Supporting Information

Assembly of Fluorinated Benzodiazepines via Rh(III)-Catalysed [5+2] Annulation of *N*-Benzo[*d*]imidazole Indolines with 2,2-Difluorovinyl Tosylate

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Supporting Information

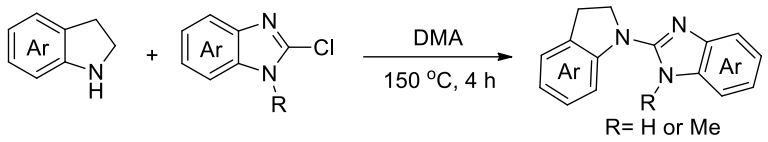
Contents

I. General

NMR spectra were recorded on JEOL 400 NMR (^{1}H 400 MHz; ^{13}C 100 MHz) in $CDCl_3$, DMSO-*d*$_6$ or CD_3OD. Abbreviations for data quoted are s, singlet; brs, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. The residual solvent signals were used as references and the chemical shifts converted to the TMS scale ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-*d*$_6$: δ_H = 2.50 ppm, δ_C = 39.52 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.00 ppm). Mass spectra and High-Resolution Mass Spectra (HRMS) were measured on an agilent TOF-G6230B mass spectrometer and Thermo-DFS mass spectrometer. X-ray single-crystal diffraction was conducted on HyPix diffractometer. Thin-layer chromatographies were done on pre-coated silica gel 60 F254 plates (Merck). Silica gel 60H (200-300 mesh) and preparative TLC (200x200 mm, 0.2-0.25 mm in thickness) manufactured by Qingdao Haiyang Chemical Group Co. (China) were used for general chromatography. 2,2-Difluorovinyl tosylate was synthesized according to published procedures.[S1] Other chemicals were purchased from commercial suppliers and were dried and purified if necessary. No attempts were made to optimize yields for substrate synthesis.

II. Experimental Information and Characterization Data

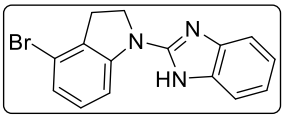
General procedure for synthesis of *N*-benzo[*d*]imidazole indolines 1:



N-Benzo[*d*]imidazole indoline substrates were synthesized according to a reported procedure:[S2] The mixture of indoline (1.5 equiv) and 2-chloro-1*H*-benzo[*d*]imidazole (1.0 equiv) in DMA (2 M) were stirred at 150 °C for 4 h, the reaction was monitored by TLC. Afterwards, the mixture was treated with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: PE/EA) to give the corresponding *N*-benzo[*d*]imidazole indolines **1**.

1a-c, **1e-m** and ***N*-Me 1a** are known compounds and all data were in agreement with that reported. [S2]

2-(4-bromoindolin-1-yl)-1*H*-benzo[*d*]imidazole (1d)



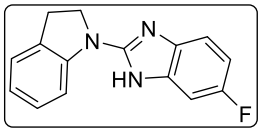
This compound was obtained in 30% yield (0.942 g) as brown solid. Eluent: PE/EA = 2/1, R_f = 0.4.

^{1}H NMR (**400 MHz**, **DMSO-*d*$_6$**): δ 11.77 (s, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.43-7.28 (m, 2H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.09-6.99 (m, 3H), 4.20 (t, *J* = 8.7 Hz, 2H), 3.25 (t, *J* = 8.7 Hz, 2H).

^{13}C NMR (**100 MHz**, **DMSO-*d*$_6$**): δ 150.2, 145.2, 131.0, 129.5, 123.2, 118.6, 112.1, 48.2, 29.0.

HRMS (ESI) calculated for $C_{15}H_{13}BrN_3$ ($[M+H]^+$): 314.0287; found: 314.0284.

6-fluoro-2-(indolin-1-yl)-1*H*-benzo[*d*]imidazole (1n)



This compound was obtained in 15% yield (0.380 g) as white solid. Eluent: PE/EA = 1/1, R_f = 0.7.

^{1}H NMR (**400 MHz**, **DMSO-*d*$_6$**): δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.56-7.48 (m, 1H), 7.39-7.28 (m, 3H), 7.16-7.06 (m, 2H), 4.30 (t, *J* = 8.2 Hz, 2H), 3.33 (t, *J* = 7.6 Hz, 2H).

^{13}C NMR (**100 MHz**, **DMSO-*d*$_6$**): δ 157.8 (d, *J* = 238.4 Hz), 146.3, 140.1, 132.5, 127.5, 125.7, 124.0, 113.03 (d, *J* = 11.1 Hz), 112.8, 110.6 (d, *J* = 24.2 Hz), 99.6 (d, *J* = 28.3 Hz), 51.2, 27.5.

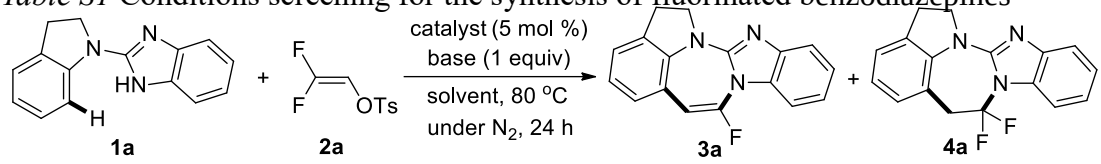
^{19}F NMR (376 MHz, DMSO-*d*$_6$): δ -118.70.

HRMS (ESI) calculated for $C_{15}H_{13}FN_3$ ($[M+H]^+$): 254.1088; found: 254.1088.

Optimization studies:

The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv), catalyst (5 mol %) and base (0.1 mmol, 1.0 equiv) in the solvent (1.0 mL) was stirred at 80 ºC for 24 h in an oil bath. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding monofluorinated benzodiazepine **3a** and *gem*-difluorinated benzodiazepine **4a**.

Table S1 Conditions screening for the synthesis of fluorinated benzodiazepines[a]



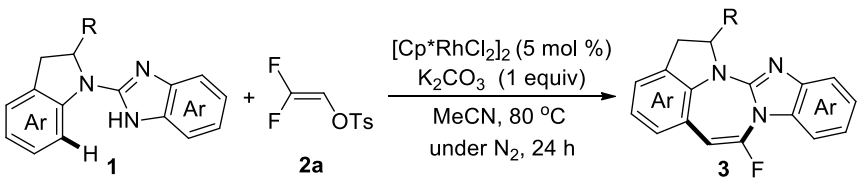
entry	catalyst	base	solvent	yield (%)	
				3a	**4a**
1[b,c]	$[Cp^*RhCl_2]_2$	CsOAc	MeOH	14	14
2[b,c]	$[Cp^*RhCl_2]_2$	CsOAc	DCE	12	-
3[b]	$[Cp^*IrCl_2]_2$	CsOAc	MeOH	n.d.	
4[b,d]	$[Cp^*Co(CO)I_2]$	CsOAc	MeOH	n.d.	n.d.
5[b]	$[CyRuCl_2]_2$	CsOAc	MeOH	n.d.	n.d.
6[b]	$[CyOsCl_2]_2$	CsOAc	MeOH	n.d.	n.d.
7	$[Cp^*RhCl_2]_2$	CsOAc	MeOH	36	32
8	$[Cp^*RhCl_2]_2$	CsOAc	DCE	42	12
9	$[Cp^*RhCl_2]_2$	CsOAc	MeCN	62	n.d.
10	$[Cp^*RhCl_2]_2$	CsOAc	dioxane	24	<5
11	$[Cp^*RhCl_2]_2$	CsOAc	DMF	19	n.d.
12	$[Cp^*RhCl_2]_2$	CsOAc	THF	67	7
13	$[Cp^*RhCl_2]_2$	CsOAc	EtOH	25	22

14	$[Cp^*RhCl_2]_2$	CsOAc	DMSO	<5	n.d.
15	$[Cp^*RhCl_2]_2$	CsOAc	acetone	47	n.d.
16	$[Cp^*RhCl_2]_2$	CsOAc	DCM	48	12
17	$[Cp^*RhCl_2]_2$	CsOAc	TFE	<5	n.d.
18	$[Cp^*RhCl_2]_2$	CsOAc	HFIP	<5	n.d.
19	$[Cp^*RhCl_2]_2$	CsOAc	toluence	22	n.d.
20	$[Cp^*RhCl_2]_2$	CsOAc	^{i}PrOH	<5	n.d.
21	$[Cp^*RhCl_2]_2$	CsOAc	^{t}AmOH	40	<5
22	$[Cp^*RhCl_2]_2$	CsOAc	^{t}BuOH	50	<5
23	$[Cp^*RhCl_2]_2$	CsOAc	EG	8	20
24	$[Cp^*RhCl_2]_2$	CsOAc	HMPA	n.d.	n.d.
25	$[Cp^*RhCl_2]_2$	KOPiv	MeCN	41	n.d.
26	$[Cp^*RhCl_2]_2$	NaOAc	MeCN	34	n.d.
27	$[Cp^*RhCl_2]_2$	KOAc	MeCN	11	<5
28	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	MeCN	23	n.d.
29	$[Cp^*RhCl_2]_2$	Na_2CO_3	MeCN	69	<5
30	$[Cp^*RhCl_2]_2$	K_2CO_3	MeCN	89	n.d.
31	$[Cp^*RhCl_2]_2$	K_3PO_4	MeCN	67	n.d.
32	$[Cp^*RhCl_2]_2$	Cs_2CO_3	MeCN	78	n.d.
33[e]	$[Cp^*RhCl_2]_2$	K_2CO_3	MeCN	71	n.d.
34[f]	$[Cp^*RhCl_2]_2$	K_2CO_3	MeCN	79	n.d.
35	$[Cp^ERhCl_2]_2$	CsOAc	MeOH	n.d.	n.d.
36	$[Cp^{*Bn}RhCl_2]_2$	CsOAc	MeOH	30	31
37	$[Cp^{*Cy}RhCl_2]_2$	CsOAc	MeOH	22	26
38	$[Cp^{2Ph}RhCl_2]_2$	CsOAc	MeOH	22	24
39	$[Cp^*RhCl_2]_2$	KOPiv	MeOH	19	20

40	$[Cp^*RhCl_2]_2$	$Zn(OAc)_2$	MeOH	24	31
41	$[Cp^*RhCl_2]_2$	K_3PO_4	MeOH	9	29
42	$[Cp^*RhCl_2]_2$	$NaHCO_3$	MeOH	23	23
43	$[Cp^*RhCl_2]_2$	K_2HPO_4	MeOH	18	20
44	$[Cp^*RhCl_2]_2$	NaOAc	MeOH	34	35
45	$[Cp^*RhCl_2]_2$	LiOAc	MeOH	15	16
46	$[Cp^*RhCl_2]_2$	KOAc	MeOH	21	23
47	$[Cp^*RhCl_2]_2$	Na_2CO_3	MeOH	35	35
48	$[Cp^*RhCl_2]_2$	K_2CO_3	MeOH	29	50
49[e]	$[Cp^*RhCl_2]_2$	K_2CO_3	MeOH	39	30
50[f]	$[Cp^*RhCl_2]_2$	K_2CO_3	MeOH	30	41
51[g]	$[Cp^*RhCl_2]_2$	K_2CO_3	MeOH	31	34

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (5 mol %) and base (1 equiv) in solvent (0.1 M) for 24 h under an atmosphere of N_2, ^{1}H-NMR yields were reported using 1,3,5-trimethoxybenzene as the internal standard. [b]The reaction was conducted without exclusion of air or moisture. [c]Isolated yields were reported. [d]10 mol % of $Cp^*Co(CO)I_2$ was used. [e]2,2-Difluorovinyl 4-(trifluoromethyl)benzenesulfonate was used as the coupling partner. [f]2,2-Difluorovinyl 2,4,6-trimethylbenzenesulfonate was used as the coupling partner. [g]The reaction was conducted at 50 °C. n.d.: not detected; EG: ethylene glycol.

General procedure for the synthesis of monofluorinated benzodiazepine 3:

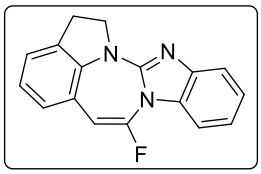


The mixture of *N*-benzo[*d*]imidazole indoline **1** (0.2 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (0.2 mmol, 1.0 equiv) in MeCN (2.0 mL) was stirred at 80 °C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under

reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding monofluorinated benzodiazepine product **3**.

Characterization of products 3:

7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3a)



This compound was obtained in 87% yield (48.2 mg) as yellow solid, m.p.: 149-150 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.27-7.22 (m, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.46 (d, *J* = 13.9 Hz, 1H), 4.23 (t, *J* = 8.8 Hz, 2H), 3.03 (t, *J* = 8.8 Hz, 2H).

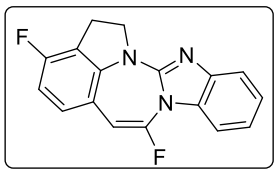
^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 154.3, 147.5 (d, *J* = 256.4 Hz), 143.6, 142.5, 132.4 (d, *J* = 1.7 Hz), 131.9, 127.7 (d, *J* = 4.5 Hz), 125.0, 123.9, 123.5, 122.4 (d, *J* = 1.3 Hz), 117.9 (d, *J* = 9.1 Hz), 117.6, 112.6 (d, *J* = 14.4 Hz), 93.2 (d, *J* = 31.9 Hz), 49.9, 27.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -101.12 (d, *J* = 16.2 Hz).

HRMS (ESI) calculated for $C_{17}H_{13}FN_3$ ($[M+H]^+$): 278.1088; found: 278.1086.

Scale-up synthesis of 3a: To a round bottom flask was added *N*-benzo[*d*]imidazole indoline **1a** (1.0 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (1.0 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (1.0 mmol, 1.0 equiv) in MeCN (10.0 mL), the mixture was stirred at 80 ^{o}C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by silica gel column chromatography (eluent: PE/EA = 10/1) to give the corresponding monofluorinated benzodiazepine product **3a** in 90% yield (0.249 g).

3,7-difluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3b)



This compound was obtained in 76% yield (44.8 mg) as yellow solid, m.p.: 173-175 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

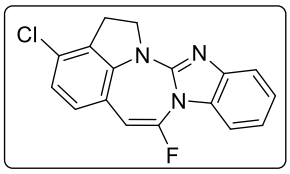
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.29-7.24 (m, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 1H), 6.66-6.56 (m, 1H), 6.49 (t, *J* = 8.2 Hz, 1H), 5.46 (d, *J* = 13.7 Hz, 1H), 4.31 (t, *J* = 8.9 Hz, 2H), 3.07 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 159.5 (dd, *J* = 247.5, 1.5 Hz), 153.4, 147.1 (dd, *J* = 256.7 Hz), 146.0 (d, *J* = 8.6 Hz), 142.2, 132.36 (d, *J* = 2.2 Hz), 129.34 (dd, *J* = 8.3, 4.8 Hz), 123.6, 122.7 (d, *J* = 1.3 Hz), 118.5 (d, *J* = 23.5 Hz), 117.9, 113.8 (dd, *J* = 9.2, 3.4 Hz), 112.7 (d, *J* = 14.4 Hz), 110.6 (d, *J* = 21.1 Hz), 92.6 (d, *J* = 32.6 Hz), 50.5, 23.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -102.32 (d, *J* = 18.5 Hz), -118.31.

HRMS (ESI) calculated for $C_{17}H_{12}F_2N_3$ ($[M+H]^+$): 296.0994; found: 296.0988.

3-chloro-7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3c)



This compound was obtained in 85% yield (52.8 mg) as yellow solid, m.p.: 191-193 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.7.

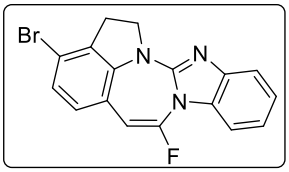
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.30-7.26 (m, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 5.46 (d, *J* = 13.8 Hz, 1H), 4.30 (t, *J* = 8.8 Hz, 2H), 3.09 (t, *J* = 8.9 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 153.4, 147.5 (d, *J* = 256.2 Hz), 144.6, 142.3, 132.3, 130.8 (d, *J* = 1.4 Hz), 130.4, 128.9 (d, *J* = 4.6 Hz), 123.7 (d, *J* = 4.5 Hz), 122.7, 117.9, 116.2 (d, *J* = 9.3 Hz), 112.7 (d, *J* = 14.6 Hz), 92.5 (d, *J* = 32.8 Hz), 49.8, 27.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -101.08 (d, *J* = 18.6 Hz).

HRMS (ESI) calculated for $C_{17}H_{12}ClFN_3$ ($[M+H]^+$): 312.0698; found: 312.0692.

3-bromo-7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*h i*]indole (3d)



This compound was obtained in 63% yield (44.7 mg) as yellow solid, m.p.: 174-175 °C. Eluent: PE/EA = 5/1, R_f = 0.7.

^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.41 – 7.36 (m, 1H), 7.29-7.25 (m, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.08-7.03 (m, 1H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.52 (d, *J* = 8.1 Hz, 1H), 5.45 (d, *J* = 13.8 Hz, 1H), 4.34-4.26 (m, 2H), 3.07 (t, *J* = 8.9 Hz, 2H).

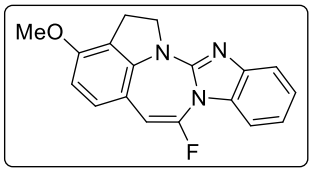
^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 153.6, 147.6 (d, *J* = 256.8 Hz), 144.4, 142.3, 132.5, 132.4 (d, *J* = 2.2 Hz), 129.1 (d, *J* = 4.7 Hz), 126.6, 123.7, 122.8 (d, *J* = 1.4 Hz), 119.7 (d, *J* = 1.7 Hz), 117.9, 116.9 (d, *J* = 9.4 Hz), 112.7 (d, *J* = 14.5 Hz), 92.58 (d, *J* = 32.8 Hz), 49.4, 29.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -100.76 (d, *J* = 16.2 Hz).

HRMS (ESI) calculated for $C_{17}H_{12}BrFN_3$ ($[M+H]^+$): 356.0193; found: 356.0186.

7-fluoro-3-methoxy-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1

-*hi*]indole (3e)



This compound was obtained in 78% yield (47.8 mg) as yellow solid, m.p.: 212-214 °C. Eluent: PE/EA = 5/1, R_f = 0.3.

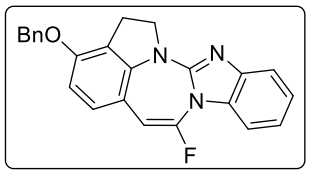
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.41-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 7.04 (td, *J* = 7.8, 1.3 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 13.8 Hz, 1H), 4.35-4.27 (m, 2H), 3.80 (s, 3H), 3.00 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 156.6, 153.7, 146.4 (d, *J* = 252.4 Hz), 144.9, 142.3, 132.4 (d, *J* = 1.9 Hz), 129.1 (d, *J* = 4.8 Hz), 123.4, 122.3 (d, *J* = 1.4 Hz), 119.5, 117.6, 112.6 (d, *J* = 14.5 Hz), 110.6 (d, *J* = 9.0 Hz), 105.7, 93.0 (d, *J* = 32.0 Hz), 55.5, 50.5, 24.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -104.34 (d, *J* = 19.0 Hz).

HRMS (ESI) calculated for $C_{18}H_{15}FN_3O$ ($[M+H]^+$): 308.1194; found: 308.1187.

3-(benzyloxy)-7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3f)



This compound was obtained in 88% yield (67.3 mg) as orange solid, m.p.: 167-169 °C. Eluent: PE/EA = 5/1, R_f = 0.6.

^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.41-7.36 (m, 5H), 7.36-7.31 (m, 1H), 7.30-7.26 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 8.2 Hz, 1H), 6.36

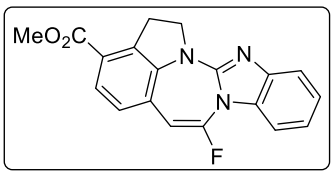
(d, *J* = 8.3 Hz, 1H), 5.46 (d, *J* = 14.0 Hz, 1H), 5.04 (s, 2H), 4.29 (t, *J* = 8.8 Hz, 2H), 3.04 (t, *J* = 8.7 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 155.6, 153.6, 146.5 (d, *J* = 254.2 Hz), 144.9, 142.3, 136.8, 132.4 (d, *J* = 1.1 Hz), 129.1 (d, *J* = 4.8 Hz), 128.7, 128.1, 127.2, 123.4, 122.3, 120.0, 117.6, 112.6 (d, *J* = 14.8 Hz), 110.8 (d, *J* = 8.9 Hz), 107.0, 92.9 (d, *J* = 32.0 Hz), 70.0, 50.5, 24.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -104.30 (d, *J* = 17.6 Hz).

HRMS (ESI) calculated for $C_{24}H_{19}FN_3O$ ($[M+H]^+$): 384.1507; found: 384.1502.

methyl 7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole-3-carboxylate (3g)



This compound was obtained in 71% yield (47.3 mg) as yellow solid, m.p.: 205-207 °C. Eluent: PE/EA = 4/1, R_f = 0.3.

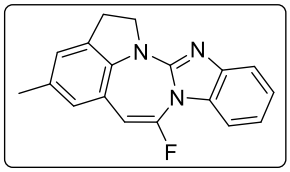
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29-7.24 (m, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.08-7.02 (m, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.48 (d, *J* = 14.0 Hz, 1H), 4.29 (t, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 3.42 (t, *J* = 8.9 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 166.3, 153.5, 148.6 (d, *J* = 256.9 Hz), 144.4, 142.5, 134.7, 132.3 (d, *J* = 1.4 Hz), 127.7 (d, *J* = 4.5 Hz), 126.3, 125.5, 123.8, 122.7, 122.2 (d, *J* = 9.8 Hz), 117.9, 112.7 (d, *J* = 14.6 Hz), 92.5 (d, *J* = 32.8 Hz), 52.1, 50.3, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -98.53 (d, *J* = 18.9 Hz).

HRMS (ESI) calculated for $C_{19}H_{15}FN_3O_2$ ($[M+H]^+$): 336.1143; found: 336.1138.

7-fluoro-4-methyl-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3h)



This compound was obtained in 85% yield (49.7 mg) as yellow solid, m.p.: 147-149 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

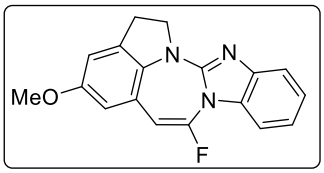
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.35 (d, *J* = 7.7 Hz, 1H), 7.26-7.22 (m, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.73 (s, 1H), 6.43 (s, 1H), 5.44 (d, *J* = 13.9 Hz, 1H), 4.22 (t, *J* = 8.8 Hz, 2H), 2.99 (t, *J* = 8.8 Hz, 2H), 2.17 (s, 3H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 154.7, 147.6 (d, *J* = 256.4 Hz), 142.5, 141.2, 133.6, 132.4 (d, *J* = 1.7 Hz), 132.1, 128.1 (d, *J* = 4.7 Hz), 125.6 (d, *J* = 1.3 Hz), 123.5, 122.2 (d, *J* = 1.4 Hz), 117.6, 117.5, 112.6 (d, *J* = 14.3 Hz), 93.3 (d, *J* = 31.9 Hz), 50.1, 27.5, 20.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -101.13 (d, *J* = 16.4 Hz).

HRMS (ESI) calculated for $C_{18}H_{15}FN_3$ ($[M+H]^+$): 292.1245; found: 292.1238.

7-fluoro-4-methoxy-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3i)



This compound was obtained in 69% yield (42.3 mg) as yellow solid, m.p.: 155-156 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.3.

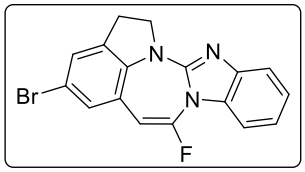
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.31-7.21 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.52 (s, 1H), 6.22 (s, 1H), 5.49 (dd, *J* = 13.5, 2.6 Hz, 1H), 4.26 (t, *J* = 8.7 Hz, 2H), 3.72 (s, 3H), 3.04 (t, *J* = 8.5 Hz, 2H).

^{13}C{^{1}H} NMR (**101 MHz**, **$CDCl_3$**): δ 156.9, 155.2, 147.9 (d, *J* = 257.2 Hz), 142.6, 137.1, 133.4, 132.3 (d, *J* = 1.5 Hz), 123.5, 122.2, 118.6 (d, *J* = 9.4 Hz), 117.5, 112.7 (d, *J* = 4.6 Hz), 112.5 (d, *J* = 14.1 Hz), 110.4, 93.2 (d, *J* = 32.5 Hz), 55.8, 50.1, 27.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -99.89 (d, *J* = 17.5 Hz).

HRMS (ESI) calculated for $C_{18}H_{15}FN_3O$ ($[M+H]^+$): 308.1194; found: 308.1187.

4-bromo-7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3j)



This compound was obtained in 55% yield (39.1 mg) as yellow solid, m.p.: 157-159 °C. Eluent: PE/EA = 5/1, R_f = 0.6.

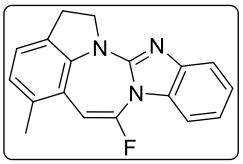
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.37 (d, *J* = 7.5 Hz, 1H), 7.29-7.25 (m, 1H), 7.14-7.09 (m, 1H), 7.08-7.03 (m, 2H), 6.78 (d, *J* = 1.4 Hz, 1H), 5.43 (d, *J* = 13.7 Hz, 1H), 4.31-4.23 (m, 2H), 3.06 (t, *J* = 8.9 Hz, 2H).

^{13}C{^{1}H} NMR (**101 MHz**, **$CDCl_3$**): δ 153.7, 148.1 (d, *J* = 256.4 Hz), 142.7, 142.3, 134.0, 132.3 (d, *J* = 1.6 Hz), 130.0 (d, *J* = 4.7 Hz), 127.6, 123.7, 122.7, 119.6 (d, *J* = 9.7 Hz), 117.8, 116.0, 112.7 (d, *J* = 14.5 Hz), 92.1 (d, *J* = 33.1 Hz), 50.2, 27.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -99.37 (d, *J* = 18.8 Hz).

HRMS (ESI) calculated for $C_{17}H_{12}BrFN_3$ ($[M+H]^+$): 356.0193; found: 356.0186.

7-fluoro-5-methyl-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3k)



This compound was obtained in 53% yield (30.8 mg) as yellow solid, m.p.: 103-105 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

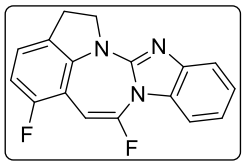
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.41 (d, *J* = 7.7 Hz, 1H), 7.31-7.27 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.77 (d, *J* = 12.8 Hz, 1H), 4.34 (t, *J* = 8.7 Hz, 2H), 3.05 (t, *J* = 8.6 Hz, 2H), 2.23 (s, 3H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 156.8, 147.1 (d, *J* = 257.2 Hz), 145.5, 142.6, 135.1 (d, *J* = 4.4 Hz), 132.2 (d, *J* = 1.8 Hz), 130.3, 125.8, 124.7, 123.5, 122.3, 117.7, 117.5 (d, *J* = 7.8 Hz), 112.3 (d, *J* = 11.5 Hz), 92.3 (d, *J* = 31.8 Hz), 50.0, 27.5, 19.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -98.23 (d, *J* = 16.2 Hz).

HRMS (ESI) calculated for $C_{18}H_{15}FN_3$ ($[M+H]^+$): 292.1245; found: 292.1240.

5,7-difluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3l)



This compound was obtained in 49% yield (28.8 mg) as yellow solid, m.p.: 146-148 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.7.

^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.31-7.27 (m, 1H), 7.16-7.03 (m, 2H), 6.89-6.85 (m, 1H), 6.55-6.51 (m, 1H), 5.72 (d, *J* = 13.5 Hz, 1H), 4.36-4.28 (m, 2H), 3.03 (t, *J* = 8.8 Hz, 2H).

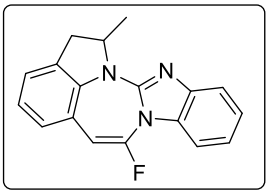
^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 158.8 (dd, *J* = 246.8, 4.8 Hz), 153.8, 147.8 (d, *J* = 257.5 Hz), 145.0 (d, *J* = 6.1 Hz), 142.3, 132.4, 127.0, 125.2 (d, *J* = 10.3 Hz), 123.7,

122.7 (d, *J* = 1.1 Hz), 117.8, 112.7 (d, *J* = 14.1 Hz), 110.0 (d, *J* = 22.8 Hz), 107.0 (dd, *J* = 19.1, 9.3 Hz), 86.4 (dd, *J* = 35.4, 8.0 Hz), 51.0, 26.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -98.77 (d, *J* = 16.9 Hz), -120.98.

HRMS (ESI) calculated for $C_{17}H_{12}F_2N_3$ ($[M+H]^+$): 296.0994; found: 296.0987.

7-fluoro-1-methyl-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3m)



This compound was obtained in 93% yield (54.1 mg) as yellow solid, m.p.: 116-118 °C. Eluent: PE/EA = 5/1, R_f = 0.8.

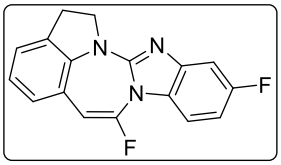
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.39 (d, *J* = 7.7 Hz, 1H), 7.29-7.24 (m, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 7.3 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.60 (d, *J* = 12.7 Hz, 1H), 5.15-5.05 (m, 1H), 3.38 (dd, *J* = 16.2, 10.0 Hz, 1H), 2.57 (dd, *J* = 16.2, 4.4 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 155.4, 147.4 (d, *J* = 256.4 Hz), 143.6, 142.6, 132.1 (d, *J* = 1.9 Hz), 131.2, 127.6 (d, *J* = 4.6 Hz), 125.1 (d, *J* = 1.1 Hz), 124.1, 123.4, 122.3 (d, *J* = 1.2 Hz), 118.5 (d, *J* = 8.8 Hz), 117.6, 112.5 (d, *J* = 13.0 Hz), 94.0 (d, *J* = 31.6 Hz), 57.1, 35.6, 21.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -100.21 (d, *J* = 16.4 Hz).

HRMS (ESI) calculated for $C_{18}H_{15}FN_3$ ($[M+H]^+$): 292.1245; found: 292.1240.

7,11-difluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3n)



This compound was obtained in 45% yield (25.3 mg) as yellow solid, m.p.: 159-161 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

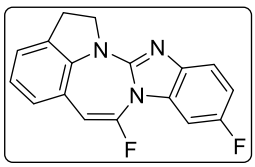
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.29-7.25 (m, 1H), 7.03-6.98 (m, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.87-6.77 (m, 2H), 6.66 (d, *J* = 7.5 Hz, 1H), 5.53 (d, *J* = 14.0 Hz, 1H), 4.24 (t, *J* = 8.8 Hz, 2H), 3.06 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): 159.2 (d, *J* = 238.1 Hz), 154.5, 147.1 (d, *J* = 256.2 Hz), 143.5, 138.7, 132.3 (d, *J* = 12.8 Hz), 132.0, 127.8 (d, *J* = 4.6 Hz), 125.2 (d, *J* = 1.1 Hz), 124.0, 117.8 (d, *J* = 9.8 Hz), 117.6 (d, *J* = 9.2 Hz), 110.7 (d, *J* = 24.1 Hz), 100.5 (dd, *J* = 29.9, 14.9 Hz), 93.7 (d, *J* = 31.7 Hz), 50.0, 27.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -102.34 (d, *J* = 16.4 Hz), -119.85 (t, *J* = 13.8 Hz).

HRMS (ESI) calculated for $C_{17}H_{12}F_2N_3$ ($[M+H]^+$): 296.0994; found: 296.0988.

7,10-difluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3n')



This compound was obtained in 37% yield (22.9 mg) as yellow solid, m.p.: 173-175 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.6.

^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.15 (dt, *J* = 9.0, 4.5 Hz, 1H), 7.05 (dd, *J* = 9.1, 2.4 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.82-6.70 (m, 2H), 6.63 (d, *J* = 7.5 Hz, 1H), 5.48 (d, *J* = 13.9 Hz, 1H), 4.23 (t, *J* = 8.8 Hz, 2H), 3.05 (t, *J* = 8.8 Hz, 2H).

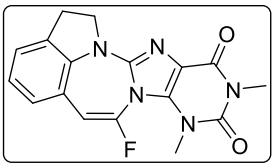
^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 160.0 (d, *J* = 237.3 Hz), 155.5, 147.3 (d, *J* = 254.9 Hz), 143.5, 143.4 (d, *J* = 3.3 Hz), 132.0, 128.7, 127.8 (d, *J* = 4.7 Hz), 125.1,

124.2, 117.9 (d, *J* = 9.3 Hz), 112.8 (dd, *J* = 14.7, 9.8 Hz), 109.43 (dd, *J* = 24.8, 1.9 Hz), 104.4 (d, *J* = 25.1 Hz), 93.3 (d, *J* = 31.9 Hz), 49.9, 27.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -101.39 (d, *J* = 17.4 Hz), -119.60 – -119.84 (m).

HRMS (ESI) calculated for $C_{17}H_{12}F_2N_3$ ($[M+H]^+$): 296.0994; found: 296.0988.

7-fluoro-9,11-dimethyl-1,2-dihydroindolo[1',7':3,4,5][1,3]diazepino[1,2-*e*]purine-10,12(9*H*,11*H*)-dione (3o)



This compound was obtained in 98% yield (67.5 mg) as yellow solid, m.p.: 252-254 ºC. Eluent: PE/EA = 2/1, R_f = 0.5.

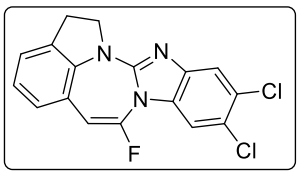
^{1}H NMR (**400 MHz, $CDCl_3$**): δ 7.03 (d, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 8.4 Hz, 1H), 4.26 (t, *J* = 8.5 Hz, 2H), 3.49 (s, 3H), 3.36 (s, 3H), 3.07 (t, *J* = 8.5 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 160.3, 152.7, 151.7, 150.4, 144.93 (d, *J* = 270.1 Hz), 144.88, 132.7, 128.1 (d, *J* = 4.6 Hz), 125.7, 125.3, 119.7 (d, *J* = 7.2 Hz), 102.5 (d, *J* = 3.7 Hz), 96.3 (d, *J* = 29.9 Hz), 49.4, 30.1, 28.4, 27.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -87.00.

HRMS (ESI) calculated for $C_{17}H_{15}FN_5O_2$ ($[M+H]^+$): 340.1204; found: 340.1202.

10,11-dichloro-7-fluoro-1,2-dihydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (3p)



This compound was obtained in 70% yield (50.2 mg) as yellow solid, m.p.: 205-207

°C. Eluent: PE/EA = 5/1, R_f = 0.7.

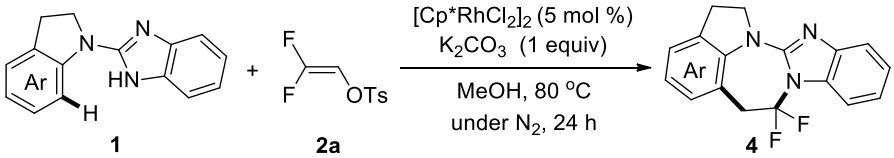
^{1}H NMR (**400 MHz**, **$CDCl_3$**): δ 7.39 (s, 1H), 7.33 (d, *J* = 4.1 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.5 Hz, 1H), 5.51 (d, *J* = 14.2 Hz, 1H), 4.22 (t, *J* = 8.8 Hz, 2H), 3.06 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (**100 MHz**, **$CDCl_3$**): δ 155.1, 146.7 (d, *J* = 255.0 Hz), 142.8, 142.3, 132.1, 131.5 (d, *J* = 2.2 Hz), 128.0 (d, *J* = 4.6 Hz), 127.3, 125.72 (d, *J* = 1.2 Hz), 125.4, 124.4, 118.6, 117.5 (d, *J* = 8.9 Hz), 113.9 (d, *J* = 15.8 Hz), 93.8 (d, *J* = 31.2 Hz), 50.1, 27.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -102.21 (d, *J* = 17.1 Hz).

HRMS (ESI) calculated for $C_{17}H_{11}Cl_2FN_3$ ($[M+H]^+$): 346.0309; found: 346.0308.

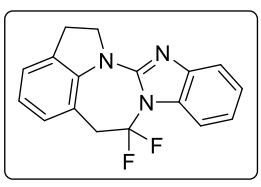
General procedure for the synthesis of *gem*-difluorinated benzodiazepines 4:



The mixture of *N*-benzo[*d*]imidazole indoline **1** (0.2 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.2 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (0.2 mmol, 1.0 equiv) in MeOH (2.0 mL) was stirred at 80°C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding difluorinated benzodiazepine product **4**.

Characterization of products 4:

7,7-difluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4a)



This compound was obtained in 50% yield (29.8 mg) as yellow solid, m.p.: 114-116 °C. Eluent: PE/EA = 5/1, R_f = 0.5. Monofluorinated benzodiazepine **3a** was formed in 25% yield (13.8 mg) under this condition.

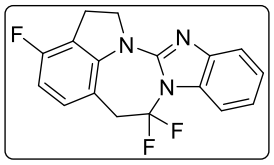
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.28-7.16 (m, 2H), 7.15-7.09 (m, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.58 (t, *J* = 8.6 Hz, 2H), 3.69 (t, *J* = 10.5 Hz, 2H), 3.25 (t, *J* = 8.6 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.8, 141.5, 141.4, 132.7, 131.8, 128.9, 125.1, 123.7, 123.3, 121.2, 118.8 (t, *J* = 251.5 Hz), 117.3, 114.3 (t, *J* = 5.9 Hz), 113.0 (t, *J* = 7.2 Hz), 52.0, 40.6 (t, *J* = 30.2 Hz), 27.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.22 (t, *J* = 10.9 Hz).

HRMS (ESI) calculated for $C_{17}H_{14}F_2N_3$ ($[M+H]^+$): 298.1150; found: 298.1149.

3,7,7-trifluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4b)



This compound was obtained in 48% yield (30.2 mg) as yellow solid, m.p.: 128-130 °C. Eluent: PE/EA = 5/1, R_f = 0.6. Monofluorinated benzodiazepine **3b** was formed in 23% yield (13.6 mg) under this condition.

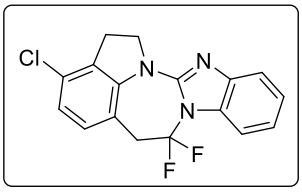
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.58 (m, 1H), 7.53 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.28-7.21 (m, 1H), 7.16-7.11 (m, 1H), 7.03 (dd, *J* = 8.4, 5.2 Hz, 1H), 6.71 (t, *J* = 8.3 Hz, 1H), 4.66-4.58 (m, 2H), 3.67 (t, *J* = 10.4 Hz, 2H), 3.28 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.3 (d, *J* = 243.3 Hz), 147.2, 142.6 (d, *J* = 6.2 Hz), 141.3, 132.8, 127.0 (d, *J* = 2.5 Hz), 125.1 (d, *J* = 10.1 Hz), 123.8, 121.6, 118.6 (t, *J* = 250.3 Hz), 117.5, 113.1 (t, *J* = 7.7 Hz), 108.9 (d, *J* = 23.3 Hz), 102.6 (dt, *J* = 12.4, 6.0 Hz), 53.0, 32.8 (td, *J* = 31.7, 5.0 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.88 (t, *J* = 10.4 Hz), -122.40 (d, *J* = 14.9 Hz).

HRMS (ESI) calculated for $C_{17}H_{13}F_3N_3$ ($[M+H]^+$): 316.1056; found: 316.1053.

3-chloro-7,7-difluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4c)



This compound was obtained in 52% yield (34.5 mg) as yellow solid, m.p.: 112-114 °C. Eluent: PE/EA = 5/1, R_f = 0.5. Monofluorinated benzodiazepine **3c** was formed in 17% yield (10.6 mg) under this condition.

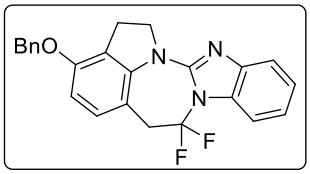
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.26-7.21 (m, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.04-6.95 (m, 2H), 4.60 (t, *J* = 8.7 Hz, 2H), 3.68 (t, *J* = 10.3 Hz, 2H), 3.28 (t, *J* = 8.8 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.2, 142.5, 141.2, 132.7, 131.1, 130.4, 130.3, 123.8, 123.1, 121.6, 118.5 (t, *J* = 252.2 Hz), 117.5, 113.1 (t, *J* = 7.3 Hz), 112.4 (t, *J* = 5.9 Hz), 51.8, 40.35 (t, *J* = 30.3 Hz), 27.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.52 (t, *J* = 11.7 Hz).

HRMS (ESI) calculated for $C_{17}H_{13}ClF_2N_3$ ($[M+H]^+$): 332.0761; found: 332.0758.

3-(benzyloxy)-7,7-difluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4d)



This compound was obtained in 35% yield (28.2 mg) as yellow solid, m.p.: 192-194 °C. Eluent: PE/EA = 5/1, R_f = 0.6. Monofluorinated benzodiazepine **3f** was formed in 30% yield (22.9 mg) under this condition.

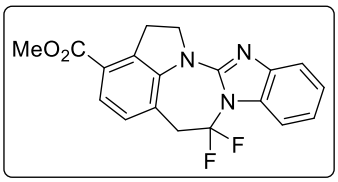
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.44-7.36 (m, 4H), 7.36-7.31 (m, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.15-7.09 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 2H), 4.65-4.54 (m, 2H), 3.65 (t, *J* = 10.5 Hz, 2H), 3.24 (t, *J* = 8.7 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.5, 147.9, 142.7, 141.4, 136.9, 132.8, 130.2, 128.8, 128.2, 127.3, 123.7, 121.2, 119.2, 118.9 (t, *J* = 251.8 Hz), 117.3, 113.1 (t, *J* = 7.3 Hz), 107.4 (t, *J* = 6.0 Hz), 107.2, 70.2, 52.6, 40.1(t, *J* = 29.9 Hz), 25.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.81.

HRMS (ESI) calculated for $C_{24}H_{20}F_2N_3O$ ($[M+H]^+$): 404.1569; found: 404.1566.

methyl 7,7-difluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole-3-carboxylate (4e)



This compound was obtained in 57% yield (40.5 mg) as yellow solid, m.p.: 156-157 °C. Eluent: PE/EA = 5/1, R_f = 0.5.

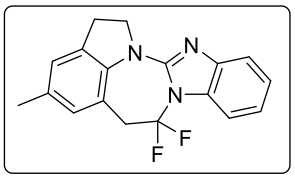
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.27-7.23 (m, 1H), 7.18-7.10 (m, 2H), 4.62 (t, *J* = 8.7 Hz, 2H), 3.92 (s, 3H), 3.73 (t, *J* = 10.3 Hz, 2H), 3.61 (t, *J* = 8.7 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 166.4, 147.5, 142.7, 141.2, 135.1, 132.7, 129.3, 127.1, 124.6, 123.9, 121.5, 118.4 (t, *J* = 251.4 Hz), 118.2 (t, *J* = 5.7 Hz), 117.5, 113.0 (t, *J* = 6.9 Hz), 52.3, 52.2, 40.8 (t, *J* = 30.3 Hz), 29.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.82 – -66.80 (m).

HRMS (ESI) calculated for $C_{19}H_{16}F_2N_3O_2$ ($[M+H]^+$): 356.1205; found: 356.1198.

7,7-difluoro-4-methyl-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4f)



This compound was obtained in 48% yield (29.9 mg) as yellow solid, m.p.: 167-169 °C. Eluent: PE/EA = 5/1, R_f = 0.5. Monofluorinated benzodiazepine **3h** was formed in 20% yield (11.7 mg) under this condition.

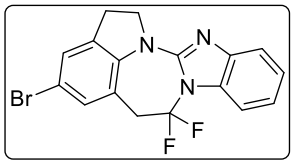
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 4.55 (t, *J* = 8.7 Hz, 2H), 3.66 (t, *J* = 10.5 Hz, 2H), 3.22 (t, *J* = 8.6 Hz, 2H), 2.33 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.0, 141.5, 139.2, 133.2, 132.7, 132.0, 129.2, 125.9, 123.6, 121.1, 118.9 (t, *J* = 251.6 Hz), 117.2, 114.0 (t, *J* = 5.8 Hz), 113.0 (t, *J* = 7.3 Hz), 52.1, 40.6 (t, *J* = 30.1 Hz), 27.6, 20.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.15 (t, *J* = 11.3 Hz).

HRMS (ESI) calculated for $C_{18}H_{16}F_2N_3$ ($[M+H]^+$): 312.1307; found: 312.1304.

4-bromo-7,7-difluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4g)



This compound was obtained in 45% yield (33.6 mg) as yellow solid, m.p.: 168-170 °C. Eluent: PE/EA = 50/1, R_f = 0.2. Monofluorinated benzodiazepine **3j** was formed in 18% yield (12.8 mg) under this condition.

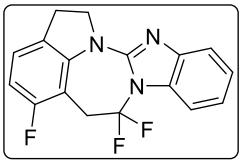
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.56 (m, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.32-6.96 (m, 4H), 4.61-4.52 (m, 2H), 3.74-3.59 (m, 2H), 3.31-3.19 (m, 2H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.3, 141.2, 140.7, 134.2, 132.7, 131.5, 128.2, 123.8, 121.6, 118.4 (t, *J* = 252.0 Hz), 117.5, 115.6 (t, *J* = 6.1 Hz), 115.2, 113.1 (t, *J* = 7.1 Hz), 52.3, 40.4 (t, *J* = 30.7 Hz), 27.5.

