Supporting Information

Switching from *gem*-difluorovinylation to carboxylation: ligand-enabled palladium-catalyzed Heck annulation of alkene-tethered aryl halides with sodium difluorochloroacetate

Yu Xia*, Wenqi Li, Minzhu Wei, Yonghong Zhang, Bin Wang, Shaofeng Wu, and Chenjiang Liu*

Urumqi Key Laboratory of Green Catalysis and Synthesis Technology, Key Laboratory of Oil and Gas Fine Chemicals, Ministry of Education & Xinjiang Uygur Autonomous Region, State Key Laboratory of Chemistry and Utilization of Carbon Based Energy Resources, College of Chemistry, Xinjiang University, Urumqi 830017, P. R. China

E-mail; 18509487642@163.com; pxylcj@126.com

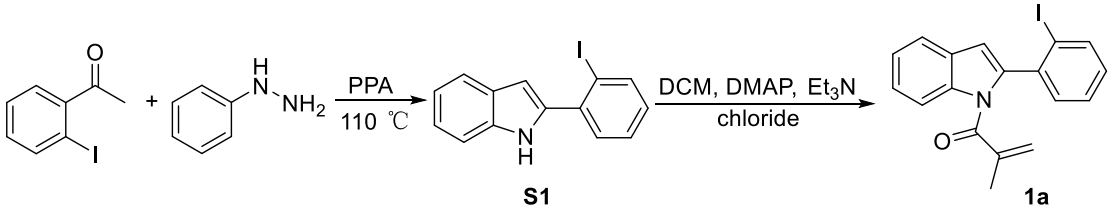
Table of contents

1. General information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker 800 MHz or Bruker Avance NEO 600 (600, 151, 201 and 565 MHz, respectively) NMR spectrometer. ^{1}H and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0, $CDCl_3$ (δ(^{1}H), 7.26 ppm; δ(^{13}C), 77.16 ppm), DMSO-d6 (δ(^{1}H), 2.50 ppm; δ(^{13}C), 39.51 ppm). Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hertz (Hz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The HRMS analysis was obtained on an Agilent6540 UHD Q-TOF mass spectrometer. The melting point was recorded on BÜCHI (M-560) and uncorrected. The X-ray single crystal diffraction data were collected on a Bruker D8 VENTURE. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60 F254 plates and viewed by UV light (254 nm). Column chromatographic purification was performed using 200-300 mesh silica gel. Materials. All the chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. Substrates **1** were synthesized in the lab by the reported procedures.

2. Preparation of Substrates

2.1 General Procedure for the Synthesis of Substrates 1a,1b-1h

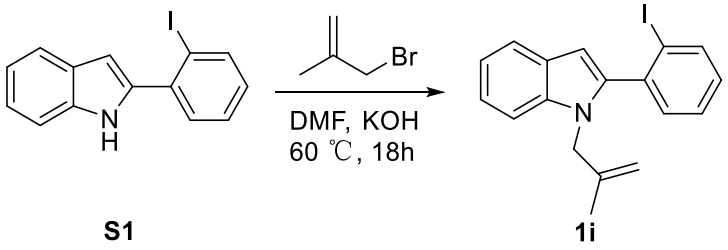


Step I: A mixture of 2-iodoacetophenone (5.0 mmol, 1.23 g), phenylhydrazine (6.0 mmol, 1.2 equiv, 0.65 g) and polyphosphoric acid (PPA, 15.0 g) was added to a round bottom flask and stirred at 110 ºC for 6 h. After the completion of the reaction, the

residue was quenched with ice water and extracted into ethyl acetate. The organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography (petroleum ether/EtOAc) to give the corresponding substituted indole **S1** (70%, 1.12 g).

Step II: According to a literature procedure, to the solution of indole **S1** (3.5 mmol, 1.12 g) and DMAP (0.7 mmol, 0.2 equiv, 85 mg) in DCM (7 mL, 0.5 M) was added Et_3N (7 mmol, 2.0 equiv, 0.71 g) and chloride (4.2 mmol, 1.2 equiv, 0.44 g) at 0 °C. The solution was warmed up to room temperature and stirred for overnight. The mixture was diluted with DCM (20 mL) and saturated NH_4Cl solution (20 mL). The organic and aqueous layers were separated. The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue, which was purified by flash chromatography and then recrystallized from petroleum ether/EtOAc to afford the product **1a** (50%, 677 mg). Procedure for the synthesis of substrates **1b-1h** is similar to **1a**.

2.2 Synthesis of Substrates 1i-1k



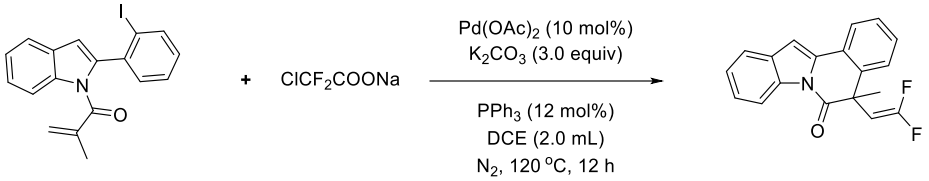
S1 **1i**

A solution of S1 (6.0 mmol, 1.91 g) in 10 mL of DMF and powdered KOH (7.8 mmol, 1.3 equiv, 437 mg) was stirred at 60 °C for 10 min, cooled to rt, and treated with 3-bromo-2-methylprop-1-ene (8.9 mmol, 1.5 equiv, 1.20 g). The reaction mixture was stirred at 60 °C for 18 h, poured onto ice and diluted with 15 mL of EtOAc. The combined organic layers were washed with H_2O, brine and dried by Na_2SO_4, concentrated in vacuo and purified by chromatography on SiO_2 (petroleum ether) to afford the desired product **4a** (63%, 1.41 g). Procedure for the synthesis of substrates **1j**, **1k** is similar to **1i**.

3 General Procedures, optimized reaction conditions and Mechanism studies

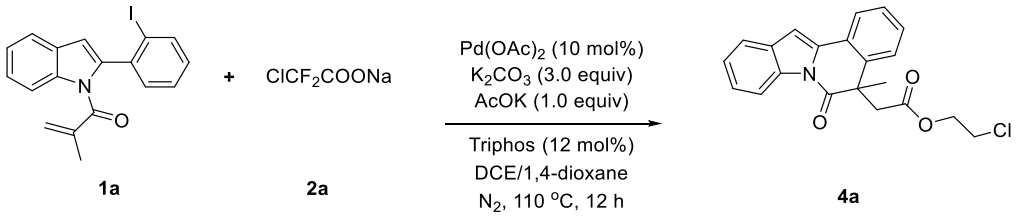
3.1 General procedures and gram-scale reaction

3.1.1 General procedure for 3a and 4a



1a **2a** **3a**

To a well dried 25 mL sealed tube with magnetic stir bar, 1-(2-(2-iodophenyl)-1*H*-indol-1-yl)-2-methylprop-2-en-1-one **1a** (77.6 mg, 0.2 mmol), chlorodifluoroacetate **2a** (60.1 mg, 0.4 mmol), $Pd(OAc)_2$ (4.4 mg, 10 mol%), K_2CO_3 (83.2 mg, 0.6 mmol), PPh_3 (6.2 mg, 12 mol%) were dissolved in 2.0 mL DCE, resulting mixture was stirred at 120 °C (oil bath) for 12 h. When the reaction was finished, the reation mixture was extracted by EtOAc (3 x 30 mL) and H_2O. The organic layer was dried over by Na_2SO_4, filtered and the solvent removed in vacuo. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20:1 to 5:1, v/v) to provide pure product **3a** (53.5 mg, 93% yield).

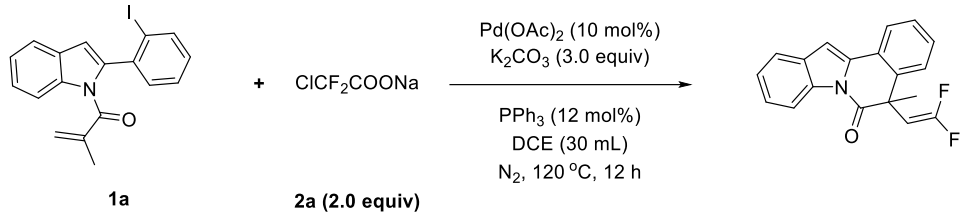


1a **2a** **4a**

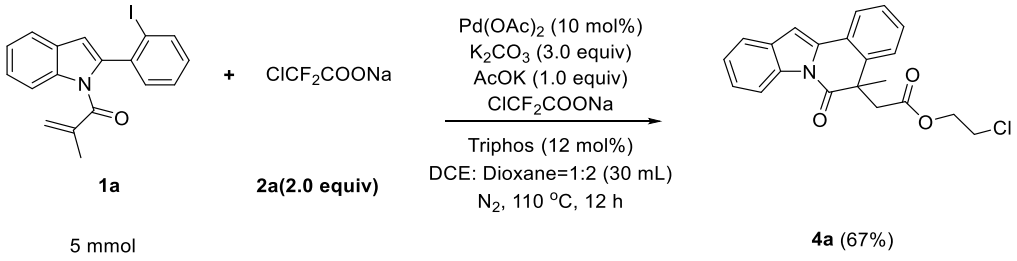
To a well dried 25 mL sealed tube with magnetic stir bar, 1-(2-(2-iodophenyl)-1*H*-indol-1-yl)-2-methylprop-2-en-1-one **1a** (77.6 mg, 0.2 mmol), chlorodifluoroacetate **2a** (60.2 mg, 0.4 mmol), $Pd(OAc)_2$ (4.4 mg, 10 mol%), K_2CO_3 (83.2 mg, 0.6 mmol), AcOK (19.6 mg, 0.2 mmol), Triphos (15.4 mg, 12 mol%) were dissolved in DCE/Dioxane = 1/2 (v/v, 4 mL), resulting mixture was stirred at 110 °C (oil bath) for 12 h. When the reaction

was finished, the reation mixture was extracted by EtOAc (3 x 30 mL) and H_2O. The organic layer was dried over by Na_2SO_4, filtered and the solvent removed in vacuo. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 50:1 to 4:1, v/v) to provide pure product **4a** (62.6 mg, 85% yield).

3.1.2 gram-scale reaction



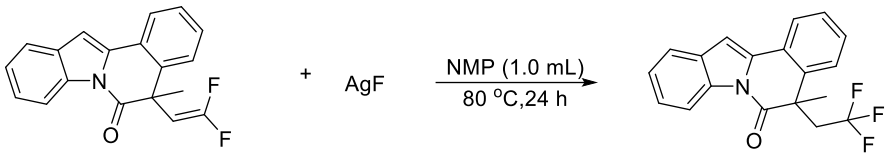
To a well dried 100 mL sealed tube with magnetic stir bar, 1-(2-(2-iodophenyl)-1*H*-indol-1-yl)-2-methylprop-2-en-1-one **1a** (1.94 g, 5 mmol), chlorodifluoroacetate **2a** (1.53 g, 10 mmol), $Pd(OAc)_2$ (0.11 g, 10 mol%), K_2CO_3 (2.10 g, 15 mmol), PPh_3 (0.31 g, 12 mol%) were dissolved in 30 mL DCE, resulting mixture was stirred at 120 °C (oil bath) for 12 h. When the reaction was finished, the reaction mixture was extracted by EtOAc (3 x 30 mL) and H_2O. The organic layer was dried over by Na_2SO_4, filtered and the solvent removed in vacuo. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20/1 to 5/1, v/v) to provide pure product **3a** (1.13 g, 73% yield).



To a well dried 100 mL sealed tube with magnetic stir bar, 1-(2-(2-iodophenyl)-1*H*-indol-1-yl)-2-methylprop-2-en-1-one **1a** (1.94 g, 5 mmol), chlorodifluoroacetate **2** (1.53 g, 10 mmol), $Pd(OAc)_2$ (0.11 g, 10 mol%), K_2CO_3 (2.10 g, 15 mmol), AcOK (0.49 g, 5 mmol), Triphos (0.38 g, 12 mol%) were dissolved in 30 mL DCE/1,4-dioxane (v/v = 1/2), resulting mixture was stirred at 110 °C (oil bath) for 12 h. When the reaction was finished, the reation mixture was partitioned between EtOAc (3 x 30 mL) and H_2O.

The organic layer was dried over Na_2SO_4, filtered and the solvent removed in vacuo. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 50:1 to 4:1, v/v) to provide pure product **4a** (1.23 g, 67% yield).

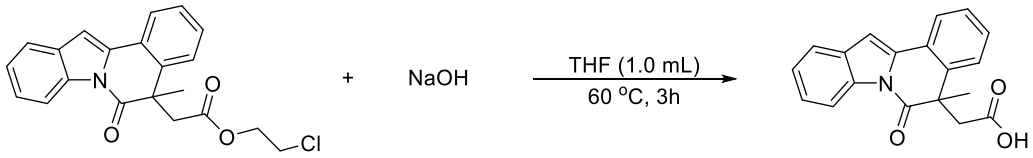
3.2 General Procedure for the Synthesis of Compound 5a



3a (0.25 mmol) 3.0 equiv **5a** yield: 76%

According to a modified literature procedure, to a stirred solution of 5-(2,2-difluorovinyl)-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one **3a** (77.3 mg, 0.25 mmol) in NMP (3 mL), AgF (136.8 mg, 0.75 mmol) was added at room temperature. The resultant solution was further stirred at 80 °C (oil bath) for 24 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and the resulting mixture was extracted with EtOAc (3 × 10 mL). Combined organic layer was dried over Na_2SO_4, filtered, and all of the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20:1 to 5:1, v/v) afford 5-methyl-5-(2,2,2-trifluoroethyl)-3,5-dihydroindolo[2,1-*a*]isoquinolin-6(2*H*)-one **5a** as a yellow oil in 76% yield (62.5 mg).

3.3 General Procedure for the Synthesis of Compound 5b



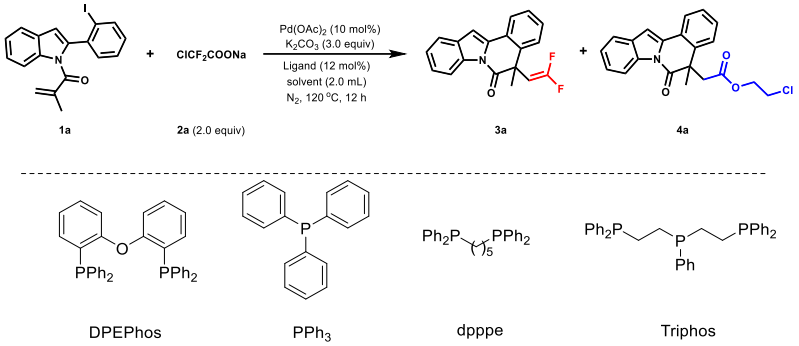
4a (0.33 mmol) 2.5 M aq.(0.5 mL) **5b** yield: 95%

According to a modified literature procedure, to a stirred solution of 2-chloroethyl 2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate **4a** (121.1 mg, 0.33

mmol) in THF (1 mL), NaOH (2.5 M aq., 0.5 mL) was added at room temperature. The resultant solution was further stirred at 60 °C (oil bath) for 3 h. After completion, as indicated by TLC, the reaction mixture was cooled to room temperature and the resulting mixture was extracted with EtOAc (3 × 10 mL). Combined organic layer was dried over Na_2SO_4, filtered, and all of the volatiles were evaporated under reduced pressure. The resultant residue was purified by silica gel column chromatography (eluent: petroleum ether/EtOAc = 20:1 to 5:1, v/v) afford 2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetic acid **5b** as a yellow oil in 95% yield (95.6 mg).

3.4 Optimized reaction conditions[a]

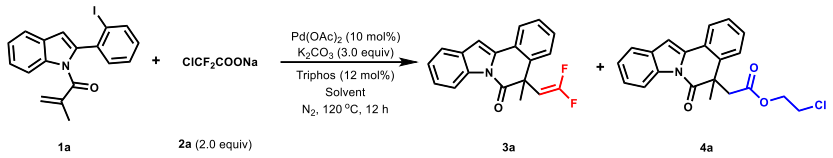
Table S1 Optimization of the reaction conditions



Entry	[Pd]	Ligand	Base	Sol.	Yield 3a	Yield 4a (%)[b]
1	**$Pd(OAc)_2$**	**PPh_3**	**K_2CO_3**	DCE	**93**	trace
2	$Pd(TFA)_2$	PPh_3	K_2CO_3	DCE	31	11
3	$PdCl_2$(dippp)	PPh_3	K_2CO_3	DCE	trace	trace
4	$Pd(OAc)_2$	DPEphos	K_2CO_3	DCE	27	13
5	$Pd(OAc)_2$	dpppe	K_2CO_3	DCE	75	18
6	$Pd(OAc)_2$	dppm	K_2CO_3	DCE	43	trace
7	$Pd(OAc)_2$	PPh_3	AcONa	DCE	NR	NR
8	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DCE	NR	NR
9	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DCE	11	ND
10	$Pd(OAc)_2$	PPh_3	K_2CO_3	1,4-dioxane	NR	NR
11	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	trace	ND
12[c]	$Pd(OAc)_2$	PPh_3	K_2CO_3	DCE	66	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv.), [Pd] (10 mol%), ligand (12 mol%), base (3.0 equiv.) and solvent (2.0 mL) at 120 ℃ for 12 h under a N_2 atmosphere. [b]Isolated yield. NR = no reaction. [c] $Pd(OAc)_2$ (5 mol%). $PdCl_2$(dippp) = dichloro(1,3-bis(diphenylphosphino)propane)palladium(II).

Table S2 Optimization of the reaction conditions



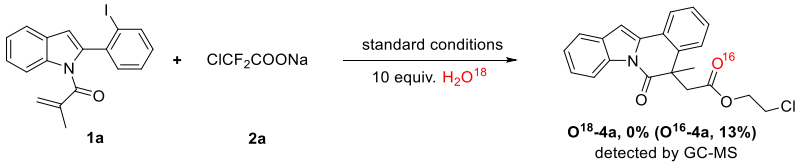
1a 2a (2.0 equiv) 3a 4a

Entry	Ligand	Base	Sol.	Yield 3a	Yield 4a (%)[b]
1	Triphos	K_2CO_3	DCE	6	43
2	Triphos	K_2CO_3	DCE/DMA	11	0
3[c]	Triphos	K_2CO_3	DCE/1,4-dioxane	trace	60
4[c]	DPEphos	K_2CO_3	DCE/1,4-dioxane	trace	24
5[c]	PPh_3	K_2CO_3	DCE/1,4-dioxane	32	trace
6[c]	Triphos	Cs_2CO_3	DCE/1,4-dioxane	trace	trace
7[c]	Triphos	K_3PO_4	DCE/1,4-dioxane	trace	trace
8[c,d]	Triphos	K_2CO_3	DCE/1,4-dioxane	17	74
9[c,d,e]	Triphos	K_2CO_3	DCE/1,4-dioxane	12	78
10[d,e,f]	Triphos	K_2CO_3	DCE/1,4-dioxane	trace	85
11 [d,e,f,g]	Triphos	K_2CO_3	DCE/1,4-dioxane	trace	ND
12 [d,e,f,h]	Triphos	K_2CO_3	DCE/1,4-dioxane	trace	ND
13 [d,e,f, i]	Triphos	K_2CO_3	DCE/1,4-dioxane	NR	NR
14 [d,e,f, j]	Triphos	K_2CO_3	DCE/1,4-dioxane	trace	53
15 [d,e,f, k]	Triphos	K_2CO_3	DCE/1,4-dioxane	ND	ND
16 [d,e,f, l]	Triphos	K_2CO_3	DCE/1,4-dioxane	ND	ND

[a]Reaction conditions: 1a (0.2 mmol), 2a (2.0 equiv.), [Pd] (10 mol%), ligand (12 mol%), base (3.0 equiv.) and solvent (2.0 mL) at 120 °C for 12 h under a N_2 atmosphere. [b]Isolated yield. [c]DCE/1,4-dioxane =1/1 (v/v, 2.0 mL). [d]KOAc(1.0 equiv) was added. [e]110°C. [f] DCE/1,4-dioxane = 1/2 (v/v, 4.0 mL). [g] **2a** changed by $ClCF_2COOEt$. [h]**2a** changed by $BrCF_2TMS$. [i]**2a** changed by KOAc. [j] $Pd(OAc)_2$ (5 mol%). [k] DCE changed by DCM. [l] DCE changed by $BrCH_2CH_2Br$.

3.5 Mechanism studies

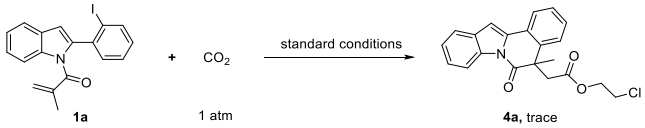
3.5.1 Control experiments



1a 2a

O^{18}-4a, 0% (O^{16}-4a, 13%) detected by GC-MS

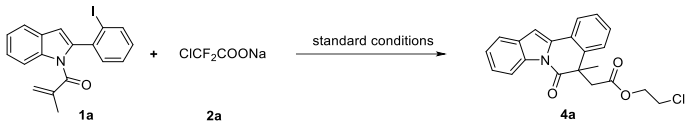
When added 10 equiv. H_2O^{18}, we did not detect $C{=}O^{18}$. So, the source of carbonyl could not come from $Pd{=}CF_2$ hydrolysis.

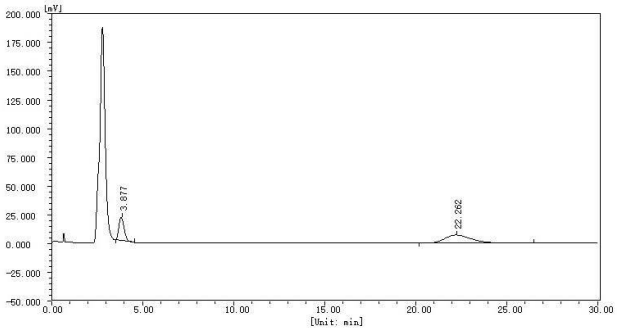


1a 1 atm **4a**, trace

When we replaced $ClCF_2COONa$ with CO_2 gas (1 atm), we could obtain **4a** in trace yield. So, we think that the concentration of CO_2 from $ClCF_2COONa$ in solvent is much more than CO_2 gas.

3.5.2 GC-MS for CO_2 Concentration

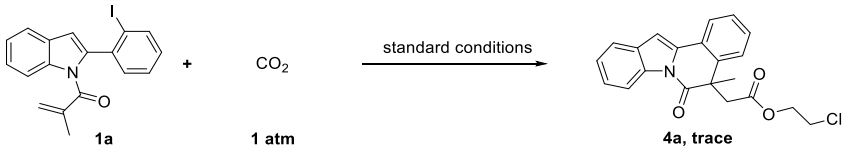


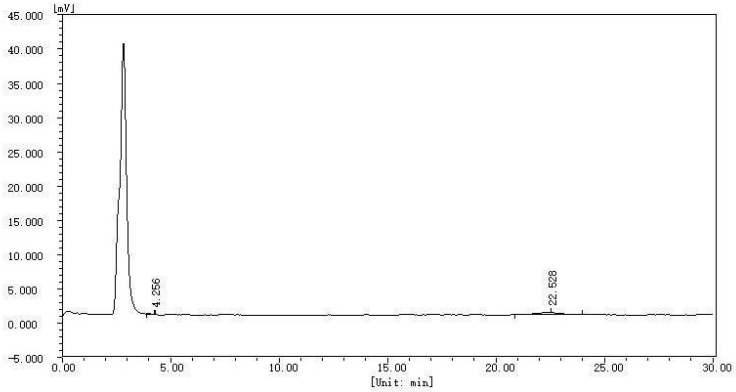


Analysis result(external standard method)

Entry	Component	Retention time [min]	Full width at half maxima [min]	peak height [uV]	peak area [uV*s]	peak area [%]	content [mg/m3]	peak type
1	CO	3.877	0.317	20620.4	426679.2	36.6414	80067.6406	BB
2	CO2	22.262	1.576	7114.8	741253.1	63.3586	308061.1563	BB
			Total:	27935.1	1169932.3	100.0000	388128.7969	

Subsequently, we detected the concentration of CO_2 in solvent. The experiment result showed that the CO_2 concentration coming from $ClCF_2COONa$ is very high.



