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Biological Activity Studies of Some Synthesized Novel Furan and Pyran Derivatives

Esma SARİ[1], Hakan ASLAN[1,3], Şeyma DADI[2], Atilla ÖKTEMER[1], Elif LOĞOĞLU[2*]

[1] *Department of Chemistry, Faculty of Sciences, Ankara University, Ankara, Turkey*

[2] *Department of Chemistry, Faculty of Sciences, Gazi University, Ankara, Turkey*

[3] *Department of Chemistry, Faculty of Arts and Sciences, Sinop University, Sinop, Turkey*

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Abstract

In this study, some novel furan and pyran derivatives were synthesized as mentioned in our previous report [1]. The novel furan and pyran derivatives were investigated for antibacterial activity against gram-positive/negative bacteria and fungus. The antibacterial and antifungal activities were determined by the disc diffusion method (DISC) and minimum inhibition concentration (MIC) against the tested bacteria and fungus. The inhibition zones were compared with those of reference discs which were studied in our previous work [2]. Reference discs used for control were as follows ketoconazole, ampicillin, tetracycline, penicillin, chloramphenicol, and gentamicin. From the results it could be said that some of the chemical compound can be used as a raw medicine sources.

1. INTRODUCTION

Human struggle against the affliction of disease, decay and death is eternal. The deterioration of human population due to an enhanced prevalence of infectious diseases is becoming a global problem. The contemporary treatment of infectious diseases involves administration of a multidrug regiment over a long period of time [3]. However, the spread of multidrug-resistant strains of fungus and bacteria the reduced number of drugs available, makes it necessary to discover new classes of antifungal and antibacterial compounds that inhibit these resistant mechanisms. This has led to a search for therapeutic alternatives, particularly among medicinal plants and compounds isolated from them, used for their empirically antimicrobial properties [4]. Thus, many organic forms in recent years have been defined as antimicrobial compound including flavonoids, phenolic acids, aglycones and their esters, alcohols, phenolic aldehydes and ketones, quinones, coumarins, steroids, aminoacids, benzimidazole and benzylpyrimidine [5, 6]

Many of the pyrans have been used as precursors for the synthesis of pharmacologically active compounds such as HIV protease inhibitors [7], antifungals [8], cardiotonics [9], anticonvulsants [10], antimicrobials [11], pheromones [12], natural pigments [13], antitumor agents [14], and plant growth regulators [15, 16]. Also, furan derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the furan nucleus is an important synthetic strategy in drug discovery. Medical properties of furan include anticancer, antidepressant, antianxiolytic, analgesic, anti-inflammatory, muscle relaxant, antihypertensive, anti-arrhythmic, antimicrobial like antibacterial or antifungal or antiviral, anti-aging agents, anti-ulcer, antihistaminic, anti-cholinergic, anti-parkinsonism, anti-diuretic, and inhibition of sickle cell formation [17].

Nowadays, because of pathogenic bacterial resistance against all known antibiotics, there is a need to identify many new chemicals that could be used as antibiotics. Therefore, scientists must study new

*Corresponding author, e-mail: logoglu@gazi.edu.tr

chemicals to see whether medicinal raw material may have antibiotic action or not [18]. In our previous work we saw that some furan derivates have good activity against some bacteria and fungi than some known antibiotics such as gentamicin and penicillin [2]. Because of furan and pyran derivatives promise to use as a raw material for medicinal applications, these compounds were investigated for antibacterial properties. In this study, we reported that some novel furan and pyran derivatives showed significant antibacterial activities towards various bacteria.

2. EXPERİMENTAL

2.1. Synthesis of Furan and Pyran Derivatives

A 100 mL three-neck flask equipped with thermometer, nitrogen gas passing the exit gas trap pipe and a reflux condenser and then MAH and acetic acid were heated at 80 ºC under nitrogen atmosphere until MAH was completely dissolved.

After dissolution, 2 ml of acetic acid solution with unsaturated alcohol and active methylene compound solution was added to the flask at 80 ºC.

