

## Supporting Information

### **New chalcone derivatives: synthesis, antiviral activity and mechanism of action**

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## Contents

<b>1. General information .....</b>	<b>2</b>
<b>2. Biological assays .....</b>	<b>2</b>
2.1 The purification of TMV .....	2
2.2 Curative activities against TMV in vivo of the target compounds .....	2
2.3 Protective activities against TMV in vivo of the target compounds .....	2
2.4 Inactive activities against TMV in vivo of the target compounds .....	3
<b>3. The effect of the compounds on the morphology of TMV particles ...</b>	<b>3</b>
<b>4. Studies of molecular docking modes .....</b>	<b>3</b>
<b>5. MST Studies.....</b>	<b>3</b>
<b>6. FT Studies .....</b>	<b>4</b>
<b>7. Characterization of the target compounds.....</b>	<b>4</b>
<b>8. <sup>1</sup>H NMR, <sup>13</sup>C NMR, <sup>19</sup>F NMR and HRMS data of the compounds .....</b>	<b>16</b>

## 1. General information

$^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and  $^{19}\text{F}$  NMR spectra were obtained on a Brookfield Ascend-400 spectrometer (Bruker Germany) using  $\text{DMSO-}d_6$  or  $\text{CDCl}_3$  as the solvent. High-resolution mass spectrometry (HRMS) data were confirmed with a Thermo Scientific Q Exactive (Thermo, USA). The melting points of the target products were measured using a X-4B microscope melting point apparatus (Electronic physical optical instrument Co., Ltd., Shanghai, China). The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All first-order splitting patterns were assigned based on the appearance of the multiplet. Splitting patterns that could not be easily interpreted were designated as multiplet (m). Analytical thin-layer chromatography (TLC) was performed on silica gel GF<sub>254</sub> (400 mesh). All of the reagents and reactants were purchased from commercial suppliers and analytical reagent grade or chemically pure without purification or further drying were used in the experiment.

## 2. Biological assays

### 2.1 The purification of TMV

The leaves of *Nicotiana tabacum* cv. K326 inoculated with TMV were selected, and the purification of TMV was carried out according to the previously reported methods (G. V. Gooding, et al. *Phytopathology*, 1967, **57**, 1285–1287).

### 2.2 Curative activities against TMV in vivo of the target compounds

The leaves of *N. tabacum* L. growing at the same ages were selected to evaluate the anti-TMV activities. The virus was dipped and inoculated on the whole leaves, which were scattered with silicon carbide beforehand. After 30 min, the leaves were washed with water and natural drying. The compound solution was smeared on the right side, and the solvent was smeared on the left side. The inoculated plants were placed at  $28 \pm 1$  °C and 10000 Lux for 3 to 5 days. The cultivated plants were selected to count the number of local lesions and calculate the inhibition rate of the target compounds. Each experiment was set for three repetitions.

### 2.3 Protective activities against TMV in vivo of the target compounds

The compounds solution was smeared on the right side of the growing *N. tabacum* L. leaves. After 24 h, the virus was dipped and inoculated on the whole leaves, which were scattered with silicon carbide beforehand. As a control, the solvent was smeared on the left side. Then, the leaves were washed with water after inoculation for 30 min. The inoculated plants were placed at  $28 \pm 1$  °C and 10000 Lux for 3 to 5 days. The cultivated plants were

selected to count the number of local lesions and calculate the inhibition rate of the target compounds. Each experiment was set for three repetitions. Three repetitions were conducted for each compound.

## **2.4 Inactive activities against TMV in vivo of the target compounds**

The mixture of virus solution with the compounds were inoculated on the right side leaves of the growing *N. tabacum* L. at the same ages 30 minutes later, as a control, the mixture of solvent with virus solution were inoculated on the left side leaves at the same ages. And silicon carbide was spread on the whole leaves before inoculation. Then, the leaves were washed with water after 30 min. The inoculated plants were placed at  $28 \pm 1$  °C and 10000 Lux for 3 to 5 days. The cultivated plants were selected to count the number of local lesions and calculate the inhibition rate of the target compounds. Each experiment was set for three repetitions.

## **3. The effect of the compounds on the morphology of TMV particles**

To observe the effect of the compounds on the morphology of TMV particles, the samples were processed according to the methods reported in the literature with minor modifications. Preparing a concentration of 400 mg.L<sup>-1</sup> of the compound **5d** solution, then mixed with TMV virus solution in equal volume to obtain 200 mg.L<sup>-1</sup> of the compound **5d** solution. Ribavirin was used as the positive control. The blank control (CK) is TMV particles, without adding any compounds. After mixing for 30 minutes, the mixture was adsorbed by a 200-mesh copper mesh carbon support membrane and counterstained with 1% phosphotungstic acid with a pH of 7.4. After drying, the morphology of TMV particles was observed under transmission electron microscopy with a FEI Talos F200C at 200 kV.

## **4. Studies of molecular docking modes**

The interaction modes of the target compounds with TMV coat protein (TMV CP) were investigated by Discovery Studio 4.5 software. The results of molecular docking were processed according to the previous method. Compounds **5d**, **5g** and **5k** with excellent to poor inhibitory activities against TMV were selected to dock with TMV CP (PDB code: 1EI7).

## **5. MST Studies**

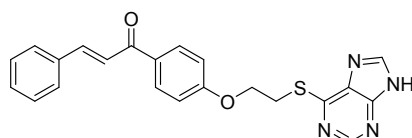
TMV CP was purified according to a previously described method. A range of concentrations of the required compounds (range from 2–5 mM) were incubated with 0.1 mM of purified recombinant TMV CP for 5 min with the Monolith NT Protein Labeling Kit Red (Nano Temper Technologies, München, Germany) in assay buffer (10 mM Tris/HCl and 100 mM sodium chloride, pH=7.4). The sample was loaded into the NanoTemper glass  
3

capillaries and microthermophoresis carried out using 20% LED power. The dissociation constant (K<sub>d</sub>) values were calculated from the duplicate reads of three separate experiments using the mass action equation in the NanoTemper software.

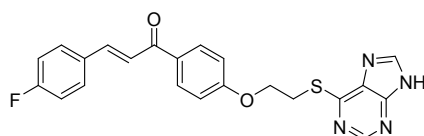
## 6. FT Studies

TMV CP was purified according to a previously described method. The concentration of the test compounds is 2 mM. Firstly, the fluorescence determination method of TMV CP was selected, and the fluorescence curve of the protein was measured to find the highest point of the fluorescence curve and determine the wavelength range corresponding to the highest point. Then, the interaction between the small molecule and the protein was tested, and the force was determined by the fluorescence quenching curve of the protein. A 5  $\mu$ L small molecule drug was added into the protein to make it fully in contact with the small molecule. Meanwhile, the time is timed at the moment of contact, and the normal action time is about 30 s. The fluorescence values were measured as soon as the time was up. This step is generally repeated 16 times, collecting data 16 times, and drawing graphs for data analysis (FluorEssence 5.0).

## 7. Characterization of the target compounds

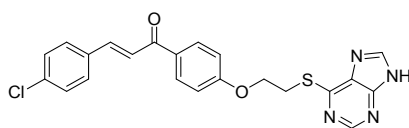


*(E)*-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-phenyl-prop-2-en-1-one (**4a**): Yellow solid, m.p. 161.9–163.7 °C, yield, 44%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 13.56 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.18 (d, *J* = 8.5 Hz, 2H, 1-Ph-H), 7.94 (d, *J* = 12.8 Hz, 1H, 3-CH=), 7.89–7.86 (m, 2H, 3-Ph-H), 7.72 (dd, *J* = 15.6, 3.3 Hz, 1H, 2-CH=), 7.45 (d, *J* = 2.9 Hz, 3H, 3-Ph-H), 7.18 (d, *J* = 7.5 Hz, 2H, 1-Ph-H), 4.43 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 3.79 (t, *J* = 6.5 Hz, 2H, -S-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$ : 187.9 (s), 162.6 (s), 152.0 (s), 152.0 (s), 143.7 (s), 135.3 (s), 131.5 (s), 131.5 (s), 131.1 (s), 130.9 (s), 130.9 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.3 (s), 129.3 (s), 122.5 (s), 115.1 (s), 115.1 (s), 67.1 (s), 27.2 (s); HRMS (ESI): calcd for C<sub>22</sub>H<sub>19</sub>N<sub>4</sub>O<sub>2</sub>S ([M+H]<sup>+</sup>), 403.12170; found, 403.12232.

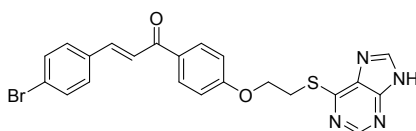


*(E)*-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**4b**): Yellow solid, m.p.

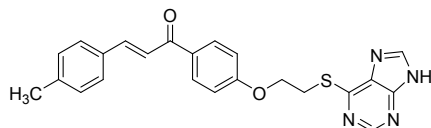
141.0–143.0 °C, yield, 41%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.59 (s, 1H, -NH-), 8.79 (s, 1H, Imidazole-H), 8.50 (s, 1H, Pyrimidine-H), 8.20 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 8.01–7.95 (m, 3H, 3-CH=, 3-Ph-H), 7.73 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.31 (t, *J* = 8.8 Hz, 2H, 3-Ph-H), 7.20 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.44 (t, *J* = 6.7 Hz, 2H, -O-CH<sub>2</sub>-), 3.81 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-); <sup>19</sup>F NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: -109.90 (s); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 187.7 (s), 162.8 (s), 162.6 (s), 162.5 (s), 152.0 (s), 152.0 (s), 142.4 (s), 132.0 (s), 132.0 (s), 131.7 (s), 131.6 (s), 131.5 (s), 131.1 (s), 122.4 (s), 122.4 (s), 116.5 (s), 116.3 (s), 115.0 (s), 67.1 (s), 36.3 (s), 31.2 (s), 27.1 (s); HRMS (ESI): calcd for C<sub>22</sub>H<sub>18</sub>FN<sub>4</sub>O<sub>2</sub>S ([M+H]<sup>+</sup>), 421.11221; found, 421.11290.



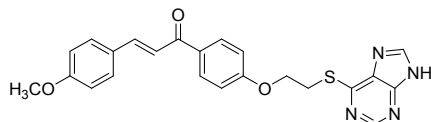
(*E*)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**4c**): White solid, m.p. 165.9–166.7 °C, yield, 58%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.76 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.19 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.99 (d, *J* = 15.6 Hz, 1H, 3-CH=), 7.94 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.70 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.53 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.19 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.43 (t, *J* = 6.7 Hz, 2H, -O-CH<sub>2</sub>-), 3.80 (t, *J* = 6.7 Hz, 2H, -S-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 187.7 (s), 162.7 (s), 152.0 (s), 152.0 (s), 142.2 (s), 142.2 (s), 135.4 (s), 134.3 (s), 131.6 (s), 131.6 (s), 131.0 (s), 131.0 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.4 (s), 123.2 (s), 115.1 (s), 115.1 (s), 67.1 (s), 27.1 (s); HRMS (ESI): calcd for C<sub>22</sub>H<sub>18</sub>ClN<sub>4</sub>O<sub>2</sub>S ([M+H]<sup>+</sup>), 437.08289; found, 437.08335.



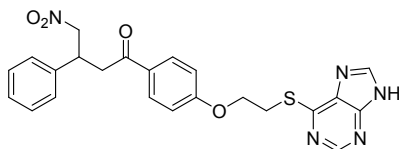
(*E*)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-bromophenyl)prop-2-en-1-one (**4d**): White solid, m.p. 185.7–186.4 °C, yield, 50%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.76 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.19 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.99 (d, *J* = 15.6 Hz, 1H, 3-CH=), 7.94 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.70 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.53 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.19 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.43 (t, *J* = 6.7 Hz, 2H, -O-CH<sub>2</sub>-), 3.80 (t, *J* = 6.7 Hz, 2H, -S-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 187.7 (s), 162.7 (s), 162.7 (s), 152.0 (s), 152.0 (s), 142.2 (s), 135.4 (s), 134.3 (s), 131.6 (s), 131.6 (s), 131.0 (s), 131.0 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.4 (s), 129.4 (s), 123.2 (s), 123.2 (s), 115.1 (s), 115.1 (s), 67.1 (s), 27.1 (s); HRMS (ESI): calcd for C<sub>22</sub>H<sub>17</sub>BrNaN<sub>4</sub>O<sub>2</sub>S ([M+Na]<sup>+</sup>), 503.01404; found, 503.01478.



*(E)*-1-(4-(2-((9*H*-purin-6-yl)thio)ethoxy)phenyl)-3-(*p*-tolyl)prop-2-en-1-one (**4e**): Yellow solid, m.p. 177.0–179.0 °C, yield, 52%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.59 (s, 1H, -NH-), 8.78 (s, 1H, Imidazole-H), 8.49 (s, 1H, Pyrimidine-H), 8.18 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.91 (d, *J* = 15.5 Hz, 1H, 3-CH=), 7.78 (d, *J* = 8.1 Hz, 2H, 3-Ph-H), 7.70 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.28 (d, *J* = 8.0 Hz, 2H, 3-Ph-H), 7.19 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.44 (t, *J* = 6.7 Hz, 2H, -O-CH<sub>2</sub>-), 3.81 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 2.36 (s, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 188.0 (s), 162.5 (s), 152.0 (s), 152.0 (s), 143.8 (s), 141.0 (s), 132.6 (s), 131.4 (s), 131.4 (s), 131.4 (s), 131.2 (s), 130.0 (s), 130.0 (s), 130.0 (s), 129.3 (s), 129.3 (s), 129.3 (s), 121.4 (s), 115.0 (s), 115.0 (s), 67.1 (s), 27.2 (s), 21.6 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>NaS ([M+Na]<sup>+</sup>), 439.11945; found, 439.11992.

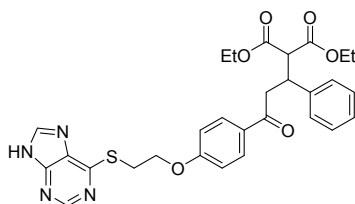


*(E)*-1-(4-(2-((9*H*-purin-6-yl)thio)ethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**4f**): Yellow solid, m.p. 157.7–158.6 °C, yield, 42%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.59 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.17 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.86 (d, *J* = 8.6 Hz, 3H, 3-CH=, 3-Ph-H), 7.69 (d, *J* = 15.5 Hz, 1H, 2-CH=), 7.18 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.02 (d, *J* = 8.8 Hz, 2H, 3-Ph-H), 4.42 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 3.80 (t, *J* = 6.7 Hz, 2H, -S-CH<sub>2</sub>-), 3.36 (s, 3H, -OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 187.7 (s), 162.4 (s), 162.4 (s), 161.7 (s), 161.7 (s), 152.0 (s), 152.0 (s), 143.7 (s), 131.3 (s), 131.3 (s), 131.2 (s), 131.2 (s), 131.2 (s), 127.9 (s), 127.9 (s), 127.9 (s), 119.9 (s), 115.0 (s), 114.8 (s), 114.8 (s), 67.1 (s), 55.8 (s), 27.1 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>NaS ([M+Na]<sup>+</sup>), 455.11414; found, 455.11483.

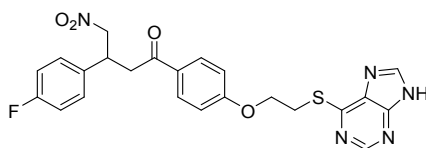


1-(4-(2-((9*H*-purin-6-yl)thio)ethoxy)phenyl)-4-nitro-3-phenylbutan-1-one (**5a**): White solid, m.p. 99.0–100.0 °C, yield, 20%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.46 (s, 1H, Pyrimidine-H), 7.92 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.36 (s, 2H, 3-Ph-H), 7.29 (t, *J* = 7.4 Hz, 2H, 3-Ph-H), 7.22 (t, *J* = 7.2 Hz, 1H, 3-Ph-H), 7.12 (d, *J* = 8.8 Hz, 2H, 1-Ph-H), 5.00–4.83 (m, 2H, -CH<sub>2</sub>-NO<sub>2</sub>), 4.38 (t, *J* = 6.5 Hz, 2H, -O-CH<sub>2</sub>-), 4.08–3.98 (m, 1H, -CH-), 3.77 (t, *J* = 6.4 Hz, 2H, -S-CH<sub>2</sub>-), 3.55–3.40 (m, 2H, -CO-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.2 (s), 162.6 (s), 158.3 (s), 152.0 (s), 152.0 (s), 149.8 (s), 143.6 (s), 140.6 (s), 140.6 (s), 130.8 (s), 130.8 (s), 130.1 (s), 128.9

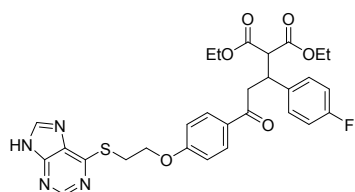
(s), 128.9 (s), 128.3 (s), 128.3 (s), 127.6 (s), 114.9 (s), 80.2 (s), 67.1 (s), 41.2 (s), 41.2 (s), 27.0 (s); HRMS (ESI): calcd for  $C_{23}H_{21}N_5O_4NaS$  ( $[M+Na]^+$ ), 486.11960; found, 455.12065.



*Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-oxo-1-phenylpropyl)malonate (5b)*: Off-white solid, m.p. 82.7–83.9 °C, yield, 43%;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ : 13.58 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.87 (d,  $J = 8.9$  Hz, 2H, 1-Ph-H), 7.29 (d,  $J = 7.2$  Hz, 2H, 3-Ph-H), 7.21 (t,  $J = 7.4$  Hz, 2H, 3-Ph-H), 7.17–7.08 (m, 3H, 3-Ph-H, 1-Ph-H), 4.38 (t,  $J = 6.6$  Hz, 2H, -O-CH<sub>2</sub>-), 4.19–4.08 (m, 2H, -CO-CH<sub>2</sub>-), 3.98–3.92 (m, 2H, -S-CH<sub>2</sub>-), 3.84–3.75 (m, 4H, 2 $\times$ -CH<sub>2</sub>-), 3.65–3.56 (m, 1H, -CH-), 3.31–3.24 (m, 1H, -CH-COO-), 1.16 (t,  $J = 7.1$  Hz, 3H, -CH<sub>3</sub>), 0.85 (t,  $J = 7.1$  Hz, 3H, -CH<sub>3</sub>);  $^{13}C$  NMR (100 MHz,  $DMSO-d_6$ )  $\delta$ : 196.4 (s), 168.4 (s), 168.4 (s), 167.8 (s), 162.4 (s), 162.4 (s), 152.0 (s), 152.0 (s), 141.0 (s), 141.0 (s), 130.7 (s), 130.7 (s), 130.2 (s), 128.9 (s), 128.9 (s), 128.4 (s), 128.4 (s), 127.2 (s), 114.9 (s), 114.9 (s), 67.1 (s), 61.7 (s), 61.1 (s), 57.4 (s), 42.4 (s), 41.3 (s), 39.8 (s), 14.3 (s), 14.0 (s); HRMS (ESI): calcd for  $C_{29}H_{30}N_4O_6NaS$  ( $[M+Na]^+$ ), 485.17719; found, 485.17783.



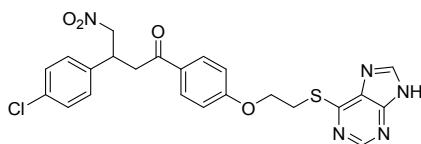
*1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)-4-nitrobutan-1-one (5c)*: White solid, m.p. 125.1–126.1 °C, yield, 22%;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ : 13.59 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.93 (d,  $J = 8.8$  Hz, 2H, 1-Ph-H), 7.43 (dd,  $J = 8.5, 5.6$  Hz, 2H, 3-Ph-H), 7.13 (dt,  $J = 8.7, 4.3$  Hz, 4H, 3-Ph-H, 1-Ph-H), 5.01–4.82 (m, 2H, -CH<sub>2</sub>-NO<sub>2</sub>), 4.39 (t,  $J = 6.4$  Hz, 2H, -O-CH<sub>2</sub>-), 4.08–4.01 (m, 6.8 Hz, 1H, -CH-), 3.77 (t,  $J = 6.3$  Hz, 2H, -S-CH<sub>2</sub>-), 3.55–3.41 (m, 2H, -CO-CH<sub>2</sub>-);  $^{19}F$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$ : -115.51 (s);  $^{13}C$  NMR (100 MHz,  $DMSO-d_6$ )  $\delta$ : 196.1 (s), 162.9 (s), 162.6 (s), 160.5 (s), 158.3 (s), 152.0 (s), 149.8 (s), 143.6 (s), 136.7 (s), 130.8 (s), 130.7 (s), 130.3 (s), 130.2 (s), 130.0 (s), 115.8 (s), 115.6 (s), 114.9 (s), 114.9 (s), 80.2 (s), 67.1 (s), 41.2 (s), 39.1 (s), 27.0 (s); HRMS (ESI): calcd for  $C_{23}H_{20}FN_5O_4NaS$  ( $[M+Na]^+$ ), 504.11060; found, 504.11122.



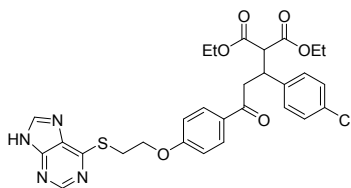
*Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-fluorophenyl)-3-oxo-1-phenylpropyl)malonate (5d)*:



Yellow solid, m.p. 110.0–112.0 °C, yield, 27%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.58 (s, 1H, -NH-), 8.73 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.86 (d, *J* = 8.3 Hz, 2H, 1-Ph-H), 7.39–7.28 (m, 2H, 3-Ph-H), 7.14–6.98 (m, 4H, 3-Ph-H, 1-Ph-H), 4.36 (d, *J* = 5.8 Hz, 2H, -O-CH<sub>2</sub>-), 4.21–4.07 (m, 2H, -CO-CH<sub>2</sub>-), 3.96 (s, 2H, -S-CH<sub>2</sub>-), 3.88–3.72 (m, 4H, 2×-CH<sub>2</sub>-), 3.59 (dd, *J* = 16.4, 7.8 Hz, 1H, -CH-Ph), 3.28 (d, *J* = 16.2 Hz, 1H, -COO-CH-), 1.15 (t, *J* = 6.9 Hz, 3H, -CH<sub>3</sub>), 0.86 (t, *J* = 6.9 Hz, 3H, -CH<sub>3</sub>); <sup>19</sup>F NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: -116.00 (s); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.4 (s), 168.3 (s), 167.8 (s), 167.8 (s), 162.5 (s), 162.5 (s), 160.3 (s), 152.0 (s), 152.0 (s), 137.2 (s), 137.2 (s), 131.9 (s), 130.8 (s), 130.7 (s), 130.1 (s), 130.1 (s), 130.1 (s), 115.2 (s), 115.0 (s), 114.1 (s), 67.1 (s), 61.8 (s), 61.2 (s), 57.3 (s), 42.4 (s), 40.6 (s), 27.1 (s), 14.3 (s), 14.0 (s); HRMS (ESI): calcd for C<sub>29</sub>H<sub>29</sub>FN<sub>4</sub>O<sub>6</sub>NaS ([M+Na]<sup>+</sup>), 603.16772; found, 603.16840.

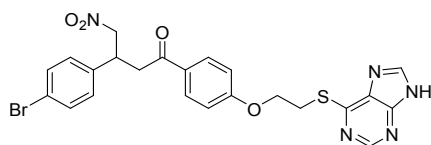


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-chlorophenyl)-4-nitrobutan-1-one (**5e**): White solid, m.p. 106.3–107.3 °C, yield, 35%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.58 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 2H, Pyrimidine-H), 7.92 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.41 (d, *J* = 8.6 Hz, 2H, 3-Ph-H), 7.36 (d, *J* = 8.6 Hz, 2H, 3-Ph-H), 7.12 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 5.01–4.83 (m, 2H, -CH<sub>2</sub>-NO<sub>2</sub>), 4.38 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.06–4.00 (m, 1H, -CH-), 3.77 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 3.55–3.41 (m, 2H, -CO-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.0 (s), 162.6 (s), 162.6 (s), 152.0 (s), 152.0 (s), 152.0 (s), 139.6 (s), 139.6 (s), 132.3 (s), 130.8 (s), 130.8 (s), 130.3 (s), 130.3 (s), 130.3 (s), 123.0 (s), 128.9 (s), 128.9 (s), 114.9 (s), 80.0 (s), 67.1 (s), 41.0 (s), 39.3 (s), 39.2 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>20</sub>ClN<sub>5</sub>O<sub>4</sub>NaS ([M+Na]<sup>+</sup>), 564.03070; found, 564.03116.

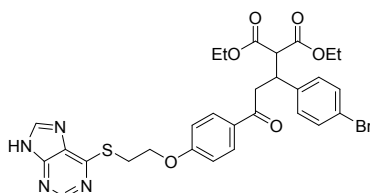


Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-chlorophenyl)-3-oxo-1-phenylpropyl)malonate (**5f**): Yellow solid, m.p. 57.3–58.3 °C, yield, 40%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.86 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.32 (d, *J* = 8.6 Hz, 2H, 3-Ph-H), 7.27 (d, *J* = 8.6 Hz, 2H, 3-Ph-H), 7.10 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.37 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.20–4.08 (m, 2H, -CO-CH<sub>2</sub>-), 3.99–3.82 (m, 4H, 2×-CH<sub>2</sub>-), 3.76 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 3.59 (d, *J* = 16.9, 9.6 Hz, 1H, -CH-Ph), 3.31–3.28 (m, 1H, -COO-CH-), 1.16 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>), 0.88 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.3 (s), 168.2 (s), 167.7 (s), 167.7 (s), 162.5 (s), 8

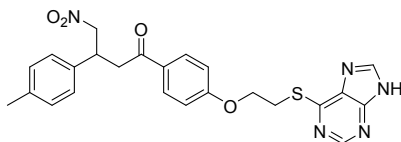
162.5 (s), 152.0 (s), 152.0 (s), 152.0 (s), 140.1 (s), 131.8 (s), 131.8 (s), 130.8 (s), 130.8 (s), 130.7 (s), 130.7 (s), 130.1 (s), 128.4 (s), 128.4 (s), 114.9 (s), 114.9 (s), 67.1 (s), 61.8 (s), 61.3 (s), 57.1 (s), 42.2 (s), 40.6 (s), 27.1 (s), 14.3 (s), 14.00 (s); HRMS (ESI): calcd for C<sub>29</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>6</sub>NaS ([M+Na]<sup>+</sup>), 619.13800; found, 619.13885.



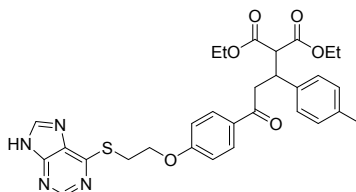
**1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-bromophenyl)-4-nitrobutan-1-one (5g):** White solid, m.p. 60.0–61.5 °C, yield, 21%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.92 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.28 (d, *J* = 8.7 Hz, 2H, 3-Ph-H), 7.12 (d, *J* = 8.9 Hz, 2H, 3-Ph-H), 6.84 (d, *J* = 8.7 Hz, 2H, 1-Ph-H), 4.98–4.76 (m, 2H, -CH<sub>2</sub>-NO<sub>2</sub>), 4.39 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.07–3.93 (m, 1H, -CH-Ph), 3.77 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 3.51–3.39 (m, 2H, -CO-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.3 (s), 162.6 (s), 158.8 (s), 158.8 (s), 152.0 (s), 152.0 (s), 152.0 (s), 132.3 (s), 132.3 (s), 130.8 (s), 130.8 (s), 130.1 (s), 129.3 (s), 129.3 (s), 114.9 (s), 114.9 (s), 114.3 (s), 114.3 (s), 80.4 (s), 67.1 (s), 55.4 (s), 41.3 (s), 39.2 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>20</sub>BrN<sub>5</sub>O<sub>4</sub>NaS ([M+Na]<sup>+</sup>), 564.03070; found, 564.03116.



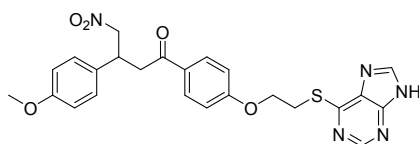
**Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-bromophenyl)-3-oxo-1-phenylpropyl)malonate (5h):** Yellow solid, m.p. 54.5–55.5 °C, yield, 27%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.86 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.40 (t, *J* = 7.6 Hz, 2H, 3-Ph-H), 7.26 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.10 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 4.38 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.18–4.09 (m, 2H, -CO-CH<sub>2</sub>-), 3.98–3.95 (m, 1H, -CH<sub>2</sub>-), 3.85 (q, *J* = 7.0 Hz, 3H, -CH<sub>2</sub>-), 3.77 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 3.62–3.55 (m, 1H, -CH-Ph), 3.31–3.26 (m, 1H, -COO-CH-), 1.16 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>), 0.89 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.3 (s), 168.2 (s), 167.8 (s), 167.8 (s), 152.0 (s), 140.6 (s), 131.3 (s), 131.3 (s), 131.3 (s), 131.2 (s), 131.2 (s), 131.2 (s), 130.7 (s), 130.7 (s), 130.7 (s), 130.1 (s), 120.4 (s), 114.9 (s), 114.9 (s), 114.9 (s), 67.1 (s), 61.8 (s), 61.3 (s), 57.0 (s), 42.2 (s), 40.7 (s), 27.1 (s), 14.3 (s), 14.0 (s); HRMS (ESI): calcd for C<sub>29</sub>H<sub>29</sub>BrN<sub>4</sub>O<sub>6</sub>NaS ([M+Na]<sup>+</sup>), 663.08722; found, 663.08834.



1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-4-nitro-3-(p-tolyl)butan-1-one (**5i**): Yellow solid, m.p. 85.2–86.1 °C, yield, 23%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.58 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.46 (s, 1H, Pyrimidine-H), 7.91 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.24 (d, *J* = 8.1 Hz, 2H, 3-Ph-H), 7.09 (dd, *J* = 10.4, 8.5 Hz, 4H, 3-Ph-H, 1-Ph-H), 4.98–4.79 (m, 2H, -CH<sub>2</sub>-NO<sub>2</sub>), 4.38 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.05–3.95 (m, 1H, -CH-), 3.76 (t, *J* = 6.6 Hz, 2H, -S-CH<sub>2</sub>-), 3.51–3.36 (m, 2H, -CO-CH<sub>2</sub>-), 2.22 (s, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.2 (s), 162.6 (s), 158.3 (s), 152.0 (s), 149.8 (s), 143.6 (s), 137.4 (s), 136.8 (s), 130.8 (s), 130.8 (s), 130.1 (s), 129.5 (s), 129.5 (s), 129.5 (s), 128.1 (s), 128.1 (s), 114.9 (s), 114.9 (s), 80.3 (s), 67.1 (s), 60.2 (s), 41.2 (s), 27.1 (s), 21.0 (s); HRMS (ESI): calcd for C<sub>24</sub>H<sub>23</sub>N<sub>5</sub>O<sub>4</sub>NaS ([M+Na]<sup>+</sup>), 500.13559; found, 500.13630.

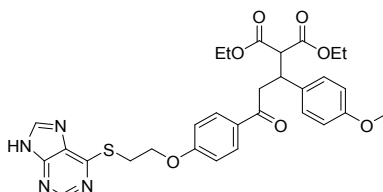


Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-oxo-1-(p-tolyl)propyl)malonate (**5j**): White solid, m.p. 66.5–67.6 °C, yield, 36%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.62 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H), 8.50 (s, 1H, Pyrimidine-H), 7.90 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.19 (d, *J* = 8.0 Hz, 2H, 3-Ph-H), 7.12 (d, *J* = 8.9 Hz, 2H, 3-Ph-H), 7.03 (d, *J* = 7.9 Hz, 2H, 1-Ph-H), 4.40 (t, *J* = 6.6 Hz, 2H, -O-CH<sub>2</sub>-), 4.17 (dd, *J* = 8.8, 7.1 Hz, 2H, -CO-CH<sub>2</sub>-), 3.95 (d, *J* = 3.2 Hz, 2H, -S-CH<sub>2</sub>-), 3.90–3.16 (m, 4H, 2×-CH<sub>2</sub>-), 3.62–3.56 (m, 1H, -CH-), 3.31–3.27 (m, 1H, -CH-COO-), 2.21 (s, 3H, Ph-CH<sub>3</sub>), 1.18 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>), 0.90 (t, *J* = 7.1 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 196.4 (s), 168.4 (s), 168.4 (s), 167.8 (s), 167.8 (s), 162.4 (s), 162.4 (s), 152.0 (s), 152.0 (s), 138.0 (s), 136.2 (s), 130.7 (s), 130.7 (s), 130.2 (s), 129.0 (s), 129.0 (s), 128.7 (s), 128.7 (s), 114.8 (s), 114.8 (s), 67.1 (s), 61.7 (s), 61.1 (s), 57.5 (s), 42.4 (s), 40.8 (s), 27.1 (s), 21.1 (s), 14.3 (s), 14.0 (s); HRMS (ESI): calcd for C<sub>30</sub>H<sub>32</sub>N<sub>4</sub>O<sub>6</sub>NaS ([M+Na]<sup>+</sup>), 599.19287; found, 599.19348.

