medical sciences forum

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Abstract

Investigation of Pyrazoline-Based Aromatic Sulfamates as Carbonic Anhydrase Isoforms I, II, IX, and XII Inhibitors †

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† Presented at the 8th International Electronic Conference on Medicinal Chemistry, 1–30 November 2022; Available online: https://ecmc2022.sciforum.net/.

Abstract: Four new series of aromatic sulfamates were synthesized and investigated for the inhibition of four human (*h*) isoforms of zinc enzyme carbonic anhydrase, *h*CA I, II, IX, and XII. The reported derivatives, obtained through the sulfamoylation reaction of the corresponding phenolic precursors, bear 3,5-diarylpyrazoline moieties as spacers between the benzenesulfamate fragment, which binds the zinc ion from the active site as well as from the tail of the inhibitor. Pyrazolines are biologically privileged scaffolds, endowed with a versatile biological activity, such as an anti-proliferative action. The derivatives were tested for the inhibition of the cytosolic in the *h*CA I and II (off-target isoforms) and the transmembrane, as well as in the tumor-associated hCA IX and XII enzymes (anticancer drug targets). Generally, the hCA I was not effectively inhibited, whereas many low nanomolar inhibitors were evident in the hCA II (KIs in the range of 0.42–90.1 nM), IX (KIs in the range of 0.72–63.6 nM), and XII (KIs in the range of 0.88–85.2 nM). The best substitution fragments at the pyrazoline ring included: for the CA II, a 4-sulfamic group on the 3-aryl, the halogens on the 5-aryl, a methoxy group on the 3-aryl, and a 4-sulfamate group on the 5-aryl; for the CA IX and the CA XII, they included the sulfamic group on the 3- or 4-position of the 5-aryl and an electron-withdrawing group on the 4-postion of the 3-aryl ring.

Keywords: pyrazolines; sulfamates; carbonic anhydrase; enzyme inhibition

Citation: Moi, D. Investigation of Pyrazoline-Based Aromatic Sulfamates as Carbonic Anhydrase Isoforms I, II, IX, and XII Inhibitors. *Med. Sci. Forum* **2022**, *14*, 14. https://doi.org/10.3390/ECMC2022-13257

Academic Editor: Alfredo Berzal-Herranz

Published: 1 November 2022

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ECMC2022-13257/s1. Conference poster.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.