Antimalarial and Antitumor Evaluation of Novel C-10 Non-Acetal Dimers of 10β-(2-Hydroxyethyl) deoxoartemisinin

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Abstract

Four series of C-10 non-acetal dimers were prepared from key trioxane alcohol 10β-(2-hydroxyethyl)deoxoartemisinin (9b). All of the dimers prepared displayed potent low nanomolar antimalarial activity versus the K1 and HB3 strains of Plasmodium falciparum. The most potent compound assayed was phosphate dimer 14a, which was greater than 50 times more potent than the parent drug artemisinin and about 15 times more potent than the clinically used acetal artemether. In contrast to their potent activity versus malaria parasites, virtually all of the dimers expressed poor anticancer activity apart from the trioxane phosphate ester dimers 14a and 14b, which expressed nanomolar growth inhibitory (GI50) values versus a range of cancer cell lines in the NCI 60 human cell line screen. Further detailed studies on these dimers in vitro in HL60 cells demonstrate that both phosphate ester dimers (14a and 14b) are more potent than the anticancer agent doxorubicin. Interestingly, phosphate ester monomers 9c and 9d, antimalarially active in the low nanomolar region versus P. falciparum, are inactive as anticancer agents even at concentrations in the millimolar region. This observation emphasizes the importance of two trioxane units for high antiproliferative activity, and we propose that the nature of the linker in dimers of this type plays a crucial role in imparting potent anticancer activity.