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ORIGINAL ARTICLE

An Inclusive Disquisition on Thiazoles as Possible Antifungal Agents

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ABSTRACT

In recent years, antifungal medications have become increasingly ineffective due to antifungal resistance, which is one of the largest concerns facing the globe today. The inception of novel heterocycles that have substantial biological consequences has become vital owing to the advent of several epidemics and resistant bacteria. Numerous hybrid compounds are presently undergoing varying phases of clinical testing and could eventually be utilized in the therapeutic settings to address a range of ailments. In this overview, Nitrogen and sulfur-based heterocyclic aromatic compounds play a substantial and crucial role in medicine and the production of pharmacologically active substances. Thiazoles are highlighted for their crucial role, attributed to their wide array of biological activities within the field of medicinal chemistry. The emergence of antifungal resistance poses a considerable public health challenge as it diminishes the efficacy of antifungal treatments, leading to heightened rates of illness, mortality, and healthcare expenses. Given the foregoing, we have compiled an inventory of the most current developments in thiazoles as antifungal agents, encompassing papers reported from 2020 to 2024.

Keywords: Antifungal; Thiazoles

1 INTRODUCTION

In 1887, Hantzsch and Weber were the first to document thiazole, a heterocyclic compound with a five-membered ring containing both sulfur and nitrogen atoms. [1]

Heterocyclic compound with sulfur atom plays a key role in the drug discovery technique. One of these compounds is the thiazole ring. Thiazole, also known as 1,3-thiazole, is a pale-yellow flammable liquid characterized by a scent reminiscent of pyridine. Its molecular formula is C_3H_3NS, with a molecular weight of 85.128 g/mol, and it typically boils within the temperature range of 116–118°C. [2] Its aromatic nature arises from the delocalization of a lone pair of electrons originating from the sulfur atom, leading to the formation of a 6π-electron system. Furthermore, its pronounced aromaticity is evidenced by proton nuclear magnetic resonance, with the chemical shift values of each proton within the thiazole ring typically ranging between 7.27 and 8.77 ppm. [3] According to Hückel's rule, the density of the six π electrons indicates that electrophilic substitution primarily occurs at the C5 carbon, while nucleophilic substitution predominantly takes place at the C2 carbon. [4] Thiazole's reactivity, particularly because of the acidic proton on its C2 position, makes it a versatile building block in organic synthesis. This reactivity allows for various functionalization's and transformations, leading to the creation of diverse chemical compounds with potentially valuable properties. Thiazole derivatives find applications in medicinal chemistry, agrochemicals, materials science, and more, contributing significantly to the development of new chemical entities with desired characteristics.

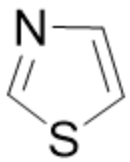

Figure 1: Thiazole

Thiazole exhibits aromaticity due to the delocalization of π-electrons across the five-membered ring system, including the sulfur atom. This delocalization, facilitated by resonance, stabilizes the molecule and contributes to its overall reactivity and properties. Thiazole's versatile reactivity allows it to

participate in a wide range of chemical reactions, including substitution, cycloaddition, oxidation, arylation, dimerization, and photochemical reactions, among others. [5] This reactivity arises from the presence of various functional groups that can be modified or transformed under suitable reaction conditions. The ability of thiazole to undergo such diverse reactions makes it a valuable building block in organic synthesis, enabling the construction of complex molecular structures and the development of novel chemical entities for various applications. Numerous novel chemical compounds with a wide spectrum of pharmacological properties have been produced as a result of these heterocycle alterations. [6] Many therapeutically authorized thiazole-containing drugs with a wide range of pharmaceutical properties are a reflection of its broad biological impact. Thiazole heterocycles serve as the bioactive core of numerous drugs, exhibiting a broad spectrum of pharmacological activities. Many thiazole-based compounds have shown efficacy as chemotherapeutic agents against various diseases, including cancer, fungal infections, bacterial infections, viral infections, and leishmaniasis. The chemical framework of thiazole is well recognized for its wide range of physiologically active properties. Numerous powerful pharmacologically active compounds, including the antibacterial drug Cefotaxime, the antifungal drug Isavuconazole, the antivirus drug Ritonavir, the antiparasitic drug Nitazoxanide, the anticancer drug Ixabepilone, the CNS drug Pramipexole, the gastrointestinal drug Nizatidine, the Angio-cardiopathic drug Arotinolol, the urinary infectious drug Mirabegron, the musculoskeletal drug Meloxicam, the musculoskeletal drug Febuxostat, and others typically include thiazoles. [7]

