Supporting Information

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

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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 Technologies 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:

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

$C_{num}$: 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:

\[
(\%) = \frac{(C_{\text{num}} - T_{\text{num}})}{C_{\text{num}}} \times 100%
\]

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

\(T_{\text{num}}\): average local lesion number smeared with compounds

### 2.2. Antibacterial activity in vitro

Antibacterial activities of the title compounds 4a–4w against *Xanthomonas axonopodis pv. citri* (Xac), *Xanthomonas oryzae pv. 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°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 a microplate 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 \(I = (C - T)/C \times 100\%\). 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 axonopodis pv. citri (Xac), Xanthomonas oryzae pv. oryzae (Xoo) and Ralstonia solanacearum (Rs) were evaluated by using the turbidimeter test in vitro, commercial agricultural antibacterial Bismethiazol 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 bismethiazol. 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:

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

$C_{tur}$: 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 µg/mL, 50.0 µg/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°C 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.

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

({E}-1-{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°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.28 (d, $J = 8.0$ Hz, 2H, Ar-(4-NO$_2$)-3,5-H), 8.16 (dd, $J = 17.9, 9.8$ Hz, 5H, Ar-(4-Oh)-2,6-2H, Ar-CH=, Ar-(4-NO$_2$)-3,5-2H), 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-$d_6$) $\delta$ 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$_{28}$N$_4$O$_5$S $[M+H]^+$: 589.19040, found 589.18872.

({E}-1-{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-$d_6$) $\delta$ 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)-3,4,5,3,4-3H, Ar-(2-OCH$_2$)-6-H), 7.14 – 6.95 (m, 2H, Ar-(2-OCH$_2$)-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$_2$)-S-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-$d_6$) $\delta$ 192.43 (s, C=O), 169.86 (s), 158.58 (s), 157.00 (s), 156.04 (s), 137.40 (s), 135.67 (s), 135.43 (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$_4$O$_5$S $[M+H]^+$: 546.18459, found 546.18304.

({E}-1-{4-{[(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: 136.5-137.2°C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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), 7.58 – 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$_3$) $\delta$ 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$_4$O$_5$S $[M+H]^+$: 546.18459, found 546.18341.
yellow oil, yield: 53%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 189.37 (s, C=O), 169.96 (s), 162.90 (s), 161.94 (s), 160.33 (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$_{32}$H$_{32}$N$_2$O$_6$S [M+H]$^+$: 576.1915, found 576.19379.

$^{(E)}$-1-(4-((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$^\circ$C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 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$_6$) $\delta$ 187.81 (s, C=O), 169.81 (s), 162.54 (s), 156.75 (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$_{32}$N$_2$O$_6$S [M+H]$^+$: 516.17402, found 516.17401.

$^{(E)}$-1-(4-((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$^\circ$C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 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$_6$) $\delta$ 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$_{32}$H$_{32}$N$_2$O$_6$S [M+H]$^+$: 506.15329, found 506.15274.

$^{(E)}$-3-(2,4-dimethoxyphenyl)-1-(4-((5,6-dimethyl-1,2,4-triazin-3-yl)thio)ethoxy)phenylprop-2-en-1-one (4g): yellow oil, yield: 66%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 189.24 (s, C=O), 169.71 (s), 162.95 (s), 162.42 (S-8).
7.93 (d, J = 8.5 Hz, 1H, Ar-(4-CH=)), 7.28 (m, 7H, 7Ar-H), 7.13 – 7.00 (m, 1H, Ar-CH=), 6.99 – 6.80 (m, 2H, Ar-(4-CH=)), 7.35 (m, 6H, 6Ar-H), 7.22 (d, J = 8.3 Hz, 1H, Ar-(3,4-2-OCH3)-2-H), 7.16 (s, 1H, Ar-(3,4-2-OCH3)-3-H), 7.03 (d, J = 8.6 Hz, 2H, Ar-(4-CH=)), 6.88 (t, J = 8.1 Hz, 1H, Ar-(3,4-2-OCH3)-6-H), 4.48 (t, J = 6.5 Hz, 2H, -OCH2-), 3.93 (d, J = 10.2 Hz, 2H, -OCH2-), 3.76 (t, J = 6.5 Hz, 2H, -SCH2-); 13C NMR (101 MHz, CDCl3) 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, -OCH2-), 56.01 (s, -OCH3), 29.61 (s, -SCH2-); HRMS calcd for C13H12ClN2O5S [M+H]+: 576.19519, found 576.19373.

