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Original article

Synthesis, antimicrobial activity and QSARs of new benzoxazine-3-ones

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Abstract

New ethyl 3,4-dihydro-3-oxo-4,6,7-trisubstituted-2*H*-1,4-benzoxazine-2-acetate derivatives were synthesized and their structures were elucidated by IR, ^{1}H NMR and mass spectral data. Antimicrobial activity of the compounds was investigated by using the method of twofold serial dilution technique against different Gram-positive, Gram-negative bacteria and some *Candida* species in comparison to standard drugs. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity having MIC values of 6.25–100 μg/ml against the tested microorganisms. The QSAR analysis of a set of these compounds tested for growth inhibitory activity against *Candida krusei* was performed by using the computer-assisted multiple regression procedure. The activity contributions for substituent effects of these compounds were determined from the correlation equation for predictions of the lead optimization.

Keywords: 1,4-Benzoxazine-3-one; Antibacterial activity; Antifungal activity; QSAR

1. Introduction

The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side effects [1–4]. Therefore, the development of new and different antimicrobial drugs is a very important objective and much of the research program efforts are directed towards the design of new agents.

A group of 1,4-benzoxazine-3-ones was isolated from maize, wheat and rye several years ago [5–9]. 2,4-Dihydroxy-1,4-benzoxazine-3-one, DIBOA (Fig. 1) and its methoxy derivative DIMBOA (Fig. 1) have been shown to inhibit germination of spores of the phytopathogenic fungi [10]. They play an important role in the chemical defence of cereals against deleterious pests such as insects, pathogenic fungi and bacteria [11–14]. These molecules are present naturally in the plants as glucosides from which the aglycones are released rapidly by enzymatic hydrolysis after physical and biological injury of the plants and they exhibit antifungal, antibacterial and insecticide properties [15,16]. Only a limited number of compounds containing 1,4-benzoxazine ring system have been studied for their chemotherapeutic activity. Ofloxacin (Fig. 1) is one of the antimicrobial agents possessing the 1,4-benzoxazine ring system in its structure. All these observations prompted us to investigate this heterocyclic system to ascertain if it would offer any advantage over the other known clinically used antimicrobial drugs [17,18].

The common method for preparing 1,4-benzoxazine ring having ethyl acetate group at position 2 is by heating aminophenols with ethyl 2,3-dibromopropanoate and potassium carbonate in acetone [19].

Michael addition method is used for preparing 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-2-acetates. Reaction of various *o*-aminophenols with maleic anhydride refluxed in ethanol in the presence of triethylamino or ether or benzene gives 1,4-benzoxazine-3-ones with ethyl acetate group at position 2 in

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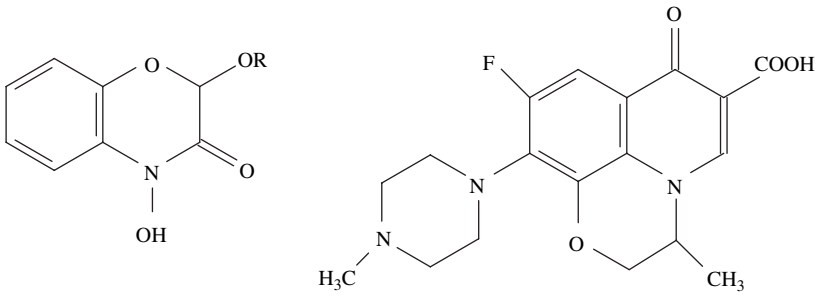


1 DIBOA, R=H
2 DIMBOA, R=OCH_3

3 OFLOXACIN

Fig. 1. Biologically active 1,4-benzoxazines.

%30 yield [20–22]. Another similar method is heating *o*-aminophenol with fumaric acid chloride monoethylester. This reaction gives the fumaramides which upon treatment with potassium carbonate in ethanol produced 3-oxo-2*H*-1,4-benzoxazine-2-acetates in %26–90 yield [22,23].

