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ORIGINAL PAPER

Design, solvent-free synthesis and antibacterial activity evaluation of new coumarin sulfonamides

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Abstract
A simple cost-effective and green method was presented for the synthesis of coumarin bis sulfonamides. Seventeen novel coumarin sulfonamides were synthesized in good to high yield and purity in six steps starting from 2-amino thiazole, aniline, and 4-methoxy aniline. All of the reactions have been done under green conditions without using any hazardous solvent. The chemical structures of the products were elucidated by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and elemental analysis. Also, the anti-bacterial properties of the synthesized sulfonamides were investigated using two strains of Staphylococcus (gram-positive) and Escherichia coli (gram-negative) bacteria.

Keywords Coumarin · Sulfonamide · Solvent-free · Antibacterial

Introduction

Coumarins with synthetic and natural origin constitute a large group of heterocyclic compounds. Many compounds which contain the coumarin moiety were reported to show a wide range of valuable biological activities in medicinal and pharmaceutical areas, such as anti-inflammatory [1], antiviral [2], anti-Alzheimer [3], antitumor [4], and anticancer [5]. In the development of newer antimicrobials, coumarins have been identified as plant antibacterial agents with bacterial-growth inhibitory potential, particularly against Gram-positive species [6]. Sulfonamide derivatives belong to the most important class of antibacterial agents [7]. Several compounds bearing sulfonamide groups exhibit other important biological properties, such as antitumor [8], antidiabetic type 2 [9], and antifungal activities [10]. Commonly, sulfonamides are prepared from sulfonyl chlorides and amines [11]. Synthesis of sulfonamides under solvent-free conditions have attracted great interest because of significant environmental and economic advantages [12, 13]. Aryl sulfonyl chlorides are typically prepared via electrophilic aromatic substitution using an excess of chlorosulfonic acid, or oxidative chlorination of thiols and sulfides [14, 15]. Direct synthesis of sulfonamides obtained from sulfonic acids, onepot synthesis of sulfonamides from Grignard reagents and SO_2, and also from aryl iodide are some other reported methods [16, 17].

Coumarin-sulfonamide is an important structural motif that is a core and integral part of different therapeutic scaffolds and analogues [18–22]. Several hybrid drugs including both the coumarin and sulfonamide moieties were designed and synthesized to improve biological activities such as COX-2 inhibitors (compound A) [23], antioxidant activity (compound B) [24], and anti-proliferative agents (compound C) [25] (Fig. 1). Recently, Alshibl et al. synthesized new coumarin-sulfonamide hybrids as an antioxidant, antimicrobial, and anti-inflammatory agents [26]

In view of the antibacterial activity of sulfonamides and coumarins, a combination of coumarin nucleus with sulfonamide moieties is attractive as a versatile platform for the development of a new class of antibacterial agents. As a

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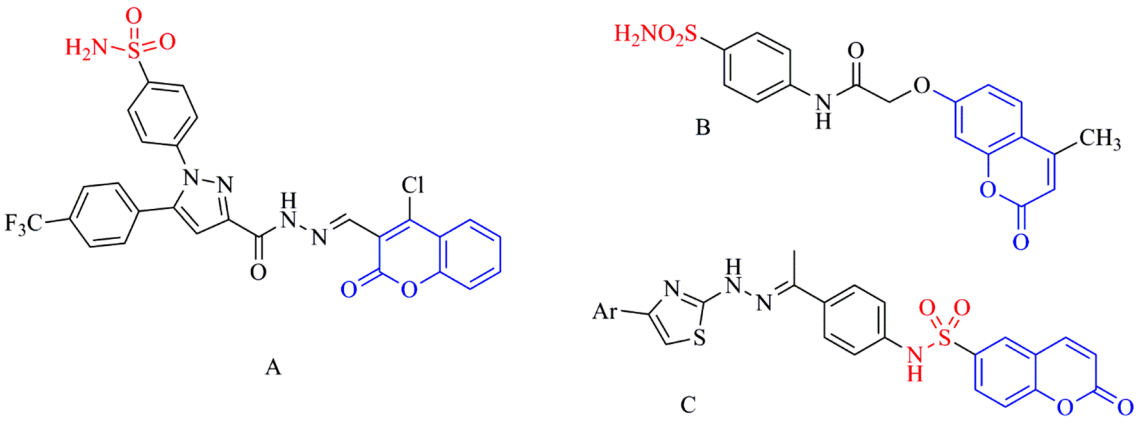


Fig. 1 Examples of hybrid drugs including both the coumarin and sulfonamide moieties

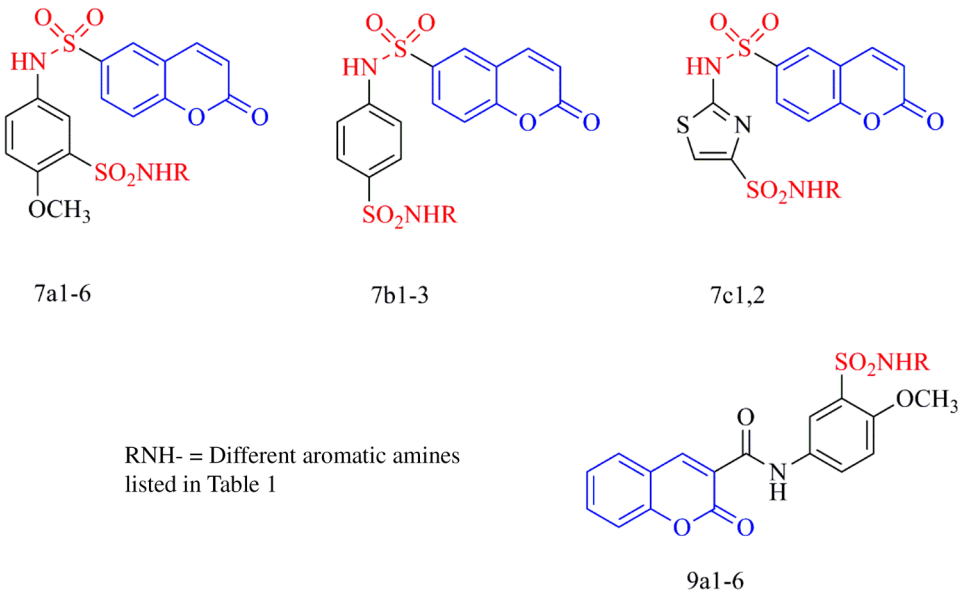
part of our research effort to explore novel antibacterial compounds [27–31] herein, we report the solvent-free synthesis of a series of novel coumarin compounds having biologically active sulfonamide moiety.

