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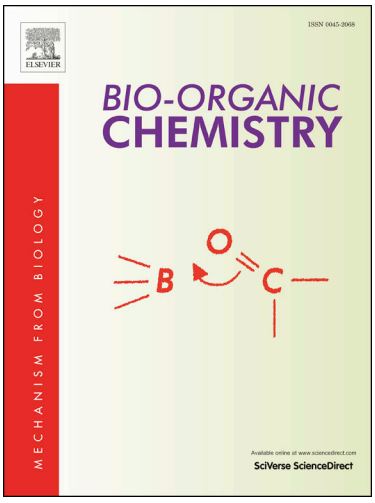

Ethylenic conjugated coumarin thiazolidinediones as new efficient antimicrobial modulators against clinical methicillin–resistant *Staphylococcus aureus*

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Title page

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Ethylenic conjugated coumarin thiazolidinediones as new efficient antimicrobial modulators against clinical methicillin-resistant *Staphylococcus aureu*s

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Abstract:

In an effort for the development of novel antimicrobial agents, ethylenic conjugated coumarin thiazolidinediones as potential multi-targeting new antimicrobial compounds were synthesized through convenient procedures from commercially available resorcinol and were evaluated for their antimicrobial potency. Bioactive evaluation revealed that some of the prepared compounds showed strong antimicrobial activities towards the tested microorganisms including clinically drug-resistant strains. Especially, propargyl derivative **12b** exhibited effective anti-MRSA potency with MIC value of 0.006 μmol/mL, which was highly advantageous over clinical antibacterial drug norfloxacin. Compound **12b** showed rapid killing effect, low toxicity against hepatocyte LO2 cells line, and no obvious drug resistance development against MRSA. Preliminary exploration of action mechanism manifested that molecule **12b** acted upon MRSA through forming stable supramolecular complex with bacterial DNA which might impede DNA replication. Molecular docking showed that compound **12b** could bind with DNA-gyrase through hydrogen bonds.

***Keywords*:** Coumarin, Thiazolidinedione, Antimicrobial, MRSA, DNA

1. Introduction

In recent years, antibiotic-resistant pathogens have spread rapidly since its emergence, which is one of the greatest threats to modern medicinal development and mankind [1]. *Staphylococcus aureus* (*S. aureus*), notorious for its ability to produce a series of virulence factors, is categorized as kind of fatal pathogen responsible for community- and hospital-acquired infections [2,3]. Particularly, the complicated treatments of methicillin-resistant *S. aureus* (MRSA) infections have increased the morbidity and mortality of patients [4]. Isolated strains of MRSA have developed resistance to a series of antibacterial drugs, including β-lactams, macrolides, fluoroquinolones, glycopeptides and oxazolidinones [5]. However, the emergence of multi-resistant MRSA strain and complicated treatments mean that it is urgent for researchers to explore new treatment strategies [6].

Poor penetration of compounds across the microbial membrane is the greatest challenge for the discovery of novel antimicrobial drugs. Natural products have been used to treat disease for thousands of years and play an essential role in the discovery and development of drugs [7]. Some natural products, which can break through the penetration barriers, are historically significant as lead compounds for antimicrobials [8]. Coumarins are a vast class of natural products widely occurring as secondary plant metabolites [9]. More than 1800 different natural and synthetic coumarins have been discovered and applied to date, and many of them exhibited high level of biological activities including insecticidal, antioxidant, anticancer, anti-HIV, antimicrobial, and antibiotic [10–12]. Series of naturally occurring coumarin based antibiotics such as novobiocin, chlorobiocin and coumermycin A1 have been used successfully in clinic (Fig. 1). Especially, novobiocin has a good inhibitory effect on DNA gyrase, which exerts antibacterial ability *via* inhibition of ATPase activity of bacterial DNA gyrase in competition with ATP binding to the B subunit of the enzyme [13,14]. In addition, some investigators have focused on structural modification of the coumarin skeleton in the benzene ring, lactone ring or both, and found that the resulted coumarin derivatives showed good antimicrobial potential [15]. Consequently, the in-depth researches toward coumarin compounds for potential antimicrobial agents have gained much more attentions.

Fig. 1

Thiazolidinedione is an important heterocyclic fragment in design and development of novel medicinal agents concerning biological activity, including antihyperglycemic, anticancer, antiarthritic, antiinflammatory and antimicrobial [16,17]. The unique five membered structure of thiazolidinedione ring with carbonyl groups at 2- and 4-positions which acts as electron-accepting group along with NH and –S– as electron-donating groups is favorable to effectively interact with biologically important species such as DNA, enzymes and receptors [18]. The representative exploration of clinical thiazolidinedione drugs like pioglitazone and its analogues as antidiabetic agents, and GSK1059615 as first clinical PI3K inhibitor [19,20], have been motivating medicinal chemists to develop more effective bioactive molecules from the thiazolidinedione moiety. Especially, the substitution at 5-position of thiazolidinedione brings out the greatest change in structure and properties of thiazolidinedione with potent antimicrobial activity [21]. Furthermore, the introduction of different substituents on

NH group of thiazolidinedione, which might be beneficial to improve solubility and interaction with biomolecular targets, has been an important and prevalent strategy to modify thiazolidinedione analogues for the potential clinical drugs [22].

Molecular hybridization strategy is to integrate two or more pharmacophoric units into one molecular scaffold with possibly different modes of action [23]. The multifunctional attributes of these hybrids offer multiple biological activities, high selectivity and favorable pharmacokinetics, which renders hybrid molecules a rationally attractive source for current drug discovery [24]. In our previous work, we found that the introduction of thiazolidinedione to berberine showed great capacity to treat microorganisms, especially MRSA. The antibacterial mechanism showed that the suppression was accounted for dual roles of blocking bacterial DNA replication and intercalating into DNA with excellent antimicrobial activity [25]. In view of the above factors, it is quite interesting for us to combine the thiazolidinedione moiety and coumarin ring *via* an ethylenic bond bridge to develop a new structural framework of potentially antimicrobial agents (Fig. 2).

Fig. 2

The design of target ethylenic conjugated coumarin thiazolidinediones were mainly based on the following three considerations: (1) the ethylenic bond-bridged new π-conjugated skeleton expanded the conjugated system of coumarin ring and helpfully enhanced the DNA binding affinity of target molecules; (2) the different coupled positions of coumarin ring with thiazolidinedione were considered with aim to evaluate their contribution to antimicrobial activities; (3) various alkyl and unsaturated hydrocarbon chains with different lengths were introduced in order to regulate the binding affinity as well as lipid-water partition coefficient, while the substituents like chloro- and fluoro- on phenyl groups were considered to affect the pharmacological properties by modulating lipophilicity and cell membrane permeability, thus influencing the rate of transport and absorption of drugs.

All the synthesized ethylenic conjugated coumarin thiazolidinediones were characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectral analysis, and were screened for their antibacterial and antifungal activities *in vitro*. Compound **12b** was selected to be further investigated for its interaction with DNA to explore the DNA binding efficacy and antimicrobial mechanism. To identify the effect of **12b** on cell viability, the cytotoxicity was tested against human hepatocyte LO2 cell line. Bacterial membrane permeabilization was implemented to evaluate drug uptake. Further experiments including bactericidal kinetic assay, drug resistance development, and theoretical investigation of molecular docking were also performed to verify the prospect of the most active compound.

2. Results and discussion

2.1. Chemistry

The commercial resorcinol, malic acid, ethylacetoacetate and 4-chloroacetoacetate were employed as starting materials to synthesize the target ethylenic conjugated coumarin thiazolidinediones, which were prepared *via* multistep reactions including cyclization, formylation, hydrolysis, oxidation, electrophilic substitution and Knoevenagel condensation reaction, as outlined in **Schemes 1** and **2**. Condensation of resorcinol **1** with malic

acid, ethylacetoacetate or 4-chloroacetoacetate ethyl ester in concentrated sulfuric acid at 0 °C respectively afforded coumarin derivatives **2a–b** and **5** with high yields (81.2–90.0%). Compounds **2a–b** were easily formylated by hexamethylenetetramine (HMTA) using glacial acetic acid as solvent to produce the corresponding coumarin aldehydes **3a–b** in yields of 10.0–24.0%. The hydrolysis of 4-chloromethyl-7-hydroxycoumarin **5** in boiling water produced 7-hydroxy-4-(hydroxymethyl) coumarin **6** with 92.0% yield, which was further oxidized by manganese dioxide to give 4-formyl-7-hydroxycoumarin **7** in yield of 41.0%. Intermediates **3a–b** and **7** underwent condensation reaction with thiazolidinedione in anhydrous ethanol using piperidine as base to afford the target compounds **4a–b** and **8** with moderate yields of 51.9–66.0%.

The antibacterial activities of all the ethylenic conjugated coumarin thiazolidinediones (**4a-b** and **8**) were tested, and we found that 4-methyl-8-thiazolidinedionyl coumarin derivative **4b** showed more efficient antimicrobial ability than compounds **4a** and **8**. On the purpose of investigating the essential influence of various substituents on the antimicrobial activity, the structure of compound **4b** was further modified by various substituents including aliphatic bromides, benzyl halides and 2-bromoethanol. Much effort in modifying the 7-hydroxyl group of compound **4b** is confronted with the side reaction of NH substitution. According to previous researches, NH group should be preserved to increase aqueous solubility and enhance DNA affinity. Therefore, another synthetic route was adopted starting from compound **3b** as shown in **Scheme 2**. The 7-hydroxyl group of compound **3b** was substituted by a variety of saturated or unsaturated alkyl bromides using potassium carbonate as base in *N,N*-dimethylformamide (DMF) at 80 °C to give corresponding aliphatic derivatives **9a–g** and **11a–b** with good yields (73.1–85.8%). They were further reacted with thiazolidinedione to produce the various desirable ethylenic conjugates of coumarin thiazolidinediones **10a–g** and **12a–b** in 48.6–75.4% yields, respectively. A series of target phenyl coumarin thiazolidinediones derivatives **15a–e** were also synthesized under similar reaction conditions from intermediate **3b** by reacting with the substituted benzyl chlorides and then condensing with thiazolidinedione. In order to investigate whether the substituents at NH group would decrease, retain or improve the antimicrobial activity, the target compounds **13a–b** were effectively prepared by similar reaction starting from intermediates **12a–b** with the same aliphatic bromides. All the newly synthesized ethylenic conjugated coumarin thiazolidinediones were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectra.

