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Design, Molecular Modeling, Synthesize, and Biological Evaluation of Some Dual Inhibitors of Soluble Epoxide Hydrolase (sEH) and Cyclooxygenase 2 (COX-2)

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Abstract : Dual inhibition of COX-2 and sEH enzymes represents one of the distinct pharmaceutical approaches for the treatment of inflammation, pain, cancers, and other diseases. The discovery of these inhibitors for treatment is a great deal of attention because of some advantages such as increased efficacy, a promising safety profile, ease of formulation, and better target engagement. In this research, based on the structure-activity relationship of COX-2 and sEH inhibitors, some amide derivatives with oxadiazole and dihydropyrimidinone rings against sEH and COX-2 enzymes were developed. The designed compounds showed high affinity to the active site of both enzymes in docking studies and were synthesized in good yield and characterized by IR, Mass, 1HNMR, and 13CNMR. All of the novel compounds exhibited considerable in-vitro sEH and COX-2 inhibitory activities in comparison with 12-(3-Adamantan-1-yl-ureido)- dodecanoic acid and celecoxib (a potent urea-based sEH inhibitor and selective nonsteroidal anti-inflammatory drug, respectively). Ethyl 6-methyl-4-(4-(4-(methylsulfonyl)benzamido)phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate was found to be the most selective COX-2 inhibitor (COX-2/COX-1 ratio: 683) with IC50 value of 2.1 nM targeting sEH enzyme.

Keywords : COX-2, dual inhibitors, sEH, synthesis
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