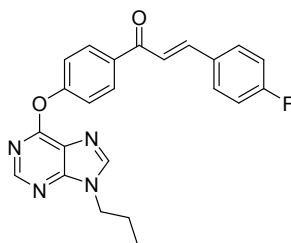


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-methoxyphenyl)-4-nitrobutan-1-one (**5k**): White solid, m.p. 71.5–72.5 °C, yield, 28%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 13.57 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.4

7 (s, 1H, Pyrimidine-H), 7.92 (d,  $J = 8.9$  Hz, 2H, 1-Ph-H), 7.28 (d,  $J = 8.7$  Hz, 2H, 3-Ph-H), 7.12 (d,  $J = 8.9$  Hz, 2H, 3-Ph-H), 6.84 (d,  $J = 8.7$  Hz, 2H, 1-Ph-H), 4.96–4.77 (m, 2H,  $-\text{CH}_2-\text{NO}_2$ ), 4.38 (t,  $J = 6.6$  Hz, 2H,  $-\text{O}-\text{CH}_2-$ ), 4.04–4.92 (m, 1H,  $-\text{CH}-$ ), 3.77 (t,  $J = 6.6$  Hz, 2H,  $-\text{S}-\text{CH}_2-$ ), 3.70 (s, 3H,  $-\text{CH}_3$ ), 3.50–3.39 (m, 2H,  $-\text{CO}-\text{CH}_2-$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 196.3 (s), 162.6 (s), 162.6 (s), 158.8 (s), 158.8 (s), 152.0 (s), 152.0 (s), 132.3 (s), 132.3 (s), 130.8 (s), 130.8 (s), 130.8 (s), 130.1 (s), 129.3 (s), 129.3 (s), 129.3 (s), 114.9 (s), 114.3 (s), 114.3 (s), 80.4 (s), 67.1 (s), 55.4 (s), 41.3 (s), 39.2 (s); HRMS (ESI): calcd for  $\text{C}_{24}\text{H}_{23}\text{N}_5\text{O}_5\text{NaS}$  ( $[\text{M}+\text{Na}]^+$ ), 516.13080; found, 516.13121.

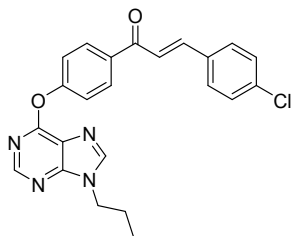


*Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-methoxyphenyl)-3-oxopropyl)malonate (5I)*: Yellow solid, m.p. 64.5–65.6 °C, yield, 38%;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 13.58 (s, 1H,  $-\text{NH}-$ ), 8.75 (s, 1H, imidazole-H), 8.48 (s, 1H, Pyrimidine-H), 7.87(d,  $J = 8.9\text{Hz}$ , 2H, 1-Ph-H), 7.19 (d,  $J = 8.7$  Hz, 2H, 3-Ph-H), 7.10 (d,  $J = 8.9$  Hz, 2H, 1-Ph-H), 6.77 (d,  $J = 8.7$  Hz, 2H, 3-Ph-H), 4.38 (t,  $J = 6.6$  Hz, 2H,  $-\text{O}-\text{CH}_2-$ ), 4.14 (t,  $J = 7.1$  Hz, 2H,  $-\text{CO}-\text{CH}_2-$ ), 3.93–3.80 (m, 4H,  $2\times-\text{CH}_2-$ ), 3.77 (t,  $J = 6.6$  Hz, 2H,  $-\text{S}-\text{CH}_2-$ ), 3.67 (s, 3H,  $-\text{OCH}_3$ ), 3.58–3.52 (m, 1H,  $-\text{CH}-\text{Ph}$ ), 3.26–3.19 (m, 1H,  $-\text{COO}-\text{CH}-$ ), 1.16 (t,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ ), 0.88 (t,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$ : 196.5 (s), 168.4 (s), 167.8 (s), 162.4 (s), 162.4 (s), 158.4 (s), 158.4 (s), 152.0 (s), 152.0 (s), 132.8 (s), 130.7 (s), 130.7 (s), 130.7 (s), 130.2 (s), 129.9 (s), 129.9 (s), 129.9 (s), 114.9 (s), 113.8 (s), 113.8 (s), 67.1 (s), 61.7 (s), 61.1 (s), 57.6 (s), 55.4 (s), 55.4 (s), 42.5 (s), 27.1 (s), 14.3 (s), 14.1 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{32}\text{N}_4\text{O}_7\text{NaS}$  ( $[\text{M}+\text{Na}]^+$ ), 615.18744; found, 615.18839.

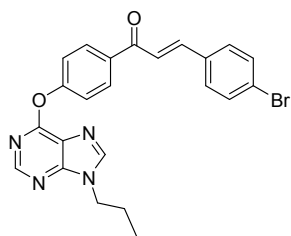


*(E)-3-(4-fluorophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (7a)*: White solid, m.p. 117.3–118.5 °C, yield 49%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.54 (s, 1H, Imidazole-H), 8.17–8.13 (m, 2H, 1-Ph-H), 8.07 (s, 1H, Pyrimidine-H), 7.80 (d,  $J = 15.7$  Hz, 1H, 3-CH=), 7.64 (d,  $J = 2.9$  Hz, 2H, 3-Ph-H), 7.51 (s, 1H, 2-CH=), 7.44 (d,  $J = 8.6$  Hz, 2H, 3-Ph-H), 7.11 (dd,  $J = 10.7, 6.0$  Hz, 2H, 1-Ph-H), 4.27 (dd,  $J = 9.2, 4.9$  Hz, 2H, 9- $\text{CH}_2-$ ), 2.01–1.95 (m,

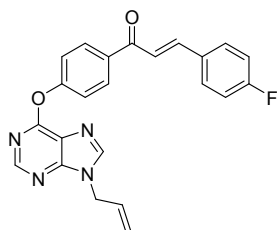
2H, 9-CH<sub>2</sub>-), 1.02–0.97 (m, 3H, -CH<sub>3</sub>); <sup>19</sup>F NMR (400 MHz, CDCl<sub>3</sub>) δ: -108.93 (s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 188.9 (s), 165.3 (s), 162.8 (s), 159.6 (s), 156.2 (s), 153.5 (s), 151.8 (s), 143.5 (s), 135.5 (s), 131.1 (s), 131.1 (s), 130.4 (s), 130.3 (s), 122.0 (s), 122.0 (s), 121.7 (s), 121.5 (s), 121.5 (s), 116.3 (s), 116.0 (s), 46.0 (s), 23.4 (s), 11.2 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>19</sub>FN<sub>4</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>), 425.13773; found, 425.13843.



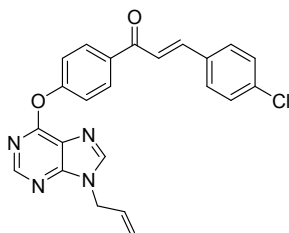
*(E)*-3-(4-chlorophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (**7b**): White solid, m.p. 140.5–141.4 °C, yield 47%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.59 (s, 1H, Imidazole-H), 8.51 (s, 1H, Pyrimidine-H), 8.31 (d, *J* = 8.8 Hz, 2H, 1-Ph-H), 8.05 (d, *J* = 15.6 Hz, 1H, 3-CH=), 7.97 (d, *J* = 8.5 Hz, 2H, 3-Ph-H), 7.78 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.58–7.49 (m, 4H, 3-Ph-H, 1-Ph-H), 4.27 (t, *J* = 7.0 Hz, 2H, -CH<sub>2</sub>-), 1.94–1.85 (m, 2H, -CH<sub>2</sub>-), 0.88 (t, *J* = 7.4 Hz, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 188.4 (s), 159.2 (s), 156.8 (s), 154.0 (s), 151.6 (s), 145.8 (s), 143.0 (s), 135.6 (s), 135.2 (s), 134.1 (s), 131.1 (s), 131.1 (s), 131.0 (s), 131.0 (s), 129.4 (s), 129.4 (s), 123.2 (s), 122.5 (s), 122.5 (s), 121.4 (s), 45.6 (s), 23.1 (s), 11.4 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>), 441.10837; found, 441.10887.



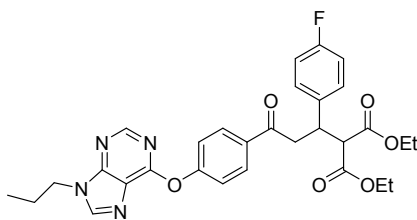
*(E)*-3-(4-bromophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (**7c**): Yellow solid, m.p. 140.0–140.9 °C, yield 47%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 8.47 (s, 1H, Imidazole-H), 8.07 (d, *J* = 8.7 Hz, 2H, 1-Ph-H), 7.99 (s, 1H, Pyrimidine-H), 7.70 (d, *J* = 15.7 Hz, 1H, 3-CH=C-), 7.47 (dd, *J* = 13.2, 2.3 Hz, 5H, 2-CH=C-, 3-Ph-H), 7.37 (d, *J* = 8.7 Hz, 2H, 1-Ph-H), 4.21 (t, *J* = 7.2 Hz, 2H, 9-CH<sub>2</sub>-), 1.95–1.90 (m, 2H, 9-CH<sub>2</sub>-), 0.94 (s, 3H, -CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 188.9 (s), 159.6 (s), 156.2 (s), 153.5 (s), 151.8 (s), 143.5 (s), 143.5 (s), 135.4 (s), 133.8 (s), 132.3 (s), 132.3 (s), 130.4 (s), 130.4 (s), 129.8 (s), 129.8 (s), 124.9 (s), 122.3 (s), 122.0 (s), 122.0 (s), 121.7 (s), 46.0 (s), 23.4 (s), 11.2 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>), 485.05771; found, 485.05836.



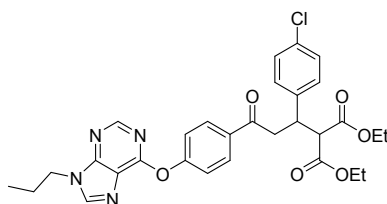
*(E)*-1-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (**7d**): Yellow solid, m.p. 128.9–129.9 °C, yield 58%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.57 (s, 1H, Imidazole-H), 8.52 (s, 1H, Pyrimidine-H), 8.30 (d, *J* = 8.8 Hz, 2H, 1-Ph-H), 8.04–7.97 (m, 3H, 3-CH=, 3-Ph-H), 7.80 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.55–7.51 (m, 2H, 3-Ph-H), 7.33 (t, *J* = 8.9 Hz, 2H, 1-Ph-H), 6.13 (dd, *J* = 17.1, 10.3 Hz, 1H, 9-CH=C-), 5.25 (dd, *J* = 10.3, 1.3 Hz, 1H, 9-C=CH<sub>2</sub>), 5.11 (dd, *J* = 17.1, 1.3 Hz, 1H, 9-C=CH<sub>2</sub>), 4.97 (dd, *J* = 4.1, 1.4 Hz, 2H, 9-CH<sub>2</sub>-); <sup>19</sup>F NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: -109.55 (tt, *J* = 8.9, 5.6 Hz); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 188.4 (s), 165.2 (s), 162.7 (s), 159.3 (s), 156.7 (s), 153.8 (s), 151.8 (s), 145.6 (s), 143.3 (s), 135.3 (s), 133.4 (s), 131.8 (d, *J* = 3.7 Hz), 131.7 (s), 131.0 (s), 122.5 (s), 122.3 (s), 122.3 (s), 121.3 (s), 118.4 (s), 118.4 (s), 116.5 (s), 116.3 (s), 46.0 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>17</sub>FN<sub>4</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>), 423.12216; found, 423.12278.



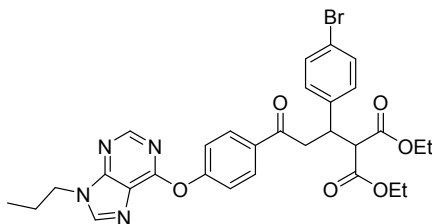
*(E)*-1-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**7e**): Yellow solid, m.p. 80.6–81.7 °C, yield 46%; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ: 8.56 (s, 1H, Imidazole-H), 8.52 (s, 1H, Pyrimidine-H), 8.30 (d, *J* = 8.8 Hz, 2H, 1-Ph-H), 8.04 (d, *J* = 15.6 Hz, 1H, 3-CH=), 7.97 (dd, *J* = 8.9, 2.0 Hz, 2H, 3-Ph-H), 7.78 (d, *J* = 15.6 Hz, 1H, 2-CH=), 7.57–7.53 (m, 2H, 3-Ph-H), 7.53–7.51 (m, 2H, 1-Ph-H), 6.17–6.08 (m, 1H, 9-CH=), 5.25 (dd, *J* = 10.3, 1.3 Hz, 1H, 9-C=CH<sub>2</sub>), 5.10 (dd, *J* = 17.1, 1.3 Hz, 1H, 9-C=CH<sub>2</sub>), 4.96 (d, *J* = 5.5 Hz, 2H, 9-CH<sub>2</sub>-); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ: 188.4 (s), 159.3 (s), 156.8 (s), 153.8 (s), 151.8 (s), 145.7 (s), 143.0 (s), 135.6 (s), 135.2 (s), 134.2 (s), 133.4 (s), 131.1 (s), 131.1 (s), 131.0 (s), 131.0 (s), 129.4 (s), 129.4 (s), 123.2 (s), 122.5 (s), 121.3 (s), 118.4 (s), 118.4 (s), 46.0 (s); HRMS (ESI): calcd for C<sub>23</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub>Na ([M+Na]<sup>+</sup>), 439.09277; found, 439.09322.



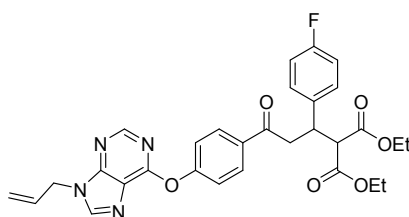
*Diethyl 2-(1-(4-fluorophenyl)-3-oxo-3-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)propyl)malonate (8a)*: White solid, m.p. 92.0–93.7 °C, yield 36%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.44 (s, 1H, Imidazole-H), 7.97 (d,  $J = 4.6$  Hz, 2H, 1-Ph-H), 7.94 (s, 1H, Pyrimidine-H), 7.29 (d,  $J = 8.7$  Hz, 2H, 3-Ph-H), 7.20 (q,  $J = 3.5$  Hz, 2H, 3-Ph-H), 6.88 (t,  $J = 8.7$  Hz, 2H, 1-Ph-H), 4.19 (dd,  $J = 12.4, 5.3$  Hz, 1H, Ph-H), 4.16–4.09 (m, 4H, 2 $\times$ -CH $_2$ -), 3.91 (q,  $J = 7.1$  Hz, 2H, 9-CH $_2$ -), 3.72 (d,  $J = 9.7$  Hz, 1H, -CH-COO-), 3.49–3.35 (m, 2H, -CH $_2$ -CO-), 1.94–1.88 (m, 2H, 9-CH $_2$ -), 1.19 (s, 3H, -CH $_3$ ), 1.00–0.93 (m, 6H, 2 $\times$ -CH $_3$ );  $^{19}\text{F}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : -115.39 (s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 196.0 (s), 168.2 (s), 167.7 (s), 163.0 (s), 160.6 (s), 159.5 (s), 156.3 (s), 153.5 (s), 151.8 (s), 143.5 (s), 136.1 (s), 134.1 (s), 130.0 (s), 129.9 (s), 129.9 (s), 122.0 (s), 122.0 (s), 121.7 (s), 115.4 (s), 115.2 (s), 61.8 (s), 61.5 (s), 57.5 (s), 46.0 (s), 42.6 (s), 40.0 (s), 23.4 (s), 14.1 (s), 13.8 (s), 11.2 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{31}\text{FN}_4\text{O}_6\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 585.21155; found, 585.21198.



*Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)propyl)malonate (8b)*: White solid, m.p. 112.2–113.4 °C, yield 38%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.53 (s, 1H, Imidazole-H), 8.06 (s, 1H, Pyrimidine-H), 8.04 (d,  $J = 8.1$  Hz, 2H, 1-Ph-H), 7.38 (d,  $J = 7.9$  Hz, 2H, 1-Ph-H), 7.25 (s, 4H, 3-Ph-H), 4.29 (t,  $J = 6.9$  Hz, 2H, 9-CH $_2$ -), 4.25–4.15 (m, 3H, -CH-Ph, -CH $_2$ -), 4.01 (dd,  $J = 13.6, 6.7$  Hz, 2H, -CH $_2$ -), 3.81 (d,  $J = 9.4$  Hz, 1H, -CH-COO-), 3.59–3.44 (m, 2H, -CH $_2$ -CO-), 2.00 (dd,  $J = 14.1, 7.0$  Hz, 2H, 9-CH $_2$ -), 1.27 (t,  $J = 6.7$  Hz, 3H, -CH $_3$ ), 1.08 (t,  $J = 6.8$  Hz, 3H, -CH $_3$ ), 1.01 (t,  $J = 7.0$  Hz, 3H, -CH $_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.9 (s), 168.2 (s), 167.6 (s), 159.5 (s), 156.4 (s), 153.5 (s), 151.8 (s), 143.5 (s), 139.0 (s), 134.0 (s), 132.9 (s), 130.0 (s), 130.0 (s), 129.7 (s), 129.7 (s), 128.6 (s), 128.6 (s), 121.9 (s), 121.9 (s), 121.7 (s), 61.8 (s), 61.5 (s), 57.3 (s), 46.0 (s), 42.3 (s), 40.1 (s), 23.4 (s), 14.1 (s), 13.8 (s), 11.2 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{31}\text{ClN}_4\text{O}_6\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 601.18182; found, 601.18243.

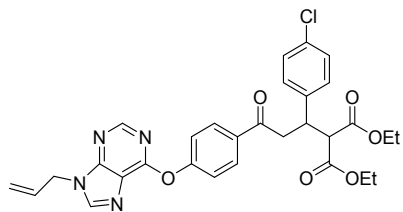


*Diethyl 2-(1-(4-bromophenyl)-3-oxo-3-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)propyl)malonate (8c)*: White solid, m.p. 128.2–129.6 °C, yield 57%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.44 (s, 1H, Imidazole-H), 7.98 (s, 1H, Pyrimidine-H), 7.95 (d,  $J = 8.7$  Hz, 2H, 1-Ph-H), 7.30 (dd,  $J = 10.8, 8.6$  Hz, 4H, 3-Ph-H), 7.11 (d,  $J = 8.4$  Hz, 2H, 1-Ph-H), 4.20 (t,  $J = 7.2$  Hz, 2H,  $-\text{CH}_2-$ ), 4.17–4.07 (m, 3H,  $-\text{CH}_2-$ , Ph-CH-), 3.92 (q,  $J = 7.1$  Hz, 2H, 9- $\text{CH}_2-$ ), 3.71 (s, 1H,  $-\text{CH}-\text{COO}-$ ), 3.50–3.36 (m, 2H,  $-\text{CH}_2-\text{CO}-$ ), 1.96–1.87 (m, 2H, 9- $\text{CH}_2-$ ), 1.18 (d,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ ), 0.99 (t,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ ), 0.93 (t,  $J = 7.4$  Hz, 3H,  $-\text{CH}_3$ );  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.9 (s), 168.1 (s), 167.6 (s), 159.5 (s), 156.4 (s), 153.5 (s), 151.8 (s), 143.5 (s), 139.6 (s), 134.0 (s), 131.5 (s), 131.5 (s), 130.1 (s), 130.1 (s), 130.0 (s), 130.0 (s), 121.9 (s), 121.9 (s), 121.7 (s), 121.1 (s), 61.8 (s), 61.6 (s), 57.3 (s), 46.0 (s), 42.2 (s), 40.1 (s), 23.4 (s), 14.1 (s), 13.8 (s), 11.2 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{31}\text{BrN}_4\text{O}_6\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 645.13135; found, 645.13192.



*Diethyl 2-(3-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-1-(4-fluorophenyl)-3-oxopropyl)malonate (8d)*: White solid, m.p. 125.8.2–126.3 °C, yield 46%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.45 (s, 1H, Imidazole-H), 7.99 (s, 1H, Pyrimidine-H), 7.95 (d,  $J = 8.7$  Hz, 2H, 1-Ph-H), 7.29 (d,  $J = 8.6$  Hz, 2H, 3-Ph-H), 7.19 (dd,  $J = 8.5, 5.3$  Hz, 2H, 3-Ph-H), 6.87 (t,  $J = 8.6$  Hz, 2H, 1-Ph-H), 6.06–5.96 (m, 1H, 9- $\text{CH}=\text{C}-$ ), 5.30 (d,  $J = 10.2$  Hz, 1H, 9- $\text{C}=\text{CH}_2$ ), 5.19 (d,  $J = 17.0$  Hz, 1H, 9- $\text{C}=\text{CH}_2$ ), 4.85 (d,  $J = 5.7$  Hz, 2H, 9- $\text{CH}_2-$ ), 4.14 (dt,  $J = 9.8, 4.3$  Hz, 3H,  $-\text{CH}-\text{Ph}$ ,  $-\text{CH}_2-$ ), 3.91 (q,  $J = 7.1$  Hz, 2H,  $-\text{CH}_2-$ ), 3.72 (d,  $J = 9.6$  Hz, 1H,  $-\text{CH}-\text{COO}-$ ), 3.48–3.35 (m, 2H,  $-\text{CH}_2-\text{CO}-$ ), 1.18 (t,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ ), 0.97 (t,  $J = 7.1$  Hz, 3H,  $-\text{CH}_3$ );  $^{19}\text{F}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : -115.41 (s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 196.0 (s), 168.2 (s), 167.7 (s), 163.1 (s), 160.6 (s), 159.6 (s), 156.3 (s), 153.3 (s), 152.0 (s), 143.3 (s), 136.1 (d,  $J = 3.3$  Hz), 134.1 (s), 131.3 (s), 130.0 (s), 130.0 (s), 130.0 (s), 121.9 (s), 121.6 (s), 119.6 (s), 119.6 (s), 115.4 (s), 115.2 (s), 61.8 (s), 61.5 (s), 57.5 (s), 46.2 (s), 42.6 (s), 40.0 (s), 14.1 (s), 13.8 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{29}\text{FN}_4\text{O}_6\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 583.19558; found, 583.19633.





Diethyl 2-(3-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-1-(4-chlorophenyl)-3-oxopropyl)malonate (**8e**): White solid, m.p. 78.3–80.3 °C, yield 48%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.45 (s, 1H, Imidazole-H), 8.00 (s, 1H, Pyrimidine-H), 7.95 (d,  $J = 8.7$  Hz, 2H, 1-Ph-H), 7.29 (d,  $J = 8.7$  Hz, 2H, 3-Ph-H), 7.17 (s, 4H, 3-Ph-H, 1-Ph-H), 6.01 (ddt,  $J = 16.0, 10.3, 5.7$  Hz, 1H, 9-CH=), 5.30 (d,  $J = 10.2$  Hz, 1H, 9-C=CH<sub>2</sub>), 5.19 (d,  $J = 17.0$  Hz, 1H, 9-C=CH<sub>2</sub>), 4.85 (d,  $J = 5.7$  Hz, 2H, 9-CH<sub>2</sub>-), 4.19–4.07 (m, 3H, -CH-Ph, -CH<sub>2</sub>-), 3.92 (q,  $J = 7.1$  Hz, 2H, -CH<sub>2</sub>-), 3.72 (d,  $J = 9.6$  Hz, 1H, -CH-COO-), 3.50–3.36 (m, 2H, -CO-CH<sub>2</sub>-), 1.19 (t,  $J = 7.1$  Hz, 3H, -CH<sub>3</sub>), 0.99 (t,  $J = 7.1$  Hz, 3H, -CH<sub>3</sub>);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 195.9 (s), 168.2 (s), 167.6 (s), 159.5 (s), 156.3 (s), 153.3 (s), 152.1 (s), 143.4 (s), 139.0 (s), 134.0 (s), 132.9 (s), 131.3 (s), 130.0 (s), 130.0 (s), 129.7 (s), 129.7 (s), 128.6 (s), 128.6 (s), 122.0 (s), 122.0 (s), 119.6 (s), 119.6 (s), 61.8 (s), 61.6 (s), 57.3 (s), 46.2 (s), 42.3 (s), 40.1 (s), 14.1 (s), 13.8 (s); HRMS (ESI): calcd for  $\text{C}_{30}\text{H}_{29}\text{ClN}_4\text{O}_6\text{Na}$  ( $[\text{M}+\text{Na}]^+$ ), 599.16602; found, 599.16678.

## 8. $^1\text{H}$ NMR, $^{13}\text{C}$ NMR, $^{19}\text{F}$ NMR and HRMS data of the compounds

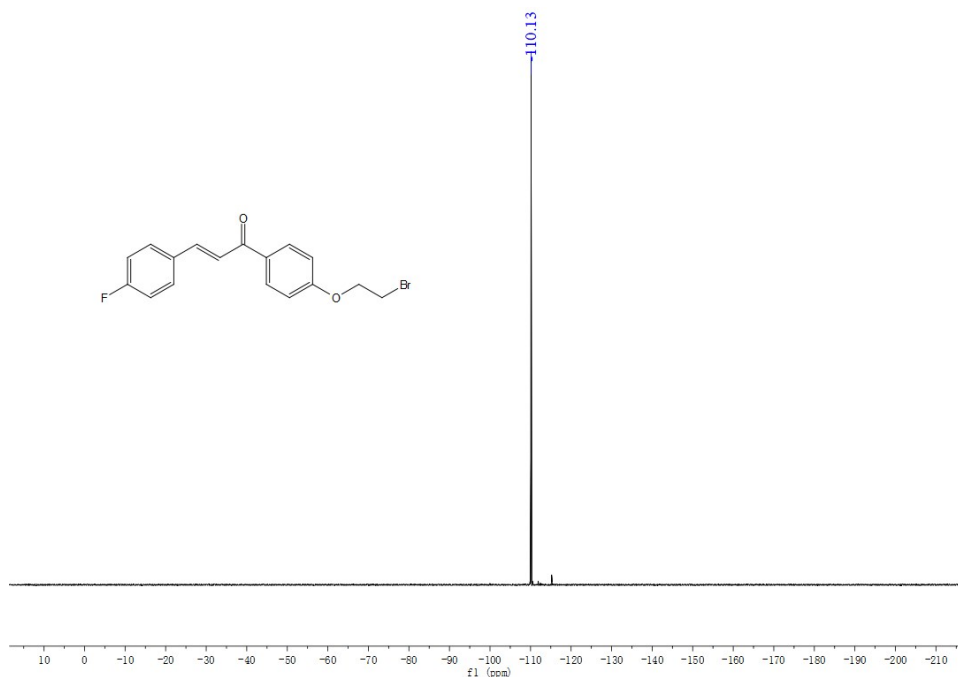


Figure S1.  $^{19}\text{F}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz) spectrum of intermediate **2b**

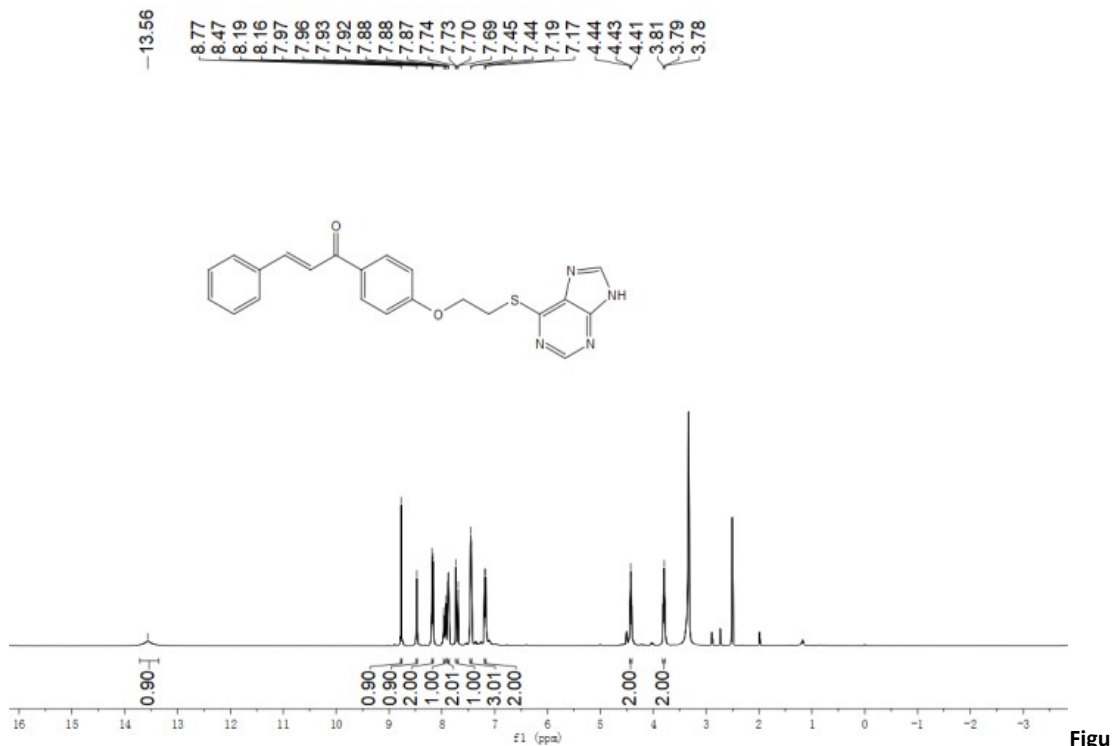


Figure S2.

re S2. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 4a

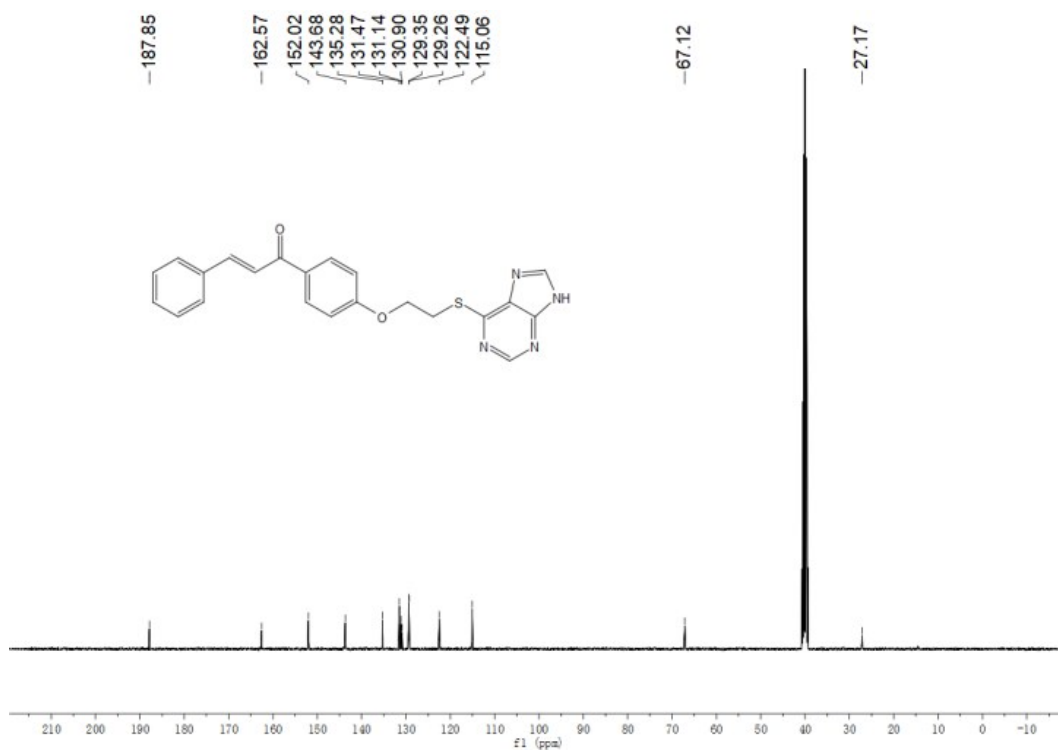
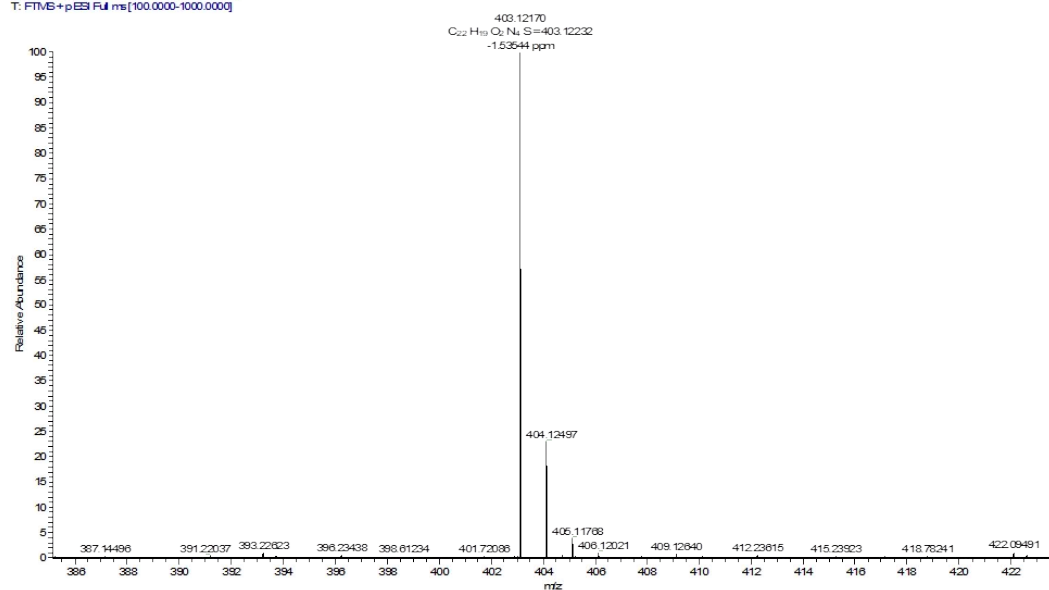


