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ADVANCES IN STRUCTURAL AND PHARMACOLOGICAL INSIGHTS OF FIVE-MEMBERED RING SYSTEMS: UNVEILING THE POTENTIAL OF TRIAZOLES IN ANTIFUNGAL THERAPY AND BEYOND

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ABSTRACT

This study explores the structural properties of various five-membered ring systems, including symmetrically or asymmetrically arranged triazoles, oxadiazoles, dithiazoles, and thiadiazoles with three heteroatoms. Emphasis lies on synthesizing and assessing the pharmacological impact of triazoles, showcasing a broad spectrum of activity: anti-fungal, anti-bacterial, anti-inflammatory, and anti-cancer. Triazoles have revolutionized treatment possibilities, now effective against conditions like aspergillosis, candidiasis, and cryptococcal meningitis. Despite existing antifungal therapies, unacceptably high mortality rates persist with these infections. This has spurred the development of antifungal agents targeting specific fungal elements, fueled by rapid progress in molecular mycology. As we enter a new antifungal therapy era, the outlook is promising. The pursuit of targeted antifungals, alongside expanding treatment options, exemplifies our growing capacity to combat systemic fungal diseases. In this dynamic landscape, advancements continue to unfold despite the challenges posed, enhancing our ability to confront systemic fungal infections more comprehensively.

KEYWORDS: Anti-fungal drugs, Triazoles derivatives, Heteroatoms, Biosynthesis, Chemotherapy.

INTRODUCTION

Across the world, health agencies and researchers are expressing significant worry over the rapid escalation of antimicrobial resistance, particularly in the context of multidrug-resistant bacteria and fungi.[1,2] Consequently, there is a growing imperative for the development of novel antimicrobial agents that are not only more potent and less harmful but also safer. This drive has led to the creation of innovative classes of antimicrobials with fresh mechanisms of action and enhanced structural modifications, aimed at bolstering their efficacy and expanding their range of activity. Lately, there has been a rising emphasis on the pursuit of integrating two active fragments within a single molecule.[3] Through the implementation of this approach, diverse drug molecules individually engage distinct biological targets, yielding advantageous outcomes.[4] Various N-bridged heterocyclic compounds, including triazole, have garnered recent attention owing to their biological functionalities. Triazole, one member of an isomeric duo of chemical compounds, is represented by the molecular formula $C_2H_3N_3$. This aromatic heterocyclic ring possesses a foundational structure.[5] Triazole derivatives exhibit a variety of pharmacological attributes, encompassing antimicrobial effects,[6-10] anti-tubercular capabilities,[11] anti-cancer potentials,[12,13] anti-convulsant tendencies,[14] analgesic qualities,[15] and anti-viral activities.[16] A series of therapeutically interesting drugs have also been developed using triazoles, including the blocking of H1/H2 histamine receptors, CNS stimulants, anti-depressants, and sedatives.[17] Most commonly, fluconazole, itraconazole, and voriconazole are used as anti-mycotics.[18,19]

Despite its stability to degradation, the triazole moiety can hydrogen bond, allowing it to bind biomolecular targets and increase solubility.[20] Furthermore, triazoles have been used increasingly frequently in the construction of bioactive and functional molecules to connect two pharmacophores to provide a bifunctional drug.[21-23] Significantly, within medicinal chemistry, there has been a distinct focus on the bioisosteric substitution of the triazole moiety with its bioisoster, the triazole. This concept has played a pivotal role in the exploration and advancement of innovative triazole-based drugs. It expands the chemical landscape of triazole frameworks, resulting in compounds that exhibit

potent attributes or significantly elevate biological activities.[24]

