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Synthesis of New Three-Component Derivatives of 1, 3, 4-Oxadiazole and Evaluation of Their In Vitro Antibacterial and Antifungal Properties

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ABSTRACT

Background and objectives: Antibiotic resistance is a major public health challenge. The pervasive antibiotic misuse can lead to increased antibiotic resistance. Thus, there is a need for discovery of new compounds against drug-resistant microorganisms. We synthesized new series of 1, 3, 4-oxadiazole derivatives (4a-4d) and evaluated the antibacterial and antifungal activity of the derivatives against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Aspergillus fumigatus* and *Aspergillus flavus*.

Methods: The new derivatives of 1, 3, 4-oxadiazole were synthesized using a single-stage, high-yield method. The structure of the new compounds was confirmed by infrared spectroscopy, carbon-nuclear magnetic resonance and hydrogen-nuclear magnetic resonance. Then, antibacterial and antifungal activities of the prepared derivatives (1 mg/ml) were evaluated by determining minimum inhibitory concentration and minimum bactericidal/fungicidal concentration using the agar well diffusion method.

Results: All synthesized compounds, especially (4d) with methoxyphenyl group, exhibited powerful antibacterial activity against the tested bacteria. However, the compounds had no antifungal effect.

Conclusion: Our findings indicate the antibacterial potential of the novel synthetic 1, 3, 4-oxadiazole compounds.

Keywords: Anti-bacterial agents, Antifungal agents, Oxadiazoles.

INTRODUCTION

Antibiotics are powerful medicines that fight certain infections and can save lives when used properly (1). They either stop bacteria from reproducing or destroy them (2). However, the pervasive antibiotic misuse can lead to antibiotic resistance (3). Therefore, it is necessary to seek novel antibacterial agents (4). Gram-positive pathogens exhibit an immense genetic repertoire to adapt and develop resistance to virtually all available antimicrobials (5). In 2017, the World Health Organization (WHO) has published a list of antibiotic-resistant priority pathogens, which present a great threat to humans. The list is categorized based on the urgency of need for new antibiotics as critical, high and medium priority, in order to guide and promote research and development of new antibiotics. Due to their distinctive structure, gram-negative bacteria are more resistant than gram-positive bacteria, and cause significant morbidity and mortality worldwide (6). Some species of fungi are also naturally resistant to antifungal drugs. For example, fluconazole is not effective against infections caused by *Aspergillus* (7). Resistance can also develop over time when fungi are exposed to antifungal drugs. So far, different classes of oxadiazoles have been synthesized (8). Oxadiazoles are non-β-lactam class of antibiotics with five-membered heterocyclic aromatic rings containing two carbon, two nitrogen and one oxygen atoms. Among their different structures, 1, 3, 4-oxadiazole is known for high reactivity and the possibility of adding more functional groups (9). This structure also has antibacterial (10), antifungal (11), antitubercular (12), antiviral (13), anticancer (14) and antimalarial properties (15). The purpose of this study is to synthesize new series of oxadiazoles structures and evaluate antibacterial and antifungal activity of 1, 3, 4-oxadiazole derivatives against some gram-positive (*S. aureus* PTCC 1189, *S. epidermidis* PTCC 1436) and gram-negative (*A. baumannii* PTCC1855, *K. pneumonia* PTCC1290) bacteria as well as some fungi (*A. fumigates* PTCC5009, *A. flavus* PTCC5006).

MATERIALS AND METHODS

This experimental research was conducted in the microbiology laboratory of Islamic Azad University, Tehran branch in 2020. Starting materials, solvents and culture media (nutrient agar/broth and sabouraud dextrose agar/broth) were purchased from Merck Co., Germany. Infrared (IR) spectrum was measured using the Shimadzu IR-460 spectrometer. Nuclear magnetic resonance (NMR) spectrum was obtained using the Bruker DRX-300 AVANCE spectrometer (^{1}H NMR at 300 Hz, ^{13}C NMR at 75 Hz) in acetone. Chromatography columns were prepared using silica gel powder (Merck, Germany). All bacterial and fungal strains (*S. aureus* PTCC 1189, *S. epidermidis* PTCC 1436, *A. baumannii* PTCC1855, *K. pneumonia* PTCC1290, *A. fumigates* PTCC5009, *A. flavus* PTCC5006) were obtained from the Iranian Industrial Microorganisms Collection Center in lyophilized form.

