

Novel Synthetic Compounds as Potential Anticryptococcal Agents

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Abstract: Cryptococcosis, an invasive fungal infection that affects both immunocompromised and immunocompetent individuals, has emerged as an important public health problem in Africa, Asia, and America. The limited number of antimycotic drugs available to treat this disease, their side effects and toxicity, and the emergence of resistant strains support the search for more effective and less toxic compounds. This review compiles examples of novel synthetic compounds, which could be used as templates for developing novel drugs for the treatment of *Cryptococcus* infections.

Keywords: Antifungal, azole, cryptococcosis, *Cryptococcus*, heterocycles, natural product derivatives, peptide, phospholipidic compounds.

INTRODUCTION

Cryptococcosis is an invasive fungal disease caused by *Cryptococcus* species and accounts for more than 600,000 deaths annually worldwide and is one of the most life-threatening fungal infections in humans [1]. The *Cryptococcus* species are transmitted by inhalation of environmental spores or desiccated yeast cells. *C. neoformans* and *C. gattii* are responsible for most of the clinical cases of cryptococcosis [2]. The primary sites of cryptococcal infection are the lungs and skin, but the most serious manifestation of the disease occurs when they infect the central nervous system, causing severe meningoencephalitis, which is fatal in 100% of untreated cases [3]. HIV-infected patients and other immunocompromised individuals are more susceptible to *C. neoformans* infection, whereas healthy individuals are susceptible to *C. gattii* infection [4]. Cryptococcosis has surpassed tuberculosis as an infectious cause of HIV-AIDS-associated mortality in some parts of the world [5].

In order to reduce the incidence of mortality in cryptococcosis-infected individuals, treatment is critical. However, the number of available antimycotic drugs for treatment of *Cryptococcus*-related diseases is limited.

Combination of amphotericin B (AMB) with flucytosine (5-FC) is the recommended induction therapy for cryptococcal meningoencephalitis, severe pulmonary cryptococcosis, or cryptococemia [6]. AMB is a polyene that binds the fungal cell membrane ergosterol, altering its permeability and allowing the cytoplasmic contents to leak out, leading to cell death. Despite its effectiveness, its well-known side effects and toxicity, especially nephrotoxicity, limit its usage [7]. Furthermore, amphotericin B requires intravenous administration, limiting its use in areas without medical infrastructure. 5-FC is a pyrimidine analog, which is converted into 5-fluorouracil (5-FU) within the cytosol of susceptible fungal cells. 5-FC itself has no antifungal activity; however, 5-FU causes RNA miscoding and inhibits DNA synthesis. Unfortunately, 5-FC is not widely available in most of Africa and Asia where the disease burden is highest [8]. In resource-limited settings, fluconazole (FCZ) constitutes the primary treatment of cryptococcal disease in AIDS

patients. FCZ shares the same mechanism of action as that of other azole compounds, which will be discussed later. Nevertheless, cases of fluconazole resistance in cryptococcal disease has been reported [9]. A few novel molecules effective against *Cryptococcus* are being pursued partly to avoid the increased cost of developing a novel antifungal agent from the initial stages of drug development. Therefore, repurposing drugs commonly used in medical clinic is an attractive approach to identifying novel anticryptococcal agents since it could potentially reduce the cost and time of drug development [10].

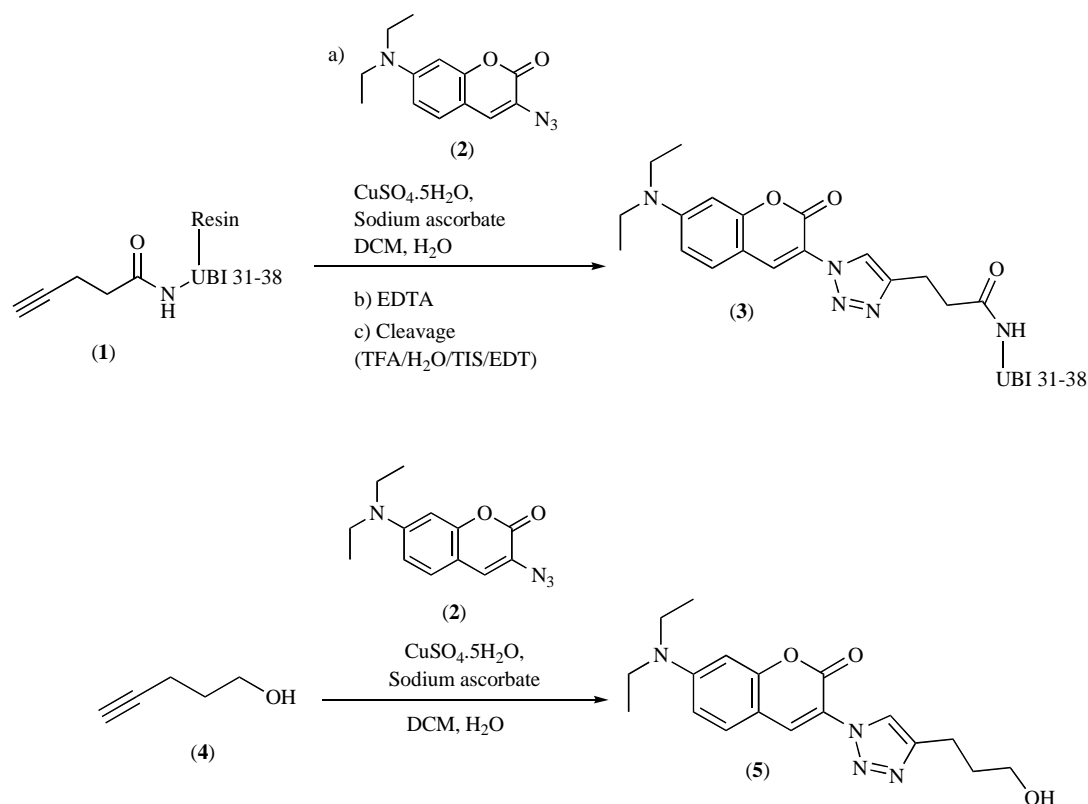
The aim of this review is to identify promising scaffolds for the development of novel anticryptococcal agents. Our efforts were focused on synthetic substances with similar or superior potency than the standard antifungal agents. The potential anticryptococcal agents were grouped in the following five classes: i) peptide-based agents, ii) azole-based agents, iii) non-azole heterocycles, iv) semi-synthetic derivatives of natural products, and v) phospholipidic compounds, among others.

PEPTIDE-BASED AGENTS

Antimicrobial peptides (AMP) offer an ideal blueprint for future therapies for a range of fungal diseases [11]. AMP are low-molecular weight proteins with a broad spectrum of antimicrobial activity [12]. AMPs constitute a major component of the natural defense system and are produced by microorganisms as well as multicellular organisms of both the vegetal and animal kingdoms [13, 14]. AMPs possess a diverse portfolio of structures and a broad-spectrum of activity, having decreased propensity for the development of resistance by the target cells as well as a distinguished antifungal mechanism of action when compared with the standard antifungal agents [15, 16].

The antifungal activity and consequent therapeutic potential of AMPs have been recognized since the 1990s. To date, five antifungal peptides have reached the clinical stage of drug development and currently, four of these clinical trials are ongoing [11]. Various strategies have been used to develop more efficient antifungals from parent peptides. For instance, Belaid and Hani [17] synthesized shorter analogues of the peptide dermaseptin S4 (DS-S4; a constituent of frog skin secretion) to improve its biological profile. Although DS-S4 has antimicrobial activity, its use is limited owing to its high hemolytic activity. The analogs S4(1-16)a (ALWKTLLKKVLLKAAAKNH₂) and DS-S4(1-12)a (ALWMTLL

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Scheme 1. Synthesis of the anticryptococcal peptide-coumarin conjugate.

