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Synthesis of some novel 1,3,4-oxadiazole derivatives and evaluation of their antimicrobial activity

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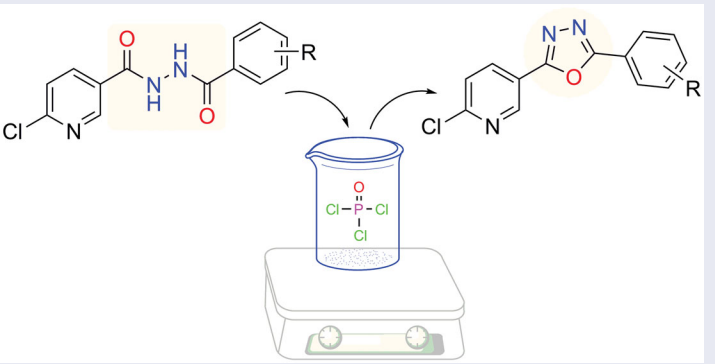
ABSTRACT

Treatment for microbial infections still remains an important health problem for researchers around the world. Despite a broad range of antimicrobial drugs today, there are certain obstacles associated with the use of antimicrobial agents such as drug resistance and toxicity. Thus, medicinal chemists concentrate on designing novel antimicrobial drugs. In the search for new antimicrobial agents; 1,3,4-oxadiazole compounds have come forward due to their hydrolytic stability, good chemical and thermal stability. In the scope of this work, 2-(6-chloropyridin-3-yl)-5-(substitutedphenyl)-1,3,4-oxadiazole (**4a**–**4i**) were synthesizedusing 6-chloro-*N*′-(substitutedbenzoyl)nicotinohydrazide (**3a**–**3i**). These compounds were screened for their antimicrobial activities against as gram-positive bacteria *S. aureus*, *E. faecalis*, as gram-negative bacteria *E. coli*, *P. aeruginosa*, as yeast *C. parapsilosis*, *C. albicans*, *C. glabrata*. Among the 1,3,4-oxadiazole compounds, **4h** against *E. faecalis* and **4b**, **4f** and **4g** against *E. coli* have been found to exhibit as much as potency chloramphenicol with MIC_{50} values of 62.50 μg/mL.

GRAPHICAL ABSTRACT



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Introduction

Microbial resistance to antibiotics is increasing day by day and it is estimated that 700,000 people die from antibiotic-resistant infectious worldwide every year.[1]

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These deaths will reach about 10 million people from these infectious diseases each year by 2050.[2] Although many antibacterial agents were discovered and used for clinical therapy, the incidence of fungal and bacterial infections has increased dramatically in recent years.[3] As the bacterial resistance to antibiotics, the bacterial infection has become one of the life-threatening diseases worldwide.[4] Therefore, the development of new antifungal and antibacterial agents is urgently needed.[5]

1,3,4-Oxadiazoles display a wide range of biological activities such as antifungal, antiviral, antibacterial, antitubecular, anticancer, antidiabetic, anticonvulsant activity.[6–9] 1,3,4-Oxadiazole cores are very good bioisosteres of amide and ester functionalities among heterocyclic compounds.[10] Hence, they play an important role in biological activity by hydrogen bonding interaction with different receptors or enzymes.[11] 1,3,4-Oxadiazoles found wide applications in medicinal, pesticidal, polymer and material science.[12] Medicinal chemists have shown an interest in oxadiazole rings for a long time due to their remarkable electron-accepting properties, hydrolytic stability, photoluminescence, good chemical, and thermal stability.[13] The potent pharmacological activities of 1,3,4-oxadiazoles are due to the toxophoric –N=C–O– linkage, easily reacting with the nucleophilic centers of the microorganism cells.[14] It was reported that 1,3,4-oxadiazole derivatives act by affecting the normal physiological functions of bacteria, their purine metabolism pathways and impairing their cell membrane permeability.[15] There are many studies in the literature showing that oxadiazole structures have antimicrobial activity.[16–19]

