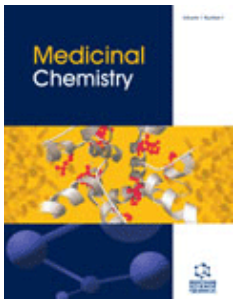

Synthesis and Evaluation of Antifungal and Antitrypanosomastid Activities of Symmetrical 1,4-Disubstituted-1,2,3-Bistriazoles Obtained by CuAAC Conditions

(E-pub Abstract Ahead of Print)

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Abstract:

Background: The trypanosomatids, such as the protozoan Leishmania spp., have a demand by ergosterol, which is not present in the membrane from mammal cells. The suppression of the synthesis of ergosterol would be a new target of compounds with leishmanicidal activity, and bistriazole has showed trypanocidal activity by this mechanism. The incidence of fungal infections has increased at an alarming rate over the last decades. This is related both to the growing population of immune-

compromised individuals and to the emergence of strains that are resistant to available antifungals. Therefore, there is a challenge for the search of potential new antifungal agents. Objective: the study aimed to synthesized 1,4-disubstituted-1,2,3-bistriazoles by optimized copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) and evaluate their antifungal and antitrypanosomastid activities. Method: The synthesis of symmetrical bistriazoles with diazides as spacers was planned to be performed following the CuAAC reaction strategy. For evaluation of best conditions to synthesis of symmetrical bistriazoles hex-1-yne 2 was choose as leading compound, and a variety of catalyst were employed, choosing (3:1) alkyne:diazide stoichiometric relationship employing CuSO4.5H2O as best condition. For the preparation of diversity in the synthesis of symmetrical bistriazoles, a 1,3-diazide-propan-2-ol 1a and 1,3-diazidepropane 1b were reacted with seven different alkynes, furnishing eleven symmetrical bistriazoles 9-13a,b and 14a. All compounds were essayed to cultures of promastigotes of L. amazonensis (1 x 106 cells mL-1) in the range of 0.10 - 40.00 µg mL-1 and incubated at 25ºC. After 72 h of incubation, the surviving parasites were counted. To antifungal essay the minimum inhibitory concentrations (MIC) for yeasts and filamentous fungi were determined. Each compound was tested in 10 serial final concentrations (64 to 0.125 µg mL-1). Results: eleven 1,4-disubstituted-1,2,3-bistriazoles were synthesized and their structures were confirmed by IR, 1H and 13C-NMR and Mass spectral analysis. The antifungal and antitrypanosomastid activities were evaluated. The best result to antifungal activity was reached by bistriazole 11a, that showed the same MIC of fluconazole (32 µg mL-1) against Candida krusei ATCC 6258, an emerging and potentially multidrug-resistant fungal pathogen. Due their intrinsically biological activity versatility, five derivatives compounds showed leishmanicidal inhibitory activity between 15.0 and 20.0% at concentrations of 20 and 40.0 µg mL-1. Among these compounds the derivative 13a showed best IC50 value of 63.34 µg mL-1 (182.86 µM).

Keywords: antifungal activity, antitrypanosomastid activity, symmetrical bistriazoles, CuAAC methodology.

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