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Bioorganic & Medicinal Chemistry Letters 15 (2005) 595–597

Bioorganic & Medicinal Chemistry Letters

# Novel spiroanellated 1,2,4-trioxanes with high in vitro antimalarial activities

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Received 18 October 2004; revised 13 November 2004; accepted 17 November 2004

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**Abstract**—A remarkable increase in antimalarial in vitro activity was achieved by integration of spiroadamantane motifs in 6-alkylidene 1,2,4-trioxanes **3a**–**h** via diastereoselective photooxygenation of allylic alcohols and subsequent $BF_3$-catalyzed peroxyacetalization with adamantanone to give the active compounds **3e**–**h**.

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## 1. Introduction

The development of new antimalarial substances has been recognized as a pressing challenge in recent years.[1] The search for efficient and less toxic compounds exhibiting high activity against *malaria tropica* is of special interest because multidrug resistances exist already in many places with this most aggressive pathogen of the *Plasmodium falciparum* species.[2] Besides the well established quinoline derivatives, compounds are currently tested as pharmaceutical leads that interact with different locations of infected erythrocytes. Cyclic peroxides play a special role both because of their structure and the possible mode of action. These compounds are structurally derived from the naturally occurring sesquiterpene lactone *artemisinin* (*qinghaosu*), a compound with a 1,2,4-trioxane core structure.[3] Also 1,2-dioxanes as occurring in *yinghaosu A* and *C* show high antimalarial activities.[4] Extensive work has been published on the total synthesis of artemisinin,[5] the preparation of derivatives[6] as well as on the elucidation of the peroxide-specific mode of action.[7] Semisynthetic derivatives have been reported from the research groups of Posner[8] and Haynes,[9] fully synthetic spirobicyclic peroxides from Jefford and co-workers[10] and 'dual systems', with 1,2,4-trioxanes linked to quinolines, by Meunier and co-workers.[11] The heme iron(II)-initiated dissociative one electron reduction step has been recognized as the triggering process from studies on the redox behavior,[12] as well as on secondary products and accordingly on adducts to cell components.[13] Recent studies by Krishna and co-workers have shown that artemisinin acts as a strong inhibitor of the calcium-transport enzyme PfATP6 and thus might act more selectively than expected from the notion of radical-induced parasite damage.[14]

Motivated by our studies on the photooxygenation of allylic alcohols,[15] we have recently applied this route for a simple approach to mono- and bicyclic 1,2,4-trioxanes.[16,17] The underlying concept (Scheme 1) transfers terpenoid secondary allylic alcohols **1** into the 1,2,4-trioxanes **3** by way of photooxygenation and subsequent peroxyacetalization. The former compounds are easily accessible by alkylation of α,β-unsaturated aldehydes or by reduction of the corresponding ketones.

By means of this route a multitude of monocyclic compounds were synthesized, albeit only with moderate in vitro antimalarial activities.[16] From the work by Jefford and co-workers[10] it was known that spiroanellation of a cyclopentane ring at the C3 position of the trioxane structure results in a considerable activity increase. Thus, we have applied this concept for the syntheses of compounds **3**. The adduct **3a** with acetone as the carbonyl component showed comparatively low activities against *Plasmodium falciparum* in the order of

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*Keywords*: Peroxides; Antimalarial; Synthesis.

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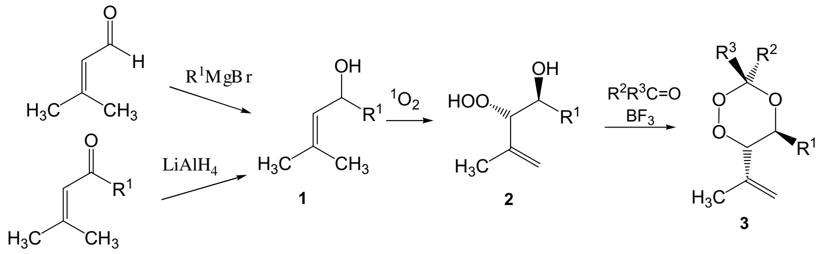
doi:10.1016/j.bmcl.2004.11.043