Figure S3. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 4a



Fig

re S4. HRMS of compound 4a

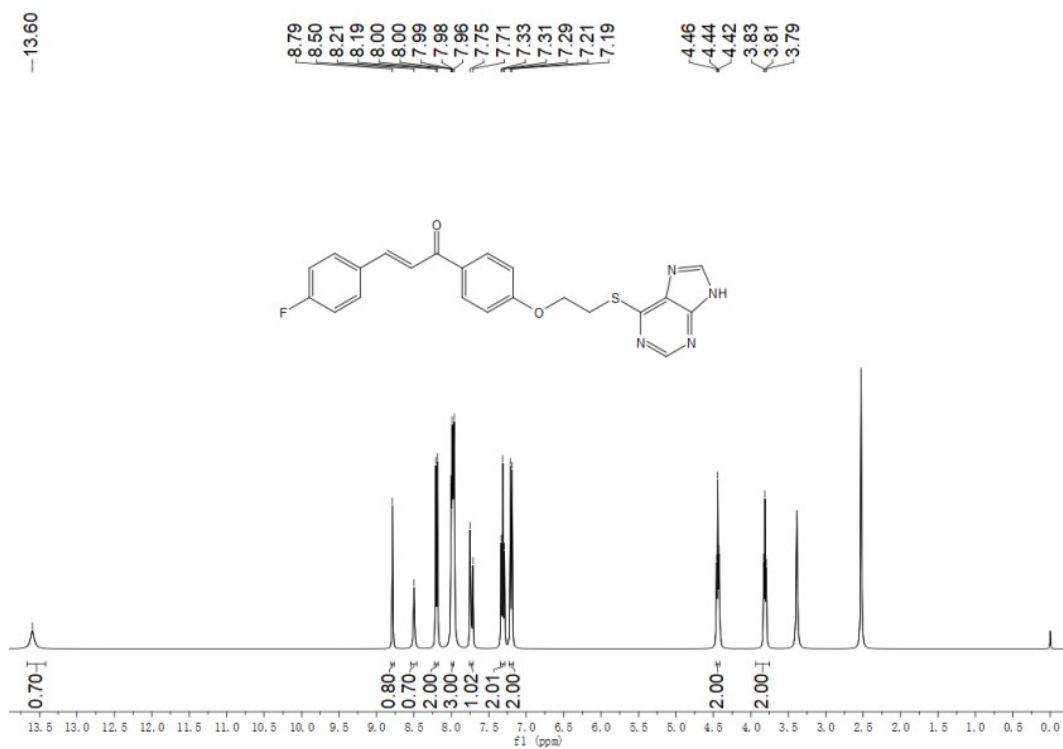


Figure S5. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 4b

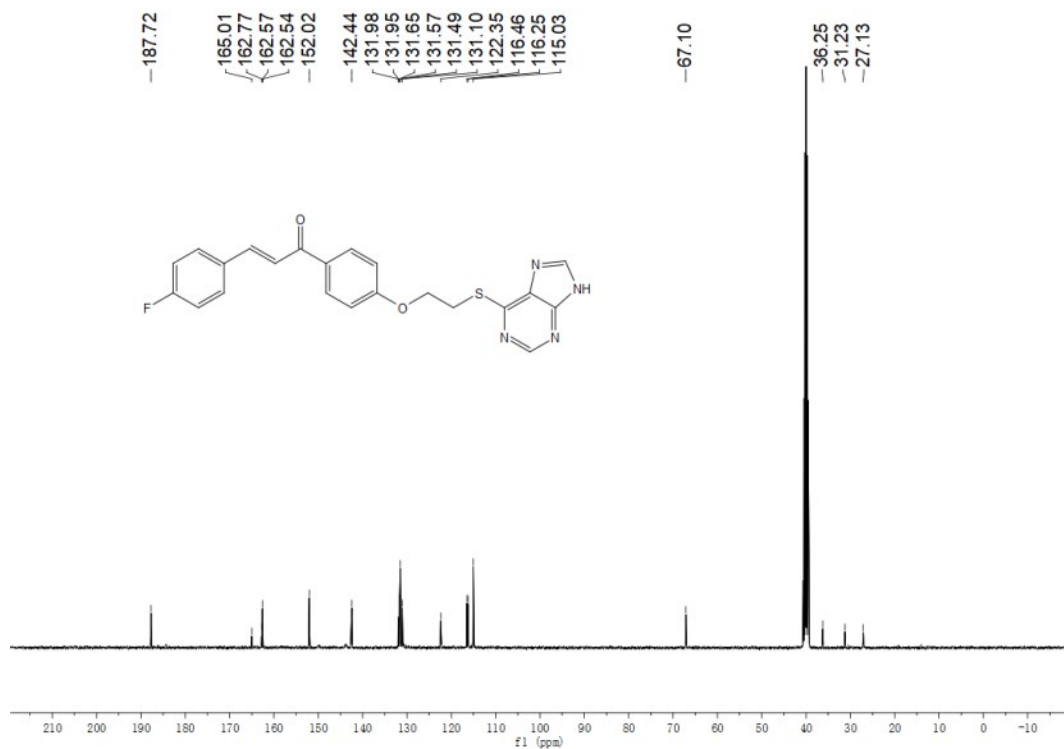


Figure S6. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 4b

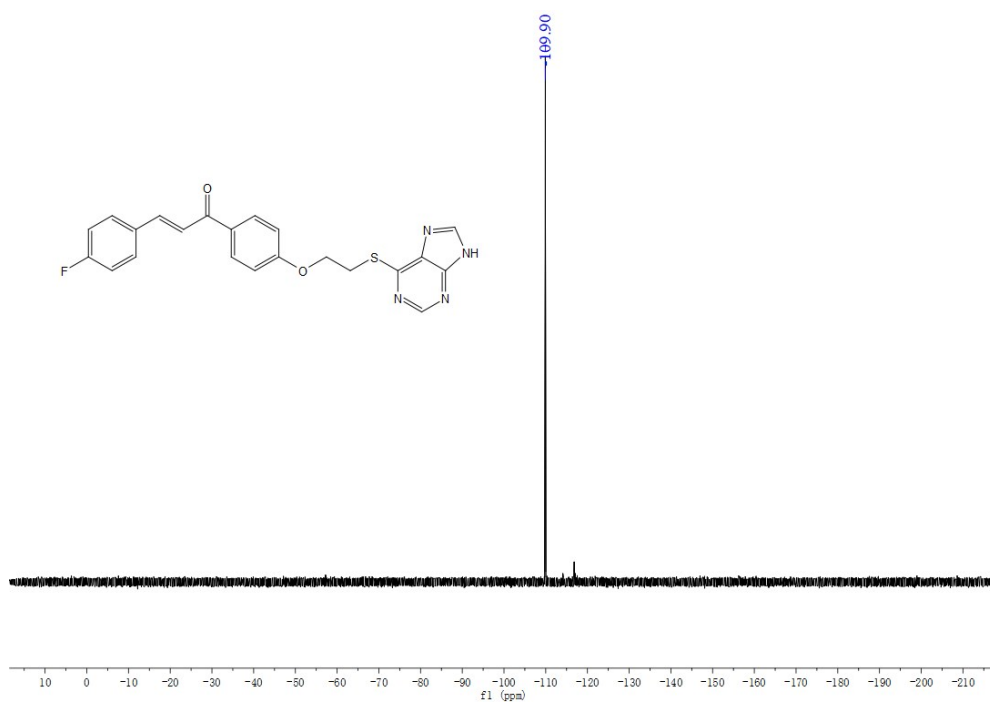


Figure S7. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 4b

2019112210( 439 RT: 0.38 AV: 1 NL: 9.94E7  
T: FTMS+pESI Full ms[100.0000-1000.0000])

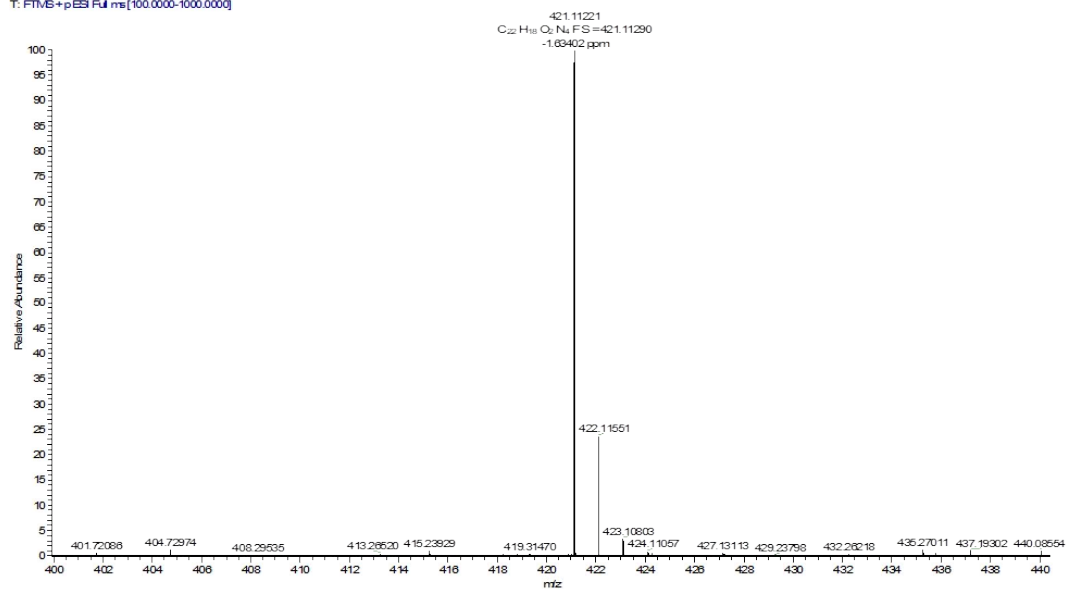


Figure S8. HRMS of compound 4b

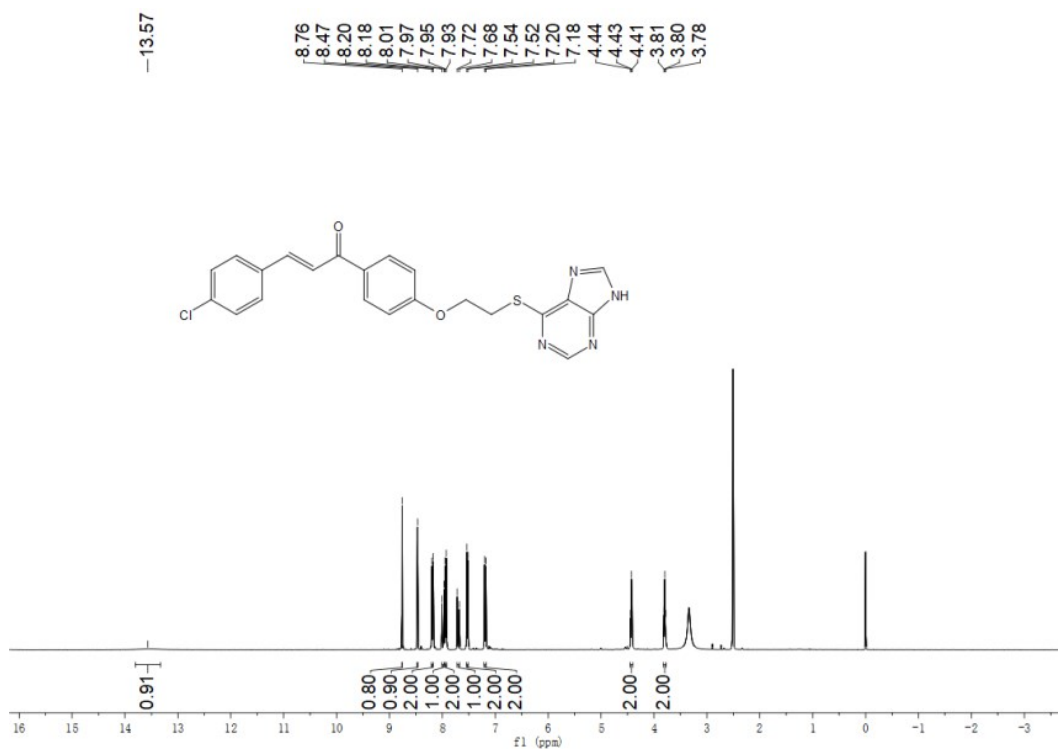


Figure S9. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 4c

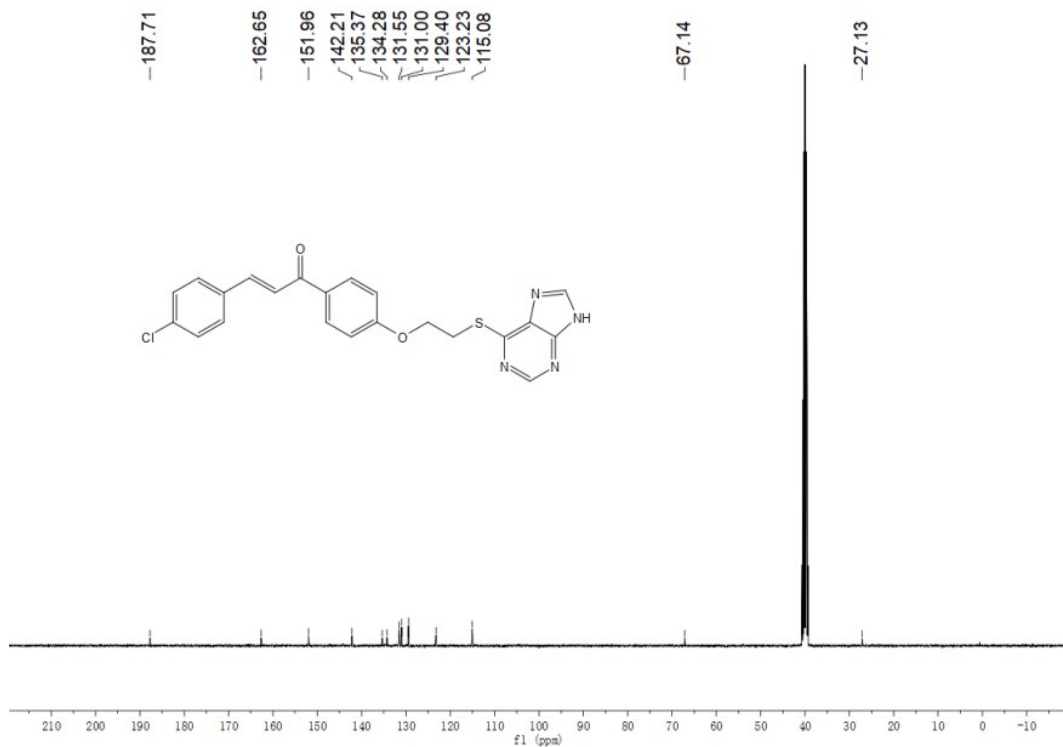


Figure S10. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 4c

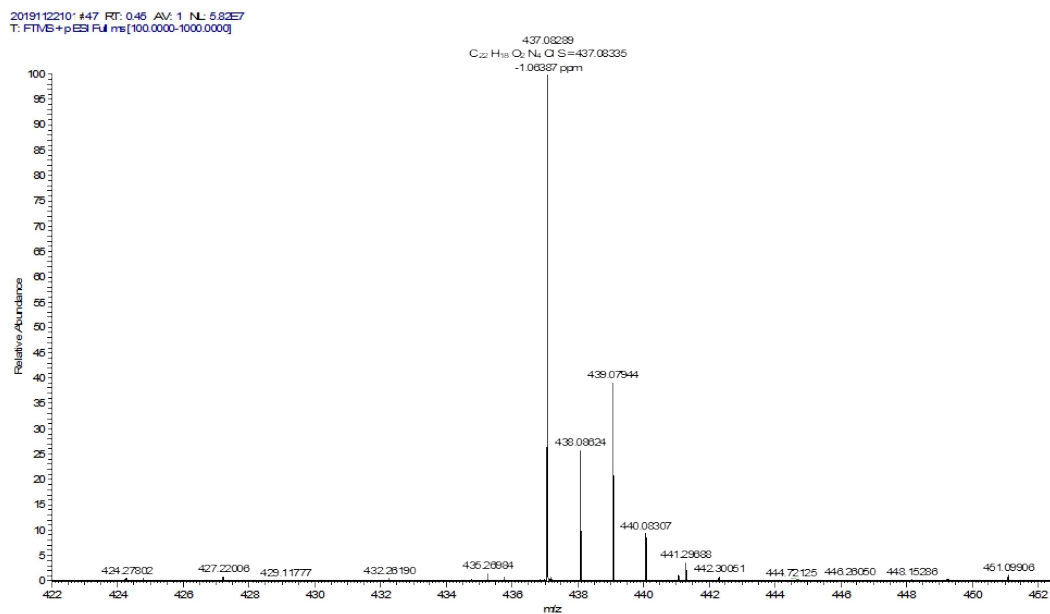
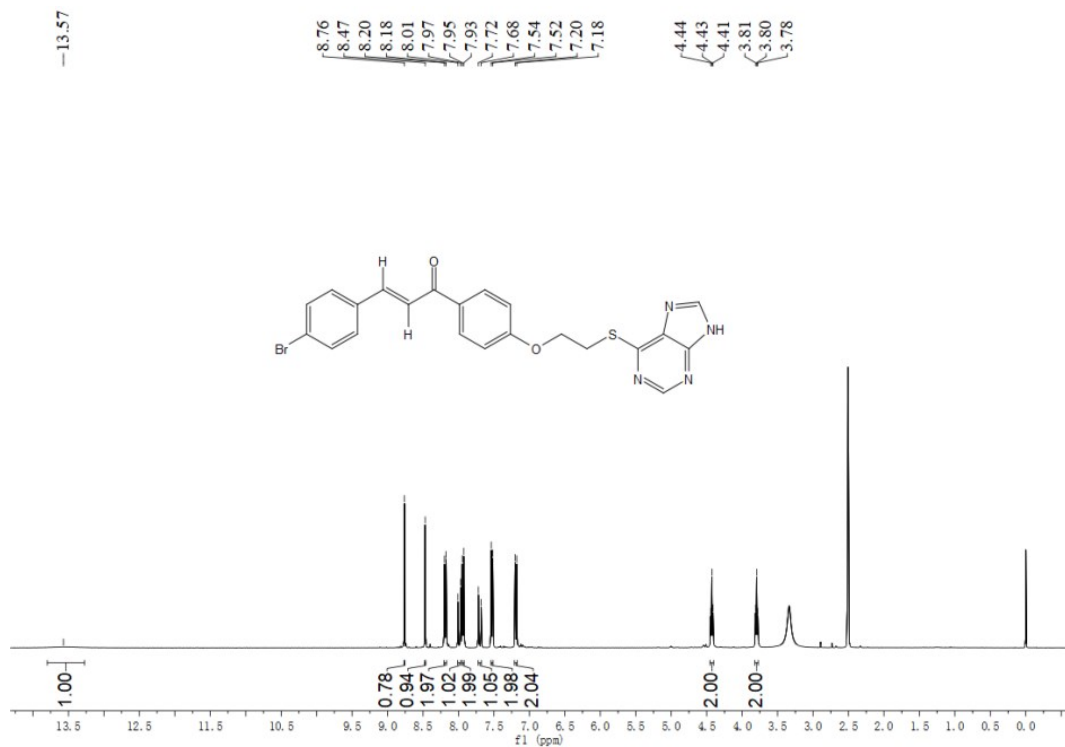
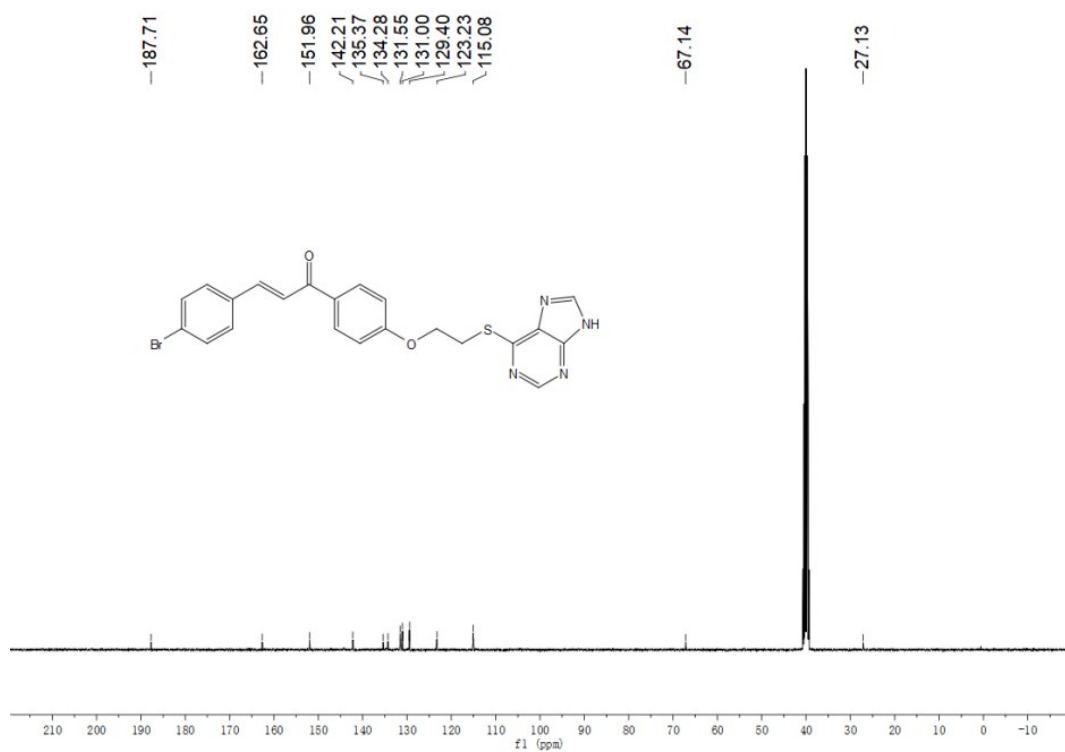


Figure S11. HRMS of compound 4c



**Figure S12.**  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **4d**



**Figure S13.**  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **4d**

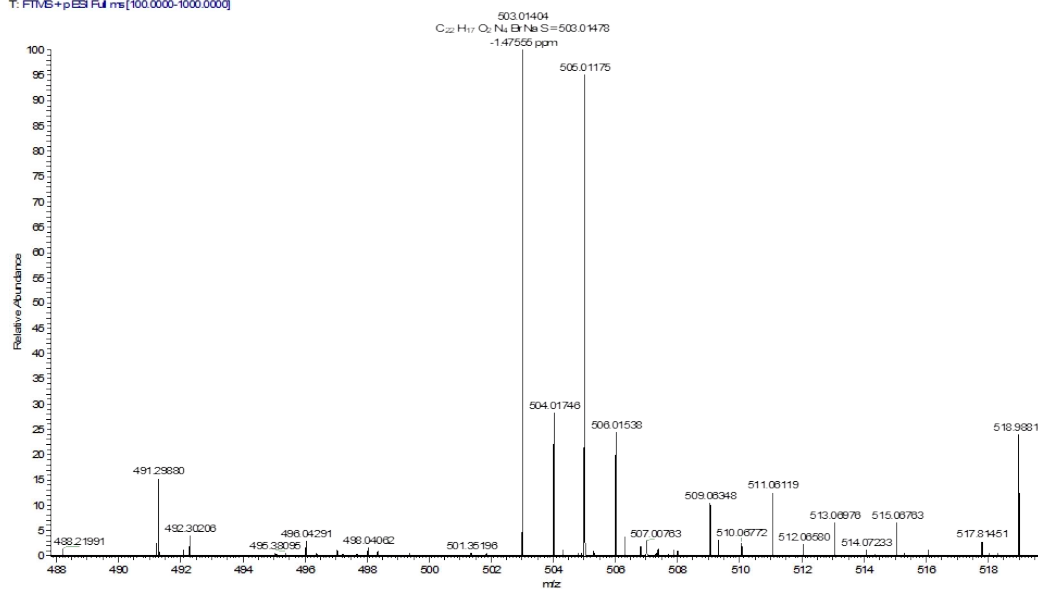


Figure S14. HRMS of compound 4d



Figure S15. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 4e



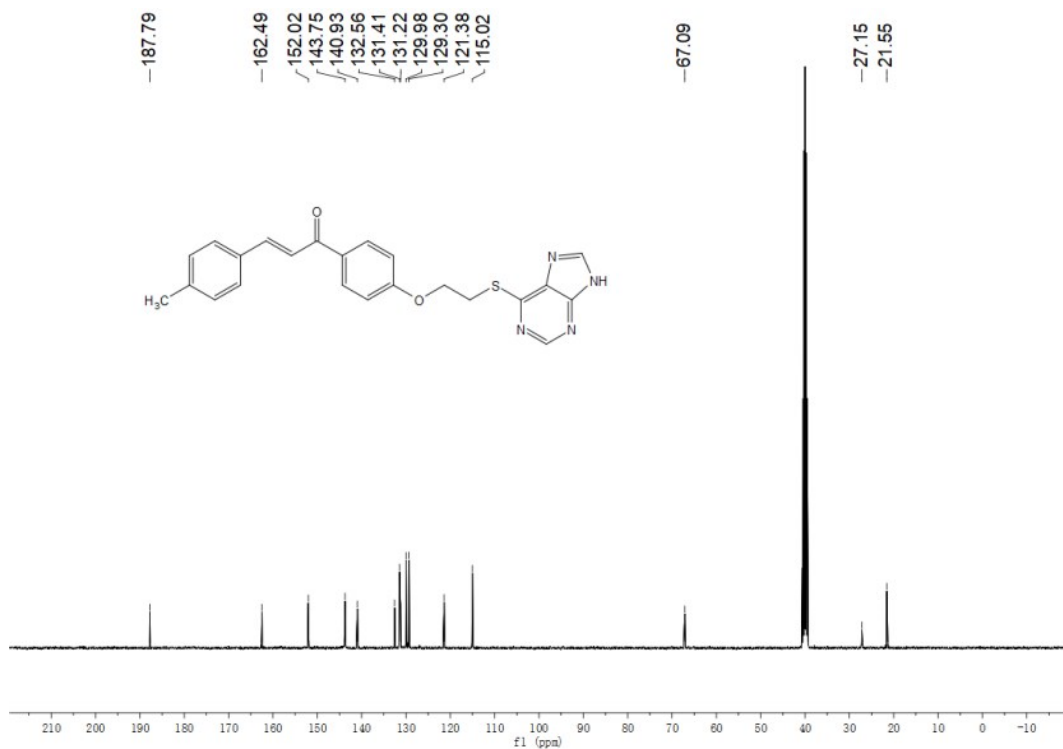


Figure S16. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 4e

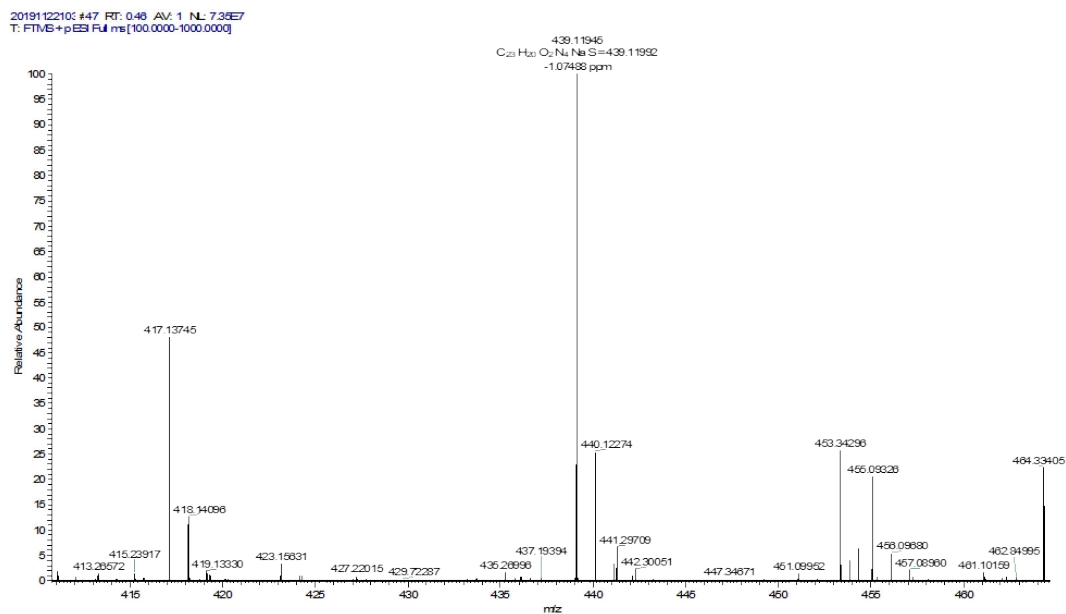


Figure S17. HRMS of compound 4e

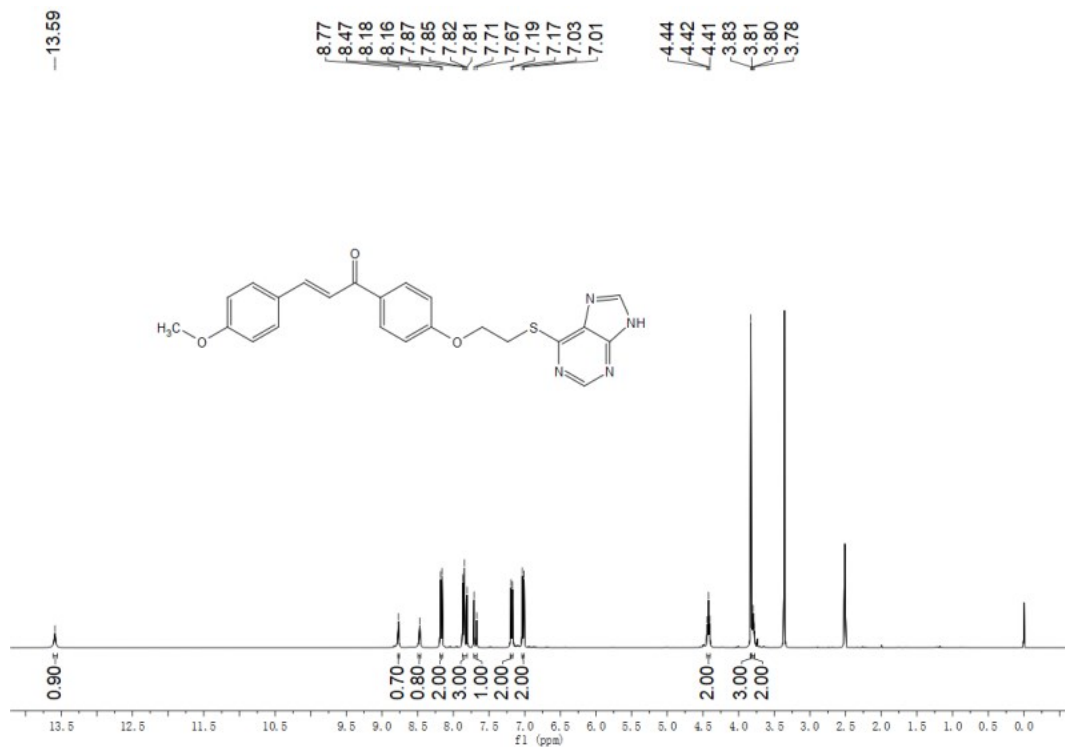


Figure S18.  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz) spectrum of compound **4f**

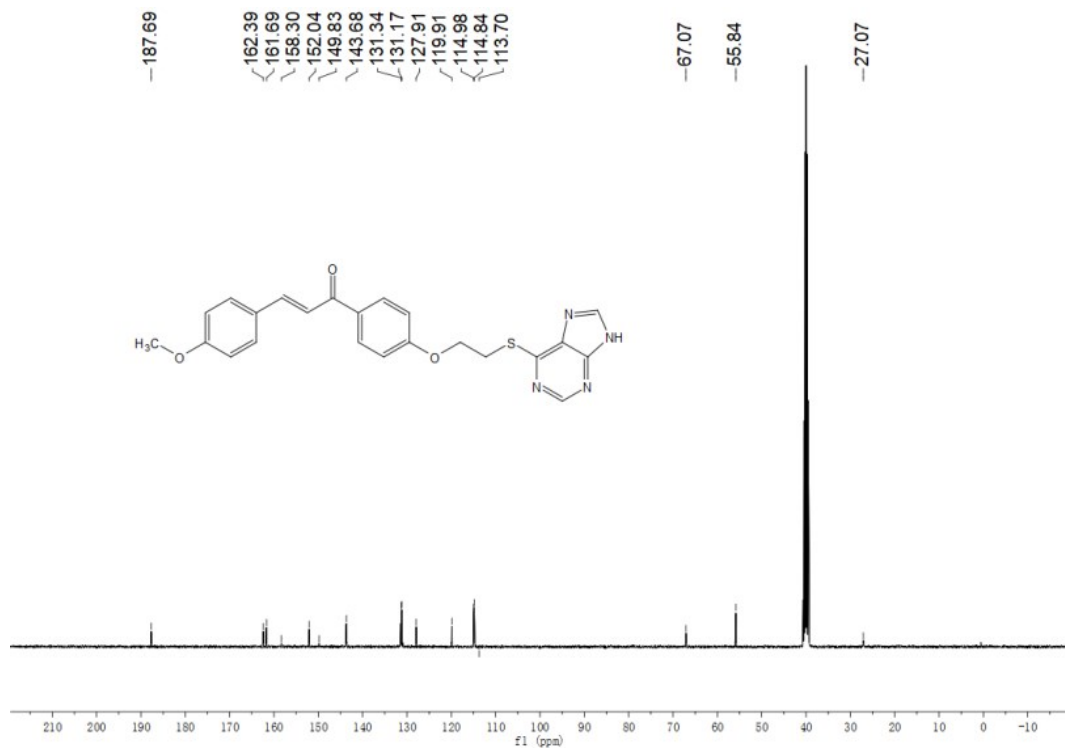


Figure S19.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 400 MHz) spectrum of compound **4f**

