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ONE-POT AND THREE-COMPONENT SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NEW 1,2,4-TRIAZINE-COUMARINS

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Abstract – A series of 1,2,4-triazine-coumarins were prepared by a one-pot, three-component condensation of 1,2-diarylethane-1,2-diones, thiosemicarbazide and 2-coumaryloxy-methyloxiranes using K_2CO_3 as a catalyst in aqueous medium. This three-component reaction offers several advantages such as simple procedure, environmentally friendly and high yields. The resulting products were characterized by ^{1}H NMR, ^{13}C NMR, HRMS and melting points. Furthermore, all newly synthesized compounds were evaluated for their α-glucosidase inhibitory activity. As a result, the majority of the screened compounds displayed potent inhibitory activity with IC_{50} values in the range of 32.57±0.21 to 148.77±3.23 μM, when compared to the standard acarbose (IC_{50} = 876.14±2.46 μM)

INTRODUCTION

Multicomponent reactions (MCRs) are processes in which three or more components are combined in a single chemical step to form products. The advantages of MCRs are saving time, higher yields, atom economy and less waste produced. MCRs have proved to be valuable tools in organic and medicinal chemistry for the synthesis of biologically important compounds, including natural and pharmaceutically active compounds.[1]

1,2,4-Triazine is a prominent structural core system found in many biologically active natural products such as fervenulin, toxoflavin, and reurhycin.[2] The chemistry of 1,2,4-triazines has received considerable attention because of their synthetic and effective biological importance. Most methods for the preparation of 1,2,4-triazines are the double condensation of a 1,2-dicarbonyl unit with an amidrazone.[3-6] In the past few decades, a large number of natural and synthetic 1,2,4-triazine derivatives have been reported to exhibit various biological activities including antimalarial,[7] anticonvulsant,[8] antifungal,[9]

anti-inflammatory,[10] anticancer,[11] anti-HIV[12] and neuroprotective[13] activities. For example, lamotrigine is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder.[14,15] 5-Aryl-6-(4-methylsulfonyl)-3-(metylthio)-1,2,4-triazine have been developed as selective cyclooxygenase-2 inhibitors.[10] 2-(5*H*-[1,2,4]Triazino[5,6-*b*]indol-3-ylthio)-1-arylethanone, a fused triazinoindole derivatives, have been reported in the literature to possess potent α-glucosidase inhibitory activity (Figure 1).[16]

Coumarin derivatives are an important class of naturally organic compounds, which are predominantly found in higher plants. Coumarin derivatives are of great interest due to their diverse structural features and versatile biological properties, such as anticancer,[17] antimalarial,[18] anti-inflammatory,[19] antioxidant,[20] antitubercular[21] and antimicrobial[22] activities. Several drugs, possessing a coumarin group, like warfarin, dicoumarol and acenocoumarol, have been approved for clinic use.[23,24] Furthermore, recent studies have shown that numbers of compounds containing the coumarin skeleton act as α-glucosidase inhibitors.[25-28] Such as, Khan et al. have reported that biscoumarin derivatives can act as a new class of potent α-glucosidase inhibitors (Figure 1).[25]

Over the years, molecular hybrid-based approaches had gained more attention by researchers to discover some promising chemical architectures, which containing two or more bioactive pharmacophores and displaying significant medicinal profiles.[29] In view of these observations and in continuation of our interest in the synthesis of biologically active heterocyclic compounds,[30-33] we herein report a facile method for the preparation of a new series of heterocyclic compounds containing 1,2,4-triazine and coumarin pharmacophoric groups in a single molecular framework, and evaluated for their α-glucosidase inhibitory activity.

