Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

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

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Contents

1. General information

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were obtained on a Brookfield Ascend-400 spectrometer (Bruker Germany) using DMSO-d_6 or $CDCl_3$ 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_{254} (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 ± 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 ± 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 ± 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−1 of the compound **5d** solution, then mixed with TMV virus solution in equal volume to obtain 200 mg.L−1 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

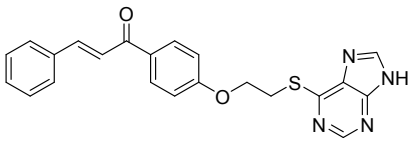
TMV CP was purified according to a previously described method. A range of concentrations of the required compounds (range from 2—5 mM) were incubated with 0.1 mM of purified recombinant TMV CP for 5 min with the Monolith NT Protein Labeling Kit Red (Nano Temper Technologies, München, Germany) in assay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

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

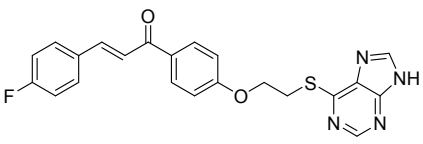
6. FT Studies

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 μL 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

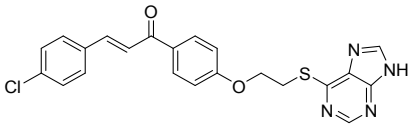


(E)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-phenyl-prop-2-en-1-one ***(4a)***: Yellow solid, m.p. 161.9−163.7 °C, yield, 44%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.56 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.18 (d, J = 8.5 Hz, 2H, 1-Ph-H), 7.94 (d, J = 12.8 Hz, 1H, 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_2-), 3.79 (t, J = 6.5 Hz, 2H, -S-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 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 $C_{22}H_{19}N_4O_2S$ ([M+H]$^+$), 403.12170; found, 403.12232.

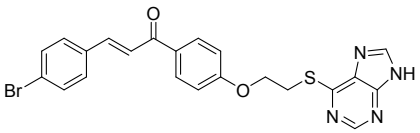


(E)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one ***(4b)****:* Yellow solid, m.p.

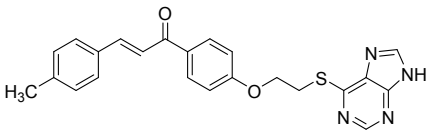
141.0−143.0 °C, yield, 41%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.59 (s, 1H, -NH-), 8.79 (s, 1H, Imidazole-H), 8.50 (s, 1H, Pyrimidine-H), 8.20 (d, J = 8.9 Hz, 2H, 1-Ph-H), 8.01−7.95 (m, 3H, 3-CH=, 3-Ph-H), 7.73 (d, J = 15.6 Hz, 1H, 2-CH=), 7.31 (t, J = 8.8 Hz, 2H, 3-Ph-H), 7.20 (d, J = 8.9 Hz, 2H, 1-Ph-H), 4.44 (t, J = 6.7 Hz, 2H, -O-CH_2-), 3.81 (t, J = 6.6 Hz, 2H, -S-CH_2-); ^{19}F NMR (400 MHz, DMSO-d_6) δ: -109.90 (s); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{22}H_{18}FN_4O_2S$ ([M+H]$^+$), 421.11221; found, 421.11290.



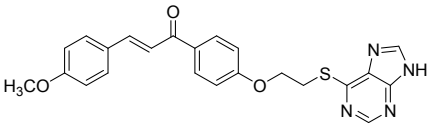
(E)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one ***(4c)***: White solid, m.p. 165.9−166.7 °C, yield, 58%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.76 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.19 (d, J = 8.9 Hz, 2H, 1-Ph-H), 7.99 (d, J = 15.6 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_2-), 3.80 (t, J = 6.7 Hz, 2H, -S-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{22}H_{18}ClN_4O_2S$ ([M+H]$^+$), 437.08289; found, 437.08335.



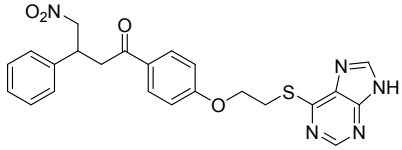
(E)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-bromophenyl)prop-2-en-1-one ***(4d)***: White solid, m.p. 185.7−186.4 °C, yield, 50%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.76 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.19 (d, J = 8.9 Hz, 2H, 1-Ph-H), 7.99 (d, J = 15.6 Hz, 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_2-), 3.80 (t, J = 6.7 Hz, 2H, -S-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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), 123.2 (s), 123.2 (s), 115.1 (s), 115.1 (s), 67.1 (s), 27.1 (s); HRMS (ESI): calcd for $C_{22}H_{17}BrNaN_4O_2S$ ([M+Na]$^+$), 503.01404; found, 503.01478.



(E)-1-(4-(2-((9H-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%; ^{1}H NMR (400 MHz, DMSO-d_6) 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_2-), 3.81 (t, J = 6.6 Hz, 2H, -S-CH_2-), 2.36 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{20}N_4O_2NaS$ ([M+Na]$^+$), 439.11945; found, 439.11992.

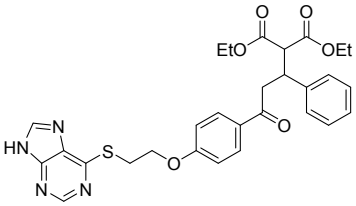


(E)-1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (***4f***): Yellow solid, m.p. 157.7–158.6 °C, yield, 42%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.59 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 8.17 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.86 (d, *J* = 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_2-), 3.80 (t, *J* = 6.7 Hz, 2H, -S-CH_2-), 3.36 (s, 3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{20}N_4O_3NaS$ ([M+Na]$^+$), 455.11414; found, 455.11483.

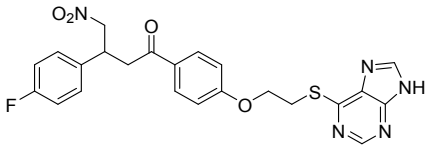


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-4-nitro-3-phenylbutan-1-one (***5a***): White solid, m.p. 99.0−100.0 °C, yield, 20%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.46 (s, 1H, Pyrimidine-H), 7.92 (d, *J* = 8.9 Hz, 2H, 1-Ph-H), 7.36 (s, 2H, 3-Ph-H), 7.29 (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_2-NO_2), 4.38 (t, *J* = 6.5 Hz, 2H, -O-CH_2-), 4.08−3.98 (m, 1H, -CH-), 3.77(t, *J* = 6.4Hz, 2H, -S-CH_2-), 3.55−3.40 (m, 2H, -CO-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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

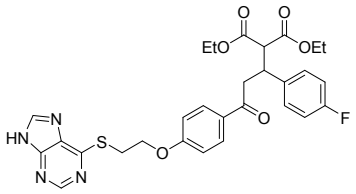
(s), 128.9 (s), 128.3 (s), 128.3 (s), 127.6 (s), 114.9 (s), 80.2 (s), 67.1 (s), 41.2 (s), 41.2 (s), 27.0 (s); HRMS (ESI): calcd for $C_{23}H_{21}N_5O_4NaS$ ([M+Na]$^+$), 486.11960; found, 455.12065.



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%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 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_2-), 4.19−4.08 (m, 2H, -CO-CH_2-), 3.98−3.92 (m, 2H, -S-CH_2-), 3.84−3.75 (m, 4H, 2×-CH_2-), 3.65−3.56 (m, 1H, -CH-), 3.31−3.24 (m, 1H, -CH-COO-), 1.16 (t, J = 7.1 Hz, 3H, -CH_3), 0.85 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 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.

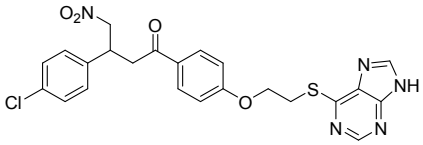


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)-4-nitrobutan-1-one (***5c***): White solid, m.p. 125.1−126.1 °C, yield, 22%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.59 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.93 (d, J = 8.8 Hz, 2H, 1-Ph-H), 7.43 (dd, J = 8.5, 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_2-NO_2), 4.39 (t, J = 6.4 Hz, 2H, -O-CH_2-), 4.08−4.01 (m, 6.8 Hz, 1H, -CH-), 3.77 (t, J = 6.3 Hz, 2H, -S-CH_2-), 3.55–3.41 (m, 2H, -CO-CH_2-); ^{19}F NMR (400 MHz, DMSO-d_6) δ: -115.51 (s); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 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.

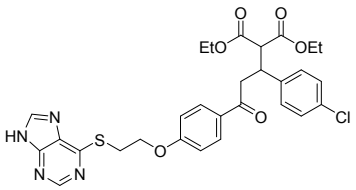


Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-fluorophenyl)-3-oxo-1-phenylpropyl)malonate (***5d***):

Yellow solid, m.p. 110.0−112.0 °C, yield, 27%; ^{1}H NMR (400 MHz, DMSO-d_6) 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_2-), 4.21−4.07 (m, 2H, -CO-CH_2-), 3.96 (s, 2H, -S-CH_2-), 3.88−3.72 (m, 4H, 2×-CH_2-), 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_3), 0.86 (t, J = 6.9 Hz, 3H, -CH_3); ^{19}F NMR (400 MHz, DMSO-d_6) δ: -116.00 (s); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{29}H_{29}FN_4O_6NaS$ ([M+Na]$^+$), 603.16772; found, 603.16840.

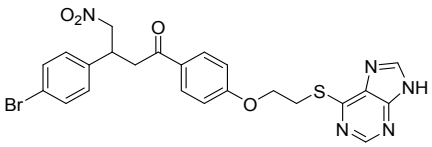


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-chlorophenyl)-4-nitrobutan-1-one ***(5e)***: White solid, m.p. 106.3−107.3 °C, yield, 35%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.58 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 2H, Pyrimidine-H), 7.92 (d, J = 8.9 Hz, 2H, 1-Ph-H), 7.41 (d, J = 8.6 Hz, 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_2-NO_2), 4.38 (t, J = 6.6 Hz, 2H, -O-CH_2-), 4.06−4.00 (m, 1H, -CH-), 3.77 (t, J = 6.6 Hz, 2H, -S-CH_2-), 3.55−3.41 (m, 2H, -CO-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{20}ClN_5O_4NaS$ ([M+Na]$^+$), 564.03070; found, 564.03116.

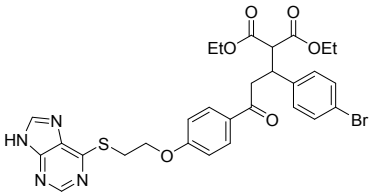


Diethyl 2-(3-(4-(2-((9*H*-purin-6-yl)thio)ethoxy)phenyl)-*1-(4-chlorophenyl)-3-oxo-1-phenylpropyl)malonate* ***(5f)***: Y ellow solid, m.p. 57.3−58.3 °C, yield, 40%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.86 (d, J = 8.9 Hz, 2H, 1-Ph-H), 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_2-), 4.20–4.08 (m, 2H, -CO-CH_2-), 3.99−3.82 (m, 4H, 2×CH_2-), 3.76 (t, J = 6.6 Hz, 2H, -S-CH_2-), 3.59 (d 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_3), 0.88 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 196.3 (s), 168.2 (s), 167.7 (s), 167.7 (s), 162.5 (s),

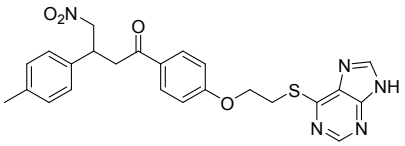
162.5 (s), 152.0 (s), 152.0 (s), 152.0 (s), 140.1 (s), 131.8 (s), 131.8 (s), 130.8 (s), 130.8 (s),130.7 (s),130.1 (s), 128.4 (s), 128.4 (s), 114.9 (s), 114.9 (s), 67.1 (s), 61.8 (s), 61.3 (s), 57.1 (s), 42.2 (s), 40.6 (s), 27.1 (s), 14.3 (s), 14.00 (s); HRMS (ESI): calcd for $C_{29}H_{29}ClN_4O_6NaS$ ([M+Na]$^+$), 619.13800; found, 619.13885.



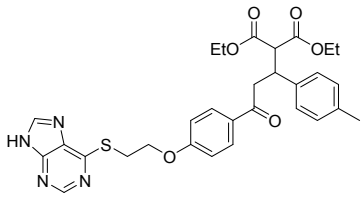
1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-bromophenyl)-4-nitrobutan-1-one (***5g***): White solid, m.p. 60.0–61.5 °C, yield, 21%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.92 (d, J = 8.9 Hz, 2H, 1-Ph-H), 7.28 (d, J = 8.7 Hz, 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_2-NO_2), 4.39 (t, J = 6.6 Hz, 2H, -O-CH_2-), 4.07–3.93 (m, 1H, -CH-Ph), 3.77 (t, J = 6.6 Hz, 2H, -S-CH_2-), 3.51–3.39 (m, 2H, -CO-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{20}BrN_5O_4NaS$ ([M+Na]$^+$), 564.03070; found, 564.03116.



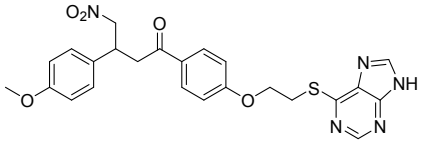
Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-bromophenyl)-3-oxo-1-phenylpropyl)malonate (***5h***): Yellow solid, m.p. 54.5–55.5 °C, yield, 27%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.74 (s, 1H, Imidazole-H), 8.47 (s, 1H, Pyrimidine-H), 7.86 (d, J = 8.9 Hz, 2H, 1-Ph-H), 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_2-), 4.18–4.09 (m, 2H, -CO-CH_2-), 3.98–3.95 (m, 1H, -CH_2-), 3.85 (q, J = 7.0 Hz, 3H, -CH_2-), 3.77 (t, J = 6.6 Hz, 2H, -S-CH_2-), 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_3), 0.89 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 196.3 (s), 168.2 (s), 167.8 (s), 162.5 (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 $C_{29}H_{29}BrN_4O_6NaS$ ([M+Na]$^+$), 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%; ^{1}H NMR (400 MHz, DMSO-d_6) 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_2-NO_2), 4.38 (t, J = 6.6 Hz, 2H, -O-CH_2-), 4.05–3.95 (m, 1H, -CH-), 3.76 (t, J = 6.6 Hz, 2H, -S-CH_2-), 3.51–3.36 (m, 2H, -CO-CH_2-), 2.22 (s, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{24}H_{23}N_5O_4NaS$ ([M+Na]$^+$), 500.13559; found, 500.13630.

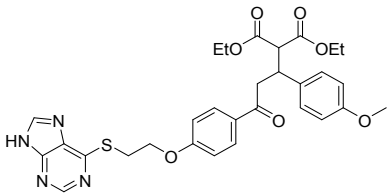


Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-oxo-1-(p-tolyl)propyl)malonate ***(5j)***: White solid, m.p. 66.5–67.6 °C, yield, 36%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.62 (s, 1H, -NH-), 8.77 (s, 1H, Imidazole-H),8.50 (s, 1H, Pyrimidine-H), 7.90 (d, J = 8.9 Hz, 2H, 1-Ph-H), 7.19 (d, J = 8.0 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_2-), 4.17(dd, J = 8.8, 7.1 Hz, 2H, -CO-CH_2-), 3.95(d, J = 3.2 Hz, 2H, -S-CH_2-), 3.90–3.16(m, 4H, 2×-CH_2-), 3.62–3.56 (m, 1H,-CH-), 3.31–3.27(m, 1H, -CH-COO-), 2.21 (s, 3H, Ph-CH_3), 1.18 (t, J = 7.1 Hz, 3H, -CH_3), 0.90 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{30}H_{32}N_4O_6NaS$ ([M+Na]$^+$), 599.19287; found, 599.19348.

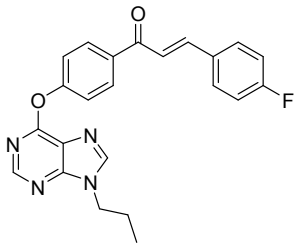


1-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-3-(4-methoxyphenyl)-4-nitrobutan-1-one ***(5k)***: White solid, m.p. 71.5–72.5 °C, yield, 28%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.57 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.4

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, -CH_2-NO_2), 4.38 (t, *J* = 6.6 Hz, 2H, -O-CH_2-), 4.04–4.92 (m, 1H, -CH-), 3.77 (t, *J* = 6.6 Hz, 2H, -S-CH_2-), 3.70 (s, 3H, -CH_3), 3.50–3.39 (m, 2H, -CO-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 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 $C_{24}H_{23}N_5O_5NaS$ ([M+Na]$^+$), 516.13080; found, 516.13121.

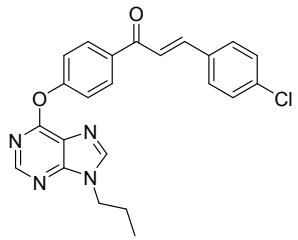


Diethyl 2-(3-(4-(2-((9H-purin-6-yl)thio)ethoxy)phenyl)-1-(4-methoxyphenyl)-3-oxopropyl)malonate (***5l***): Yellow solid, m.p. 64.5–65.6 °C, yield, 38%; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 13.58 (s, 1H, -NH-), 8.75 (s, 1H, Imidazole-H), 8.48 (s, 1H, Pyrimidine-H), 7.87(d, *J* = 8.9Hz, 2H, 1-Ph-H), 7.19 (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, -O-CH_2-), 4.14 (t, *J* = 7.1 Hz, 2H, -CO-CH_2-), 3.93–3.80 (m, 4H, 2×-CH_2-), 3.77 (t, *J* = 6.6 Hz, 2H, -S-CH_2-), 3.67 (s, 3H, -OCH_3), 3.58–3.52 (m, 1H, -CH-Ph), 3.26–3.19 (m, 1H, -COO-CH-), 1.16 (t, *J* = 7.1 Hz, 3H, -CH_3), 0.88 (t, *J* = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) *δ*: 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 $C_{30}H_{32}N_4O_7NaS$ ([M+Na]$^+$), 615.18744; found, 615.18839.

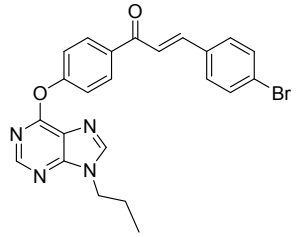


(E)-3-(4-fluorophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (***7a***): White solid, m.p. 117.3−118.5 °C, yield 49%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 8.54 (s, 1H, Imidazole-H), 8.17–8.13 (m, 2H, 1-Ph-H), 8.07 (s, 1H, Pyrimidine-H), 7.80 (d, *J* = 15.7 Hz, 1H, 3-CH=), 7.64 (d, *J* = 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-CH_2-), 2.01–1.95 (m,

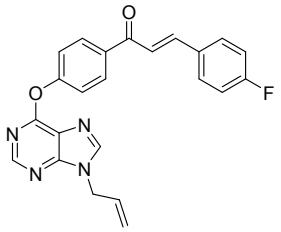
2H, 9-CH_2-), 1.02–0.97 (m, 3H, -CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ: -108.93 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.9 (s), 165.3 (s), 162.8 (s), 159.6 (s), 156.2 (s), 153.5 (s), 151.8 (s), 143.5 (s), 135.5 (s), 131.1 (s),131.1 (s), 130.4 (s), 130.3 (s), 122.0 (s), 122.0 (s), 121.7 (s), 121.5 (s), 121.5 (s), 116.3 (s), 116.0 (s), 46.0 (s), 23.4 (s), 11.2 (s); HRMS (ESI): calcd for $C_{23}H_{19}FN_4O_2Na$ ([M+Na]$^+$), 425.13773; found, 425.13843.



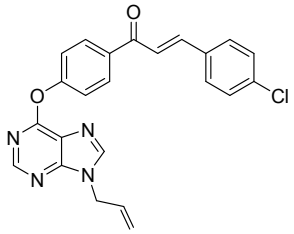
(E)-3-(4-chlorophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (***7b***): White solid, m.p. 140.5–141.4 °C, yield 47%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.59 (s, 1H, Imidazole-H), 8.51 (s, 1H, Pyrimidine-H), 8.31 (d, J = 8.8 Hz, 2H, 1-Ph-H), 8.05 (d, J = 15.6 Hz, 1H, 3-CH=), 7.97 (d, 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_2-), 1.94–1.85 (m, 2H, -CH_2-), 0.88 (t, J = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{19}ClN_4O_2Na$ ([M+Na]$^+$), 441.10837; found, 441.10887.



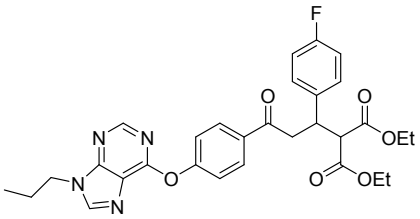
(E)-3-(4-bromophenyl)-1-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)prop-2-en-1-one (***7c***): Yellow solid, m.p. 140.0−140.9 °C, yield 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (s, 1H, Imidazole-H), 8.07 (d, J = 8.7 Hz, 2H, 1-Ph-H), 7.99 (s, 1H , Pyrimidine-H), 7.70 (d, J = 15.7 Hz, 1H, 3-CH=C-), 7.47 (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_2-), 1.95–1.90 (m, 2H, 9-CH_2-), 0.94 (s, 3H,-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{19}BrN_4O_2Na$ ([M+Na]$^+$), 485.05771; found, 485.05836.



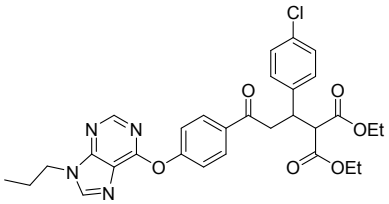
(E)-1-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (***7d***): Yellow solid, m.p. 128.9−129.9 °C, yield 58%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.57 (s, 1H, Imidazole-H), 8.52 (s, 1H, Pyrimidine-H), 8.30 (d, J = 8.8 Hz, 2H, 1-Ph-H), 8.04−7.97 (m, 3H, 3-CH=, 3-Ph-H), 7.80 (d, 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_2), 5.11 (dd, J = 17.1, 1.3 Hz, 1H, 9-C=CH_2), 4.97 (dd, J = 4.1, 1.4 Hz, 2H, 9-CH_2-); ^{19}F NMR (400 MHz, DMSO-d_6) δ: -109.55 (tt, J = 8.9, 5.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{17}FN_4O_2Na$ ([M+Na]$^+$), 423.12216; found, 423.12278.



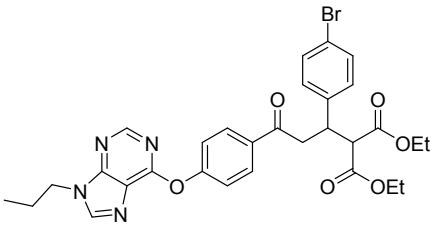
(E)-1-(4-((9-allyl-9H-purin-6-yl)oxy)phenyl)-3-(4-chlorophenyl)prop-2-en-1-one (***7e***): Yellow solid, m.p. 80.6−81.7 °C, yield 46%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.56 (s, 1H, Imidazole-H), 8.52 (s, 1H, Pyrimidine-H), 8.30 (d, J = 8.8 Hz, 2H, 1-Ph-H), 8.04 (d, J = 15.6 Hz, 1H, 3-CH=), 7.97 (dd, 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_2), 5.10 (dd, J = 17.1, 1.3 Hz, 1H, 9-C=CH_2), 4.96 (d, J = 5.5 Hz, 2H, 9-CH_2-); ^{13}C NMR (100 MHz, DMSO-d_6) 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 $C_{23}H_{17}ClN_4O_2Na$ ([M+Na]$^+$), 439.09277; found, 439.09322.



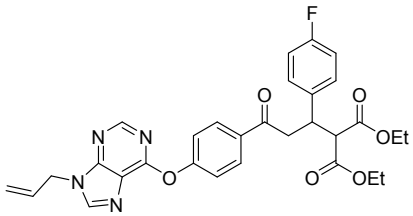
Diethyl 2-(1-(4-fluorophenyl)-3-oxo-3-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)propyl)malonate (***8a***): White solid, m.p. 92.0–93.7 °C, yield 36%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H,Imidazole-H), 7.97 (d, J = 4.6 Hz, 2H, 1-Ph-H), 7.94 (s, 1H, Pyrimidine-H), 7.29 (d, J = 8.7 Hz, 2H, 3-Ph-H), 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×-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×-CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ: -115.39 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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 $C_{30}H_{31}FN_4O_6Na$ ([M+Na]$^+$), 585.21155;found, 585.21198.



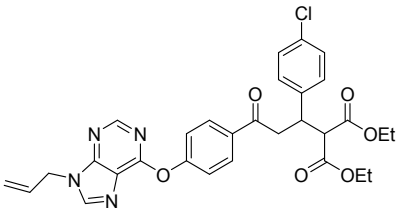
Diethyl 2-(1-(4-chlorophenyl)-3-oxo-3-(4-((9-propyl-9H-purin-6-yl)oxy)phenyl)propyl)malonate (***8b***): White solid, m.p. 112.2–113.4 °C, yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (s, 1H, Imidazole-H), 8.06 (s, 1H, Pyrimidine-H), 8.04 (d, *J* = 8.1 Hz, 2H, 1-Ph-H), 7.38 (d, *J* = 7.9 Hz, 2H, 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}C NMR (100 MHz, $CDCl_3$) δ: 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); HR MS (ESI): calcd for $C_{30}H_{31}ClN_4O_6Na$ ([M+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}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H, Imidazole-H), 7.98 (s, 1H, Py rimidine-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, -CH_2-), 4.17–4.07 (m, 3H, -CH_2-, Ph-CH-), 3.92 (q, J = 7.1 Hz, 2H, 9-CH_2-), 3.71 (s, 1H, -CH-COO-), 3.50–3.36 (m, 2H, -CH_2-CO-), 1.96–1.87 (m, 2H, 9-CH_2-), 1.18 (d, J = 7.1 Hz, 3H, -CH_3), 0.99 (t, J = 7.1 Hz, 3H, -CH_3), 0.93 (t, J = 7.4 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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), 13 4.0 (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 $C_{30}H_{31}BrN_4O_6Na$ ([M+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}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (s, 1H, Imidazole-H), 7.99 (s, 1H, P yrimidine-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-CH=C-), 5.30 (d, J = 10.2 Hz, 1H, 9-C=CH_2), 5.19 (d, J = 17.0 Hz, 1H, 9-C=CH_2), 4.85 (d, J = 5.7 Hz, 2H, 9-CH_2-), 4.14 (dt, J = 9.8, 4.3 Hz, 3H, -CH-Ph, -CH_2-), 3.91 (q, J = 7.1 Hz, 2H, -CH_2-), 3.72 (d, J = 9.6 Hz, 1H, -CH-COO-), 3.48–3.35 (m, 2 H, -CH_2-CO-), 1.18 (t, J = 7.1 Hz, 3H, -CH_3), 0.97 (t, J = 7.1 Hz, 3H, -CH_3); ^{19}F NMR (400 MHz, $CDCl_3$) δ: -115.41 (s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 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 $C_{30}H_{29}FN_4O_6Na$ ([M+Na]$^+$), 583.19558; foun d, 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}H NMR (400 MHz, $CDCl_3$) δ: 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_2), 5.19 (d, J = 17.0 Hz, 1H, 9-C=CH_2), 4.85 (d, J = 5.7 Hz, 2H, 9-CH_2-), 4.19−4.07 (m, 3H, -CH-Ph, -CH_2-), 3.92 (q, J = 7.1 Hz, 2H, -CH_2-), 3.72 (d, J = 9.6 Hz, 1H, -CH-COO-), 3.50−3.36 (m, 2H, -CO-CH_2-), 1.19 (t, J = 7.1 Hz, 3H, -CH_3), 0.99 (t, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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 $C_{30}H_{29}ClN_4O_6Na$ ([M+Na]$^+$), 599.16602; found, 599.16678.

