

RECENT DEVELOPMENTS IN ANTIFUNGAL AGENTS

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ABSTRACT

Life threatening invasive fungal infections is a major problem in immunocompromised patients. Standard antifungal agents so far have been quite successful, but some of them have limited use because of toxicity and drug resistance and even their clinical efficacy in some invasive fungal infections, such as aspergillosis and fusariosis, is not optimal. Among the several widely used antifungal drugs, azoles are most frequently prescribed in various types of fungal infections. Some new antifungal agents have demonstrated therapeutic potential and may provide additional options for the treatment of fungal infections and may help to overcome the limitations of current drugs. This review briefly discusses currently available antifungal agents and primarily concerns with recent developments in antifungal agents including lipid formulation of polyenes, novel azoles, echinocandins, sordarins, nikkomycins, monoclonal antibody, aminocandin and interferon- γ -1b.

Keywords: Antifungal agents, Newer approaches, Azoles, Echinocandins.

INTRODUCTION

The incidences of invasive fungal infections (IFIs) have increased gravely since 1980s, worldwide, especially in the immunocompromised persons.¹ IFIs are characterized by high morbidity and mortality. Although IFIs are now more frequent, they are still difficult to diagnose, prevent and treat.² *Candida* and *Aspergillus* spp. are the most common fungal pathogens with the highest mortality; emerging fungal pathogens such as *Zygomycetes*, *Fusarium* spp. and *Scedosporium* spp. are also important.³⁻⁴ During the past two decades, a number of different classes of antifungal agents have been discovered. The newer antifungal agents are potent and less toxic, but their clinical efficacy in some IFIs is not ideal.⁵⁻⁶ Hence, intensive efforts in antifungal drug discovery are still required to develop more promising and convincing antifungal agents.

RISK FACTORS FOR FUNGAL INFECTIONS

Immunosuppression and breakdown of anatomical barriers such as the skin are the major risk factors for fungal infections.⁷ Patients with prolonged and deep neutropenia (haematological malignancy patients), defective T-lymphocyte function (associated with organ transplantation and HIV infection), impaired macrophage function (particularly of pulmonary macrophages), barrier defects (associated with invasive medical procedures), vascular catheters, active cancer, corticosteroid therapy, administration of broad spectrum antibiotics, allogeneic hematopoietic stem cell transplantation (HSCT), haemodialysis and peritoneal dialysis, prolonged intensive care unit (ICU) stay, total parenteral nutrition, mucosal *Candida* spp. colonization and renal failure are most common risk factors and therefore most likely to receive prophylactic therapy.⁸⁻¹¹

MANAGEMENT OF FUNGAL INFECTIONS

Empirical antifungal therapy consists of liposomal amphotericin B, itraconazole, voriconazole, or caspofungin. Voriconazole is the treatment of choice in patients with invasive aspergillosis. Liposomal amphotericin B is a good alternative and caspofungin is reserved for salvage treatment. Use of fluconazole is reserved for non-neutropenic patients.¹² Management of IFIs comprises chemoprophylaxis, preemptive, empirical and directed antifungal therapy. Fluconazole (400 mg/d) in allergic transplant recipients and posaconazole (600 mg/d) in patients during AML/MDS induction chemotherapy and in patients with GvHD are drug of choice for antifungal prophylaxis.¹³

Liposomal amphotericin B has proven significantly more effective than voriconazole for empirical therapy of neutropenic cancer patients. No trials have compared voriconazole and amphotericin B

for treatment of aspergillosis under optimal conditions.¹⁴ The increase in zygomycosis in the hematopoietic cell transplantation setting can be due to the increased use of Voriconazole.¹²

Limited pediatric data are available comparing antifungal agents in children with proven or suspected IFIs. Children are less prone to develop nephrotoxicity with a liposomal amphotericin B compared to conventional amphotericin B.¹⁵ Prophylactic systemic antifungal therapy reduces the incidence of IFIs in very low birth weight infants. There are currently limited data available on the long term neurodevelopment consequences for infants exposed to this condition.¹⁶