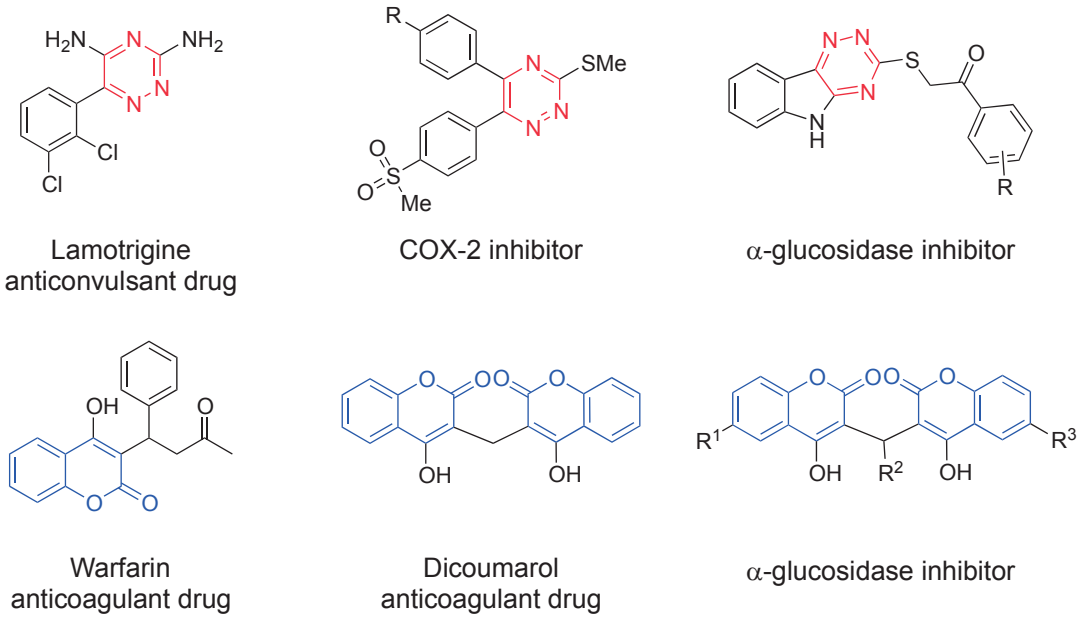
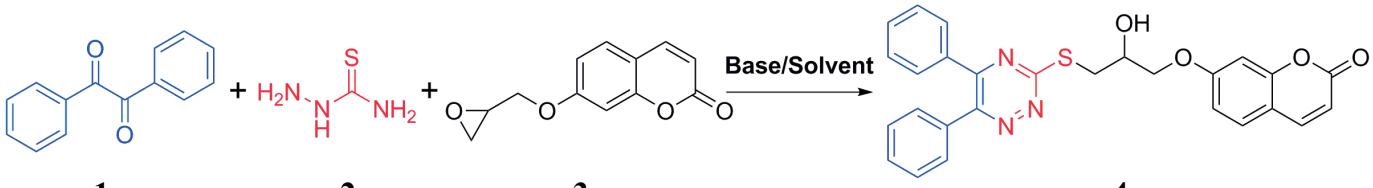


Figure 1. The structures of some commercial drugs and pharmacologically active compounds

RESULTS AND DISCUSSION

As a part of our endeavor to synthesized bioactive heterocycles, herein we report the facile one-pot synthesis of a new class of 1,2,4-triazine-coumarins from 1,2-diarylethane-1,2-diones (**1**), thiosemicarbazide (**2**) and 2-coumaryloxy-methyloxiranes (**3**) in aqueous medium. Our synthetic methodology was based on the reaction of epoxy groups with mercapto nucleophiles (SH) under basic condition. Reaction of 1,2-diarylethane-1,2-diones (**1**) with thiosemicarbazide (**2**) under basic condition provides 5,6-diaryl-1,2,4-triazine-3-thiols as intermediates, which react in situ with 2-coumaryloxy-methyloxiranes (**3**) to produce 1,2,4-triazine-coumarins (**4a**-**4g**). All of the synthesized compounds are new and not reported in the literature till date.

To optimize the reaction conditions, we initially investigated the reaction of benzil (**1a**), thiosemicarbazide (**2**), and 7-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one (**3a**) in ethanol at reflux conditions in the presence of Na_2CO_3 as a catalyst. From this reaction, the desired 7-(3-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (**4a**) was obtained in moderate yield (46%, Table 1, entry 1). Screening of various solvents such as aqueous EtOH (2:1), aqueous EtOH (1:1) and H_2O revealed that water was the most efficient reaction medium for this transformation (Table 1, entries 2–4). Then, the varieties of base catalysts and solvents were investigated for the present transformations (Table 1, entries 5-20). The results have been summarized in Table 1. We found that the base and solvent have profound effects on the reaction yield. Thus, the best yield was achieved by employing K_2CO_3 as base in water at 100 °C.



