RATIONAL DRUG DESIGN FOR GIARDIASIS

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ABSTRACT

Giardiasis is the most common form of non-bacterial diarrhea in North America with over 2.5 million cases occurring annually in the United States. It is caused by the parasite Giardia lamblia, which is classified as a category B organism by the Centers for Disease Control in response to bioterrorism threats. Currently Tindamax is the only FDA approved treatment for giardiasis but has been shown to be carcinogenic in mice and rats. The long-term goal of this project is to develop new drug candidates for alternative treatments of giardiasis.

Class II Giardia fructose-1,6-diphosphate aldolase catalyzes the reversible condensation of dihydroxyacetone phosphate with glyceraldehyde 3-phosphate to produce D-fructose 1,6-bisphosphate in glycolysis, a central metabolic pathway. Class II Giardia fructose-1,6-diphosphate has been shown to be essential to Giardia lamblia growth by RNAi gene knock-out experiments. In addition, this enzyme does not exist in human cells. Therefore, it is an ideal anti-parasitic drug target.

We report a rational inhibitor design, synthesis and single-point in vitro assay against Class II Giardia fructose-1,6-diphosphate aldolase. Five inhibitors were tested, among which two were synthesized in our lab and three were commercially available. Structure-activity relationship analysis identified the phosphate group as important for inhibition activity as well as the flexibility of the inhibitor backbone. Pyranone moiety proved to be a less effective Zn anchor owing to its large size. In addition, protein purification of Class II Giardia fructose-1,6-diphosphate aldolase was explored.

Future work will include exploration of the role of the sulfonamide anchor, molecular modeling via a Linux workstation (e.g. Autodock 4.0) and a thorough in-vitro study (e.g. Michaelis-Menten kinetics, Lineweaver-Burk plots, etc.). Four more designed inhibitors will be tested. Once a nanomolar level inhibitor is identified, inhibitor selectivity will be determined followed by the development of the X-ray crystal structure of the enzyme-inhibitor complex and in-vivo biological evaluation.