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Perspective

Antifungal Development and the Urgency of Minimizing the Impact of Fungal Diseases on Public Health

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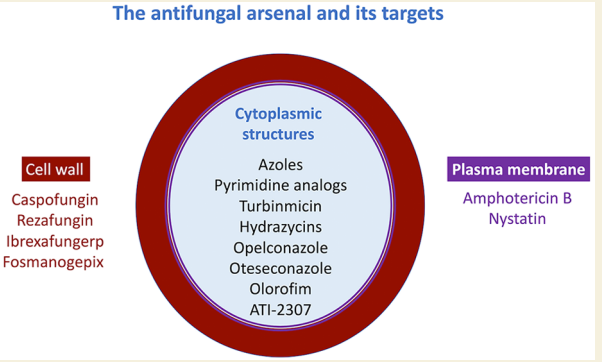
ABSTRACT: Fungal infections are a major public health problem resulting from the lack of public policies addressing these diseases, toxic and/or expensive therapeutic tools, scarce diagnostic tests, and unavailable vaccines. In this Perspective, we discuss the need for novel antifungal alternatives, highlighting new initiatives based on drug repurposing and the development of novel antifungals.



KEYWORDS: *Antifungals drugs, Antifungal pipeline, Fungal infections, Emerging fungal species, Neglected diseases*

THE NEED FOR NEW ANTIFUNGALS

Nearly 6 million different species of fungi exist, and about 600 of them can cause human disease. Fungal diseases represent a health concern, because of high mortality rates and constant problems with antifungal resistance.[1] There are no licensed vaccines to prevent fungal diseases.

Fungal diseases have an extreme impact on public health. More than one million humans die every year from fungal diseases, a dramatic scenario that is aggravated by scarce funding for research,[2] lack of awareness of public health authorities[3] reduced global access to antifungals,[4] antifungal resistance,[5] and insufficient alternatives for accurate diagnosis.[6] The number of cases of fungal infections is still growing, notably in immunocompromised patients, but there are still a few options of treatment and the ones available are linked to high costs and toxicity.[4,7−9] Many mycoses require hospitalization, and the most appropriate drugs for combating them have low availability in territories where fungal infections are more prevalent.[3,9−11] This problem is aggravated by the growing emergence of species resistant to the available therapies.[12−15]

There are four main families of antifungals: polyenes, which bind to ergosterol and produce membrane pores; azoles, which inhibit sterol 14 demethylase and reduce the levels of ergosterol at the plasma membrane; echinocandins, which inhibit the synthesis of β-1,3-glucan in the wall, and pyrimidine analogues, which inhibit the synthesis of RNA and DNA.[16−19] The most frequently used antifungals are all associated with therapeutic failures. Amphotericin B, for example, is highly toxic, and its less toxic pharmaceutic preparations are excessively expensive.[7,9] Among the azoles, an increase in the antifungal resistance has been continuously reported in *Candida* spp., *Cryptococcus* spp. and *Aspergillus* spp.[20−22] Emergence of resistance can be associated with the development of aneuploidy when azoles are used as monotherapy.[23−26] Even the newest azoles, including isavuconazole, which is indicated mainly for the treatment of aspergillosis, candidiasis, and mucormycosis, were linked to the emergence of resistant isolates.[27] The resistance mechanisms are likely similar to those that lead to fluconazole resistance.[27,28] Echinocandins have also been associated with resistance due to amino acid changes in the FKS-subunits of glucan synthase.[16] Monotherapy with pyrimidine analogues drug is also commonly associated with resistance.[29−31] The need for more alternatives to fight fungal infections led to the search for novel drugs and cellular targets. Recently, turbinmicin was identified as a promising and safe antifungal targeting the vesicular trafficking pathway.[32] Other examples include small molecules targeting protein splicing[33] and hydrazycins inhibiting the synthesis of fungal sphingolipids.[34]

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Antifungal resistance is now a topic that necessarily includes *Candida auris,* an emerging fungal pathogen that has gained great importance in recent years due to its intrinsic resistance to antifungals and great ability to spread in the environment, affecting especially immunocompromised patients in the hospital environment.[35−37] *C. auris* was first reported in 2009 at a Japanese hospital and since then, it was associated with disease in more than 30 countries from all continents.[20,37−41] In the US, for example, the Centers for Disease Control and Prevention (CDC) reported a significant increase in *C. auris* infections, from 309 cases in 2013 to 1012 cases in 2018.[42] The impact of the emergence of *C. auris* on public health is directly linked to the fact that *C. auris* can be resistant to azoles, echinocandins, and polyenes.[39,43] In fact, multidrug-resistant (MDR) isolates have been frequently reported worldwide, including resistance to two or more classes of antifungals.[13,44−46] Some of the *C. auris* isolates show an alarmingly low susceptibility to amphotericin B.[12,13,20,35,41,42] In this scenario, drugs affecting *C. auris* growth have been continuously investigated, with considerable progress reported for molecules affecting the fungal mitochondria, plasma membrane, biofilms, and cell wall.[47,48]

