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Synthesis and Antifungal Activity of Thioxanthone Derivatives

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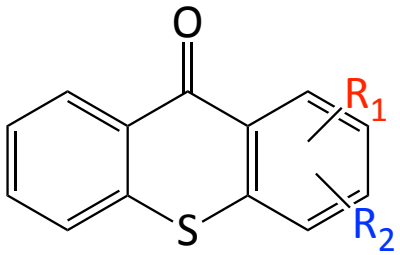
Synthesis and Antifungal Activity of Thioxanthone Derivatives

Fungal infections

Potential new antifungal drugs

Synthetic small thioxanthones



Broad antifungal activity against filamentous fungi strains, including azole-resistant

Abstract: Systemic fungal infections by filamentous fungi, particularly in the immunocompromised population, represent a serious threat to public health. The increase of resistant strains to classic antifungal drugs, especially azoles, is a global health problem and some infections become almost impossible to treat. Furthermore, the emergence of multidrug-resistant fungal species, such as *Scedosporium* spp. and *Fusarium* spp., as etiological agents, pose a challenge in the treatment. On the other hand, superficial fungal infections by dermatophytes have a high incidence affecting around 20 to 30 % of the healthy human population. Therefore, the discovery and development of new antifungal compounds with a broad-spectrum and able to modulating and/or eradicating antifungal resistance have become an essential and urgent strategy. 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 were evaluated. 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 building blocks, and showed interesting results against most of the isolates tested, including strains intrinsically resistant or 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 the thioxanthone derivatives as new models for antifungal agents for the treatment of systemic and superficial fungal infections.

Keywords: tioxanthones; antifungal activity; fungal infections

Introduction

Fungal Infections

Systemic Infections

90 %

immunocompromised population

- *Candida* spp.
- *Cryptococcus* spp.
- *Aspergillus* spp.

Filamentous Fungi

Superficial Infections

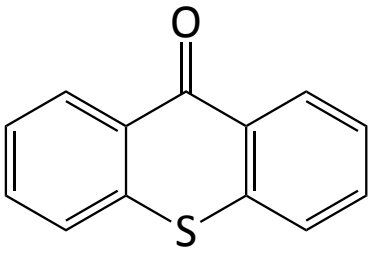
20-30 %

healthy population

- *Candida* spp.
- *Trichophyton* spp.
- *Microsporum* spp.
- *Nannizzia* spp.
- *Epidermophyton* spp.