^{19}F NMR (376 MHz, $CDCl_3$):δ -67.28 – -67.17 (m).

HRMS (ESI) calculated for $C_{17}H_{13}BrF_2N_3$ ($[M+H]^+$): 376.0255; found: 376.0254.

5,7,7-trifluoro-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4h)



This compound was obtained in 41% yield (25.8 mg) as yellow solid, m.p.: 156-158 °C. Eluent: PE/EA = 5/1, R_f = 0.5. Monofluorinated benzodiazepine **3l** was formed in 19% yield (11.2 mg) under this condition.

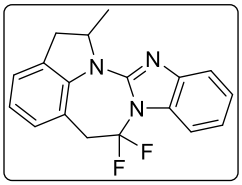
^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.29-7.21 (m, 1H), 7.18-7.08 (m, 2H), 6.78-6.69 (m, 1H), 4.60 (t, *J* = 8.7 Hz, 2H), 3.79 (t, *J* = 10.3 Hz, 2H), 3.22 (t, *J* = 8.7 Hz, 2H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.3 (d, *J* = 244.5 Hz), 147.2, 142.6 (d, *J* = 6.2 Hz), 141.3, 132.8, 127.0 (d, *J* = 2.5 Hz), 125.1 (d, *J* = 10.1 Hz), 123.8, 121.6, 118.6 (t, *J* = 252.8 Hz), 117.5, 113.1 (t, *J* = 7.7 Hz), 108.9 (d, *J* = 23.4 Hz), 102.6 (dt, *J* = 12.4, 6.0 Hz), 53.0, 32.8 (td, *J* = 31.7, 5.0 Hz), 26.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -67.88 (t, *J* = 10.4 Hz), -122.40 (d, *J* = 14.9 Hz).

HRMS (ESI) calculated for $C_{17}H_{13}F_3N_3$ ($[M+H]^+$): 316.1056; found: 316.1052.

7,7-difluoro-1-methyl-1,2,6,7-tetrahydrobenzo[4',5']imidazo[2',1':2,3][1,3]diazepino[6,7,1-*hi*]indole (4i)



This compound was obtained in 50% yield (31.0 mg) as yellow solid, m.p.: 171-173 ^{o}C. Eluent: PE/EA = 5/1, R_f = 0.5.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60 (dd, *J* = 8.0, 3.3 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.25-7.17 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.43-5.32 (m, 1H), 3.73-3.60 (m, 2H), 3.55 (dd, *J* = 16.3, 9.8 Hz, 1H), 2.72 (d, *J* = 16.2 Hz, 1H), 1.52 (d, *J* = 6.5 Hz, 3H).

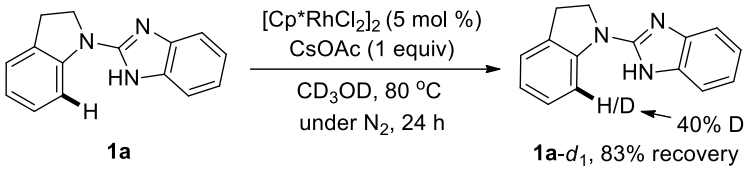
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 147.7, 141.4, 141.1, 132.6 (d, *J* = 1.6 Hz), 130.8, 128.8, 125.4, 123.7, 123.6, 121.4, 118.92 (dd, *J* = 251.2, 247.4 Hz), 117.2, 115.1 (d, *J* = 11.1 Hz), 113.0 (d, *J* = 11.2 Hz), 59.8, 40.20 (t, *J* = 29.8 Hz), 35.8, 21.7.

^{19}F NMR (376 MHz, CDCl$_3$): δ -68.80 – -67.44 (m), -65.11 – -64.50 (m).

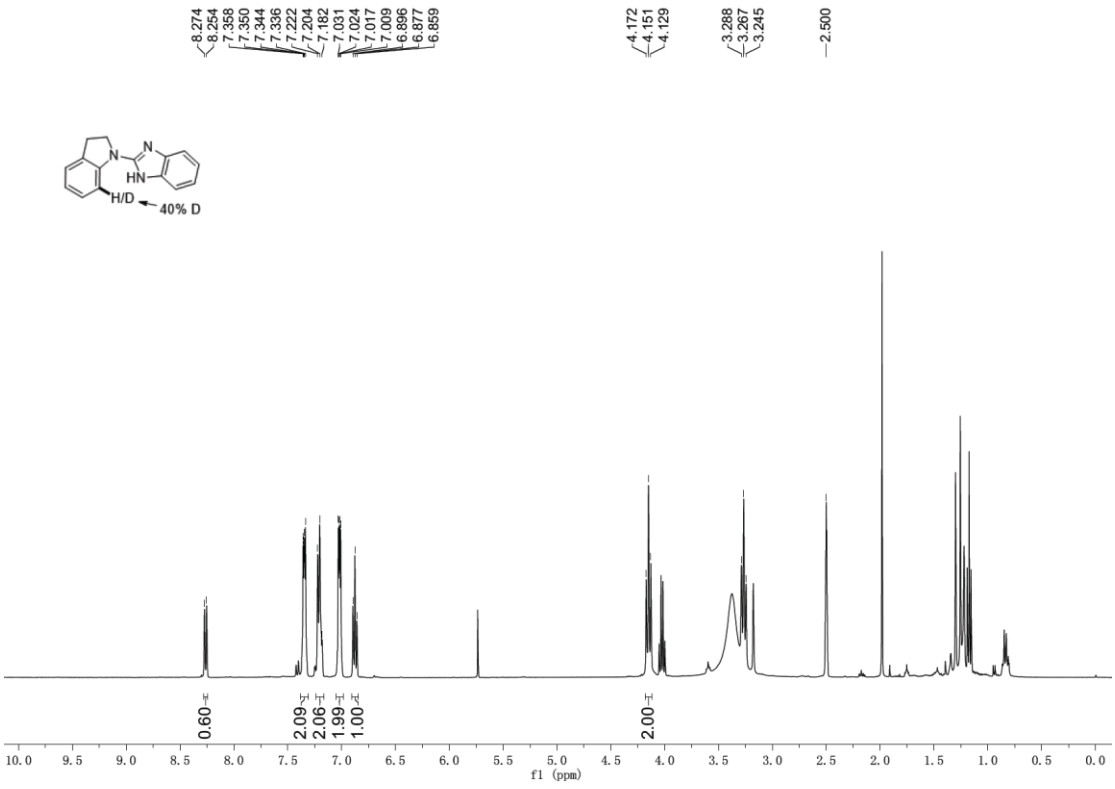
HRMS (ESI) calculated for $C_{18}H_{16}F_2N_3$ ($[M+H]^+$): 312.1307; found: 312.1303.

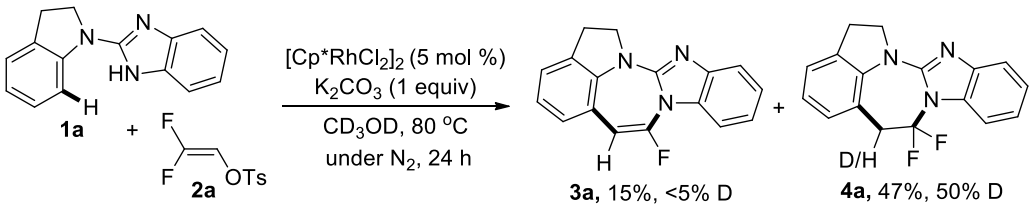
III. Mechanistic Studies

Deuterium-labeling experiments:

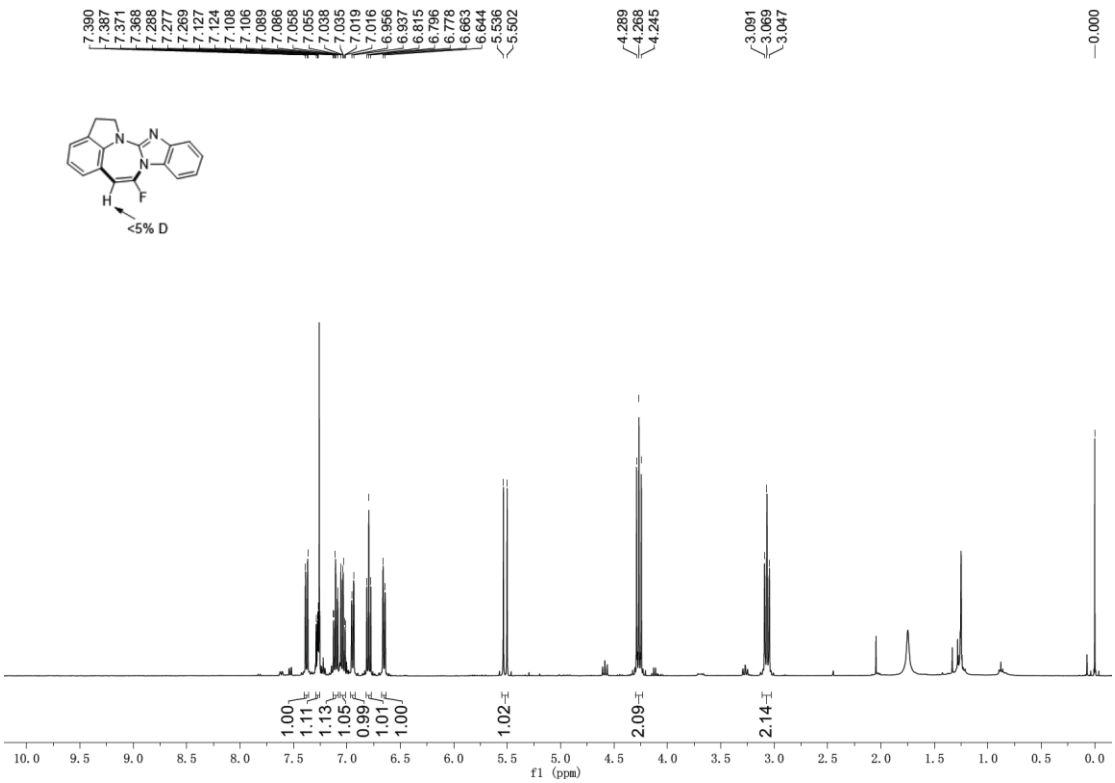


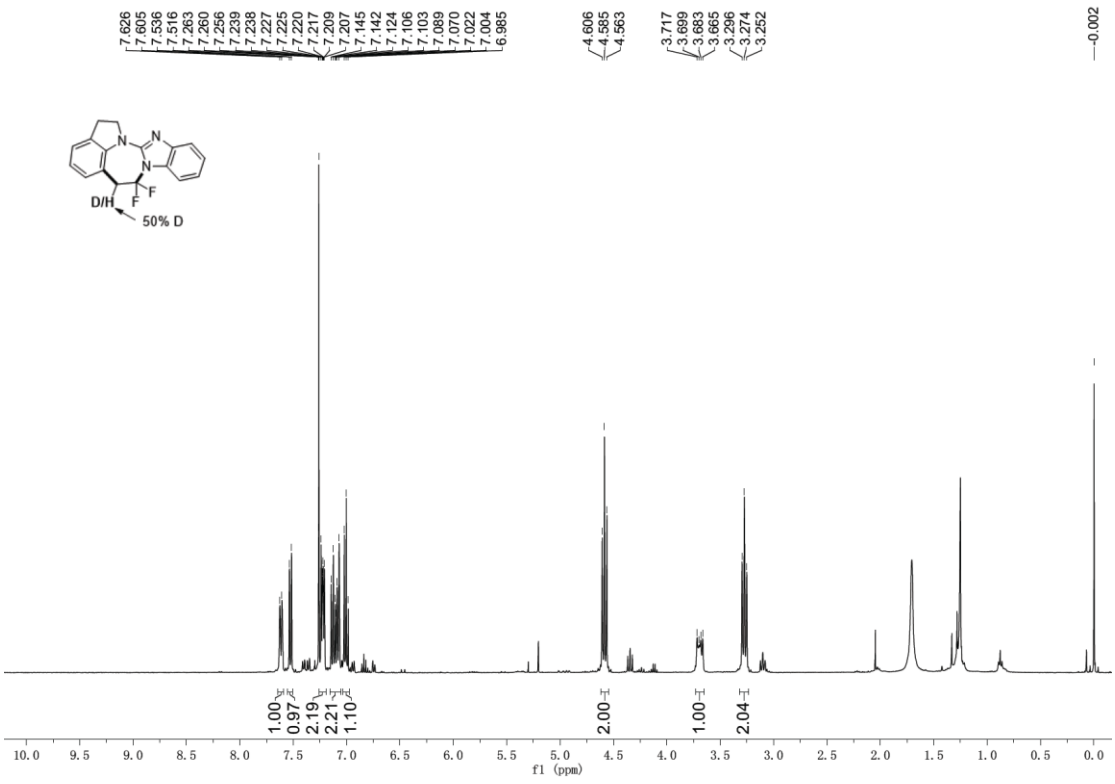
The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and CsOAc (0.1 mmol, 1.0 equiv) in CD_3OD (1.0 mL) was stirred at 80 ^{o}C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and **1a** was recovered by preparative TLC in 83% (19.8 mg) yield and analyzed by ^{1}H-NMR spectroscopy. 40% deuteration was observed on the basis of the doublet at δ 8.26 (0.60H).



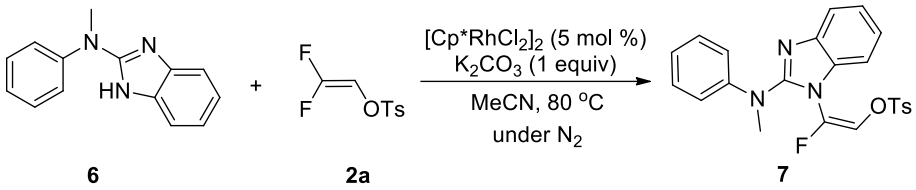


The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (0.1 mmol, 1.0 equiv) in CD_3OD (1.0 mL) was stirred at 80 °C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and **3a** was obtained by preparative TLC in 15% (4.1 mg) yield and analyzed by ^{1}H-NMR spectroscopy. No obvious deuterium incorporation was found in **3a**. **4a** was obtained by preparative TLC in 47% (14.0 mg) yield and analyzed by ^{1}H-NMR spectroscopy. 50% deuteration was observed on the basis of the multiplet at δ 3.72-3.66 (1.0H).





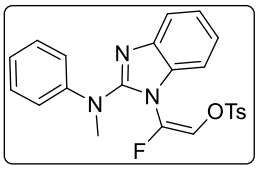
Control experiments:



6 **2a** **7**

The mixture of *N*-methyl-*N*-phenyl-1*H*-benzo[*d*]imidazol-2-amine **6** (0.1 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (0.1 mmol, 1.0 equiv) in MeCN (1.0 mL) was stirred at 80 °C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding product **7** (5.3 mg, 12%).

(*E*)-2-fluoro-2-(2-(methyl(phenyl)amino)-1*H*-benzo[*d*]imidazol-1-yl)vinyl 4-methylbenzenesulfonate (7)



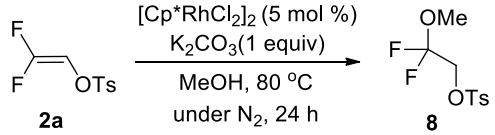
This compound was obtained in 12% yield (5.3 mg) as colorless oil. Eluent: PE/EA = 5/1, R_f = 0.6.

^{1}H NMR (**400 MHz, CD_3OD**): δ 7.51-7.47 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.35-7.30 (m, 2H), 7.23-7.18 (m, 2H), 7.17-7.11 (m, 4H), 6.97-6.92 (m, 1H), 6.70 (d, *J* = 2.6 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 3.52 (s, 3H), 2.35 (s, 3H).

^{13}C{^{1}H} NMR (**100 MHz, $CDCl_3$**): δ 152.9 (d, *J* = 1.5 Hz), 146.0, 145.0, 142.9 (d, *J* = 260.6 Hz), 141.9, 133.7 (d, *J* = 4.9 Hz), 130.9, 129.9, 129.6, 127.7, 125.8, 123.7, 123.3, 121.6, 120.4, 119.7, 117.4, 109.0, 41.7, 21.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -119.87.

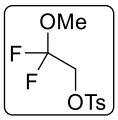
HRMS (ESI) calculated for $C_{23}H_{21}FN_3O_3S$ ($[M+H]^+$): 438.1282; found: 438.1275.



2a **8**

The mixture of 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (5 mol %) and K_2CO_3 (0.1 mmol, 1.0 equiv) in MeOH (1.0 mL) was stirred at 80 ^oC in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding product **8** (10.9 mg, 41%).

2,2-difluoro-2-methoxyethyl 4-methylbenzenesulfonate (8)



This compound was obtained in 41% yield (10.9 mg) as colorless oil. Eluent: PE/EA = 5/1, R_f = 0.4.

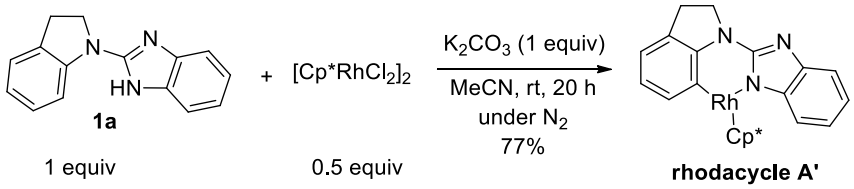
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 4.19 (t, *J* = 8.1 Hz, 2H), 3.53 (s, 3H), 2.46 (s, 3H).

^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 145.6, 132.3, 130.1, 128.2, 120.8 (t, *J* = 263.6 Hz), 66.8 (t, *J* = 38.4 Hz), 50.54 (t, *J* = 7.1 Hz), 21.8.

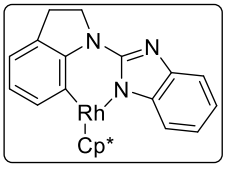
^{19}F NMR (376 MHz, CDCl$_3$): -83.71 (d, *J* = 12.5 Hz)

HRMS (ESI) calculated for $C_{10}H_{13}F_2O_4S$ ($[M+H]^+$): 267.0497; found: 267.0497.

Synthesis and catalytic reactivity of rhodacycle A':



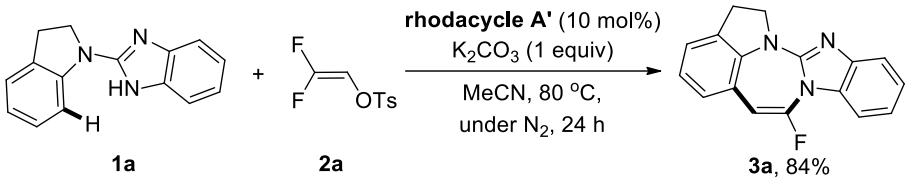
The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), $[Cp^*RhCl_2]_2$ (0.05 mmol, 0.5 equiv) and K_2CO_3 (0.1 mmol, 1.0 equiv) in MeCN (1.0 mL) was stirred at room temperature for 20 h under an atmosphere of N_2. Afterwards, the mixture was filtered to remove the insoluble precipitate and resulted in the ^{1}H-NMR pure rhodacycle A' in 77% isolated yield.



^{1}H NMR (**400 MHz, DMSO-*d*$_6$**): δ 7.50 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.27-7.20 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 7.0 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 4.26-4.14 (m, 2H), 3.34-3.27 (m, 2H), 1.44 (s, 15H).

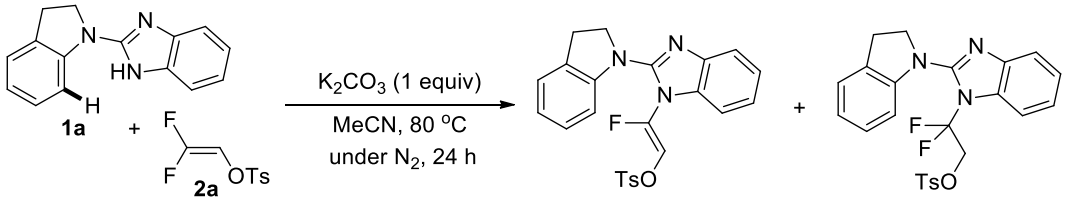
^{13}C{^{1}H} NMR (**100 MHz**, **DMSO-*d*$_6$**): δ 148.2, 142.7, 139.2, 137.6, 135.0, 130.1, 129.8, 127.5, 123.9, 121.5, 121.4, 121.3, 115.5, 111.0, 101.02, 100.97, 94.42, 94.36, 47.8, 28.1, 9.0.

HRMS (ESI) calculated for $C_{25}H_{27}N_3Rh$ ([M+H]$^+$): 472.1255; found: 472.1251.



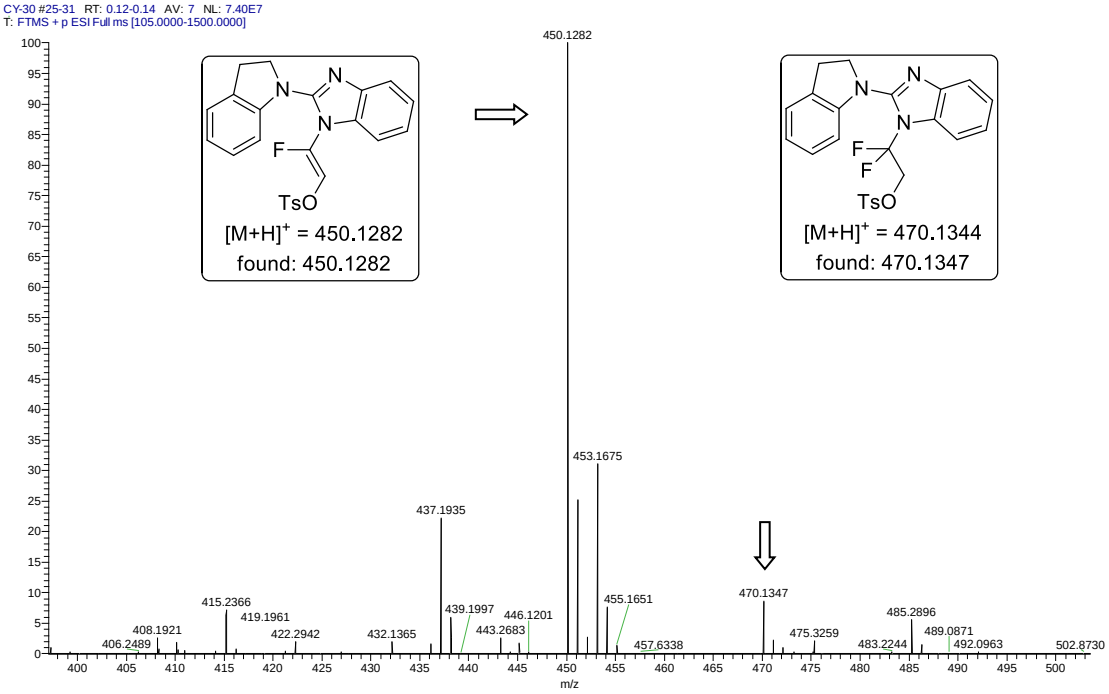
The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv), rhodacycle A' (10 mol %) and K_2CO_3 (0.1 mmol, 1.0 equiv) in MeCN (1.0 mL) was stirred at 80 °C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the solvent was removed under reduced pressure and the mixture was purified by preparative TLC (eluent: PE/EA = 5/1) to give the corresponding product **3a** (23.3 mg, 84%).

Detection of potential intermediates:

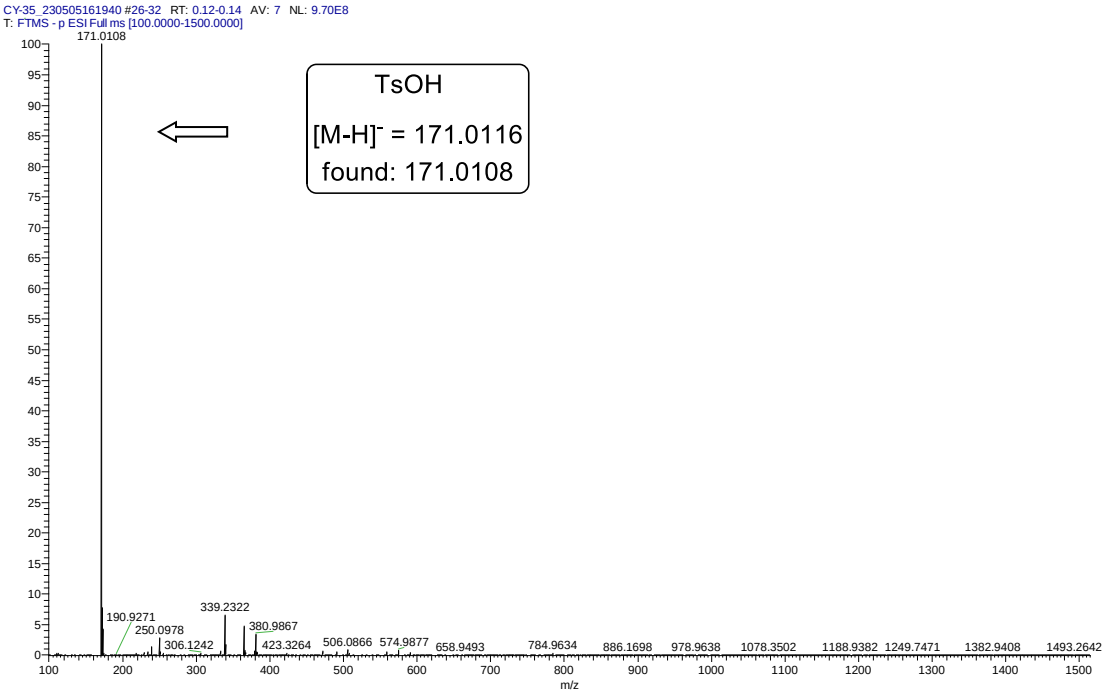


The mixture of *N*-benzo[*d*]imidazole indoline **1a** (0.1 mmol, 1.0 equiv), 2,2-difluorovinyl tosylate **2a** (0.1 mmol, 1.0 equiv) and K_2CO_3 (0.1 mmol, 1.0 equiv)

in MeCN (1.0 mL) was stirred at 80 °C in an oil bath under an atmosphere of N_2 for 24 h. Afterwards, the mixture was analyzed by LC-HRMS and both *N*-alkenylation intermediate and nucleophilic addition intermediate could be detected.

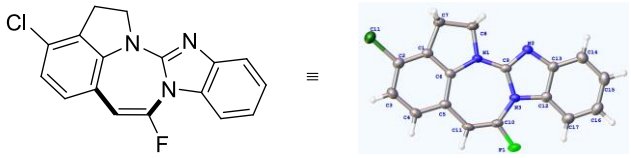


Another LC-HRMS analysis of the crude reaction mixtures under both conditions A and B revealed that the formation of TsOH could be detected.



IV. X-Ray Crystallographic Data

Compound 3c (CCDC 2213792):



Experimental: A suitable crystal was selected and on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 150.00(10) K during data collection.

Crystal Data for $C_{17}H_{11}ClFN_3$ (*M* =311.74 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 19.5807(14) Å, *b* = 4.7294(3) Å, *c* = 14.8063(10) Å, *β* = 106.738(7) °, *V* = 1313.04(16) Å^3, *Z* = 4, *T* = 150.00(10) K, μ(Mo Kα) = 0.302 mm^{-1}, *Dcalc* = 1.577 g/cm^3, 5097 reflections measured (4.344° ≤ 2Θ ≤ 50°), 2317 unique (R_{int} = 0.0212, R_{sigma} = 0.0314) which were used in all calculations. The final R_1 was 0.0361 (I > 2σ(I)) and wR_2 was 0.0897 (all data).

Table S2 Crystal data and structure refinement for 0062.

Identification code	0062
Empirical formula	$C_{17}H_{11}ClFN_3$
Formula weight	311.74
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	19.5807(14)
b/Å	4.7294(3)
c/Å	14.8063(10)
α/°	90
β/°	106.738(7)
γ/°	90
Volume/Å^3	1313.04(16)
Z	4
ρ_{calc}g/cm^3	1.577
μ/mm^{-1}	0.302
F(000)	640.0
Crystal size/mm^3	0.15 × 0.13 × 0.12

Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	4.344 to 50
Index ranges	$-20 \leq h \leq 23$, $-5 \leq k \leq 4$, $-17 \leq l \leq 10$
Reflections collected	5097
Independent reflections	2317 [R_{int} = 0.0212, R_{sigma} = 0.0314]
Data/restraints/parameters	2317/0/199
Goodness-of-fit on F^2	1.036
Final R indexes [I>=2σ (I)]	R_1 = 0.0361, wR_2 = 0.0837
Final R indexes [all data]	R_1 = 0.0445, wR_2 = 0.0897
Largest diff. peak/hole / e $Å^{-3}$	0.20/-0.27

Table S3 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 0062. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
Cl1	118.3(3)	9307.2(11)	3606.4(4)	37.55(17)
F1	3927.8(6)	1282(2)	4092.5(8)	37.3(3)
N1	2102.4(8)	2815(3)	5137.8(10)	24.2(4)
N2	2706.9(8)	-712(3)	6138.9(10)	23.5(4)
N3	3209.4(8)	635(3)	5010.1(10)	21.9(3)
C1	1249.3(10)	5913(4)	4347.2(12)	22.8(4)
C2	929.7(10)	7753(4)	3626.7(13)	26.9(4)
C3	1240.6(11)	8338(4)	2919.0(13)	30.2(5)
C4	1874.5(10)	7000(4)	2941.2(13)	28.0(4)
C5	2219.9(9)	5107(4)	3650.6(12)	22.6(4)
C6	1883.5(9)	4601(3)	4351.0(12)	20.9(4)
C7	1013.5(10)	4981(4)	5179.7(13)	29.2(4)
C8	1607.7(10)	3000(4)	5719.4(13)	28.4(4)
C9	2652.8(9)	949(4)	5420.1(12)	20.9(4)
C10	3300.4(10)	2052(4)	4223.9(13)	24.8(4)
C11	2897.9(10)	3878(4)	3635.3(12)	25.2(4)
C12	3661.9(10)	-1472(4)	5552.8(12)	23.3(4)
C13	3332.1(10)	-2250(4)	6239.5(13)	23.9(4)
C14	3628.1(10)	-4296(4)	6900.9(14)	30.3(5)
C15	4258.7(11)	-5555(4)	6870.4(14)	33.1(5)
C16	4584.5(11)	-4754(4)	6191.5(14)	33.0(5)
C17	4297.1(10)	-2712(4)	5521.3(13)	29.1(4)

Table S4 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for 0062. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	33.1(3)	40.5(3)	40.8(3)	4.5(2)	13.5(2)	10.2(2)
F1	29.9(6)	56.0(7)	33.0(7)	5.7(6)	20.2(5)	7.4(6)
N1	27.1(8)	29.2(8)	20.9(8)	2.6(6)	14.2(7)	2.7(7)
N2	25.2(8)	25.7(8)	21.7(8)	1.3(6)	10.0(7)	-1.3(7)
N3	22.5(8)	26.7(8)	18.7(8)	-3.1(6)	9.4(6)	-2.5(7)
C1	25.7(10)	22.8(9)	21.6(10)	-4.4(7)	9.3(8)	-4.5(8)
C2	26.4(10)	27.1(10)	27.4(10)	-4.8(8)	7.9(8)	-1.3(8)
C3	34.1(11)	31.3(10)	25.0(10)	4.2(8)	8.4(9)	0.0(9)
C4	34.0(11)	29.7(10)	22.2(10)	0.0(8)	11.0(8)	-5.3(9)
C5	25.5(10)	24.2(9)	20.0(9)	-5.3(8)	9.7(8)	-6.4(8)
C6	24.0(9)	20.3(9)	18.9(9)	-4.0(7)	7.0(7)	-5.3(8)
C7	30.1(10)	32.5(10)	29.7(11)	1.1(9)	16.2(9)	2.5(9)
C8	30.3(11)	34.0(11)	27.6(10)	0.3(8)	18.9(9)	1.6(9)
C9	21.8(9)	23.7(9)	18.7(9)	-5.8(7)	8.6(7)	-5.3(8)
C10	23.6(10)	32.5(10)	22.0(10)	-5.4(8)	12.4(8)	-3.8(8)
C11	29.0(10)	32.9(10)	18.3(9)	-2.0(8)	13.9(8)	-6.8(9)
C12	24.6(10)	25.0(9)	19.5(9)	-6.2(8)	4.7(7)	-3.0(8)
C13	23.9(10)	24.4(9)	23.0(10)	-5.5(8)	6.1(8)	-2.8(8)
C14	32.0(11)	31.3(11)	26.4(11)	-0.2(8)	6.6(8)	-3.2(9)
C15	32.0(11)	30.6(10)	30.5(11)	-1.6(9)	-0.9(9)	0.7(9)
C16	26.0(10)	35.1(11)	36.1(12)	-9.2(9)	6.0(9)	2.0(9)
C17	27.1(10)	34.3(10)	26.4(10)	-7.7(8)	8.4(8)	-2.5(9)

Table S5 Bond Lengths for 0062.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C2	1.7430(19)	C2	C3	1.383(3)
F1	C10	1.348(2)	C3	C4	1.385(3)
N1	C6	1.402(2)	C4	C5	1.398(3)
N1	C8	1.472(2)	C5	C6	1.400(2)
N1	C9	1.362(2)	C5	C11	1.455(3)
N2	C9	1.302(2)	C7	C8	1.528(3)
N2	C13	1.395(2)	C10	C11	1.316(3)
N3	C9	1.400(2)	C12	C13	1.402(3)
N3	C10	1.398(2)	C12	C17	1.388(3)
N3	C12	1.419(2)	C13	C14	1.380(3)
C1	C2	1.379(3)	C14	C15	1.383(3)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C6	1.387(3)	C15	C16	1.389(3)
C1	C7	1.501(2)	C16	C17	1.383(3)

Table S6 Bond Angles for 0062.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	N1	C8	110.78(14)	C5	C6	N1	128.44(17)
C9	N1	C6	132.12(15)	C1	C7	C8	103.97(14)
C9	N1	C8	117.04(15)	N1	C8	C7	105.11(14)
C9	N2	C13	105.33(15)	N1	C9	N3	125.56(16)
C9	N3	C12	105.42(14)	N2	C9	N1	120.83(16)
C10	N3	C9	127.75(15)	N2	C9	N3	113.60(15)
C10	N3	C12	126.82(15)	F1	C10	N3	109.32(15)
C2	C1	C6	119.45(16)	C11	C10	F1	118.60(16)
C2	C1	C7	129.92(17)	C11	C10	N3	132.09(17)
C6	C1	C7	110.62(16)	C10	C11	C5	128.83(16)
C1	C2	Cl1	119.19(14)	C13	C12	N3	104.61(15)
C1	C2	C3	120.77(18)	C17	C12	N3	134.19(17)
C3	C2	Cl1	120.03(15)	C17	C12	C13	121.20(17)
C2	C3	C4	118.53(18)	N2	C13	C12	111.05(16)
C3	C4	C5	123.16(17)	C14	C13	N2	128.17(17)
C4	C5	C6	115.91(17)	C14	C13	C12	120.78(17)
C4	C5	C11	119.36(16)	C13	C14	C15	118.37(19)
C6	C5	C11	124.70(17)	C14	C15	C16	120.43(19)
C1	C6	N1	109.38(15)	C17	C16	C15	122.20(19)
C1	C6	C5	122.17(17)	C16	C17	C12	117.02(18)

Table S7 Torsion Angles for 0062.

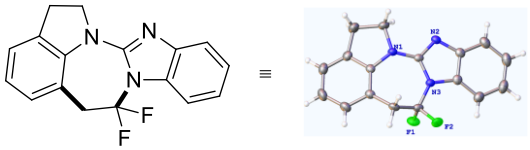
A	B	C	D	Angle/°	A	B	C	D	Angle/°
Cl1	C2	C3	C4	-178.06(14)	C8	N1	C9	N2	4.2(2)
F1	C10	C11	C5	-177.37(16)	C8	N1	C9	N3	-174.35(16)
N2	C13	C14	C15	-179.85(17)	C9	N1	C6	C1	174.85(17)
N3	C10	C11	C5	2.8(3)	C9	N1	C6	C5	-5.3(3)
N3	C12	C13	N2	-0.23(19)	C9	N1	C8	C7	-174.04(15)
N3	C12	C13	C14	179.81(16)	C9	N2	C13	C12	0.0(2)
N3	C12	C17	C16	179.99(18)	C9	N2	C13	C14	179.94(18)
C1	C2	C3	C4	1.0(3)	C9	N3	C10	F1	176.04(15)
C1	C7	C8	N1	-3.37(19)	C9	N3	C10	C11	-4.1(3)
C2	C1	C6	N1	-179.30(15)	C9	N3	C12	C13	0.37(18)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C2	C1	C6	C5	0.8(3)	C9	N3	C12	C17	-179.22(19)
C2	C1	C7	C8	-178.63(18)	C10	N3	C9	N1	-2.7(3)
C2	C3	C4	C5	-0.7(3)	C10	N3	C9	N2	178.67(16)
C3	C4	C5	C6	0.4(3)	C10	N3	C12	C13	-178.73(16)
C3	C4	C5	C11	-177.79(17)	C10	N3	C12	C17	1.7(3)
C4	C5	C6	N1	179.68(16)	C11	C5	C6	N1	-2.2(3)
C4	C5	C6	C1	-0.5(3)	C11	C5	C6	C1	177.61(16)
C4	C5	C11	C10	-179.18(19)	C12	N3	C9	N1	178.24(16)
C6	N1	C8	C7	3.6(2)	C12	N3	C9	N2	-0.42(19)
C6	N1	C9	N2	-172.80(17)	C12	N3	C10	F1	-5.1(2)
C6	N1	C9	N3	8.6(3)	C12	N3	C10	C11	174.77(19)
C6	C1	C2	Cl1	177.99(13)	C12	C13	C14	C15	0.1(3)
C6	C1	C2	C3	-1.1(3)	C13	N2	C9	N1	-178.45(15)
C6	C1	C7	C8	2.2(2)	C13	N2	C9	N3	0.27(19)
C6	C5	C11	C10	2.8(3)	C13	C12	C17	C16	0.5(3)
C7	C1	C2	Cl1	-1.1(3)	C13	C14	C15	C16	0.4(3)
C7	C1	C2	C3	179.80(19)	C14	C15	C16	C17	-0.4(3)
C7	C1	C6	N1	0.0(2)	C15	C16	C17	C12	0.0(3)
C7	C1	C6	C5	-179.90(16)	C17	C12	C13	N2	179.42(15)
C8	N1	C6	C1	-2.3(2)	C17	C12	C13	C14	-0.5(3)
C8	N1	C6	C5	177.54(17)					

Table S8 Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 0062.

Atom	*x*	*y*	*z*	U(eq)
H3	1028.73	9601.89	2438.84	36
H4	2080.16	7380.45	2461.04	34
H7A	560.46	3995.7	4977.53	35
H7B	967.07	6585.45	5565.96	35
H8A	1847.01	3763.09	6337.85	34
H8B	1417.5	1150.92	5795.86	34
H11	3070.06	4464	3142.33	30
H14	3409.06	-4815.57	7356.01	36
H15	4466.03	-6946.14	7307.28	40
H16	5009.93	-5620.98	6187.47	40
H17	4519.59	-2192.32	5069.73	35

Compound 4a (CCDC 2213793):



Experimental: A suitable crystal was selected and on a SuperNova, Dual, Cu at zero, AtlasS2 diffractometer. The crystal was kept at 150.00(10) K during data collection.

Crystal Data for $C_{17}H_{13}F_2N_3$ (*M* =297.30 g/mol): monoclinic, space group $P2_1/c$ (no. 14), *a* = 11.6045(10) Å, *b* = 8.9631(8) Å, *c* = 13.1233(10) Å, *β* = 99.803(7) °, *V* = 1345.1(2) $Å^3$, *Z* = 4, *T* = 150.00(10) K, μ(Mo Kα) = 0.109 mm^{-1}, *Dcalc* = 1.468 g/cm^3, 5944 reflections measured (5.53° ≤ 2Θ ≤ 49.998°), 2370 unique (R_{int} = 0.0230, R_{sigma} = 0.0322) which were used in all calculations. The final R_1 was 0.0387 (I > 2σ(I)) and wR_2 was 0.0936 (all data).

Table S9 Crystal data and structure refinement for exp_2968.

