Міністерство охорони здоров'я України
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Матеріали X науково-практичної конференції з міжнародною участю

НАУКОВО-ТЕХНІЧНИЙ ПРОГРЕС І ОПТИМІЗАЦІЯ ТЕХНОЛОГІЧНИХ ПРОЦЕСІВ СТВОРЕННЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

присвячена пам'яті завідувача кафедри управління та економіки фармації з технологією ліків, доктора фармацевтичних наук, професора Тараса Андрійовича Грошового

17-18 жовтня 2024 року

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MOLECULAR DOCKING STUDIES OF 3*H*-THIAZOLO[4,5-*b*]PYRIDINE-2-ONE DERIVATIVES AS POTENTIAL COX-1/2 INHIBITORS

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Actuality. The development of anti-inflammatory drugs occupies an important role in the field of modern pharmacology. Cyclooxygenases (COX-1 and COX-2) are the key enzymes involved in the arachidonic acid cascade. Classical non-steroidal anti-inflammatory drugs (NSAIDs) are diverse group of compounds used for the treatment of inflammation exerting their anti-inflammatory, analgesic, and antipyretic effects through the non-selective inhibition of both COX isoforms. In the past decade fused thiazole-based derivatives became an integral part of new anti-inflammatory agents' discovery. A wide range of synthetic thiazole-bearing derivatives have been studied for their anti-inflammatory properties including COX-1/COX-2 inhibitory action [1].

The objectives. Introduction of molecular modeling methods within the computer-aided drug discovery process allows to minimize the time and costs for construction and development of new biologically active substances and may accelerate and facilitate the identification of novel COX-1/2 inhibitors among fused thiazole-scaffold bearing compounds.

Materials and methods. The objects of the precent research were three series of 37 N^3, C^5 and C^6 substituted 3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives, synthesized at Danylo Halytsky Lviv National Medical University. Probing the action mechanism of thiazolopyridines as anti-exudative agents was performed through molecular docking studies towards COX1/2. Docking, filtering and poses grouping according to the Estimated Affinity were carried out using SeeSar13.1.0 software [2].

Results. The structures of COX-1 in complex with Celecoxib (PDB entry 3KK6) and human COX-2 in complex with Rofecoxib (PDB entry 3KK6) were downloaded from Protein Data Bank. Co-crystalized ligands were extracted from the binding sites. Docking of the set of 37 ligands, Mefenamic acid and Ibuprofen as references were carried out utilizing two workflows: Standard docking and Template Docking. Visual inspection of poses and their Lipophilic Ligand efficiency (LLE) evaluation led us to choose Template docking outcomes with Ibuprofen as the template for further analysis. All poses were checked and transferred to the Analyzer Mode. Molecules were grouped by the pose of each compound with the best estimated activity. The analysis of docking results against COX-1 allowed to conclude, that all docked ligands had the proper orientation in the binding site of COX-1, most common amino acid residues of the protein

for hydrogen binding with ligands were ARG-120 and SER-530, the HYDE scores of the most active ligands exceed that ones for Celecoxib.

Docking results against COX-2 revealed that hydrogen bonds in most ligand-receptor complexes were formed between Oxygen atom of thiazole ring and TYR-355 amino acid residue. Favourable HYDE scores corresponded to Sulfur atom of thiazole ring and/or C^3 and C^5 carbons of phenyl substituent in N^3 position of fused scaffold contributions. Non-favorable contributions referred to Oxygen atom of thiazole ring. At the same time, in both docking procedures for the ligands under study their Estimated Affinity towards COX-2 was significantly lower than that one for Ibuprofen despite they were able to achieve proper orientations.

Conclusions. The number of hit compounds under study showed high Estimated Affinity, proper binding orientation and significant HYDE scores towards proposed protein targets. However, no exact correlation between experimental pharmacological activities and docking scores was found.

Acknowledgement: O. K. thanks Universidad San Pablo CEU for a Postdoctoral Contract for Ukrainian Researchers 2022-2024.

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