Structure synthesis

1, 3, 4-oxadiazole compounds were synthesized using a single-stage, high yield method. The chemical structure of all synthesized compounds was investigated using IR spectroscopy, H-NMR and C-NMR. First, N-Iso-cyan-imino-triphenyl-phosphoran (1mmol, 0.3 g) was dissolved in dichloromethane (7 ml) with 2-pyridine carbaldehyde. Next, carboxylic acid derivatives and cinnamic acid derivatives (1mmol) were added. The solution was stirred for 24 hours on a magnetic stirrer at 37 ^{oC}. The solvent was removed by evaporation, and the viscous residue was purified by flash column chromatography [silica gel powder: petroleum ether–ethyl acetate (5:1)]. Thin-layer chromatography and NMR indicated that there was no side product.

Preparation of compound concentrations

One mg/ml of synthesized compounds powder (1:10 ratios) was dissolved in dimethyl sulfoxide (99%). The resulting solution was kept at -18℃ in sterile test tubes.

Antibacterial activity

Minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)/ minimum fungicidal concentration (MFC) of the synthesized compounds were evaluated using agar well diffusion method according to the Clinical & Laboratory Standards Institute standards (16).

Preparation of bacterial and fungal suspensions

The lipophilic ampoules containing *S. aureus*, *S. epidermidis*, *A. baumannii* and *K.*

pneumoniae were transferred to nutrient broth and incubated for 24 hours at 37 °C. *A. flavus* and *A. fumigatus* were transferred to sabouraud dextrose broth and incubated for 24 hours at 37 °C. Using a sampler, 1 ml from 24-hour culture of microbial suspension was transferred to a tube containing sterile nutrient broth to reach turbidity of the microbial suspension equal to half McFarland standard (1.5×10^9 CFU/ml).

Agar well diffusion method

To perform this experiment, wells of 5 mm in diameter were created by a sterile pipette in agar media containing bacterial or fungal suspension. The wells were then filled with the synthesized compounds (4a-4d). Ciprofloxacin and fluconazole were used as the positive controls. The plates were incubated at 37 °C for 24 hours. The experiment was performed in triplicate.

Broth dilution method

The antibacterial and antifungal activity of the compounds was evaluated by broth dilution method. First, 10 µl of inoculums containing 1.5×10^{-9}C.F.U/ml of tested microorganism was added to sterile test tubes. Different concentrations (1.95-1000 µg/ml) of the synthesized compounds were added to the test tubes. Lowest concentration of the compounds that inhibited growth of bacteria was recorded as the MIC. Lowest concentration that reduced the viability of bacteria and fungi by ≥99.9% was recorded as the MBC and MFC, respectively.

RESULTS

Chemistry

Results of IR spectroscopy, C-NMR and H-NMR of all compounds are shown in figure 2.

The synthesis of derivatives was performed in a single step with high efficiency (4a-4d) and the structures were determined after purification.

Table 1-Antibacterial and antifungal activities of 1, 3, 4-oxadiazol derivatives by agar well diffusion method.

Microorganism												
K. pneumonia PTCC1290			*A. baumannii* PTCC1855			*S. epidermidis* PTCC 1436			*S. aureus* PTCC 1189			Compounds
MBC	MIC	IZ	MBC	MIC	IZ	MBC	MIC	IZ	MBC	MIC	IZ	
NA	NA	11.33 ± 0.5	1000	100	31.66±0.5	1000	500	38.66±0.5	1000	500	36.66±0.5	4a
NA	NA	14.66 ± 0.5	NA	NA	16.66±0.5	1000	500	39.66±0.5	500	125	42.33±0.5	4b
NA	NA	13.66 ± 0.5	NA	NA	20.66±0.5	1000	500	36.66±0.5	500	125	41.33±0.5	4c
NA	NA	17.33 ± 1.15	125	62.50	48.66±0.5	125	62.50	47.66±0.5	62.50	31.25	53.66±0.5	4d
1000	500	30.5± 0.3	62.50	31.25	51.66±0.5	62.50	31.25	56.66±0.5	31.25	15.62	64.66±0.5	Cip

