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Original Article

Synthesis and Antimicrobial Evaluation of New Series of 1,3,4-Oxadiazole Containing Cinnamic Acid Derivatives

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Abstract

Background: New drugs must be designed and synthesized for combating resistant pathogens. In this study, antibacterial and antifungal activities of 4 new derivatives of 1,3,4-oxadiazole were assessed against 8 bacterial and 2 fungal pathogens.

Methods: To this end, the cinnamic acid derivatives were dissolved in acetonitrile solvent and N-iso-ciano-imino-triphenyl-phosphorane was added to the above-mentioned solution, followed by applying Petroleum ether and Ethyl acetate as solvent and base. Then, antimicrobial susceptibility tests were used to determine inhibition zone diameter, minimum inhibitory concentration, the minimum bactericidal concentration (MBC), and minimum fungicidal concentration (MFC) values.

Results: The chemical structure of all compounds was characterized with infrared spectra, 1H-NMR, and 13C-NMR. A variety of inhibitory effects were observed by the synthesized compounds. Methoxyphenyl derivative (3c) affected bacterial strains, especially *Streptococcus mutans*. Other compounds also had antibacterial properties. Additionally, compound 3c showed the greatest effect on fungal samples, especially *Aspergillus flavus*.

Conclusions: In general, our new derivatives of 1,3,4-oxadiazole are able to destroy Gram-positive bacteria**.** In addition, developing new derivatives of 1,3,4-oxadiazole in future research can improve therapeutic properties. It seems that with the addition of other functional groups and increasing the destructive power of compounds, inhibitory effects on fungal samples can also be observed.

Keywords: Oxadiazoles, Antibacterial activity, Antifungal activity, Methoxyphenyl

Background

The increase of drug resistance in bacteria and fungi has increased the need for new drug compounds (1). In addition, improper use of drugs and mutations in pathogens have increased drug resistance (2). As a result, the discovery, design, and synthesis of new antimicrobial compounds have become inevitable requirements in the field of treatment (3). 1,3,4-oxadiazole derivatives are biologically active organic compounds. 1,3,4-Oxadiazole is a N_2 (nitrogen) and O_2 (oxygen) containing heterocycle and one of the 4 isomers of oxadiazoles. 1,3,4-oxadiazole itself is not generally used in chemistry, but many of its derivatives are significant (4). For instance, raltegravir is an anti-HIV drug which contains a 1,3,4-oxadiazole ring (5). Other pharmaceutical drugs containing the 1,3,4-oxadiazole ring include fenadiazole (6), zibotentan (7), and doxazosin (8). Numerous available functional groups in 1,3,4-oxadiazole have given them diverse therapeutic properties such as antibacterial (9), antifungal (10), anti-cancer (11), antioxidant (12), anti-malarial (13), and anti-inflammatory (14). The varied biological properties of 1,3,4-oxadiazole prompted us to synthesize several derivatives of this family via the reaction of different carboxylic acid derivatives and 2-pyridinecarboxaldehyde, and their antimicrobial properties were assessed against a wide range of bacterial and fungal pathogens.

Methods

Chemicals

All the required materials were prepared from Merck Company (Germany) and used without further purification. The infrared spectrum was measured by a Shimadzu IR-460 spectrometer. Nuclear magnetic resonance spectrum was obtained by a Bruker DRX-300 AVANCE spectrometer (1H NMR at 300 Hz, 13C NMR at 75 Hz) in $CDCl_3$. Chromatography columns were prepared using silica gel powder (Merck, Germany).

One-Step Process for the Synthesis of 1,3,4-Oxadiazole Derivatives (3a-d)

According to Figures 1 and 2, N-iso-ciano-imino-triphenyl-phosphorane [2] through its isocyanide carbon, separates acidic hydrogen from cinnamic acid derivatives [1] to form ion pairs [5]. Then, the protonated carbon

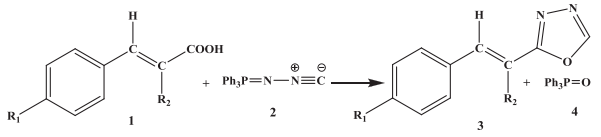


Figure 1. Overall Reaction.