2019112210x #43 RT: 0.42 AL: 1 NL: 172E8  
T: FTMS+pES Full ms[100.0000-1000.0000]

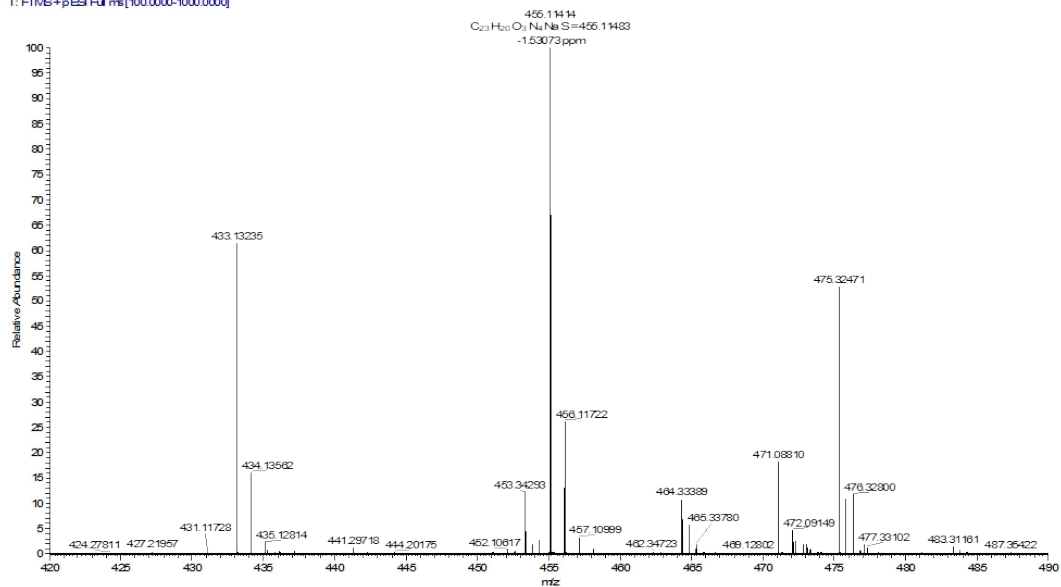


Figure S20. HRMS of compound 4f

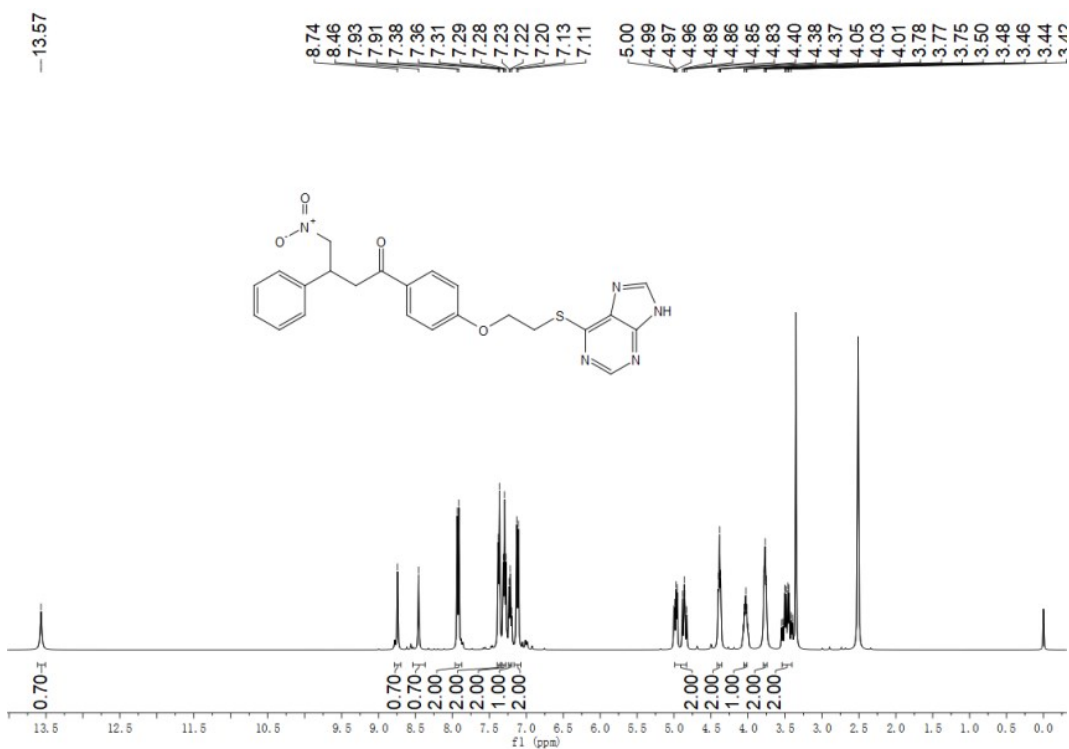


Figure S21. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5a

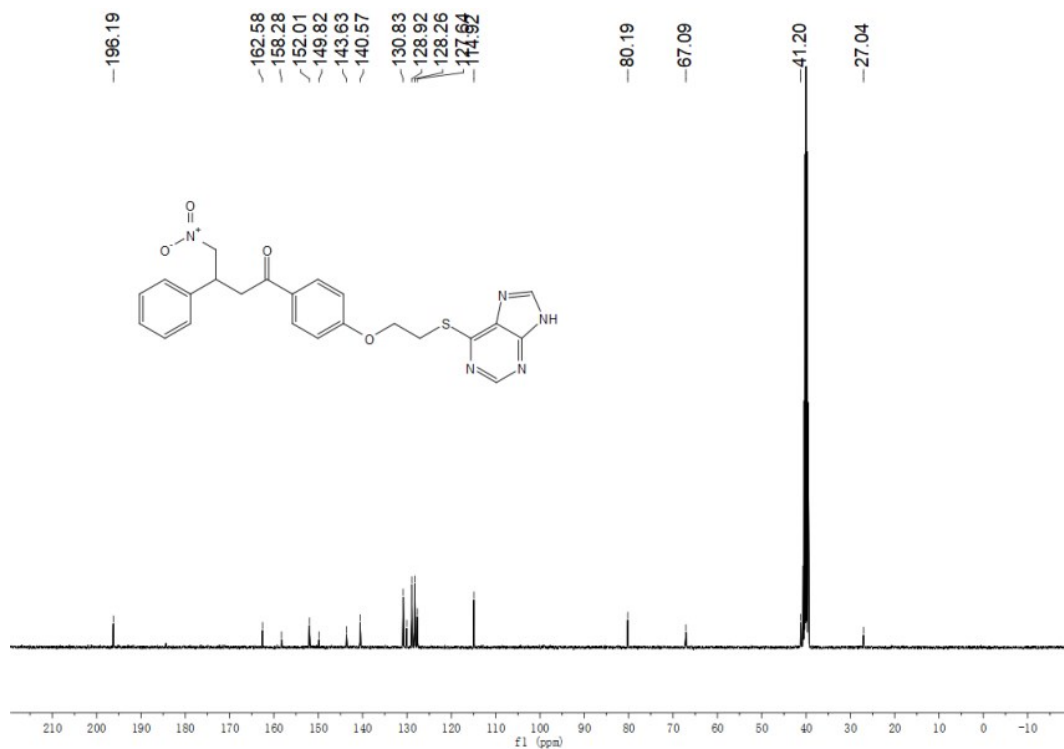


Figure S22. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5a

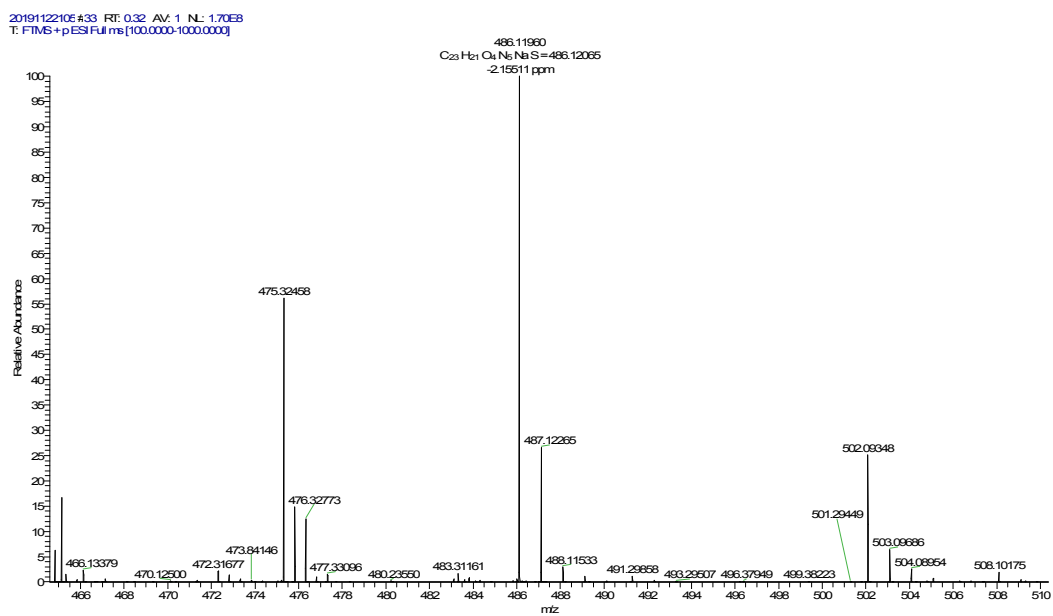


Figure S23. HRMS of compound 5a

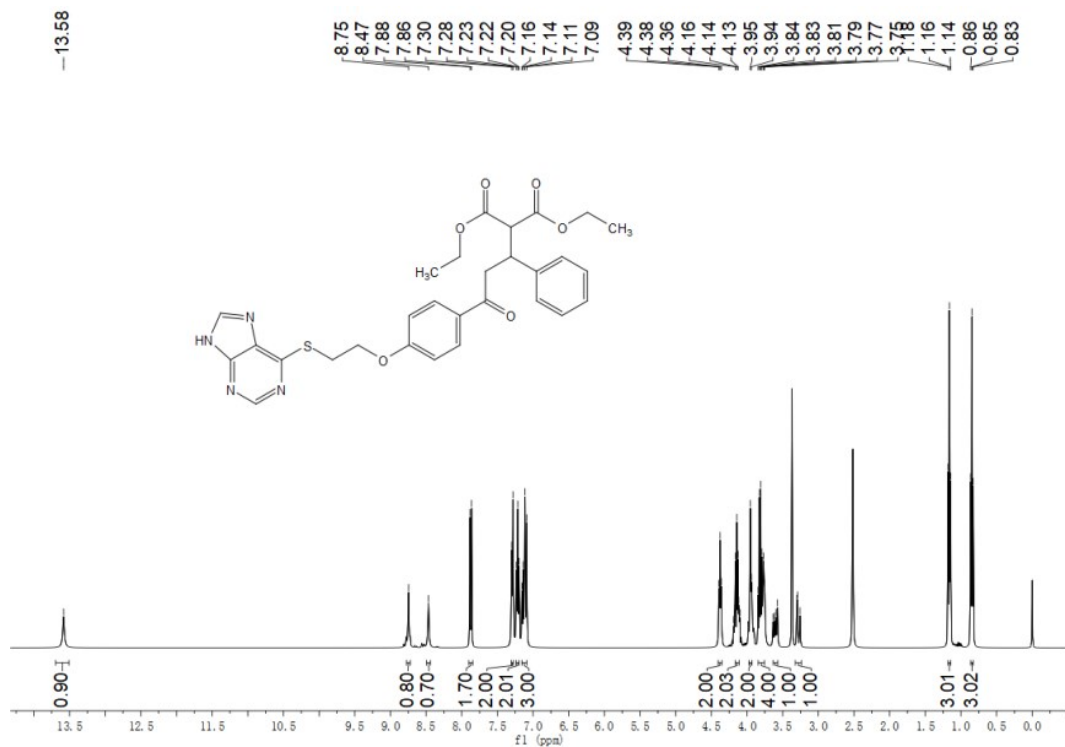


Figure S24.  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **5b**

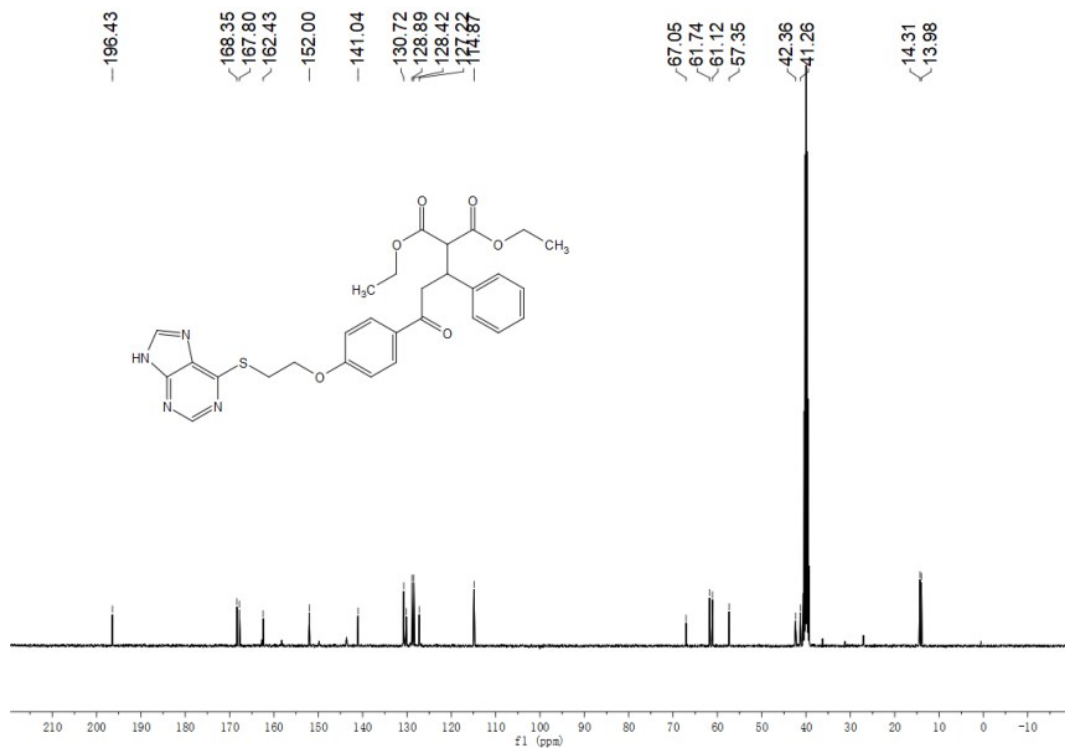


Figure S25.  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **5b**

2019112106 #43 RT: 0.42 AL: 1 NL: 82 E7  
T: FTMS+pES Full ms[100.0000-1000.0000]

