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Molecular hybrids based on 2-(3-R-1,2,4-triazol-5-yl)anilines as potential chemotherapeutic agents

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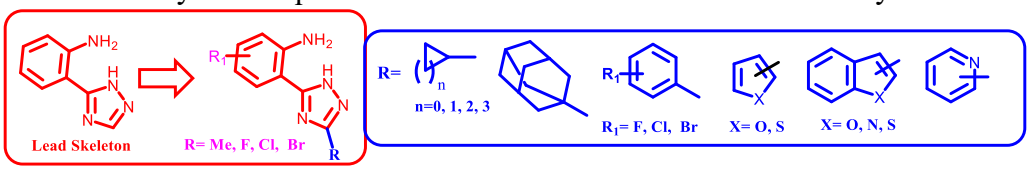
Introduction. The complexity and diversity of antibiotic resistance mechanisms remains the main factor that encourages scientists to further search for the new chemotherapeutic agents. In most of cases, the design is aimed at modifying known drugs, new “small” molecules synthesis, hybrid molecules composing, polypeptides developing, preparation of complexes with transition metals, etc [1-3]. Thus, the development of synthesis methods and evaluation of the chemotherapeutic effect of hybrid molecules created by combining of 2-(3-R-1,2,4-triazol-5-yl)anilines with molecular fragments is an urgent problem of medical chemistry.

Materials and methods. Organic synthesis, spectral methods (HPLC-MS, ^{1}H and ^{13}C NMR spectra, X-ray analysis), *in vitro* (microbiological screening, anticancer screening on 60 cancer cell lines according to NCI methodology) and *in silico* (ProTox-II, ADME analysis, SAR-, QSAR-, molecular docking) methods.

Results and discussion. The molecular docking study was performed for the combinatorial library of 2-(3-R-1,2,4-triazol-5-yl)anilines (Fig. 1) to estimate their affinity to the some enzymes (DNA gyrase (PDB ID; 2XCT); transmembrane receptor (PDB ID; 2IVU); epidermal growth factor receptor (PDB ID - 2ITY); ras-related protein Rab-9A (PDB ID: 1WMS), 50S ribosomal protein L19 (PDB ID: 6WQN), sterol 14-alpha demethylase (PDB ID: 5TZ1), etc.). The obtained satisfactory results served as a prerequisite for their synthesis. In this case, the target products were obtained by a "one-pot three-step" synthesis from 4-hydrazinoquinazoline or 2-aminobenzonitrile and carboxylic acid derivatives.



The in vitro studies confirmed the results of the docking and allowed us to identify highly active antitumor (GI_{50} 3.8-7.0 μM), antimicrobial (MIC 5.2-62.4 μM) and antifungal (MIC 30.6-200 μM) agents. The ADME analysis and the created SAR and QSAR models showed the direction of further enhancement of the chemotherapeutic effect.

Conclusions. A strategy for the search for new hybrid molecules, namely insufficiently known [2-(3-R-1*H*-[1,2,4]-triazol-5-yl)]anilines, which provided the purposeful introduction of certain structural motifs into the desired target products to enhance chemotherapeutic action, has been developed and successfully implemented. Among the obtained compounds, high active antibacterial, antifungal and antitumor agents were identified, which confirms the reasonableness of further structural modification of this class of compounds.

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