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New Biological Targets in Fungi and Novel Molecule under Development: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Antifungal therapeutics is confronted today with the challenge of drug resistance of most fungal germs to current antifungal drugs. Faced with this situation, the search for new and more efficient antifungal molecules that avoid the phenomenon of drug resistance becomes an urgent task. The design of new antifungal drugs acting on new biological targets and/or by innovative mechanisms of action is essential in the fight against fungal infections. Current advances in molecular biology have identified new targets for the development of new antifungal therapy. Several biological targets for the development of new antifungal agents are currently being explored. Amongst these, the most promising are BET (Bromodomain and Extra-Terminal) proteins, Homoserine transacetylase (HTA), mannan cell wall, Glycosylphosphatidylinositols (GPI) anchor biosynthesis, Histone deacetylases, Sphingolipid biosynthesis, D9 fatty acid desaturase and Chitin biosynthesis. This review summarizes the new biological targets and their inhibitors under development as potential new antifungal drugs.

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1. INTRODUCTION

Fungal pathogens are responsible for widespread infections which constitute a major public health problem. It is estimated that approximately 2 million people are ill and 800,000 die each year [1,2]. Fungi are saprophytes of the body surface and mucous membranes (vagina, throat, intestine). However, they can cause fungal infections in humans in certain favorable situations [3,4]. Thus, they can cause localized and/or disseminated or even invasive fungal infections when they develop uncontrollably in the bloodstream or in certain internal organs (kidney, heart, brain) [5,6]. Fungal infections are managed by a group of drugs called antifungal agents [7,8]. This therapeutic arsenal is limited to four classes of antifungal molecules, among which echinocandins and azoles are the most prescribed [9]. The overuse of this therapy has favored the emergence of drug-resistant fungal strains [10,11]. Faced with this alarming situation, several solutions can be envisaged. One is the rational use of fungal drugs that are still effective through good prescribing practices. The other, in the field of pharmacochemistry, is the development of new, more effective antifungal drugs capable of circumventing the chemoresistance induced by fungi. The objective of this review is to provide an overview of new biological targets and antifungal agents under development.

2. CURRENT ANTIFUNGAL DRUGS AND THEIR BIOLOGICAL TARGETS

One of the challenges in the fight against fungal infections is to find an effective and better tolerated antifungal treatment. To date, the four classes of antifungal molecules available for the treatment of fungal infections are polyene macrocycles, fluoropyrimidines, azoles and echinocandins. Their action is to prevent the proliferation of fungi by acting at different levels of the fungal cell: The fungal wall, the fungal membrane and the genetic material.

2.1 Drugs with Action on the Fungal Wall

The wall is the contact zone between the fungus and its environment. It is necessary for the life of the fungus because nutrients are absorbed through this wall. It does not exist in higher eukaryotes, nor in plants, nor in bacteria. The wall is rigid and has a protective role against osmotic pressure variations by maintaining the intracellular oncotic pressure stable against chemical agents (bleach), against solar radiation. It is involved in adhesion phenomena (because it contains sugars which confer these properties). It is also the seat of numerous hydrolytic enzymes (synthesis) which participate in the nutrition of the fungus. It is therefore a potential target for the destruction of the fungus. Only one therapeutic class is currently active on the fungal wall. These are the echinocandins. Echinocandins are lipopeptides of natural origin and hemisynthesis obtained from certain fungi, including *Aspergillus rugulovavus* and *Zalerion Arboricola*. They have fungicidal activity on *Candida* species and fungistatic activity on *Aspergillus* species [12,13]. Structurally, echinocandins are cyclic hexapeptides with a lipid chain attached to the α-amino group of ornithine. They have one of the characteristic amino acids homotyrosine and ornithine. Depending on the number of hydroxyl groups on the amino acids, there are three derivatives from this class of antifungals, which are currently used in therapy. These are Caspofungin, Micafungin (Fig. 1) and Anidulafungin [14,15]. Echinocandins act on the fungal wall by inhibiting β-(1-3)-D-glucan synthase. This enzyme consists of a catalytic subunit FKS and a regulatory subunit Rho1 and is involved in the biosynthesis of β-(1-3) -D-glucan, an essential component of the fungal wall that ensures its integrity and rigidity. Thus, the inhibition of β-(1-3)-D-glucan synthesis confers to this class a fungistatic activity (especially on *Aspergillus*): by blocking the synthesis of the wall, which leads to a stop of the fungus growth. It also has a fungicidal activity (on *Candida*). By losing its integrity, an osmotic instability, which will be at the origin of the fragility and the sensitivity of the wall, appears. This leads to cell lysis and therefore to the death of the fungal cell [13,16-18]. Echinocandins are used for the treatment of digestive candidiasis, invasive aspergillosis refractory to treatment with Amphotericin B or Itraconazole [14,15] Micafungin is used in some cases for the prophylaxis of *Candida* infections [17]. It is particularly indicated for antifungal prophylaxis in bone marrow transplant patients [13-19].

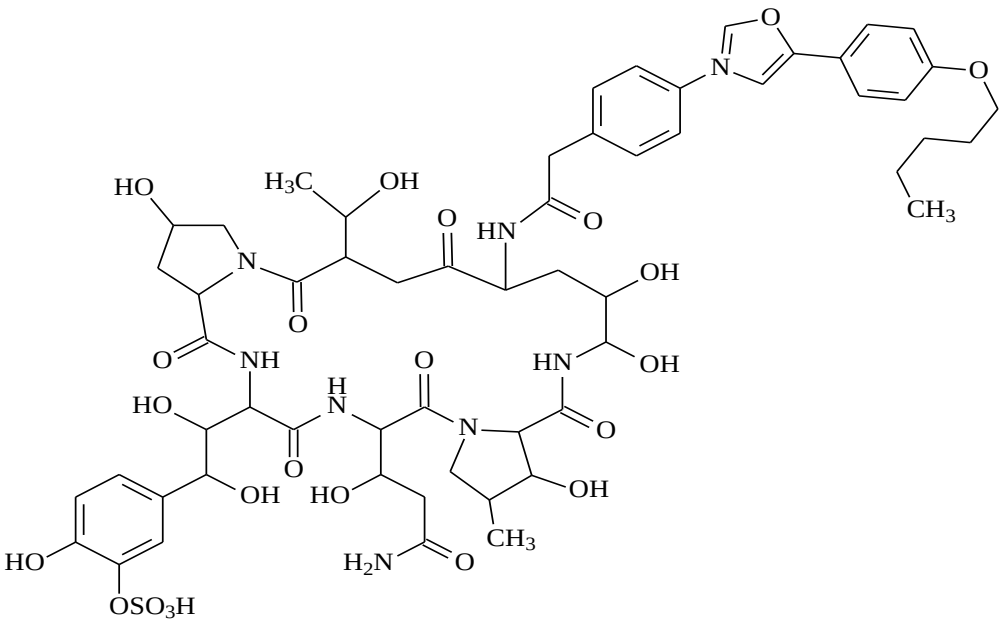


Fig. 1. Chemical structure of micafungin

2.2 Drugs Acting on the Fungal Membrane

Like mammalian cells, fungi have a plasma membrane, also called plasmalemma. It consists of a phospholipid bilayer, proteins and sterols. The main sterol membrane of fungi is ergosterol (equivalent to cholesterol in plants). Because of its essential role in the constitution of the fungal membrane, ergosterol would be an excellent target for molecules. The main chemical classes acting on the fungal membrane are the antifungal azoles and the polyenes.

2.2.1 Antifungal azoles

The azoles constitute a relatively homogeneous family of antifungal agents of total synthesis. They have a therapeutic activity of fungistatic nature. They are by far the most clinically used class of all other classes of antifungals. For 50 years, they have been the subject of constant study and improvement. These molecules are used in the treatment of both local and systemic fungal infections [20]. From a structural point of view, they are divided into two families, depending on whether they have two or three nitrogen molecules in their nitrogen ring (Fig. 2): Imidazoles (two nitrogens) They include Miconazole, Ketoconazole and Econazole. They are characterized by a 5-membered diazotized heterocycle. This heterocycle is always substituted at the nitrogen atom in position 1 by a side chain of β-arylalkoxy β-dichlorophenyl ethyl type. The nitrogen atoms occupy positions 1 and 3. The imidazole structure is present in various natural elements such as histamine, histidine and nucleic acids. The triazoles are Itraconazole, Fluconazole and Posaconazole, which have a heterocycle with 3 nitrogen atoms in their chemical structure. This heterocycle, which is also substituted in position 1 by the same side chain, is most often found in antifungal azoles with a systemic effect [21]. Antifungal azoles act at the level of membrane sterols by blocking the biosynthesis of ergosterol following the inhibition of 14α-sterol demethylase, a cytochrome P450 enzyme responsible for the transformation of lanosterol into ergosterol, which is essential for the construction of the fungal membrane [22,23]. The oxidative reaction would take place as a result of the interaction between the azoles at their pyridine nitrogen atom in position 3 or 4 and the heme iron of cytochrome P450. This complex thus formed would be at the origin of the blocking of the site of occupation of oxygen, hence the oxidative action. The latter would result in ergosterol depletion and accumulation of lanosterol and other sterols methylated [22] at position 14. These changes render the membrane more fragile and alter the activity of several membrane-bound enzymes responsible for the fungistatic activities of azoles. This mechanism of interaction of azoles with cytochrome P450 in both microorganisms and mammals would be responsible for the adverse effects and hepatotoxicity attributed to some azoles such as Ketoconazole. Triazoles have a

