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Abstract

Synthesis and Antifungal Activity of Thioxanthone Derivatives †

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Abstract: Systemic fungal infections caused by filamentous fungi, particularly in the immunocompromised population, represent a serious threat to public health. The increase in resistant strains to classic antifungal drugs, especially azoles, is a global health problem, with some infections becoming almost impossible to treat. Furthermore, the emergence of new multidrug-resistant fungal species, such as *Scedosporium* spp. and *Fusarium* spp., as etiological agents, poses a challenge in treatment. On the other hand, superficial fungal infections caused by dermatophytes have a high incidence rate, affecting approximately 20 to 30% of the healthy human population. Therefore, the discovery and development of new broad-spectrum antifungal compounds able to modulate and/or eradicate antifungal resistance have become an essential and urgent task. Taking into account that thioxanthones are privileged structures and bioisosteres of xanthones, three thioxanthones were synthesized and, subsequently, their activity as potential agents against filamentous fungi was evaluated. A minimum inhibitory concentration and minimum lethal concentration was tested against clinically relevant species using the broth microdilution method. The derivatives were synthesized through aromatic nucleophilic substitution reactions using a chlorinated thioxanthone and a primary amine as the building blocks. This showed interesting results against most of the isolates tested, including intrinsically resistant strains or those that acquired resistance to fluconazole or other azoles; among the tested compounds, one of the thioxanthone showed more promising activity. These findings highlight the potential value of thioxanthone derivatives as new models for antifungal agents for the treatment of systemic and superficial fungal infections.

Keywords: thioxanthones; antifungal activity; fungal infections

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