After the reaction mixture was controlled by thin layer chromatography, water was added. When the reaction was over, the organic phase was extracted with chloroform. The organic phase washed twice with water and once with saturated NaCl solution. In the next step, mixture was dried over anhydrous Na_2SO_4. The crude product was purified by column and preparative thin layer chromatography. The synthesis of furan and pyran derivatives could see from Figure 1.

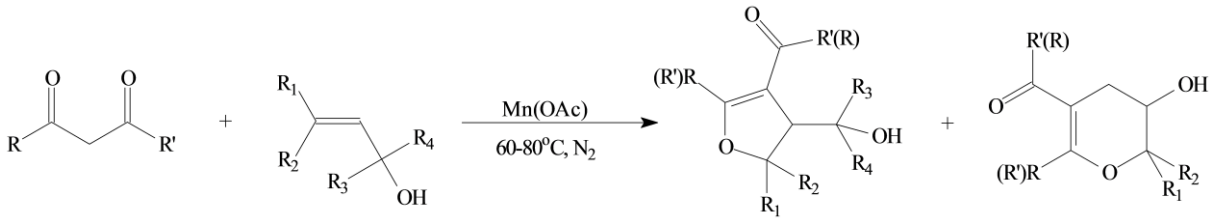


Figure 1. *Synthesis of furan and pyran derivatives*

2.2. Test Microorganisms and Medium

Antibacterial activity were investigated for *Bacillus licheniformis* M30 , *Bacillus megaterium* M22, *Bacillus circulans* M34, *Bacillus subtilis* B1 , *Bacillus subtilis* M33 , *Bacillus cereus* B9, *Staphylococcus aureus ATCC* 653, *Micrococcus luteus* M3, *Escherichia coli* ATCC 25922 , *Pseudomonas aeruginosa* P7.

Bacterial strains which are preserved in Nutrient Agar at 4 ºC were cultured overnight at 37 ºC in Nutrient Broth for antibacterial activity tests.

2.3. Antibacterial Testing

Disc diffusion method was used for antibacterial activity. Muller Hinton Agar was poured into each sterile petri dish after injecting cultures (300µl) of microorganisms and distributing medium in petri dish homogeneously. All the tested compounds were dissolved in DMSO to give a solution of 5 mg/mL. Solutions were filtered with a pore size of 0.2 µm. Whatman filter paper no. 1 was used to prepare discs approximately 6 mm in diameter, which are placed in a Petri dish and sterilized in a hot air oven. Discs were placed on agar plates. Empty sterilized discs were each impregnated with 50 µl of compounds. The plates were incubated at 37 ºC for 24 h and inhibition zones were measured in millimeters at the end of incubation period. The solvent control (DMSO) did not show any antibacterial activity. The inhibition zones were compared with those of reference discs which were studied in our previous work. Reference

discs used for control are as follows ketoconazole, ampicillin, tetracycline, penicillin, chloramphenicol, and gentamicin [2]. The diameters of disc diffusion method's results are showed in Table 2.

2.3. Determination of MIC

Minimum inhibitory concentration (MIC) is the lowest concentrations of an antimicrobial that will inhibit the visible growth of a microorganism. Minimum inhibitory concentrations are important in diagnostic laboratories to confirm resistance of microorganisms to an antimicrobial agent and also to monitor the activity of new antimicrobial agents [19].

MICs were determined by micro dilution broth method following the procedures recommended by the National Committee for Clinical Laboratory Standards [20]. Appling DMSO solvent of the synthesized compounds started with a maximum concentration of 1000 µg/mL and then reduced it by successive two fold dilutions of that stock solution to prepare 500, 250 and 125 µg/mL using a calibrated micropipette. The minimum inhibitory concentrations of compounds are showed in Table 3.