KKVLKNH₂) exhibited the highest activity against *C. neoformans* (MIC <2 µg.mL⁻¹). In addition, structural modification attenuated the hemolytic activity (>250 and 64 µg.mL⁻¹, respectively) compared to the hemolytic activity of DS-S4 (16 µg.mL⁻¹).

Lactoferrin is a natural defense iron-binding protein known to possess antibacterial, antimycotic, antiviral, antineoplastic, and anti-inflammatory properties [18]. A modified peptide sequence (CFQWKRAMRKVR; HLOpt2) based on amino acid residues 20-31 of the *N*-terminal of human lactoferrin (hLF) was investigated *in vitro* for activity against *C. neoformans*. The HLOpt2 exhibited higher fungicidal effect (minimum microbicidal concentration = 12 µg.mL⁻¹) than its natural counterpart HL10 (CFWQQRNMRKVR) (MMC = 50 µg.mL⁻¹) and the parental hLF peptide (MMC > 2000 µg.mL⁻¹) [19].

Penetratin is a synthetic cell-penetrating peptide derived from the third helix of the homeodomain of the Antennapedia protein of *Drosophila melanogaster*, with a positive charge of 8. Penetratin and a series of related peptides were synthesized and tested for their efficacy against fungal pathogens [20-22]. The peptide HFRWRQIKIWFQNR[O]KWKK-NH₂ was the most active derivative against *C. neoformans* ATCC 32264 since it inhibited fungal growth by 95% at 6.25 µM [21].

Masman *et al.* [23, 24] synthesized and tested novel tetra- and octapeptides structurally related to fragments of α -melanocyte-stimulating hormone (α -MSH), which is reported to have both anti-inflammatory and antimicrobial effects [25]. The most prominent peptide (HFKWGRFV-NH₂) inhibited *C. neoformans* growth by 95% at 25 µM.

The conjugation of AMPs to non-peptide bioactive compounds represents another approach for the development of novel antifungal agents. Indeed, our group [26] synthesized, *via* copper(I)-catalyzed azide-alkyne cycloaddition, a novel peptide-coumarin conjugate 3 (Scheme 1) and investigated its potential as an an-

ticryptococcal agent. As for the synthesis, an alkyne-decorated peptidyl resin (UBI 31-38) 1 and 3-azido-7-diethylaminocoumarin 2 were chosen owing to their antimicrobial properties [27-29]. The novel conjugate exhibited antimicrobial activity against *C. gattii* and *C. neoformans*, and also against a fluconazole-resistant strain of *C. gattii*. The peptide-coumarin conjugate 3 was active in the range of 0.04 to 0.18 µmol.mL⁻¹. Its subunits, peptide UBI 31-38, the alkyne-decorated peptide UBI 31-38, and 3-azido-7-diethylaminocoumarin, as well as a coumarin-triazole analog 5 were less active, suggesting that the peptide, coumarin, and triazole moieties have a synergistic effect. Treatment of *C. gattii* with the peptide-coumarin conjugate enhanced the production of reactive oxygen species leading to an oxidative burst that may play an important role in the microorganism growth inhibition [26].

Avrahami and Shai [30] presented a novel approach based on bioconjugation of synthetic lipopeptides with antifungal activity. Lipophilic acids of different lengths were attached to the *N*-terminus of magainin, an antibacterial peptide isolated from the skin of *Xenopus laevis*. The main goal of the above study was to increase peptide hydrophobicity and its ability to self-associate without altering the properties of the peptidic chain. Palmitic acid-magainin conjugate was the most active compound against *C. neoformans* with an MIC value of 1.56 µM, which was much lower than that of an analog of magainin (magainin-2; MIC > 50 µM) [31].

Arnusch *et al.* [32] designed a small series of amphiphilic compounds consisting of trimeric histidine-histidine dipeptides conjugated to fatty acids of various lengths, using the triazacyclophane (TAC) scaffold (Fig. 1). The anti-*C. neoformans* activity of compound 7 was pH-dependent; anti-*C. neoformans* activity was observed at pH 5.5 (MIC = 3.12 µM) and the compound was inactive at pH 7.5 (MIC > 100 µM). In addition, compound 7 was nontoxic to murine macrophages even at 200 µM. The pH-dependency of the

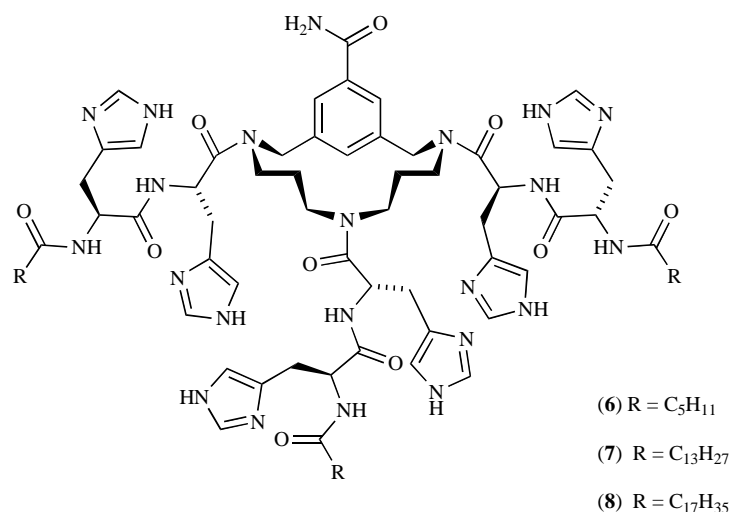


Fig. (1). Structures of pH-dependent trivalent ultrashort peptides.

lipopeptide activity was previously reported by Makovitzki and Shai [33]. According to these authors, the positive charge of histidine-containing lipopeptides plays an important role in controlling cell-specific activity at different pHs.

It is noteworthy that in general, native lipopeptides possess a broad spectrum of antimicrobial activity. Some lipopeptides from the echinocandin class such as caspofungin, micafungin, and anidulafungin are already used in clinics; however, they are not active against *C. neoformans* [34].

Combinatorial chemistry is another strategy used for the identification of peptide-based antimicrobial agents. Dubbed AMT1 **9** and cyclo-AMT1 **12** are hexapeptides that were identified from a synthetic combinatorial library [35]. Based on the antifungal properties of AMT1 peptides, Grimaldi *et al.* [36] synthesized the analogues AMT2 **10**, cyclo-AMT2 **13**, AMT3 **11**, and cyclo-AMT3 **14** (Fig. 2), which bear one or two more His residues than the parent AMT1s. All synthesized peptides were active against *C. neoformans*, with MIC₉₀ values comparable to that of fluconazole (2-64 µg.mL⁻¹). In this study, the cyclopeptides were, in general, more active than their linear homologues. The superior antifungal profile of such cyclopeptides might result from the appropriated orientation of the side chain of the amino acid residues, which optimize the peptide-membrane interactions, and/or their improved stability against proteolytic degradation [36].

AZOLE-BASED AGENTS

The antifungal activity of benzimidazole was described for the first time in 1944 [37]. However, development of novel azole compounds as antifungal drugs gained increased interest in the 1960s [38]. Although the discovery of ketoconazole in 1978 represented an important advance from the earlier imidazole derivatives, triazole analogues gained attention owing to their low susceptibility to metabolic degradation, enhanced target specificity, increased potency, and broad spectrum of activity [39-41]. Currently, four triazole-based compounds (fluconazole, itraconazole, posaconazole, and voriconazole) are used in clinical settings for prophylaxis and/or treatment of systemic fungal infections [42].

