AUCTORES
Globalize your Research

Journal of Biotechnology and Bioprocessing

Maryam Kouhkan
*

Open Access

Research Article

Antibacterial Activity of 1,3,4-Oxadiazole Derivatives Against Methicillin-Resistant Staphylococcus Aureus

Maryam Kouhkan[1*], Ali Souldozi[2], Hajar Alizadeh[3]

[1]Young Researchers and Elite Club, Urmia Branch, Islamic Azad University, urmia, Iran

[2]Faculty of science, Urmia Branch, Islamic Azad University, Urmia, Iran

[3]Research Department of chromatography, Iranian Academic Center for Education, culture and Research, Urmia, Iran.

***Corresponding Author:** Maryam Kouhkan, Young Researchers and Elite Club, Urmia Branch, Islamic Azad university, urmia, Iran.

Received Date: April 26, 2022; **Accepted Date:** May 20, 2022; **Published Date:** June 09, 2022.

Citation: Maryam Kouhkan, A Souldozi, H Alizadeh. (2022) Antibacterial Activity Of 1,3,4-Oxadiazole Derivatives Against Methicillin-Resistant Staphylococcus Aureus. *J. Biotechnology and Bioprocessing*, 3(3); **DOI:** 10.31579/2766-2314/078

Abstract

Background: Antimicrobial resistance is a major problem in treatment and public health, which has been increasing over the last few decades so we need to take a very serious strategy to overcome this challenge. We have previously synthesized new series of (5-aryl-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol derivatives (4a-4f) in fairly high yields. Here, we have evaluated the antibacterial activity of these derivatives against methicillin-resistant Staphylococcus aureus.

Methods: The agar well diffusion and agar dilution methods were used for determination of inhibition zoon (IZ) and minimum inhibitory concentration (MIC) of compounds during preliminary evaluation of antibacterial activity.

Results: The title compounds have exhibited significant antibacterial activity against methicillin-resistan Staphylococcus aureus.

Conclusions: The results show that the synthesized compounds can be suitable options for preparation of selective inhibitor antibiotics of methicillin-resistant Staphylococcus aureus.

Keywords: 1,3,4-oxadiazol; staphylococcus aureus; antibiotic resistance

Introduction

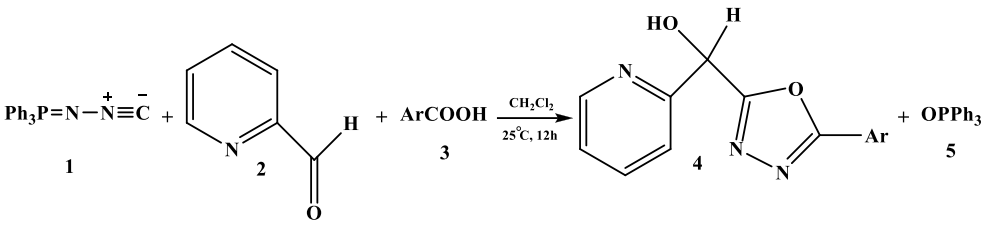
Staphylococcus aureus is a common pathogenic bacteria that causes a wide variety of human infections including, cellulitis, boils, infective endocarditis, toxic shock syndrome, surgical site infections, endocarditis, osteomyelitis and septic arthritis [1].The world spread use of antibiotics play a major role in leading to emergence of drug-resistant pathogens such as methicillin-resistant Staphylococcus aureus (MRSA). MRSA is a major global health threat that become as a world concern and important challenge in the pharmacy world. MRSA and other antibiotic-resistant infectious bacteria has become broadly resistant to many types of antibiotics and make medications ineffective. Because of this problem we need to develop new antibiotic formulation to fight this epidemic.

Due to increasing of microbial resistance to existing antibiotics, new chemical compounds have been synthesized by oxadiazol with different aromatic substituted with a wide range of biological activities such as antibacterial [2], antifungal [3], analgesic [4], anti-inflammatory [5], antiviral [6], anticancer [7], antihypertensive [8], anticonvulsant [9] and anti-diabetic properties [10]. Research revealed that heterocyclic compounds containing halogen atoms are unique option due to halogens operation to act as hydroxy mimic agent. So substitution of halogens by oxadiazol and pyridine substituents have impressive role in designing new pharmacophores as antimicrobial agents. In our previous study, we synthsised (5-aryl-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol, in a one-pot reaction and evaluated their antimicrobial activity against some patojenic microorganism [11,12]. Follow these study we continued our research to evaluate the antibacterial activity of these antimicrobial agents against MRSA.

