Düzce University
Journal of Science & Technology

Research Article

(3-(4-chlorophenyl)-4,5-dihydroisoxazole-4,5-diyl)dimethanol Compound: Antibacterial Activity, Antifungal Activity and Calculated Structural Parameters

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DOI: 10.29130/dubited.944684

ABSTRACT

We intended to quantify the antibacterial and antifungal activity results of 4,5-dihydroisoxazole dimethanol compound (1a) against several bacteria and fungi and also calculate some structural parameters (theoretical descriptors) of compound (1a) with this work. Microdilution broth procedures were studied using microdilution wells for the minimal inhibitory concentrations (MICs) test. Compound (1a) exhibited fair activities against all the bacteria and fungi. Compound (1a) has been a good result (MIC = 50 µg/ml) against particularly *P. aeruginosa*. The structure of compound (1a) was drawn, and geometrical optimization was done using the Ab initio (RHF/3-21G) level.

Keywords: *Antimicrobial activity, Dihydroisoxazole dimethanol compound, MIC*

(3-(4-klorofenil)-4,5-dihidroizoksazol-4,5-diil)dimetanol Bileşiği: Antibakteriyel Aktivite, Antifungal Aktivite ve Hesaplanmış Yapısal Parametreler

ÖZ

Bu çalışma ile, 4,5-dihidroizoksazol dimetanol bileşiğinin (1a) çeşitli bakteri ve mantara karşı antibakteriyel ve antifungal aktivite sonuçlarını ölçmeyi ve ayrıca (1a) bileşiğinin bazı yapısal parametrelerini (teorik tanımlayıcıları) hesaplamayı amaçladık. Mikrodilüsyon kuyucukları kullanılarak minimal inhibisyon konsantrasyonları (MİK) testi için mikrodilüsyon broth prosedürleri çalışılmıştır. Bileşik (1a), tüm bakteri ve mantara karşı etkili aktiviteler sergilemiştir. Bileşik (1a), özellikle *P. aeruginosa*'ya karşı iyi bir sonuç (MİK = 50 µg/ml) vermiştir. Bileşik (1a) 'nın yapısı çizilmiştir ve geometrik optimizasyonu Ab initio (RHF/3-21G) seviyesi kullanılarak yapılmıştır.

Anahtar Kelimeler: *Antimikrobiyal aktivite, Dihidroizoksazol dimetanol bileşiği, MİK*

Received: 29/05/2021, Revised: 20/10/2021, Accepted: 31/10/2021

I. INTRODUCTION

Infections caused by pathogenic microorganisms pose a concern in many areas. Compared to other causes, infectious diseases cause the death of many people worldwide in human history. In recent years, scientific research has focused on exploring new antibacterial, antifungal, and antiviral (pharmacological active) agents. Antibiotics, due to the drug resistance to microbes resulting from inappropriate, unnecessary, and unconscious use of them, have lost their effects at present [1-6].

Highly resistant bacteria (methicillin and vancomycin-resistant *S. aureus* (MRSA/VRSA) and vancomycin-resistant *E. faecalis* (VRE)) in intensive care units increase medical costs and risking the patient's life, leading to various complications from 1988 to the present [7-10]. Nowadays, the difficulty is encountered in treating multidrug-resistant *P. aeruginosa* infections produced in patients hospitalized in intensive care for a long time. So that, *P. aeruginosa* bacteria show the strongest resistance problems associated with nosocomial infections and multi-resistant strains [11,12]. *S. mutans* bacteria, which causes dental caries, periodontal diseases, and periapical diseases in people who do not do well with oral care, also contribute to mixed infections when the clinical dimension progresses, and we may have difficulties in treatment [13].

Hence, new drugs and particularly new drug classes are needed to struggle with this clinical resistance combined with new approaches and chemicals [14]. Therefore, as a result of multidisciplinary studies with chemistry trying to overcome resistances.