Scheme 1

Scheme 2

2.2. Analysis of configuration (E or Z)

When thiazolidinedione was reacted with coumarin aldehydes **3**, **7**, **9**, **11** and **14** respectively by the Knoevenagel condensation, theoretically there are two isomers on tautomeric equilibrium. In order to identify the structure of the isomers, the single crystal of the compound **13a** was cultured and the single crystal X-ray diffraction analysis (Fig. 3) showed that the thiazolidinedione fragment and coumarin ring *via* an ethylenic bond bridge generated a new structural type with *Z* configuration. It was possible that the *E* configuration was generally unstable, and it easily converted to the Z configuration.

2.3. Biological activity

All newly synthesized ethylenic conjugated coumarin thiazolidinediones were evaluated for *in vitro* antibacterial and antifungal activity against five Gram-positive bacteria, six Gram-negative bacteria and four fungal strains recommended by the Clinical and Laboratory Standard Institute (CLSI) using the referenced antimicrobial drugs norfloxacin and fluconazole as positive controls.

2.3.1. Antibacterial activity

The result for antibacterial activity (Table 1) showed that some of the newly synthesized ethylenic conjugated coumarin thiazolidinediones exhibited potent efficacy comparable to reference drug norfloxacin against the tested bacterial stains.

We sought to establish the structure-activity relationship (SAR) for this class of compounds by introducing thiazolidinedione on the three different coumarin rings, and then choosen the best antimicrobial activity coumarin ring and modified the C-7 hydroxyl group of coumarin skeleton by different length of "C-linker" aliphatic chains, hydroxyethyl fragment and substituted aromatic rings to investigated their antimicrobial effects. Preliminary biological screening showed that 8-thiazolidinedionyl coumarin derivatives 4a and 4b possessed slightly better antibacterial efficacy than 4-thiazolidinedionyl coumarin derivative 8. At the same time, 4-methyl-8-thiazolidinedionyl coumarin 4b was superior to coumarin 4a without substitution at the C-4 position of 8-thiazolidinedionyl group in antibacterial activity, especially against Gram-negative bacteria. Most of the 7-hydroxyl thiazolidinedione coumarin derivatives exhibited moderate to good antibacterial activities against MRSA, *K. pneumonia* and *A. baumanii*, demonstrating the rationality of our design strategy.

Compounds **10a–b** and **12a–b** displayed excellent antibacterial activity with MIC (0.006 to 0.012 μmol/mL) against MRSA in comparison with norfloxacin with MIC = 0.025 μmol/mL. Particularly, compounds **12a** and **12b** were the most potent inhibitors of MRSA (MIC = 0.006 μmol/mL), which showed 4-fold higher inhibitory activity than norfloxacin. Ethylenic conjugated coumarin thiazolidinediones **12a-b** with short unsaturated alkyl chain showed better inhibitory activity than short saturated alkyl derivatives **10a** and **10b** against MRSA. Compounds with long saturated alkyl chain (i.e., **10c**, **10d**, **10e**, **10f**) didn't suppress the growth of MRSA effectively. The above results demonstrated that the introduction of the short unsaturated hydrocarbons and aliphatic chains could significantly strengthen antibacterial activity, which might regulate the lipid-water partition coefficient and binding affinity to target enzymes. Furthermore, when the NH position of compounds **12a** and **12b** were substituted by the same unsaturated hydrocarbons, the antibacterial abilities decreased about 56 folds with MIC values of 0.167 and 0.338 μmol/mL, indicating that the NH group could strengthen antibacterial ability by its weak interactions with biological targets.

Most of derivatives with MIC (0.047 to 0.387 μmol/mL) were found to improve antibacterial activities against *K. pneumonia* in comparison with norfloxacin (MIC = 0.401 μmol/mL). Especially, compound **12b** was identified as the most potent inhibitor of *K. pneumonia* (MIC = 0.047μmol/mL), around 9-fold higher inhibitory activity than norfloxacin. Noticeably, coumarin halophenyl derivatives **15b**–**d** also had higher levels of bacterial growth inhibition activities against *K. pneumonia* with MIC values of 0.311, 0.139 and 0.278 μmol/mL, respectively. This

manifested that the lipophilicity and membrane permeability might be increased by the introduction of halogen atoms, which could be helpful for the rate of absorption as well as transportation of drugs to strengthen the antibacterial activities.

The antibacterial evaluation showed that MRSA was sensitive to most of the ethylenic conjugated coumarin thiazolidinediones, especially compounds **12a** and **12b**. Most of target compounds could not inhibit the growth of *S. aureus* ATCC 25923, *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. coli, E. faecalis, P. aeruginosa, E. coli* ATCC 25922 effectively. Modification of compound **4b** indicated that the short unsaturated hydrocarbon and alkyl chain derivatives at the C-7 of coumarin ring were much more potent than the other substituents.

Table 1

2.3.2. Antifungal activity

The data for antifungal activity listed in **Table S1** displayed that most of the target ethylenic conjugated coumarin thiazolidinediones showed comparable or better antifungal activity than reference drug. Compounds **10a**–**b** and **12a**–**b** (MIC = 0.006–0.012 μmol/mL) exhibited superior inhibition against the growth of *A. fumigates*, at least 139 folds more potent than fluconazole (MIC = 1.672 μmol/mL). It was found that the short unsaturated hydrocarbon and alkyl chains significantly strengthened antifungal activity. Similarly, benzyl derivatives had better activities than ethylenic conjugated coumarin thiazolidinediones unsubstituted at C-7 hydroxyl group. In the series of compounds **15a**–**e**, compound **15e** showed the best anti-*A. fumigates* activity. It implied that strong electron-withdrawing groups on phenyl ring were beneficial to antifungal activities. Notably, *C. tropicals* was more valuable to compounds **4b**, **10a**–**b**, **12a**–**c** and **15a**–**e** (MICs = 0.023–0.371 μmol/mL) than fluconazole (MIC = 0.836 μmol/mL).

All the antimicrobial results revealed that the antimicrobial efficacies of ethylenic conjugated coumarin thiazolidinediones is due to not only the modification of thiazolidinedione on coumarin ring but also the substitution at 7-position of coumarin skeleton. In particular, ethylenic conjugated coumarin thiazolidinedione compound **12a** bearing a propenyl chain and compound **12b** with a propinyl chain exhibited unprecedentedly effective inhibition toward MRSA with the same low MIC (0.006 μmol/mL), and they could be further studied as potentially antimicrobial agents.

2.4. Bactericidal kinetics

It is well-known that antibacterial effect can be evaluated through the rate of bactericidal activity [26]. To explore the antibacterial potency of compound **12b**, the kinetics of killing MRSA were investigated for compound **12b** bearing a propinyl chain. As shown in Fig. 4, compound **12b** (4 × MIC) was superior to norfloxacin with 5 log CFU/mL reduction within 3 h, suggesting that it possessed bacteriostatic and bactericidal effects.

Fig. 4

*2.5. Development of resistance to compound **12b***

The ever-growing risk of bacterial resistance is a critical concern, and it is the most dreadful that the various

antimicrobial resistant bacterial strains caused serious complications [27]. However, antibacterial agents that induce the death of resistant bacterial strains are deficient [28]. Thus, researches on the resistance of the highly active compound **12b** against the microbial strains were significantly essential. Due to the excellent effect of compound **12b** against MRSA, the susceptible MRSA was chosen as an experimental strain for measuring drug resistance, and norfloxacin was taken as control. The bacterial resistance of compound **12b** remained unchanged after 16 passages, whereas MRSA developed resistance against norfloxacin after six passages, suggesting that compound **12b** was harder to induce drug resistance than norfloxacin (Fig. 5).

Fig. 5

2.6 Cytotoxicity

Cytotoxicity is an important consideration for the development of potential drug candidates. Therefore, compound **12b** was further examined for their cytotoxicity by MTT assay against the growth of human hepatocyte LO2 cells [29]. It was evident from the results (Fig. 6) that the compound **12b** didn't show any appreciable cytotoxicity and cells were significantly alive even after 24 h or 48 h, and more than 95% of cells were viable at the lowest concentration (0.8 μM). Therefore, compound **12b** showed the low toxicity, implying no obvious harm to the human body.

Fig. 6

2.7. Bacterial membrane permeabilization

Bacterial membrane active agents are topical antibacterial compounds that permeabilize bacterial membranes, thus enhancing drug uptake. While Gram-positive bacteria are surrounded by an inner membrane and a thick layer of cell wall [30], this structure forms a physical barrier that renders Gram-positive bacteria naturally resistant to many antibacterial agents. These facts adequately illustrate the significance of membrane active molecules. Herein, the disruption of bacterial membrane of compound **12b** was evaluated by utilizing propidium iodide (PI) dye. If it can target or interact with cell membrane, compound **12b** will pass through the compromised cell membranes and increase fluorescence with a complex formed by DNA. The fluorescence intensity of experimental group (in the presence of compound **12b**) gradually increased with time and then stabilized, while the control group almost showed no change (Fig. 7). It indicated that compound **12b** could effectively permeate the membrane of MRSA.

Fig. 7

*2.8. Interactions of compound **12b** with MRSA DNA*

Previous work revealed that coumarins could effectively interact with DNA through its excellent DNA binding affinity [31]. As is well known to us, DNA is used for storing genetic information to continue the life and can also be considered as a multiple-site target for the design and synthesis of efficient antimicrobial drugs [32]. Therefore, to investigate the possible antimicrobial mechanism, the binding behavior of compound **12b** with isolated

drug-resistant MRSA DNA were investigated by UV-vis spectroscopy using spectral probe of neutral red.

*2.8.1. Absorption spectra of DNA in the presence of compound **12b***

The UV-Vis absorption in Fig. 8 showed a red-shift peak for the maximum absorption of DNA with proportional increasing concentrations of compound **12b**. It was observed that the absorption value of **12b**-DNA complex was a little smaller than the simply sum of free DNA and free compound **12b**, in line with previous studies [33,34], which suggested the hypochromism of the complex of DNA and compound **12b**. This implied the intercalation of the aromatic chromophore of compound **12b** into the helix and the aromatic chromophore was in close proximity to the DNA bases.

Fig. 8

2.8.2. Absorption spectra of NR interaction with DNA

In order to further explore the mode of action of molecule **12b** and MRSA DNA, this work used neutral red (NR) as spectral probe. As shown in Fig. S2, with the increasing concentration of MRSA DNA, the NR absorption peak around 460 nm gradually decreased and a new band at around 530 nm appeared, which accounted for the formation of DNA–NR complex. At the same time, the formation of DNA-NR complex was also revealed by the signal occurrence of an isosbestic point at 504 nm.

*2.8.3. Absorption spectra of competitive interaction of compound **12b** and NR with DNA*

The competitive binding of NR and compound **12b** with DNA was shown in Fig. 9. With the increasing concentration of compound **12b**, the maximum absorption peak of DNA-NR complex at 530 nm decreased, which was opposite with the absorption of free NR as the concentrations of DNA increased. This showed that compound **12b** replaced NR and intercalated in the double helices of MRSA DNA. Therefore, it was further manifested that compound **12b** could exert the antibacterial activities by intercalating into DNA to block its replication.

