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Antimalarial pyrido[1,2-a]benzimidazole derivatives with mannich base side chains: synthesis, pharmacological evaluation and reactive metabolite trapping studies

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A novel series of pyrido[1,2- a]benzimidazoles bearing Mannich base side chains and their metabolites were synthesized and evaluated for in vitroăantiplasmodium activity, microsomal metabolic stability, reactive metabolite (RM) formation, and in vivo antimalarial efficacy in a mouse model. Oral administration of one of the derivatives at 4 Œ 50 mg/kg reduced parasitemia by 95% in Plasmodium berghei-infected mice, with a mean survival period of 16 days post-treatment. The in vivo efficacy of these derivatives is likely a consequence of their active metabolites, two of which showed potent in vitroăantiplasmodium activity against chloroquine-sensitive and multidrug-resistant Plasmodium falciparum (P.ăfalciparum) strains. Rapid metabolism was observed for all the analogues with <40% of parent compound remaining after 30 min of incubation in liver microsomes. RM trapping studies detected glutathione adducts only in derivatives bearing 4-aminophenol moiety, with fragmentation signatures showing that this conjugation occurred on the phenyl ring of the Mannich base side chain. As with amodiaquine (AQ), interchanging the positions of the 4-hydroxyl and Mannich base side group or substituting the 4-hydroxyl with fluorine appeared to block bioactivation of the AQ-like derivatives though at the expense of antiplasmodium activity, which was significantly lowered.
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