Recent Advances in Antifungal Agents

Tamás Lóránd[1,*] and Béla Kocsis[2]

[1]*University Pécs, Faculty of Medicine, Department of Biochemistry and Medical Chemistry, H-7624 Pécs, Szigeti út 12., Hungary;* [2]*University Pécs, Faculty of Medicine, Department of Medical Microbiology and Immunology, H-7624 Pécs, Szigeti út 12, Hungary*

Abstract: New antifungals are needed in the medicine because of more aggressive and invasive diagnostic and therapeutic methods used, rapid emergence of resistant and new opportunistic fungi, increasing number of patients suffering from immunosuppressive situations e.g., AIDS, transplantation, cancer, etc. Several classes of new antifungal agents are discussed here including some new members of known families. Voriconazole, posaconazole and ravuconazole, are novel triazoles that inhibit the ergosterol synthesis. These drugs overcome problems associated with the ineffectivity of fluconazole against some *Aspergillus* spp. or the variable bioavailability of itraconazole. Echinocandins (caspofungin, anidulafungin and micafungin) represent a new family of antifungal agents that inhibit 1,3-β-glucan synthase. Nikkomycins targeting the chitin synthase, show activity against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Sordarin derivatives that block the fungal protein synthesis can be considered as a promising new class of antifungal agents for the treatment of *Candida* and *Pneumocystis* infections.

Key Words: Voriconazole, posaconazole, ravuconazole, echinocandins, nikkomycins, sordarins.

1. INTRODUCTION

It is a tendency all over the world that the incidence of the mycotic, especially the serious fungal infections (invasive candidiasis [1], aspergillosis [2-3], etc.) has increased during the last decades. It is partly due to the fact that the number of immunocompromised persons is growing: HIV infection, bone marrow and organ transplantation, malignancy and aggressive anticancer drug therapy, etc. are associated with immunosuppression and they can induce opportunistic, life-threatening mycotic infections. To save a patients' life we need quick diagnostic procedures (e.g. galactomannantest [4-5], PCR method for detection of fungi [6], antifungal sensitivity tests [7-8], etc.) to start proper therapy as soon as possible. In this struggle we optimally try to use the old antifungal drugs, sometimes in combinations to diminish the development of antidrug resistance [9]. On the other hand, modification of old drugs to improve their antifungal efficiency and the development of new drugs against novel targets, are continuously needed [10-13].

The antifungal armamentarium applies three classes of natural products (griseofulvin, polyenes and echinocandins) and four families of synthetic compounds (allylamines, azoles, flucytosine and phenylmorpholines) with clinical values against fungal infections. The azoles remain the most widely used family of antifungals against a broad range of mycoses. Recently, the search for new molecular targets for antifungal agents by modern genomic methods has brought considerable knowledge. Some natural antifungal agents were discovered with new mode of actions, including inhibition of the synthesis of the fungal cell wall components. Among these compounds are the β-(1,3)-glucan synthesis inhibitor echinocandins, or chitin synthesis inhibitor nikkomycins, or the inhibitors of mannoprotein synthesis such as pradimycin and benanomycin. In addition some other new targets such as protein synthesis (inhibited by e.g. sordarins), sphingolipid synthesis (inhibitors are e.g. viridofungin or khafrefungin), and mitochondrial electron transport (inhibited by compound UK2) have emerged [14].

This review focuses on some new antifungal azoles and on some new promising classes of antifungal agents (echinocandins, nikkomycins, and sordarins). It should be noted that FDA recently approved three members of the candins (caspofungin **10**, anidulafungin **11** and micafungin **13**) for clinical use. Previously several review articles reported about the developments in this field, one of them written by Vicente and co-workers offered a perspective of this topic [15].

2. INHIBITORS OF THE FUNGAL STEROL SYNTHESIS

The family of antifungal azoles, discovered in the 1960s, is a large class of synthetic compounds that has been extremely popular due to its advantageous properties (broad spectrum, chemical stability, oral applicability). The azoles can be divided into two subfamilies: imidazoles and triazoles. Almost all of the recently developed azoles are triazoles.

The azole antifungal agents block the synthesis of ergosterol, a major component of fungal cytoplasmic membranes. They prevent the 14-α-demethylation of lanosterol into ergosterol in the ergosterol synthetic pathway [16]. Additionally, they may also inhibit the post-squalene synthesis segments such as the oxidosqualene cyclase and the C-24-methyltransferase [17]. The latter step can be promising, because the mammalian cholesterol has no methyl group at C-24. In addition the azoles can also inhibit the last step, the Δ22-desaturase step in some fungal species [18]. Thus exposure of fungi to an azole results in the depletion of ergosterol

*Address correspondence to this author at University Pécs, Faculty of Medicine, Department of Biochemistry and Medical Chemistry, H-7624 Pécs, Szigeti út 12., Hungary; E-mail: tamas.lorand@aok.pte.hu

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and increase of 14-α-methylated sterols [19]. This interferes with the functions of ergosterol in fungal membranes and disturbs both the structure and the functions of the membrane. Because ergosterol also plays a hormone-like ("sparking") role in fungal cells, which stimulates growth [20], the net effect of azoles is the inhibition the fungal growth [21]. A simple schematic representation was provided for the biological mechanisms and pathways mentioned in the article (Fig. **1**).

the individual structure of the azoles. The conformation and inhibition of the active site of P450 enzymes for different fungi species and for mammals are diverse [16] and it will be an important area for the antifungal research. The extent of the antifungal effect of each azole is determined by the exact interaction between the drug and the specific P450 enzyme. In addition some data have been published about the interaction between sterols, azoles and the protoporphyrine active site [22]. The Figs. (**2,3**) depict some of the most significant