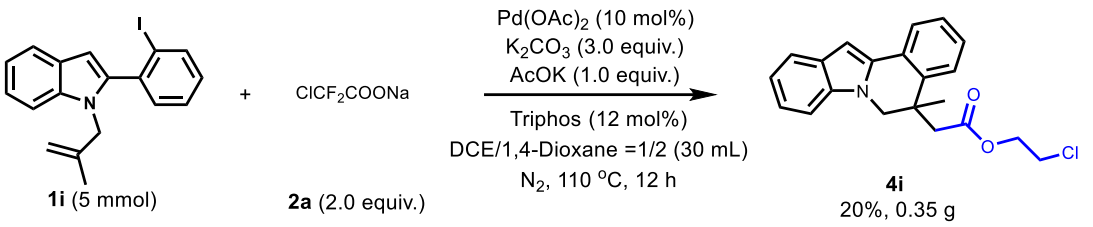


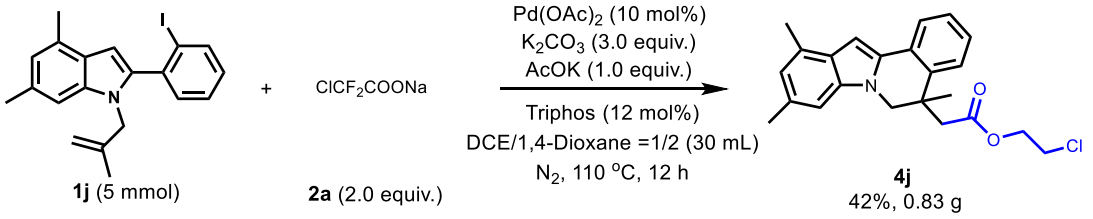
analysis result(external standard method)

Entry	Component	Retention time [min]	Full width at half maxima [min]	peak height [uV]	peak area [uV*s]	peak area [%]	content [mg/m3]	peak type
1	CO	4.256	0.391	70.0	898.0	2.7839	898.0179	BB
2	CO2	22.528	1.275	358.1	31359.6	97.2161	13032.8799	BB
			Total:	428.0	32257.6	100.0000	13930.8978	

We also detected the concentration of CO_2 in solvent, which CO_2 came from CO_2 gas. The experiment result showed that the CO_2 concentration coming from CO_2 gas is very low. The low CO_2 concentration in solvent may not facilitate the reaction.

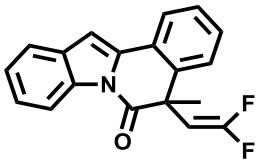
3.6 Gram-scale





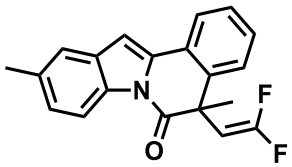
The reaction of *N*-allyl indole **1j** with **2a** was performed on a gram scale, furnishing the corresponding product product **4j** in 42% yield (0.83 g). The reaction of *N*-allyl indole **1i** with **2a** was performed on a gram scale, furnishing the corresponding product product **4i** in 20% yield (0.35 g).

4. Characterization Data

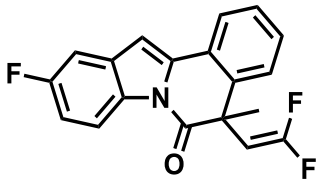


5-(2,2-difluorovinyl)-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3a): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 57.5 mg, 93% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.47 (dd, J = 8.8, 4.0 Hz, 1H), 7.82 – 7.81 (m, 1H), 7.41 – 7.38 (m, 3H), 7.24 (dd, J = 8.0, 2.4 Hz, 1H), 7.08 (td, J = 8.8, 2.4 Hz, 1H), 6.99 (s, 1H), 4.74 (dd, J = 25.6, 3.2 Hz, 1H), 1.83 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.1, 156.7(dd, *J* = 296.0, 289.9 Hz), 138.5, 135.6, 135.2, 130.8, 129.2, 127.9, 127.3, 125.6, 124.9, 123.9, 120.7, 116.7, 103.7, 84.5 (dd, *J* = 27.2, 13.6 Hz), 46.1 (dd, *J* = 4.5, 1.5 Hz), 30.2 (d, *J* = 3.0 Hz). **^{19}F NMR** (565 MHz, $CDCl_3$) δ -2.94 (d, *J* = 33.9 Hz), -6.09 (d, *J* = 39.6 Hz). **HRMS** (ESI) m/z Calcd for $C_{19}H_{14}F_2NO$ $[M+H]^+$:

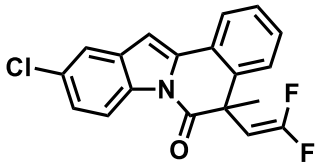
310.1044; Found: 310.1038.



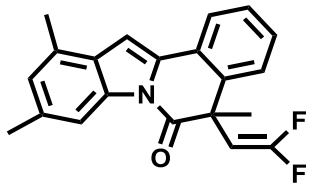
5-(2,2-difluorovinyl)-5,10-dimethylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3b): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 32.0 mg, 51% yield. Yellow oil. **^{1}H NMR** (600 MHz, DMSO) δ 8.27 (d, J = 8.4 Hz, 1H), 8.02 (dd, J = 6.0, 4.0 Hz, 1H), 7.50 (dd, J = 7.2, 4.2 Hz, 1H), 7.44 (s, 1H), 7.43 – 7.41 (m, 2H), 7.34 (s, 1H), 7.18 (d, J = 8.4 Hz, 1H), 5.25 (dd, J = 28.2, 3.6 Hz, 1H), 2.40 (s, 3H), 1.74 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.2, 155.2 (dd, *J* = 286.9, 292.9 Hz), 138.2, 135.0, 133.9, 132.9, 130.7, 129.2, 127.8, 127.4, 126.4, 123.9, 122.8, 120.7, 115.5 (d, *J* = 6.0 Hz), 103.6, 85.5 (dd, *J* = 25.7, 12.1 Hz), 45.2 (dd, *J* = 4.53, 1.5 Hz), 29.5, 21.0. **^{19}F NMR** (565 MHz, DMSO) δ -5.06 (d, *J* = 45.2 Hz), -8.88 (d, *J* = 45.2 Hz). **HRMS** (ESI) m/z Calcd for $C_{20}H_{16}F_2NO$ $[M+H]^+$: 324.1200; Found: 324.1195.



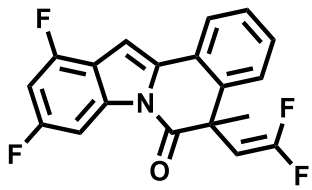
5-(2,2-difluorovinyl)-10-fluoro-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3c): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 58.8 mg, 91% yield. Yellow oil. **^{1}H NMR** (600 MHz, DMSO) δ 8.38 (dd, J = 9.0, 4.8 Hz, 1H), 8.03 – 8.02 (m, 1H), 7.52 – 7.49 (m, 1H), 7.45 – 7.40 (m, 3H), 7.37 (s, 1H), 7.17 (td, J = 9.0, 3.0 Hz, 1H), 5.22 (dd, J = 28.2, 3.6 Hz, 1H), 1.73 (s, 3H).**^{13}C NMR** (151 MHz, DMSO) δ 170.3, 159.6 (d, *J* = 240.1 Hz), 155.3 (dd, *J* = 286.9, 292.9 Hz), 138.5, 136.7, 131.8 (d, *J* = 4.5 Hz), 131.2, 129.5, 127.9, 127.4, 124.1, 122.4, 117.1 (d, *J* = 9.1 Hz), 112.6, 112.4, 106.5, 106.4, 103.3 (d, *J* = 3.0 Hz), 85.3 (dd, *J* = 25.7, 12.1 Hz), 45.3 (dd, *J* = 6.0, 1.5 Hz), 29.4. **^{19}F NMR** (565 MHz, DMSO) δ -5.99(d, *J* = 45.2 Hz), -6.42(d, *J* = 45.2 Hz), -39.79. **HRMS** (ESI) m/z Calcd for $C_{20}H_{16}F_2NO$ $[M+H]^+$: 328.0949; Found: 328.0944.



10-chloro-5-(2,2-difluorovinyl)-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one(3d): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 61.8 mg, 90% yield. Yellow oil. **^{1}H NMR** (600 MHz, DMSO) δ 8.36 (d, J = 9.0 Hz, 1H), 8.03 (dd, J = 7.2, 1.2 Hz, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.52 – 7.50 (m, 1H), 7.46 – 7.41 (m, 2H), 7.37 – 7.35 (m, 2H), 5.23 (dd, J = 28.2, 3.6 Hz, 1H), 1.74 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 170.5, 155.3 (dd, *J* = 294.45, 286.9 Hz), 138.5, 136.5, 133.2, 132.0, 129.7, 129.0, 127.9, 127.4, 124.9, 124.2, 122.3, 120.2, 117.2, 102.9, 85.3 (dd, *J* = 25.7, 12.1 Hz), 45.3 (d, *J* = 3.0 Hz), 29.4 (d, *J* = 1.5 Hz). **^{19}F NMR** (565 MHz, DMSO) δ -4.82(d, *J* = 39.6 Hz), -8.46(d, *J* = 45.2 Hz). **HRMS** (ESI) m/z Calcd for $C_{19}H_{13}ClF_2NO$ $[M+H]^+$: 344.0654; Found: 344.0648.

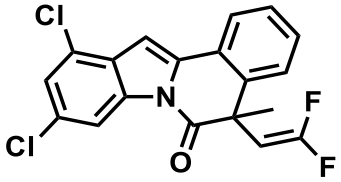


5-(2,2-difluorovinyl)-5,9,11-trimethylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3e): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 44.4 mg, 66% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.05 (s, 1H), 6.99 (s, 1H), 4.74 (dd, J = 26.4, 4.0 Hz, 1H), 2.55 (s, 3H), 2.48 (s, 3H), 1.82 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 171.2, 156.7 (dd, J = 293.5, 287.4 Hz), 138.2, 136.1, 135.8, 134.0, 129.8, 128.8, 128.1, 127.8, 127.3, 126.8, 124.0, 123.7, 114.5, 102.3, 84.6 (dd, J = 28.1, 14.1 Hz), 46.1 (d, J = 4.0 Hz), 30.1 (d, J = 4.0 Hz), 22.0, 18.6. **^{19}F NMR** (565 MHz, $CDCl_3$) δ -3.11(d, *J* = 39.6 Hz), -6.28 (d, *J* = 39.6 Hz). **HRMS** (ESI) m/z Calcd for $C_{21}H_{18}F_2NO$ $[M+H]^+$: 328.1357; Found: 338.1351.

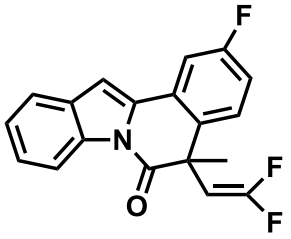


5-(2,2-difluorovinyl)-9,11-difluoro-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3f): Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 34.5 mg, 50% yield. Yellow solid. Melting point: 85.6 – 86.3 ºC. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.08 (dd, J = 8.8, 1.6 Hz, 1H), 7.80 (dd, J = 6.6, 3.2 Hz, 1H), 7.41 – 7.37 (m, 3H), 7.06 (s,

1H), 6.82 (td, J = 9.6, 2.4 Hz, 1H), 4.74 (dd, J = 26.4, 3.2 Hz, 1H), 1.82 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 171.3, 161.3 (dd, *J* = 245.2, 12.1 Hz), 156.8 (dd, *J* = 293.5, 287.4 Hz), 155.0 (dd, *J* =251.3, 14.1 Hz), 138.3, 136.6 (dd, *J* = 16.8, 12.1 Hz), 135.5 (d, *J* = 4.0 Hz), 129.6, 128.1, 127.3, 123.8, 123.1, 116.1 (d, *J* = 20.1 Hz), 100.6 (d, *J* = 4.3 Hz), 100.50 (d, *J* = 4.3 Hz), 100.4, 100.2 (d, *J* = 4.9 Hz), 100.1, 98.6, 84.3 (dd, *J* = 28.1, 16.8 Hz), 46.2 (dd, *J* = 6.0, 4.0 Hz), 30.1 (d, *J* = 2.0 Hz) **^{19}F NMR** (565 MHz, DMSO) δ -2.54 (d, *J* = 39.6 Hz), -5.81 (d, *J* = 33.9 Hz), -34.71 (d, J = 4.4 Hz), -40.80 (d, J = 5.4 Hz). **HRMS** (ESI) m/z Calcd for $C_{20}H_{16}F_2NO$ $[M+H]^+$: 346.0855; Found: 346.0850.

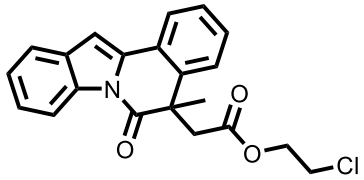


9,11-dichloro-5-(2,2-difluorovinyl)-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3g) : Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 50.0 mg, 66% yield. Yellow solid. Melting point: 114.5 – 115.4 °C. **^{1}H NMR** (600 MHz, DMSO) δ 8.31 (d, J = 1.2 Hz, 1H), 8.16 (dd, J = 7.8, 1.2 Hz, 1H), 7.53 (dd, J = 8.4, 1.2 Hz, 1H), 7.50 (d, J = 1.8 Hz, 1H), 7.49 – 7.46 (m, 2H), 7.44 (td, J = 7.8, 1.8 Hz, 1H), 5.24 (dd, J = 28.2, 3.6 Hz, 1H), 1.76 (s, 3H). **^{13}C NMR** (151 MHz, DMSO) δ 170.8, 155.4 (dd, *J* = 286.9, 294.5 Hz), 138.4, 136.9, 135.1, 130.0, 129.6, 128.1, 128.0, 127.3, 125.4, 124.6, 124.1, 122.0, 114.6, 100.9, 85.1 (dd, *J* = 27.2, 12.1 Hz), 45.6 (dd, *J* = 4.5, 1.5 Hz), 29.2 (d, *J* = 1.5 Hz). **^{19}F NMR** (565 MHz, DMSO) δ -4.75 (d, *J* = 39.6 Hz), -8.16 (d, *J* = 39.6 Hz). **HRMS** (ESI) m/z Calcd for $C_{19}H_{12}Cl_2F_2NO$ $[M+H]^+$: 378.0264; Found: 378.0259.

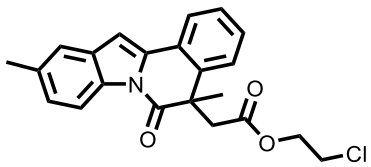


5-(2,2-difluorovinyl)-2-fluoro-5-methylindolo[2,1-*a*]isoquinolin-6(5*H*)-one (3h):

Eluent: petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 46.4 mg, 71% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.77 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.72 (dd, J = 9.6, 2.4 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.61 (dd, J = 8.8, 5.6 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.31 (td, J = 8.8, 3.2 Hz, 1H), 4.97 (dd, J = 25.6, 3.2 Hz, 1H), 2.05 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 170.8, 162.2 (d, *J* = 247.2 Hz), 156.7 (dd, *J* = 295.5, 289.4 Hz), 135.6, 134.3, 134.1 (d, *J* = 2.0 Hz), 130.5, 129.5 (d, *J* = 8.0 Hz), 126.1, 125.6 (d, *J* = 8.0 Hz), 125.0, 121.0, 116.8, 116.6 (d, *J* = 22.1 Hz), 110.0 (d, *J* = 24.12 Hz), 104.7, 84.5 (dd, *J* = 28.1, 14.1 Hz), 45.8 (dd, *J* = 6.0, 4.0 Hz), 30.3 (d, *J* = 2.0 Hz). **^{19}F NMR** (565 MHz, DMSO) δ -5.99(d, *J* = 45.2 Hz), -6.42(d, *J* = 45.2 Hz), -36.25. **HRMS** (ESI) m/z Calcd for $C_{20}H_{16}F_2NO$ $[M+H]^+$: 328.0949; Found: 328.0944.

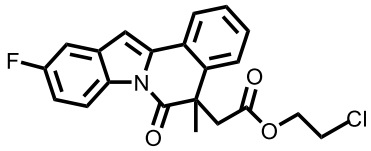


2-chloroethyl 2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate(4a): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 62.6 mg, 85% yield. Yellow solid. Melting point: 88.3 – 89.0 °C. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.63 – 8.57 (m, 1H), 7.89 – 7.87 (m, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.39 – 7.32 (m, 5H), 7.07 (s, 1H), 4.05 – 3.99 (m, 2H), 3.79 (d, J = 16.8 Hz, 1H), 3.26 (t, J = 6.0 Hz, 2H), 3.19 (d, J = 17.4 Hz, 1H), 1.64 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 172.5, 169.9, 137.7, 135.6, 153.5, 130.7, 129.1, 127.7, 125.4, 125.3, 124.8, 124.7, 124.2, 120.6, 116.8, 103.3, 64.2, 46.4, 44.2, 41.0, 30.4. **HRMS** (ESI) m/z Calcd for $C_{21}H_{19}ClNO_3$ $[M+H]^+$: 368.1054; Found: 368.1048.

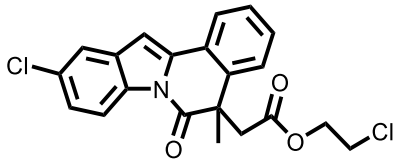


2-chloroethyl 2-(5,11-dimethyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate(4b): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 54.2 mg, 71% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.43 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 5.6, 3.2 Hz, 1H), 7.39 (s, 1H), 7.36 – 7.33 (m, 3H), 7.19 (dd, J = 8.8, 1.6 Hz,

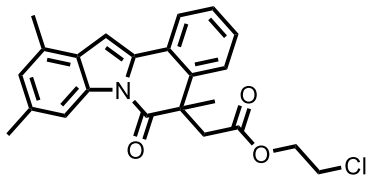
1H), 6.99 (s, 1H), 4.04 – 3.97 (m, 2H), 3.78 (d, J = 17.6 Hz, 1H), 3.24 (td, J = 6.4, 1.6 Hz, 2H), 3.17 (d, J = 16.8 Hz, 1H), 2.47 (s, 3H), 1.63 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.3, 170.0, 137.6, 135.5, 134.3, 133.8, 131.0, 129.0, 127.6, 126.7, 125.3, 124.9, 124.1, 120.6, 116.4, 103.2, 64.2, 46.3, 44.1,41.0, 30.4, 21.6. **HRMS** (ESI) m/z Calcd for $C_{22}H_{21}ClNO_3$ $[M+H]^+$: 382.1210; Found: 382.1205.



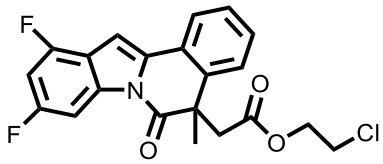
propyl 2-(10-fluoro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4c): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 55.4 mg, 76% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.77 (dd, J = 8.9, 4.7 Hz, 1H), 8.11 – 8.10 (m, 1H), 7.63 – 7.59 (m, 3H), 7.51 – 7.49 (m, 1H), 7.32 (td, J = 9.0, 2.6 Hz, 1H), 4.27 (td, J = 5.5, 1.2 Hz, 2H), 4.02 (d, J = 17.2 Hz, 1H), 3.52 (t, J = 5.7 Hz, 2H), 3.44 (d, J = 17.2 Hz, 1H), 1.88 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.4, 170.0, 160.4 (d, J = 239.2 Hz), 137.9, 137.1, 131.9 (d, J = 2.0 Hz), 131.85, 129.4, 127.7, 125.4, 124.3 (d, J = 16.9 Hz), 117.8 (d, J = 9.0 Hz), 112.9, 112.8, 106.3, 106.2, 102.9 (d, J = 4.2 Hz), 64.3, 46.2, 44.2, 41.1, 30.4. **HRMS** (ESI) m/z Calcd for $C_{21}H_{18}ClFNO_3$ $[M+H]^+$: 386.0959; Found: 386.0954.



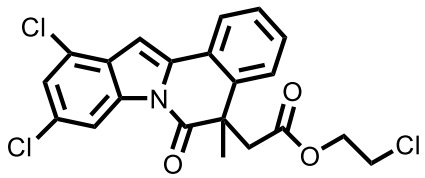
2-chloroethyl 2-(10-chloro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4d): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 66.8 mg, 83% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.49 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 7.2, 0.8 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.40 – 7.34 (m, 3H), 7.31 (dd, J = 8.0, 1.6 Hz, 1H), 6.99 (s, 1H), 4.04 – 4.01 (m, 2H), 3.77 (d, J = 16.8 Hz, 1H), 3.28 (t, J = 6.4 Hz, 2H), 3.19 (d, J = 17.6 Hz, 1H), 1.63 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.5, 170.0, 137.8, 136.8, 133.9, 132.0, 130.2, 129.5, 127.8, 125.4, 125.3, 124.4, 124.3, 120.2, 117.8, 102.4, 64.3, 46.3, 44.2, 41.1, 30.4. **HRMS** (ESI) m/z Calcd for $C_{21}H_{18}Cl_2NO_3$ $[M+H]^+$: 402.0663; Found: 402.0658.



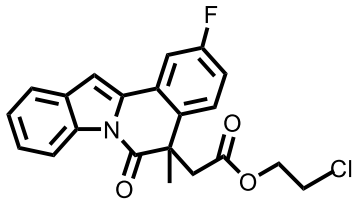
2-chloroethyl 2-(5,9,11-trimethyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4e): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 58.6 mg, 74% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.89 (dd, J = 6.6, 2.0 Hz, 1H), 7.36 – 7.32 (m, 3H), 7.08 (s, 1H), 6.99 (s, 1H), 4.06 – 3.99 (m, 2H), 3.79 (d, J = 17.2 Hz, 1H), 3.29 – 3.24 (m, 2H), 3.18 (d, J = 17.2 Hz, 1H), 2.56 (s, 3H), 2.49 (s, 3H), 1.63 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.6, 170.0, 137.3, 135.7, 134.3, 129.6, 128.6, 128.0, 127.5, 126.6, 125.3, 125.0, 123.9, 114.6, 101.9, 64.1, 46.3, 44.1, 41.0, 30.4, 22.0, 18.6. **HRMS** (ESI) m/z Calcd for $C_{23}H_{23}ClNO_3$ $[M+H]^+$: 396.1367; Found: 396.1361.



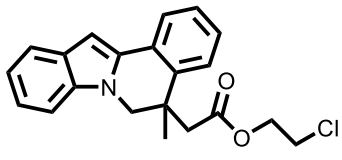
2-chloroethyl 2-(9,11-difluoro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4f): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 43.6 mg, 54% yield. Yellow solid. Melting point: 110.0 – 111.1 °C. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.8, 1.6 Hz, 1H), 7.87 – 7.86 (m, 1H), 7.40 – 7.34 (m, 3H), 7.10 (s, 1H), 6.83 (td, J = 9.6, 2.4 Hz, 1H), 4.04 (t, J =5.6 Hz, 2H), 3.76 (d, J = 17.6 Hz, 1H), 3.31 (t, J = 5.6 Hz, 2H), 3.21 (d, J = 17.6 Hz, 1H), 1.64 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.8, 170.0, 161.7 (d, J = 11.5 Hz), 160.5 (d, J = 11.1 Hz), 155.6 (d, J = 14.2 Hz), 154.4 (d, J = 14.4 Hz), 137.5, 136.6 (d, J = 15.4 Hz), 135.8 (d, J = 3.9 Hz), 129.5, 127.9, 125.4, 124.3, 124.1, 116.0 (d, J = 20.0 Hz), 100.8 (d, J = 4.2 Hz), 100.6 (d, J = 4.3 Hz), 100.2, 100.0 (d, J = 5.7 Hz), 99.9, 98.3, 64.4, 46.4, 44.3, 41.1, 30.4, 29.8. **HRMS** (ESI) m/z Calcd for $C_{21}H_{17}ClF_2NO_3$ $[M+H]^+$: 404.0865; Found: 404.0860.



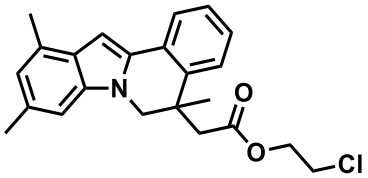
2-chloroethyl 2-(9,11-dichloro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4g): petroleum ether/EtOAc = 20:1 to 5:1 (v/v). New compound. 52.4 mg, 60% yield. Yellow solid. Melting point: 131.2 – 132.3 °C. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.54 – 8.53 (m, 1H), 7.90 (dd, J = 5.4, 0.8 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.35 (dd, J = 8.0, 1.6 Hz, 1H), 7.33 (d, J = 1.6 Hz, 1H), 7.12 (s, 1H), 4.04 (td, J = 5.6, 3.2 Hz, 2H), 3.76 (d, J = 16.8 Hz, 1H), 3.32 (t, J = 5.6 Hz, 2H), 3.21 (d, J = 17.6 Hz, 1H), 1.63 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.8, 170.0, 137.7, 136.7, 135.8, 131.0, 129.8, 128.3, 127.9, 126.1, 125.4, 124.7, 124.5, 124.0, 115.7, 100.9, 64.4, 46.4, 44.2, 41.1, 30.3. **HRMS** (ESI) m/z Calcd for $C_{21}H_{17}Cl_3NO_3$ $[M+H]^+$: 436.0274; Found: 436.0269.