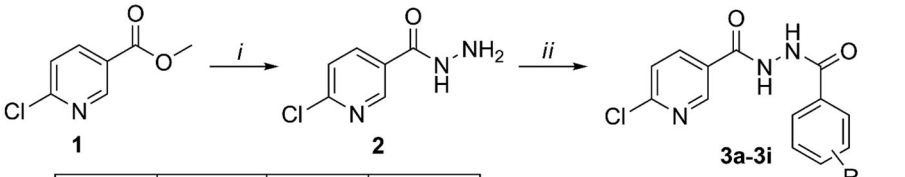
Trans-translation in bacteria is carried out by transfer-messenger RNA (tmRNA). ArfA and ArfB which are two alternative ribosome rescue factors can take over when translation is missing or insufficient. Ribosomal stalling is a serious problem, and bacteria lacking arfA cannot survive without tmRNA. In addition, even if pathogenic bacteria manage to survive in the absence of translation, they often lose their virulence.[20] Trans-translation has been an attractive target for the discovery of new antibiotics because this pathway is required for virulence or viability in most bacterial pathogens, but not in eukaryotes, so translation inhibitors can act as antibiotics and have also low toxicity on the ribosomes of host cells.[21,22] 1,3,4-oxadiazole cores lead to ribosomal stalling during bacterial protein synthesis and they were also identified as trans-translation inhibitors after the high-throughput screening.[20,23]

On the other hand, compounds containing substituted-2-chloro-pyridine moiety are commonly applied in medicinal and pesticide chemistry because of their highly antifungal, antiviral and antibacterial activities.[24] As a result, in the light of the above-mentioned pharmacological importance of oxadiazoles prompted us the synthesis of novel 2,5-disubstituted-1,3,4-oxadiazoles and investigate their inhibitory activity against various microbial strains in the present study.

Results and discussion

Chemistry

The substituted-1,3,4-oxadiazole derivatives were obtained in three different steps as given in Scheme 1. Firstly, *methyl 6-chloropyridine-3-carboxylate* (**1**) was reacted with hydrazine hydrate to afford *6-chloronicotinohydrazide* (**2**). Hydrazide compound was



Comp.	R	Comp.	R
3a, 4a	4-NO_2	**3f, 4f**	3-CH_3
3b, 4b	2,6-diF	**3g, 4g**	3-CF_3
3c, 4c	2,6-diCl	**3h, 4h**	4-OCH_3
3d, 4d	4-SCF_3	**3i, 4i**	4-CN
3e, 4e	4-OCF_3		

Scheme 1. Synthesis of target compounds. Reagents: (*i*) hydrazine hydrate, ethanol; (*ii*) dichloromethane, triethylamine, substituted benzoyl chloride; (*iii*) phosphorus oxychloride.

obtained from nucleophilic substitution reaction of hydrazine with ester compound. In the second step, the reaction of hydrazide compound (**2**) with different substituted benzoyl chloride in dichloromethane gave the acyl hydrazide derivatives (**3a**–**3i**). The interaction between hydrazides and substituted benzoyl chloride in the basic medium such as TEA (or pyridine, NAOH) resulted in an unsymmetrical 1,2-diacylhydrazines. The synthesis of 1,3,4-oxadiazole compounds (**4a**–**4i**) was carried out as a result of the cyclodehydration of 1,2-diacylhydrazines using phosphorus oxychloride ($POCl_3$) as a dehydration agent in high yield. This reaction can be completed with other dehydration agents such as sulfuric acid, phosphoric acid, trifluoroacetic acid, phosphorus pentachloride instead of $POCl_3$. The structures of the synthesized compounds have been determined by using IR, ^{1}H-NMR, ^{13}C-NMR spectral data and elemental analysis results.

In the IR spectrum, N-H stretching bands of acyl hydrazide derivatives (**3a**–**3i**) were detected at 3155–3219 cm^{-1} and the sharp stretching bands between 1631 and 1697 cm^{-1} have been attributed to the C=O bond. The disappearances of N-H and C=O stretching bands in the IR spectrum of 1,3,4-oksadiazole derivatives (**4a**–**4i**) showed the synthesis of the oxadiazole ring successfully. In addition, C=N absorption bands belonging to the oxadiazole ring were observed in the range of 1604–1638 cm^{-1}.

