

Supporting Information

Synthesis and Spectroscopic Properties of Fluorinated Coumarin Lysine Derivatives

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Umeå University, Department of Chemistry, 90187 Umeå, Sweden

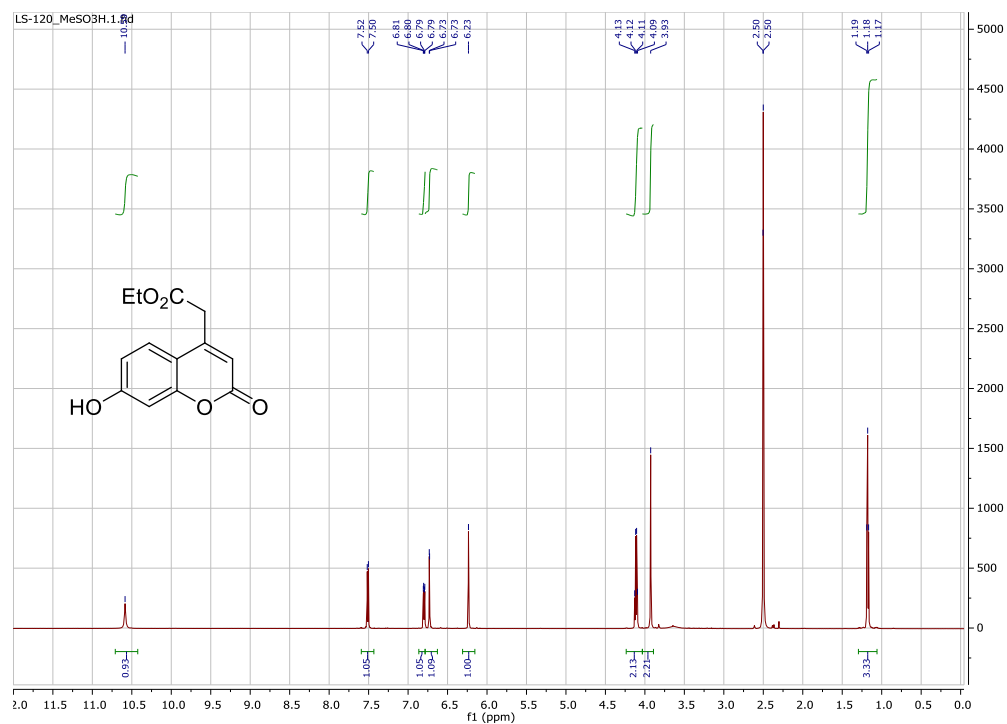
E-mail: Christian.Hedberg@chem.umu.se

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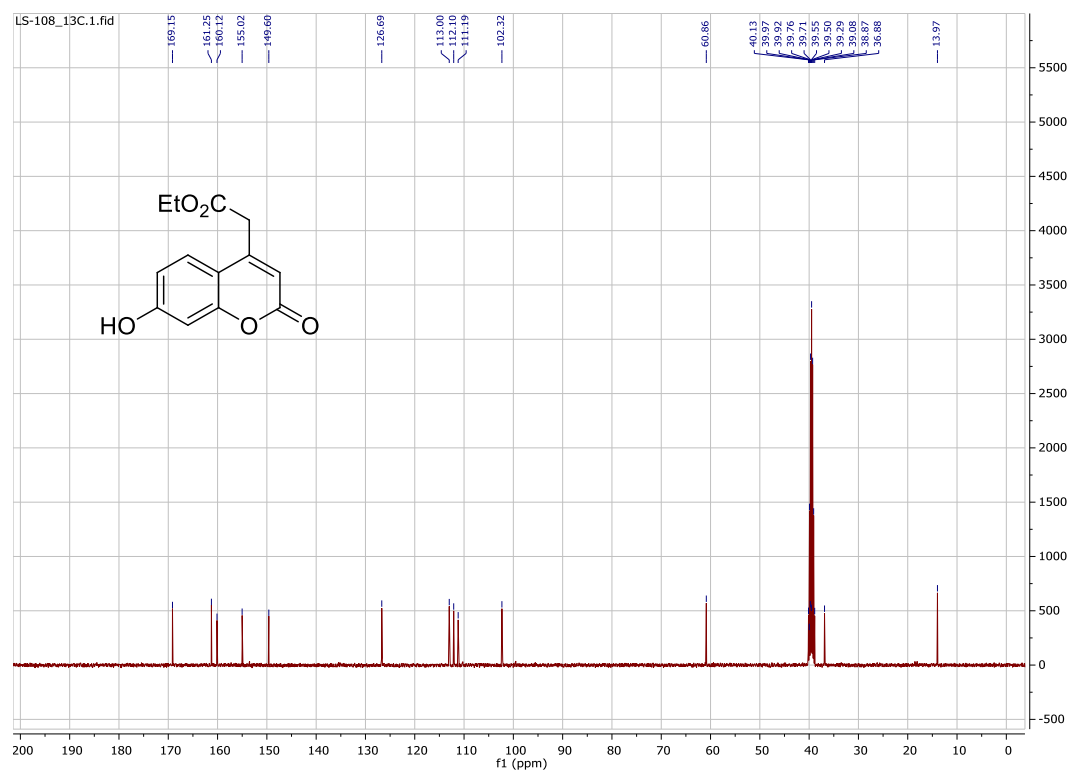
1. Copies of ^1H , ^{13}C and ^{19}F NMR spectra	S2
2. Spectroscopic Studies	S41

1. Copies of ^1H , ^{13}C and ^{19}F NMR spectra

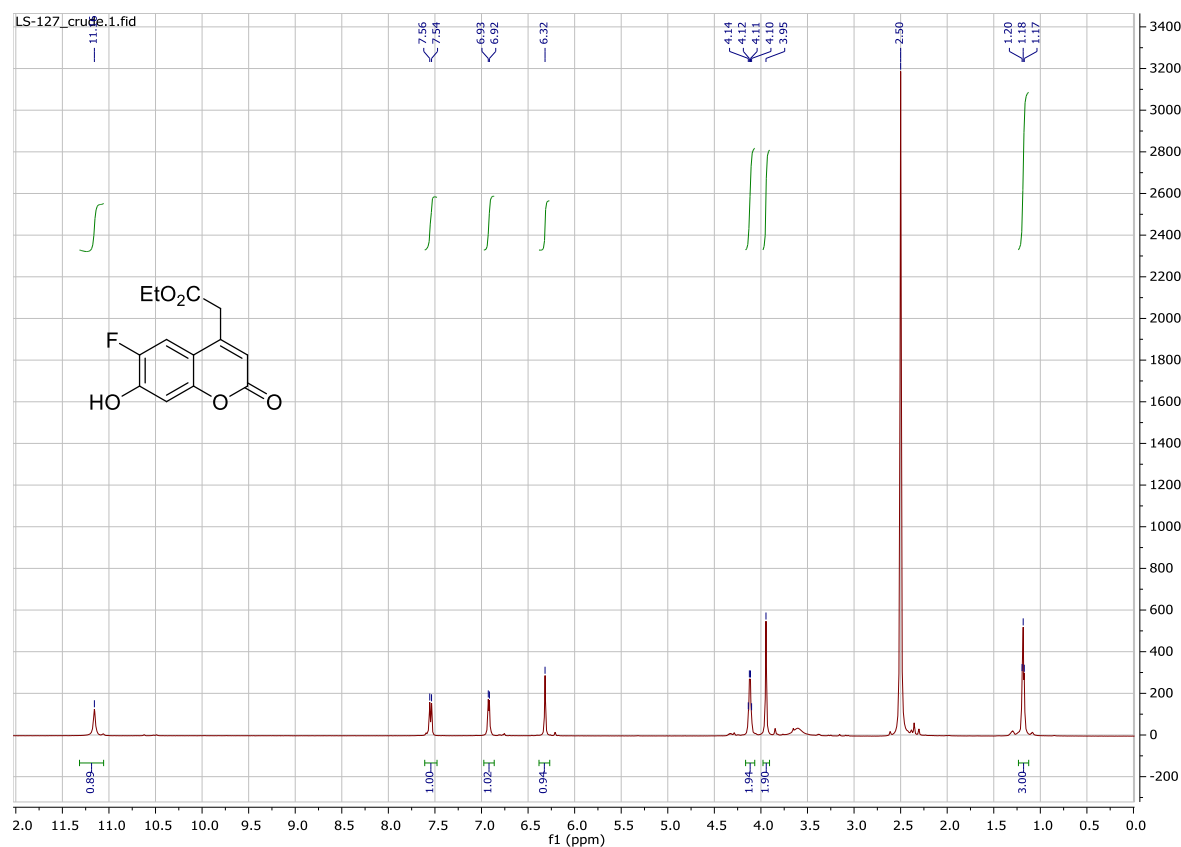
^1H NMR (600 MHz, $\text{DMSO}-d_6$) of 8a



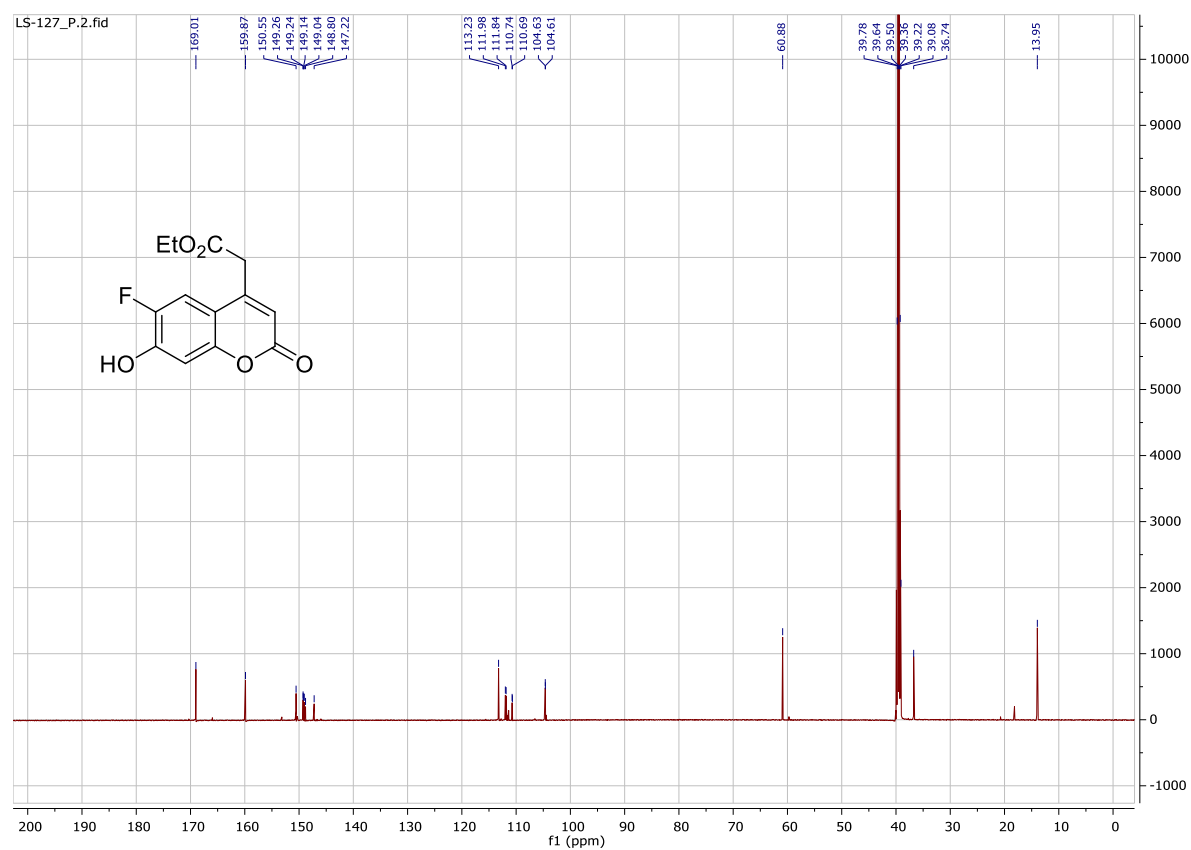
^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) of 8a



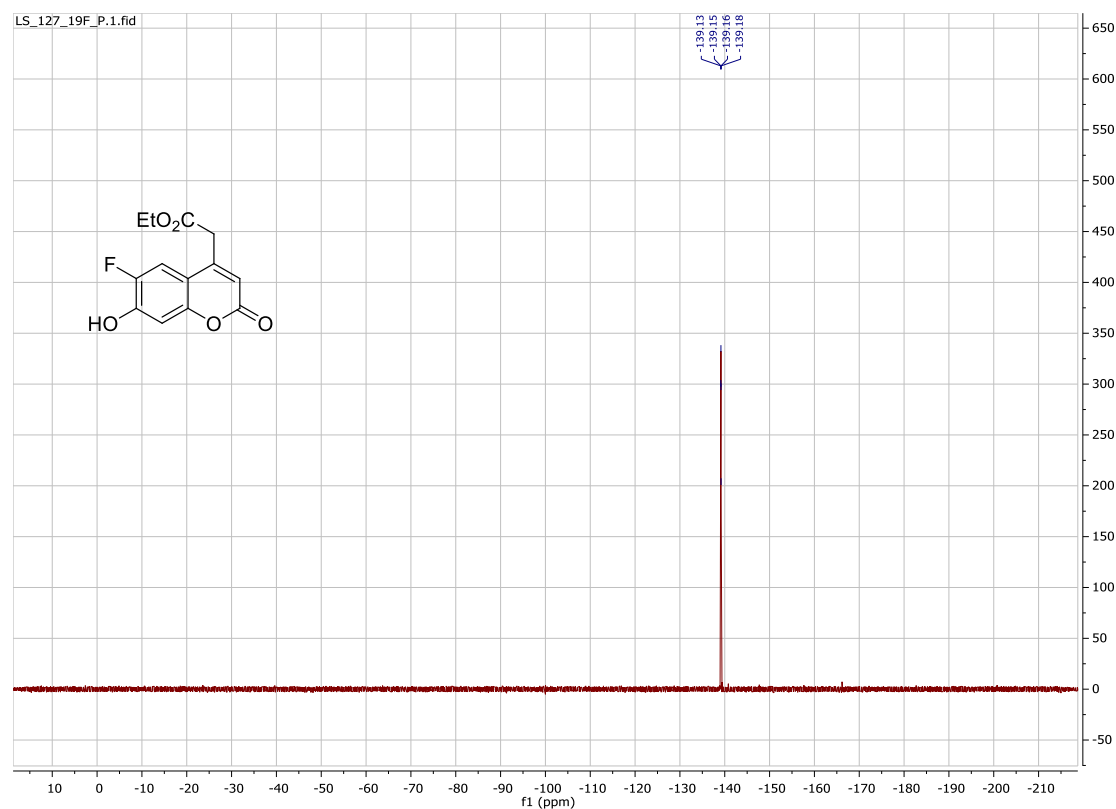
¹H NMR (600 MHz, DMSO-*d*₆) of 8b



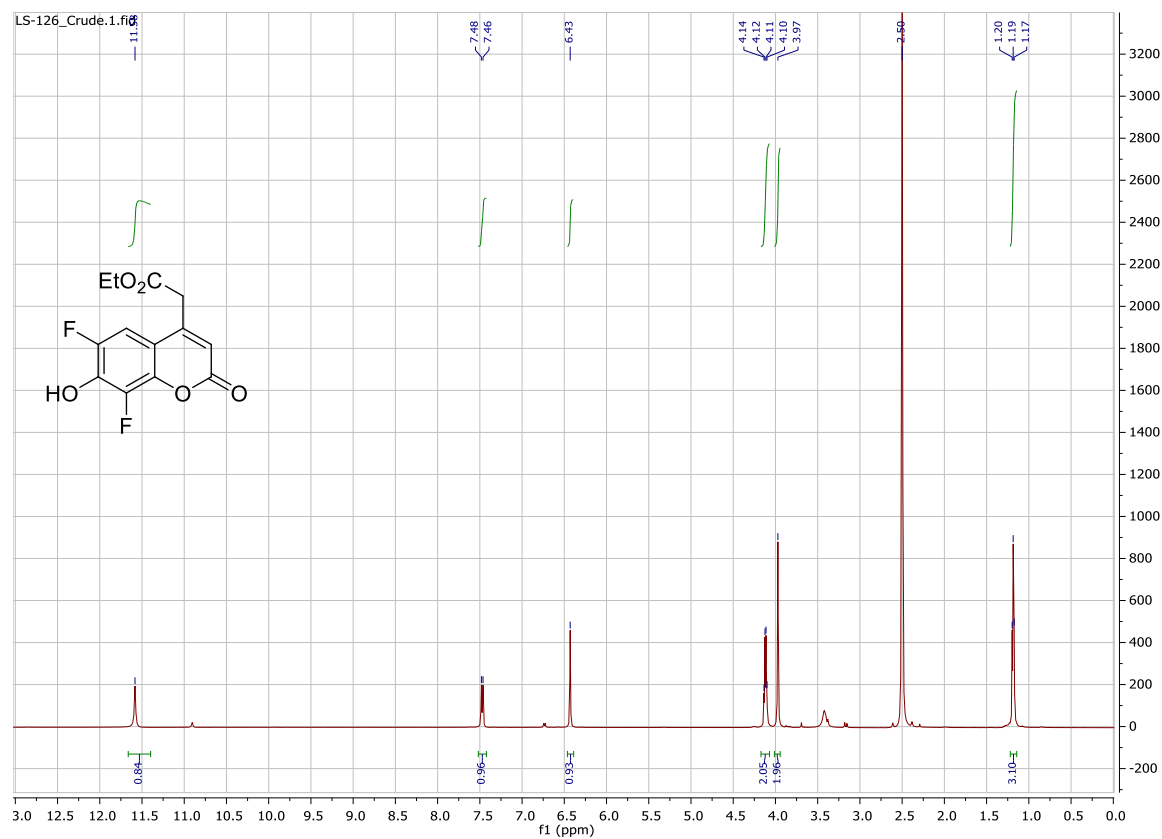
¹³C NMR (150 MHz, DMSO-*d*₆) of 8b



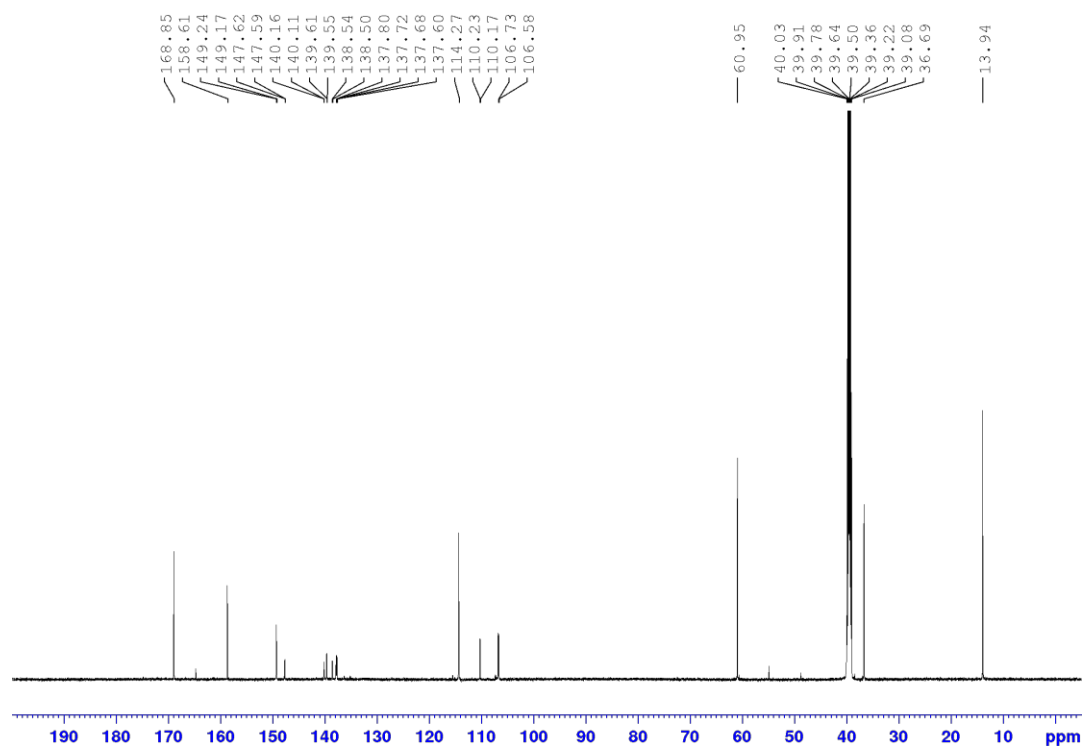
^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) of **8b**



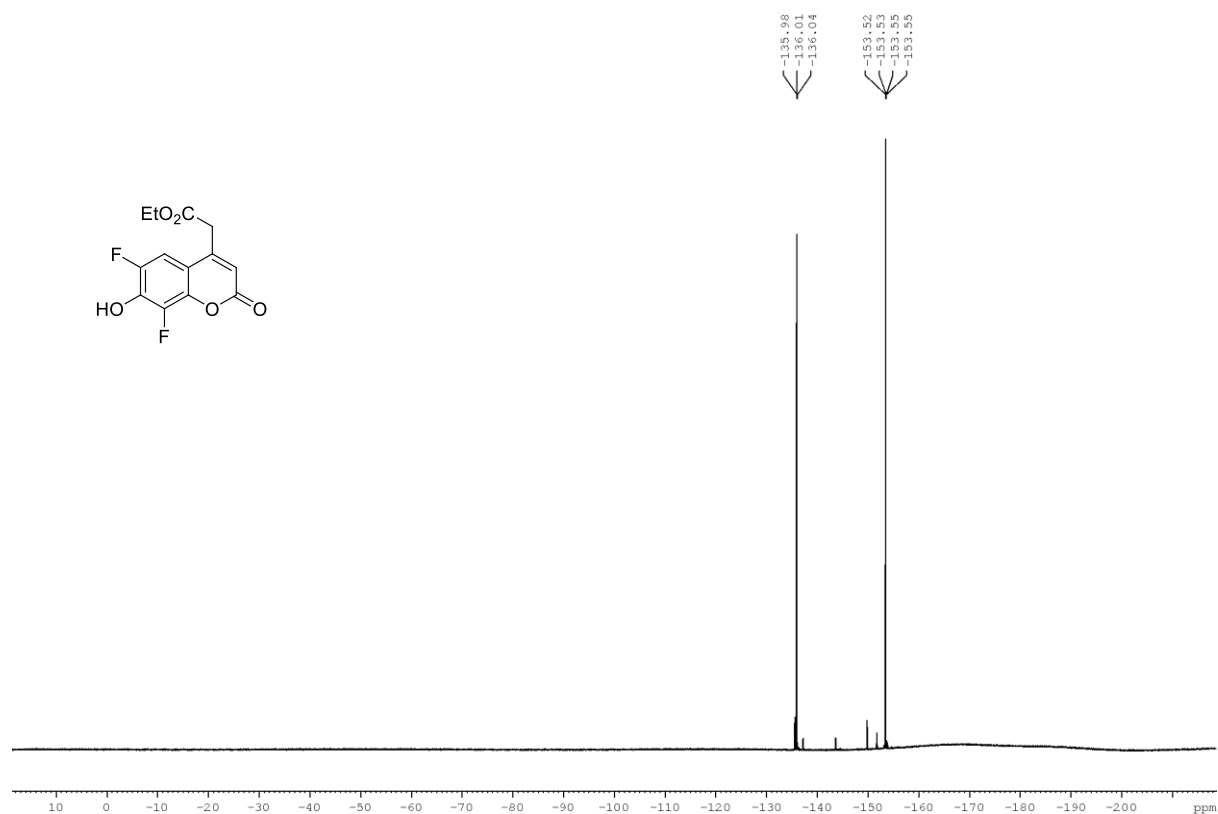
^1H NMR (400 MHz, $\text{DMSO}-d_6$) of **8c**