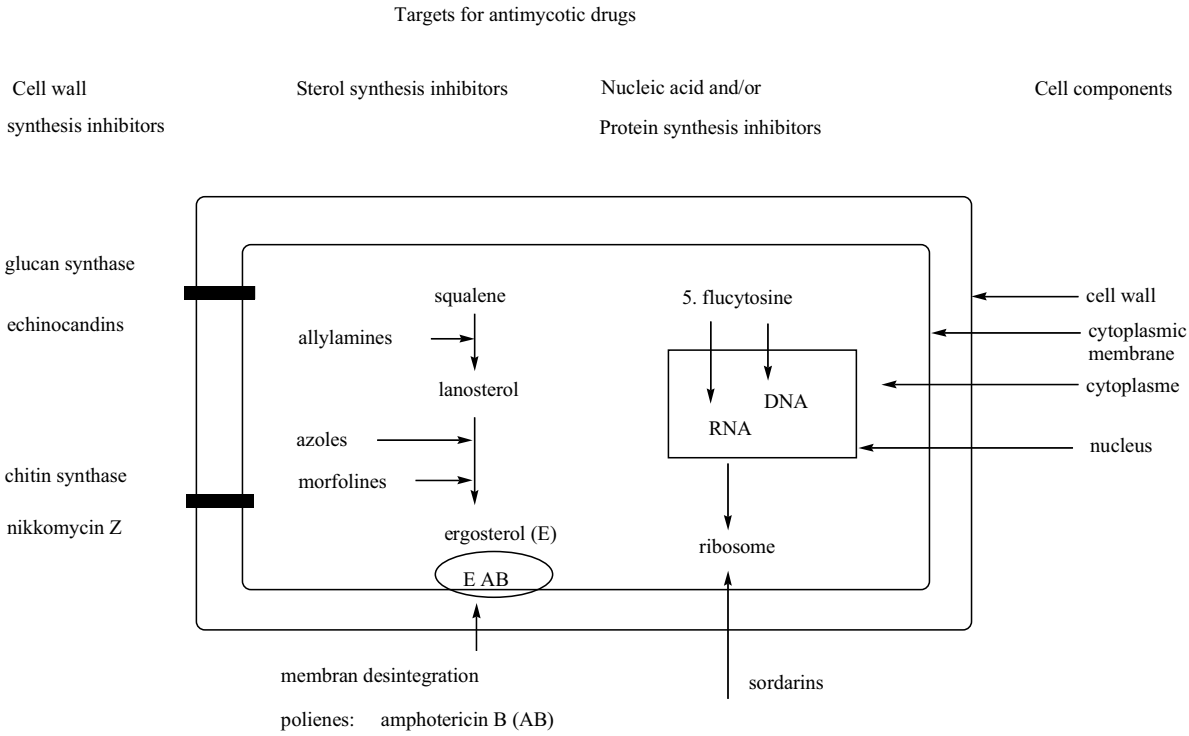


Fig. (1).

The target of these agents is the cytochrom P450-Erg11p or Cyp51p enzyme with monooxygenase activity. Currently there is only one known crystal structure for Cyp51p isolated from *Mycobacterium tuberculosis* [22]. These proteins contain an iron protoporphyrin unit at the active site. The azoles bind to the iron ion *via* the nitrogen atom (N-3 of imidazole or N-4 of triazole). The other part of the azole molecule binds to an apoprotein and this interaction is determined by standard azoles as ketoconazole (**1**), fluconazole (**2**) and intraconazole (**3**).

The new generation of azoles contains a triazole ring to increase the binding to the P450 enzyme. Several modifications were performed in the structure of the azoles. The fluconazole skeleton was modified with an α–O-methyl group yielding agents with anti-*Aspergillus* activity.

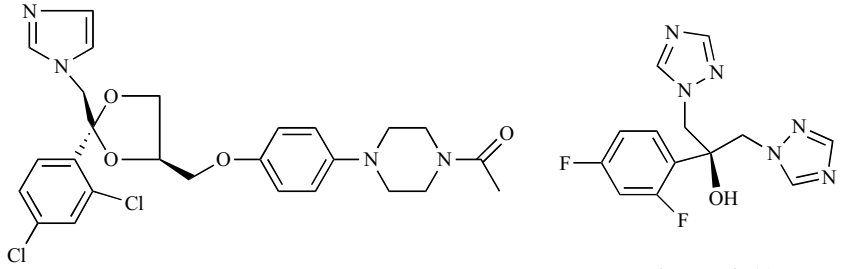
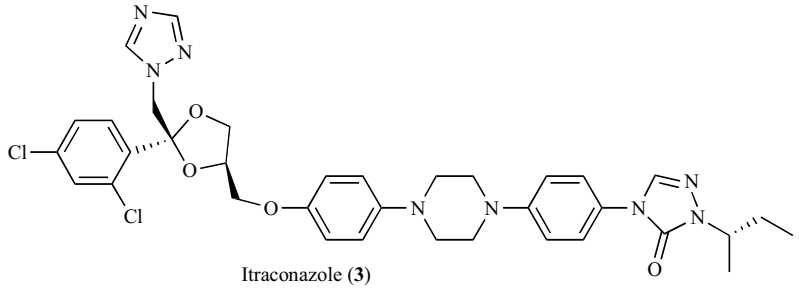


Fig. (2).

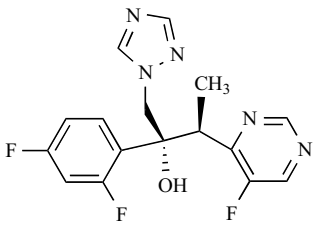


Itraconazole (**3**)

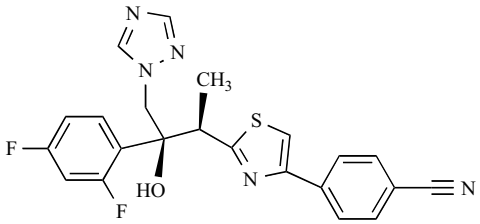
Fig. (3).

The modification of the ketoconazole skeleton, which is the extension of the side chain, enhances the binding of the azole to the P450 apoprotein [23].

The three new triazoles are voriconazole (**4**), ravuconazole (**5**) and posaconazole (**6**) (Figs. **4-5**). Voriconazole is a modern azole related to fluconazole (**2**), in which the triazole ring was replaced with a fluoropyrimidine group and a methyl group was added to the propanol backbone. Voriconazole proved to exert *in vitro* fungistatic effect against several *Candida* spp. (MIC= 0.015-1 μg/mL) [24] and a fungicidal activity toward several *Aspergillus* spp. [25]. In clinical trials this drug showed good *in vivo* efficacy against several fungal pathogens including *Candida*, *Aspergillus*, and *Scedosporium* [26]. Voriconazole is superior to amphotericin B for the treatment of life-threatening invasive aspergillosis [27]. At 3 months, voriconazole-treated patients had a better survival rate (70.8%) than amphotericin B recipients (57.9%) and fewer adverse events were registered except for transient visual disturbances. One great advantage of voriconazole is that it can penetrate the blood-brain barrier and therefore this drug is a good choice to treat central nervous system aspergillosis [28]. *In vitro* studies, animal models and limited clinical reports suggest that combination of amphotericin B and voriconazole may be beneficial against invasive aspergillosis [29]. Voriconazole use in pediatric patients was summarized by Zaoutis [30] and it was suggested that children required higher doses than adults for successful outcome.



