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ANTIBACTERIAL EFFECT OF SOME 3-IMINO-4-SUBSTITUTED-1,2,5-THIADIAZOLIDINE 1,1-DIOXIDES

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ABSTRACT

Organosulfur compound's functionality constitutes an essential class of therapeutic agents in current medicinal chemistry. Especially sulfonamides called sulfa drugs were performed as both chemotherapeutic agents and useful antibacterial derivatives developed for medicine. The sulfamides in the same family with the sulfonamides have similar biological activities. In our research, it was studied with some 3-imino-4-substituted-1, 2, 5-thiadiazolidine 1,1-dioxides (ISTDs- 4a-d, four samples) that are five-membered cyclosulfamides. These compounds were previously synthesized and structurally characterized. The goals of this study are to investigate minimum inhibition concentration (MIC) values and antibacterial effects of these ISTDs compounds on *Bacillus subtilis* NRRL B-209^T, *Escherichia coli* ATCC®25922^T, *Micrococcus luteus* NRRL B-1018^T, *Nocardia abscessus* DSM 44432^T, *Nocardia cyriacigeorgica* DSMZ 44484^T, *Pseudomonas aeruginosa* NRRL B-2679^T *Staphylococcus aureus* ATCC®6538^T, *Streptomyces murinus* ISP 5091^T.

Keywords: Sulfonamides, Microdilution MIC, MBC

1. INTRODUCTION

Increasing incidences of bacterial infections all over the world have driven the search and improve new antibacterial compounds. The main problem is the increasing antimicrobial resistance of pathogenic bacteria worldwide. For example, for nocardiosis treatment, combination therapy trimethoprim (TMP) and sulfamethoxazole (SMX) has been preferred for many years. Not surprisingly, as the therapies for nocardiosis can spread out for many months, resistance to TMP-SMX has arisen. Especially in patients with systemic infection and immunosuppressed, this treatment regimen was insufficient because of the differences in antibiotic resistance patterns among *Nocardia* species. This antibiotic resistance is the main reason which is limited treatment options, and later, the combination of various antibiotics with TMP-SMX was recommended in these patients.

On the other hand, many antimicrobial agents are more successful in Gram-positive bacteria rather than Gram-negative bacteria [1]. Scientists faced an antibiotic resistance profile by Gram-negative bacteria like *P. aeruginosa*, which caused septicemia [2]. Though the need for novel antimicrobials is rising, the development of such agents has decreased year by year [3]. From this point of view, we focused our attention on the ISTD compounds, which have also been synthesized characterized by Assistant Professor Dr. Aliye GEDİZ ERTÜRK who studies at Ordu University Faculty of Science and Arts, Department of Chemistry. Also, these ISTD constructs published in the literature [4, 5]. The same synthesis methods which are mentioned in published literature were used in this study. The sulfamide functional group (–HNSO₂NH–) is one of the essential pharmacophores for both bioorganic and medicinal chemistry [6]. The fascinating biological and chemical properties in the sulfamide terminal can be based on its structural similarity with urea (–HNCONH–) [7, 8].

Additionally, in recent years, the studies of new thiadiazole 1, 1-dioxide compounds have become very important for biological and medicinal reasons. Notably, the structure of the five-membered -1, 2,

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5-thiadiazolidine-1,1-dioxides from cyclic sulfamide derivatives could be adapted to interact with different biological receptors selectively. It is well recognized to have their essential roles as antibacterial [9], HIV protease [10], serine protease [11], antibiotics [6, 12] carbonic anhydrase enzyme inhibitor [13], antiepileptic, antidiabetic, diuretic, anti-glaucoma, anticonvulsant, anti-obesity, anticancer, anti-pain, and anti-infective agents [4], agonists in serotonin receptors for Alzheimer disease [14]. From this perspective, we planned to screen the antimicrobial activity of the ISTD compounds. In this study, we selected pathogenic Gram-negative and Gram-positive bacteria that included actinomycetes (*Micrococcus luteus*, *Nocardia abscessus*, *N. cyriacigeorgica*, and *Streptomyces murinus*), too. Several antimicrobial screening methods (disk diffusion, E-test, etc.) can use for this purpose. However, because of the slow reproduction of actinomycetes species and the difficulties in preparing inoculum due to their filamentous structure, the liquid microdilution method is recommended for routine antibiotic susceptibility tests in these strains by CLSI [15]. The bacteriostatic effect is known as the arrest and development of bacterial cells. The indicator of bacteriostatic efficacy is the minimum inhibitory concentration (MIC). The MIC value can be defined as the lowest concentration of the antimicrobial agent in which the microorganism visibly inhibits the microorganism. MIC, also known as the gold standard used to determine the susceptibility of a microorganism against to an antimicrobial agent, is determined by international standard methods [16]. Here we have screened the antibacterial effects of some 3-imino-4-substituted-1,2,5-thiadiazolidine 1,1-dioxides (ISTDs- 4a-d, four samples) compounds by minimum inhibition concentration (MIC) values of Gram-positive bacteria which include actinomycetes, and Gram-negative bacteria. This study is the first evaluation report of these compounds.