Microorganism						
A. flavus PTCC5006			*A. fumigates PTCC5009*			Compounds
MFC	MIC	IZ	MFC	MIC	IZ	
NA	NA	11.33± 0.5	NA	NA	NA	4a
1000	1000	11.33± 0.5	1000	1000	12.33± 0.5	4b
NA	NA	11.66± 0.5	NA	NA	NA	4c
NA	NA	11.66± 0.5	NA	NA	11.66± 0.5	4d
NA	NA	11.33± 0.5	NA	NA	11.66± 0.5	Fl

Results are related to 1 mg/ml of each compound.
NA: no activity
Cip: Ciprofloxacin
Fl: Fluconazole

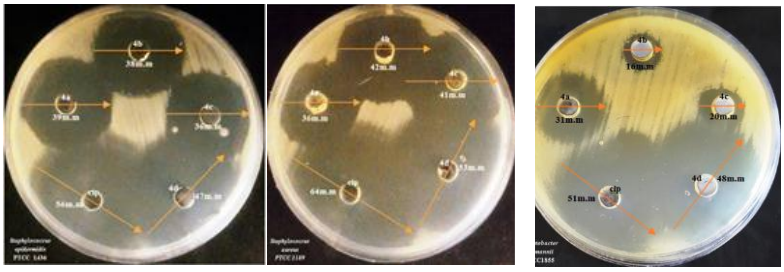
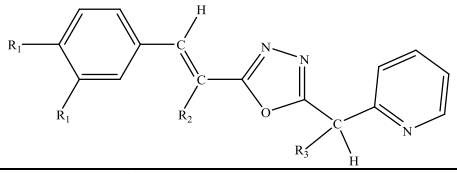


Figure 1- Inhibition zone of compounds (1 mg/ml) against *S. aureus* PTCC 1189, *S. epidermidis* PTCC 1436 and *A. baumannii* PTCC1855

[4a] **(Z)-N-(2-(3, 4-Di (R_1) phenyl)-1-(5-((R_3) (pyridin-2-yl) methyl)-1, 3, 4-oxadiazol-2-yl) vinyl) (R2).**

$R_{1=}$ -Chloride
$R_{2=}$ -$COHNCH_3$
$R_{3=}$ -OH

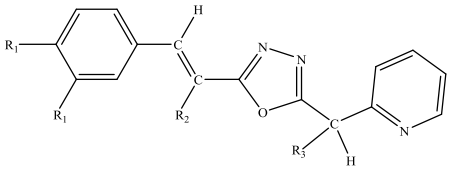


Spectral information

White powder, m.p. 131 ºC, yield 84% (0.21g).
IR (KBr) (vmax, Cm^{-1}): 3424, 3102, 2822, 2741, 1602, 1399, 1102, 1017.
^{1}HNMR (300.13 MHz, $CDCl_3$): δH=5.87 (s, 1H, OH), 5.21 (s, H, CH Aliphatic), 7.47-7.49 (m, 1H, CH, Arom), 7.54-7.71 (m, 3H, CHArom), 7.99 (t, 3JHH= 7.5 Hz, 1C, Arom), 8.25 (d, 3JHH=7.2 Hz, 2H, CH Arom), 8.48 (d, 3JHH= 7.8Hz, 1H, CH Arom), 8.92-8.93 (m, 1H, Arom).
^{13}CNMR (75.467 MHz, $CDCl_3$): δC= 67.22 (CH-OH), 127.90, 128.05, 129.25, 131.89, 131.93 (5CH, Phenyl), 125.79, 133.27, 137.24, 150.21 (4CH, Arom, Pyridine), 122.81, 151.43 (2C), 160.86, 164.06.

