

Drugs in Clinical Development for Fungal Infections

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Abstract Despite increasing rates of invasive fungal infections being reported globally, only a single antifungal drug has been approved during the last decade. Resistance, toxicity, drug interactions and restricted routes of administration remain unresolved issues. This review focuses on new antifungal compounds which are currently in various clinical phases of development. We discuss two azoles with a tetrazole moiety that allows selective activity against the fungal CYP: VT-1161 for *Candida* infections and VT-1129 for cryptococcal meningoencephalitis. We also discuss two glucan synthesis inhibitors: CD101, an echinocandin with an increased half-life, and SCY-078 with oral bioavailability and increased activity against echinocandin-resistant isolates. Among the polyenes, we discuss MAT023, an encochleated amphotericin B formulation that allows oral administration. Two novel classes of antifungal drugs are also described: glycosylphosphatidylinositol inhibitors, and the leading drug APX001, which disrupt the integrity of the fungal wall; and the orotomides, inhibitors of pyrimidine synthesis with the leading drug F901318. Finally, a chitin

synthesis inhibitor and progress on human monoclonal antifungal antibodies are discussed.

Key points

Several antifungal drugs have reached clinical stage development.

Two azoles, VT-1161 and VT-1129, are designed to selectively inhibit the fungal CYP51 and treat *Candida* spp and cryptococcal meningitis, respectively.

SCY-078 and CD101, are novel glucan synthesis inhibitors with oral bioavailability and increased half-life, respectively.

An orally administered encochleated formulation of amphotericin B has reached phase 2 to treat chronic mucocutaneous candidiasis.

APX001, a glycosylphosphatidylinositol inhibitor, and F901318, a pyrimidine synthesis inhibitor, are the lead compounds in two novel antifungal drug classes.

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1 Background

Fungal infections contribute substantially to human morbidity and mortality. Twenty-five percent of the global population, or 1.7 billion people, suffer from common superficial skin and nail fungal disease. While invasive

fungal infections (IFI) have a lower incidence, they are associated with higher mortality rates than tuberculosis or malaria [1, 2]. A million people each year die from IFIs, mostly caused by *Cryptococcus*, *Candida*, *Aspergillus* and *Pneumocystis* spp. [1]. During the past few decades, an increase in the incidence of IFI has been described, associated with the rising number of patients at risk as a result of solid organ and blood marrow transplantations, immunosuppressive therapy, invasive surgery, advanced age, and neoplastic disease [3].

Despite newer therapeutic options, such as β -glucan synthesis inhibitors and third-generation triazoles (posaconazole and voriconazole), antifungal drugs have modest impact in reducing the high mortality rate, in part due to delayed diagnosis. Unresolved issues like toxicity, drug interactions, restricted routes of administration, narrow spectrum, reduced bioavailability at the target tissues, and emerging resistance, stress the need to develop new molecules to overcome these difficulties [1–5].

Only one antifungal drug has been approved in the past decade. Isavuconazole is a new extended spectrum triazole with in vitro activity against *Candida* species, most *Aspergillus* species, *C. neoformans*, other non-*Candida* yeasts, *Scedosporium apiospermium*, dimorphic and dermatiaceous fungi, and emerging pathogens such as *Exserohilum rostratum* and variable activity against several Mucorales [6, 7].

Isavuconazole obtained FDA approval in March 2015 for the treatment of invasive aspergillosis, based on non-inferiority trials compared with voriconazole [8] and was approved for the treatment of mucormycosis, based on a matched case-control analysis comparing this drug to historic controls of the global Fungiscope Registry [9]. The ACTIVE trial compared isavuconazole to caspofungin for the treatment of candidemia or other invasive *Candida* infections, but publicly released data from Astellas failed to show non-inferiority. The trial has been completed, but results have not been published at this time (Clinical Trial NCT00413218) [10].

This drug is available in intravenous and oral formulations, as a prodrug (isavuconazonium sulfate) with attractive characteristics like a water soluble intravenous formulation, excellent oral bioavailability, predictable pharmacokinetics and few adverse effects (AEs) like nausea, vomiting and diarrhea. Unlike other triazoles, which are associated with QTc interval prolongation, most studies have not shown this association with isavuconazole. Temporary QTc interval shortening was noted to occur in a dose and concentration manner. The clinical significance of this finding is currently unknown, but patients with familial short-QT syndrome should not receive this agent [11]. Elevations in hepatic enzymes may occur, as with other azoles. Visual disturbances or photosensitivity have not

been described [6, 7]. Several questions remain unanswered, including cross resistance among azoles and drug-drug interactions since isavuconazole is a substrate for CYP3A4/3A5, a moderate inhibitor of CYP3A4 and has inductive effects on CYP2B6. Even though routine therapeutic drug monitoring is not usually required, correlation between serum concentrations and AE or efficacy have not been fully assessed at this time, and further investigation is warranted [11]. In addition, isavuconazole has limited activity against *Fusarium* spp. and *S. apiospermium* and no activity against *S. prolificans* [6, 7]. Higher minimum inhibitory concentrations (MICs) have been described for *Candida glabrata*, *C. guilliermondi* [12] and *Aspergillus niger* [13]. Some in vitro studies suggest that posaconazole may be more active against the Mucorales than isavuconazole [14, 15]. Finally, urine elimination of isavuconazole is negligible, so this agent is unlikely to be useful for urinary tract infections [6, 7].

This review focuses on recent antifungal agents currently in late preclinical or clinical stage development (Table 1).

2 Agents in Clinical Stage Development

Few antifungal agents have emerged from the antifungal pipeline after the approval of the echinocandins (micafungin, caspofungin and anidulafungin) and issues such as limited activity spectrum, tolerability or antifungal resistance remain unresolved. Discovery of new fungal-specific targets is challenging due to metabolic and structural similarities between the fungal and mammalian eukaryotic cells.

2.1 Azoles

Viamet Pharmaceuticals is developing several metalloenzyme inhibitors of lanosterol 14 α -demethylase (CYP51), including VT-1161 and VT-1129 [16–18], which are directed to the treatment of *Candida* infections and cryptococcal meningitis, respectively. Unlike previous azoles, which contain an imidazole or triazole moiety that binds the human cytochrome, VT-1161 and VT-1129 have a tetrazole moiety with improved target selectivity (Fig. 1). Both have showed strong binding of *C. albicans* CYP51 due to the attenuated interaction between the metal binding groups and the heme cofactor. As a result, it does not bind to the human CYP5 (Fig. 2) [18–20].