1a **2** **3a** **4a**

Scheme 1. Optimization of reaction conditions for the synthesis of **4a**

Table 1. Optimization of reaction conditions[a]

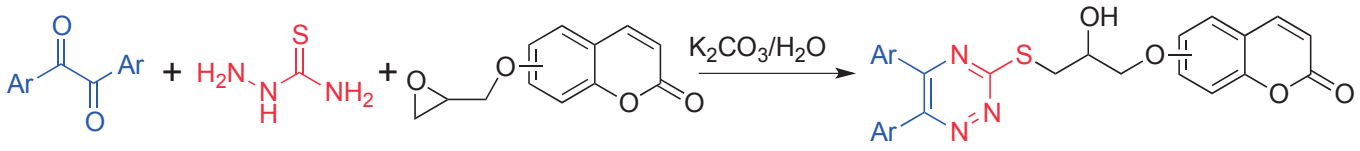
Entry	Base	Solvent	T (°C)	Time (h)	Yield[b] (%)
1	Na_2CO_3	EtOH	100	7	46
2	Na_2CO_3	EtOH/H_2O (2:1)	78	7	49
3	Na_2CO_3	EtOH/H_2O (1:1)	100	7	51
4	Na_2CO_3	H_2O	100	7	76
5	K_2CO_3	EtOH	100	7	58
6	K_2CO_3	EtOH/H_2O (2:1)	78	7	63

7	K_2CO_3	EtOH/H_2O (1:1)	100	7	64
8	K_2CO_3	H_2O	100	7	87
9	Cs_2CO_3	EtOH	100	7	54
10	Cs_2CO_3	EtOH/H_2O (2:1)	78	7	51
11	Cs_2CO_3	EtOH/H_2O (1:1)	100	7	53
12	Cs_2CO_3	H_2O	100	7	79
13	NaOH	EtOH	100	7	42
14	NaOH	EtOH/H_2O (2:1)	78	7	57
15	NaOH	EtOH/H_2O (1:1)	100	7	61
16	NaOH	H_2O	100	7	81
17	KOH	EtOH	100	7	53
18	KOH	EtOH/H_2O (2:1)	78	7	57
19	KOH	EtOH/H_2O (1:1)	100	7	64
20	KOH	H_2O	100	7	75

[a]Reactions were performed with benzil (1 mmol), thiosemicarbazide (1 mmol), base (1.5 mmol), 7-(oxiran-2-ylmethoxy)-2*H*-chromen-2-one (1 mmol), and solvent (20 mL).

[b] Isolated yield.

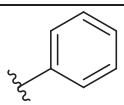
With the optimized reaction conditions in hand, we then explored the scope of this promising reaction by varying the structures of 1,2-diarylethane-1,2-diones (**1**), and 2-coumaryloxy-methyloxiranes (**3**) (Scheme 2). All the reactions proceeded smoothly and gave the corresponding products in good yields (Table 2). The results indicate that the present reaction system has wide substrate scope.

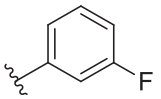
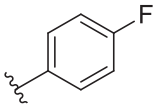
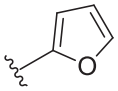
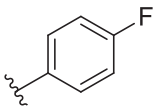
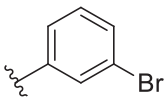
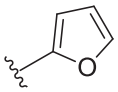


1a-1e **2** **3a-3b** **4a-4g**

Scheme 2 One-pot synthesis of 1,2,4-triazine-coumarins **4a-4g**

Table 2. Synthesis and α-glucosidase inhibitory activity of 1,2,4-triazine-coumarins (**4a-4g**)

Entry	Compound	Ar	Coumarin position	Yield[a] (%)	α-Glucosidase IC_{50} (μM)[b]
1	**4a**		7	87	96.35±1.97

2	**4b**		7	83	66.76±0.82
3	**4c**		7	81	48.19±0.27
4	**4d**		7	91	148.77±3.23
5	**4e**		3	89	60.14±0.45
6	**4f**		3	86	32.57±0.21
7	**4g**		3	82	102.35±1.13

[a] Isolated yield; [b] Acarbose is standard for α-glucosidase inhibition activity (IC_{50} = 876.14±2.46 μM).

