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Antimicrobial activity of new benzazolyl *N*-sulfonyl amidines

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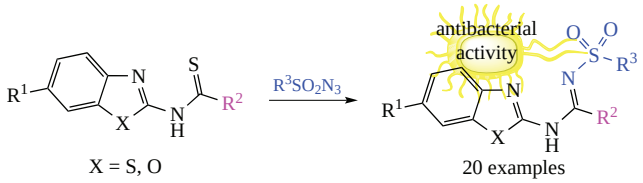
The reactions of *N*-(benz[*d*]oxazol-2-yl)- or *N*-(benzo[*d*]-thiazol-2-yl)-substituted carbothioamides with sulfonyl azides proceed as replacement of thioxo substituent by the sulfonylimino group to afford the corresponding *N′*-sulfonylated amidines. Acetic acid thioamides react smoothly upon boiling in ethanol, while for thioamides of trifluoroacetic and benzoic acids heating to 80–90 °C was required. Among hybrid molecules thus prepared, bacteriostatic-, bactericidal- and fungistatic-active against *S. aureus* and *C. albicans* representatives were found.



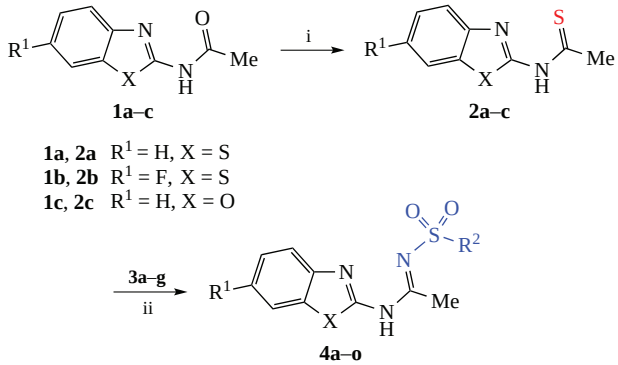
Keywords: thioamides, sulfonamides, amidines, benzoxazole, benzothiazole, cycloaddition, antimicrobial activity.

Various benzothiazole derivatives exhibit antitumor[1] and antibacterial activity against gram-positive and gram-negative bacteria.[2] Benzoxazoles are structural isosters of the nitrogenous bases of adenine and guanine, which allows them to easily interact with biological receptors.[3] On the other hand, *N*-sulfonyl amidines as a new chemotype of organic compounds inhibit cell differentiation and destroy bone tissue, and exhibit antiresorptive activity,[4] inhibit the transport of dopamin[5] and casein kinase.[6]

Hybrid molecules containing simultaneously benzoxazole or benzothiazole moieties and an *N*-sulfonyl amidine group are not described. However, the combination of these bioactive residues can change the spectrum of their action and lead to substances that exhibit different types of activity. Therefore, the synthesis of such compounds is of interest in terms of searching for new biologically active substances in this series.

Among the known methods for the synthesis of *N*-sulfonyl amidines,[7] we focused on the recently elaborated method based on reaction of thioamides with sulfonyl azides. It was previously used for the preparation of methylene active[5,8] and hetero-aromatic[9] sulfonyl amidines, as well as sulfonyl amidines containing a fragment of 2-aminobenzimidazole.[6]

In this study, we have employed the reaction of thioamides with azides for the synthesis of novel biologically active compounds containing benzoxazole and benzothiazole fragments and the sulfonylamidine function (Scheme 1). Starting thioamides **2** were synthesized by a two-step method from aminobenzazoles and the corresponding acylation reagent (acetyl chloride, trifluoroacetic anhydride or benzoyl chloride) with subsequent thionation of formed amides **1** with the Lawesson's reagent.[10] By varying the solvent type, temperature, and reagent ratio using thioamides **2a**,**c** and sulfonyl azide **3b** as the model compounds, we determined the optimal process conditions, namely, boiling in ethanol the thioamide/azide mixture in 1 : 2 molar ratio (for experimental details, see Online Supplementary Materials). Under these conditions, a series of



Scheme 1 *Reagents and conditions*: i, Lawesson's reagent (0.55 equiv.), 1,4-dioxane, reflux, 10–21 h; ii, **3a–g** (2 equiv.), EtOH, reflux, 2–21 h.

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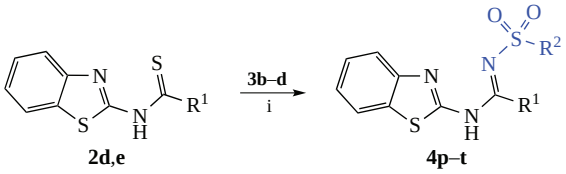
new sulfonyl amidines **4a**–**o** was obtained from thioamides **2a**–**c** and sulfonylazides **3a**–**g** (see Scheme 1).†

Contrary to thioamides **2a**–**c**, their analogues **2d**,**e** bearing either trifluoromethyl or phenyl substituents at the $C(S)NH_2$ group did not react with sulfonyl azides under the above conditions. We found that the desired reaction could be promoted by heating neat reactants at 80–90 °C to afford *N*-sulfonyl amidines **4p**–**t** in 55–68% yields (Scheme 2).‡

The structure of *N*-sulfonyl amidines **4a**–**t** was confirmed by ^1H and ^{13}C NMR spectroscopy, including 2D HMBC and HSQC experiments, and by mass spectrometry. In mass spectra of the electron impact of all compounds, there was a peak for the molecular ion. In the ^1H NMR spectra of compounds **4a**–**o**, the signals for the Me protons at the amidine C atom appeared in the region of 2.56–2.82 ppm, and all the spectra contained the required number of signals of aromatic protons. In the spectra of amidines **4a**–**o**,**s**,**t**, there were signals for NH protons at 11.85–12.90 ppm. In the ^{13}C NMR spectra of all compounds **4**, the diagnostic signals for the amidine carbon were observed at 162.5–166.1 ppm (**4a**–**o**,**s**,**t**) and 150.7 ppm (**4p**–**r**). Existence of *N*-sulfonyl amidines in tautomeric form bearing NH group was proved by ^1H–^{15}N 2D HSQC spectra earlier.[5]

The proposed mechanism for the formation of target compounds **4** includes the 1,3-dipolar cycloaddition of the C=S bond of thioamides **2** to the azide group of sulfonyl azides **3**, accompanied by the release of molecular nitrogen and elemental sulfur from the initially formed 1,2,3,4-thiatriazoline, which was established previously.[8] The observed deceleration of the reaction by the introduction of an electron-acceptor substituent into a thioamide molecule is in agreement with the reaction of a cycloaddition with inverse electronic demand.

Seven synthesized amidines **4d**,**f**,**h**,**j**,**m**,**n**,**t** were tested for antimicrobial activity. Using the Gen5 software, the dependence of optical density indicators on the growth of bacterial and yeast cells was determined in different concentrations of chemical compounds. The analysis of the obtained data showed that five of these compounds exhibit antimicrobial activity against *S. aureus* and yeast fungi *C. albicans*. At the same time, all



2d,**e**

d $R^1 = CF_3$
e R^1 = Ph

4p–t

p $R^1 = CF_3$, R^2 = Ph, 65%
q $R^1 = CF_3$, R^2 = 4-MeC_6H_4, 55%
r $R^1 = CF_3$, R^2 = 4-FC_6H_4, 55%
s $R^1 = R^2$ = Ph, 60%
t R^1 = Ph, R^2 = 4-MeC_6H_4, 68%

Scheme 2 *Reagents and conditions*: i, **3b**–**d** (2 equiv.), neat, 80–90 °C, 9–17 h.

† *General method for the synthesis of* N′*-sulfonyl amidines* **4a**–**o**. A solution of the corresponding thioamide **2a**–**c** (1.0 mmol, 1.0 equiv.) and sulfonyl azide **3a**–**g** (2.0 mmol, 2.0 equiv.) in anhydrous ethanol (4 ml) was refluxed for 9–21 h. The reaction mixture was cooled, the formed precipitate was collected by filtration and crystallized from ethanol. For compound characterization, see Online Supplementary Materials.