Identification code	exp_2968
Empirical formula	$C_{17}H_{13}F_2N_3$
Formula weight	297.30
Temperature/K	150.00(10)
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.6045(10)
b/Å	8.9631(8)
c/Å	13.1233(10)
α/°	90
β/°	99.803(7)
γ/°	90
Volume/$Å^3$	1345.1(2)
Z	4
$\rho_{calc}g/cm^3$	1.468
μ/mm^{-1}	0.109
F(000)	616.0
Crystal size/mm^3	0.12 × 0.11 × 0.09
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	5.53 to 49.998
Index ranges	-13 ≤ h ≤ 13, -10 ≤ k ≤ 9, -15 ≤ l ≤ 15

Reflections collected	5944
Independent reflections	2370 [R_{int} = 0.0230, R_{sigma} = 0.0322]
Data/restraints/parameters	2370/0/199
Goodness-of-fit on F^2	1.070
Final R indexes [I>=2σ (I)]	R_1 = 0.0387, wR_2 = 0.0886
Final R indexes [all data]	R_1 = 0.0455, wR_2 = 0.0936
Largest diff. peak/hole / e $Å^{-3}$	0.16/-0.23

Table S10 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_2968. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	***x***	***y***	***z***	**U(eq)**
F1	5029.7(9)	5666.3(12)	1793.6(7)	33.3(3)
F2	5784.2(9)	3671.0(11)	2550.7(7)	34.1(3)
N1	3729.3(11)	6637.7(15)	4126.2(9)	21.9(3)
N2	5629.1(11)	7106.5(15)	4948.3(9)	23.0(3)
N3	5474.8(11)	5604.9(15)	3549.1(9)	20.8(3)
C1	1847.3(14)	7147(2)	3347.2(12)	26.3(4)
C2	854.0(15)	6969(2)	2609.8(13)	32.9(4)
C3	849.0(15)	5893(2)	1849.6(14)	34.9(5)
C4	1820.4(15)	5005(2)	1839.4(12)	30.5(4)
C5	2833.0(14)	5157.6(19)	2575.5(11)	23.3(4)
C6	2826.0(14)	6268.8(18)	3311.6(11)	20.9(4)
C7	3828.6(14)	4095.1(19)	2607.8(12)	25.3(4)
C8	5004.0(14)	4783.5(19)	2638.3(11)	23.2(4)
C9	4904.9(13)	6450.6(17)	4208.8(11)	19.4(3)
C10	6736.9(14)	6725.0(19)	4778.2(12)	23.6(4)
C11	7817.1(15)	7135(2)	5339.3(13)	31.4(4)
C12	8814.1(16)	6639(2)	5005.7(14)	36.4(5)
C13	8743.7(15)	5756(2)	4126.3(15)	36.5(5)
C14	7681.8(15)	5321(2)	3559.9(13)	31.3(4)
C15	6680.4(14)	5813.2(19)	3906.5(12)	23.4(4)
C16	3327.3(15)	7839(2)	4769.3(12)	27.8(4)
C17	2071.1(15)	8160(2)	4269.8(14)	38.3(5)

Table S11 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_2968. The Anisotropic displacement factor exponent takes the form:

$-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
F1	48.6(6)	32.9(6)	19.2(5)	3.6(4)	8.0(4)	-2.9(5)
F2	38.3(6)	27.1(6)	37.4(6)	-9.9(4)	7.9(4)	8.5(5)
N1	26.0(7)	21.0(8)	18.7(7)	-3.1(5)	4.2(5)	1.6(6)
N2	28.2(7)	21.8(8)	18.4(6)	-0.1(6)	2.0(5)	0.2(6)
N3	24.7(7)	19.1(8)	18.7(6)	-1.1(5)	4.0(5)	2.0(6)
C1	26.0(9)	26.1(10)	28.4(9)	2.4(7)	9.2(7)	-0.2(8)
C2	25.5(9)	35.7(12)	38.0(10)	7.2(8)	6.4(7)	3.4(8)
C3	27.6(9)	41.2(12)	33.0(10)	3.3(8)	-3.6(7)	-6.7(9)
C4	34.7(10)	29.0(10)	26.1(9)	-1.7(8)	0.3(7)	-6.3(8)
C5	29.0(9)	20.1(9)	21.1(8)	1.7(7)	5.0(6)	-3.0(7)
C6	24.2(8)	20.0(9)	19.1(8)	4.4(6)	5.5(6)	-2.4(7)
C7	35.2(9)	20.1(9)	19.7(8)	-4.0(7)	2.0(7)	-1.9(8)
C8	33.9(9)	18.4(9)	17.8(8)	1.2(6)	5.8(6)	7.1(7)
C9	27.3(8)	15.0(9)	16.2(7)	2.3(6)	4.8(6)	0.9(7)
C10	28.7(9)	19.2(9)	22.2(8)	5.8(7)	2.2(6)	-0.3(7)
C11	34.4(10)	28.1(10)	28.9(9)	4.7(8)	-2.3(7)	-2.8(8)
C12	27.4(9)	34.0(11)	44.7(11)	11.6(9)	-2.5(8)	-2.5(9)
C13	26.1(9)	36.4(12)	48.1(11)	13.0(9)	9.2(8)	5.7(8)
C14	32.3(10)	29.7(11)	32.9(9)	4.7(8)	8.8(7)	5.1(8)
C15	26.7(9)	19.1(9)	24.2(8)	6.5(7)	3.6(6)	1.0(7)
C16	34.7(9)	24.6(10)	25.0(8)	-5.0(7)	8.0(7)	4.6(8)
C17	33.3(10)	41.6(12)	40.7(10)	-9.4(9)	8.4(8)	8.4(9)

Table S12 Bond Lengths for exp_2968.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
F1	C8	1.3664(18)	C2	C3	1.386(3)
F2	C8	1.3648(19)	C3	C4	1.382(3)
N1	C6	1.403(2)	C4	C5	1.395(2)
N1	C9	1.360(2)	C5	C6	1.388(2)
N1	C16	1.491(2)	C5	C7	1.492(2)
N2	C9	1.310(2)	C7	C8	1.491(2)
N2	C10	1.385(2)	C10	C11	1.391(2)
N3	C8	1.431(2)	C10	C15	1.398(2)
N3	C9	1.3988(19)	C11	C12	1.379(3)
N3	C15	1.410(2)	C12	C13	1.390(3)
C1	C2	1.382(2)	C13	C14	1.382(3)
C1	C6	1.389(2)	C14	C15	1.390(2)

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C17	1.501(2)	C16	C17	1.521(2)

Table S13 Bond Angles for exp_2968.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C6	N1	C16	109.65(13)	F1	C8	C7	111.35(13)
C9	N1	C6	129.83(13)	F2	C8	F1	104.38(11)
C9	N1	C16	116.75(13)	F2	C8	N3	106.37(12)
C9	N2	C10	105.42(13)	F2	C8	C7	108.20(14)
C9	N3	C8	129.97(13)	N3	C8	C7	116.92(13)
C9	N3	C15	105.62(12)	N1	C9	N3	126.22(14)
C15	N3	C8	124.20(13)	N2	C9	N1	120.79(14)
C2	C1	C6	120.02(16)	N2	C9	N3	112.98(13)
C2	C1	C17	130.08(16)	N2	C10	C11	128.85(15)
C6	C1	C17	109.87(14)	N2	C10	C15	111.14(14)
C1	C2	C3	119.00(17)	C11	C10	C15	120.01(15)
C4	C3	C2	120.26(16)	C12	C11	C10	118.43(17)
C3	C4	C5	121.94(17)	C11	C12	C13	120.89(17)
C4	C5	C7	120.93(15)	C14	C13	C12	121.87(17)
C6	C5	C4	116.62(16)	C13	C14	C15	116.92(17)
C6	C5	C7	122.29(14)	C10	C15	N3	104.78(13)
C1	C6	N1	110.48(14)	C14	C15	N3	133.35(16)
C5	C6	N1	127.37(15)	C14	C15	C10	121.87(16)
C5	C6	C1	122.10(15)	N1	C16	C17	105.20(13)
C8	C7	C5	115.90(14)	C1	C17	C16	104.75(14)
F1	C8	N3	108.77(13)				

Table S14 Torsion Angles for exp_2968.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
N1	C16	C17	C1	-1.70(19)	C9	N1	C16	C17	160.93(14)
N2	C10	C11	C12	-178.60(16)	C9	N2	C10	C11	179.68(17)
N2	C10	C15	N3	-1.51(18)	C9	N2	C10	C15	0.18(18)
N2	C10	C15	C14	178.02(15)	C9	N3	C8	F1	94.70(18)
C1	C2	C3	C4	0.7(3)	C9	N3	C8	F2	-153.38(14)
C2	C1	C6	N1	179.79(15)	C9	N3	C8	C7	-32.4(2)
C2	C1	C6	C5	-2.6(2)	C9	N3	C15	C10	2.16(16)
C2	C1	C17	C16	-179.73(18)	C9	N3	C15	C14	-177.29(18)
C2	C3	C4	C5	-0.5(3)	C10	N2	C9	N1	-177.79(14)

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C3	C4	C5	C6	-1.1(2)	C10	N2	C9	N3	1.31(18)
C3	C4	C5	C7	174.29(16)	C10	C11	C12	C13	0.3(3)
C4	C5	C6	N1	179.87(15)	C11	C10	C15	N3	178.94(15)
C4	C5	C6	C1	2.7(2)	C11	C10	C15	C14	-1.5(2)
C4	C5	C7	C8	129.74(16)	C11	C12	C13	C14	-1.0(3)
C5	C7	C8	F1	-59.29(17)	C12	C13	C14	C15	0.3(3)
C5	C7	C8	F2	-173.43(12)	C13	C14	C15	N3	-179.71(17)
C5	C7	C8	N3	66.59(19)	C13	C14	C15	C10	0.9(2)
C6	N1	C9	N2	167.48(15)	C15	N3	C8	F1	-79.31(18)
C6	N1	C9	N3	-11.5(3)	C15	N3	C8	F2	32.60(19)
C6	N1	C16	C17	0.62(18)	C15	N3	C8	C7	153.54(15)
C6	C1	C2	C3	0.8(3)	C15	N3	C9	N1	176.78(15)
C6	C1	C17	C16	2.3(2)	C15	N3	C9	N2	-2.26(17)
C6	C5	C7	C8	-55.1(2)	C15	C10	C11	C12	0.9(2)
C7	C5	C6	N1	4.5(3)	C16	N1	C6	C1	0.84(18)
C7	C5	C6	C1	-172.64(15)	C16	N1	C6	C5	-176.59(15)
C8	N3	C9	N1	1.9(3)	C16	N1	C9	N2	11.9(2)
C8	N3	C9	N2	-177.12(14)	C16	N1	C9	N3	-167.08(14)
C8	N3	C15	C10	177.40(14)	C17	C1	C2	C3	-176.97(18)
C8	N3	C15	C14	-2.0(3)	C17	C1	C6	N1	-2.00(19)
C9	N1	C6	C1	-156.09(16)	C17	C1	C6	C5	175.59(15)
C9	N1	C6	C5	26.5(3)					

Table S15 Hydrogen Atom Coordinates ($Å \times 10^4$) and Isotropic Displacement Parameters ($Å^2 \times 10^3$) for exp_2968.

Atom	*x*	*y*	*z*	U(eq)
H2	198.95	7561.14	2623.49	40
H3	189.44	5769.48	1344.41	42
H4	1798.29	4284.09	1326.75	37
H7A	3858.19	3465.19	3212.72	30
H7B	3668.14	3455.13	2004.24	30
H11	7865.7	7730.05	5925.61	38
H12	9543.58	6897.91	5373.93	44
H13	9430.41	5448.99	3913.08	44
H14	7639.35	4725.85	2974.03	38
H16A	3808.02	8723.93	4767.34	33
H16B	3363.89	7506.47	5477.46	33
H17A	1537.46	7943.13	4744.56	46

Atom	*x*	*y*	*z*	U(eq)
H17B	1978.99	9196.99	4059.65	46

V. General Procedure for the Biological Evaluation

Cell culture:

Human cancer cells MCF-7, A549, HepG2, BEAS-2B were purchased from American Type Culture Collection (ATCC, Shanghai, China). MCF-7, HepG2 and BEAS-2B cells were cultured with Dulbecco's Modified Eagle Medium cell culture medium (DMEM, Gibco, USA) supplemented with 10% FBS (Gibco, USA). A549 cells were cultured with RPMI-1640 medium (Gibco, USA) supplemented with 10% FBS. All of them were cultured in 5% CO_2 at 37 °C in an incubator (Thermo Scientific, USA).

***In Vitro* Cytotoxicity Assay:**

Cells were plated in 96-well microtiter plates at a density of 5×10^3/well and incubated in a humidified atmosphere with 5% CO_2 at 37 °C for 24 h. The tested compound was added into triplicate wells with same concentration (10 μM) and 0.5% DMSO for the control. After they had been incubated for 48 h, 10 μL of CCK8 (Cell Counting Kit-8) solution was added into each well, and the plate was incubated for an additional 1 h. The absorbance (OD) was read on a microplate reader at 450 nm to measure the cell viability (%). All experiments were performed for three times.

Table S16 Cell viability measured by treating with 10 μM of the tested compounds

	Cell Viability（%） (mean ± SEM, *n* = 3)			
Compounds	MCF-7	A549	HepG2	BEAS-2B
DMSO	96.5±0.32	94.6±0.42	94.6±0.34	98.0±1.16

3a	96.5±4.09	97.2±1.14	94.8±2.76	97.1±1.71
3b	90.7±7.15	76.3±2.06	94.3±5.65	93.3±3.54
3c	92.3±2.48	82.7±2.31	90.9±4.07	88.92±0.83
3d	91.4±5.97	86.8±2.50	93.8±4.54	89.6±1.09
3g	96.1±5.49	85.2±1.56	90.9±2.71	93.7±1.87
3j	93.7±9.82	87.2±1.96	92.7±5.08	67.7±3.57
3k	63.9±5.22	67.5±1.96	94.5±9.89	64.8±5.24
3l	55.0±2.12	92.0±3.15	67.3±2.91	69.3±3.67
3m	98.4±1.25	94.3±4.40	93.8±2.85	92.9±3.40
3n	96.8±9.68	98.4±2.71	92.4±1.91	98.8±1.26
3n'	81.3±7.12	81.2±1.12	78.4±3.62	76.7±4.55
3o	68.8±7.53	67.2±2.87	76.8±1.22	70.9±2.73
4a	74.7±8.20	77.4±1.61	78.3±9.28	80.0±7.42
4b	91.4±3.36	65.2±2.87	74.5±9.24	91.6±4.63
4c	99.7±4.15	94.1±1.82	90.0±2.54	96.2±2.80
4e	87.4±6.60	95.4±6.22	96.2±0.99	95.1±1.89
4f	91.6±6.88	94.5±2.05	92.8±2.24	85.6±3.21
4g	94.3±5.32	99.7±2.19	115.2±3.6	86.9±6.30
4h	98.0±2.99	94.1±5.77	99.1±0.88	81.2±2.53

Colony formation assay:

MCF-7 cells in the logarithmic growth phase were plated in a 6-well plate at a density of 1000 cells per well. After 96 h, cells were incubated with DMSO (0.1%) or compound **3l** (1.25 μM, 2.5 μM, 5 μM, 10 μM or 20 μM) for 48 h, and then were cultured in drug-free medium for 7 days. The cell colonies were fixed with 4% paraformaldehyde for 10 minutes, stained with crystal violet for 20 minutes, and then photographed. All experiments were performed for three times.

Flow cytometry (FCM) analysis of cell apoptosis:

Apoptotic cell death was determined by flow cytometry analysis using Annexin V-FITC and propidium iodide (PI) assay kit (BD, PharMingen, San Diego, CA). After being cultured for 24 h, the cells were treated by different concentrations (0, 2.5, 5, 10 μM) of compound **3l** for 18 h. MCF-7 cells were collected, washed with cold PBS, suspended in 5 μL of Annexin V binding buffer and stained with 5 μL of PI. The cells were mixed gently, incubated in the dark for 20 minutes, and washed. The samples were analyzed with a FACS (Beckman Coulter, USA).

Statistical analysis:

All cell culture experiments were performed independently for at least three times and in triplicate each time. All the data were processed and statistically analyzed using SPSS and GraphPad software, and the data in bar graphs are presented as mean value ± standard deviation (SD). The statistical significance (**P < 0.05) was calculated by ANOVA (one-way analysis of variance).

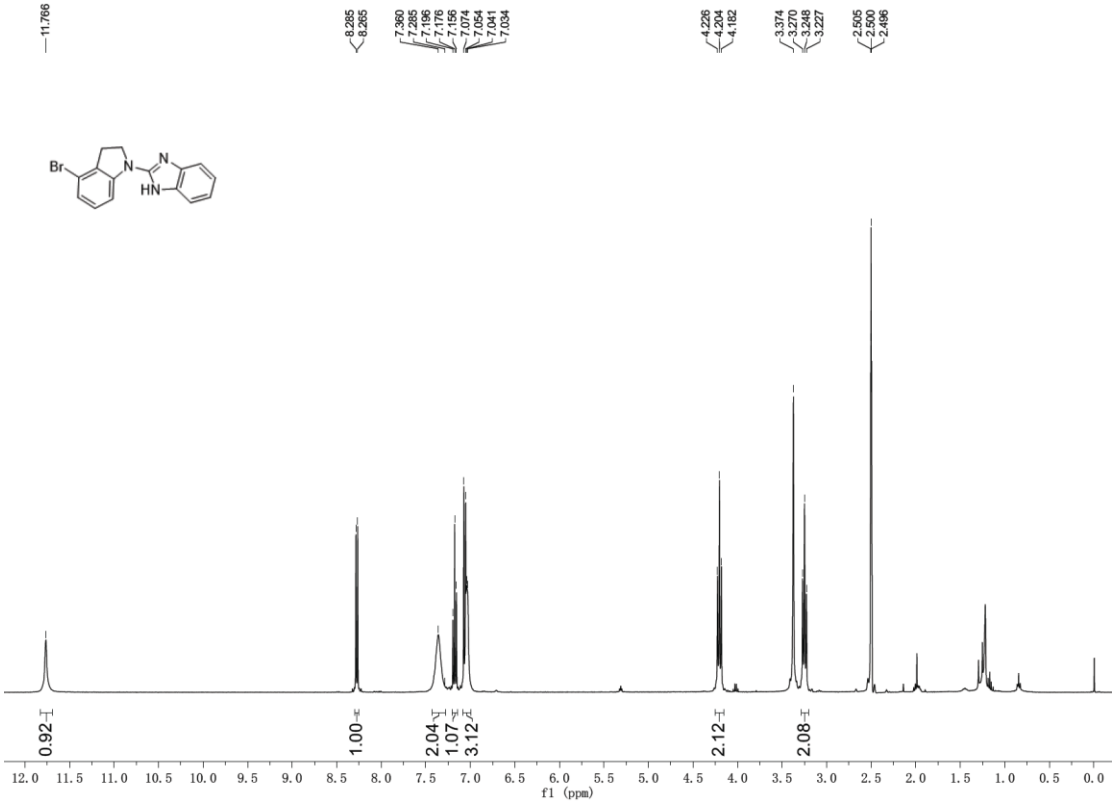
VI. References

[S1] S. Zhao, X. Cai, Y. Lu, J. Hu, Z. Xiong, J. Jin, Y. Li, H. Wang and J.-Q. Wu, Cp*Ir(III) and Cp*Rh(III)-catalyzed annulation of salicylaldehydes with fluorinated vinyl tosylates, *Chem. Commun.*, 2022, **58**, 8966.

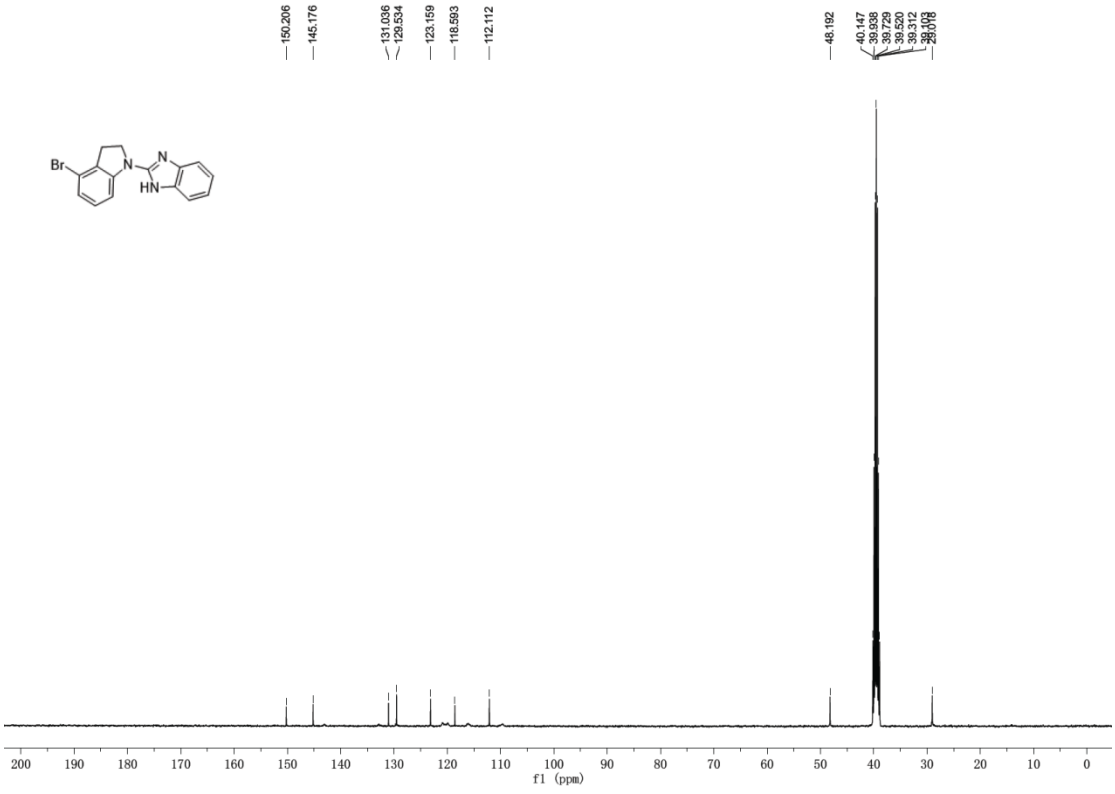
[S2] (a) N. Martínez-Yáñez, J. Suárez, A. Cajaraville, J. A. Varela and C. Saá, Rh(III)-catalyzed [5+2] oxidative annulation of cyclic arylguanidines and alkynes to 1,3-benzodiazepines. A striking mechanistic proposal from DFT, *Org. Lett.*, 2019, **21**, 1779; (b) Y. Yang, K. Zhang, J. Yang, G. Zhu, W. Chen, C. Zhang, Z. Zhou and W. Yi, Ru(II)-catalyzed and acidity-controlled tunable [5+1]/[5+2] annulation for building ring-fused quinazolines and 1,3-benzodiazepines, *Chem. Commun.*, 2020, **56**, 11315.

VII. Copies of NMR Spectra

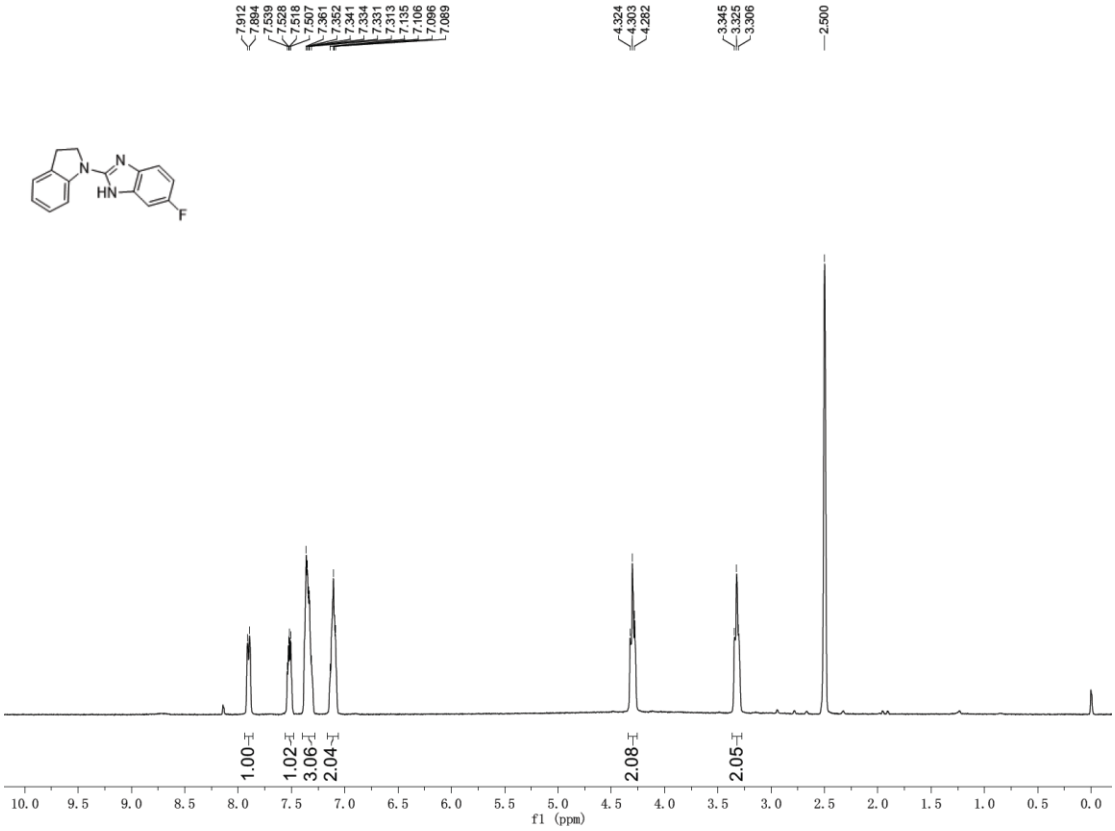
^{1}H-NMR of **1d** (DMSO-d_6, 400 MHz)



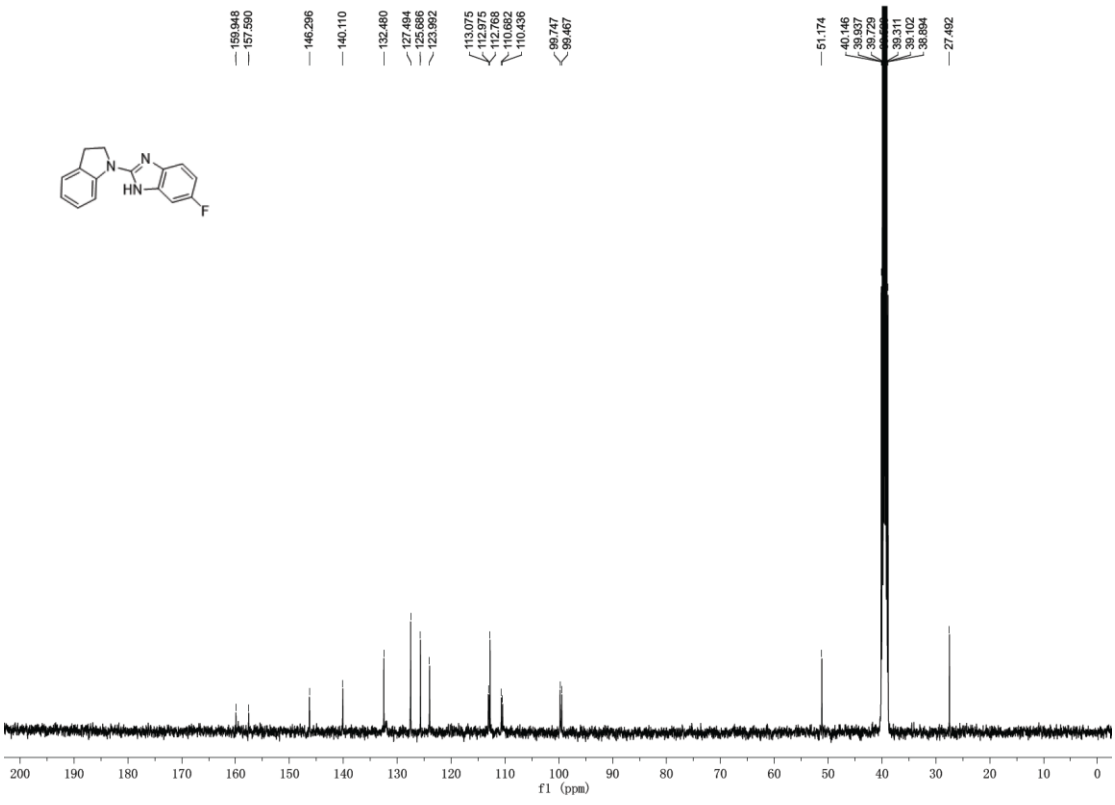
^{13}C{^{1}H}-NMR of **1d** (DMSO-d_6, 100 MHz)



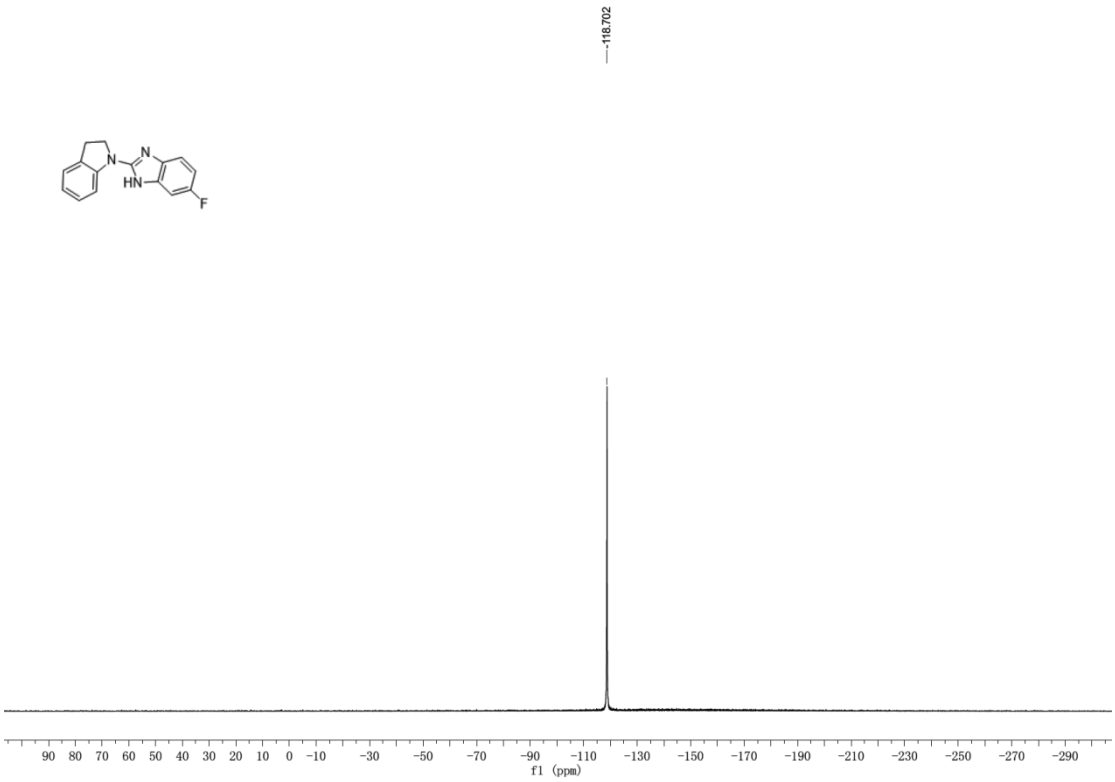
^{1}H-NMR of **1n** (DMSO-d_6, 400 MHz)



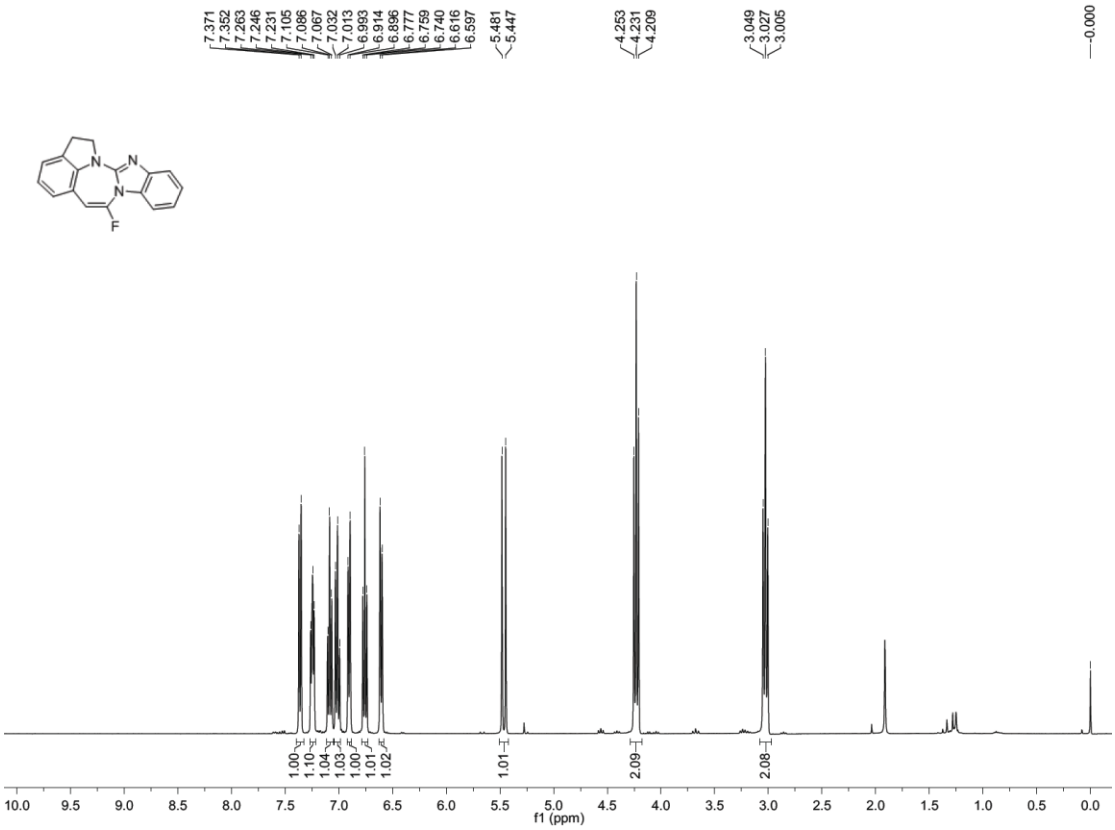
^{13}C{^{1}H}-NMR of **1n** (DMSO-d_6, 100 MHz)



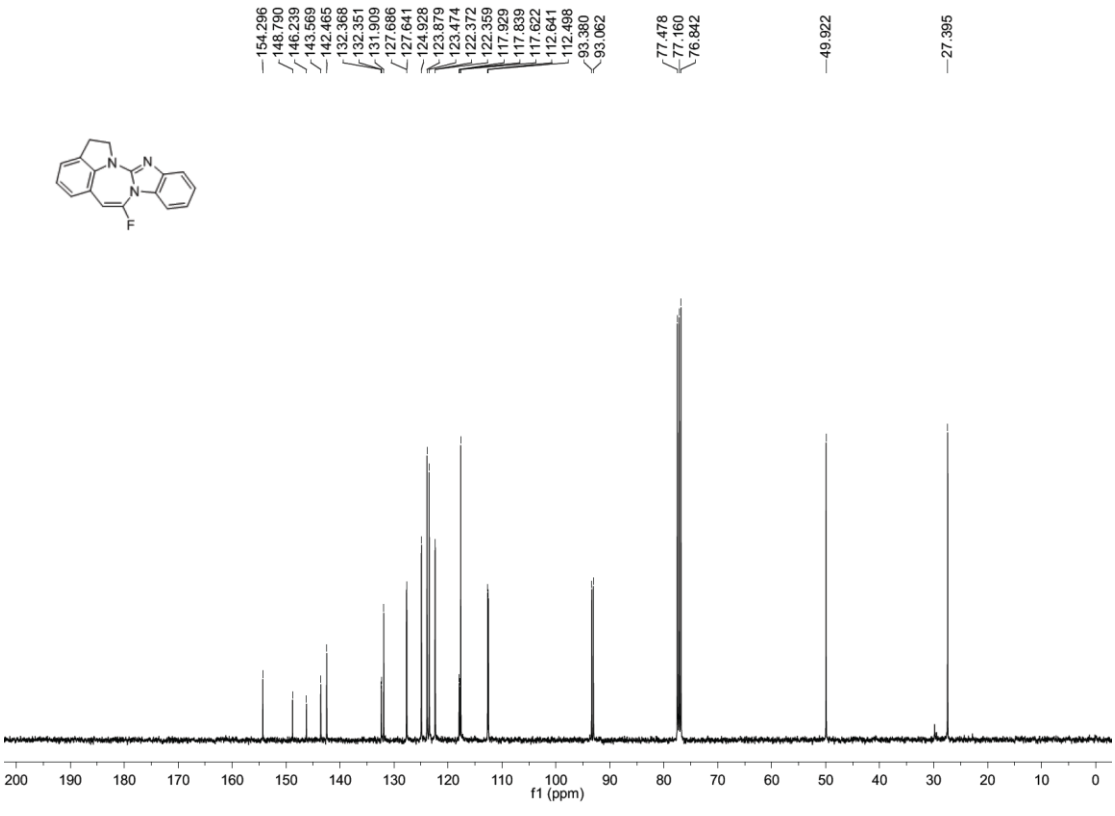
^{19}F-NMR of **1n** (DMSO-d_6, 376 MHz)



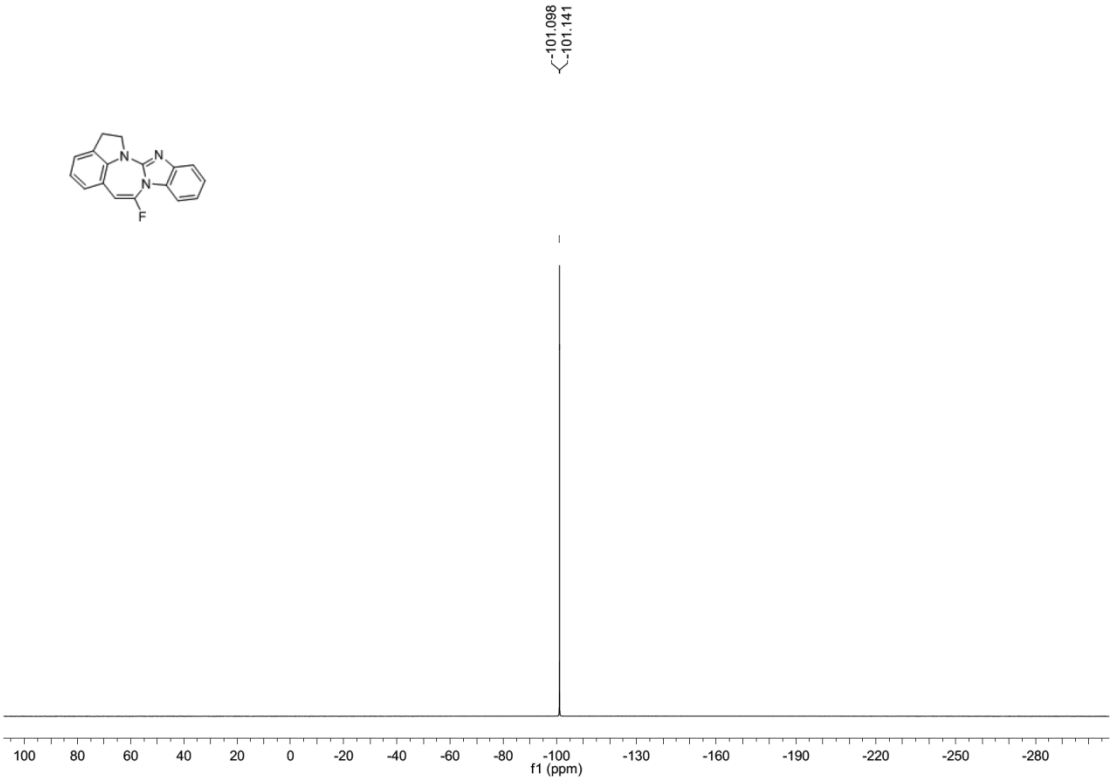
^{1}H-NMR of **3a** ($CDCl_3$, 400 MHz)



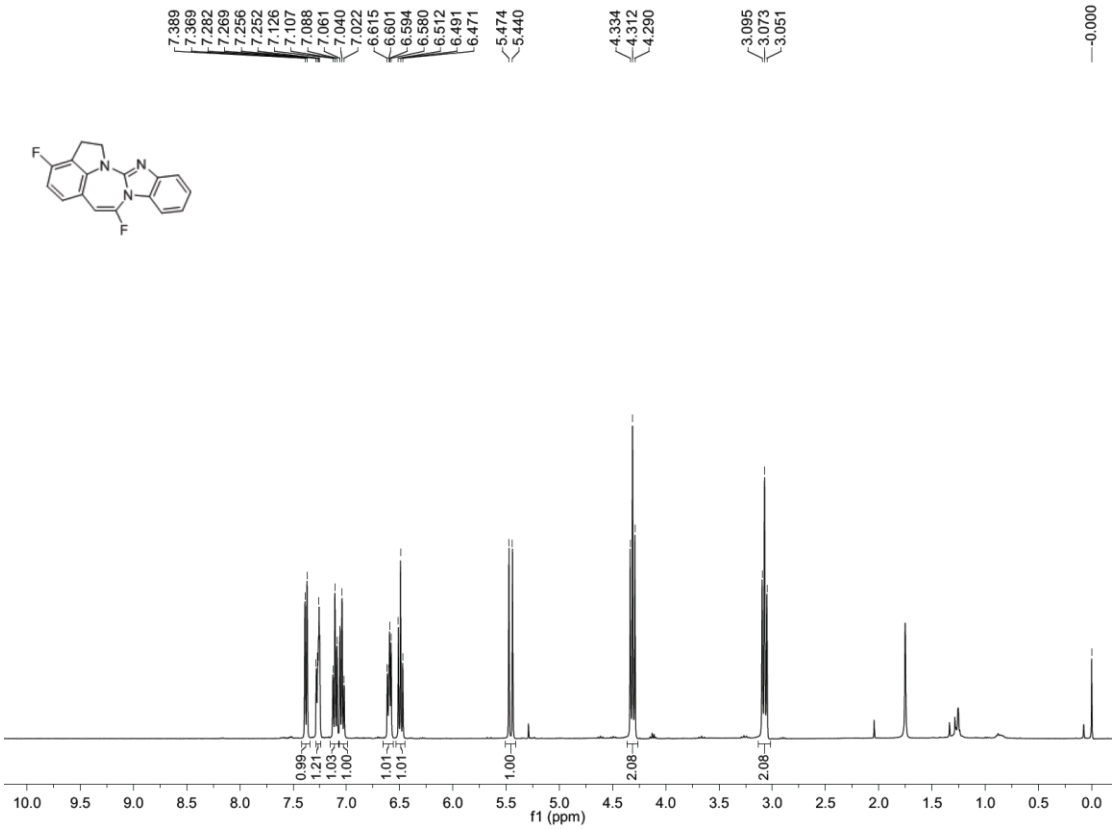
^{13}C{^{1}H}-NMR of **3a** ($CDCl_3$, 100 MHz)



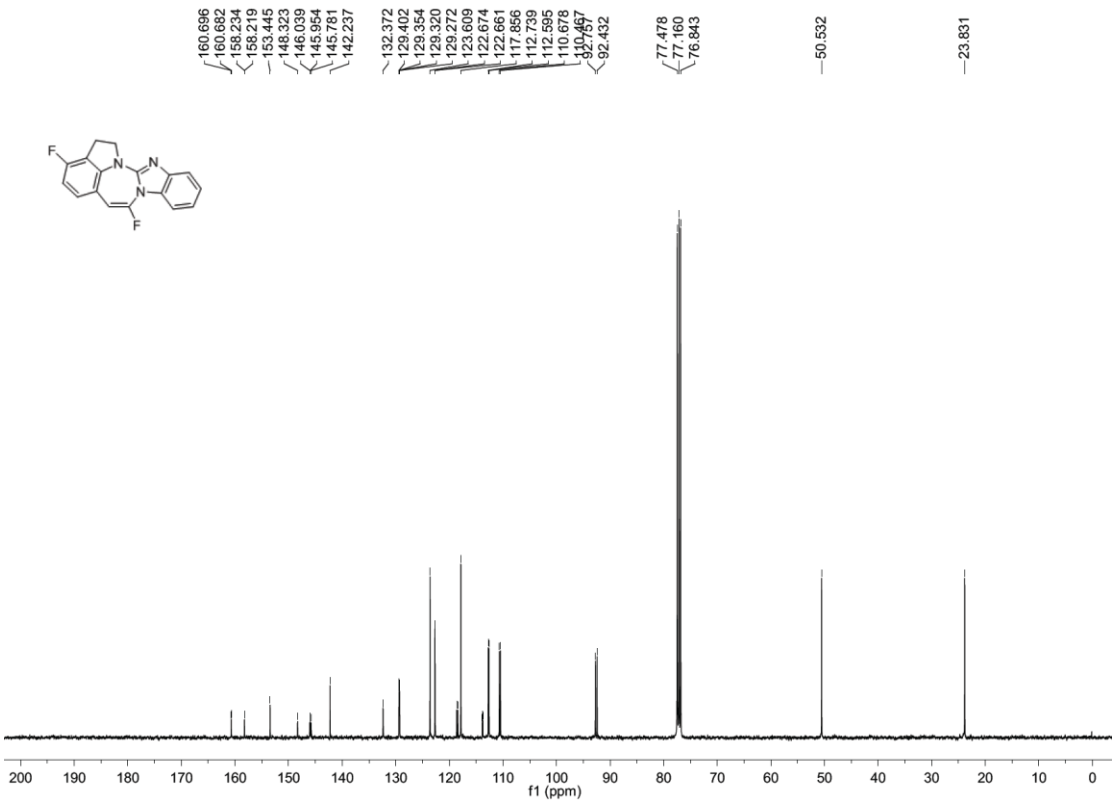
^{19}F-NMR of **3a** ($CDCl_3$, 376 MHz)



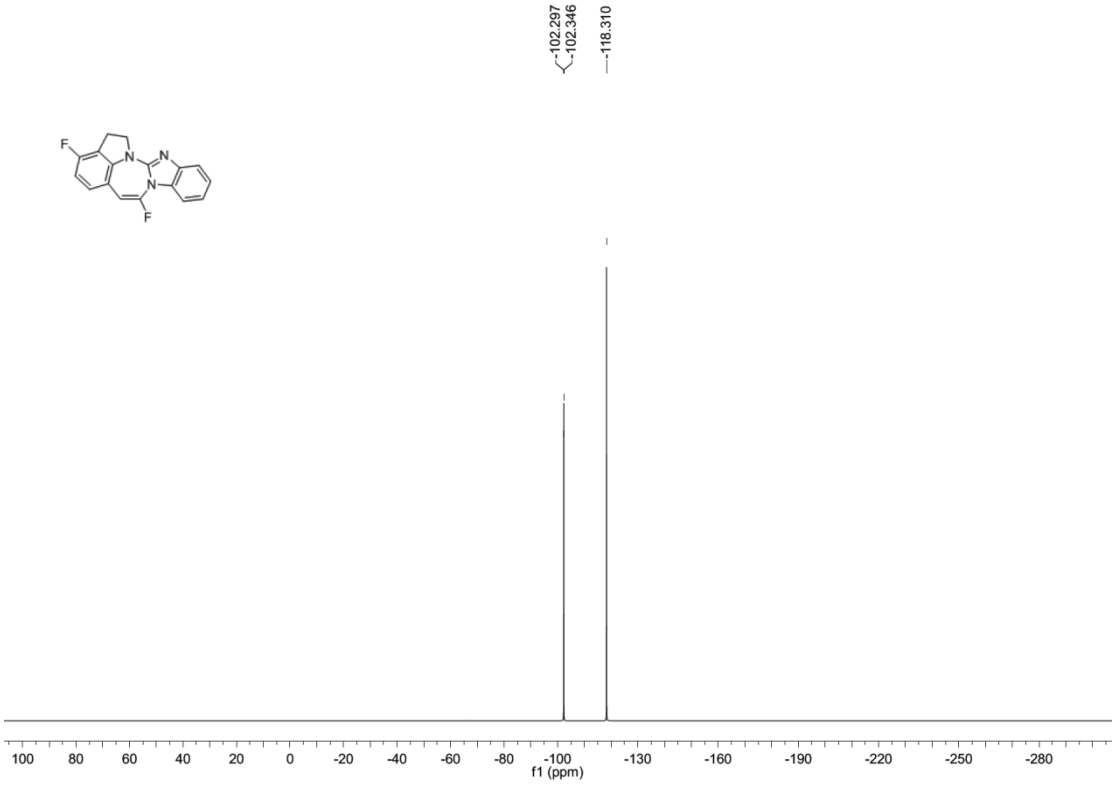
^{1}H-NMR of **3b** ($CDCl_3$, 400 MHz)