Antifungal resistance is not only problematic in *C. auris*. *Aspergillus* species, in particular *A. fumigatus*, are mostly responsible for mold infections, affecting mainly immunocompromised patients.[49] *Aspergillus* spp. frequently cause fatal respiratory diseases.[50,51] In this genus, novel resistant variants of previously susceptible pathogens have been reported.[5] Mold infections caused by non-*Aspergillus* species have also increased significantly, including cases of life-threatening infections.[51,52] Such diseases range from superficial to severe invasive infections including immunocompetent patients.[52,53] *Fusarium*, *Scedosporium*, *Lomentospora*, and mucormycete species are the main causative agents of these mold infections.[41,50,54] Several of them are resistant to the currently available antifungals.[50,54]

The already dynamic picture connecting fungal diseases and public health has become even more complex since the beginning of 2020 with the pandemic scenario of coronavirus disease (COVID-19) caused by SARS-CoV-2. Fungal diseases were associated with COVID-19 mostly in individuals with weakened immune status in intensive care units (ICUs).[55,56] Mucormycosis, a mold infection mostly caused by *Rhizopus* species, was frequently associated with COVID-19 with high morbidity and mortality.[14,57] Diseases caused by *Aspergillus*, *Lichtheimia*, *Mucor*, *Lomentospora* and *Candida auris* also impacted COVID-19 patients negatively.[55,56,58] This complex scenario illustrates the urgency for new antifungal therapies.

A BETTER USE FOR EXISTING TOOLS: THE OPTIMIZED APPLICATION OF THE CURRENTLY AVAILABLE ANTIFUNGALS

A few years ago, Kneale and colleagues claimed that "national governments without access to antifungal drugs should address this health system deficiency urgently to improve clinical outcomes from serious fungal disease", a conclusion based on the striking variability in the price of antifungals between countries.[4] In fact, in developing countries the cost of treating mycoses patients with liposomal amphotericin B can exceed USD 100,000.[9] Amphotericin B and flucytosine are not available in most of the countries that are heavily affected by fungal diseases.[59] This scenario illustrates the need for rethinking the access to antifungal treatment and diagnosis. As previously proposed, rapid diagnostic tools and the rational use of already available antifungal agents would likely have a major impact in reducing deaths.[60]

The successful, rational use of antifungals in clinics demands a plan of access, as illustrated in the case of cryptococcal meningitis. In this disease, it was recently demonstrated that, compared to the treatment currently recommended by the World Health Organization (WHO), a regimen of a single dose of 10 mg/kg of liposomal amphotericin B followed by 14 days of treatment with 100 mg/kg/day of flucytosine and 1200 mg/day of fluconazole had a similar efficacy and fewer adverse events.[61] This observation will likely benefit clinical practice. However, as well pointed out by Falci and Pasqualotto,[62] a major issue is whether this regimen can be made available and affordable in regions that are most heavily affected by cryptococcosis, including the sub-Saharan Africa, Latin America, and Southeast Asia. They properly remind readers that only four countries in sub-Saharan Africa have access to liposomal amphotericin B[62] and it is unavailable in most public health systems in Latin America. The situation is similar, if not worse, for other fungal neglected diseases. Therefore, changes in clinical practice and the development of novel antifungals must be accompanied by a plan of effective implementation for populations that are affected by fungal diseases.

NEW ANTIFUNGAL ALTERNATIVES

More effective, less toxic, and affordable antifungal drugs have the potential to save thousands of lives. The pace of knowledge generation of antifungals is slower than that of, for instance, antibacterial agents.[63] However, in recent years, solid progress has been made in the field of antifungals, as follows below.