Results and discussion

Chemistry

According to the pharmaceutical properties of coumarin and sulfonamides, we design and synthesized several sulfonamides and disulfonamides derived from coumarin and some amino sulfonamides (Fig. 2). At first, *p*-anisidine (1a), aniline (1b), and 2-aminothiazol (1c) were acylated using acetic anhydride under solvent and base-free conditions. The corresponding acetamides (2a–c) were obtained just by the addition of water and filtration as a powder in high yield and purity and used in the next step without further purification (Fig. 3). In the second step chlorosulfonic acid was added to acetamides 2a–c at 0 °C. Acetamide sulfonyl chlorides 3a–c were obtained as a white powder that was washed with water until neutral pH (Fig. 4). The next step is the synthesis of acetamide sulfonamides (**4a**$_{1–6}$, **4b**$_{1–3}$, **4c**$_{1,2}$). Based on our previous work on solvent-free reactions [32–35], this method was used in this step (Fig. 5). The procedure is simply mixing of acetamide sulfonyl chlorides (**3a**–**c**) with an amine in the presence of $NaHCO_3$ at room temperature in the absence of any solvent. The products were obtained after an easy work-up by the addition of water, then filtration and dring. As it was shown in Table 1, a wide range of structurally and electronically varied amines with electron-donating and

Fig. 2 The general structure of synthesized cumarine sulfonamides



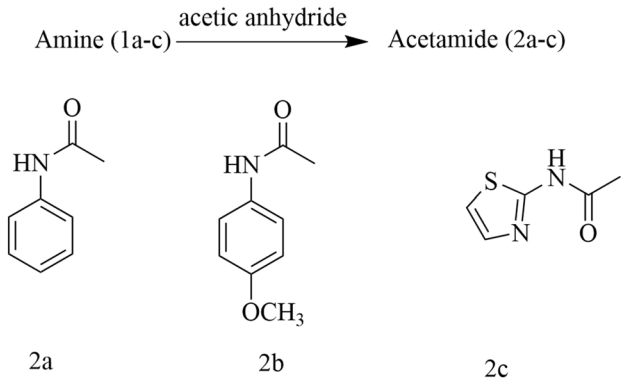


Fig. 3 The synthetic route for the preparation of acetamides (2a, 2b, 2c)

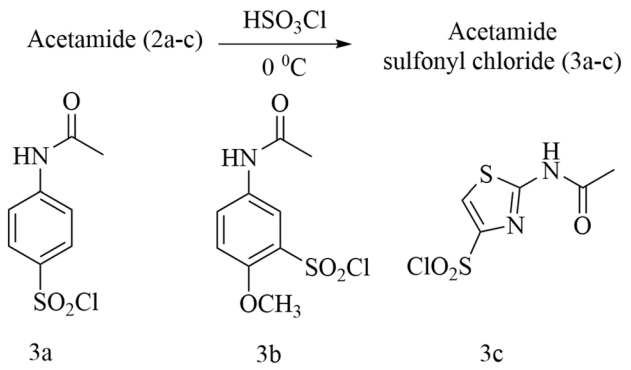


Fig. 4 The synthetic route of acetamide sulfonyl chlorides (3a, 3b, 3c)

electron-withdrawing groups were subjected to the reaction with synthesized acetamide sulfonyl chlorides **3a–c,** and the corresponding acetamide sulfonamides (**4a$_{1–6}$, 4b$_{1–3}$, 4c$_{1,2}$**) were obtained in 85–95% yield with high purity by this simple procedure (Table 1).

In the next step, for the synthesis of amine sulfonamides (**5a$_{1–6}$, 5b$_{1–3}$, 5c$_{1,2}$**), the prepared acetamide sulfonamides (**4a$_{1–6}$, 4b$_{1–3}$, 4c$_{1,2}$**) were hydrolyzed using acidic conditions. (Fig. 5). A mixture of acetamide sulfonamides, H_2SO_4 70%, and H_2O was refluxed for 30 min. The reaction was controlled by TLC. After completion of the reaction, the solution was cooled and natural with NaOH. The precipitate was filtered and washed with water. As it was shown in Table 2, Amine sulfonamides were obtained in 83–95% yields with high purity and used in the next step without any purification.

Synthesis of new coumarin sulfonamides derived from coumarin-6-sulfonyl chloride (6)

Finally for the synthesis of coumarin sulfonamides, amine sulfonamides (5a$_{1–6}$, 5b$_{1–3}$, 5c$_{1,2}$), was reacted with coumarin-6-sulfonyl chloride (6) that was synthesized by chlorosulfonation of coumarin using chlorosulfonic acid at 0 °C according to our previous work [13]. The reactions were carried out in the presence of $NaHCO_3$, at room temperature, under solvent-free conditions (Fig. 6). After completion of the reaction, the mixture was washed with water and the precipitate was filtered and dried. As it was shown in Table 3, the structurally varied amine sulfonamides with electron-donating and electron-withdrawing groups (5a$_{1–6}$ and 5b$_{1–3}$) as well as amine sulfonamides derived from thiazol as heterocycle ones (5c$_{1,2}$) were treated with coumarin sulfonyl chloride after a short reaction time and produced the corresponding coumarin bissulfonamides (**7a$_{1–6}$, 7b$_{1–3}$,**

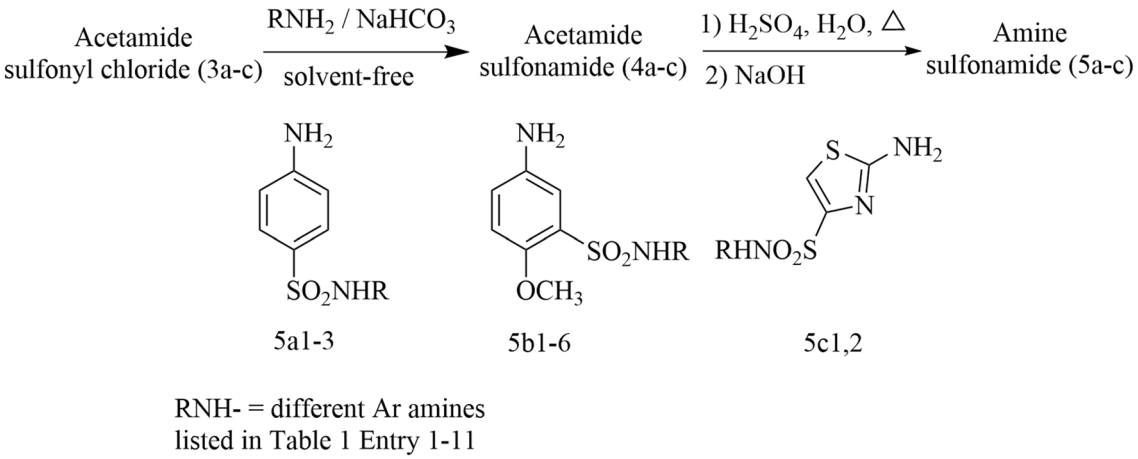
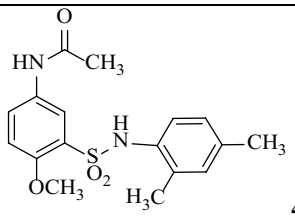
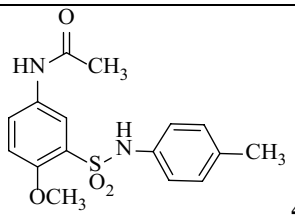
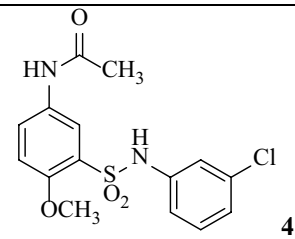
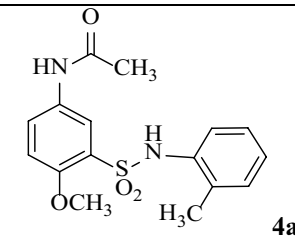
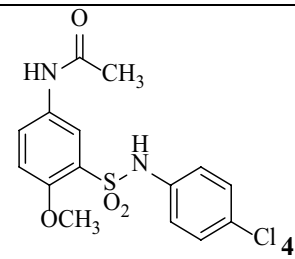
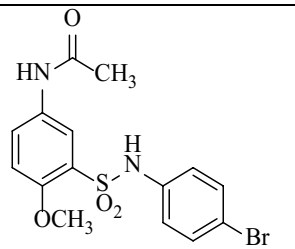


Fig. 5 The synthetic route of amine sulfonamides (5a$_{1–6}$, 5b$_{1–3}$, 5c$_{1,2}$)

