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Research Article

Synthesis and Evaluation of Antibacterial Activity of Novel Disubstituted 1,3,4-Oxadiazoles Derivatives Containing Fluorine Substituent

Naeimeh Nazari[1], Ali Souldozi[2*]

[1] Department of Biology, Urmia Branch, Islamic Azad University, Urmia, Iran.

[2] Department of Chemistry, Urmia Branch, Islamic Azad University, Urmia, Iran.

***Corresponding Author:** Ali Souldozi, Department of Chemistry, Urmia Branch, Islamic Azad University, Urmia, Iran.

Received date: May 29, 2023; Accepted date: June 07, 2023; Published date: June 15, 2023

Citation: Naeimeh Nazari, Ali Souldozi, (2023), Synthesis and Evaluation of Antibacterial Activity of Novel Disubstituted 1,3,4-Oxadiazoles Derivatives Containing Fluorine Substituent, *J, Biotechnology and Bioprocessing*, 4(3); DOI: 10.31579/2766-2314/102

Abstract

In the present study a new series of antibacterial agents (4a-f) was designed, synthesized and evaluated for antibacterial activity against different gram positive (Staphylococcusaureus, Staphylococcus epidermidis, Bacillus cereus) and gram negative (listeria monocytogenes, Escherichia coli, Pseudomonas aeroginosa) bacteria. New derivatives of oxadiazoles were prepared by one-pot reaction of N-isocyanoiminotriphenylphosphorane, carboxylic acid derivatives and 2-pyridinecarboxaldehyde, in the presence of acetonitrile solvent. The broth macro dilution and well agar diffusion methods were used for determination of inhibition zone (IZ) and minimum inhibitory concentration (MIC) during preliminary evaluation of antimicrobial activity. The (MIC) values of tested compounds revealed that all compounds have displayed significant antibacterial activity against Staphylococcusaureus and Staphylococcus epidermidis (with MIC values in the range of 31 to 125µg/mL).

Key Words: N-isocyaniminotriphenylphosphorane; 1,3,4-oxadiazoles; antibacterial activity

1.Introduction

Widespread antibiotic resistance appeared over the last 60 years and generates a serious challenge to the medical pundits. Despite the presence of antibiotics in structural and vaccination programmes, infectious diseases are major causes of morbidity and mortality worldwide. Thus, there is essential need to novel insights into development of drugs with new mechanisms of action. Among the wide variety of heterocycles that have been explored for developing new therapeutic molecules, 1,3,4-oxadiazoles become promising moiety in the structure of drugs [1,2]. 1,3,4-Oxadiazole are known to show antibacterial [3,4], antifungal [5], analgesic [6], anti-inflammator [7,8], antitubercular [9], pesticidal [10]. anti-HIV [11]and anti-cancer [12]. The improvement in activity due to the presence of aromatic moiety in the molecules that increases the lipophilicity and affects the subdividing of molecules into membranes and comfort hydrophobic interactions of the molecules with specific binding sites on either receptor or enzymes is well established [13]. In recent years, a number of new 1,3,4-oxadiazole derivatives as antibacterial agents have been reported. The main modifications of these compounds were focused on triflouromethyl and flourophenyl groups [14]. In this research, we designed and synthesized new series of fluorinated 1,3,4-oxadiazoles derivatives and evaluated there in vitro antibacterial activity against against some pathogenic bacteria.

2. Experimental procedure

2.1 Materials and Methods

Chemistry 1H (300.13 MHz) and 13C (75.47 MHz) NMR measurements were recorded on a Bruker 250 spectrometer in CDCl3 with tetramethylsilane as internal standard. IR spectra were measured on a Shimadzu IR-460 spectrometer. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. N-isocyanoiminotriphenylphosphorane 2 was prepared based on a reported procedure [15,16]. Other starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Flash chromatography columns were prepared from Merck silica gel powder. The structures of the products were deduced from their IR, 1H NMR and 13C NMR spectra.

2.2 General Procedure for the Preparation of products (4a-f)

To a magnetically stirred solution of N-isocyanoiminotriphenylphosphorane (1) (0.302 g, 1 mmol) in CH3CN (8 ml) was added drop-wise a solution of 2(1 mmol) in CH3CN (7 ml) over 15 min. The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and the viscous residue was purified by flash column chromatography (silica gel; petroleum ether–ethyl acetate (10:3). The solvent was removed under reduced pressure and the products (4a–f) were obtained.