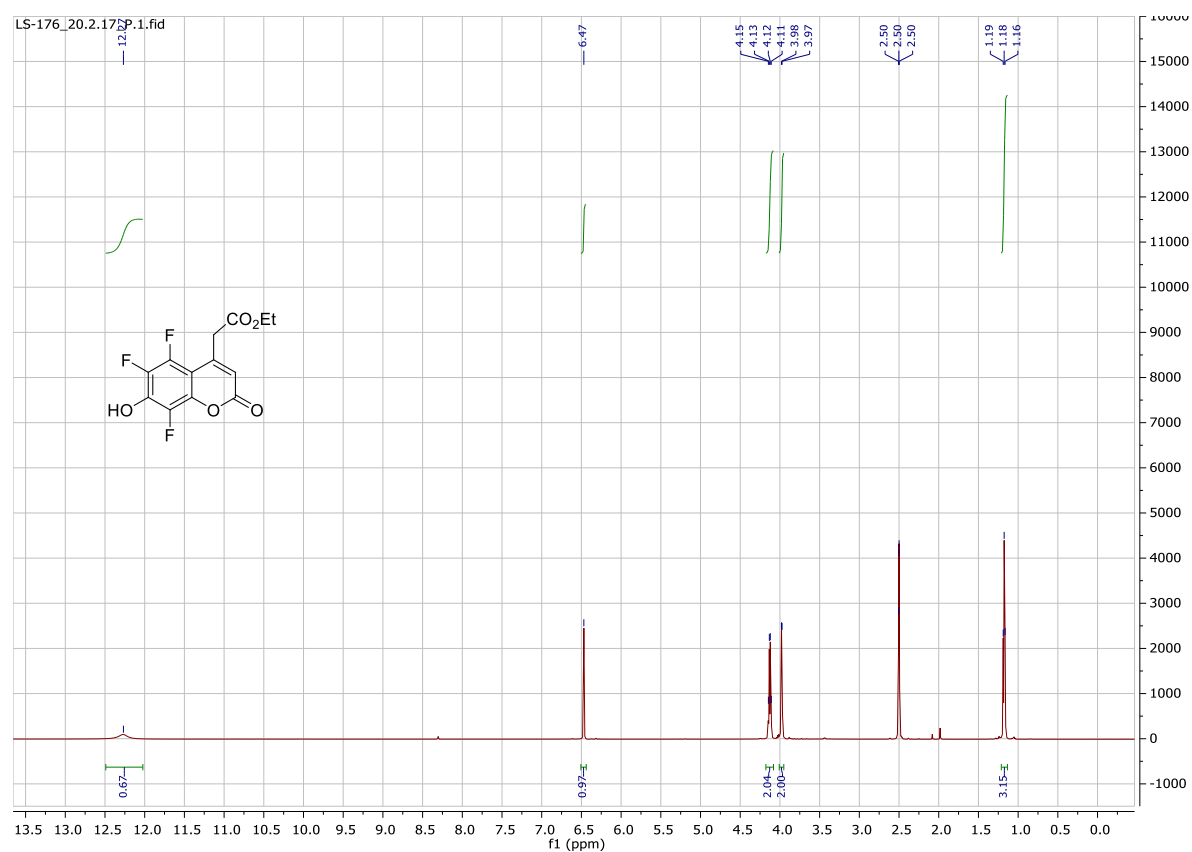
^{13}C NMR (150 MHz, DMSO- d_6) of 8c



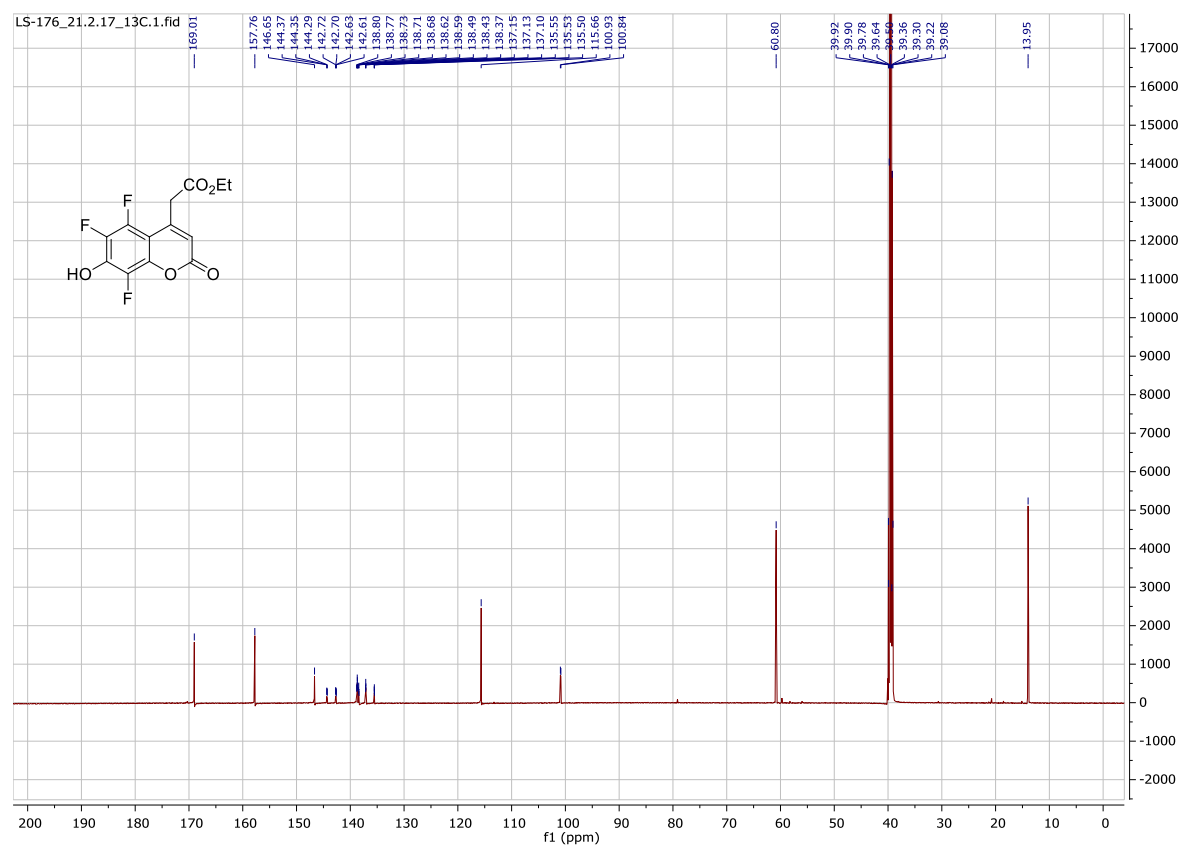
^{19}F NMR (376 MHz, DMSO- d_6) of 8c



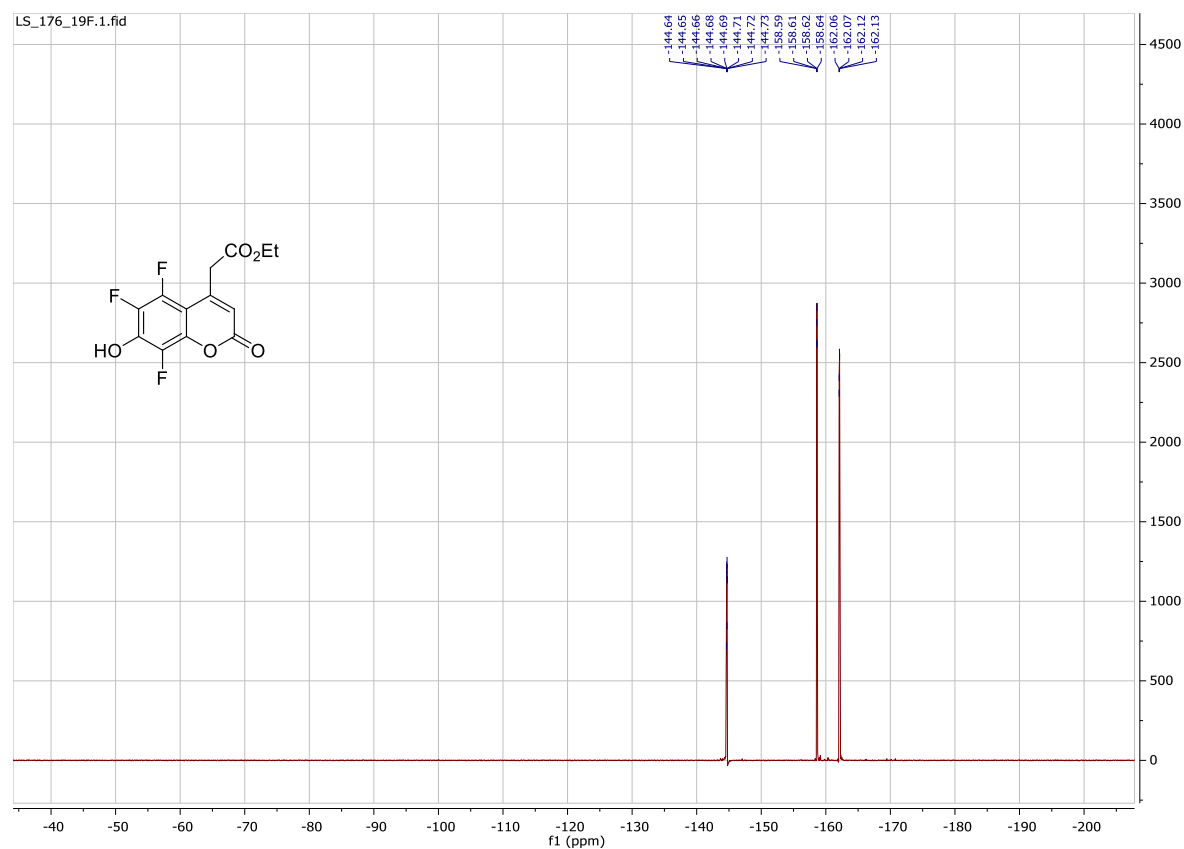
¹H NMR (400 MHz, DMSO-*d*₆) of 8d



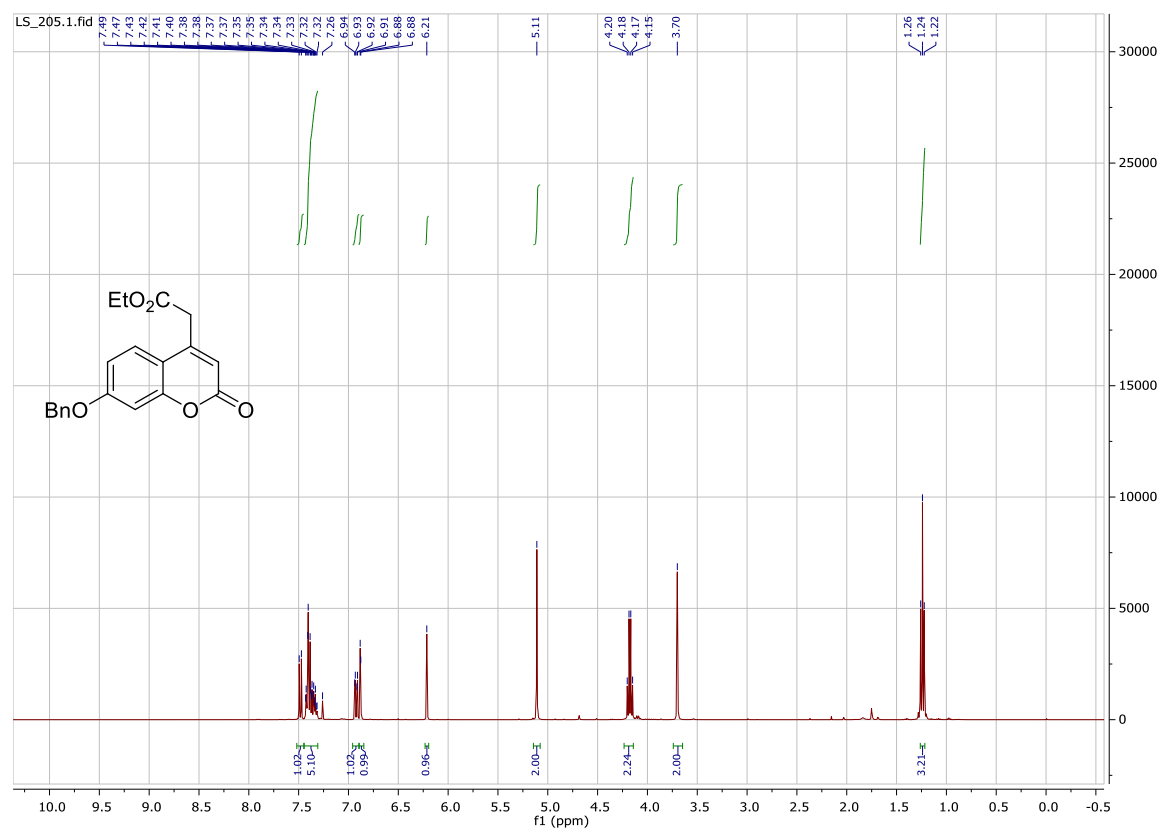
¹³C NMR (151 MHz, DMSO-*d*₆) of 8d



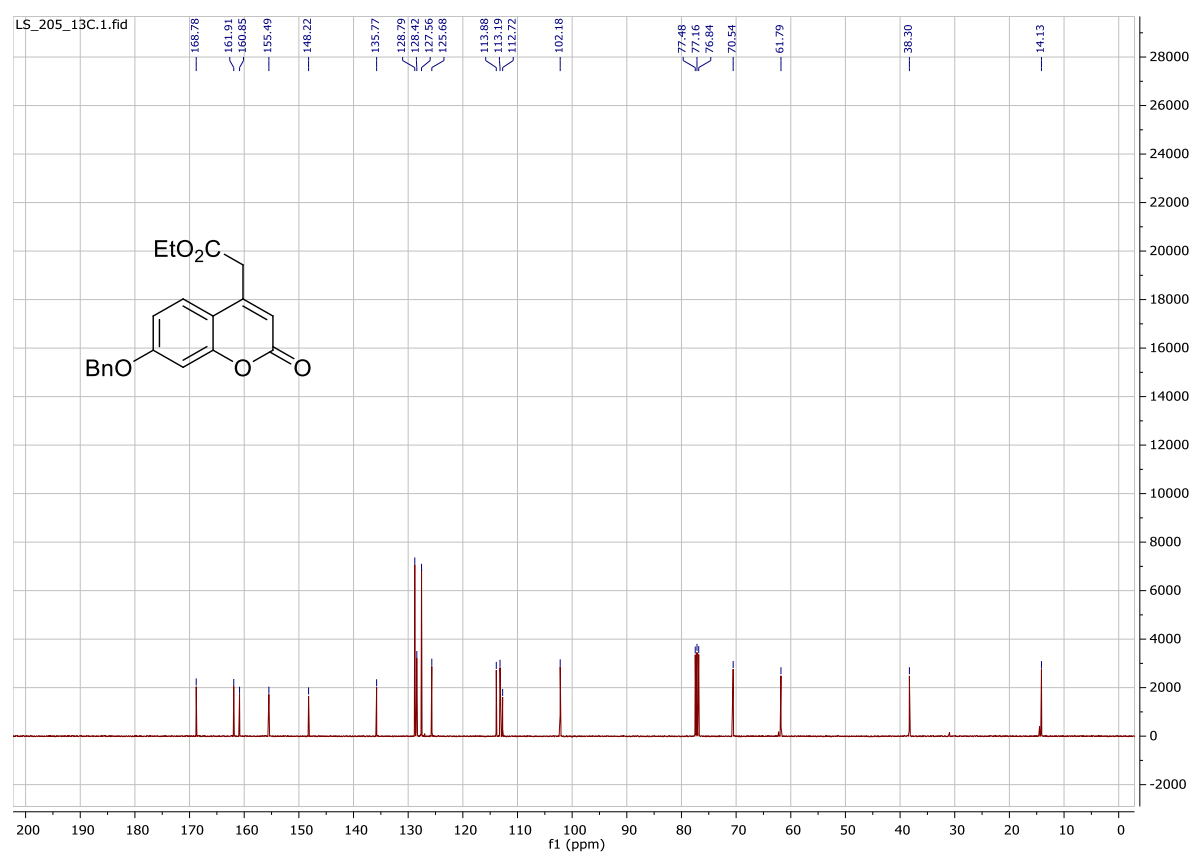
^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) of 8d



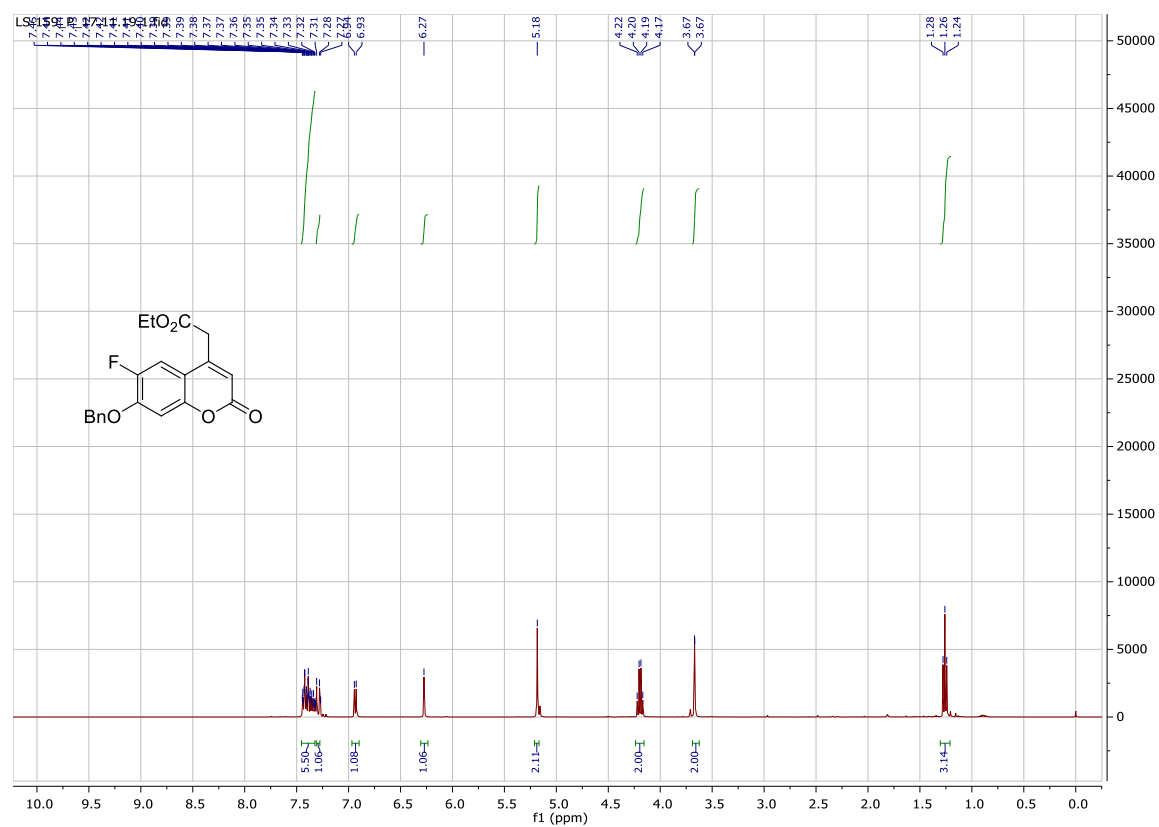
^1H NMR (400 MHz, CDCl_3) of 9a



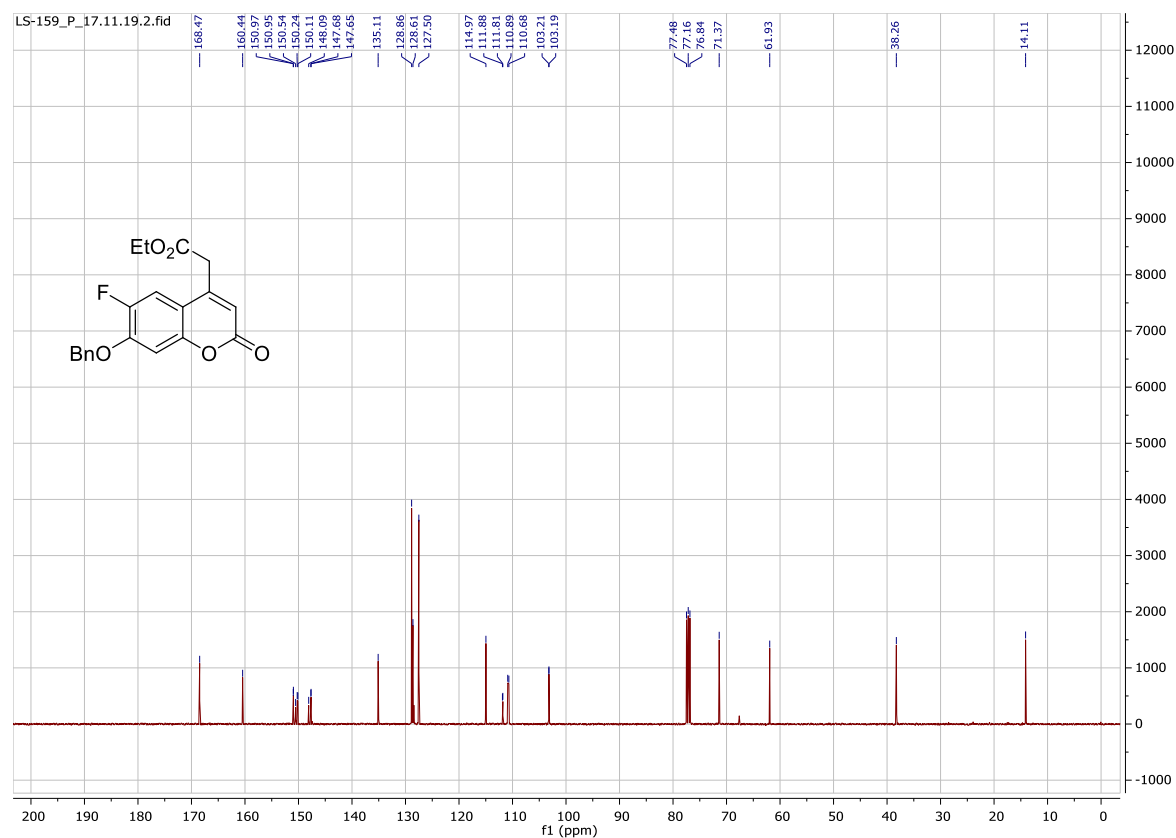
^{13}C NMR (100 MHz, CDCl_3) of 9a



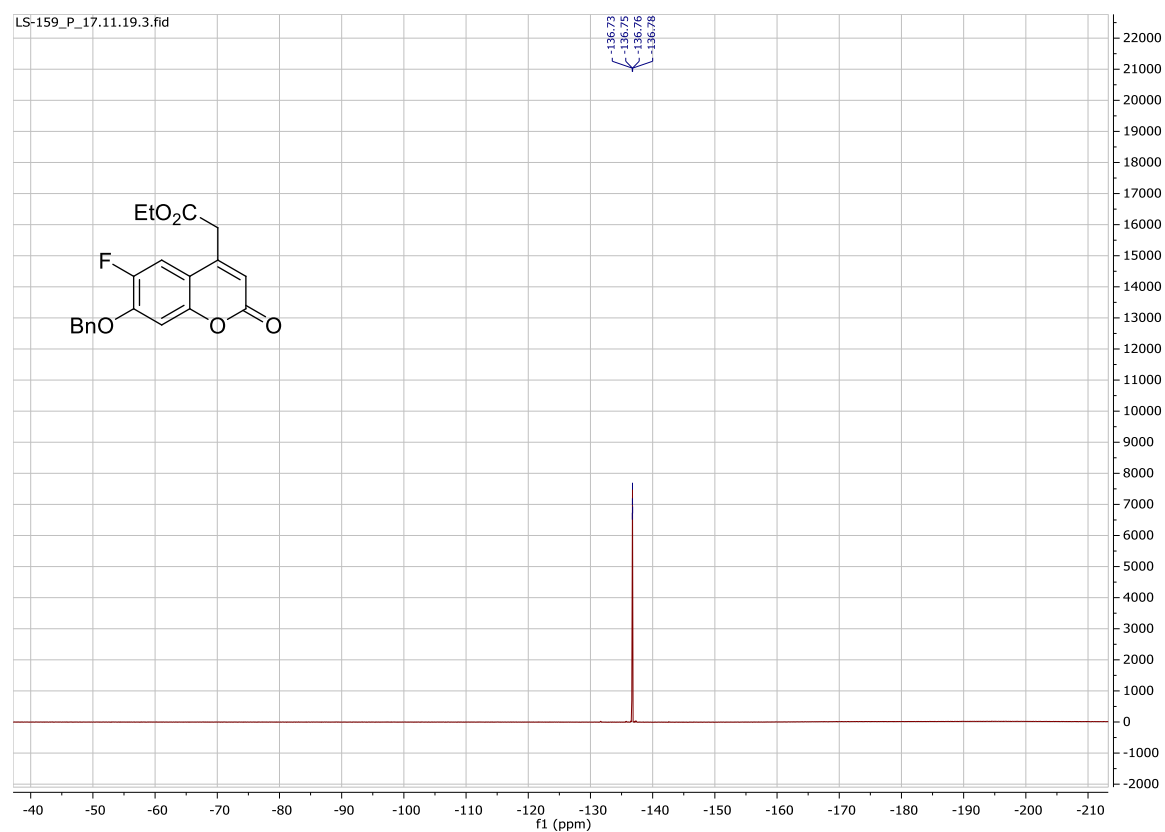
^1H NMR (400 MHz, CDCl_3) of 9b



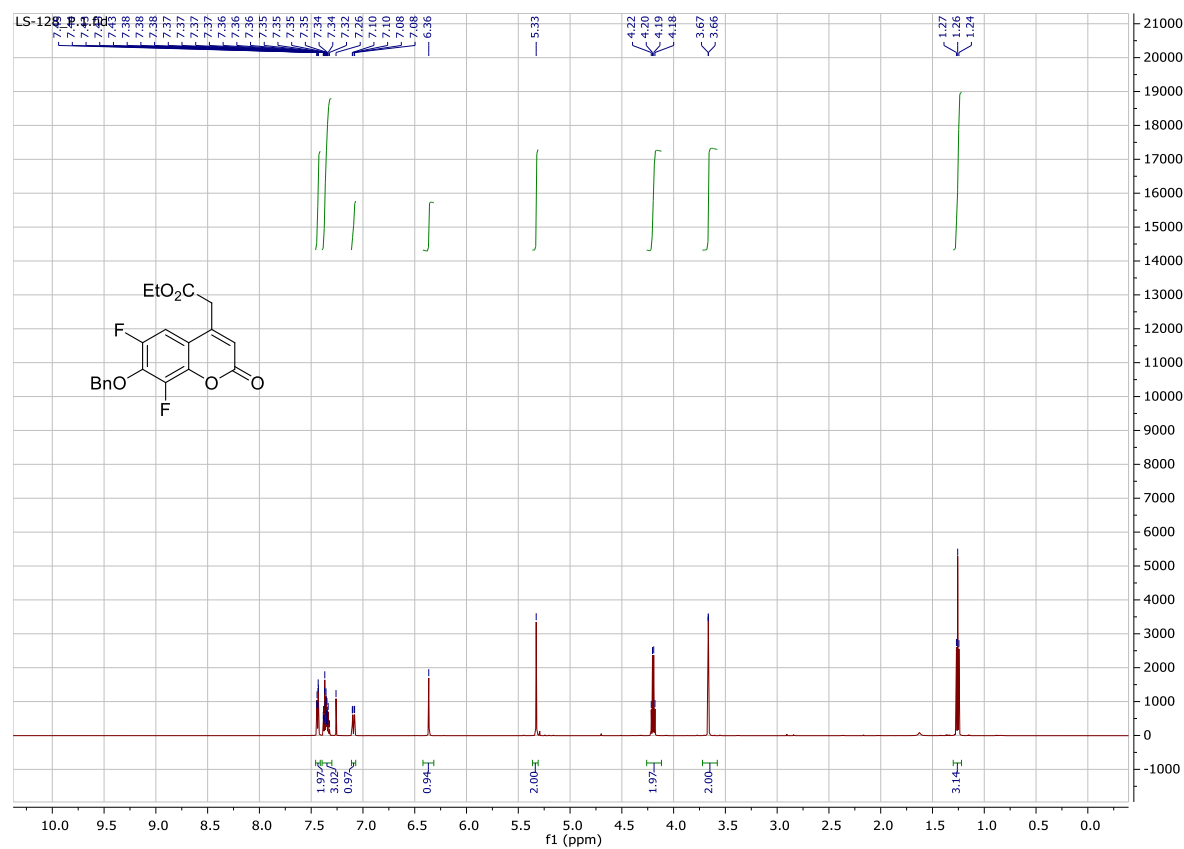
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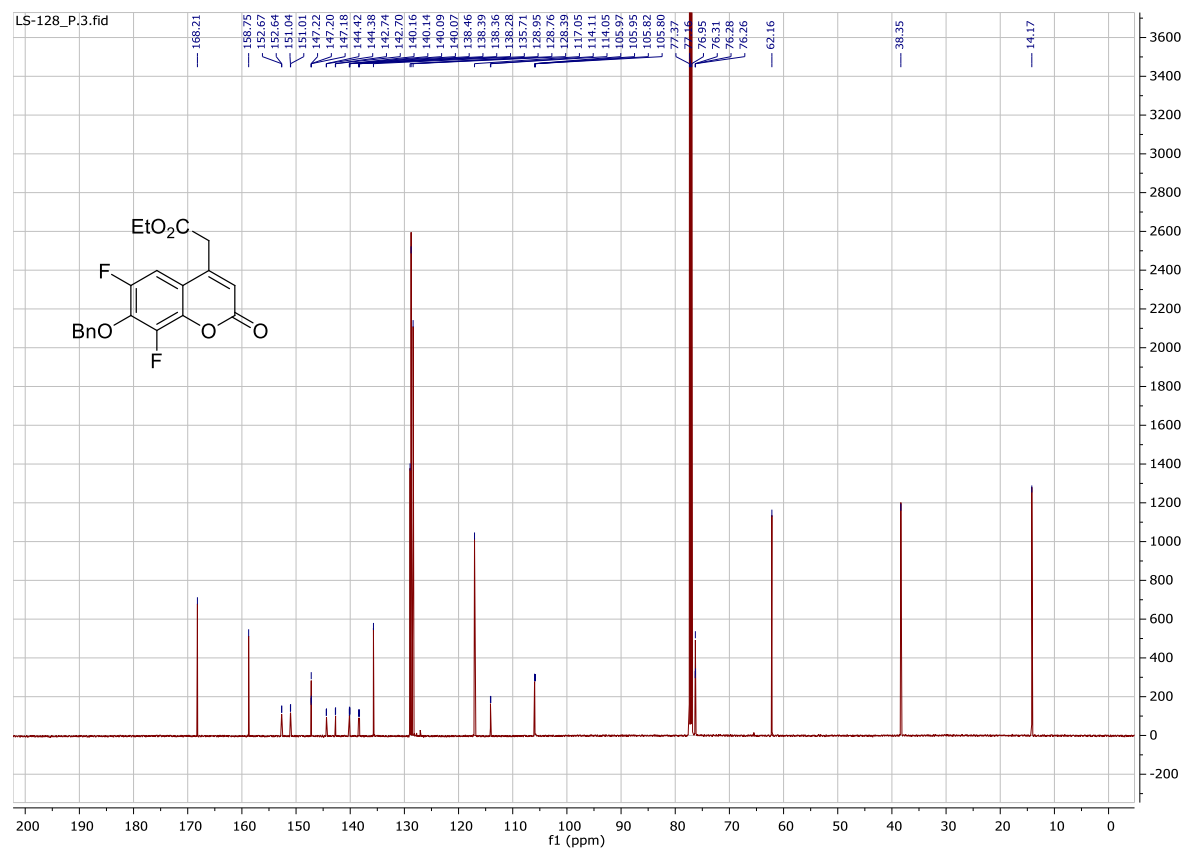
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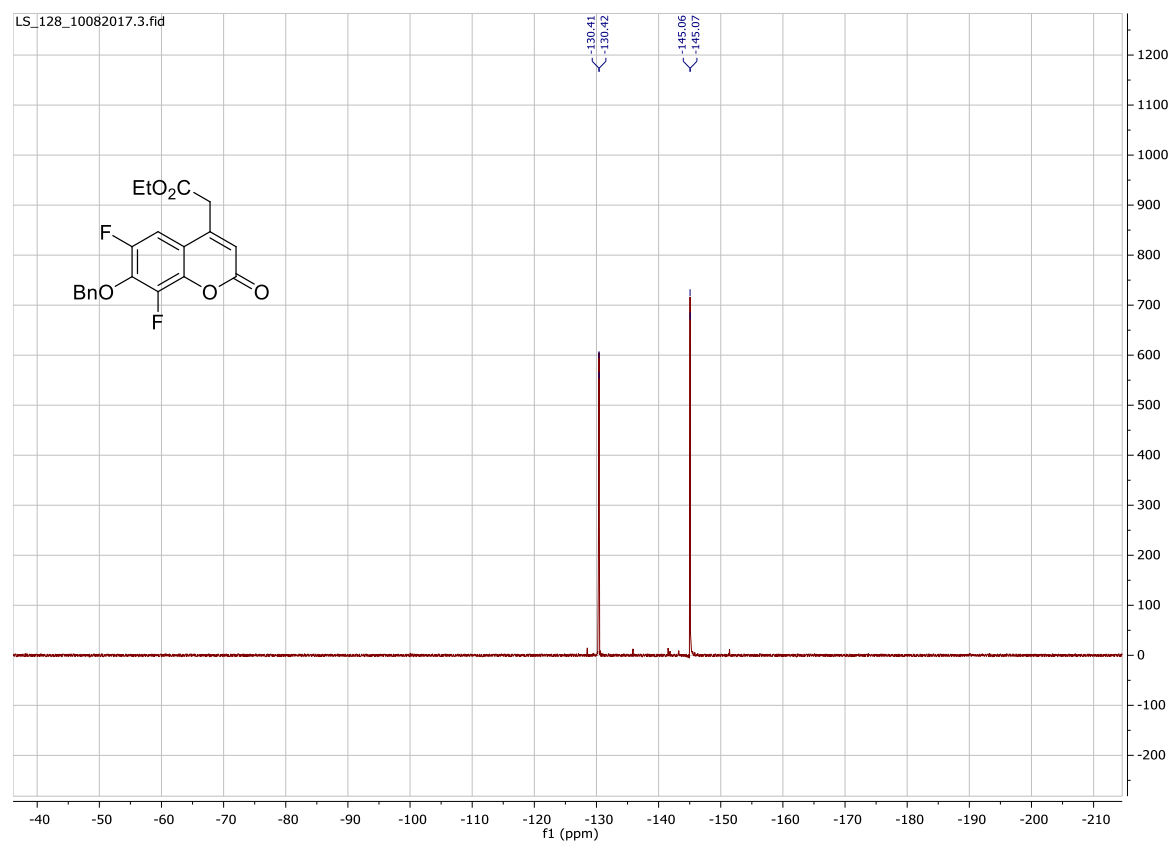
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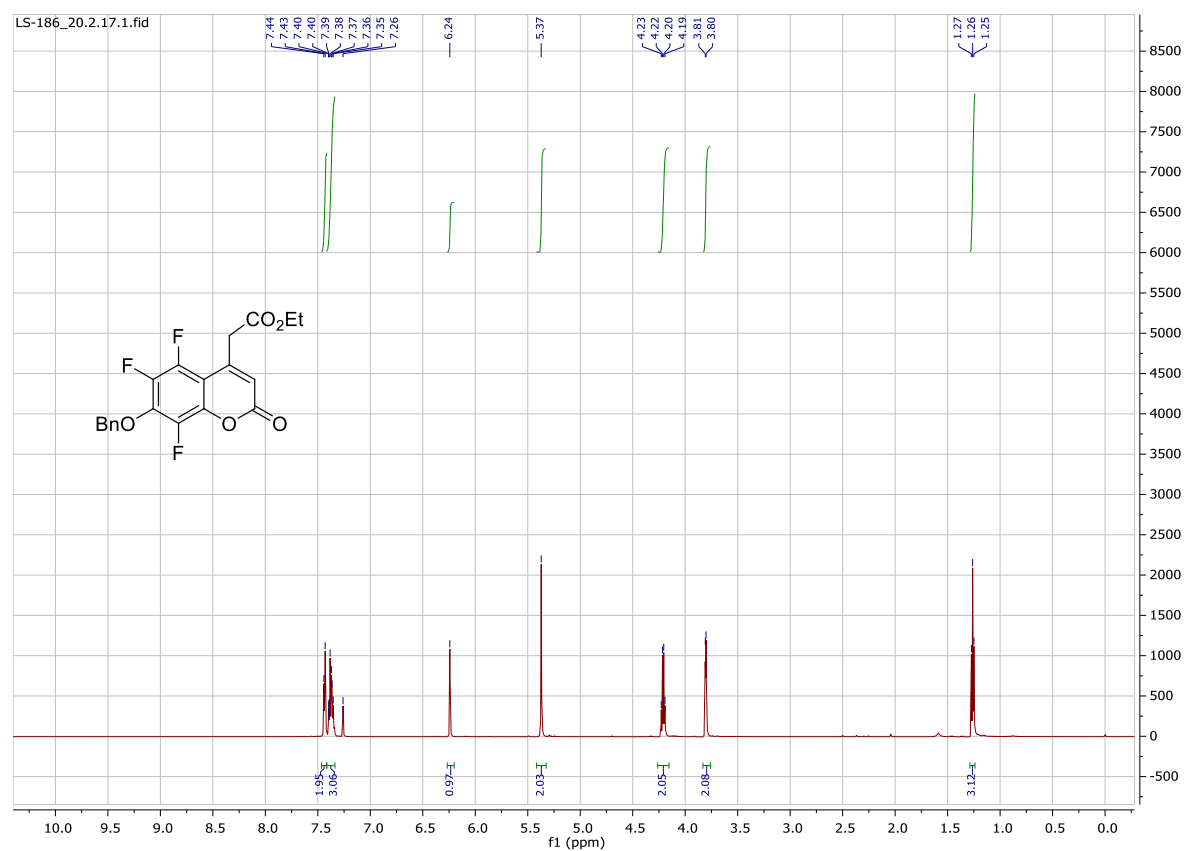
^{13}C NMR (151 MHz, CDCl_3) of 9c



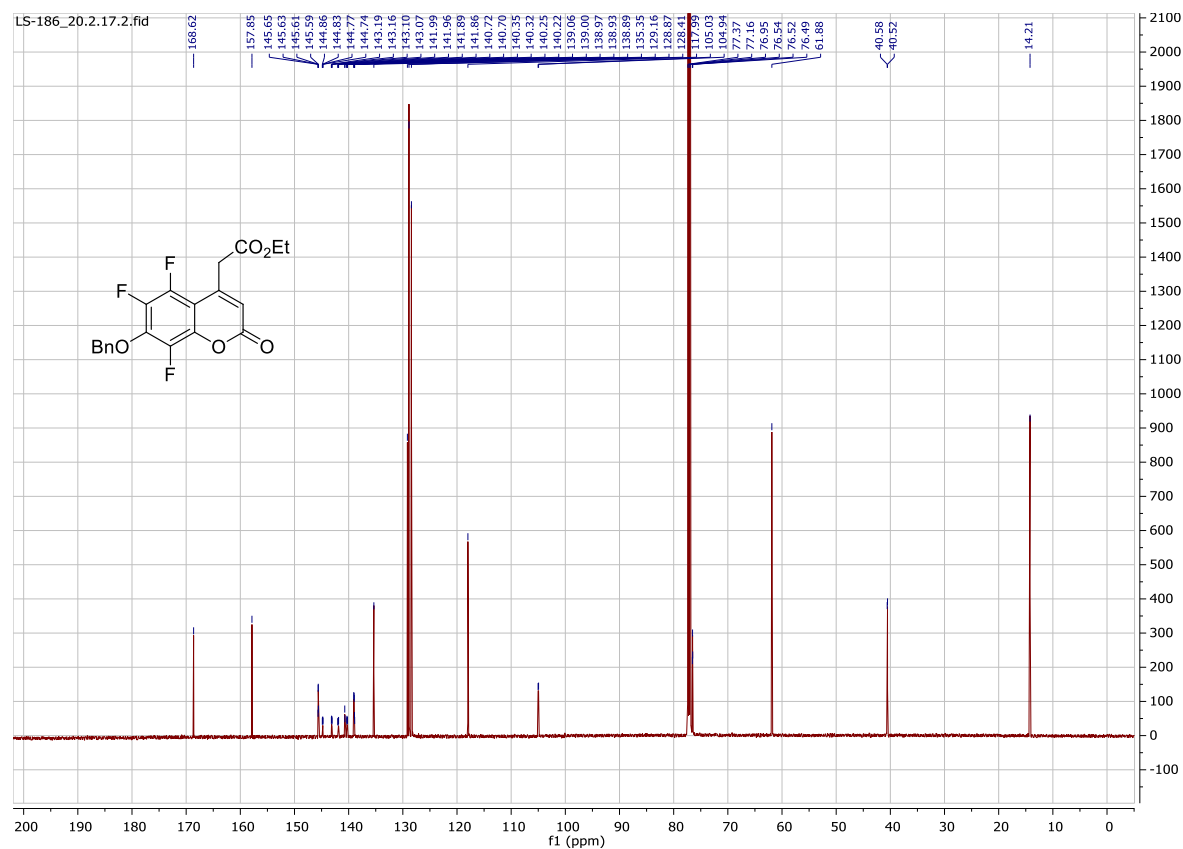
^{19}F NMR (376 MHz, CDCl_3) of 9c



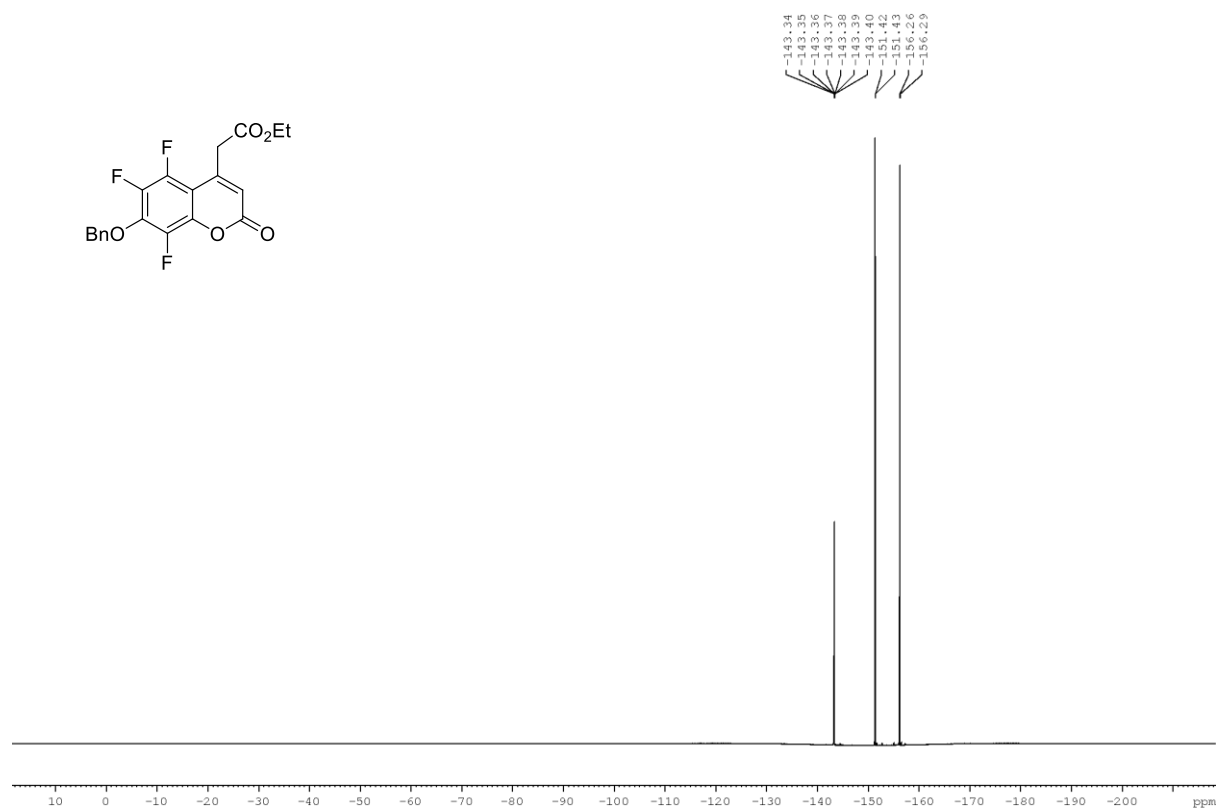
^1H NMR (600 MHz, CDCl_3) of 9d



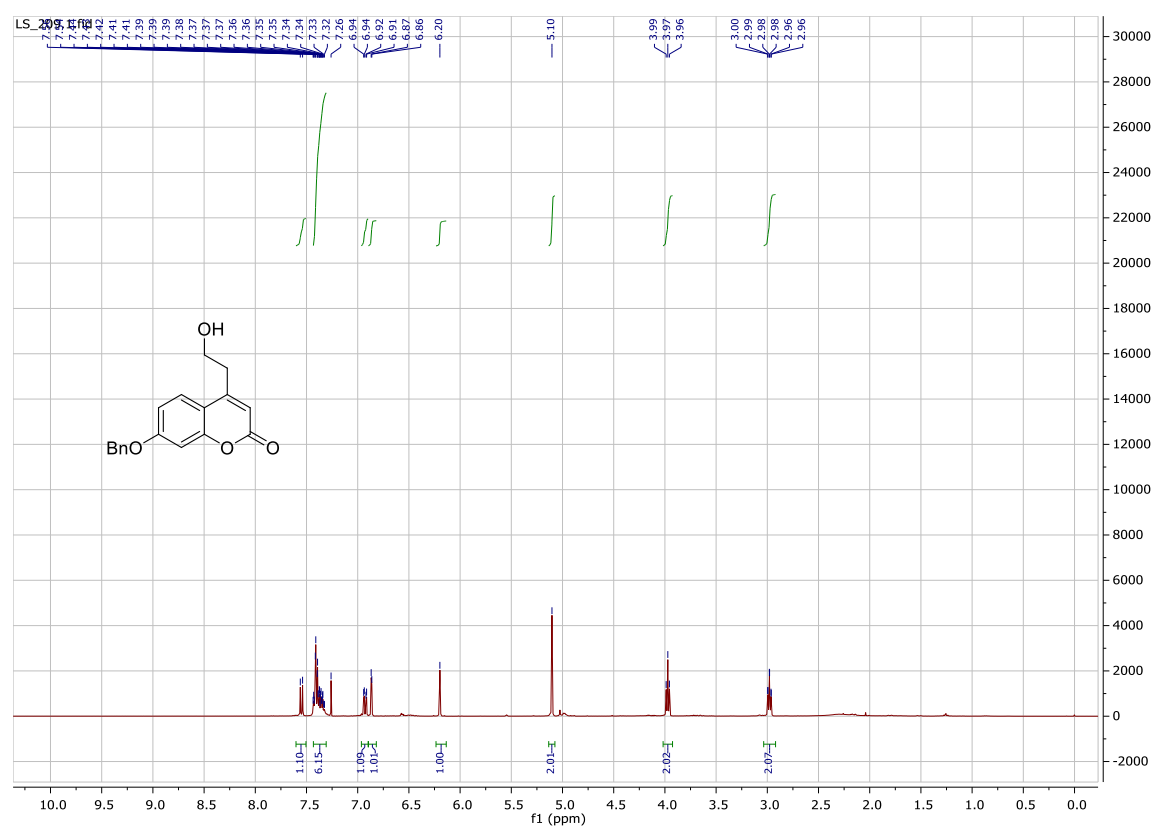
^{13}C NMR (151 MHz, CDCl_3) of 9d



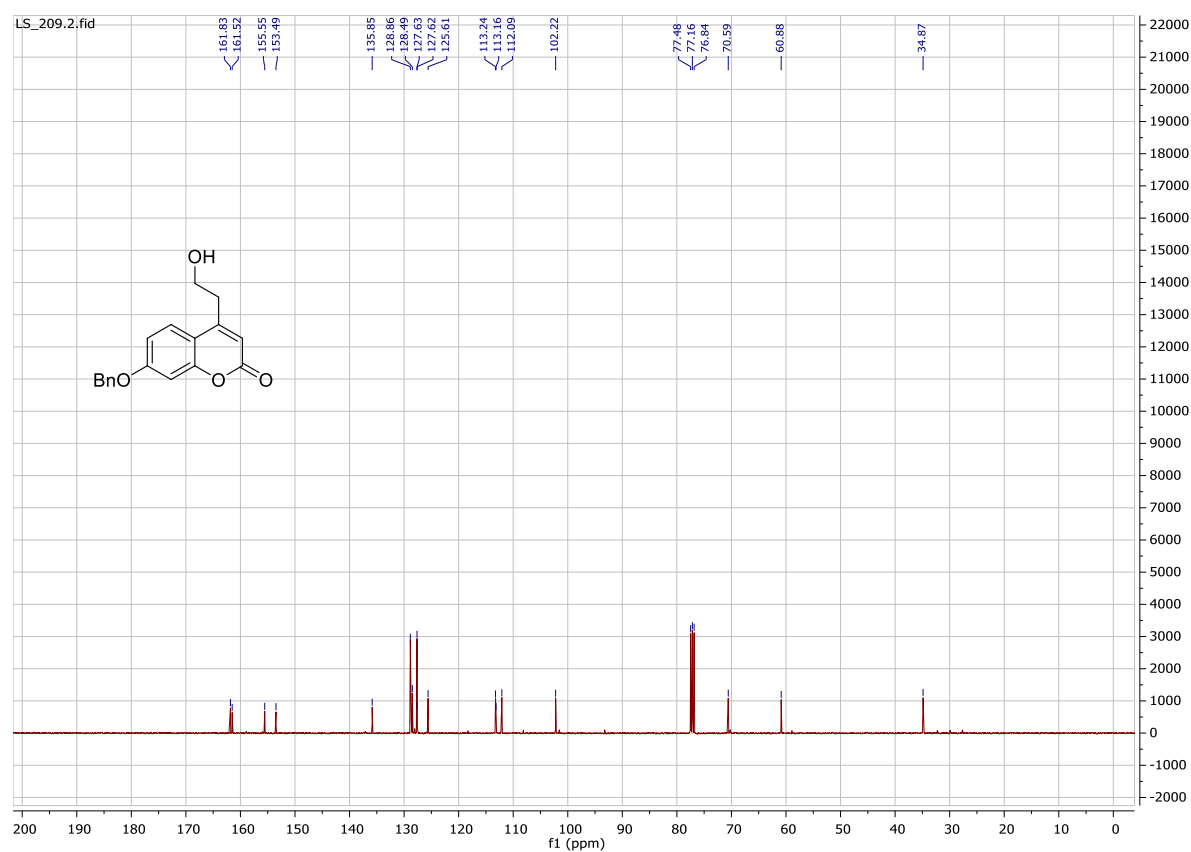
^{19}F NMR (376 MHz, CDCl_3) of 9d



^1H NMR (400 MHz, CDCl_3) of 11a



^{13}C NMR (100 MHz, CDCl_3) of 11a



Chemical structure: O=C1OC(=C(C=C(C=C1)OC(F)=C)COC2=CC=CC=C2)O

¹H NMR spectrum (CDCl₃) showing peaks from 0.00 to 7.56 ppm. Integration values are provided below the baseline: 6.62, 1.04, 1.00, 2.07, 2.07, 2.05, 1.07.

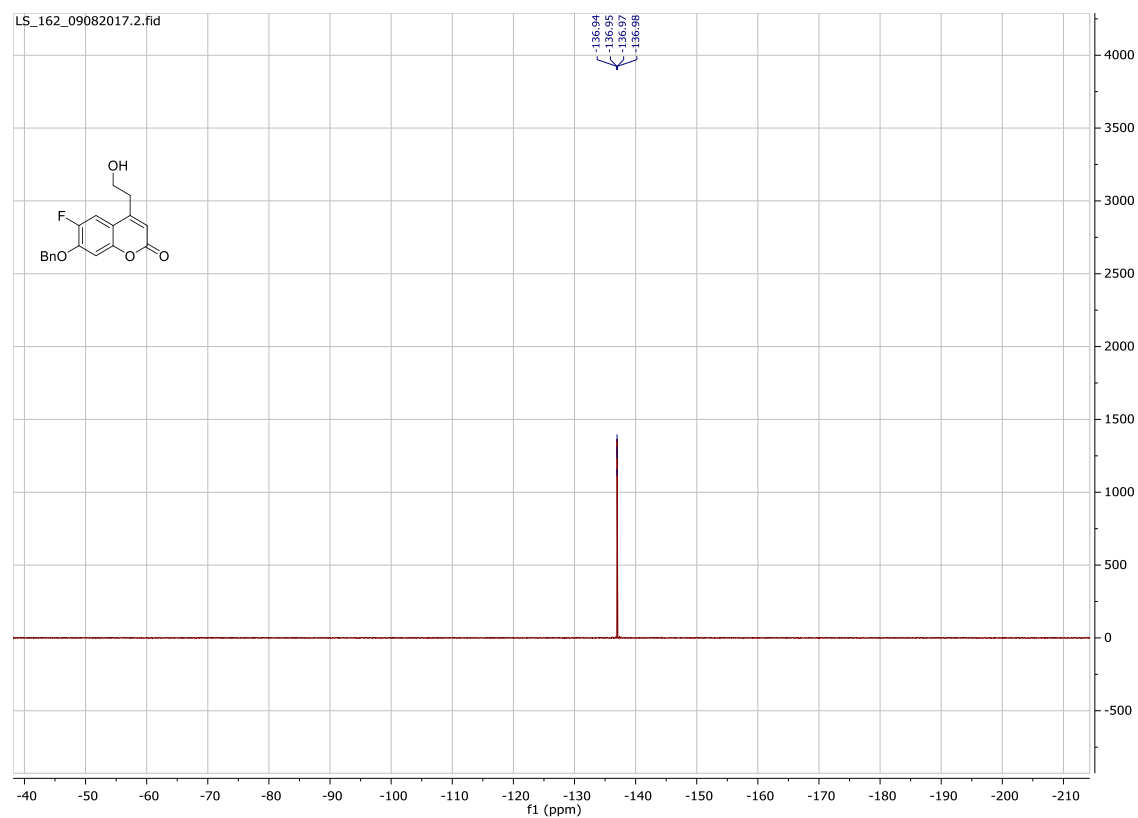
LS-162_7.11.16.2.fid

O=C1C=CC(=C(C=C1)OC(=O)C2=CC=C(C=C2)F)OC3=CC=CC=C3

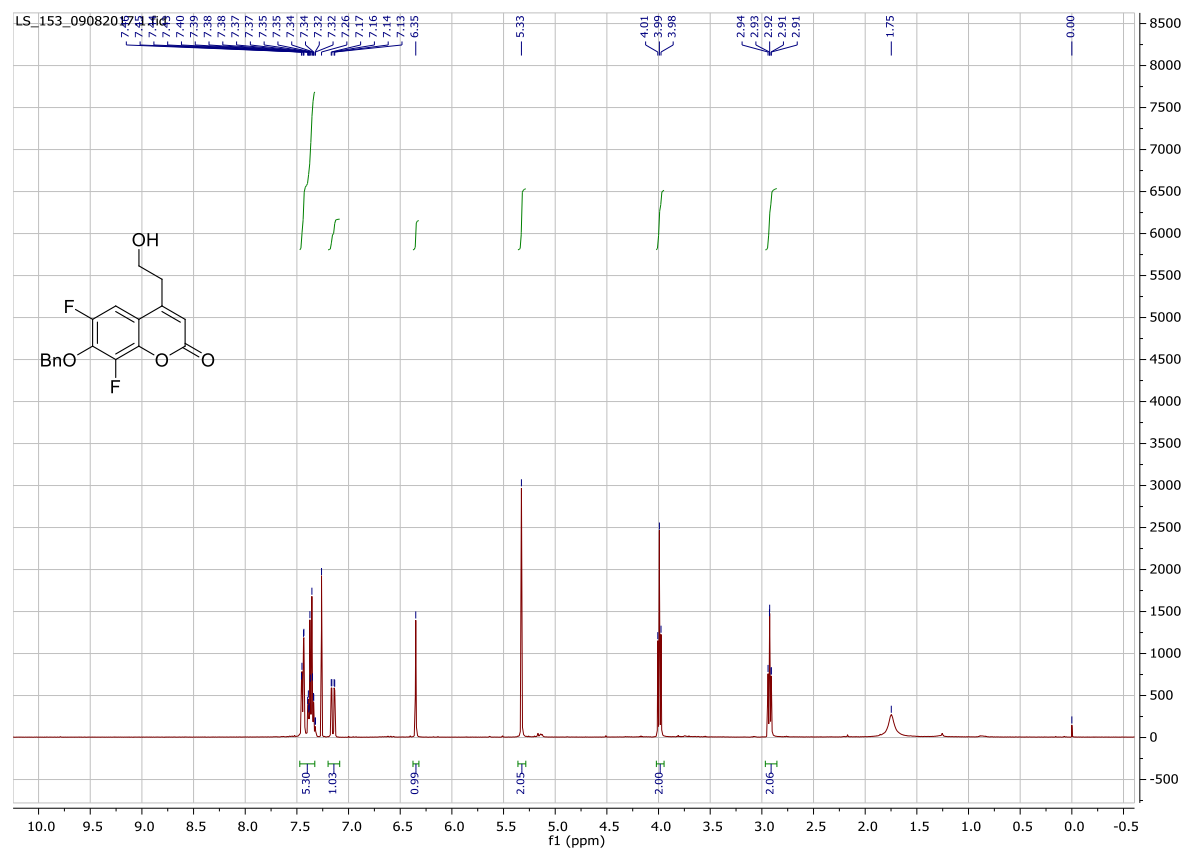
161.08
152.90
152.87
151.01
150.99
150.66
150.15
150.03
148.22
135.20
128.86
128.71
127.60
113.21
112.42
112.35
110.84
107.22
103.31
103.31
77.48
77.16
76.84
71.47
60.72
34.87

f1 (ppm)

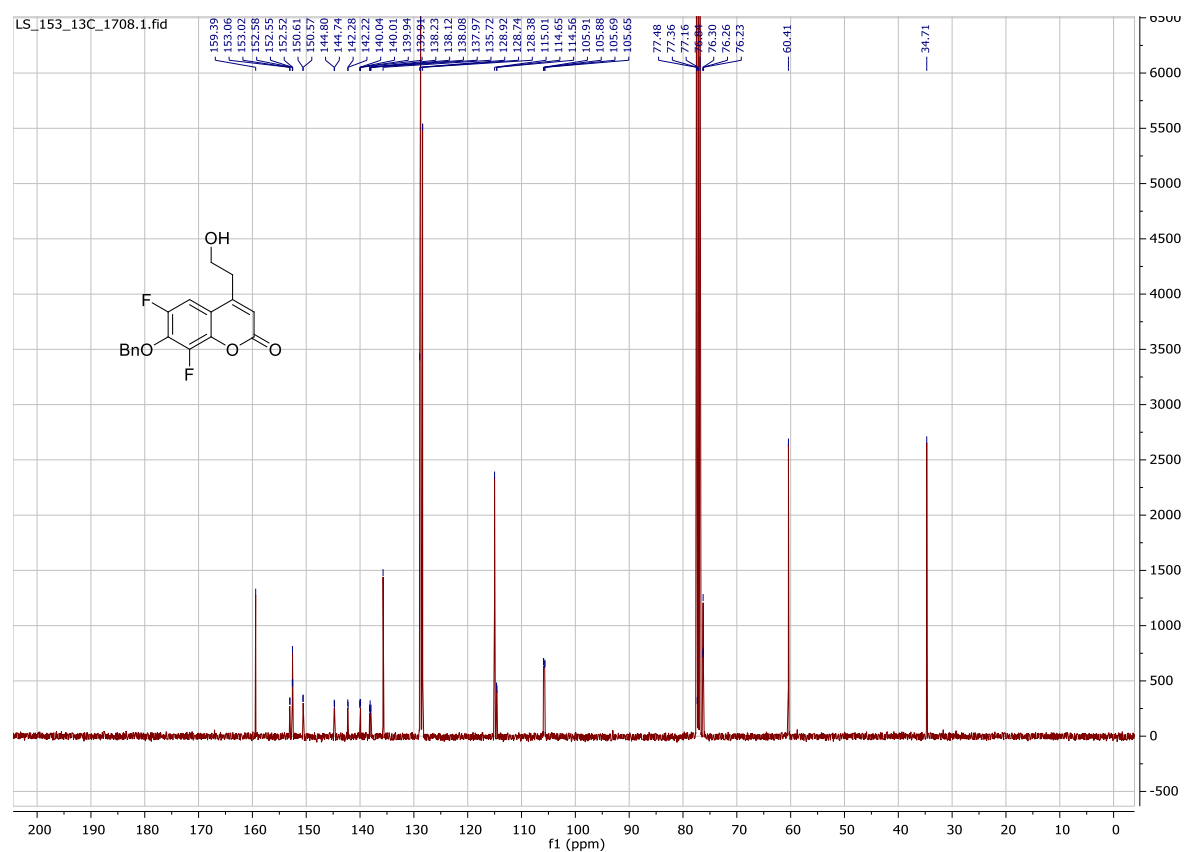
¹⁹F NMR (376 MHz, CDCl₃) of 11b



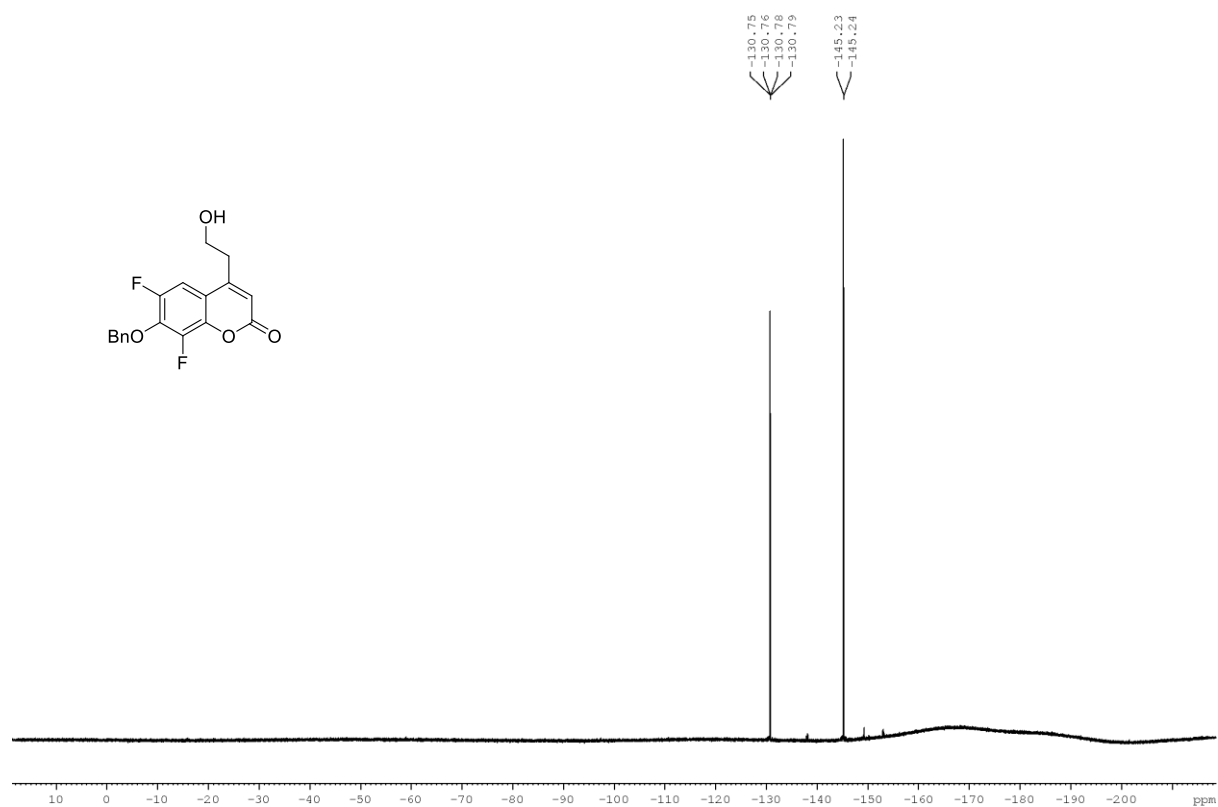
¹H NMR (400 MHz, CDCl₃) of 11c



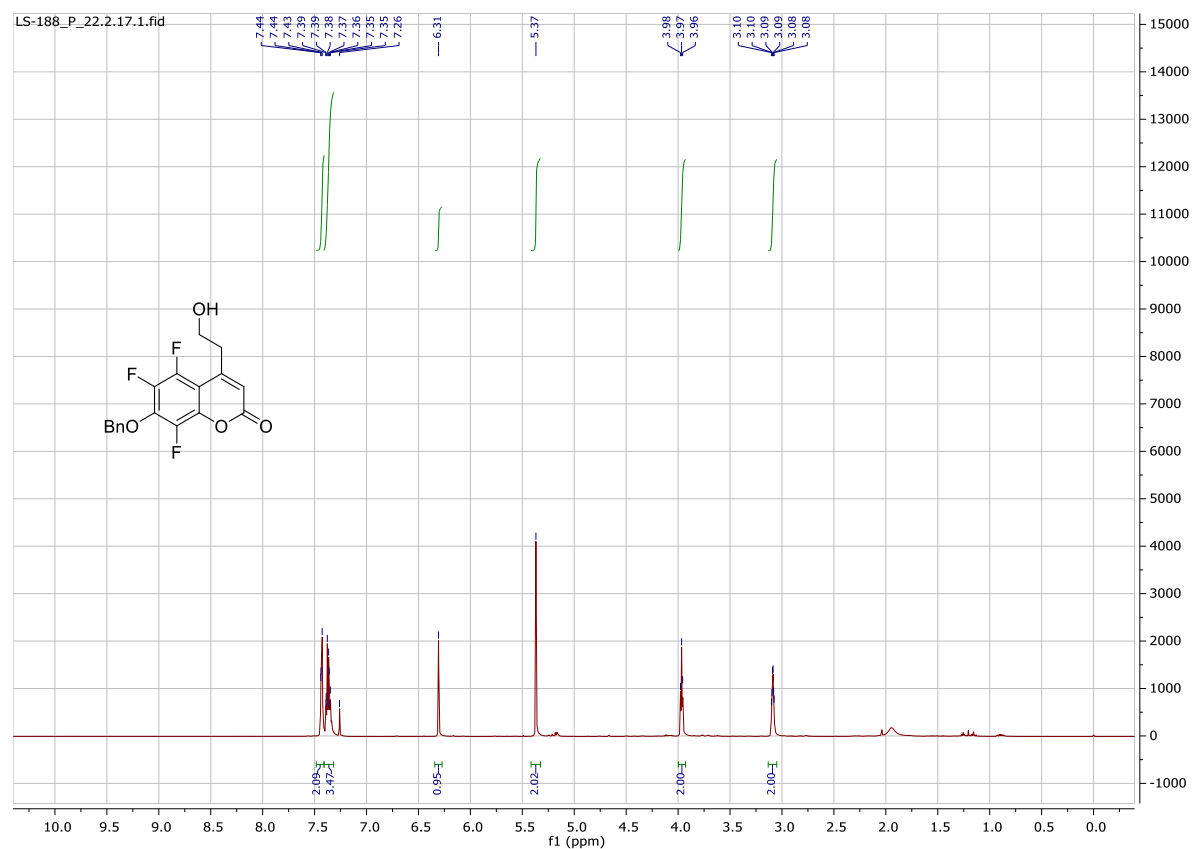
^{13}C NMR (100 MHz, CDCl_3) of 11c



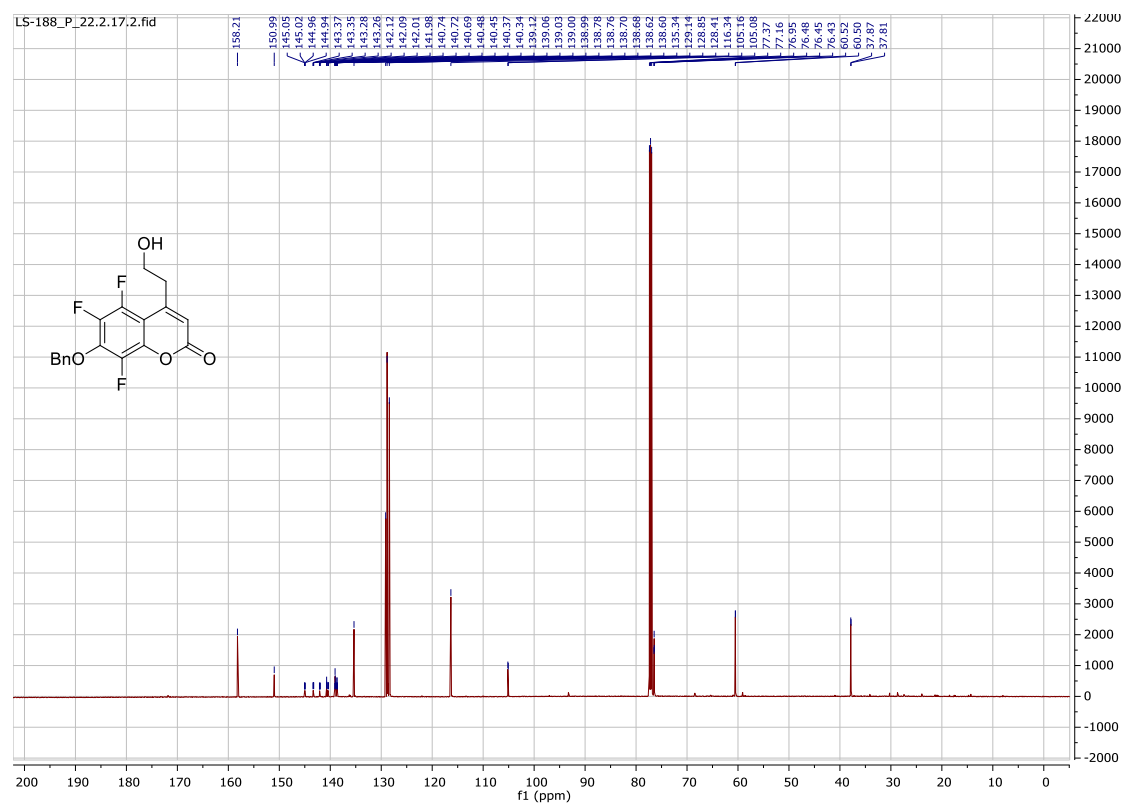
^{19}F NMR (376 MHz, CDCl_3) of 11c



¹H NMR (600 MHz, CDCl₃) of 11d



¹³C NMR (151 MHz, CDCl₃) of 11d



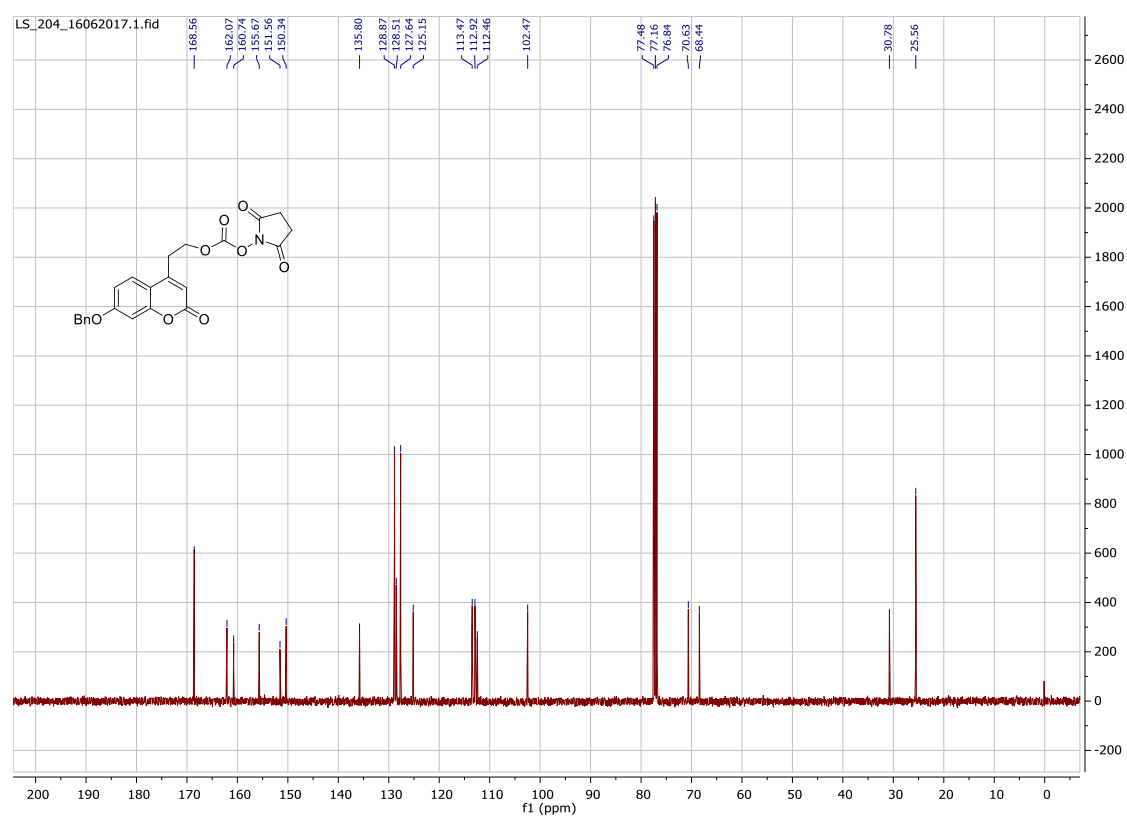
O=C1C=CC2=C(C=C1)C(=C(C=C2)C(F)(F)C(=C3C=C(C=C3)OC(=O)C)F)F