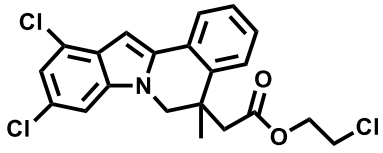
propyl 2-(2-fluoro-5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate(4h): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 40.2 mg, 55% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.57 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, J = 8.8, 2.4 Hz, 1H), 7.40 (td, J = 7.2, 0.8 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.31 (dd, J = 8.8, 5.6 Hz, 1H), 7.07 (dd, J = 8.0, 2.4 Hz, 1H), 7.05 (s, 1H), 4.05 – 4.02 (m, 2H), 3.79 (d, *J* = 17.6 Hz, 1H), 3.31 – (m, 2H), 3.15 (d, *J* = 17.6 Hz, 1H), 1.62 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 172.2, 169.9, 161.9 (d, *J* = 245.2 Hz), 135.6, 134.4 (d, *J* = 2.9 Hz), 133.5 (d, *J* = 2.4 Hz), 130.4, 127.4 (d, *J* = 8.6 Hz), 126.7, 125.8, 124.8, 120.9, 116.8, 110.4, 110.3, 104.4, 64.3, 46.1, 44.3, 41.1, 30.4. **HRMS** (ESI) m/z Calcd for $C_{21}H_{18}ClFNO_3$ $[M+H]^+$: 386.0959; Found: 386.0954.



propyl 2-(5-methyl-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate(4i): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 44.6 mg, 67% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.78 (dd, J = 14.Z, 7.2 Hz, 2H), 7.71 (td, J = 7.2, 0.8 Hz, 1H), 7.67 (td, J = 8.0, 1.6 Hz, 1H), 7.61 – 7.59 (m, 1H), 7.50 – 7.48 (m, 1H), 5.01 (d, J = 12.0 Hz, 1H), 4.59 – 4.56 (m, 1H), 4.51 – 4.48 (m, 1H), 4.24 (d, J = 12.0 Hz, 1H), 3.92 – 3.86 (m, 2H), 2.93 (d, J = 14.4 Hz, 1H), 2.85 (d, J = 14.4 Hz, 1H), 2.01 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 170.6, 138.8, 137.0, 135.0, 128.8, 128.1, 128.0, 127.8, 124.9, 124.9, 122.0, 120.9, 120.1, 109.2, 97.0, 64.1, 49.3, 43.0, 41.5, 37.9, 22.9. **HRMS** (ESI) m/z Calcd for $C_{21}H_{21}ClNO_2$ $[M+H]^+$: 354.1261; Found: 354.1255.

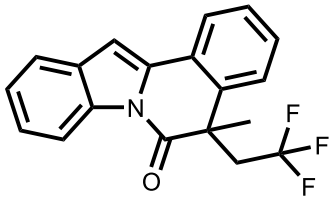


2-chloroethyl 2-(5,9,11-trimethyl-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4j): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 63.4 mg, 83% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.82 (dd, J = 7.7, 1.1 Hz, 1H), 7.43 (dd, J = 7.8, 0.6 Hz, 1H), 7.36 (td, J = 7.2, 0.8 Hz, 1H), 7.30 (td, J = 7.2, 0.8 Hz, 1H), 7.09 (s, 1H), 6.89 (s, 1H), 6.81 (s, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.26 – 4.23 (m, 1H), 4.19 – 4.14 (m, 1H), 3.85 (d, J = 12.0 Hz, 1H), 3.60 – 3.53 (m, 2H), 2.60 (s, 3H), 2.58 (s, 1H), 2.52 (s, 1H), 2.51 (s, 3H), 1.66 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 170.7, 138.5, 137.2, 133.9, 132.1, 130.0, 128.4, 127.7, 127.6, 126.6, 124.9, 124.6, 122.3, 106.8, 95.4, 64.1, 49.4, 42.9, 41.5, 37.9, 22.8, 22.0, 18.8. **HRMS** (ESI) m/z Calcd for $C_{23}H_{25}ClNO_3$ $[M+H]^+$: 382.1574; Found: 382.1568.

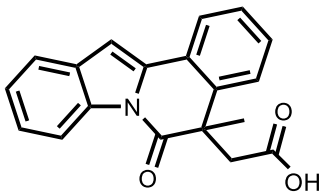


2-chloroethyl 2-(9,11-dichloro-5-methyl-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetate (4k): petroleum ether/EtOAc = 20:1 to 5:1 (v/v).New compound. 61.8 mg, 73% yield. Yellow oil. **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.80 – 7.79 (m, 1H), 7.42 (dd, J

= 7.2, 1.6 Hz, 1H), 7.35 (pd, J = 7.2, 1.6 Hz, 2H), 7.31 (d, J = 0.8 Hz, 1H), 7.12 (d, J = 1.6 Hz, 1H), 6.92 (s, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.28 – 4.26 (m, 1H), 4.21 – 4.18 (m, 1H), 3.82 (d, J = 12.0 Hz, 1H), 3.59 (dt, J = 5.6, 4.8 Hz, 2H), 2.49 (dd, J = 52.8, 14.4 Hz, 2H), 1.62 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 170.4, 138.9, 137.5, 136.2, 128.8, 128.0, 127.6, 127.2, 126.4, 126.3, 125.2, 124.9, 120.3, 108.1, 95.7, 64.3, 49.4, 42.8, 41.6, 37.9, 22.7. **HRMS** (ESI) m/z Calcd for $C_{21}H_{19}Cl_3NO_2$ $[M+H]^+$: 422.0481; Found: 422.0476.



5-methyl-5-(2,2,2-trifluoroethyl)indolo[2,1-*a*]isoquinolin-6(5*H*)-one (5*a*) : petroleum ether/EtOAc = 100:1 to 50:1 (v/v). New compound. 62.5 mg, 76% yield. Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.4 Hz, 1H), 7.90 – 7.88 (m, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.39 (m, 3H), 7.37 (dd, *J* = 14.5, 1.1 Hz, 1H), 7.34 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.07 (s, 1H), 3.48 (dq, *J* = 15.2, 10.5 Hz, 1H), 2.87 (dq, *J* = 15.3, 9.8 Hz, 1H), 1.73 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 171.0, 135.5, 135.3, 135.1, 130.8, 128.8, 128.0, 126.8, 125.6, 125.3(q, J = 279.4 Hz)125.0, 124.4, 124.3, 124.1, 120.7, 116.9, 103.8, 44.9 (q, J = 1.5 Hz), 43.9 (q, J = 27.2 Hz), 31.0. **^{19}F NMR** (565 MHz, $CDCl_3$) δ 16.56. **HRMS** (ESI) m/z Calcd for $C_{19}H_{15}F_3NO$ $[M+H]^+$: 330.1106; Found: 330.1100.



2-(5-methyl-6-oxo-5,6-dihydroindolo[2,1-*a*]isoquinolin-5-yl)acetic acid (5b): petroleum ether/EtOAc = 10:1 to 5:1 (v/v). Known compound, 95.6 mg, 95% yield. Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.52 (d, *J* = 8.0 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.57 – 7.55 (m, 1H), 7.36 – 7.33 (m, 1H), 7.31 –7.30 (m, 1H), 7.29 – 7.27 (m, 2H), 7.24 (s, 1H), 7.22 – 7.19 (m, 1H), 6.96 (s, 1H), 3.66 (d, *J* = 17.7 Hz, 1H),

3.04 (d, *J* = 17.6 Hz, 1H), 1.50 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 176.0, 172.5, 137.5, 135.4, 130.7, 129.0, 127.5, 125.2, 124.9, 124.6, 124.5, 124.2, 120.5, 116.7, 103.2, 46.0, 43.2, 30.6.

5. X-Ray Crystallography Data of 3h and 4a

The suitable crystals were selected on a XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystals were kept at 100.03(10) K during data collection. Using Olex2, the structures were solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimisation.

7. Dolomanov, O. V., Bourhis, L. J., Gildea, R. J, Howard, J. A. K. & Puschmann, H. J. Appl. Cryst. 2009, 42, 339-341.

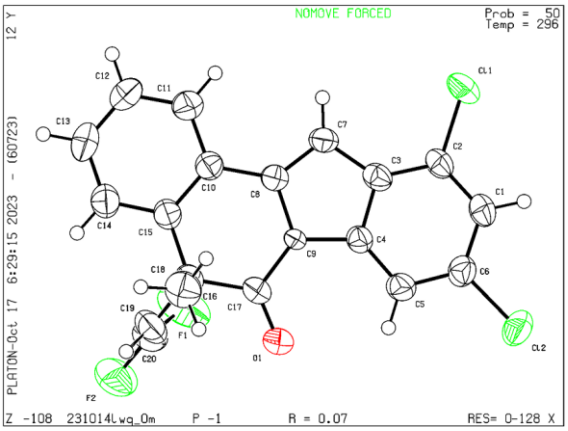
8. Sheldrick, G. M. Acta Cryst. 2015, A71, 3-8.

9. Sheldrick, G. M. Acta Cryst. 2015, C71, 3-8.

Single-crystals suitable for X-ray diffraction analysis were grown from the recrystallization in dichloromethane and petroleum ether (1/1, v/v) at 25 ºC. Thermal ellipsoids of the crystal structures of **3h** was set at 50%.

Identification code	CCDC 2323817
Empirical formula	$C_{20}H_{11}Cl_2F_2O$
Formula weight	376.19
Temperature/K	296.15
Crystal system	triclinic
Space group	P-1
a/Å	8.872(3)
b/Å	10.069(3)
c/Å	10.305(3)
α/°	111.594(5)
β/°	96.066(5)
γ/°	104.973(5)
Volume/Å^3	806.0(4)
Z	2
ρ_{calc}g/cm^3	1.550
μ/mm^{-1}	0.429

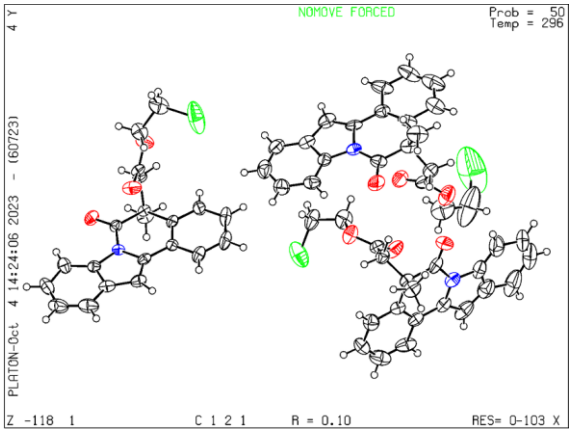
F(000)	382.0
Crystal size/mm^3	0.2 × 0.15 × 0.1
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.862 to 52.74
Index ranges	-11 ≤ h ≤ 11, -12 ≤ k ≤ 10, -12 ≤ l ≤ 12
Reflections collected	4542
Independent reflections	3236 [R_{int} = 0.0198, R_{sigma} = 0.0474]
Data/restraints/parameters	3236/0/227
Goodness-of-fit on F^2	1.065
Final R indexes [I>=2σ (I)]	R_1 = 0.0667, wR_2 = 0.1961
Final R indexes [all data]	R_1 = 0.0962, wR_2 = 0.2202
Largest diff. peak/hole / e Å^{-3}	0.62/-0.40



X-Ray Crystallography Data of 4a

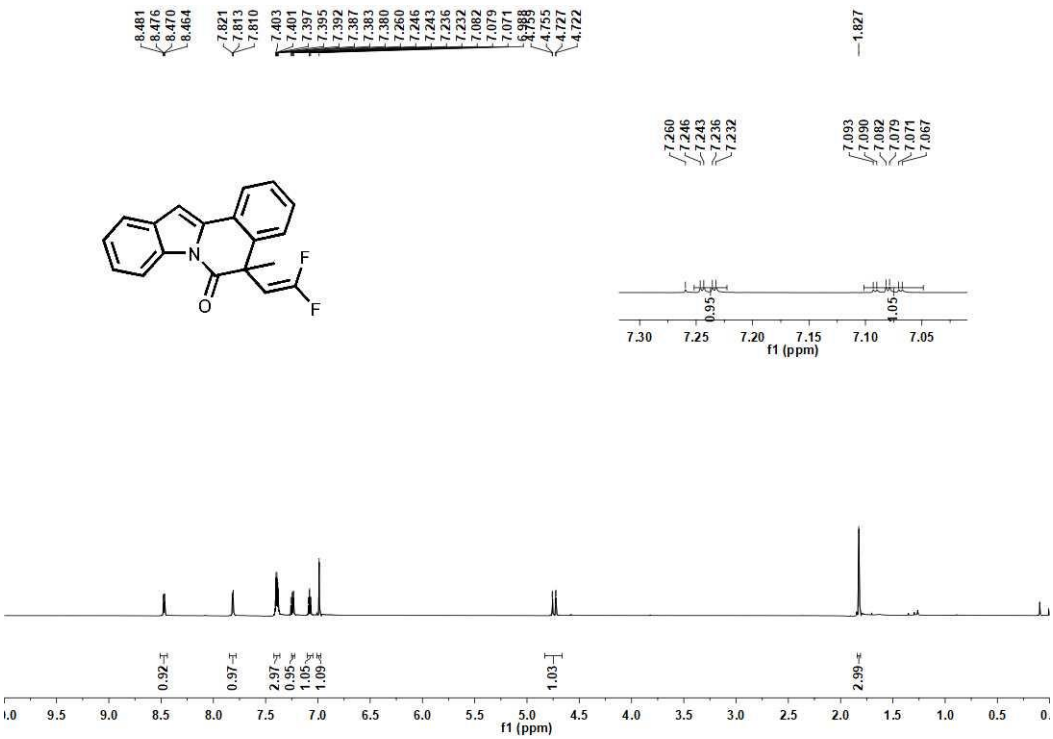
Identification code	CCDC 2323815
Empirical formula	$C_{21}H_{18}ClNO_3$
Formula weight	367.81
Temperature/K	296.15
Crystal system	monoclinic
Space group	C2
a/Å	24.627(8)
b/Å	6.889(2)
c/Å	32.225(11)
α/°	90
β/°	96.899(10)
γ/°	90
Volume/Å^3	5427(3)
Z	12
ρ_{calc}g/cm^3	1.350
μ/mm^{-1}	0.232
F(000)	2304.0
Crystal size/mm^3	? × ? × ?

Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	1.272 to 49.998
Index ranges	$-23 \leq h \leq 29$, $-7 \leq k \leq 8$, $-38 \leq l \leq 38$
Reflections collected	13448
Independent reflections	8455 [R_{int} = 0.0567, R_{sigma} = 0.0864]
Data/restraints/parameters	8455/1/706
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.1045, wR_2 = 0.2818
Final R indexes [all data]	R_1 = 0.1205, wR_2 = 0.2950
Largest diff. peak/hole / e $Å^{-3}$	0.77/-0.42
Flack parameter	0.21(8)

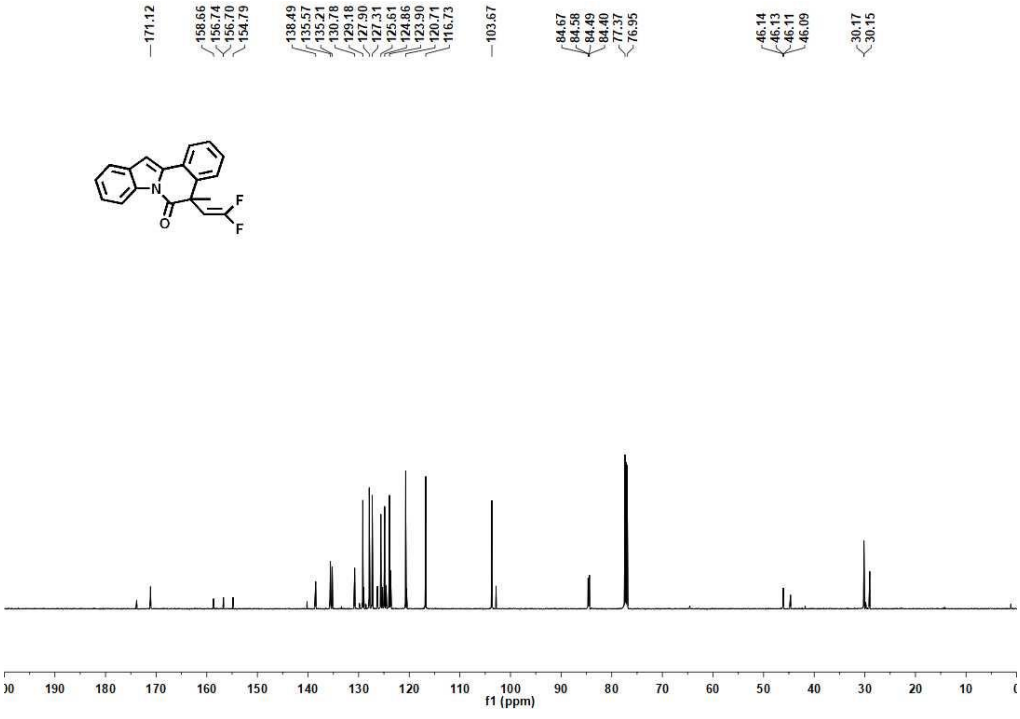


6. NMR Spectra

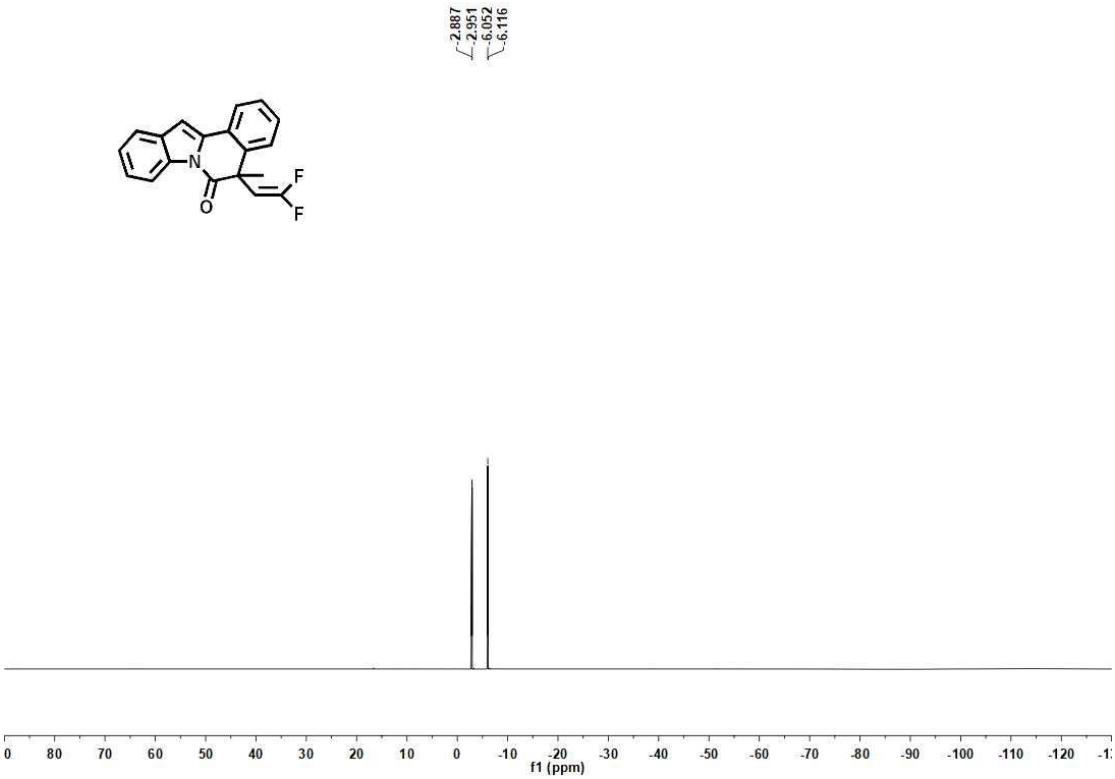
^{1}H NMR of product 3a in $CDCl_3$ (800 MHz)



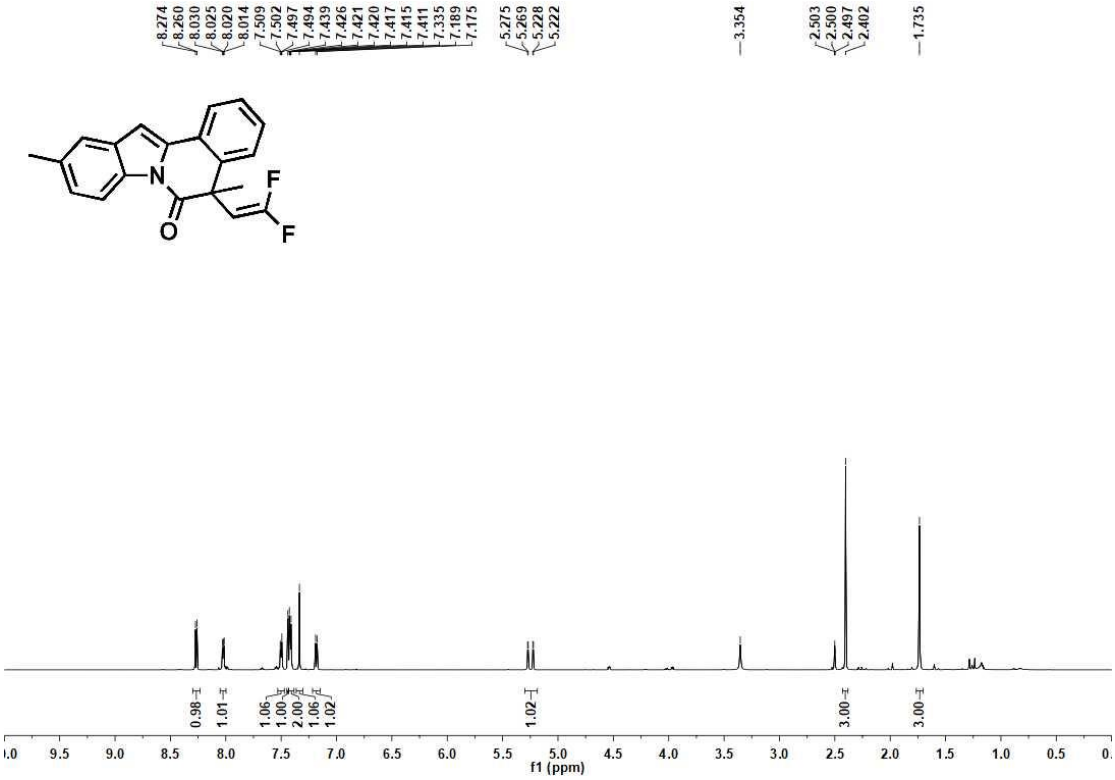
^{13}C NMR of product 3a in $CDCl_3$ (151 MHz)



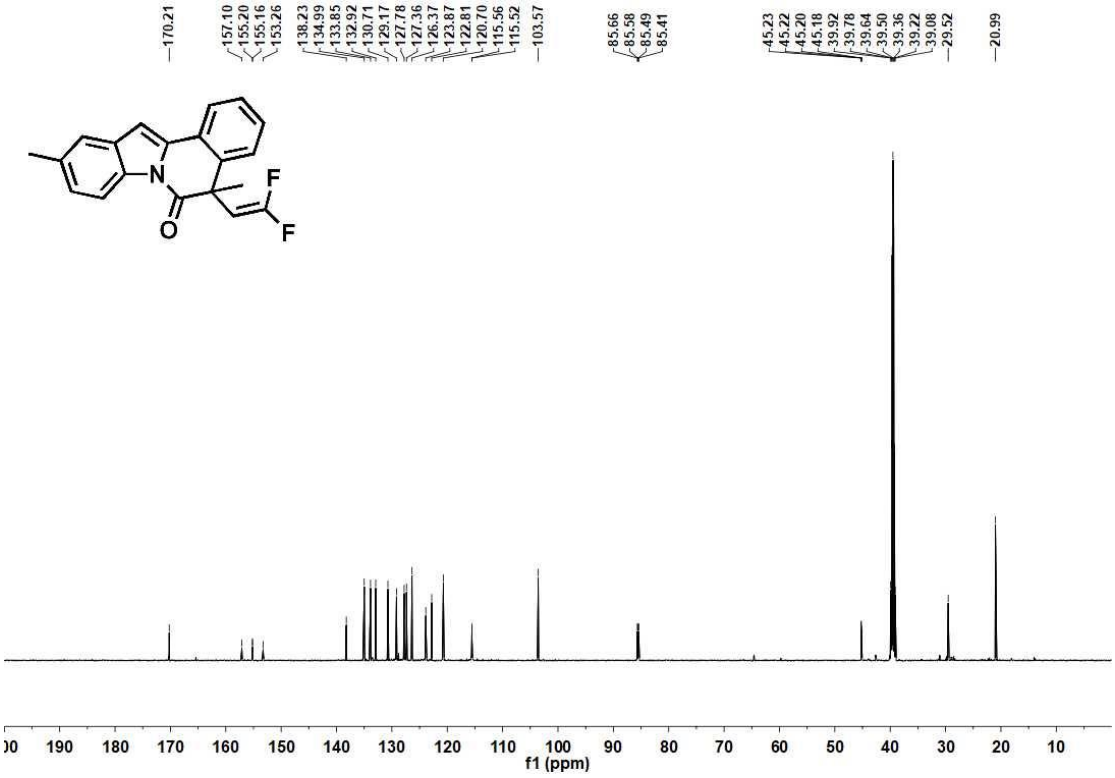
^{19}F NMR of product 3a in DMSO (565 MHz)



