

## Electronic Supplementary Information

for

### Two-stage one-pot synthetic strategy for the key triazone-triazole intermediate of ensitrelvir (S-217622), an oral clinical candidate for treating COVID-19

Wei Hu,<sup>a</sup> Xiang Zhang,<sup>a</sup> Yuanchang Liu,<sup>a</sup> Teng Liu,<sup>a</sup> Jiale Wen,<sup>a</sup> Xiaopeng Peng,<sup>a,b</sup> Xin

Xie,<sup>\*a,b</sup> Weiming Chen<sup>\*a,b</sup>

<sup>a</sup> School of Pharmaceutical Sciences; <sup>b</sup> Key Laboratory of Prevention and Treatment of  
Cardiovascular and Cerebrovascular Disease, Ministry of Education,  
Gannan Medical University, Ganzhou 341000, Jiangxi, China.

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## HPLC methods for compound 2,4, 8, 9 and 10

a) Sample preparation: about 0.100 mg/mL for compound 2, 4, 8, and 9; about 0.127 mg/mL for compound 10. The solution was filtered and performed HPLC test as following method.

b) HPLC method:

Equipment: Waters e2695 Separation Module

Column: Inertsustain™ 5 μm, 4.6×250 mm

Mobile phase: 50% acetonitrile in water

Dilute: 50% acetonitrile in water

Flow: 1 mL/min

Wavelength: 254 nm

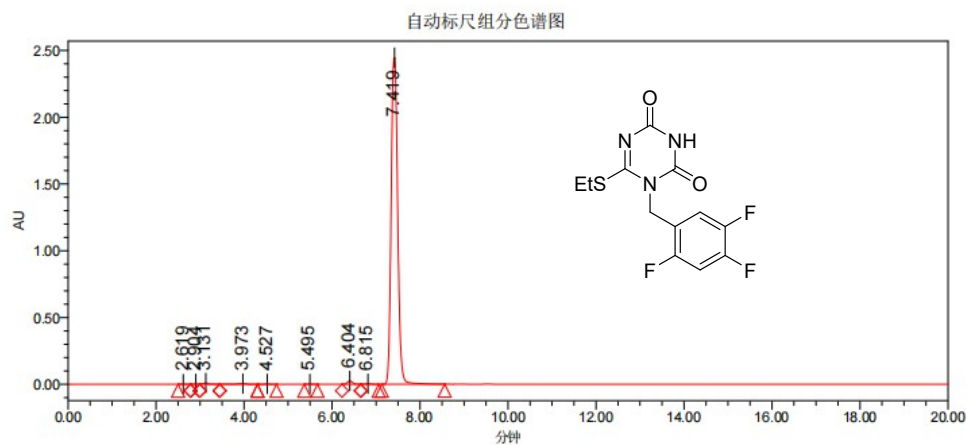
Column Temp: 25°C

Volume: 10 μL

Time: 20 min

c) Data Treatment

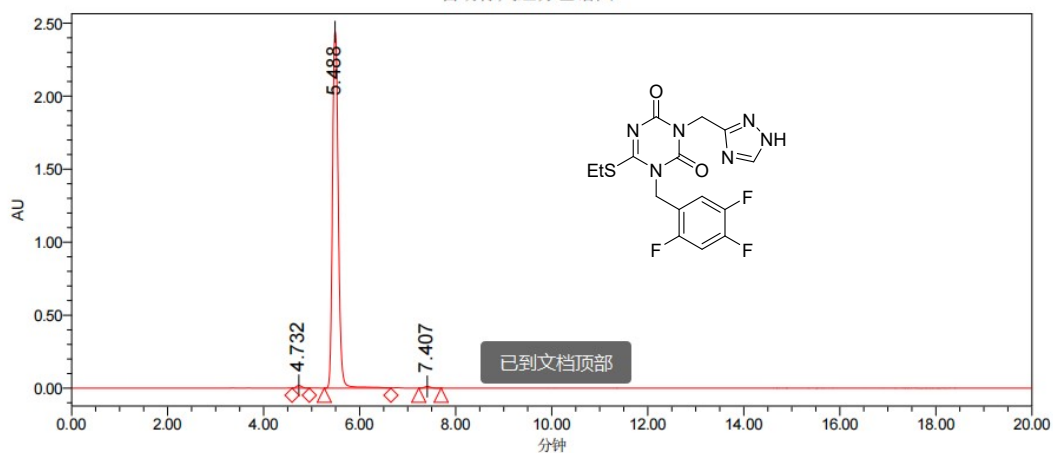
RRT: 7.419 min for compound 2; 7.100 min for compound 4; 5.488 min for compound 8;  
7.701 min for compound 9; 12.711 min for compound 10



处理通道说明: 2998 Ch1 254 纳米@4.8 纳米

	处理通道说明	保留时间 (分钟)	面积 (微伏秒)	% 面积	高度 (微伏)
1	2998 Ch1 254 纳米@4.8 纳米	2.619	11767	0.05	1778
2	2998 Ch1 254 纳米@4.8 纳米	2.904	16468	0.06	2916
3	2998 Ch1 254 纳米@4.8 纳米	3.131	92162	0.36	10497
4	2998 Ch1 254 纳米@4.8 纳米	3.973	96741	0.38	5529
5	2998 Ch1 254 纳米@4.8 纳米	4.527	21840	0.09	3160
6	2998 Ch1 254 纳米@4.8 纳米	5.495	11823	0.05	1771
7	2998 Ch1 254 纳米@4.8 纳米	6.404	205155	0.80	25593
8	2998 Ch1 254 纳米@4.8 纳米	6.815	39992	0.16	4524
9	2998 Ch1 254 纳米@4.8 纳米	7.419	25002679	98.06	2444715

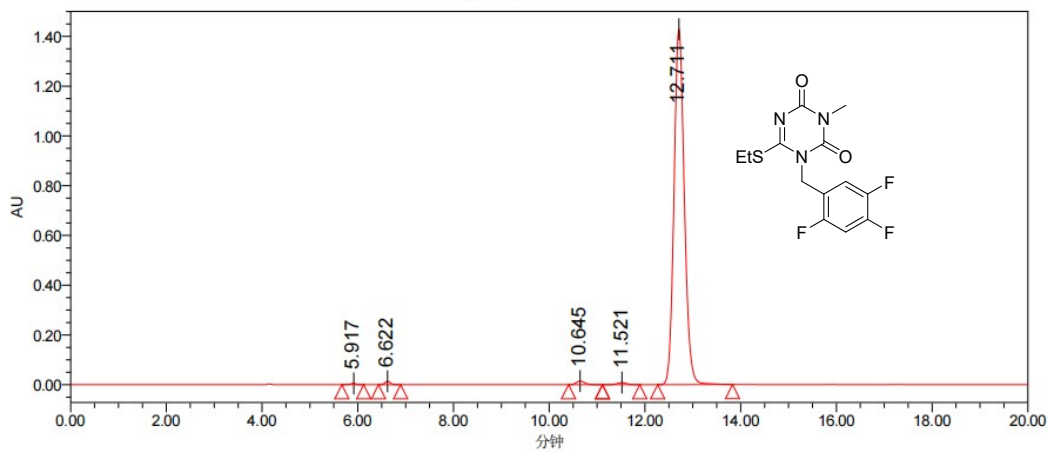
自动标尺组分色谱图



处理通道说明: 2998 Ch1 254 纳米@4.8 纳米

	处理通道说明	保留时间 (分钟)	面积 (微伏秒)	% 面积	高度 (微伏)
1	2998 Ch1 254 纳米@4.8 纳米	4.732	149710	0.72	18011
2	2998 Ch1 254 纳米@4.8 纳米	5.488	20642832	98.79	2441243
3	2998 Ch1 254 纳米@4.8 纳米	7.407	103461	0.50	11575

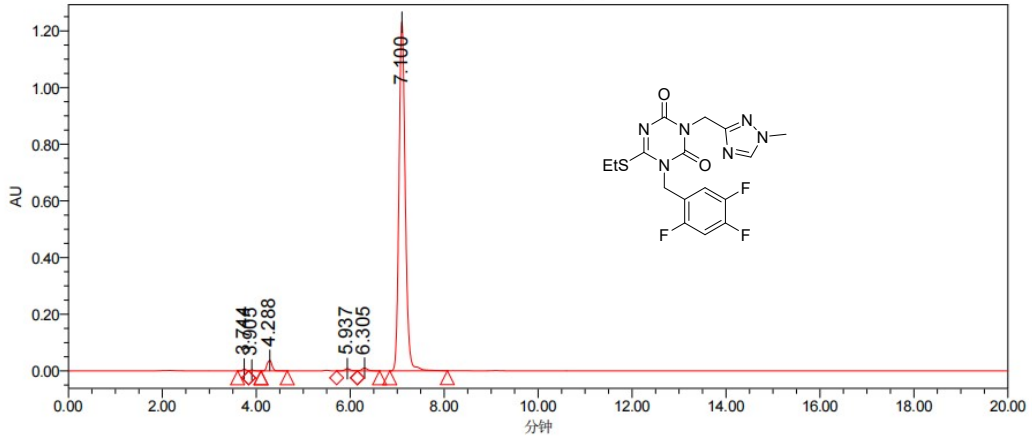
自动标尺组分色谱图



处理通道说明: 2998 Ch1 254 纳米@4.8 纳米

	处理通道说明	保留时间 (分钟)	面积 (微伏秒)	% 面积	高度 (微伏)
1	2998 Ch1 254 纳米@4.8 纳米	5.917	46878	0.21	5359
2	2998 Ch1 254 纳米@4.8 纳米	6.622	108834	0.50	13360
3	2998 Ch1 254 纳米@4.8 纳米	10.645	182641	0.84	14635
4	2998 Ch1 254 纳米@4.8 纳米	11.521	115516	0.53	8437
5	2998 Ch1 254 纳米@4.8 纳米	12.711	21357171	97.92	1428295

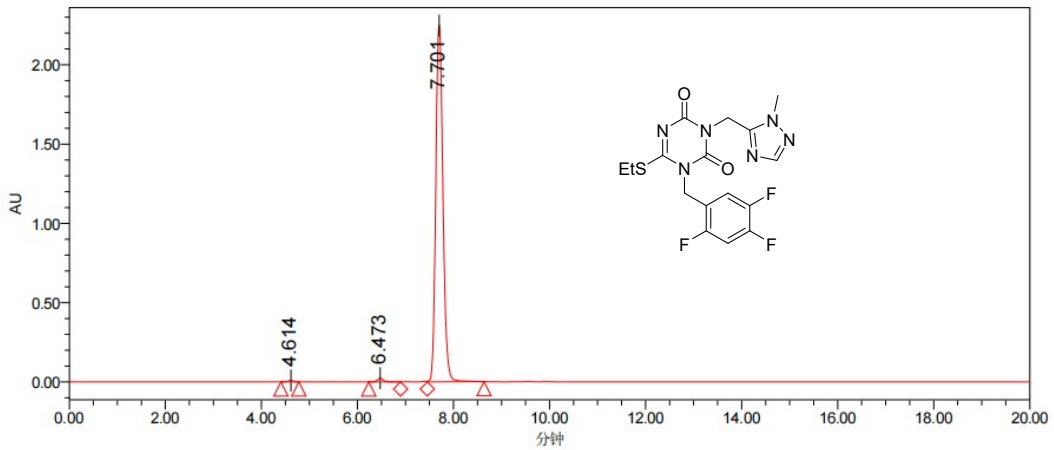
自动标尺组分色谱图



处理通道说明: 2998 Ch1 254 纳米@4.8 纳米

	处理通道说明	保留时间 (分钟)	面积 (微伏秒)	% 面积	高度 (微伏)
1	2998 Ch1 254 纳米@4.8 纳米	3.744	33507	0.28	6211
2	2998 Ch1 254 纳米@4.8 纳米	3.905	18630	0.16	3120
3	2998 Ch1 254 纳米@4.8 纳米	4.288	273643	2.29	37101
4	2998 Ch1 254 纳米@4.8 纳米	5.937	68231	0.57	7649
5	2998 Ch1 254 纳米@4.8 纳米	6.305	87704	0.74	9929
6	2998 Ch1 254 纳米@4.8 纳米	7.100	11442119	95.96	1230699

