Invention of the Dual Plasmepsin IX/X Inhibitor MK-7602 — A Promising Next Generation Antimalarial Agent from an Efficient Academic/Industrial Collaboration

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Abstract

Drug resistance to first-line antimalarials – including artemisinin – is increasing, resulting in a critical need for the discovery of new agents with novel mechanisms of action. In collaboration with the Walter and Eliza Hall Institute and with funding from the Wellcome Trust, a phenotypic screen of Merck's aspartyl protease inhibitor library identified a series of plasmepsin X (PMX) hits that were more potent than chloroquine. Inspired by a PMX homology model, efforts to optimize potency resulted in the discovery of a central bicyclic subseries with leads that, in addition to potently inhibiting PMX, also inhibit another essential aspartic protease, plasmepsin IX (PMIX). Further optimization of potency, PK and selectivity profile resulted in the invention of **MK-7602**, a very potent PMIX/X dual inhibitor with robust *in vivo* efficacy at multiple stages of the malaria parasite lifecycle and excellent off-target activity and resistance profiles.