Fig. 9

2.9. Molecular docking

To further rationalize the observed antimicrobial activity, a flexible ligand-receptor docking investigation was undertaken against gyrase-DNA complex (PDB code: 2XCS) [35,36]. Molecular docking (Fig. 10) demonstrated that the carbonyl group of thiazolidinedione moiety could bind with the active site ARG1122 in a non-covalent binding mode. The oxygen atom of carbonyl group in thiazolidinedione ring was adjacent to the ARG1122, forming two hydrogen bonds with distances of 2.8 and 3.3 Å, respectively. The hydrogen bonds could be helpful for the stability of the **12b**-DNA complex, which might be responsible for the good inhibitory efficacy of compound **12b** against MRSA.

Fig. 10

3. Conclusion

A class of new ethylenic conjugated coumarin thiazolidinediones as potential antimicrobial agents were developed *via* some appropriate and productive synthetic routes. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectra. The antimicrobial evaluation *in vitro* revealed that some target compounds manifested better efficacy toward the tested strains of bacteria and fungi in comparison with the reference drugs norfloxacin and fluconazole. Moreover, the SAR study indicated that the type of substituents on the 7-hydroxyl group of coumarin skeleton was an important influencing factor on antimicrobial potency and most of the aliphatic and benzyl substituents exerted relatively potent antimicrobial activities. Especially, compound **12b**, the ethylenic conjugated coumarin thiazolidinediones with propargyl group, exhibited excellent unexpected interference and inhibitory ability toward MRSA (MIC = 0.006 μmol/mL) and drug-resistant *A. fumigates* (MIC=0.012 μmol/mL). In addition, it showed no toxicity against LO2 cell line and did not prompt resistance development in MRSA. Preliminary mechanism studies demonstrated that the active molecule **12b** might target on cell membrane and DNA by intercalating into MRSA DNA to form a steady **12b**-DNA complex, which might shut off DNA replication to inhibit the growth of MRSA. Moreover, molecular calculation study showed the binding between compound **12b** and gyrase-DNA complex though hydrogen bonds. These results strongly demonstrated that compound **12b** bearing propargyl group at C-7 position of coumarin ring would have enormous possibilities as new bactericidal compound, especially as a multi-targeting anti-MRSA agent.

4. Experimental protocols

4.1. General methods

All commercially available solvents and reagents were purchased without further purification. Melting points were determined with X–6 melting point apparatus. TLC analysis was done using pre-coated silica gel plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on AVANCE III 600 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts were reported in parts per million (ppm), the coupling constants (*J*) were expressed in hertz (Hz) and signals were described as singlet (s), doublet (d), triplet (t), quartet (q) as well as multiplet (m). Mass spectra were recorded on an LCMS-2010A, the high-resolution mass spectra (HRMS) were analyzed by an IonSpec FTICR mass spectrometer with ESI resource.

*4.1.1. General procedures for the preparation of hydroxycoumarin and coumarin aldehydes (***2a**–**b**, **3a–b** and **5**–**7***)*

Compound **2a**–**b**, **3a–b** and **5**–**7** were obtained according to the synthetic methods reported in literature [37,38].

*4.1.2. General procedures for the preparation of aliphatic and aromatic coumarin derivatives (***9a–f**, **11a–c** and **14a–e***)*

Compound **9a–f**, **11a–c** and **14a–e** were obtained through the previously reported methods in literature [39].

*4.1.3. Synthesis of 7-ethoxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**9a**)*

Compound **3b** (350 mg, 1.7 mmol) and potassium carbonate (355 mg, 2.6 mmol) were stirred in N,N-Dimethylformamide (50 mL) at 80 ^{o}C for 1 h, then the bromoethane (280 mg, 2.6 mmol) was added and the

temperature maintained at 80 °C for 6 h. After cooling at room temperature, the reaction mixture was diluted with water (25 mL) and extracted with chloroform (3 × 20 mL). The organic phase was concentrated under vacuum. The crude product was purified by gel column chromatography (eluent, petroleum ether/chloroform (20/1, V/V)) to afford the desired compound **9a** (321 mg, 80.6%) as yellow solid. Mp: 210–212 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.65 (s, 1H, C*H*O), 7.72 (d, *J* = 8.9 Hz, 1H, coumarin-5-*H*), 6.93 (d, *J* = 8.9 Hz, 1H, coumarin-6-*H*), 6.19 (s, 1H, coumarin-3-*H*), 4.24 (q, *J* = 6.9 Hz, 2H, OCH_2CH$_3$), 2.41 (s, 3H, coumarin-4-CH_3), 1.52 (t, *J* = 6.9 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 187.1 (*C*HO), 162.6 (O*C*=O), 159.6, 155.2, 151.9, 130.6, 113.5, 112.9, 112.6, 108.6, 65.4 (O*C*H$_2$), 18.8 (coumarin-4-*C*H$_3$), 14.5 (OCH$_2$*C*H$_3$) ppm.

*4.1.4. Synthesis of 4-methyl-2-oxo-7-propoxy-2H-chromene-8-carbaldehyde (**9b**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 1-bromopropane (320 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **9b** (342 mg, 81.7%) as light yellow solid. Mp: 158–159 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.67 (s, 1H, C*H*O), 7.72 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 6.93 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.19 (s, 1H, coumarin-3-*H*), 4.12 (t, *J* = 6.4 Hz, 2H, OCH_2CH$_2$CH$_3$), 2.41 (s, 3H, coumarin-4-CH_3), 1.94–1.88 (m, 2H, OCH$_2$CH_2CH$_3$), 1.09 (t, *J* = 7.4 Hz, 3H, O(CH$_2$)$_2$CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 187.1 (*C*HO), 162.8 (O*C*=O), 159.6, 155.3, 151.8, 130.6, 113.5, 113.0, 112.6, 108.6, 71.1 (O*C*H$_2$), 22.4, 18.8 (coumarin-4-*C*H$_3$), 10.4 ppm.

*4.1.5. Synthesis of 7-butoxy-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**9c**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 1-bromobutane (356 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **9c** (380 mg, 85.8%) as yellow solid. Mp: 154–155 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.65 (s, 1H, C*H*O), 7.72 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 6.93 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.18 (s, 1H, coumarin-3-*H*), 4.16 (t, *J* = 6.4 Hz, 2H, OCH_2(CH$_2$)$_2$CH$_3$), 2.41 (s, 3H, coumarin-4-CH_3), 1.89–1.83 (m, 2H, OCH$_2$CH_2CH$_2$CH$_3$), 1.58–1.51 (m, 2H, O(CH$_2$)$_2$CH_2CH$_3$), 1.00 (t, *J* = 7.4 Hz, 3H, O(CH$_2$)$_3$CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 187.1 (*C*HO), 162.9 (O*C*=O), 159.6, 155.2, 151.9, 130.6, 113.5, 113.0, 112.6, 108.6, 69.4 (O*C*H$_2$), 30.9, 19.1, 18.8 (coumarin-4-*C*H$_3$), 13.7 ppm.

*4.1.6. Synthesis of 7-(decyloxy)-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**9f**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 1-bromodecane (575 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **9f** (476 mg, 81.3%) as yellow solid. Mp: 201–202 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H, C*H*O), 7.97 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.22 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.30 (s, 1H, coumarin-3-*H*), 4.21 (t, *J* = 6.4 Hz, 2H, OCH_2(CH$_2$)$_8$CH$_3$), 2.42 (s, 3H, coumarin-4-CH_3), 1.80–1.74 (m, 2H, OCH$_2$CH_2(CH$_2$)$_7$CH$_3$), 1.44 (dd, *J* = 15.0, 7.5 Hz, 2H, O(CH$_2$)$_2$CH_2(CH$_2$)$_6$CH$_3$), 1.33 (t, *J* = 10.7 Hz, 2H, O(CH$_2$)$_3$CH_2(CH$_2$)$_5$CH$_3$), 1.28–1.22 (m, 10H, O(CH$_2$)$_4$(CH_2)$_5$CH$_3$), 0.85 (t, *J* = 6.9 Hz, 3H, O(CH$_2$)$_9$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 187.46 (*C*HO), 163.21 (O*C*=O), 159.62, 154.08, 153.71, 132.48, 113.64, 112.65, 112.16, 109.88, 69.86 (O*C*H$_2$), 31.74, 31.13, 29.37, 29.10, 28.82, 25.77, 22.53, 18.8 1(coumarin-4-*C*H$_3$), 14.55, 14.38 ppm.

*4.1.7. Synthesis of 7-(allyloxy)-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**11a**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 3-bromoprop-1-ene (315 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **11a** (327 mg, 78.7%) as yellow solid. Mp: 172–173 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.68 (s, 1H, C*H*O), 7.73 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 6.94 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.20 (s, 1H, coumarin-3-*H*), 6.06 (ddd, *J* = 15.5, 10.2, 4.8 Hz, 1H, C*H*=CH_2), 5.54 (d, *J* = 17.2 Hz, 1H, CH=CH_2), 5.37 (d, *J* = 10.7 Hz, 1H, CH=CH_2), 4.75 (d, *J* = 4.7 Hz, 2H, OCH_2), 2.42 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.2 (*C*HO), 160.2 (O*C*=O), 157.7, 153.7, 150.1, 129.8 (CH*C*=CH_2), 128.8, 116.8 (CHC=*C*H_2), 112.0, 111.4, 111.0, 107.3, 68.2 (O*C*H_2), 17.0 ppm.

*4.1.8. Synthesis of 4-methyl-2-oxo-7-(prop-2-yn-1-yloxy)-2H-chromene-8- carbaldehyde (**11b**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 3-bromoprop-1-yne (309 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **11b** (301 mg, 73.1%) as yellow solid. Mp: 206–207 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.45 (s, 1H, C*H*O), 8.02 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.27 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.32 (s, 1H, coumarin-3-*H*), 5.08 (s, 2H, OCH_2), 3.70 (s, 1H, C≡C*H*), 2.43 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 187.3 (*C*HO), 161.3 (O*C*=O), 159.4, 154.2, 153.5, 132.2, 114.4, 113.1, 112.6, 110.3, 79.9 (*C*≡CH), 78.6 (C≡*C*H), 57.6 (O*C*H_2), 18.8 (coumarin-4-*C*H_3) ppm.