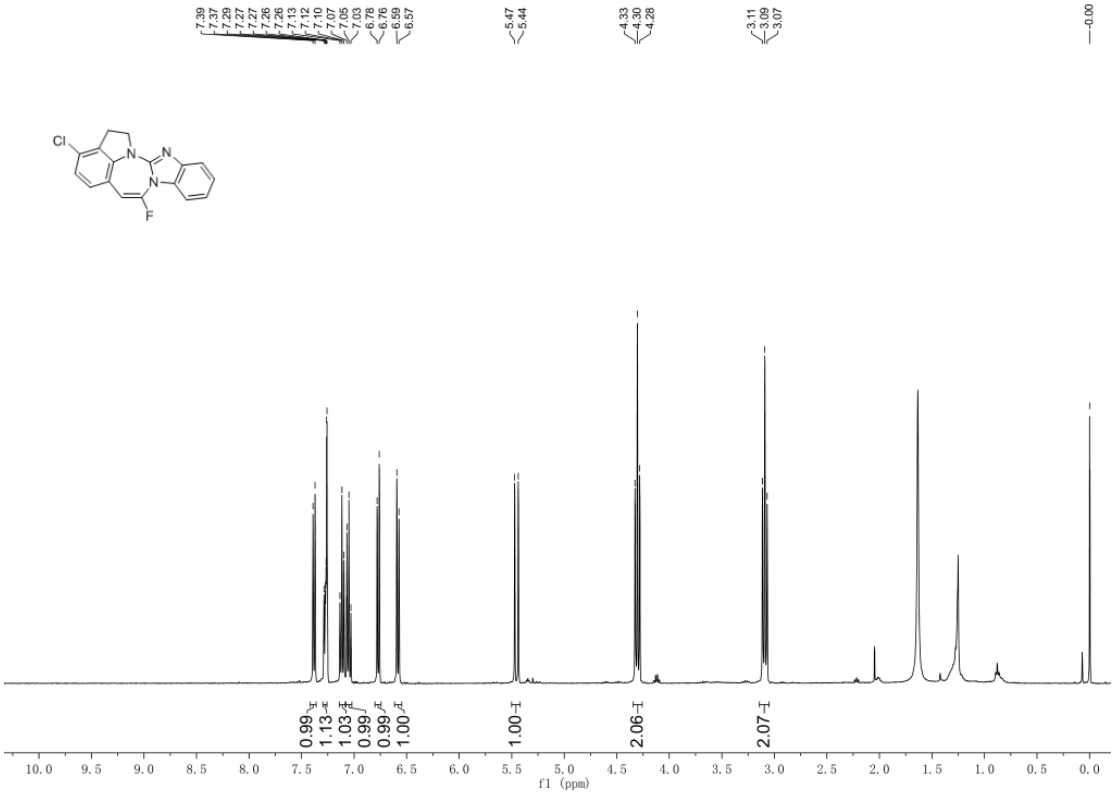
^{13}C{^{1}H}-NMR of **3b** ($CDCl_3$, 100 MHz)



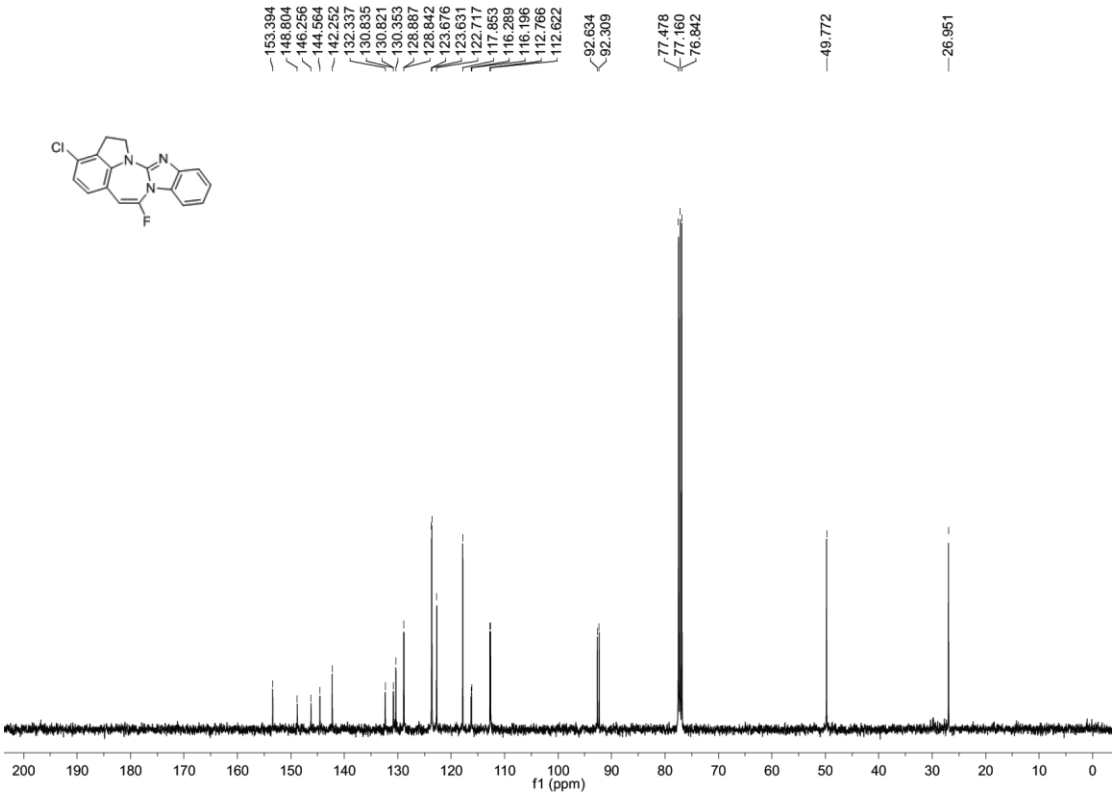
^{19}F-NMR of **3b** ($CDCl_3$, 376 MHz)



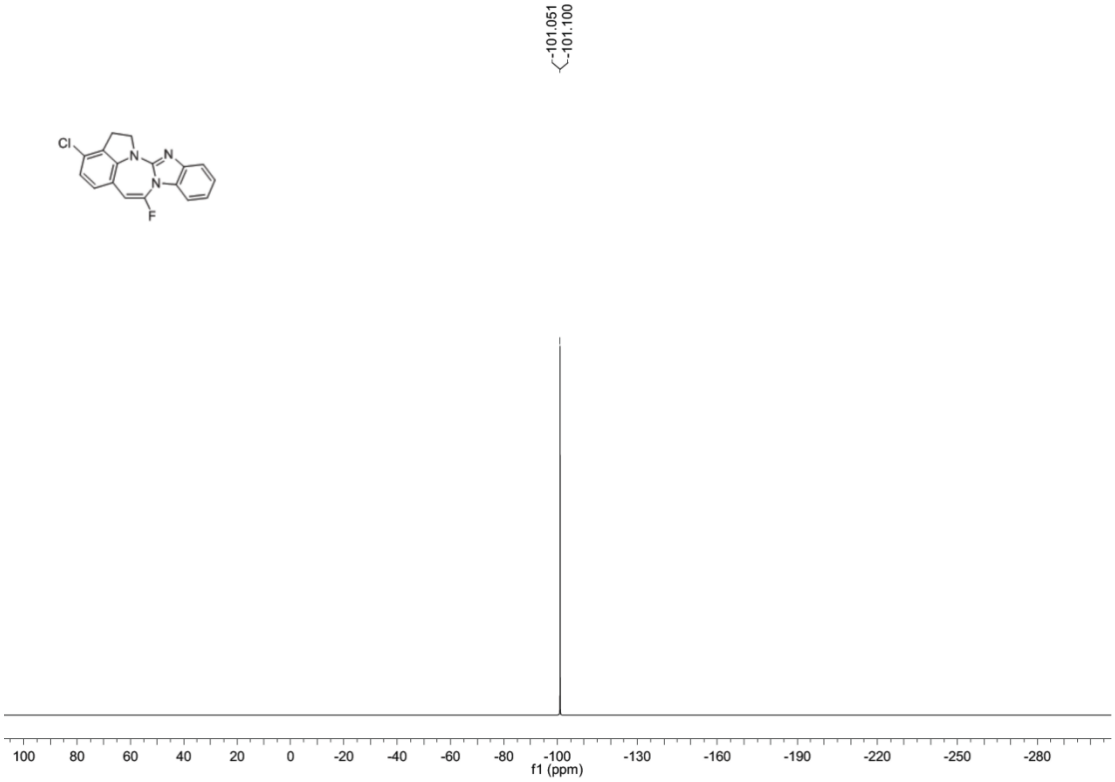
^{1}H-NMR of **3c** ($CDCl_3$, 400 MHz)



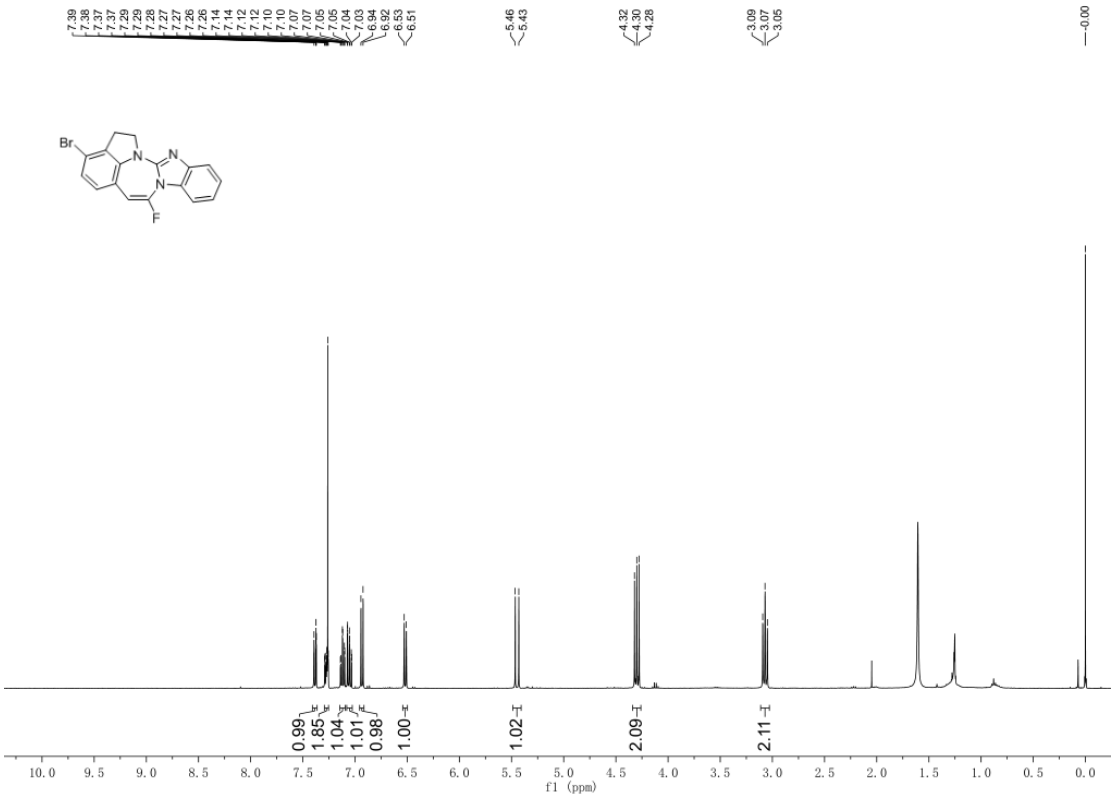
^{13}C{^{1}H}-NMR of **3c** ($CDCl_3$, 100 MHz)



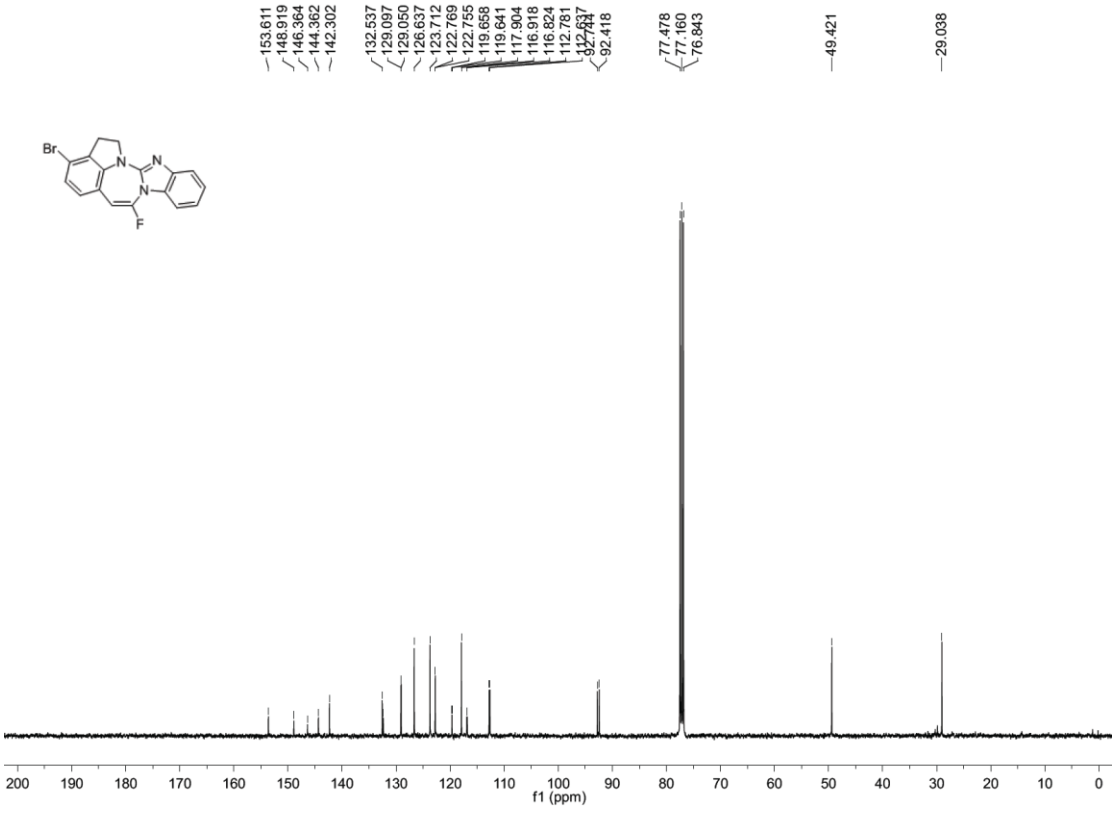
^{19}F-NMR of **3c** ($CDCl_3$, 376 MHz)



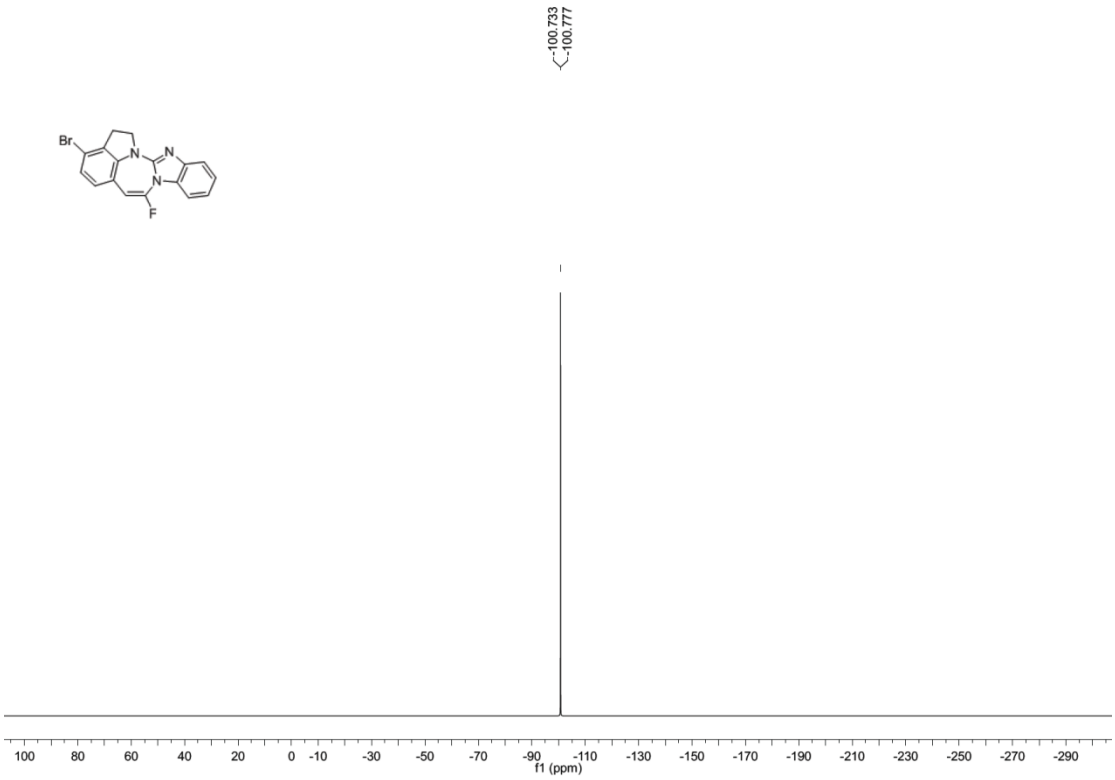
^{1}H-NMR of **3d** ($CDCl_3$, 400 MHz)



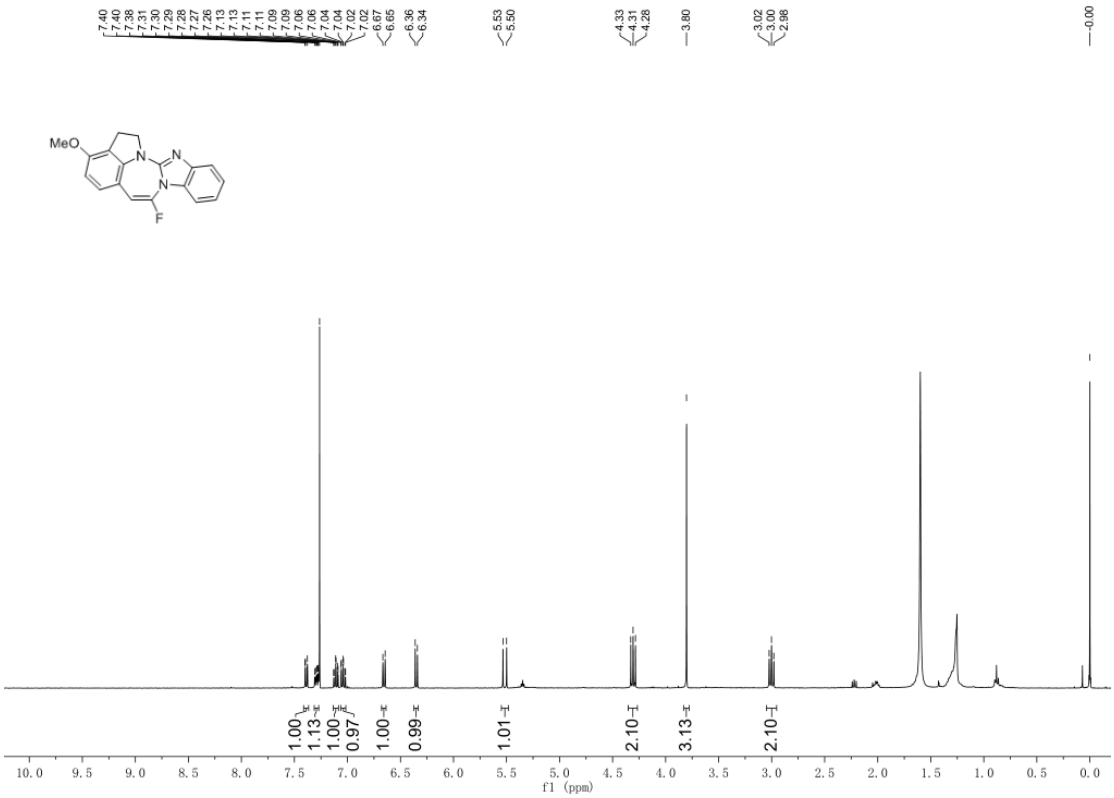
^{13}C{^{1}H}-NMR of **3d** ($CDCl_3$, 100 MHz)



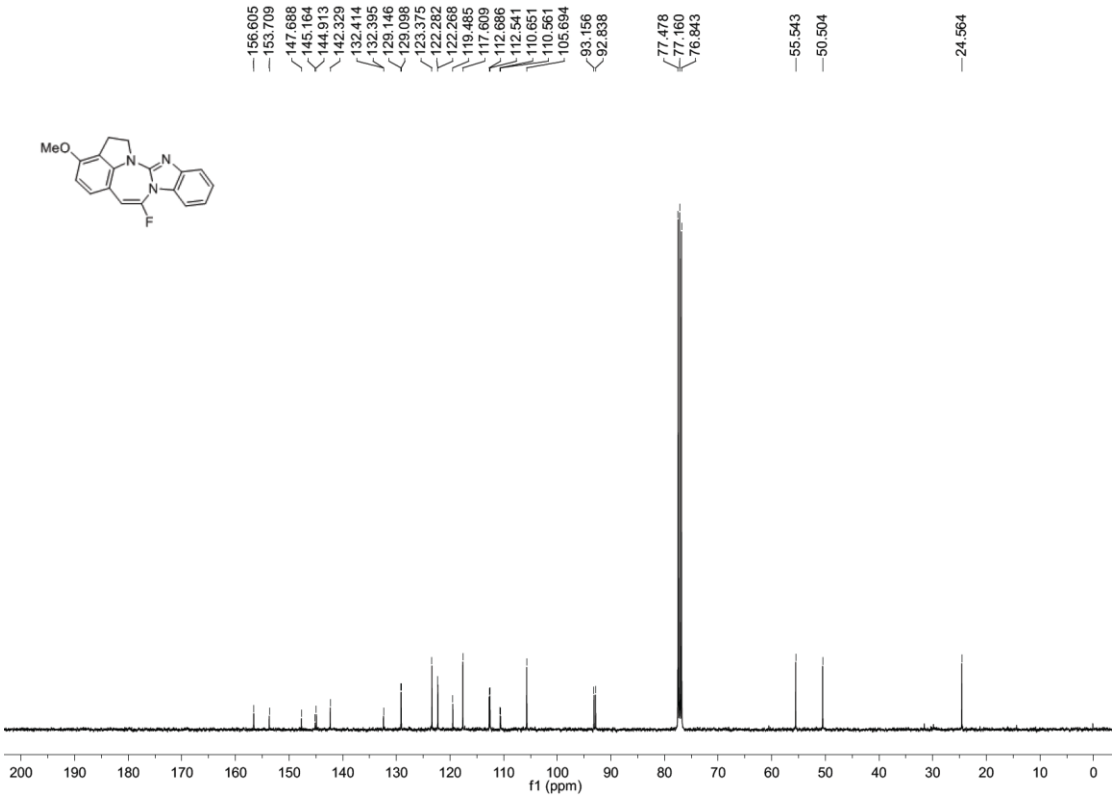
^{19}F-NMR of **3d** ($CDCl_3$, 376 MHz)



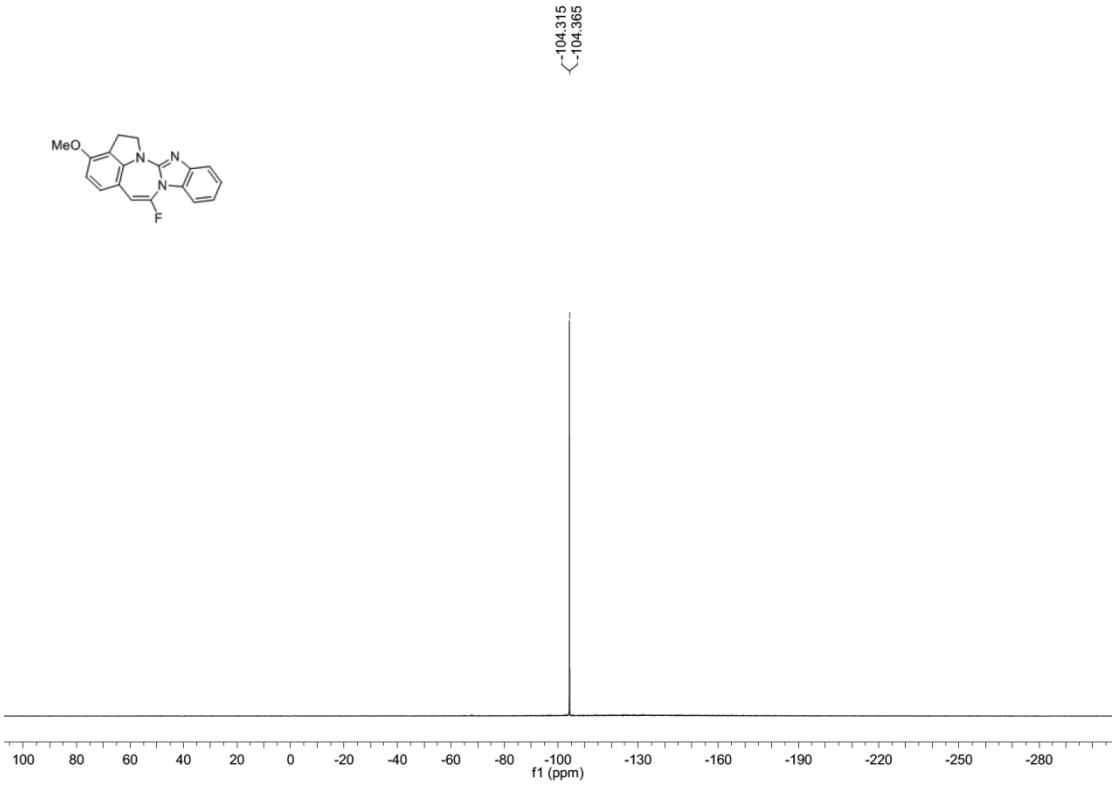
^{1}H-NMR of **3e** ($CDCl_3$, 400 MHz)



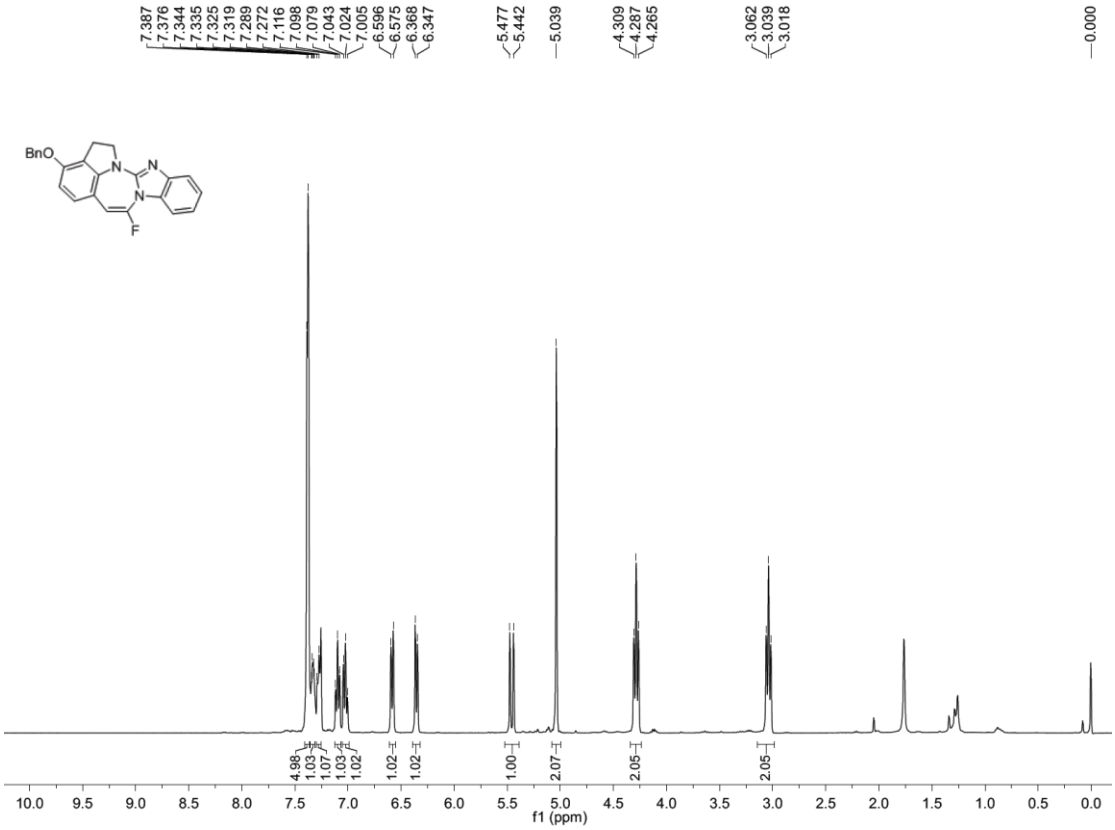
^{13}C{^{1}H}-NMR of **3e** ($CDCl_3$, 100 MHz)



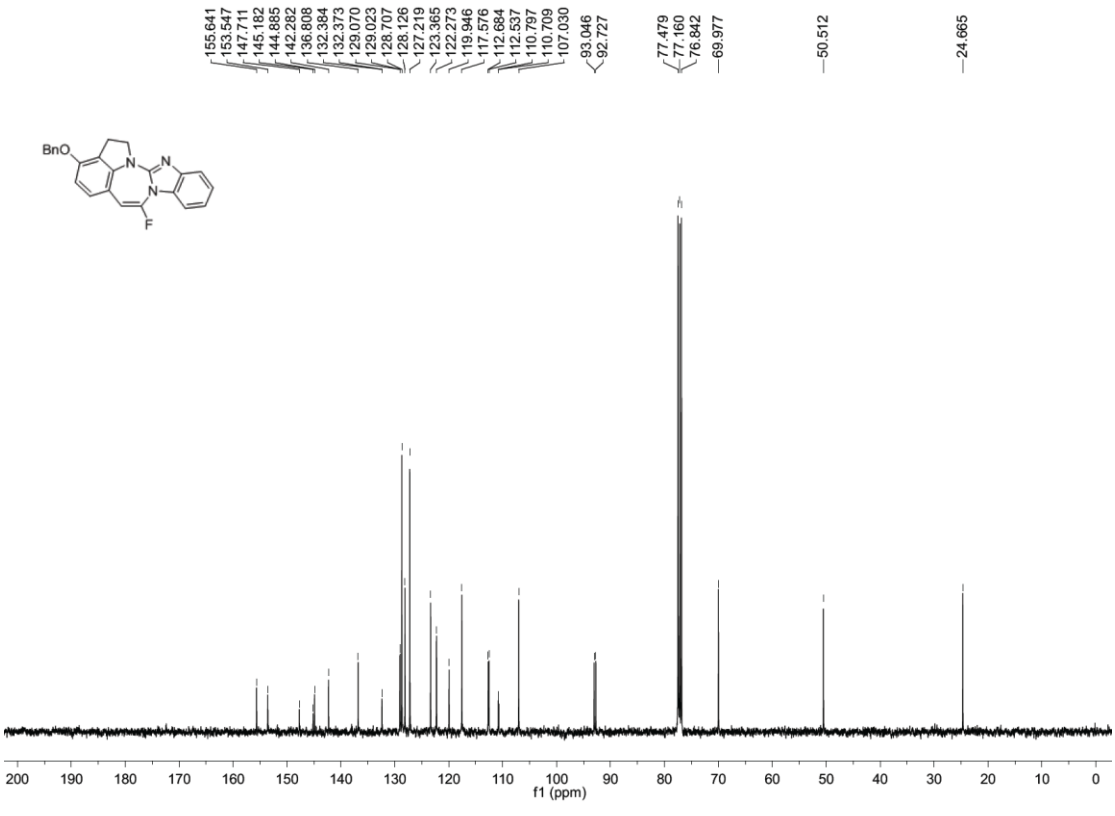
^{19}F-NMR of **3e** ($CDCl_3$, 376 MHz)



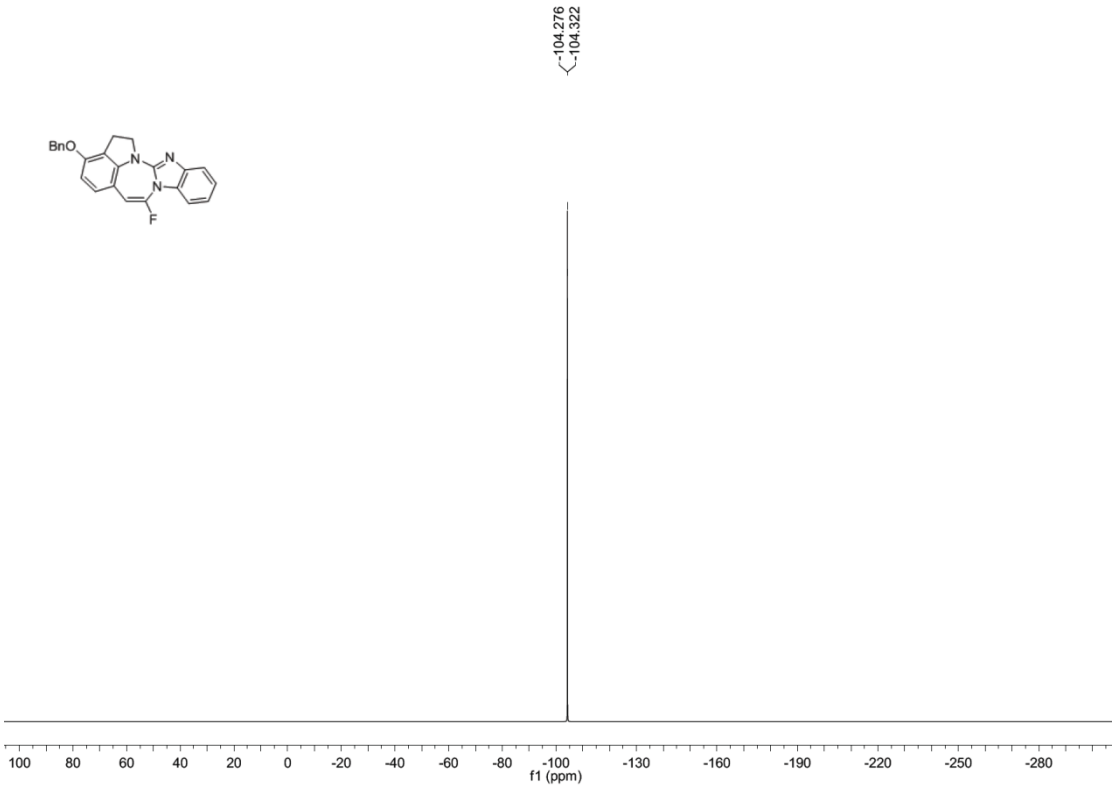
^{1}H-NMR of **3f** ($CDCl_3$, 400 MHz)



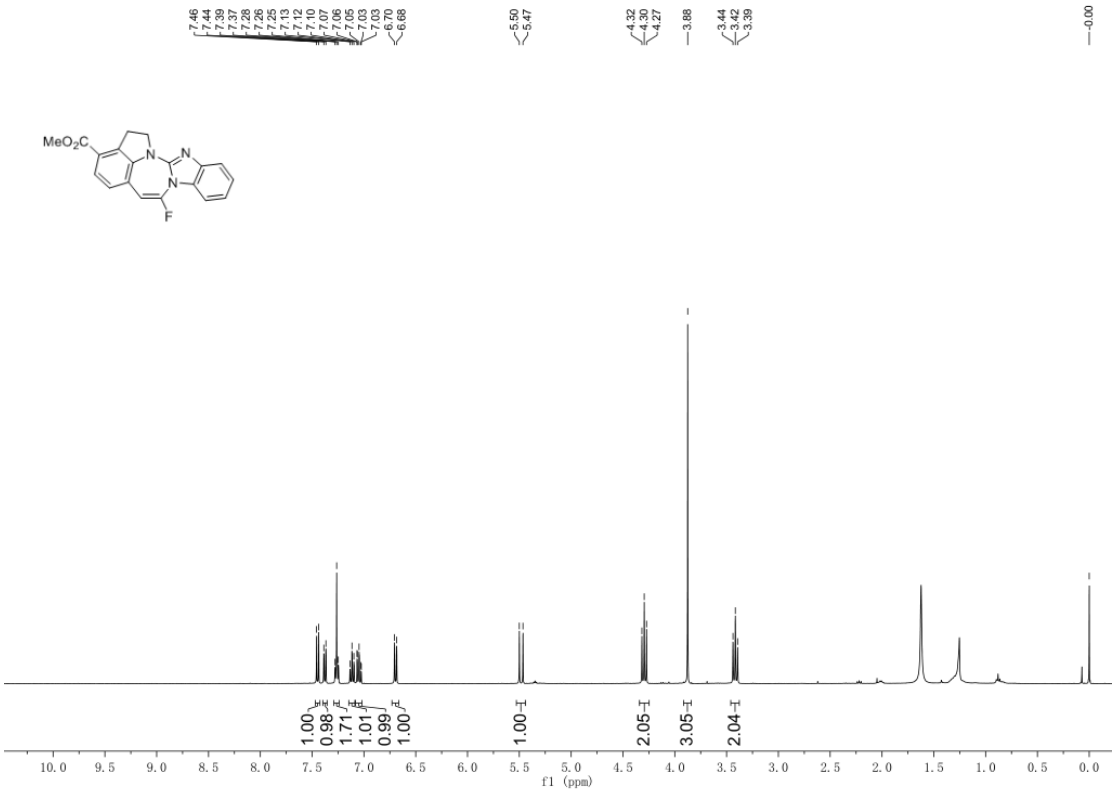
^{13}C{^{1}H}-NMR of **3f** ($CDCl_3$, 100 MHz)



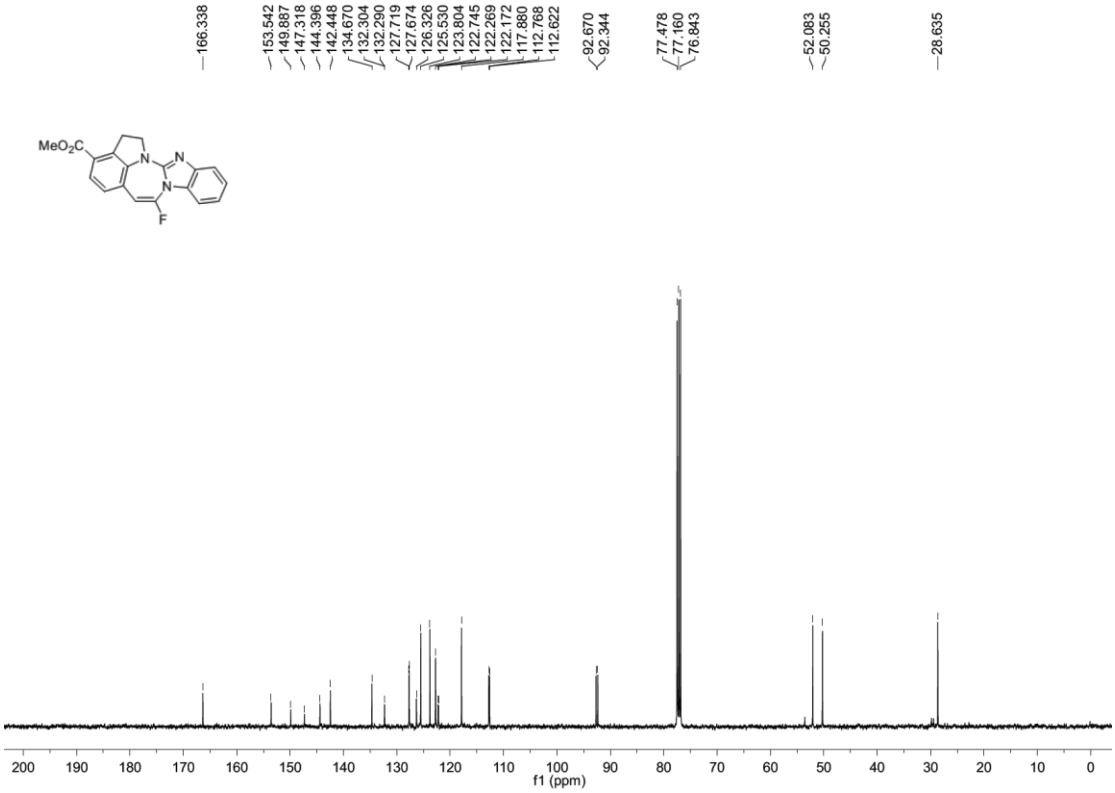
^{19}F-NMR of **3f** ($CDCl_3$, 376 MHz)



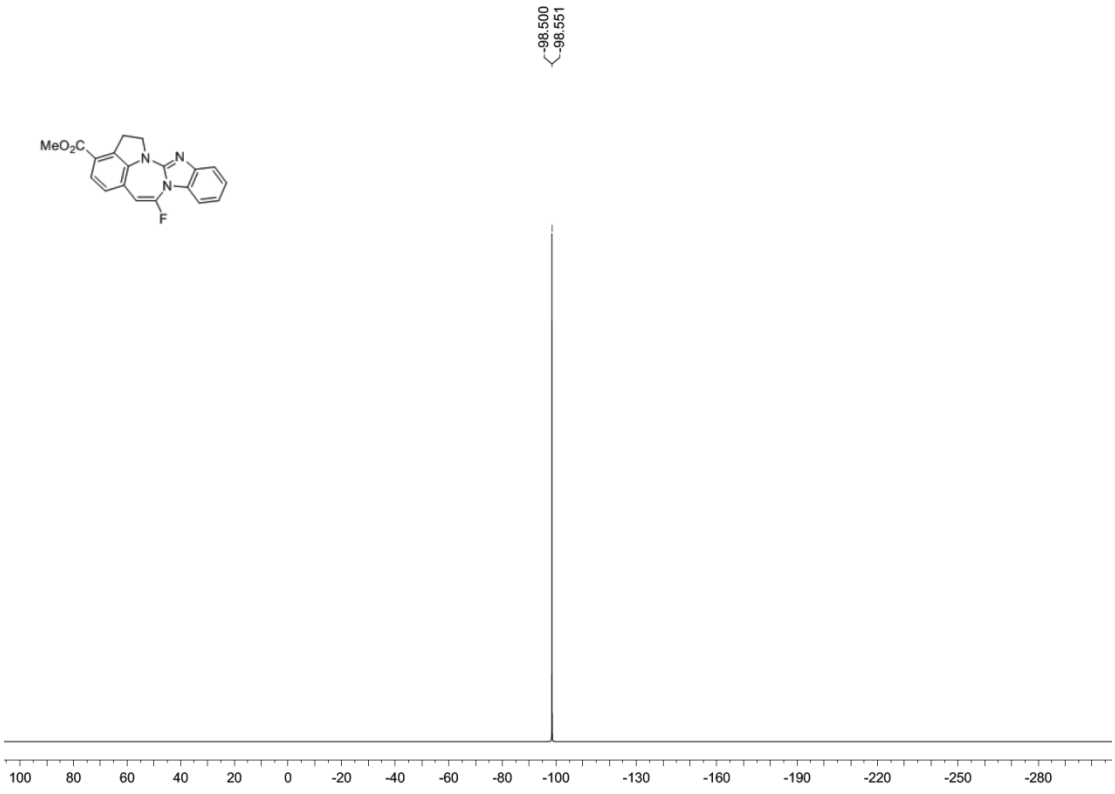
^{1}H-NMR of **3g** ($CDCl_3$, 400 MHz)



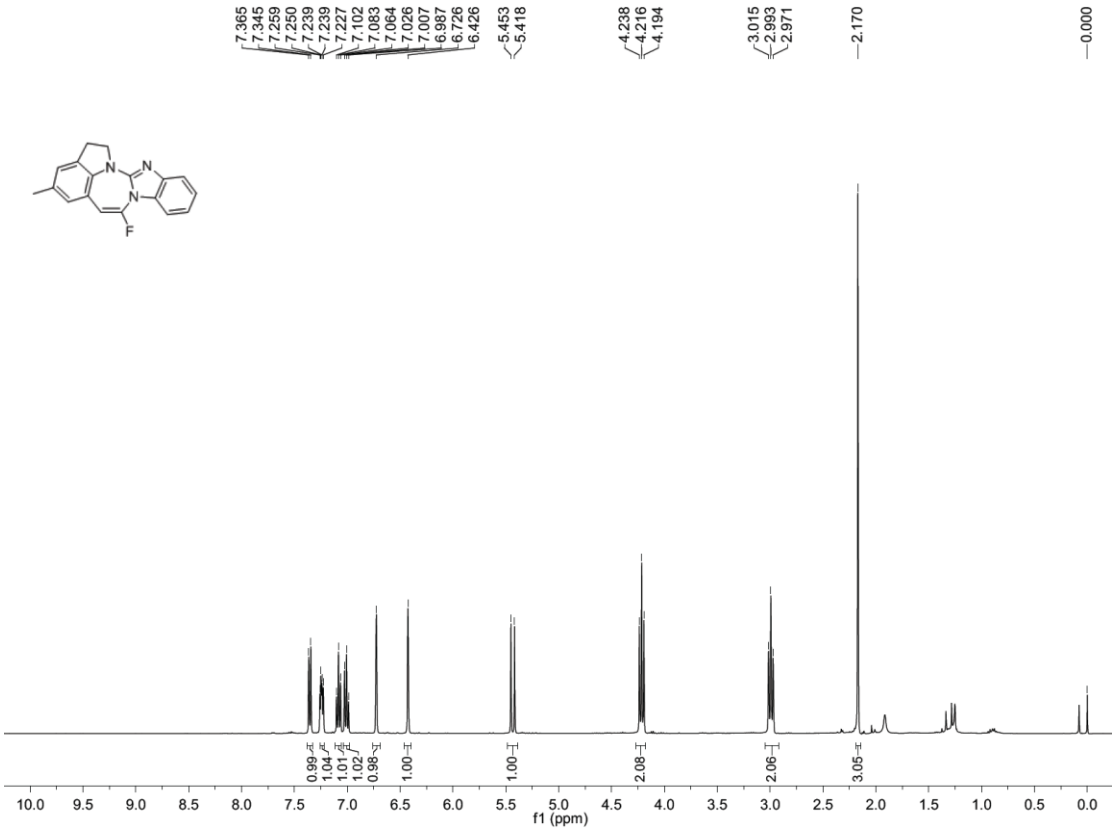
^{13}C{^{1}H}-NMR of **3g** ($CDCl_3$, 100 MHz)



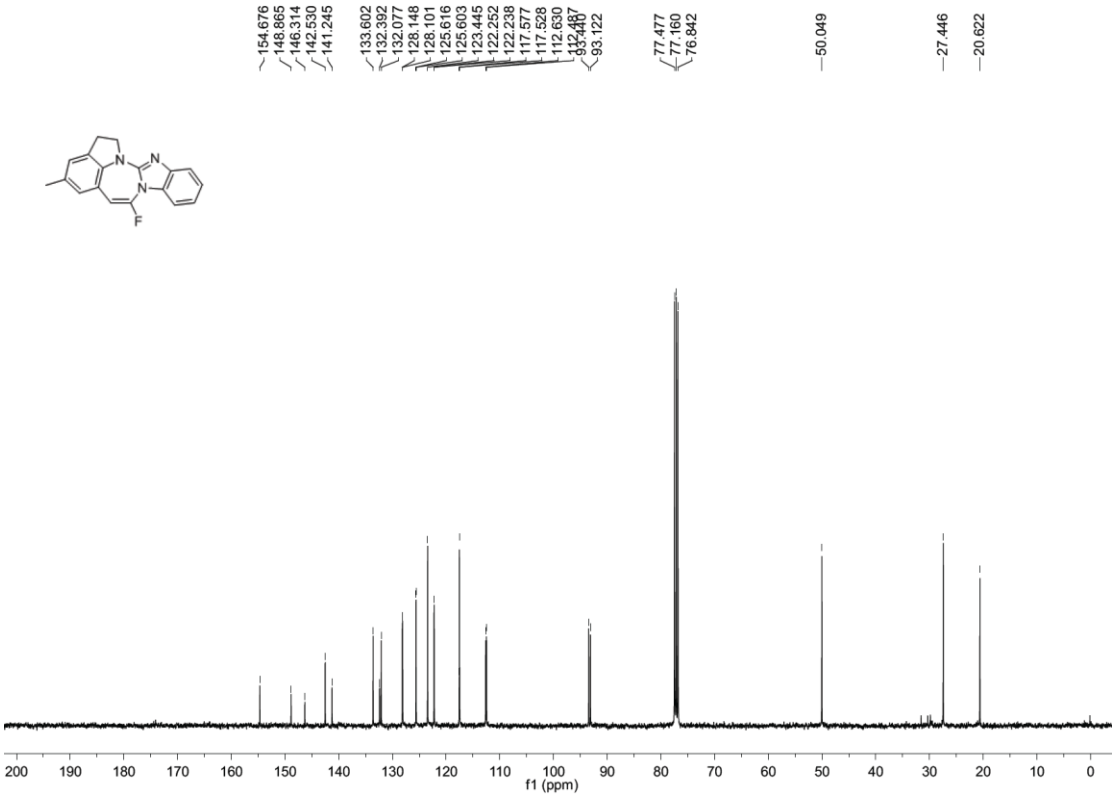
^{19}F-NMR of **3g** ($CDCl_3$, 376 MHz)



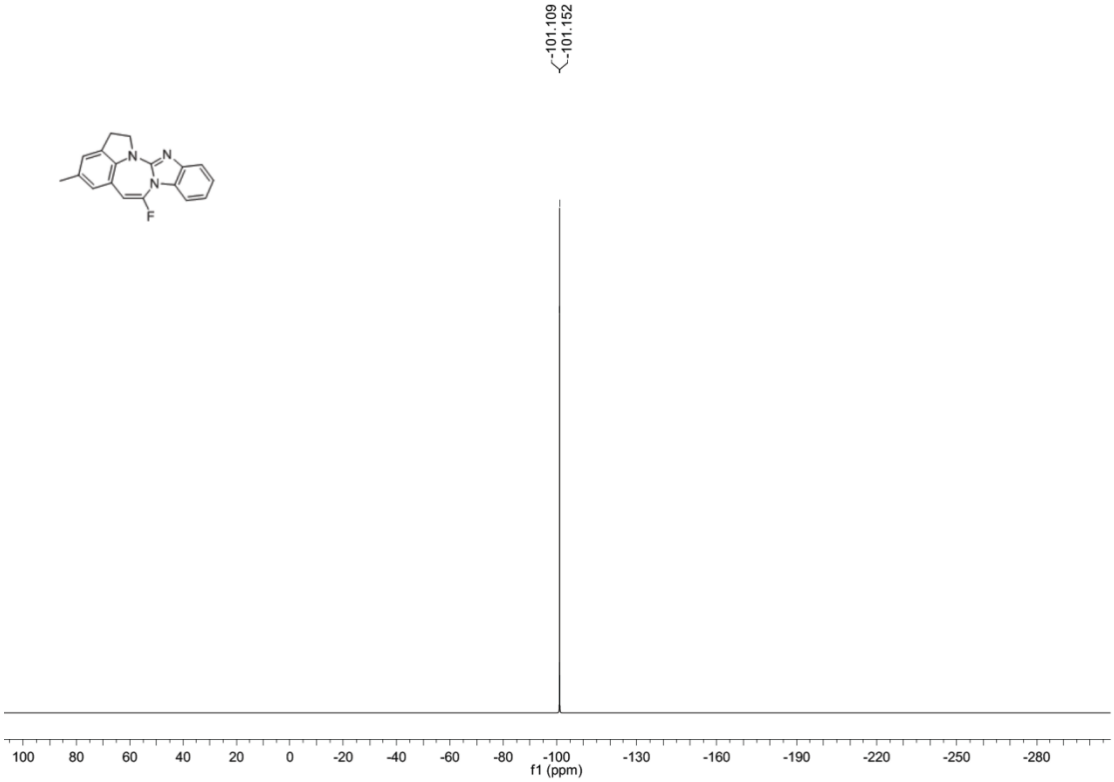
^{1}H-NMR of **3h** ($CDCl_3$, 400 MHz)



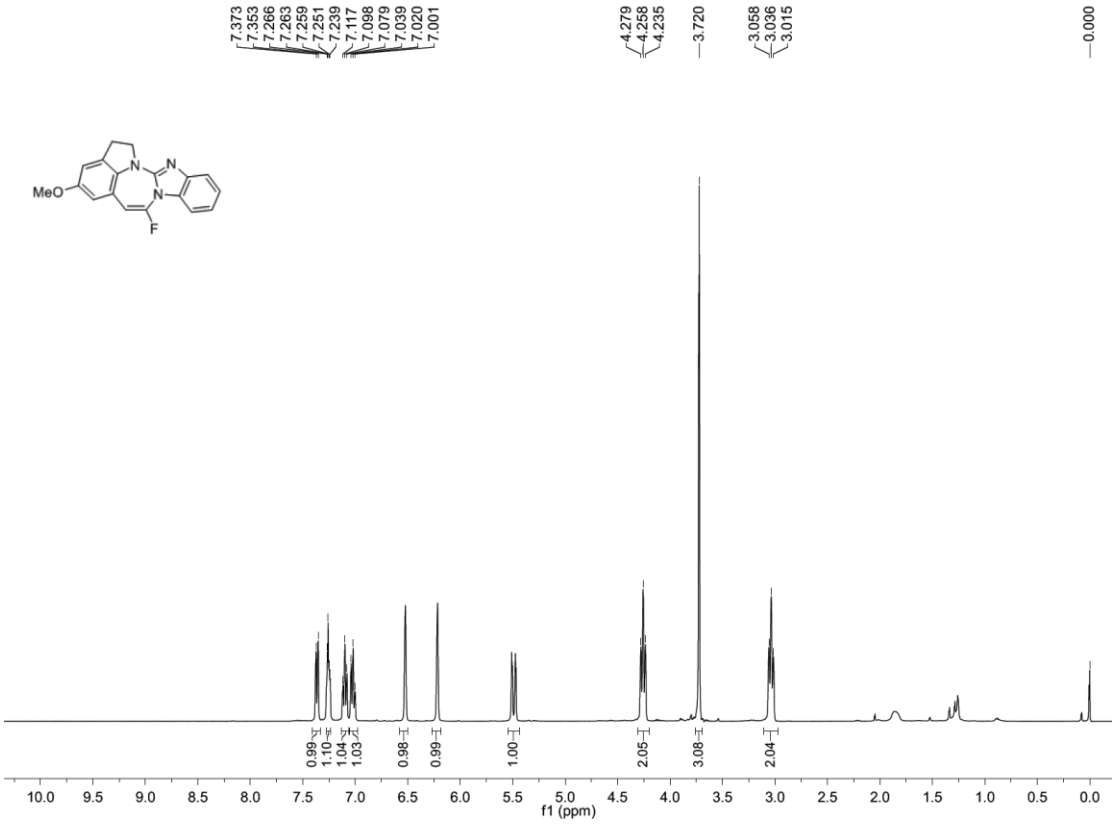
^{13}C{^{1}H}-NMR of **3h** ($CDCl_3$, 100 MHz)



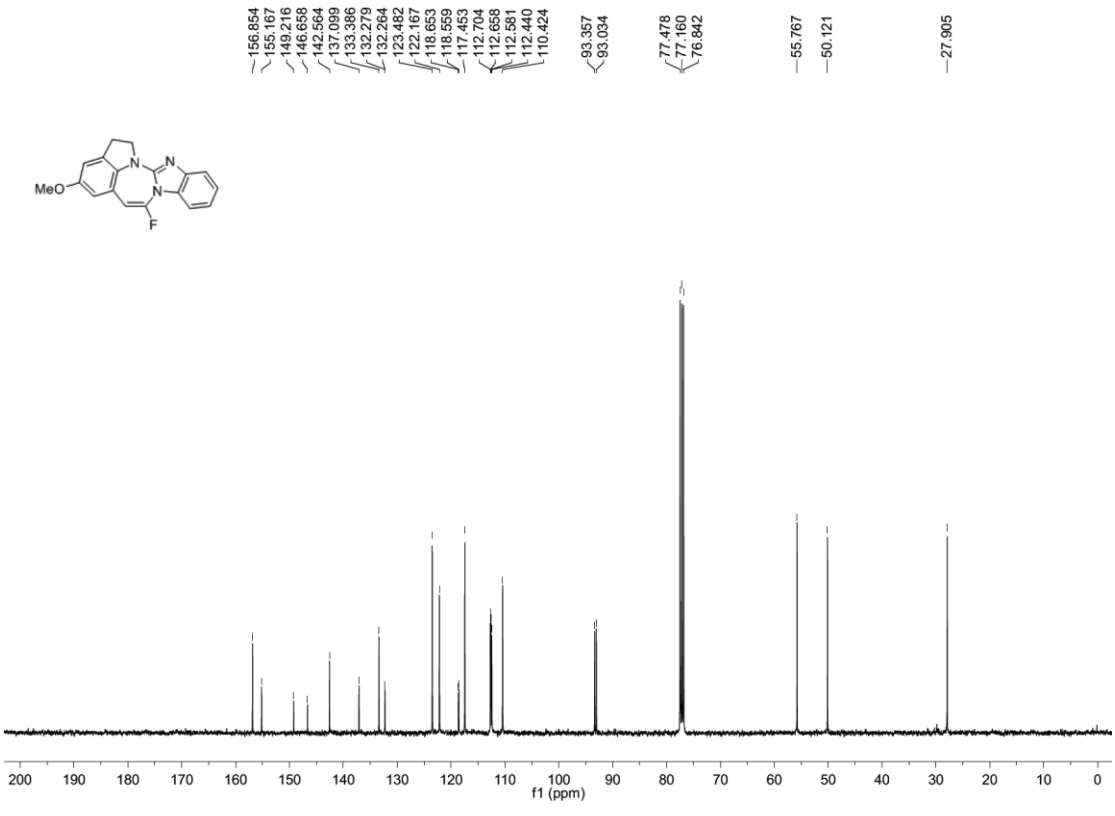
^{19}F-NMR of **3h** ($CDCl_3$, 376 MHz)



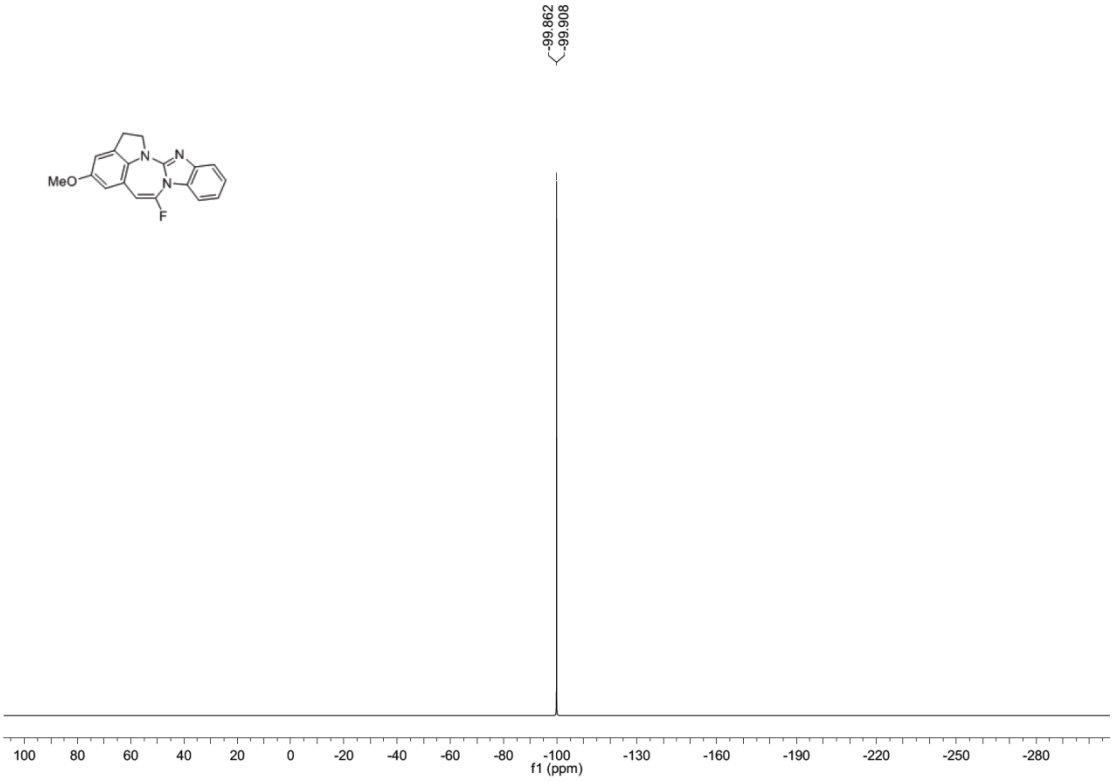
^{1}H-NMR of **3i** ($CDCl_3$, 400 MHz)



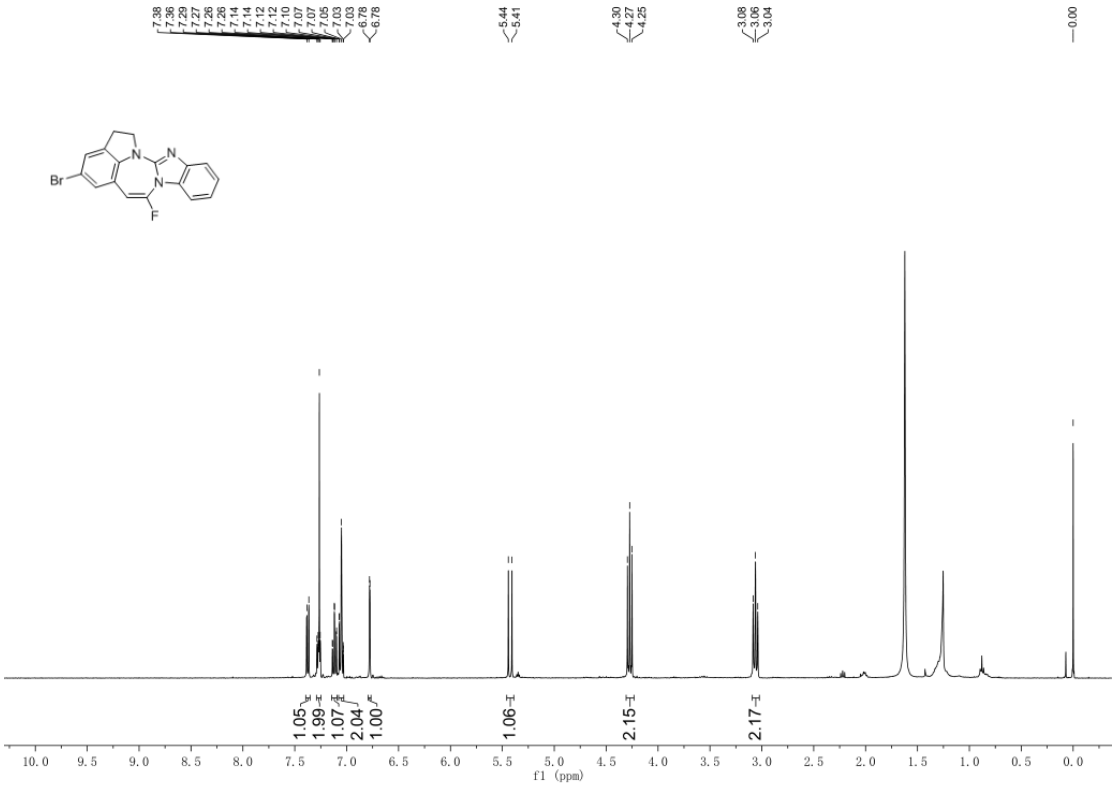
^{13}C{^{1}H}-NMR of **3i** ($CDCl_3$, 100 MHz)



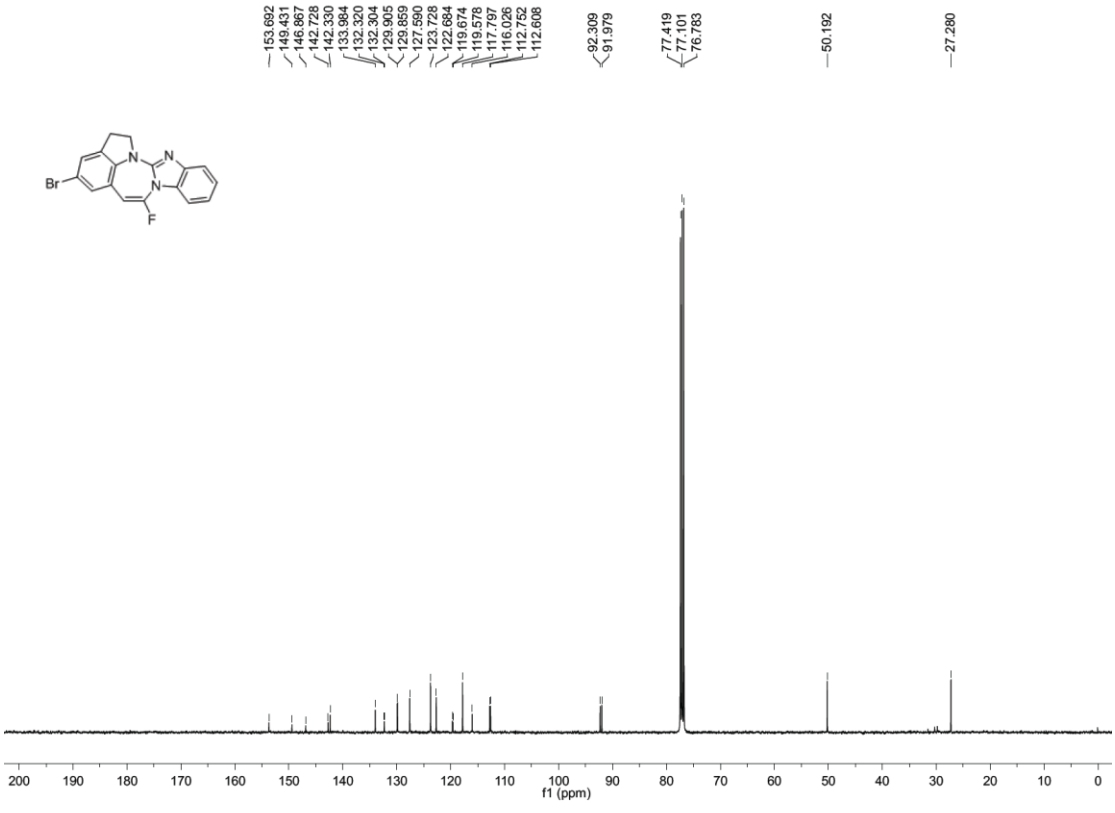
^{19}F-NMR of **3i** ($CDCl_3$, 376 MHz)



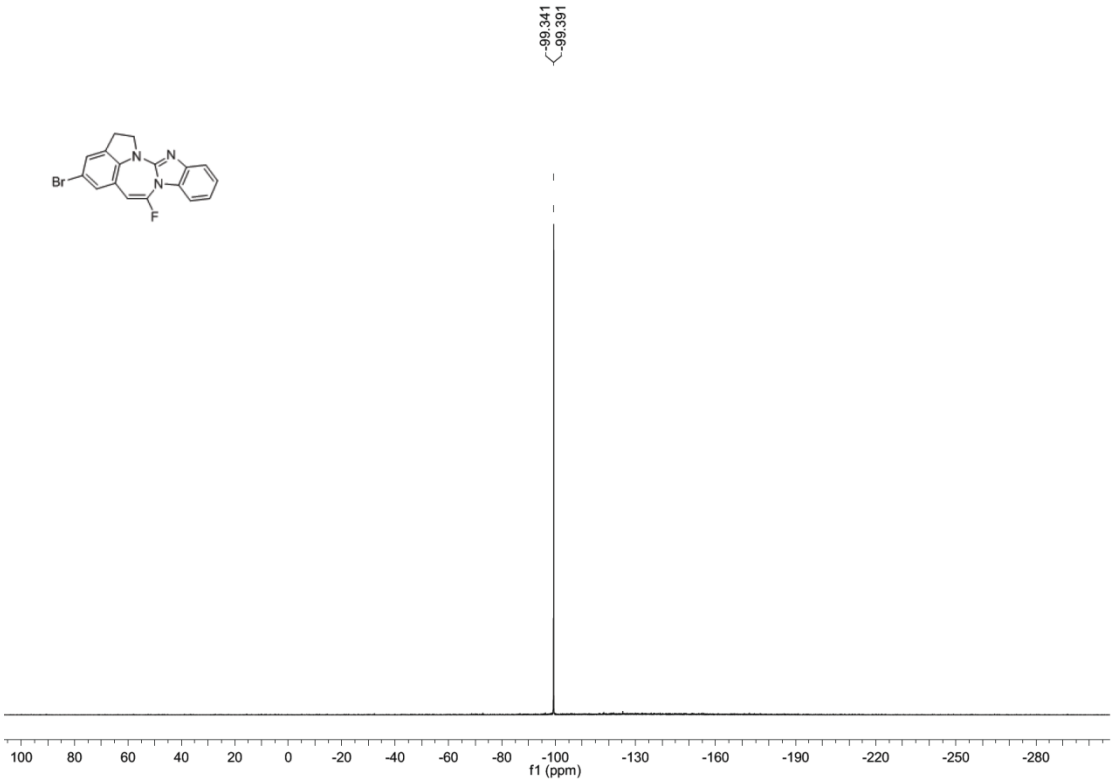
^{1}H-NMR of **3j** ($CDCl_3$, 400 MHz)



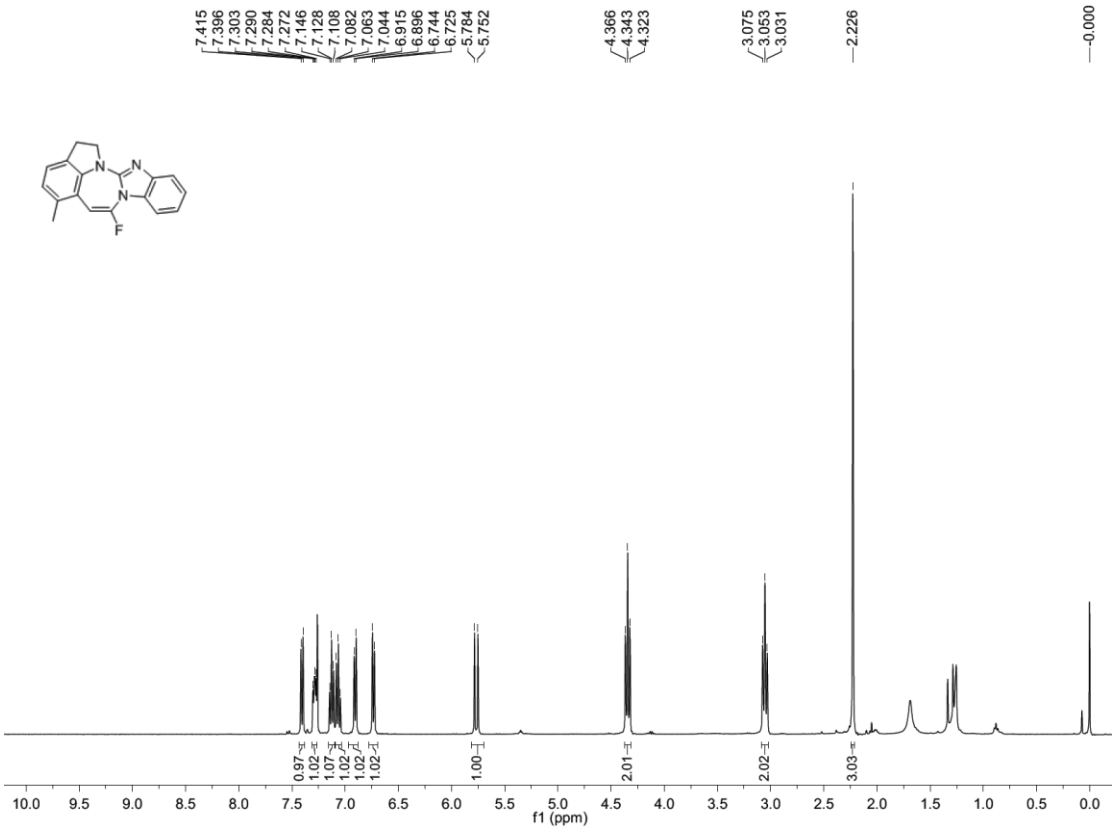
^{13}C{^{1}H}-NMR of **3j** ($CDCl_3$, 100 MHz)



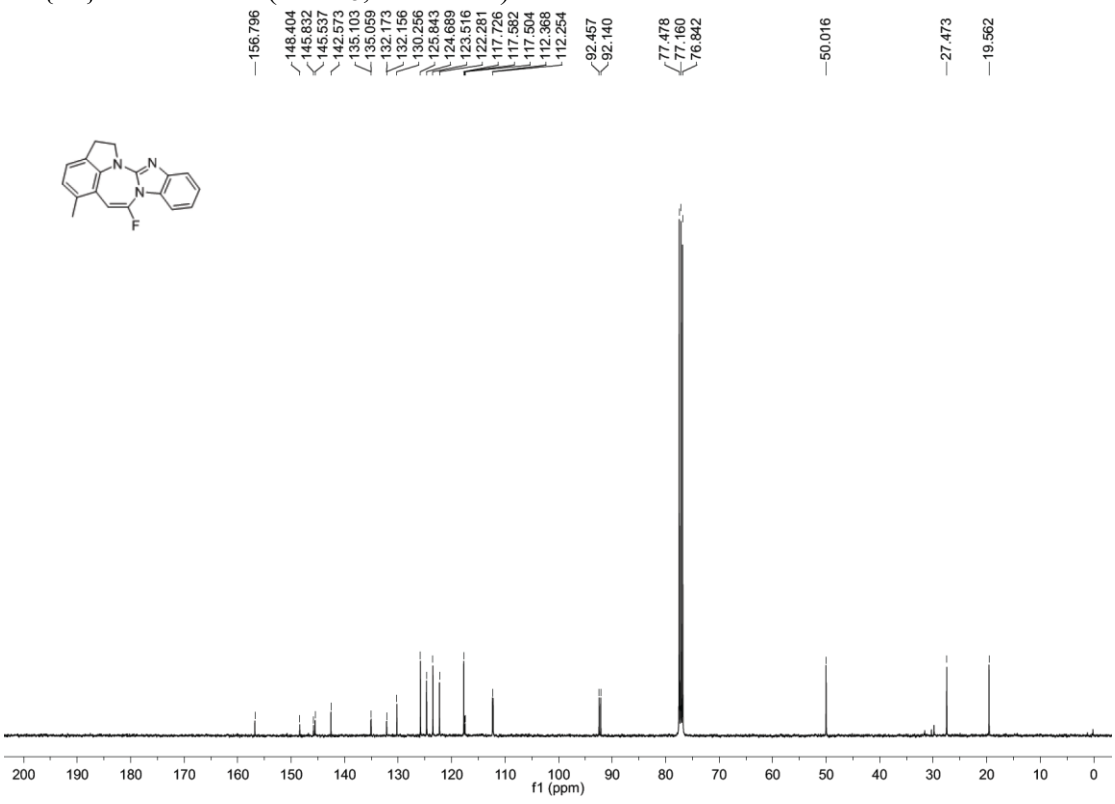
^{19}F-NMR of **3j** ($CDCl_3$, 376 MHz)



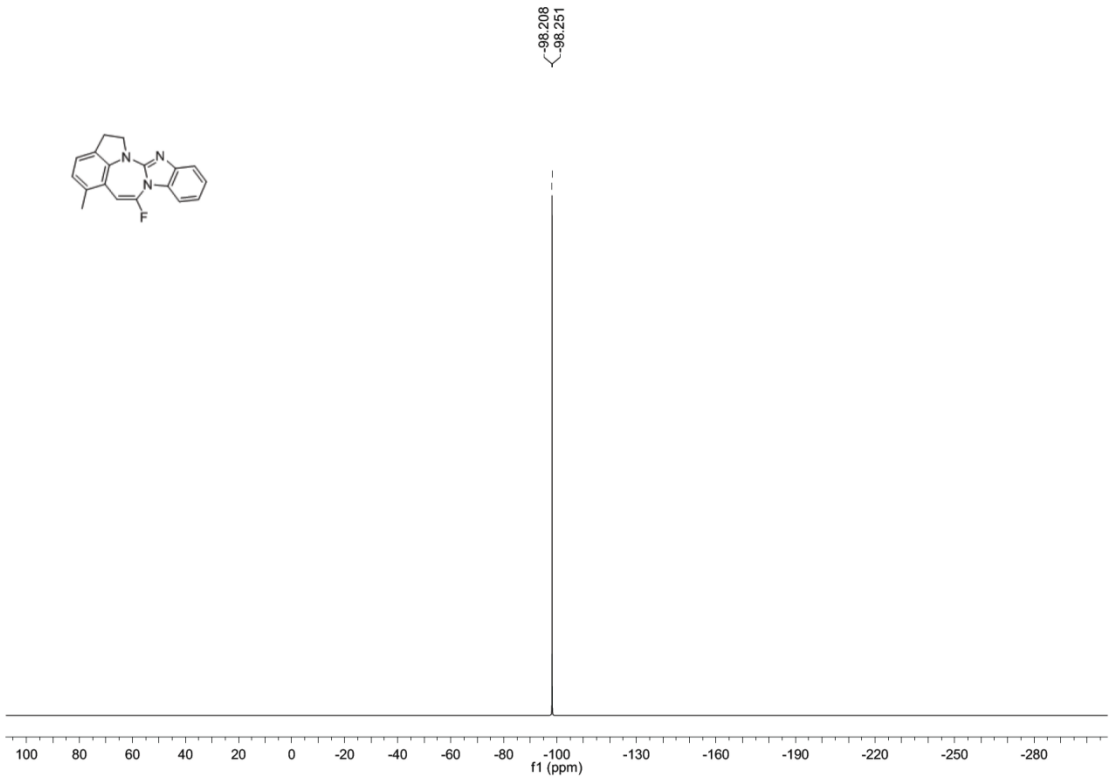
^{1}H-NMR of **3k** ($CDCl_3$, 400 MHz)



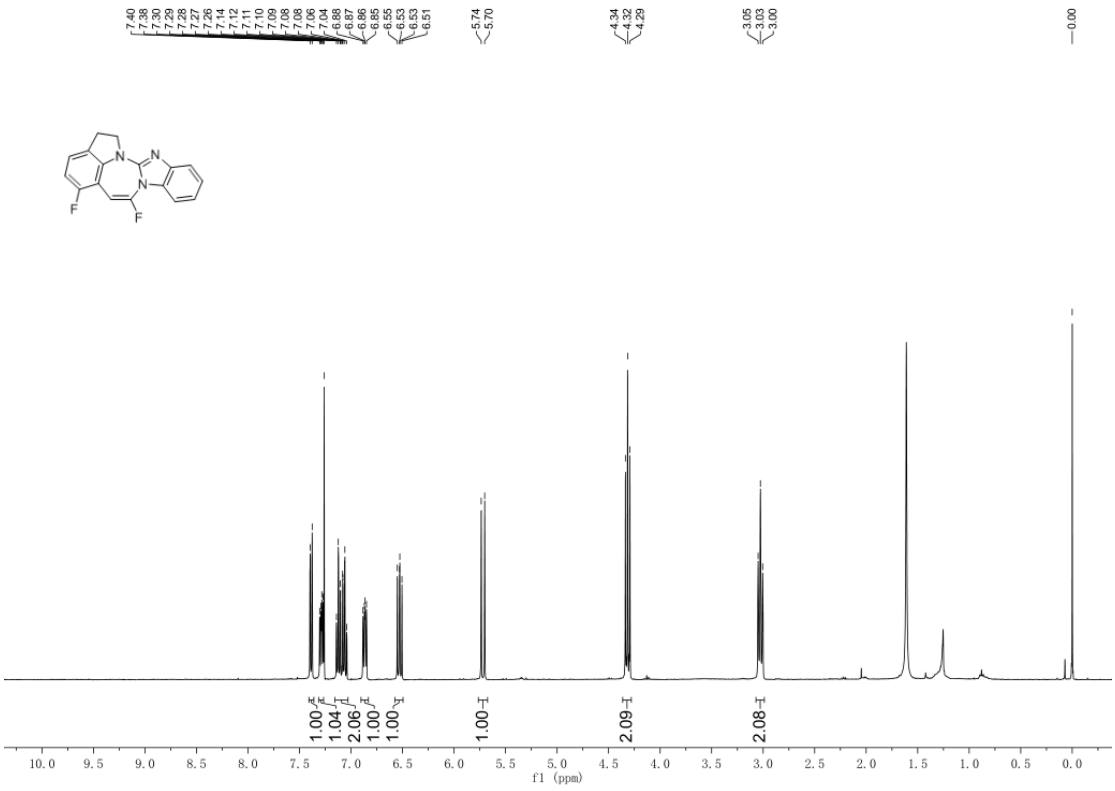
^{13}C{^{1}H}-NMR of **3k** ($CDCl_3$, 100 MHz)



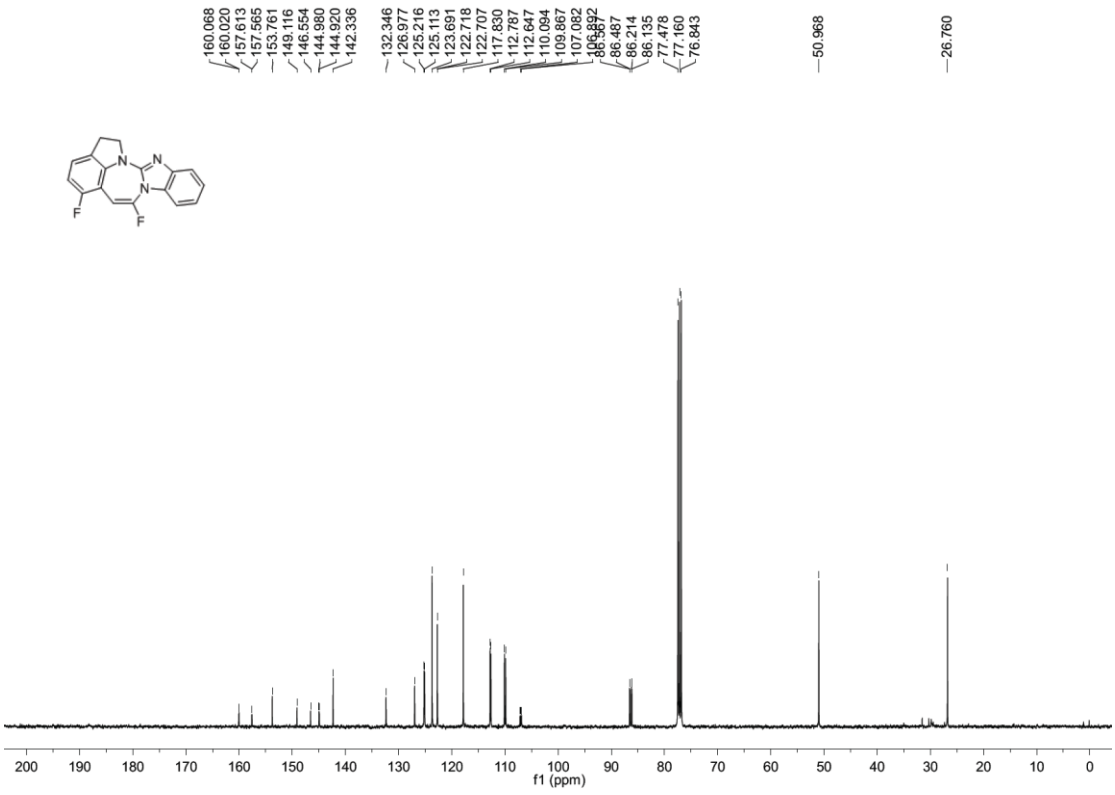
^{19}F-NMR of **3k** ($CDCl_3$, 376 MHz)



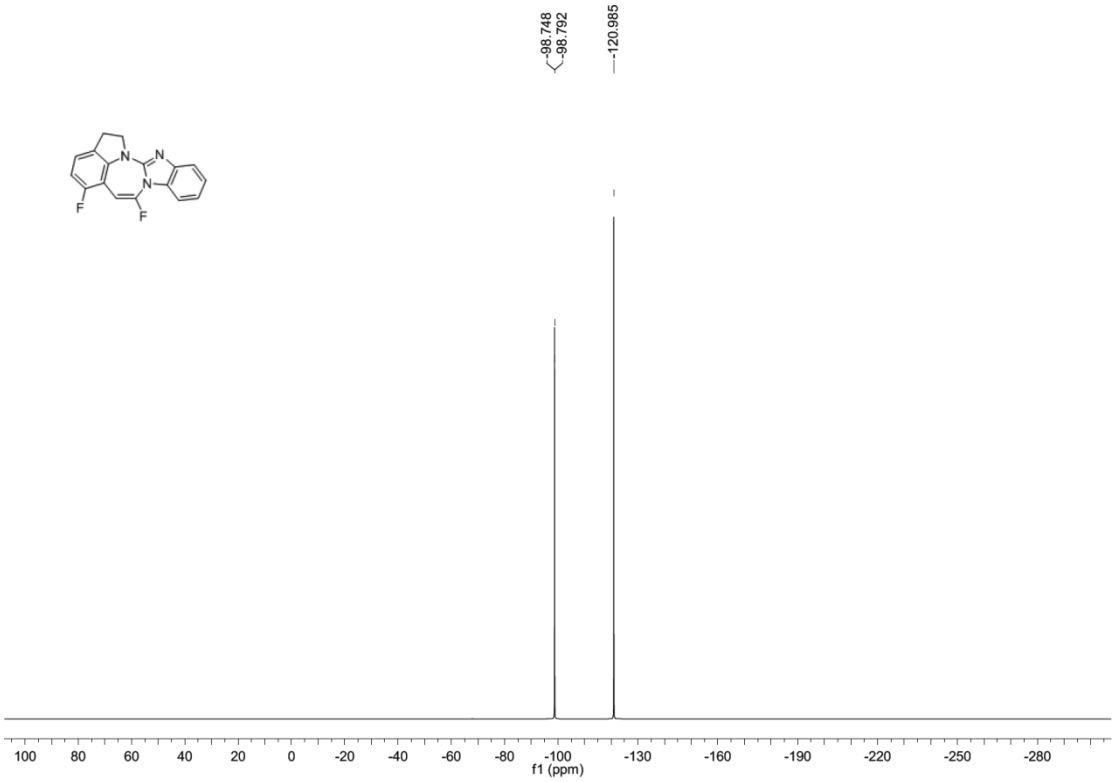
^{1}H-NMR of **3l** ($CDCl_3$, 400 MHz)



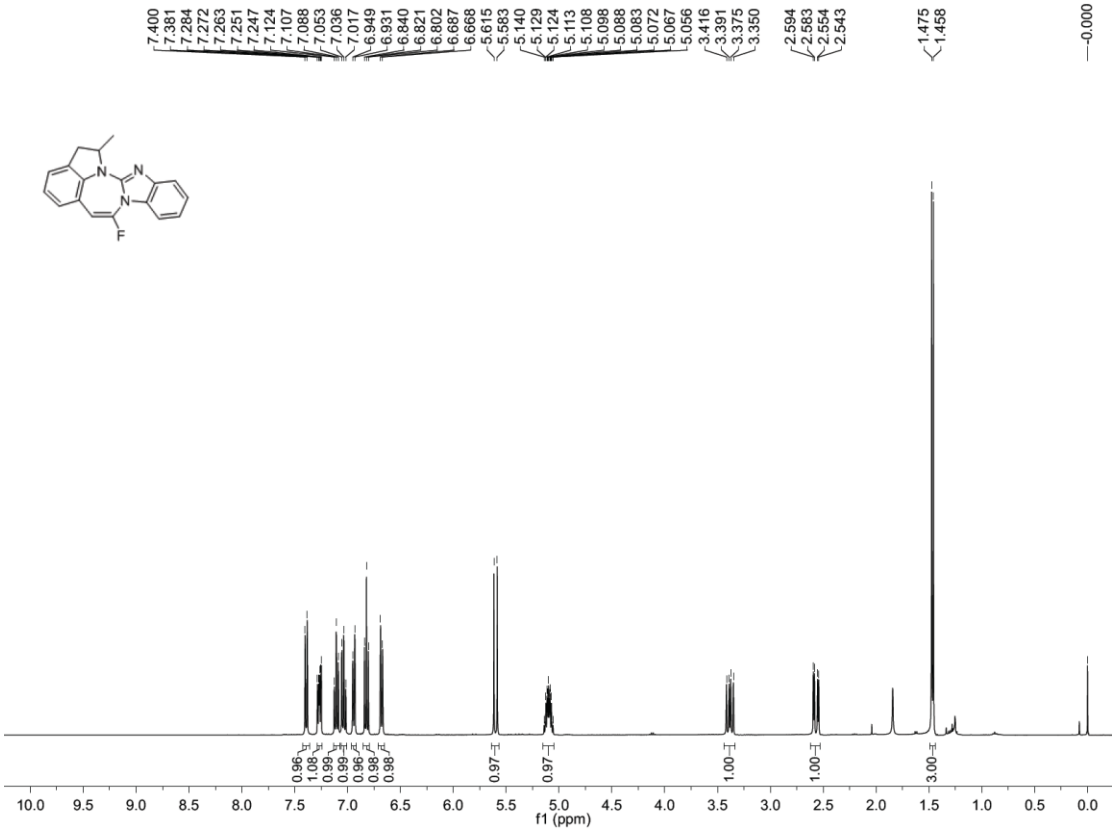
^{13}C{^{1}H}-NMR of **3l** ($CDCl_3$, 100 MHz)



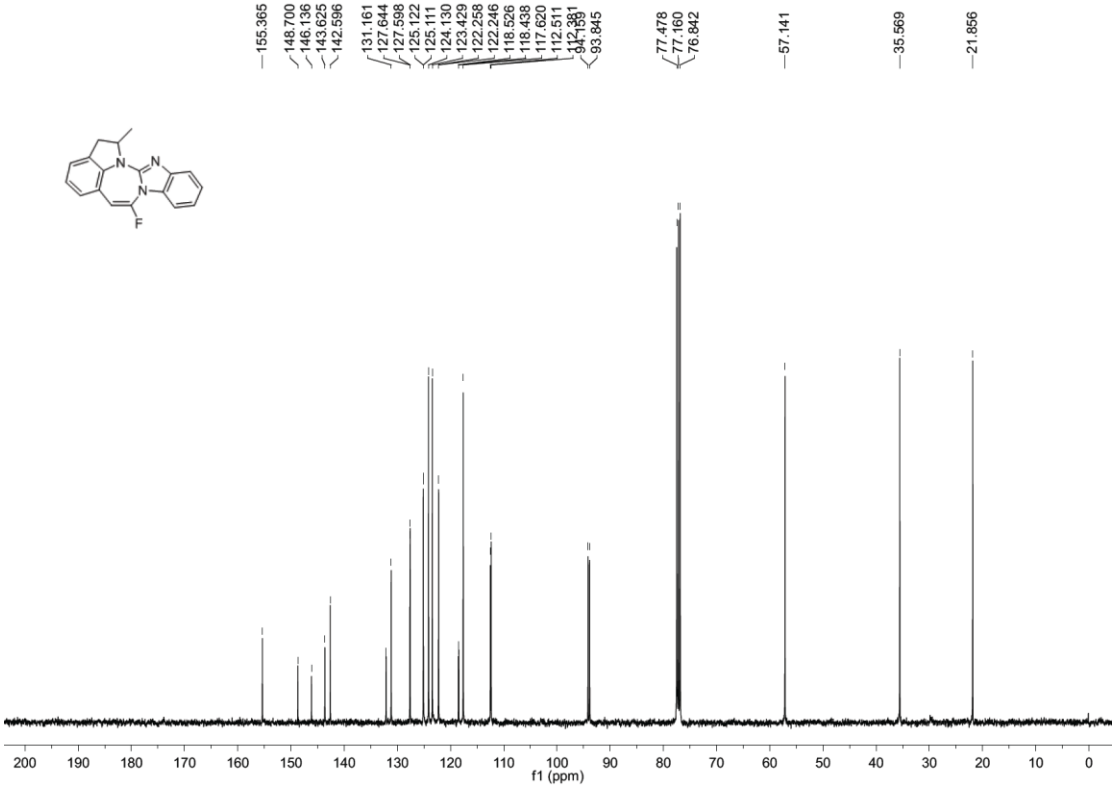
^{19}F-NMR of **3l** ($CDCl_3$, 376 MHz)



