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A Two-pronged Attack: Dual Inhibition of Plasmodium falciparum M1 and M17 Metalloaminopeptidases by a Novel Series of Hydroxamic acid-based Inhibitors.

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Malaria is caused by parasites of the genus Plasmodium, with Plasmodium falciparum (Pf) causing the most deaths. The prevention and treatment of Pf malaria is becoming increasingly difficult due to the spread of drug resistant parasites. New therapeutics with a novel mode of action are desperately required. Two Plasmodium falciparum aminopeptidases, PfA-M1 and PfA-M17, play crucial roles in the erythrocytic stage of infection, and have been validated as potential antimalarial targets. Using compound-bound crystal structures of both enzymes, we were able to identify key similarities and differences in the mechanism of inhibitor binding by PfA-M1 versus PfA-M17, which we exploited to design inhibitors capable of potently inhibiting both enzymes. The resultant hydroxamic acid-based inhibitors represent the first compounds capable of potent dual inhibition of both PfA-M1 and PfA-M17. The compounds additionally possess nanomolar activity against 3D7 malaria parasites and no observable cytotoxicity, and are therefore extremely attractive lead molecules for further development into antimalarial therapeutics with a novel mode of action.

Keywords or phrases (comma separated)

falciparum malaria, aminopeptidase, inhibitors, hydroxamic acid, structure-based drug discovery

Summary

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