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Antibacterial Activities of 5-Nitro-2-uryl and 5-Nitro-2-Imidazolyl Derivatives of 1,3,4-Thiadiazole

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ABSTRACT

Introduction: Nitrofurans and nitroimidazoles are broad-spectrum antimicrobial agents, which affect the microbial DNA. The aim of the present study was to evaluate the new derivatives of these two groups of antimicrobials against certain Gram-positive and Gram-negative bacterial strains. **Materials and Methods:** Seven new derivatives of nitrofurans and nitroimidazoles were synthesized, and 6.4 mg of each derivative was dissolved in dimethyl sulfoxide. Then, 8 serial dilutions (0.5, 1, 2, 4, 8, 16, 32, and 64 µg/ml) of each derivative was prepared using Muller-Hinton broth, and the minimum inhibitory concentration for each derivative was measured and compared to ciprofloxacin (standard). **Results:** All the derivatives had no antibacterial effects against Gram-negative bacteria (minimum inhibitory concentration > 64 µg/ml); only 2-(5-nitro-2-furyl)-5-(n-pentylsulfunyl)-1,3,4-thiadiazole exhibited mild antibacterial effects against Klebsiella pneumonia (minimum inhibitory concentration of 16-32 µg/ml). The antibacterial effects of the derivatives against Gram-positive bacteria also showed variations from complete inhibition of the growth of Staphylococcus epidermidis and Bacillus subtilis (minimum inhibitory concentration < 0.5 µg/ml) by 2-(5-nitro-2-furyl)-5-(n-buthylthio)-1,3,4-thiadiazole to no inhibition of S. epidermidis and streptococcus pyogenes. **Conclusion:** These compounds have weak antibacterial effects; only two derivatives showed antibacterial effects similar to that of the positive control.

INTRODUCTION

The major drawbacks in the treatment of microbial infections are microbial resistance and the adverse effects of old antibiotics (1). In recent times, the excessive increase in microbial resistance, especially among Gram-positive bacteria, has increased the need for new compounds that have a large antimicrobial effect (2). Therefore, a new class of antimicrobial compounds are needed to combat the antimicrobial resistance. These new agents can be extracted from plant sources (3) or synthesized in vitro (4).

Nitrofurans are chemical compounds that contain the 5-nitrofuran ring in their molecular structure (5). This group acts as a bacteriostatic agent against a wide range of Gram-positive and Gram-negative bacteria and has bactericidal activity at higher doses. They create superoxide and toxic oxygen radicals under reducing conditions, which oxidize the vital components of the cell and disrupt the normal functioning of the bacteria, fungi, and protozoa (5). Moreover, nitrofurans are used as pharmacophores to achieve more effective compounds, and because of their excretion in the urine, these compounds are a good choice for the treatment of urinary tract infections (6). Nitroimidazoles are imidazole derivatives with a nitro group that are effective against anaerobic bacteria and parasitic infections such as Trichomonas vaginalis and Entamoeba histolytica (7). These reducing agents cause the breakdown of DNA, which depends on the A and T content, and also inhibit the repairing of the DNA damages (8). In addition, the 1,3,4-thiadiazole acts as the cornerstone in the development of pharmacological substances. According to previous research, this ring has antibacterial antifungal, antihistaminic, anticholinergic, and anti-inflammatory effects (9).

In the present study, the antibacterial effects of the 1,3,4-thiadiazole ring of the 5-nitrofurazone and 5-nitroimidazole derivatives against eight most common bacterial

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species were evaluated.