The synthesis and antimicrobial activity results of some 4,5-dihydroisoxazole derivatives have been reported in the literature [15-17]. There is not any report about discussing 4,5-dihydroisoxazole-4,5-diyldimethanol compounds antimicrobial activity backward. Therefore, compound (1a) is an essential new molecule because of contains two –OH bonds bound in a close position of a heterocyclic system containing C=N, N-O bonds. We reacted with 4,5-dihydroisoxazole-4,5-diyldimethanol compound and substituted phenylboronic acid to synthesize important antimicrobial substituted dioxaborepino compounds (MIC = 25-100 μg/ml) in our previous study [18]. Developing remarkable boron agents shows different modes of activity against various biological goals [19-27]. These biological targets include significant effects such as dermatologic anti-inflammatory application, antimalarial agents, potential inhibitors of SARS-CoV-2 main protease, antifungal activity, antimicrobial activity, anticancer, antibacterial, antiviral and antiparasitic activities. So that, compound (1a) is a new drug agent active substance that can be used as an intermediate form for new biologically active molecule synthesis.

In that research, we intended to identify *in vitro* antibacterial and antifungal activity of compound (1a) and calculate the important physicochemical parameters by theoretical calculations.

II. MATERIALS AND METHODS

A. EXPERIMENTAL

The synthesis, spectroscopic and analytical data of 4,5-dihydroisoxazole dimethanol compound (1a) (Figure 1) is in the literature [18], [28].

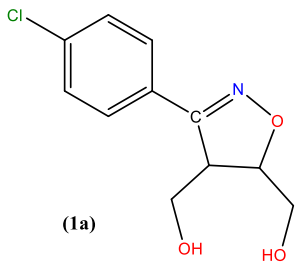

Figure 1. *Structure of compound (1a)*

B. ANTIMICROBIAL ACTIVITY

The antimicrobial activity of the compound (1a) has been evaluated against three Gram-positive bacteria (*Staphylococcus aureus* (ATCC 25983), *Enterococcus faecalis* (ATCC 29212) and *Streptococcus mutans* (ATCC 25175)), two Gram-negative bacteria (*Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 25922)) and one fungi (*Candida albicans* (ATCC 90028)) by their minimal inhibitory concentration (MIC) (Table 1) via broth microdilution susceptibility tests [18], [29-31]. Microdilution broth procedures were studied using multiwell microdilution plates (sterile, disposable 96 U-shaped wells). The compound (1a) was weighed and dissolved in sterile (pure) ethanol (Sigma) to prepare a stock solution (2000 µg/ml). In the studied concentrations, ethanol did not effect the microorganisms.

For the antibacterial activity studies (*S. aureus*, *E. faecalis*, *P. aeruginosa*, *E. coli*, and *S. mutans*), the dilution of compound (1a) solution was done in the wells of microdilution plates by Mueller-Hinton Broth (Oxoid) [29]. All the inoculated plates were incubated at 35 °C for 16–20 h. For the antibacterial activity study of *S. mutans*, Mueller-Hinton Broth (Oxoid) with 2-5% lyophilized horse blood was used (Figure 2) [30]. All the inoculated plates were incubated at 35 °C for 36−48 h with 5–10 % CO_2. The concentration range was 1600-0.04 µg/ml. For the antifungal activity studies (*C. albicans*), the dilution of compound (1a) solution was done in the wells of microdilution plates with RPMI medium with L-glutamine buffered, pH = 7, with MOPS (Sigma) [31]. The MIC plates were incubated at 37 °C for 48 h. The concentration range was the same as above (1600-0.04 µg/ml). Reference compounds were obtained from the manufacturers for the tests.

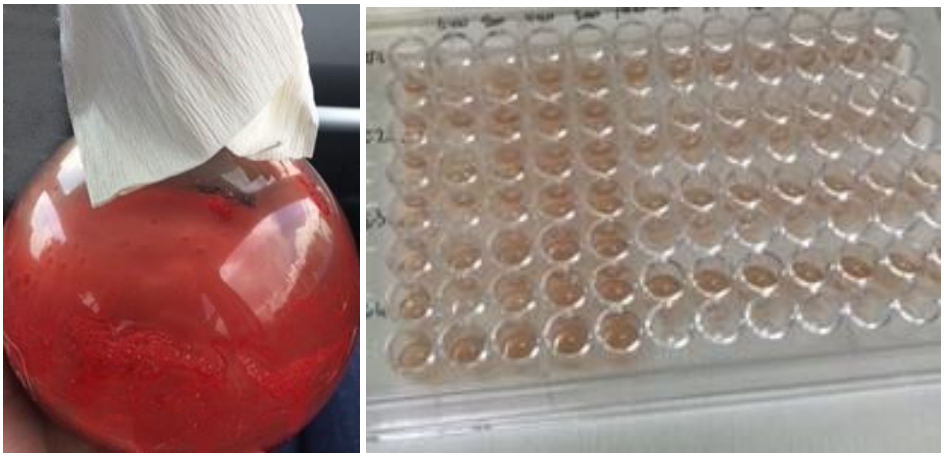

Figure 2. *Horse blood in baloonjoje for the antibacterial activity study of S. mutans (left); microdilution plates for S. mutans (right)*