Overview of routine antifungal drugs

Polyenes

Polyene antifungal agents, mainly nystatin and amphotericin B form complexes with ergosterol of fungal cell membrane and disrupt the fungal plasma membrane, resulting in increased membrane permeability, leakage of the cytoplasmic contents and death of the fungal cell. Hence the polyenes are fungicidal and have the broadest spectrum of antifungal activity of any of the clinically available agents. The affinity of the polyenes for ergosterol in fungal cells is higher than the affinity for cholesterol in mammalian cells, thus they are less toxic to mammalian cells.^{9,17-18} Amphotericin B is the drug of choice for meningeal and severe disseminated sporotrichosis and for meningeal and life threatening disseminated blastomycosis and histoplasmosis and for histoplasma endocarditis.¹⁹

Azoles

The initial azole compounds were the imidazoles, namely clotrimazole, miconazole and ketoconazole, which were then followed by the triazoles, fluconazole and itraconazole. The azoles inhibit fungal cytochrome P450-3A dependent C-14 α -demethylase, responsible for the conversion of lanosterol to ergosterol. This leads to the depletion of ergosterol in the fungal cell membrane.^{20,21}

Clotrimazole was discovered in 1969²² and it cannot be given parenterally, has poor oral absorption and is used for the treatment of oral and vaginal candidosis.²³ Miconazole was also discovered in 1969 and also has poor oral bioavailability. An intravenous preparation of miconazole has suboptimal efficacy and clinically it is not used much. Miconazole is a useful topical agent for the treatment of superficial mycoses.²¹

Ketoconazole was discovered in 1978 and has a good oral absorption and a broad spectrum of activity. Although it may be hepatotoxic and produce endocrine abnormalities by suppression of testosterone and ACTH stimulated cortisol synthesis, has low toxicity. Oral ketoconazole is effective in candidosis,

coccidioidomycosis, blastomycosis, histoplasmosis, paracoccidioidomycosis and cutaneous dermatophyte infections. It is highly protein bound and has poor CNS penetration.²⁴

Fluconazole was formulated in 1981. It is metabolically stable and has low plasma protein binding. It is active by both oral and intravenous routes with identical pharmacokinetics. Fluconazole is well tolerated and has a very low incidence of side effects and a broad spectrum of antifungal activity, except against *Aspergillus* spp.²⁵ Fluconazole is extremely effective for the treatment of oropharyngeal and oesophageal candidosis, especially in patients with AIDS or cancer, in vaginal candidosis and peritonitis or disseminated candidosis, including in neutropenic patients and in hepatosplenic candidosis.²⁶⁻²⁷ Fluconazole is as effective as amphotericin B in non-neutropenic patients with candidaemia and is the preferred for the treatment of funguria and fungal urinary tract infections.^{19,28} Long term oral fluconazole is used in patients with candida endocarditis to prevent relapse after initial therapy of amphotericin B.²⁹ Fluconazole has been used successfully for pulmonary or disseminated cryptococcosis and for acute cryptococcal meningitis, especially in AIDS patients.³⁰

Itraconazole was discovered in 1986 and has broad spectrum antifungal activity, including *Aspergillus* spp. It was available in oral form only and may be given once daily.²³ Itraconazole has established efficacy as primary treatment and maintenance of mild to moderate non-meningeal histoplasmosis in HIV-infected patients and for prevention of relapse in AIDS patients with disseminated histoplasmosis.³¹

Echinocandins

The echinocandins are cyclic lipopeptide fungicidal agents. They act by preventing cell wall synthesis by non-competitive inhibition of 1,3- β -D-glucan synthase, an enzyme absent in mammalian cells.⁵ This inhibition is highly specific and exposure to these drugs leads to cell death.⁶

Allylamines and thiocarbamates

Allylamines and thiocarbamates are synthetic fungicidal agents, act by reversible, non-competitive inhibition of squalene epoxidase, an enzyme required for conversion of squalene to lanosterol along with squalene cyclase. In fungal cells, if squalene is not converted to lanosterol, the conversion of lanosterol to ergosterol is prevented. This led to ergosterol depletion, which affects fungal cell membrane structure and function. There are two allylamine antifungal agents, naftifine and terbinafine, and one thiocarbamate, talnaftate are in clinical use. Naftifine is available as topical preparation whereas terbinafine as an oral systemic agent. Naftifine is considered as promising topical agent for treatment of dermatophyte infections.²⁵

