SYNTHESIS AND EVALUATION OF β-SUBSTITUTED FOSMIDOMYCIN ANALOGUES AS INHIBITORS OF 1-DEOXY-D-XYLULOSE 5-PHOSPHATE REDUCTOISOMERASE

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Blocking the MEP pathway for isoprenoid biosynthesis offers interesting prospects for inhibiting Plasmodia growth. Fosmidomycin (1) and its homologue FR900098 (2) potently inhibit 1-deoxy-d-xylulose-5-phosphate reductoisomerase (Dxr), a key enzyme in this pathway. Although fosmidomycin is a remarkably safe antimalarial agent, low oral absorption, short serum half-life and malaria recrudescence preclude its use in monotherapy. The development of more lipophilic Dxr inhibitors able to passively permeate into cells with improved pharmacokinetic properties could lead to more efficacious agents. Previously, we discovered that analogue 4, featuring a 2,4-dichlorophenyl substituent in α-position of the phosphonate, surpasses fosmidomycin's potency in inhibiting P. falciparum growth. Here we explored the introduction of aryl or aralkyl substituents at the β-position of the known hydroxamate analogue 3.

INTRODUCTION & GOAL

I. Synthesis of β-aryl analogues

SYNTHESIS

BIOLOGICAL RESULTS

Table 1. IC50 ± sd values for recombinant Dxr from P. falciparum and MIC50 values against in vitro growth of P falciparum K1 strain.

We studied the effect of introducing substituents in β-position of the hydroxamate analogue 3. While direct addition of a β-aryl moiety resulted in poor P. falciparum Dxr inhibition, longer linkers between the carbon backbone and the phenyl ring were generally associated with better binding to the enzyme. X-ray structures of the parasite Dxr-inhibitor complexes show that the "longer" compounds generate a substantially different flap structure, in which a key tryptophan residue is displaced, and the aromatic group of the ligand lies between the tryptophan and the hydroxamate’s methyl group. Several analogues emerged as highly potent inhibitors of Plasmodium falciparum in vitro growth. In some cases (e.g. compounds 7b and 7f) good Dxr inhibitory activity failed to translate in good in vitro activity against the parasite, which may be due to inefficient uptake. Compounds 5a-d likewise failed to inhibit EcDxr and MboDxr while 6c was optimal for inhibition of these enzymes.

CONCLUSIONS