New 3-(3-benzenesulfonylguanidinyl)thiourea derivatives with activity against methicillin-resistant *Staphylococcus* spp.

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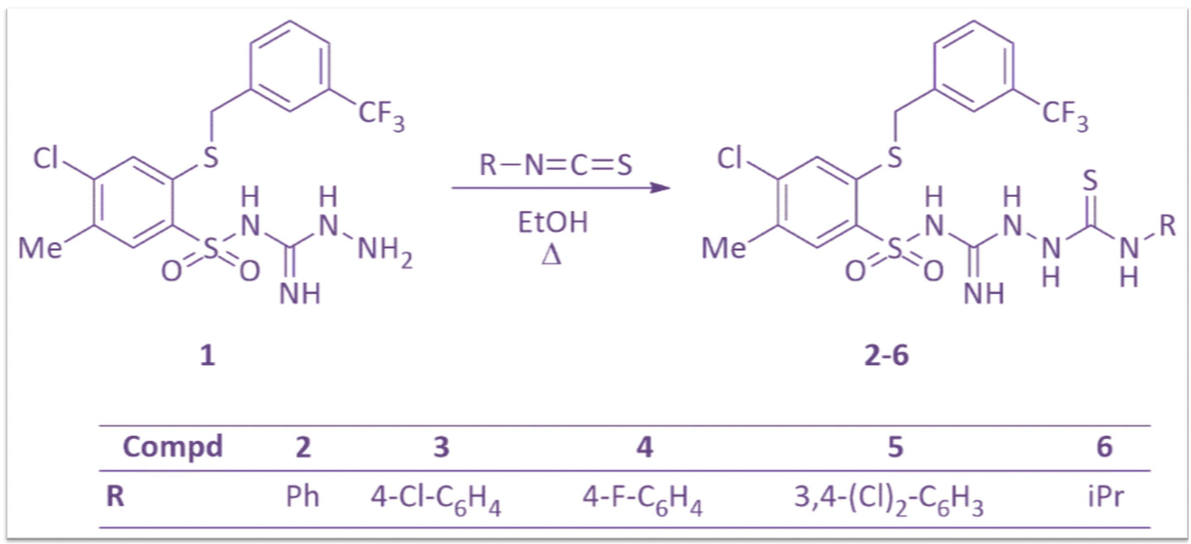
Introduction

Methicilin-resistant staph, especially MRSA, has become major problems of modern epidemiology and chemotherapy. One of the methods of combating the growing resistance of bacterial strains is the search for new antibacterial agents. The numerous studies prove that the novel class of promising compounds with activity against *Staphylococcus spp.*, including MRSA, comprises derivatives with thiosemicarbazide fragment [1-2]. This encourages us to the incorporation of the mentioned structural element to the benzenesulfonamide skeleton. As a result, a series of new 3-(3-benzenesulfonylguanidinyl) thiourea derivatives were synthesized.

Synthesis

The designed compounds **2-6** were obtained by nucleophilic addition of *N*-amino-*N'*-{4-chloro-5-methyl-2-[(3-trifluoromethylphenyl)methylthio]benzenesulfonyl} guanidine with appropriate isothiocyanates with variable R substituents. The reaction was carried out in boiling ethanol under reflux, with stirring for 1.5 – 72h. The final compounds were isolated by filtration and further crystallization. The identity of the products was confirmed by spectroscopic methods – infrared spectroscopy and proton nuclear magnetic resonance.



Compd	2	3	4	5	6
R	Ph	4-Cl-C_6H_4	4-F-C_6H_4	3,4-$(Cl)_2$-C_6H_3	iPr

Antibacterial activity

The synthesized compounds **2-6** were tested for antibacterial activity against *Staphylococcus aureus*, methicilin-resistant *S. aureus* (MRSA), *Staphylococcus epidermidis*, methicilin-resistant *S. epidermidis* (MRSE), *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The studies were carried out using the micro-dilution method, with 11 different concentration of compounds in the range from 0.0975 µg/ml to 100 µg/ml. The results were expressed as MIC (minimal inhibitory concentration, the lowest concentration of compound which prevents visible growth of bacteria) and MBC (minimal bactericidal concentration, the lowest concentration of compound that results in bacterial death) values. The obtained data showed that the derivatives **2-6** did not inhibit the growth of Gram-negative bacteria whereas their activity against Gram-positive strains was remarkable.

Compd	*S. aureus*		MRSA		*S. epidermidis*		MRSE	
	MIC [µg/ml]	MBC [µg/ml]	MIC [µg/ml]	MBC [µg/ml]	MIC [µg/ml]	MBC [µg/ml]	MIC [µg/ml]	MBC [µg/ml]
2	6.25	12.5	>100	>100	12.5	25	>100	>100
3	3.125	6.25	3.125	>100	1.56	3.125	>100	>100
4	3.125	6.25	>100	>100	6.25	12.5	>100	>100
5	3.125	6.25	3.125	3.125	3.125	6.25	3.125	6.25
6	6.25	12.5	>100	>100	6.25	12.5	>100	>100

The best antibacterial activity was noticed for compound **5** (R = 3,4-$(Cl)_2C_6H_3$) which inhibited growth of all tested Staphylococcus strains and displayed bactericidal effect (MIC = 3.125 µg/ml, MBC in the range of 3.125 – 6.25 µg/ml). Derivative **3** (R = 4-Cl-C_6H_4) showed potency similar to that of **5** against non-methicilin resistant staph (MIC = 3.125 µg/ml, MBC = 6.25 µg/ml against *S. aureus*, MIC = 1.56 µg/ml, MBC = 3.125 µg/ml against *S. epidermidis*), however it did not affect MRSE and its effect against MRSA was only bacteriostatic.

REFERENCES: [1] Kowalczyk A. et al. *J. Mol. Sci.* **22** (2021) 3881; [2] El-Sharief M.A.M.Sh.et al. *Eur. J. Med. Chem.* **67** (2013) 263.

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