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Dimethyl 2-Hydroxy-1-Methyl-3-[2-Oxo-2-Phenylethylidene]-2-Phenyl-1,2-Dihydro-3H-Pyrrole-4,5-Dicarboxylate: A Potential Lead Compound as Anti-Gram-Positive and Anti-Gram-Negative Agent

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Abstract: The aim of this study was to determination the biological activity of some new synthesized pyrrole compounds. The activity against Gram-positive and Gram-negative bacteria of dimethyl 2-hydroxy-1-methyl-3-[2-oxo-2-phenylethylidene]-2-phenyl-1,2-dihydro-3H- pyrrole-4,5-dicarboxylate I was tested *in vitro* using six reference bacterial strains. e.g., *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Enterobacter earogenes* and *Pseudomonas aeruginosa*. Compound I was active against all strains tested by disk diffusion method in ranging from 15 to 27 mm per 70 μg disk. In conclusion, this compound might be used as a basic to modification in order to synthesize new antibacterial agents.

Key words: Anti-bacterial activity, disk diffusion method, gram-positive bacteria, gram-negative bacteria, pyrrole compounds

INTRODUCTION

Gram-positive and Gram-negative bacteria are a significant cause of hospital acquired and community infections and may induce diseases associated with serious levels of morbidity and mortality. Moreover, antibiotic resistance of Gram-positive pathogens, such as *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter earogenes* and *Pseudomonas aeruginosa* has become one of the major worldwide health problems (Kuhn *et al*., 2000; Schillaci *et al*., 2005). The notion that the global dissemination of microbial drug resistance observed in the antibiotic era is related to the selective pressure generated by the use of antibiotics in clinical and veterinary practices, animal husbandry and agriculture is supported by studies that have clearly correlated the emergence and dissemination of resistance with the use of antibiotics (Gustafsson *et al*., 2003; Pallecchi *et al*., 2007).

Simple nitrogen-containing heterocycles receive a considerable attention in the literature, as a consequence of their unique biological properties and their role as farmacophores of historical importance (Boulton and McKillop, 1984). Accordingly, antimicrobial activity of these compounds has been reported by El-Desouky *et al*. (2007), Bacchi *et al*. (1998), Massa *et al*. (1990) and Raimondi *et al*. (2006).

Recently the synthesis of highly functionalized 3-alkylidene-2,3-dihydro-1H-pyrrole-2-ol derivatives (Bacchi *et al*., 1998) has been reported. In this study, we report antibacterial activities of dimethyl 2-hydroxy-1-methyl-3-[2-oxo-2-phenylethylidene]-2-phenyl-1,2-dihydro-3H-pyrrole-4,5-dicarboxylate I against Gram-positive bacteria and gram-negative bacteria.

MATERIALS AND METHODS

Synthesis: This study was conducted from 1 April 2007 to April 2008 in Microbiology Department of Kurdistan University of Medical Science and Chemistry Department of Kurdistan University. Dimethyl 2-hydroxy-1-methyl-3-[2-oxo-2-phenylethylidene]-2-phenyl-1,2-dihydro-3H-pyrrole-4,5-dicarboxylate I (Fig. 1) was synthesized by methods described by Nasiri and Pourdavaie (2007).

Microorganisms: The strains used were *Staphylococcus aureus* (PTCC-1231), *Bacillus cereus* (PTCC-1045), *Bacillus subtilis* (PTCC-1023), *Escherichia coli* (PTCC 1127), *Enterobacter aerogenes* (PTCC-1221) and *Pseudomonas aeruginosa* (PTCC-1074).

Determination of antibacterial activity by disk diffusion method: Colonies were suspended in phosphate buffered

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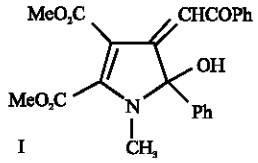


Fig. 1: Dimethyl 2-hydroxy-1-methyl-3-[2-oxo-2-phenylethylidene]-2-phenyl-1,2-dihydro-3H-pyrrole-4,5-dicarboxylate I molecular structure

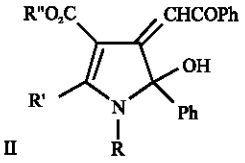
saline to an OD (480 nm) of approximately 0.2 and this suspension was inoculated onto Mueller-Hinton Agar (Merck, Germany) using cotton swabs (Coutant *et al*., 1996). Sterilized filter paper discs (Whatman type 1, 0.6 cm in diameter) were placed on the surface of agar. The tested compound was dissolved in dichloromethane to obtain a 1 mg mL^{-1} solution. The solution was diluted and added to each filter paper disk (50 to 500 μg $disk^{-1}$). The control, dichloromethane was added to the filter paper. All prepared disks were incubated at 37°C for 48 h. Inhibitory zone was observed at the points of inoculation after incubation at 37°C for 24 h was recorded. The inhibition zone diameter was measured (including the filter paper disc, 6 mm in diameters) using Vernier calipers and expressed in millimeters. Dichloromethane disk alone showed no inhibition zone. An amoxicillin standard (25 μg) was used for comparative purposes and quality control of the method (Skov *et al*., 2001).

RESULTS AND DISCUSSION

Compound I was tested for its *in vitro* anti-bacterial activity on a group of Gram-positive and Gram-negative bacteria. The anti-bacterial activities of compound I, expressed as inhibition zone (mm), are shown in (Table 1) along with the activity of amoxicillin for comparison. Compound I was found to be active against all strains tested in 75 μg $disk^{-1}$.

To extend of antibacterial effects of similar derivatives of compound I, we examined the antibacterial activities of compounds IIa-e (Fig. 2) against Gram-positive and Gram-negative bacteria. Unexpectedly the results show no inhibition zone in compare to standard amoxicillin disk. The sizes of the molecules II, as shown in Fig. 2, are bigger than the molecule I. It seems that the antimicrobial activities of the title compounds are related to the size of the molecule.

The results as shown in Table 1, there is a significance discrepancy in the diameter zone of inhibition between Gram-positive and Gram-negative bacteria. Gram-negative bacteria has two membranes in cell



II	R	R'	R"
a	Me	CO_2Et	Et
b	Et	CO_2Me	Me
c	^iPr	CO_2Me	Me
d	Bn	CO_2Me	Me
e	Me	CH_2CO_2Me	Me

Fig. 2: 3-Alkylidene-2,3-dihydro-1H-pyrrole-2-ol derivatives IIa-e molecular structures

Table 1: Antibacterial activity of compound I (as expressed in mm) compare with amoxicillin standard disk (25 μg)

Microorganisms	Compound I	Amoxicillin
Staphylococcus aureus (PTCC-1231)	27	30
Bacillus cereus (PTCC-1045)	20	27
Bacillus subtilis (PTCC-1023)	20	20
Escherichia coli (PTCC-1127)	15	18
Enterobacter aerogenes (PTCC-1221)	15	19
Pseudomonas aeruginosa (PTCC-1074)	14	17
Min	14	17
SD	4.9	5.3

envelope, therefore, it is suggest that this compound may can access easily into Gram-positive bacteria than Gram-negative ones.

In conclusion, these data of the anti-bacterial activity of compound I, showed a good inhibitory effect of this compound on growth of selected bacteria by disk diffusion method. Also the simple functional exchange in 3-alkylidene-2,3-dihdro-1H-pyrrole-2-ol derivatives, be able to vanished the antibacterial activities against Gram-positive and Gram-negative bacteria. We think that compound I might be a potential lead compound in the discovery of new anti-Gram-positive and Gram-negative agents.

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