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Antimalarial chemotherapy: Artemisinin-derived dimer carbonates and thiocarbonates

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ABSTRACT

Several 2-carbon-linked trioxane dimer secondary alcohol carbonates **14** and thiocarbonates **15**, combined with mefloquine and administered in a low single oral dose, prolonged the survival times of malaria-infected mice much more effectively than the popular monomeric antimalarial drug artemether plus mefloquine. Three dimer carbonates **14** and one dimer thiocarbonate **15** partially cured malaria-infected mice.

In 2013, a total of 107 countries reported malaria as an ongoing epidemic exposing an estimated 3.4 billion people to the *Plasmdium falciparum* malaria parasites.[1] Nearly one million people, mostly children, die each year from infection with malaria.[2–4] While ongoing efforts have been made toward the development of a fully prophylactic malaria vaccine, only partial success has been reported.[5,6] The efficacy of antimalarial chemotherapy using standard drugs like chloroquine is being severely compromised by widespread parasite resistance.[7,8] Therefore, the discovery of a new class of peroxide-containing antimalarials such as artemisinin (**1**)[9] and its first generation derivatives artemether (**2**) and sodium artesunate (**3**) has led to their widespread use (Fig. 1). Indeed, the World Health Organization (WHO) now recommends artemisinin combination therapy (ACT) as standard operating procedure, combining a fast-acting but short-lived trioxane with a long-lasting adjuvant.[10] Current examples of combinations include artemether (**2**) plus lumefantrine (**4**),[11] artesunate (**3**) plus mefloquine (**5**), and artesunate (**3**) plus pyronaridine (**6**).[12] An ideal regimen for curing infected people is a single low oral dose of ACT. Toward this goal, others[13–18] and we[19–22] have prepared several artemisinin derivatives that cure malaria-infected mice.

Guided by structure–activity relationships (SAR), ongoing efforts have been made toward improving the oral bioavailability and minimizing the metabolic shortcomings of artemisinin and its first generation derivatives.[23] Tethering two artemisinin units together through the C10 position forms a C10 non-acetal dimeric trioxane structure, which has proven often to be more antimalarially potent than its corresponding monomeric counterpart.[24–26] We have highlighted the high efficacy of a low single oral dose ACT using new artemisinin-derived trioxane dimers with linkers of different length: 5-carbon (**7**),[27] 4-carbon (**8**),[28] 3-carbon (**9**),[29,30] and 2-carbon (**10**, Fig. 2). Two-carbon-linked trioxane dimer ketone **10** (prepared from artemisinin in 36% overall yield) and especially some of its oxime NH-aryl carbamates **11** are effective antimalarials,[31] as are 2-carbon-linked dimer secondary alcohols **12a** and **12b**; using only a single low oral dose of several NH-aryl carbamate derivatives **13** combined with mefloquine hydrochloride substantially prolonged the survival times of malaria-infected mice (Scheme 1).[31,32]

Encouraged by our recent results,[31,32] we prepared a novel series of 2-carbon-linked dimer carbonates **14a–l** and thiocarbonates **15a–c** (Scheme 2). The log*P* values for all of these orally bioavailable dimer carbonates **14a–l** and thiocarbonate **15a–c** range between 7.3 and 9.3.[33] The log*P* value of parent secondary alcohol **12b** is 6.0.[33] The log*P* of artemether (**2**) is 3.5.[33] Facile conversion of parent secondary alcohol **12b** was accomplished in one step from commercially available chloroformates and thiochloroformates,

Abbreviations: SAR, structure–activity relationship; ACT, artemisinin combination therapy; HPLC, high performance liquid chromatography; DMAP, 4-dimethylaminopyridine; Py, pyridine.