2.1.1 VT-1161

VT-1161 is active in vitro and in vivo against *C. albicans*, *C. glabrata* and *C. parapsilosis*, even in isolates with

Table 1 Antifungal agents in clinical phase of development

Agent	Action mechanism	Advantage	Use
VT-1161	Inhibitor of lanosterol demethylase	Tetrazole moiety with high affinity to the fungal CYP51	<i>Candida</i> infections
VT-1129	Inhibitor of lanosterol demethylase	Tetrazole moiety with high affinity to the fungal CYP51	Cryptococcal meningoenzephalitis
SCY-078	Glucan synthase inhibitor	Oral bioavailability Activity despite resistance mutations	Invasive <i>Candida</i> infections
CD101	Glucan synthase inhibitor	Increased half-life Reduced toxicity	Invasive <i>Candida</i> infections. <i>Aspergillus</i> infections
CAmB	Ergosterol binding, pore formation in the fungal membrane, K and Mg efflux resulting in cell death	Oral bioavailability Reduced toxicity Broad spectrum activity	<i>Candida</i> and <i>Aspergillus</i> infections, cryptococcal meningoenzephalitis
MAT2203	Ergosterol binding, formation of pores in the fungal membrane, K and Mg efflux resulting in cell death.	Oral bioavailability Reduced toxicity Broad spectrum activity	Invasive Candidiasis, Aspergillosis
Nikkomycin Z	Inhibits fungal wall synthesis through inhibition of chitin synthases	Fungal specific target	Coccidioidomycosis, histoplasmosis and blastomycosis
APX001	Inhibits Gwt1, GPI-anchor protein synthesis	Fungal specific target Affects multiple virulence factors	<i>Candida</i> spp <i>Aspergillus</i> spp <i>Scedosporium</i>
F901318	Inhibits DHODH, pyrimidine synthesis pathway.	Fungal specific target Broad spectrum antifungal	<i>Aspergillus</i> spp Dimorphic fungi <i>Scedosporium</i> , <i>Fusarium</i> spp

GPI glycosylphosphatidylinositol, DHODH dihydroorotate dehydrogenase

reduced susceptibility or resistance to fluconazole or the echinocandins due to ERG11 point mutations, over-expression of CDR1, CDR2, MDR1 and FKS1 hot spot mutations [21, 22]. Pharmacokinetic information from murine models shows high oral absorption (73%), a long half-life (>48 h) and rapid penetration in vaginal tissue [23]. A murine model of vulvovaginal candidiasis showed in vivo efficacy and reduced fungal burden at 1 and 4 days posttreatment, using both fluconazole-sensitive and highly resistant yeasts [23]. Two animal models of invasive candidiasis showed reduced kidney yeast burden, and increased survival in mice treated with VT-1161, including those infected with a fluconazole- and caspofungin-resistant *C. albicans* isolate [18, 24].

Gebremariam et al. [25] demonstrated increased survival in neutropenic mice infected with *Rhizopus arrhizus* var. *arrhizus*, where VT-1161 it was found to be as effective as liposomal amphotericin (LAmB). Of note, VT-1161 had elevated minimal inhibitory concentration (MIC) values for *R. arrhizus* var. *delemar* (>32 µg/mL). Therefore, additional studies are required to evaluate the activity of this drug against other Mucorales. Shubitz et al. [26] demonstrated in vitro antifungal activity of VT-1161

against clinical isolates of *Coccidioides immitis* and *C. posadasii* as well as significant reduction of fungal burden and increased survival time in lethal respiratory and CNS murine models. Comparisons with fluconazole demonstrated equivalence or superiority of VT-116. The drug prevented dissemination of infection to a greater extent than fluconazole apparently because of a longer half-life and high plasma levels, which makes it an attractive alternative as a therapeutic agent [26].

Several clinical studies of VT-1161 have been completed. A phase 2a, randomized, double-blind study evaluated the efficacy and safety of VT-1161 compared to fluconazole in the treatment of patients with moderate-to-severe acute vulvovaginal candidiasis (VVC), and showed clinical cure rates similar to fluconazole, with greater mycological cure (93 vs 73%) and fewer recurrences during follow-up. VT-1161 was determined to be safe and well tolerated in this trial [27].

The REVIVE trial, a phase 2b randomized double blind, placebo-controlled trial comparing low or high doses of VT-1161 in patients with recurrent VVC, and showed complete cure rates of 32–42 vs 0–7% in the placebo arm ($p \leq 0.0001$). Also, a recurrence rate of 65.6% in the

