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Original article

Synthesis, biological evaluation and docking studies of 4-aryloxymethyl coumarins derived from substructures and degradation products of vancomycin

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ABSTRACT

Two series of 4-aryloxymethyl coumarins derived from the reaction of 4-bromomethyl coumarins with ethyl gallate and ethyl ester of N-Benzoyl tyrosine have been synthesized. Gallate ethers **3a**–**3g** and tyrosine derivatives **4e**–**4j** were most effective against *Entercoccus faecalis*. They were also found to be effective against *Aspergillus niger* and *Candida albicans*. Comparative docking studies with novobiocin have indicated better binding ability and higher '*C*' score values than novobiocin.

1. Introduction

Coumarins are a group of bioactive molecules, found extensively in nature with a wide range of structural modifications [1]. They exhibit antiviral [2], anti-cancer [3,4], anti-fungal [5], anti-inflammatory [6,7], anti-HIV [8] properties. They have been known to be particularly effective against Gram-positive species [9]. Coumarin based anti-biotics viz. novobiocin and clorobiocin affect the functioning of DNA gyrase, which is the basis for their broad spectrum antibacterial activity [10].

Hydroxy coumarins like scopoletin and gallic acid have been found to occur in *Pelargonium sidoides*, *Pelargonium reniforme* [14] and other plant species, exhibiting a range of biological activities [11–14]. Ester conjugates of 7-hydroxy coumarin with gallic acid have been found to be anti-proliferative against human cancer cell lines [15], methyl gallates with bis-aryl ether linkage and tyrosine moiety are common substructures to the anti-biotics of vancomycin family [16,17]. Naturally occurring bromotyrosine derivatives have been found to possess anti-microbial effect on the methicillin resistant *S. aureus* (MRSA) [18]. 4-aryloxymethyl coumarins with alkoxy and chloro substituents were found to be effective against *E. coli* [19].

Incorporation of bio-compatible fragments like vanillin and paracetamol has resulted in 4-aryloxymethyl coumarins exhibiting anti inflammatory activity (Fig. 1) [20].

In view of the importance associated with the above cited moieties in their potent anti-microbial activity, it was thought of considerable interest to employ derivatives of gallic acid and N-Benzoyl tyrosine for the generation of new 4-aryloxymethyl coumarins which are represented in the Scheme 1.

2. Chemistry

4-Bromoethylacetoacetate obtained from bromination of ethylacetoacetate, was treated with various substituted phenols under Pechmann cyclisation conditions using neat sulphuric acid as condensing agent. The reaction resulted in the formation of substituted 4-bromomethyl-coumarins **1** [21]. The allylic nucleophilic displacement was brought about by the reaction of **1** with ethyl gallate **2** (prepared from gallic acid and ethanol) to obtain compounds **3a**–**3j**.

4-Bromomethyl coumarins **1** were also condensed with *N*-benzoyl tyrosine ethyl ester, to obtain compounds **4a**–**4j**. In both

