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Supporting Information

Novel chalcone derivatives containing a 1,2,4-triazines moiety: design, synthesis, antibacterial and antiviral activities

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Content

1.Experimental section

Melting points of synthesized compounds (**4a-4w**) were measured by a uncorrected XT-4 Binocular Microscope (Beijing Tech. Instrument, China). Using DMSO-d_6 as the solvent and TMS as an internal standard, a JEOL-ECX 500 NMR spectrometer (JEOL, Japan) were used to record the ^{1}H and ^{13}C NMR spectra of target compounds. HRMS data were measured on Thermo Scientific Q Exactive mass spectrometer(Thermo Scientific Inc., St Louis, MO, USA). The micro thermophoresis of the compound and TMV CP was determined by a micro thermophoresis instrument (NanoTemper Tchnologies GmbH, Germany); the fluorescence spectroscopy of the compound interacting with TMV CP was determined by FluoroMax-4 fluorescence spectrometer (HORIBA Scientific, France). All reagents and solvents purchased from Chinese Chemical Reagent Company are analytical or chemical pure.

2. Biological activities tests

2.1. Antiviral activities *in vitro*

2.1.1. Curative activity of the target compounds against TMV *in vivo*

Growing *N. tabacum* L. leaves of the same age were selected. The leaves were inoculated with TMV (concentration of 6×10^{-3} mg/mL) by dipping and brushing the whole leaves, which had previously been scattered with silicon carbide. The leaves were then washed with water after inoculation for 0.5 h. The compound solution was smeared on the left side of the leaves, and the solvent was smeared on the right side as the control. The number of local lesions was counted and recorded 3–4 d after inoculation. Three replicates were set up for each.

2.1.2. Protection activity of the target compounds against TMV *in vivo*

The compound solutions were smeared on the left side of the *N. tabacum* L. leaves, and the solvents were smeared on the right side as the control sample for growing *N*. tabacum L. leaves. After 12 h, crude TMV (concentration of 6×10^{-3} mg/mL) was inoculated on whole leaves at the same concentration on each side of the leaves, which were previously scattered with silicon carbide. After 0.5 h, the leaves were washed with water and then dried. The number of local lesions was recorded 3–4 d after inoculation. Three replicates were used for each compound. The inhibitory rate (I %) of the compound was calculated according to the following formula:

$$(I\ \%)= (C_{num} - T_{num})/ C_{num}\times 100\%$$

C_{num}: average local lesion number of control(not treated with compounds)

T_{num}: average local lesion number smeared with drugs

2.1.3. Inactivation activity of the title compounds against TMV *in vivo*

The virus was inhibited after it was mixed with a compound solution of the same volume for 30 min. The

right side of the *N. tabacum* L. leaves was then inoculated with the solvent and virus mixture for control. All of the leaves were previously scattered with silicon carbide. The number of local lesions was recorded three to four days after the inoculation. Three replications were reproduced for each compound. The inhibition rates (*I* %) of the compounds were calculated according to the following formula:

$$(I\ \%) = (C_{num} - T_{num})/\ C_{num} \times 100\%$$

C_{num}: average local lesion number of control(not treated with compounds)

T_{num}: average local lesion number smeared with compounds

2.2. Antibacterial activity *in vitro*

Antibacterial activities of the title compounds **4a**–**4w** against *Xanthomonas axonopodispv. citri (Xac), Xanthomonas oryzaepv. oryzae (Xoo)* and *Ralstonia solanacearum* (*Rs*) were evaluated by using the turbidimeter test *in vitro*. Dimethyl sulfoxide in sterile distilled water served as a blank control. Bismerthiazol and Thiodiazole-Copper served as positive controls. Approximately 4 mL of solvent NB (1.5 g beef extract, 2.5 g peptone, 0.5 g yeast powder, 5.0 g glucose,and 500 mL distilled water; pH 7.0–7.2) containing Xoo , Rs and Xac, incubated in the phase of logarithmic growth, was added to 5 mL of solvent NB containing different concentrations of the test compounds and positive control, such as 100, 50 μg/mL (for preliminary bioassay), 100, 50, 25, 12.5, 6.25 μg /mL, or 25, 12.5, 6.25, 3.125, 1.5625 μg /mL (for EC_{50} detection, depend on the bioactivity of different compounds, the concentration was chosen as two times the decline trend). The inoculated test tubes were incubated at 28 ± 1^{O}C and continuously shaken at 180 rpm for 24–48 h until the bacteria were incubated in the logarithmic growth phase. The growth of the cultures was monitored on amicroplate reader by measuring the optical density at 595 nm (OD_{595}) given by turbidity corrected values = $OD_{\text{bacterial wilt}}$ - $OD_{\text{no bacterial wilt}}$, and the inhibition rate I was calculated by *I = (C - T)/C * 100%*. C is the corrected turbidity values of bacterial growth on untreated NB (blank control), and T is the corrected turbidity values of bacterial growth on treated NB. By using the SPSS 17.0 software and the obtained inhibition rates at different concentrations, a regression equation was provided. The results of antibacterial activities (expressed by EC_{50}) against *Xoo, Rs* and *Xac* were calculated from the equation. The experiment was repeated three times.

Antibacterial activities of the title compounds **4a**–**4w** against *Xanthomonas axonopodispv. citri (Xac), Xanthomonas oryzaepv. oryzae (Xoo)* and *Ralstonia solanacearum* (*Rs*) were evaluated by using the turbidimeter test *in vitro*, commercial agricultural antibacterial Bismerthiazol and Thiodiazole-Copper were used as control. The test compounds were dissolved in 150 μL of dimethylformamide and diluted with 0.1% (v/v)Tween-20 to prepare two concentrations of 200 and 100 μg/mL. 1 mL of the liquid sample was added to the non-toxic nutrient broth (NB: 1.5 g of beef extract, 2.5 g of peptone, 0.5 g of yeast powder, 5.0 g of glucose and 500 mL of distilled water, pH 7.0–7.2) liquid medium in 4 mL tubes. Then, 40 μL of NB containing *Rs* was added to 5 mL of solvent NB containing the test compounds or bismerthiazol. The inoculated test tubes were incubated at (30±1) °C under continuous shaking at 180/min for 48 h. The culture growth was monitored spectrophotometrically by measuring the optical density at 600 nm (OD_{600}) and expressed as corrected turbidity. The relative inhibitory rate (*I* %) compared with a blank assay was calculated as follows:

$$I\% = (C_{tur} - T_{tur})/C_{tur} \times 100\%$$

C_{tur}: the corrected turbidity value of bacterial growth on untreated NB;

T_{tur}: the corrected turbidity value of bacterial growth on treated NB.

Similarly, the solvent of *Xoo and Xac* were SM (10.0 g of peptone, 5.0 g of glucose, 1.0 g of casein acid hydrolysate, 1000 mL of distilled water, pH 7.0–7.2).

2.3. Expression and purification of TMV CP

The expression vector, pET28a-TMV CP, containing the full-length TMV CP gene, was stored at -80°C in our lab. A freshly transformed overnight culture of *Escherichia coli* strain *BL21(DE3)* containing the plasmid pET28a-TMV CP was transferred to 1 L Luria broth. The cells were grown at 37 °C in Luria-Bertani medium supplemented with 50 μg/mL kanamycin, and with an OD_{600} of 0.8. The cells were shaken at 200 rpm. Then protein expression was induced with 0.8 mM IPTG at 16 °C overnight. The cells were harvested by centrifugation and then stored at -80 °C. When analyzed, the cells were resuspended in lysis buffer (20 mM PB, 500 mM NaCl, 30 mM imidazole, 5 mM *β*-mercaptoethanol and 5% glycerol, pH 7.2) and then lysed at 4 °C by sonication. The lysate was clarified by centrifugation at 12, 000 g for 30 min at 4 °C, the soluble supernatants were loaded onto a 5 mL Ni-NTA column (GE Healthcare, USA), and the protein was eluted with a linear gradient of 30-350 mM imidazole (pH 7.2). The crude protein was performed at 4 °C using a desalting column (GE Healthcare, USA) attached to an AKTA purifier protein liquid chromatography system (GE Healthcare, USA), and the fractions containing target protein with His-tags were pooled, concentrated to a suitable concentration by ultrafiltration (10 kDa cut-off). The

dealt protein concentration was determined using a Genequant100 (GE Healthcare, USA), and stored at -80 °C until further analysis.

2.4. Interaction studies between 4l and TMV CP

The binding was calculated for MST Monolith NT. 115 (Nano Temper Technologies, Germany). A range of ligands from 0 μM to 5 μM were incubated with 0.5 μM of purified recombinant proteins for 5 min with a NT-647 dye (Nano Temper Technologies, Germany) and was used in the thermophoresis experiment at a final concentration of 20 nM. A 16 point dilution series was made for selected compounds in DMSO. Each compound dilution series was subsequently transferred to protein solutions in 10 mM Tris-HCl and 100 mM sodium chloride pH 7.5, 0.05% Tween-20. After a 15 min incubation of the labeled TMV CP with each dilution point (1:1 mix) at room temperature, samples were filled into standard capillaries (NanoTemper Technologies, Germany). Measurements were taken on a Monolith NT.115 microscale thermophoresis system (NanoTemper Technologies, Germany) under a setting of 20% LED and 40% IR laser. Laser on time was set at 30 s, and laser-off time was set at 5 s. The Kd values were calculated from the duplicate reads of three separate experiments using the mass action equation in the Nano Temper software.

2.5. Molecular docking

Molecular docking. The molecular docking was performed by using DS-CDocker implemented in Discovery Studio (version 4.5). The coat protein subunit amino acid sequence of tobacco mosaic virus (TMV) was searched by the UniProt database. The Protein BLAST server was used to search the template protein and the homologies of TMV-CP sequences were aligned. Homology modeling of TMV-CP was carried out using Create Homology Models, which is a module integrated in Discovery Studio. The obtained models were evaluated by Ramachandran plots. The 3D structures of the compounds were constructed using the Sketching module and optimized by the Full Minimization module. All parameters are default during the docking process.

2.6. Scanning electron microscopy

In this assay, 1.5 mL *Ralstonia solanacearum* (*Rs*) cells incubated at the logarithmic phase were centrifuged and washed with PBS (pH = 7.1), and re-suspended in 1.5 mL of PBS buffer (pH = 7.1). After that, bacteria *Ralstonia solanacearum* (*Rs*) was incubated with compound **4a** at concentration of 12.5 *μ*g/mL, 50.0 *μ*g/mL, and an equivalent volume of DMSO (solvent control) for 4 h at room temperature. After incubation, these samples were washed 3 times with PBS (pH = 7.1). Subsequently, the bacterial cells were fixed for 8 h at 4℃ with 2.5% glutaraldehyde, and then dehydrated with graded ethanol series and pure tert-butanol (2 times with 10 min/time).

Following dehydration, samples were freezing dried and coated with gold, and visualized using Nova Nano SEM 450.

2.7 . ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectrum of the title compounds

*(E)-1-(4-(4-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)butoxy)phenyl)-3-(4-nitrophenyl)prop-2-en-1-one (**4a**):* yellow solid, yield: 51%, m.p: 90.1–91.2^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 8.0 Hz, 2H, Ar(4-NO_2)-3,5-2H), 8.16 (dd, J = 17.9, 9.8 Hz, 5H, Ar(4-OH)-2,6-2H, Ar-CH=, Ar(4-NO_2)-2,6-2H), 7.78 (d, J = 15.6 Hz, 1H, Ar-CO=CH), 7.53 – 7.33 (m, 10H, 10Ar-H), 7.14 – 7.02 (m, 2H, Ar(4-OH)-3,5-2H), 4.17 (t, J = 12.8 Hz, 2H, -OCH_2-), 3.40 (d, J = 6.3 Hz, 2H, -SCH_2-), 1.97 (s, 4H, -CH_2-CH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.53 (s, C=O), 170.48 (s), 163.37 (s), 155.97 (s), 154.39 (s), 148.42 (s), 141.83 (s), 140.76 (s), 135.63 (d, J = 19.4 Hz), 131.65 (s), 131.23 (s), 130.46 (s), 130.17 (d, J = 14.3 Hz), 129.72 (s), 128.89 (d, J = 6.2 Hz), 126.55 (s), 124.38 (s), 115.01 (s), 67.99 (s, -OCH_2-), 30.16 (s, -SCH_2-), 28.19 (s, -CH_2-), 25.99 (s, -CH_2-); HRMS calcd for $C_{34}H_{29}N_4O_4S$ $[M+H]^+$: 589.19040, found 589.18872.

*(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**4b**):* yellow oil, yield: 41%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 – 7.73 (m, 1H, Ar-CH=), 7.51 (ddd, J = 8.6, 5.8, 3.9 Hz, 2H, Ar(2-OH)-6-H, Ar-H), 7.48 – 7.36 (m, 9H, 9Ar-H), 7.36 – 7.19 (m, 4H, Ar(2-OH)-3,4,5-3H, Ar(2-OCH_3-)-6-H), 7.14–6.95 (m, 2H, Ar (2-OCH_3-)-3.4-2H), 6.91 (dd, J = 13.9, 6.7 Hz, 1H, Ar-CO=CH), 6.78 – 6.68 (m, 1H, Ar(2-OCH_3-)-5-H), 4.48 (dt, J = 29.4, 6.1 Hz, 2H, -OCH_2-), 3.86 – 3.76 (m, 3H, -OCH_3), 3.75 – 3.69 (m, 2H, -SCH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.43 (s, C=O), 169.86 (s), 158.58 (s), 157.00 (s), 156.04 (s), 154.55 (s), 137.40 (s), 135.67 (s), 135.43 (s), 133.53 (s), 132.45 (s), 131.22 (s), 130.60 (s), 130.33 (s), 130.13 (s), 129.80 (dd, J = 27.2, 22.1 Hz), 128.78 (t, J = 13.7 Hz), 127.35 (s), 123.30 (s), 121.46 (s), 121.16 (s), 113.67 (s), 112.14 (s), 67.04 (s, -OCH_2-), 56.09 (s, -OCH_3-), 29.71 (s, -SCH_2-). HRMS calcd for $C_{33}H_{28}N_3O_3S$ $[M+H]^+$: 546.18459, found 546.18304.

*(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(2-methoxyphenyl)prop-2-en-1-one (**4c**)*: yellow solid, yield: 46%, m.p: 136.5–137.8^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 15.8 Hz, 1H, Ar-CH=), 8.01 – 7.96 (m, 2H, Ar-(4-OH)-2,6-2H), 7.64 – 7.57 (m, 2H, Ar-(2-OCH_3)-6-H, Ar-H), 7.55 – 7.48 (m, 4H, 4Ar-H), 7.45 – 7.28 (m, 7H, 5Ar-H, Ar-CO=CH, Ar-(2-OCH_3)-4-H), 7.04 – 6.99 (m, 2H, Ar-(4-OH)-3,5-2H), 6.95 (dd, J = 16.9, 7.9 Hz, 2H, Ar-(2OCH_3)-3,5-2H), 4.44 (dt, J = 26.0, 6.6 Hz, 2H, -OCH_2-), 3.90 (d, J = 8.1 Hz, 3H, -OCH_3), 3.74 (dt, J = 7.6, 4.5 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.31 (s, C=O), 162.12 (s), 158.76 (s), 155.87 (s), 154.27 (s), 139.59 (s), 135.09 (d, J = 8.3 Hz), 131.64 (d, J = 14.4 Hz), 130.96 (d, J = 17.1 Hz), 129.82 (s), 129.56 (s), 129.36 (s), 129.14 (s), 128.62 (d, J = 6.5 Hz), 124.14 (s), 122.72 (s), 120.74 (s), 114.44 (s), 111.26 (s), 55.57 (s, -OCH_2-), 29.67 (d, J = 10.1 Hz, -SCH_2-); HRMS calcd for $C_{33}H_{28}N_3O_3S$ $[M+H]^+$: 546.18459, found 546.18341.

*(E)-3-(2,4-dimethoxyphenyl)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one (**4d**)*: yellow oil, yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 24.1, 12.3 Hz, 3H, Ar-CH=, Ar-(4-OH)-2,6-2H), 7.56 – 7.48 (m, 6H, Ar(2,4-2-OCH_3)-H, 5Ar-H), 7.43 – 7.27 (m, 6H, 5Ar-H, Ar-CO=CH), 7.00 (d, J = 8.7 Hz, 2H, Ar-(4-OH)-3.5-2H), 6.50 (dd, J = 8.5, 2.2 Hz, 1H, Ar(2,4-2-OCH_3)-3-H), 6.45 (d, J = 2.1 Hz, 1H, Ar(2,4-2-OCH_3)-5-H), 4.46 (t, J = 6.5 Hz, 2H, -OCH_2-), 3.88 – 3.78 (m, 6H,-OCH_3), 3.74 (t, J = 6.5 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.37 (s, C=O), 169.96 (s), 162.90 (s), 161.94 (s), 160.33 (s), 155.84 (s), 154.24 (s), 139.72 (s), 135.09 (d, J = 9.6 Hz), 131.99 (s), 131.03 (s), 130.77 (d, J = 4.9 Hz), 129.81 (s), 129.45 (d, J = 18.2 Hz), 128.60 (d, J = 6.4 Hz), 120.22 (s), 117.30 (s), 114.37 (s), 105.45 (s), 98.48 (s), 66.53 (s), 55.53 (d, J = 7.3 Hz, -OCH_2-), 29.63 (s, -SCH_2-); HRMS calcd for $C_{34}H_{30}N_3O_4S$ $[M+H]^+$: 576.19515, found 576.19379.

*(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-phenylprop-2-en-1-one (**4e**)*: yellow solid, yield: 64%, m.p: 124.1–125.2^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 – 8.10 (m, 2H, Ar-(4-OH)-2,6-2H), 8.00 – 7.86 (m, 3H, Ar-CH=, Ar-CO=CH, Ar-H), 7.72 (dd, J = 15.6, 5.8 Hz, 1H, Ar-H), 7.51 – 7.33 (m, 13H, 13Ar-H), 7.16 (t, J = 8.4 Hz, 2H, Ar-(4-OH)-3,5-2H), 4.54 – 4.47 (m, 2H, -OCH_2-), 3.79 (dd, J = 18.6, 12.3 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.81 (s, C=O), 169.81 (s), 162.54 (s), 156.27 (s), 154.75 (s), 143.70 (s), 135.57 (d, J = 17.9 Hz), 135.27 (s), 131.65 – 131.61 (m), 131.61 – 131.06 (m), 130.93 (s), 130.15 (s), 129.77 (d, J = 6.0 Hz), 129.32 (d, J = 9.5 Hz), 128.90 (d, J = 6.3 Hz), 122.46 (s), 115.06 (s), 66.82 (s, -OCH_2-), 29.42 (s, -SCH_2-); HRMS calcd for $C_{32}H_{26}N_3O_2S$ $[M+H]^+$: 516.17402, found 516.17401.

*(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(furan-2-yl)prop-2-en-1-one (**4f**)*: white solid, yield: 38%, m.p: 119.3–120.5^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 – 7.91 (m, 3H, Ar(4-OH)-2,6-2H, furan-5-H), 7.59 – 7.33 (m, 12H, 10Ar-H, furan-CH=, Ar-CO=CH), 7.12 (dt, J = 7.2, 5.7 Hz, 3H, Ar(4-OH)-3,5-2H, furan-3-H), 6.69 (dd, J = 3.2, 1.7 Hz, 1H, furan-4-H), 4.49 (dd, J = 7.8, 4.8 Hz, 2H, -OCH_2-), 3.76 (t, J = 6.4 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.19 (s, C=O), 169.81 (s), 162.46 (s), 156.33 (s), 154.78 (s), 151.70 (s), 146.50 (s), 135.57 (d, J = 14.4 Hz), 131.15 (t, J = 9.4 Hz), 130.22 (d, J = 12.4 Hz), 129.74 (s), 128.91 (d, J = 3.8 Hz), 119.12 (s), 117.12 (s), 115.11 (s), 113.55 (s), 66.80 (s, -OCH_2-), 29.31 (s, -SCH_2-); HRMS calcd for $C_{30}H_{24}N_3O_3S$ $[M+H]^+$: 506.15329, found 506.15274.

*(E)-3-(2,4-dimethoxyphenyl)-1-(4-(2-((5,6-dimethyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one (**4g**)*: yellow oil, yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 12.2, 9.8 Hz, 3H, Ar-CH=, Ar(4-OH)-2,6-2H), 7.54 (dd, J = 12.1, 8.0 Hz, 2H, Ar(2,4-2-OCH_3)-6-H, Ar-CO=CH), 7.01 (d, J = 8.8 Hz, 2H, Ar(4-OH)-3,5-2H), 6.58 – 6.42 (m, 2H, Ar(2,4-2-OCH_3)-3,5-H), 4.45 – 4.32 (m, 2H, -OCH_2-), 3.86 (d, J = 19.5 Hz, 6H, -OCH_3), 3.70 – 3.56 (m, 2H, -SCH_2-), 2.54 (d, J = 53.7 Hz, 6H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.24 (s, C=O), 169.71 (s), 162.95 (s), 162.42

(d, *J* = 93.1 Hz), 160.29 (s), 159.02 (s), 153.97 (s), 139.62 (s), 131.88 (s), 130.71 (d, *J* = 9.7 Hz), 120.08 (s), 117.19 (s), 114.34 (s), 105.45 (s), 98.40 (s), 66.43 (s, -OCH_2-), 55.52 (d, *J* = 7.5 Hz, -OCH_3), 29.38 (s, -SCH_2-), 21.70 (s, -CH_3), 19.07 (s, -CH_3); HRMS calcd for $C_{24}H_{26}N_3O_4S$ $[M+H]^+$: 452.16385, found 452.16281.

(E)-3-(2-chlorophenyl)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one ***(4h)***: yellow solid, yield: 44%, m.p: 125.5–126.3^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 15.7, 5.4 Hz, 1H, Ar-CH=), 7.93 (d, *J* = 8.5 Hz, 1H, Ar-(4-OH)-2-H), 7.86 – 7.76 (m, 1H, Ar-(4-OH)-6-H), 7.70 – 7.65 (m, 1H, Ar-H), 7.55 (td, *J* = 12.9, 7.1 Hz, 1H, Ar-H), 7.44 (ddd, *J* = 21.4, 14.2, 6.5 Hz, 4H, 4Ar-H), 7.37 – 7.19 (m, 8H, 8Ar-H), 7.13 – 7.00 (m, 1H, Ar-CO=CH), 6.99 – 6.80 (m, 2H, Ar-(4-OH)-3.5-2H), 4.39 (dt, *J* = 11.6, 7.0 Hz, 2H,- OCH_2-), 3.77 – 3.63 (m, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.52 (s, C=O), 169.90 (s), 162.41 (d, *J* = 2.4 Hz), 155.90 (s), 154.29 (s), 139.80 (s), 135.41 (s), 135.06 (d, *J* = 7.9 Hz), 133.45 (s), 131.29 – 130.61 (m), 130.29 (s), 129.83 (s), 129.59 (s), 129.36 (s), 128.64 (d, *J* = 6.7 Hz), 127.79 (s), 127.08 (s), 124.59 (d, *J* = 16.1 Hz), 114.55 (s), 66.55 (s, -OCH_2-), 29.58 (s, -SCH_2-); HRMS calcd for $C_{32}H_{25}ClN_3O_2S$ $[M+H]^+$: 550.13505, found 550.13385.

(E)-3-(3,4-dimethoxyphenyl)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one ***(4i)***: yellow solid, yield: 49%, m.p: 106.9–107.2^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 2H, Ar-(4-OH)-2,6-2H), 7.74 (d, *J* = 15.6 Hz, 1H, Ar-CH=), 7.52 (t, *J* = 8.4 Hz, 4H, 3Ar-H, Ar-CO=CH), 7.45 – 7.28 (m, 7H, 7Ar-H), 7.22 (d, *J* = 8.3 Hz, 1H, Ar-(3,4-2-OCH_3)-2-H), 7.16 (s, 1H, Ar-(3,4-2-OCH_3)-5-H), 7.03 (d, *J* = 8.6 Hz, 2H, Ar-(4-OH)-3,5-2H), 6.88 (t, *J* = 8.1 Hz, 1H, Ar-(3,4-2-OCH_3)-6-H), 4.48 (t, *J* = 6.5 Hz, 2H, -OCH_2-), 3.93 (d, *J* = 10.2 Hz, 6H, -OCH_3), 3.76 (t, *J* = 6.5 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.74 (s, C=O), 169.92 (s), 162.16 (s), 155.87 (s), 154.28 (s), 151.31 (s), 149.26 (s), 144.21 (s), 135.07 (d, *J* = 8.2 Hz), 131.62 (s), 131.04 (s), 130.79 (s), 129.81 (s), 129.56 (s), 129.34 (s), 128.61 (d, *J* = 7.6 Hz), 128.08 (s), 123.01 (s), 119.85 (s), 114.46 (s), 111.18 (s), 110.18 (s), 66.55 (s, -OCH_2-), 56.01 (s, -OCH_3), 29.61 (s, -SCH_2-); HRMS calcd for $C_{34}H_{30}N_3O_4S$ $[M+H]^+$: 576.19519, found 576.19373.

(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-methoxyphenyl)prop-2-en-1-one ***(4j)***: yellow solid, yield: 59%, m.p: 85.3–86.1^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 5.9 Hz, 2H, Ar-(4-OH)-2,6-2H), 7.76 (dd, *J* = 15.5, 3.0 Hz, 1H, Ar-CH=), 7.59 – 7.46 (m, 6H, 3Ar-H, Ar-(4-OCH_3)-2,6-2H, Ar-CO=CH), 7.35 (dddd, *J* = 23.7, 15.5, 5.9, 1.7 Hz, 7H, 7Ar-H), 7.03 – 6.98 (m, 2H, Ar-(4-OH)-3,5-2H), 6.92 – 6.87 (m, 2H, Ar-(4-OCH_3)-3,5-2H), 4.49 – 4.42 (m, 2H, -OCH_2-), 3.80 (d, *J* = 2.0 Hz, 3H, -OCH_3-), 3.73 (dd, *J* = 11.5, 4.7 Hz, 2H, -SCH_2-);^{13}C NMR (101 MHz, $CDCl_3$) δ 188.61 (s, C=O), 169.94 (s), 162.14 (s), 161.54 (s), 155.83 (s), 154.26 (s), 143.83 (s), 135.09 (d, *J* = 10.2 Hz), 131.63 (s), 131.05 (s), 130.77 (s), 130.17 (d, *J* = 3.0 Hz), 129.84 (s), 129.47 (d, *J* = 19.9 Hz), 128.62 (d, *J* = 7.2 Hz), 127.79 (s), 119.54 (s), 114.44 (d, *J* = 4.4 Hz), 66.55 (s, -OCH_2-), 55.42 (s, -OCH_3), 29.60 (s, -SCH_2-); HRMS calcd for $C_{33}H_{28}N_3O_3S$ $[M+H]^+$: 546.18459, found 546.18298.

(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(3-nitrophenyl)prop-2-en-1-one (***4k***): yellow oil, yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.38 (m, 1H, Ar-(4-NO_2)-2-H), 8.19 – 8.11 (m, 1H, Ar-CH=), 8.03 – 7.95 (m, 2H, Ar-(4-OH)-3,5-2H), 7.88 (t, *J* = 7.5 Hz, 1H, Ar-(4-NO_2)-4-H), 7.73 (t, *J* = 13.0 Hz, 1H, Ar-CO=CH), 7.63 (dd, *J* = 15.6, 5.7 Hz, 1H, Ar-(4-NO_2)-6-H), 7.57 – 7.46 (m, 5H, Ar-(4-NO_2)-5-H, 4Ar-H), 7.45 – 7.29 (m, 6H, 6Ar-H), 7.00 (t, *J* = 11.3 Hz, 2H, Ar-(4-OH)-2.6-2H), 4.44 (dt, *J* = 22.8, 6.0 Hz, 2H, -OCH_2-), 3.74 (h, *J* = 6.2 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.55 (s, C=O), 169.86 (s), 162.63 (s), 155.81 (s), 154.26 (s), 148.59 (s), 140.78 (s), 136.80 (s), 135.06 (d, *J* = 10.2 Hz), 134.32 (s), 131.04 (s), 130.74 (s), 129.93 (d, *J* = 16.4 Hz), 129.46 (d, *J* = 21.3 Hz), 129.33 – 129.17 (m), 128.61 (d, *J* = 7.1 Hz), 124.41 (s), 122.30 (s), 114.64 (s), 66.62 (s, -CH_2-), 29.54 (s, -SCH_2-); HRMS calcd for $C_{32}H_{25}N_4O_4S$ $[M+H]^+$: 561.15910, found 561.15698.

