Antibacterial and Antifungal Activities of 2-Arylidene-4-(4-Methylphenyl)but-3-en-4-olides and their Pyrrolone Derivatives

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Starting from 3-3-(4-methyl-benzoyl)propionic acid and using appropriate reagents, some new 2-arylidene-4-(4-methylphenyl)but-3-en-4-olides (IIIa-g) and their corresponding pyrrolone derivatives (IVa-d) have been synthesized. These compounds were evaluated for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* as well as antifungal activity against *Candida albicans*. The compounds have considerable antifungal activity and moderate antibacterial activity.

γ-Lactones are well-known heterocycles of biological interest. Butenolides consist of unsaturated γ-lactone rings, which are also known as 2, 3 and 2, 5-dihydrofuran-2-ones. Some well-known lactones of natural origin are santonin, cardiac glycosides, sesquiterpene lactones and patulin (an antibiotic)[1-3]. A wide range of biological activities are exhibited by this class of compounds, such as anthelmintic, ascaricidal, antifungal, antiinflammatory, antitumor and antiviral[1-7]. The γ-lactone ring present in butenolide derivatives is significantly reactive and can be utilized for the synthesis of nitrogen heterocycles, i.e., pyrrolones of potential biological activities[8-12] like antifungal, antibacterial and antiinflammatory. In view of potential biological activity of members of γ-lactone ring system, it was of interest to us to prepare some new derivatives in this class.

In the present communication, a series of 2-arylidene-4-(4-methylphenyl)but-3-en-4-olides (IIIa-g) and 3-arylidene-5-(4-methylphenyl)-2(3*H*)-pyrrolones (IVa-d) were screened for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* as well as antifungal activity against *Candida albicans*, the synthesis of which has been reported in our previous communication[13].

The starting compound, i.e., 3-(4-methyl-benzoyl) propionic acid (II), was obtained by the condensation of succinic anhydride with dry toluene in presence of anhydrous aluminium chloride, following Friedel-Craft's acylation reaction conditions. 2-Arylidene-4-(4-methylphenyl)but-3-en-4-olides (IIIa-g) were synthesized from 3-(4-methyl-benzoyl)propionic acid (II) by treating it with different aromatic aldehydes in the presence of triethylamine in acetic anhydride. Some of the selected butenolides (IIIa-d) were treated with dry ammonia gas at room temperature to obtain 3-arylidene-5-(4-methyl phenyl)-2(3*H*)-pyrrolones (IVa-d). The synthesized compounds were characterized by elemental analysis, IR, ^{1}H NMR and mass spectral data. The compounds were synthesized according to Scheme 1.

All the compounds were screened for their antimicrobial activity against the microorganisms, viz, *Staphylococcus aureus* (NCTC-6571), *Escherichia coli* (ATCC-25922) and *Candida albicans* (ATCC-10231), in meat peptone agar medium at a concentration of 100 μg/ml by cup plate method[14]. Compounds inhibiting growth of one or more of the above microorganisms were further tested for minimum inhibitory concentration (MIC). A solution of the compounds was prepared in dimethylformamide (DMF) and a series of doubling dilutions prepared with sterile pipettes. To each of a series of sterile stoppered test tubes, a standard volume of nutrient broth medium was added. A control tube containing no antimicrobial agent was included. The inoculum consisting of an overnight broth culture of microorganisms was added to separate tubes. The tubes were incubated at 37° for 24 h and examined for turbidity. The tube with highest dilution showing no turbidity was the one containing compound with MIC. Results are presented in Table 1.

3-(2,4-Dichloro-benzylidene)-5-(4-methylphenyl)-2(3*H*) pyrrolone (compound IVb) showed excellent activity

