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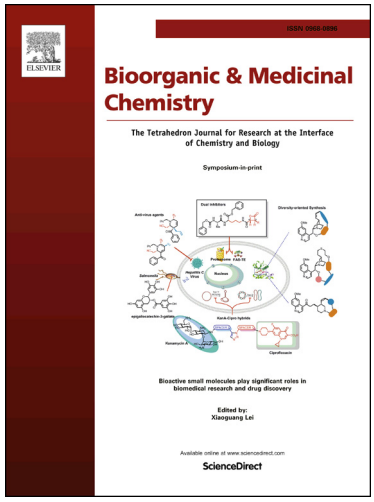

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Synthesis and Evaluation of Symmetric Acyclic Nucleoside Bisphosphonates as Inhibitors of the *Plasmodium falciparum, Plasmodium vivax* and Human 6-Oxopurine Phosphoribosyltransferases and the Antimalarial Activity of Their Prodrugs

Petr Špaček,[a] Dianne T. Keough,[b] Marina Chavchich,[c] Martin Dračínský,[a] Zlatko Janeba,[a] Lieve Naesens,[d] Michael D. Edstein,[c] Luke W. Guddat,[b*] and Dana Hocková,[a*]

[a]*The Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo nám. 2, CZ-16610 Prague 6, Czech Republic*

[b]*School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Queensland, 4068, Australia*

[c]*Department of Drug Evaluation, Australian Army Malaria Institute, Enoggera, Brisbane, Queensland 4051, Australia*

[d]*KU Leuven - Rega Institute for Medical Research, Laboratory of Virology and chemotherapy Herestraat 49, B-3000 Leuven, Belgium*

Keywords: malaria; acyclic nucleoside phosphonates; bisphosphonates; phosphoramidate prodrug; hypoxanthine-guanine-[xanthine] phosphoribosyltransferase

Abstract:

Two new series of symmetric acyclic nucleoside bisphosphonates (ANbPs) have been synthesised as potential inhibitors of the *Plasmodium falciparum* (*Pf*) and *vivax* (*Pv*) 6-oxopurine phosphoribosyltransferases. The structural variability between these symmetric ANbPs lies in the number of atoms in the two acyclic linkers connecting the N^9 atom of the purine base to each of two phosphonate groups and the branching point of the acyclic moiety relative to the purine base, which occurs at either the alpha or beta positions. Within each series, six different 6-oxopurine bases have been attached. In general, the ANbPs with either guanine or hypoxanthine have lower K_i values than for those containing either the 8-bromo or 7-deaza 6-oxopurine bases. The lowest K_i values obtained for the two parasite enzymes were 0.1 μM (*Pf*) and 0.2 μM (*Pv*) for this series of compounds. Two phosphoramidate prodrugs of these inhibitors exhibited antimalarial activity against *Pf* in infected erythrocyte cell culture