(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one (***4l***): white solid, yield: 58%, m.p: 162.1–163.3^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.95 (m, 2H, Ar-(4-OH)-2,6-2H), 7.80 – 7.71 (m, 1H, Ar-CH=), 7.66 – 7.59 (m, 2H, 2Ar-H), 7.56 – 7.48 (m, 4H, Ar-(4-F)-2,6-2H, Ar-CO=CH, Ar-H), 7.47 – 7.28 (m, 7H, 7Ar-H), 7.13 – 6.99 (m, 4H, Ar-(4-F)-3,5-2H), 4.52 – 4.44 (m, 2H, -OCH_2-), 3.83 – 3.69 (m, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.46 (s, C=O), 169.89 (s), 165.21 (s), 162.71 (s), 162.35 (s), 155.91 (s), 154.30 (s), 142.79 (d, *J* = 15.5 Hz), 135.06 (d, *J* = 7.3 Hz), 131.54 – 131.18 (m), 131.16 – 130.77 (m), 130.27 (d, *J* = 8.5 Hz), 129.84 (d, *J* = 2.9 Hz), 129.75 – 129.16 (m), 128.61 (dd, *J* = 7.8, 4.8 Hz), 121.55 (t, *J* = 4.5 Hz), 116.21 (s), 115.99 (s), 114.51 (d, *J* = 2.9 Hz), 66.54 (s, -OCH_2-), 29.59 (s, -SCH_2-); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.70 – -114.21 (m), -116.59 (s), -119.69 (s); HRMS calcd for $C_{32}H_{25}FN_3O_2S$ $[M+H]^+$: 534.16460, found 534.16296.

(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(2-fluorophenyl)prop-2-en-1-one (***4m***): white solid, yield: 44%, m.p: 126.1–127.2^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (t, *J* = 6.9 Hz, 2H, Ar-(4-OH)-2,6-2H), 7.97 (d, *J* = 15.7 Hz, 1H, Ar-CH=), 7.83 (dd, *J* = 18.1, 12.3 Hz, 1H, Ar-H), 7.50 – 7.44 (m, 5H, 5Ar-H), 7.44 – 7.35 (m, 5H, Ar-CO=CH, 4Ar-H), 7.33 (dd, *J* = 13.2, 5.8 Hz, 3H, Ar(2-F)-2,3,6-3H), 7.16 (d, *J* = 8.9 Hz, 2H, Ar(2F)-5-H Ar-(4-OH)-3-H), 7.11 – 6.98 (m, 1H, Ar-(4-OH)-5-H), 4.49 (dt, *J* = 20.8, 6.4 Hz, 2H, -OCH_2-), 3.83 – 3.69 (m, 2H, -SCH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.61 (s, C=O), 169.81 (s), 162.69 (s), 156.27 (s), 154.75 (s), 135.55 (d, *J* = 17.7 Hz), 134.86 (s), 132.94 (s), 131.52 (s), 131.07 (d, *J* = 37.0 Hz), 130.84 – 130.70 (m), 130.14 (s), 129.70 (t, *J* = 12.4 Hz), 128.90 (d, *J* = 6.4 Hz), 125.44 (s), 124.57 (s), 122.92 (s), 116.65 (s), 116.44 (s), 115.14 (s), 66.84 (s, -OCH_2-), 29.40 (s, -SCH_2-); ^{19}F NMR (376 MHz, DMSO-d_6) δ -114.23 (d, *J* = 6.6 Hz), -116.41 (ddd, *J* = 16.1, 11.8, 6.0 Hz), -119.23 (s); HRMS calcd for $C_{32}H_{25}FN_3O_2S$ $[M+H]^+$: 534.16460, found 534.16296.

(E)-3-(4-(dimethylamino)phenyl)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one (***4n***): yellow oil, yield: 66%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 11.6, 3.8 Hz, 2H, Ar-(2-OH)-6-H, Ar-C=CH),

7.56 – 7.47 (m, 6H, Ar-(2-OH)-3,4,5-3H, Ar-($N(CH_3)_2$ -2,6-2H), 7.44 – 7.34 (m, 5H, 5Ar-H), 7.33 – 7.27 (m, 3H, 3Ar-H), 7.03 (t, *J* = 7.1 Hz, 2H, 2Ar-H), 6.63 (d, *J* = 8.2 Hz, 2H, Ar-($N(CH_3)_2$-3,5-2H), 4.49 (t, *J* = 6.2 Hz, 2H, -OCH_2-), 3.73 (t, *J* = 6.2 Hz, 2H,- SCH_2-), 2.94 (t, *J* = 8.7 Hz, 6H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 192.94 (s, C=O), 170.09 (s), 156.61 (s), 155.75 (s), 154.13 (s), 151.86 (s), 144.60 (s), 135.16 (d, *J* = 8.6 Hz), 132.22 (s), 130.98 (s), 130.50 (t, *J* = 3.6 Hz), 129.83 (s), 129.44 (d, *J* = 14.4 Hz), 128.59 (d, *J* = 7.2 Hz), 122.79 (s), 122.26 (s), 121.22 (s), 112.74 (s), 111.88 (s), 67.01 (s, -OCH_2-), 40.10 (s, -SCH_2-), 29.91 (s, -CH_3); HRMS calcd for $C_{34}H_{31}N_4O_2S$ $[M+H]^+$: 559.21622, found 559.21564.

(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-methylthiazol-2-yl)prop-2-en-1-one ***(4o)*****:** yellow solid, yield: 34%, m.p: 69.6–70.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.61 (s, 1H, thiazole-CH=CH), 7.87 (dd, *J* = 15.3, 0.8 Hz, 1H, Ar-(2-OH)-6-H), 7.74 – 7.69 (m, 1H, thiazole-H), 7.55 – 7.48 (m, 4H, Ar-(2-OH)-4,5-2H, Ar-H, CO=CH), 7.45 – 7.28 (m, 8H, 8Ar-H), 7.07 – 6.99 (m, 2H, Ar-H, Ar-(2-OH)-2-H), 4.64 – 4.39 (m, 2H, -OCH_2-), 3.82 (dt, *J* = 30.4, 6.3 Hz, 2H, -SCH_2-), 2.68 – 2.38 (m, 3H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 191.01 (s, C=O), 169.86 (s), 157.21 (s), 156.45 (s), 155.84 (s), 154.22 (s), 152.77 (s), 135.05 (d, *J* = 6.5 Hz), 133.54 (s), 131.33 (s), 131.06 (d, *J* = 5.0 Hz), 130.25 (s), 129.85 (d, *J* = 9.9 Hz), 129.58 (d, *J* = 3.2 Hz), 129.33 (s), 128.96 (s), 128.83 – 128.24 (m), 128.24 – 127.97 (m), 121.36 (s), 112.50 (s), 66.79 (s, -OCH_2-), 29.96 (s, -SCH_2-), 15.73 (s, -CH_3); HRMS calcd for $C_{30}H_{25}N_4O_2S_2$ $[M+H]^+$: 537.14134, found 537.14056.

(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(m-tolyl)prop-2-en-1-one ***(4p)***: yellow oil, yield: 56%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.55 – 7.49 (m, 2H, Ar-CH=CH, Ar-(2-OH)-6-H), 7.42 (s, 1H, Ar-(2-OH)-4-H), 7.38 (dt, *J* = 3.8, 2.8 Hz, 4H, 3Ar-H, Ar-(2-OH)-5-H), 7.35 – 7.27 (m, 3H, CO=CH, 2Ar-H), 7.23 (dd, *J* = 8.9, 4.4 Hz, 3H, Ar-(3-CH_3)-6-H, 2Ar-H), 7.20 – 7.13 (m, 3H, 3Ar-H), 7.13 – 7.07 (m, 1H, Ar-(3-CH_3)-5-H), 7.01 (d, *J* = 7.6 Hz, 1H, Ar-(3-CH_3)-2-H), 6.90 (dd, *J* = 11.0, 4.3 Hz, 2H, Ar-(3-CH_3)-4-H, Ar-(2-OH)-3-H), 4.42 – 4.32 (m, 2H, -OCH_2-), 3.65 – 3.56 (m, 2H, -SCH_2-), 2.21 (d, *J* = 5.8 Hz, 3H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 192.72 (s, C=O), 169.96 (s), 156.98 (s), 155.79 (s), 154.18 (s), 143.27 (s), 138.54 (s), 135.29 – 134.92 (m), 133.00 (s), 131.11 (d, *J* = 11.1 Hz), 130.68 (s), 130.14 – 129.13 (m), 129.01 – 128.46 (m), 126.93 (s), 125.90 (s), 121.29 (s), 112.65 (s), 67.02 (s, -OCH_2-), 29.97 (s, -SCH_2-), 21.41 (s, -CH_3); HRMS calcd for $C_{33}H_{28}N_3O_2S$ $[M+H]^+$: 530.18967, found 530.18909.

(E)-3-(4-bromophenyl)-1-(4-(2-((5,6-dimethyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one ***(4q)***: yellow solid, yield: 44%, m.p: 174.2–175.7°C; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89 – 7.81 (m, 1H, Ar-(4-OH)-2-H), 7.69 (dd, *J* = 15.9, 6.0 Hz, 1H, Ar-(4-OH)-6-H), 7.61 – 7.52 (m, 1H, Ar-CH=CH), 7.39 (dd, *J* = 12.0, 4.9 Hz, 1H, Ar-(4-Br)-3-H), 7.33 (d, *J* = 3.6 Hz, 1H, r-(4-Br)-5-H), 7.12 – 7.04 (m, 1H, Ar-(4-Br)-2-H), 6.97 (t, *J* = 5.8 Hz, 2H, Ar-(4-Br)-6-H), 6.90 (dt, *J* = 15.5, 9.1 Hz, 2H, CO=CH, Ar-(4-OH)-3-H), 5.30 (s, 1H, Ar-(4-OH)-5-H), 4.46 – 4.29 (m,

2H, -OCH_2-), 3.61 (ddd, *J* = 24.4, 12.2, 5.4 Hz, 2H, -SCH_2-), 2.74 – 2.55 (m, 3H, -CH_3), 2.53 – 2.36 (m, 3H, -CH_3); ^{13}C NMR (101 MHz, DMSO) δ 187.70 (s, C=O), 179.20 (s), 162.77 (s), 160.33 (s), 157.71 (s), 150.51 (s), 142.30 (s), 134.59 (s), 132.32 (s), 131.52 (s), 131.20 (s), 130.96 (s), 124.24 (s), 123.25 (s), 114.98 (s), 67.56 (s, -OCH_2-), 36.26 (s, -SCH_2-), 31.24 (s, -CH_3), 28.33 (s, -CH_3); HRMS calcd for $C_{22}H_{21}BrN_3O_2S$ $[M+H]^+$: 470.05324, found 469.94470.

(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-isopropylphenyl)prop-2-en-1-one ***(4r)***: yellow solid, yield: 61%, m.p: 118.5–119.4°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.79 (m, 2H, Ar-(4-OH)-2,6-2H), 7.71 – 7.63 (m, 1H, Ar-CH=CH), 7.47 – 7.35 (m, 7H, 4Ar-H, Ar-($CH(CH_3)_2$-2,6-2H, CO=CH), 7.30 (d, *J* = 7.4 Hz, 1H, Ar-H), 7.26 – 7.10 (m, 8H, 5Ar-H, Ar-($CH(CH_3)_2$-3,5-2H, Ar-(4-OH)-3-H), 6.90 (d, *J* = 8.9 Hz, 1H, Ar-(4-OH)-5-H), 4.33 (dt, *J* = 18.2, 6.6 Hz, 2H, -OCH_2-), 3.71 – 3.55 (m, 2H, -SCH_2-), 2.87 – 2.74 (m, 1H, -CH-), 1.19 – 1.08 (m, 6H, 2CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.76 (s, C=O), 169.93 (s), 162.23 (s), 155.89 (s), 154.28 (s), 151.76 (s), 144.14 (s), 135.08 (d, *J* = 8.6 Hz), 132.74 (s), 131.51 (s), 131.07 (s), 130.86 (s), 129.86 (d, *J* = 2.7 Hz), 129.58 (s), 129.37 (s), 128.63 (dd, *J* = 7.0, 3.2 Hz), 127.10 (s), 120.95 (s), 114.49 (s), 66.54 (s, -OCH_2-), 34.15 (s, -SCH_2-), 29.60 (s, -CH-), 23.84 (d, -CH_3); HRMS calcd for $C_{35}H_{32}N_3O_2S$ $[M+H]^+$: 558.22097, found 558.21973.

(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-fluorophenyl)prop-2-en-1-one ***(4s)***: yellow oil, yield: 47%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.59 (m, 2H, Ar-(2-OH)-6-H, Ar-CH=CH), 7.56 – 7.45 (m, 5H, 2Ar-H, Ar-(4-F)-2,6-2H, CO=CH), 7.43 – 7.27 (m, 8H, 8Ar-H), 7.05 – 6.97 (m, 3H, Ar-(2-OH)-3,4,5-3H), 6.96 – 6.79 (m, 2H, Ar-(4-F)-3,5-2H), 4.54 – 4.41 (m, 2H, -OCH_2-), 3.80 – 3.65 (m, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.33 (s, C=O), 169.87 (s), 156.97 (s), 155.84 (s), 154.24 (s), 141.52 (s), 135.10 (d, *J* = 12.0 Hz), 133.16 (s), 130.92 (d, *J* = 36.1 Hz), 130.57 (d, *J* = 8.4 Hz), 129.87 (d, *J* = 5.0 Hz), 129.78 – 129.27 (m), 128.87 – 128.29 (m), 126.88 (d, *J* = 2.0 Hz), 121.32 (s), 116.15 (s), 115.93 (s), 112.56 (s), 66.77 (s, -OCH_2-), 29.96 (s, -SCH_2-); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.70 – -114.21 (m), -116.59 (s), -119.69 (s). HRMS calcd for $C_{32}H_{25}FN_3O_2S$ $[M+H]^+$: 534.16460, found 534.16296.

(E)-1-(2-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(thiophen-2-yl)prop-2-en-1-one ***(4t)***: white solid, yield: 61%, m.p: 139.8–140.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (dd, *J* = 32.6, 8.8 Hz, 2H, Ar-(2-OH)-6-H, thiophene-CH=CH), 7.89 (dd, *J* = 15.3, 4.7 Hz, 1H, thiophene-5-H), 7.78 (d, *J* = 5.0 Hz, 1H, thiophene-2-H), 7.68 (d, *J* = 3.4 Hz, 1H, Ar-H), 7.58 – 7.44 (m, 6H, Ar-(2-OH)-4,5-2H, CH=CO, 3Ar-H), 7.44 – 7.32 (m, 4H, 4Ar-H), 7.23 – 7.10 (m, 4H, 2Ar-H, thiophene-4-H, Ar-(2-OH)-3-H), 4.51 (t, *J* = 5.6 Hz, 2H), 3.76 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.23 (s, C=O), 169.82 (s), 162.46 (s), 156.26 (s), 154.74 (s), 140.31 (s), 136.45 (s), 135.56 (d, *J* = 16.2 Hz), 133.05 (s), 131.25 (s), 131.03 (s), 130.63 (s), 130.15 (s), 129.76 (d, *J* = 5.2 Hz), 129.15 (s), 128.90 (d, *J* = 5.8 Hz), 120.72 (s), 115.05 (s), 66.79 (s, -OCH_2-), 29.37 (s, -SCH_2-); HRMS calcd for $C_{30}H_{24}N_3O_2S_2$ $[M+H]^+$: 522.13044, found

522.12964.

(E)-3-(4-chlorophenyl)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)prop-2-en-1-one ***(4u)***: white solid, yield: 66%, m.p: 144.9–145.1°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.7 Hz, 2H, Ar-(4-OH)-2,6-2H), 7.73 (d, *J* = 15.6 Hz, 1H, Ar-CH=CH), 7.52 (ddd, *J* = 26.0, 14.9, 7.4 Hz, 7H, 2Ar-H, Ar-(4-Cl)-2,3,5,6,-4H, CO=CH), 7.44 – 7.30 (m, 8H, 8Ar-H), 7.04 (d, *J* = 8.7 Hz, 2H, Ar-(4-OH)-3,5-2H), 4.59 – 4.39 (m, 2H, -OCH_2-), 3.81 (dt, *J* = 13.1, 5.3 Hz, 2H, -SCH_2-); ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.36 (s, C=O), 169.88 (s), 162.42 (s), 155.92 (s), 154.31 (s), 142.51 (s), 136.21 (s), 135.06 (d, *J* = 7.1 Hz), 133.59 (s), 131.38 – 130.71 (m), 129.92 – 129.86 (m), 129.86 – 129.41 (m), 129.28 (d, *J* = 12.1 Hz), 128.64 (d, *J* = 7.8 Hz), 122.29 (s), 114.55 (s), 66.55 (s, -OCH_2-), 29.59 (s, -SCH_2-); HRMS calcd for $C_{32}H_{25}N_3O_2SCl$ $[M+H]^+$: 550.13505, found 550.13403.

(E)-3-(4-chlorophenyl)-1-(4-(3-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)propoxy)phenyl)prop-2-en-1-one ***(4v)***: yellow oil, yield: 37%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 – 8.25 (m, 2H, Ar-(4-NO_2)-3,5-2H), 8.21 – 8.11 (m, 4H, Ar-(4-OH)-3,5,-2H, Ar-(4-NO_2)-2,6-2H), 7.77 (t, *J* = 12.6 Hz, 1H, Ar-CH=CH), 7.57 – 7.31 (m, 11H, CO=CH, 10Ar-H), 7.15 – 7.05 (m, 2H, Ar-(4-OH)-2,6,-2H), 4.26 (dt, *J* = 19.5, 6.0 Hz, 2H, -OCH_2-), 3.50 (q, *J* = 7.3 Hz, 2H, -SCH_2-), 2.35 – 2.23 (m, 2H, -CH_2-); ^{13}C NMR (101 MHz, DMSO-d_6) δ 187.54 (s, C=O), 170.28 (s), 163.22 (s), 155.97 (s), 154.43 (s), 148.43 (s), 141.82 (s), 140.80 (s), 135.71 (s), 135.49 (s), 131.67 (s), 131.28 (s), 130.57 (s), 130.19 (d, *J* = 12.3 Hz), 129.73 (d, *J* = 4.8 Hz), 128.89 (d, *J* = 5.6 Hz), 126.53 (s), 124.39 (s), 115.00 (s), 67.13 (s, -OCH_2-), 28.94 (s, -SCH_2-), 27.29 (s,-CH_2-); HRMS calcd for $C_{33}H_{27}N_4O_4S$ $[M+H]^+$: 575.17475, found 575.17383.

(E)-1-(4-(2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxy)phenyl)-3-(4-methylthiazol-5-yl)prop-2-en-1-one ***(4w)***: yellow solid, yield: 40%, m.p: 141.2–142.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H, thiazole-5-H), 7.95 (dd, *J* = 11.3, 4.7 Hz, 3H, Ar-(4-OH)-2,6-2H, thiazole-CH=CH), 7.56 – 7.49 (m, 4H, CO=CH, 3Ar-H), 7.46 – 7.30 (m, 6H, 6Ar-H), 7.22 (t, *J* = 9.7 Hz, 1H, Ar-H), 7.06 – 6.99 (m, 2H, Ar-(4-OH)-3,5-2H), 4.48 (t, *J* = 6.6 Hz, 2H, -OCH_2-), 3.81 – 3.69 (m, 2H, -SCH_2-), 2.60 (s, 3H, -CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.36 (s, C=O), 169.86 (s), 162.47 (s), 156.76 (s), 155.89 (s), 154.28 (s), 152.62 (s), 135.04 (d, *J* = 6.7 Hz), 132.89 (s), 131.16 – 130.65 (m), 129.82 (s), 129.58 (s), 129.33 (d, *J* = 3.2 Hz), 128.63 (d, *J* = 7.0 Hz), 123.30 (s), 114.56 (s), 66.54 (s, -OCH_2-), 29.54 (s, -SCH_2-), 15.81 (s, -CH_3); HRMS calcd for $C_{30}H_{25}N_4O_2S_2$ $[M+H]^+$: 537.14134, found 537.14032.

^{1}H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectrum of the title compounds

Figure S1. ^{1}H NMR spectrum of compound **4a**

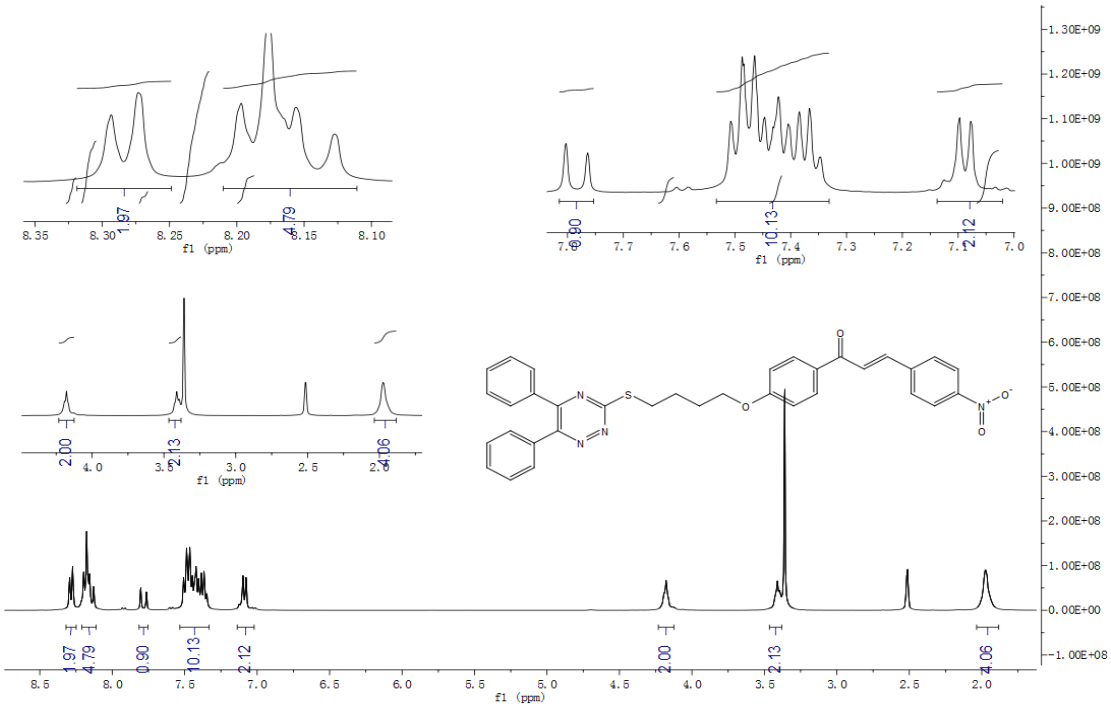

Figure S2. ^{13}C NMR spectrum of compound **4a**

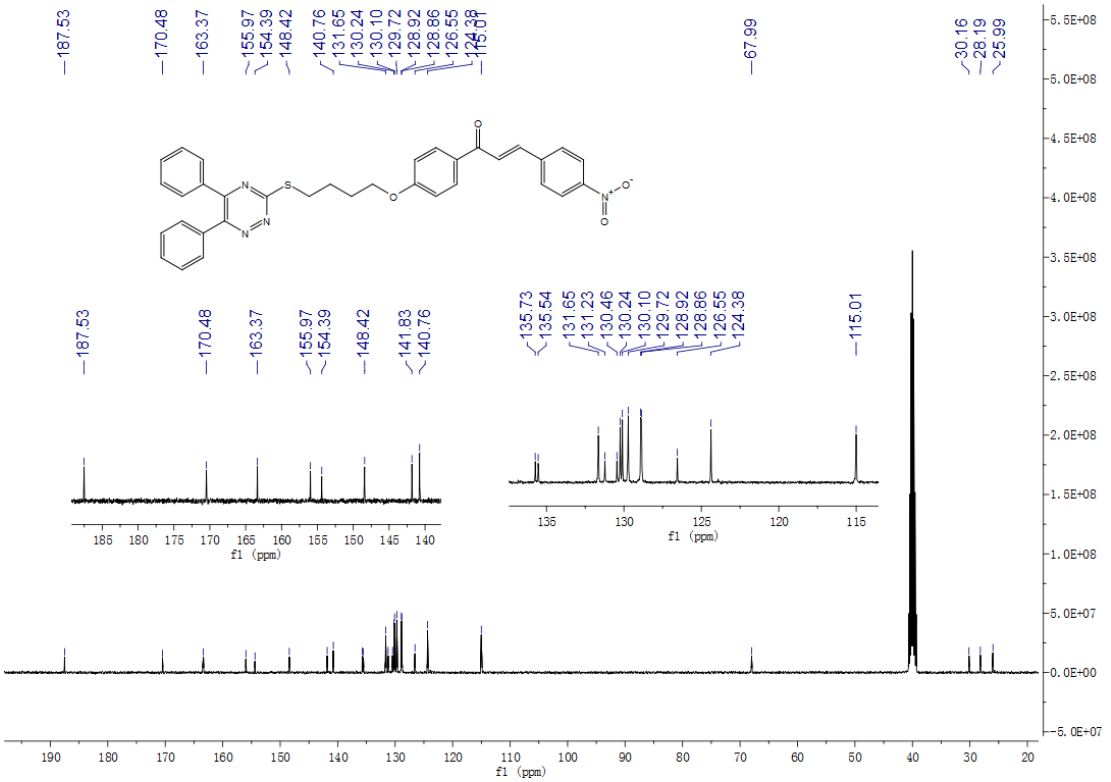

Figure S3. HRMS spectrum of compound **4a**

2018060504 #203 RT: 2.01 AV: 1 NL: 1.47E4
T: FTMS + p ESI Full ms [100.0000-1000.0000]