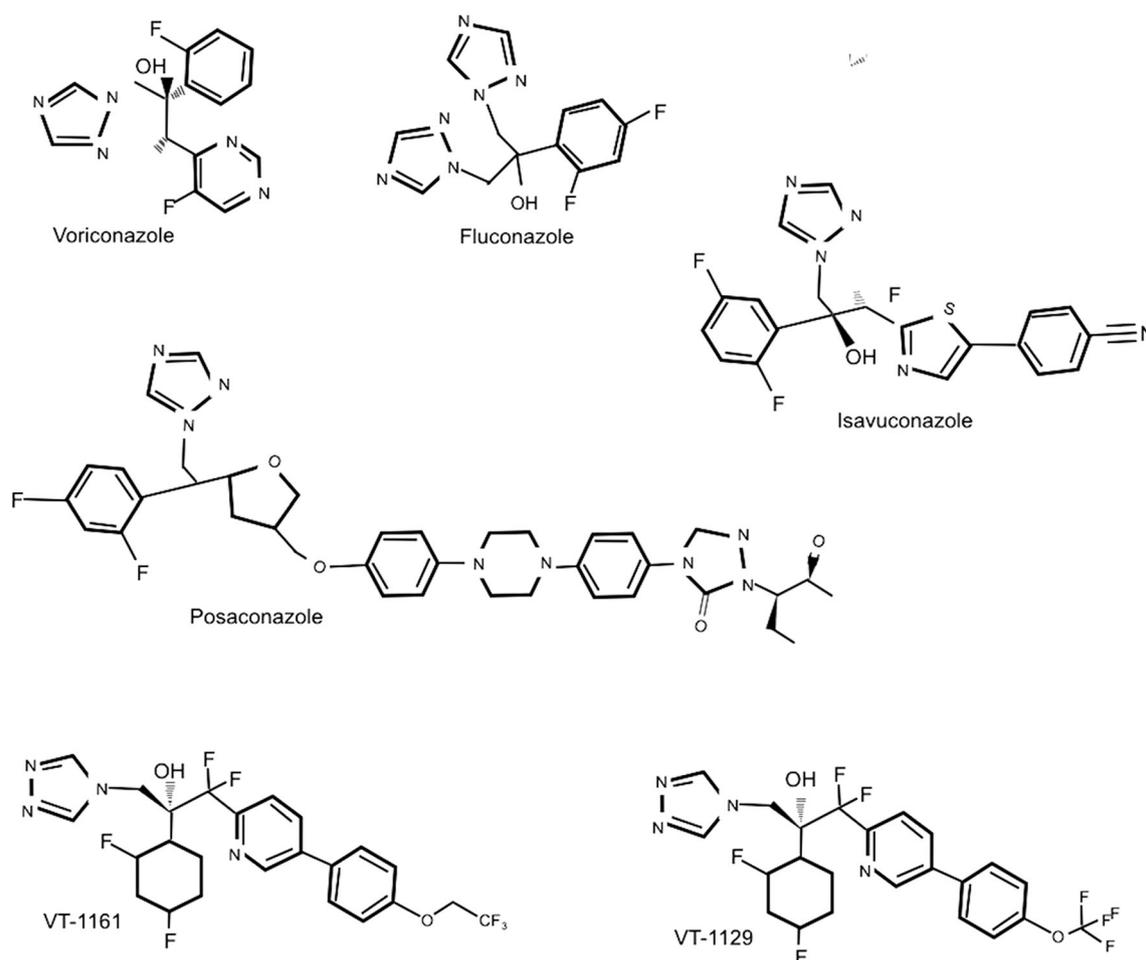


Fig. 1 Chemical structures of azoles and the novel tetrazoles VT-1161 and VT-1129

placebo arm vs 0% in the VT-1161 arm through 48 weeks was seen. VT-1161 was safe and well tolerated in all dosing arms [28].

The RENOVATE study, a phase 2b randomized trial, compared four once-weekly treatment regimens to placebo, for the treatment of moderate-to-severe onychomycosis and showed complete cure of 61–72% at week 48 vs <10% in the placebo arm. The median improvement of nail involvement was as high as 92 vs 13% in the placebo arm. The drug was safe and achieved increased cure rates up to week 60 [29].

2.1.2 VT-1129

VT-1129 is a promising oral agent against *Cryptococcus* species, which has received fast track, orphan drug designation and is considered a qualified infectious disease product (QIDP) by the FDA for the treatment of cryptococcal meningitis. Viamet is currently conducting a phase

1 clinical trial in healthy volunteers in the USA [17]. Recently, Lockhart et al. [30], tested the in vitro activity of VT-1129 against 180 isolates of *C. neoformans* and 321 isolates of *C. gattii*. Overall, VT-1129 demonstrated potent activity against *C. neoformans* with MIC values ranging between ≤ 0.015 and 2 $\mu\text{g/mL}$ at the 50% inhibition of growth endpoint and between ≤ 0.015 –4 $\mu\text{g/mL}$ at the 100% endpoint. The VT-1129 MIC at both the 50 and 100% inhibition endpoints were significantly lower than that observed with fluconazole. In addition, VT-1129 maintains potent activity against isolates with elevated MICs ($\geq 8 \mu\text{g/mL}$) and dose-dependent susceptibility (MIC 16–32 $\mu\text{g/mL}$). Only 1 of 6 fluconazole-resistant isolates showed a VT-1129 MIC $\leq 0.025 \mu\text{g/mL}$ [31]. Among *C. gattii*, potent activity was observed, with MIC values ranging between ≤ 0.015 –1 $\mu\text{g/mL}$ at the 50% inhibition of growth endpoint and between 0.06 $\geq 8 \mu\text{g/mL}$ at the 100% endpoint. Of note, VGII and VGIII isolates had higher MIC values, similar to the known elevated MICs for azoles in

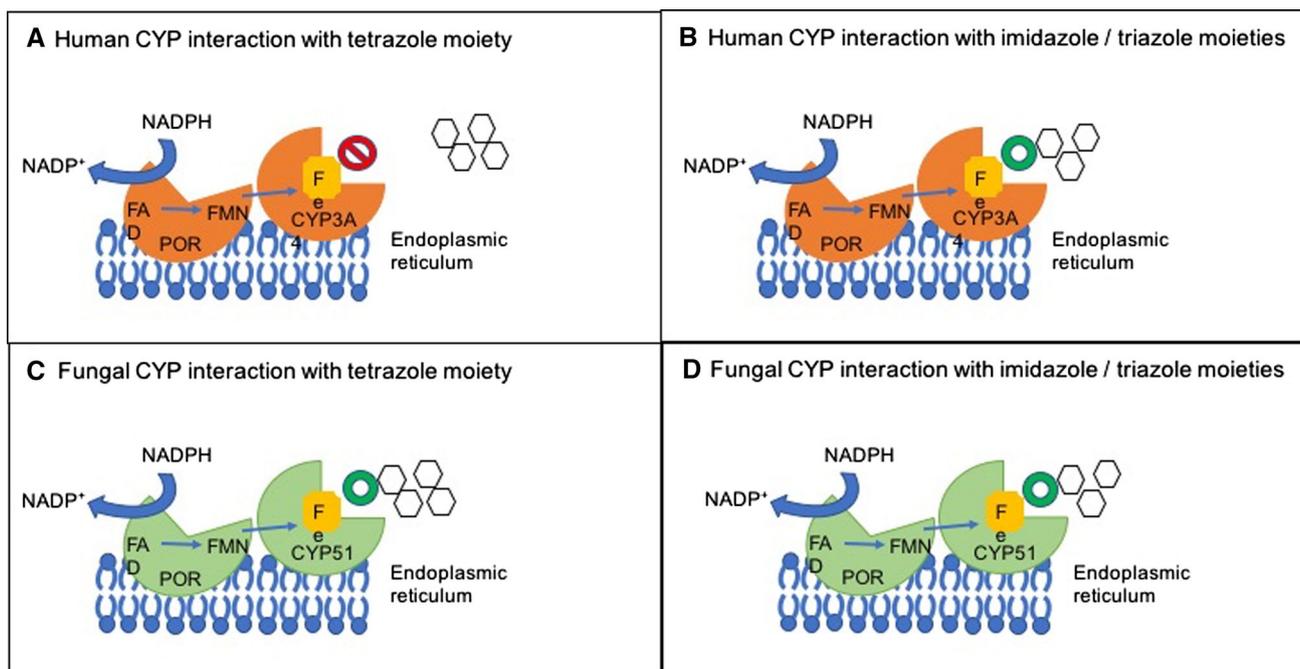


Fig. 2 Tetrazole interaction with the human and fungal CYP450. The human CYP3A4 is moderately inhibited by imidazole and triazole antifungal agents because of an interaction between the metal binding groups (MBG) of azoles and the heme cofactor located at the CYP enzyme active site. Novel tetrazoles were designed to contain a MBG with reduced affinity to the human CYP while maintaining an even