(E)-1-[4-(2-(5,6-diphenyl-1,2,4-triazin-3-yl)thio)ethoxypyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (4j): yellow solid, yield: 59%; m.p: 85.3–86.1°C; 1H NMR (400 MHz, CDCl3) δ 7.98 (t, J = 5.9 Hz, 2H, Ar-(4-CH=)), 7.76 (dd, J = 15.5, 3.0 Hz, 1H, Ar-CH=), 7.59 – 7.46 (m, 6H, 3Ar-H, Ar-(4-OCH3)-2-6-2H, Ar-CO=CH), 7.35 (dddd, J = 23.7, 15.5, 5.9, 17 Hz, 7H, 7Ar-H), 7.03 – 6.98 (m, 2H, Ar-(4-CH=)), 6.92 – 6.87 (m, 2H, Ar-(4-OCH3)-3-5-2H), 4.49 – 4.42 (m, 2H, -OCH2-), 3.80 (d, J = 2.0 Hz, 3H, -OCH3), 3.73 (dd, J = 11.5, 4.7 Hz, 2H, -SCH2-); 13C NMR (101 MHz, CDCl3) 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, -OCH3), 55.42 (s, -OCH3), 29.60 (s, -SCH2-); HRMS calcd for C31H28N2O5S [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$_3$) $\delta$ 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-CH=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$_3$) $\delta$ 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, 1H, Ar-CH=), 124.11 (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$_2$O$_5$S [M+H]$^+$: 561.15910, found 561.15698.

(E)-1-(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$^\circ$C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 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-C=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$_3$) $\delta$ 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$_3$) $\delta$ -113.70 – -114.21 (m), -116.59 (s), -119.69 (s); HRMS calcd for C$_{32}$H$_{25}$FN$_2$O$_5$S [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$^\circ$C; $^1$H NMR (400 MHz, DMSO-d$_6$) $\delta$ 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-C=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-OMe)-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$_6$) $\delta$ 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$_6$) $\delta$ -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$_2$O$_5$S [M+H]$^+$: 534.16460, found 534.16296.

(E)-3-(4-(dimethylamino)phenyl)-1-(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$_3$) $\delta$ 7.61 (dd, $J$ = 11.6, 3.8 Hz, 2H, Ar-(2-OH)-6-H, Ar-CH=), S-10.
(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°C; 1H NMR (400 MHz, CDCl₃) 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)-4,5,2-H, 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), 6.44 – 4.39 (m, 2H, -OCH₂-), 3.82 (dt, J = 30.4, 6.3 Hz, 2H, -SCH₂-), 2.68 – 2.38 (m, 3H, -CH₃); 13C NMR (101 MHz, CDCl₃) 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, -OCH₂-), 29.96 (s, -SCH₂-), 15.73 (s, -CH₃); HRMS calcd for C₃₉H₆₅N₇O₄S [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-toly)prop-2-en-1-one (4p): yellow oil, yield: 56%; 1H NMR (400 MHz, CDCl₃) 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-CH₃)-6-H, 2Ar-H), 7.20 – 7.13 (m, 3H, 3Ar-H), 7.13 – 7.07 (m, 1H, Ar-(3-CH₃)-5-H), 7.01 (d, J = 7.6 Hz, 1H, Ar-(3-CH₃)-2-H), 6.90 (dd, J = 11.0, 4.3 Hz, 2H, Ar-(3-CH₃)-4-H, Ar-(2-OH)-3-H), 4.42 – 4.32 (m, 2H, -OCH₂-), 3.65 – 3.56 (m, 2H, -SCH₂-), 2.21 (d, J = 5.8 Hz, 3H, -CH₃); 13C NMR (101 MHz, CDCl₃) 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, -OCH₂-), 29.97 (s, -SCH₂-), 21.41 (s, -CH₃); HRMS calcd for C₃₉H₃₉N₇O₄S [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; 1H NMR (400 MHz, CDCl₃) 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, S-11
2H, -OCH₂-), 3.61 (ddd, J = 24.4, 12.2, 5.4 Hz, 2H, -SCH₂-), 2.74 – 2.55 (m, 3H, -CH₃), 2.53 – 2.36 (m, 3H, -CH₂); ¹³C NMR (101 MHz, DMSO-d₆) 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, -OCH₂-), 36.26 (s, -SCH₂-), 31.24 (s, -CH₃), 28.33 (s, -CH₃); HRMS calcd for C₂₃H₂₂BrN₃O₂S [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-isopropylphenoxy)prop-2-en-1-one (4r): yellow solid, yield: 61%, m.p: 118.5–119.4°C; ¹H NMR (400 MHz, CDCl₃) 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(CH₃)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(CH₃)₂}-3,5,2-2H, 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, -OCH₂-), 3.71 – 3.55 (m, 2H, -SCH₂-), 2.87 – 2.74 (m, 1H, -CH₂), 1.19 – 1.08 (m, 6H, 2CH₃);