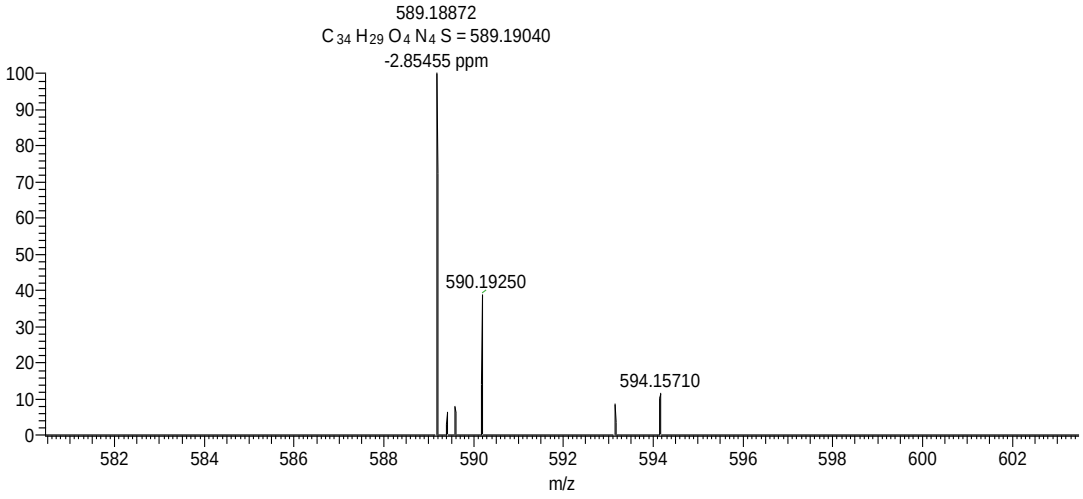

Figure S4. ^{1}H NMR spectrum of compound **4b**

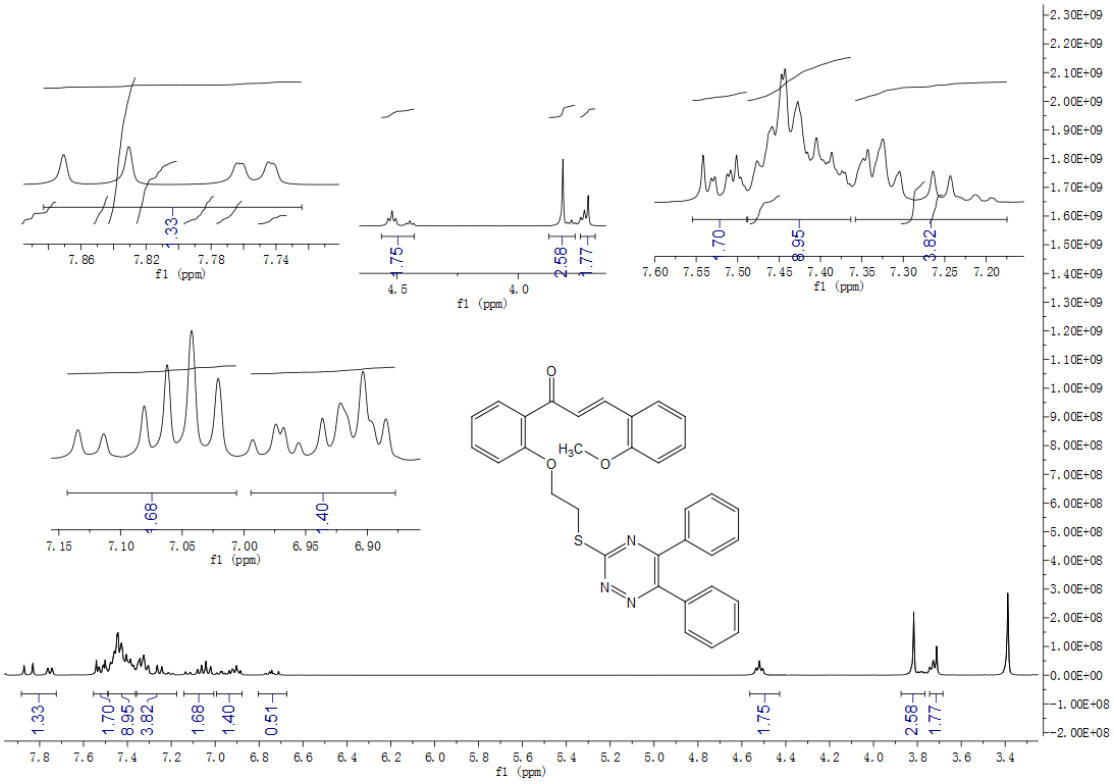

Figure S5. ^{13}C NMR spectrum of compound **4b**

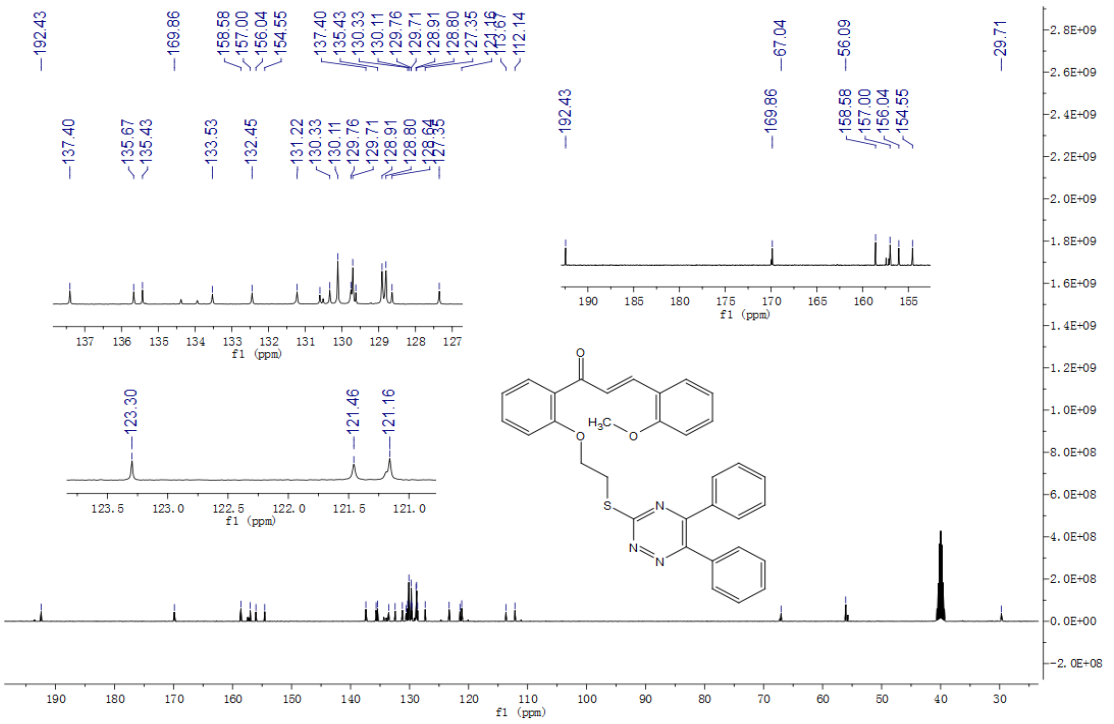

Figure S6. HRMS spectrum of compound **4b**

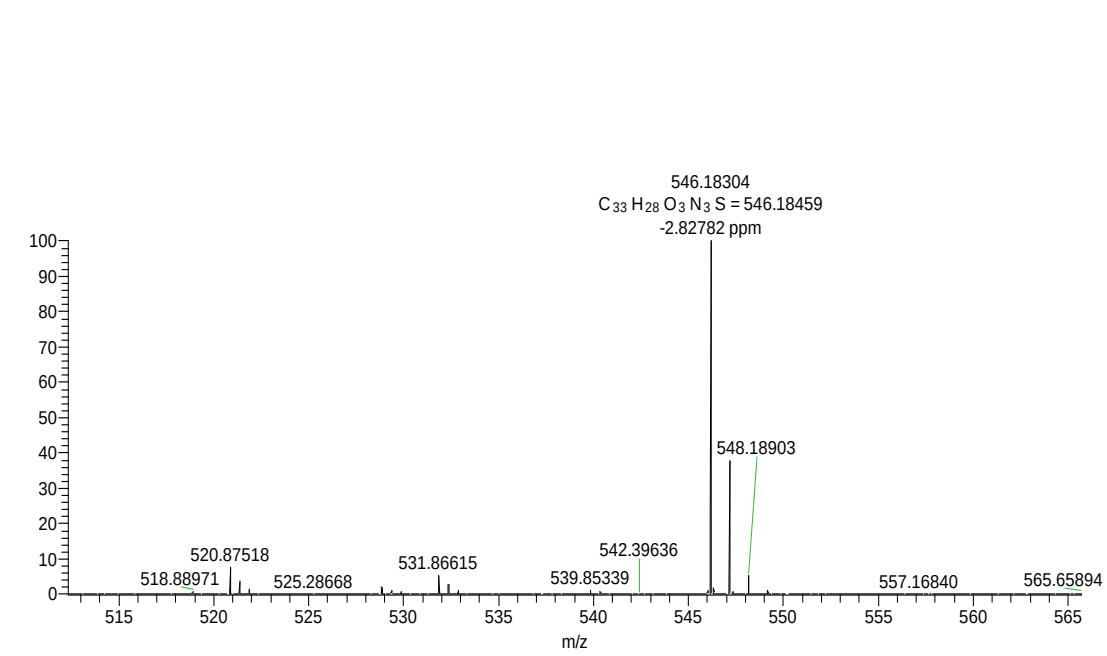

Figure S7. ^{1}H NMR spectrum of compound **4c**

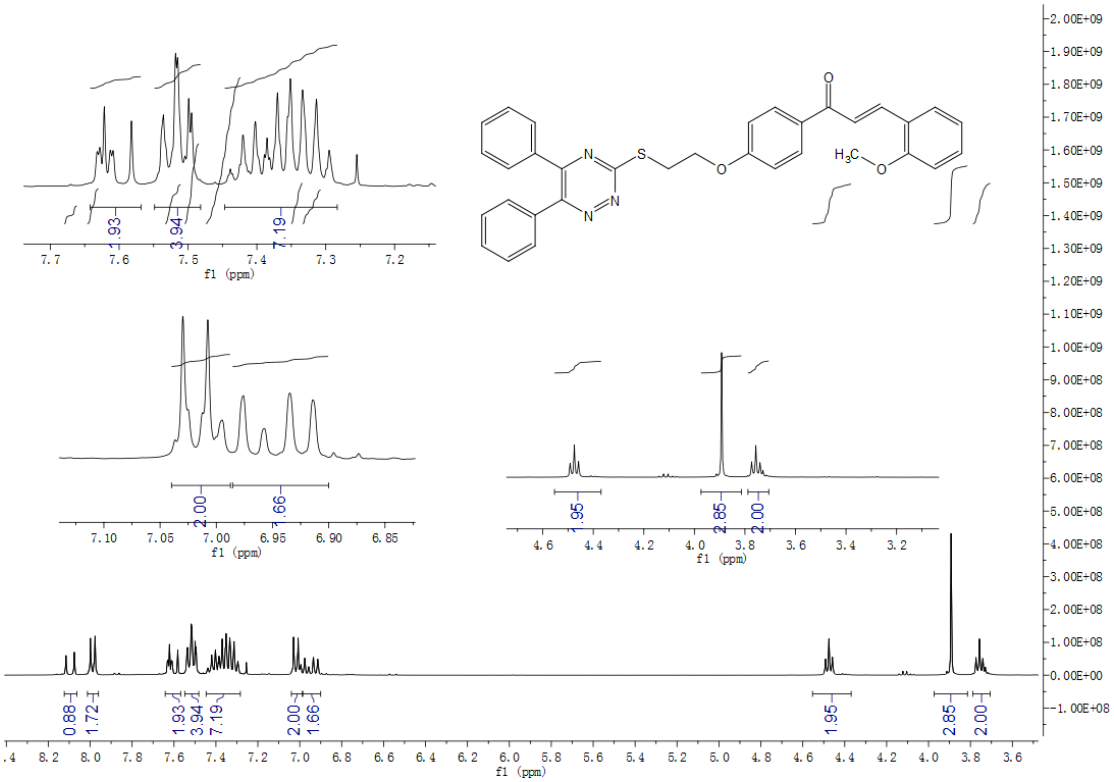

Figure S8. ^{13}C NMR spectrum of compound **4c**

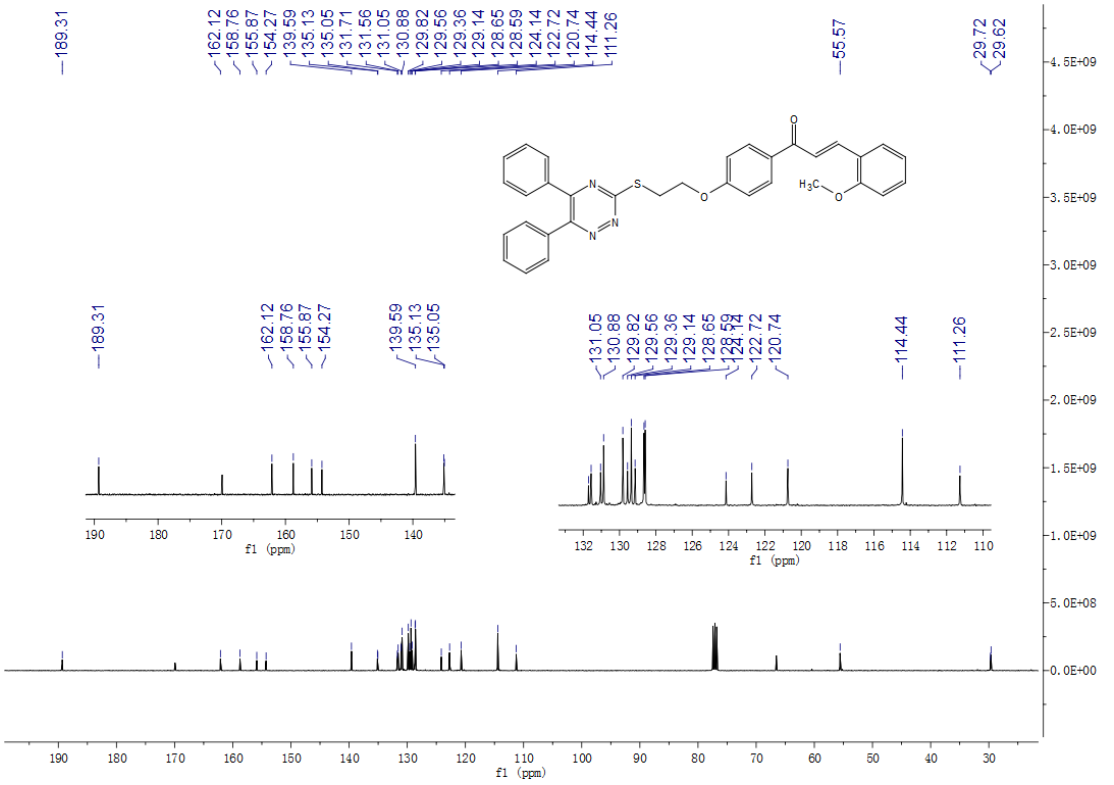

Figure S9. HRMS spectrum of compound **4c**

2018060547 #157 RT: 1.52 AV: 1 NL: 4.81E7
T: FTMS + p ESI Full ms [100.0000-1000.0000]

