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Synthesis and Antibacterial Evaluation of Coumarin–Thiazole Derivatives with IC_{50} Determination

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ABSTRACT

The rapid emergence of antimicrobial resistance has become a significant global health challenge, reducing the effectiveness of existing antibiotics and necessitating the discovery of new antibacterial agents. Among pathogenic microorganisms, Staphylococcus aureus is responsible for a wide range of infections, including skin infections, pneumonia, septicemia, and hospital-acquired diseases. In this study, a series of novel coumarin–thiazole derivatives (CT-1–CT-6) were synthesized and evaluated for their antibacterial activity against Staphylococcus aureus. The synthesis was achieved through a multistep reaction involving the formation of 3-acetyl coumarin from salicylaldehyde and ethyl acetoacetate, followed by bromination to produce bromoacetyl coumarin. Subsequent reaction with thiourea generated a coumarin–thiazole intermediate, which was further condensed with various substituted aromatic aldehydes to obtain the final derivatives. The synthesized compounds were characterized by melting point determination and thin layer chromatography to confirm their purity. Antibacterial activity was assessed using the agar well diffusion method, and the inhibitory potential of selected compounds was further evaluated through IC_{50} determination. The results demonstrated that compounds CT-1 and CT-4 exhibited comparatively higher antibacterial activity, producing inhibition zones of 18 mm and 17 mm, respectively, against Staphylococcus aureus. Compounds CT-3 and CT-5 showed moderate activity, while CT-2 and CT-6 displayed relatively lower antibacterial effects. IC_{50} analysis revealed that CT-1 (15.2 µg/mL) exhibited the highest antibacterial potency among the synthesized derivatives, followed by CT-4 (16.8 µg/mL) and CT-3 (19.5 µg/mL), whereas the reference drug ciprofloxacin demonstrated the strongest activity with an IC_{50} of 4.1 µg/mL. Preliminary structure–activity relationship analysis suggested that electron-withdrawing substituents on the aromatic ring may enhance antibacterial activity. These findings indicate that coumarin–thiazole hybrid scaffolds represent promising candidates for further development of antibacterial agents.

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1. INTRODUCTION:

The rapid emergence of antimicrobial resistance has become a major global health concern. The increasing resistance of pathogenic bacteria to commonly used antibiotics has reduced the effectiveness of many available therapeutic agents, thereby creating an urgent need for the development of new antimicrobial compounds [1]. Among the various bacterial pathogens, *Staphylococcus aureus* is one of the most significant causes of infections in humans, including skin infections, pneumonia, septicemia, and other hospital-acquired infections [2]. Therefore, the discovery of new antibacterial agents with improved activity remains an important area of pharmaceutical research. Coumarin derivatives represent an important class of heterocyclic compounds widely distributed in natural products and medicinal chemistry [3]. Numerous studies have demonstrated that coumarin-based molecules exhibit a broad spectrum of biological activities, including antimicrobial, antioxidant, anti-inflammatory, anticancer, and anticoagulant properties. Because of their structural versatility and pharmacological potential, coumarin derivatives have attracted considerable interest for the development of new therapeutic agents. Thiazole is another important heterocyclic scaffold that is frequently found in many biologically active molecules and pharmaceutical drugs. Compounds containing the thiazole ring have been reported to possess various biological activities such as antibacterial, antifungal, anti-inflammatory, and anticancer effects. The presence of heteroatoms such as nitrogen and sulfur in the thiazole ring contributes to its ability to interact with biological targets [4].

The combination of two biologically active heterocyclic systems within a single molecule is a commonly used strategy in medicinal chemistry to enhance biological activity. Hybrid molecules containing both coumarin and thiazole moieties have been reported to exhibit promising pharmacological properties, particularly antimicrobial activity. The incorporation of different substituents on the aromatic ring may further influence the biological activity of these compounds. Based on these considerations, the present study was undertaken to synthesize a series of novel coumarin–thiazole derivatives and evaluate their antibacterial activity against *Staphylococcus aureus*. The synthesized compounds were screened using the agar well diffusion method, and their inhibitory potential was further assessed through IC_{50} determination.