*4.1.9. Synthesis of 7-((2-fluorobenzyl)oxy)-4-methyl-2-oxo-2H-chromene-8- carbaldehyde (**14a**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 1-(chloromethyl)-2-fluorobenzene (376 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **14a** (411 mg, 77.5%) as yellow solid. Mp: 255–257 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.51 (s, 1H, C*H*O), 8.03 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.77 (d, *J* = 5.1 Hz, 1H, Ph-4-*H*), 7.53 (d, *J* = 2.8 Hz, 1H, coumarin-6-*H*), 7.44–7.41 (m, 2H, Ph-3,5-2*H*), 7.35 (d, *J* = 9.0 Hz, 1H, Ph-6-*H*), 6.34 (s, 1H, coumarin-3-*H*), 5.43 (s, 2H, OCH_2), 2.43 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 187.4 (*C*HO), 162.1 (O*C*=O), 159.5, 154.4, 153.6, 133.9, 132.8, 132.6, 130.5, 130.3, 129.9, 127.9, 114.3, 112.5, 110.3, 68.8 (O*C*H_2), 18.8 (coumarin-4-*C*H_3) ppm.

*4.1.10. Synthesis of 7-((4-fluorobenzyl)oxy)-4-methyl-2-oxo-2H-chromene-8- carbaldehyde (**14b**)*

According to the similar preparation of compound **9a**, compound **3b** (350 mg, 1.7 mmol), 1-(chloromethyl)-4-fluorobenzene (376 mg, 2.6 mmol) and potassium carbonate (355 mg, 2.6 mmol) were employed to produce the pure product **14b** (424 mg, 79.9%) as yellow solid. Mp: 248–249 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.71 (s, 1H, C*H*O), 7.72 (d, *J* = 8.9 Hz, 1H, coumarin-5-*H*), 7.47 (dd, *J* = 8.5, 5.4 Hz, 2H, Ph-2,6-2*H*), 7.09 (t, *J* = 8.6 Hz, 2H, Ph-3,5-2*H*), 6.98 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.21 (d, *J* = 0.9 Hz, 1H, 1H, coumarin-3-*H*), 5.25 (s, 2H, OCH_2), 2.41 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ

186.9 (*C*HO), 163.5 (O*C*=O), 161.9, 161.6, 159.4, 155.7, 151.8, 131.2, 130.6, 128.8, 115.8, 115.7, 114.0, 113.4, 113.0, 109.2, 70.5 (O*C*H_2), 18.8 (coumarin-4-*C*H_3) ppm.

*4.1.11. Synthesis of 7-((3,4-dichlorobenzyl)oxy)-4-methyl-2-oxo-2H-chromene-8-carbaldehyde (**14c**)*

According to the similar preparation of compound **9a**, compound **3b** (300 mg, 1.47 mmol), 1,2-dichloro-4-(chloromethyl)benzene (431 mg, 2.21 mmol) and potassium carbonate (305 mg, 2.21 mmol) were employed to produce the pure product **14c** (230 mg, 43.2%) as white solid. Mp: 248–249 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H, C*H*O), 8.02 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.85 (s, 1H, Ph-5-*H*), 7.69 (d, *J* = 8.3 Hz, 1H, Ph-2-*H*), 7.53 (d, *J* = 8.2 Hz, 1H, coumarin-6-*H*), 7.27 (d, *J* = 9.0 Hz, 1H, Ph-6-*H*), 6.34 (s, 1H, coumarin-3-*H*), 5.40 (s, 2H, OCH_2), 2.43 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 187.52 (*C*HO), 132.52, 131.25, 129.70, 127.94, 112.46, 110.24, 69.46 (O*C*H_2), 18.82 (coumarin-4-*C*H_3) ppm.

*4.1.12. Synthesis of (Z)-5-((7-hydroxy-2-oxo-2H-chromen-4-yl)methylene)thiazolidine-2,4-dione (**8**)*

Compound **7** (200 mg, 1.06 mmol), thiazolidine-2,4-dione (186 mg, 1.59 mmol) and piperidine (15 mg) were stirred in ethanol (20 mL) at 80 °C for 12 h. Upon completion of the reaction, the residue was filtered and washed with ethanol, and the crude product was further purified by column chromatography (eluent, petroleum ether /chloroform (1/1, V/V)) to afford the desired compound **8** (200 mg, 65.3%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.88 (s, 1H, N*H*), 10.76 (s, 1H, O*H*), 7.88 (s, 1H, C=C*H*), 7.64 (d, *J* = 8.8 Hz, 1H, coumarin-5-*H*), 6.83 (dd, *J* = 8.7, 2.3 Hz, 1H, coumarin-6-*H*), 6.78 (d, *J* = 2.3 Hz, 1H, coumarin-8-*H*), 6.22 (s, 1H, coumarin-3-*H*) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.44 (S*C*=O), 166.66 (C*C*=ONH), 162.46 (O*C*=O), 160.16, 155.70, 148.07, 133.93, 127.18, 124.29, 113.85, 110.46, 109.99, 103.25 ppm; HRMS (ESI) calcd. for $C_{13}H_7NO_5S$ $[M-H]^+$, 287.9967, found, 287.9966.

4.1.13. Synthesis of (Z)-5-((7-hydroxy-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**4a** *)*

According to the similar preparation of compound **8**, compound **3a** (190 mg, 1.0 mmol), thiazolidine-2,4-dione (176 mg, 1.5 mmol) were employed to produce the pure product **4a** (150 mg, 51.9%) as orange solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.89–7.83 (m, 2H, C=C*H*, coumarin-4-*H*), 7.44 (d, *J* = 8.7 Hz, 1H, coumarin-5-*H*), 6.65 (s, 1H, coumarin-6-*H*), 6.09–6.05 (m, 1H, coumarin-3-*H*) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.09 (S*C*=O), 170.70 (C*C*=ONH), 165.44 (O*C*=O), 160.64, 154.85, 145.42, 131.45, 126.48, 123.88, 115.67, 109.25, 108.91 ppm; HRMS (ESI) calcd. for $C_{13}H_7NO_5S$ $[M+H]^+$, 290.0123, found, 290.0125; $[M+Na]^+$, 311.9943, found, 311.9940.

*4.1.14. Synthesis of (Z)-5-((7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**4b**)*

According to the similar preparation of compound **8**, compound **3b** (204 mg, 1.0 mmol), thiazolidine-2,4-dione (175 mg, 1.5 mmol) were employed to produce the pure product **4b** (200 mg, 66.0%) as orange solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.09 (s, 1H, N*H*), 7.93 (s, 1H, C=C*H*), 7.71 (d, *J* = 8.8 Hz, 1H, coumarin-5-*H*), 6.94 (d, *J* = 8.8 Hz, 1H, coumarin-6-*H*), 6.22 (s, 1H, coumarin-3-*H*), 2.39 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.03 (S*C*=O), 167.98 (C*C*=ONH), 159.67 (O*C*=O), 154.21, 152.96,

128.80, 127.84, 124.27, 113.01, 112.49, 110.95, 108.48, 18.76 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{14}H_9NO_5S$ $[M+H]^+$, 304.0280, found, 304.0282.

*4.1.15. Synthesis of (Z)-5-((7-ethoxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**10a**)*

According to the similar preparation of compound **8**, compound **9a** (334 mg, 1.44 mmol), thiazolidine-2,4-dione (253 mg, 2.16 mmol) were employed to produce the pure product **10a** (256 mg, 53.7%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H, N*H*), 7.88 (s, 1H, C=C*H*), 7.84 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.18 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.29 (d, *J* = 0.8 Hz, 1H, coumarin-3-*H*), 4.31 (d, *J* = 7.0 Hz, 2H, OCH_2CH$_3$), 2.42 (d, *J* = 0.6 Hz, 3H, coumarin-4-CH_3), 1.42 (t, *J* = 7.0 Hz, 3H, OCH$_2$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.60 (S*C*=O), 167.72 (C*C*=ONH), 159.49 (O*C*=O), 159.09, 153.95, 152.32, 128.99, 123.76, 113.77, 111.97, 109.79, 109.16, 65.50 (O*C*H$_2$), 18.71 (coumarin-4-*C*H$_3$), 14.78 ppm; HRMS (ESI) calcd. for $C_{16}H_{13}NO_5S$ $[M+H]^+$, 332.0593, found, 332.0592.

*4.1.16. Synthesis of (Z)-5-((4-methyl-2-oxo-7-propoxy-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**10b**)*

According to the similar preparation of compound **8**, compound **9b** (224 mg, 0.99 mmol), thiazolidine-2,4-dione (175 mg, 1.49 mmol) were employed to produce the pure product **10b** (170 mg, 49.7%) as white solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.53 (s, 1H, N*H*), 7.88 (s, 1H, C=C*H*), 7.84 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.19 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.29 (s, 1H, coumarin-3-*H*), 4.20 (t, *J* = 6.7 Hz, 2H, OCH_2CH$_2$CH$_3$), 2.43 (s, 3H, coumarin-4-CH_3), 1.82 (dt, *J* = 14.2, 7.1 Hz, 2H, OCH$_2$CH_2CH$_3$), 0.99 (t, *J* = 7.4 Hz, 3H, OCH$_2$CH$_2$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.60 (S*C*=O), 167.69 (C*C*=ONH), 159.49 (O*C*=O), 159.34, 153.97, 152.22, 129.06, 123.79, 113.80, 111.99, 109.90, 109.30, 71.22 (O*C*H$_2$), 22.26, 18.73 (coumarin-4-*C*H$_3$), 10.68 ppm; HRMS (ESI) calcd. for $C_{17}H_{15}NO_5S$ $[M+H]^+$, 346.0749, found, 346.0750.

*4.1.17. Synthesis of (Z)-5-((7-butoxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**10c**)*

According to the similar preparation of compound **8**, compound **9c** (128 mg, 0.49 mmol), thiazolidine-2,4-dione (87 mg, 0.74 mmol) were employed to produce the pure product **10c** (105 mg, 59.3%) as light yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H, N*H*), 7.88 (d, *J* = 1.3 Hz, 1H, C=C*H*), 7.86–7.83 (m, 1H, coumarin-5-*H*), 7.19 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.29 (s, 1H, coumarin-3-*H*), 4.24 (t, *J* = 6.6 Hz, 2H, OCH_2(CH$_2$)$_2$CH$_3$), 2.41 (d, *J* = 12.1 Hz, 3H, coumarin-4-CH_3), 1.82–1.75 (m, 2H, OCH$_2$CH_2CH$_2$CH$_3$), 1.7–1.40 (m, 2H, O(CH$_2$)$_2$CH_2CH$_3$), 0.94 (dd, *J* = 12.3, 4.9 Hz, 3H, O(CH$_2$)$_3$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.58 (S*C*=O), 167.67 (C*C*=ONH), 159.49 (O*C*=O), 159.35, 153.99, 152.22, 129.06, 123.82, 113.81, 111.98, 109.90, 109.31, 69.53 (O*C*H$_2$), 30.84, 19.08, 18.74 (coumarin-4-*C*H$_3$), 14.07 ppm; HRMS (ESI) calcd. for $C_{18}H_{17}NO_5S$ $[M+H]^+$, 360.0906, found, 360.0905.

