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Research paper

Rhodium-catalyzed C-H bond activation for the synthesis of quinonoid compounds: Significant Anti-*Trypanosoma cruzi* activities and electrochemical studies of functionalized quinones

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ABSTRACT

Thirty four halogen and selenium-containing quinones, synthesized by rhodium-catalyzed C-H bond activation and palladium-catalyzed cross-coupling reactions, were evaluated against bloodstream trypomastigotes of *T. cruzi*. We have identified fifteen compounds with IC_{50}/24 h values of less than 2 μM. Electrochemical studies on A-ring functionalized naphthoquinones were also performed aiming to correlate redox properties with trypanocidal activity. For instance, (*E*)-5-styryl-1,4-naphthoquinone **59** and 5,8-diiodo-1,4-naphthoquinone **3**, which are around fifty fold more active than the standard drug benznidazole, are potential derivatives for further investigation. These compounds represent powerful new agents useful in Chagas disease therapy.

1. Introduction

Chagas disease, caused by *Trypanosoma cruzi* (*T. cruzi*), is classified as a neglected tropical disease by the World Health Organization. This disease has high morbidity and mortality rates, affects 5–7 million people and displays a limited response to therapy [1]. It is transmitted to humans by triatomine vectors, blood transfusions, oral and congenital routes and less commonly, by organ transplantation, and laboratory accidents [2]. Chagas disease is characterized by two clinical phases: a short, acute phase defined by patent parasitemia and a long, progressive chronic phase. The acute phase appears shortly after infection and is frequently asymptomatic. After 2–3 months, in most infected individuals, a host/parasite balance is achieved, leading to the chronic phase. Approximately two thirds of infected individuals remain in the indeterminate chronic form, but after 10–30 years, the other third will develop a symptomatic chronic disease with digestive and/or cardiac disturbances [3]. Two current major concerns are outbreaks of acute Chagas disease associated with the ingestion of contaminated food [4], and the disease's emergence in non-endemic areas such as North America and Europe, due to the immigration of infected individuals [5].

T. cruzi is a hemoflagellate protozoan and its life cycle involves distinct forms during its passage through vertebrate and invertebrate hosts. The trypomastigote form ingested by the insect differentiates into the proliferative epimastigote form, which, on reaching the posterior intestine of the insect, differentiates into the metacyclic form. The latter, following invasion of vertebrate host cells, undergoes differentiation into the amastigote form, which, after several reproductive cycles, transforms into the trypomastigote form, responsible for the dissemination of the infection.

The current treatment for Chagas disease is restricted to two nitroheterocyclic drugs, benznidazole (Bz) and nifurtimox (Nif),