Chemical structure: O=C1OC(=O)N1CCOCc2c(=O)oc3ccc(cc23)C4=CC=CC=C4

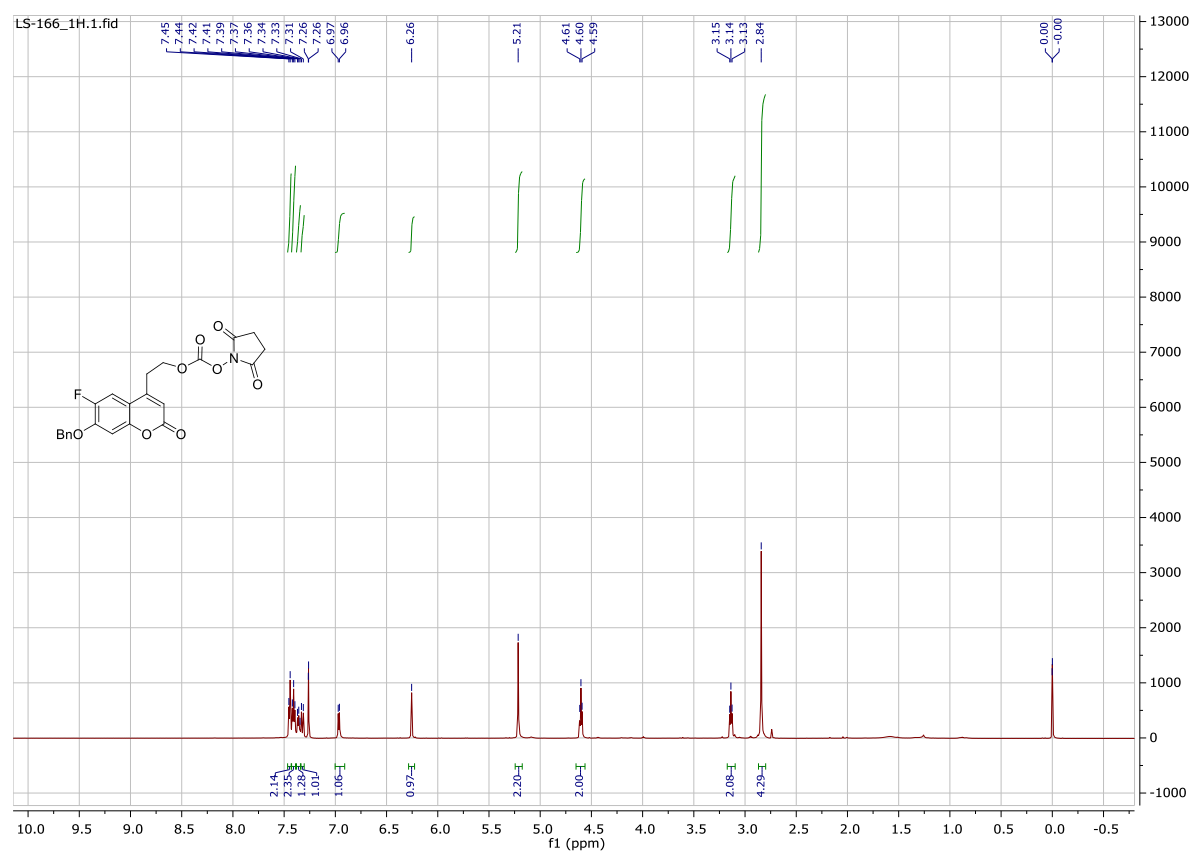
¹H NMR spectrum (ppm):

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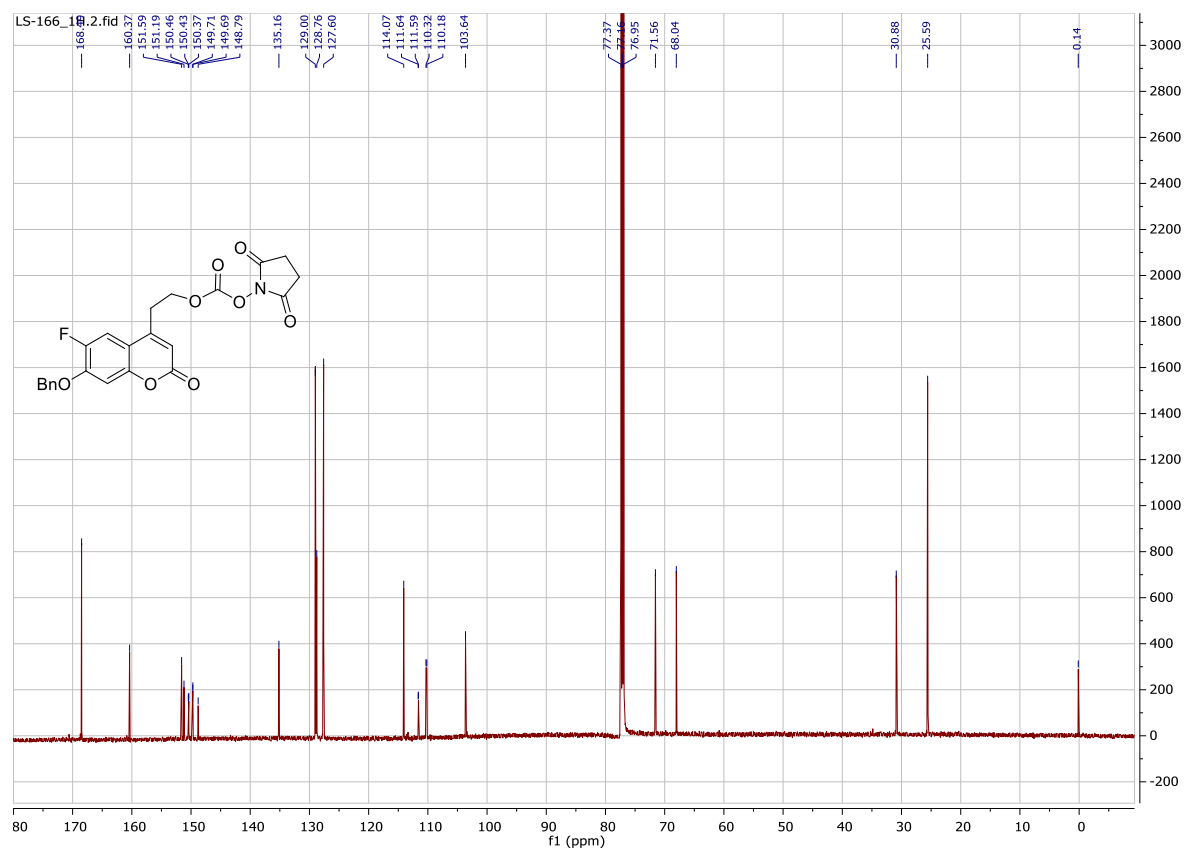
¹³C NMR (100 MHz, CDCl₃) of 12a



