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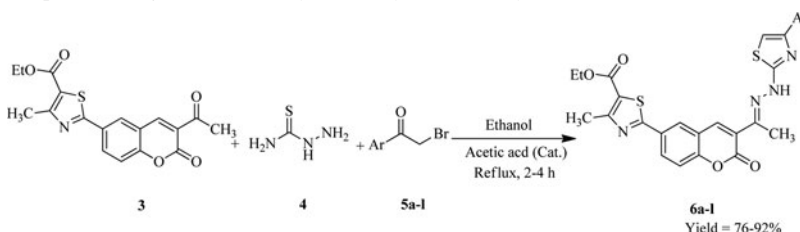
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## SYNTHESIS AND ANTIBACTERIAL EVALUATION OF NOVEL 3,6-DISUBSTITUTED COUMARIN DERIVATIVES

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**Abstract** A novel series of 3,6-disubstituted coumarin derivatives were synthesized by the reaction of ethyl-2-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-methylthiazole-5-carboxylate with thiosemicarbazide and various phenacyl bromides / 3-(2-bromoacetyl)-2H-chromen-2-ones / 2-(2-bromoacetyl)-3H-benzo[f]chromen-3-one in ethanol having catalytic amount of acetic acid under reflux conditions with good yields. All the synthesized compounds were fully characterized by spectral studies and evaluated for their *in vitro* antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus subtilis* (Gram positive), *Escherichia coli*, and *Azotobacter* (Gram negative) bacterial strains. Activity results revealed that the compound **6h** against *Escherichia coli* and compound **6i** against *Pseudomonas aeruginosa* and *Escherichia coli* have shown maximum zones of inhibition. Remaining compounds showed moderate to good activity against all the tested bacterial strains compared with the standard drug cefotaxime.

**Keywords** Antibacterial activity; 3,6-disubstituted coumarins; thiazole

## INTRODUCTION

The natural and synthetic coumarin derivatives played an important role in medicinal chemistry because of their biological and pharmacological properties. Hence the synthesis of various coumarin derivatives occupied an important place

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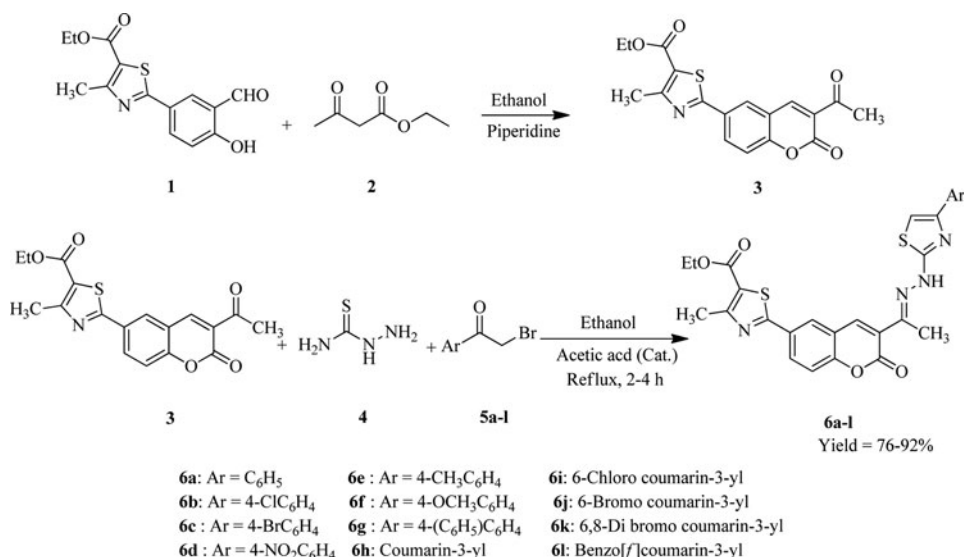
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in organic synthesis. Coumarins and their derivatives displayed antimicrobial,<sup>[1,2]</sup> antiviral,<sup>[3]</sup> anticancer,<sup>[4]</sup> anti-inflammatory,<sup>[5]</sup> antioxidant,<sup>[6]</sup> anti-HIV,<sup>[7]</sup> and antiasthmatic<sup>[8]</sup> activities. These also act as acetylcholinesterase<sup>[9]</sup> and monoamine oxidase<sup>[10]</sup> inhibitors for depression and Alzheimer's disease. In particular, 3,6-disubstituted coumarins act as mechanism-based inhibitors of thrombin and factor Xa.<sup>[11]</sup> Similarly, numerous biologically active molecules have thiazole rings as an integral part of their structure. This nucleus constitutes an integral part of all the available penicillins<sup>[12]</sup> for controlling bacterial diseases. The literature survey revealed that thiazoles act as antimicrobial,<sup>[13,14]</sup> antitumor,<sup>[15]</sup> anti-inflammatory,<sup>[16]</sup> anticonvulsant,<sup>[17]</sup> and anticoagulant<sup>[18]</sup> agents. In view of the therapeutic properties of these moieties (coumarins and thiazoles), as well as in continuation of our earlier studies on coumarin derivatives,<sup>[19–21]</sup> we report the design and synthesis of a novel series of 3,6-disubstituted coumarin derivatives under conventional method.<sup>[22,23]</sup>