NEWER APPROACHES IN ANTIFUNGAL AGENTS

Polyenes

Liposomal nystatin is a new formulation of conventional drug, nystatin. Nystatin is not used much clinically due to its toxicity, but liposomal form can be used for systemic administration with reduced toxicity. *In vitro* activity of liposomal nystatin is maintained against variety of yeasts and moulds, including *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp. The mechanism for generation of lower liposomal nystatin MICs is still not known.³² Liposomal preparation of nystatin has been studied in neutropenic animals with invasive pulmonary aspergillosis and disseminated aspergillosis. Studies showed improved survival and reduced tissue burden of *Aspergillus* with liposomal nystatin.³³⁻³⁴ As an alternative delivery system to liposomes, niosomal gel formulation of nystatin has also shown potential in the treatment of fungal infection by providing a prolonged release profile.³⁵

Liposomal amphotericin B is a lipid formulation of the broad spectrum antifungal drug, amphotericin B. It was developed to improve the tolerability profile of amphotericin B deoxycholate, which was for many decades considered as the standard drug of antifungal treatment. Liposomal amphotericin B was as effective as empirical treatment for confirmed IFIs in several randomized,

double-blind trials in adult and pediatric patients.³⁶ In several trials, liposomal amphotericin B had shown similar efficacy to amphotericin B deoxycholate and amphotericin B lipid complex as empirical treatment in adult and paediatric patients with febrile neutropenia. For the treatment of confirmed IFIs, liposomal amphotericin B was more effective than amphotericin B deoxycholate in patients with disseminated histoplasmosis and AIDS, and was noninferior to amphotericin B deoxycholate in patients with acute cryptococcal meningitis and AIDS. In one another infusion related reaction study and nephrotoxicity study, liposomal amphotericin B was significantly less toxic than conventional amphotericin B.³⁷

Amphotericin B colloidal dispersion (ABCD) is composed of amphotericin B complexed with cholesteryl sulfate, consisting a disk-like structure.³⁸ After infusion; ABCD is rapidly removed from the blood by reticuloendothelial system and then re-released to the circulation. Plasma clearance and volume of distribution increase with escalating doses of ABCD.³⁹ Compared to the conventional amphotericin B, peak serum levels are lower with ABCD. Amphotericin B binding with low density lipoprotein (LDL) fraction is also lower after administration of ABCD compared with conventional amphotericin B.⁴⁰ Other formulations of amphotericin B has also been reported with some advantages, such as submicronic emulsion of amphotericin B has been reported as suitable for decreasing nephrotoxicity of the drug and improved uptake by infected macrophages.⁴¹

Azoles

Voriconazole and posaconazole are novel triazoles that overcome the problems associated with the ineffectivity of fluconazole against some *Aspergillus* spp. or the variable bioavailability of itraconazole. Voriconazole has a chemical structure similar to fluconazole and has broad antifungal activity including activity against *Aspergillus* spp.⁴²⁻⁴³ Voriconazole has both oral and intravenous formulations and it is widely distributed into body tissues including brain, lung, liver, myocardium, spleen, kidneys and cerebrospinal fluid. It is 60% protein bound and has a lower incidence of adverse events.⁴⁴ Voriconazole is a suitable alternative to amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever.⁴⁵

Posaconazole is an extended spectrum antifungal drug, active against a broad range of fungal pathogens, including *Aspergillus* spp, *Fusarium* spp, and *Zygomycetes*. Posaconazole lack an intravenous formulation and exhibit erratic drug absorption.⁴⁶ Posaconazole suspension is a good alternative to conventional antifungal agents for prevention and treatment of IFIs in high-risk populations.⁴⁷ Posaconazole can be reserved for prophylaxis in patients at high risk for IFIs, as salvage therapy in refractory or resistant infections.⁴⁸ Many studies have demonstrated prophylactic utility of posaconazole in neutropenic patients with acute myelogenous leukemia or myelodysplastic syndrome and in patients with graft-versus-host disease following allogeneic stem cell transplantation, which led to the approval of the drug in USA.⁴⁹⁻⁵⁰

Isavuconazole, ravuconazole and albaconazole are newer generation triazoles and have shown potent *in vitro* activity against *Candida*, *Cryptococcus*, *Aspergillus* spp. and against several fungal pathogens resistant to other azoles, and they are currently in various stages of development.⁵¹ However, these compounds have demonstrated limited activity against species of *Fusarium*, *Scedosporium* and *Zygomycetes*. Isavuconazole and ravuconazole have been developed both as intravenous and oral formulations, and are suitable candidates for the treatment of various IFIs.⁵²

