

TITLE: DETERMINATION OF THE EFFECTIVENESS OF NITROFURANS AND INDOLIC DERIVATIVES AGAINST *Histoplasma capsulatum* AND TOXICITY IN CELL MONOLAYERS AND THREE-DIMENSIONAL MODELS

AUTHORS: VASO, C.O.¹; GONÇALVES, L.C.¹; COSTA-ORLANDI, C.B.¹; BILA, N.M.¹; SILVA, R.A.M.¹; TAYLOR, M.L.²; SCIPIONE, L.³; MENDES-GIANNINI, M.J.¹; FUSCO-ALMEIDA, A.M.¹

INSTITUTION: ¹Faculdade de Ciências Farmacêuticas/UNESP – Araraquara (Rodovia Araraquara/Jaú Km 1, Núcleo de Proteômica, CEP 14800-903, Araraquara- SP, Brasil); ²Departamento de Microbiología y Parasitología, Facultad de Medicina, Universidad Nacional Autónoma de México, México; ³Department of “Chimica e Technologie del Farmaco”, Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185 Rome, Italy.

ABSTRACT

Histoplasma capsulatum is a dimorphic fungi that causes histoplasmosis, a systemic and endemic mycosis of worldwide incidence. In Brazil, this mycosis mainly affects the southeast region, causing serious public health problems. Humans acquires the infection by inhaling the microconidia present in nature, which preferentially affect the lungs, resulting in a series of clinical manifestations, ranging from moderate to severe, depending on the patient's clinical condition. The treatment requires the use of systemic antifungal agents such as amphotericin B and itraconazole, which may cause nephro and hepatotoxicity. Adverse effects are consequences of the similarity of the fungal to the mammalian cells. This fact, coupled with the limited number of antifungal drugs, makes the development of new antifungal agents that target fungal exclusive targets and with reduced toxicity extremely necessary. Thus, this study aims to verify the anti-*Histoplasma* activity of nitrofurans and indole derivatives, as well as to assess their toxicity in monolayers and in the three-dimensional model of lung epithelial cells and fibroblasts. The susceptibility tests were conducted according to the document M27-A3, proposed by the *Clinical and Laboratory Standards Institute* (CLSI, 2008), with minor modifications. The spheroids, developed in agarose gel, were formed from lung epithelial and fibroblasts cells (A549 and MRC-5). The cytotoxicity of the compounds with the best minimum inhibitory concentration (MIC) values was evaluated in monolayers and in three-dimensional models by staining with resazurin. The best MIC values were obtained by 15 of 47 compounds, with MIC values between 0.5 and 15.6 µg / mL. It is concluded that nitrofuran and indolic derivatives are promising compounds for the treatment of infections caused by *Histoplasma capsulatum* and that three-dimensional models can better mimic the toxicity of compounds or drugs than cellular monolayers.

Keywords: Antifungal agents, fungal infection, resistance, toxicity

Agency: CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) process 134559/2018-5 and FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo).