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Antibacterial Activity of Some 4-Pyridinone Derivatives Synthesized from 4-Pyrones

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Antibacterial activity of total 11 newly synthesized compounds of 4-pyrone and 4-pyridinone derivatives were determined against standard bacterial test microorganisms by the tube dilution technique. Most of the compounds, except compound 11, exhibited antimicrobial activity towards the gram-negative bacterium *Escherichia coli*, while other compounds inhibited either 1 or 2 or 3 the growth of test microorganisms. Antibacterial activities of the compounds were exhibited strong activity and some were moderate activity while none of compounds did not inhibit the growth of *S. aureus, S. pyogenes, E. facealis* and *B. subtilis*.

Key Words: Pyridinone, Pyrone, Antibacterial activity.

INTRODUCTION

Pharmaceutical antibiotics are widely used for the medical treatment of microbial infective diseases. Consequently, tons of antibiotics are annually administered to humans and animals, especially to livestock. Most of these antibiotics often contaminate sewage sludge and manure, used as fertilizer for agricultural land[1] while a growing concern about the continuing problem of antibiotic-resistant pathogens is compelling the pharmaceutical industry to search for novel antimicrobial agents[2]. Multidrug resistant bacterial infections increases day by day and most clinicians try to cure most infectious disease by antibiotics, conventional agents. Although broad cellbased screens have been utilized for the discovery of new antimicrobial agents particularly for natural product screening, newly synthesized compounds may be alternative antibacterial agents instead of antibiotics owing to evaluation of bacterial resitance. Pyridinones derivatives synthesized from pyrones, an interesting class of organic compounds with diverse chemical and pharmacological applications. Consequently, 4(1H)-pyridinone derivatives have attracted more and more attention due to their interesting pharmacological properties[3]. The preparation of compounds with 4(1H)-pyridinone moiety has widely been reported[4,5]. Also, the 2-pyrone sub-unit is an important synthetic building block found in numerous biologically active natural products, for which there has been considerable

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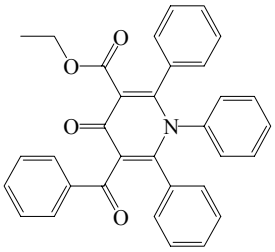
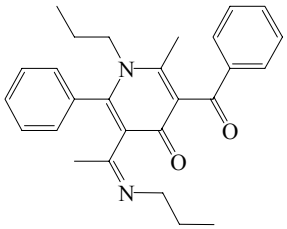
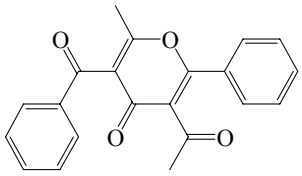
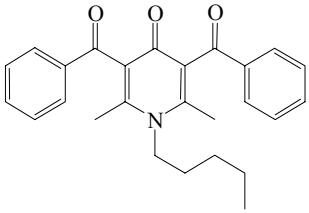
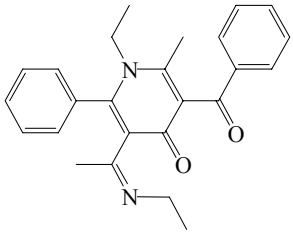
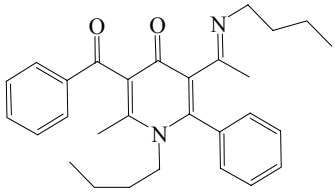
recent interest[6]. The reaction of primary amines with 4(1H)-pyrones to form 4(1H)-pyridinones is known for more than 90 years[7]. Pyrones and its 4(1H)-pyridinones derivatives have a wide spectrum of bioactivities including antibacterial[8,9], antifungal[10], antimalarial, cardiotonic agents[11,12], antihypertensive[13], antineoplastic[14], antiinflammatory[15], analgesic[16,17]. Pyridinones has also undergone clinical trials for the treatment of Parkinson's disease[18,19] and Thalassemia disease[20]. It is well also known that the 4(1H)-pyridinone ring, which is analogous to catechol and has chelating ability, is considered to play a significant role in antimicrobial activity[21].

