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Orally Bioavailable Antimalarial 4(1*H*)-Quinolone and 4(1*H*)-Quinolone Prodrugs with Single-Dose Cures

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For approximately half a century, 4(1*H*)-quinolones such as endochin or ICI 56, 780 were known to be causal prophylactic and potent erythrocytic stage agents in avian but not in mammalian malaria models. Hit-to-lead optimization of endochin lead to 4(1*H*)-quinolones ELQ-300 and P4Q-391, which target the liver, the blood as well as the transmitting stages of the parasite (*Sci. Transl. Med.* 2013, 5, 177ra37). However, poor aqueous solubility severely limits absorption and oral bioavailability and therefore impedes preclinical development of this class of antimalarials Herein, we disclose a general prodrug approach that converts promising lead compounds, such as antimalarial 4(1*H*)-quinolones, into aminoalkoxycarbonyloxymethyl (amino AOCOM) ethers that display significantly improved aqueous solubility and enhanced oral bioavailability. The prodrug is autarkic, independent of biotransformations, and animal-independent as it activates via a pH-triggered intramolecular cyclization reaction. Amino AOCOM ether prodrugs of antimalarial 4(1*H*)-quinolones were shown to possess pharmacokinetic and efficacy profiles significantly improved relative to the corresponding parent compounds (> 50-fold improvement of Cmax and AUC). One of the most promising 3-aryl-4(1*H*)-quinolone preclinical candidates was further shown to provide single-dose cures in a rodent malaria model at an unprecedentedly low oral dose of 3 mg/kg, without the use of an advanced formulation technique.

Biography:

Dr. Roman Manetsch received his PhD in Chemistry in 2002 from the University of Basel under the guidance of Wolf-Dietrich Woggon. He joined the group of K. Barry Sharpless at the Scripps Research Institute working on click chemistry. In 2005, he moved to the University of South Florida and established a research group focusing on medicinal chemistry. In 2014, Dr. Manetsch assumed a position of an Associate Professor at Northeastern University. His current research focuses on lead discovery and optimization using synthetic chemistry in close conjunction with mass spectrometry.