

## Design and evaluation against *Leishmania amazonensis* novel thiophene-thiazolidine hybrid derivatives direcionados ao alvo cysteine protease B

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### ABSTRACT

The term neglected diseases refers to a set of pathologies that affect approximately 1 billion individuals worldwide, who live in social exclusion and poverty, resulting in a major global public health problem. In this sense, pharmacotherapy against trypanosomiasis, leishmaniasis and Chagas disease remains ineffective, especially against the chronic forms of these. Therefore, in a study recently reported by our research group, the derivative LQM83 was obtained, a thiophene-thiazolidine molecular hybrid, in which it showed potential inhibition against cruzain, with  $IC_{50} = 2.4 \mu M$ . Thus, cysteine proteases correspond to potential druggable targets common to both parasites, comprising a class of proteolytic enzymes expressed in different organisms that participate in the regulation of several physiological and pathological processes. In this sense, cysteine protease B (CPB) constitutes an important virulence factor related to all evolutionary forms of leishmaniasis. Based on this, foreseeing a direct contribution to the improvement of the anti-Chagasic and leishmanicidal therapeutic arsenal, 47 new derivatives were obtained, with yields between 58-95% and a relative purity level greater than 99%. Evaluation against the amastigote forms of *Leishmania amazonensis* highlighted the promising compounds **26e**, **26f** and **28c**, with  $IC_{50}$  value of 3.22; 4.5 and 3.39  $\mu M$ , respectively. In addition, they presented  $CC_{50}$  value of 96.28, 63.95 and 61.6  $\mu M$ , with  $SI = 29.90$ ; 14.21 and 18.17, respectively. In addition, **26f** presented  $IC_{50}$  value of 34.24  $\mu M$  against the proposed enzyme target rCPB 2.8. Finally, these data suggest a new scaffold for the development of potential compounds against this serious disease, which are safe, low-cost and accessible, especially to individuals who are in a situation of socioeconomic vulnerability.