Table 1 Yields/reaction times for the preparation of acetamide sulphonamides

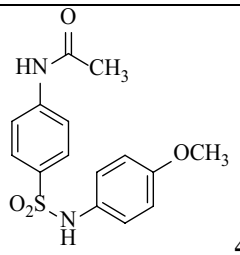
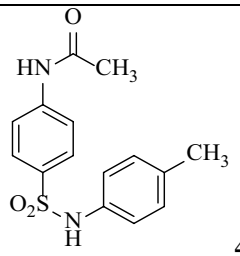
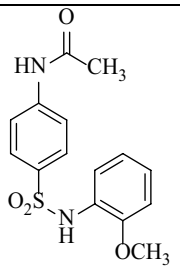
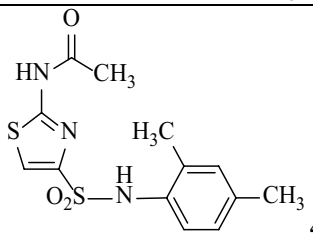
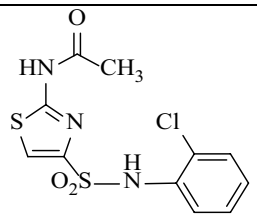
Entry	Amine	Acetamide sulfonamide (4) (product number)	Time (min)	Yield (%)
1	$(Me)_2$-2,4-PhNH2	 **4a$_1$**	22	90
2	Me-4-$PhNH_2$	 **4a$_2$**	30	91
3	Cl-3-$PhNH_2$	 **4a$_3$**	35	89
4	Me-2-$PhNH_2$	 **4a$_4$**	25	90
5	Cl-4-$PhNH_2$	 **4a$_5$**	45	85
6	Br-4-$PhNH_2$	 **4a$_6$**	38	90

7c$_{1,2}$) in moderate to high yield. The chemical structures of the synthesized coumarin bissulfonamides were elucidated by IR, ^{1}H NMR, and ^{13}C NMR.

Synthesis of new coumarin sulfonamides derived from coumarin-3-carbonyl chloride(8)

In continuation to this work, we designed and synthesized another series of coumarin sulfonamides derived from

Table 1 (continued)

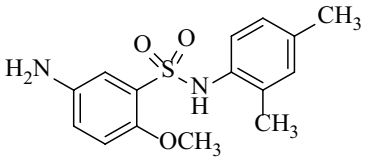
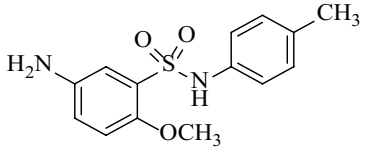
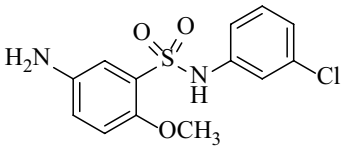
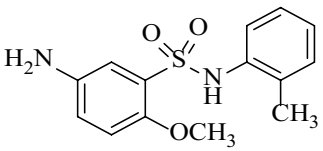
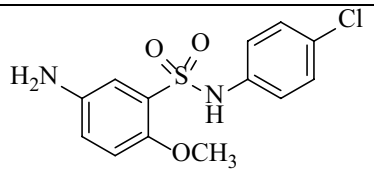
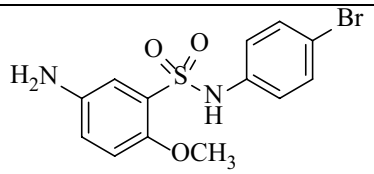
7	MeO-4-$PhNH_2$	 **4b₁**	15	95
8	Me-4-$PhNH_2$	 **4b₂**	25	92
9	MeO-2-$PhNH_2$	 **4b₃**	30	90
10	$(Me)_2$-2,4-$PhNH_2$	 **4c₁**	35	89
11	Cl-2-$PhNH_2$	 **4c₂**	40	85

coumarin-3-carbonyl chloride (8) and aminosulfonamides $\mathbf{5a_{1–6}}$. To do this, coumarin-3-carboxylic acid was reacted with thionyl chloride under reflux conditions. Coumarin-3-carbonyl chloride (**8**) was obtained in high yield and used in the next step without any purification. Then, aminosulfonamides $\mathbf{5a_{1–6}}$ were reacted with coumarin-3-carbonyl chloride **8** in the presence of $NaHCO_3$ under solvent-free conditions (Fig. 7). The results were shown that all of the reactions were done in a short reaction time and the coumarin sulfonamides $\mathbf{9a_{1–6}}$ were obtained in 80–95% yield in high purity (Table 3). The products were characterized by IR, ^{1}H NMR, ^{13}C NMR.

Antibacterial activity

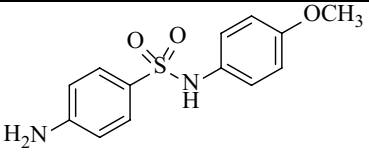
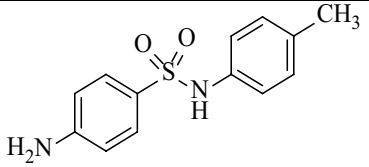
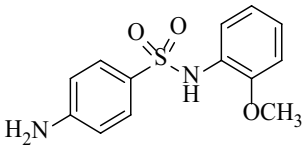
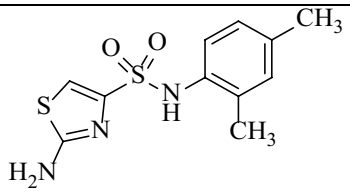
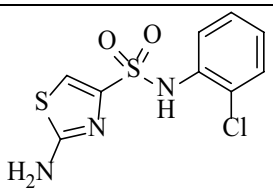
All of the synthesized coumarin bissulfonamides ($7a_{1–6}$, $7b_{1–3}$, $7c_{1,2}$) were screened for their antibacterial activity against Escherichia coli (ATCC35218) as Gram-negative and Staphylococcus aureus (ATCC 6538) as Gram-positive bacterial strains using the conventional agar-dilution method [17]. These results show that coumarin bissulfonamides derived from aniline, 2-aminothiazol, and p-anisidin that is contained electron-withdrawing substitutions in para position ($7a_{5,6}$, $7b_{1–3}$, $7c_{1,2}$) have higher antibacterial activity against the Gram-negative bacteria than that against Gram-positive bacteria. But coumarin bissulfonamides derived

Table 2 Yields/reaction times for the preparation of amine sulphonamides

Entry	Amine	Amine sulfonamide (5) (product number)	Time (min)	Yield (%)
1	$(Me)_2$-2,4-PhNH2	 **5a$_1$**	25	95
2	Me-4-$PhNH_2$	 **5a$_2$**	23	94
3	Cl-3-$PhNH_2$	 **5a$_3$**	35	90
4	Me-2-$PhNH_2$	 **5a$_4$**	25	93
5	Cl-4-$PhNH_2$	 **5a$_5$**	40	89
6	Br-4-$PhNH_2$	 **5a$_6$**	30	92

from p-anisidin that is contained electron-withdrawing substitutions in meta or electron-donating substituents in ortho and para position ($7a_{2-4}$) have lower antibacterial activity against the Gram-negative bacteria than that against Gram-positive bacteria. Compound $7b_1$ derived from aniline that is contained para-OMe substitution has the highest activity compared with $7b_2$ and $7b_3$. Compound $7b_2$ has the lowest antibacterial activity against the Gram-positive

Table 2 (continued)

7	MeO-4-$PhNH_2$	 **$5b_1$**	18	92
8	Me-4-$PhNH_2$	 **$5b_2$**	20	95
9	MeO-2-$PhNH_2$	 **$5b_3$**	22	90
10	$(Me)_2$-2,4-$PhNH_2$	 **$5c_1$**	35	85
11	Cl-2-$PhNH_2$	 **$5c_2$**	45	83

bacteria and compound $7c_2$ has the most potent antibacterial activity against the Gram-positive and Gram-negative bacteria.

