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Synthesis and antimicrobial activity of 3-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)propanamides

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Introduction. The problem of antibiotic resistance is a key topic for modern drug-discovery. Thenopyrimidine scaffold is considered as a privileged for discovery of antibacterials with diverse suggested mechanism of action starting from bacterial TrmD and N-acetyltransferases to dihydropteroate synthase inhibition. All these mechanisms are promising in tackling of antibiotic resistance. Modification of thienopyrimidine core with the propanoic acid fragment is simple and conveniently produces the series of amides. In this case modification of amide fragment is a flexible instrument for modification of the molecular parameters (e.g. solubility, lipophilicity etc.). We decided to synthesize the series of 3-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)propanamides and to test their antimicrobial activity against the standard bacterial strains and a strain of *C. albicans*.

Materials and methods. All the solvents and commercially available reagents including chromatography grades we obtained from Enamine Ltd. and used without additional purification. Methods of organic synthesis and analysis of organic compounds like ^{1}H and ^{13}C NMR spectroscopy, LC-MS were used. According to the WHO recommendations reference strains from the American Type Culture Collection (ATCC) were used as test organisms, including the Gram-positive (*S.aureus* ATCC 25923, *B. subtilis* ATCC 6633) and Gram-negative (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853) microorganisms. The antifungal activity was studied against *Candida* spp. fungi (*C. albicans* ATCC 885-653). Antibacterial and antifungal studies were performed by Dr. Tatyana P. Osolodchenko, PhD in Biology and her colleagues from Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine (Kharkiv).

Results and discussion. We used the readily available 3-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)propanoic acid, which was prepared in two step procedure as the starting compound for further amide coupling promoted by CDI. The reaction with the esters of glycine, beta-alanine and imide of glutamic acid was carried out smoothly under these conditions. We also managed to use tryptamine as the amine component. The developed work-up is very simply and requires just removal of the solvent and treatment with water for isolation of the most of the products. All of the synthesized compounds showed moderate antimicrobial activity against all of the test strains. The most activity was determined against *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633 strains and amide with tryptamine was identified as the most active.

Conclusions. The efficient method for preapartion of 3-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)propanamides has been developed. The isolation procedure for the final step requres only removal of the solvent and washing with water which is very beneficial and economical. The obtained amides were identified as promising antibacterials in the tests against bacterial and fungal strains. The most active compound is *N*-[2-(1*H*-indol-3-yl)ethyl]-3-(4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-yl)propanamide, which dispalyed high or at least moderate activity against all of the test-strains. Mostly the compounds of this esires were determined to be active aginst *Staphylococcus aureus* ATCC 25923 and *Bacillus subtilis* ATCC 6633 strains.