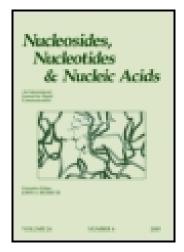
This article was downloaded by: [Tufts University]

On: 10 October 2014, At: 07:54 Publisher: Taylor & Francis

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered

office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides and Nucleotides

Publication details, including instructions for authors and subscription information:

http://www.tandfonline.com/loi/Incn19

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

Johanna Soenens $^{\rm a}$, Guido François $^{\rm b}$, Elfride Van den Eeckhout $^{\rm a}$ & Piet Herdewijn $^{\rm a}$

^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 Published online: 16 Feb 2007.

To cite this article: Johanna Soenens, Guido François, Elfride Van den Eeckhout & Piet Herdewijn (1995) Synthesis of 3'-Amino-3'-deoxyadenosine Derivatives as Potential Drugs for the Treatment of Malaria, Nucleosides and Nucleotides, 14:3-5, 409-411

To link to this article: http://dx.doi.org/10.1080/15257779508012396

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms &

Conditions of access and use can be found at $\underline{\text{http://www.tandfonline.com/page/terms-and-conditions}}$

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

Johanna Soenens¹, Guido François^{2*}, Elfride Van den Eeckhout¹ and Piet Herdewijn^{1*}

¹Department of Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Universiteit

Gent, Harelbekestraat 72, B-9000 Gent, Belgium

²Laboratory 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 protozoa¹ and is the origin of enormous suffering, morbidity, and mortality, especially in the pantropical area². The need for new antimalarials is urgent, given the rapid and worldwide spread of *Plasmodium falciparum* strains resistant against commonly used drugs³. 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 product⁶. 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-N⁶-benzoyladenosine was obtained by coupling with silylated N⁶-benzoyladenine using the method of Vorbrüggen⁷. Alkaline hydrolysis of all protecting

410 SOENENS ET AL.

$$H_{N}$$
 H_{N} H_{N

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

TABLE 1. IC50-values of 3'-substituted 3'-amino-3'-deoxyadenosine.

COMPOUND	IC50 (μM)
R ₁	32
R ₂	18
R3	13
R4	8
R5	32
R ₆	7

groups and catalytic reduction of the azido function in methanol yielded 3'-amino-3'-deoxyadenosine⁸.

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 without protecting the hydroxyl groups (SCHEME 1). The newly synthesized compounds were identified by ¹H-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 Jensen¹¹. 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 (R4 and R6) displayed a high antiplasmodial activity, with IC50 values below 8 μ M. All of them inhibited the parasite growth significantly (IC50 < 32 μ M, 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.
- Desjardins, R.E.; Canfield, C.J.; Haynes, J.D.; Chulay, J.D. Antimicrob. Agents Chemother. 1979, 16, 710-718.
- 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.