In regard to sulfonamides **$9a_{1–6}$**, compared with coumarin bissulfonamides ($7a_{1–6}$, $7b_{1–3}$, $7c_{1,2}$), antibacterial activity, reduced. Overall, coumarin sulfonamides contained chloro and bromo substitutions have higher antibacterial activity against the Gram-negative bacteria (Escherichia coli) and coumarin sulfonamides contained alkyl substitutions have the same activity against the Gram-negative and Gram-positive bacteria.

The diameters of the zones of inhibition for compounds ($7a_{1–6}$, $7b_{1–3}$, $7c_{1,2}$) with a concentration of 2.5 mg/mL are listed in Table 3 and compared with those of reference standards ampicillin and chloramphenicol.

Conclusions

We introduced an easy and green method for the preparation of several structurally varied novel coumarin sulfonamides and coumarin disulfonamides. The reactions are characterized by simple reaction procedures, easy separation, and high yields. Also, most steps were carried out under solvent-free conditions, and the products were separated in high purity. Furthermore, the synthesized coumarin sulfonamides were shown moderate to good antibacterial activity against E. coli and S. aureus microorganisms.

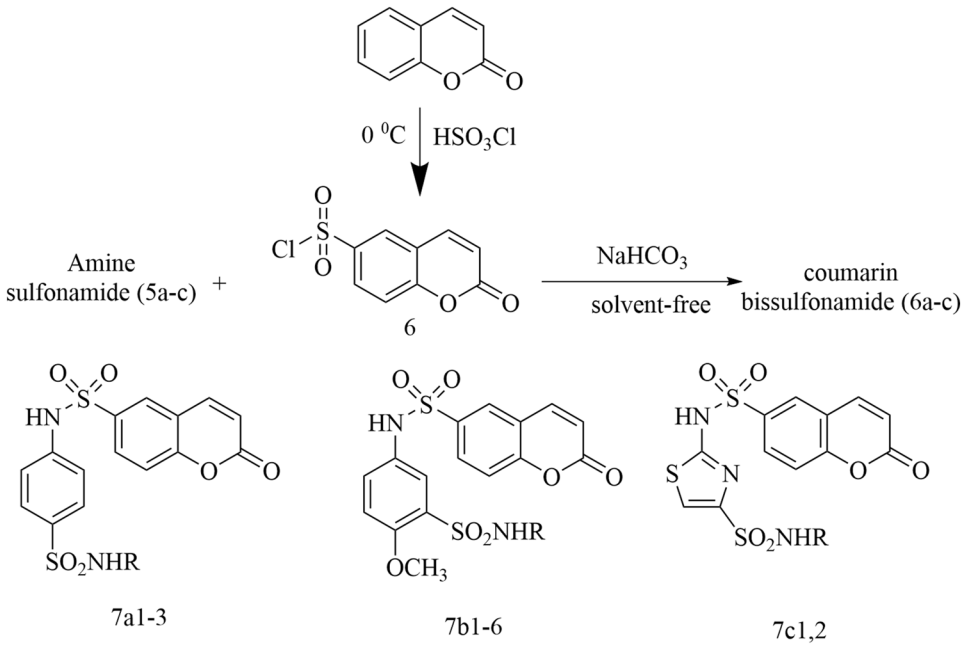


Fig. 6 The synthetic route of coumarin bissulfonamides ($7a_{1–6}$, $7b_{1–3}$, $7c_{1,2}$)

Experimental

Materials and measurements

All chemicals were purchased from Merck and Fluka chemical companies. Infrared spectra were recorded on a Perkin–Elmer VIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker (400 MHz) FT spectrometer in $CDCl_3$ and DMSO-d6. All of the reactions were conducted open to the atmosphere and the yields refer to the isolated products.

Synthesis of 2-Oxo-2H-chromene-6-sulfonyl chloride (6)

Chlorosulfonic acid (0.5 ml) was added slowly to coumarin (1 mmol, 0.146 g), at 0 °C and stirred for 30 min and then at room temperature for 60 min. After completion of the reaction (as it was shown by TLC) the mixture was poured into ice. The solid product was filtered, washed with cold water (10 ml) until the pH of water become about 7 and then dried. The product was obtained as white solid in 94% yield with high purity and used in the end step without any purification, m.p = 98–100 °C; white solid; R_f = 0.4 (50% ethyl acetate, 50% *n*-hexane); IR (KBr, cm^{-1}) = 1734 (CO), 1373, 1168 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 6.51 (1H,d, J = 9.6 Hz), 7.35 (1H,d, J = 8.4 Hz), 7.82 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 7.99 (1H,d, J = 2.0 Hz), 8.15 (1H,d, J = 9.6 Hz); ^{13}C NMR(100 MHz, DMSO) δ(ppm) = 116.5, 116.9, 118.5, 125.9, 129.7, 144.3, 144.8, 154.0, 160.4.

General procedure for the synthesis of Acetamides (2a–c)

The mixture of amine (10 mmol) and acetic anhydride (20 mmol) was triturated in mortar for 20 min at room temperature. The reaction was controlled by TLC. Then, the water was added (100 ml), and the solid products were filtered, washed with water, and dried. Acetamides (2a–c) were obtained as a powder in 84–87% yield and used in the next step without further purification.

General procedure for the synthesis of acetamide sulfonyl chlorides (3a–c)

Chlorosulfonic acid (0.6 ml) was added dropwise to acetamides ***2a–c*** (1 mmol) at 0 °C. The progress of the reactions was controlled by TLC. After completion of the reaction, the mixture was poured into ice and stirred for 5 min. Then, the mixture was filtered, washed with cold water until the pH of water becomes about 7. Then the solid product was dried at room temperature. The products were obtained as a white powder in 84–85% yield and used in the next step without further purification.

Table 3 Yield/reasction time data for the preparation of coumarin bissulfonamides (7a1–6, 7b1–3, 7c1,2) and coumarin sulfonamides (9a1–6) and their Antibacterial Activities

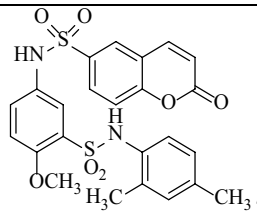
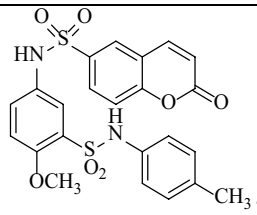
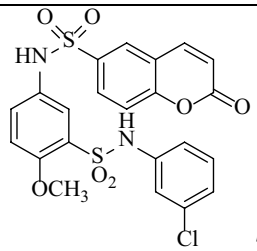
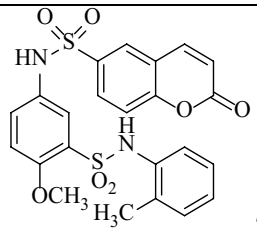
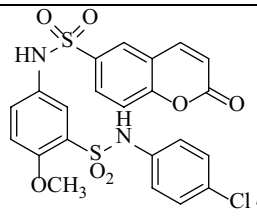
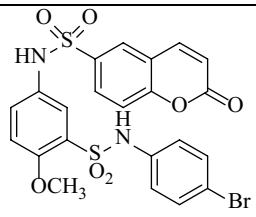
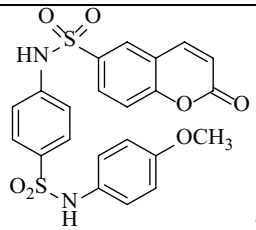
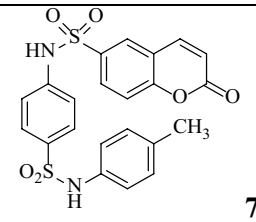
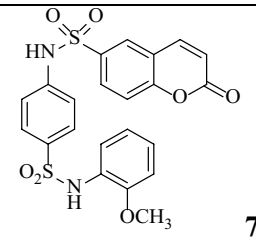
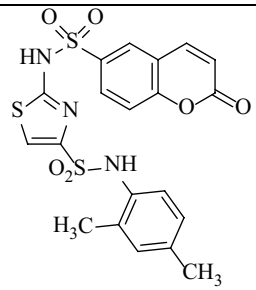
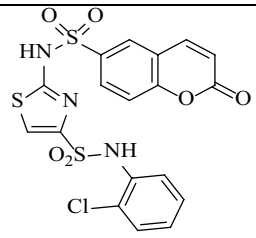
Entry	Coumarin sulfonamide (product number)	Time (min)	Yield[b] (%)	S. aureus (ATCC6538)	E. coli (ATCC35218)
1	 **7a$_1$**	22	87	12	11
2	 **7a$_2$**	24	89	14	11
3	 **7a$_3$**	35	86	14	11
4	 **7a$_4$**	25	88	14	14
5	 **7a$_5$**	45	85	12	14