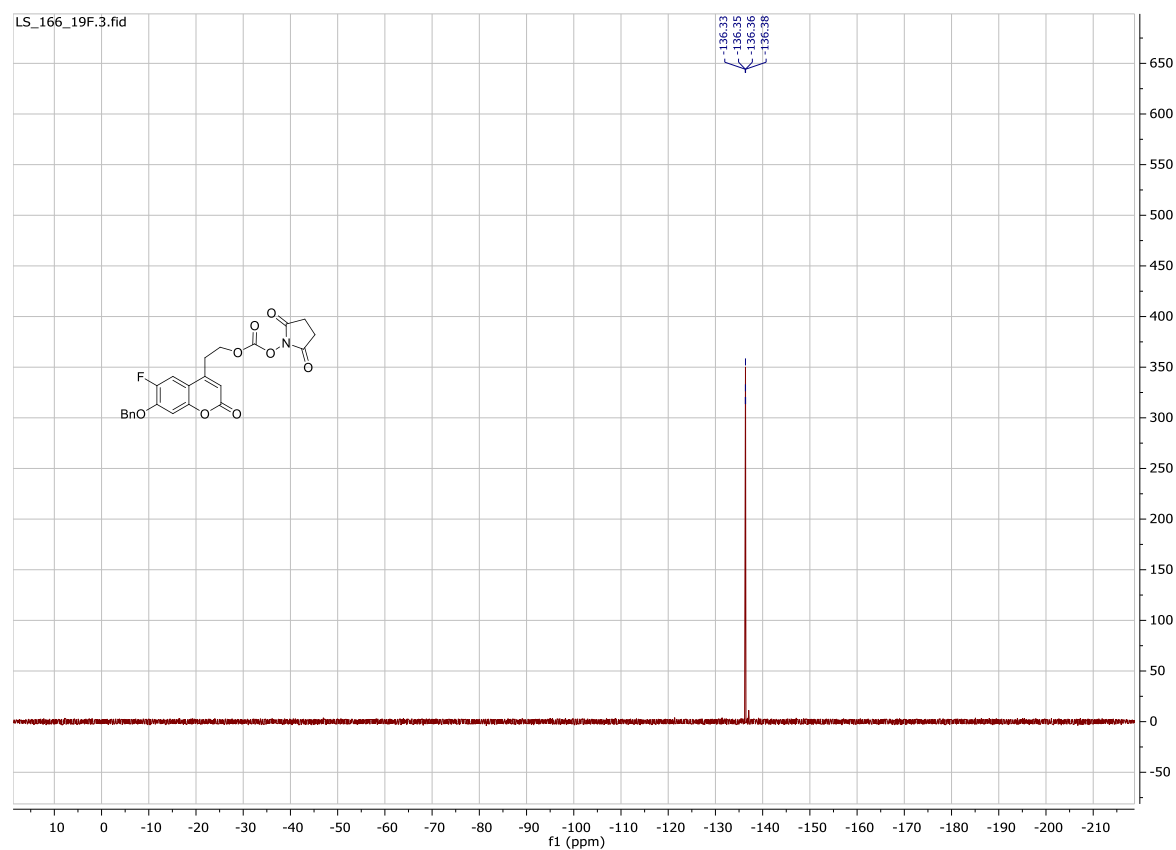
¹H NMR (600 MHz, CDCl₃) of 12b



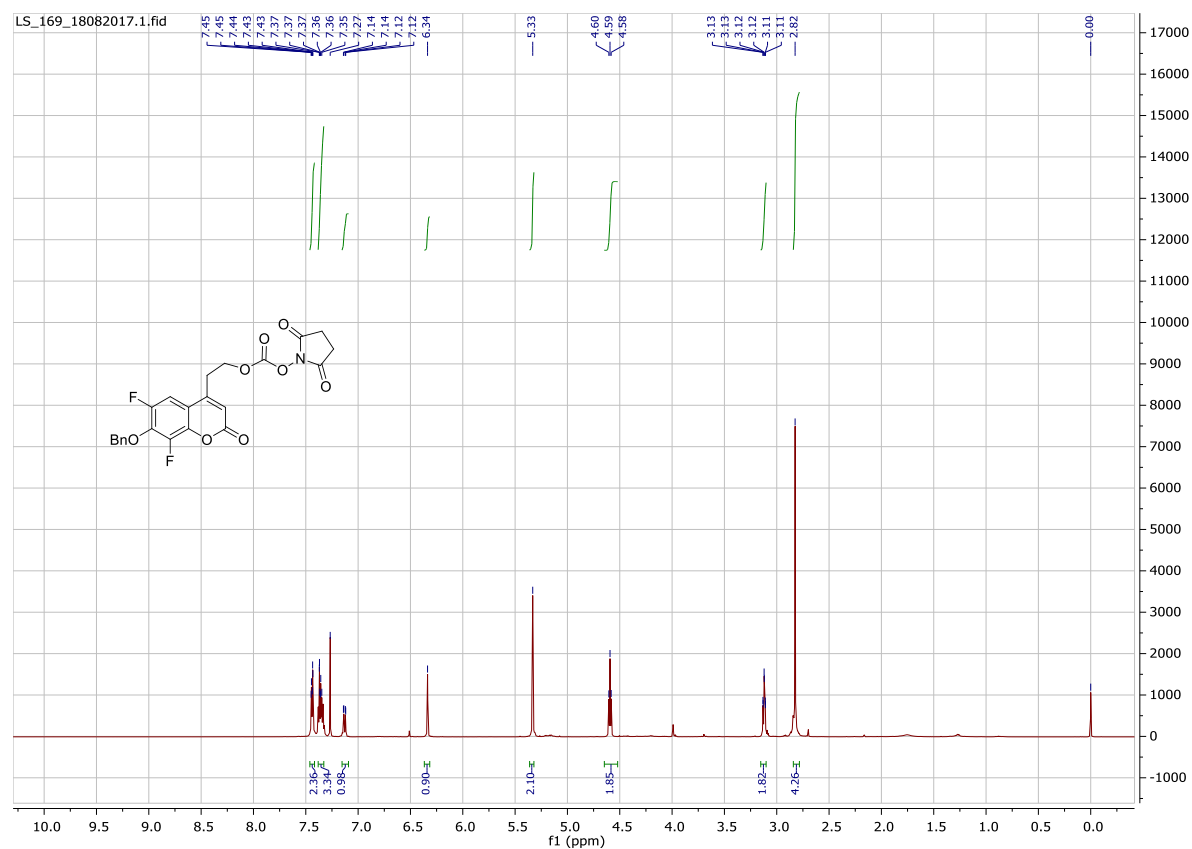
^{13}C NMR (151 MHz, CDCl_3) of 12b



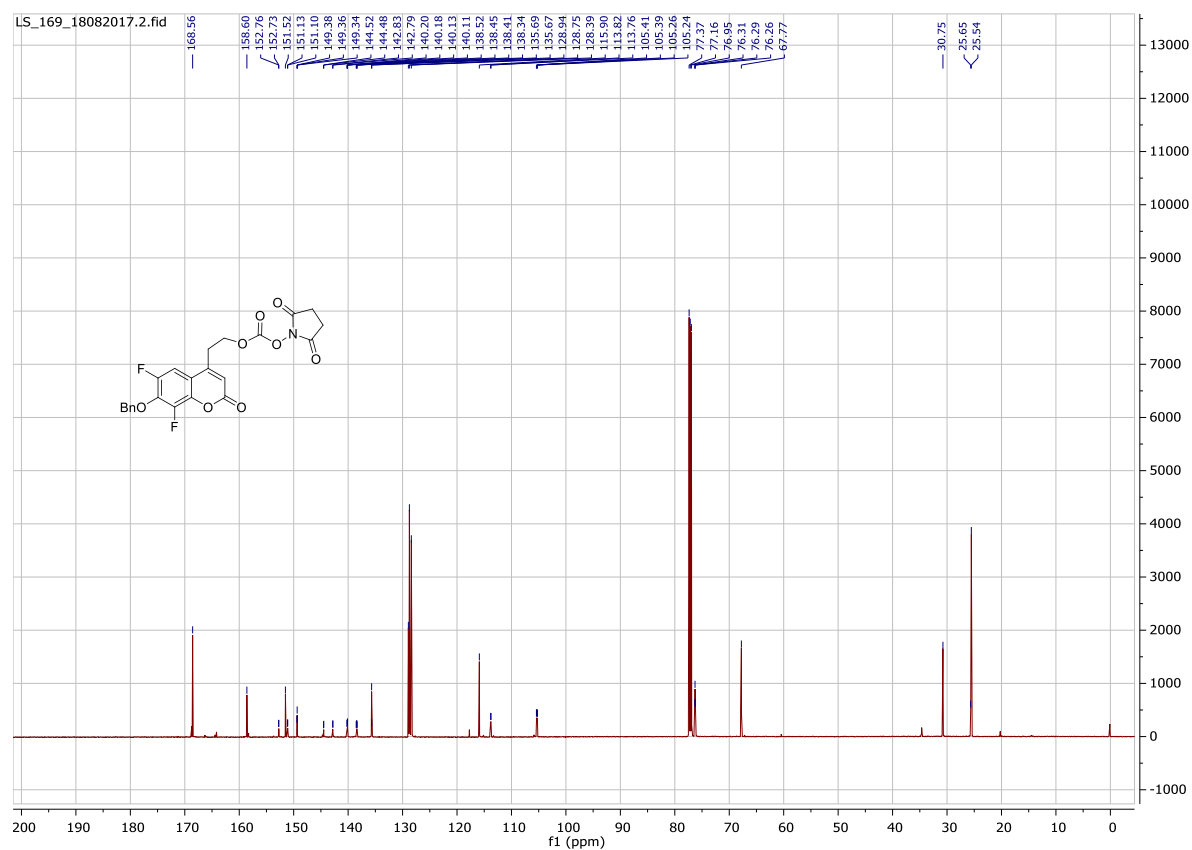
^{19}F NMR (376 MHz, CDCl_3) of 12b



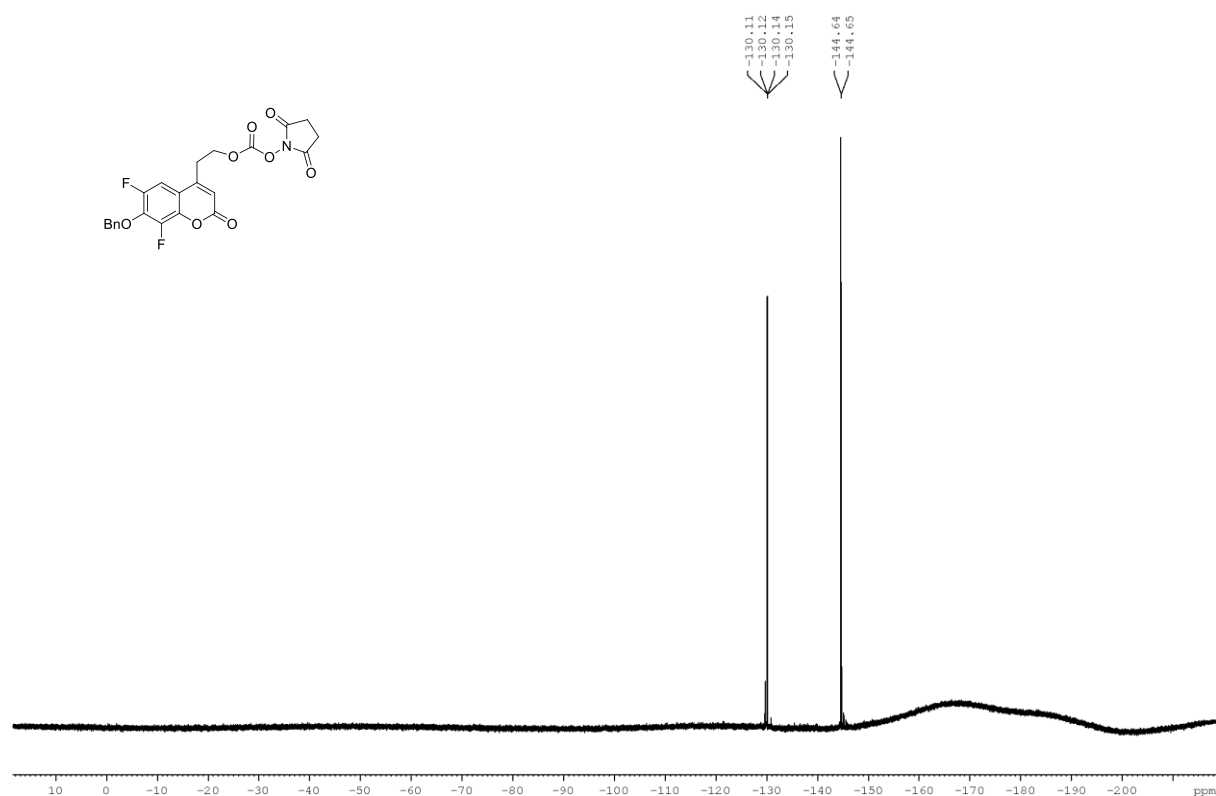
¹H NMR (600 MHz, CDCl₃) of 12c



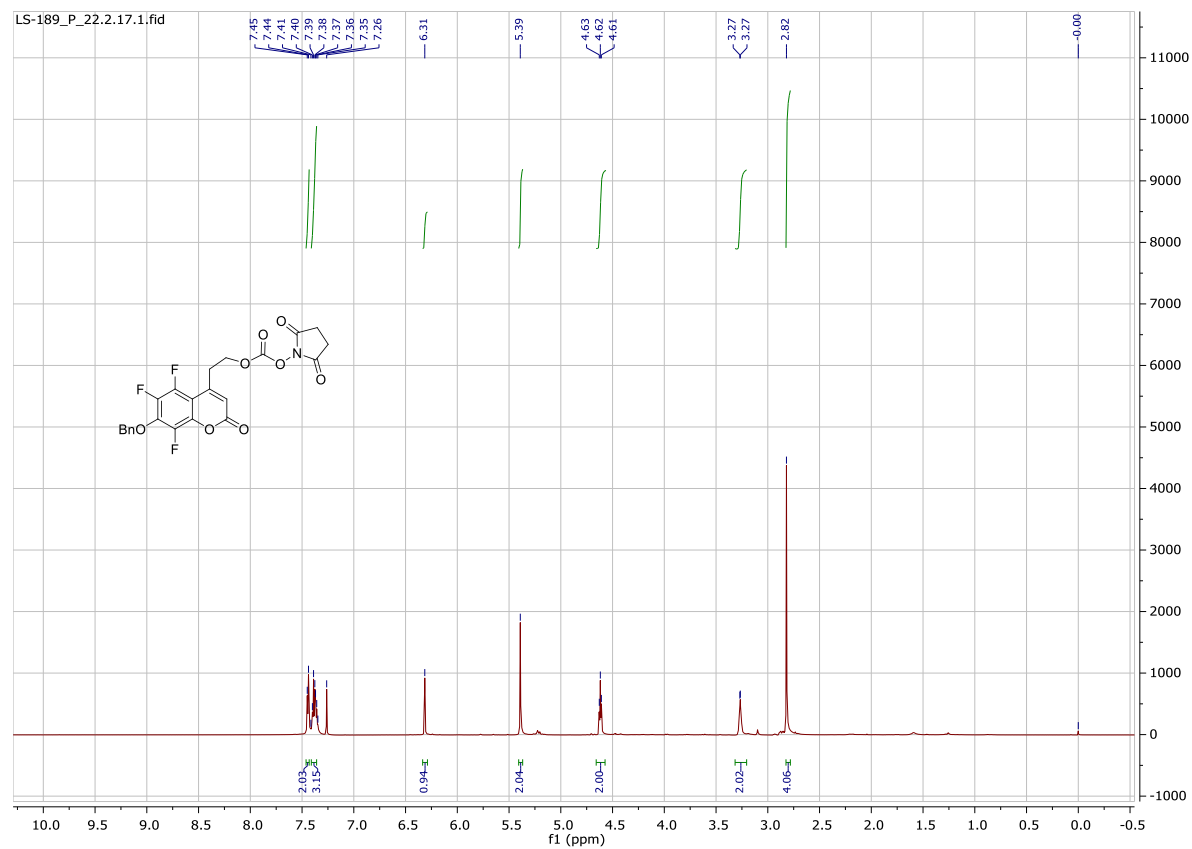
¹³C NMR (151 MHz, CDCl₃) of 12c



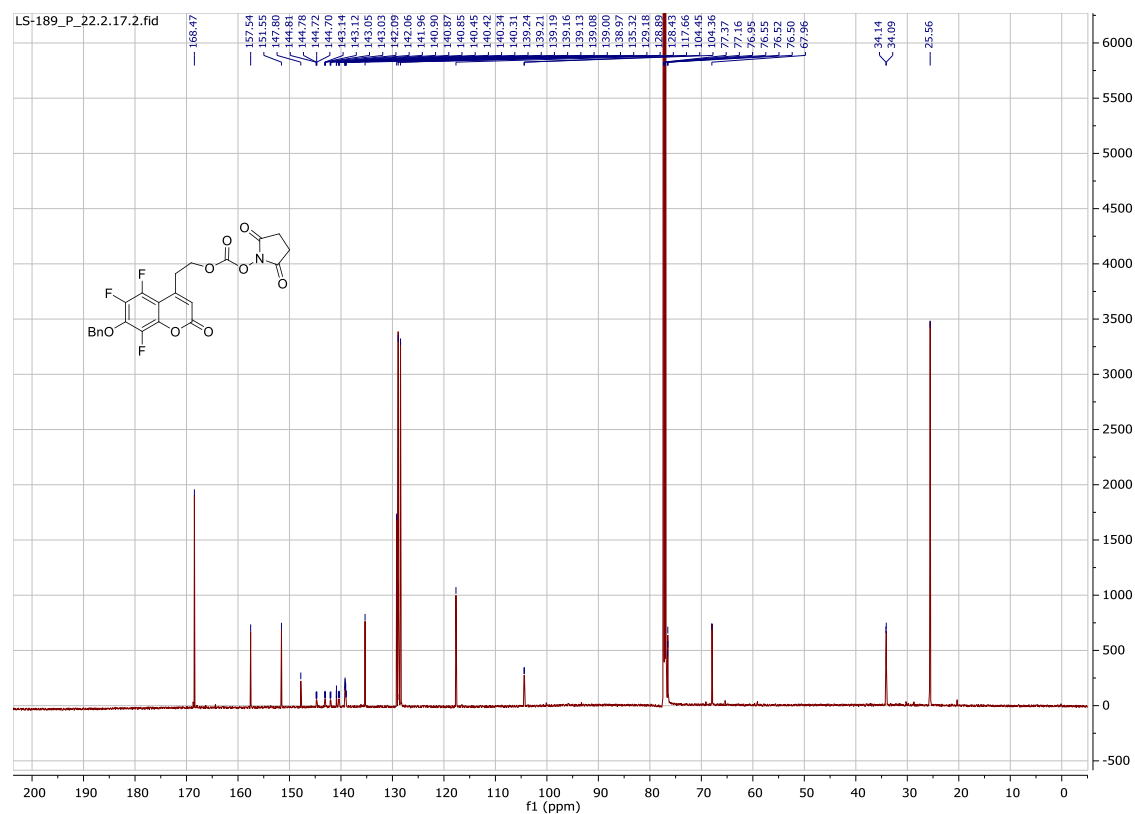
^{19}F NMR (376 MHz, CDCl_3) of 12c



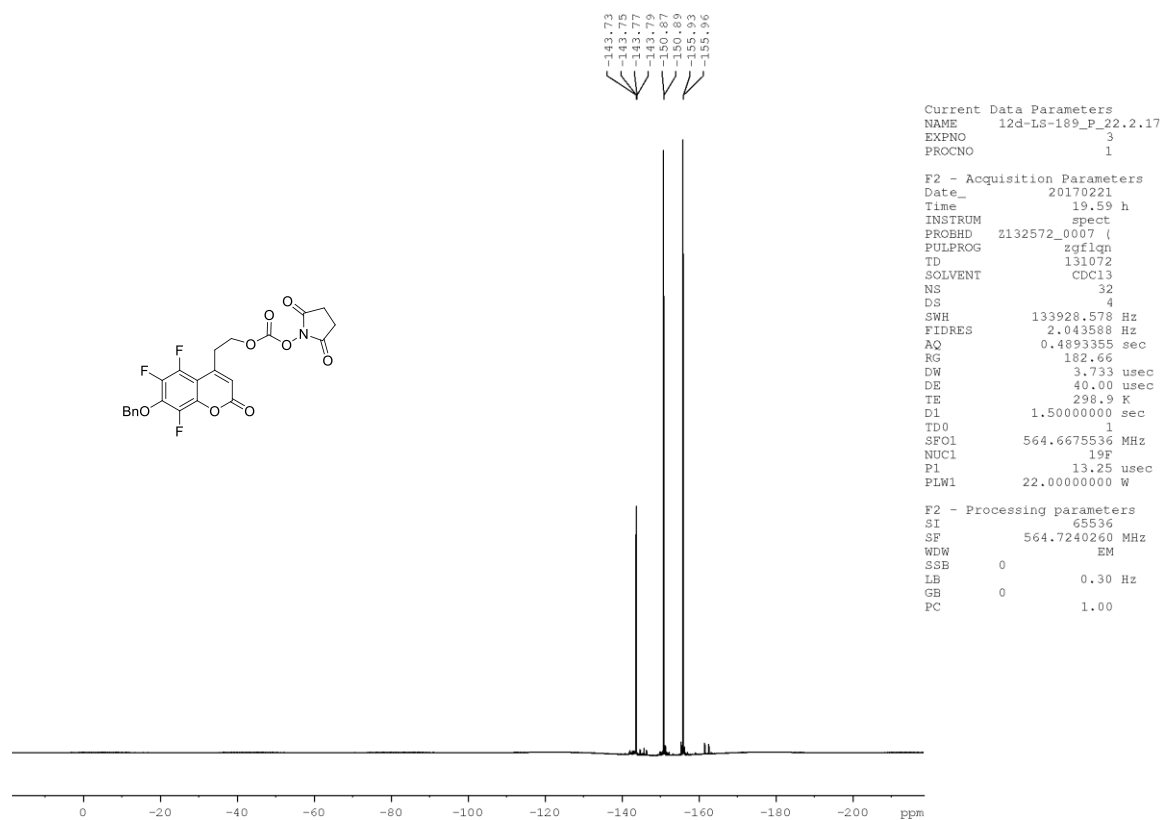
^1H NMR (600 MHz, CDCl_3) of 12d



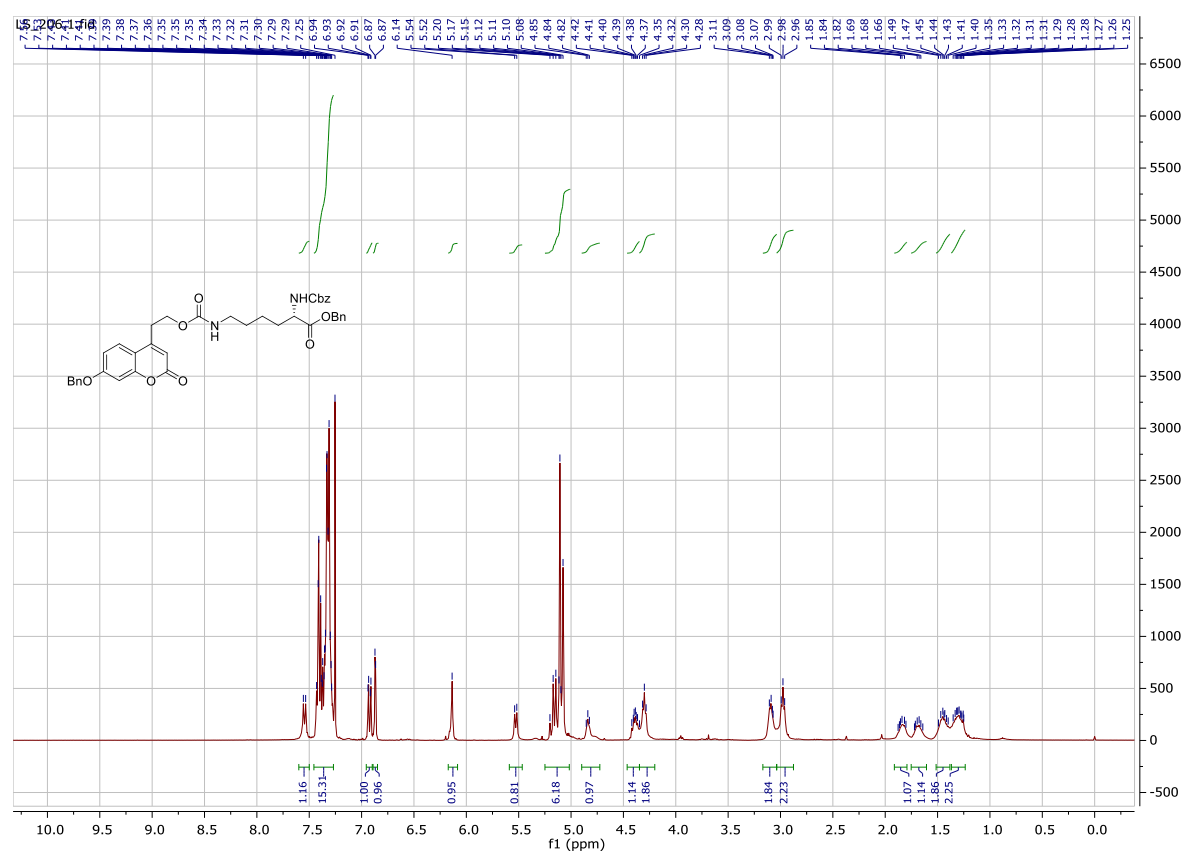
¹³C NMR (151 MHz, CDCl₃) of 12d



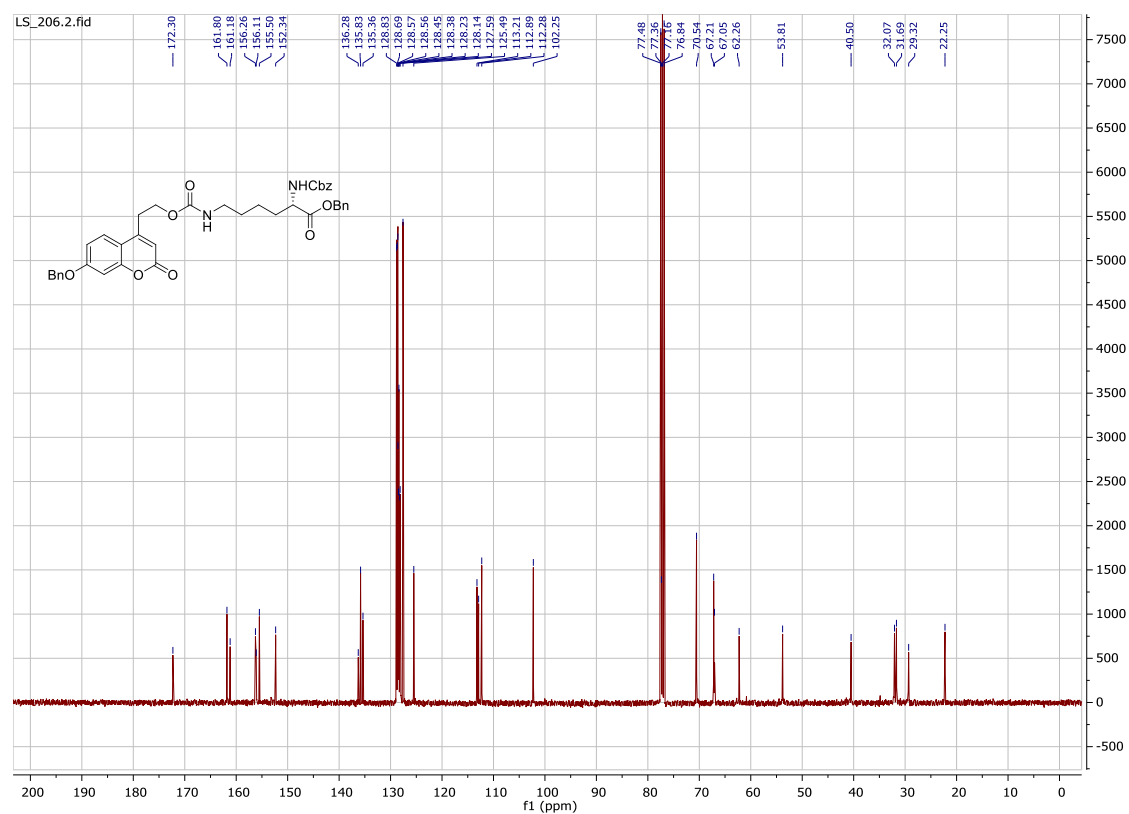
¹⁹F NMR (376 MHz, CDCl₃) of 12d



^1H NMR (400 MHz, CDCl_3) of 14a



^{13}C NMR (100 MHz, CDCl_3) of 14a



[illegible]

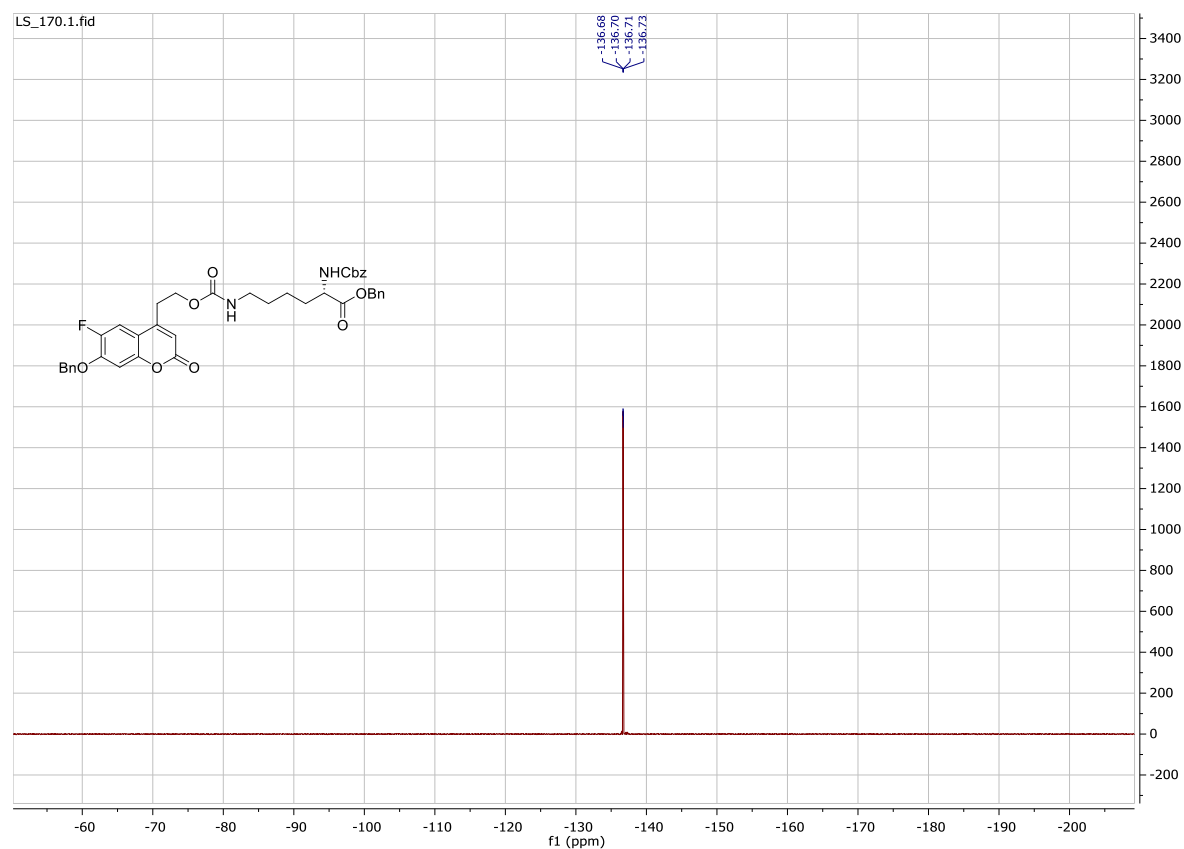
LS-170_P.5.fid

Chemical structure of the compound (170) is shown in the top left corner. The structure is a substituted benzofuran derivative with a fluorine atom, a benzyloxy group, and a side chain containing an amide and a carbamate group.

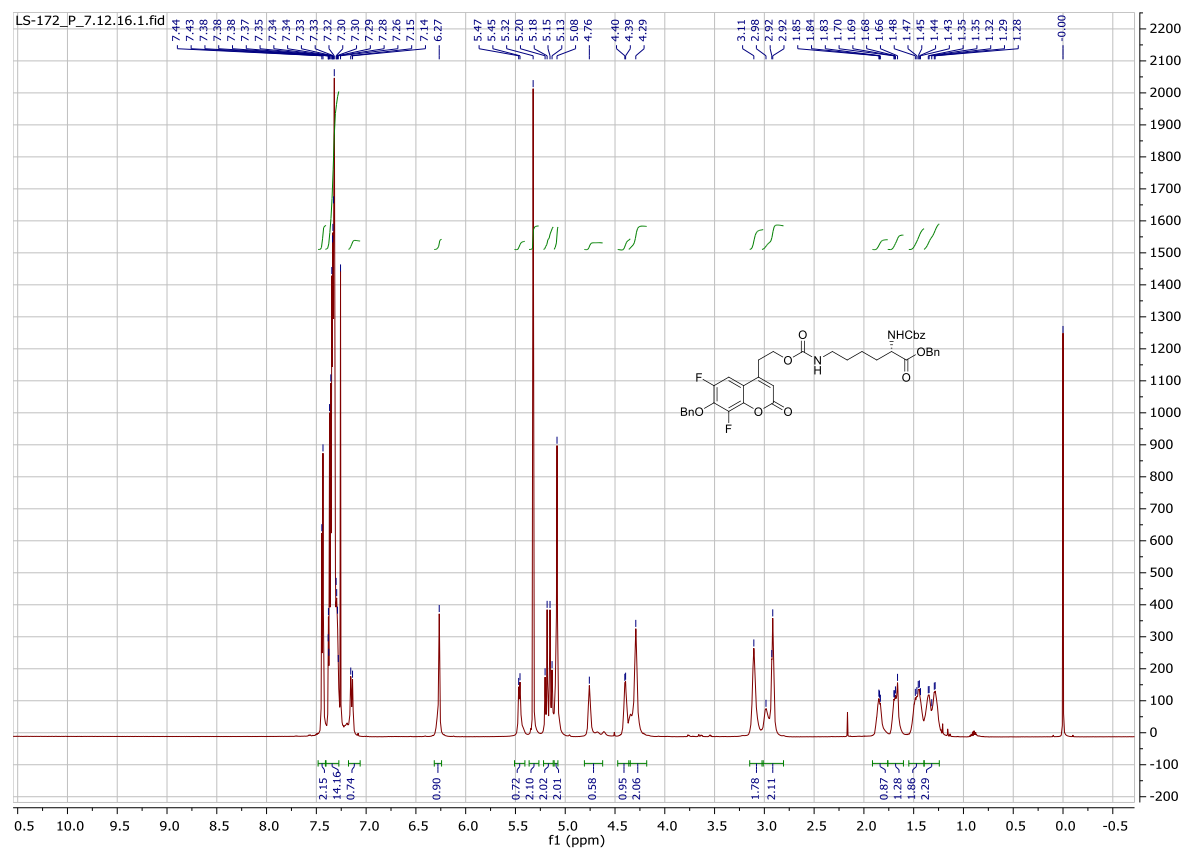
13C NMR spectrum (f1 (ppm)) showing peaks at the following chemical shifts (ppm):

- 172.32
- 160.80
- 156.17
- 156.12
- 151.88
- 150.98
- 150.16
- 150.03
- 148.23
- 136.32
- 135.40
- 135.20
- 133.82
- 128.70
- 128.62
- 128.60
- 128.43
- 128.28
- 128.20
- 127.57
- 113.35
- 112.17
- 112.10
- 110.70
- 110.49
- 103.38
- 103.30
- 77.48
- 76.84
- 71.45
- 67.36
- 67.11
- 62.05
- 53.82
- 40.57
- 32.15
- 31.72
- 29.34
- 22.27

