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Structural Analysis of Time-dependent and Time-independent Inhibitor Binding by Prostaglandin H2 Synthase

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Beamline(s): X12C, X8C

Introduction: Nonsteroidal antiinflammatory drugs (NSAIDs) block prostanoid biosynthesis by inhibiting prostaglandin H2 synthase. NSAIDs are either rapidly reversible competitive inhibitors or slow tight binding inhibitors of this enzyme. The different modes of inhibition correlate with clinically important differences in isoform selectivity. Hypotheses have been advanced to explain the different inhibition kinetics, but no structural have been available to test them.

Methods and Materials: Crystal structures of prostaglandin H2 synthase in complex with four different, but structurally related, inhibitors were determined and refined, using high resolution data obtained with synchrotron radiation. Two of the inhibitors were time-dependent, and the other two were time-independent.

Results: The four inhibitors bind to the same site and adopt similar conformations. In all four complexes, the enzyme structure is essentially identical, exhibiting only minimal differences in the inhibitor binding site.

Conclusions: These results argue conclusively against hypotheses that seek to explain the difference between time-dependent and time-independent inhibition by invoking global conformation differences or different inhibitor binding sites. Instead, they suggest the different modes of NSAID binding result from differences in the speed and efficiency with which inhibitors can disrupt the hydrogen bonding network that protects the active center.



Electron density for the NSAID ibuprofen, bound in the active site of its target enzyme, prostaglandin H2 synthase