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Simultaneous utilization of structure-activity and structure-property relationships for the rational design and synthesis of 3-diarylether-4(1h)-quinolones: A new class of antimalarials

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There are over 300 million malaria cases annually and over one million deaths. The staggering mortality rates combined with the global emergence of chemical resistance that the *parasite Plasmodium* falciparum has developed towards many of the common antimalarials compelled us to extend our research efforts to this growing problem. The need for developing new antimalarial drugs is very important. Our approach focuses on the optimization of historically relevant antimalarials such as endochin which possessed liabilities such as poor solubility, in vivo activity or lingering toxicity issues. Through these optimization efforts using both SAR and structure-property relationship (SPR) studies a more suitable candidate could be designed that contained superior properties.

The drug design process included not only the identification of liabilities for known compounds but also the synthesis and optimization of numerous analogs guided by SAR. All compounds were tested in vitro for antimalarial activity and characterized in parallel for physicochemical properties such as solubility, permeability, and $\log D_{7.4}$. Insights from both the antimalarial activity as well as the physicochemical properties were simultaneously examined to determine which analogs would be advanced in the design process. The quinolone P4Q-391 emerged as the leading candidate from within our lab which targets the liver and blood stages, including the transmission stages (gametocytes). In mouse models of malaria, a single oral dose of 0.03 mg/kg prevented sporozoite-induced infections and a dose of 1 mg/kg achieved complete cures of patent infections. P4Q-391 is a preclinical candidate with the potential to aid in eradication of the disease.

Biography

R. Matthew Cross completed his Ph.D. in 2011 from the University of South Florida with Prof. Roman Manetsch where he worked on the design and synthesis of complex 4(1H)-quinolones and developed methods to prepare these scaffolds in novel manners. He is currently an American Cancer Society post-doctoral fellow at The Scripps Research Institute working with Prof. Dale L. Boger on the design and synthesis of complex vinblastine alkaloid analogs possessing electrophilic moieties capable of generating irreversible inhibitors. He is author of 9 papers in reputed journals and has 2 US patents.

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