**Scheme 1.** Synthesis of 1,2,4-trioxanes **3** via singlet oxygen ene reaction of allylic alcohols **1** and BF$_3$ catalyzed peroxyacetalization.

magnitude for chloroquine (Table 1). The spiroanellation of cyclopentane rings to different β-hydroxy hydroperoxide **2** resulted in noticeably more active compounds (e.g., **3c**,**d**). This structure/activity correlation was originally interpreted in the literature as evidence for the formation of reactive C-radicals following the primary mesolytic cleavage of the peroxy bond. Spiroanellation of cyclohexane rings gave a further increase in activity by a factor of 10. This suggested investigation of the spiroadamantane[18] connection. The products **3e**–**h** (in yields of 25–50% from the corresponding β-hydroxy hydroperoxides by treatment with adamantanone in the presence of catalytic amounts of BF$_3$, Fig. 1) showed consistently excellent activities against *Plasmodium falciparum* in the range of the natural artemisinin accompanied by low cytotoxicity, even when compared with the recently reported highly active adamantane-containing trioxolanes.[19]

**Table 1.** Activity profile of 1,2,4-trioxanes **3a**–**h**: in vitro activities against *P. falciparum* (K1 strain); cytotoxicity against the mammalian cell line L-6

| | *P. falciparum* (μg/mL) | IC$_{50}$ (nM) | Cytotoxicity IC$_{50}$ (μg/mL) |
|---|---|---|---|
| *Chloroquine* | 0.0638 | 200 | — |
| *Artemisinin* | 0.0008 | 2.8 | — |
| *Mefloquine* | — | — | 1.9 |
| **3a** | 0.2253 | 1309 | ND |
| **3b** | 0.0024 | 10.6 | 0.82 |
| **3c** | 0.0088 | 36.6 | 3.7 |
| **3d** | 0.00065 | 3.1 | 0.46 |
| **3e** | 0.0013 | 4.9 | 1.7 |
| **3f** | 0.00054 | 1.9 | 0.74 |
| **3g** | 0.0014 | 4.8 | 2.6 |
| **3h** | 0.00053 | 1.8 | 1.4 |

The selectivity index (IC$_{50}$ for the mammalian cell line L-6/IC$_{50}$ for *P. falciparum*) reaches a highly promising factor of 1000 for the highly active compounds. In subsequent work, in vivo experiments in the malaria mouse model are scheduled, which are supposed to show if these 1,2,4-trioxanes can be applied for the treatment of malaria. All compounds described herein were synthesized free of the sensitizing dyestuff via photooxygenation in polymer supports;[20] compound **3g** was additionally characterized by means of an X-ray structure analysis (Fig. 2). The central peroxide ring appears as a nearly perfect cyclohexane chair with the two alkyl substituents at C5 and C6 in equatorial positions.[21]

In summary, we have reported an efficient and stereoselective route to 1,2,4-trioxanes. The process described herein yields a multitude of mono- and spirobicyclic 6-alkenyl-1,2,4-trioxanes with highly flexible substituent pattern and, in part, excellent antimalarial activities. Further improvement in pharmaceutical properties is