DRUG REPURPOSING

Repurposing of drugs consists of finding new applications for already known and clinically approved drugs.[64,65] Repurposing is cheaper and faster than the conventional process of drug development discovery.[66−69] A classic—and the oldest—example of drug repurposing is aspirin, which was marketed in 1899 as an analgesic and first repositioned in the 1980s as an antiplatelet aggregation drug.[70]

In the case of pathogenic fungi, drug repurposing emerged as a promising approach to combat *C. neoformans*,[47,71−74] *Candida* spp. (including *C. auris*),[47,75−82] *Aspergillus* spp.,[83] *Scedosporium* and *Lomentospora* species,[54] the chromoblastomycosis agents *Fonsecaea pedrosoi*, *F. monophora*, *F. nubica*, *Cladophialophora carrionii*, *Phialophora verrucosa*, *Exophiala jeanselmei*, *E. dermatitidis*, and *Rhinocladiella similis*,[84] and the dimorphic fungi *Sporothrix* spp.[85] These studies revealed a collection of molecules with potential to be applied in the treatment of the diseases caused by members of the above-mentioned genera. In fact, examples of antifungal candidates that were clinically tested are available. For instance, sertraline, a selective serotonin reuptake inhibitor antidepressant, showed *in vivo* and *in vitro* anticryptococcal activity.[86,87] The antifungal mechanism of action of sertraline remains unknown. However, a few putative mechanisms have been suggested, including cell death mediated by the insertion of sertraline into the phospholipid membrane layers of intracellular organelles,[88] inhibition of ergosterol synthesis through sertraline binding to lanosterol 14-demethylase

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(CYP51) protein,[89] and alterations in the lipid metabolism.[90] Sertraline was clinically tested as an adjunctive antifungal therapy in HIV-infected individuals with cryptococcal meningitis.[91] Antifungal treatment using sertraline as an adjuvant resulted in faster cryptococcal cerebrospinal fluid clearance with decreased relapse.[92] However, serious adverse events were associated with sertraline treatment, including persistent psychosis and aggressive behavioral changes, which led to treatment interruption.[91] Although sertraline failed to achieve the expected therapeutic effects, novel derivatives of this drugs were recently designed by scaffold hopping, and they showed improved anticryptococcal activity both in vitro and *in vivo*.[93] Similarly, a derivative of haloperidol caused fungal membrane damage and down-regulation of ERG11 and MDR1 genes when used in combination with fluconazole.[94] These observations illustrate how drug repurposing and development of new drugs can be efficiently connected. There are several ongoing initiatives for repurposing drugs against cryptococcosis and other mycoses,[47,68,73,76,95−98] which may result in new therapeutic alternatives in a near future.

ANTIFUNGALS UNDER DEVELOPMENT

In the following paragraphs, we will illustrate the recent activity resulting in candidates for developing novel antifungals.

Inhibition of the 14-demethylase enzyme is a known mechanism of action of the classic azoles and the recently identified antifungals opelconazole (PC945) and oteseconazole (VT-1161). Opelconazole (developed by Pulmocide Ltd., London, UK) is an inhaled triazole presenting wide-spectrum activity against *Candida* (including *C. auris*), *Aspergillus*, *Rhyzopus*, and *Cryptococcus* spp.[99] Opelconazole acts through the inhibition of lanosterol 14-demethylase (CYP51A1), impairing the conversion of lanosterol to ergosterol. Deficient ergosterol synthesis affects fungal membranes and prevents growth.[99] Preclinical studies showed that nebulization with opelconazole resulted in an increased drug concentration in the lungs of rats.[28,99,100] The triazole manifested no safety concerns in preclinical studies[101] and showed persistent action on epithelial cells and hypha *in vitro*. In mice, intranasal treatment with opelconazole was more efficient against *A. fumigatus* than voriconazole or posaconazole.[102] Opelconazole was successfully and safely used to treat a refractory *Aspergillus* bronchial infection in a lung transplant patient.[103] A human clinical trial revealed that opelconazole was well tolerated in both healthy subjects and subjects with mild asthma, with no evidence of acute bronchospasm/irritancy.[100] Phase 2 clinical trials with lung transplant patients are ongoing in the United States (ClinicalTrials.gov Identifier: NCT05037851), which places opelconazole as a promising candidate to be clinically used as an antifungal agent.