In the ^{1}H-NMR spectrum of acyl hydrazide compounds (**3a**–**3i**), the protons in the ortho position of the pyridine ring were shifted to the downfield at 8.90–8.92 ppm and the para protons at 8.30–8.35 ppm, and the meta protons were shifted to the upfield at 7.71–7.74 ppm due to the effect of nitrogen in pyridine ring. The NH protons of the acyl hydrazide groups resonated as one or two singlet peaks at 10.48–11.01 ppm. In the ^{1}H-NMR spectrum of oxadiazole compounds (**4a**–**4i**), the disappearance of the NH peaks is one of the key factors that the oxadiazole ring has been synthesized successfully. In addition, the protons in the ortho position of the pyridine ring were shifted to the downfield at 9.04–9.20 ppm and the para protons at 8.45–8.59 ppm, and the meta protons at 7.79–7.85 ppm.

In the ^{13}C-NMR spectrum, the imine carbon of the pyridine ring produced signals in the range of 152.77–153.83 ppm. The carbonyl carbons of acyl hydrazide derivatives were recorded between 160.30 ppm and 165.91 ppm. The two signals in the range of 159.64–165.09 ppm were attributed to the two carbon atoms in the oxadiazole ring.

Biological activity

Antimicrobial activity results

The antibacterial and antifungal activity of the synthesized compounds were investigated against some bacteria such as *S. aureus*, *E. faecalis*, *E. coli*, *P. aeruginosa,* and some fungi against *C. parapsilosis*, *C. albicans*, *C. glabrata* by calculating minimum inhibitory concentration (MIC_{50}). Chloramphenicol for bacteria and ketoconazole for yeast were used as standard drugs. The results of antimicrobial activities of synthesized compounds were summarized in Table S1.

When the activities of the compounds against bacteria and fungi are compared; generally, the compounds were more effective on the bacteria than fungi used in this study. There is no significant activity of the compounds against *Candida* species. However, all acylhydrazide and 1,3,4-oxadiazole derivatives showed similar antibacterial activity with MIC_{50} value of 62.5 µg/mL against *P. aeruginosa* when compared with chloramphenicol (MIC_{50} = 62.5 µg/mL).

Among 1,3,4-oxadiazoles, the compound **4h** carrying methoxy substituent at the para position of the aromatic ring indicated similar antibacterial activity to chloramphenicol with MIC_{50} value of 62.5 µg/mL against *E. faecalis*. The most active compounds against *E. coli* with MIC_{50} values of 62.5 µg/mL were **4b**, **4f** and **4g** bearing 2,6-difluorophenyl, 3-methylphenyl and 3-trifluoromethylphenyl, respectively. The most effective compounds against bacterial species generally had the oxadiazole structure. Among the compounds, the most active derivatives usually carry oxadiazole structures. When looking at the most effective derivatives in oxadiazole structures, it generally bears electron-donating groups (compound **4h** has methoxy; **4f** has methyl substituent) or halogen substituents (**4b** has bearing 2,6-difluoro, **4g** has 3-trifluoromethyl) in their structure. *P. aeruginosa*, is one of the most resistant agents of nosocomial infections which are a major cause of morbidity and mortality.[25] For this reason, the effectiveness of the synthesized compounds against *P. aerouginosa* is extremely important.

Druglikeness and ADMET prediction

The evaluation of physicochemical and pharmacokinetic properties facilitates the prioritization and optimization of chemical structures.[26] The drug-likeness is one of the most used tools to predict the solubility and permeability of compounds and hence their qualification as a drug candidates.[27] Therefore we evaluated the drug-likeness properties of all 1,3,4-oxadiazoles and they did not violate Lipinski and Veber rules. The oxadiazole derivatives also have a good bioavailability score (Table S2).

The assessment of absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of compounds is also extremely important in the drug development and discovery process.[28] An oral drug candidate must be absorbed through intestinal cell membranes before it can reach systemic circulation. Human intestinal

absorption (HIA) of a drug is the essential prerequisite for its oral bioavailability ($F_{20\%}$) and apparent efficacy. Another alternative route to the human intestinal epithelium, human colon adenocarcinoma cell lines (Caco-2), has been widely used to predict *in vivo* drug permeability. The green color for HIA, Caco-2 permeability and $F_{20\%}$ indicates good absorption.

VD is a parameter that indicates whether the drug is well distributed in the systemic circulation. The green color for VD indicates that the distributions of the compounds may be good. The yellow color for BBB penetration demonstrates that the blood-brain barrier crossing of the compounds is predicted to be moderate, except for 4i. Thus, it indicates that central side effects may be less.

