

Supplementary material

Synthesis and in vitro anticancer evaluation of novel flavonoid-  
based amide derivatives as regulator of PI3K/AKT signal pathway  
for TNBC treatment

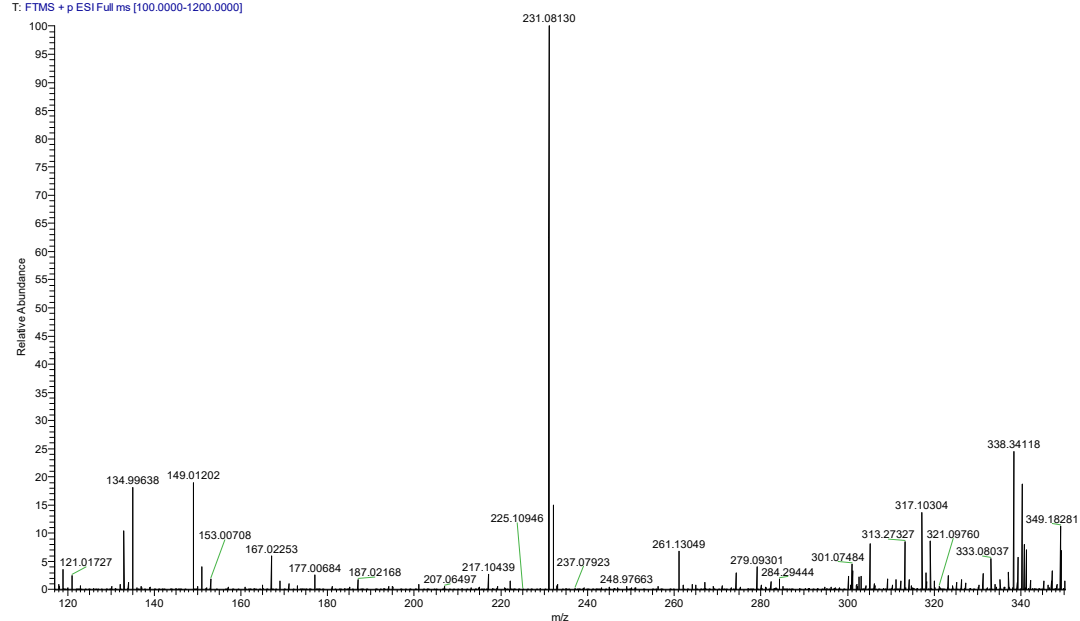
Dailong Zha<sup>#</sup>, Yingqi Luo<sup>#</sup>, Yuanzhi Li<sup>#</sup>, Yingfan Liu<sup>#</sup>, Zehong Lin, Chujie Lin,  
Siyue Chen, Jiangping Wu, Lihong Yu, Shaobin Chen, Peiquan Zhang, Wenhao Wu\*,  
Chao Zhang\*

Guangzhou Municipal and Guangdong Provincial Key Laboratory of Molecular  
Target & Clinical Pharmacology, the NMPA and State Key Laboratory of Respiratory  
Disease, School of Pharmaceutical Sciences and the Fifth Affiliated Hospital,  
Guangzhou Medical University, Guangzhou 511436, China

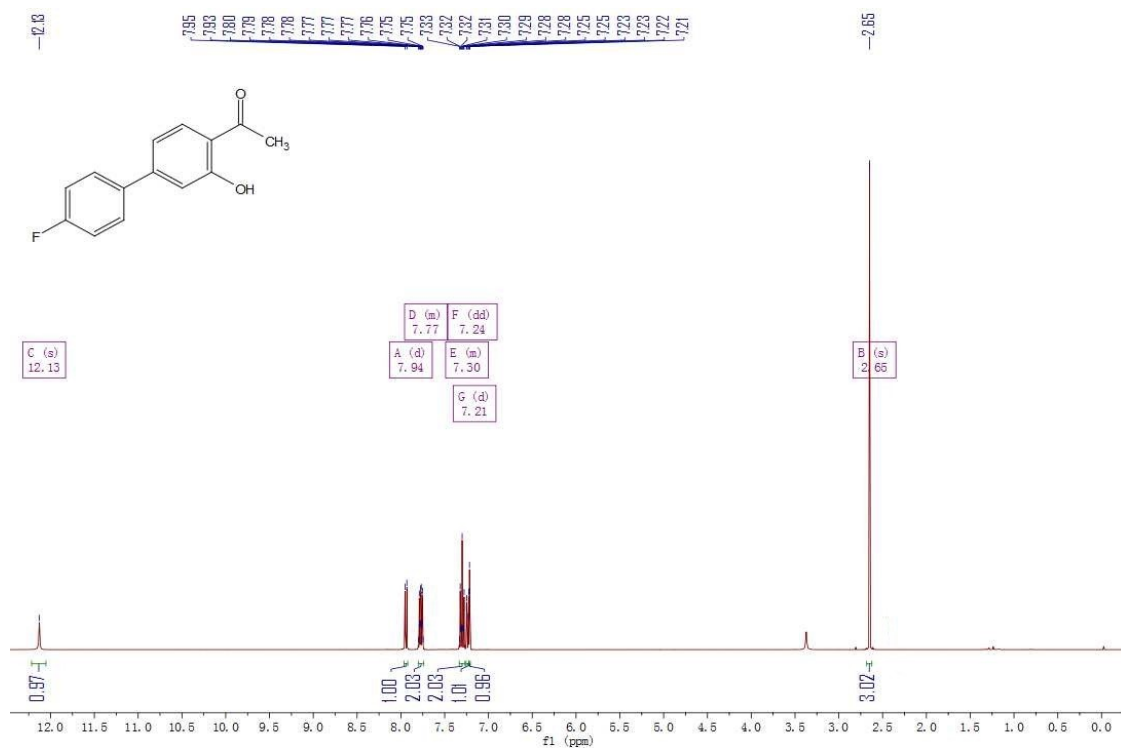
# 1. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound 3

## HRMS

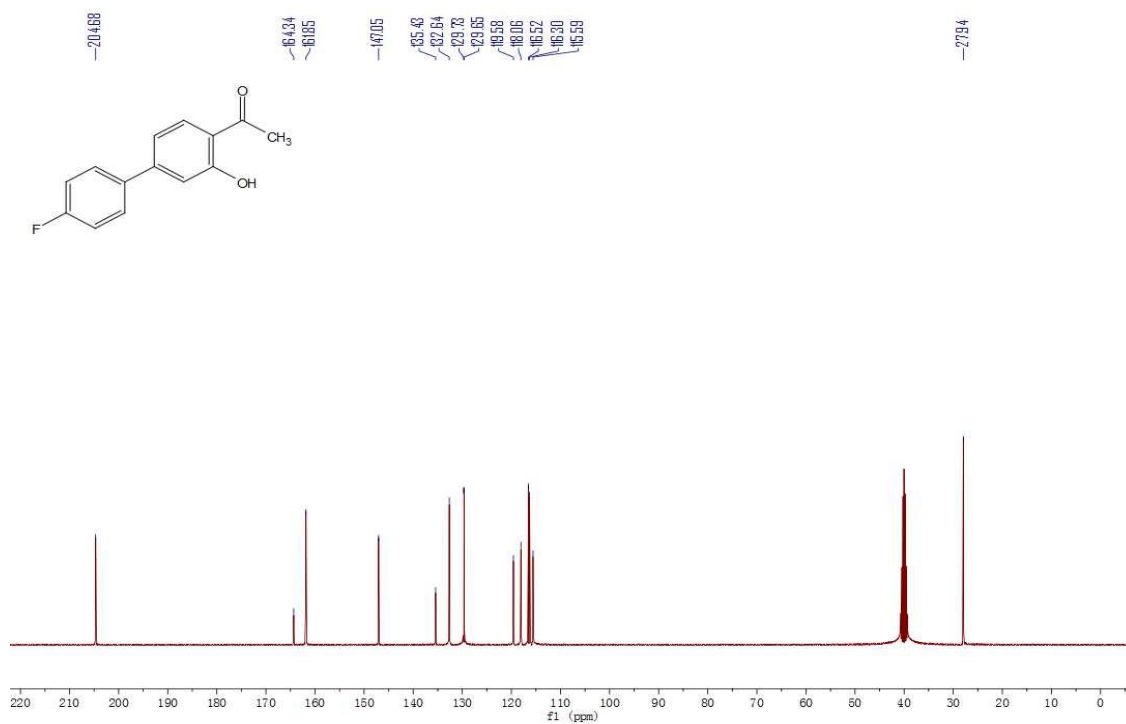
G28 #14-23 RT: 0.06-0.10 AV: 10 NL: 1.89E8  
T: FTMS + p ESI Full ms [100.0000-1200.0000]



## <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



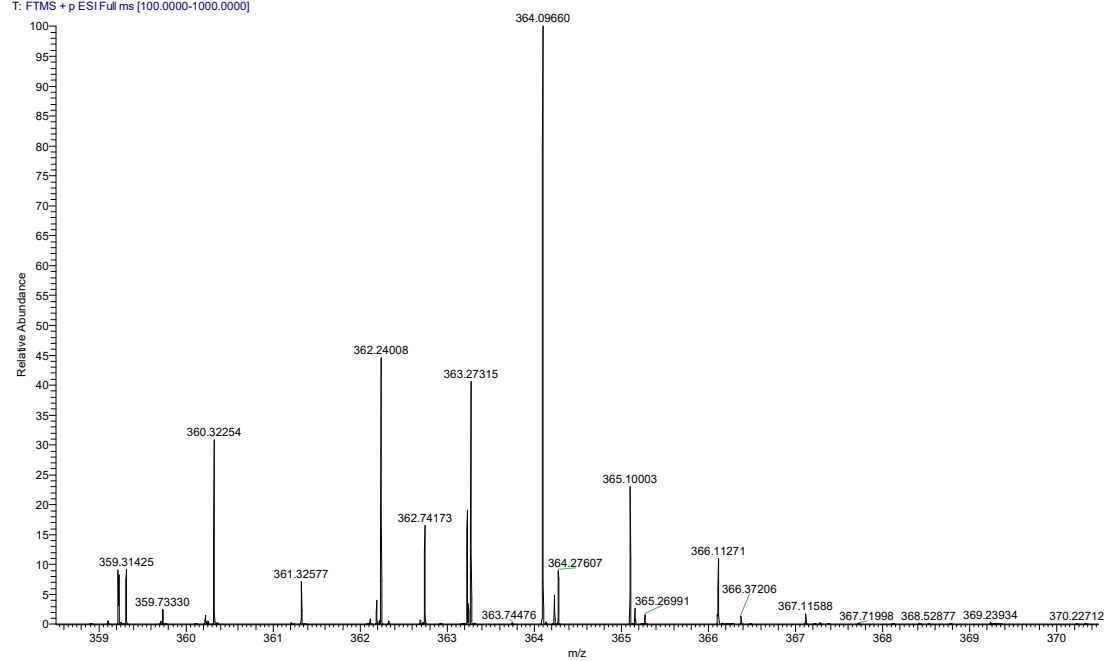
## <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



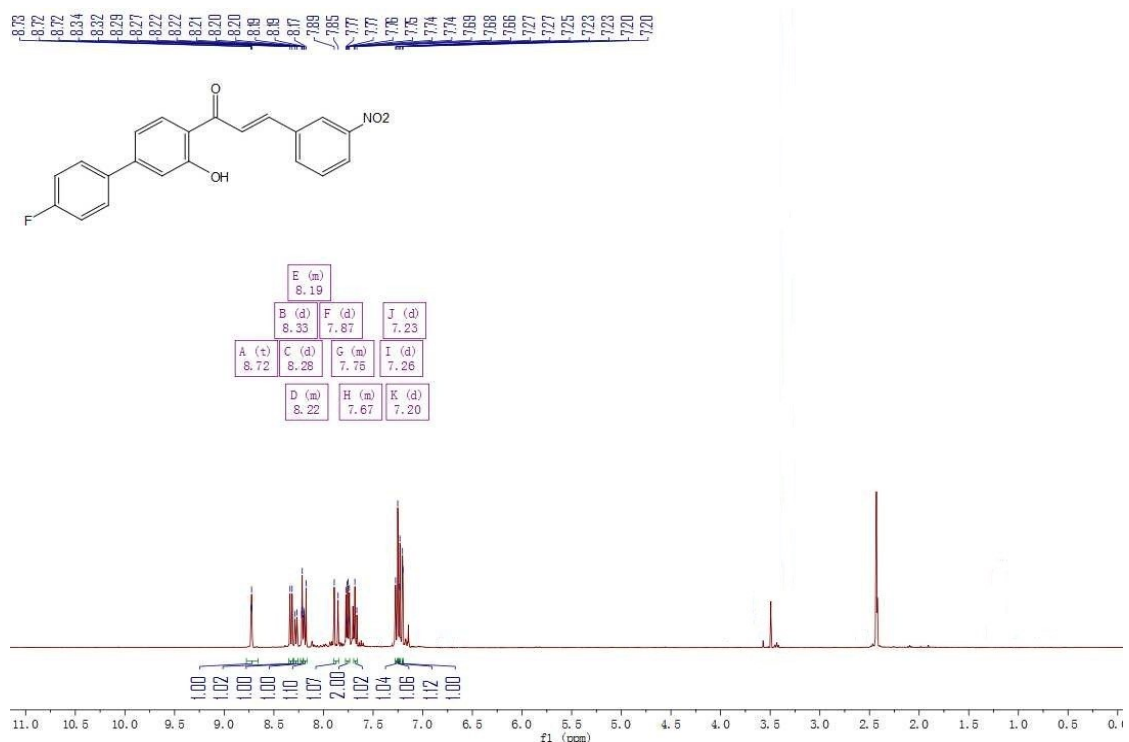
## 2. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound 4

### HRMS

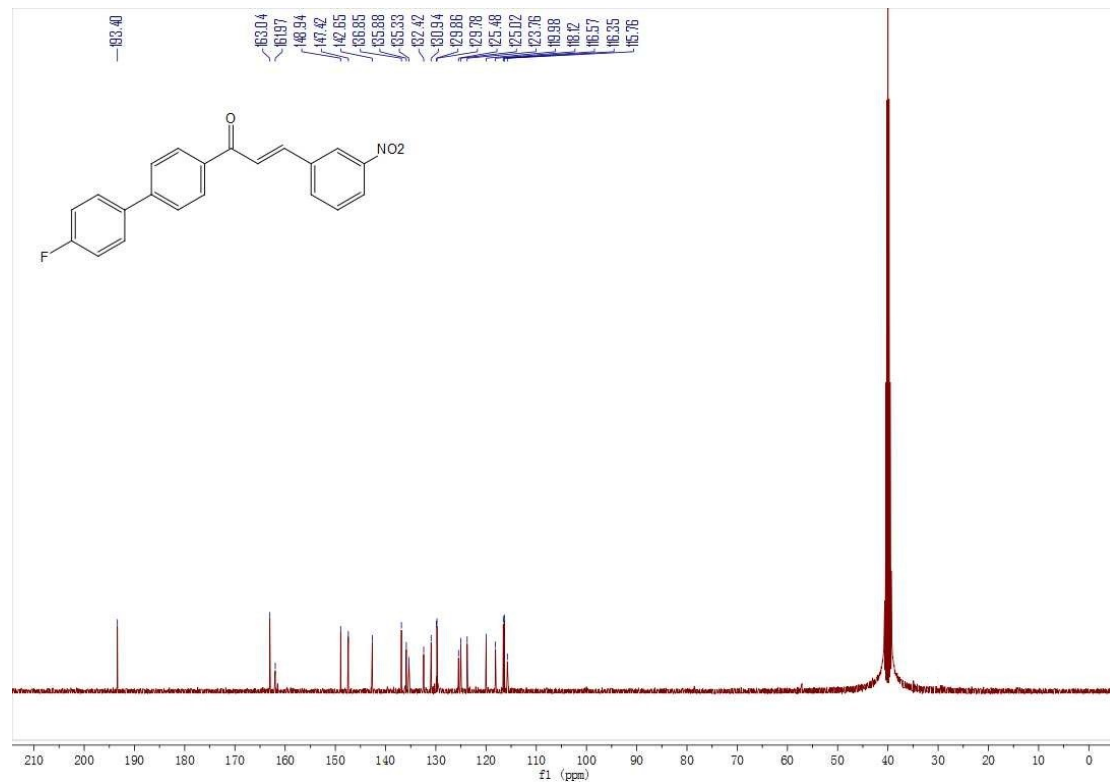
CDL-26 #8-20 RT: 0.04-0.10 AV: 13 NL: 2.97E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



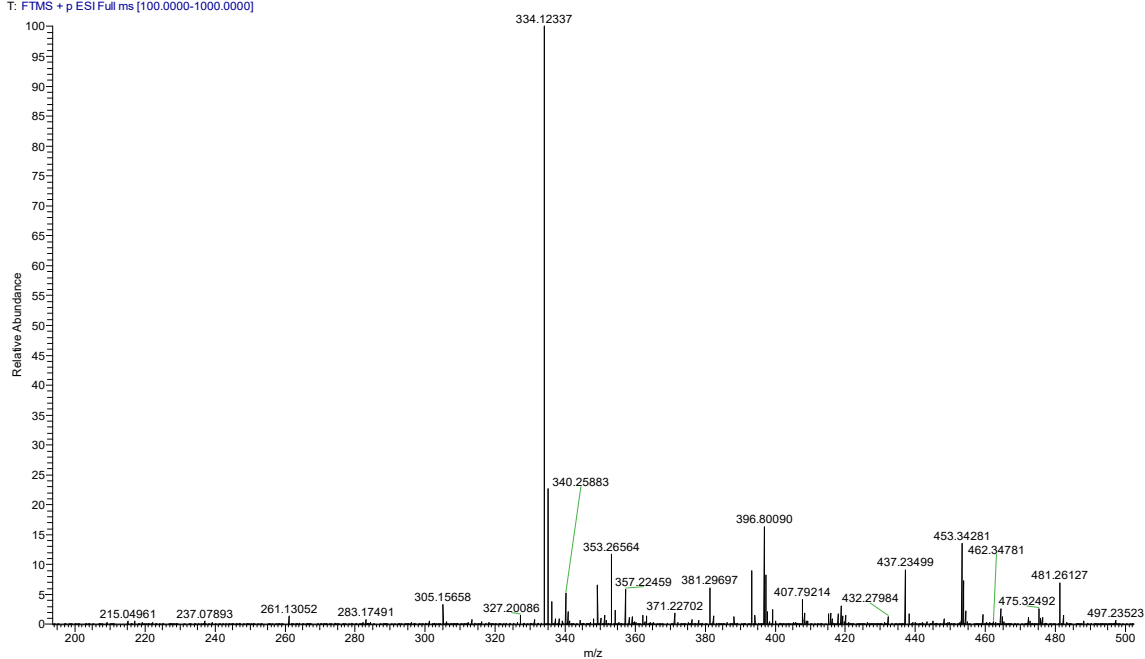
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



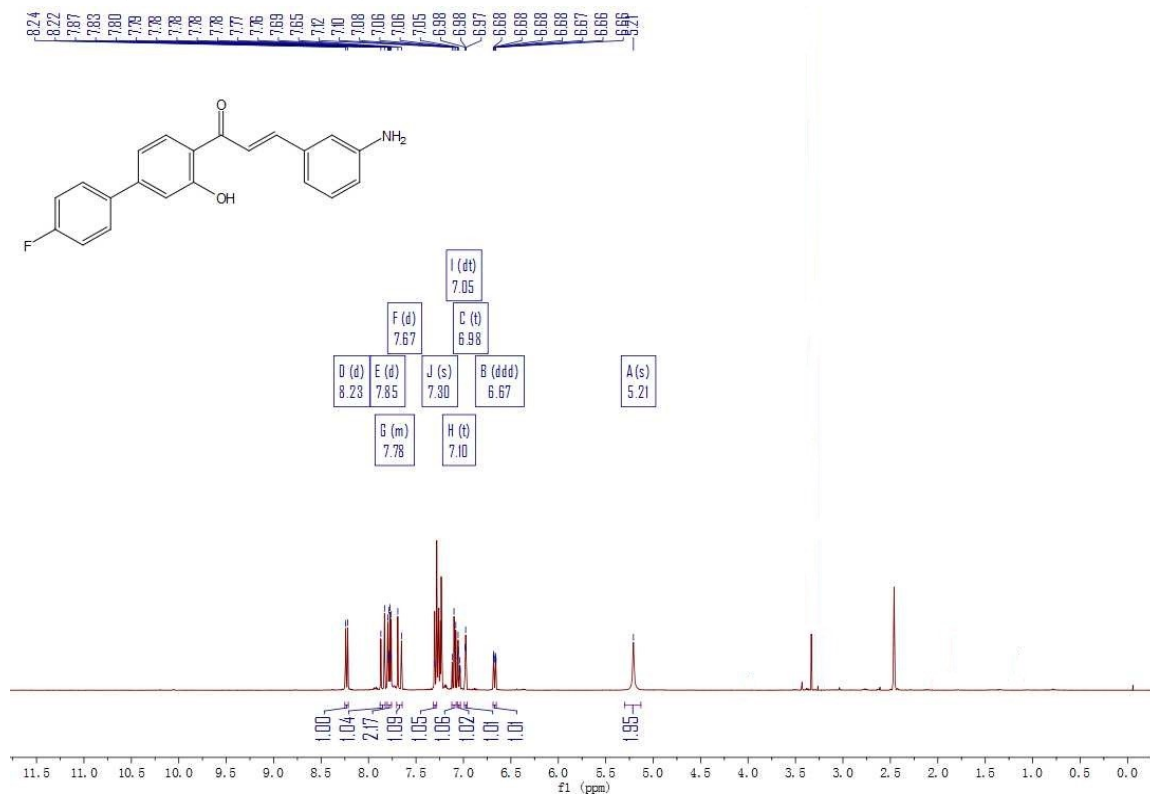
3. HRMS spectra,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR of compound 5

# HRMS

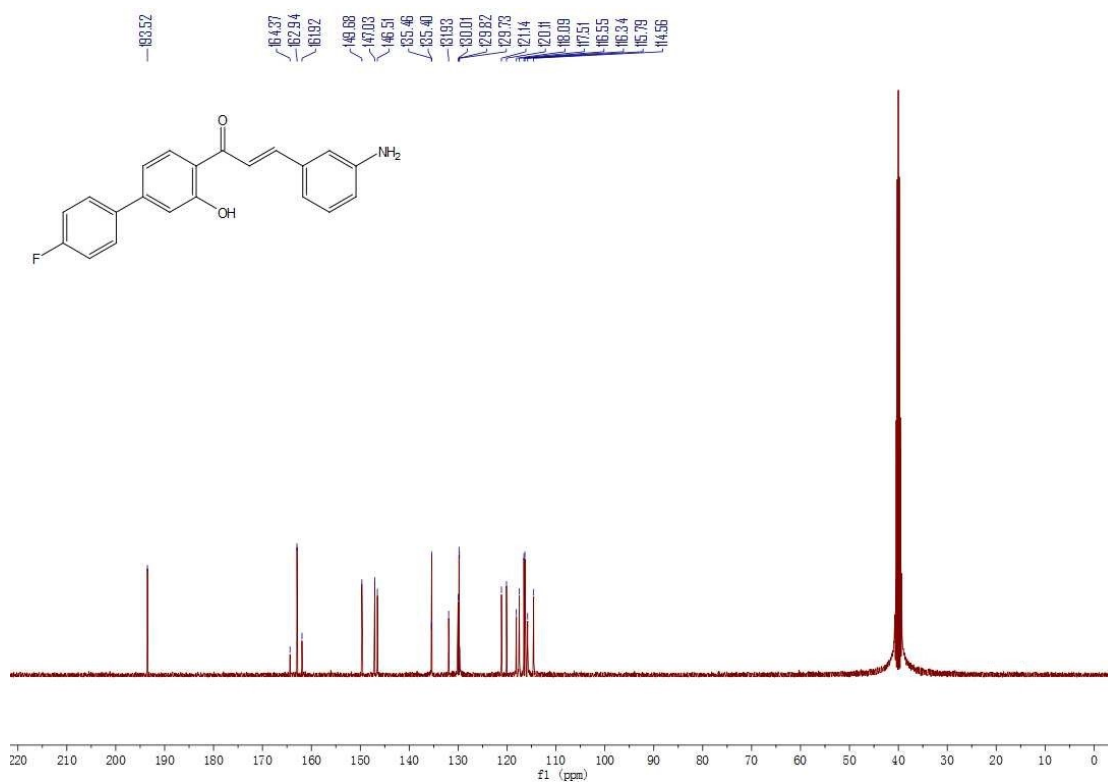
Q2 #12-22 RT: 0.05-0.10 AV: 11 NL: 7.66E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



# <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



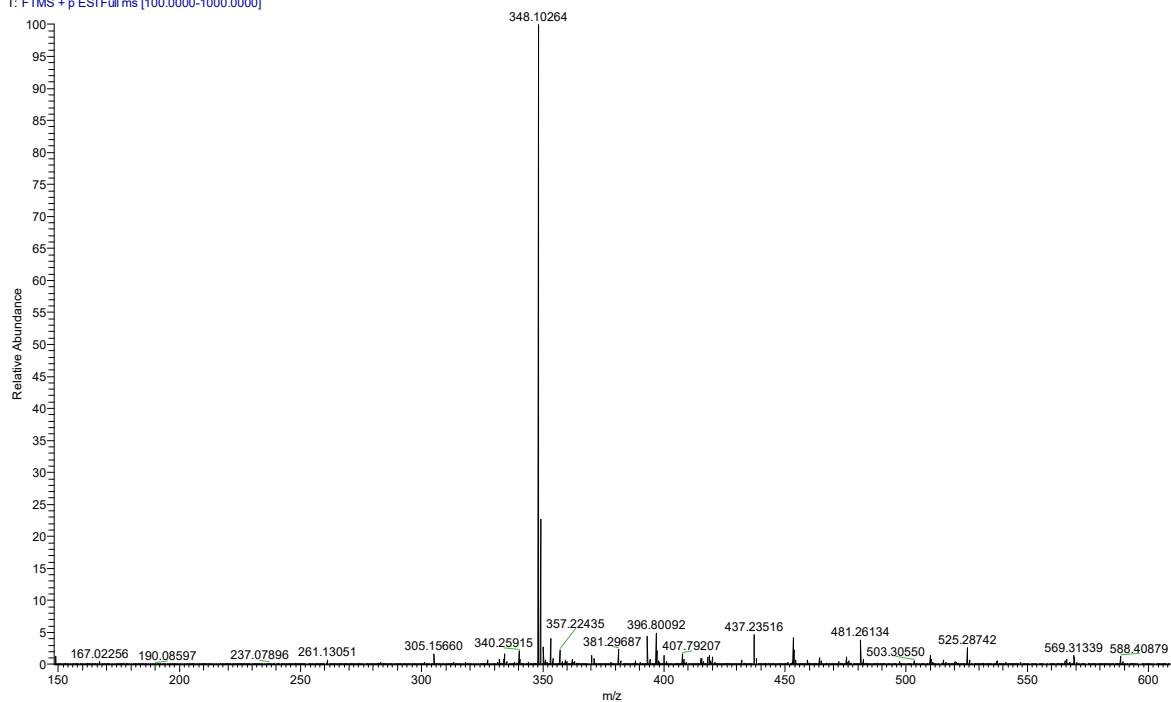
# <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



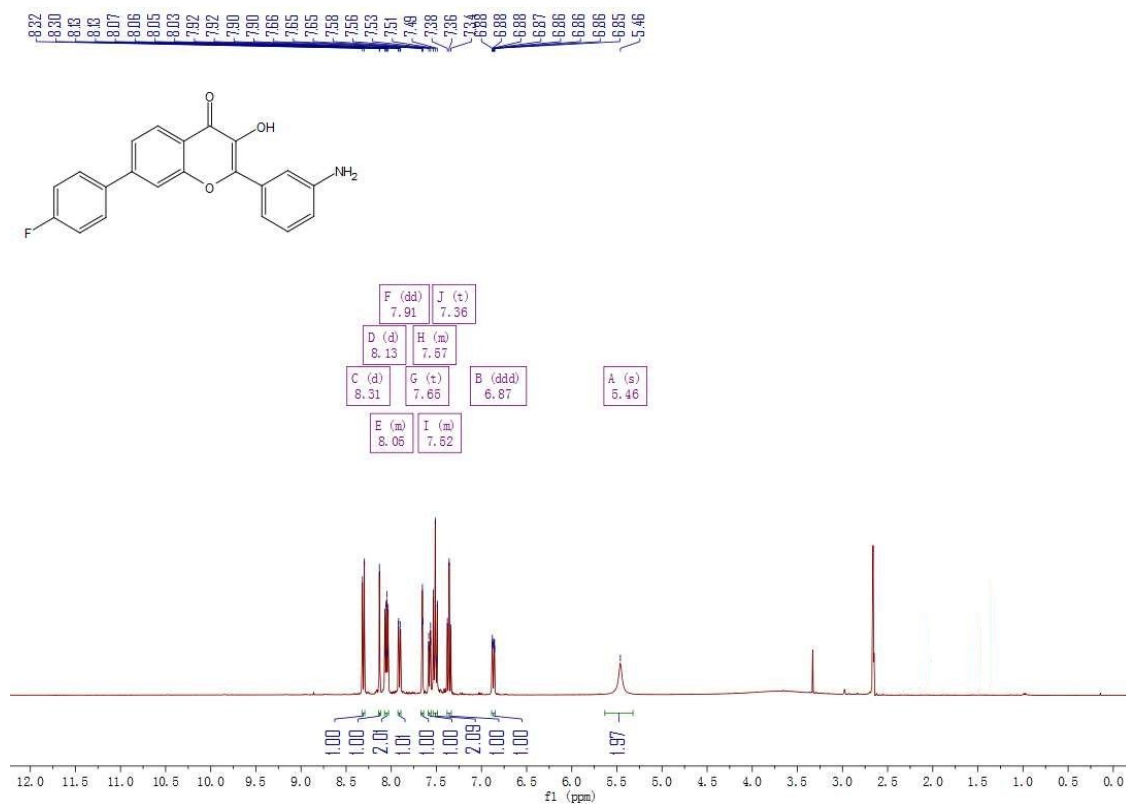
#### 4. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound 6

##### HRMS

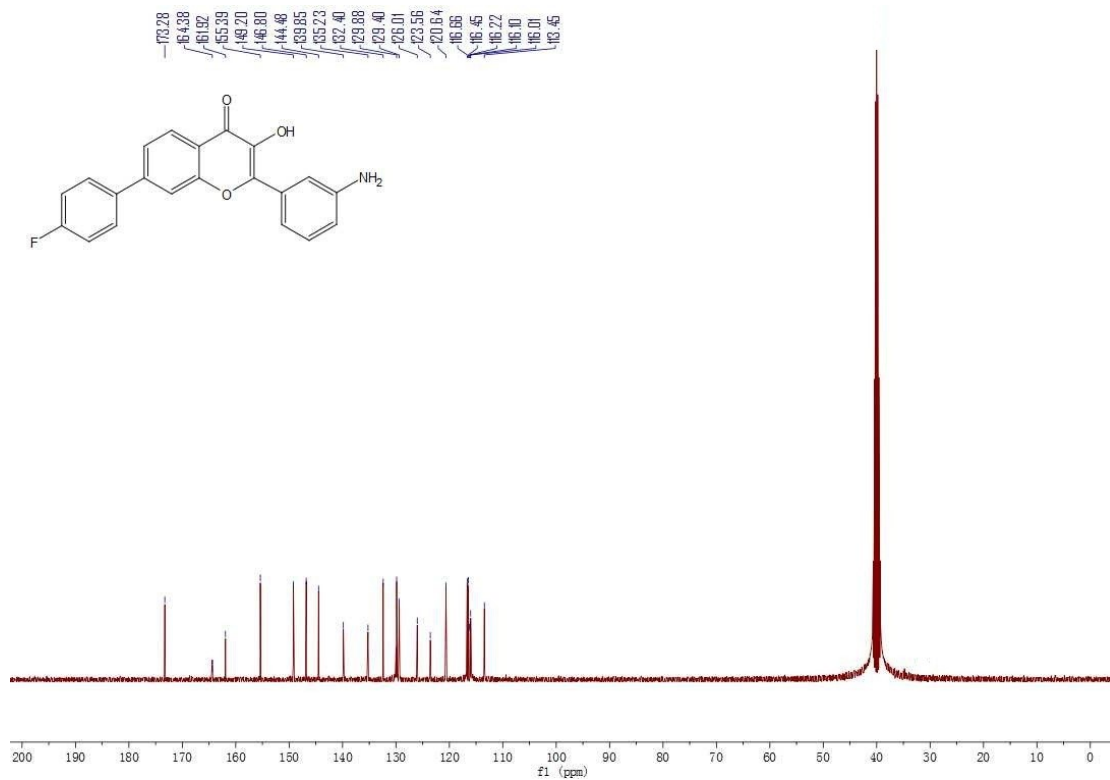
Q1 #9-24 RT: 0.04-0.11 AV: 16 NL: 1.42E9  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



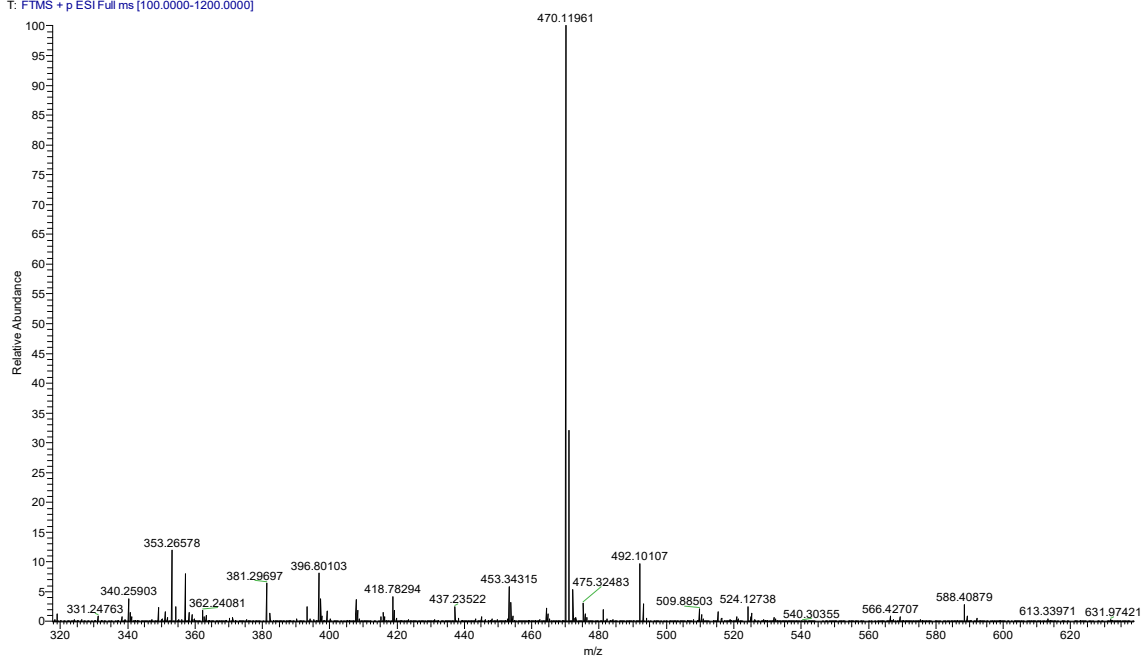
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



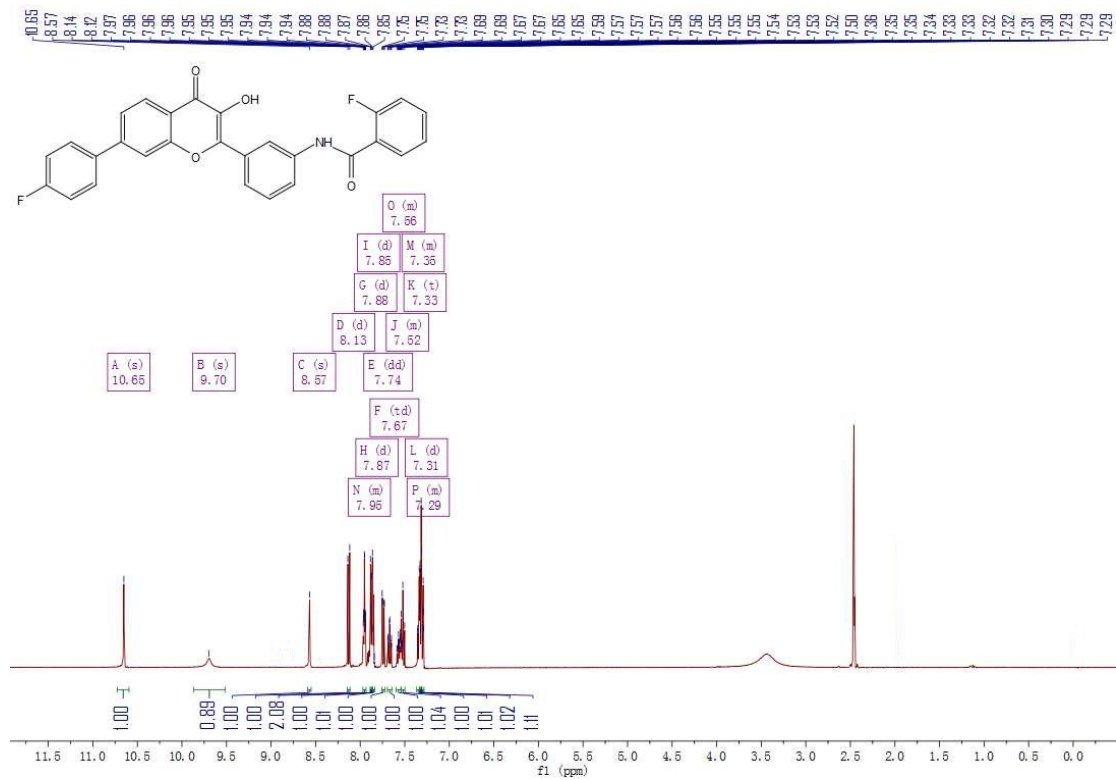
## 5. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound 7a

### HRMS

G26 #12-23 RT: 0.05-0.10 AV: 12 NL: 9.29E8  
T: FTMS + p ESI Full ms [100.0000-1200.0000]

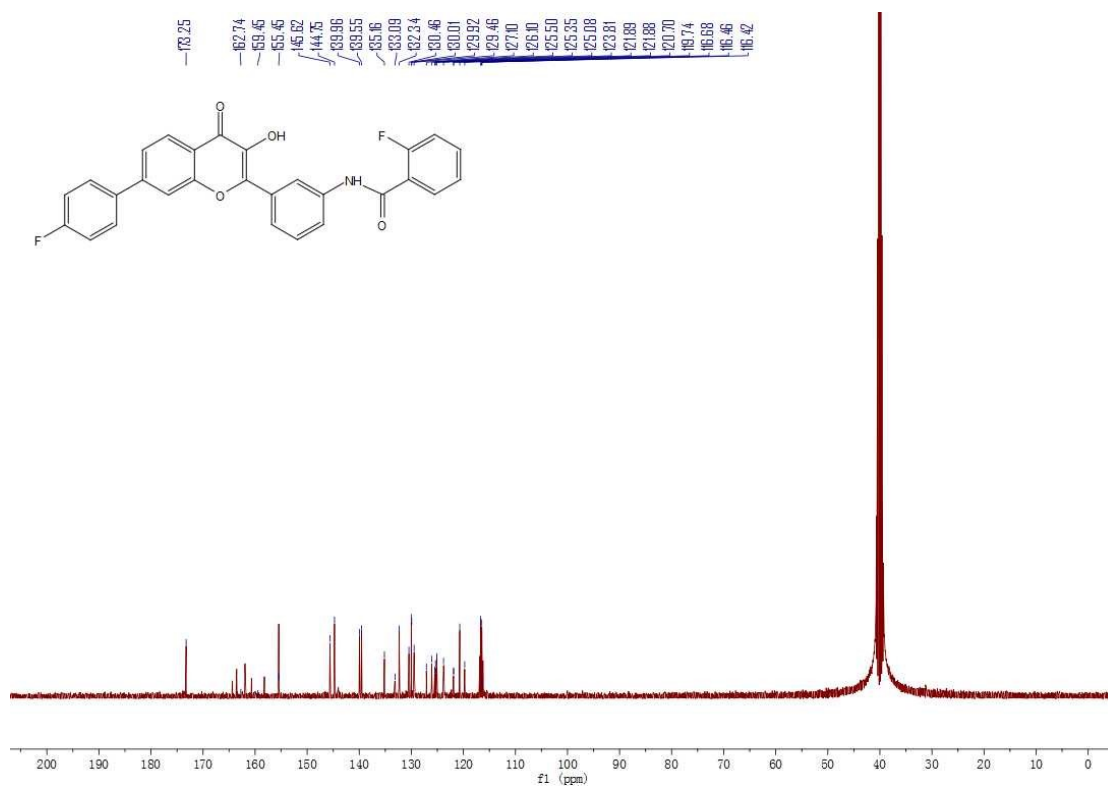


### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)





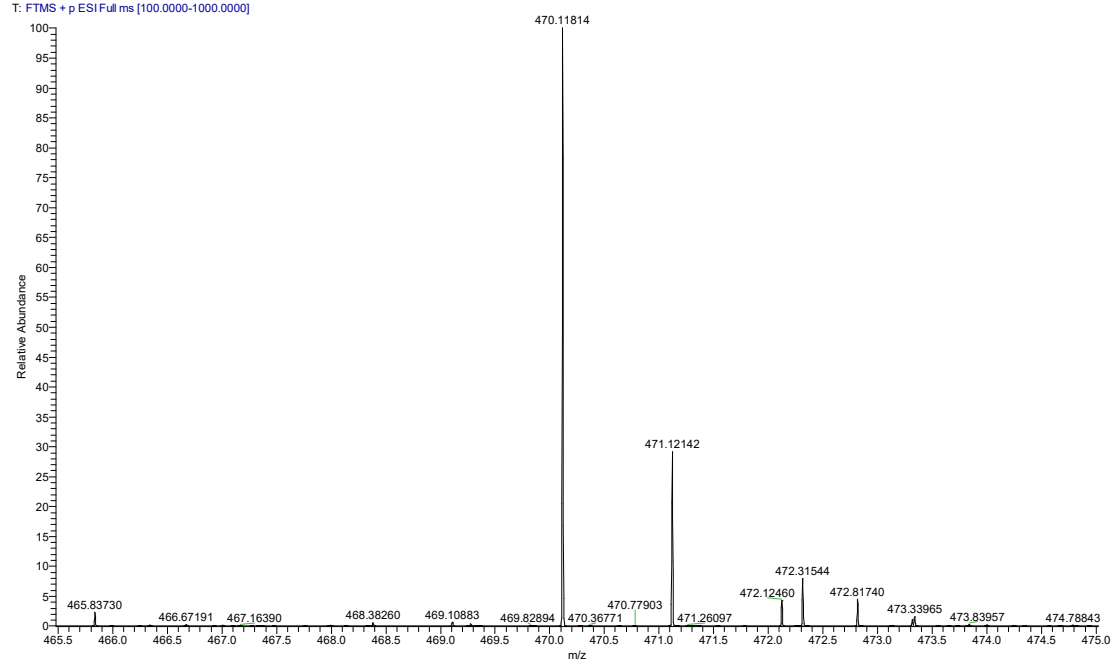
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



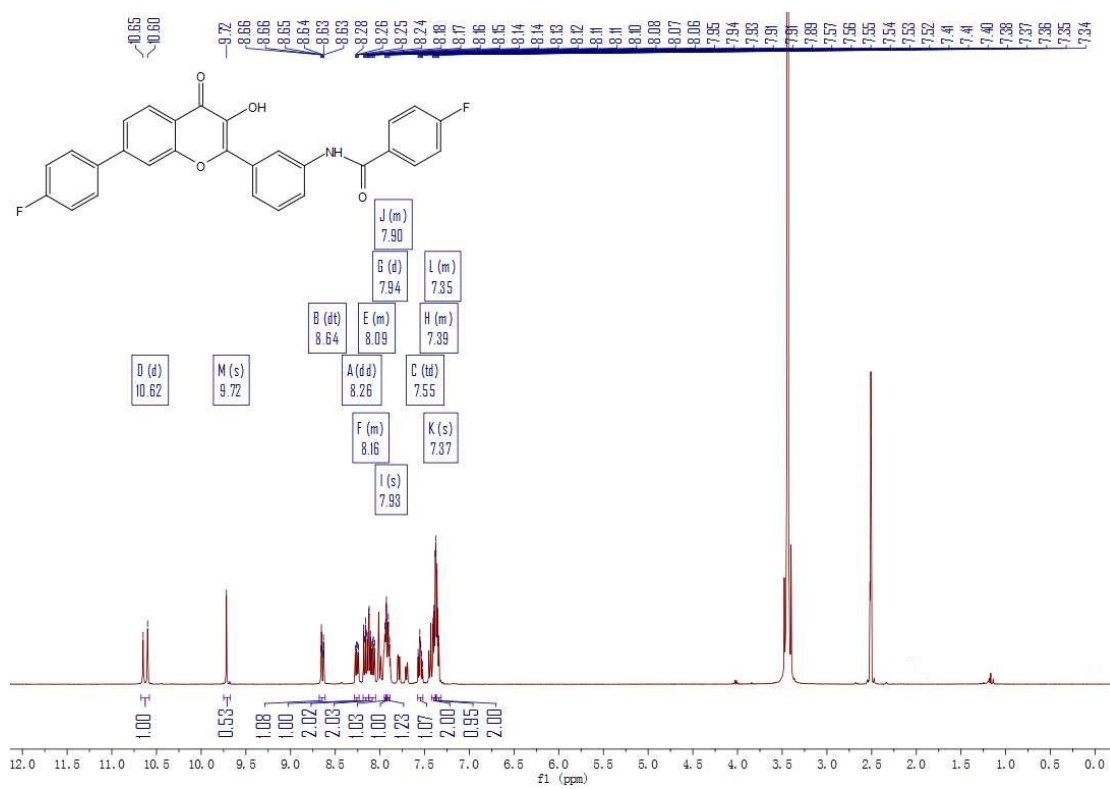
## 6. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7b

### HR MS

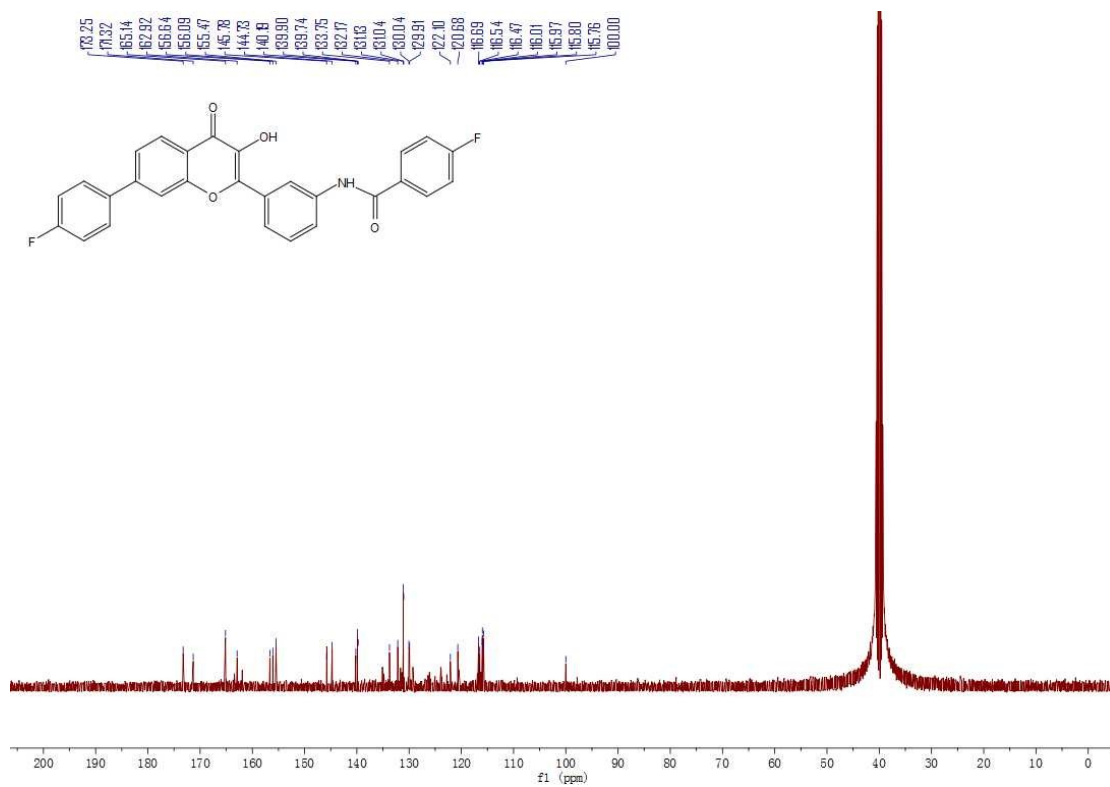
CDL-16 #6-24 RT: 0.03-0.11 AV: 19 NL: 1.99E7  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



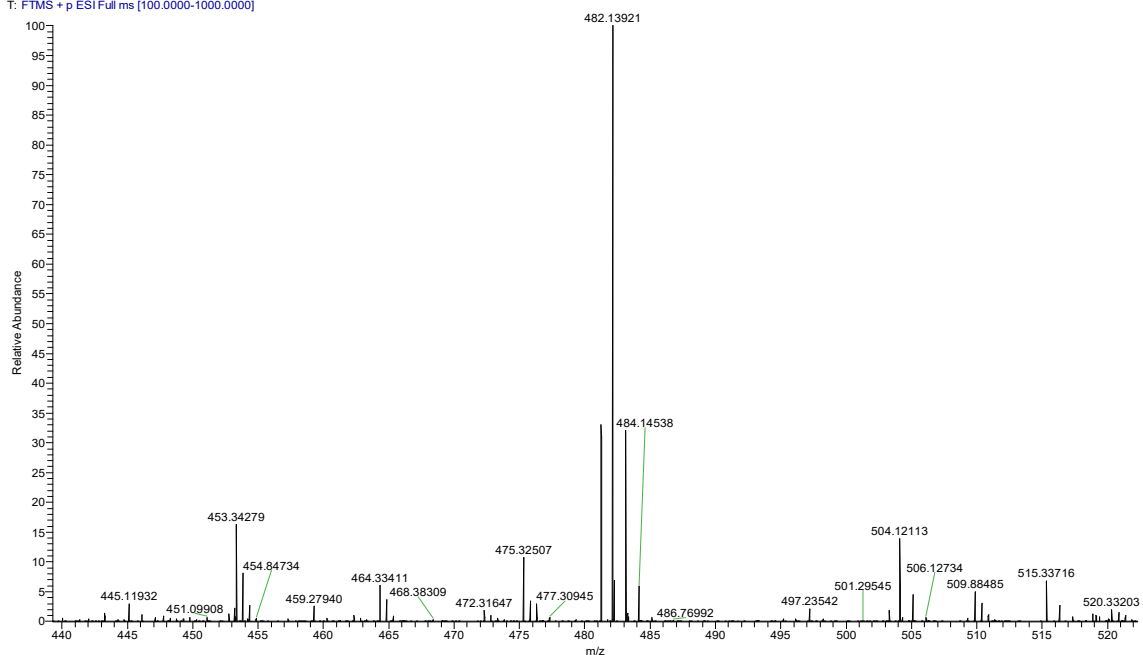
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



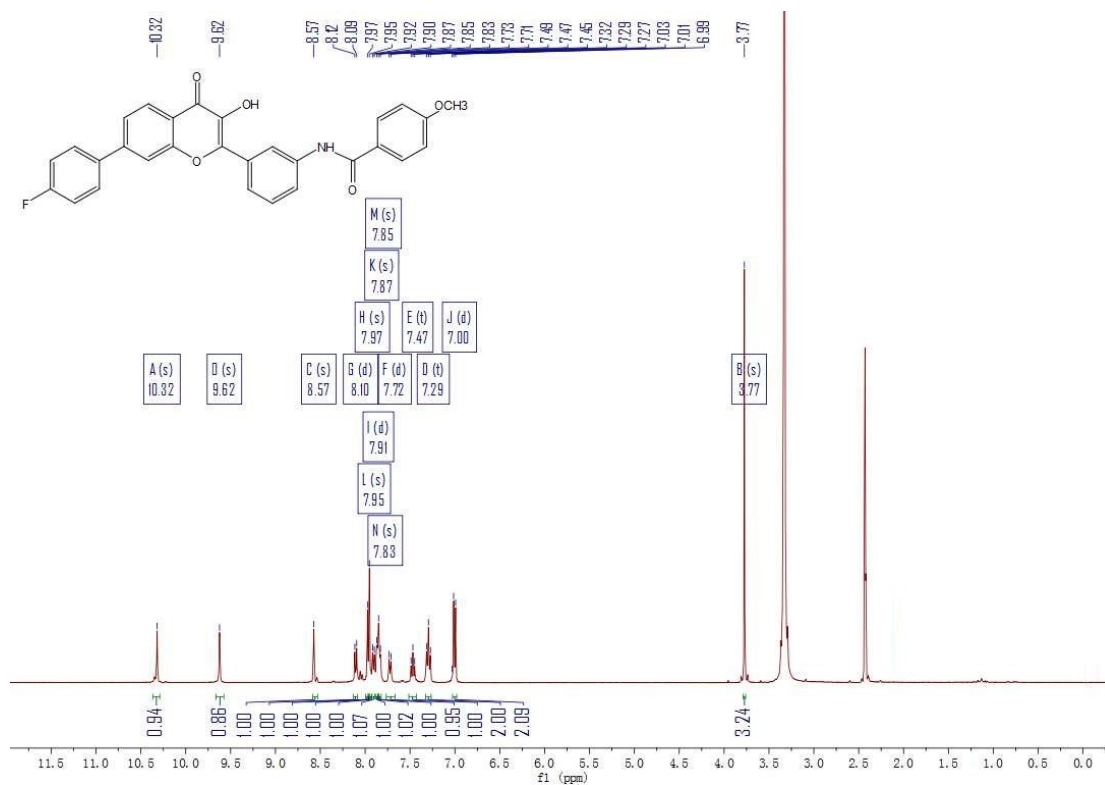
## 7. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7c**

### HRMS

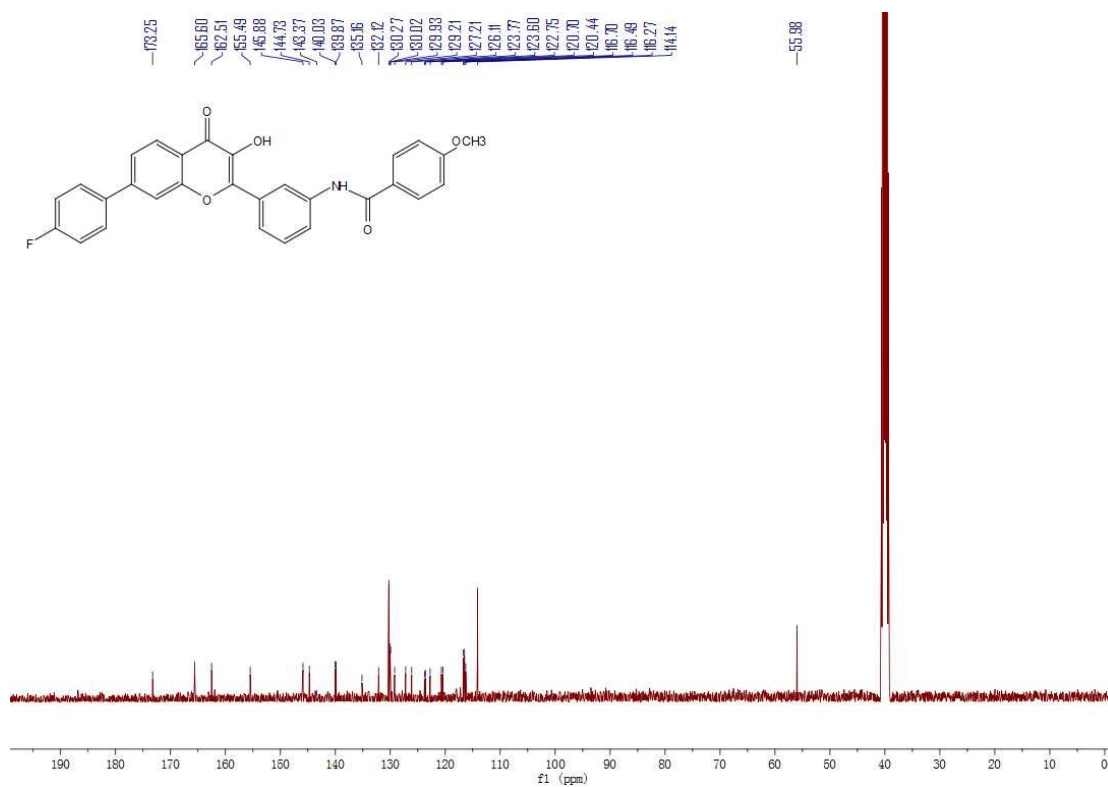
Q9 #10-19 RT: 0.05-0.09 AV: 10 NL: 2.46E8  
T: FTMS + p ESI Full ms (100.0000-1000.0000)



### <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



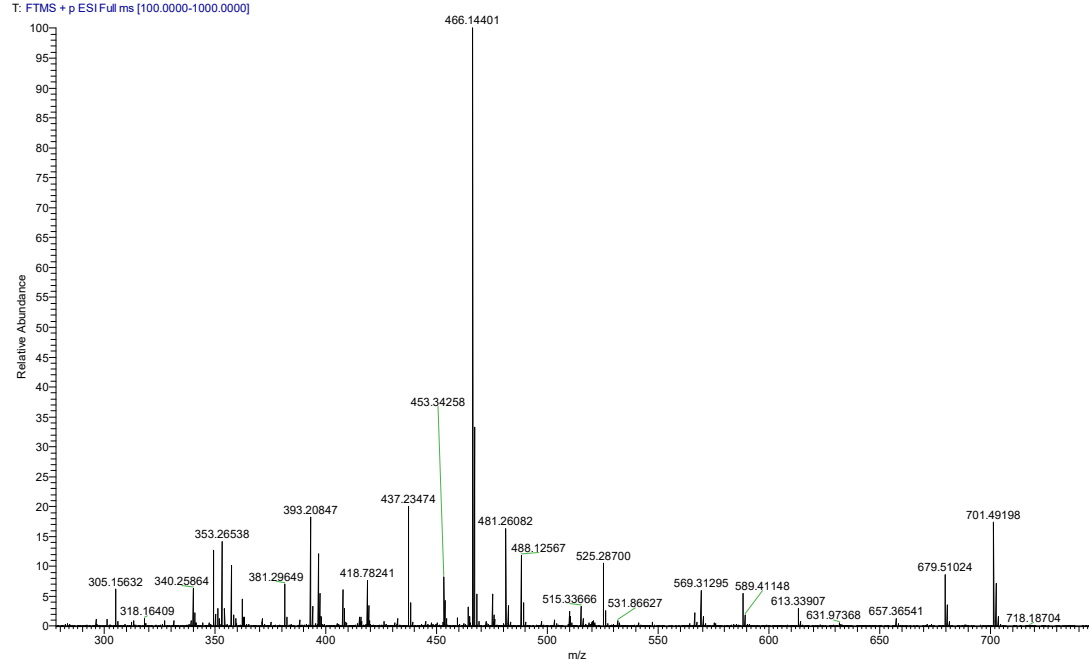
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