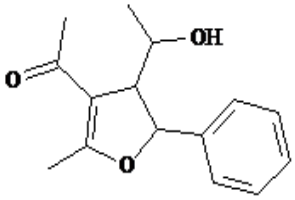
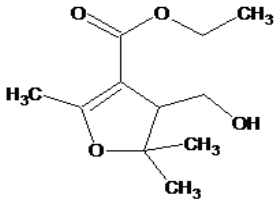
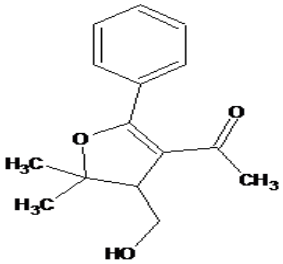
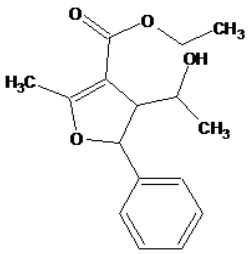
3. RESULT AND DISCUSSION

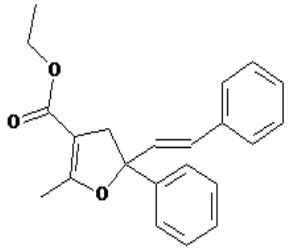
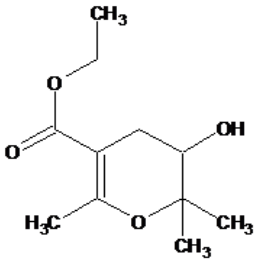
3.1. The Structures of Synthesized Furan and Pyran Derivatives and Results

The synthesized furan derivates were 1-[4-(1-hydroxyethyl)-2-methyl-5-phenyl-4,5 dihydrofuran-3-il]ethanone (1); 1-(4-Hydroxymethyl-5,5-dimethyl-2-phenyl-4,5-dihydro-furan-3-il)ethanone (2); Ethyl 2-methyl-5-phenyl-5-styryl-4,5-dihydro-furan-3-carboxylate (3); Ethyl 4-hydroxymethyl-2,5,5-trimethyl-4,5-dihydro-furan-3-carboxylate (4); Ethyl 4-(1-hydroxy-ethyl)-2-methyl-5-phenyl-4,5-dihydro-furan-3-carboxylate (5).

The synthesized pyran was Ethyl 5-hydroxy-2,6,6-trimethyl-5,6-dihydro-4H-pyran-3-carboxylate (6). Structures of compounds were determined with IR , 1H-NMR and 13C-NMR. IR , 1H-NMR and 13C-NMR and these results could be seen from previously reported literature by us [1]. The structures of compounds are given in Table 1.

Table 1. *The structures of compounds*

Compound No	Structure	Compound No	Structure
1		4	
2		5	

Compound No	Structure	Compound No	Structure
3		6	

3.2. Antibacterial Activity Results

All synthesized compounds were screened for their antibacterial activities. The results of the antibacterial activities are shown in Table 2 and 3, respectively. The results revealed that most of the synthesized compounds showed variable degrees of inhibition against the tested bacteria.

Table 2. *Inhibition zone diameters of compounds*

Bacterial Strain	Inhibition zones of the tested compounds (mm)					
	1	2	3	4	5	6
E. coli ATCC 25922	---	10	---	11	17	15
B.megaterium M22	---	---	---	---	10	9
M. luteus M3	---	---	---	---	---	---
B.cereus B9	---	---	---	---	---	---
B.licheniformis M30	---	---	---	---	---	---
S. aureus ATCC 6538	13	14	10	12	10	11
B. circulans M34	14	13	9	14	11	---
B. subtilis B1	---	---	---	---	---	---
P. aeruginosa P7	10	11	11	---	---	---
B. subtilis M33	11	11	11	---	---	12

The minimum inhibitory concentration (MIC) of the synthesized compounds was determined against *E.coli* ATCC 25922, *B.megaterium* M22, *M. luteus* M3, *B.cereus* B9, *B.licheniformis* M30, *S. aureus ATCC* 6538, *B. circulans* M34, *B. subtilis* B1, *P. aeruginosa* P7, *B. subtilis* M33 using a standard broth dilution technique. All the MIC results are presented in Table 3. The obtained data reported that compounds have growth inhibitory effects on some of the bacteria showing MIC values between 125 and 1000 μg/mL.

