Abstract

Design of Potential Antimalarial Agents Based on a Homology Model of *Plasmodium falciparum* Glucose-6-Phosphate Dehydrogenase †

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There currently exists a dire need for safe and inexpensive new antimalarial drugs, which are effective against multiple life cycle stages of *Plasmodium falciparum*, and act through mechanisms that differ from those of the available drugs to prevent drug resistance. The enzyme glucose-6-phosphate dehydrogenase (G6PD) of *P. falciparum* has emerged as a promising target for antimalarial drug discovery, due to its key role in parasite development and survival and its protective effect against malaria infection observed under human G6PD deficiency conditions. Here, we describe the construction of a homology model of *Pf*G6PD, which has enabled the identification of key structural differences as compared with the human enzyme. We have exploited these changes to rationally design a novel family of substrate analog-based inhibitors that can be endowed with selectivity towards *Pf*G6PD. Several compounds display micromolar affinity, good selectivity, and low cytotoxicity, but weak antiplasmodial activity in phenotypic assays, likely as a result of a poor internalization of the compounds in the parasite cell. Future hit optimization should focus on improving the physicochemical/pharmacokinetic properties of this class of compounds.

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