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# Thiazolidinedione derivatives as novel GPR120 agonists for the treatment of type 2 diabetes

**Xuekun Wang,[*a] Guoxia Ji,[ab] Xinyu Han,[a] Huiran Hao,[a] Wenjing Liu,[a] Qidi Xue,[a] Qinghua Guo,[a] Shiben Wang,[a] Kang Lei[a] and Yadi Liu[*c]**

[a] School of Pharmaceutical Sciences, Liaocheng University, 1 Hunan Street, Liaocheng 252059, China

[b] School of Chemistry and Chemical Engineering, Liaocheng University, 1 Hunan Street, Liaocheng 252059, China

[c] State Key Laboratory of Food Science and Technology, Jiangnan University, Wuxi 214122, China

* Correspondence: liuyadi@jiangnan.edu.cn (Y.L.); wangxuekun@lcu.edu.cn and xuekunwang0610@126.com (X.W.); Tel.: +86-0635-823-9087 (X.W.)

## Experimental section

### 1. Molecular modeling using Discovery Studio (DS) 2020

#### 1.1 Build homology models protocol

(1) Load all templates structures into a Molecule Window.

(2) Open an existing alignment of the template sequences and the model sequence into the Sequence Window. Note that the template sequences in the Sequence Window are automatically linked with the template structures in the Graphics View.

(3) Open the Macromolecules | Create Homology tools tools and click Build Homology Models... to open the Build Homology Models dialog

(4) Set the following parameters: Input Sequence Alignment, Input Model Sequence, Input Template Structures, and other parameters are default values.

(5) Click Run to start the calculation.

(6) Analyzing results: Analyzing output models, PDF energy and Troubleshooting.

#### 1.2 CDOCKER protocol

(1) Load the model with the lowest discrete optimized protein energy (DOPE) score r into the Graphics View.

(2) Ensure that the receptor has hydrogens added and atom valencies are satisfied so that atoms can be properly typed.

(3) Open the Define and Edit Binding Site tool panel and click Define Site from Current Selection to find and define binding site spheres (XYZ: 63.705570 16.903153 13.898603, Radius: 10.0) .

(4) Open the Receptor-Ligand Interactions | Dock Ligands tools and click Dock Ligands (CDOCKER) to open the Dock Ligands (CDOCKER) dialog.

(5) Set the following parameters: Input Receptor, Input Ligands, Input Site Sphere, and other parameters are default values.

(6) Click Run to start the calculation.

### 2. Chemistry

All commercially available materials and reagents were used without purification unless

otherwise indicated. Purification by column chromatography was performed using silica gel (200–300 mesh). Melting points of target compounds **1g**–**10g** were determined on a x-5 micro melting point apparatus, which was uncorrected. The NMR spectra (500 MHz for $^{1}$H NMR and 125 MHz for $^{13}$C NMR spectra) were recorded using a Bruker AVANCE NEO 500 instrument. Chemical shifts are shown as values relative to the internal standard (tetramethylsilane), and coupling constants (*J* values) are given in hertz (Hz). High-resolution mass spectrometry was conducted using a UPLC G2-XS Qtof spectrometer (Waters) with the electrospray ionization Fourier transform ion cyclotron resonance (ESI-FTICR) technique. High-performance liquid chromatography (HPLC) data were obtained using a Shimadzu LC-20AT (Japan).

$^{1}$H-NMR, $^{13}$C-NMR, HRMS and HPLC of target compounds

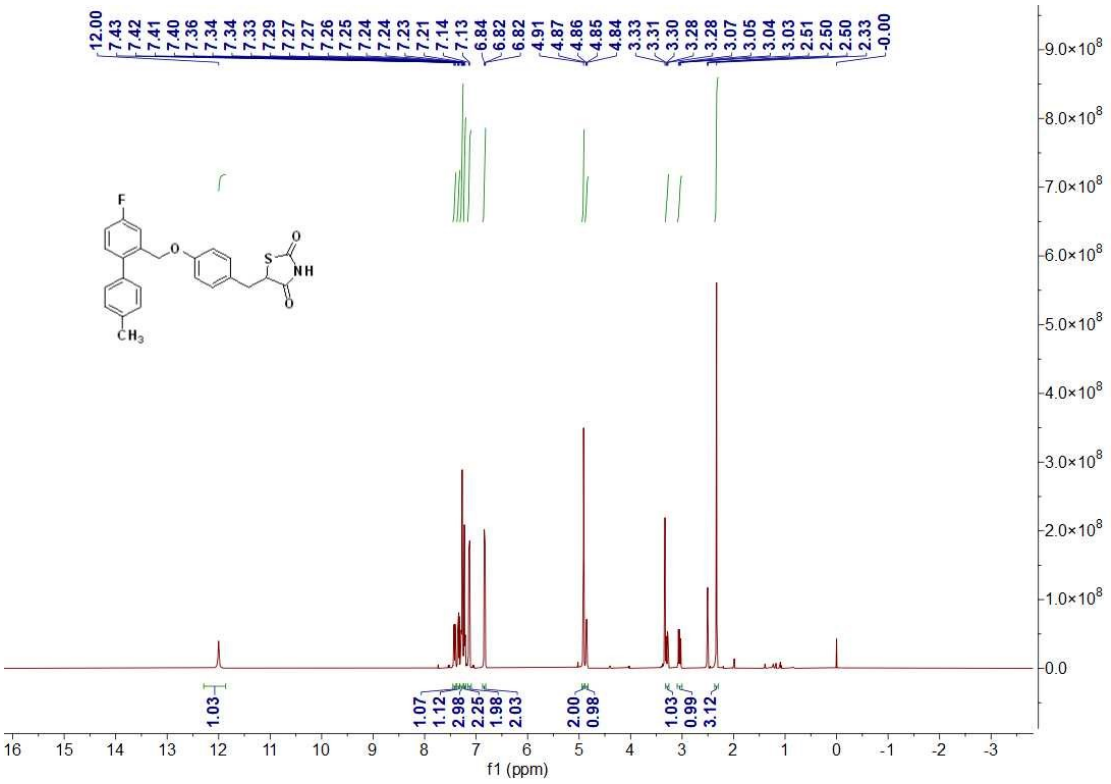



**Figure S1**. $^{1}$H NMR spectrum **1g**.

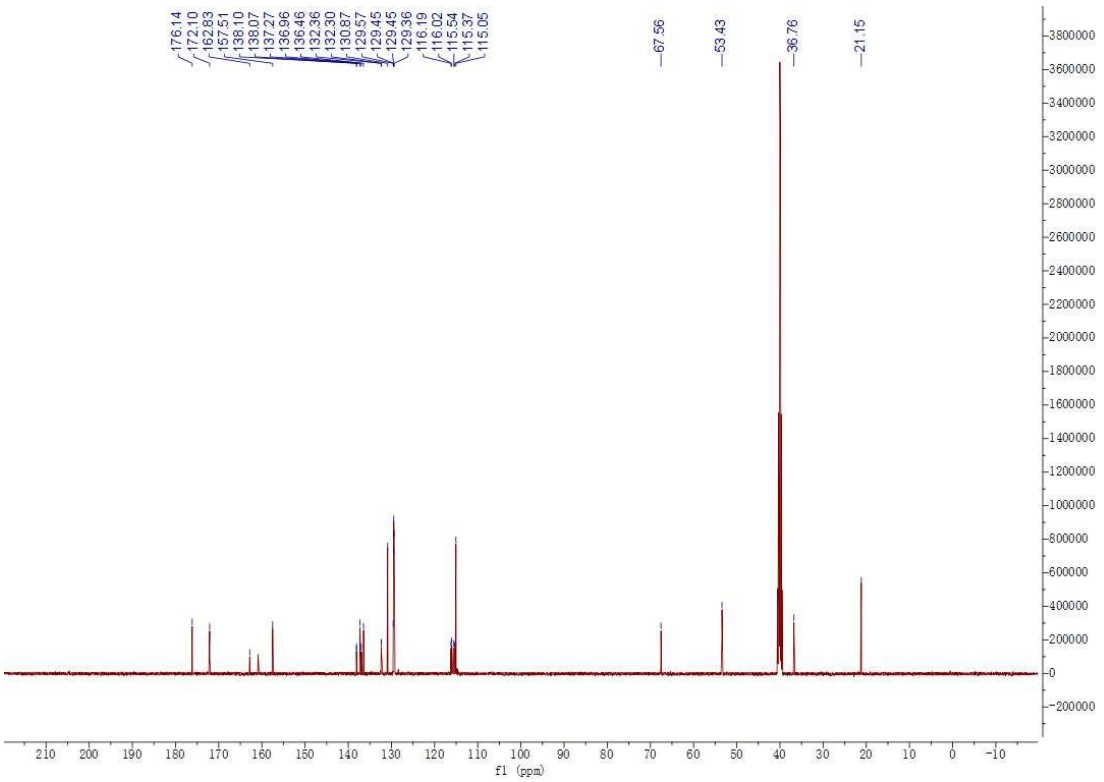



**Figure S2**. $^{13}C$ NMR spectrum **1g**.

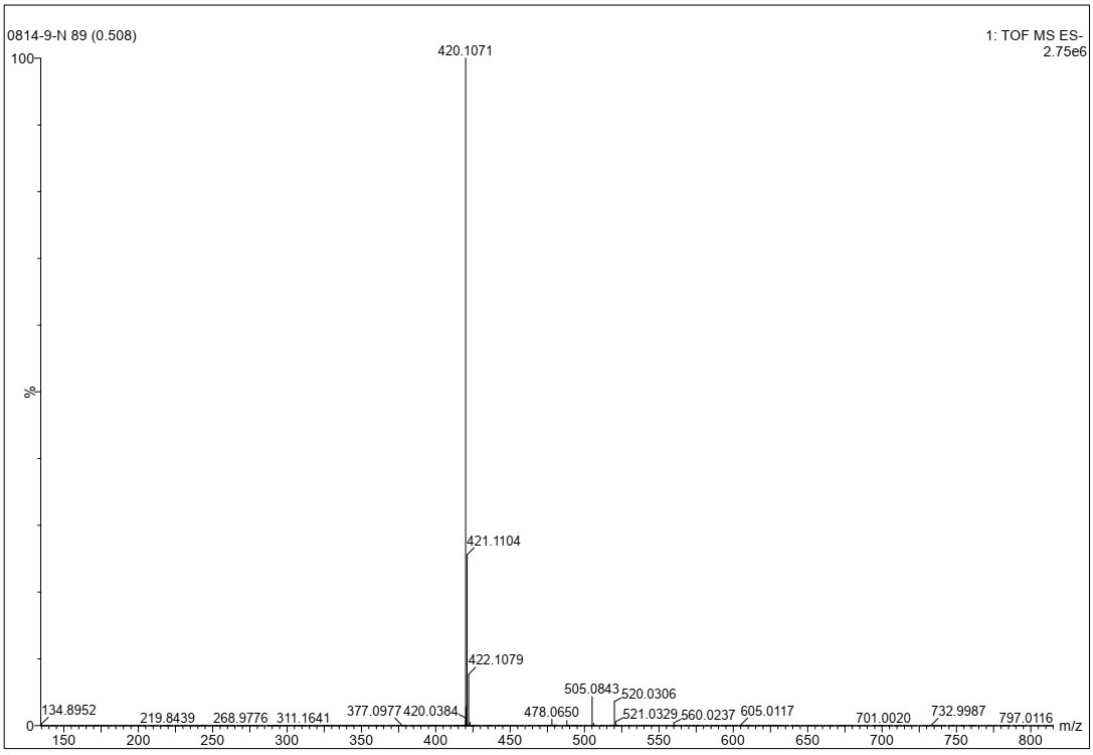
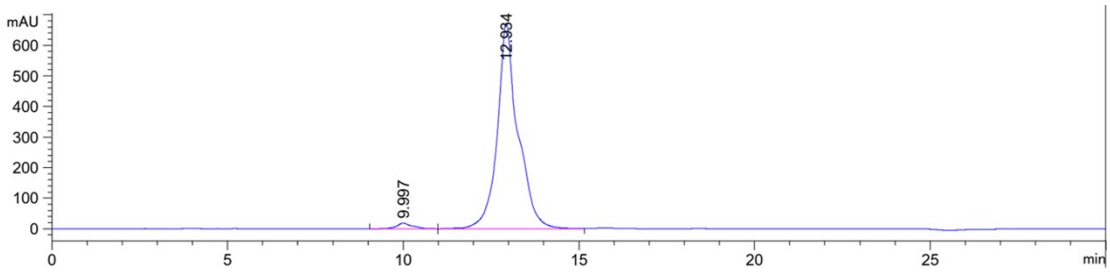



**Figure S3**. HRMS spectrum **1g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 9.997 | BV | 0.4319 | 584.98920 | 18.55167 | 2.0730 |
| 2 | 12.934 | VV | 0.5657 | 2.76343e4 | 672.03967 | 97.9270 |

