ФАРМАЦЕВТИЧНА ХІМІЯ ТА ФАРМАКОГНОЗІЯ

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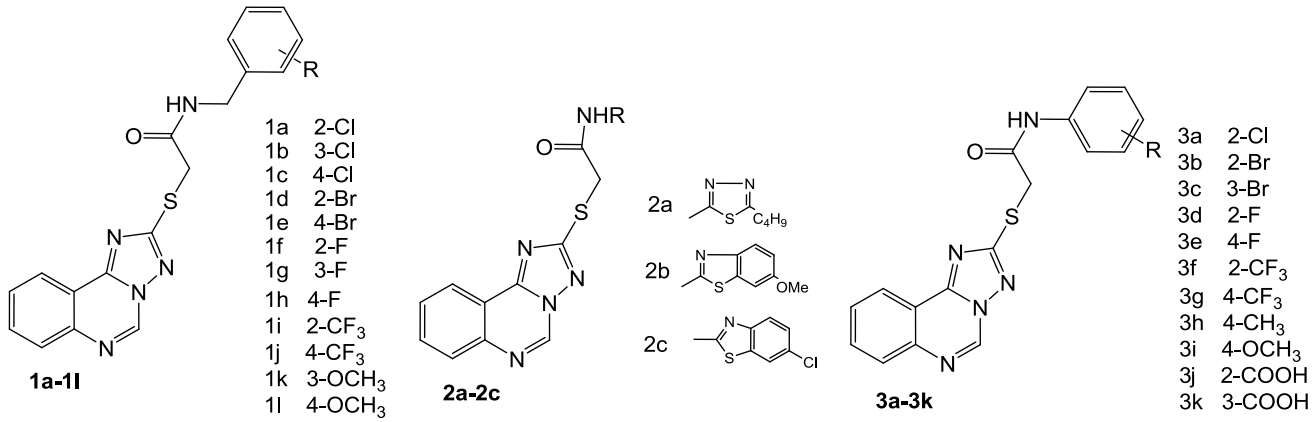
N-(PHENYL, BENZYL, HETARYL)-2-([1, 2, 4]TRIAZOLO [1,5-*C*]-QUINAZOLIN-2-YLTHIO)ACETAMIDES' MOLECULAR DOCKING STUDIES TO *ESCHERICHIA COLI* DIHYDROFOLATE REDUCTASE

Continuing the novel effective antimicrobials agents investigation among *N*-(phenyl,benzyl,hetaryl)-2-([1,2,4]triazolo [1,5-*c*]quinazolin-2-ylthio)acetamides it was decided to predict the presence of the possible antibacterial mechanism by *in silico* flexible molecular docking [1].

The corresponding new series of substances were synthesized and evaluated for structure by spectral methods (FT-IR, LC-MS, ^{1}H NMR) and elemental analysis (Picture 1).



