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 the one of most very important problem that affects immunocompromised patients due to AIDS and cancer.[1]

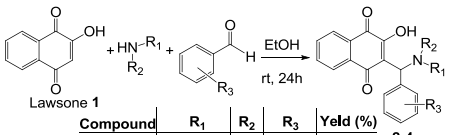
Azoles are the most widely antifungal drugs acting on the inhibition of the 14α-demethylase enzyme, very important therapeutic target.[2] Additionally, the generation of reactive oxygen species (ROS) is very important for antifungal activity and the naphthoquinones, as lawsone, are known compounds with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

In this work, we have been synthesized new enolaminas 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**).

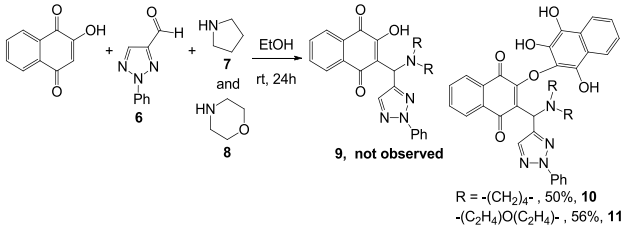
Scheme 1. Multicomponent Mannich reaction with lawsone.



Compound	R_1	R_2	R_3	Yeld (%)
2	- $(CH_2)_4$ -	----	- H	40
3	- $(CH_2)_4$ -	----	- 4-NO_2	46
4	-Ph-4-NO_2	- H	- 4-NO_2	82

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**, in 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 for *C. albicans* (ATCC 14053), *C. glabrata* (ATCC 2001) and *C. krusei* (ATCC 34135).

Table 1. Minimum inhibitory concentration (MIC).

Compound	MIC (µg/mL)		
	C.albicans	*C.glabrata*	*C.krusei*
2	$9{,}7x10^{-1}$	-	-
3	$5{,}0x10^{-1}$	-	-
4	-	-	-
10	$29{,}4x10^{-5}$	-	-
11	$12{,}9x10^{-5}$	-	-
Fluconazole	625	19,53	78,12
Amphotericin B	5,0	$19{,}5x10^{-1}$	$2{,}4x10^{-1}$

(-) Totally inactive (MIC ≥ 200 µg/ml).

All compounds were characterized with IR, NMR and high resolution mass spectrometry.

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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