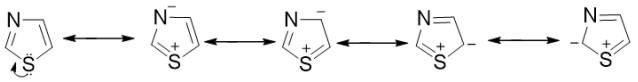

Figure 2: The Resonance Structure of Thiazole

The molecular composition of numerous natural products and physiologically active substances typically contains a thiazole molecule. Studies conducted on medicinal chemistry has shown that the thiazole molecules have an indispensable function in treating numerous kinds of illnesses. The broad-spectrum antifungal agent is abafungin. The fungicide and parasite i.e. thiabendazole, a novel DNA-binding gyrase B blocker. [8] Because of their excellent versatility in substitution placement i.e. substitutes can be incorporated at positions C-2, C-4, and C-5—thiazoles. Hence these frameworks are widely used in drug design [9–11]. Furthermore, the thiazole ring has garnered a lot of interest in agrochemical science due to the striking physiological functions of many thiazole derivatives. [12] It serves as a crucial element found in the structural framework of numerous naturally found, medicinally and physiologically active chemicals, including pharmaceuticals that have been offered commercially, including bleomycin, pramipexole, febuxostat, vitamin B, ritonavir, penicillin-G, tiazofurin, abafungin, sulfathiazole, and sulfazole. [13]

The chemical study of thiazoles has currently been intensively developed due to the comparatively straightforward synthesis of a large range of compounds, allowing examining the relationship between their structure and characteristics. [14] Largazole, a thiazole-based natural product, was discovered to be a potent anticancer drug that works by inhibiting histone deacetylases (HDACs). [15] Dasatinib, dabrafenib, and alpelisib are currently used to treat acute lymphoblastic leukemia, advanced melanoma, and breast cancer, respectively. Furthermore, the thiazole-based natural compounds patellamide A, ixabepilone, and epothilones possess clinical applications in the treatment of resistant prostate cancer, metastatic breast cancer, ovarian cancer, and rectal cancer. [8] The synthesis and design of azole-based heterocycles are of considerable interest because of their extensive applications in the pharmaceutical and agrochemical sectors for treating infections, diseases, and pests. [16] Thiazole moiety is commonly found in the structure of numerous natural products as well as physiologically active chemicals. Thiazole moiety has played an important role in medicinal chemistry research, with therapeutic effects against a variety of diseases. Thiazole moiety is commonly found in the structure of numerous natural products as well as physiologically active chemicals. Thiazole moiety has played an important role in medicinal chemistry research, with therapeutic effects against a variety of diseases. [17]

2 SYNTHESIS OF THIAZOLE DERIVATIVES

2.1 Hantzsch synthesis

Various synthetic methods of thiazole rings include 'Hantzsch synthesis' (Figure 3) methods because of its simplicity, which can incorporate various functional groups and has been most frequently used. This approach uses the condensation reaction of α-haloketone with nucleophilic reagents such thioamide, thiourea, ammonia thiocarbamate, or dithiocarbamate derivatives. [17]

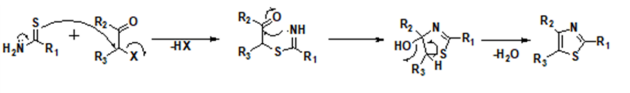

Figure 3: Hantzsch synthesis of thiazole

2.2 Cook-Heilbron synthesis

Cook and Heilbron discovered the Cook-Heilbron synthesis (Figure 4), which involves reaction of α-aminonitriles or α-aminoamides with carbon disulfide to produce a thiazole ring. The Cook-Heilbron method established 5-aminothiazoles in which substitution happened at position 2 through the reaction of aminonitrile with salt and esters

of thioacids, carbon disulfide, or isothiocyanates under mild conditions. [18]