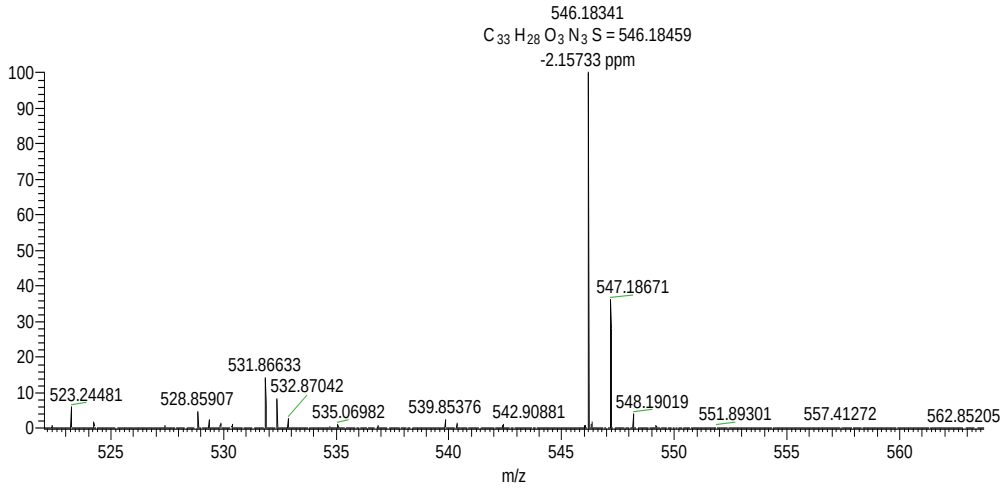

Figure S10. ^{1}H NMR spectrum of compound **4d**

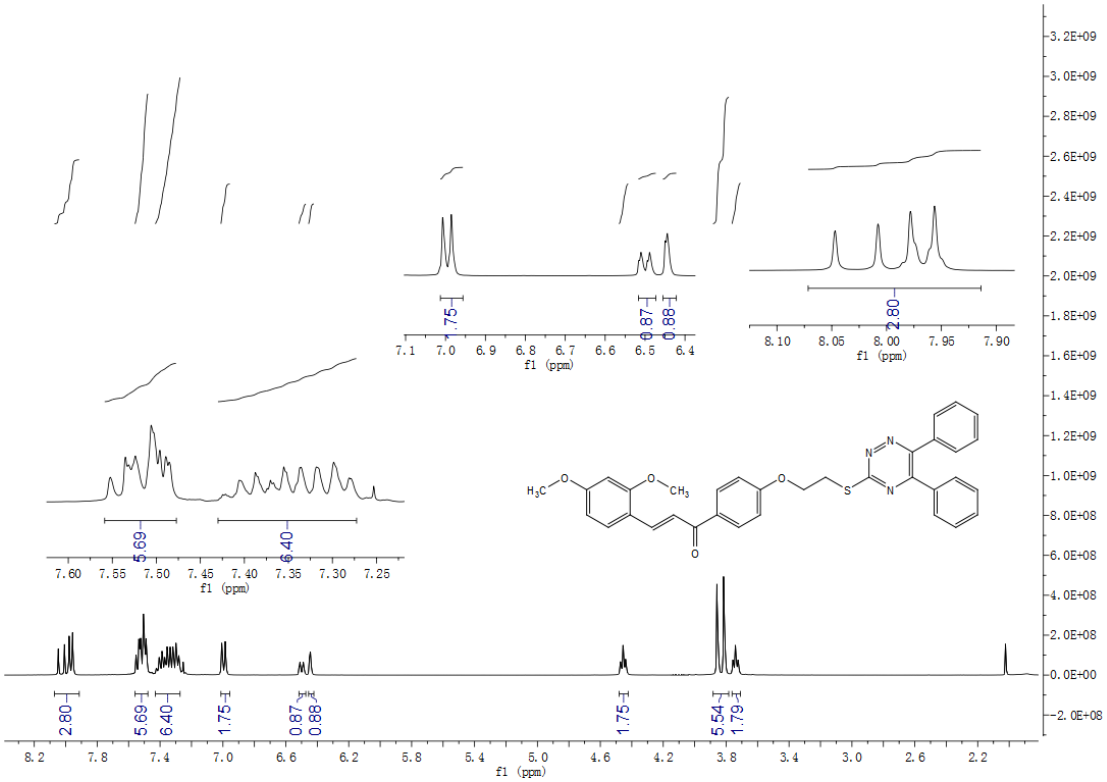

Figure S11. ^{13}C NMR spectrum of compound **4d**

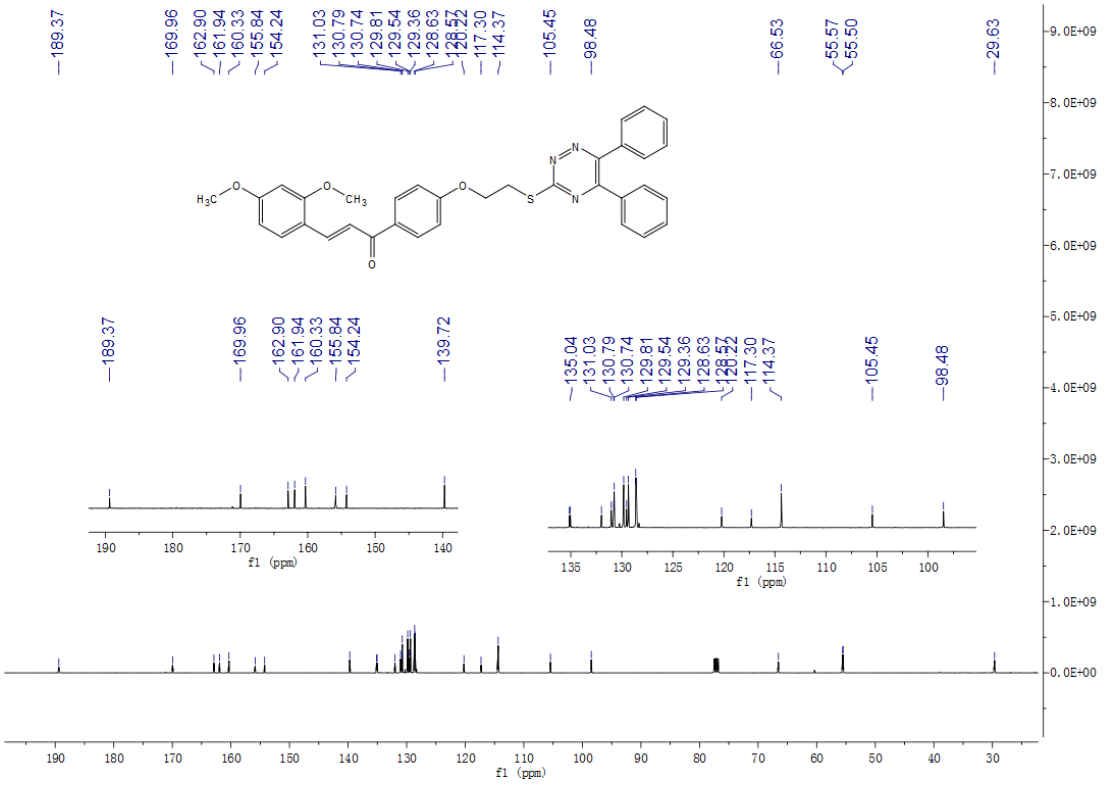

Figure S12. HRMS spectrum of compound **4d**

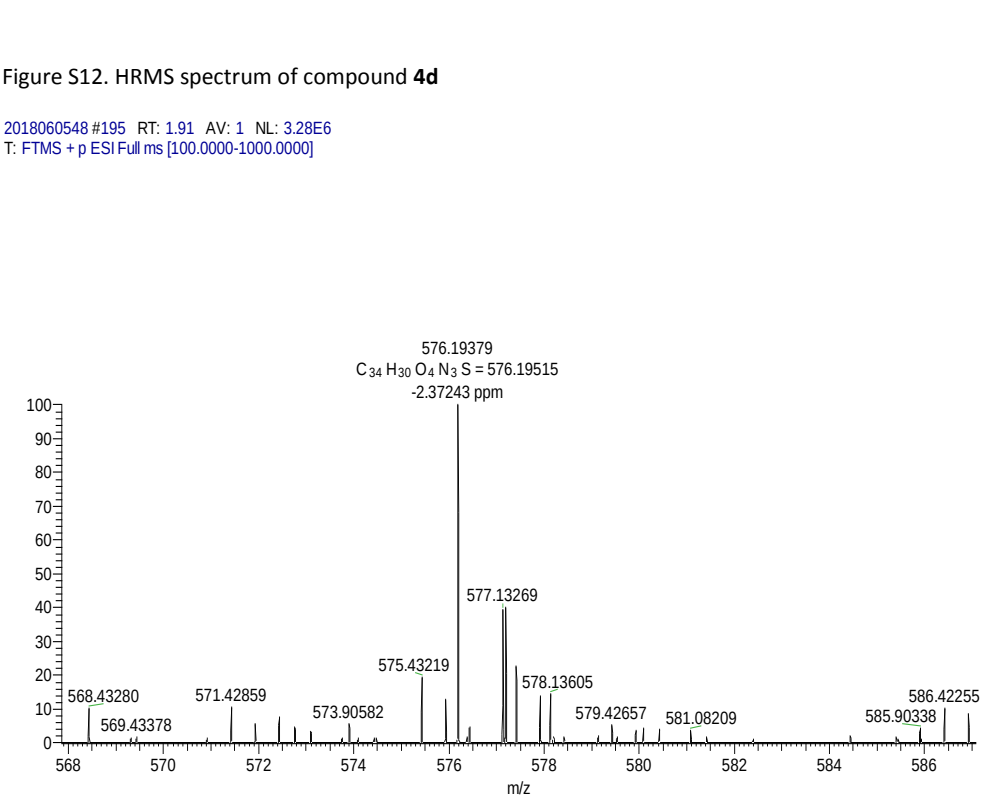

Figure S13. ^{1}H NMR spectrum of compound **4e**

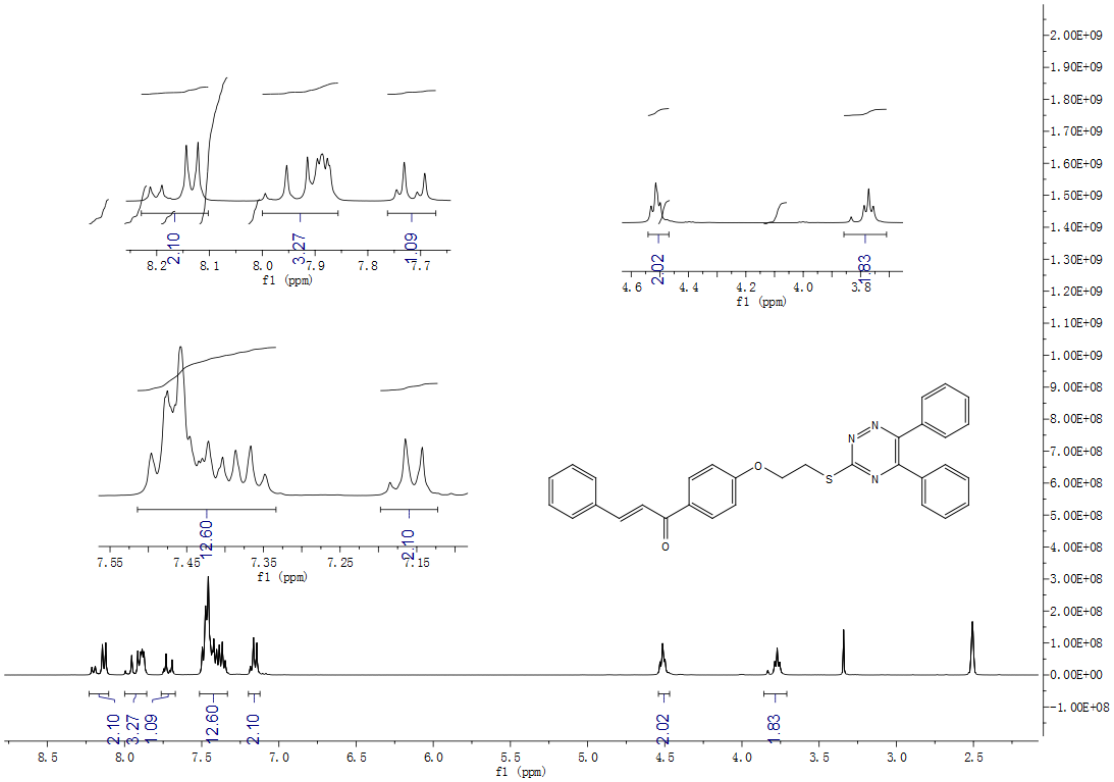

Figure S14. ^{13}C NMR spectrum of compound **4e**

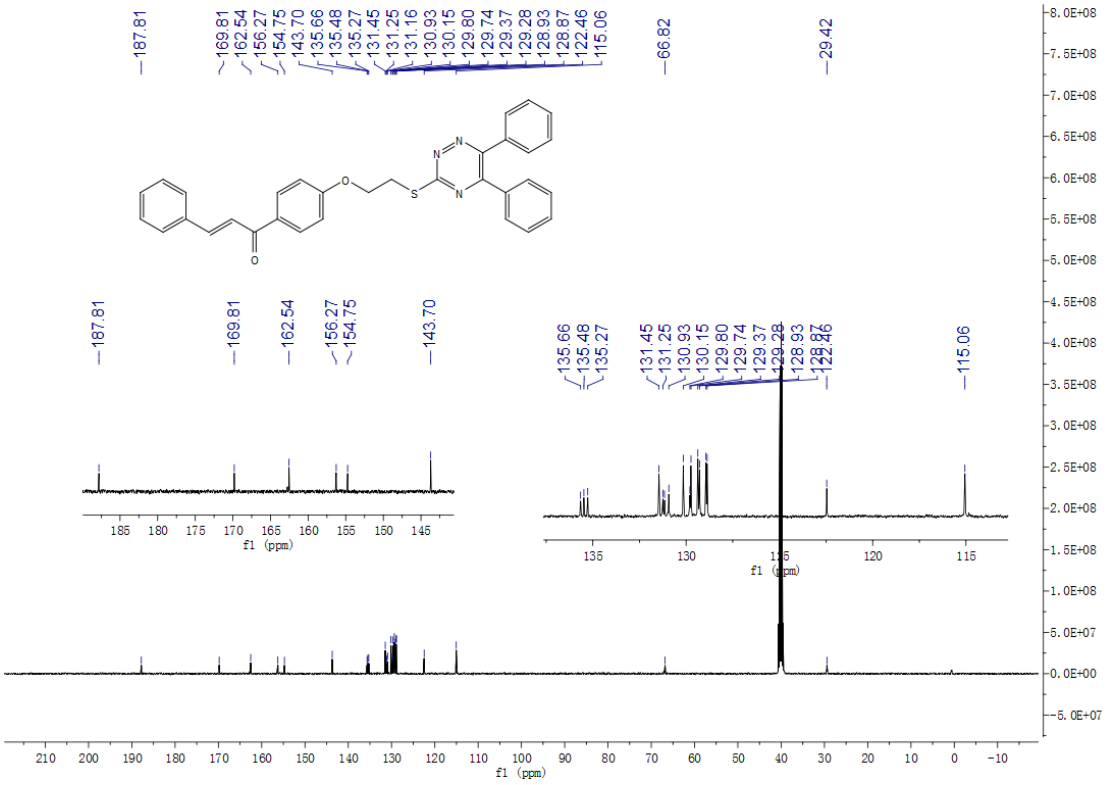

Figure S15. HRMS spectrum of compound **4e**

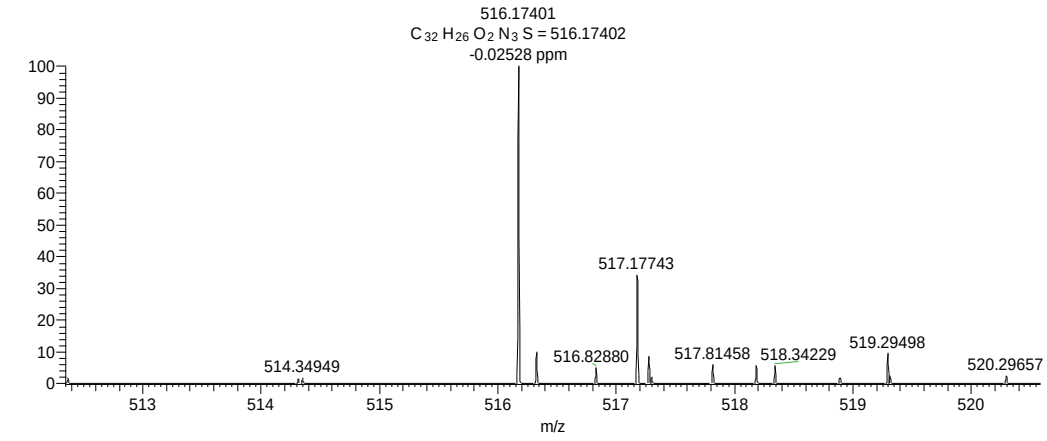

Figure S16. ^{1}H NMR spectrum of compound **4f**

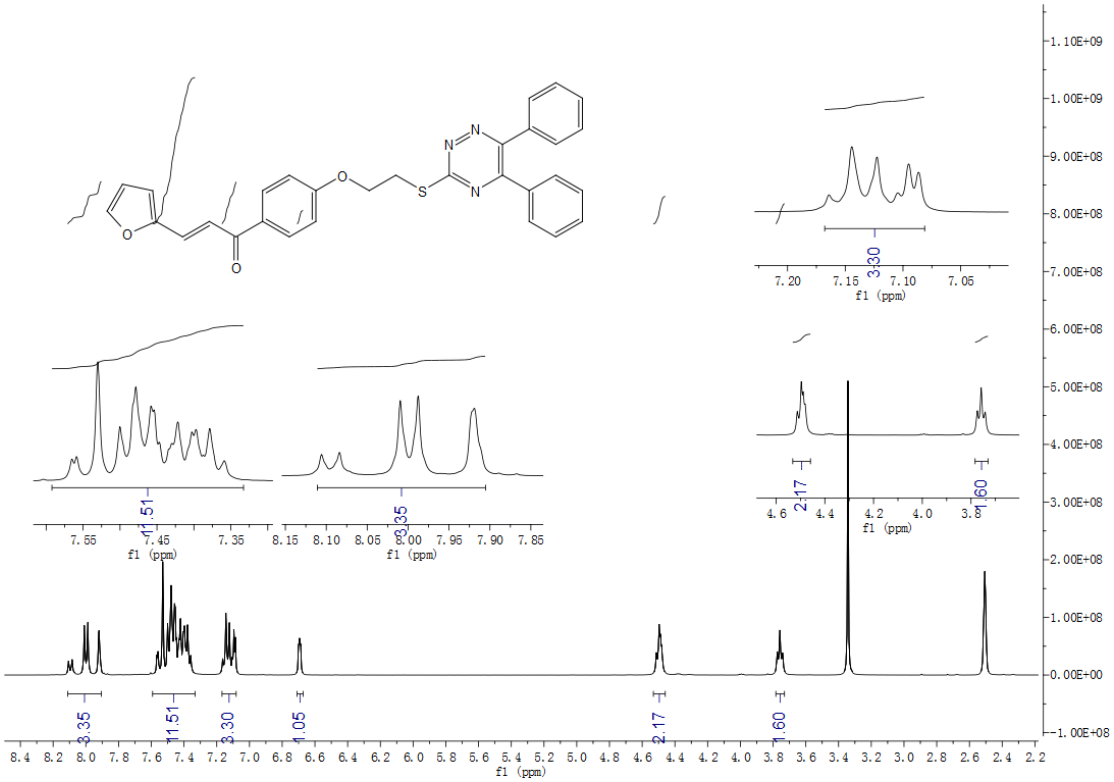

Figure S17. ^{13}C NMR spectrum of compound **4f**

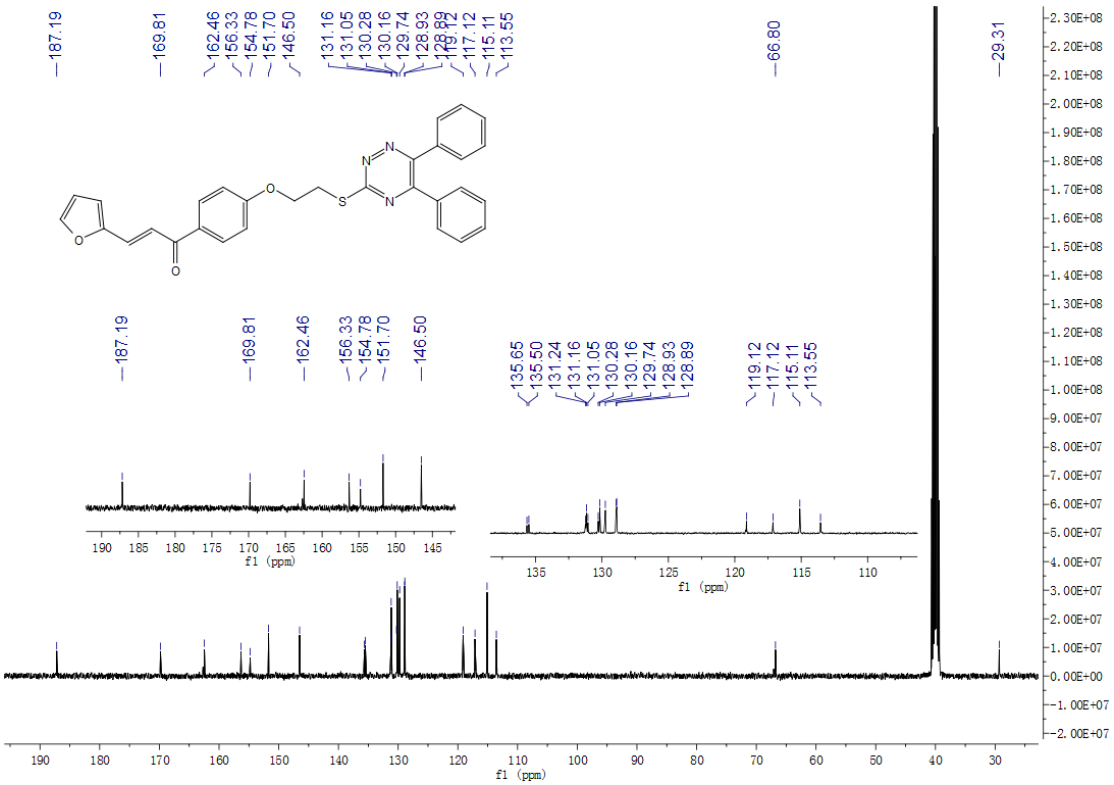

Figure S18. HRMS spectrum of compound **4f**

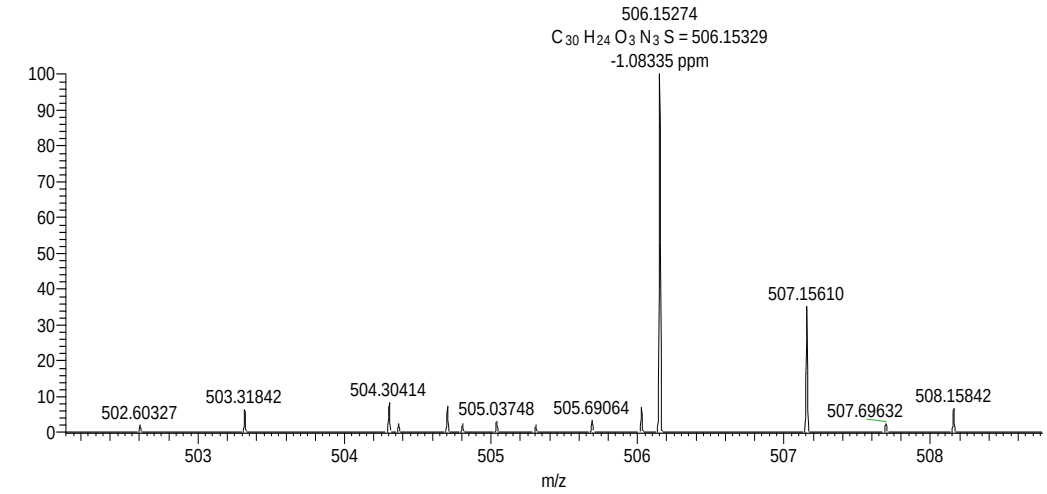

Figure S19. ^{1}H NMR spectrum of compound **4g**

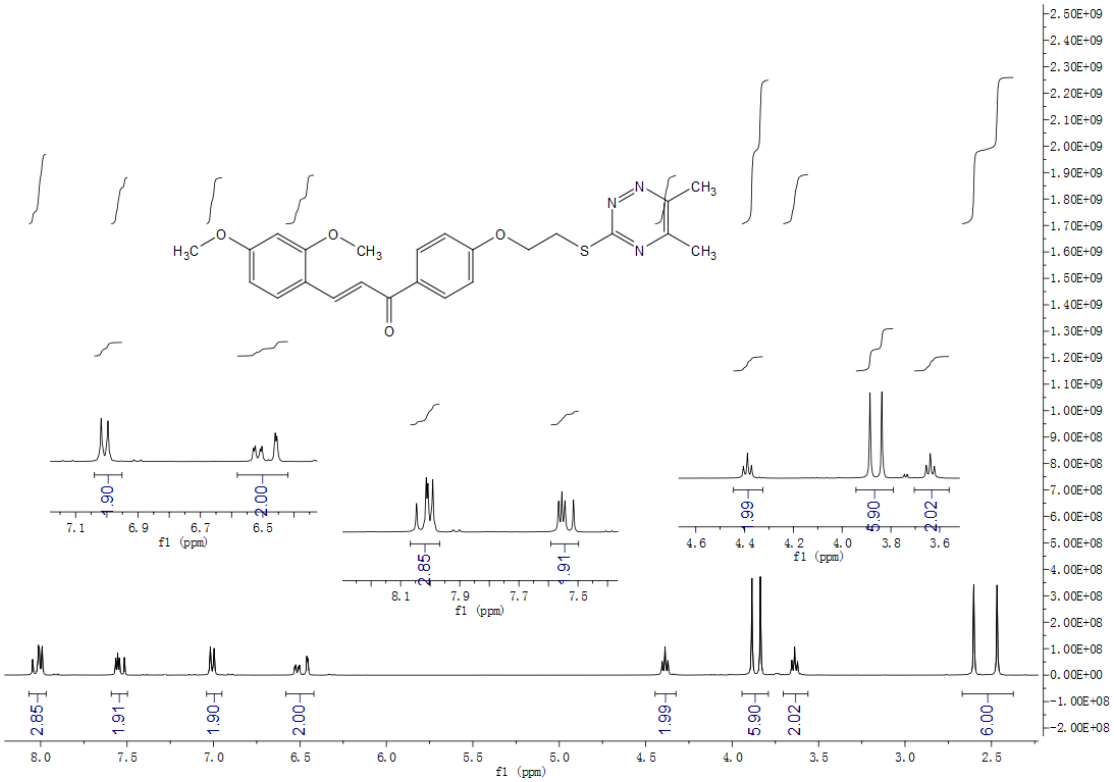

Figure S20. ^{13}C NMR spectrum of compound **4g**