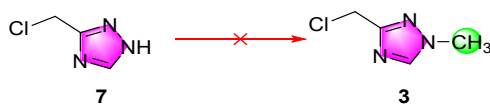
自动标尺组分色谱图



处理通道说明: 2998 Ch1 254 纳米@4.8 纳米

	处理通道说明	保留时间 (分钟)	面积 (微伏秒)	% 面积	高度 (微伏)
1	2998 Ch1 254 纳米@4.8 纳米	4.614	72660	0.31	9074
2	2998 Ch1 254 纳米@4.8 纳米	6.473	197562	0.84	23153
3	2998 Ch1 254 纳米@4.8 纳米	7.701	23293388	98.85	2246756

***Trials of preparation 3 from 7***

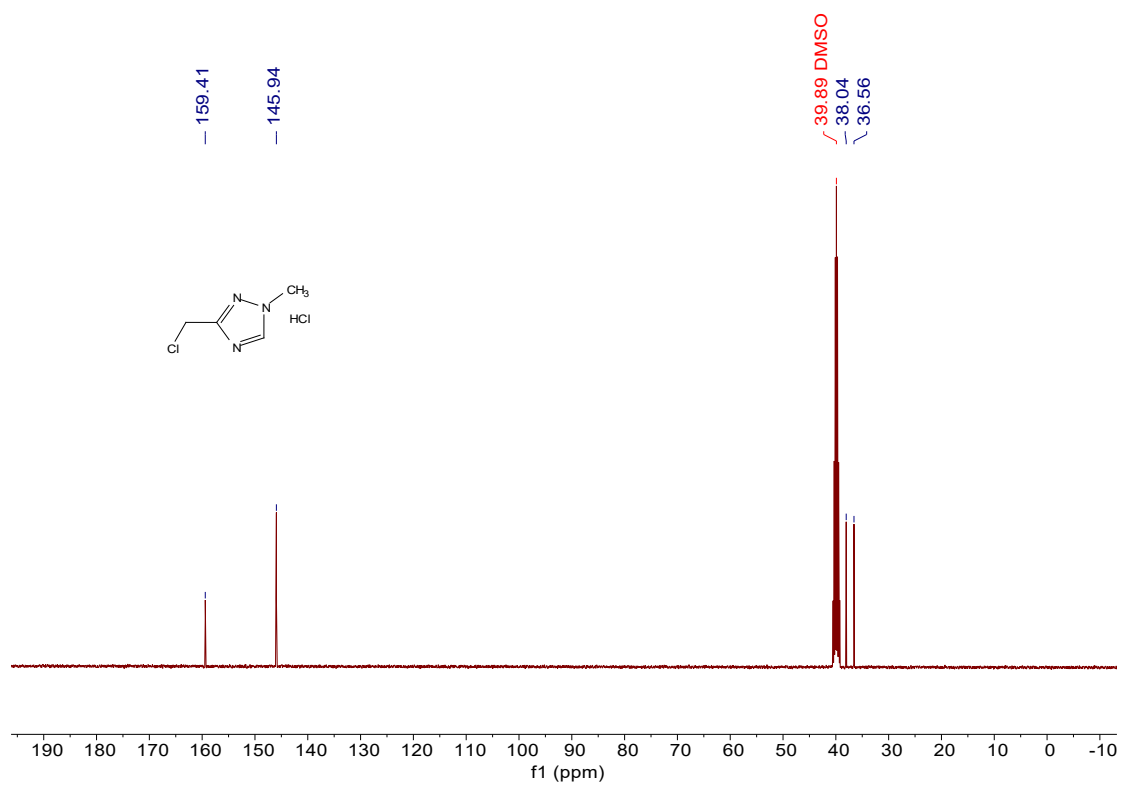
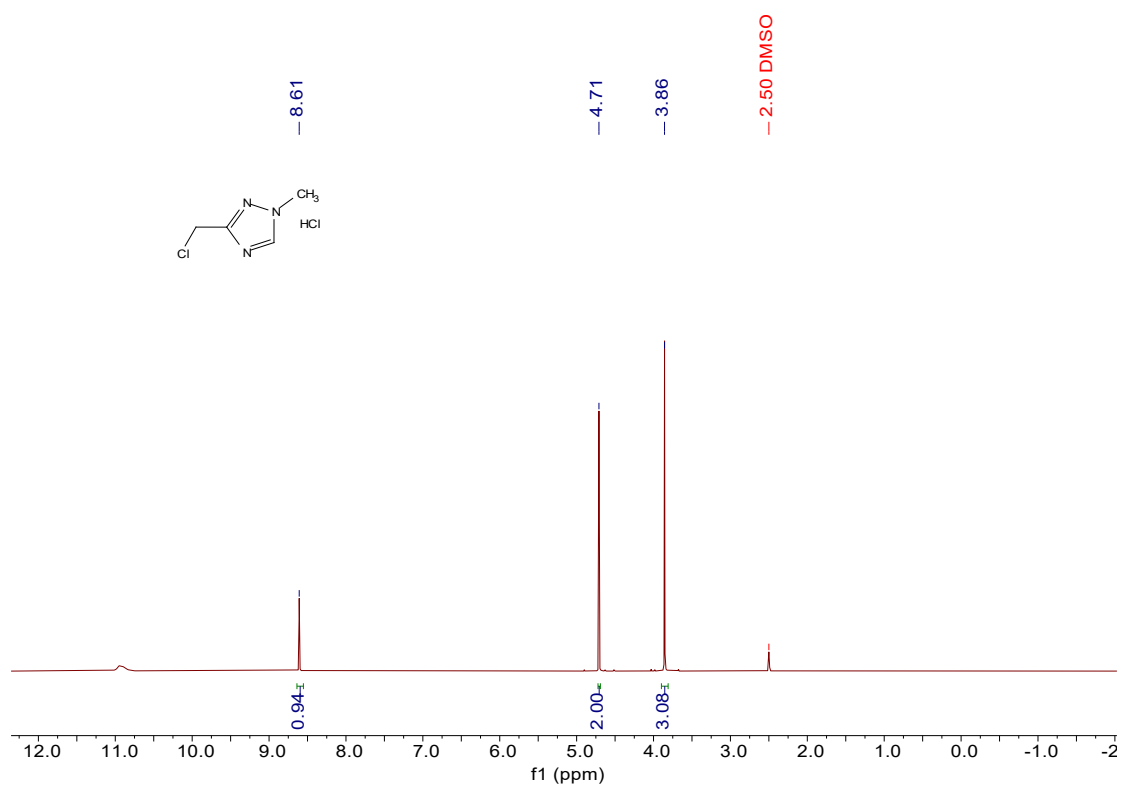


Entry	Reagents and conditions <sup>a</sup>	Yield <sup>b</sup>
1	TEA (1.2 equiv.), MeI (1.1 equiv.), DCM	No product
2	K <sub>2</sub> CO <sub>3</sub> (2.2 equiv.), MeI (1.1 equiv.), DMF	No product
3	K <sub>2</sub> CO <sub>3</sub> (2.2 equiv.), MeI (1.1 equiv.), ACN	No product
4	K <sub>2</sub> CO <sub>3</sub> (2.2 equiv.), MeI (1.1 equiv.), Acetone	No product
5	K <sub>2</sub> CO <sub>3</sub> (2.2 equiv.), Me <sub>2</sub> SO <sub>4</sub> (1.1 equiv.), Acetone	No product
6	Ph <sub>3</sub> P (1.1 equiv.), DIAD (1.1 equiv.), CH <sub>3</sub> OH	No product
7	Me <sub>3</sub> O <sup>+</sup> BF <sub>4</sub> <sup>-</sup> (1.1 equiv.), EA	No product

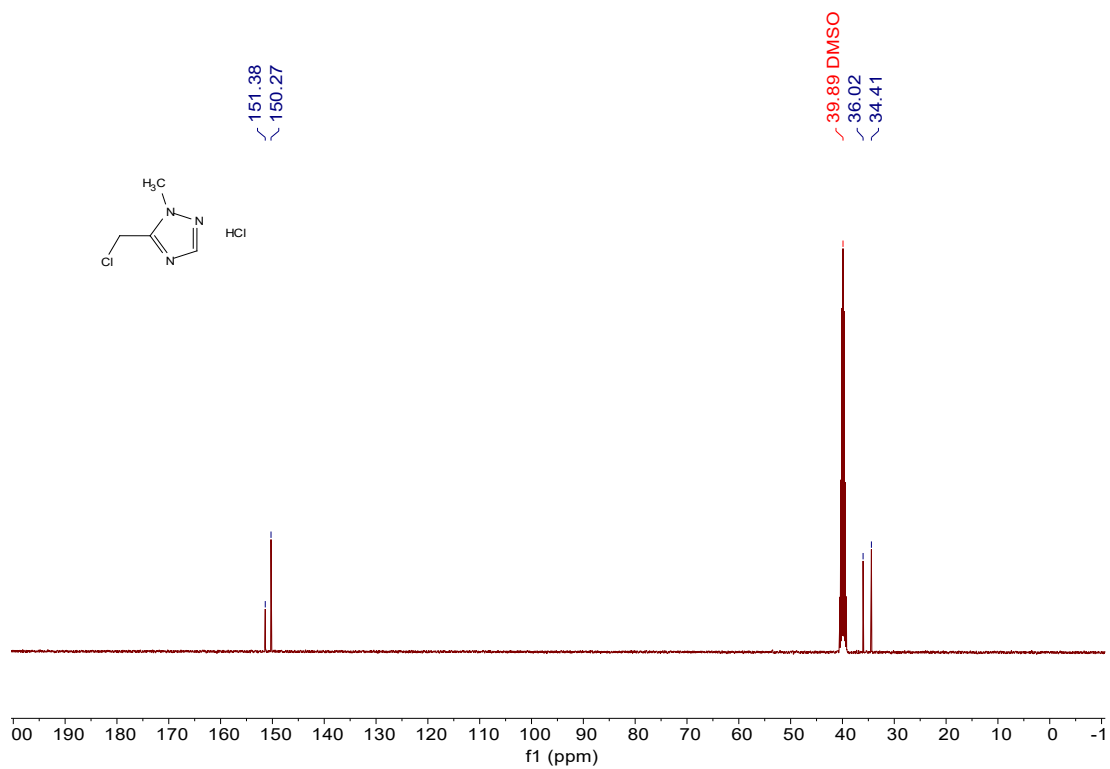
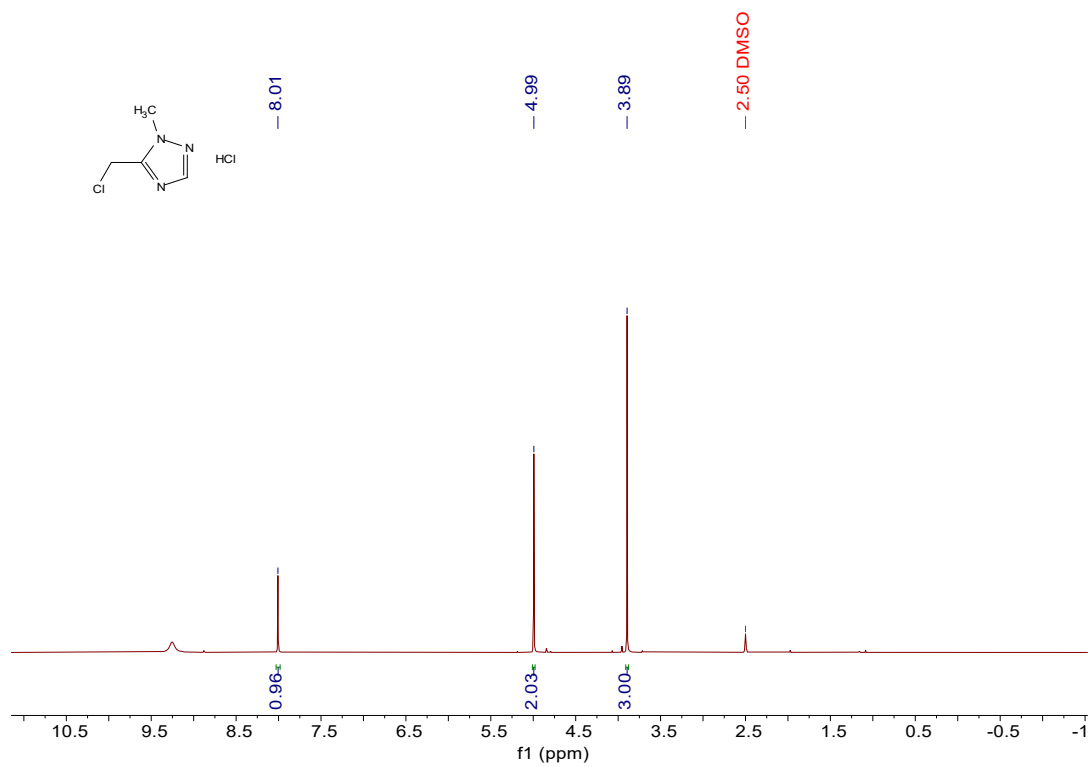
Notes: <sup>a</sup> 100 mg of base **7** was used for reaction. <sup>b</sup> By TLC.