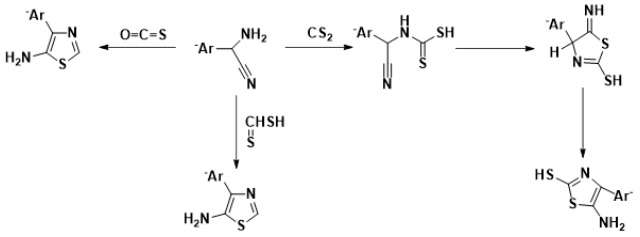

Figure 4: Cook-Heilbron synthesis of Thiazoles

2.3 *Gabriel synthesis*

Gabriel synthesis is another synthetic technique for producing thiazole compounds. The reaction of α-acylamino ketones or amino acetal with phosphorous pentasulfide yielded 2,5-disubstituted thiazoles in good yields (Figure 5). [19, 20]

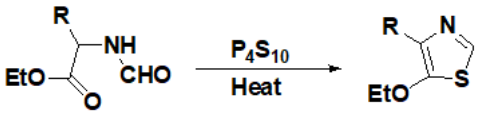

Figure 5: Gabriel synthesis of Thiazoles

Condensation of equimolar mixture of thiourea and α-haloketones or aldehyde to produce 2-aminothiazole (Figure 6).

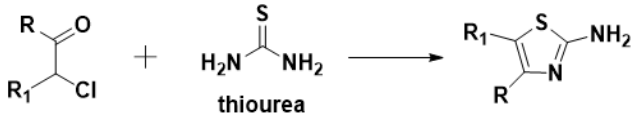

Figure 6: Synthesis of 2-aminothiazoles

2.4 *Reactions with thioamides*

Thioamides and α-halo carbonyl compounds were reacted to form thiazoles (Figure 7) with alkyl, aryl, arylalkyl, or heteroaryl functional groups at positions 2, 4, or 5. [21]

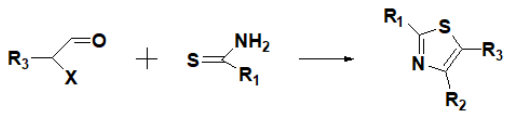

Figure 7: Synthesis of 2,4, or 5 substituted Thiazoles

The thiazole target compounds were synthesized via refluxing thiourea with aromatic ketone and Sodium Dichloroiodate ($NaICl_2$).

Figure 8: 2-aminothiazoles synthesis

R=C_6H_5, 4-CH_3-C_6H_4, 4-NH_2-C_6H_4, 4-OCH_3-C_6H_4

Heravi et al. proposed a very effective method of synthesis. The reaction was completed at room temperature by grinding the appropriate amount of phenacyl bromide with thioacetamide in order to yield the designated 2,4-disubstituted Thiazoles.

Figure 9: 2,4-disubstituted Thiazoles synthesis

R=C_6H_5, 4-CH_3-C_6H_4, 4-NH_2-C_6H_4, 4-OCH_3-C_6H_4

A simple methodology for synthesizing thiazole-2-thiones from nitrobenzene, chalcones, and carbon disulfide is presented. In one pot, one C-S bond and two C-N bonds are formed using a [3+2] cycloaddition reaction with NaOH as the base. [22]

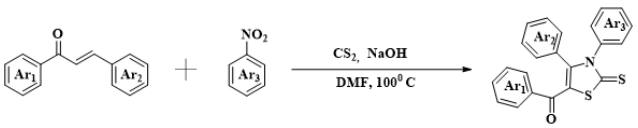

Figure 10: Synthesis of Thiazole-2-thiones

3 THIAZOLE DERIVATIVES AS EXTRUSIVE ANTIFUNGAL AGENTS

Invasive fungal infections have a high morbidity, death, and economic cost. In recent times, an increasing frequency of fungal infection and antifungal resistance is occurring, prompting the development of innovative antifungal medicines. [23]Fungal complications affect a large number of people around the world, leading to higher hospitalizations and death rates, and the demand for innovative antifungals is rising with the emergence of resistance and immunocompromised individuals. Fungi-related illnesses impact more than a billion people globally, with more than 150 million having severe, life-threatening conditions, resulting in nearly 1.7 million deaths each year. [23] Fungi produce a variety of diseases in humans, ranging from allergy syndromes to superficial, disfiguring, and life-threatening

