

MODIFICATION OF KETOCONAZOLE IN IMIDAZOLIUM SALT AND DETERMINATION OF THE ANTIFUNGAL ACTIVITY ON *CANDIDA* SP.

Pippi, B.¹, Soares, L.A.², Bergamo, V. Z.¹, Machado, G.R.M¹, Danielli, L. J.³, Dalla Lana, D. F.³, Schrekker, H.S.², Donato, R.K.², Fuentefria, A. M.^{1,3}

¹Programa de Pós Graduação em Microbiologia Agrícola e do Ambiente - Universidade Federal do Rio Grande do Sul (Sarmiento Leite – 500 - 90050-170 - Porto Alegre - RS), ²Instituto de Química, Universidade Federal do Rio Grande do Sul (Bento Gonçalves – 9500 - 91501-970 - Porto Alegre – RS), ³Programa de Pós Graduação em Ciências Farmacêuticas - Universidade Federal do Rio Grande do Sul (Ipiranga – 2752 - 90610-000 - Porto Alegre - RS)

Despite the introduction of a new generation of antifungal agents and use of combination therapy, antimicrobial resistance is still a challenge for the treatment of fungal diseases. Infections caused by *Candida* sp. showed a substantial increase in recent decades possibly due to reduced susceptibility to antifungal agents available. The resistance in *Candida* establishes a worrying clinical problem, resulting in a high mortality rate, as well as an economic problem due to prolonged hospital. The azoles are important antifungal drugs and widely used. Coinciding with this increasing use, the resistance to this class has been extensively observed. Face of this situation, there is a clear need for new antimicrobial options with the ability to eliminate the adaptation strategies developed by these microorganisms and improve the efficiency of medicines. Therefore, the objective was to modify the antifungal Ketoconazole in imidazolium salt and check the activity on *Candida* isolates. The Ketoconazole modification in imidazolium salt was performed by adapting methods described in the literature. The strategy consisted in the use of ketoconazole as a neutral imidazole precursor for forming an imidazolium salt derivative itself (named C₁₆KetoconazolMeS). Thereafter, it checked the Minimum Inhibitory Concentration (MIC) of Ketoconazole and C₁₆KetoconazolMeS against 17 isolates of *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis*. The MIC was determined by the broth microdilution method according M27-A3 protocol (CLSI 2008). It was observed improvement in activity of Ketoconazole modified to nine isolates. It is worth highlighting that the isolates which were more susceptible to C₁₆KetoconazolMeS are resistant to ketoconazole or presented low sensitivity to this antifungal. Thus, this change in the Ketoconazole molecule may be useful in the future as an alternative for the treatment of patients with no clinical improvement when administered Ketoconazole. For this, further studies are needed to evaluate the mechanism of action and toxicity of this substance.

Keywords: Ketoconazole, Imidazolium Salt, *Candida*, antifungal, resistance

Agency encouragements: CAPES, CNPq