[4b] **(Z)-N-(2-(3, 4- Di (R_1) phenyl)-1-(5-((R_3) (pyridin-2-yl) methyl)-1, 3, 4-oxadiazol-2-yl) vinyl) (R_2).**

$R_{1=}$ -Bromide
$R_{2=}$ -$COHNCH_3$
$R_{3=}$ -OH

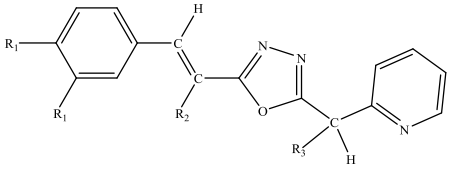


Spectral information

White powder, m.p. 131 ºC, yield 84% (0.21g).
IR (KBr) (vmax, Cm^{-1}): 3425, 3103, 2823, 2742, 1603, 1400, 1103, 1018.
^{1}HNMR (300.13 MHz, $CDCl_3$): δH=5.88 (s, 1H, OH), 5.22 (s, H, CH Aliphatic), 7.48-7.50 (m, 1H, CH, Arom), 7.55-7.72 (m, 3H, CHArom), 8 (t, 3JHH= 7.6 Hz, 1C, Arom), 8.26 (d, 3JHH=7.3 Hz, 2H, CH Arom), 8.49 (d, 3JHH= 7.9Hz, 1H, CH Arom), 8.93-8.95 (m, 1H, Arom).
^{13}CNMR (75.467 MHz, $CDCl_3$): δC= 67.23 (CH-OH), 127.91, 128.06, 129.26, 131.90, 131.94 (5CH, Phenyl), 125.8, 133.28, 137.25, 150.22 (4CH, Arom, Pyridine), 122.82, 151.45 (2C), 160.86, 164.06.

[4c] **(Z)-N-(2-(3, 4- Di (R_1) phenyl)-1-(5-((R_3) (pyridin-2-yl) methyl)-1, 3, 4-oxadiazol-2-yl) vinyl) (R_2).**

$R_{1=}$ -Flour
$R_{2=}$ -$COHNCH_3$
$R_{3=}$ -OH

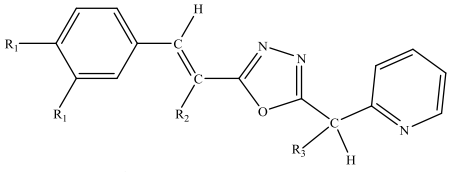


Spectral information

White powder, m.p. 131 ºC, yield 84% (0.21g).
IR (KBr) (vmax, Cm^{-1}): 3423, 3101, 2821, 2740, 1601, 1398, 1101, 1016.
^{1}HNMR (300.13 MHz, $CDCl_3$): δH=5.86 (s, 1H, OH), 5.2 (s, H, CH Aliphatic), 7.46-7.48 (m, 1H, CH, Arom), 7.53-7.7 (m, 3H, CHArom), 7.79 (t, 3JHH= 7.4 Hz, 1C, Arom), 8.24 (d, 3JHH=7.1 Hz, 2H, CH Arom), 8.47 (d, 3JHH= 7.7Hz, 1H, CH Arom), 8.91-8.92 (m, 1H, Arom).
^{13}CNMR (75.467 MHz, $CDCl_3$): δC= 67.21 (CH-OH), 127.85, 128.01, 129.21, 131.85, 131.92 (5CH, Phenyl), 125.71, 133.21, 137.25, 150.25 (4CH, Arom, Pyridine), 122.83, 151.45 (2C), 160.85, 164.05.

