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DISCUSSION AND CHARACTERIZATION OF ANTIFUNGAL PROPERTIES OF SOME 1,2,4-TRIAZOLE DERIVATIVES

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ABSTRACT

Fungal infections have become a serious global health concern, affecting millions of people each year. The rising incidence of these infections can be attributed to several factors, including an increasing number of immunocompromised individuals, widespread use of antibiotics, and the evolution of drug-resistant fungal strains Therefore, the aim of this study was to conduct a comparative discussion and analysis of the antifungal activity of 1,2,4-triazole derivatives using modern literature data. Based on the findings, specific conclusions were drawn to guide future research directions in the development of promising antifungal agents. An analysis of scientific publications in recent years focused on the antifungal properties of 1,2,4-triazole derivatives highlights the undeniable potential of these compounds as a source of new biologically active agents. Numerous studies point to the possibility of continuous modification and innovative improvement of molecules to enhance their antifungal activity. A promising approach involves modifying 1,2,4-triazole derivatives by incorporating halogen-aromatic fragments into their structure. This modification may not only enhance antifungal properties or increase their effectiveness but also reduce the overall toxicity of the compounds. Based on the literature review, 2-(((3-(2-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-4-yl)imino)methyl)phenol meets these criteria and, in our view, warrants further investigation as a potential antifungal agent.

KEYWORDS: 1,2,4-triazole derivatives, antifungal activity, chemical structure features, *in silico* studies, *in vitro* studies, comparative analysis.

INTRODUCTION

Fungal infections have become a serious global health concern, affecting millions of people each year. The rising incidence of these infections can be attributed to several factors, including an increasing number of immunocompromised individuals, widespread use of antibiotics, and the evolution of drug-resistant fungal strains.[1] Consequently, there is an urgent need to develop new antifungal agents with improved efficacy, safety, and resistance profiles.

Antifungal drugs play a crucial role in the treatment and prevention of fungal infections. They are used to treat superficial mycoses, such as dermatophytosis, as well as systemic mycoses, including invasive candidiasis and aspergillosis. The availability of effective antifungal agents is of utmost importance, as some fungal infections can lead to severe morbidity and mortality if left untreated.[2,3]

The current arsenal of antifungal compounds includes four major classes: polyenes, azoles, echinocandins, and allylamines. Among these, azole antifungals are the most widely used due to their broad-spectrum activity and relatively low toxicity. However, the widespread and prolonged use of azoles has led to the emergence of drug-resistant fungal strains, limiting the efficacy of these agents.[4]

Moreover, existing antifungal drugs are associated with various side effects, drug interactions, and a narrow therapeutic index, further restricting their use. The scientific evidence presented by the authors emphasizes the urgent need for the development of new antifungal agents with novel mechanisms of action, improved safety profiles, and enhanced therapeutic potential.[5]

Therefore, the **aim** of this study was to conduct a comparative discussion and analysis of the antifungal activity of 1,2,4-triazole derivatives using modern literature data. Based on the findings, specific conclusions were drawn to guide future research directions in the development of promising antifungal agents.

MATERIALS AND METHODS

The 1,2,4-triazole framework has garnered significant interest as a core structure in the development of new antifungal agents. 1,2,4-Triazoles are a class of heterocyclic compounds characterized by a five-membered ring containing three nitrogen atoms and two carbon atoms. Unique properties of triazoles, such as their ability to form strong hydrogen bonds and high lipophilicity, make this framework an attractive candidate for drug design.

Many derivatives of 1,2,4-triazole have demonstrated promising antifungal activity, with some even surpassing the efficacy of existing azole antifungal drugs. Fluconazole, itraconazole, and voriconazole are widely used azole antifungal agents that incorporate the 1,2,4-triazole moiety in their structures.[6,7]

RESULTS AND DISCUSSION

The development of new 1,2,4-triazole derivatives as antifungal agents requires a systematic approach that combines rational computational strategies, synthetic chemistry, and biological evaluation of inefficacy. Rational compound design involves modifying the 1,2,4-triazole core to introduce new functional groups aimed at enhancing antifungal activity while minimizing the likelihood of resistance development.[8]

Recent advancements in molecular modeling, including molecular docking, have facilitated the rational design of 1,2,4-triazole derivatives with optimized pharmacological profiles. These *in silico* tools enable researchers to predict the binding affinity and selectivity of designed compounds for their target proteins, making it easier to identify promising candidates for synthesis and biological evaluation as antifungal agents.[9]

Synthetic chemistry plays a crucial role in the development of new 1,2,4-triazole derivatives. Diverse synthetic pathways and strategies have been employed to access a wide range of 1,2,4-triazole derivatives with various functional groups. This diversity allows for the exploration of structure-activity relationships (SAR) and the optimization of pharmacokinetic and pharmacodynamic properties.[10]

Invasive fungal infections (IFIs) are increasingly becoming major infectious diseases worldwide, and the limited efficacy of existing drugs leads to significant morbidity and mortality due to the lack of effective antifungal agents and severe drug resistance. In this study, the authors presented a series of benzimidazole-1,2,4-triazole derivatives as typical antifungal compounds, whose activity was tested *in vitro* against four fungal strains: *C. albicans, C. glabrata, C. krusei*, and *C. parapsilopsis*.[11]

The synthesized compounds demonstrated significant antifungal potential, particularly against *C. glabrata.* This highlights the promising role of benzimidazole-1,2,4-triazole derivatives as potential candidates for further development in antifungal therapy.

