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**Structural Comparison of the Binding Mode of a Thioxolone Ester Product to Classic Sulfonamide Inhibitors in Carbonic Anhydrase II.** C. Genis<sup>1</sup>, S.Z. Fisher<sup>1</sup>, L. Govindasamy<sup>1</sup>, M. Agbandje-McKenna<sup>1</sup>, J. N.Orwenyo<sup>2</sup>, J. Kiddle<sup>2</sup>, R. McKenna<sup>1</sup>,<sup>1</sup>Dept. of Biochemistry and Mol. Biol., Coll. of Med., Univ. of Florida, Gainesville, FL, <sup>2</sup>Dept. of Chemistry, Western Michigan Univ., Kalamazoo, MI.

Carbonic anhydrases (CAs) are zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide. The role of this reaction in physiology has made it a target of many therapeutic approaches, as enzyme inhibition is related to the treatment of glaucoma, hypertension, epilepsy, and altitude sickness. Most CA inhibitors currently known are sulfonamide-based. Thioxolone (6-hydroxy-1, 3-benzoxathiol-2-one), is a novel non-sulfonamide that has been found to have CA inhibitory activity.

The structure determined, from CA II crystals soaked with thioxolone at 1.6 Å resolution, revealed the ester product 4-mercaptobenzene-1, 3- diol bound in the active site. This work has shown the hydrolytic catalysis of CA II on thioxolone and gives a structural basis for the understanding the inhibitory nature of the resultant ester product. This result also provides information on which amino acids are important for the ester product binding and possible CA isoform specificity. This binding mode will also be compared to currently used sulfonamide-based CA inhibitors.