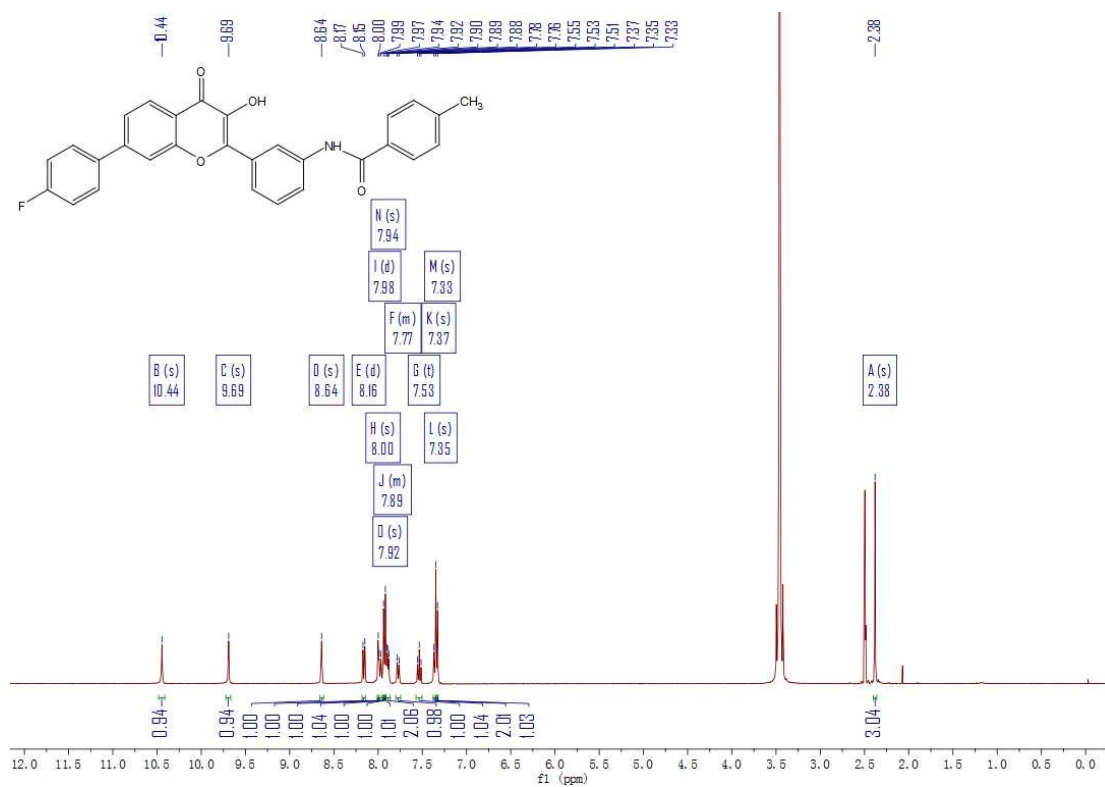
## 8. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7d

### HRMS

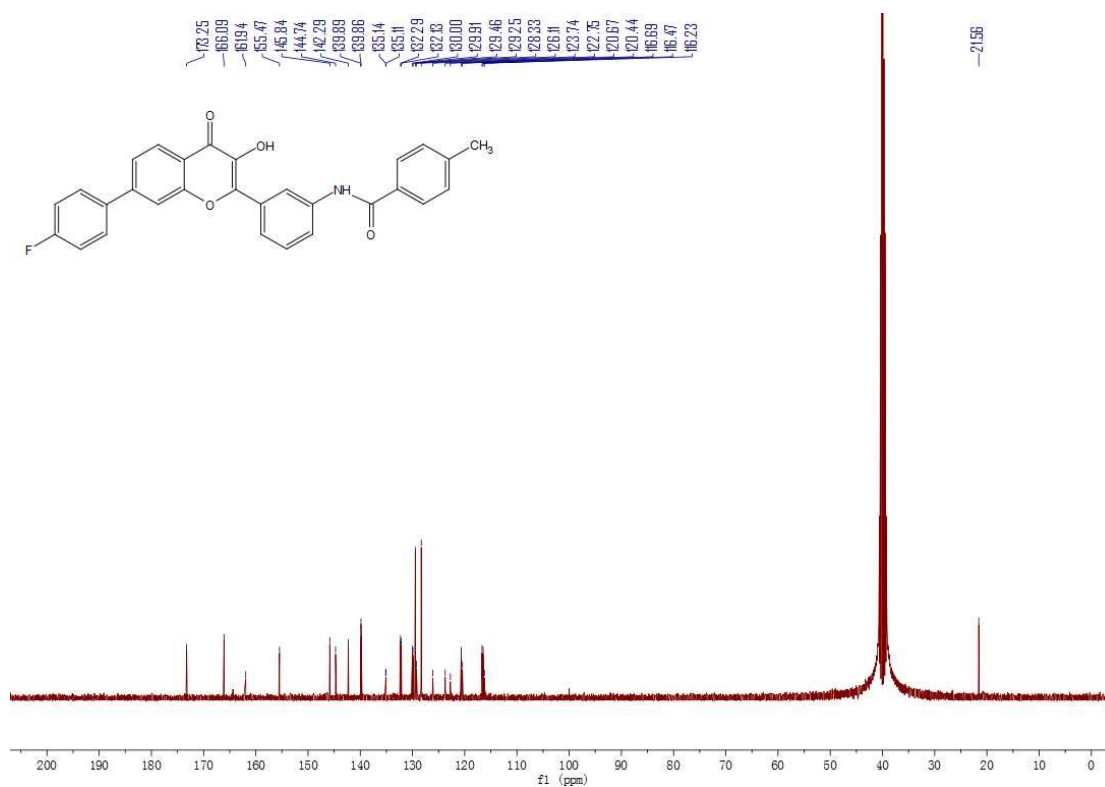
Q10 #12-21 RT: 0.06-0.10 AV: 10 NL: 5.70E8  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



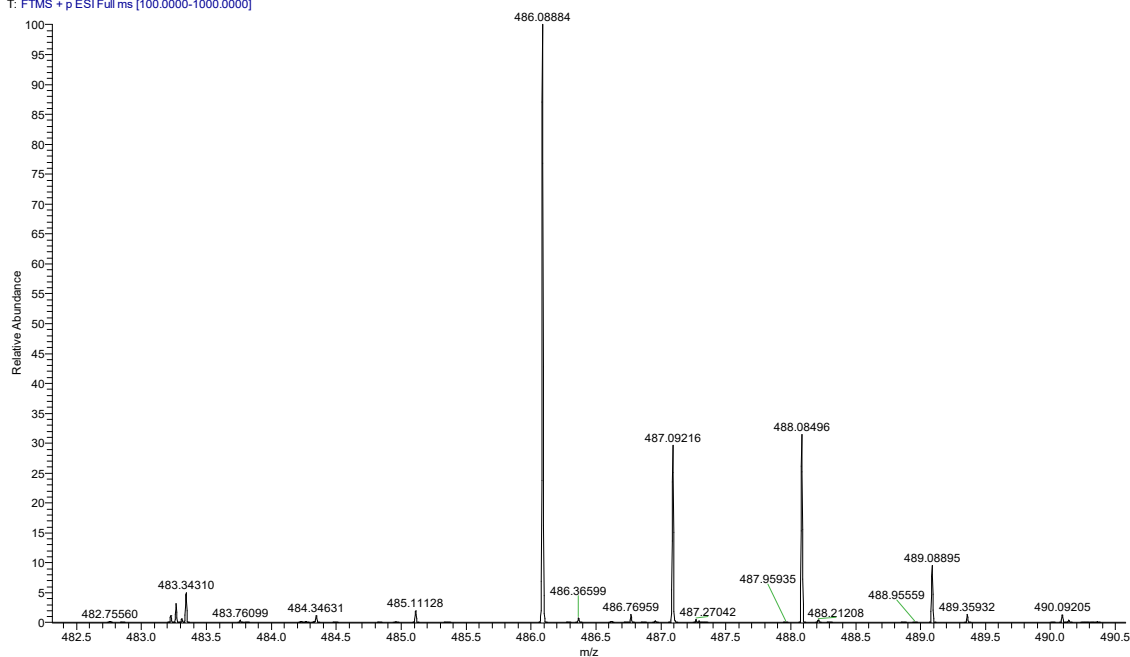
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



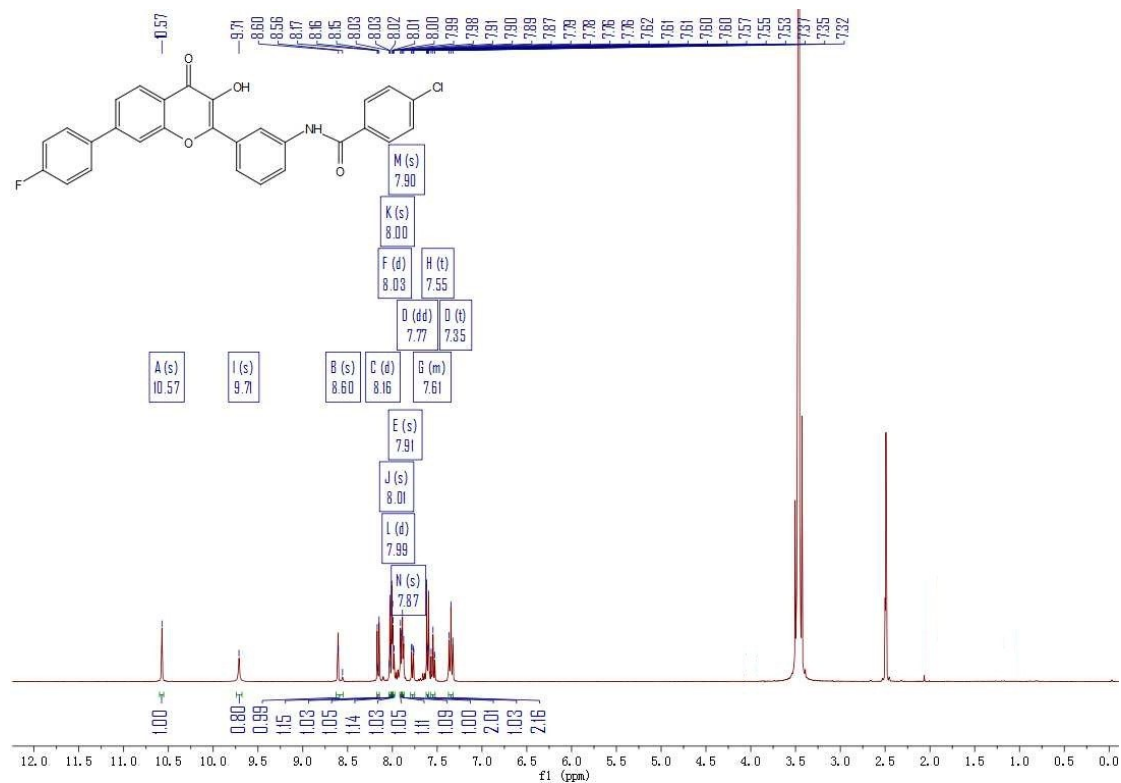
## 9. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7e**

### HRMS

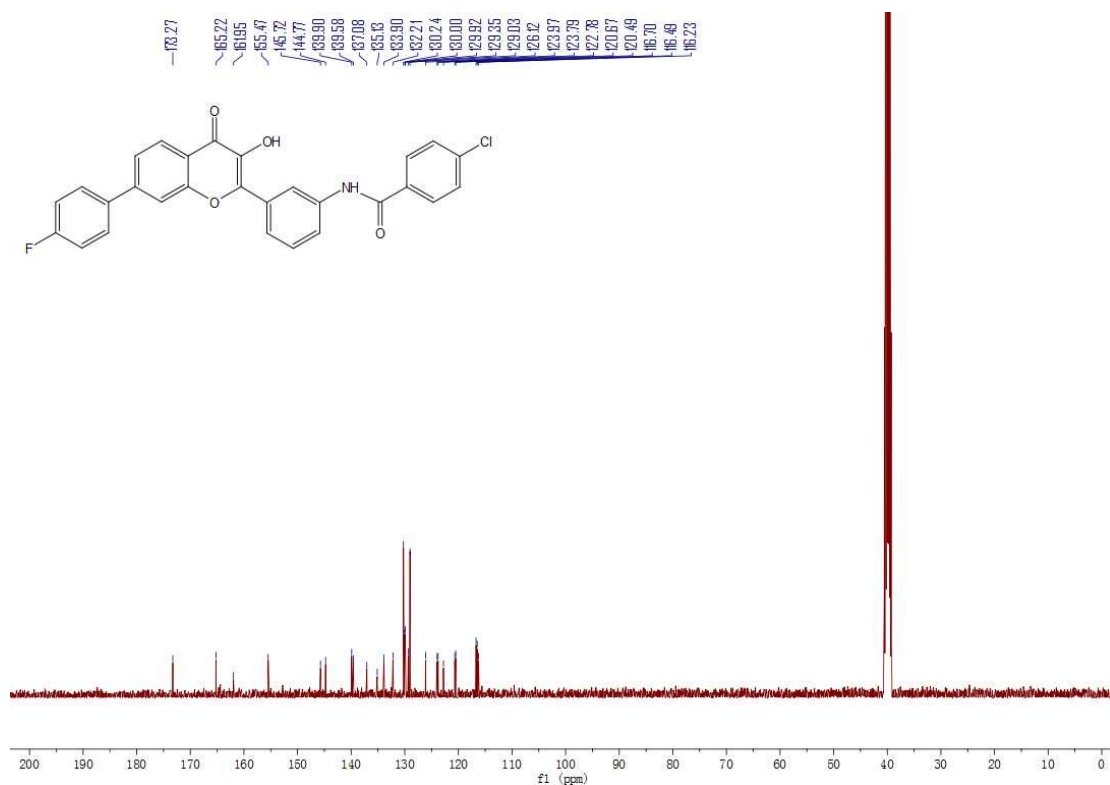
CDL-17 #6-21 RT: 0.03-0.10 AV: 16 NL: 2.32E7  
T: FTMS → p ESI Fullms [100.0000-1000.0000]



### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



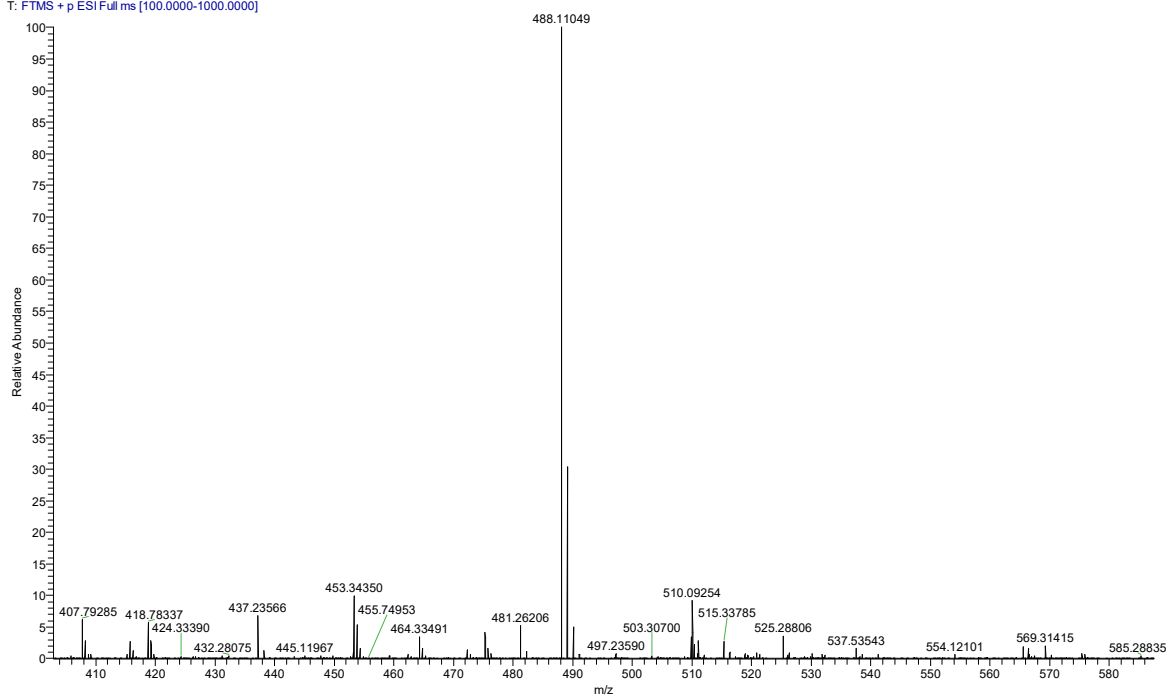
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



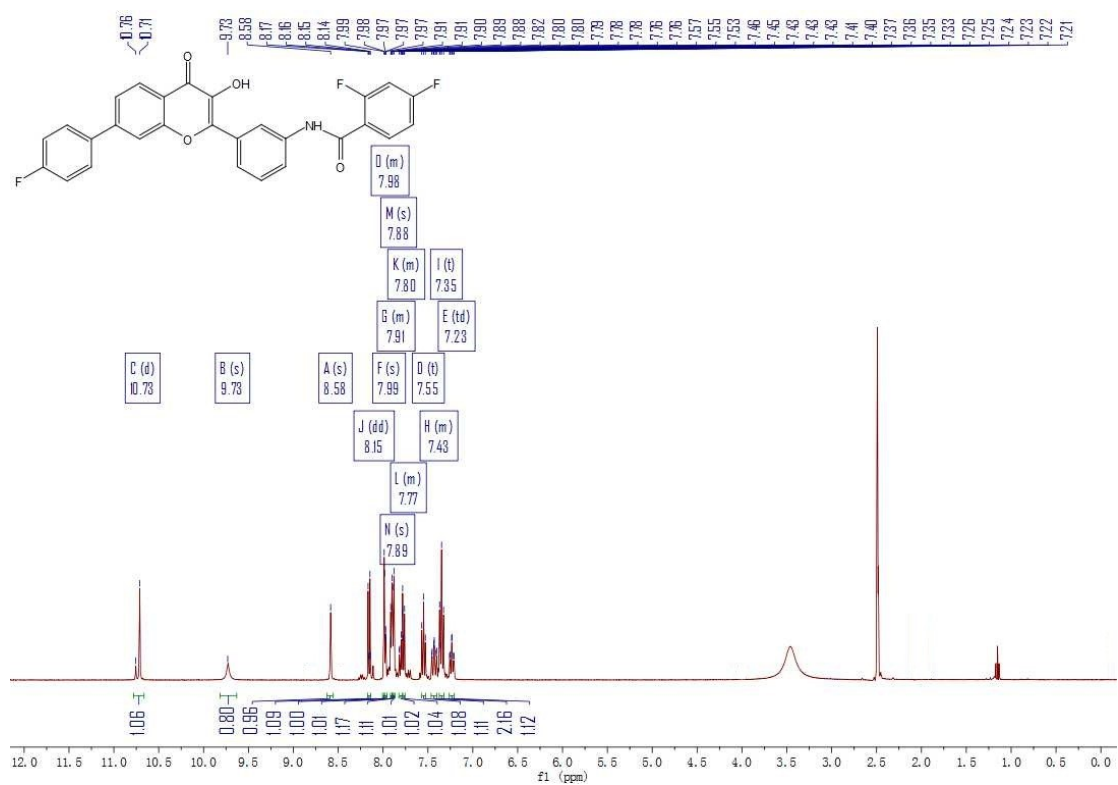
## 10. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7f

### HRMS

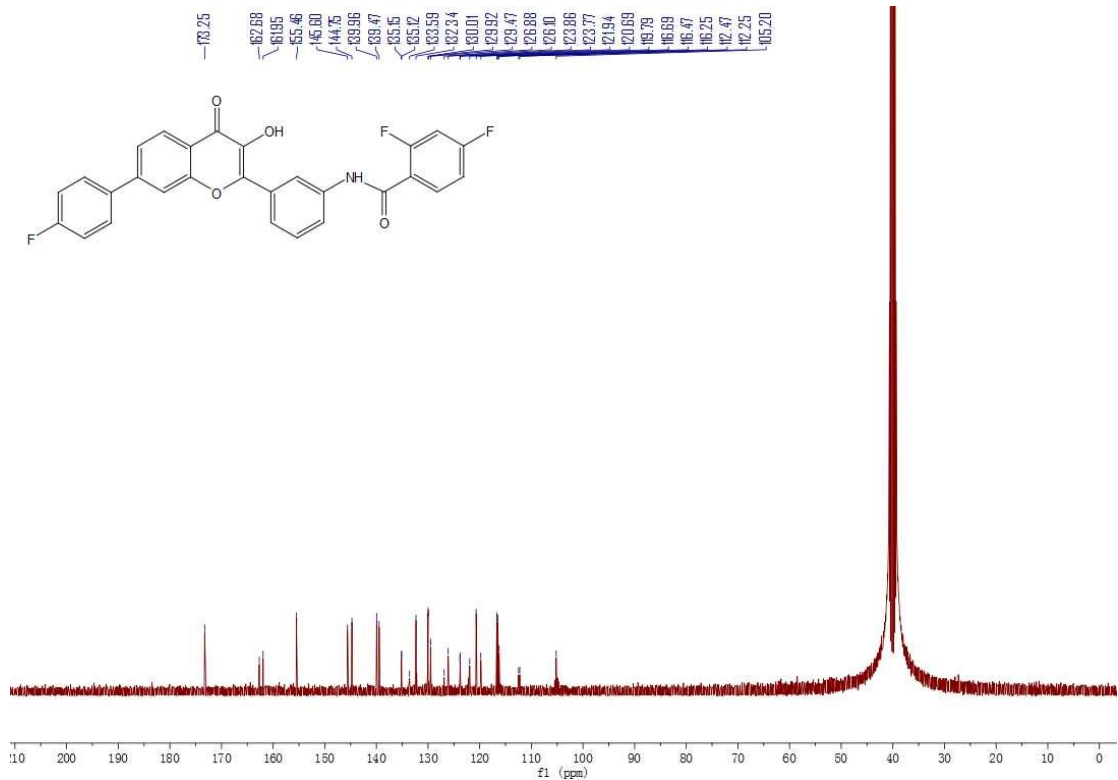
ZX-26 #19-27 RT: 0.08-0.12 AV: 9 NL: 3.67E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)

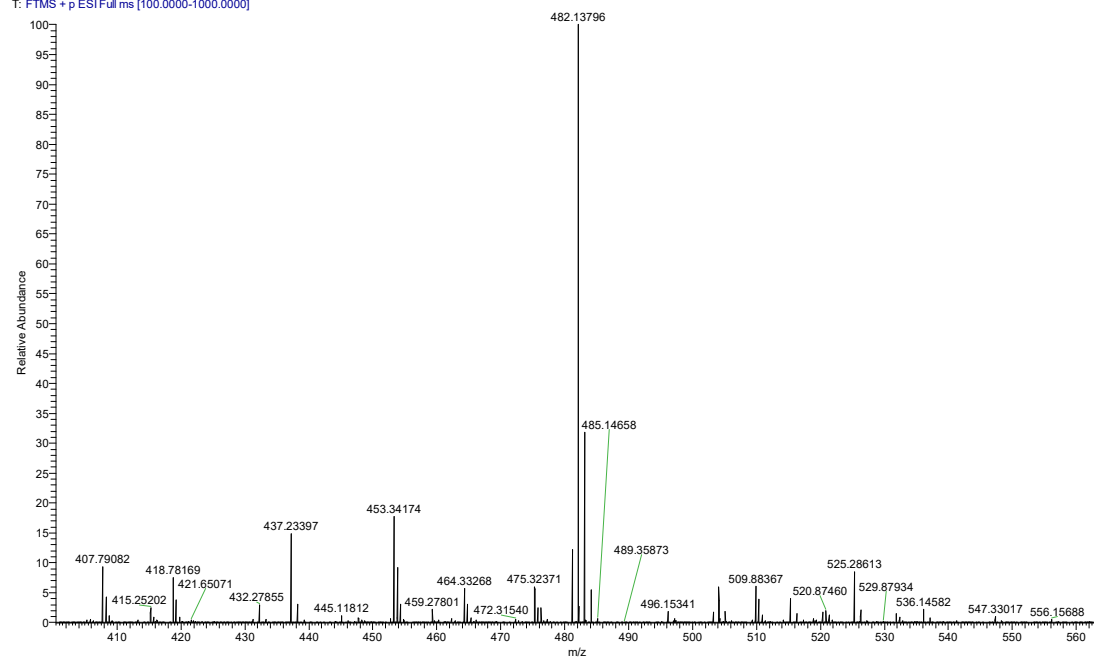




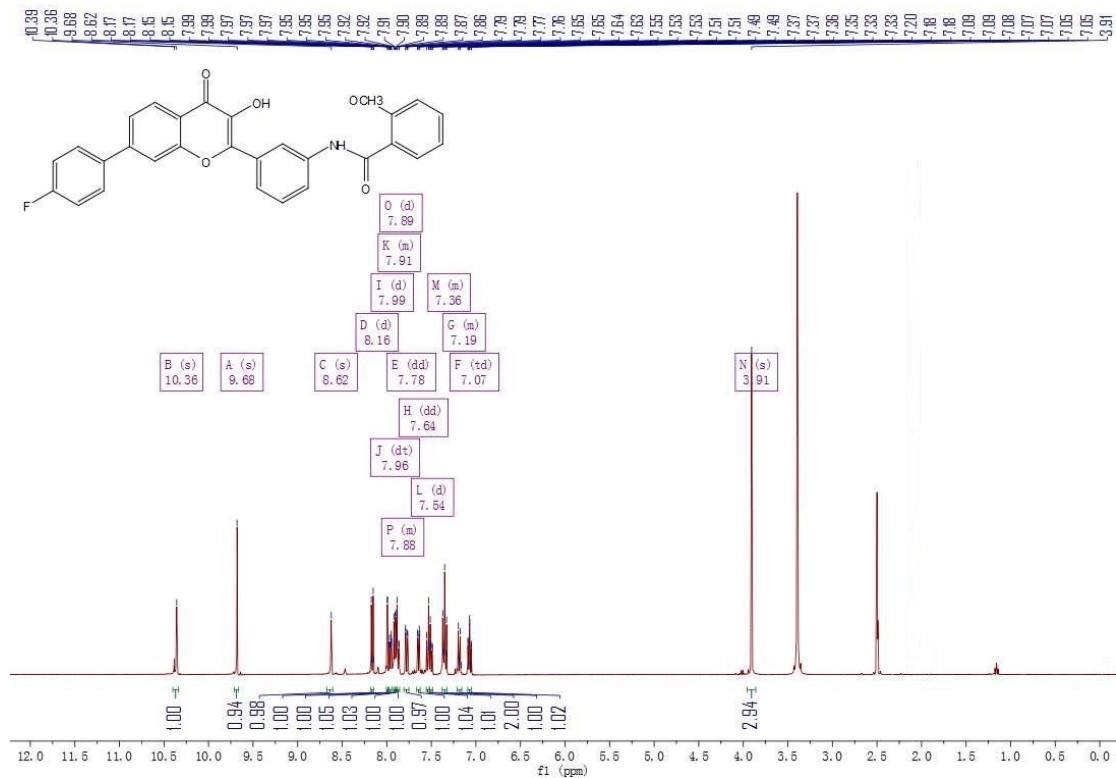
# 11. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7g**

## HRMS

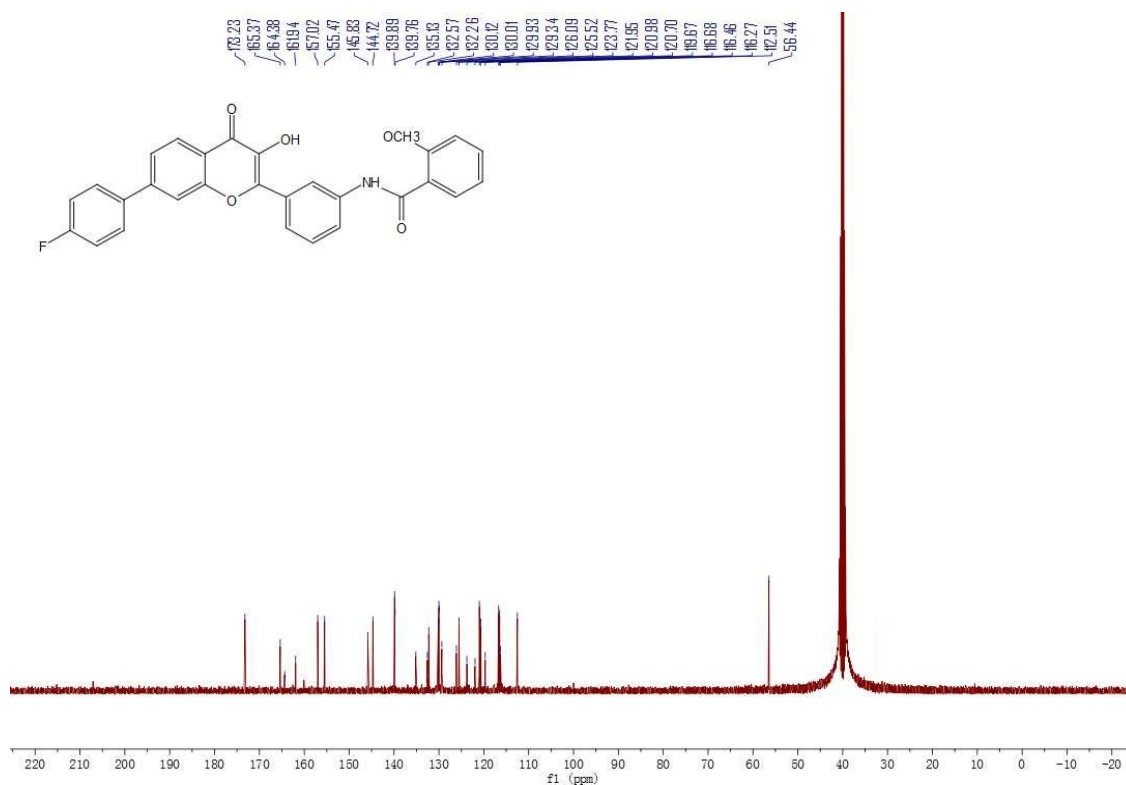
CDL-18 #7-25 RT: 0.04-0.12 AV: 19 NL: 2.77E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



