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Efficiency of newly prepared thiazole derivatives against some cutaneous fungi

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ABSTRACT

A series of fourteen novel synthesized arylazothiazole and arylhydrazothiazole derivatives were tested for their antifungal activity and structure-activity relationship. The activity of the compounds depends mainly on the side chains of the nucleus compound. The antifungal activity was more significant when both side chains are aromatic > one aromatic and one aliphatic and substituted aromatic with CH_3 or OCH_3 > non-substituted > substituted aromatic with chloro- or nitro-groups. Thiazole derivatives **7a, 7c, 7e, 7f, 7 g, 7i, 7 m,** and **11a** showed the most effective as antifungal compounds and were comparable with fluconazole as antifungal reference drug when investigated against *Candida albicans*, *Microsporum gypseum* and *Trichophyton mentagrophytes*. The minimum inhibitory concentration (MIC) reached 2 μg/mL in the case of *C. albicans* for compounds **7a, 7b, 7c** and **11a** and measured 4 μg/mL in the case of *M. gypseum* and *T. mentagrophytes* for the same compounds. The minimum fungicidal concentration (MFC) for the same compounds was 4 μg/mL for *C. albicans* and ranged from 8 to 32 μg/mL for the other two fungi. The results revealed that compounds **7c** and **11a** were the most antifungal compounds against the test fungi regarding keratinase activity and ergosterol biosynthesis. The *in vivo* efficacy of synthesized thiazoles **7c** and **11a** applied at their respective MFC was more effective in the treatment of skin infection of guinea pigs previously inoculated with the test fungi as compared with fluconazole. The Molecular Operating Environment (MOE) software was used to analyze the docking poses and binding energies of compound **11a** and keratinase. The computational studies supported the biological activity results.

1. Introduction

Dermatophyte fungi are common pathogens that can invade keratinous tissues. The number of people affected by dermatophytes in the last three decades has increased; the reasons for this increase include the aging population, increased numbers of immunocompromised patients (transplants, HIV), diabetes, and alternative circumstances that have an effect on the immunity of the overall population.[1] Dermatomycosis could be a nonfatal condition, however, is difficult to eradicate, often necessitating long-run treatment. Azole and its derivatives are an important class of compounds which possess diverse biological activities including anti-microbial,[2] antifungal,[3] antibacterial,[4] anticonvulsant,[5] anti-cancer,[6] hypoglycemic,[7] antitubercular,[8] and anti-inflammatory.[9] In recent years, the synthesis of these heterocyclic compounds has received considerable attention. Thiazole ring is one of the most important heterocyclic compounds used in the manufacture of wide range of pharmaceuticals. For example, Talipexole and Pramipexole with a 2-aminothiazole moiety are used as antiparkinsonian drugs and dopamine agonists, sulfathiazole (antimicrobial), thiabenzadole (antifungal drug), Ritonavir (antiretroviral), Cefdinir (bacteriocidal antibiotic of the cephalosporin class of antibiotics), Epothilones (cancer drugs), and Simeprevir (a drug for the treatment and cure of hepatitis C). Although the antifungal agents such as ketoconazole, griseofulvin and more recently, allylamines and triazoles have been commercially used to treat dermatomycoses, resistance to the different drugs appears very frequently. This is mainly because different tineas (produced by diverse etiological agents) tend to be empirically treated with the same drugs[10] and as a consequence the dermatomycoses tend to persist, greatly diminishing the quality of life of persons suffering from these infections.[11] Since one of the strategies for avoiding the appearance of antifungal resistance is the treatment of fungal infection with the appropriate antifungal agent when the etiological agent is known, new antifungal agents that

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selectively inhibit a single fungal species are urgently needed and will help to overcome the above problems.[12]

Thiazole derivatives are reported to exhibit diverse biological activities as antimicrobial,[13–15] antioxidant,[16] antitubercular,[17] anticonvulsant,[18] anticonvulsant, and anticancer[19] agents. Moreover, many derivatives of thiazoles are used as selective cyclooxygenase-2 inhibitors,[20] in addition to their use as 5-HT3 receptor antagonists,[21] and as potent and selective acetyl Co-A carboxylase-2 inhibitors.[22] Furthermore, the interesting properties of thiazole derivatives in relation to the various changes in the structures of compounds they incorporated is worth studying for the synthesis of some less toxic and more potent drugs.[23]

In earlier work,[24] the authors published the synthesis and antifungal preliminary screening of a series of 14 arylazothiazole and 4 arylhydrazothiazole derivatives. Since these compounds are promising, the present research reports more details for the effectiveness of the synthesized compounds as promising agents against the skin infecting fungi.