2. MATERIALS AND METHODS:

2.1 Materials:

All chemicals and reagents used in the present study were of analytical grade and used without further purification. Salicylaldehyde, ethyl acetoacetate, thiourea, substituted aromatic aldehydes, bromine (Br_2), glacial acetic acid, ethanol, dimethyl sulfoxide (DMSO), nutrient agar, and nutrient broth were obtained from standard commercial chemical suppliers. Ciprofloxacin was used as the reference antibacterial drug. Distilled water was used for the preparation of all experimental solutions. The bacterial strain Staphylococcus aureus was obtained from the microbiology laboratory and maintained on nutrient agar slants at 4 °C until further use.

2.2 Instruments:

Melting points of the synthesized compounds were determined using a digital melting point apparatus and were uncorrected. Microbiological experiments were conducted under aseptic conditions in a laminar airflow cabinet. Bacterial cultures were incubated in a bacteriological incubator maintained at 37 °C.

2.3 Synthesis of Coumarin–Thiazole Derivatives:

The synthetic pathway employed for the preparation of coumarin–thiazole derivatives is illustrated in Figure 1.

Step 1: Synthesis of 3-Acetyl Coumarin:

Salicylaldehyde (10 mmol) and ethyl acetoacetate (15 mmol) were dissolved in ethanol in a round-bottom flask. A few drops of piperidine were added as a catalyst and the reaction mixture was refluxed for approximately 3 hours. After completion of the reaction, the mixture was cooled and poured into crushed ice. The precipitated product was filtered, washed with cold water, and dried to obtain 3-acetyl coumarin.

Step 2: Synthesis of Bromoacetyl Coumarin:

3-Acetyl coumarin (1 mmol) was dissolved in acetonitrile and treated with bromine solution under continuous stirring. The reaction mixture was maintained at approximately 50 °C until completion as monitored by TLC. After completion, the solvent was evaporated and the

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product was purified to obtain bromoacetyl coumarin [5].

Step 3: Formation of Coumarin–Thiazole Intermediate:
Bromoacetyl coumarin (1 mmol) was reacted with thiourea (1 mmol) in ethanol under reflux conditions for 4–5 hours. After completion of the reaction, the mixture was allowed to cool to room temperature and the precipitated product was filtered and recrystallized from ethanol to obtain the coumarin–thiazole intermediate.

Step 4: Synthesis of Final Coumarin–Thiazole Derivatives:
The coumarin–thiazole intermediate (1 mmol) was condensed with substituted aromatic aldehydes (1 mmol) in ethanol containing a few drops of glacial acetic acid. The reaction mixture was refluxed for approximately 4 hours. After cooling to room temperature, the precipitated product was filtered, washed with petroleum ether, and recrystallized from ethanol to obtain the final coumarin–thiazole derivatives [6].

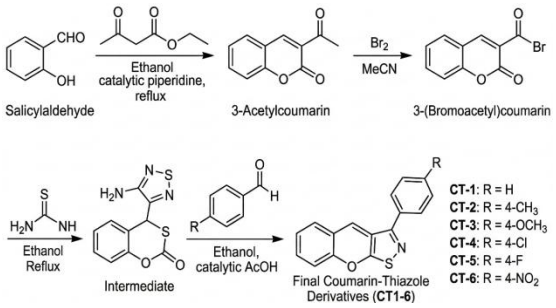

Figure 1. Synthetic pathway for the preparation of coumarin–thiazole derivatives.

2.4 Characterization of Synthesized Compounds:

The synthesized compounds were characterized by determining their melting points and by thin layer chromatography to confirm their purity. Infrared spectra were recorded using an FTIR spectrophotometer to identify characteristic functional groups present in the synthesized compounds[7]. The synthesized derivatives were coded according to the substituted aromatic aldehydes used in the final condensation reaction, as described in Table 1.

Table 1. List of synthesized coumarin–thiazole derivatives

Compound Code	Substituent (R)
CT-1	Phenyl
CT-2	4-Methoxyphenyl
CT-3	4-Hydroxyphenyl
CT-4	4-Chlorophenyl
CT-5	3-Nitrophenyl
CT-6	3,4-Dimethoxyphenyl

2.5 Evaluation of Antibacterial Activity:

The antibacterial activity of the synthesized compounds was evaluated using the agar well diffusion method against selected Gram-positive and Gram-negative bacterial strains.

