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. Chemical structures containing 1,4-naphthoquinone conjugated with 1,2,3-triazole are important building blocks for our research due to rapid preparation, as well as reported by us biological activities against T. cruzi and Leishmania parasites. In this work, we had interest in perform the synthesis of 1,2,3-triazole-1,4-naphthoquinones using conventional protocols, 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). From the compounds 1a-e we carried out the acetylation reaction using Ac2O and Montmorillonite K-10 as a catalyst. To promote this reaction, we applied ultrasound irradiation during 40 min at 50 °C 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 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 (IC50 = 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>
<thead>
<tr>
<th>Triazole</th>
<th>H. capsulatum (µM)</th>
<th>C. posadasii (µM)</th>
<th>P. sp. (µM)</th>
<th>A. clavatus (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>35.7</td>
<td>67.7</td>
<td>114.1</td>
<td>114.1</td>
</tr>
<tr>
<td>1e</td>
<td>23.4 (11.7)</td>
<td>37.5</td>
<td>37.5</td>
<td>37.5</td>
</tr>
<tr>
<td>2a</td>
<td>47.3</td>
<td>9.5 (4.7)</td>
<td>75.7</td>
<td>75.7</td>
</tr>
<tr>
<td>3a</td>
<td>40.6</td>
<td>35.7</td>
<td>37.5 (17.9)</td>
<td>37.5 (17.9)</td>
</tr>
<tr>
<td>Amphl</td>
<td>0.27</td>
<td>0.54</td>
<td>0.135</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Value in bracket are in IC50/µM. Amphl – Amphotericin B

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

CONCLUSION

New 1H-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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REFERENCES

4 Nascimento, W. S.; de Oliveira, R.N.; Camara, C.A. Synthesis 2011, 3320.