

Novel antimalarial agents targeting *Plasmodium falciparum* spermidine synthase by way of rational-based drug design.

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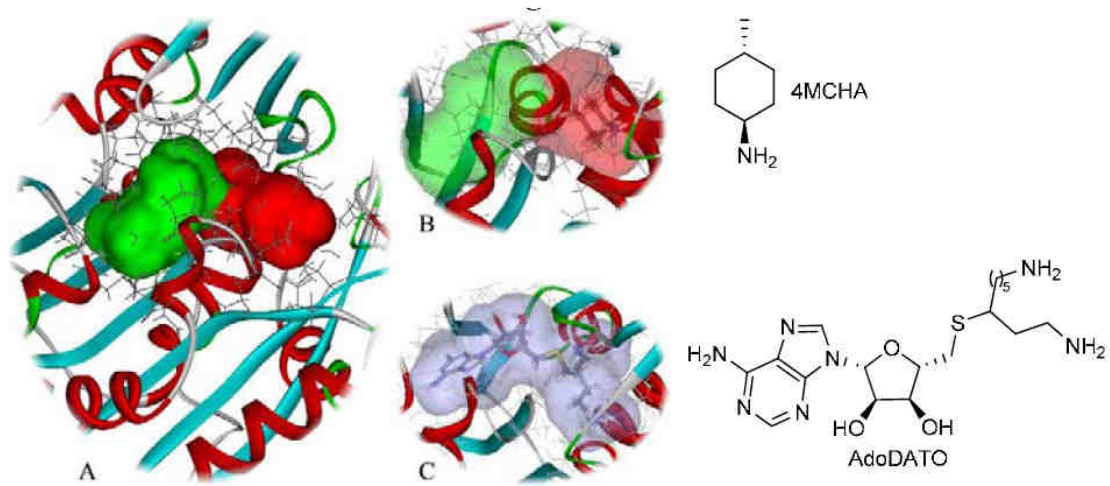
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A variety of parasite biochemical processes and associated targets, which seem promising candidates for rational drug design and subsequent inhibition of parasite proliferation, are currently under investigation. Polyamines have been shown to be essential to parasite survival and of particular interest is the *Plasmodial* synthesis of spermidine through the action of spermidine synthase. Inhibition of this enzyme has been shown to totally block parasite schizogony. Furthermore, unlike *P. falciparum*, mammalian systems have several pathways to control the synthesis, uptake, interconversion and efflux of polyamines and therefore even compounds which prove not to be totally selective for *P. falciparum* should prove not to be toxic to mammalian cells - thus rendering *P. falciparum* spermidine synthase a particularly attractive target.

Significant advances in multifunctional protein and ligand modelling tools have changed the way in which medicinal chemists approach new lead design. Specifically, receptor-based drug design techniques which utilise a 3D structure of the target protein have been found to be very effective. Fortunately, three crystal structures of *P. falciparum* spermidine synthase (with ligands and the apo form) are available, allowing for a rational drug design approach. This project therefore aims to integrate various modelling techniques, chemistry and biochemistry in the rational design, synthesis and evaluation of novel chemical entities capable of inhibiting the growth of malaria parasites by specifically targeting *P. falciparum* spermidine synthase. Through this highly collaborative approach, it is envisaged that at least one new lead compound with inhibitory action against *P. falciparum* spermidine synthase will be obtained. Specific objectives include:

1. The design of novel inhibitors using rational based drug design techniques

2. Syntheses of novel compounds or modification of existing compounds
3. *In vitro* assays (enzyme and whole cell) for inhibitory capacity



- A) *PjSpdSyn* showing the adenosine binding region in green and the putrescine binding region in red.
 B) The putrescine competitive inhibitor bound in the putrescine region of the site.
 C) The AdoDATO competitive inhibitor which mimics the entire adenosine-putrescine natural substrate complex filling the entire site.