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Structure-Based Drug Design: Inhibitors of Purine Nucleoside Phosphorylase (PNP).
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Purine nucleoside phosphorylase catalyzes the reversible phosphorolysis of purine ribo- and 2'-deoxyribonucleosides to the base and ribose or 2'-deoxyribose-1-phosphate. The enzyme has been isolated from a variety of eucaryotic and procaryotic organisms and functions in the purine salvage pathway. Because of the high levels of PNP in humans, an inhibitor with a K_i of around 1-10 nM (K_m of inosine 30-35 μM) will probably be necessary for effective inhibition *in vivo*, whereas the most potent known inhibitor of the human erythrocytic enzyme has a K_i of 67 nM. We have used the three-dimensional structure of human erythrocytic PNP as determined by X-ray crystallography to design more potent inhibitors of this enzyme. The methodology employed utilizes the X-ray data on the native enzyme and on enzyme-inhibitor complexes, computer modeling of the enzyme active site and of the enzyme-inhibitor complexes, and organic synthesis, in an iterative process. Candidate inhibitors were designed by a team of crystallographers, molecular modelers, and synthetic organic chemists. Proposed compounds were then screened by modeling the enzyme-inhibitor complexes. Candidates with good steric and chemical fit to the active site were then synthesized and their IC_{50}'s determined. The actual structures of a number of the enzyme-inhibitor complexes were then determined by X-ray analysis and related to the IC_{50}'s and to the models. This approach has allowed us to prepare several families of potent inhibitors with IC_{50}'s in the 6-30 nM range. The inhibition is competitive with respect to inosine and noncompetitive with respect to phosphate. The structures of inhibitors and their interactions with PNP will be described. Selected inhibitors have been shown to effectively inhibit PNP in whole cells and in rats, and to reduce the catabolic cleavage of 2',3'-dideoxyinosine (ddI) and other purine nucleosides. The half-life and AUC of ddI in rats are tripled in the presence of a PNP inhibitor.

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A Soluble Form of Intercellular Adhesion Molecule-1 Inhibits Rhinovirus Infection. *K. Last-Barney, *S.D. Marlin, *C. Cahill, *R. Jejer, *D. Fortugno-Erikson, *M. O'Neill, **F. Hayden, and *V.J. Merluzzi. *Boehringer Ingelheim Pharmaceuticals, Inc., 90 East Ridge, Ridgefield, CT 06877 USA. and **University of Virginia School of Medicine, Charlottesville, VA 22908 USA.

Rhinoviruses belong to the picornavirus family and are responsible for approximately 50% of common colds. The majority of rhinoviruses and some coxsackieviruses share a common cell surface receptor on human cells. Recently, Intercellular Adhesion Molecule-1 (ICAM-1) has been identified as the cellular receptor for the major group of rhinoviruses. We have constructed and purified a soluble form of the normally membrane-bound ICAM-1 molecule (sICAM-1). sICAM-1 inhibits cytopathic effects (CPE) of several major group rhinoviruses and coxsackieviruses that bind to the same receptor (IC_{50} ~ 1ug/ml). The inhibition of CPE by sICAM-1 is more pronounced on WI-38 cells than HeLa cells. In addition, sICAM-1 does not inhibit CPE induced by minor group rhinoviruses, coxsackie B viruses, poliovirus I and herpes simplex I virus. In addition to inhibition of CPE, sICAM-1 inhibits the binding of radiolabelled (^{35}S-methionine) rhinovirus 14 (major subgroup) to H1 HeLa cells (45% inhibition at 50ug/ml).