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Analysis of Biological Activity of Sulfamide Derivatives as Antimicrobial Agents

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Abstract: Sulfamides are significant compounds because of their biological effects on bacteria, fungi, and cancer. The antimicrobial and anticancer properties of sulfamide derivatives have been demonstrated in several microbial strains and cancer cell lines. They have worked mostly in the field of medicinal chemistry. Numerous microbiological pathogens are known to be resistant to the antibacterial effects of sulfamide derivatives. The most significant microorganisms in command of hospital-acquired nosocomial infections include *Acinetobacter baumannii* (*A. baumannii*), Methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida albicans* (*C. albicans*), and *Candida parapsilosis* (*C. parapsilosis*). Multiple antibiotics can no longer treat these illnesses. Therefore, it is crucial to develop new antimicrobial agents. Three previously made compounds were tested for their antibacterial properties against these pathogens, including *3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1-dimethyl sulfamide* **(4)** and *3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1,1-dimethyl sulfamide* **(5)**. Using the disc diffusion method, antimicrobial activity was assessed, and values for the minimum inhibitory concentration (MIC) were calculated for zone formation seen in the tested pathogens. The results of the investigation demonstrated that sulfamide derivatives stopped the growth of bacteria against *A. baumannii* with zone widths of 7-9 mm, but had no impact on MRSA, *C. albicans*, and *C. parapsilosis*. Sulfamide derivatives' MIC values against *A. baumannii* were discovered to be 3.90 g/ml. These results provide us the ability to evaluate these sulfamide derivatives as potential new antibacterial therapies for *A. baumannii*.

Keywords: sulfamide; *A. baumannii*; MRSA; *C. albicans*; *C. parapsilosis*; antimicrobial activity.

1. Introduction

Antibiotic usage in clinical settings has grown in importance to treat infectious infections [1]. Antibiotic resistance, however, is one of contemporary medicine's biggest, fastest-growing concerns. Antibiotic resistance is a global public health issue that, as resistant organisms proliferate, has the potential to increase a variety of morbidities and fatalities [2]. Long-term antibiotic exposure causes bacteria to evolve stronger defense mechanisms, making them resistant to antibiotics [3]. So, the usage of antibiotics and their negative effects result in antibiotic resistance. A serious public health issue is the rise in antibiotic-resistant bacteria [4].

A. baumannii, a Gram-negative bacillus bacterium, is one of the most challenging resistant organisms to get rid of [5,6]. The capacity of the species, *A. baumannii*, to infect immunocompromised individuals makes it most well known [7]. It now possesses genes that

make it almost immune to the ability of any antibiotic to treat *A. baumannii*, making it a common resistant bacteria in hospitals. As a result, infections picked up in hospitals are far more prevalent and present a serious risk. *A. baumannii* has been related to various unique nosocomial illnesses, including meningitis, skin and soft tissue infections, wound infections, urinary tract infections, and meningitis. Infections related to the bloodstream and ventilator are also extremely dangerous and have high death rates. [8,9].

Gram-positive staphylococci are what cause MRSA, one of the most serious diseases. MRSA is a common infection in hospitals and the general populace [10]. MRSA is a typical source of hospital-acquired infections, including bacteremia, septicemia, endocarditis, skin and soft tissue infections, and bone infections [11]. Although penicillin was the first antibiotic to treat serious S. aureus infections, resistance quickly developed when it was used in patients. Methicillin was created due to research into new antibiotics to battle *S. aureus* bacteria that were resistant to penicillin. Regrettably, MRSA initially appeared in the UK in 1960 to prevent its usage [12].

Invasive candidiasis is a significant source of morbidity and mortality in hospitals [13]. *C. albicans* is prevalent in human microflora organisms, despite opportunistic human infections being the primary cause of candidemia and candidiasis globally[14]. A switch in morphologies is a key component of pathogenicity. Infections produced by species other than *C. albicans* are becoming more frequent, despite the fact that *C. albicans* is the most common cause of invasive candidiasis [14]. An opportunistic human pathogen called *C. parapsilosis* is increasingly being blamed for nosocomial bloodstream infections in hospitalized patients. Additionally connected to *C. parapsilosis* is the development of candidemia by intravascular devices [16].

