TITLE: ANTIFUNGAL ACTIVITY OF NITROGEN HETEROCYCLES AGAINST PARACOCCIDIOIDES SPP

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ABSTRACT:

Paracoccidioides brasiliensis and *P. lutzii* belong to a group of thermodimorphic fungi and cause paracoccidioidomycosis (PCM), mycosis restricted to the regions of Latin America. The infection is acquired by inhaling conidia that primarily settle in the lungs, and can spread to other organs. The treatment of PCM is commonly performed with administration of antifungals of the class of azoles, sulfonamides and amphotericin B. The toxicity and side effects of antifungals, added over the long treatment time, has boosted research by new bioactive compounds. Nitrogen heterocycles are useful substances, mainly due to their biological properties, which means that many of them are used in medicines for various diseases. In the search for new active principles, efforts have been made to synthesize these types of compounds, mainly nitrogen bicycles and tricycles, products that have differentiated nuclei widely distributed with different chemical and biological functions. We evaluated the antifungal activity of 22 heterocyclic compounds as well as cytotoxicity in Balb 3T3 cells and hemolytic potential. We selected compound D128 for proteomic analyzes in *Paracoccidioides* spp. to elucidate its mode of action. 7 compounds had Minimum Inhibitory Concentration (MIC) below of 7.8 μg/mL, and did not show cytotoxicity in fibroblast cells. The D128 compound was the most promising, with MIC of 1.95 μg/mL, cytotoxicity > 500 μg/mL, and no hemolytic effect. D128 presented synergic effect with amphotericin B. The total of 238 proteins were identified in the proteomic analyzes, being 41 down, and 28 up regulated. We suggest that the processes of obtaining energy, cell cycle and protein synthesis are compromised, due to the high number of repressed proteins belonging to this class. The results indicate that D128 is a promising antifungal prototype.

Keywords: *Paracoccidioides* spp., nitrogen heterocycles, antifungal

Development Agency: Instituto Nacional de ciência e tecnologia- Interação patógeno hospedeiro (INCT –IPH), Fundação de Amparo à Pesquisa do Estado de Goiás (FAPEG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de aperfeiçoamento de pessoal de nível superior (CAPES)