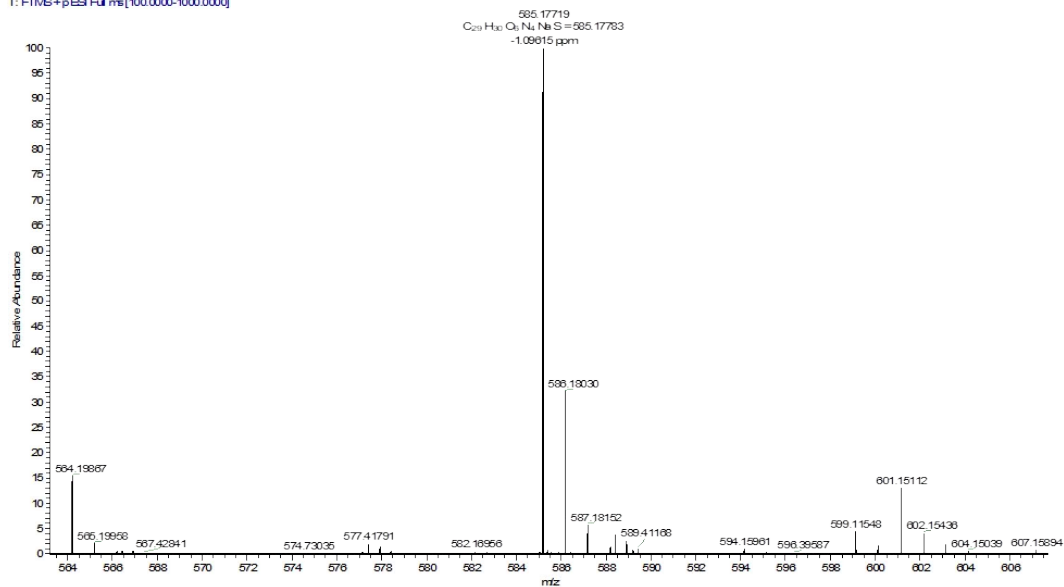


Figure S26. HRMS of compound 5b

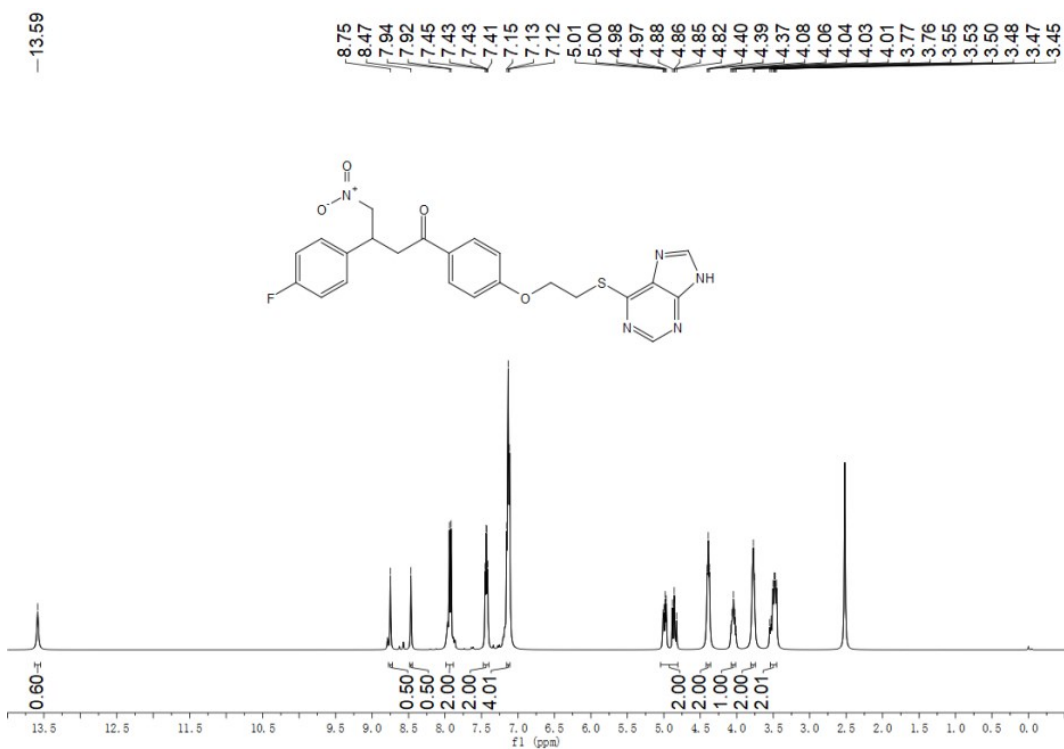


Figure S27. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5c

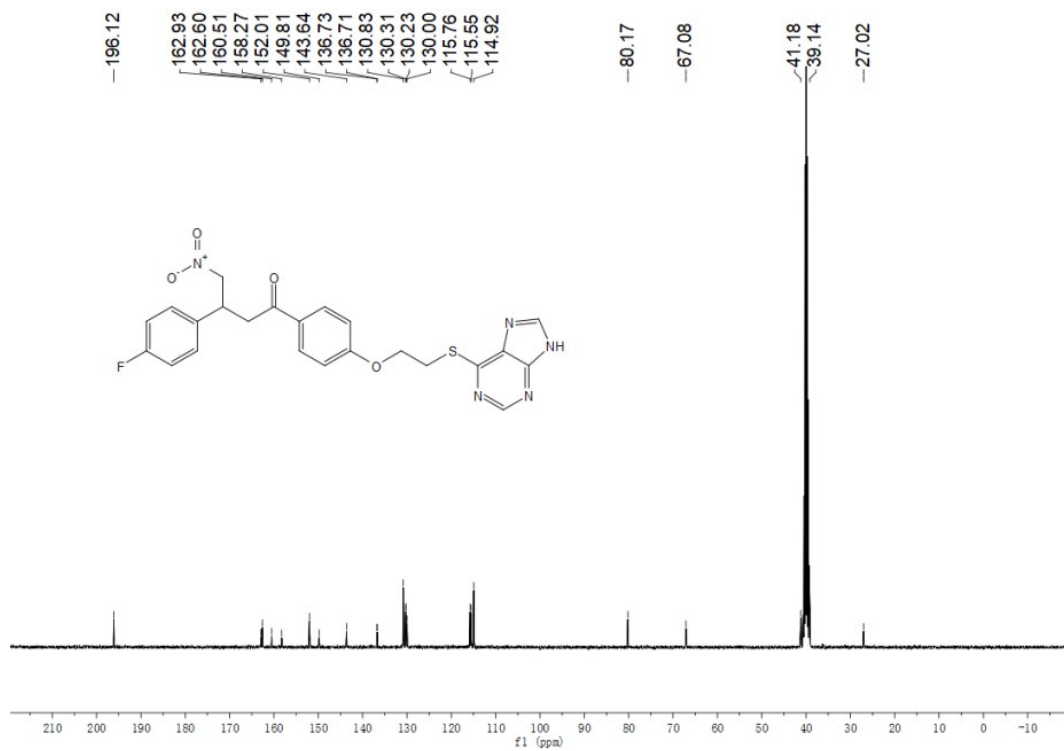


Figure S28. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5c



Figure S29. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5c

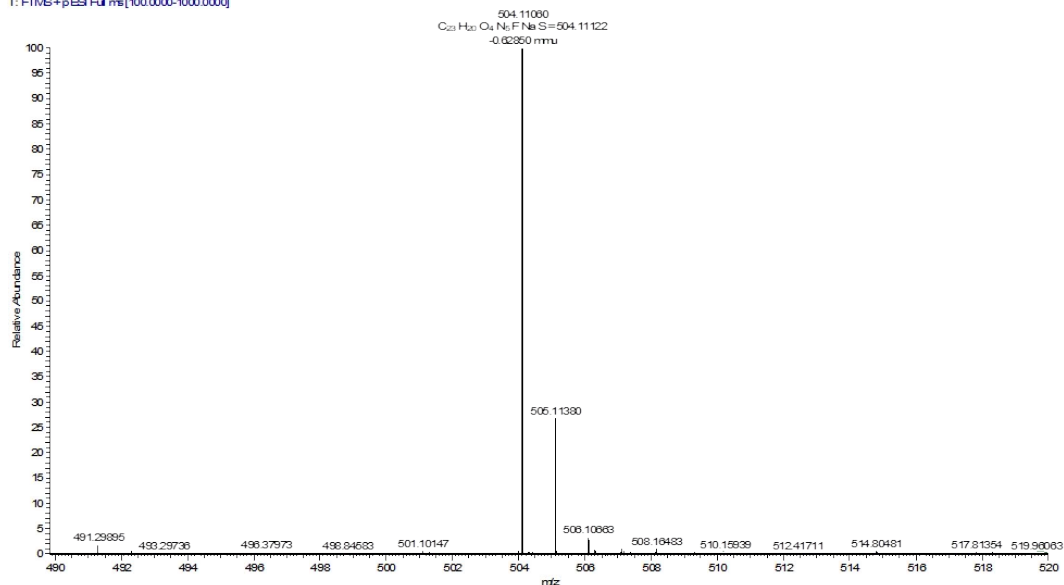


Figure S30. HRMS of compound 5c

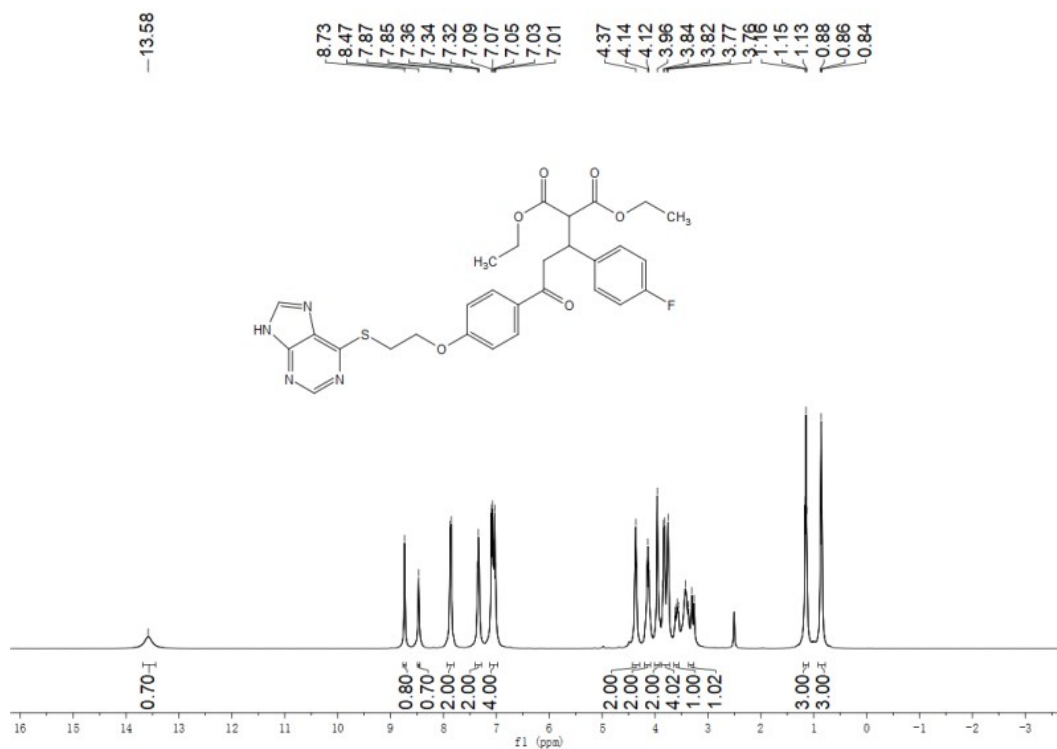


Figure S31. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5d



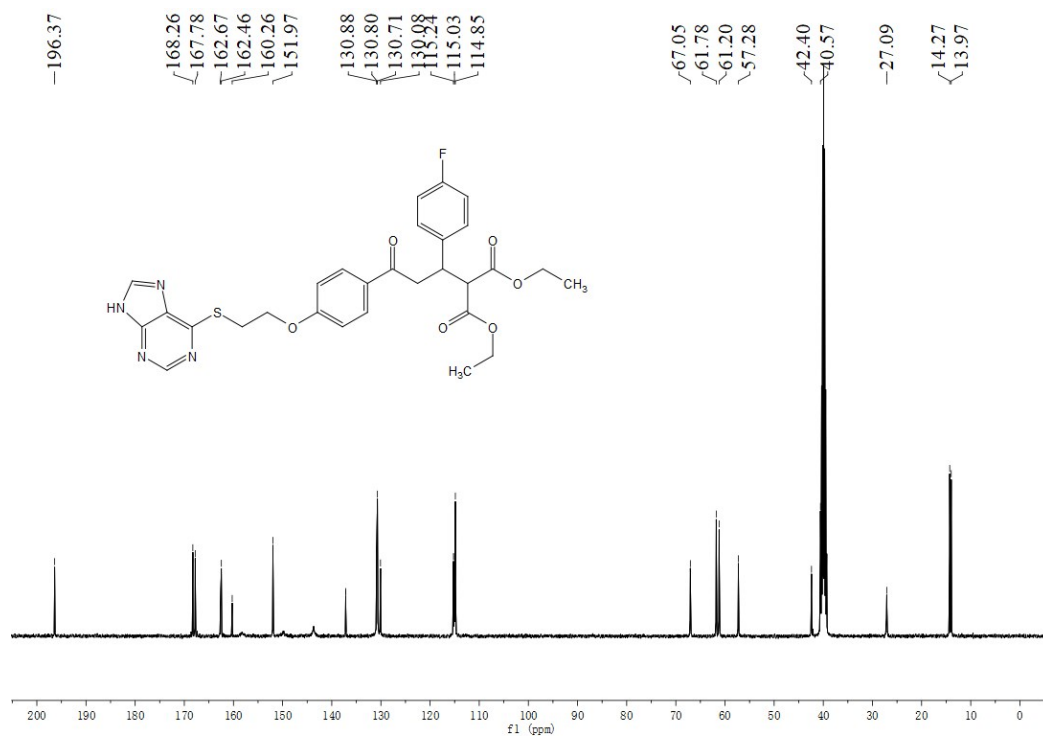


Figure S32. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5d

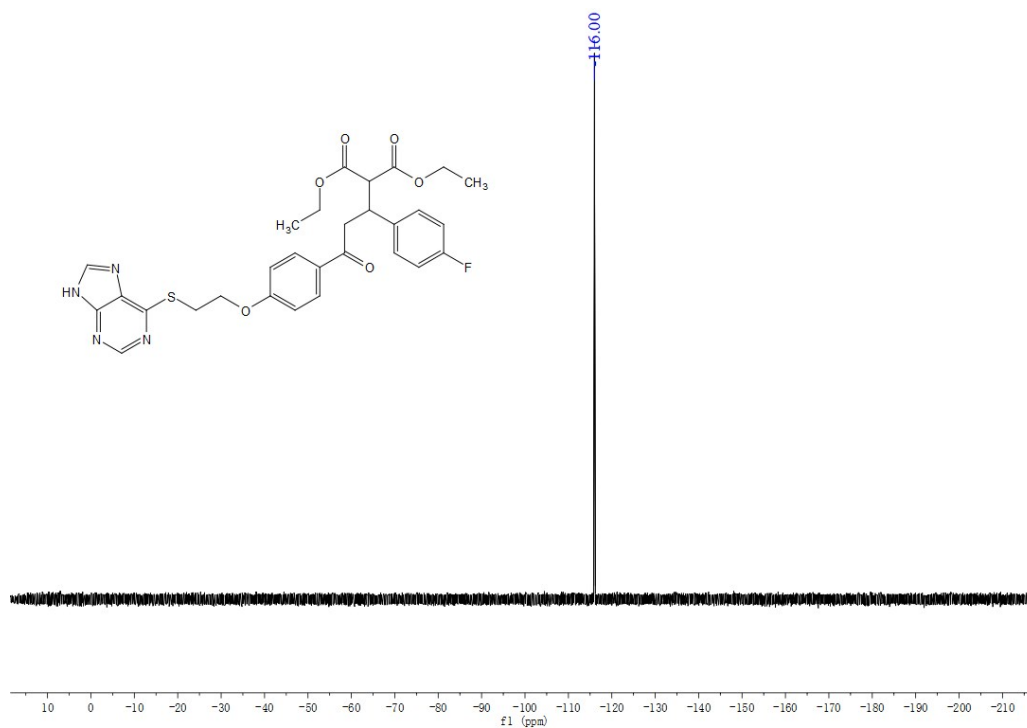


Figure S33. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5d

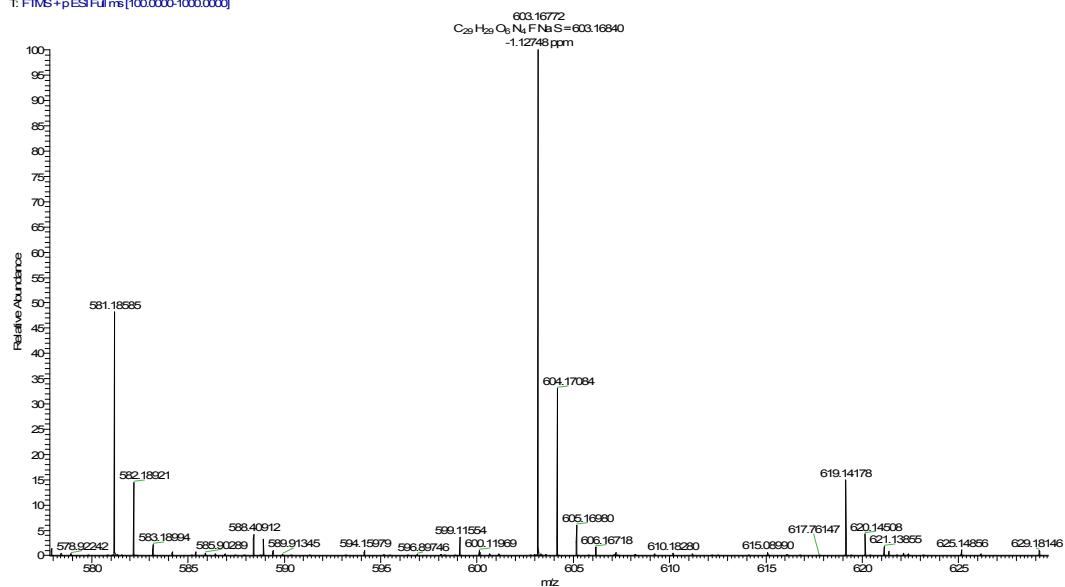


Figure S34. HRMS of compound 5d

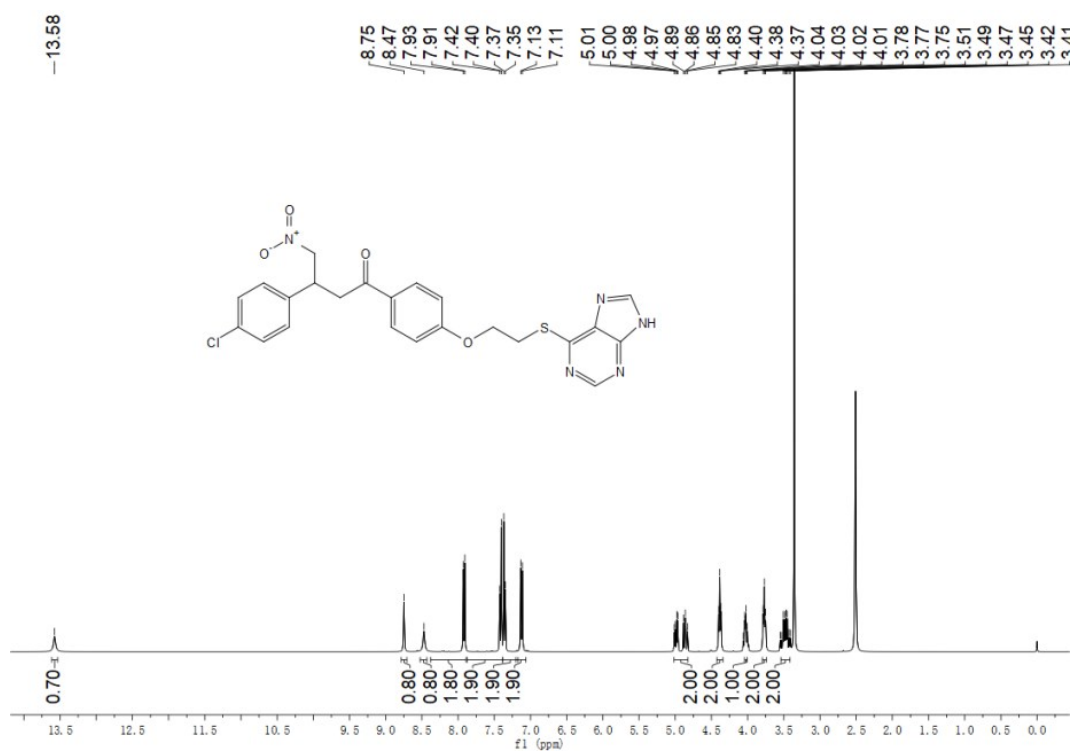


Figure S35. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5e

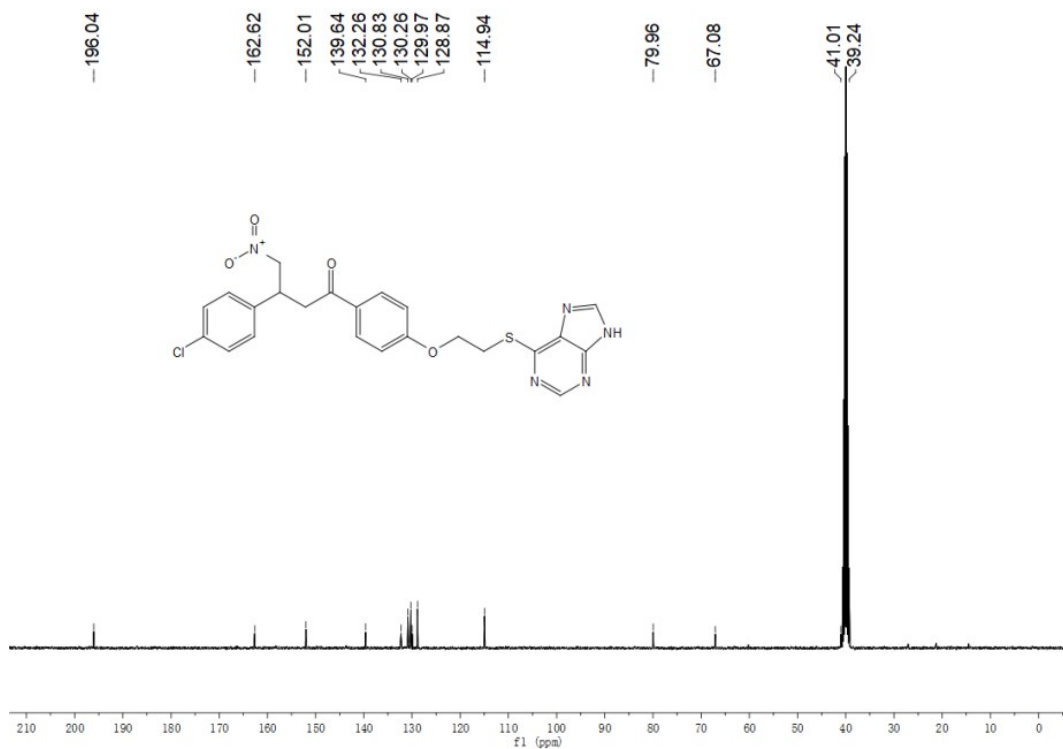


Figure S36. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5e

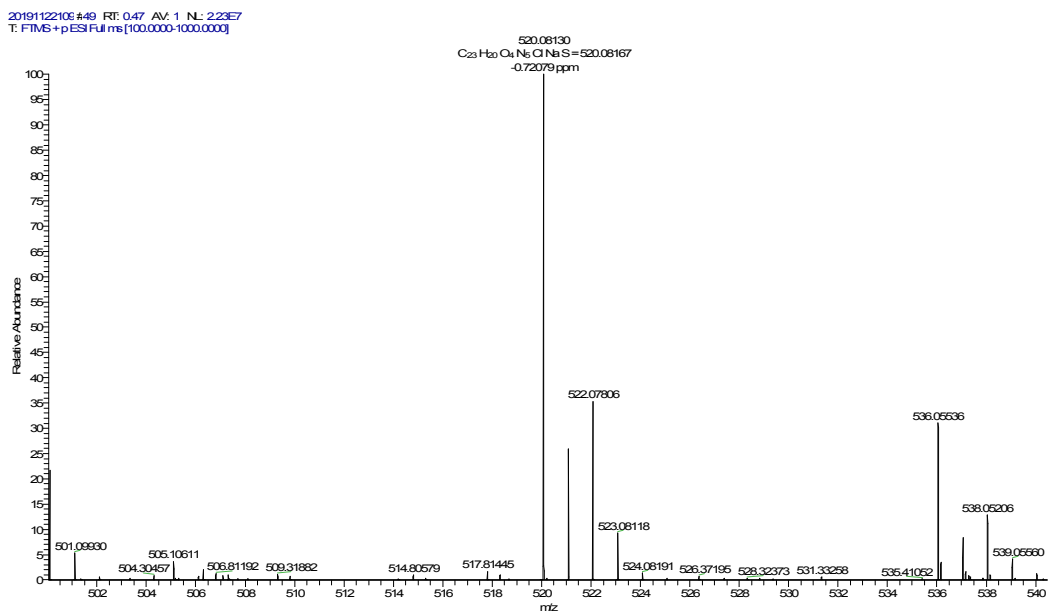


Figure S37. HRMS of compound 5e

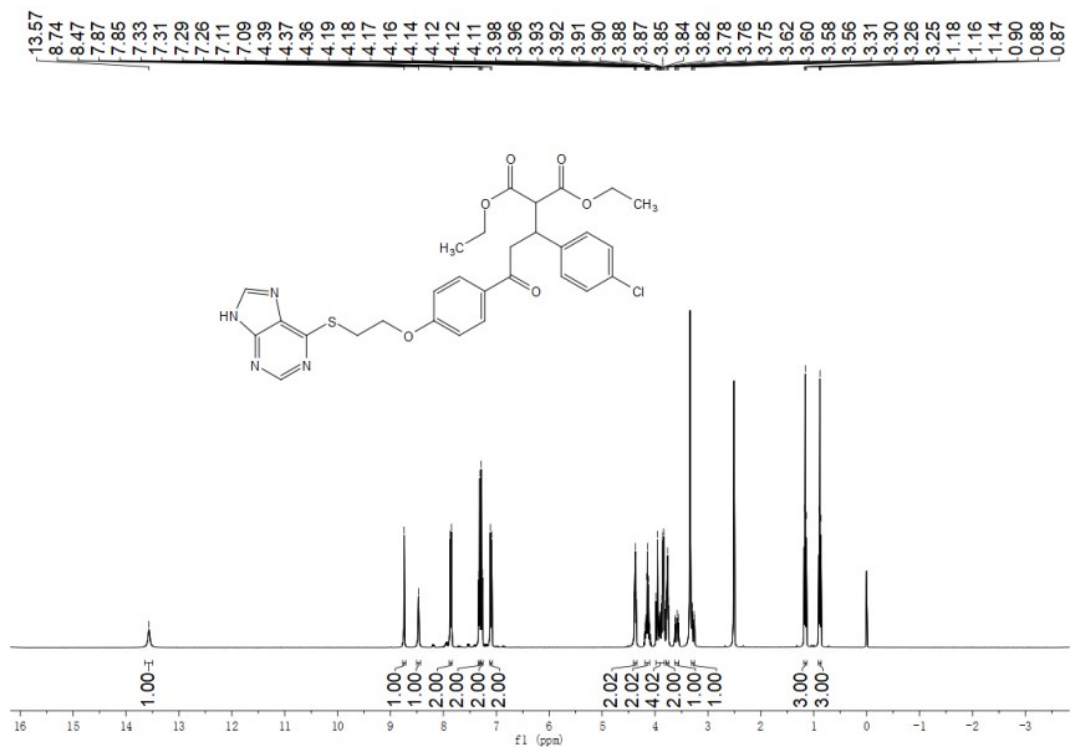


Figure S38. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5f

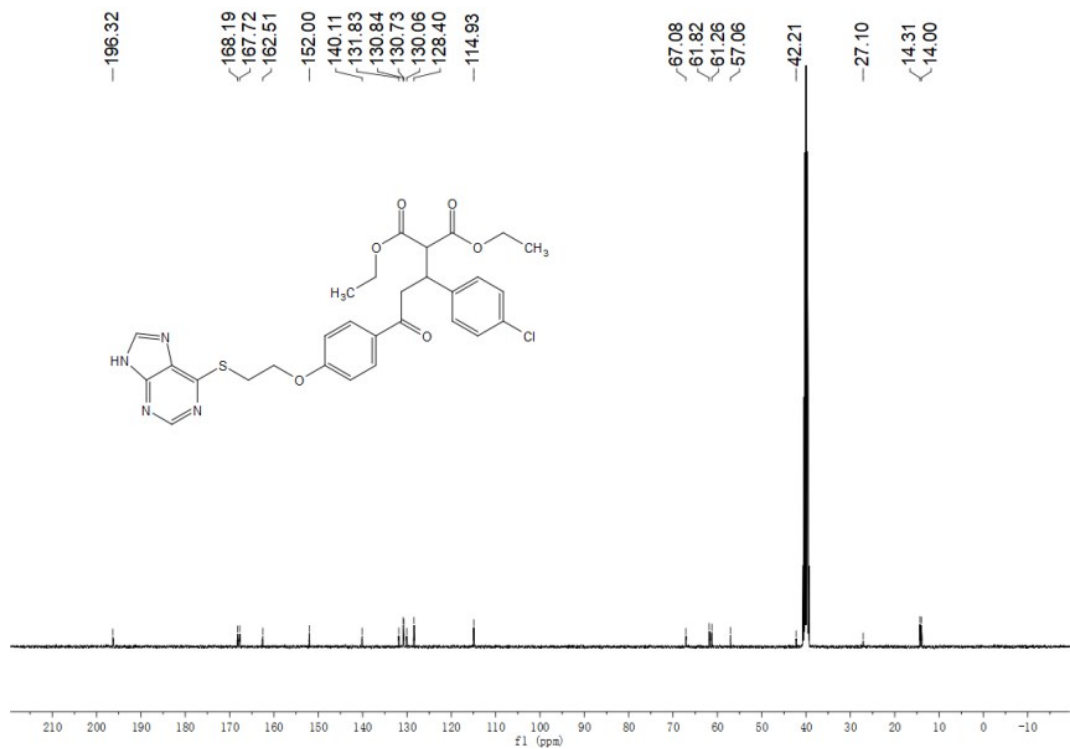


Figure S39. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5f

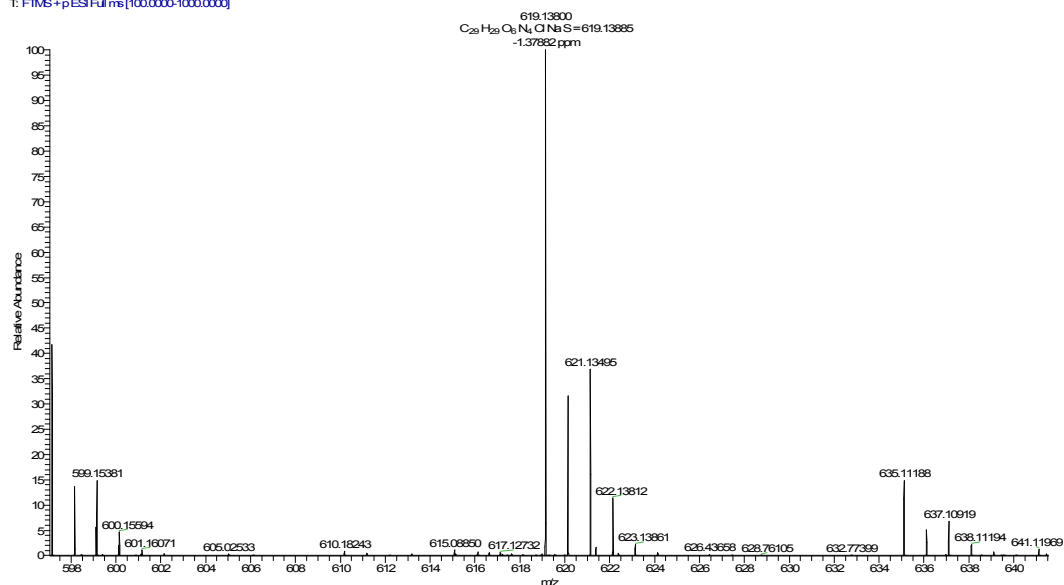


Figure S40. HRMS of compound 5f

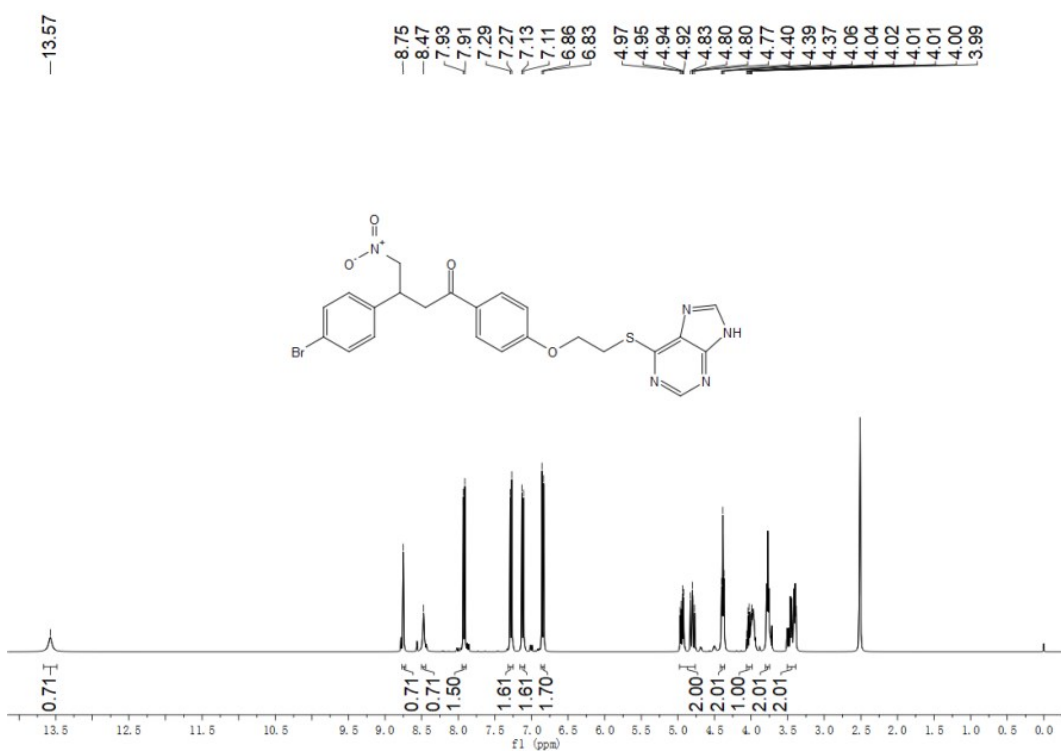


Figure S41. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5g

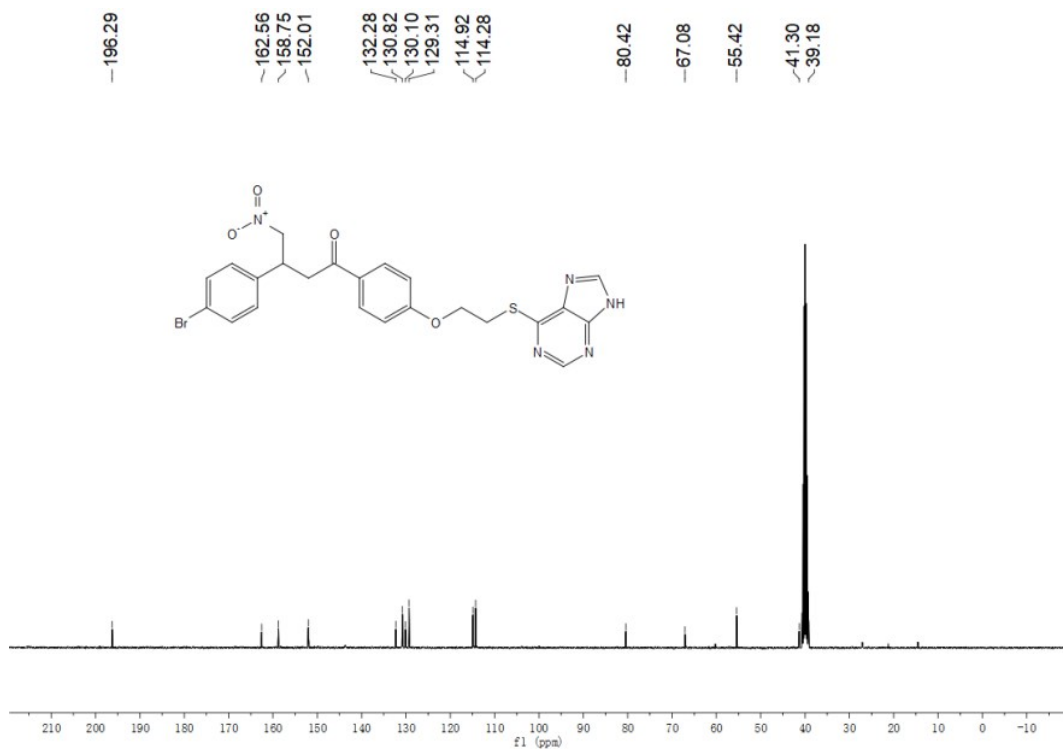


Figure S42. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5g

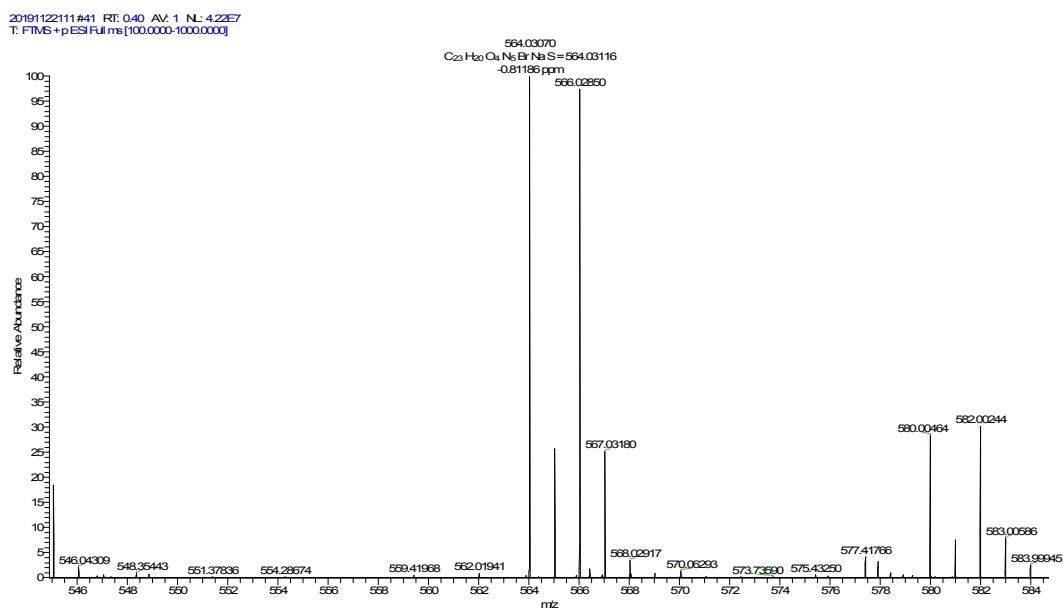


Figure S43. HRMS of compound 5g

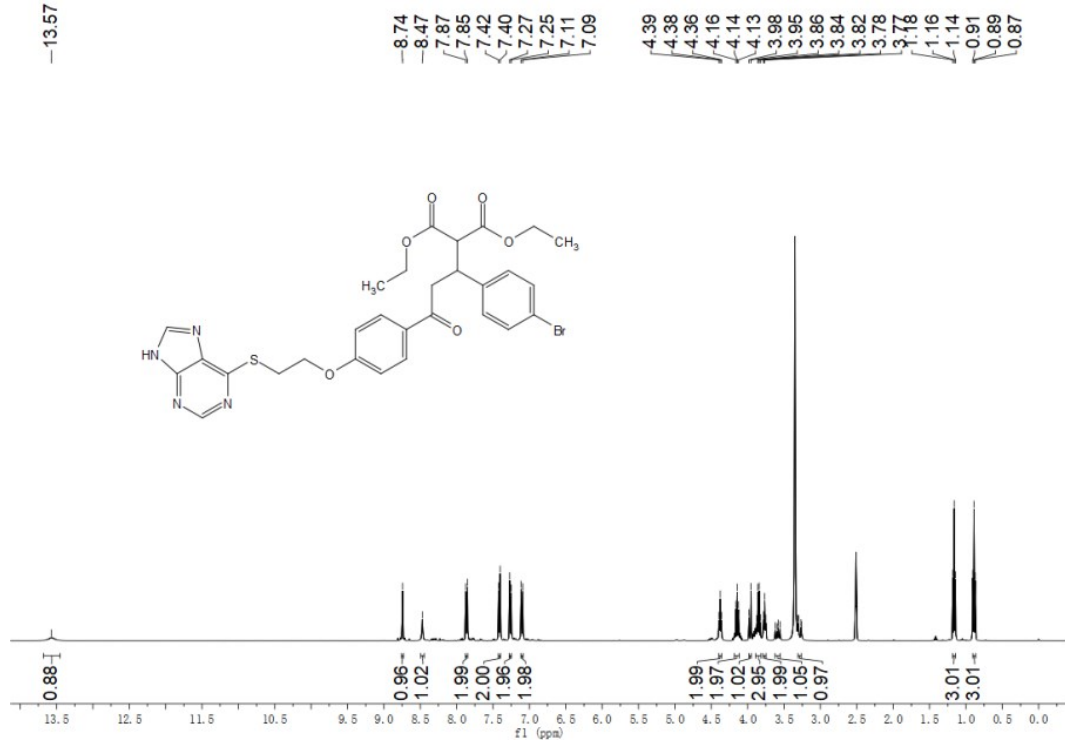


Figure S44. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5h

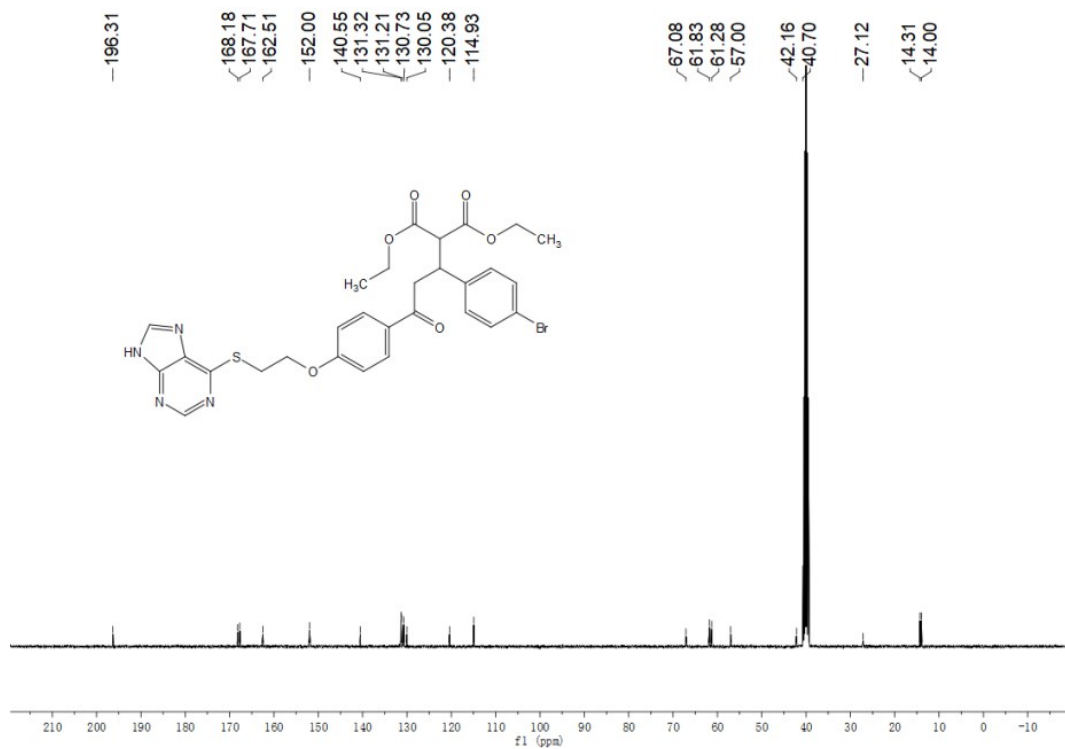


Figure S45. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5h

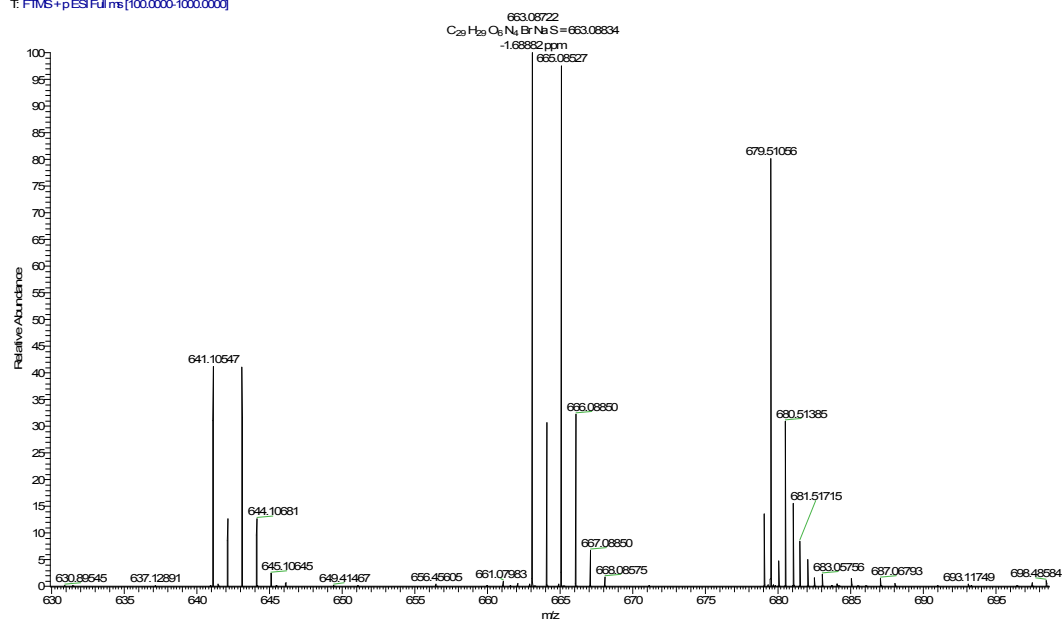


