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Molecular screening of N-((5-phenyl-6,11-dihydro-5H-[1,2,4]triazolo[1′,5′:1,6]pyrido[3,4-b]indol-2-yl)methyl)-R-carboxylic acid, their esters and amides

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Introduction. Derivatives of 1,2,4-triazole and indole are considered as "privileged" structures and reliable chemical platforms for rational design of pharmacologically active molecules. Compounds with a 1,2,4-triazole fragment show a wide range of activity, including antifungal (fluconazole, itraconazole, voriconazole, posaconazole), anxiolytic/antipsychotic (alprazolam, triazolam), antitumor (anastrozole, letrozole), as well as cardio- and hepatoprotective (thiotriazoline). The indole pharmacophore is characterized by polyfunctionality with proven antifungal, antiprotozoal, antiaggregant, antialzheimer, antiparkinsonian, antioxidant, and antitumor effects, which are realized through a variety of molecular targets and mechanisms of action.
The purpose of the study was to substantiate the prospects of N-((5-phenyl-6,11-dihydro-5H-[1,2,4]triazolo[1′,5′:1,6]pyrido[3,4-b]indol-2-yl)methyl)-R-carboxylic acid, their esters and amides as candidates for new biologically active substances.
Materials and methods. Molecular docking was applied for detailed analysis of "ligand-target" interactions, localization of binding sites, and quantification of energies and spatial configurations. Ligand preparation was performed using MarvinSketch 6.3.0, HyperChem 8, and AutoDockTools 1.5.6; protein structures were prepared in Discovery Studio 4.0 and AutoDockTools 1.5.6. Calculations were performed in AutoDock Vina with comparison of binding modes and affinities, taking into account energy and steric criteria.
Results and discussion. Molecular docking of the studied series (1 acid, 5 esters, 10 amides) showed that amides of N-((5-phenyl-6,11-dihydro-5H-[1,2,4]triazolo[1′,5′:1,6]pyrido[3,4-b]indol-2-yl)methyl)-R-carboxylic acid have the highest affinity to relevant targets, forming stable complexes through hydrogen bonding and π-stacking and, accordingly, appear most promising for potential antifungal, anti-inflammatory, antioxidant, and antitumor activity. Esters showed slightly worse binding energy values, but kept the correct orientation of the pharmacophore core, which allows them to be considered as potential promising BARs. Acid, in turn, showed worse stabilization in hydrophobic pockets of protein targets. Collectively, this allows the amides to be singled out as primary leader structures for further in vitro study.
Conclusions. N-((5-phenyl-6,11-dihydro-5H-[1,2,4]triazolo[1′,5′:1,6]pyrido-[3,4-b]indol-2-yl)methyl)-R-carboxylic acid amides are a promising class of compounds for further in vitro studies of antifungal, anti-inflammatory, antioxidant and antitumor activities.

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