Isavuconazole (BAL4815) has shown *in vitro* activity against a large number of clinically important yeasts and moulds including *Aspergillus*, *Fusarium*, *Scedosporium*, *Candida*, *Zygomycetes* and *Cryptococcus* spp. But the drug has reduced *in vitro* activity against *Histoplasma capsulatum*. *In vivo* efficacy has been studied in murine models of invasive aspergillosis and candidiasis. Additionally, some potential pharmacokinetic and drug-drug interaction advantages are exhibited by this compound over existing drugs.⁵³ In one study, isavuconazole has shown a good activity against *Zygomycetes*, in

which none of the isolates tested had minimum inhibitory concentration (MIC) greater than 4 µg/ml.^{54,55} Isavuconazole's MICs are within one dilution of voriconazole's MICs for most *Candida* species.⁵⁶ Protein binding is approximately 95% and dose fractionation studies reveal that the amount of time that the area under the curve of free drug concentration is above the MIC, as with other azoles.⁵⁷ Clinical trials are currently in progress to demonstrate the safety and efficacy of isavuconazole for the treatment and prevention of IFIs.⁵⁸ BAL8557 is a water soluble prodrug of isavuconazole. The water solubility makes it unnecessary to administer the drug by a cyclodextrin carrier molecule. A study involving immunocompromised adults with esophageal candidiasis demonstrated that BAL8557 administration once in a week is comparable to fluconazole therapy.⁵⁹ Multiple dose pharmacokinetic study of isavuconazole after intravenous infusion and oral administration of BAL8557 have showed half-life of the drug approximately 117 hours in healthy volunteers.⁶⁰

Ravuconazole is a broad spectrum agent, active against *Candida* spp., *Cryptococcus neoformans*, *Aspergillus fumigatus*, dermatophytes and dematiaceous fungi. Ravuconazole is differentiated from posaconazole and voriconazole by its extended half-life, in one study it was 192 hrs.⁶¹ *In vitro* activity of ravuconazole also appears a little advantageous compared with posaconazole and voriconazole for treatment of yeasts or molds.⁶² Ravuconazole 200 mg once in a week is marginally effective,⁶³ but ravuconazole 400 mg and 100 mg once in a week are not effective in treating onychomycosis.

Albaconazole, in Phase 2 studies showed unique pharmacokinetics and excellent tolerability efficacy superior to fluconazole in vulvocandidiasis after single administration and excellent activity in toenail onychomycosis and tinea pedis when administered once-weekly. The drug has demonstrated high *in vitro* activity against pathogenic yeasts, dermatophytes and filamentous fungi.⁶⁴ Albaconazole has proven effective in many fluconazole resistant strains and has excellent safety profile. *In vivo* antifungal activity has been demonstrated in candidiasis, aspergillosis, cryptococcosis, scedosporosis and trypanosomiasis.⁶⁵ Albaconazole has trypanocidal activity *in vivo* and is capable of inducing radical parasitological cure, although natural resistance was also reported. The molecule can be used in long-term therapy with minimal toxicity and hence applicable as potentially useful candidate for the treatment of human Chagas' disease.⁶⁶ In one another study, despite limited penetration into the subarachnoid space, albaconazole was as effective as fluconazole for the treatment of cryptococcal meningitis in rabbits.⁶⁷ Most clinical trials with albaconazole have targeted mucocutaneous fungal infections. Although this drug appears to be well tolerated, but cross-resistance is a concern in azole family.^{52,64}

Echinocandins

The echinocandins are synthetically modified lipopeptides, originally derived from fermentation broths of various fungi and offer potential advantages over other classes of agents.⁶⁸⁻⁶⁹ Three echinocandins, caspofungin, micafungin and anidulafungin have excellent *in vitro* activities against invasive strains of *Candida* without developing echinocandin resistance among *Candida* spp.⁷⁰ All three echinocandins have similar spectrum of activity and they do not possess *in vitro* activity against important basidiomycetes including *Cryptococcus*, *Rhodotorula* and *Trichosporon*.^{51,71}

