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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

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CURRENT TRENDS IN THE DEVELOPMENT OF POTENTIAL ANTIMICROBIAL DRUG CANDIDATES AMONG CONDENSED THIAZOLO[4,5-*b*]PYRIDINE DERIVATIVES

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Actuality. Discovery of innovative drug candidates is one of the relevant tasks of modern medical and pharmaceutical science. The thiazole core is a versatile scaffold for the development of new drugs and biologically active agents [1]. The recent publications, dealing with synthesis and pharmacological screening of thiazole-bearing heterocycles and their activity mechanisms [2-4], indicate the relevance of further drug discovery among novel derivatives of the specified chemical class.

The objectives. The precent work is devoted to the systematic study and generalization of the main trends in the field of potential antimicrobial drug candidates development of among condensed thiazolo[4,5-*b*]pyridine derivatives.

Materials and methods. The complex of general scientific methods of searching and systematizing literary references, analysis and comparison of information from various sources was used, followed by generalization of new and promising directions.

Results. Thiazolo[4,5-*b*]pyridine derivatives have been extensively evaluated as antimicrobial agents. Abd El-Mahmoud reported antimicrobial and antifungal screening for 5-amino-2-thioxo-2,3,4,7-tetrahydro-1,3-thiazolo-[4,5-*b*]pyridine-6-carbonitriles [5]. All compounds showed moderate antimicrobial activity against Staphylococcus aureus (*St*). Some compounds from this series showed moderate antimicrobial activity against Bacillus subtilis (*B.C.*) and Proteus vulgaris (*P. vulgaris*). The lead compound was highly active against Aspergillus flavus (*A. flavus*).

El-Sofany *et al*. reported *in vitro* antimicrobial and antifungal activity evaluation of novel spiro[cyclohexane-1,2'-thiazolo[4,5-*b*]pyridine derivatives [6]. SAR analysis revealed that open-chain sugar moieties introduction played a significant role in antimicrobial activity increasing. It was also shown that acetylated aldoses were less active than non-acylated ones and the activity increased by increasing the number of -OH groups rather than -OAc groups in the open-chain sugar nucleus.

Lozynsky *et al.* reported antimicrobial activity *in vitro* evaluation for 5,7-substituted 3*H*-thiazolo[4,5-*b*]pyridin-2-ones [7]. It was shown that the antibacterial effect did not depend on the substituents at C^5 and C^7 positions. The presence of amide fragment was favorable for antimicrobial potency.

Conclusions. The current trends in discovery of new active pharmaceutical ingredients among condensed thiazolo[4,5-*b*]pyridine derivatives exhibiting antimicrobial activity was based on structural modification strategy of the core condensed scaffold at C^2, C^5, C^6, and C^7 positions followed by pharmacological screening.

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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