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Synthesis of *O*-sulfonylated derivates of phenylpropanoid Mannich bases as potential antifungal agents

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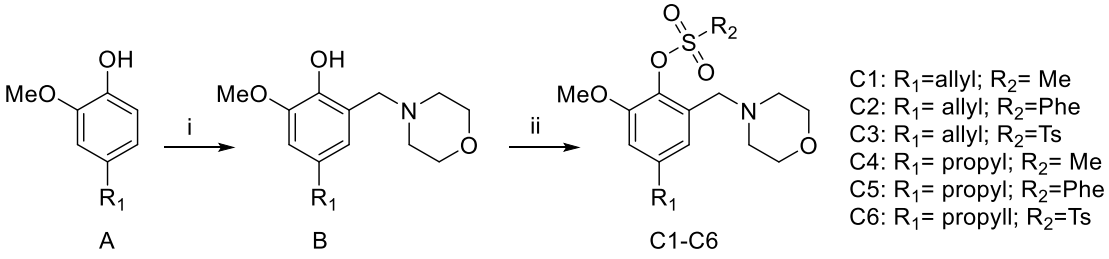
ABSTRACT

This research focuses on the synthesis and characterization of a series of sulfonate esters from a Mannich base prepared previously and known for its antifungal activity[1, 3]. This starting compound was synthesized from eugenol and morpholine, exhibiting fungistatic properties against various *Candida* spp.[1, 3]. Now, inspired by the work of Ahmad and co-workers[2], who reported significant antimicrobial activity of sulfonate esters derived directly from eugenol, we aimed to functionalize that Mannich base as sulfonates, expecting to discover promising products as antifungals. We also used dihydroeugenol to compare the influence of side chain in biological activity. The synthesis route used was as follows (Scheme 1):



i: morpholine, formaldehyde, EtOH, HCl_{cat}, reflux; ii: respective sulphonyl chloride, TEA, THF, 25 °C

Scheme 1: Synthesis route to the *O*-sulfonylated derivatives C1-C6.

The products were evaluated *in vitro* against *Candida* spp. and *Criptococcus* spp. and fluconazole was used as the control drug. Compounds C3 and C6 demonstrated good activity against *Candida krusei* and *Criptococcus neoformans.* When compared to the starting molecules, eugenol and dihydroeugenol, an excellent improvement was observed in potency, being at least 5-10 times higher than the starting materials, it is worth noting that there was no significant difference between eugenol and dihydroeugenol compounds in antifungal activity. These sulfonate derivatives are good candidates for further optimization.

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