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Prediction and introduction of novel selective COX-2 inhibitors as anti-inflammatory and anti-cancer agents using structure-based virtual screening and molecular dynamics simulation

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Introduction and background: Cyclooxygenase-2 (COX-2) is a promising anti-inflammatory drug target, and overexpression of this enzyme is furthermore associated with some cancers and neurodegenerative diseases [1]. COX-2 plays acritical role in promoting stem cell regeneration and proliferation. Given the well-known effects of COX-2 on cancer stem cells, which are currently recognized as the main cell type for tumor metastasis and recurrence [2]. In this study, we introduce novel small molecular hits to inhibit COX-2 using structure-based virtual screening technique.

Methods: Candidate compounds were collected from ZINC databases and subjected to some filtering processes in subsequent steps. The filtering criteria included pharmacokinetic (ADMET) properties as well as *in silico* COX-2 inhibition prediction, molecular docking and molecular dynamics simulation.

Results: This study was carried out in two stages. A library of more than four thousand compounds was established on the basis of 50% structural similarity with celecoxib. At the second step, following criteria were considered to choose the best compounds: The highest scoring obtained by PyRx software, pharmacokinetic properties based on the drug-likeness criteria using Molinspiration web server, evaluation of COX-2 inhibitor activity by PASS program, ADMET properties for analysis of disposition of these compounds within an organism using a proper server, the highest binding energy and the best interactions with the active site residues performed for the last filtered compounds using the Autodock software, and further analysis of the interactions of these compounds with the COX-2 active site residues by molecular dynamic simulation.

Discussion and Conclusion: Molecular docking simulation was carried out to identify interactions of the filtered molecules. Molecular dynamics confirmed the superior inhibitory ability of selected compounds over the known COX-2 inhibitor, celecoxib. Analyses of the molecular docking and dynamic simulation results showed that the selected hits are more stable and potent than celecoxib in the COX-2 binding site.

Keywords: virtual screening, molecular docking, PASS, COX-2

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