Міністерство освіти і науки України
Навчально-науковий медичний інститут
Національного технічного Університету
«Харківський політехнічний інститут»

«АКТУАЛЬНІ ПИТАННЯ СУЧАСНОЇ МЕДИЦИНИ ТА ФАРМАЦІЇ»

Збірник тез доповідей І Міжнародної науково-практичної конференції

19–20 вересня 2024 року

Харків – 2024

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MOLECULAR DOCKING STUDIES OF 3*H*-THIAZOLO[4,5-*b*]PYRIDINE DERIVATIVES AS POTENTIAL LIPOXYGENASE INHIBITORS

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Nowadays the discovery of effective antioxidant agents among low-molecular-weight organic molecules is a recent problem that requires new methodological approaches implementation, while it is also the society relevant task [1]. Both thiazole and pyridine scaffolds are of the highest priority in modern medicinal chemistry [2, 3]. Numerous reports concerning variety biological effects possessed by thiazolopyridine derivatives have been currently published including their discovery as potent antioxidant agents [4].

One of the antioxidant action mechanisms can be exerted through the inhibition enzymes' activity which are responsible for reactive oxygen species (ROS) producing, thereby reducing oxidative stress. The objective of the precent study was

to fulfil molecular docking studies of novel 3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives towards lipoxygenase (LOX) as one of ROS-producing enzymes. LOX-5 is the enzyme that catalyses the oxidation of polyunsaturated fatty acids to form lipid hydroperoxides, which can lead to membrane damage and inflammation.

The objects of the precent research were three series of condensed 3*H*-thiazolo[4,5-*b*]pyridine derivatives, synthesized at Danylo Halytsky Lviv National Medical University [5–7]: (a) the 1st series included N^3 substituted derivatives containing phenyl, propanenitrile, propanoic acid and phenylpropanamide moieties as N^3-substituents while they comprised hydroxyl group at C^5 position; (b) the 2nd series comprised compounds incorporated substituted phenyl diazonium or alkyl substituents at C^6 position of the core scaffold; (c) the 3rd series included derivatives incorporated chloroacetate, chlorobenzoate, benzyloxybenzoate, methoxyphenyl acrylate and substituted phenyltriazolecarboxylate moieties as the substituents at C^5 position of the core scaffold (Fig.). The antioxidant activity evaluation of all tested compounds was reported as a spectrophotometric DPPH assay based on the ability of antioxidant drug candidates possess free radical scavenging potency. Compounds of all three series were found to exhibit moderate and low antioxidant effects.