broad-spectrum including *Candida*, *Aspergillus*, *Fusarium*, *Penicillium*, *Scedosporium*, *Cryptococcus* as well as dimorphic fungi and dermatophytes in contrast to imidazoles which are only active on *Candida* and *Aspergillus* [24].

2.2.2 The polyenes

Polyenes are cyclic molecules which take their name from the chromophore group which characterizes them. This group is formed by several conjugated double bonds. Thus, polyenes are also called polyene macrolides [25]. They are naturally occurring antifungal agents obtained from bacteria of the genus Streptomyces. They have an amphoteric character, due to the presence of several conjugated double bonds on one side of the ring (hydrophobic character), and hydroxyl groups (OH) on the other side (hydrophilic character) [13]. The two main polyenes used are Amphotericin B and Nystatin. These molecules are amphiphilic but bulky and therefore poorly resorbed [26]. The antifungal polyenes act on the plasma membrane by binding irreversibly to ergosterol. Thus, thanks to its amphoteric character, which allows it to associate with the lipid bilayer of the fungal membrane, it forms pores and channels that increase the transmembrane permeability to monovalent cations such as sodium and potassium. The loss of membrane fluidity leading to uncontrolled exchange of electrolytes (Na^+; K^+) is thought to be the cause of fungal death. Antifungal polyenes are used therapeutically in the treatment of superficial and disseminated mycoses, particularly in oral, digestive, cutaneous and vaginal candidiasis. They are used in deep mycoses, visceral and Candida septicemia, for the treatment of meningitis with *Cryptococcus neoformans*. In addition, they can be used for the prevention of candidiasis in subjects at risk [14,15].