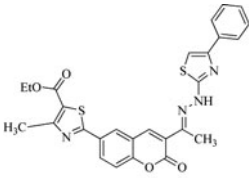
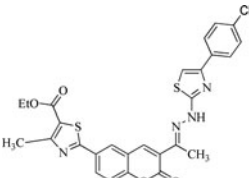
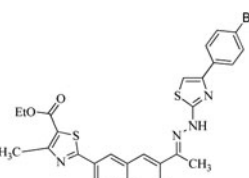
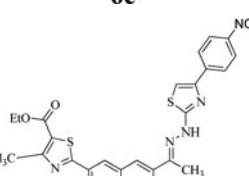
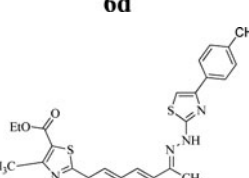
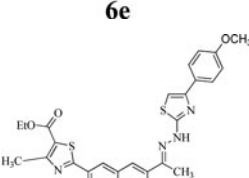
## RESULTS AND DISCUSSION

Ethyl-2-(3-acetyl-2-oxo-2*H*-chromen-6-yl)-4-methylthiazole-5-carboxylate (**3**) was prepared from ethyl-2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**1**) and ethylacetoacetate (**2**) in the presence of a base by Knoevenagel reaction. The title compounds, 3,6-disubstituted coumarin derivatives (**6a–l**) that incorporated two important pharmacophores (coumarin, thiazole heterocycle), were synthesized by one-pot multicomponent condensation of ethyl-2-(3-acetyl-2-oxo-2*H*-chromen-6-yl)-4-methylthiazole-5-carboxylate (**3**), thiosemicarbazide (**4**), and various phenacyl bromides (**5a–g**) / 3-(2-bromoacetyl)-2*H*-chromen-2-one derivatives (**5h–k**) / 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**5l**) in ethanol with a catalytic amount of acetic acid under reflux conditions (Scheme 1) with good yields (Table 1). All the synthesized compounds were confirmed by spectroscopic (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR,



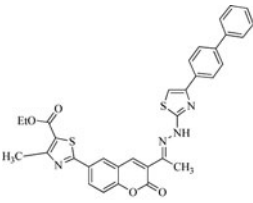
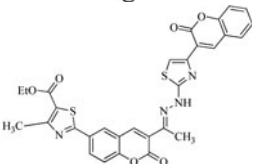
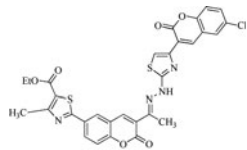
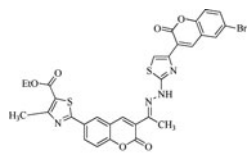
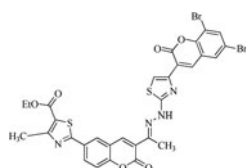
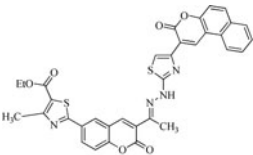
**Scheme 1.** Synthesis of 3,6-disubstituted coumarin derivatives.

**Table 1.** Synthesis of 3,6-disubstituted coumarin derivatives (**6a–l**)

Entry <sup>a</sup>	Compound	Time (h)	Yield (%) <sup>b</sup>
1	 <p><b>6a</b></p>	2	88
2	 <p><b>6b</b></p>	3	90
3	 <p><b>6c</b></p>	3	89
4	 <p><b>6d</b></p>	3	82
5	 <p><b>6e</b></p>	2	86
6	 <p><b>6f</b></p>	2	92

(Continued)

Table 1. Continued

Entry <sup>a</sup>	Compound	Time (h)	Yield (%) <sup>b</sup>
7	 <b>6g</b>	3	84
8	 <b>6h</b>	4	87
9	 <b>6i</b>	4	78
10	 <b>6j</b>	3	80
11	 <b>6k</b>	2	76
12	 <b>6l</b>	3	84

<sup>a</sup>Reaction conditions: 4-substituted phenacyl bromide (**5a–g**) / 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**5h–k**) / 2-(2-bromoacetyl)-3*H*-benzo[*f*]chromen-3-one (**5l**) (1 mmol), thiosemicarbazide (4.1 mmol), and ethyl-2-(3-acetyl-2-oxo-2*H*-chromen-6-yl)-4-methylthiazole-5-carboxylate (3.1 mmol), ethanol + cat. acetic acid, reflux.

