Antimalarial benzimidazole derivatives incorporating phenolic mannich base side chains inhibit microtubule and hemozoin formation: structure-activity relationship and in vivo oral efficacy studies

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A novel series of antimalarial benzimidazole derivatives incorporating phenolic Mannich base side chains at the C2 position, which possess dual asexual blood and sexual stage activities, is presented. Structure-activity relationship studies revealed that the 1-benzylbenzimidazole analogues possessed submicromolar asexual blood and sexual stage activities in contrast to the 1H-benzimidazole analogues, which were only active against asexual blood stage (ABS) parasites. Further, the former demonstrated microtubule inhibitory activity in ABS parasites but more significantly in stage II/III gametocytes. In addition to being bona fide inhibitors of hemozoin formation, the 1H-benzimidazole analogues also showed inhibitory effects on microtubules. In vivo efficacy studies in Plasmodium berghei-infected mice revealed that the frontrunner compound 41 exhibited high efficacy (98% reduction in parasitemia) when dosed orally at 4 x 50 mg/kg. Generally, the compounds were noncytotoxic to mammalian cells.

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