(5-(2-fluorophenyl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol (4a)

White powder, m.p. 122 ºC, yield 74%

IR (KBr) (vmax , Cm-1): 3416, 3064, 2927, 1685, 1609, 1491, 1437, 1191, 1117, 722.

1HNMR (300.13 MHz, CDCl3): δH= 6.24 (s, CH, Aliphatic), 6.63 (s, 1H, OH), 7.31-7.37 (m, 2H, CH, Ar), 7.64-7.67 (m, 1H, CH, Ar), 7.88-7.91 (m, 1H, CH, Ar), 7.93-8.01(m, 1H, CH, Pyridine ring), 8.23-8.26 (m, 1H, CH, Pyridine ring), 8.47-8.51 (m, 1H, CH, Pyridine ring), 8.88-8.93 (m, 1H, CH, Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 66.7 (CH-OH), 116.8 (1C, d, 2JCF= 22.3 Hz, Ar), 119.4 (1C, d, 2JCF= 10.4 Hz, Ar), 124.4 (1CH, d, 4JCF= 4.1 Hz, C Ar), 131.8 (1CH, d, 3JCF= 1.4 Hz, Ar), 134.6 (1CH, d, 3JCF= 9.0 Hz, Ar), 124.9, 128.4, 137.5, 150.5 (4 CH Pyridine ring), 155.4 and 166.8 (1C, d, 1JCF= 256.8 Hz, Ar), 158.3 (1C, Pyridine ring), 161.9 (1C, oxadiazol ring), 165.1 and 164.1 (1C, d, 3JCF= 22.9 Hz, oxadiazol ring).

(5-(3-fluorophenyl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol (4b)

White powder, m.p. 125 ºC, yield 71%.

IR (KBr) (vmax , Cm-1): 3435 (br), 3055, 2924, 2855, 1677, 1549, 1463, 1370, 1216, 1180, 1091, 998.

1HNMR (300.13 MHz, CDCl3): δH= 6.16 (s, 1H, CH aliphatic), 6.54 (s, 1H, OH), 7.31-7.36 (m, 1H, CH, Ar), 7.54-7.64 (m, 1H, CH, Ar), 7.64-7.67 (m, 1H, CH, Ar), 7.94-7.98 (m, 2H, CH, Ar), 8.01-8.06 (m, 1H, CH, Pyridine ring), 8.46 (d, 1H, 3JHH= 8.1 Hz, CH, Pyridine ring), 8.92-8.93 (m, 1H, CH Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 66.8 (CH-OH), 114.9 (d, 1H, 2JCF= 24.4 Hz, CH Ar), 120.0 (d, 1CH, 2JCF= 21.2 Hz, Ar), 123.7 (d, 1C, 3JFC= 3.4 Hz, Ar), 126.1 (d, 1CH, 4JFC= 3.2 Hz, Ar), 125.7, 128.2, 137.3, 150.2 (4 CH Pyridine ring), 157.7 and 167.5 (d, 1C, 1JFC= 352.2 Hz, Ar), 158.2 (1C, Pyridine ring), 161.7, 166.8 (2C).

(5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol (4c)

White powder, m.p. 128 ºC, yield 77%

IR (KBr) (vmax , Cm-1):3406, 3057, 2928, 1677, 1607, 1491, 1438, 1185, 1115, 716.

1HNMR (300.13 MHz, CDCl3): δH= 6.23 (s, CH, Aliphatic), 6.61 (s, 1H, OH), 7.47-7.48 (m, 2H, CH, Ar), 7.64-7.71 (m, 2H, CH, Ar), 7.53-7.55 (m, 1H, CH, Pyridine ring), 7.99-8.04 (m, 1H, CH Ar), 8.42-8.45 (d, 1H,3JHH= 7.5 Hz, CH Ar), 8.89-8.91 (m, 1H, CH Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 67.0 (CH-OH), 115.5 (2CH, d, 2JCF= 22.1 Hz, CH Ar), 132.0 (2CH, d, 3JCF= 9.0 Hz, CH Ar), 162.4 and 167.4 (1C, d, 1JCF= 250.4 Hz, C Ar), 127.4 (1C Ar), 125.7, 128.2, 137.2, 150.2 (4 CH Pyridine ring), 158.2 (1C, Pyridine ring), 161.7, 166.8 (2C).

