Structural modifications and SAR studies on natural *alpha*-mangostin and its derivatives against *Trypanosoma cruzi* amastigotes

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Introduction

Mangosteen is a fruit tree (*Garcinia mangostana*, L.) of Asian origin, naturally occurring in Malaysia, Myanmar, Thailand, Philippines, Sri Lanka, and India. In 1855, *alpha*-mangostine (Mgt) (**1**, **Figure 1**) was identified among the main xanthones obtained from the pericarp of the mangosteen fruit. This compound has a broad spectrum of biological activities, as anti-inflammatory, antitumor, cardioprotective, antidiabetic, antibacterial, antifungal, antiparasitic, antioxidant and antiobesity agents.[1] Chagas disease (CD) or American trypanosomiasis is a parasitic disease that results from infection by the hemoflagellate protozoan *Trypanosoma cruzi*. Transmission of (CD) occurs mainly through the bite of an infected triatomine insect in an individual. It can also occur through the placenta or breastfeeding or, less commonly, from oral contamination. Although the acute phase of the infection is asymptomatic, some individuals acquire the chronic phase. This phase is characterized by the appearance of severe degenerative disorders in the host's vital organs, usually culminating in death. Only two drugs that are nearly 100 years old are used to treat CD, the nitroimidazole derivatives benznidazole and nifurtimox. However, neither of these drugs is effective during the chronic phase and both cause numerous toxic side effects.[2]

Results and discussion

The structural potential of the natural xanthone, Mgt **1** (**Figure 1**), its structural, physico-chemical characteristics, and its synthetic versatility classify it as a very interesting precursor in medicinal chemistry.[3] Herein structural modifications were carried out in Mgt, as hydrogenation (Pd/C), generating the reduced derivative; intramolecular acidic cyclization, leading to the formation of cyclic derivatives; and The acetylation reactions allowed exploring the different reactivity of phenolic hydroxyl groups, with the insertion of acetate substituents in different ways. Also, through the *O*-alkylation reaction, which allowed the insertion of the methyl portion to the fused ring system of the natural product, with these transformations it was possible to verify that the development of the activity is dependent on punctual changes. In this way, the insertion position, the type, and the characteristics of the substituents, allow to modulate the cytotoxicity of the derivatives (**Figure 1**).

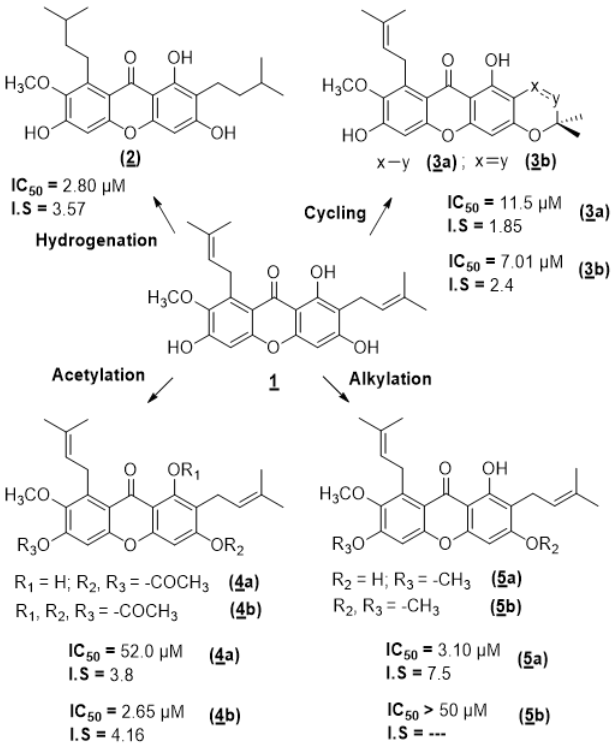

Figura 1. *Alpha*-mangostin derivatives; toxic activity (IC_{50}) against *T. cruzi* amastigotes; and selectivity index (S.I.).

Conclusions

The synthetic modifications performed in natural xanthone pointed out structural features responsible for potentiating its toxic effects on amastigotes of *T. cruzi* as well as modulating its toxicity on the mammalian host cells.

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