Alkylation of 2*H*-1,4-benzoxazine-3-one derivatives occurs at the ring nitrogen. Using alkyl halides and sodium hydride as bases is the most common method for alkylation [24,25].

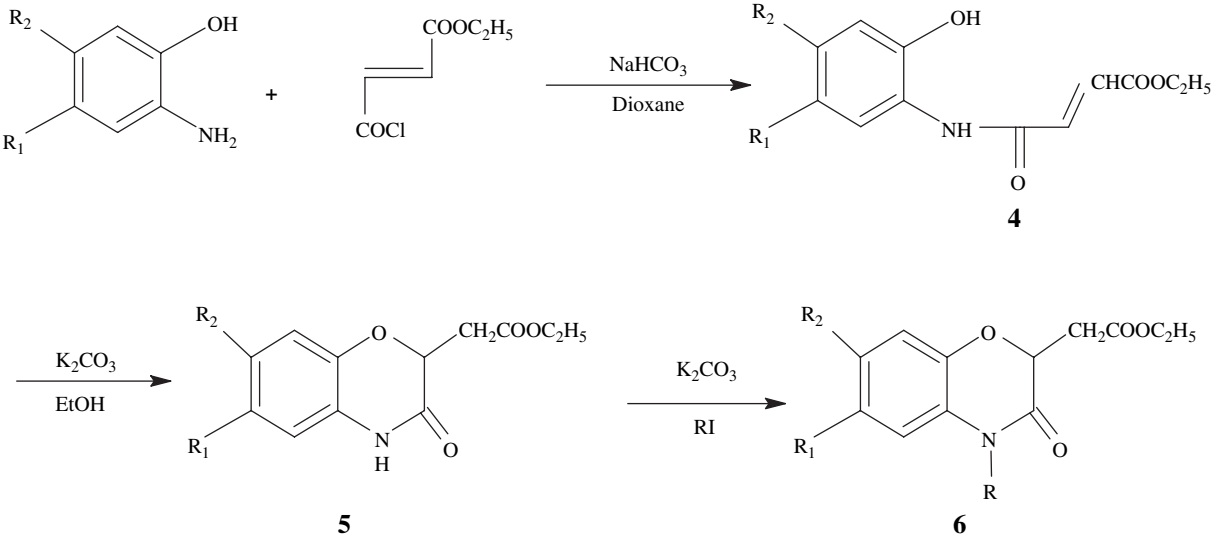
In this research, some novel ethyl 3,4-dihydro-3-oxo-6 and/or 7-disubstituted-2*H*-1,4-benzoxazine-2-acetate compounds and their *N*-alkylated derivatives were synthesized in order to interpret their antifungal activity against different *Candida* species and antibacterial activity against different Gram-positive and Gram-negative bacteria. The target of this research was to observe differences between the derivatives with free NH and *N*-alkylated ones towards antimicrobial activity. The alkylated derivatives were synthesized to avoid the behaviour of free NH as a hydrogen bond donor. 2D-QSAR analysis was also aimed to explain clearly the relation of physicochemical parameters with the activity. QSAR analysis of these compounds was performed by multiple regression analysis in order to predict the lead optimization for antifungal activity against *Candida krusei*.

2. Chemistry

Monoethyl fumaryl chloride was added to a mixture of appropriate *o*-aminophenol and sodium bicarbonate in dioxane. The prepared phenylcarbamoyl acrylate derivatives **4** were then stirred with potassium carbonate in ethanol at room temperature to form compound **5**. Alkylated compounds **6** were prepared by stirring compound **5** in acetone with methyliodide and/or ethyliodide and potassium carbonate (Scheme 1).

3. Results and discussion

A series of ethyl 3,4-dihydro-3-oxo-4,6,7-trisubstituted-2*H*-1,4-benzoxazine-2-acetate derivatives (**7**–**23**) have been synthesized by using a three-step procedure as shown in Scheme 1. All of the derivatives were supported by spectral data. The IR and ^{1}H NMR spectra are in agreement with the proposed



Scheme 1. Synthesis of 1,4-benzoxazine derivatives.