Azole antifungals are competitive inhibitors of the fungal cytochrome P450 sterol 14 α -demethylase (CYP51), which catalyzes a key step in the biosynthesis of ergosterol, a yeast-specific sterol that plays an important role in the permeability and fluidity of fungal membranes [43].

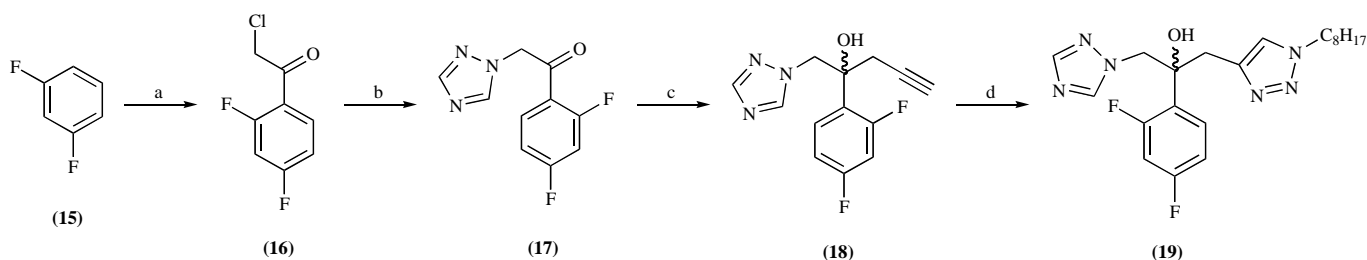
The broad use of azoles has led to the appearance of fungal plant and human pathogens with decreased susceptibilities or development of resistances to various azoles antifungals [43-45]. Moreover, several drawbacks of the commercially available azoles, such as narrow spectrum, low oral bioavailability, and hepatic toxicity, remain to be overcome, requiring the ongoing search for novel azoles [46].

Since, azole derivatives are considered to be the most rapidly expanding group of antifungal compounds [47], we do not aim to cover all related publications in this review, but to briefly discuss the most notable novel azole derivatives having activity against *Cryptococcus*.

Triazoles have two possible structural isomers, *i.e.*, 1,2,4-triazole and 1,2,3-triazole. The synthetic methodologies to prepare 1,2,4-triazole have been previously reviewed and will not be discussed here [48-52]. Regarding the available methods for the synthesis of 1,2,3-triazoles, copper(I)-catalyzed azide-alkyne cycloaddition ("click" reaction) [53, 54] is the most widely used method for the synthesis of such class of heterocycles.

Pore *et al.* [55] synthesized the conjugates fluconazole/bile acid employing a click reaction as a key-step. The goal was to synthesize novel bioconjugates having the amphiphilic nature of bile acids and the antifungal activity of fluconazole. However, the novel conjugates presented a weak anti- *C. neoformans* activity (MIC values from 12.5 to >50 µg.mL⁻¹) when compared to fluconazole (MIC = 1.0 µg.mL⁻¹). This research group [56] also synthesized fluconazole analogues containing long alkyl chains in the 1,2,3-triazole ring (Scheme 2). Compound **19** had the highest activity against *C. neoformans*, with MIC value of 0.002 µg.mL⁻¹.

In an attempt to find novel antifungal triazoles, Konosu *et al.* synthesized the compound CS-758 **20** (Fig. 3; known also as R-120758) [57], a novel 1,2,4-triazole bearing a 1,3-dioxane ring, which proved to be a potent anti-*C. neoformans* agent *in vitro* and *in vivo*. Triazole CS-758 has a lower MIC value (MIC \leq 0.008-0.016 µg.mL⁻¹) than fluconazole (MIC = 1-16 µg.mL⁻¹), itraconazole (MIC = 0.016-0.12 µg.mL⁻¹), and amphotericin B (MIC = 0.12-0.25 µg.mL⁻¹). Dose values of the CS-758 that successfully treat 50% of the animals (ED₅₀) infected with *C. neoformans* TIMM1855 and TIMM0362 were 3.1 and 5.0 mg.kg⁻¹, respectively; while ED₅₀ of fluconazole for these two strains were 45 and 50 mg.kg⁻¹, respectively [58].



Scheme 2. Synthesis of 1,2,3-triazole containing fluconazole analogue **19**. Reagents and conditions: (a) AlCl_3 , 1,2-dichloroethane, chloroacetyl chloride; (b) 1,2,4-triazole, NaHCO_3 , toluene; (c) Zn, propargyl bromide, DMF/THF; (d) 1-azidooctane, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (5 mol%), sodium ascorbate (40 mol%), DMF/ H_2O (4:1).

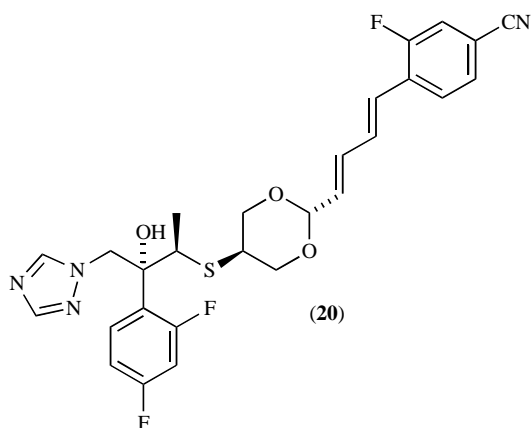


Fig. (3). Chemical structure of CS-758 [R-120758 (**20**)].

In several studies [46, 59-66], molecular modeling has been used for the rational design of novel antifungal 1,2,4-triazole derivatives. A series of novel compounds was synthesized using an oxirane triazole **21** as key intermediate, and many of them demonstrated activity against *C. neoformans* (Scheme 3).

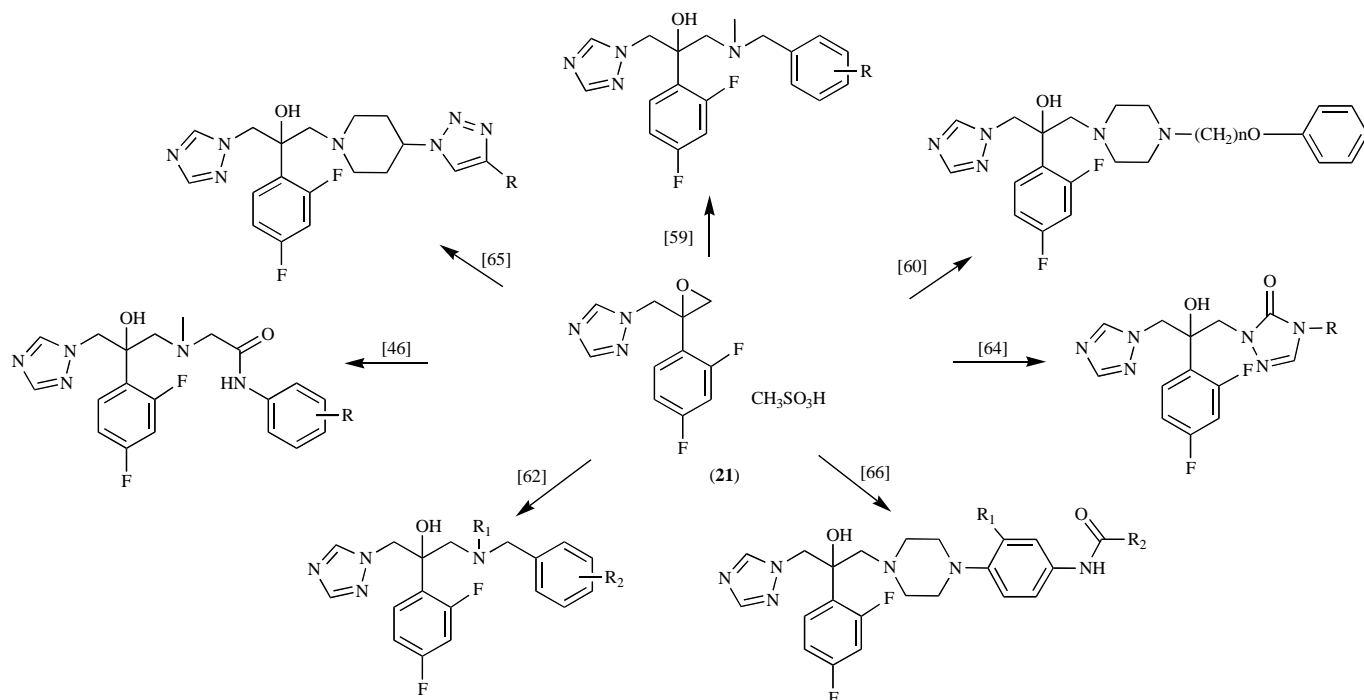
For instance, Xu *et al.* [66] synthesized a series of novel 1,2,4-triazole derivatives bearing a 4-(4-substituted-phenyl) piperazine