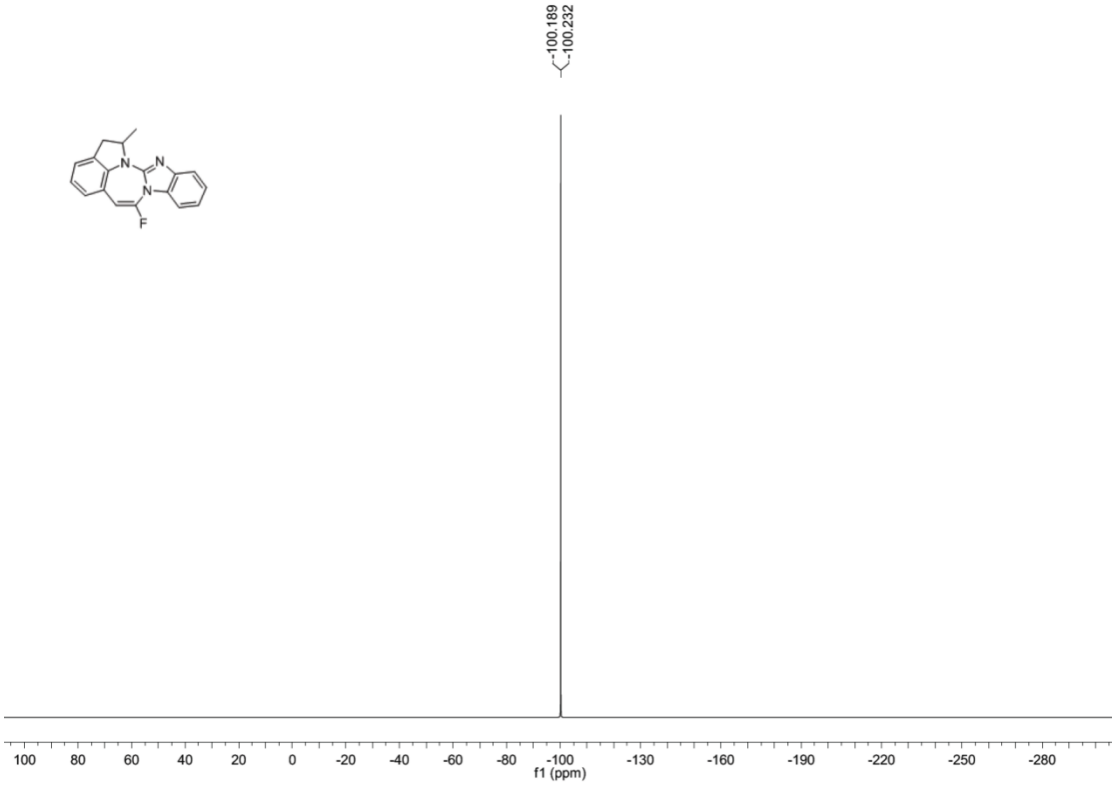
^{1}H-NMR of **3m** ($CDCl_3$, 400 MHz)



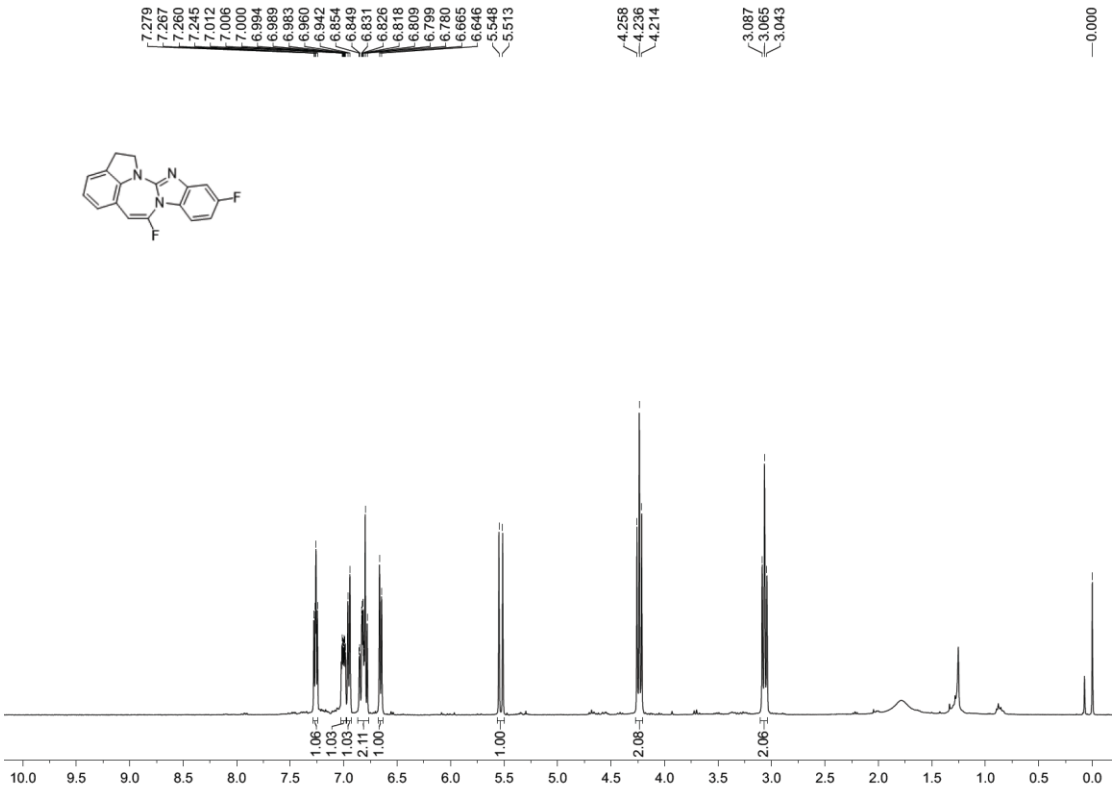
^{13}C{^{1}H}-NMR of **3m** ($CDCl_3$, 100 MHz)



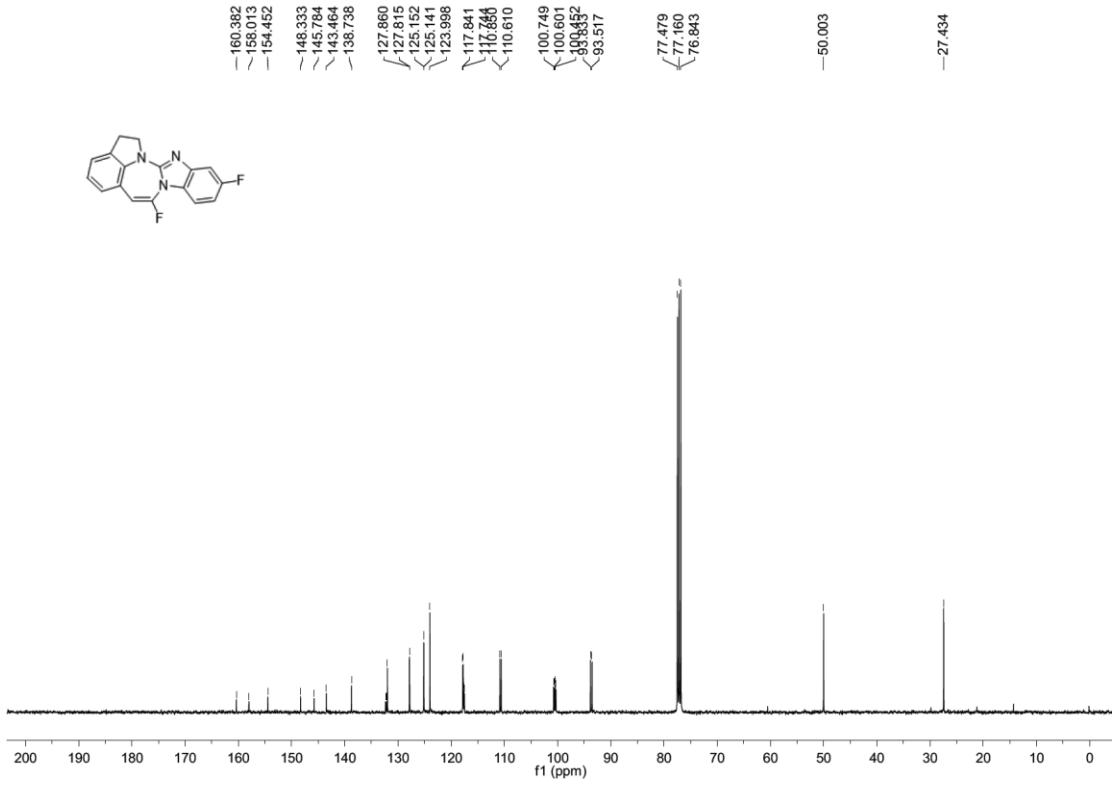
^{19}F-NMR of **3m** ($CDCl_3$, 376 MHz)



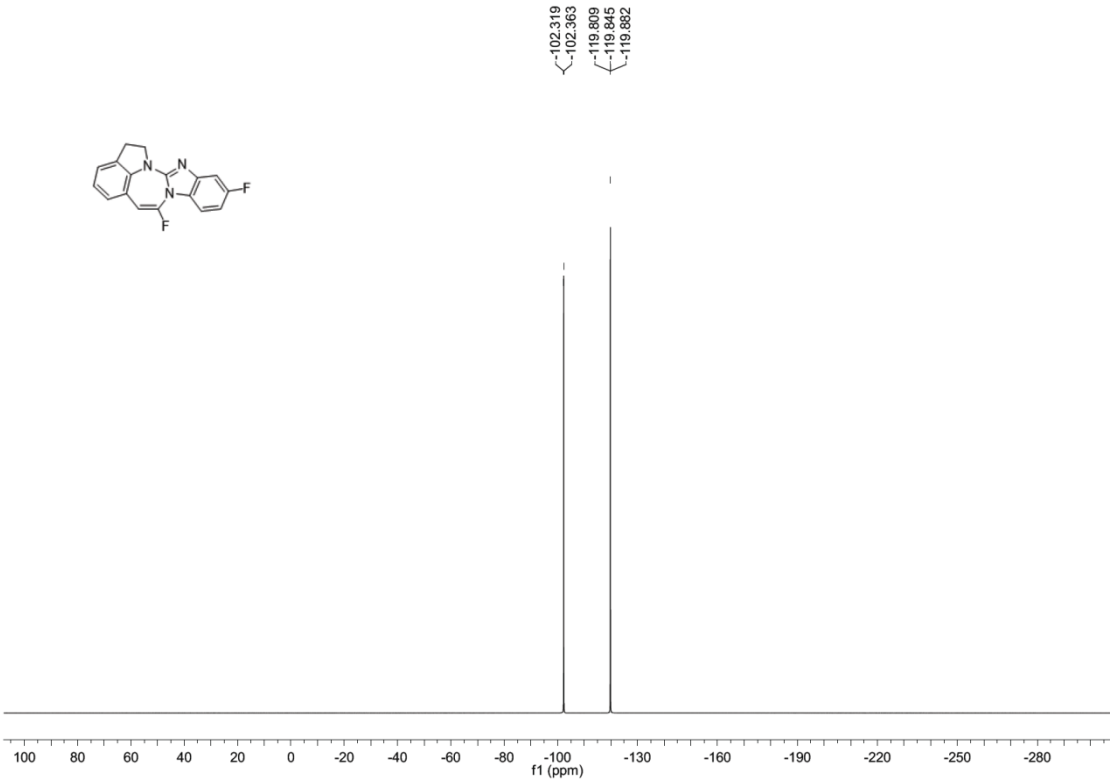
^{1}H-NMR of **3n** ($CDCl_3$, 400 MHz)



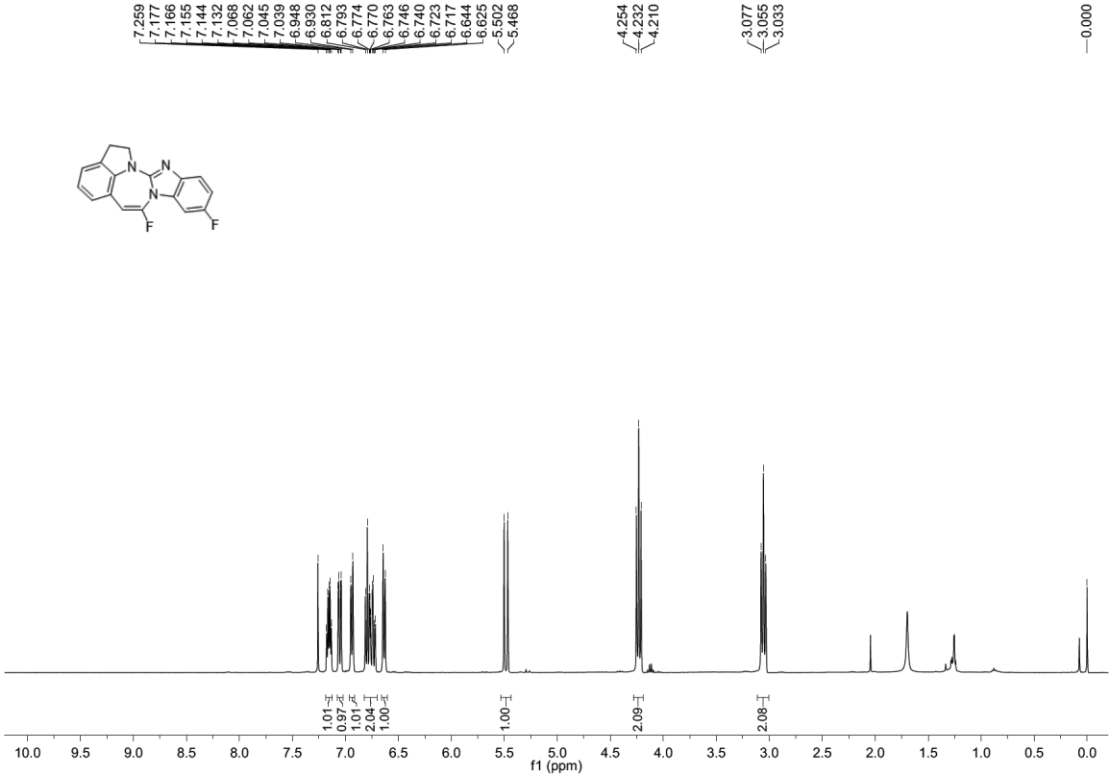
^{13}C{^{1}H}-NMR of **3n** ($CDCl_3$, 100 MHz)



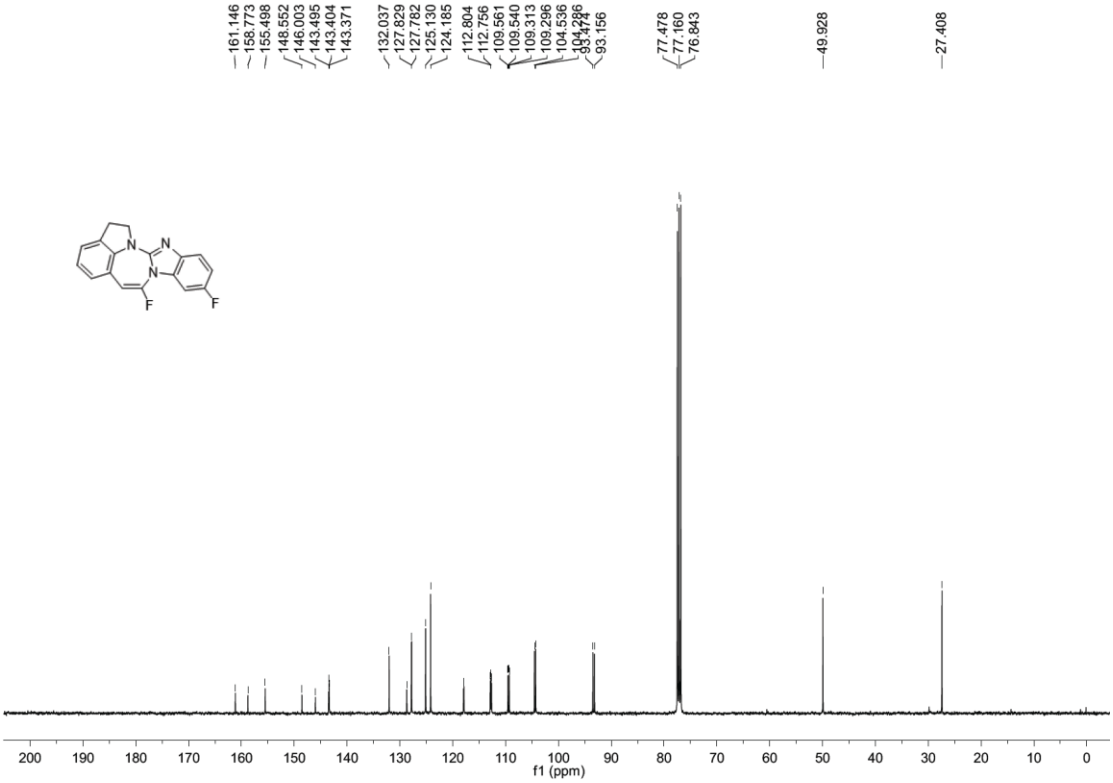
^{19}F-NMR of **3n** ($CDCl_3$, 376 MHz)



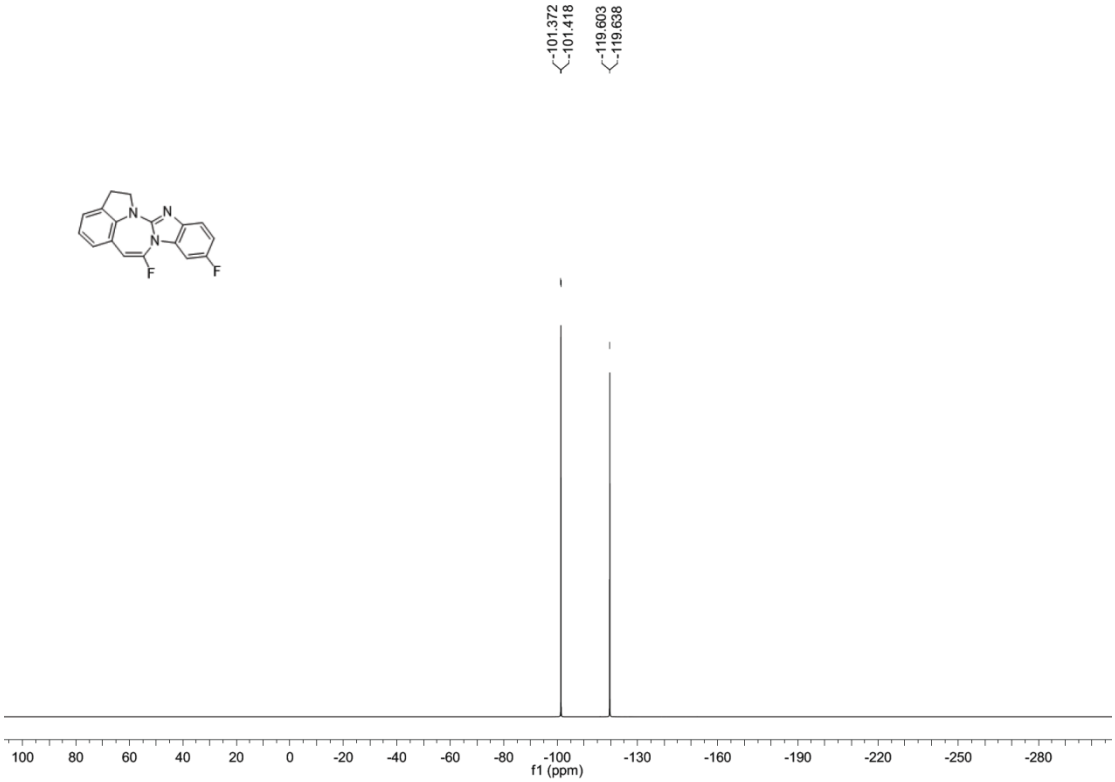
^{1}H-NMR of **3n'** ($CDCl_3$, 400 MHz)



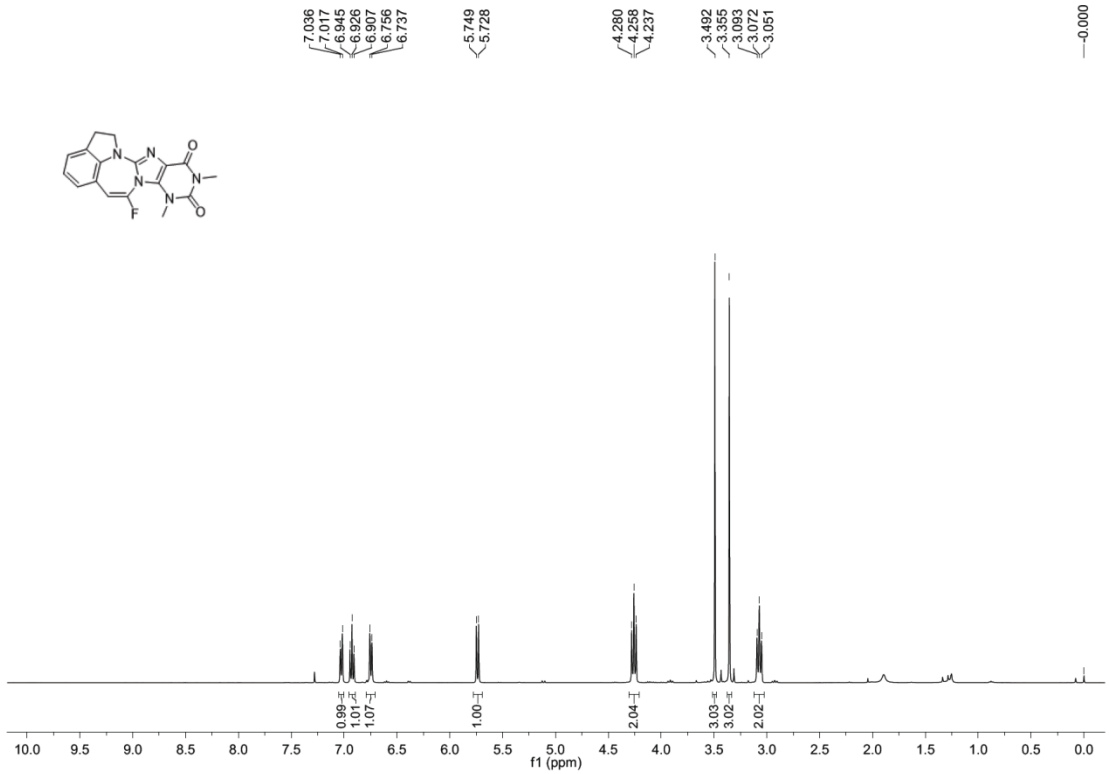
^{13}C{^{1}H}-NMR of **3n'** ($CDCl_3$, 100 MHz)



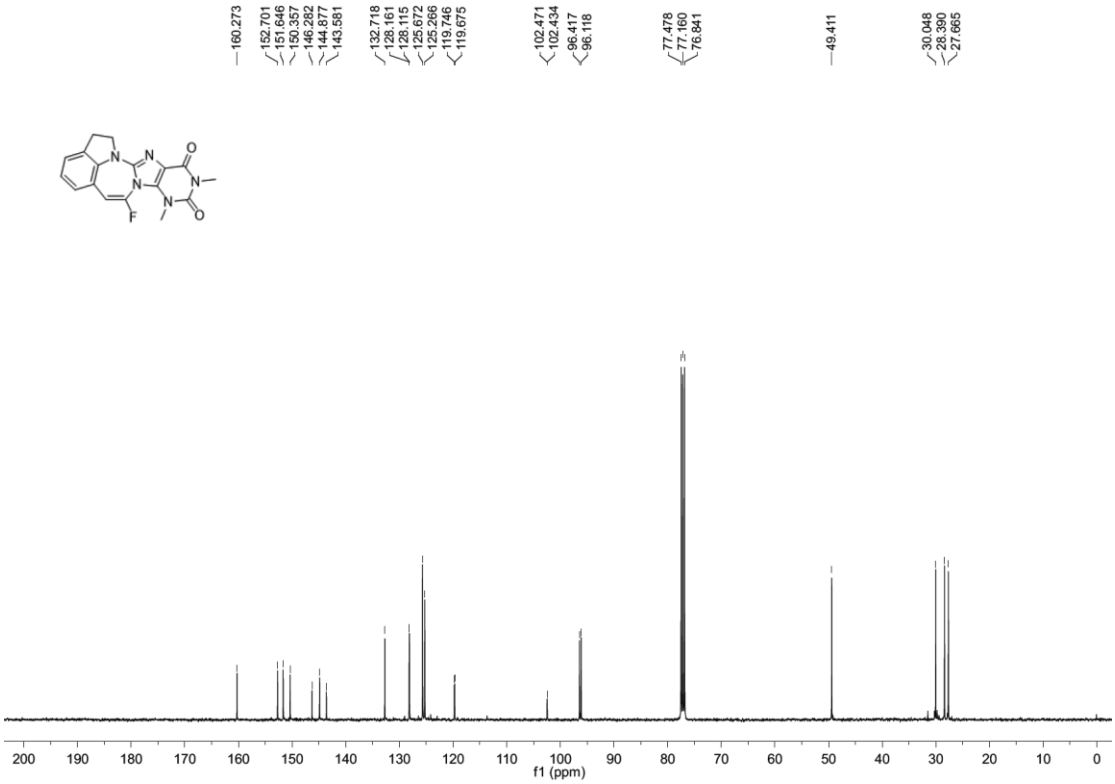
^{19}F-NMR of **3n'** ($CDCl_3$, 376 MHz)



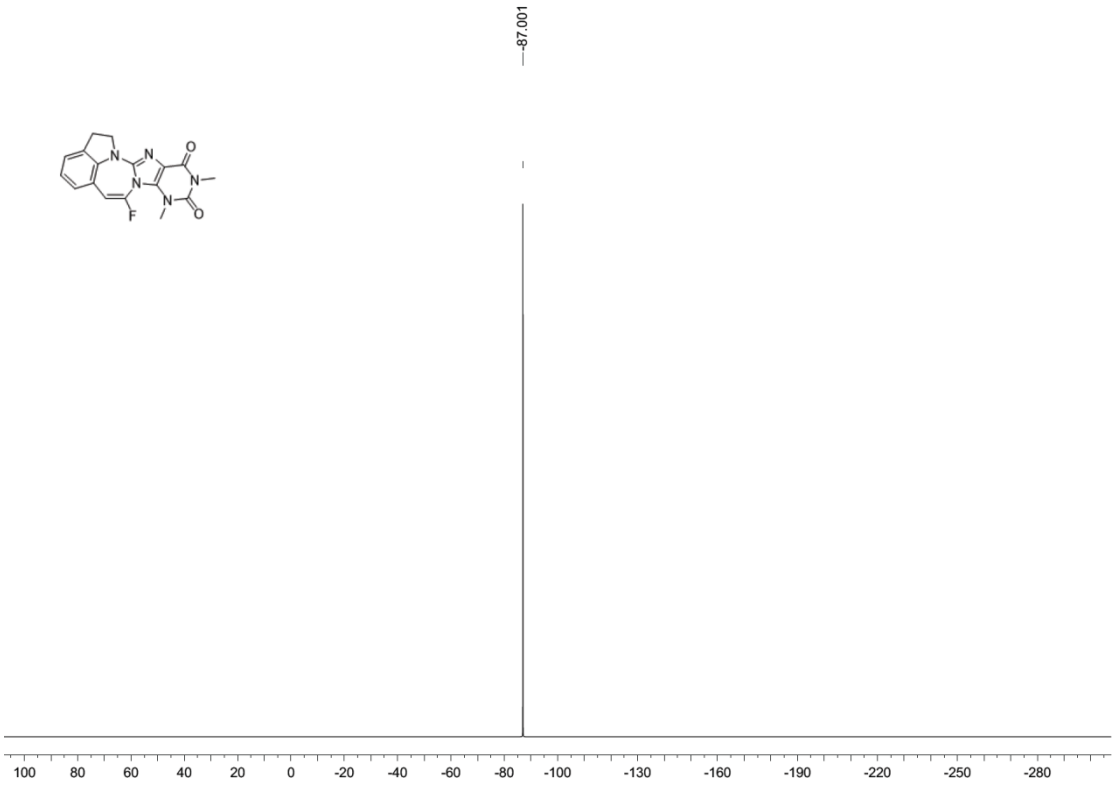
^{1}H-NMR of **3o** ($CDCl_3$, 400 MHz)



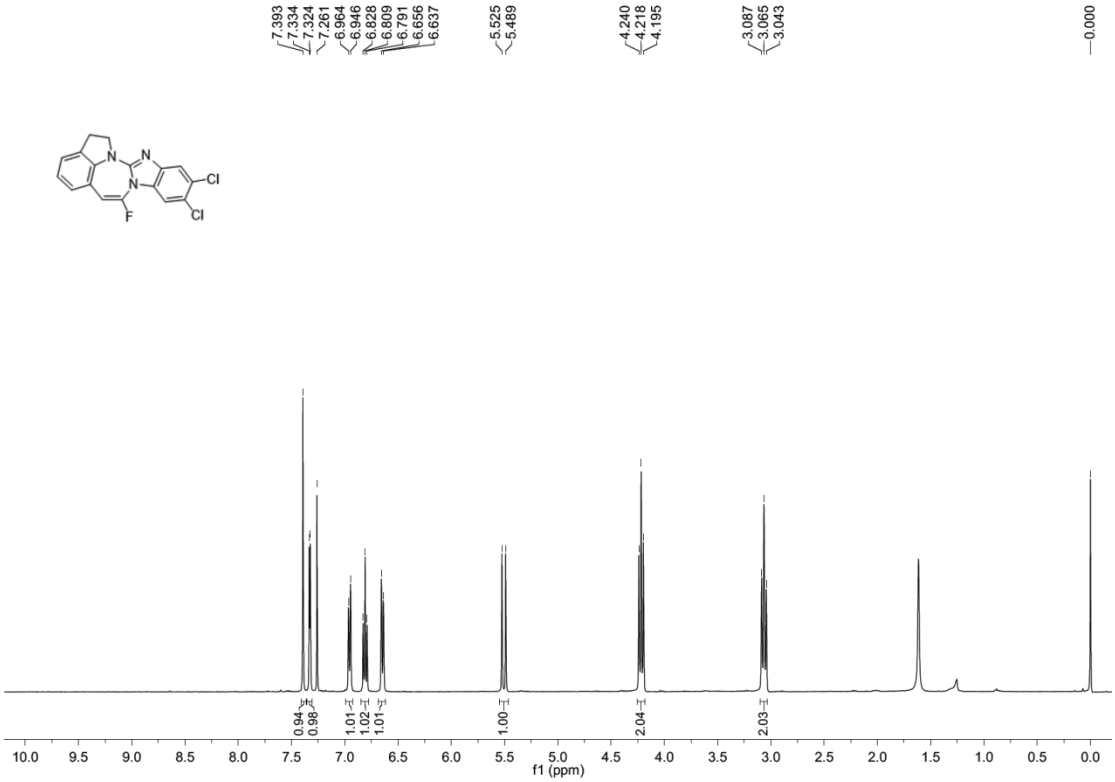
^{13}C{^{1}H}-NMR of **3o** ($CDCl_3$, 100 MHz)



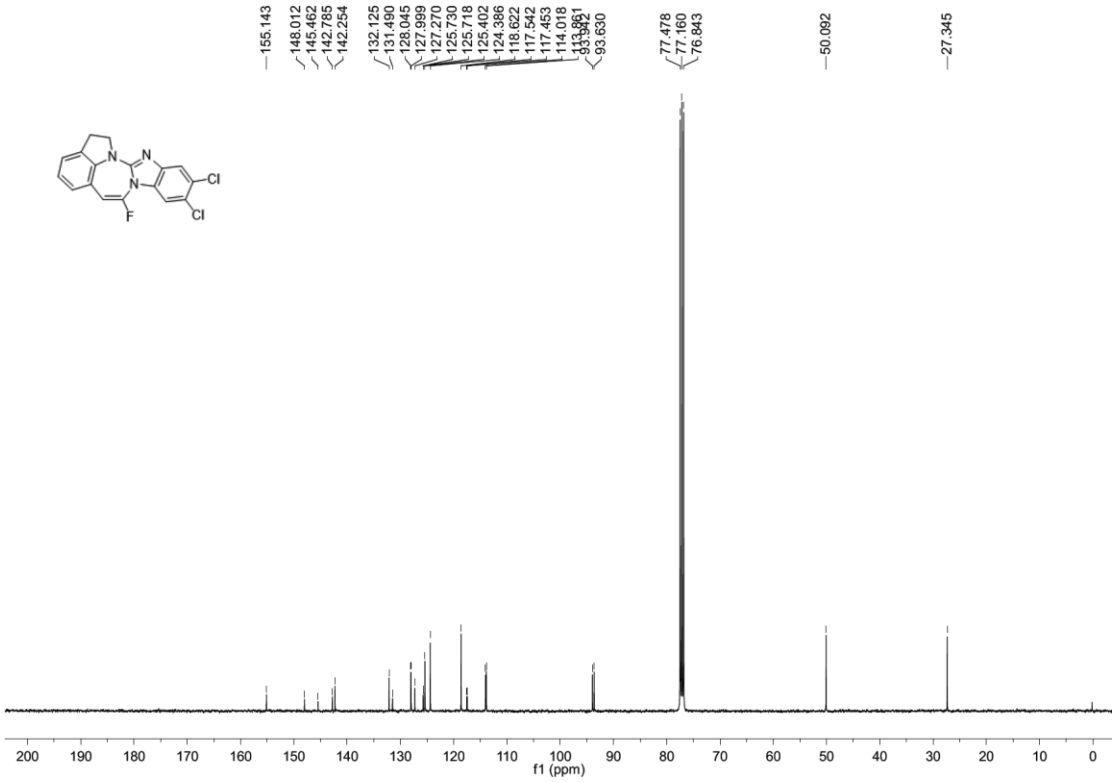
^{19}F-NMR of **3o** ($CDCl_3$, 376 MHz)



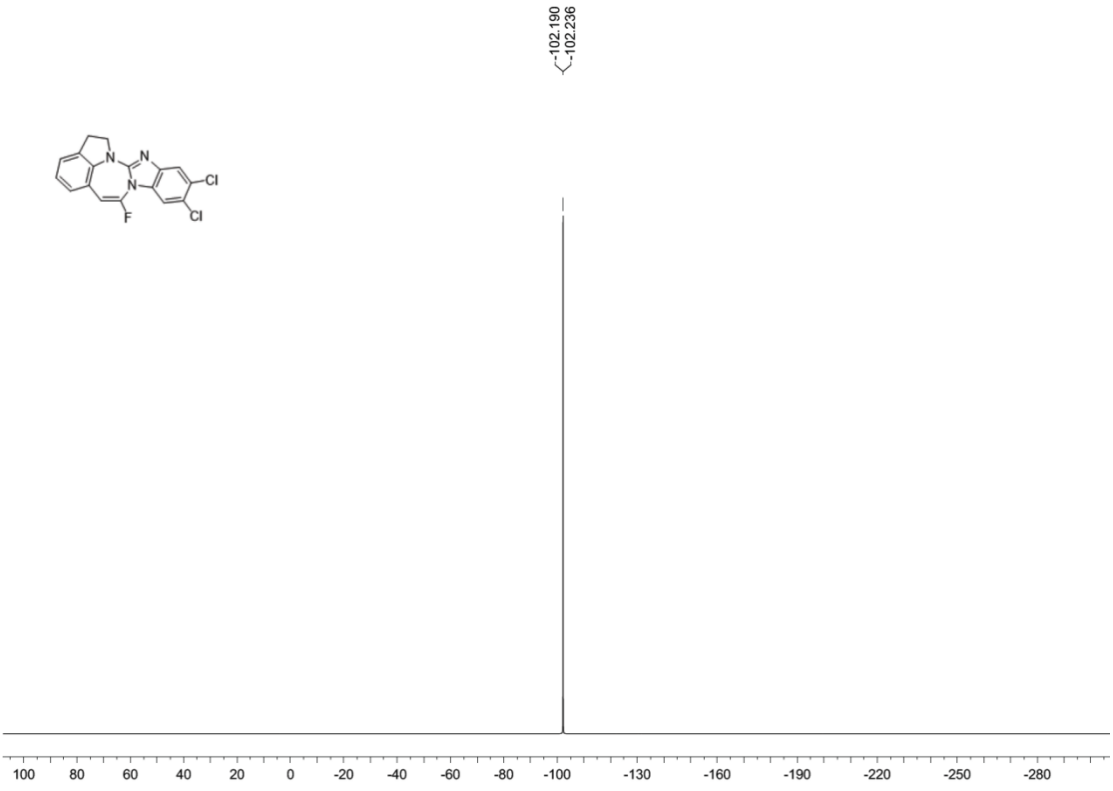
^{1}H-NMR of **3p** ($CDCl_3$, 400 MHz)



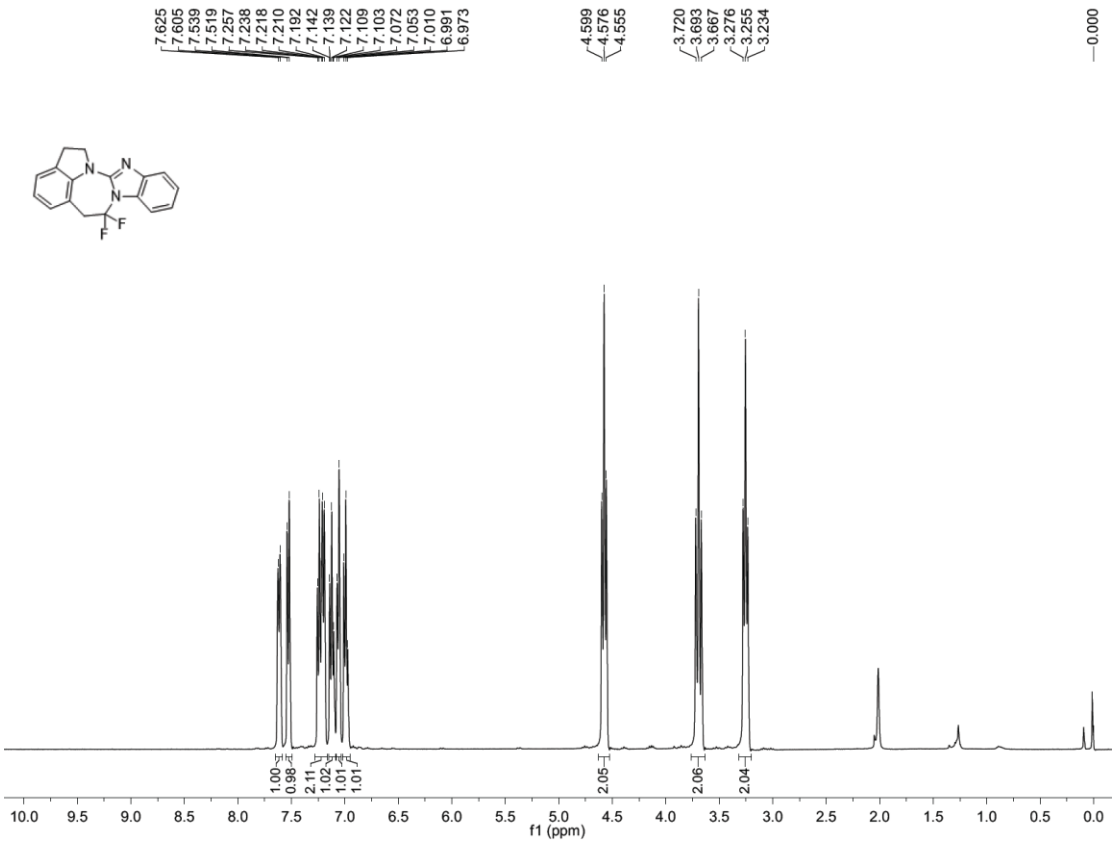
^{13}C{^{1}H}-NMR of **3p** ($CDCl_3$, 100 MHz)



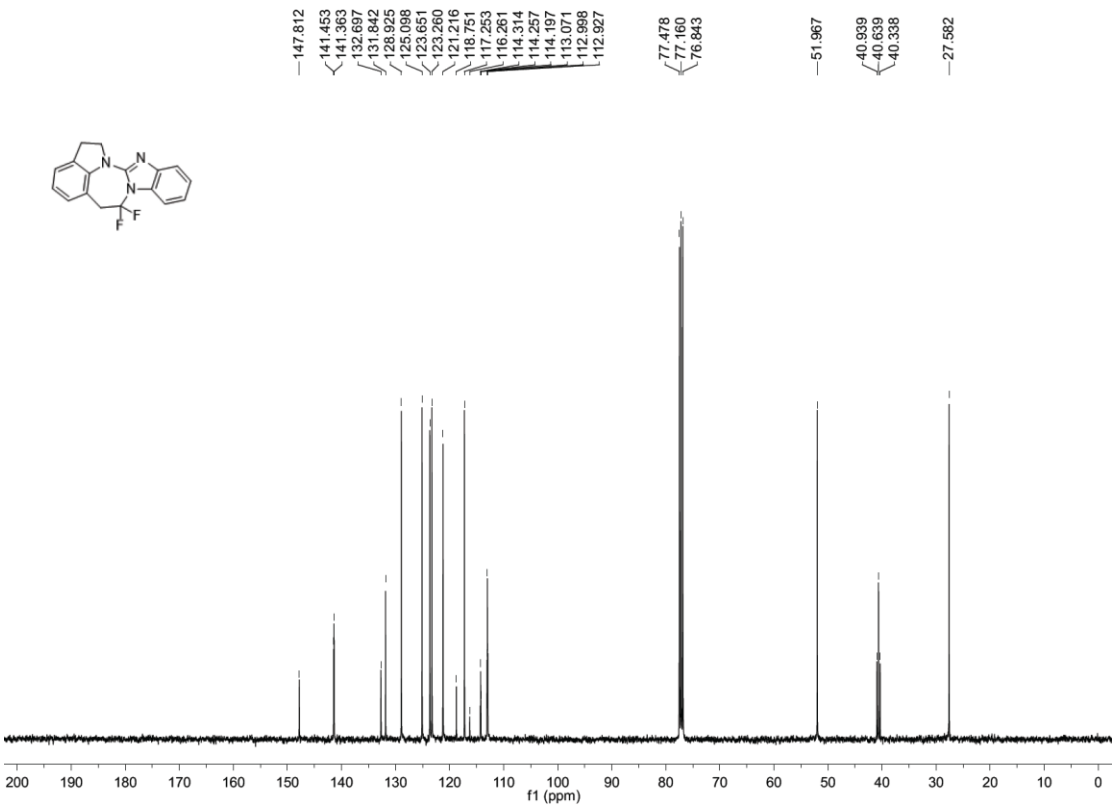
^{19}F-NMR of **3p** ($CDCl_3$, 376 MHz)



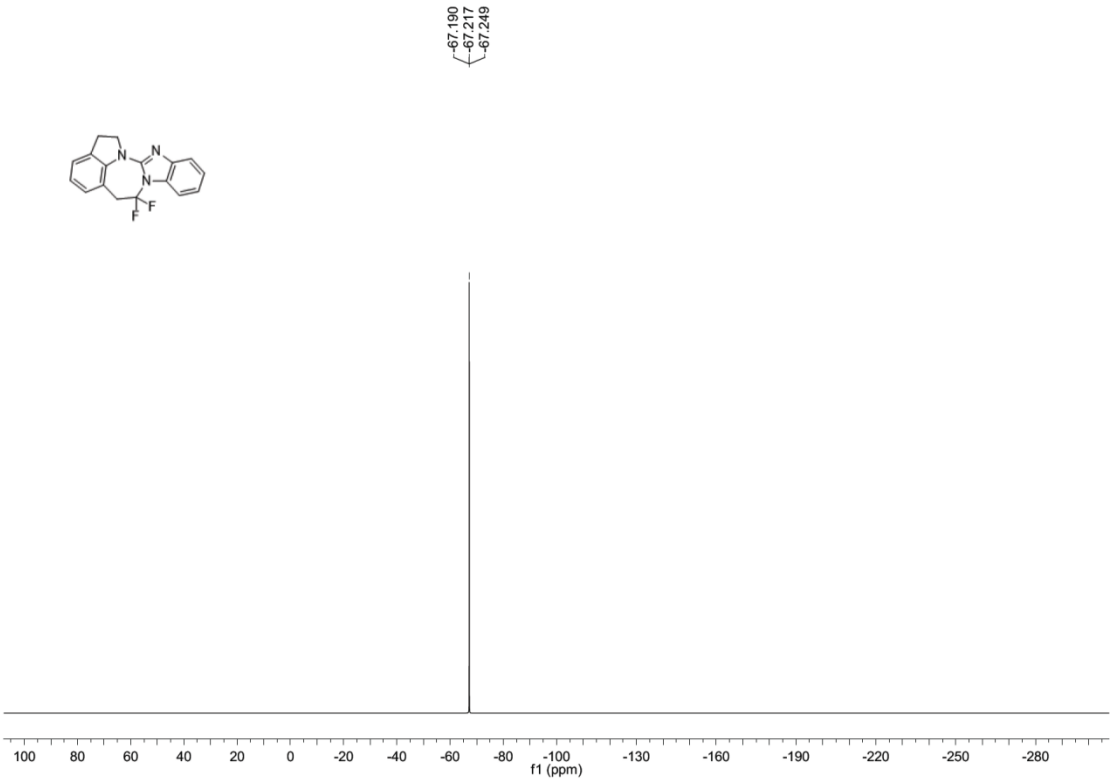
^{1}H-NMR of **4a** ($CDCl_3$, 400 MHz)



