TITLE: ANTIFUNGAL ACTIVITY EVALUATION OF ARYL AND HETEROARYL CHALCONES AGAINST *PARACOCCIDIOIDES* SPP. AND STRUCTURE-ACTIVITY RELATIONSHIP ANALYSIS

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ABSTRACT:

Paracoccidioides spp, a dimorphic pathogenic fungus, is the etiologic agent of paracoccidioidomycosis (PCM). PCM is an endemic disease that affects at least 10 million people in Latin America, causing severe public health problems. The drugs used against pathogenic fungi have various side effects and limited efficacy; therefore, there is an inevitable and urgent medical need for the development of new antifungal drugs. Chalcones, are secondary metabolites, precursors to the biosynthesis of flavonoids. Chemically, chalcones are classified as 1,3-diaryl-2-propen-1-ones and possess a broad spectrum of properties including antifungal activity. They are considered privileged structures for research and development of new drugs, due numerous possibilities of structural modifications in their aromatic rings. We evaluated the antifungal activity of 32 chalcones, as well as cytotoxicity in Balb 3T3 cells and hemolytic potential. Based on the experimental results, the structure-activity relationship (SAR) analysis was performed to reveal the structural fragments responsible for antifungal activity. Eight compounds exhibited Minimum Inhibitory Concentration (MIC) less than or equal to of 3.9 μg/mL, and not show cytotoxicity in fibroblast cells at concentrations below 31.5 μg/mL. Anyone chalcone caused significant hemolysis at concentrations below 1000 μg/mL. Due the better results, we selected compound Labmol75 to evaluate the interaction with itraconazole, amphotericin B and sulfamethoxazole/trimethoprim. The SAR studies indicated that the substitution of aryl ring B by 5-nitrofuran was favorable to biological activity, and methoxy groups in position R_{10} decrease the activity antifungal. The results indicate that chalconas are promising antifungal prototype, in particular the Labmol75 compound.

Keywords: *Paracoccidioides* spp, heteroaryl chalcones, structure-activity relationship, antifungal

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