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Review Article

A Review Article on Novel Antifungal Agents with Different Heterocyclic Nucleus

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ABSTRACT

The health of immunosuppressed individuals worldwide is greatly affected by the widespread and increasing burden of fungal infections. The emergence of resistant species like Candida auris and Aspergillus fumigatus have highlighted the limitations of conventional antifungal agents, including azoles, polyenes, and echinocandins. New agents with different heterocyclic nuclei have emerged from the discovery of new antifungal drugs, resulting in improved pharmacological profiles and unique mechanisms of action. A groundbreaking new treatment for vulvovaginal candidiasis is Ibrexafungerp, the first oral triterpenoid-glucan synthases inhibitor. For candidemia, echinocandin, also known as rezafungin (long-acting antibiotic), provides convenient once-weekly dosing. A targeted approach to prevent recurrent cases of vulvovaginal candidiasis is provided by the next-generation tetrazole, Otesconazole. Both Fosmanogepix and pyrimidine biosynthesis inhibit Gwt1, with the latter being an antifungal, and both are effective against rare molds and resistant strains. In addition, treatments such as isavuconazole (Cresemba), micafungin and posaconozole continue to expand.'. Heterocyclic scaffolds are considered promising antifungal innovations, with emphasis on their structural properties, mechanisms, efficacy, and safety. The advancement of research in clinical evaluation and heterocyclic chemistry is expected to enhance the antifungal potential, while also addressing existing therapeutic gaps in treating both invasive and resistant fungal infections.

INTRODUCTION

Fungal infections represent a growing global health challenge, particularly among immunocompromised individuals such as those with HIV/AIDS, cancer, or undergoing organ transplantation. Over the past decades, the emergence of resistant fungal strains—such as Candida auris and Aspergillus fumigatus—has

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further complicated the treatment landscape. Traditional antifungal agents, including azoles, polyenes, and echinocandins, though effective, have limitations such as toxicity, drug-drug interactions, and emerging resistance [1]. In response to these challenges, recent years have witnessed significant advancements in antifungal drug development. Several novel agents with unique mechanisms of action and improved pharmacological profiles have been approved or are in late-stage clinical development [2]. These include Ibrexafungerp (SCY-078), a triterpenoid glucan synthase inhibitor approved for vulvovaginal candidiasis, and Rezafungin a long-acting echinocandin approved for candidemia and invasive candidiasis. Additionally, fosmanogepix, an inhibitor of the fungal enzyme Gwt1, and olorofim, an orotomide class antifungal, have shown promise in treating invasive mold infections [3]. This review aims to provide an updated overview of these recently approved antifungal agents, discussing their mechanisms of action, spectrum of activity, clinical trial outcomes, and potential roles in addressing antifungal resistance and treatment gaps.