moiety, with compounds **22** and **23** (Fig. 4) being the most active against *C. neoformans* with MIC values comparable to that of voriconazole ($\text{MIC}_{80} = 0.0156 \mu\text{g} \cdot \text{mL}^{-1}$).

Activity against *Cryptococcus* was also demonstrated for other classes of azoles, including imidazole [67-71], thiazole [72-75], tetrazole [76, 77], oxadiazole [78], and pyrazole [79].

NON-AZOLE HETEROCYCLES

Benzofuran scaffolds have potent biological properties. Studies show that these compounds exhibit promising antifungal activity by inhibiting the enzyme *N*-myristoyltransferase (Nmt) [80-82]. This cytosolic monomeric enzyme catalyzes the transfer of myristate from myristoyl-CoA to the *N*-terminal glycine of a number of eukaryotic cellular proteins and viral proteins and has been proven to be essential for the viability of important pathogenic fungi, including *C. neoformans* and *C. albicans* [83, 84]. Thus, Nmt has been identified as a potential chemotherapeutic target for the development of novel fungicidal drugs with a new mode of action [80]. In 2003, Masubuchi *et al.* synthesized a number of novel benzofuran derivatives with potent antifungal activity, based on the promising inhibitory activity presented by compound **24** (Fig. 5) against *C. albicans* Nmt [85]. Analogue **25**, named RO-09-4879, proved to be the most active compound of the series, with a MIC ($6.9 \mu\text{mol} \cdot \text{L}^{-1}$) that is about six-fold lower than that of fluconazole (MIC of 41.0



Scheme 3. Synthesis of 1,2,4-triazole derivatives using the oxirane intermediate **21**.

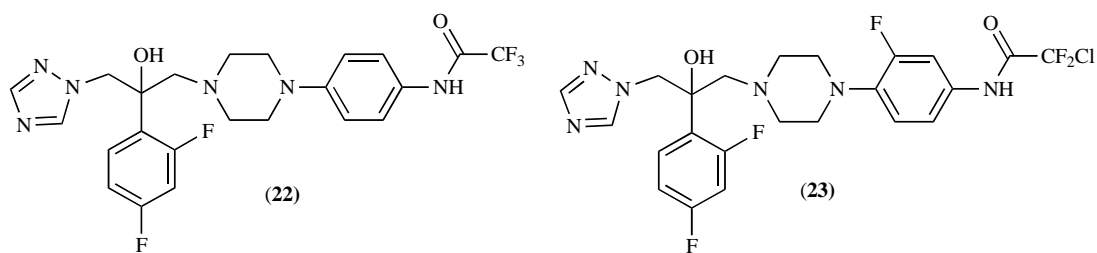


Fig. (4). 1,2,4-triazole derivatives with a 4-(4-substitutedphenyl) piperazine side chain active against *C. neoformans*.

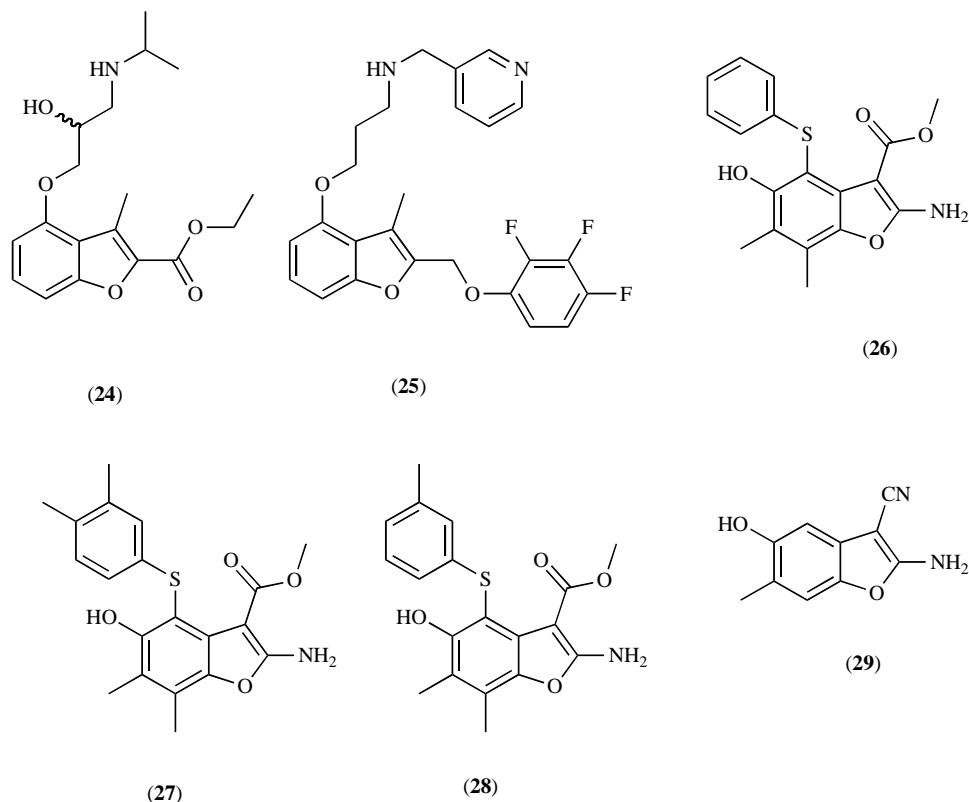


Fig. (5). Examples of benzofuran derivatives with potent anticryptococcal activity.

$\mu\text{mol.L}^{-1}$) against *C. neoformans*. Ryu *et al.* [86] also synthesized a series of benzofuran-5-ol derivatives and evaluated their *in vitro* antifungal activity against species of *Candida* and *Aspergillus* as well as against *C. neoformans*. Compounds **26**, **27**, and **28**, with MICs of $1.6 \mu\text{g.mL}^{-1}$, and **29**, with MIC of $3.2 \mu\text{g.mL}^{-1}$, were more potent than fluconazole against *C. neoformans*.