## <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



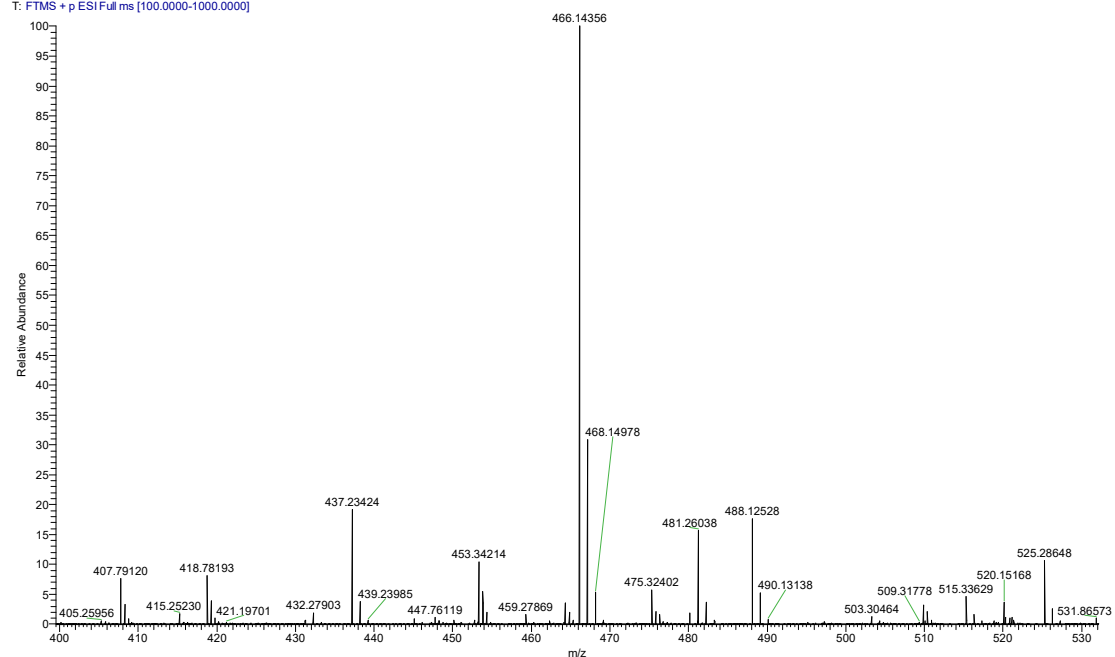
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



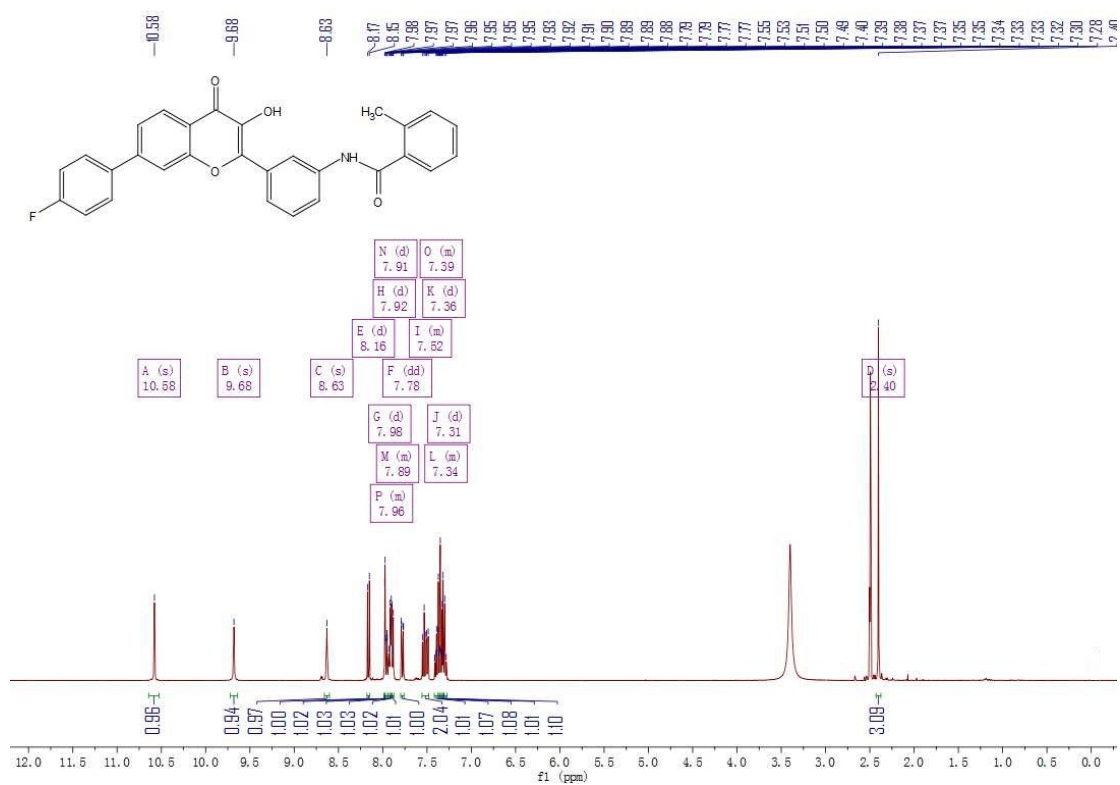
## 12. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7h

### HRMS

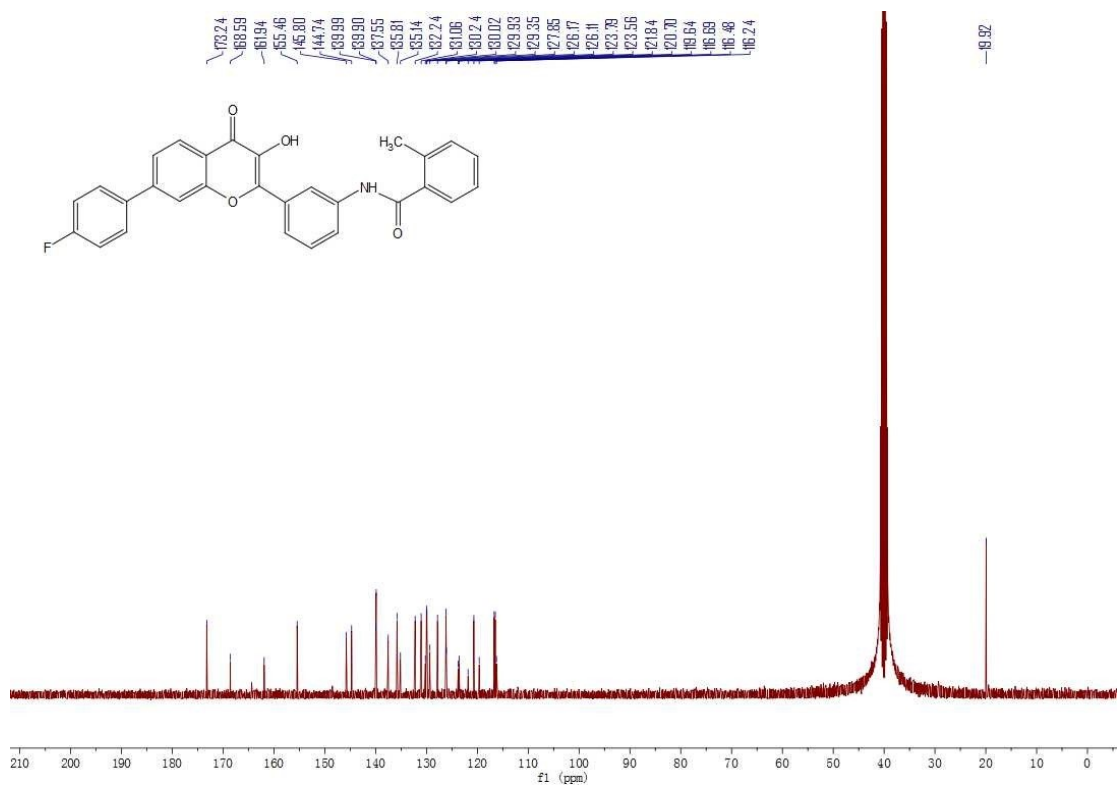
CDL-19 #7-23 RT: 0.04-0.11 AV: 17 NL: 2.96E8  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



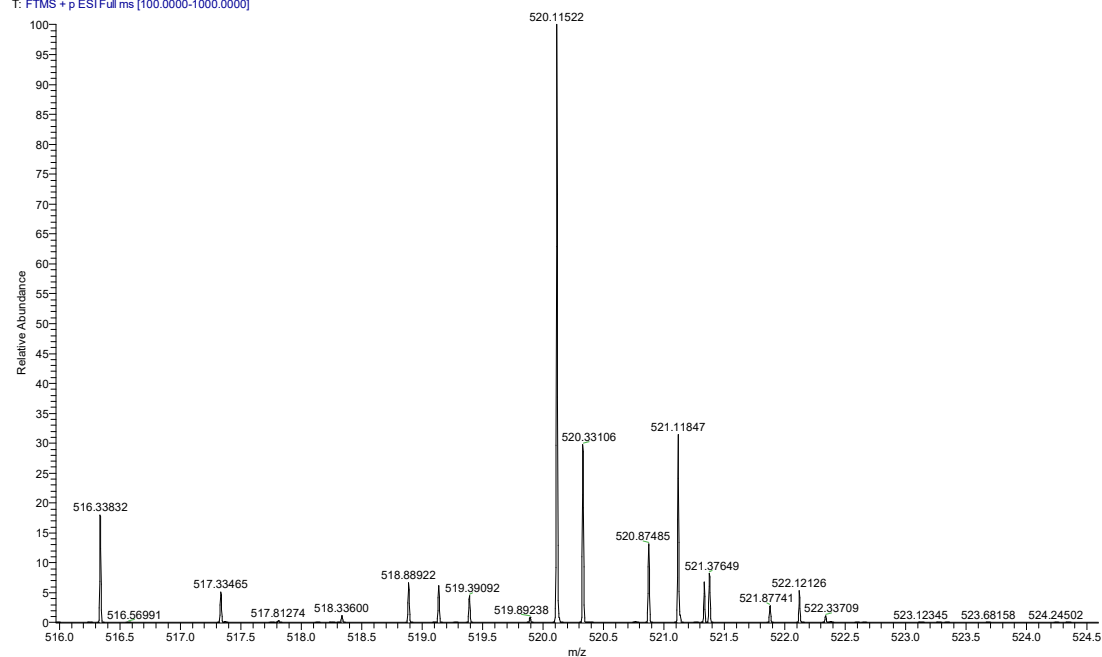
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



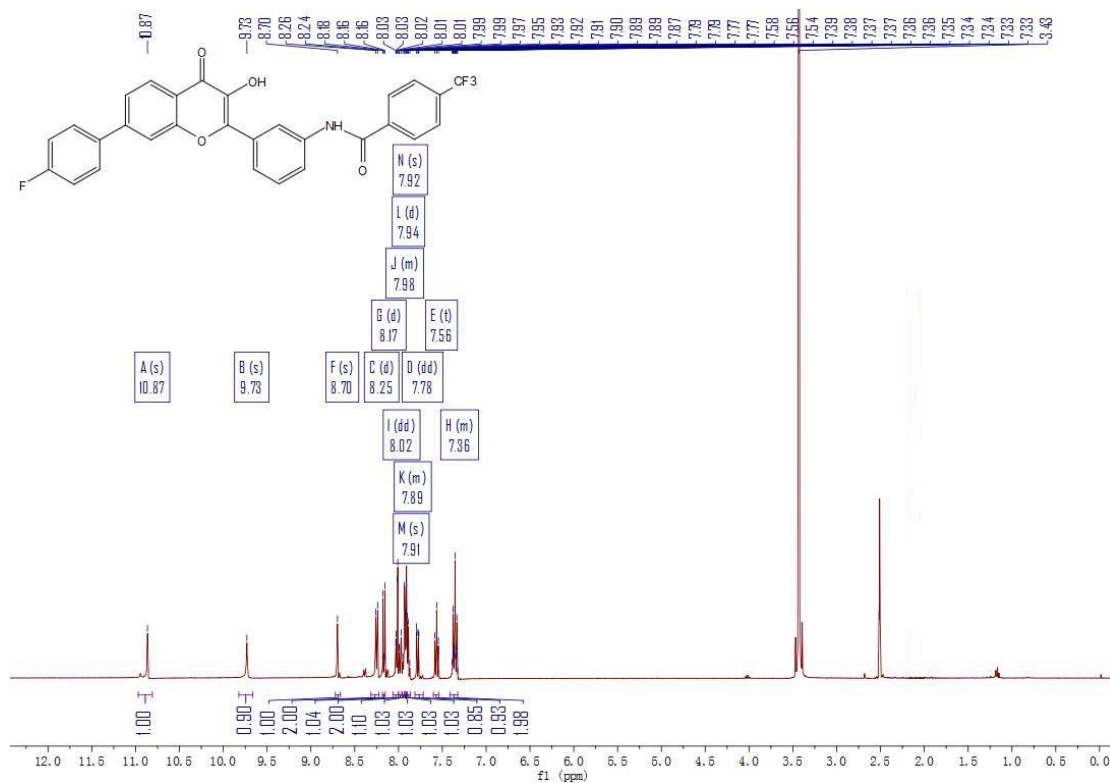
### 13. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7i**

#### HRMS

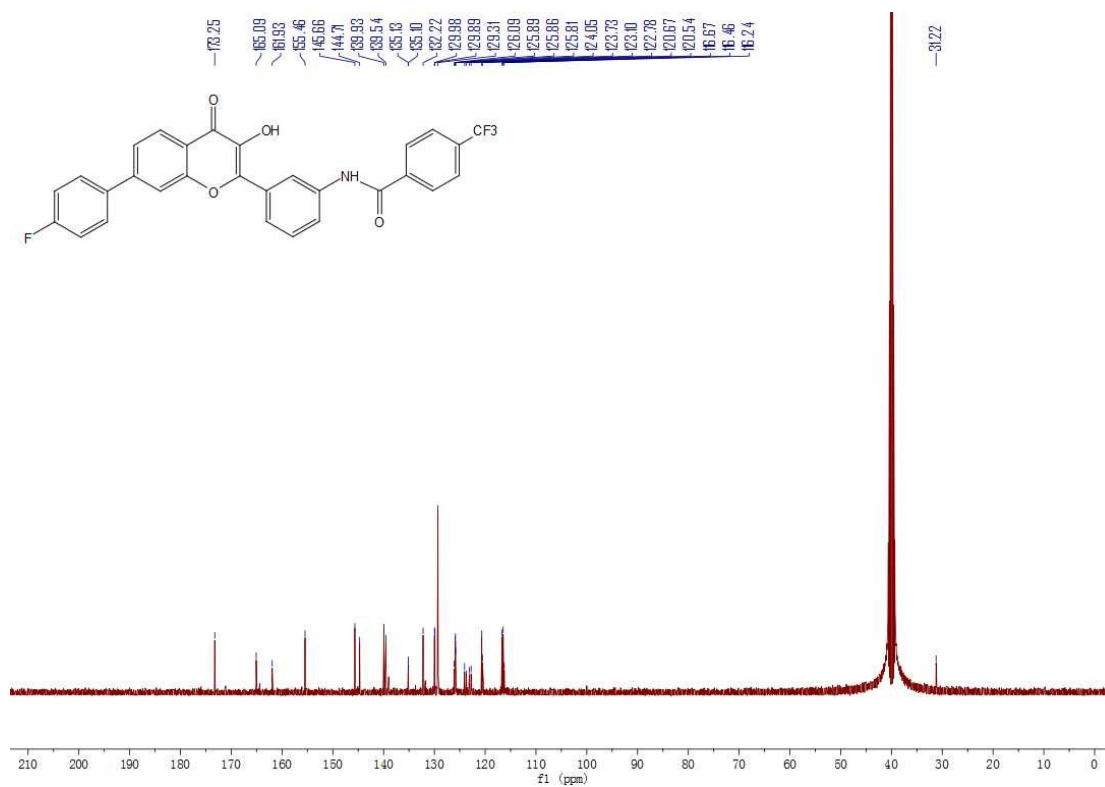
CDL-20 #7-23 RT: 0.04-0.11 AV: 17 NL: 2.41E7  
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#### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



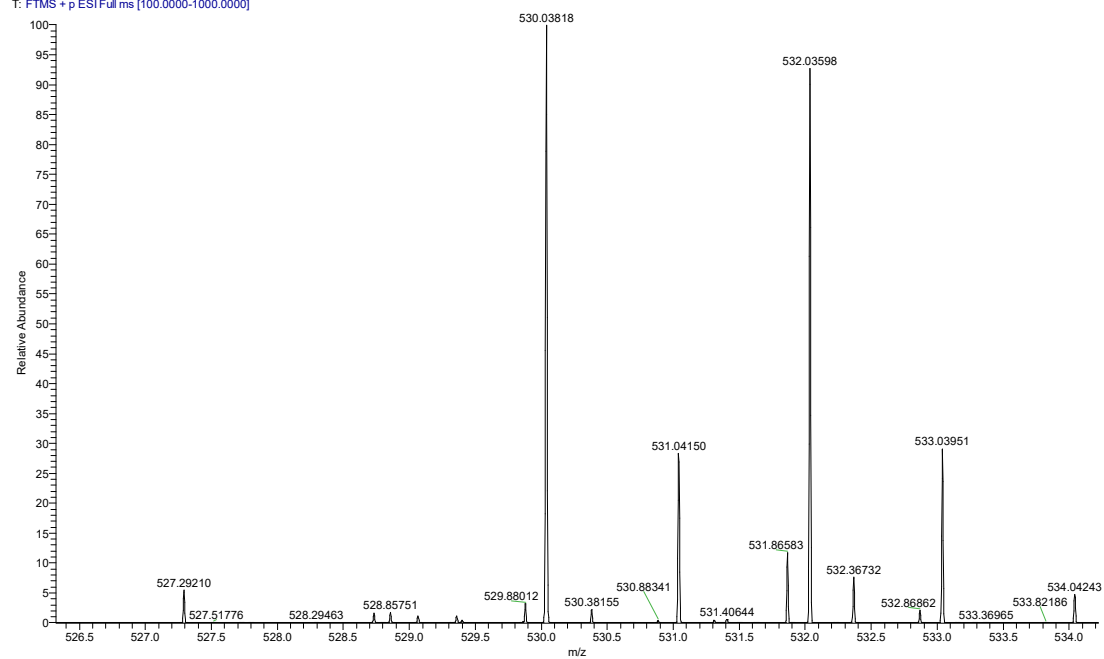
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



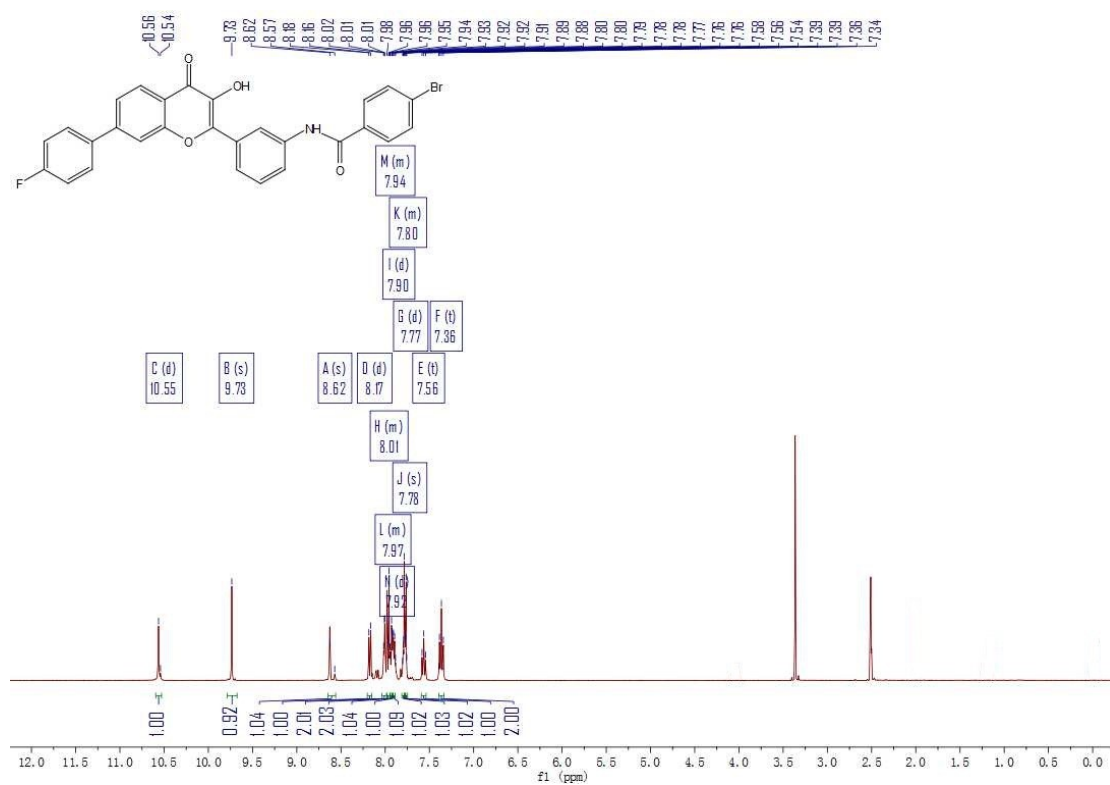
#### 14. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7j

##### HR MS

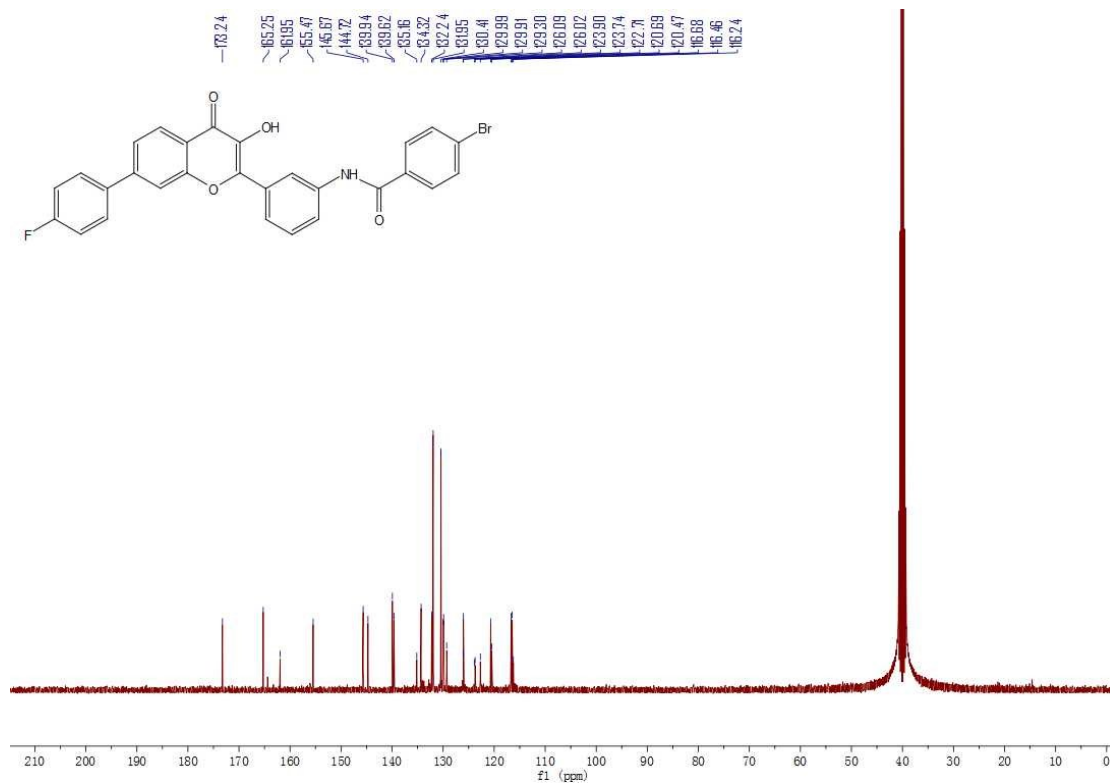
CDL-21 #7-25 RT: 0.03-0.11 AV: 19 NL: 1.80E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



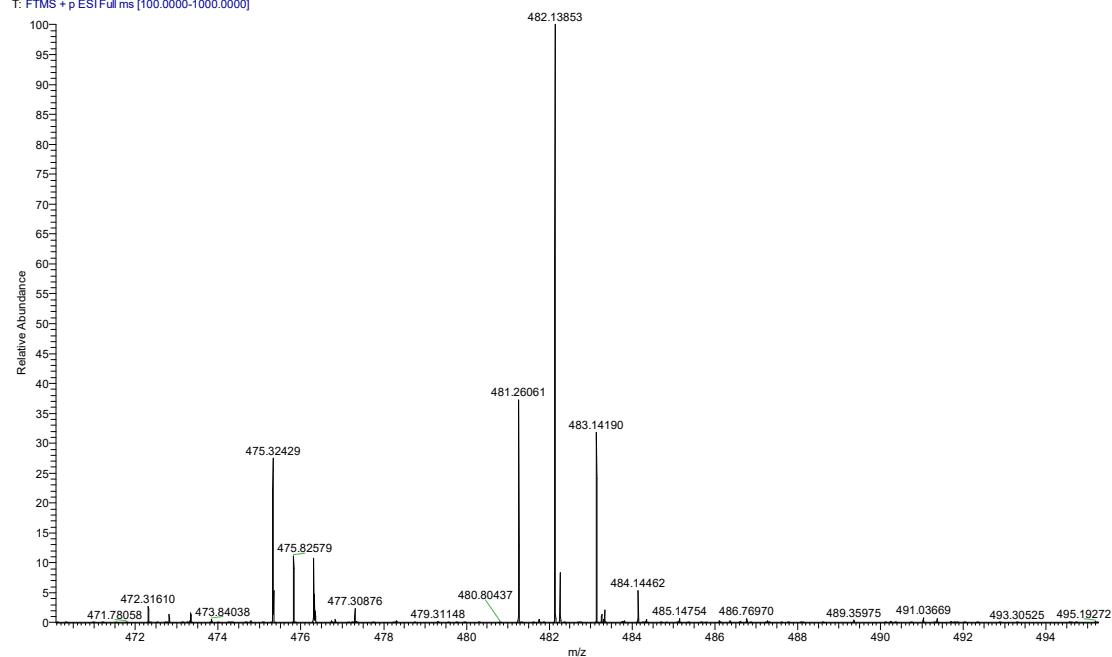
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



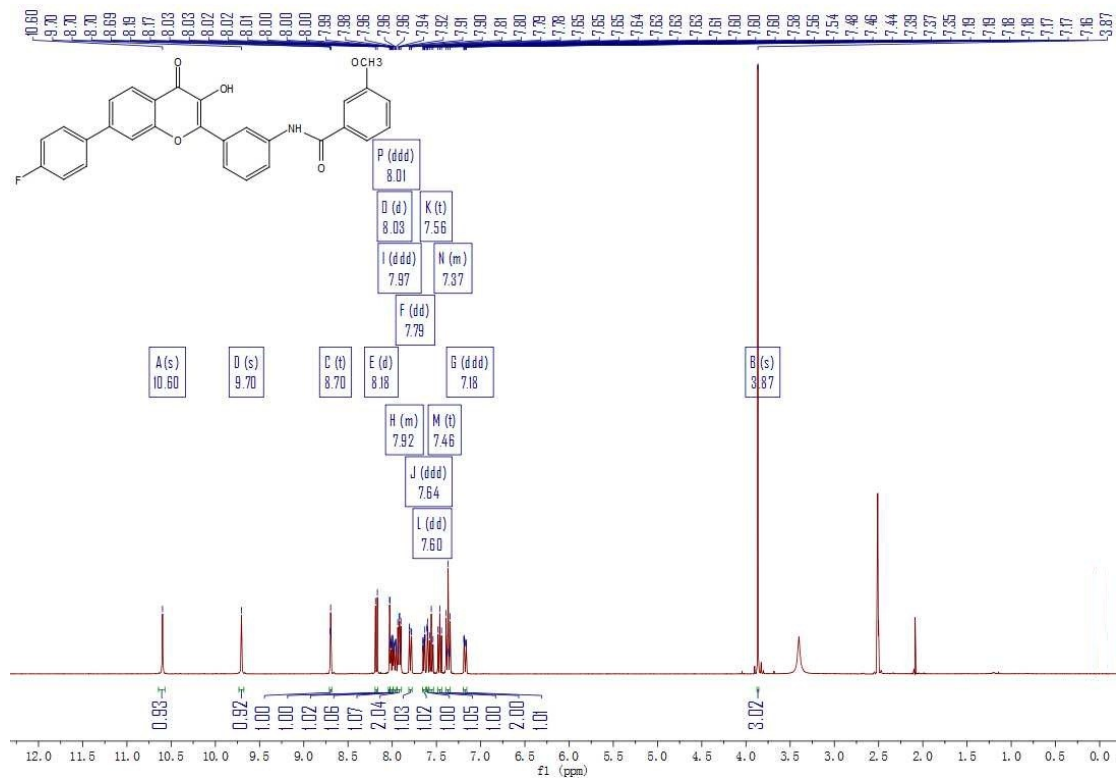
# 15. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7k**

## HRMS

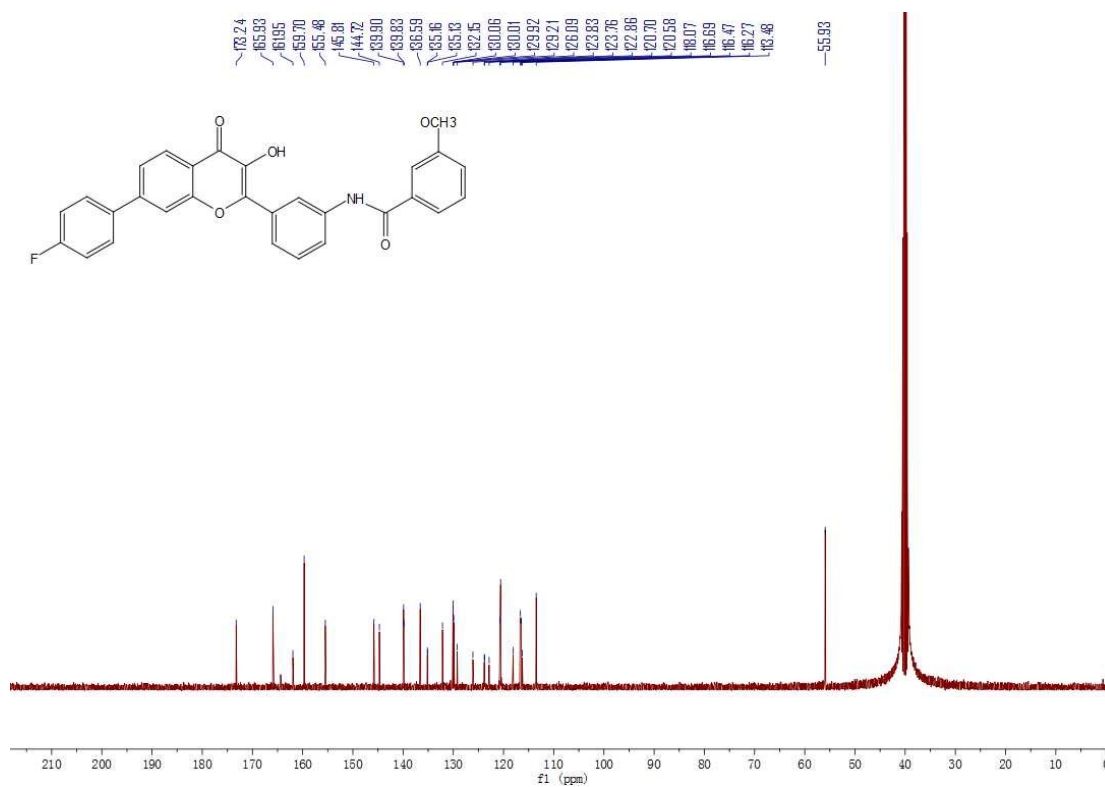
CDI-22 #9-23 RT: 0.05-0.11 AV: 15 NL: 6.19E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



## <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



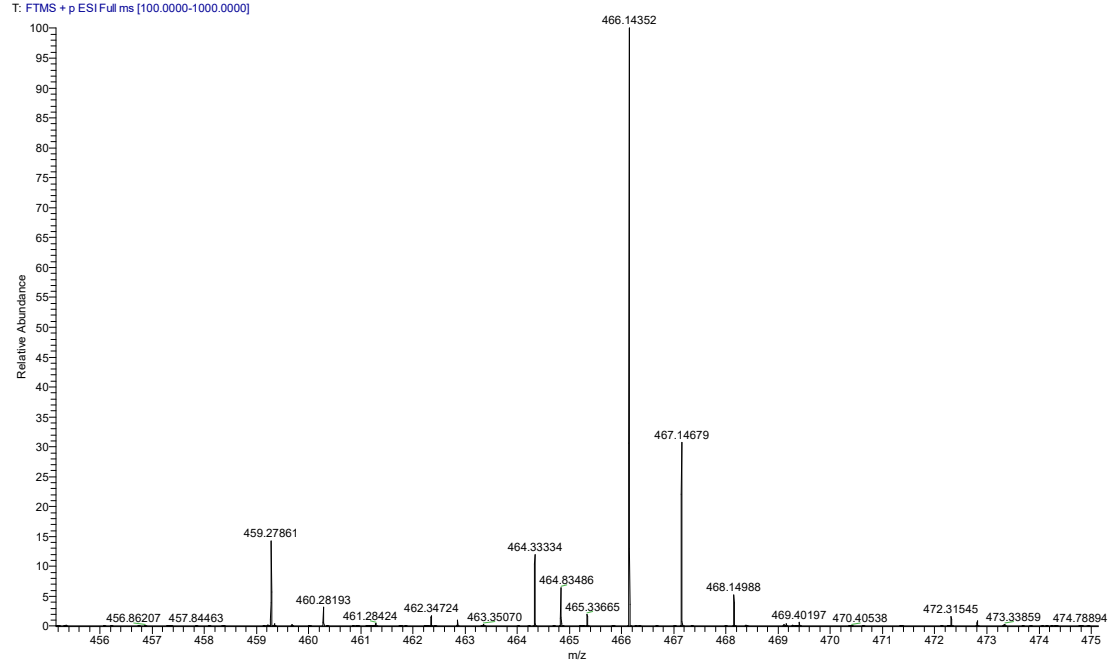
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



## 16. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 71

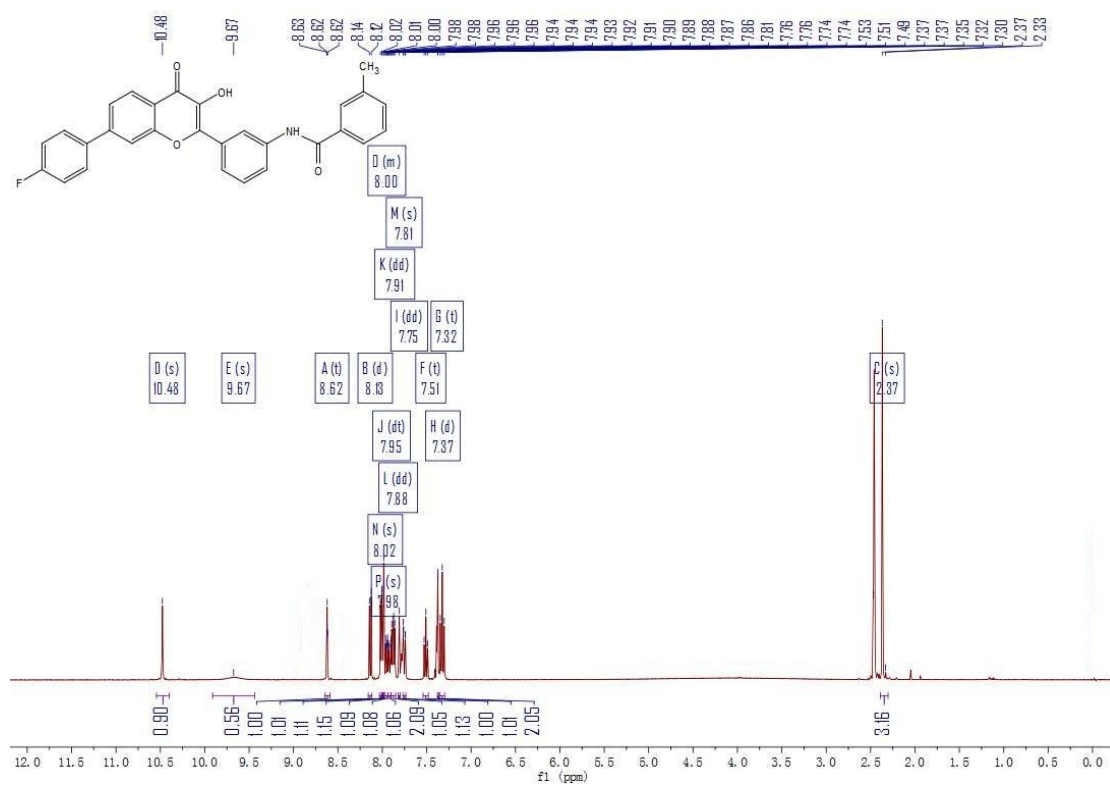
### HRMS

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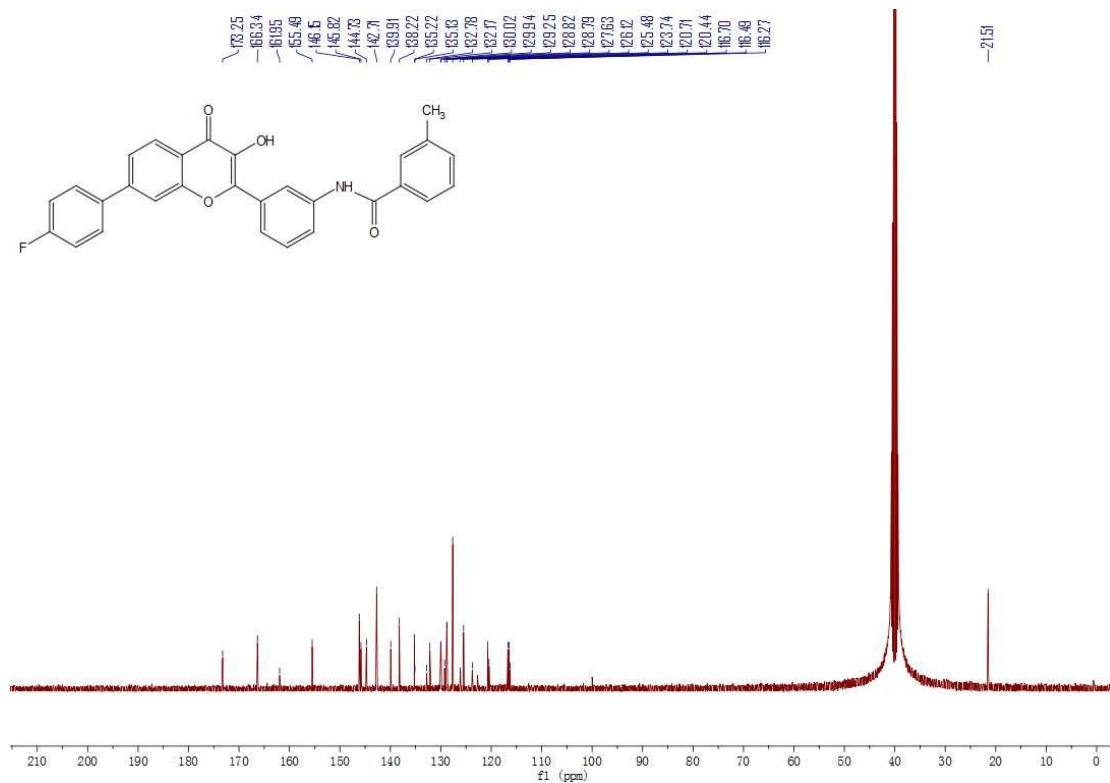




<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



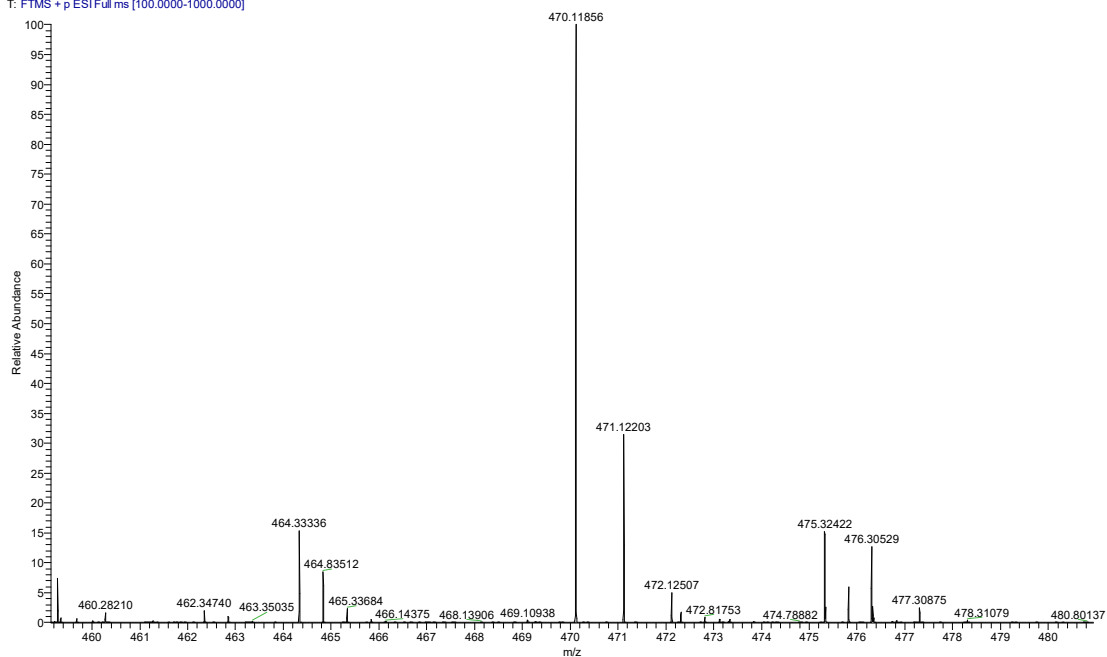
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



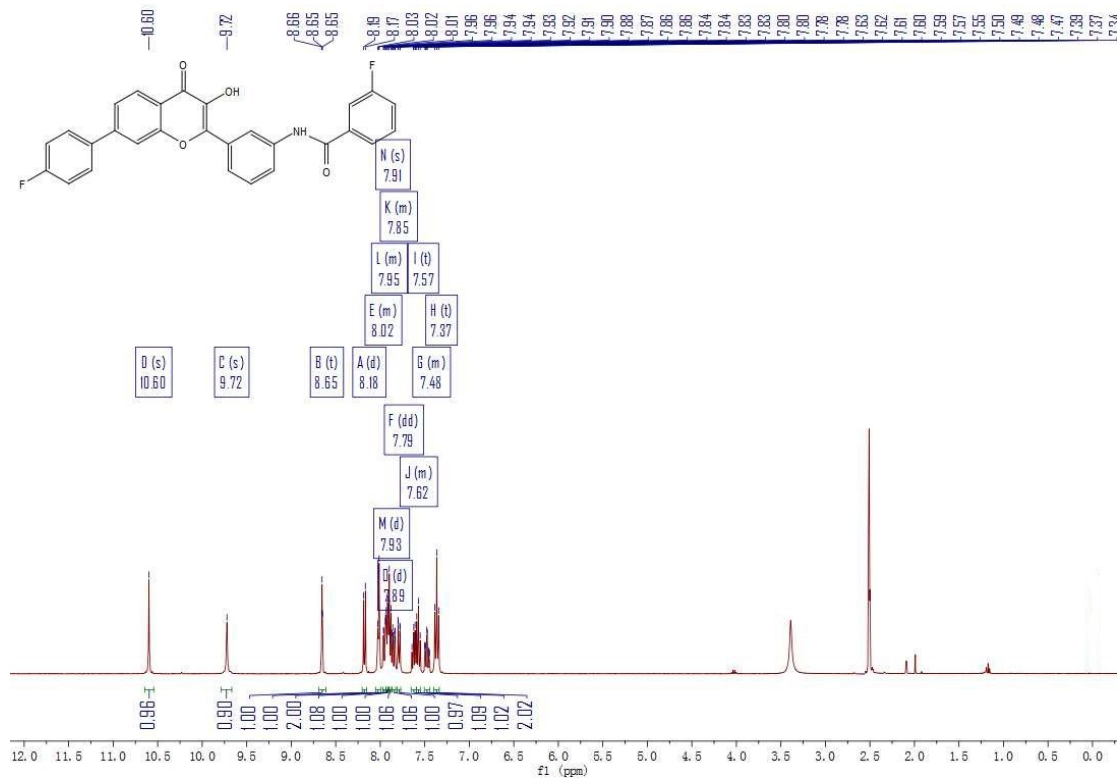
# 17. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7m**

## HRMS

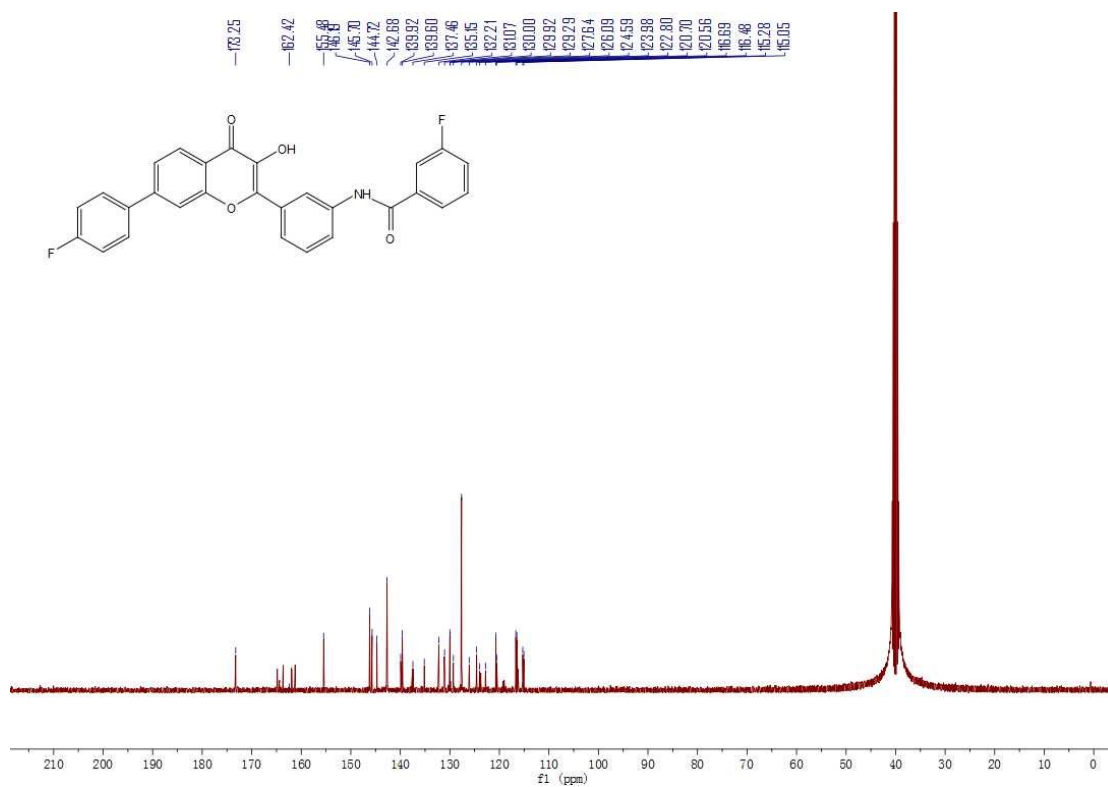
CDL-24 #5-25 RT: 0.03-0.12 AV: 21 NL: 9.52E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



## <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



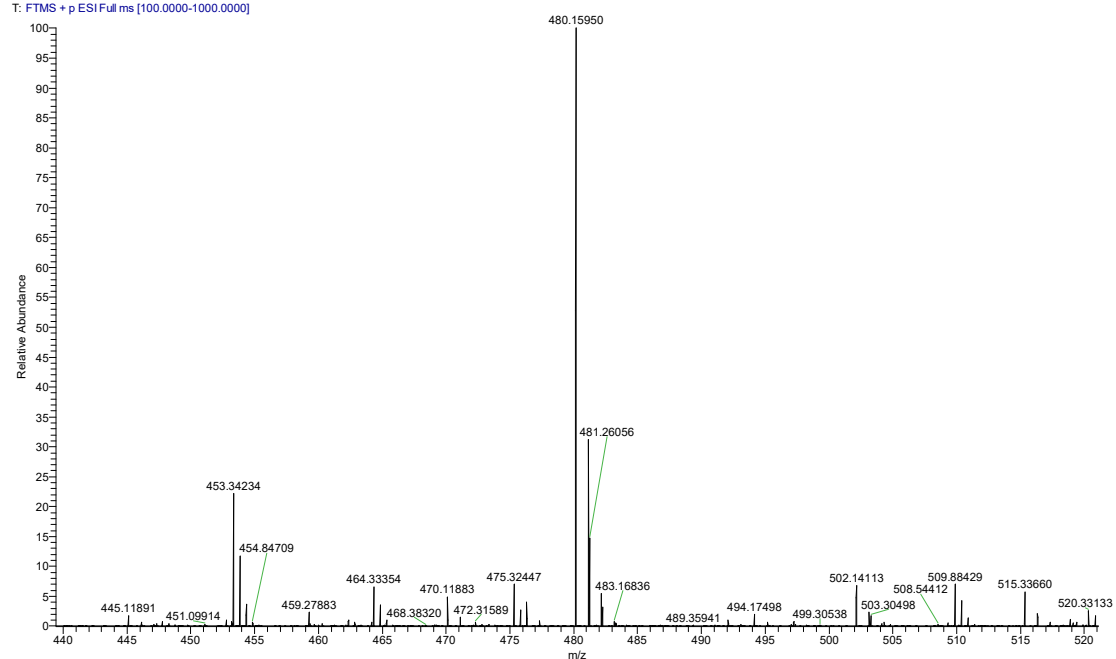
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



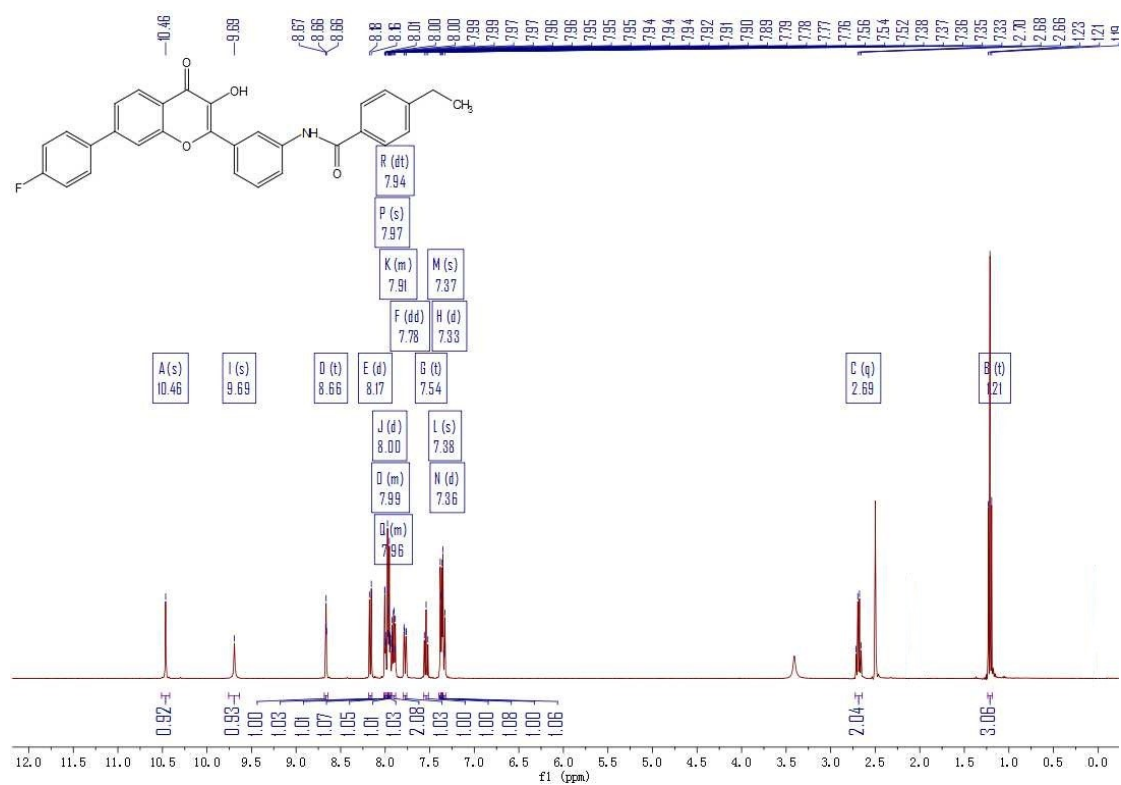
## 18. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound **7n**

### HRMS

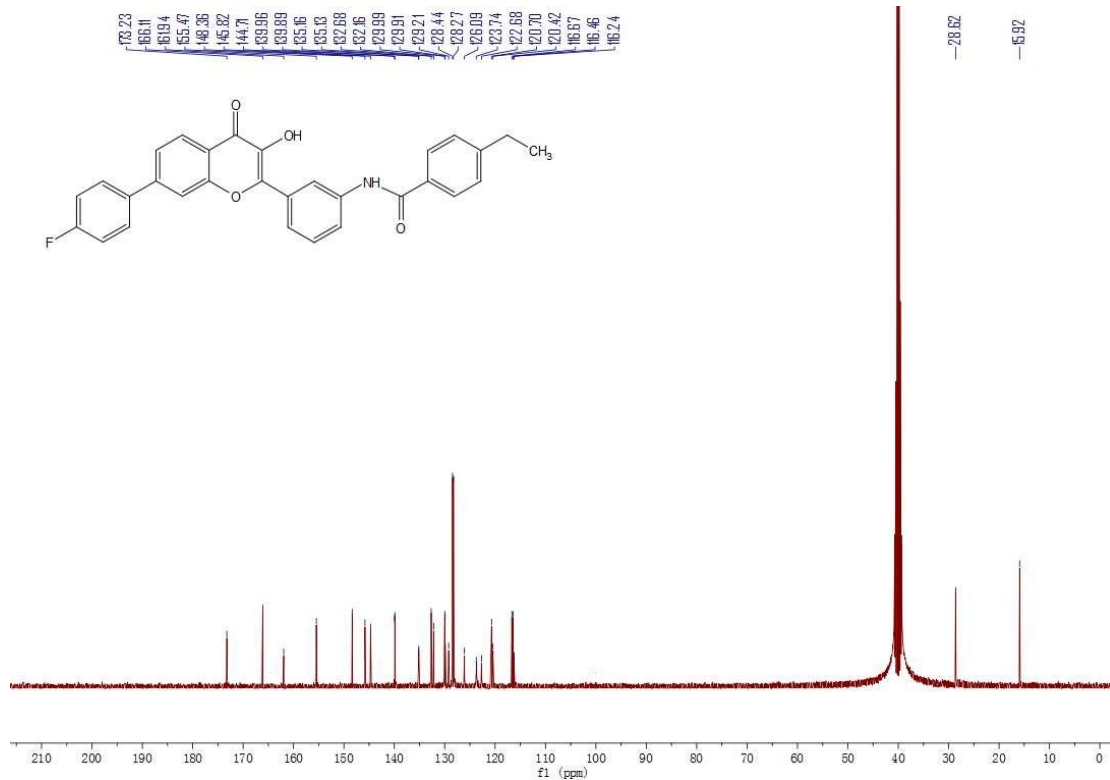
CDL-25 #5-24 RT: 0.03-0.11 AV: 20 NL: 1.82E8  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



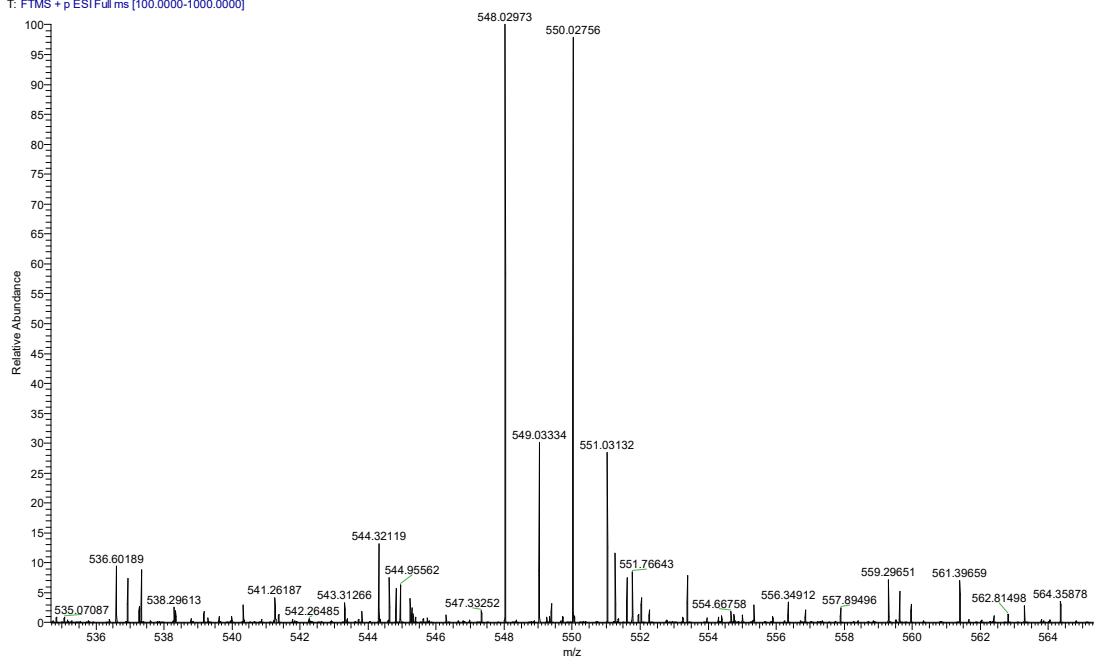
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



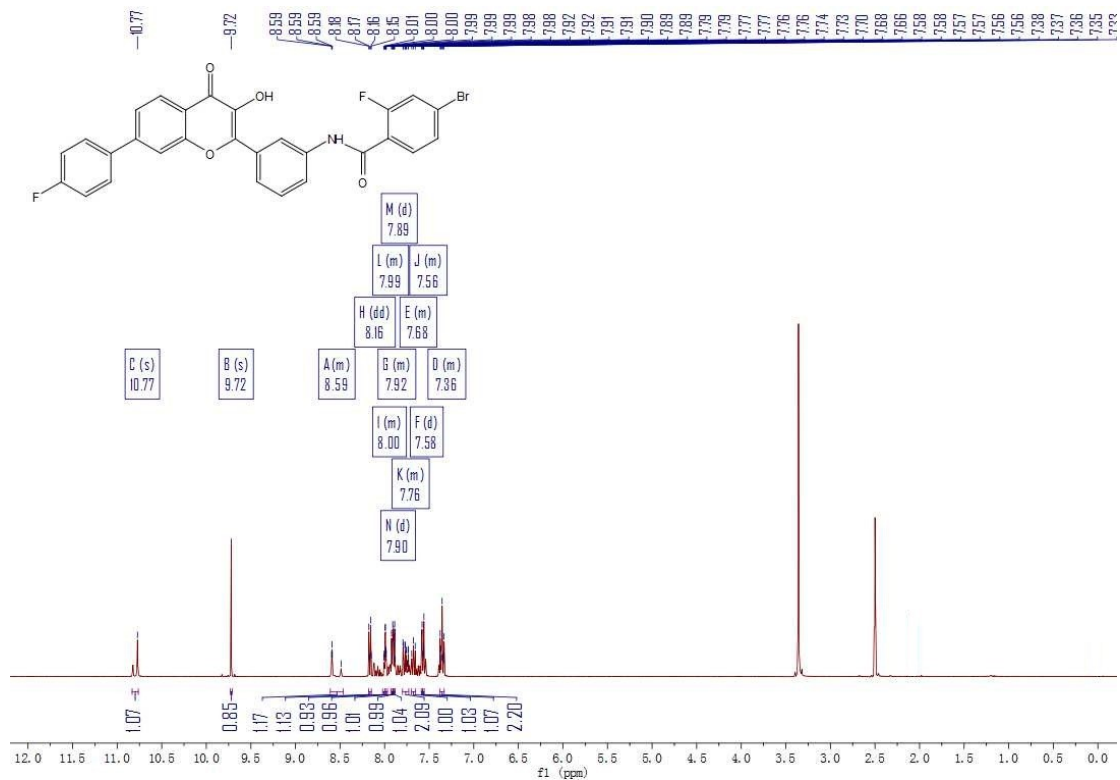
# 19. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **70**

## HRMS

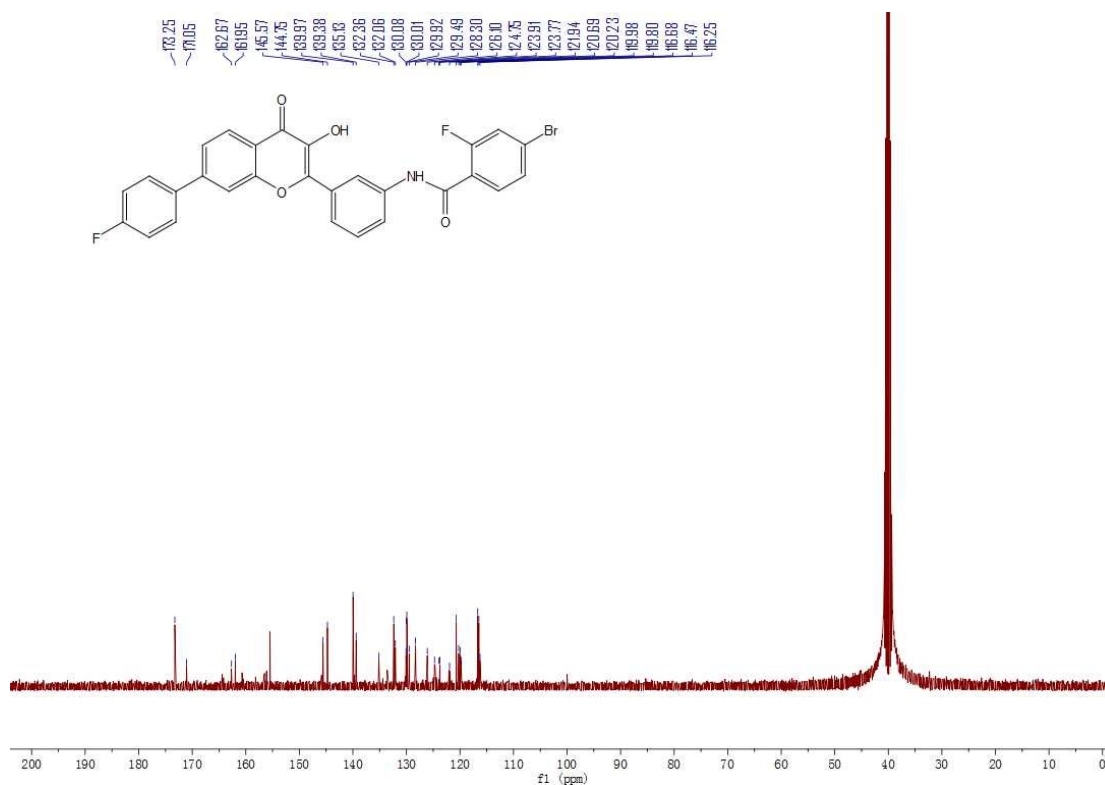
C6 #8-25 RT: 0.04-0.11 AV: 18 NL: 9.97E6  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



## <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



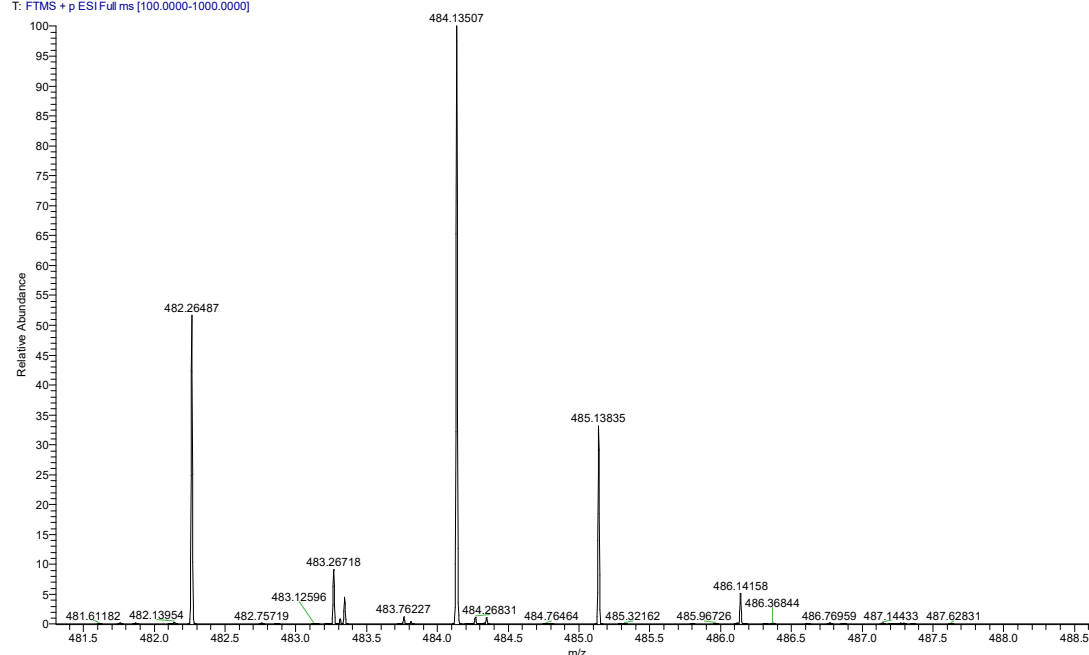
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



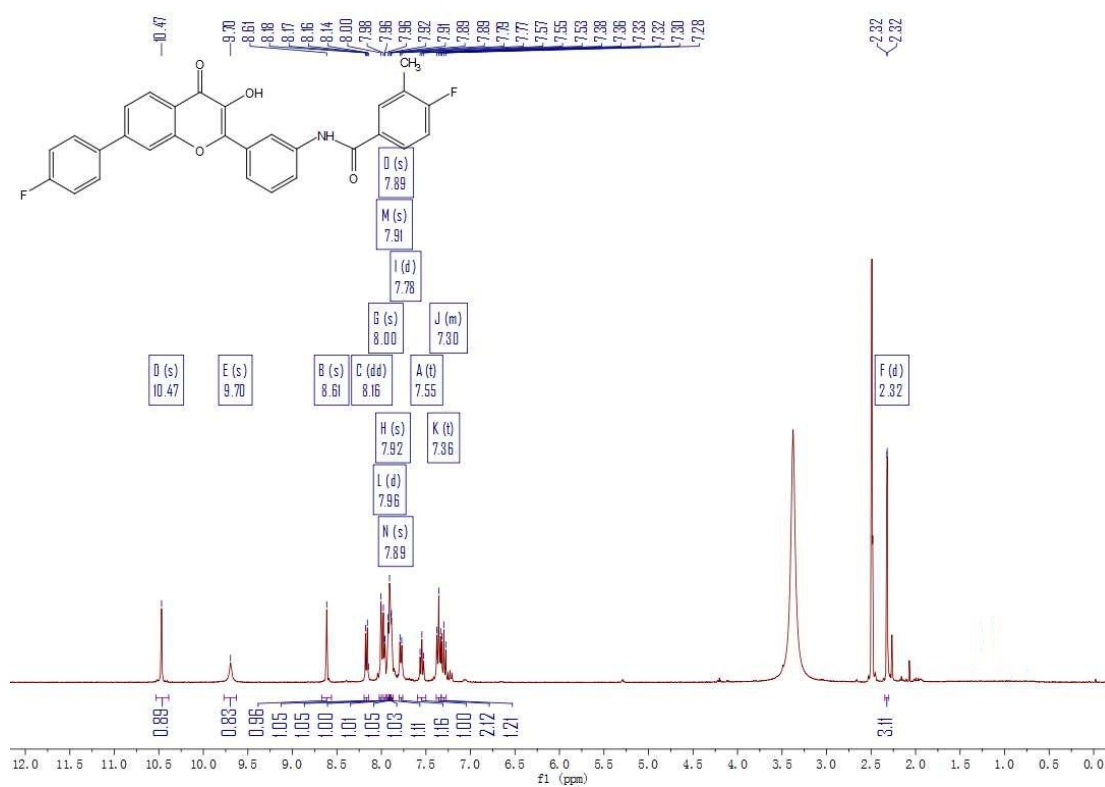
## 20. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound 7p

### HRMS

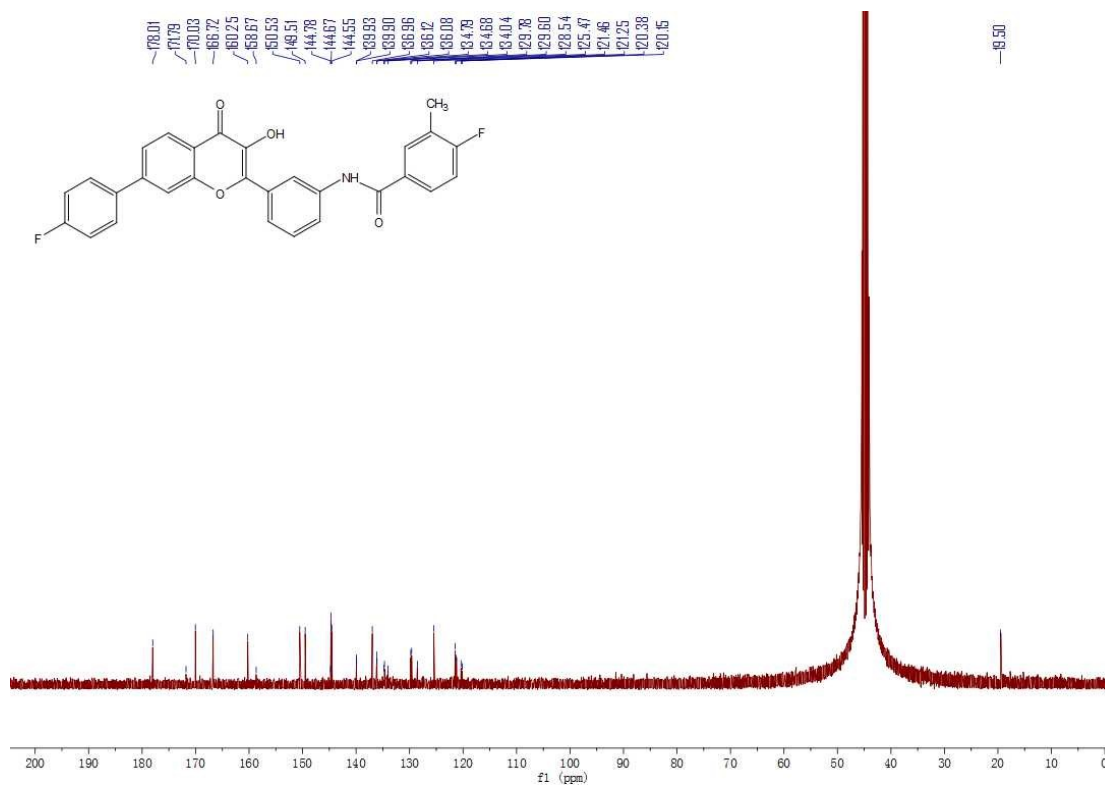
C7 #8-23 RT: 0.04-0.11 AV: 16 NL: 3.49E7  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



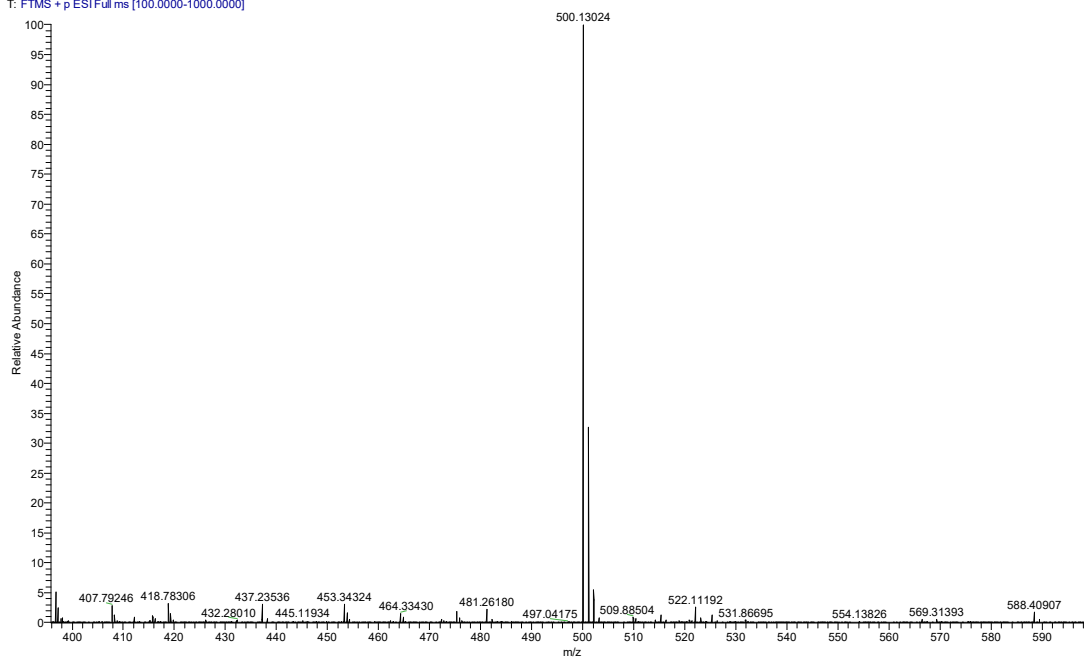
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



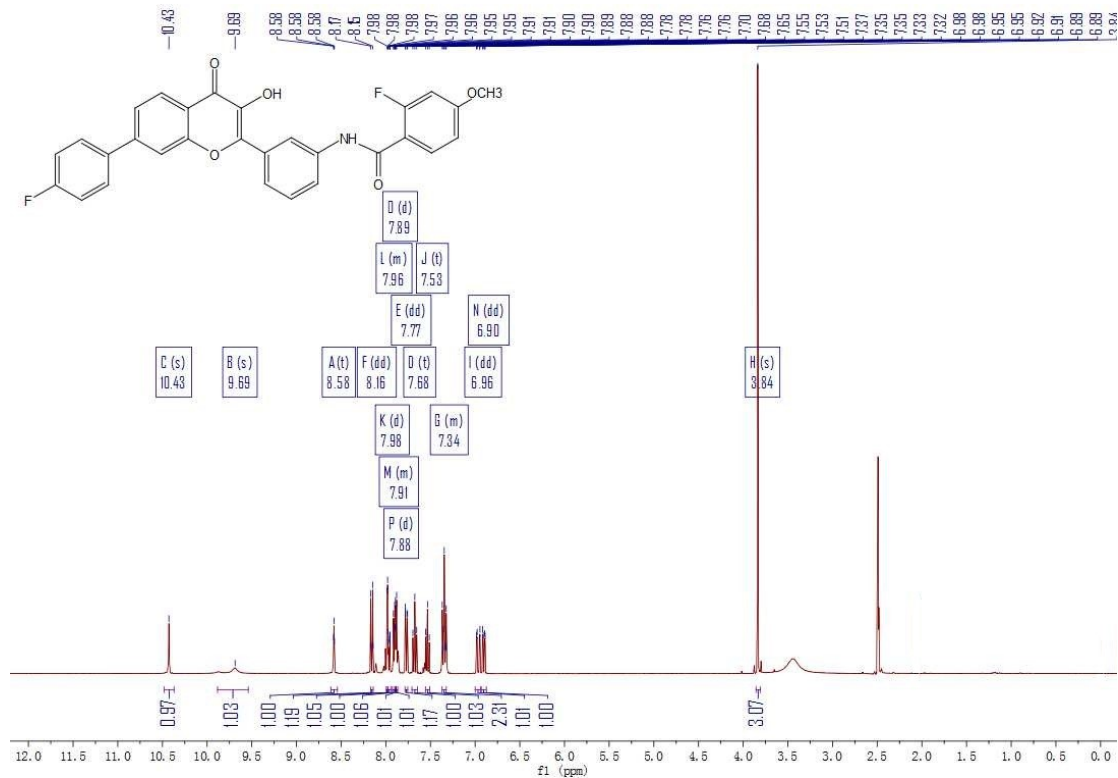
## 21. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7q**

### HRMS

CG #8-22 RT: 0.04-0.10 AV: 15 NL: 8.49E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]

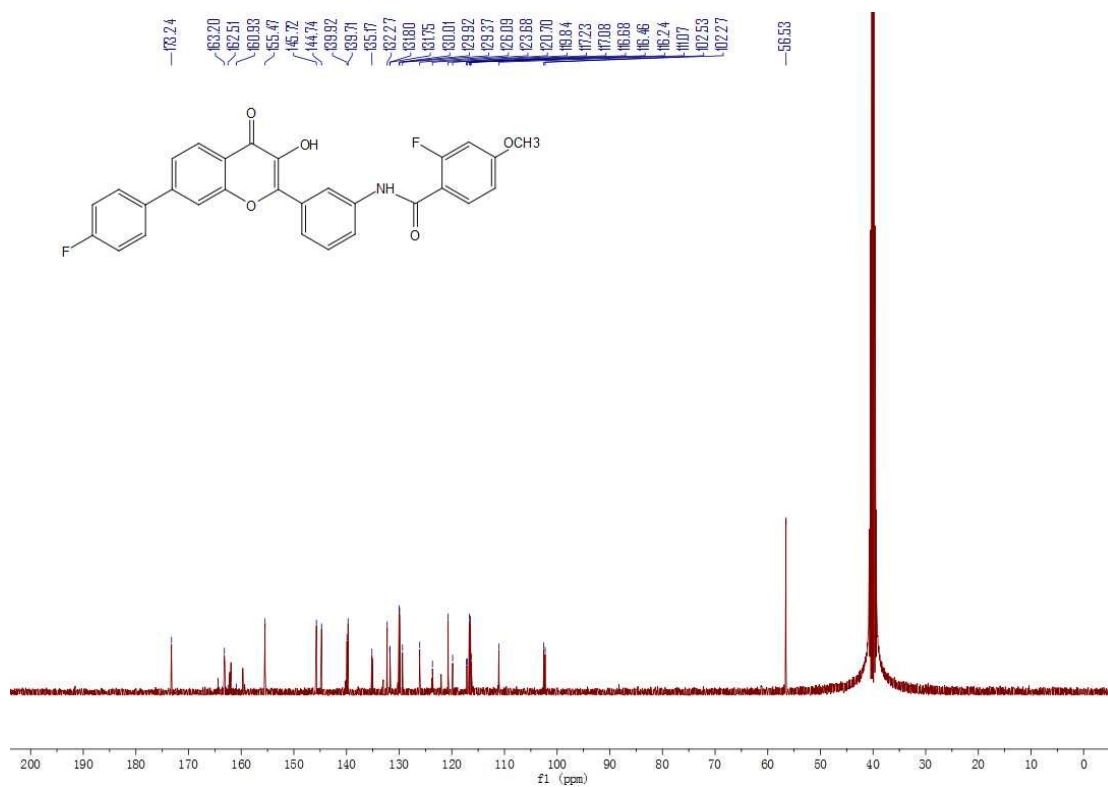


### <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)





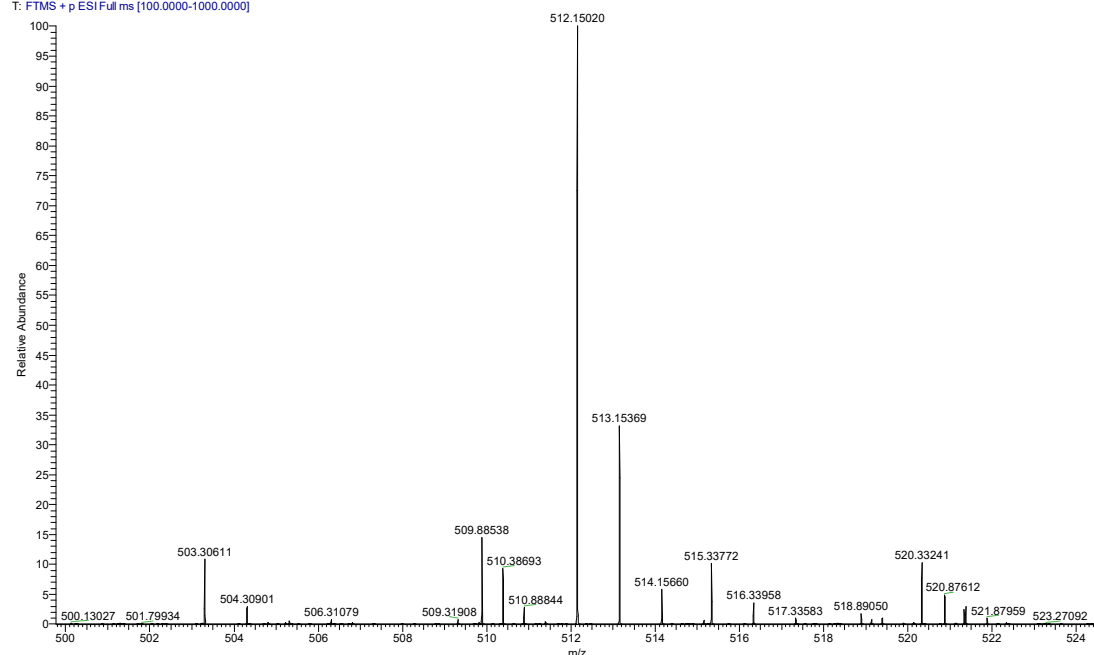
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



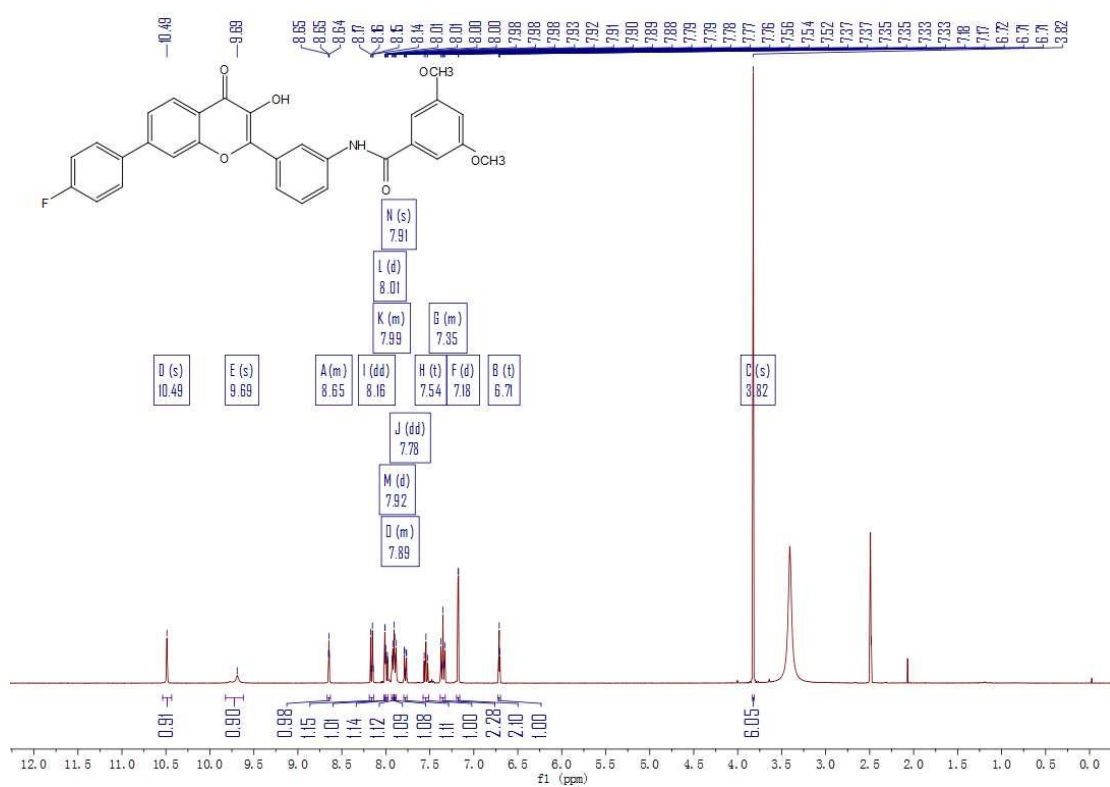
## 22. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound **7r**

### HRMS

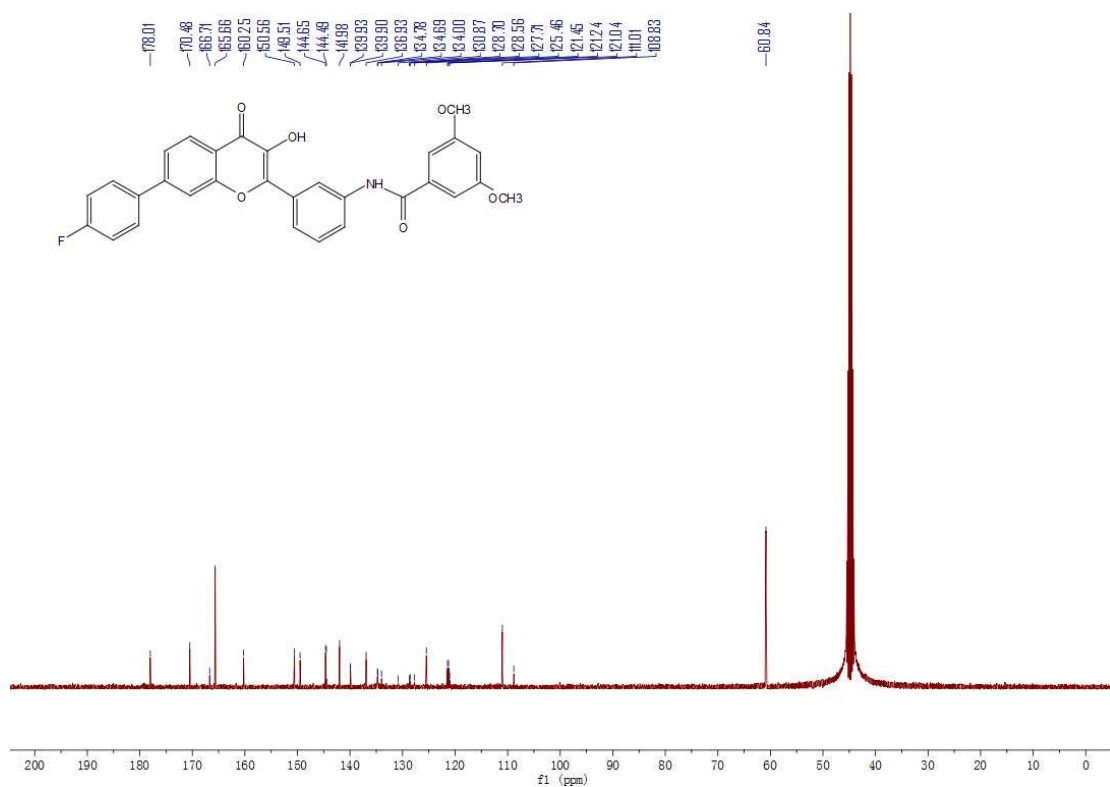
C9 #6-22 RT: 0.04-0.10 AV: 15 NL: 1.33E8  
T: FTMS -> p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



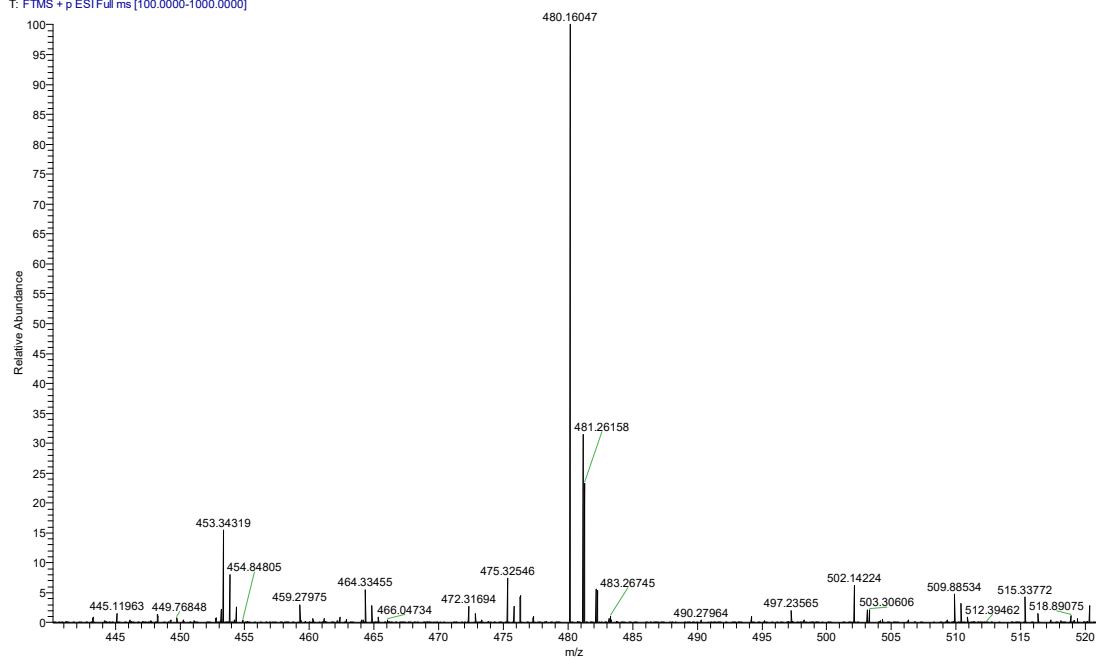
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



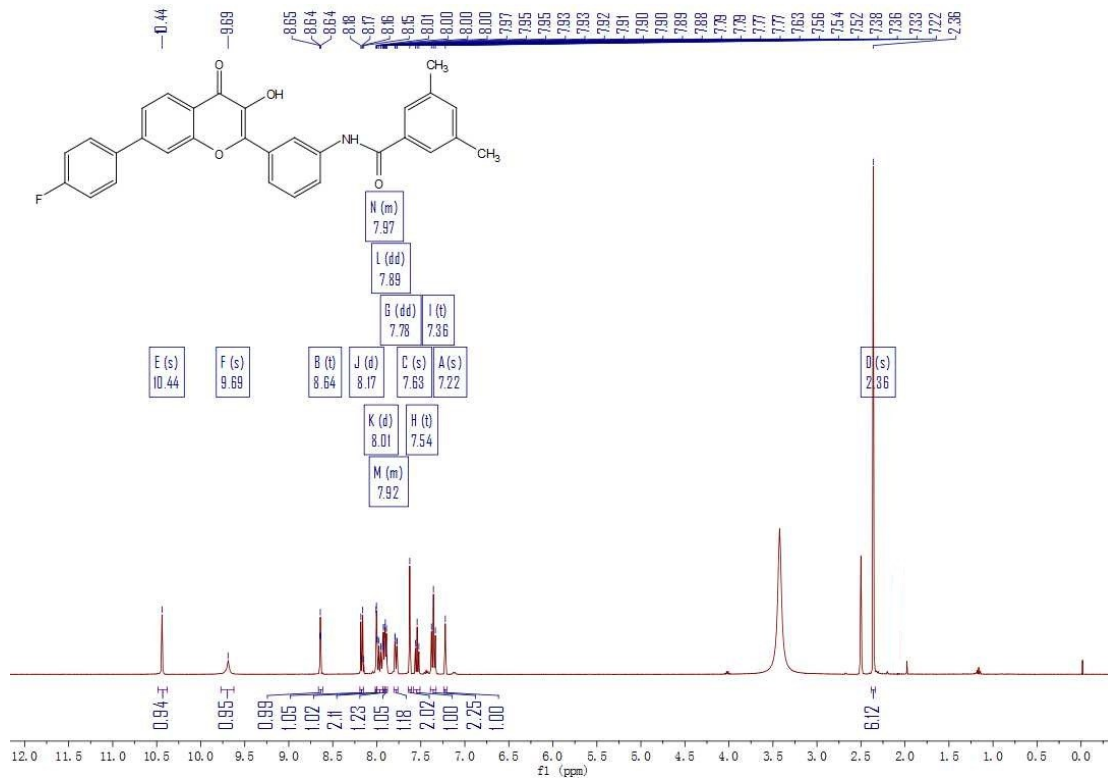
## 23. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7s**

### HRMS

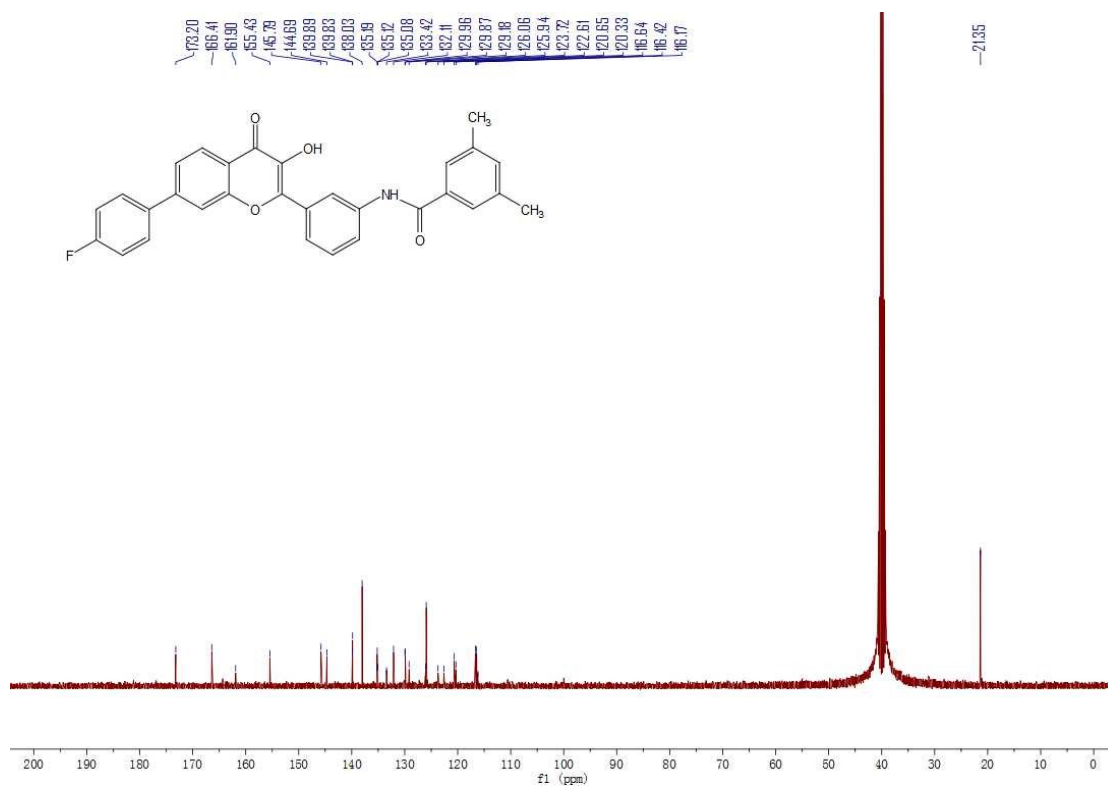
C10 #4-23 RT: 0.02-0.11 AV: 20 NL: 2.17E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



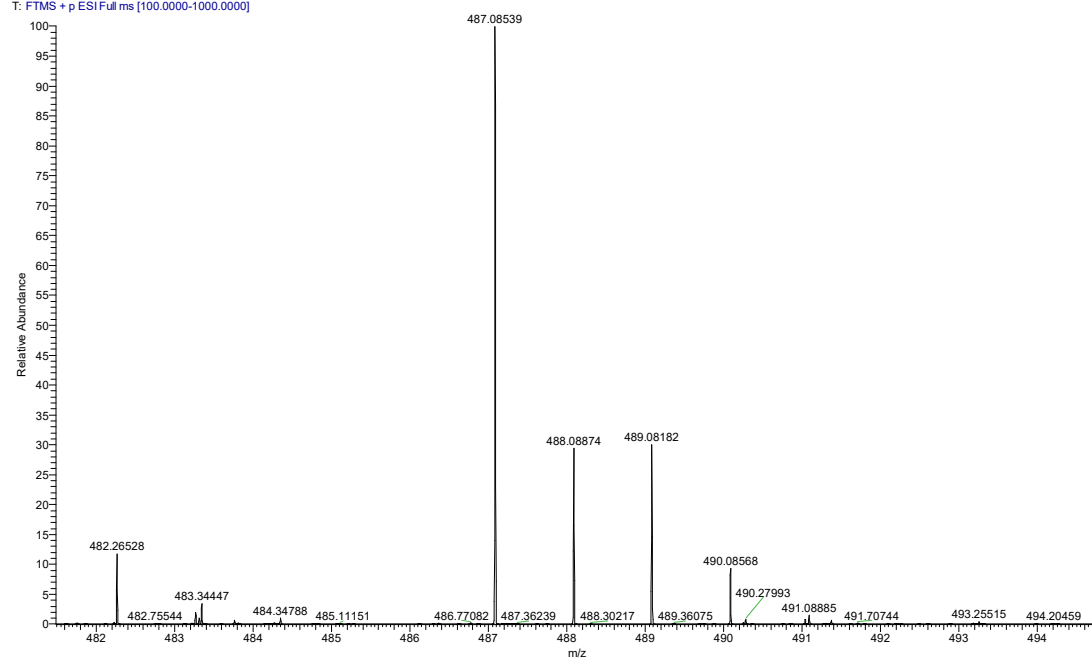
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



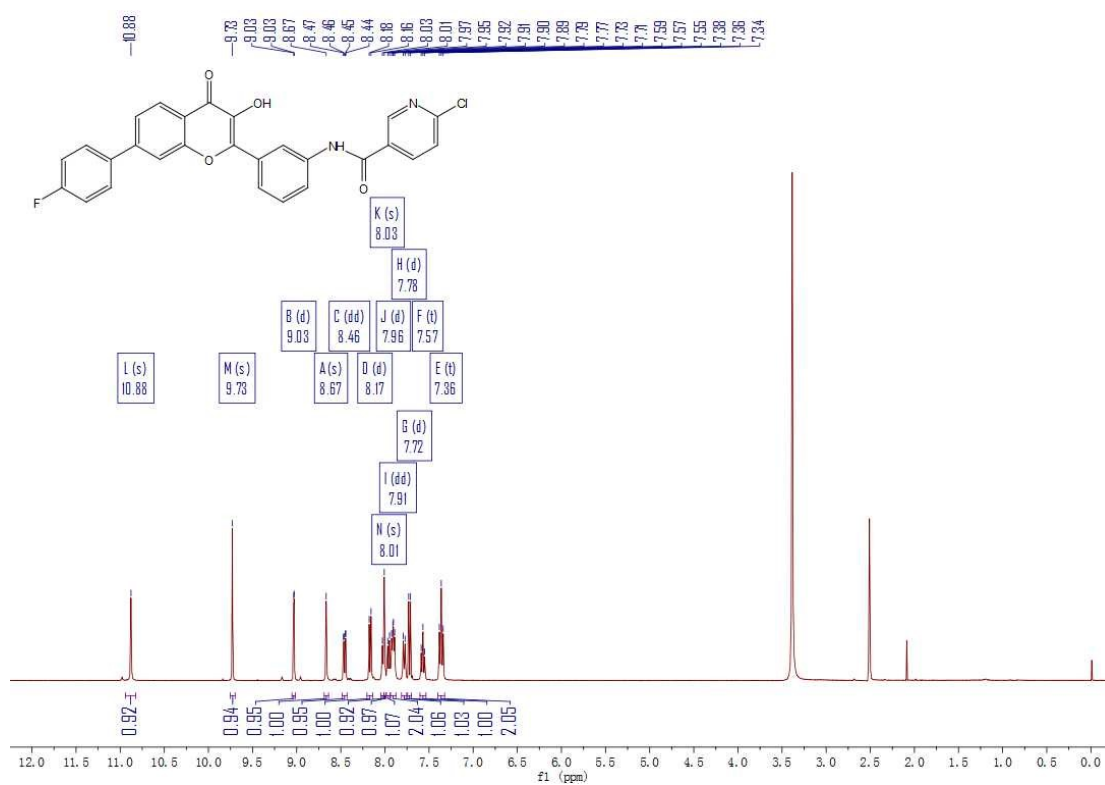
## 24. HRMS spectra, $^1\text{H}$ NMR and $^{13}\text{C}$ NMR of compound **7t**

### HRMS

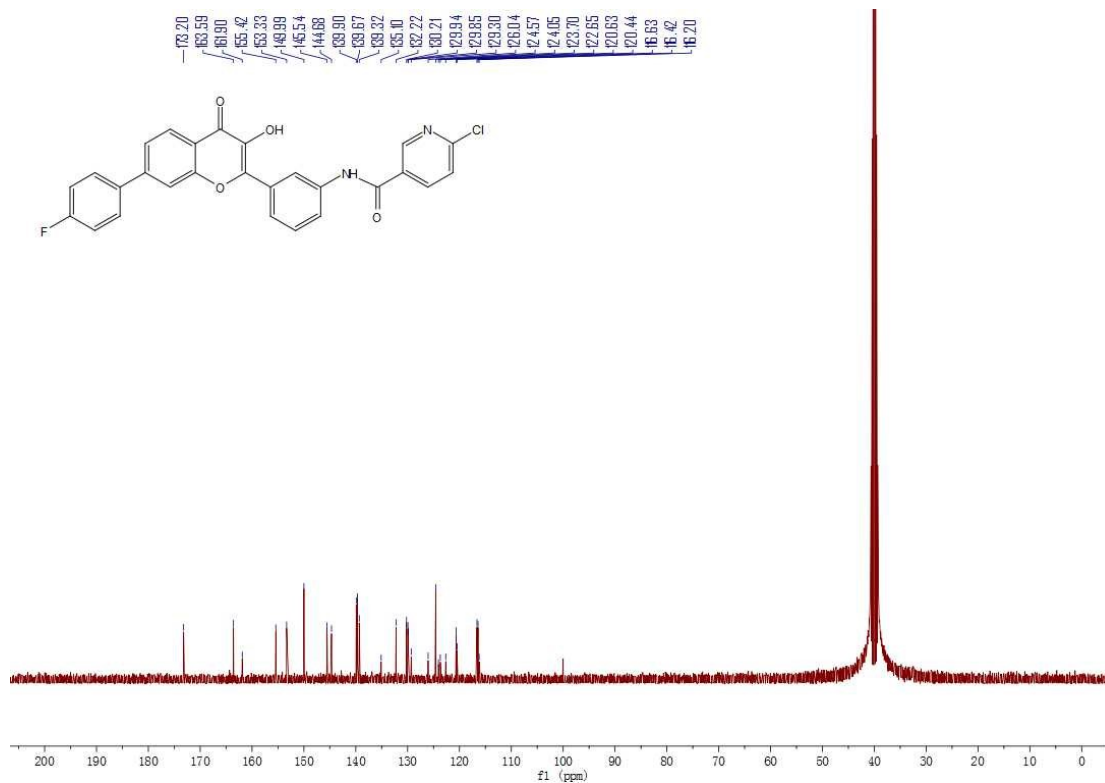
C11 #8-25 RT: 0.04-0.11 AV: 18 NL: 5.83E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



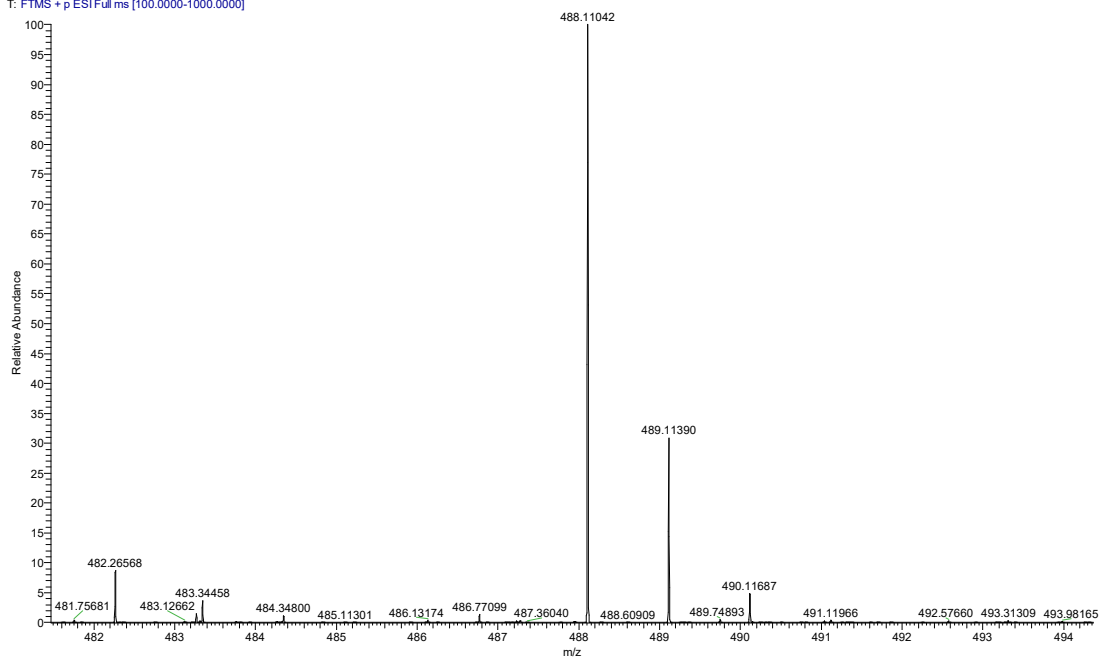
<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)



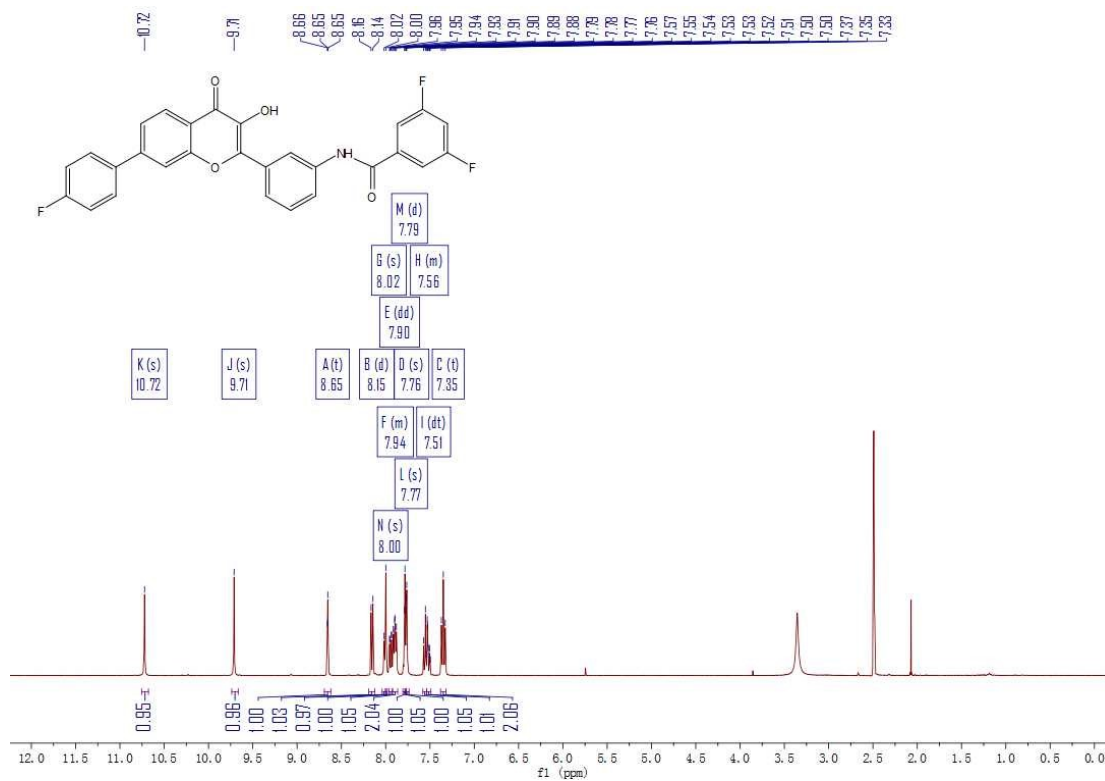
## 25. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7u**

### HRMS

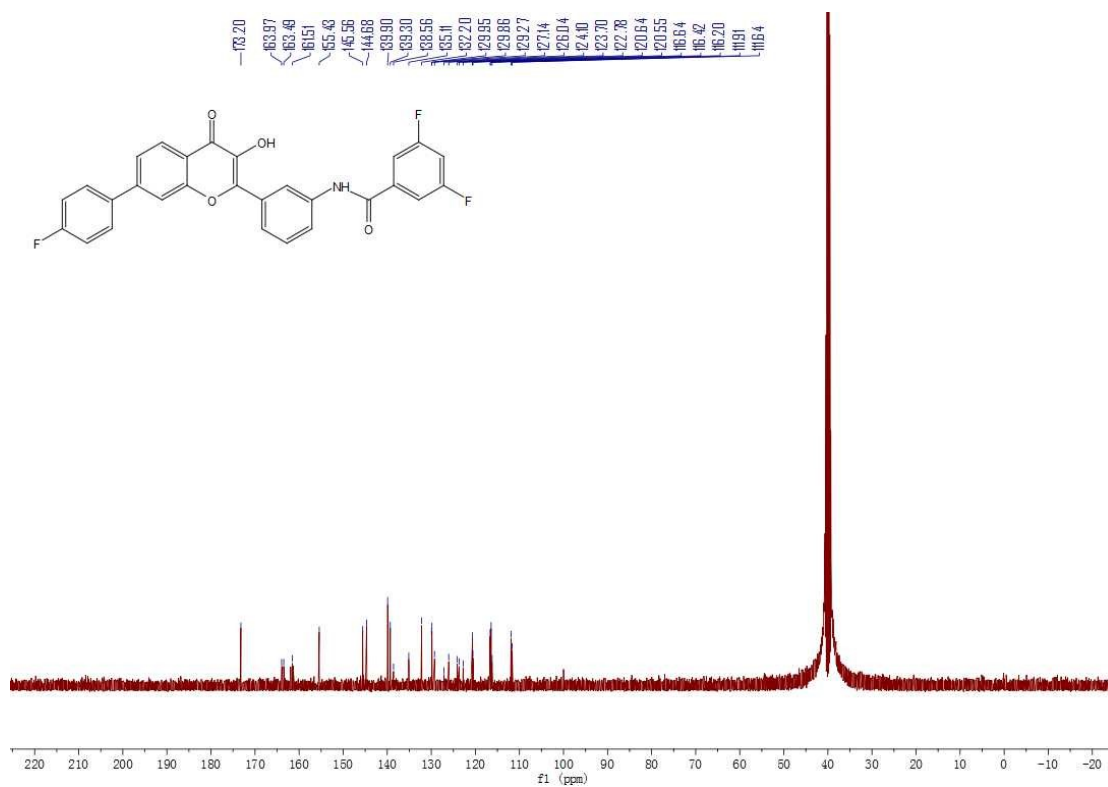
C12 #10-22 RT: 0.05-0.10 AV: 13 NL: 5.74E7  
T: FTMS +p ESI Full ms [100.0000-1000.0000]



### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



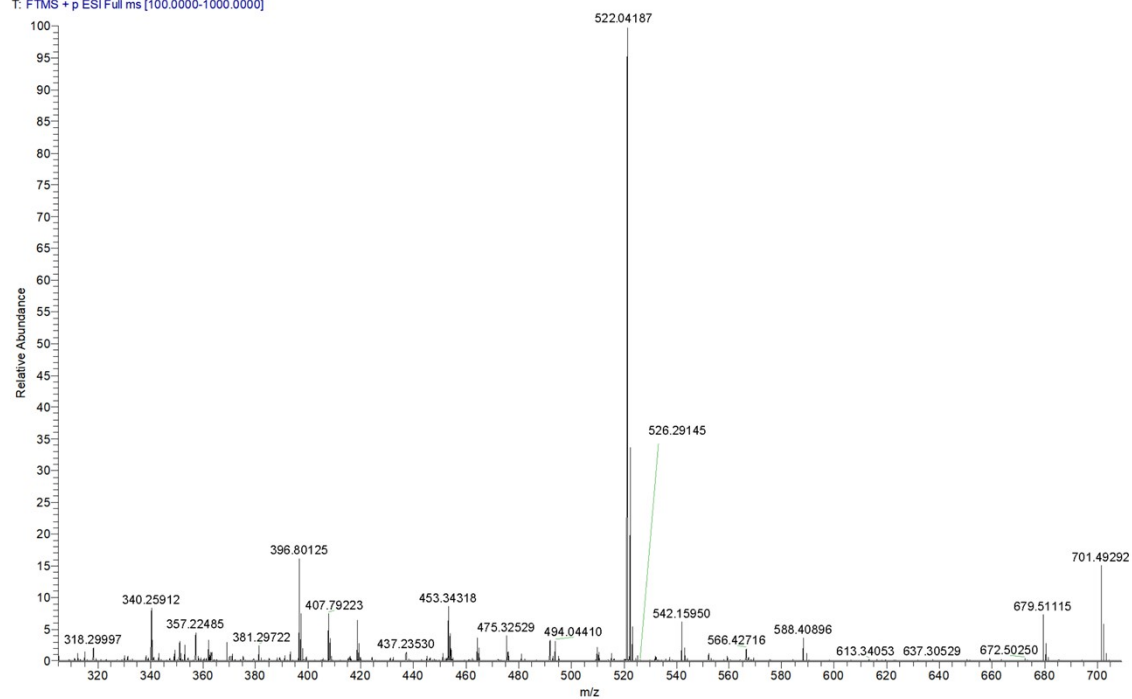
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



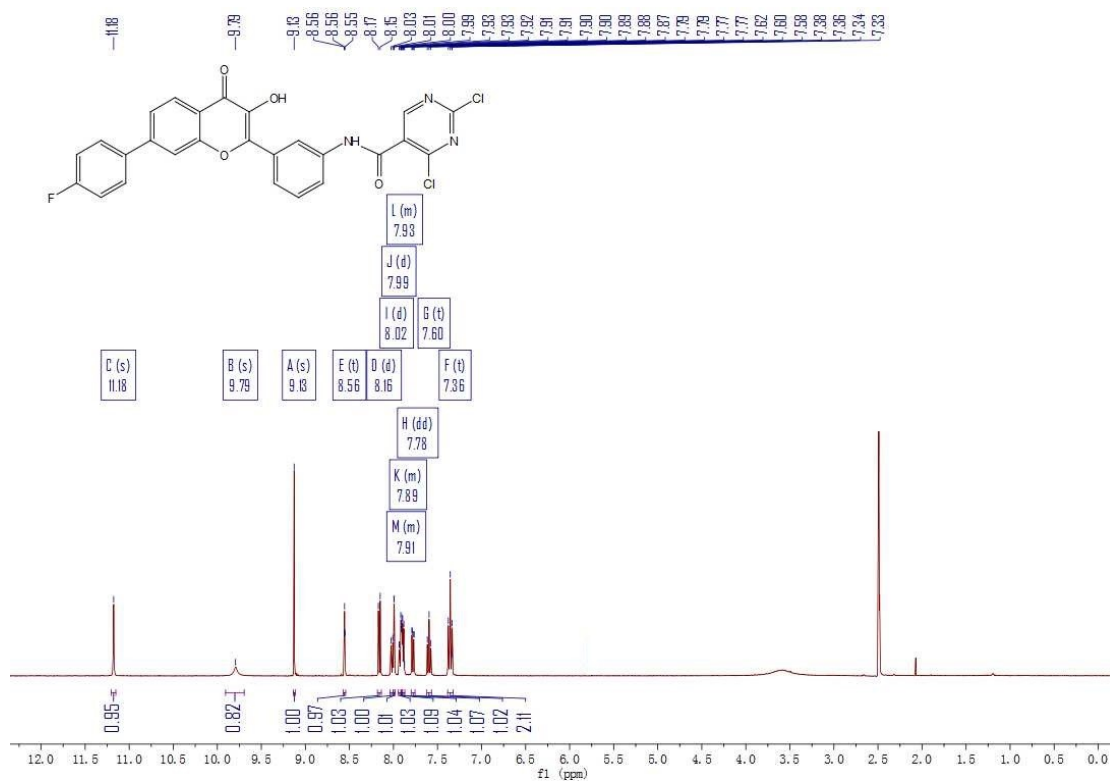
26. HRMS spectra,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR of compound 7v

HRMS

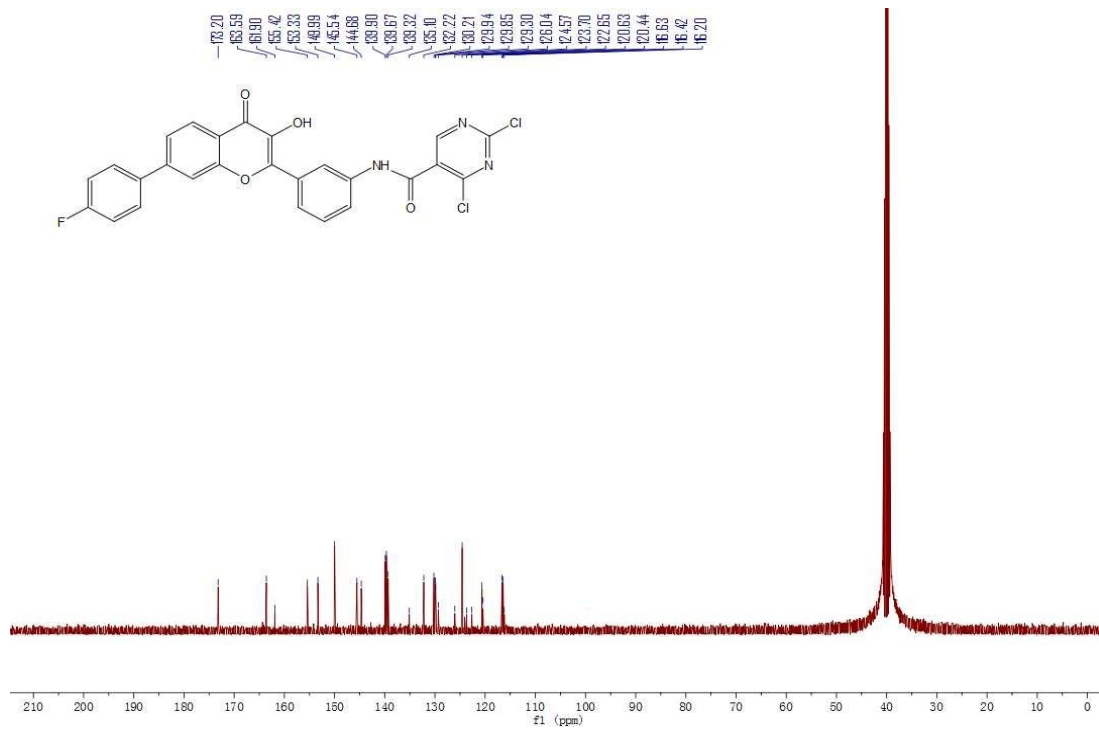
L3 #6-24 RT: 0.03-0.11 AV: 19 NL: 2.94E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)

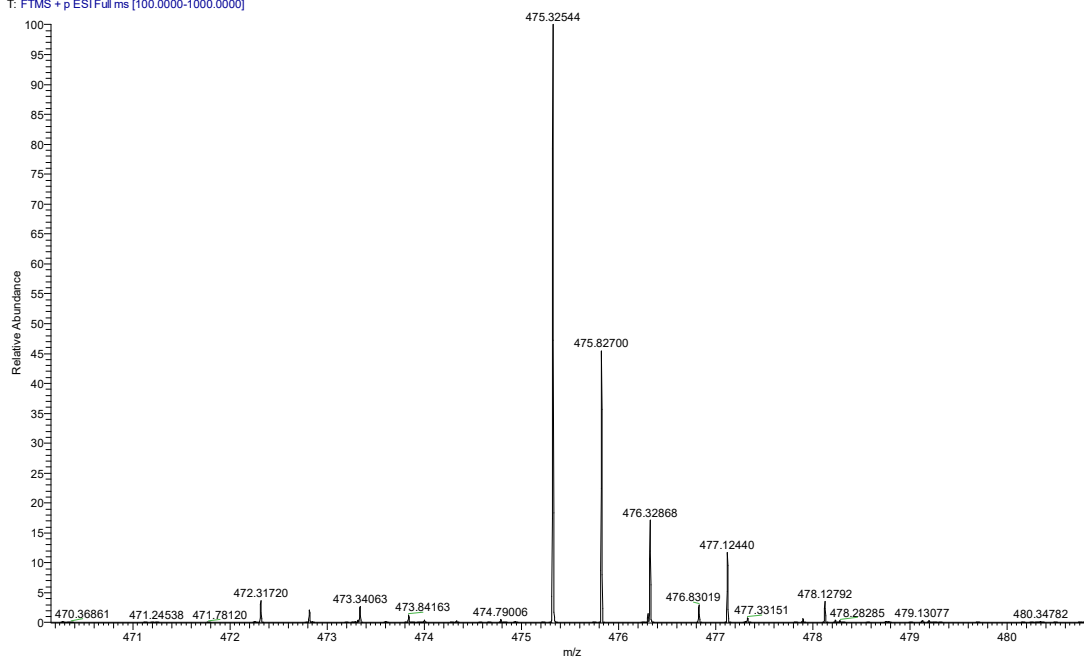




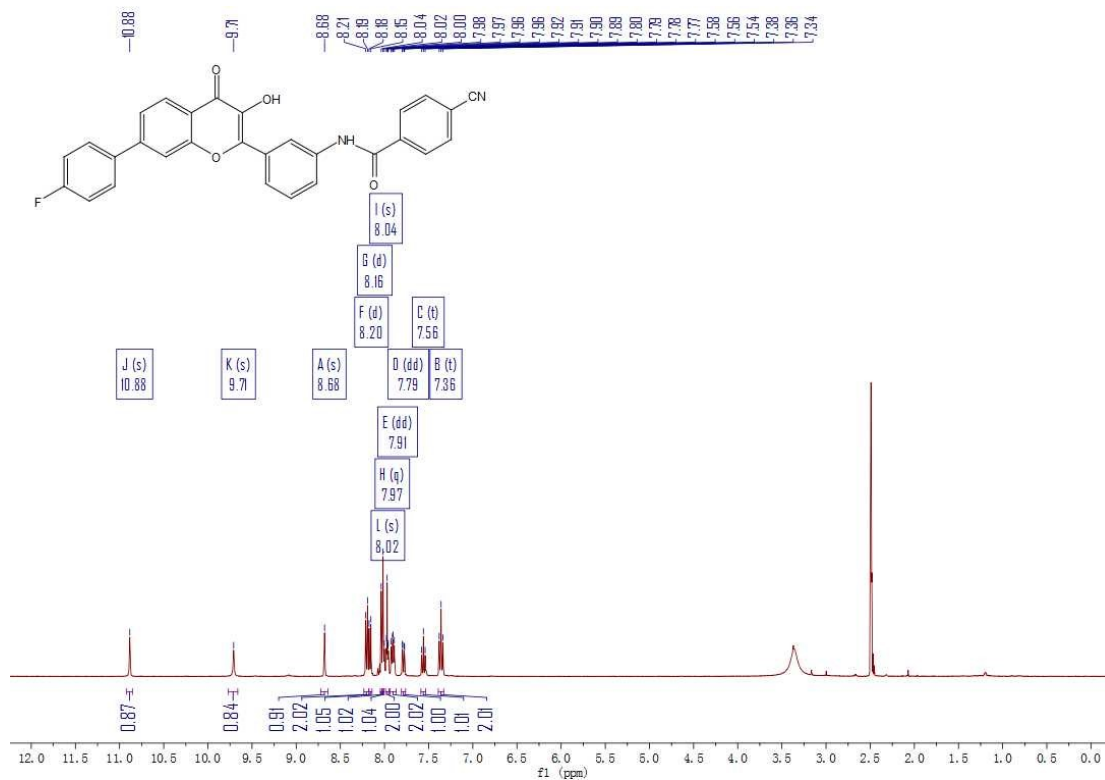
## 27. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7w**

### HRMS

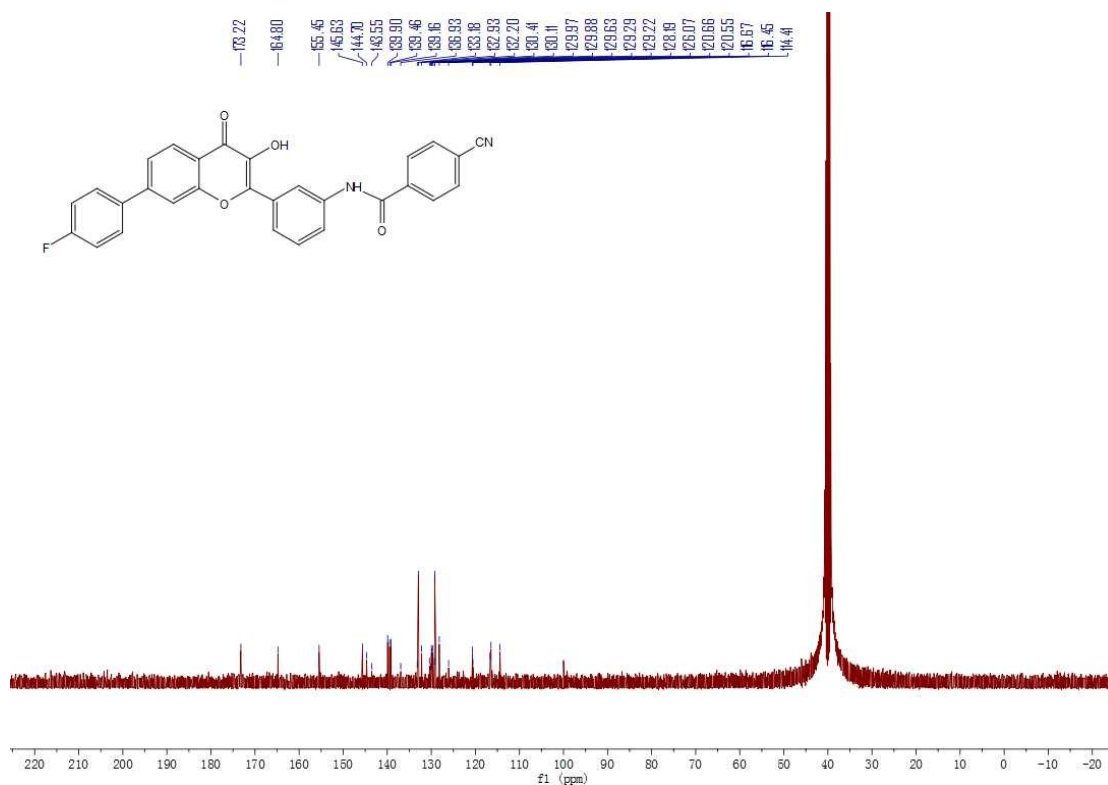
C14 #9-23 RT: 0.04-0.11 AV: 15 NL: 5.15E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



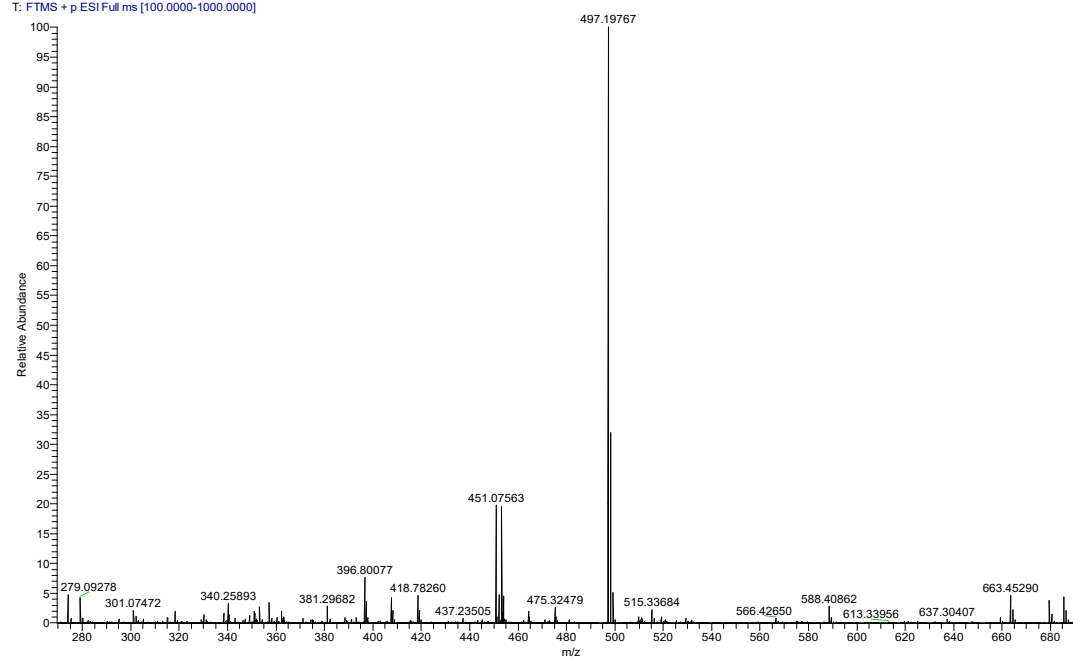
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



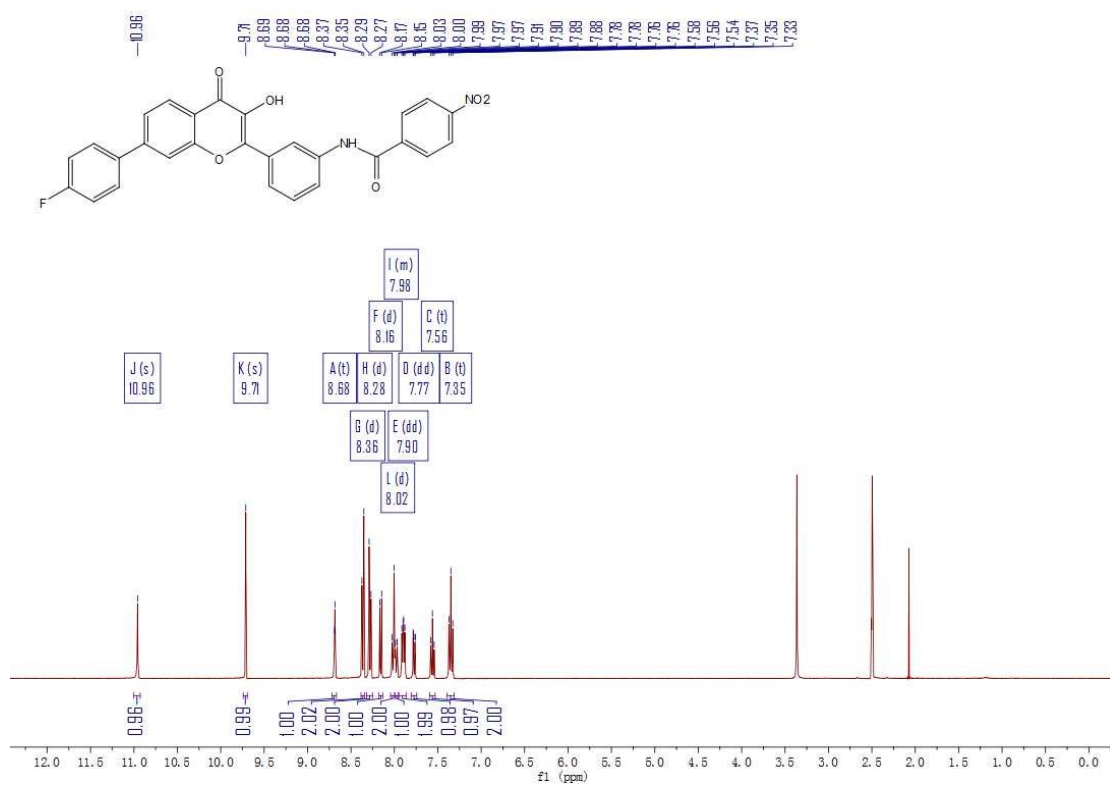
28. HRMS spectra,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR of compound 7x

HRMS

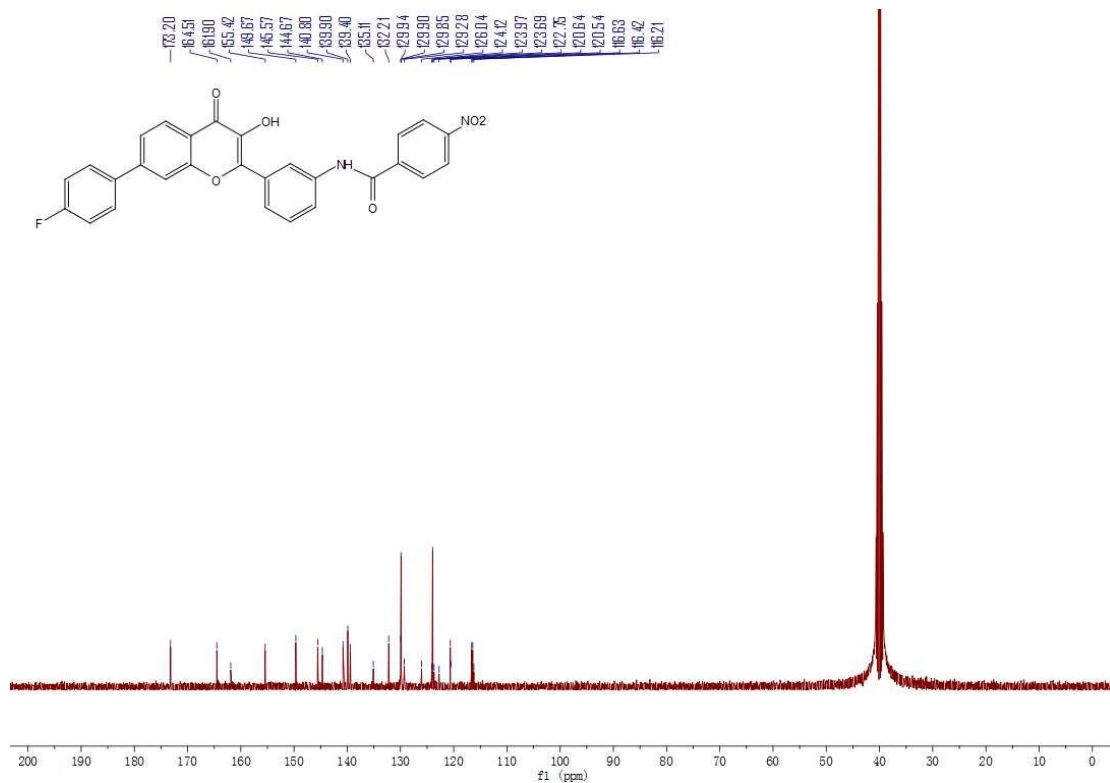
L23 #8-24 RT: 0.04-0.11 AV: 17 NL: 4.93E8  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



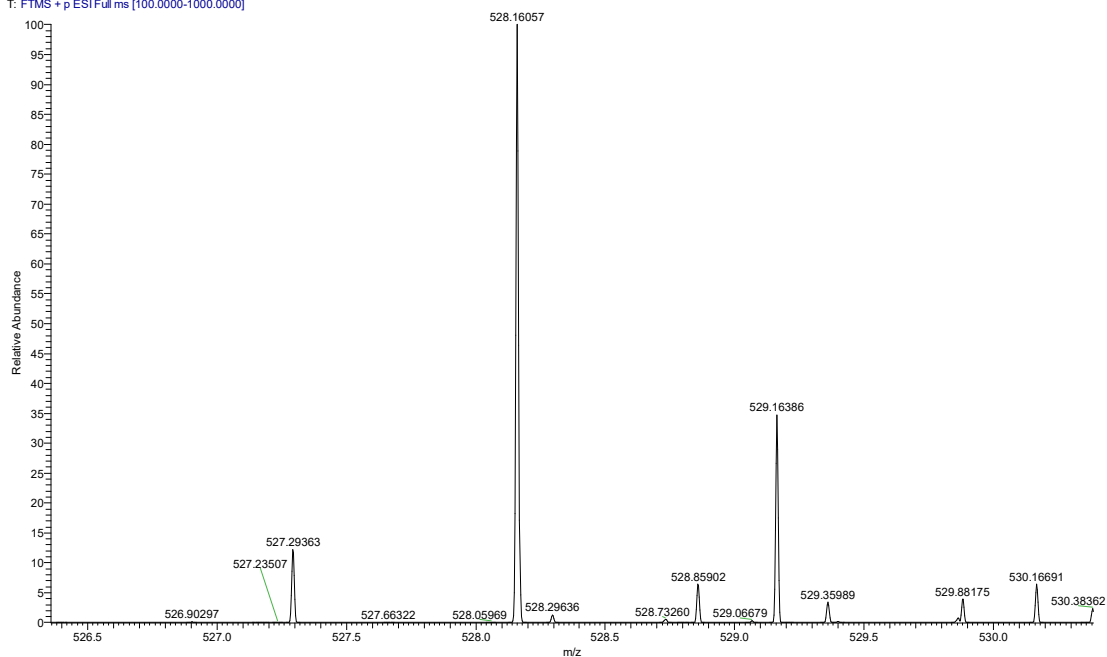
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 101 MHz)



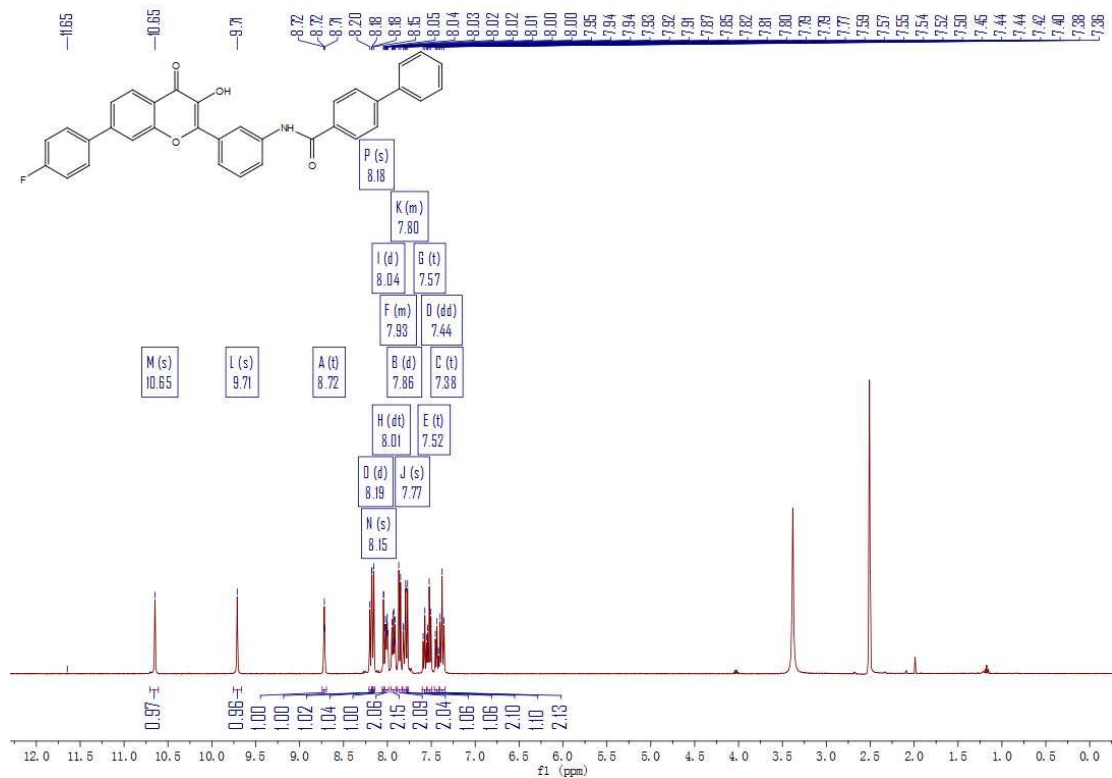
## 29. HRMS spectra, <sup>1</sup>H NMR and <sup>13</sup>C NMR of compound **7y**

### HRMS

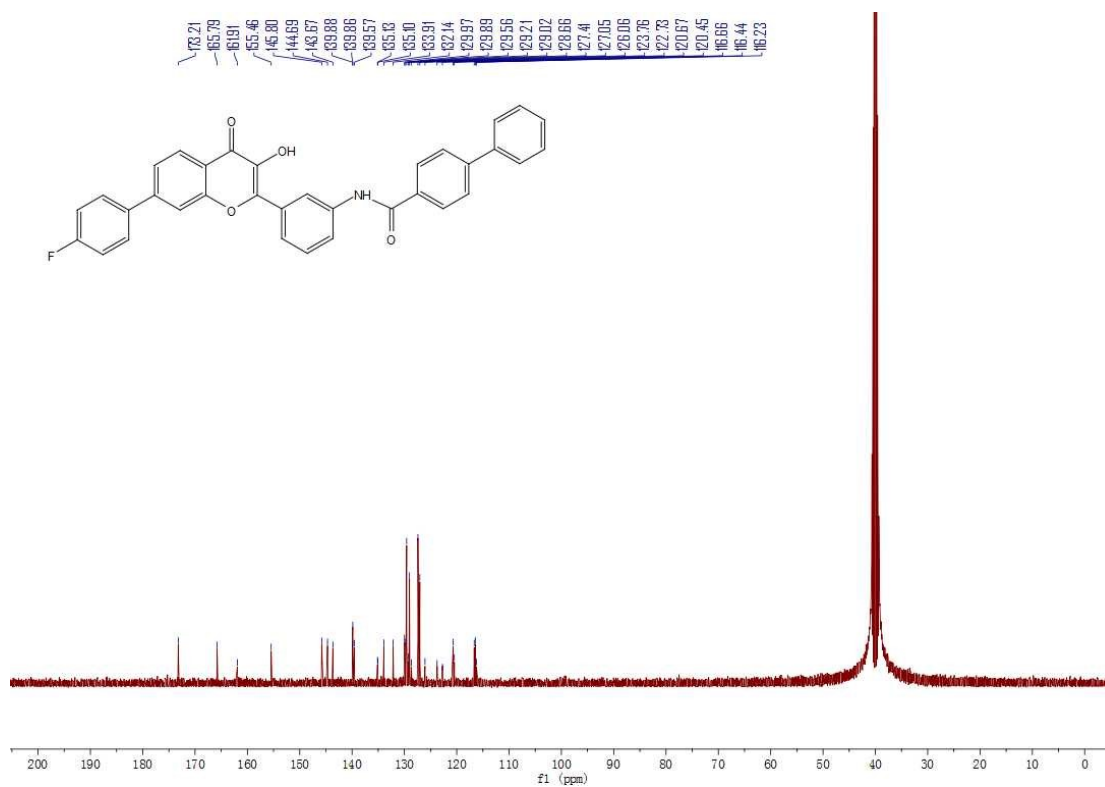
C16 #9-22 RT: 0.04-0.10 AV: 15 NL: 2.17E7  
T: FTMS + p ESI Full ms [100.0000-1000.0000]



### <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz)



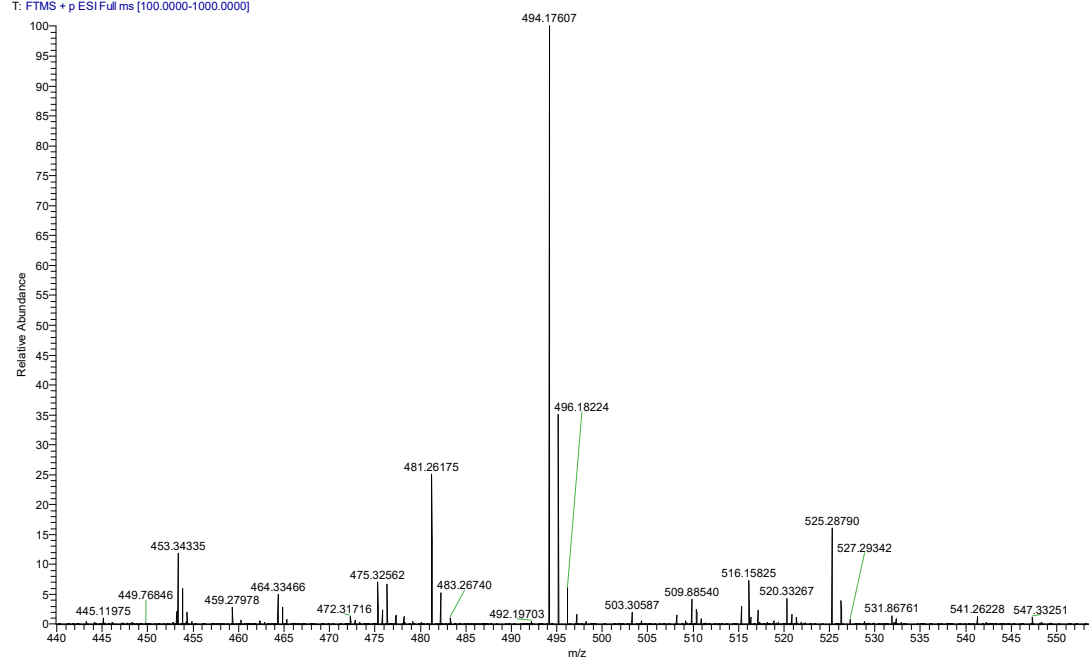
$^{13}\text{C}$  NMR (DMSO- $d_6$ , 101 MHz)



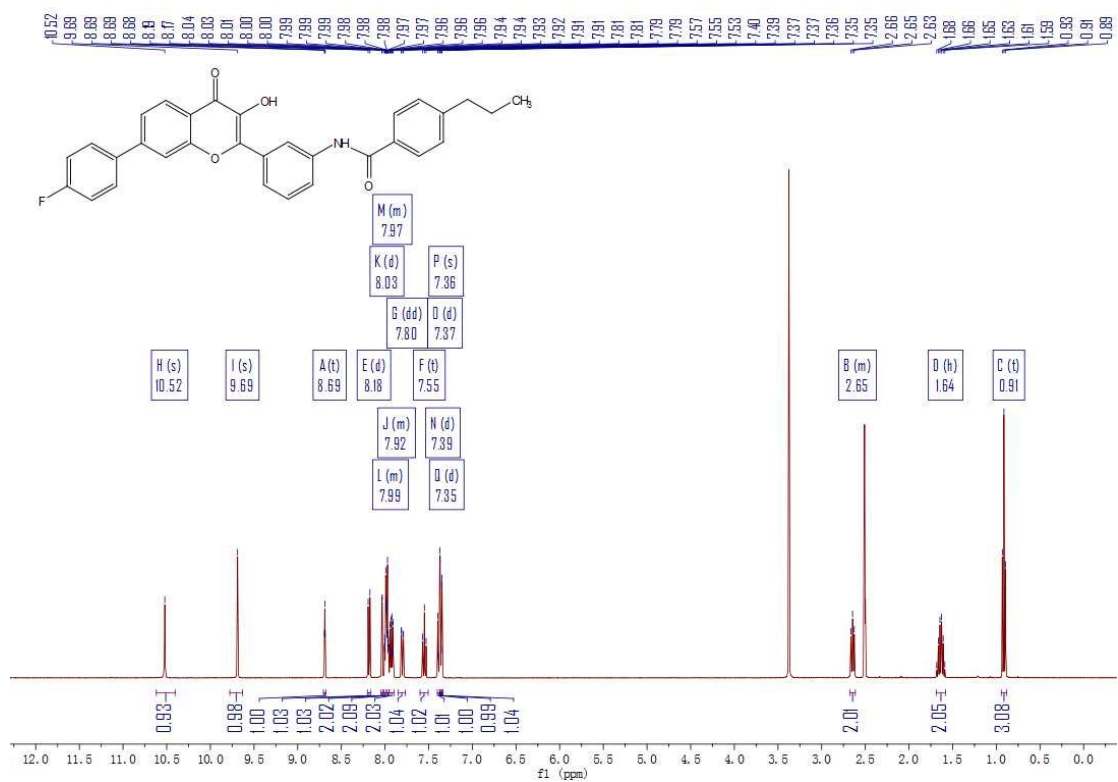
30. HRMS spectra,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR of compound **7z**

HRMS

C17 #8-24 RT: 0.04-0.11 AV: 17 NL: 3.07E8  
T: FTMS → p ESI Full ms [100.0000-1000.0000]



<sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz)



<sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 101 MHz)

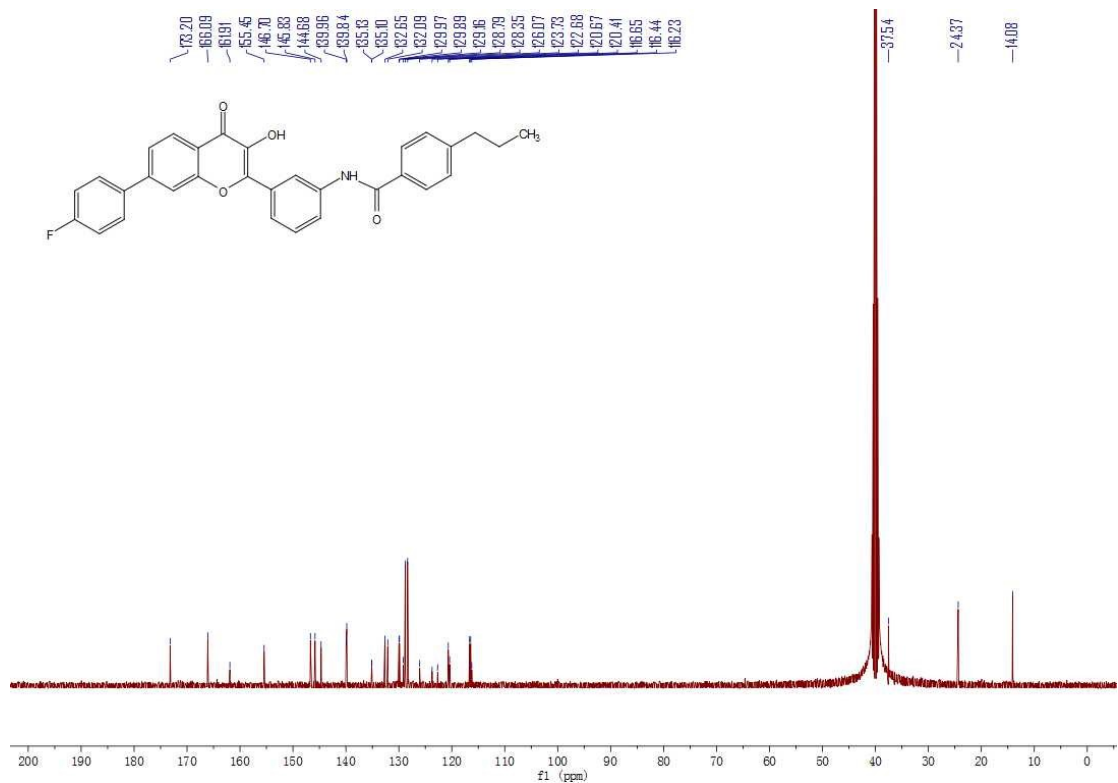


Table S1. Cytotoxicity assessment of compound **7t** on normal cell lines of HUVEC and MCF-10A

Compound	IC <sub>50</sub> (μmol/L)	
	HUVEC	MCF-10A
<b>7t</b>	32.47 ± 1.34	28.64 ± 2.18
<b>5-Fu</b>	12.37 ± 1.54	18.96 ± 1.49