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Structural Studies of Human Carbonic Anhydrase II in Complex with 3 Novel Inhibitors. S.Z. Fisher, L. Govindasamy, M. Agbandje-McKenna, R. McKenna, Dept of Biochem and Mol Bio, Univ. of Florida, Gainesville, FL, 32610.

The human carbonic anhydrases (HCAs) are zinc metalloenzymes that catalyze the hydration/dehydration reaction of $\text{CO}_2/\text{HCO}_3^-$. HCAs have been prominent drug targets, as enzyme inhibition is related to the treatment of various disorders (eg. glaucoma, hypertension). Recent literature also suggests that some cancers display an over-expression of some HCA isoforms. Because of the conserved nature of this family of enzymes, it has been difficult to design inhibitors that can preferentially target specific HCA isoforms. To understand the binding mode of inhibitors we have examined the crystal structures of HCA II complexed with 3 compounds (6-hydroxy-1,3-benzoxathiol-2-one; benzenesulfonamide-iminodiacetate- Cu^{2+} and; succinyl-thiadiazolyl- α,α -difluoromethanesulfonamide), that each represents a novel class of CA inhibitors. Crystals of wild type HCA II were soaked with inhibitors and their structures solved to 1.6 Å. The 3 HCA II complex structures are examined and residues important for drug binding are described and compared with native HCA II and each other. These inhibitors are then compared to other HCAs to assess if they exhibit binding properties that might provide isoform specificity.