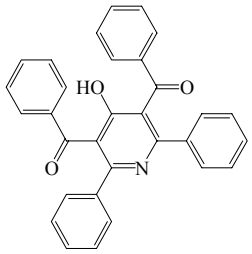
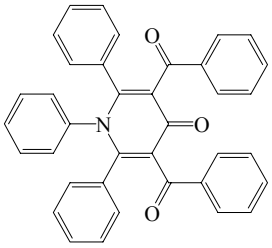
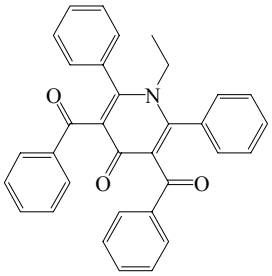
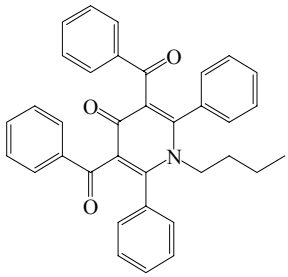
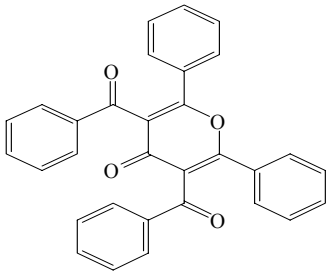
In view of the wide biological importance of 4(1H)-pyridinones, it is worthwhile to examine synthesized derivatives of 4(1H)-pyridinones, which may be explored as potentially microbial activity. We therefore had a desire to test compounds that have synthesized from pyrone with a view to identifying promising antimicrobial activity. The present study aims to screen the antibacterial activities of some new derivatives of 4-pyridinones synthesized by reactions of various pyrones with primary amines (unpublished data) with the final goal to synthesize potential pharmaceuticals.

EXPERIMENTAL

The componds synthesized by Eskinoba[22] were provided from Organic Laboratory, Department of Chemistry, Yüzüncü Yil University, Van, Turkey. They have synthesized these compounds and defined by analytical methods, IR spectra, ^{1}H NMR and ^{13}C NMR spectra analysis. 3,5-Dibenzoyl -2,6-diphenyl-4-pyrone, 3-benzoyl-5-ethoxycarbonyl-2,6-diphenyl-4-pyrone were synthesized according to the published procedures[23]. The compounds (Table-1) were tested *in vitro* for their antimicrobial activity against Gram-positive and Gram-negative by the standard dilution method in nutrient broth medium[24]. The minimum inhibitory concentration (MIC) values in lg/mL were reported. Standard bacteria strains used were *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Proteus vulgaris, Staphylococcus aureus, Streptococcus pyogenes, Enterococcus facealis, Bacillus subtilis, Salmonella enteridis, Xanthomonas compestris* obtained from Yüzüncü Yil Üniversity, Science & Art Faculty, Biology Department, Van, Turkey. Bacterial standard strains were maintained on nutrient agar slants were subcultured in petridishes prior to use. Each microorganisms and antibiotics were repeated in triplicate. Microdilution broth susceptibility assay was used for the antimicrobial evaluation of compounds. Stock solutions of the samples were prepared in distilled water and serial dilutions were ranged from 2 to 128 µg/mL in microtest tubes and than transferred into 10 mL test tubes containing 5 mL nutrient broth. After inoculation with test microorganisms, incubate overnight. One tube without inoculation used as negative control while one

TABLE-1
NEW SYNTHESIZED COMPOUNDS OF 4-PYRONES AND 4-PYRIDINONES DERIVATIVES

Compd. No.	Compound name	Structure
1	3-Benzoyl-5-ethoxycarbonyl-1,2,6-triphenyl-4(1*H*)-pyridinone (3d)	
2	3-Benzoyl-1-propyl-5-(1-propyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	
3	3-Acetyl-5-benzoyl-2-phenyl-6-methyl-4-pyrone	
4	3,5-Dibenzoyl-2,6-dimethyl-1-pentyl-4(1*H*)-pyridinone	
5	3-Benzoyl-1-ethyl-5-(1-ethyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	
6	3-Benzoyl-1-butyl-5-(1-butyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	

Compd. No.	Compound name	Structure
7	3,5-Dibenzoyl-2,6-diphenyl-4-hydroxypyridine	
8	3,5-Dibenzoyl-1,2,6-triphenyl-4(1*H*)-pyridinone	
9	3,5-Dibenzoyl-1-ethyl-2,6-diphenyl-4(1*H*)-pyridinone	
10	3,5-Dibenzoyl-1-butyl-2,6-diphenyl-4(1*H*)-pyridinone	
11	3,5-Dibenzoyl-2,6-diphenyl-4-pyrone	

was positive control that contained Penicllium G antibiotic. After incubation 37 ºC overnight, the first tube with clear appearance was determined as MIC.