higher affinity to the fungal CYP51 (lanosterol demethylase) [18]. *NADPH* nicotinamide adenine dinucleotide reduced form, *NADP*⁺ nicotinamide adenine dinucleotide phosphate oxidized form, *FAD* flavin adenine dinucleotide, *FMN* flavin mononucleotide, *POR* P450 oxidoreductase, *Fe* Iron in the heme cofactor Modified from Nebert et al. [98]

this molecular subtype [30]. VT-1129 showed improved efficacy in two murine models of cryptococcal meningitis, achieving undetectable colony-forming units (CFU) in the brain of intrathecally infected immunocompetent mice, as well as increased 30-day survival in comparison with fluconazole [24, 32]. Also, VT-1129 has shown potent efficacy in a murine systemic candidiasis model [18].

2.2 Glucan Synthesis Inhibitors

Drugs in this class have become the first-line therapy against invasive infections with *Candida* isolates, due to their potency, broad spectrum, and fewer AEs. However, until now they were only available as intravenous formulations due to the very large size and low bioavailability of the lipopeptides.

2.2.1 SCY-078

SCY-078 (previously MK-3118) is a novel, potent—and structurally distinct glucan synthase inhibitor, derived from enfumafungin, which has the advantage of oral bioavailability in addition to an intravenous formulation. Chemical modification of enfumafungin led to improved pharmacokinetic properties and oral bioavailability by tethering the alkyl groups proximal to the basic amino group of the

C3 side chain to preclude oxidative *N*-demethylation (Fig. 3) [33]. It is being developed by Scynexis [34, 35], and has received a QIDP designation from the FDA. This compound has shown in vitro activity as potent as caspofungin against *C. albicans*, *C. tropicalis* and *C. krusei*, but higher (eightfold) potency against *C. glabrata* strains. It also retains activity against fluconazole-resistant strains and isolates harboring mutations in the hotspot of *fks1* or *fks2*, which confer resistance to echinocandins [36, 37]. SCY-078 showed in vitro activity against 71 *Aspergillus* isolates obtained from participating centers in the 2008–2010 ARTEMIS and SENTRY surveillance programs [36], which included wild-type (WT) and antifungal-resistant strains of *Aspergillus*. The minimum effective concentration (MEC) endpoint was selected due to the lack of complete inhibition of *Aspergillus* species seen with the echinocandins. The activity of SCY-078 was less than caspofungin, with MEC₉₀ of 0.12–0.25 vs 0.03–0.06 µg/mL. Both caspofungin and SCY-078 were active against the itraconazole-resistant isolates (MIC ≥ 4 µg/mL) with a MEC range from 0.03–0.5 µg/mL for SCY-078 [36]. Interestingly, the sites of mutations in *fks* that are associated with resistance to the echinocandins are different than those causing decreased susceptibility to the enfumafungin derivatives [37, 38]. In a murine model of invasive candidiasis, SCY-078 achieved the stasis endpoint and the

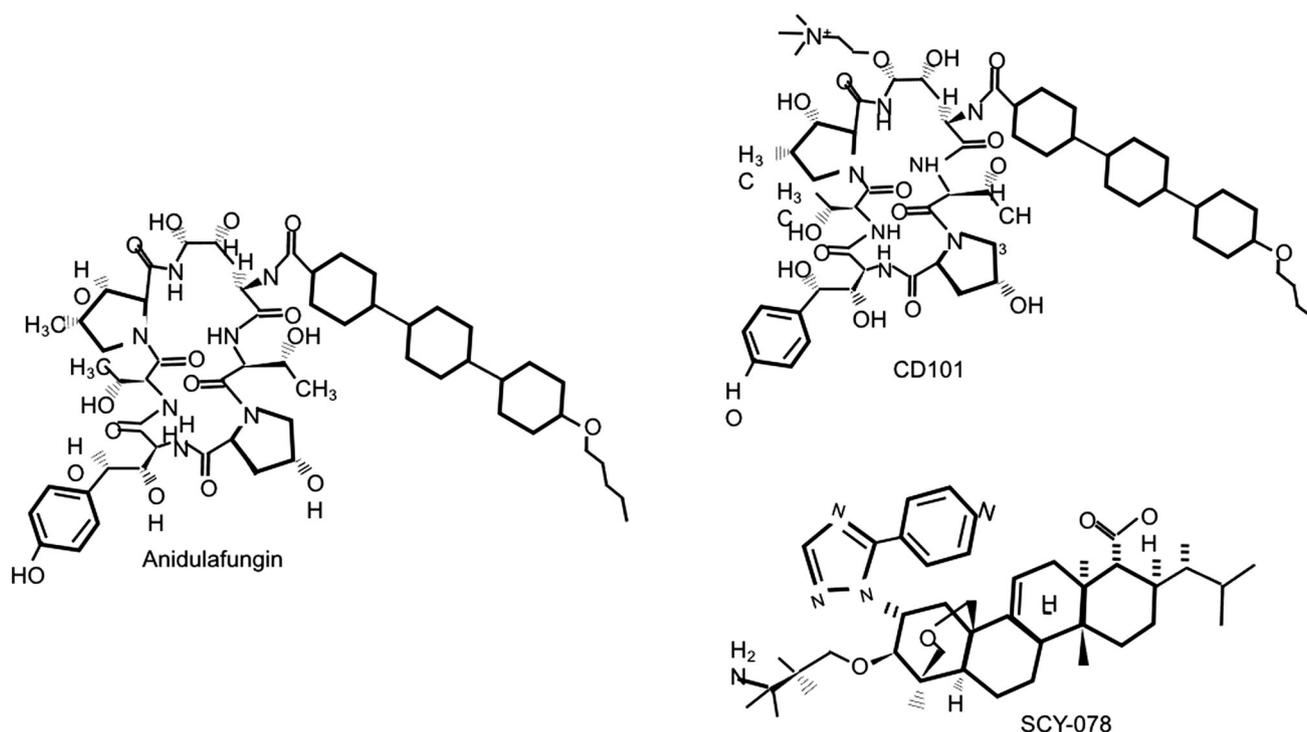


Fig. 3 Chemical structure of anidulafungin and novel echinocandins

1-log kill endpoint. A trend toward lower pharmacodynamic targets was observed for *C. glabrata* and *C. parapsilosis* in comparison to *C. albicans*, consistent with previous echinocandin results. Current in vivo data demonstrate that SCY-078 is a promising oral option for *Candida* infections, including invasive candidiasis. The results of human pharmacokinetic data, MIC distribution, and protein-binding data will allow the determination of susceptibility breakpoints [39]. Also, SCY-078 appears to be active against *Paecilomyces variotti* and modestly active against *S. prolificans*. This drug has little activity in vitro against the Mucorales or *Fusarium* spp [40].

Two phase two studies in humans have been completed, and results were presented at the 27th ECCMID Conference, 2017. The first study was a multicenter, active controlled, blinded proof-of-concept trial (ClinicalTrials.gov NCT02679456), which randomized 96 women with acute moderate-to-severe VVC to receive SCY-078 or fluconazole. Clinical cure was higher for patients receiving oral SCY-078 compared to oral fluconazole at the test-of-cure visit. Also, a higher clinical cure rate at the end of the observation period (4 months) in comparison to fluconazole (88 vs 65%, $p = 0.04$) and a lower recurrence rate (4 vs 15%) was seen. However, this was a pilot study not powered to demonstrate a statistically significant difference [41]. The other phase 2 study (ClinicalTrials.gov NCT 0224406) was a multicenter, multinational, randomized, open-label study following 3–10 days of echinocandin

therapy, which evaluated the pharmacokinetics, safety and tolerability of SCY-078 as an oral step-down treatment in 27 patients with invasive candidiasis. The study met its primary objective by confirming the oral daily dose of 750 mg to be safe and well tolerated. No discontinuations due to AEs or serious AEs were seen. Mild-to-moderate gastrointestinal events such as diarrhea, nausea, vomiting, abdominal pain or discomfort were seen and were comparable to the fluconazole arm. No mycological failure was reported in the study drug arm [42].

2.2.2 CD101

CD101 (formerly SP3025) is a novel echinocandin, being developed by Cidara Therapeutics (San Diego, CA, USA), which has a modification in the choline moiety at the cyclic echinocandin core (Fig. 3) that allows increased solubility, and stability in plasma, aqueous and buffered solutions and elevated temperature, as well as reduced toxicity. A reduced rate of AEs was seen in animal models, in comparison to anidulafungin. The stability in plasma and lack of degradation products contribute to the long half-life across species and increased safety observed for CD101. It has been granted QIDP and fast track designation by the FDA. This drug is being developed as a once-weekly intravenous formulation for the treatment and prevention of invasive fungal infections and for topical treatment of acute and recurrent VVC [43]. CD101 has shown comparable

in vitro efficacy to the echinocandins against *Candida* and *Aspergillus* spp. in a panel which included highly resistant isolates, through both the CLSI and EUCAST broth microdilution interpretative criteria. The activity of CD101 against both WT and fks mutant strains of *Candida* spp. was comparable to that of anidulafungin, whereas caspofungin was two to fourfold less active than either CD101 or anidulafungin. Both CD101 and anidulafungin were most active against *Aspergillus* (*A. fumigatus*, *A. flavus*, *A. niger*, *A. terreus*) with MEC values of ≤ 0.06 mg/dL. Likewise, caspofungin was fourfold less active [44].

Preclinical studies have shown metabolic stability with no biotransformation in liver microsomes or hepatocytes, high protein binding and minimal inhibition of CYP450 enzymes. The design of CD101 provides chemical stability of the attached choline, preventing opening of the ring. In a neutropenic mice model, there were no microscopic changes in the livers of animals who received CD101, while administration of anidulafungin resulted in hepatocyte necrosis. After incubation with glutathione, no reactive intermediate formation was seen with CD101, while the ring-opening degradation pathway showed evidence of reactive intermediate formation of anidulafungin. Caspofungin has been shown to undergo spontaneous chemical degradation and formation of reactive intermediates. Hepatotoxicity seen with anidulafungin and caspofungin maybe due to the inherent chemical lability generating potentially reactive intermediates [45]. The potential for resistance to CD101 has been characterized in a study of spontaneous mutations and serial passages, with caspofungin and anidulafungin as comparators. Even though CD101 had a low spontaneous mutation frequency, *C. glabrata* strains had the highest number of mutants for all drugs overall, while *C. parapsilosis* and *C. krusei* had the lowest mutation frequency. Mutants demonstrating reduced susceptibility to CD101 occurred at similar frequencies to anidulafungin and caspofungin, while cross resistance among CD101 and the echinocandins was broadly observed. The weekly dose could be beneficial in improving efficacy over smaller daily doses and may have advantages in resistance prevention by maintaining drug levels in excess of the mutant prevention concentration; however, clinical and microbiological outcomes are pending [46].

CD101 demonstrated potent antifungal efficacy in a neutropenic mouse model of *C. albicans* and *Aspergillus* infection [45, 47, 48].

Two phase 1 clinical trials have also been completed. A single ascending dose trial and a multiple ascending dose trial, which established the safety and pharmacokinetic profile of intravenous CD101 in healthy subjects (ClinicalTrials.gov NCT02516904) (ClinicalTrials.gov NCT02551549).

In addition, a phase 2 multicenter, randomized, double-blind study will evaluate the safety, tolerability and efficacy of CD101 in patients with candidemia. The study will compare weekly CD101 injections vs daily caspofungin followed by optional oral fluconazole step down, and is currently recruiting patients (ClinicalTrials.gov NCT02734862).

The RADIANT trial was a multicenter, randomized, open-label, active-controlled, dose-ranging trial that enrolled 125 patients into 2 arms of topical CD101 (a gel and an ointment) and oral fluconazole. Unpublished results from Cidara showed lower clinical and mycological cure in the CD101 arms compared to fluconazole, leading to discontinuation of the topical formulations [49].