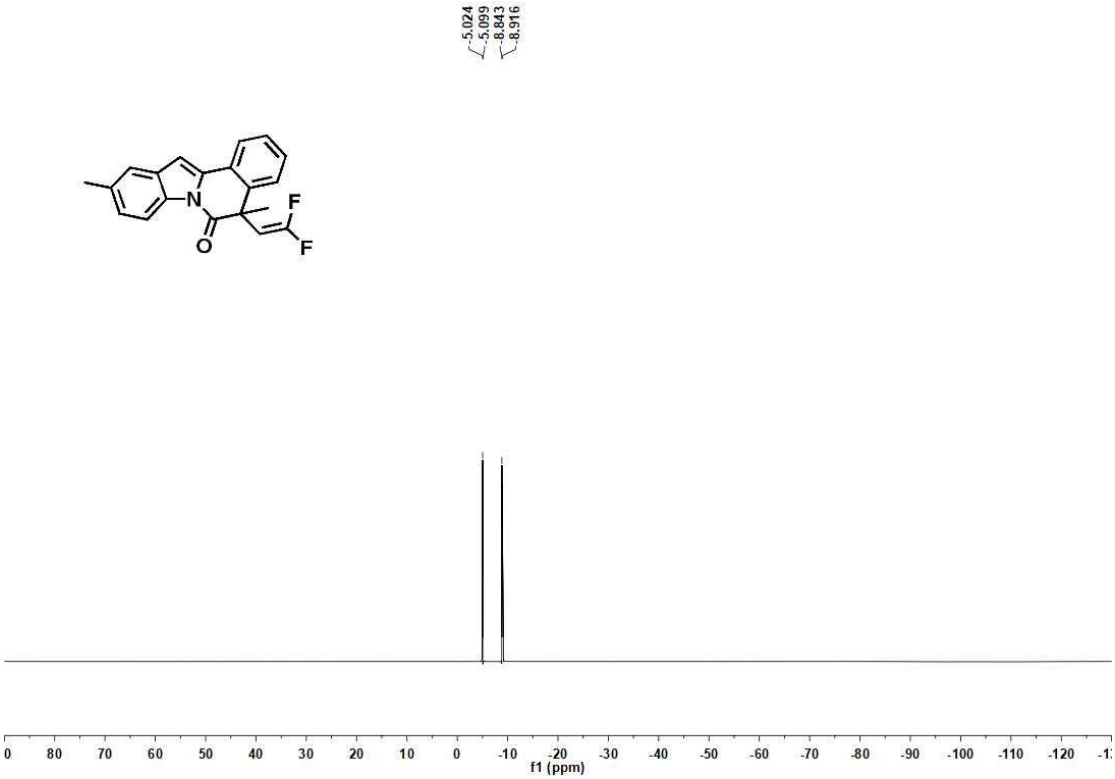
^{1}H NMR of product 3b in DMSO (600 MHz)



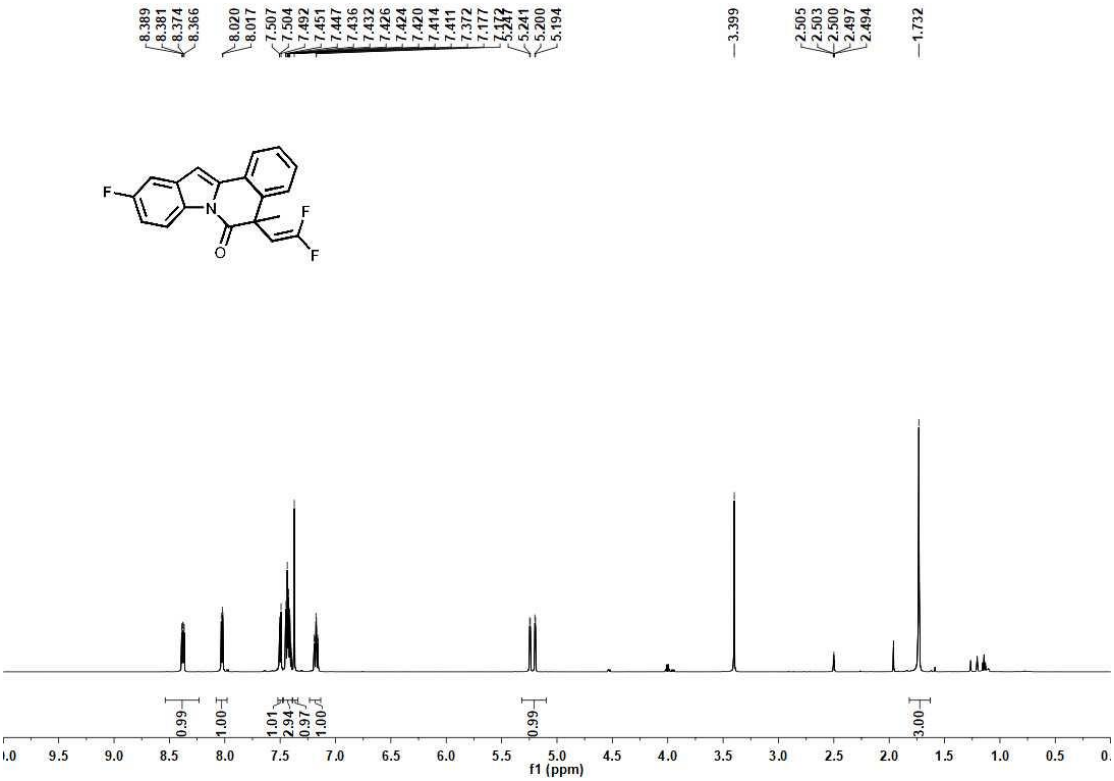
^{13}C NMR of product 3b in DMSO (151 MHz)



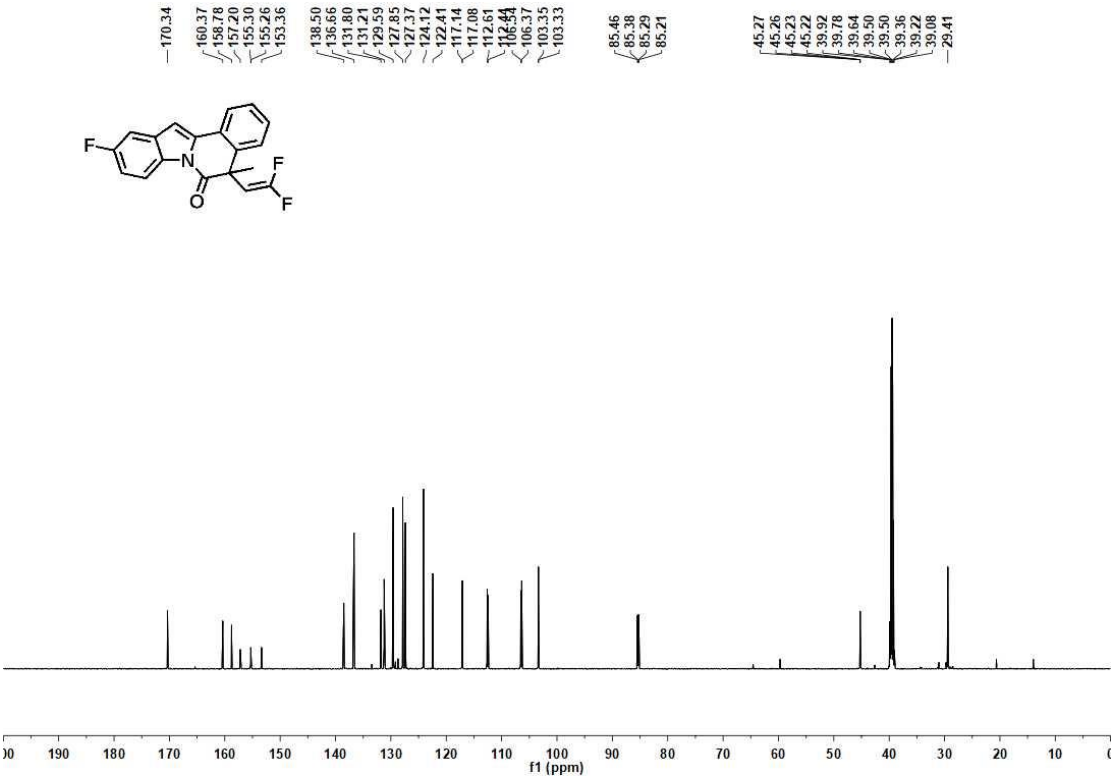
^{19}F NMR of product 3b in DMSO (565 MHz)



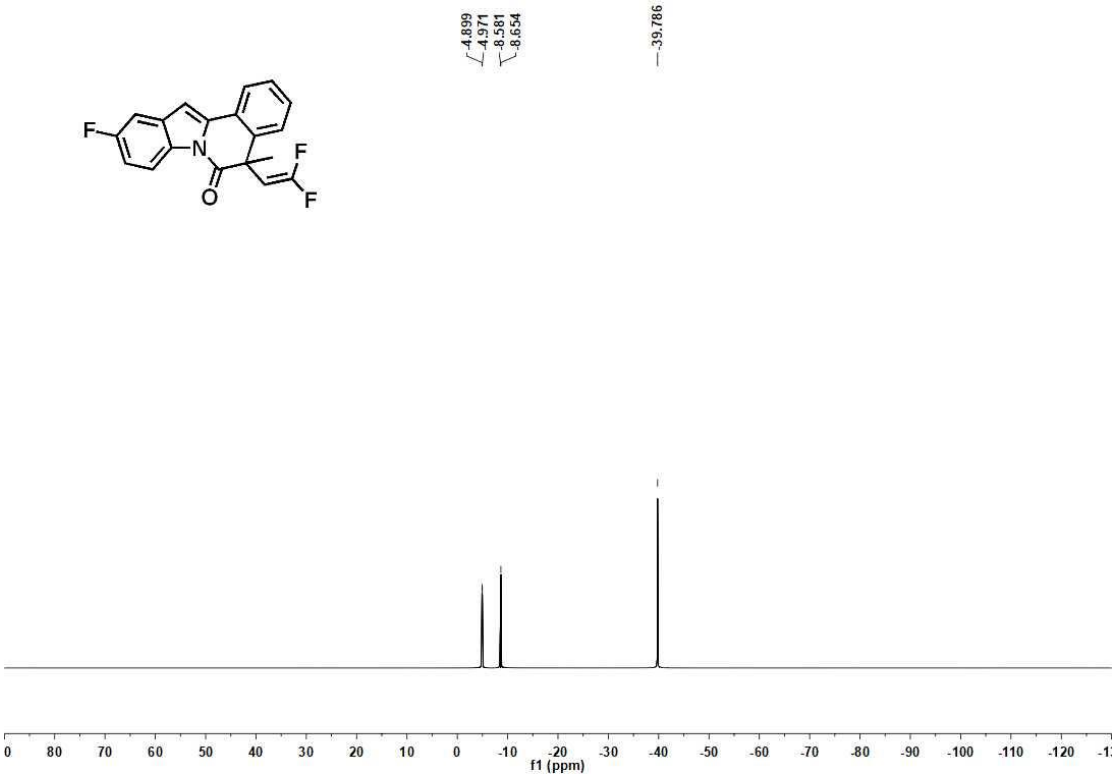
^{1}H NMR of product 3c in DMSO (600 MHz)



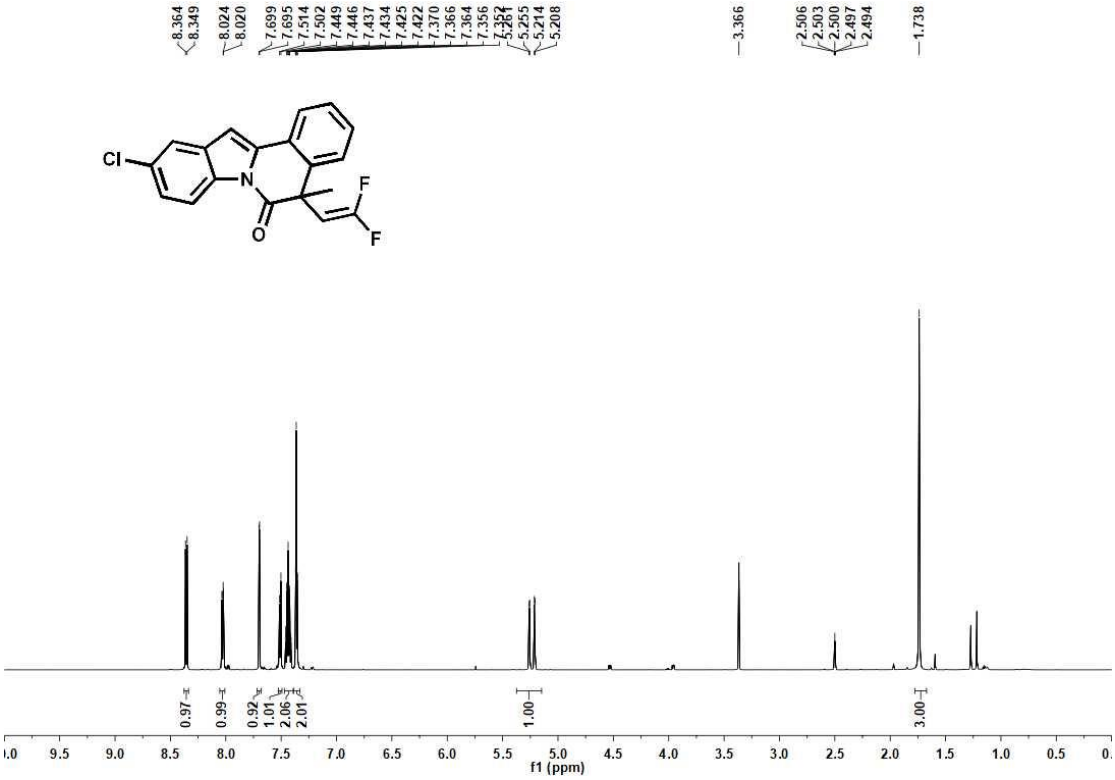
^{13}C NMR of product 3c in DMSO (151 MHz)



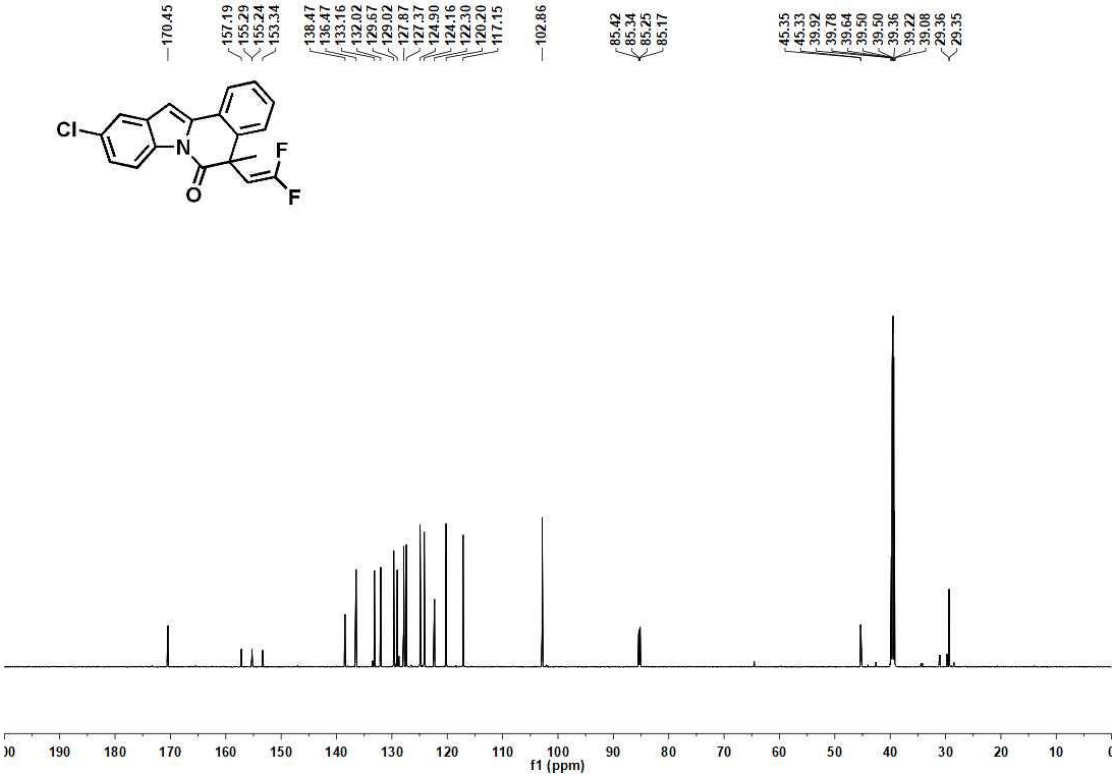
^{19}F NMR of product 3c in DMSO (565 MHz)



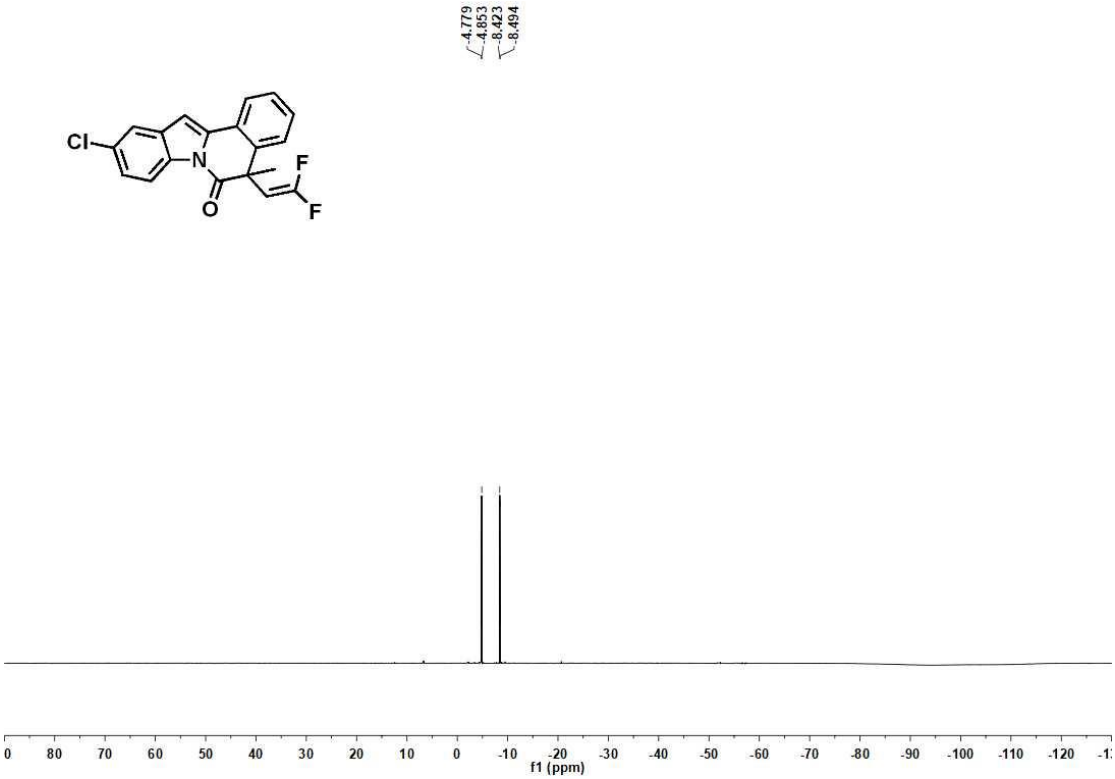
^{1}H NMR of product 3d in DMSO (600 MHz)



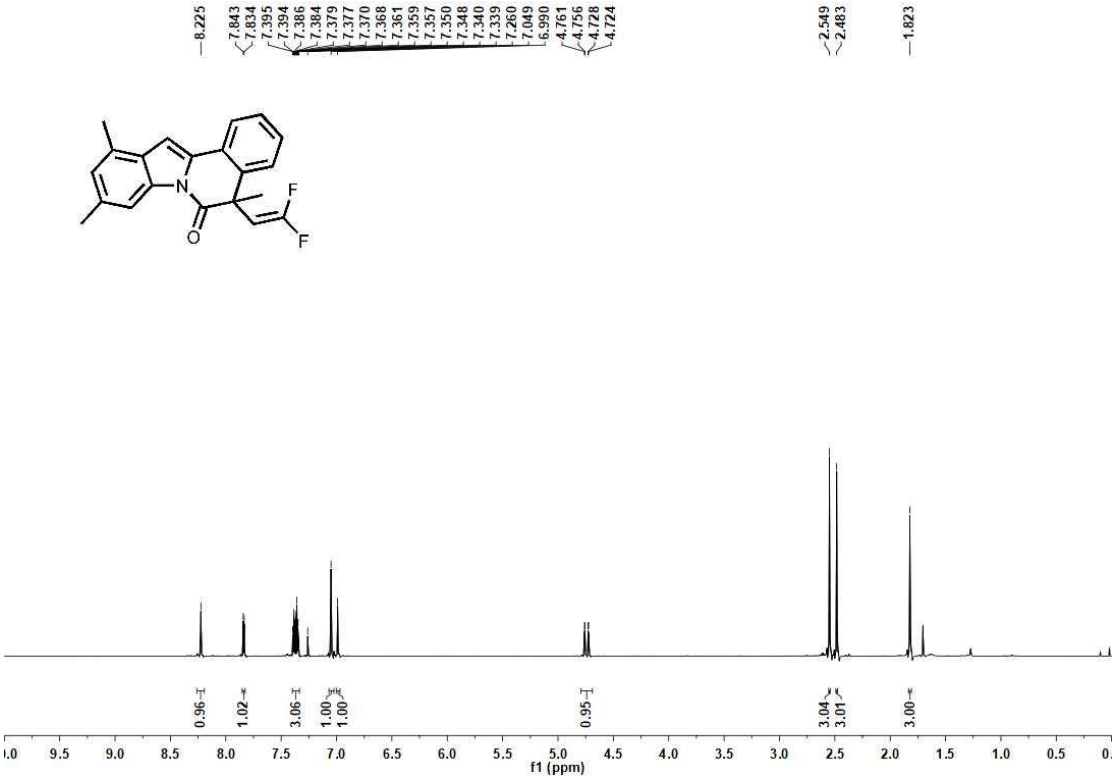
^{13}C NMR of product 3d in DMSO (151 MHz)



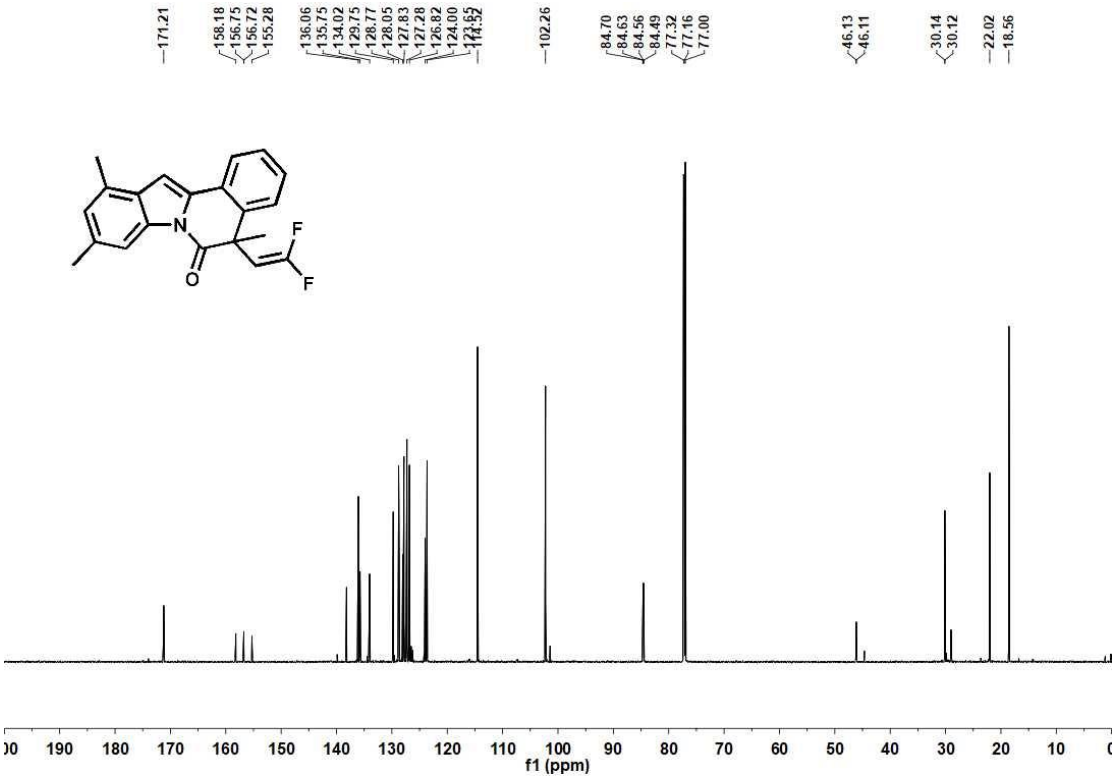
^{19}F NMR of product 3d in DMSO (565 MHz)



