Target- and Phenotypic-based Drug Discovery against Pathogenic Trypanosomatids

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INTRODUCTION: The Trypanosomatidae family consists of protozoan parasites that cause Chagas disease (Trypanosoma cruzi), Sleeping sickness disease (Trypanosoma brucei) and the different manifestations of leishmaniasis (Leishmania spp). The treatment of trypanosomiasis and leishmaniasis relies on drugs that present high toxicity, resistance and low affordability. **OBJECTIVES:** An important research line of our laboratory aims at identifying and characterizing novel drug-like compounds targeting essential and unique components of the metabolism from pathogenic trypanosomatids, owing major limitations of the current chemotherapy and the lack of perspectives for vaccine development. **MATERIALES Y METHODS:** We have implemented two complementary strategies to search for anti-trypanosomal agents from a growing home-made chemical library of > 600 compounds: 1) a target-based approach against trypanothione synthetase (TryS), an enzyme exclusive and essential to trypanosomatids that produces the major thiol redox cofactor of these organisms; 2) a phenotypic-based approach that in addition to wildtype parasites uses transgenic cell lines from pathogenic trypanosomes expressing a redox biosensor for high-content analysis aimed to infer compound mode of action. **RESULTS AND DISCUSSION:** Applying these two strategies we have identified potent (low µM to nM) and selective (selectivity index >50) inhibitors of tritryp TryS and antiproliferative agents towards infective *Trypanosoma brucei*, *Leishmania infantum* (visceral leishmaniasis) and *L. braziliensis* (cutaneous leishmaniasis). Using the redox reporter cell lines we were able to discriminate compounds whose cytotoxicity involved or not alteration of the parasite intracellular redox homeostasis. **CONCLUSIONS:** We have identified N^5-substituted paullones (benzo[2,3]azepino [4,5-b]indol-6-ones) as potent (nM) and selective inhibitors of TryS from *Leishmania infantum*. Screening with GFP-redox reporter trypanosomatids allows the identification of compounds altering intracellular redox homeostasis.

Key words: trypanothione synthetase, trypanosomatids, redox homeostasis.
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