<sup>b</sup>Yields refers to isolated products.

and mass) and elemental analysis. In IR spectra, the presence of lactone and imine functional groups was confirmed by absorption at  $\nu$  1717–1742 and 1598–1631  $\text{cm}^{-1}$  respectively, as well as other characteristic absorption bands.  $^1\text{H}$  NMR spectroscopic analysis revealed the diagnostic resonances for the coumarin (4-H) protons at  $\delta$  8.54–8.76 ppm as singlets. In addition, the molecular ion peak from the mass spectra and elemental analyses data further support the formation of products.

### Antibacterial Activity

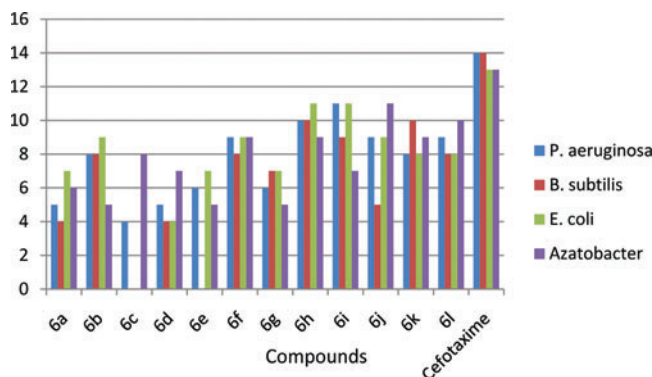
All the newly synthesized compounds (**6a–l**) were assessed for their *in vitro* antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus subtilis* (Gram positive), *Escherichia coli*, and *Azotobacter* (Gram negative) bacterial strains with compared to standard antibiotic drug cefotaxime. Zone of inhibition (mm) values for analogues and positive control drug cefotaxime at were determined by agar disc diffusion method.<sup>[24]</sup> The bacterial strains were grown and maintained on nutrient agar plates. All the compounds and standard were dissolved in dimethylsulfoxide (DMSO; 100  $\mu\text{g}/\text{mL}$  and 30  $\mu\text{g}/\text{mL}$  respectively) and transferred to each disc with the help of micropipette. After 24 h incubation at 37  $^{\circ}\text{C}$ , the resulting zone of inhibition was measured.

The antibacterial data revealed that almost all the compounds **6a–l** have shown moderate to good antibacterial activity (Table 2). Compounds **6f**, **6h–k**, and **6l** have shown good activity whereas compounds **6a**, **6b**, **6d**, **6g** have shown moderate activity against both Gram-positive and Gram-negative strains. Compound **6c** is inactive towards *Bacillus subtilis* and *Escherichia coli*, whereas compound **6e** is inactive only on *Bacillus subtilis*. In the overview of antibacterial data, compound **6h** against *Escherichia coli* and compound **6i** against *Pseudomonas aeruginosa* and *Escherichia coli* have shown maximum zones of inhibition (11 mm) when compared with the

**Table 2.** Antibacterial activity of 3,6-disubstituted coumarin derivatives [zone of inhibition (ZOI) values of the compounds at 100  $\mu\text{g}/\text{mL}$  and positive control drug cefotaxime at 30  $\mu\text{g}/\text{mL}$ ]

Analogue	Zone of inhibition (mm)			
	Gram positive		Gram negative	
	<i>Pseudomonas aeruginosa</i>	<i>Bacillus subtilis</i>	<i>Escherichia coli</i>	<i>Azotobacter</i>
6a	5	4	7	6
6b	8	8	9	5
6c	4	—	—	8
6d	5	4	4	7
6e	6	—	7	5
6f	9	8	9	9
6g	6	7	7	5
<b>6h</b>	10	10	11	9
<b>6i</b>	11	9	11	7
6j	9	5	9	11
6k	8	10	8	9
6l	9	8	8	10
Cefotaxime	14	14	13	13

Note. — indicates not active.