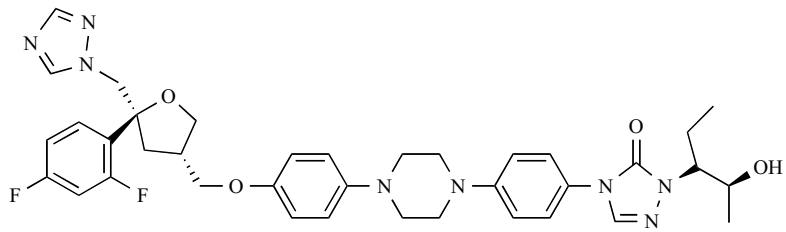
Voriconazole (**4**)



Ravuconazole (**5**)

Fig. (4).

Voriconazole (**4**) has good pharmacokinetic properties (good oral bioavailability) and it is metabolized in the liver by the CYP3A4 and CYP2C19. Because of point mutation in the gene encoding CYP2C19, some part of the populations are poor, while other parts are extensive metabolizers [32]. Therefore, there is a potential for interaction with drugs also metabolized by this system. Thus according to clinical trials voriconazole increased the plasma level of cyclosporine, omeprazole, benzodiazepines etc. [33]. The main side effect included visual disturbances (increased brightness and blurred vision) observed with one third of the treated patients [34]. In addition, the elevation of liver function test (20%), skin



Posaconazole (**6**)

Fig. (5).

rashes and photosensitivity were also mentioned in 1-2 % of patients [35].

A detailed report summarizes the resistance mechanisms of azoles [30]. Several possibilities exist, including increased drug efflux, modification or overexpression of the target enzyme and cholesterol import by *Aspergillus*. In addition, there is an emerging importance of HSP90, a molecular chaperone, playing a role in folding, transport and maturation of regulatory proteins required in stress conditions and in emergence of drug resistance to azoles and echinocandin [31].

Ravuconazole (**5**) is structurally related to fluconazole (**2**) and voriconazole (**4**). This new agent together with voriconazole and posaconazole was studied using 239 clinical isolates of *Aspergillus* spp. and other filamentous fungi [36]. They exhibited excellent *in vitro* activity against these fungi showing higher activity than amphotericin B against *Aspergillus* spp. and offered important advantages over itraconazole (spectrum and potency). In a report from the SENTRY Antimicrobial Surveillance Program (2003) ravuconazole was highly active against pathogenic *Candida* and *Aspergillus* spp. regardless of geographic origin [37]. It was developed for oral administration having a very long half-life time (~100 h) [38] and its toxicity was low with the only reported side effect being headache. In a randomized, double-blind, placebo-controlled study ravuconazole was effective and safe for treatment of onychomycosis [39].

Posaconazole (**6**) was discovered as a hydroxylated derivative of Sch 51048, a structurally resembling compound to itrazonazole (**3**) [40]. Posaconazole is a substrate for CYP 450 enzymes; however, interactions with drugs also metabolized with CYP3A4 system are expected [41]. This drug is a fungicidal agent having broad spectrum and potent activity against pathogens as *Candida*, *Aspergillus*, *Fusarium* spp. (e.g. MIC: *C. albicans* of 0.06 μg/mL, *C. krusei* of 0.5 μg/mL) [42- 44]. Therefore posaconazole can be used for both prophylaxis [45] and salvage therapy of infections caused by a broad spectrum of fungi such as oropharyngeal and esophageal candidiasis, invasive aspergillosis, fusariasis, or especially zygomycosis (mucormycosis). Both adults and children were treated but detailed results of the pediatric patients have not yet been available [30, 46]. Greenberg and coworkers used orally administered posaconazole to treat patients suffering from active zygomycosis with a near 80% success rate. At the same time the drug was well-tolerated. They plan further investigations to evaluate the real role of posaconazole treatment for zygomycosis [47]. The drug's absorption is enhanced by co-administration with food [48] especially high in fat [12]. It has a long terminal half-life (15-35 h) and it is metabolized by the liver. Its adverse effects are mild, including headache and gastrointestinal problems [49].

3. GLUCAN BIOSYNTHESIS INHIBITORS

The fungal glucan biosynthesis proved to be a very good target in the recent history of antifungal agents leading to the development of several new inhibitory agents such as caspofungin (**10**), anidulafungin (**11**) and micafungin (**13**).

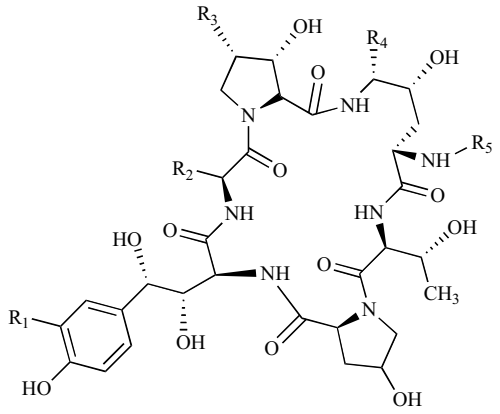
The glucan polysaccharide consists of *D*-glucose monomers attached to each other by β–(1,3)-glucan or β–(1,6)-glucan linkages. This component is essential for the cell assuring important physical properties [50]. Inhibition of the glucan synthase causes a decreased incorporation of glucose to the glucan polymer; thus, the inhibitors cause the lysis of the susceptible fungal cells. The fungal cell wall has no counterpart in the mammalian cells. Therefore it can be an ideal target for the discovery of new antifungal agents. This target of the echinocandins was studied in *Saccharomyces cerevisiae*. In glucan biosynthesis, a transmembran complex of two proteins (Fks1p and Fks2p) is involved that is regulated by a GTP binding peptide, Rho1p. The calcineurin pathway also regulates this procedure [51]. The homologues for these gene products were discovered at the pathogenic *C. albicans*, but the Fks2p homologue was not found in the growing cells [52]. The echinocandins bind to the Fks1p protein as non-competitive inhibitors of the glucan biosynthesis. However, it is doubtful, whether Fks1p is a catalytic subunit or the binding site of the echinocandins to Fks1p is an internal or external to the cell membrane.

