Synthesis and Preliminary Evaluation of Leishmanicidal Activity of Gibillimbol B derivatives

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Introduction

Visceral leishmaniosis is most commonly diagnosed in undeveloped countries, counting 500,000 new cases every year. The use of drugs such as amphotericin B and sodium stibogluconate are limited mainly by toxicity. Furthermore, the treatment, expensive and administered intravenously, requires a long-term commitment from the patient. Gibillimbol B is an alkenylphenol isolated from *Piper malacophyllum*, and its leishmanicidal activity against *Leishmania infantum chagasi* was recently determined by our group, leading to EC_{50} values of 23.32 and 22.06 µg/mL for promastigote and amastigote forms of the parasite, respectively.[1] The proposed mechanism for the action of gibillimbol B is membrane disruption of the parasite. Moreover, the selectivity index (EC_{50}/CC_{50} in NCTC mammalian cells) for gibillimbol B was 2.7, showing certain (but low) selectivity to the parasite cells. Our objective was to synthesize gibillimbol B derivatives to allow molecular exploitation of the pharmacophore, as well as preliminary SAR data of these compounds to improve the leishmanicidal activity.

Results and Discussion

Based on the structure of the gibillimbol B, 5 compounds (figure 1) were synthesized through classical synthetic methods (esterification, aminolysis of acyl chlorides, aldol condensation and reductive amination). These derivatives present new functional groups in the alkenyl side chain of the prototype, which may help to optimize the biologic activity through additional interactions with the target.

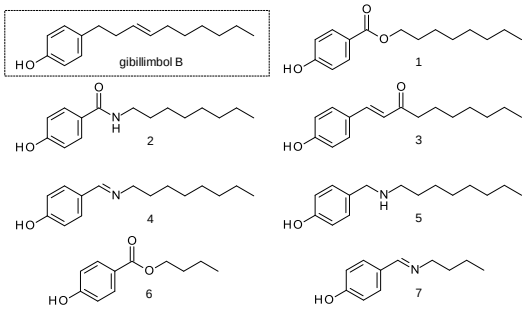

Figure 1. Analogues of gibillimbol B.

To evaluate the leishmanicidal activity, promastigotes forms of *L. (L.) infantum chagasi* were maintained in a 96-well plates containing 10^6 cells/well. Test compounds were diluted in DMSO and M-119 medium to obtain a concentration of 300 µg/mL. The plates were incubated with the parasites for 24h at 24 °C. Viability (% of death) was determined using MTT assay at 550 nm. The results are presented in the table 1.

Table 1. Leishmanicidal activity of the derivatives.

Compound	% death
1	50 (poorly active)
2	100 (highly active)
3	90 (active)
4	100 (highly active)
5	50 (poorly active)
6	50 (poorly active)
7	100 (highly active)

According to the preliminary results, it is possible to verify the ester group (**1**) led to poor activity, possibly due to its metabolic unstability. Amide (**2**) and imine (**4** and **7**) derivatives were the most active, killing 100% of the parasites at 300 µg/mL. The alkyl chain length does not appear to influence on activity, since **4** and **7** showed same potency. The aldol derivative (**3**) was also active, showing that the carbonyl group as well as the unsaturation can positively contribute to the activity. As the amine (**5**) derivative is also poorly active, it is possible to define the importance of the unsaturation on activity.

Conclusions

The results allowed concluding the synthetic methodology was successful to obtain the derivatives. 3 compounds (**2**, **3** and **4**) showed preliminary good activity, and led to some SAR insights to evaluate a new set of compounds to improve the activity.

Acknowledgements

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[1] Oliveira, A. *et al. Exp. Parasitol.* **2012**, *132*, 383.