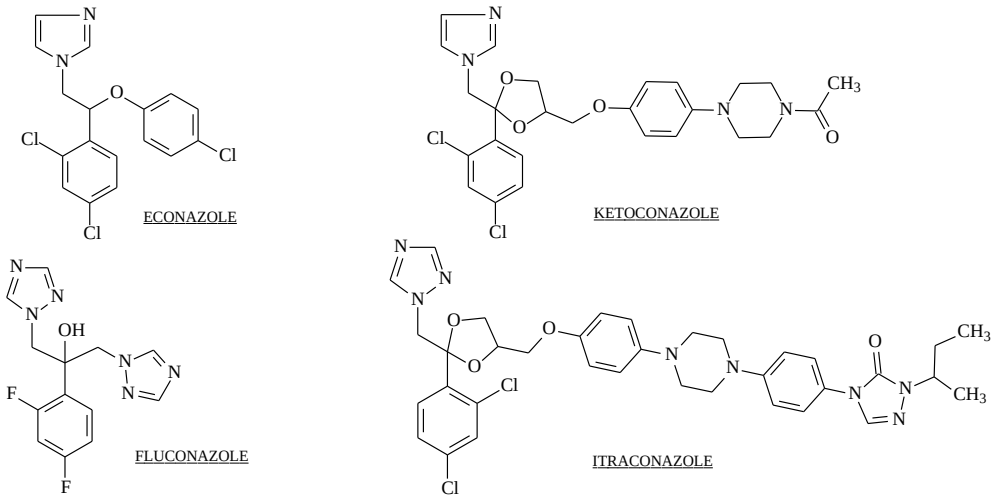


Fig. 2. Chemical structure of some antifungal azoles

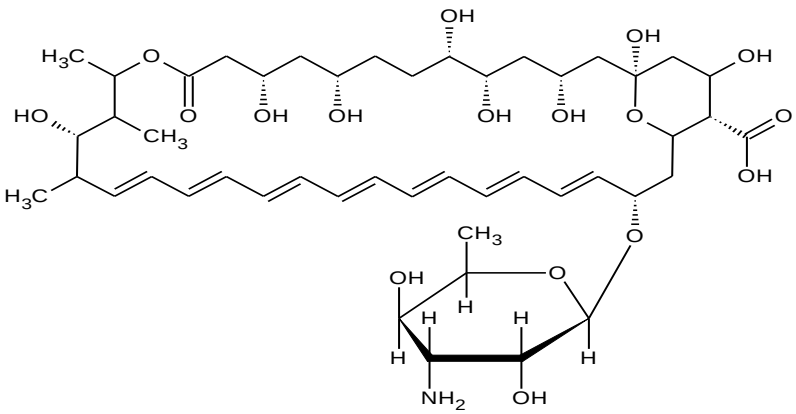


Fig. 3. Chemical structure of amphotéricine B

2.3 Drugs Acting on the Genetic Material

The genetic material represented by nucleic acids, is present at different levels of fungal cells, notably the nucleus and the mitochondria. Fungal cells have a nucleus that is generally small compared to other eukaryotes, about 2 to 3 µm in diameter, with small chromosomes. The nucleus is surrounded by a nuclear envelope that consists of two membrane units separated by a peri-nuclear space. DNA is associated with proteins to form chromatin. These proteins contain histones which are basic proteins of the same nature as those found in other eukaryotic organelles, and heterogeneous acidic proteins. Estimates of the number of chromosomes in fungi are between 2 and 18 haploids. As for mitochondria, they are in the cytoplasm of fungal cells. They appear circular, oval or elongated, but are often branched. Each mitochondrion has a smooth outer membrane and an inner membrane that extends into a ridge that penetrates the matrix. The tricarboxylic acid cycle takes place in the matrix while electron transport and ATP production take place at the cristae. Mitochondria contain DNA that can form a nucleoside in the center of the matrix. This mitochondrial DNA, encodes for some components of electron transport (cytochrome C and adenosine triphosphate subunits), and for some structural RNAs of mitochondrial ribosomes and for some mitochondrial tRNAs. Mitochondrial DNA usually forms 1-20% of the total DNA of the cell. Fluoropyrimidines are the only therapeutic class acting at the nucleic acid level [13-15]. The only representative in antifungal therapeutics is 5-Fluoro-cytosine (5-FC), a structural analog of cytosine. 5-FC acts as a pro-drug via 2 mechanisms. On the one hand, it disrupts protein synthesis by substitution of uracil by 5-fluorouracil (5-FU) in the fungal Ribonucleic Acid (RNA). On the other hand, it alters the biosynthesis of fungal Deoxyribonucleic Acid (DNA) by inhibition of Thymidylate Synthetase (TS). However, for 5-FC to exert its antifungal action, it must first enter the fungal cell, in competition with cytosine, via more or less specific transporters, such as cytosine permease or pyrimidine transporters. It must then be converted into 5-FU by cytosine deaminase. Finally, 5-FU is converted to 5-fluorouridine mono phosphate (FURMP) by uridine phosphoribosyl transferase (UPRT). Thus, this mechanism results in the blockage of cell multiplication [13]. 5-FC is used therapeutically in the treatment of systemic mycoses such as septicemic and diffuse candidiasis, cryptococcosis of meningeal or encephalic location and certain forms of aspergillosis. It has a synergistic action with Amphotericin B [14,15].

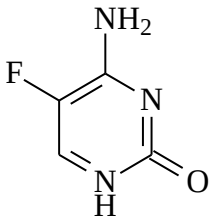


Fig. 4. Chemical structure of 5-fluorocytosine

3. NEW BIOLOGICAL TARGETS AND ANTIFUNGAL UNDER DEVELOPMENT

The efficacy of current antifungal agents is reduced due to the drug resistance of fungi to most antifungal agents. The resulting therapeutic failures are worrying, especially since the proportion of drug-resistant fungi in certain regions can reach more than 20% for some fungal species [27]. One of the major challenges of antifungal drug research is to direct the antifungal drugs under development towards new biological targets with innovative mechanisms of action. This would have the impact of preventing the emergence of cross-resistance while having a synergistic action with existing antifungal drugs. Several new biological targets related to these essential mechanisms of fungal survival are being explored to develop new antifungal agents.

3.1 BET (Bromodomain and Extra-Terminal) Proteins

These BET proteins, which exist in both humans and fungi, are involved in the regulation of gene expression, through a link that allows them to bind to chromatin. Indeed, the cellular genome is organized in the form of chromatin by particular proteins, the histones. Histones can undergo various chemical modifications, including acetylation of their lysines. BET proteins have two particular regions, called bromodomains (BD1 and BD2), whose hydrophobic pocket recognizes acetylated histone lysines. This binding is essential for the action and proper expression of genes [28,29]. In contrast to that of males, the Bdf1bromodomains of the levator have their larger binding pockets. Recent studies have found that Bdf1, a BET protein, is essential for the survival and virulence of *Candida albicans* [30], then *Saccharomyces cerevisiae* [31] and

Candida glabatra [32]. Thus, this protein is a new potential therapeutic target in the fight against fungi. In this same study Mietton et al identified 125 and 44 compounds with selective action for fungal BD1 and BD2 respectively, out of 80,000 different chemical compounds that were tested. In particular, several compounds with a dibenzothiazepinone structure showed IC_{50} values in the micromolar range (from 1.7 µM to more than 20 µM). The structural difference between the bromodomains of the fungal Bdf1 and the human BET protein is thought to be the reason for the selectivity of the activity, without antagonizing the human BET function [30,33].