There are many applications for the sulfamide (H2NSO2NH2) functional group in medicinal chemistry [17]. Sulfamides and their derivatives have a variety of biological characteristics, including those that suppress norovirus, cancer, and bacteria [18]. For instance, the wide-spectrum antibiotic Doripenem **1** is a mono-substituted sulfamide with therapeutic benefits [19]. Sulfamide medicine Quinagolide **2** has antihyperprolactinemia and dopaminergic properties [20]. Recently developed sulfamide compound 7 (JNJ-26990990) **3** is a powerful anticonvulsant [21].

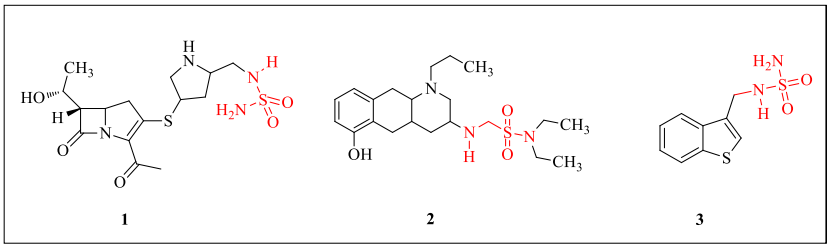

Figure 1. Some biologically active sulfamide derivatives **1-3** [19, 20, 21].

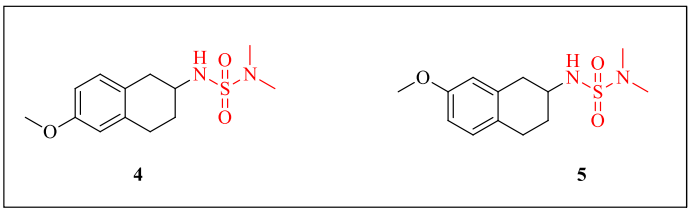

Figure 2. Sulfamide derivatives **4-5** [22].

In the present investigation, the antimicrobial effects of previously synthesized *3-(6-methoxy-1,2,3,4-tetrahydronaphthalin-1-yl)-1,1-dimethyl sulfamide* **4** and *3-(7-methoxy-*

1,2,3,4-tetrahydronaphthalin-1-yl)-1,1-dimethyl sulfamide **5** [22] were evaluated against *A. baumannii*, MRSA, *C. albicans* and *C. parapsilosis*.

2. Materials and Methods

2.1.Strains of fungi and bacteria.

As part of the study, the antibacterial activity of two derivatives synthesized from sulfamide was examined. *A. baumannii* ATCC BAA-1605, MRSA ATCC 43300, *C. albicans* ATCC 10231, and *C. parapsilosis* ATCC 22019 were the strains used in this study. The antibacterial activity was evaluated using the minimum inhibitory concentration (MIC) and disc diffusion techniques.

2.2. Antimicrobial research using disc diffusion analysis.

For the disc diffusion test, the microbial inoculum was created in accordance with 0.5 McFarland and then planted on Petri dishes. Sulfamide derivatives created in three replications at a concentration of 10 µg/ml (5 µg active compound + 250 µl DMSO + 4750 µl dH_2O) were adsorbed onto discs and placed in Petri dishes. The antibacterial susceptibility of isolates was tested using the zone diameters obtained after 24 hours of incubation at 37°C for bacterial strains and 30°C for fungal species. Positive controls for the antibacterial and antifungal tests were Netilmicin and amphotericin B. In each test, DMSO was utilized as a negative control [23].

2.3. Antimicrobial research using MIC assays.

The disc diffusion test was used to determine the MIC values of sulfamide derivatives. The 96-well plates were added 100 µl of MHB and 100 µl of the synthetic medication to each well to calculate the MIC values. The wells were filled with 100 µl of 0.5 MacFarland bacterial culture inoculum, which was then incubated for 24 hours using the serial dilution method. After the 24-hour incubation period, the turbidity of the wells was measured spectrophotometrically (at 600 nm), and MIC values were calculated [24].

3. Results and Discussion

3.1. Antibacterial activity.

Using disc diffusion and microdilution techniques, the antibacterial activity of sulfamide compounds against MRSA and *A. baumannii* strains was investigated (Table 1). The study's findings demonstrated that sulfamide compounds have antibacterial activity against *A. baumannii* isolates but not against MRSA isolates. Figure 3 displays images of compounds **4** and **5** that exhibit antibacterial activity by disc diffusion.

Table 1. Disc diffusion analysis results of sulfamide compounds.

Bacteria isolations	**Compounds**						**Positive Control****
	(4)	**(5)**					
***A. baumannii* ATCC BAA- 1605**	0,7*	0,9*					1,2
MRSA ATCC 43300	-	-					1,0

* zone diameter (cm) ** Positive control: netilmicin

The study evaluated the minimum inhibitory concentration (MIC) of compounds **4** and **5**, which exhibit antibacterial activity in *A. baumannii* (Table 2).

Table 2. MIC values of sulfamide compounds.

Bacterial isolations	Compounds	
	(4)	**(5)**
***A. baumannii* ATCC BAA- 1605**	3,90625	3,90625

[1]MIC is calculated as the concentration value µg / ml.

The results of the disc diffusion test demonstrated that the sulfamide derivatives **4** and **5** are zone inhibitors of bacterial growth on *A. baumannii* isolates. The methoxy groups carry methoxy groups, and both molecules with the activities are equivalent to the benzene ring in the benzene ring. The antibacterial effects of sulfamide derivatives on diverse bacterial isolates have been researched in the literature [25]. According to Abbaz *et al.*, sulfamide derivatives have no effect on Gram-positive bacteria but have an antimicrobial effect on Gram-negative bacteria [26]. In our work, the antibacterial activity of sulfamide derivative compounds was not seen against the MRSA isolate, which contains Gram-positive bacteria, or the *A. baumannii* isolate, which contains Gram-negative bacteria. The literature was found to support these conclusions.

Figure 3. Disc diffusion test of results.

3.2. Antifungal properties.

Disc diffusion was used to assess the antifungal activity of sulfamide compounds against isolates of *C. albicans* and *C. parapsilosis*. Sulfamide compounds demonstrated no antifungal efficacy against isolates of *C. albicans* and *C. parapsilosis*, according to the study (Table 3).

Table 3. Disc diffusion analysis results of sulfamide compounds.

Fungal Isolations	Compounds*		Positive Control**
	(4)	**(5)**	
C. albicans* ATCC *10231	-	-	1,0
***C. parapsilosis* ATCC 22019**	-	-	1,1

*zone diameter (cm) ** Positive control: Amphotericin B

Sulfamide derivatives' antifungal activities have been researched in the literature. In the investigation conducted by Oleksiyenko *et al.*, sulfamide derivatives were demonstrated to have strong antifungal activity against *C. albicans* [27]. However, no zone formation that would prevent the growth of sulfamide derivatives **4** and **5** against *C. albicans* and *C. parapsilosis* was found in our experiment. This is because, while sulfamide is present in the

skeletal structure, its derivatives with different substituents can have a variety of biological functions, each of which needs a different substituent.

4. Conclusions

The antibacterial properties of the sulfamide derivatives **4** and **5** were studied. The sulfamide derivatives of *C. albicans*, *C. parapsilosis*, and MRSA showed little effect. The antibacterial activity of sulfamide derivatives was only discovered against an isolate of *A. baumannii*. The results showed that sulfamide derivatives are effective against isolates of *A. baumannii*, and can be used to treat diseases caused by *A. baumannii*.

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Conflicts of Interest

The authors declare no conflict of interest.

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