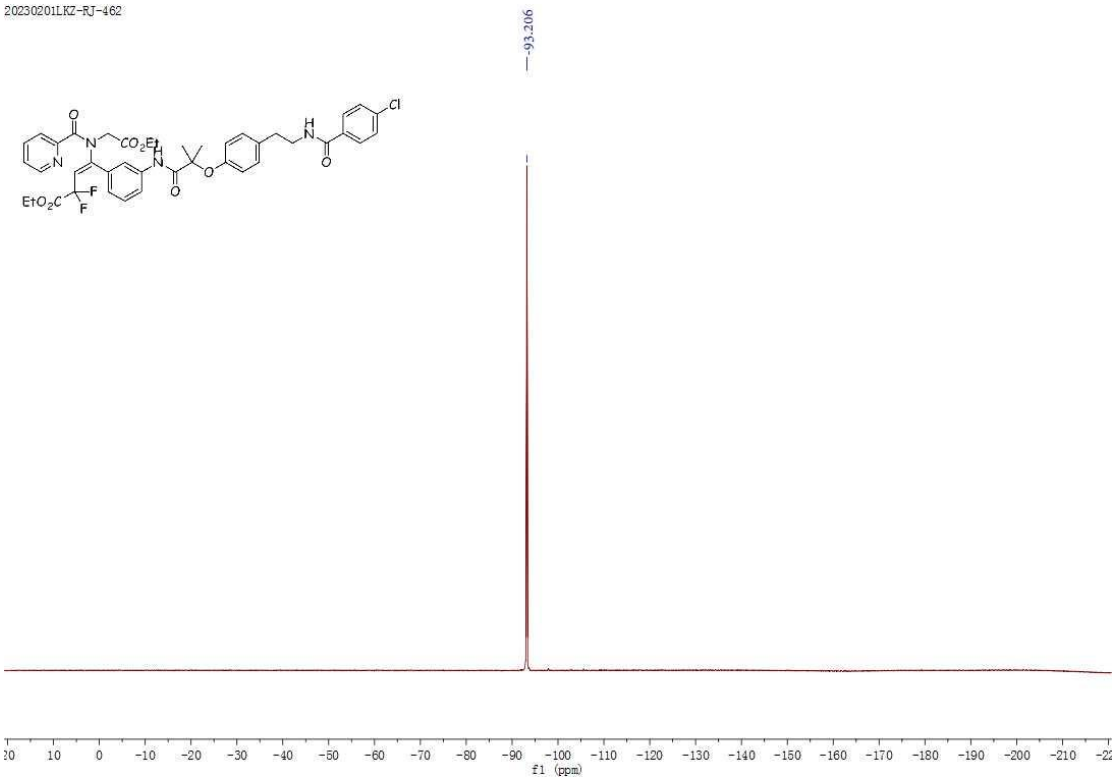
^{19}F – NMR spectrum of compound – **7e** (376 MHz, $CDCl_3$)



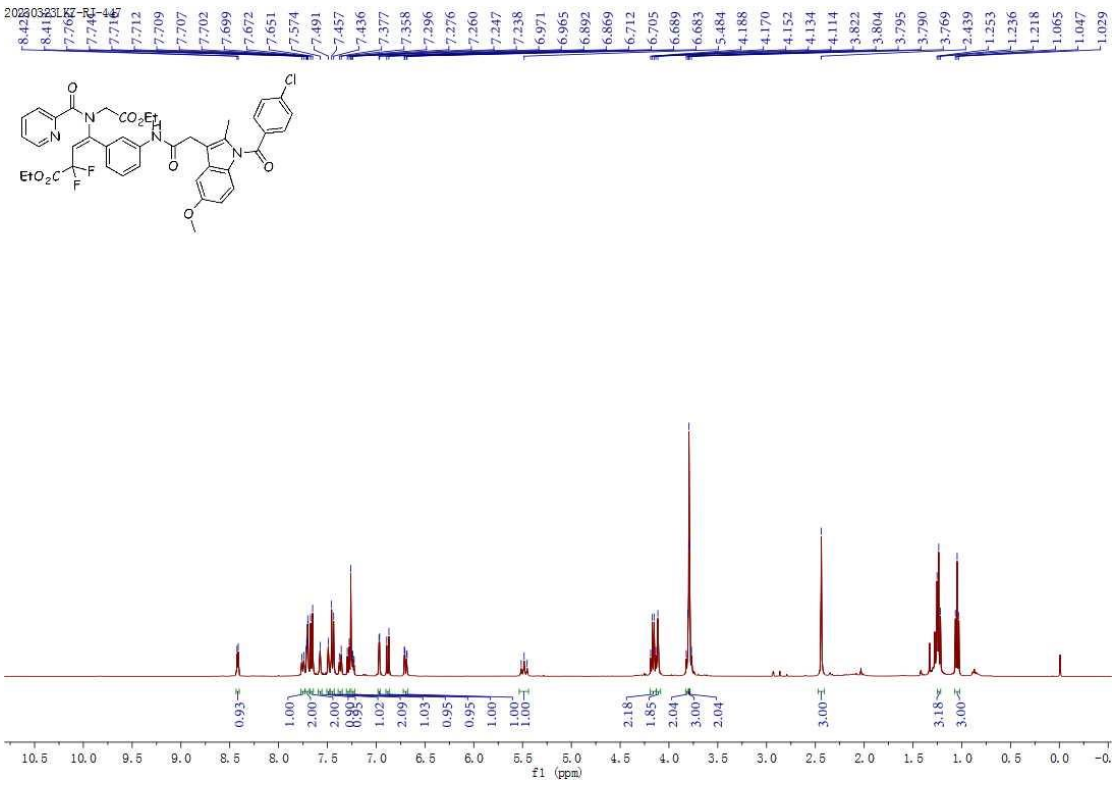
^{1}H – NMR spectrum of compound – **7f** (400 MHz, $CDCl_3$)



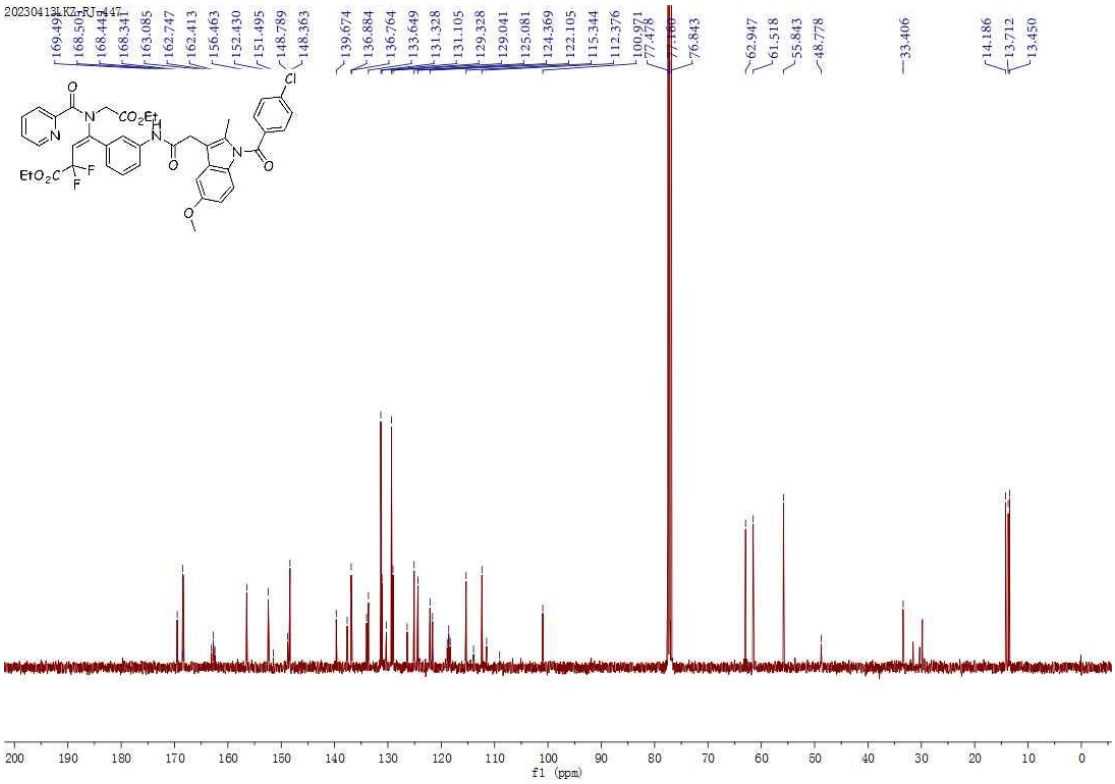
^{13}C – NMR spectrum of compound – **7f** (100 MHz, $CDCl_3$)



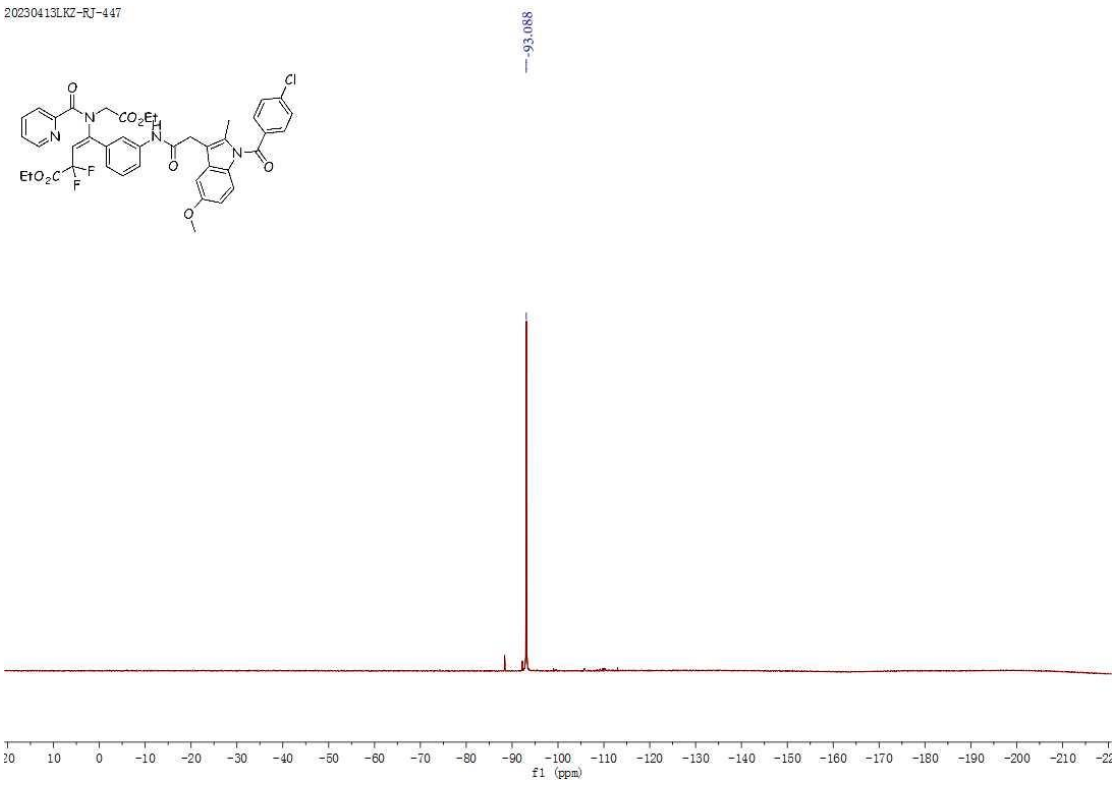
^{19}F – NMR spectrum of compound – **7f** (376 MHz, $CDCl_3$)



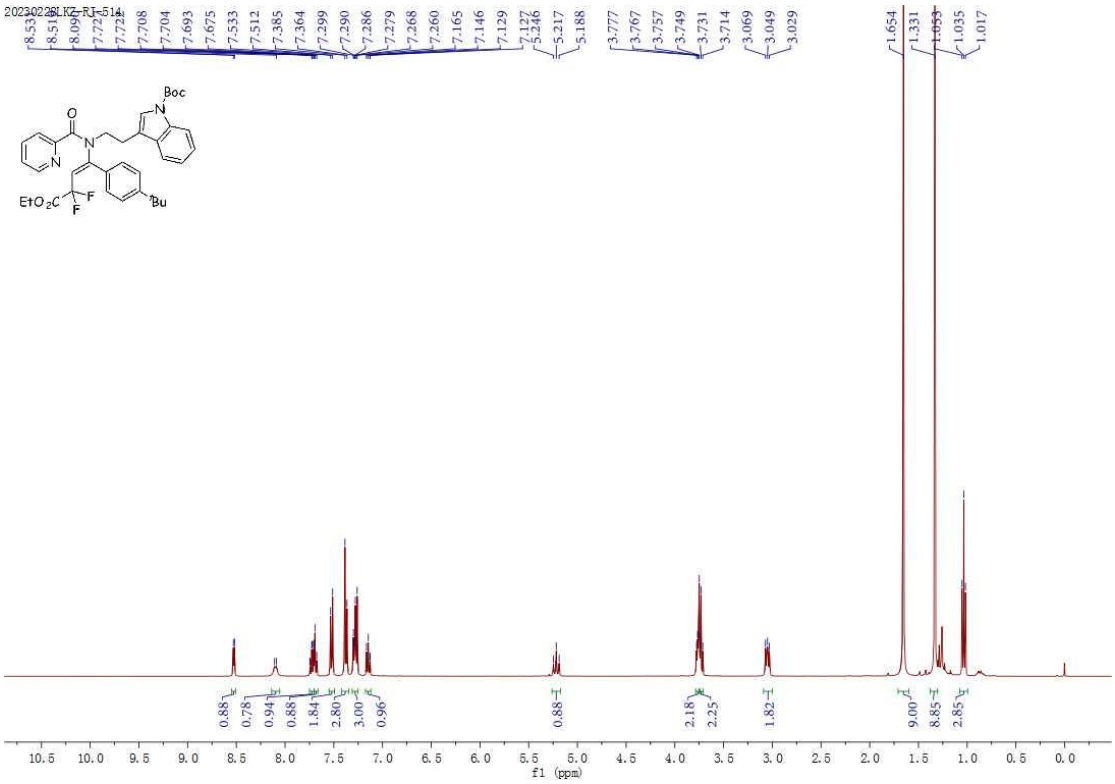
^{1}H – NMR spectrum of compound – **7g** (400 MHz, $CDCl_3$)



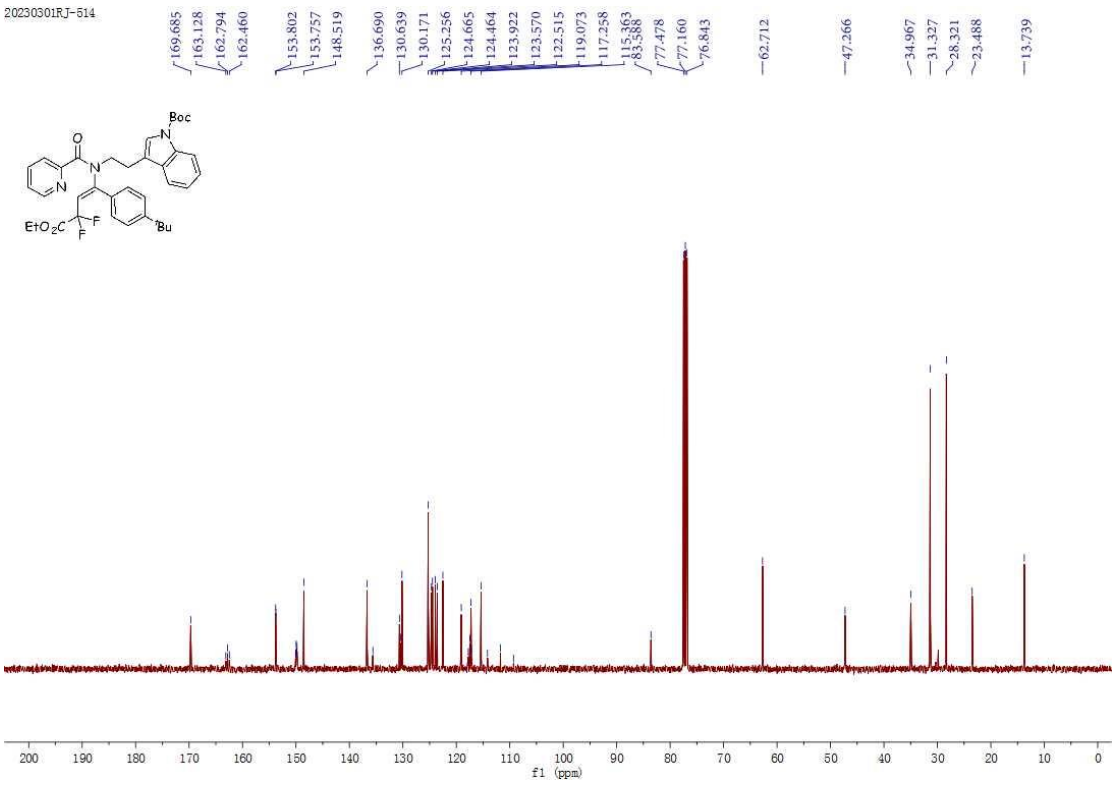
^{13}C – NMR spectrum of compound – **7g** (100 MHz, $CDCl_3$)



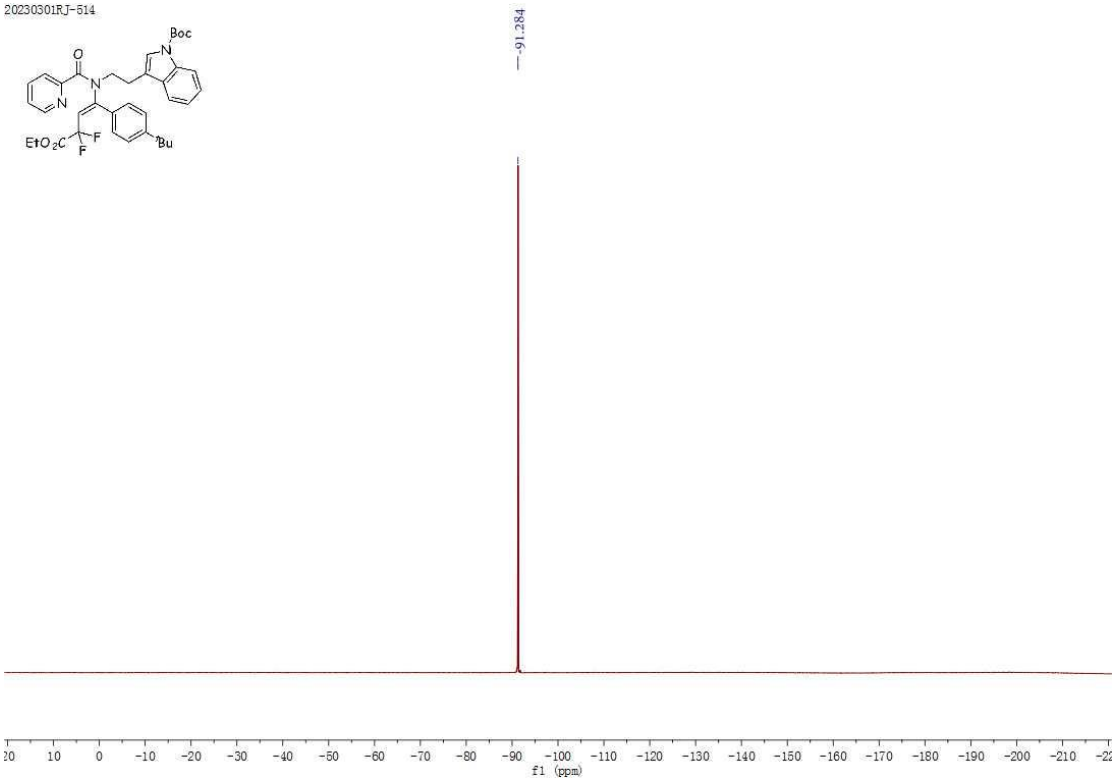
^{19}F – NMR spectrum of compound – **7g** (376 MHz, $CDCl_3$)



