Structural insights on three series of anti-malarial N-myristoyltransferase inhibitors

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A promising area of research on novel anti-malarial drugs has been the disruption of the acylation of key proteins during the parasitic life cycle. Inhibition of an enzyme responsible for one type of acylation, N-myristoylation, has been observed to have pleiotropic effects with severe impacts on parasite development, growth, and multiplication. In *Plasmodium falciparum,* N-myristoyltransferase (NMT) co-translationally catalyzes the transfer of a 14-carbon moiety from myristoyl coenzyme A to a glycine residue at the amino terminus of a wide range of proteins. This acyl chain is important for the localization of NMT-substrates to specific membranes, allowing them to play roles in host-cell invasion, parasite motility, and protein trafficking and degradation. As a result, NMT has been validated as a therapeutic target for diseases such as malaria.

Several drug series have been developed that strongly inhibit function of *Plasmodium falciparum* NMT. In this work, we demonstrate the conformation of two distinct inhibitor series bound to the related *Plasmodium vivax* NMT enzyme in the presence of the myristoyl-CoA cofactor. In addition, we will structurally explore a single point mutation that confers resistance to one series of inhibitors while having little effect on other.