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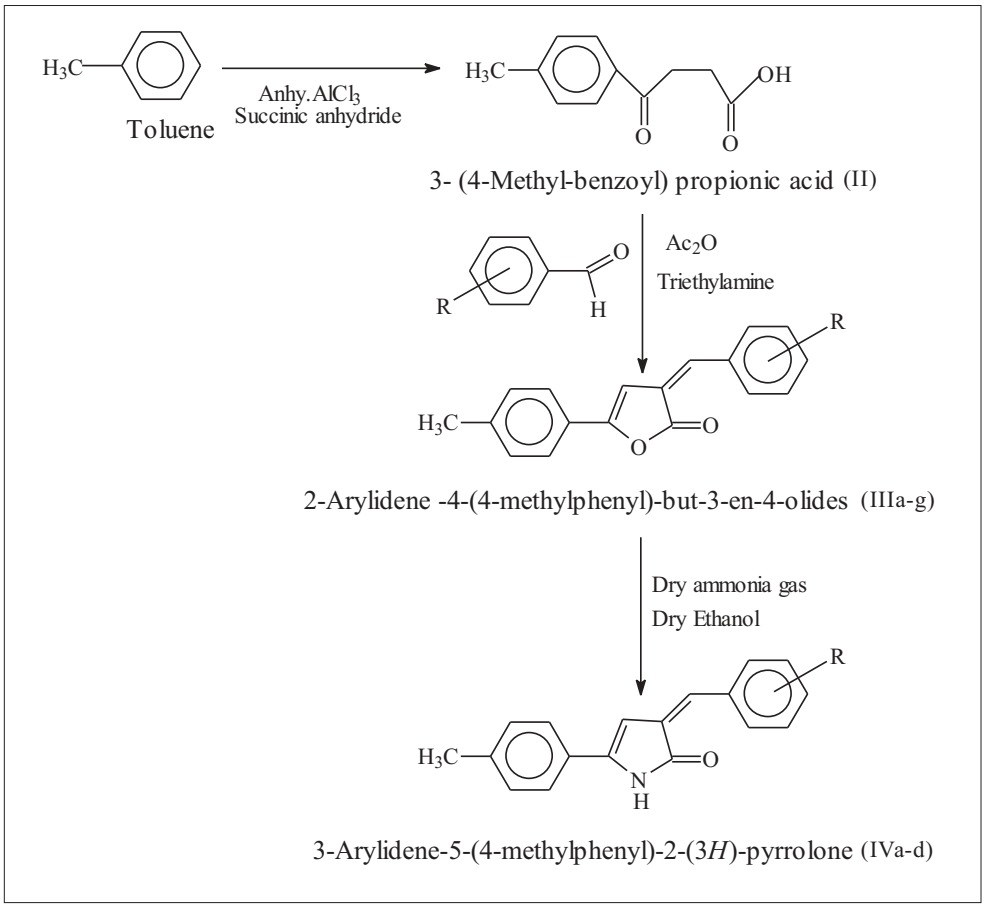

Scheme 1: Synthetic route of title compounds

against *Candida albicans* with MIC-25 µg/ml and good activity against *Staphylococcus aureus* with MIC-50 µg/ml. 3-Benzylidene-5-(4-methylphenyl)-2(3*H*) pyrrolone (compound IVa) exhibited good activity against *Staphylococcus aureus* and *Candida albicans* with MIC-50 µg/ml. Both the compounds were active against *Escherichia coli* with MIC-100 µg/ml. Majority of the compounds were insignificant in their action against *Escherichia coli.*

TABLE 1: ANTIMICROBIAL ACTIVITY (MIC*) OF THE COMPOUNDS IIIA-G AND IVA-D

Compound		Antibacterial activity		Antifungal activity
No.	R	*S. aureus*	*E. coli*	*Candida albicans*
IIIa	H	-	-	>100
IIIb	2,4-$(Cl)_2$	>100	-	>100
IIIc	3,4-$(OCH_3)_2$	-	-	-
IIId	2-$OCOCH_3$	-	-	-
IIIe	2,4-$(OCOCH_3)_2$	-	-	-
IIIf	4-Br	>100	>100	>100
IIIg	4-N-$(CH_3)_2$	-	-	-
IVa	H	50	>100	50
IVb	2,4-$(Cl)_2$	50	>100	25
Ivc	3,4-$(OCH_3)_2$	>100	-	-
IVd	2-OH	-	-	>100

*= in µg/ml; -= insignificant activity

An analysis of results showed that introduction of chloro groups (electron withdrawing) in arylidene ring increases antimicrobial action, while introduction of hydroxyl and methoxy group (electron donating) decreases the antimicrobial activity. The replacement of oxygen atom in the butenolide ring by nitrogen atom (pyrrolones) enhances antimicrobial action.

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