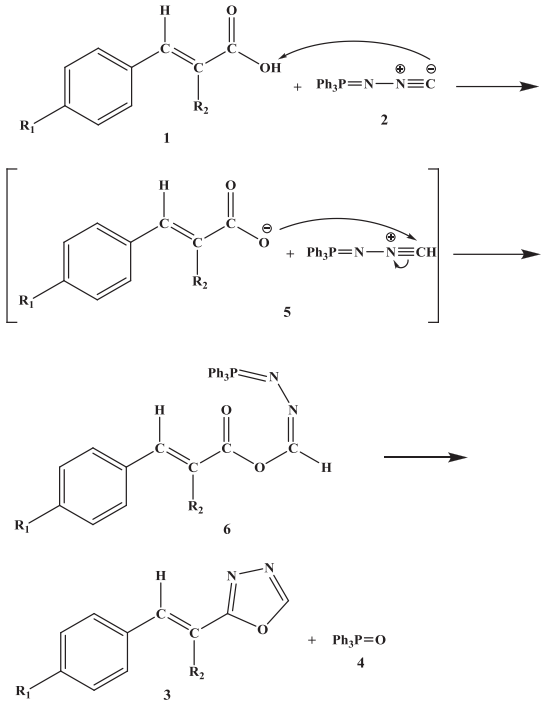


Figure 2. Reaction Theory

of N-iso-ciano-imino-triphenyl-phosphorane is attacked by the anion of cinnamic acid derivatives (Figure 3) and an intermediate is created [6]. The intermediate [6] reacts with the intramolecular Wittig to form product [3] together with triphenylphosphine oxide [4]. It is noteworthy that these structures were synthesized for the first time.

Antimicrobial Assay

Microorganisms

Culture media (Mueller-Hinton agar, Mueller-Hinton broth, Sabouraud dextrose agar) were obtained from Merck Company (Germany). Gram-negative and gram-positive bacterial and fungal strains were prepared from the Iranian Industrial Microorganisms Collection Center (Lyophilized). Microbiological tests were performed using a Memmert-INC153T2T3 incubator. Gram-negative strains included *Escherichia coli* (PTCC 1276), *Proteus mirabilis* (PTCC1793), *Salmonella typhi* (PTCC1609), and *Pseudomonas aeruginosa* (PTCC1310). Gram-positive strains included *Staphylococcus epidermidis* (PTCC1435), *Staphylococcus aureus subsp. aureus* (PTCC1917), *Streptococcus mutans* (PTCC1683), and *Streptococcus pseudopneumoniae* (PTCC1662). Fungal strains included *Candida albicans* (PTCC5027) and *Aspergillus flavus* (PTCC5018). Inhibition zone and Broth microdilution (minimum bactericidal concentration [MBC], minimum inhibitory concentration [MIC] and minimum fungicidal concentration [MFC]) were applied to evaluate antibacterial and antifungal susceptibility tests (11). The results were reported as the mean of three independent experiments.

Inhibition Zone

After preparing the suspension of bacteria and fungi (separately) in the tube with distilled water and adjusting the turbidity of the suspensions to match 0.5 McFarland standard (1.5×10^6 CFU/mL), some of each suspension was removed with sterile cotton swabs and was cultivated as grass in Mueller-Hinton agar medium for bacterial culture and Sabouraud dextrose agar for fungal culture. Then, wells were made in the plate by Pasteur pipette. Then, 10 µL of solutions prepared from oxadiazole derivatives (at concentrations of 0.5 mg/mL), ciprofloxacin (positive control for bacteria), and clotrimazole (positive control for fungi) was injected into the wells. Positive control samples were used to compare their growth areas with new compounds. Finally, the plates were closed and they were incubated for 24 hours at 37°C for bacterial samples and 48 hours at 35°C for fungal samples. After the time mentioned, the plates were examined for the presence of growth inhibition zone (15).

Minimum Inhibitory Concentration Experiment

MIC of the compounds was determined using the two-fold serial dilution method (bacterial-fungal). Concentrations of 1000, 500, 250, 125, 62.50, 31.25, and 15.62 µg/mL were prepared in sterile molten Mueller-Hinton agar from the stock solution. The microplates were inoculated with 1.5×10^6 CFU/mL of bacterial suspension at 37°C for 24 hours. The MIC was defined as the lowest concentration of the compounds that prevented visible growth of microorganisms after 24 hours of incubation. The antibacterial activity of the compounds was compared with ciprofloxacin as standard antibacterial agents. Next, the fungal suspension was made and adjusted to turbidity equivalent to a 0.5 McFarland standard (1.5×10^6 CFU/mL). The inoculated agar was poured into the assay plate and allowed to cool down on a leveled surface. Once the medium solidified, wells were created on the agar, and 70 µL of the antifungal agents was poured into each well. After adding the synthesized compounds, the plate was incubated at 35°C for 48 hours (16). Antifungal susceptibility test was performed by the agar dilution method. Stock solutions of 1,3,4-oxadiazole derivatives were prepared at a concentration of 0.5 mg/mL in dimethyl sulfoxide (0.001 g of each derivative in