Caspofungin is the first echinocandin to get FDA approval for use in the US. It has excellent clinical activity against *Candida* and *Aspergillus* spp., but lacks significant activity against *Cryptococcus neoformans*.⁷² Caspofungin is cidal for all *Candida* species and is static against *Aspergillus* species. It also possesses activity against *Pneumocystis jiroveci*.⁷³ Caspofungin appears to be an alternative to triazoles or amphotericin B in oesophageal candidiasis and an alternative to amphotericin B in invasive candidiasis and aspergillosis.⁷⁴ Caspofungin is as effective as liposomal amphotericin B when used as empirical antifungal therapy in patients with persistent fever and neutropenia.⁷⁵ Caspofungin has been evaluated as prophylaxis in patients with acute myelogenous leukemia or high-risk myelodysplastic syndrome.⁷⁶ Caspofungin is as efficient as fluconazole in patients with advanced HIV infection and documented

Candida esophagitis.⁷⁷ Caspofungin has been well tolerated parenteral therapeutic option for HIV patients with oropharyngeal and/or esophageal candidiasis.⁷⁸ Caspofungin is well tolerated in pediatric patients and equally efficient in patients with invasive aspergillosis and candidiasis as with previous adult studies for the same indication.⁷⁹ Caspofungin is effective and well tolerated agent in IFIs involving solid organ transplant (SOT) recipients.^{80,81} Caspofungin is effective and safe in invasive candidiasis including peritonitis, abdominal abscesses and arthritis.⁸²

Micafungin has been found to be effective, well-tolerated and safe with minimum effective dose of 12.5 mg in the treatment of oesophageal candidiasis.⁸³ Intravenous micafungin is as efficacious as intravenous fluconazole in the primary treatment of oesophageal candidiasis.⁸⁴ Micafungin 100 mg daily and 150 mg daily are noninferior to a standard dosage of caspofungin for the treatment of candidemia and other forms of invasive candidiasis.⁸⁵ Micafungin is more effective and safe than fluconazole in neutropenic patients and may provide an option for prophylaxis in patients undergoing HSCT.⁸⁶ Micafungin is a cost-effective prophylactic antifungal therapy compared to fluconazole in HSCT recipients and also if the local fungal epidemiology indicates a high level of resistance to fluconazole.⁸⁷⁻⁸⁸ Micafungin is cost-effective also compared to caspofungin in the treatment of systemic *Candida* infections.⁸⁹ Micafungin in combination with other drugs is an option for the treatment of invasive aspergillosis in pediatric patients.⁹⁰ Micafungin has been appeared to be a valuable new treatment for esophageal candidiasis in HIV-positive patients.⁹¹

Anidulafungin is novel echinocandin antifungal agent with potent activity against *Candida* spp. Anidulafungin has shown *in vitro* activity against 2,235 clinical isolates of *Candida* with highest activity against *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. kefyr*. Anidulafungin has also shown activity against fluconazole resistant isolates.⁹² Anidulafungin has similar safety profile to that of fluconazole. Anidulafungin is as safe and effective as oral fluconazole for the treatment of esophageal candidiasis.⁹³ Anidulafungin has been shown to be noninferior to fluconazole in the treatment of invasive candidiasis.⁹⁴ Study carried out for the evaluation of safety and efficacy of anidulafungin in patients with invasive candidiasis, including candidemia has indicated no dose response for safety parameters.⁹⁵ In a phase 2 open-label, dose-ranging study in patients with candidemia, anidulafungin was effective in eradicating *Candida* spp. with highest susceptibility towards *C. albicans* and *C. glabrata* and lowest against *C. parapsilosis*.⁹⁶

Sordarin derivatives

The sordarins are novel class of antifungal agents inhibiting protein synthesis in pathogenic fungi targeting elongation factor 2. Elongation factor 2 promotes displacement of transfer RNA from the A site to the P site and movement of the ribosome along messenger RNA.⁹⁷ These agents have been appeared to have activity against *Candida* spp. except *C. krusei* and *C. lusitanae*. Their greatest activity is against *C. albicans*, *C. glabrata*, and *C. tropicalis*.⁹⁸ Sordarin derivatives have produced dosage-related efficacy against *C. albicans* in a murine model of disseminated candidiasis.⁹⁹ But these agents have not shown sufficient activity against disseminated *Aspergillus* infection.¹⁰⁰ Sordarin derivatives are effective in treating *P. carinii pneumonia* (PCP) and can be considered as a promising novel class of antifungal agents for the treatment of *Candida* and *Pneumocystis* infections.