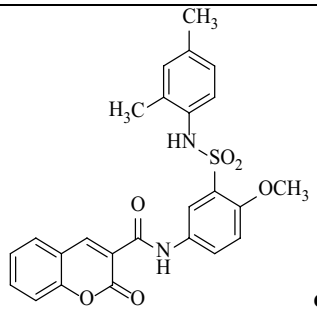
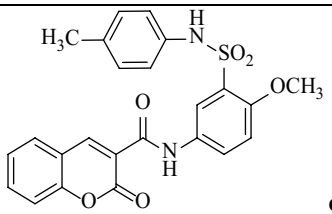
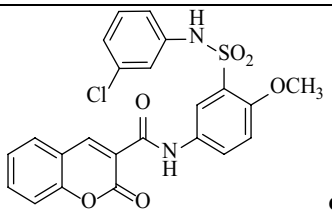
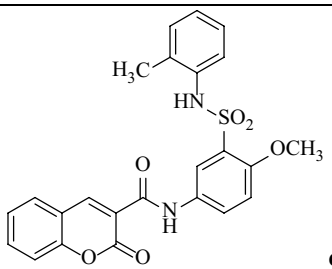
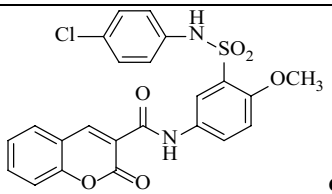
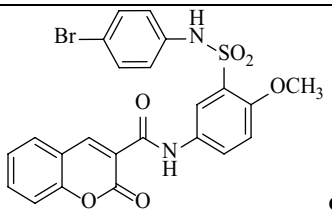
Table 3 (continued)

6	 **7a₆**	38	85	12	14
7	 **7b₁**	25	87	14	17
8	 **7b₂**	25	87	6	15
9	 **7b₃**	30	86	13	16
10	 **7c₁**	35	80	12	16
11	 **7c₂**	40	85	17	20

General procedure for the synthesis of acetamide sulfonamides (4a–c)

The procedure is simply grinding of 1 mmol acetamide sulfonyl chlorides (**3a–c**) with an amine (1 mmol) in a mortar in the presence of $NaHCO_3$ (0.5 g) at room temperature in the absence of any solvent. The reaction was controlled by TLC. After completion of the reaction the water was added (25 ml)

Table 3 (continued)

12	 **9a$_1$**	20	95	8	8
13	 **9a$_2$**	22	90	8	10
14	 **9a$_3$**	30	83	10	8
15	 **9a$_4$**	21	94	8	8
16	 **9a$_5$**	40	80	9	10
17	 **9a$_6$**	35	82	9	10
18	Ampicillin	–	–	17	9
19	Chloramphenicol	–	–	12	14

[a]Each value is an average of three independent determinations. [b] Isolated yield

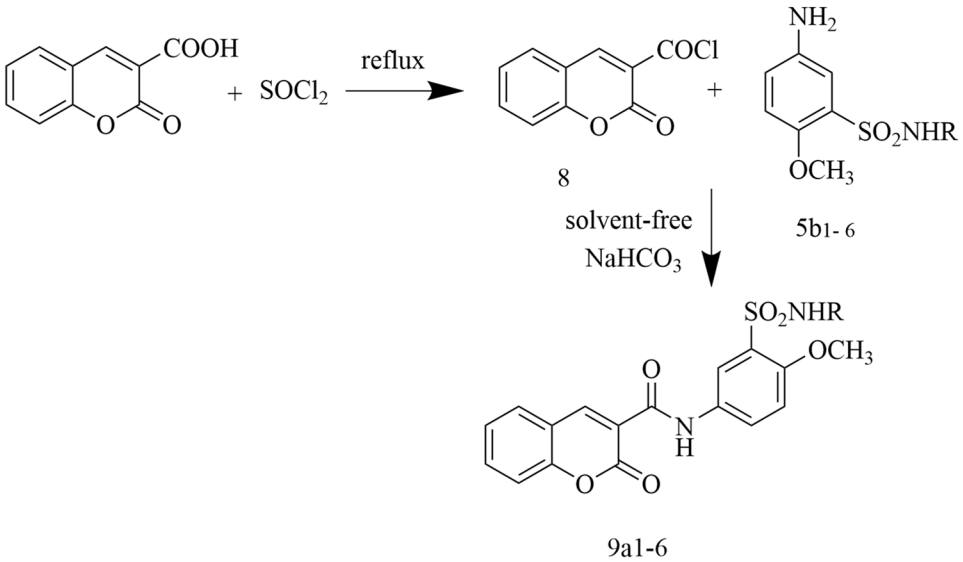


Fig. 7 The synthetic route for synthesizing coumarin sulfonamides ($9a_{1-6}$)

and stirred for 15 min. Then the mixture was filtered and dried. The products were obtained in 85–95% yields with high purity and used in the next step without any purification.

General procedure for the synthesis of amino sulfonamides (5a–c)

A mixture of 4 mmol acetamide sulfonamides, 3.6 ml H_2SO_4 70%, and 8 ml H_2O was refluxed for 30 min. The reaction was controlled by TLC. After completion of the reaction, the solution was cooled and natural with NaOH (5%). The precipitate was filtered, washed with water, and dried. Amine sulfonamides were obtained in 83–95% yields with high purity and used in the next step without any purification.

General procedure for the synthesis of coumarin disulfonamides (7a–c)

A mixture of amino sulfonamide (1 mmol), coumarin sulfonyl chloride (1 mmol), and $NaHCO_3$ (0.5 g) was triturated in the mortar at room temperature under solvent-free conditions. The reaction was controlled by TLC. After completion of the reaction, water was added and stirred for 5 min. Then the mixture was filtered washed with additional water and dried. Coumarin disulfonamides were obtained in high purity and elucidated by IR, ^{1}H-NMR, and ^{13}C-NMR.