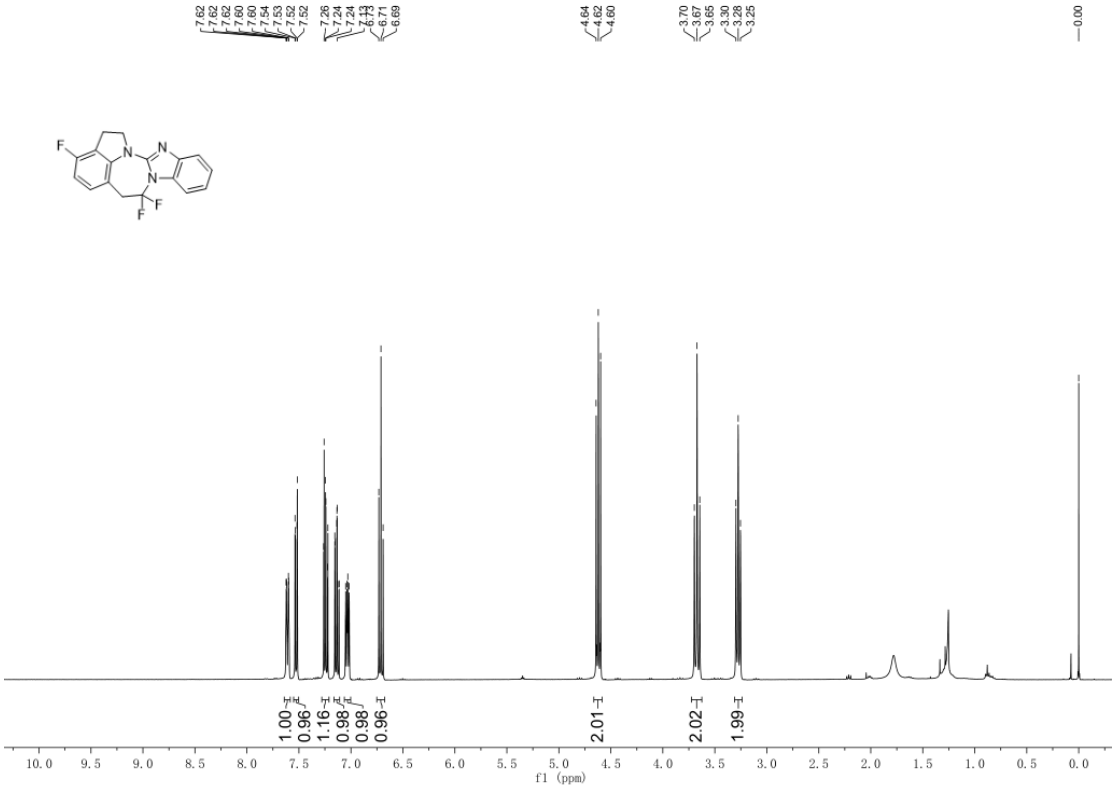
^{13}C{^{1}H}-NMR of **4a** ($CDCl_3$, 100 MHz)



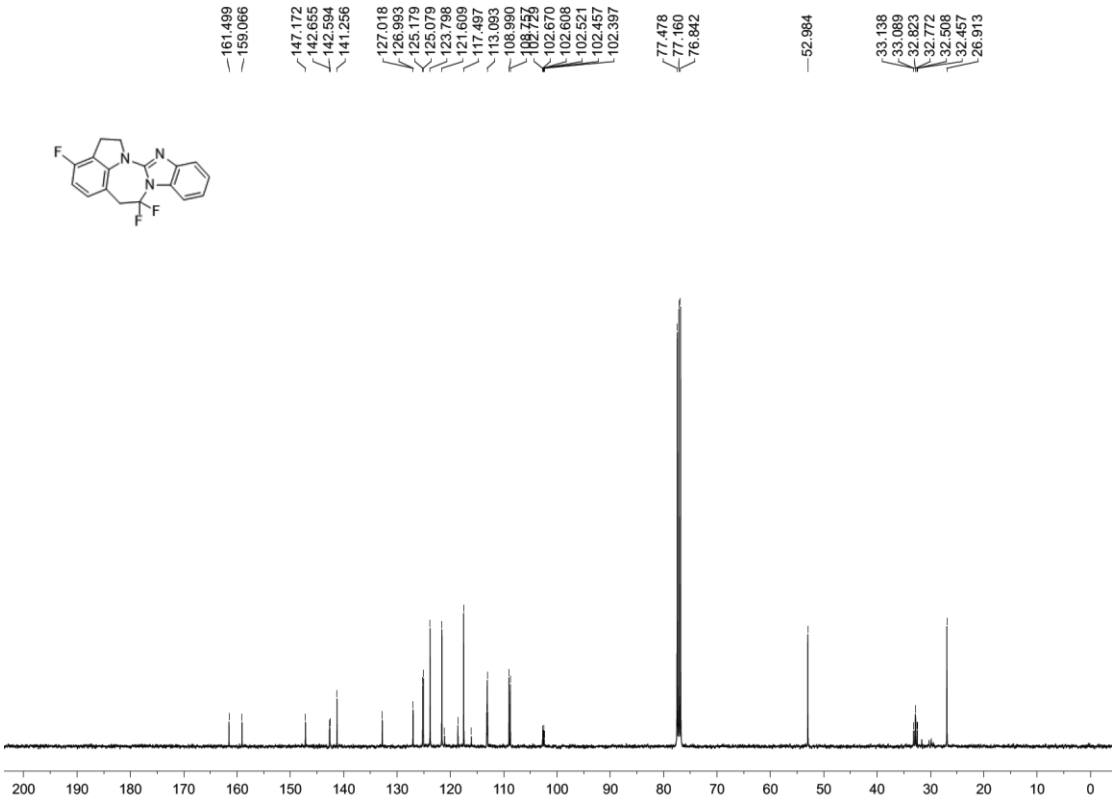
^{19}F-NMR of **4a** ($CDCl_3$, 376 MHz)



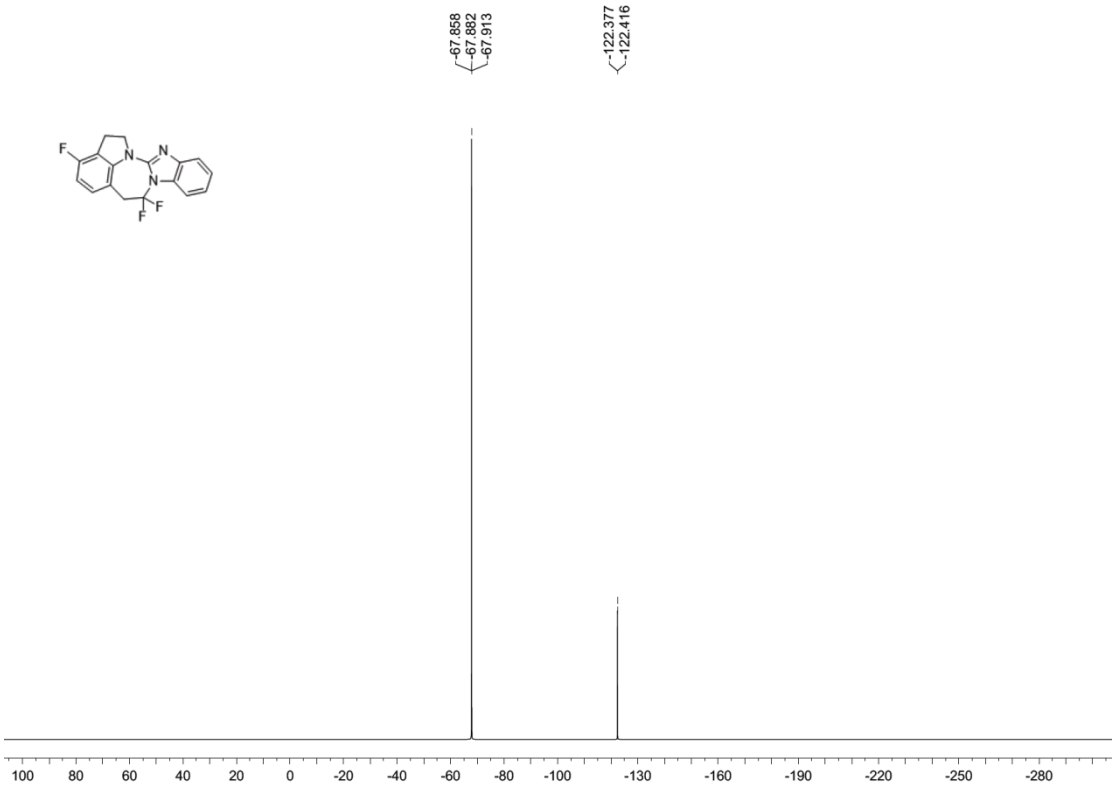
^{1}H-NMR of **4b** ($CDCl_3$, 400 MHz)



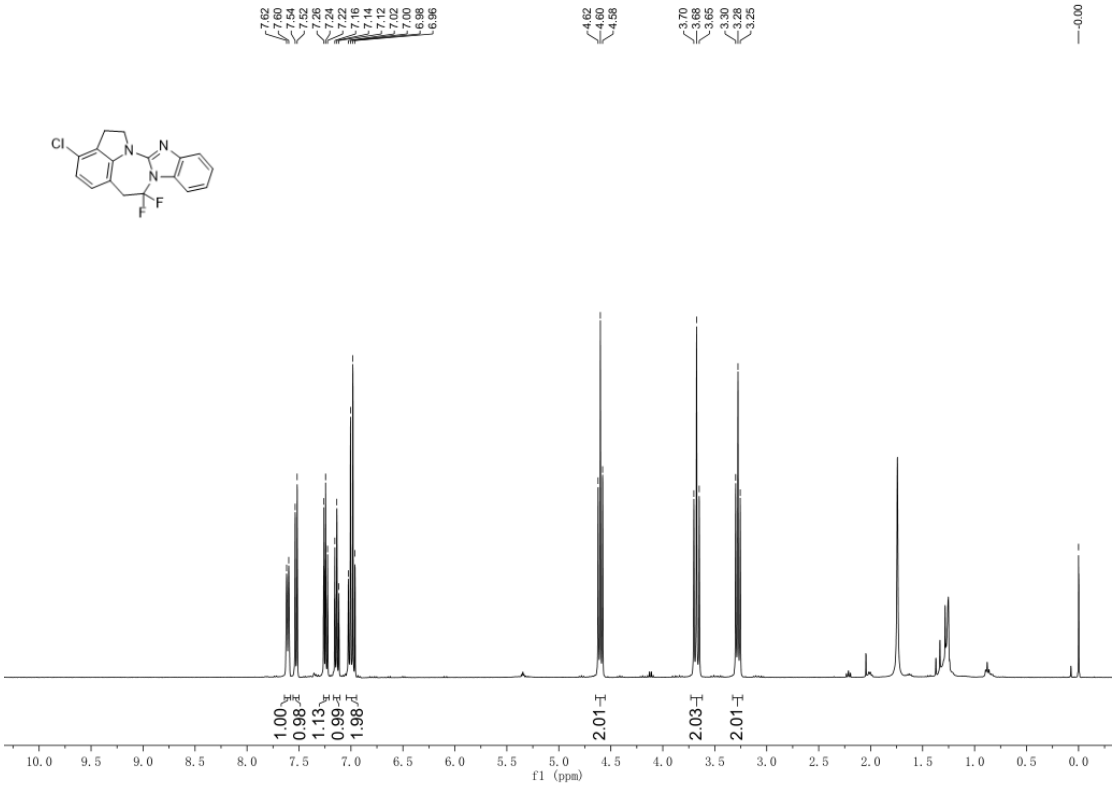
^{13}C{^{1}H}-NMR of **4b** ($CDCl_3$, 100 MHz)



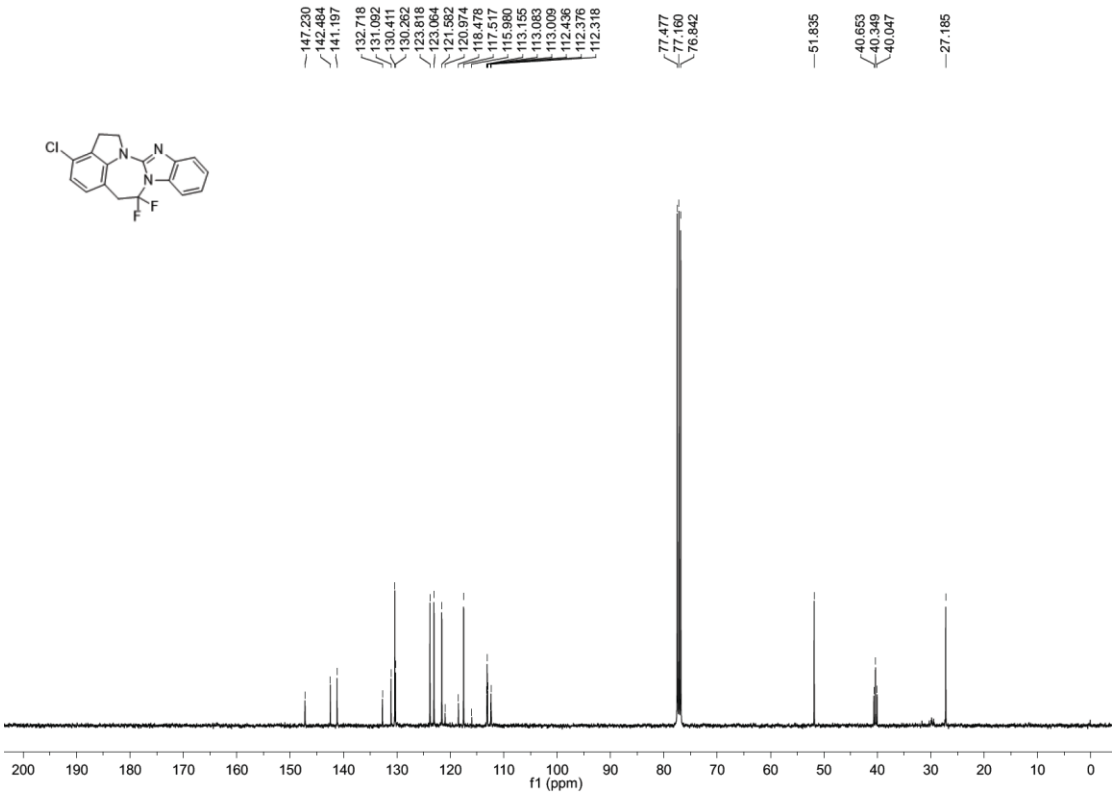
^{19}F-NMR of **4b** ($CDCl_3$, 376 MHz)



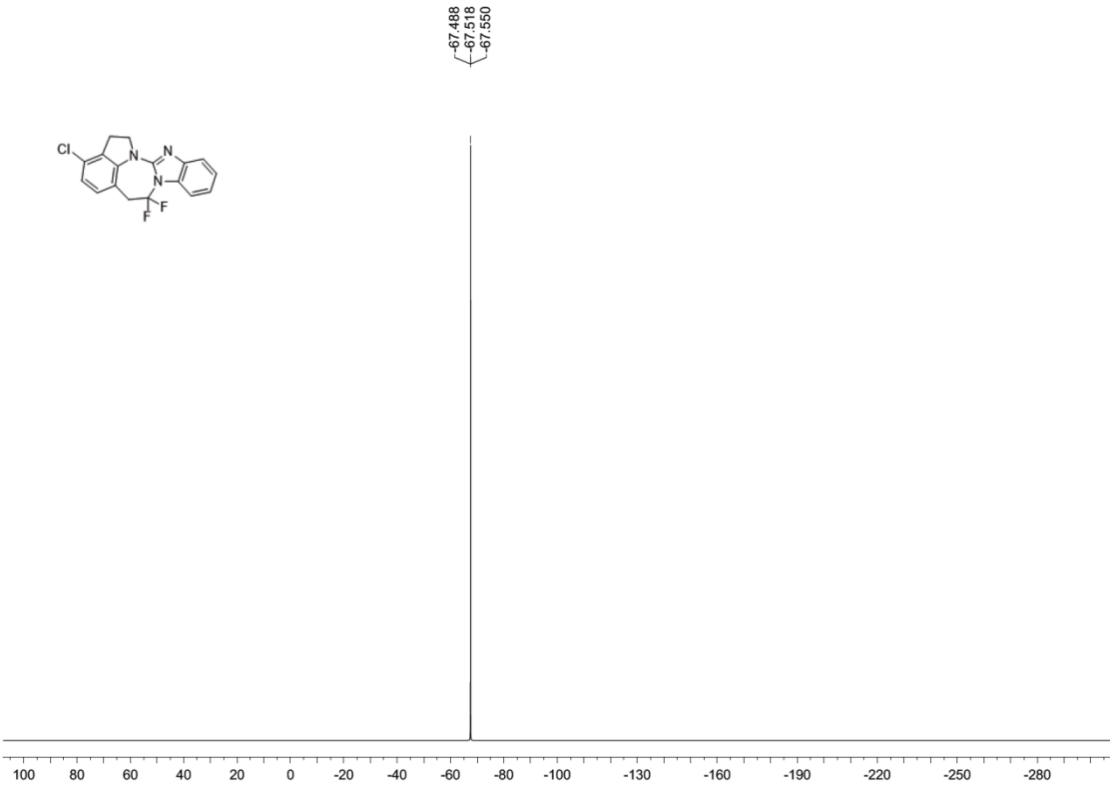
^{1}H-NMR of **4c** ($CDCl_3$, 400 MHz)



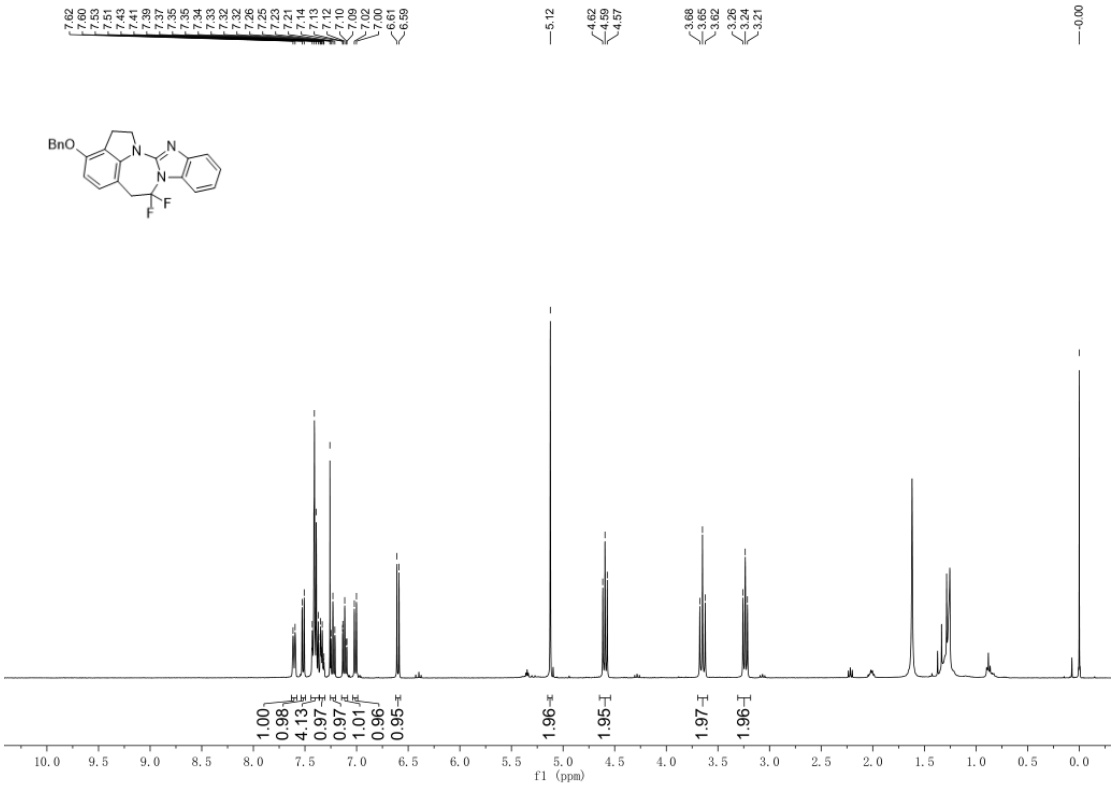
^{13}C{^{1}H}-NMR of **4c** ($CDCl_3$, 100 MHz)



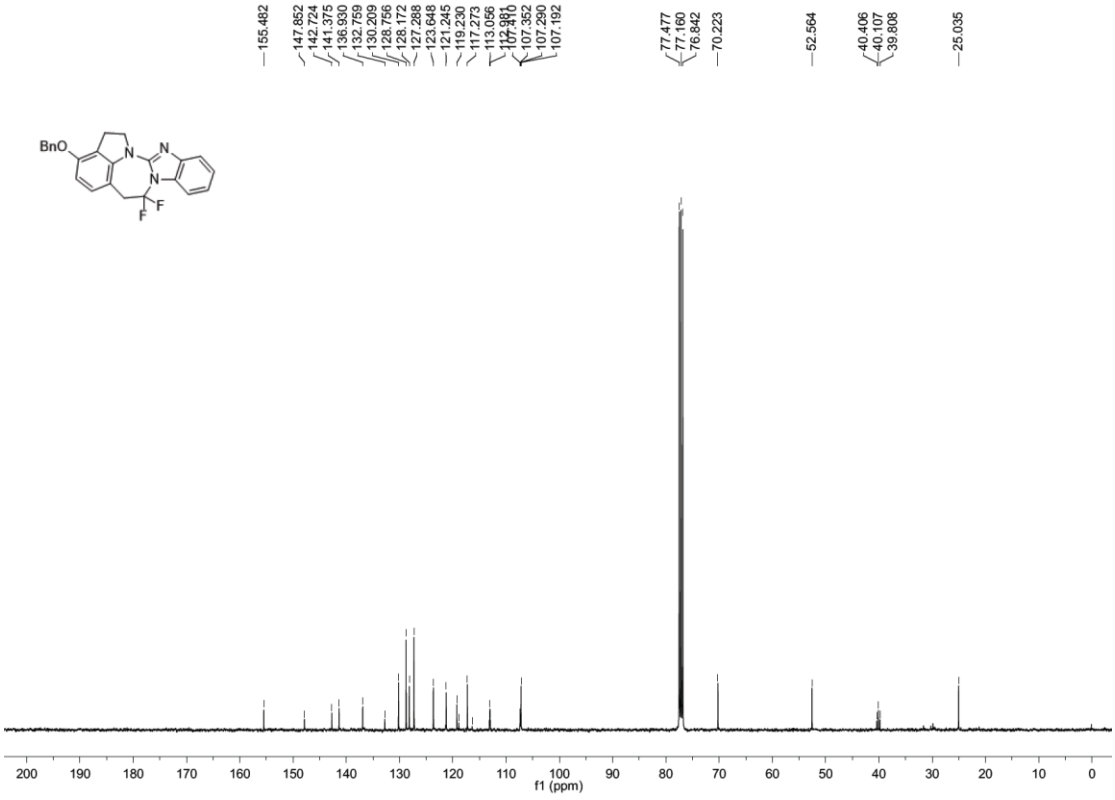
^{19}F-NMR of **4c** ($CDCl_3$, 376 MHz)



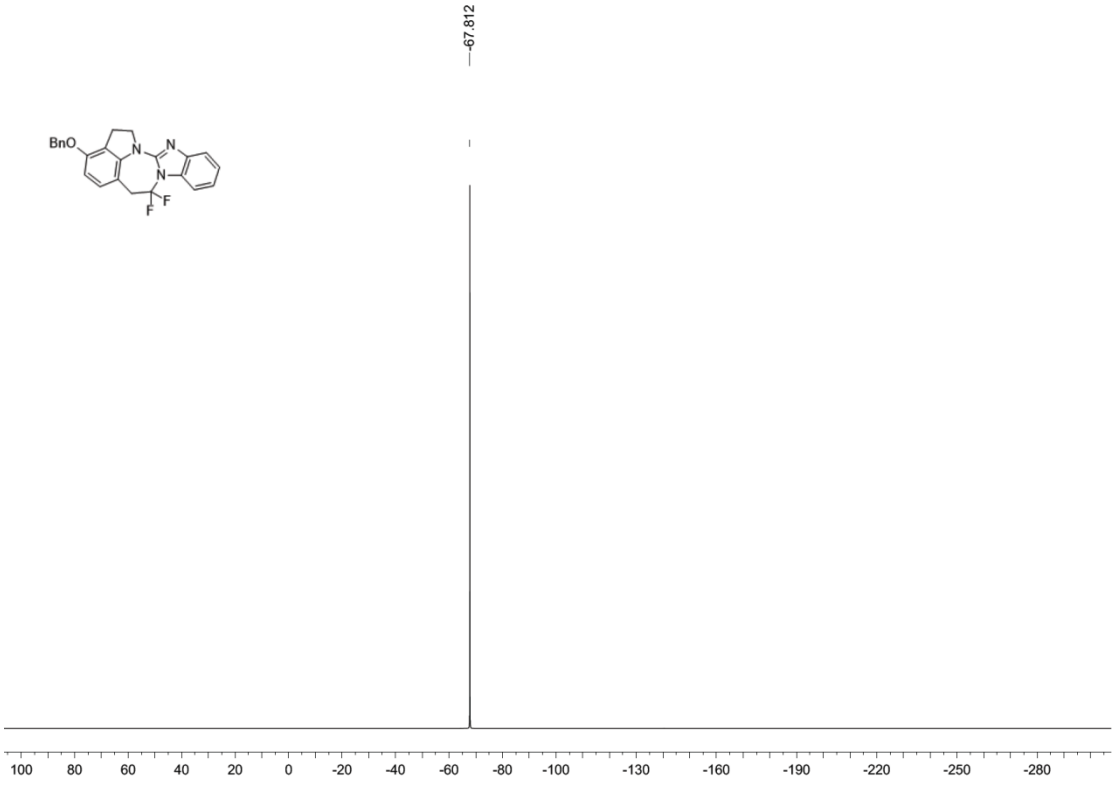
^{1}H-NMR of **4d** ($CDCl_3$, 400 MHz)



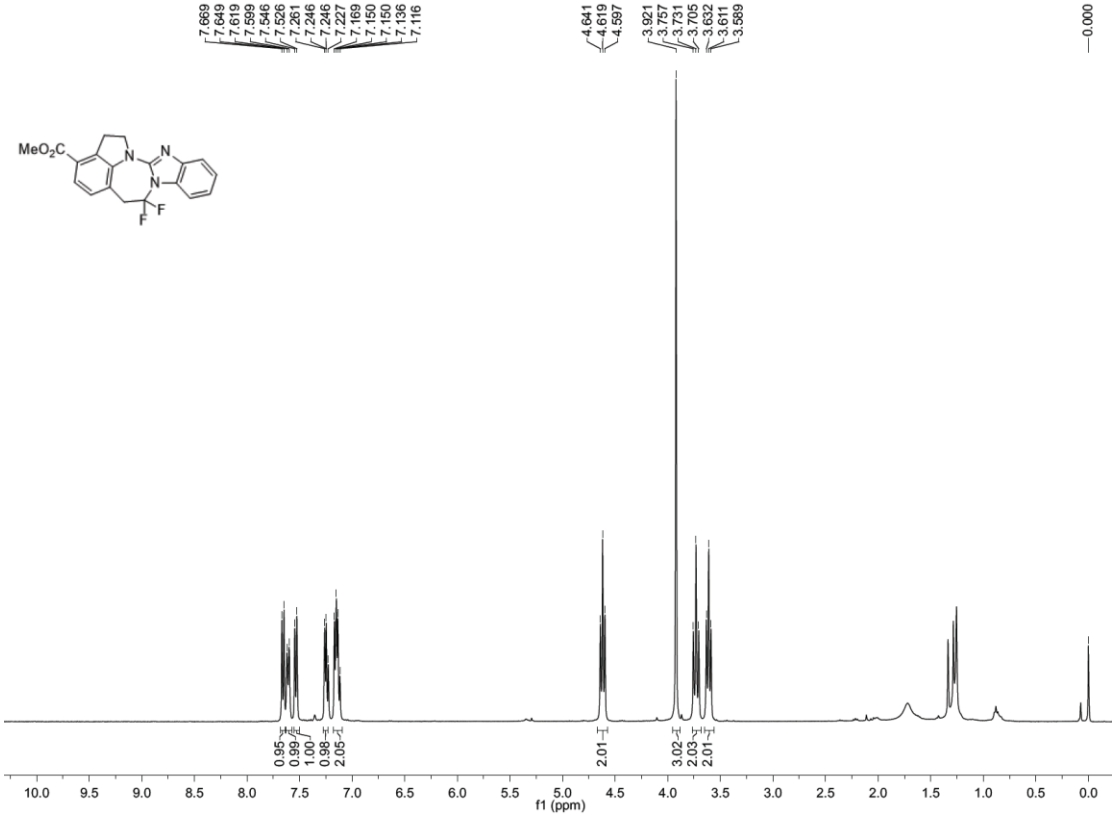
^{13}C{^{1}H}-NMR of **4d** ($CDCl_3$, 100 MHz)



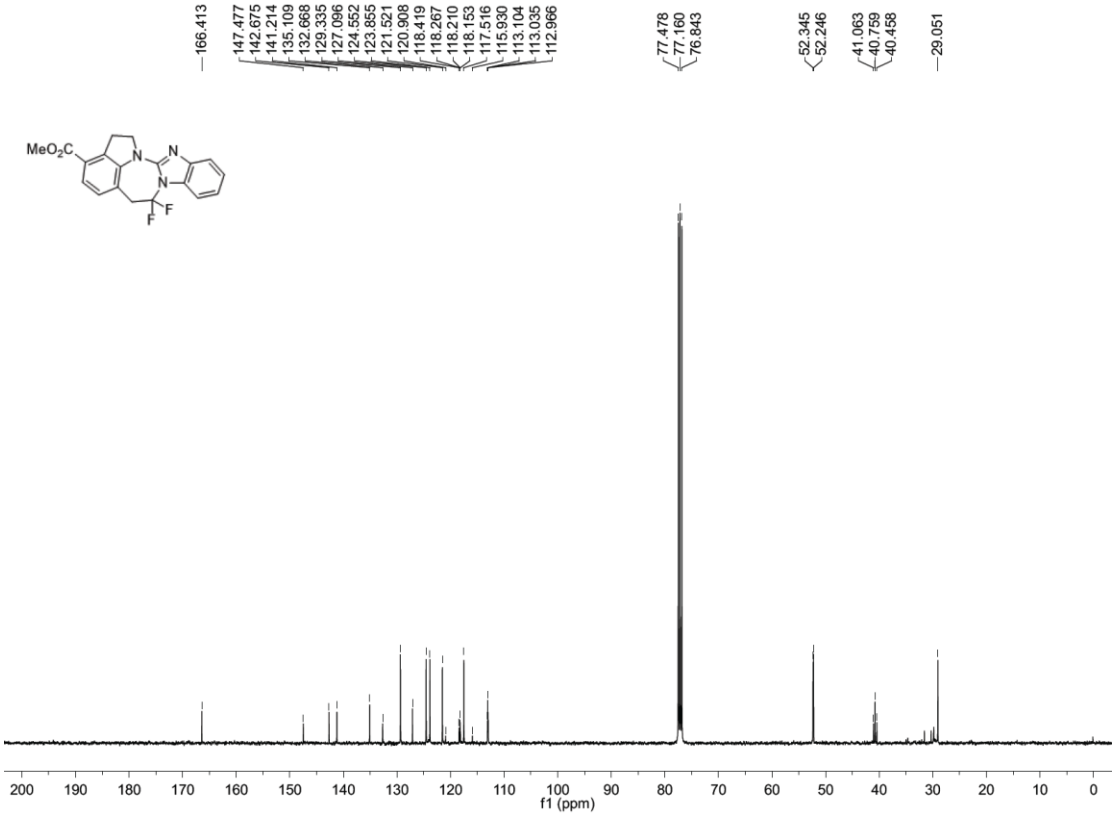
^{19}F-NMR of **4d** ($CDCl_3$, 376 MHz)



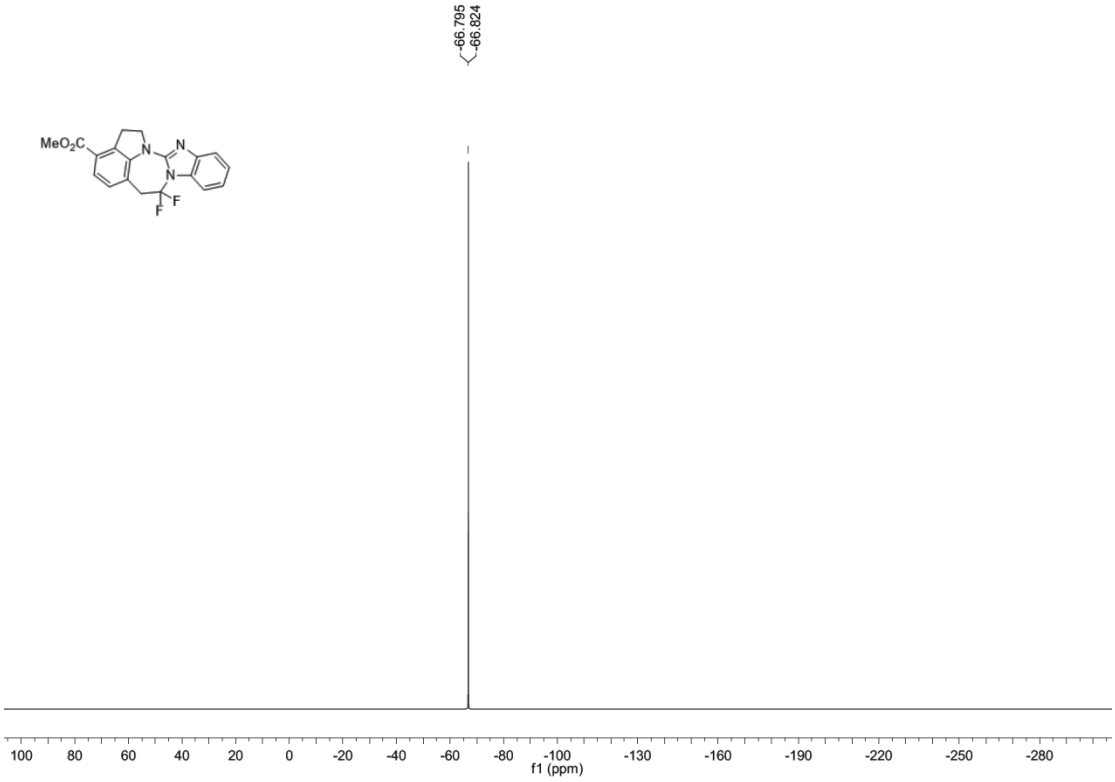
^{1}H-NMR of **4e** ($CDCl_3$, 400 MHz)



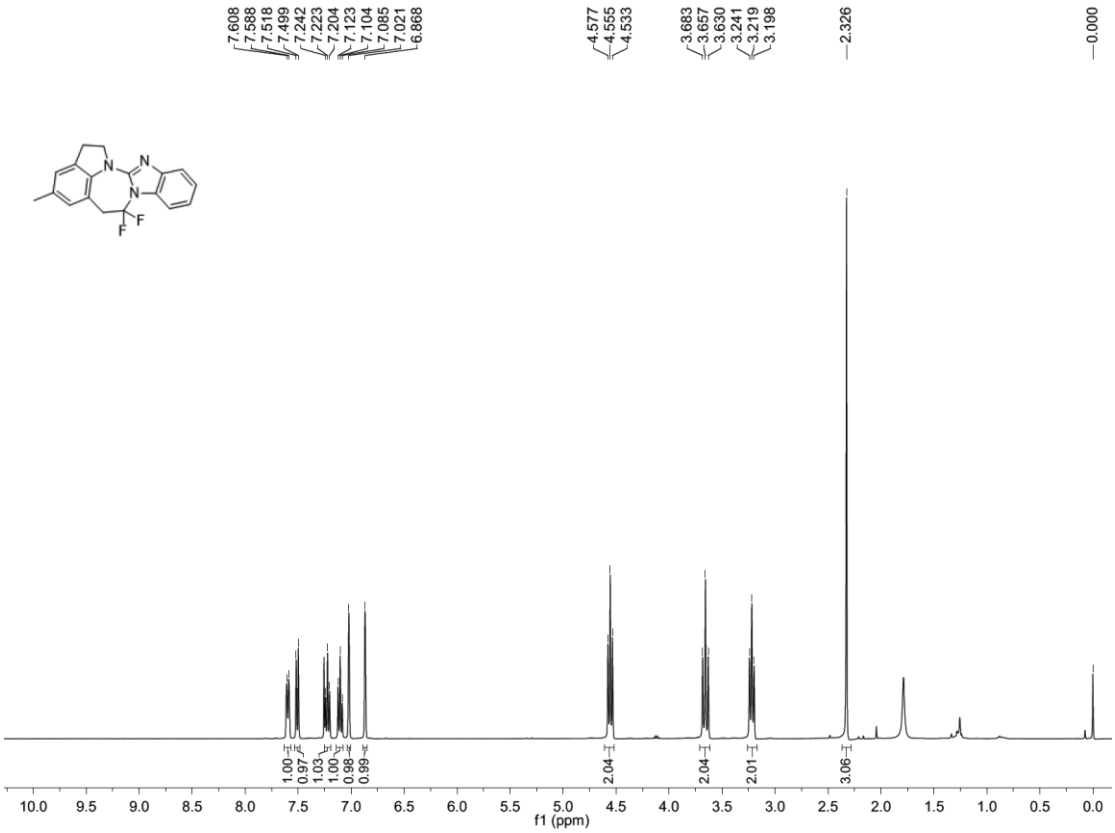
^{13}C{^{1}H}-NMR of **4e** ($CDCl_3$, 100 MHz)



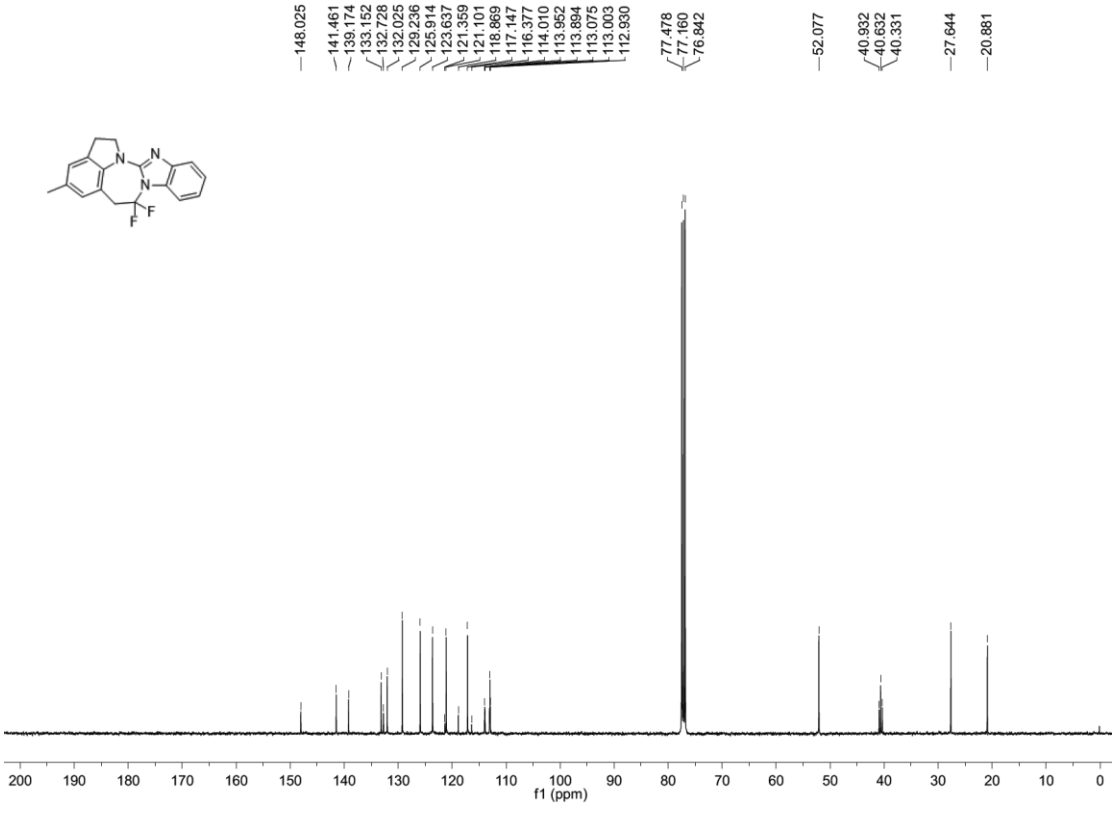
^{19}F-NMR of **4e** ($CDCl_3$, 376 MHz)



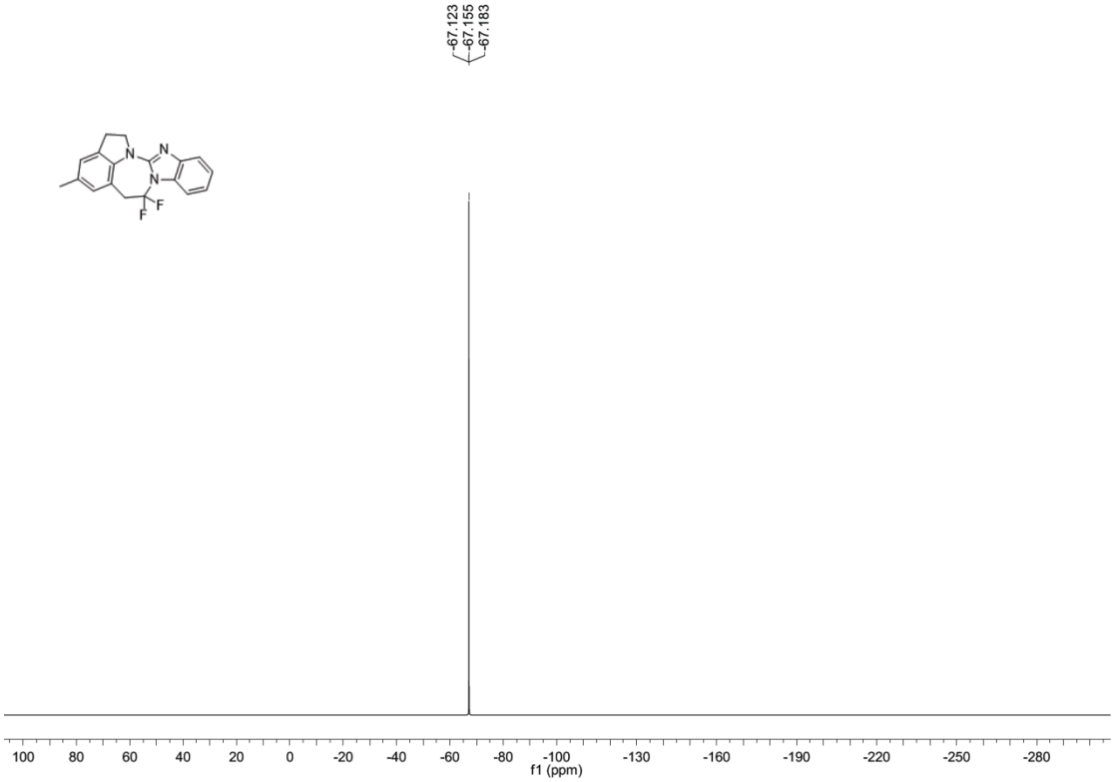
^{1}H-NMR of **4f** ($CDCl_3$, 400 MHz)