2 mL of DMSO). Next, 1.6 mL of molten Sabouraud dextrose agar was poured into sterile microplates and allowed to cool to 50°C. Then, 0.4 mL of dilutions prepared from the stock solutions of the clotrimazole was added in descending order of concentration. In addition, 10 µL of the standardized fungal inoculum was added to all microplates except for the sterility control. The microplates were incubated at 35°C for 7 days and visualized for growth. The lowest concentration that inhibited the growth of fungi was defined as the MIC. All experiments were performed in duplicate and results were reported as mean ± standard deviation.

MBC and MFC Experiments

To determine the MBC and the MFC of the synthesized compounds, a loopful was taken from the MIC tubes and streaked on Mueller-Hinton agar for bacterial culture and Sabouraud dextrose agar for fungal culture. Growth was observed after incubation at 37°C for 24 hours. The lowest concentration at which no growth was observed was determined as the MIC and MFC (17).

Results and Discussion

Chemicals

Structures, Infrared, C-NMR, and H-NMR of all compounds were obtained (Figure 4).

Determination of the In Vitro Antibacterial and Antifungal Properties

Antibacterial and antifungal properties of new derivatives of 1,3,4-oxadiazole (3a-3d) were evaluated in terms of their structures (Figure 4). The inhibition zone diameters of the synthesized compounds against the tested bacteria and fungi are presented in Tables 1 and 2.

As shown in Table 1, the greatest effect of compound 3a was observed on *S. mutans* with IZ=31.33 ± 0.50 mm,

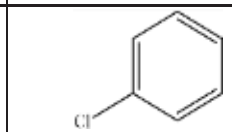
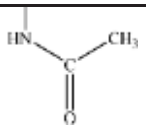
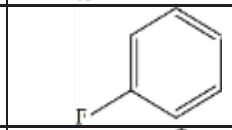
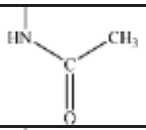
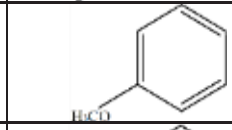
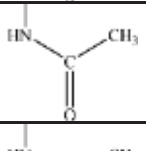
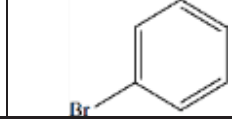
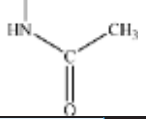
	R_1	R_2
3a		
3b		
3c		
3d		

Figure 3. Functional Groups .

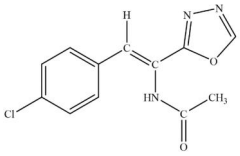
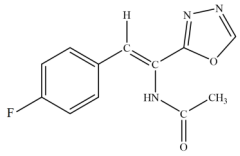
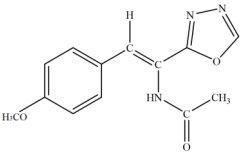
(Z)-N-(2-(4-chlorophenyl)-1-(1, 3, 4-oxadiazol-2-yl) vinyl) acetamide (3a)	
	**IR (KBr) (ν_{max}, cm^{-1}):** 3443, 2855, 1577, 1376, 1119, 926 **^{1}HNMR (300 MHz, $CDCl_3$):** δ_H=6.70 (S, 1H, OH), 6.18 (S, 1H, CH aliphatic), 7.37-7.55 (M, H-H, C-H Arom), 7.57-7.93 (M, H, C-H Arom), 7.93-7.98 (M, H-H, C-H Arom), 8.11-8.13 (M, H, C-H Arom), 8.11-8.24 (M, H-H, C-H Arom), 8.42-8.45 (M, H, C-H Arom), 8.86-8.92 (M, H-H, C-H Arom). **^{13}CNMR (75 MHz, $CDCl_3$):** δ_C= 68.90 (CH-OH), 127.79, 128.40, 128.56, 130.60, 131.90, 132.02, 137.25, 150.195 (8CH, Arom), 128.178, 135.473, 158.337 (3-C Arom), 161.7, 164.1 (C-C, Oxadiazole).
(Z)-N-(2-(4-Fluorophenyl)-1-(1, 3, 4-oxadiazol-2-yl) vinyl) acetamide (3b)	
	**IR (KBr) (ν_{max} , Cm^{-1}):** 3054, 2854, 1548, 1369, 1179, 997. **^{1}HNMR (300 MHz, $CDCl_3$):** δ_H= 6.15 (S, CH, aliphatic), 6.53 (S, H, OH), 7.30-7.35 (M, H, C-H Arom), 7.53-7.63 (M, H, CH Arom), 7.63-7.66 (M, H, C-H Arom), 7.93-7.97 (m, H-H, CH Arom), 8.0-8.05 (M, H, C-H Arom), 8.45 (d, H, 3JHH= 8.1 Hz, CH Arom), 8.91-8.92 (M, H, C-H Arom) **^{13}CNMR (75 MHz, $CDCl_3$):** δ_C= 66.7 (CH-OH), 114.8 (d, 1H, 2JCF= 24.4 Hz, C-H Arom), 119.99 (d, 1CH, 2JCF= 21.2, Arom), 123.6 (d, 1C, 3JFC= 3.4, Arom), 125.6, 128.1, 137.2, 150.1 (4 C-H Arom), 158.1, 161.6, 166.7 (3C).
(Z)-N-(2-(4-methoxyphenyl)-1-(1, 3, 4-oxadiazol-2-yl) vinyl) acetamide (3c)	
	**IR (KBr) (ν_{max}, cm^{-1}):** 3432, 2922, 1666, 1535, 1491, 1377, 1224, 921. **^{1}HNMR (300 MHz, $CDCl_3$):** δ_H= 3.92 (S, 3H, OCH3), 6.13 (s, 1H, CH aliphatic), 6.52 (s, 1H, OH), 7.14-7.18 (m, 1H, CH Arom), 7.47 (t, 1H, 3JHH= 8.1 Hz, Arom), 7.62-7.65 (m, 1H, CH Arom), 7.72-7.74 (M, H, C-H Arom), 7.82 (d, 1H, 3JHH=8.1 Hz, CH Arom), 7.98 (t, 2H, 3JHH =7.8 Hz, CH Arom), 8.476 (d, 1H, 3JHH = 8.1 Hz, CH Arom), 8.915-8.929 (M, H, C-H Arom). **^{13}CNMR (75 MHz, $CDCl_3$):** δ_C= 55.63 (CH3), 68.39 (CH-OH), 112.19, 119.54, 120.38, 125.75, 128.04, 130.39, 137.19, 150.20 (8CH, Arom), 123.93, 151.58, 160.07, 160.84, 166.01 (5C-).
(Z)-N-(2-(4-boromophenyl)-1-(1, 3, 4-oxadiazol-2-yl) vinyl) acetamide (3d)	

Figure 4. The Final Structure of Compounds and their Spectral Information.

MIC=125 mg/mL, and MBC=250 mg/mL. This result can be due to the presence of chlorophenyl group in the main compound (18). The greatest effect of compound 3b was observed on *S. aureus* with IZ=24.66 ± 0.50 mm, MIC=500 mg/mL, and MBC=1000 mg/mL. This result can be due to the presence of fluorophenyl group in the main compound (19). The greatest effect of compound 3c was observed on *S. mutans* with IZ=39.33 ± 0.50 mm, MIC=62.50 mg/mL, and MBC=125 mg/mL. This result can be due to the presence of methoxyphenyl group in the main compound (9). The greatest effect of compound 3d was observed on *S. epidermidis* with IZ=28.66 ± 0.50 mm, MIC=250 mg/mL, and MBC=500 mg/mL. This result can be due to the presence of bromophenyl group in the main compound (20).

As shown in Table 2, the greatest effect is related to compound 3c on *A. flavus* with IZ=33.33 ± 0.50 mm, MIC=250 mg/mL, and MFC=500 mg/mL. This result can be due to the presence of methoxyphenyl group in the main compound.

As shown in Tables 1 and 2, the significant results obtained in this study displayed that most of the synthesized compounds performed very well against the gram-positive samples; however, compound 3C showed acceptable inhibitory effects with high IZ, MIC, and MBC among all.

