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Synthesis and Evaluation of the Antifungal Activity of 2-(Substituted-Amino)-4,5-Dialkyl-Thiophene-3-Carbonitrile Derivatives

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SUMMARY. Fifteen 2-[(substituted-benzylidene)-amino]-5-methyl-thiophene-3-carbonitrile (**3a-g**) and 2-[(substituted-benzylidene)-amino]-4,5-cycloalkyl-thiophene-3-carbonitrile derivatives (**4a-h**) were synthesized and screened for their *in vitro* antifungal activity against 42 clinical isolates of *Candida* (representing 4 different species) and 2 isolates of *Criptococcus*. The antifungal activities of these compounds were compared to fluconazole and amphotericin B as standard agents. All compounds presented fungicidal activity at different doses, but a few compounds showed moderate or poor antifungal activity when compared with the standard drugs. The *Cryptococcus* strains were more sensitive than those of the genus *Candida,* and compound **4d** was the most active, with MFC values varying between 100-800 μg/mL. A preliminary SAR study demonstrated that the presence of a cycloalkyl ring linked to the thiophene moiety is essential for antifungal activity, and that the best antifungal candidates are cyclohexyl compounds (**4d-f**). The results suggest that thiophene derivatives may be interesting compounds for the further development of antifungal drugs.

KEY WORDS: Antifungal activity, *Candida, Criptococcus neoformans,* Gewald reaction, Minimal Fungicidal Concentration, Thiophene derivatives.

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