Furthermore, numerous investigations have highlighted the noteworthy influence of halogen-containing substituents, particularly alkyl chains, on antimicrobial properties. Antifungal azoles feature one or multiple azole rings. Although both imidazole and triazole comprise five-membered heterocyclic rings, imidazole consists of two nitrogen atoms within each ring, contrasting with triazole's three nitrogen atoms. However, it's crucial to underline that in comparison to imidazoles (e.g., clotrimazole, ketoconazole, miconazole), triazoles exhibit greater target specificity, potency, and a broader spectrum of activity.[25,26]

Triazole's chemistry

Molecularly, triazole is one of two isomeric compounds containing two carbons and three nitrogen, with the formula C2H3N3. It is known that triazoles exist in two different isomeric forms, namely 1,2,3-triazole (A) and 1,2,4-triazole (B) (fig.1).

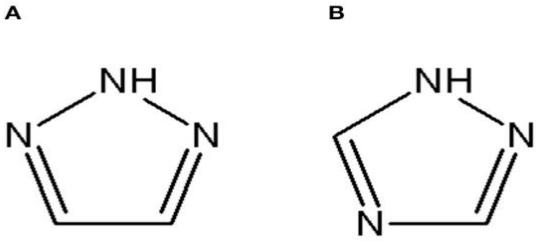

Fig. 1: Triazole's isomeric form.

Triazoles are heterocyclic aromatic compounds that are based on basic elements. As compared to other organic compounds with three adjacent nitrogen atoms, triazoles are extraordinarily stable. In contrast, flash vacuum pyrolysis at 500 °C leads to the loss of molecular nitrogen (N2) and the formation of aziridine. By ring-chain tautomerism, certain triazoles can be easily cleaved.

Bio-synthesis of triazole derivatives

The preparation of substituted 1,2,3-triazoles can be achieved using the azide-alkyne Huisgen cycloaddition process, wherein a 1,3-dipolar cycloaddition reaction takes place with the involvement of a catalyst (as illustrated in fig. 2) or ruthenium (as depicted in fig. 3).[27]

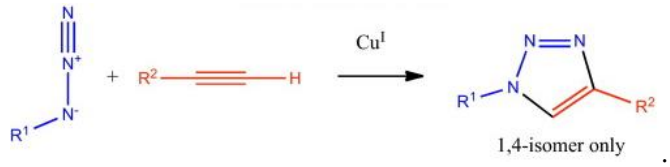

Fig. 2: Azide-alkyne cycloaddition (Copper catalyst).

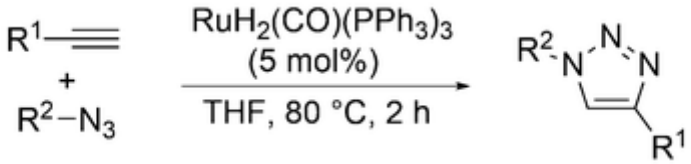

Fig. 3: Azide-alkyne cycloaddition (Ruthenium catalyst).

In figures 4, and 5 we present some new synthetic methods for 1,2,3-triazoles.

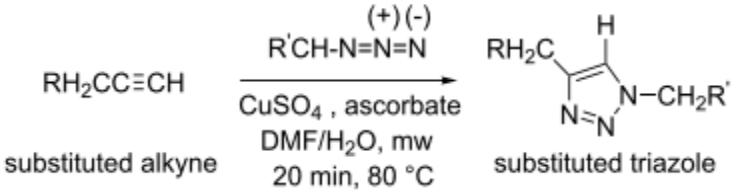

Fig. 4: Azide-alkyne cycloadditions (Copper-sulfate).

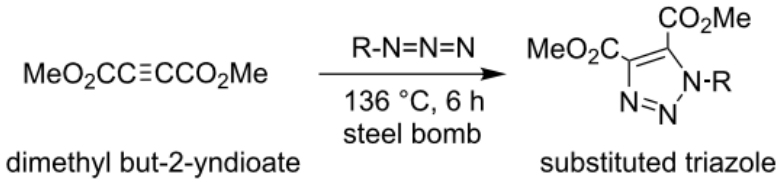

Fig. 5: Azide–dimethylbut-2-yne-dioate cycloaddition.

Bioisosteric replacement of a triazole ring results in an antifungal interaction with elevated selectivity. Triazole antifungal medications effectively address both superficial and deep-seated candidiasis infections.[30] Numerous literature surveys have underscored the pivotal role of triazole nuclei in fungal treatment. Presented below are diverse triazole derivatives synthesized by various research groups, demonstrating their inherent antifungal attributes. The synthesized compounds underwent assessment for their anti-fungal activity against *Candida albicans, Cryptococcus neoformans, Benjaminiella poitrasii, Yarrowia lipolytica, and Fusarium oxysporum.*[20]

Commencing with 4-azido-8-trifluoromethylquinoline as the initial substrate, Holla and colleagues synthesized triazole derivatives. These derivatives were subsequently evaluated against Candida albicans utilizing a 1,3-dipolar cycloaddition reaction.

Several synthesized compounds exhibited remarkable antifungal potency, notably including compounds such as 1-(1-(8-trifluoromethylquinolin-4-yl)-5-methyl-1H-1,2,3-triazol-4-yl)-4-(thiophen-3-yl)but-2-en-1-one (A) and 1-(8-trifluoromethylquinolin-4-yl)-N-(2-(thiophen-3-yl)ethylidene)-1H-1H-1,2,3-triazol-4-carbohydrate (B) (depicted in Fig. 6).

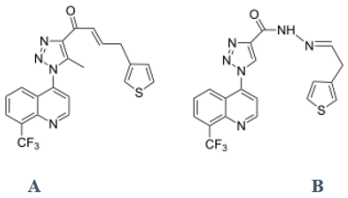

Fig. 6: Triazole compounds A and B showing antifungal activity against *Candida albicans.*[31]

Ezabadi synthesized a collection of ten novel 5-[2-(substituted sulfamoyl)-4,5-dimethoxybenzyl]-4-aryl-1,2,4-triazole-3-thione compounds. These compounds were subjected to testing against fungal species including Aspergillus flavus, Aspergillus versicolor, Aspergillus ochraceus, Aspergillus niger, Trichoderma viride, and Penicillium funiculosum. Notably, among these compounds, 5-[2-(N,N-diethylsulfamoyl)-4,5-dimethoxybenzyl]-4-(4-chlorophenyl)-1,2,4-triazole-3-thione (6, depicted in Figure 4) exhibited the highest level of activity.[32] Hussain *et al* synthesized various 4-amino-2-[4-(4-substituted phenyl)-5-sulfanyl-4H1,2,4-triazol-3-yl] and 4-amino-2-[4-amino-5-[(4-substituted phenyl)amino]-4H-1,2,4-triazol-3-yl]phenol derivatives. Using a cup plate method, they were evaluated for their antifungal activity against Aspergillus niger. Aspergillus niger was inhibited by 4-amino-2-(4-chlorophenyl)-5-mercapto-4H-1,2,4,-triazol3-yl)phenol. This compound has a chloro group as a para group on the phenyl ring.[33] Sztanke and collaborators devised a strategy for crafting unsubstituted and 3-substituted-7-aryl-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazoles. Through cyclocondensation reactions employing triethyl orthoformate, phenoxyacetic acid derivatives, and carbon disulfide, biologically active 1-aryl-2-hydrazonoimidazolidines were successfully synthesized. These compounds were evaluated for their antifungal efficacy against Aspergillus niger and Fusarium oxysporum. Notably, the compound demonstrating the most substantial antifungal activity was 7-(3-chlorophenyl)-6,7-dihydro-5Himidazo[2,1-c][1,2,4]triazole-3-thiol.[34]

