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3-Alkoxy-1,2-Dioxolanes: Synthesis and Evaluation as Potential Antimalarial Agents

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Abstract

A number of 3-alkoxy-1,2-dioxolanes exhibit promising levels of antimalarial activity against Plasmodium falciparum. A new route to the 1,2-dioxolane core is reported based on tandem peroxidation/cyclization of enones.

Keywords: Malaria, peroxide, 3-alkoxy-1,2-dioxolane, dioxolane

Malaria is a global health epidemic affecting approximately 250 million people and causing over 800000 deaths annually. The peroxide artemesinin, along with closely related artesunate and arteether, are a critical part of therapies against drug-resistant strains of P. falciparum, the most virulent form of the disease. Strong antimalarial activity has also been observed with a number of artemisinin analogues. However, reports of delayed parasite clearance in patients receiving artemisinin combination therapy (ACT) have led to renewed interest in structurally distinct classes of peroxides. Promising levels of antimalarial activity have been observed from a number of relatively simple peroxide skeletons. Struck by the high antimalarial activity of 1,2,4-
trioxolanes (ozonides), one of which is currently in phase III trials, we became interested in nearly isosteric 3-alkoxy-1,2-dioxolanes. We now report the synthesis of a number of alkoxydioxolanes along with in vitro antimalarial data.

The antimalarial activity of artemisinin is believed to derive from Fe(II)-mediated fragmentation of the peroxide to generate intermediate alkoxy radicals, which undergo rapid β-fragmentation or 1,5-hydrogen abstraction to generate reactive carbon radicals. The ozonides discussed above have also been established to undergo Fe(II)-mediated cleavage to generate carbon radicals. 1,2-Dioxolanes, which are nearly isosteric with ozonides, would appear to offer a promising platform for development of new peroxide antimalarials. However, to date, few 1,2-dioxolanes have demonstrated significant antimalarial activity. One reason may be the lack of an α-oxygen, resulting in a reduced propensity for β-scission in the derived alkoxy radicals. We postulated that suitably substituted 3-alkoxy-1,2-dioxolanes might be excellent antimalarial candidates, providing a stable framework that would undergo activation by Fe(II) to furnish α-oxygenated alkoxy radicals predisposed toward β-scission (Scheme 1).

Scheme 1
Competing Modes of Alkoxydioxolane Activation

3-Alkoxy-1,2-dioxolanes are available from the corresponding 1,2-dioxolan-3-ols via acid- or base-promoted etherification. We initially pursued the 3,5,5-trimethyl-1,2-dioxolan-3-ol (1) and 5-butyl-3,5-dimethyl-1,2-alkoxydioxolan-3-ol (3) core structures (Scheme 2). A number of methods have been reported for the synthesis of 1,2-dioxolanols, including base-mediated addition of hydrogen peroxide to α,β-unsaturated ketones, radical oxygenation of cyclopropanols, thermolysis of aza-hydroperoxides, or addition of singlet oxygen to methylallyl aldehydes. However, none of these methods have been generally applied. Peroxide 1 was readily prepared through base-mediated addition of hydrogen peroxide to mesityl oxide. However, as feared, application of similar conditions to the more hydrophobic 4-methyl-3-octen-2-one (2) mainly furnished the product of nucleophilic epoxidation. Fortunately, cobalt-mediated oxygenation of 2, originally envisaged as a route to an intermediate 3-trialkylsilyperoxy alkanone, directly afforded the desired 1,2-dioxolan-3-ol 3. Acid-catalyzed transterification to form the alkoxydioxolanes could be conducted on the 1,2-dioxolanol-3-ols (not shown) but proceeded more cleanly on the corresponding trimethylsilyl ethers (1a and 3a; Table 1). Three of the alkoxydioxolanes (5, 7, and 8) demonstrated significant in vitro activity against P. falciparum with dioxolane 8 displaying an IC50 less than 100 nM. On the basis of these results, we became interested in surveying influences of the following structural elements: a spirocyclic constraint at C1/C2, the size of the C3 alkoxide, and the nature of the putative radical leaving group at C3.