Material and Methods

Chemistry:

A group of (5 aryl 1,3,4 oxadiazol 2 yl)(pyridin 2 yl)methanol derivatives 4a-4f (Ar: (a=4- CH2-Ph), (b=3-CH2-Ph), (c= 5-Naphthalen), (d=4-Br-ph), (e=3-Br-ph), (f= ph))were synthesized using previously published methods [11,12](Scheme 1).



Scheme 1: *Synthesis of (5-aryl-1,3,4-oxadiazol-2-yl)(pyridine-2-yl)methanol derivatives.*

	Ar
4a	4- CH_2-Ph
4b	3-CH_2-Ph
4c	5-Naphthalen
4d	4-Br-ph
4e	3-Br-ph
4f	ph

Antibacterial Activity:

Agar Diffusion Method

Antibacterial activity of title compounds were tested against MRSA ATCC 700698. This bacterium was obtained from Shiraz University of Medical Sciences. The standardization of bacterial inoculum was done following the to Clinical & Laboratory Standards Institute (CLSI). Briefly, bacterial strain were inoculated into Mueller Hinton broth (MHB) and then were incubated for 12 h at 35 oC to achieve the turbidity of 0.5 McFarland units. Standardized bacterial inoculum by concentrations of 1.5×108 cfu/mL (colony-forming units per milliliter, CFU/mL) colony was used for antibacterial screening. The antibacterial activity of the prepared compounds were screened using the well diffusion method [13-15]. In the first, the compounds, Ceftizoxime and ciprofloxacin were dissolved in dimethyl sulfoxide (DMSO) to get solutions with concentration of 1mg/ml. Melted and sterilized Muller Hinton Agar (MHA, Merck, Germany) (250 ml) was transferred into sterile Petri dish and seeded with 100 µl inoculum, containing 1.5×108 cells/ml of bacteria. After making wells in agar, 70 µl of compounds was transferred to each well, and 70 µl of DMSO was inoculated into another well as a negative control. In the last step the antibacterial potential of compounds was determined by measuring the zone around each well in millimeters after incubation for 24h. Ceftizoxime and ciprofloxacin used with the same method as broad-spectrum standard antibacterial agents. Experiments performed at least three times and data were expressed as mean±standard deviation.

Determination of Minimum Inhibitory Concentration of Compounds

In the second step, the MICs of the title compounds plus reference drugs were determined by agar dilution method. Experiments were performed with eight different concentrations of title compounds, Ceftizoxime and ciprofloxacin (1000, 500, 250, 125, 62.5, 31. 25, 15 and 7 µg/mL) to prepare doubling serial dilutions. In both methods Negative and Positive Control plate were prepared in the same way and Concentrations as compounds. Agar dilution plates were incubated at 37OC for 18h. The MIC was recorded as the lowest concentration of compound that inhibited bacterial growth completely [16,17].

Results and Discussion

The emergence of Antibiotic resistance is occurring in all parts of the world and menace the effectiveness of drugs to treat common infectious diseases. This crisis is result of overuse and misuse of treatment by these medications. The Centers for Disease Control and Prevention (CDC) publishes list of bacteria which new antibiotics are urgently needed and methicillin-resistant Staphylococcus aureus has classified in critical group. This pathogenic bacterium has become resistant to most antibiotics, but the remarkable point about this microorganism is its resistance to all beta-lactam antibiotics such as penicillins and cephalosporins [18]. This crisis make us to move towards the non-benalactam antibiotics. We have previously demonstrated that the novel synthesized oxadiazol compounds by our research group, possess antimicrobial activity against Staphylococcus epidermidis, Bacillus cereus , Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Candida tropicalis and Candida albicans.In this study all the synthesized compounds (4a-4f) were evaluated for their in vitro antibacterial activity against methicillin-resistant Staphylococcus aureus and the results were summarized in Chart 1and 2. The results revealed that all tested compounds have significant antimicrobials activity against Staphylococcus aureus with IZ values in the range of 16 -25, All tested compounds (4a-4f) inhibit the growth of MRSA but compounds 4a, 4b and 4C have shown more promising antimicrobial activity with MIC values of of 62µg/ mL. The antibacterial screening results demonstrated that antibacterial activity of above compounds are notably more as compared to standard drugs Ceftizoxime however, they showed poor activity compared with ciprofloxacin (Figure 1). No zone of inhibition was seen around the well containing DMSO (Negative control).

The results of the study revealed that the presence of lipophilicity moiety like: 4-phenyl methyl (4a), 3-phenyl methyl (4b) and 5-naphthalene (4c) increase the antimicrobial activity of compounds against MRSA. Additionally, nitrogen atom of pyridine moiety enhance the antimicrobial activities of title oxadiazol derivatives, which can be attributed to charge

delocalization and conversion in chemical structure [19]. As mentioned before, in addition to the high antimicrobial power of the tested derivatives, the proposed one-step method for the synthesis of compounds, can provide an efficient and impressive method for other pharmaceutical fields with time efficiency and less energy input. Continuation of study is required to evaluate the synergistic effect of synthesized compounds, and assess their safety and efficacy.

