FEATURES OF ALIPHATIC ALDEHYDES APPLYING IN THREE-COMPONENT INTERACTION WITH ACTIVE METHYLENE NITRILES AND 1-ETHYL-1*H*-2,1-BENZOTHIAZIN-4(3*H*)-ONE 2,2-DIOXIDE

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Introduction. 2-Amino-4*H*-pyran core is a structural motif of well-known biologically active compounds. The most straightforward route to this heterocyclic system is a three-component interaction of enol-nucleophiles with carbonyl compounds and active methylene nitriles. Various types of carbonyls were applied in this reaction, among which (*het*)arenecarbaldehydes and isatins are the most common one. Unlike these, aliphatic aldehydes have been studied poorly and rarely occurred in the literature as a possible component of such interactions. 1-R-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxides being utilized in the reaction allow to fuse 2-amino-4*H*-pyran core with another known pharmacophore – 1*H*-2,1-benzothiazine 2,2-dioxide. We suspected that such combination might lead to increase of certain kinds of biological activity, for instance, antimicrobial. This is due to the numbers of 2-amino-4*H*-pyrans and 1*H*-2,1-benzothiazine 2,2-dioxides proved to be highly efficient antimicrobial agents.

Aim. Our research was focused on the scope and limitations of three-component 2-amino-4*H*-pyrans synthesis based on the aliphatic aldehydes, 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide and active methylene nitriles and also on the confirmation of the synthesized compounds structure. We were additionally inspired in evaluation of antimicrobial activity of the obtained 2-amino-4*H*-pyrans.

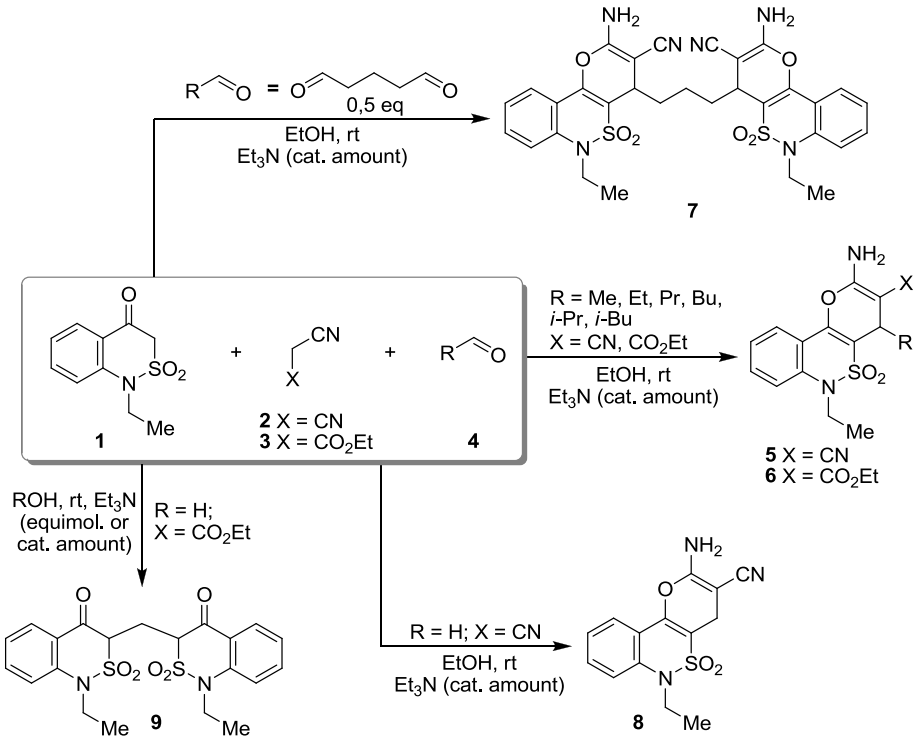
Materials and methods. We used different methods of organic synthesis as well as double serial dilution method in liquid growth medium to evaluate antimicrobial activity of synthesized compounds. We also employed ^{1}H and ^{13}C NMR spectroscopy to prove the structure of previously mentioned ones.

Results and discussion. Our investigations showed that three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide 1 with saturated aliphatic aldehydes 4 and malononitrile 2 proceeded under quite mild conditions and resulted into formation of 2-amino-6-ethyl-4-alkyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazin-3-carbonitrile 5,5-dioxides 5 in moderate to high yields. The use of formaldehyde in the reaction allows to obtain 4-unsubstituted condensed 2-amino-4*H*-pyran 8. To date, there is no information in the literature about the possible application of aliphatic dialdehydes in the discussed three-component interactions. Therefore, we decided to utilize glutaric aldehyde with the purpose of obtaining of a

new class of 2-amino-4*H*-pyran bis-derivatives in which two fragments are linked by polymethylene bridge. As the result 1,3-bis(2-amino-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-3-carbonitrile-4-yl 5,5-dioxide)propan 7 was obtained in high yield.

Replacement of malononitrile 2 with ethyl cyanoacetate 3 in the three-component reaction led to decrease of the reaction efficiency and yields of target ethyl 2-amino-4*H*-pyran-3-carboxylates 6. Thus, in the case of glutaraldehyde we were not able to obtain desired bis-derivative. When formaldehyde was introduced in three-component interaction with 1 and 3 we got the unexpected result and the isolated product was bis(1-ethyl-1*H*-2,2-dioxido-2,1-benzothiazin-4(3*H*)-on-3-yl)methane 9. Taking into account the results we obtained before in the cases of (*het*)arenecarbaldehydes it was interesting, that product 9 was obtained in dicarbonyl form though one could expect to isolate it as triethylammonium salt.

Despite of our expectations, the 2-amino-4*H*-pyrans showed a low level of antimicrobial activity. The only activity against *C. albicans* was significant for these derivatives.



Conclusion. In the course of the research we synthesized the series of 4-alkyl substituted 2-amino-3-R-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxides *via* three-component interaction of 1-ethyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide with aliphatic aldehydes and active methylene nitriles. Application of various aliphatic aldehydes as well as active methylene nitriles allows to establish certain regularities of the three-component interaction. Evaluation of antimicrobial activity of the synthesized compounds revealed their low potential to create antimicrobial drugs.