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Research paper

Synthesis and antimalarial activity of quinones and structurally-related oxirane derivatives

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ABSTRACT

A series of eighteen quinones and structurally-related oxiranes were synthesized and evaluated for *in vitro* inhibitory activity against the chloroquine-sensitive 3D7 clone of the human malaria parasite *Plasmodium falciparum*. 2-amino and 2-allyloxynaphthoquinones exhibited important antiplasmodial activity (median inhibitory concentrations (IC_{50}) < 10 μM). Oxiranes **6** and **25**, prepared respectively by reaction of α-lapachone and tetrachloro-*p*-quinone with diazomethane in a mixture of ether and ethanol, exhibited the highest antiplasmodial activity and low cytotoxicity against human fibroblasts (MCR-5 cell line). The active compounds could represent a good prototype for an antimalarial lead molecule.

1. Introduction

Naphthoquinones and derivatives are important due to their demonstrated activity against several pathogenic microorganisms such as *Trypanosoma cruzi* (protozoan that causes American leishmaniasis or Chagas' Disease) [1–3], *Plasmodium falciparum* and *Plasmodium berghei* (protozoans that cause severe human and rodent malaria, respectively) [4,5], and human immunodeficiency virus (HIV) [6] and insects such as the mosquito species *Aedes aegypti* [7]. The naphthoquinones lapachol (**1**) and β-lapachone (**2**) are isolated from South American trees of the genus *Tabebuia* that have been used traditionally by indigenous people to treat many parasitic infections, including malaria [8].

Compound **1** has been used in the past as a co-adjuvant in the treatment of malignant solid tumors but its use was discontinued due to concerns about its toxicity [9,10]. Later, hydroxypropyl-β-cyclodextrin-encapsulated β-lapachone (**2**) was named ARQ501 (ArQule Inc.) and investigated in a phase II clinical [11] in combination with Taxol® or gemcitabine [12,13]. An important variation, the water-soluble prodrug of **2**, ARQ 761 (Code C99146, structure not reported) [14], is currently in clinical trial [15] and requires less solvent in the formulation for intravenous administration and consequently less hemolytic anemia is associated with administration of ARQ 761.

The antitumor mechanism of action of quinones is based on redox cycling that represents a cyclic process of reduction of a compound, followed by (auto)-oxidation of the reaction product and generation of reactive oxygen species (ROS) [16]. Conversely, the reduction reaction of the quinone moiety via acceptance of one or two electrons followed by oxidation by oxygen cause the formation of ROS. Also, it is known that reactive oxygen species formed in excess in the intracellular environment are able to activate the intrinsic pathway of apoptosis by the permeabilization of mitochondria and activation of caspase 9. This may be the mechanism responsible for the cytotoxic action of these substances, both on micro-organisms, as well as on tumor cells [17].

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The general structures of compounds **1** and **2** have been widely exploited in medicinal chemistry as prototypes for new candidates against cancer and parasitic infections. Atovaquone (**3**) is synthesized starting from **1** and is used as a therapeutic drug in the treatment or prevention of mild cases of infection by *Plasmodium vivax* (in combination with proguanil) [18–20], although there have been cases of resistance reported [21]. It also can be used for pneumocystosis, toxoplasmosis and babesiosis (usually in combination with azithromycin). Two similar compounds, buparvaquone (**4**) and parvaquone (**5**), are pharmaceuticals for veterinary use (Fig. 1).

Substitution of a carbonyl of naphthoquinone by another group has generated new compounds with important biological activities. Also, epoxynaphthoquinones distributed in nature and the natural 6α-acetoxygedunin (**8**) exhibit interesting biological activities [22]. Substance **6** was synthesized from α-lapachone and was the only oxirane that showed high trypanocidal activity with excellent minimal cytotoxicity in VERO cells. Comparatively, oxirane **7** exhibited similar trypanocidal activity to β-lapachone (**2**). The major mechanism of trypanocidal action of naphthoquinones is by inducing intracellular damage caused by oxidative stress due to the quinonoid moiety. Our group synthesized compounds **6** [23] and **7** [24] and found that they inhibited the serine proteinase of *T. cruzi* leading to interference in the establishment of infections [25–27]. Recently we have shown that oxirane **6** has leishmanicidal effects on *Leishmania (Viannia) braziliensis* and *L. amazonensis* [28]. This compound was able to cause death of promastigote and amastigote forms of *Leishmania* spp. after 3 h of exposure [29].