Chemotherapy over fungal infections

Microorganisms that invade epithelial tissue can cause fungal infections. Molds, rusts, yeasts, and mushrooms are all members of the fungal kingdom. A fungus is heterotrophic, which means it obtains nutrients from the environment, not from inside itself (Like a plant does with photosynthesis). In contrast to eukaryotic cells, fungi share a number of biochemical targets with them. Several fungal organelles produce toxicity in the cell wall. The most important problem in phytopathology is systemic fungal infections, particularly in patients with weakened immune systems.[35]

The issue of multi-drug resistant bacteria is gaining heightened attention, as conventional antimicrobial treatments often prove inadequate in specific instances. The quest for novel antimicrobial agents remains imperative, given the growing resistance of certain microorganisms to synthetic antifungal compounds.

Presently, within clinical contexts, azoles stand as the prevailing category of antifungal agents.[36]

A dramatic increase in invasive fungal infections (IFI) has been observed worldwide over the past two decades.[37,38] Diagnosing, preventing, and treating IFIs is difficult due to their high morbidity and mortality. Among the most common nosocomial pathogens in the United States, Candida spp. ranks fourth in terms of crude mortality rate (40%).[39] There has been an increase in the transmission of fungal pathogens, such as *Aspergillus spp*., *Zygomycetes*, *Fusarium spp*., and *Scedosporium spp*., in recent years. Patients with haematological malignant diseases may be resistant to currently available antifungals, resulting in a 70% mortality rate.[40]

In the past, amphotericin B was the only antifungal available to treat IFIs. Triazoles were introduced at the beginning of the 1990s and accelerated drug development. There were three lipid formulations of amphotericin B (AMB) and two first-generation triazoles offered new treatment options for Candida infections (fluconazole (9) and itraconazole (10). In some cases, these antifungals are more effective than amphotericin B and less toxic than many of these drugs.[41]

Mechanism

Three nitrogen atoms are contained in a five-membered ring of fluconazole, an antifungal triazole. The triazole itraconazole works similarly to voriconazole and posaconazole is currently under investigation as an antifungal drug. Lanosterol to ergosterol conversion is inhibited by these drugs.[42] Triazoles function as inhibitors of cytochrome P450 14α-demethylase. This enzyme plays a pivotal role in converting lanosterol to ergosterol during cell wall synthesis. The azole ring's basic nitrogen forms a binding interaction with the heme iron of the fungal cytochrome P450, thereby impeding the binding of substrate and oxygen. The resultant inhibition of the 14α-demethylase leads to sterol accumulation, triggering alterations in permeability and functional disruptions in membrane proteins. Fig. 7 shows an inhibitor pathway for ergosterol biosynthesis.[43]

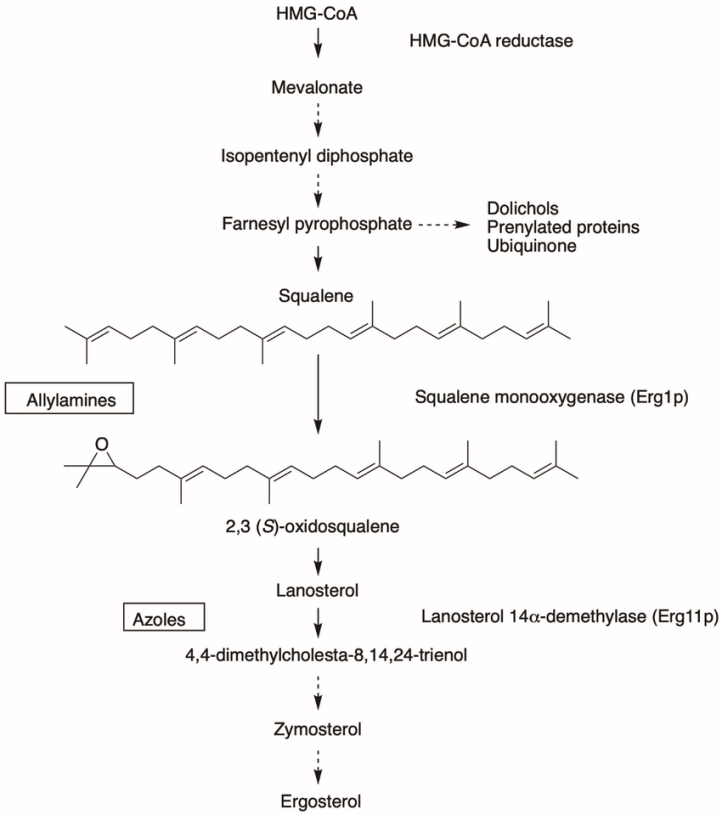

Fig. 7: Ergosterol biosynthesis.

Generation of triazoles derivatives

Ist Generation

Fluconazole

Among the fungistatic agents that fluconazole acts on are *C.albicans, C.tropicalis, and C.glabrata*. Patients with meningitis, cryptococcal meningitis, systemic and mucosal candidiasis, histoplasmosis, coccidioidal meningitis, or other infections may benefit from fluconazole treatment.[44-46]

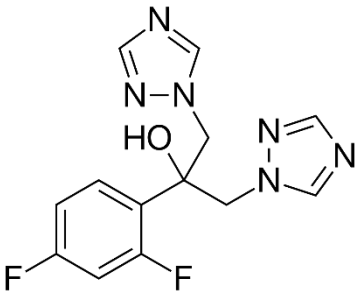

Fig. 8: Fluconazole structure.

Itraconazole

There are some strains of Cryptococcus neoformans that are resistant to itraconazole's fungicidal activity. Fungal infections that start in the lungs and spread throughout the body are treated with it in capsule form taken orally. In addition to treating nail fungal infections with itraconazole, it can also treat skin infections. It is possible to treat oral candidiasis with oral solutions.[47-50]

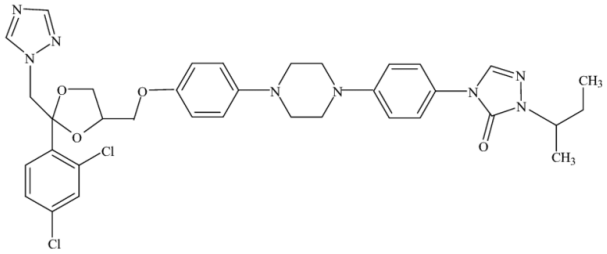

Fig. 9: Itraconazole structure.

In addition to constipation, heartburn, gum bleeding, headaches, and dizziness, itraconazole may induce several prevalent side effects. Excessive fatigue, nausea, vomiting, sensations of tingling or numbness in extremities, as well as challenges in breathing or swallowing, are also potential adverse effects.

Pharmacokinetics

Ist Generation

Despite their good tolerance, triazoles have the potential for drug–drug interactions because they interfere with oxidative metabolism mediated by cytochrome P450. Oral intake of fluconazole is almost 100% bioavailable, the drug circulates in the blood in its free form, it undergoes negligible hepatic metabolism, and it is excreted unchanged in the urine. As a result of its high protein binding and extensive hepatic metabolism, itraconazole is readily absorbed by the gastrointestinal tract and is excreted in an inactive form through the liver and kidneys. Food and gastric pH do not affect the oral bioavailability of fluconazole, which is 94% absorbed. Itraconazole is excreted unchanged in urine with a half-life of 25–30 hours. As a result of cytochrome P450 3A4 metabolism, it produces an active metabolite that is excreted in the feces within 30–64 hours.[42]

IInd Generation

Voriconazole

Voriconazole made its debut in the commercial realm in 2002 and was subsequently endorsed as a preferred frontline treatment for conditions including oesophageal candidiasis, *candidaemia*, invasive *aspergillosis*, skin infections caused by *Candida*, *abscesses*, kidney and bladder wall infections, wound infections, as well as infections originating from *S. apiospermum* and *Fusarium* species.[51] It is available as an oral medication as well as an intravenous treatment and has excellent bioavailability (90%). If there is renal failure, however, it isn't affected by the liver's metabolism. The kidneys secrete sulfobutyl ether-cyclodextrin sodium into the bloodstream for oral administration, which solubilizes it for intravenous administration.[52]