Nitrogen-containing heterocyclic compounds have also been shown to exhibit anticryptococcal properties [87-99]. Quinoxaline derivative **30** (Fig. 6) proved to be more active against *C. neoformans* than the reference drug miconazole, with MIC value of $6.25 \mu\text{g.mL}^{-1}$ [87]. Pyrazino[2,1-*a*]isoquinolin derivatives **31** and **32** (Fig. 6) (MIC values of $2.0 \mu\text{g.mL}^{-1}$) have shown to be twice as active as fluconazole against this microorganism [90]. In 2011, Boateng *et al.* [99] showed that the *N*-alkyl 3-substituted phenylthioquinolinium salts **33** and **34** (Fig. 6) are as effective as amphotericin B in inhibiting the *in vitro* growth of *C. neoformans*, with MIC values of 5.0 and $1.3 \mu\text{g.mL}^{-1}$, respectively. Additionally, compound **35** (Fig. 6) was effective in reducing brain cryptococcal infection in a murine model. Other examples of nitrogen heterocyclic compounds that exhibit promising anticryptococcal activity include quinazolines [92, 97], quinolones [95], benzothiazoles [96], and azaindoles [98].

SEMISYNTHETIC DERIVATIVES OF NATURAL PRODUCTS

The contribution of natural products towards the development of novel agents for the treatment of fungal infections is indisputable. In recent years, the search for novel antifungal agents, including anticryptococcal compounds, of natural origin, has greatly increased.

Sordarin **36** (also known as SL2266) [100] (Fig. 7), a natural product isolated from the fungus *Sordaria araneosa*, had notable antifungal activity [101]. Its structure contains a fragment aglycon, with a unique tetracyclic diterpene core and also a unusual 6-deoxy-glycoside residue, attached through a $\beta(1,2\text{-cis})$ -glycoside linkage. The first total synthesis of sordarin was reported by Narasaka's group, in 2006 [102]. In this work, the natural product was obtained from the condensation of two fragments, **37** and **38** (Fig. 7). The synthesis of sordarin ethyl ester **37** is depicted in Scheme 4.

Since its discovery, many derivatives of sordarin have been synthesized and their antifungal activities have been evaluated. GR135402 **39**, a sordarin-derivative isolated from *Graphium putredinis* [103], and four semisynthetic derivatives [GM160575 **40**,

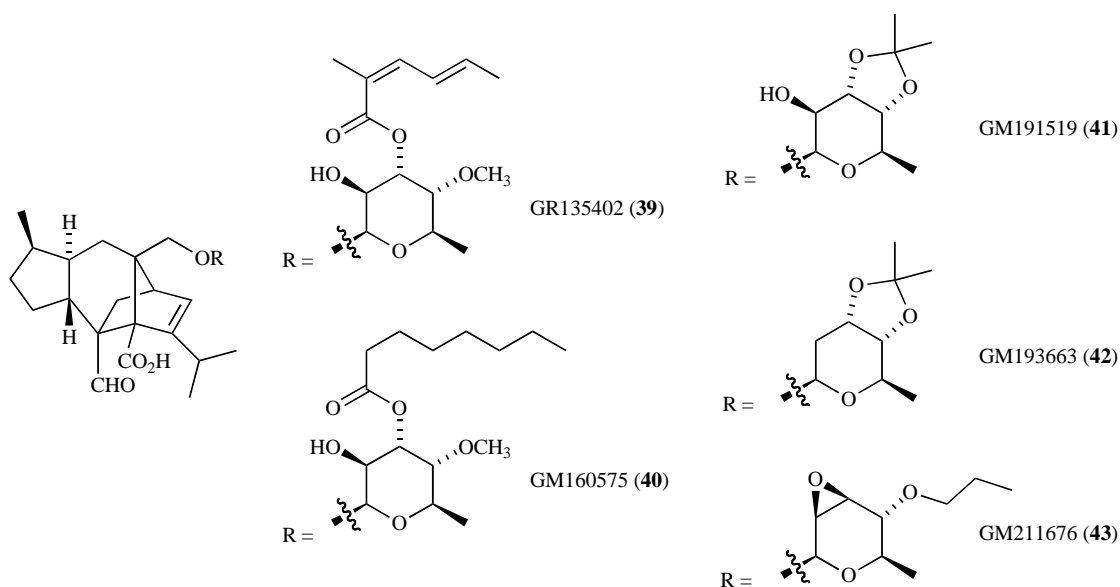
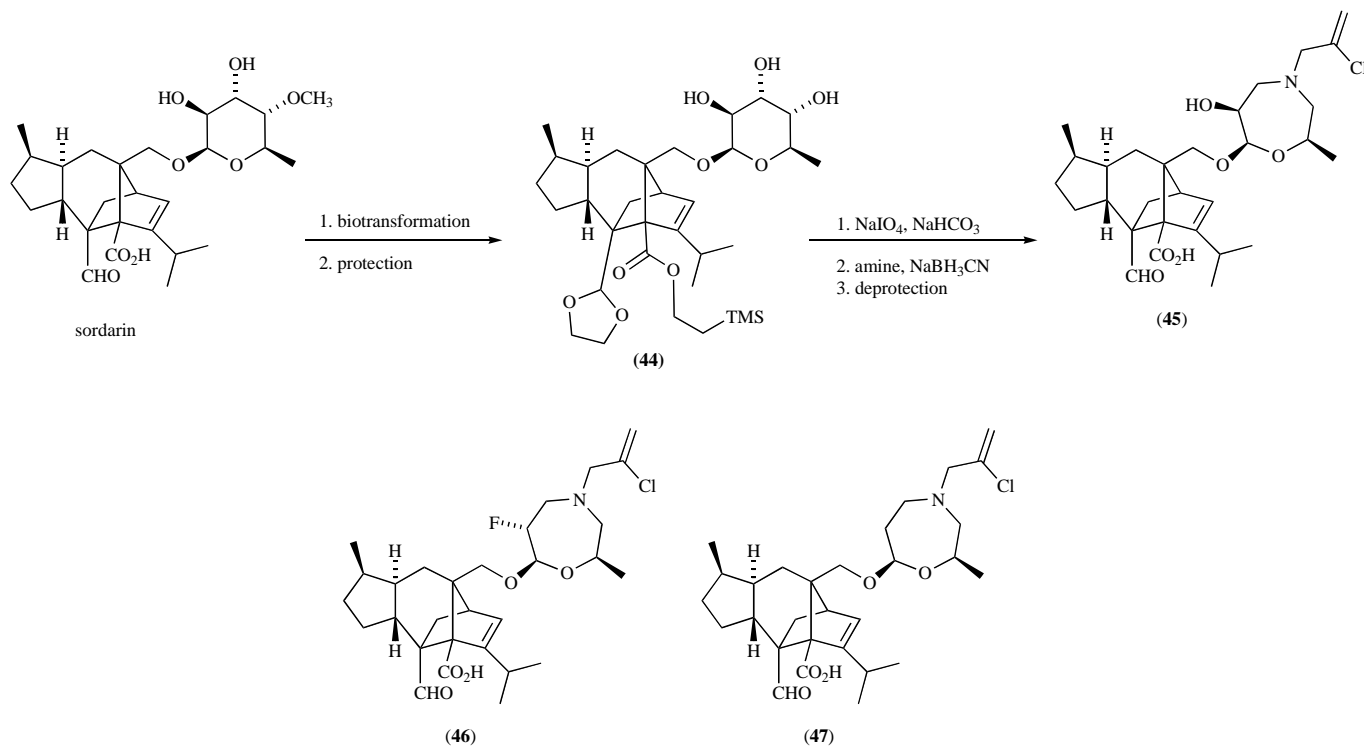


Fig. (8). Chemical structures of sordarin derivatives GR135402, GM160575, GM191519, GM193663, and GM211676.



Scheme 5. Synthesis of sordarin derivatives containing the oxazepine core with potential anticryptococcal activity.