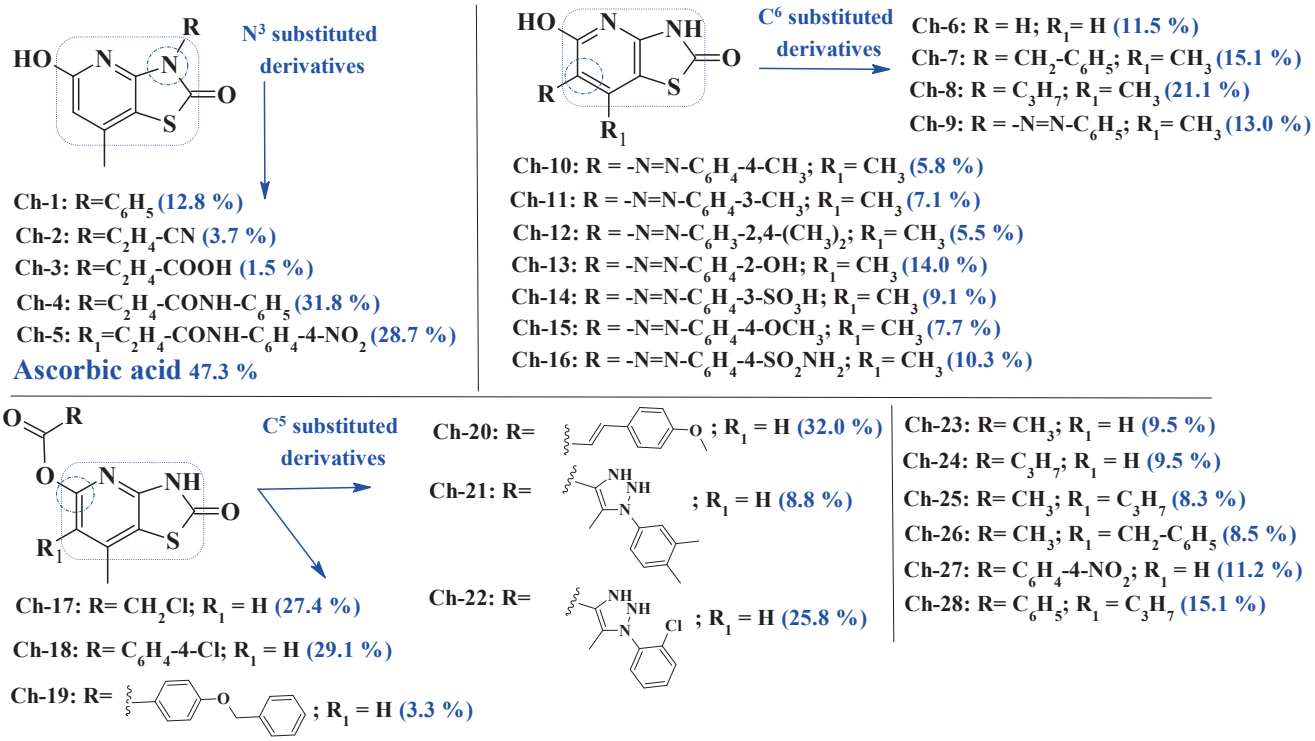

Fig. Chemical structures of condensed 3*H*-thiazolo[4,5-*b*]pyridine-2-one derivatives and their antioxidant activity.

Probing the action mechanism of 3*H*-thiazolo[4,5-*b*]pyridin-2-one derivatives as antioxidants was performed through molecular docking studies towards lipoxygenase. Docking studies, filtering and poses grouping according to the Estimated Affinity towards the biotarget were carried out using SeeSar13.1.0 software (BioSolveIT, Sankt Augustin, Germany) [8]. The crystal structures of

lipoxygenase were downloaded from Protein Data Bank using the Protein Mode of the software. Two structures of LOX-5 were downloaded: PDB entry 3O8Y - a 2.39 Å resolution structure of LOX-5 without ligands; PDB entry 6N2W – a 2.71 Å resolution structure of LOX-5 with co-crystallized ligand NDGA (Masoprocol, 4-[(2r,3s)-3-[(3,4-dihydroxyphenyl)methyl]-2-methylbutyl]benzene-1,2-diol).

Binging site of LOX-5 in 3O8Y PDB entry were detected using Binding Site Mode of SeeSAR. The PDB entry 6N2W was selected among other entries using Search for similar binding site tool of SeeSAR Binding Site Mode module. Both LOX-5 structures showed the highest similarity of their binding sites. The binding sites of both LOX-5 entries (3O8Y and 6N2V) were overlayed. The final site consisting of 27 amino acids residues for the further ligands docking was acquired and fixed. The key residues that showed interactions with the co-crystalized ligand NDGA were detected as ARG-596 and HIS-600. Then the co-crystalized ligand was extracted from 6N2W structure of the protein, and docking was carried out using chain B of LOX-5. Docking of 28 ligands' set and Ascorbic acid as a reference were carried out utilizing two workflows: Standard docking and Docking with a template (co-crystalized NDGA ligand was used as a template). The best pose solutions were determined, the physiochemical parameters were calculated in the Docking mode, and 3*D* conformational similarity scanning of molecules was carried out in the Analyser mode. The HYDE score was used to estimate the binding affinity of the molecules (Tab.).

Table

Comparison of experimental antioxidant activity of some thiazolopyridines and HYDE scores for their complexed with LOX-5

No	ID	Experimental antioxidant activity (DPPH scavenging)	The highest HYDE Scores, kJ/mol
1.	Ch-22	25.8 %	-7.5; -4.4
2.	Ch-5	28.7 %	-6.4; -3.4
3.	Ch-24	9.5 %	-6.4; -6.2
4.	Ch-27	11.2 %	-5.3; -5.2
5.	Ch-28	15.1 %	-6.2; -4.5
6.	Ch-3	1.5 %	-5.3; -4.7
7.	Ch-11	7.1 %	-7.2; -3.3
8.	Ch-12	5.5 %	-3.8; -3.4
9.	Ch-10	5.8 %	-3.8; -3.4
10.	Ch-18	29.1 %	-9.2; -5.8; 3.2; 0.9
11.	Ch-1	12.8 %	-8.3; -5.7; 1.0
12.	Ch-13	14.0 %	-6.1; -4.1; 1.9; 1.5
13.	Ch-17	27.4 %	-6.2; -3.7
14.	Ch-20	32.0 %	-6.6; -4.8; 4.4; 2.9

As a result, Standard docking procedure allowed to obtain 370 poses for 28 ligands as outcome, while docking with the template lead to 271 poses. Visual inspection of poses and their LLE (Lipophilic Ligand efficiency) evaluation led us to the conclusion that all docked ligands had the proper orientation in the binding site of LOX-5. The

highest Estimated Affinity towards LOX-5 was identified for C^5 substituted thiazolo[4,5-*b*]pyridines with docking studies. However, the Hyde Scores for significant number of ligands do not correspond to their experimental antioxidant activity. Thus, the mechanism of their antioxidant action may be not considered as LOX-5 inhibiting.

Acknowledgements. O. K. thanks Universidad San Pablo CEU for a Postdoctoral Contract for Ukrainian Researchers 2022-2024. O. K. is grateful to BioSolveIT Team for possibility to use BioSolveIT software with the license of Spring 2024 Scientific Challenge winner.

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DETERMINATION OF CHLORAMBUCIL BY METHOD HPLC USING THE AZODERIVATION REACTION

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Chlorambucil (C), a bifunctional alkylating agent, has long been used in the