The structures of newly synthesized compounds were confirmed by their ^{1}H NMR and elemental analysis. The ^{1}H NMR spectrum of **4a** exhibited three signals at 3.46, 3.65 and 4.15 ppm, attributed to two CH_2 and one CH groups. Two doublet signals at 6.28 and 7.97 ppm were attributed to C4-H and C3-H of coumarin ring, respectively. The double-double peak of C6-H of coumarin ring was observed at 6.92 ppm. The double peak of C5-H and C8-H of coumarin ring were observed at 7.60 and 6.97 ppm, respectively. The ten aromatic hydrogen atoms of 5,6-diphenyl-1,2,4-triazine were appeared as a multiplet signals at 7.35-7.50 ppm. The total number of protons matched perfectly with its structure. Moreover, in their ^{13}C NMR spectra, the number of signals equals the number of different carbons in the molecule.

All of the synthesized 1,2,4-triazine-coumarins **4a**-**4g** were evaluated for α-glucosidase inhibition activity in accordance with standard procedures with minor modification,[34] in comparison to acarbose as a standard inhibitor. The results were summarized in **Table 2**. The majority of the screened compounds displayed potent α-glucosidase inhibitory activity, with IC_{50} values in the range of 32.57±0.21 to 148.77±3.23 μM. Among them, compound **4f** represented the most potent α-glucosidase inhibitory activity with IC_{50} values of 32.57±0.21 μM, as compared to the standard drug acarbose (IC_{50} = 876.14±2.46 μM, The value of IC_{50} is similar to previous literature report[34,35]).

EXPERIMENTAL

Chemistry

All starting materials and reagents were purchased from commercial suppliers. Melting points were determined on an X-4 microscope melting point apparatus (Shanghai instrument physical optics instrument Co., LTD) and were uncorrected. TLC was performed on 0.20 mm Silica Gel 60 F_{254} plates (Qingdao Ocean Chemical Factory, Shandong, China). Nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz on a JNM spectrometer (JEOL Ltd.) and reported in parts per million.

General procedure for preparation of 1,2,4-triazine-coumarins derivatives (4a–4g)

A mixture of 1,2-diarylethane-1,2-diones (1 mmol), thiosemicarbazide (1 mmol) and K_2CO_3 (1.5 mmol) in H_2O (20 mL) was stirred at 100 ºC for 5 h. Then 2-coumaryloxy-methyloxiranes (1 mmol) was added to the mixture and stirred under the reflux conditions for 2 h. After completion of reaction, the mixture was extracted with CH_2Cl_2 and then concentrated in vacuo. The residue was purified by silica gel column chromatography to obtain title products.

7-(3-((5,6-Diphenyl-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4a)

Yellow solid (87%). mp 78-79 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.46 (dd, 1H, J = 13.6 Hz, 6.8 Hz), 3.65 (dd, 1H, J = 13.6 Hz, 5.2 Hz), 4.15-4.25 (m, 3H), 6.28 (d, 1H, J = 9.6 Hz), 6.92 (dd, 1H , J = 8.8 Hz, 2.4 Hz), 6.97 (d, 1H , J = 2.4 Hz), 7.35-7.50 (m, 10H), 7.60 (d, 1H, J = 8.4 Hz), 7.97 (d, 1H, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.6, 69.6, 70.8, 101.8, 112.8, 113.0, 113.5, 128.7, 128.8, 129.0, 129.4, 129.8, 129.9, 131.3, 134.8, 134.9, 143.5, 154.4, 155.8, 156.1, 161.3, 161.7, 170.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{22}N_3O_4S$: 484.1331, found: 484.1321.