2. Materials and methods

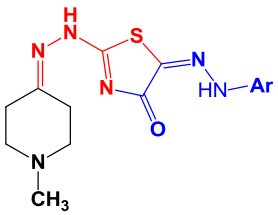
2.1. Investigated compounds

The tested arylazothiazole and arylhydrazothiazole derivatives and their structural formulas are shown in Schemes 1 and 2.

The tested compounds were screened by the Pan Assay Interference Compounds (PAINC) remover tool to remove the possible PAINS compounds.[25] The compounds in this study have passed the Pain filter.

2.2. Test fungi

Three skin infecting fungi namely; *Candida albicans*, *Microsporum gypseum* (*Nannizzia gypsea*) and *Trichophyton mentagrophytes* were used in this study. *C. albicans* was obtained from the department of microbiology, faculty of medicine, Cairo University and was originally isolated from the oral cavity of patient attending the university hospital. The other fungi were obtained from culture collections of the first author and were originally isolated from the dermatology clinics at Kasr Elainy hospitals. The identification of the test fungi was confirmed by reviewing and comparing the same species deposited at Assiut University Mycological Center (AUMC), Egypt. The fungi were stored in Sabouraud dextrose (SD) broth (Oxoid) with 20% glycerol at 30 °C and propagated on potato dextrose agar (PDA, Oxoid) plates incubated at 30 °C before each test. The inocula were prepared from a 7-day-old culture in the case of *C. albicans* and 14-day-old cultures for the dermatophytes.



11a-d

Cpd No.	Ar
a	Ph
b	4-ClC_6H_4
c	3-ClC_6H_4
d	4-$NO_2C_6H_4$

Scheme 2. Investigated arylhydrazothiazole derivatives **11a–d**.

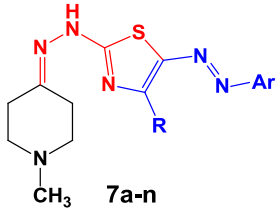
2.3. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC)

MIC is the lowest drug concentration required to inhibit the growth of the organism by 50% in comparison to the drug-free controls.[26] Broth microdilution method was performed according to the Clinical and Laboratory Standards Institute (CLSI) M38-A2 guidelines.[27] Each compound was dissolved in DMSO before its dilution in Sabouraud's dextrose broth medium to obtain the final concentration ranging from 1 to 256 μg/mL. Fluconazole was used as positive control and the solvent of the compounds as negative blank. The microdilution plates inoculated with the test fungus were incubated at 30 ± 2 °C and were read visually after 48 h of incubation in the case of *C. albicans* and after 72 h for *M. gypseum* and *T. mentagrophytes*. The fungal growth was indicated by the appearance of mycelia growth or turbidity.

The *in vitro* MFC activity was determined for each thiazole derivative as previously described by Espinel-Ingroff[28] and Espinel-Ingroff et al.[29] After 72 h in case of *C. albicans*, and 96 h for *M. gypseum* and *T. mentagrophytes*, 20 μL was subcultured from each well that showed complete inhibition (100% or an optically clear well), from the last positive well (growth similar to that for the growth control well), and from the growth control (drug-free medium) onto Sabouraud dextrose agar plates. The plates were incubated at 30 °C until growth was seen in the control subculture. The MFC was the lowest drug concentration that showed either no growth or fewer than three colonies (approximately 99–99.5% killing activity).

2.4. Keratinase activity assay

In this experiment, the effect of thiazole compounds showing considerable toxicity, namely; **7a, 7c, 7e, 7f, 7g, 7i,** and **7m** was evaluated at applied at their respective MIC values. The test dermatophytes were inoculated into keratinase induction medium[30] (Muhsin and Aubaid, 2000) amended with one of the tested compounds. Fluconazole was used as positive control. The cultures



7a-n

Cpd No.	R	Ar	Cpd No.	R	Ar
a	Ph	Ph	h	CH_3	2-$CH_3C_6H_4$
b	Ph	4-$CH_3C_6H_4$	i	CH_3	4-$CH_3OC_6H_4$
c	Ph	4-$CH_3OC_6H_4$	j	CH_3	4-ClC_6H_4
d	Ph	4-ClC_6H_4	k	CH_3	2-ClC_6H_4
e	Ph	4-$NO_2C_6H_4$	l	CH_3	3-ClC_6H_4
f	CH_3	Ph	m	CH_3	4-$NO_2C_6H_4$
g	CH_3	4-$CH_3C_6H_4$	n	CH_3	2,4-$(Cl)_2C_6H_3$

Scheme 1. Investigated arylazothiazole derivatives **7a–n**.