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Original Article

Evaluation of some *o*-benzenedisulfonimido-sulfonamide derivatives as potent antimicrobial agents

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ABSTRACT

Background and Aims: The discovery of new antimicrobials to overcome antimicrobial resistance has always been an important topic for sustainable world health. Since the sulfonamide carrying heterocyclic compounds present a number of advantages as biologically active compounds, in our work reported herein, a small collection of previously synthesized *o*-benzenedisulfonimido-sulfonamide derivatives were assayed to determine antimicrobial profiles against ten different microorganisms in search of finding promising new antibacterial/antifungal agents.
Methods: Eight compounds and their standards were tested against seven bacterial and three fungal strains, including members of Gram-positive, Gram-negative bacteria, and *Candida spp*., using the microbroth dilution method to measure their MIC (minimum inhibitory concentration) values.
Results: All assayed molecules showed different inhibitory effects on ten different targets, with considerable MIC values. Particularly, compound **2** exhibited better antimicrobial activity against the largest number of assayed microorganisms.
Conclusion: Further modification and development of *o*-benzenedisulfonimido-sulfonamide derivatives and additional *in vitro* studies against putative targets may result in new antimicrobial drug candidates in the near future.
Keywords: *o*-benzenedisulfonimide, sulfonamide, antibacterial agents, Gram-positive bacteria, Gram-negative bacteria, antifungal agents, *Candida spp*.

INTRODUCTION

Antimicrobial resistance is one of the most challenging worldwide health and development threats facing human beings. Misuse or overuses of antimicrobials are leading to untreatable infections caused by multi- and pan-resistant bacteria (also known as "superbugs"), viruses, fungus, and other microorganisms. According to World Health Organization (WHO), investing in research and development of new antimicrobials is an essential part of strategic global action plans on antimicrobial resistance (WHO 2021; WHO 2015).

Heterocyclic compounds have always attracted much attention for drug discovery because of their versatile chemical structures with various pharmacological potentials. Phthalimides are a class of cyclic imides involved in a huge number of promising biological properties, such as antihyperlipidemic (Alaa et al., 2011), analgesic (Banarouei, Davood, Shafaroodi, Saeedi, &Shafiee, 2019), anticonvulsant (TabatabaeiRafiei et al., 2020), anti-inflammatory (Abdel-Aziz et al., 2020), anticancer (Oliveira et al., 2021), antiviral (Mandić et al., 2020), antitubercular (Phatak et al. 2019), and antimicrobic (Singh et al. 2015; Holanda et al., 2020). In addition, chlorthalidone

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(diuretic), lenalidomide (immunomodulator), thalidomide and pomalidomide (multiple myeloma treatment), phosmet (insecticide) and apremilast (phosphodiesterase 4 (PDE4) inhibitor) are examples of clinically used phthalimide derivatives (**Figure 1**).

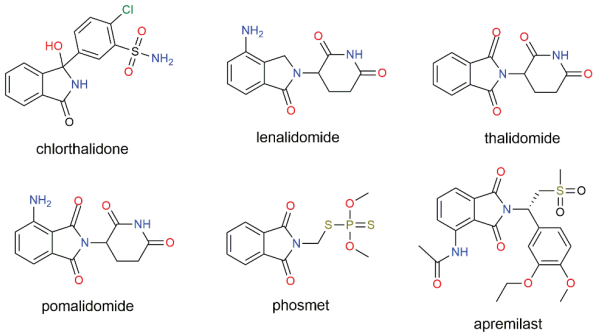


Figure 1. Clinically used phthalimide-based drugs.

Similarly, sulfonamides have been reported to show a broad pharmacological profile (Apaydın&Török, 2019; Azevedo-Barbosa, Dias, Franco, Hawkes, &Carvalho, 2020) for example, antibacterial (Nunes, Manaia, Kolvenbach, &Corvini, 2020), antifungal (Pippi et al., 2020), antiviral (Supuran, Innocenti, Mastrolorenzo, &Scozzafava, 2004), diuretics (Turza, Borodi, Miclaus, &Kacso, 2020), anticancer (Wan, Fang, Chen, Deng, & Tang, 2021), carbonic anhydrase inhibitor (Angeli et al., 2021; Hewitt et al., 2021; Petreni et al., 2021), anti-tubercular (Chen et al., 2021), antimalarial (Karpina et al., 2021), and so on. There area number of pharmacological agents that belong to different therapeutic classes derived from sulfanilamide, which is accepted as the first modern chemotherapeutic drug discovered by Domagk as an antibacterial prodrug named Prontosil (Scozzafava et al., 1999; Greenwood, 2010; Kalgutar, Jones, &Sawant, 2010). Moreover, sulfonamides are the most broadly used antibiotic class throughout the world and in clinical use since 1968 (Connor, 1998). They act as inhibitors of the dihydropteroate synthase (DHPS), which is a crucial enzyme for bacterial folic acid synthesis, resulting in the blocking of DNA replication in bacteria. Unlike bacteria, mammals are not able to synthesize their folate and must get folate from their diet, therefore the biosynthetic pathway of bacterial folate production is a selective and attractive target for antimicrobial therapy (Bermingham&Derrick, 2002; Capasso&Supuran, 2014).

To date, many sulfonamide-bearing heterocycles have been reported as strong antimicrobial agents against Gram-negative/positive, and even bacterial strains and fungus which developed multidrug resistance (Sayed, Kamal El-Dean, Ahmed, &Hassanien, 2018; Verma et al., 2020). In this work, to take advantage of both structures, sulfonamide, and phthalimide, we investigated the antibacterial activity of a series of sulfonamide compounds incorporating *ortho*-benzenedisulfonimid moieties (**1**-**6**) which were previously synthesized and evaluated as carbonic anhydrase inhibitors (CAIs) by Güzel-Akdemir and co-workers (**Figure 2**) (Güzel-Akdemir, Akdemir, Isik, Vullo, &Supuran, 2013). In our efforts to discover new potent antimicrobial agents, here we report that six compounds were assayed against a panel of seven bacteria and three fungi. MIC values of the molecules were determined and their antimicrobial profiles were discussed.

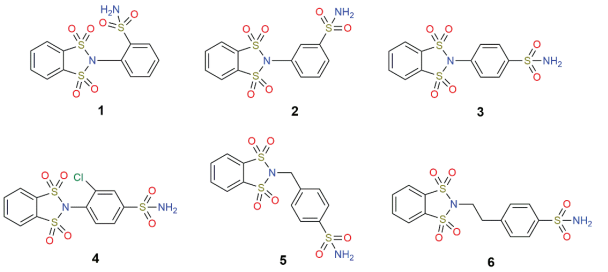


Figure 2. Potent antimicrobial *o*-benzenedisulfonimido-sulfonamide derivatives **(1-6).**

MATERIAL AND METHODS

Chemistry

Commercial sources of chemicals used and properties of utilized devices for characterization and analyzing of compounds were reported in work previously published work by Güzel-Akdemir's group (Güzel-Akdemir et al., 2013).

Synthesis of o-benzenedisulfonimide derivatives (1–6)

A solution of *o*-benzenedisulfonyl chloride in 20 mL of dry dichloromethane (CH_2Cl_2) was prepared and added to a mixture of a substituted benzenesulfonamide derivative in 25 mL of dichloromethane (CH_2Cl_2) including 1.0 mL of Et_3N in 60 min. (see **Scheme 1**). Then, the mixing process was continued at room temperature overnight. The obtained crude product was washed first with aqueous HCl, 5% $NaHCO_3$, and then water, and after that dried with anhydrous $MgSO_4$. The yielded mixture was filtrated and the excess solvent was evaporated, recrystallized from EtOH. (Güzel-Akdemir et al., 2013).

Antimicrobial activity studies

Antibacterial activity of six molecules were studied *in vitro* with microbroth dilution method against *Staphylococcus aureus* ATCC 29213 (meticillin susceptible *Staphylococcus aureus*, MSSA), *Enterococcus facealis* ATCC 29212, *Escherichia coli* ATCC 25922, *Klebsiella pneumonia* ATCC 4352, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus epidermidis* ATCC 12228 and *Proteus mirabilis* ATCC 14153. Antifungal activity was assayed *in vitro* against *Candida albicans* ATCC 10231, *Candida parapsilosis* ATCC 22019 and *Candida tropicalis* ATCC 750. The evaluation of antibacterial and antifungal activity was done using microbroth dilution method according to CLSI (Clinical Laboratory Standards Institute) guidance (CLSI 2000, CLSI 2006). As a test medium, for bacteria a Mueller-Hinton broth, and for yeast a Roswell Park Memorial Institute (RPMI-1640) medium were used. Serial two-fold dilutions were prepared beginning from 5000 to 4.9 µg/ml in the medium. The inoculum was produced utilizing a 4-6 h broth culture of each bacteria type, and 24 h culture of yeast strains set to a turbidity equivalent to 0.5 McFarland standard, diluted in broth medium to obtain an eventual concentration of 5 x 10^5cfu/ml for bacteria, and 5 x 10^5cfu/ml for yeast in the test plate. To prevent evaporation, plates were protected with plastic bags. Incubation of trays including Mueller-Hinton broth was performed at 35°C for 18-20 h and for the trays including RPMI-1640 medium at 35°C for 46–50 h. In addition, dimethyl sulfoxide (DMSO), used as a solvent in our experiments, was measured against each test strain for its antibacterial or antifungal effects.

Antibacterial or antifungal activity was taken into account in the evaluation of these results .MICs of the newly synthesized compounds were determined. The MIC was described as the lowest concentration of compound which gives the total inhibition of visible growth.

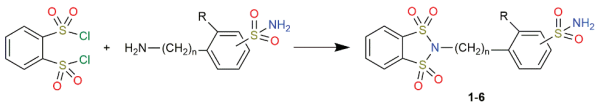
RESULTS AND DISCUSSION

Chemistry

As outlined in **Scheme 1**, the reaction of *o*-benzendisulfonyl chloride with suitable aminosulfonamides yielded various benzenesulfonamides (*-ortho*, *-meta* and *-para* substituted derivatives) with alkyl chains of different lengths between the benzenesulfonamide and the *ortho*-benzenedisulfonamide structures. The structures and characterization of previously synthesized compounds **1**-**6** were confirmed by analytical and spectral data (Güzel-Akdemir et al., 2013).

Antimicrobial activity

Our six-membered small collection of *o*-benzenedisulfonimido-sulfonamides was evaluated for their antibacterial and antifungal potency against members of Gram-negative/positive bacteria, and *Candida spp.*, as outlined in **Table 1**. As reference antimicrobials, ciprofloxacin for antibacterial assays, and fluconazole for antifungal assays were studied. Also, it is founded that reference antimicrobials MIC values were within the CLSI quality control limits. All tested compounds showed antibacterial or antifungal activity in a broad range of MIC values (**Table 1**).Compound **2**, especially, showed better activity against tested bacteria, and fungal strains. These results suggest that compound **2** might be a better therapeutic investigation option among others. But the obtained MIC values of the compounds are still fairly high, so further studies are needed.



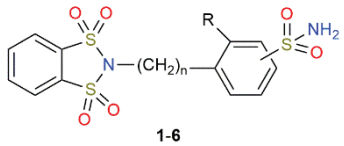
Scheme 1. General synthesis pathway of *o*-benzenedisulfonimido-sulfonamide derivatives **(1-6)**.

Among the tested derivatives, compound **2** with *–meta* sulfonamide moiety at phenyl ring and no additional alkyl chain between linked to *o*-benzenedisulfonimid structure showed the best antimicrobial activity. Particularly, compound **2** had the lowest MIC values against the bacterial strains *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and fungal strain *C. tropicalis* ATCC 750. Compared to the *-ortho* and *-para* analogs of **2**, namely compound **1** and **3**, the *-meta* sulfonamide substitution seems to be beneficial for antimicrobial activity. The remaining derivatives **4**, **5**, and **6** showed a similar antimicrobial potency against tested strains with each other and compounds **1** and **3**. Accordingly, an additional alkyl chain as a linker or a chlorine substitution at phenyl ring made no remarkable changes for the MIC values of the aforementioned compounds. But the chlorine substitution at phenyl ring (compound **4**) has improved the antibacterial activity a little against the *S. aureus* ATCC 29213.

CONCLUSION

In summary, we investigated the potential antimicrobial activity of previously synthesized six *o*-benzenedisulfonimido-sul-

Table 1. Antimicrobial activities of compounds 1-6.



1: n= 0, R= H, *o*-SO_2NH_2 **4:** n= 0, R= Cl, *p*-SO_2NH_2
2: n= 0, R= H, *m*-SO_2NH_2 **5:** n= 1, R= H, *p*-SO_2NH_2
3: n= 0, R= H, *p*-SO_2NH_2 **6:** n= 1, R= H, *p*-SO_2NH_2

		Compounds and MIC[a] value µg/ml						
		1	**2**	**3**	**4**	**5**	**6**	**Reference antimicrobials**
Microorganisms	*S. aureus* ATCC 29213	625	312.5	2500	625	1250	1250	0.25 (Ciprofloxacin)
	E. faecalis ATCC 29212	1250	625	2500	1250	1250	1250	0.5 (Ciprofloxacin)
	E. coli ATCC 25922	1250	1250	2500	1250	1250	1250	0.125 (Ciprofloxacin)
	K. pneumoniae ATCC 4352	1250	1250	2500	1250	1250	1250	0.5 (Ciprofloxacin)
	P. aeruginosa ATCC 27853	1250	1250	2500	1250	1250	1250	0.5 (Ciprofloxacin)
	S. epidermidis ATCC 12228	1250	1250	2500	1250	1250	1250	0.125 (Ciprofloxacin)
	P. mirabilis ATCC 14153	1250	1250	2500	1250	1250	1250	0.5 (Ciprofloxacin)
	C. albicans ATCC 10231	625	625	1250	625	625	625	0.5 (Fluconazole)
	C. parapsilosis ATCC 22019	1250	625	2500	625	1250	1250	0.5 (Fluconazole)
	C. tropicalis ATCC 750	1250	625	2500	1250	1250	1250	1.0 (Fluconazole)

[a] MIC: Minimum inhibitory concentration of the compounds required to suppress a visible growth

fonamide derivatives against ten different bacterial and fungal strains with *in vitro* assays. For all the tested compounds, antibacterial and antifungal activities were obtained and compound **2** with *-meta* sulfonamide substitution without an alkyl spacer between two main structures of molecule showed more promising antimicrobial activity. It is possible to develop more effective antimicrobial candidates by using *o*-benzenedisulfonimido-sulfonamides in different substitution patterns as a key structure, and it is also a prospective idea that further *in vitro* tests may be performed to investigate their potential against different microorganisms.

Peer-review: Externally peer-reviewed.

Informed Consent: Written consent was obtained from the participants.

Author Contributions: Conception/Design of Study- Ö.G.A., K.D.Y., F.N.Y., B.Ö.Ç.; Data Acquisition- Ö.G.A., K.D.Y., F.N.Y., B.Ö.Ç.; Data Analysis/Interpretation- Ö.G.A., K.D.Y.; Drafting Manuscript- Ö.G.A., K.D.Y., G.Y.;Critical Revision of Manuscript- Ö.G.A., K.D.Y., F.N.Y., B.Ö.Ç.; Final Approval and Accountability- Ö.G.A., K.D.Y., F.N.Y., B.Ö.Ç.

Conflict of Interest: The authors have no conflict of interest to declare

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