7-(3-((5,6-Bis(3-fluorophenyl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4b)

Yellow solid (83%). mp 125-127 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.45 (dd, 1H, J = 13.6 Hz, 7.6 Hz), 3.64 (dd, 1H, J = 13.6 Hz, 5.2 Hz), 4.12-4.25 (m, 3H), 5.70 (d, 1H, J = 5.2 Hz), 6.27 (d, 1H, J = 9.6 Hz), 6.91 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 6.96 (d, 1H, J = 2.4 Hz), 7.23-7.36 (m, 6H), 7.42-7.45 (m, 2H), 7.59 (d, 1H, J = 8.8 Hz), 7.97 (d, 1H, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.5, 69.5, 70.8, 101.8, 112.8, 113.1, 113.6, 116.2 (d, 1C, J = 21.0 Hz), 116.7 (d, 1C, J = 21.0 Hz), 117.0 (d, 1C, J = 21.0 Hz), 118.5 (d, 1C, J = 21.0 Hz), 125.2 (d, 1C, J = 2.9 Hz), 125.6 (d, 1C, J = 2.9 Hz), 129.0, 130.5 (d, 1C, J = 7.6 Hz), 130.5 (d, 1C, J = 7.6 Hz), 136.5 (d, 1C, J = 7.6 Hz), 136.5 (d, 1C, J = 7.6 Hz), 143.4, 153.1, 154.6, 155.8, 161.2, 161.5 (d, 1C, J = 246.9 Hz), 161.6 (d, 1C, J = 246.9 Hz), 161.6, 171.0; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{20}F_2N_3O_4S$: 520.1143, found: 520.1132.

7-(3-((5,6-Bis(4-fluorophenyl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4c)

Yellow solid (81%). mp 66-67 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.46 (dd, 1H, J = 13.6 Hz, 6.8 Hz), 3.63 (dd, 1H, J = 13.6 Hz, 5.2 Hz), 4.13-4.26 (m, 3H), 6.28 (d, 1H, J = 9.6 Hz), 6.92 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 6.97 (d, 1H, J = 2.4 Hz), 7.22-7.29 (m, 4H), 7.48-7.56 (m, 4H), 7.60 (d, 1H, J = 8.8 Hz), 7.98 (d, 1H, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.6, 69.5, 70.8, 101.8, 112.8, 113.0, 113.5, 116.1 (d, 4C, J = 21.9 Hz), 129.0, 130.7 (d, 1C, J = 3.8 Hz), 130.9 (d, 1C, J = 3.8 Hz), 131.3 (d, 2C, J = 8.6 Hz), 132.1

(d, 2C, *J* = 8.6 Hz), 143.4, 153.3, 154.8, 155.8, 161.2, 161.6, 162.5 (d, 1C, *J* = 252.7 Hz), 165.0 (d, 1C, *J* = 252.7 Hz), 170.6; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{20}F_2N_3O_4S$: 520.1143, found: 520.1132.

7-(3-((5,6-Di(furan-2-yl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4d)

Yellow solid (91%). mp 151-152 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.48 (dd, 1H, *J* = 13.6 Hz, 6.8 Hz), 3.62 (dd, 1H, *J* = 8.8 Hz, 4.8 Hz), 4.15-4.26 (m, 3H), 5.69 (d, 1H, *J* = 5.2 Hz), 6.29 (d, 1H, *J* = 9.6 Hz), 6.76-6.79 (m, 2H), 6.92-6.97 (m, 2H), 6.99 (d, 1H, *J* = 2.4 Hz), 7.05 (d, 1H, *J* = 2.8 Hz), 7.60 (d, 1H, *J* = 8.8 Hz), 7.96-8.00 (m, 2H), 8.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.7, 69.8, 70.8, 101.9, 112.4, 112.8, 113.0, 113.2, 113.2, 113.5, 119.4, 129.0, 143.1, 143.5, 144.2, 144.4, 147.6, 147.7, 147.8, 155.8, 161.3, 161.7, 170.5; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{18}N_3O_6S$: 464.0916, found: 464.0907.

3-(3-((5,6-Bis(4-fluorophenyl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4e)