(5-(3,4-difluorophenyl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol (4d)

White powder, m.p. 140 ºC, yield 81%

IR (KBr) (vmax , Cm-1): 3412, 3062, 2926, 1683, 1601, 1486, 1431, 1185, 1112, 718.

1HNMR (300.13 MHz, CDCl3): δH= 6.20 (s, CH, Aliphatic), 6.61 (s, 1H, OH), 7.46-7,54 (m, 2H, Ar), 7.64-7.71 (m, 1H, Ar), 7.96-8.01 (m, 1H, Pyridine ring), 8.21-8.25 (m, 1H, Pyridine ring), 8.44-8.46 (m, 1H, Pyridine ring), 8.87-8.91 (m, 1H, Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 66.8 (CH-OH), 116.7 (1CH, d, 3JCF= 22.6 Hz, CH Ar), 119.2-120.1 (1CH, d of d, 3JCF= 2.0 Hz, 2JCF= 16.9 Hz, CH Ar), 126.1-126.5 (1CH, d of d, 4JCF= 2.3 Hz, 3JCF= 3.5 Hz, CH Ar), 127.4 (1CH , q, 3JCF= 3.8 Hz, CH Ar), 149.0-149.5 and 155.0-155.5 (1CF, d of d, 2JCF= 12.8 Hz, 1JCF= 257.9 Hz), 145.0-145.6 and 155.0-155.5 (1CF, d of d, 2JCF= 12.8 Hz, 1JCF= 257.9 Hz, CF Arom), 124.7, 128.2, 137.3, 150.2 (4CH, Pyridine ring), 158.3(1C, Pyridine ring), 161.8, 166.8 (2C).

pyridin-2-yl(5-(3-(trifluoromethyl) phenyl)-1,3,4-oxadiazol-2-yl) methanol (4e)

White powder, m.p. 143 ºC, yield 84%

IR (KBr) (vmax , Cm-1): 3408, 3062, 2931, 1678, 1610, 1497, 1442, 1190, 1118, 718.

1HNMR (300.13 MHz, CDCl3): δH= 6.21 (s, CH, Aliphatic), 6.64 (s, 1H, OH), 7.61-7.64 (m, 1H, CH, Ar), 7.81-7.88 (m, 1H, CH, Ar), 8.34-8.38 (m, 2H, CH, Ar), 7.95-7.99 (m, 1H, CH, Pyridine ring), 8.03-8.08 (m, 1H, CH, Pyridine ring), 8.45 (1H, d, 3JHH= 8 Hz, Pyridine ring), 8.94-8.97 (m, 1H, CH, Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 66.9 (CH-OH), 107.4, 118.3, 129.1, 139.9 (1C, q, 1JCF= 272.2 Hz, Ar), 127.3 (1CH, q, 3JCF= 3.8 Hz, Ar), 129.5, 130.8, 132.1, 133.5 (1C, q, 2JCF= 33.2 Hz, Ar), 129.3, 133.5 (2CH, Ar), 130.8 (1C, Ar), 130.5 (1CH, q, 3JCF= 3.8 Hz, Ar), 125 .8, 128.4, 137.4, 150.3 (4 CH, Pyridine ring), 158.4 (1C, Pyridine ring), 161.8, 166.9 (2C, Oxadiazol ring).

pyridin-2-yl(5-(4-(trifluoromethyl) phenyl)-1,3,4-oxadiazol-2-yl) methanol(4f)

White powder, m.p. 146 ºC, yield 85%

IR (KBr) (vmax , Cm-1): 3412, 3071, 2931, 1679, 1610, 1496, 1444, 1189, 1117, 715.

