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Synthesis and Antimalarial Activity of 2-Methoxyprop-2-yl Peroxides Derivatives

Laure Cointeaux,[a] Jean-François Berrien,[a,*] Viviane Peyrou,[a] Olivier Provot,[a] Liliane Ciceron,[b] Martin Danis,[b] Anne Robert,[c] Bernard Meunier[c] and Joëlle Mayrargue[a,*]

[a]*UPRES A 8076 BioCIS, Laboratoire de synthèse et conception des molécules d'intérêt thérapeutique, Faculté de Pharmacie, rue J.-B. Clément, F-92296 Châtenay Malabry Cedex, France*

[b]*INSERM U511, Immuno-biologie cellulaire et moléculaire des infections parasitaires, Groupe hospitalier Pitié-Salpétrière, F-75013 Paris, France*

[c]*Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077 Toulouse cedex 4, France*

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Abstract—2-Methoxyprop-2-yl peroxides were synthesized and evaluated in vitro against *Plasmodium falciparum*. These acyclic artemisinin-related peroxides revealed moderate to good activity but were devoid of alkylating property towards the synthetic model of heme Mn^{II}-TPP.

Malaria is the most widespread infection disease. It is world widespread and affects about 300 million people causing from one to three million deaths every year. Moreover *Plasmodium* resistance to classical therapy such as choroquine has considerably increased. Artemisinin **1** and related trioxanes have received considerable attention as alternative therapy since their fast antimalarial activity was maintained against chloroquine resistant strains of *Plasmodium falciparum*.[1] Their antimalarial activity was dependent of endoperoxide interaction with intraparasitic heme. Monoelectronic transfer from iron(II) to peroxide function resulted in the cleavage of endoperoxide bond with primary formation of an unstable oxygen centred radical, rearrangement and creation of a C centred radical.[2] Such a radical was able to alkylate the hemin as it has been experimentally shown with manganese(II) tetraphenyl porphyrin (Mn^{II}–TPP)[3] or more recently with hemin.[4] That would be lethal for the parasite through the accumulation of non polymerisable redox-active heme adducts.[5] These radicals may also be responsible for the alkylation of proteins[6,7] and that could also be lethal for the *Plasmodium*.[7] However, the final mechanism responsible of the death of the parasite has not yet been definitely determined (Fig. 1).[8]

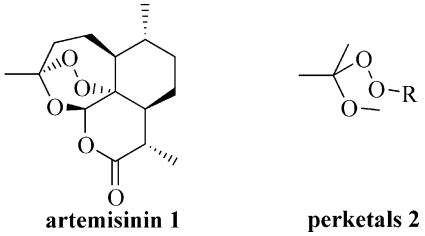

Figure 1.

As a part of our research on antimalarial peroxide with simple synthetic access, we focused our attention on 2-methoxyprop-2-yl peroxides **2**. These perketals have been previously developed by Dussault as useful synthetic precursors of hydroperoxides.[9] We used this procedure which proved to be a far superior method compared to others for preparing our sensitive hydroperoxides.[10] We have also focused our attention on these simple accessed linear perketals **2** for their biological properties. We reported recently their powerful trichomonacidal activity.[11,12] Anaerobic *Trichomonas vaginalis* was, for example, 10 times more sensible to

*Corresponding author. Tel.: +33-1-4683-5686; fax: +33-1-4683-5323; e-mail: jean-francois.berrien@chimorg.u-psud.fr

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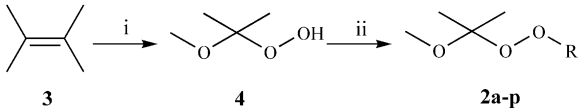
2-methoxyprop-2-yl hexadec-1-yl peroxide than to the reference compound Metronidazole.[12]

Perketals **2** could also constitute acyclic analogues of artemisinin **1** and related trioxanes since they both contained an α-alkoxyperoxide function essential for antimalarial activity.[13] We reported herein the synthesis and antimalarial activity of a series of 2-methoxyprop-2-yl peroxides.

Synthesis

2-Methoxyprop-2-yl peroxides were prepared according to Dussault procedure.[9a] Ozonolysis of 2,3-dimethylbutene **3** in methanol afforded 2-methoxyprop-2-yl hydroperoxide **4** that reacted with alkyl bromides **5a–p** under mild conditions to give perketals **2a–p** into moderate to good yields (Scheme 1).[11,12]



Scheme 1. Synthesis of perketals **2a–p**. Reagents and conditions: (i) O_3, MeOH, −78 °C; (ii) RBr **5a–p**, CsOH, BHT, DMF, rt.