2.3 Polyenes

Amphotericin B (AmB) is a broad-spectrum fungicidal antibiotic used primarily in the treatment of life-threatening fungal infections. It is a polyene macrolide with a therapeutic efficacy that is limited due to poor solubility in aqueous solutions. The first formulation incorporated AmB in deoxycholate (DAmB) micelles, which led to rapid release of AmB and rapid binding to plasma lipoproteins. The addition of this bile salt surfactant brought additional toxicity, including acute infusion-related reactions (fever, chills, nausea, vomiting) anemia (due to red blood cell membrane damage), and dose-related nephrotoxicity. In order to attenuate toxicity, lipid formulations of AmB were developed: liposomal AmB (Ambisome[®]) and AmB lipid-complex (Abelcet[®]). Abelcet[®] is AmB complexed with two lipids that aggregate in large compounds, which are recognized in blood by macrophages and are taken up rapidly to the mononuclear phagocyte system. AmBisome[®] is a liposomal formulation supplied as lyophilized powder which must be reconstituted. These liposomes accumulate at sites of fungal infections, bind to fungal membranes, penetrate into the fungal cytoplasm and release the drug. Because of its small size, it avoids recognition by the mononuclear phagocyte system. Even though clinical outcomes are similar, the use of Ambisome[®] results in reduced nephrotoxicity and infusion-related reactions. Neither the liposome drug delivery vehicle or the lipid complex allow oral administration, which has led to continuous research for alternative drug-delivery platforms [50, 51].

2.3.1 Cochleate Drug Formulations

Chochleate drug formulations are lipid-based drug vehicles that have the potential to deliver hydrophobic drugs such as AmB. They were first described in 1975 by Papahadjopoulos et al. [52], as an intermediate in the preparation of

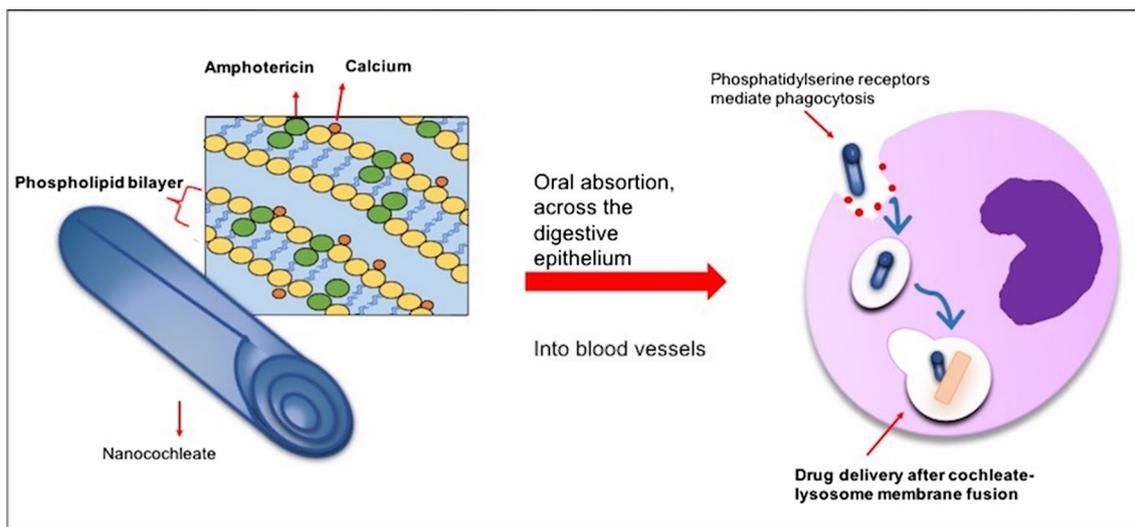


Fig. 4 Structure and targeted delivery of encochleated Amphotericin B. Nanocochleates are cylindrical structures that consist of multiple lipid bilayers that encapsulate hydrophobic drugs like amphotericin B. After oral administration they cross the digestive epithelium into the blood vessels. When they reach the phagocytes of the

reticuloendothelial system, both membranes fuse and the drug is delivered directly to the cytoplasm. Alternatively the nanocochleate reaches the lysosome after phagocytosis, membranes fuse and the drug is liberated [57].

unilamellar vesicles. Cochleates are stable phospholipid-divalent cation precipitates with a multilayered structure consisting of large, continuous, solid, lipid bilayer sheets rolled up in a spiral, with no internal aqueous space [53–55]. Jin and Zarif described a method to prepare nanometer-sized cochleates [53, 54, 56]. These structures are formed spontaneously when calcium ions are added to phosphatidylserine in physiological saline. They act as membrane fusion intermediates, due to high tension at the bilayer edges and increased cell-cochleate contact as a result of size reduction (Fig. 4) [55]. This structure protects the associated “enococheated” molecules from degradation, resulting in a stable, nontoxic, highly efficacious AmB lipid particle, with the potential to overcome the poor oral bioavailability of AmB [52, 55]. Nanocochleates are more stable than liposomes because they are less susceptible to oxidation, resist enzyme degradation and have the potential for slow or timed release of the biologic molecule. Absorption takes place in the intestine, where nanocochleates cross the digestive epithelium and deliver their cargo molecules into the blood vessel. Nanocochleates are recognized and phagocytized by the reticuloendothelial system, similar to Abelcet®. The drug is delivered to the target cell cytoplasm by two mechanisms: (1) when phagocytosis occurs, the nanocochleate contacts the lipid membrane of lysosomes in the cytoplasm and delivers the drug content after fusion with the lysosome; (2) alternatively, when the nanocochleate approximates the cell membrane of the target cell, the fusion of both membranes results in direct delivery of the drug into the cytoplasm [57].

reticuloendothelial system, both membranes fuse and the drug is delivered directly to the cytoplasm. Alternatively the nanocochleate reaches the lysosome after phagocytosis, membranes fuse and the drug is liberated [57].

Animal models have shown extensive tissue distribution and penetration of cochleated amphotericin B (CAmB) on target organs (lungs, liver, spleen and kidneys) after administration of a single intravenous dose. The liver acts as a reservoir, releasing AmB at a slow rate and increasing its potential for the treatment of systemic fungal infections and deep mycoses [51].

CAmB has been shown to be as effective as intraperitoneally administered DAMB in protecting against mortality and reducing the fungal burden of tissues in murine models of systemic candidiasis and invasive aspergillosis. Oral administration of CAmB was similarly efficacious compared to Ambisome® in murine models of visceral leishmaniasis, disseminated aspergillosis and systemic candidiasis. CAmB has been described as lacking toxicity in vitro and in vivo [54, 58, 59].