Another new antifungal targeting 14-demethylase is oteseconazole (VT-1161), developed by Mycovia Pharmaceuticals, USA. Oteseconazole is an orally administered azole that was recently approved by the U.S. Food and Drug Administration agency (FDA) for the treatment of recurrent vulvovaginal candidiasis.[104] Oteseconazole also showed activity *in vitro* against several fungal species such as *Cryptococcus* spp., Mucorales, *Coccidioides immitis*, *Trichophyton rubrum*, and *Rhizopus arrhizus*.[11]

Rezafungin (CD101) is a second-generation echinocandin[105] that is in Phase 3 of development (ClinicalTrials.gov Identifier: NCT02734862). Rezafungin manifests promising pharmacokinetic/pharmacodynamic properties and, as other echinocandins, acts as an inhibitor of β-1,3-D-glucan synthase, a cell-wall enzyme complex required to maintain the regular cell-wall structure.[99,105] Rezafungin results from the addition of a choline moiety to the echinocandin structure resulting in a higher affinity for 1,3-β-D-glucan synthase.[106] This modification led to a prolonged half-life with improvement of *in vitro* activity against the pathogens *Candida* spp. (including *C. auris*), *Pneumocystis jirovecii*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, and *Aspergillus* spp.[28,106−108] This new echinocandin manifested optimized pharmacokinetic/pharmacodynamic profiles after single or weekly intravenous doses.[28,108]

Ibrexafungerp is a triterpenoid that also targets 1,3-β-D-glucan synthase. The drug was approved by the FDA in January 2021 for the treatment of vaginal infections with *Candida*. Ibrexafungerp is mainly recommended for the treatment of candidiasis among patients with refractory responses to echinocandin and/or azoles. Ibrexafungerp is orally bioavailable, making it the only oral glucan synthase inhibitor developed so far. Besides being active against *Candida* species, ibrexafungerp also controls the growth of a variety of *Aspergillus* species.[28,109−111]

Some of the new antifungals in the development pipeline exert their activities through novel mechanisms of action. Fosmanogepix (APX001) is a novel antifungal that is currently in Phase 2 trial (ClinicalTrials. gov Identifier: NCT04240886). It controls fungal growth through the inhibition of Gwt1, an enzyme responsible for anchoring mannoproteins through the glycosylphosphatidylinositol (GPI) biosynthesis pathway at the fungal cell surface.[112−114] These anchored mannoproteins are essential for fungal adhesion to mucosal and epithelial surfaces within the host prior to colonization.[99] An essential part of the GPI biosynthesis pathway is an acyl transfer reaction that is catalyzed by Gwt1. This enzyme is responsible for adding an acyl group to the inositol unit of glucosaminyl phosphatidylinositol (GlcN-PI), a key step in the biosynthesis of GPI anchors.[114] The active compound of fosmanogepix, manogepix, has broad spectrum activity, including antifungal effects against *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp., *Fusarium* spp., *Scedosporium* spp., and *L. prolificans*.[114−119] Fosmanogepix can reach the central nervous system, which places this drug as potential candidate to fight cryptococcal meningitis.[28,114,120,121] A recent study in mice demonstrated that fosmanogepix is synergistic with amphotericin B against invasive pulmonary aspergillosis, invasive mucormycosis, and invasive fusariosis.[122]

Olorofim (F901318) belongs to the orotomides class of antifungals. Olorofim interrupts pyrimidine synthesis by inhibiting the enzyme dihydroorotate dehydrogenase.[11,123] Dihydroorotate dehydrogenase participates in the *de novo* pyrimidine biosynthesis pathway, which is required for DNA, RNA, protein, and cell wall syntheses.[123] This drug is a potential anti-*Aspergillus* candidate, being active against azole resistant strains.[28,113,124−126] Olorofim also presents activity at relatively low MICs against *L. prolificans* and species of *Scedosporium*,[127] *Histoplasma*, *Blastomyces*, and *Coccidioides*.[28,128] The drug is also active against dermatophytes species such as *Trichophyton* spp., *Epidermophyton* spp., and *Microsporum* spp.[129] Olorofim lacks activity against *Candida*, *Cryptococcus*, and *Mucorales* species. Currently, olorofim is in