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

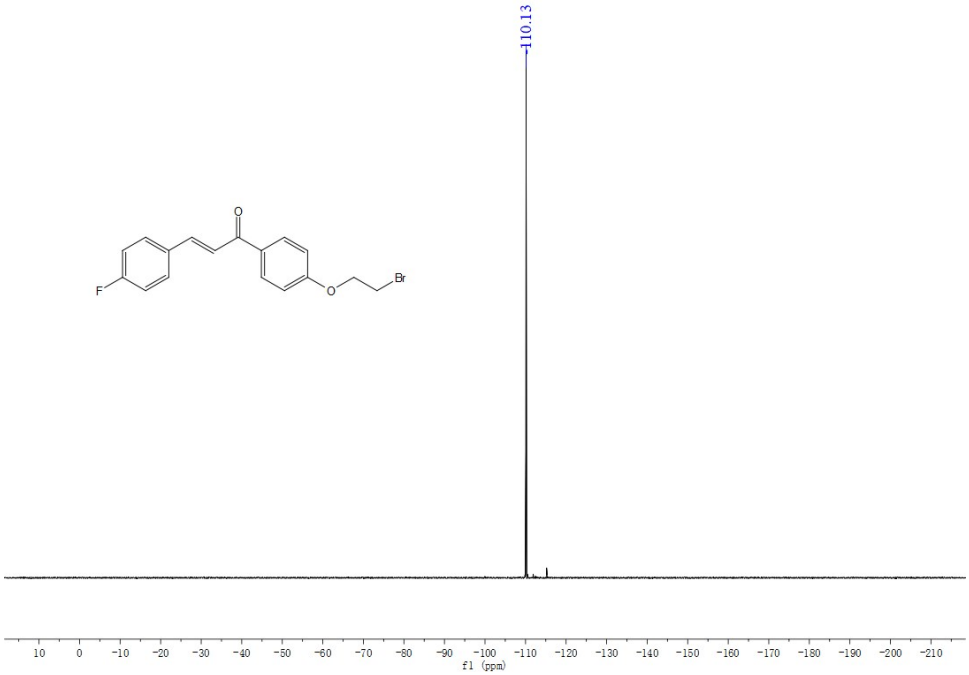


Figure S1. ^{19}F NMR (DMSO-d_6, 400 MHz) spectrum of intermediate **2b**

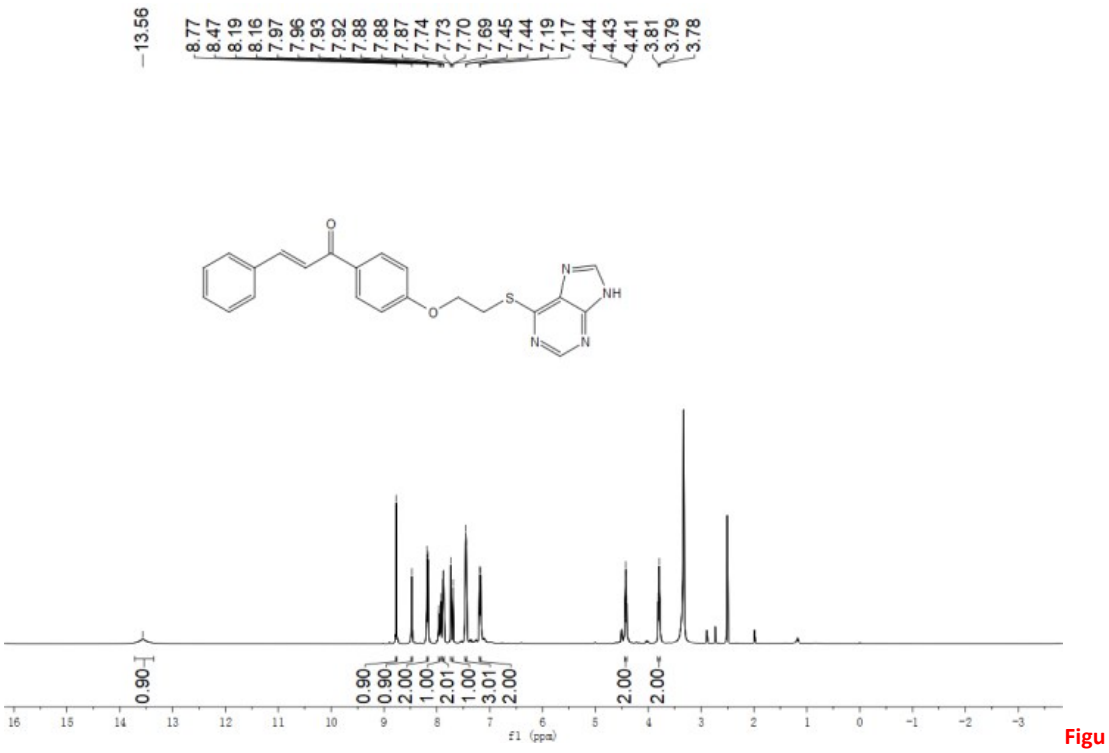


Figure S2. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4a**

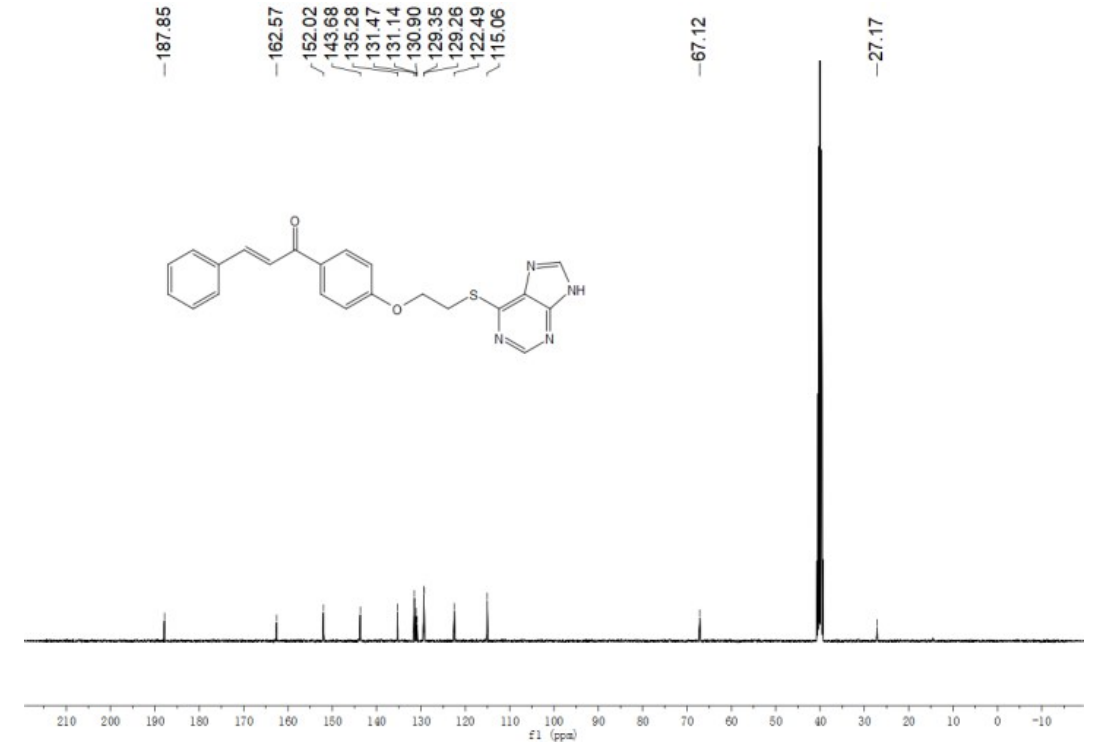


Figure S3. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4a**

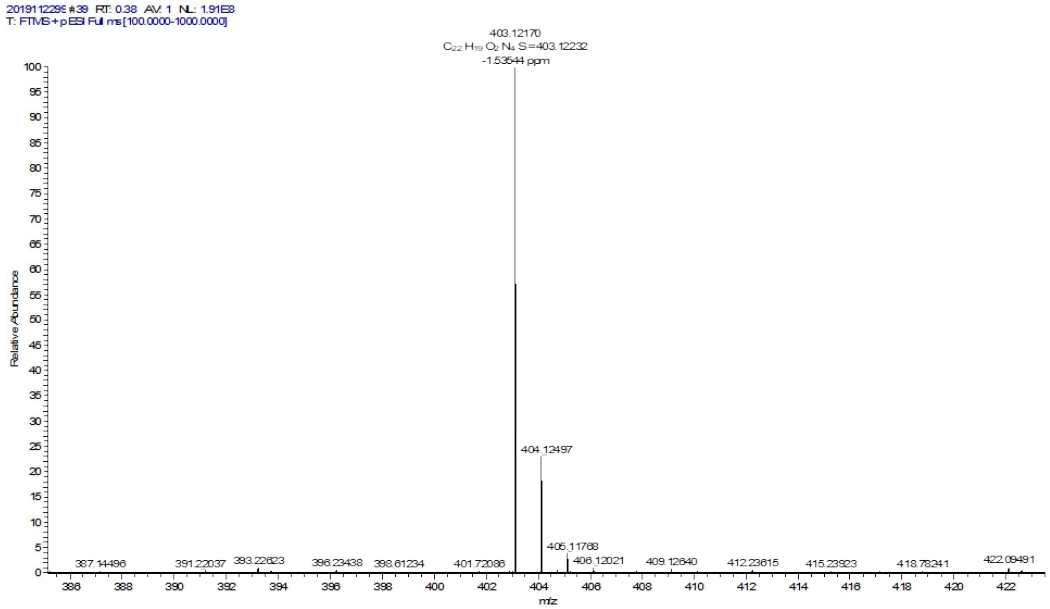


Figure S4. HRMS of compound **4a**

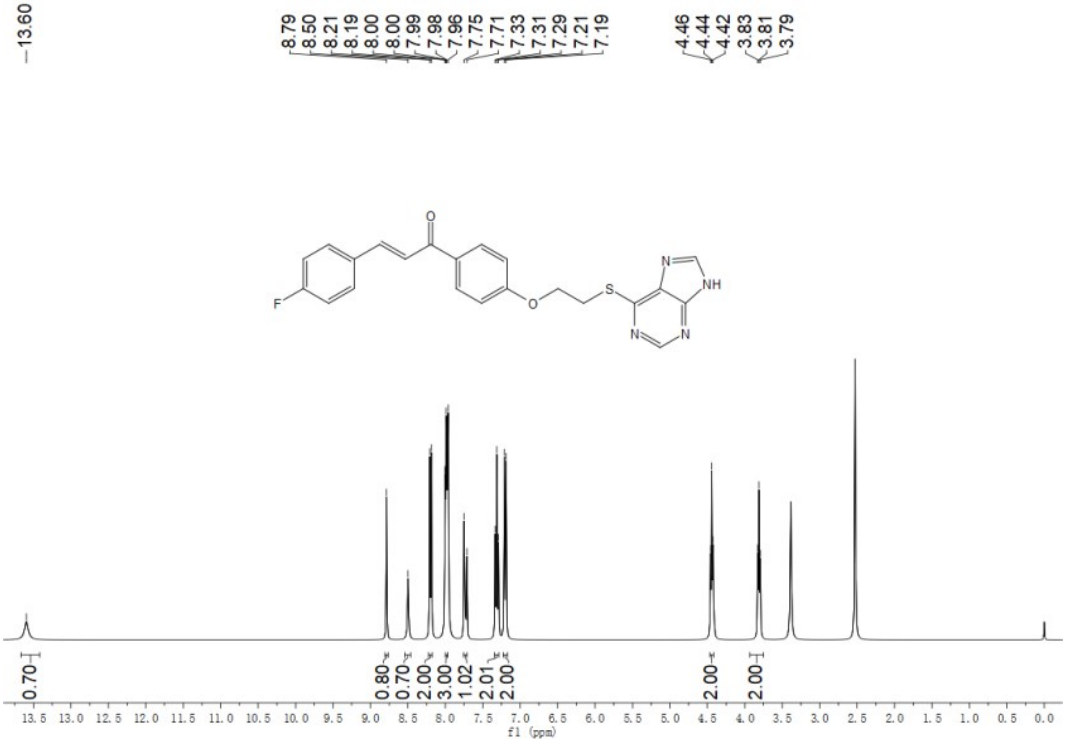


Figure S5. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4b**

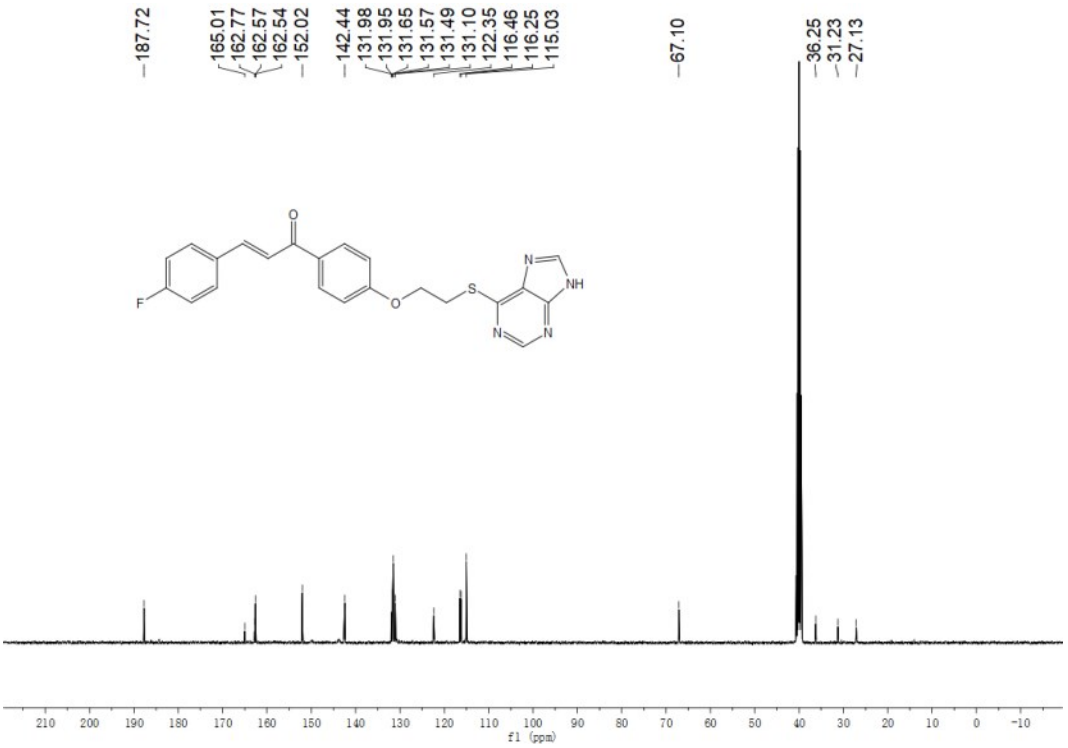


Figure S6. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4b**

Figure S7. ^{19}F NMR (DMSO-d_6, 400 MHz) spectrum of compound **4b**

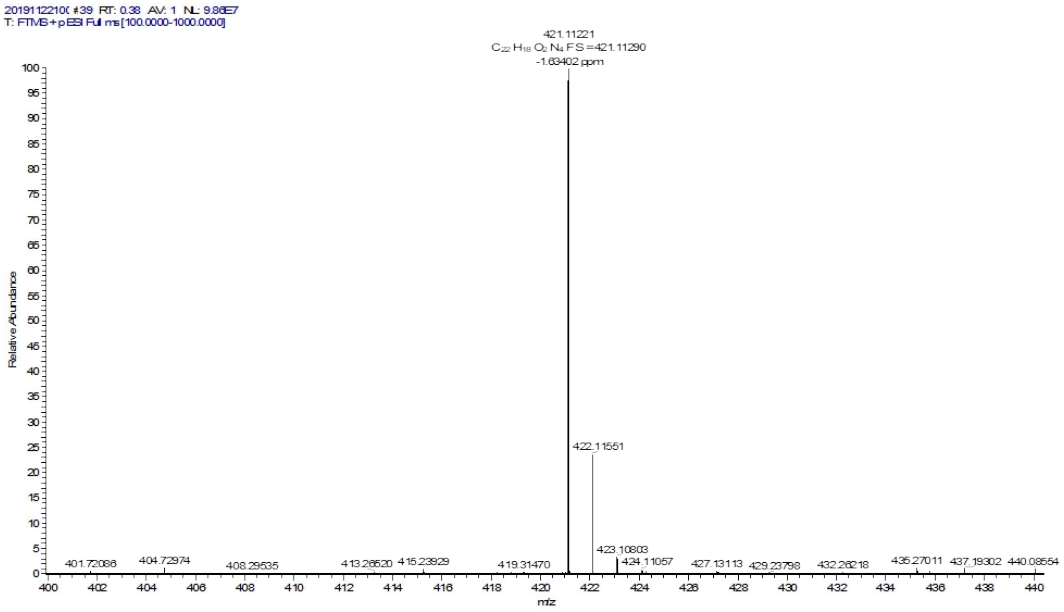


Figure S8. HRMS of compound **4b**

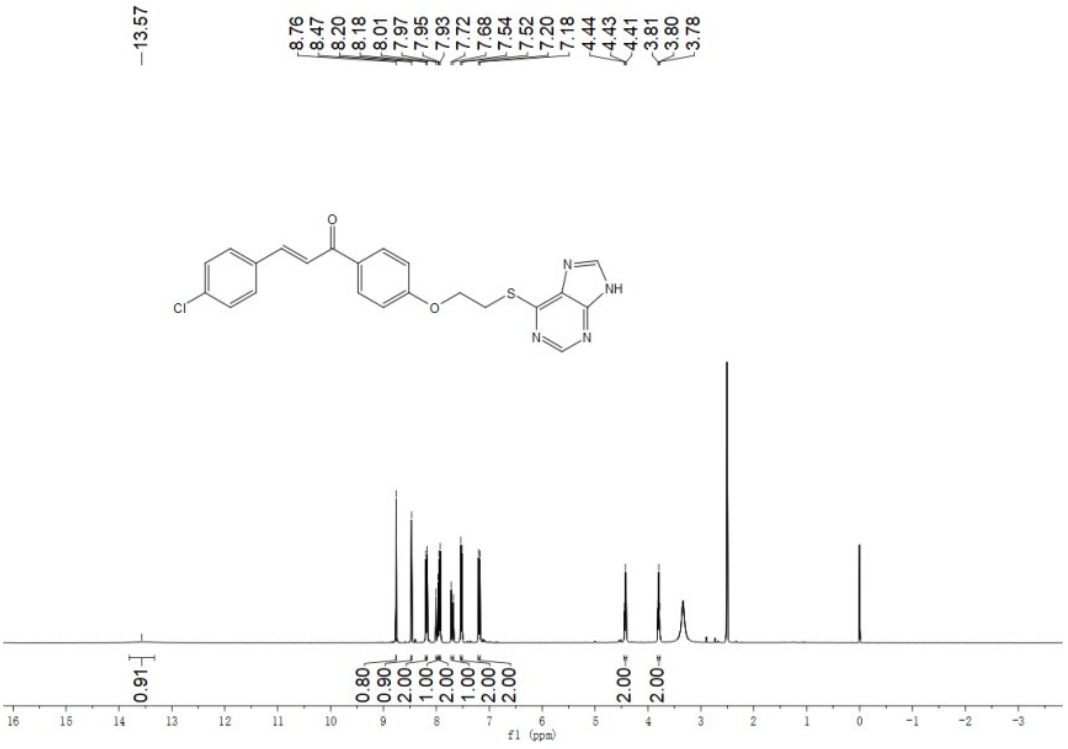


Figure S9. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4c**

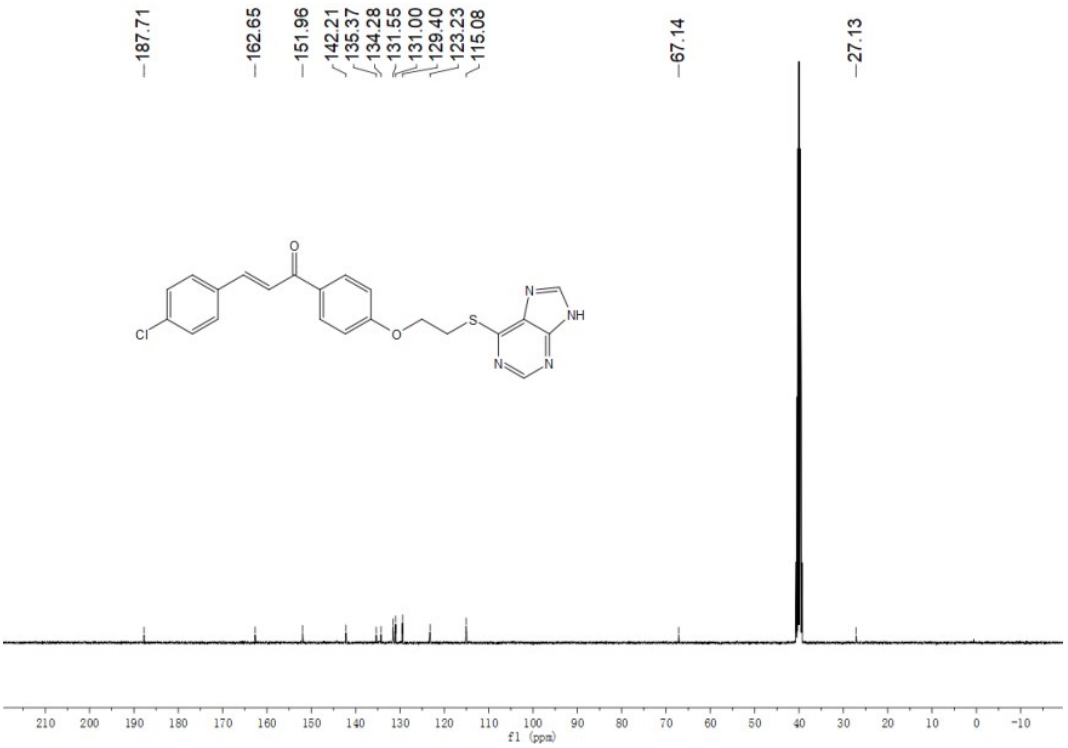


Figure S10. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4c**

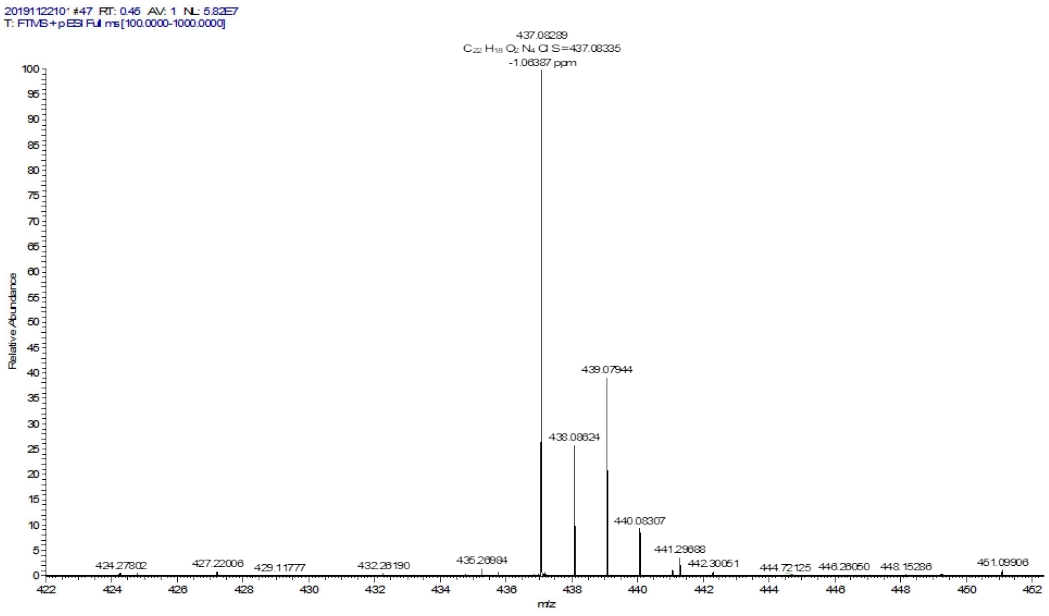


Figure S11. HRMS of compound **4c**

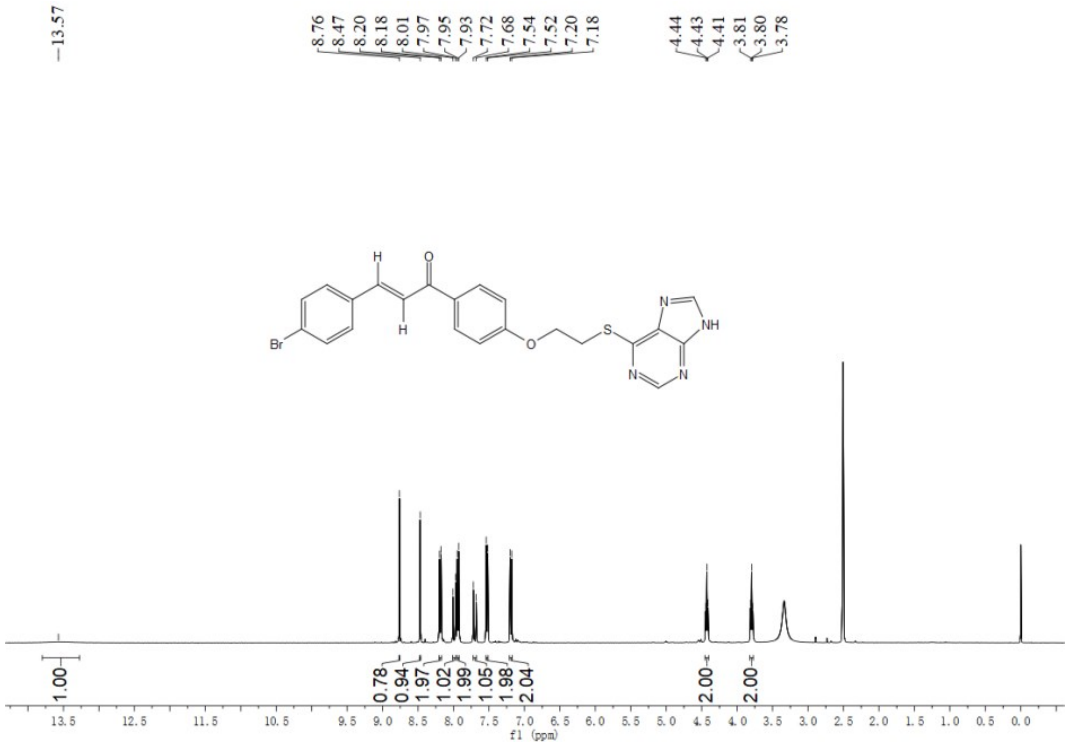


Figure S12. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4d**

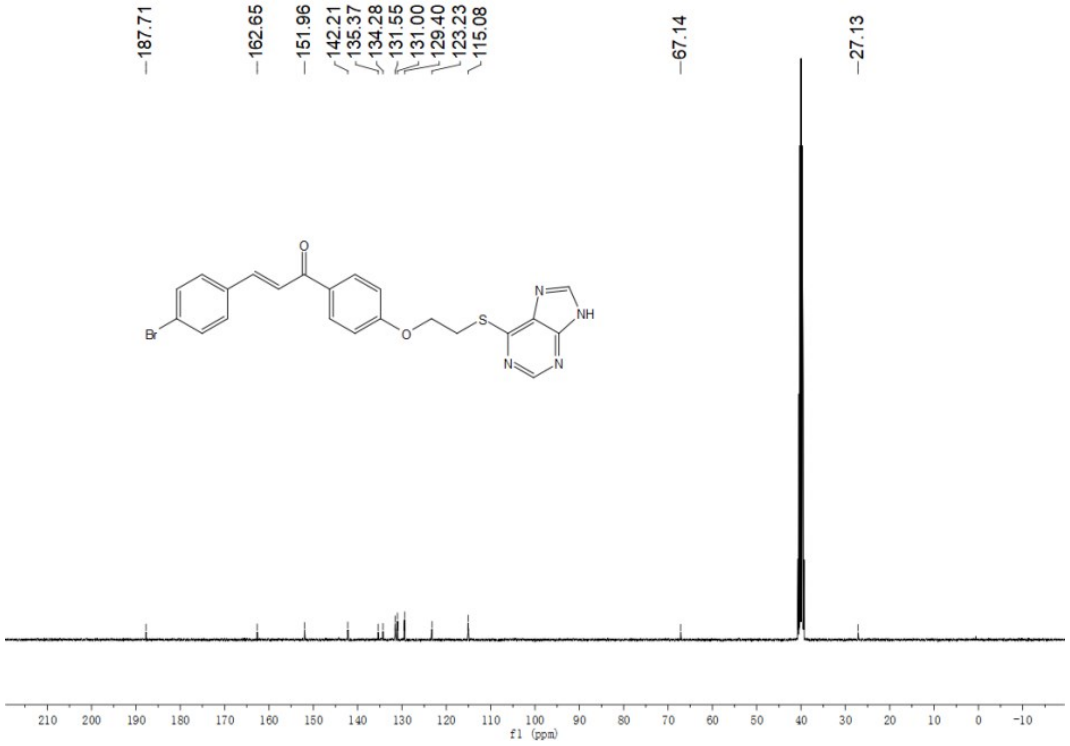