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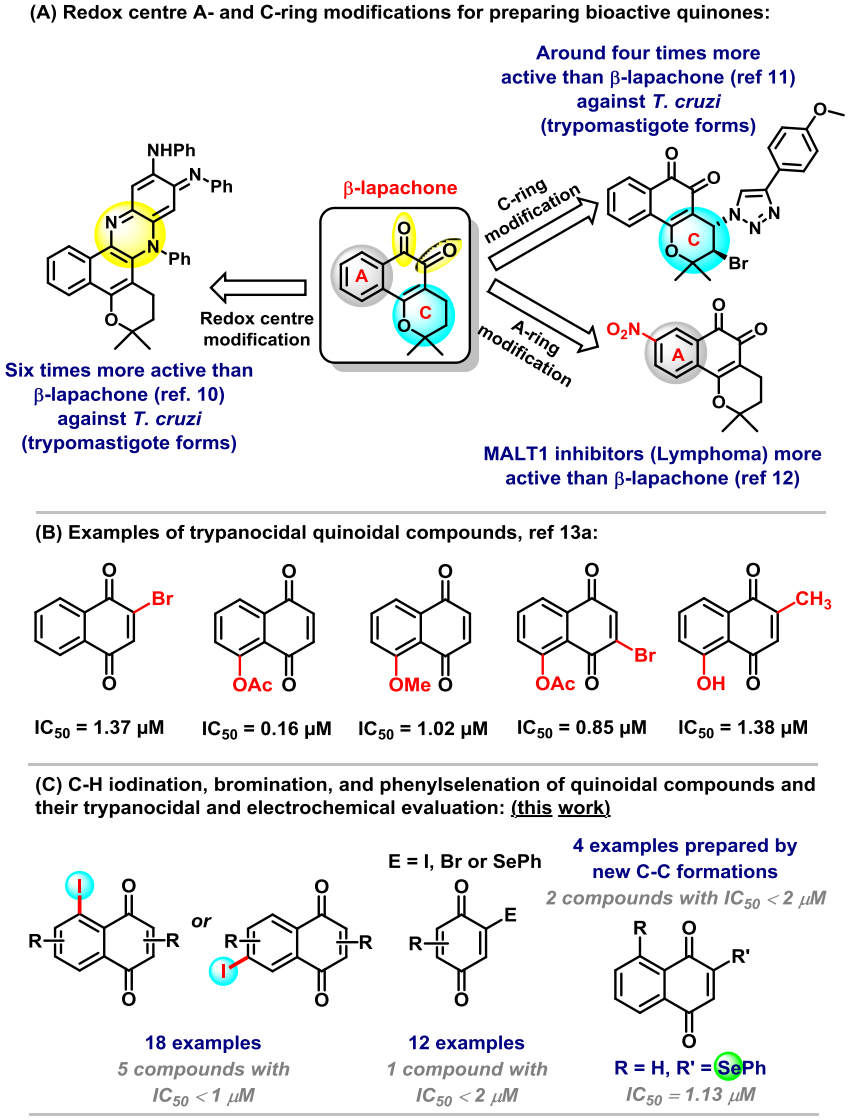
and their efficacy varies according to the phase of the disease, with their effectiveness decreasing with advancement of the infection [6]. The major limitations of these drugs are their limited and variable curative activity in the established chronic form of the disease and their toxic effects, leading to treatment abandonment in several instances [7]. These drawbacks justify the urgent need to identify better drugs to treat chagasic patients. In this context, an intensive research program has focused upon the search for alternative natural, semi-synthetic and synthetic lead compounds [8].

Over the last few years, our group has dedicated efforts to the synthesis and identification of novel naphthoquinoidal compounds with potent antiparasitic activity [9]. In this context, we have modified the "redox centre" A- and C-rings of lapachones with the aim of preparing new bioactive compounds [9c]. For instance, a simple redox centre modification of β-lapachone led to a phenazine derivative with trypanocidal activity about two and six times higher than benznidazole and the original quinone, respectively [10]. Intrinsically related to this strategy, we have demonstrated that appendage of a triazole group to the C-ring of β-lapachone affords a derivative four times more active against the parasite than the naphthoquinoidal precursor [11]. Recently, Lim and co-workers [12] described the synthesis and evaluation of A-ring modified lapachones, which show activity against cancer cells (Scheme 1A); this study is of direct relevance to the strategies outlined herein.

Salomão and co-workers have reported the trypanocidal activity of C-2 and C-5 substituted naphthoquinones, as well as evidence for their mode of action [13]. As shown in Scheme 1B, in assays performed in the absence of blood and with incubation at 37 °C several compounds presented IC_{50} values of <2 μM against *T. cruzi*. For instance, further assays with 5-acetoxy-1,4-naphthoquinone (IC_{50} = 0.16 μM) revealed activity against the proliferative forms of *T. cruzi*, intracellular amastigotes and epimastigotes. In experiments with this latter parasite form, this compound led to mitochondrial swelling, vacuolization, and flagellar blebbing, as well as a remarkable decrease in the mitochondrial membrane potential and a discrete increase of ROS production. Such redox dependent effects are likely reliant on the acetyl group facilitating quinone reduction, as previously demonstrated by electrochemical analysis [13b]. These results show that A-ring substituted naphthoquinones can kill *T. cruzi* and highlight the importance of synthesizing and evaluating new quinoidal compounds against parasites.

Recently, our group has embarked on a research program aimed



Scheme 1. Overview.