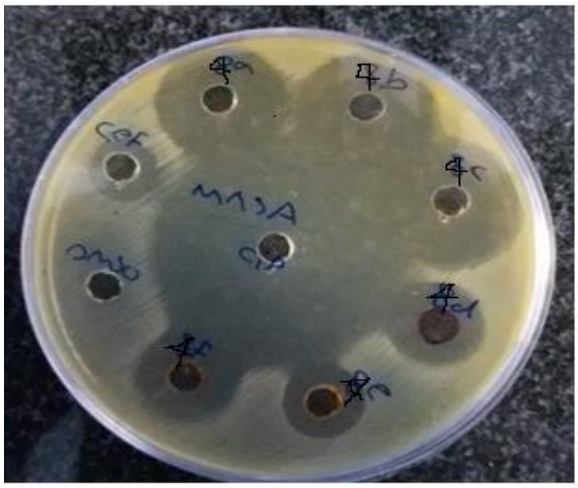


Figure1: *Inhibition zone of compounds against methicillin-resistant Staphylococcus aureus in 1mg/ml concentration*

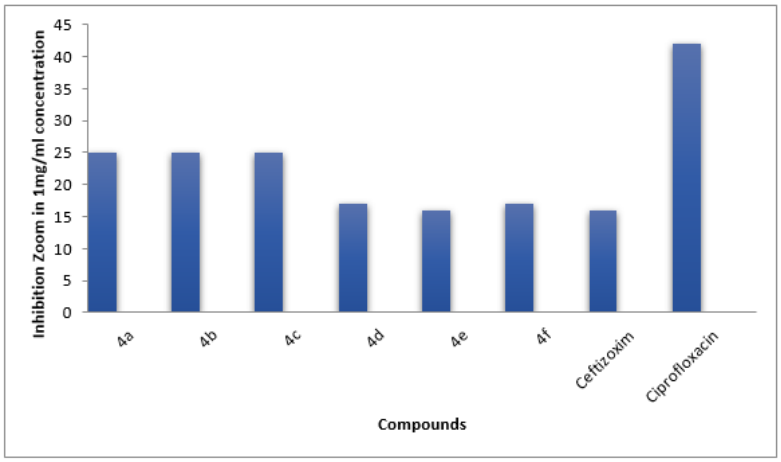


Chart 1: *Antibacterial activity of 5-aryl-1,3,4-oxadiazol derivatives by Agar well diffusion (1mg/ml)*

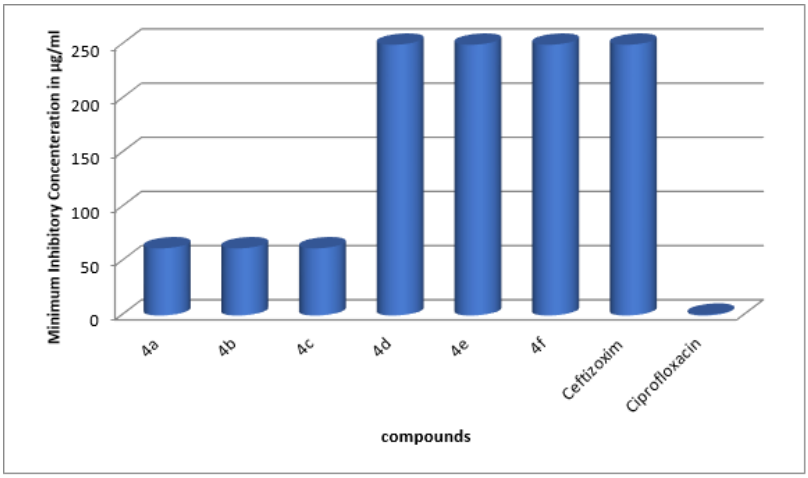


Chart 2: *In vitro antibacterial activity of (5-aryl-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol derivatives by agardilution method(µg/mL)*

Conclusion

The results show that these newly synthesized compounds could be good option toward the development of non-β-lactam antibiotics for treatment of infections caused by MRSA or enhancement of conventional antibiotics activity against MRSA.

Acknowledgments

The authors gratefully thank the Azad university of Urmia for providing this research.

Ethical Considerations

No manipulation or something similar were carried out on any animals.

Compliance with ethical guidelines

This article does not contain any studies involving animals performed or human participants performed by any of the authors.

Funding

The authors received no specific funding for this work.

Conflict of interest

We declare that we have no conflict of interest and the ethical principles for this research have been respected.