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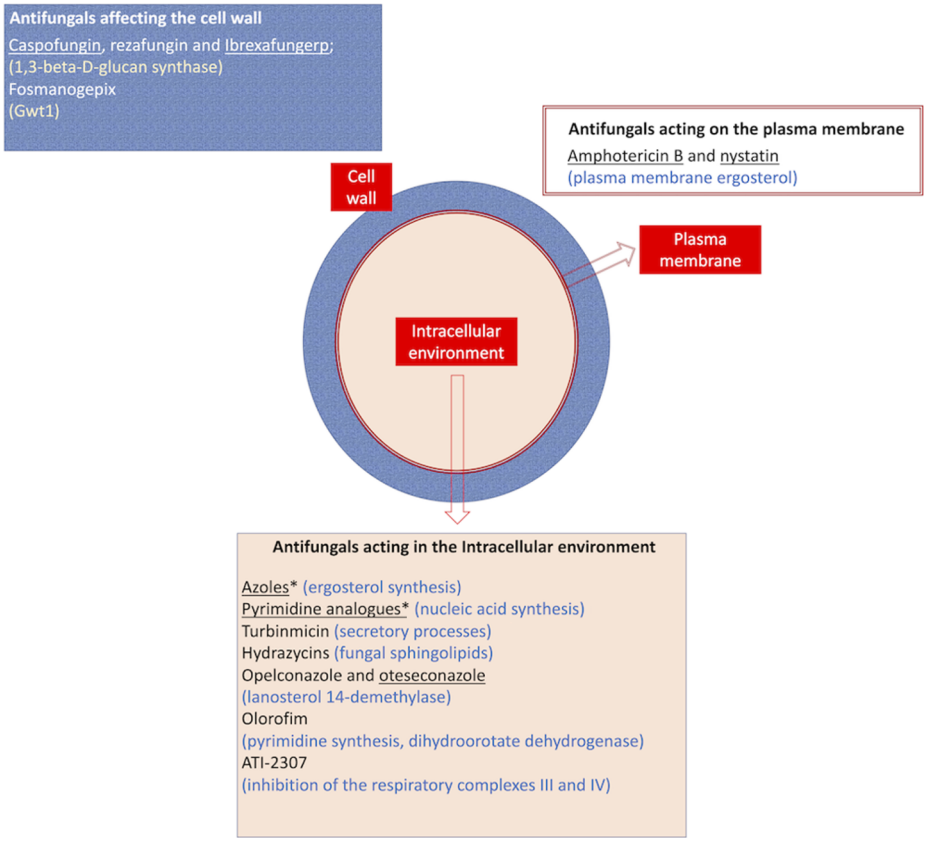

Figure 1. Summary of the current scenario of antifungal therapy. Drugs were classified according to their cellular sites of action, and their targets are described in parentheses. Antifungals that were approved for clinical use were underlined, while the other drugs are under different stages of development. Asterisks denote drug families that have been extensively reviewed before, so individual compounds were not listed. Please refer to Figure 2 for structural details of the listed antifungals.

phase 2 trial for invasive fungal infections in patients without other alternatives, and in phase 3 trial for comparison with amphotericin B for invasive aspergillosis.[28,113,125]

ATI-2307 (T-2307) is an arylamidine that presents antifungal activity against *Cryptococcus* spp.,[130,131] *Candida* spp. including *C. auris*,[131−135] and *Aspergillus* spp.[131] Its mechanism of action requires the inhibition of the respiratory complexes III and IV in fungal mitochondria.[136] This drug reaches the mitochondria through a polyamine transporter related to the uptake of spermine and spermidine. ATI-2307 then promotes disruption of the mitochondrial membrane potential, leading to dysfunction.[136−138] ATI-2307 passed through phase 1 trial.[139] Phase 2 study is about to begin.[113]

PERSPECTIVES

Currently available and under development antifungals are summarized in Figure 1.

The need for changes in the fight against fungal infections is unquestionable. Considering the urgency in improving treatment, prevention and diagnosing of fungal infections, we believe some multidisciplinary actions could attenuate the damage imposed by these diseases on public health. We list below actions that we believe would be beneficial for fighting fungal diseases:

(1) Increase the awareness that fungal diseases are widely neglected, and that programs to fight them are necessary worldwide. In this sense, WHO developed the first global fungal priority pathogens list to define research and development priorities to align investments with public health needs.[140] This is a commendable action that will likely stimulate funding agencies to launch programs to combat the most important fungal diseases. In addition, promoting the teaching of Medical Mycology in undergraduate or graduate programs of medical and biological sciences will likely expand the awareness of fungal diseases at all levels.

(2) Improve funding to stimulate research and technological development in the field of fungal diseases. As already discussed in this manuscript, funding for fungal research is smaller than that available for other areas with similar impact on public health. As scientists in this field, we empirically see that we and other colleagues must compete for funding with scientists from all fields of infectious diseases. Mycology-focused programs aiming at developing tools to prevent, treat and combat fungal diseases will likely have a tremendous impact on the generation of knowledge and innovation in this area.

(3) Make the rational use of already existing tools accessible globally. The understanding that fungal diseases mostly affect neglected populations is essential for the implementation of programs to combat lethal mycoses with governmental support. The clear correlation between low socioeconomic status and incidence of lethal mycoses is an alert to public health decision makers that making tools accessible is not less

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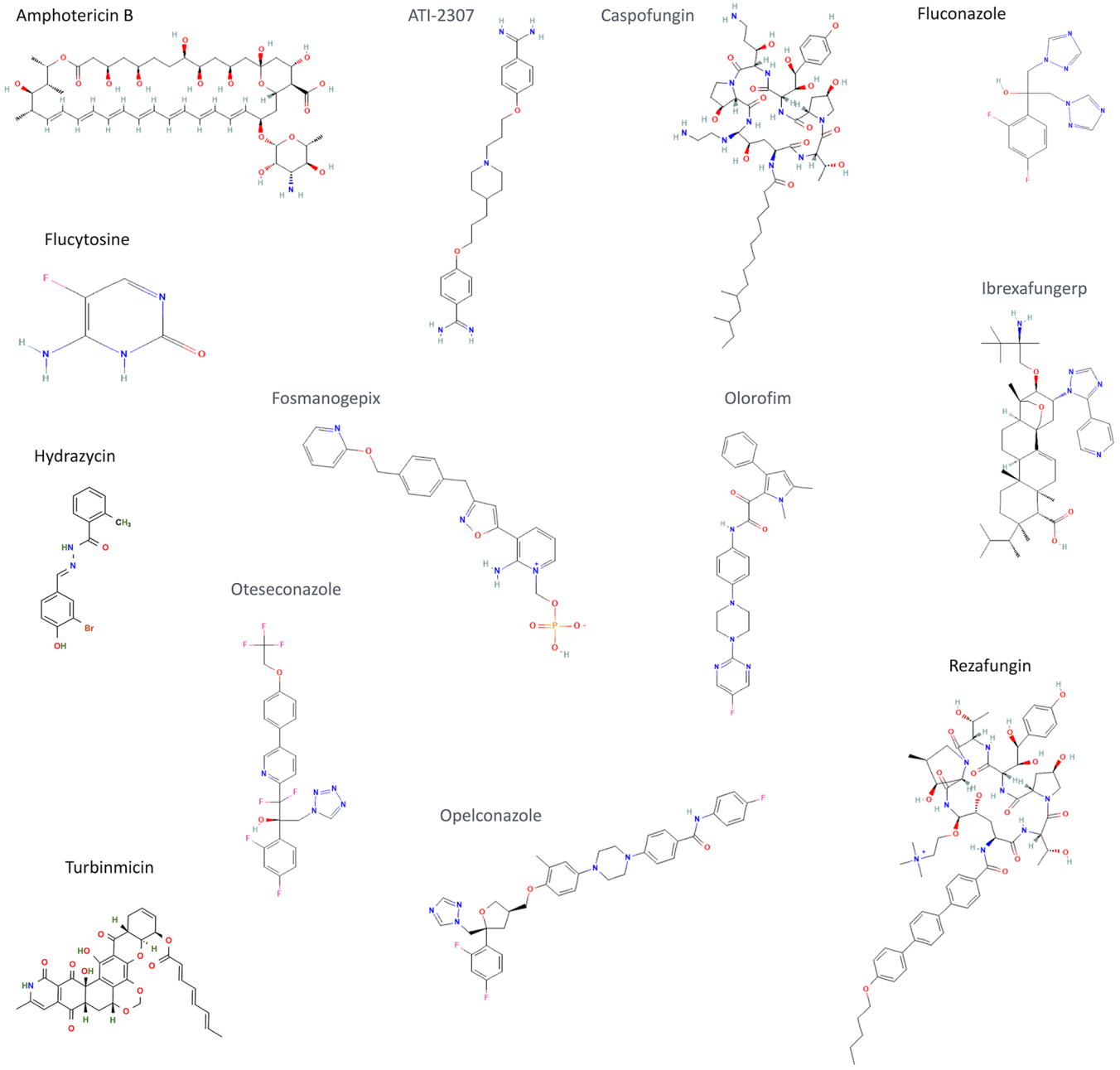

Figure 2. Structural aspects of clinically approved or under development antifungals. Structures were obtained from Pubchem (https://pubchem.ncbi.nlm.nih.gov; no permission for reproduction required, according to the Pubchem citation guidelines; https://pubchemdocs.ncbi.nlm.nih.gov/citation-guidelines). Amphotericin B, fluconazole, and flucytosine illustrate some of the structural aspects of polyenes, azoles, and pyrimidine analogues, respectively.

important than developing and/or using them rationally.

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