C. STRUCTURAL AND THEORETICAL PARAMETERS

We also have studied structural descriptors against antibacterial and antifungal activities of compound (1a). The geometrical optimization of compound (1a) has been carried out by Ab initio (RHF/3-21G)

parameterization in the Hyperchem package (Figure 3) for calculations [32]. Some structural parameters (Van der Waals Surface Area-Approx (SAA), Van der Waals Molecular Volume (MV), Molar Refractivity (MR), Polarizability (polar), Magnitude of Dipolar Moment (μ), Axes of Dipolar Moments (μ; Dx, Dy, Dz), the Calculated log of Octanol-Water Partition Coefficient (clogP), RMS Gradient, Hydration Energy (HE), Energy of Binding (E_b), Electronic Energy (EE), Nuclear Energy (NE) and Mass) of the optimized compound (1a) were calculated by (RHF/3-21G) level (Table 2).

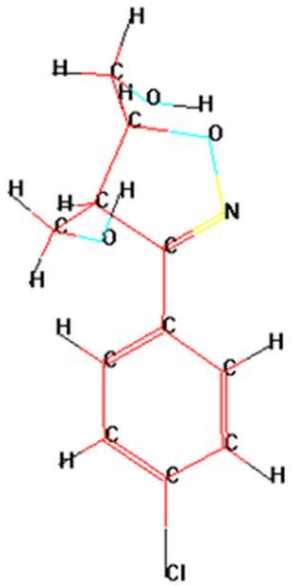

Figure 3. *Minimum energy conformation of compound (1a) (RHF/3-21G level)*

Computer aid is supported to discipline the experimental notice. Drug discovery studies are driven by innovation and knowledge, employing a combination of experimental and computational methods in these days [33].

III. RESULTS AND DISCUSSION

The conclusions of biological activities are given in Table 1 and shown graphically in Figure 4. Compound (1a) showed activity against all Gram-negative bacteria, Gram-positive bacteria, and fungi. Compound (1a) displayed antimicrobial activity with MIC = 50-200 μg/ml against *S. aureus, E. faecalis, P. aeruginosa, E. coli, S. mutans* and *C. albicans*.

Table 1. *Antimicrobial activity results (MIC) of compound (1a)*

Compound and References	MIC in μg/ml (*p*MIC)					
	S. aureus ATCC 25983	*E. faecalis* ATCC 29212	*P. aeruginosa* ATCC 27853	*E. coli* ATCC 25922	*S. mutans* ATCC 25175	*C. albicans* ATCC 90028
1a	100 (0.383)	100 (0.383)	50 (0.684)	100 (0.383)	100 (0.383)	200 (0.082)
Ampicillin	0.78	0.78	–	6.25	≤ 0.25	–
Ciprofloxacin	0.25	0.25	0.25	0.04	–	–
Fluconazole	–	–	–	–	–	0.25

Compound (1a) has been found to be the most active against bacteria at MIC values of 50-100 µg/ml among the tested microorganisms. (1a) exhibited antifungal activity with MIC value 200 µg/ml against *C. albicans*.

The results showed that (1a) had been good activity (MIC = 50 µg/ml) against *P. aeruginosa*, which is causing a nosocomial infection and often resistant to antibiotic therapy among the tested microorganisms. This situation gives us hope for future treatment options.

