



A RESEARCH FOR SOME OXAZOLIDINONES TO EVALUATE THEIR ANTIMICROBIAL ACTIVITY

YENİ OKSAZOLİDİNONLARIN ANTİMİKROBİYAL AKTİVİTELERİNİ DEĞERLENDİREN BİR ARAŞTIRMA

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ABSTRACT

Objectives: In this research, antimicrobial activity of some new oxazolidinone derivatives were evaluated against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolate and *C. albicans* ATCC 10231.

Material and Method: Formerly obtained and published 10 oxazolidinones were tested against antimicrobial activity and this evaluation was carried out in Mueller-Hinton broth and Sabouraud dextrose broth.

Result and Discussion: Compounds E5, and E9 showed antimicrobial activity against both bacteria and fungi with 25 µg/mL and 50 µg/mL, respectively. Our present research and the others have shown that the electro-negativity degree is very important for the biological activity.

Keywords: antimicrobial activity; linezolid; oxazolidinon

ÖZ

Amaç: Bu çalışmada, bazı yeni oksazolidinon türevlerinin antimikrobiyal etkileri *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, metisilin-dirençli *Staphylococcus aureus* (MRSA) klinik izolatu ve *C. albicans* ATCC 10231'e karşı incelenmiştir.

Gereç ve Yöntem: Daha önce elde edilen ve yayınlanan 10 oksazolidinonların antimikrobiyal aktivitesi test edilmiştir ve çalışma Mueller-Hinton broth ve Sabouraud dekstroz broth içinde gerçekleştirilmiştir.

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Sonuç ve Tartışma: E5 ve E9 bileşikleri, sırasıyla, 25 µg/mL ve 50 µg/mL ile hem bakteri hem de mantarlara karşı antimikrobiyal aktivite göstermiştir. Bizim bu araştırmamız ve diğer bazı çalışmalar, elektro-negatiflik derecesinin biyolojik aktivite için çok önemli olduğunu göstermiştir.

Anahtar Kelimeler: antimikrobiyal aktivite; linezolid; oksazolidinon

INTRODUCTION

Oxazolone scaffold is a prominent structure for the drugs, such as linezolid, which is active against methicillin-resistant *Staphylococcus aureus*. Indeed, oxazolone based derivatives have shown diverse biological and pharmacological applications such as antibacterial [1-3], anticancer [4,5] antimycobacterial against tuberculosis [6], antioxidant [7,8] and antidiabetic [9] activity.

Linezolid [10] (Fig. 1), is the first oxazolidinone derivative introduced by Pharmacia to be used in the treatment of infections caused by combined drug-resistant gram-positive bacteria such as hospital infection and community-acquired pneumonia and skin infections and was approved in 2000 [1].

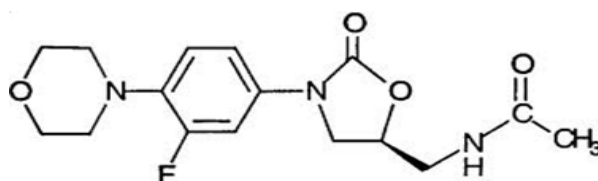


Figure 1. Linezolid

In this study, antimicrobial activities of a group of oxazolidinone derivative compounds, which had previously been reported for synthesis, structure elucidation and antioxidant effects, were evaluated for antimicrobial activity against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolate and *C. albicans* ATCC 10231 were investigated.

In this research, 4-(substituted-benzylidene)-2-(substituted-phenyl)oxazole-5(4H)-one derivatives (**E1-E10**) have been evaluated for their antimicrobial activity. Synthesis procedure and antioxidant activity results of the compounds was published by Kuş *et al.* in 2017 [11].

The molecular structure of the compounds (**E1-E10**) is shown in Figure 2.

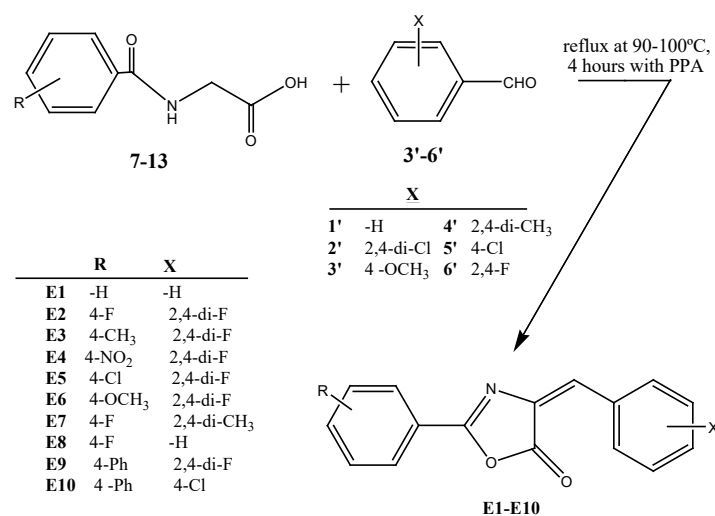


Figure 2. Molecular structure of designed compounds (**E1-E10**)

MATERIAL AND METHOD

Antibacterial and Antifungal Assay

The final compounds and the standards were dissolved in 12.5% DMSO at concentrations of 200 µg/ml. Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56 and 0.78 µg/ml concentrations with Mueller-Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the 2-fold serial dilution technique [12-14].

