Structural Snapshots of K. lactis Purine Nucleoside Phosphorylase Trapped with Transition State Analog Inhibitors

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The use of transition state analogs to inhibit protein and enzyme activity has an extremely powerful application to medical and biochemical disciplines. Kluyveromyces lactis, along with many other microorganisms, is a purine auxotroph, meaning that it depends upon a host or outside source for purines. Purines are vital for DNA synthesis in a pathway known as the purine salvage pathway. By using transition state analogs to block the binding to purine nucleoside phosphorylases, a main component of the salvage pathway, one can effectively destroy large populations of pathogenic organisms, and this technique has been applied to some major diseases such as malaria and tuberculosis. In addition, this technique can be applied to treat autoimmune diseases and T-cell cancers by starving the purine-sensitive cells in humans. However, with the further expansion of the transition state analog as a medical application, further testing must be done to understand the behavior of these analogs with specific organisms and their respective PNP's. The most important reason for this is to test how the inhibitors will be effected by resistance of a pathogenic organism, however because clinical trials cannot show whether or not resistance will play a role in the efficacy of the inhibitor a different method must be used. This has led to the use of x-ray crystallography in order to the determine of the structure of an obstructively mutated purine nucleoside phosphorylase bound with transition state analog inhibitors DADMe-ImmucillinH and DADMe-ImmucillinG, the "ultimate inhibitors". This project was succesfully able to show the ability of the inhibitors to enter the active site of the protein desipte purposefully obstructive mutations on the catalytic sites.

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