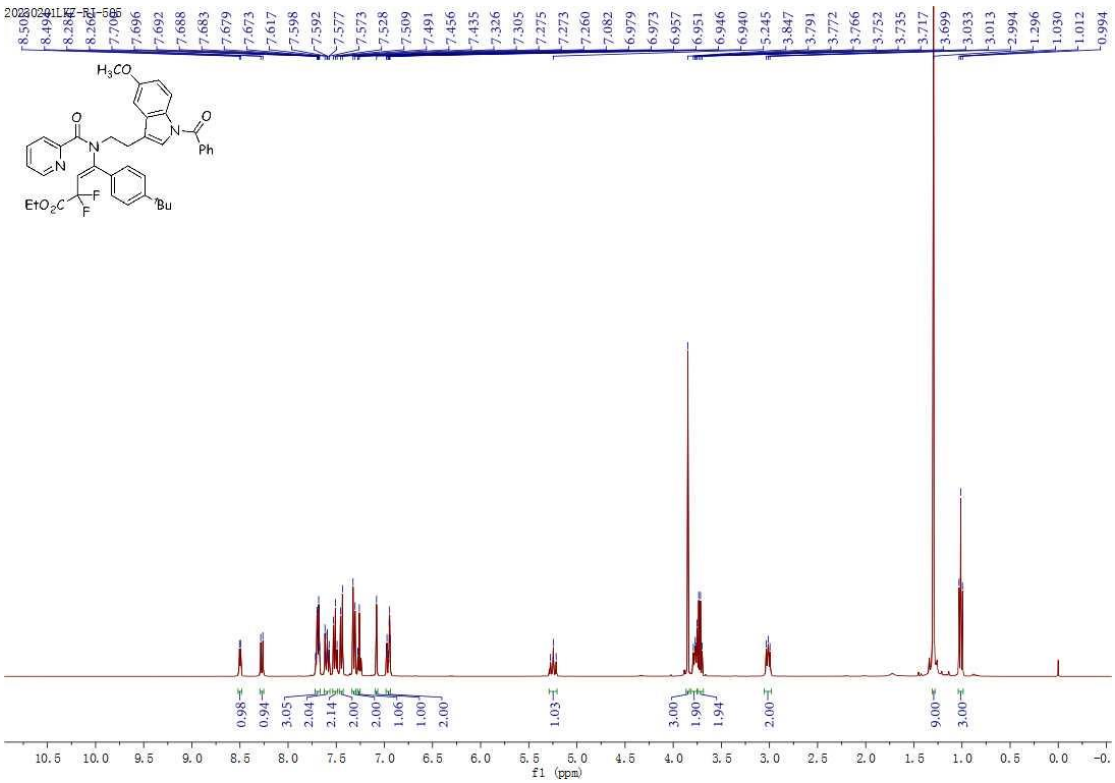
^{1}H – NMR spectrum of compound – **7h** (400 MHz, $CDCl_3$)



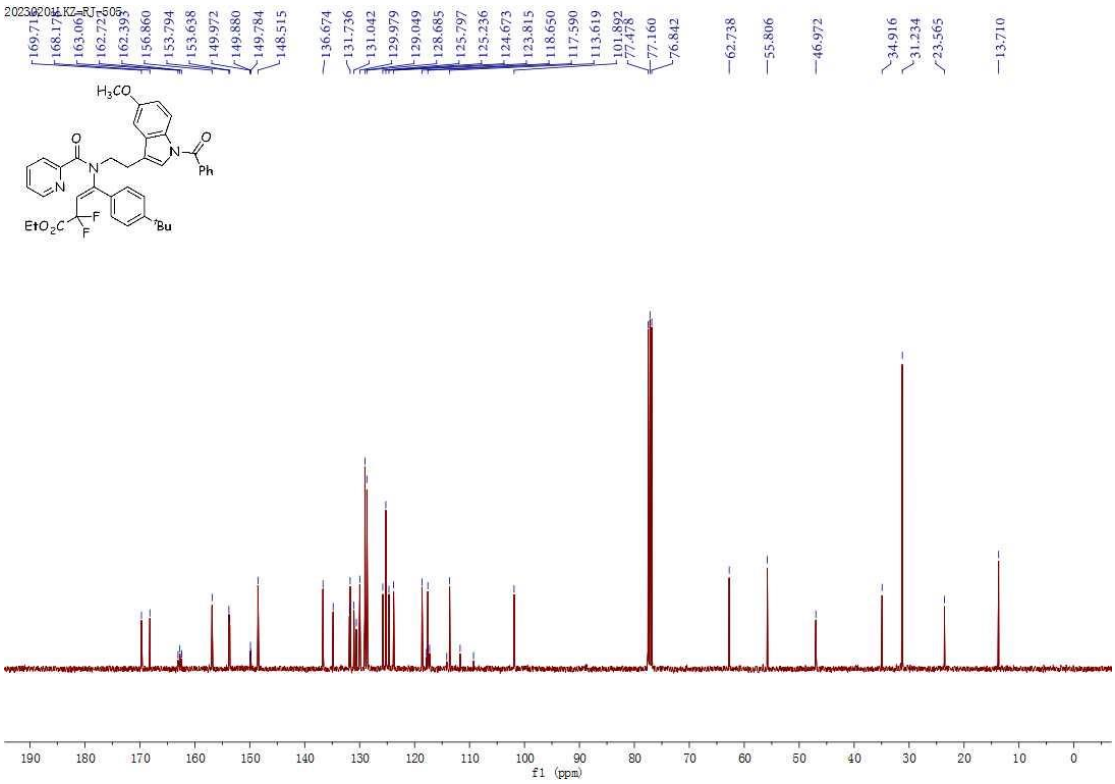
^{13}C – NMR spectrum of compound – **7h** (100 MHz, $CDCl_3$)



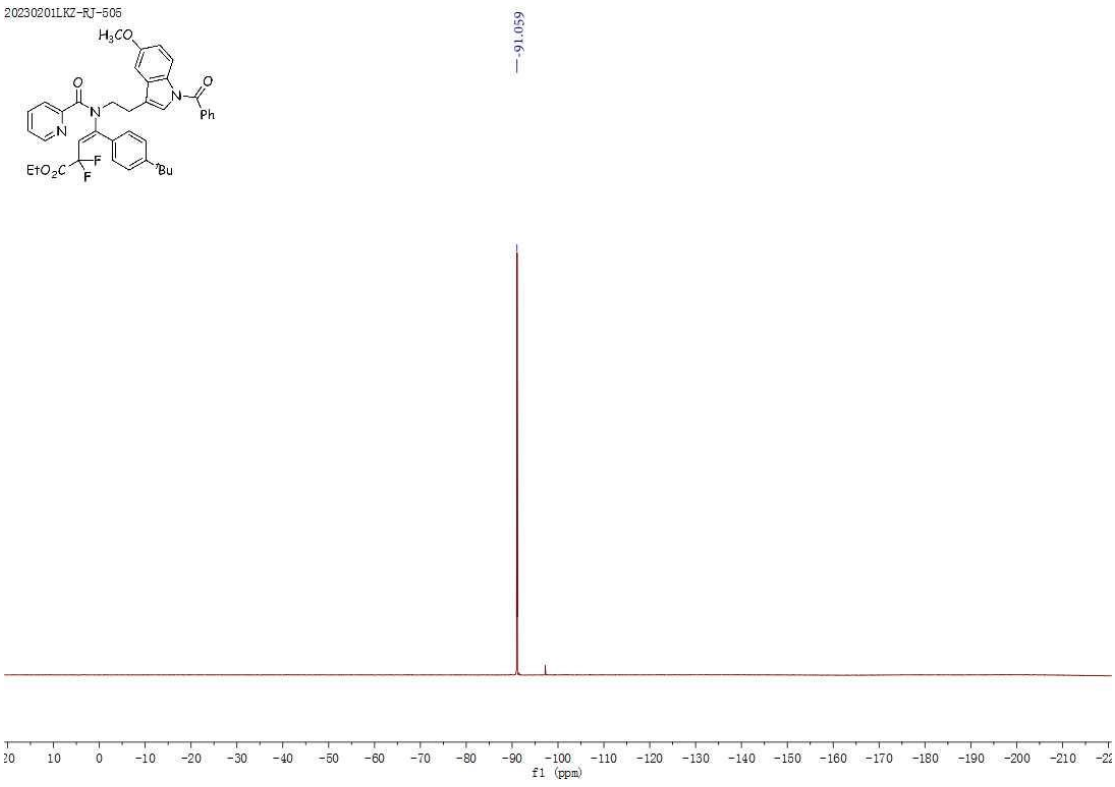
^{19}F – NMR spectrum of compound – **7h** (376 MHz, $CDCl_3$)



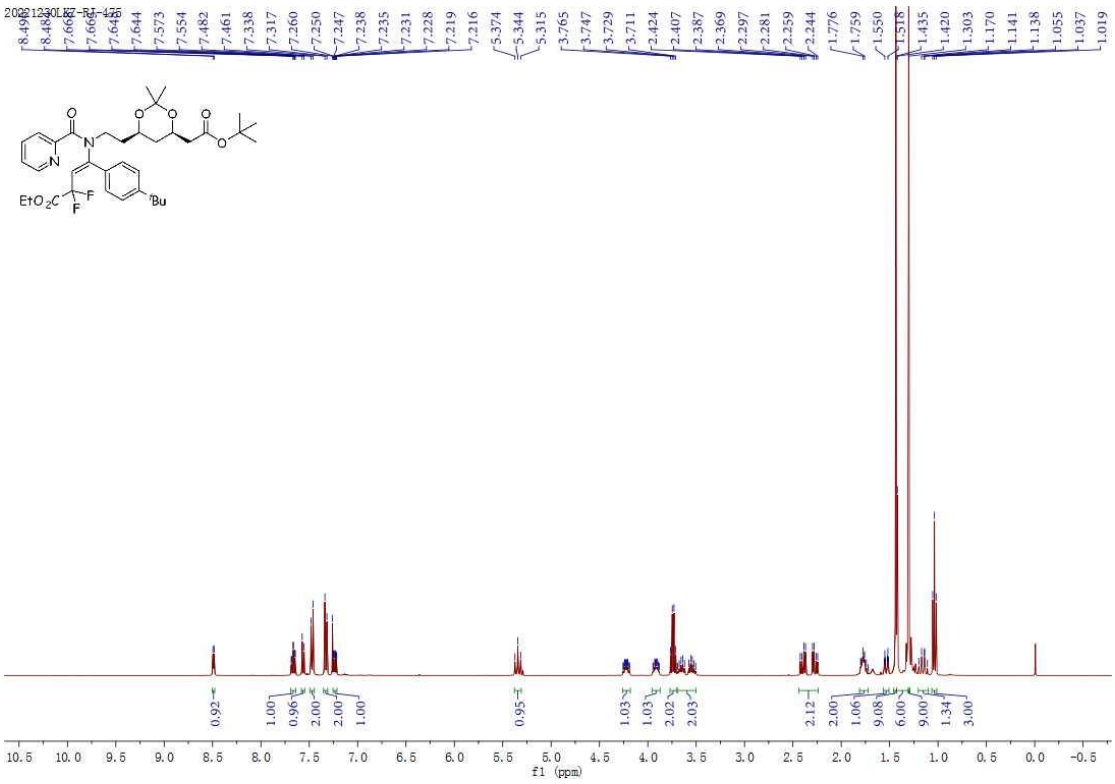
^{1}H – NMR spectrum of compound – **7i** (400 MHz, $CDCl_3$)



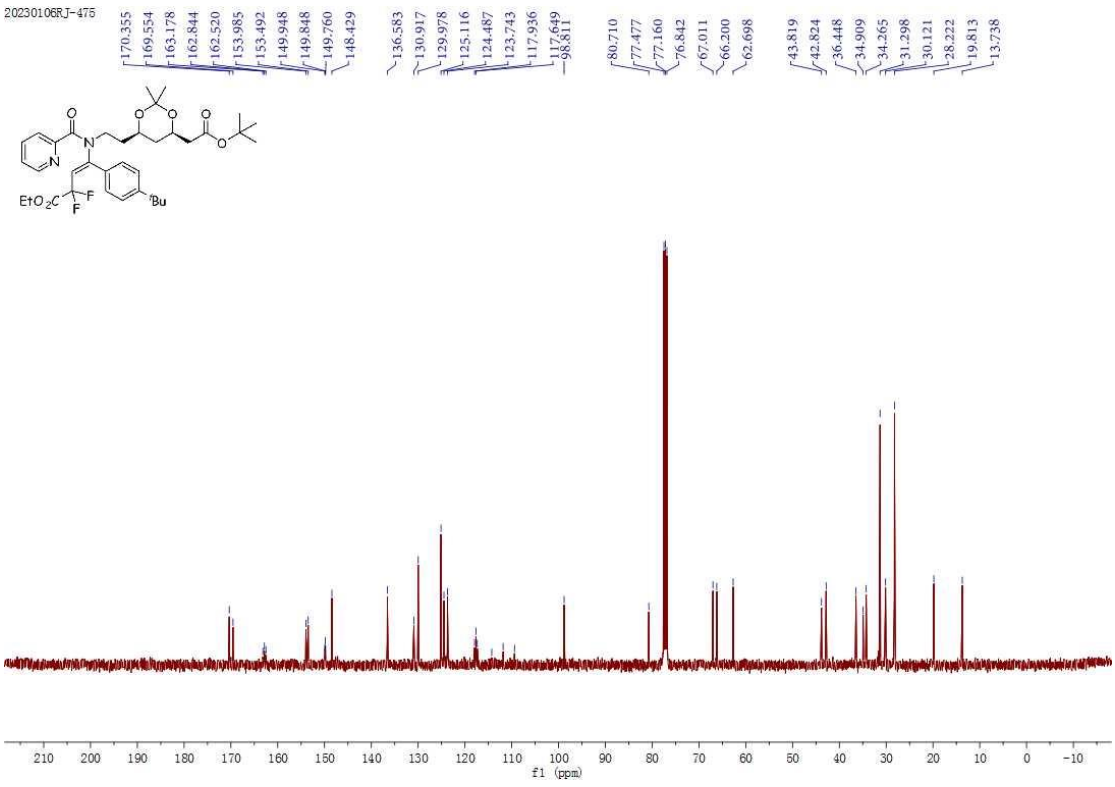
^{13}C – NMR spectrum of compound – **7i** (100 MHz, $CDCl_3$)



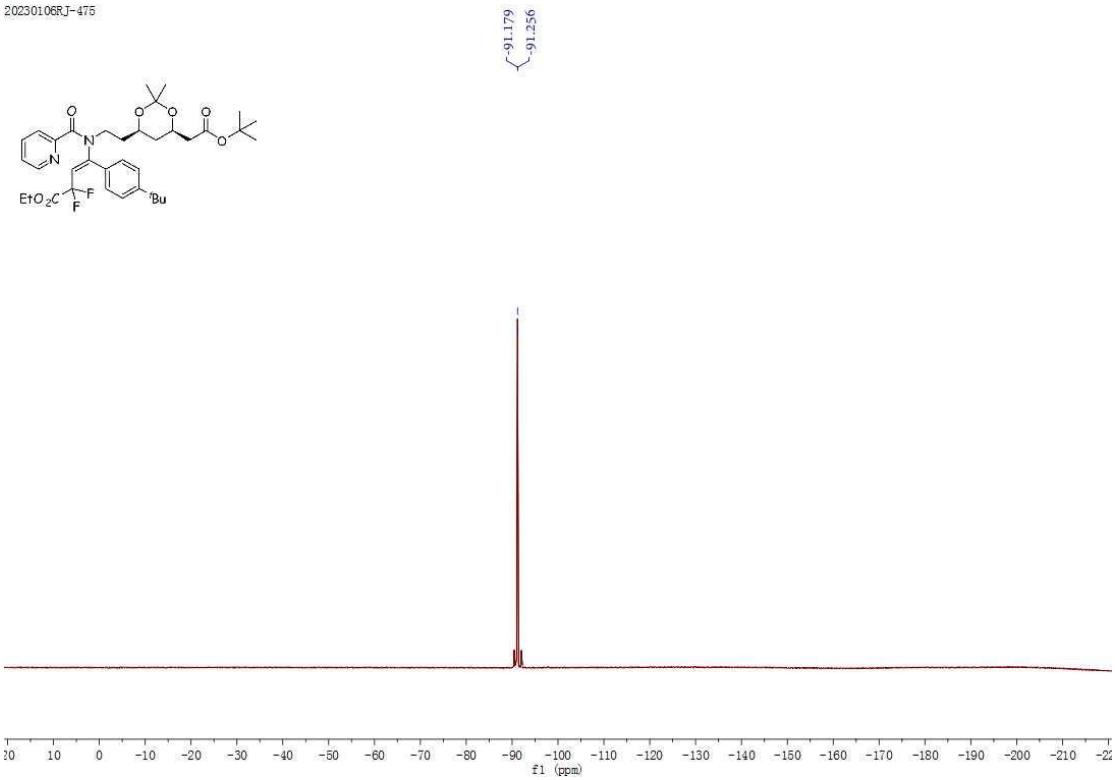
^{19}F – NMR spectrum of compound – **7i** (376 MHz, $CDCl_3$)



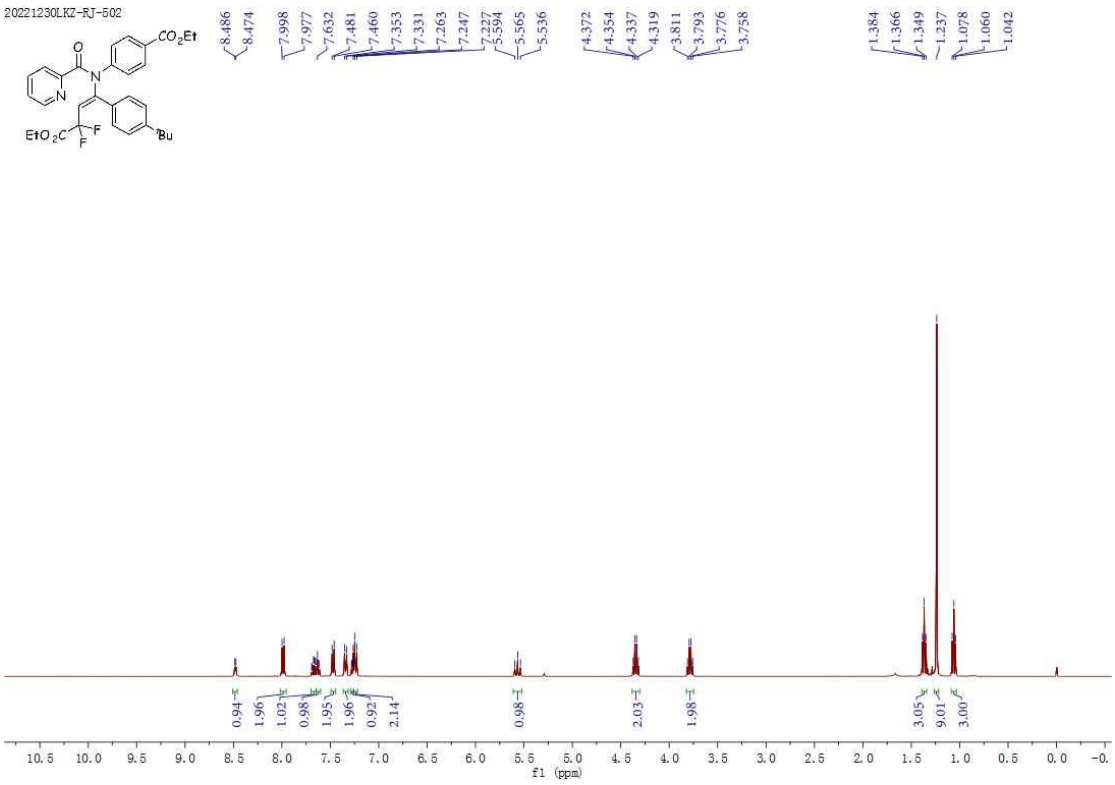
^{1}H – NMR spectrum of compound – **7j** (400 MHz, $CDCl_3$)



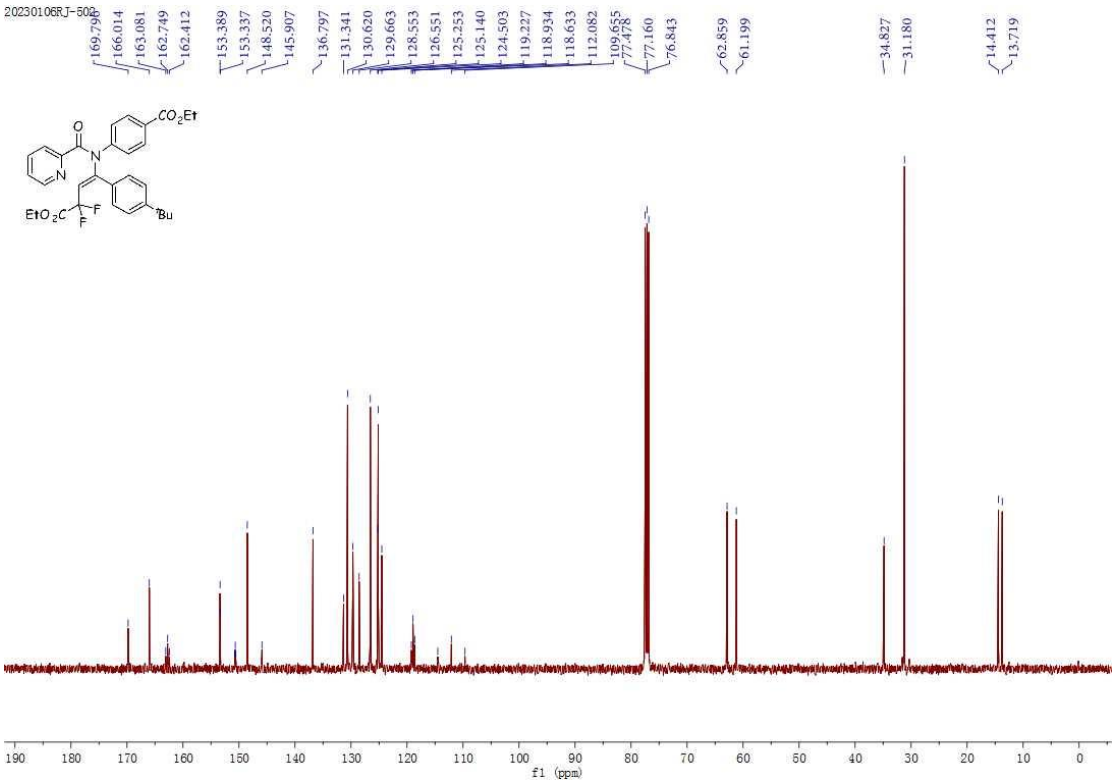
^{13}C – NMR spectrum of compound – **7j** (100 MHz, $CDCl_3$)