References

1. Karen Green (2012), Methicillin-ResistantStaphylococcus aureus An Update. TIBDN 4(3):1-4.
2. Selvakumar K, Anandarajagopal K, Rajamanickam V, Ajaykumar T V, Jesindha B (2011). 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3h) thionederivatives: synthesis, characterization and antimicrobial evaluation. Int. J. Pharm. Sci. Rev. Res 6(1):64-67.
3. Dalia H. S (2013). Synthesis, Characterization, Anti-Bacterial and Anti-Fungal Activities of New Quinoxaline 1,4-di-N-Oxide Derivatives. Int. J. Org. Chem 3:65-72.
4. Asif H, Moham A. (2009). Synthesis of novel 1,3,4-oxadiazole derivatives and their biological properties. Acta Pharm 59:223-233.
5. Ali, A., Mousavi, Z., Tajik, M., Assarzadeh, MJ., Shafiee, A. (2014). Synthesis, analgesic and anti-inflammatory activities of new methylimidazolyl-1,3,4-oxadiazoles and 1,2,4-triazoles. Daru. 22 (1):22-34.
6. Tashfeen A, Shahid H, Najim A.A, Roberta L, Paolo L.C (2008). In vitro antitumor and antiviral activities of new benzothiazole and 1,3,4-oxadiazole-2-thione derivatives. Acta Pharm 58:135-149.
7. Sanmati K. J, Arvind K. Y, Pragya N (2011). 3D QSAR Analysis on Oxadiazole Derivatives as Anticancer Agents. Int. J. Pharm. Sci. Drug Res 3(3):230-235.
8. Rakesh S, Anuja Ch (2014). various approaches for synthesis of 1,3,4-oxadiazole derivatives and their pharmacological activity. World J. Pharm. Pharm. Sci. 3(10): 1474-1505.
9. Mohammad S.Y and Mohammad W.A (2009). Synthesis And Anticonvulsant Activity of Substituted Oxadiazole And Thiadiazole Derivatives. Acta Poloniae Pharmaceutica. 66(4):393-397.
10. Nouraddin H,Soodeh S,Mohamad B.D, Mohammad H, Mehdi Kh ans (2013). Synthesis and Antidiabetic Evaluation of Benzenesulfonamide Derivatives. Iran. J. Pharm. Res. 12 (2):325-330.
11. Salar Salari Lak, Ali Souldozi, Reza Talebi (2017). Synthesis and Evaluation of Antibacterial Activity of 1,3,4-Oxadiazoles Derivatives Containing Pyridine Ring. J Chem Pharm Res. 9(2):141-146.
12. Maryam Kouhkan, Fatemeh Karimi, Ali Souldozi and Jalil Rashedi (2017). in vitro antimicrobial activity of new substituted 1,3,4-oxadiazole derivatives. Int. J. Adv. Res. 5(5): 146-147.
13. Fatemeh Karimi, Ali Souldozi and Nima Hoseini.Jazani (2015). One-pot synthesis of 2-aryl-1,3,4-oxadiazole derivatives as potential antibacterial agents. JCPR. 7(10): 1028-1033.
14. Maryam Kouhkan, Nima Hoseini.jazani, Ali Souldozi, Minoo Zardashti and Narges Darabi (2015). Solvent free synthesis of alkyl 2-(dialkylamino)-phenylthiazole-5carboxylates derivatives and in vitro antimycobacterial activity of these compounds against Mycobacterium smegmatis. JCPR. 7(7):338-345.
15. Samija M, Kemal D, Elma V, AMAR O, Dženita S, Davorka Z (2013). synthesis of biscoumarin derivatives as antimicrobial agents. Asian J Pharm Clin Res 6(3):132-134.
16. Jolanta Nawrot, Modranka and Ewa Nawrot (2007). Bsynthesis, spectroscopy and alkylating properties of pd(ii) complexes of phosphorohydrazones of coumarin and chromone with potential antibacterial activity. Acta Poloniae Pharmaceutica ñ Drug Research. 63(5):429-434.
17. Masomi F, Hassanshahian M. (2016). Antimicrobial Activity of Five Medicinal Plants on Candida Albicans. 10(6):39-43.
18. Donatella Tondi , Federica Morandi, Richard Bonnet, M Paola Costi, Brian K Shoichet. (2005). Structure-based optimization of a non-beta-lactam lead results in inhibitors that do not up-regulate beta-lactamase expression in cell culture. 127(13):4632-4639.
19. John Sadgrove N and Lloyd Jones G (2019). Petri Dish to Patient: Bioavailability Estimation and Mechanism of Action for Antimicrobial and Immunomodulatory Natural Products. Front Microbiol. 10:2470.