¹³C NMR (101 MHz, CDCl₃) 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, -OCH₂-), 34.15 (s, -SCH₂-), 29.60 (s, -CH₂), 23.84 (d, -CH₃); HRMS calcd for C₃₅H₃₂N₅O₅S [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%; ¹H NMR (400 MHz, CDCl₃) 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, -OCH₂-), 3.80 – 3.65 (m, 2H, -SCH₂-); ¹³C NMR (101 MHz, CDCl₃) 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, -OCH₂-), 29.96 (s, -SCH₂); ¹⁵F NMR (376 MHz, CDCl₃) δ -113.70 – -114.21 (m), -116.59 (s), -119.69 (s). HRMS calcd for C₃₂H₃₂F₈N₅O₅S [M+H]⁺: 534.16460, found 534.16296.

(E)-1-{2-[(5,6-diphenyl-1,2,4-triazin-3-yl)thio]ethoxy}phenyl)-3-(thiophen-2-y1)prop-2-en-1-one (4t): white solid, yield: 61%, m.p: 139.8–140.2°C; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (101 MHz, DMSO-d₆) 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, -OCH₂-), 29.37 (s, -SCH₂); HRMS calcd for C₃₉H₂₈F₁₀N₅O₅S [M+H]⁺: 522.13044, found S-12
\( (E)-3-(4\text{-chlorophenyl})-1-(4-(2-((5,6\text{-diphenyl}-1,2,4\text{-triazin-3-yl)thio})ethoxy)phenyl)prop-2\text{-en-1-one} \) (4u):
white solid, yield: 66\%; \( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)) \d 7.99 (d, \( J = 8.7 \text{ Hz}, 2\text{H}, \text{Ar}-(4\text{-OH})-2,6\text{-2H}), 7.73 (d, \( J = 15.6 \text{ Hz}, 1\text{H}, \text{Ar}-\text{CH}=\text{CH}), 7.52 (\text{ddd}, \( J = 26.0, 14.9, 7.4 \text{ Hz}, 7\text{H}, 2\text{Ar}-\text{H}, \text{Ar}-(4\text{-Cl})-2,3,5,6,-4\text{H}, \text{CO}=\text{CH}), 7.44 – 7.30 (m, 8\text{H}, 8\text{Ar}-\text{H}), 7.04 (d, \( J = 8.7 \text{ Hz}, 2\text{H}, \text{Ar}-(4\text{-OH})-3,5\text{-2H}), 4.59 – 4.39 (m, 2\text{H}, \text{-OCH}$_2$), 3.81 (dt, \( J = 13.1, 5.3 \text{ Hz}, 2\text{H}, \text{-SCH}$_2$); \( ^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\)) \d 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 \text{ 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 \text{ Hz}), 128.64 (d, \( J = 7.8 \text{ Hz}), 122.29 (s), 114.55 (s), 66.55 (s, \text{-OCH}$_2$), 29.59 (s, \text{-SCH}$_2$); HRMS calcld for C$_{32}$H$_{27}$N$_2$O$_2$SCl [M+H]$^+$: 550.13505, found 550.13403.