Another important role of β–(1,3)-glucan is its immunomodulatory effects. For example it competitively inhibits the macrophage ingestion of a capsular *Cryptococcus neoformans* [53]. Depending on the concentration, it can either induce or inhibit the macrophage release of tumor necrosis factor-α [54].

The echinocandins (candins) discovered in the 1970s from *Aspergillus nidulans* and *A. rugulosus* [55] belong to lipopeptides. They are fungal secondary metabolites, cyclic hexapeptides *N*-acylated with different aliphatic carboxylic acids [56]. All of the following agents belong to the class of candins. Echinocandin B (**7**) has a linoleoyl acyl chain, while the lipopeptides of *Coleophoma empedri* posses a palmitoyl moiety, they are more soluble than the echinocandins. The third group is the pneumocandins, e.g. pneumocandin B (**8**), having a miristoyl unit attached to the ring (Fig. **6**).

The cilofungin (LY121019) (**9**, Fig. **6**) was the first echinocandin B analogue of potent antifungal activity and relatively low toxicity [57]. Its acyl group is a 4-(n-octyloxy) benzoyl side chain. This analogue showed activity mostly against the *C. albicans* and *C. tropicalis* strains. The synthetic modifications aimed to increase of the water solubility and to widen its antifungal spectrum.

The first agent from the pneumocandins was the caspofungin (**10**, Fig. **6**), formerly reported as MK-0991 and L-743,872- approved by the FDA in 2004 [58]. This is a semisynthetic drug, a water soluble aminoderivative of pneumocandin B_0 (**8**). It proved to be a very potent fungicidal agent against *Candida* spp., *Aspergillus* spp. (e.g. *A. fumigatus*, *A. flavus*) [12], *Pneumocystis carinii, Coccidioides immitis, Blastomyces dermatitidis* and *Histoplasma capsulatum* [59], but inactive against *C. neoformans* and *Fusaria* spp. [12]. American scientists have recently performed sentinel surveillance for the emergence of *in vitro* resistance to caspofungin [60]. In clinical studies, caspofungin was mostly used in „salvage" therapy of patients suffering from acute invasive and esophageal candidiasis [11] or aspergillosis. In a study nearly 40% of patients responded to this treatment beneficially. The response to caspofungin was slightly better than that of amphotericin B. Several studies in progress aim to find the proper role of caspofungin in treatment of pediatric patients [30]. The members of the echinocandin class are available only in parenteral formulation and are not metabo-



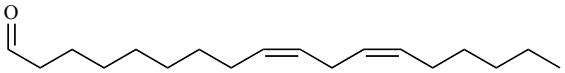
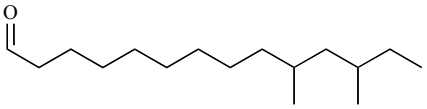
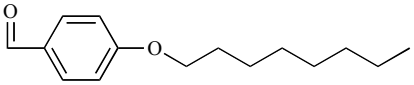
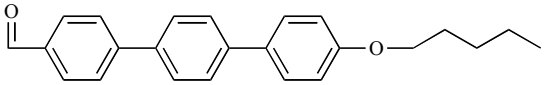
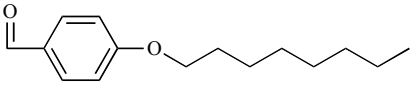
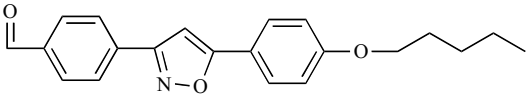
	R_1	R_2	R_3	R_4	R_5
Echinocandin B (**7**)	H	CH_3CHOH	CH_3	OH	
Pneumocandin B_0 (**8**)	H	$NH_2(CO)CH_2CHOH$	H	OH	 = DMM
Cilofungin (**9**)	H	CH_3CHOH	CH_3	OH	
Caspofungin (**10**)	H	$NH_2(CH_2)_2CHOH$	H	$NH(CH_2)_2NH_2$	DMM
Anidulafungin (**11**)	H	CH_3CHOH	CH_3	OH	
FR 131535 (**12**)	$HOSO_3$	$NH_2(CO)CH_2CHOH$	CH_3	OH	
Micafungin (**13**)	$HOSO_3$	$NH_2(CO)CH_2CHOH$	CH_3	OH	

Fig. (6).

lized by the liver. Unlike the azoles they are not substrates, inhibitors or inducers of the cytochrome P450 enzyme [61], therefore, their tolerability is generally good [12]. As regards to the resistance to caspofungin, few *Candida* strains showed decreased susceptibility toward caspofungin because of amino acid mutation in Fks1p membrane protein [62]. In order to find an optimal semisynthetic echinocandin of potent antifungal activity structure-activity relationship studies have been done [63]. According to these studies the optimal activity requires a cLogP > 3.5 and a linearly rigid geometry.

Anidulafungin or V-echinocandin (**11**, Fig. **6)** - also named as VER002, previously known as LY303366 - is a new semisynthetic echinocandin derivative. The acyl sidechain has a terphenyl head and a C5 tail. It was approved by the FDA in 2006 [58] and has a wider antifungal spectrum and lower toxicity than the earlier echinocandins e.g. cilofungin (**9)** [64]. Vazquez reported that this drug showed good activity against *Candida* (e.g. MIC of 0.03-0.25 μg/mL *for C. albicans*, and of 0.12-1.0 μg/mL for *C. krusei*, respectively, etc.) and *Aspergillus* spp. [64-65]. It is available in parenteral administration, while oral formulation is under development [30]. Its half-life (~18 h) is the longest among the echinocandins. It is used for treatment of esophageal and invasive candidiasis. Combination with fluconazole is possible because their target molecules are different [66].

Japanese scientists prepared FR131535 (**12)** having a 4-(n-octyloxy) benzoyl side chain and a sulphate group on the dihydroxyhomotyrosine unit [67]. This water soluble lipo-

peptide displayed a potent *in vitro* and *in vivo* antifungal activity and a decreased haemolytic activity.