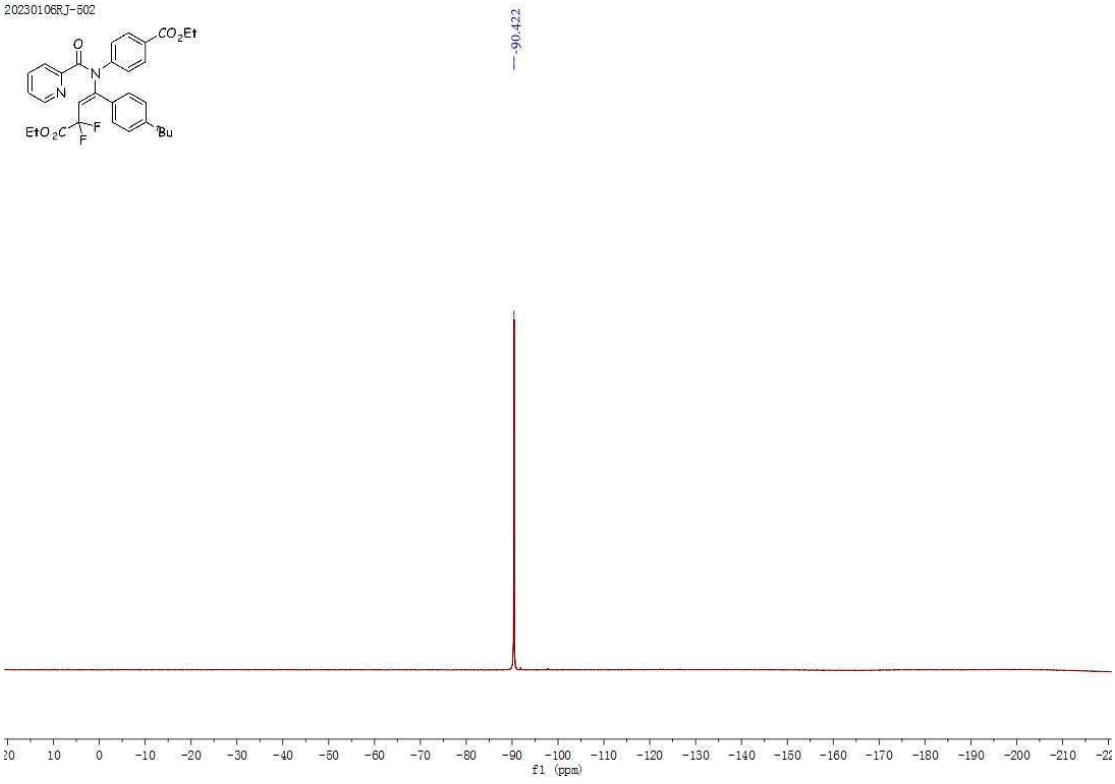
^{19}F – NMR spectrum of compound – **7j** (376 MHz, $CDCl_3$)



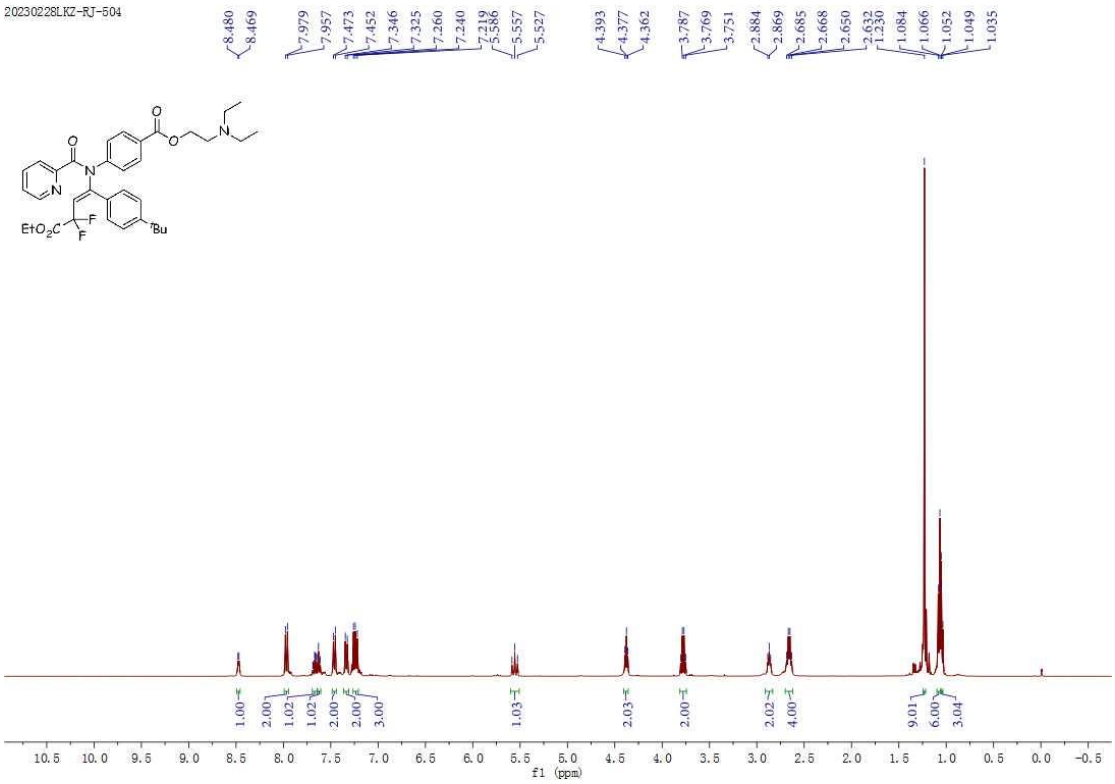
^{1}H – NMR spectrum of compound – **7k** (400 MHz, $CDCl_3$)



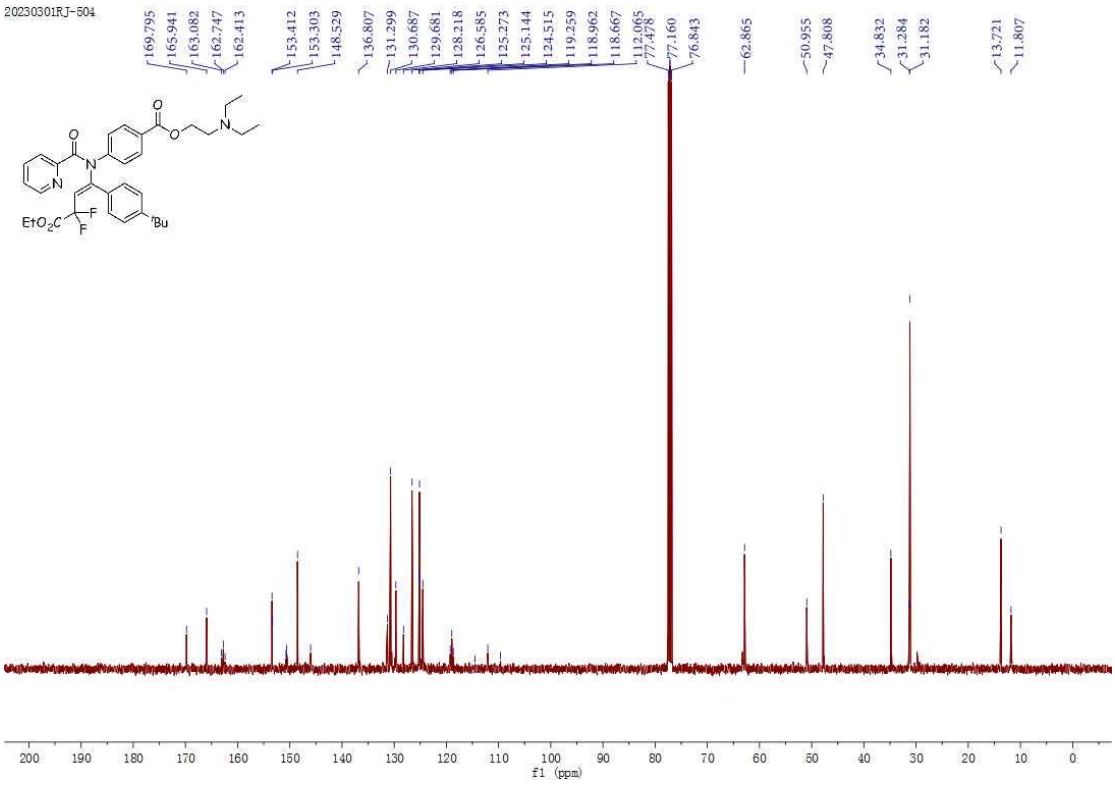
^{13}C – NMR spectrum of compound – **7k** (100 MHz, $CDCl_3$)



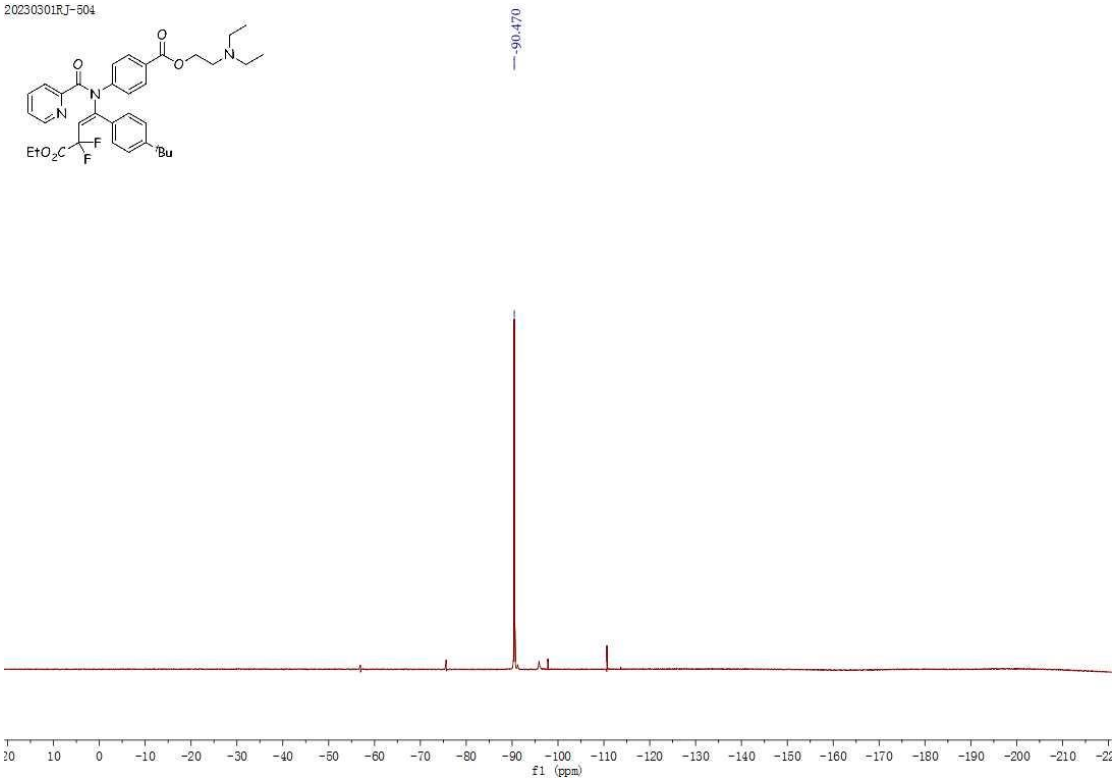
^{19}F – NMR spectrum of compound – **7k** (376 MHz, $CDCl_3$)



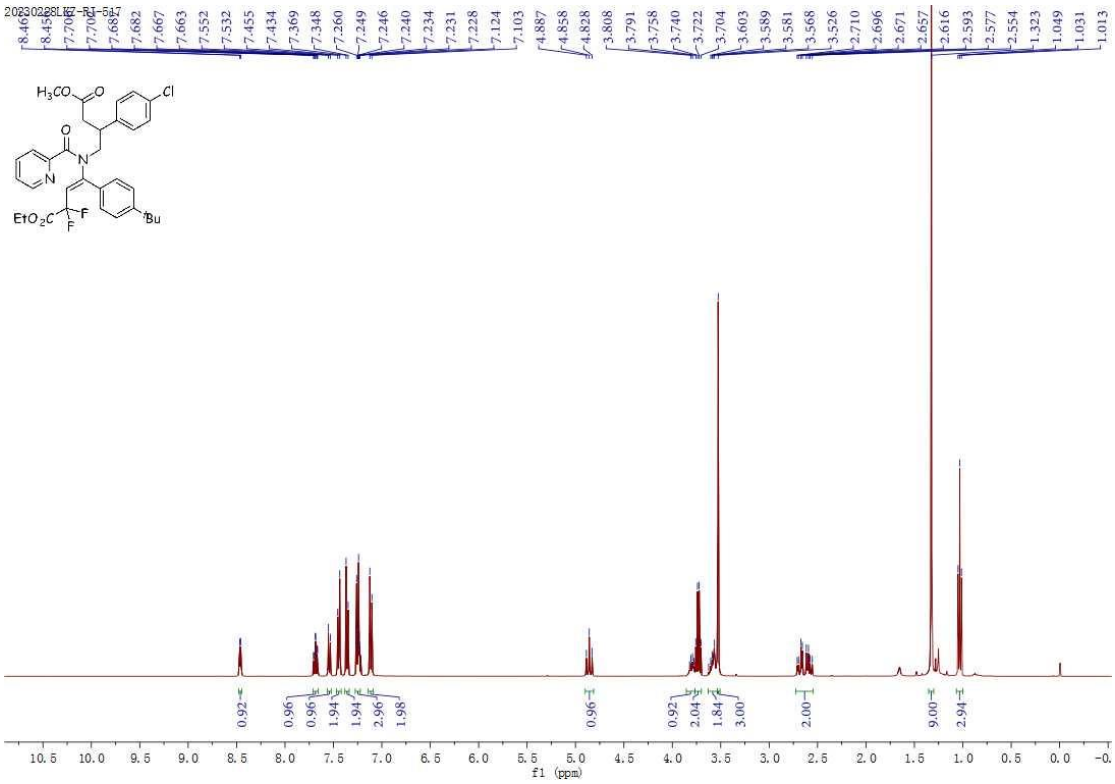
^{1}H – NMR spectrum of compound – **7l** (400 MHz, $CDCl_3$)



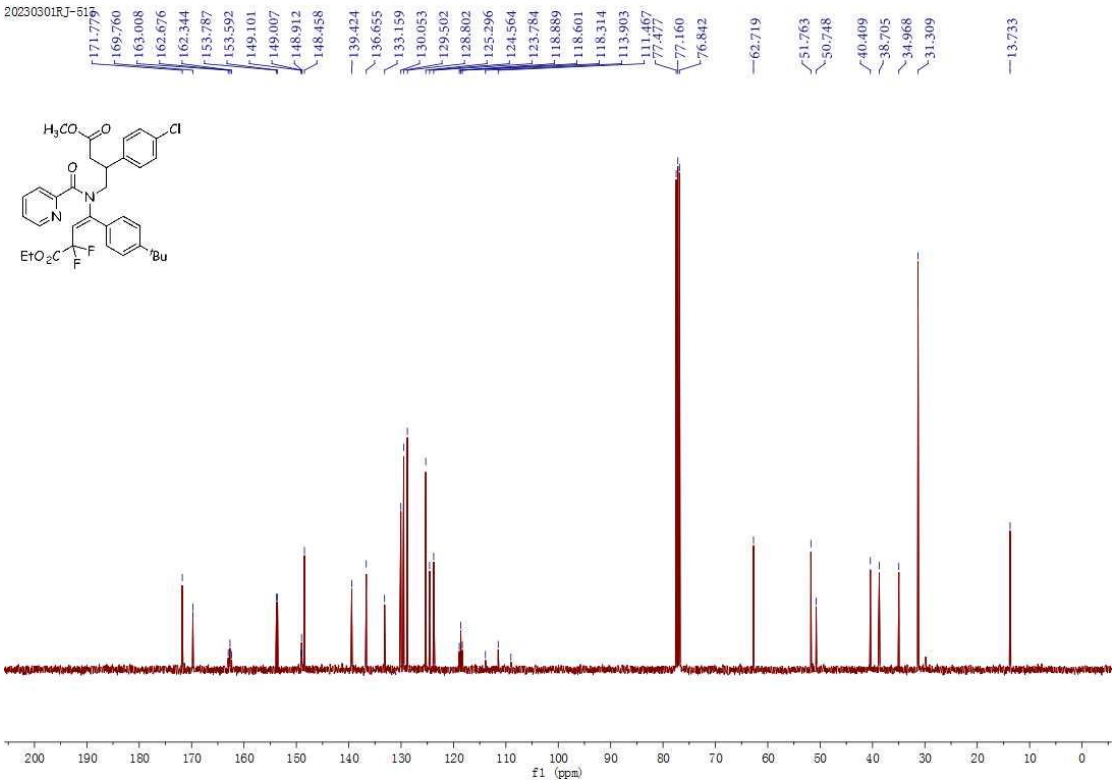
^{13}C – NMR spectrum of compound – **7l** (100 MHz, $CDCl_3$)



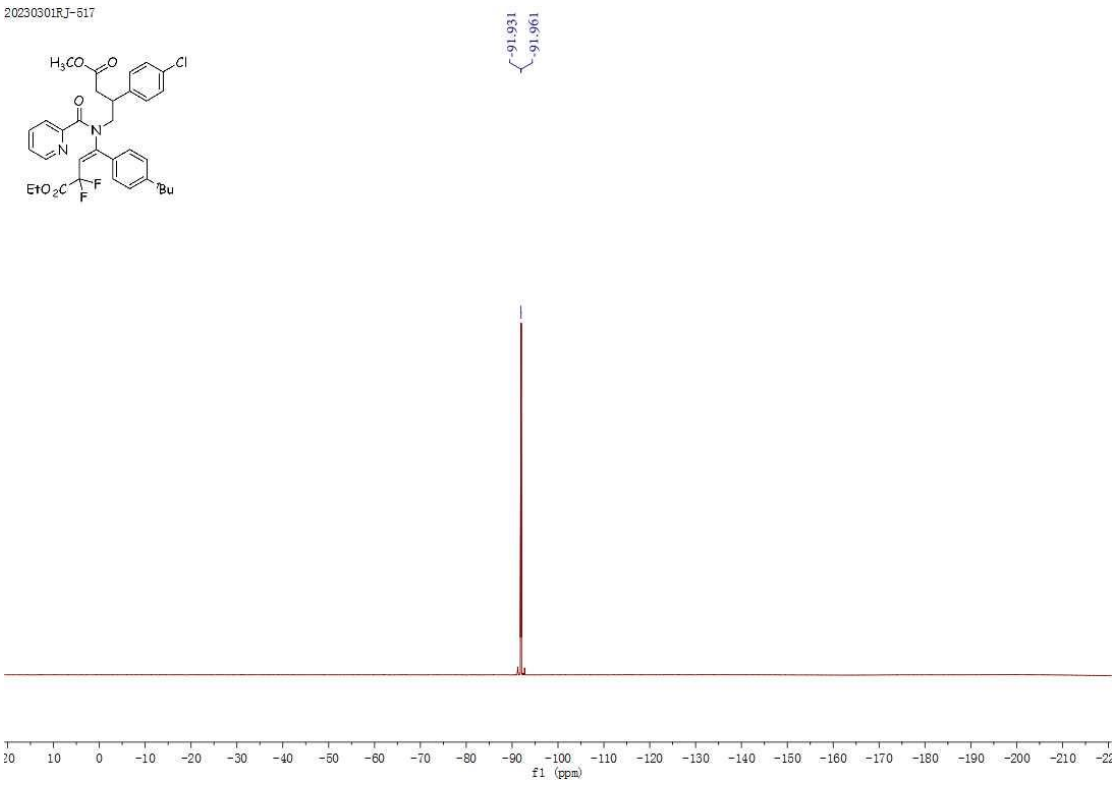
^{19}F – NMR spectrum of compound – **7l** (376 MHz, $CDCl_3$)