\( (E)-3-(4\text{-chlorophenyl})-1-(4-(3-((5,6\text{-diphenyl}-1,2,4\text{-triazin-3-yl)thio})proproxy)phenyl)prop-2\text{-en-1-one} \) (4v):
yellow oil, yield: 37\%; \( ^1\text{H NMR} \) (400 MHz, DMSO-d$_6$) \d 8.32 – 8.25 (m, 2\text{H}, \text{Ar}-(4\text{-NO$_2$})-3,5\text{-2H}), 8.21 – 8.11 (m, 4\text{H}, \text{Ar}-(4\text{-OH})-3,5\text{-2H}, \text{Ar}-(4\text{-NO$_2$})-2,6\text{-2H}), 7.77 (t, \( J = 12.6 \text{ Hz}, 1\text{H}, \text{Ar}-\text{CH}=\text{CH}), 7.57 – 7.31 (m, 11\text{H}, \text{CO}=\text{CH}, 10\text{Ar}-\text{H}), 7.15 – 7.05 (m, 2\text{H}, \text{Ar}-(4\text{-OH})-2,6\text{-2H}), 4.26 (dt, \( J = 19.5, 6.0 \text{ Hz}, 2\text{H}, \text{-OCH}$_2$), 3.50 (q, \( J = 7.3 \text{ Hz}, 2\text{H}, \text{-CH}$_2$), 2.35 – 2.23 (m, 2\text{H}, \text{-CH}$_2$); \( ^{13}\text{C NMR} \) (101 MHz, DMSO-d$_6$) \d 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 \text{ Hz}), 129.73 (d, \( J = 4.8 \text{ Hz}), 128.89 (d, \( J = 5.6 \text{ Hz}), 126.53 (s), 124.39 (s), 115.00 (s), 67.13 (s, \text{-OCH}$_2$), 28.94 (s, \text{-SCH}$_2$), 27.29 (s, \text{-CH}$_2$); HRMS calcld for C$_{32}$H$_{27}$N$_2$O$_2$S [M+H]$^+$: 575.17475, found 575.17383.

\( (E)-1-(4-(2-((5,6\text{-diphenyl}-1,2,4\text{-triazin-3-yl)thio})ethoxy)phenyl)-3-(4\text{-methylthiazol}-5\text{-yl})prop-2\text{-en-1-one} \) (4w):
yellow solid, yield: 40\%; \( m.p: 144.9-145.1^\circ\text{C}; \) \( ^1\text{H NMR} \) (400 MHz, CDCl$_3$) \d 8.71 (s, 1\text{H}, thiazole-5-H), 7.95 (dd, \( J = 11.3, 4.7 \text{ Hz}, 3\text{H}, \text{Ar}-(4\text{-OH})-2,6\text{-2H}, \text{thiazole-CH}=\text{CH}), 7.56 – 7.49 (m, 4\text{H}, \text{CO}=\text{CH}, 3\text{Ar}-\text{H}), 7.46 – 7.30 (m, 6\text{H}, 6\text{Ar}-\text{H}), 7.22 (t, \( J = 9.7 \text{ Hz}, 1\text{H}, \text{Ar}-\text{H}), 7.06 – 6.99 (m, 2\text{H}, \text{Ar}-(4\text{-OH})-3,5\text{-2H}), 4.48 (t, \( J = 6.6 \text{ Hz}, 2\text{H}, \text{-OCH}$_2$), 3.81 – 3.69 (m, 2\text{H}, \text{-SCH}$_2$), 2.60 (s, 3\text{H}, \text{-CH}$_3$); \( ^{13}\text{C NMR} \) (101 MHz, CDCl$_3$) \d 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 \text{ Hz}), 132.89 (s), 131.16 – 130.65 (m), 129.82 (s), 129.58 (s), 129.33 (d, \( J = 3.2 \text{ Hz}), 128.63 (d, \( J = 7.0 \text{ Hz}), 123.30 (s), 114.56 (s), 66.54 (s, \text{-OCH}$_2$), 29.54 (s, \text{-SCH}$_2$), 15.81 (s, \text{-CH}$_3$); HRMS calcld for C$_{32}$H$_{29}$N$_2$O$_2$S$_2$ [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]

589.18872
C\textsubscript{34} H\textsubscript{29} O\textsubscript{4} N\textsubscript{4} S = 589.19040
-2.85455 ppm

590.19250
594.15710

m/z
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

2018060546 #147  RT: 1.43  AV: 1  NL: 1.02E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{33}H_{28}O_{3}N_{3}S = 546.18459
-2.82782 ppm

m/z
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]

C$_{33}$H$_{28}$O$_3$N$_3$S $\delta$ 546.18459

m/z 546.18341

Relative Abundance

523.24481 528.85907 531.86633 532.87042 535.06982 535.87042 539.85376 542.90881 544.19301 547.18671

546.18459 $\pm$ 2.15733 ppm
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

2018060548 #195 RT: 1.91 AV: 1 NL: 3.28E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]
568 570 572 574 576 578 580
m/z