1HNMR (300.13 MHz, CDCl3): δH= 6.22 (s, CH, Aliphatic), 6.62 (s, 1H, OH), 7.88 (2H, d, 3JHH= 8 Hz, Ar), 8.17 (2H, d, 3JHH= 8.0 Hz, Ar), 7.94-8.01(m, 1H, CH, Pyridine ring), 8.03-8.09 (m, 1H, CH, Pyridine ring), 8.47 (1H, d, 3JHH= 8.0 Hz, Pyridine ring), 8.87-8.92 (m, 1H, CH, Pyridine ring).

13CNMR (75.467 MHz, CDCl3): δC= 67.0 (CH-OH), 125.5 (2CH, q, 3JCF= 3.6 Hz, Ar), 130.1 (2CH, Ar), 130.5, 131.9, 133.3, 134.8 (1C, q, 2JCF= 32.2 Hz, Ar), 105.7, 117.8, 129.9, 142.0 (1C, q, 1JCF= 272.6 Hz, Ar), 134.8 (1C, Ar), 125.7, 128.3, 137.2, 150.3 (4 CH Pyridine ring), 158.4 (1C, Pyridine ring), 161.9, 166.9 (2C, Oxadiazol ring).

3. Antibacterial evaluation

3.1 Agar well diffusion method

The antibacterial activity of synthesized compounds was investigated against Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, listeria monocytogenes ATCC 23074, Pseudomonas aeroginosa ATCC 27853, Bacillus cereus ATCC 11778, Staphylococcus epidermidis ATCC 14990 by agar well diffusion and broth dilution methods [15-16].

The standardization of each bacterial inoculum was done following the following them to Clinical & Laboratory Standards Institute (CLSI) [17].

Briefly, each microorganism after inoculation into Mueller Hinton broth (Merck, Germany) was prepared to turbidity standard of 0.5 McFarland. The prepared suspension from tested bacteria was transferred on solidified agar and spreaded uniformly. Synthetic antibacterial agents were dissolved in dimethyl sulfoxide (DMSO) to get stock with concentration of 1mg/ml [18,19]. After punching wells in agar using a sterile glass tube, 70µl of compounds and DMSO were transferred to each well. The zones around each well against defined bacteria after incubation for 24h, determinated the antibacterial power of each compound [20]. Ceftizoxime, Ciprofloxacin and DMSO were used with the same method as positive control and negative control respectively.

3.2 Broth dilution Method

In the next step for determination the lowest concentration of an antimicrobial agents that inhibits the visible growth of the tested microorganism (MIC value), broth dilution method was used [21]. In this study, eight sterile tubes were used for each compound and after transferring the broth culture medium into the tubes, dilution was done and 10µL of inoculum contained 1.5×106 C.F.U/ml of tested microorganism was added to each test tubes. After the incubation, the tubes were checked for the minimum inhibitory concentration concentration point. Ceftizixime, ciprofloxacin and DMSO respectively were also observed for comparative tests. Minimum Bactericidal Concentration (MBC) values were determined by subculturing of the tested tubes on agar media that show no visible bacterial growth [22].

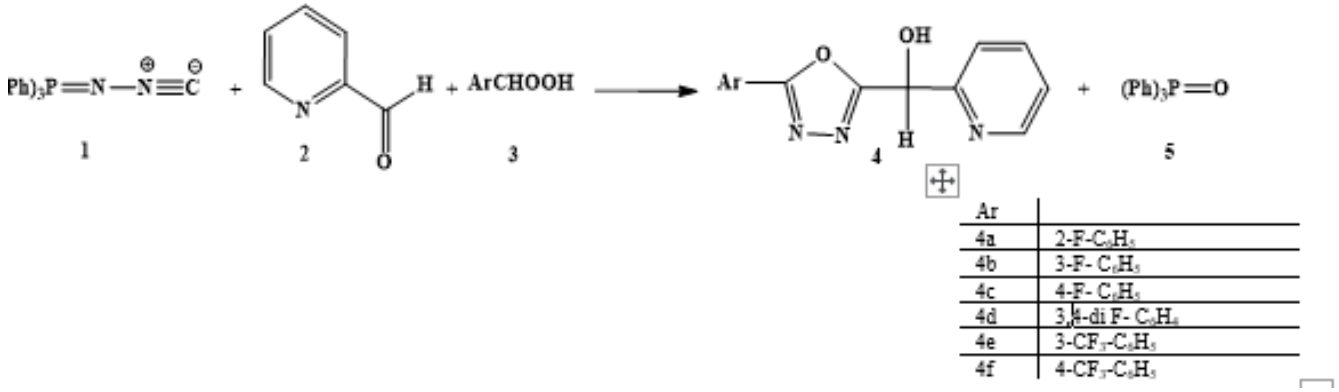
3.3 Statistical analysis

We used Excel to do some basic data on three independent experiments,and the results are expressed as mean ± SEM.