Table 1. Antibacterial Properties of 1,3,4-Oxadiazole Compounds (3a-d)

Bacterial Strains		1,3,4-Oxadiazole Compounds				Antibiotic Ciprofloxacin
		3a	3b	3c	3d	
1276	IZ	15.33 ± 0.50	17.33 ± 0.50	13.33 ± 0.50	15.33 ± 0.50	35.33 ± 0.50
	MIC	≥1000	500	-	500	62.50
	MBC	≥1000	≥1000	-	≥1000	125
1793	IZ	14.33 ± 0.50	20.33 ± 0.50	12.33 ± 0.50	15.33 ± 0.50	22.33 ± 0.50
	MIC	-	500	-	500	500
	MBC	-	≥1000	-	≥1000	≥1000
1609	IZ	14.33 ± 0.50	15.33 ± 0.50	15.33 ± 0.50	12.33 ± 0.50	21.33 ± 0.50
	MIC	≥1000	500	500	-	500
	MBC	≥1000	≥1000	≥1000	-	≥1000
1310	IZ	11.33 ± 0.50	11.33 ± 0.50	11.33 ± 0.50	10.33 ± 0.50	30.33 ± 0.50
	MIC	-	-	-	-	125
	MBC	-	-	-	-	250
1435	IZ	24.66 ± 0.50	23.66 ± 0.50	27.66 ± 0.50	28.66 ± 0.50	41.66 ± 0.50
	MIC	500	500	≤250	250	31.25
	MBC	≥1000	≥1000	500	500	62.50
1917	IZ	22.66 ± 0.50	24.66 ± 0.50	25.66 ± 0.50	23.66 ± 0.50	29.66 ± 0.50
	MIC	500	500	250	500	125
	MBC	≥1000	≥1000	500	≥1000	250
1683	IZ	31.33 ± 0.50	20.33 ± 0.50	39.33 ± 0.50	21.66 ± 0.50	35.66 ± 0.50
	MIC	125	500	62.50	500	62.50
	MBC	250	≥1000	125	≥1000	125
1662	IZ	20.33 ± 0.50	25.66 ± 0.50	26.33 ± 0.50	22.66 ± 0.50	41.66 ± 0.50
	MIC	500	500	≤250	500	31.25
	MBC	≥1000	≥1000	500	≥1000	62.50

Note. IZ (mm): inhibition zone; MIC (μg/mL^{-1}): Minimum inhibitory concentration; MBC (μg/mL^{-1}): minimum bactericidal concentration.

Table 2. Antifungal Properties of 1,3,4-Oxadiazole Derivatives (3a-d)

Fungal Strains		1,3,4-Oxadiazole Derivatives				Antifungal Clotrimazole
		3a	3b	3c	3d	
5027	IZ	11.33 ± 0.50	11.33 ± 0.50	12.33 ± 0.50	10.33 ± 0.50	29.33 ± 0.50
	MIC	-	-	500	-	250
	MFC	-	-	≥1000	-	500
5018	IZ	21.33 ± 0.50	25.33 ± 0.50	33.33 ± 0.50	19.33 ± 0.50	40.33 ± 0.50
	MIC	500	500	250	-	31.25
	MFC	≥1000	≥1000	500	-	62.50

Note. IZ (mm): inhibition zone; MIC (μg/mL^{-1}): minimum inhibitory concentration; MFC (μg/mL^{-1}); minimum fungicidal concentration

Conclusions

In general, 1,3,4-oxadiazoles are multi-functionalized compounds with a variety of biological properties; therefore, synthesis of their new derivatives is of great importance. This study evaluated the antibacterial and antifungal effects of all 4 synthesized 1,3,4-oxadiazole derivatives on pathogenic bacteria and fungi. These

compounds, chiefly methoxyphenyl, showed relatively acceptable antibacterial effects on Gram-positive strains such as *S. mutans* and *S. epidermidis*, as well as Gram-negative strains such as *P. mirabilis*. In addition, good to excellent antifungal activities were observed for compound 3c. Our results show that 1,3,4-oxadiazole derivatives would be helpful structures for the possible development of new drugs; however, this result needs to be confirmed by other extensive clinical trials that will be part of our future plans. Furthermore, the easy workup procedure, high yield, and short reaction times make the method a useful addition for preparing modern pharmaceutical synthetics.

These derivatives were synthesized for the first time and the relevant tests were done to ensure the biological properties of the compounds. This study was done to provide new structures and confirm the existence of antibacterial and antifungal activity of the compounds. In future research, several concentrations will be used for other resistant bacteria and cell lines as well as MTT assay and so on.

Conflict of Interests

The authors declare that they have no competing interests.

Acknowledgements

This study was conducted as a part of the author's PhD thesis (Code: 10330507951009) at Islamic Azad University, Central Tehran Branch.

Ethical Approval

The disclaimer implies that ethical principles were considered in relation to the proposed work and no ethical issues were found to be applied to this study.

Authors' Contribution

YSA: supervision, writing original draft, reviewing, and editing. NZA: data analysis. AS: investigation, methodology.

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