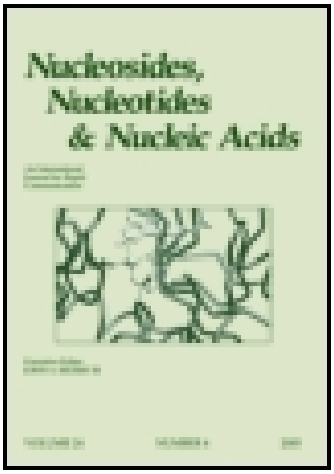

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Synthesis of 3′-Amino-3′-deoxyadenosine Derivatives as Potential Drugs for the Treatment of Malaria

Johanna Soenens [a] , Guido François [b] , Elfride Van den Eeckhout [a] & Piet Herdewijn [a]

[a] Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences , Universiteit Gent , Harelbekestraat, 72, B-9000, Gent, Belgium

[b] Laboratory of Protozoology , Prince Leopold Institute of Tropical Medicine , Nationalestraat, 155, B-2000, Antwerpen, Belgium

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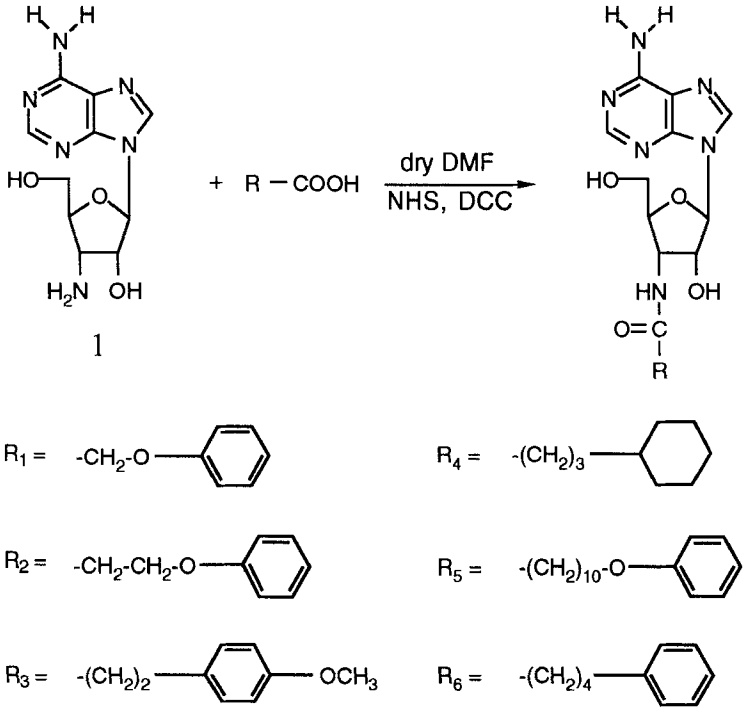
SYNTHESIS OF 3'-AMINO-3'-DEOXYADENOSINE DERIVATIVES AS POTENTIAL DRUGS FOR THE TREATMENT OF MALARIA

Johanna Soenens[1], Guido François[2*], Elfride Van den Eeckhout[1] and Piet Herdewijn[1*]
[1]*Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Universiteit Gent, Harelbekestraat 72, B-9000 Gent, Belgium*
[2]*Laboratory of Protozoology, Prince Leopold Institute of Tropical Medicine, Nationalestraat 155, B-2000 Antwerpen, Belgium*

Abstract
A series of 3'-substituted 3'-amino-3'-deoxyadenosine analogues were synthesized and subsequently tested against the human malaria parasite *Plasmodium falciparum in vitro*. Several amongst them displayed pronounced antiplasmodial activities.

Malaria is still by far the most important disease caused by protozoa[1] and is the origin of enormous suffering, morbidity, and mortality, especially in the pantropical area[2]. The need for new antimalarials is urgent, given the rapid and worldwide spread of *Plasmodium falciparum* strains resistant against commonly used drugs[3]. Since certain nucleoside analogues are known to inhibit the growth of malaria parasites *in vitro*[4], we describe here a new series of 3'-amino-3'-deoxyadenosine analogues and a first exploration of their antiplasmodial potential.

The synthesis of these compounds was performed in 10 steps starting from D-xylose. The 1,2 and 3,5 hydroxyl groups of D-xylose were simultaneously protected by treatment with acetone and sulfuric acid in the presence of anhydrous copper sulfate. The 1,2-O-isopropylidene derivative was obtained by hydrolysis with hydrochloric acid (0.2%)[5]. Its 5-hydroxyl group was selectively protected by a p-toluoyl group. Conversion of the 3-hydroxyl group into the triflic ester and subsequent nucleophilic displacement with sodium azide in dimethylformamide (DMF) yielded 40 % of 3-azido-1,2-O-isopropylidene-5-O-(p-toluoyl)-3-deoxy-D-ribofuranose besides an equal percentage of an elimination product[6]. Removal of the isopropylidene group and simultaneous O-acetylation yielded 72 % of 3-azido-1,2-di-O-acetyl-5-O-(p-toluoyl)-3-deoxy-D-ribofuranose[6]. 3'-azido-2'-O-acetyl-5'-O-(p-toluoyl)-3'-deoxy-N^6-benzoyladenosine was obtained by coupling with silylated N^6-benzoyladenine using the method of Vorbrüggen[7]. Alkaline hydrolysis of all protecting



SCHEME 1. Synthesis of 3'-substituted 3'-amino-3'-deoxyadenosine analogues.

TABLE 1. IC_{50}-values of 3'-substituted 3'-amino-3'-deoxyadenosine.

COMPOUND	IC_{50} (μM)
R_1	32
R_2	18
R3	13
R_4	8
R_5	32
R_6	7

groups and catalytic reduction of the azido function in methanol yielded 3'-amino-3'-deoxyadenosine[8].

The six final compounds were synthesized by amidation of the 3'-amino function of 3'-amino-3'-deoxyadenosine (**1**) with different carboxylic acids using dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (NHS) as coupling agents[9] without protecting the hydroxyl groups (SCHEME 1). The newly synthesized compounds were identified by ^{1}H-NMR and elemental analysis.

The antiplasmodial activities of the final compounds were tested against asexual blood forms of *P. falciparum* (NF 54, clone A1A9)[10] *in vitro*, continuously maintained following the method of Trager and Jensen[11]. The test procedure[12,13,14] was based upon the measurement of incorporation of radiolabelled (^{3}H) hypoxanthine by actively dividing cells. Two of the examined deoxyadenosine analogues (R_4 and R_6) displayed a high antiplasmodial activity, with IC_{50} values below 8 µM. All of them inhibited the parasite growth significantly ($IC_{50} < 32$ µM, see TABLE 1).

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We wish to thank Mrs C. Dochez and Mr L. Hendrix for their contribution to the *P. falciparum* experiments and Mrs C. Van Overmeir for her skilful technical assistance. We gratefully acknowledge the financial support by the Vlaams Instituut voor de Bevordering van het Wetenschappelijk-Technologisch Onderzoek in de Industrie (IWT), Flanders.

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