Figure S13. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4d**

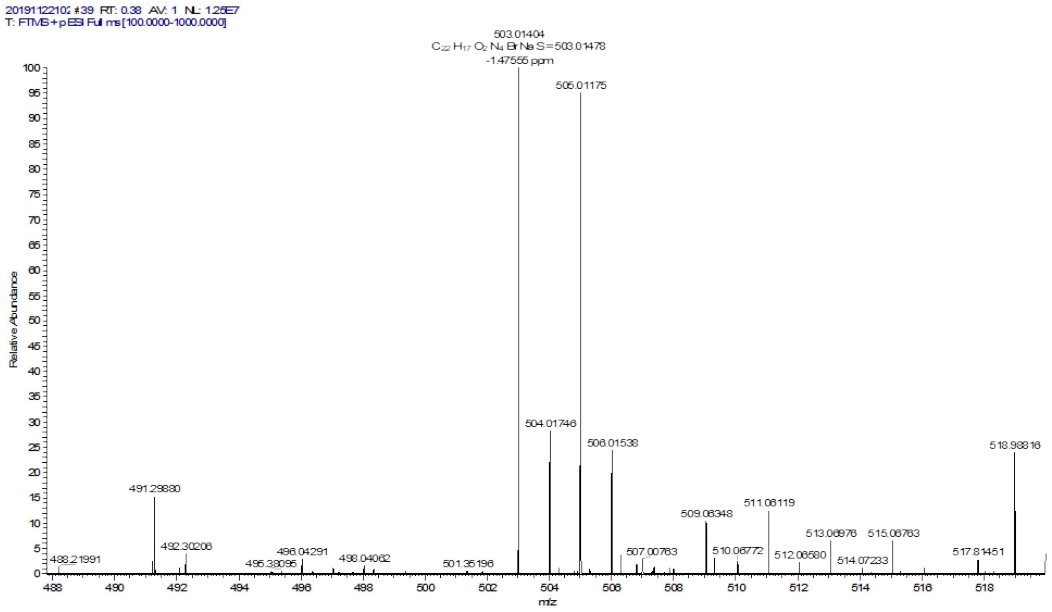


Figure S14. HRMS of compound **4d**

Figure S15. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4e**

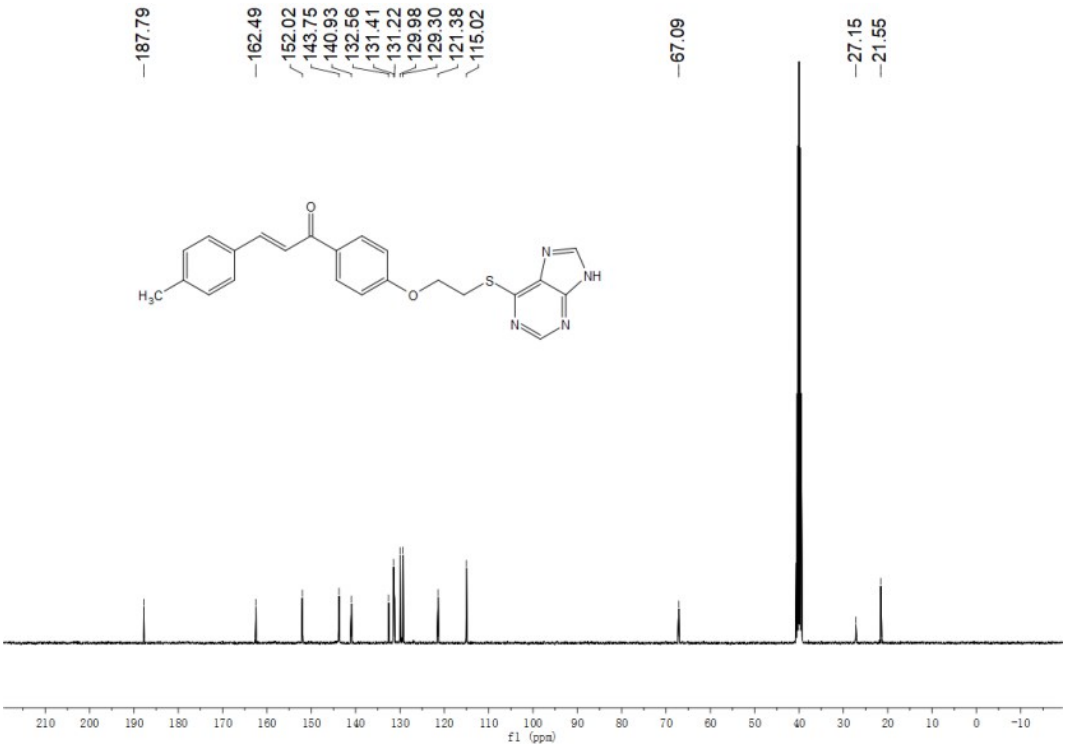


Figure S16. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4e**

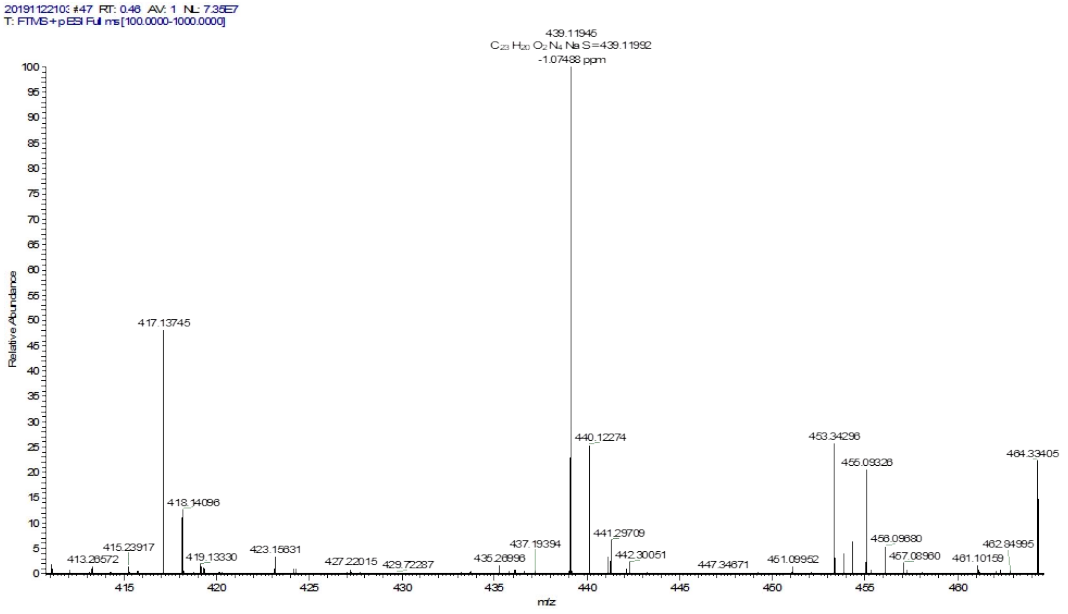


Figure S17. HRMS of compound **4e**

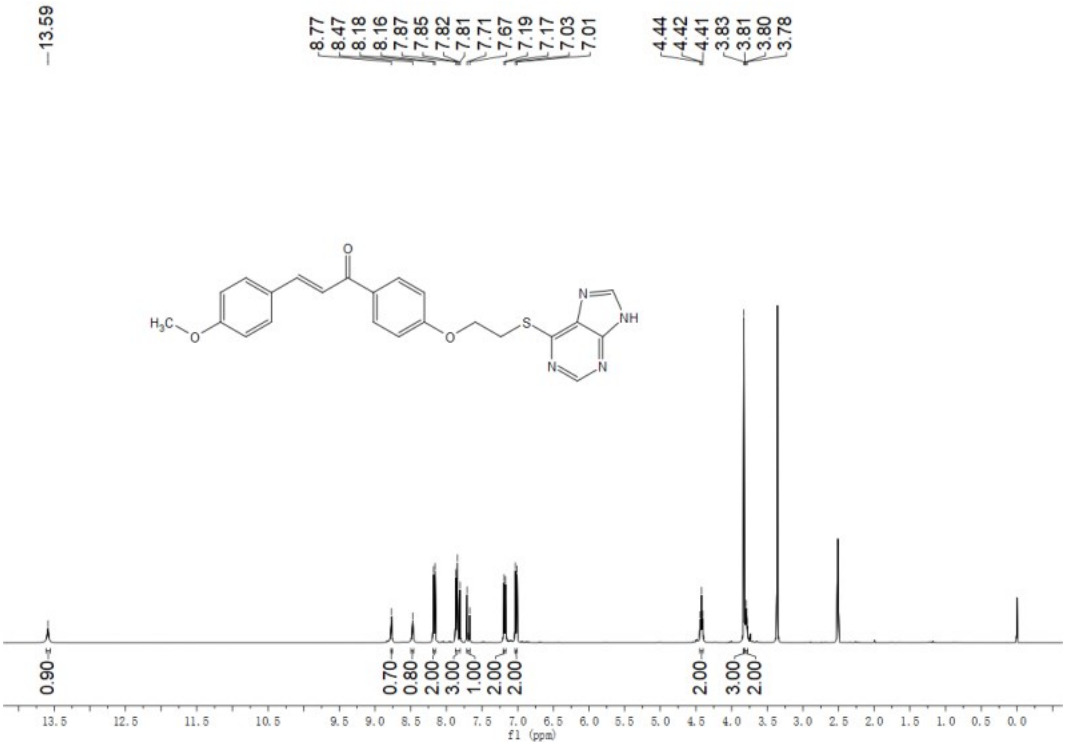


Figure S18. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **4f**

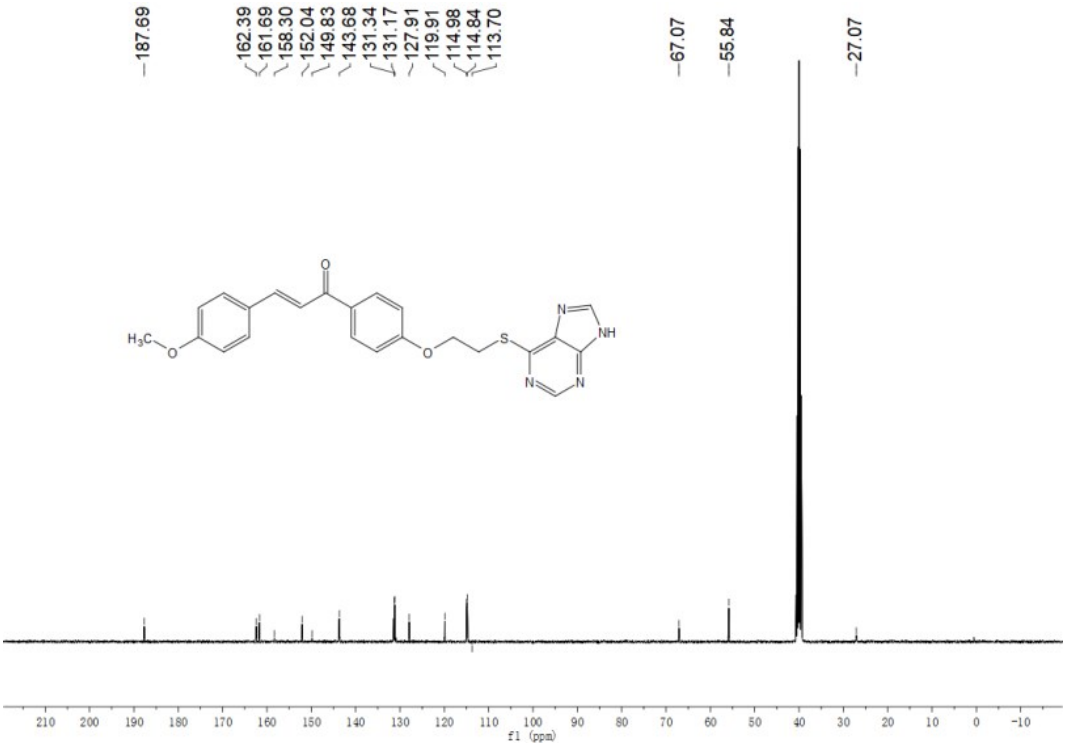


Figure S19. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **4f**

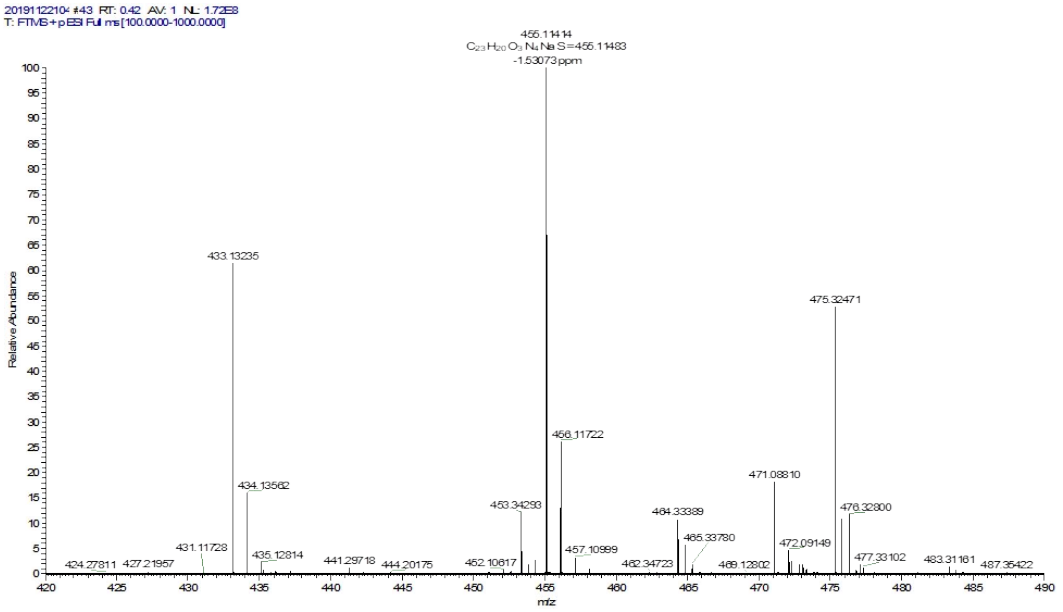


Figure S20. HRMS of compound **4f**

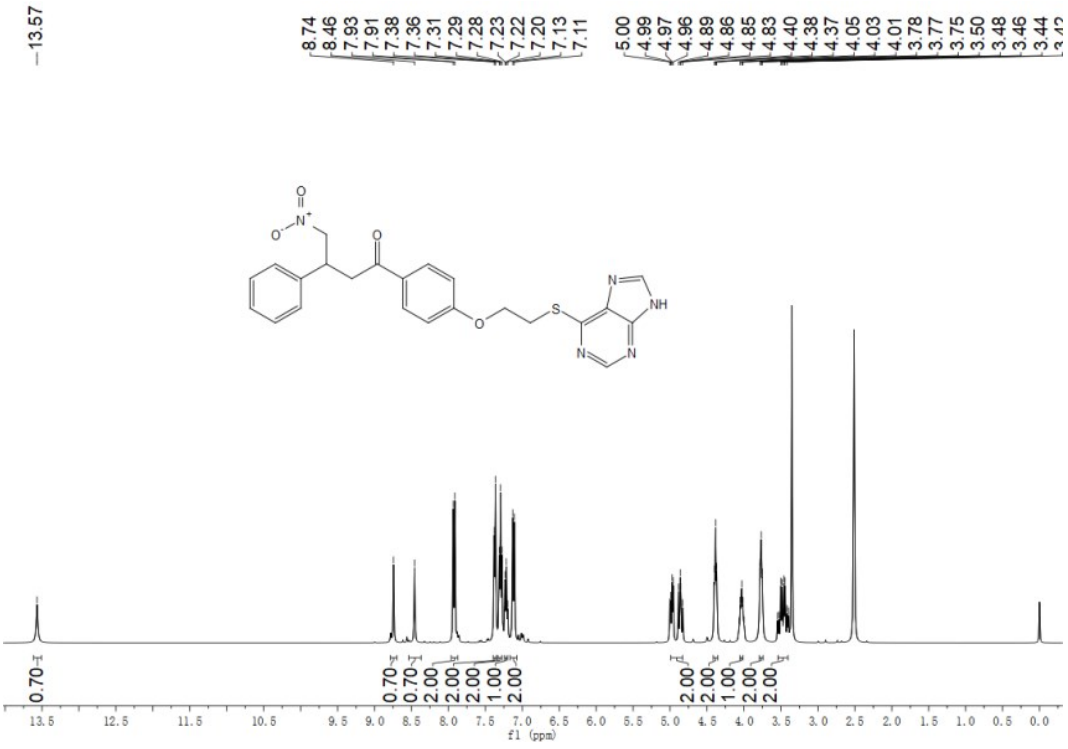


Figure S21. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5a**

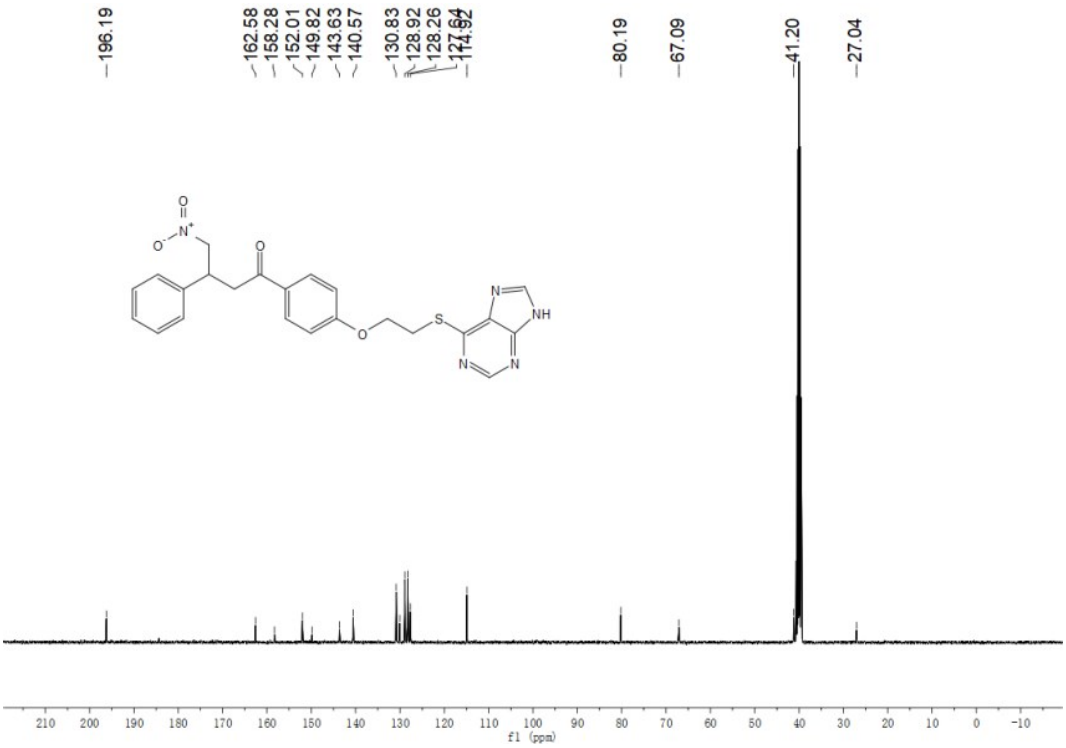


Figure S22. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5a**

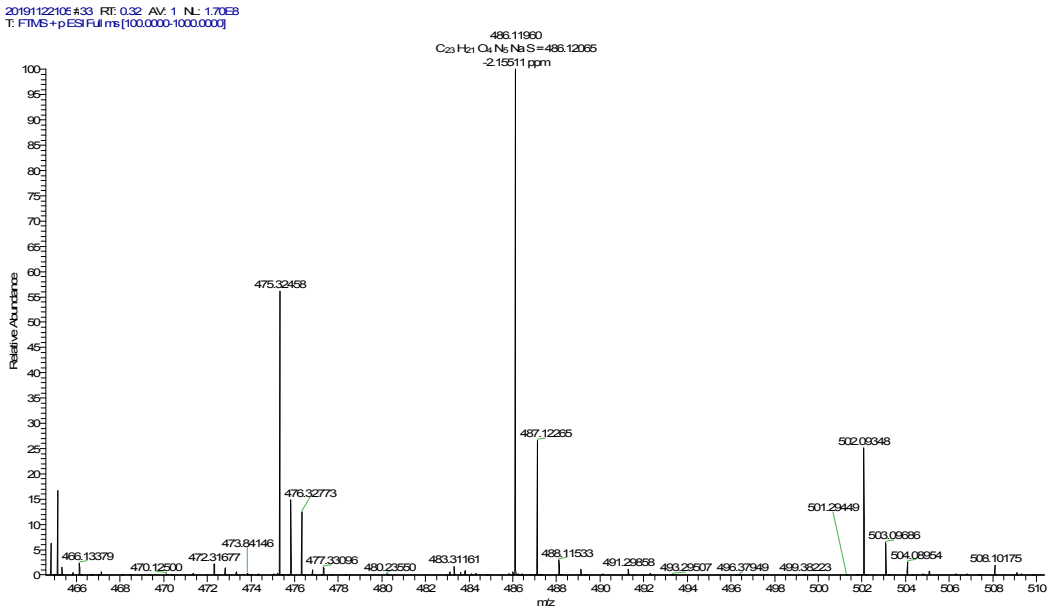


Figure S23. HRMS of compound **5a**

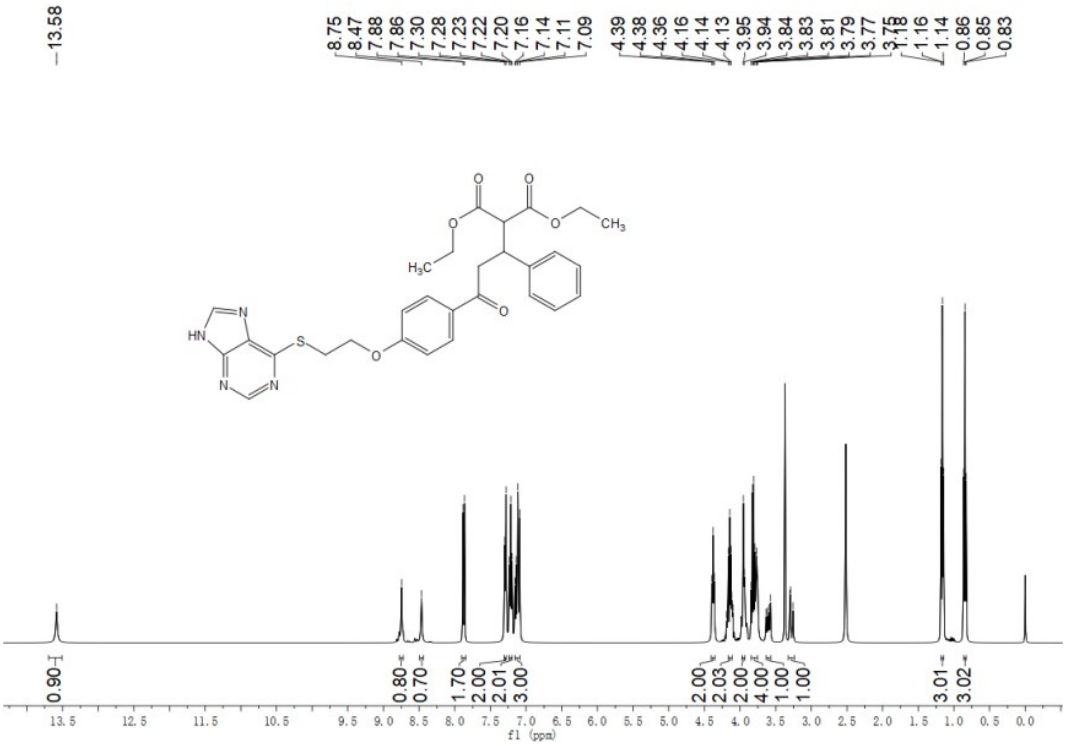


Figure S24. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5b**

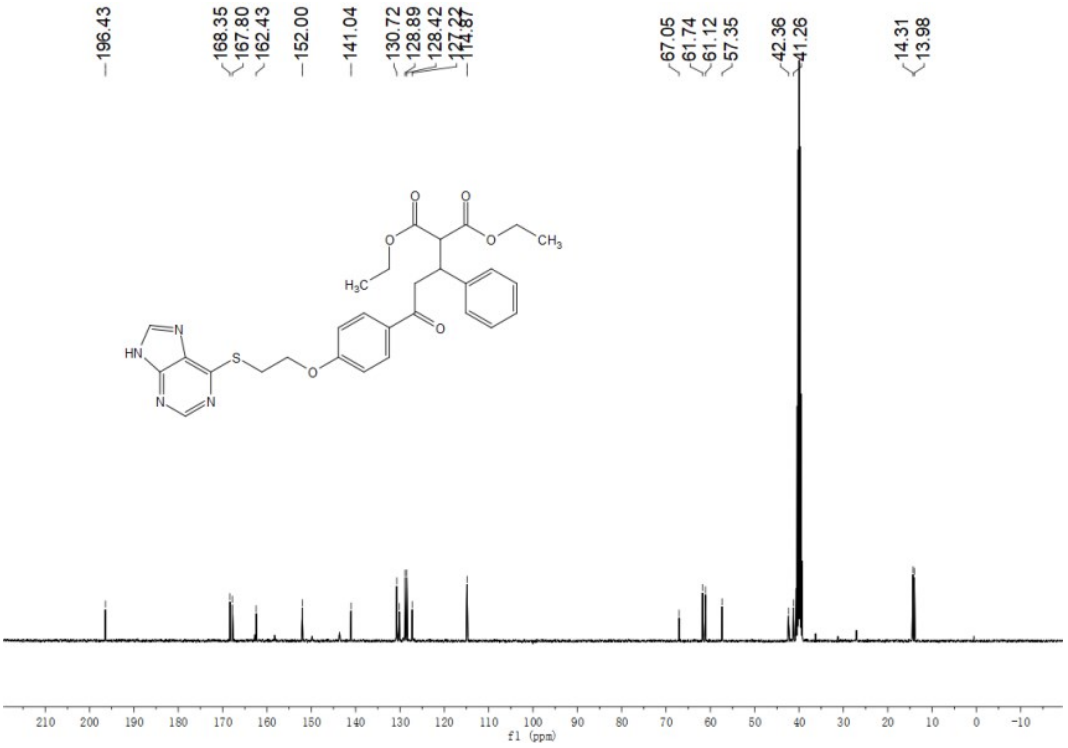


Figure S25. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5b**

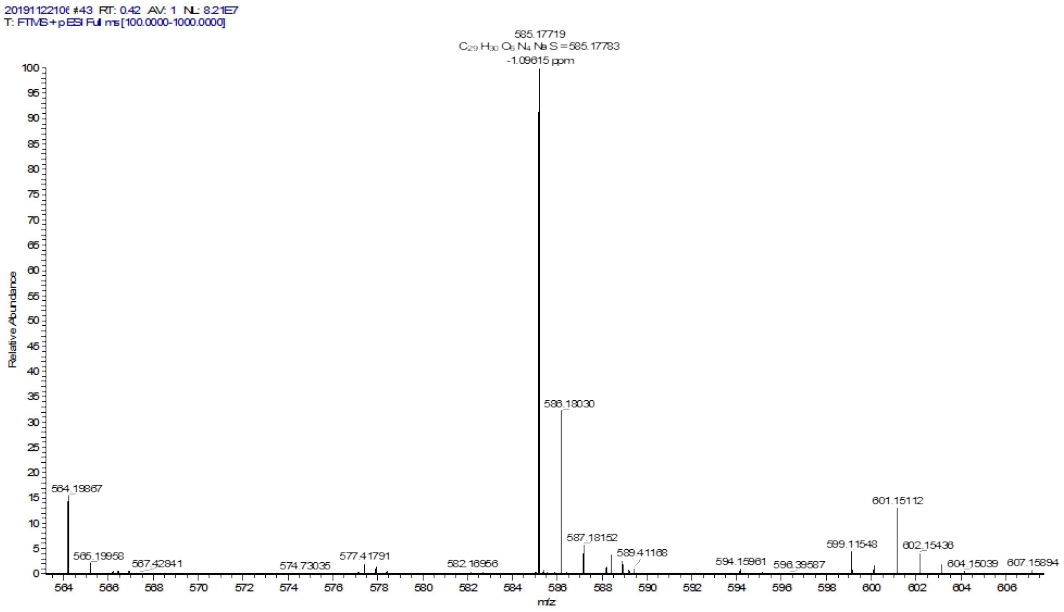


Figure S26. HRMS of compound **5b**

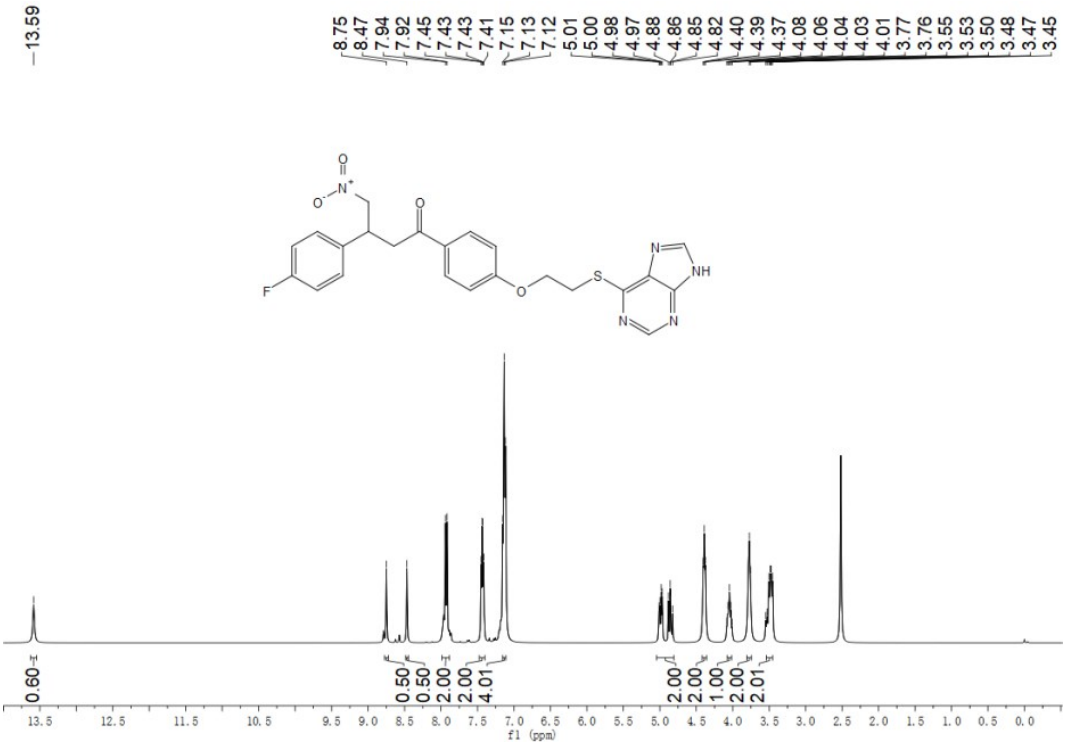