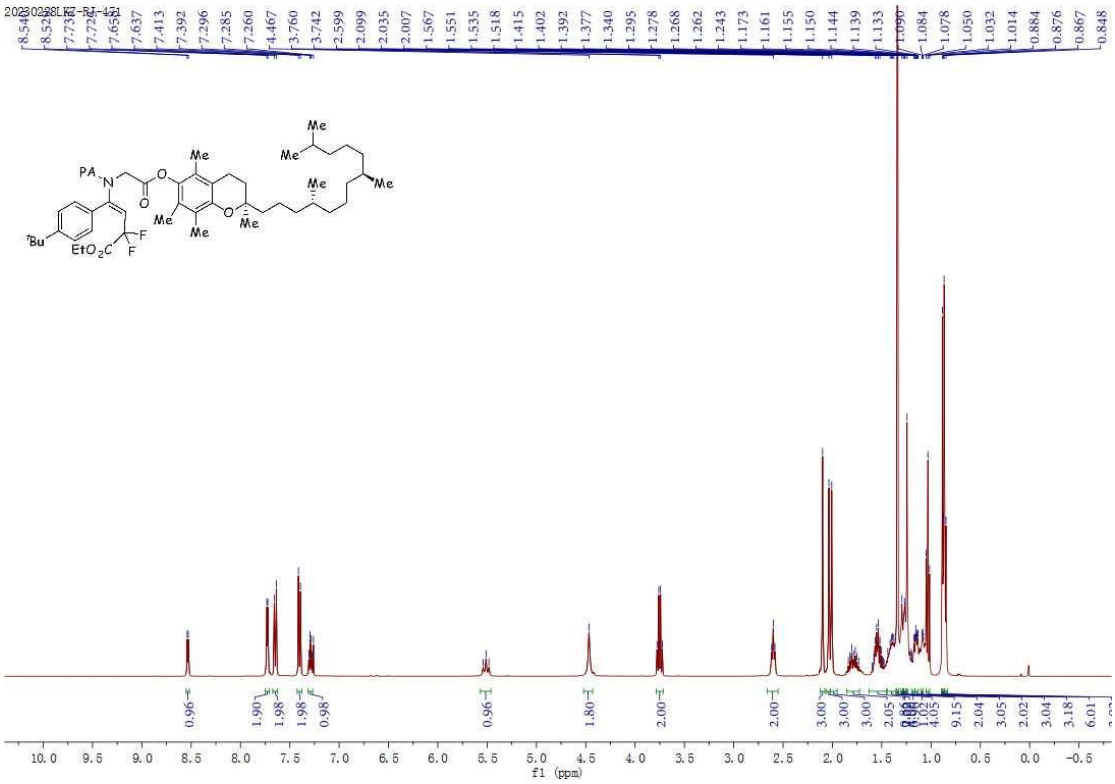
^{1}H – NMR spectrum of compound – **7m** (400 MHz, $CDCl_3$)



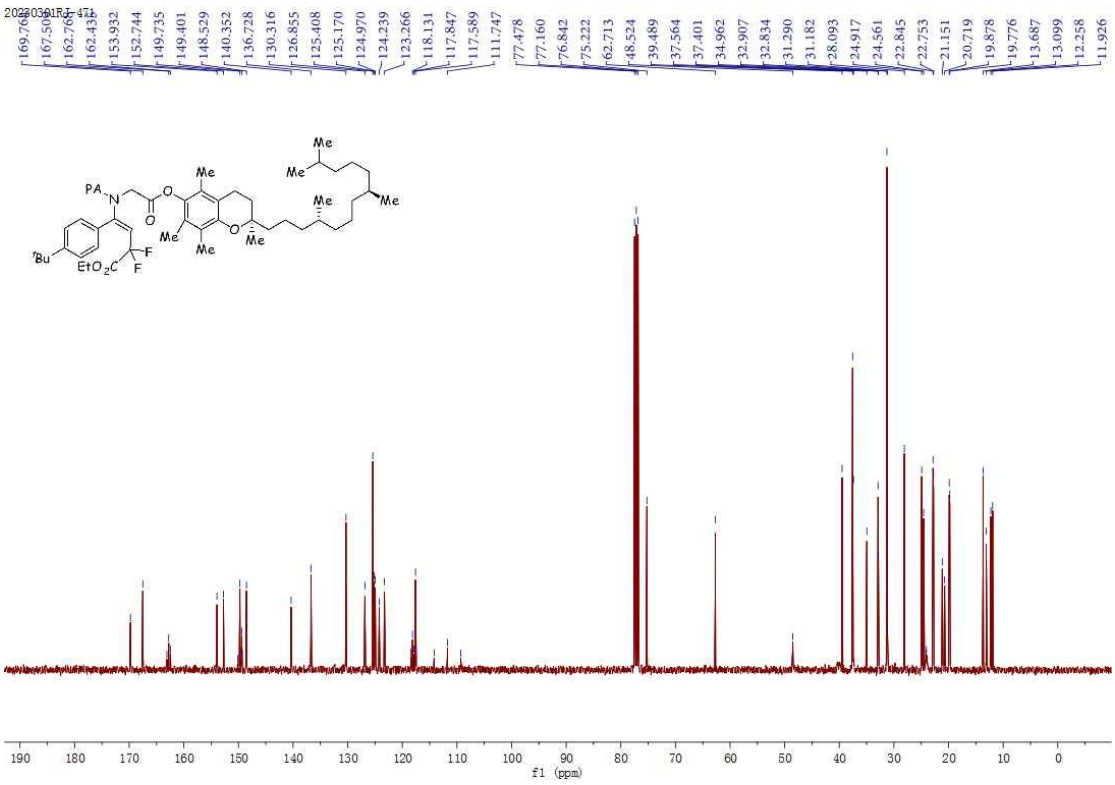
^{13}C – NMR spectrum of compound – **7m** (100 MHz, $CDCl_3$)



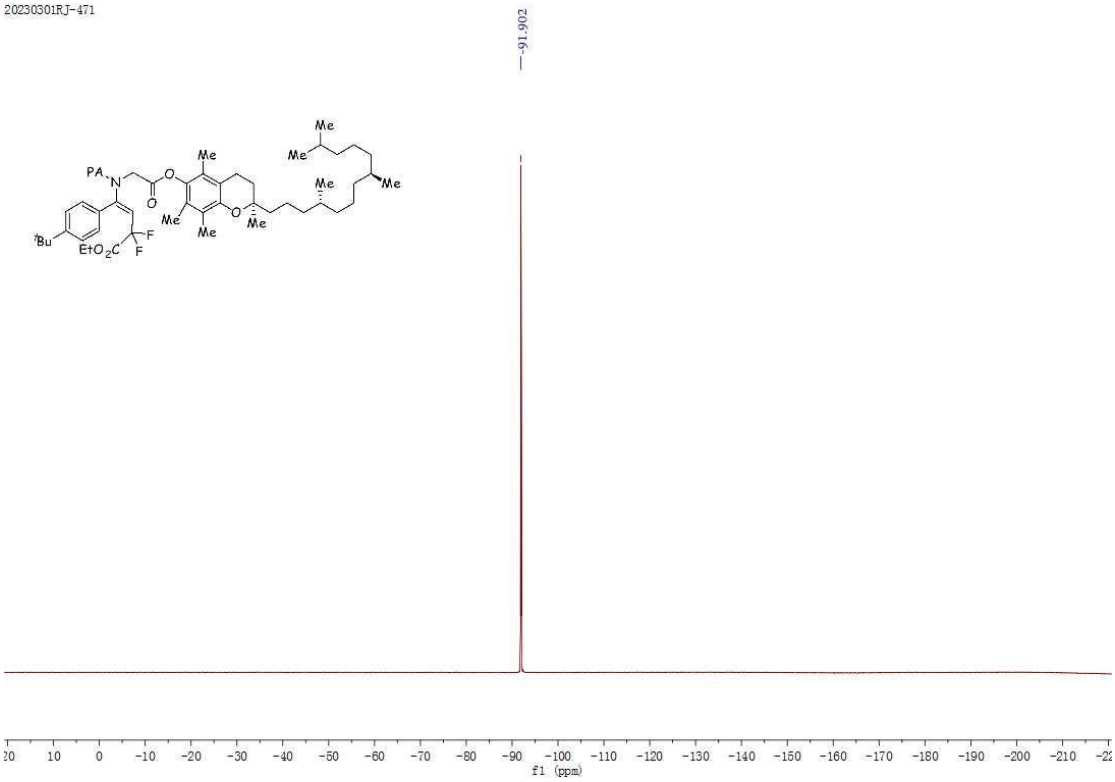
^{19}F – NMR spectrum of compound – **7m** (376 MHz, $CDCl_3$)



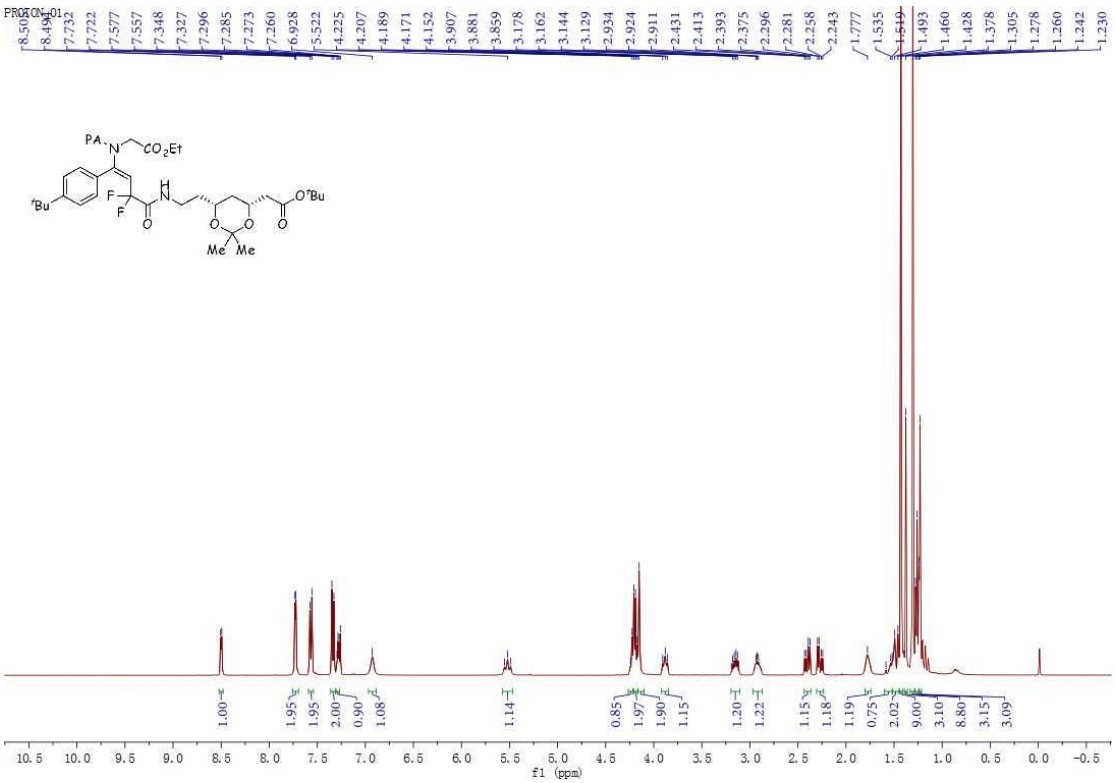
^{1}H – NMR spectrum of compound – **7n** (400 MHz, $CDCl_3$)



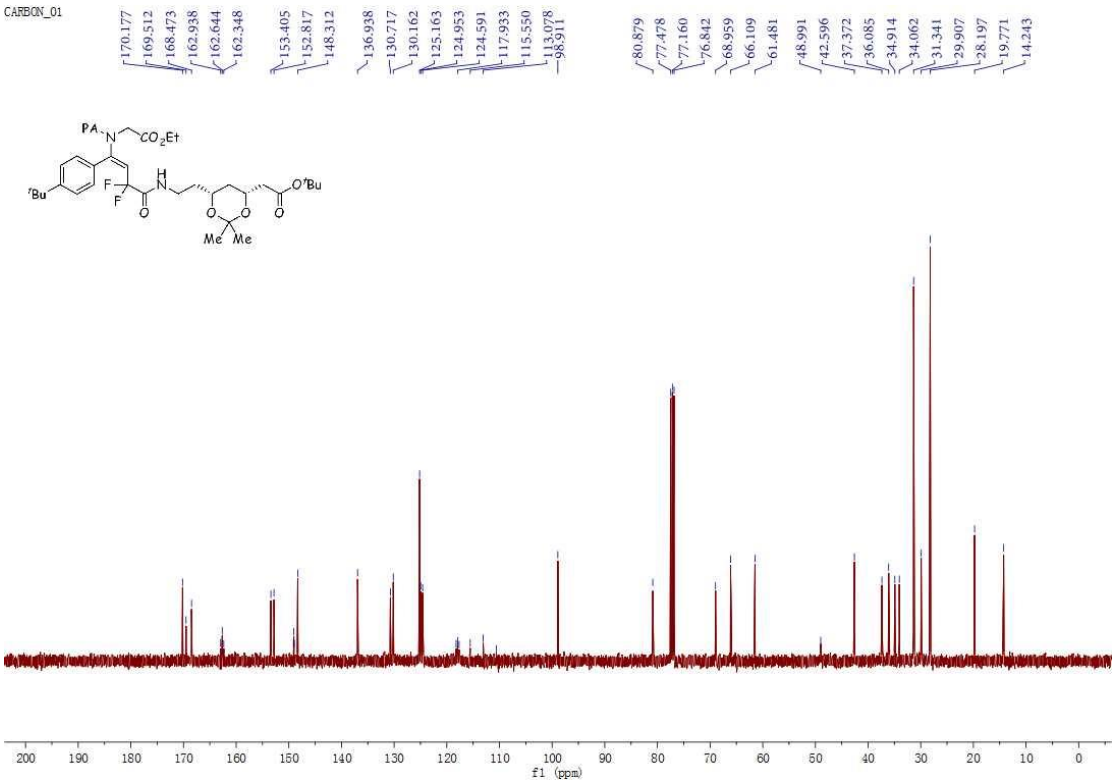
^{13}C – NMR spectrum of compound – **7n** (100 MHz, $CDCl_3$)



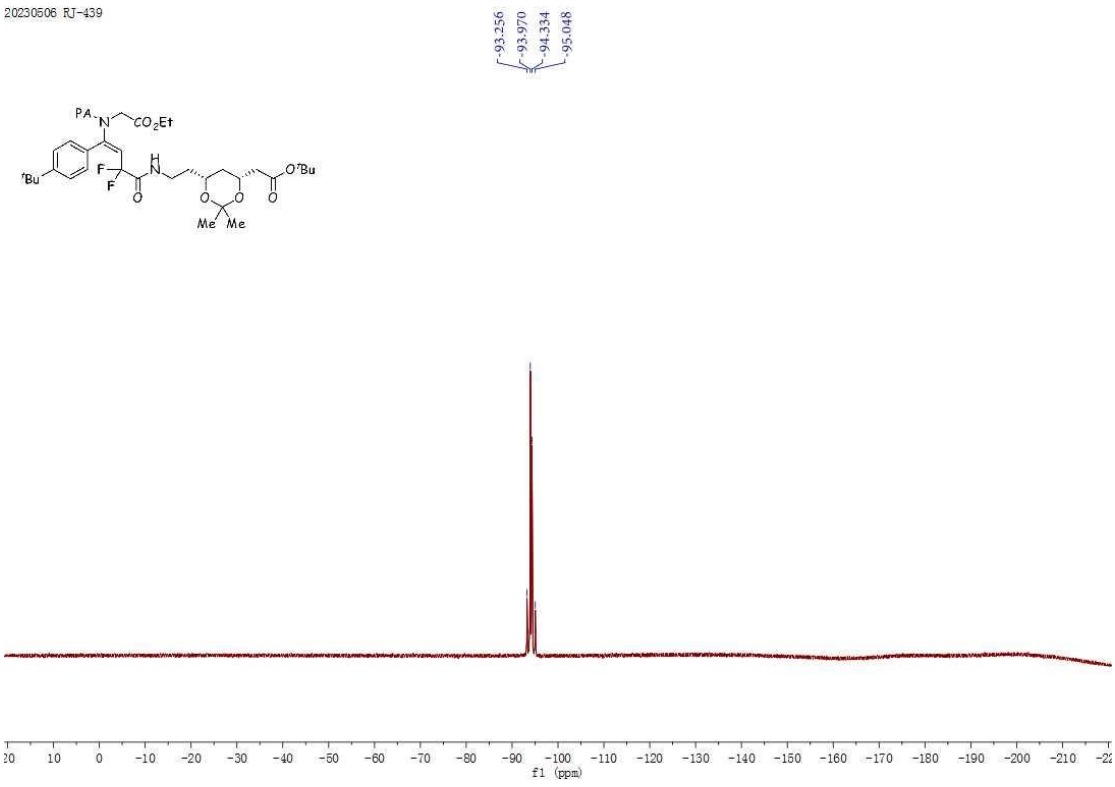
^{19}F – NMR spectrum of compound – **7n** (376 MHz, $CDCl_3$)



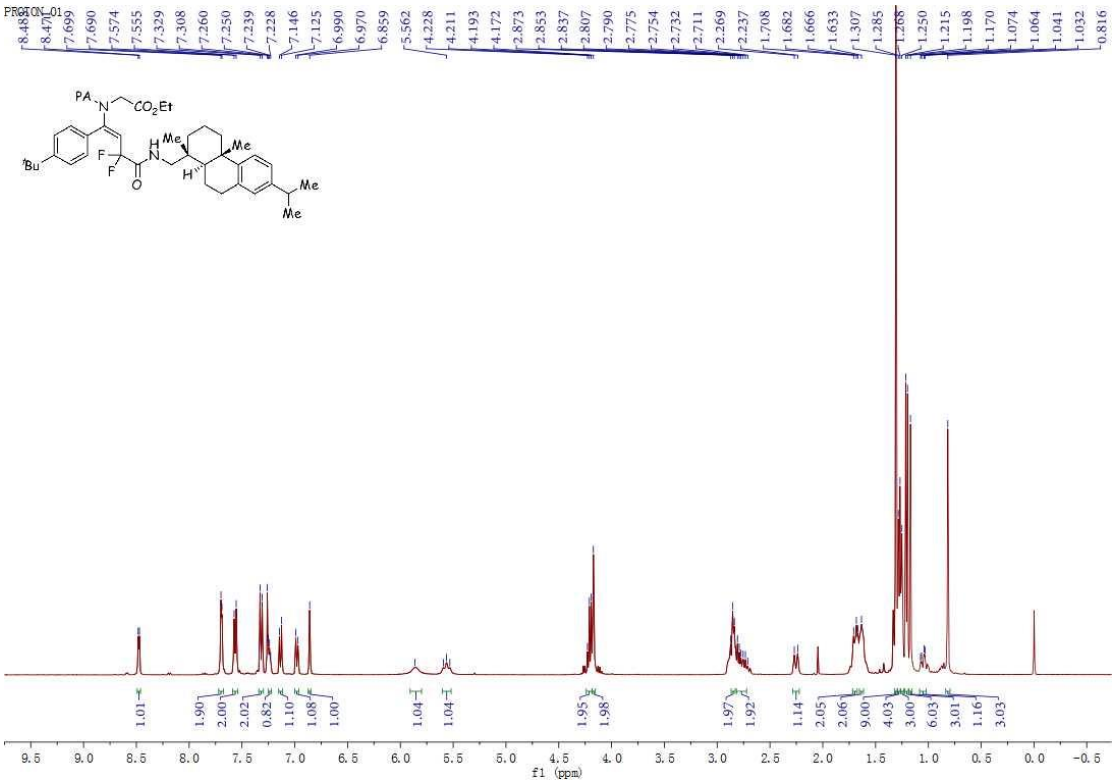
^{1}H – NMR spectrum of compound – **7o** (400 MHz, $CDCl_3$)