Figure S46. HRMS of compound 5h

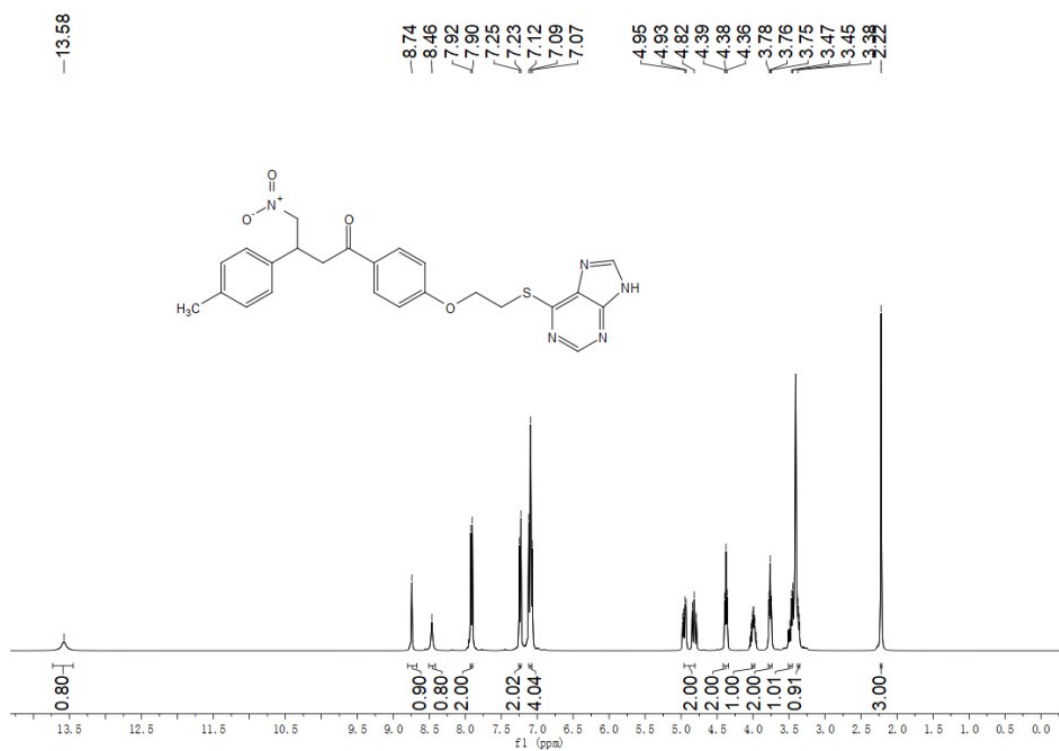


Figure S47. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5i



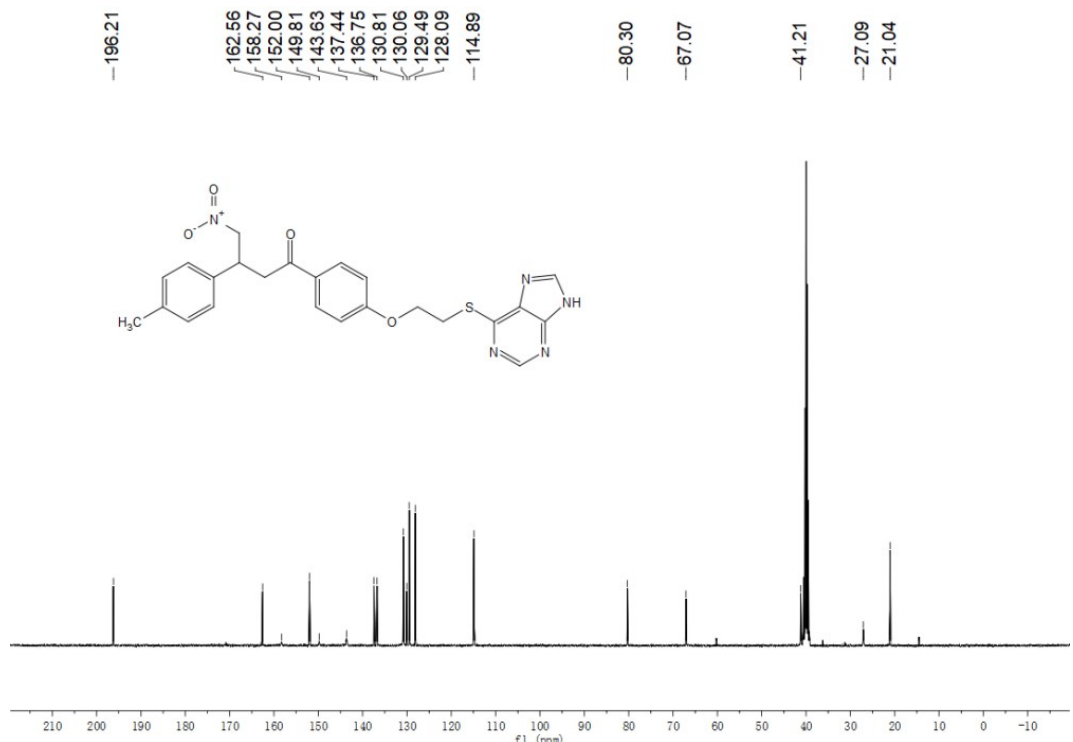


Figure S48. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5i

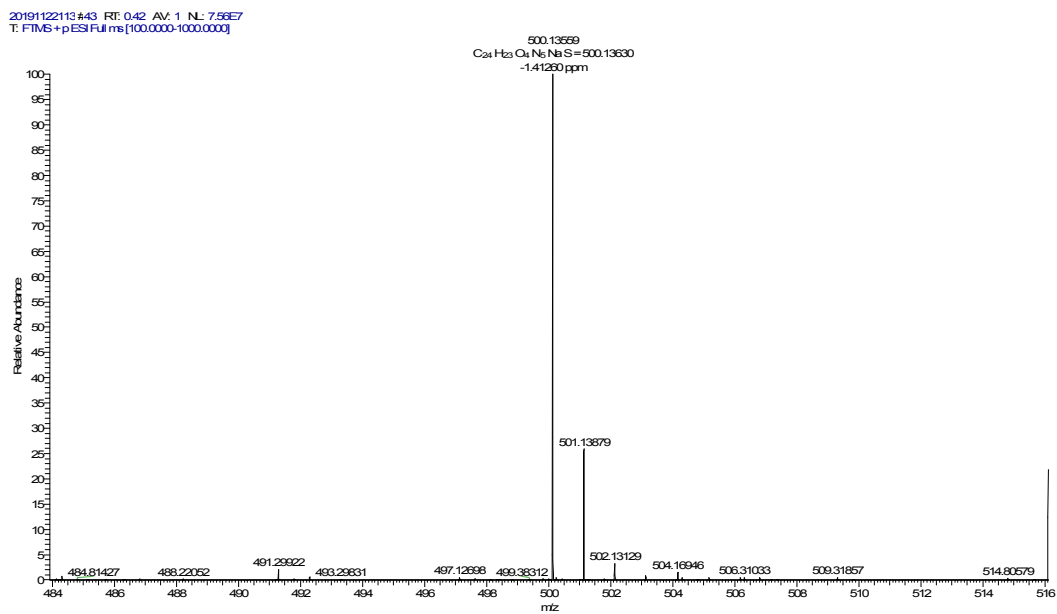
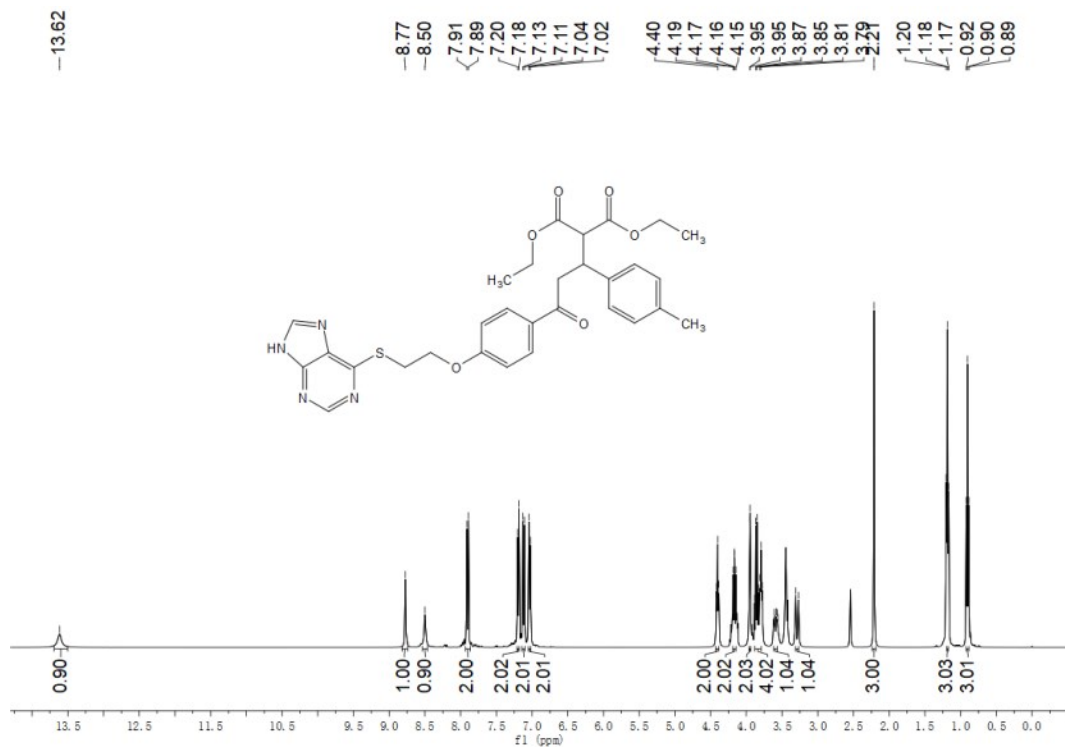
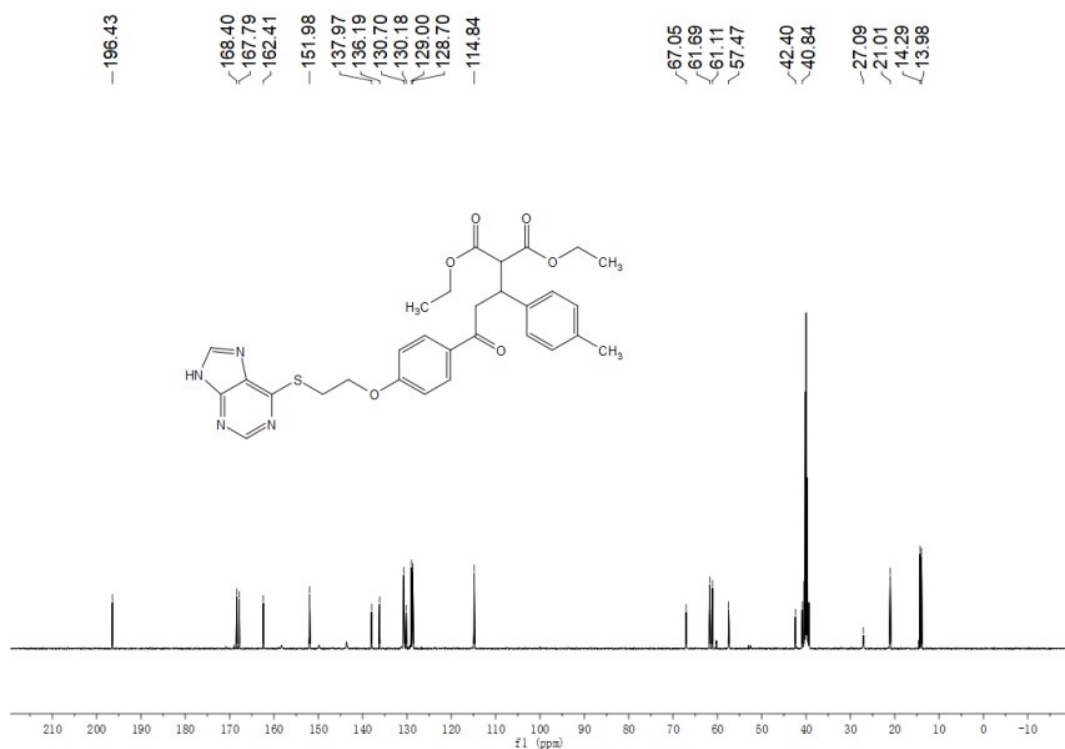


Figure S49. HRMS of compound 5i



**Figure S50.**  $^1\text{H}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **5j**



**Figure S51.**  $^{13}\text{C}$  NMR ( $\text{DMSO-}d_6$ , 400 MHz) spectrum of compound **5j**

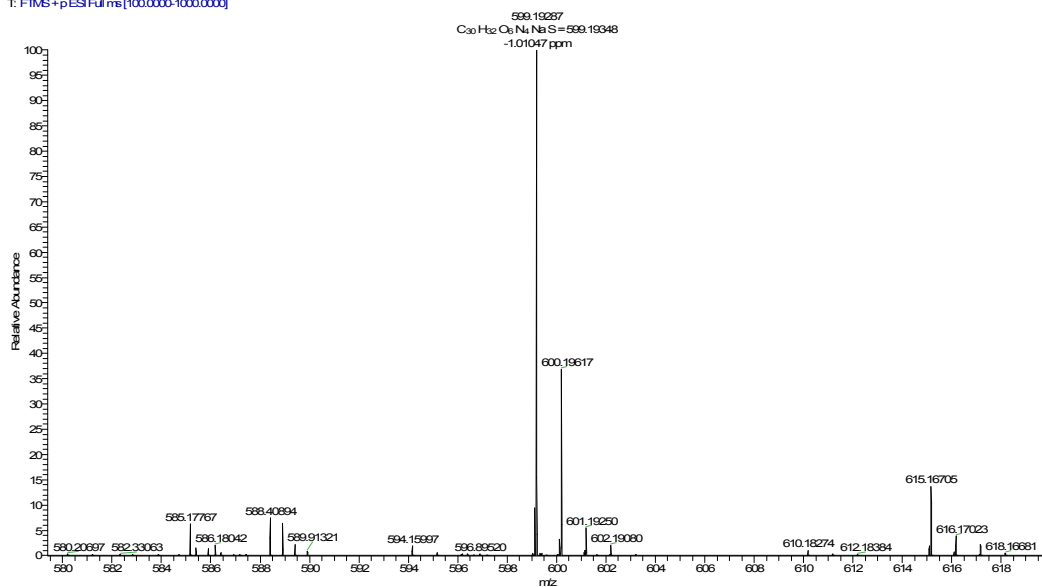


Figure S52. HRMS of compound 5j

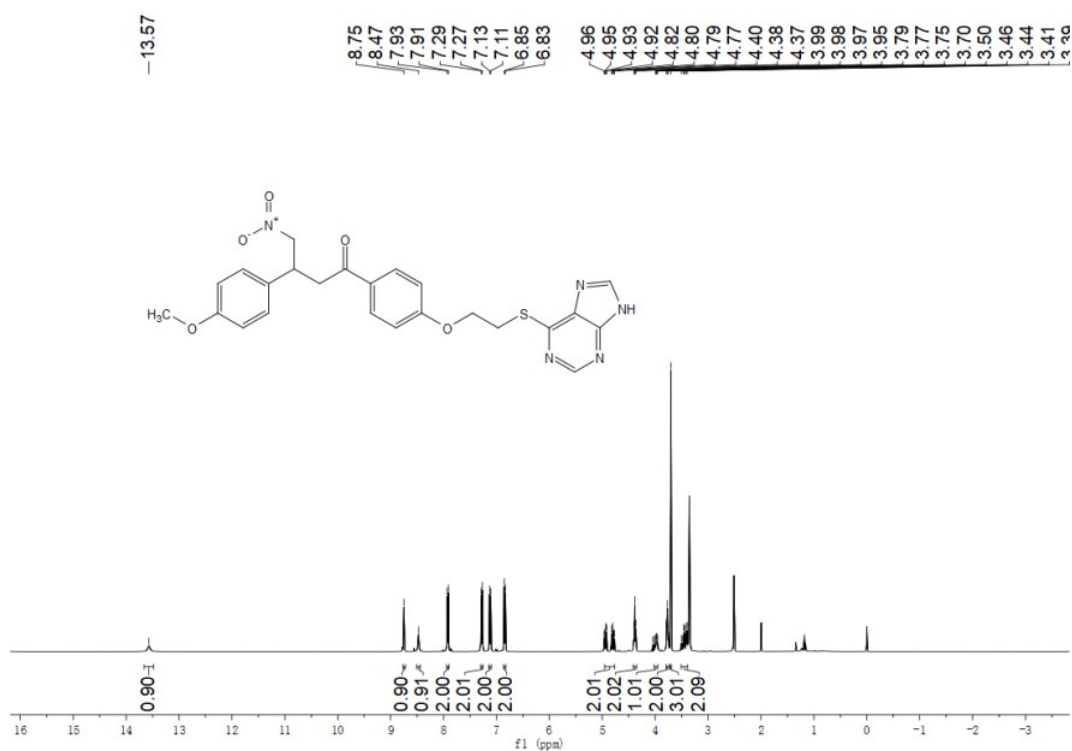


Figure S53. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 5k

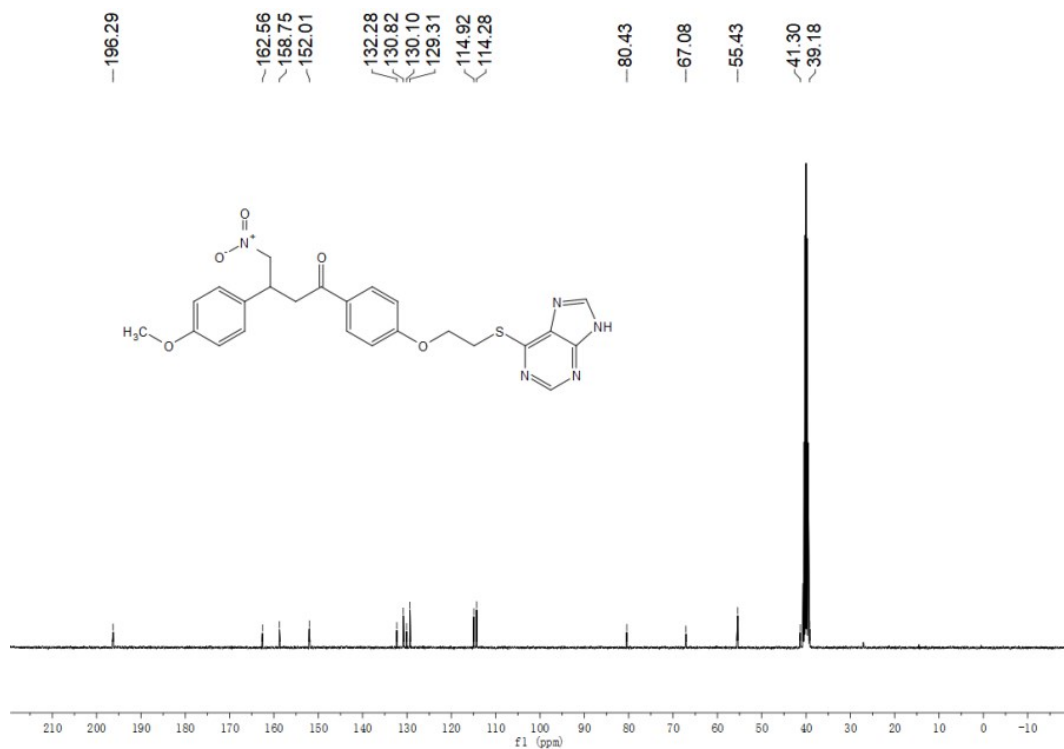


Figure S54.  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 400 MHz) spectrum of compound 5k

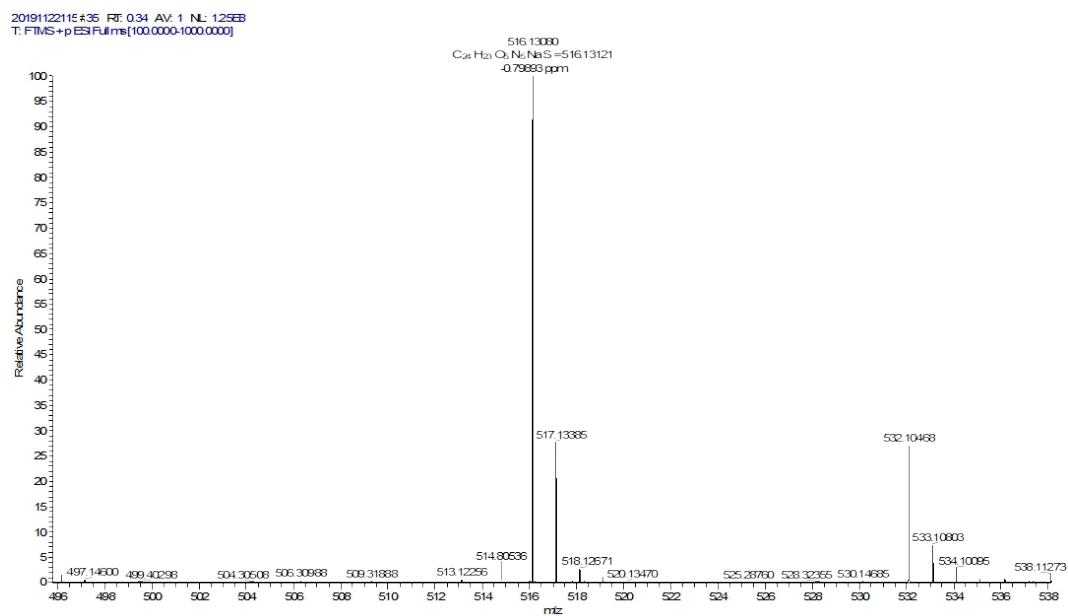


Figure S55. HRMS of compound 5k

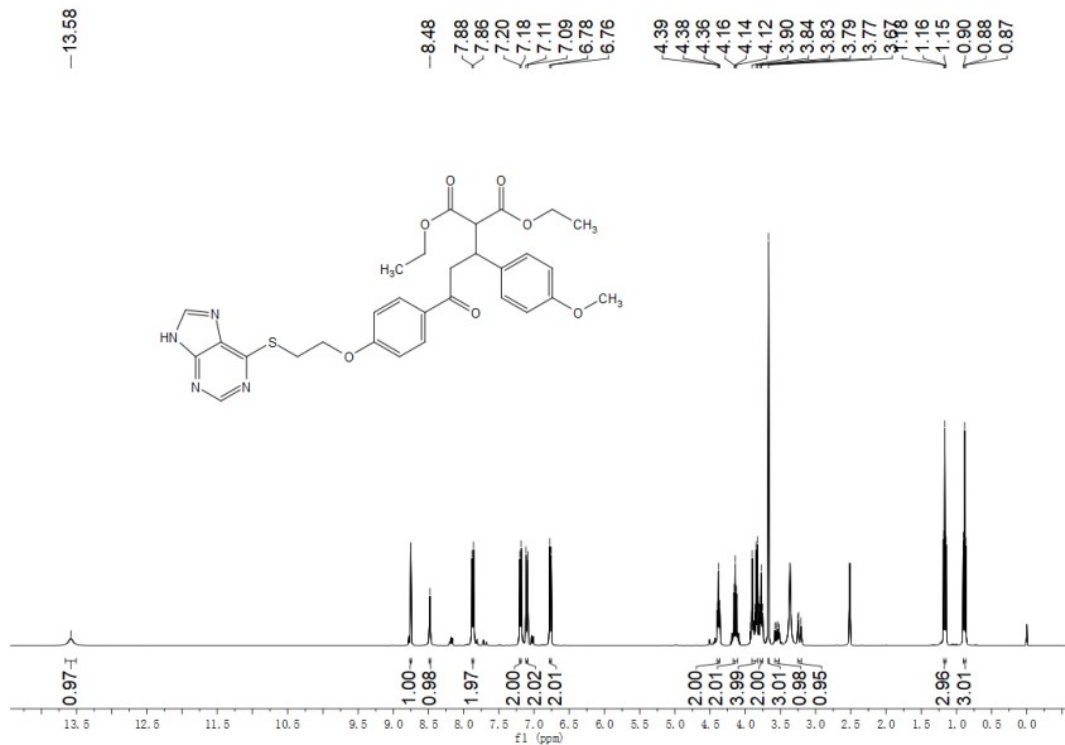


Figure S56. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5I

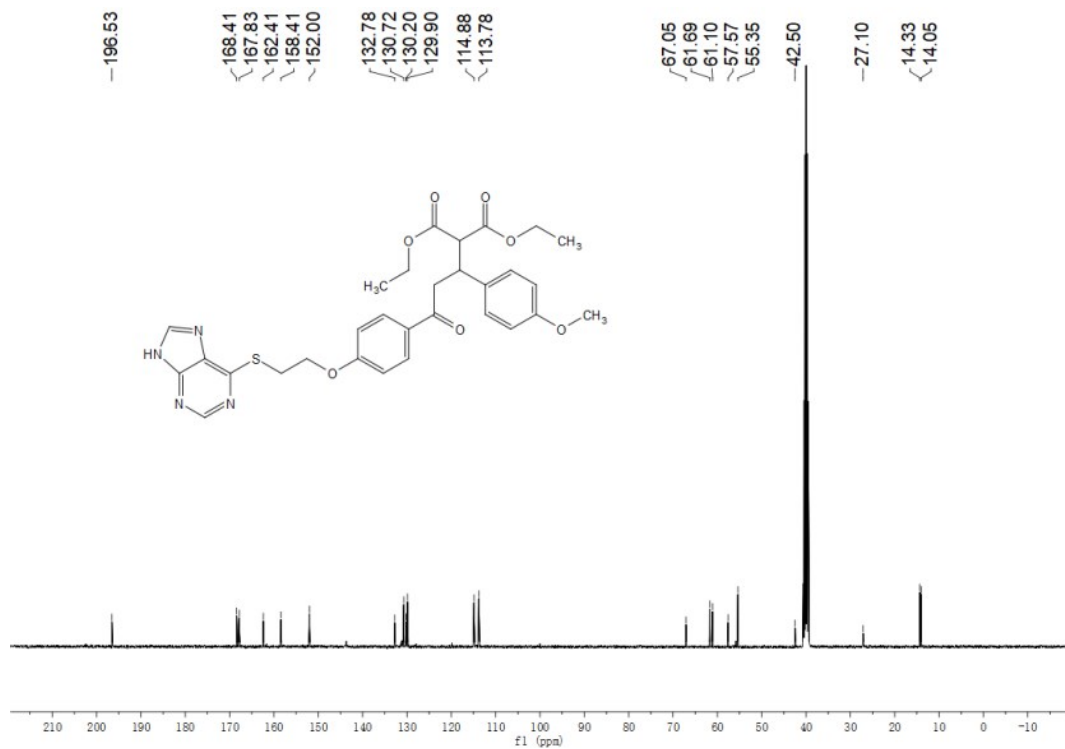


Figure S57. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 5I

20191122116#35 RT: 0.34 AV: 1 NL: 2.17E8  
T: FTMS+pESI Full ms [100.0000-1000.0000]

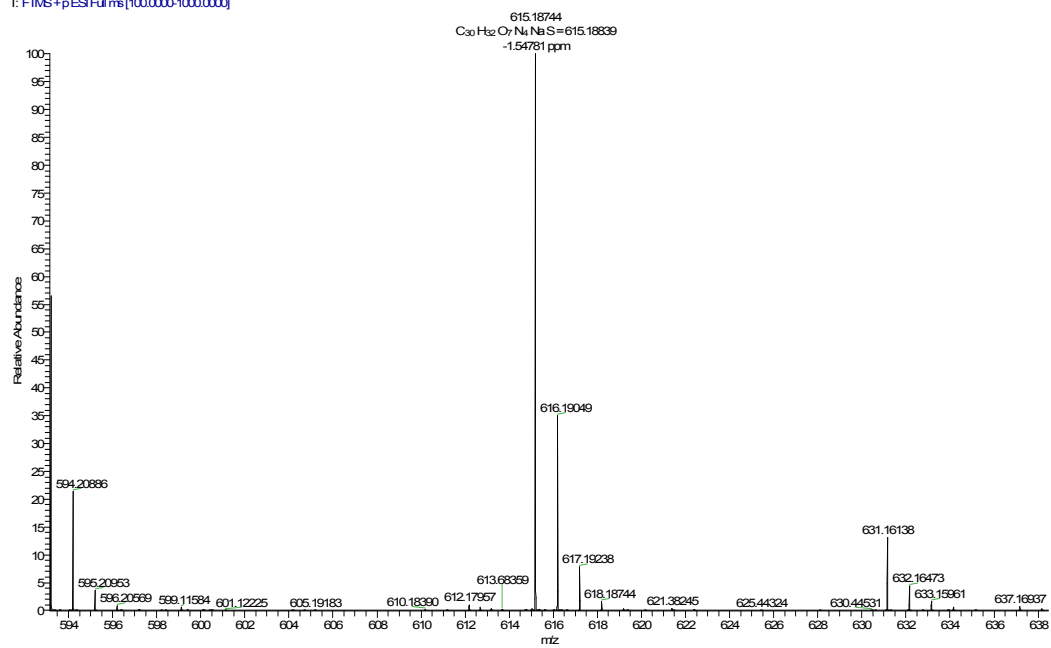


Figure S58. HRMS of compound 5I

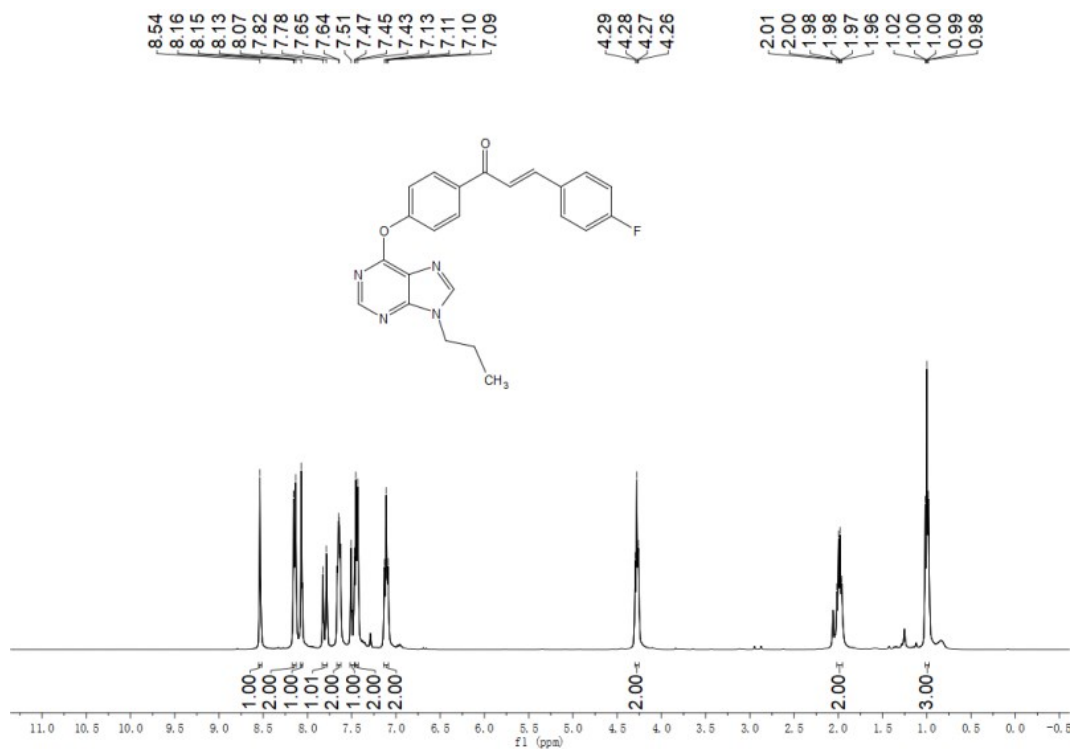


Figure S59. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 7a

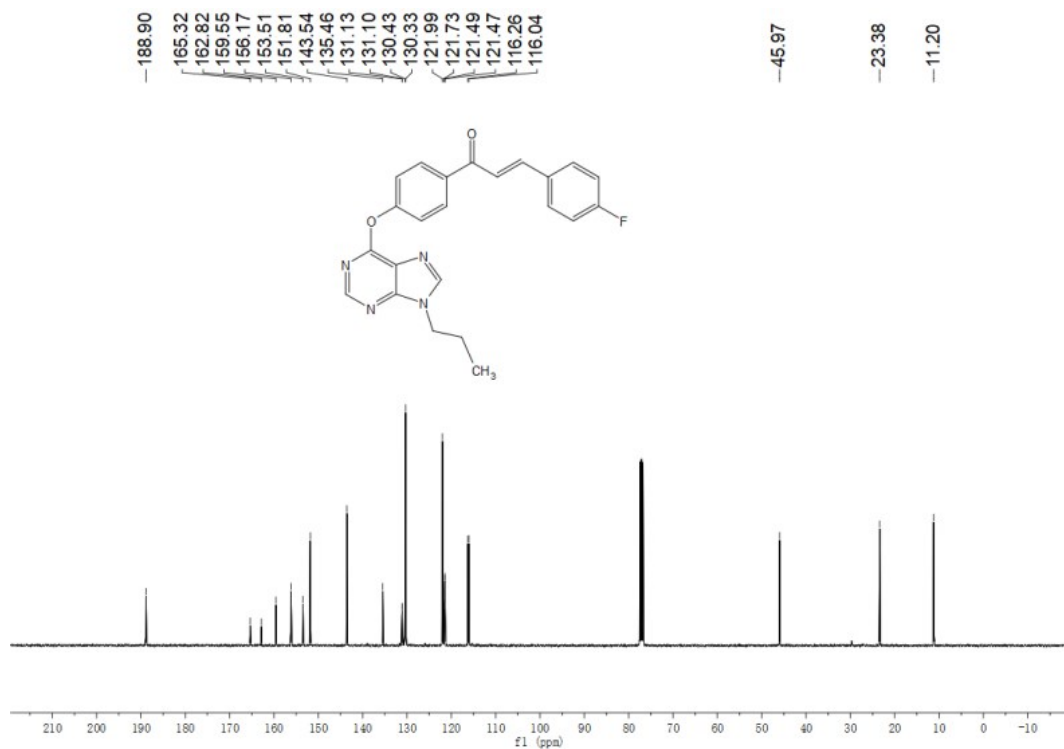


Figure S60.  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of compound **7a**



Figure S61.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of compound **7a**

2019112217 #43 RT: 0.42 AV: 1 NL: 1.63EB  
T: FTMS+p-ESI Full ms [100.0000-1000.0000]

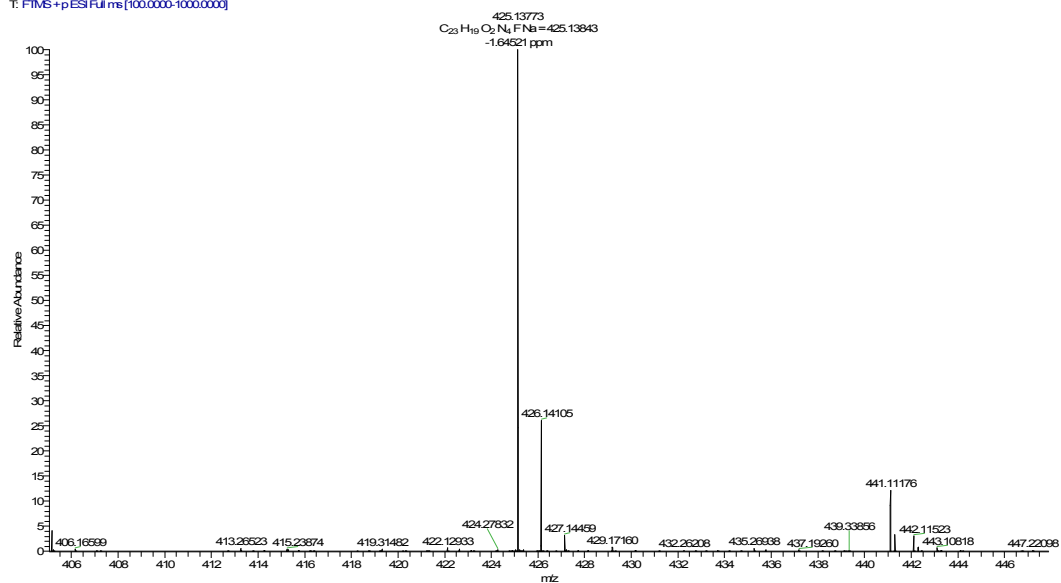


Figure S62. HRMS of compound 7a

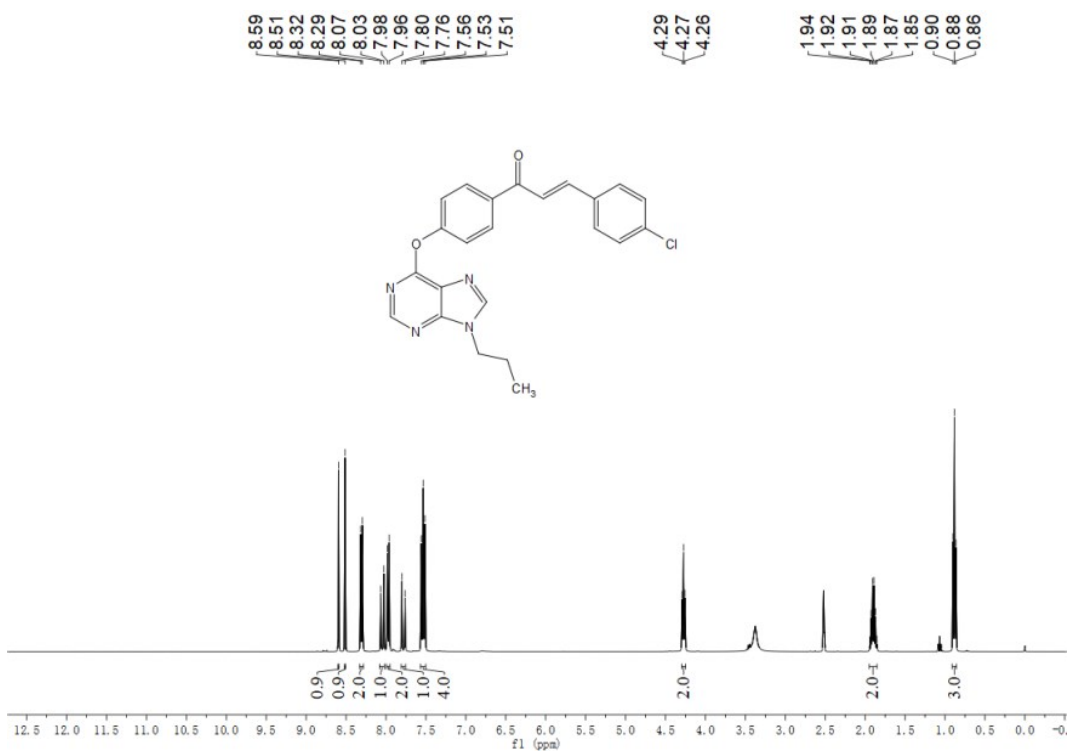


Figure S63. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz) spectrum of compound 7b



