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Abstract

Synthesis, ADME/T, and Carbonic Anhydrase Binding of Hydroxycarboxamide Compounds †

Abdeslem Bouzina [1,*], Yousra Ouafa Bouone [1], Rachida Mansouri [2] and Nour-Eddine Aouf [1]

[1] Laboratory of Applied Organic Chemistry, Bioorganic Chemistry Group, Chemistry Department, Sciences Faculty, Badji-Mokhtar-Annaba University, Box 12, Annaba 23000, Algeria
[2] Environment, Modeling and Climate Change Department, Environmental Research Center (CRE), Annaba 23000, Algeria
* Correspondence: bouzinaabdeslem@yahoo.fr
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Abstract: The interconversion of carbon dioxide and the bicarbonate ion is carried out by carbonic anhydrases (CA), which are ubiquitous metalloenzymes with Zn in their active site. Disorder of CA enzymes can cause several diseases such as glaucoma, epilepsy, obesity, and cancer. Many existing drugs have shown effective inhibition of CAs including Acetazolamide, Dorzolamide, Methazolamide, and Valdecoxib. In order to conceive new agents inhibiting CAs, two small molecules were synthesized and characterized by the usual spectroscopic methods. The prepared compounds were obtained by the condensation of dimedone and cyclohexanedione with CSI (chlorosulfonyl isocyanate) in the presence of methanol as a proton donor. The synthesized derivatives contain a primary amide group ($CONH_2$) bio-isostere of the sulfonamide group (SO_2NH_2) which is present in the quasi-totality of CAs inhibitors. The interactions between our new synthesized molecules and the active site of CAII were determined using docking simulation (PDB: 2AW1); the results showed great stability of these compounds inside the active site with the presence of metallic and hydrogen bonds similar to the ones present between CAII and the reference Valdecoxib. Pharmacokinetic properties and toxicity were predicted using *in silico* tool SwissADME and Molsoft.

Keywords: carbonic anhydrase; Hydroxycarboxamide; molecular docking; ADMET

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