2. MATERIALS AND METHODS

2.1. Chemicals

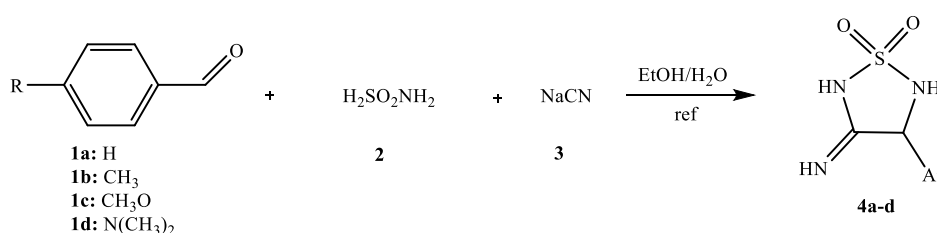
All chemicals and solvents were purchased from Sigma Chemical Company (Sigma Aldrich, Germany), Merck (Merck KGaA Darmstadt, Germany), and deionized water was used for all the performed analysis (MP Minipure dest up, Turkey). Media Mueller-Hinton Agar (MHA) and MHB were purchased from Oxoid.

2.2. Apparatus

McFarland Densitometer (Biosan Den-1, Turkey), vortex and pH meter (Jeio Tech ON-02, Korea), incubator (Nüve EN 500, Turkey), all micropipettes which used in the study are BRAND® (Sigma Aldrich, Germany), autoclave (Nüve OT 4060, Turkey) class II Biological safety cabinet (Esco Airstream®, Singapore).

2.3. ISTD Test Substances

ISTD test substances (**4a-d**) that previously synthesized and structurally characterized are available in the literature (Scheme 1) [4, 5, 17]. Investigated ISTD test substances are listed in Table 1. The studied compounds



Scheme 1. The synthesis route of ISTDs (**4a-d**)

Table 1. Evaluation of antimicrobial activity of ISTDs (**4a-d**).

Compound	Ar-	Name
4a	Phenyl	3-Imino-4-phenyl-1,2,5-thiadiazolidine 1,1-dioxide
4b	p-Tolyl	3-Imino-4-(4'-tolyl)-1,2,5-thiadiazolidine 1,1-dioxide
4c	p-Anisyl	3-Imino-4-(4'-anisyl)-1,2,5-thiadiazolidine 1,1-dioxide
4d	p-(Dimethylamino)phenyl	3-Imino-4-(4'-dimethylamino)phenyl-1,2,5-thiadiazolidine 1,1-dioxide

2.4. Antibacterial Activity Tests

Dilution tests are based on the fact that the bacteria growth is visible in the microplate wells containing the dilutions of the antimicrobial agent or on the surface of the agar. Depending on the amount of the substance to be dissolved, the micro or macro dilution method is preferred [15]. We provide pathogenic bacteria of the study from culture collections, which are listed in Table 2 by alphabetical order.

Table 2. Microorganism that used for antibacterial activity tests.