Spectral data of the synthesized coumarin disulfonamides ($7a_{1-6}$, $7b_{1-3}$, $7c_{1,2}$)

N-(3-(N-(2,4-dimethylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6- sulfonamide **($7a_1$):** Color = Light Violet; m.p = 244–248 °C; Yield = 87%; R_f = 0.30 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3256 (N–H), 1729 (CO), 1158, 1338 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 1.99 ($3H_{Me}$, s), 2.17 ($3H_{Me}$, s), 3.81 ($3Ho_{Me}$, s), 6.63 ($1H_{arom}$, d, J = 9.56 Hz), 6.67 ($1H_{arom}$, d, J = 7.68 Hz), 6.73 ($1H_{arom}$, d), 6.89 ($1H_{arom}$, s), 7.14 ($1H_{arom}$, d, J = 8.4 Hz), 7.28 ($1H_{arom}$, s), 7.32 ($1H_{arom}$, d, J = 7.96 Hz), 7.47 ($1H_{arom}$, d, J = 8.2 Hz), 7.69 ($1H_{arom}$, d, J = 7.6 Hz), 8.09 ($1H_{arom}$, s), 8.15 ($1H_{arom}$, d, J = 9.16 Hz), 9.18 (s, $1H_{N-H}$), 10.24 (s, $1H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 17.34, 20.31, 56.08, 113.56, 117.55, 117.78, 118.84, 123.02, 126.33, 127.57, 127.97, 128.38, 129.05, 129.42, 131.00, 132.04, 134.24, 134.82, 135.53, 143.40, 153.61, 155.75, 159.07.

N-(3-(N-(4-methylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6-sulfonamide **($7a_2$):** Color = Cream; m.p = 150–153 °C; Yield = 89%; R_f = 0.27 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3263 (N–H), 1732 (CO), 1161, 1339 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 2.14 ($3H_{Me}$, s), 3.81 ($3Ho_{Me}$, s), 6.65 ($1H_{arom}$, d, J = 9.6 Hz), 6.85 ($2H_{arom}$, d, J = 8.3 Hz), 6.89 ($2H_{arom}$, d, J = 8.4 Hz), 7.06 ($1H_{arom}$, d, J = 9.2 Hz), 7.24 ($1H_{arom}$, dd, J_1 = 2.4 Hz, J_2 = 2.8 Hz), 7.50 ($1H_{arom}$, d, J = 2.8 Hz), 7.53 ($1H_{arom}$, d, J = 8.8 Hz), 7.76($1H_{arom}$, dd, J = 2 Hz), 8.12 ($1H_{arom}$, d, J = 2.4 Hz), 8.16 ($1H_{arom}$, d, J = 10 Hz), 9.87 (s, $1H_{N-H}$), 10.32 (s, $1H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 20.69, 56.76, 114.20, 118.11, 118.31, 119.39, 120.14, 124.23, 127.12, 128.12, 128.74, 129.72, 129.86, 130.01, 133.25, 135.37, 135.54, 143.93, 153.98, 156.28, 159.57.

N-(3-(N-(3-chlorophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6-sulfonamide **($7a_3$):** Color = Light Violet; m.p = 158–163 °C; Yield = 86%; R_f = 0.3 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3184 (N–H), 1711 (CO), 1164, 1341 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ

(ppm) = 3.80 ($3Ho_{Me}$, s), 6.64 ($1H_{arom}$, d, J = 9.6 Hz), 6.95 ($1H_{arom}$, d, J = 7.6 Hz), 7.02 ($2H_{arom}$, m), 7.10 ($1H_{arom}$, d, J = 9.2 Hz), 7.17 ($1H_{arom}$, t, J = 8 Hz), 7.28 ($1H_{arom}$, dd, J_1 = 2.4 Hz, J_2 = 2.8 Hz), 7.53 ($1H_{arom}$, d, J = 8.8 Hz), 7.56 ($1H_{arom}$, d, J = 2.8 Hz), 7.78($1H_{arom}$, dd, J_1 = 2.4 Hz, J_2 = 2 Hz), 8.11 ($1H_{arom}$, d, J = 2 Hz), 8.15 ($1H_{arom}$, d, J = 9.6 Hz), 10.36 (s, $2H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.84, 114.43, 117.92, 118.14, 118.35, 119.09, 119.43, 123.79, 124.14, 126.78, 128.09, 129.04, 129.95, 131.08, 133.66, 135.43, 139.66, 143.86, 154.05, 156.33, 159.58.

N-(3-(N-(2-methylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6-sulfonamide (**7a$_4$**)**:** Color = Light Violet; m.p = 126–129 °C; Yield = 88%; R_f = 0.45 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3258 (N–H), 1733 (CO), 1158, 1332 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 2.10 ($3H_{Me}$, s), 3.80 ($3Ho_{Me}$, s), 6.64 ($1H_{arom}$, d, J = 9.6 Hz), 6.86 ($1H_{arom}$, d, J = 7.6 Hz), 6.95 ($1H_{arom}$, d, J = 7.6 Hz), 7.02 ($1H_{arom}$, m), 7.09 ($1H_{arom}$, d, J = 7.2 Hz), 7.14 ($1H_{arom}$, m), 7.32 ($1H_{arom}$, d, J = 2.4 Hz), 7.34($1H_{arom}$, d, J = 2.4 Hz), 7.48($1H_{arom}$, d, J = 8.8 Hz), 7.71($1H_{arom}$, dd, J = 2.4 Hz), 8.07 ($1H_{arom}$, d, J = 2 Hz), 8.14 ($1H_{arom}$, d, J = 9.6 Hz), 9.29 (s, $1H_{N-H}$), 10.23 (s, $1H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 17.91, 56.58, 114.09, 115.64, 118.06, 118.27, 119.34, 123.66, 126.53, 126.61, 128.04, 128.66, 128.85, 128.97, 129.80, 129.95, 130.94, 134.58, 135.28, 135.47, 143.92, 154.10, 156.23, 159.61.

N-(3-(N-(4-chlorophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6-sulfonamide (**7a$_5$**)**:** Color = Light Violet; m.p = 181–184 °C; Yield = 85%; R_f = 0.24 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3205 (N–H), 1715 (CO), 1156, 1349 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 3.74 ($3Ho_{Me}$, s), 6.59 ($1H_{arom}$, d, J = 9.6 Hz), 6.94 ($1H_{arom}$, d, J = 9.2 Hz), 6.97 ($2H_{arom}$, dd, J = 8.8 Hz), 7.09 ($1H_{arom}$, d), 7.13 ($2H_{arom}$, dd, J = 8.8 Hz), 7.47 ($1H_{arom}$, d, J = 2.4 Hz), 7.48 ($1H_{arom}$, d), 7.80 ($1H_{arom}$, dd, J = 2 Hz), 8.09($1H_{arom}$, d), 8.16 ($1H_{arom}$, d, J = 9.6 Hz), 10.18 (s, $2H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.75, 114.13, 117.60, 117.98, 119.13, 121.05, 123.54, 126.66, 127.72, 128.31, 129.18, 130.13, 134.17, 137.52, 138.21, 144.12, 152.21, 155.65, 159.75.

N-(3-(N-(4-bromophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-6-sulfonamide (**7a$_6$**)**:** Color = Light Violet; m.p = 183–185 °C; Yield = 85%; R_f = 0.24 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3204 (N–H), 1718 (CO), 1156, 1349 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 3.79 ($3Ho_{Me}$, s), 6.65 ($1H_{arom}$, d, J = 10 Hz), 6.94 ($2H_{arom}$, d, J = 8 Hz), 7.07 ($1H_{arom}$, d, J = 8.8 Hz), 7.24 ($1H_{arom}$, d, J = 8 Hz), 7.31 ($2H_{arom}$, d, J = 8.4 Hz), 7.57 ($2H_{arom}$, m), 7.79($1H_{arom}$, d, J = 8.4 Hz), 8.14($1H_{arom}$, s), 8.18($1H_{arom}$, d, J = 9.6 Hz), 10.26 (s, $1H_{N-H}$), 10.38 (s, $1H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.81, 114.37, 116.09, 118.15, 118.44, 119.43, 121.50, 124.26, 126.70, 128.13, 128.96, 129.82, 129.97, 132.19, 135.46, 137.53, 143.82, 153.99, 156.33, 159.52.