## SPECTROSCOPIC DATA

$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO-}d_6$  of compound **3**

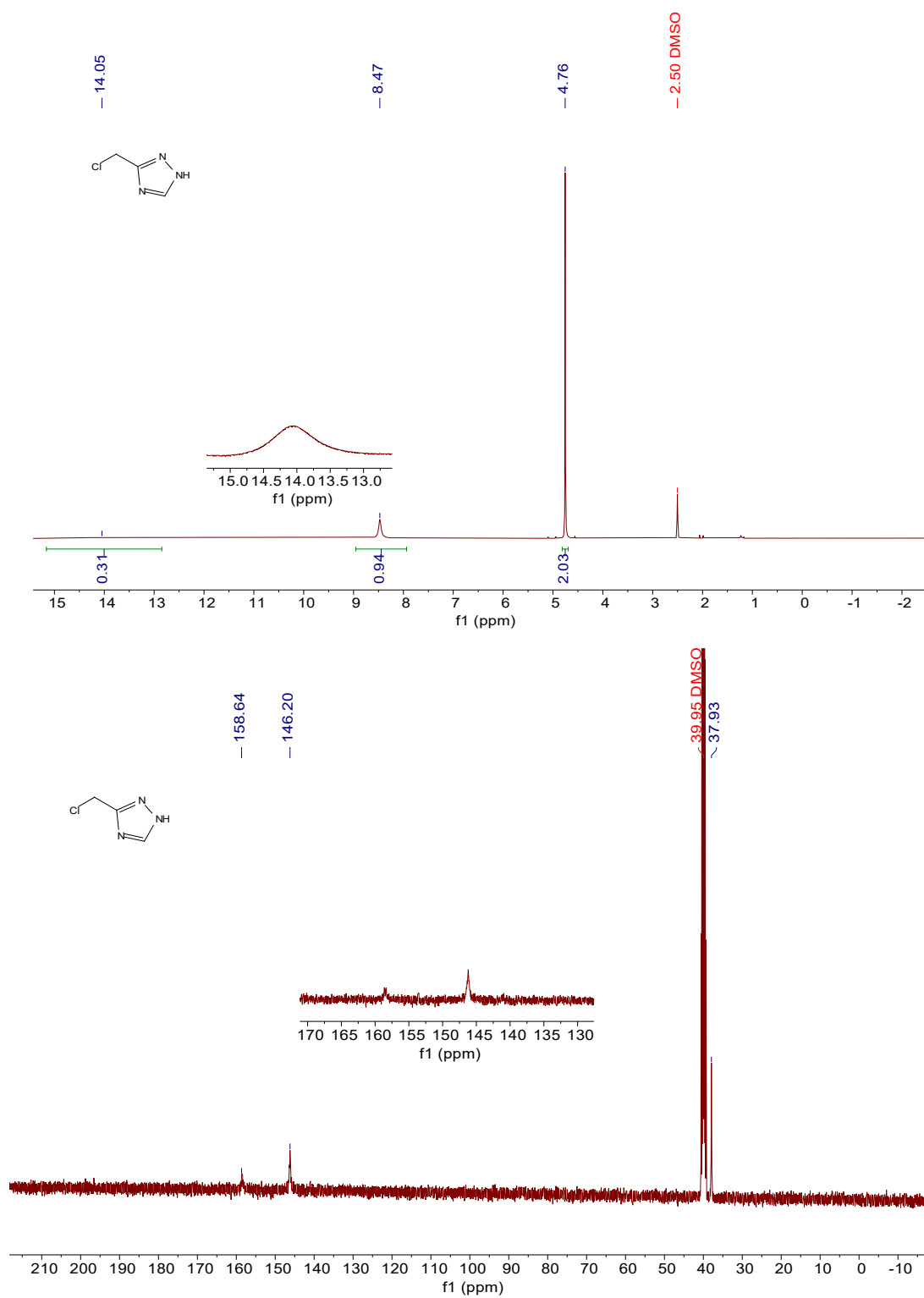


$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO-}d_6$  of compound **3a**

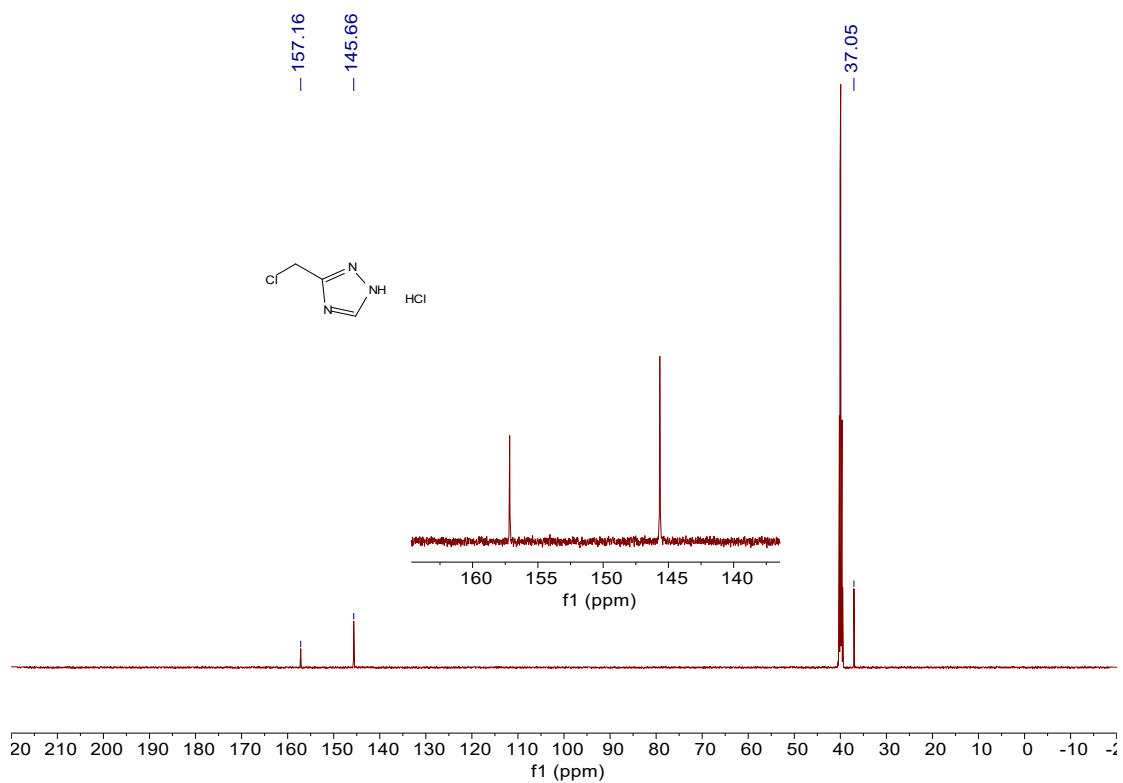
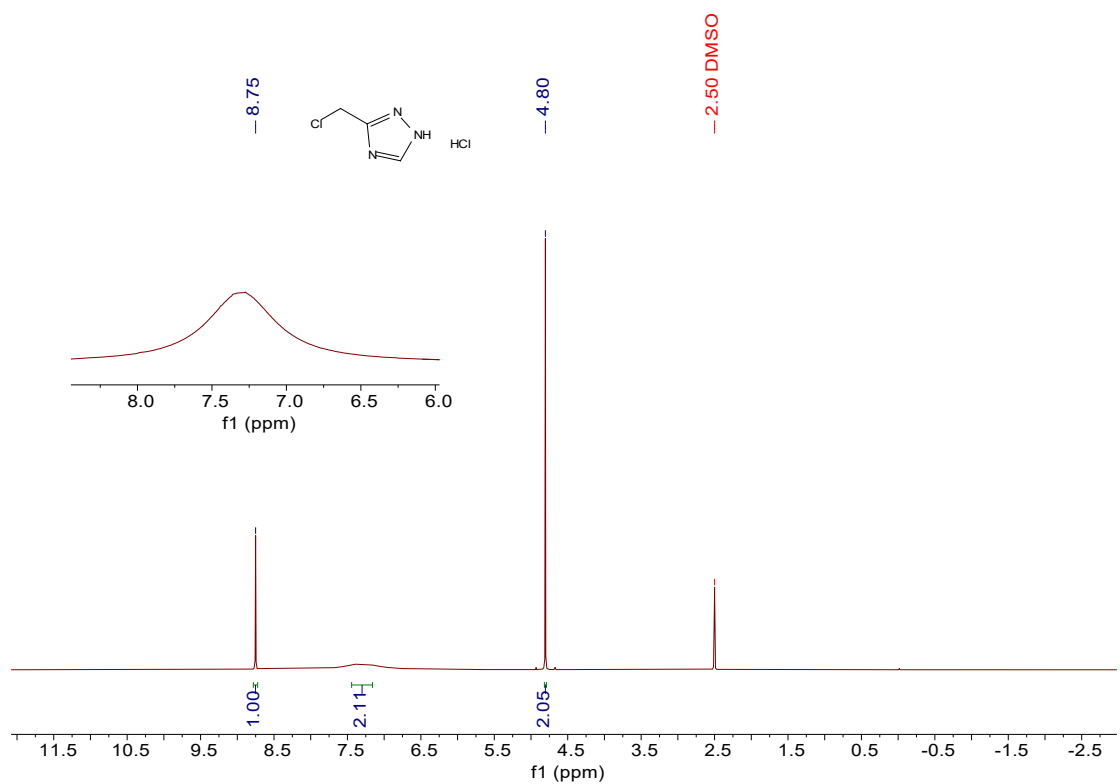