**Figure S4**. HPLC spectrum **1g**.

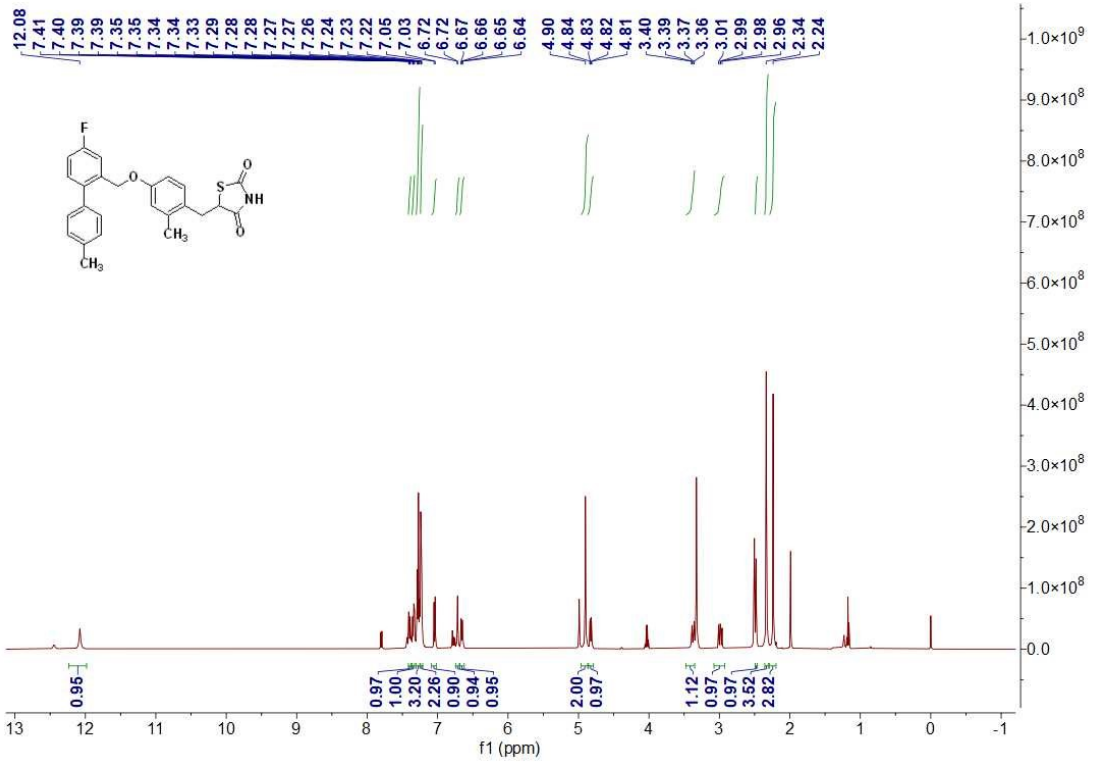



**Figure S5**. $^{1}$H NMR spectrum **2g**.

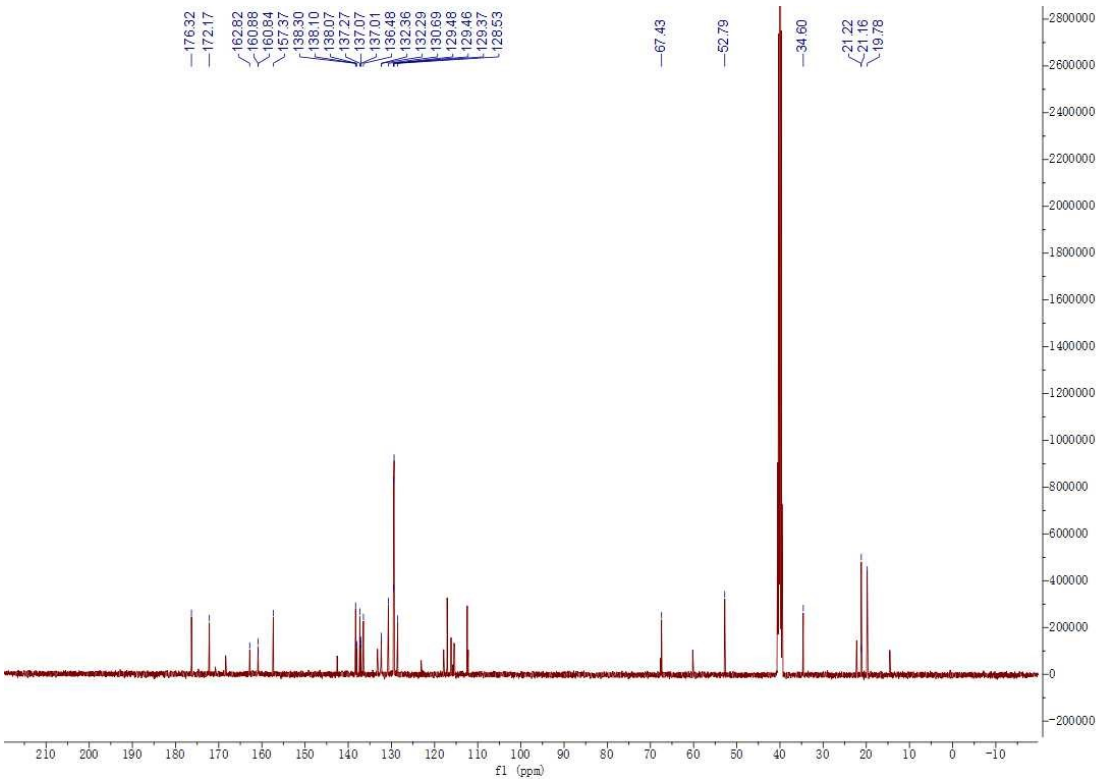



**Figure S6**. $^{13}C$ NMR spectrum **2g**.

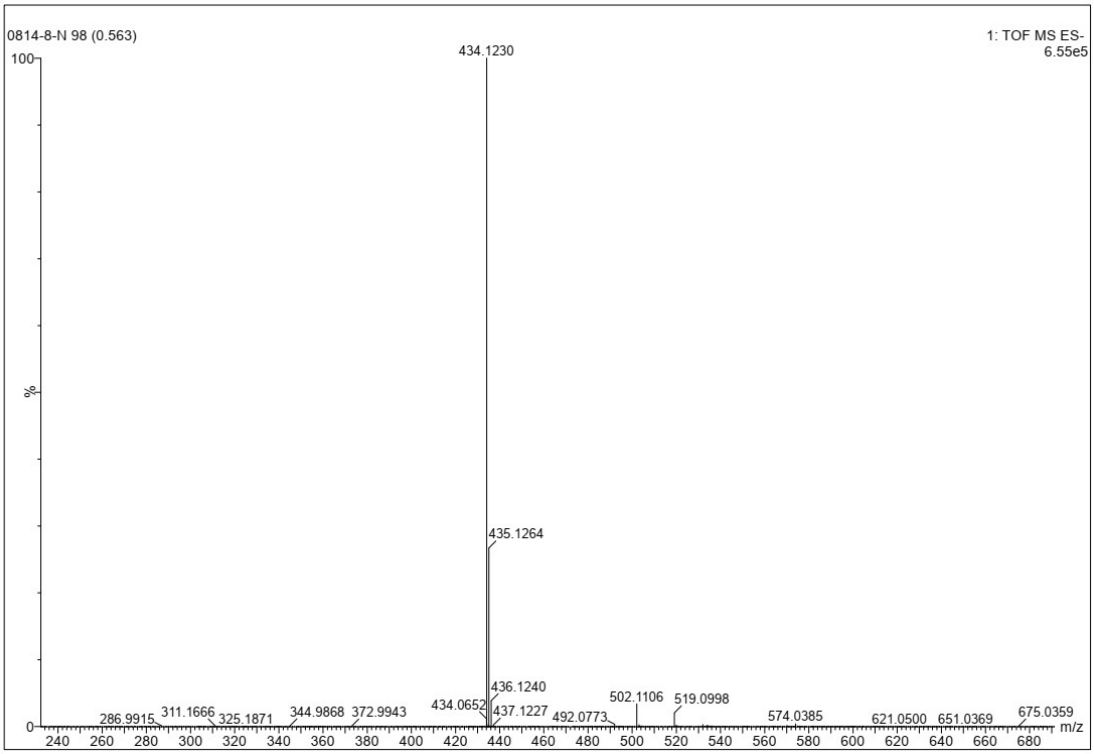
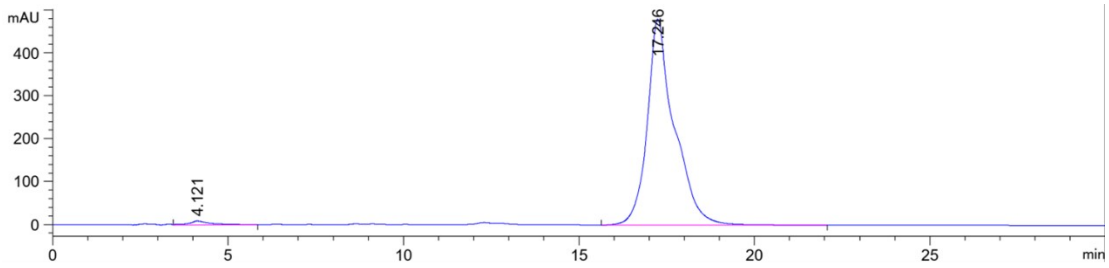



**Figure S7**. HRMS spectrum **2g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 4.121 | VB | 0.5746 | 380.25537 | 9.00652 | 1.4492 |
| 2 | 17.246 | BB | 0.7466 | 2.58586e4 | 479.95581 | 98.5508 |