The implementation of modern mathematical techniques helps in the selection of important informative indicators and in aggregating the information about a worker's psychophysiological state to correctly evaluate the efficiency in their professional activity and risks (6). A new technology of video survey was developed to determine the quality of performance of the occupational duties (7). To analyze the most valuable psychological and behavioral characteristics of a worker, some authors build factor models that are useful in selecting staff (8). The external assessments of the workers' technique proved to be productive for analyzing the efficiency of their professional activity and its connection with psychophysiological characteristics (9). The framework "modular approach" serves to increase the effectiveness of a worker's professional suitability evaluation (10). This technique is based on splitting the initial data into key components; then, the received "modular" information is considered separately with respect to the differences between the data in the selected subgroups. This approach allows to develop some deeper understanding of the role of the individual components underlying the selection procedure and to show their possible interconnection. Some indicators that have an impact on the ability to provide the occupational activities are identified based on factor analysis. Important psychophysiological factors are cognitive abilities, communication and computer skills, physical abilities, interpersonal communication skills, ability to provide security, independence, ability to adapt to the structure of a particular activity, and more specific abilities that are related to the problem performance (11). However, the key factors that cause stress and pressure on the workers of different occupations are different. In the electric power engineering industry, information loading is too important (12). The determination of disabilities emphasizes the importance of psychophysiological selection for the prevention of traffic safety but unfortunately do not provide any solution to get an occupational risk evaluation (13). The quantitative results of such an investigation only affirm that the frequency of errors by female operators is 2.16 times higher than by men.

Regardless of some success in the investigation, we observed a lack of clear quantitative results concerning the risk of loss or depletion in the efficiency of occupational duties during the work life. Furthermore, because of the incomplete investigation of these issues, there are still no approaches for the evaluation of the efficiency in reducing the risk factor in occupational psychophysiological selection. Thus, we need a methodology to evaluate the risks by using a certain number of psychophysiological characteristics. The aim of our investigation is to develop an approach for the quantitative evaluation of the efficiency of risk reduction in a worker's occupational activity, probability of health, and safety depletion during the entire life period of work.

MATERIALS AND METHODS

Thioglycolate media, dimethyl sulfoxide (DMSO), Mueller-Hinton broth (MHB) and Mueller-Hinton agar (MHA), nutrient agar, soybean casein digest agar (SCDA) and soybean casein digest broth (SCDB), bromine monochloride (BrCl), and sulfuric acid (H2SO4) were purchased from Merck (Germany). All other chemical compounds were of analytical grade and were available commercially. Evaluated bacterial strains included the Gram-positive bacteria Staphylococcus epidermidis (PTCC1114), Bacillus subtilis (PTCC1023), Sterptococcus pyogenes (PTCC1447), and Micrococcus luteus (PTCC1110) and Gram-negative bacteria Escherichia coli (PTCC1330), Pseudomonas aeruginosa (PTCC1074), Klebsiella pneumonia (PTCC1053), and Serratia marcescens (PTCC1621).

We synthesized 7 new derivatives of (5-nitro-2-furyl)- and (5-nitro-2-imidazolyl)-1,3,4-thiadiazole in the Pharmacochemistry lab of Tehran University. The molecular weight, formula, chemical name, and chemical structure of the synthesized compounds are presented in Table 1 and Figure 1, respectively.

Table 1. Molecular weight, chemical formula, and name of synthesized compounds

Code	Molecular weight	Chemical formula	Chemical name
1	285.34	$C_{10}H_{11}N_3O_3S_2$	2-(5-nitro-2-furyl)-5-(n-buthylthio)-1,3,4-thiadiazole
2	299.37	$C_{11}H_{13}N_3O_3S_2$	2-(5-nitro-2-furyl)-5-(n-penthylthio)-1,3,4-thiadiazole
3	315.37	$C_{11}H_{13}N_3O_4S_2$	2-(5-nitro-2-furyl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole
4	317.34	$C_{10}H_{11}N_3O_5S_2$	2-(5-nitro-2-furyl)-5-(n-butylsulfunyl)-1,3,4-thiadiazole
5	331.37	$C_{11}H_{13}N_3O_5S_2$	2-(5-nitro-2-furyl)-5-(n-pentylsulfunyl)-1,3,4-thiadiazole
6	299.37	$C_{10}H_{13}N_5O_2S_2$	2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-butylthio)-1,3,4-thiadiazole
7	329.40	$C_{11}H_{15}N_5O_3S_2$	2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole

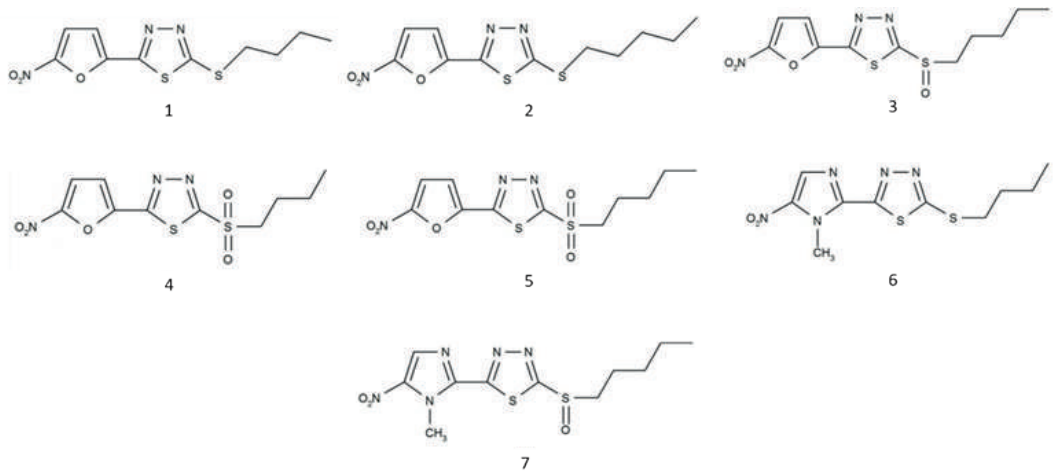

Figure 1. Chemical structure of the synthesized compounds. Compounds were numbered based on Table 1.

Thioglycolate broth (3%) was prepared and autoclaved at 121°C for 15 min. This media was used for transport of the lyophilized bacteria to the 4% SCDA. Also, 3% SCDB was prepared in sterile tubes to activate the bacterial strains before experiments. Moreover, 2% nutrient agar was used for the preparation of batch plates, as a microbial reservoir, and for overnight culture, 3.8% MHA for antibacterial sensitivity testing, and 2.1% MHB for serial dilution.

First, 6.4 g of each derivative was added to DMSO, and the final volume was made up to 5 ml using distilled water to get a 1280 µg/ml solution. Then, eight serial dilutions of 5, 10, 20, 40, 80, 160, 320, and 640 µg/ml were prepared using MHB and MIC (10, 11). Two other tubes with MBH, one without samples and the other with a bacterium, as negative and positive controls, respectively, were prepared. Moreover, two positive and negative control tubes were considered for DMSO. All of these dilutions were again diluted in the 1:10 using MHB in Petri dish and the final dilutions of 0.5, 1, 2, 4, 8, 16, 32, and 64 µg/ml were prepared.

The 0.5 McFarland standard with a turbidity of 1.5 × 108 cells/ml was prepared using 0.05 ml of 1.175 w/v BrCl and 9.95 ml of 1% H2SO4. This standard had 74.3% transmittance and absorbance of 0.08-0.1.

Lyophilized bacterial species were activated and cultured on the MHA, and then, transferred to MHB and incubated at 30-35°C (depending on the temperature requirement of the bacterial species) for 18 h. The turbidity of the bacterial suspensions was compared to the 0.5 McFarland standard, and if appropriated, 5 µl of each was transferred to MHA and incubated at 35-37°C for 18 h. Finally, the minimum inhibitory concentration (MIC) was measured as the minimum concentration of each sample which prevented the bacterial growth and recorded (12). Ciprofloxacin, as a routine antibiotic, was also evaluated. Ciprofloxacin was chosen because the first- and second-generation fluoroquinolones like ciprofloxacin have an excellent potency against Gram-negative bacteria and a good activity against the Gram-positive bacteria with little corneal toxicity (13, 14).

