Indoles Hit-to-Lead for Chagas Disease: Lessons Learned within the LOLA consortium

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Abstract

Chagas disease (CD) is a neglected tropical disease (NTD) that affects around 6 million people worldwide. Most of the affected patients live in Latin America, leaving a trail of health, social, and economic impact in the region.1 Current treatment is unsatisfactory, making it imperative to discover and develop new and safer drugs.2 Under the Lead Optimization Latin America (LOLA) consortium3, an innovative and collaborative network focused on drug discovery for NTDs, we herein present the hit-to-lead work done for a series of substituted indoles that showed good potency against Trypanosoma cruzi. After initial identification of hits via phenotypic screening of commercial libraries, more than 200 analogues were designed, synthesized, and screened. Early lead compounds LOLA702 and LOLA715 with improved in vitro properties were obtained. LOLA702 was progressed for an in vivo proof-of concept in an acute model for CD, showcasing strong local capabilities for early-stage drug discovery efforts for CD.

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