[4d] **(Z)-N-(2-(3, 4- Di (R_1) phenyl)-1-(5-((R_3) (pyridin-2-yl) methyl)-1, 3, 4-oxadiazol-2-yl) vinyl) (R_2).**

$R_{1=}$ -Methoxy
$R_{2=}$ -$COHNCH_3$
$R_{3=}$ -OH



Spectral information

White powder, m.p. 135 ºC, yield 79% (0.22g).
IR (KBr) (vmax, cm^{-1}): 3435, 3066, 2924, 2847, 1668, 1583, 1537, 1512, 1493, 1434, 1379, 1289, 1226, 1047, 921.
1HNMR (300.13 MHz, $CDCl_3$): δH= 3.94 (3H, OCH3, s), 6.15 (s, 1H, CH aliphatic), 6.54 (s, 1H, OH), 7.16-7.18 (m, 1H, CH Arom), 7.49 (t, 1H, 3JHH= 8.2 Hz, Arom), 7.64-7.67 (m, 1H, CH Arom), 7.74-7.76 (m, 1H, CH Arom), 7.84 (d, 1H, 3JHH=8.2 Hz, CH Arom), 7.9 (t, 2H, 3JHH =7.8 Hz, CH Arom), 8.478 (d, 1H, 3JHH = 8.2 Hz, CH Arom), 8.917-8.931 (m, 1H, CH Arom).
13CNMR (75.467 MHz, $CDCl_3$): δC= 55.65 (CH3), 68.42 (CH-OH), 112.22, 119.58, 120.34, 125.77, 128.08, 130.45, 137.24, 150.25 (8CH, Arom), 123.95, 151.54, 160.09, 160.88, 166.04.

Figure 2- Structural and spectral information of new derivatives of 1, 3, 4-oxadiazoles

Determination of the in vitro antibacterial and antifungal activity

Antibacterial and antifungal activities of the prepared 1, 3, 4-oxadiazole derivatives (4a-4d) moieties were evaluated. The diameters of inhibition zone (IZ) for each compound are reported in table 1. Compound (4d) with methoxyphenyl group showed powerful antibacterial activity against *S. aureus*, *S. epidermidis* and *A. baumannii* (Figure 1). Other compounds also showed acceptable antibacterial effects. However, the compounds showed no notable antifungal activity.

DISCUSSION

The objective of this study was to evaluate the antibacterial and antifungal activities of 1, 3, 4-oxadiazole derivatives against some pathogenic bacteria and fungi. In recent years, a number of new 1, 3, 4-oxadiazole analogues has been introduced as potential antimicrobial agents (17). The latest study about 1, 3, 4-oxadiazole with methoxyphenyl group reported that methoxyphenyl group in 1, 3, 4-oxadiazole structure have favorable antibacterial effect against gram-positive and gram-negative bacteria (18), which is in line with our findings. In our study, (Z)-N-(2-(4-methoxyphenyl)-1-(5-(hydroxyl (pyridin-2-yl) methyl)-1, 3, 4-oxadiazol-2-yl) vinyl) acetamide (4d) showed comparable antibacterial activity to that of the reference drug. This may be due to the presence of methoxyphenyl along with hydroxyl and (pyridin-2-yl) methyl. This finding is similar to results of some previous studies (19, 20). In our study, we synthesized new 1, 3, 4-oxadiazole derivatives with inhibitory properties against gram-positive and gram-negative bacteria. However, the compound exhibited no antifungal activity. In our previous study, the two-component derivatives of 1, 3, 4-oxadiazole with methoxyphenyl group showed acceptable antibacterial effect against *A. baumannii*. It seems that increasing the number of side chains attached to 1, 3, 4-oxadiazole contributed to the increased antibacterial properties (21). In the present study, the presence of chlorophenyl, bromophenyl, fluorophenyl and methoxyphenyl rings caused a considerable decrease in the antifungal potential of the compound while increasing the antibacterial properties. Therefore, it can be inferred that in similar structures, the presence of these groups, especially methoxy phenyl group, enhances the antimicrobial activity. It is suggested to use other functional groups of carboxylic acids in the synthesis of new derivatives. It seems that the ability of oxadiazole structures is influenced by addition of different functional groups.