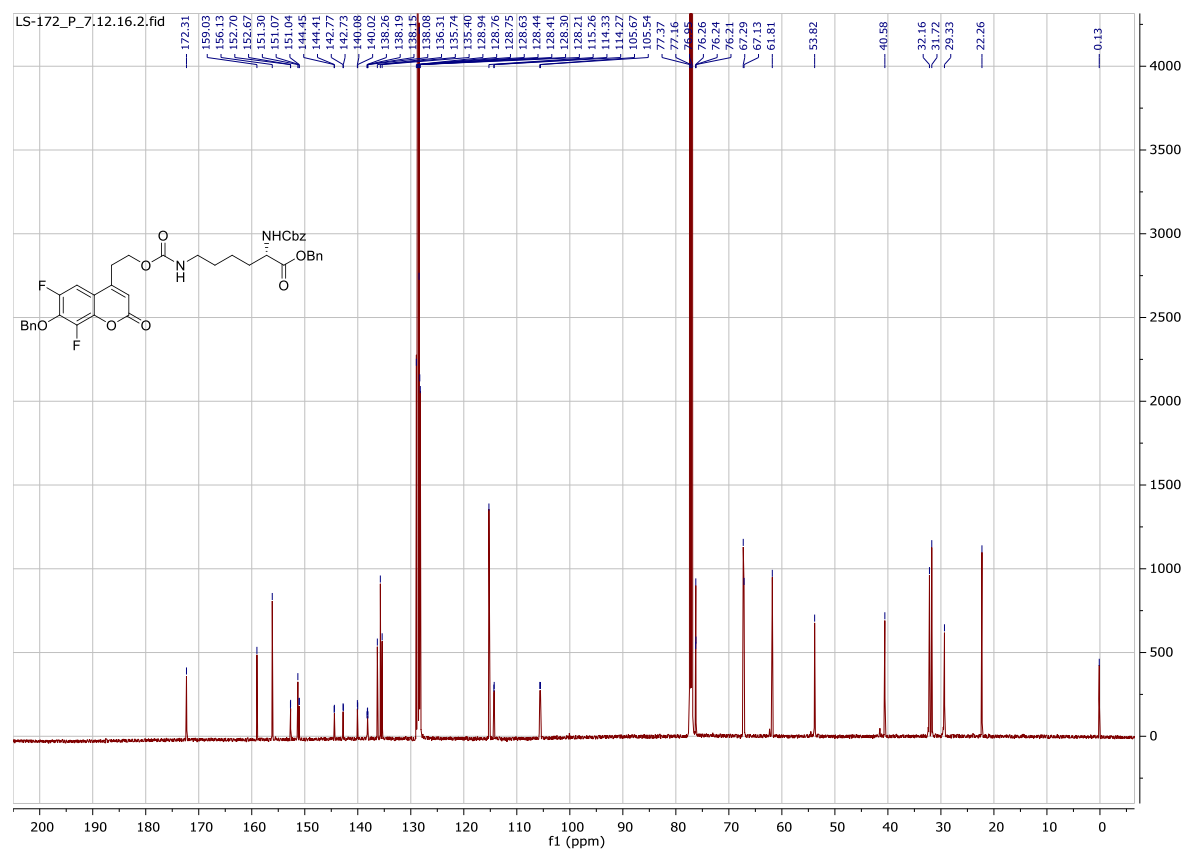
^{19}F NMR (376 MHz, CDCl_3) of 14b



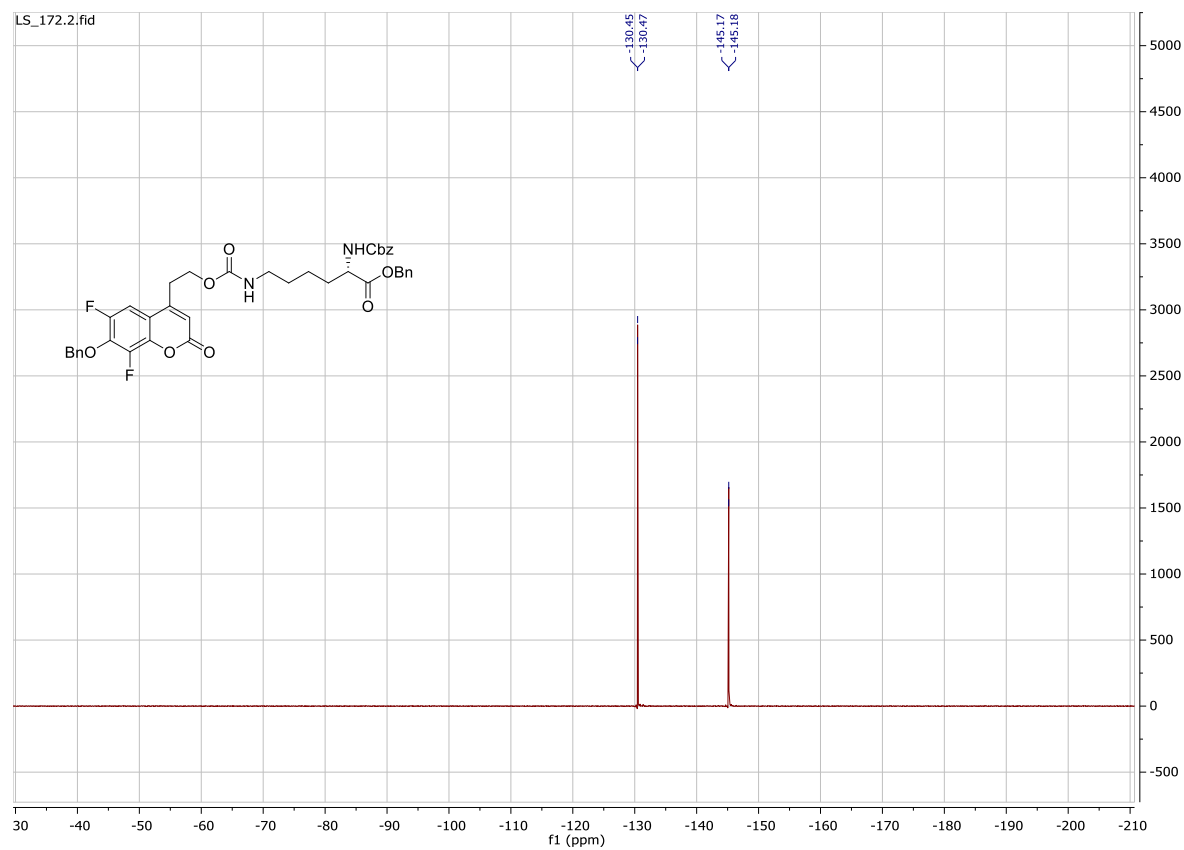
^1H NMR (600 MHz, CDCl_3) of 14c



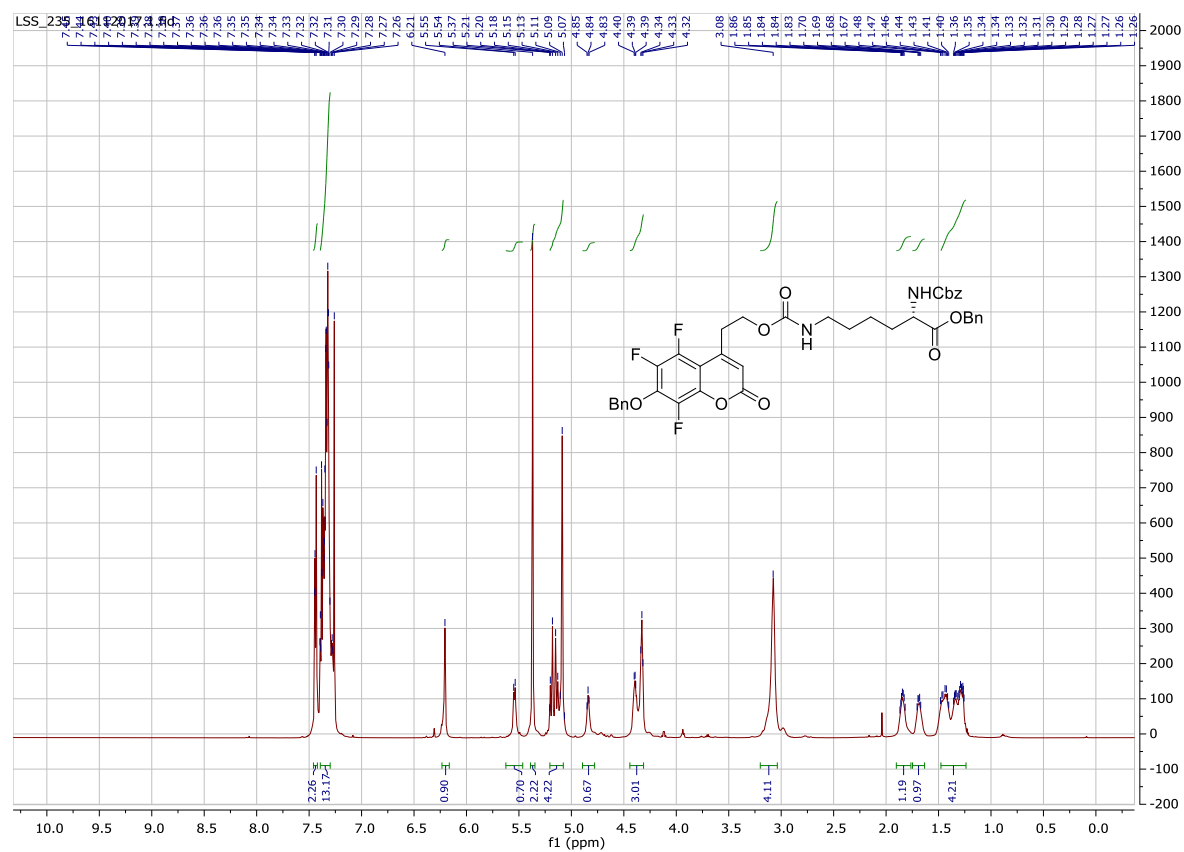
¹³C NMR (151 MHz, CDCl₃) of 14c



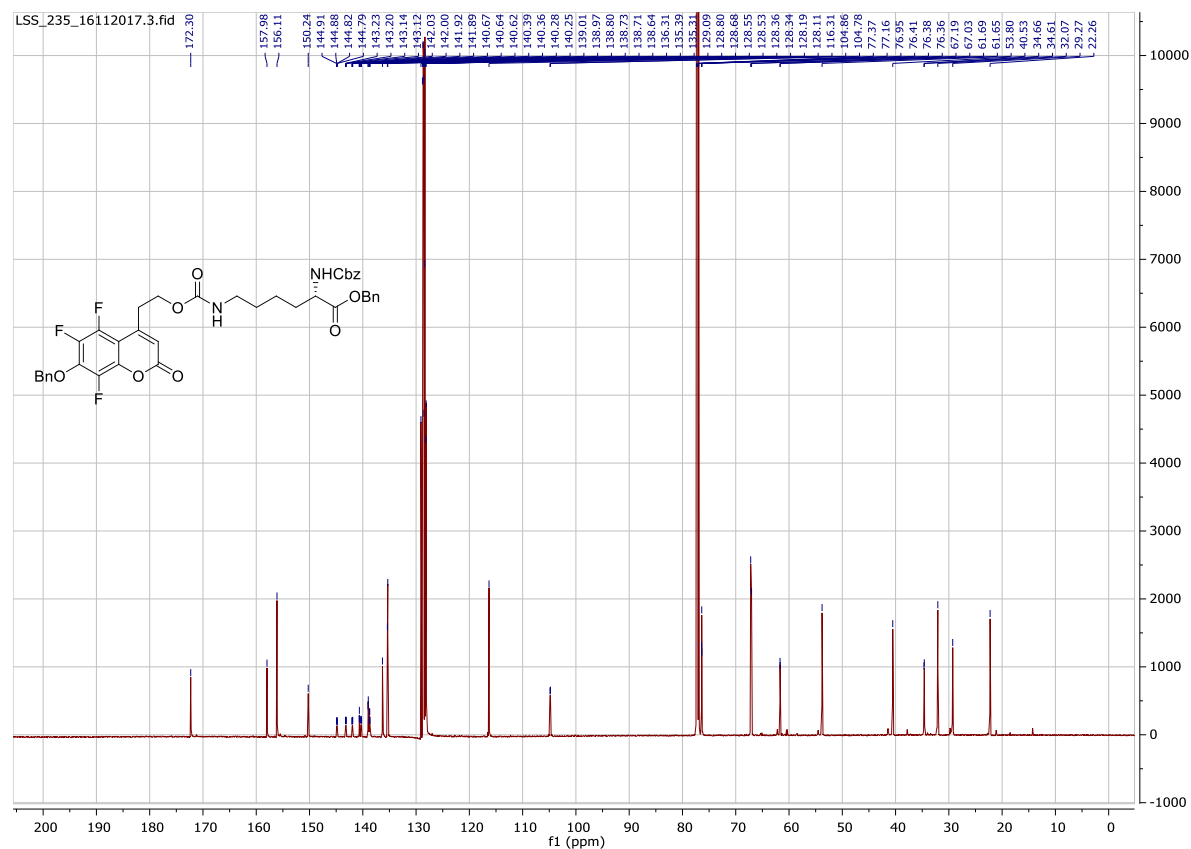
¹⁹F NMR (376 MHz, CDCl₃) of 14c

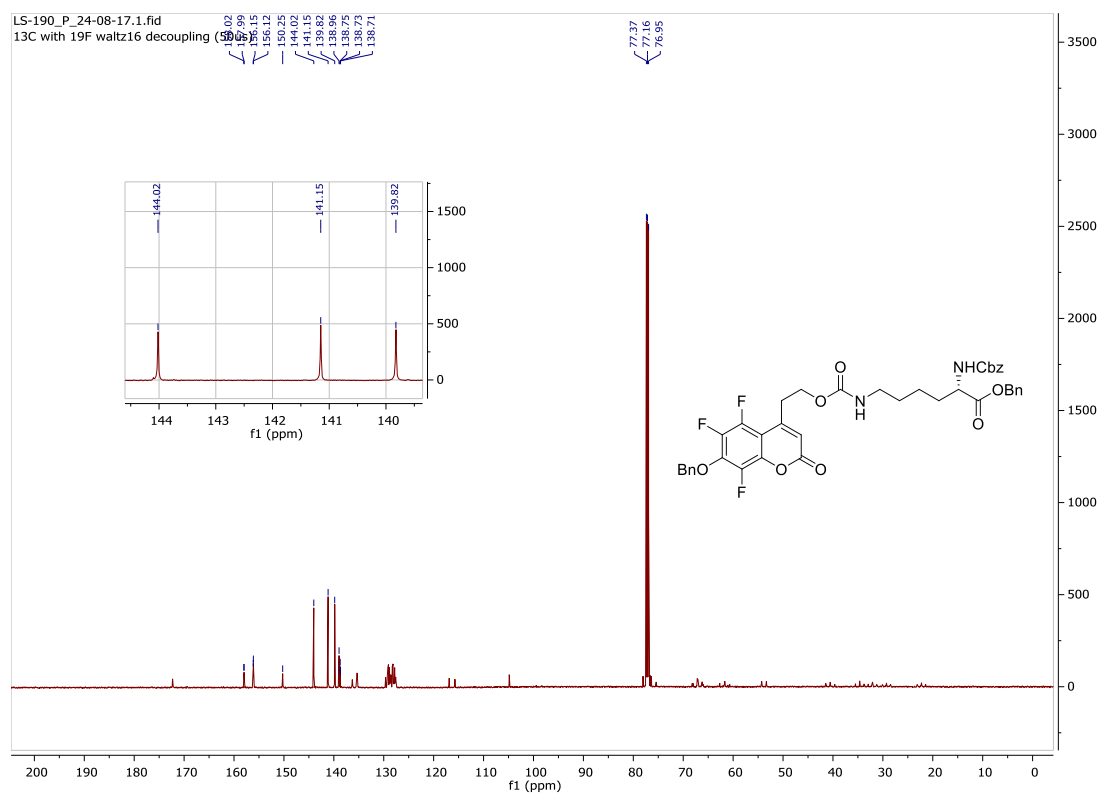


^1H NMR (600 MHz, CDCl_3) of 14d

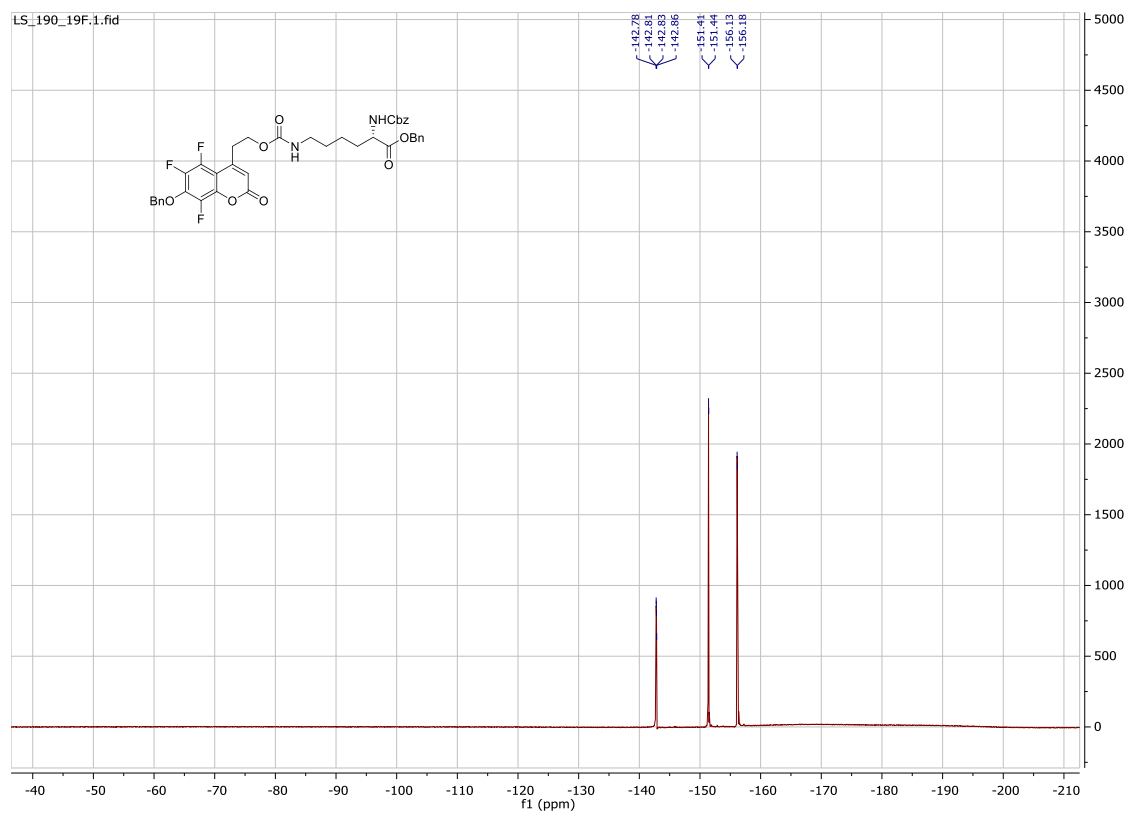


^{13}C NMR (151 MHz, CDCl_3) of 14d

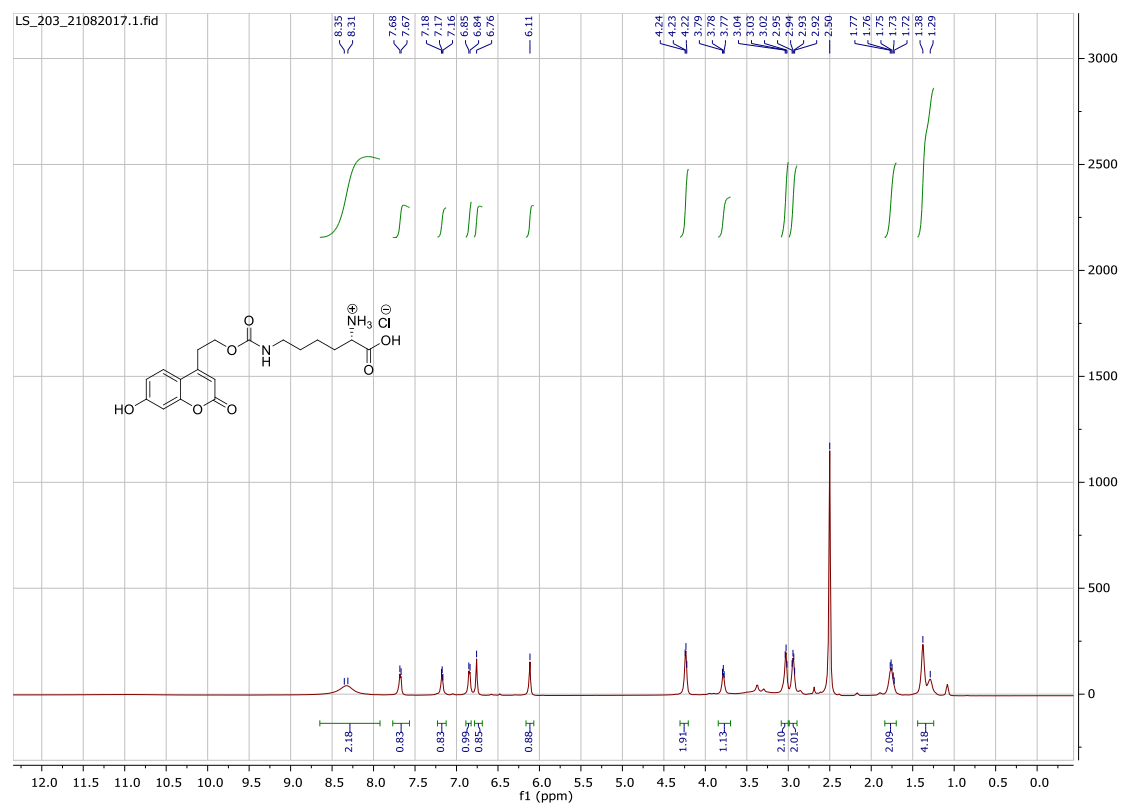




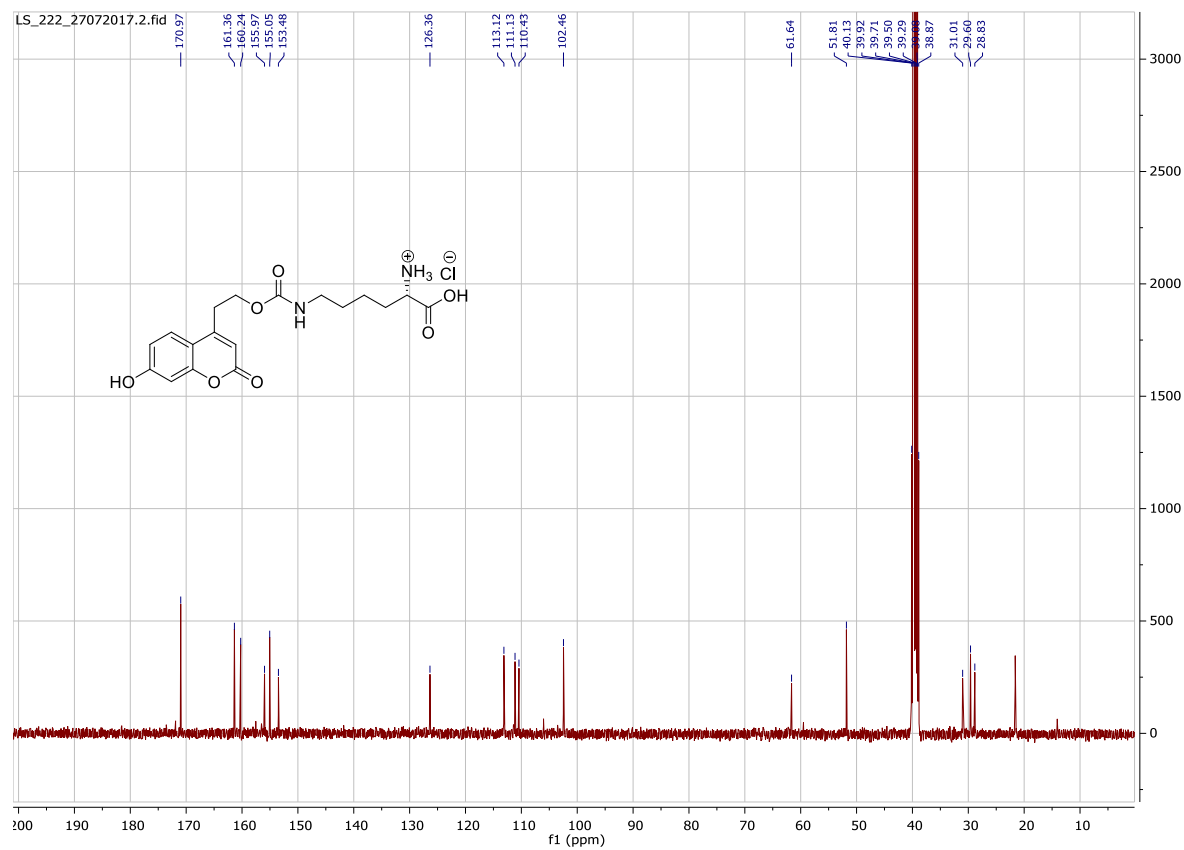
¹⁹F NMR (376 MHz, CDCl₃) of 14d



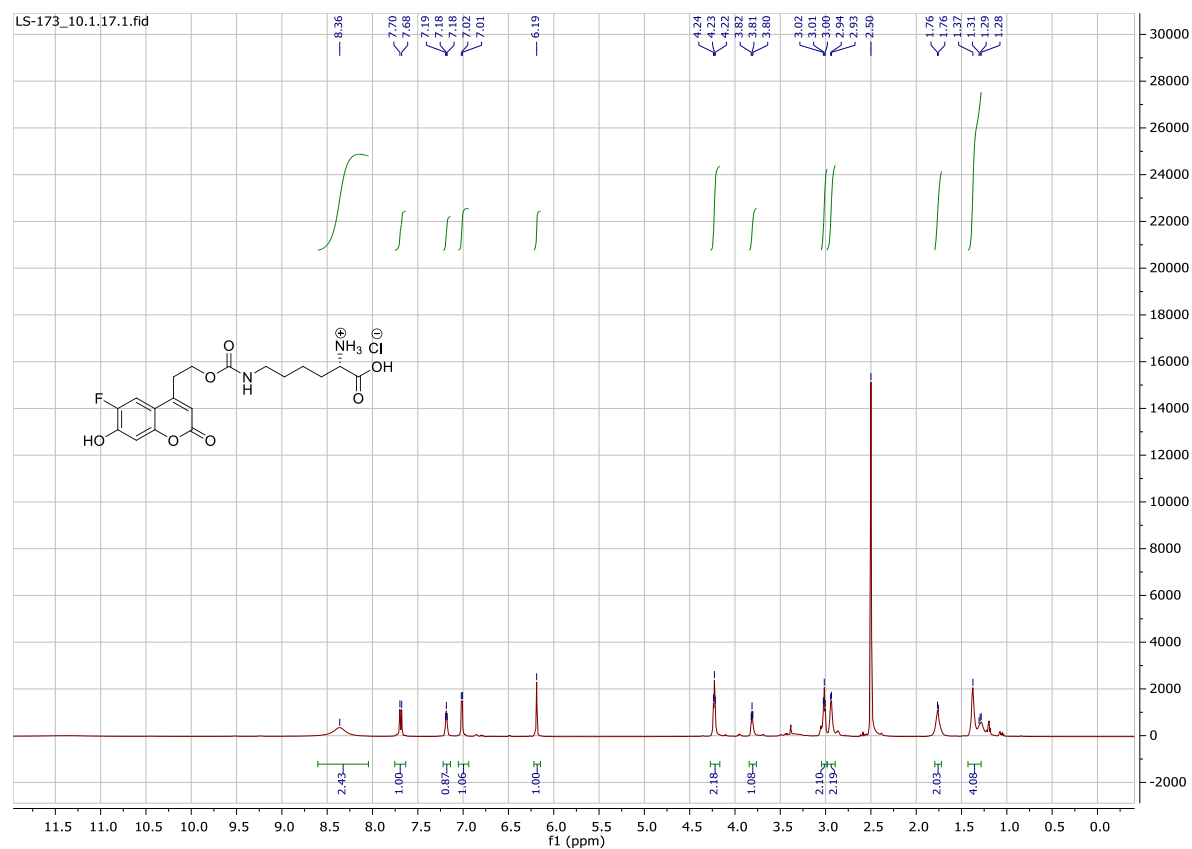
¹H NMR (600 MHz, DMSO-*d*₆) of 1



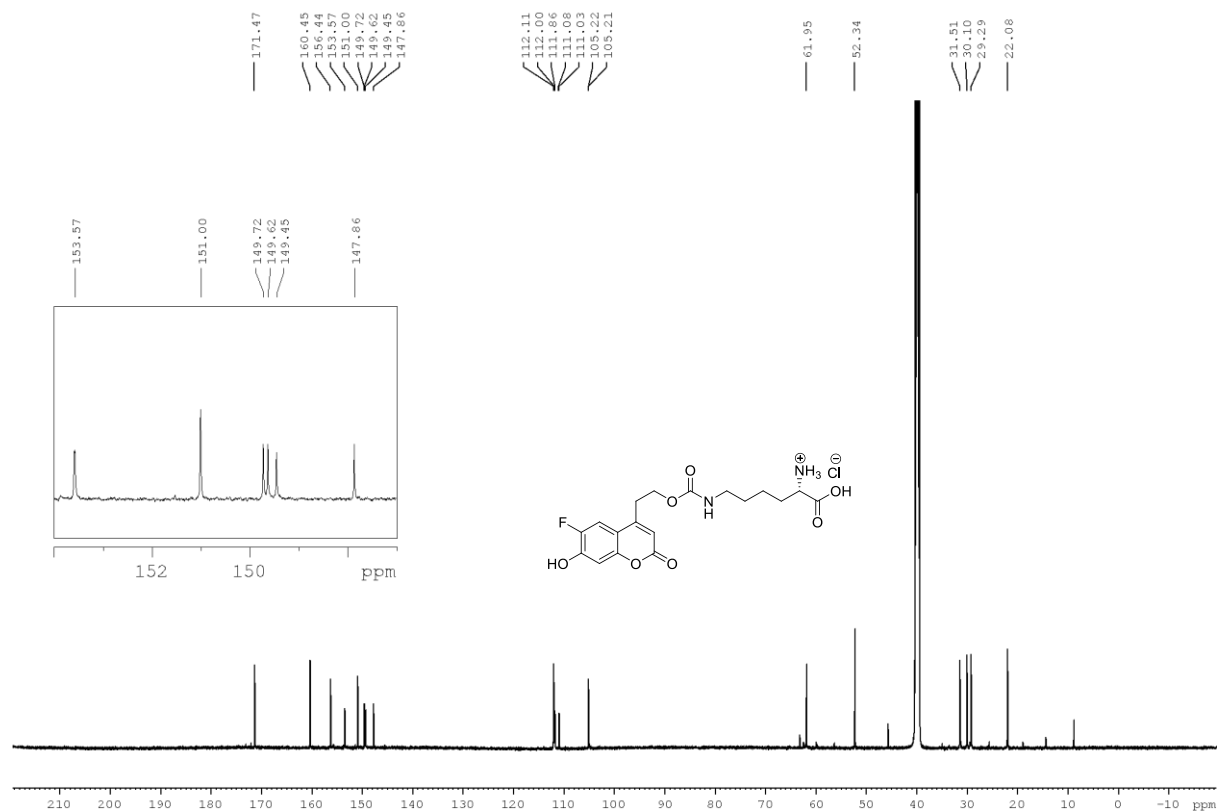
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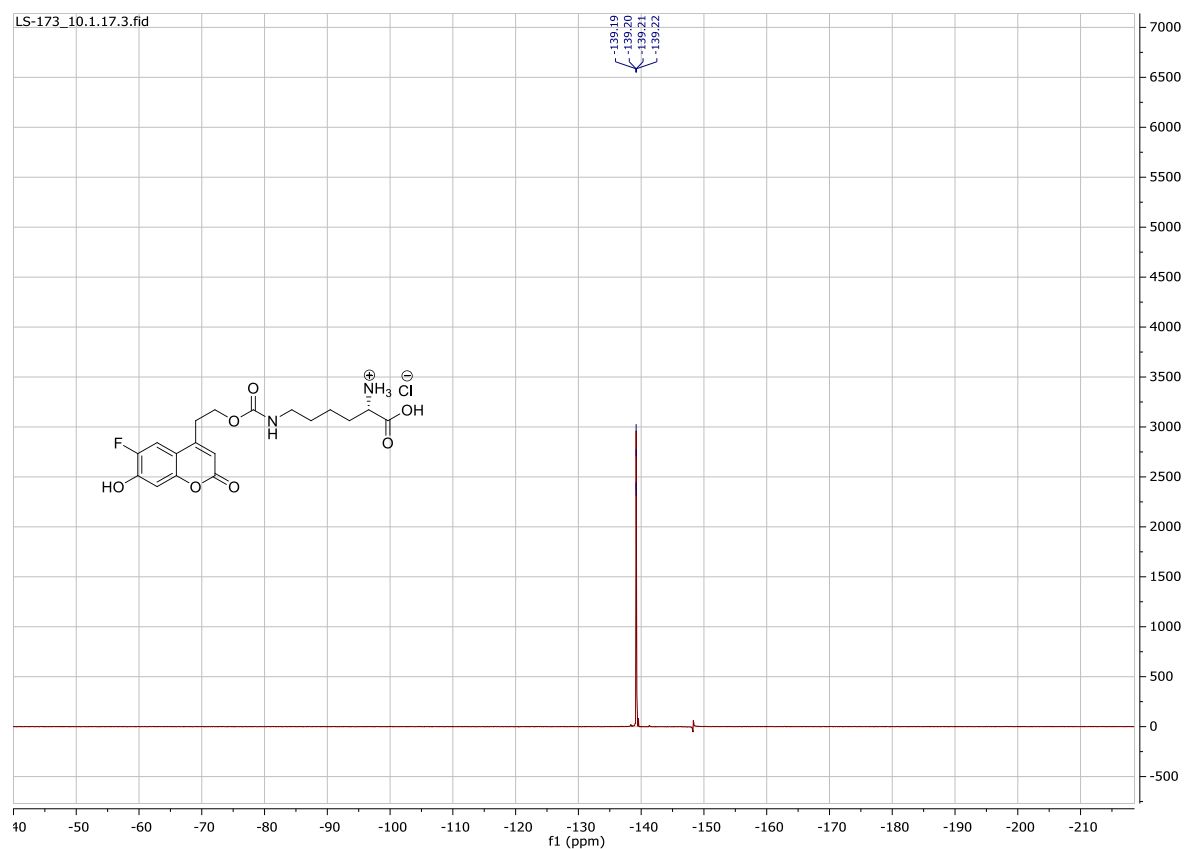
¹H NMR (600 MHz, DMSO-*d*₆) of 4



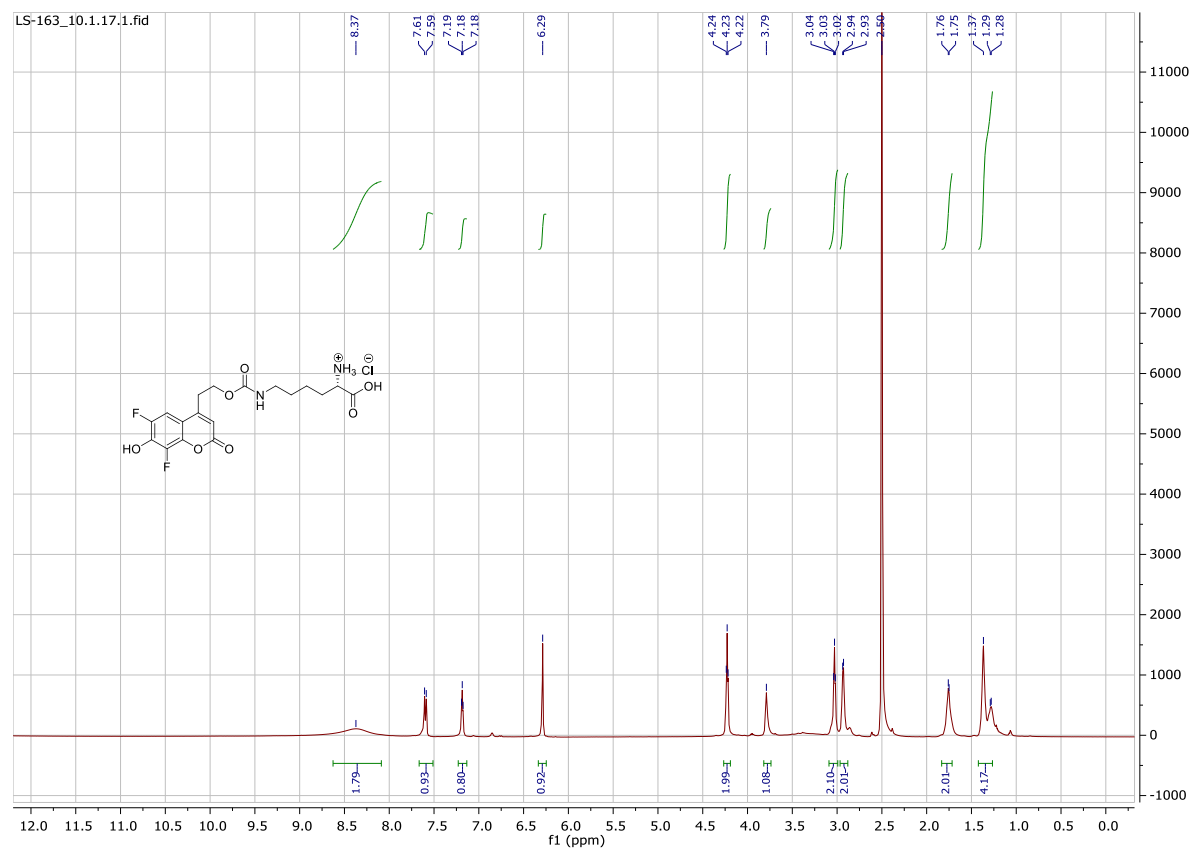
¹³C NMR (151 MHz, DMSO-*d*₆) of 4



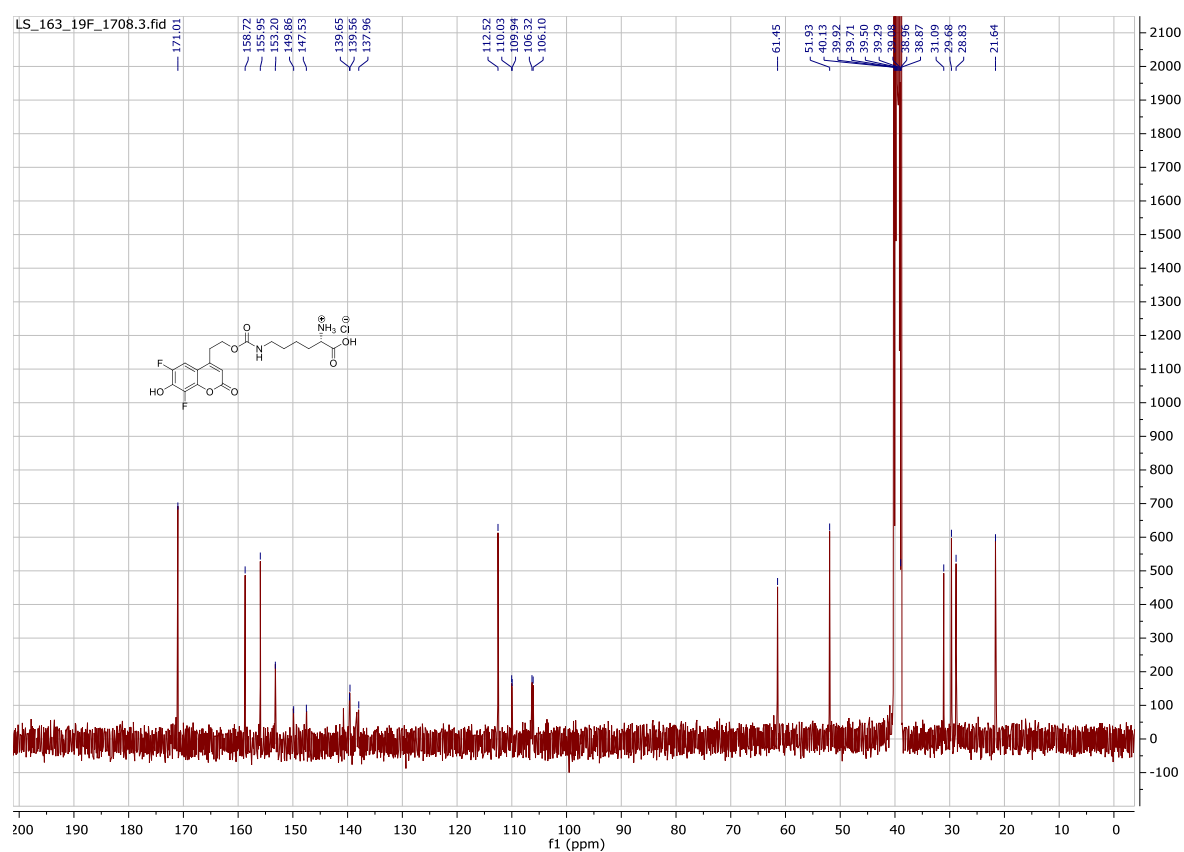
^{19}F NMR (565 MHz, CDCl_3) of 4



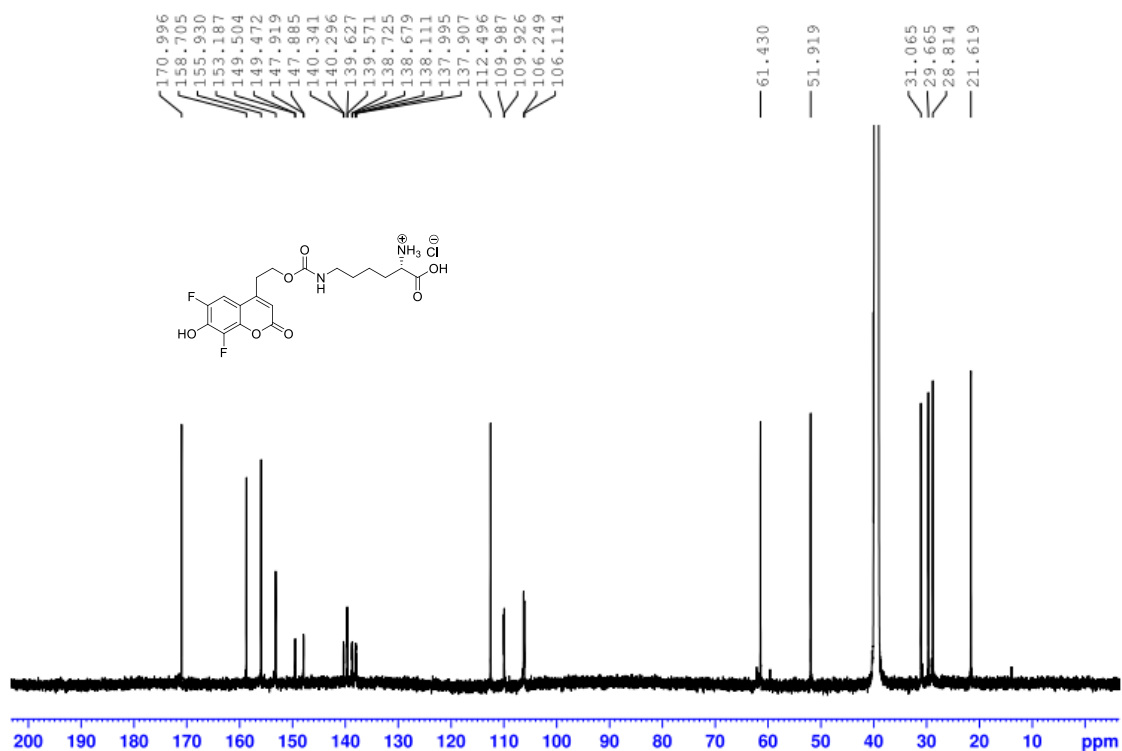
^1H NMR (600 MHz, $\text{DMSO}-d_6$) of 5

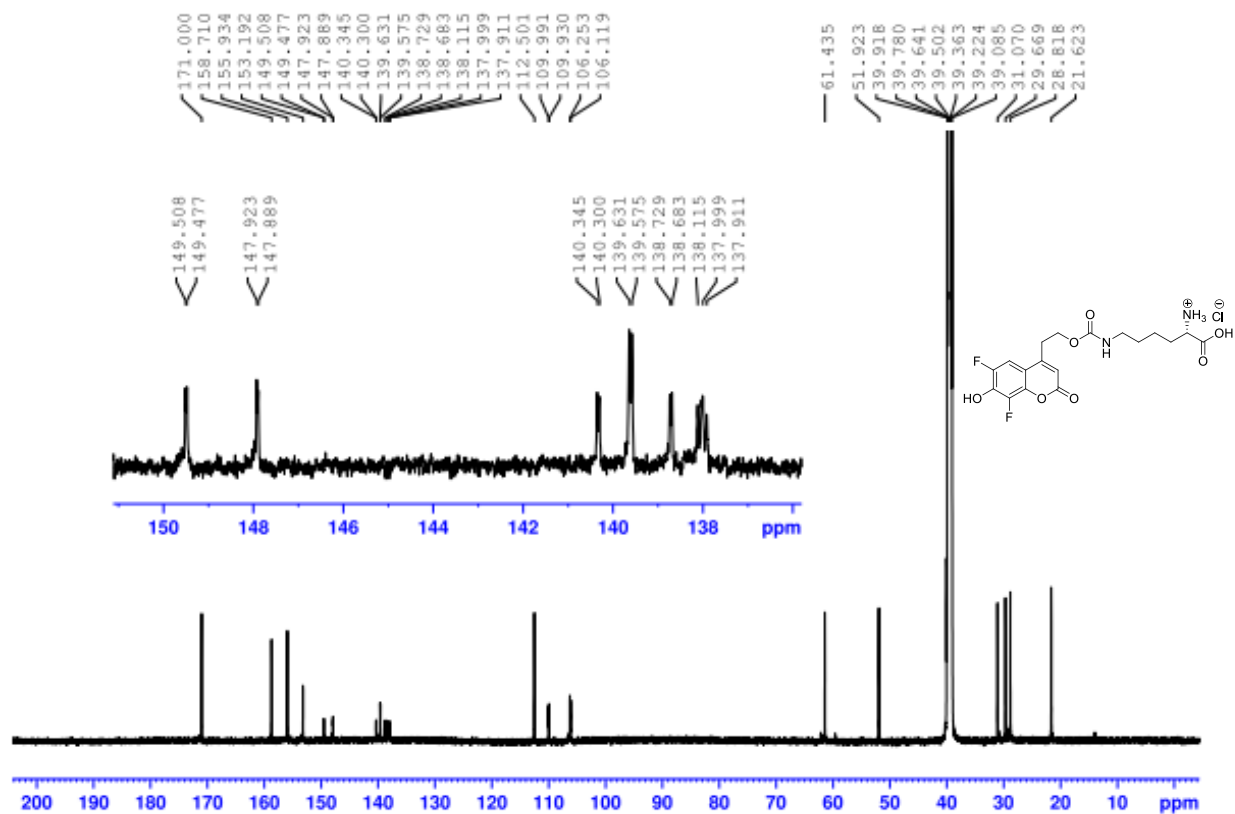


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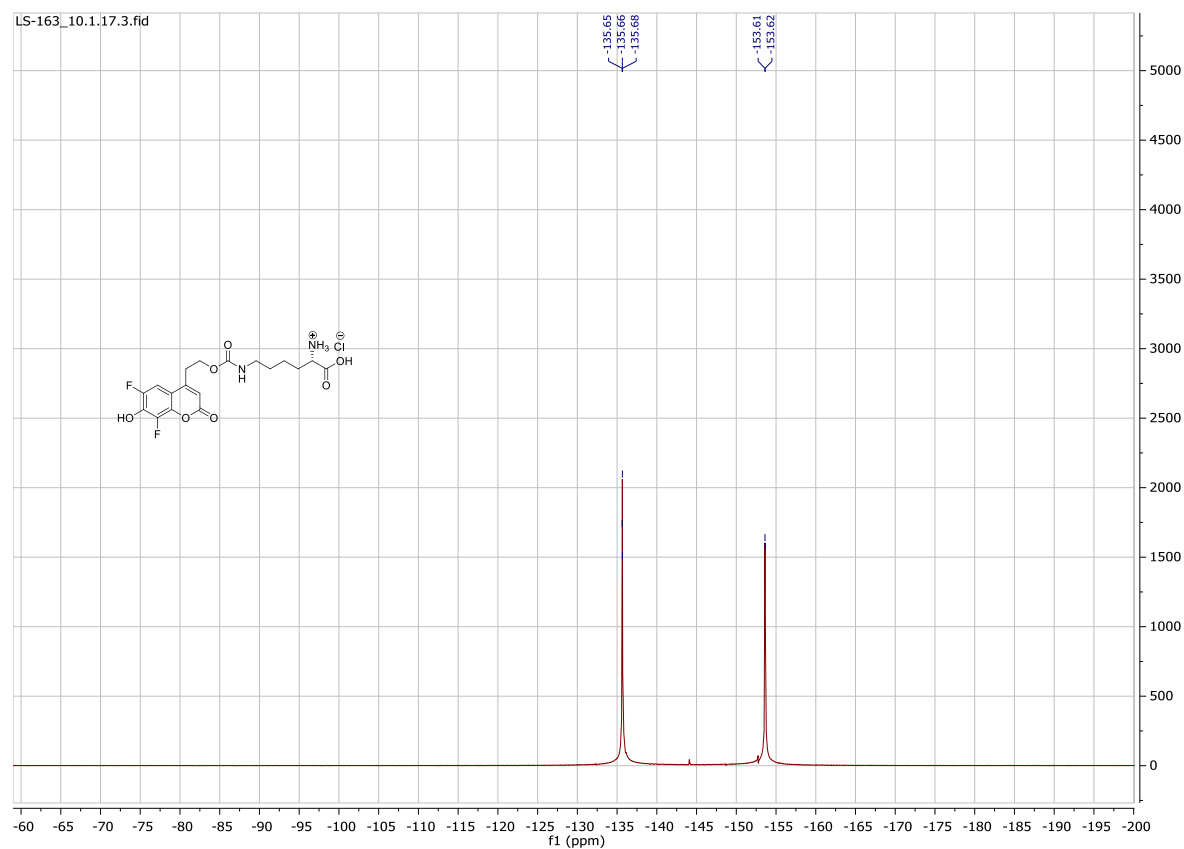