Resistance to antifungals agents

New and effective antifungal agents



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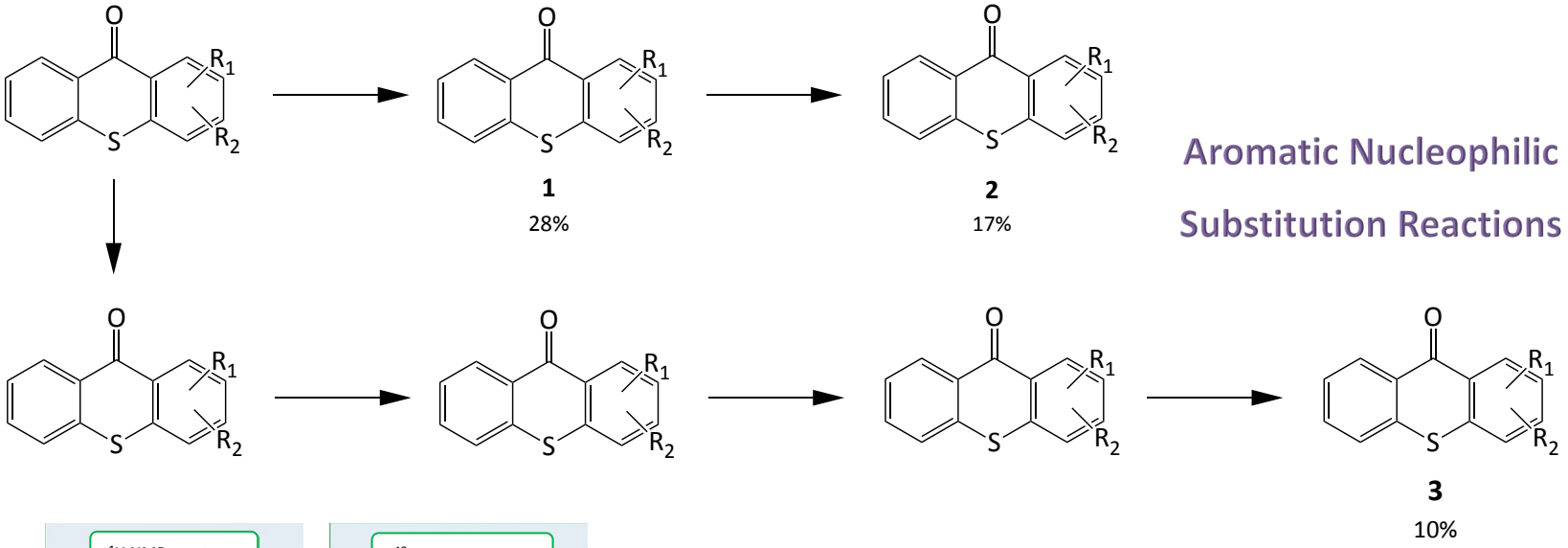
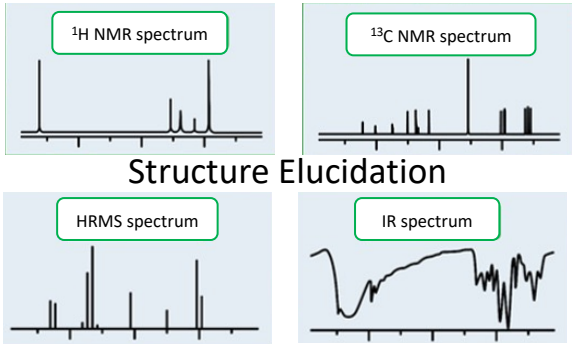
Results and Discussion



Aromatic Nucleophilic Substitution Reactions



Structure Elucidation

3 Aminothioxanthones

Potential Novel Antifungal Compounds

Results and Discussion

Broth microdilution method

CLSI: M38-A2

Fluconazole (FL) as a reference drug

Table 1. Antifungal activity (MIC[1] and MFC[1], μg/mL) of thioxanthone derivatives against filamentous fungi strains.

Filamentous Fungi Strains	Compounds						FL	
	1		8		9			
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
Aspergillus fumigatus ATCC 240305	32	>128	32	>128	64	≥128	≥128	>128
A. fumigatus C111	32	>128	32	>128	64	64	≥128	>128
A. niger ATCC 16404	32	>128	32	>128	128	>128	≥128	>128
A. flavus F44	>128	>128	>128	>128	>128	>128	128	>128
Fusarium solani FF125	64	>128	128	>128	>128	>128	≥128	>128
F. oxysporum FF115	64	128	64	64	128	128	64	>128
Scedosporium spp.	8	8	16	16	32	32	4	16
Lichtheimia spp.	16	16	32	64	64	64	64	>128
Mucor spp.	16	16	16	16	32	32	>128	>128
Dermatophytes								
Trichophyton rubrum FF5	16	16	8	8	32	32	1	64
T. mentagrophytes FF7	16	16	16	32	32	64	8	32
Nannizzia gypsea FF3	16	32	16	16	32	64	32	≥128
Microsporum canis FF1	32	64	16	32	32	64	32	≥128

[1] MIC: minimal inhibitory concentration and MFC: minimal fungicidal concentration

CLSI. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi*, Approved Standard–2nd ed.; Document M38-A2; CLSI: Wayne, PA, USA, 2008.

Conclusions

Thioxanthones as new models for developing innovative antifungal agents.

3 (Amino)thioxanthones showed interesting results against drug-resistant strains of filamentous fungi.

Potential interest as an alternative to the conventional treatment of fungal infections, and in the prevention and control of persistent infections.

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