RESULTS

The results of the MIC analysis of the different derivatives are presented in Table 2. As demonstrated, the 2-(5-nitro-2-furyl)-5-(n-buthylthio)-1,3,4-thiadiazole showed no antibacterial effects against Gram-negative bacteria (MIC > 64 µg/ml), but completely inhibited the growth of S. epidermidis and B. subtilis (MIC < 0.5 µg/ml). This derivative had a MIC of 8-16 µg/ml against M. luteus and 0.5-1 µg/ml against S. pyogenes. The 2-(5-nitro-2-furyl)-5-(n-penthylthio)-1,3,4-thiadiazole also showed no antibacterial effects against Gram-negative bacteria (MIC > 64 µg/ml), but completely inhibited the growth of S. epidermidis, B. subtilis, and S. pyogenes (MIC < 0.5 µg/ml). This derivative had a MIC of 0.5-1 µg/ml against M. luteus.

The 2-(5-nitro-2-furyl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole showed no antibacterial effects against Gram-negative bacteria and S. epidermidis (MIC > 64 µg/ml). This derivative had a MIC of 16-32 µg/ml against M. luteus, B. subtilis, and S. pyogenes. The 2-(5-nitro-2-furyl)-5-(n-butylsulfunyl)-1,3,4-thiadiazole also showed no antibacterial effects against Gram-negative bacteria and S. epidermidis (MIC > 64 µg/ml), but this derivative had a MIC of 4-8 µg/ml against M. luteus, 16-32 µg/ml against B. subtilis, and 32-64 µg/ml against S. pyogenes.

The 2-(5-nitro-2-furyl)-5-(n-pentylsulfunyl)-1,3,4-thiadiazole had no antibacterial effects against S. pyogenes, and all of the Gram-negative bacteria (MIC > 64 µg/ml), except K. pneumonia (MIC of 16-32 µg/ml). This derivative also had a MIC of 8-16 µg/ml against M. luteus and B. subtilis, and 16-32 µg/ml against S. epidermidis. The 2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-butylthio)-1,3,4-thiadiazole showed no antibacterial effects against Gram-negative bacteria (MIC > 64 µg/ml), but completely inhibited the growth of S. epidermidis and B. subtilis (MIC < 0.5 µg/ml). The MIC of this derivative was 32-64 µg/ml against M. luteus, and 0.5-1 µg/ml against S. pyogenes. Finally, the derivative 2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole showed no

Table 2. Growth of different Gram-positive and Gram-negative bacteria in different concentration of the derivatives, ciprofloxacin, positive and negative controls

Agents	Concentration	Bacterial strains							
		EC	PA	SM	KP	SE	ML	BS	SP
2-(5-nitro-2-furyl)-5-(n-buthylthio)-1,3,4-thiadiazole	64	+	+	+	+	-	-	-	-
	32	+	+	+	+	-	-	-	-
	16	+	+	+	+	-	-	-	-
	8	+	+	+	+	-	+	-	-
	4	+	+	+	+	-	+	-	-
	2	+	+	+	+	-	+	-	-
	1	+	+	+	+	-	+	-	-
	0.5	+	+	+	+	-	+	-	+
2-(5-nitro-2-furyl)-5-(n-penthylthio)-1,3,4-thiadiazole0	64	+	+	+	+	-	-	-	-
	32	+	+	+	+	-	-	-	-
	16	+	+	+	+	-	-	-	-
	8	+	+	+	+	-	-	-	-
	4	+	+	+	+	-	-	-	-
	2	+	+	+	+	-	-	-	-
	1	+	+	+	+	-	-	-	-
	0.5	+	+	+	+	-	+	-	-
2-(5-nitro-2-furyl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole	64	+	+	+	+	+	-	-	-
	32	+	+	+	+	+	-	-	-
	16	+	+	+	+	+	+	+	+
	8	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+
	2	+	+	+	+	+	+	+	+
	1	+	+	+	+	+	+	+	+
	0.5	+	+	+	+	+	+	+	+
2-(5-nitro-2-furyl)-5-(n-butylsulfunyl)-1,3,4-thiadiazole	64	+	+	+	+	+	-	-	-
	32	+	+	+	+	+	-	-	+
	16	+	+	+	+	+	-	+	+
	8	+	+	+	+	+	-	+	+
	4	+	+	+	+	+	+	+	+
	2	+	+	+	+	+	+	+	+
	1	+	+	+	+	+	+	+	+
	0.5	+	+	+	+	+	+	+	+