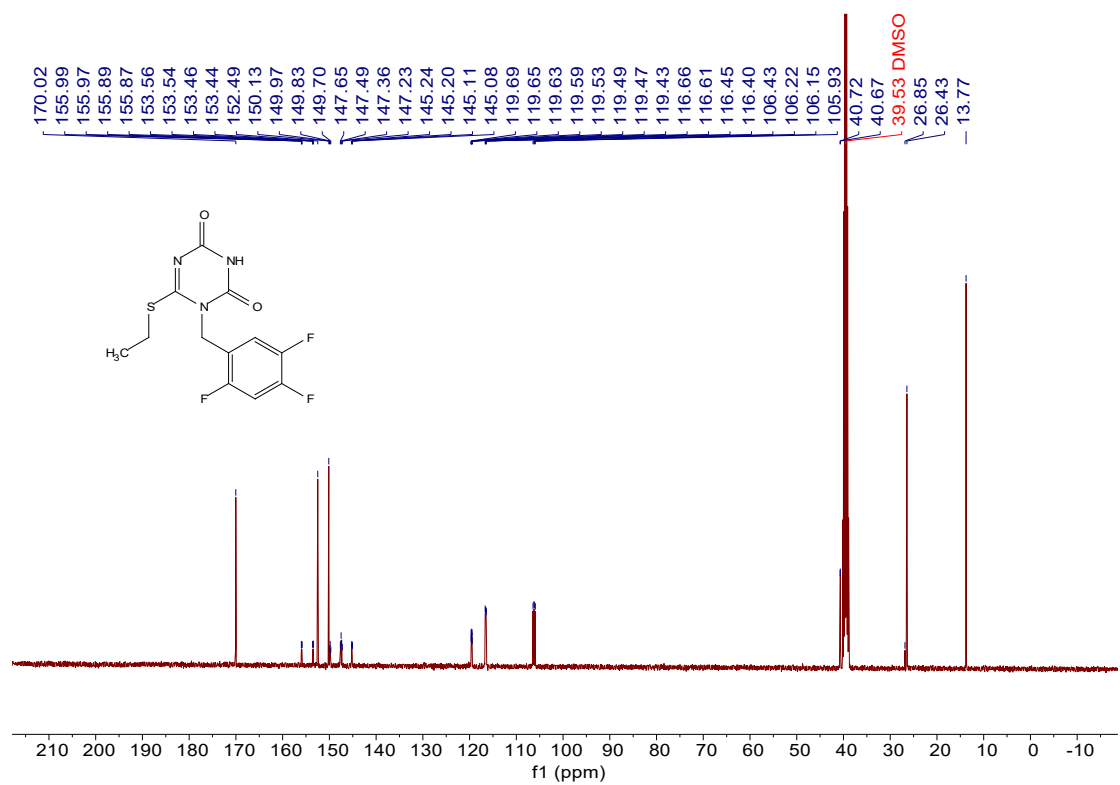
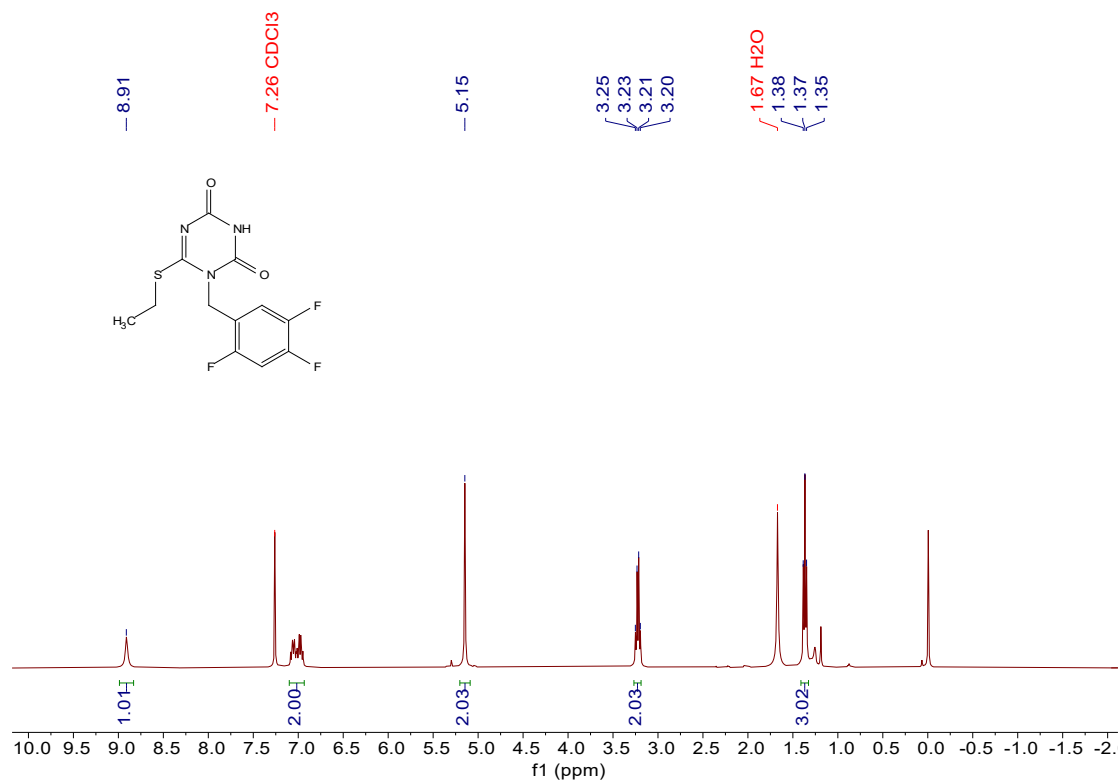
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO-}d_6$  of compound 7



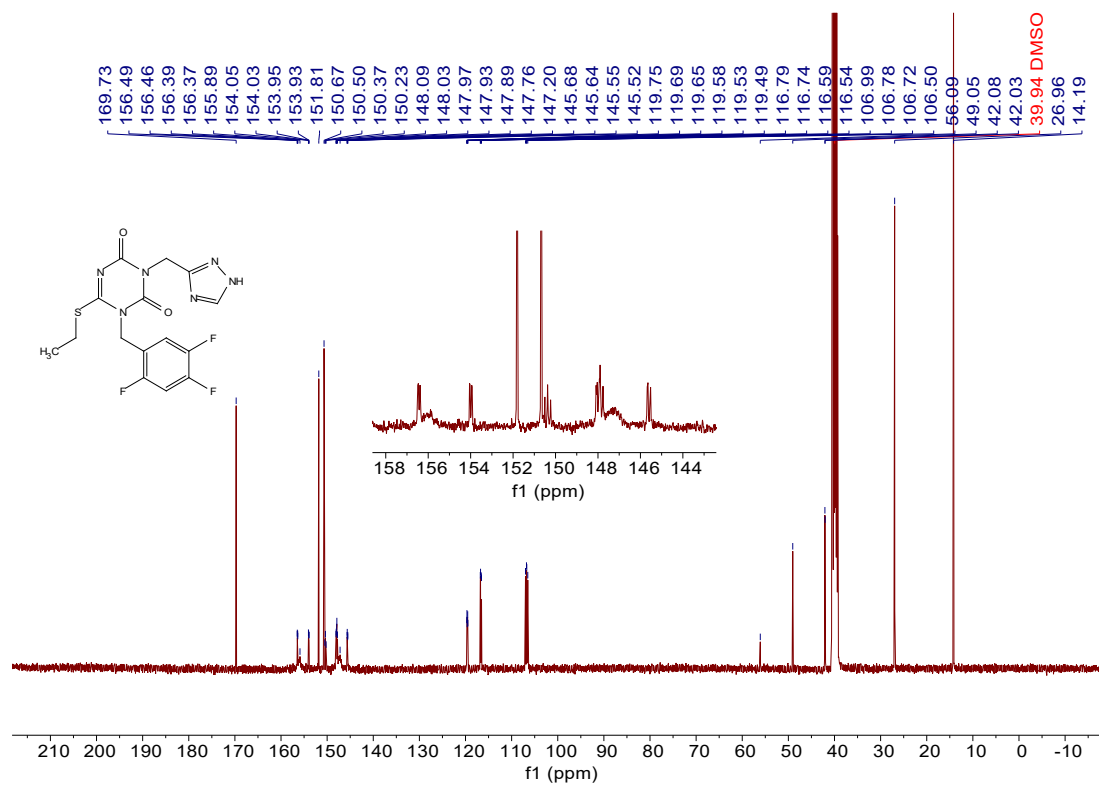
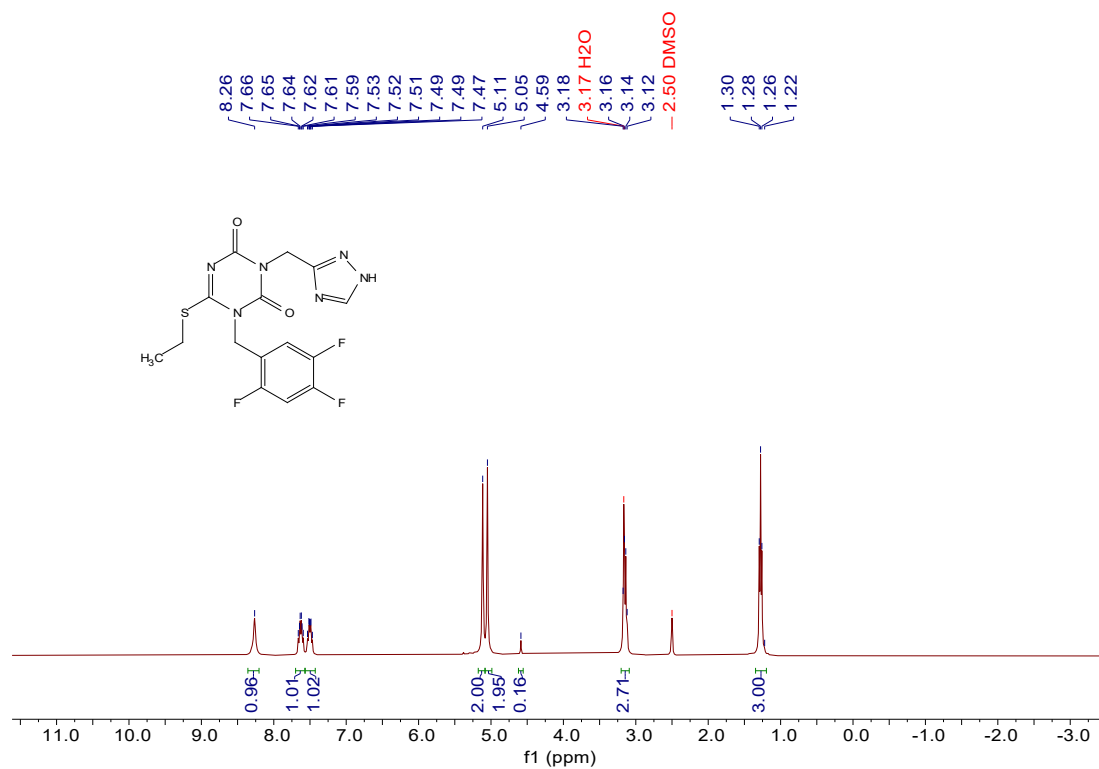
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO-}d_6$  of compound **7·HCl**