GM191519 **41**, GM193663 **42**, and GM211676 **43**] (Fig. 8) were evaluated for their ability to inhibit *in vitro* protein synthesis and cell growth in different species of pathogenic fungi, including *C. neoformans* [104]. Experimental results indicate that sordarin analogs exert their antifungal effects by inhibiting specific protein synthesis of fungi by binding to elongation factor-2 (EF-2) and P0 (a ribosomal stalk protein). The sordarin analogs inhibit the elongation cycle in yeasts but do not affect protein synthesis machinery in mammalian systems, which in turn may indicate that these compounds demonstrate selectivity to fungi. In addition, sordarin derivatives exhibit promising MIC values against *C. neoformans*. For derivatives GR135402 and GM160575, MIC values of 0.25

$\mu\text{g}\cdot\text{mL}^{-1}$ were observed, while for sordarin the MIC value was 125 $\mu\text{g}\cdot\text{mL}^{-1}$ [104].

In 2002, Serrano-Wu *et al.* synthesized a series of sordarin derivatives containing the oxazepine core as potential antifungal agents [105]. Sordarin was submitted to demethylation by biotransformation in the presence of *Nocardia* spp and protection steps, yielding triol **44**. Treatment of **44** with sodium periodate followed by reductive amination and deprotection yielded oxazepine **45**, containing the 2-chloroallyl group (Scheme 5). Compound **45** presented a similar MIC value to that observed for sordarin (MIC = 8.0 $\mu\text{g}\cdot\text{mL}^{-1}$) against *C. neoformans*. The fluorinated **46** and desoxy **47** analogues also exhibited potent anti- *C. neoformans*

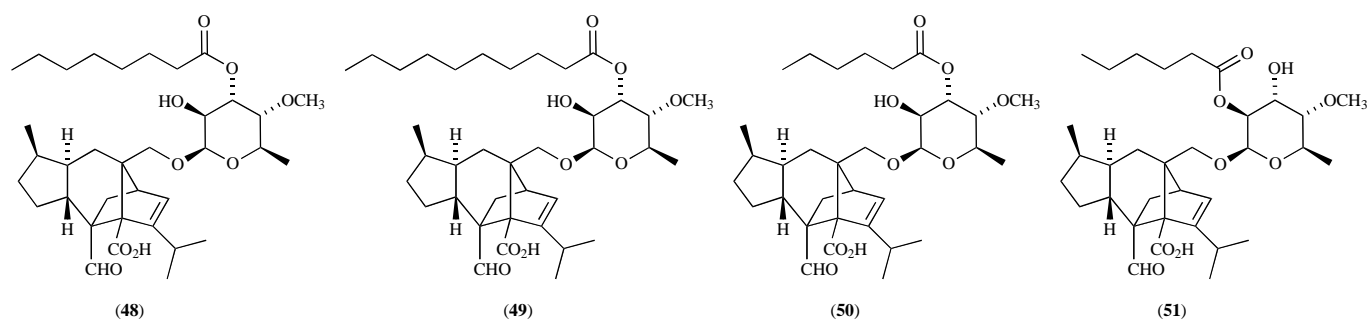


Fig. (9). Examples of O-acyl sordarin derivatives with potential anticryptococcal activities.

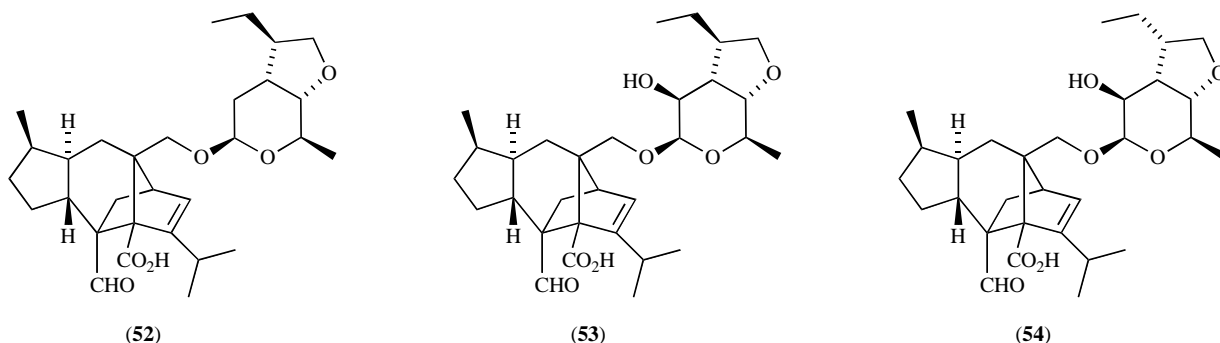


Fig. (10). Tetrahydrofuran sordarin derivatives with pronounced anticryptococcus properties.

mans activity with MIC values of 16.0 and 1.0 $\mu\text{g}\cdot\text{mL}^{-1}$, respectively.

Based on the superior activity of derivative GR135402 to that of sordarin, and to assess whether 3'-substitution may have a role in binding to EF-2 and P0 and/or uptake in whole cells, Arribas *et al.* synthesized and evaluated a series of novel 3'-O-acyl and alkyl sordarins [106]. Ester derivatives **48** and **49** (Fig. 9), with large lipophilic chains, demonstrated the best antifungal activity against *C. neoformans*, with MIC values of 0.25 and 1.0 $\mu\text{g}\cdot\text{mL}^{-1}$, respectively, while sordarin presented a MIC value $>125 \mu\text{g}\cdot\text{mL}^{-1}$. Additionally, the authors verified the importance of the esterification position for antifungal activities of this class of compounds, since the hexanoate derivative at 3' **50** (MIC = 16.0 $\mu\text{g}\cdot\text{mL}^{-1}$) (Fig. 9) is nearly twice as potent as the analogous **51** (Fig. 9) substituted in the 2' (MIC = 31.0 $\mu\text{g}\cdot\text{mL}^{-1}$). From these results, the authors conclude that the derivatization of the 3'-hydroxyl group of sordarin to yield aliphatic esters affords very potent antifungal compounds [106].

In the search for novel derivatives with increased antifungal activity, Bueno *et al.* synthesized a number of novel 3',4'-fused dioxolane and dioxane derivatives of sordarin, in order to evaluate the effect of reducing conformational flexibility of the pyranose ring on the antifungal activity. In this study, the role of the hydroxyl group at 2' position of the pyranose ring was also evaluated. Thus, 2'-deoxy analogues and derivatives with change in 2'-OH stereochemistry were synthesized [107]. Although the modification of sordarin pyranose ring by fusing either a dioxolane or a dioxane ring to the C3'-C4' bond led to a broadening of the spectrum of action when compared to that of 3'-O-substituted derivatives previously published [106], none of derivatives showed higher antifungal activity than the natural product (GR135402) against *C. neoformans*. Similar results were obtained by Castro *et al.*, as the 2',3'-fused oxirane and thiirane derivatives, which were synthesized proved substantially less active than GR135402 [108].

On other hand, the attachment of tetrahydrofuran rings to the C3'-C4' bond of the original sugar moiety dramatically enhanced the antifungal activity of sordarin analogues. Based on promising antifungal activity presented by derivative GM193663 (Fig. 8),

Bueno *et al.* synthesized a series of novel analogues bearing alkyl substituted tetrahydrofuran rings fused to C3'-C4' bond with pronounced anticryptococcal activity [109]. Derivatives **52**, **53**, and **54** (Fig. 10) were the most potent, with MIC values $< 0.25 \mu\text{g}\cdot\text{mL}^{-1}$.

Replacement of sugar moiety with a morpholinyl ring also leads to a significant increase in activity against various pathogenic fungi, including *C. neoformans*. Compound **55** (Fig. 11), a synthetic 5'-6'-substituted azasordarin derivative exhibited MIC value $< 0.008 \mu\text{g}\cdot\text{mL}^{-1}$ against this microorganism, one of the potent sordarin derivatives already described [110].