**Figure S8**. HPLC spectrum **2g**.

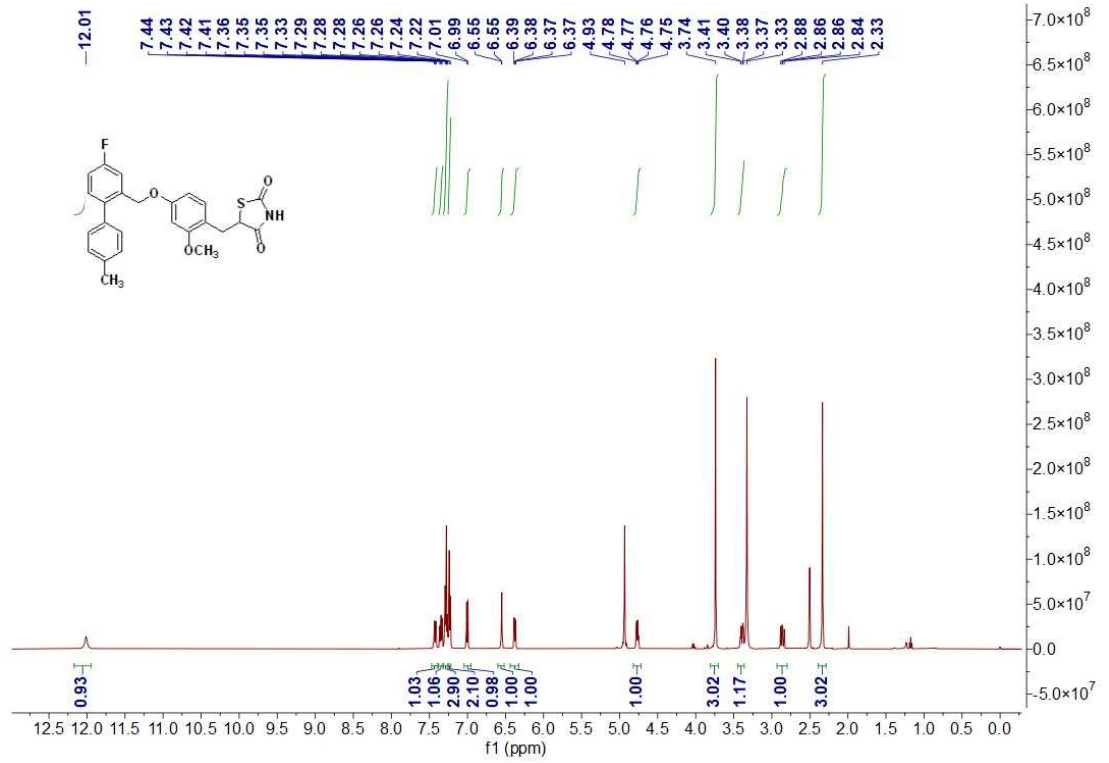



**Figure S9**. $^{1}$H NMR spectrum **3g**.

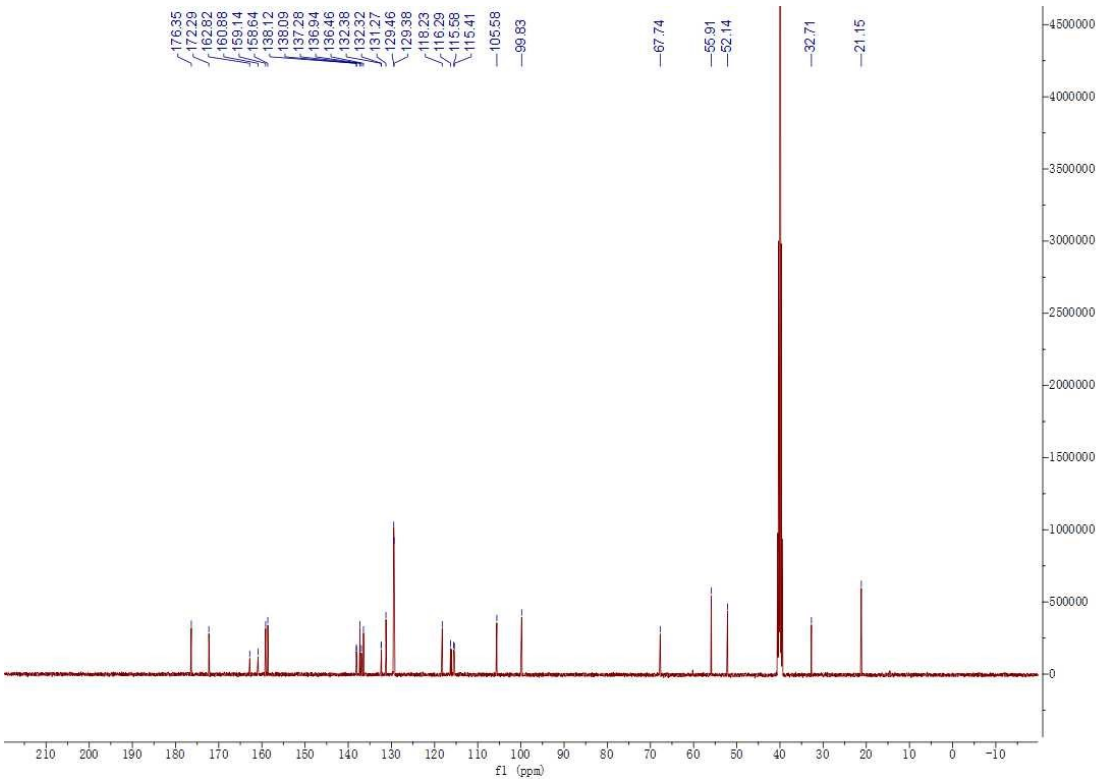



**Figure S10**. $^{13}C$ NMR spectrum **3g**.

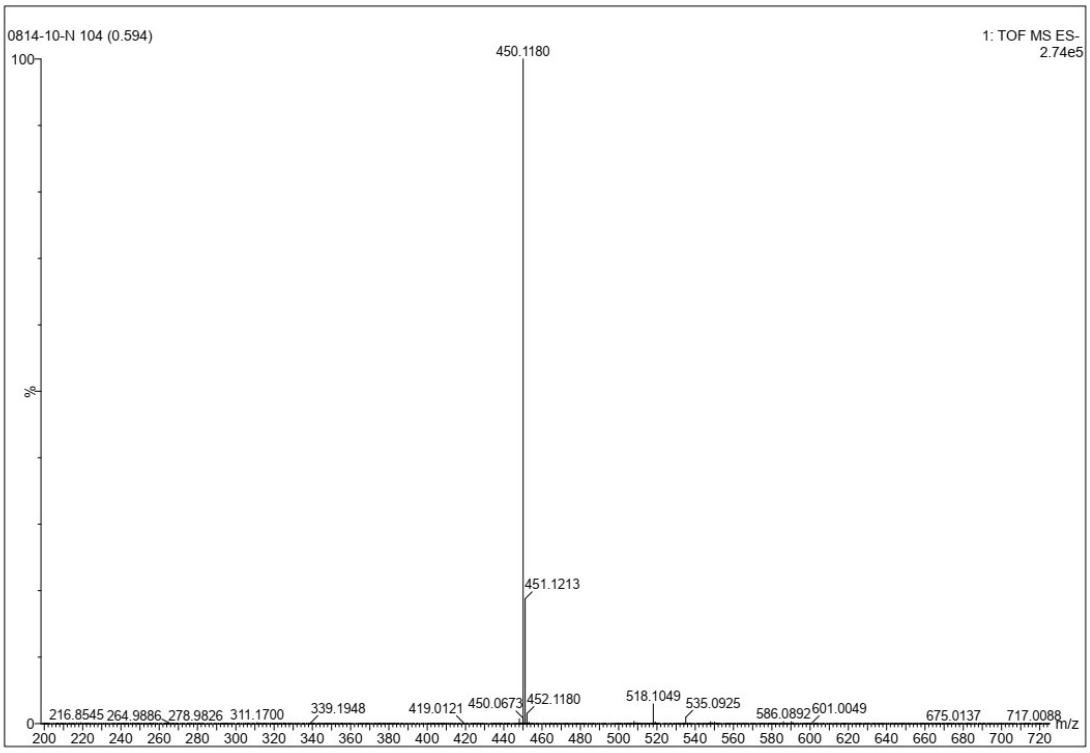
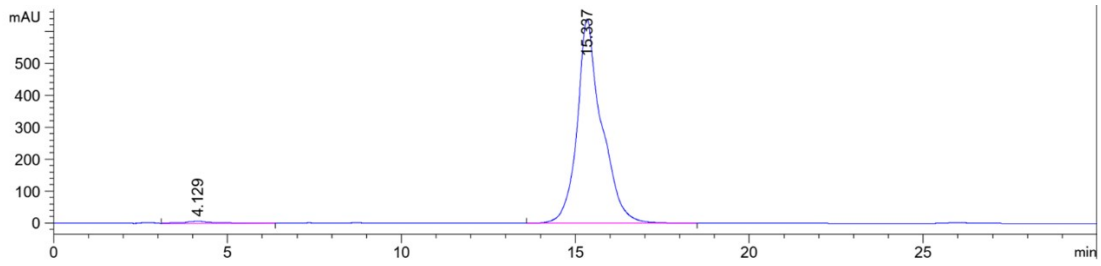



**Figure S11**. HRMS spectrum **3g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 4.129 | BV | 0.7292 | 402.69363 | 7.17066 | 1.2667 |
| 2 | 15.337 | BV | 0.6772 | 3.13882e4 | 638.82086 | 98.7333 |

**Figure S12**. HPLC spectrum **3g**.

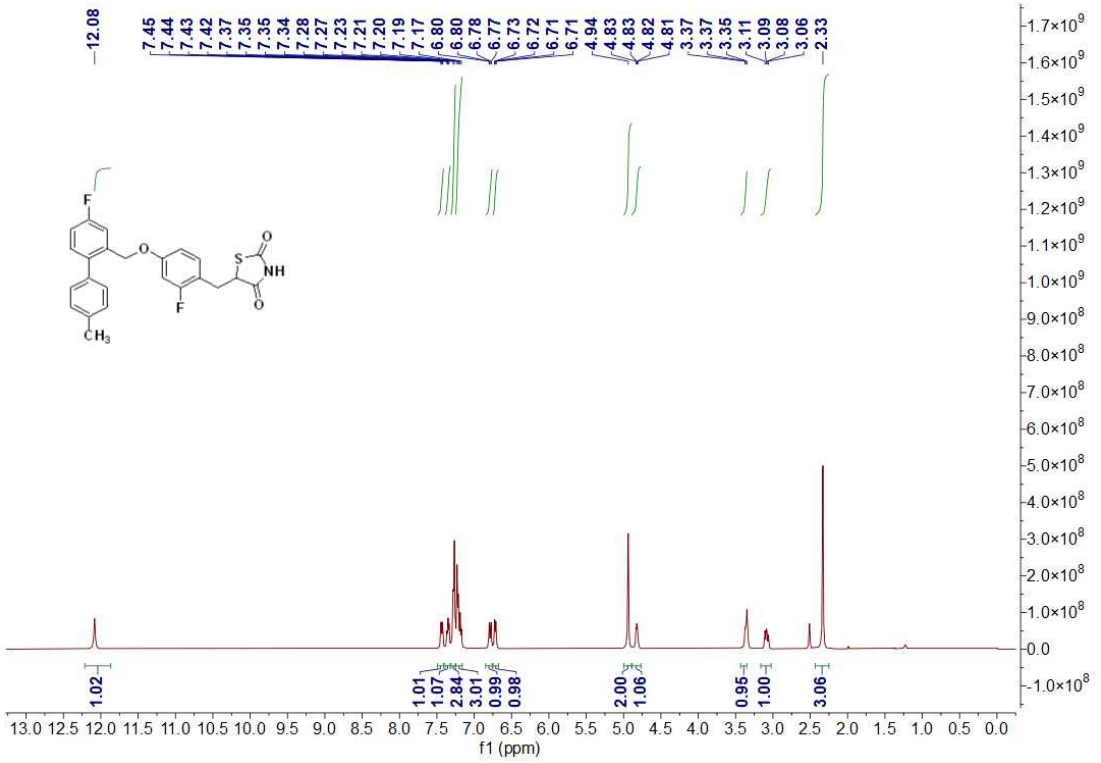



**Figure S13**. $^{1}$H NMR spectrum **4g**.

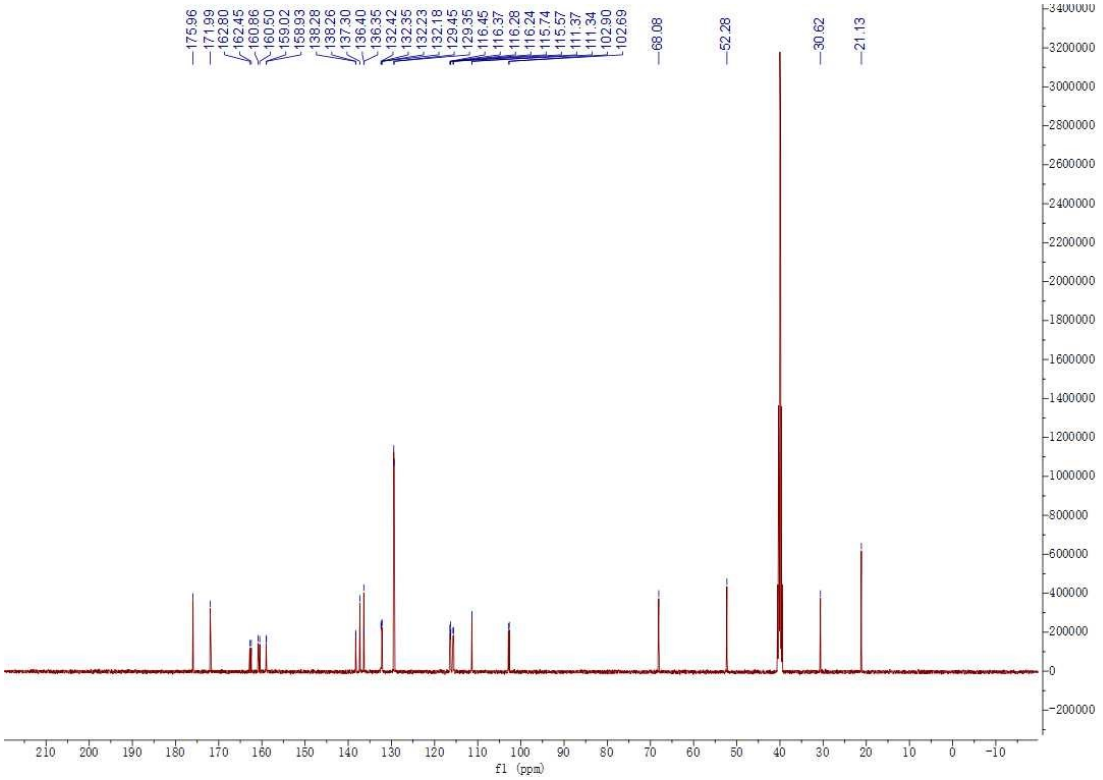



**Figure S14**. $^{13}C$ NMR spectrum **4g**.

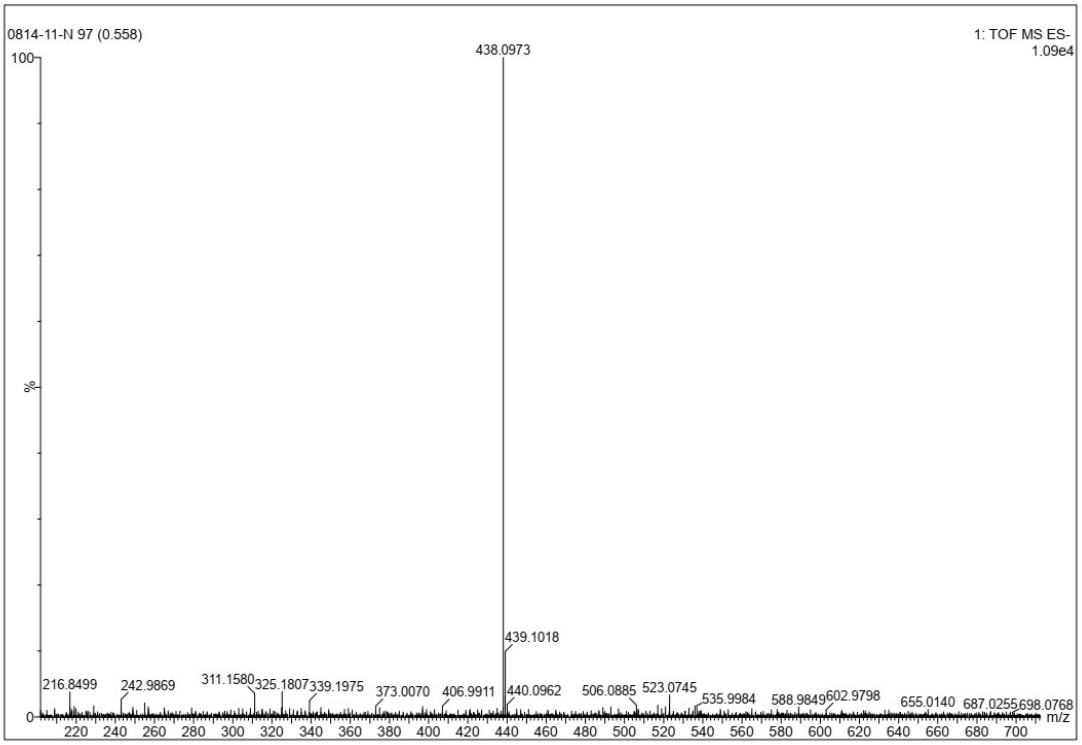
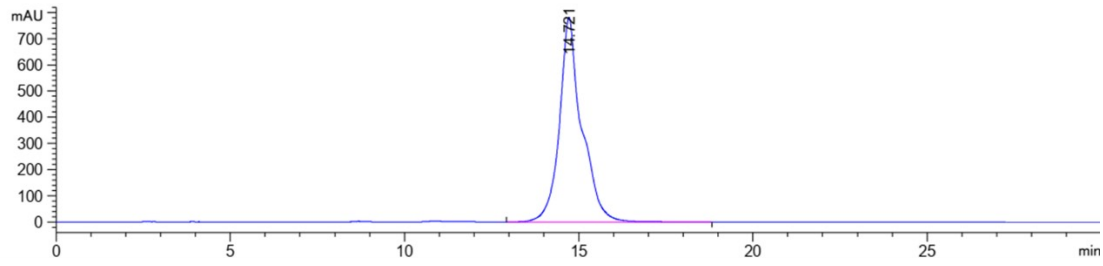