Figure S27. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5c**

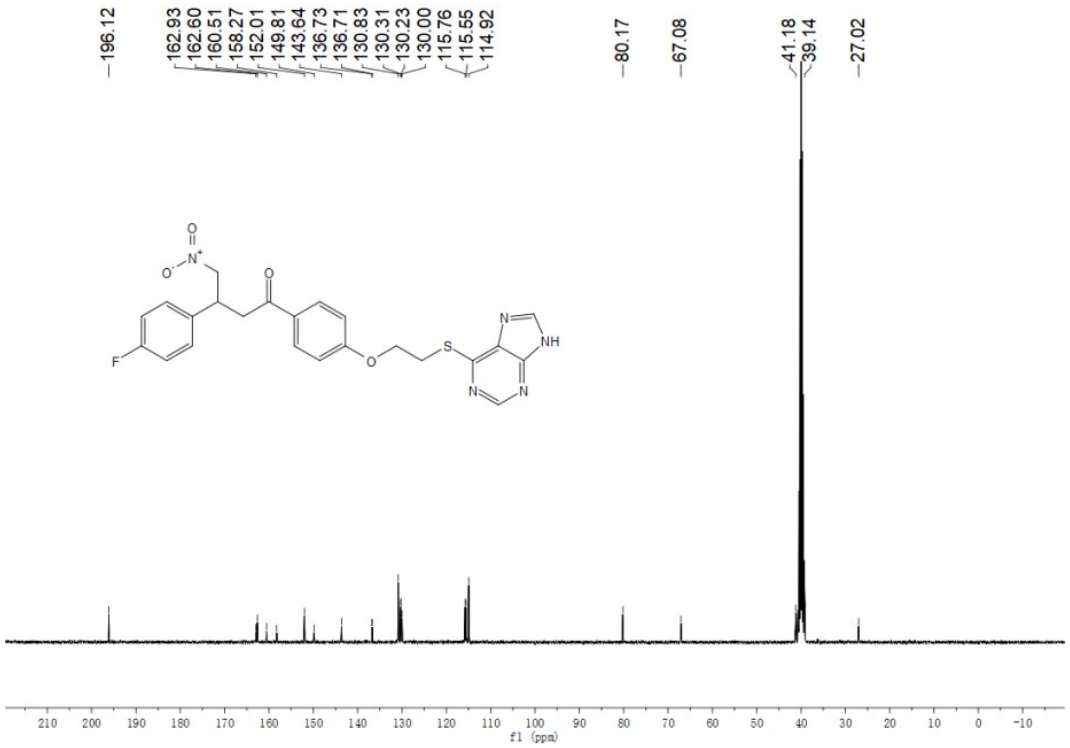


Figure S28. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5c**

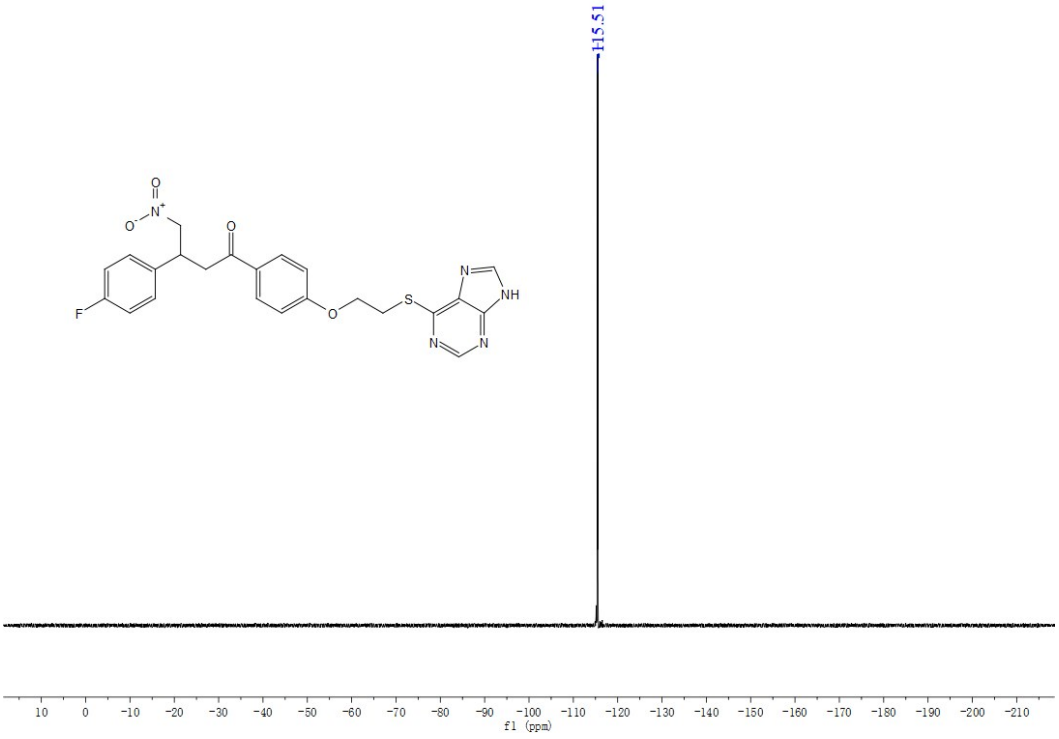


Figure S29. ^{19}F NMR (DMSO-d_6, 400 MHz) spectrum of compound **5c**

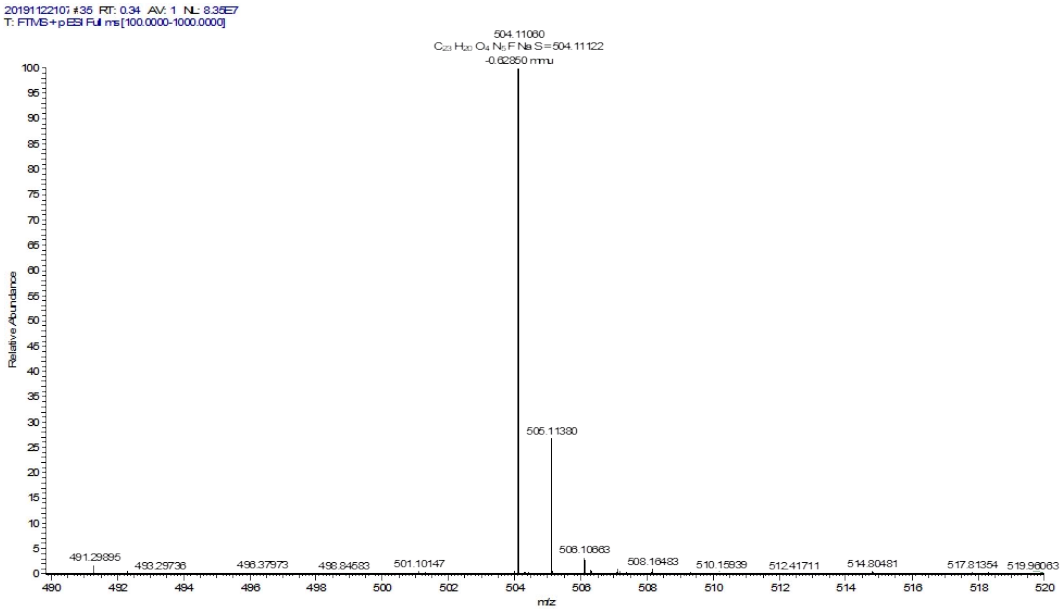


Figure S30. HRMS of compound **5c**

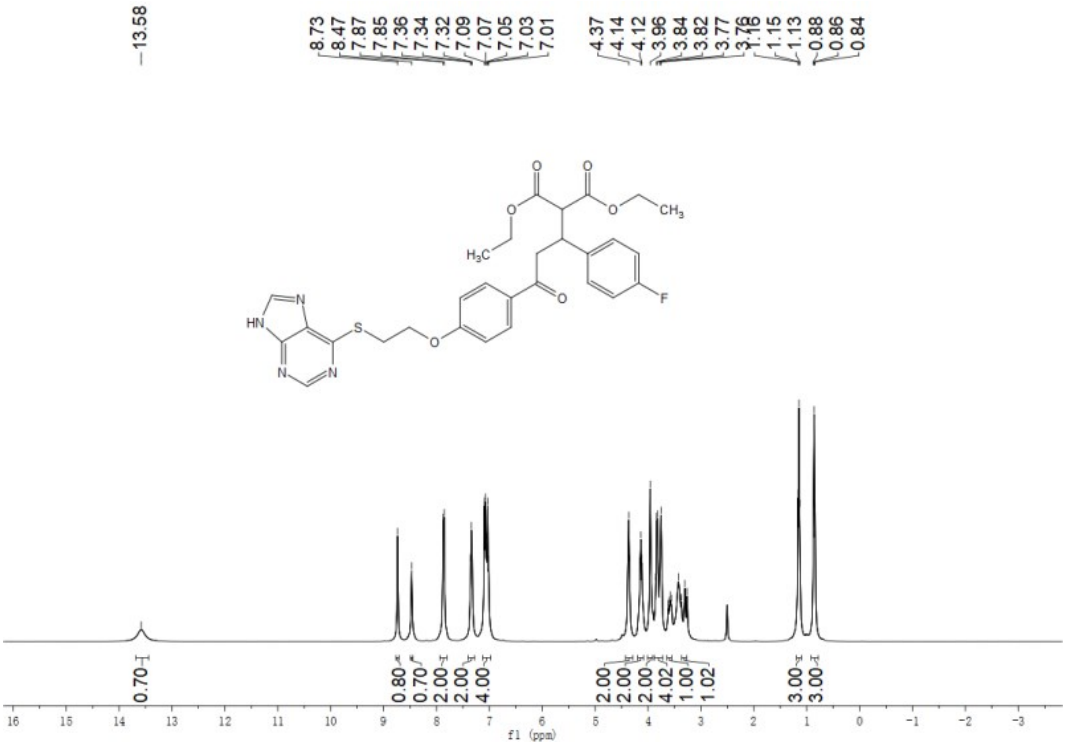


Figure S31. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5d**

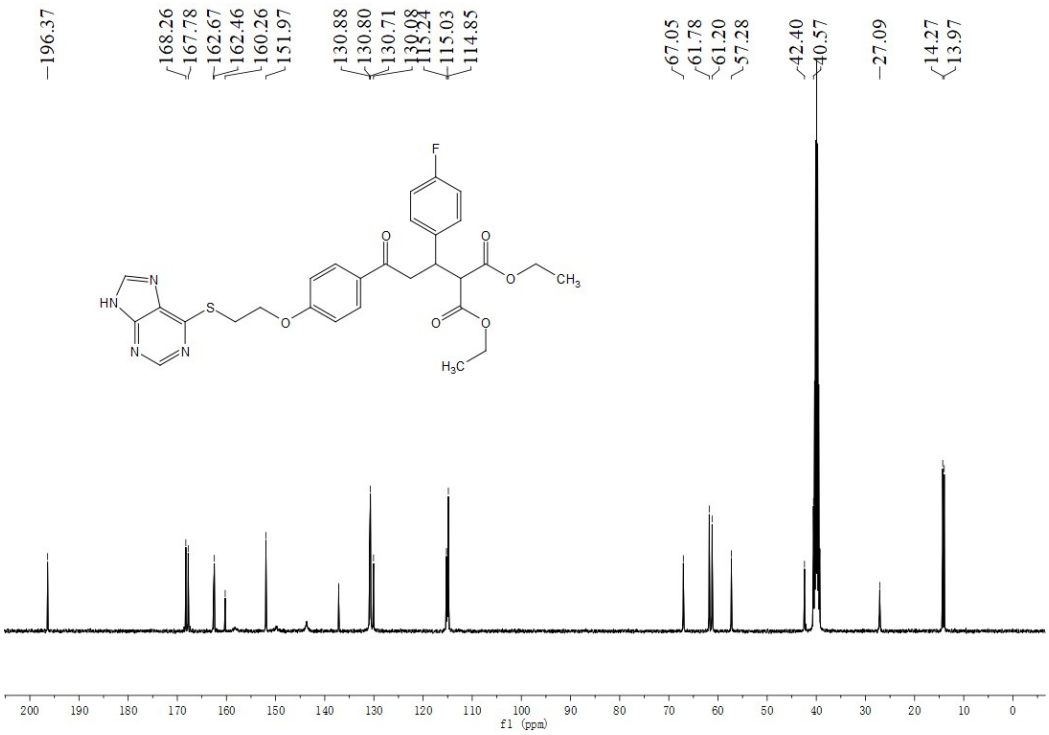


Figure S32. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5d**

Figure S33. ^{19}F NMR (DMSO-d_6, 400 MHz) spectrum of compound **5d**

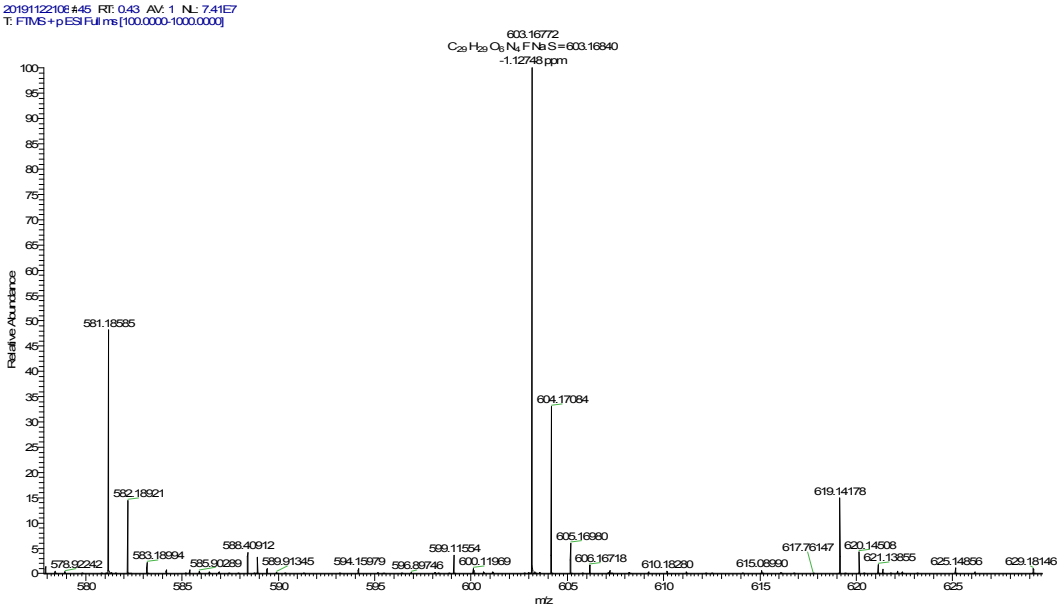


Figure S34. HRMS of compound **5d**

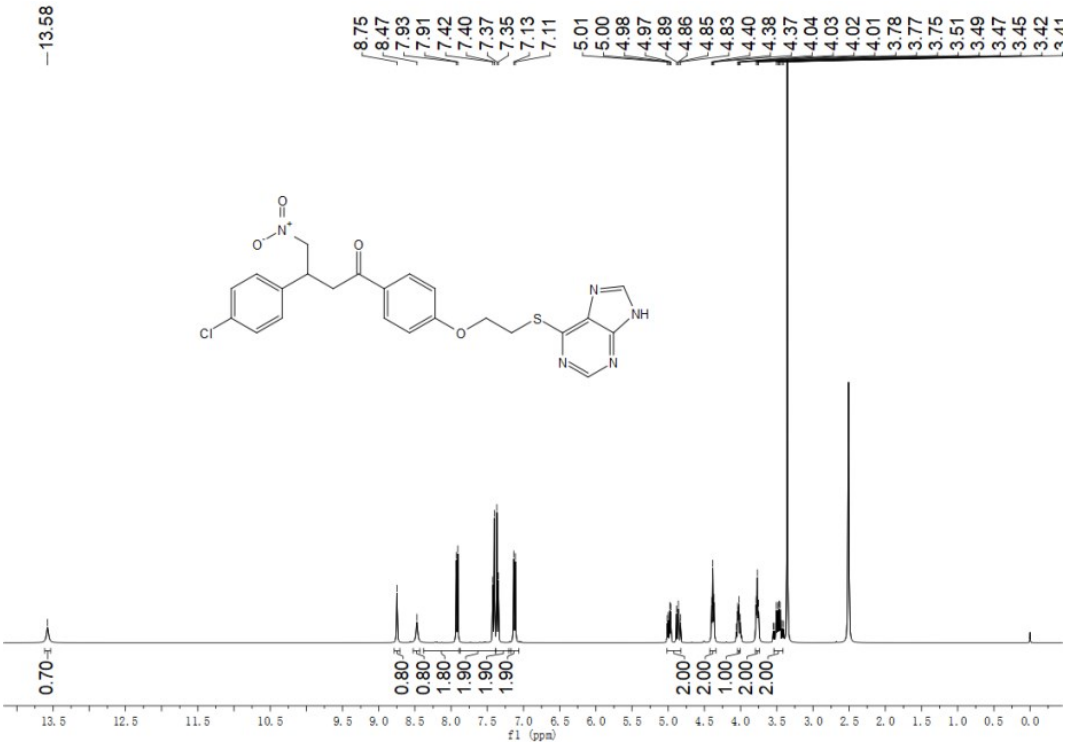


Figure S35. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5e**

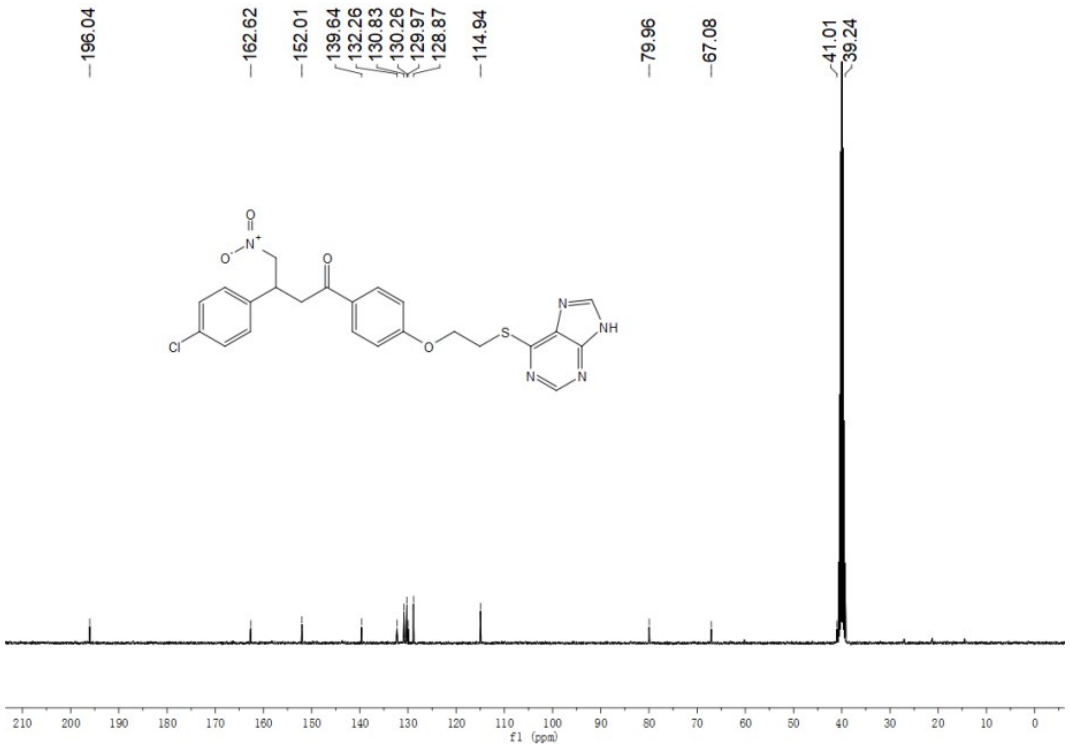


Figure S36. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5e**

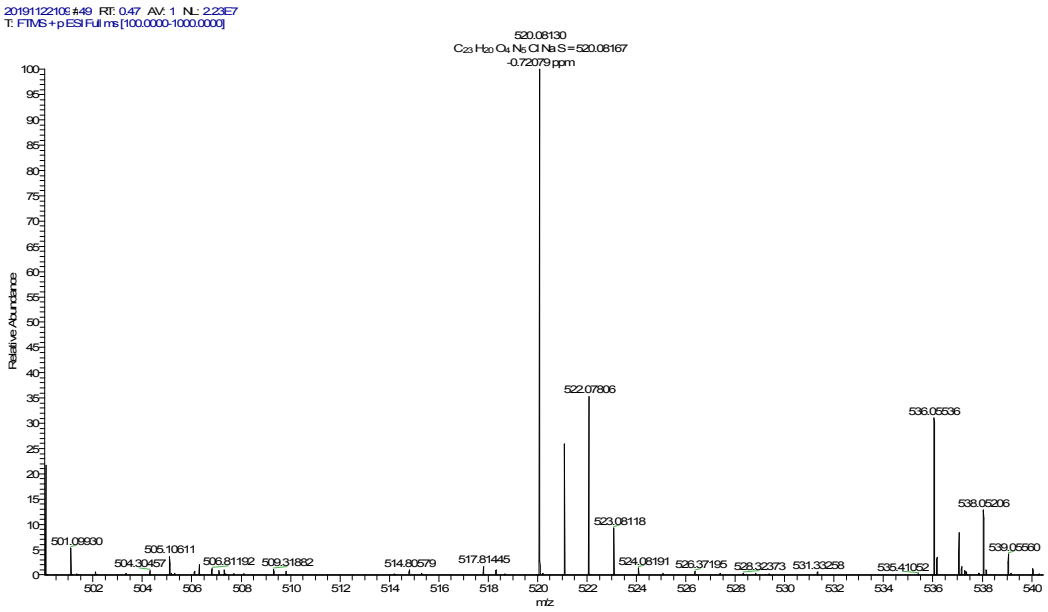


Figure S37. HRMS of compound **5e**

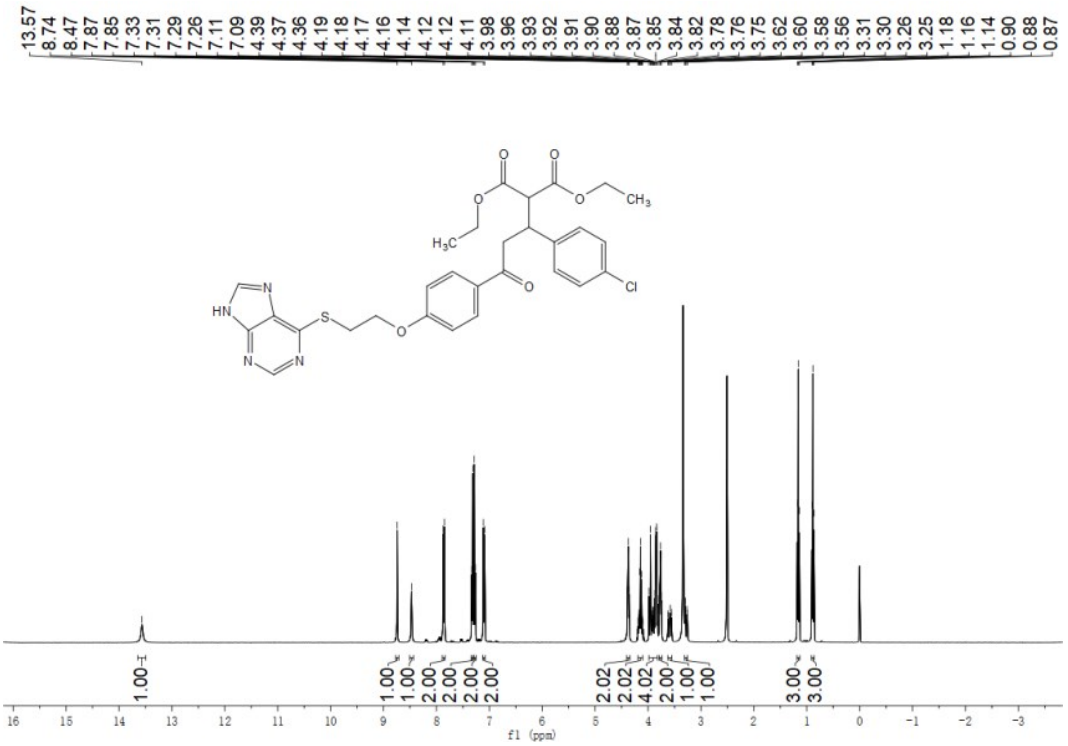


Figure S38. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5f**

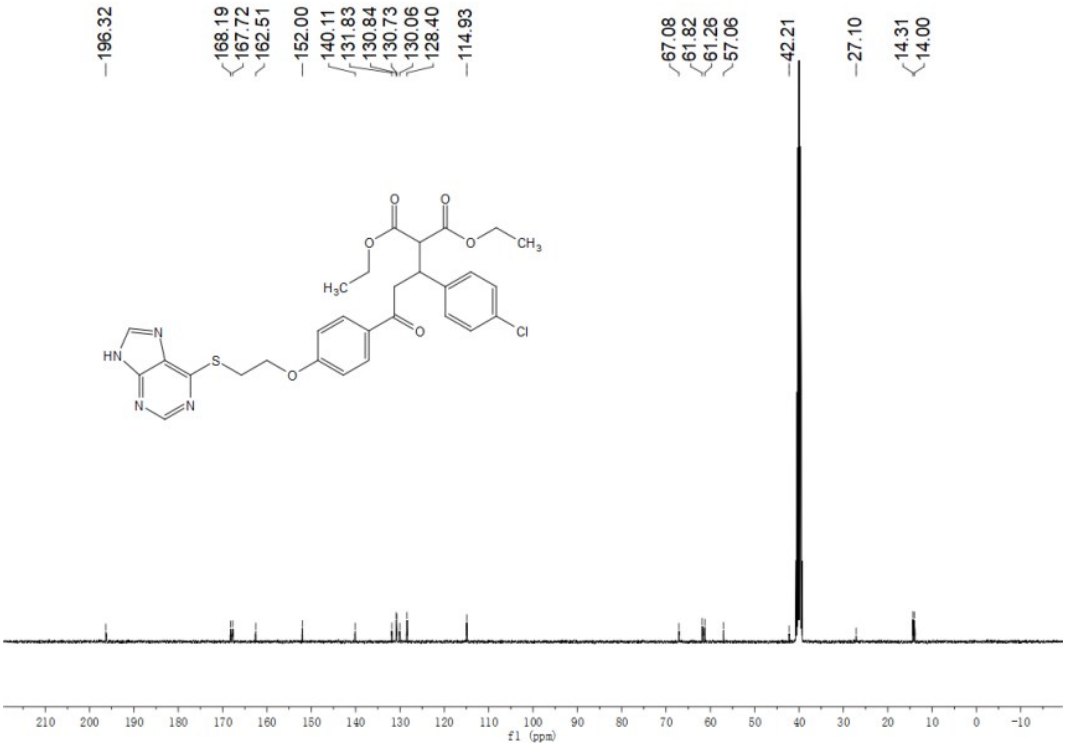


Figure S39. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5f**

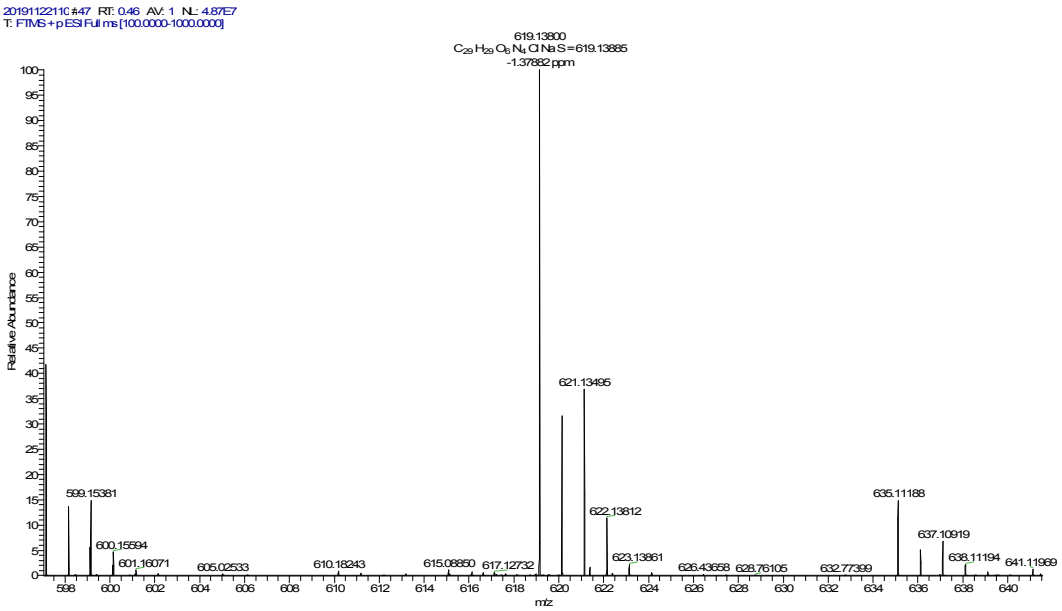