RESULTS AND DISCUSSION

11 of the newly synthesized 4-pyrones and 4-pyridinone derivatives were examined for their antibacterial activity against a panel of organisms including clinical isolates. The results are presented in Table-2. Comparable potent inhibitors of various kinds of new synthesised compounds against these test microorganisms have been reported[25-29]. From the data in Table-2, it is evident that the antibacterial activity is manifested in the different bacteria and it is possible to discern some structure-activity relationships. All the compounds were not demonstrated activity *vs. S. aureus, S. pyogenes, E. facealis* and *B. subtilis* bacteria since most of compounds have shown microbial activity against at least one test microorganisms. With the exception of compounds 11, all the pyrone and pyrinidone derivatives tested are active against *E. coli* and minimal inhibitory concentrations (MICs) were recorded as the minimum concentration of compound, which inhibits the growth of tested microorganisms. MICs were recorded as 64 µg/L for all compounds.Compound 9 and 10 showed similar anbacterial activities against *B. subtilis* while compound 6 inhibited *P. vulgaris* growth. However, compound 4 prevented *E. coli, P. aerogenes* and *K. pneumonia* growth. It was also observed that all of the compounds have different antimicrobial activity ranges against all tested bacteria when compared with penicllin G. On the other hand, the compounds 11 (3,5-dibenzoyl-2,6-diphenyl-4-pyrone) does not show any inhibitory effects on the growth of test microorganisms during the assay. This may be owing to unsufficient dissolution of compound 11 in distilled water. Most of the studied compounds showed mild activities against different microbes while they show good activity against *Escherichia coli*. However the antimicrobial activities of the 4-pyridinone derivatives against certain microbes exhibited that are potential for pharmacological assays. The inhibitory of compounds concentrations as low as 64 µg/L is clearly shown in Table-2. As expected, the degree of inhibition increases with increasing componds concentrations. It should be noted however that low concentration of componds is not able to show biological activity. The results clearly suggest that the presence of pyridinone and pyrone derivatives is key to inhibitory activity. Present findings are in good agreement with study of Aytemur *et al.*[21] reported that amide derivatives of 4(1H)-pyridinone were exhibited antimicrobial activities against the bacteria *S. aureus, E. faecalis, E. coli*, *P. aeruginosa* and the fungi *Candida albicans, Candida krusei* and *Candida parapsilosis*.

TABLE-2
ANTIMICROBIAL ACTIVITIES OF THE COMPOUNDS AGAINST TEST MICROORGANISMS

Compd. No.	Compounds	Test microorganisms									
		EC	PA	KP	PV	SA	SP	EF	BS	SE	XC
1	3-Benzoyl-5-ethoxycarbonyl-1,2,6-triphenyl-4(1*H*)-pyridinone	64	-	-	-	-	-	-	-	-	-
2	3-Benzoyl-1-propyl-5-(1-propyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	-	64	-	-	-	-	-	-	-	-
3	3-Acetyl-5-benzoyl-2-phenyl-6-methyl-4-pyrone	64	-	64	-	-	-	-	-	-	-
4	3,5-Dibenzoyl-2,6-dimethyl-1-pentyl-4(1*H*)-pyridinone	64	64	64	-	-	-	-	-	-	-
5	3-Benzoyl-1-ethyl-5-(1-ethyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	64	-	-	-	-	-	-	-	-	64
6	3-Benzoyl-1-butyl-5-(1-butyliminoethyl)-6-phenyl-2-methyl-4(1*H*)-pyridinone	64	-	-	64	-	-	-	-	-	-
7	3,5-Dibenzoyl-2,6-diphenyl-4-hydroxypyridin	64	-	64	-	-	-	-	-	-	-
8	3,5-Dibenzoyl-1,2,6-triphenyl-4(1*H*)-pyridinone	64	-	-	-	-	-	-	-	-	-
9	3,5-Dibenzoyl-1-ethyl-2,6-diphenyl-4(1*H*)-pyridinone	64	-	-	-	-	-	-	-	64	-
10	3,5-Dibenzoyl-1-butyl-2,6-diphenyl-4(1*H*)-pyridinone	64	-	-	-	-	-	-	-	64	-
11	3,5-Dibenzoyl-2,6-diphenyl-4-pyrone	-	-	-	-	-	-	-	-	-	-
12	Penicilin g (control)	64	64	64	64	64	64	64	64	64	64

EC = *Escherichia coli*; PA = *Pseudomonas aureoginosa*; KP = *Klebsiella pneumonia*; PV = *Proteus vulgaris*;
SA = *Staphylococcus aureus*; SP = *Streptococcus pyogenes*; EF = *Enterococcus facealis*; BS = *Bacillus subtilis*;
SE = *Salmonella enteridis*; XC = *Xanthomonas compestris*
MICs (as μg/mL); Control compound: Penicilin G

In conclusion, the antibacterial activity of newly synthesized 4-pyridinone and 4-pyrone derivatives were determined. Some of 4-pyrone and 4-pyridinone derivatives have been identified as promising new antibacterial agents against *E. coli, P. aerogenosia, Klebsiella pneumonia, P. vulgaris, S. enteridis* and *X. compestris* (Table-2). However, further pharmacological investigation is needed for these componds.

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