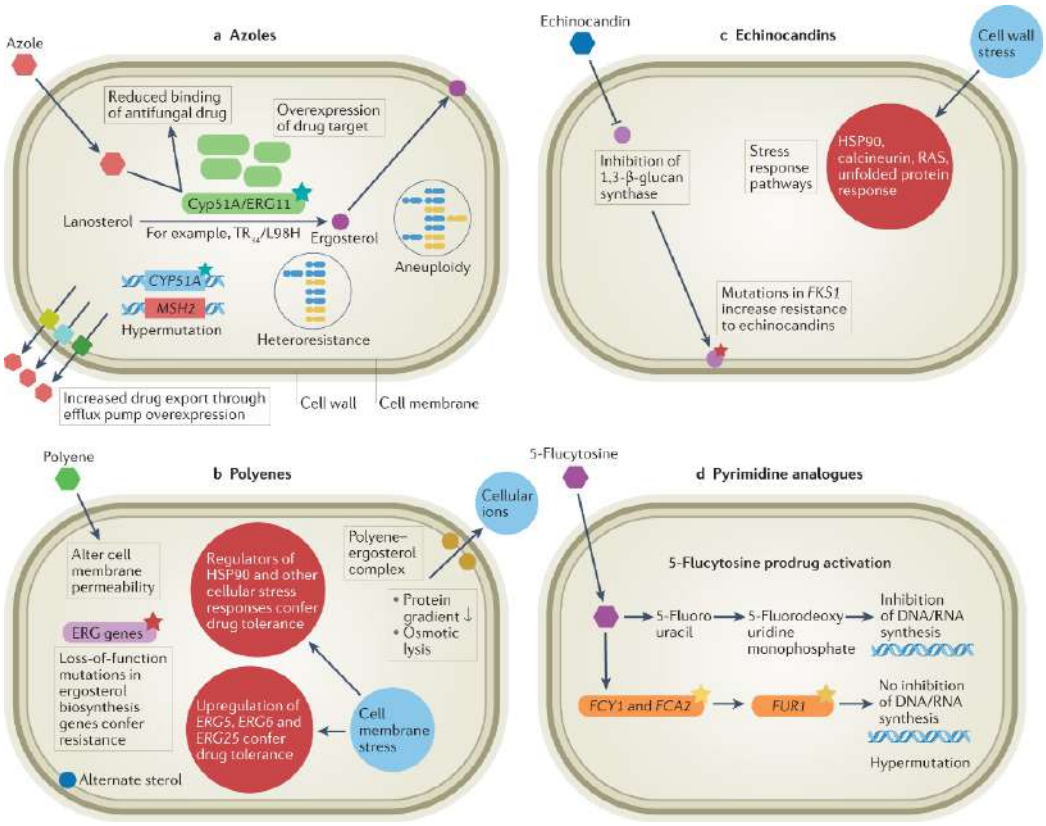

Fig.No:1 Tackling of Emerging Treat of Anti-Fungal Resistance to Human Health

Novel FDA Approved Medications

- Ibrexafungerb
- Oteseconazole
- Rezafungin
- Fosmanogepix
- Cresemba
- Micafungin [zydus]
- Olorofim

- Posaconazole injection [Aurobindo generic]

1. **IBREXAFUNGERB**

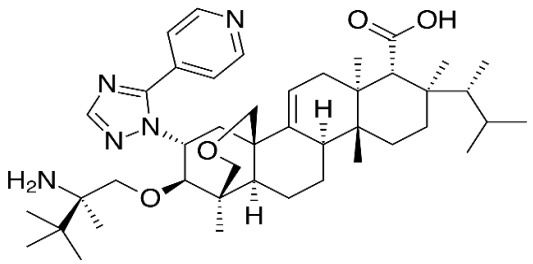

Fig No.2: Structure of Ibrexafungerb

Pentacyclic triterpene nucleus (from enfumafungin), which forms the rigid core. A strategically attached 1,2,4-triazole ring linked to the core via a pyridinyl group, enhancing its binding to β-(1,3)-D-glucan synthase Ibrexafungerp is built around a triterpenoid core nucleus, derived from a natural product called enfumafungin (a pentacyclic triterpene glycoside). Core nucleus (triterpenoid scaffold) Ibrexafungerp is a novel oral triterpenoid antifungal agent and the first in a new class called the "fungerps". It was developed to overcome the limitations of current antifungals, particularly in the setting of drug resistance [4]. Approved by the U.S. FDA in June 2021, ibrexafungerp represents a significant advancement, especially due to its broad-spectrum activity and oral bioavailability. It is a triterpenoid antifungal agent with a unique chemical structure derived from enfumafungin. The enzyme (1→3)-β-D-glucan synthase, which is essential for the synthesis of fungal cell walls, is the specific target of this glucan synthase inhibitor. Ibrexafungerp binds to a different location on this enzyme than echinocandins, which may result in activity against certain strains of the enzyme that are resistant to echinocandins. Its mechanism of action involves Ibrexafungerp inhibits (1→3)-β-D-glucan synthase, an essential enzyme involved in the biosynthesis of β-glucan, a critical component of the fungal cell wall. This leads to cell wall weakening, osmotic instability, and ultimately fungal cell death. Similar target to echinocandins, but ibrexafungerp binds to a different site, reducing cross-resistance. It is fungicidal against Candida spp and fungistatic agains Aspergillus. Used for Acute Vulvovaginal Candidiasis (VVC) It demonstrated efficacy against Candida albicans and azole-resistant strains of Candida.