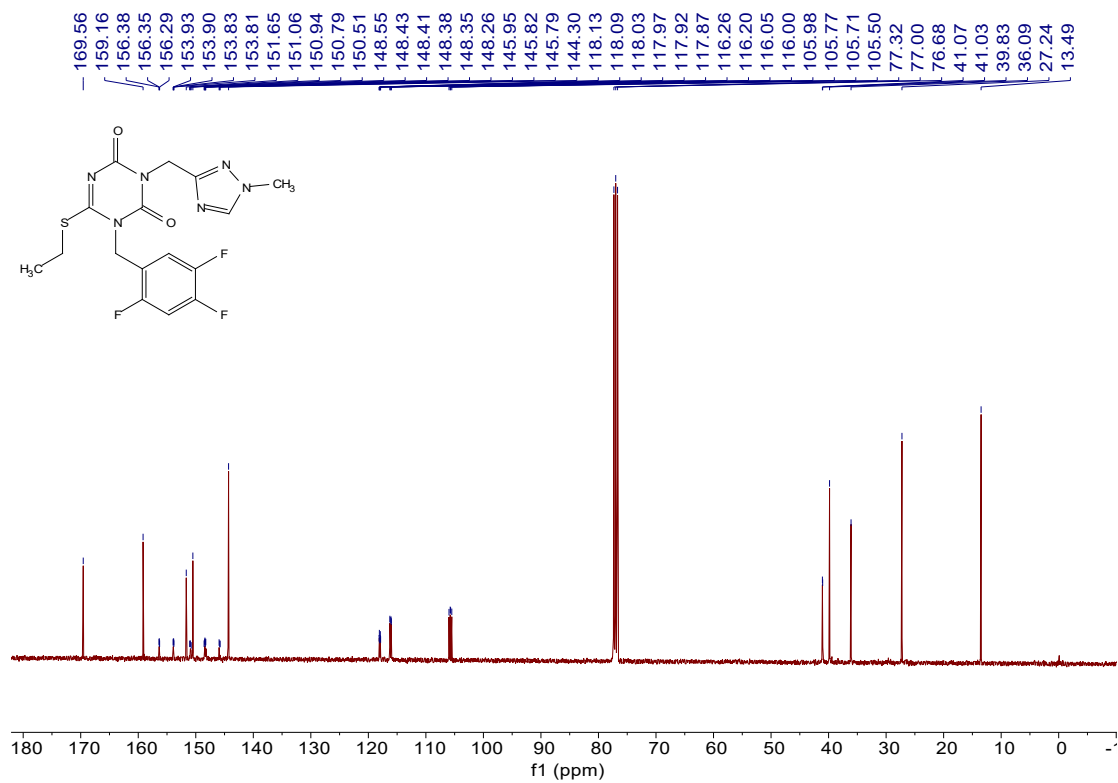
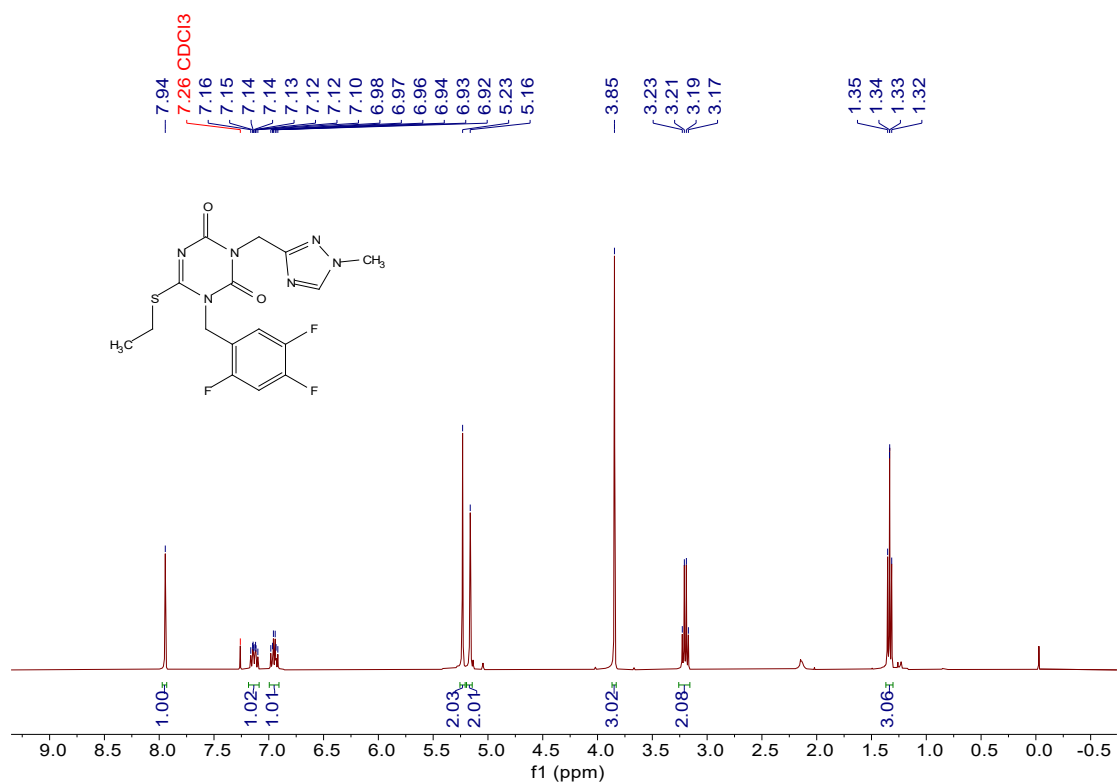
$^1\text{H}$  NMR (400 MHz) in  $\text{CDCl}_3$  and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO}-d_6$  of compound **2**



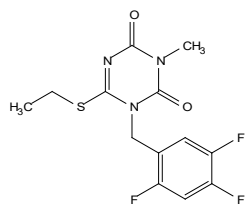
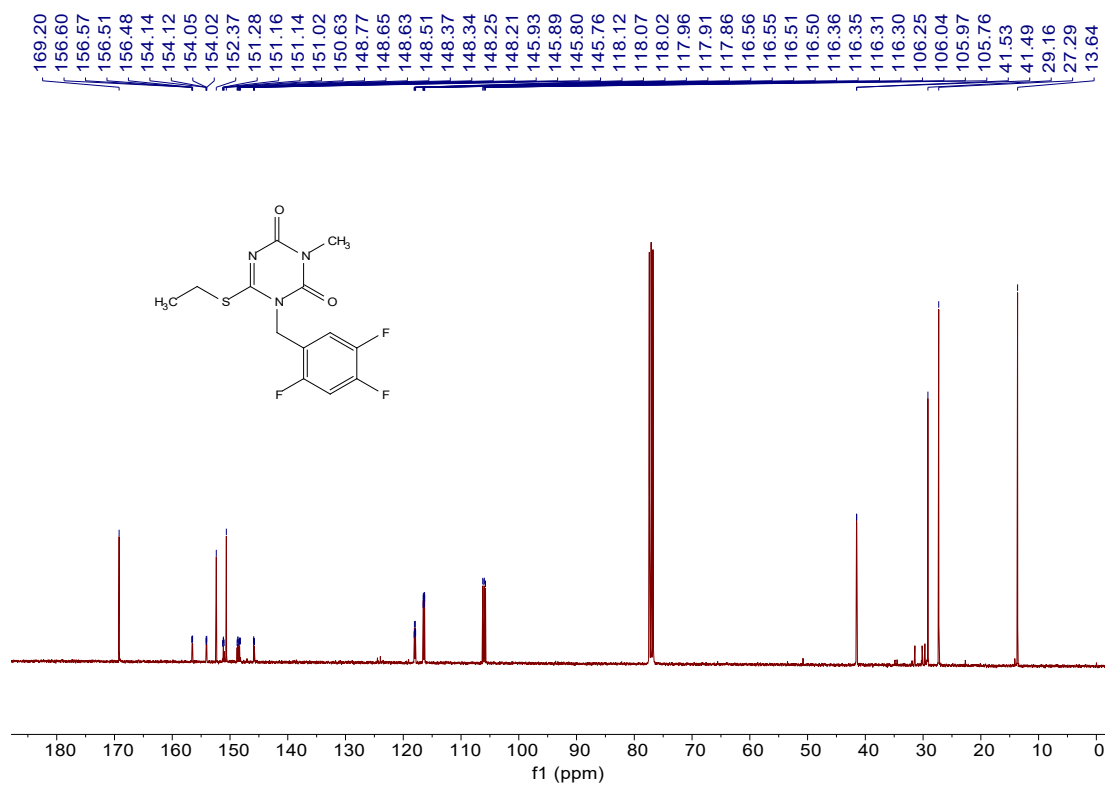
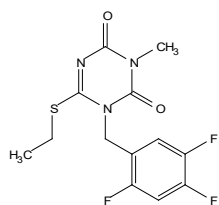
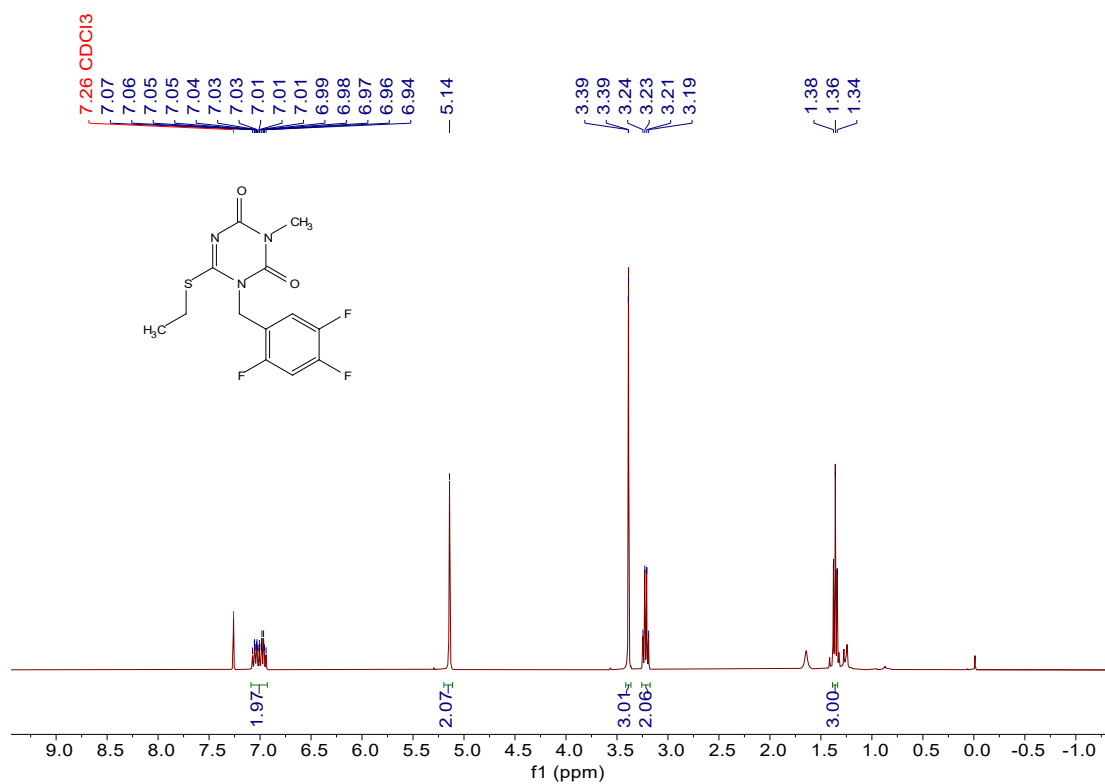
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{DMSO-}d_6$  of compound **8**



