Antimalarial Pyrido[1,2-a]benzimidazoles

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A novel class of antimalarial pyrido[1,2-a]benzimidazoles were synthesized and evaluated for antiplasmodial activity and cytotoxicity following hits identified from screening commercially available compound collections. The most active of these, TDR86919 (4c), showed improved in vitro activity vs the drug-resistant K1 strain of Plasmodium falciparum relative to chloroquine (IC(50) = 0.047 muM v 0.17 muM); potency was retained against a range of drug-sensitive and drug-resistant strains, with negligible cytotoxicity against the mammalian (L-6) cell line (selectivity index of <600). 4c and several close analogues (as HCl or mesylate salts) showed significant efficacy in P. berghei infected mice following both intraperitoneal (ip) and oral (po) administration, with <90% inhibition of parasitemia, accompanied by an increase in the mean survival time (MSD). The pyrido[1,2-a]benzimidazoles appeared to be relatively slow acting in vivo compared to chloroquine, and metabolic stability of the alkylamino side chain was identified as a key issue in influencing in vivo activity
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