CONCLUSION

Based on our findings, the synthesized compounds, especially compound 4d (methoxy phenyl group), could be utilized in designing more potent antibacterial agents, particularly against *S. aureus*, *S. epidermidis* and *A. baumannii*. Further studies are required to assess cytotoxicity of such compounds.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

1. Singh N, Yeh PJ. *Suppressive drug combinations and their potential to combat antibiotic resistance*. The Journal of antibiotics. 2017; 70(11): 1033-42. [View at Publisher] [DOI:10.1038/ja.2017.102] [PubMed] [Google Scholar]

2. Alshon A, Almiahi Y. *Client's Attitude Regarding Antibiotics Misuse in Primary Health Care Centers*. Indian Journal of Forensic Medicine & Toxicology. 2020; 14(2): 1009-11. [View at Publisher] [PubMed]

3. Jensen CS, Nielsen SB, Fynbo L. *Concluding Remarks on 'Risking Antimicrobial Resistance*'. Risking Antimicrobial Resistance: Springer. 2019; 199-208. [View at Publisher] [DOI:10.1007/978-3-319-90656-0_12] [Google Scholar]

4. Hellewell L, Bhakta S. *Chalcones, stilbenes and ketones have anti-infective properties via inhibition of bacterial drug-efflux and consequential synergism with antimicrobial agents*. Access Microbiology. 2020;2(4):e000105. [View at Publisher] [DOI:10.1099/acmi.0.000105] [PubMed] [Google Scholar]

5. Hover BM, Kim S-H, Katz M, Charlop-Powers Z, Owen JG, Ternei MA, et al. *Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens.* Nature microbiology. 2018; 3(4): 415-22. [View at Publisher] [DOI:10.1038/s41564-018-0110-1] [PubMed] [Google Scholar]

6. Shrivastava SR, Shrivastava PS, Ramasamy J. *World health organization releases global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.* Journal of Medical Society. 2018; 32(1): 76. [DOI:10.4103/jms.jms_25_17] [Google Scholar]

7. Leonardelli F, Macedo D, Dudiuk C, Cabeza MS, Gamarra S, Garcia-Effron G. *Aspergillus fumigatus intrinsic fluconazole resistance is due to the naturally occurring T301I substitution in Cyp51Ap*. Antimicrobial agents and chemotherapy. 2016; 60(9): 5420-6. [View at Publisher] [DOI:10.1128/AAC.00905-16] [PubMed] [Google Scholar]

8. Boström J, Hogner A, Llinàs A, Wellner E, Plowright AT. *Oxadiazoles in medicinal chemistry*. Journal of medicinal chemistry. 2012; 55(5): 1817-30. [View at Publisher] [DOI:10.1021/jm2013248] [PubMed] [Google Scholar]

9. Pibiri I, Lentini L, Melfi R, Tutone M, Baldassano S, Galluzzo PR, et al. *Rescuing the CFTR protein function: Introducing 1, 3, 4-oxadiazoles as translational readthrough inducing drugs*. European journal of medicinal chemistry. 2018; 159: 126-42. [View at Publisher] [DOI:10.1016/j.ejmech.2018.09.057] [PubMed] [Google Scholar]

10. Sarveahrabi Y, Souldozi A, Talebi R. *2-Substituent Synthesis of 5-3-Methoxyphenyl and 5-4-Methoxyphenyl-1, 3, 4-Oxadiazoles, 2-Yl-Pyridine-2-Yl-Methanol in Positions of 2 and 3 of 1, 3, 4-Oxadiazoles Containing Halogen and the Evaluation of Their Antibacterial Properties.* Navid No. 2020; 22(72): 1-13. [View at Publisher] [Google Scholar]

11. Capoci IRG, Sakita KM, Faria DR, Rodrigues Vendramini FAV, Arita GS, de Oliveira AG, et al. *Two new 1, 3, 4-oxadiazoles with effective antifungal activity against Candida albicans.* Frontiers in microbiology. 2019; 10: 2130. [View at Publisher] [DOI:10.3389/fmicb.2019.02130] [PubMed] [Google Scholar]

12. Patel RV, Kumari P, Chikhalia KH. *New quinolinyl-1,3,4-oxadiazoles: synthesis, in vitro antibacterial, antifungal and antituberculosis studies.* Med Chem. 2013 1;9(4):596-607. [View at Publisher] [DOI:10.1002/slct.201802227] [PubMed] [Google Scholar]