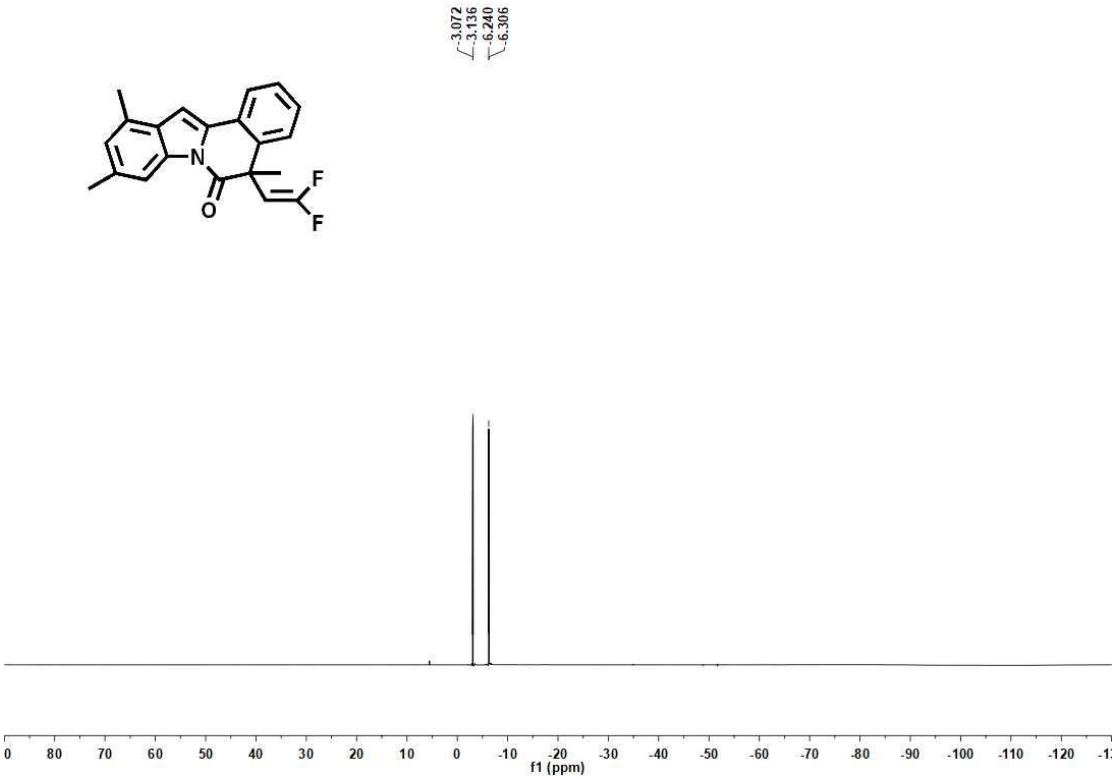
^{1}H NMR of product 3e in $CDCl_3$ (800 MHz)



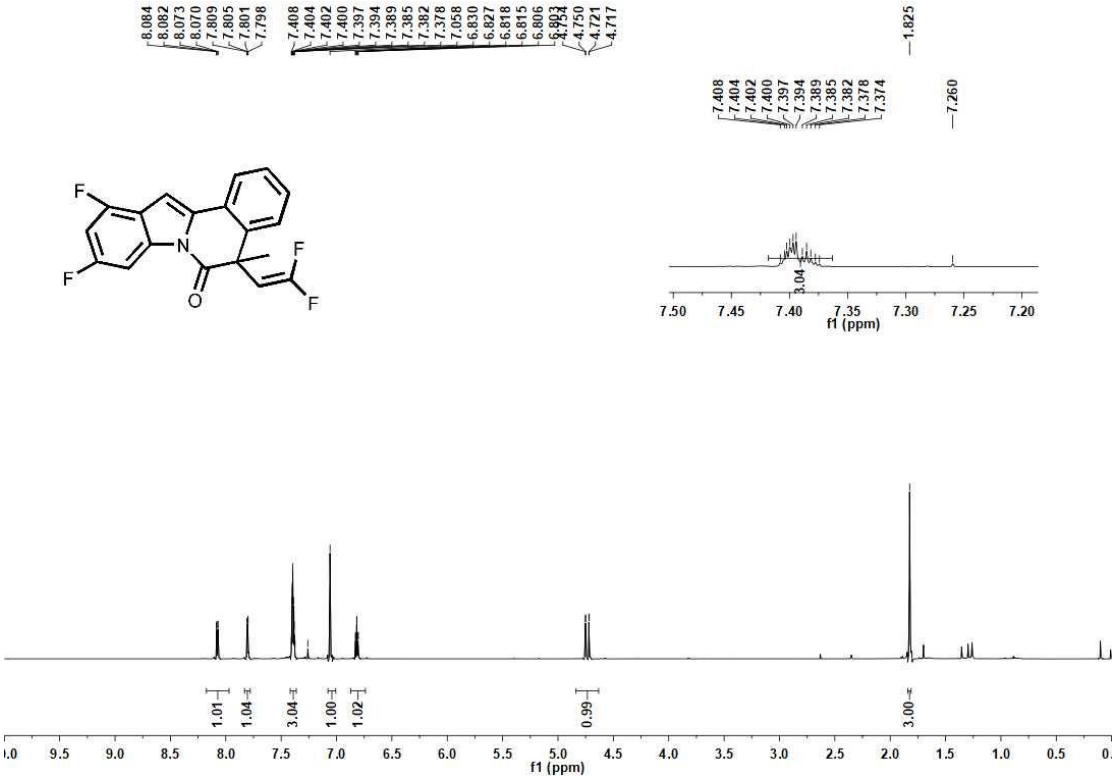
^{13}C NMR of product 3e in $CDCl_3$ (201 MHz)



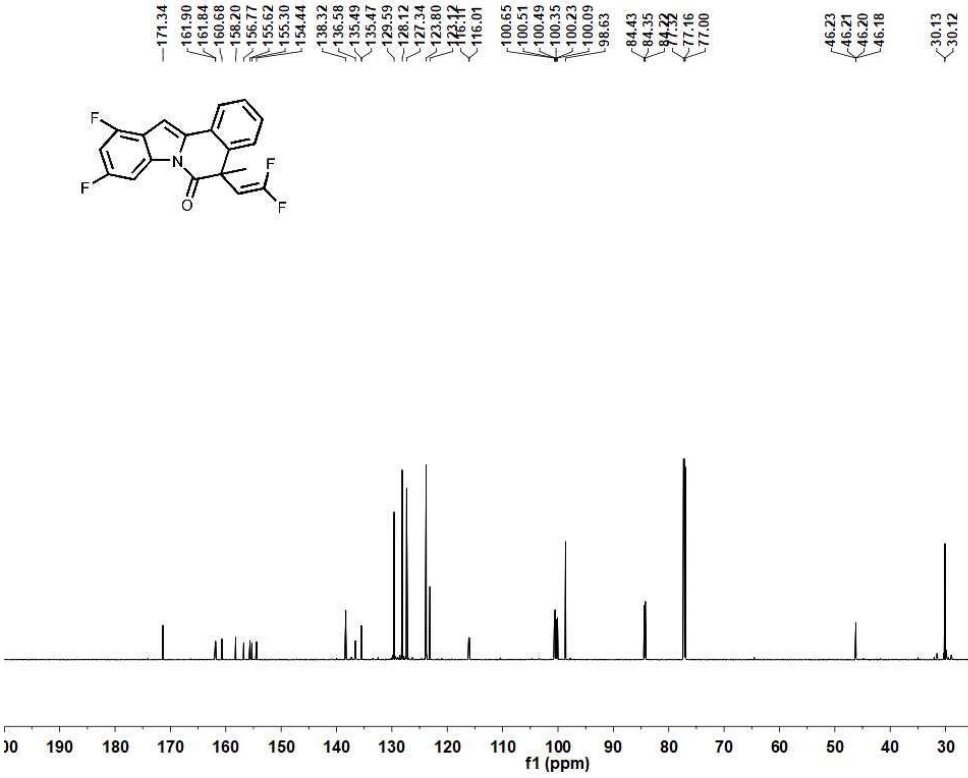
^{19}F NMR of product 3e in DMSO (565 MHz)



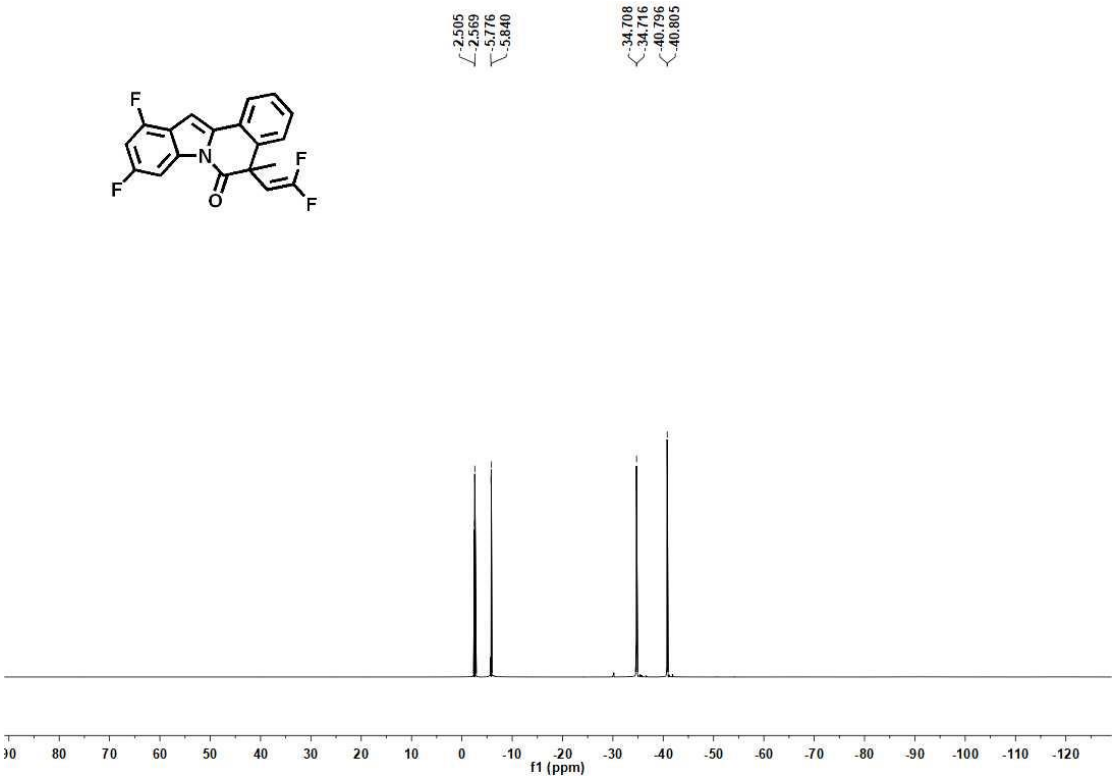
^{1}H NMR of product 3f in $CDCl_3$ (800 MHz)



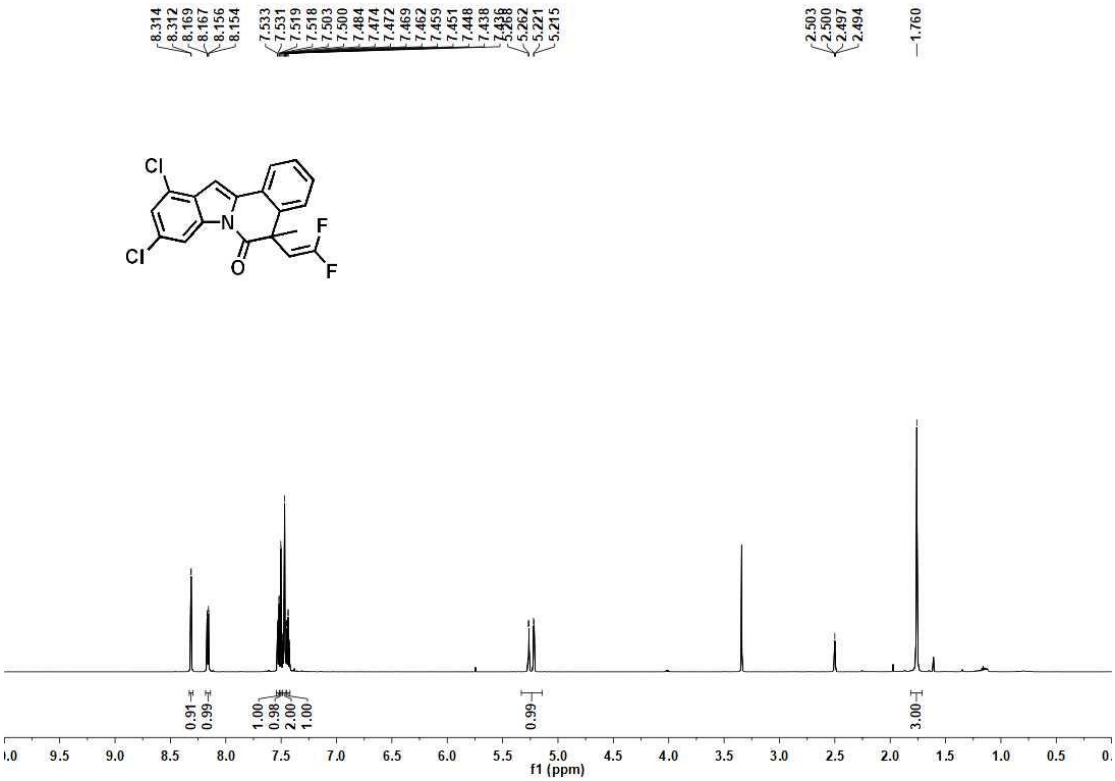
^{13}C NMR of product 3f in $CDCl_3$ (201 MHz)



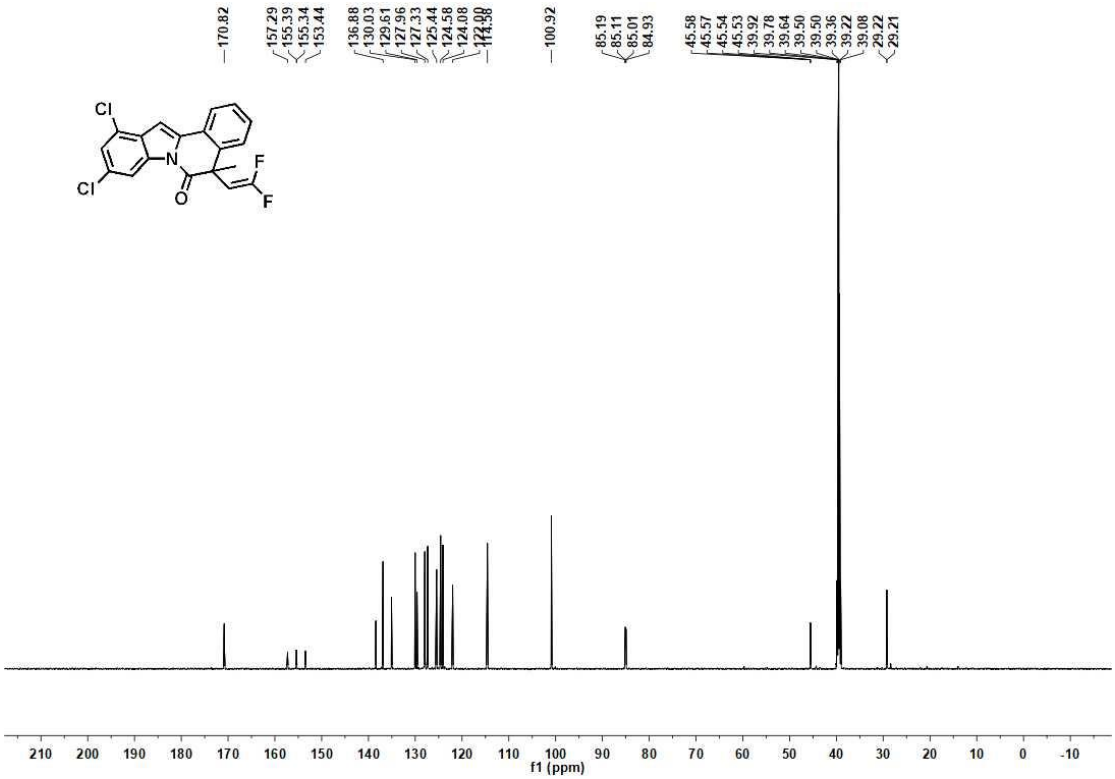
^{19}F NMR of product 3f in DMSO (565 MHz)



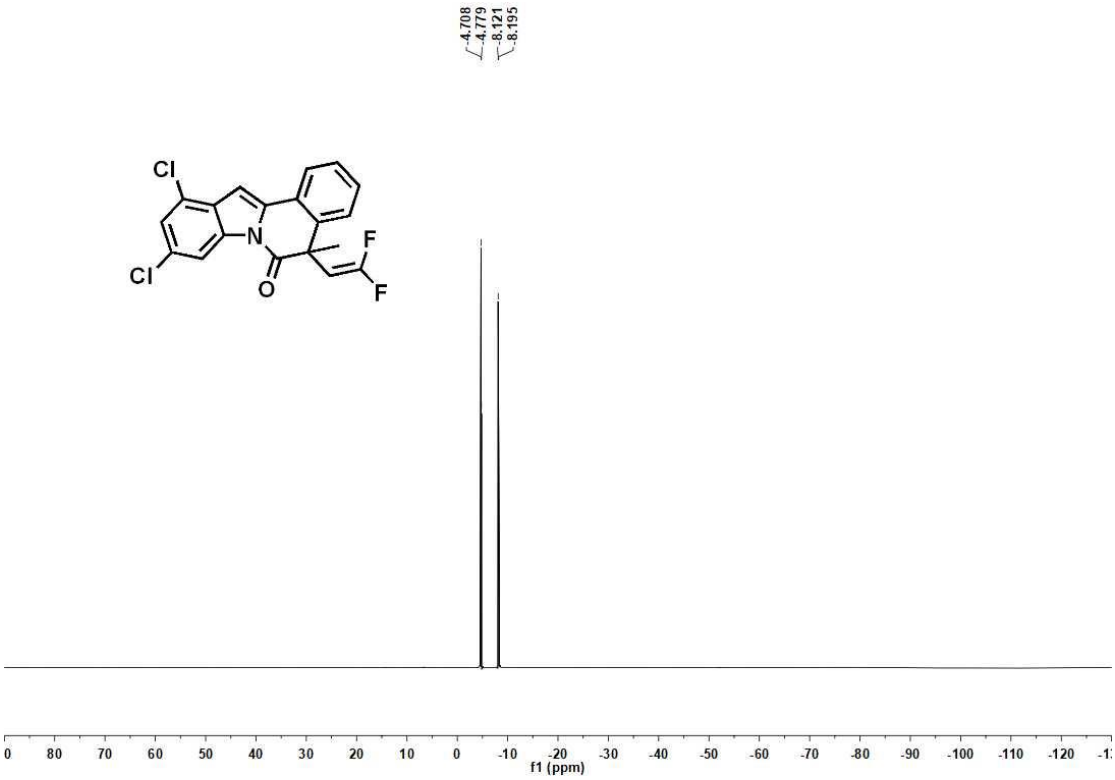
^{1}H NMR of product 3g in DMSO (600 MHz)



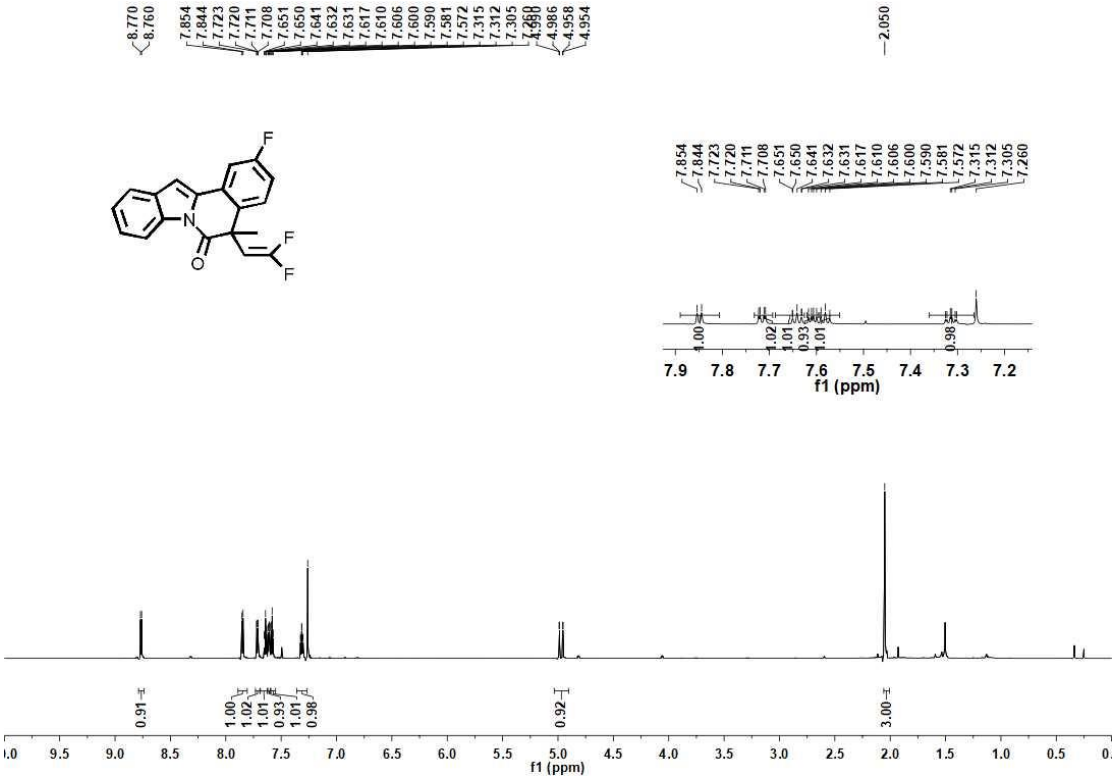
^{13}C NMR of product 3g in DMSO (151 MHz)



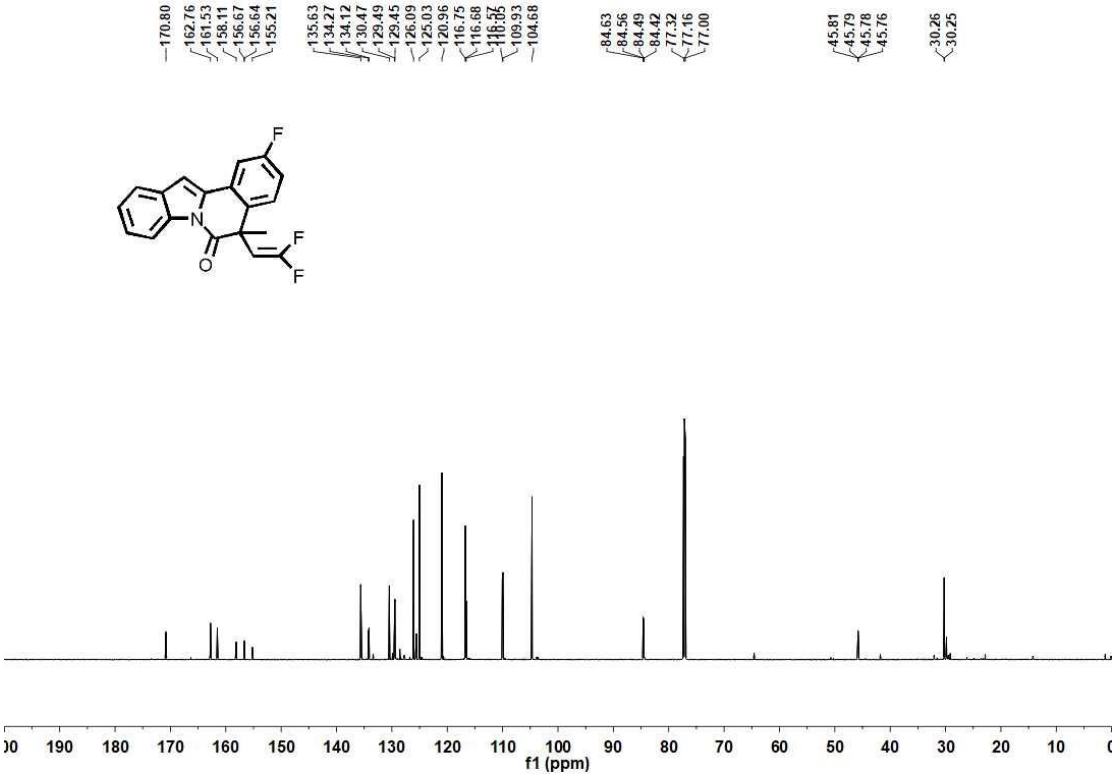
^{19}F NMR of product 3g in DMSO (565 MHz)