CYP enzymes are responsible for the metabolism of drugs. In silico data showed all compounds are substrates as well as an inhibitor for CYP2D6 and CYP3A4. Compounds **4e**, **4h** and **4i** have an excellent clearance rate (CL), but other compounds showed a low clearance rate. All compounds have a moderate half-life ($T_{1/2}$) time.

Toxicity risk assessment is essential to avoid some problems later in the drug discovery and development process.[29] The green color indicates that all compounds did not show mutagenic, tumorigenic, irritant and reproductive effects. We also evaluated their cardiotoxicity (hERG), hepatotoxicity (H-HT), and Ames mutagenicity risks. All compounds have no cardiotoxicity risks. Compounds **4b**, **4e,** and **4i** are not safe for the liver, but the other compounds have lower hepatotoxicity. Ames test showed that all compounds exert no mutagenicity effects such as genetic damage and mutations except **4a**. We showed that the most active compounds, especially **4b, 4f, 4g,** and **4h** had acceptable ADMET properties mentioned above (Table S3).

Experimental

All chemicals and reagents were supplied from Sigma-Aldrich (St. Louis, MO, USA) or Merck Chemical Company (Darmstadt, Germany) and used without further purification. Melting points were determined on a Stuart SMP II apparatus (Cole-Parmer Ltd. Staffordshire, UK) and are uncorrected. The IR spectra were recorded using a Shimadzu FTIR 8400S spectrometry (Shimadzu Corp., Kyoto, Japan). The NMR spectra were taken on a Bruker spectrometer, operating at 300–600 MHz (^{1}H-NMR), and 100–125 MHz (^{13}C-NMR) (Bruker Bioscience, Billerica, MA, USA). Chemical shifts (δ) were expressed in parts per million relative to tetramethylsilane used as the internal reference. Analytical TLC was carried out on silica gel F254 (Merck) plates (0.25 mm thickness). Elemental analysis was performed on CHNS-Thermo Scientific Flash 2000 (Waltham, MA, USA).

Chemicals

General synthesis procedure for compound 2

To a solution of *methyl 6-chloropyridine-3-carboxylate* (0.02 mol) in ethanol (20 mL) was added 8 mL (98%) of hydrazine monohydrate. The mixture was refluxed for 6–8 h. The precipitate was filtered, dried and purified from methanol.[30] Yield: 75%; m.p. 173.5–174.0 °C. *Rf* = 0.35 (petroleum ether/ethylacetate, v/v = 1/9). (CAS Registry Number: 168893-66-1).[31]

General synthesis procedure for compound 3a–3i

Compound **2** (0.5 mmol) is stirred in 15 mL of dichloromethane (CH_2Cl_2) at room temperature for half an hour. Triethylamine (1 mmol) and appropriate benzoyl chloride (0.5 mmol) derivatives were added to the solution of hydrazide. It was refluxed for 6–8 h. After monitoring by thin-layer chromatography (TLC), the excess solvent was evaporated under a vacuum. Acyl derivatives were crystallized from methanol.[32]

General synthesis procedure for compound 4a–4i

Carbohydrazide derivatives (**3a**–**3i**) were taken in a bottom flask. 15 mL of phosphorus oxychloride was added and heated in a water bath at 75–80 °C for 6 h. At the end of the reaction, the solid material is poured into an ice-water mixture. The precipitate was filtered, dried and crystallized from methanol.[33]

Characterization data for selected compounds

2-(6-Chloropyridin-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (4a)

Yield: 77%; m.p. 216.2–216.5 °C. *Rf* = 0.80 (petroleum ether/ethylacetate, v/v = 1/9). IR (ν, cm^{-1}): 3047 (aromatic=C-H), 1620 (C=N), 1516 (NO_2 asym.), 1336 (NO_2 sym.), 1103 (aromatic C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm): δ 7.83 (d, J = 8.4 Hz, 1H, pyridine meta proton), 8.41–8.50 (m, 4H, Ar-H), 8.58 (d, J = 8.4 Hz, 1H, pyridine para proton), 9.20 (d, 1H, J = 2.1 Hz, pyridine orto proton). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 119.14, 124.45, 125.06, 128.11, 128.17, 128.48, 137.65, 147.94, 149.29, 153.28 (C=N), 162.32 (oxadiazole C=N), 163.08 (oxadiazole C=N). Anal. Calcd for $C_{13}H_7ClN_4O_3$: C 51.59, H 2.33, N 18.51. Found: C 51.37, H 2.35, N 18.45%.

