Elisabeth Davioud-Charvet

Drug Development against Disulfide Reductases from Parasites and Cancer Cells

Goal

Design, synthesis and mechanism of disulfide reductase inhibitors and redox-cyclers that affect the redox equilibrium of parasites and cancer cells.

Background

The aim of our interdisciplinary research is to substantiate NADPH-dependent disulfide reductase inhibitors as antiparasitic and cytostatic agents. Such compounds are active per se but, in addition, they can reverse thiol-based resistance against other drugs in parasites and tumour cells. Our strategy is based on the synthesis of subversive substrates or catalytic inhibitors, fluorine-based suicide-substrates, uncompetitive inhibitors, photoreactive inhibitors (as tools for photoaffinity labeling studies) of the selected targets, namely the glutathione reductases (GR) of the malarial parasite *Plasmodium falciparum* and man, the thioredoxin reductases (TrxR) of *P. falciparum* and man, the trypanothione reductase (TR) from *Trypanosoma cruzi*, and the thioredoxin-glutathione reductase (TGR) of *Schistosoma mansoni*.

Research Highlights

Our strategy for inhibitor optimization is based on the design and the synthesis of dual drugs that act as “Trojan horses” drugs consisting of a short chloroquine analogue – active against malaria per se – linked to a GR inhibitor. This strategy was validated in the current malaria project with new functionalized 4-aminoquinolines derivatives that were found to be active in the low nanomolar range against the erythrocytic stages of *P. falciparum* and in mouse malaria models. Besides the dual drugs, a series of low-weight naphthoquinones revealed potent antimalarial effects against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum* both in vitro and in vivo (patent). Regarding the basic research part of the whole project introduction of fluorine allowed us to identify the enzymic intermediate – an enzymic species containing reduced flavin – responsible for GR-catalyzed naphthoquinone reduction. In future work the aim is to identify the relevant physiological binding site of these naphthoquinones, especially those inducing a cooperative behaviour in GR catalysis. For leishmanias and trypanosomes various unsaturated Mannich bases acting by TR inactivation were produced and revealed potent trypanocidal effects against pentamidine-sensitive and -resistant strains of *Trypanosoma brucei in vitro*. Current efforts include the chemistry of 1,4-naphthoquinones and Mannich bases derivatives as antiparasitic drug-
candidates (against malaria, trypanosomiasis, and schistosomiasis), studies on the mechanism and the regulation of disulfide reductase in vivo (malaria, trypanosomiasis).

Selected Publications 2004 - 2007


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Fig. 1: Synthesis of fluorine-based naphthoquinone derivatives as mechanism-based inhibitors of NADPH-dependent glutathione reductases (GR).

Fig. 2: X-ray structure of the human GR active site bound to the naphthoquinone-derived inhibitor.

Fig. 3: Crystals of human GR alkylated by a fluorine-based inhibitor.