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Synthesis and Antimalarial Activity of 2-Methoxyprop-2-yl peroxides derivatives.

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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 devoided of alkylating property towards the synthetic model of haeme Mn^{II} – TPP.

Malaria is the most widespread infection disease. It is worldwide aspread 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 *P. falciparum*.¹ Their antimalarial activity was dependent of endoperoxide interaction with intraparasitic haeme. Mono-electronic transfert from iron (II) to peroxide function resulted in the cleavage of endoperoxide bond with primary formation of an unstable oxygen centered radical, rearrangement and creation of a C centered radical.² Such a radical was able to alkylate the haemin as it has been experimentally shown with manganese (II) tetraphenyl porphyrin (Mn^{II} – TPP)³ or more recently with haemin.⁴ That would be lethal for the parasite through the accumulation of non polymerisable redox-active haeme 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.⁸

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 trichomonocidal activity.^{11,12} Anaerobic *Trichomonas vaginalis* was for example ten times more sensible to 2-methoxyprop-2-yl hexadec-1-yl peroxide than to the reference compound Metronidazole.¹²

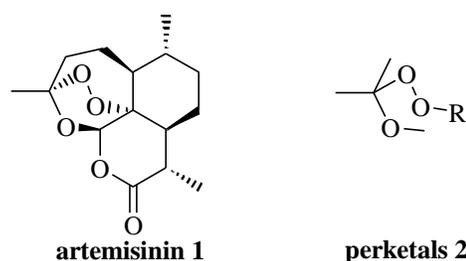


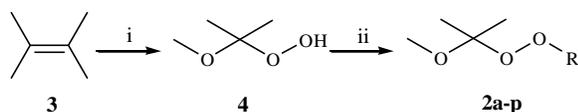
Figure 1.

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, *i.e.* 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.^{11, 12}



Scheme 1. Synthesis of perketals **2a-p**. Reagents and conditions: (i) O₃, 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 IC₅₀ 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 *i.e.* 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 CH₂-CH₂-CO₂H or O-CH₂-CO₂H. They showed a weak activity against *P. falciparum* (respectively 36 and 14 % inhibition *in vitro* at 4.10⁻⁵ M). It appeared clearly that introduction of a polar function on this alkyl chain is deleterious for a good antimalarial activity.

Alkylating properties

Two of the most potent compounds, **2k** and **2m** were evaluated for they alkylating property of the haeme following the Meunier model.³ They both were incubated with a manganese (II) complex of tetraphenylporphyrin generated *in situ* by *n*-Bu₄NBH₄ reduction of Mn^{III}(TPP)Cl. After demetallation, the tetraphenyl-porphyrin was recovered unchanged in both cases. These perketals **2k,m** didn't alkylated haeme model, as unlike artemisinin³ and other related trioxanes.¹⁵ However it was not excluded that they could interact with haeme to generate radicals that had no haeme alkylating property as it was reported for other peroxides.¹⁶ They showed a different mechanism of action albeit they could be assimilated to linear trioxane analogues.

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

Compound ^{a,b}	Structure	Activity ^c IC ₅₀ , nM
2a^a		1 650 ^d
2b^b		1 550 ^e
2c^b		800 ^e
2d^b		2 600 ^e
2e^b		520 ^e
2f^a		660 ^e
2g^a		3 200 ^e
2h^b		12 800 ^e
2i		6 950 ^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		1 330 ^e
Chloroquine		170 ^e
Artemisinin		55
Artemether		14

For physicochemical data see ^a ref 11, ^b ref 12. ^c experiments were conducted in duplicate. ^d artemisinin was the reference compound. ^e artemether was the reference compound.

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