4. Results and Discussion

4.1 Chemistry

We found that 3-fluorobenzoic acid derivatives 3a reacted with 2-pyridinecarbaldehyde 2 and N-isocyanoiminotriphenylphosphorane 1 in CH3CN react in a 1:1:1 ratio at room temperature to produce (5-(3-fluorophenyl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol 4a and, as a by-product, Ph3P=O 5 (Scheme 1). The reaction proceeded smoothly and cleanly under mild conditions in 74% yield, and no side reactions were observed. The other aromatic carboxylic acids also reacted smoothly to give similar products 4b-4f in yields of 71, 85% (Scheme1). We tried using the simple ketone analogous, 1-(2-pyridyl)-1-ethanone instead of 2-pyridinecarbaldehyde 2 in this reaction, but no corresponding products of type 4 were observed (Scheme1).

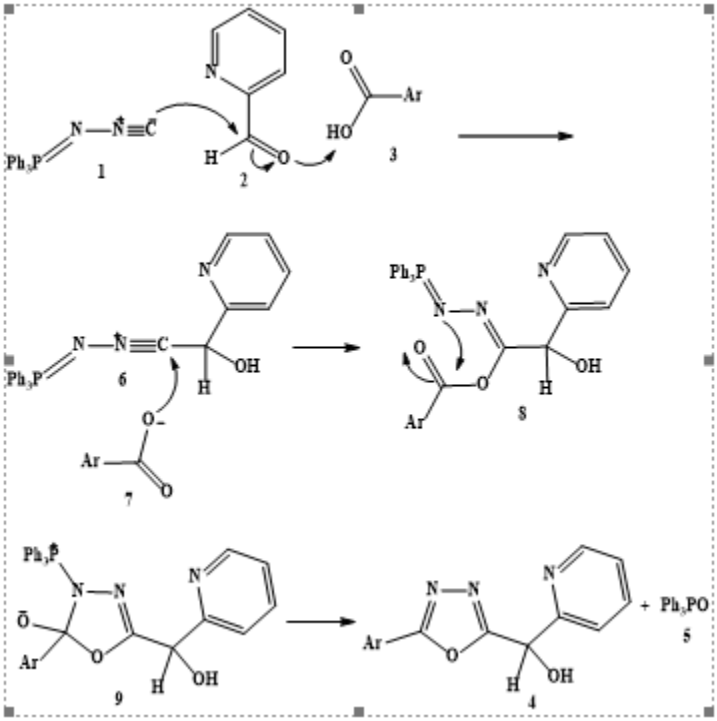


Ar	
4a	2-F-C_6H_5
4b	3-F- C_6H_5
4c	4-F- C_6H_5
4d	3,4-di F- C_6H_4
4e	3-CF_3-C_6H_5
4f	4-CF_3-C_6H_5

Scheme 1: Synthesis of (5-(fluoroaryl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol (4a-f)

The structures of the products were deduced from their IR, 1H and 13C NMR data. The 1H-NMR spectrum of 4a consisted of a singlet for CH aliphatic (δ= 6.24 ppm), a singlet for OH (δ= 6.63 ppm), exchangeable by D2O and multiple at δ= 7.31-8.93 ppm for the aromatic hydrogen atoms. The 1H decoupled 13C NMR spectrum of 4a showed eleven distinct resonances, partial assignment of these resonances is given in the experimental. The 1H and 13C NMR spectra of compounds 4b- 4f were similar to those of 4a, except for the aromatic moiety, which exhibited characteristic signals with appropriate chemical shifts.

