Poster Presentation

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Development of selective inhibitors against malarial M1 family aminopeptidase

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Malaria caused by Plasmodium parasites have developed resistance to most of the currently available antimalarial drugs including artemisinin combination chemotherapeutic strategy, to be the last line of defense for malaria treatment. Therefore novel antimalarial drugs are urgently required to combat malaria. Plasmodium falciparum aminopeptidase N (PfAPN), play a crucial role in the asexual erythrocytic stage of infection and have been validated as a potential antimalarial drug target. Herein we have designed and synthesized several leucine derivatives displaying inhibition at nanomolar range against PfAPN. One of the compound exhibited an impressive specificity (≈50 fold) against the PfAPN enzyme compared to the mammalian homolog. Most of these compounds showed minimal cytotoxicity on mammalian cells and selected compounds were active on the Plasmodium falciparum 3D7 strain. In this study, we also provide the structural basis for the inhibition using X-ray crystallography. Our data provide important insights for the rational, structure-based design of more potent and selective inhibitors of this enzyme that may eventually provide new therapies for malaria.
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