2.5.1 Preparation of Bacterial Inoculum:

Bacterial cultures of *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* were grown overnight in nutrient broth at 37 °C. The turbidity of the bacterial suspension was adjusted to obtain a standardized inoculum suitable for antibacterial testing [8].

2.5.2 Agar Well Diffusion Method:

Sterile nutrient agar medium was prepared and poured into sterile Petri plates and allowed to solidify. The bacterial inoculum was evenly spread on the agar surface using a sterile cotton swab. Wells of approximately 6 mm diameter were made in the agar using a sterile cork borer. Solutions of the synthesized compounds were prepared in dimethyl sulfoxide (DMSO) and introduced into the wells. Ciprofloxacin was used as the reference antibacterial drug and DMSO served as the negative control. The plates were incubated at 37 °C for 24 hours under aerobic conditions [9].

2.6 Determination of IC_{50}:

The IC_{50} values of the synthesized compounds were determined by evaluating antibacterial inhibition at different concentrations. Serial dilutions of the test compounds were prepared in DMSO and tested against selected bacterial strains under similar experimental conditions. The IC_{50} value was defined as the concentration of compound required to inhibit 50 % of bacterial growth [10]. The percentage inhibition of bacterial growth was calculated using the following equation:

$$\text{Inhibition (\%)} = 1 - \frac{A_{\text{Sample}}}{A_{\text{control}}} \times 100$$

A_{sample} represents the absorbance of the test sample and $A_{control}$ represents the absorbance of the control.

3. RESULTS AND DISCUSSION:

3.1 Chemistry:

A series of coumarin–thiazole derivatives were successfully synthesized through a multistep reaction involving the formation of the coumarin nucleus followed by thiazole ring formation and condensation with substituted aromatic aldehydes. The synthetic route adopted in the present work is illustrated in Figure 1. Initially, salicylaldehyde was reacted with ethyl acetoacetate in the presence of piperidine to obtain 3-acetyl coumarin. Bromination of the obtained compound produced bromoacetyl coumarin, which on reaction with

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thiourea resulted in the formation of the coumarin–thiazole intermediate. The final derivatives were obtained by condensation of this intermediate with different substituted aromatic aldehydes in ethanol using glacial acetic acid as a catalyst. The synthesized compounds were obtained in moderate to good yields and appeared as crystalline solids. The purity of the compounds was confirmed by thin layer chromatography. The physical characteristics of the synthesized derivatives are summarized in Table 2.

Table 2. Physical characteristics of synthesized coumarin–thiazole derivatives

Compound Code	Substituent (R)	Yield (%)	Melting Point (°C)	Appearance
CT-1	Phenyl	72	210–212	Pale yellow solid
CT-2	4-Methoxyphenyl	69	218–220	Yellow crystalline solid
CT-3	4-Hydroxyphenyl	74	225–227	Off-white solid
CT-4	4-Chlorophenyl	76	230–232	Yellow solid
CT-5	3-Nitrophenyl	71	235–237	Light brown solid
CT-6	3,4-Dimethoxyphenyl	68	221–223	Pale yellow solid

3.2 Antibacterial Activity:

The antibacterial activity of the synthesized coumarin–thiazole derivatives was evaluated against the Gram-positive bacterial strain Staphylococcus aureus using the agar well diffusion method. The antibacterial activity was determined by measuring the diameter of the inhibition zone formed around the wells containing the test compounds after incubation. Ciprofloxacin was used as the reference antibacterial drug. The observed inhibition zones for the synthesized compounds are presented in Table 3, and a representative agar diffusion plate is shown in Figure 3. Among the tested derivatives, CT-1 and CT-4 exhibited relatively higher antibacterial activity, producing larger inhibition zones compared to other synthesized compounds. Compounds CT-3 and CT-5 showed moderate antibacterial activity, whereas CT-2 and CT-6 displayed comparatively lower inhibition against Staphylococcus aureus. As expected, the reference drug ciprofloxacin produced the largest inhibition zone, confirming the validity of the assay (Figure 2).