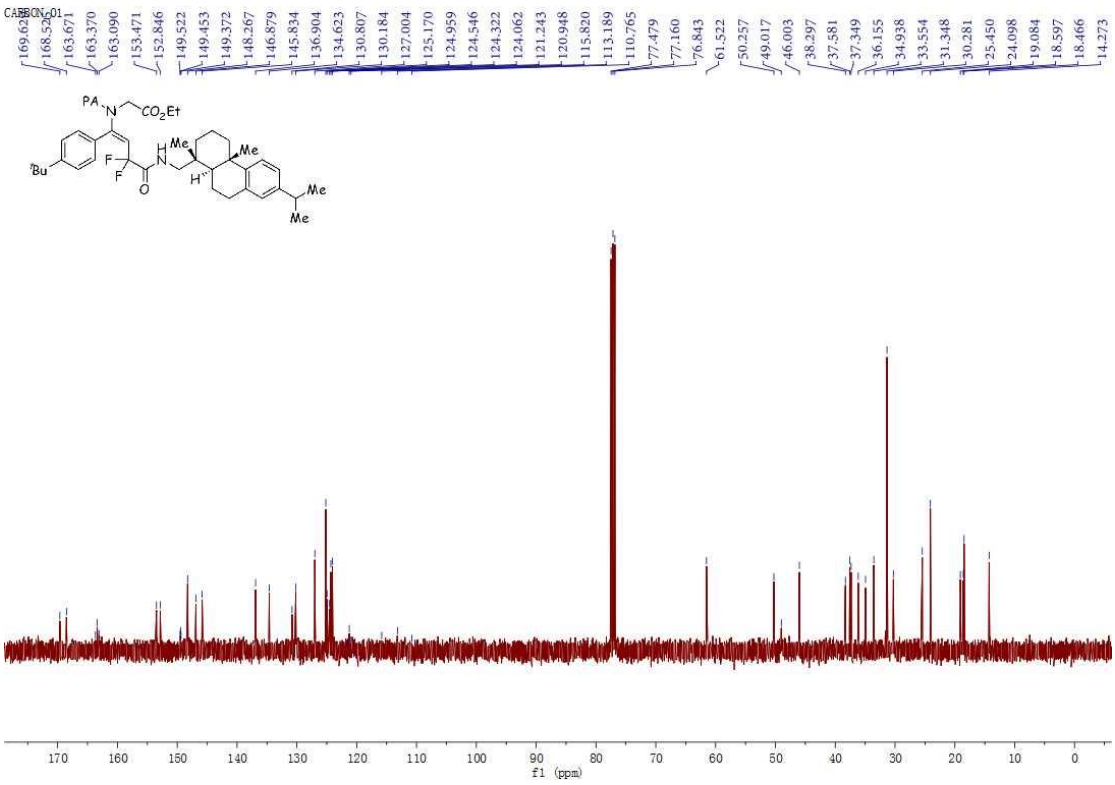
^{13}C – NMR spectrum of compound – **7o** (100 MHz, $CDCl_3$)



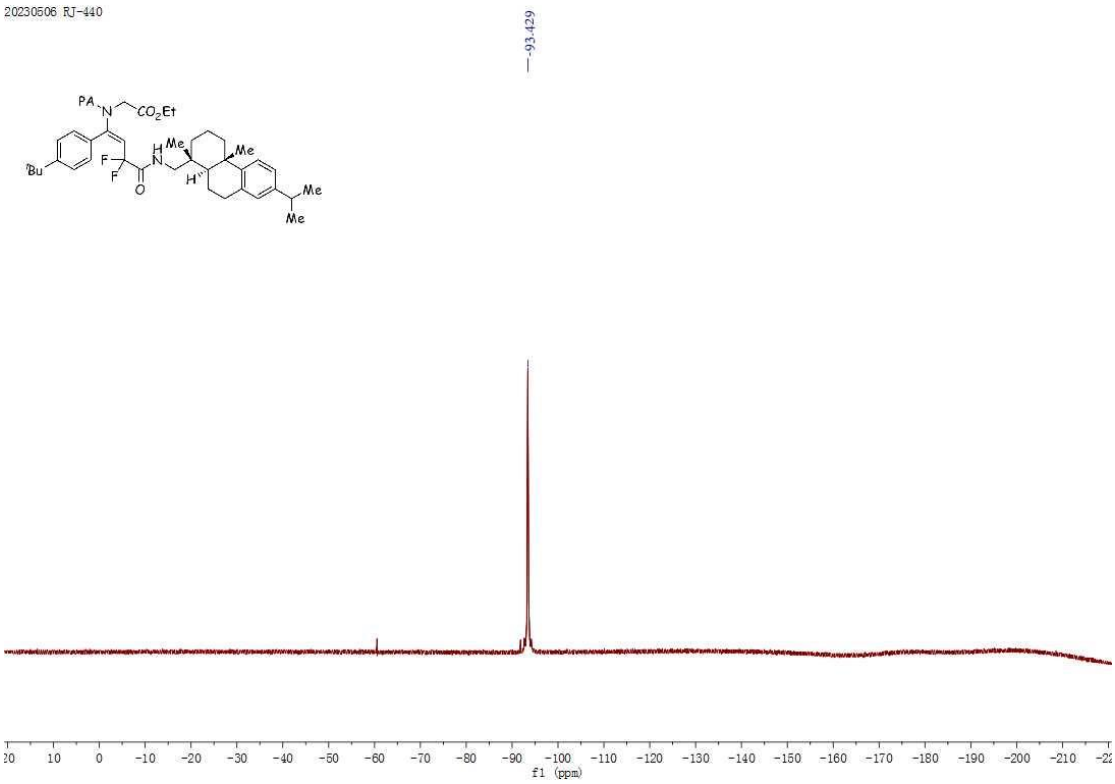
^{19}F – NMR spectrum of compound – **7o** (376 MHz, $CDCl_3$)



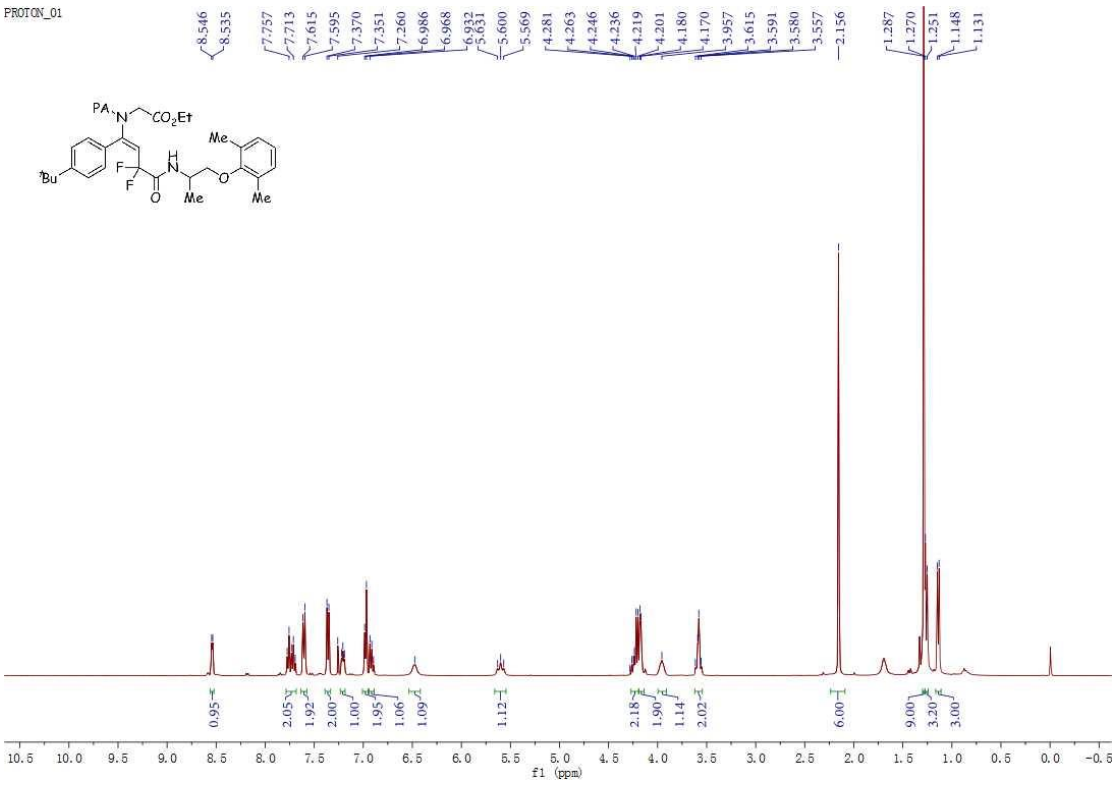
^{1}H – NMR spectrum of compound – **7p** (400 MHz, $CDCl_3$)



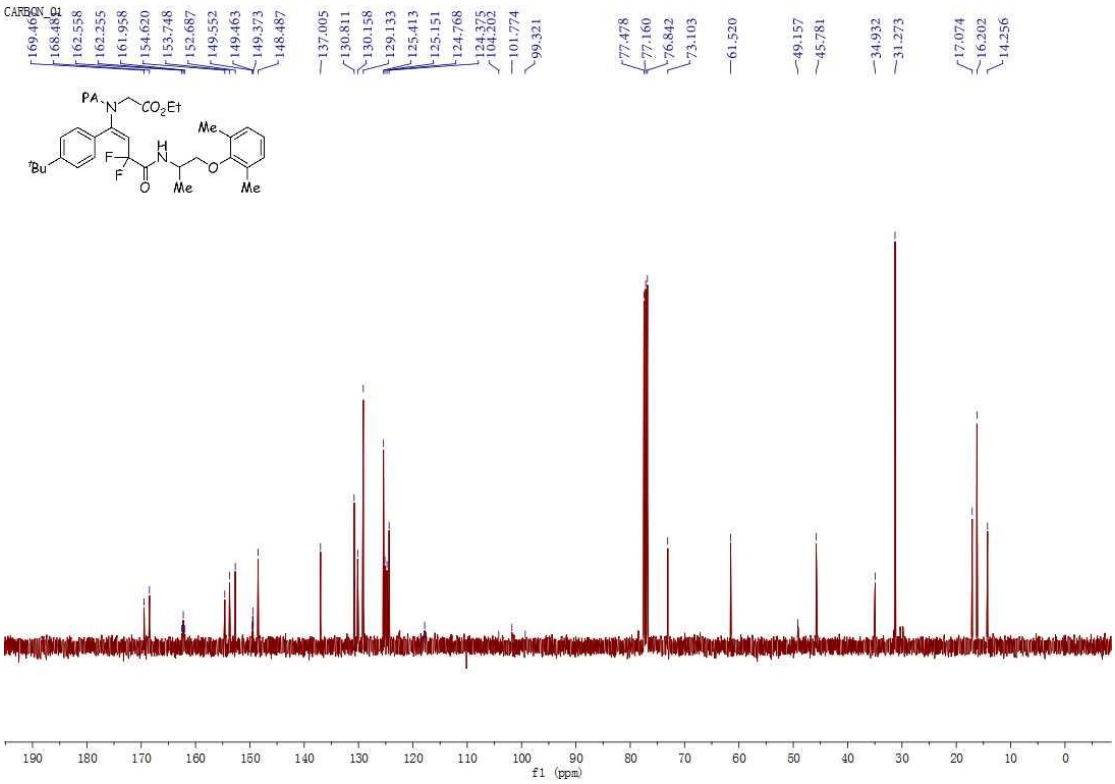
^{13}C – NMR spectrum of compound – **7p** (100 MHz, $CDCl_3$)



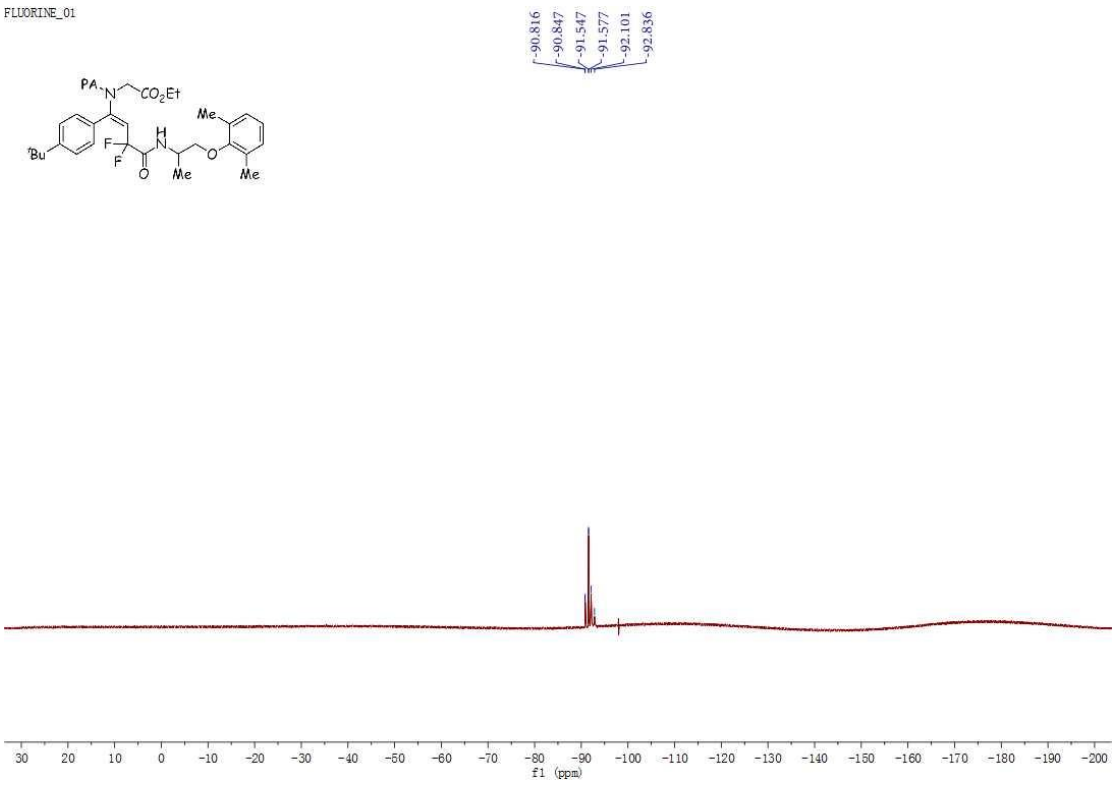
^{19}F – NMR spectrum of compound – **7p** (376 MHz, $CDCl_3$)



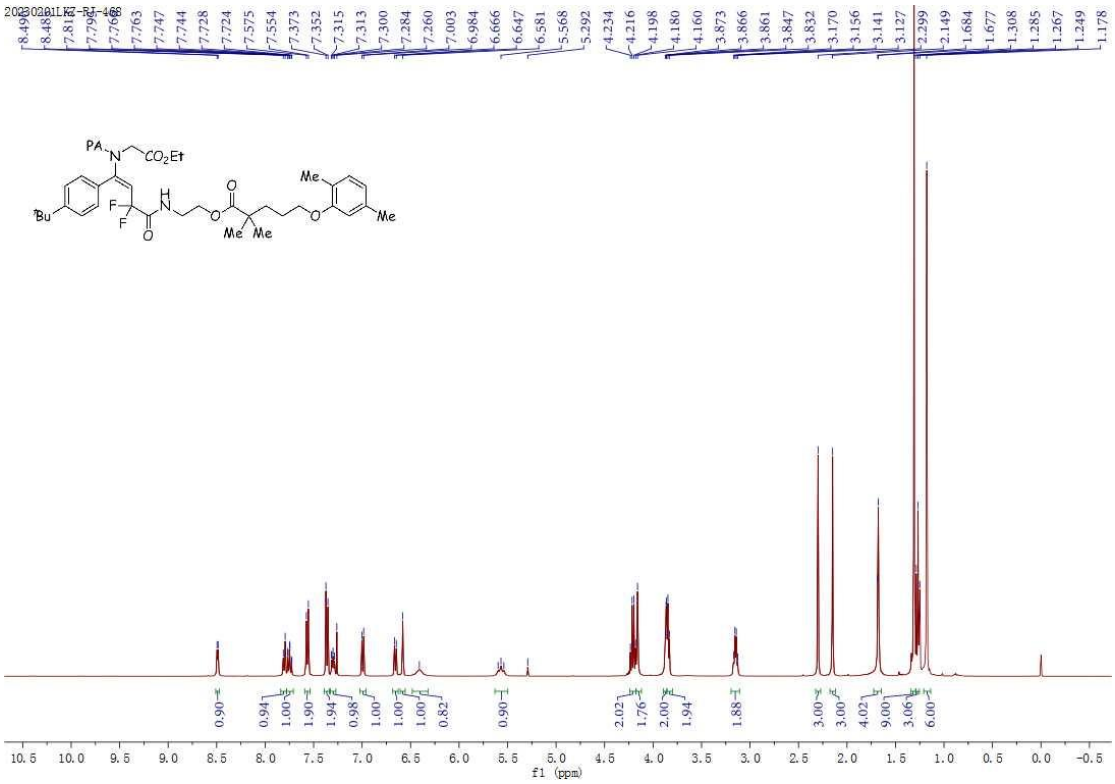
^{1}H – NMR spectrum of compound – **7q** (400 MHz, $CDCl_3$)



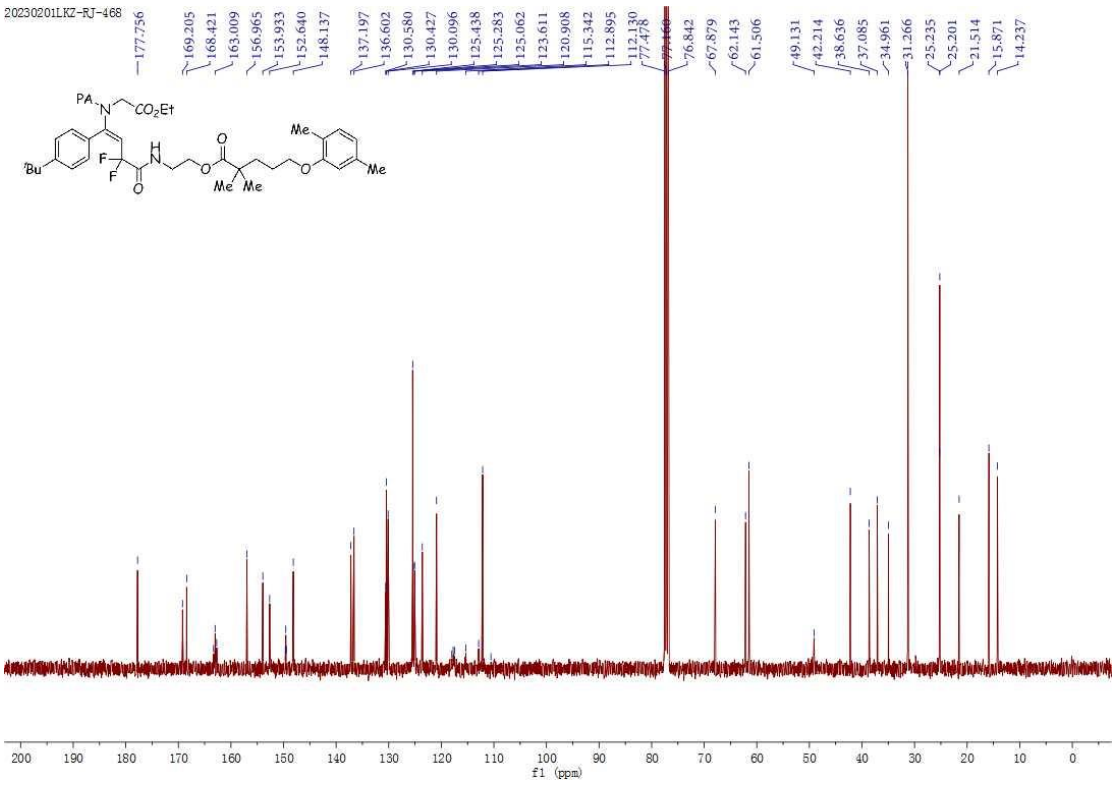
^{13}C – NMR spectrum of compound – **7q** (100 MHz, $CDCl_3$)