Micafungin or FK463 (**13**, Fig. **6)** is one of the most recently available echinocandin derivatives whose usage was approved by the FDA in 2005 [58]. It was prepared by modifications of the natural echinocandin B skeleton, by subsequent enzymatic deacylation followed by reacylation of the hexapeptide with a special isoxazole containing benzoyl-like side chain [68].

Micafungin displayed high *in vitro* fungicidal activity against different *Candida* spp. (*C. albicans, C. tropicalis, C. glabrata, C. kefyr,* etc.) and fungistatic effect against *Aspergillus* spp. But it proved to be as inactive against *C. neoformans* as the other candins [69].

It was also superior *in vivo* compared to fluconazole in murine model upon intravenous injection [70]. It is available in parenteral formulation with a half-life of 12 h. Micafungin (**13)** is comparable to fluconazole in treatment of esophageal candidiasis. Pediatric doses are well-tolerated [30]. It is an optimal agent for prophylaxis of invasive mycoses in high risk patients e.g. undergoing haematopoietic stem cell transplantation [71] and for treatment alone or in combination with other systemic antifungal agents (e.g. itra-, voriconazole) against acute invasive aspergillosis [72].

The search for new inhibitors of the glucan biosynthesis with improved pharmacokinetic properties resulted in a new class of antifungal agents, called acidic triterpenes. This is a unique class of the glucan biosynthesis inhibitors. Some of them are glycosides such as enfumafungin (**14**), isolated from *Hormonema* spp. [73] and ascosteroside (**15**), isolated from *Ascotricha amphitricha* [74] (Fig. **7**). These agents also selectively inhibit the β–(1,3)-glucan assembly. Among them enfumafungin is the most active against pathogenic strains (*C. albicans, C. glabrata, C. guillermondii*, *C. krusei, C. lusitaniae, A. fumigatus*) *in vitro*. However these types of drugs showed a much lower activity against the *C. neoformans* strains.

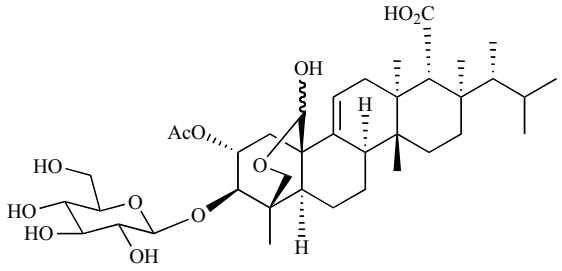
4. THE CHITIN SYNTHESIS INHIBITORS

Chitin is an essential polysaccharide in the fungal cell wall that is important in determining cell shape, for cytokinesis and as a possible antifungal drug target [75]; although percentage of chitin in the cell-wall is only about 1 % [15]. Chitin is a practically insoluble homoglycane polymer consisting of β-(1,4)-linked *N*-acetylglucosamine units. It is well separated from the glucan in the cell-wall, but it is covalently linked to it in order to strengthen the cell-wall. In regards to chitin synthase enzymes of *S. cerevisiae,* three different kinds are known to exist [76]. Chitin synthase I plays an important role in the repair functions, chitin synthase II is involved in the septum formation between the mother and daughter cells, and chitin synthase III is involved in the synthesis of the lateral chitin in the cell-wall. While chitin is essential for the fungi, it is absent in the human organism. Based on these facts the chitin synthesis inhibitors can be rather selective antifungal agents. Therefore chitin synthase signifies an attractive target of the research for antifungal agents. The inhibitors of the chitin synthesis can be considered as peptide-nucleosides, such as nikkomycins and polyoxins. The first group has been isolated from *Streptomyces tendae,* the second one from *S. cacaoi* var. *asoensis*. About twenty compounds belong to the family of nikkomycins, among these the nikkomycin X (**16**) and nikkomycin Z (**17**) (Fig. **8**) show the highest activity.

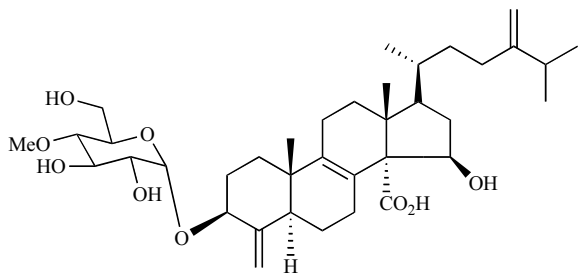
The genes responsible for biosynthesis of nikkomycin Z were determined to improve the quantity and quality of the produced drug [82]. Nikkomycins act as competitive antagonists because of their structural similarity to the UDP-GlcNAc [77] (Fig. **9**). They are practically inactive toward bacteria, plants and animals. In addition they are easily decomposed in the nature [78].

The nikkomycin Z (**17**) is active toward the highly chitinous dimorphic fungal pathogens, e.g. *C. immitis*, *B. dermatitidis* and *H. capsulatum* [79]. This drug can inhibit chitin synthase I and III, but not II of *S. cerevisiae*. It has little to no activity against *C. albicans, C. tropicalis* [38]. This activity depends on the cultural conditions; the components of media [80] can influence the quantity of transporter proteins in fungi [13]. However it is ineffective against *Aspergillus* spp. It can be used in combination with caspofungin showing fungicidal activity against *A. fumigatus*. However, combination of nikkomycin Z with polyenes or triazoles does not induce synergistic effect [81]. In animal models nikkomycin Z could induce some activity [83], but further study is needed to clarify if nikkomycin Z will have clinical usefulness. So far it has only been known that healthy volunteers well-tolerated 2 g of orally given drug [13].

Modifications of the terminal amino acid moiety of nikkomycin Z (**17**) have been made to improve the chitin syn-

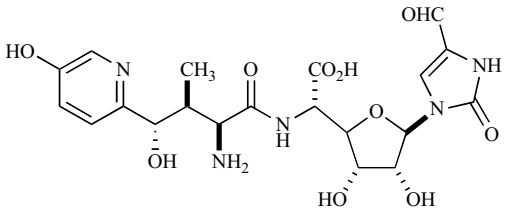


Enfumafungin (**14**)

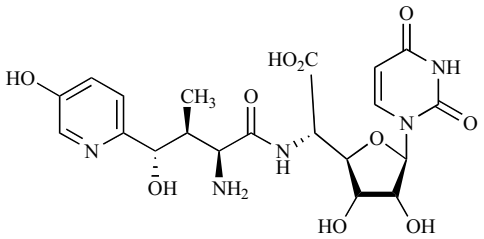


Ascosteroside (**15**)

Fig. (7).



