CONSTRUCTION OF NEW ANTIMICROBIAL AGENTS BASED ON THIENO[2,3-d]PYRIMIDINES

Vlasov S. V., Vlasova O. D., Severina H. I., Georgiyants V. A.
National University of Pharmacy, Kharkiv, Ukraine
pharmchem.vlasov@gmail.com

Introduction. The growing resistance of microorganisms to existing antibiotics is a big problem for modern society. Approaches to overcome this problem can be both a combination of drugs, a more rational use of antibiotics in medicine and animal husbandry on the one hand. On the other hand, it is important to study new mechanisms of antimicrobial action and search for new compounds that could affect certain bacterial processes and inhibit the growth of microorganisms in this way. One of these promising mechanisms is the inhibition of the bacterial enzyme TrmD, which is significantly different in its structure from its counterparts in humans and animals. Selective inhibitors of bacterial TrmD may be an interesting potential, especially since recent studies have allowed deciphering the structure of some of them, which may help in the development of ligand molecules. It is also known that thieno[2,3-d]pyrimidine is a promising scaffold for TrmD inhibitors.

Aim. Optimization of the search algorithm for new antimicrobial agents among thieno[2,3-*d*]pyrimidine-6-carboxylic acid amides and 6-heterylthieno[2,3-*d*]pyrimidines.

Materials and methods. Methods of organic synthesis and analysis (^{1}H, ^{13}C NMR, LC-MS), methods of antimicrobial activity research (diffusion in agar, serial dilutions), methods of molecular docking.

Results and discussion. As a result of systematic synthetic studies, effective methods for obtaining thieno[2,3-*d*]pyrimidine-6-carboxylic acids containing various substituents in positions 2 and 4 were developed. We also developed an effective procedure for obtaining of thieno[2,3-*d*]pyrimidine-4-carboxylic acids and 4-methylthieno[2,3-*d*]pyrimidine-6-carboxylic acid based on reactions catalyzed by Pd complexes. Methodics for obtaining amides of the corresponding acids using 1,1'-carbonyldiimidazole were developed, and the possibility of one-pot preparation of benzimidazole under conditions similar to amidation was also shown. The selectivity of alkylation of the obtained hybrids of thieno[2,3-*d*]pyrimidine with benzimidazole were investigated using benzyl chlorides and chloroacetamides as alkilators (DMFA-K_2CO_3 conditions). A hybrid of thieno[2,3-*d*]pyrimidine with an isoelectronic analog of benzimidazole, imidazo[1,2-*a*]pyridine was constructed. Antimicrobial activity screening and modeling of binding to the active site of TrmD isolated from *P. aeruginosa* were performed for all the obtained compounds. in many cases, a correlation was found between significant *in vitro P. aeruginosa* growth inhibition results and good docking results.

Conclusions. An effective strategy for development of new antimicrobial agents active against *P. aeruginosa* among functionalized thieno[2,3-*d*]pyrimidine derivatives and hydrides of heterocycles with this heterocyclic system was tested.