Poster Presentation

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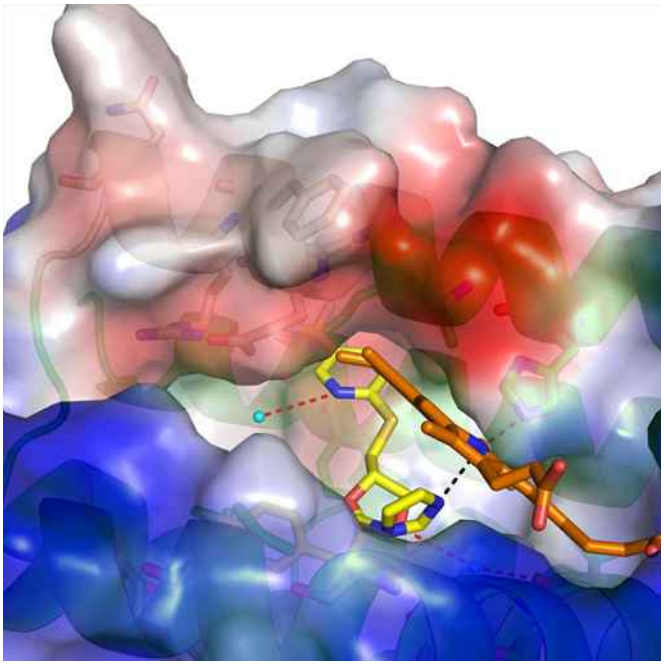
Structural insights into heme oxygenase-1 inhibition by azole-based compounds

M. Rahman[1], D. Vukomanovic[1], J. Vlahakis[2], W. Szarek[2], K. Nakatsu[1], Z. Jia[1]

[1]Queen's University, Department of Biomedical & Biological Sciences, Kingston, Canada, [2]Queen's University, Department of Chemistry, Kingston, Canada

The development of heme oxygenase (HO) inhibitors, especially those that are isozyme-selective, promises powerful pharmacological tools to elucidate the regulatory characteristics of the HO system. HO is known to have cytoprotective properties with a role in several disease states; thus, it is an enticing therapeutic target. Traditionally, given their structural similarity with heme, the metalloporphyrins have been used as competitive HO inhibitors. However, given heme's important role in several other proteins (e.g. cytochromes P450, nitric oxide synthase), nonselectivity is an unfortunate side-effect. Reports that azalanstat and other non-porphyrin molecules inhibited HO led to a multi-faceted effort to develop novel compounds as potent, selective inhibitors of HO. This resulted in the creation of non-competitive HO-selective inhibitors, including a subset with isozyme selectivity for HO-1. Using X-ray crystallography, the structures of several complexes of HO-1 with novel inhibitors have been elucidated, providing insightful information regarding the salient features required for inhibitor binding. This included the structural basis for non-competitive inhibition, flexibility and adaptability of the inhibitor binding pocket, and multiple, potential interaction subsites, all of which can be exploited in future drug-design strategies. The structures revealed a common binding mode, despite different structural fragments, with the flexibility to accommodate bulkier substituents via "induced fit". Compounds bind to the distal side of heme through an azole ''anchor" which coordinates with the heme iron. Expansion of the distal pocket, mainly due to distal helix flexibility, allows accommodation of the compounds, with a distal hydrophobic pocket providing further stabilization yet without displacing heme or the critical Asp140 residue. Rather, binding displaces a catalytically critical water molecule and disrupts an ordered hydrogen-bond network involving Asp140.

[1] *Mona N. Rahman, Dragic Vukomanovic, Jason Z. Vlahakis, et al., Journal of the Royal Society Interface, 2012, 10, 20120697,* ***[2]*** *Mona N. Rahman, Jason Z. Vlahakis, Dragic Vukomanovic, et al., PLoS One, 2012, 7, e29514,* ***[3]*** *Mona N. Rahman, Jason Z. Vlahakis, Dragic Vukomanovic, et al., Journal of Medicinal Chemistry, 2009, 52, 4946-4950*



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