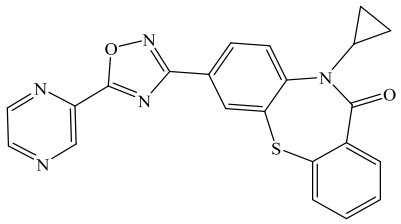


Fig. 5. Chemical structure of dibenzothiazepinone a Bdf1 inhibitor

3.2 Homoserine Transacetylase (HTA)

Amino acid biosynthesis is a promising anti-infective target, as many of these biosynthetic pathways are absent in mammals. In fungi, the methionine biosynthetic pathway from aspartate is one of the targets being explored [34]. Indeed, methionine is an important amino acid because of its involvement in several fungal processes. It is essential for protein synthesis and is the *N*-terminal amino acid of most proteins. In addition, it is involved in the synthesis of *S*-adenosylmethionine (a major methylating agent), DNA and thiol-functional enzymes. Therefore, inhibition of homoserine transacetylase (HTA), the essential enzyme in the first step of methionine biosynthesis is a promising target. In the search for antifungal agents, Yamaguchi et al isolated (S)-2-amino-5-hydroxy-4-oxopentanoic acid (RI-331) from a *Streptomyces* sp. This compound which exhibited antifungal activity on *Candida albicans* was found to be nontoxic in mice. The inhibition of protein synthesis by RI-331 was found to be due to the depletion of several amino acids such as threonine, methionine, isoleucine and serine in the cell pool. These results suggest the possibility that certain steps in amino acid metabolic pathways, particularly those involved in the biosynthesis of threonine, methionine and isoleucine, may be a primary target of RI-331 action [35].

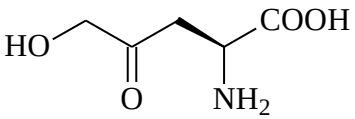
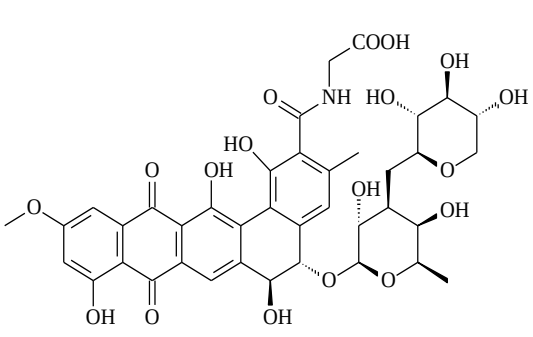


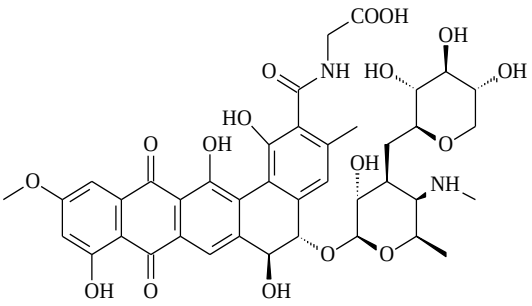
Fig. 6. Chemical structure of RI-331

3.3 Mannan Cell Wall

The cell wall is made of mannans which are polysaccharides composed mainly of mannose monomer. This term also designates the *N*-glycans carried by certain yeast glycoproteins. This mannan, especially its branched form, has been identified as a potential target for certain antifungal agents such as Pramicidine and Benanomycin. Indeed, the binding to the branched mannan would cause a rapid leakage of potassium ions and small cytosolic molecules such as amino acids and nucleic acids leading to the death of the fungal cells [36]. If the development of Benanomycin A was interrupted in clinical phase because of its hepatic toxicity, research is underway to find new molecules capable of inhibiting this biological target.