2.Oteseconazole

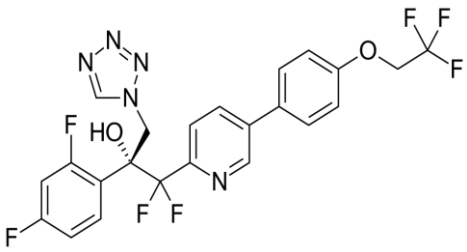

Fig No. 3: Structure of Oteseconazole

The nucleus (core structural scaffold) present in Oteseconazole is a tricyclic fused ring system, specifically a tetrahydrocyclopenta quinoline structure, which is further substituted with triazole and difluorophenyl groups. In females who are not pregnant or of reproductive potential, oteseconazole, an antifungal drug, is used to lower the risk of recurrent vulvovaginal candidiasis (RVVC) It's an orally administered azole antifungal agent, specifically a selective inhibitor of fungal lanosterol 14α-demethylase. Oteseconazole (brand name: Vivjoa) is a novel oral antifungal agent from the tetrazole class, developed primarily for the treatment and prevention of vulvovaginal candidiasis (VVC), including recurrent vulvovaginal candidiasis (RVVC). It was developed by Mycovia Pharmaceuticals and received FDA approval in April 2022 for prevention of RVVC in females who are not of reproductive potential. Oteseconazole is structurally related to the azole class of antifungals (e.g., fluconazole) but is uniquely designed to: Increase specificity for fungal targets. Minimize interactions with human

cytochromeP450 enzymes. It Provide a favorable safety profile, especially in long-term use [5]. Oteseconazole functions by inhibiting the fungal enzyme lanosterol 14α-demethylase (CYP51), which plays a crucial role in the biosynthesis of ergosterol, a key structural component of fungal cell membranes. It Supports long-term and prophylactic use in chronic/recurrent fungal infections. It is Particularly useful in fluconazole-resistant Candida strains. Used orally, unlike some antifungals (e.g., echinocandins) that require intravenous administration.

3.Rezafungin

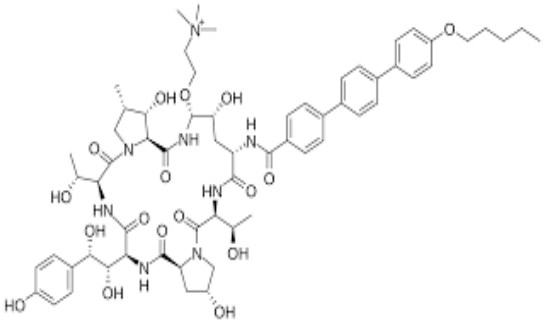

Fig No. 4: Structure of Rezafungin

Rezafungin doesn't have a nucleus itself, it acts on structures within the fungal cells that do possess a nucleus. In 2023, the FDA and EMA approved Rezafungin to treat invasive candidiasis and candidemia in adults with limited & long-acting echinocandin antifungal. It works by inhibiting the enzyme 1,3-β-D-glucan synthase, which is essential for the biosynthesis of β-1,3-D-glucan, a key component of the fungal cell wall. This inhibition leads to fungal cell wall disruption, resulting in osmotic instability and cell lysis, particularly in Candida species. It has Loading dose: 400 mg IV on Day 1. Maintenance dose: 200 mg IV once weekly Administered over approximately 1 hour. Clinical response and mycological clearance determine how long a treatment should last. Rezafungin was non-inferior to caspofungin in clinical cure rates for candidemia/invasive candidiasis [6].

4.Fosmanogepix

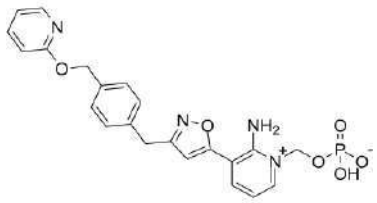

Fig No.5: Structure of Fosmanogepix

The nucleus present in Fosmanogepix (active form: manogepix) Manogepix contains a substituted tetrahydrocarbazole nucleus as its core scaffold. This structure is a fused tricyclic system consisting of a benzene ring fused to pyrrole ring and cyclohexene ring (saturated portion). This forms the tetrahydrocarbazole nucleus, which is chemically similar to carbazole but partially saturated (four hydrogen atoms added) Fosmanogepix is a prodrug that is rapidly converted in the body to its active form, manogepix. Manogepix works by inhibiting the fungal enzyme Gwt1 (glycosylphosphatidylinositol-anchored cell wall transfer protein 1). This enzyme is crucial for anchoring mannoproteins to the fungal cell wall, which is essential for cell viability, integrity, adhesion, pathogenicity, and evasion of host recognition. By disrupting this process, manogepix leads to fungal cell death. This unique mechanism of action allows it to retain potency against many resistant strains, including those resistant to echinocandins and azoles [7]. Fosmanogepix demonstrates broad-spectrum activity against a wide range of yeasts and molds which includes:

- Candida species: Including drug-resistant strains like Candida auris, C. albicans, C. glabrata, and C. tropicalis.

- Rare and emerging molds: Including Scedosporium, Lomentospora prolificans, and Fusarium species, as well as some activity against Mucorales * Cryptococcus and Coccidioides immitis

- It is primarily being investigated for the treatment of invasive fungal infections that are often difficult to treat and can be deadly.