The R-135853, **56** (Fig. 11), a novel sordarin derivative that possesses a 1,4-oxazepane ring moiety, exhibited potent activity against clinical isolates of *C. neoformans* with MIC₉₀ value of 0.5 $\mu\text{g}\cdot\text{mL}^{-1}$. The compound was thirty-two times more potent than fluconazole (MIC₉₀ = 16 $\mu\text{g}\cdot\text{mL}^{-1}$) against *C. neoformans* [111].

In 2009, a novel sordarin derivative FR290581, **57**, (Fig. 11) was reported. The FR290581 contains a trisubstituted tetrahydrofuran ring, which replaces the typical acetal structure of sordarin. The FR290581 showed moderate activity *in vitro* against *C. neoformans*, with MIC value of 4.0 $\mu\text{g}\cdot\text{mL}^{-1}$ against this microorganism [112].

Artemisinin **58** (Fig. 12), a natural product derived from the Chinese herb Qing Hao (*Artemisia annua* L., family: Asteraceae) is known as an effective antimalarial agent [113]. The interesting biological properties presented by this substance have encouraged the development of a large number of derivatives with potential applications in medicinal chemistry. In this context, Galal *et al.* synthesized a series of artemisinin derivatives and evaluated their antifungal activities against opportunistic pathogens, including *C. neoformans*. Anhydrodihydro-artemisinin **59** (Fig. 12) demonstrated more potent antifungal activity against *C. neoformans* than amphotericin B (MIC values of 0.195 and 0.625 $\mu\text{g}\cdot\text{mL}^{-1}$, respectively). Interestingly, these compounds presented selective activity against this microorganism with little or no activity against *C. albicans* [114].

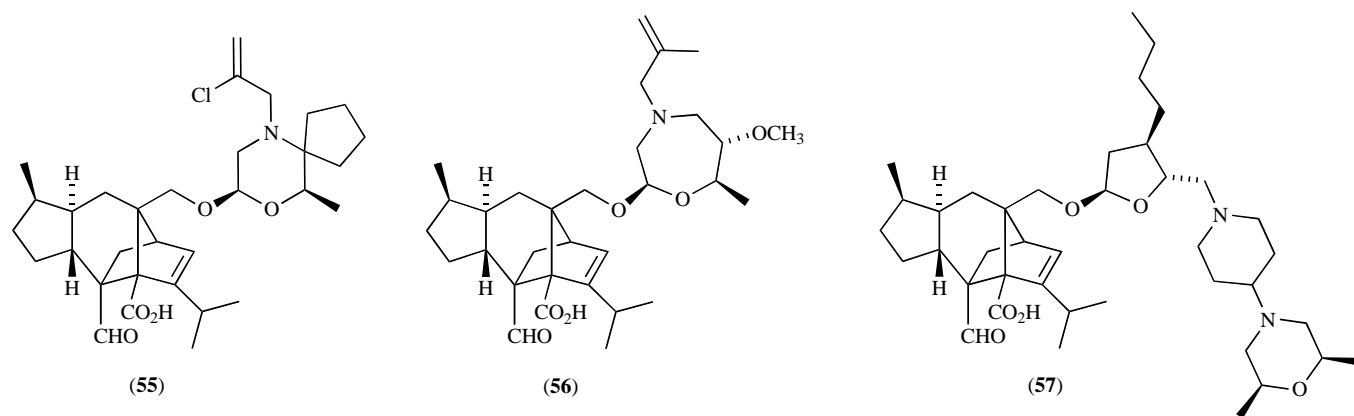


Fig. (11). Chemical structures of sordarin derivatives containing morpholinyl and oxazepane rings.

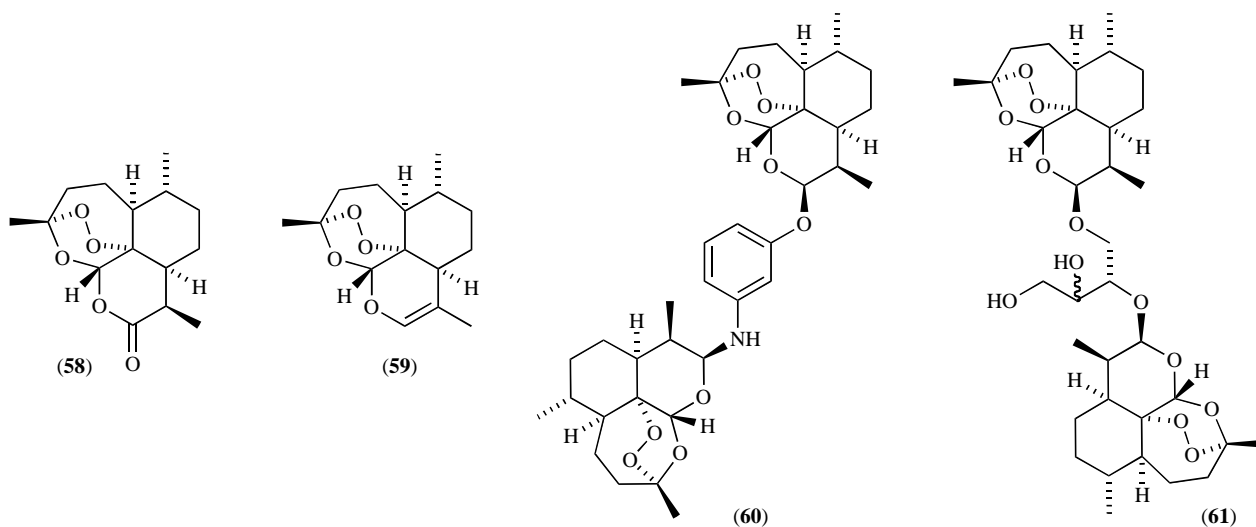


Fig. (12). Examples of artemisinin derivatives with potential anticryptococcal activities.

Artemisinin dimers also exhibit pronounced antifungal activity. In a work published in 2009, Slade *et al.* evaluated the antifungal activity of various dihydroartemisinin acetal dimers against various pathogenic fungi, including *C. neoformans*. Similarly, the synthesized dimers exhibited selective activity against *C. neoformans*, with the compounds **60** and **61** (Fig. 12) displaying enhanced activity compared to amphotericin B [115].

Other examples of natural products and derivatives with promising anticryptococcal properties include chlorogenic acid [116, 117], phloroglucinol [118], guttiferone-A [119], berberine [120, 121], carvacrol [122], galbonolide [123], nucleosides [124], gallic acid [125], indolizidines [126], puupehanol [127], and coruscanone A [128].

PHOSPHOLIPIDIC COMPOUNDS

Phospholipids have exhibited a promising antifungal activity against various pathogenic fungi including *Cryptococcus* species. A number of phospholipids and their derivatives, isolated from natural sources or obtained from synthesis, have been evaluated for their antifungal properties [129-135]. In 1995, Bierer *et al.*, evaluated the antifungal activity of irlbacholine **62** (Fig. 13), a natural phospholipid isolated from *Irlbachia alata* and *Anthocleista galonensis*, against pathogenic fungi including *C. neoformans*. This compound presented potent activity against *C. neoformans* in biological assays with MIC value of 0.04 $\mu\text{g}\cdot\text{mL}^{-1}$ [129]. Motivated by these results, Lu *et al.* [130] synthesized and evaluated the anti-

fungal activities of some irlbacholine derivatives. Compounds **63** and **64**, (known as miltefosine) (Fig. 13) also showed promising anticryptococcal activity with MIC values of 0.5 $\mu\text{g}\cdot\text{mL}^{-1}$.