2.3.2 MAT2203

MAT2203 (Matinas BioPharma Holdings, Inc, NJ, USA) is an orally administered encochleated formulation of AmB, which received QIDP designation as well as fast track status from the FDA for the treatment of invasive candidiasis and aspergillosis in August 2015 [60].

In an abstract presented at the ICAAC in 2015, mice with invasive candidiasis receiving oral CAmB at 10 mg/kg, had quantifiable levels of AmB in the liver, lung and kidneys and the maximal level was achieved early in the treatment schedule. In contrast, mice receiving DAMB showed lower tissue concentrations at early times, but nearly tenfold higher levels in liver and lung by day 11.

Mice receiving oral CAmb at 2 mg/kg showed 100% survival and a 4-log reduction in CFU in lung and kidney. Infected mice showed AmB concentrations at least five to tenfold higher than uninfected animals, supporting the theory of targeted therapy [61].

Oral MAT2203 demonstrated a positive safety and tolerability profile in a phase 1 single-dose (200–800 mg), double-blind, dose escalating pharmacokinetic study in 48 healthy volunteers. No serious AEs were reported, and no abnormalities in laboratory including renal function were observed. Mild gastrointestinal disorders were seen [62].

Enrollment is currently underway for the phase 2a NIH/NIAID-funded clinical study with oral MAT2203 (200–800 mg) in patients with refractory mucocutaneous candidiasis, to evaluate the efficacy, safety, tolerability and pharmacokinetics (ClinicalTrials.gov NCT02629419). The potential oral delivery of a polyene is the main advantage of this drug.

2.4 Chitin Synthases Inhibitors

Nikkomycins are compounds derived from *Streptomyces ansochromogenes* and *S. tendae*, which interfere with the fungal wall synthesis acting as a competitive inhibitor of chitin synthases (Fig. 5) [63]. This is a fungal specific target since mammalian hosts do not possess chitin. This agent has shown activity against endemic fungi in animal models of coccidioidomycosis, histoplasmosis and blastomycosis, some activity against yeasts and no activity against filamentous fungi [64–67]. In an experimental mouse model of coccidioidomycosis, nikkomycin Z (NikZ) showed a fungicidal effect, being able to sterilize the lungs of 7/8 mice treated for 6 days [64]. In vivo, this agent has been shown to be superior to azoles in murine models of systemic coccidioidomycosis and blastomycosis [64, 65].

Preclinical studies have shown NikZ was well tolerated in animals, without detectable toxicity; however, a short half-life after intravenous and oral administration (15 min and 1 hour, respectively) was observed [64]. NikZ was well tolerated in human studies after single increasing oral doses up to 2000 mg, without AE, and a half-life of 2.5 hours was observed [68].

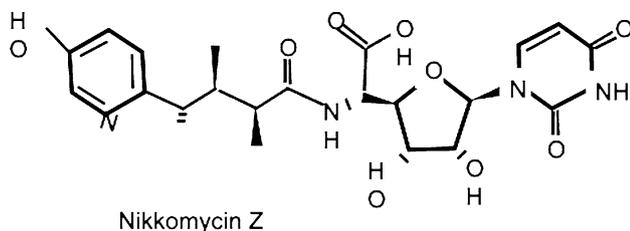


Fig. 5 Chemical structure of nikkomycin Z

Even though this agent was first described in the 1970s, it was not until 2005 when the drug was transferred to Valley Fever Solutions Inc, that there was renewed interest in its development and it finally received a QIDP designation from the FDA in October 2014. A phase I trial has been completed, which enrolled 32 healthy subjects to evaluate safety and tolerability of 250 mg, 500 mg and 750 mg of NikZ (ClinicalTrials.gov NCT00834184). Recently, a pharmacokinetic modeling study based on a study of murine pulmonary coccidioidomycosis, suggested that a 250–500 mg twice daily oral dose in humans, could provide a 24-hour AUC similar to those that showed efficacy in infected mice and dogs [69].

A phase II trial was underway for patients with coccidioidal pneumonia; however, it had to be terminated due to recruitment challenges and lack of funding (ClinicalTrials.gov NCT00614666). This drug is currently being developed as an orphan drug for the treatment of coccidioidomycosis.

2.5 Glycosylphosphatidylinositol Inhibitors

Glycosylphosphatidylinositol inhibitors (GPI) such as gepinacin and APX001 (Amlyx Pharmaceuticals, San Diego, CA, USA), belong to a novel class of antifungal agents that act through the inhibition of Gwt1, a conserved fungal enzyme [70]. APX001 is the prodrug of E1210, which exhibits highly selective antifungal activity by inhibiting inositol acyltransferase (an essential step in the production of GPI anchor proteins) within the endoplasmic reticulum of fungi [71]. GPI-anchored proteins become covalently linked to β -1,3-glucan following translocation to the cell surface and help to maintain the integrity of the fungal cell wall. Also, GPI-anchored proteins have a role in adherence and invasion of host tissues, hyphal growth, biofilm formation, filamentation and sensing the environment. When GPI-anchor synthesis is disrupted, β -glucan is unmasked leading to increased recognition of *Candida* by immune cells [70, 71].

APX001 exhibits broad spectrum in vitro activity against *Candida spp*, including fluconazole resistant isolates (except for *C. krusei*), *A. fumigatus*, *A. niger*, *A. flavus*, *A. terreus*, *Fusarium*, *Pseudallescheria boydii*, *S. prolificans* and *P. lilacinus* [72]. This drug showed dose-dependent efficacy and resulted in higher survival rates in comparison with control mice, in murine models of invasive candidiasis, oropharyngeal candidiasis, pulmonary aspergillosis and disseminated fusariosis [73].

APX001 has received orphan drug designation and QIDP by the FDA. Currently, Amlyx Pharmaceuticals has initiated phase 1 trials to evaluate safety, tolerability and pharmacokinetics of intravenous (ClinicalTrials.gov

NCT02956499) and oral (ClinicalTrials.gov NCT02957929) formulations of APX001.

