Development of amidoxime 5-nitrofuran-3-carboxylate derivatives bioactivated by *Leishmania infantum* nitroreductases

Fabiana Maia Santos Urbancg Moncorvo[1], Oscar Leonardo Avendano Leon[2], Youssef Kabri[2], Christophe Curti[2], Patrice Vanele[2], Eduardo Caio Torres-Santos[1]

1- Laboratório de Bioquímica de Tripanosomatídeos, Instituto Oswaldo Cruz, FIOCRUZ, Rio de Janeiro, RJ, Brazil;
2 - Laboratoire de Pharmaco-Chimie Radicalaire, Faculté de Pharmacie, Aix Université Marseille, France

The therapeutic arsenal for leishmaniasis has become outdated, with unacceptable side effects and increasing cases of resistance. Therefore, ongoing research to discover new low-cost antileishmanial compounds suitable for oral administration is of fundamental importance. Several studies have demonstrated that amidoxime-containing compounds exhibit leishmanicidal activity. In the group's previous work, a series of 4,5-dihydrofuran derivatives containing an amidoxime group was optimized against *Leishmania amazonensis* promastigotes, focusing on position 3 of the dihydrofuran ring by introducing aliphatic fractions containing an ester group, leading to the derivative OSC75 (IC_{50} = 6.3 µM). To further enhance activity while minimizing toxicity, an additional hit-to-lead optimization round was conducted. This study aimed to compare the antileishmanial activity of furan and thiophene derivatives with or without a nitro group (OSC245, OSC254, OSC255, and OSC256). Nitro derivatives have significant potential for drug development due to the presence of nitroreductases in trypanosomatids, which are not homologous to those in humans. This distinction enables selective bioactivation of drug candidates, leading to parasite-specific toxicity. Antileishmanial activity was evaluated in *L. amazonensis* promastigotes, with all derivatives showing activity and inhibiting parasite growth, with IC_{50} values ranging from 7.6 to 78 µM. The nitro-containing derivatives OSC254 (IC_{50} = 7.6 µM) and OSC256 (IC_{50} = 29.1 µM) were more potent than their non-nitro counterparts. To further investigate the nitro-activation hypothesis, the potency of these compounds will be compared in wild-type (*LiWT*) *Leishmania infantum* promastigotes and those overexpressing type 1 nitroreductase (*LiNTR1*).

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