2-(5-nitro-2-furyl)-5-(n-pentylsulfunyl)-1,3,4-thiadiazole	64	+	+	+	-	-	-	-	+
	32	+	+	+	-	-	-	-	+
	16	+	+	+	+	+	-	-	+
	8	+	+	+	+	+	+	+	+
	4	+	+	+	+	+	+	+	+
	2	+	+	+	+	+	+	+	+
	1	+	+	+	+	+	+	+	+
	0.5	+	+	+	+	+	+	+	+
2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-butylthio)-1,3,4-thiadiazole	64	+	+	+	+	-	-	-	-
	32	+	+	+	+	-	+	-	-
	16	+	+	+	+	-	+	-	-
	8	+	+	+	+	-	+	-	-
	4	+	+	+	+	-	+	-	-
	2	+	+	+	+	-	+	-	-
	1	+	+	+	+	-	+	-	-
	0.5	+	+	+	+	-	+	-	+
2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-pentylsulfinyl)-1,3,4-thiadiazole	64	+	+	+	+	+	-	-	-
	32	+	+	+	+	+	+	-	+
	16	+	+	+	+	+	+	-	+
	8	+	+	+	+	+	+	-	+
	4	+	+	+	+	+	+	-	+
	2	+	+	+	+	+	+	+	+
	1	+	+	+	+	+	+	+	+
	0.5	+	+	+	+	+	+	+	+
Ciprofloxacin	64	-	-	-	-	-	-	+	-
	32	-	-	-	-	-	-	+	-
	16	-	-	-	-	-	-	+	-
	8	-	-	-	-	-	+	+	-
	4	-	-	-	-	-	+	+	-
	2	-	-	-	-	-	+	+	-
	1	+	-	-	-	+	+	+	-
	0.5	+	+	-	-	+	+	+	+
	0.25	+	+	-	-	+	+	+	+

Controls								
PC	+	+	+	+	+	+	+	+
NC	-	-	-	-	-	-	-	-
DMSO PC	+	+	+	+	+	+	+	+
DMSO NC	-	-	-	-	-	-	-	-

Abbreviations:
SE, Staphylococcus epidermidis (PTCC1114); BS, Bacillus subtilis (PTCC1023); SP, Streptococcus pyogenes (PTCC1447); ML, Micrococcus luteus (PTCC1110); EC, Escherichia coli (PTCC1330); PA, Pseudomonas aeruginosa (PTCC1074); KP, Klebsiella pneumonia (PTCC1053); SM, Serratia marcescens (PTCC1621); PC, positive control; NC, negative control.

antibacterial effects against Gram-negative bacteria and S. epidermidis (MIC > 64 µg/ml), but had a MIC of 32-64 µ g/ml against M. luteus, 2-4 µg/ml against B. subtilis, and 32-64 µg/ml against S. pyogenes.

Ciprofloxacin as a routine antibiotic was also evaluated, and all the microorganisms except B. subtilis were sensitive to it. The MIC of ciprofloxacin was 1-2 µg/ml, 0.05-1 µg/ml, 0.5-1 µg/ml, < 0.25 µg/ml, <0.25 µg/ml, 1-2 µg/ml, and 8-16 µg/ml against E. coli, P. aeruginosa, S. pyogenes, K. pneumonia, S. marcescens, S. epidermidis, and M. luteus, respectively.

DISCUSSION

In the present study, the antibacterial effects of the newly synthesized derivatives of (5-nitro-2-furyl) and (5-nitro-2-imidazolyl)-1,3,4-thiadiazole against some important Gram-positive and Gram-negative bacterial strains were evaluated. A wide range of derivatives were prepared using an effective anti-Gram-positive and negative nitrofuran ring and a nitroimidazole group, which has anti-anaerobic and anti-parasitic function, and added to the 1,3,4 thiadiazole core. However, our synthesized compounds had lower antibacterial activities compared to ciprofloxacin. All the bacteria were grown in the presence of these compounds, and only mild antibacterial effects against Gram-positive bacteria were detected.