Figure S40. HRMS of compound **5f**

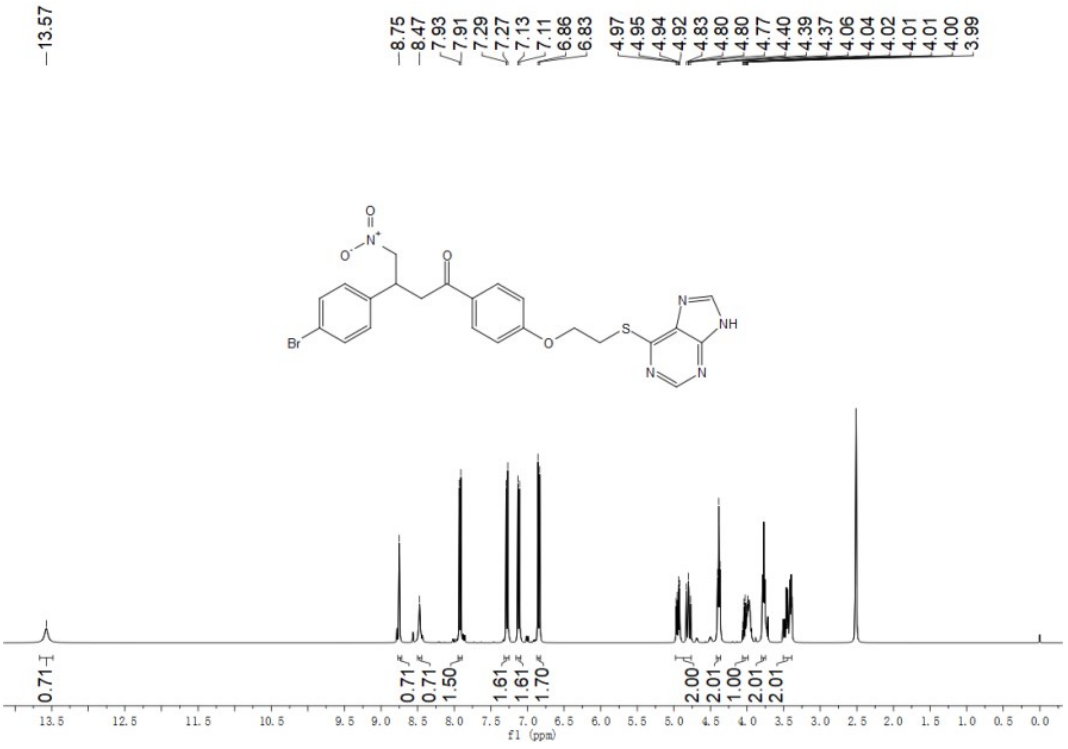


Figure S41. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5g**

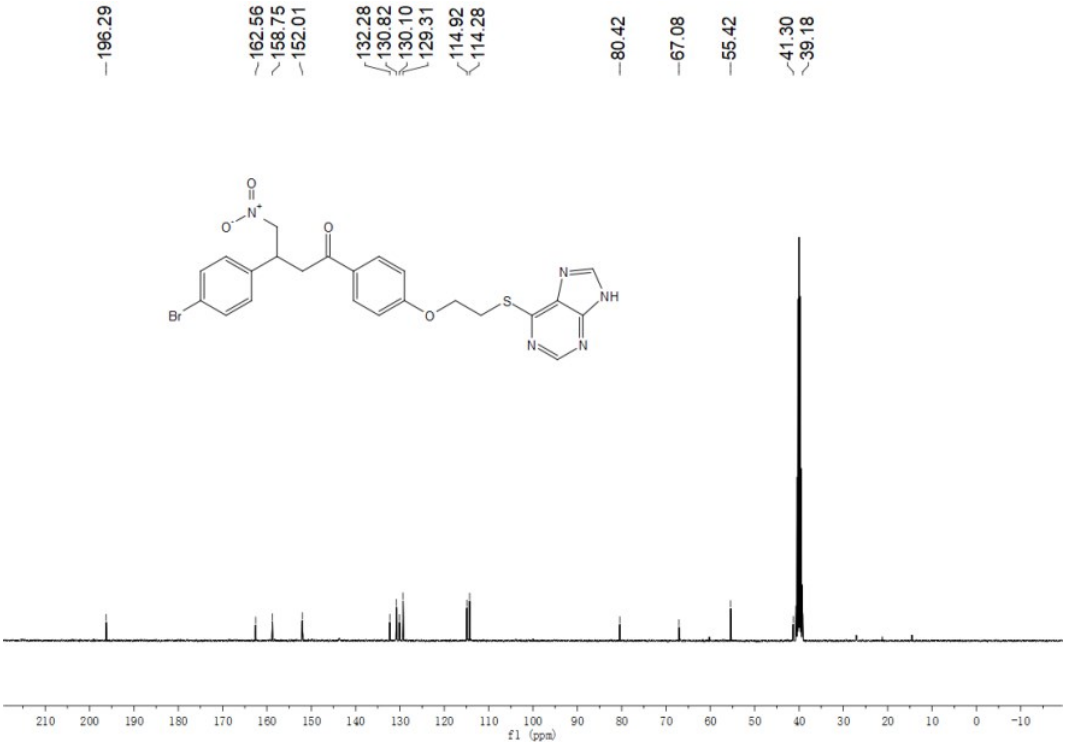


Figure S42. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5g**

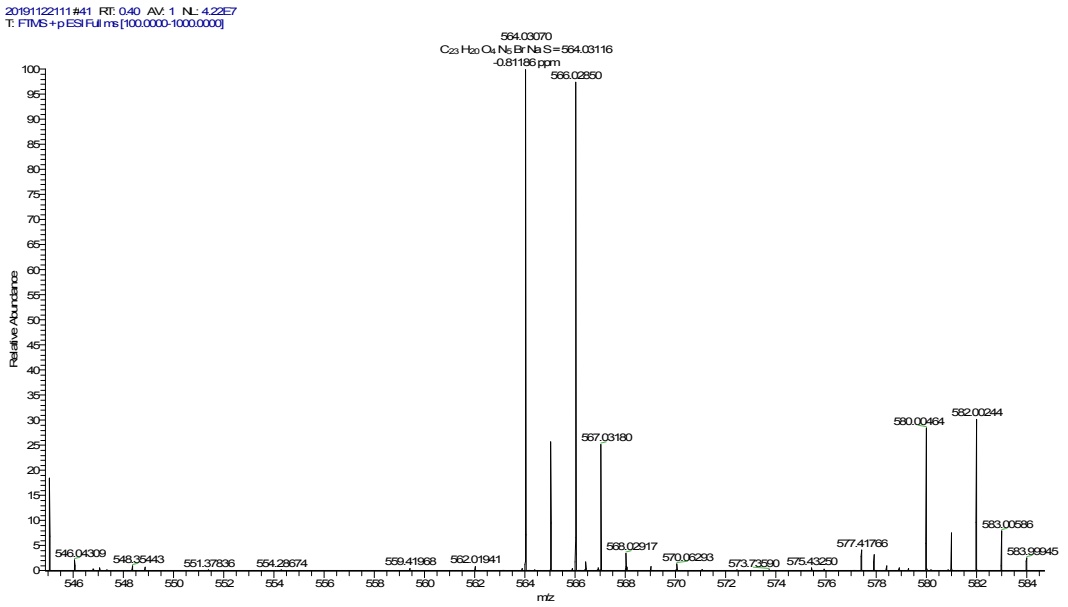


Figure S43. HRMS of compound **5g**

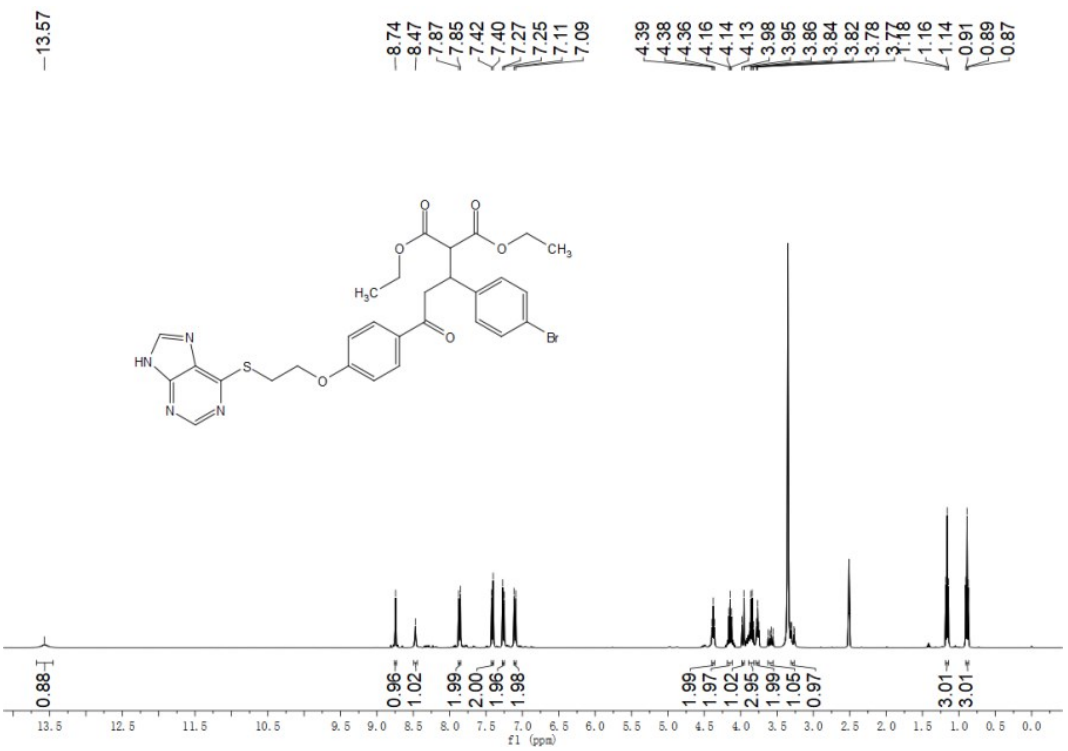


Figure S44. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5h**

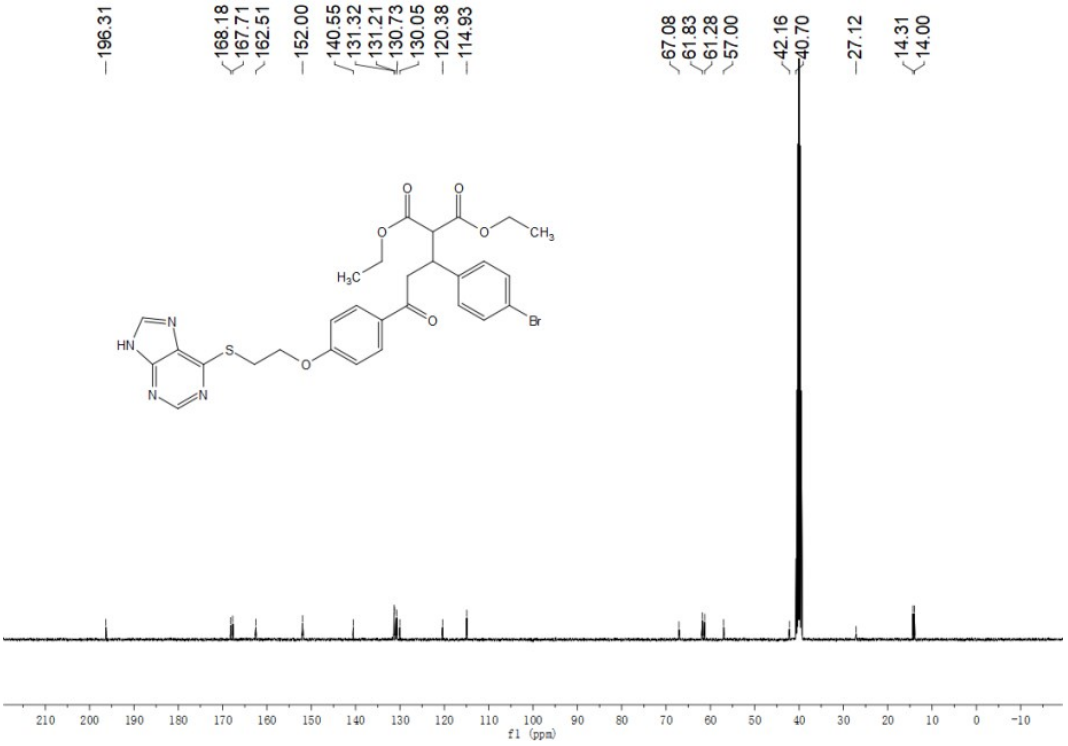


Figure S45. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5h**

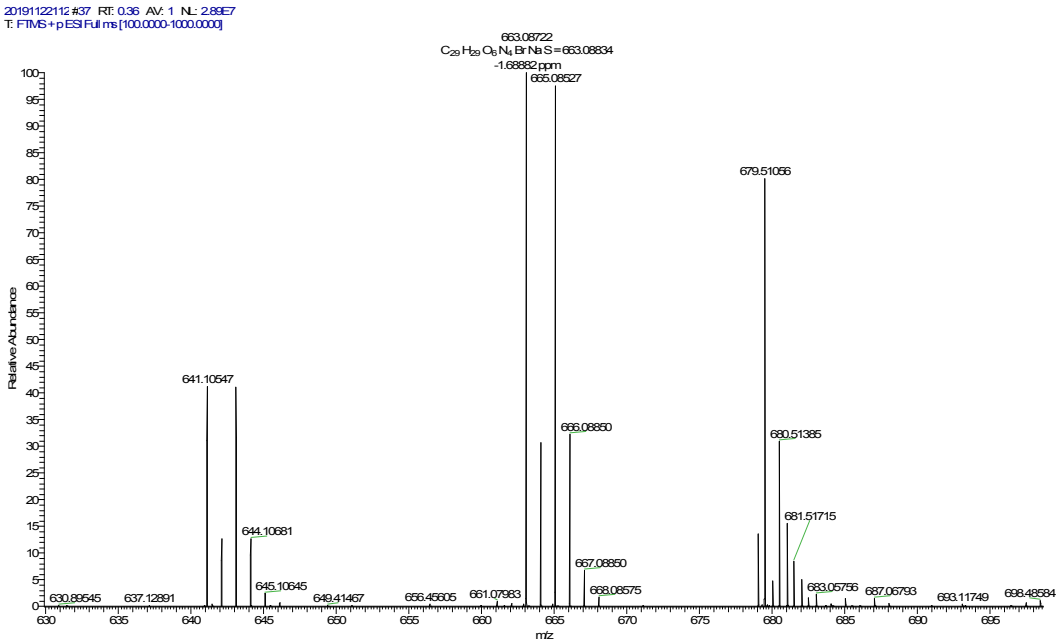


Figure S46. HRMS of compound **5h**

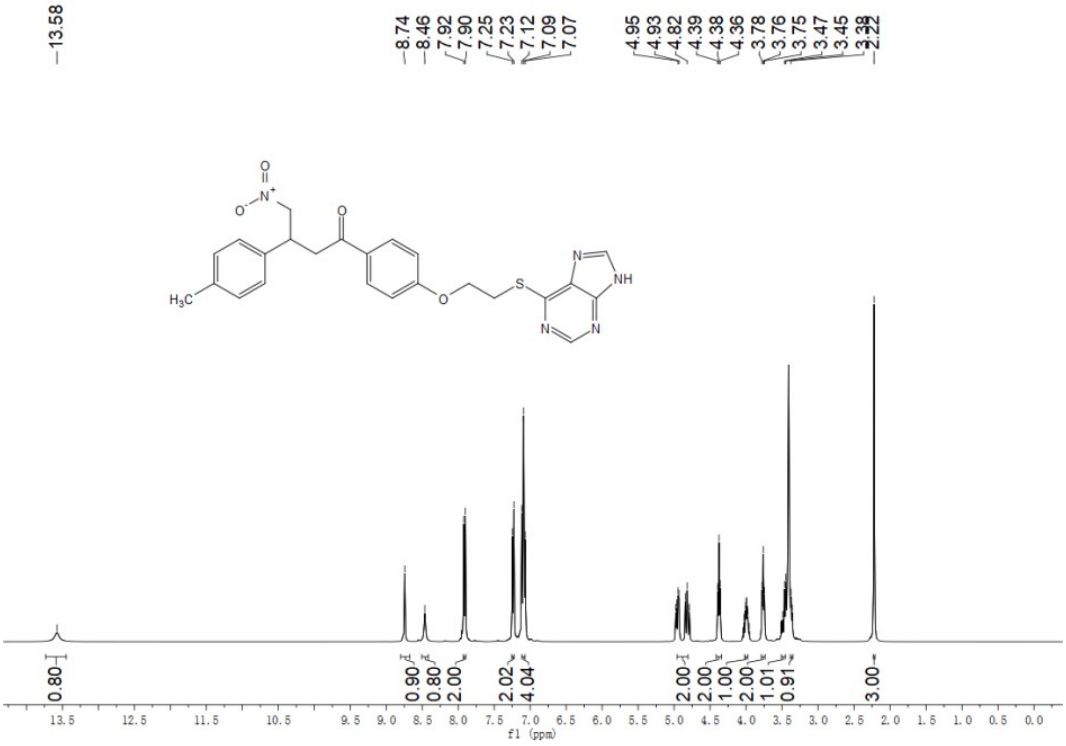


Figure S47. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5i**

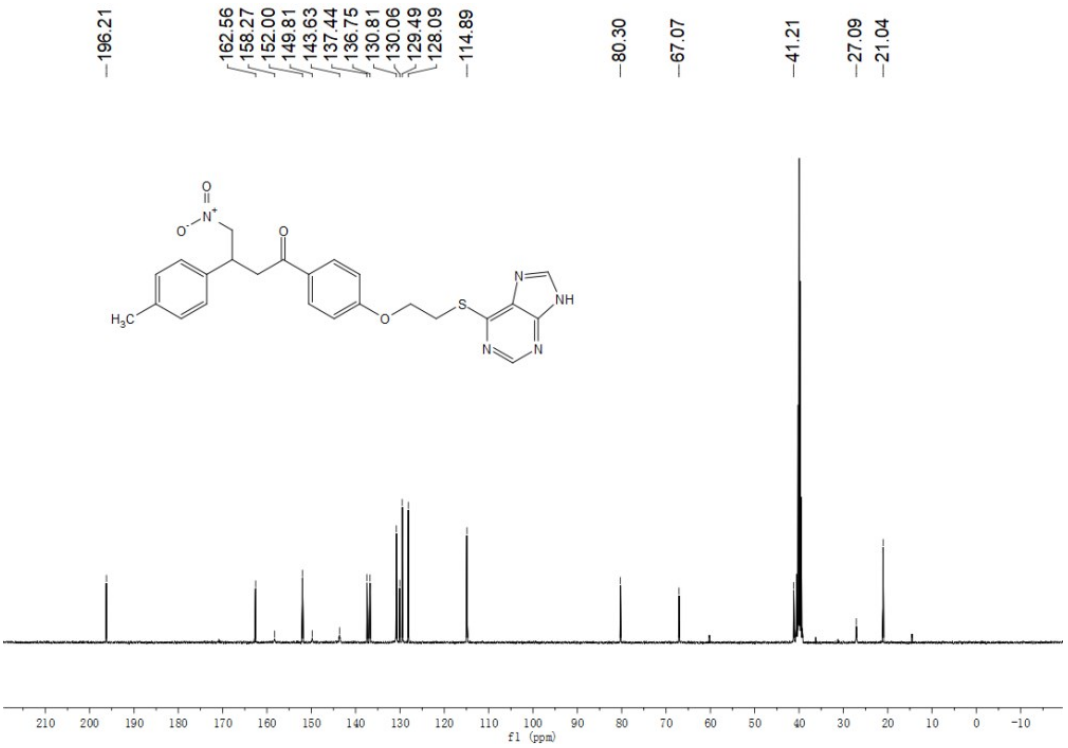


Figure S48. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5i**

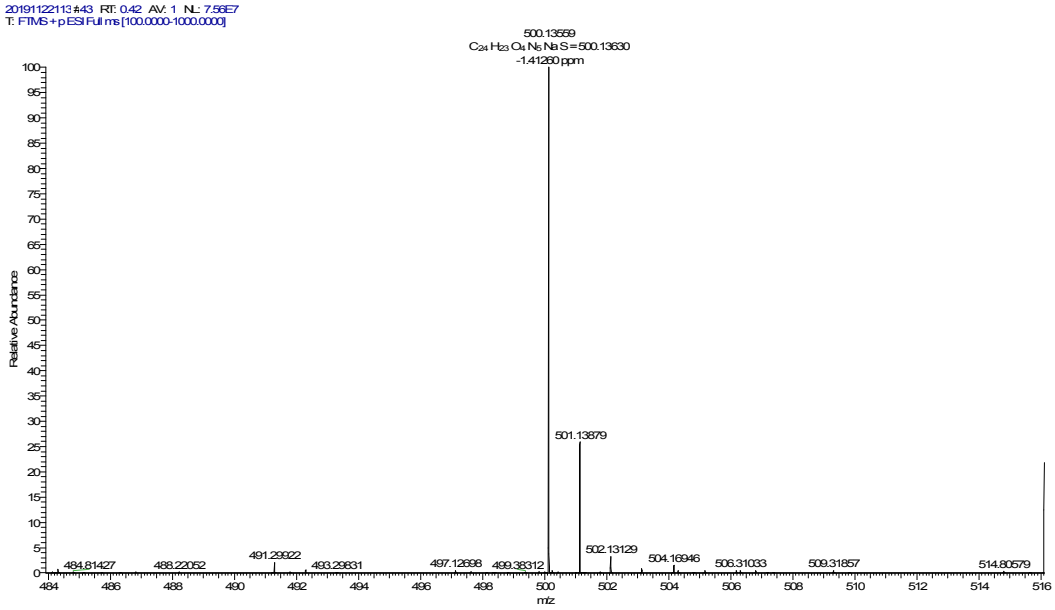


Figure S49. HRMS of compound **5i**

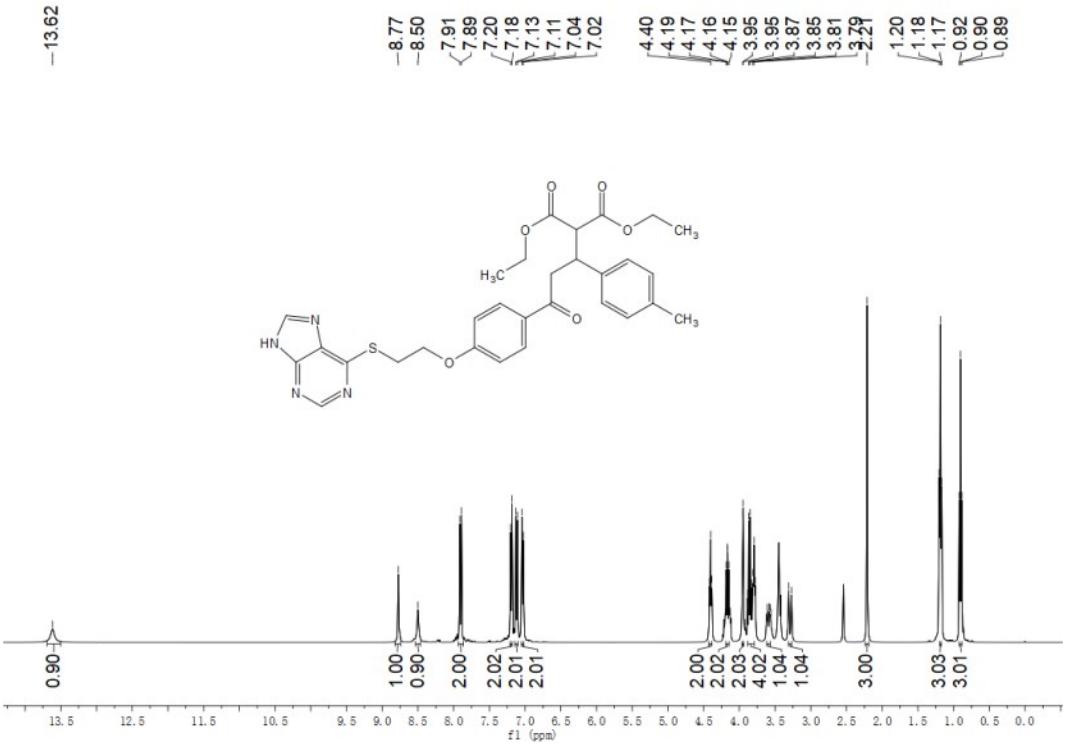


Figure S50. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5j**

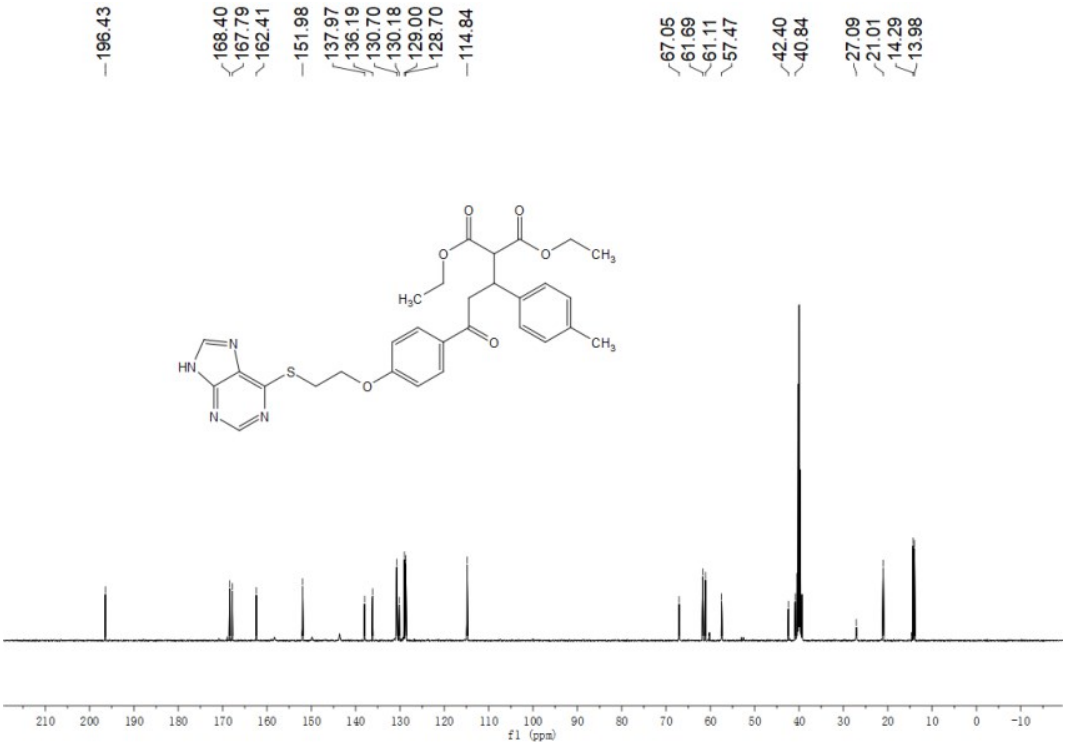


Figure S51. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5j**

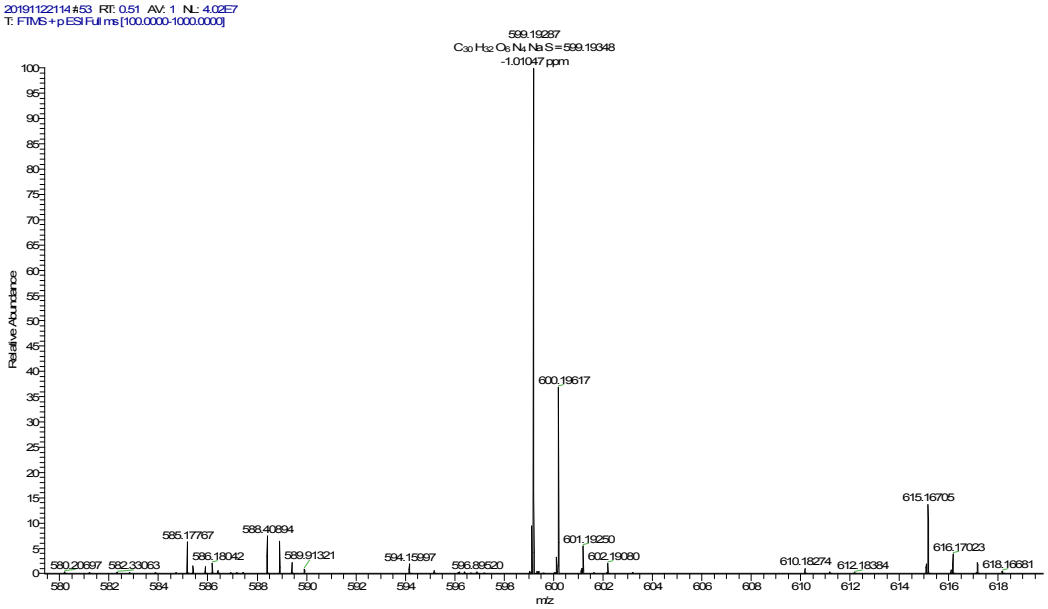


Figure S52. HRMS of compound **5j**

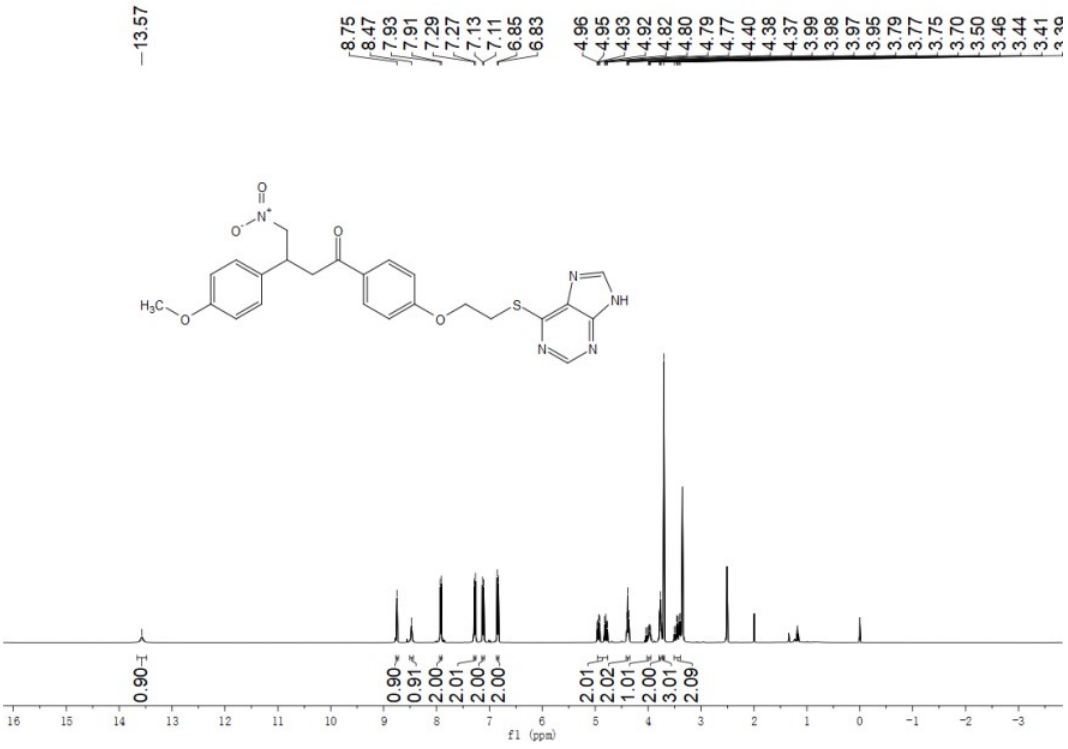