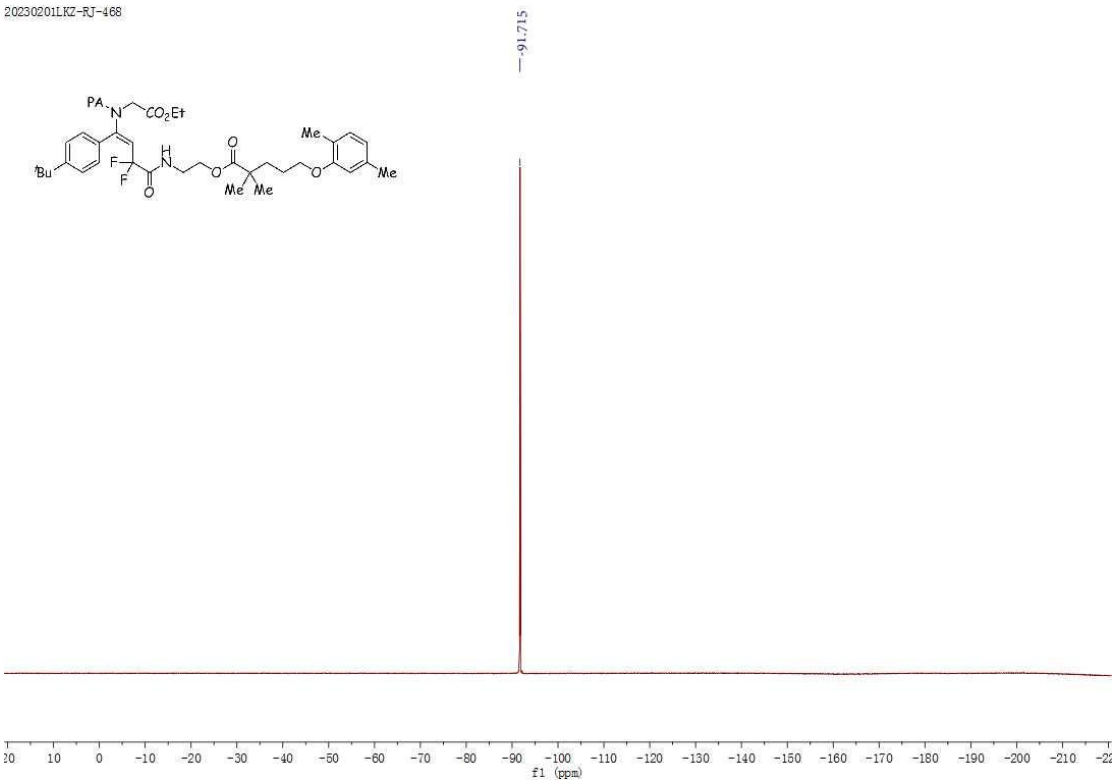
^{19}F – NMR spectrum of compound – **7q** (376 MHz, $CDCl_3$)



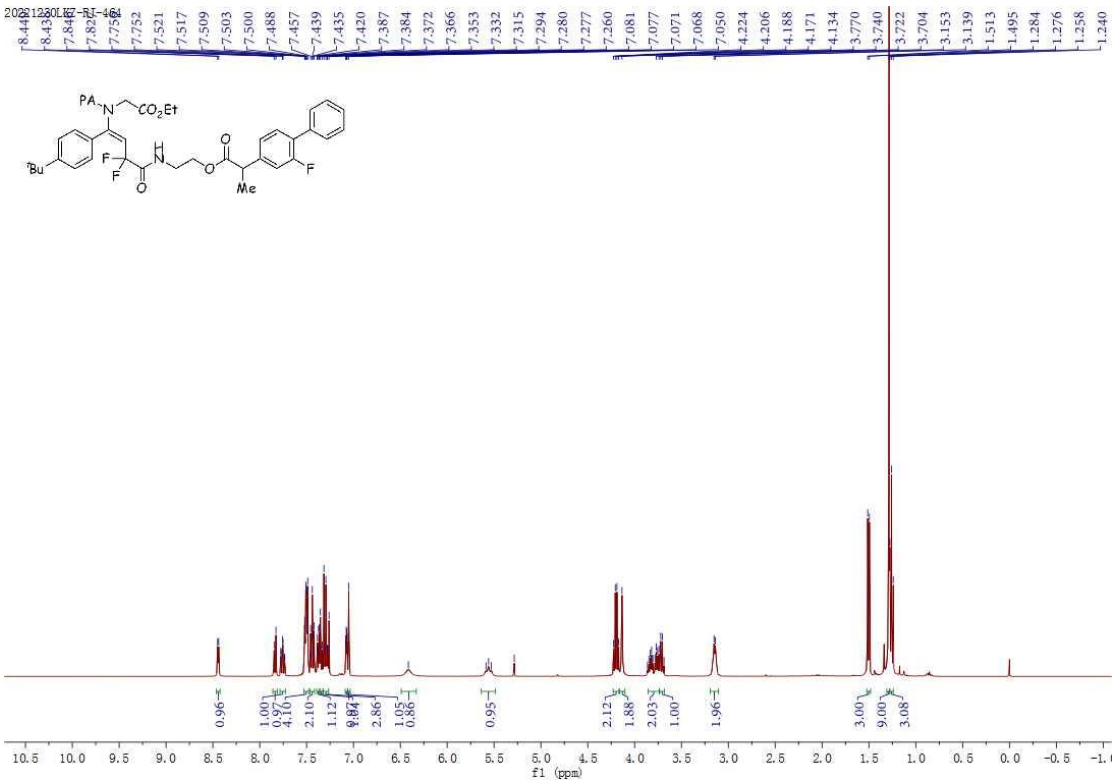
^{1}H – NMR spectrum of compound – **7r** (400 MHz, $CDCl_3$)



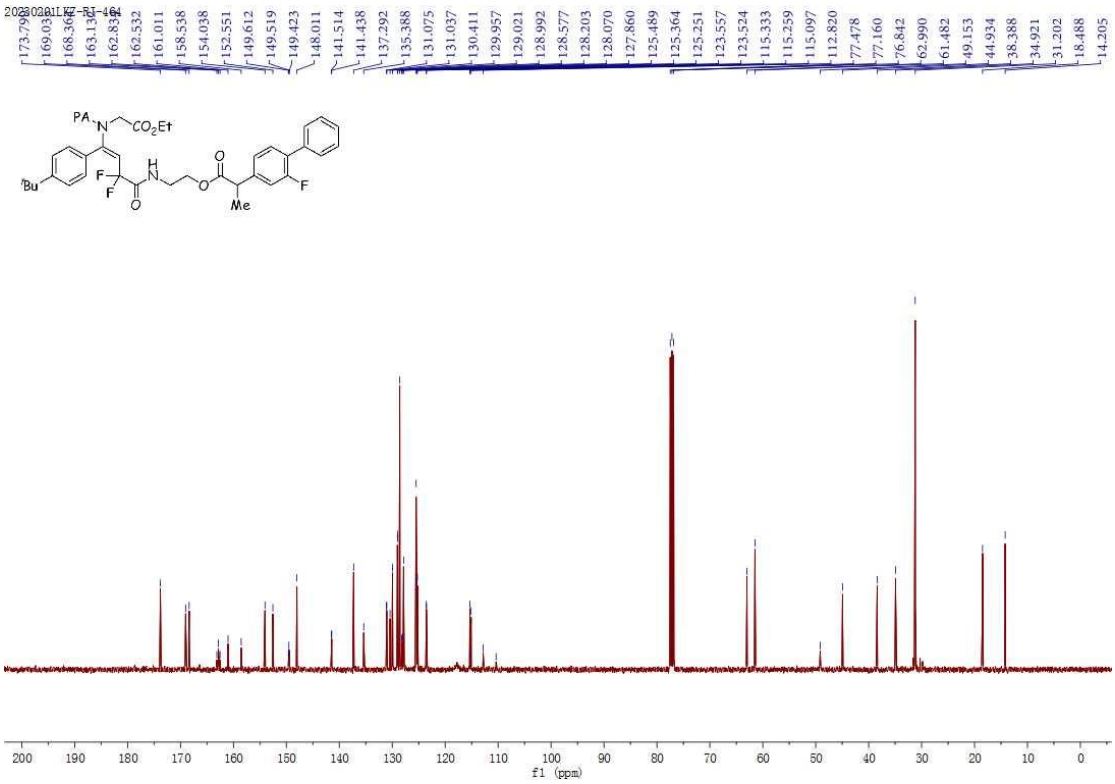
^{13}C – NMR spectrum of compound – **7r** (100 MHz, $CDCl_3$)



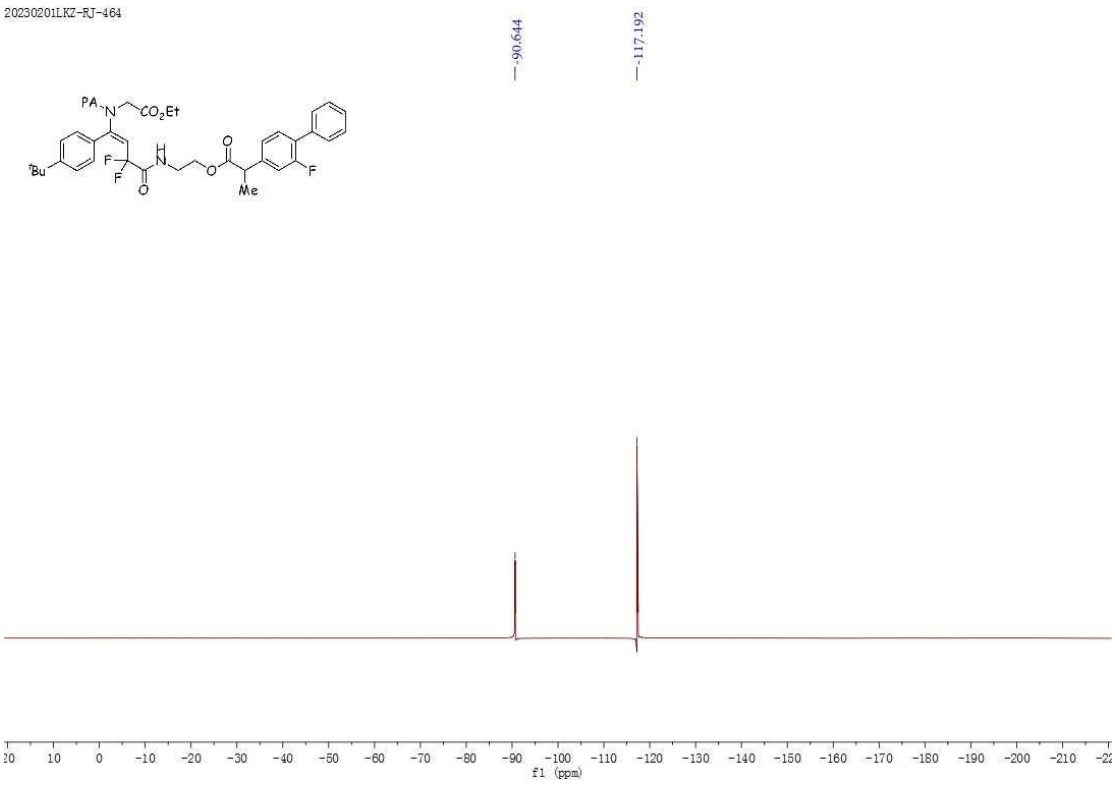
^{19}F – NMR spectrum of compound – **7r** (376 MHz, $CDCl_3$)



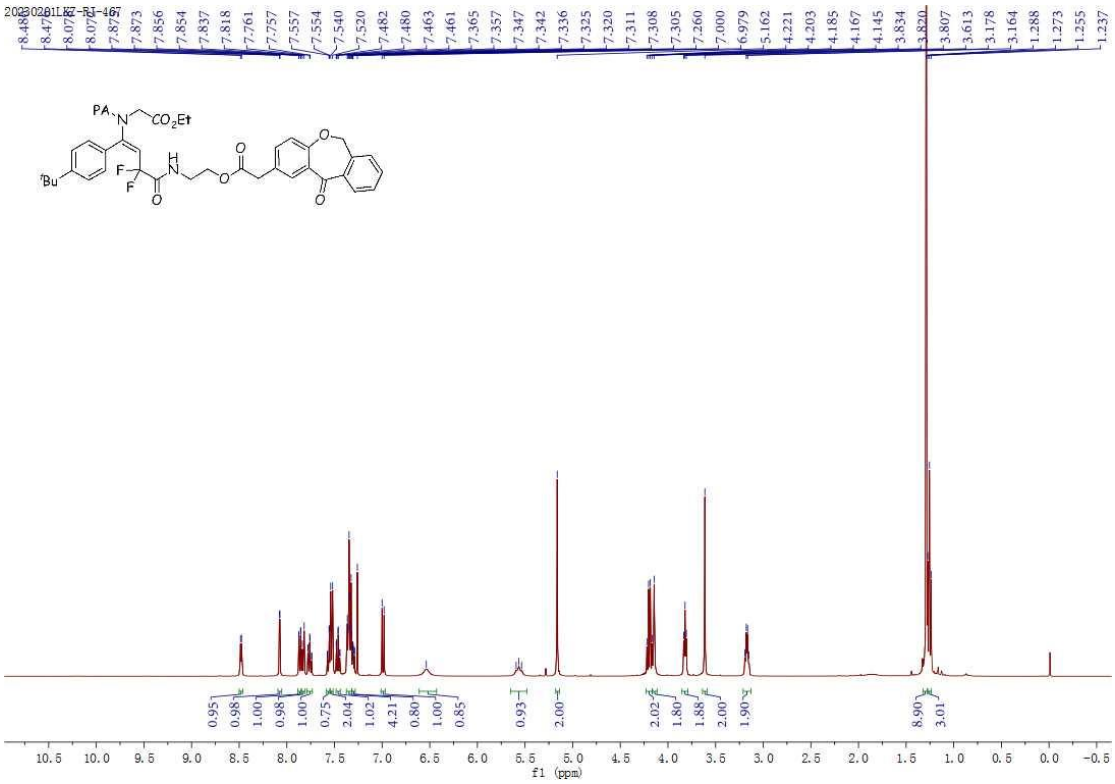
^{1}H – NMR spectrum of compound – **7s** (400 MHz, $CDCl_3$)



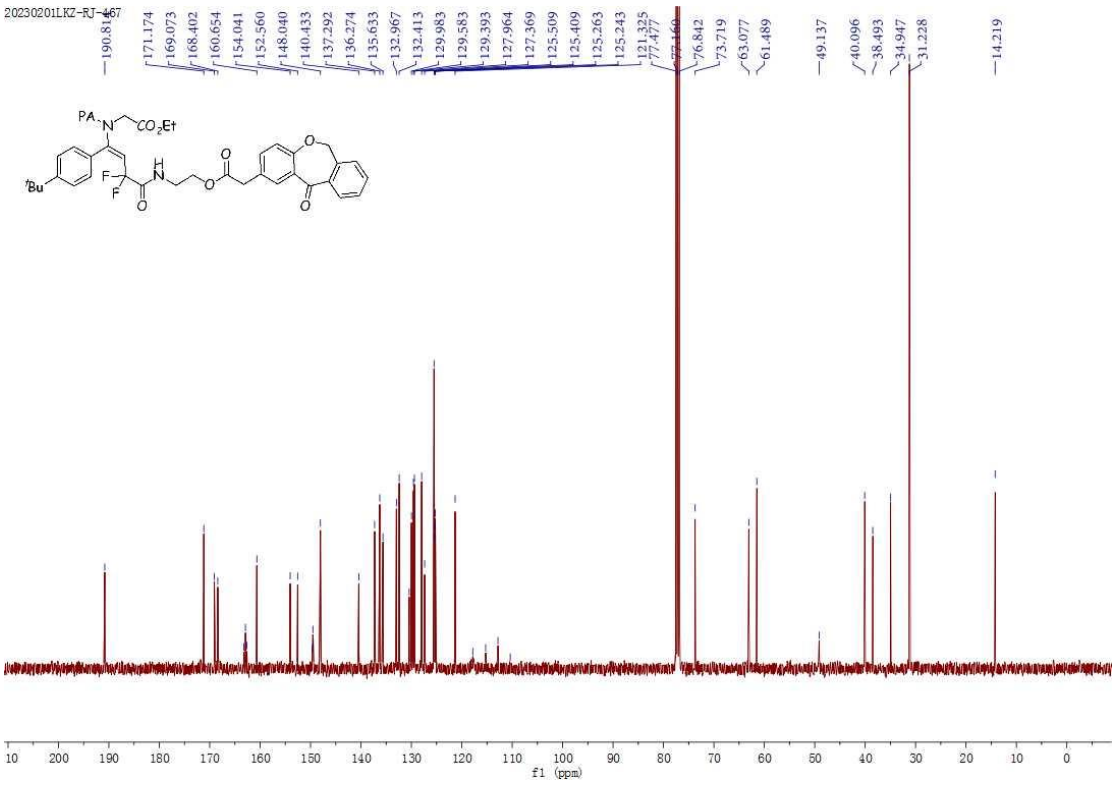
^{13}C – NMR spectrum of compound – **7s** (100 MHz, $CDCl_3$)



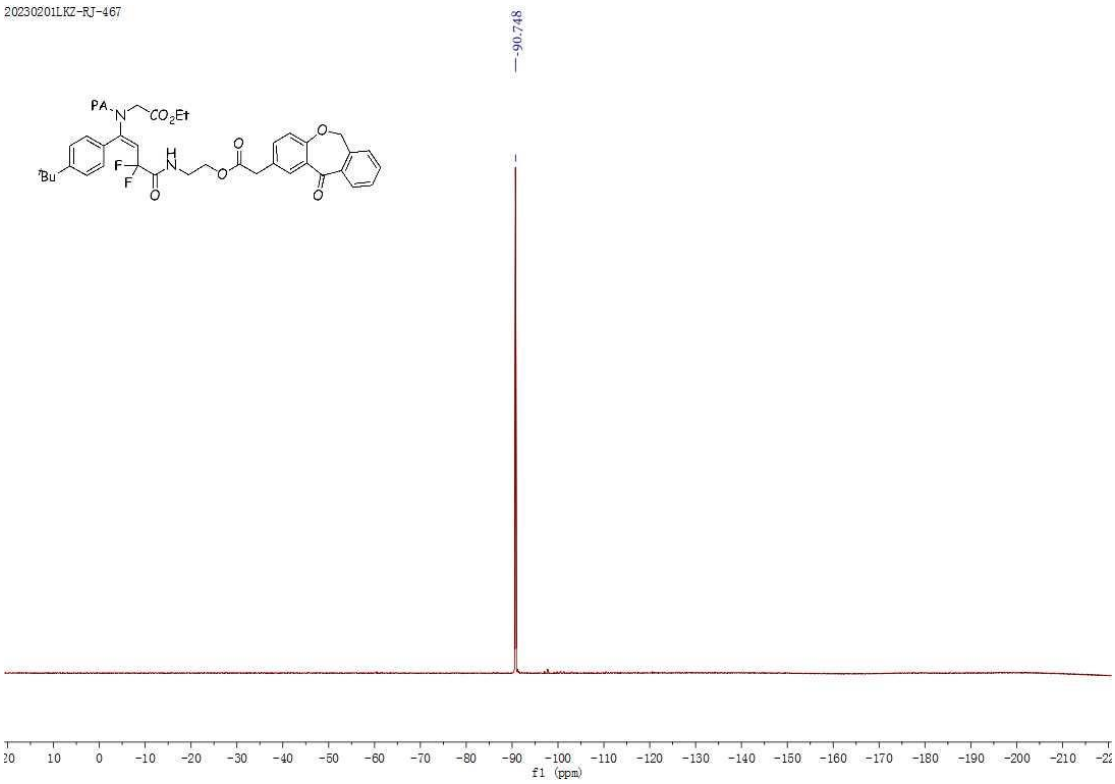
^{19}F – NMR spectrum of compound – **7s** (376 MHz, $CDCl_3$)



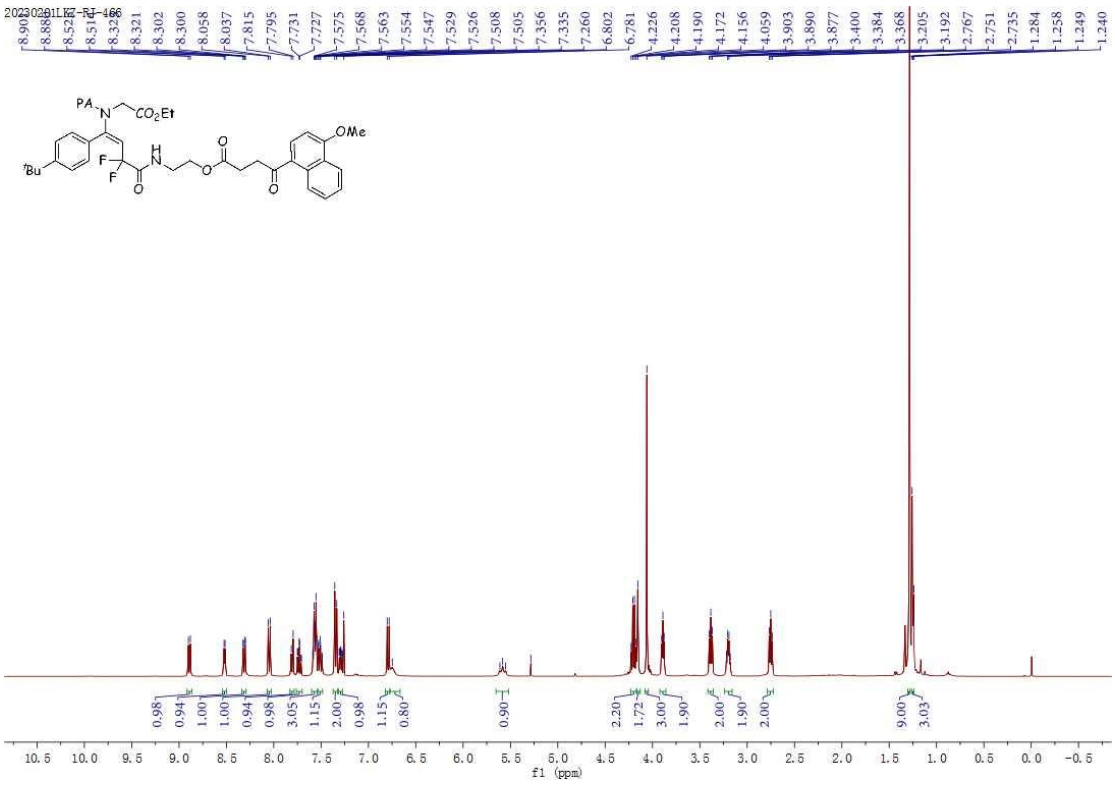
^{1}H – NMR spectrum of compound – **7t** (400 MHz, $CDCl_3$)



