



DRUG DESIGN, SYNTHESIS, AND IN VITRO ANTI-LEISHMANIA EVALUATION OF NOVEL 2-AMINOTHIOPHENE-3-CARBOXAMIDE DERIVATIVES AGAINST *L. infantum*

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ABSTRACT

BACKGROUND Leishmaniasis is a group of diseases caused by protozoan parasites, predominantly affecting vulnerable populations. The most fatal form, Visceral Leishmaniasis (VL), is transmitted mainly by *Leishmania donovani* and *L. infantum*, with approximately 1 million new cases annually (WHO, 2023). Current treatments face challenges such as high toxicity, complex administration, resistant cases, and high costs, creating an urgent need for new VL-specific drugs. In this context, 2-aminothiophene compounds have demonstrated a broad spectrum of biological activities, notably including anti-Leishmania efficacy, as evidenced previously by our research group (LUNA et al., 2023; SOUSA et al., 2023; FÉLIX et al., 2020).

OBJECTIVES This study aims to evaluate the antileishmanial activity of new synthetic 2-aminothiophene-3-carboxamide derivatives obtained from 2-aminothiophene-3-carbonitrile prototypes against *L. infantum*.

METHODS 2-aminothiophene-3-carboxamide derivatives were synthesized by Gewald reaction varying the cyclic ketones (cyclohexanone, cycloheptanone, cyclooctanone, and 1-boc-4-piperidone). Final compounds were obtained by reacting each Gewald adduct with 1H-indole-3-carboxaldehyde derivatives. Anti-leishmanial activity was performed *in vitro* against the promastigote form of *L. infantum* and their toxicities against RAW 264.7 macrophages.

RESULTS AND DISCUSSION Fifteen compounds were synthesized and their chemical structures were confirmed by ¹H and ¹³C NMR. Among the assayed compounds, eight presented anti-leishmanial activity at concentrations below 8 μM, and cytotoxicity greater than 246 μM. Notably, compounds 6AMD3, 8AMD5, and 6BOC2 emerged as the most potent, exhibiting IC₅₀ values close to 5 μM, and with selectivity index about 40 times, being higher than the reference drug amphotericin B. A comparative analysis between the 3-carboxamide derivatives synthesized in this study and the 3-carbonitrile derivatives previously evaluated against *L. amazonensis* suggests that the presence of the 3-carbonitrile is not essential for anti-leishmanial activity (FÉLIX et al., 2016). Furthermore, this comparison indicates that substitution with the 3-carboxamide group does not necessarily lead to compounds with superior activity compared to the 3-carbonitrile derivatives.

CONCLUSION Our findings reveal that 2-aminothiophene-3-carboxamide derivatives present anti-leishmanial activity against *L. infantum*, and the presence of the 3-carbonitrile radical is not essential for anti-leishmania activity. Taken together, these findings suggest that 2-aminothiophene-3-carboxamide are promising candidates for drug development for VL.

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