Disrupting *Pf*AMA1-*Pf*RON2 protein-protein interaction by conformationally restricted peptidomimetic inhibitor to stop the malaria parasite invasion into red blood cells

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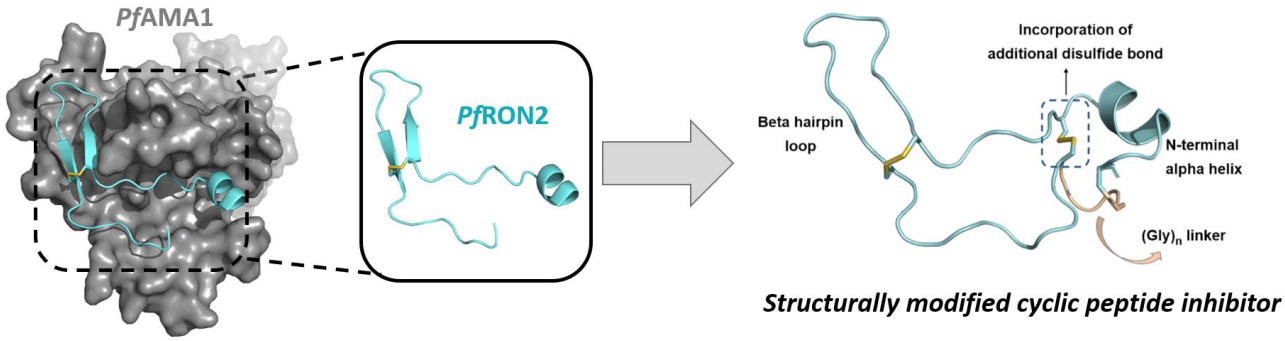
Malaria is a mosquito-borne disease caused by *Plasmodium* species, the deadliest of which is *Plasmodium falciparum*. There is no fully effective vaccine reported till date to tackle malaria. Further, the widespread resistance of the frontline medicine 'artemisinin combination therapy' is also responsible for the delayed control over the disease. Therefore, there is an urgent need to develop a potential alternative anti-malarial therapeutic. Unlike small-molecule drugs, peptide or mini-protein based inhibitors are promising due to their larger interacting surface area leading to the high specificity and less toxicity. [1] Moreover, like antibodies, they do not demand low temperature supply chains. In all apicomplexan parasites a unique invasion mechanism exists that involves moving junction formation between the host cell and the parasite. [2] For *P. falciparum*, two parasitic proteins, named Apical Membrane Antigen 1 (*Pf*AMA1) and Rhoptry Neck Protein 2 (*Pf*RON2), strongly interact with each other, and form the moving junction. Our aim here is to disrupt the *Pf*AMA1-*Pf*RON2 protein-protein interactions by natural or non-natural peptides or proteins, resulting in the inhibition of the *P. falciparum* merozoite invasion into red blood cells.



Structurally modified cyclic peptide inhibitor

Therefore, with the help of molecular dynamics simulations we deciphered the crucial interactions for stabilizing *Pf*AMA1-*Pf*RON2 complex. [3] Furthermore, we implemented the findings for the strategic design of a potential cyclic peptide inhibitors mimicking the *Pf*RON2 backbone to target *Pf*AMA1-*Pf*RON2 interactions. [4]

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