A control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions as those used in our experiments and this was found to be the cultures were obtained from Mueller-Hinton broth (Difco) for all the bacterial strains after 24 h of incubation at 37 °C. *C. albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at 25 °C. Testing was carried out in Mueller-Hinton broth and Sabouraud dextrose broth (Difco) and the 2-fold serial dilution technique was applied [12-14].

The final inoculum size was 10⁵ CFU/ml for the antibacterial assay and 10⁴ CFU/ml for the antifungal assay. A set of tubes containing only inoculated broth was used as controls. After incubation for 24 h at 37 °C for the antibacterial assay and for 48 h at 25 °C for the antifungal assay, the last tube with no growth of the microorganism and/or yeast was recorded to represent the MIC (µg/ml) [12-14]. All tests were carried in duplicated as a control.

RESULT AND DISCUSSION

All described new oxazole derivatives (**E1-E10**), were evaluated *in vitro* for antibacterial activity against *S. aureus* ATCC 25923, *E. coli* ATCC 25922 and *B. subtilis* ATCC 6633, MRSA clinical isolate, and antifungal activity against *C. albicans* ATCC 10231.

Tested almost all of the compounds were having 2,4-difluoro substituent as **X** group.

The MIC values obtained are listed in Table 1 along with the reference antibiotics. All of the compounds have shown low antibacterial activity.

Table 1. Antibacterial activities of new oxazole-5(4*H*)-one derivatives (MIC values ($\mu\text{g/ml}$))

Comp.	R	X	<i>C. albicans</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	MRSA
E1	-H	-H	> 200	> 200	> 200	> 200	> 200
E2	4-F	2,4-difluoro	100	100	100	100	100
E3	4-CH ₃	2,4-difluoro	100	50	100	100	100
E4	4-NO ₂	2,4-difluoro	50	100	100	100	-
E5	4-Cl	2,4-difluoro	50	25	100	100	100
E6	4-OCH ₃	2,4-difluoro	> 200	> 200	> 200	> 200	> 200
E7	4-F	2,4-dimethyl	> 200	> 200	> 200	> 200	> 200
E8	4-F	-H	> 200	> 200	> 200	> 200	> 200
E9	4-Ph	2,4-difluoro	50	25	100	100	-
E10	4-Ph	4-Cl	> 200	> 200	> 200	> 200	> 200
Ampicillin			-	3.125	3.125	1.78	25
Fluconazole			3.125	-	-	-	-

Only compounds **E5**, and **E9** showed higher antibacterial activity against *S. aureus* with 25 $\mu\text{g/mL}$ and **E4**, **E5**, and **E9** displayed low antifungal activity against *C. albicans* with MIC values of 50 $\mu\text{g/mL}$.

None of the other compounds showed any antimicrobial activity. The results displayed that, if there are chloro or phenyl groups at 4 positions of phenyl, the antimicrobial activity against *S. aureus* is improved a little bit higher as 25 $\mu\text{g/mL}$. 4-NO₂, 4-Cl, and 4-Ph derivatives are more effective against *C. albicans* with 50 $\mu\text{g/mL}$ than the other derivatives.

Electronegative atoms are very important for biological activity. The potency of atomic electronegativity is very important for biological activity. The results displayed that, if there are chloro or phenyl groups at 4 positions of phenyl, the antimicrobial activity against *S. aureus* is improved a little bit higher as 25 $\mu\text{g/mL}$. 4-NO₂, 4-Cl, and 4-Ph derivatives are more effective against *C. albicans* with 50 $\mu\text{g/mL}$ than the other derivatives.

Both this research and El-Gohary and Shaaban's article have similar results. It is interesting that why chloro substituent effective and fluoro not. Maybe the most electronegative atom which is fluoro is not suitable for this molecule to show antimicrobial activity. At the same time, another

sample is that El-Gohary and Shaaban have been published 2-[[((2-(4-chloro/bromophenyl)-2-oxo)-ethylthio)methyl]-5-nitro-1*H*-benzimidazole (**5b/5c**) derivatives in 2017 [3]. Bromo derivative (**5c**) is more effective than chloro (**5b**) derivative. Because of that, we can say that electronegativity is very important to biological activity.

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To explain this situation, there are several examples. One of this examples is that El-Gohary and Shaaban have been published 2-[[((2-(4-chloro/bromophenyl)-2-oxo)-ethylthio)methyl]-5-nitro-1*H*-benzimidazole (**5b/5c**) derivatives in 2017 [3]. Bromo derivative (**5c**) is more effective than chloro (**5b**) derivative. Because of that, it can be said that electro-negativity is very important to biological effect.

In conclusion, our present research and the others have shown that the electro-negativity degree is highly important for the biological activity. This will be taken into account when conducting studies later on.

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