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Sulfonamide carbonic anhydrase inhibitors: zinc coordination and tail effects influence inhibitory efficacy and selectivity for different isoforms[#]

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Abstract. The metalloenzyme carbonic anhydrase (CA, EC 4.2.1.1) is effectively inhibited by primary sulfonamides which coordinate as anions to the zinc ion from its active site. Inhibition of CAs has pharmacologic applications in the treatment of many diseases, but many sulfonamides are promiscuous inhibitors of most isoforms known to date, leading to side effects of these drugs. In a series of 4-aryl-benzenesulfonamides with effective inhibitory action against human (h) isoforms hCA I, II, IX and XII and selectivity for some of them, we demonstrate by means of X-ray crystallographic studies of enzyme-inhibitor adducts, that the tail present on the benzenesulfonamide scaffold significantly contributes to the observed inhibition/selectivity profile. This study may bring additional information for the structure-based drug design of effective/isoform-selective zinc-binding CA inhibitors.

Keywords: carbonic anhydrase; Zn(II) coordination; zinc enzyme; sulfonamide; X-ray crystallography

[#]Dedicated to Carlo Mealli.

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