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Synthesis, trypanocidal activity and molecular modeling studies of 2-alkylaminomethylquinoline derivatives

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ABSTRACT

Research and development of new drugs effective in the treatment of *Trypanosoma cruzi* infections are a real need for the 16 million people infected in the Americas. In a previous work, a quinoline derivative substituted by a 2-piperidylmethyl moiety showed to be active against Chagas disease and was considered a lead compound for further optimization. A series of ten analogous derivatives were tested against epimastigotes as a first approach. In view of their promising results, six of them were evaluated against the blood and intracellular replicative forms of the parasite in humans. Among them, compound **12** which possesses a 6-acetamidohexylamino substituent showed remarkable improvement in activity against epimastigotes, trypomastigotes and amastigotes compared with the structure lead, as well as a good selectivity index for the two parasite stages present in humans. In addition, treatment of infected mice with compound **12** induced a significant reduction in parasitemia compared with non-treated mice. Molecular modeling studies were performed by computational methods in order to elucidate the factors determining these experimental bioactivities.

1. Introduction

Chagas disease, also known as American trypanosomiasis, is caused by the flagellate protozoan *Trypanosoma cruzi*. One century after its discovery, Chagas disease still remains a major health problem in Latin America [1]. In the past two decades, migration of thousands of paucisymptomatic infected persons from rural to urban areas in South America and from endemic regions to developed countries has changed the epidemiology of the disease [2,3]. Nowadays, it is an important public health issue in South America and an emerging disease in Europe and North America [4,5]. Chagas disease is characterized by an acute phase with high parasitemia, followed by an indeterminate stage that can last for years without signs or symptoms. Major complications, such as disability due to chronic cardiomyopathy and stroke, occur in 20–30% of patients in the chronic phase of disease [6].

Prophylactic and therapeutic vaccines have been pursued for decades but sterilizing immunity has not been achieved yet [7–10]. Therefore, chemotherapy remains the only treatment option for controlling infection once acquired, but none of the different chemotherapeutic strategies used in the past has proven consistently successful. Although other chemicals have been recently analyzed in the therapy of trypanosomiasis and several natural products such as quinone and terpene derivatives have also shown trypanocidal activity [11–13], the treatment modalities for trypanosomatid infections mostly rely on drugs that date back over 50 years and suffer from poor efficacy, high toxicity, and increasing resistance [14]. Accordingly, research and development of new drugs effective in the treatment of *T. cruzi* infections are a real need and novel strategies for drug design are required [15,16].

To develop other alternative drugs, new compounds have been searched based on empirical screening or ethnopharmacological studies. Thus, 2-substituted quinolines isolated from a Bolivian

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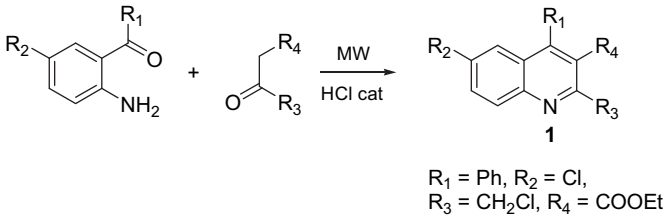
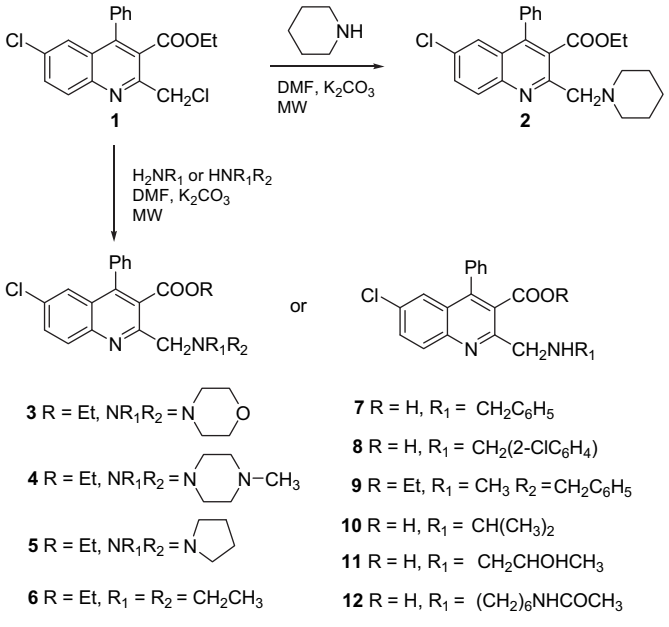


Scheme 1. Synthesis of quinolines *via* the Friedländer reaction.