Scheme 2
Synthesis of Dioxolanol Core Structures

Table 1
Initial Alkoxydioxolane Synthesis and Bioassay

The synthesis of 1,2-dioxolanes incorporating a spirocyclic constraint is illustrated in Scheme 3. Prins reaction of methylene cyclohexane with acetaldehyde or phenylacetaldehyde furnished homoallyl alcohols 9 and 10, which
underwent Swern oxidation to furnish β,γ-unsaturated ketones 11 and 12. Co-mediated dioxygenation (O₂, Et₃SiH) by a modification of Isayama's protocol directly furnished 1,2-dioxolan-3-ols 13 and 14. Although the dioxolanols could be carried on directly, purification was more easily conducted on the derived trimethylsilyl ethers, 13a and 14a. Dioxolanol 17, which incorporates a better radical leaving group (benzyl) at C₃, was prepared via a benzyl/methallyl ketone, as illustrated in Scheme 4.

We were unsuccessful in applying a similar approach to a more hindered 1,2-dioxolan-3-ol (20) incorporating both a C₅/C₅′ spirocycle and a branched side chain at C₃ (not shown). However, this target could be prepared via dioxygenation of a cyclopropanol. As illustrated in Scheme 5, conversion of dicyclohexylketone to the corresponding trimethylsilyl enol ether, followed by Simmons–Smith cyclopropanation, furnished trimethylsilyloxycyclopropane 18, accompanied by varying amounts of 19, presumably reflecting during work up. Desilylation with TBAF furnished a tetrasubstituted cyclopropanol (19), which could be converted to 20 by stirring in benzene under an atmosphere of oxygen.

Acid-catalyzed S₅⁻¹ transetherification of the dioxolanols or their trimethylsilyl ethers with primary alcohols furnished 3-alkoxydioxolanes 21−25 (Table 2). The alkoxydioxolanes proved to possess remarkable chemical stability, failing to react with either PPh₃ (≥24 h, room temperature) or i-Bu₂AlH (≥4 h, room temperature).

The results of in vitro testing for compounds 21−25 (Table 2), when taken together with the results described in Table 1, suggest clear trends in terms of antimalarial structure–activity relationships. Activity is enhanced by a spirocyclohexyl constraint at C₅/C₅′ and by the presence of steric bulk at C₃. Dioxolanes 21 and 25, which combine a spirocyclohexyl unit with either a bulky C₃ alkyl substituent or a large C₃ alkoxide displayed IC₅₀ values below 10 nM.

Finally, we were interested in investigating the Fe(II) reactivity of the alkoxydioxolanes, and, in particular, the extent of cleavage of the derived alkoxy radicals (see Scheme 1). Alkoxydioxolane 25, one of our most active of our initial leads, underwent reaction with FeBr₂ to furnish the corresponding 3-hydroxyester in 80% yield (reaction illustrated in Scheme 1), supporting the postulated formation and fragmentation of an alkoxy-substituted alkoxy radical 12,13. Similar results have been reported for a monocyclic alkoxydioxolane.

In conclusion, we have developed new and expanded routes to 1,2-dioxolan-3-ols and 3-alkoxy-1,2-dioxolanes. The latter are demonstrated to provide a highly promising platform for development of a new family of antimalarial peroxides.
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Supporting Information Available
Complete experimental procedures and characterization data; $^1$H and $^{13}$C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Notes
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Supplementary Material

References


16. Several alternatives to Fe(II)-mediated formation of reactive radicals have been proposed as the basis for the biological activity of peroxide antimalarials. For an excellent overview of this discussion, see O'Neill P. M.; Barton V. E.; Ward S. A. The Molecular Mechanism of Action of Artemisinin—The Debate Continues. Molecules 2010, 15, 1705–1721. [PubMed]


26. Reported in vitro antimalarial activity is based upon an average of two independent assays using the [3H]-hypoxanthine incorporation method with the P. falciparum strain NF54 obtained from MR4: Huber W.; Koella J. C. A comparison of three methods of estimating EC50 in studies of drug resistance of

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