Pramicidine



Benanomycine A

Fig. 7. Chemical structure of pramicidine and benanomycine A

3.4 Biosynthesis of the Anchor Glycosyl Phosphatidy linositol (GPI)

A glycosylphosphatidylinositol is a glycolipid that allows the anchoring of various molecules, in particular proteins to cell membranes. It is a complex molecule that acts as a membrane anchor. In fungi of the genus Candida, the presence of this GPI anchor is essential for growth, virulence and resistance to macrophages so that different enzymes catalyzing the biosynthesis of the GPI anchor have been proposed as potential antifungal targets. Thus, the inositol acylase encoded by the GwtI gene is one of these targets that were first identified [37] in 2003. The search for an inhibitor of inositol acylase led to the discovery of the compound E1210, which has remarkable antifungal activity in vitro and in vivo. This compound has been particularly successful in the treatment of disseminated candidiasis caused by azole-resistant Candida albicans or Candida tropicalis species. The second target that has been identified is the mannose ethanolamine phosphotransferase encoded by the MCD4 gene. This enzyme is thought to be involved in the final step of GPI formation in yeast. In addition, the mannose ethanolamine phosphotransferase inhibitors M720 and M743 showed a better affinity for this enzyme compared to its human analogue. This makes them a promising target [38].

3.5 Biosynthesis of Chitin

Chitin and glucan are the main constituents of the fungal wall. In fungi, chitin is an essential component of the lateral wall that surrounds and protects the fungal cells from the environment. It would participate in the rigidity of the fungal wall, which is why its biosynthesis is important for the survival of the fungus. Indeed, chitin being absent in mammals, the inhibition of its biosynthesis constitutes a promising biological target for the development of new selective antifungals [39]. To this end, several inhibitors of chitin synthetase (the enzyme responsible for chitin biosynthesis) are being explored. Among these, Polyoxins and Nikkomyxins have been the most studied. Polyoxins and Nikkomyxins are substances of natural origin extracted from various species of streptomycetes due to their structural analogy, they act as competitive inhibitors of chitin synthetase at the origin of their antifungal action. The lack of chitin in the cell wall eventually leads to osmotic lysis and death of the fungus [39]. More recently Ji et al reported the chitin synthetase inhibitory activities of phosphoramidate derivatives of coumarin. Among these, compound 7t (IC_{50}= 0.8mM) was shown to have superior anticandidosic performance compared to polyoxin B (IC_{50}=0.16Mm) [40].

3.6 Fatty Acid Desaturase D9

Unsaturated fatty acids are essential components of fungal cells. In *Saccharomyces cerevisiae*, stearoyl-coenzyme A (coA) desaturase 1 (OLE1) affects cell vitality through regulation of oleic or palmitoleic acid production. Thus, deletion of OLE1 results in an auxotrophic yeast strain (Designated OLE1 KO) that requires unsaturated fatty acids for growth and not saturated fatty acids [41,42]. Furthermore, the production of unsaturated fatty acids (UFAs) by OLE1 KO yeast cells is significantly reduced, suggesting that OLE1 is essential for UFA production. Furthermore, disruption of OLE1 also reduces fungal virulence upon systemic infection. Therefore, OLE1 is a promising antifungal target [43]. Thus, Philipp and al were interested in EV-086 (natural diyne furan fatty acid) as an inhibitor of fungal delta-9 fatty acid desaturation. The latter interferes with the biosynthesis of membrane components like azoles, polyenes and allylamines but by a different mechanism of action. EV-086 has a broad in vitro antifungal spectrum of action directed towards the genera *Candida sp*, *Aspergillus sp* and *Trichophyton sp*. However, its in vivo efficacy has been validated in a fungal infection model against dermatophytosis of guinea pig skin [44].

3.7 Biosynthesis of Sphingolipids

Sphingolipids are essential components of fungal and mammalian cell membranes. Although the structures of these lipids of fungal and mammalian origin are similar, the biosynthetic pathways are different. The difference is in the final steps, namely, the conversion of sphingosine to sphingolipids. The first step of the biosynthetic pathway is catalyzed by inositol phosphoceramide (IPC) synthase, an enzyme located in the golgi apparatus. Inositol phosphoceramide was proposed as an antifungal target after the discovery of Aureobasidin A and Galbonolide A which are potent inhibitors of it [45,46]. Aureobasidin A is particularly active against the genus *Candida sp*, but its mechanism of action remains unknown. Aureobasidin A has also shown activity against the yeast Saccharomyces cerevisiae. In some

Aureobasidin-resistant mutants of *S. cerevisiae*, genome sequencing identified the AUR1 (Aureobasidin Resistance) gene as responsible for this resistance. Furthermore, deletion of the AUR1 gene in resistant mutants is lethal to the yeast. Thus, AUR1 may represent a new target for the identification of IPC synthase inhibiting compounds [47].

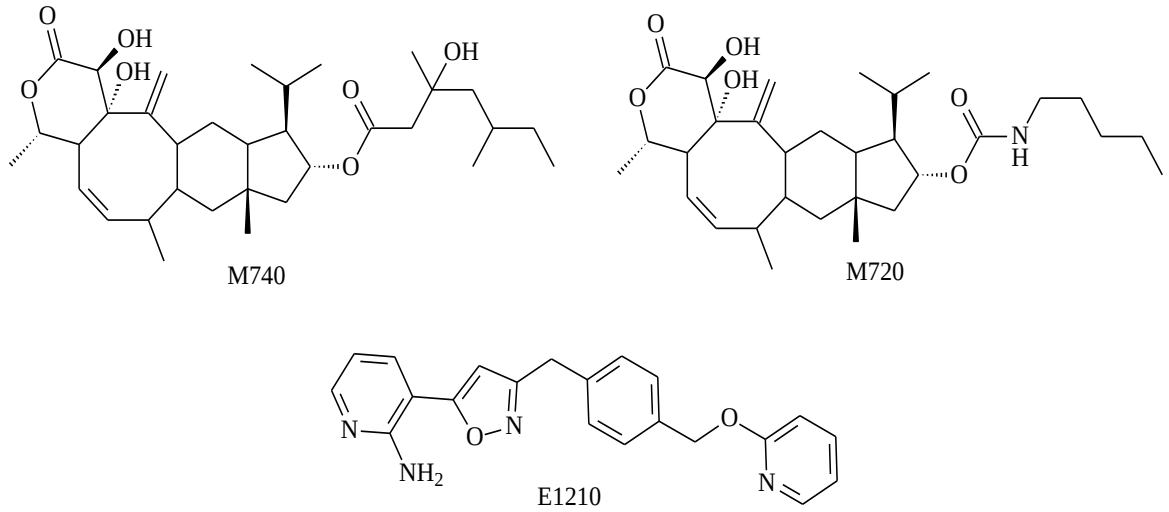


Fig. 8. Chemical structure of compounds M740, M720 and E1210

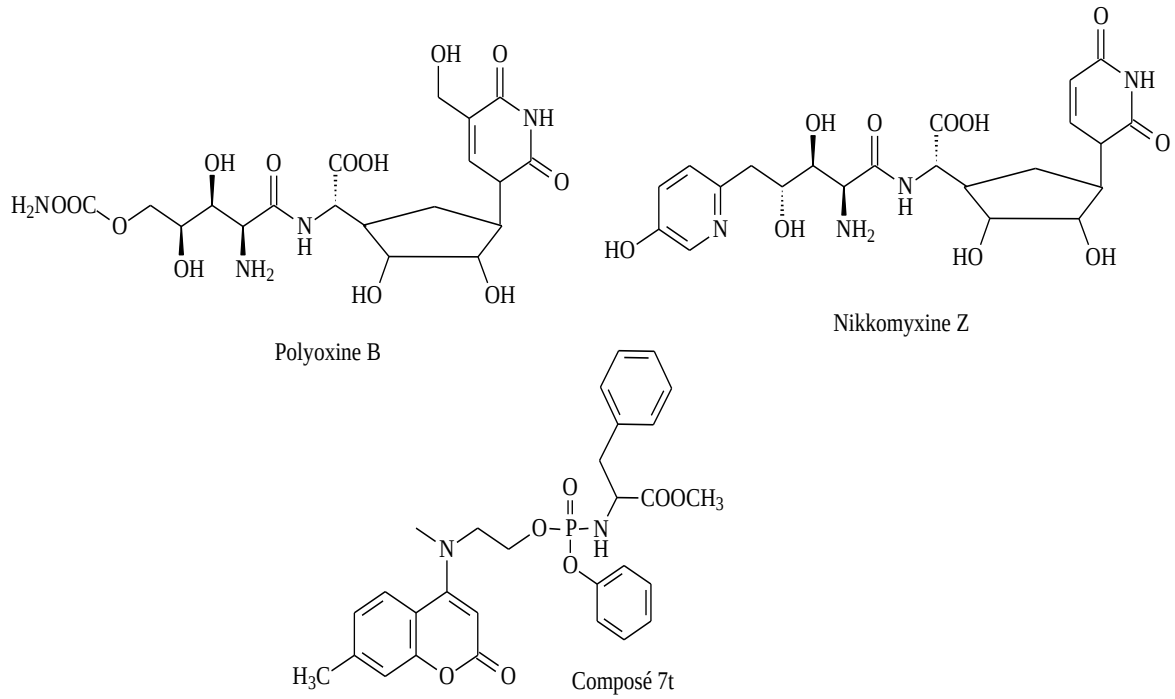


Fig. 9. Chemical structure of Polyoxine B, nikkomyxine Z and compound 7t

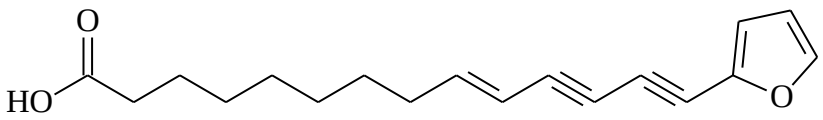


Fig. 10. Chemical structure of EV-086

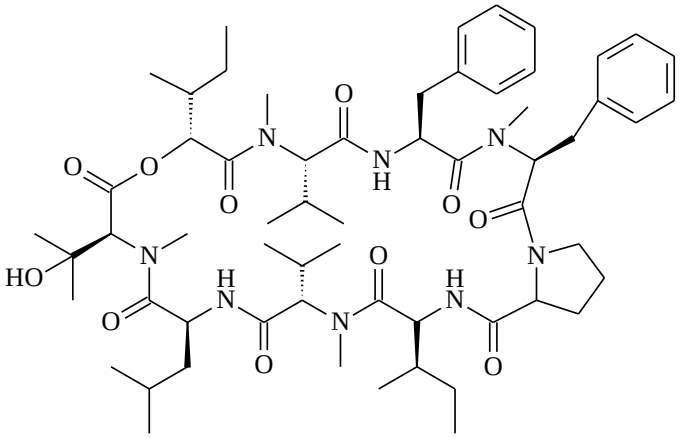


Fig. 11. Chemical structure of auréobasidine A

3.8 Histone Deacetylases

Histone deacetylases (HDACs) are a family of enzymes that deacetylate acetyl-lysine residues at the ends of histones and other proteins. Histone deacetylases are actively involved in the control of the stress response. Their inhibition is thought to limit fungal development, virulence, biofilm formation and dissemination in the infected host. The best known HDAC inhibitor is Trichostatin A, a naturally occurring chiral organic hidroxamic acid from the Streptomyces hygroscopicus strain [48]. Histone deacetylases (HDACs) are a family of enzymes that deacetylate acetyl-lysine residues at the ends of histones and other proteins. Histone deacetylases are actively involved in the control of the stress response. Their inhibition is thought to limit fungal development, virulence, biofilm formation and dissemination in the infected host. The best known HDAC inhibitor is Trichostatin A, a naturally occurring chiral organic hidroxamic acid from the *Streptomyces hygroscopicus* strain [48].