invasive fungal infections (IFDs), which impact over a billion people globally. [24] Candidiasis is the most common fungal illness among immunocompromised patients. *Candida parapsilosis*, a non-albicans *Candida* species, has emerged as a serious disease. *Candida parapsilosis* is one of the non-albicans *Candida* species that has become a serious problem. The human skin is commensal with *C. parapsilosis*. It can be primarily observed in the alimentary canal, surfaces of mucous membranes, and cuticles in addition to the dermis. The primary antifungals employed for curing candidiasis are azole prescribed drugs and echinocandins. In accordance with Chinese fungal therapy principles, antifungal medication prescription is strictly limited and necessitates the supervision of a physician or above. Fluconazole, voriconazole, itraconazole, amphotericin, caspofungin, garlicin pills, and sodium bicarbonate mouthwash are some of the medicines used for antifungal purposes. [25]

In 1944, Woolley reported that Benzimidazole was the first azole to exhibit antifungal action. However, it wasn't until 1958 that an azole antifungal medication was invented. [26] The demand for azole chemicals for antifungal drugs began when chlormidazole was introduced to the market. [27] Immediately after the development of novel azoles, three new antifungal azoles emerged as topical agents: econazol in 1974, Janssen's miconazole concurrently, and Bayer AG's clotrimazole in 1969. Miconazole is known to be effective in treating vulvovaginal candidiasis, oropharyngeal candidiasis, tineacorporis, tineapedis, and tineacruris. [28] When ketoconazole was first released in 1981, it has been identified as a second-generation imidazole. [29] This molecule was the first azole to be made available orally to treat systemic fungal infections, and despite the other imidazoles, its effects were not only effective in treating superficial mycoses. [30] The FDA suggests that clotrimazole is secure and efficient in treating and preventing cutaneous, vulvovaginal, oropharyngeal, and other superficial dermatological infections. The Food and Drug Administration has granted approval for luliconazole, the recently introduced first-generation azole, which has a special vinyl-imidazole structure. *Trichophyton rubrum, Microsporum gypseum*, and *Epidermophyton floccosum* are among the dermatophytes that it has a broad-spectrum topical action against. [31]

A next-generation azole (tetrazole), oteseconazole is more selective for fungal lanosterol 14α demethylase (CYP51). A new family of antifungal called fosmanogepix blocks the fungal Gwt1 protein, which is necessary for mannoprotein trafficking and attachment to the outer cell wall and cell membrane. [32] Rezafungin is an innovative antifungal echinocandin that contributes chemical similarities with anidulafungin. [33] Similar to other echinocandin antifungals, it breaks down fungal cell walls by preventing β-1,3-D-glucan from being biosynthesised. [34] In 1990, the US Food and Drug Administration (FDA) authorized fluconazole as the first triazole to treat infections caused by *Candida* and *Cryptococcus* species. A significant worry in recent years has been the registration of isavuconazole, posaconazole, voriconazole, [35] and itraconazole [36] among various fungal species. [37]

The newly formed arylazothiazoles [38] and arylhydrazothiazoles [39] were introduced and their antifungal properties assessed. The thiazole compounds shown strong antifungal potential against *Trichophyton mentagrophytes, Microsporum gypseum*, and *Candida albicans* in terms of keratinase activity and ergosterol production. The outcomes were contrasted with the conventional medication, fluconazole. When both side chains were aromatic, the antifungal action was shown to be more potent. Two of the series chemicals demonstrated strong antifungal effects by inhibiting the formation of keratinase and ergosterol. [40]

Reported pharmacological activities of Thiazole derivatives are given in **Supplementary table**.