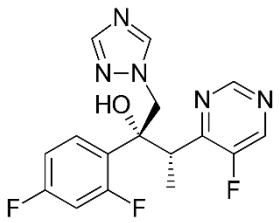

Figure 10: Voriconazole structure.

When Voriconazole is taken in combination with drugs that influence cytochrome P450 3A4 (terfenadol, cisapride, etc.), their serum levels are increased. Several drugs should be avoided, including cyclosporine, rifampicin, carbamazepine, ritonavir, and long-acting barbiturate drugs.

The effects of voriconazole on *Aspergillus* species have been demonstrated in a variety of studies.[53] Belonging to the group of 14β-demethylase inhibitors, antifungal triazoles exert their antifungal effects by interacting with and binding to this enzyme.[54] Voriconazole is well absorbed from the mouth, but its pharmacokinetics are nonlinear. There is low protein binding in cerebrospinal fluid, and levels are several times higher in cerebrospinal fluid than in plasma. Voriconazole is eliminated through oxidative hepatic metabolism, and only small amounts remain in the urine unchanged.

Posaconazole

A hydroxylated analogue of itraconazole, posaconazole is a drug that works differently from itraconazole. Food and Drug Administration (FDA) approved it as a prophylactic against invasive Candida and Aspergillus infections in 2006 when it became available in Europe.

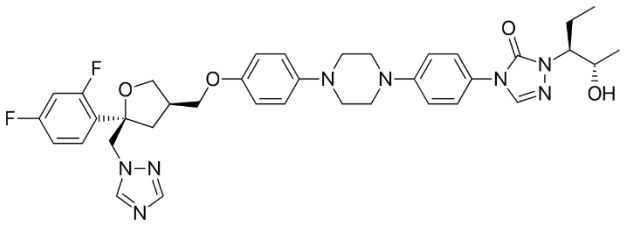

Figure 11: Posaconazole structure.

The drug has a wide range of antifungal activity against Candida spp. Other opportunistic filamentous and dimorphic fungi, including *C.neoformans, Aspergillus spp., Rhizopus spp., B.dermatitidis, C.immitis, H.capsulatum*,[55-59] are resistant to older azoles. On an empty stomach, posaconazole is bioavailable in 8–47%, which increases by 400% after eating a fatty meal.[60] In addition to metabolizing the drug in the liver, approximately 77% of the unaltered drug is excreted in the feces as well as a small amount in the urine.[61] Aside from *zygomycosis and invasive fusariosis*, posaconazole was effective against *coccidioidomycosis, c.meningitis*, and other central nervous system fungal infections.[62]

Ravuconazole

In phase II clinical trials, ravuconazole is being investigated as a triazole. As well as yeast isolates that are resistant to fluconazole, it is highly active against Candida species, Candida neoformans, and other fungi. It was demonstrated that ravuconazole is highly active against Aspergillus spp., based on an in vitro study of 923 clinical isolates of filamentous fungi other than dermatophytes. It also inhibits other species of hyaline filamentous fungi, zygomycetes, and black moulds. The results of this study showed that ravuconazole was active against 56.2% of the mucorales tested. Itraconazole, however, was active against only one-third of the isolates, and voriconazole was ineffective against almost all mucorales tested.[64]