Figure S53. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5k**

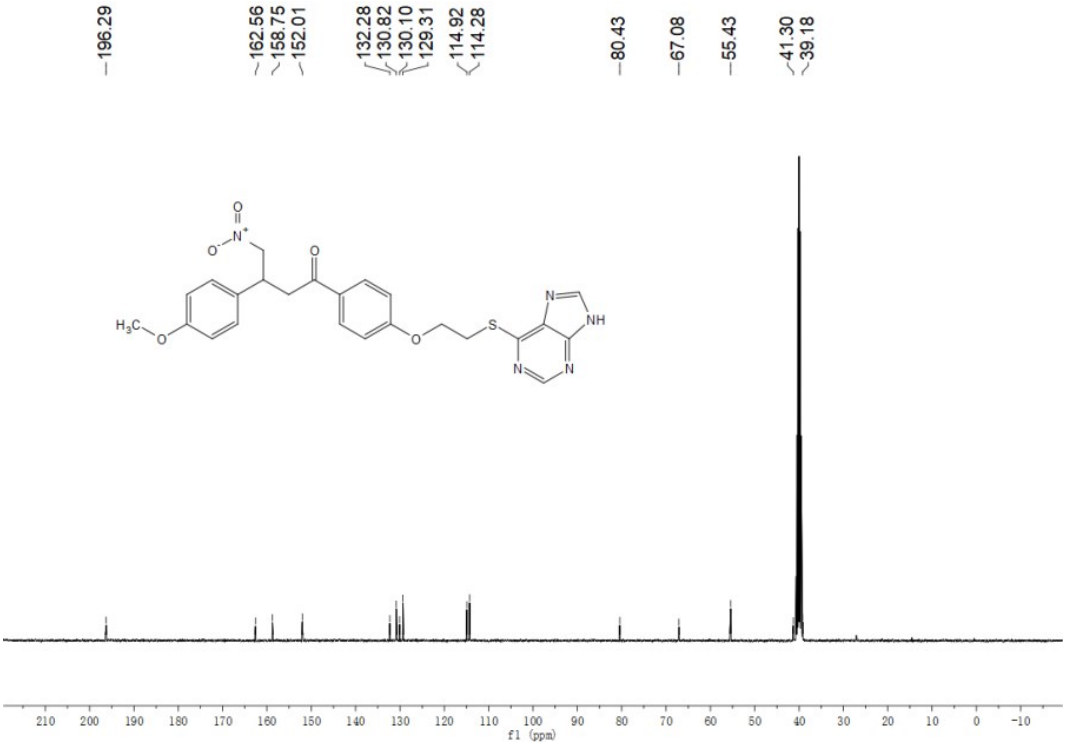


Figure S54. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5k**

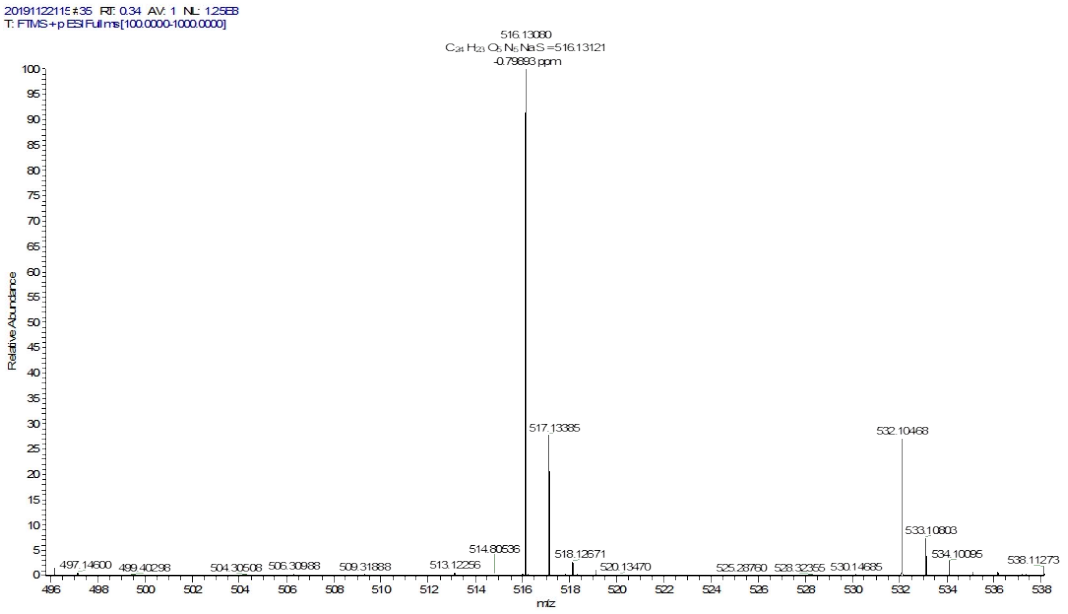


Figure S55. HRMS of compound **5k**

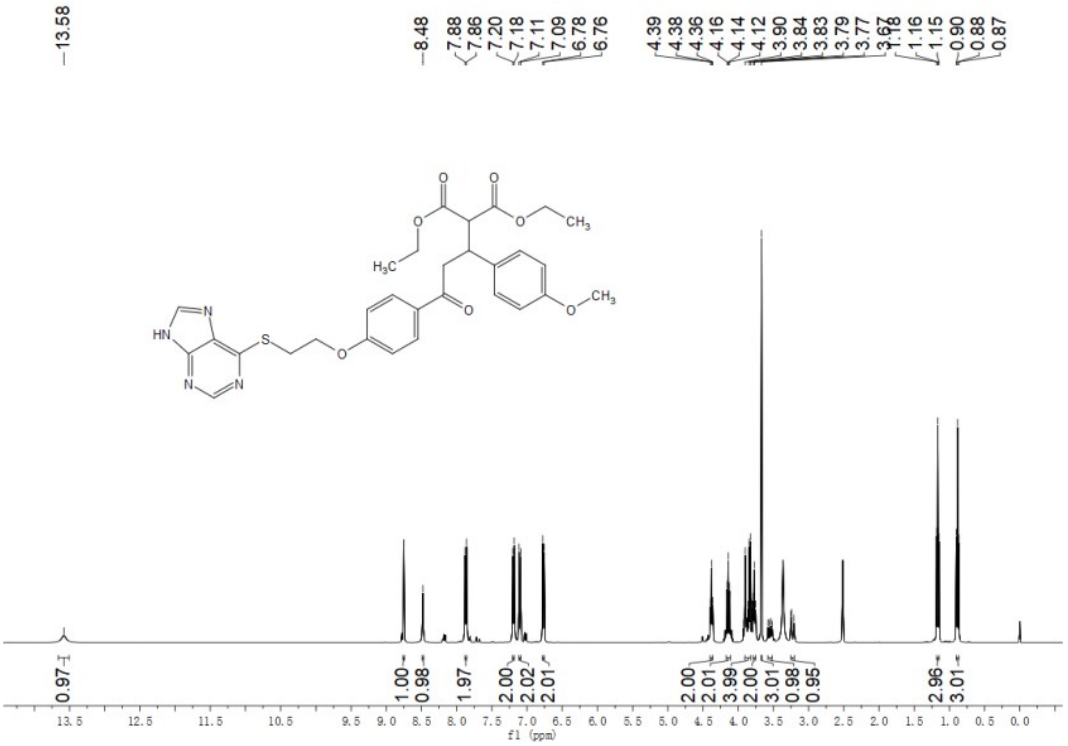


Figure S56. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **5l**

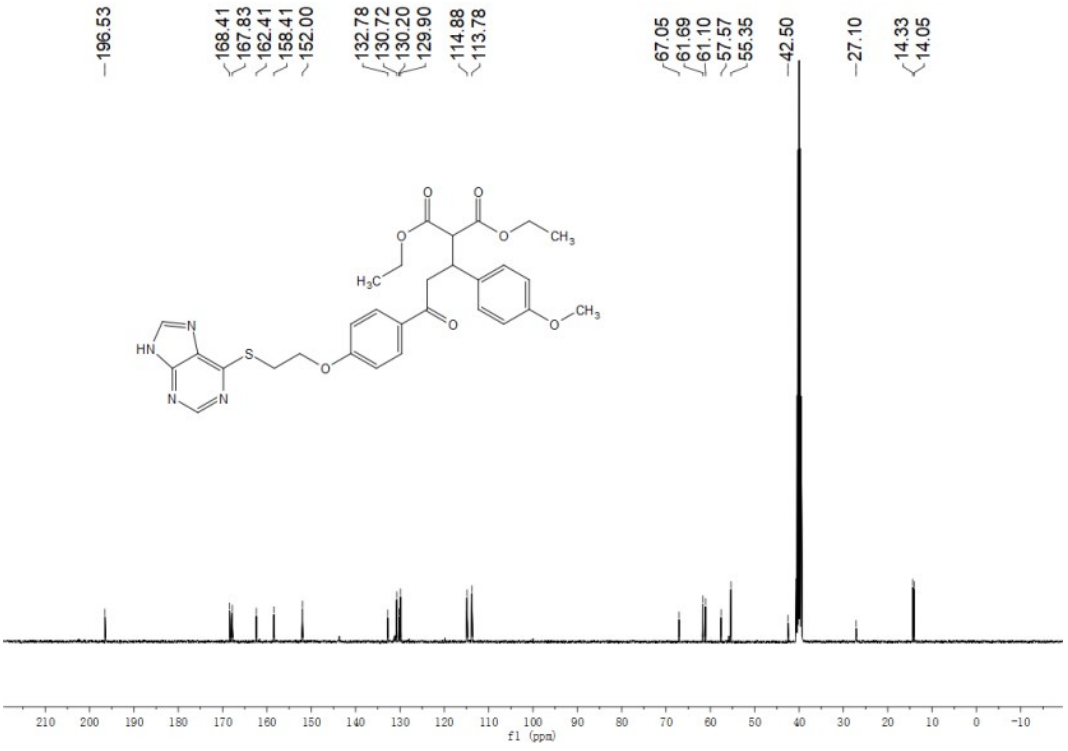


Figure S57. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **5l**

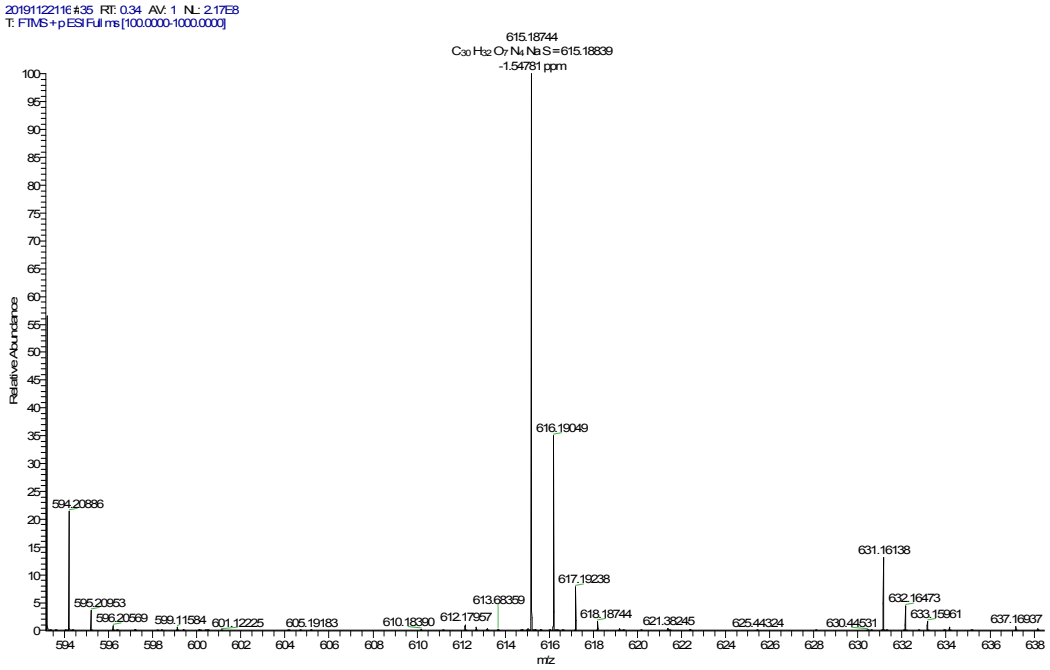


Figure S58. HRMS of compound **5l**

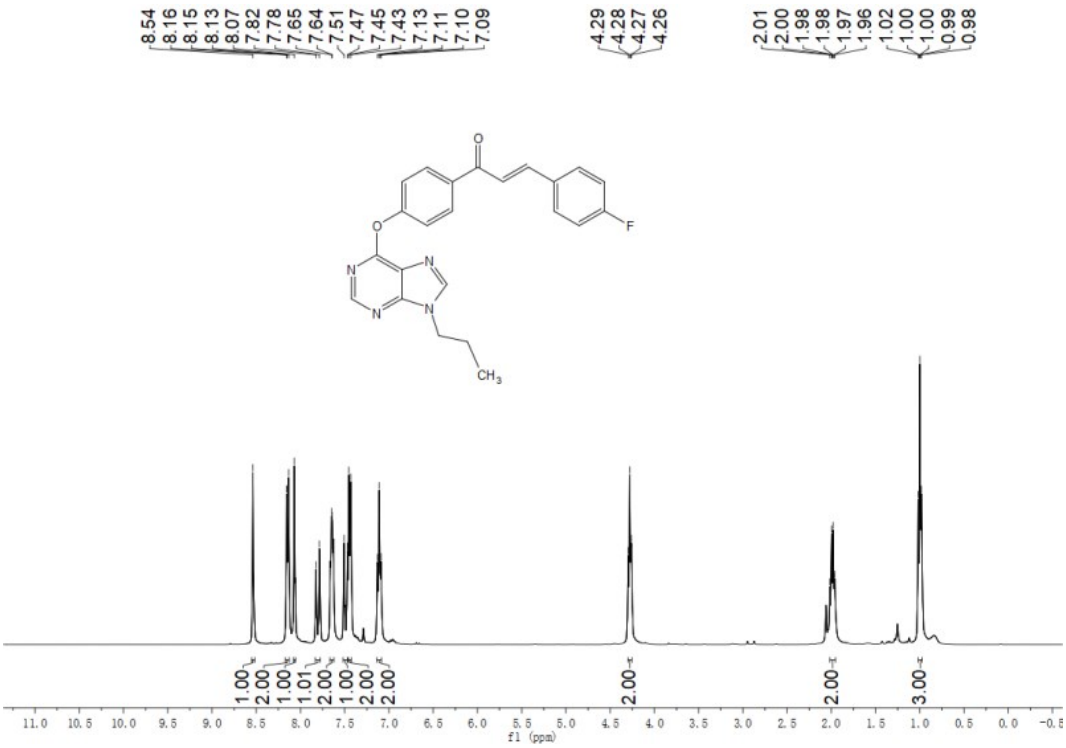


Figure S59. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **7a**

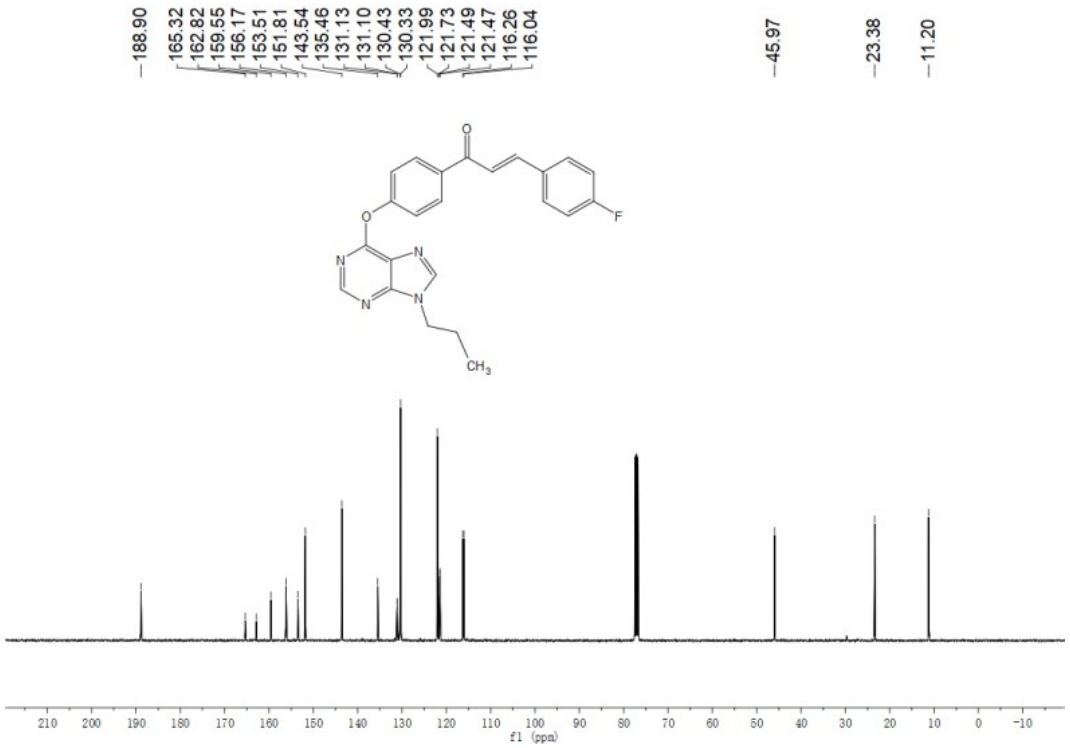


Figure S60. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **7a**

Figure S61. ^{19}F NMR ($CDCl_3$, 400 MHz) spectrum of compound **7a**

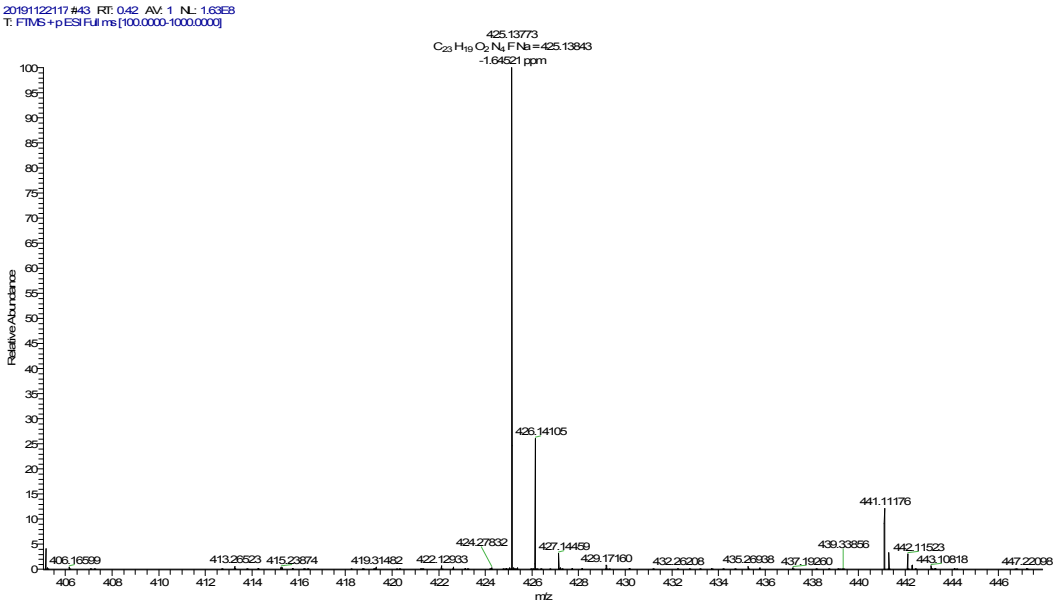


Figure S62. HRMS of compound **7a**

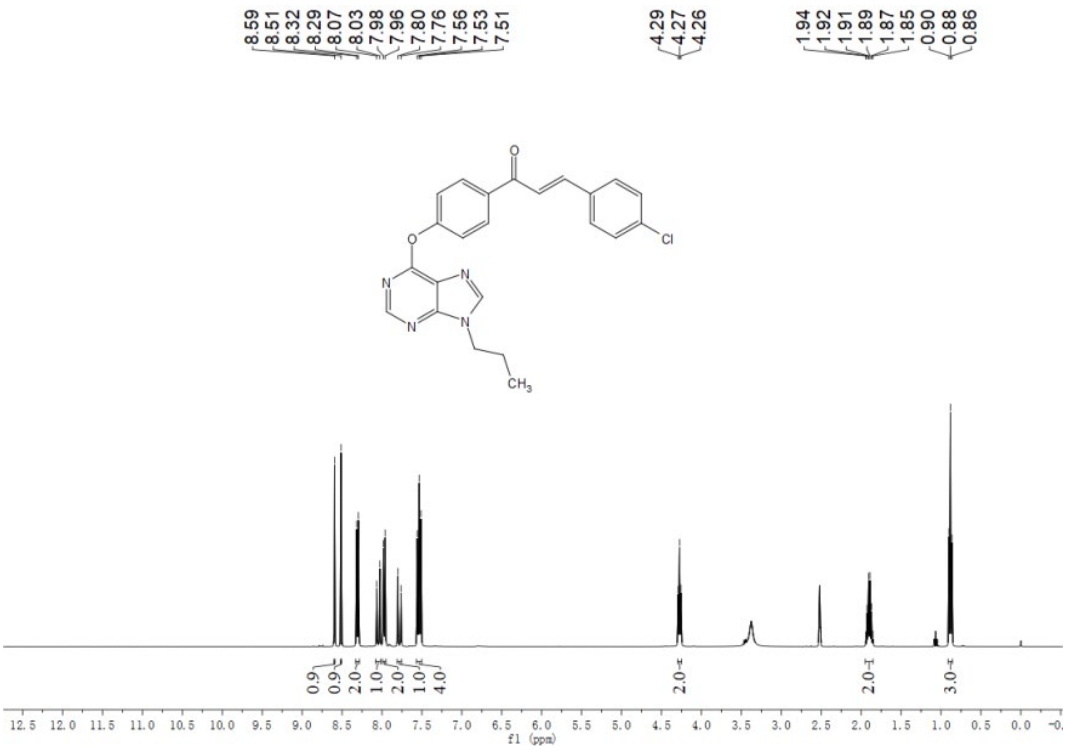


Figure S63. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **7b**

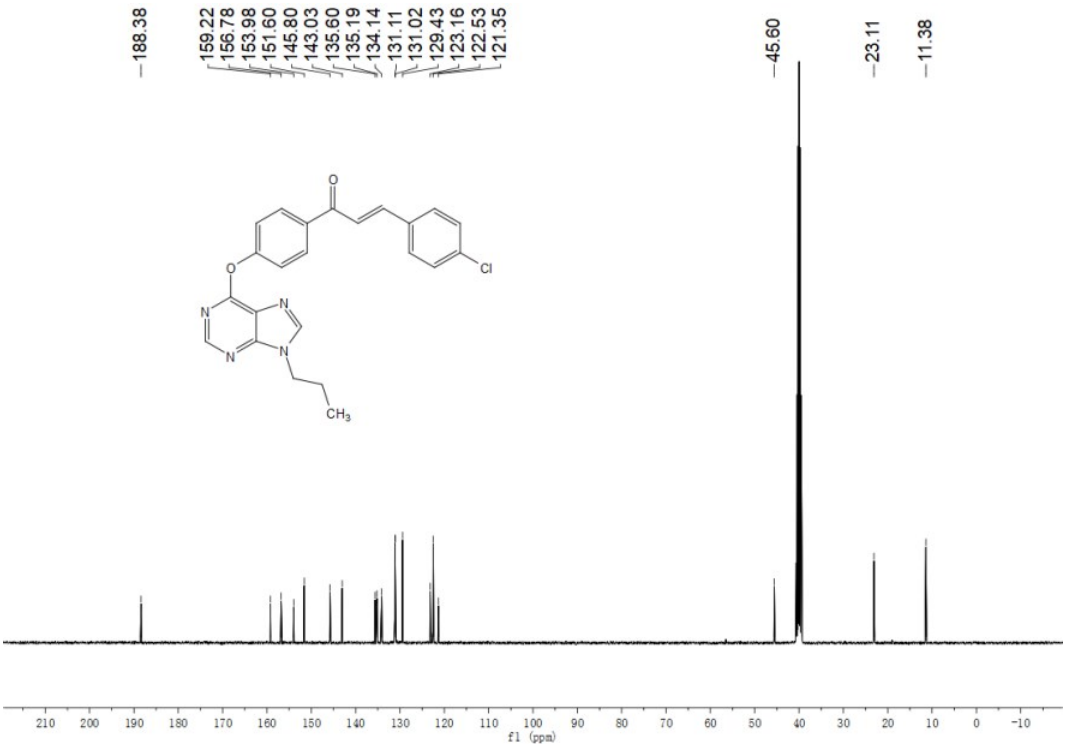


Figure S64. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **7b**

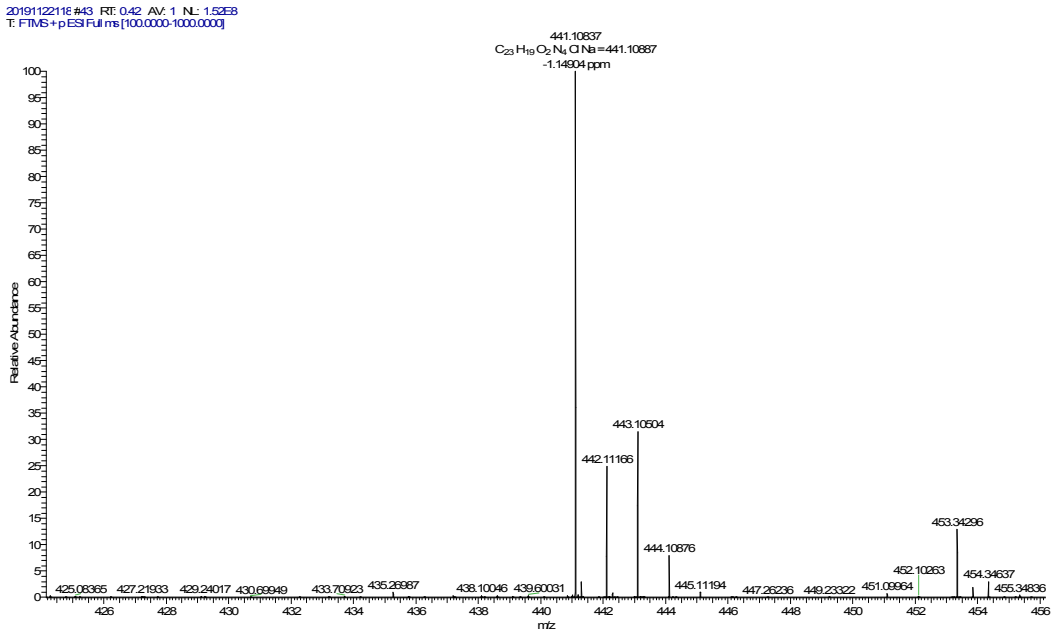


Figure S65. HRMS of compound **7b**

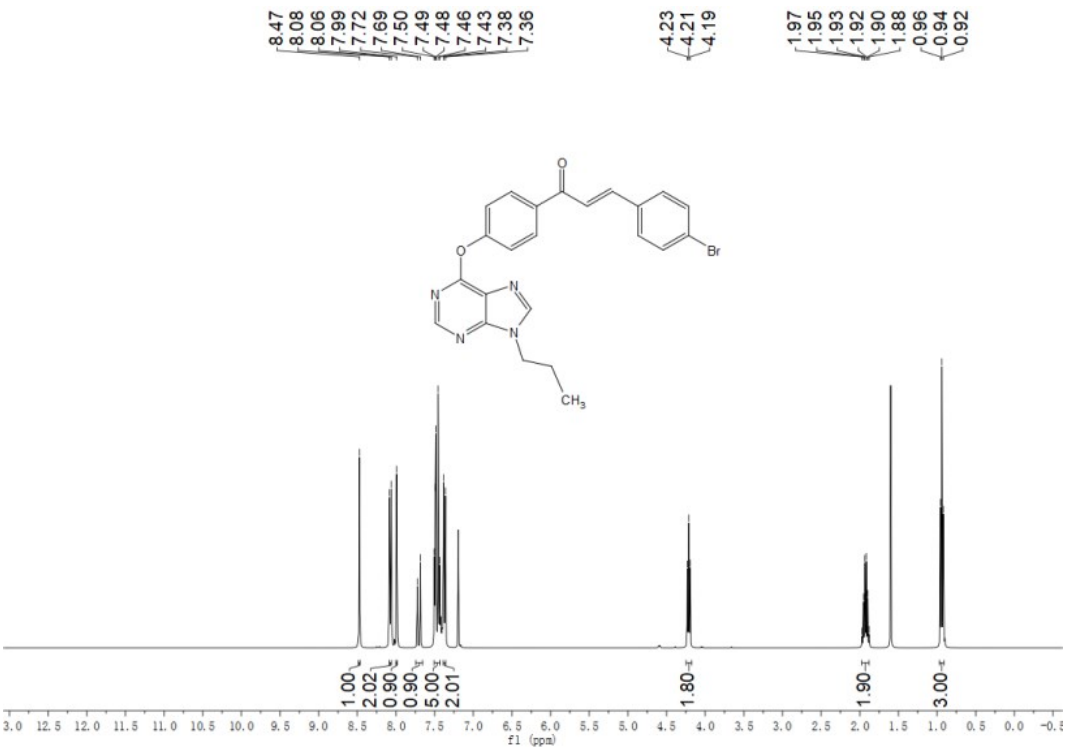


Figure S66. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **7c**