Fungal ailments that affect agriculture causes significant perennial monetary losses to landowners globally. Plant infections produced by virulent fungus severely impede healthy development of crops, which leads to a major drop in agricultural output and nutritional value. [43]For instance, in areas where wheat is grown, *F. graminearum* leads wheat head blight (Duan et al., 2019)16, while *F. moniliforme* typically leads to corn ear rot, a damaging disease that reduces corn output. Commercial fungicides that are currently the primary means of preventing and controlling phytopathogenic fungus; nevertheless, over usage of these kind of fungicides has resulted in environmental contamination, poisoning, and a surge in drug susceptibility. The rise in microbial susceptibility and many pandemics has created an imperative for new heterocyclic molecules with strong physiological activity. Fungal resistance to biocides was exacerbated by the overuse of antifungal medications. For agrochemical researchers, creating novel lead antifungal chemicals is a clicking and challenging issue. [16]

One of the most widely used classes of heterocycles and antifungal agents are azoles. Because of their biological relevance and structural variety, clubbed azoles have emerged as a desirable option for new antibacterial lead chemicals. [17] Chemical fungicides are essential for plant protection and are regarded as one of the most economical and effective solutions. There are many different kinds of chemical fungicides that have been manufactured and traded over time. Scaffold hopping and bioisosterism are design strategies that can enhance the pharmacological characteristics of lead compounds and lower the possibility of cross-resistance. These tactics were used to optimize the structural framework of lead compounds in the production of pharmaceutical drugs or pesticides. [44]

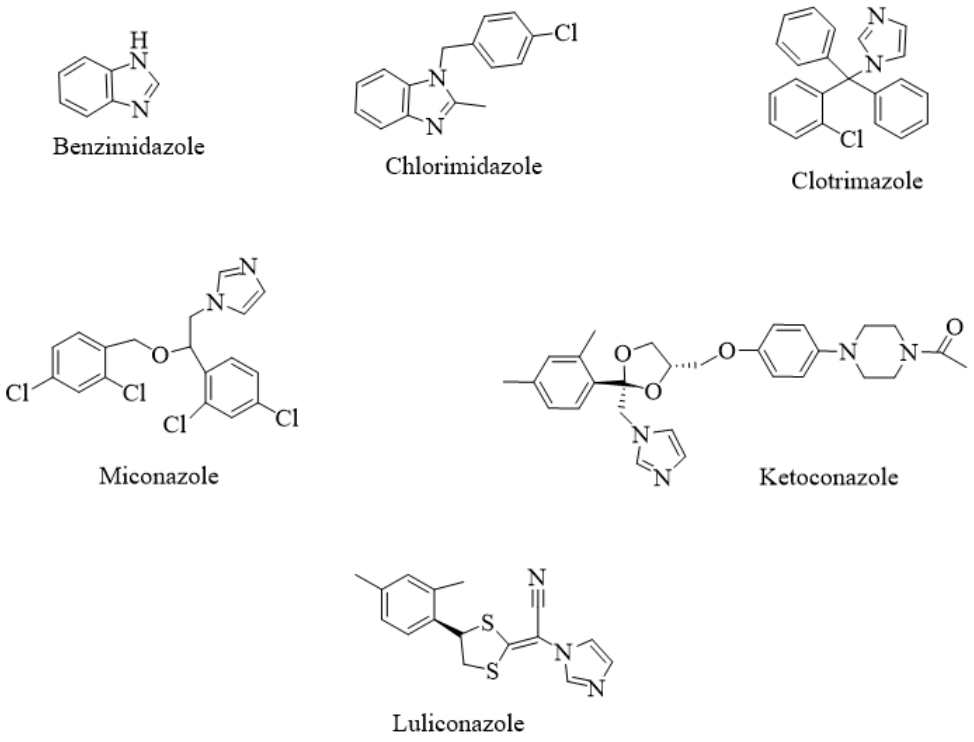

Figure 11: Structures and approval dates of imidazole antifungal drugs [37, 41]