Spectral activity and its resistance

A triazole is active against *C.albicans*, Candida species that are not albicans, *C.neoformans*, and dimorphic fungi. Except for voriconazole and selected investigational triazoles, their efficacy against non-albicans *Candida* varies, with limited potency against *C.glabrata* and ineffectiveness against *C.krusei*. Various *Aspergillus* species and dematiaceous molds are particularly affected by itraconazole and voriconazole. Fusarium species are also effective against voriconazole. It is often due to alterations in membrane-associated sterol compositions, changes in ergosterol biosynthesis pathways, genetic mutations in enzymes, or overexpression of genes that fungal resistance to antifungal triazoles arises. Allogeneic hematopoietic stem cell transplants and chronic granulomatous disease can be caused by prolonged exposure to azoles. Those with chronic recurrent oropharyngeal candidiasis who are HIV-infected also show secondary resistance.[65-67]

Other importance

It is possible to use triazoles as proton conductors in fuel cells instead of water. Membrane conductivity is enhanced when they are introduced into dry environments. In addition to functioning as proton donors and acceptors, these compounds possess amphoteric qualities. Water replacements are increasingly appealing due to their amphoteric natures and high-temperature mobility. For membrane leaching to be prevented, small molecules must be immobilized. It is noteworthy that 4,5-Dicyano-1H-1,2,3-triazole (DCTz) showed a proton conductivity of approximately 1 mS/cm in dry conditions at 100°C. No external proton sources were present in composites of 4,5-dicyano-1H-1,2,3-triazole and polyacrylonitrile.[68]

By using the [3+2] Huisgen dipolar cycloaddition approach, we synthesized novel heteroleptic iridium complexes containing a substituted 4-phenyl cyclometalating ligand. Various substituents were introduced to the triazole nucleus using this technique to create a set of bidentate ligands. It took meticulous preparation to prepare a diverse assortment of luminescent ionic iridium complexes.[70]

Prospectives in future

Existing antifungal agents available in the market are plagued by a range of shortcomings, encompassing toxicity, limited activity spectrum, fungistatic rather than fungicidal properties, and potential drug interactions. Given the high prevalence of fungal infections among immunocompromised patients, there's a mounting call for novel antifungal agents exhibiting both broad activity spectrums and favorable pharmacokinetic characteristics. This demand for potent, safe, and widely effective antifungal agents has catalyzed the development of new systemically active antifungal triazoles. This pursuit persists despite the introduction of ketoconazole, driven by concerns over its toxicity and limited penetration into cerebrospinal fluid. Fluconazole presently stands as the preferred option for severe Candida species and Candida neoformans infections. However, its efficacy against Aspergillus species is limited due to weak inhibition of lanosterol 14α-demethylase. Earlier triazole compounds like SCH 39304 (genoconazole), SCH 42427 (saperaconazole), and Bay R 8783 (electrazole) faced discontinuation due to safety apprehensions. SCH 56592 displays potent antifungal activity against Aspergillus spp. and Candida spp. Another promising triazole, D0870, exhibits variable plasma pharmacokinetics and limited anti-aspergillus potency. Further developments encompass fluconazole derivatives such as voriconazole and ER 30346 (BMS 207147). BMS 207147 showcases robust antifungal potential against Candida spp., Candida neoformans, Aspergillus fumigatus, and Trichosporon beigelii. Voriconazole, although potent, raises concerns regarding ocular toxicity. ER 30346 emerges as a prime candidate with exceptional anti-aspergillus activity. Meanwhile, SCH 56592, a hydroxylated itraconazole analogue, boasts significant *in vitro* and *in vivo* potency.

CONCLUSION

An innovative phase of antifungal chemotherapy has begun with azole antifungal drugs. The mechanism of action of these drugs is similar, however their pharmacokinetics and toxicities differ greatly. The repertoire of this compound group could be further enhanced by the development of emerging potent compounds. Clinical trials have recently improved the efficacy and safety of conventional amphotericin B therapy with new broad-spectrum triazoles. The mortality rate from invasive fungal infections remains high despite these advances. Developing new compounds, improving diagnostic approaches, and restoring the immune system are the crucial steps to overcoming this challenge.

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