*4.1.18. Synthesis of (Z)-5-((4-methyl-2-oxo-7-(pentyloxy)-2H-chromen-8-yl)methylene)thiazolidine2,4-dione (**10d**)*

According to the similar preparation of compound **8**, compound **9d** (217 mg, 0.79 mmol), thiazolidine-2,4-dione (139 mg, 1.19 mmol) were employed to produce the pure product **10d** (175 mg, 59.4%) as yellow solid. Mp: 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.53 (s, 1H, N*H*), 7.87 (s, 1H, C=C*H*), 7.84 (d, *J* =

8.9 Hz, 1H, coumarin-5-*H*), 7.19 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.29 (s, 1H, coumarin-3-*H*), 4.22 (t, *J* = 6.6 Hz, 2H, OCH_2(CH_2)$_3$$CH_3$), 2.42 (s, 3H, coumarin-4-CH_3), 1.84–1.77 (m, 2H, OCH_2CH_2(CH_2)$_2$$CH_3$), 1.42–1.31 (m, 4H, O($CH_2$)$_2$(C$H_2$)$_2$$CH_3$), 0.88 (t, *J* = 7.2 Hz, 3H, O(CH_2)$_4$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.74 (S*C*=O), 159.52 (C*C*=ONH), 159.35 (O*C*=O), 154.02, 152.24, 129.01, 123.81, 113.84, 111.99, 109.97, 109.37, 69.80 (O*C*H_2), 28.43, 28.00, 22.22, 18.74 (coumarin-4-*C*H_3), 14.28 ppm; HRMS (ESI) calcd. for $C_{19}H_{19}NO_5S$ $[M+Na]^+$, 366.0882, found, 366.0880.

*4.1.19. Synthesis of (Z)-5-((7-(hexyloxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (***10e***)*

According to the similar preparation of compound **8**, compound **9e** (195 mg, 0.68 mmol), thiazolidine-2,4-dione (119 mg, 1.02 mmol) were employed to produce the pure product **10e** (128 mg, 48.6%) as white solid. Mp: 240–242 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H, N*H*), 7.87 (s, 1H, C=C*H*), 7.84 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.18 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.29 (d, *J* = 1.1 Hz, 1H, coumarin-3-*H*), 4.22 (t, *J* = 6.6 Hz, 2H, OCH_2(CH_2)$_4$$CH_3$), 2.42 (d, *J* = 0.9 Hz, 3H, coumarin-4-CH_3), 1.82–1.77 (m, 2H, OCH_2CH_2(CH_2)$_3$$CH_3$), 1.44–1.38 (m, 2H, O($CH_2$)$_2CH_2$($CH_2$)$_2$$CH_3$), 1.33–1.27 (m, 4H, O($CH_2$)$_3$(C$H_2$)$_2$$CH_3$), 0.86 (t, *J* = 7.1 Hz, 3H, O(CH_2)$_5$CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.53 (S*C*=O), 167.64 (C*C*=ONH), 159.49 (O*C*=O), 159.33, 153.97, 152.24, 129.16, 128.98, 123.81, 113.81, 111.99, 109.94, 109.34, 69.80 (O*C*H_2), 31.72, 29.34, 29.08, 28.70, 25.79, 22.53, 18.73 (coumarin-4-*C*H_3), 14.36 ppm; HRMS (ESI) calcd. for $C_{20}H_{21}NO_5S$ $[M+Na]^+$, 410.1038, found, 410.1037.

*4.1.20. Synthesis of (Z)-5-((7-(decyloxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**10f**)*

According to the similar preparation of compound **8**, compound **9f** (215 mg, 0.62 mmol), thiazolidine-2,4-dione (109 mg, 0.93 mmol) were employed to produce the pure product **10f** (205 mg, 74.5%) as light yellow solid. Mp: 225–227 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.52 (s, 1H, N*H*), 7.88 (s, 1H, C=C*H*), 7.84 (d, *J* = 8.8 Hz, 1H, coumarin-5-*H*), 7.19 (d, *J* = 8.9 Hz, 1H, coumarin-6-*H*), 6.29 (s, 1H, coumarin-3-*H*), 4.23 (t, *J* = 6.1 Hz, 2H, OCH_2(CH_2)$_8$$CH_3$), 2.42 (s, 3H, coumarin-4-CH_3), 1.82–1.76 (m, 2H, OCH_2CH_2(CH_2)$_7$$CH_3$), 1.39 (d, *J* = 6.6 Hz, 2H, O(CH_2)$_2$CH_2(CH_2)$_6$$CH_3$), 1.27 (d, *J* = 44.9 Hz, 12H, O(CH_2)$_3$(CH_2)$_6$$CH_3$), 0.85 (t, *J* = 6.5 Hz, 3H, O(CH_2)$_9$$CH_3$) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.53 (S*C*=O), 167.64 (C*C*=ONH), 159.49 (O*C*=O), 159.33, 153.97, 152.24, 129.16, 128.98, 123.81, 113.81, 111.99, 109.94, 109.34, 69.80 (O*C*H_2), 31.72, 29.34, 29.08, 28.70, 25.79, 22.53, 18.73 (coumarin-4-*C*H_3), 14.36 ppm; HRMS (ESI) calcd. for $C_{24}H_{29}NO_5S$ $[M+H]^+$, 444.1845, found, 444.1846.

*4.1.21. Synthesis of (Z)-5-((7-(2-hydroxyethoxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**10g**)*

According to the similar preparation of compound **8**, compound **9g** (51 mg, 0.21 mmol), thiazolidine-2,4-dione (37.5 mg, 0.32 mmol) were employed to produce the pure product **10g** (41 mg, 56.3%) as white solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71 (d, *J* = 8.9 Hz, 1H, C=C*H*), 7.32 (s, 1H, coumarin-5-*H*), 7.14 (d, *J* = 8.9 Hz, 1H, coumarin-6-*H*), 6.24 (s, 1H, coumarin-3-*H*), 4.19 (t, *J* = 5.2 Hz, 2H, OC$H_2$$CH_2$OH), 3.78 (t, *J* = 5.2

Hz, 2H, OCH_2CH_2OH), 2.42 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 181.36 (S*C*=O), 175.98 (C*C*=ONH), 160.11 (O*C*=O), 159.25, 153.93, 151.65, 141.96, 126.42, 114.71, 113.76, 113.52, 111.75, 109.23, 71.06 (OCH_2), 59.92, 22.91 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{16}H_{13}NO_6S$ $[M+H]^+$, 348.0536, found, 348.05301.

*4.1.22. Synthesis of (Z)-5-((7-(allyloxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (***12a***)*

According to the similar preparation of compound **8**, compound **11a** (200 mg, 0.82 mmol), thiazolidine-2,4-dione (144 mg, 1.23 mmol) were employed to produce the pure product **12a** (212 mg, 75.4%) as yellow solid. Mp: > 250 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.53 (s, 1H, N*H*), 7.90 (s, 1H, C=C*H*), 7.85 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.18 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.31 (d, *J* = 1.1 Hz, 1H, coumarin-3-*H*), 6.13–6.06 (m, 1H, OCH_2CH=CH_2), 5.43 (dd, *J* = 17.3, 1.6 Hz, 1H, CH=CH_2), 5.33 (dd, *J* = 10.6, 1.4 Hz, 1H, CH=CH_2), 4.86 (d, *J* = 5.3 Hz, 2H, OCH_2CH=CH_2), 2.43 (d, *J* = 0.9 Hz, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.63 (S*C*=O), 167.75 (C*C*=ONH), 159.46 (O*C*=O), 158.77, 153.97, 152.22, 133.04 (C*C*H=CH), 129.28, 128.93, 123.62, 118.94 (CCH=*C*H), 114.00, 112.12, 110.01, 109.60, 70.06 (OCH_2), 18.74 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{17}H_{13}NO_5S$ $[M+H]^+$, 344.0593, found, 344.0595.

*4.1.23. Synthesis of (Z)-5-((4-methyl-2-oxo-7-(prop-2-yn-1-yloxy)-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (***12b***)*

According to the similar preparation of compound **8**, compound **11b** (320 mg, 1.32 mmol), thiazolidine-2,4-dione (232 mg, 1.98 mmol) were employed to produce the pure product **12b** (268 mg, 59.5%) as white solid. Mp: > 250 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 12.54 (s, 1H, N*H*), 7.92 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.89 (s, 1H, C=C*H*), 7.26 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.34 (s, 1H, coumarin-3-*H*), 5.12 (d, *J* = 2.1 Hz, 2H, OCH_2), 3.70 (s, 1H, C≡C*H*), 2.44 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.61 (S*C*=O), 167.67 (C*C*=ONH), 159.40 (O*C*=O), 157.54, 153.94, 152.23, 129.52, 128.87, 123.31, 114.50, 112.43, 110.31, 109.76, 79.94 (*C*≡CH), 78.56 (C≡*C*H), 56.99, 49.07, 18.76 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{17}H_{11}NO_5S$ $[M+Na]^+$, 364.0256, found, 364.0258.

*4.1.24. Synthesis of (Z)-3-allyl-5-((7-(allyloxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**13a**)*

According to the similar preparation of compound **9a**, compound **12a** (88 mg, 0.26 mmol), 3-bromoprop-1-ene (35 mg, 0.29 mmol) and potassium carbonate (40 mg, 0.29 mmol) were employed to produce the pure product **13a** (50 mg, 50.2%) as yellow solid. Mp: > 250 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 8.06 (s, 1H, C=C*H*), 7.88 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.20 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.32 (d, *J* = 0.9 Hz, 1H, coumarin-3-*H*), 6.09 (ddd, *J* = 15.9, 10.6, 5.3 Hz, 1H, OCH_2CH=CH_2), 5.90–5.84 (m, 1H, NCH_2CH=CH_2), 5.43 (dd, *J* = 17.3, 1.5 Hz, 1H, OCH_2CH=CH_2), 5.33 (dd, *J* = 10.6, 1.3 Hz, 1H, OCH_2CH=CH_2), 5.20–5.16 (m, 2H, NCH_2CH=CH_2), 4.88 (d, *J* = 5.3 Hz, 2H, OCH_2CH=CH_2), 4.26 (d, *J* = 5.4 Hz, 2H, NCH_2CH=CH_2), 2.43 (d, *J* = 0.6 Hz, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.69 (S*C*=O), 165.74 (C*C*=ONH), 159.40 (O*C*=O),

158.83, 153.99, 152.34, 133.00, 131.70, 129.27, 126.81, 124.88, 119.03, 117.97, 114.06, 112.17, 109.76, 109.67, 109.53, 70.13, 43.89, 18.76 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{20}H_{17}NO_5S$ $[M+H]^+$, 384.0906, found, 384.0906; $[M+Na]^+$, 406.0725, found, 406.0726.

