

Antitrypanosomal Benzoxazinone Series: Hit-to-Lead Campaign and Multiparametric Optimization

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Abstract

Lead Optimization Latin America (LOLA) is an ongoing project focused on the development of new chemical entities that target Chagas disease, a tropical neglected disease that affects 6 million people worldwide and is endemic in our region. In this context, we present the hit-to-lead campaign of a Benzoxazinone series based on initial phenotypic screening of commercial libraries. After hit assessment, we started the SAR expansion obtaining 79 compounds that were designed, synthesized, and tested against intracellular T. cruzi amastigotes. Furthermore, we also performed cytotoxicity, permeability, microsomal clearance, solubility and metabolite identification assays. As a result, LOLA779 was identified as an early lead showing submicromolar potency and balanced properties that merited the progression for a single dose in vivo PK study in mice. Finally, representative compounds were tested in T. cruzi-cidal assay and against a panel of discrete type units (DTUs) to shed light on the Benzoxazinones possible mode of action.

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Keywords

- Chagas disease
- Benzoxazinones
- Drug Discovery
- SAR
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