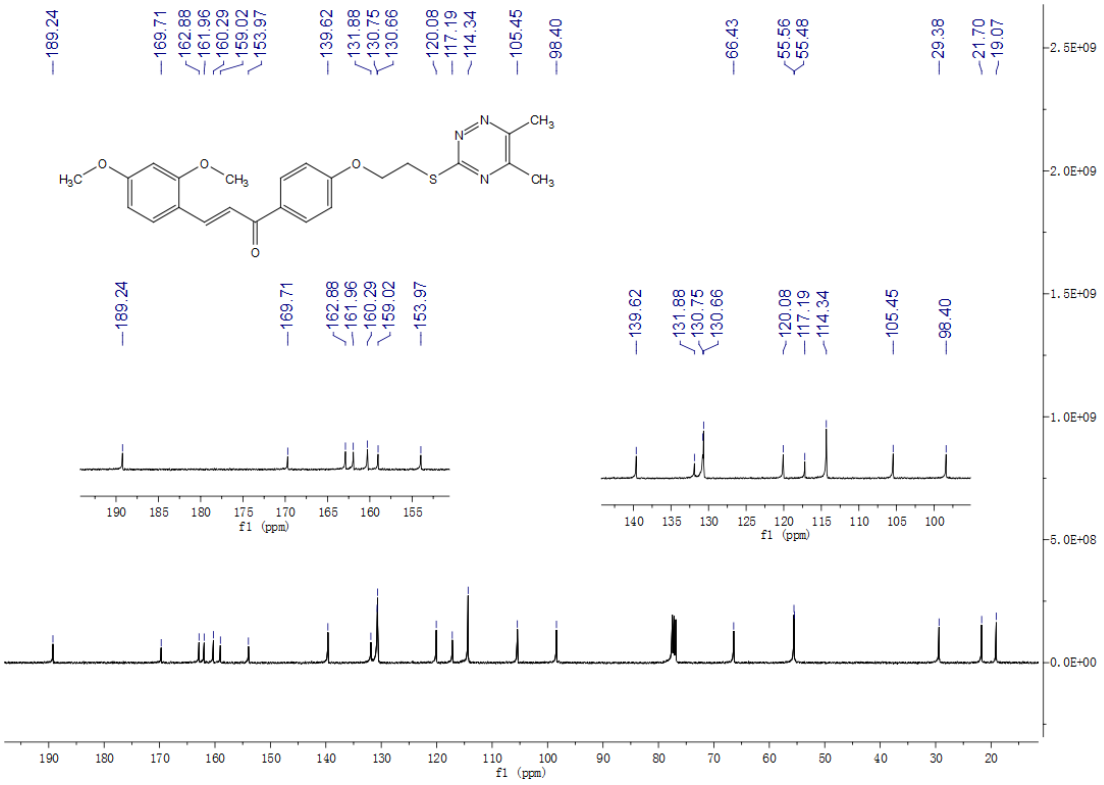

Figure S21. HRMS spectrum of compound **4g**

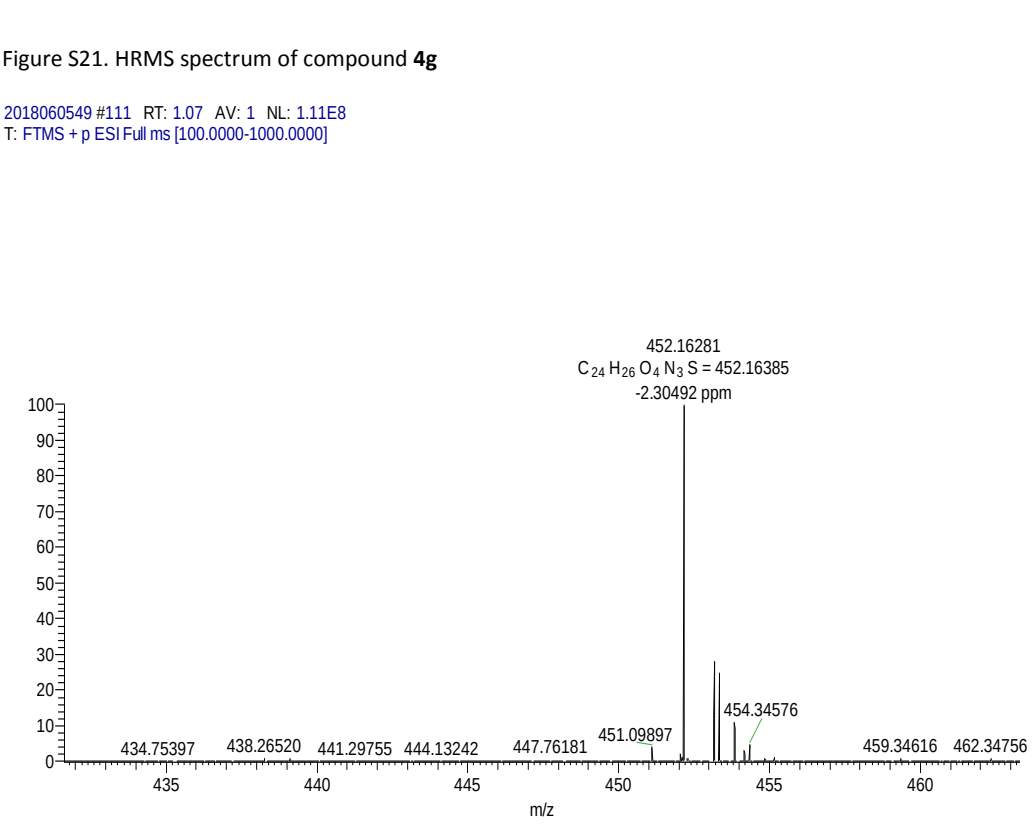

Figure S22. ^{1}H NMR spectrum of compound **4h**

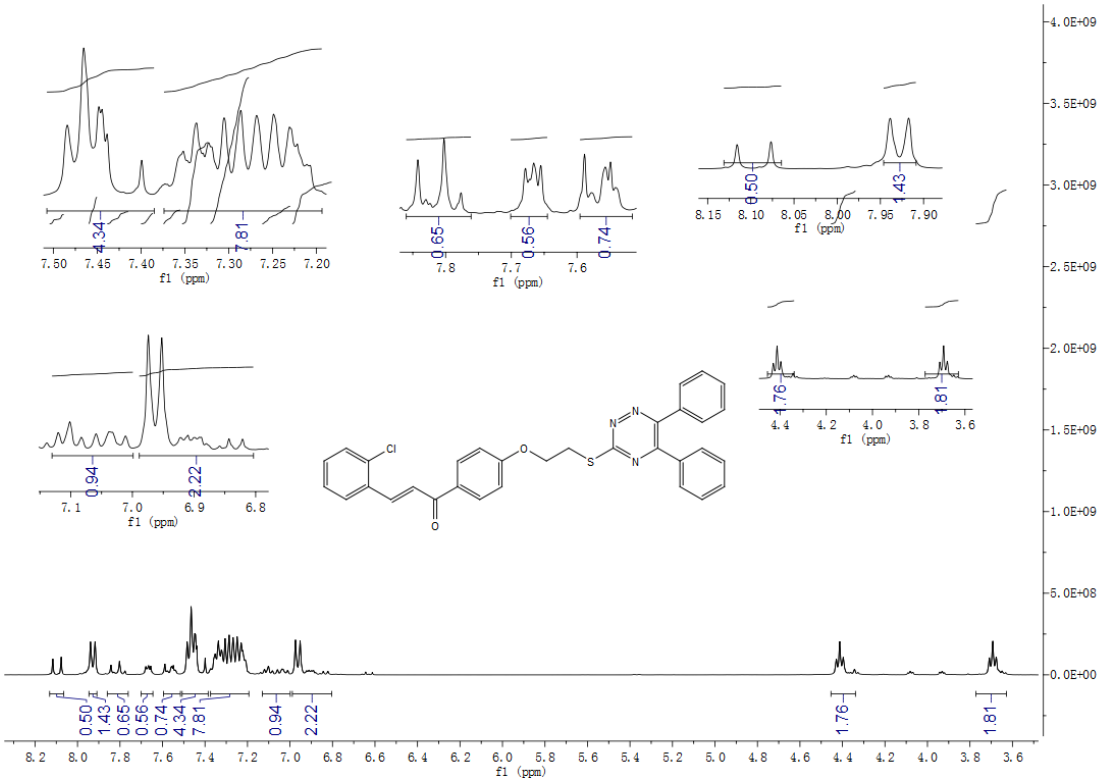

Figure S23. ^{13}C NMR spectrum of compound **4h**

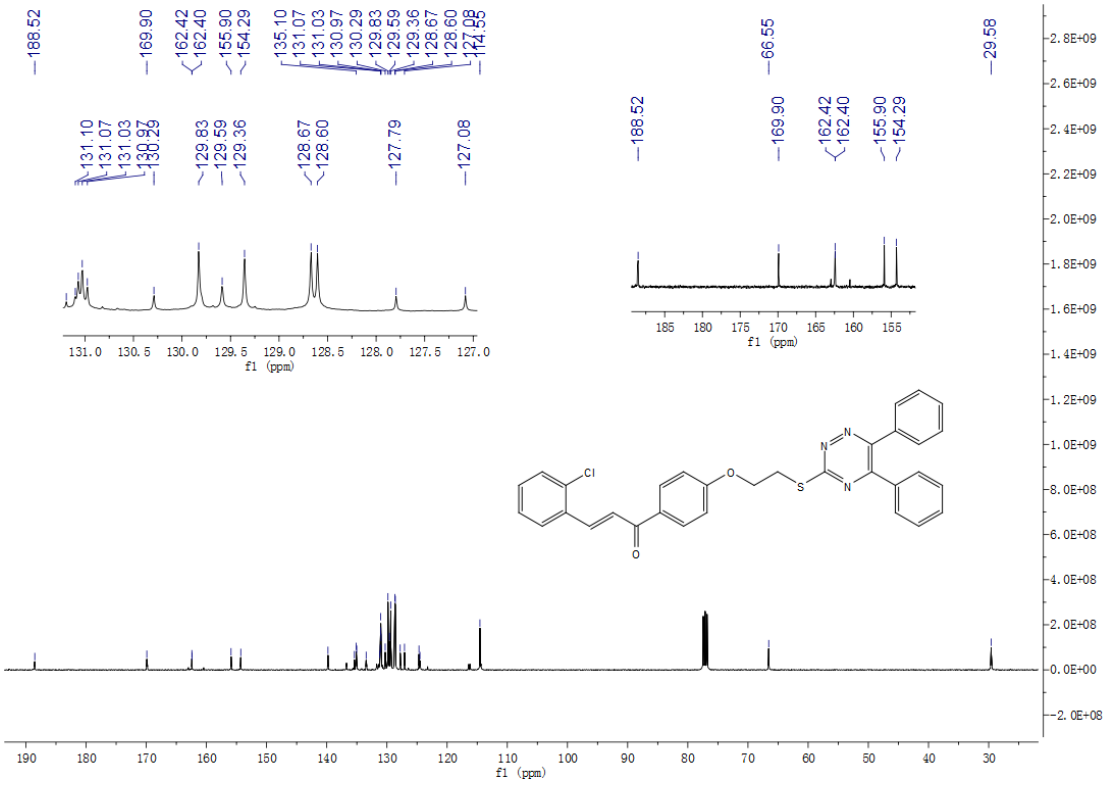

Figure S24. HRMS spectrum of compound **4h**

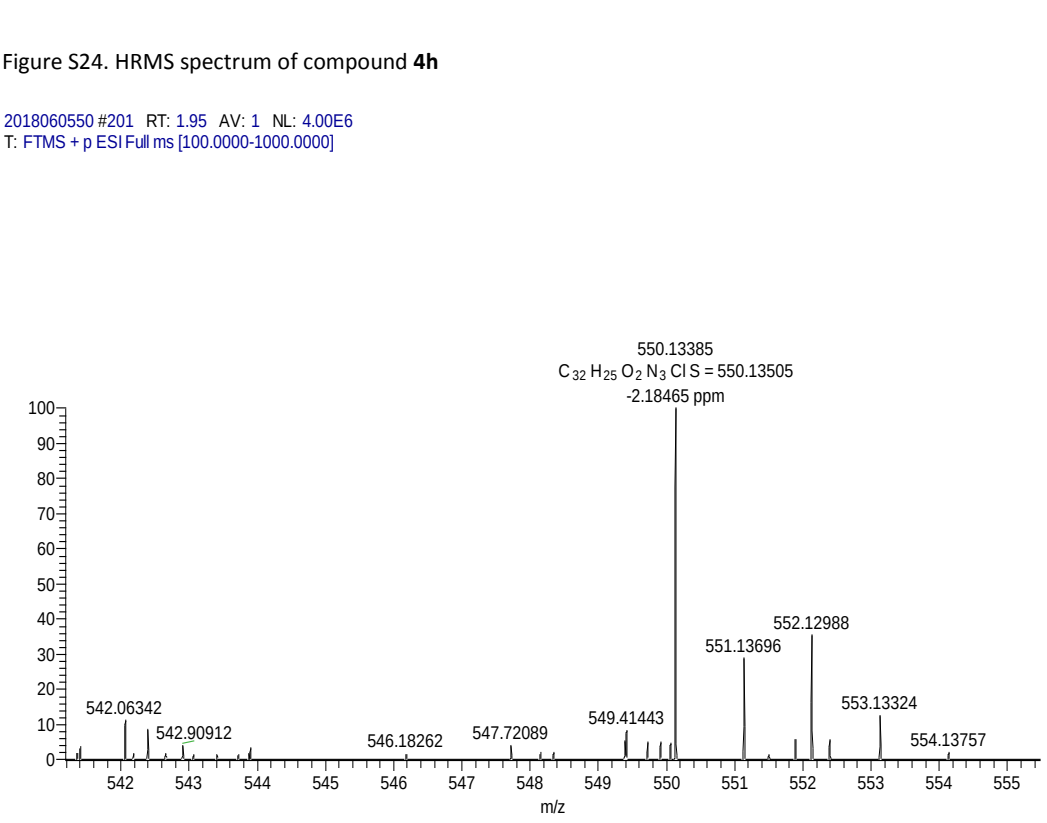

Figure S25. ^{1}H NMR spectrum of compound **4i**

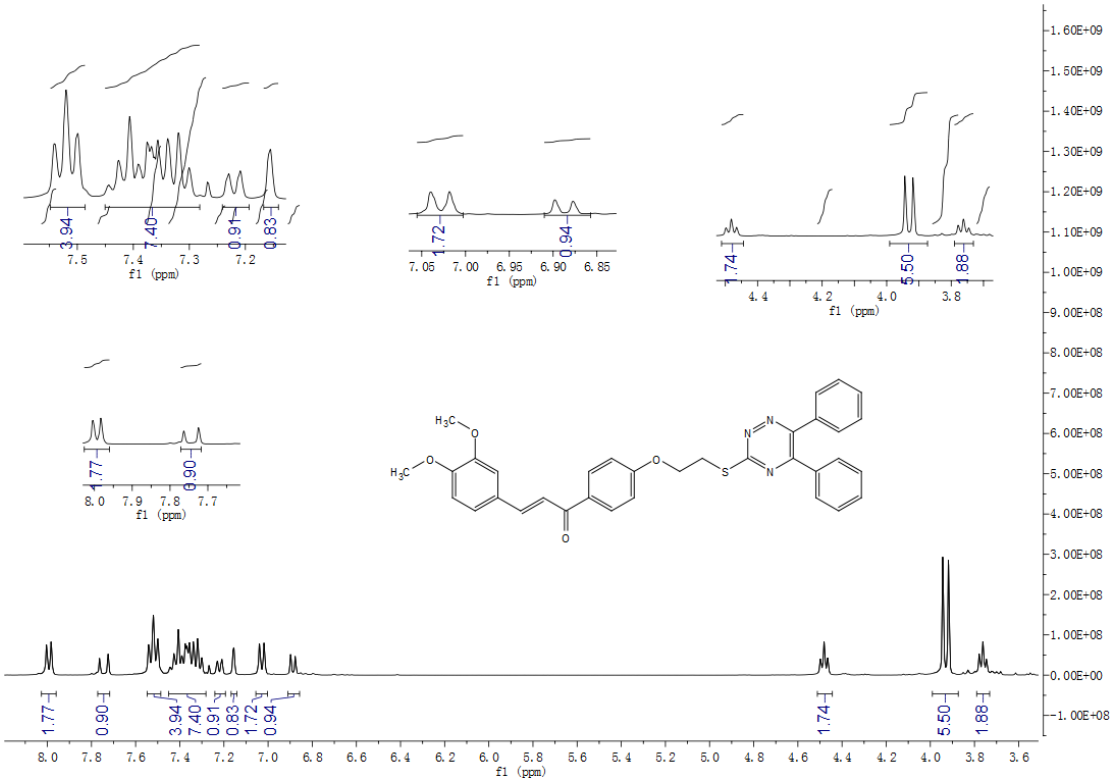

Figure S26. ^{13}C NMR spectrum of compound **4i**

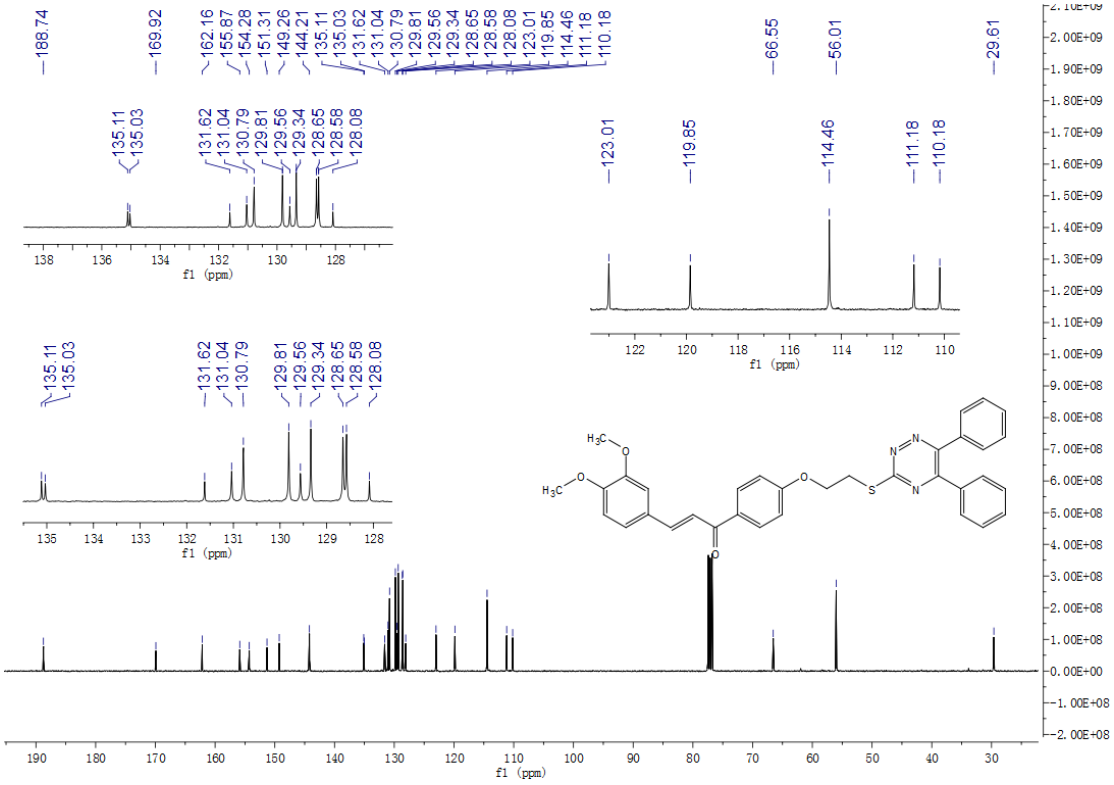

Figure S27. HRMS spectrum of compound **4i**

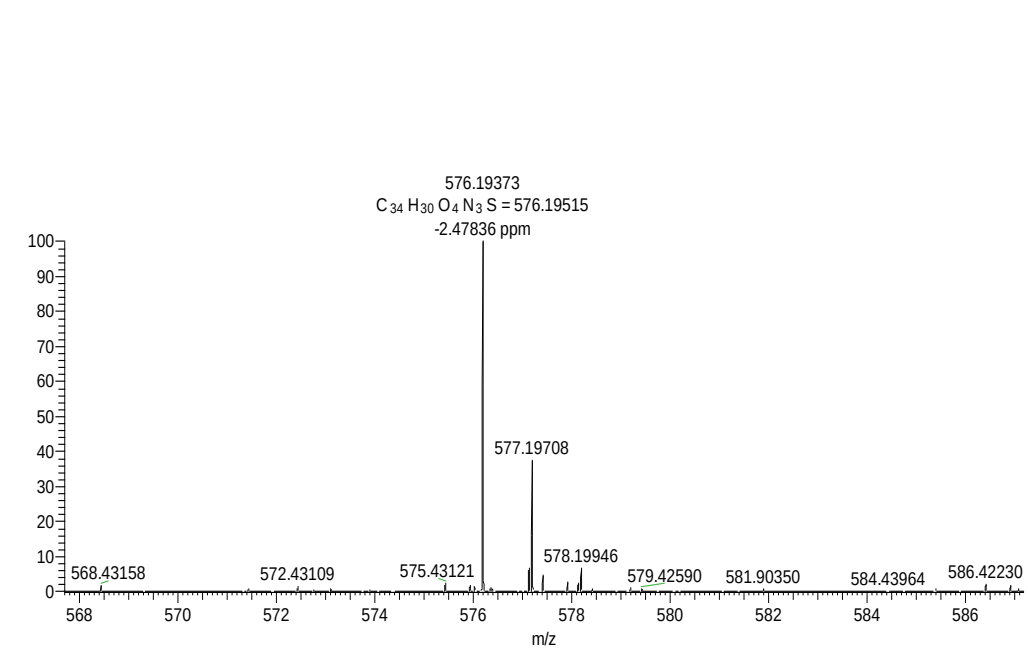

Figure S28. ^{1}H NMR spectrum of compound **4j**

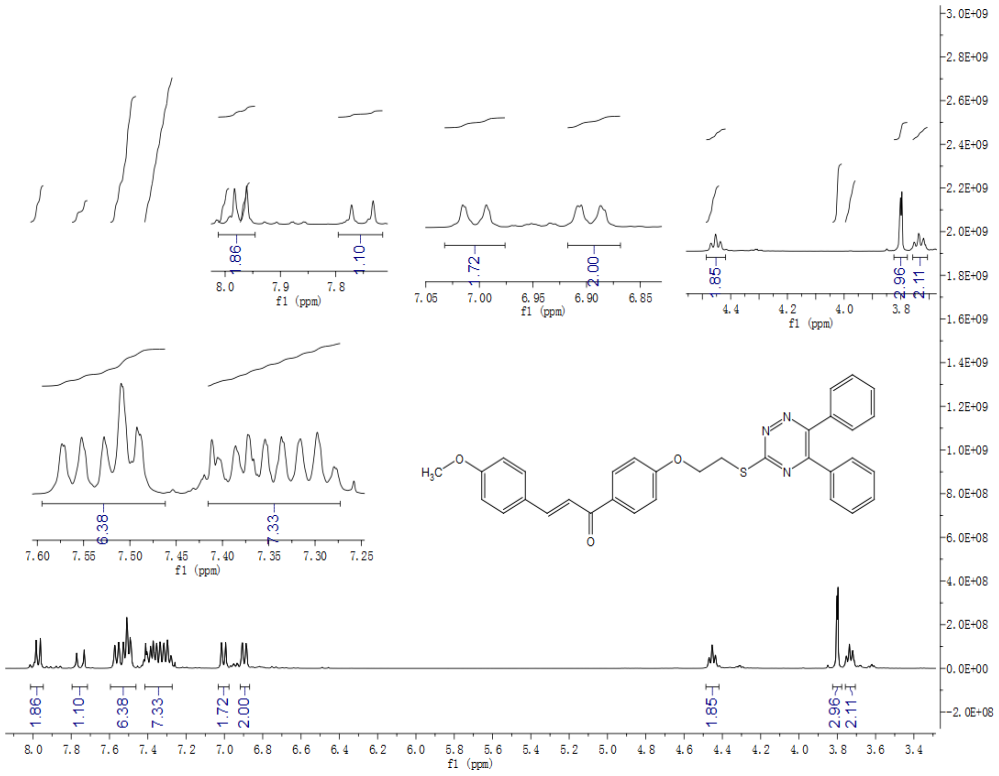

Figure S29. ^{13}C NMR spectrum of compound **4j**

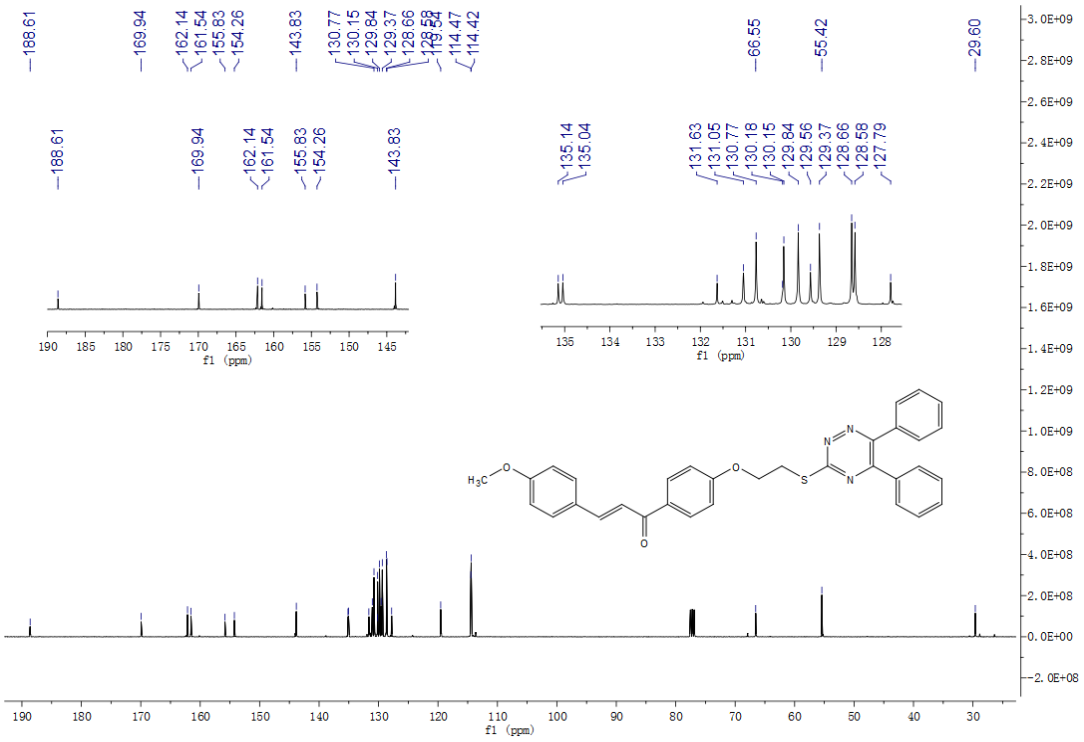

Figure S30. HRMS spectrum of compound **4j**

2018060552 #203 RT: 2.00 AV: 1 NL: 4.97E4
T: FTMS + p ESI Full ms [100.0000-1000.0000]