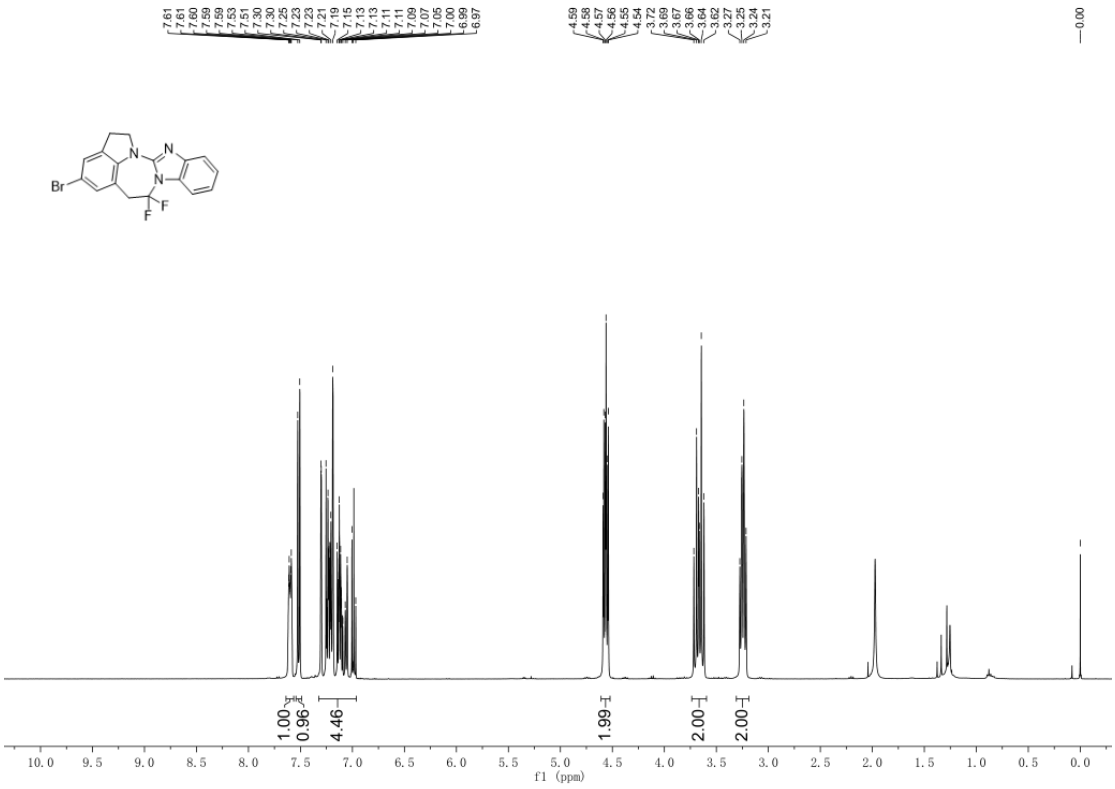
^{13}C{^{1}H}-NMR of **4f** ($CDCl_3$, 100 MHz)



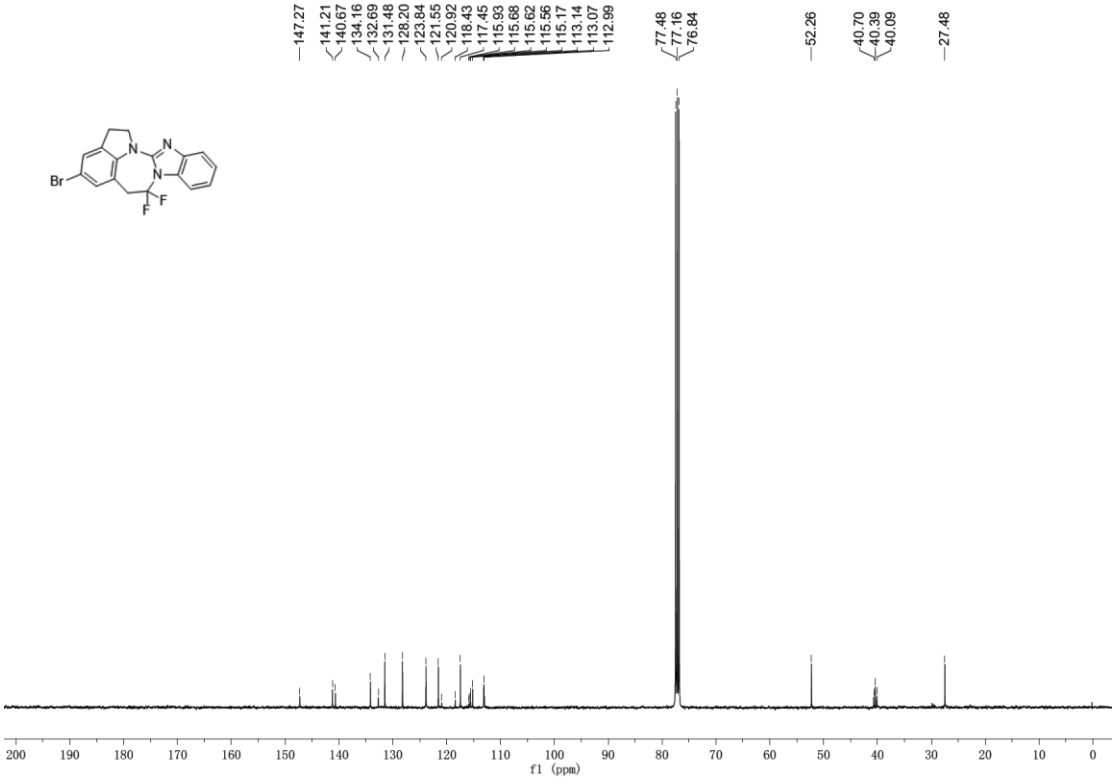
^{19}F-NMR of **4f** ($CDCl_3$, 376 MHz)



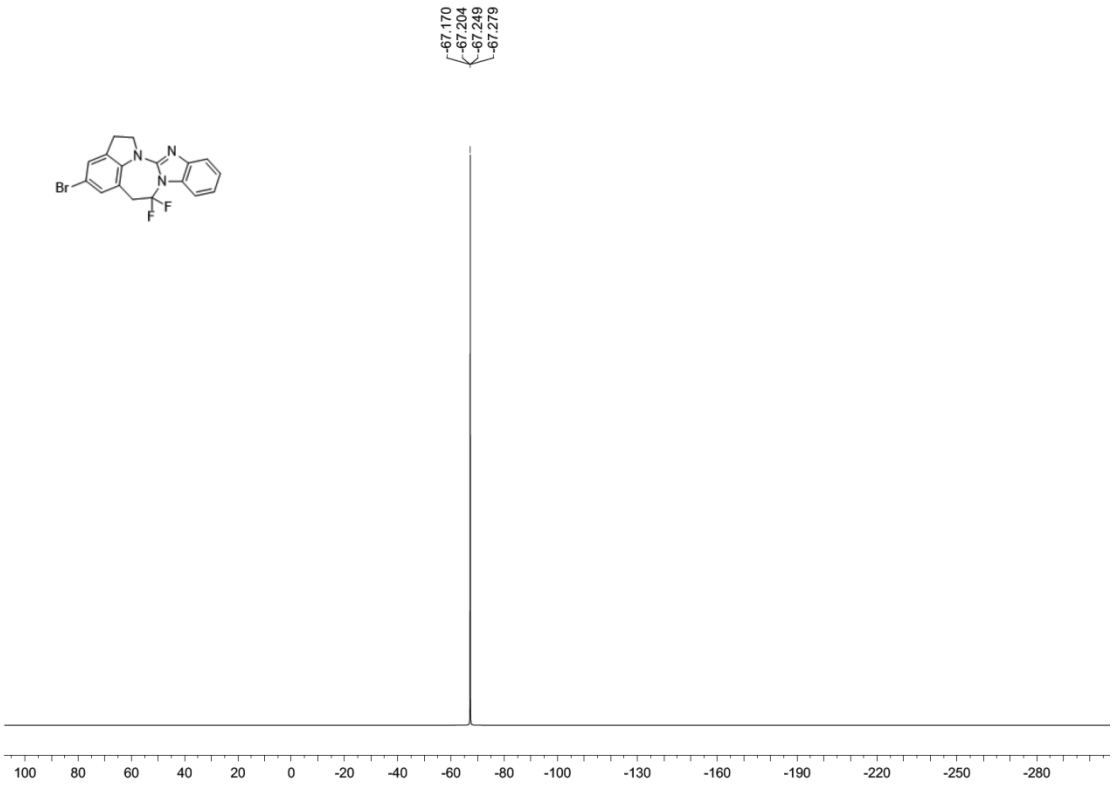
^{1}H-NMR of **4g** ($CDCl_3$, 400 MHz)



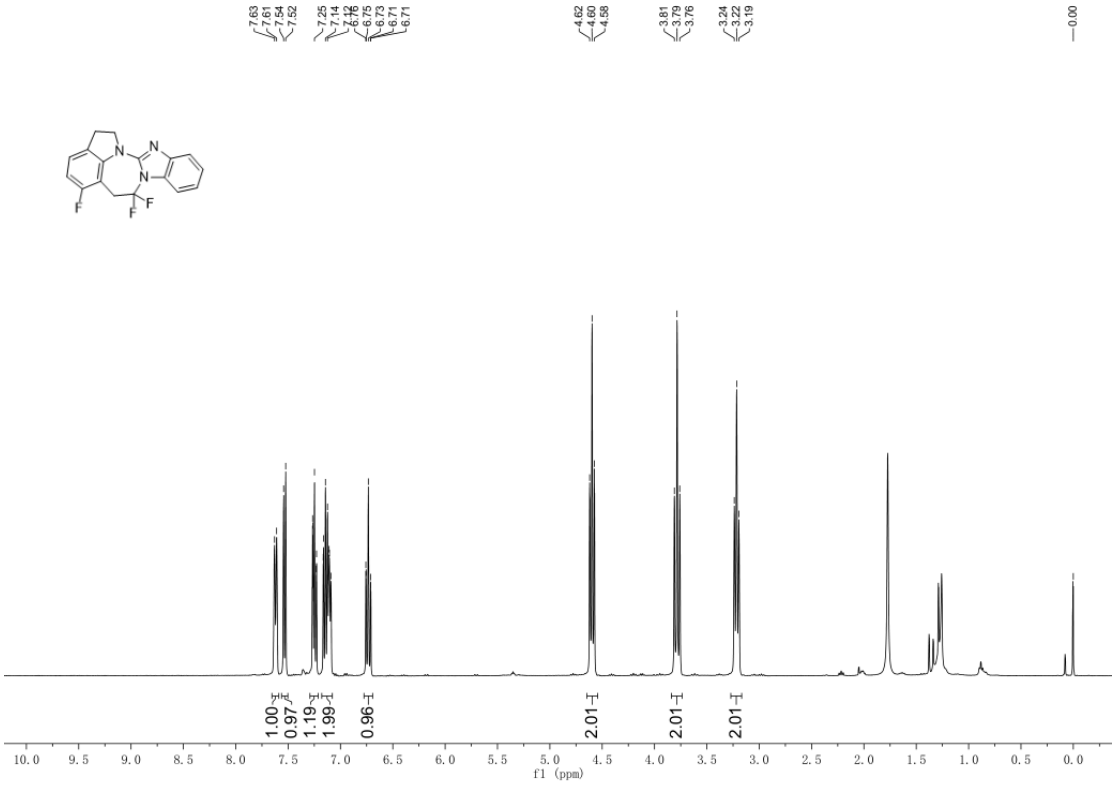
^{13}C{^{1}H}-NMR of **4g** ($CDCl_3$, 100 MHz)



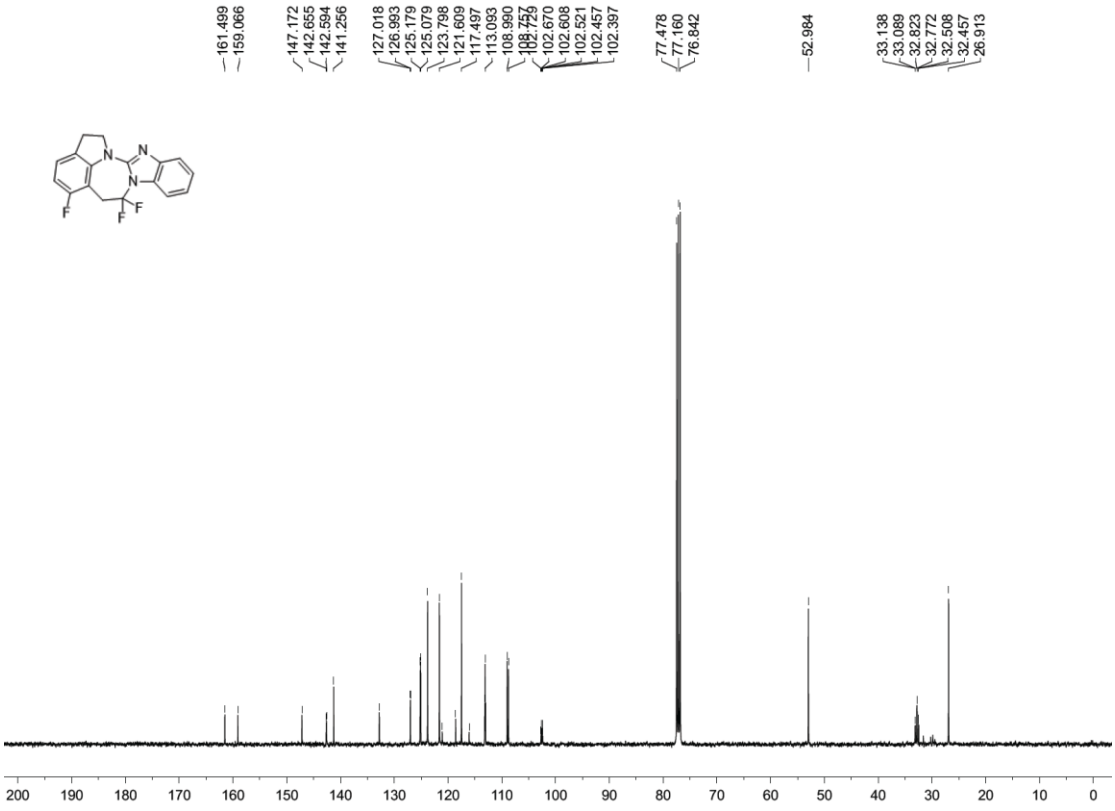
^{19}F-NMR of **4g** ($CDCl_3$, 376 MHz)



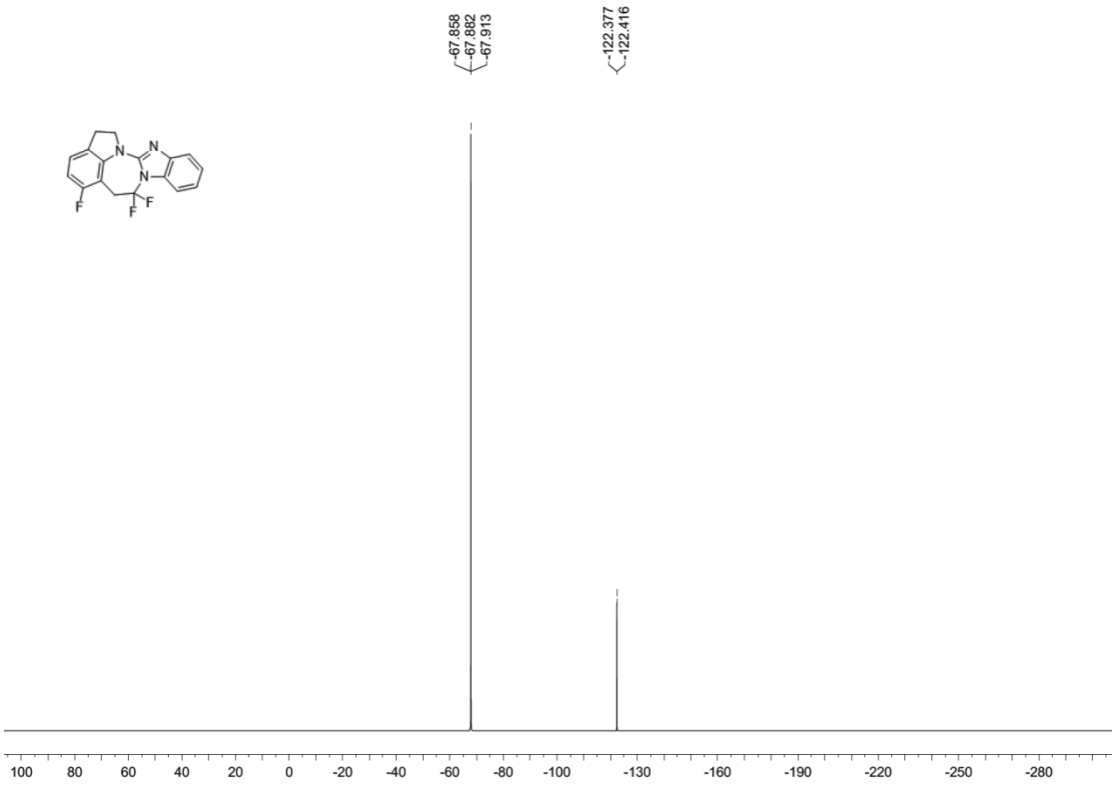
^{1}H-NMR of **4h** ($CDCl_3$, 400 MHz)



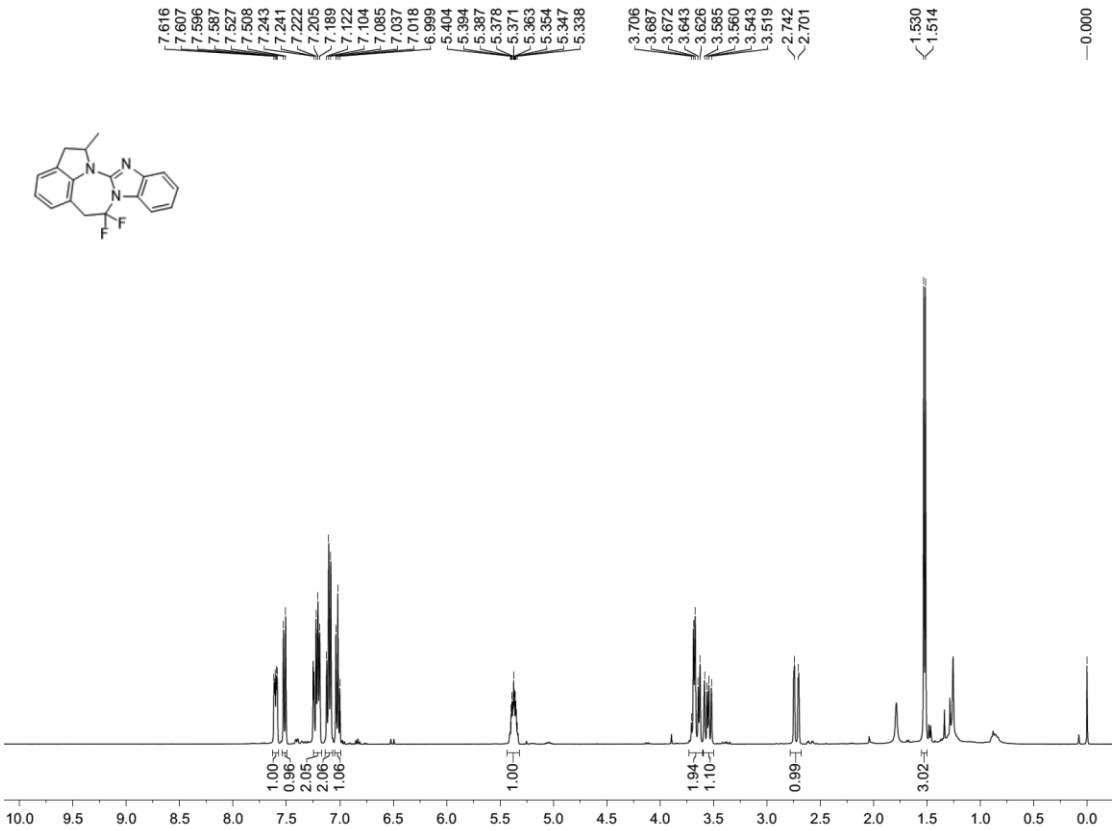
^{13}C{^{1}H}-NMR of **4h** ($CDCl_3$, 100 MHz)



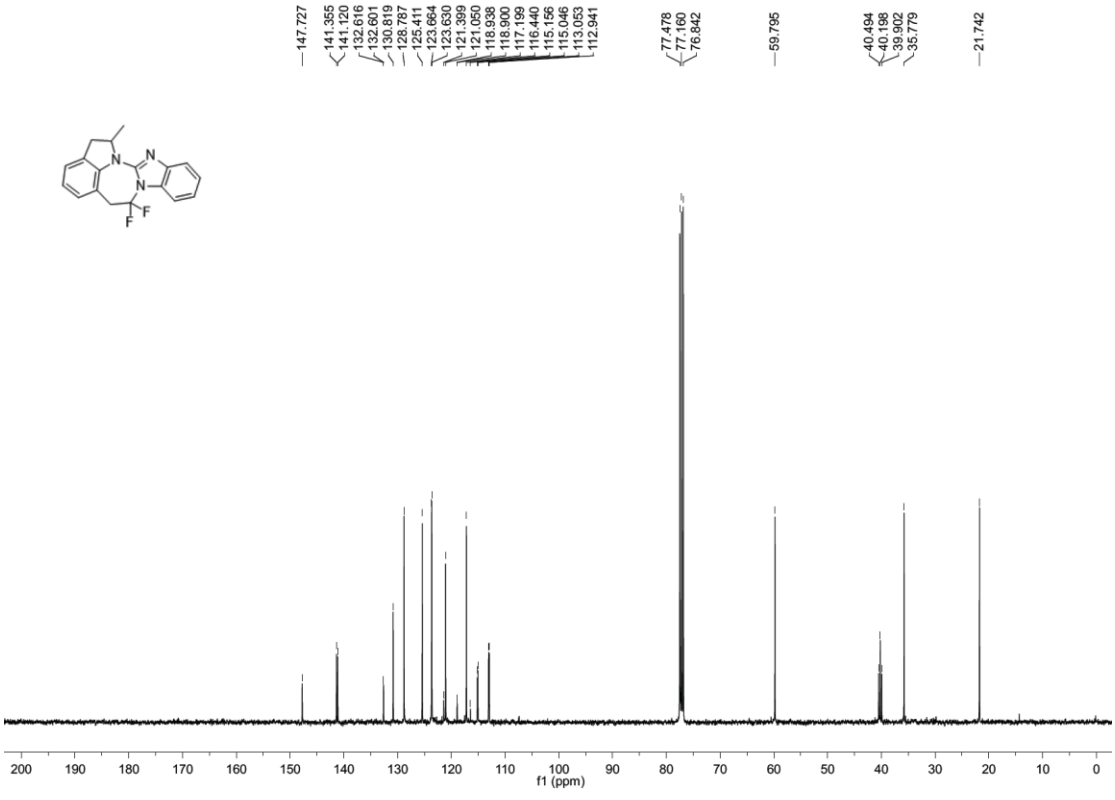
^{19}F-NMR of **4h** ($CDCl_3$, 376 MHz)



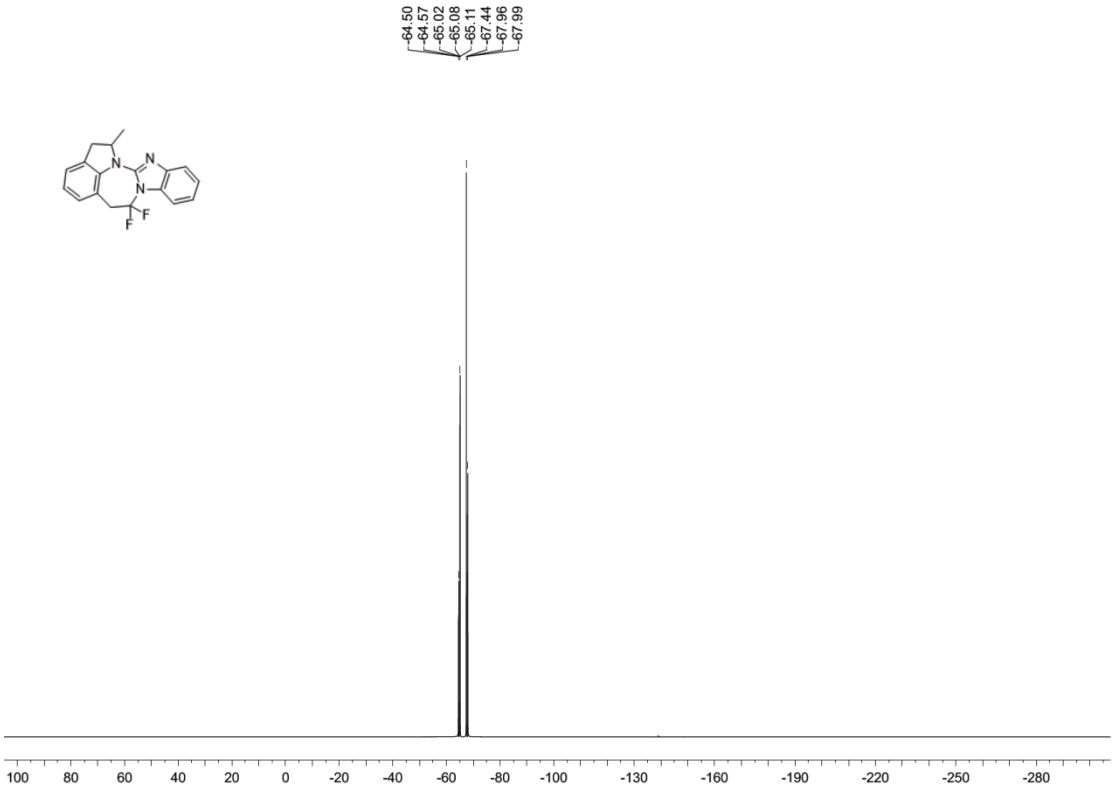
^{1}H-NMR of **4i** ($CDCl_3$, 400 MHz)



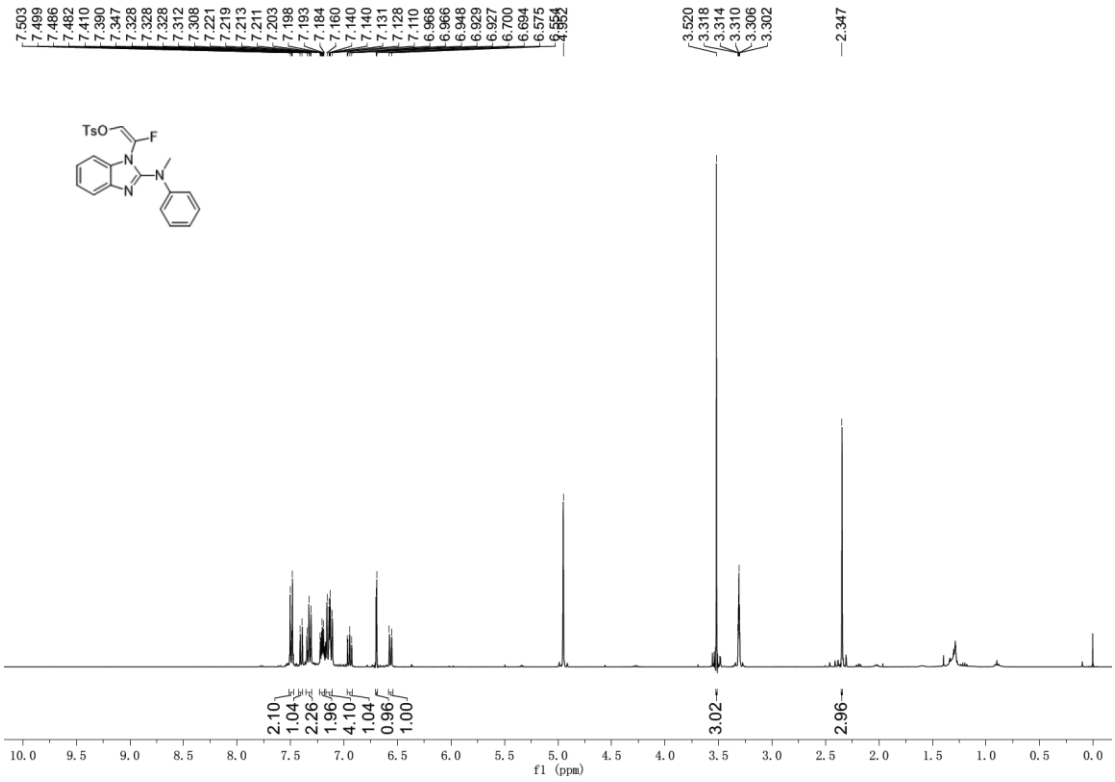
^{13}C{^{1}H}-NMR of **4i** ($CDCl_3$, 100 MHz)



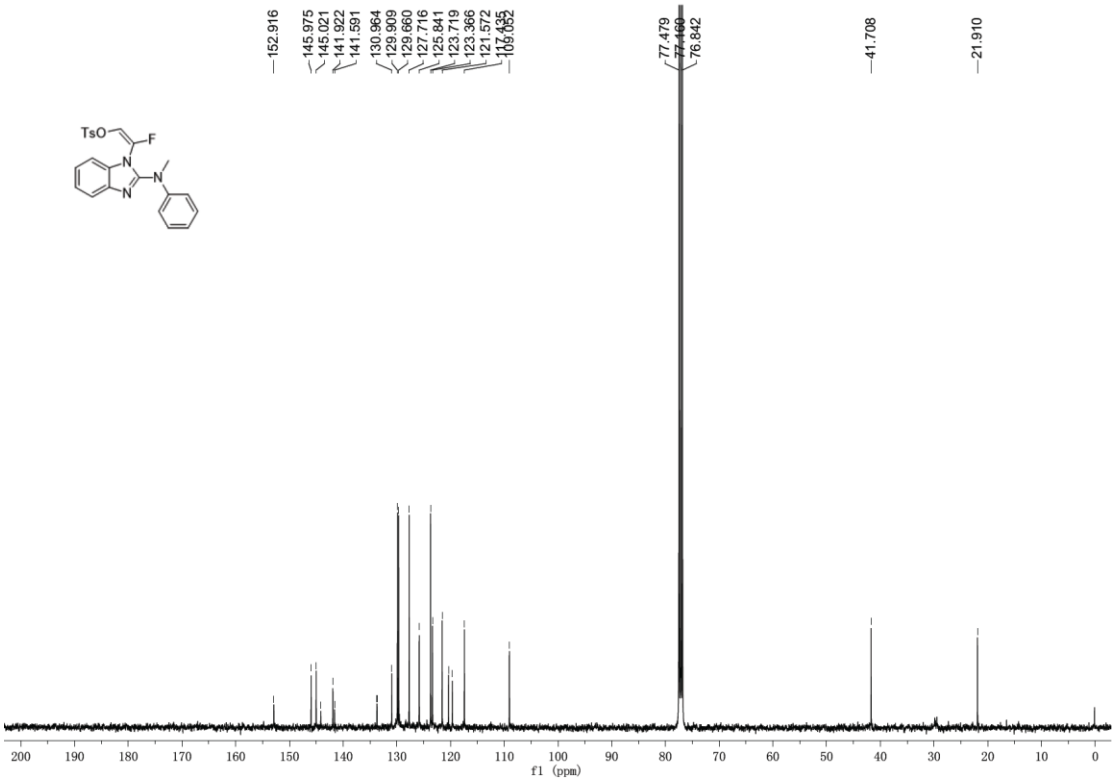
^{19}F-NMR of **4i** ($CDCl_3$, 376 MHz)



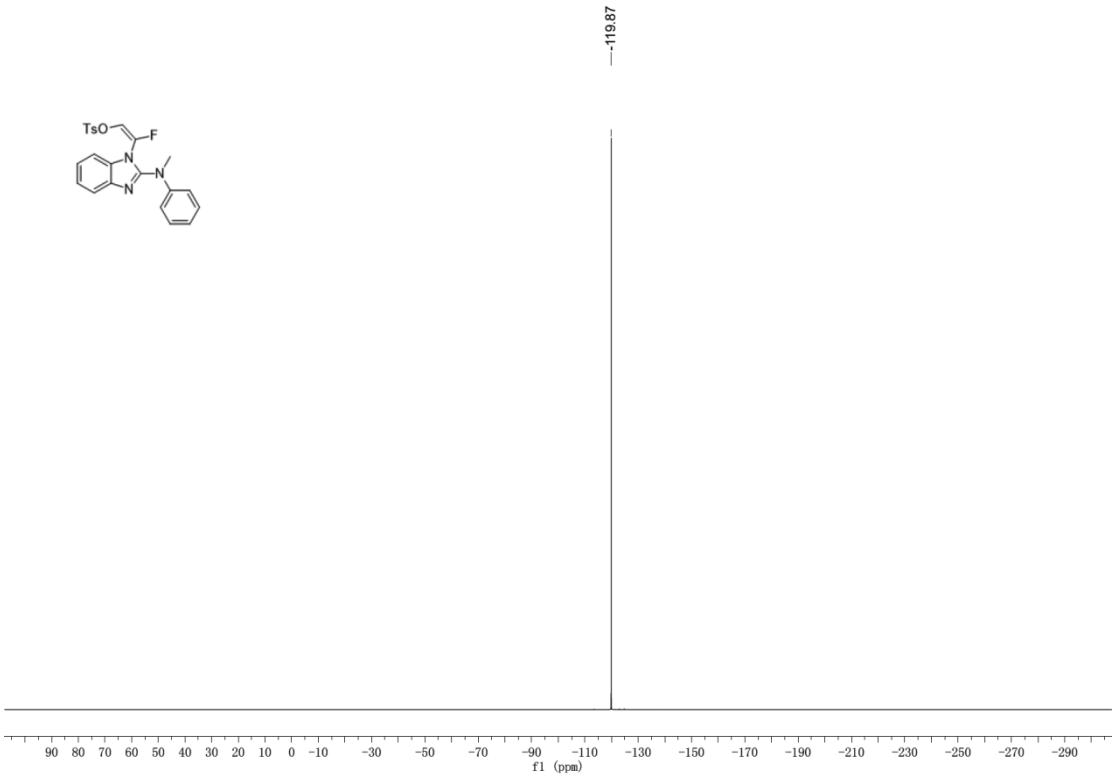
^{1}H-NMR of **7** (CD_3OD, 400 MHz)



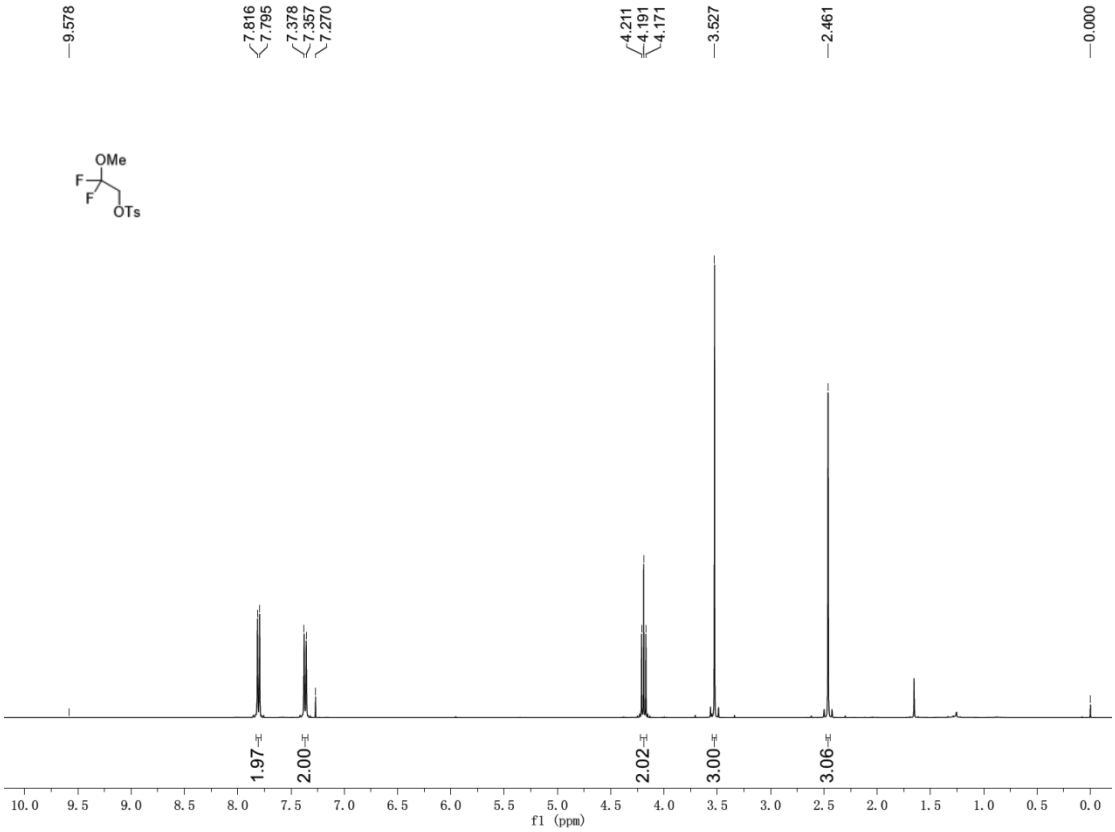
^{13}C{^{1}H}-NMR of **7** ($CDCl_3$, 100 MHz)



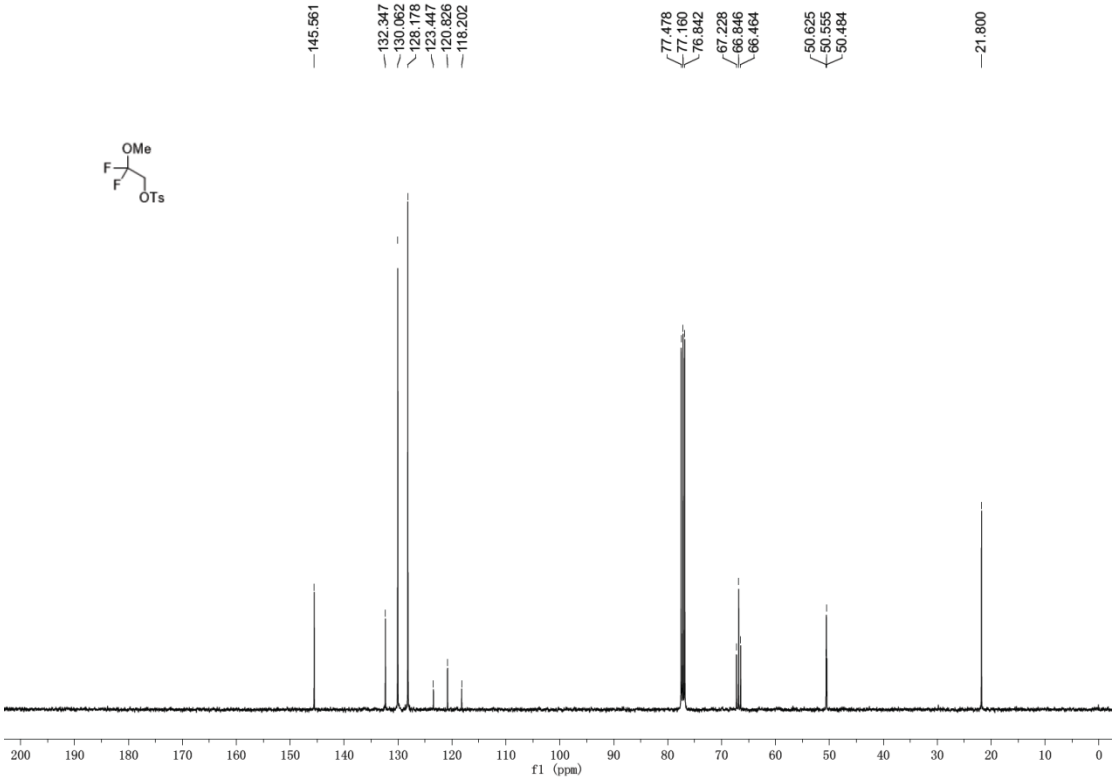
^{19}F-NMR of **7** ($CDCl_3$, 376 MHz)



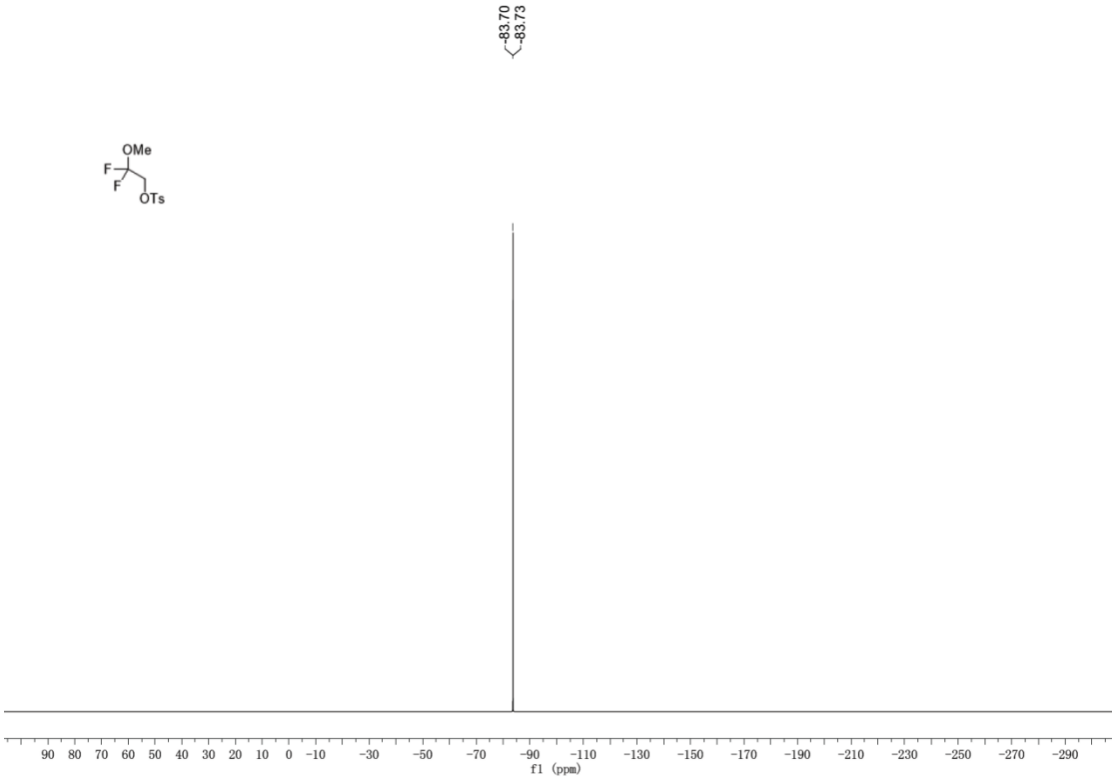
^{1}H-NMR of **8** (CD_3OD, 400 MHz)



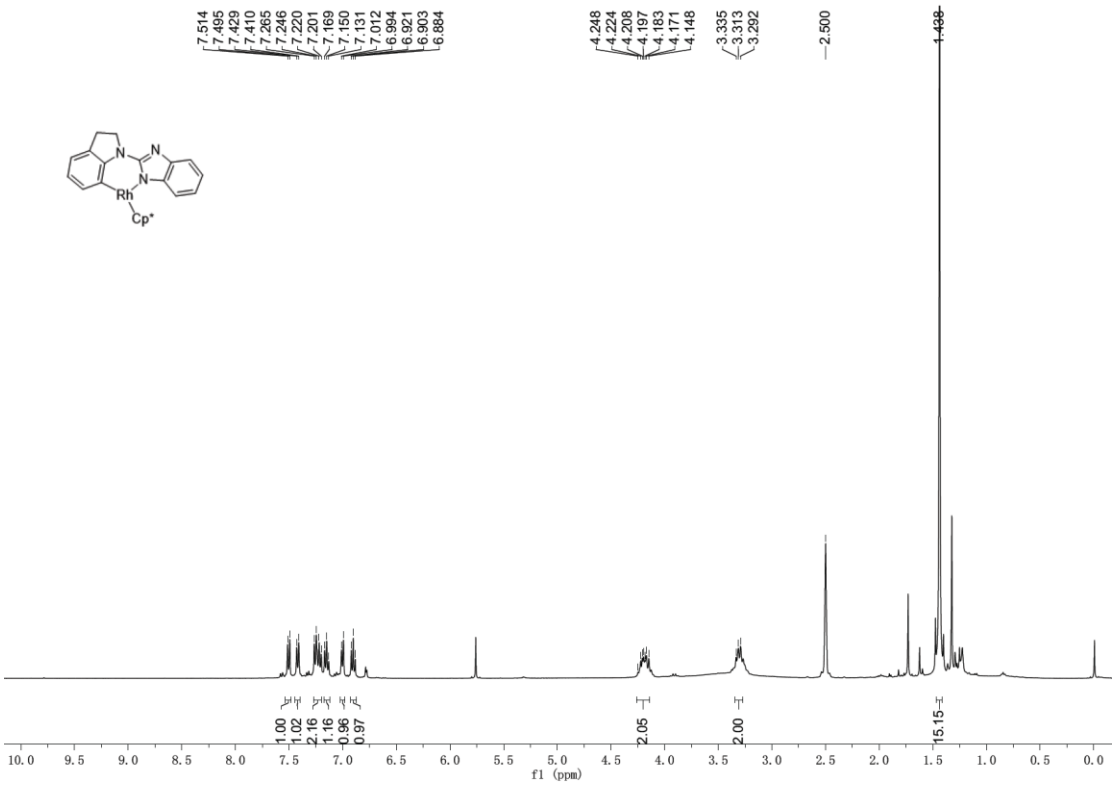
^{13}C{^{1}H}-NMR of **8** ($CDCl_3$, 100 MHz)



^{19}F-NMR of **8** ($CDCl_3$, 376 MHz)



^{1}H-NMR of **rhodacycle A'** (DMSO-d_6, 400 MHz)



^{13}C{^{1}H}-NMR of **rhodacycle A'** (DMSO-d_6, 100 MHz)