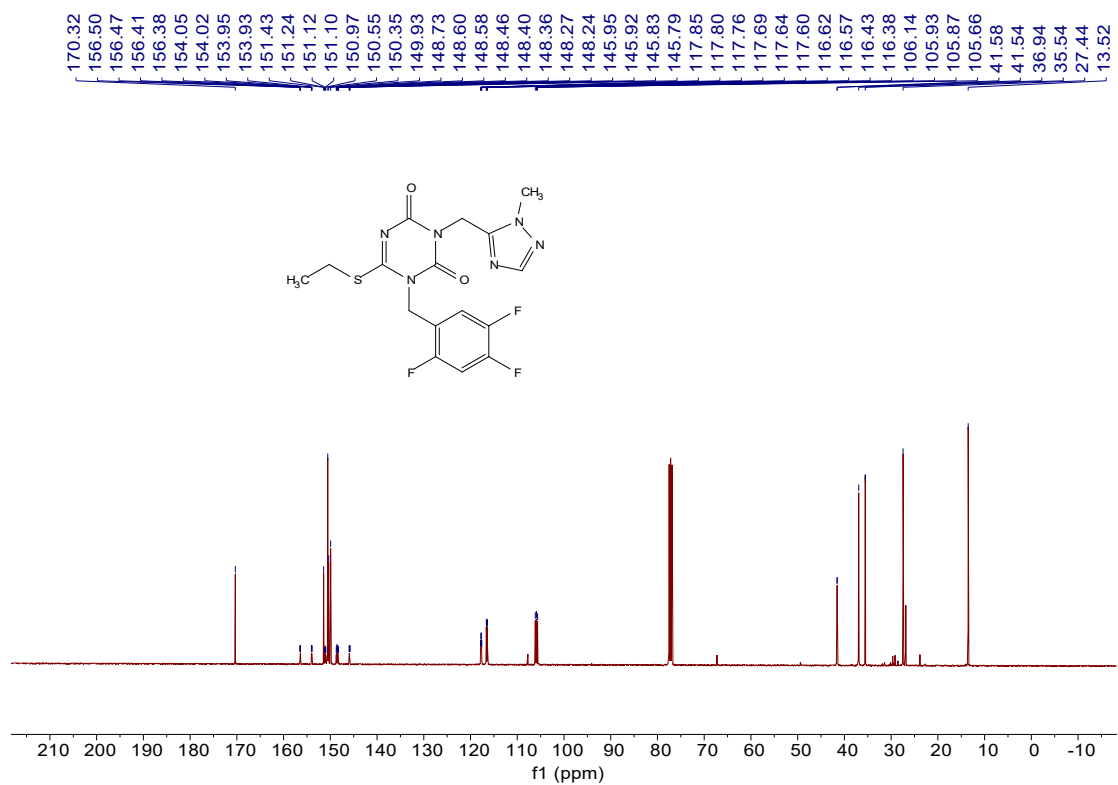
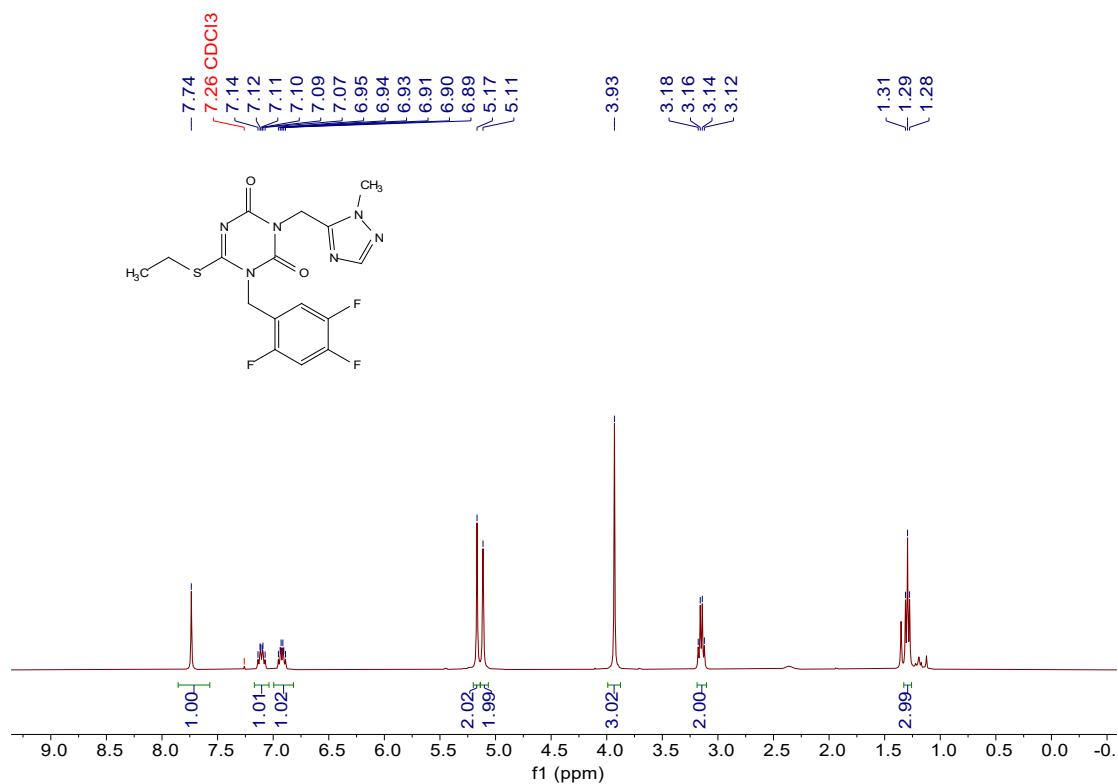
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{CDCl}_3$  of compound **4**



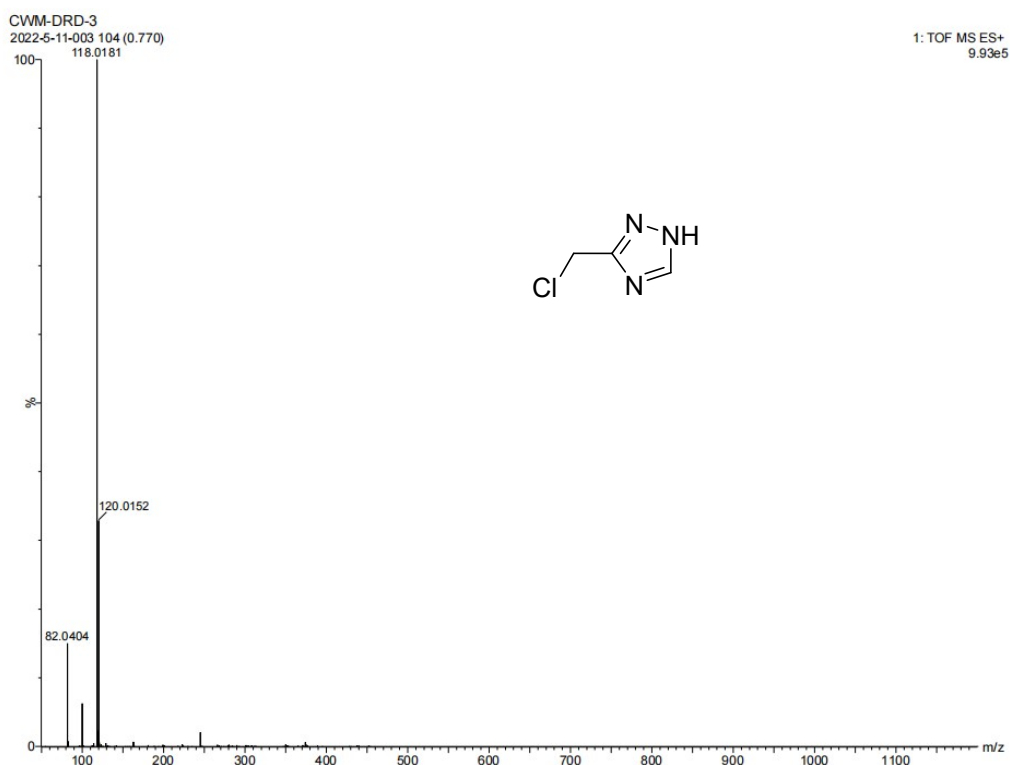
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{CDCl}_3$  of compound **9**



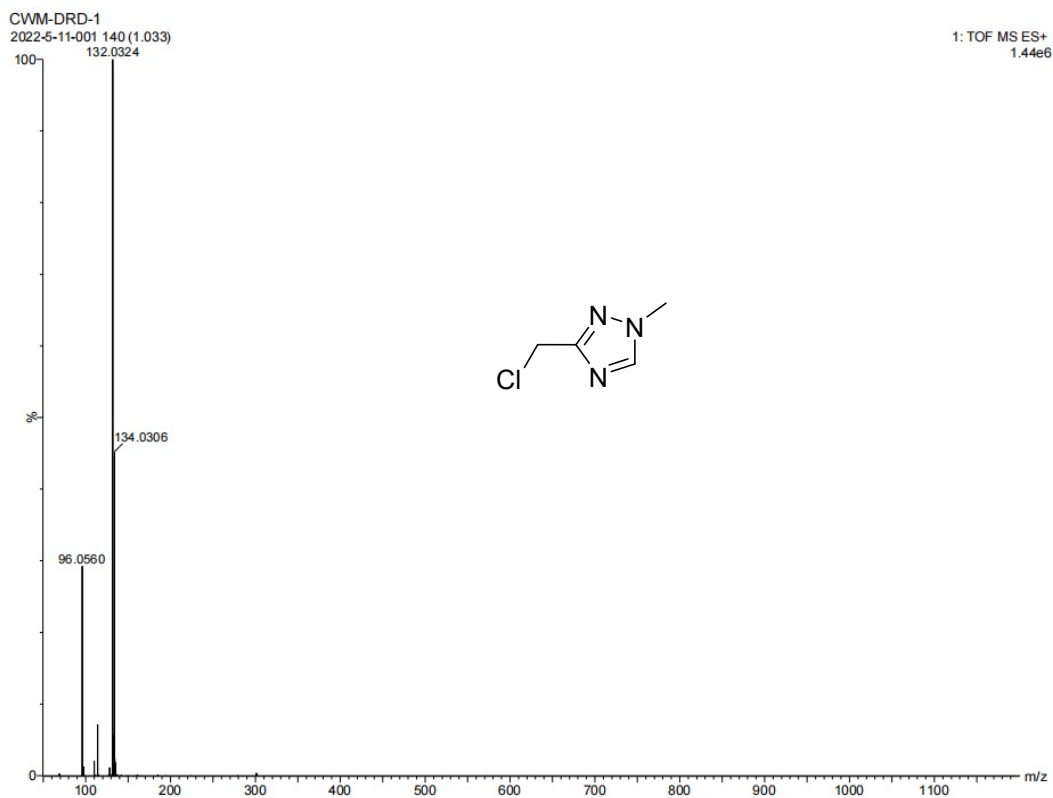
$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) in  $\text{CDCl}_3$  of compound **10**