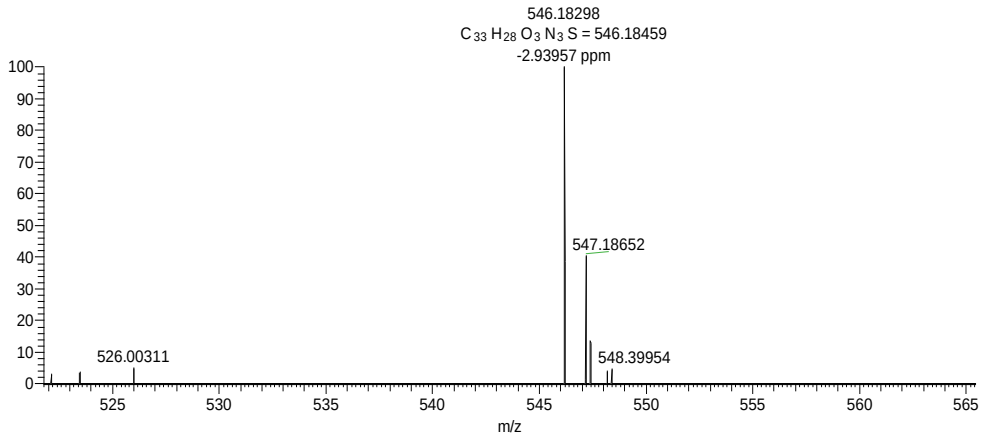

Figure S31. ^{1}H NMR spectrum of compound **4k**

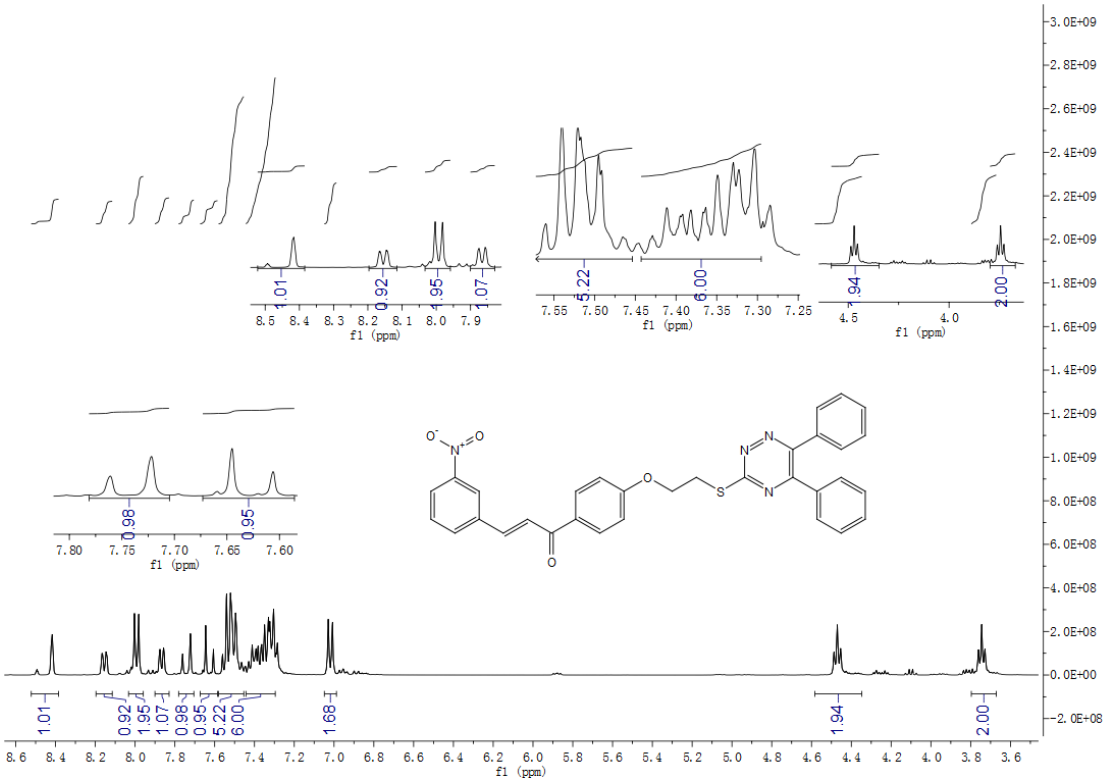

Figure S32. ^{13}C NMR spectrum of compound **4k**

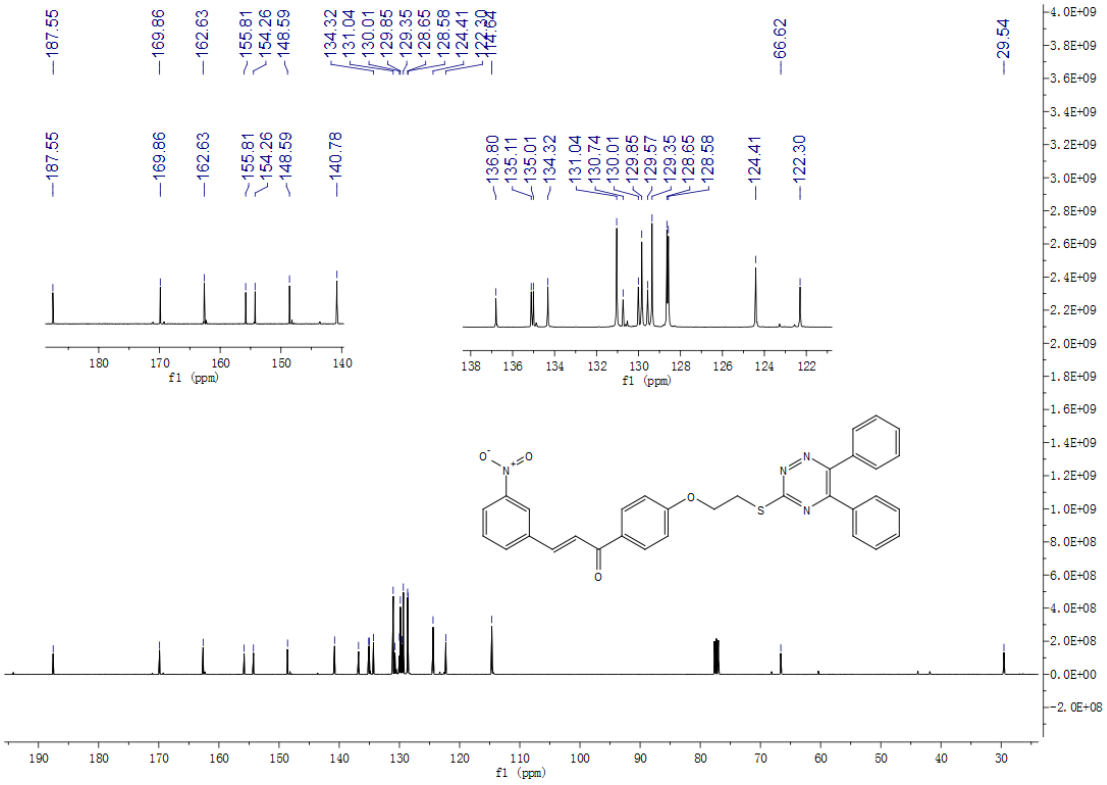

Figure S33. HRMS spectrum of compound **4k**

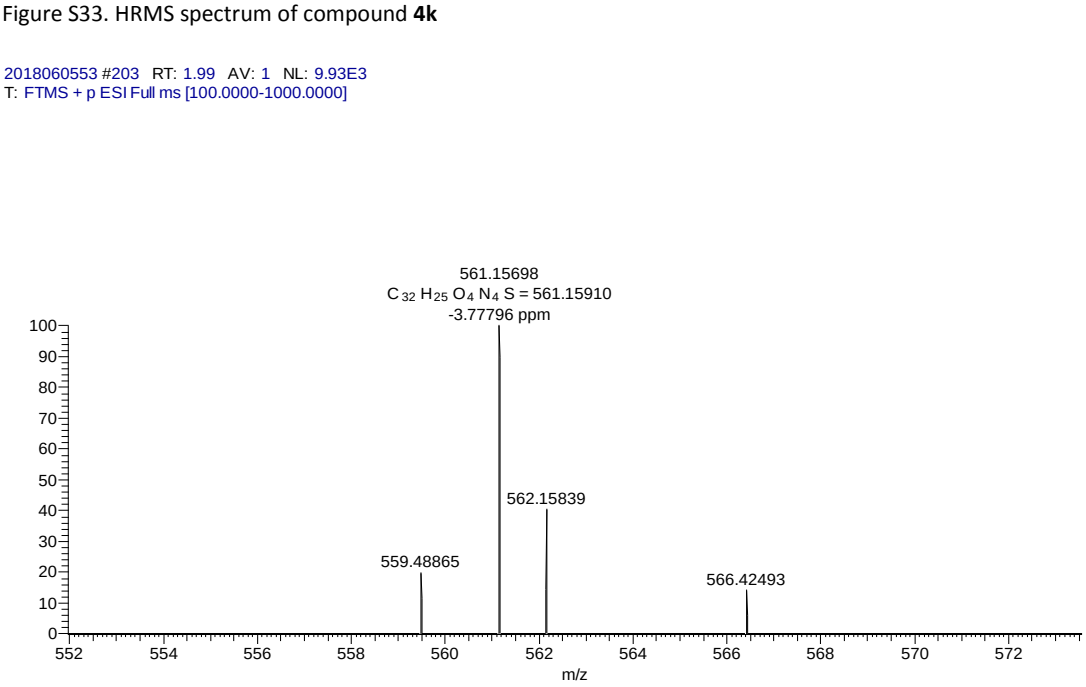

Figure S34. ^{1}H NMR spectrum of compound **4l**

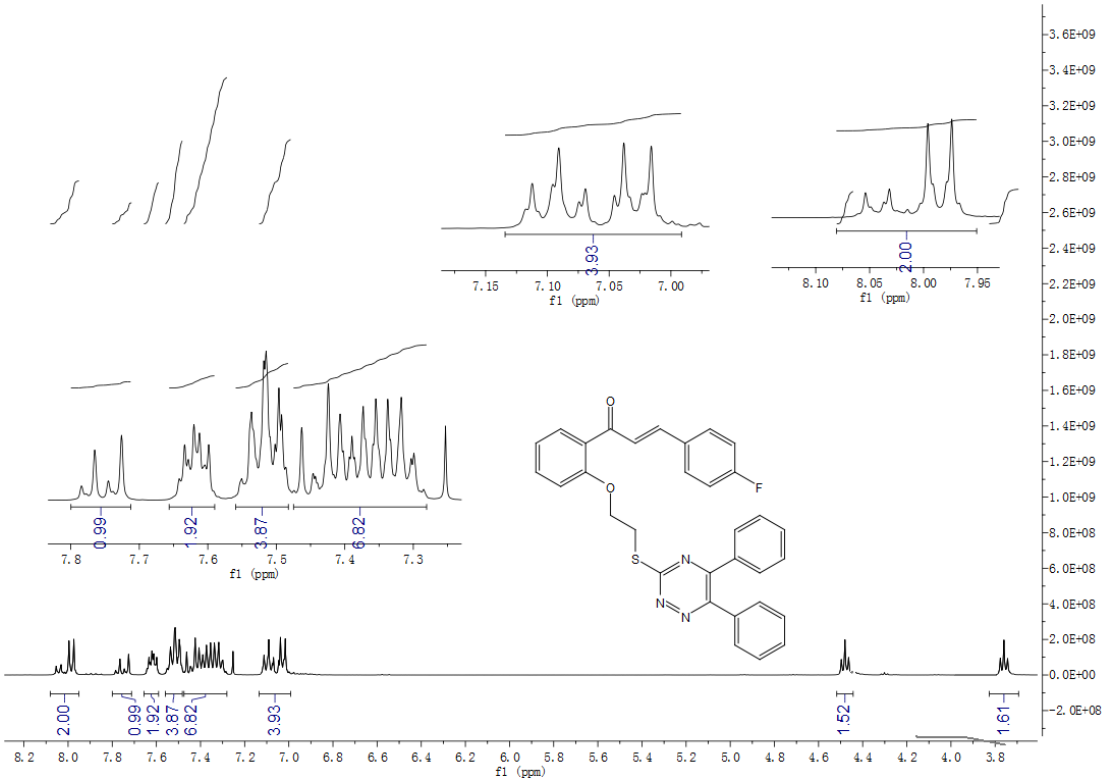

Figure S35. ^{13}C NMR spectrum of compound **4l**

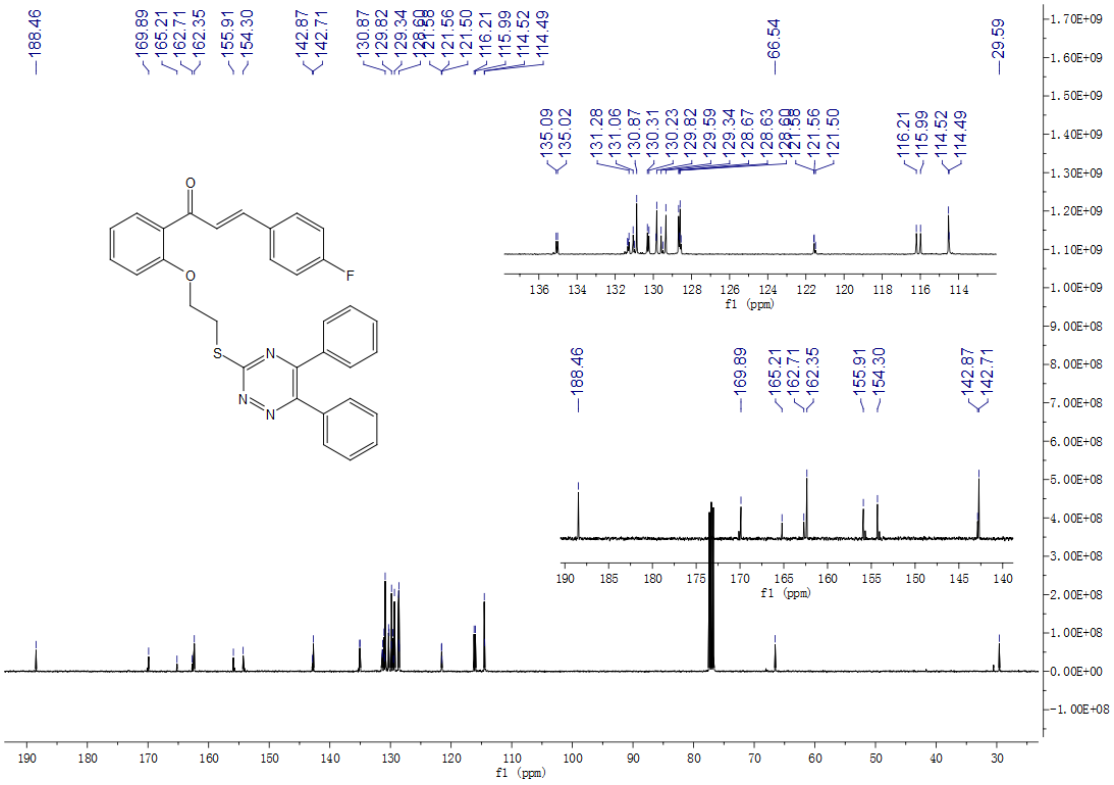

Figure S36. ^{19}F NMR spectrum of compound **4l**

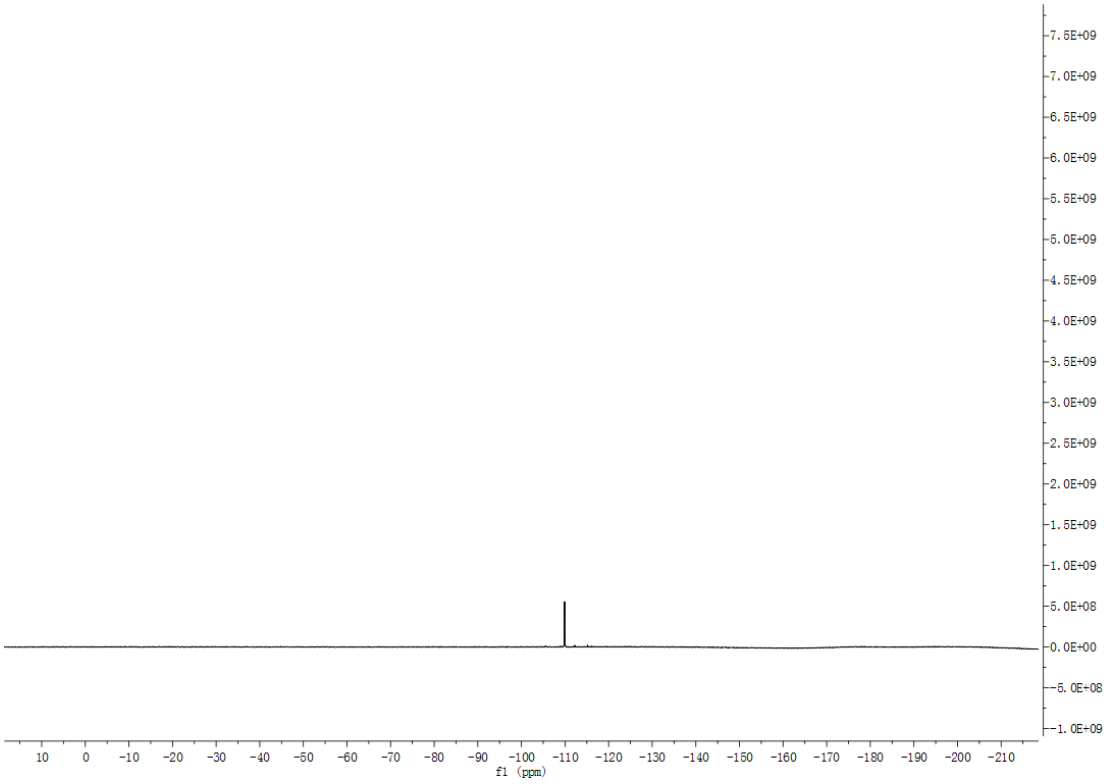

Figure S37. HRMS spectrum of compound **4l**

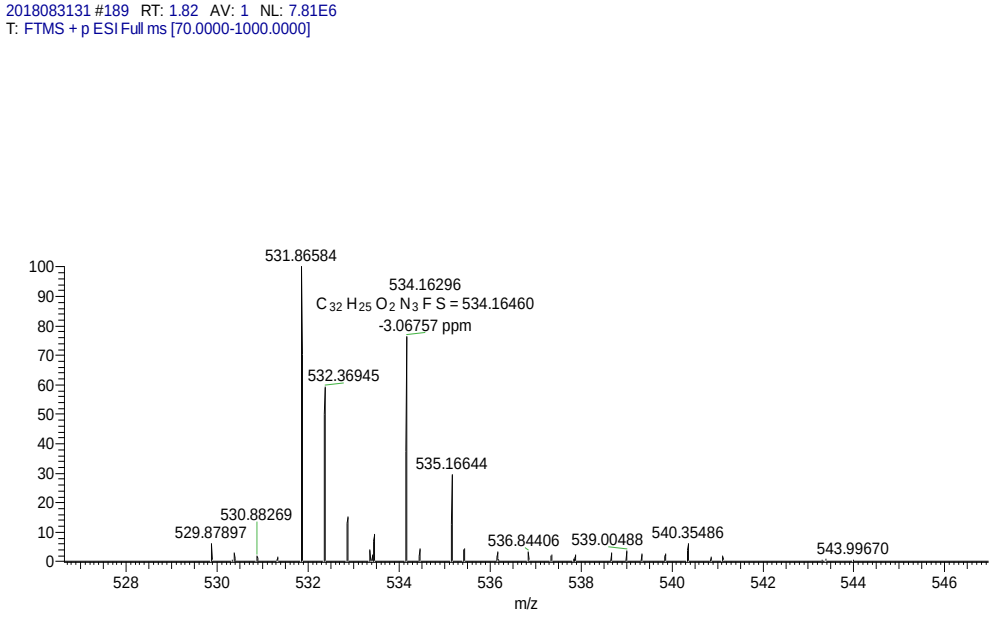

Figure S38. ^{1}H NMR spectrum of compound **4m**

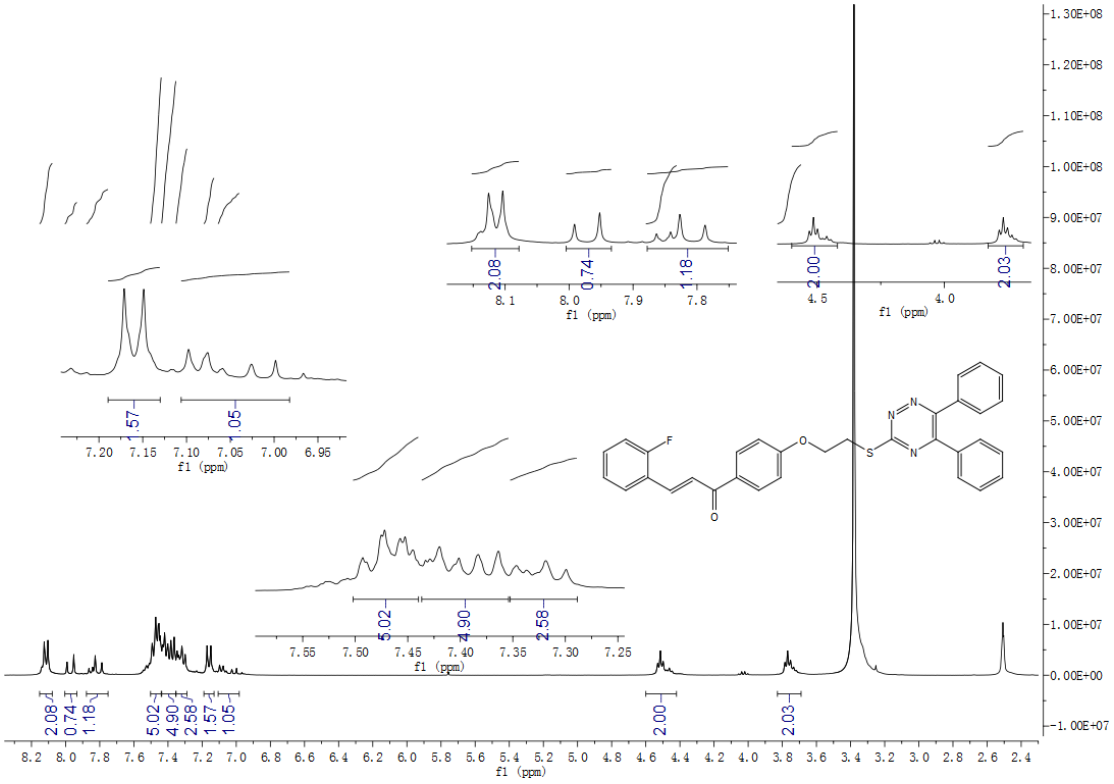

Figure S39. ^{13}C NMR spectrum of compound **4m**

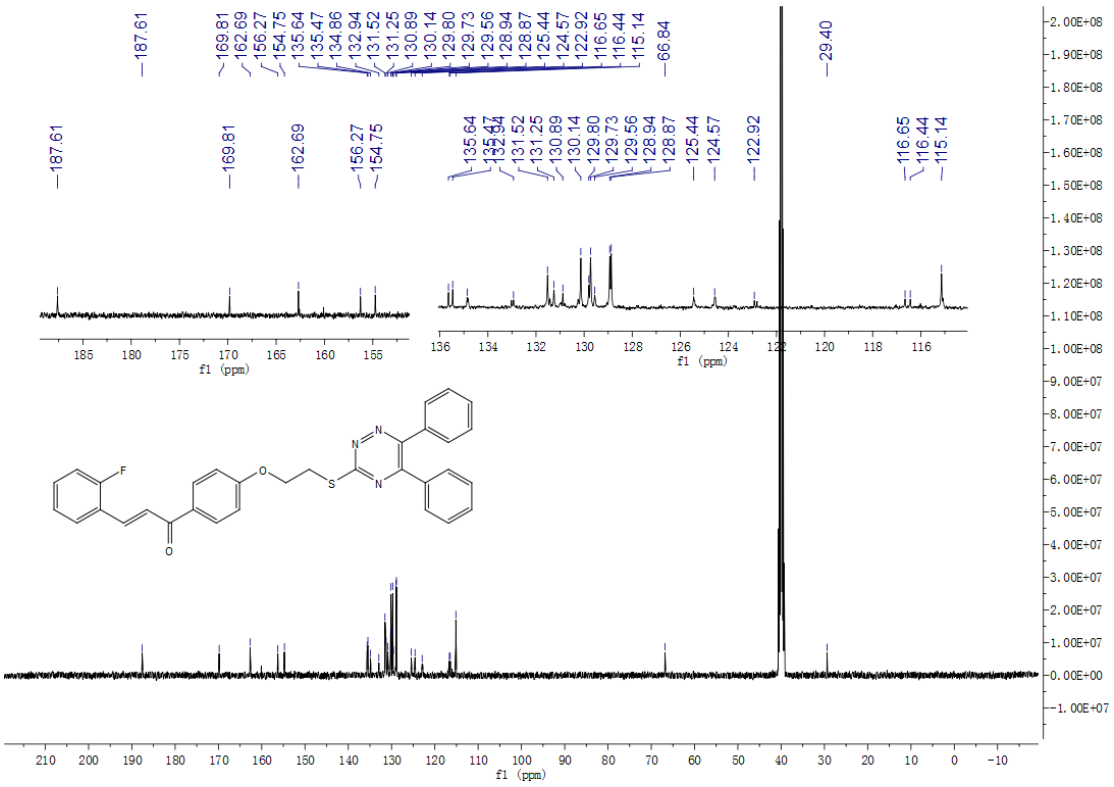

Figure S40. ^{19}F NMR spectrum of compound **4m**

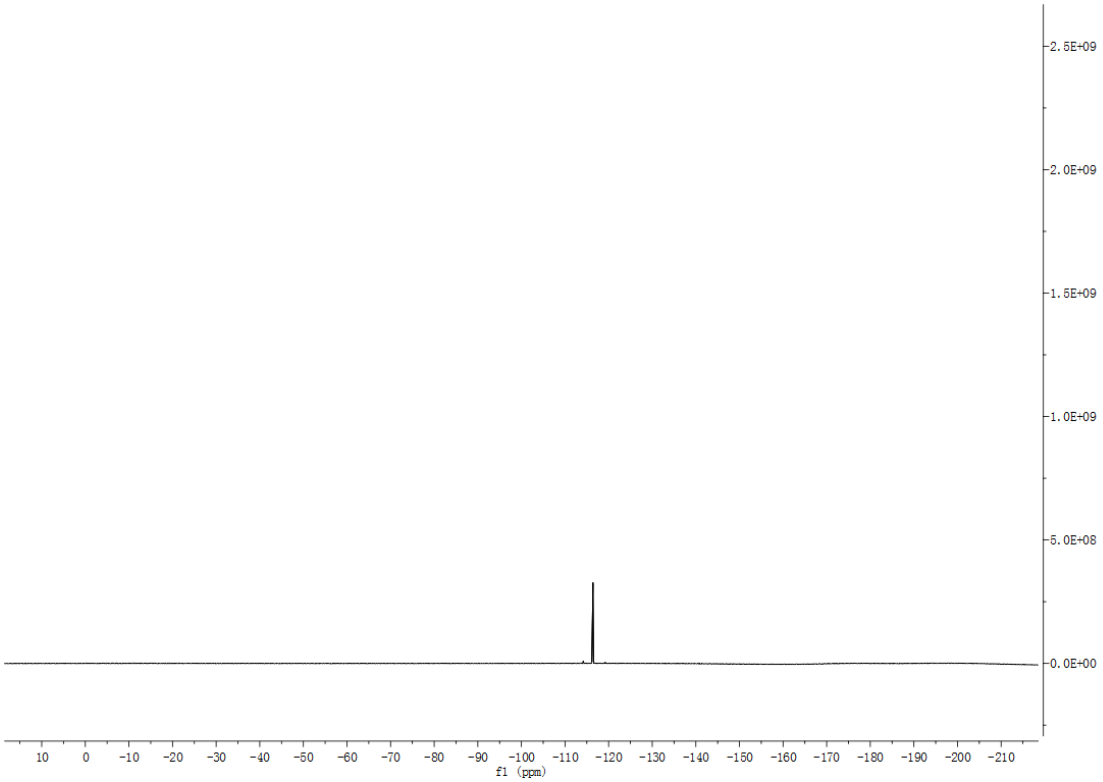

Figure S41. HRMS spectrum of compound **4m**

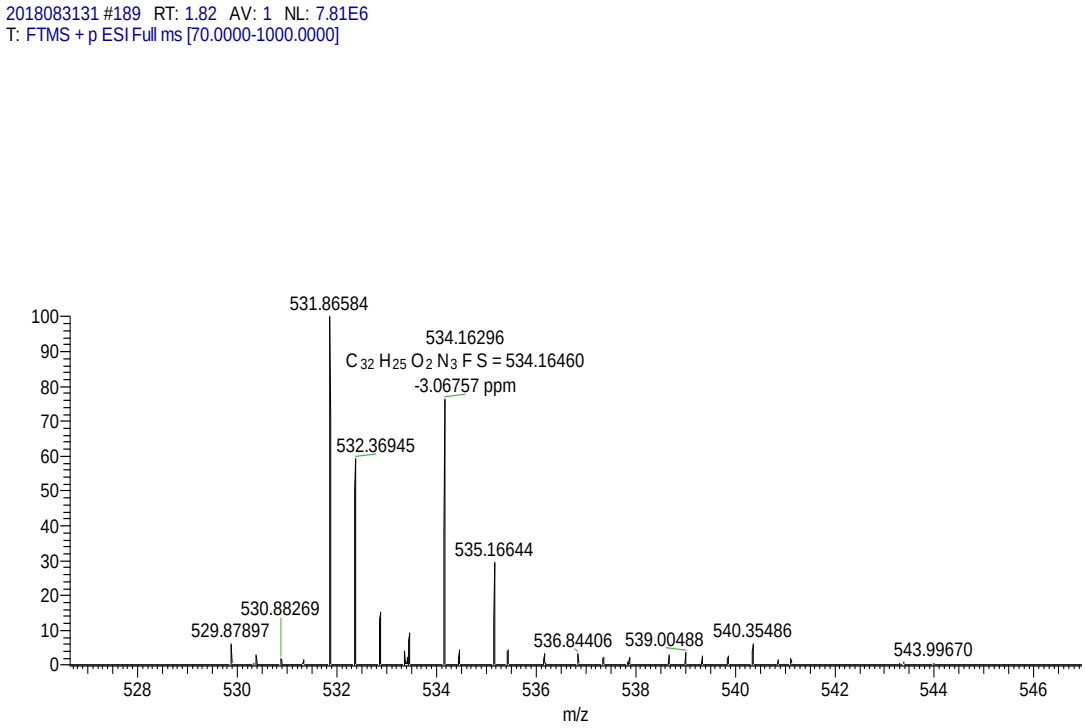

Figure S42. ^{1}H NMR spectrum of compound **4n**

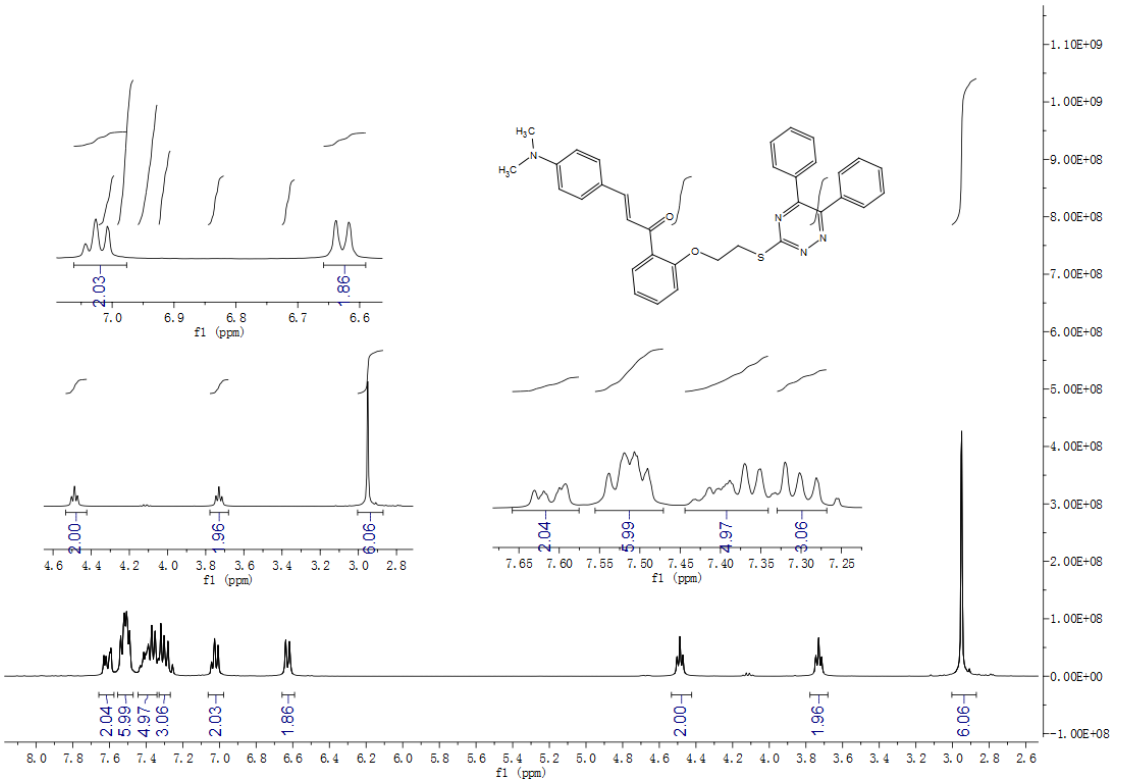

Figure S43. ^{13}C NMR spectrum of compound **4n**

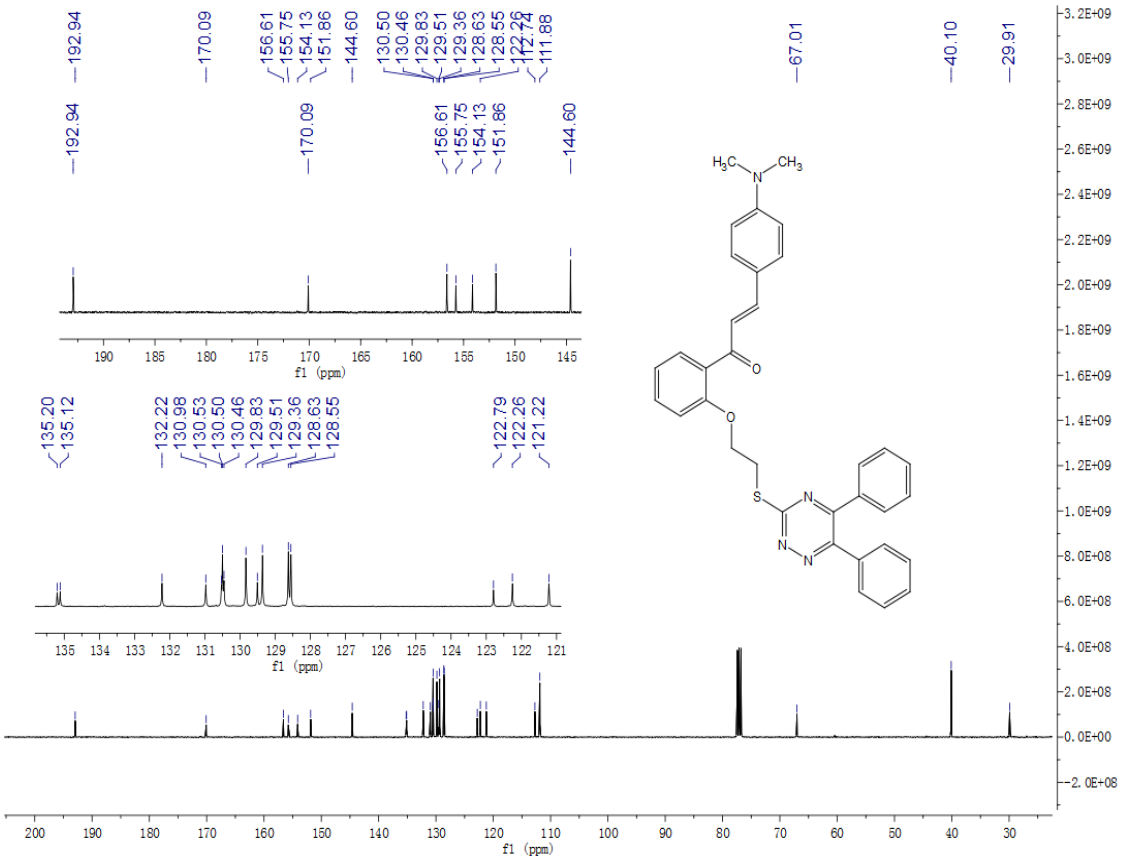

Figure S44. HRMS spectrum of compound **4n**

2018080718 #169 RT: 1.66 AV: 1 NL: 1.50E7
T: FTMS + p ESI Full ms [100.0000-1000.0000]