Organism name	Culture collection	Culture collection number
<i>Bacillus subtilis</i>	Agricultural Research Service Culture Collection, USA (formerly NRRL)	NRRL B-209 ^T
<i>Escherichia coli</i>	American Type Culture Collection, USA	ATCC®25922 ^T
<i>Micrococcus luteus</i>	Agricultural Research Service Culture Collection, USA (formerly NRRL)	NRRL B-1018 ^T
<i>Nocardia abscessus</i>	German Collection of Microorganisms and Cell Cultures, Germany	DSM 44432 ^T
<i>Nocardia cyriacigeorgica</i>	German Collection of Microorganisms and Cell Cultures, Germany	DSMZ 44484 ^T
<i>Pseudomonas aeruginosa</i>	Agricultural Research Service Culture Collection, USA (formerly NRRL)	NRRL B-2679 ^T
<i>Staphylococcus aureus</i>	American Type Culture Collection, USA	ATCC®6538 ^T
<i>Streptomyces murinus</i>	International Cooperative Project for Description and Deposition of Type Cultures of <i>Streptomyces</i>	ISP 5091 ^T

All bacterial type strains were cultured in the Mueller-Hinton Agar at 37°C. Antibacterial activity tests were performed with Microdilution Minimum Inhibitory Concentration (MIC), MIC₅₀, and Minimum Bactericidal Concentration (MBC) methods to find antimicrobial sensitivities of selected pathogens on agar plates, according to the CLSI procedures

2.5. Assessment of Minimum Inhibition Concentration (MIC)

The broth microdilution method was followed for the antibacterial screening by using 96 well plates according to the Clinical and Laboratory Standards Institute's standard procedures, (Corning) [18-21]. For MIC, two-fold serial dilutions of the ISTDs were performed. Dilutions of the ISTDs were performed by sterile MHB and DMSO. Growth control (bacteria/fungus and growth media without the ISTDs samples) and sterility check (growth media) were used for each test (first and second well). PSA (Penicillin & Streptomycin and Amphotericin Antibiotic) used for control purposes. We used our calculations by modifying them to 100 µL of the well content. Bacterial inoculation was performed at last rank in the wells and after the McFarland adjustment was made. All the procedure was completed within thirty minutes. Microplates were incubated at 37°C in a 250 rpm orbital shaker and checked for visible bacterial colony formation in the wells after 16-24-48 h. For non-actinomycetes, at the end of the twentieth hour, at the end of forty-eight hours for actinomycetes, the presence of visible bacterial growth in the wells was noted and, the MIC value was determined. The readings of MIC results were started at the lowest concentration. The MIC value was determined as the concentration of the substance in the first well (the lowest concentration of the ISTDs) where there was no visible bacterial growth. The MIC test was repeated three times for each sample [22].

2.6. Determination of MIC₅₀ Value

The MIC₅₀ value was determined by counting the colonies in the petri plates to determine the MBC value. Concentration value that reduces the number of inoculated pathogenic bacteria by half was determined as MIC₅₀ [23]. It is a generally preferred method while working with large isolate groups. It is especially useful in the detection and treatment of isolates showing multiple resistance development [18].

2.7. Assessment of Minimum Bactericidal Concentration (MBC)

It is the method used to determine the lowest sulfonamide concentration (mg / L or µg / mL) that kills 99.9% of the bacterial cells [24]. 100 µL of the bacterial-sulfonamide solution was pipetted out from each well in which no visible bacterial growth was detected, to the Müller Hinton Agar surface and, spread by swap. The plates were cultured at 35-37°C for 24-48h. If the number of bacteria was over 300 colonies in a petri dish, the sulfonamide concentration was deemed ineffective. The lowest sulfonamide concentration at which no colony development was observed was determined as the MBC value. A blank test was finished by the same means without sulfonamide. The counting was done in triplicate every time.

3. RESULTS

The antimicrobial effect of each sulfonamide was investigated by MIC and MBC methods. To determine the range of inhibition of microbial growth of each sulfonamide, we prepared a total of 11 different concentrations of the test apparatus by two-fold serial dilution and designed twenty-six sets for detecting the useful MIC and MBC concentrations.

4b and 4d were influential on all microorganisms in the study. Besides, only 4b and 4d had shown the antibacterial effect on *B. subtilis* NRRL B-209^T. Experiments have shown that the lowest effective doses of 4b and 4d were determined as 0.0625 mg /mL and also for 4a and 4c as 0.125 mg/mL. The most sensitive species to all sulfonamides used in the study was *M. luteus* NRRL B-1018^T (Table 3).