*4.1.25. Synthesis of (Z)-5-((4-methyl-2-oxo-7-(prop-2-yn-1-yloxy)-2H-chromen-8-yl)methylene)-3-(prop-2-yn-1-yl)thiazolidine-2,4-dione (**13b**)*

According to the similar preparation of compound **9a**, compound **12b** (150 mg, 0.44 mmol), 3-bromo-1-propyne (58 mg, 0.484 mmol) and potassium carbonate (61 mg, 0.44 mmol) were employed to produce the pure product **13b** (98 mg, 58.8%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.07 (s, 1H, C=C*H*), 7.95 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.28 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.35 (s, 1H, coumarin-3-*H*), 5.14 (d, *J* = 2.1 Hz, 2H, OCH_2CCH), 4.43 (d, *J* = 2.4 Hz, 2H, NCH_2CCH), 3.71 (t, *J* = 2.1 Hz, 1H, OCH_2CC*H*), 3.33 (t, *J* = 2.4 Hz, 1H, NCH$_2$CC*H*), 2.45 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.14 (S*C*=O), 165.03 (C*C*=ONH), 159.31 (O*C*=O), 157.60, 153.95, 152.37, 129.33, 126.67, 125.21, 114.56, 112.49, 110.01, 109.82, 80.04, 78.48, 77.65, 74.98, 57.09, 31.00, 18.76 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{20}H_{13}NO_5S$ $[M+H]^+$, 380.0593, found, 380.0594.

*4.1.26. Synthesis of (Z)-5-((7-((2-fluorobenzyl)oxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**15a**)*

According to the similar preparation of compound **8**, compound **14a** (232 mg, 0.74 mmol), thiazolidine-2,4-dione (130 mg, 1.11 mmol) were employed to produce the pure product **15a** (205 mg, 67.4%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.44 (s, 1H, N*H*), 7.87 (d, *J* = 8.8 Hz, 2H, coumarin-5-*H*, C=C*H*), 7.55 (dd, *J* = 7.5, 6.4 Hz, 1H, ph-4-*H*), 7.46–7.41 (m, 1H, ph-3-*H*), 7.32 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 7.28–7.22 (m, 2H, ph-5,6-2*H*), 6.30 (s, 1H, coumarin-3-*H*), 5.43 (s, 2H, OCH_2), 2.43 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.54 (S*C*=O), 167.72 (C*C*=ONH), 161.72 (O*C*=O), 160.08, 159.42, 158.85, 153.96, 152.13, 131.23, 129.65, 128.99, 125.05, 123.45, 123.17, 116.02, 115.88, 114.37, 112.30, 110.44, 109.78, 65.59, 18.74 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{21}H_{14}FNO_5S$ $[M+H]^+$, 412.0655, found, 412.0653.

*4.1.27. Synthesis of (Z)-5-((7-((4-fluorobenzyl)oxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**15b**)*

According to the similar preparation of compound **8**, compound **14b** (87 mg, 0.27 mmol), thiazolidine-2,4-dione (48 mg, 0.41 mmol) were employed to produce the pure product **15b** (56 mg, 50.5%) as light yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.51 (s, 1H, N*H*), 7.90 (s, 1H, C=C*H*), 7.85 (d, *J* = 8.9 Hz, 1H, coumarin-5-*H*), 7.54–7.50 (m, 2H, ph-2,6-2*H*), 7.24 (dd, *J* = 16.5, 8.4 Hz, 3H, ph-3,5-2*H*, coumarin-6-*H*), 6.31 (s, 1H, coumarin-3-*H*), 5.39 (s, 2H, OCH_2), 2.42 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.55 (S*C*=O), 167.69 (C*C*=ONH), 163.22 (O*C*=O), 161.60, 159.43, 158.92, 153.97, 152.14, 132.56, 130.50, 129.48, 128.94, 123.62, 115.91, 115.77, 114.18, 112.21, 110.32, 109.86, 70.38, 18.73 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{21}H_{14}FNO_5S$ $[M+Na]^+$, 434.0474, found, 434.0474.

*4.1.28. Synthesis of (Z)-5-((7-((2,4-dichlorobenzyl)oxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**15c**)*

According to the similar preparation of compound **8**, compound **14c** (276 mg, 0.76 mmol), thiazolidine-2,4-dione (134 mg, 1.14 mmol) were employed to produce the pure product **15c** (185 mg, 52.9%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.48 (s, 1H, N*H*), 7.87 (d, *J* = 7.4 Hz, 2H, ph-3-*H*, C=C*H*), 7.70 (d, *J* = 2.0 Hz, 1H, coumarin-5-*H*), 7.59 (d, *J* = 8.3 Hz, 1H, ph-5-*H*), 7.48 (dd, *J* = 8.3 Hz, 1H, ph-6-*H*), 7.28 (d, *J* = 9.1 Hz, 1H, coumarin-6-*H*), 6.32 (d, *J* = 1.0 Hz, 1H, coumarin-3-*H*), 5.42 (s, 2H, OCH_2), 2.43 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.47 (S*C*=O), 167.65 (C*C*=ONH), 159.38 (O*C*=O), 158.62, 153.91, 152.09, 134.48, 134.33, 132.83, 132.07, 129.75, 129.53, 129.00, 128.07, 123.44, 114.51, 112.39, 110.52, 109.83, 68.29, 18.73 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{21}H_{13}Cl_2NO_5S$ $[M+H]^+$, 461.9970, found, 461.9969.

*4.1.29. Synthesis of (Z)-5-((7-((3,4-dichlorobenzyl)oxy)-4-methyl-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**15d**)*

According to the similar preparation of compound **8**, compound **14d** (230 mg, 0.64 mmol), thiazolidine-2,4-dione (113 mg, 0.96 mmol) were employed to produce the pure product **15d** (178 mg, 60.3%) as yellow solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.46 (s, 1H, NH), 7.85–7.80 (m, 2H, ph-5-*H*, C=C*H*), 7.74 (d, *J* = 1.7 Hz, 1H, coumarin-5-*H*), 7.66 (d, *J* = 8.3 Hz, 1H, ph-2-*H*), 7.44 (dd, *J* = 8.3, 1.8 Hz, 1H, ph-6*H*), 7.20 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.30 (d, *J* = 0.8 Hz, 1H, coumarin-3-*H*), 5.40 (s, 2H, OCH_2), 2.42 (s, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.62 (S*C*=O), 158.42 (C*C*=ONH), 153.91 (O*C*=O), 151.95, 137.83, 131.65, 131.15, 129.90, 128.10, 114.34, 112.25, 109.78, 69.37, 18.71 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{21}H_{13}Cl_2NO_5S$ $[M+H]^+$, 461.9964, found, 461.99619.

*4.1.30. Synthesis of (Z)-5-((4-methyl-7-((4-nitrobenzyl)oxy)-2-oxo-2H-chromen-8-yl)methylene)thiazolidine-2,4-dione (**15e**)*

According to the similar preparation of compound **8**, compound **14e** (254 mg, 0.75 mmol), thiazolidine-2,4-dione (132 mg, 1.13 mmol) were employed to produce the pure product **15e** (100 mg, 30.4%) was obtained as white solid. Mp: > 250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.49 (s, 1H, N*H*), 8.28–8.25 (m, 2H, ph-3,5-2*H*), 7.94 (d, *J* = 21.2 Hz, 1H, C=C*H*), 7.85 (d, *J* = 9.0 Hz, 1H, coumarin-5-*H*), 7.73–7.70 (m, 2H, ph-2,6-2*H*), 7.21 (d, *J* = 9.0 Hz, 1H, coumarin-6-*H*), 6.32 (d, *J* = 1.0 Hz, 1H, coumarin-3-*H*), 5.59 (s, 2H, OCH_2), 2.41 (d, *J* = 6.2 Hz, 3H, coumarin-4-CH_3) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 159.45 (S*C*=O), 159.05 (C*C*=ONH), 158.48 (O*C*=O), 153.95, 152.11, 147.70, 144.25, 128.76, 128.60, 125.98, 124.09, 114.43, 112.36, 112.02, 109.80, 109.37, 69.79, 18.73 (coumarin-4-*C*H_3) ppm; HRMS (ESI) calcd. for $C_{21}H_{14}N_2O_7S$ $[M+H]^+$, 439.0600, found, 439.0601.

Conflicts of interest

There are no conflicts to declare.

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Lists of table and scheme captions

Table 1. *In vitro* antibacterial data as MIC (μmol/mL) for target compounds **8, 4a–b, 10a–g, 12a–b, 13a–b and 15a–e**.[a]

Compds	Gram-positive bacteria[b]					Gram-negative bacteria[c]					
	MRSA	*E. f.*	*S. a.*	*S. a.* 25923	*S. a.* 29213	*K. p.*	*E. c.*	*P. a.*	*A. b.*	*P. a.* 27853	*E. c.* 25922
8	0.886	0.886	0.886	1.772	1.772	0.886	1.772	0.886	1.772	0.886	0.443
4a	1.772	0.886	0.443	1.772	1.772	1.772	1.772	1.772	0.886	1.772	0.886
4b	0.422	0.106	0.422	0.422	0.422	0.422	0.422	0.211	0.422	0.422	0.422
10a	0.012	0.773	0.193	0.773	0.773	0.387	0.773	0.387	0.387	0.773	0.773
10b	0.012	0.742	0.012	0.742	0.742	0.371	0.742	0.371	0.371	0.371	0.742
10c	1.426	1.426	1.426	1.426	1.426	1.426	1.426	1.426	1.426	1.426	1.426
10d	0.343	0.686	1.372	1.372	0.686	0.343	1.372	0.343	0.686	1.372	1.372
10e	0.331	0.331	0.661	0.331	0.661	0.331	0.331	0.661	0.331	0.331	0.661
10f	1.155	1.155	1.155	1.155	1.155	1.155	1.155	1.155	1.155	1.155	1.155
10g	0.369	0.184	0.369	0.369	0.369	0.369	0.369	0.184	0.184	0.369	0.184
12a	0.006	0.746	0.023	0.746	0.746	0.373	0.746	0.373	0.373	0.373	0.746
12b	0.006	0.751	0.375	0.751	0.047	0.047	0.751	0.188	0.188	0.188	0.375
13a	0.167	0.668	0.334	0.668	0.668	0.334	0.668	0.668	0.334	0.668	0.334
13b	0.338	0.338	0.338	0.675	0.338	0.675	0.675	0.338	0.675	0.675	0.338
15a	0.039	0.156	0.311	0.039	0.311	0.623	0.311	0.311	0.311	0.156	0.311
15b	0.311	0.156	0.311	0.156	0.311	0.311	0.623	0.311	0.156	0.156	0.311
15c	0.278	0.278	0.555	0.278	0.278	0.139	0.278	0.278	0.278	0.278	0.139
15d	0.139	0.278	0.278	0.278	0.278	0.278	0.278	0.278	0.139	0.278	0.139
15e	0.584	0.292	0.292	0.146	0.584	0.292	0.292	0.584	0.292	0.292	0.584
A[d]	0.025	0.006	0.025	0.100	0.003	0.401	0.200	0.025	0.802	0.013	0.025

[a]Minimum inhibitory concentrations were determined by micro broth dilution method for microdilution plates. [b]MRSA, methicillin-resistant *Staphylococcus aureus* N315; *E. f.*, *Enterococcus faecalis*; *S. a.*, *Staphylococcus aureus*; *S. a.* 25923, *Staphylococcus aureus* ATCC 25923; *S. a.* 29213, *Staphylococcus aureus* ATCC 29213; [c]*K. p.*, *Klebsiella pneumonia*; *E. c.*, *Escherichia coli*; *P. a.*, *Pseudomonas aeruginosa*; *A. b.*, *Acinetobacter baumanii*; *P. a.* 27853, *Pseudomonas aeruginosa* ATCC 27853; *E. c.* 25922, *Escherichia coli* ATCC 25922 . [d]A = Norfloxacin

Fig. 1. Drug molecules containing coumarin scaffold.