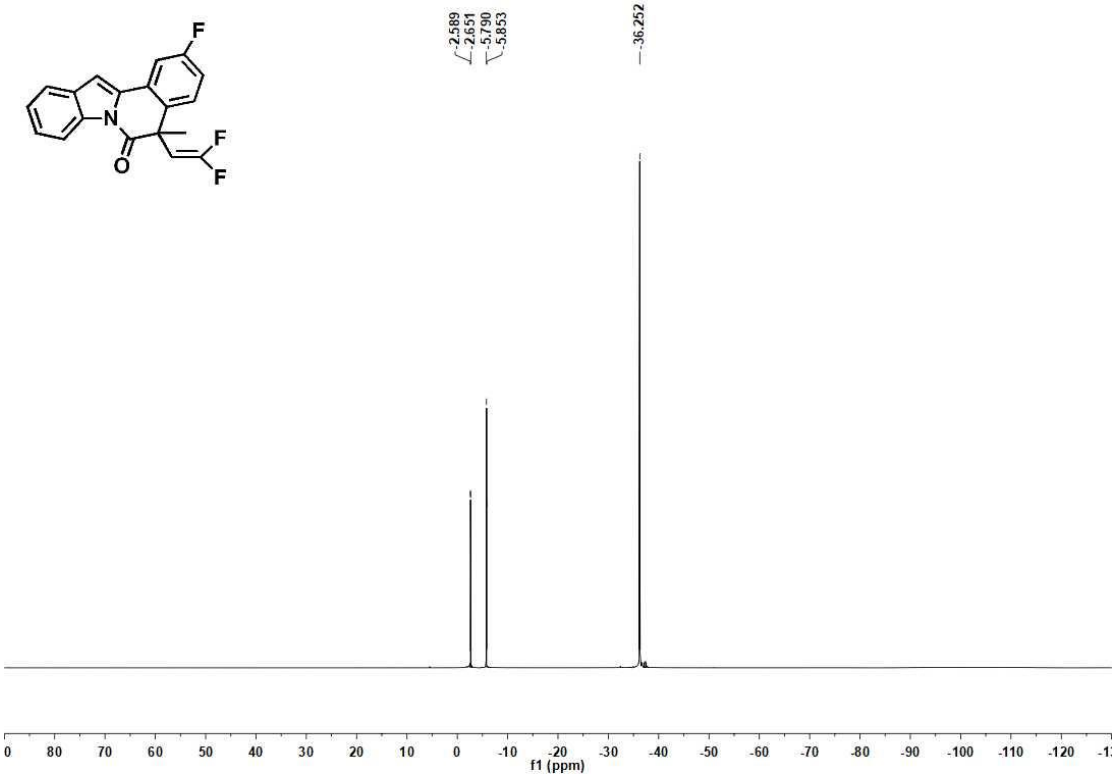
^{1}H NMR of product 3h in $CDCl_3$ (800 MHz)



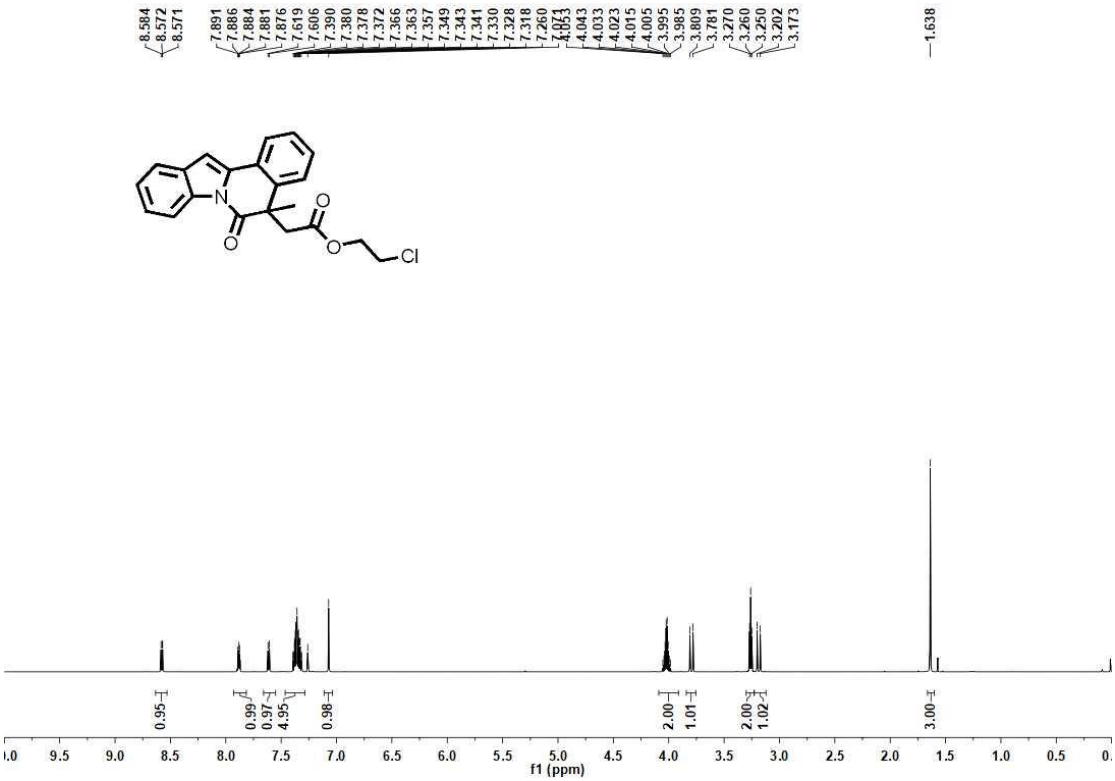
^{13}C NMR of product 3h in $CDCl_3$ (201 MHz)



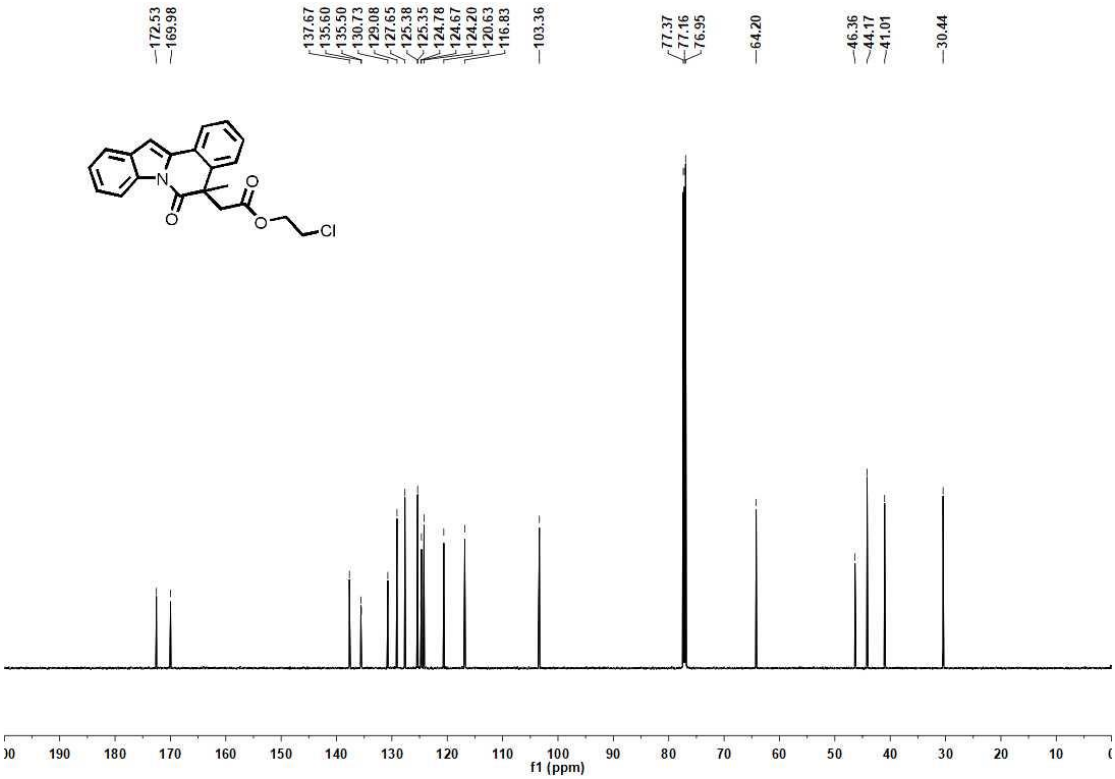
^{19}F NMR of product 3h in DMSO (565 MHz)



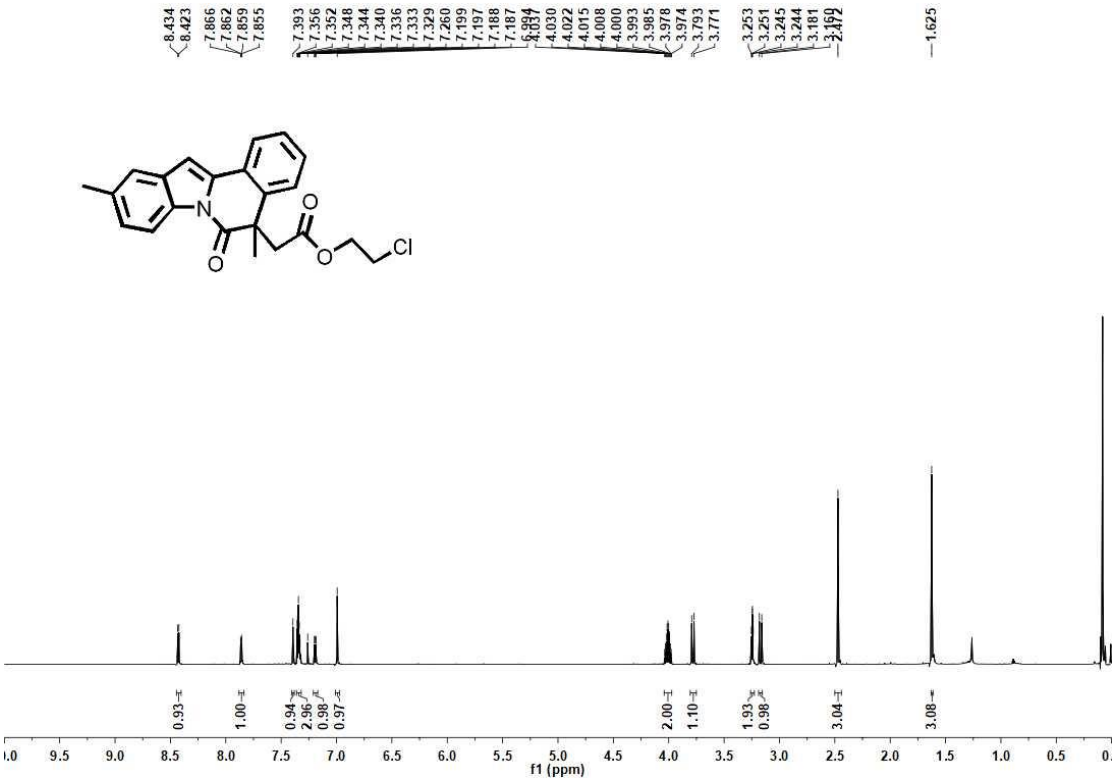
^{1}H NMR of product 4a in $CDCl_3$ (600 MHz)



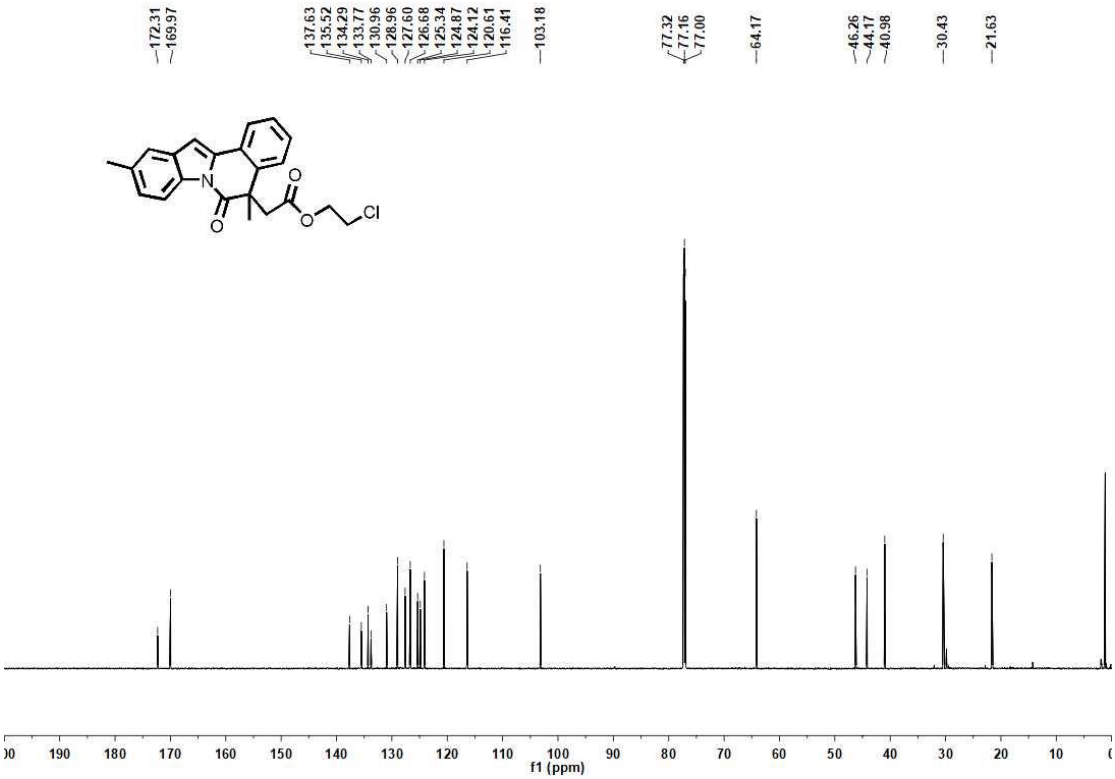
^{13}C NMR of product 4a in $CDCl_3$ (151 MHz)



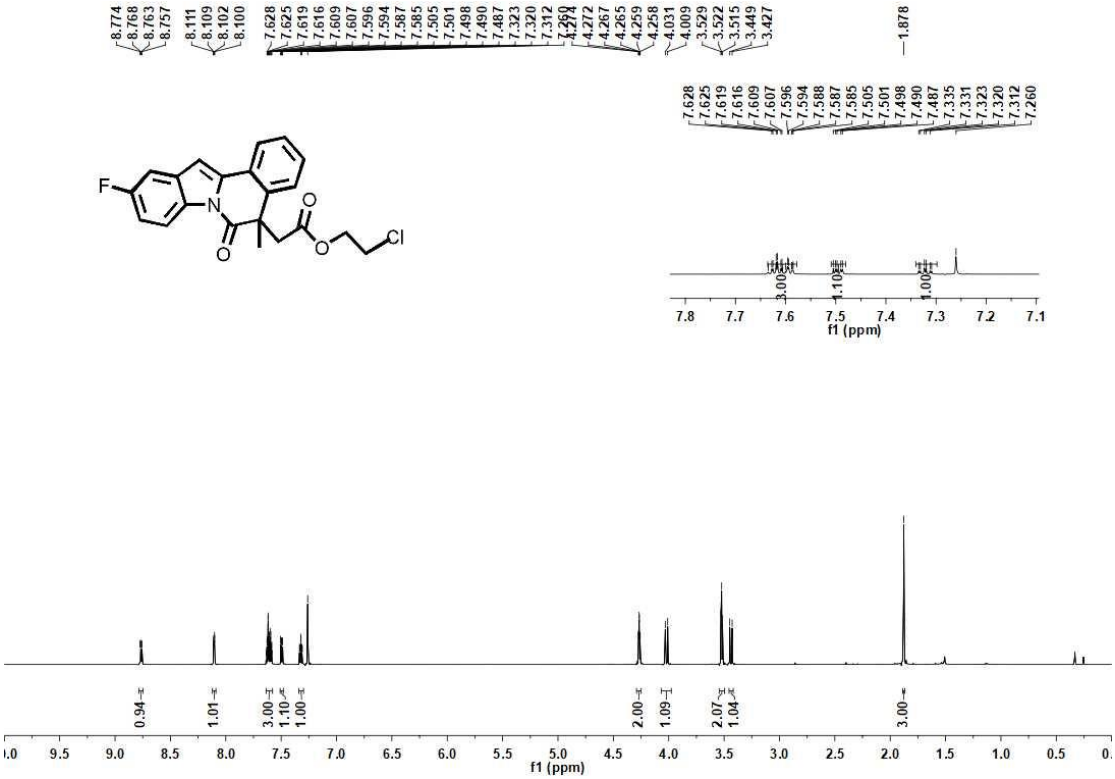
^{1}H NMR of product 4b in $CDCl_3$ (800 MHz)



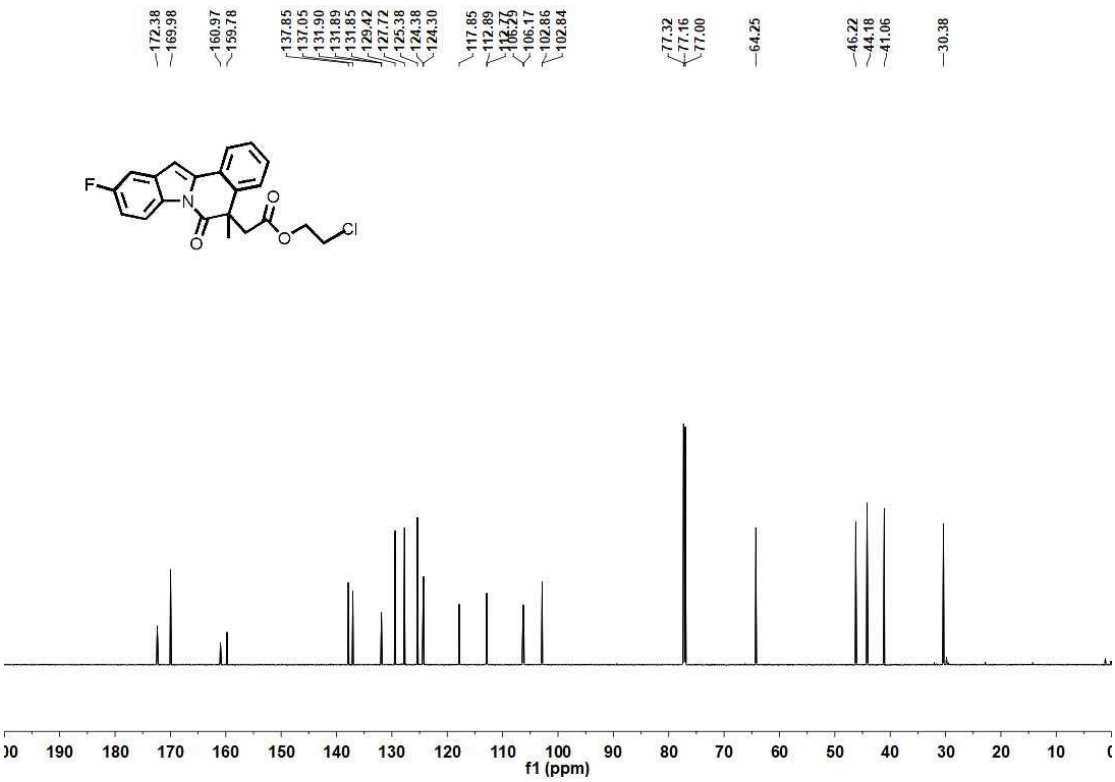
^{13}C NMR of product 4b in $CDCl_3$ (201 MHz)



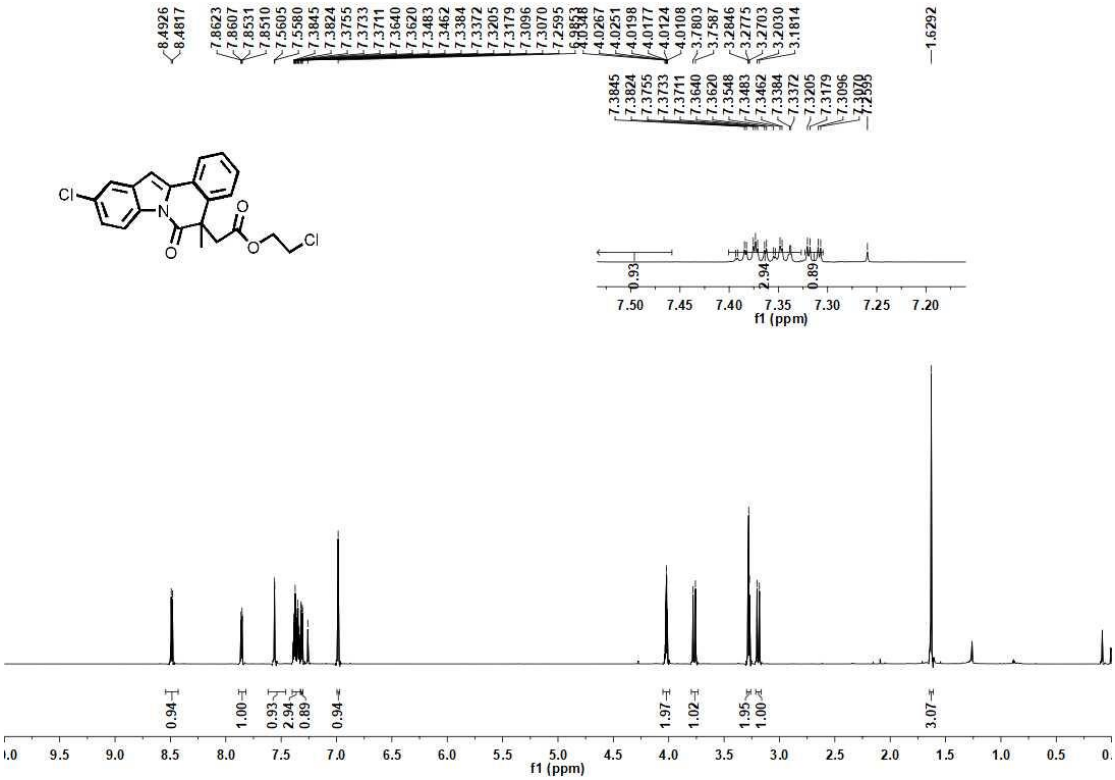
^{1}H NMR of product 4c in $CDCl_3$ (800 MHz)



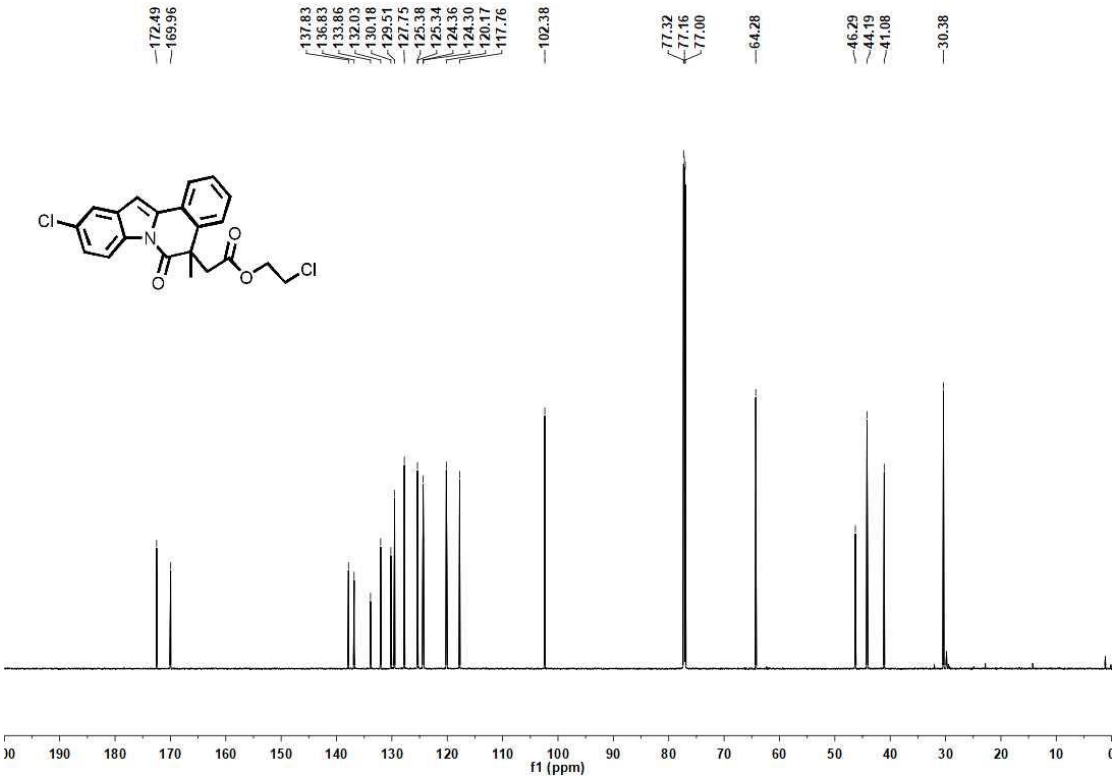
^{13}C NMR of product 4c in $CDCl_3$ (201 MHz)