Antimalarial Activity

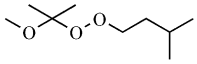
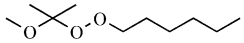
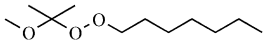
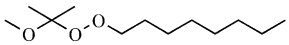
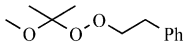
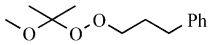
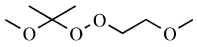
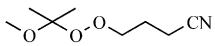
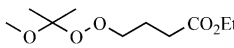
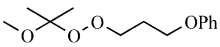
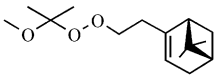
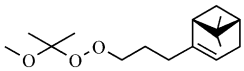
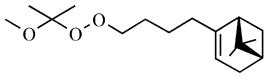
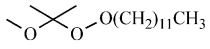
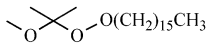
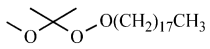
Perketals **2a–p** were evaluated in vitro against *P. falciparum* FCR3 strain.[14] They all revealed antimalarial activity with IC_{50} ranging from 10^{-5} to 10^{-7} M. The most active compounds (**2k**, **2m**) were about one eighth of the antimalarial potency of artemisinin on this strain, and were substituted with alkyl pinenyl group. Other perketals **2** with apolar radical chain tested herein had medium to good activities. The less active compounds had an alkyl chain substituted with a polar moiety, that is a nitrile (**2h**), an ester (**2i**) or in a lesser extent an ether function (**2g**). Previously reported arachidonic acid derived Dussault perketals had an alkenyl chain, end substituted with CH_2–CH_2–CO_2H or O–CH_2–CO_2H.[13] They showed a weak activity against *P. falciparum* (respectively, 36 and 14% inhibition in vitro at 4.10^{-5} M).[13] It appeared clearly that introduction of a polar function on this alkyl chain is deleterious for a good antimalarial activity.

Antimalarial activities of acyclic perketals have been previously reported in the literature but still remained weak compared to those of polycyclic compounds like artemisinin **1**.[16] However, literature reported very recently the first example of potent antimalarial acyclic perketals.[17] Some of the most active bis(alkyldioxy)-alcanes depicted in there showed in vitro about 1/8th of the artemisinin potency; therefore, to the best of our knowledge, the 2-methoxyprop-2-yl alkyl peroxides reported here are the second example of acyclic antimalarial compounds with similar potency for the most active ones (Table 1).

Alkylating Properties

Two of the most potent compounds, **2k** and **2m**, were evaluated for they alkylating property of the heme following the Meunier model.[3] They both were incubated with a manganese(II) complex of tetraphenylporphyrin generated in situ by *n*-Bu_4NBH_4 reduction of Mn^{III}(TPP)Cl. After demetallation, the tetraphenylporphyrin was recovered unchanged in both cases. These perketals **2k**,**m** did not alkylated heme model, as

Table 1. Structure and in vitro antimalarial activities of compounds **2a–p** against FCR3 *P. falciparum* strain

Compd[a,b]	Structure	Activity[c] IC_{50} (nM)
2a[a]		1650[d]
2b[b]		1550[e]
2c[b]		800[e]
2d[b]		2600[e]
2e[b]		520[e]
2f[a]		660[e]
2g[a]		3200[e]
2h[b]		12,800[e]
2i		6950[e]
2j[b]		870[e]
2k[a]		370[d]
2l[b]		600[e]
2m		480[d]
2n[b]		670[e]
2o[b]		440[e]
2p[b]		1330[e]
Chloroquine		170[e]
Artemisinin		55
Artemether		14

[a]For physicochemical data see ref 11.
[b]ref 12.
[c]Experiments were conducted in duplicate.
[d]Artemisinin was the reference compound.
[e]Artemether was the reference compound.

unlike artemisinin[3] and other related trioxanes.[18] However it was not excluded that they could interact with heme to generate radicals that had no heme alkylating property as it was reported for other peroxides.[15] They showed a different mechanism of action albeit they could be assimilated to linear trioxane analogues.

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