5.Cresemba

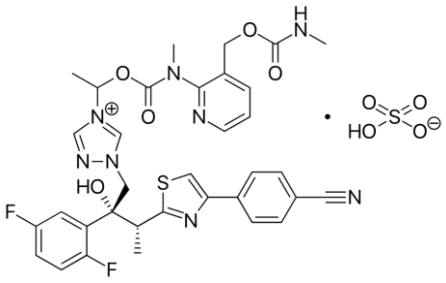

Fig No.6: Structure of Cresemba

Isavuconazole contains nuclear structures such as the triazole and thiazole rings, as well as the fluorinated and cyanated phenyl rings. Cresemba is a brand name for the antifungal medication isavuconazonium sulfate, which is a prodrug. This means it's an inactive compound that gets converted into the active drug in the body. The active substance in Cresemba is isavuconazole. Isavuconazole belongs to the triazole class of antifungal medicines. Its chemical structure contains several cyclic systems, or "nuclei":

* A 1,3-thiazole ring

* A 1,2,4-triazole ring

* A 2,5-difluorophenyl group (a benzene ring with two fluorine atoms)

* A 4-(p-cyanophenyl) group (another benzene ring with a cyano group, attached to the thiazole ring)

Isavuconazole (marketed as Cresemba) is a broad-spectrum triazole antifungal medication used to treat serious fungal infections. Isavuconazole works by inhibiting cytochrome P450-dependent lanosterol 14α-demethylase in fungi. This enzyme is crucial for the synthesis of ergosterol, a vital component of the fungal cell membrane. By disrupting ergosterol synthesis, isavuconazole leads to alterations in the structure and function of the fungal cell membrane, ultimately causing fungal cell death [8] This mechanism is similar to other azole antifungals. Isavuconazole is approved for the treatment of:

* Invasive aspergillosis (IA)

* Invasive mucormycosis (IM)

Typical Adult Dosing for Invasive Aspergillosis and Invasive Mucormycosis:

* Loading Dose: 372 milligrams (mg) of isavuconazonium sulfate (equivalent to 200 mg of isavuconazole) given every 8 hours for 6 doses (totaling 48 hours).

* Maintenance Dose: 372 mg once daily

6.Micafungin [Zydus]

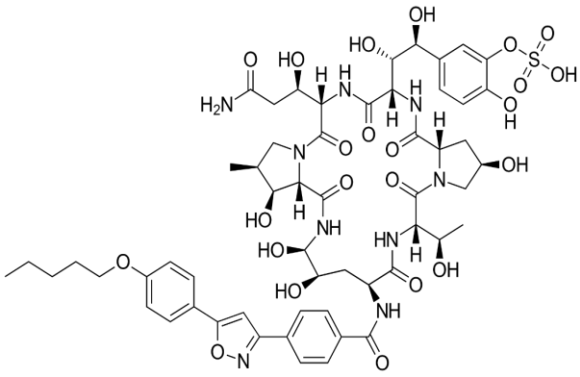

Fig No.7: Structure of Micafungin

Micafungin belongs to the echinocandin class of antifungals. Its core nucleus is based on a cyclic hexapeptide structure. This nucleus is non-ribosomal and contains: Unusual amino acids like 3,4-dihydroxyhomotyrosine Core Nucleus: Cyclic hexapeptide (echinocandin nucleus) Micafungin is an echinocandin antifungal agent used for the treatment and prevention of invasive fungal infections, primarily caused by Candida species. It is given intravenously and is a member of the class of β-1,3-D-glucan synthesis inhibitors. Micafungin inhibits the enzyme β-1,3-D-glucan synthase, which is essential for the synthesis of β-1,3-glucan, a critical component of the fungal cell wall. Inhibition leads to a loss of cell wall integrity, causing osmotic instability and cell lysis. [34] Used to treat Esophageal candidiasis**,** Candidemia and disseminated candidiasis**,** Candida peritonitis and intra-abdominal abscesses Prophylaxis of Candida infections in immunocompromised HSCT recipients [9].