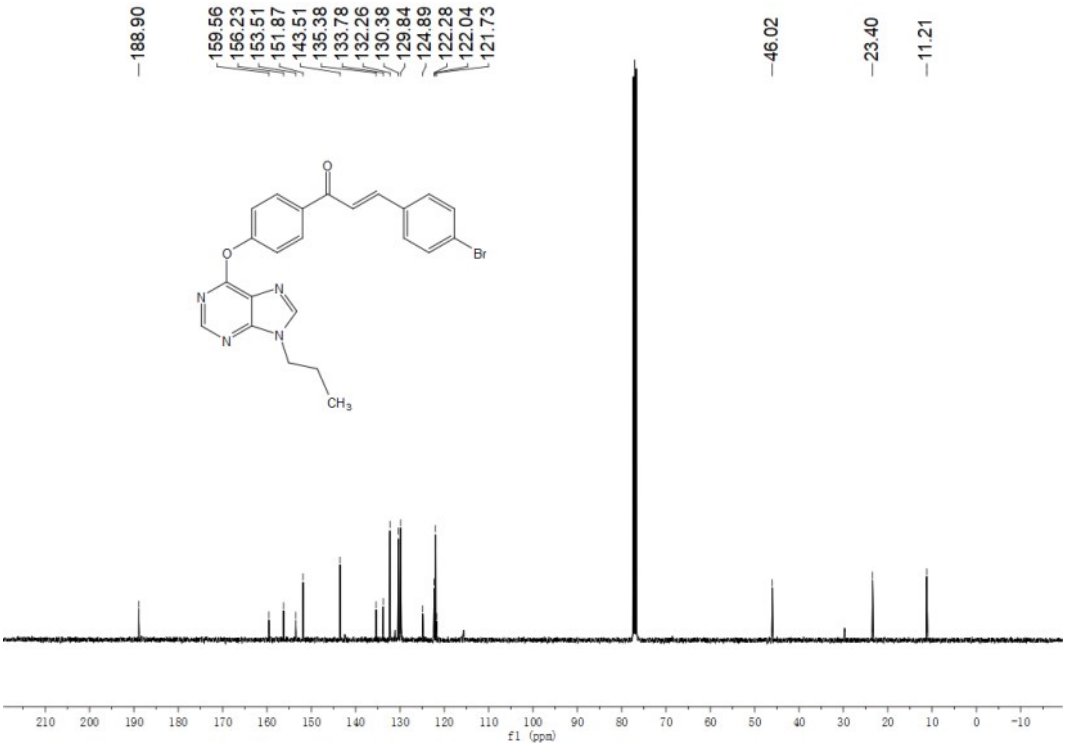


Figure S67. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **7c**

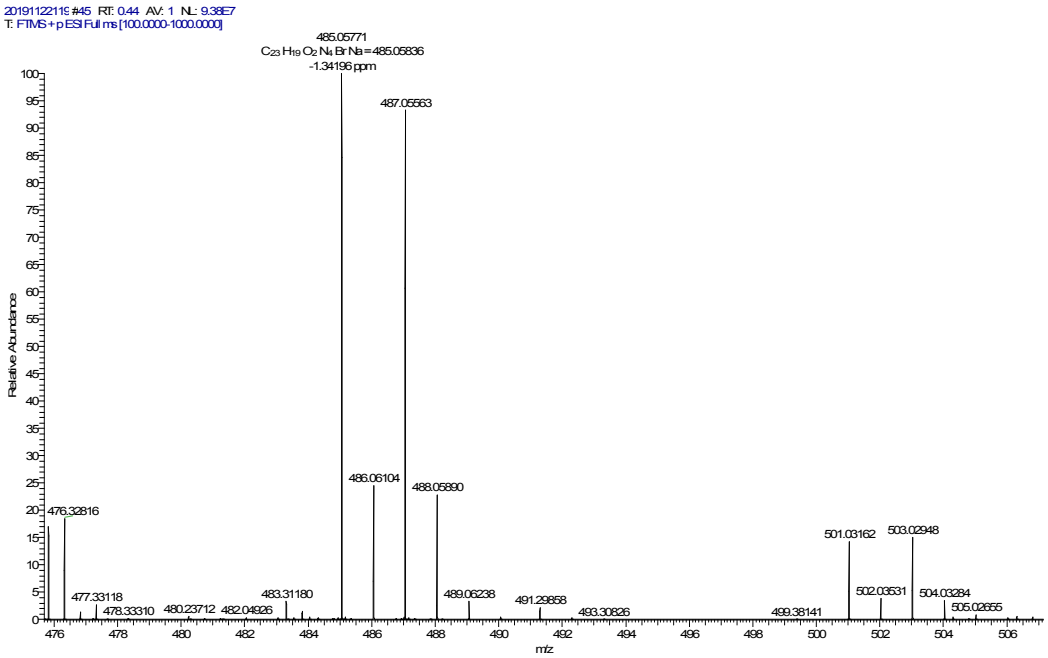


Figure S68. HRMS of compound **7c**

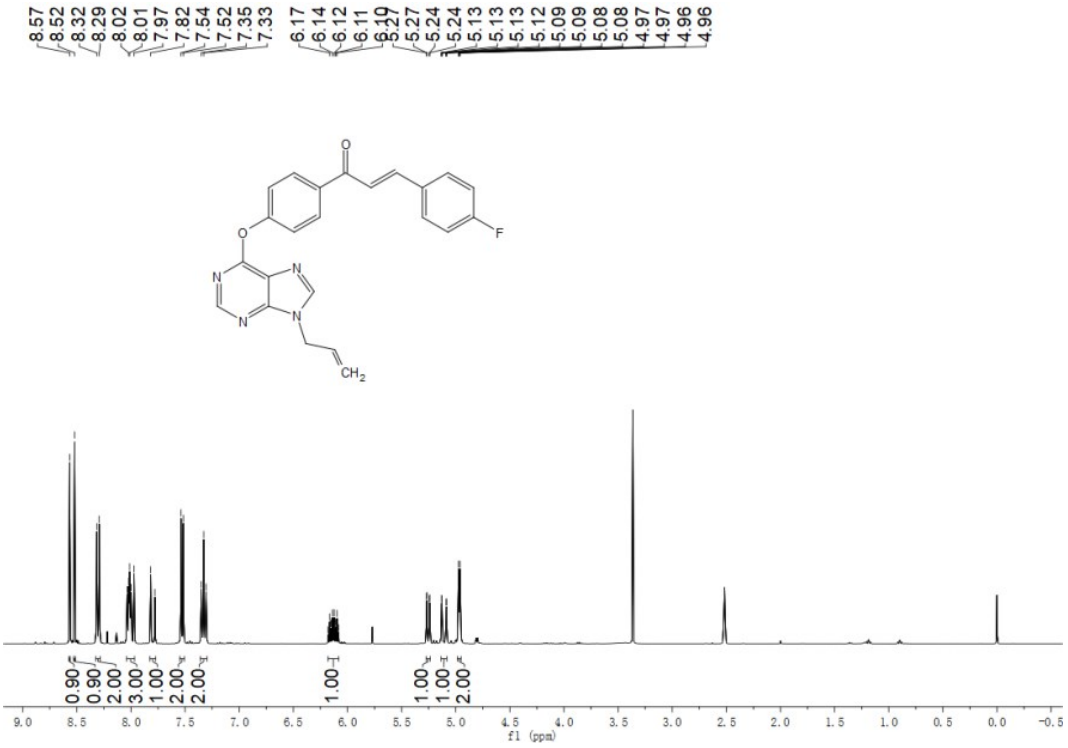


Figure S69. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **7d**

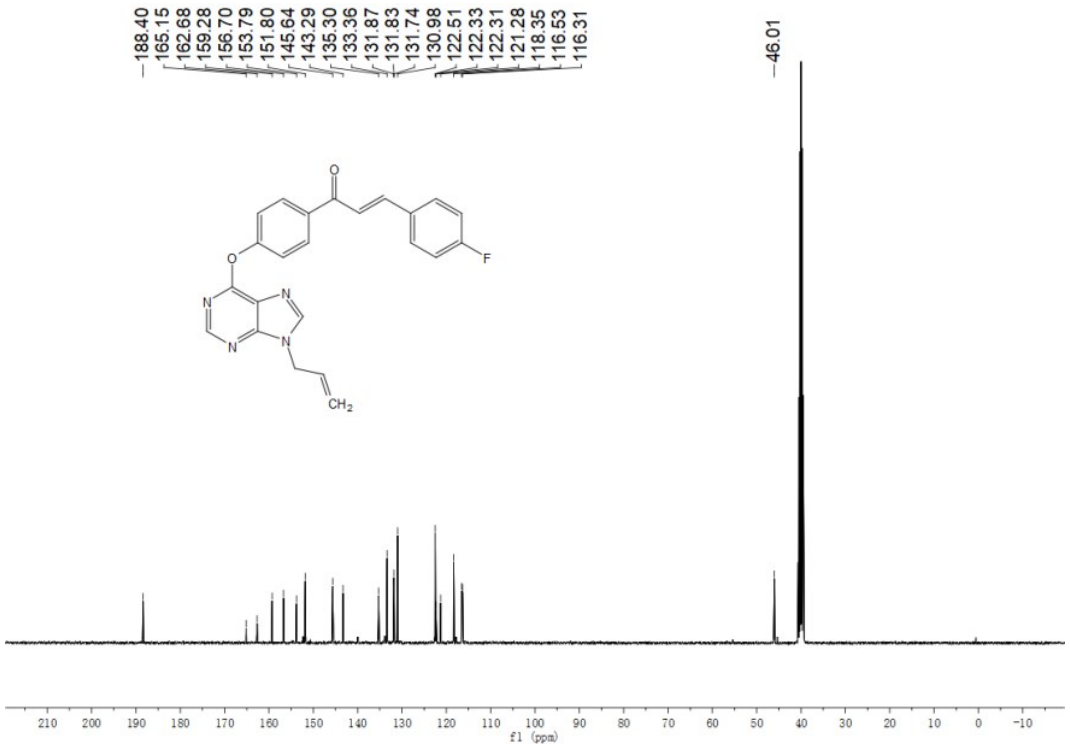


Figure S70. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **7d**

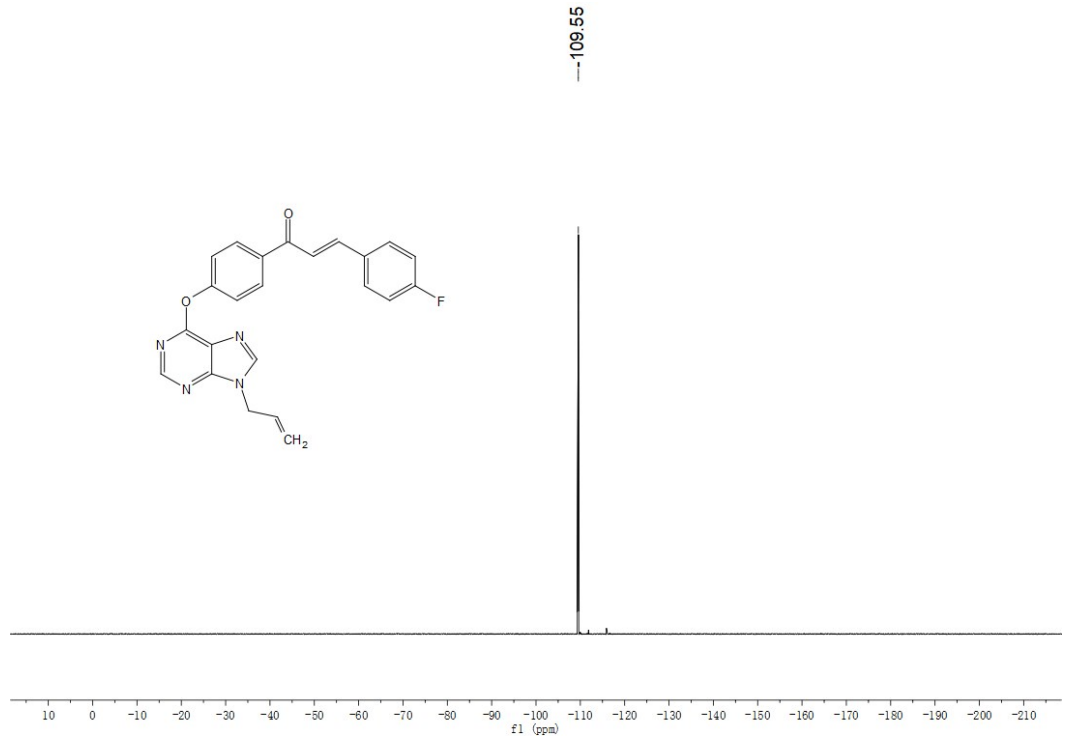


Figure S71. ^{19}F NMR (DMSO-d_6, 400 MHz) spectrum of compound **7d**

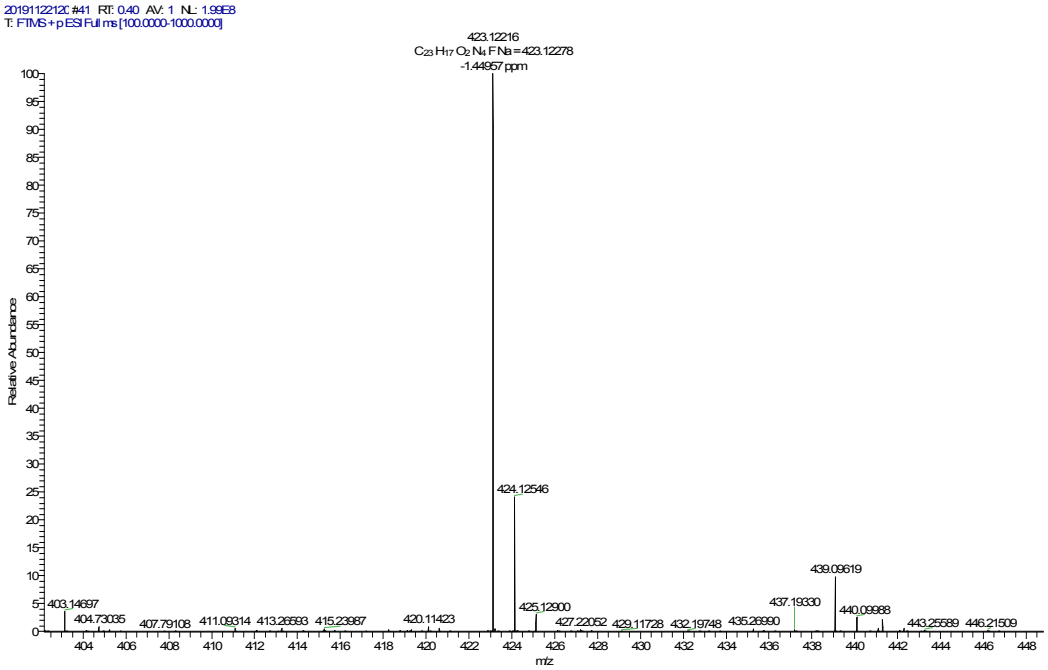


Figure S72. HRMS of compound **7d**

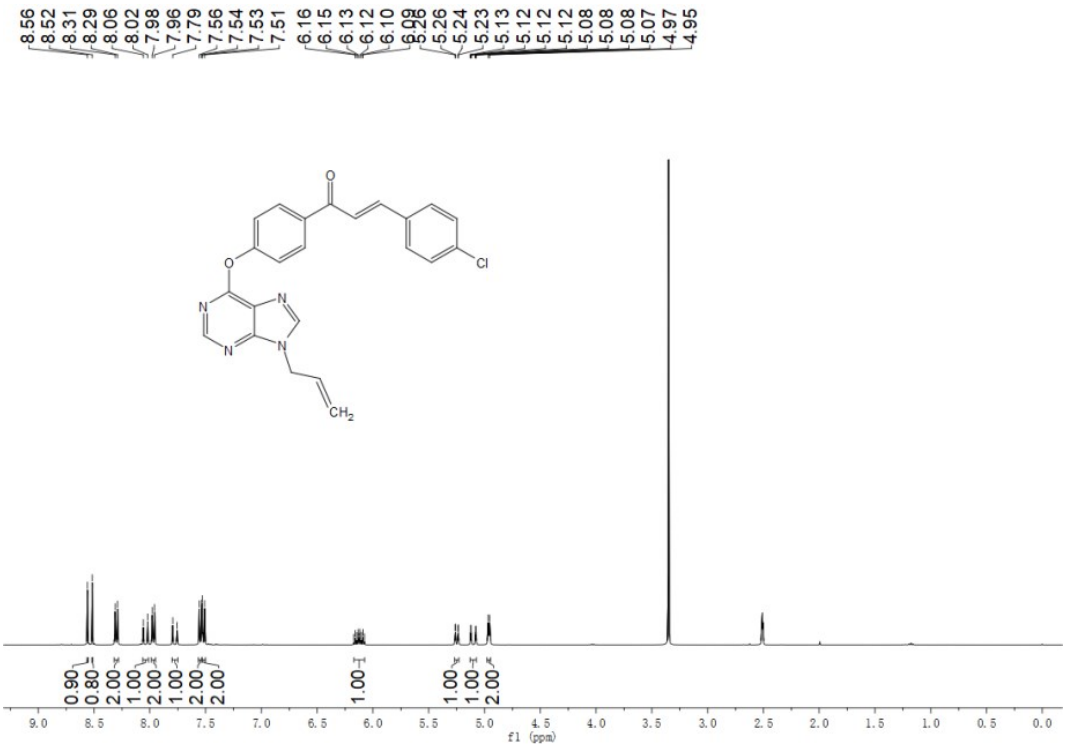


Figure S73. ^{1}H NMR (DMSO-d_6, 400 MHz) spectrum of compound **7e**

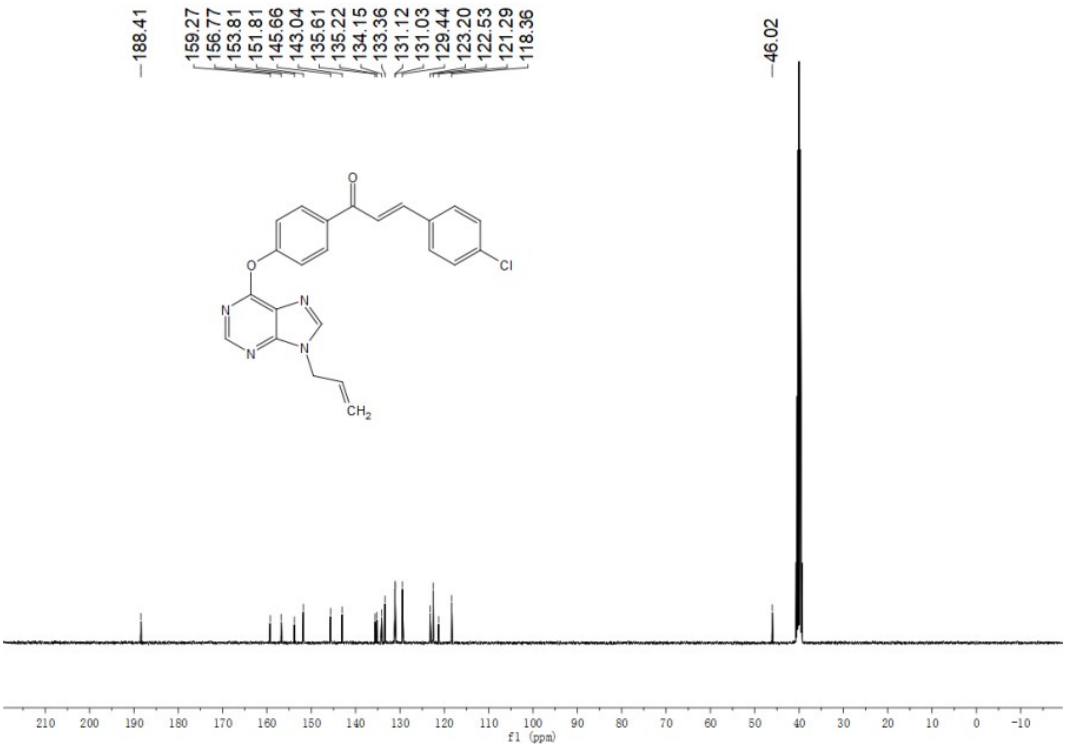


Figure S74. ^{13}C NMR (DMSO-d_6, 400 MHz) spectrum of compound **7e**

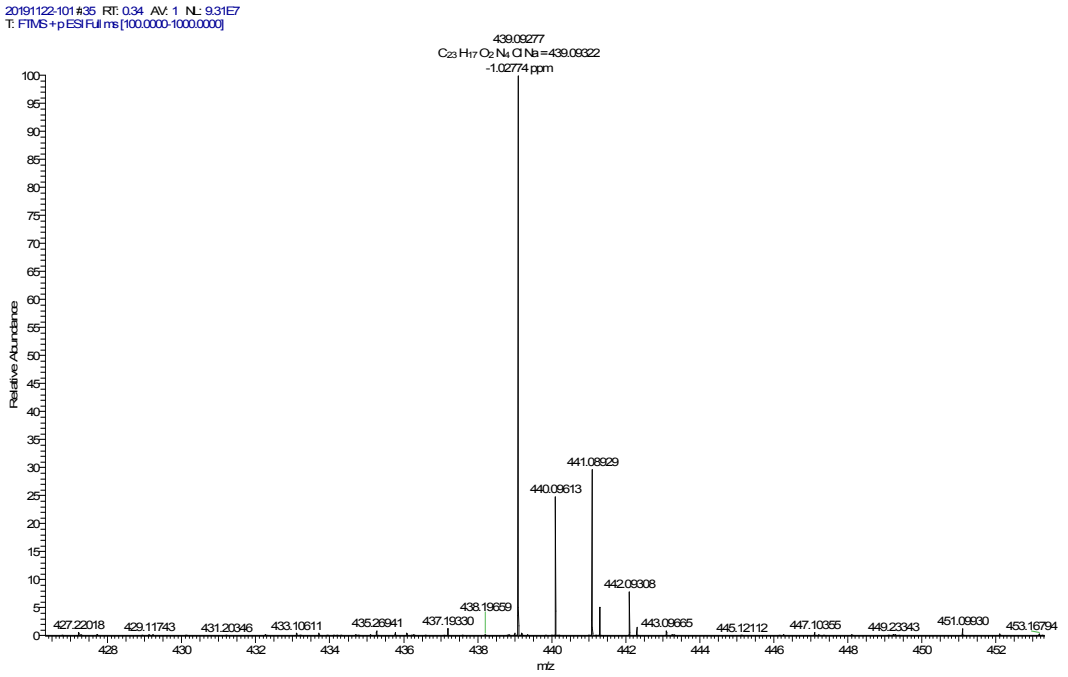


Figure S75. HRMS of compound **7e**

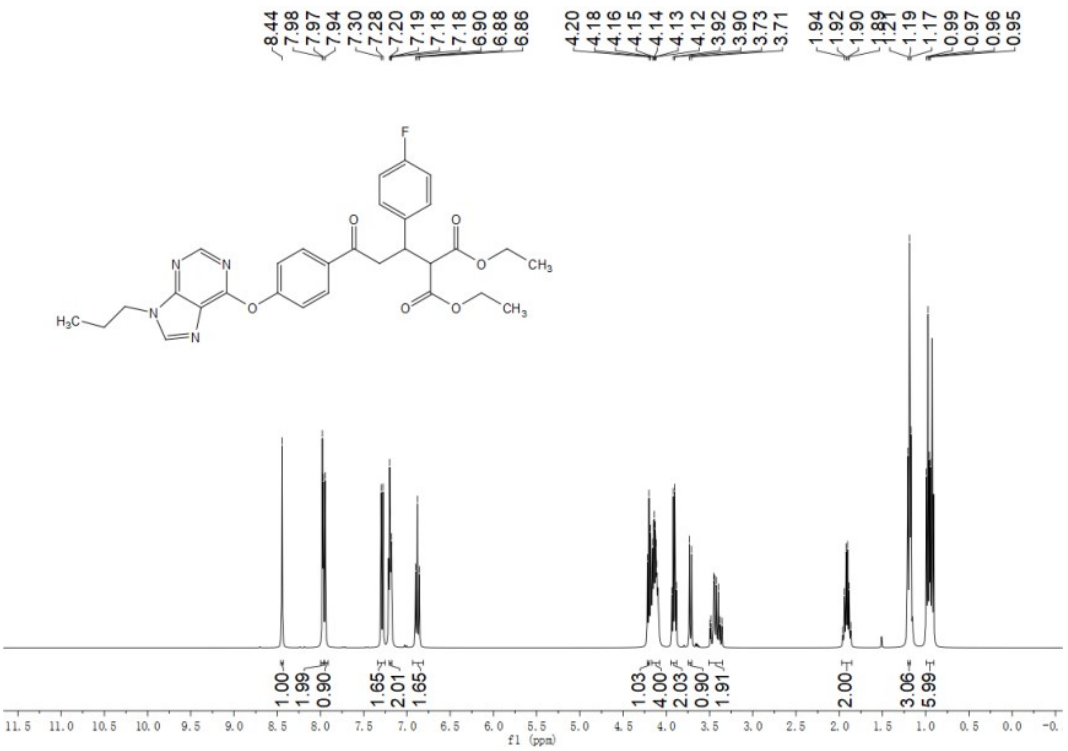


Figure S76. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8a**

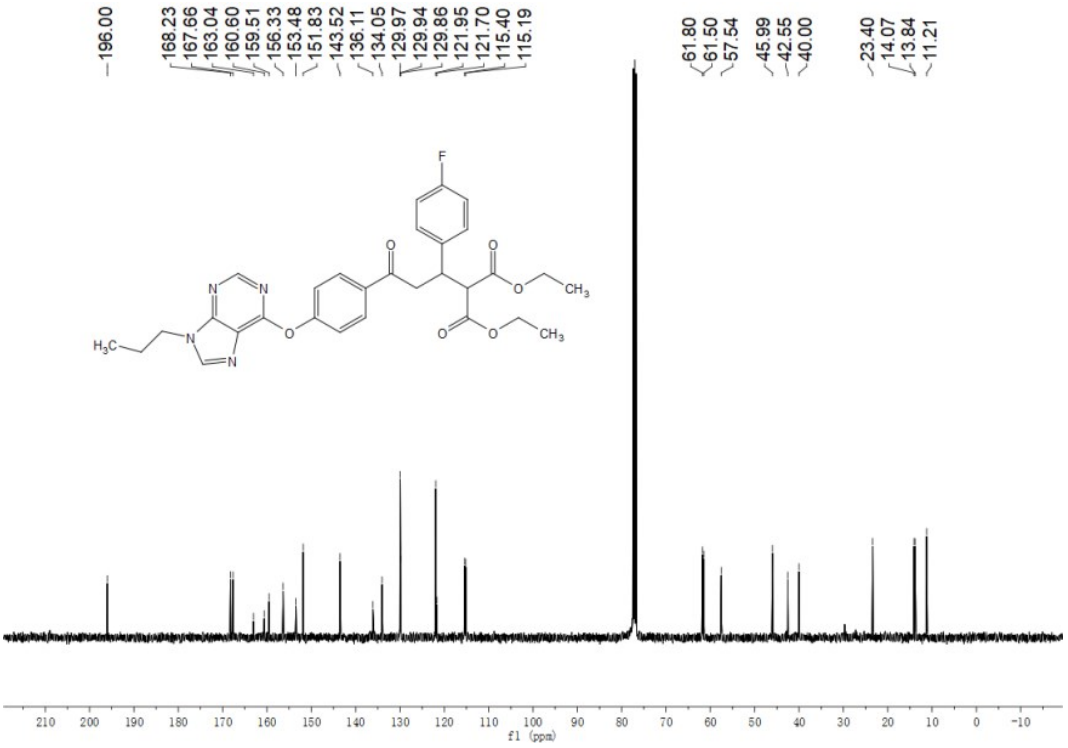


Figure S77. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **8a**

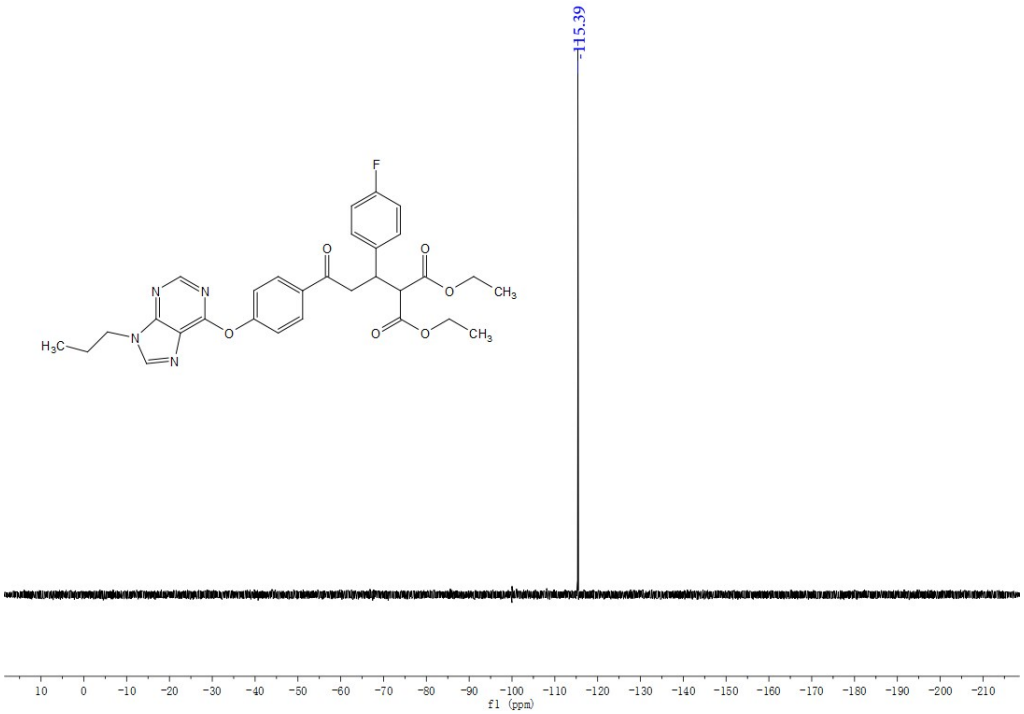


Figure S78. ^{19}F NMR ($CDCl_3$, 400MHz) spectrum of compound **8a**

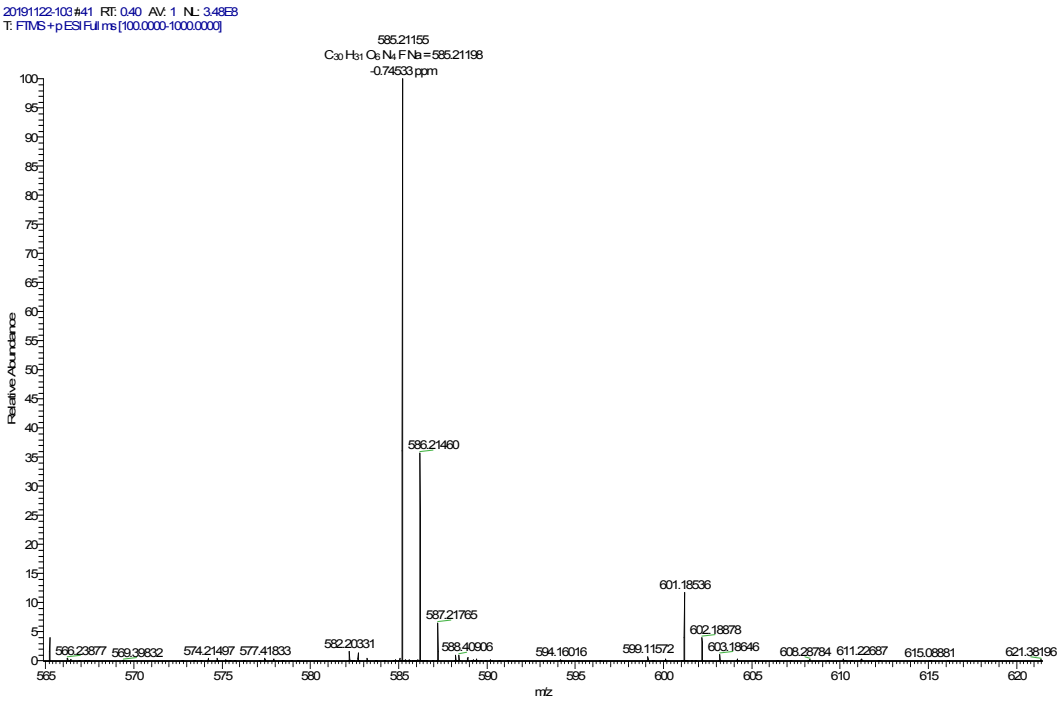