**Figure 1.** Graphical representation of antibacterial activity of 3,6-disubstituted coumarin derivatives and cefotaxime.

standard drug cefotaxime. The graphical representation of antibacterial activity of the compounds as well as standard drug cefotaxime are shown in Fig. 1.

## EXPERIMENTAL

All the reagents and solvents were purchased from Aldrich/Merck and used without further purifications. Melting points were determined in open capillaries using Stuart SMP30 apparatus and are uncorrected. The progress of the reactions as well as purity of compounds were monitored by thin-layer chromatography (TLC) with  $F_{254}$  silica-gel precoated sheets using hexane / ethyl acetate 8/2 as eluent; ultraviolet light and iodine vapors were used for detection. IR spectra were recorded on a Perkin-Elmer 100S spectrometer utilizing KBr pellets.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were obtained at 400 MHz and 100 MHz respectively on Bruker using dimethylsulfoxide ( $\text{DMSO}-d_6$ ) as solvent and tetramethylsilane (TMS) as internal standard. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit and the values are  $\pm 0.4\%$  of theoretical values. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

### General Procedure for the Synthesis of Ethyl-2-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-methylthiazole-5-carboxylate (3)

A mixture of ethyl 2-(3-formyl-4-hydroxyphenyl)-4-methylthiazole-5-carboxylate (**1**, 0.1 mol) and ethylacetoacetate (**2**, 0.12 mol) were dissolved in ethanol and cooled at  $0-5^\circ\text{C}$ . Piperidine (1 mL) was added dropwise to this mixture while stirring. The reaction mixture was left overnight, resulting in the formation of a yellow-colored solid. Purification by recrystallization from ethanol afforded the analytically pure product.

### General Procedure for the Synthesis of 3,6-Disubstituted Coumarin Derivatives (6a–l)

A mixture of ethyl-2-(3-acetyl-2-oxo-2H-chromen-6-yl)-4-methylthiazole-5-carboxylate (**3**, 1 mmol), thiosemicarbazide (**4**, 1 mmol), and various phenacyl bromides

(**5a–g**) / 3-(2-bromoacetyl)-2*H*-chromen-2-ones (**5h–k**) / 2-(2-bromoacetyl)-3*H*-benzo [*f*]chromen-3-one (**5l**) (1 mmol) were dissolved in 10 mL of absolute ethanol in the presence of a catalytic amount of acetic acid and heated at refluxing temperature for 2–4 h. The reaction was monitored by TLC. Contents were poured into ice-cold water, and the solid obtained was filtered, dried, and recrystallized in ethanol.

**Ethyl-4-methyl-2-(2-oxo-3-(1-(2-(4-phenylthiazol-2-yl)hydrazono)ethyl)-2*H*-chromen-6-yl)thiazole-5-carboxylate (**6a**)**

Pale yellow solid; mp 224–226 °C; IR (KBr,  $\text{cm}^{-1}$ )  $\nu_{\text{max}}$ : 3404 (NH), 1741 (C=O), 1718 (C=O), 1611, (C=N) 1565 (C=C);  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  1.31 (t, 3H,  $J = 7.2$  Hz), 2.29 (s, 3H), 2.71 (s, 3H), 4.28–4.33 (m, 2H), 7.29–7.44 (m, 2H), 7.55 (d, 1H,  $J = 8.8$  Hz), 7.89 (d, 2H,  $J = 7.2$  Hz), 8.19–8.22 (m, 1H), 8.30 (s, 1H), 8.56–8.62 (m, 2H), 8.74 (s, 1H), 11.45 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  14.0, 16.0, 17.1, 61.2, 104.4, 116.9, 119.5, 121.5, 125.5, 127.2, 127.4, 128.5, 129.7, 134.5, 139.9, 144.4, 154.7, 158.5, 160.2, 161.2, 167.3, 169.2; MS (ESI)  $m/z$ : 531  $[\text{M} + 1]^+$ . Anal. calcd. for  $\text{C}_{27}\text{H}_{22}\text{N}_4\text{O}_4\text{S}_2$ : C, 61.12; H, 4.18; N, 10.56. Found: C, 61.24; H, 4.06; N, 10.61.

## CONCLUSION

In conclusion, we have synthesized a novel series of 3,6-disubstituted coumarin derivatives by using conventional methods. All synthesized compounds were determined from their spectral (IR,  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR) and mass data and assessed for their in vitro antibacterial activity.

## ACKNOWLEDGMENT

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## SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the [publisher's website](#).

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