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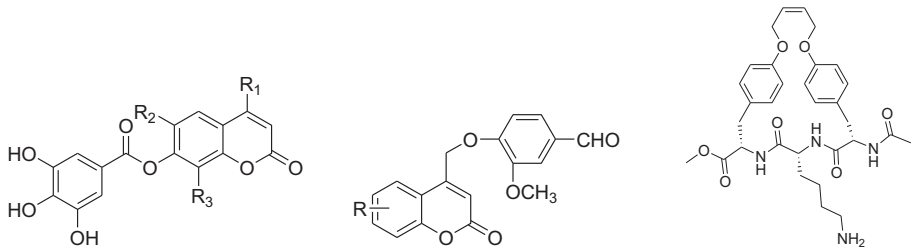
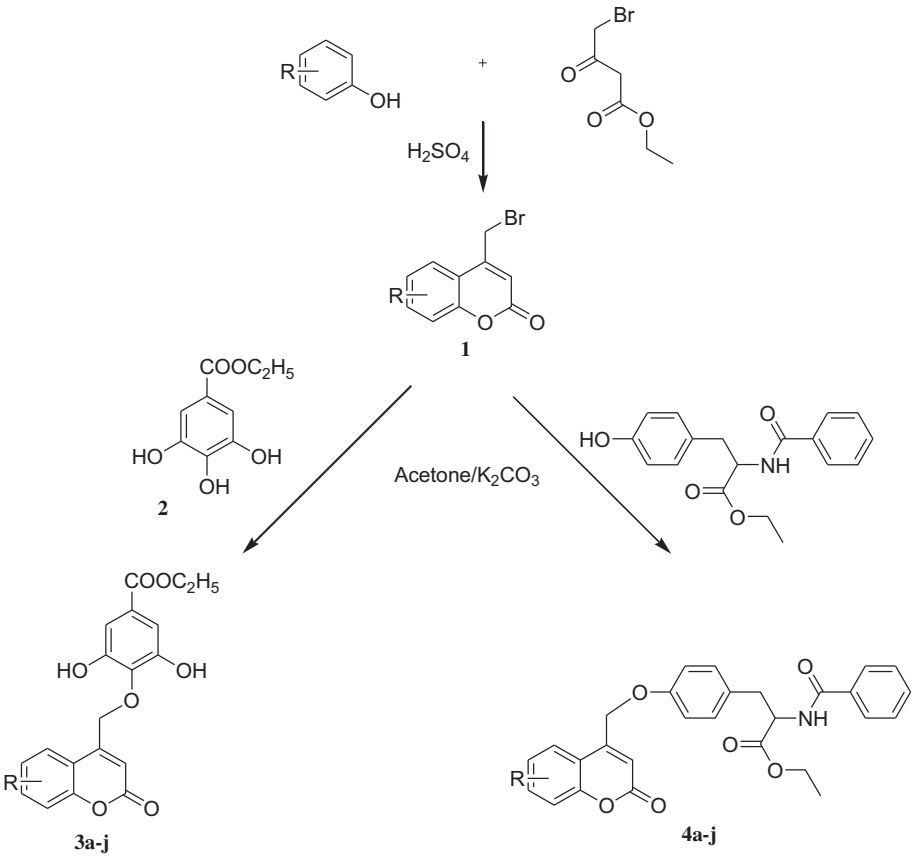


Fig. 1. Biologically active structurally related molecules.

the cases reactions were carried out in dry acetone in presence of anhydrous potassium carbonate at room temperature. Anhydrous potassium carbonate abstracts proton from phenolic –OH to give resonance stabilized phenoxide anion, which then reacts with 4-bromomethyl-coumarins to give desired compounds.

3. Results and discussion

Formation of products **3** and **4** is well supported by spectroscopic analysis. In case of compound **3a**, (R = 6-CH_3) IR spectrum exhibited two bands at 1711 cm^{-1} and 3444 cm^{-1} due to lactone and –OH stretching bands of coumarin and gallate moiety respectively. Formation of ethers **3a** was further confirmed by ^1H NMR, wherein the O–CH_2 protons appear as a singlet at 5.25 ppm which is characteristic of 4-aryloxymethyl coumarins [19]. The C_3–H of coumarin was observed at 6.73 ppm and the C_6–CH_3 protons appear as singlet at 2.34 ppm. Two aromatic protons resonating at 7.02 corresponded to the protons on gallate moiety [24], C5–H of coumarin resonated as singlet at 7.65, whereas C7–H and C8–H resonated as doublets with J = 8.0 Hz at 7.32 and 7.44 ppm respectively. Ethoxy protons appeared as triplet quartet pattern at 1.26 and 4.23 ppm with J = 7.0 Hz. The downfield D_2O exchangeable signal at 9.83 ppm corresponded to the phenolic –OH proton. ^{13}C NMR provides additional support for structure of the compounds. Lactone carbonyl resonates at 160 ppm and ester carbonyl of gallate resonates at 165 ppm, O–CH_2 resonates at 69 ppm, the methylene



R= 6-Me; 7-Me; 6-Cl; 7-Cl; 6-OMe; 7-OMe; 5,7-Me; 7,8-Me; 5,6 Benzo; 7,8 Benzo;

Scheme 1. Synthesis of gallate and tyrosinate ethers.