After comparing the antibacterial effects of the compounds based on their chemical structure, we found that the carbon chain elongation had no effects on the Gram-negative bacterial strains. Moreover, the conversion of the thio-group to sulfinyl-group decreased the antibacterial effects against S. epidermidis. In addition, increase in the length of the hydrocarbon chain from 4 to 5 and the conversion of thio-group to sulfinyl-group increased the antibacterial effect against M. luteus. Substitution of nitrofuran by nitroimidazole increased the antibacterial effects against B. subtilis. Finally, the conversion of the thio-group to sulfinyl-group and increasing the length of the hydrocarbon chain decreased the antibacterial effects against S. pyogenes, which was consistent with the results of a few studies (15, 16). The most effective compounds were 2-(5-nitro-2-furyl)-5-(n-buthylthio)-1,3,4-thiadiazole, 2-(5-nitro-2-furyl)-5-(n-penthylthio)-1,3,4-thiadiazole, and 2-(1-methyl-5-nitro-H1-imidazole-2-yl)-5-(n-butylthio)-1,3,4-thiadiazole.

Due to the dramatic increase in the number of antibiotic-resistant pathogens, the discovery or the synthesis of new antimicrobial agents has increased (17). However, there is less number of studies about the antibacterial effects of nitrofuran and nitroimidazole derivatives of the thiadiazole core. Basically, 1,3,4-thiadiazole has a good activity against various microbial strains, and scientists have focused on the synthesis of new potent antibacterial and antifungal agents by the substitution of different groups (9). Foroumadi et al. evaluated the MIC of a series of 2-(1-methyl-5-nitro-2-imidazolyl-1,3,4-thiadiazole-5-alkylsulfides, alkylsulfoxides, and alkylsulfones as antitubeculosis agents. They found that compounds with a primary alkylthio substitution showed good anti-tuberculosis activity (18). In another study, a series of 2-(5-nitro-2-furyl)-1,3,4-thiadiazole-2-sulfide, sulfoxide, and sulfone compounds were found that had a good antituberculosis activity (19). In addition, appropriate antibacterial and antifungal properties of the different derivatives of 1,3,4-thiadiazole were reported previously (20-23). However, the antibacterial activities of these compounds are very low than the routine antibiotics, such as chloramphenicol and rifampicin (24). Our findings are also parallel with the previous studies about the antibacterial effects of derivatives of 1,3,4-thiadiazole (25, 26). Some studies have also reported that certain derivatives of 1,3,4-thiadiazole exhibited higher antibacterial activity against some bacterial strains compared to the standard antibiotics (27). In the study, by Serban et al., the results showed that 1,3,4-thiadiazole derivatives are studied more because of their broad spectrum of pharmacological activities among the various isomers of thiadiazole as well as the substitution at thiadiazole ring for obtaining an improved agent regarding potency and low toxicity is challenging (28). Foroumadi et al. revealed that the MIC of a series of 2-(1-methyl-5-nitro-2-imidazolyl-1,3,4-thiadiazole-5-alkylsulfides, alkylsulfoxides, and alkylsulfones reported previously as antifungal agents, were determined using the radiometric BACTEC 460-TB methodology. They screened active compounds by serial dilutions to determine the toxicity in a VERO cell line, and the results showed that the compounds with primary alkylthio substitution had appropriate anti-tuberculosis activity. Moreover, oxidation of sulfone attenuated the anti-tuberculosis activity of methyl and propyl derivatives (29).

CONCLUSION

The derivatives had low antibacterial effects and the conversion of the thio-group to sulfinyl-group could not increase their effects. However, it seems that the C5 in the 1,3,4, thiadiazole is crucial for the antibacterial effects. Based on the in vitro nature of this research and local effects of the derivatives, further in vivo research in local and systemic diseases are highly suggested.

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NONE

AUTHOR CONTRIBUTIONS

All the authors have contributed towards conducting the experiments and preparation of the manuscript and have approved the latest version of the article.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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