Figure S79. HRMS of compound **8a**

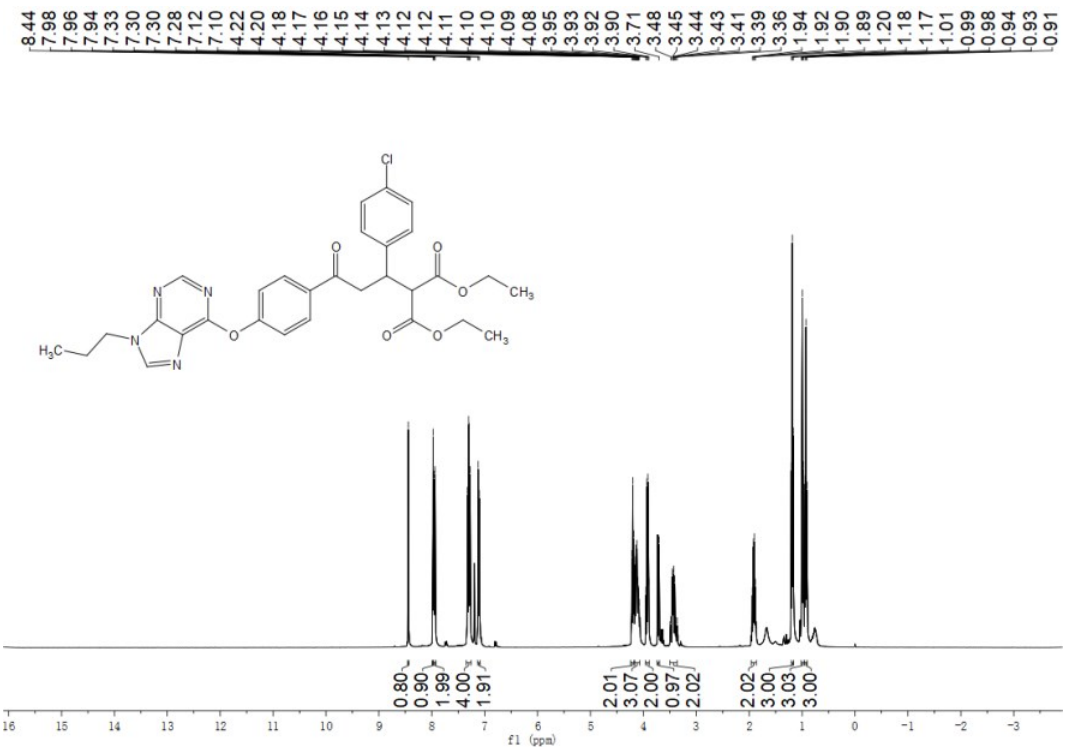


Figure S80. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8b**

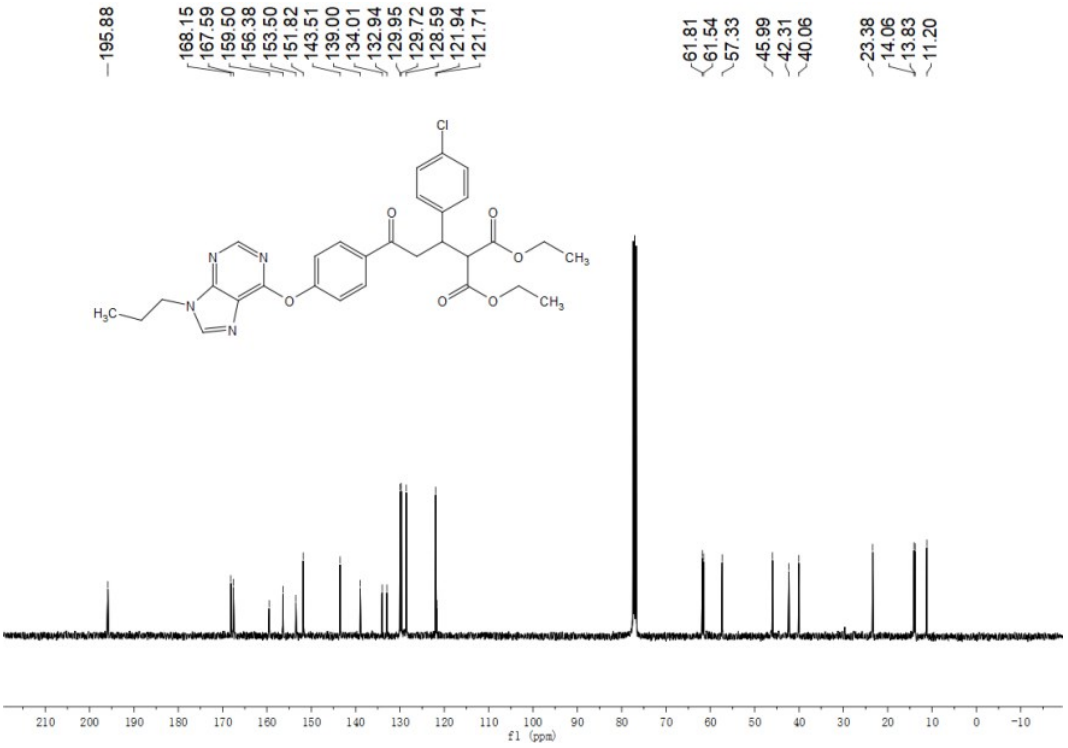


Figure S81. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **8b**

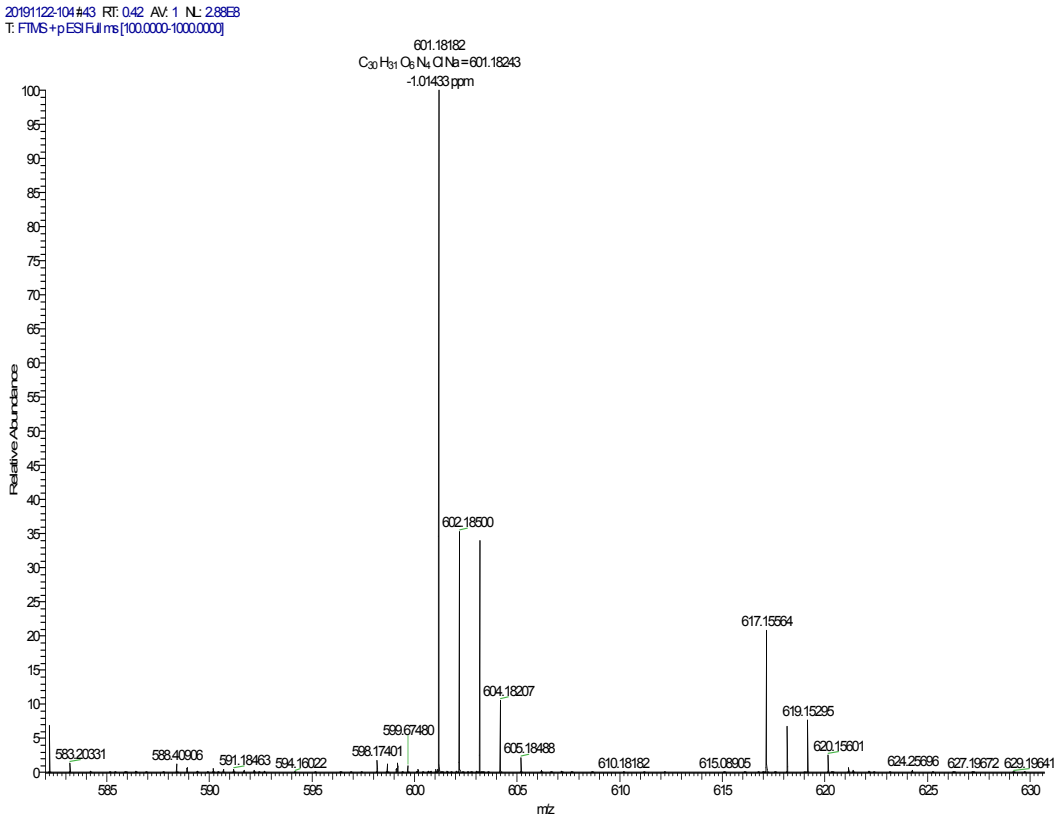


Figure S82. HRMS of compound **8b**

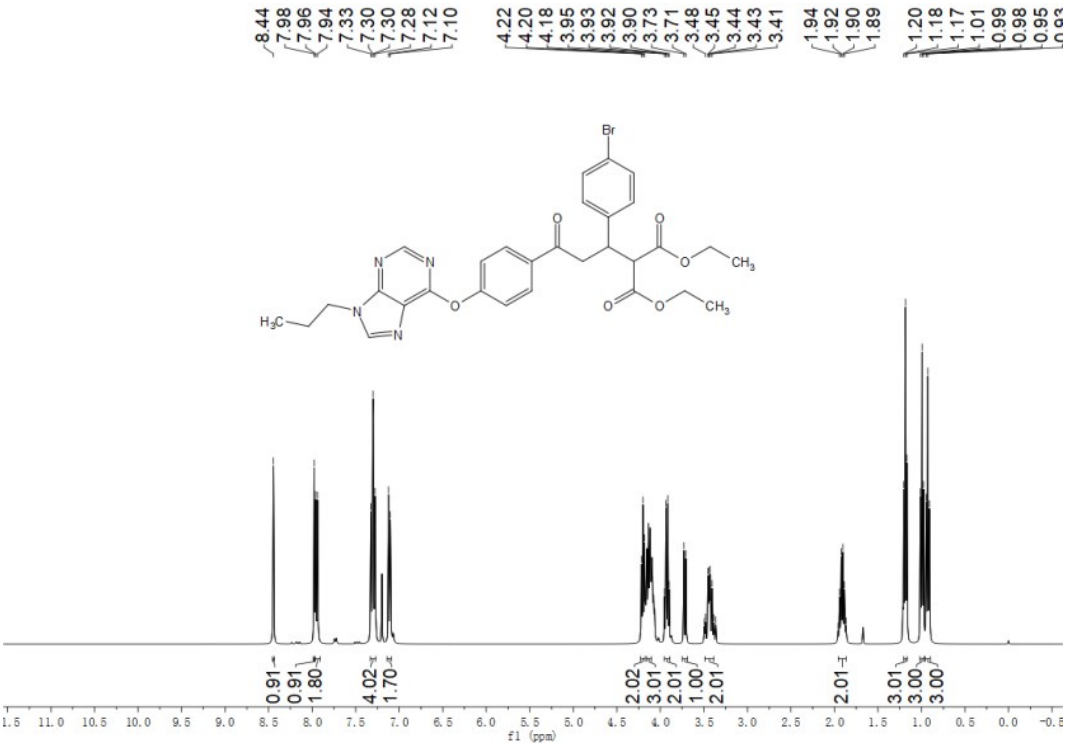


Figure S83. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8c**

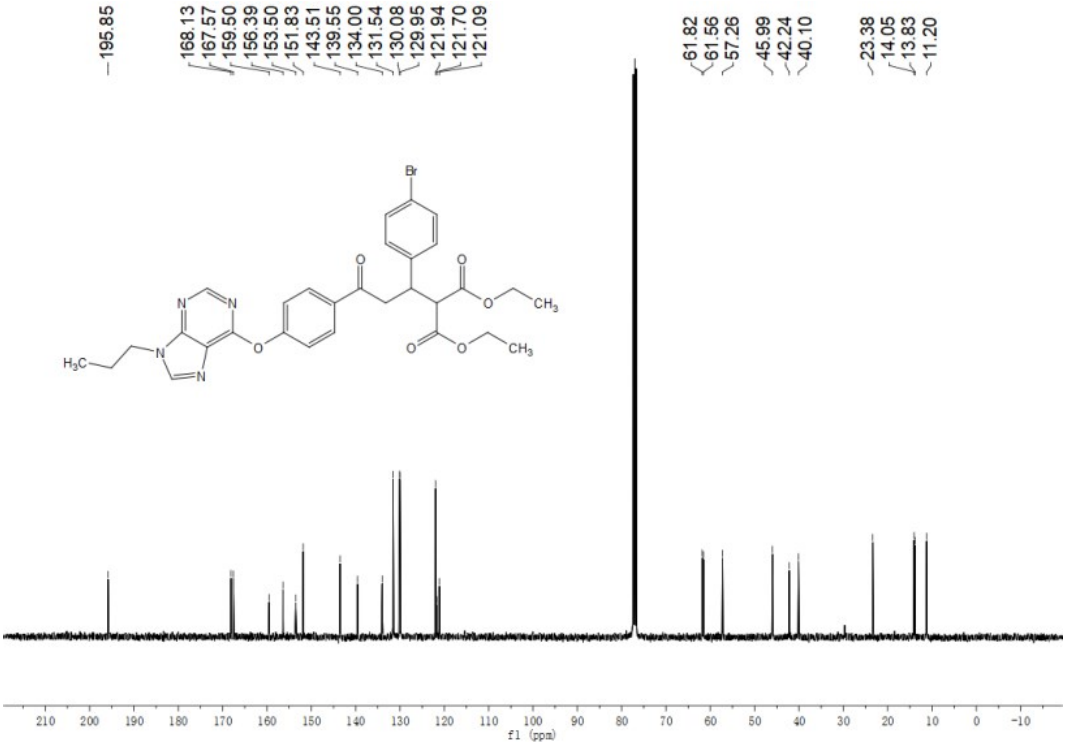


Figure S84. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **8c**

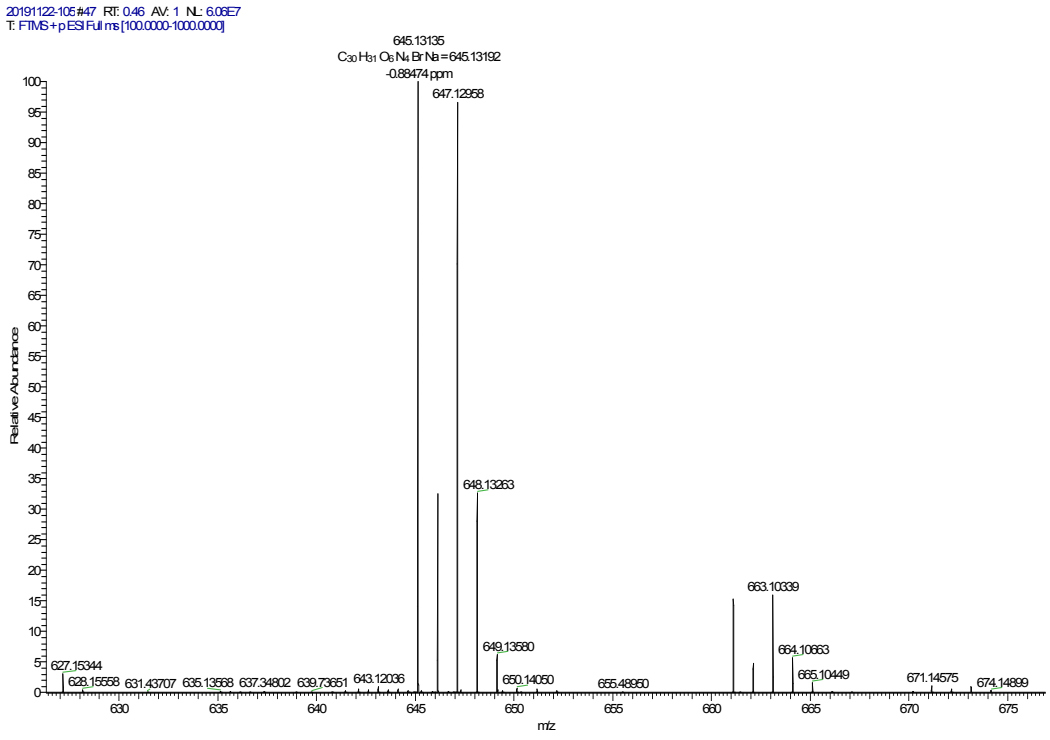


Figure S85. HRMS of compound **8c**

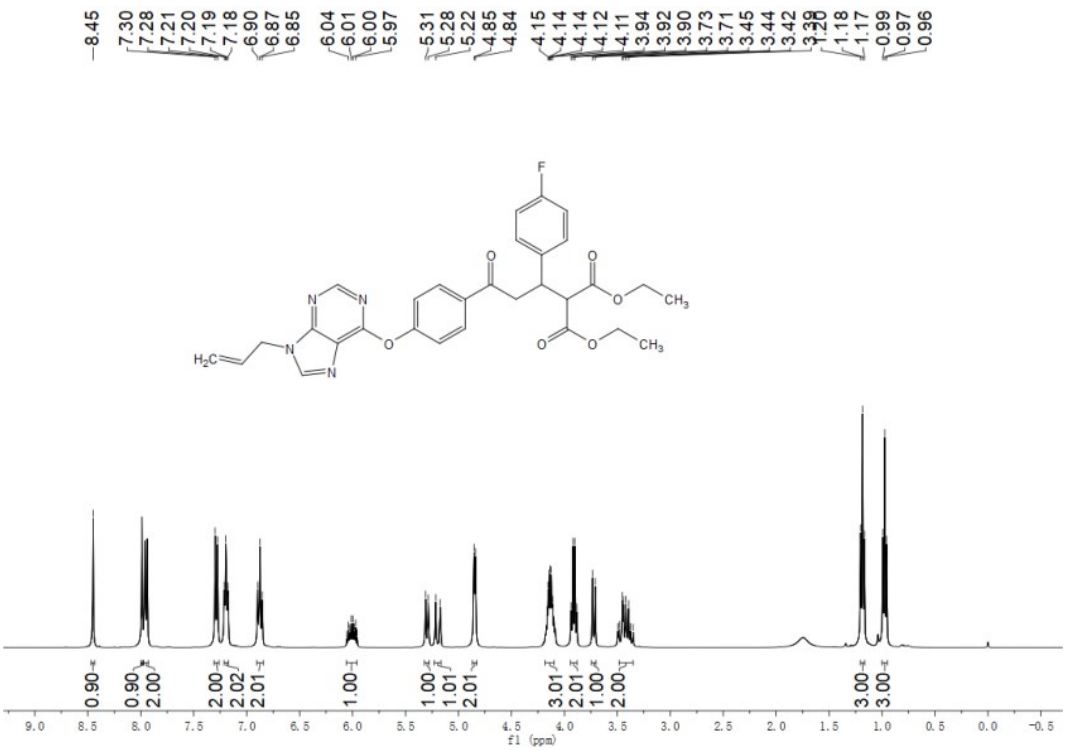


Figure S86. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8d**

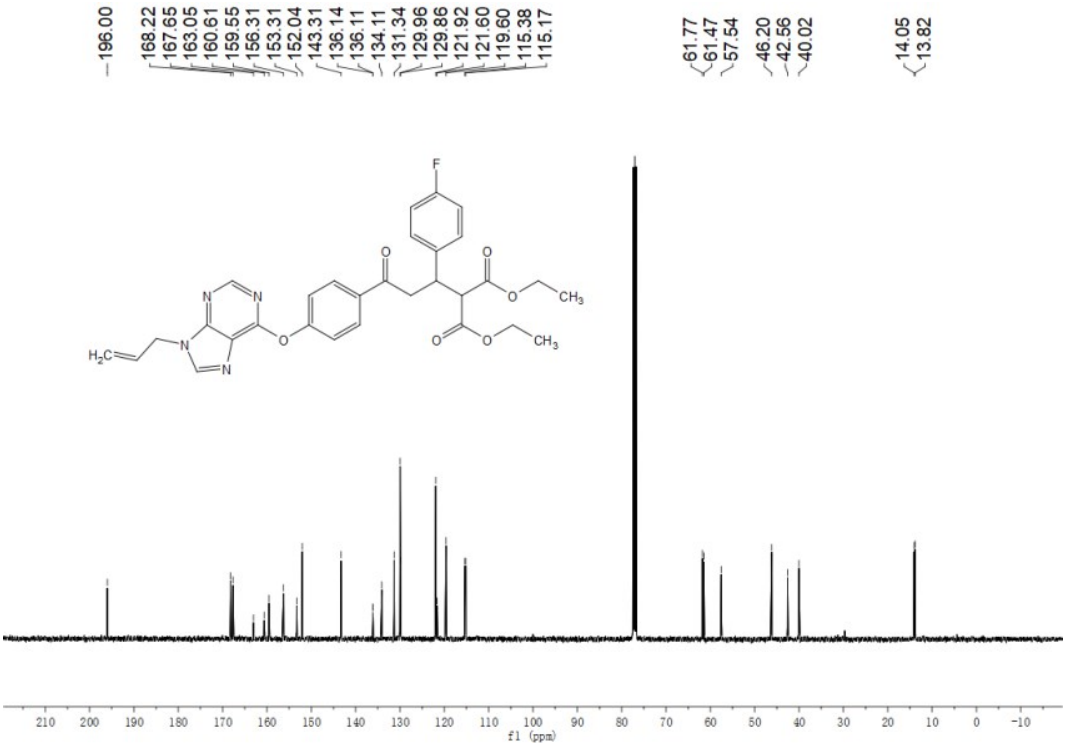


Figure S87. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **8d**

Figure S88. ^{19}F NMR ($CDCl_3$, 400 MHz) spectrum of compound **8d**

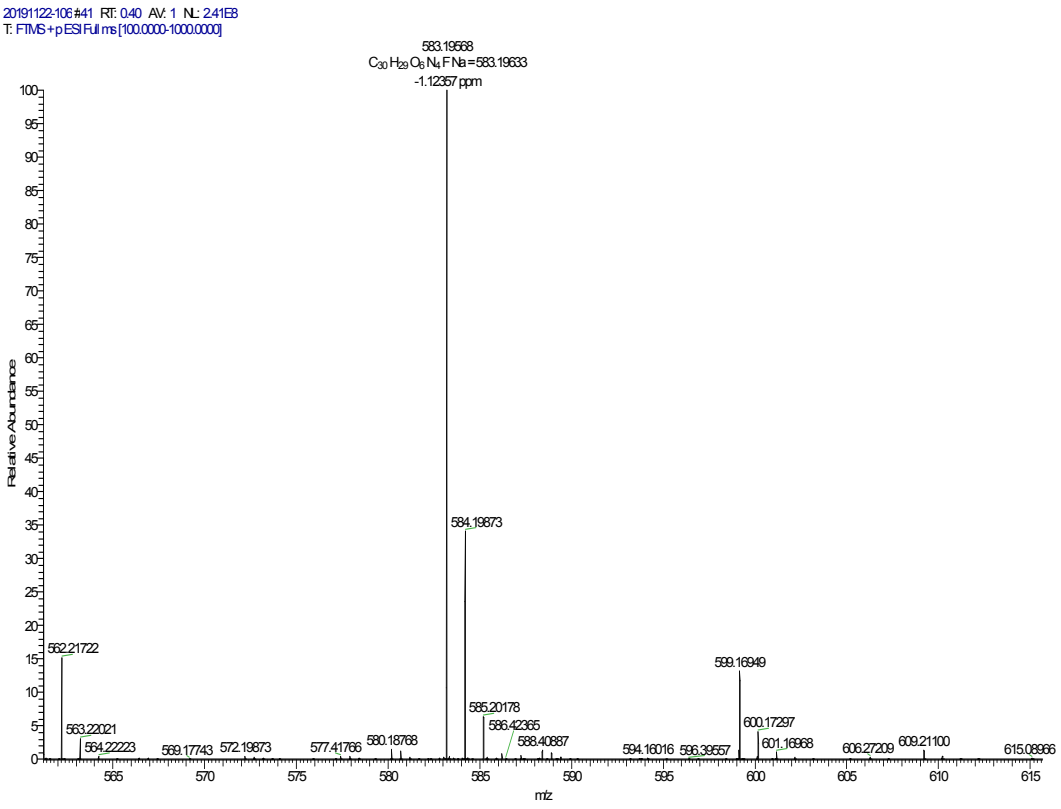


Figure S89. HRMS of compound **8d**

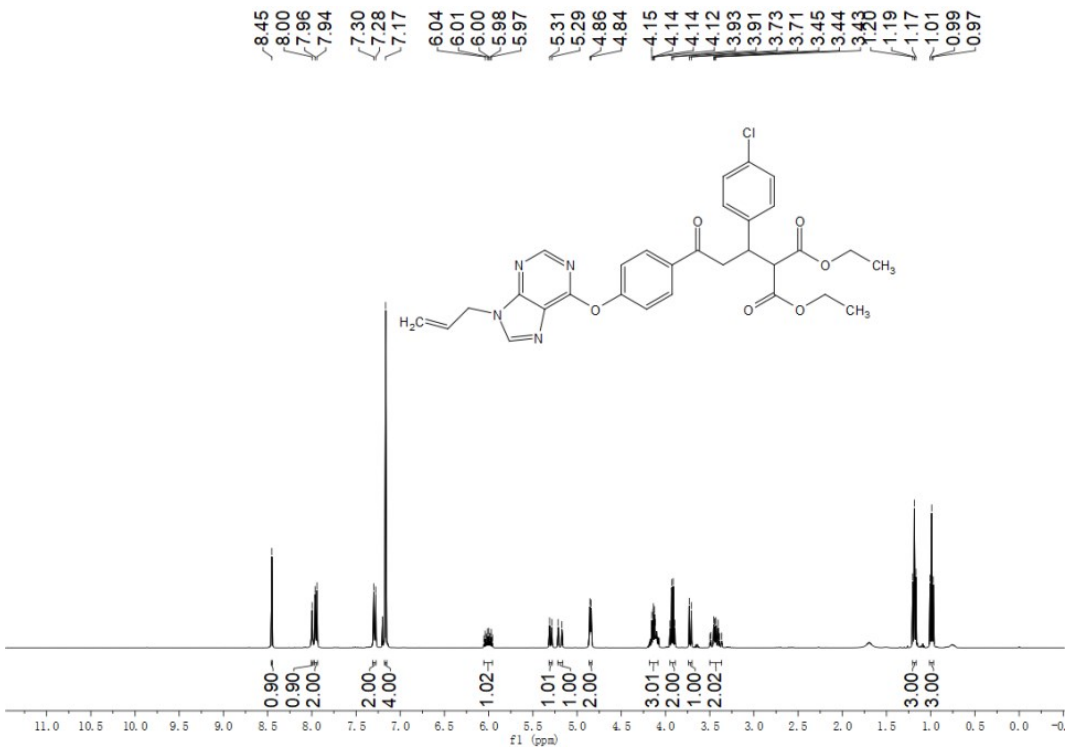


Figure S90. ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of compound **8e**

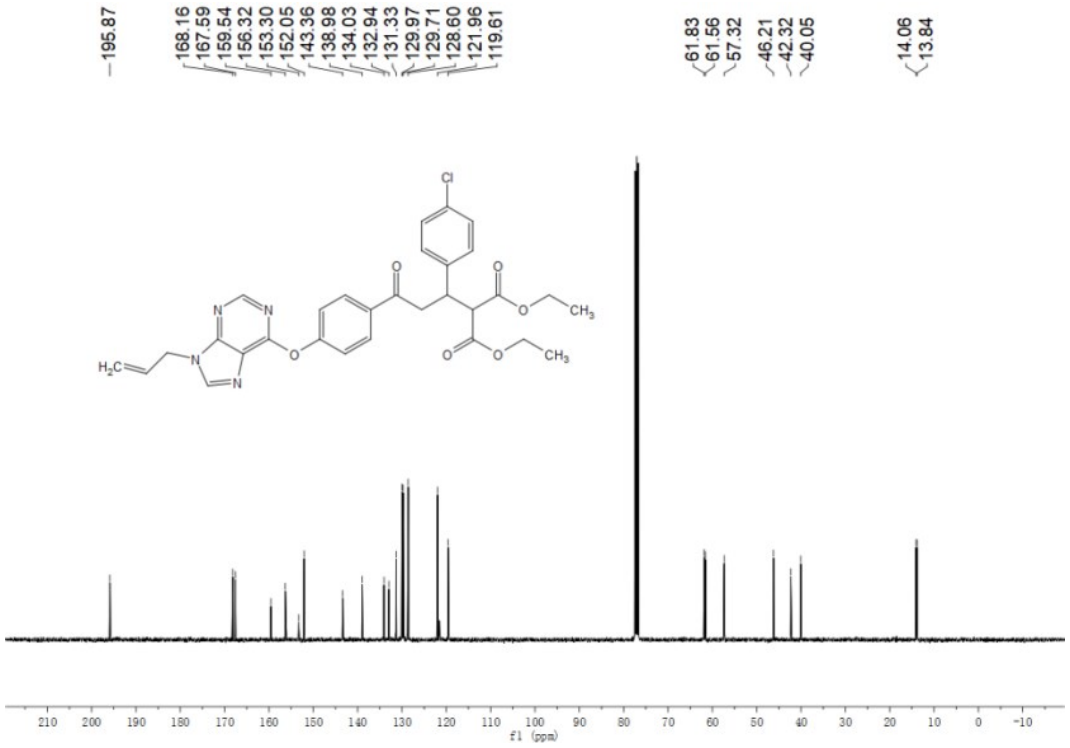


Figure S91. ^{13}C NMR ($CDCl_3$, 400 MHz) spectrum of compound **8e**

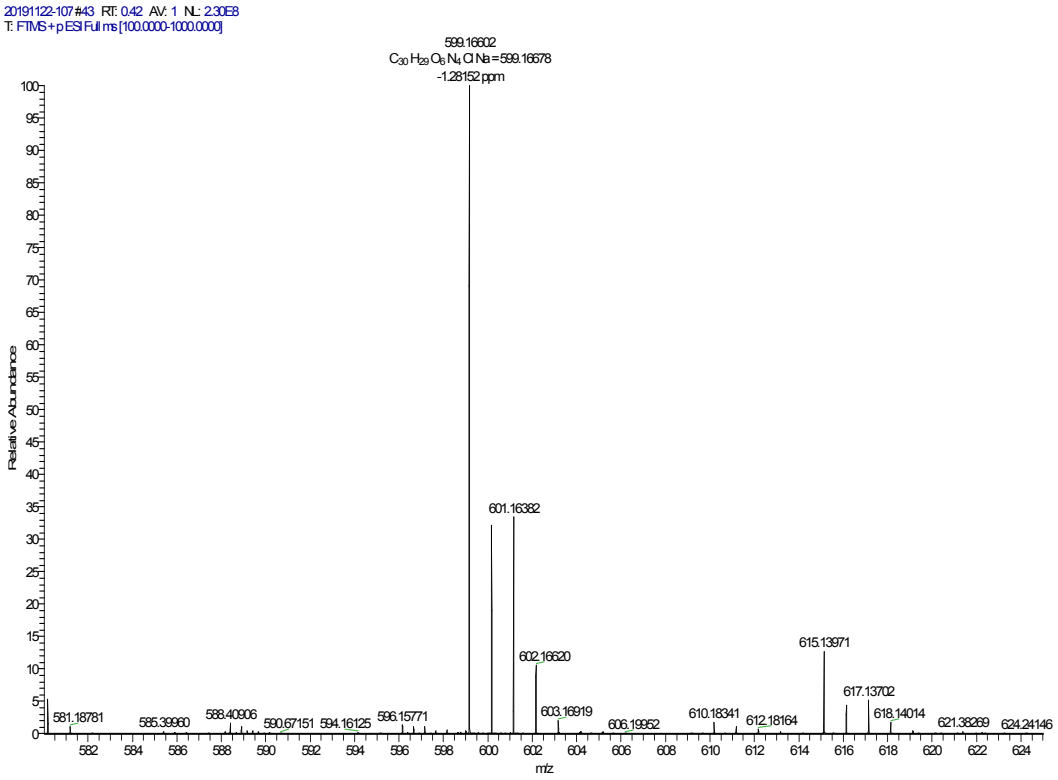


Figure S92. HRMS of compound **8e**