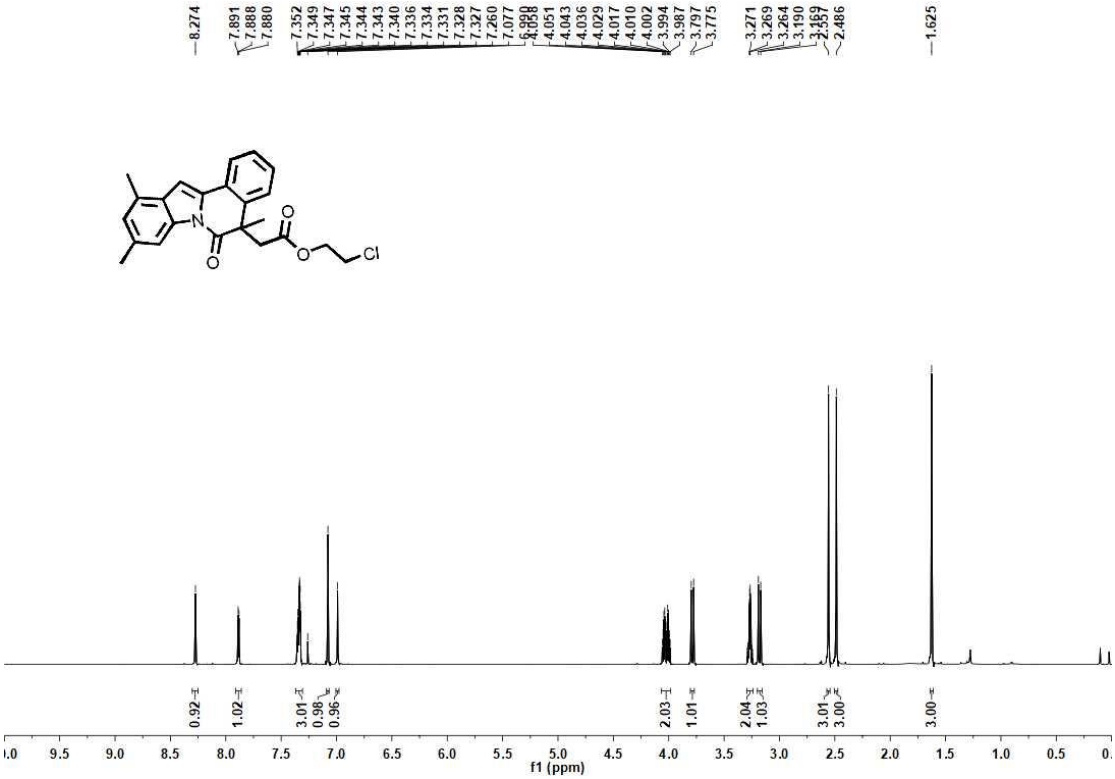
^{1}H NMR of product 4d in $CDCl_3$ (800 MHz)



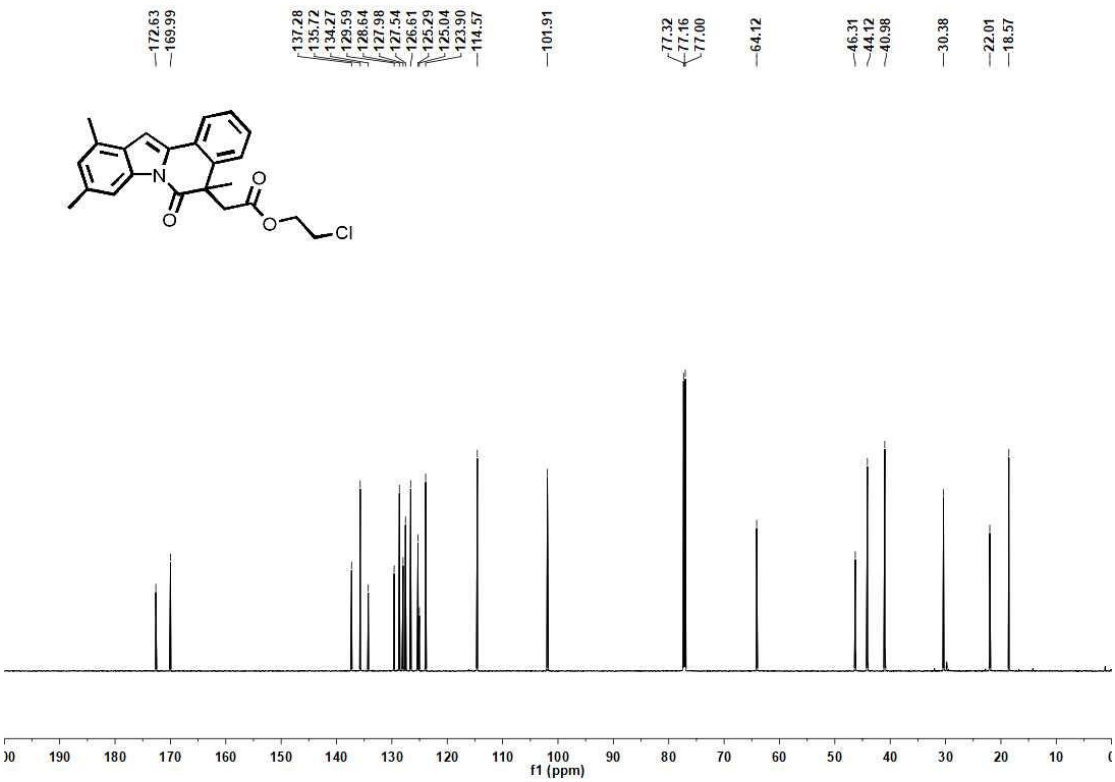
^{13}C NMR of product 4d in $CDCl_3$ (201 MHz)



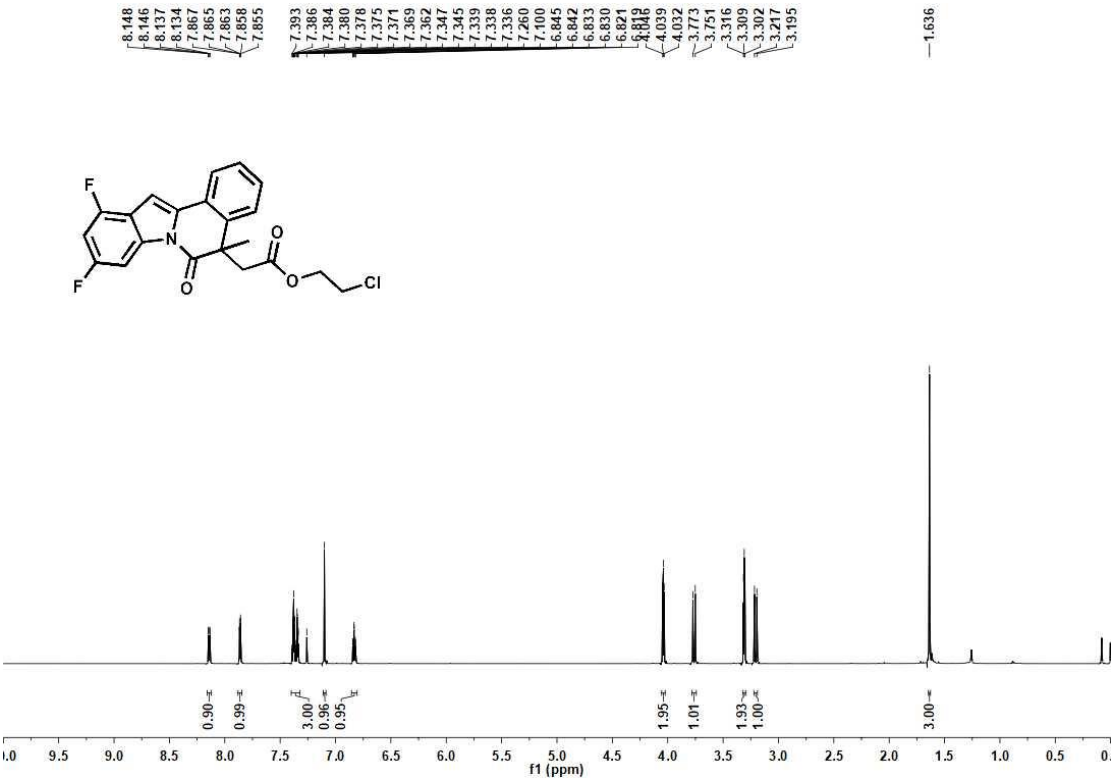
^{1}H NMR of product 4e in $CDCl_3$ (800 MHz)



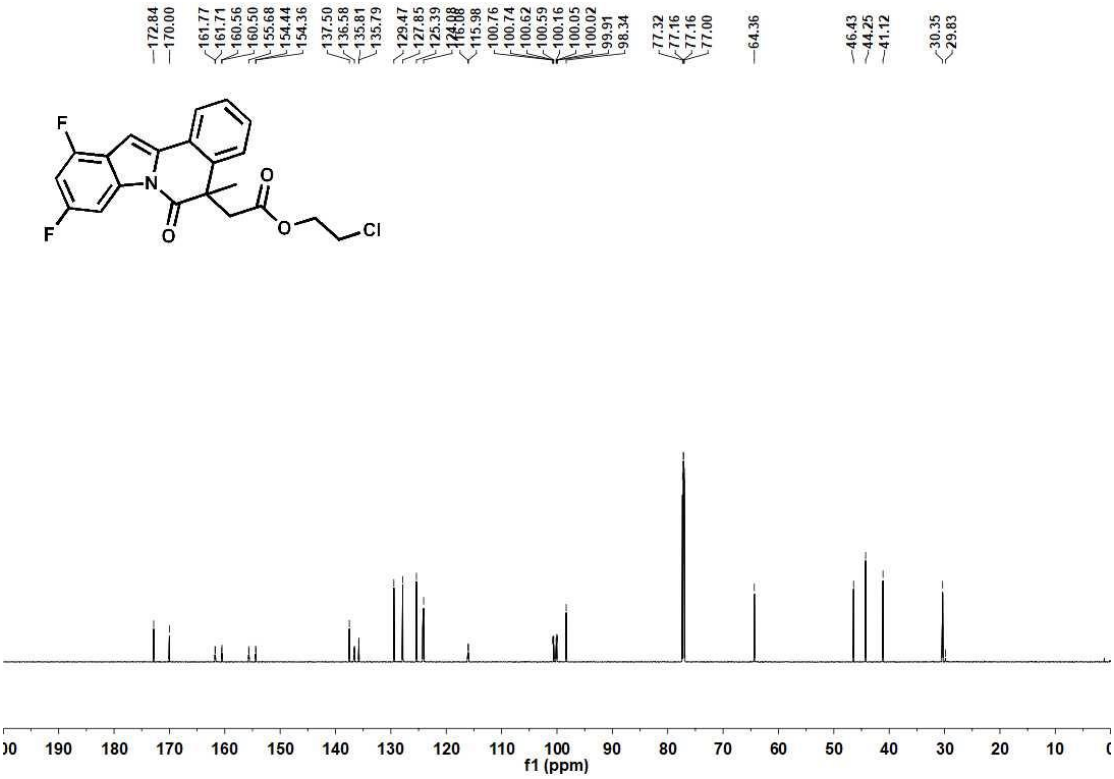
^{13}C NMR of product 4e in $CDCl_3$ (201 MHz)



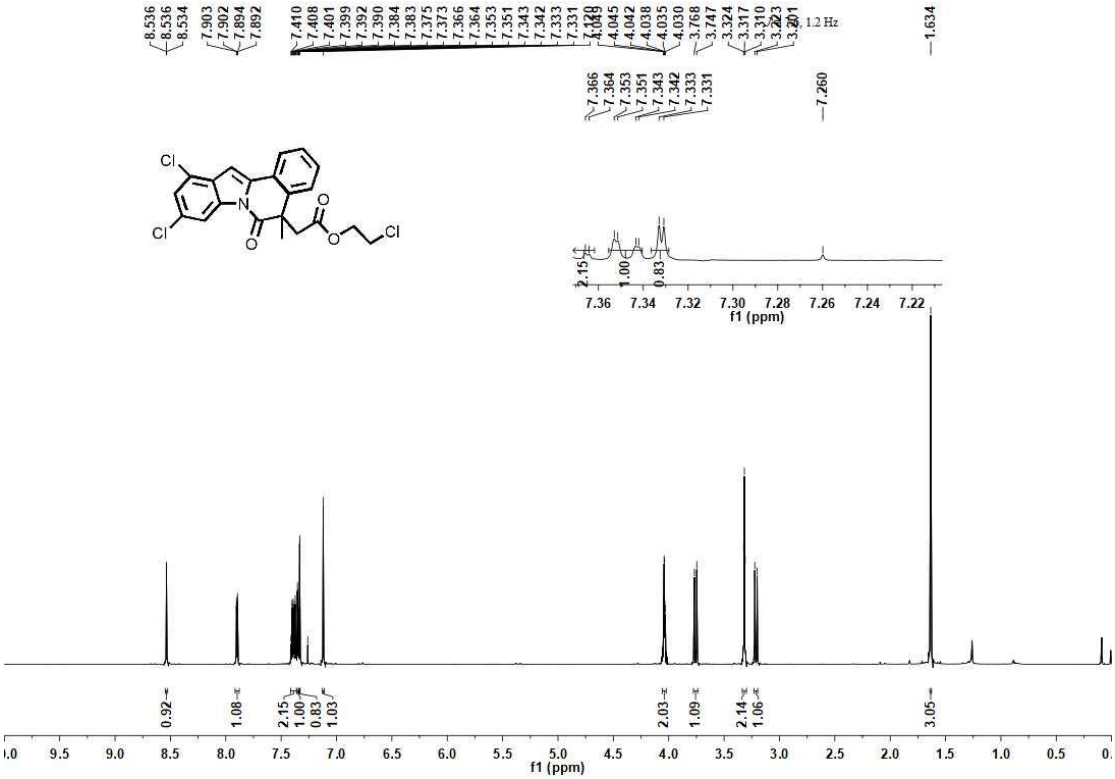
^{1}H NMR of product 4f in $CDCl_3$ (800 MHz)



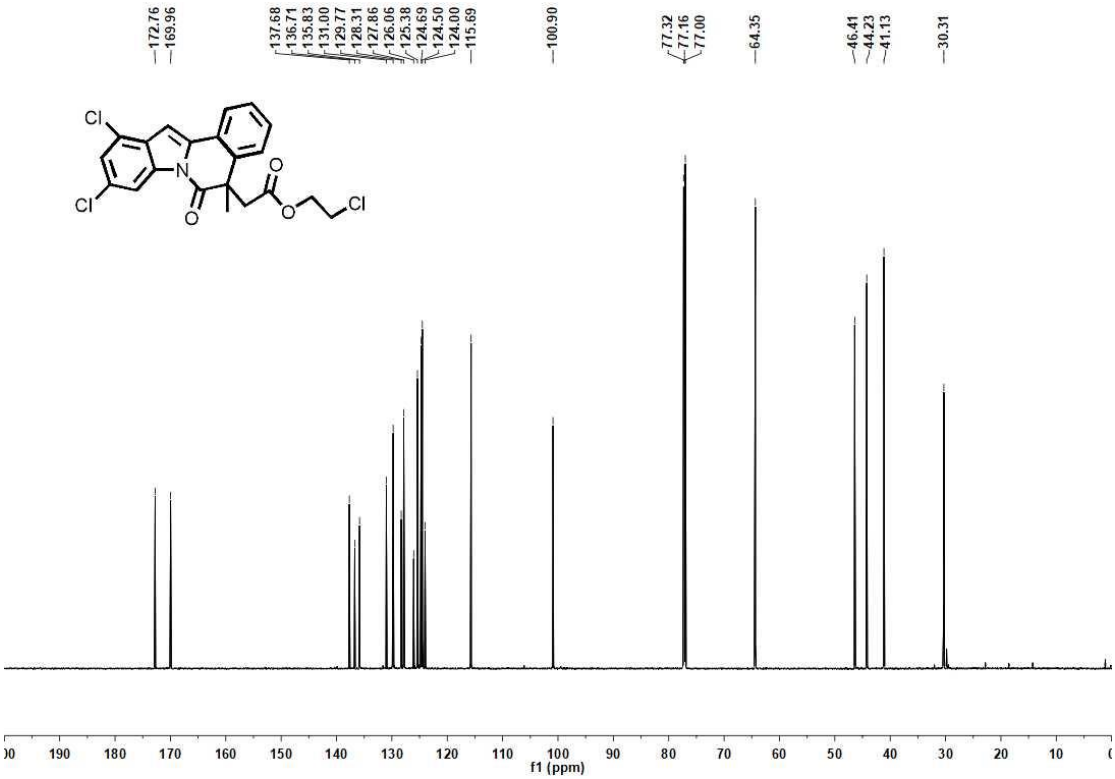
^{13}C NMR of product 4f in $CDCl_3$ (201 MHz)



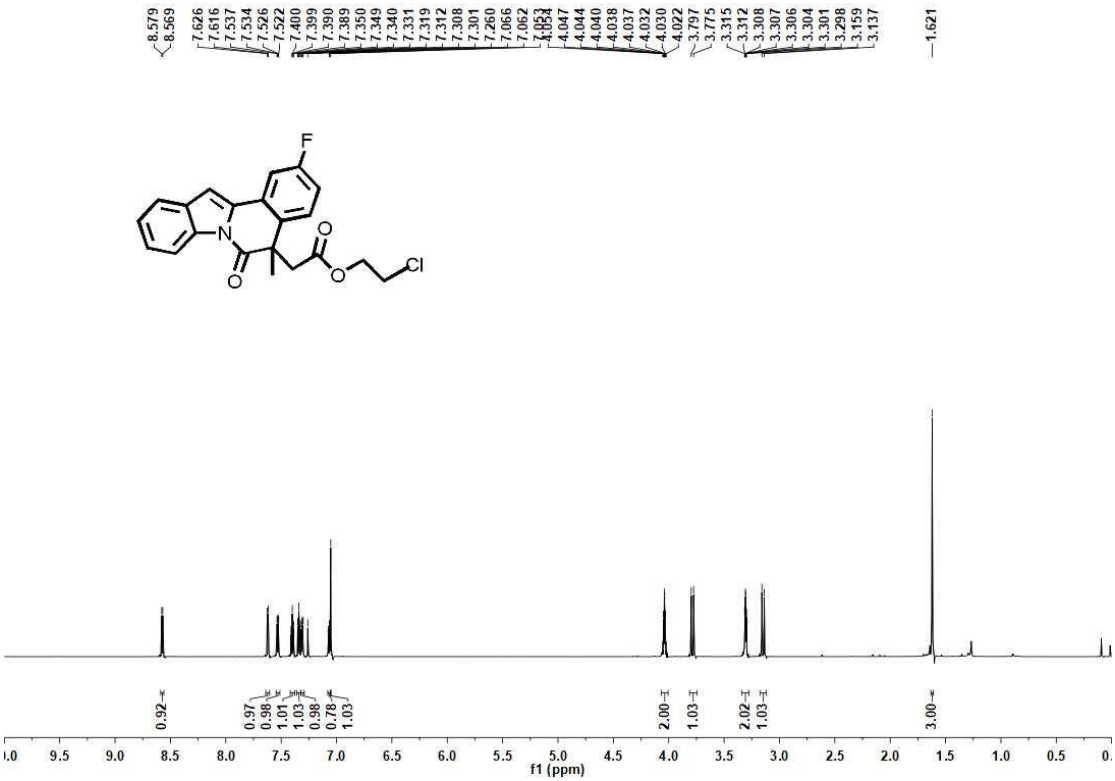
^{1}H NMR of product 4g in $CDCl_3$ (800 MHz)



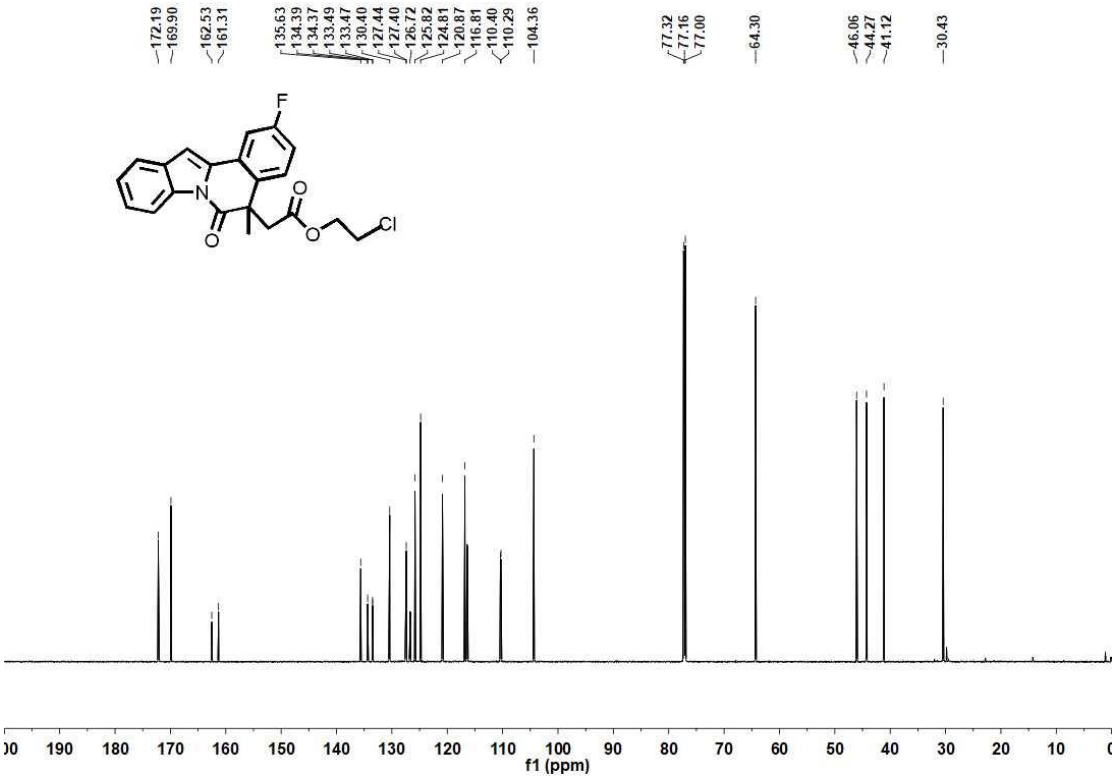
^{13}C NMR of product 4g in $CDCl_3$ (201 MHz)



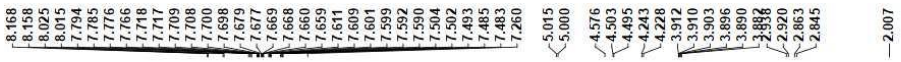
^{1}H NMR of product 4h in $CDCl_3$ (800 MHz)

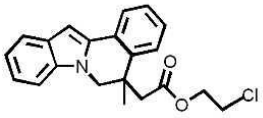


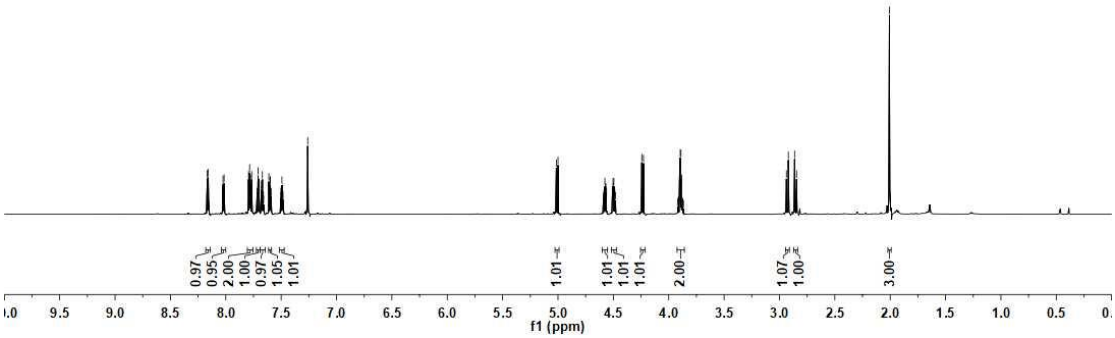
^{13}C NMR of product 4h in $CDCl_3$ (201 MHz)