An original approach to modeling new 1,2,4-triazole derivatives is proposed by a group of authors.[12] The researchers designed and synthesized a series of 1,2,4-triazole derivatives. To evaluate the potential of the synthesized compounds as antifungal agents, *in silico* studies were conducted, including ADME properties, drug-likeness, and molecular docking analysis.

The *in vitro* antifungal activity against *Candida albicans* and *Aspergillus* niger was assessed using the agar well diffusion method, measuring zones of inhibition. All compounds exhibited drug-likeness profiles. Two compounds showed the highest binding affinities, with values of -9.2 and -10.0 kcal/mol, respectively, and demonstrated promising antifungal activity.

At a concentration of 100 µg/mL, one compound exhibited inhibition zones of 19.9 mm against *C. albicans* and 20.5 mm against *A. niger*, while the other compound showed inhibition zones of 19.5 mm against *C. albicans* and 22.5 mm against *A. niger*. In comparison, the reference drug itraconazole at the same concentration demonstrated inhibition zones of 23.8 mm and 24.7 mm.

Given their activity profiles, these two compounds hold potential as candidates for further development as antifungal agents.

Some fungicidal agents lose their efficacy due to the development of resistance, raising the need for the creation of innovative antifungal treatments.[13] The 1,2,4-triazole system is one of the most significant pharmacophoric frameworks among five-membered heterocycles. The structure-activity relationship (SAR) of this nitrogen-containing heterocyclic system has demonstrated its potential antifungal activity. Therefore, another group of researchers aimed to

highlight recent advancements in the synthesis and SAR studies of 1,2,4-triazoles as a potential fungicidal framework.[13]

The authors present results of biological activity evaluations. Literature studies have shown that 1,2,4-triazole derivatives exhibit a broad spectrum of antifungal activity. This review serves as a valuable resource for other researchers in designing new potential antifungal drug candidates with high efficacy and selectivity.

Another study demonstrated that some medicinal plants containing triazole frameworks possess antifungal properties. Examples include propiconazole, triadimefon, tebuconazole, tebuconazole, propiconazole, epoxiconazole, and prothioconazole.[14]

Each year, invasive fungal infections result in 1.7 million deaths worldwide, presenting a serious challenge to global healthcare systems.[15] One of the most pressing issues is the growing resistance of various fungal pathogens to synthetic drugs. Therefore, the synthesis and the development of new 1,2,4-triazole derivatives with low toxicity remain a critical task globally.[16]

It is widely recognized that triazoles are biologically active compounds that act by inhibiting the activity of the cytochrome P450-dependent enzyme lanosterol 14α-demethylase (CYP51), a crucial enzyme in the biosynthesis of fungal ergosterol.[17] Azoles bind to the iron within porphyrins, causing a blockage in the fungal ergosterol biosynthesis pathway, which leads to the accumulation of 14-demethylated sterols.[18]

Recently, research teams synthesized a series of novel 1,2,4-triazole derivatives and evaluated their fungicidal activity.[19–30] Some of these compounds demonstrated potential activity against specific fungi. According to the authors, antifungal activity of new fluorophenyl-containing 1,2,4-triazoles was studied for the first time.[31]

The researchers found that most of the compounds exhibit moderate antifungal activity. However, one compound, 2-(((3-(2-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-4-yl)imino)methyl)phenol, showed notable sensitivity to *Candida albicans*, with its fungistatic and fungicidal activity levels measured at 3.9 μg/mL. Moreover, in some cases, patterns were identified regarding the influence of substituents on activity indicators.

An analysis of scientific publications in recent years focused on the antifungal properties of 1,2,4-triazole derivatives highlights the undeniable potential of these compounds as a source of new biologically active agents.[32,33] Numerous studies point to the possibility of continuous modification and innovative improvement of molecules to enhance their antifungal activity.

A promising approach involves modifying 1,2,4-triazole derivatives by incorporating halogen-aromatic fragments into their structure. This modification may not only enhance antifungal properties or increase their effectiveness but also reduce the overall toxicity of the compounds.

Based on the literature review, 2-(((3-(2-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-4-yl)imino)methyl)phenol meets these criteria and, in our view, warrants further investigation as a potential antifungal agent.

CONCLUSIONS

An analysis of contemporary literature underscores the significant potential of 1,2,4-triazole derivatives as powerful antifungal agents. In recent years, researchers have synthesized a vast number of new compounds, among which halogen-aromatic derivatives of 1,2,4-triazole appear particularly promising.

Chemical modification of the triazole framework with various pharmacophoric substituents has clearly and convincingly demonstrated the potential of 2-(((3-(2-fluorophenyl)-5-mercapto-4H-1,2,4-triazol-4-yl)imino)methyl)phenol as an antifungal compound. This compound shows great promise for the development of a novel, original domestic pharmaceutical product.

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