A mechanistic rationalization for this reaction is depicted in Scheme 2. On the basis of the chemistry of isocyanides, it is reasonable to assume that the first step involves nucleophilic addition of 1 to 2-pyridinecarbaldehyde 2, facilitated by its protonation with the acid 3, leading to nitrilium intermediate 6. This intermediate may be attacked by the conjugate base of the acid 7 to form the 1:1:1 adduct 8. This adduct may undergo an intramolecular aza-Wittig reaction of the iminophosphorane moiety with the ester C=O group to afford the isolated (5-(fluoroaryl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol 4 by removal of Ph3P=O 5 from intermediate 9. In this reaction, the first two reaction steps are analogous to the well-known Passerini reaction, and the final step is analogous to the well-known intramolecularaza-Wittig reaction (tandem Passerini/intramolecularaza-Wittig sequence) (Scheme 2).



Scheme 2: Plausible mechanism for the (5-(fluoroaryl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol

4-2 Measurement of antimicrobial activity using Agar well diffusion Method

The antimicrobial activity of the synthesized derivatives was measured by zone of inhibition around each well. With comparison of zone of inhibition diameters of synthetic derivatives with Ceftizoxime and Ciprofloxacin drugs, the antibacterial power of oxadiazole derivatives were determined.

As shown in Figure 1 all the Oxadiazole derivatives that were synthesized in this research show significant anti actibacterial activity against Staphylococcus aureus with IZ of 16-21, whereas an IZ of 21-24mm was observed against Staphylococcus epidermidis and their antibacterial activity are notably more in compare with Ceftizoxime. No zone of inhibition was seen around the well containing DMSO (Negative control). (Figure1 and Table1).

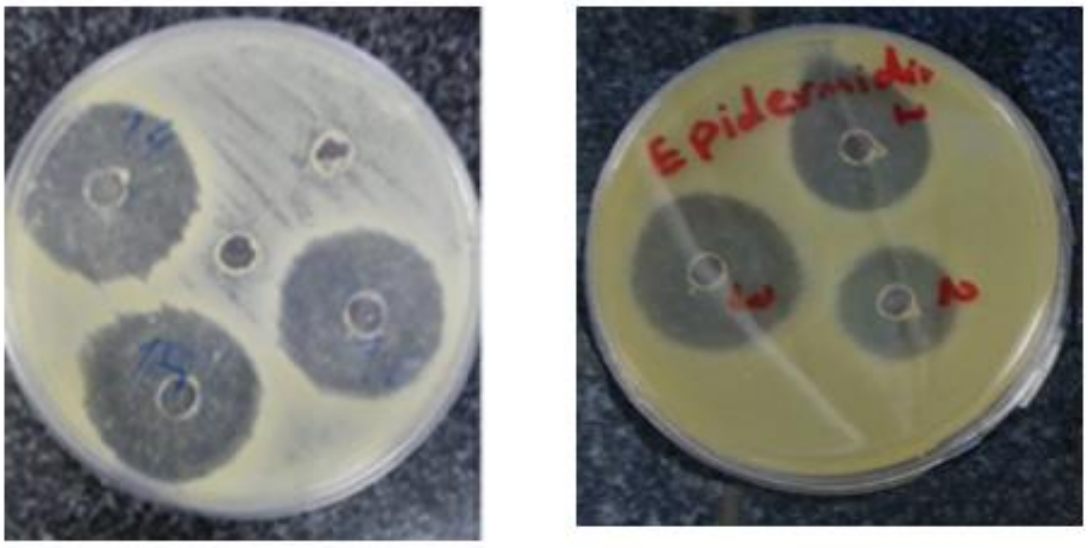


Figure 1: Inhibition zone of compounds against *Staphylococcus aureus* and *Staphylococcus epidermidis* in 1mg/ml

Compounds Code	*Staphylococcus aureus Atcc25923*	*Staphylococcus epidermidis Atcc14990*	*Escherichia coli Atcc 25922*	*Listeria monocytogenes Atcc23074*	*Bacillus cereus Atcc 11778*	*Bacillus cereus Atcc27853*
4a	*16±0.4*	*17±0.6*	*NA*	*NA*	*NA*	*NA*
4b	*18±0.7*	*17±0.5*	*NA*	*NA*	*NA*	*NA*
4c	*15±0.8*	*19±0.2*	*NA*	*NA*	*NA*	*NA*
4d	*17±0.2*	*20±0.3*	*NA*	*NA*	*NA*	*NA*
4e	*19±0.3*	*22±0.1*	*NA*	*NA*	*NA*	*NA*
4f	*21±0.6*	*24±0.3*	*NA*	*NA*	*NA*	*NA*
Ceftizoxime	*20±0.2*	*15±0.2*	*17±0.5*	*NA*	*NA*	*10±0.2*
Ciprofloxacin	*40±0.4*	*35±0.6*	*44±0.6*	*NA*	*35±0.8*	*35±0.3*