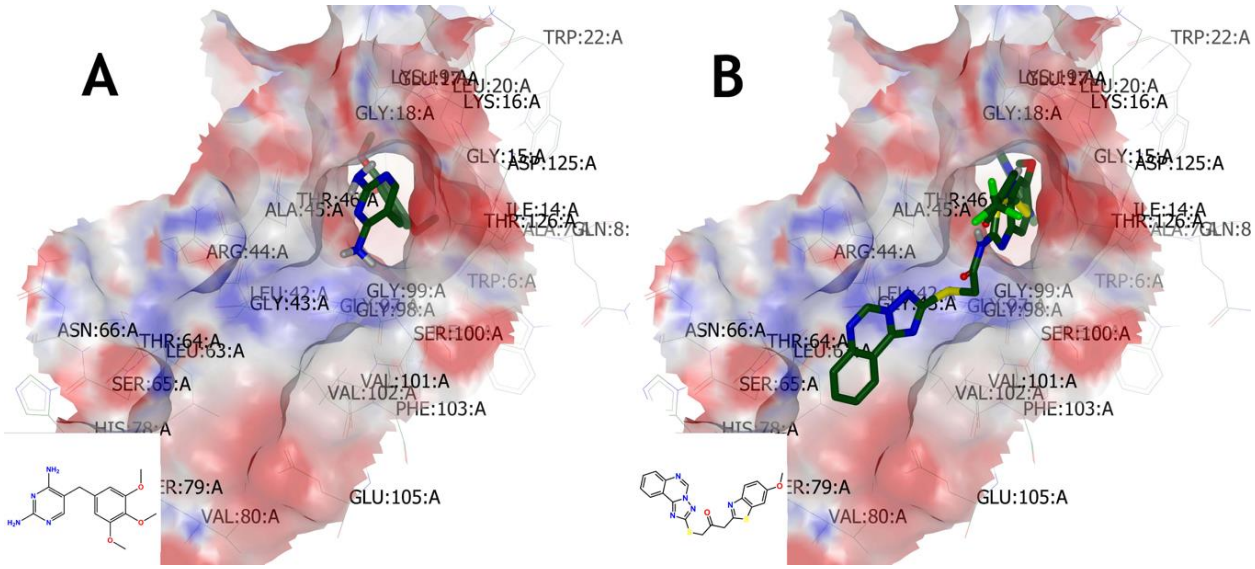
Pic. 1. Structure of the synthesized compounds

Dihydrofolate reductase (DHFR) is a classic antimicrobial drug target because it promotes the NADPH-dependent reduction of 7,8-dihydrofolate yielding 5,6,7,8-tetrahydrofolate, which is involved in

the biosynthesis of purines, thymidylate, and several amino acids [2]. Moreover investigation of hydrophobic heterocyclic dihydrophthalazines series, which were designed from antifolate drug trimethoprim, the propyl and trifluoropropyl substituents had an important role in protein stability during catalytic cycling due to flexibility – an important determinant in the fit into the inhibitor, thereby allowing it to take advantage of any available subpockets of the binding site [3].

Hence, investigation was done using the software package «OpenEye», including utilities: Fred Receptor 2.2.5, Vida 4.1.1, Flipper, Babel 3, Omega 2.4.3 and Fred 2.2.5 [4]. The crystal structure of the enzyme *E. faecalis* DHFR (4M7U.pdb) was obtained from the protein data bank and Trimetoprim was used as reference compound [3, 5]. The obtained scoring functions (Shapegauss, PLP, Chemgauss2, Chemgauss3, Chemscore, OEChemscore, Screenscore, CGO, CGT, Zapbind, Consensus Score) indicated the best possibility of the matching into the ligand-protein complex.

According to the results, practically all substances had better Consensus Scores than Trimetoprim, except of **3g**. All heterocyclic amides, namely substance **2b** had practically 5 times better affinity, than the reference, and **2a** with **2c** had a little bit worth result, but still high enough.



Pic. 2. Visual representation of a receptor-ligand interaction: active site of *E. faecalis* DHFR (4M7U.pdb) with Trimetoprim (A) and *N*-(6-methoxy-1,3-benzothiazol-2-yl)-2-([1,2,4]triazolo [1,5-*c*]quinazolin-2-ylthio) acetamide 2b (B), which has the highest Consensus Score

The visual inspection demonstrated, that substituents at the second position were flexible and rotated by the Sulfur bond and intercorporated

in the same enzyme pocket as Trimetoprim (Picture 2). Although no Hydrogen bonds were formed.

The positive influence into the affinity was made by 3-OCH_3, 2-CF_3, 2-F, 2-Cl in phenyl residue in series **1** and **3**. Interestingly, that the weakest substance **3g**, that differed from **1j** just by the absence of CH_2 fragment had negative gap of Consensus Score at 116 points.

Thus, inhibition of DHFR could be proposed as one of the possible antimicrobial activity mechanism. Nevertheless it should be proven by enzymatic studies.

References:

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