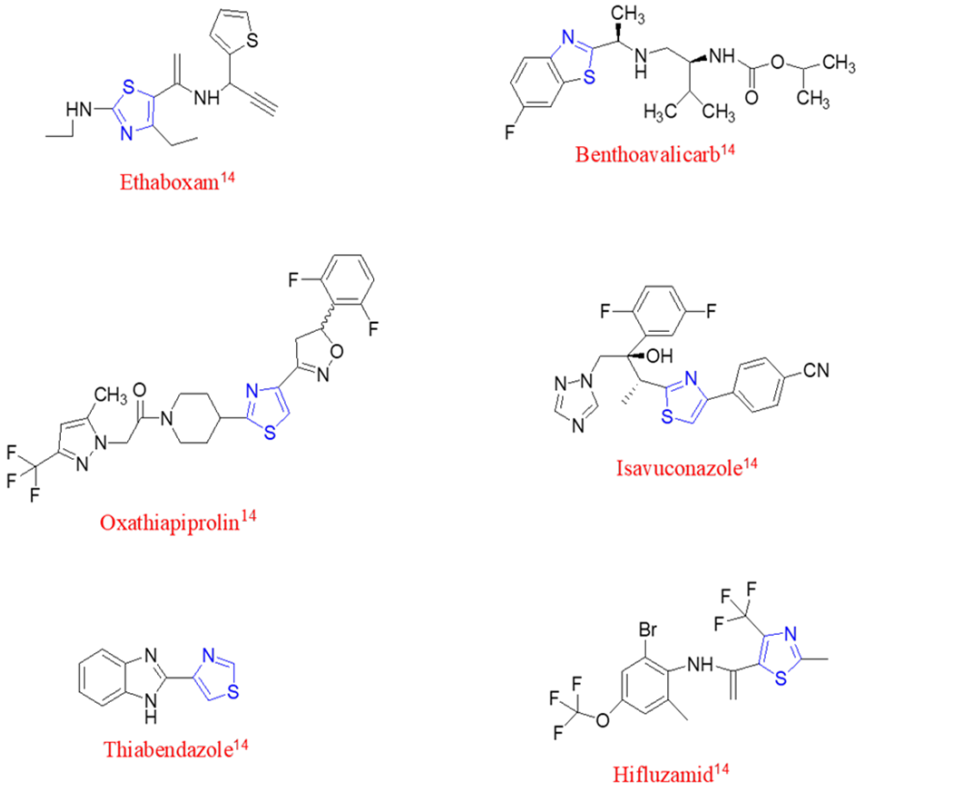

Figure 12: The structures of some commercialized thiazole fungicides [42]

4 CONCLUSION

In conclusion, thiazole derivatives have emerged as a cornerstone in the realm of organic and medicinal chemistry, attributed to their broad spectrum of biological activities. These compounds exhibit significant antimicrobial, anticancer, antitubercular, anti-inflammatory, and antioxidant properties, along with various other therapeutic applications. Their multifunctionality and structural versatility have rendered them indispensable in the design and development of innovative pharmaceutical agents. Furthermore, thiazole derivatives have been utilized in various diagnostic and therapeutic tools, underscoring their relevance beyond conventional drug development.

Despite considerable progress in the synthesis and application of thiazole-based compounds, there remains immense potential for further exploration. Advances in synthetic methodologies, including green chemistry approaches and combinatorial synthesis, can unlock new structural variants with enhanced bioactivity and reduced toxicity. Additionally, the integration of computational techniques such as molecular docking, quantitative structure-activity relationship (QSAR) analysis, and machine learning can expedite the identification of novel thiazole derivatives with targeted pharmacological effects.

Given their unparalleled biological significance, thiazole derivatives continue to attract significant attention from medicinal, synthetic, and pharmacological chemists. Future research endeavours are expected to expand their applications in emerging fields such as nanomedicine, targeted drug delivery, and theranostics, solidifying their position as a dynamic and promising class of compounds in heterocyclic chemistry and modern medicinal research.

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