Nikkomycin X (**16**)



Nikkomycin Z (**17**)

Fig. (8).

thase inhibitory activity [84]. Some of the new drug candidates showed good activity against *C. albicans* strains. While the *S*-alkyl-*L*-cystein- and *S*-aryl-*L*-cystein derivatives were weak inhibitors, the *S*-arylmethyl-*L*-cystein derivatives proved to be efficient inhibitors of chitin synthase. By analysing the complementarity between the chitin synthase and the inhibitor, compound **18** (Fig. **10**), containing a hydrophobic phenanthrenyl R group at the terminal amino acid has been reported and proved to be the most effective (IC_{50}= 0.31 μg/mL). French authors have designed some heteroaryl

These facts also prompted the synthesis of the second generation dimeric inhibitors of chitin synthase. Some authors have proposed that there are multiple active sites in the chitin chain with proper proximity and spatial orientation [87]. This structure enables the sequential transfer of two sugar units without the rotation of the chain or the enzyme. If the chitin synthase has two binding site close to each other, then it is possible to increase the binding affinity using dimers containing two UDP units. American authors have published the synthesis of several dimeric chitin synthase inhibi-

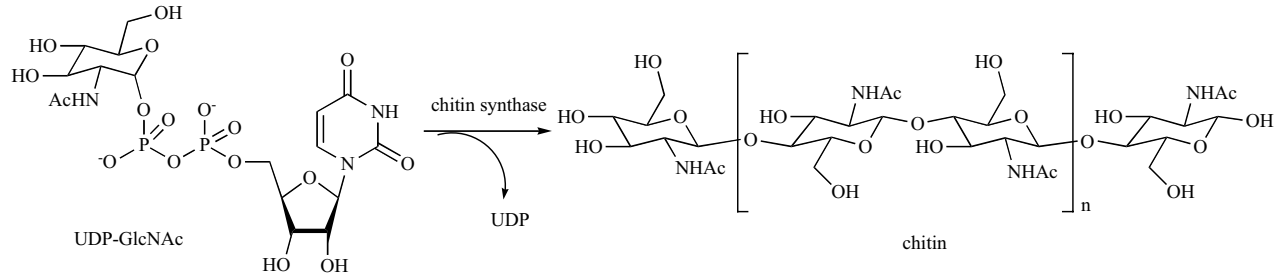
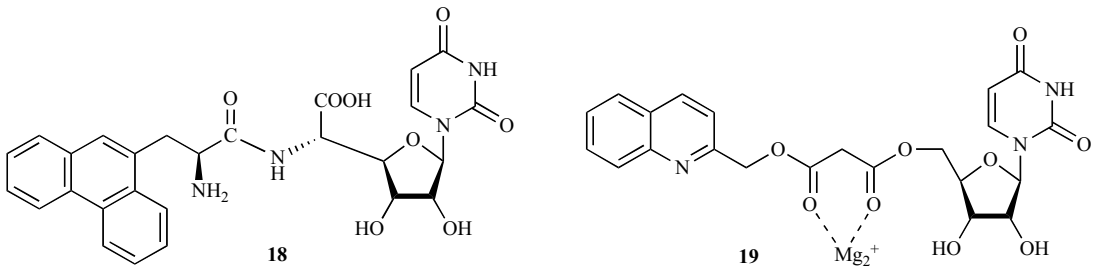


Fig. (9).

nucleoside derivatives of nikkomycin Z [85]. These novel compounds contain an uridin ring attached to a heterocycle (sugar-mimicking group) through different pyrophosphate mimetics. In these compounds the diphosphate group was replaced either with tartaric- or malonic acid units. These analogues of UDP-GlcNAc as **19** (Fig. **10**.) are stable to hydrolysis and they can form similar chelate complexes at the active site of chitin synthase with Mg^{2+} as UDP-GlcNAc. However these UDP-GlcNAc mimetics did not improve the binding affinity compared to nikkomycins [86].

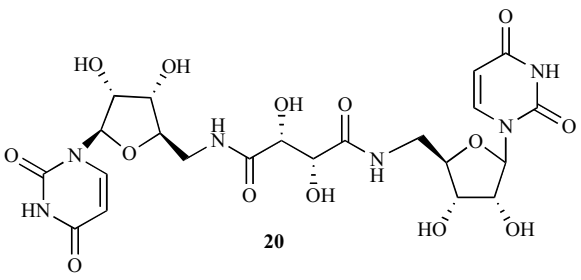
tors [86]. The dimeric amide **20** (Fig. **11**) showed increased activity compared to the monomeric control compound and its activity exceeded that of the analogues with longer linker.

Polyoxins (**22**) are similar compounds to nikkomycins. In their structure next to the uracil polyoxin C building block (**21**), a carboxyl terminal nucleoside amino acid can also be found (Fig. **12**). They show marked selective antifungal effect against the phytopathogenic fungi; however they are inactive toward bacteria, plants and animals [88]. Anti-*Candida* activity of polyoxins is a very complex question.



18 **19**

Fig. (10).

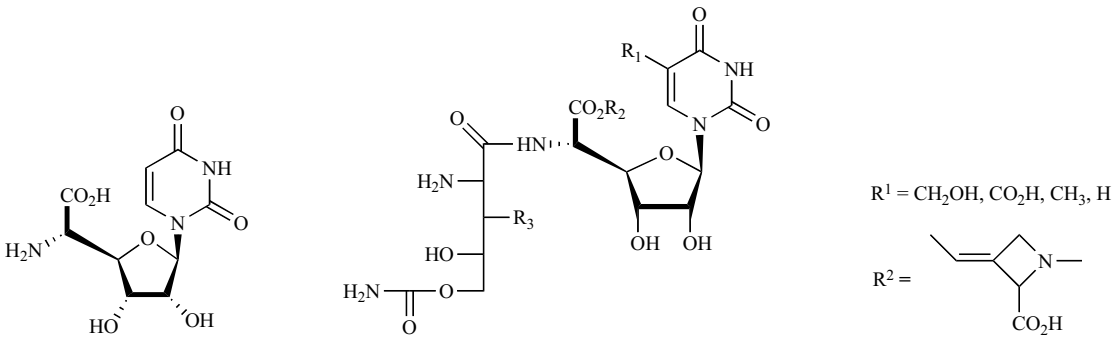


20

Fig. (11).