**Figure S15**. HRMS spectrum **4g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 14.721 | BB | 0.6169 | 3.47426e4 | 781.13025 | 100.0000 |

**Figure S16**. HPLC spectrum **4g**.

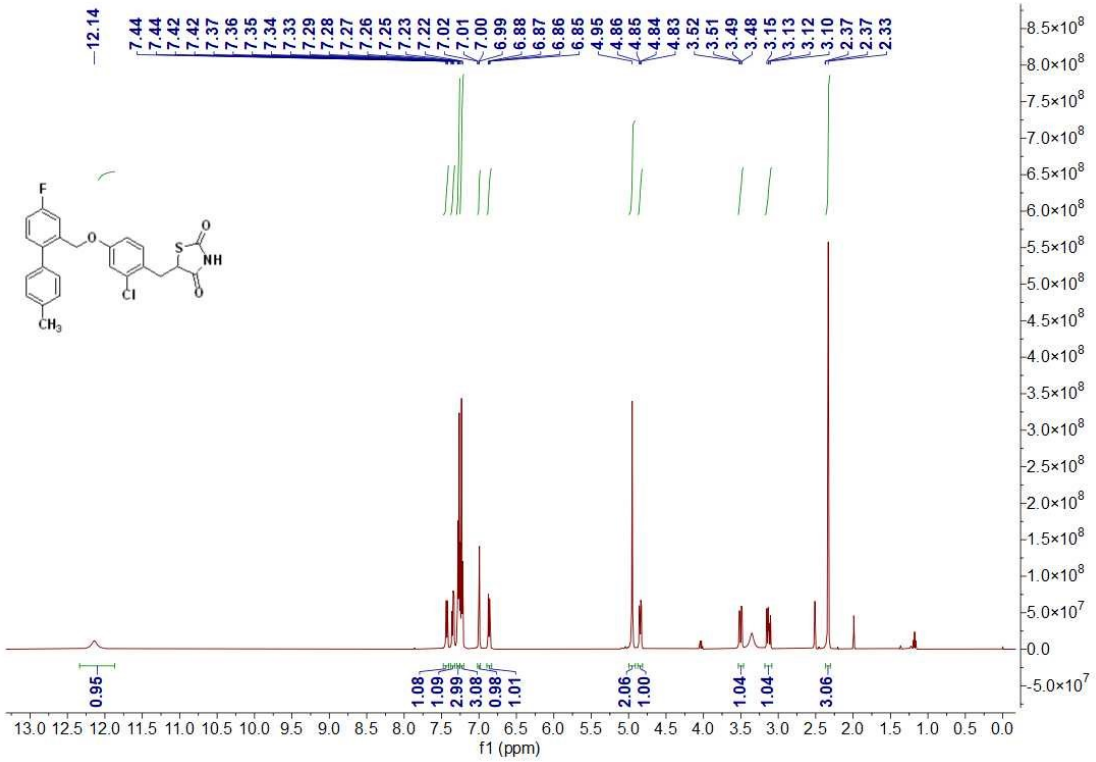



**Figure S17**. $^{1}$H NMR spectrum **5g**.

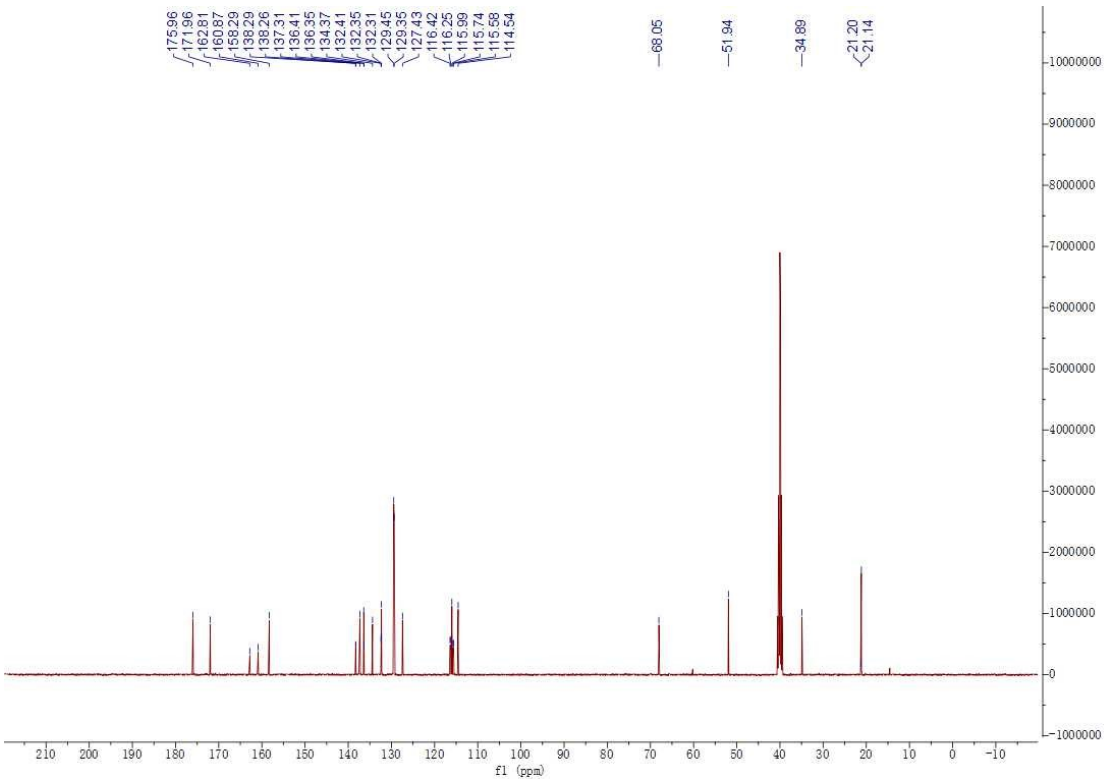



**Figure S18**. $^{13}$C NMR spectrum **5g**.

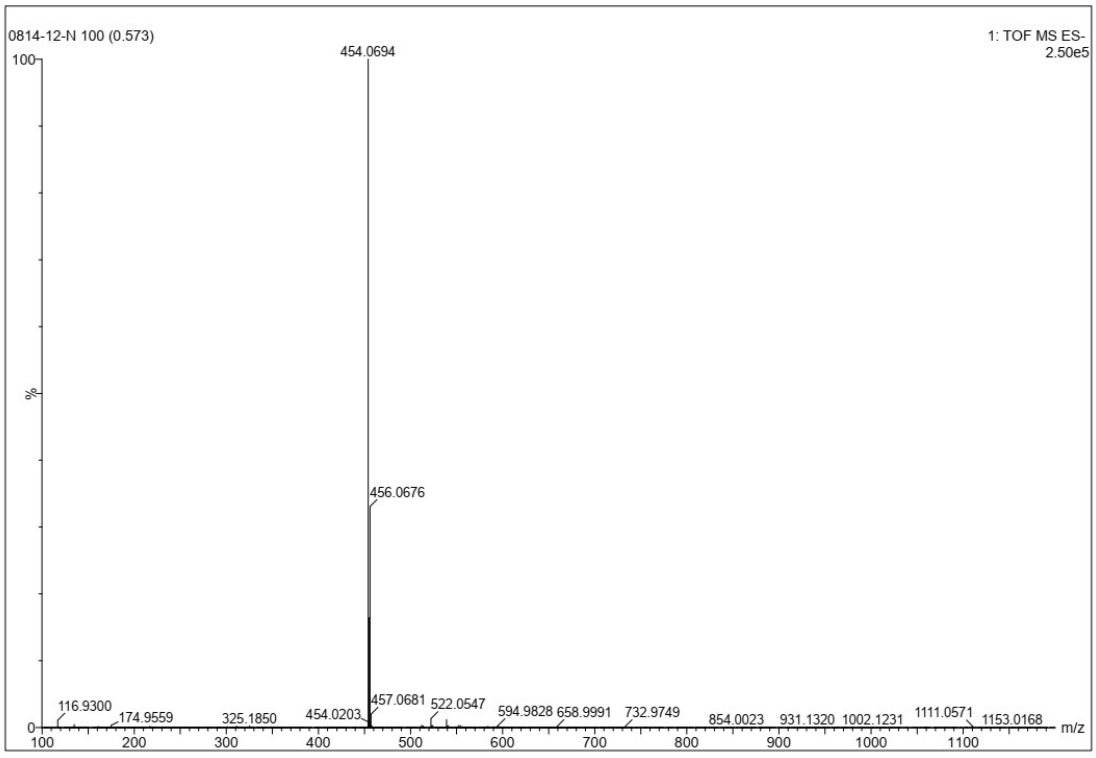
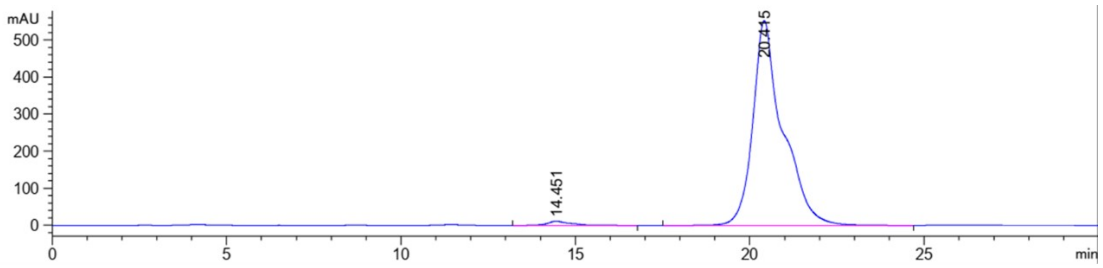



**Figure S19**. HRMS spectrum **5g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 14.451 | BB | 0.6303 | 518.60388 | 11.32303 | 1.5460 |
| 2 | 20.415 | BV | 0.8300 | 3.30258e4 | 552.03845 | 98.4540 |

