Rational Anti-Chagasic Drug Design Based on the Structure of *Trypanosoma cruzi* Dihydroorotate Dehydrogenase

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Trypanosoma cruzi is the etiological agent of Chagas' disease, considered a public health problem in Latin America. Ten to 14 million people are infected by *T.cruzi* and 40–120 million people are at risk. Dihydroorotate dehydrogenase (DHODH) is a flavin mononucleotide containing enzyme, which catalyses the oxidation of L-dihydroorotate to orotate, the fourth step and only redox reaction in the *de novo* biosynthesis of pyrimidine nucleotides. Genetic studies have shown that DHODH is essential for *T.cruzi* survival, validating the idea that this enzyme can be considered an attractive target for the development of anti-chagasic drugs. In our work, a detailed analysis of TcDHODH crystal structure has allowed us to identify promising sites that are being used for virtual screening of inhibitors. In order to identify potential anti-chagasic lead compounds, docking calculations were performed using two different docking algorithms (FlexX/Tripos and Fred/Openeye) into the 3D model of the catalytic loop of TcDHODH enzyme (pdb code 3C3N). The 8 million purchasable compounds initially tested were reduced to about 100 compounds, which are being used for *in vitro* inhibition experiments and in the structural characterization of the protein-inhibitor interaction by crystallography.

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