The intact *Candida* cells are rather insensitive to polyoxins, while the isolated chitin synthase enzymes can be inhibited by them [89]. It has been suggested that the polyoxins can enter the cells by some peptide carriers. Mehta and co-workers demonstrated that growth conditions like type of nitrogen source (amino acid or inorganic source) and presence of peptides can basically influence the MIC values of *Candida* to polyoxins [89].

As a novel class of antifungal agents' sordarins are able to interfere with the elongation step of the protein synthesis. The primary sordarin binding protein is the elongation factor eEF-2 [24, 92-93]. In addition, they stabilize the eEF-2-GDP-ribosome complex. Sordarins are rather selective inhibitors of the translation in fungi [94]. They inhibit *in vitro* translation in *C. albicans*, *C. tropicalis, C. kefyr* and *C. neoformans*. However, they do not show activity against *C. krusei, C. glabrata* and *C. parapsilosis*. These observations suggest a highly specific binding of the sordarins that can also explain the inhibition of the fungal but not mammalian protein synthesis. Sordarins inhibit the protein synthesis of the fungi by blocking eEF-2 differently to fusidic acid which binds both to EF-G (elongation factor G) or eEF-2 that is a general translocation inhibitor [92]. The selective inhibition of the eEF-2 gives an opportunity to design antifungal agents of unique mechanism of action. Several natural sordarins e.g. zofimarin (**25**), have been isolated from *Sopfiella marina* [95] (Fig. **14**). Zofimarin showed activity against *C. albicans, C. neoformans* and a lower activity against *Aspergillus* spp. Therefore several synthetic derivatives [GM193663 (**26**)



Uracil polyoxin C (**21**) Polyoxines (**22**)

$R^1 = CH_2OH, CO_2H, CH_3, H$

$R^3 = OH, H$

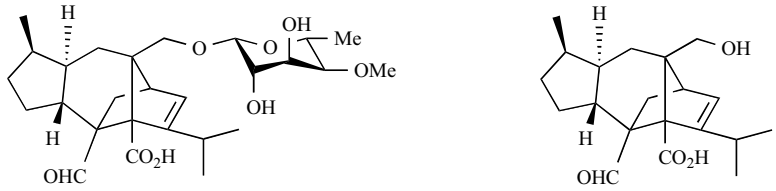
Fig. (12).

5. SORDARINS AS SELECTIVE INHIBITORS OF THE PROTEIN SYNTHESIS

Sordarin (**23**), a fungal metabolite was isolated from *Sordaria araneosa* in 1971 [90]. In its molecular architecture sordaricin (**24**), a tetracyclic diterpene aglycon of norbornane skeleton, is connected to a 6-deoxy-glycoside residue through a β–(1,2-cis)-glycoside linkage (Fig. **13**). The hydrolysis product of **23** yields a novel sugar, 6-desoxy-4-O-methyl-*D*-altrose. Sordarin exhibits potent antifungal activity against several fungi, including *C. albicans* [13, 38, 91].

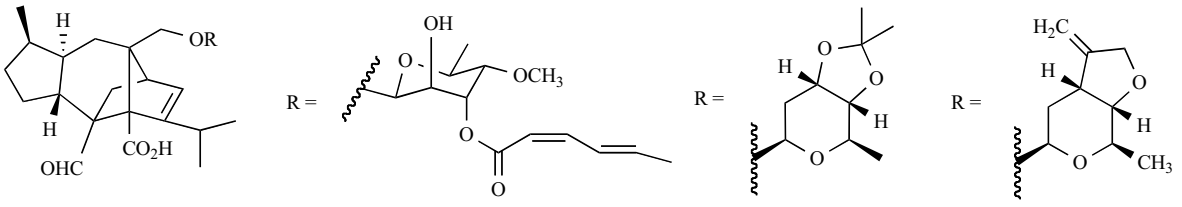
and GM237354 (**27**)] of sordarin have also been prepared (Fig. **14**). These derivatives proved to be potent antifungal agents *in vitro* against *Candida* spp. of decreased fluconazole susceptibility. In addition they were active against the *C. neoformans* and *P. carinii* strains in murine model [96, 97] but showed low activity against *A. fumigatus* strains [98].

The modification of the 6-desoxy-*D*-altrose unit was the aim of several groups. When the sugar unit was replaced with a hydrophobic group (e.g. isopentenyl) the *in vitro* antifungal activity increased [99]. Japanese authors have pre-



Sordarin (**23**) Sordaricin (**24**)

Fig. (13).



Sordaricin (**24**) Zofimarin (**25**) GM193663 (**26**) GM237354 (**27**)

Fig. (14).

pared a number of sordaricin analogues substituted with cyclohexyl ring linked by ether, thioether, amine, oxime, ester or amide, etc. bond (Fig. **15**). Some thioether and oxime derivatives (**28-30**) performed the best against *C. albicans* strains and they showed higher activity than the zofimarin standard against the *C.* non-*albicans* strains [100].

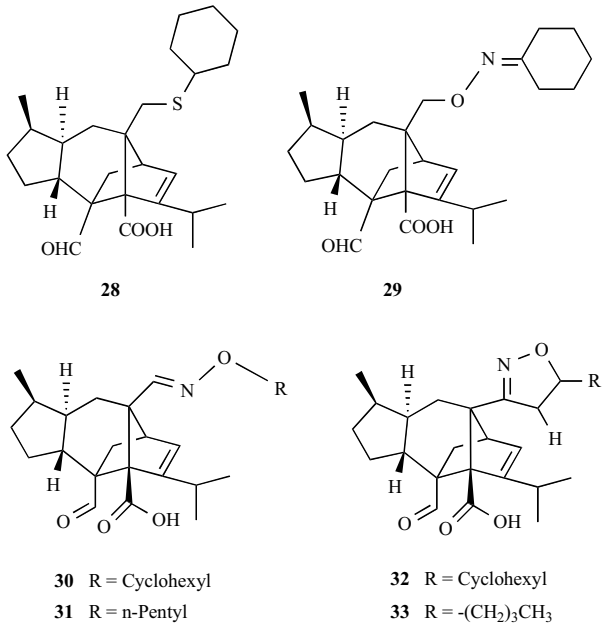


Fig. (15).