N-(4-(N-(4-methoxyphenyl)sulfamoyl)phenyl)-2-oxo-2H-chromene-6-sulfonamide (**7b$_1$**): Color = Violet; m.p = 122–125 °C; Yield = 87%; R_f = 0.26 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3249 (N–H), 1736 (CO), 1155, 1328 (SO_2);): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.66 (s, $3H_{CH3}$), 6.36 (d, $1H_{arom}$, J = 9.6 Hz), 6.74 (d, $2H_{arom}$, J = 8.4 Hz), 7.10 (d, $2H_{arom}$, J = 8.4 Hz), 7.30 (d, $2H_{arom}$, J = 8.8 Hz), 7.33 (d, $1H_{arom}$, J = 8.0 Hz), 7.35 (s, $2H_{N-H}$), 7.69 (d, $2H_{arom}$, J = 8.8 Hz), 7.89 (d, $1H_{arom}$, J = 8.0 Hz), 7.97 (d, $1H_{arom}$, J = 8.0 Hz), 7.98 (s, $1H_{arom}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 55.14, 114.40, 115.62, 118.34, 119.91, 121.20, 122.70, 128.34, 129.70, 129.72, 129.74, 130.23, 134.55, 136.40, 140.63, 142.47, 156.40, 156.69 160.92.

N-(4-(N-(4-methylphenyl)sulfamoyl)phenyl)-2-oxo-2H-chromene-6-sulfonamide (**7b$_2$**): Color = Light Cream; m.p = 203–205 °C; Yield = 87%; R_f = 0.66 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3239, 3189 (N–H), 1711 (CO), 1152, 1323 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.16 (s, $3H_{CH3}$), 6.63 (d, $1H_{arom}$, J = 9.6 Hz), 6.88 (d, $2H_{arom}$, J = 8 Hz), 6.97 (d, $2H_{arom}$, J = 8.4 Hz), 7.22 (d, $2H_{arom}$, J = 8.8 Hz), 7.55 (d, $1H_{arom}$, J = 8 Hz), 7.58 (d, $2H_{arom}$, J = 8.8 Hz), 7.93 (dd, $1H_{arom}$, J_1 = 2.4 Hz, J_2 = 2.4), 8.16 (d, $1H_{arom}$, J = 9.6 Hz), 8.29 (d, $1H_{arom}$, J = 2 Hz), 10 (s, $1H_{N-H}$), 11.05 (s, $1H_{N-H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 20.74, 118.40, 118.42, 119.06, 119.51, 121.20, 128.33, 128.84, 129.94, 129.99, 133.88, 133.91, 134.49, 134.59, 135.24, 135.33, 141.81, 143.81, 156.55, 159.53.

N-(4-(N-(2-methoxyphenyl)sulfamoyl)phenyl)-2-oxo-2H-chromene-6-sulfonamide (**7b$_3$**): Color = Dark Cream; m.p = 120–122 °C; Yield = 86%; R_f = 0.23 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3247 (N–H), 1733 (CO), 1160, 1345 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.76 (s, $3H_{CH3}$), 6.36 (d, $1H_{arom}$, J = 9.6 Hz), 6.88 (d, $2H_{arom}$, J = 8.4 Hz), 7.10 (d, $2H_{arom}$, J = 8.4 Hz), 7.30 (d, $2H_{arom}$, J = 8.8 Hz), 7.33 (d, $1H_{arom}$, J = 8.0 Hz), 7.35 (s, $2H_{N-H}$), 7.69 (d, $2H_{arom}$, J = 8.8 Hz), 7.89 (d, $1H_{arom}$, J = 8.0 Hz), 7.97 (d, $1H_{arom}$, J = 8.0 Hz), 7.98 (s, $1H_{arom}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 55.07, 110.00, 115.69, 118.34, 119.92, 121.20, 123.84, 124.76, 125.60, 125.74, 128.36, 129.64, 130.23, 133.95, 136.40, 140.63, 142.47, 149.82, 156.99 160.92.

N-(2,4-dimethylphenyl)-2-((2-oxo-2H-chromene)-6-sulfonamido)thiazole-4-sulfonamide (**7c$_1$**)**:** Color = Cream; m.p = 159–161 °C; Yield = 80%; R_f = 0.5 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3256 (N–H), 1728 (CO), 1157, 1338 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 2.01 ($3H_{Me}$, s), 2.10 ($3H_{Me}$, s), 6.62 ($1H_{arom}$, d, J = 9.6 Hz), 6.78 ($1H_{arom}$, d, J = 8 Hz), 6.89 ($1H_{arom}$, d, J = 8.4 Hz), 6.98 ($1H_{arom}$, s), 7.59 ($1H_{arom}$, d, J = 8.8 Hz),

7.84 (1H_{arom}, dd, J = 2.0 Hz), 8.07 (1H_{arom}, d, J = 2.0 Hz), 8.19 (1H_{arom}, d, J = 9.6 Hz), 9.61 (2$H_{N\text{-}H}$, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 18.02, 20.79, 118.00, 118.10, 119.21, 127.29, 127.43, 127.78, 130.30, 131.89, 131.99, 135.09, 136.79, 136.97, 143.96, 156.09, 159.85.

N-(2-chlorophenyl)-2-((2-oxo-2H-chromene)-6-sulfonamido)thiazole-4-sulfonamide **($7c_2$):** Color = Light Cream; m.p = 169–171 °C; Yield = 74%; R_f = 0.53 (60% ethyl acetate, 40% *n*-hexane); IR (KBr, cm^{-1}) = 3241 (N–H), 1731 (CO), 1162, 1343 (SO_2); ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 6.62 (1H_{arom}, d, J = 9.6 Hz), 7.26 (3H_{arom}, m), 7.42 (1H_{arom}, m), 7.60 (1H_{arom}, d, J = 2.0 Hz), 7.91 (1H_{arom}, dd, J = 2.0 Hz), 8.14 (1H_{arom}, d, J = 2.4 Hz), 8.19 (1H_{arom}, d, J = 10 Hz), 10.19 (2$H_{N\text{-}H}$, s). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 118.12, 118.20, 119.32, 127.99, 128.35, 128.49, 129.92, 129.98, 130.34, 130.47, 133.57, 133.68, 136.79, 136.89, 143.98, 156.35, 159.63.

General procedure for the synthesis of coumarin-3-carbonyl chloride (8)

Coumarin-3-carboxylic acid (1 mmol) and thionyl chloride (1.2 mmol) were refluxed for 12 h. The progress of the reaction was controled by TLC. After completion of the reaction, the excess of thionyl chloride was distilled and the product was obtained as yellow light solid that was used in the next step.

General procedure for the synthesis of coumarin sulfonamides ($9a_{1\text{-}6}$)

A mixture of amino sulfonamid ($5a_{1\text{-}6}$) (1 mmol), coumarin carbonyl chloride (1 mmol, 0.208 g) and $NaHCO_3$ (1 mmol), was triturated in mortar at room tempreture under solvent-free conditions. The reaction was controled by TLC. After completion of the reaction, water (25 ml) was added and the mixture was stired for 5 min. The precipitate was filtered and dried. Coumarin sulfonamides ($8a_{1\text{-}6}$) were obtained in 80–95% yield and elucidated by IR and ^{1}H-NMR and ^{13}C-NMR.