Yellow solid (89%). mp 170-172 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.50 (dd, 1H, *J* = 13.6 Hz, 6.8 Hz), 3.68 (dd, 1H, *J* = 13.6 Hz, 4.4 Hz), 4.25-4.34 (m, 3H), 5.83 (d, 1H, *J* = 5.6 Hz), 5.91 (s, 1H), 7.21 (t, 2H, *J* = 8.8 Hz), 7.26-7.34 (m, 2H), 7.38 (d, 1H, *J* = 8.0 Hz) , 7.47-7.54 (m, 4H), 7.64-7.68 (m, 1H), 7.92 (dd, 2H, *J* = 7.6 Hz, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.7, 69.2, 71.3, 91.1, 115.5, 116.1 (d, 4C, *J* = 21.0 Hz), 117.0, 123.0, 124.1, 130.6 (d, 1C, *J* = 2.8 Hz), 130.8 (d, 1C, *J* = 2.8 Hz), 131.2 (d, 2C, *J* = 8.2 Hz) , 132.1 (d, 2C, *J* = 8.2 Hz), 132.7, 153.4, 153.5, 154.9, 162.5 (d, 1C, *J* = 252.7 Hz), 162.8, 163.4 (d, 1C, *J* = 252.7 Hz), 165.3, 170.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{20}F_2N_3O_4S$: 520.1143, found: 520.1133.

3-(3-((5,6-Bis(3-bromophenyl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4f)

Yellow solid (86%). mp 77-78 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.49 (dd, 1H, *J* = 14.0 Hz, 6.8 Hz), 3.70 (dd, 1H, *J* = 13.6 Hz, 5.2 Hz), 4.27 (m, 3H), 5.84 (d, 1H, *J* = 5.6 Hz), 5.92 (s, 1H), 7.28-7.33 (m, 2H), 7.36-7.41 (m, 4H), 7.62-7.69 (m, 5H), 7.90 (dd, 1H, *J* = 8 Hz, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.8, 69.1, 71.3, 91.1, 115.5, 117.0, 123.0, 123.1, 123.1, 124.1, 128.0, 128.4, 130.2, 130.3, 132.1, 132.7, 132.7, 133.1, 134.6, 136.2, 136.3, 153.0, 153.4, 154.5, 162.8, 165.3, 170.9; HRMS (ESI) calcd for $[M+H]^+$ $C_{27}H_{20}Br_2N_3O_4S$: 639.9541, found: 639.9536.

3-(3-((5,6-Di(furan-2-yl)-1,2,4-triazin-3-yl)thio)-2-hydroxypropoxy)-2*H*-chromen-2-one (4g)

Brown solid (82%). mp 88-89 ºC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 3.49 (dd, 1H, *J* = 13.6 Hz, 6.4 Hz), 3.66 (dd, 1H, *J* = 13.6 Hz, 4.4 Hz), 4.26 (m, 3H), 5.82 (d, 1H, *J* = 5.6 Hz), 5.92 (s, 1H), 6.74-6.75 (m, 1H), 6.77-6.78 (m, 1H), 6.90 (d, 1H, *J* = 3.6 Hz), 7.03 (d, 1H, *J* = 3.2 Hz), 7.32-7.36 (m, 1H), 7.38 (d, 1H, *J* = 8.4 Hz), 7.63-7.67 (m, 1H), 7.94-7.96 (m, 2H), 8.02 (d, 1H, *J* = 2.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.9, 69.4, 71.4, 91.1, 112.4, 113.3, 115.5, 119.9, 119.5, 123.1, 124.1, 132.7, 143.2, 144.2, 144.4, 147.5, 147.7, 147.8, 153.3, 162.9, 165.4, 170.3; HRMS (ESI) calcd for $[M+H]^+$ $C_{23}H_{18}N_3O_6S$: 464.0916, found: 464.0909.

***In vitro* assay of α-glucosidase inhibitory activity**

The test compounds were dissolved in DMSO to prepare the required distributing concentration. α-Glucosidase inhibitory activity was assayed by using 0.1 M phosphate buffer (pH 6.8) at 37 ^{o}C. The enzyme (0.2 U/mL) in phosphate buffer saline was incubated with various concentrations of test compounds at 37 ^{o}C for 15 min. Then 1.25 mM *p*-nitrophenyl α-D-glucopyranoside was added to the mixture as a substrate. After further incubation at 37 ^{o}C for 30 min. The absorbance was measured spectrophotometrically at 405 nm. The sample solution was replaced by DMSO as a control. Acarbose was used as a positive control. All experiments were carried out in triplicates. The% inhibition has been obtained using the formula: Inhibition (%) = (1-ΔAsample/ΔAcontrol)*100%. IC_{50} value is defined as a concentration of samples inhibiting 50% of α-glucosidase activity under the stated assay conditions.

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