Another functionalization of the sordaricin was the replacement of the OH with oxime groups providing sordarin derivatives with hydrophobic sidechains [101]. The incorporation of the lipophilic oxime ether group led to higher activity than that of the natural sordarin. The most potent compound was the *n*-pentyl derivative (**31**) having as low MIC against *Candida* strains as 0.06 μg/mL. However, these oxime derivatives were inactive against *A. fumigatus* and other filamentous fungi. Some conformationally restricted oximes – isoxazoles and isoxazolines (**32-33**) - have also been synthesized, but they were ineffective against all fungal pathogens examined. The difference between the activity of the acyclic **31** and the conformationally locked **33** emphasizes the sterically sensitive interaction between the sordaricin analogues and the EF-2/ribosome assembly.

In order to broaden the antifungal spectrum of sordarin some oxirane derivatives of the sugar moiety have been prepared [102]. The direction of the synthetic project centered on the modification of 2'- and 3' positions (Fig. **16**). From these derivatives the **34** manno-derivative of β-configuration

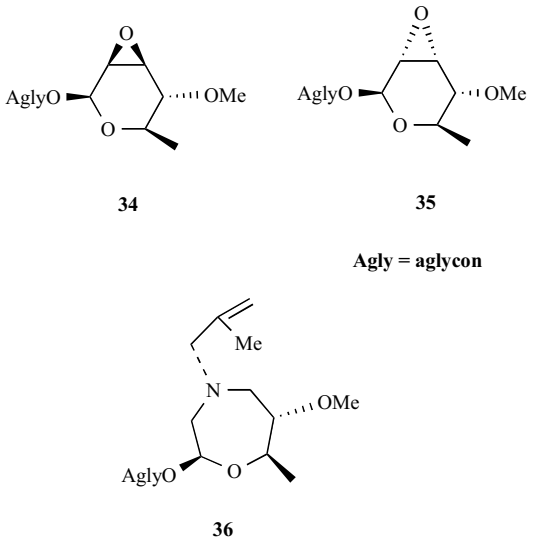


Fig. (16).

around anomeric carbon exhibited the highest *in vitro* activity against the *C. albicans*, *C. pseudotropicalis* and *C. glabrata* strains. The change in the epoxide streochemistry to the allo - configuration (**35**) diminished the bioactivity yielding a narrower spectrum compared to compound **34**. Based on these results the high antifungal activity requires β-configuration around the anomeric carbon. The more lipophilic compounds are better antifungal agents. The sordarins of good *in vitro* antifungal activity have several-fold decreased antifungal effect in the serum. Some Japanese authors designed sordarins with morpholine appendage [103] and with a larger *N*-substituted 1,4-oxazepanyl ring [104]. The *N*-(methylpropenyl) derivative (**36**) performed best against *C. albicans*, *C. parapsilosis*, *C. glabrata, C. tropicalis* and *C. neoformans* strains. In addition it exhibited excellent antifungal activity in a medium supplemented with 20% horse serum.

The synthesis of a new generation of sordarins, specifically the 3',4'-fused alkyl-tetrahydrofuran sordarins, is based on the structure of lead drug candidate GM193663 (**26**). The structural novelty of this group emerges from the replacement of an oxygen atom at the position C3' or C4' by a car-

bon atom [105]. This work afforded two sets of bicyclic compounds containing a tetrahydrofuran ring fused to C3' and C4' (**37-38**, Fig. **17**).

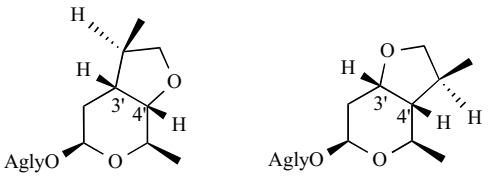
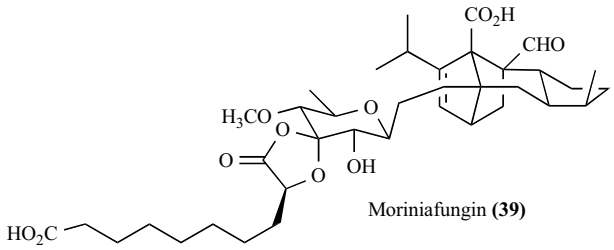


Fig. (17).

Several derivatives showed remarkable activity against *C. albicans*, *C. glabrata,* and *C. tropicalis.* The investigation gave measurable MIC values for *C. parapsilosis* and *A. flavus* strains. The configuration of the substituted carbon plays an important role in the antifungal activity. The isomers with *R*-configuration are more potent than isomers with *S*- configuration.

A novel natural sordarin moriniafungin (**39**, Fig. **18**), was isolated from *Morinia pestalozzioides* [106]. It exhibited an MIC of 6 μg/mL against *C. albicans* and IC_{50} of 0.9-70 μg/mL against other *Candida* strains. Another great progress in this field was the total synthesis of (-)-sordarin [107].



Moriniafungin **(39)**

Fig. (18).

CONCLUSIONS

The significance of fungal infections in medicine is high and becomes higher year by year. Therefore the scientists are forced to improve the old types of antifungal drugs and to develop new ones.

First group of agents described in this manuscript is the second generation of azoles, potent antifungal drugs with expanded spectrum, chemical stability and oral applicability. In spite of their fungistatic activity and long-term hepato- and endocrino-toxicity they offer real alternatives to amphotericin B in treatment (e.g. voriconazole in candidasis, aspergillosis and cryptococcosis) and prophylaxis (e.g. posaconazole in high-risk immunocompromised patient) of invasive fungal infections.

A totally new antifungal class is the echinocandin group: caspo-, anidula- and micafungin are mentioned in this review. They can inhibit the glucan synthesis in fungi. These drugs give a first-line therapeutic option in invasive candidiasis, and a second-line one in treatment of invasive aspergillosis.

Further study is needed to clarify the clinical usefulness of the natural and modified nikkomycins (chithin synthase inhibitor) and sordarins. The latters form another, new and promising groups of antifungal agents. They can specifically inhibit the biosynthesis of fungal proteins by interaction with ribosomal elongation factors.

Huge number of other molecules with antifungal activity have been isolated from natural sources (rustimicin, xylarin, SCH57404 etc.) and modified by synthesis (e.g. azole derivate TAK-157, papulacandin, etc.). Some of them are involved into microbiological investigations and clinical trials. This worldwide research work can guarantee the success in struggle against the challenges of antifungal therapy.

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