7.Olorofim

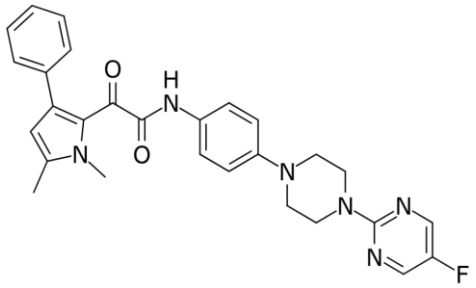

Fig No.8: Structure of Olorofim

Olorofim contains a heterocyclic aromatic nucleus, specifically [2,6-dioxo-1,2,3,6-tetrahydro-7H-pyrrolo[2,3-d] pyrimidin-4-yl] nucleus, which is a pyrrolopyrimidine core. Olorofim is a first-in-class antifungal agent in the orotomide class, developed by F2G Ltd. Unlike azoles, echinocandins, and polyenes, it has a novel mechanism of action targeting fungal pyrimidine biosynthesis. It is primarily intended for invasive mold infections, especially in azole-resistant and rare molds. [36] Olorofim belongs to the new class of antifungal drugs called orotomide. It works by targeting a specific metabolic pathway in fungi. Dihydroorotate dehydrogenase (DHODH) is inhibited by olorofim. This enzyme is crucial for the de novo pyrimidine biosynthesis pathway, which is essential for the fungus to produce the building blocks of DNA and RNA. Fungicidal Effect: By blocking this pathway, olorofim prevents the fungus from synthesizing new genetic material, halting its growth and leading to a fungicidal (cell-killing) effect. Fungal Selectivity: The fungal version of the DHODH enzyme is structurally different from the human version, allowing olorofim to selectively target the fungus without significant toxicity to human cells [10]. In clinical trials, olorofim has been administered in both an intravenous (IV) formulation and an oral formulation, which would allow for long-term treatment and a switch from IV to oral therapy. The most significant reported adverse event in a Phase 2b trial was drug-induced liver injury, though this was reversible in most cases and did not lead to discontinuation in the majority of affected patients. Other common side effects included gastrointestinal issues such as nausea, vomiting, and diarrhea.

8.Posaconazoleinjection [Aurobindo Generic]

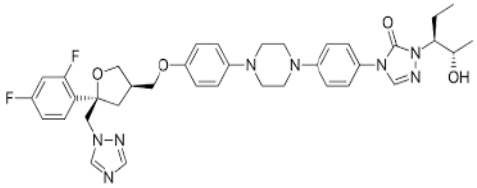

Fig No.9: Structure of Posaconazole

The primary nucleus that characterizes posaconazole as a triazole antifungal is the 1,2,4-triazole ring. This five-membered ring contains three nitrogen atoms. In addition to the triazole rings, posaconazole's structure also includes other important rings:

- Piperazine: A six-membered ring containing two nitrogen atoms.

- Tetrahydrofuran (also called oxolane): A five-membered ring containing one oxygen atom.

Posaconazole is a broad-spectrum triazole antifungal agent, primarily used in the prevention and treatment of invasive fungal infections. It was developed as a structural analog of itraconazole with improved oral bioavailability and a broader antifungal spectrum. It is especially valuable in immunocompromised patients, such as those undergoing chemotherapy or stem cell transplantation**.** Posaconazole inhibits the enzyme lanosterol 14α-demethylase, a cytochrome P450-dependent enzyme in fungi. This inhibition disrupts ergosterol biosynthesis, an essential component of the fungal cell membrane, leading to membrane dysfunction and ultimately fungal cell death. Posaconazole is used for both the treatment and prophylaxis (prevention) of invasive fungal infections. It is available in various formulations, including oral suspension, delayed-release tablets, and intravenous injection. Posaconazole is used to treat serious fungal infections, such as invasive aspergillosis, in patients who have not responded to other antifungals like amphotericin B, or who cannot tolerate them. Prophylaxis: It is used to prevent invasive fungal infections in high-risk immunocompromised patients, such as those undergoing chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS), or those receiving a hematopoietic stem cell transplant. Oropharyngeal Candidiasis (Thrush): The oral suspension form can be used to treat oropharyngeal candidiasis, especially in patients with severe infections or a weakened immune system [11].

CONCLUSION

The increasing incidence of drug-resistant fungal infections highlights the urgent need for novel antifungal agents with improved efficacy and safety. Recent advancements have introduced a new generation of antifungal drugs featuring diverse heterocyclic nuclei, which are critical for their biological activity. Compounds such as Ibrexafungerp, Fosmanogepix, and Olorofim exemplify the progress made in this area, offering unique mechanisms of action and better therapeutic outcomes compared to traditional antifungals. These innovations underline the potential of heterocyclic scaffolds in developing effective antifungal therapies. Ongoing research in heterocyclic chemistry and drug design will likely expand the antifungal arsenal addressing current clinical challenges and improving patient outcomes**.**

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