Spectral data of the synthesized coumarin sulfonamides ($9a_{1\text{-}6}$)

N-(3-(N-(2,4-dimethylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **($9a_1$):** m.p = 270–274 °C**;** Yield = 95%; R_f = 0.33 (70% ethyl acetate, 30% *n* hexane)**;** IR (KBr, cm^{-1}) = 3374, 3268 (N–H), 1710,1664 (C = O), 1336, 1161 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.12 (s, 3 H_{CH3}), 2.16 (s, 3H_{CH3}), 3.90 (s, 3H_{OMe}), 6.8 (s, 2H), 6.9 (s, 1H), 7.26 (d, 1H, J = 9.2 Hz), 7.44 (t, 1H, J = 7.2 Hz), 7.52 (d, 1H, J = 8.0 Hz), 7.89 (d, 1H, J = 8.8 Hz), 7.95 (d, 1H, J = 7.6 Hz), 8.03 (s, 1H), 8.81 (s, 1H), 9.20 (s, 1$H_{N\text{-}H}$), 10.57 (s, 1$H_{N\text{-}H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 17.9, 20.8, 56.6, 113.6, 116.7, 118.8, 120.6, 121.7,125.7, 126.4, 126.9, 127.2, 128.5, 130.6, 10.8, 131.6, 132.7, 134.6, 134.7, 136.0, 147.5, 153.2, 154.3, 160.3, 160.4.

N-(3-(N-(4-methylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **($9a_2$):** m.p = 265–270 °C**;** Yield = 90%; R_f = 0.36 (70% ethyl acetate, 30% *n*-hexane)**;** IR (KBr, cm^{-1}) = 3262 (N–H), 1707, 1666 (C = O), 1327, 1149 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 2.14 (s, 3H_{CH3}), 3.89 (s, 3H_{OMe}), 7.0 (s, 1H), 7.17 (d, 1H, J = 9.2 Hz), 7.45 (p, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.76 (p, 1H, J = 8.0 Hz), 7.8 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 7.9 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 8.2 (d, 1H, J = 2.8 Hz), 8.85 (s, 1H), 9.85 (s, 1$H_{N\text{-}H}$), 10.60 Hz (s, 1$H_{N\text{-}H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 20.7, 56.7, 113.7, 116.7, 118.8, 120.4, 120.6, 120.8, 122.4, 125.7, 126.8, 129.8, 130.6, 130.9, 133.5, 147.6, 153.2, 154.3, 160.4, 160.4.

N-(3-(N-(3-chlorophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **($9a_3$):** m.p = 257–262 °C; Yield = 83%; R_f = 0.38 (70% ethyl acetate, 30% *n*-hexane)**;** IR (KBr, cm^{-1}) = 3247 (N–H), 1715, 1665 (C = O), 1324, 1156 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (pm) = 3.86 (s, 3H_{OCH3}), 7.0 (d, 1H, J = 7.6 Hz), 7.08 (d, 1H, J = 8.0 Hz), 7.15–7.25 (m, 3H), 7.45 (t, 1H, J = 7.6 Hz), 7.52 (d, 1H, J = 8.4 Hz), 7.76 (t, 1H, J = 7.6 Hz), 7.83 (d, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 7.6 Hz), 8.32 (s, 1H), 8.87 (s, 1H), 10.37 (s, 1$H_{N\text{-}H}$), 10.64 (s, 1$H_{N\text{-}H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.81, 113.95, 116.7, 118.0, 118.8, 119.2, 120.4, 122.3, 123.8, 125.7, 126.5, 127.2, 130.7, 131.2, 133.6, 134.7, 139.8, 147.7, 153.2, 154.3, 160.4, 160.4.

N-(3-(N-(2-methylphenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **($9a_4$):** m.p = 250–255 °C**;** Yield = 94%; R_f = 0.32 (70% ethyl acetate, 30% *n*-hexane); IR (KBr, cm^{-1}) = 3305, 3245 (N–H), 1711, 1661 (C = O), 1340, 1161 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.67 (s, 3H_{Me}), 3.90 (s, 3H_{OMe}), 6.8 (t, 1H, J = 7.2 Hz), 6.93 (d, 1H, J = 8.0 Hz), 7.05 (t, 1H, J = 7.6 Hz), 7.3 (dd, 2H, J_1 = 9.2 Hz, J_2 = 8.0 Hz), 7.4 (t,1H, J = 7.2 Hz), 7.5 (d, 1H, J = 8.4 Hz), 7.77 (t, 1H, J = 7.6 Hz), 7.8 (d, 1H, J = 8.8 Hz), 7.9 (d, 1H, J = 7.6 Hz), 8.1 (s, 1H), 8.63 (s, 1$H_{N\text{-}H}$), 8.84 (s, 1$H_{N\text{-}H}$); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.2, 56.8, 112.0, 113.5, 116.7, 118.8, 120.5, 120.9, 121.7, 123.5, 125.7, 126.0, 126.3, 126.7, 127.6, 130.6, 130.7, 134.7, 147.6, 151.6, 153.4, 154.3, 160.4, 160.4.

N-(3-(N-(4-chlorophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **($9a_5$):** m.p = 265–270 °C**;** Yield = 80%; R_f = 0.34 (70% ethyl

acetate, 30% *n*-hexane); IR (KBr, cm^{-1}) = 3327, 3268 (N–H), 1709, 1664 (C = O), 1342, 1161 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.87 (s, 3H_{OCH3}), 7.19 (d, 1H, J = 9.2 Hz), 7.20 (dd, 4H, J_1 = 58.08 Hz, J_2 = 9.4 Hz), 7.46 (p, 1H, J = 7.6 Hz), 7.53 (d, 1H, J = 8.4 Hz), 7.76 (p, 1H, J = 8.0 Hz), 7.83 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 7.9 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.6 Hz), 8.27 (d, 1H, J = 2.8 Hz), 8.87 (s, 1H), 10.23 (s, 1H_{N-H}), 10.63 (s, 1H_{N-H}); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.8, 113.8, 116.7, 118.8, 120.4, 121.5, 122.4, 125.7, 126.5, 127.1, 128.2, 129.4, 130.7, 131.0, 134.7, 137.2, 147.7, 153.2, 154.34, 160.44, 160.5.

N-(3-(N-(4-bromophenyl)sulfamoyl)-4-methoxyphenyl)-2-oxo-2H-chromene-3-carboxamide **(9a$_6$):** m.p = 261–265 °C; Yield = 82%; R_f = 0.36 (70% ethyl acetate, 30% *n*-hexane); IR (KBr, cm^{-1}) = 3322 (N–H), 1709, 1663(C = O), 1333, 1160 (SO_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) = 3.41 (s, 3H_{OCH3}), 7.24 (dd, 4H, J_1 = 128.8 Hz, J_2 = 1.6 Hz), 7.18 (d, 1H, J = 9.2 Hz), 7.45 (t, 1H, J = 7.2 Hz), 7.5 (d, 1H, J = 8.0 Hz), 7.76 (p, 1H, J = 8.0 Hz), 7.82 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 7.97 (dd, 1H,, J_1 = 8.0 Hz, J_2 = 1.2 Hz), 8.28 (d, 1H, J = 2.8 Hz), 8.87 (s, 1H), 10.25 (s, 1H_{N-H}), 10.64 (s, 1H_{N-H}); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) = 56.8, 113.8, 116.2, 116.2, 116.7, 118.8, 120.3, 121.8, 122.4, 125.7, 126.4, 127.1, 130.7, 131.0, 132.3, 134.7, 137.6, 147.7, 153.1, 154.3, 160.4, 160.5.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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