13. Albratty M, El-Sharkawy KA, Alhazmi HA. *Synthesis and evaluation of some new 1, 3, 4-oxadiazoles bearing thiophene, thiazole, coumarin, pyridine and pyridazine derivatives as antiviral agents.* Acta Pharmaceutica. 2019; 69(2): 261-76. [View at Publisher] [DOI:10.2478/acph-2019-0015] [PubMed] [Google Scholar]

14. Caneschi W, Enes KB, Carvalho de Mendonça C, de Souza Fernandes F, Miguel FB, da Silva Martins J, et al. *Synthesis and anticancer evaluation of new lipophilic 1,2,4 and 1,3,4-oxadiazoles.* Eur J Med Chem. 2019 1;165:18-30 [View at Publisher] [DOI:10.1016/j.ejmech.2019.01.001] [PubMed] [Google Scholar]

15. Thakkar SS, Thakor P, Doshi H, Ray A. *1,2,4-Triazole and 1,3,4-oxadiazole analogues: Synthesis, MO studies, in silico molecular docking studies, antimalarial as DHFR inhibitor and antimicrobial activities.* Bioorg Med Chem. 2017 1;25(15):4064-4075. [View at Publisher] [DOI:10.1016/j.bmc.2017.05.054] [PubMed] [Google Scholar]

16. Rennie R, Turnbull L, Brosnikoff C, Cloke J. *First comprehensive evaluation of the MIC evaluator device compared to Etest and CLSI reference dilution methods for antimicrobial susceptibility testing of clinical strains of anaerobes and other fastidious bacterial species*. Journal of Clinical Microbiology. 2012; 50(4): 1153-7. [View at Publisher] [DOI:10.1128/JCM.05397-11] [PubMed] [Google Scholar]

17. Othman AA, Kihel M, Amara S. *1, 3, 4-Oxadiazole, 1, 3, 4-thiadiazole and 1, 2, 4-triazole derivatives as potential antibacterial agents.* Arabian Journal of Chemistry. 2019; 12(7): 1660-75. [View at Publisher] [DOI:10.1016/j.arabjc.2014.09.003] [Google Scholar]

18. Aghekyan A, Mkryan G, Panosyan H, Safaryan A, Stepanyan H. *Synthesis and Antibacterial Activity of Novel (4-Methoxyphenyl)-tetrahydropyranyl-substituted 1, 3, 4-Oxadiazoles.* Russian Journal of Organic Chemistry. 2020; 56: 281-6. [View at Publisher] [DOI:10.1134/S1070428020020177] [PubMed] [Google Scholar]

19. Guo Y, Xu T, Bao C, Liu Z, Fan J, Yang R, Qin S. *Design and synthesis of new norfloxacin-1,3,4-oxadiazole hybrids as antibacterial agents against methicillin-resistant Staphylococcus aureus (MRSA).* Eur J Pharm Sci. 2019 1;136:104966. [View at Publisher] [DOI:10.1016/j.ejps.2019.104966] [PubMed] [Google Scholar]

20. Tresse C, Radigue R, Gomes Von Borowski R, Thepaut M, Hanh Le H, Demay F, Georgeault S, Dhalluin A, Trautwetter A, Ermel G, Blanco C, van de Weghe P, Jean M, Giard JC, Gillet R. *Synthesis and evaluation of 1,3,4-oxadiazole derivatives for development as broad-spectrum antibiotics*. Bioorg Med Chem. 2019 1;27(21):115097. [View at Publisher] [DOI:10.1016/j.bmc.2019.115097] [PubMed] [Google Scholar]

21. SarveAhrabi Y, Souldozi A, Zarrabi Ahrabi N. *In Vitro Evaluation of Antimicrobial Properties of Some New 1, 3, 4-Oxadiazole Derivatives against Acinetobacter baumannii.* Infection Epidemiology and Microbiology. 2020; 6(1): 37-49. [DOI:10.29252/iem.6.1.37] [Google Scholar]

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