### HRMS of compound 7

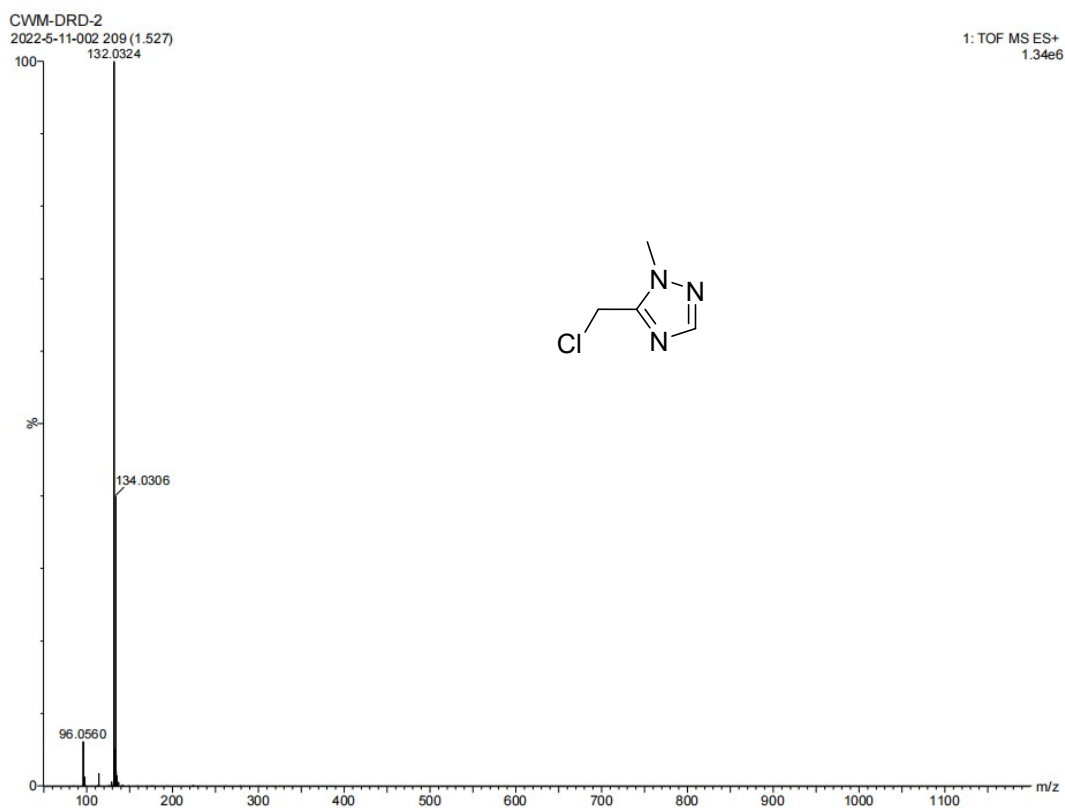


### HRMS of compound 3

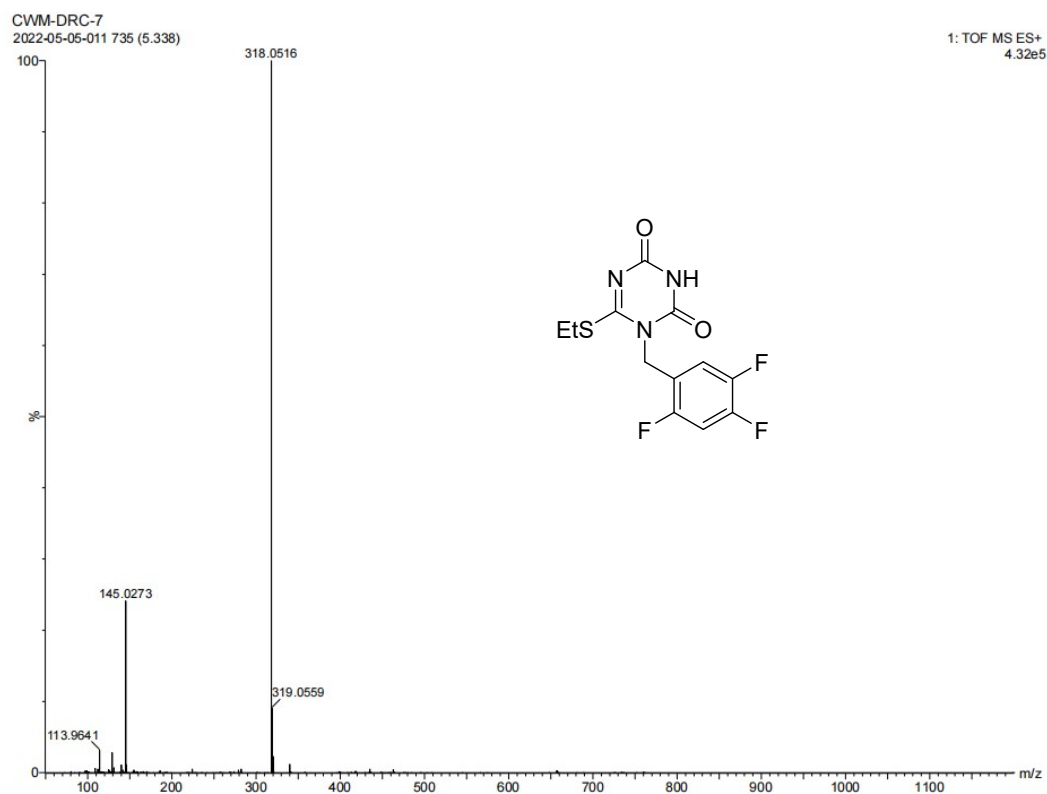




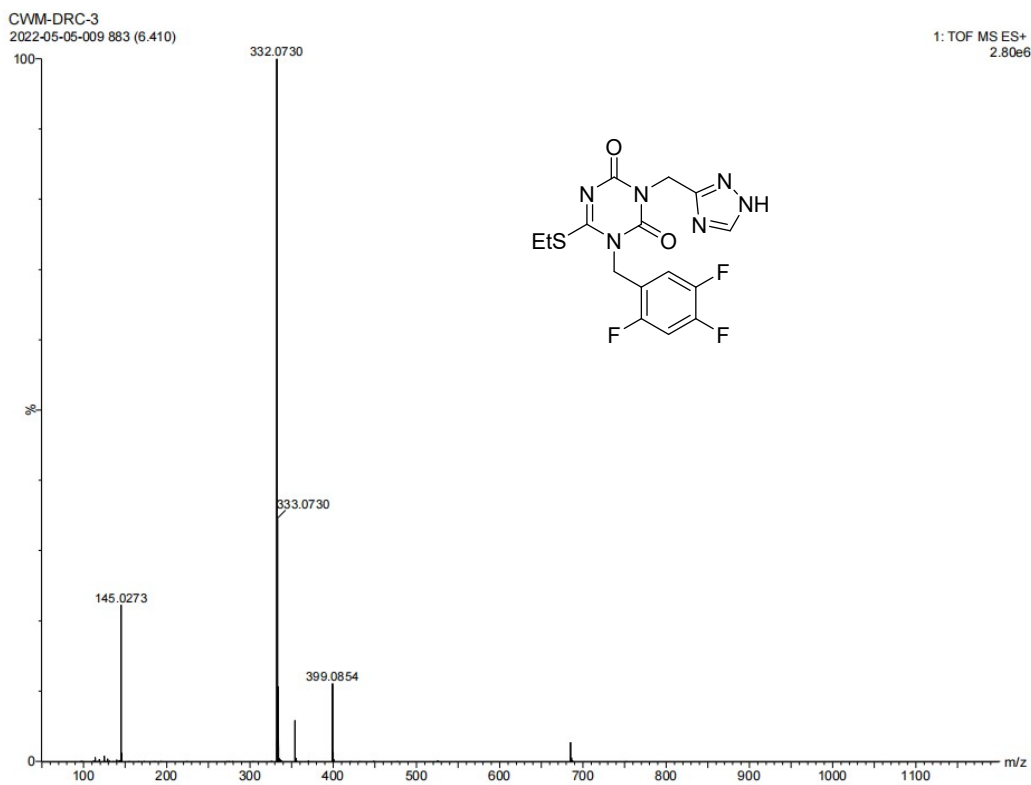
### HRMS of compound 3a



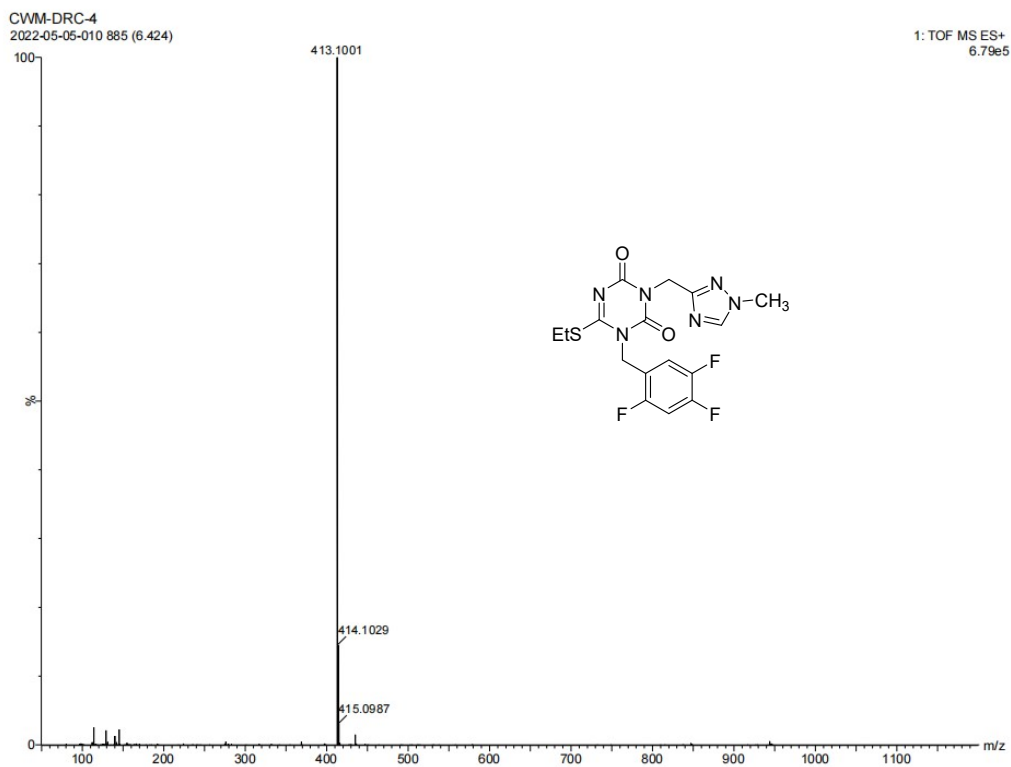
### HRMS of compound 2



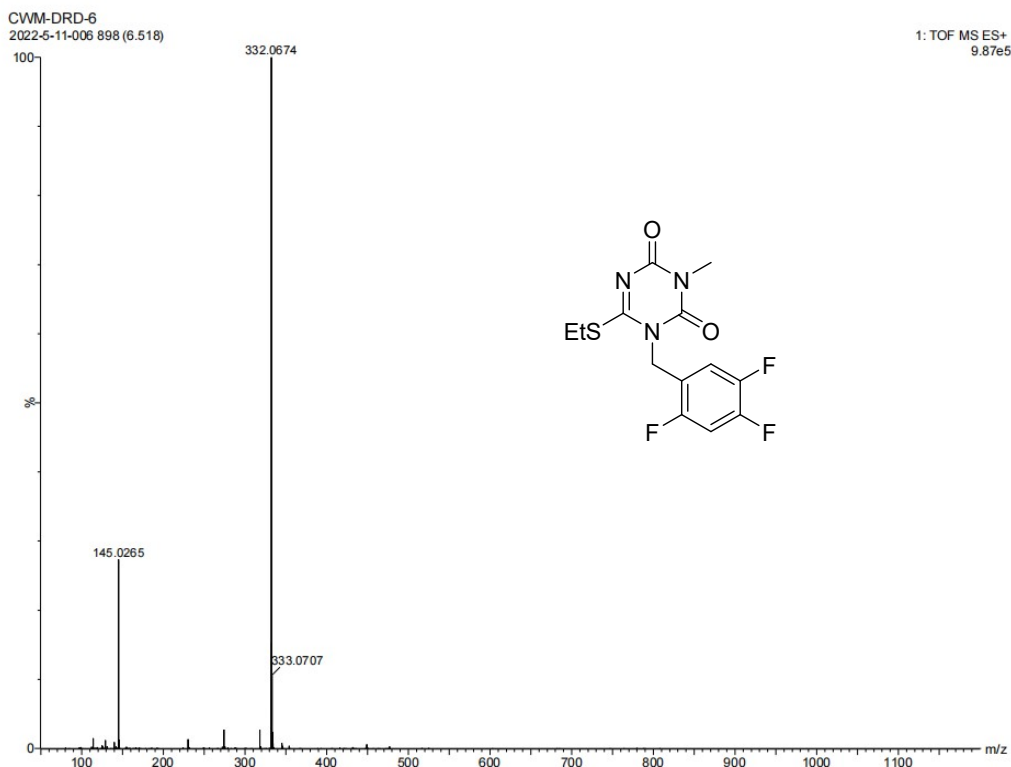