**Figure S20**. HPLC spectrum **5g**.

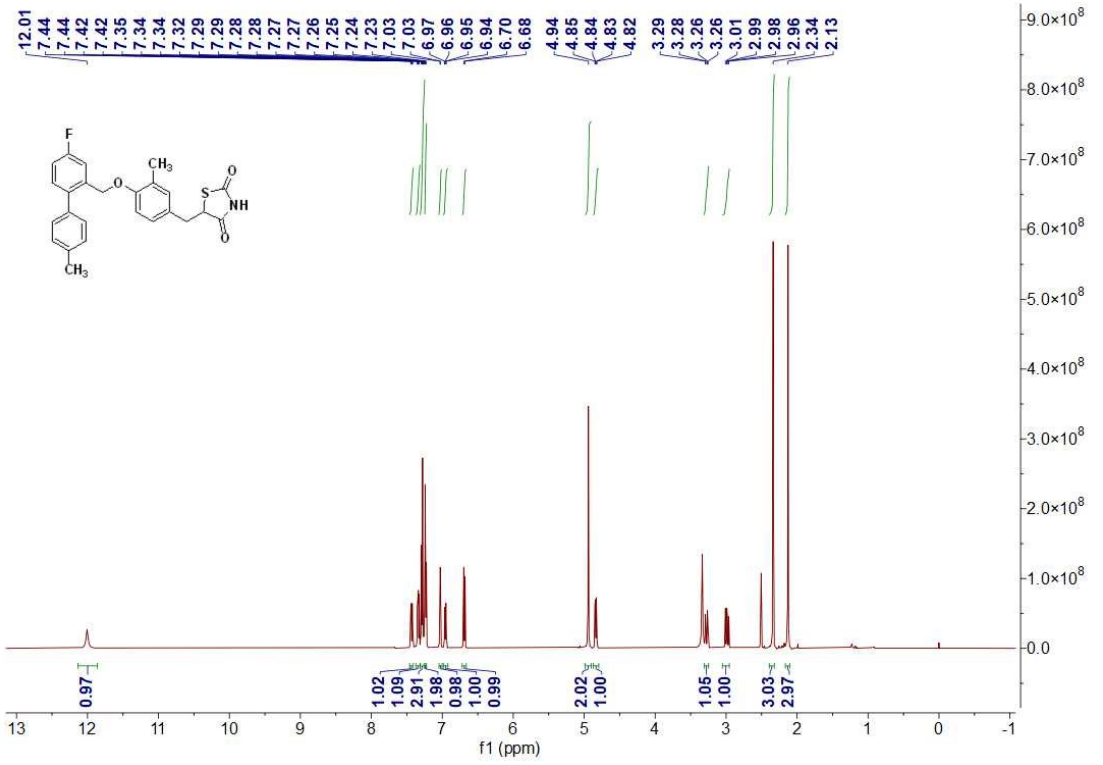



**Figure S21**. $^{1}$H NMR spectrum **6g**.

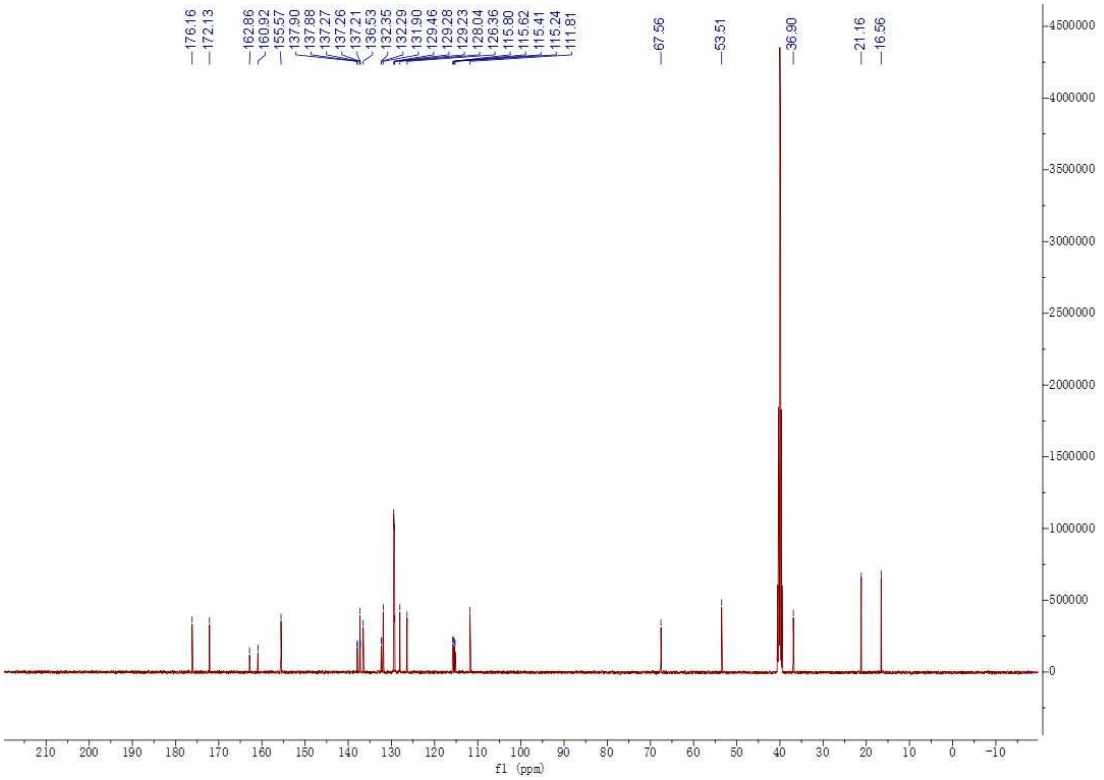



**Figure S22**. $^{13}C$ NMR spectrum **6g**.

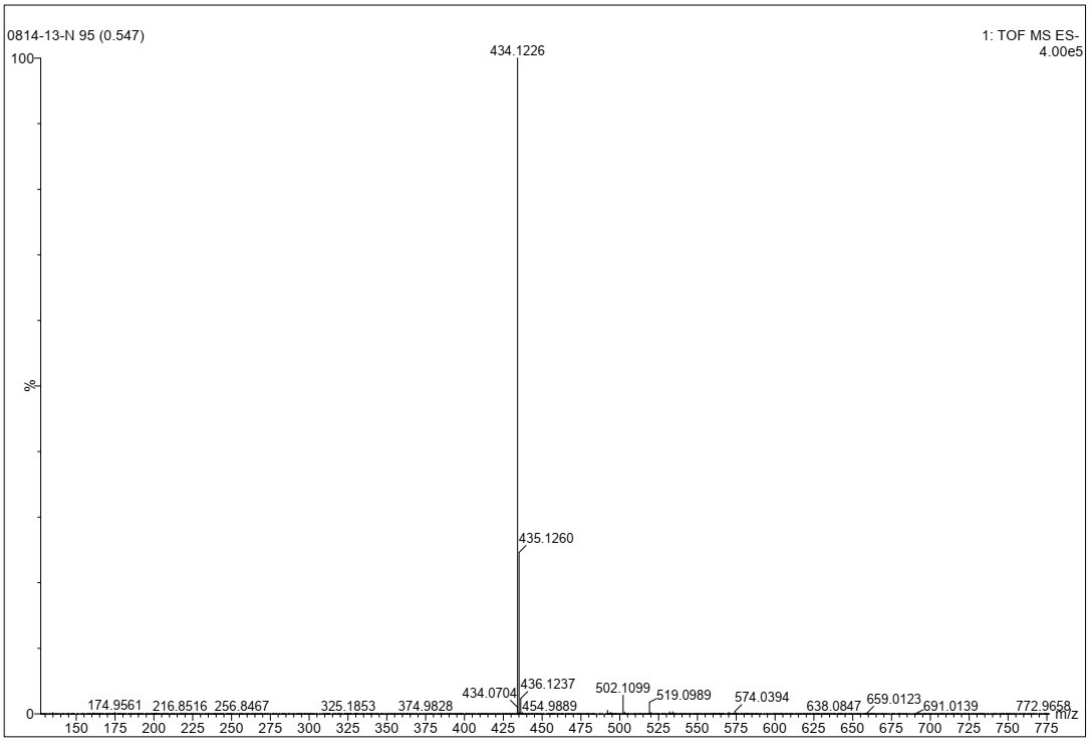
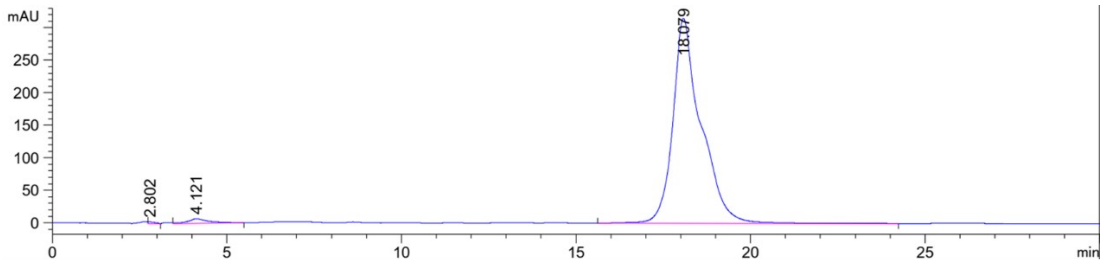



**Figure S23**. HRMS spectrum **6g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 2.802 | VB | 0.1937 | 36.98055 | 2.63521 | 0.2057 |
| 2 | 4.121 | VB | 0.5568 | 292.81927 | 7.13557 | 1.6290 |
| 3 | 18.079 | BB | 0.7755 | 1.76457e4 | 314.99933 | 98.1653 |

