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Plasmodium falciparum DHODH inhibitor complexes reveal flexible binding site

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Malaria is a preventable and treatable disease, yet annually there are still hundreds of thousands of malaria-related deaths. The disease is caused by infection with mosquito-borne Plasmodium parasites. With hundreds of millions of cases each year there is a very high potential for drug resistance and this has compromised many existing therapies. One target under investigation is the enzyme dihydroorotate dehydrogenase (DHODH) which catalyses the rate-limiting step of pyrimidine biosynthesis and is an essential enzyme in the malaria parasite. There are currently several Plasmodium-selective DHODH inhibitors under development. To investigate the potential for drug resistance against DHODH inhibitors in vitro resistance selections were carried out using known inhibitors from different structural classes [1]. These studies identified point mutations in the drug binding site which lead to reduced sensitivity to the inhibitors, and in some cases increased sensitivity to a different inhibitor, suggesting a novel combination therapy approach to combat resistance. To help understand the significance of the inhibitor binding site mutations we determined the crystal structures of P. falciparum DHODH in complex with the inhibitors Genz-669178, IDI-6253 and IDI-6273. Co-crystallisation experiments led to a new crystal form in each case. Here we describe the crystal structures, the binding modes of the inhibitors and the great flexibility of the binding site, which is able to adjust to accommodate different inhibitor series. The structural role of the resistance mutations is also discussed.

[1] *L. Ross, F. Gamo, M. Lafuente-Monasterio, et al, In vitro resistance selections for Plasmodium falciparum dihydroorotate dehydrogenase inhibitors give mutants with multiple point mutations in the drug-binding site and altered growth. J. Biol. Chem., 2014,*

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