Table 3. *The MICs of the tested compounds*

Bacterial Strain	The MICs of the tested compounds (μg/ml)					
	1	2	3	4	5	6
E. coli ATCC 25922	---	125	---	125	1000	250

Bacterial Strain	The MICs of the tested compounds (μg/ml)					
	1	2	3	4	5	6
B.megaterium M22	---	---	---	---	---	---
M. luteus M3	---	---	---	---	---	---
B.cereus B9	---	---	---	---	---	---
B.licheniformis M30	---	---	---	---	---	---
S. aureus ATCC 6538	500	500	250	500	250	250
B. circulans M34	250	500	250	500	250	---
B. subtilis B1	---	---	---	---	---	---
P. aeruginosa P7	500	250	500	---	---	---
B. subtilis M33	500	500	250	---	---	500

Table 4. *Inhibition zone diameters of reference antibiotics discs against the test bacteria [2].*

Bacteria	Inhibition zones of the antibiotics (mm)					
	Penicillin	Chloramphenicol	Tetracycline	Ampicillin	Gentamicin	Ketoconazole
S. aureus	----	----	----	9	----	----
B. subtilis	----	----	----	15	----	----
P. aeruginosa	----	----	----	----	16	----
M. luteus	31	----	9	28	----	----
B. megaterium	----	----	----	10	----	----
E.coli	19	----	----	----	----	----

3.3. Discussion

When it is compared with all other compounds, only compound 4 which does not have phenyl ring in its structure has less antibacterial activity against some of the bacteria than other compounds with phenyl ring. It was noticed that an increasing activity dependent upon the phenyl ring incorporated into structure appear to occur in this study. On the other side, *Micrococcus luteus* M3, *Bacillus cereus* B9, *Bacillus licheniformis* M30, and *Bacillus subtilis* B1 have resistance against all compounds which studied on this study. When it is analyzed structures of compounds 1 and 2 which have only difference that compound 2 has methyl group in its structure, we have seen that methyl group increase activity. While compound 2 showed 10 mm zone against *Escherichia coli ATCC* 25922, compound 1 has no zone against on it. This result directed us to consider methyl group has more influence on some bacteria like *Escherichia coli ATCC* 25922. It seems that this conclusion also comply with literature [21]. All the chemicals used in the study have more antibacterial activity against *Staphylococcus aureus ATCC* 653. Compound 6 which is only pyran derivative in this study stand out because it has activity against *Escherichia coli ATCC* 25922. When this study is compared with antibiogram of reference antibiotics positive results are obtained. All the chemicals used in this study have more potent than ampicilline against *Staphylococcus aureus ATCC* 653. By the time, compounds 1, 2, and 3 are effective on Pseudomonas aeruginosa P7 whereas raw materials required for standard antibiotics such as chloramphenicol, tetracycline, ampicilline, and ketoconazole do not have any effect. Growth of *Escherichia coli ATCC* 25922 was inhibited by all

compounds except compounds 1 and 3. However, only penicillin which is standard antibiotic has inhibition effect on *Escherichia coli ATCC* 25922. When our compounds are compared with standard antibiotics, we have seen that, in some cases, our chemicals have better results. For instance while ketoconazole and chloramphenicol have no inhibition effect growth of all bacteria were showed, all compounds showed inhibition effect on *Staphylococcus aureus ATCC* 653.

4. CONCLUSION

Newly synthesis compounds have moderate antibacterial potential against microorganisms. Thus, they can be used in the treatment of infectious diseases caused by microbes. The effect from the association of antibiotic with compounds against bacteria leads to new choices for the treatment of infectious diseases. This effect enables the use of the respective antibiotic when it is no longer effective by itself during treatment.

CONFLICTS OF INTEREST

No conflict of interest was declared by the authors.

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