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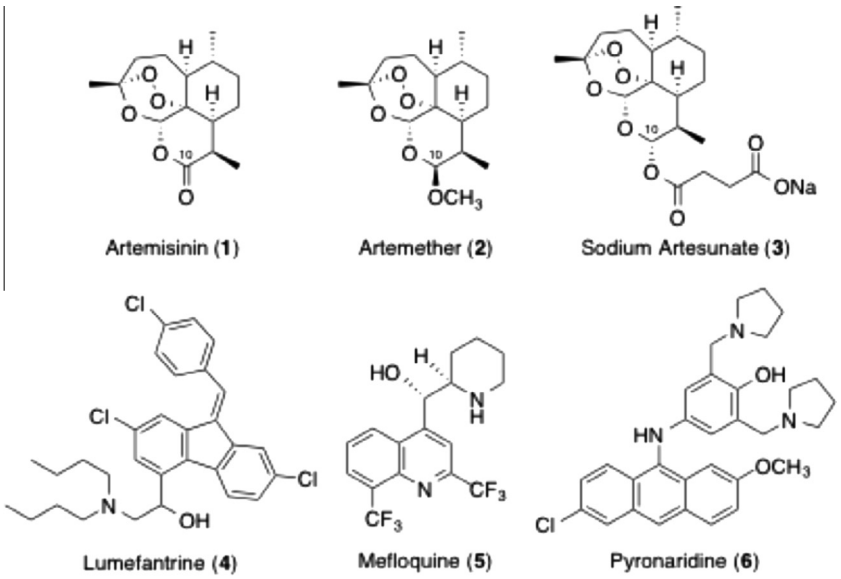


Figure 1. Artemisinin (**1**), first generation derivatives (**2** & **3**), and adjuvant therapeutic drugs used in ACT (**4**–**6**).

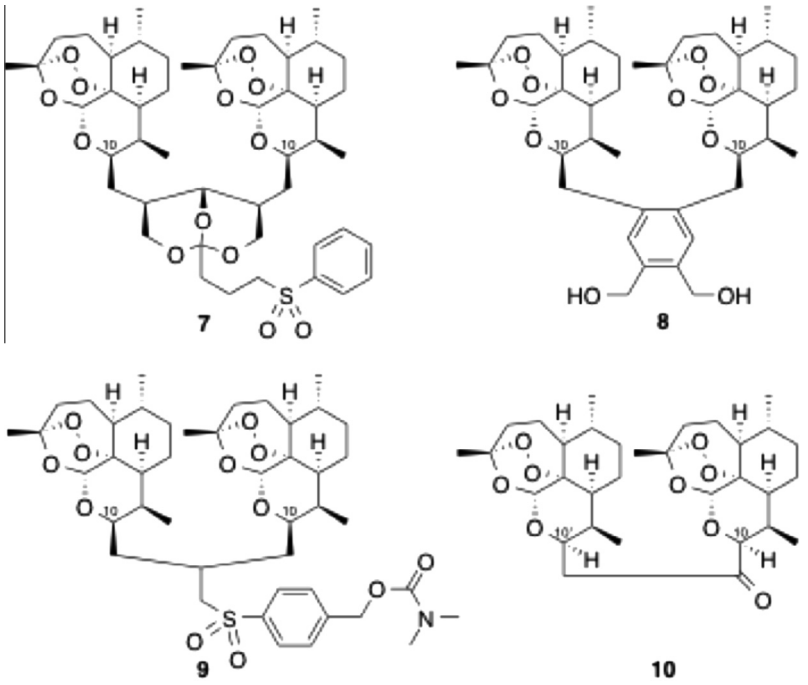
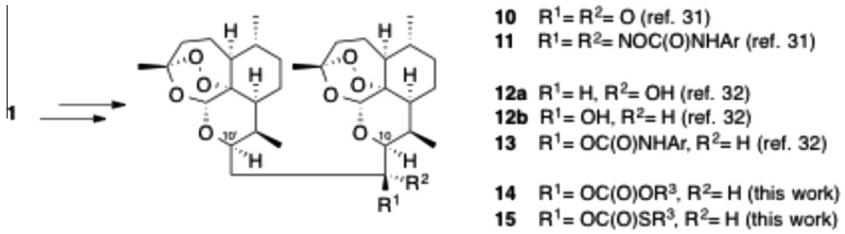


Figure 2. Representative 5-, 4-, 3-, and 2-carbon-linked dimer trioxanes.



Scheme 1. Two-carbon-linked dimer derivatives.

producing fifteen carbonates **14** and thiocarbonates **15** in moderate to high yields. In such cases where the purified product yield was less than 50% (**14b** and **14f**), starting dimer alcohol was recovered. All carbonates **14** and thiocarbonates **15** were purified by