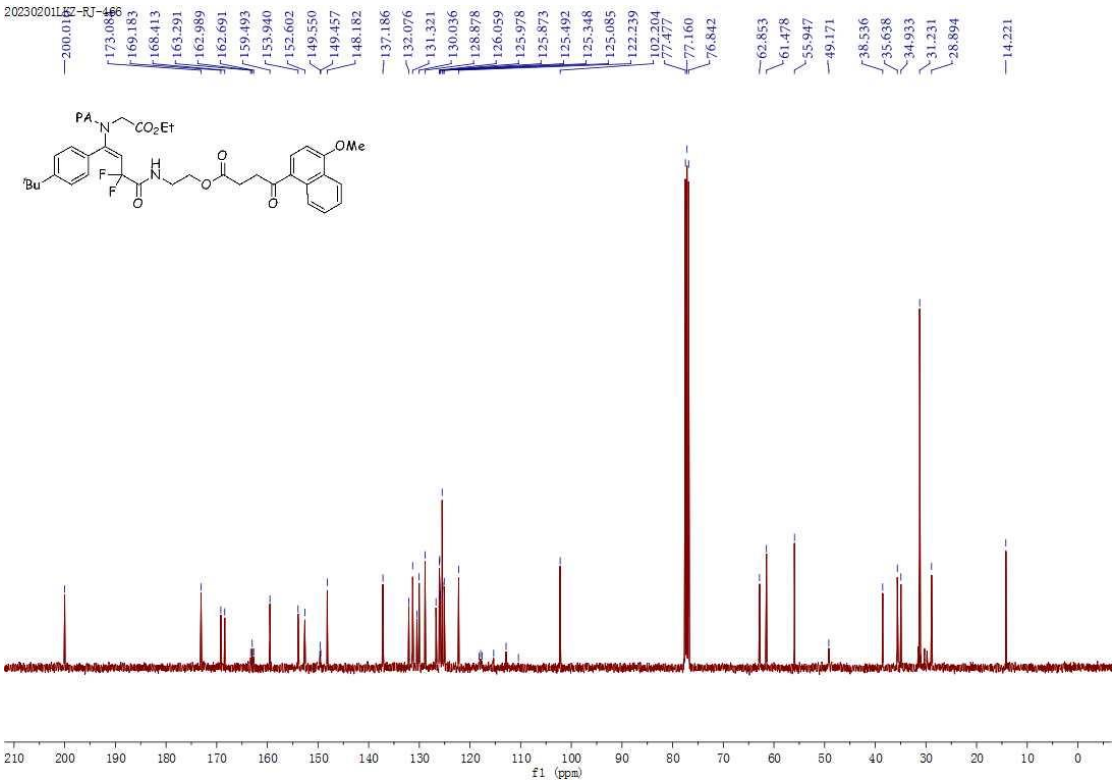
^{13}C – NMR spectrum of compound – **7t** (100 MHz, $CDCl_3$)



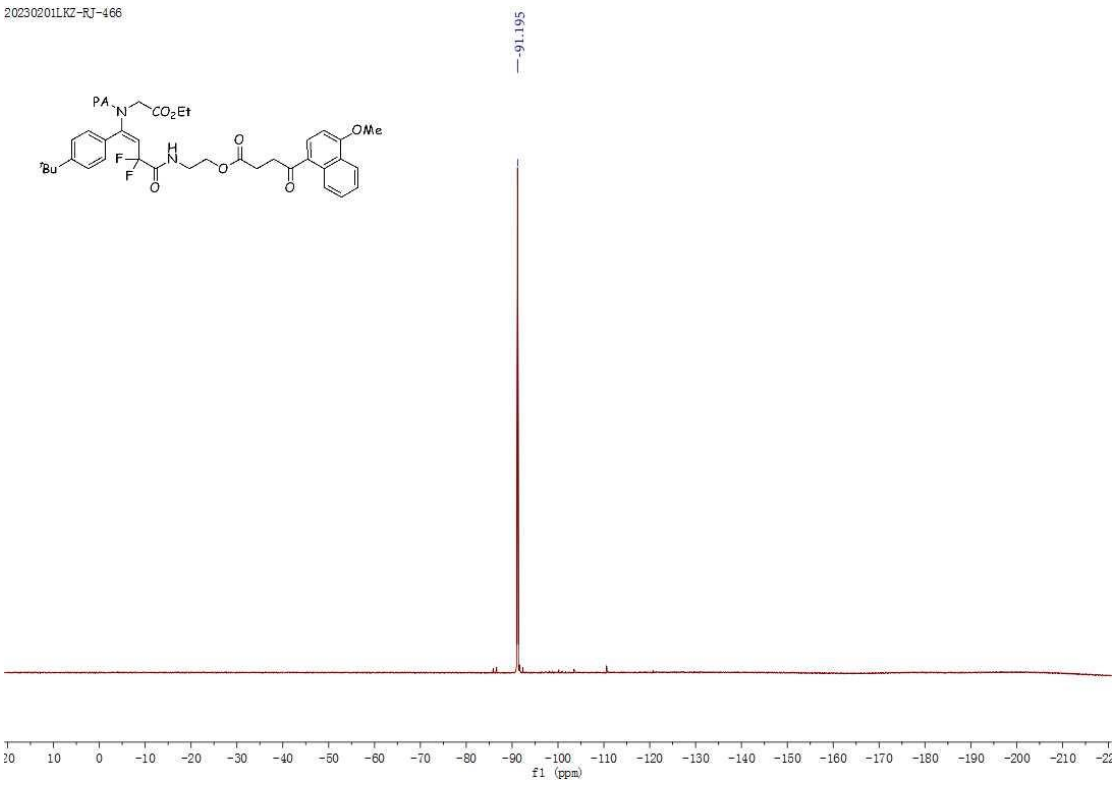
^{19}F – NMR spectrum of compound – **7t** (376 MHz, $CDCl_3$)



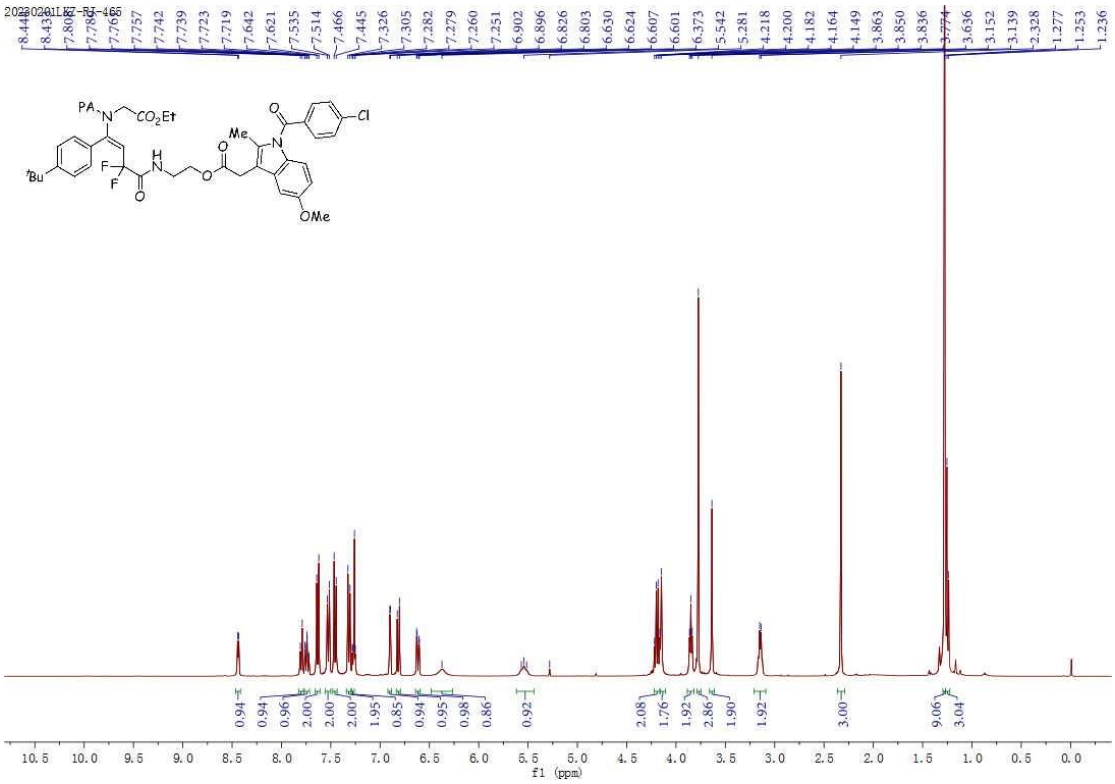
^{1}H – NMR spectrum of compound – **7u** (400 MHz, $CDCl_3$)



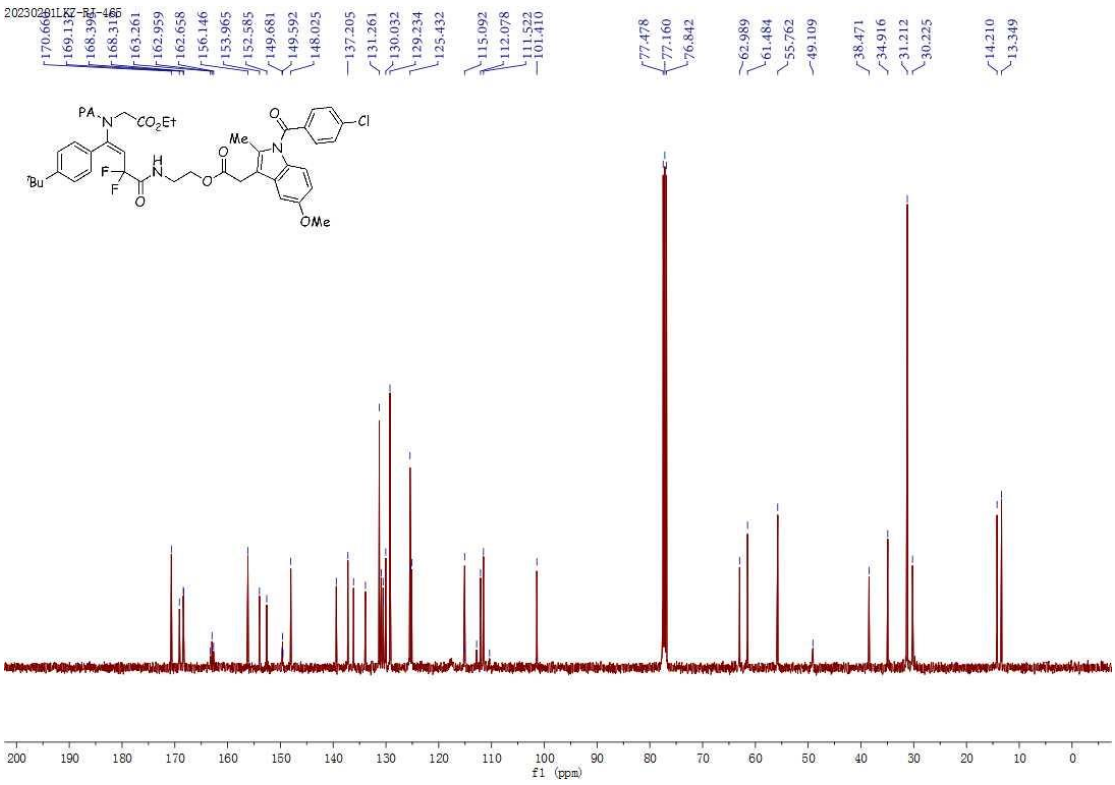
^{13}C – NMR spectrum of compound – **7u** (100 MHz, $CDCl_3$)



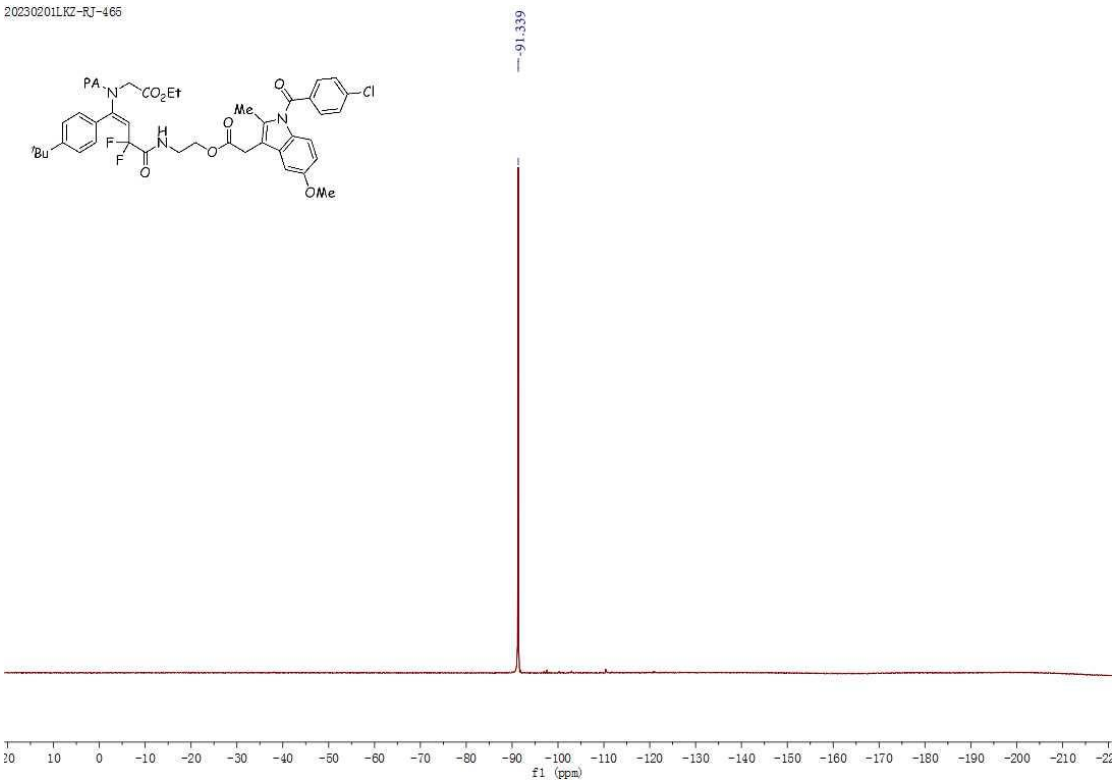
^{19}F – NMR spectrum of compound – **7u** (376 MHz, $CDCl_3$)



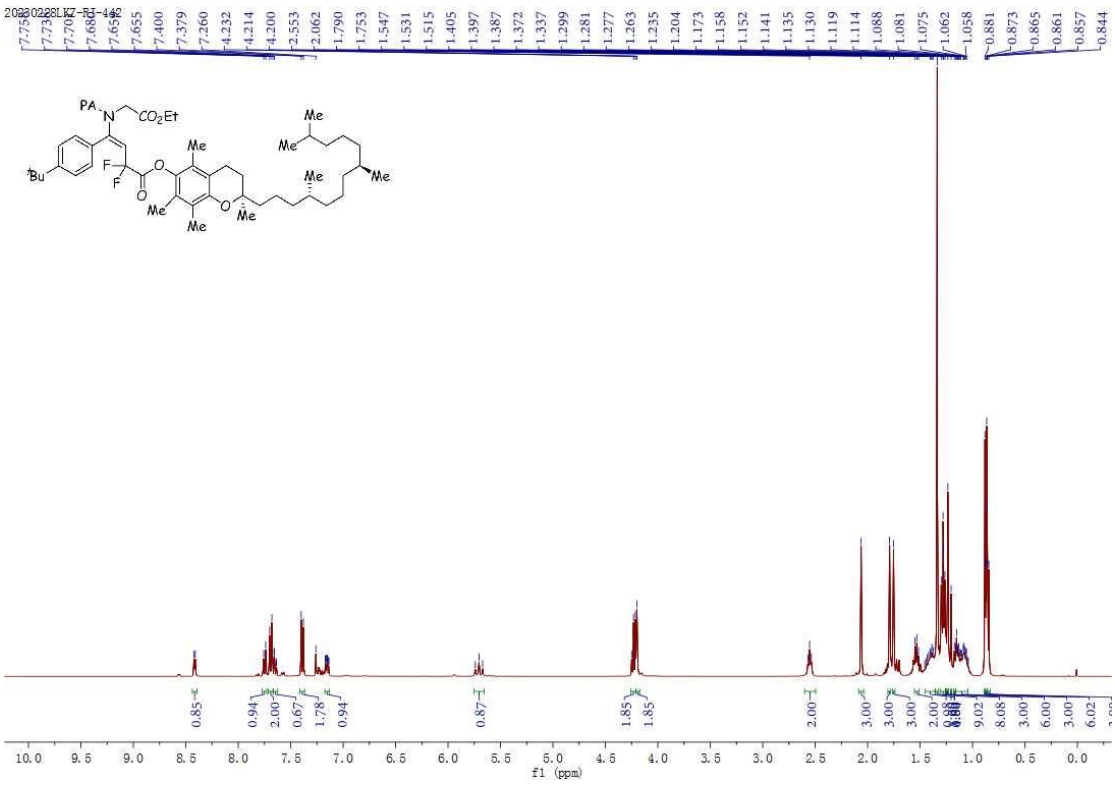
^{1}H – NMR spectrum of compound – **7v** (400 MHz, $CDCl_3$)



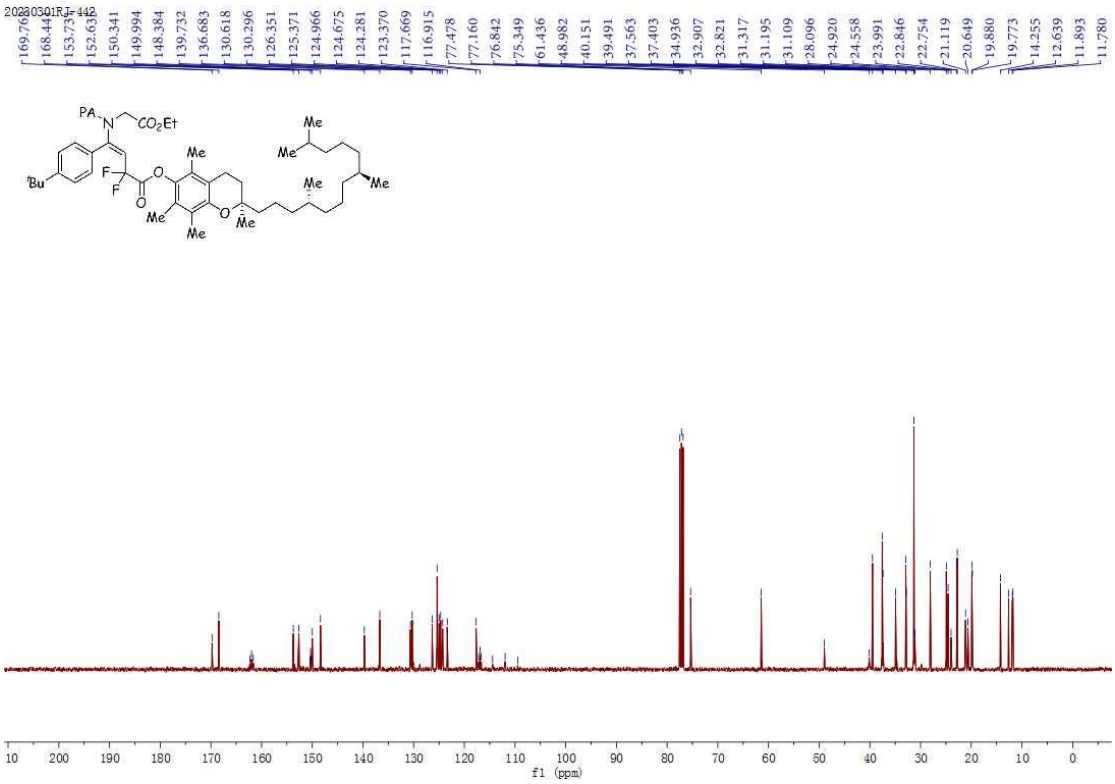
^{13}C – NMR spectrum of compound – **7v** (100 MHz, $CDCl_3$)