NA:No ActivityThe result are expressed as mean ±sem*

Table1: Antibacterial activity of (5-(fluoroaryl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol derivatives by Agar well diffusion method (1mg/ml)

Compounds Code	*Staphylococcus aureus Atcc25923*	*Staphylococcus epidermidis Atcc14990*	*Escherichia coli Atcc 25922*	*Listeria monocytogenesAtcc23074*	*Bacillus cereus Atcc 11778*	*Bacillus cereus Atcc27853*
4a	125± 2.5*	125±2.1*	500±3.7*	500±3.7*	500±3.1*	500±4.8*
4b	62.5±3.1*	125±4.0*	500±4.9*	500±3.7*	500±4.9*	500±3.8*
4c	125±3.3*	500±3.3*	500±4.5*	500±3.1*	500±3.5*	500±2.1*
4d	62.5±2.1*	62.5±3.3*	1000±4.8*	250±2.3*	500±4.5*	500±3.0*
4e	31.25±3.2*	62.5±3.1*	500±4.7*	500±2.7*	500±6.3*	500±1.5*
4f	15±4.9*	31.25±6.2*	500±5.3*	500±3.5*	500±6.4*	500±3. 4*
Ceftizoxime	125±2.0*	125±4.1*	32±3.0*	500±2.5*	62.5±3.0*	62.5±3.0*
Ciprofloxacin	0.029±1.0*	15±1.0*	0.23±1.0*	7±1.5*	15±2.0*	0.23±2.0*

NA:No Activity The result are expressed as mean ±sem*

Table2: Antibacterial activity of (5-(fluoroaryl)-1,3,4-oxadiazol-2-yl) (pyridin-2-yl) methanol derivatives by broth dilution method(µg/mL)

4.3 Determination of MIC

The minimum inhibitory concentrations (MIC) of tested compounds (4a-f) are shown in (Table2). The MBC of compounds were three-fold higher than the corresponding MIC results. Compounds 4f were the most effective against S.aureus and S.epidermidis with MIC values of 15µg/mL and 31.25µg/mL respectively. while the MIC of the compounds 4f containing 4-trifluoromethylphenyl, were determined in the range of 31 to 62 µg/ml against S.aureus and S.epidermidis.

The investigation of antibacterial screening data revealed that all the tested compounds (4a-f) showed moderate to good inhibition at µg/ml in DMSO. This report intends to explore the role of electronic environment (fluorine atoms) on antibacterial activity. In our study, ring substitution by fluorine increased the antibacterial activity of the compounds in compared to compounds of our previous research [23]. The data found in the literature matching our research and claims that the compounds with halogen substituent are the most efficient against Gram-positive bacteria, particularly against S. aureus [24, 25]. In the course of this study, derivativs 4a-f possessing pyridine ring at the C-2 position on the linker of 1,3,4-oxadiazoles was identified as showing moderately enhanced antibacterial activity against gram positive bacteria as compared to our previous report so interesting activity of compounds 4a-f against Staphylococcus aureus and Staphylococcus epidermidis, which is much stronger than that seen against Gram negative bacteria can be correlated to this lipophilic group [26]. A limited effect is detected for the compound against Escherichia coli and Pseudomonas aeroginosa (MICs 500-1000 µg mL).

5. Conclusion

As in the presented results, the compounds had good antibacterial power, but in addition to the antimicrobial power of the synthesized derivatives, the presented one-step synthesis method can also be a very suitable method for the synthesis of derivatives with high antibacterial power and low financial and time cost.

Acknowledgement

This work was supported by Islamic Azad University, Urmia Branch.

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DOI:10.31579/2766-2314/102