4a's determined bactericidal doses were 0.5 mg/mL for *S. murinus* ISP 5091^T and 1 mg/mL for *M. luteus* NRRL B-1018^T, respectively. 2 mg/mL was an effective dose of these sulfonamides for *N. abscessus* DSM 44432^T and *P. aeruginosa* ATCC®27853^T. *E. coli* ATCC®25922^T, *N. cyriacigeorgica* DSM 44484^T and *S. aureus* ATCC®25923^T were more resistant to 4a, so; minimum concentration was 4 mg/mL to see the bactericidal effect.

0.125 mg/mL, the lowest concentration of 4b, was the MBC value for *E. coli* ATCC®25922^T. 4b's effective dose for *M. luteus* NRRL B-1018^T, *B. subtilis* NRRL B-209^T and *S. murinus* ISP 5091^T was 1 mg/mL. The doses had been bactericidal effect were the same as 4a for the rest of microorganism in the study group. 4 mg/mL was the highest MBC dosage for 4b and also its effective dosage for *S. aureus* ATCC®25923^T (Figure 1) and *N. cyriacigeorgica* DSM 44484^T.

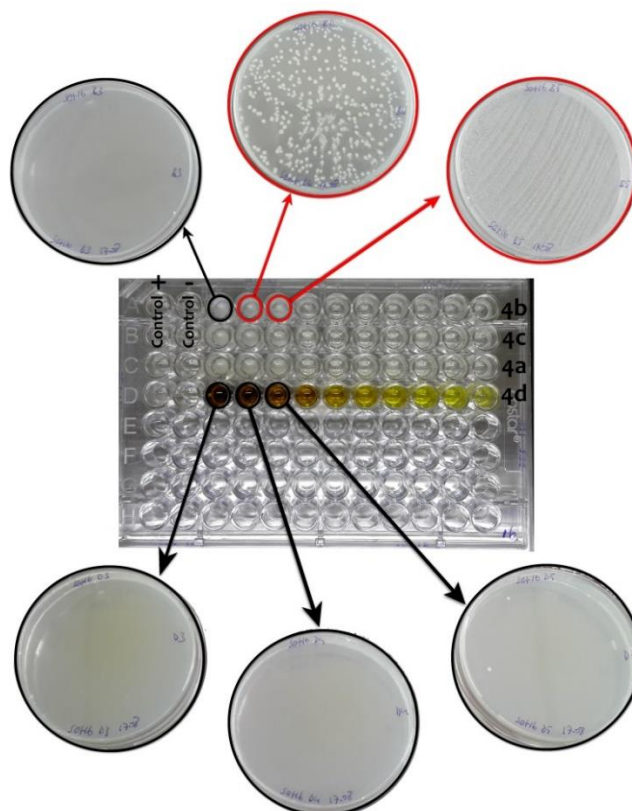


Figure 1. MIC and MBC results of *S. aureus* ATCC®6538^T to **4b** (3-Imino-4-(4'-methylphenyl)-1,2,5-thiadiazolidine 1,1-dioxide) and **4d** (3-Imino-4-(4'-(dimethylamino)phenyl)-1,2,5-thiadiazolidine 1,1-dioxide). Effective dosages were showed by black arrows, and not effective ones were indicated by red arrows.

4c's MBC dose for *E. coli* ATCC®25922^T was 0.25 mg/mL, and also this dosage is the lowest effective dosage of 4c (Figure 2). However, this sulfonamide has no bactericidal effect against *B. subtilis* NRRL B-209^T. 4 mg/mL was 4c's bactericidal dose for the rest of the bacteria in the study. 4c's MBC results were the same as 4a and 4b for *M. luteus* NRRL B-1018^T (1 mg/mL).

The lowest concentration of 4d, the same as 4b, was 0.125 mg/mL, and also the minimum effective dose for *E. coli* ATCC®25922^T. 4d's effective dose for *M. luteus* NRRL B-1018^T was 0.5 mg/mL, and for *N. cyriacigeorgica* DSM 44484^T and *S. murinus* ISP 5091^T was 1 mg/mL. Against *P. aeruginosa* ATCC®27853^T and *S. aureus* ATCC®25923^T (Figure 1), 2 mg/mL of 4d was an effective dose.