Nikkomycins

Nikkomycins act by competitive inhibition of chitin synthase, the fungal enzyme that forms chitin, a component of the fungal cell wall. Nikkomycin Z has *in vitro* and *in vivo* activity against *Histoplasma capsulatum* and *Blastomyces dermatitidis*.¹⁰¹⁻¹⁰² Nikkomycin Z has shown *in vitro* activity of against *Coccidioides immitis*.¹⁰³ However, this agent has little to no activity against *C. albicans*, *C. tropicalis* and *Cryptococcus neoformans*. It is inactive against *A. fumigatus*.¹⁰³⁻¹⁰⁴ When nikkomycin Z is combined with either fluconazole or itraconazole, shows synergic *in vitro* activity against strains of *Candida* spp., *C. neoformans* and *A. fumigatus*, and *in vivo* activity against *H. capsulatum*.¹⁰⁵⁻¹⁰⁶

Monoclonal Antibody

Human recombinant monoclonal antibody (MAB) against heat shock protein 90 (HSP90) is a potential addition to the treatment of invasive *Candida* infections. Administration of MAB HSP90 in combination with a lipid formulation of amphotericin B (either ABLC or L-AmB) has shown to improve the results as compared to alone lipid formulation of amphotericin B in patients of invasive candidiasis.¹⁰⁷ Administration of MAB HSP90 in combination with an echinocandin also appears promising in the management of invasive candidiasis.¹⁰⁸ Glucosylceramides (GlcCer) are involved in the regulation of *Cryptococcus neoformans* virulence. In one study, passive immunization with a monoclonal antibody to GlcCer significantly decreased the host inflammation and prolongs the survival of animals infected with *C. neoformans*, which represents promising therapeutic strategy in cryptococcosis.¹⁰⁹ Monoclonal antibodies may also have their role in the laboratory diagnosis purpose for some fungal infections such as invasive yeast infections.¹¹⁰

Aminocandin

Aminocandin is structurally similar to echinocandins and has the advantage of a half-life that is 3-4 times that of other echinocandins.¹¹¹ Aminocandin has demonstrated efficient activity against *Candida* and *Aspergillus* species in some animal models.¹¹² Aminocandin at doses of higher than 1 mg/kg/day is as effective as amphotericin B in improving survival and reducing organ burdens in the treatment of disseminated *C. tropicalis*.¹¹³ Aminocandin has similar *in vitro* spectrum of activity to that of echinocandins having fungicidal activity against *Candida* spp. and inhibits *Aspergillus* spp. Aminocandins have also shown to appear *in vitro* activity against some caspofungin-resistant strains of *C. glabrata*.¹¹⁴ According to one another study, aminocandin has the potential for extended interval dosing in the treatment of *C. glabrata* infections caused by susceptible isolates.¹¹⁵ Aminocandin at doses of more than 1 mg/kg is highly effective in reducing mortality and organ burden in disseminated infection caused by itraconazole susceptible and resistant *A. fumigatus*.¹¹⁶ Single doses of aminocandin are effective as treatment and prophylaxis for the treatment of invasive candidiasis.¹¹⁷

Interferon-γ-1b

Interferon-γ-1b has no inherent antifungal activity when given as a single agent but offers a way to improve the activity of effector cells of the immune system. This increased immune function represents an addition to antifungal therapy for immune compromised patients. This activity has been observed both *in vitro* and *in vivo* and led to drastic increases in the antifungal activity of these cells against a variety of fungi.¹¹⁸ This increased antifungal activity of effector cell is not limited to only a few fungi but involves many pathogenic molds and yeasts too.^{119,120}

CONCLUSION

Significant progress has been made in recent years in the development of antifungal agents. Some antifungal agents have been reformulated to reduce toxicity (such as lipoidal preparation of nystatin and amphotericin B) and some new derivatives of existing drugs (azoles and echinocandins) have been developed to enhance the potencies. Novel drug candidates can be developed through identification of novel biochemical and molecular targets of pathogenic fungi.

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