In all cases, the structure of the synthesized compounds was confirmed by the integrated use of elemental analysis, chromato-mass spectrometry, IR spectrophotometry and ^{1}H NMR spectrometry. In the analysis of chromato-mass spectra of esters of 2-((4-R-5-(5-bromothiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio) acetic acids, peaks of pseudomolecular ions were found (MH^+), m/z which correspond to the molecular weights of the studied compounds.

In the IR spectra of esters of 2-(4-(methyl, ethyl)-5-(5-bromothiophen-2-yl)-4H-1,2,4-triazol-3-ylthio) acetic acids (compounds 4-11) there are absorption bands –C=N-groups at 1633-1583 cm^{-1}, C–S-groups at 717-680 cm^{-1}, there are fluctuation bands of thiophene heterocycle in the range of 740-700 cm^{-1}, CH_2-groups at 2980-2870 cm^{-1}, absorption bands in the range of 1760-1715 cm^{-1}, which are characteristic of aliphatic esters, as well as the available absorption bands of CH_3-groups within (n_s 1340-1385 cm^{-1}, n_{as} 1475-1430 cm^{-1}). For esters of 2- (4-phenyl-5-(5-bromothiophen-2-yl)-4H-1,2,4-triazol-3-ylthio) acetic acids (compounds 12-15) are characterized by absorption bands within 1506-1496 cm^{-1}, which may indicate the presence of an aromatic radical.

Analyzing the results of spectral studies, it should be noted that in the ^{1}H NMR spectrum of methyl 2-((4-methyl-5-(5-bromothiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio)acetate (compound 4) signals of protons of methyl substituent bound to the nucleus of 1,2,4-triazole at 3.61 (3H) in the form of a singlet, signals of protons of the methyl group in the form of a singlet at 3.72 are recorded including (3H), the proton signals of the methylene group bound to the sulfur atom as a singlet at 4.10 (2H). Thiophene nucleus signals are also available, which are recorded as 2 doublets at 7.23 ppm (1H) and 7.63 ppm (1H).

Conclusions. Esterification of the corresponding 2-((4-R-5-(5-bromothiophen-2-yl)-4H-1,2,4-triazol-3-yl)thio) acetic acids with methyl, ethyl, isopropyl and butyl alcohols in the presence of catalytic amount of concentrated sulfuric acid obtained 12 new compounds. The structure of the synthesized compounds was confirmed by the complex use of elemental analysis, chromato-mass spectrometry, IR spectrophotometry and ^{1}H NMR spectrometry. Most theoretical calculations coincide with experimental data.

DEVELOPMENT OF AN INTEGRATED APPROACH TO *IN SILICO* PREDICTION OF PROBABLE PATHWAYS OF METABOLISM OF PROMISING BIOLOGICALLY ACTIVE MOLECULES

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Introduction. Nowadays, the FDA (U.S. Food and Drug Administration) has recognized that the pharmaceutical industry faces a significant challenge to improve the successful identification of candidate molecules and avoid late-stage failures due to toxicity and bad pharmacokinetics. It is well known, the metabolic transformations of pharmaceuticals profoundly impact their bioavailability, efficacy, chronic toxicity, excretion rate and route. Both the parent molecule and the metabolites may also interfere with endogenous metabolism or the metabolism of other co-administered compounds. Drug attrition due to bad pharmacokinetics in the drug discovery process leads to high developmental costs and take extra time.

Absorption, distribution, metabolism, excretion and toxicity (ADME/Tox) properties of molecules can be assessed very economically using computational methods, thus enabling further information to be used alongside target activity at the very earliest stages of drug discovery. The high impact of drug metabolism on drug efficacy and drug fate in biological systems has given rise to numerous *in silico* approaches and tools for metabolic reaction prediction in recent decades. However, each approach implemented in separate tool has its' own limitations that cannot be ignored.

Aim. This study aims to develop an integrated approach to *in silico* prediction of probable metabolic pathways of promising biologically active molecules that can help researchers to obtain certain results with high precision using freely available online tools.

Material and methods. Five free available online services with different computational algorithms for prediction of metabolic pathways were used. These were *Biotransformer*, *GLORYx*, modules Metabolism v.1 та UGT v.1 of *Xenosite WebPredictor*, *SMARTCyp*, modules SOMP RA of *Way2Drug*. Structures of known chemicals and drugs with experimentally well-established biotransformation were involved in our study (toluene, acetaminophen, bromhexine, phenobarbital etc.). Analysis of the results obtained was carried out with the purpose to develop the special point scale that when using allows each researcher to ascertain the range of probable metabolic directions and metabolites of new drug-like compounds easily.

Results and discussion. Since each online service used has its' own computational algorithm, we tested how they predict biotransformation for well-known chemicals comparing results with experimentally proven data. As each tool has its' own mode of presentation of results, we suggested certain order of use of these program products. Taking into account, that only two of the services used visualize chemical structures of metabolites predicted (*GLORYx* and *Biotransformer*), they were chosen as the first-line tools. Representation of results as chemical formulas is an important feature for non-experts in medicinal chemistry. Analysis of the results after processing in other programs (*Xenocite*, *SmartCYP* and *Way2Drug*) demands more pieces of knowledge, understanding of laws of metabolites formation under conditions of different enzymatic reactions to be exact. That is why these services were chosen as the second-line tools.

The next important point was the development of a scale that would allow, after a comprehensive study using all five selected products, to give an answer regarding the most likely metabolic pathways and to outline the generalized scheme with a high degree of confidence. Prediction of a specific metabolite in one program gives 1 point to the overall result for a given product. The appearance of this metabolite in the results of each subsequent program also gives 1 point. All points are added up. Thus, for each probable metabolite a result from 1 to 5 points is possible. In the generalized metabolic scheme, only metabolites that have a total of more than 2 points are taken into account. This way we can exclude sporadic results associated with errors in the calculation algorithms of each separate tool. Thus, the results obtained at each subsequent stage clarify the overall picture.

Conclusion. An integrated approach to *in silico* prediction of probable metabolic pathways of promising biologically active molecules was developed. It can help researchers to obtain certain results with high precision using five freely available online tools. This approach is based on the certain order of use of program products and the special point scale that when using allows each researcher to ascertain the range of probable metabolic directions and metabolites of new drug-like compounds easily.