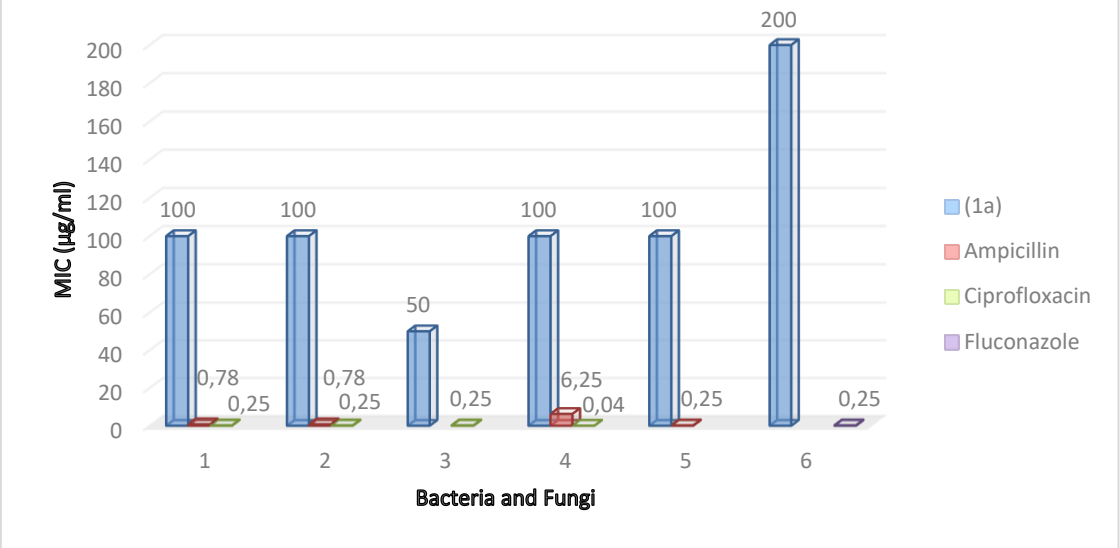

Figure 4. *Graphical representation of MIC (µg/ml) values of (1a) and references (Ampicillin, Ciprofloxacin, Fluconazole) (1 = Staphylococcus aureus, 2 = Enterococcus faecalis, 3 = Pseudomonas aeruginosa, 4 = Escherichia coli, 5 = Streptococcus mutans, 6 = Candida albicans)*

The antimicrobial activities, presented as MIC (Table 1), were transformed to *p*MIC (µmol/ml). The obtained MIC values (Table 1) and calculated various theoretical descriptors (Table 2) showed the relationship between the structure and the activity.

Table 2. *Calculated structural parameters of compound (1a)*

SAA (Å^2)	229.32
MV (Å^3)	200.95
MR (Å^3)	63.98
Polar (Å^3)	23.61
µ (D)	5.217
µ (D_x)	-3.268
µ (D_y)	3.432
µ (D_z)	-2.182
clogP	1.07
HE (kcal/mol)	-10.91
E_b (kcal/mol)	-725328.3
EE (kcal/mol)	-1478293.5
NE (kcal/mol)	752965.1
RMS	0.0907
Mass (amu)	241.67

In addition to computational results, future QSAR studies with substituted forms of compound (1a) will also give us important info concerning the organic-structural typicals of the dihydroisoxazole dimethanol compounds. QSAR has confidence in the fundamental hypothesis that compounds with close featured physicochemical properties or structures will have match activities [34]. The relationship between the molecular structure of the compounds and their biological activity is analyzed quantitatively with mathematical methods and calculated physicochemical parameters [35].

IV. CONCLUSION

Here, we report the antimicrobial activity tests of compound (1a). In the literature, there has not been evaluated the antimicrobial activity and structural studies of this compound. So, those results are very important for new studies. It is necessary to find new pharmacologically active compounds to control microbial pathogens that have become resistant to antibiotics. In this study, the sensitivities of new alternative chemical that fight pathogenic microorganisms has been investigated.

In recent years, the synthesis of new chemical compounds and their biological activity tests have a significance. Dihydroisoxazole dimethanol compound is a new type of molecule for antimicrobial agent design. Moreover, compound (1a) has -OH groups which are essential for polymerization reactions. Therefore, such dihydroisoxazole dimethanol derivatives as antimicrobial agents can be evolved and utilized to propose more potential newer substituents and therapeutics in the future.

ACKNOWLEDGMENTS: The authors declare that there is no conflict of interest. This study is based on the Project No:2019/009HD supported by Kocaeli University, BAP.

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