### HRMS of compound 8



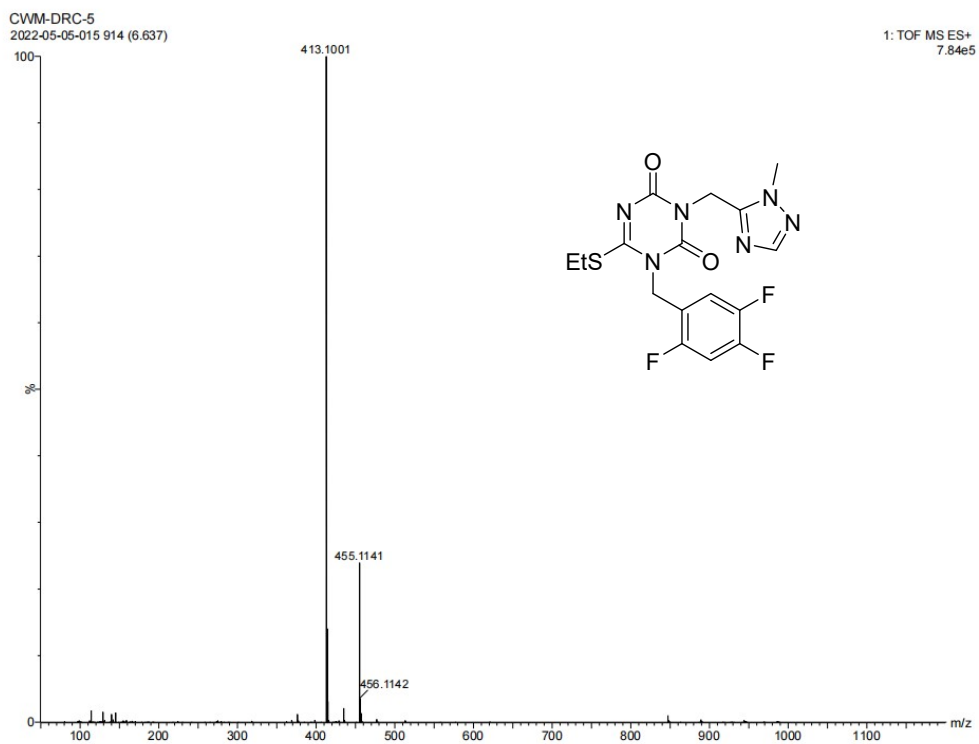
### HRMS of compound 4



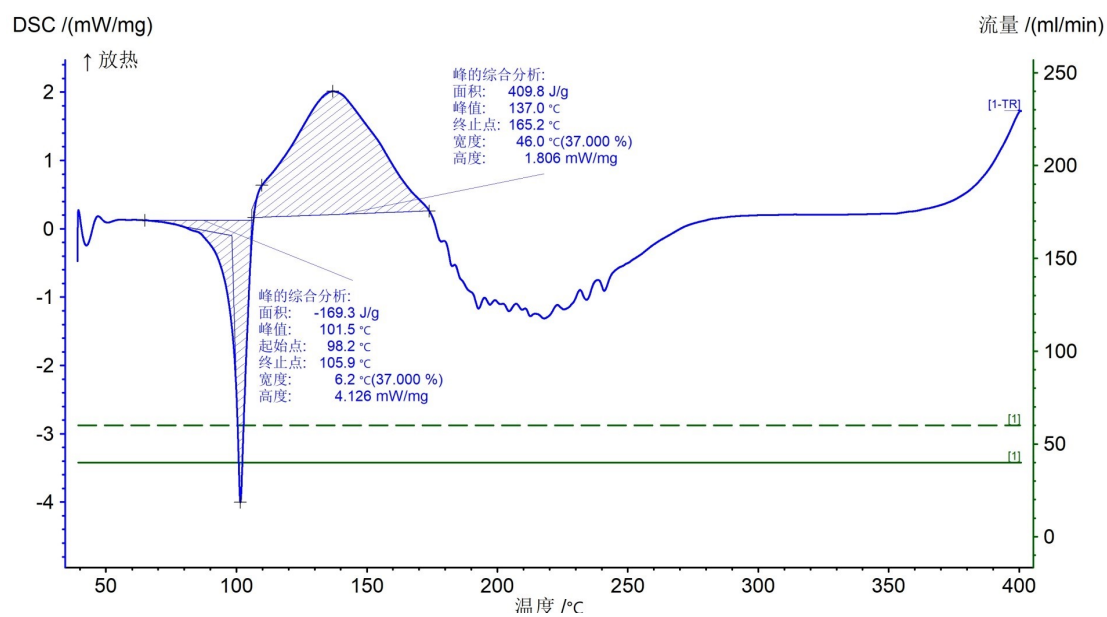
### HRMS of compound 9



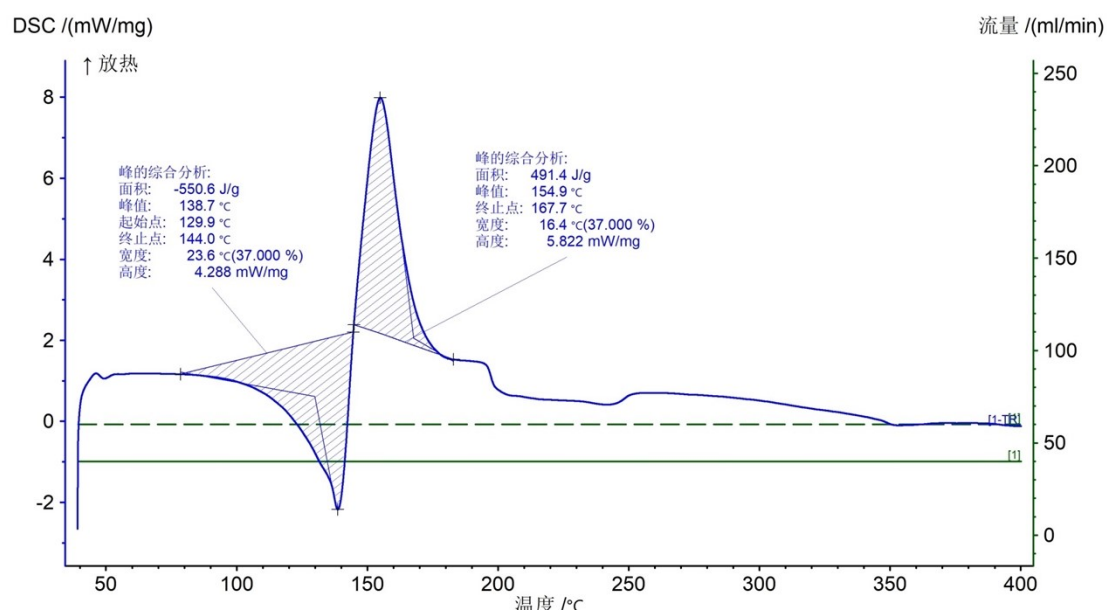
### HRMS of compound 10



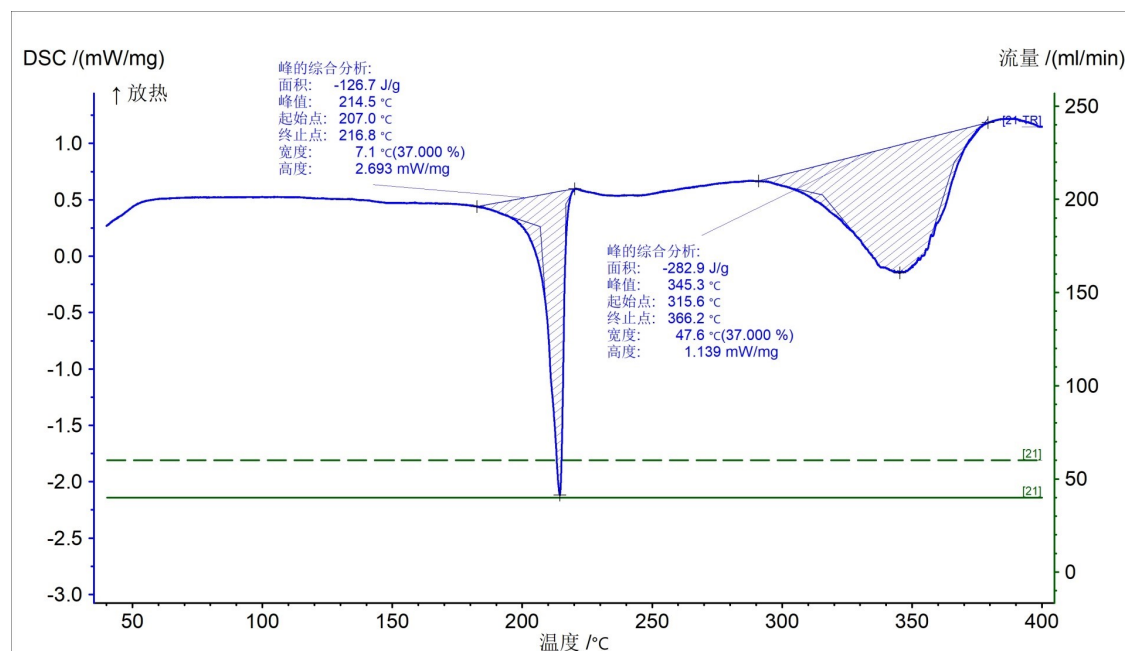
## DSC of compound 7



## DSC of compound 3



## DSC of compound 8



## DSC of compound 4

