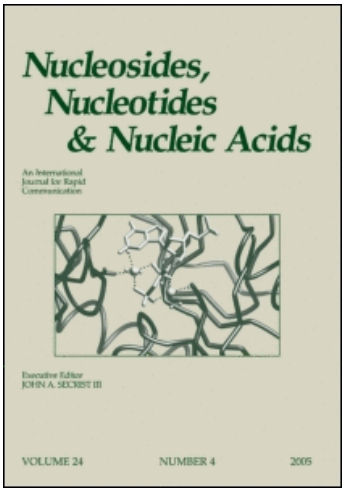



**Nucleosides, Nucleotides and Nucleic Acids**
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

# 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, Gent, Belgium [b] Laboratory of Protozoology, Prince Leopold Institute of Tropical Medicine, Antwerpen, Belgium

**To cite this Article** Soenens, Johanna , François, Guido , Eeckhout, Elfride Van den and Herdewijn, Piet(1995) 'Synthesis of 3'-Amino-3'-deoxyadenosine Derivatives as Potential Drugs for the Treatment of Malaria', Nucleosides, Nucleotides and Nucleic Acids, 14: 3, 409 — 411
**To link to this Article: DOI:** 10.1080/15257779508012396
**URL:** http://dx.doi.org/10.1080/15257779508012396

NUCLEOSIDES & NUCLEOTIDES, 14(3-5), 409-411 (1995)

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

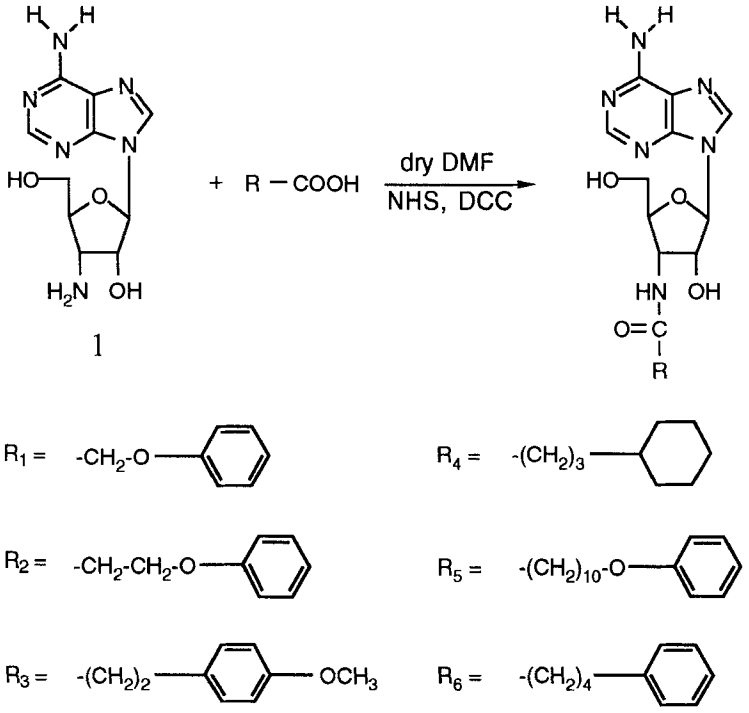
Johanna Soenens[1], Guido François[2*], Elfride Van den Eeckhout[1] and Piet Herdewijn[1*]
[1]*Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Universiteit Gent, Harelbekestraat 72, B-9000 Gent, Belgium*
[2]*Laboratory of Protozoology, Prince Leopold Institute of Tropical Medicine,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



Acknowledgments

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.

## REFERENCES

1. Wright, C.W.; Phillipson, J.D. *Phytotherapy Research* 1990, 4, 127-139.
2. Touze, J.E.; Charmot, G. *Cahiers Santé* 1993, 3, 217-219.
3. World Health Organization. *Weekly Epidemiol. Rec.* 1989, 64, 241-248.
4. Coomber, D.W.J.; O'Sullivan, W.J.; Gero, A.M. *Int. J. Parasitol.* 1994, 24, 357-365.
5. Baker, B.R.; Schaub, R.E. *J. Am. Chem. Soc.* 1955, 77, 5900-5905.
6. Ozols, A.M.; Azhayev, A.V.; Dyatkina, N.B.; Krayevsky, A.A. *Synthesis* 1980, 557-558.
7. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.* 1981, 114, 1234-1255.
8. Mengel, R.; Wiedner, H. *Chem. Ber.* 1976, 109, 433-443.
9. Wengel, J.; Motawia, M.S.; Pedersen, E.B. *J. Heterocyclic Chem.* 1992, 29, 5-9.
10. François, G.; Hendrix, L.; Wéry, M. *Ann. Soc. Belg. Méd. Trop.*, in press.
11. Trager, W.; Jensen, J.B. *Science* 1976, 193, 673-675.
12. Desjardins, R.E.; Canfield, C.J.; Haynes, J.D.; Chulay, J.D. *Antimicrob. Agents Chemother.* 1979, 16, 710-718.
13. François, G.; Bringmann, G.; Phillipson, J.D.; Aké Assi, L.; Dochez, C.; Rübenacker, M.; Schneider, C.; Wéry, M.; Warhurst, D.C.; Kirby, G.C. *Phytochemistry* 1994, 35, 1461-1464.
14. François, G.; Bringmann, G.; Dochez, C.; Schneider, C.; Timperman, G.; Aké Assi, L. *J. Ethnopharmacol.*, in press.