Recently we reported naphthoquinones with activity against *P. falciparum* [30,31]. These compounds act via ROS production. However, oxiranes act by inhibiting proteinase enzymes (Fig. 2). Protozoans comprise a very diverse group of unicellular eukaryotic organisms [32], which include *Plasmodium*, *Trypanosoma* and *Leishmania* parasites, among others. Based on the good biological activity obtained with oxiranes derived from naphthoquinones against *T. cruzi* and *Leishmania* spp. we decided to synthesize a series of oxiranes and to investigate their activity against the chloroquine-sensitive 3D7 clone of the human malaria parasite *P. falciparum*. It was assumed that these oxiranes would have antimalarial activity. The purpose of this study was to prepare oxirane derivatives of naphthoquinones and test them for antiplasmodial activity and cytotoxicity as a means to search for new antimalarial compounds. Herein we report our findings on the antiplasmodial and cytotoxic activity of these naphthoquinone-derived oxiranes.

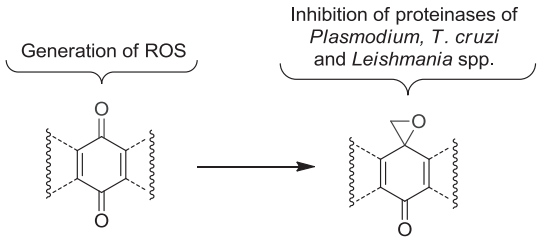

Fig. 2. General rationale used in this study.

2. Results and discussion

The substances used in the screening against the chloroquine-sensitive 3D7 clone of *P. falciparum* were prepared in one step from the appropriate quinone by adding a freshly prepared solution of diazomethane in ether (Scheme 1). The reaction proceeds by nucleophilic attack of diazomethane on the more electrophilic carbonyl of quinones **9**–**17** and fluorenone (**18**) yielding oxiranes **6**, **7**, **19**–**23**, **25** and the unexpected non-oxirane compounds **24**, **26** and **27**. In general, reaction occurred at carbonyl C-1 due to the higher electrophilicity provided by the adjacent heteroatom substituent.

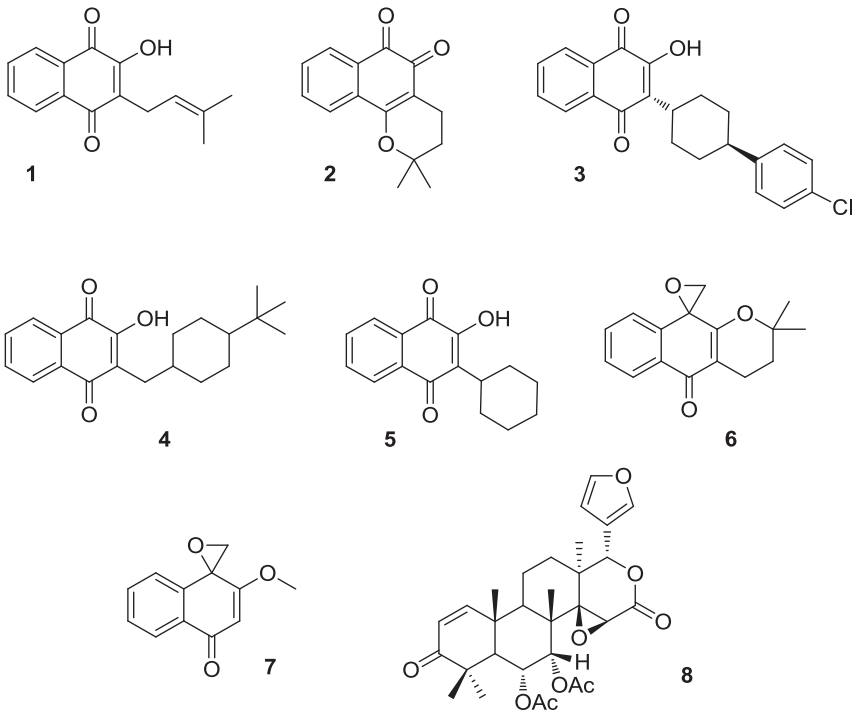

Fig. 1. Natural and synthetic substances with activity against parasitic infections.