Table 3 Antibacterial activity of synthesized coumarin–thiazole derivatives against *Staphylococcus aureus*

Compound	Zone of Inhibition (mm)
CT-1	18
CT-2	13
CT-3	15
CT-4	17
CT-5	14
CT-6	12
Ciprofloxacin	25

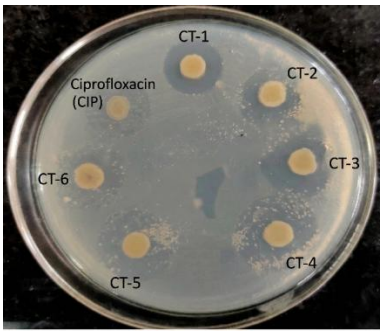

Figure 2. Agar well diffusion assay showing antibacterial activity.

3.3 IC_{50} Determination:

The compounds that exhibited comparatively higher antibacterial activity in the preliminary screening were further evaluated for IC_{50} determination. Based on the zone of inhibition results, compounds CT-1, CT-4, and CT-3 were selected for further evaluation. The IC_{50} values were determined by measuring bacterial growth inhibition at different concentrations of the synthesized compounds. The IC_{50} value represents the concentration of compound required to inhibit 50% of bacterial growth. Among the evaluated derivatives, CT-1 showed the lowest IC_{50} value among the synthesized compounds, indicating relatively higher antibacterial potency, followed by CT-4 and CT-3. However, the reference drug ciprofloxacin exhibited the strongest antibacterial activity with the lowest IC_{50} value. The calculated IC_{50} values are presented in Table 4 and Figure 3.

Table 4. IC_{50} values of selected coumarin–thiazole derivatives

Compound	IC_{50} (µg/mL)
CT-1	15.2
CT-4	16.8
CT-3	19.5
Ciprofloxacin	4.1

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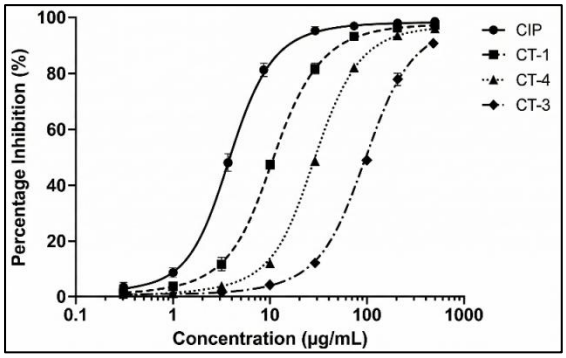

Figure 3. Dose–response curves for IC_{50} determination.

3.4 Structure–Activity Relationship (SAR):

Based on the antibacterial screening results, some preliminary structure–activity relationships were observed. The presence of different substituents on the aromatic ring significantly influenced the antibacterial activity of the synthesized compounds. Among the synthesized derivatives, compound CT-4 containing a chloro substituent on the phenyl ring showed the highest antibacterial activity among the test compounds. This may be attributed to the electron-withdrawing nature of the chloro group, which may enhance interaction with bacterial targets. Compound CT-3, containing a hydroxyl group, also exhibited moderate antibacterial activity against both Gram-positive and Gram-negative bacteria. In contrast, compounds containing methoxy substituents such as CT-2 and CT-6 showed comparatively lower antibacterial activity. These observations suggest that the nature and position of substituents on the aromatic ring play an important role in determining the antibacterial activity of coumarin–thiazole derivatives.

CONCLUSION:

In the present study, a series of coumarin–thiazole derivatives (CT-1–CT-6) were successfully synthesized using a multistep synthetic approach involving the formation of a coumarin nucleus followed by thiazole ring formation and condensation with substituted aromatic aldehydes. The synthesized compounds were evaluated for their antibacterial activity against Staphylococcus aureus using the agar well diffusion method. Among the synthesized derivatives, compounds CT-1 and CT-4 exhibited comparatively higher antibacterial activity, while CT-3 and CT-5 showed moderate activity, and the remaining compounds demonstrated relatively lower antibacterial effects. Further evaluation through IC_{50} determination indicated that CT-1 showed the lowest IC_{50} value among the synthesized compounds, suggesting improved antibacterial potency compared to other derivatives in the series. However, the reference drug ciprofloxacin showed the strongest antibacterial activity among all tested samples. The results of this study suggest that coumarin–thiazole hybrid molecules represent promising scaffolds for the development of new antibacterial agents. Further structural modification and detailed biological investigations may lead to the discovery of more potent derivatives with improved antibacterial activity.

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CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest.

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