**Figure S24**. HPLC spectrum **6g**.

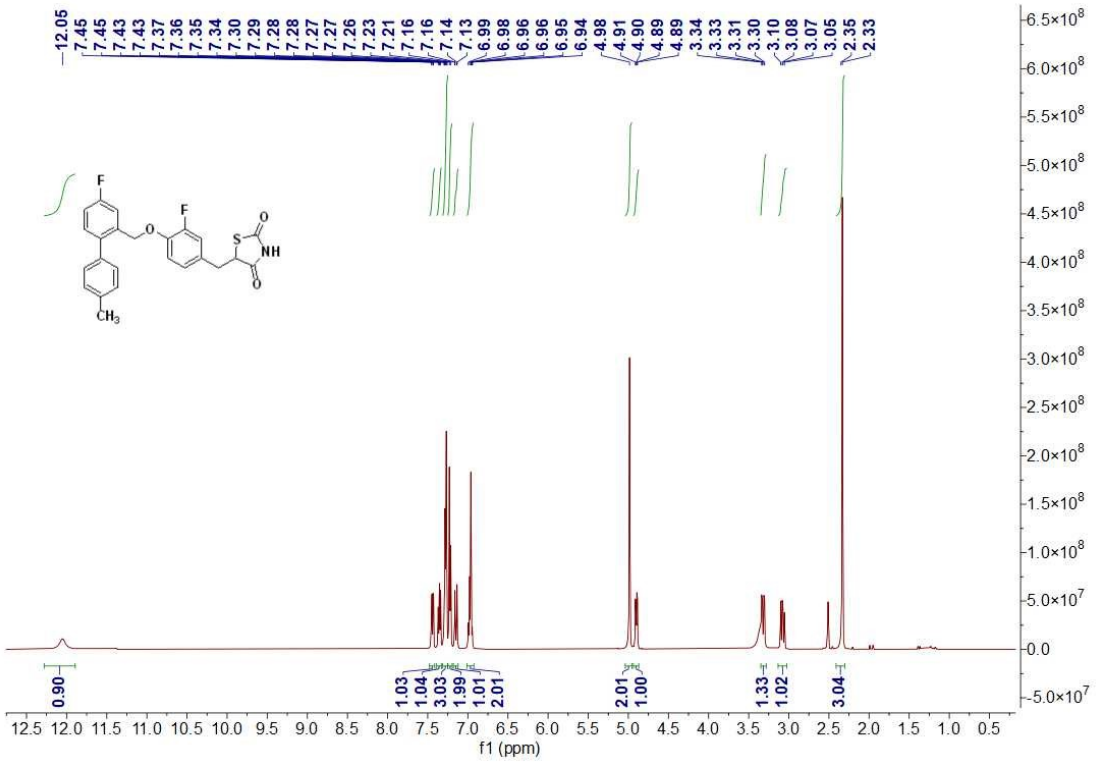



**Figure S25**. $^{1}$H NMR spectrum **7g**.

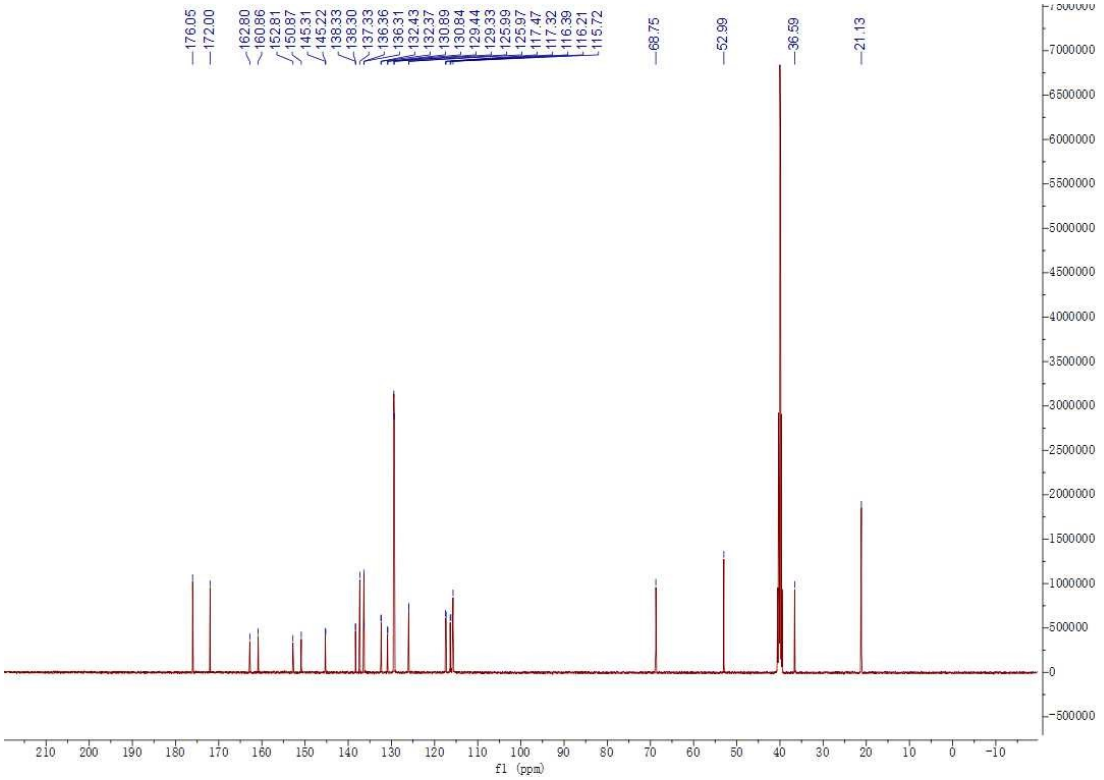



**Figure S26**. $^{13}C$ NMR spectrum **7g**.

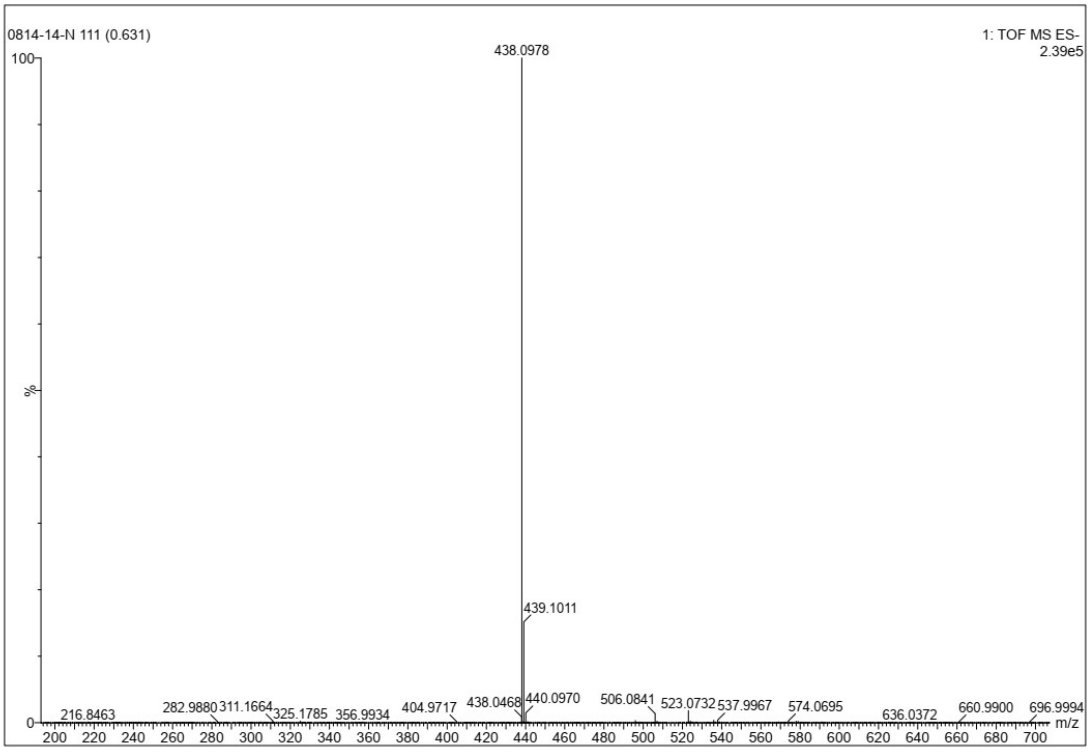
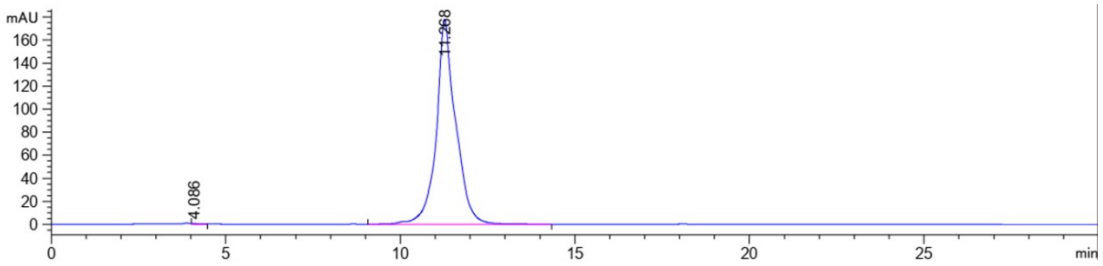



**Figure S27**. HRMS spectrum **7g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 4.086 | VV | 0.1755 | 8.10113 | 6.15752e-1 | 0.1173 |
| 2 | 11.268 | VB | 0.5281 | 6897.97949 | 178.00594 | 99.8827 |

**Figure S28**. HPLC spectrum **7g**.

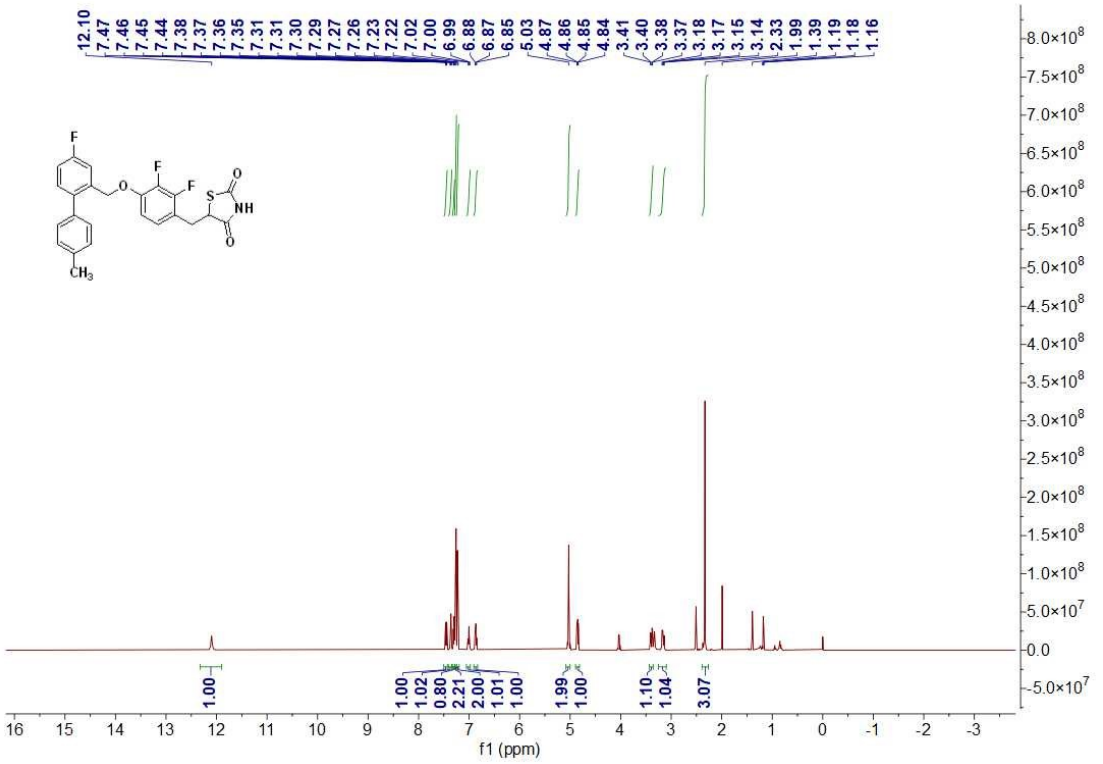



**Figure S29**. $^{1}$H NMR spectrum **8g**.

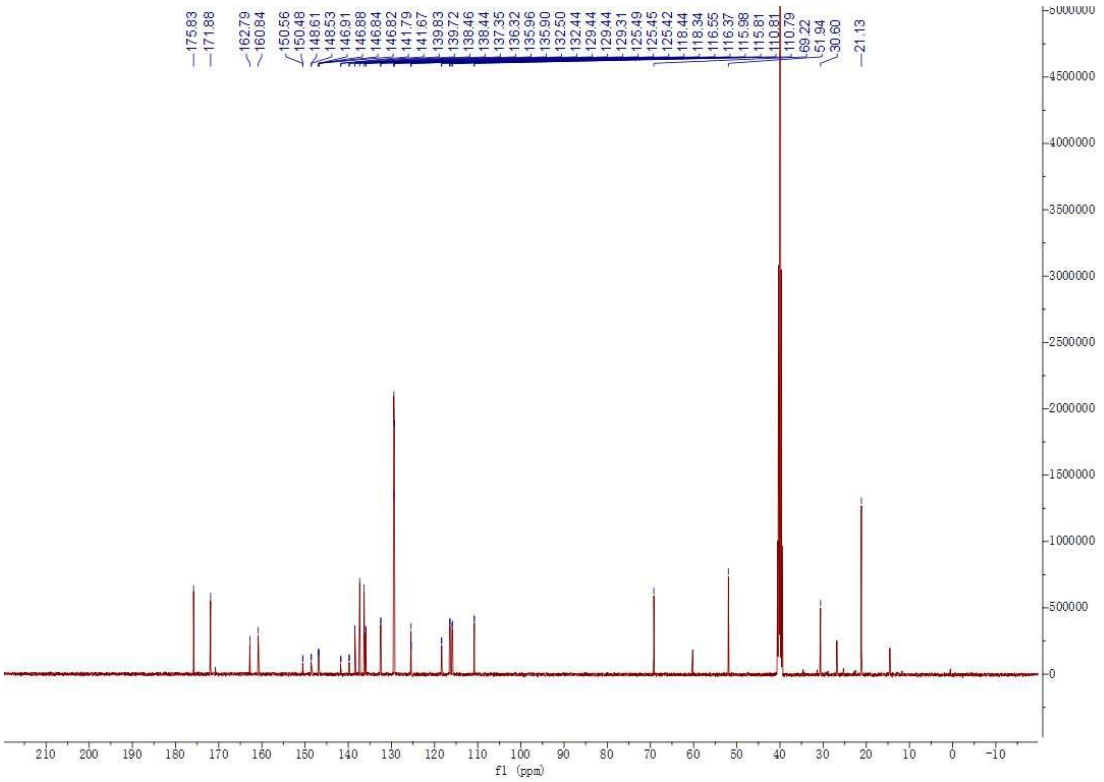



**Figure S30**. $^{13}C$ NMR spectrum **8g**.

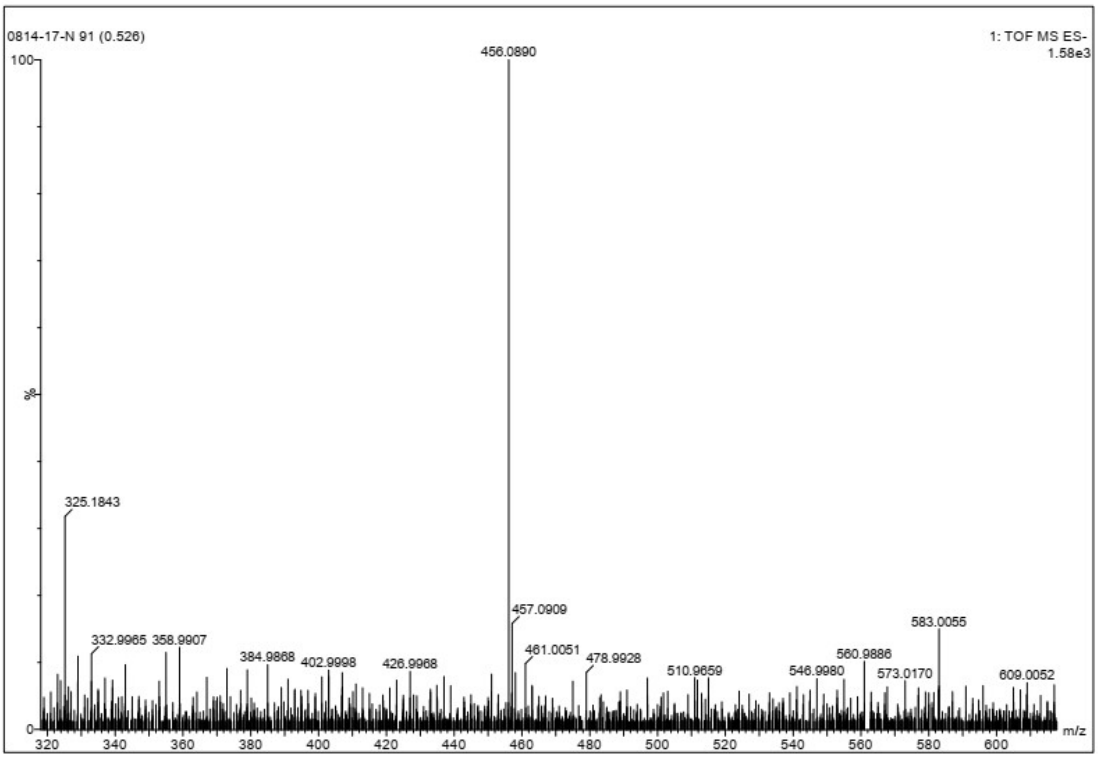
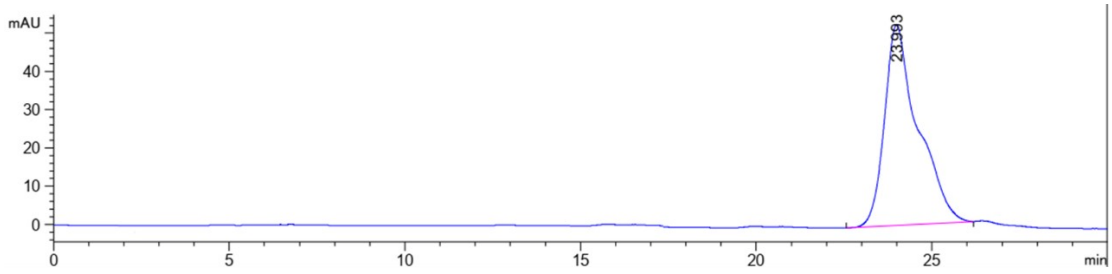



**Figure S31**. HRMS spectrum **8g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 23.993 | BB | 0.9214 | 3468.97217 | 52.46262 | 100.0000 |

**Figure S32**. HPLC spectrum **8g**.

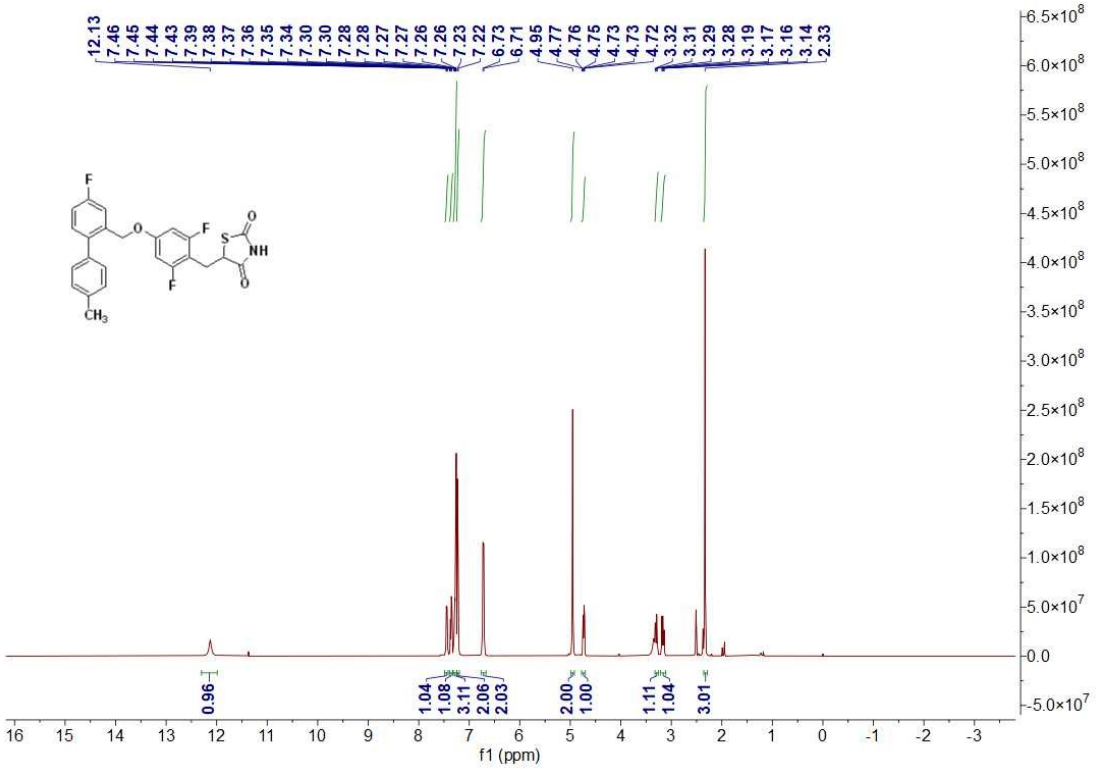



**Figure S33**. $^{1}$H NMR spectrum **9g**.

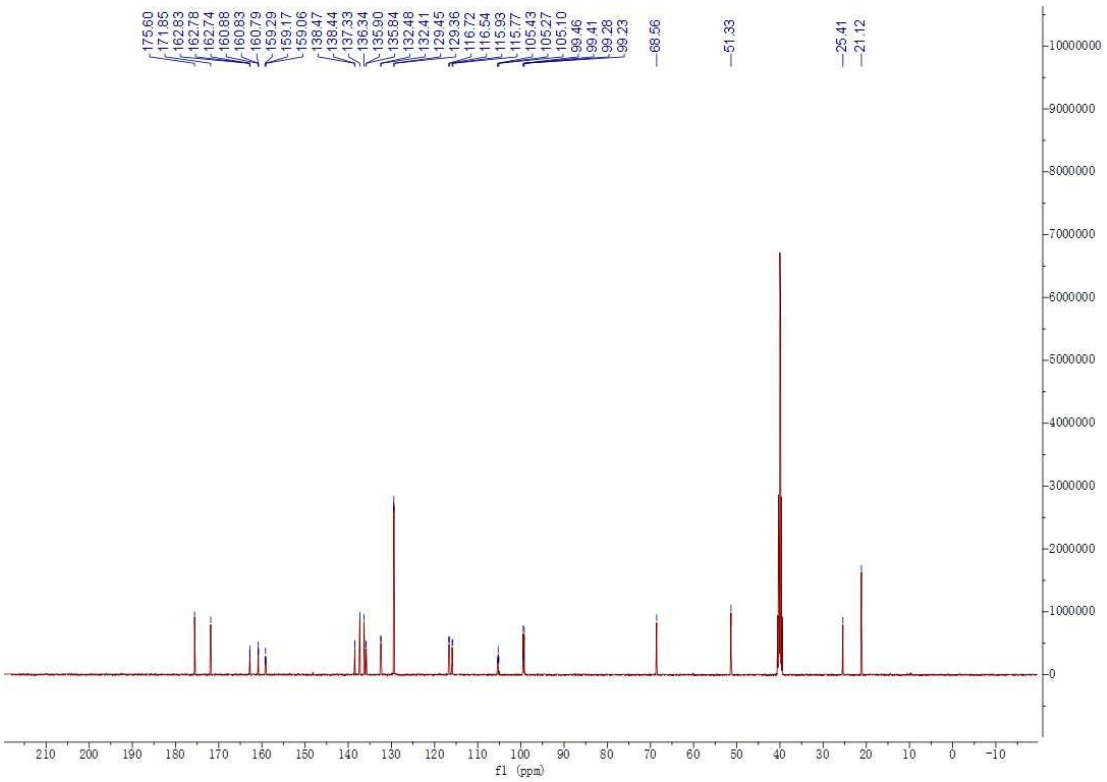



**Figure S34**. $^{13}C$ NMR spectrum **9g**.

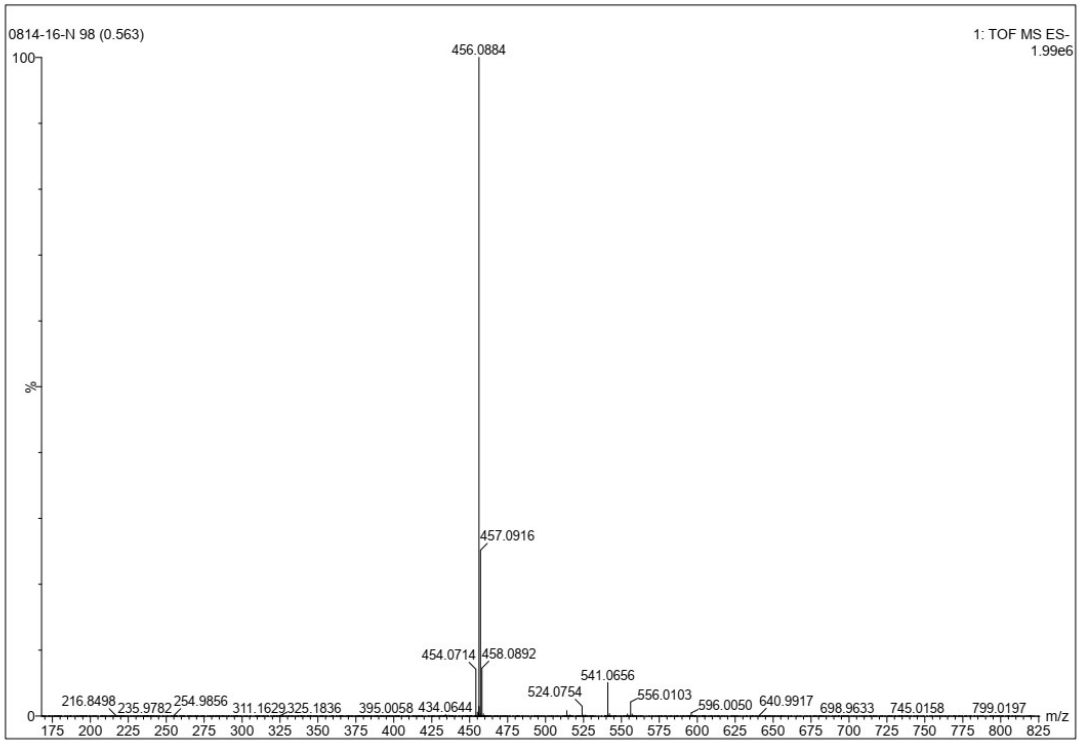
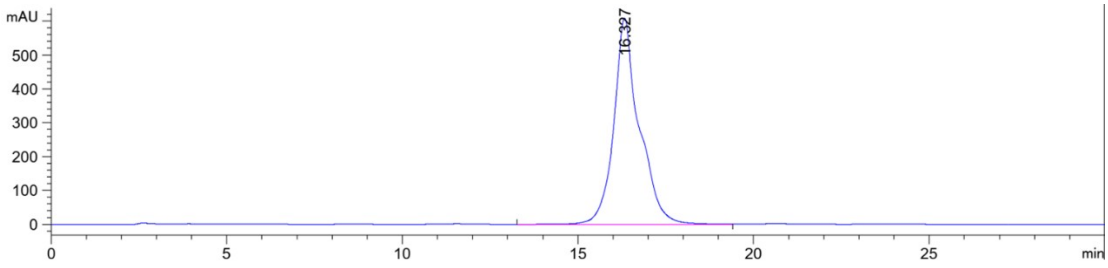



**Figure S35**. HRMS spectrum **9g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 16.327 | BV | 0.6992 | 3.08453e4 | 608.70697 | 100.0000 |

**Figure S36**. HPLC spectrum **9g**.

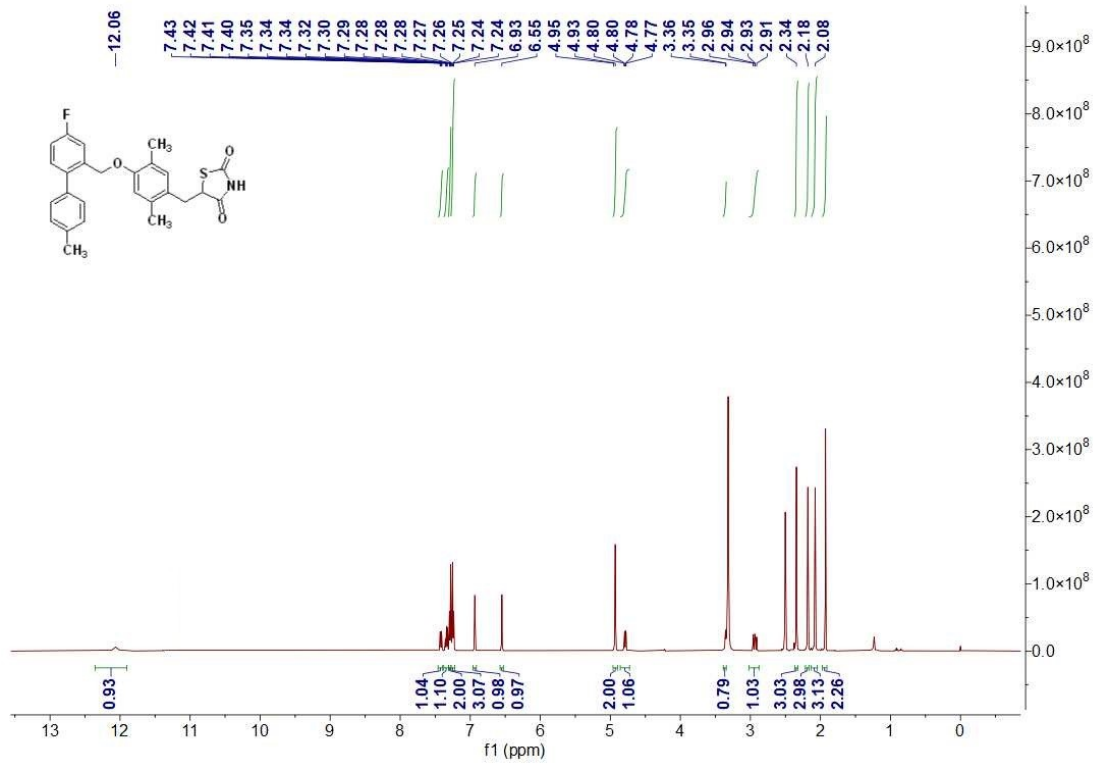



**Figure S37**. $^{1}$H NMR spectrum **10g**.

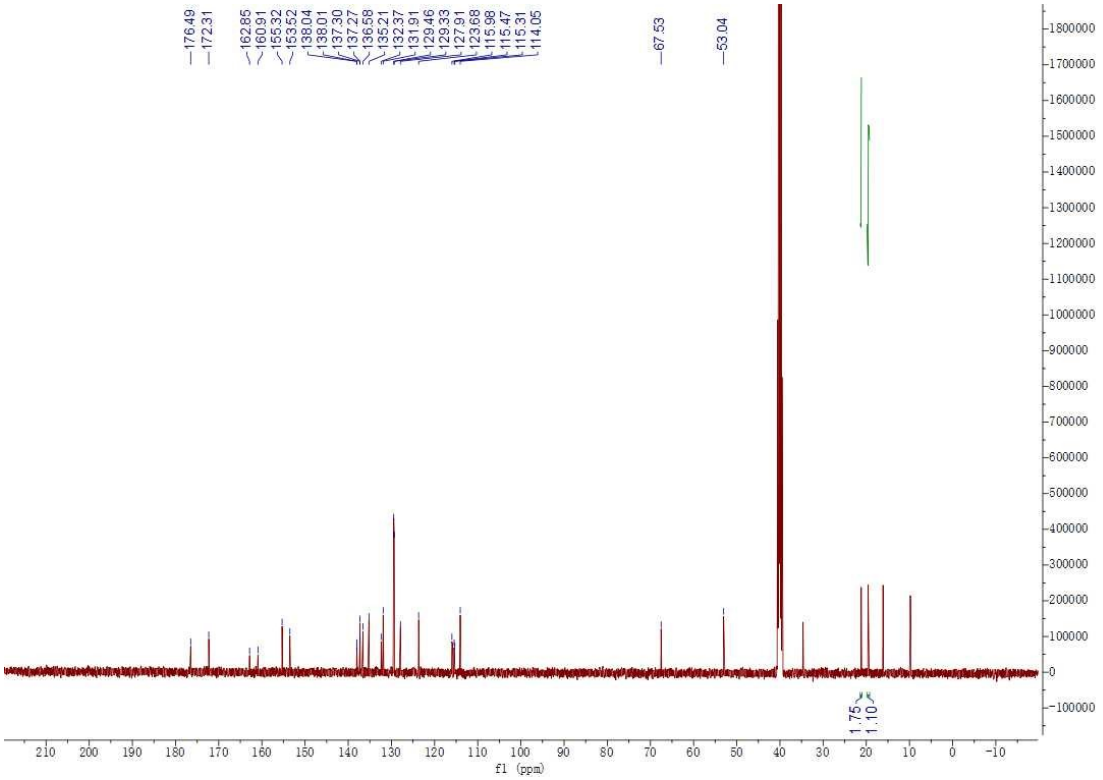



**Figure S38**. $^{13}C$ NMR spectrum **10g**.

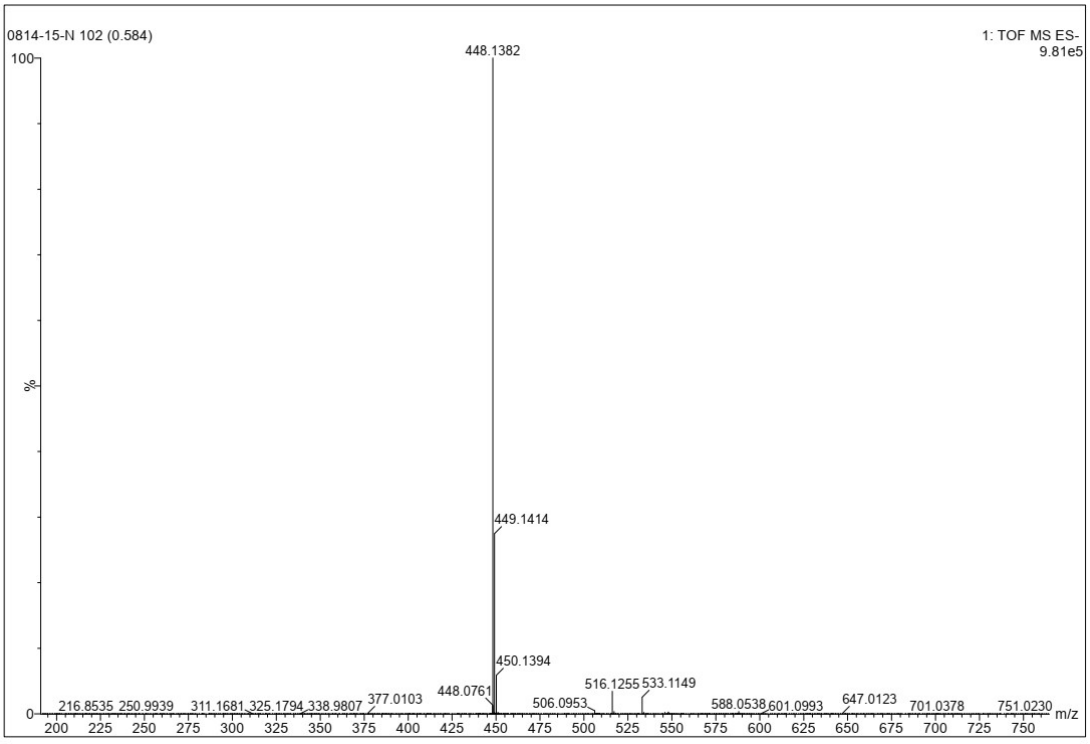
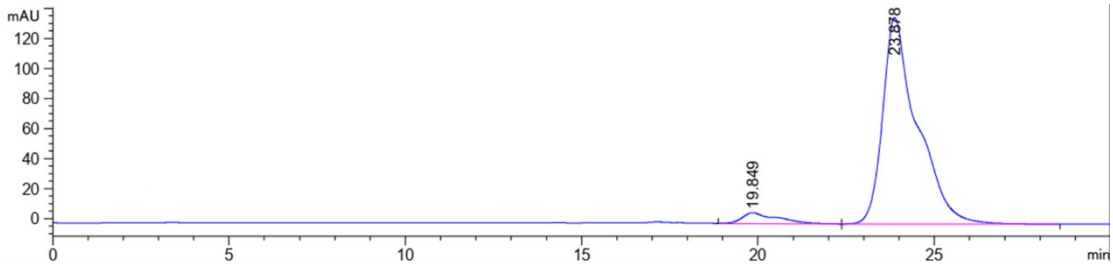



**Figure S39**. HRMS spectrum **10g**.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 19.849 | BB | 0.9169 | 491.46097 | 7.19525 | 4.9823 |
| 2 | 23.878 | BB | 0.9544 | 9372.63477 | 137.29694 | 95.0177 |

**Figure S40**. HPLC spectrum **10g**.

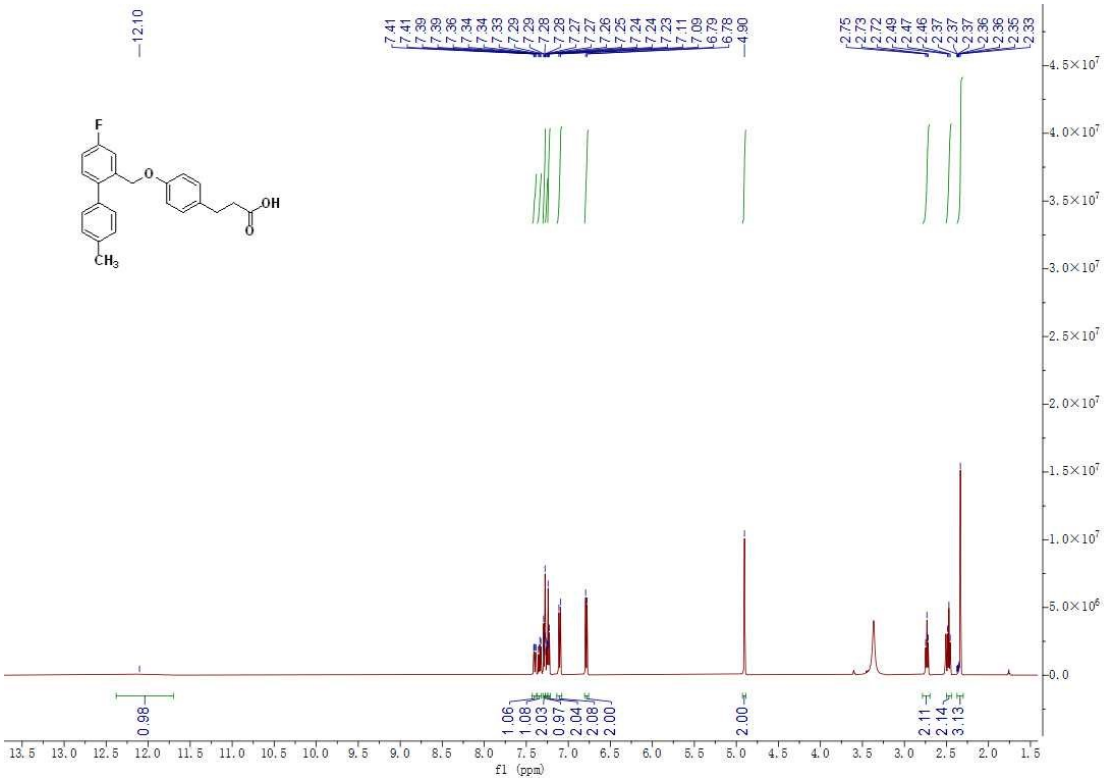



**Figure S41**. $^{1}$H NMR spectrum TUG-891.

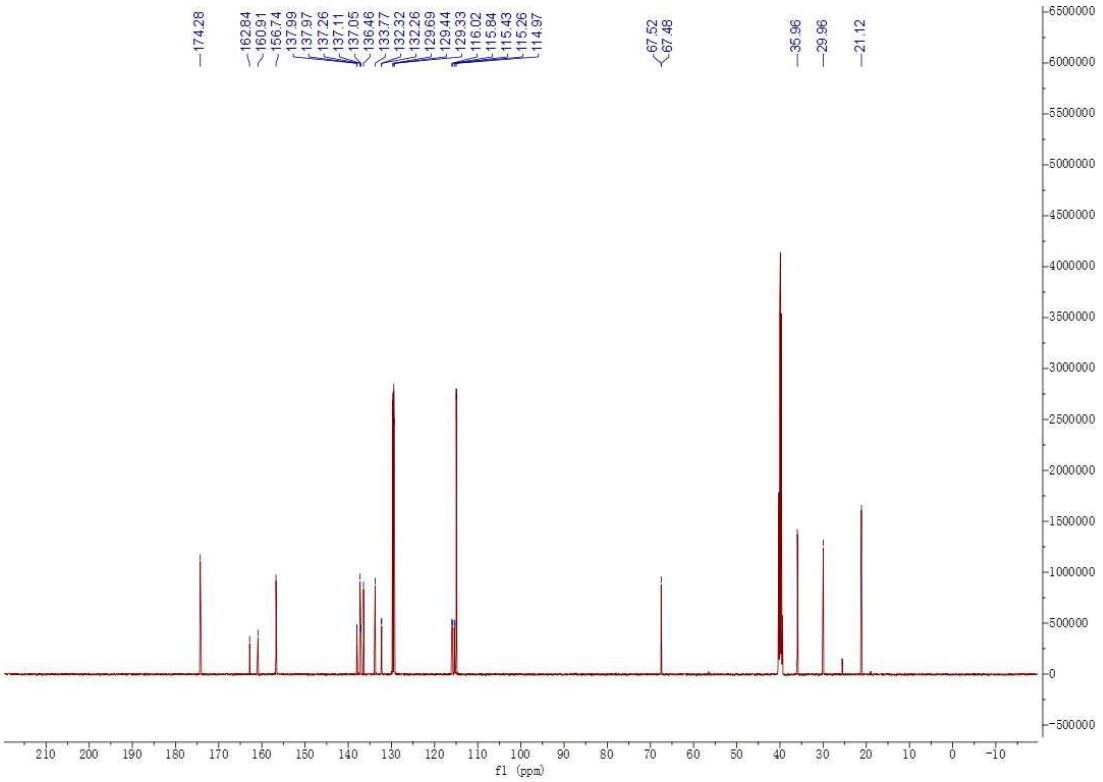



**Figure S42**. $^{13}C$ NMR spectrum TUG-891.

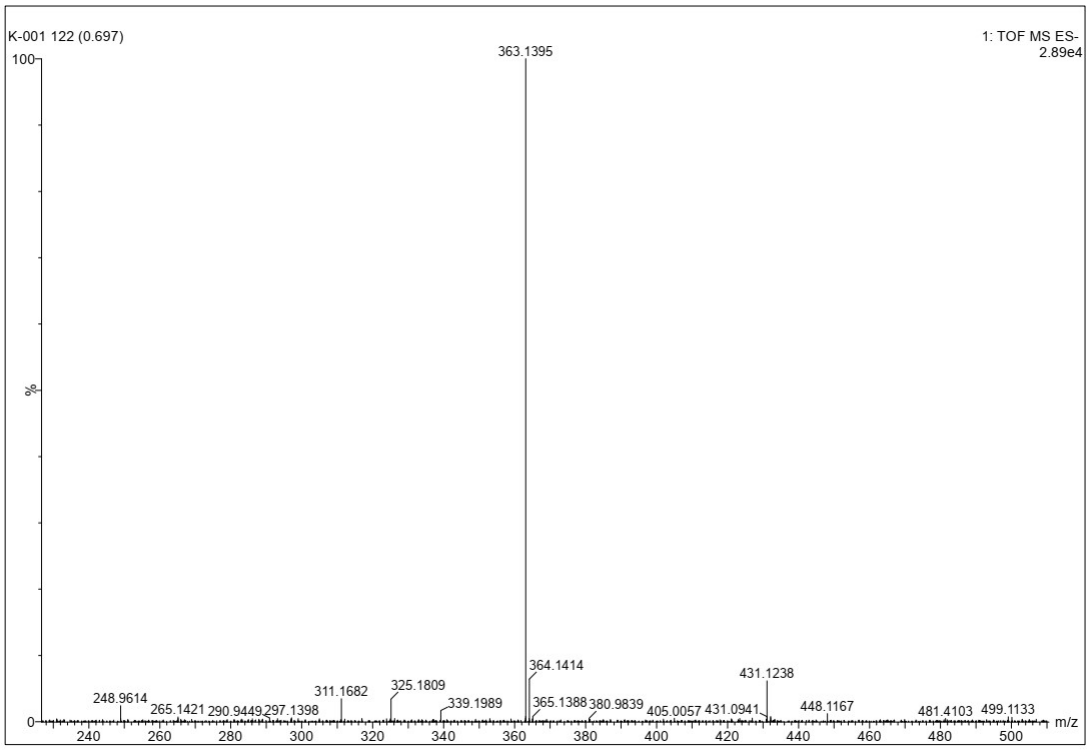
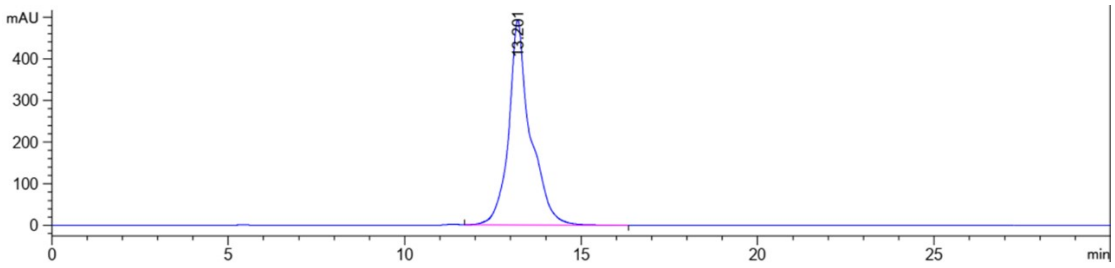



**Figure S43**. HRMS spectrum TUG-891.




| # | [min] | | [min] | [mAU*s] | [mAU] | % |
|---|---|---|---|---|---|---|
| 1 | 13.201 | BB | 0.5859 | 2.09891e4 | 491.85983 | 100.0000 |

**Figure S44**. HPLC spectrum TUG-891.