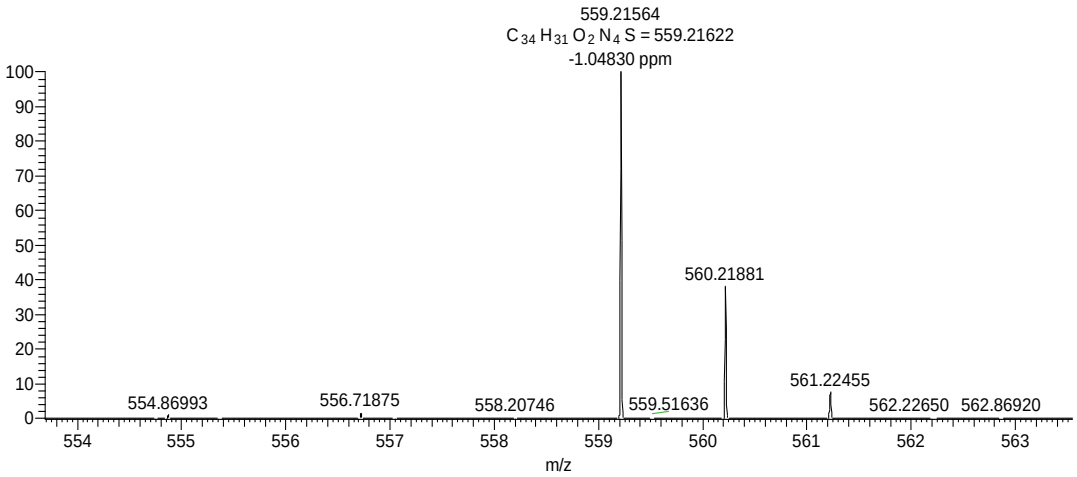

Figure S45. ^{1}H NMR spectrum of compound **4o**

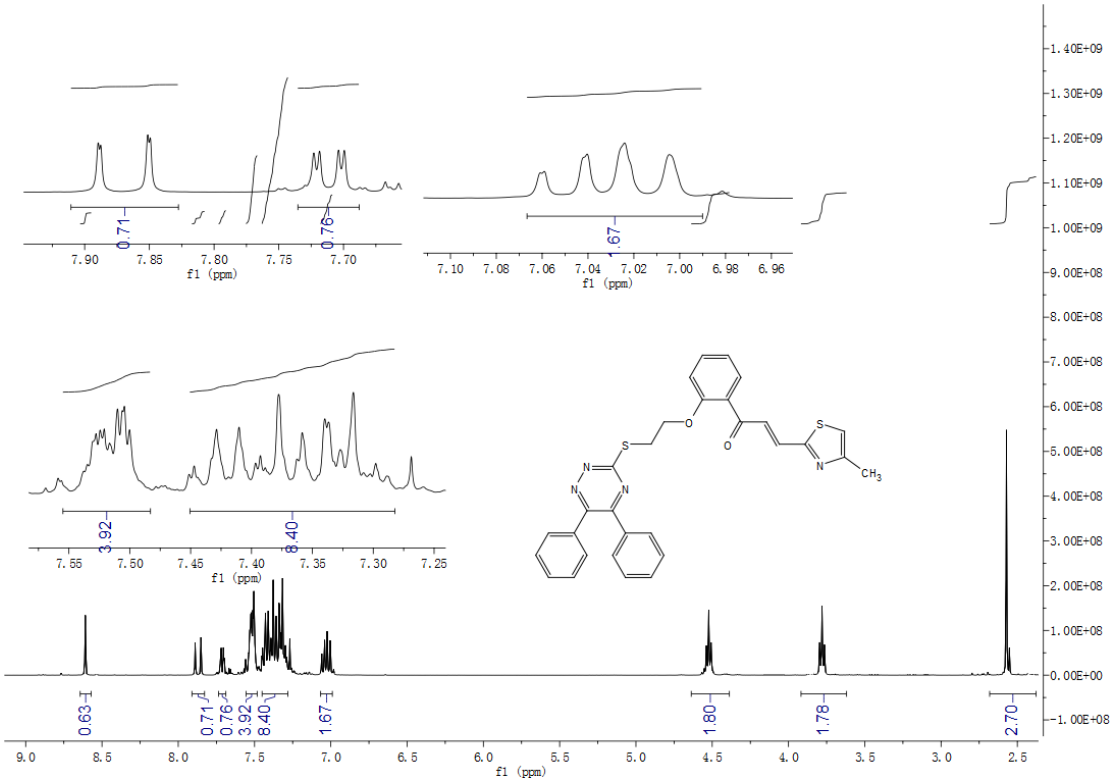

Figure S46. ^{13}C NMR spectrum of compound **4o**

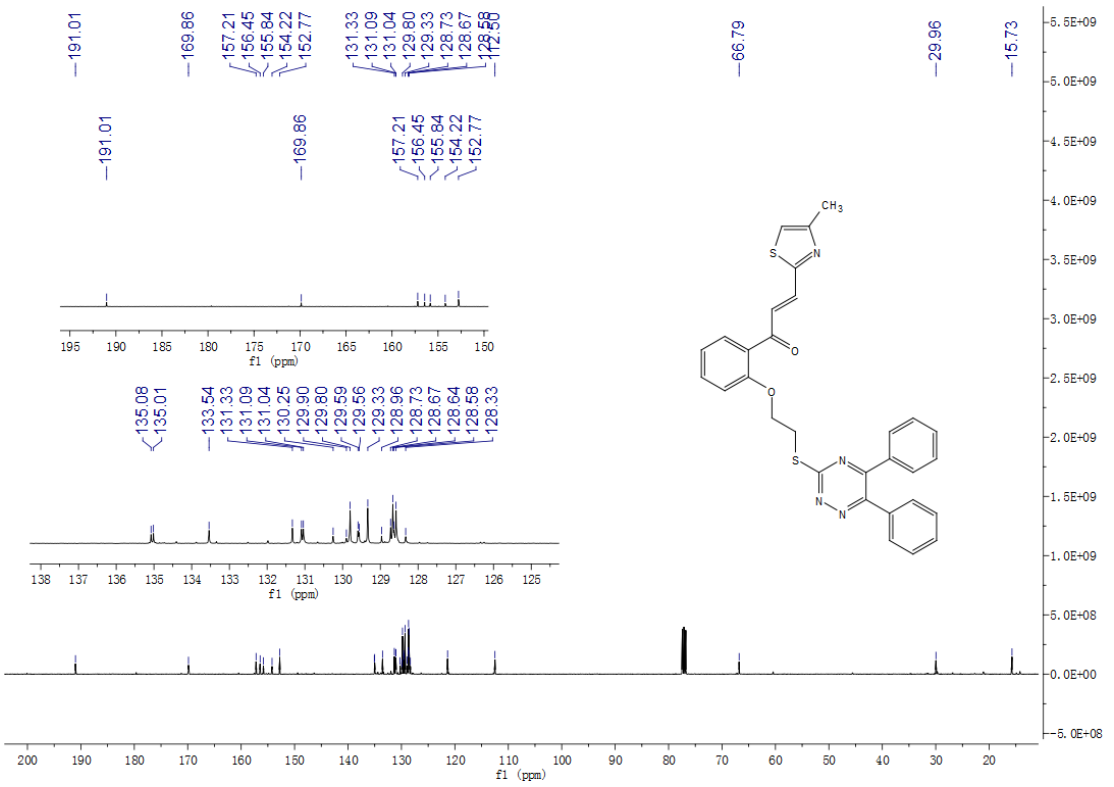

Figure S47. HRMS spectrum of compound **4o**

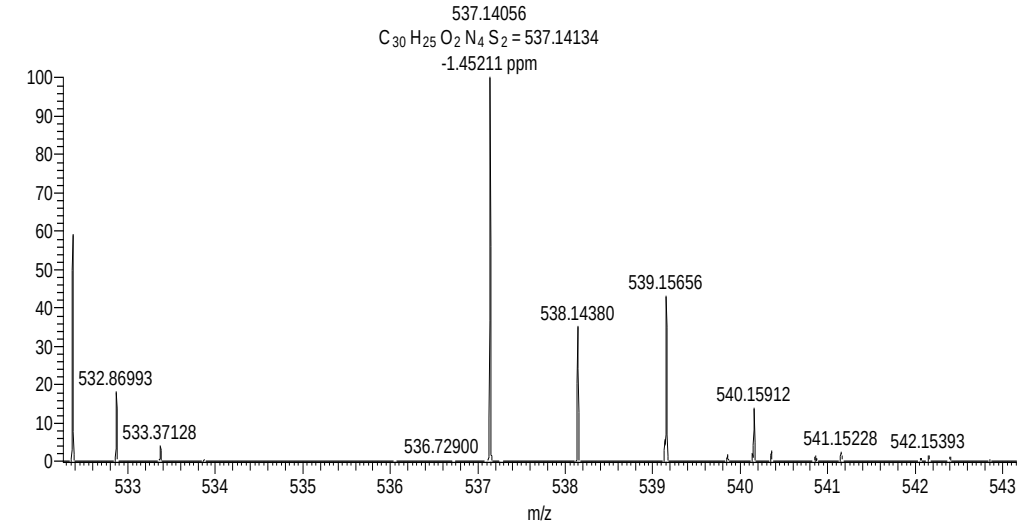

Figure S48. ^{1}H NMR spectrum of compound **4p**

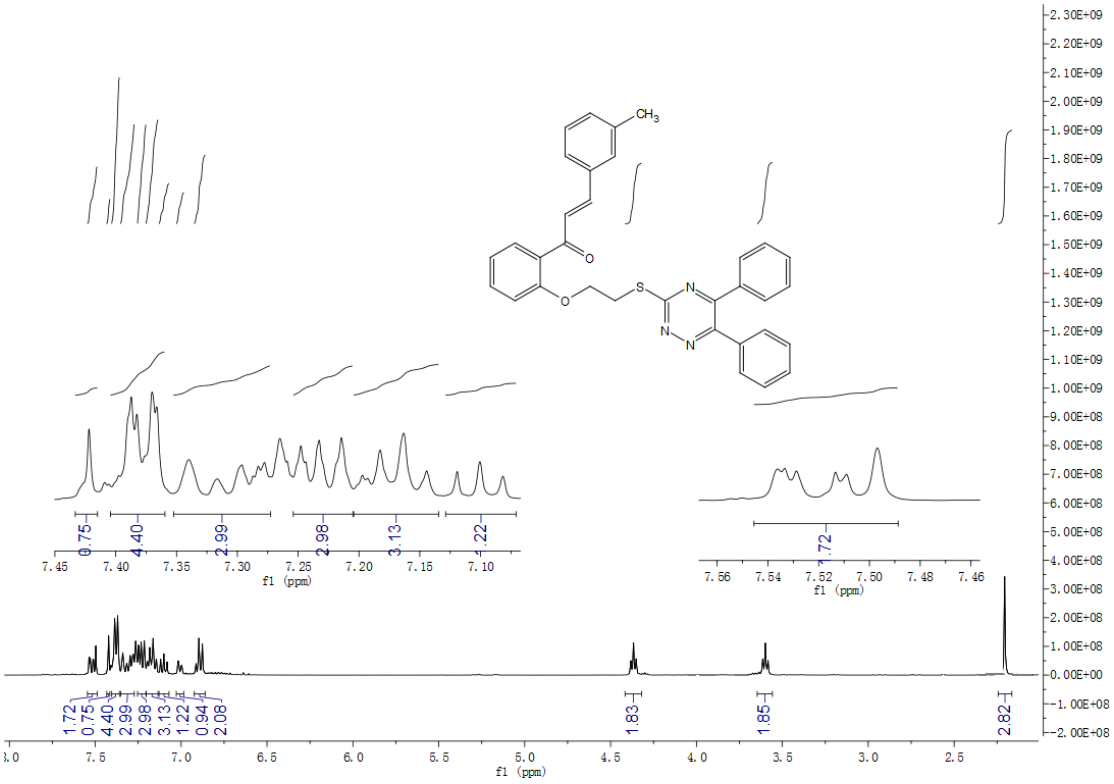

Figure S49. ^{13}C NMR spectrum of compound **4p**

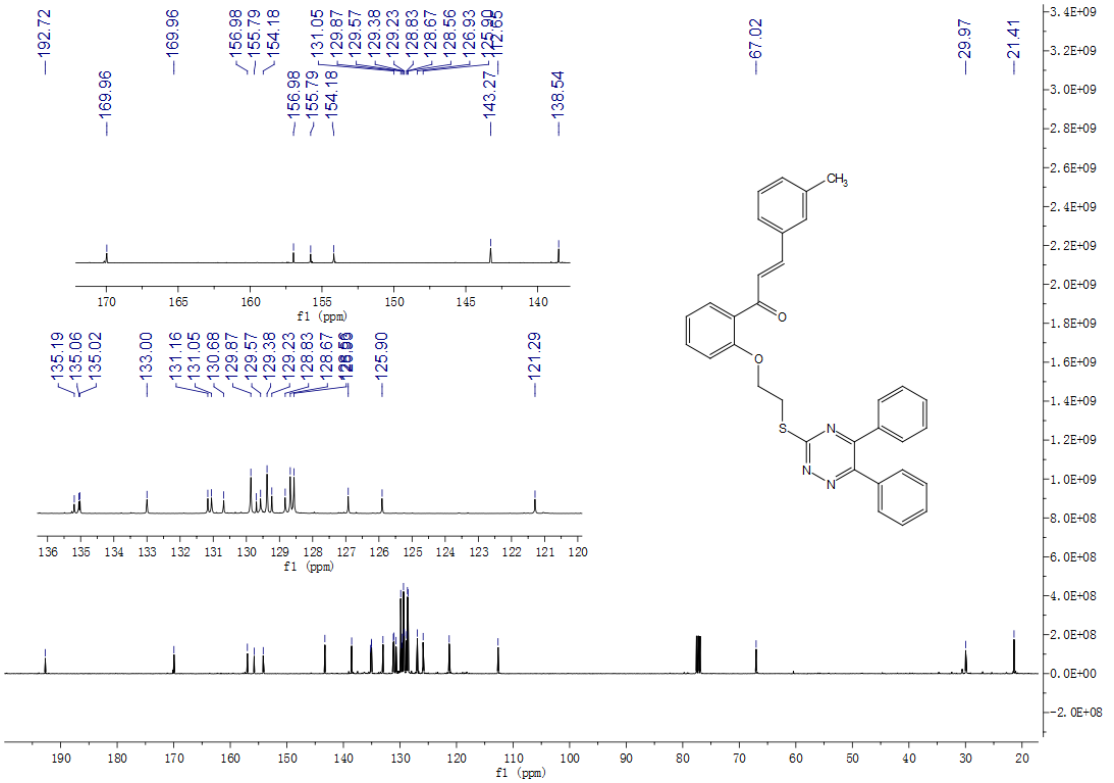

Figure S50. HRMS spectrum of compound **4p**

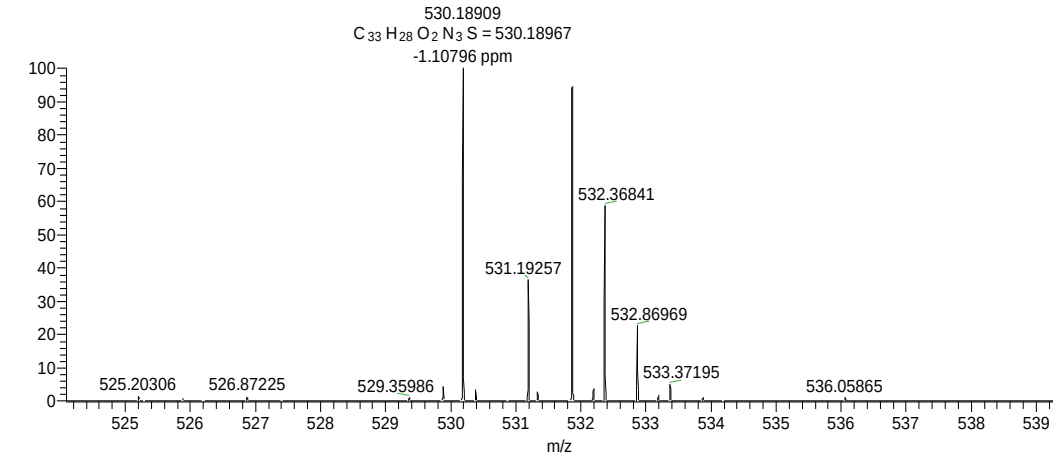

Figure S51. ^{1}H NMR spectrum of compound **4q**

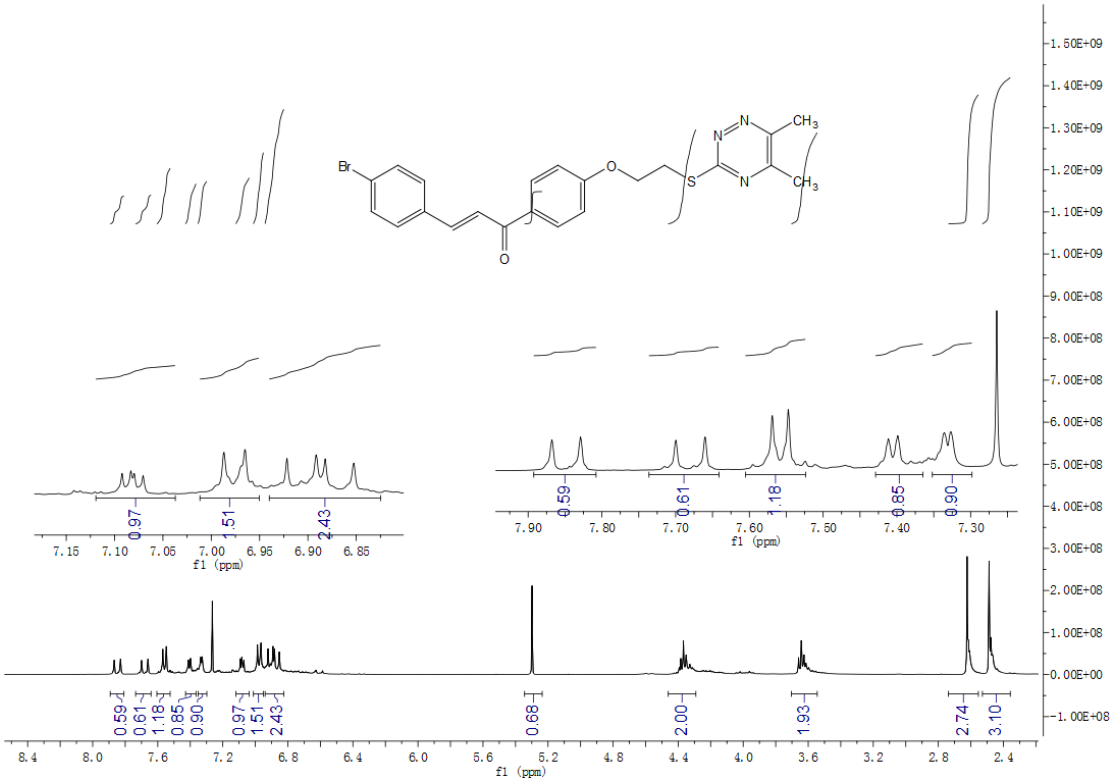

Figure S52. ^{13}C NMR spectrum of compound **4q**

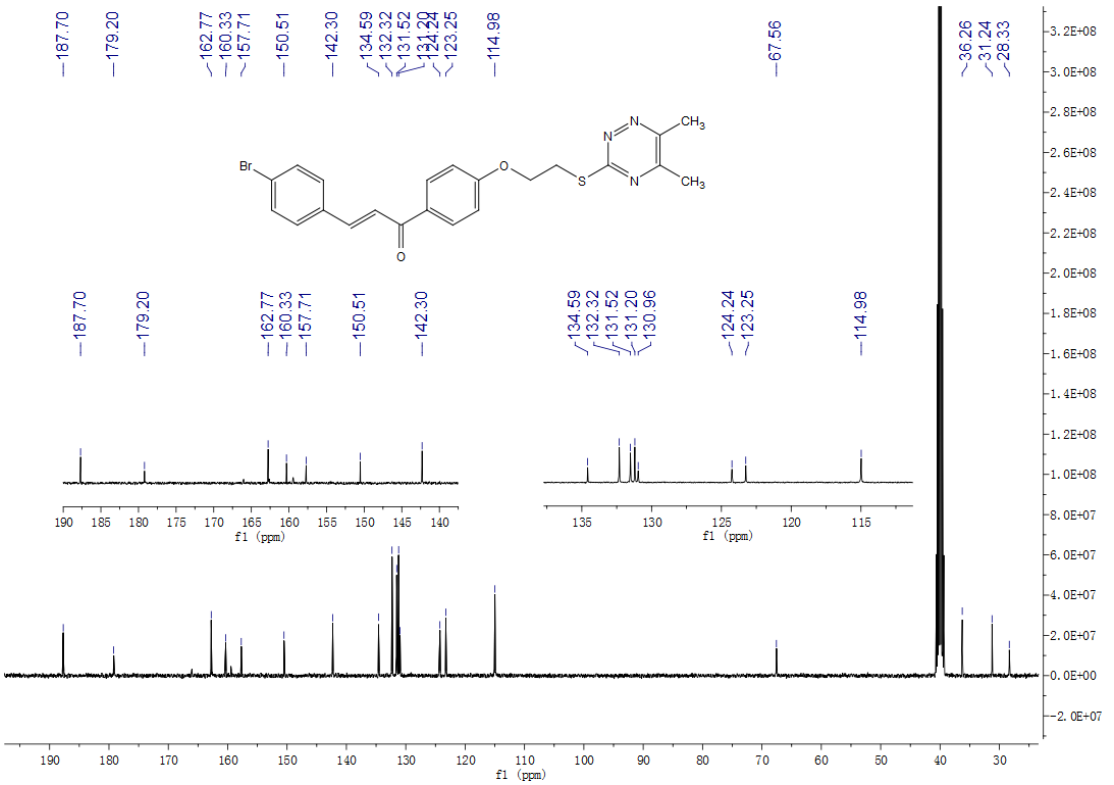

Figure S53. HRMS spectrum of compound **4q**

2018091832 #206 RT: 2.02 AV: 1 NL: 9.24E3
T: FTMS - p ESI Full ms [70.0000-1000.0000]

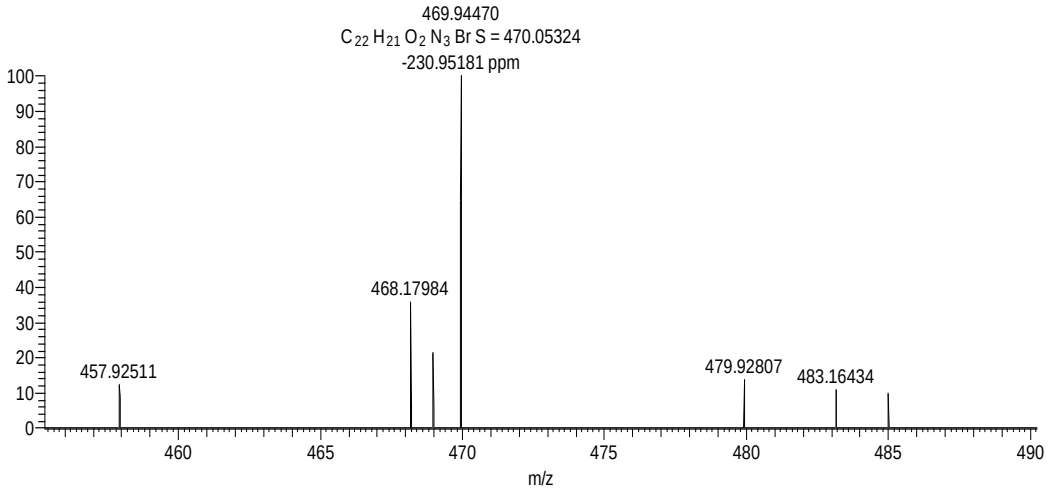

Figure S54. ^{1}H NMR spectrum of compound **4r**

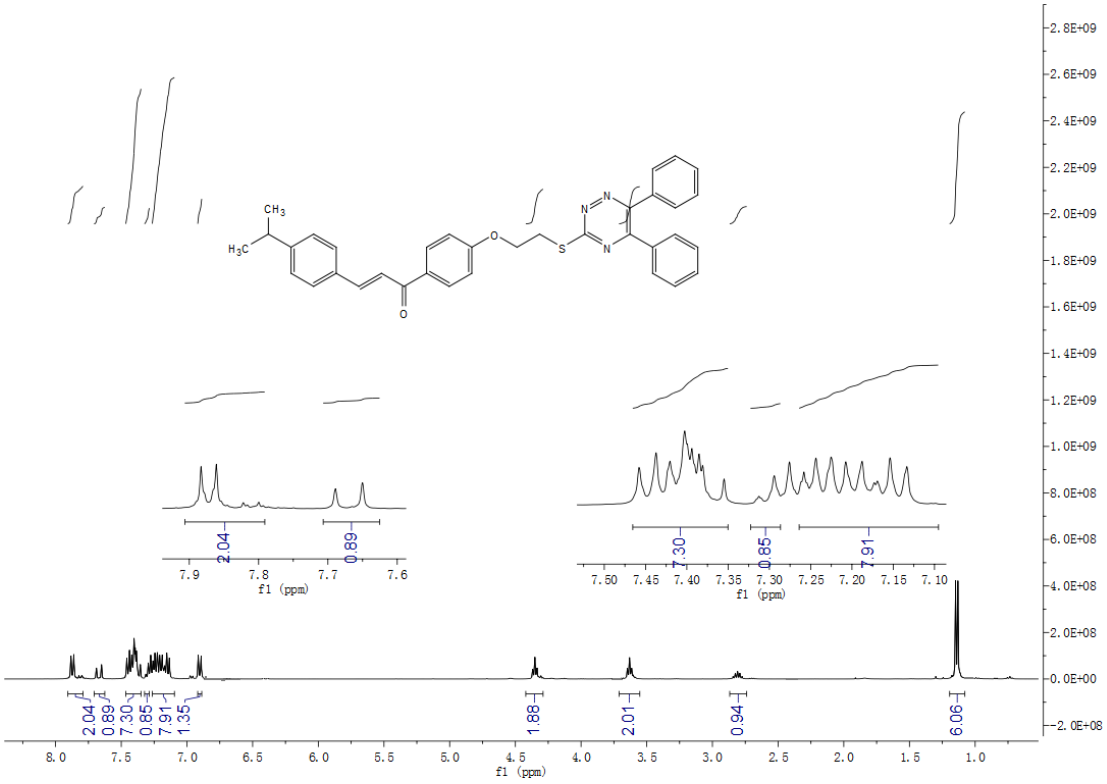

Figure S55. ^{13}C NMR spectrum of compound **4r**

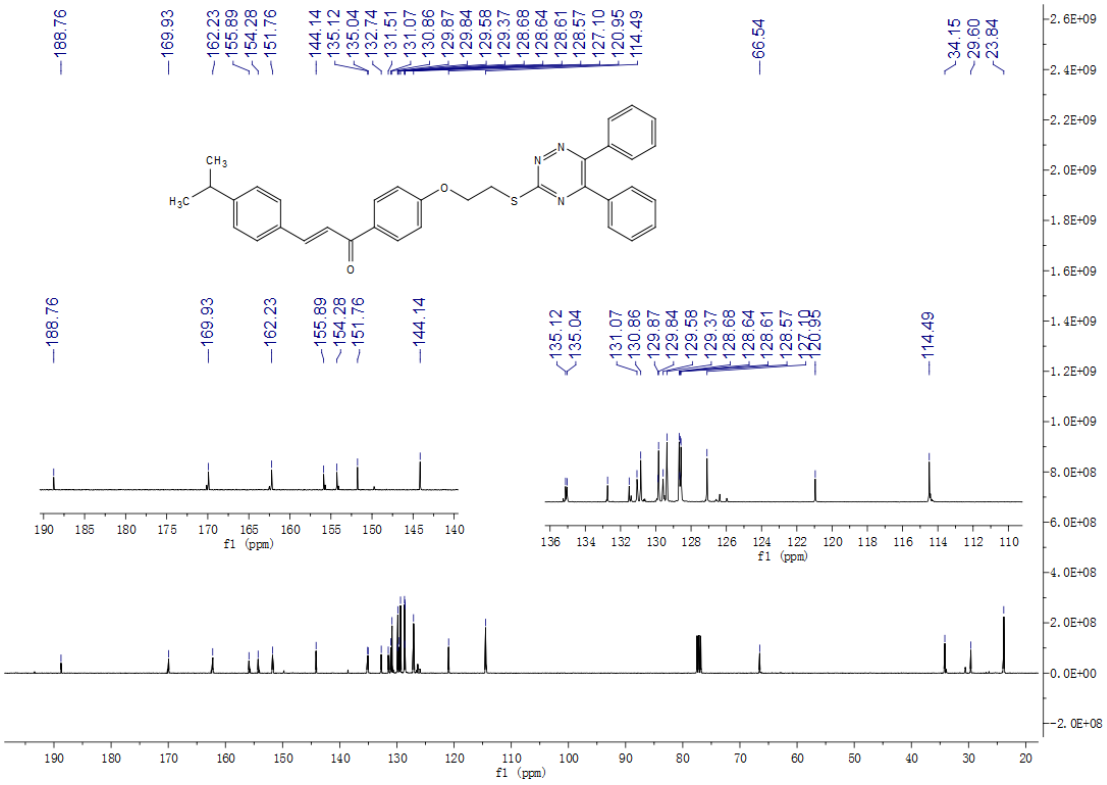

Figure S56. HRMS spectrum of compound **4r**

2018091833 #201 RT: 1.97 AV: 1 NL: 1.19E6
T: FTMS + p ESI Full ms [70.0000-1000.0000]

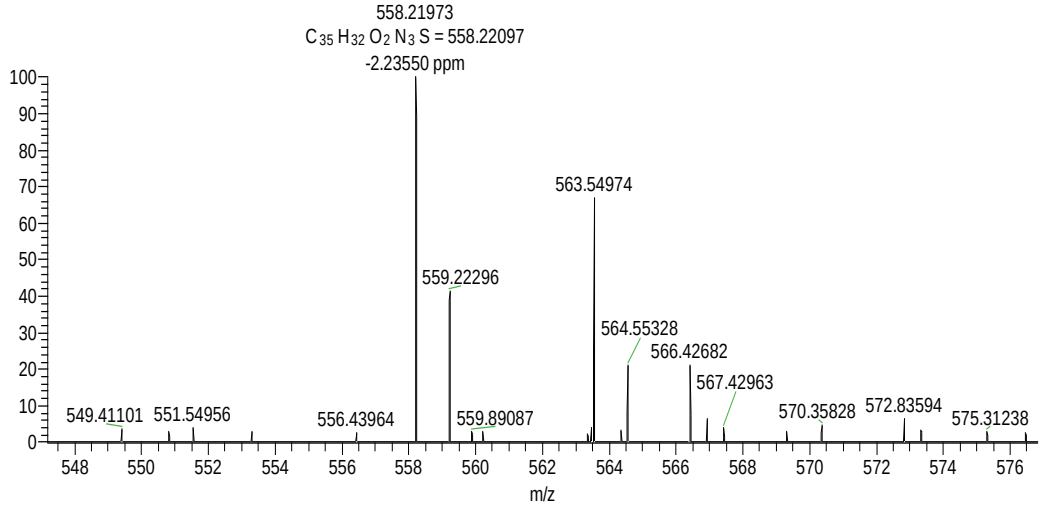

Figure S57. ^{1}H NMR spectrum of compound **4s**

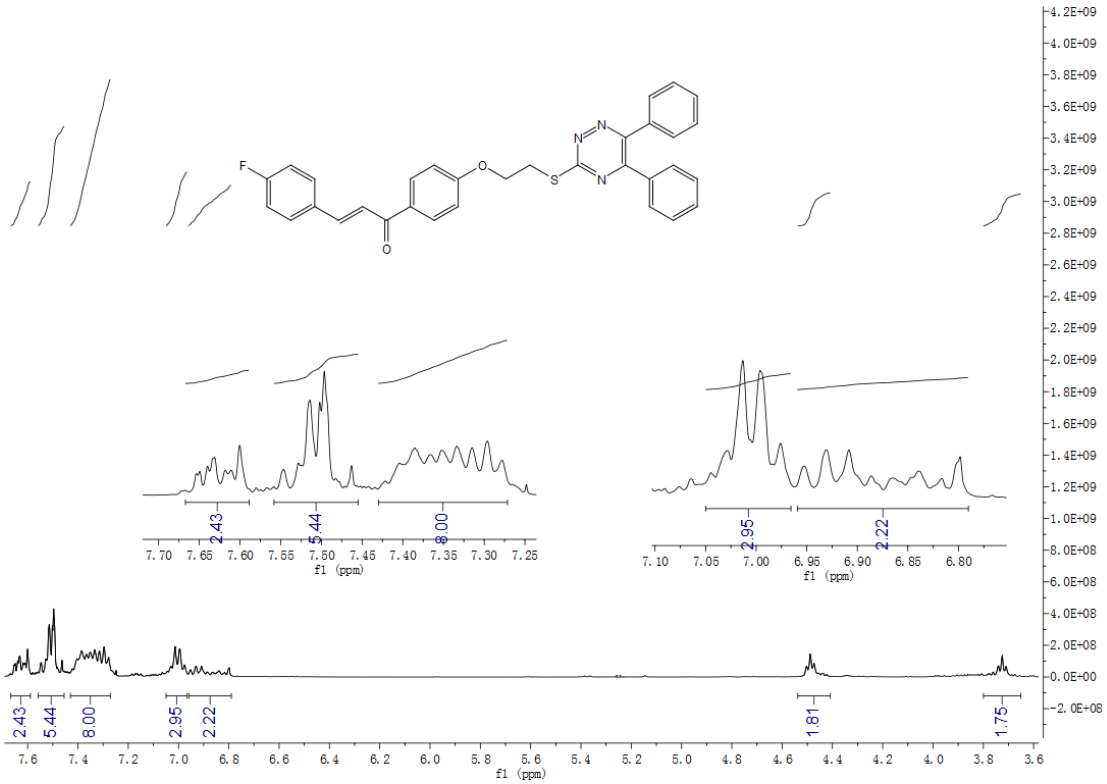

Figure S58. ^{13}C NMR spectrum of compound **4s**

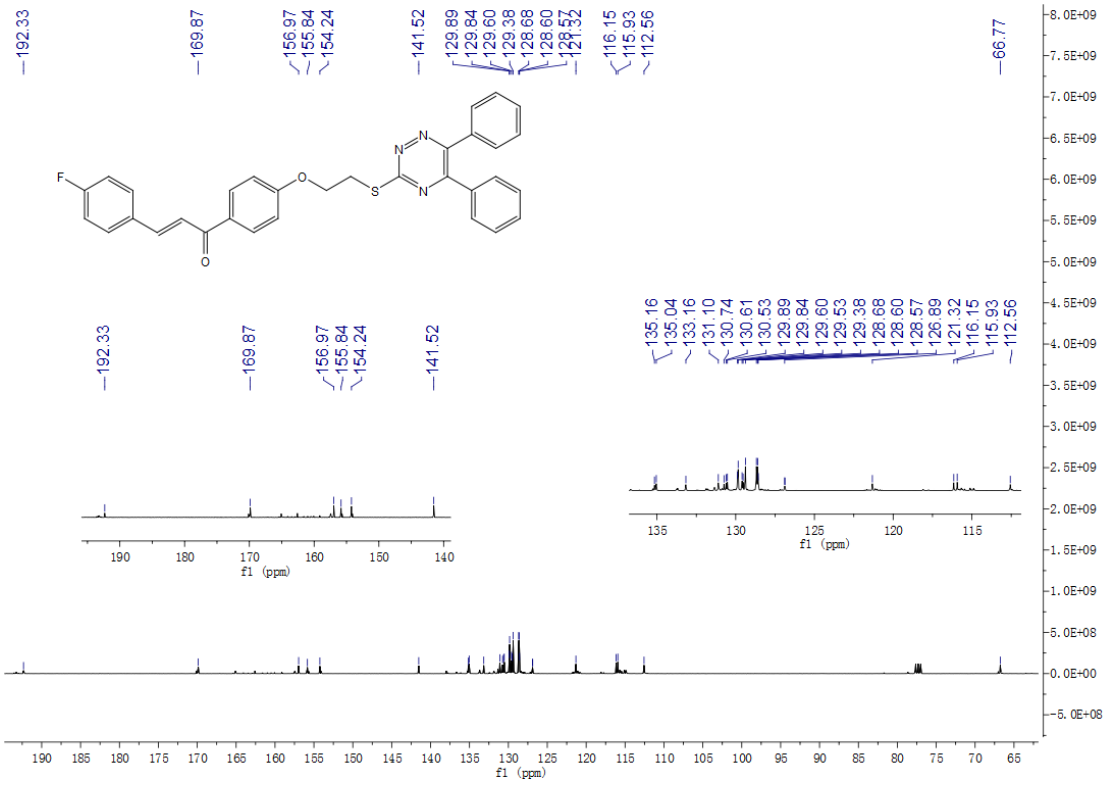

Figure S59. ^{19}F NMR spectrum of compound **4s**

Figure S60. HRMS spectrum of compound **4s**

2018083131 #189 RT: 1.82 AV: 1 NL: 7.81E6
T: FTMS + p ESI Full ms [70.0000-1000.0000]