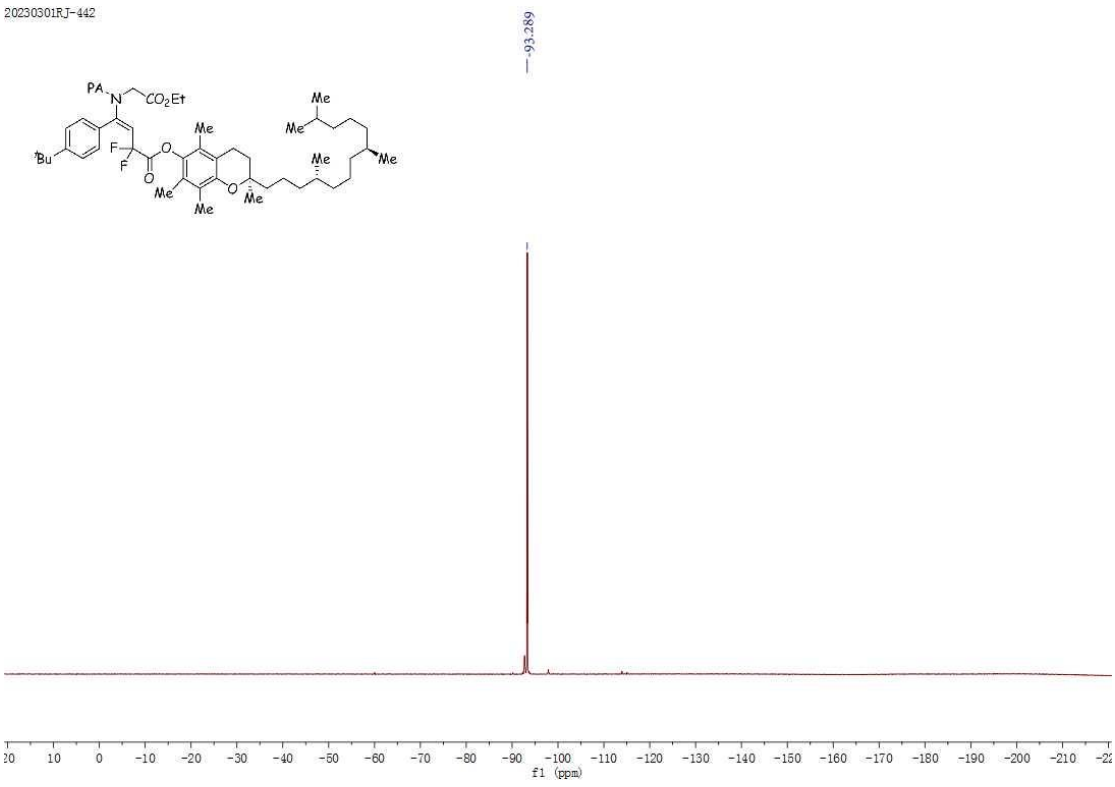
^{19}F – NMR spectrum of compound – **7v** (376 MHz, $CDCl_3$)



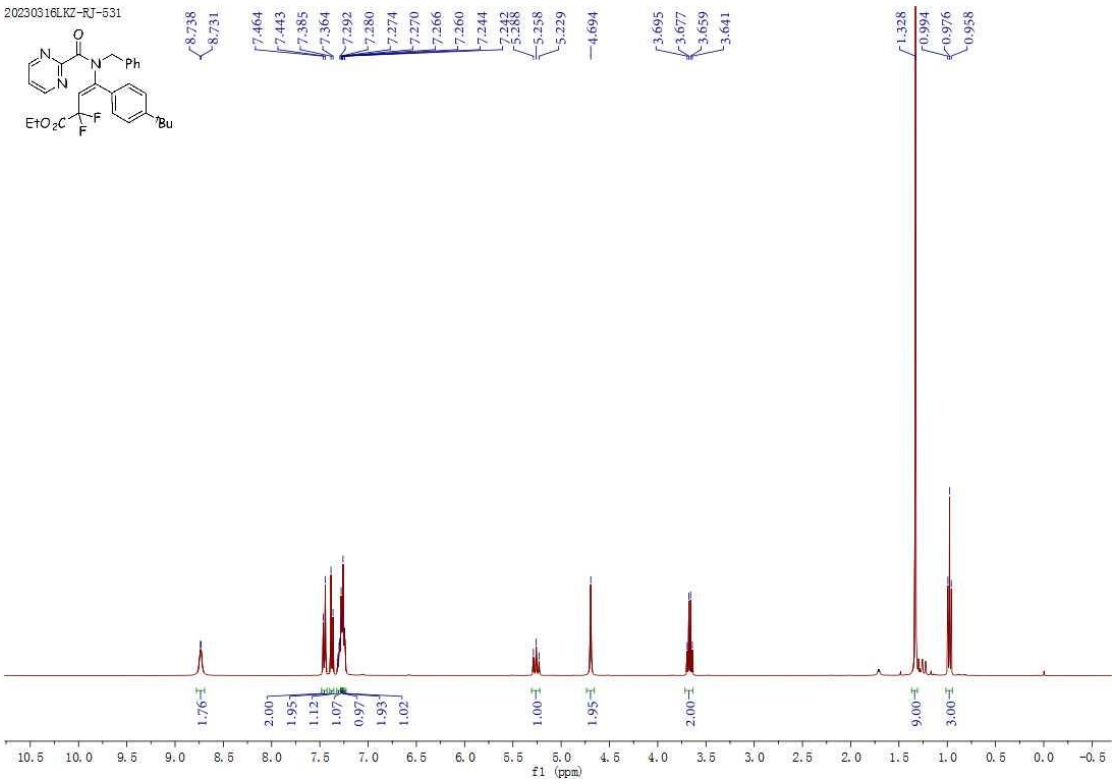
^{1}H – NMR spectrum of compound – **7w** (400 MHz, $CDCl_3$)



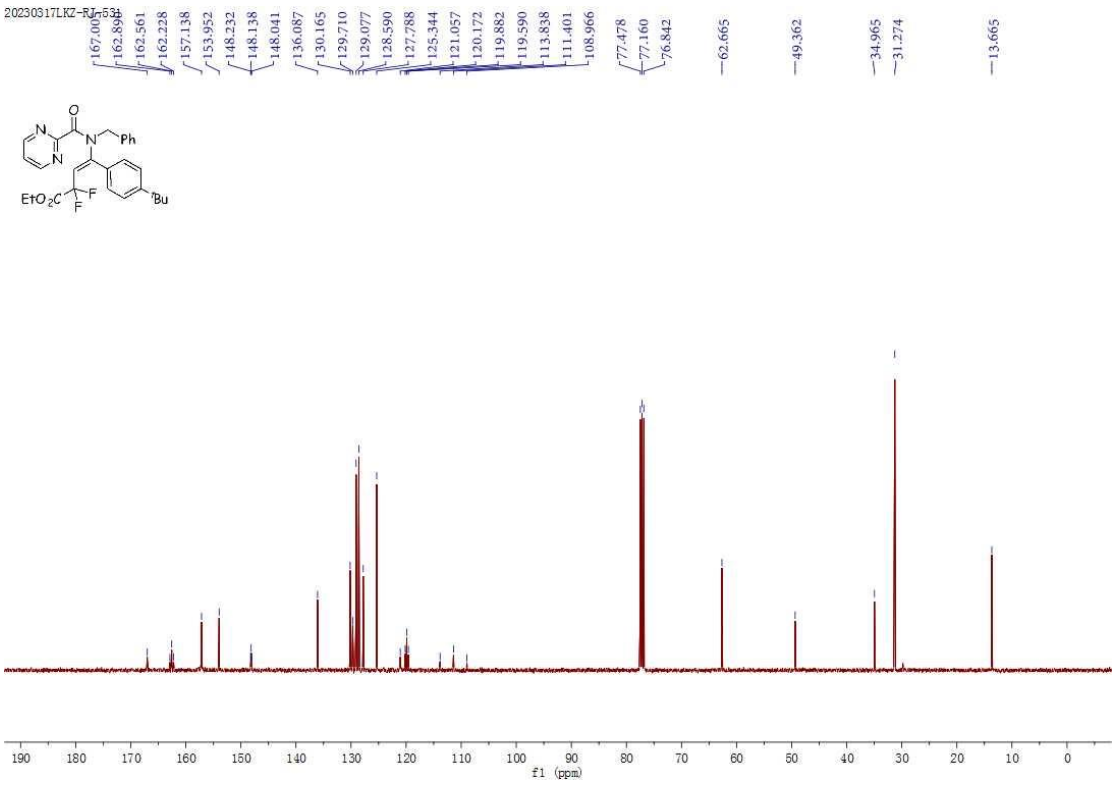
^{13}C – NMR spectrum of compound – **7w** (100 MHz, $CDCl_3$)



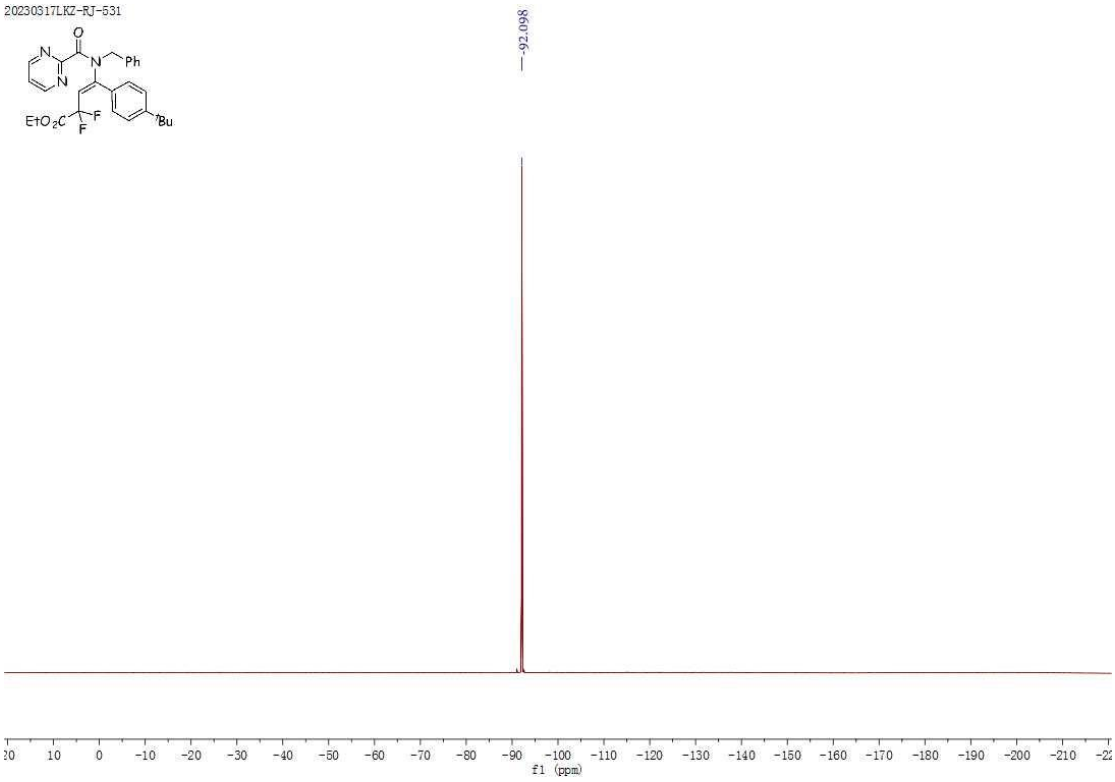
^{19}F – NMR spectrum of compound – **7w** (376 MHz, $CDCl_3$)



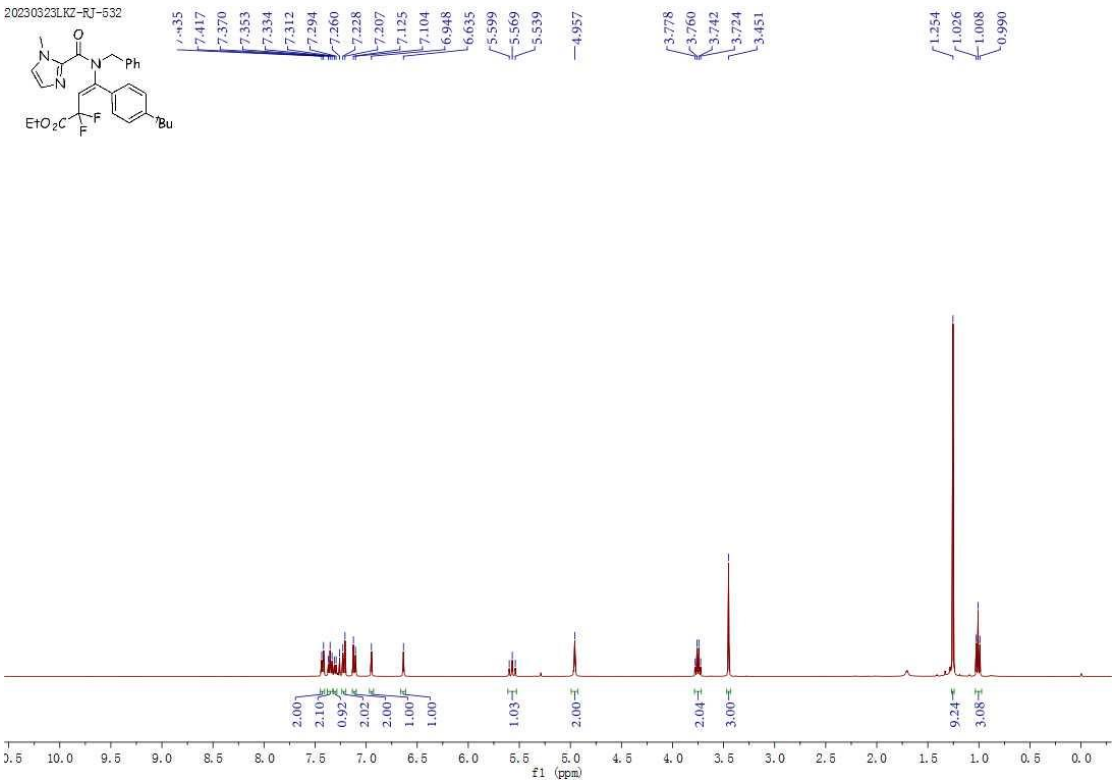
^{1}H – NMR spectrum of compound –**5a-6** (400 MHz, $CDCl_3$)



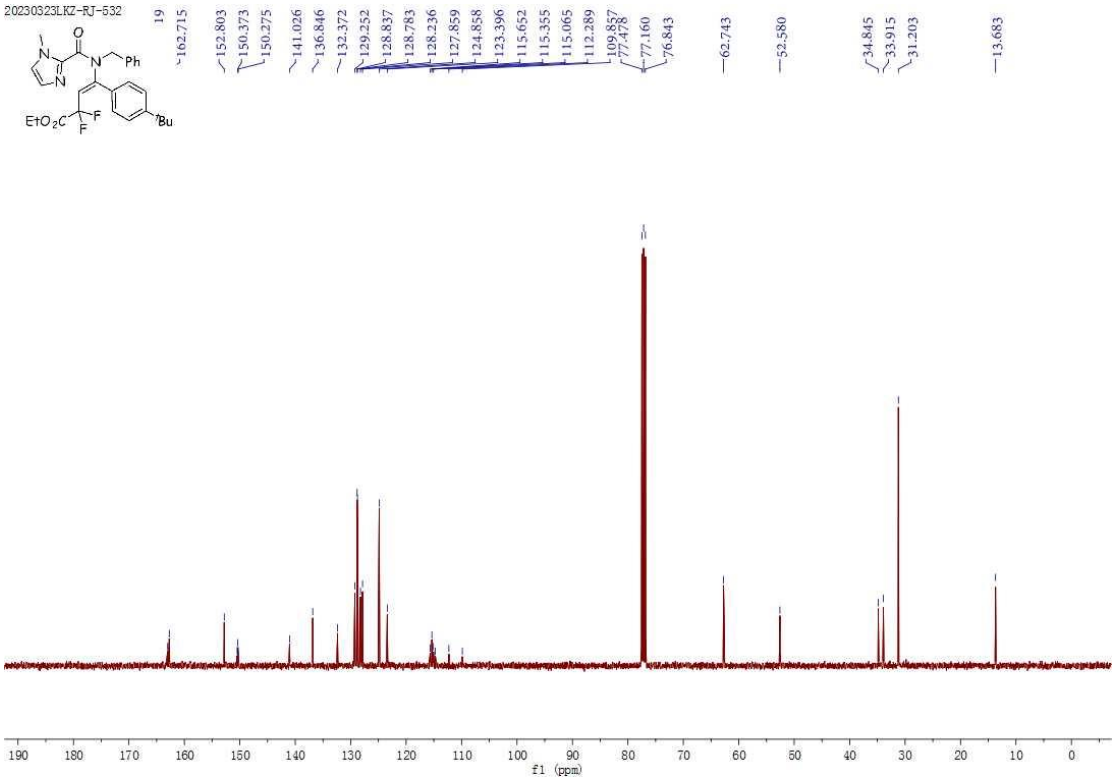
^{13}C – NMR spectrum of compound –**5a-6** (100 MHz, $CDCl_3$)



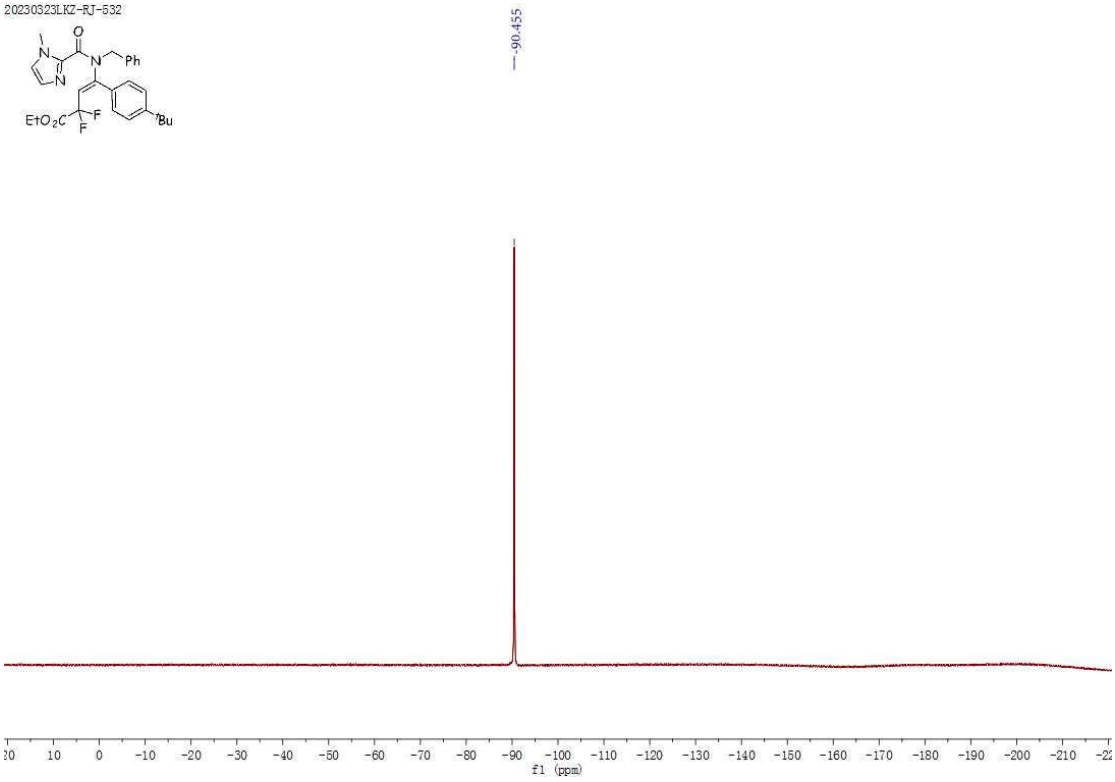
^{19}F – NMR spectrum of compound –**5a-6** (376 MHz, $CDCl_3$)



^{1}H – NMR spectrum of compound –**5a-7** (400 MHz, $CDCl_3$)



^{13}C – NMR spectrum of compound –**5a-7** (100 MHz, $CDCl_3$)



^{19}F – NMR spectrum of compound –**5a-7** (376 MHz, $CDCl_3$)