2-(6-Chloropyridin-3-yl)-5-(2,6-difluorophenyl)-1,3,4-oxadiazole (4b)

Yield: 75%; m.p. 178.8–179.1 °C. *Rf* = 0.85 (petroleum ether/ethylacetate, v/v = 1/9). IR (ν, cm^{-1}): 3093 (aromatic=C-H), 1631 (C=N), 1120 (aromatic C-Cl). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm): δ 7.39–7.44 (t, 2H, Ar-H), 7.75–7.82 (m, 2H, Ar-H and pyridine meta proton), 8.45 (d, J = 8.8 Hz, 1H, pyridine para proton), 9.04 (d, 1H, J = 2.4 Hz, pyridine orto proton). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm): δ 111.87, 113.13, 124.38, 125.23, 127.30, 132.49, 137.73, 138.76, 147.82, 149.04, 153.22 (C=N), 157.78, 158.94, 160.26 (oxadiazole C=N), 162.75 (oxadiazole C=N). Anal. Calcd for $C_{13}H_6ClF_2N_3O$: C 53.17, H 2.06, N 14.31. Found: C 53.32, H 2.05, N 14.36%.

Biological activity

Microorganisms and mediums

The following microorganisms *Enterococcus faecalis* (ATCC 51299), *Escherichia coli* (ATCC 35218), *Escherichia coli* (ATCC 25912), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 25923) are tested for antibacterial activity; *Candida albicans* (ATCC 90028), *Candida parapsilosis* (ATCC 22019), and *Candida glabrata* (ATCC 90030) were tested for anticandidal activity. All microorganisms were obtained from the culture collection of P. Microbiology Laboratory, Anadolu University. For bacterial culture Nutrient Broth (Merck) and for Candida spp. Sabouraud Dextrose Broth (Merck) was used to prepare fresh pure cultures.

Inoculum

The standardization of the microbial cells number used for susceptibility tests has critical importance for obtaining accurate and reproducible results. The recommended final inoculum amount for broth dilution was 2.5×10^5 (for antifungal susceptibility tests) or 5×10^5 (for antibacterial susceptibility tests) colony-forming units (CFU) per mL. For these reasons, all inocula were set to 0.5 McFarland standard with McFarland Tube Densitometer for accurate and reproducible results.[34]

Micro dilution broth assays

Derivatives of substances were dissolved in dimethyl sulfoxide (DMSO) and concentrations were prepared ranging from 1000 to 15,625 µg/mL. The prepared concentrations were distributed in duplicate as 100 µL for each well on the 96-well plates. After that, fresh pure bacterial and fungal cultures, which were set at 0.5 McFarland standard in Mueller Hinton Broth (Sigma-Aldrich) or Sabouraud Dextrose Broth, respectively were added to concentrations of 100 µL. After adding the bacterial and fungal cultures, the final concentrations for these derivatives were ranging from 500 to 7,8125 µg/mL. At the end of this process, all plates were incubated for 24 h for bacterial culture 48 h for yeast culture. All experimental steps were performed under the recommendations of the CLSI protocol.[35]

Druglikeness and ADMET prediction

The SwissADME server was used to evaluate drug-likeness properties of compounds (http://www.swissadme.ch/, accessed on 30 November 2021). The ADMET properties of compounds were determined using the OSIRIS property explorer (Data warrior) and ADMETlab server (https://admetmesh.scbdd.com/explanation/index, accessed on 30 November 2021).

Conclusions

In summary, we synthesized novel 2,5-disubstituted-1,3,4-oxadiazole derivatives. The compounds were investigated for their antimicrobial activity potential against four bacteria and three fungi species. Among 1,3,4-oxadiazoles, the compound **4h** against *E. faecalis*; **4b**, **4f** and **4g** against *E. coli* displayed similar antibacterial activity as chloramphenicol with MIC_{50} values of 62.5 µg/mL. In addition, all compounds exhibited similar antibacterial activity against *P. aerouginosa* as the reference standard. This may be due to the presence of a more stable oxadiazole ring which may enhance the biological potency and lipophilicity. These oxadiazole compounds also had good physicochemical and pharmacokinetic properties. Thus, we suggest that the 2,5-disubstituted-1,3,4-oxadiazole derivatives can be further optimized and developed as lead molecules for antibacterial activity.

Disclosure statement

The authors declare that they have no conflict of interest.

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