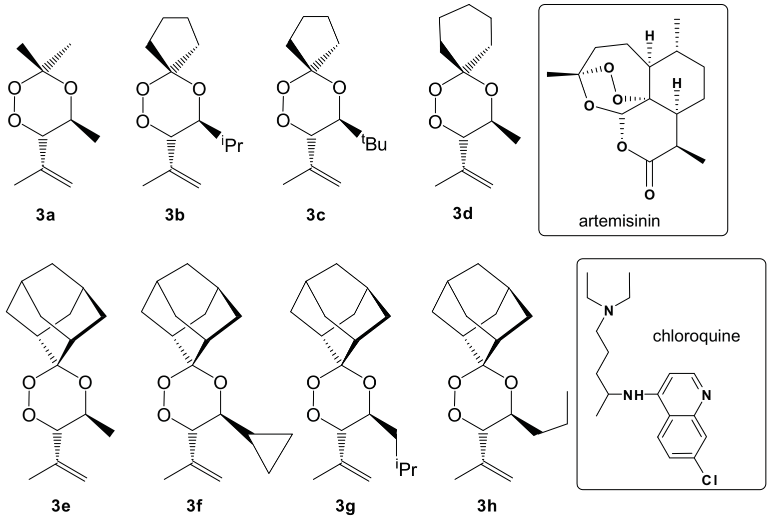


**Figure 1.** Spiroanellated 1,2,4-trioxanes **3a**–**h** with high in vitro antimalarial activities; structure of the natural and synthetic comparisons artemisinin and chloroquine.

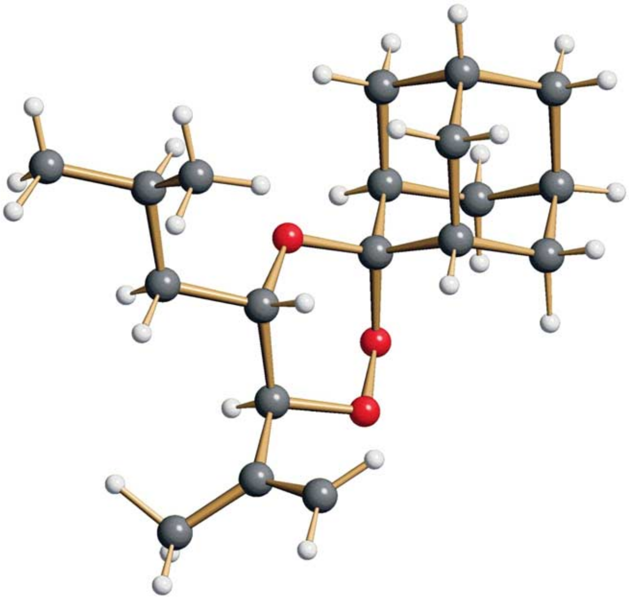


**Figure 2.** Structure of the spiroadamantane derivative **3g** in the crystal.

expected from application of naturally occurring sesquiterpene allylic alcohols.

## 2. Experimental

Synthesis of the spiroadamantane derivative **3g**: the allylic hydroperoxide **2g** (R = *i*-Bu) was synthesized following the route described in Ref. 20. A solution of 700 mg (4.0 mmol) of the hydroperoxide **2g** and 600 mg (4.0 mmol) of adamantanone in 100 mL of methylene chloride was cooled to 0 °C and treated with 0.2 mL of a solution of $BF_3$ in diethylether. The mixture was stirred at room temperature for 10 h and subsequently extracted with 50 mL of aqueous sodium bicarbonate, brine, and water. After drying of the organic phase of $MgSO_4$ and evaporation of the solvent, the crude product was purified by thick-layer chromatography (silica, eluent: ethyl acetate/*n*-hexane 1:10) resulting in 476 mg (40%) of a colorless oil, which crystallized upon standing.

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (GR 881/13-1), the Fonds der Chemischen Industrie and the University of Cologne (network project). T. T. El-Idreesy thanks the Egyptian government for a Ph.D. grant.

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21. Crystal data for **3g**: $C_{19}H_{30}O_3$ (colorless thin needles, from acetone), $M = 306.44$, monoclinic, $a = 10.682(1)$, $b = 8.716(1)$, $c = 10.611(1)$, $\beta = 117.45(1)$, space group $Pc$, Mo-$K_\alpha$, 7019 reflections measured, 3318 reflections with $I > 2\sigma(I)$, $R_1 = 0.0366$, $wR_2 = 0.0779$. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No CCDC-241154.