medicinal plant, *Galipea longiflora* Kr (Rutaceae), have shown efficacy in the experimental treatment of cutaneous leishmaniasis as well as in Balb/c mice chronically infected with *T. cruzi* [17]. Later on, the synthesis of 2-substituted quinolines and their *in vitro* biological evaluation against the causal agent of Chagas disease among other parasites was reported [18]. Another series of quinolines were also synthesized and tested and one of them exhibited promising anti-trypanosomal activity [19]. Recently, a quinoline derivative having anticancer activity (tipifarnib) and synthesized analogs have shown strong activity against *T. cruzi* [20–22]. We have previously reported a series of polysubstituted quinolines synthesized *via* the Friedländer reaction employing microwave irradiation (MW) and a catalytic amount of hydrochloric acid (Scheme 1) [23]. These products were obtained in good yields at short times and were tested *in vitro* against the parasites causing malaria, leishmaniasis, sleeping sickness and Chagas disease at the Tropical Disease Research Laboratory, World Health Organization (WHO). This kind of structures had been designed considering the antiparasitic activity of 2-substituted quinoline alkaloids, many of which were isolated from medicinal plants [24,25].

Moreover, the 2-piperidylmethyl derivative **2** was prepared in good yields from the corresponding 2-chloromethylquinoline **1** under MW (Scheme 2) and was achieved in only 6 min instead of 3 h with conventional heating. This compound was moderately active against *Plasmodium falciparum* and active against *T. cruzi* epimastigotes [23]. Then, it was selected for a secondary *in vivo* screening at WHO and this assay was later repeated at higher doses (results not shown). In view of its remarkable performance,



Scheme 2. Synthesis of compound **2** and derivatives **3**–**12** (see Table 1)

compound **2** was considered a new lead compound for further optimization of trypanocidal activity.

In this work, the preparation of 2-alkylaminomethylquinoline-3-carboxylic acid derivatives (**3**–**12**) in good yields is described (Scheme 2 and Table 1). These syntheses were carried out in refluxing methylene chloride for conventional heating whereas under MW irradiation the reactions were neat.

The final products were evaluated *in vitro* against different developmental stages of *T. cruzi* (epimastigotes, trypomastigotes and amastigotes). With the aim of establishing preliminary structure–activity relationships (SAR) studies for these compounds, density functional theory (DFT) methods were employed to evaluate electronic properties such as molecular electrostatic potentials (MEPs), charge densities, dipole moments, and HOMO–LUMO energy values.

2. Results and discussion

2.1. Synthesis and anti-epimastigote activity

A series of ten 2-alkylaminomethylquinoline derivatives of the structure lead **2** (Table 1) were designed and synthesized by taking into account principles of medicinal chemistry such as isosterism, ring transformations, open-chain analogs and the inclusion of a suitable side chain containing a second protected amino group (compound **12**). This moiety was chosen because it is a recognized structure feature necessary for antimalarial activity of quinoline derivatives [26] and it is known that many compounds are active against both parasites. In addition, synthetic derivatives of the natural alkaloid piperine possessing different alkyl chain length with an amido group at the end, showed trypanocidal activity [27]. The acetamido group was selected just to protect the primary amine and could be assumed that it cleaves under test conditions to give the more reactive free primary amine.

The series of 2-alkylaminomethylquinoline derivatives were obtained by the nucleophilic substitution reaction of a variety of alkylamines and 2-chloromethyl-quinoline **1** under MW irradiation or conventional heating. Although the product yields were quite similar for both reaction-promoting methods, the reactions proceeded to completion in between 2 and 15 min when they were MW-assisted whereas otherwise 3–6 h were needed.

As first screening, the starting material **1**, the lead compound **2** and its ten analogs **3**–**12** were assayed *in vitro* against *T. cruzi* epimastigotes, using benznidazole as reference drug. Compounds **4**, **5**, **6** and **9** exhibited IC_{50} values against epimastigotes quite close to the lead compound (8.2 μM), whereas only compound **12**, which possesses a 6-acetamidohexylamino substituent, showed a remarkable improvement in activity (3.4 μM, Table 1). The replacement of the piperidyl moiety by N-methylpiperazinyl (**4**) caused a slight decrease in activity (IC_{50} 11.8 μM), as well as the ring contraction in the pyrrolidinyl derivative **5** (IC_{50} 10.0 μM) and its open-chain analog **6** (IC_{50} 11.6 μM). When the group benzylmethylamine was introduced (**9**), the resulting activity was also slightly decreased (IC_{50} 9.7 μM). The isosteric replacement of the piperidyl ring by morpholinyl (**3**) markedly decreased the activity (IC_{50} 85.3 μM). The introduction of benzyl and 2-chlorobenzyl moieties (**7** and **8**) led to products which could not be tested because of their low solubility. The presence of the *iso*-propyl group (**10**) as well as the 2-hydroxypropyl chain (**11**) decreased the activity against epimastigotes (IC_{50} 89.6 and 50.4 μM, respectively). It is worthy to note that the ethyl ester and the carboxylic acid groups attached at position 3 do not change the electronic properties of the whole quinoline nucleus and they do not influence the parameters for the nitrogen atom at position 2, according to our computational studies in this work and trypanocidal activity in previous results