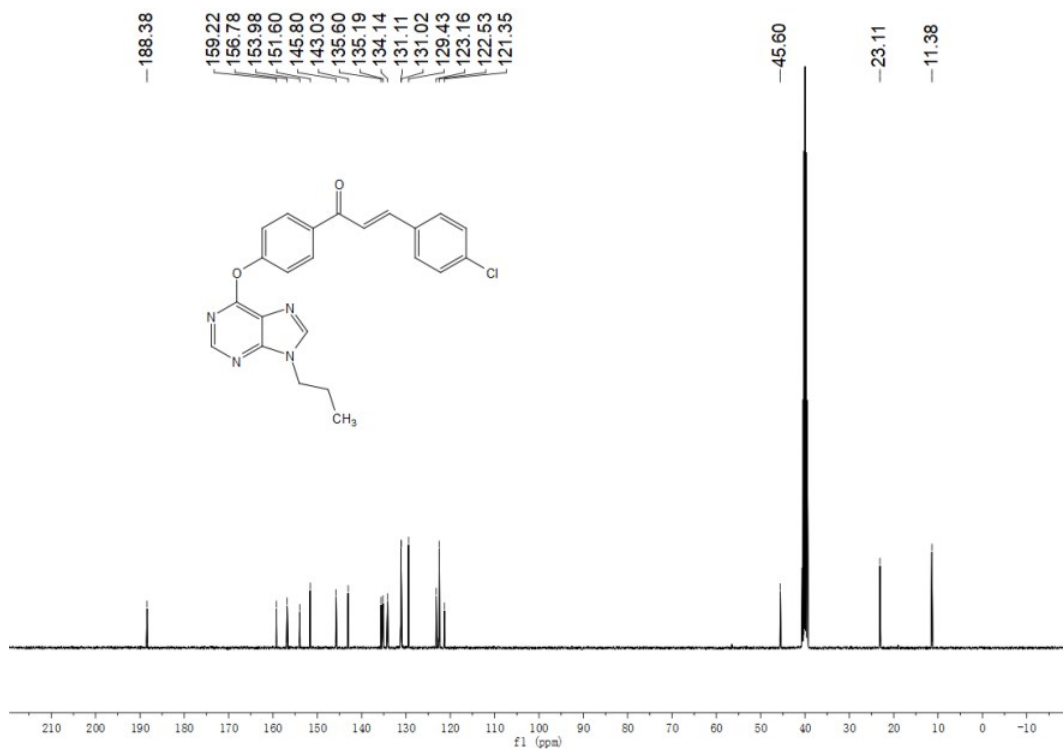


Figure S64. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 7b

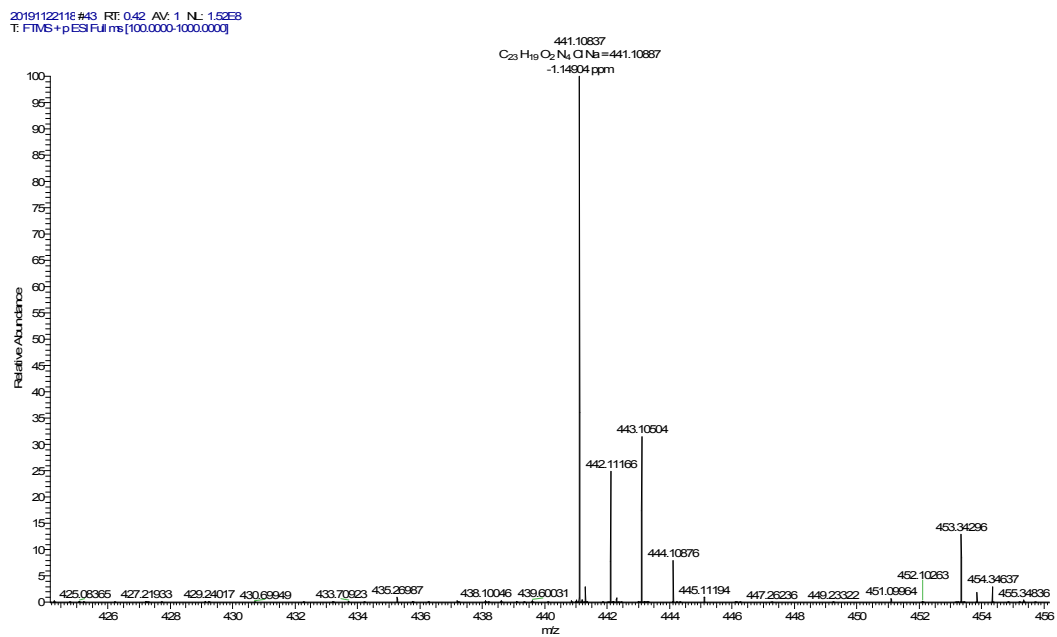
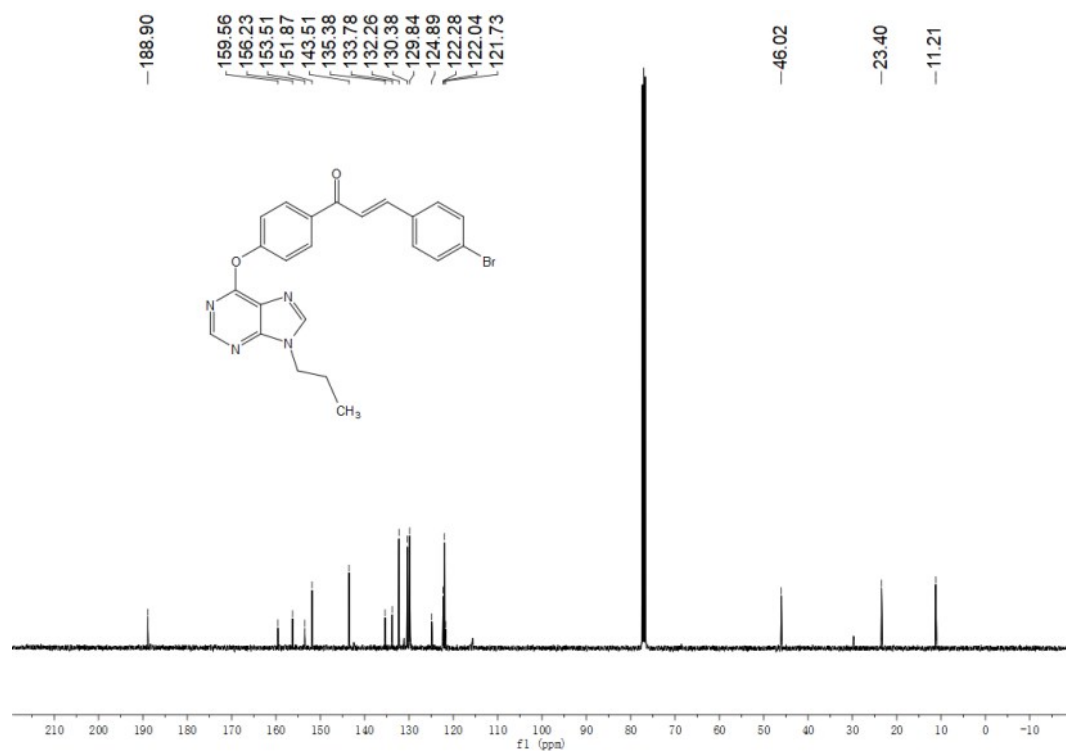
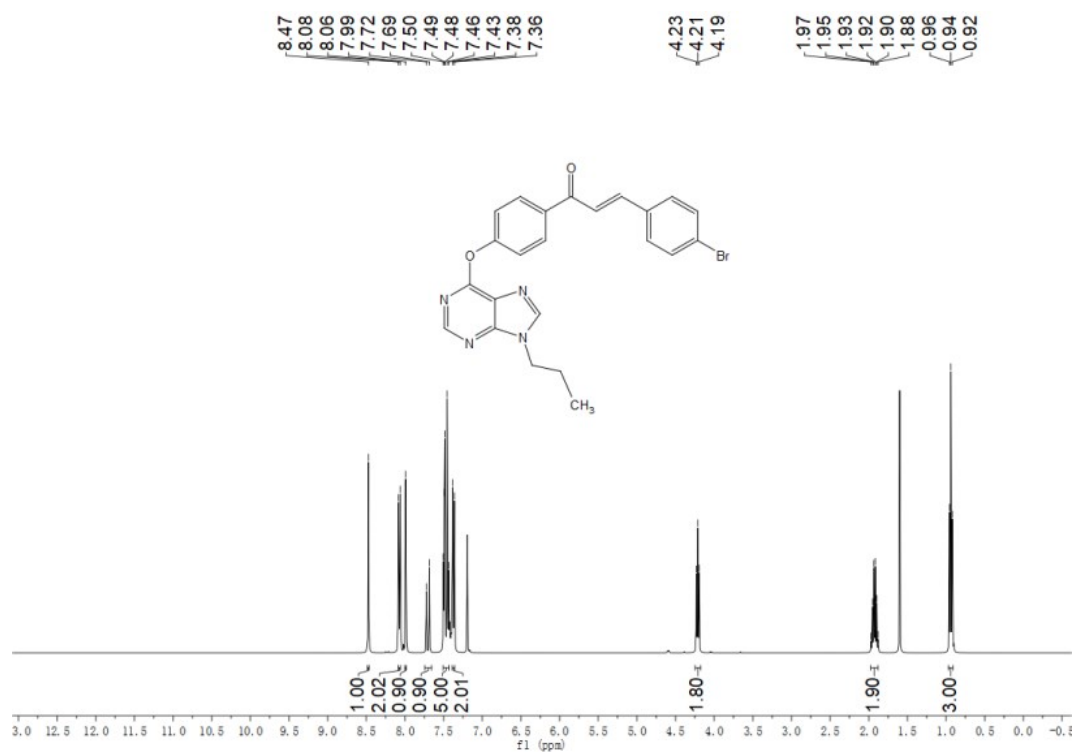


Figure S65. HRMS of compound 7b





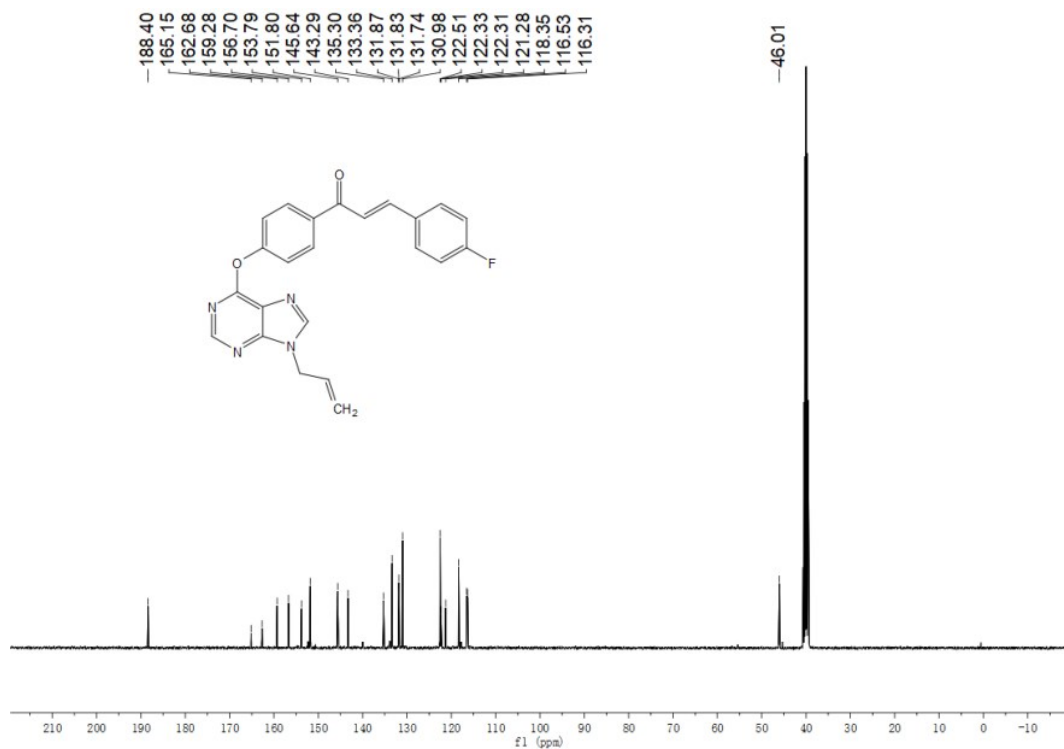


Figure S70. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 7d

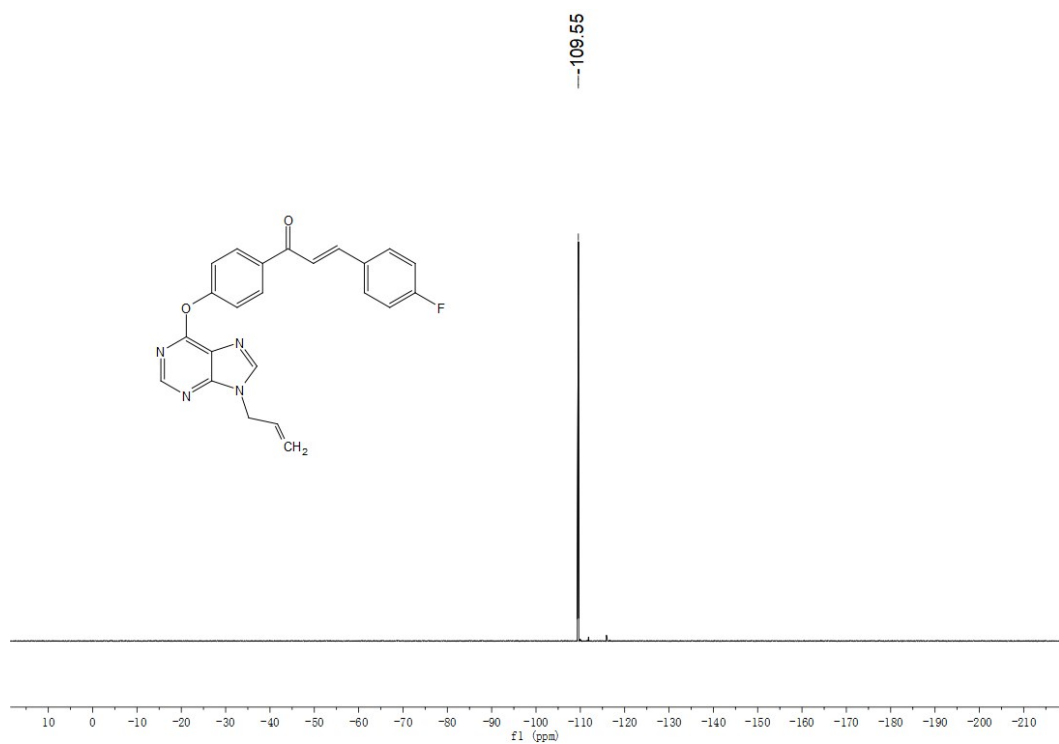


Figure S71. <sup>19</sup>F NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 7d

2019112212C #41 RT: 0.40 AV: 1 NL: 1.99E8  
T: FTMS+pESI Full ms [100.0000-1000.0000]

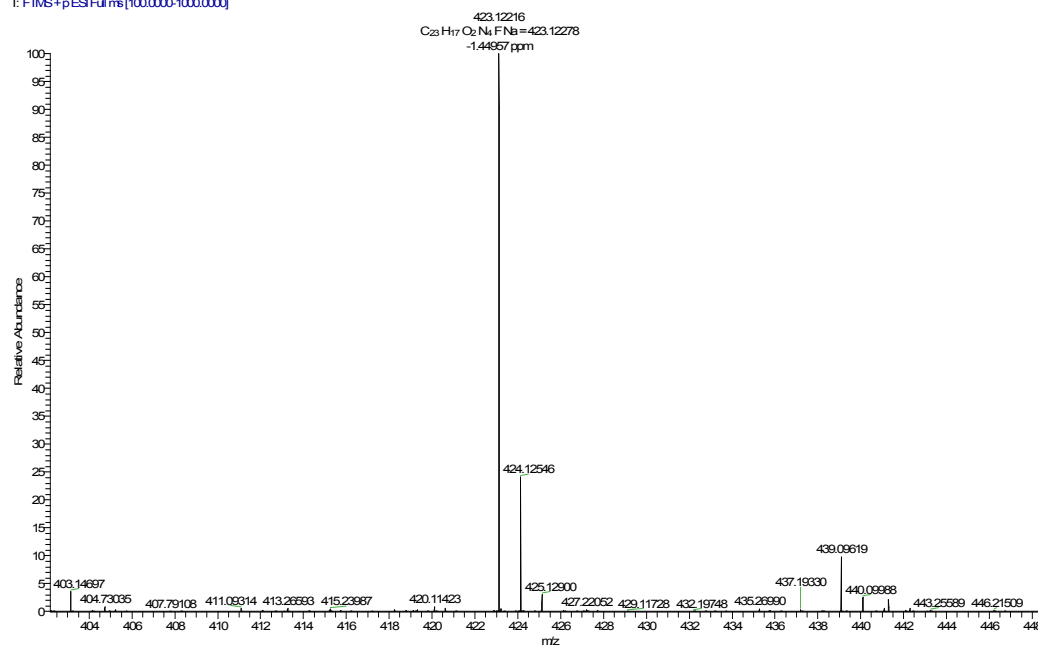


Figure S72. HRMS of compound 7d

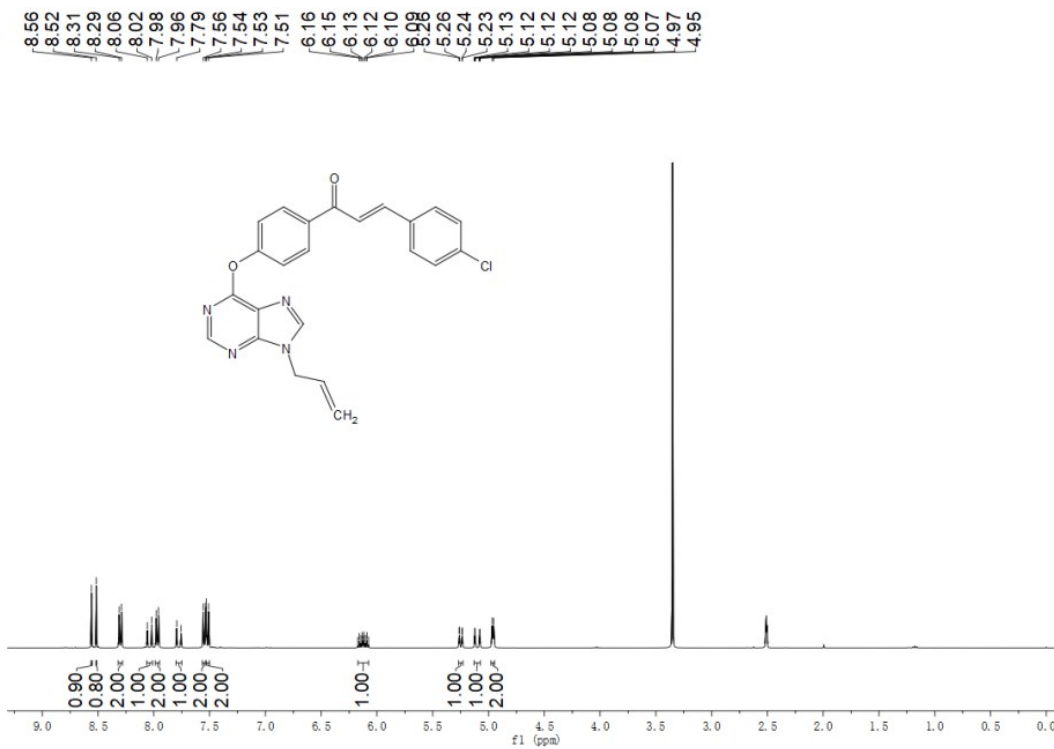


Figure S73. <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 7e

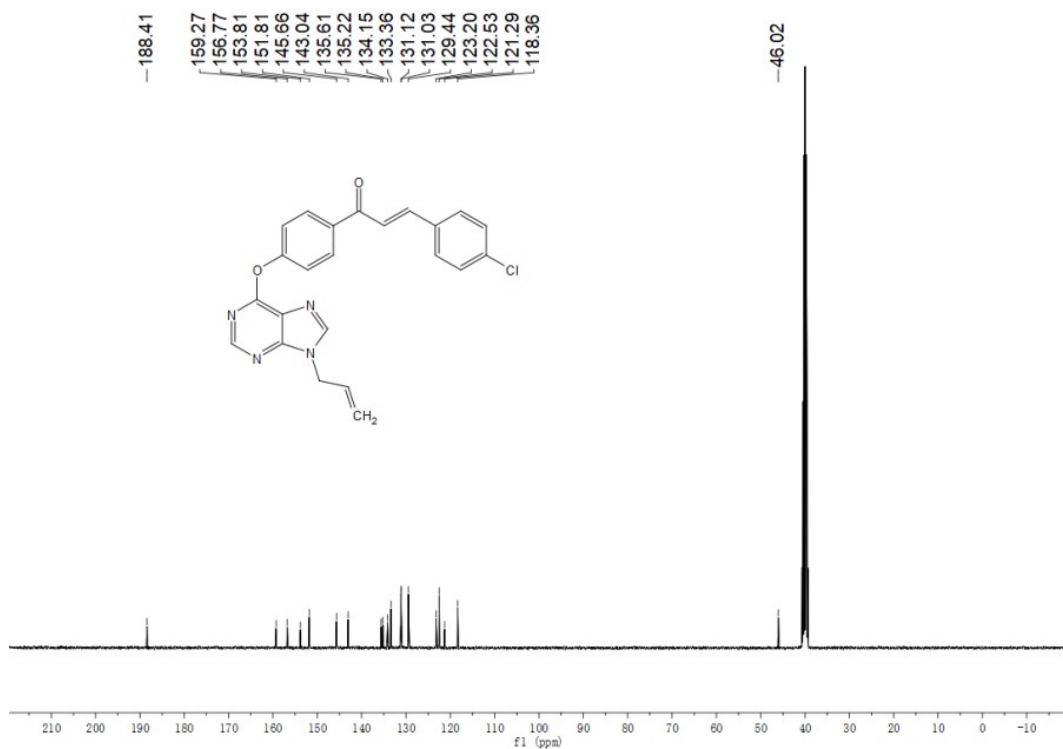


Figure S74. <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>, 400 MHz) spectrum of compound 7e

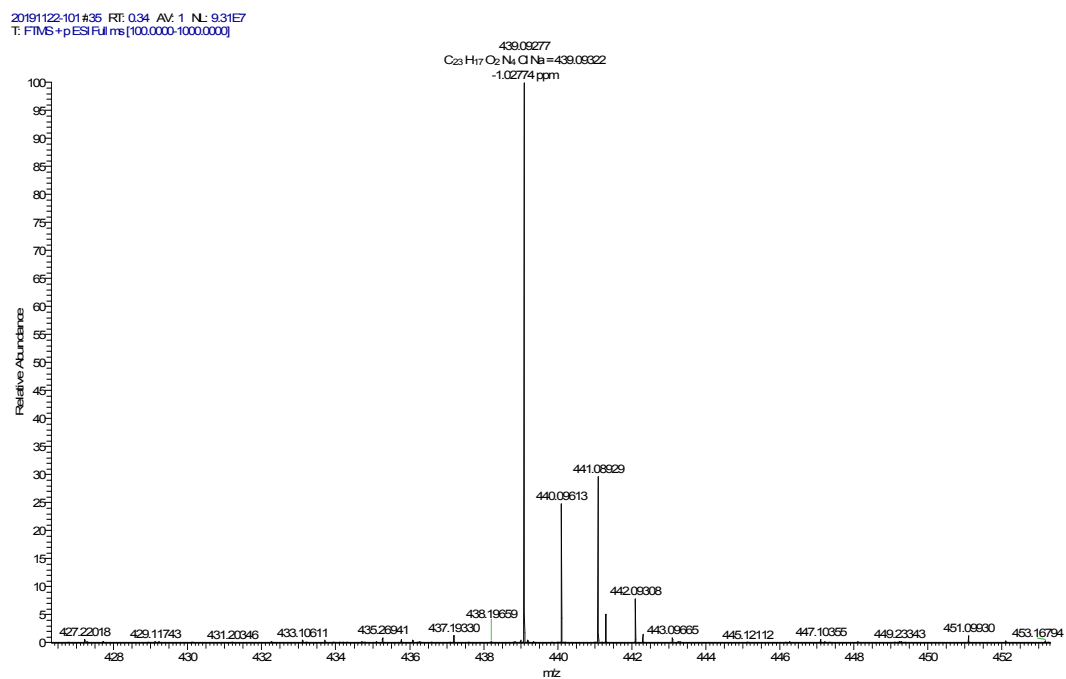


Figure S75. HRMS of compound 7e

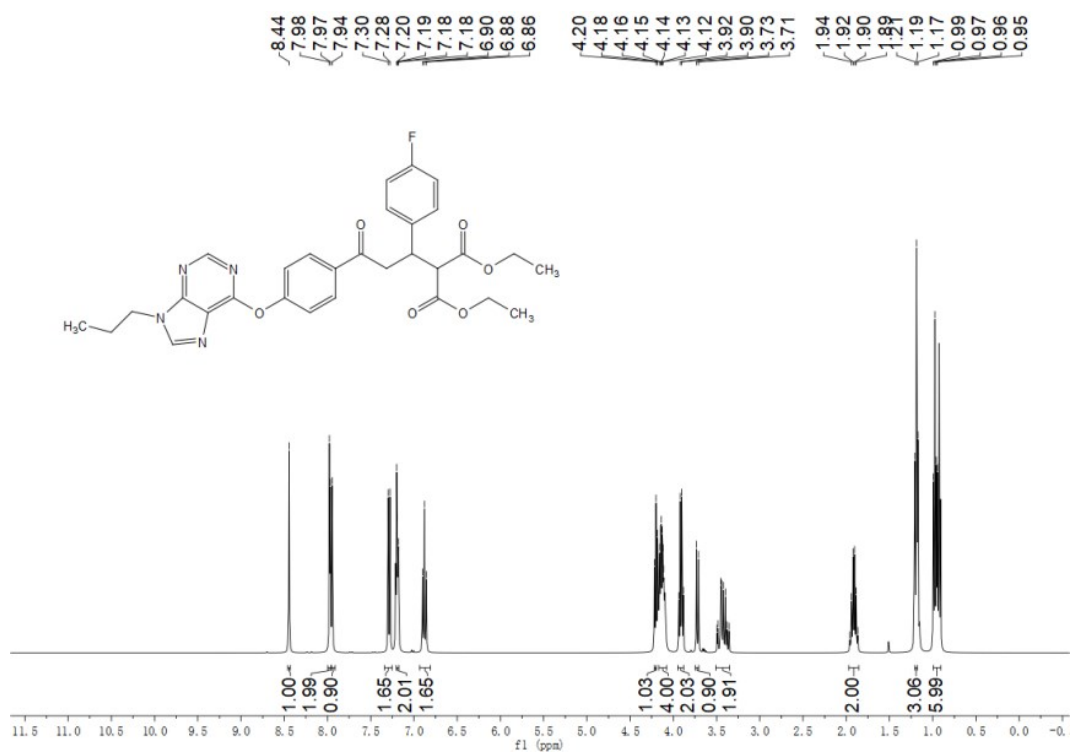


Figure S76. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8a

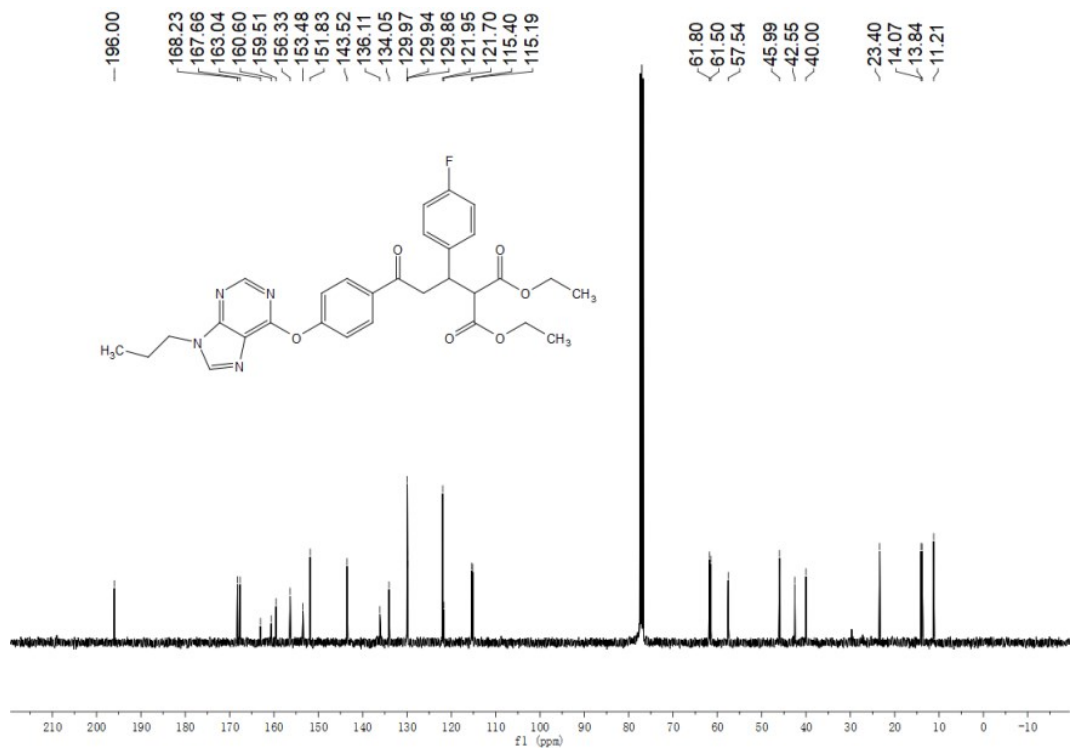


Figure S77. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8a

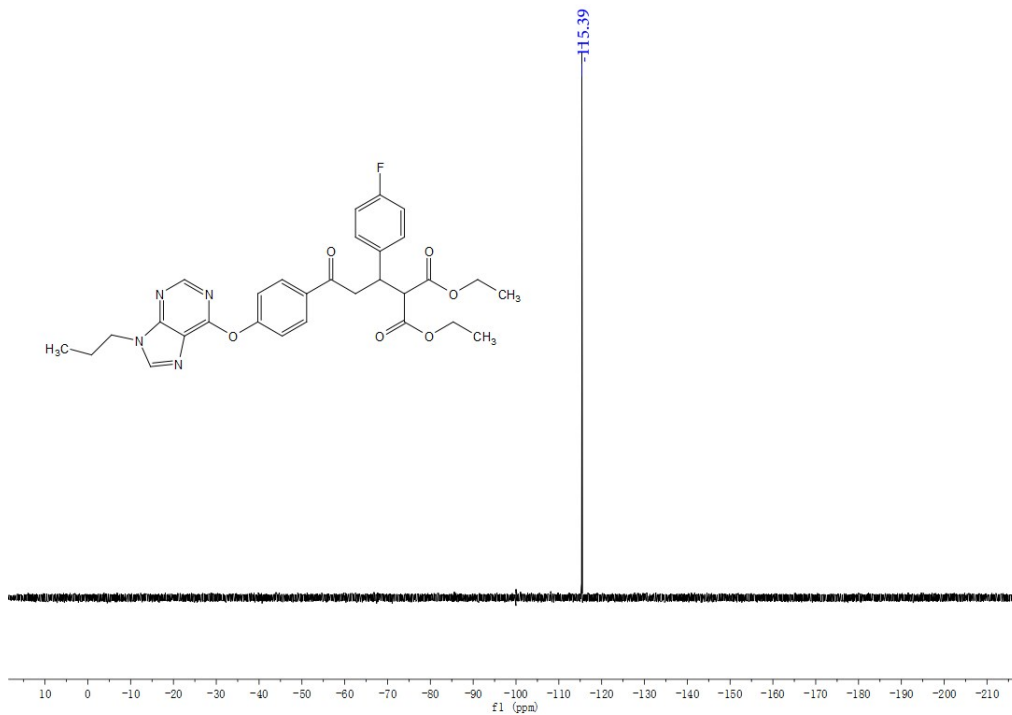


Figure S78.  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 400MHz) spectrum of compound **8a**

20191122-103 #41 RT: 0.40 Av: 1 N1: 3.48EB  
T: FTMS+pESI Full ms [100.0000-1000.0000]

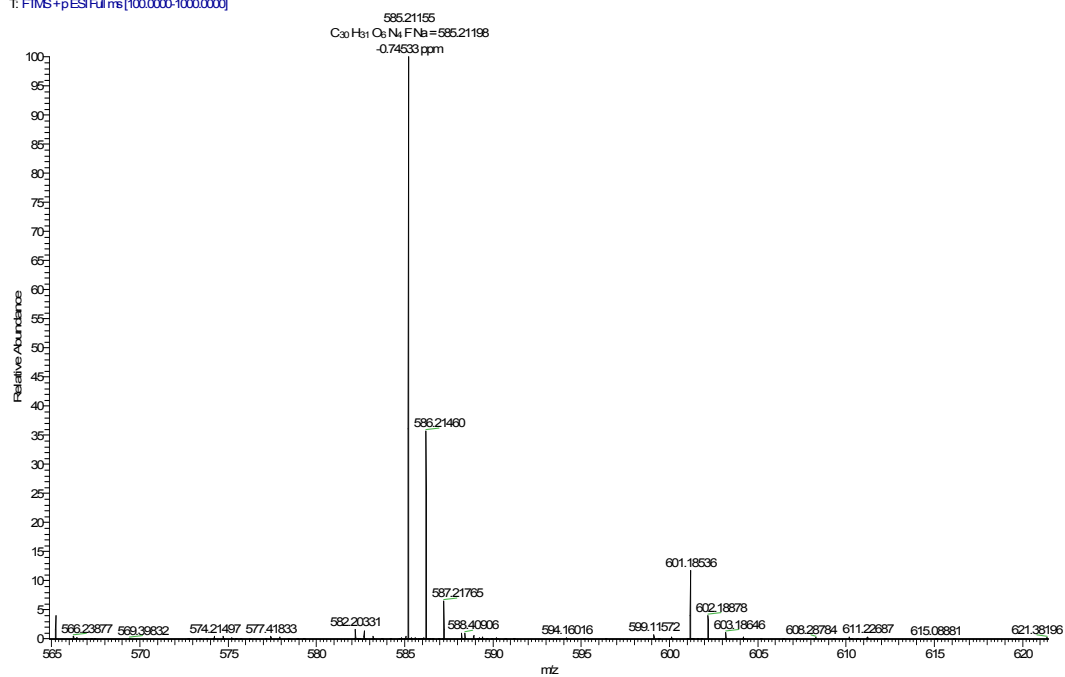


Figure S79. HRMS of compound **8a**



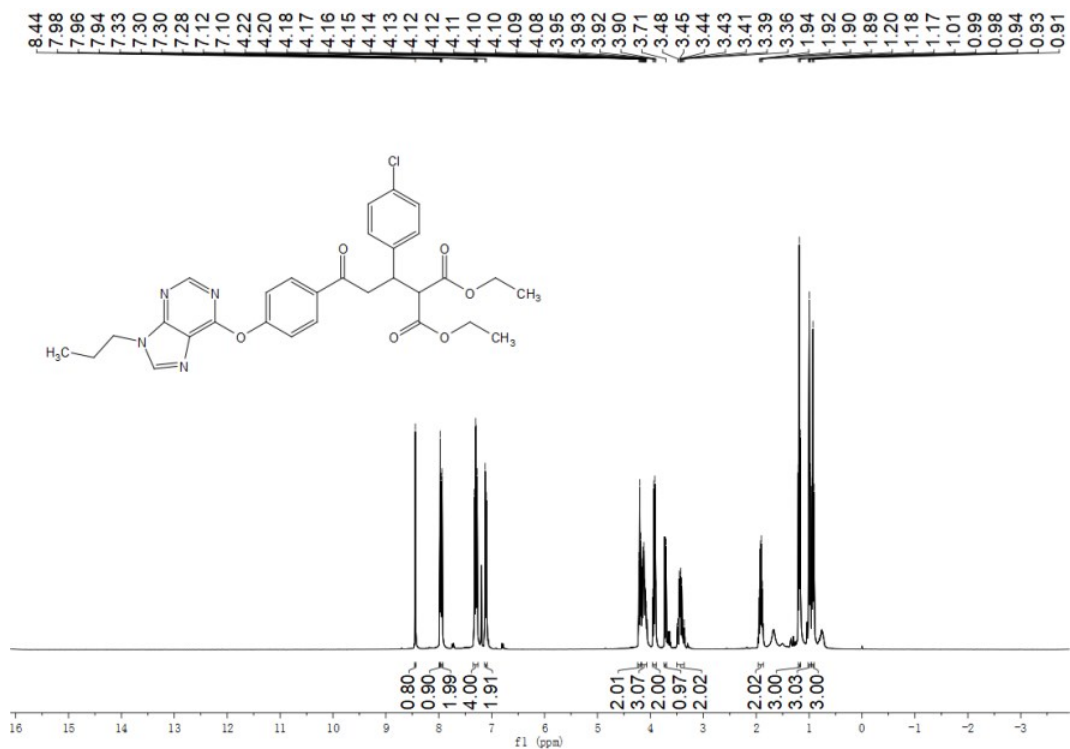


Figure S80. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8b

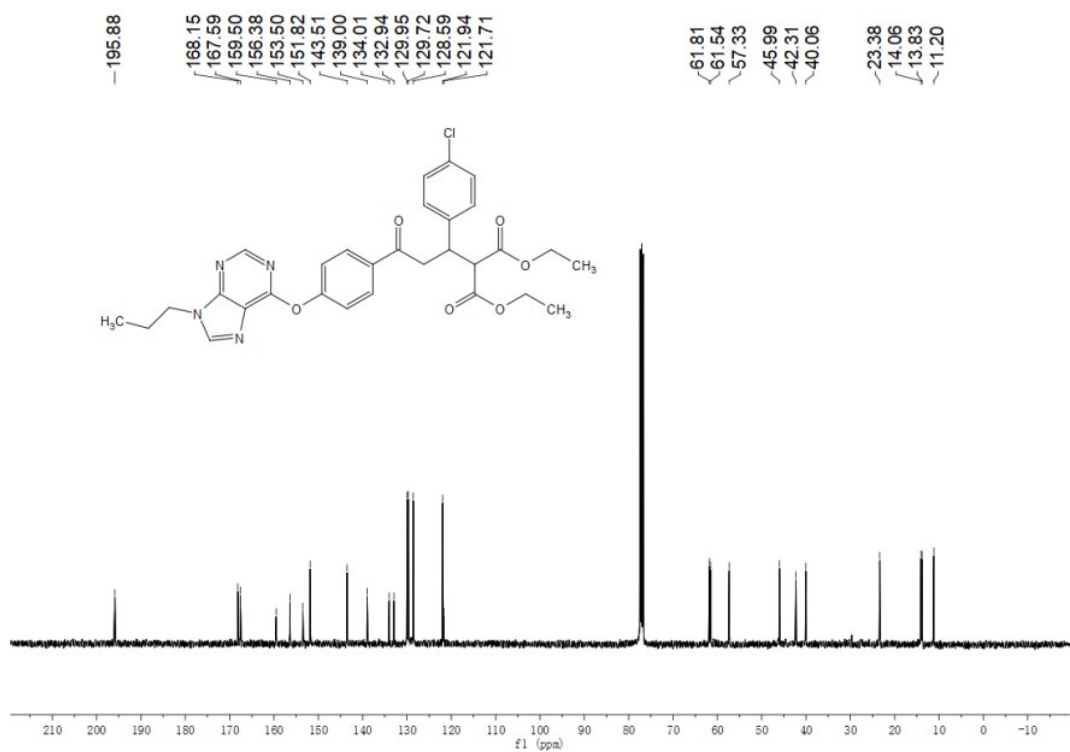


Figure S81. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8b

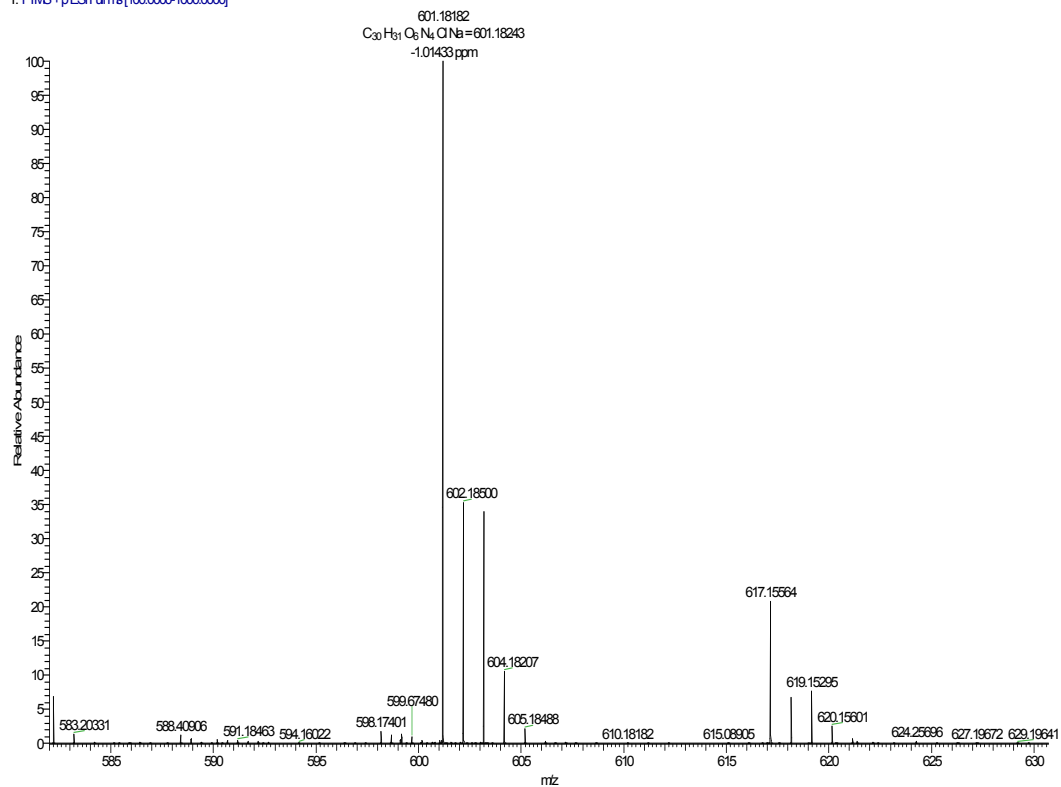


Figure S82. HRMS of compound 8b

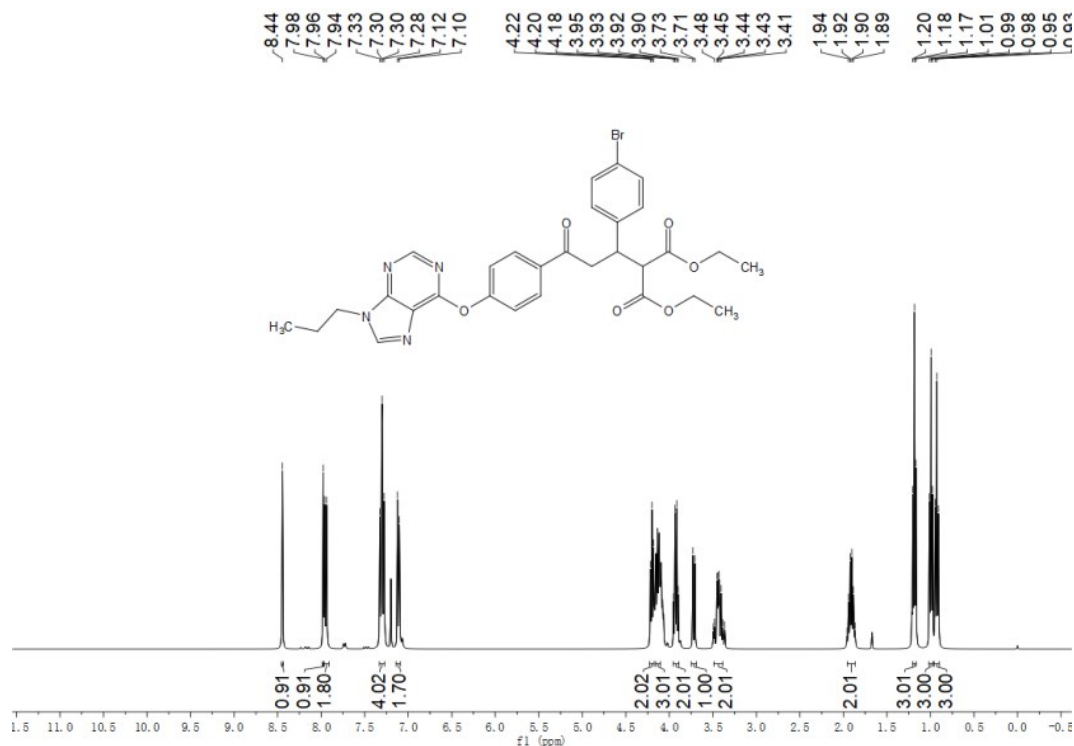


Figure S83. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8c

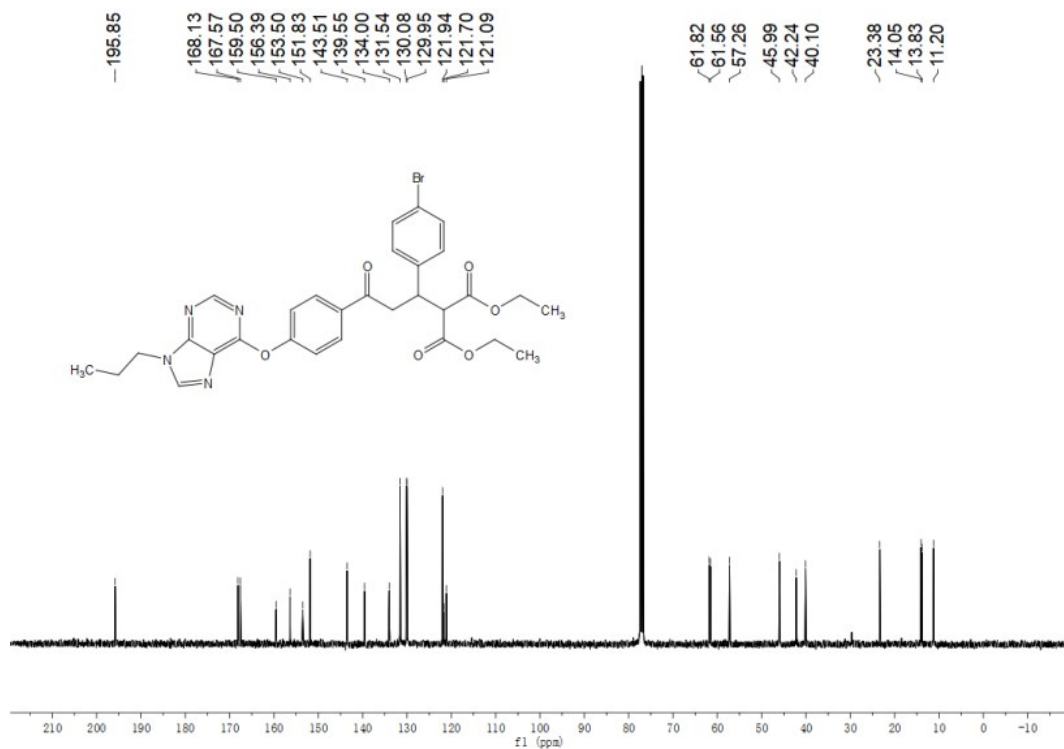


Figure S84. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound **8c**

20191122-105#47 RT: 0.46 AV: 1 N: 6.08E7  
T: FTMS+pESI Full ms [100.0000-1000.0000]

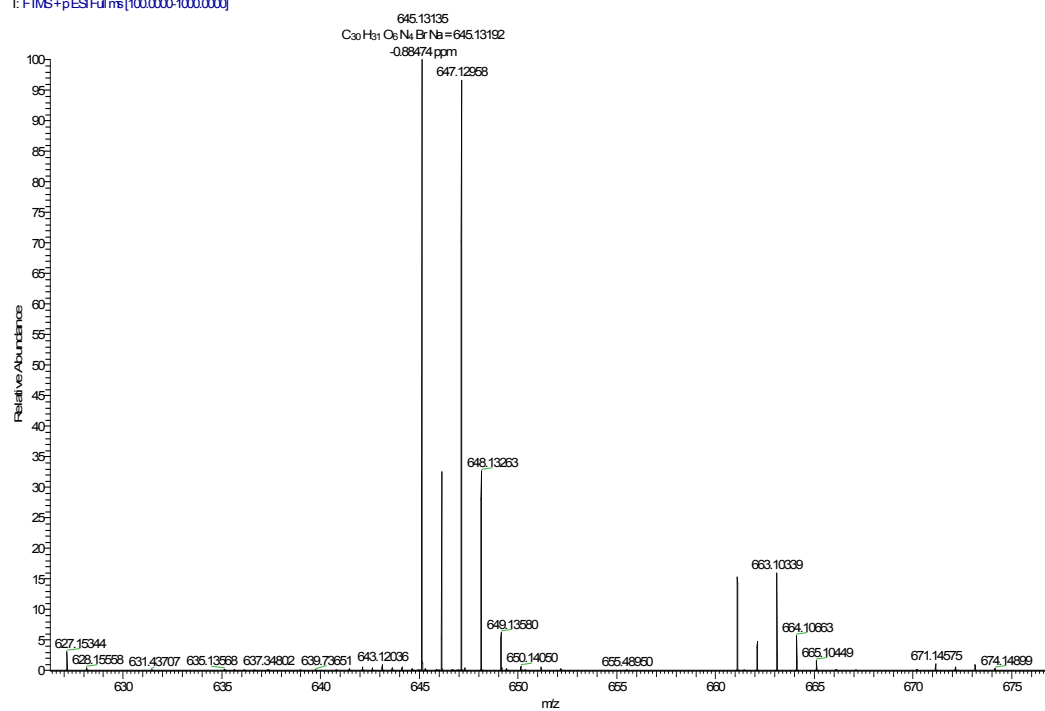


Figure S85. HRMS of compound **8c**

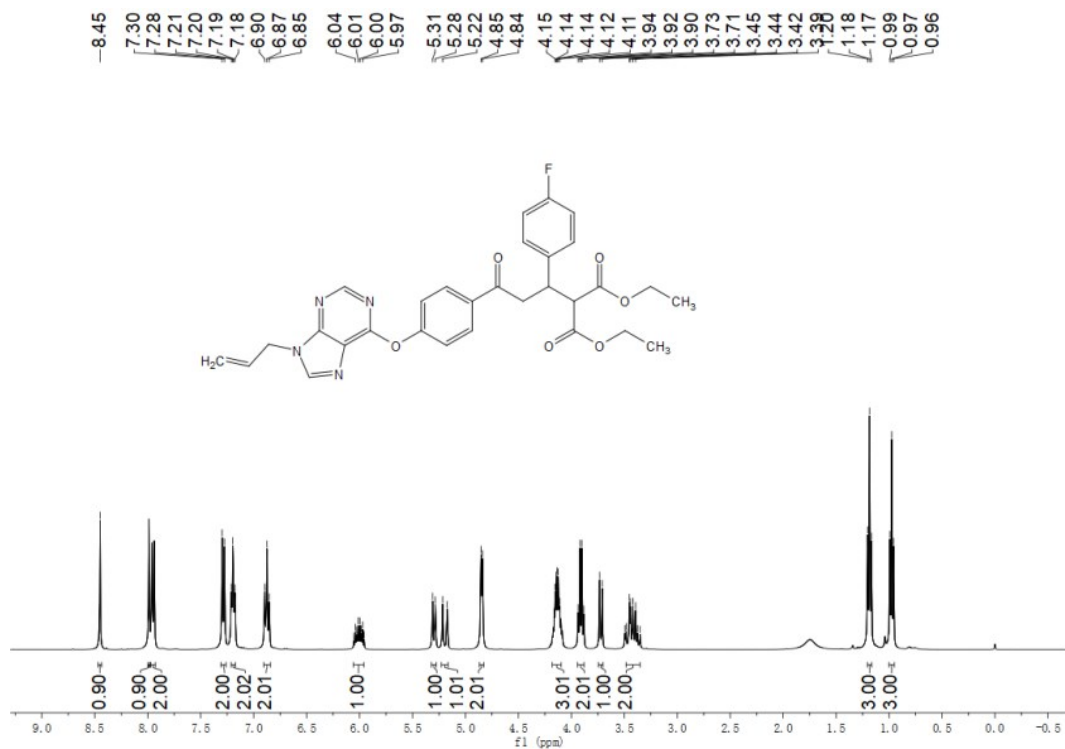


Figure S86. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8d

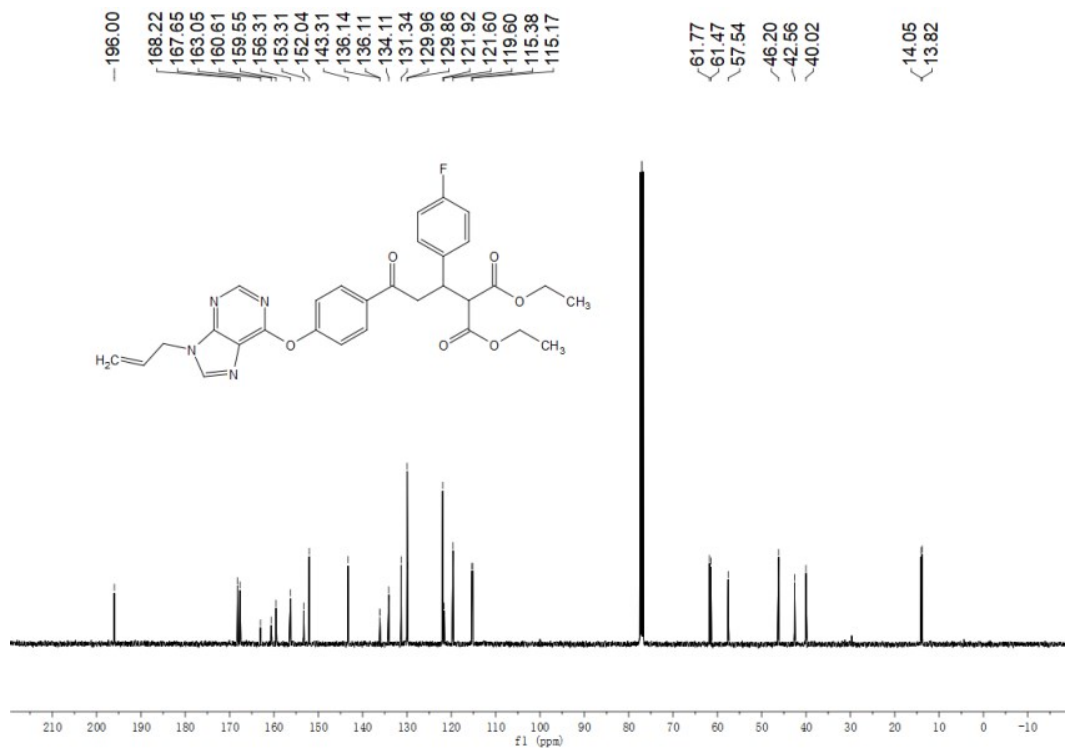
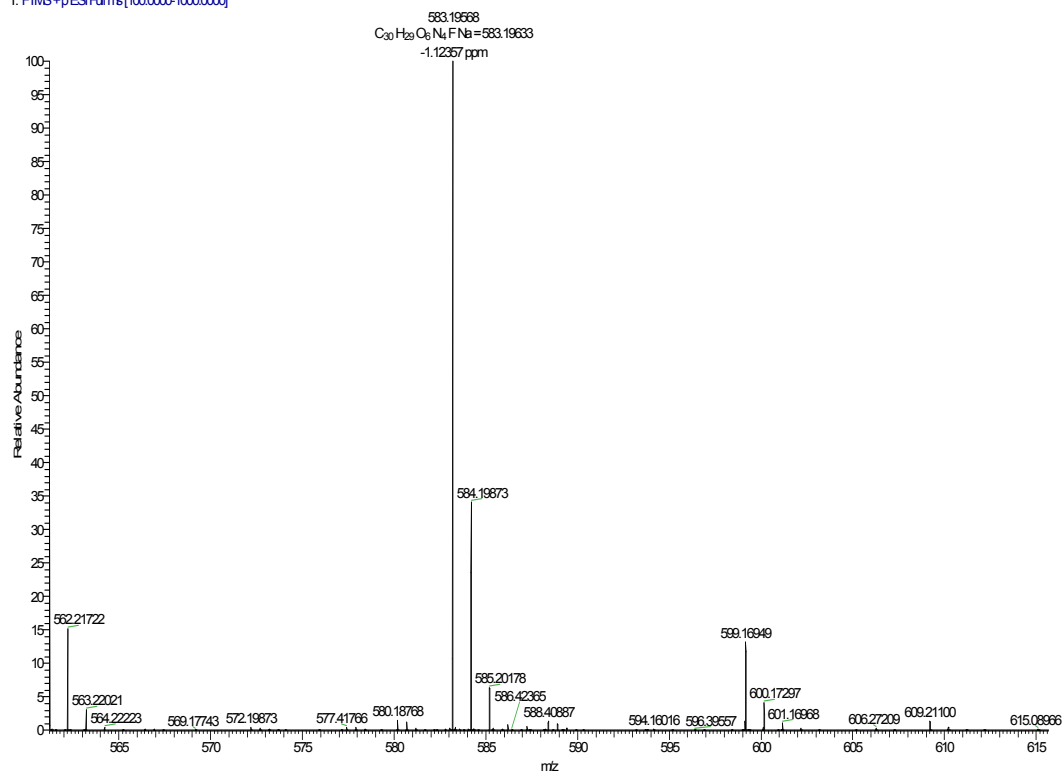


Figure S87. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8d



**Figure S88.**  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ , 400 MHz) spectrum of compound **8d**

20191122-106#41 RT: 0.40 AV: 1 NL: 241EB  
T: FIMS+pESI Full ms [100.0000-1000.0000]



**Figure S89.** HRMS of compound **8d**

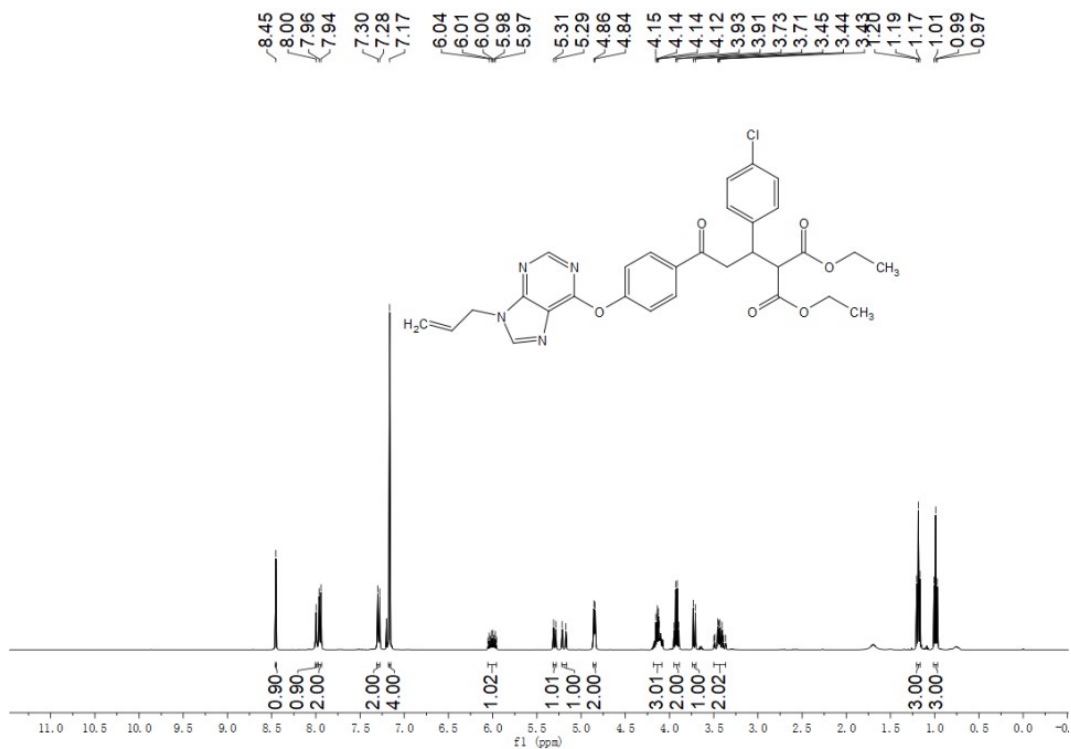


Figure S90. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8e

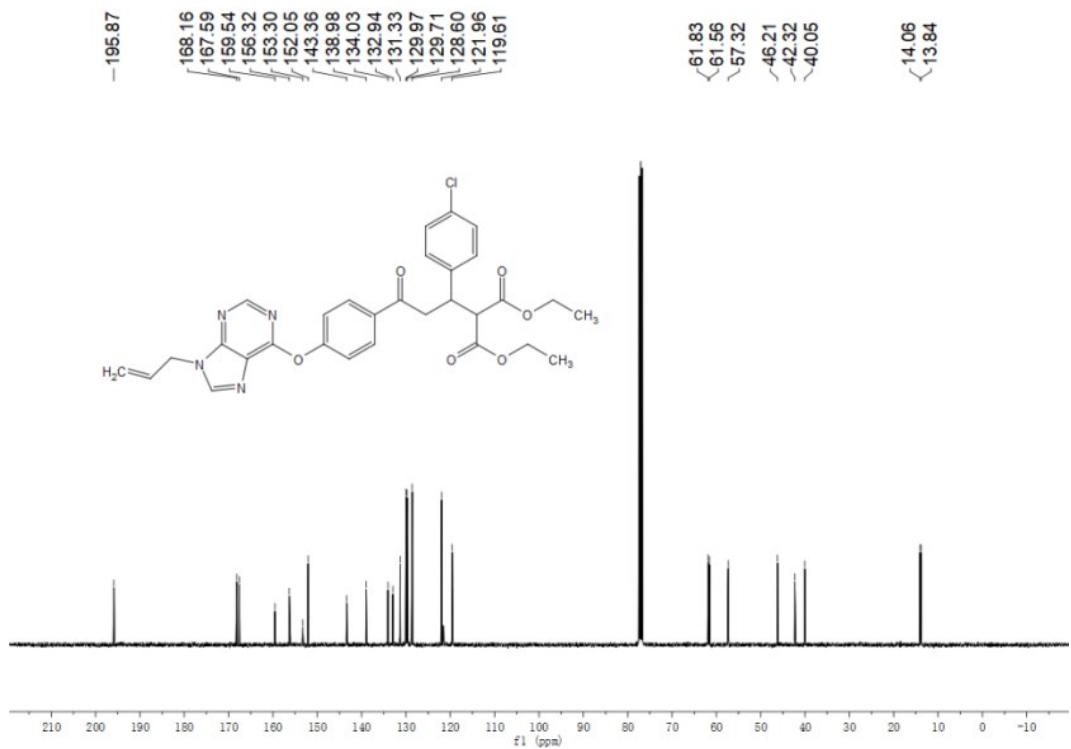


Figure S91. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 400 MHz) spectrum of compound 8e

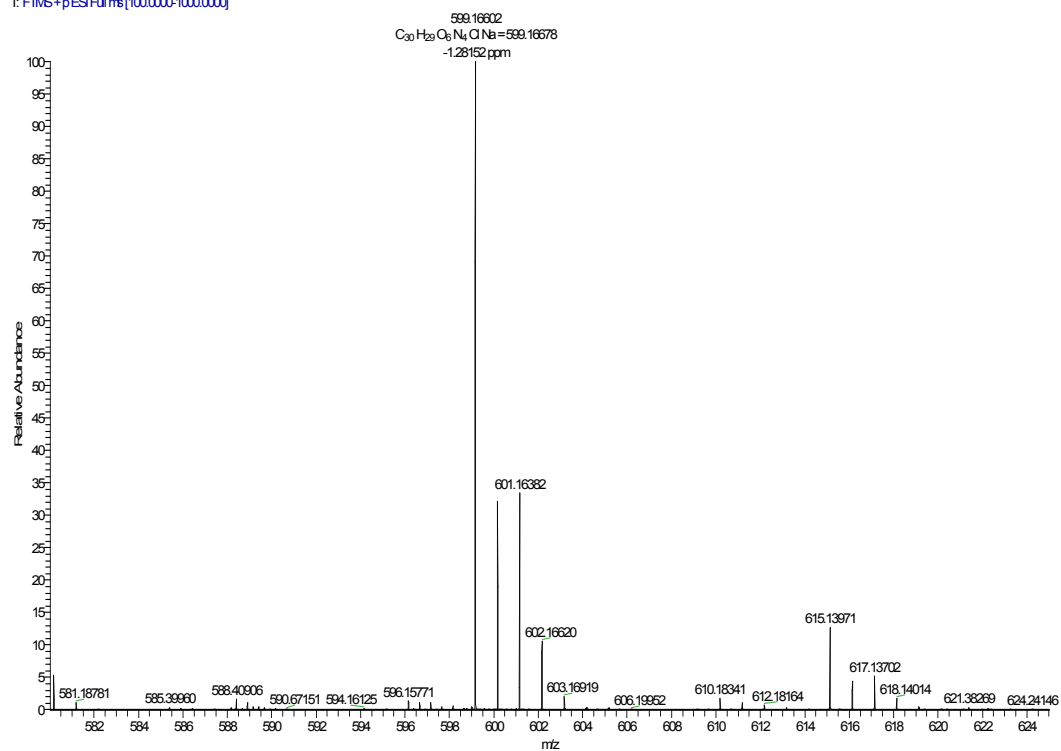


Figure S92. HRMS of compound 8e