Generally, *Nocardia* species in the study were more resistant than other bacteria. 4a and 4b's effective dosage for *N. abscessus* DSM 44432 T was 2 mg/mL, 4c, and 4d's dose was 4 mg/mL. But for *N. cyriacigeorgica* DSM 44484 T effective dosage were 4 mg/mL for 4a-c. 4d was more effective for this bacteria, and the MBC value was 1 mg/mL (Figure 3).

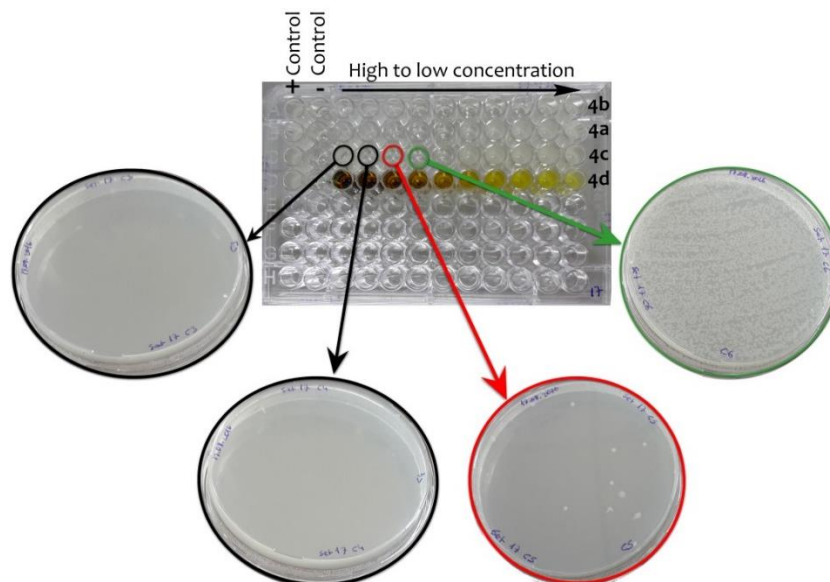


Figure 2. MIC and MBC results of *E. coli* ATCC®25922^T to **4c** (3-Imino-4-(4'-methoxyphenyl)-1,2,5-thiadiazolidine 1,1-dioxide). Bactericidal concentrations were demonstrated by black arrows, MIC₅₀ was shown a red arrow, and a non-effective dosage was represented by a green arrow.

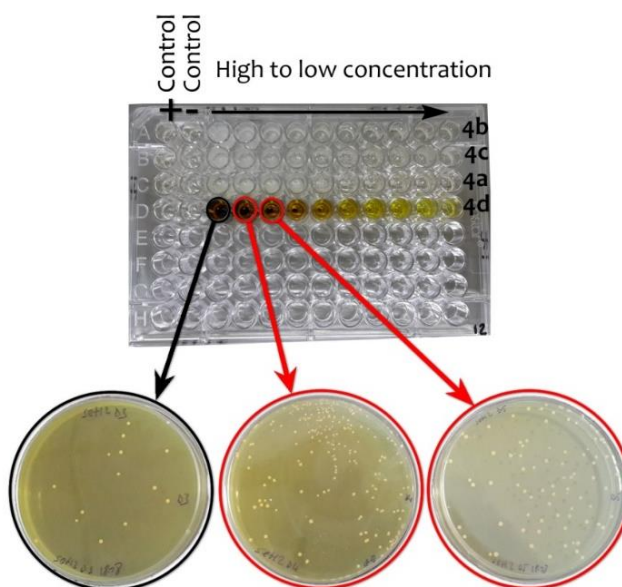


Figure 3. MIC and MBC results of *N. abscessus* DSM 44432^T against to **4d** (3-imino-4-(4'-(dimethylamino) phenyl)-1,2,5-thiadiazolidine 1,1-dioxide). MIC₅₀ was showed by black arrow.

4. DISCUSSION

In 1944 Benbow et al. first mentioned that sulfonamides could be used for many Nocardial infections. In the 1970s, combination therapy with trimethoprim and sulfamethoxazole began to be tried. Although sulfonamides are known to have an effect on both Gram-positive and Gram-negative bacteria, it is now known that in many countries, including the USA, these two are particularly preferred in the treatment of Nocardial infections [25-28]. Sulfonamides are antimicrobial agents that are particularly preferred as preventive cures in the treatment of pulmonary and cutaneous diseases or immunosuppressed patients. The most commonly used treatment method for nocardial infections in adults is oral administration of trimethoprim /sulfamethoxazole at a dose of 160/800 mg three times a day. A combined treatment for sepsis and/or nocardial infections in the central nervous system (CNS) is recommended. Patients with sepsis or CNS disease treated with sulfonamides alone were given more than 50% survival. However, it is important to note that trimethoprim /sulfamethoxazole prophylaxis is not always protective against *Nocardia* infection. Since *Nocardia* species, which can cause a nosocomial infection like *N. cyriacigeorgica*, *N. nova*, and *N. farcinica*, may develop resistance to antibiotics and sulfonamides, antibiotic susceptibility test is definitely recommended when appropriate treatment is chosen [25, 29]. Because sulfonamides display a broad range of antimicrobial activities, they are not used only for suppressing nocardial infections. According to Argyropoulou et al.'s study in 2009, sulfonamide thiazole and benzothiazole derivatives were effective on the strains of *B. subtilis* ATCC®6633, *S. aureus* ATCC®25923, and *E. coli* SPA 27. They also found that the MBC values were twice or higher than the MIC values, which were determined in all the experimental sets [24]. Our MBC and MIC results confirm that report.

On the other example, Bendjeddou et al. (2016), sulfamides derivatives containing thiophene, pyridine, benzyl, and isopentyl alkyl end revealed that the majority of the synthesized compounds were fairly active against all tested bacteria. These compounds exhibited a broad spectrum of activity with inhibition zones values 13-36 mm against Enterobacteriaceae and *S. aureus* [30].

When the antibacterial activity of cyclic sulfamide compounds linked to tetrathiafulvalene was examined, they were found to possess tremendous or modest antimicrobial activity towards the gram-negative bacteria *Escherichia coli* [9]. *P. aeruginosa*, *E. coli*, and *S. aureus* are the most frequent pathogens responsible for and the foremost causes of nosocomial infections worldwide [2, 31, 32]. Another study which was done with N-acylsulfamides, the investigator was determined no activity on the Gram-positive bacteria (*S. aureus*) conversely good activity on all the Gram-negative bacteria (*E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa*, *Acinetobacter*) by both disk diffusion and minimal inhibition concentration (MIC) methods [33].

Disc diffusion and MIC tests from semi-quantitative, *in vitro*, bacterial susceptibility testing standards developed by organizations such as the European Committee On Antimicrobial Susceptibility Testing (EUCAST) established by the European Society of Clinical Microbiology and Infectious Diseases in Europe and the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) and in the USA, and methods should be performed by experts due to factors such as strain structural differences, inoculum amount, nutrient used, incubation conditions (temperature and incubation time).

5. CONCLUSIONS

3-imino-4-substituted-1,2,5-thiadiazolidine 1,1-dioxides (ISTDs- 4a-d, four samples) were synthesized for screening antibacterial activity [34]. The results revealed that 3-Imino-4-(4'-methylphenyl)-1,2,5-thiadiazolidine 1,1-dioxide (4b) and 3-Imino-4-(4'-(dimethylamino)phenyl)-1,2,5-thiadiazolidine 1,1-dioxide (4d) displayed high inhibition potency against all microbes tested. The synthesized compounds except for 4a and 4c, having >99% inhibition potency, which is one of the most critical findings from the current work. 4b and 4d might be improved and used as effective inhibitors of these bacteria. The

successful developments of novel safe and effective drugs are faced with some challenges [35]. Generally, the major limitation of the active antimicrobial agents is high toxicity [36]. We know from previous reports, many antimicrobial agents like trimethoprim or ciprofloxacin may cause cytotoxic or genotoxic damage [37, 38]. However, the ISTD compounds in this study do not have chromosomal damage, according to Ertürk et al. 2017 [34]. As we have argued in this point, we perceive that the ISTD compounds have excellent potential for improving as a medical drug.

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