Synthesis of 1-*H*-1,2,3-triazole-1,4-naphthoquinones as potential antifungal agents

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INTRODUCTION

1,4-Naphthoquinone derivatives were found to possess remarkable biological activities, such as antimicrobial and anticancer.[1,2] Chemical structures containing 1,4-naphthoquinone conjugated with 1,2,3-triazole are important building blocks for our research due to rapid preparation,[3,4] as well as reported by us biological activities against *T. cruzi* and Leishmania parasites.[5] In this work, we had interest in perform the synthesis of 1,2,3-triazole-1,4-naphthoquinones using conventional protocols,[3,4,6] and then study their antifungal activity.

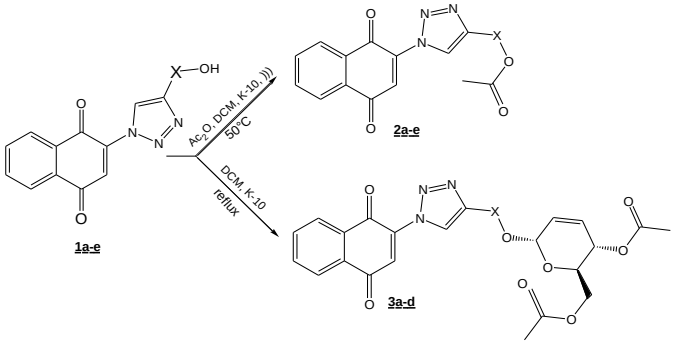
RESULTS AND DISCUSSION

We performed the synthesis of starting materials **1a-e** using a variation of Sharpless protocol for the reaction between 2-azido-1,4-naphthoquinone and terminal alkynes in 55-71% yields (Scheme).[4] From the compounds **1a-e** we carried out the acetylation reaction using Ac_2O and Montmorillonite K-10 as a catalyzer. To promote this reaction, we applied ultrasound irradiation during 40 min at 50 ^oC to give the products **2a-e** in 49-76% yields (Scheme). Then, we started to prepare the glycoside derivatives **3a-d** using the Ferrier's method [5] in 46-71% yields. With the compounds **1-3** in hands, we have chosen the triazoles **1a**, **1e**, **2a** and **3a** for preliminary screening studies (Table). In general, the antifungal activity increased from **1a** to acetylated product **2a**. The compound **2a** showed the best result for *C. posadasii* (IC_{80} = 4.7 µM). Introduction of sugar moiety in the structure **1a** enhances the antifungal activity from alcohol **1a** (114.1 µM) to the compound **3a** (17.9 µM) for *Penicillium sp.* and *A. clavatus* fungus (Table).

Table. Antifungal activities of 1,2,3-triazoles (IC_{100}/µM)

Triazole	*H. capsulatum*	*C. Posadasii*	Penicillium *sp.*	*A. clavatus*
1a	35.7	57.1	114.1	114.1
1e	23.4 (11.7)	37.5	37.5	37.5
2a	47.3	9.5 (4.7)	75.7	75.7
3a	40.6	35.7	35.7 (17.9)	35.7 (17.9)
AmphB	0.27	0.54	0.135	0.034

Value in bracket are in IC_{80}/µM. AmphB = Amphotericin-B



X= **a**: CH_2; **b**: $CH_2CH_2CH_2$; **c**: CH(Me); **d**: $CH_2CH(Me)$; **e**: $C(Me)_2$

Scheme. Synthesis of 1,2,3-triazole-1,4-naphthoquinone derivatives **2a-e** and **3a-d**

CONCLUSION

New 1*H*-1,2,3-triazole-1,4-naphthoquinones **1-3** were synthesized in moderate to good yields. The antifungal profile of **1a**, **1e**, **2a** and **3a** showed antifungal activities when compared with Amphotericin-B against *Histoplasma capsulatum, Coccidioides posadasii, Penicillium sp and Aspergillus clavatus.* These compounds may be suitable as antifungal leading for further study.

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