The compound MGCD290, another histone deacetylase inhibitor evaluated by Pfaller et al showed synergy of action with antifungal azoles against opportunistic fungal pathogens including *Candida albicans* [49].

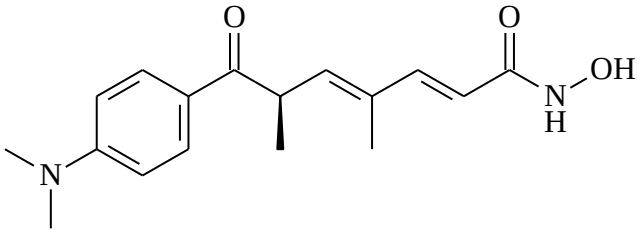


Fig. 12. Chemical structure of trichostatine A

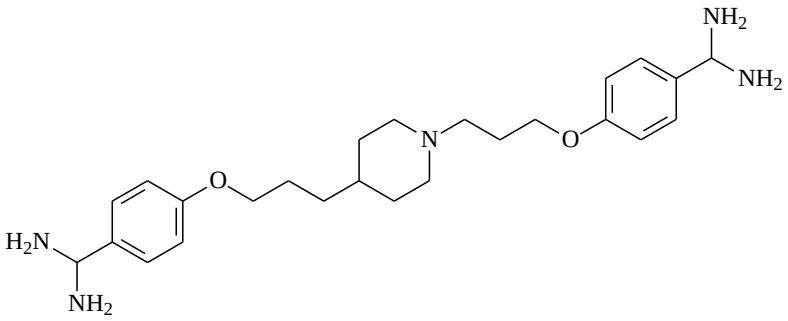


Fig. 13. Chemical structure of compound MGCD290

4. CONCLUSION

The therapeutic arsenal for the management of fungal infections is limited to four classes, of which only two are commonly used. In addition, the emergence of drug-resistant fungal strains further increases the burden of fungal control. However, hope remains with the discovery of new biological targets and the development of new antifungal drugs underway. Current advances in research will soon lead to the development of new antifungal drugs with different and/or innovative mechanisms of action. In addition, understanding the mechanisms of drug resistance to current antifungals should also help to prevent the emergence of new resistance to antifungals in development in the near future.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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