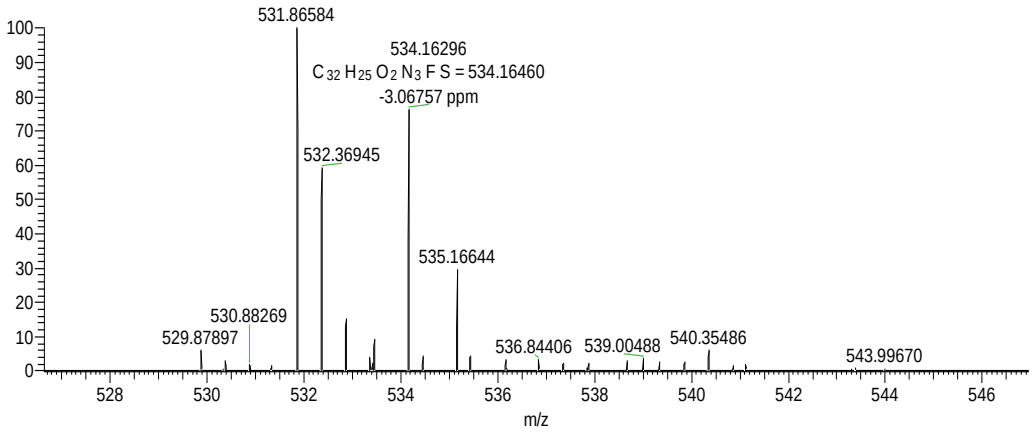

Figure S61. ^{1}H NMR spectrum of compound **4t**

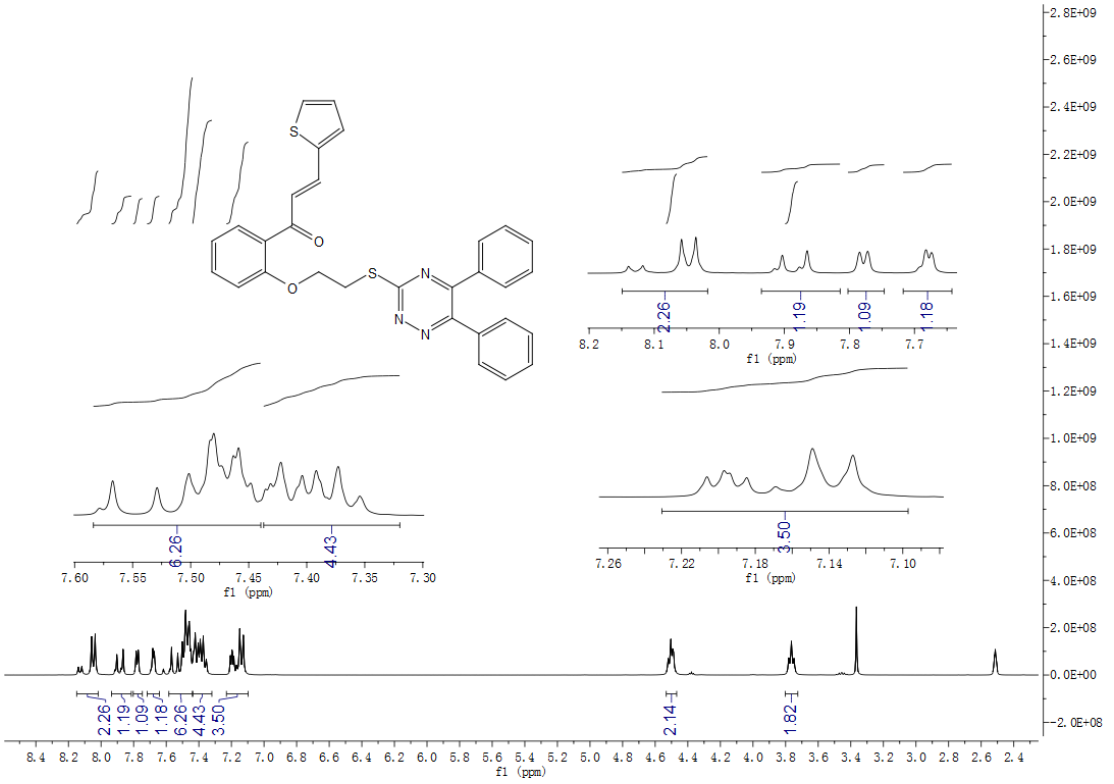

Figure S62. ^{13}C NMR spectrum of compound **4t**

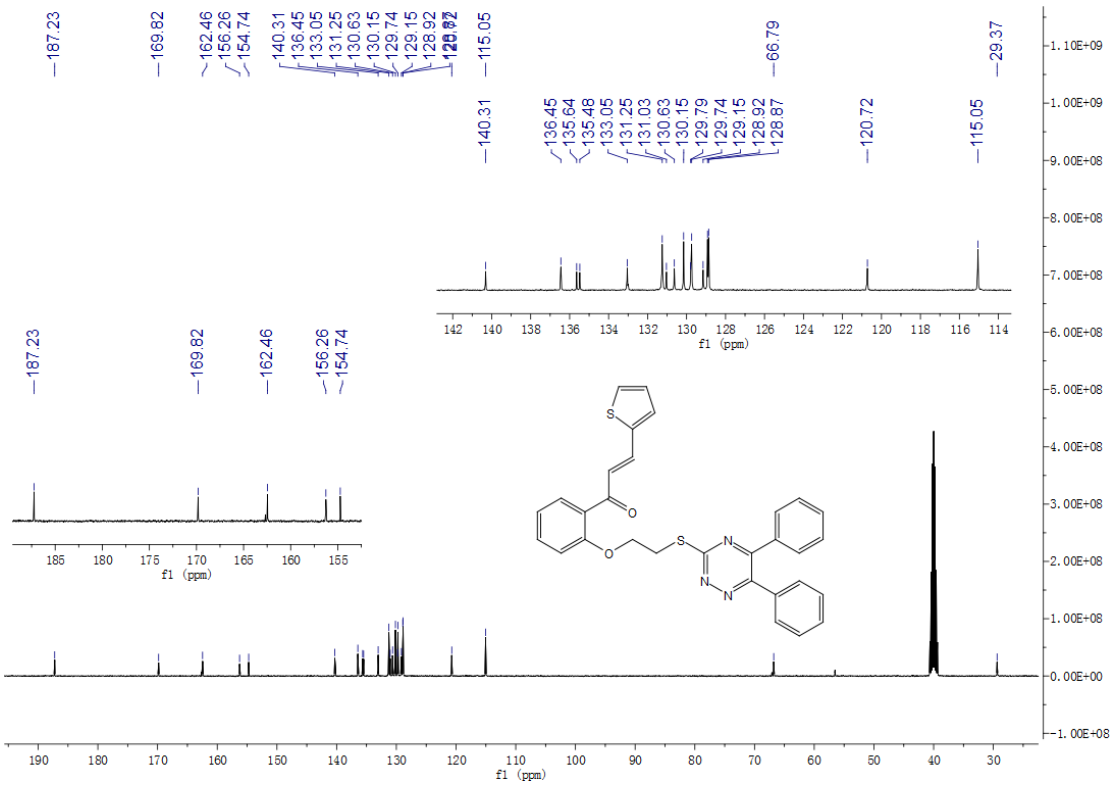

Figure S63. HRMS spectrum of compound **4t**

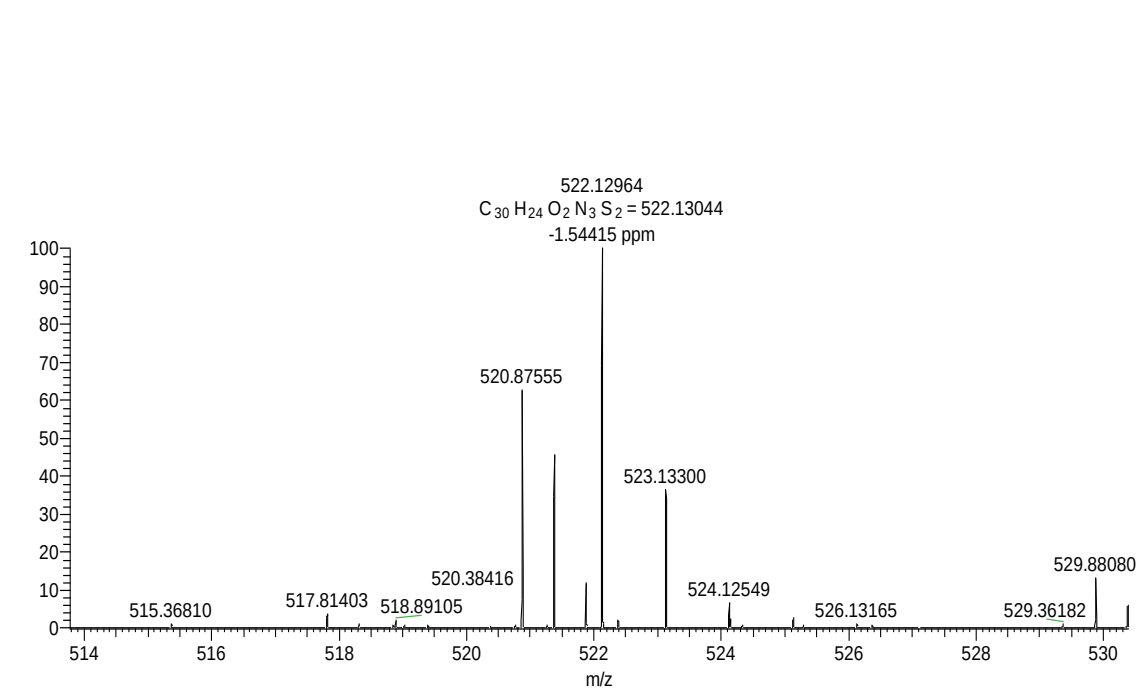

Figure S64. ^{1}H NMR spectrum of compound **4u**

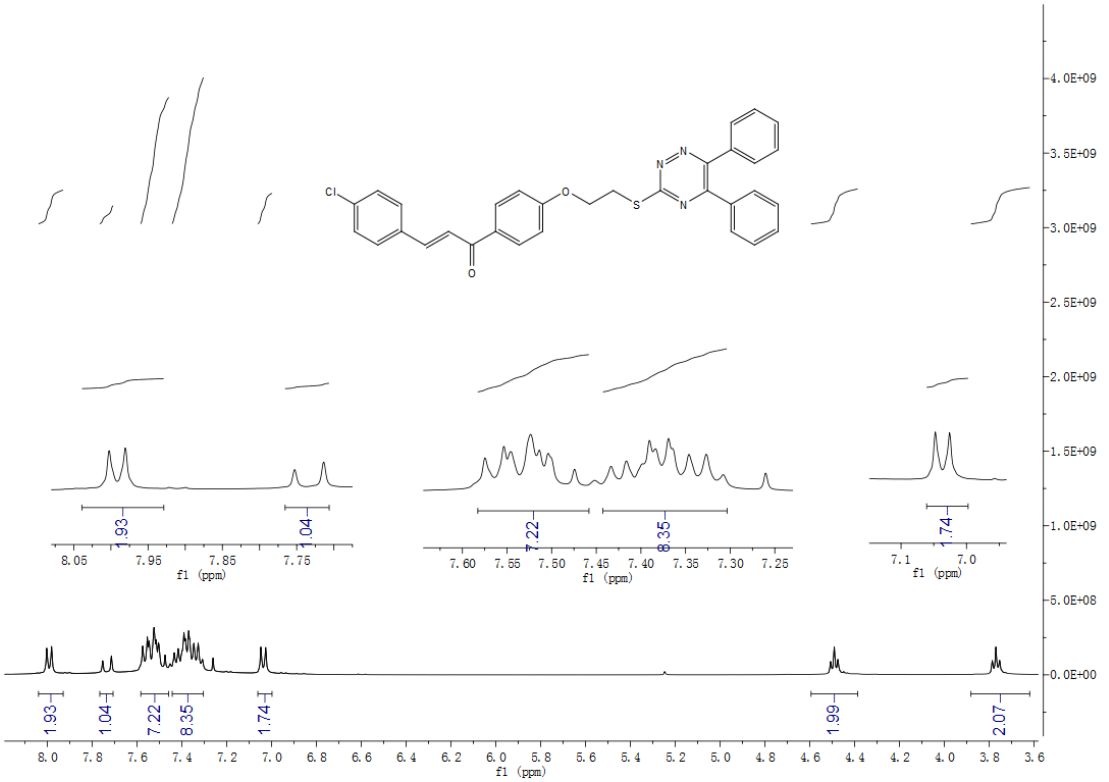

Figure S65. ^{13}C NMR spectrum of compound **4u**

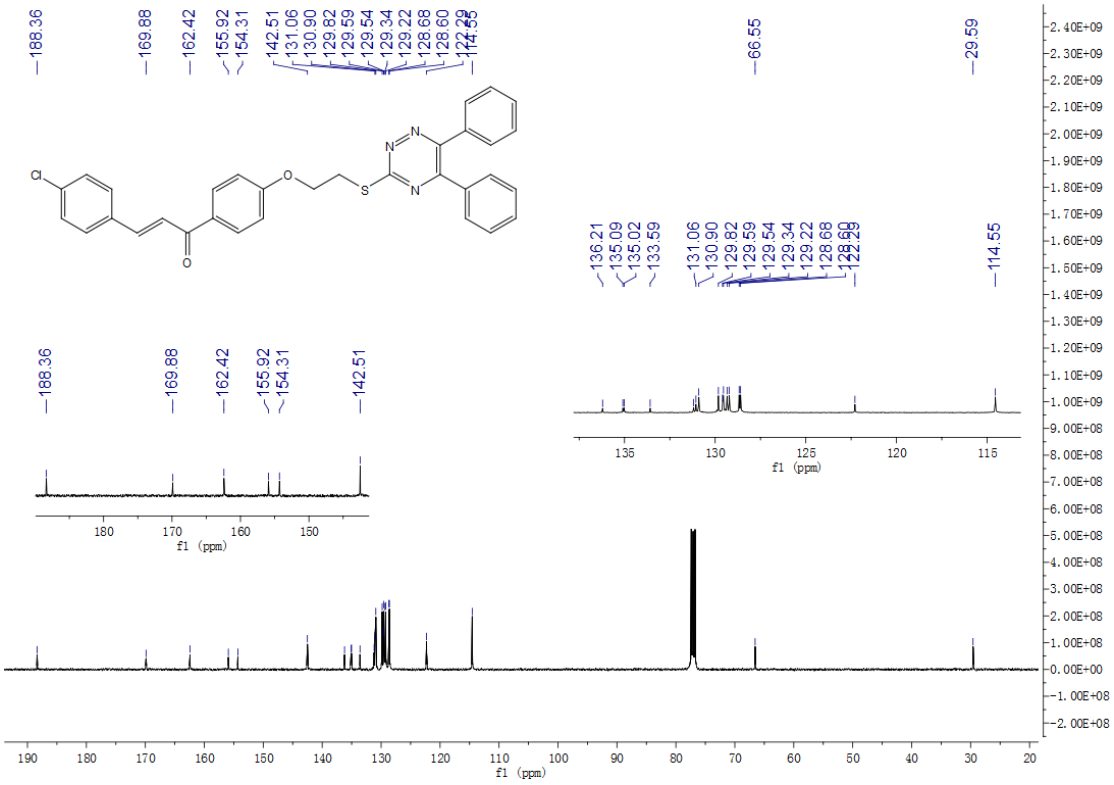

Figure S66. HRMS spectrum of compound **4u**

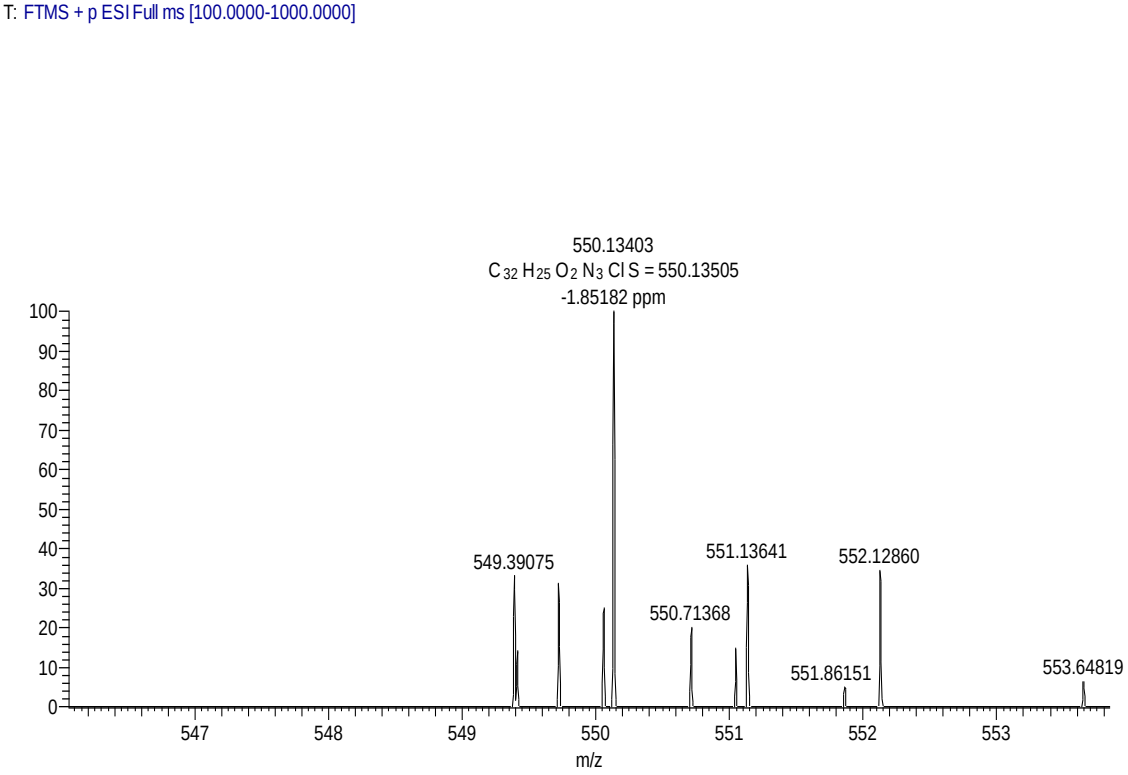

Figure S67. ^{1}H NMR spectrum of compound **4v**

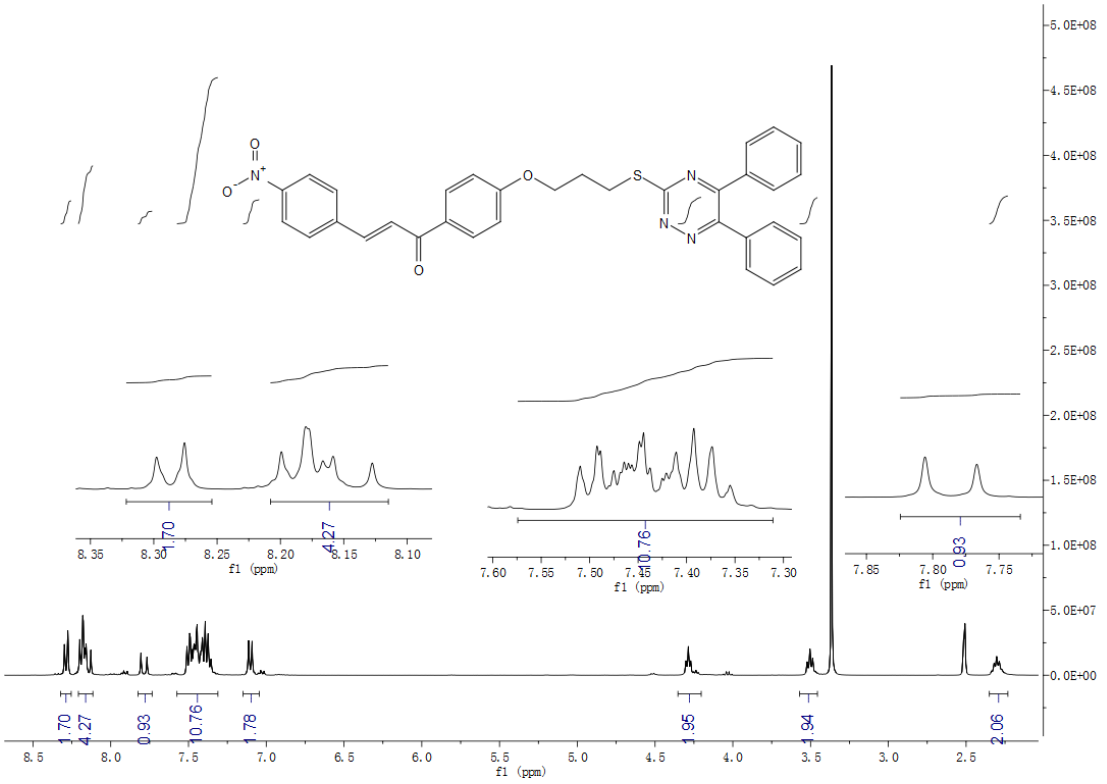

Figure S68. ^{13}C NMR spectrum of compound **4v**

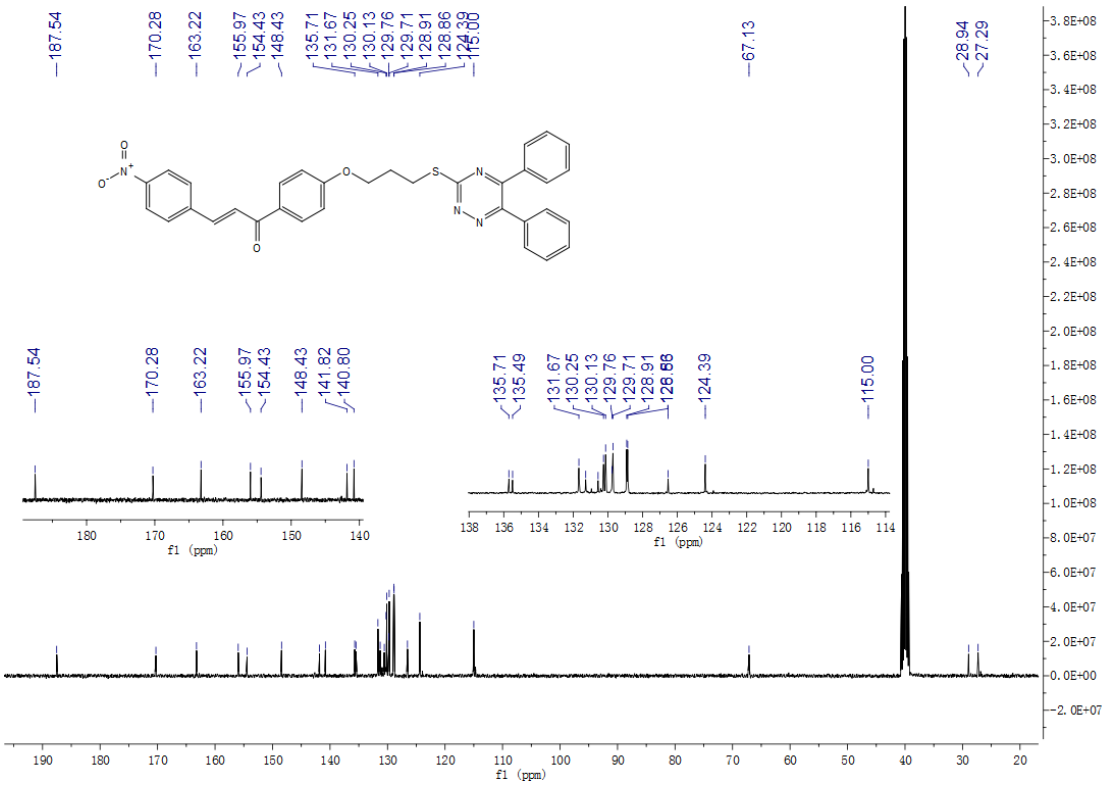

Figure S69. HRMS spectrum of compound **4v**

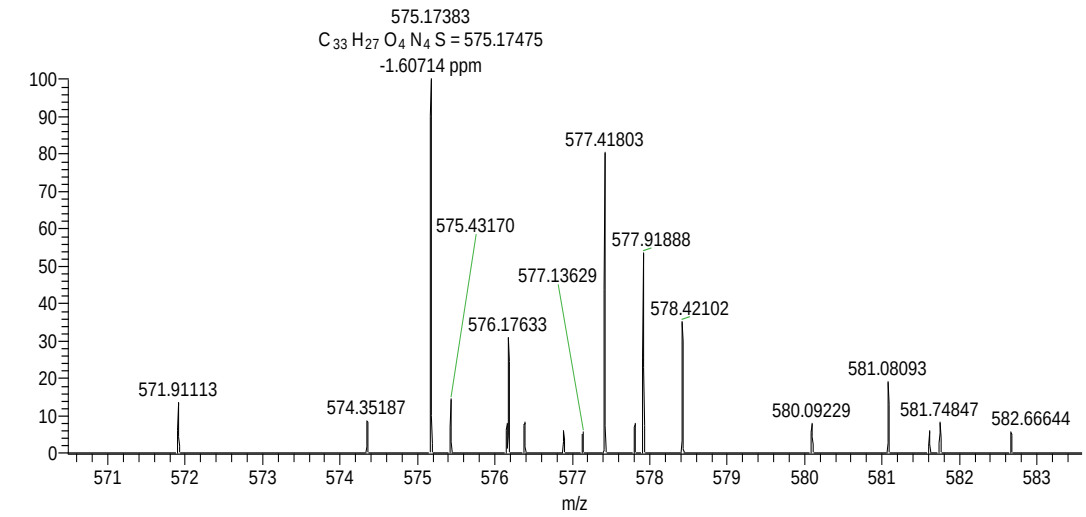

Figure S70. ^{1}H NMR spectrum of compound **4w**

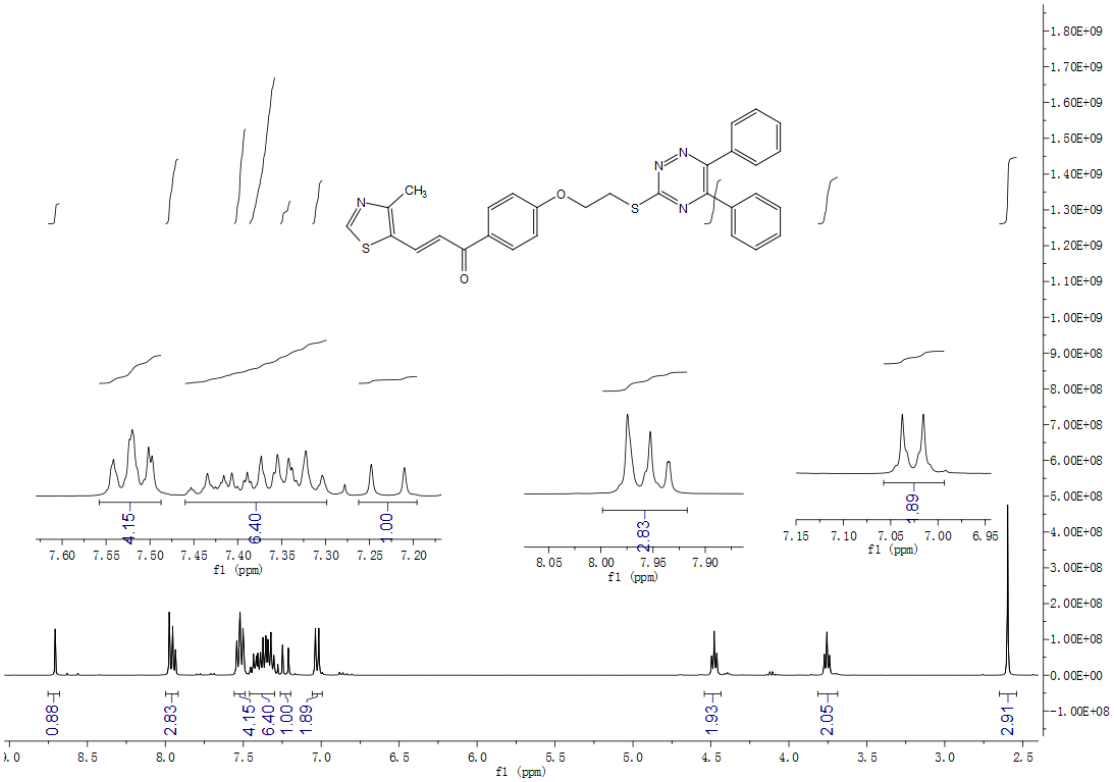

Figure S71. ^{13}C NMR spectrum of compound **4w**

Figure S72. HRMS spectrum of compound **4w**