2.6 Orotomides

F901318 is the leading drug of a novel class of antifungals, the orotomides, which is currently being developed by F2G Ltd (Eccles, UK). The mechanism of action involves the inhibition of pyrimidine biosynthesis by blocking the fungal dihydroorotate dehydrogenase (DHODH) pathway. This pathway is essential for the synthesis of DNA and is the target for many drugs. The antifungal flucytosine, antiparasitic agents against *Plasmodium* and *Toxoplasma*, antirheumatic drugs like leflunomide, and antineoplastic agents [74]. In vitro studies have shown F901318 to have a broad-spectrum activity against filamentous and dimorphic fungi, including *Aspergillus*, azole-resistant *Aspergillus* isolates, *Penicillium* spp, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Fusarium* spp and *Scedosporium* spp. Of note, there is no activity against *Candida* or the Mucorales. In vitro studies found no activity of F901318 against the human DHODH, even at the highest dose, proving fungal selectivity and predicting no target-based toxicity [75]. The drug also showed significantly improved survival in a murine model of invasive aspergillosis, compared with untreated controls and with posaconazole treatment [75, 76].

Phase 1 studies have demonstrated the safety and tolerability of intravenous and oral formulations of F901318 in healthy volunteers [77, 78]. This drug was granted Orphan Medicinal Product designation by the European Medicines Agency (EMA) Committee for the treatment of invasive aspergillosis and rare mold infections caused by *Scedosporium* species. Currently, clinical studies are being conducted to evaluate safety and pharmacokinetics of F901318 for fungal prophylaxis in patients with acute myeloid leukemia (ClinicalTrials.gov NCT02856178 and NCT03036046).

2.7 Human Monoclonal Antibody-Based Therapy

Impaired immune responses along with drug toxicity and increasing antifungal drug resistance has led to the development of antifungal antibody-based therapy as a tool to enhance antifungal treatment. Even though responses to immune sera historically showed contradictory results, it wasn't until the development of monoclonal antibodies (mAbs) that convincing evidence of protective activity against fungal pathogens was obtained [79]. Protective mAbs have been described against various components of *C. neoformans* such as the capsular polysaccharide, melanin, glucosylceramides and B-glucan [80–83]. MAb C7 is a monoclonal antibody against *C. albicans*, directed against a

cell wall mannoprotein which has shown in vitro inhibition of adherence to HEp-2 cells, inhibition of germination and direct fungicidal activity [84]. Other monoclonal antibodies have also been generated against several fungi. A mAb against an histone H2B-like protein on the surface of the fungus showed reduced fungal burden, diminished inflammation and prolonged survival in a murine model of disseminated histoplasmosis [85]. mAb A9 is directed against a cell wall glycoprotein of *A. fumigatus* which impedes hyphal development and exhibits fungicidal activity in vitro, and reduces fungal burden and increases survival in a murine model [86]. Also antiidiotypic monoclonal antibodies have been shown to inhibit *Aspergillus* growth and hyphal development in the lungs of infected mice [87]. mAb 3E is directed against of the major diagnostic antigen of *Paracoccidioides brasiliensis*, gp43; administration led to a reduced fungal burden and pulmonary inflammation after intravenous and intratracheal infection in mouse models [88]. Selected mAb administration conferred protection against an airborne challenge of *P. carini* in a mouse model [89]. mAb P6E7 produced a significant reduction in fungal burden in a mice model of *Sporothrix shenckii* infection [90]. Only two antifungal mAbs have been evaluated in clinical trials, efungumab and 18B7.

2.7.1 Efungumab

Efungumab (Mycograb, Novartis) is a recombinant mAb derived from human-generated antibody to HSP 90, a molecular chaperone used by bacteria, parasites and fungi in response to stressful stimuli, which is located on the cell wall of fungi. HSP-90 promotes formation of resistance mechanisms against azole antifungal agents and caspofungin in *C. albicans* and *A. fumigatus*. Efungumab directly binds the middle domain of Hsp90, thus inhibiting communication between the terminal domains with client proteins at the cell wall, the antibody is not able to cross the fungal wall [91]. HSP-90 inhibition renders fluconazole activity fungicidal in *C. albicans* infection. HSP-90 deletion also causes loss of viability of yeast cells [92]. Antimicrobial susceptibility studies have shown synergy of efungumab with fluconazole, AmB and casopfungin against a wide variety of *Candida* strains [93, 94]. A phase III randomized clinical trial compared the combination of efungumab and liposomal AmB vs AmB alone in patients with invasive candidiasis. Overall, clinical and mycological responses were significantly better in the combination group: *Candida* attributable mortality of 4% in the combination group vs 18% in the AmB only group, suggested a potential advantage of combination therapy. The low response in the AmB group has caused controversy [95].

Efungumab also displays in vitro activity against *C. neoformans*, which has an homologous HSP-90 [95].

Unfortunately, efungumab is no longer in the Novartis pipeline; it was discontinued in 2010 due to unresolved issues. Namely, the tendency to form aggregates during the manufacturing process, the presence of high levels of host cell proteins, which raised concerns about immunogenicity, and that the safety profile could not be established because of uncertainties concerning cytokine release syndrome [96].

2.7.2 18B7

A mAb (18B7) against the capsular polysaccharide of *C. neoformans* was well tolerated a phase I dose-escalation study. A transient reduction in the serum cryptococcal antigen titers was seen at the higher doses; however, mAb 18B7 was not detected in the CSF of any study subject [97]. Clinical efficacy data for this treatment have not been generated.

Adjunctive antibody therapy may enhance the efficacy of antifungal therapy in animal models of infection, providing a rationale for the use of combination therapy clinically.

3 Conclusion

We have reviewed selected molecules in various clinical stages of development in the antifungal pipeline. Despite the paucity of data on newer antifungal candidates since the introduction of the echinocandins, this review describes promising features of several new compounds such as improved bioavailability, a wider variety of formulations, potentially less toxicity, and improved activity against resistant isolates that will hopefully address the urgent need for therapeutic options.

Compliance with ethical standards

Conflicts of interest Relevant to this manuscript, L.O. has received grants, consulting and /or speaking fees from the following companies: Merck, Astellas, Pfizer, Cidara, Scynexis, and Gilead. J.S.O has received research grants from Senosiain, Pfizer, Merck Sharp & Dohme, Sanofi Pasteur, AstraZeneca, and bioMérieux; personal fees from Pfizer, Merck Sharp & Dohme, and Sanofi Pasteur; and non-financial support from Pfizer, Merck Sharp & Dohme, Sanofi Pasteur, and bioMérieux. M.F.G.L declares no conflict of interest.

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