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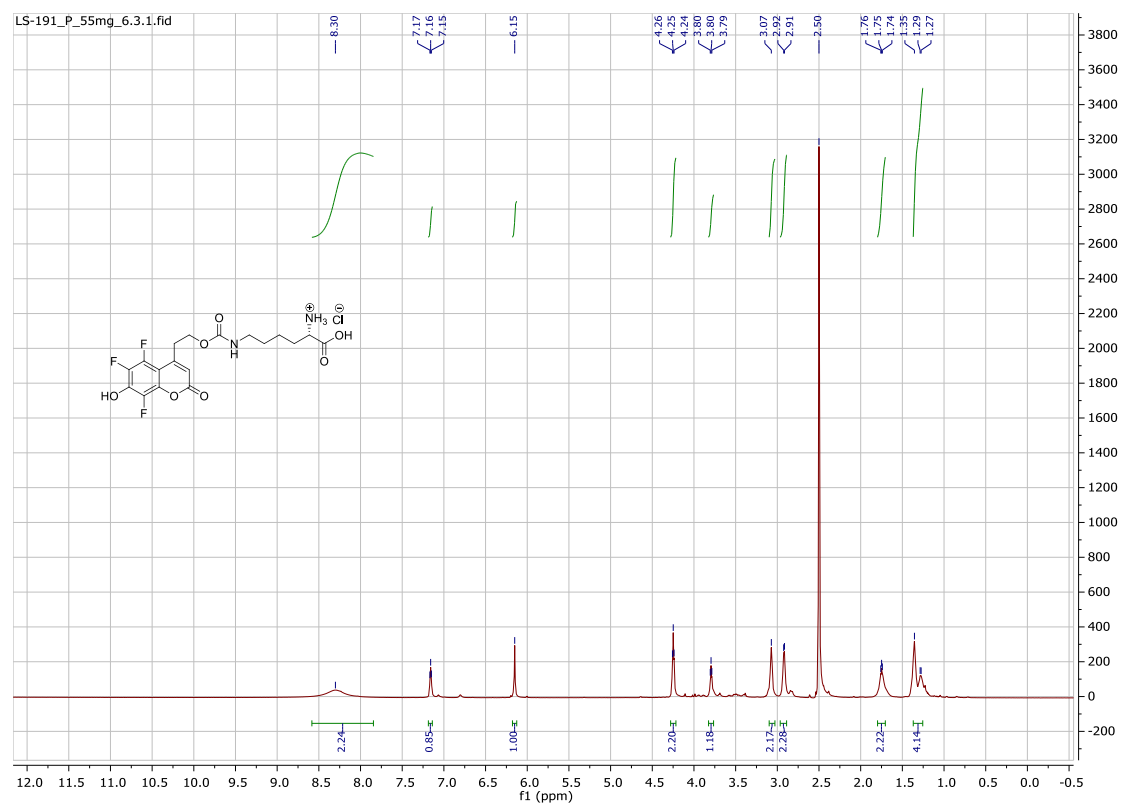




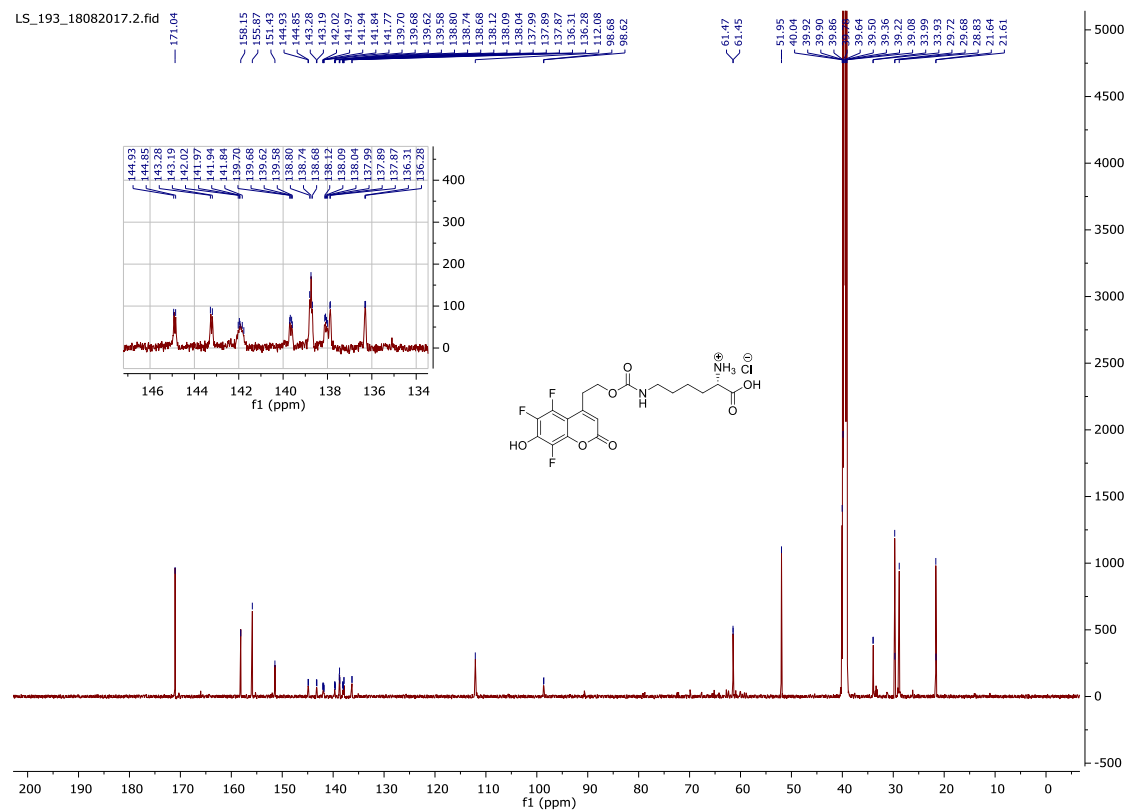
¹⁹F NMR (565 MHz, CDCl₃) of 5

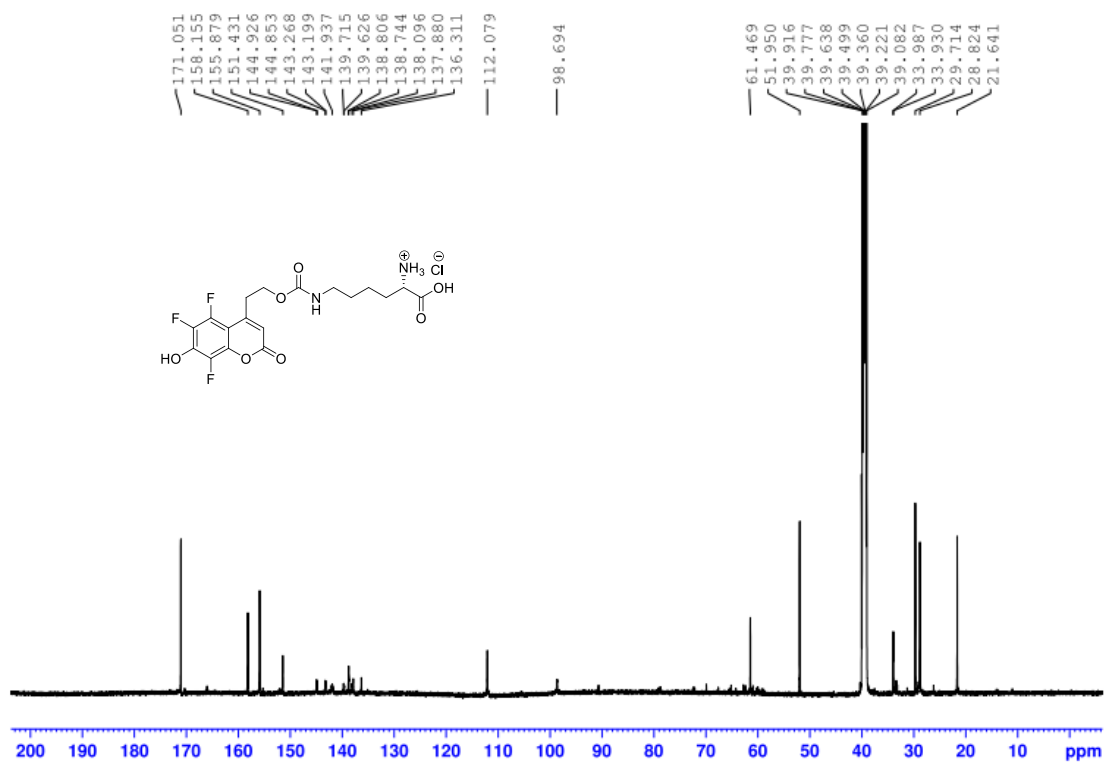
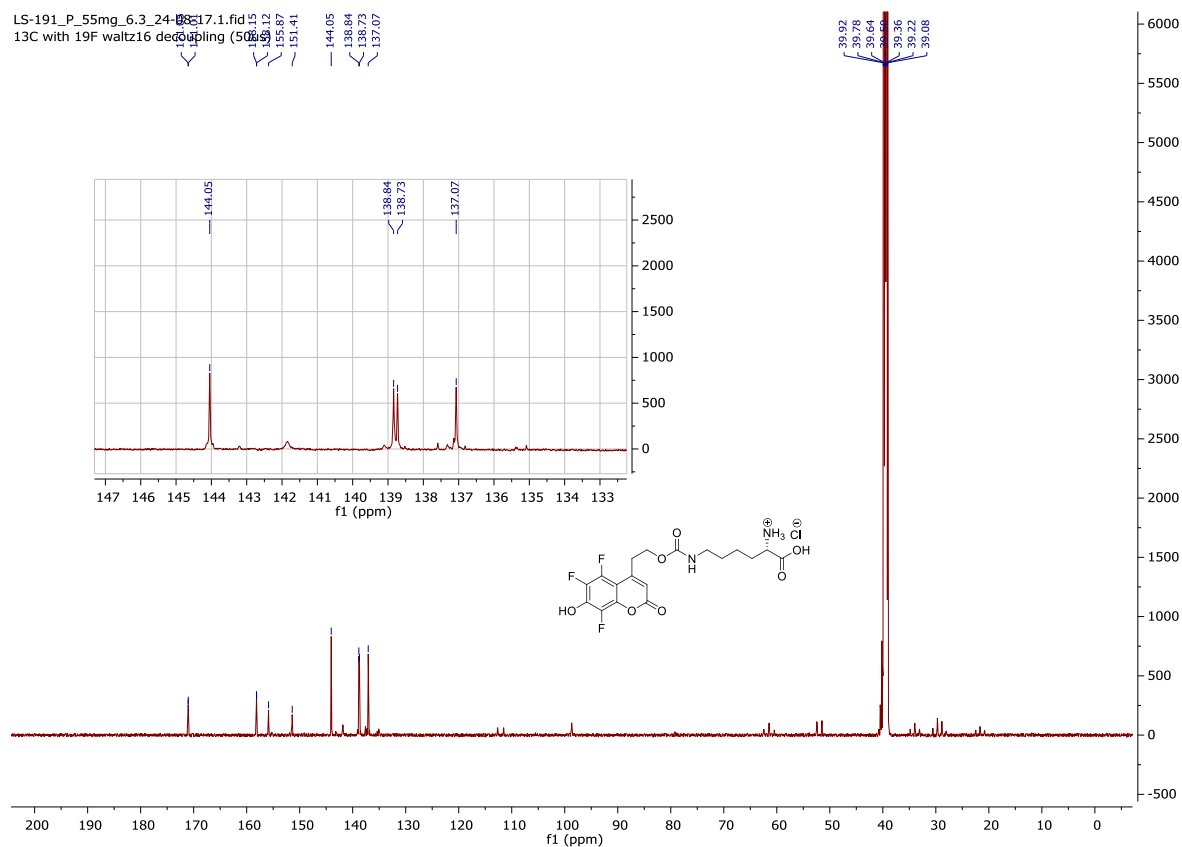


¹H NMR (600 MHz, DMSO-*d*₆) of 6

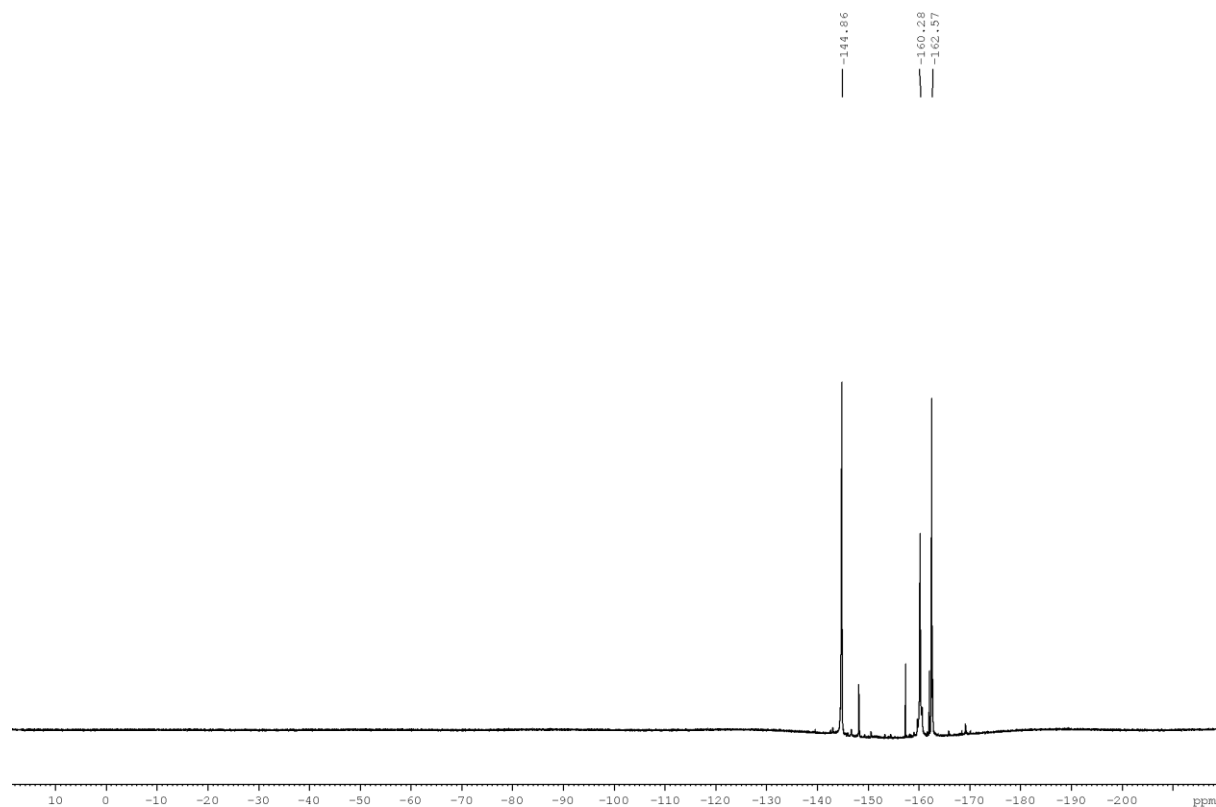


¹³C NMR (151 MHz, DMSO-*d*₆) of 6

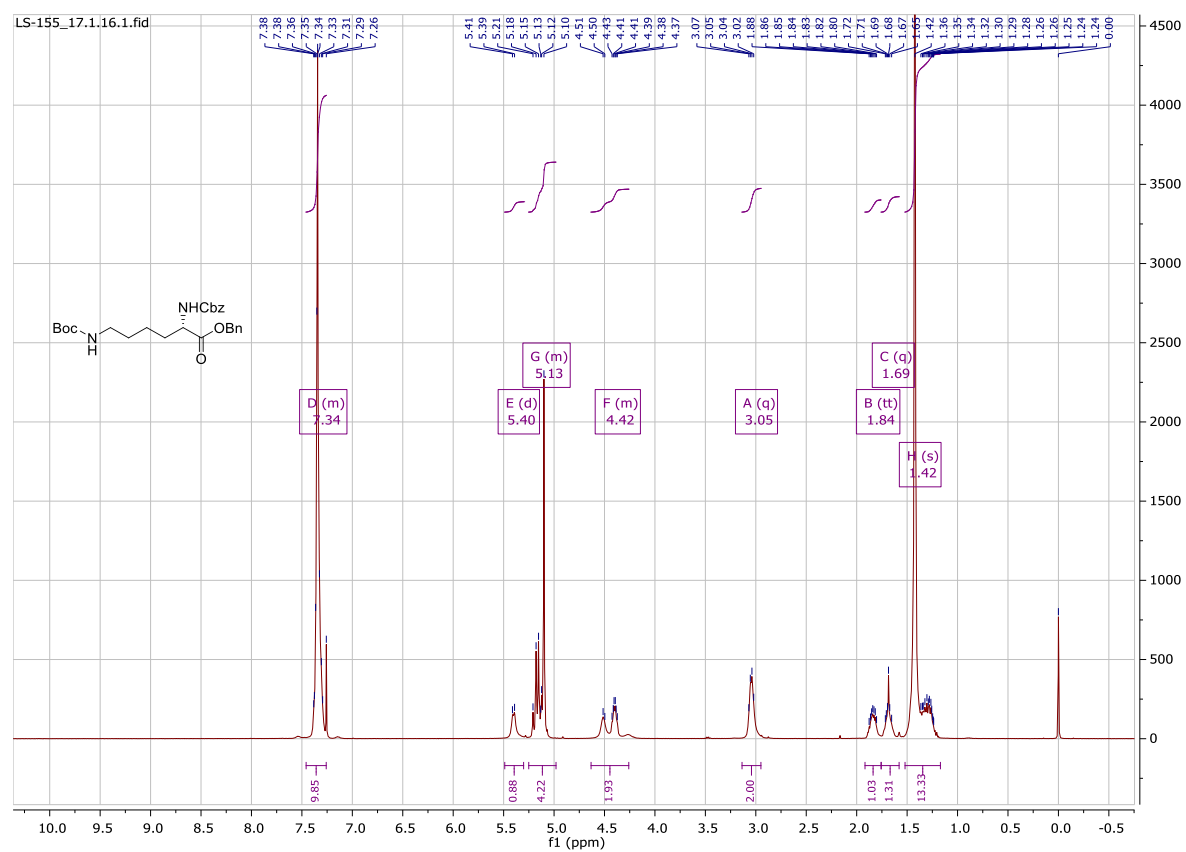




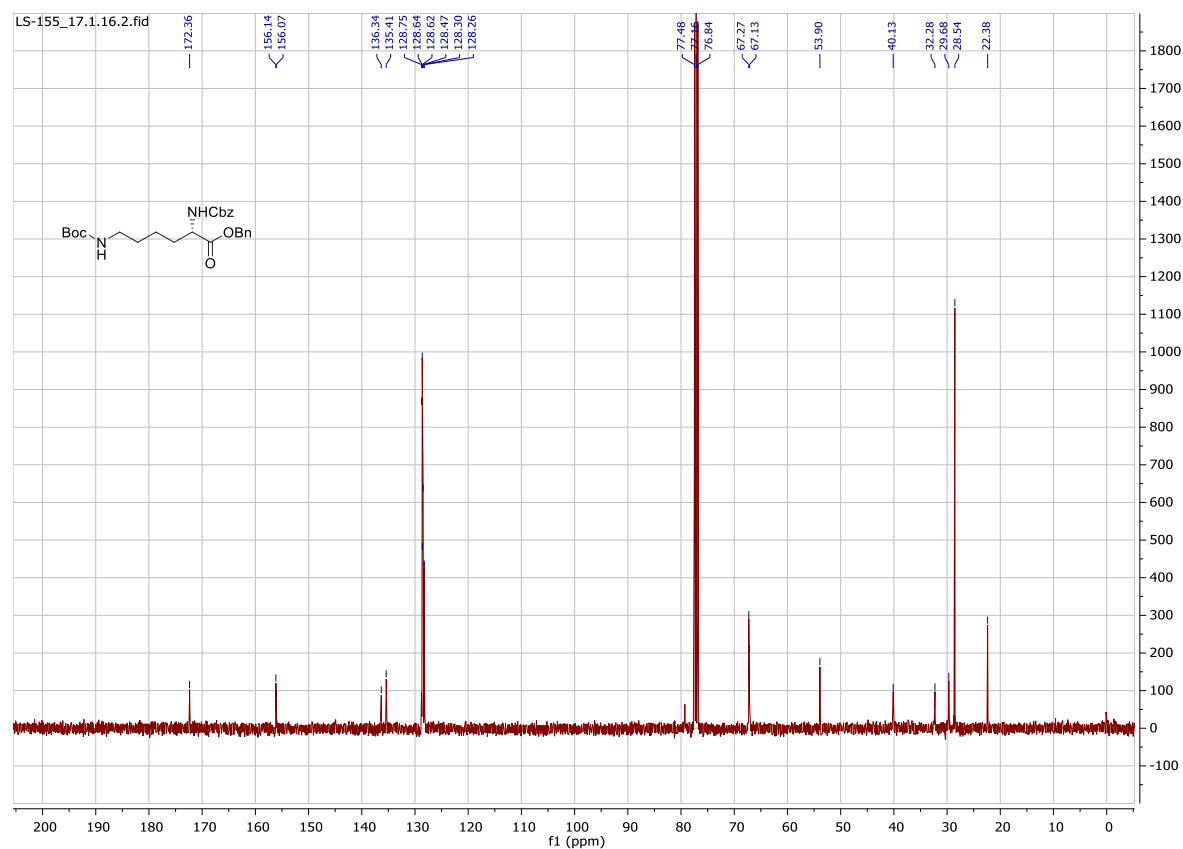
^{19}F NMR (376 MHz, CDCl_3) of 6



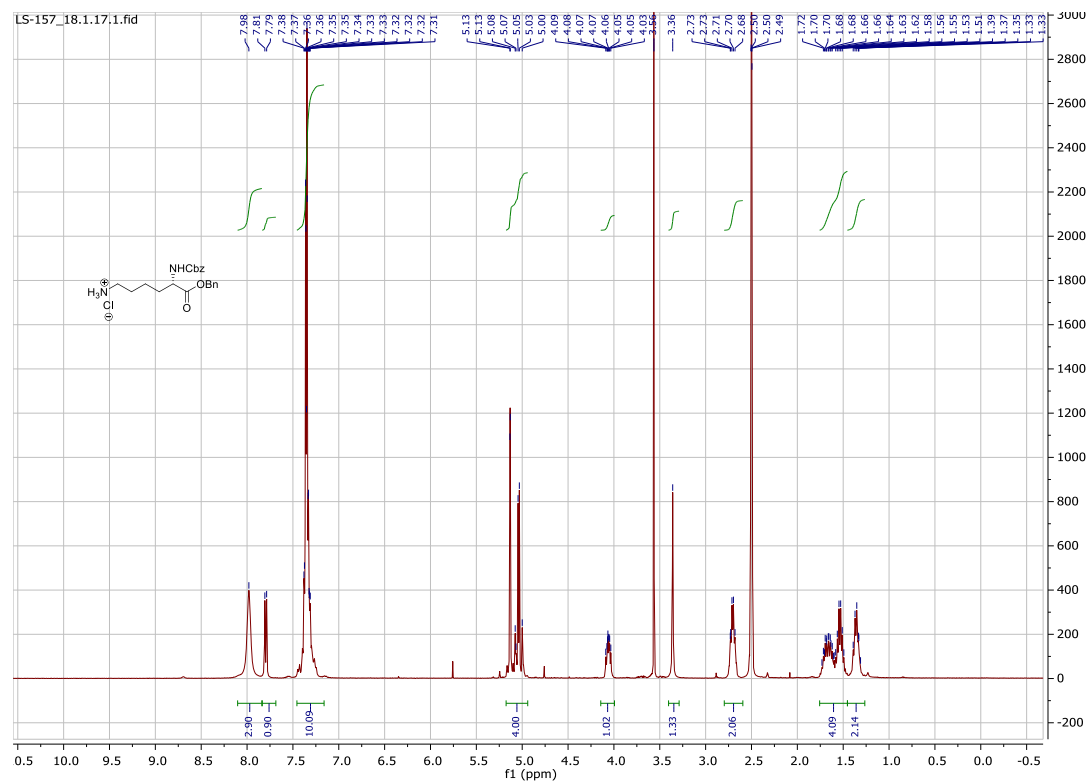
^1H NMR (400 MHz, CDCl_3) of 16



^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) of 16



^1H NMR (400 MHz, CDCl_3) of 13



LS-157_18.1.17.2.fid

Chemical structure: [NH3+]CCCC(=O)OCC1=CC=CC=C1

Peak list (ppm):

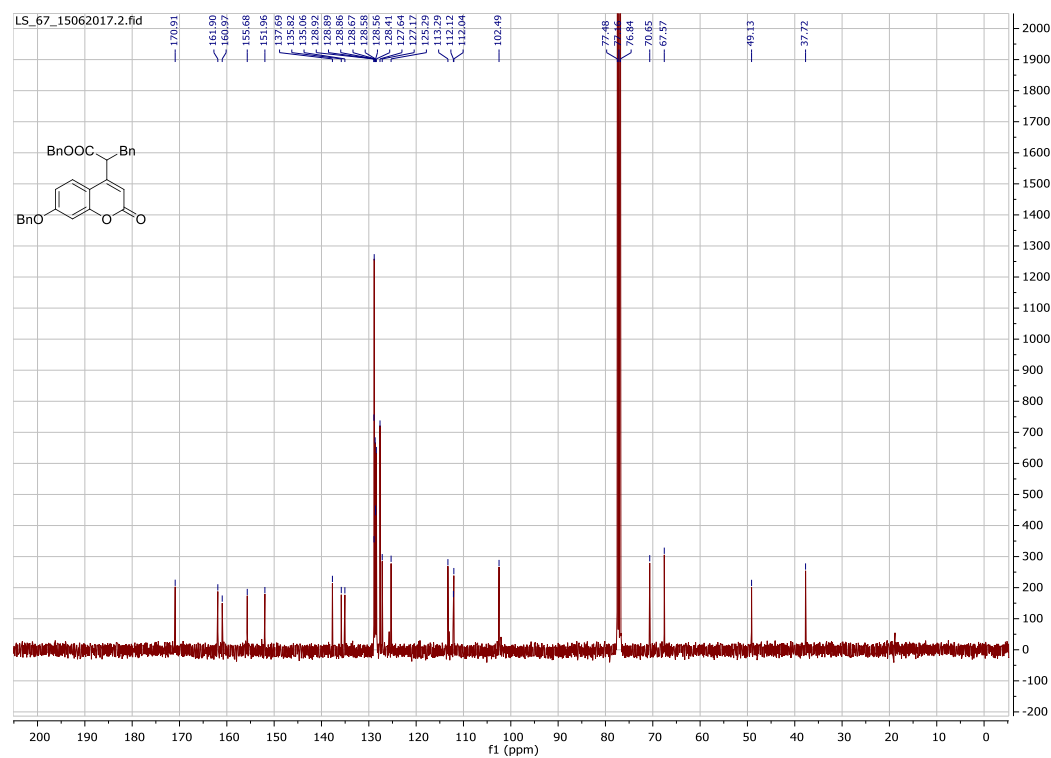
- 172.19
- 156.18
- 136.87
- 135.91
- 128.41
- 128.34
- 127.85
- 127.78
- 127.75
- 66.33
- 65.92
- 65.53
- 53.87
- 40.13
- 39.92
- 39.71
- 39.71
- 39.29
- 39.29
- 38.87
- 29.98
- 26.36
- 22.36

LS_673430620171108

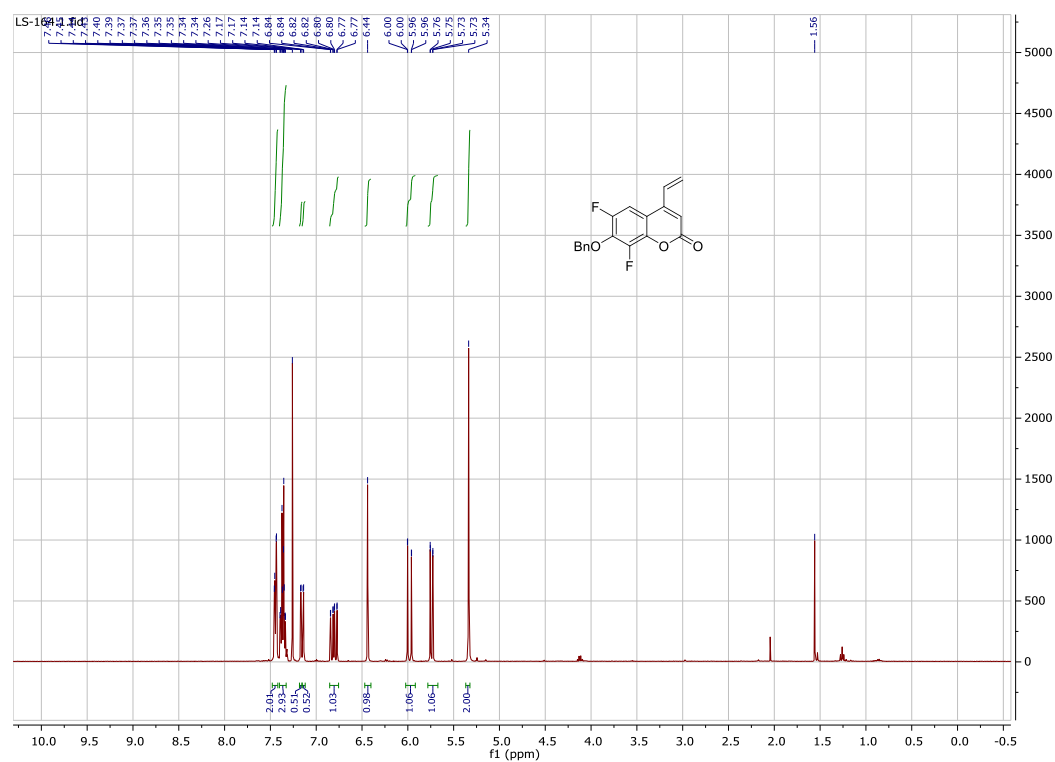
Chemical structure: O=C1C(Bn)C(=O)OC1c2ccc(Bn)cc2

¹H NMR spectrum (CDCl₃) showing peaks from 0.00 to 7.35 ppm. Integration values are provided below the peaks: 1.39, 6.43, 6.97, 4.13, 2.58, 1.00, 0.17, 2.29, 2.10, 1.10, 1.12, 1.16, and 2.39.

