LEISHMANIA MAJOR DIHYDROOROTATE DEHYDROGENASE CRYSTAL STRUCTURE AND SEARCH FOR INHIBITORS

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Dihydroorotate dehydrogenase (DHODH) catalyses the fourth sequential step in the de novo pyrimidine nucleotide synthesis pathway with the oxidation of (S)-dihydroorotate to orotate, and the aid of a flavin cofactor and an electron receptor. Pyrimidines are essential metabolites in all cells. They are required not only for DNA and RNA biosynthesis, but also for biosynthesis of phospholipids and glycoproteins. At present, there is a great interest in inhibitors of DHODH as therapeutic agents for the treatment of cancer, rheumatoid arthrits and parasitic diasease. Here, we present the molecular characterization of DHODH from *Leishmania major* (LmDHODH). *Leishmania major* is a protozoan parasite responsible for Leishmaniasis that currently threatens 350 million men, women and children in 88 countries spread in four continents (Africa, America, Europe and Asia) around the world. The crystal structure of LmDHODH has been solved by X-ray diffraction techniques in three different forms: apo, and complexed with its natural substrate, fumarate and its natural inhibitor, orotate. We have identified important residues that are involved in substrate and inhibitor specificity that can be further used for the modeling of potential ligands using the structure-based drug design approach.

In addition, we have been screening a large number of natural products and synthetic analogues in the search for inhibitors.

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