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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. The strategy was also validated in the current malaria project with new functionalized low-weight 1,4-naphthoquinones derivatives belonging to the 3-benzylmenadione series. The redox-active compounds revealed potent antimalarial effects against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum in vitro* and in mouse malaria models (EP patent). A cascade of redox reactions for antimalarial drug bioactivation involving both heme-

Fig. 1: “Drowning Plasmodium in Redox” was achieved by 3-benzylmenadione derivatives with potent antimalarial effects both in vitro and in vivo. Compounds with GR redox-cycling activity displaying the ability to reduce iron(III) to iron(II) from haemoglobin and heme species.
catalyzed oxidation reactions and the glutathione reductases from the *Plasmodium*-infected erythrocyte was proposed to be involved in the action mechanism of the 3-benzylmenadione series. The biometabolites were shown to act, in oxidized form, as the most efficient subversive substrates of both glutathione reductases of *Plasmodium*-infected erythrocytes described so far, and, in reduced form, to redox-cycle methemoglobin to hemoglobin. Ultimately, the antimalarial naphthoquinones are suggested to affect the redox equilibrium of target cells resulting in trophozoite development arrest, by drowning the parasite in its own metabolic products. For leishmania and trypanosomes various unsaturated ketones derivatives acting as trypanothione-reactive agents were produced and revealed potent trypanocidal effects against pentamidine-sensitive and -resistant strains of *Trypanosoma* and *Leishmania* species *in vitro*. Current efforts include the chemistry of prodrugs of 1,4-naphthoquinones and bis (Michael acceptors) derivatives as antiparasitic drug-candidates (against malaria, trypanosomiasis, and schistosomiasis), biochemical and enzymic studies on the mechanism and the regulation of disulfide reductase *in vivo*.

**Selected Publications 2008 - 2010**


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