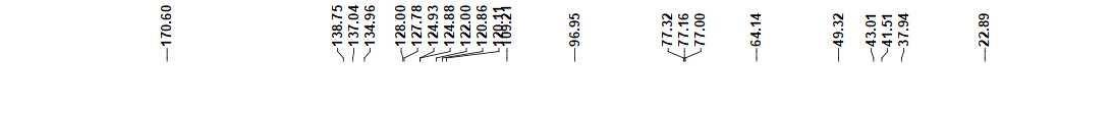
^{1}H NMR of product 4i in $CDCl_3$ (800 MHz)

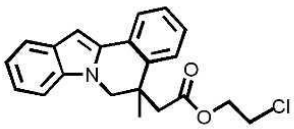


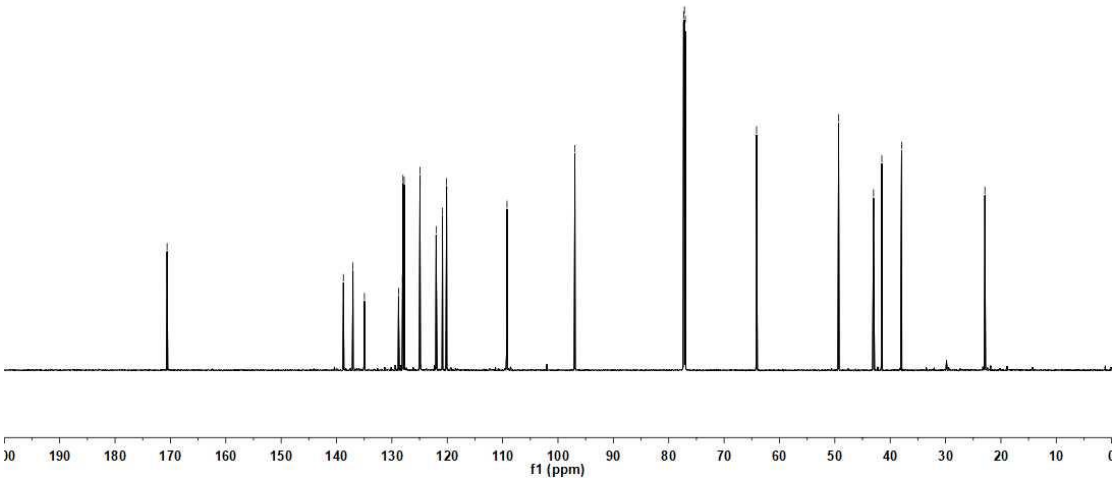




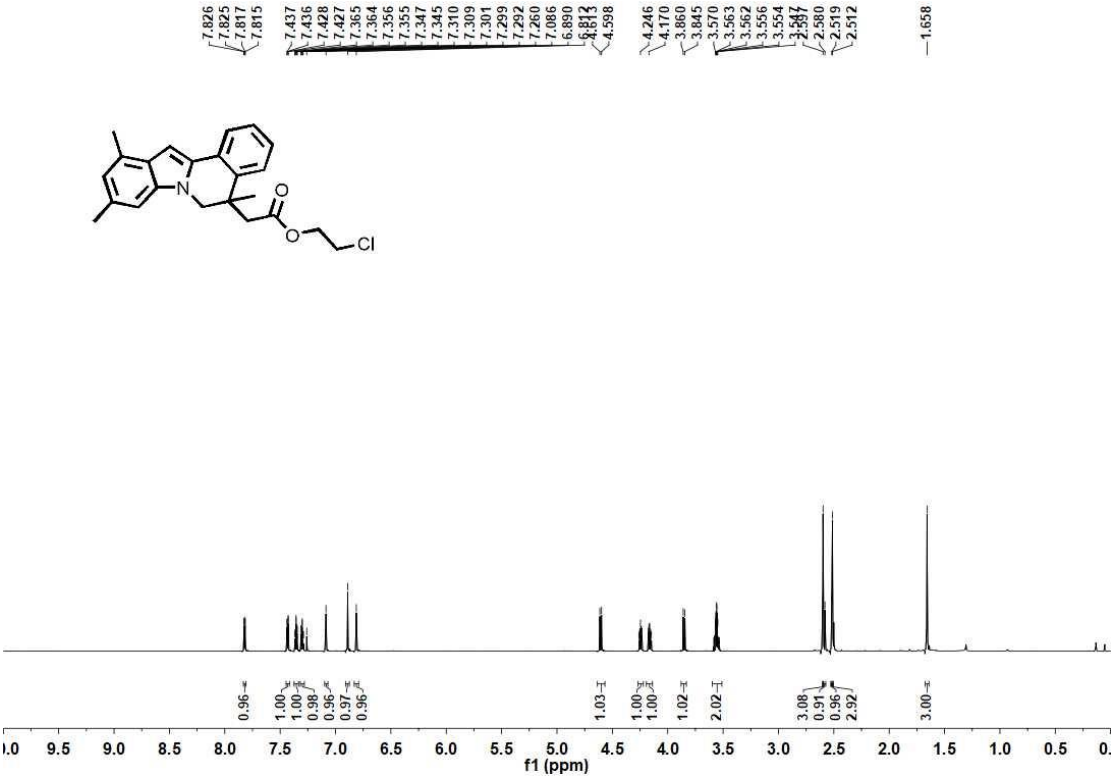
^{13}C NMR of product 4i in $CDCl_3$ (201 MHz)



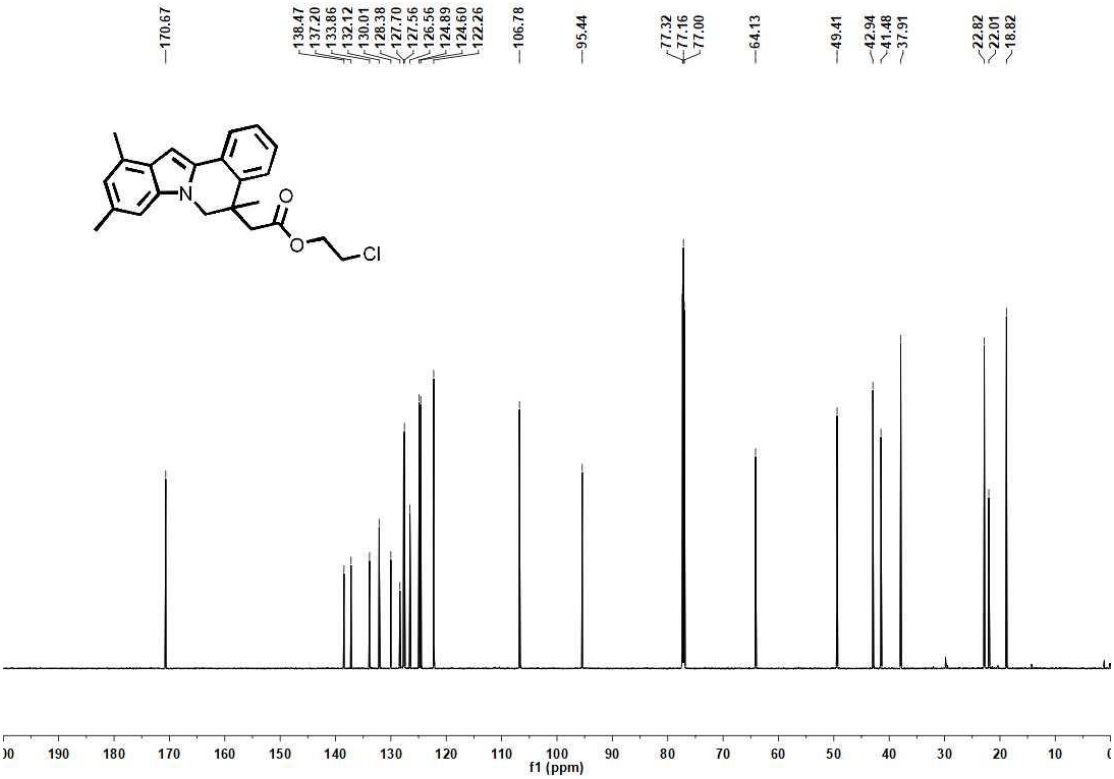




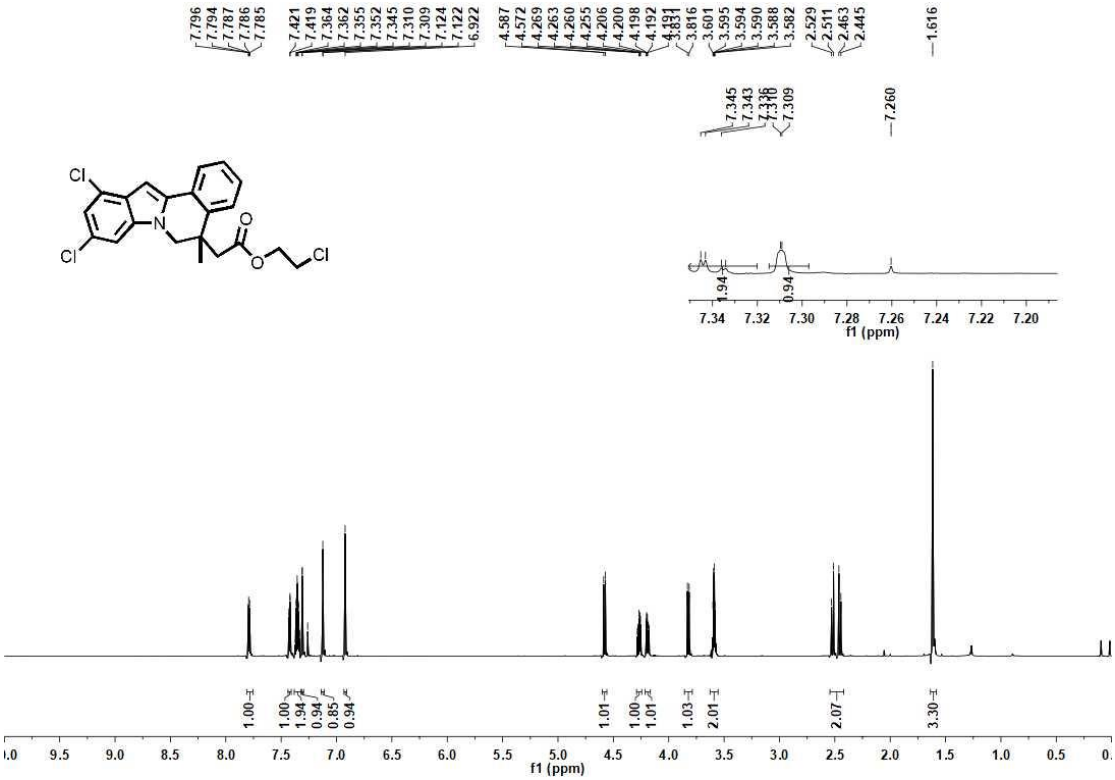
^{1}H NMR of product 4j in $CDCl_3$ (800 MHz)



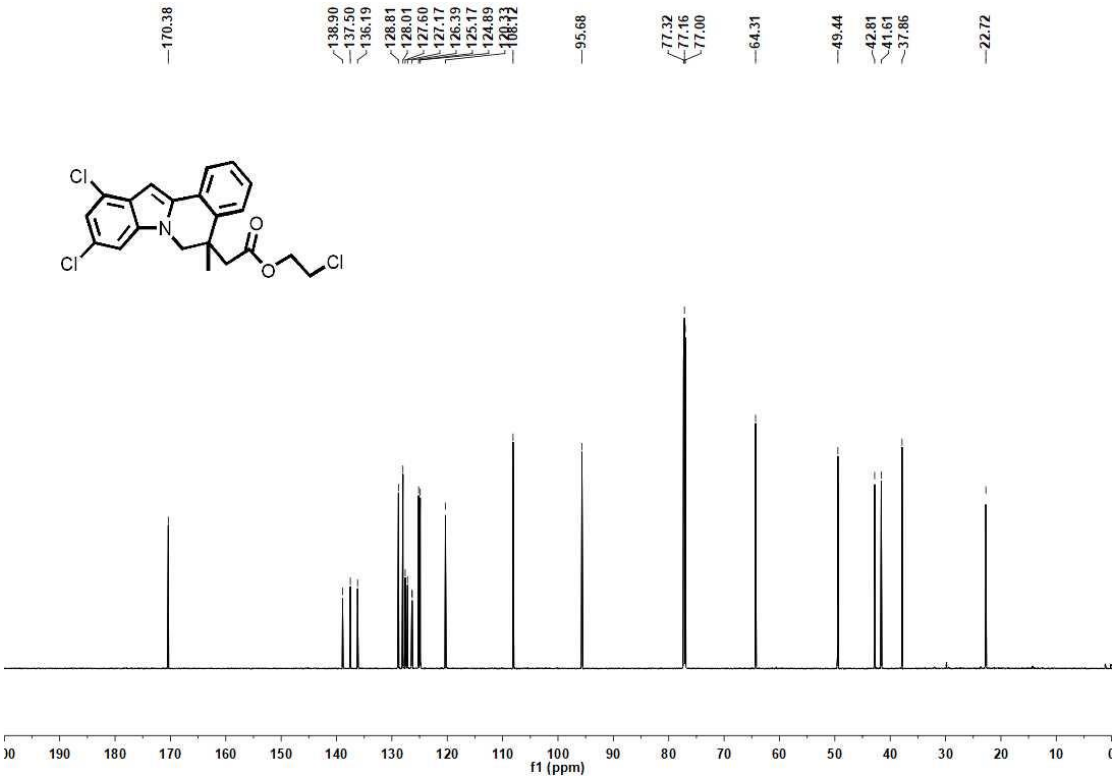
^{13}C NMR of product 4j in $CDCl_3$ (201 MHz)



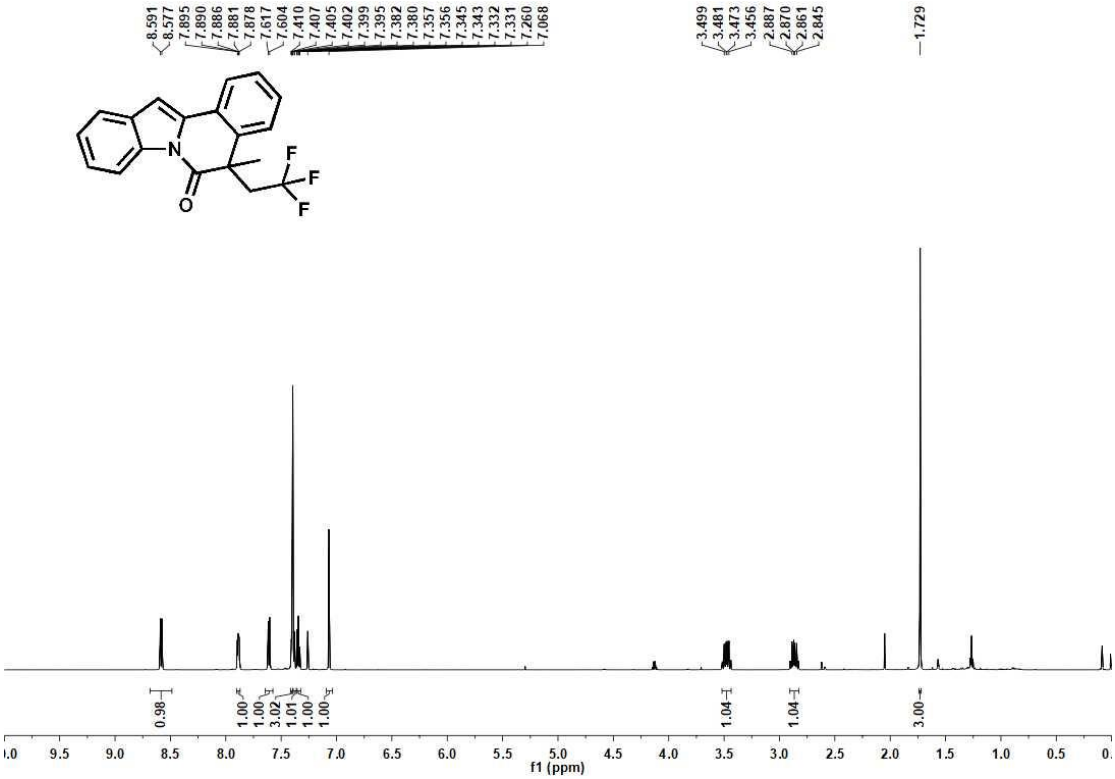
^{1}H NMR of product 4k in $CDCl_3$ (800 MHz)



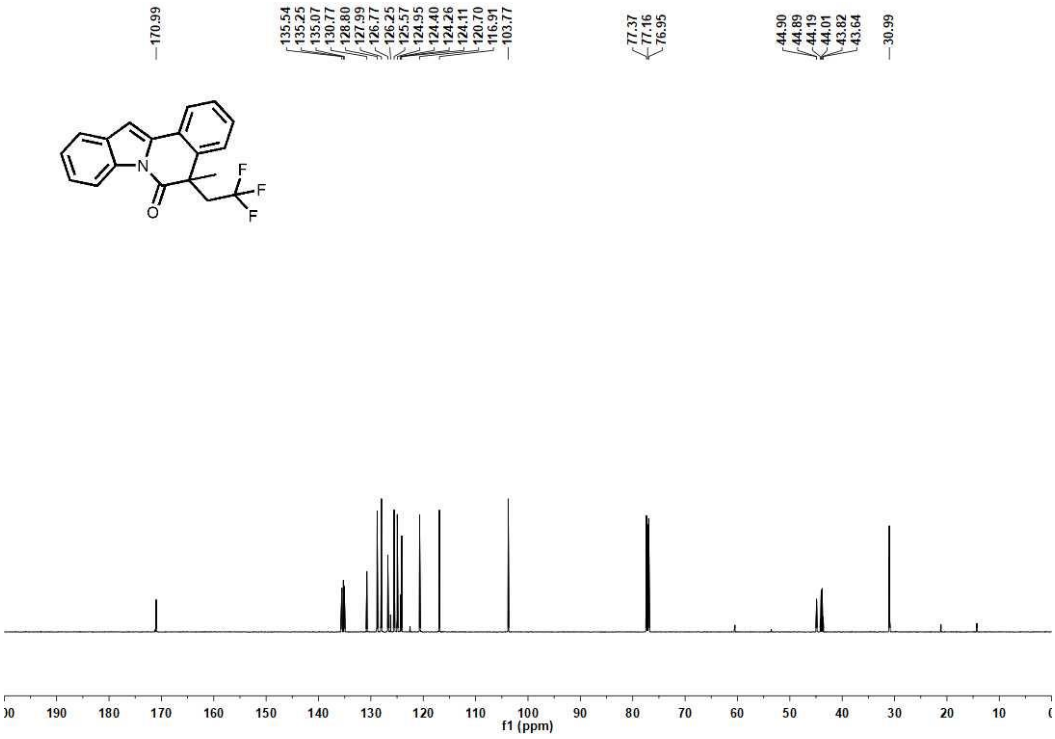
^{13}C NMR of product 4k in $CDCl_3$ (201 MHz)



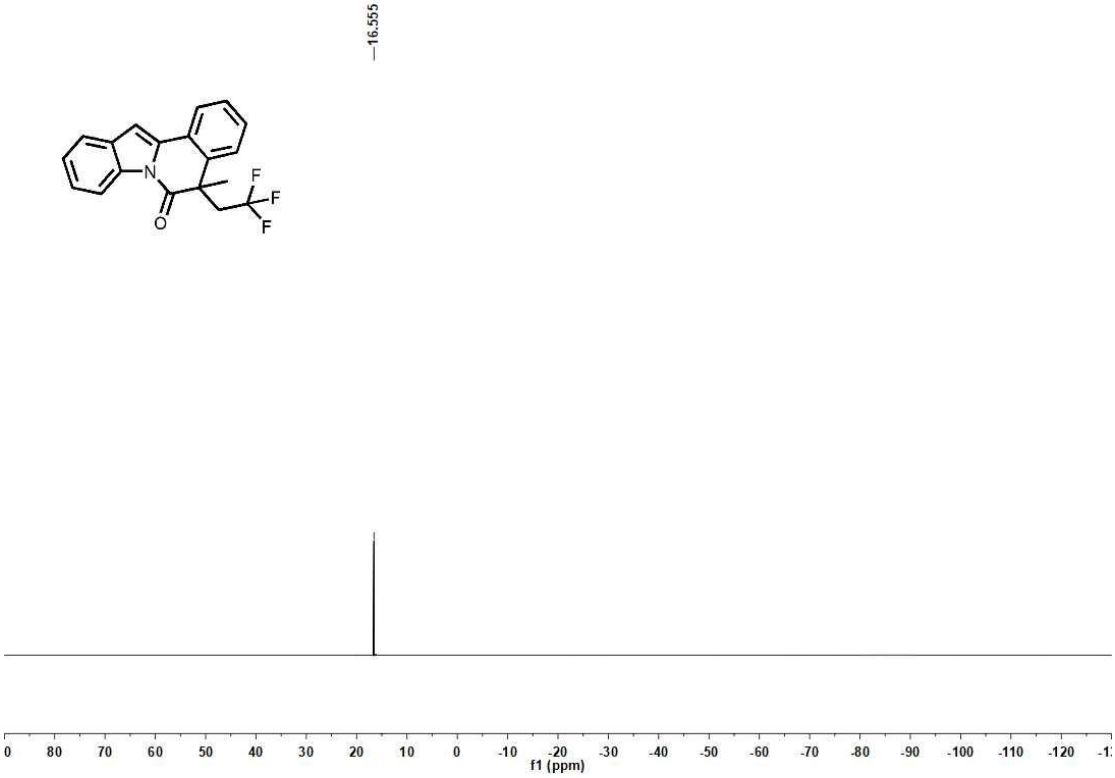
^{1}H NMR of product 5a in $CDCl_3$ (600 MHz)



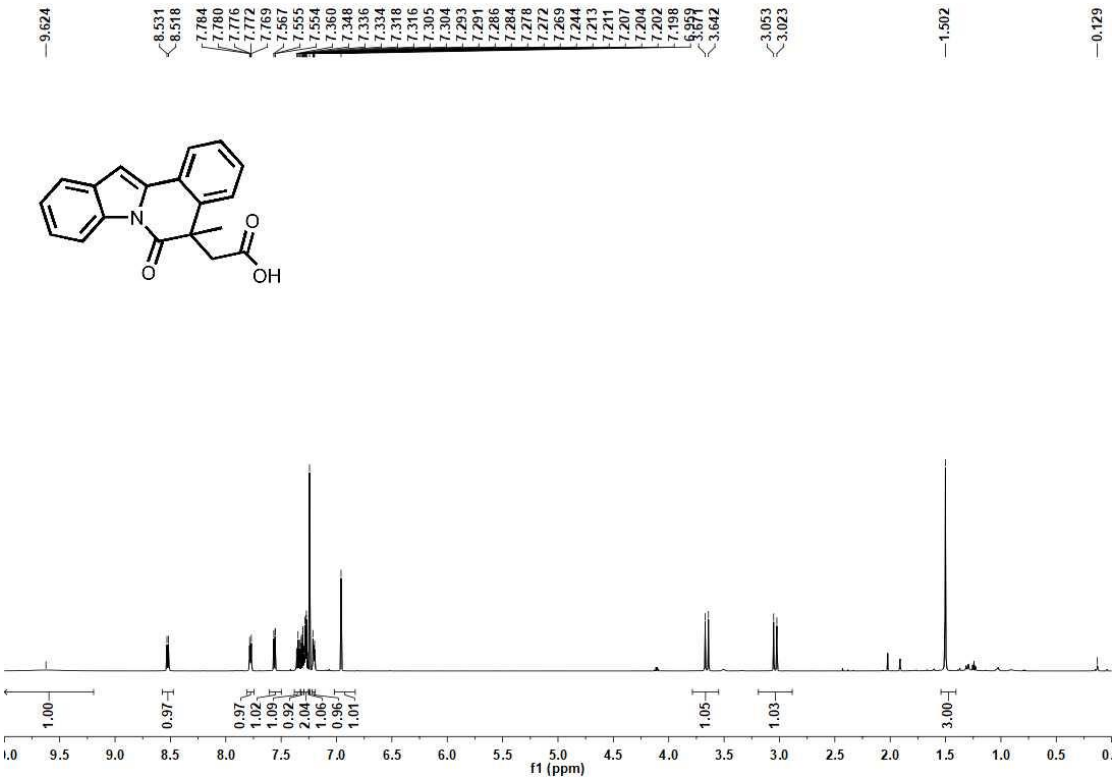
^{13}C NMR of product 5a in $CDCl_3$ (151 MHz)



^{19}F NMR of product 5a in DMSO (565 MHz)



^{1}H NMR of product 5b in $CDCl_3$ (600 MHz)



^{13}C NMR of product 5b in $CDCl_3$ (151 MHz)