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**Novel thiadiazole inhibitors of human carbonic anhydrases**

Saulius Gražulis, Lina Baranauskiene, Elena Manakova, Rasa Sukackaitė, Dmitrij Golovenko, Giedre Tamulaitiene, Daumantas Matulis
Institute of Biotechnology, Laboratory of DNA-Protein interaction, Gražiniškio 8, Vilnius, Aukštaitija :, LT-02241, Lithuania, E-mail : grazulis@ibt.lt

Human carbonic anhydrases are potential drug targets for a number of diseases. One of the novel applications is to use some of their isozymes as anti-cancer drug targets. Structure-thermodynamic property relations of novel hCA thiadiazole class inhibitors with a triple-ring system bound to hCAII will be discussed. Structures of several inhibitors are solved to atomic resolution using X-ray diffraction of hCAII-inhibitor complex crystals. The structural data are correlated with the isothermal titration calorimetry measurements. The calorimetric data together with the structures provide insight into the structural base of the tight and selective hCA inhibitor binding.

**Keywords:** carbonic anhydrase, isothermal titration calorimetry, structure-activity relation

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**Molecular basis for inhibition and resistance of glutamate racemase to a family of D-glu analogues**

Claire L Davies, Sergey N Ruzheimkov, Svetlana E Sedelnikova, Patrick J Baker, David W Rice
University of Sheffield, Department of Molecular Biology and Biotechnology, Firth Court, Western Bank, Sheffield, South Yorkshire, S10 2TN, UK, E-mail: mhp05cld@shef.ac.uk

Proteins involved in the synthesis of compounds of the bacterial cell wall have been long exploited in the development of effective antibiotics. D-glutamate is an essential component of the peptidoglycan layer, and is synthesized from L-glutamate via a co-factor independent reaction catalysed by glutamate racemase. Co-crystals of Streptococcus pneumoniae glutamate racemase, in complex with a potent inhibitor, (2R, 4S)-2-Amino-4-(2-naphthyl) methyl Pentanedioic Acid, have been grown and the structure solved using X-ray crystallographic techniques. The structure reveals that, in contrast to previously published data on the location of the inhibitor binding site by crystal soaks, the inhibitor is bound in a very similar fashion to the D-glutamate substrate. The structure has provided new insight into the narrow spectrum activity of the family of compounds to which this inhibitor belongs, and has provided clues as to how a broad spectrum antibiotic might be developed.

**Keywords:** antibiotic resistance, Inhibitor interactions, racemases

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**The LIM code for motor neuron specificity**

Mugdha Bhati, Mihwa Lee, Amy Nancarrow, Vanessa Craig, Mitchell Guss, Jacqui Matthews
University of Sydney, School of Molecular and Microbial Biosciences,
Building G08, University of Sydney, Camperdown, NSW, 2006, Australia, E-mail: m.bhati@mmb.usyd.edu.au

LIM-HD (LIM homeodomain) proteins are essential for defining cell fate, especially in the developing central nervous system. Isl-1 and Lhx-3 are two LIM-HD proteins implicated in neuronal development that form the basis of regulatory complexes in two adjacent cell types in the ventral spinal chord, V2 interneurons and motor neurons. Both cell types express Lhx-3 and the nuclear adaptor protein Ldb1, however, Isl-1 is only expressed in postmitotic motor neurons. In the two complexes, the two LIM domains of Lhx-3 mediate different protein:protein interactions that appear to be critical for the regulation of the two different cell types. In V2 interneurons, this involves a direct interaction with the LIM interaction domain (LID) of Ldb1, whereas in motorneurons Isl-1 interacts directly with Ldb1-LID and Lhx-3 binds instead to Isl-1. We are interested in characterising these interactions with the overall goal of understanding their role in neuronal development. Deletion mutagenesis analyses have revealed a 30-residue region of Isl-1 that binds the Lhx-3 LIM domains (LMIs). We have solved a crystal structure of a protein complex between Lhx3 and Isl1 to show that, despite low sequence homology, the LID from Ldb1 and Isl1 bind Lhx3 in an essentially identical manner. Binding and stability studies of these different complexes suggest that a ternary Lhx3:Isl1:Ldb1 complex can only form if the complex binds to DNA that contains Lhx3 and Isl1 recognition sequences. This work highlights a general mode of interaction between different LIM-HD proteins involved with LIM codes.

**Keywords:** protein crystallography, protein interactions, zinc finger proteins

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**Crystal structure determination of sheep (Ovis aries) methemoglobin at 2.7 Å resolution**

Neelagandam Kamariah, Sathyam moorthy Ponmuraj, Balasubramanian Moovarkumudalvan, Ponnuwamy Mondikalipurud Nanjappa Gounder
University of madras, Chennai, India, CAS in Crystallography and Biophysics, Guindy Campus, Chennai, Tamil Nadu, 600 025, India, E-mail: kng_15@yahoo.com

Hemoglobin is a tetrameric protein, which is in equilibrium between low affinity tense (T) state and high affinity relax (R) state. Mammalian hemoglobin can be broadly classified into two groups: those with intrinsically high oxygen affinity and another with low oxygen affinity. Human, rodent, dogs, pigs, horses, camels, marsupials and most primates belong to the high oxygen affinity category in contrast to cows, sheep, goats, deer, cats and lemur belong to the low oxygen affinity. In order to unravel the structure-function relationship of low affinity mammalian species, the sheep hemoglobin structure has been determined at 2.7Å resolution. The oxygen affinity of sheep hemoglobin is about 10 times lesser than the human hemoglobin and the 2,3-diphosphoglycerate, the potential allosteric effector of mammalian hemoglobin, does not alter its oxygen affinity. Sheep hemoglobin is purified from the blood plasma and crystallized in orthorhombic space group P2₁2₁2₁ with one whole biological molecule (α22) in the asymmetric unit with cell dimensions a=60.23A, b=70.695Å, c=131.479Å. The structure was solved by molecular replacement method and the final refinement converges to R=19% and Rw=25%. Obviously the overall structural features of sheep hemoglobin is found to be similar to human oxyhemoglobin, in contrast significant tertiary structural differences are observed. Comparing with human model, the shift of 2.1A in