‡ *General method for the synthesis of* N′*-sulfonyl amidines* **4p**–**t**. A mixture of the corresponding thioamide **2d**,**e** (1.0 mmol, 1.0 equiv.) and sulfonyl azide **3b**–**d** (2.0 mmol, 2.0 equiv.) was heated at 80–90 °C in an oil bath for 9–17 h. The reaction mixture was cooled, and small amount of ethanol was added. The formed precipitate was filtered off and crystallized from ethanol. For compound characterization, see Online Supplementary Materials.

Table 1 Antimicrobial activity of amidines **4d**,**f**,**h**,**j**,**m**,**n**,**t**.

Entry	Amidine	Antimicrobial activity/μg ml^{-1}					
		S. aureus		*E. coli*		*C. albicans*	
		MIC[a]	MBC[b]	MIC	MBC	MIC	MBC
1	**4d**	7.8	500.0	–	–	15.6	–
2	**4f**	2.0	500.0	–	–	2.0	–
3	**4h**	–	–	–	–	–	–
4	**4j**	2.0	1000.0	–	–	3.9	–
5	**4m**	1.0	500.0	–	–	2.0	–
6	**4n**	2.0	–	–	–	7.8	–
7	**4t**	–	–	–	–	–	–
8	dioxidine[c]	62.5	1000	3.9	62.5	–	–
9	fluconazole[c]	–	–	–	–	6.25	12.5
10	culture control	+++	+++	+++	+++	+++	+++

[a] Minimal inhibitory concentration. [b] Minimal bactericidal concentration; '–' is the absence of antimicrobial activity in the studied concentrations; '+++' is the growth of microorganisms. [c] The antimicrobial effect of the studied compounds was compared with that of dioxidine[11] and fluconazole.[12]

compounds are not active against gram-negative bacteria *E. coli* (Table 1).

Compound **4d** inhibits the growth of *S. aureus* at a concentration of 7.8 μg ml^{-1}, and the death of culture comes from exposure to the substance at a concentration of 500.0 μg ml^{-1}, its fungistatic effect is observed at a concentration of 15.6 μg ml^{-1}. Compounds **4f**,**j**,**n** have a high inhibition activity and inhibit the growth of *S. aureus* at a concentration of 2.0 μg ml^{-1}, the bactericidal effect of compound **4j** is manifested at a concentration of 1000.0 μg ml^{-1}, and compound **4f** at a concentration of 500.0 μg ml^{-1}. Compounds **4f**,**j**,**n** have a fungistatic effect in the range of concentrations of 2.0–7.8 μg ml^{-1} against *C. albicans*. More pronounced bacteriostatic, bactericidal and fungistatic action is exhibited by compound **4m**: at a concentration of 1.0 μg ml^{-1}, bactericidal action at 500.0 μg ml^{-1}, and fungistatic action at a concentration of 2.0 μg ml^{-1} against the yeast *C. albicans*. Thus, compound **4m** can be considered as a leader, which will be the object of further studies.

In summary, the synthetic methodology based on the reaction of thioamides with sulfonyl azides was successfully used to obtain hybrids of benzoxazole(thiazole) and *N*-sulfonyl amidine with good yields. A number of sulfonyl azides, including mesyl azide and arylsulfonyl azides with electron-donating (Me, MeO) and electron-withdrawing (F, NO_2, benzo[*c*][1,2,5]thiazol-4-yl) substituents reacted smoothly with benzazolyl thioamides to form the target compounds. Antimicrobial activity tests showed that most of the compounds possessed bacterio- and fungistatic activity, and compound **4m** bearing a fluorophenylsulfonyl substituent at the amidine fragment demonstrated the highest bacteriostatic, fungistatic and bactericidal activity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.019.

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