576.19379
C$_{34}$H$_{30}$O$_{4}$N$_{3}$S = 576.19515
-2.37243 ppm

577.13269
575.43219
578.13605
571.42859
586.42255
568.43280
569.43378
570.42859
572.00582
574.43280
576.43280
578.13605
580.42657
581.08209
585.90338
586.42255

S-21
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

2018080705 #153  RT: 1.51  AV: 1  NL: 2.18E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{32}H_{26}O_{2}N_{3}S = 516.17402
-0.02528 ppm

517.17743
519.29498
517.81458
518.34229
516.82880
520.29657
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

20180807 #185 RT: 1.82 AV: 1 NL: 2.96E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{30}H_{24}O_{3}N_{3}S = 506.15329
-1.08335 ppm

m/z

Relative Abundance

506.15274
503.31842
505.69064
507.69632
502.60327

507.15610
504.30414
508.15842

505.03748
507.15610

506.15274

505.69064
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

2018060549 #111 RT: 1.07 AV: 1 NL: 1.11E8
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{24}H_{26}O_{4}N_{3}S = 452.16385
-2.30492 ppm
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

2018060550 #201 RT: 1.95 AV: 1 NL: 4.00E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C32H25O2N3ClS = 550.13505
-2.18465 ppm
552.12988
551.13696
553.13324
542.06342 549.41443
547.72089 542.90912 554.13757
546.18262
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

2018060551 #139 RT: 1.35 AV: 1 NL: 3.07E7
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{34} H_{30} O_{4} N_{3} S = 576.19515
-2.47836 ppm

576.19373
577.19708
578.19946
575.43121
586.42230
579.42590
584.43964
572.43109
581.90350
568.43158
570.43109
574.43121
576
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
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 41

Figure S35. $^{13}$C NMR spectrum of compound 41
Figure S36. $^{19}$F NMR spectrum of compound 4l

Figure S37. HRMS spectrum of compound 4l

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

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

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
Figure S45. $^1$H NMR spectrum of compound 4o

Figure S46. $^{13}$C NMR spectrum of compound 4o
Figure S47. HRMS spectrum of compound 40

20180807 #141 RT: 1.39 AV: 1 NL: 2.26E7
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C30H25O2N4S2 = 537.14134
-1.45211 ppm

532.86993 533.37128 536.72900 537.14056 538.14380 539.15656 540.15912 541.15228 542.15393 543.15568
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

2018080720 #205 RT: 2.02 AV: 1 NL: 1.81E7
T: FTMS + p ESI Full ms [100.0000-1000.0000]

530.18909
C33 H28 O2 N3 S = 530.18967
-1.10796 ppm
532.36841
531.19257
532.86969
533.37195
526.87225
525.20306
529.35986
536.05865
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]

C_{22} H_{21} O_{2} N_{3} Br S = 470.05324
-230.95181 ppm
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

2018080725 #169  RT: 1.66  AV: 1  NL: 9.13E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

\[
\text{C}_{30} \text{H}_{24} \text{O}_2 \text{N}_3 \text{S}_2 = 522.13044 \text{ ppm}
\]

m/z 514 516 518 520 522 524 526 528 530

Relative Abundance

-1.54415 ppm

522.12964

520.87555

523.13300

529.88080

524.12549

517.81403

520.38416

526.13165

529.36182

515.36810

520.38416

529.88080
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

2018080726 #199  RT: 1.96  AV: 1  NL: 1.10E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{32} H_{25} O_{2} N_{3} Cl S = 550.13505
-1.85182 ppm

m/z 549.39075 550.71368 551.13641 551.86151 552.12860 553.64819

Relative Abundance 550.13403
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

2018080727 #143 RT: 1.40 AV: 1 NL: 1.10E6
T: FTMS + p ESI Full ms [100.0000-1000.0000]

C_{33}H_{27}O_{4}N_{4}S = 575.17475
-1.60714 ppm
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

2018091834 #125  RT: 1.23  AV: 1  NL: 2.65E6
T: FTMS + p ESI Full ms [70.0000-1000.0000]

C_{30}H_{25}O_{2}N_{4}S_{2} = 537.14134
-1.90663 ppm

m/z 537.14032
538.14392
531.86664
532.86951
533.86664
539.85254
543.38385
549.44757
553.30121
559.45585
520.87543
525.28638
528.85742
519.43939
521.87543
524.28638
527.85742
520.87543