Synthesis and in vitro antifungal activity of new Mannich bases derived from 2-hydroxy-1,4-naphthoquinone (Lawsone)

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INTRODUCTION

The fungal infection is one of the most very important problem that affects immunocompromised patients due to AIDS and cancer.1

Azoles are the most widely antifungal drugs acting on the inhibition of the 14a-demethylase enzyme, very important therapeutic target.2 Additionally, the generation of reactive oxygen species (ROS) is very important for antifungal activity and the naphthoquinones, as lawsone, are known compounds with higher capacity to generate ROS.3

In this work, we have been synthesized new enolamines through multicomponent Mannich reaction in lawsone with various aldehydes and amines in ethanol and analyzed the synergy effect of triazole and the ROS.

RESULTS AND DISCUSSION

In Scheme 1, is shown the scope and procedure of one-pot three-component reaction of 2-hydroxy-naphthoquinone (Lawsone, 1).

Scheme 1. Multicomponent Mannich reaction with lawsone.

Using the same previous procedure, the reaction of the aldehyde N-phenyl-1,2,3-triazole (6) with lawsone and the amines 7 and 8, was performed. Unfortunately, rather than obtaining the Mannich adducts 9, this reaction was obtained exclusively the compound 10 and 11 (Scheme 2).

Scheme 2. Synthesis of N-phenyl-1,2,3-triazole derivatives.

Compounds 10 and 11 were achieved through Michael addition in the respectively Mannich adducts formed in situ and occur due to the very low reactivity of the aldehyde triazolic 6 compared to the aldehydes used in preparation of adducts 2-4.

The synthesized compounds (2-4, 10 and 11) were evaluated for their in vitro antifungal activity against C. albicans (ATCC 14053), C. glabrata (ATCC 2001) and C. krusei (ATCC 34135).

Table 1. Minimum inhibitory concentration (MIC).

CONCLUSION

The compounds 2-4 was obtained successfully with yields ranging 40-82% and the triazoles derivatives 10 and 11 was obtained after Mannich reaction followed by Michael addition with yield 50% and 56%, respectively . The compounds 10 and 11 showed very promise antifungal activity against Candida albicans when compared with the drugs Fluconazole and Amphotericin B, evidencing the synergism between triazole and naphthoquinones.

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