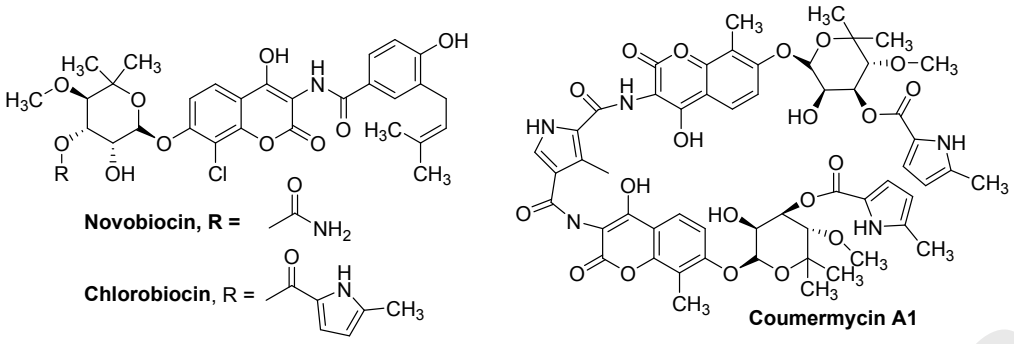


Fig. 2. Design of novel coumarin thiazolidinediones.

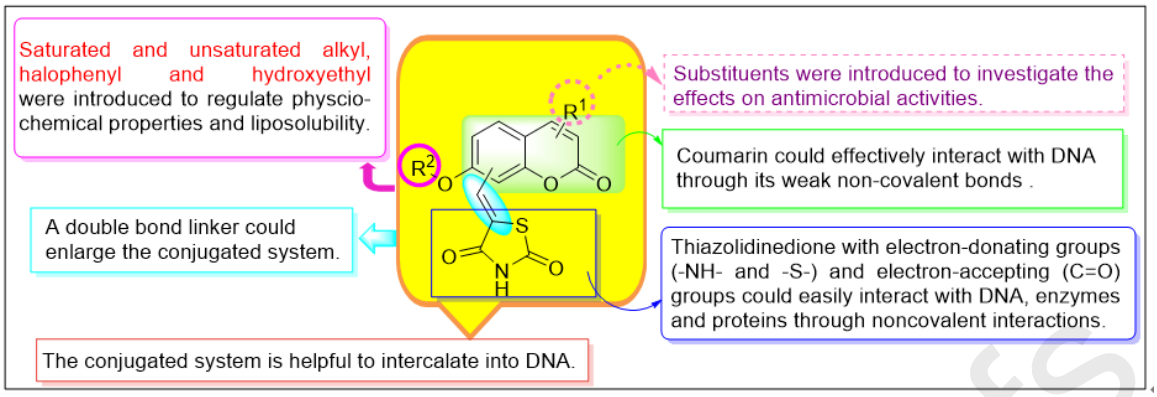


Fig. 3. The crystal structure of compound **13a**.

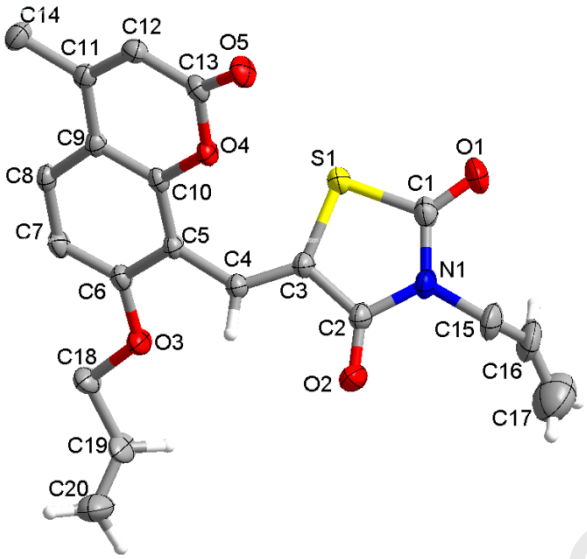


Fig. 4. Time–kill kinetics of compound **12b** (4 × MIC) against MRSA.

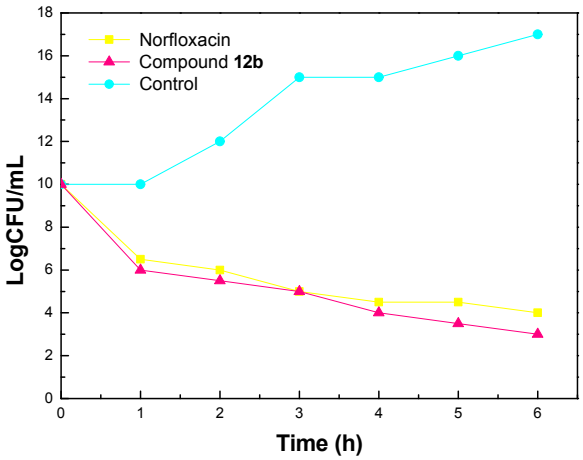


Fig. 5. Drug resistance development of compound **12b** against MRSA.

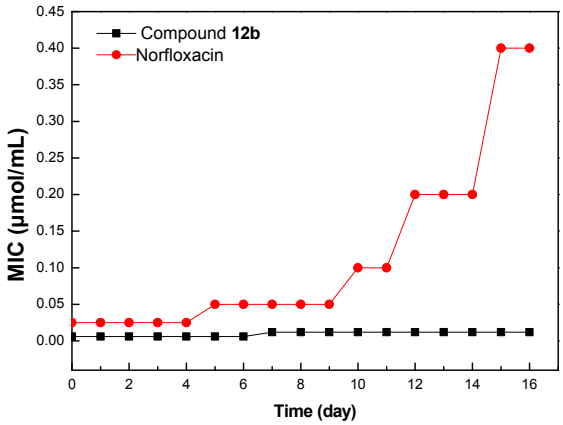


Fig. 6. Cytotoxic assay of target compound **12b** on human hepatocyte LO2 cells tested by MTT methodology.

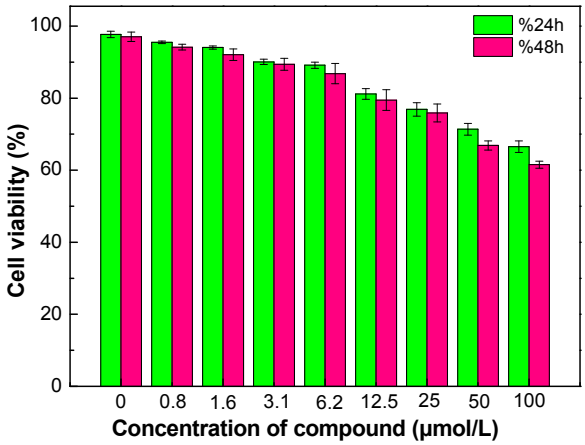


Fig. 7. Membrane permeabilization of resistant bacterial MRSA toward compound **12b** (12 × MIC).

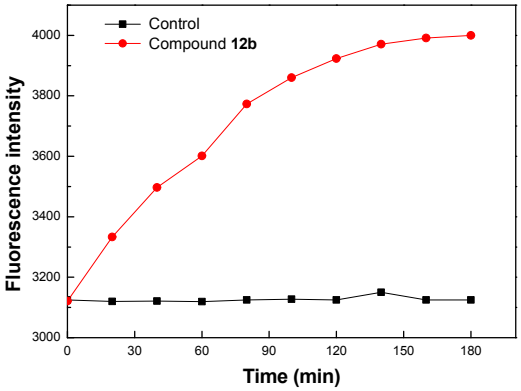


Fig. 8. UV absorption spectra of MRSA DNA with different concentrations of compound **12b** (pH = 7.4, T = 290 K). Inset: comparison of absorption at 260 nm between the value of compound **12b**–DNA complex and the sum values of free DNA and free compound **12b**. c(DNA) = 7.4 × 10^{-5} mol/L, and c(compound **12b**) = 0–2.0 ×10^{-5} mol/L for curves *a*–*i* respectively at an increment 0.25 ×10^{-5}.

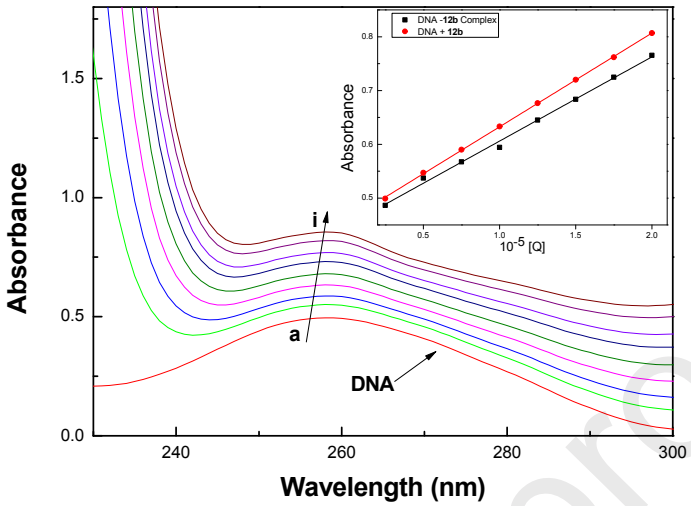


Fig. 9. UV absorption spectra of the competitive reaction between **12b** and NR with MRSA DNA. c(DNA) = 7.4 × 10^{-5} mol/L, c(NR) = 2 × 10^{-5} mol/L, and c(compound **12b**) = 0–4.5 ×10^{-5} mol/L for curves a–i respectively at increment 0.5 × 10^{-5}. (Inset) Absorption spectra of the system with the increasing concentration of **12b** in the wavelength range of 350–600 nm absorption spectra of competitive reaction between compound **12b** and NR with DNA.

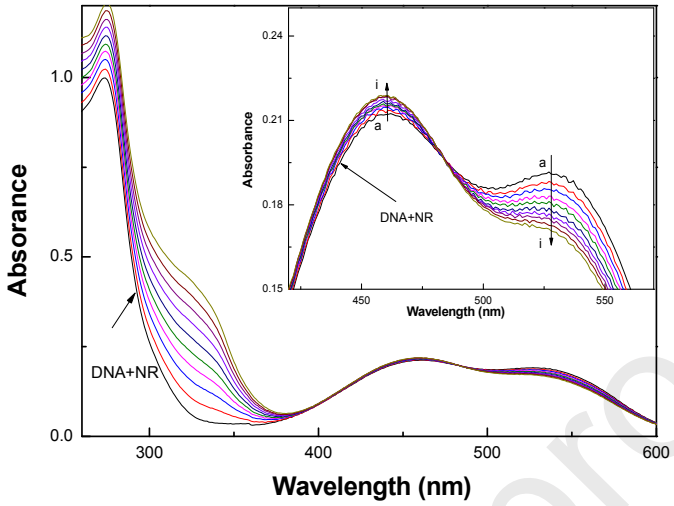
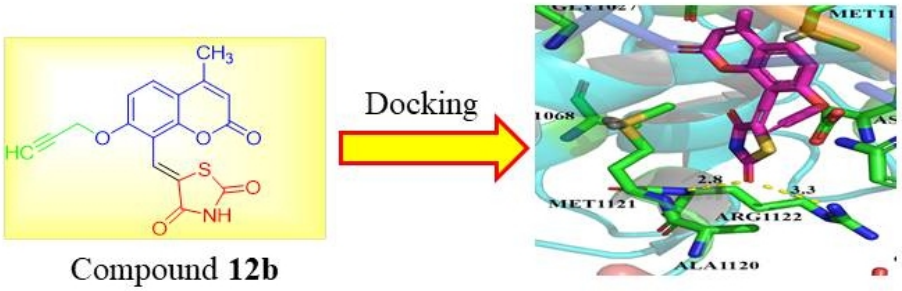
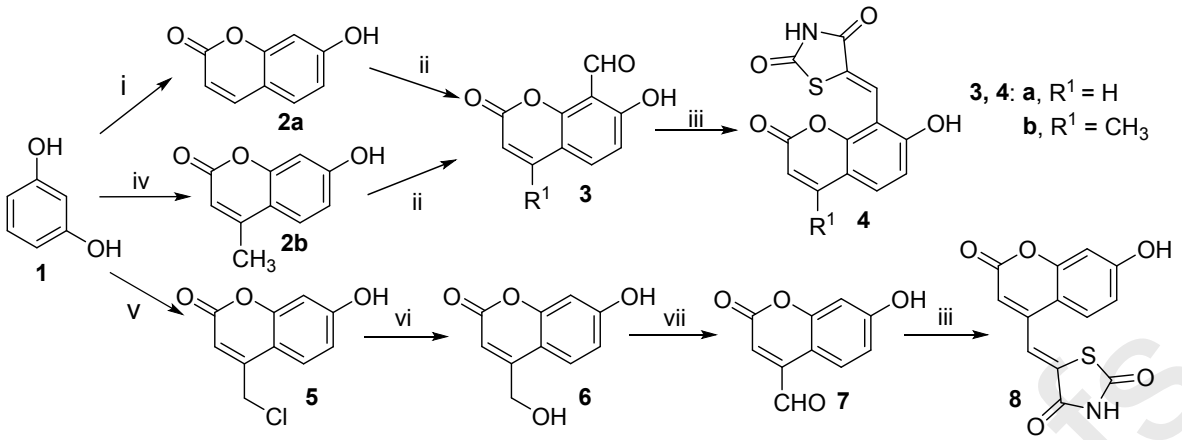


Fig. 10. Molecular modeling of compound **12b** docked in gyrase-DNA (gyrase-DNA complex code: 2XCS).

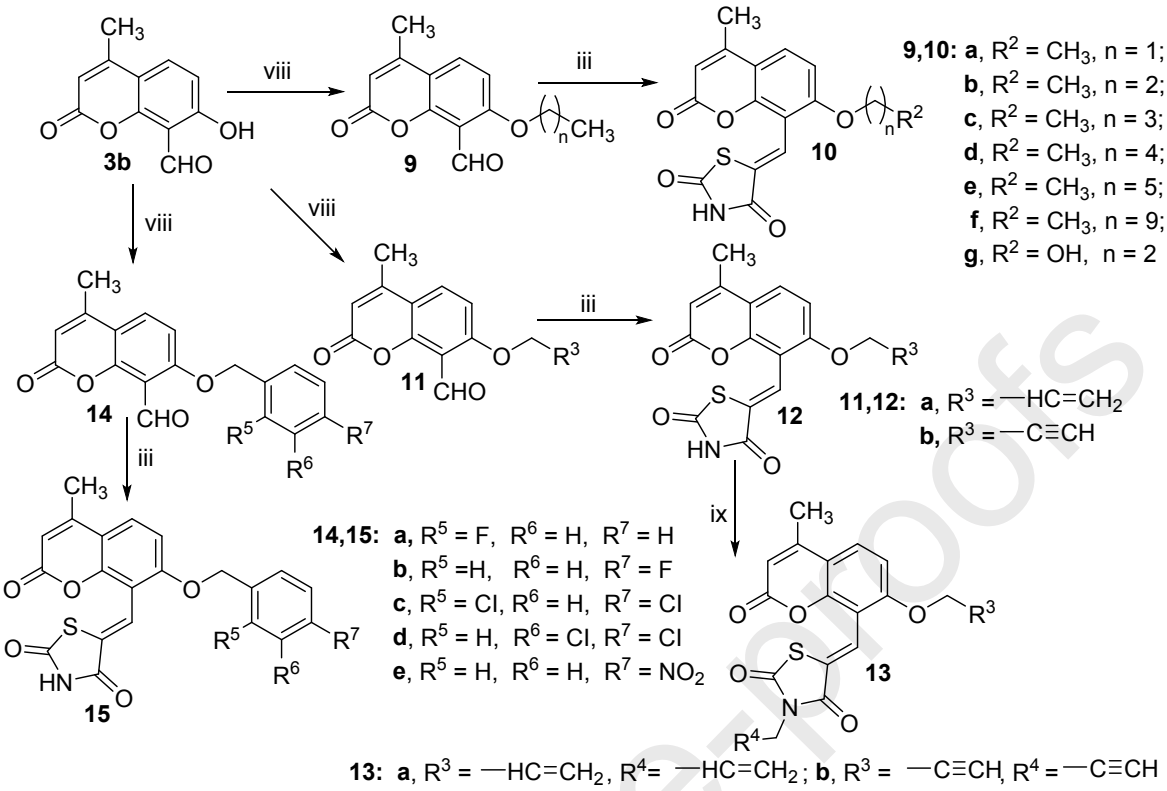


Scheme 1 Synthetic route of coumarin thiazolidinediones **1**–**8**.



Reagents and conditions: (i) 2-hydroxysuccinic acid; (ii) (a) HMTA/AcOH, 75 °C, 8 h; (b) 10% HCI, 75 °C, 1 h; (iii) thiazolidinedione, EtOH, piperidine, N_2, 80 °C; (iv) H_2SO_4, ethylacetoacetate, 0 °C, 24 h; (v) ethyl 4-chloroacetoacetate, H_2SO_4, 0 °C, 24 h; (vi) H_2O, 100 °C, 3 days; (vii) MnO_2, ethyl acetate, N_2, 80 °C, 7 h.

Scheme 2 Synthetic route of coumarin thiazolidinediones **9–15**.



Reagents and conditions: (iii) thiazolidinedione, EtOH, piperidine, N_2, 80 °C, 6 h; (viii) aliphatic bromides, benzyl halides, 2-bromoethanol, potassium carbonate, DMF, 80 °C, 4-8 h; (ix) aliphatic bromides, potassium carbonate, DMF, 80 °C, 4 h.

Graphical Abstract

Ethylenic conjugated coumarin thiazolidinediones as efficient antimicrobial modulators against clinical methicillin-resistant *Staphylococcus aureus*

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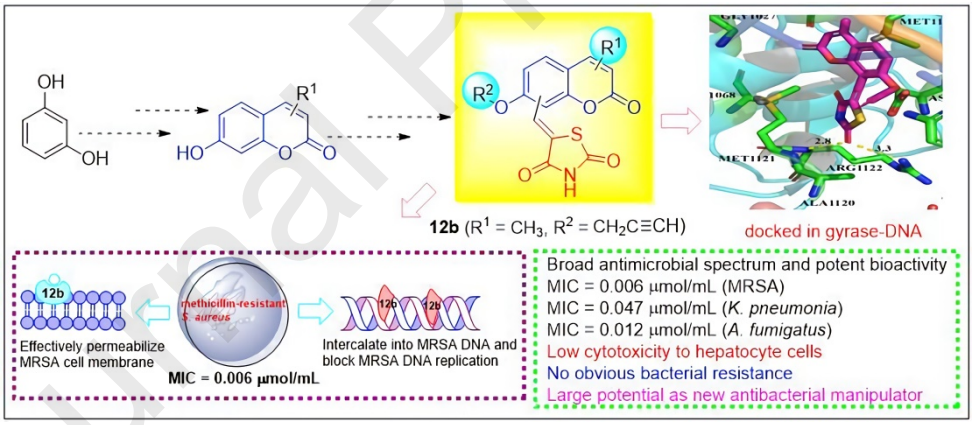
A series of novel ethylenic conjugated coumarin thiazolidinediones were synthesized and screened for their antimicrobial activities.



► Novel ethylenic conjugated coumarin thiazolidinediones with good antimicrobial potency were developed.

► Compound **12b** showed excellent inhibitory efficacy against MRSA and A. *fumigatus* with MIC values of 0.006 µmol/mL and 0.012 µmol/mL, respectively.

► Compound **12b** with low toxicity did not trigger the resistance development in bacteria.

► Molecular docking rationalized the antimicrobial activity.

► Compound **12b** could effectively permeabilize MRSA cell membrance and intercalate into DNA to block MRSA DNA replication.

Declaration of Interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: