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Antimicrobial activity evaluation of *N*-(aryl/heteroaryl)-2-chlorobenzenesulfonamide derivatives

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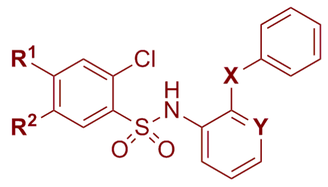
INTRODUCTION

Antibiotic resistance is currently a global problem of modern civilization. Microorganisms become resistant to drugs through acquired mechanisms. Six pathogens are responsible for the majority of deaths: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Growing drug resistance makes basic antibiotic therapy ineffective and increases the costs of polytherapy [1]. In recent years, there has been increasing interest in organic compounds that contain an aryl or a heteroarylsulfonamide group in their structure, which are characterized not only by anticancer activity but also by antimicrobial activity [2]. The presented studies follow the trend of searching for new hybrid molecules resulting from the combination of different pharmacophores with interesting biological profiles.

RESULTS & DISCUSSION

The antibacterial activity of compounds (**4 – 21**), which was found to show interesting antitumor activity [3], was performed using the micromethod of serial dilutions in broth (**Figure 1**).



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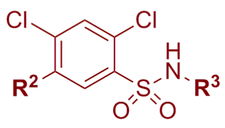


16 - 21

Compd	R^1	R^2	X	Y
4	Cl	CH_3	O	CH
5	Cl	CH_3	O	N
6	Cl	CH_3	NH	CH
7	Cl	CH_3	NH	N
8	Cl	CH_3	S	CH
9	Cl	CH_3	S	N
10	Cl	H	O	CH
11	Cl	H	NH	N
12	Cl	H	S	CH
13	Cl	H	S	N
14	H	Cl	NH	CH
15	H	Cl	NH	N

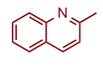
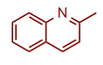
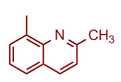
Compd	R^2	R^3
16	CH_3	
17	CH_3	
18	CH_3	
19	H	
20	H	
21	H	

Figure 1. Structures of *N*-substituted 2,4-dichloro or 2,5-dichlorobenzenesulfonamides **4–21**.

Two strains of bacteria were used for preliminary tests: one Gram-positive and one Gram-negative. Among the studied compounds only compound **16** showed activity against *Staphylococcus aureus* ATCC 6538 (MIC = 8 µg/mL), while the activity of the tested compounds against *Escherichia coli* ATCC 8739 was MIC > 128 µg/mL. Further studies were conducted on a broader spectrum of Gram-positive microorganisms: *S. aureus* ATCC43300 MRSA, *S. epidermidis* ATCC14990, *Enterococcus faecalis* ATCC 51299, *B. subtilis* ATCC 6633, *Corynebacterium diphtheriae* ZMF, 7 clinical strains of MRSA and yeast *Candida albicans* ATCC 10231. Ampicillin was used as the standard for bacteria, while for yeast, ketoconazole.

The tested compound (**16**) showed activity against the standard bacterial strains *S. epidermidis* ATCC14990 (MIC = 2 µg/mL), *S. aureus* ATCC43300 MRSA (MIC = 0.5 µg/mL), MRSA clinical strains (MIC from 1 to 4 µg/mL). For the remaining strains, the MIC value was outside the tested concentration range. The compound did not demonstrate bactericidal activity in the tested concentration range.

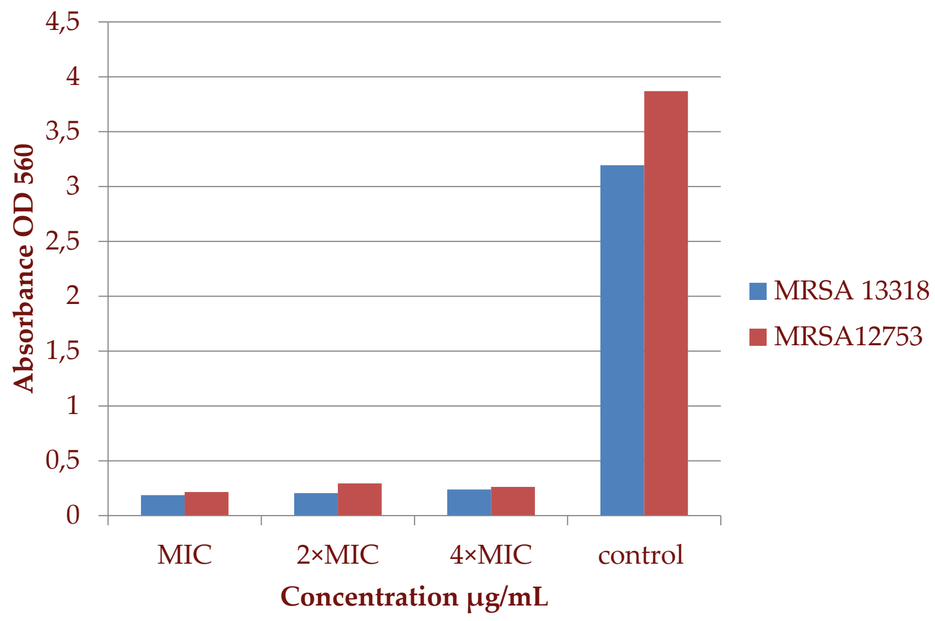


Figure 2. Effect of compound **16** on biofilm formation by MRSA strains.

Based on the obtained results, the effect of compound **16** on the bacterial biofilm formation by selected MRSA strains was assessed. The compound was tested at MIC, 2xMIC and 4xMIC concentrations. The formation of biofilm by selected MRSA strains was inhibited by 92 – 94% compared to the control (**Figure 2**). The tested compound shows bacteriostatic properties and may affect *quorum sensing* phenomenon in biofilm formation process.

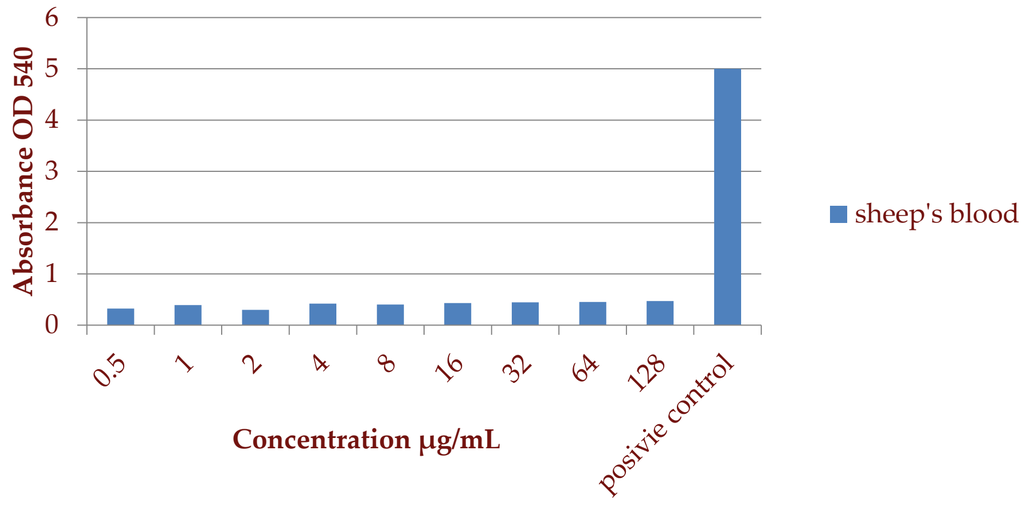


Figure 3. Haemolysis sheep blood under the influence of compound **16**.

The hemolytic activity of compound **16** against sheep blood was assessed in the range from 0.5 to 128 µg/mL (**Figure 3**). At the tested concentrations, the hemolytic activity was shown at the level of 6.5 – 9.4% compared to the positive control (1% triton- x100). The obtained results require further pharmacokinetic, bioavailability and mechanism of action studies.

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