THE PURPOSEFUL SYNTHESIS OF ANTIULCER SUBSTANCES IN THE SERIES OF 4-(R-PHENYL)-5-PHENOXYMETHYL-3-THIO-1,2,4-TRIAZOLES (4 *H*) DERIVATIVES

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Introduction. Now gastric ulcer is one of the leading diseases in gastroenterology, because this pathology is mostly affects people most able-bodied and active-age, causing severe complications, reduced work capacity, worsening the quality of life. About 10% of people develop a peptic ulcer at some point in their life. They resulted in 301,000 deaths in 2015 down from 327,000 deaths in 1990. The growing population with diseases of the gastrointestinal tract is considered to be a problematic issue of the XXI century, which is increasingly attracting the attention of scientists and practitioners in many countries. A number of synthetic drugs are available to treat ulcers. But these drugs are expensive and produce more side effects. The ideal aims of treatment of peptic ulcer disease are to relieve pain, heal the ulcer, and delay ulcer recurrence. Based on the foregoing the research of anti-ulcer drugs is actual now. Analyzing published data we found that the 1,2,4- triazoles (4*H*) derivatives is quite promising matrix for the search of the anti-ulcer agents on its basis. Careful attention to these compounds is primarily due to their high potential as possible pharmaceutical substances.

Aim. The aim of this work was to synthesize new 4-phenyl-5-(4-R-phenoxymethyl)-1,2,4-triazole-3-ylthio-1-(R_1)-acetophenones, to prove their structure and то screen these newly synthesized compounds for anti-ulcer activity.

Material and methods. The synthesis of new 4-phenyl-5-(4-R-phenoxymethyl)-1,2,4-triazole-3-ylthio-1-(R_1)-acetophenone compounds has been carried out. The synthesis of initial 4-phenyl-5- phenoxymethyl -1,2,4-triazole- 3-thiones was carried out from the corresponding phenols. Resulting from the alkylation of ethyl chloroacetate and subsequent hydrazinolysis substituted phenoxyacetic acid hydrazides were involved into interaction with phenylisothiocyanates with vigorous stirring in ethanol. Several key types of the reactions were generally used us that allowed to obtain new started 4-phenyl-5-phenoxymethyl -1,2,4-triazole- 3-thiones. The existence of thiol-thione tautomerism is known for the compounds, and thione forms predominates according to the data of ^{1}H NMR spectroscopy. To further transformations 4-phenyl-5- phenoxymethyl -1,2,4-triazole- 3-thiones synthesized were alkylated by chloroacetophenones in a homogeneous base catalysis conditions, resulting to the compounds 4-phenyl-5-4-

(R)-phenoxymethyl-1,2,4-triazole-3-ylthio-1-(R_1)-acetophenones. Reactions were monitored by thin layer chromatography carried out using pre-coated silica gel plates.

Results and discussions. Target products have been obtained with satisfactory yields. The structures of synthesized compounds were verified on the basis of elemental analysis and ^{1}H NMR-spectroscopy. The NH group protons signal after alkylation disappears in finished compounds. The signals of aromatic protons were observed in the ranges 6.75–8.20 ppm. As shown in Table 2, the signals of both methylene groups associated with sulfur and oxygen atom are common and occur. Due to the absence of protons in their surroundings they look like singlet. The signals of methylene groups have been interpreted by us in accordance with the electronegativity of neighboring atoms so – signals at 5,28-5,29 ppm has been attributed to the presence of a group OCH_2; at 5,15-5,18 ppm – group SCH_2. Methyl groups of the *tert*-butyl residue are shown on the spectra as a single signal intensity in 9 protons at 1,20-1,25 ppm. The purity of the obtained compounds determined by TLC. Prediction of biological activity derived substances was conducted using a computer program PASS. To optimize the pharmacological screening of new compounds «drug-like» parameters have been calculated and simulation of biological properties has been done. It was established that the synthesized compounds comply with Lipinski's Rule of Five and can be recommended for experimental biological tests. Based on data PASS-prediction as priority directions for experimental trials screening for anti-ukcer and anti-helicobacter activity has been chosen. By the computer program PASS *online* we can make the presumption that all compounds of the group may exhibit high anti-ulcer (probable activity (P_a) by inhibition of histamine H_2-receptor from 0.52 to 0.69) and anti-helicobacter activities (P_a from 0.50 to 0.65).

The most perspective substances for experimental biological tests were elected.

A docking study synthesized compounds to antiulcer biotargets were carried out; was established ability to «structure-leader» to inhibit histamine H_2-receptor, enzyme microsomal prostahlandynsyntaze and the growth of the pathogen Helicobacter pylori as probable mechanisms of antiulcer action.

Conclusions The group of new 4-phenyl-5-4-(R)-phenoxymethyl-1,2,4-triazole-3-ylthio-(R_1)-acetophenones have been synthesized by alkylation of initial 4-phenyl-5- phenoxymethyl -1,2,4-triazole- 3-thiones with chloroacetophenones. The structures of the synthesized compounds have been proved by elemental analysis and ^{1}H NMR spectroscopy data. All substances for which the PASS program prognosis was carried out can show themselves as potential anti-ulcer and anti-helicobacter drugs.