¹³C NMR (400 MHz, CDCl₃) of over-benzylation by-product



¹H NMR (400 MHz, CDCl₃) of elimination by-product



2. Spectroscopic Studies

UV-vis absorbance spectra were recorded on a Shimadzu UV-3101PC instrument with a compound concentration of 10 μM in KCl-HCl, citric acid- Na_2HPO_4 , trizma HCl-trizma base and Na_2CO_3 - NaHCO_3 buffer solutions. Emission spectra and lifetimes were obtained with a HORIBA Jobin Yvon Fluorolog TCSPC instrument; the absorbance in the emission wavelength range was lower than 0.1 in all measurements. The steady-state emission spectra were obtained by excitation at 320 and 360 nm, while decays were measured using LEDs at 278 and 370 nm. The quantum yields were determined relative to quinine sulfate in 0.5 M H_2SO_4 ($\Phi_f = 0.546$). Emission decays were monitored at 460 nm, and the lifetimes were analyzed using the Tcspcfit software package.¹ Solutions of the compounds in respective buffer were prepared from stock solutions in DMSO, giving a residual stock solvent concentration of $\leq 0.1\%$.

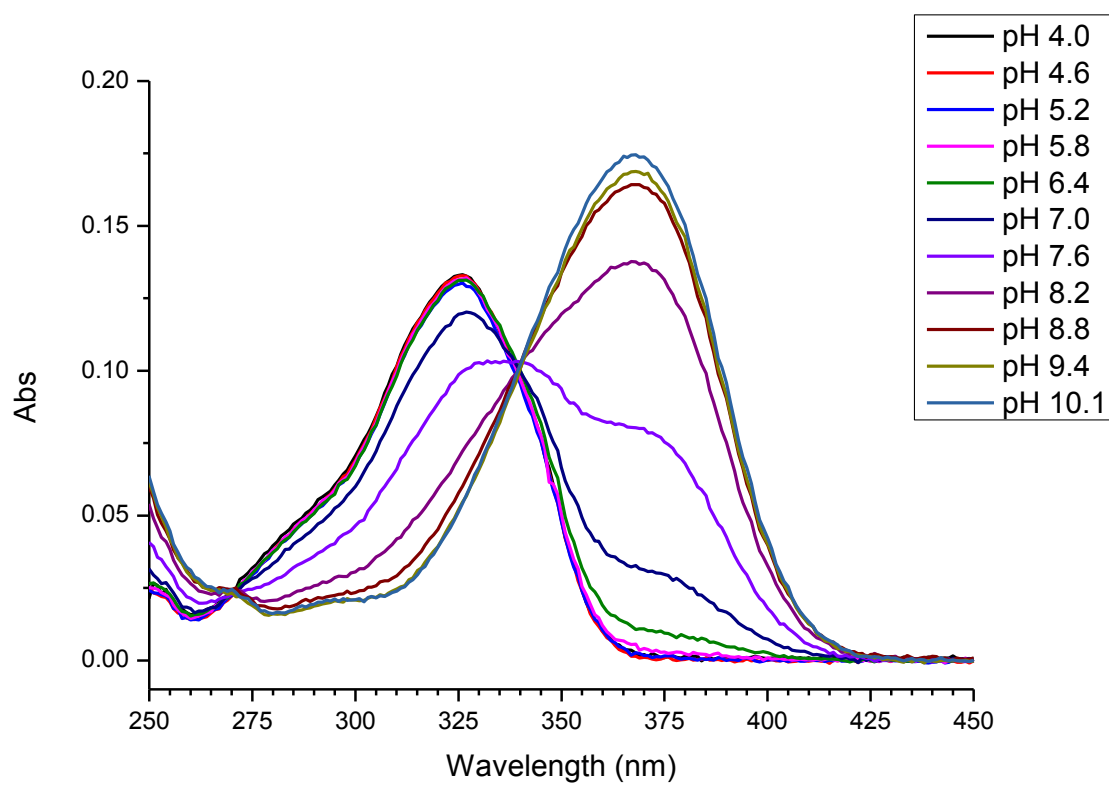


Figure S1. Absorbance of compound **1** (10 μM) at various pH:s.

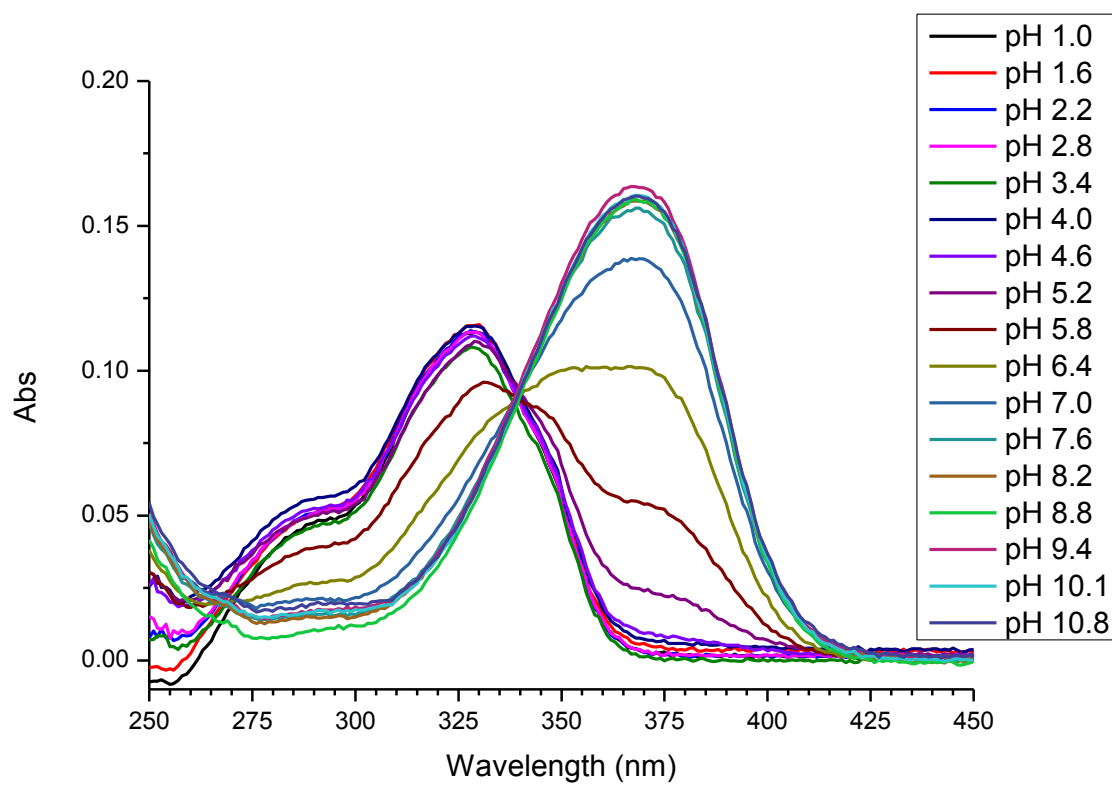


Figure S2. Absorbance of compound **4** (10 μM) at various pH:s.

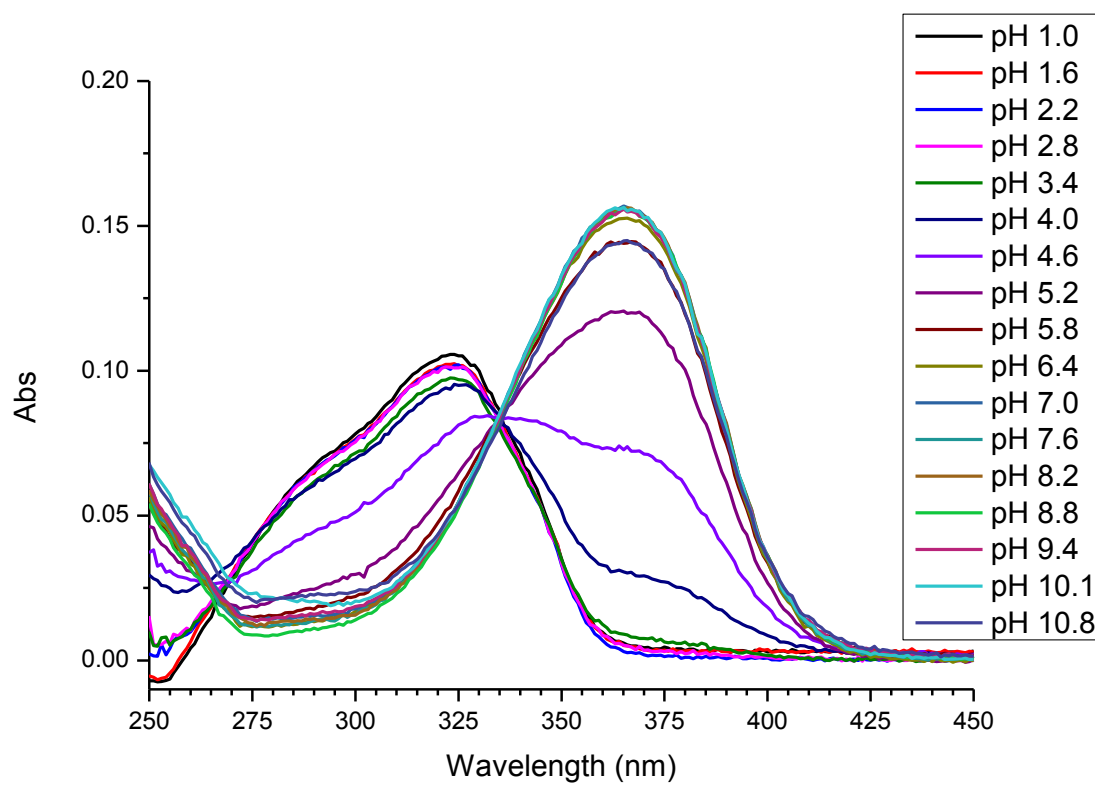


Figure S3. Absorbance of compound **5** (10 μM) at various pH:s.

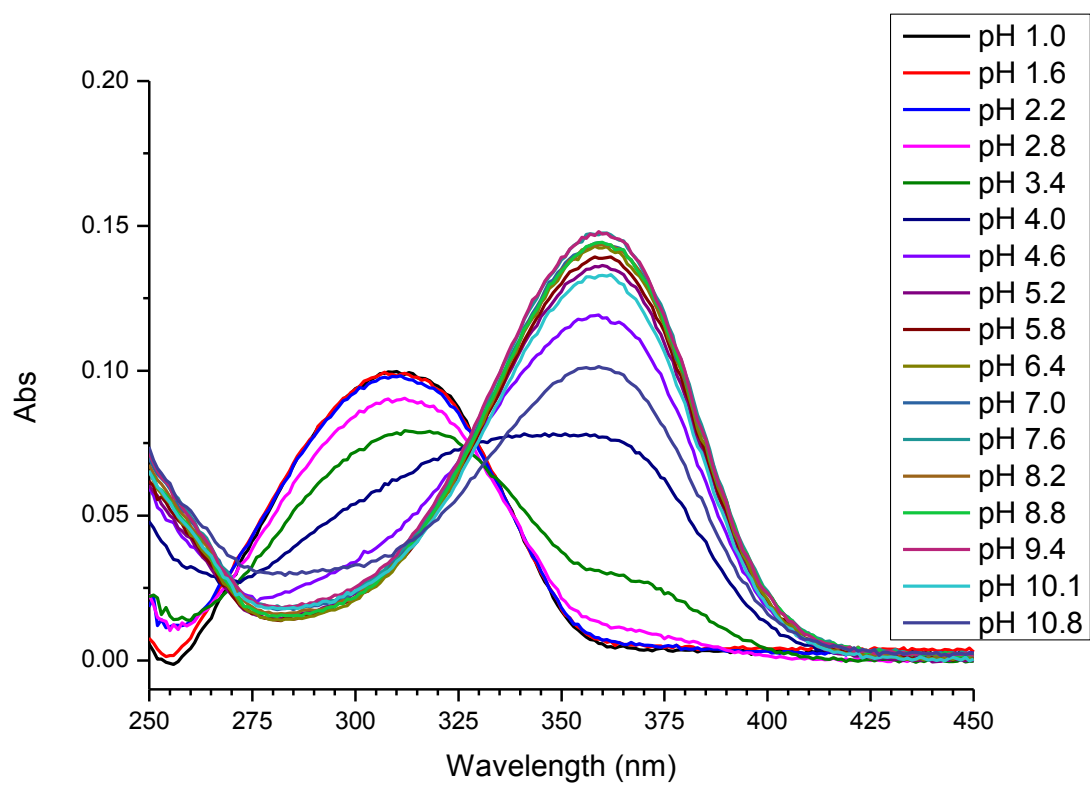


Figure S4. Absorbance of compound **6** (10 μM) at various pH:s.

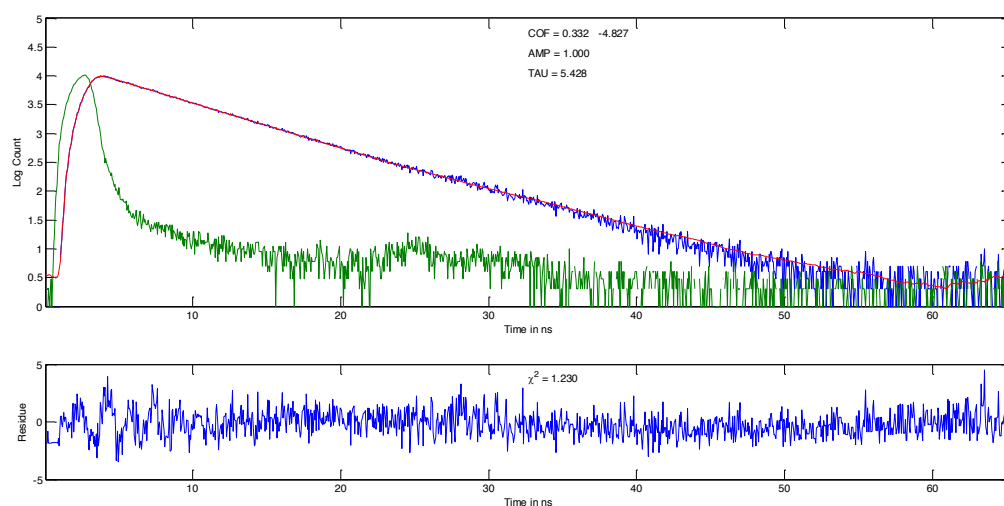


Figure S5. Fluorescence lifetime decay with fit for compound **1** (pH 10.1, ex 370 nm).

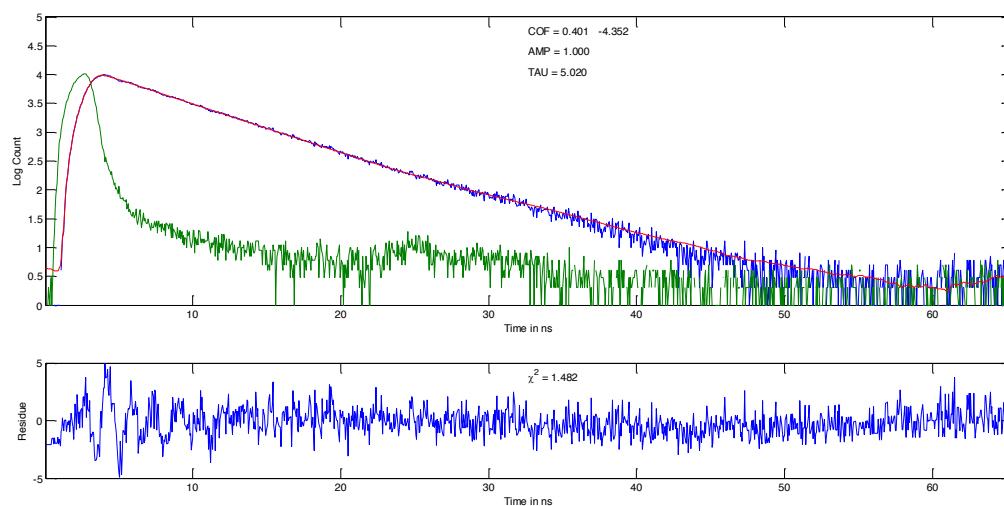


Figure S6. Fluorescence lifetime decay with fit for compound **4** (pH 10.1, ex 370 nm).

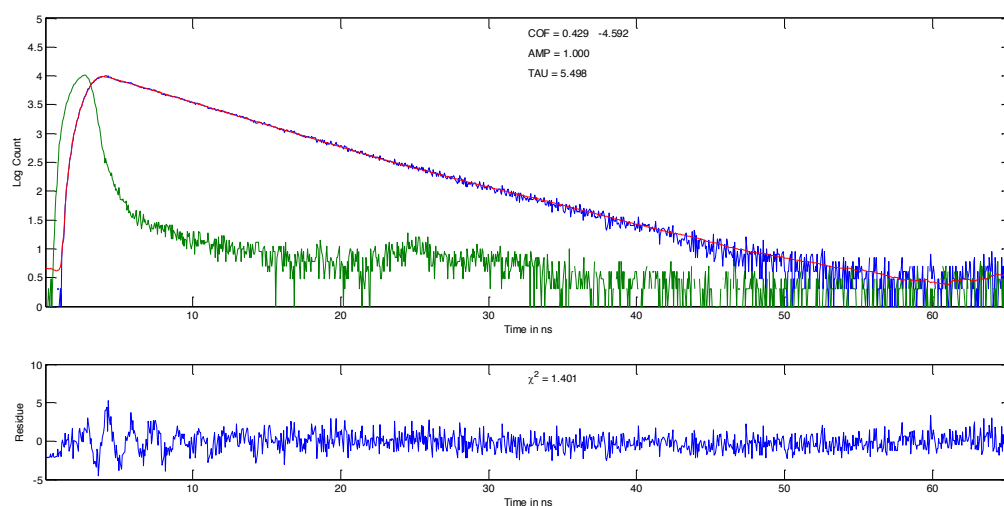


Figure S7. Fluorescence lifetime decay with fit for compound **5** (pH 10.1, ex 370 nm).

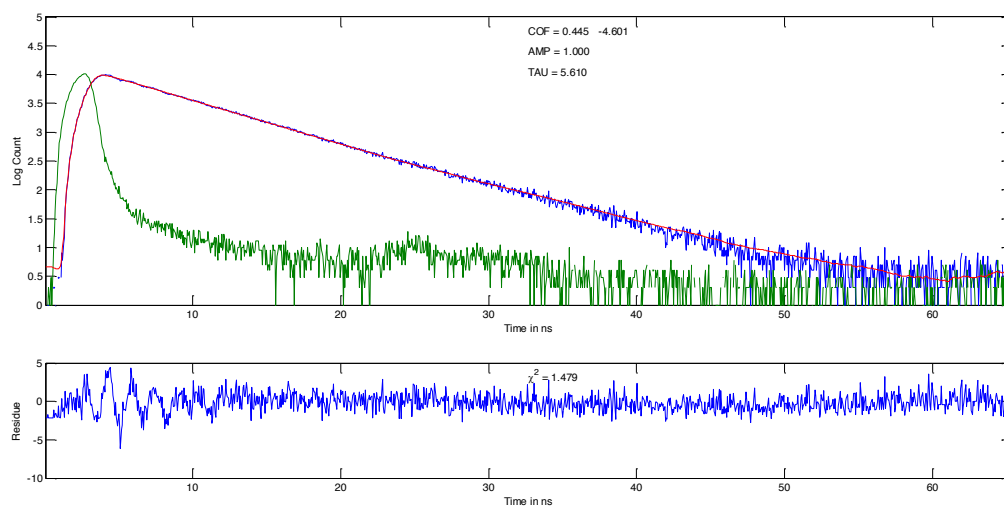


Figure S8. Fluorescence lifetime decay with fit for compound **6** (pH 10.1, ex 370 nm).

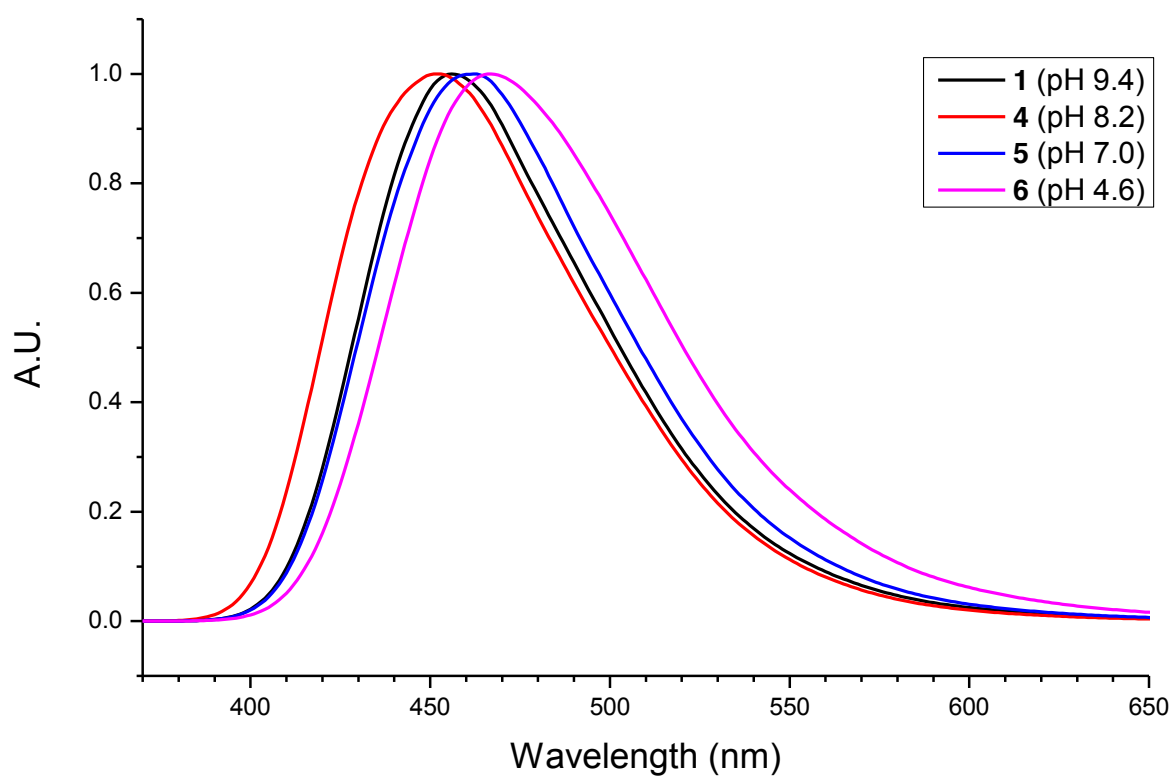


Figure S9. Smoothed and normalized emission spectra of compounds **1** and **4-6** (ex 360)

Scheme S1. Benzylation of coumarin

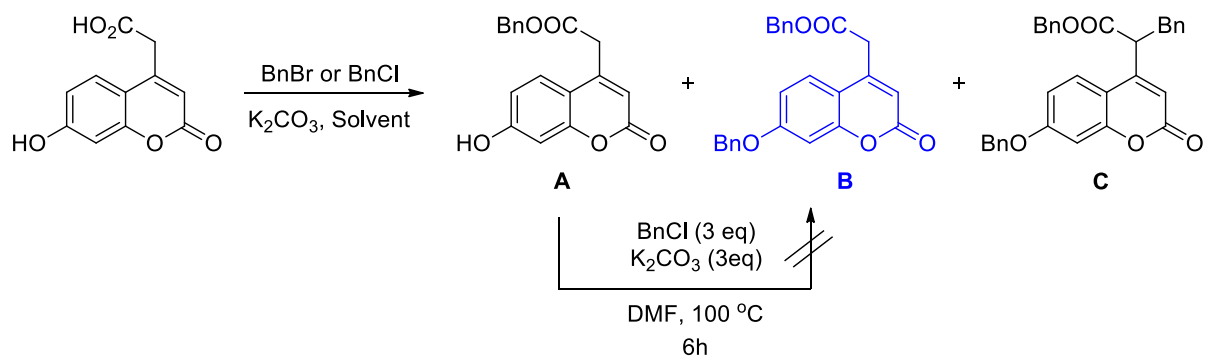
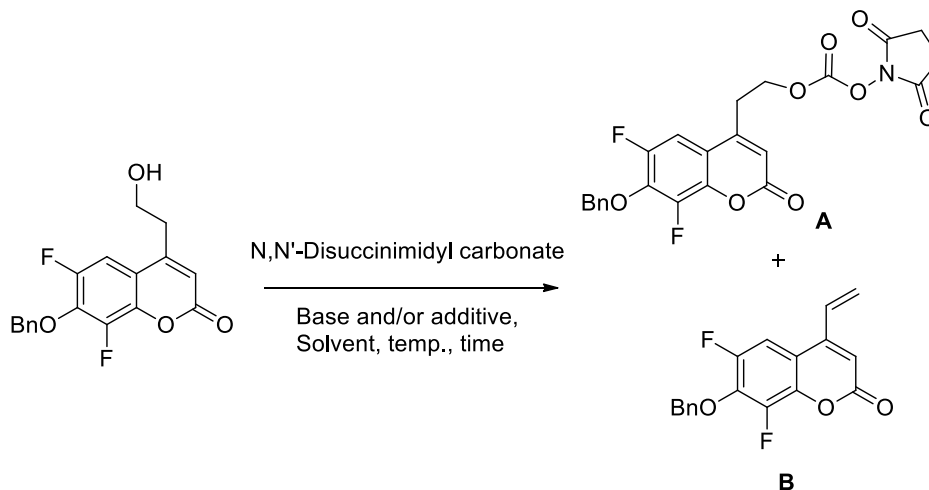


Table S1. Reaction screening conditions for benzylation of coumarin

Entry	BnBr/BnCl (eq.)	K ₂ CO ₃ (eq.)	Solvent	Temp./time	Product (A:B:C)
1	BnBr(2.5)	3	DMF	RT/2h	C+Trace A
2	BnBr (2)	2.1	DMF	RT/2h	C+Trace A

3	BnBr (2)	2.1	Acetone	RT/9h	Trace A
4	BnBr (2)	2.1	Acetone	Reflux/24h	A and C
5	BnBr (2)	2.1	Triglyme	RT/9h	Trace A
6	BnBr (2)	2.1	Triglyme	70 °C/24h	A and C
7	BnBr (2)	2.1	Toluene	RT/9h	No reaction
8	BnBr (2)	2.1	Toluene	70 °C/24h	No reaction
9	BnCl(2.0)	2.1	DMF	RT/14h	Trace A
10	BnCl(2.0)	2.1	DMF	50 °C/1.5h	20:0:0
11	BnCl(2.0)	2.1	DMF	60 °C/3.5h	40:0:0
12	BnCl(2.0)	2.1	DMF	80 °C/2.5h	100:0:0
13	BnCl(4.0)	4.2	DMF	80 °C/16h	100:0:0
14	BnCl(3.0)	3	DMF	100 °C/6h	100:0:0

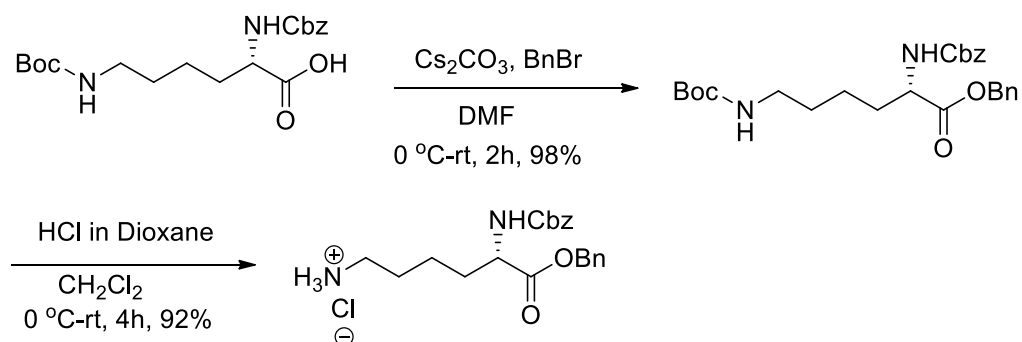
Table S2. Optimization for difluoro coumarin carbonate synthesis



Entry	Base and/or additive (eq.)	Solvent	Temp/time	A:B based on crude NMR	Yield
1	Et ₃ N (1.1 equiv.)	MeCN	0 °C-rt/1h	SM+A+B	nd
2	DIPEA (1.1 equiv.)	CH ₂ Cl ₂	0 °C-rt/12h	0:100	nd
3	Et ₃ N (1.0 equiv.)	CH ₂ Cl ₂	rt/1.5h	87:13	nd
4	DIPEA (1.0 equiv.)	CH ₂ Cl ₂	0 °C-rt/3h	68:32	nd

	+ DMAP (0.1 equiv.)				
5	DIPEA (1.0 equiv.) + DMAP (0.1 equiv.)	CH ₂ Cl ₂	0 °C-rt/3h	35:65	nd
6	DMAP (0.5 equiv.)	CH ₂ Cl ₂	rt/15min.	95:5	nd
7	DMAP (0.2+0.2 equiv.)	CH ₂ Cl ₂	0 °C- rt/30min	97:3	nd
8	DMAP (total 0.15 equiv. in 2 portions)	CH ₂ Cl ₂	0 °C-rt/42h	100:0	Quant.
9	DMAP (0.15 equiv.)	CH ₂ Cl ₂	0 °C-rt/15h	100:0	Quant.

nd: yield not determined



Scheme S2. Synthesis of CBz and benzyl protected lysine hydrochloride

References

- (1) J. Enderlein, R. Erdmann, *Optics Communications* **1997**, 134, 371.