Miltefosine is effective against visceral and cutaneous leishmaniasis and has been approved for clinical use in several countries for the treatment of this disease [133]. Additionally, miltefosine also provides pronounced antifungal activity against key fungal pathogens including species resistant to currently available drugs [132]. Miltefosine is structurally similar to natural substrates of the fungal virulence determinant phospholipase B1 (PLB1), which is a potential target for novel antifungal agents. Thus, in this work the authors also evaluated the correlation between antifungal activity and the inhibition of PLB1. The range of MIC obtained to miltefosine (0.25-4.0 $\mu\text{g}\cdot\text{mL}^{-1}$) was similar to or lower than that of fluconazole (0.5-16.0 $\mu\text{g}\cdot\text{mL}^{-1}$) against different isolates of *C. neoformans* and *C. gattii*. Furthermore, the MIC₉₀ values were similar to MFC values, indicating that miltefosine is fungicidal. The *in vivo* tests showed that oral administration of miltefosine at low doses (7.2 and 3.6 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$) for 5 days after intravenous infection with *C. neoformans* increased survival and reduced the brain and lung cryptococcal burdens. Mechanistic studies indicated that miltefosine inhibits cryptococcal PLB1 in a dose-dependent manner but only at relatively high concentrations suggesting that this is not its primary mode of action.

Although miltefosine shows promising biological properties, undesirable gastrointestinal side effects and the high hemolytic activity restrict its use [133]. Thus, Obando *et al.* [133] evaluated

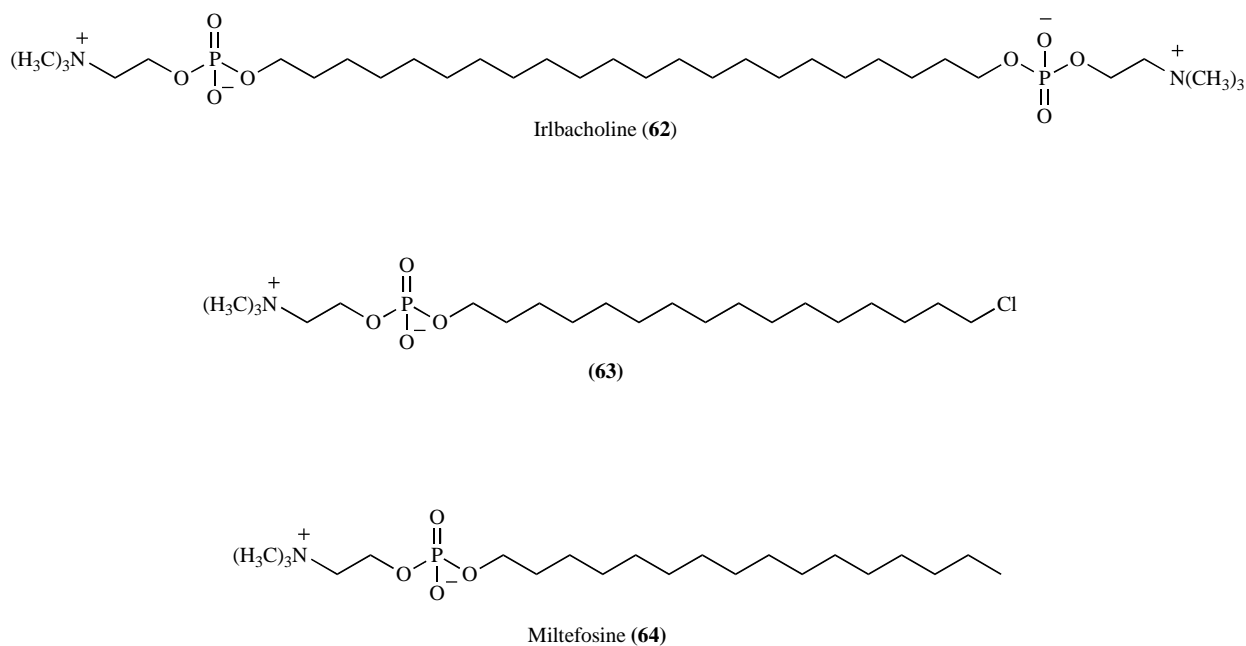


Fig. (13). Chemical structures of phospholipids with pronounced anticryptococcal activities.

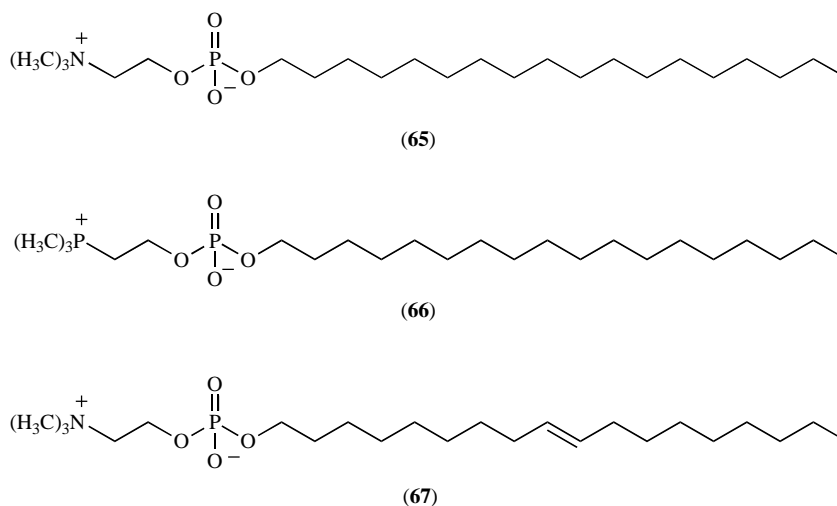
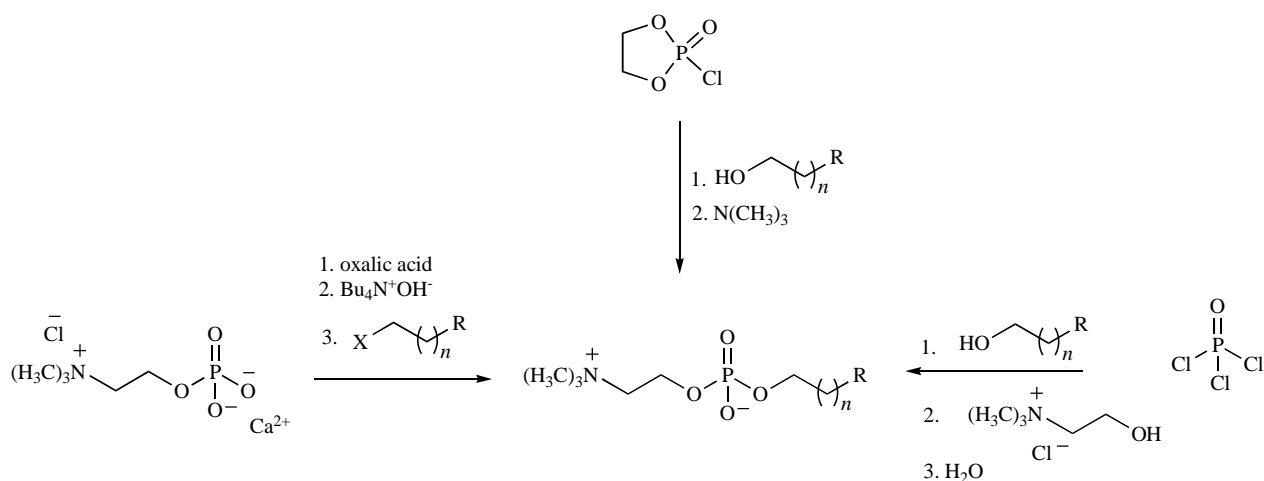


Fig. (14). Miltefosine derivatives with pronounced anticryptococcal activities.

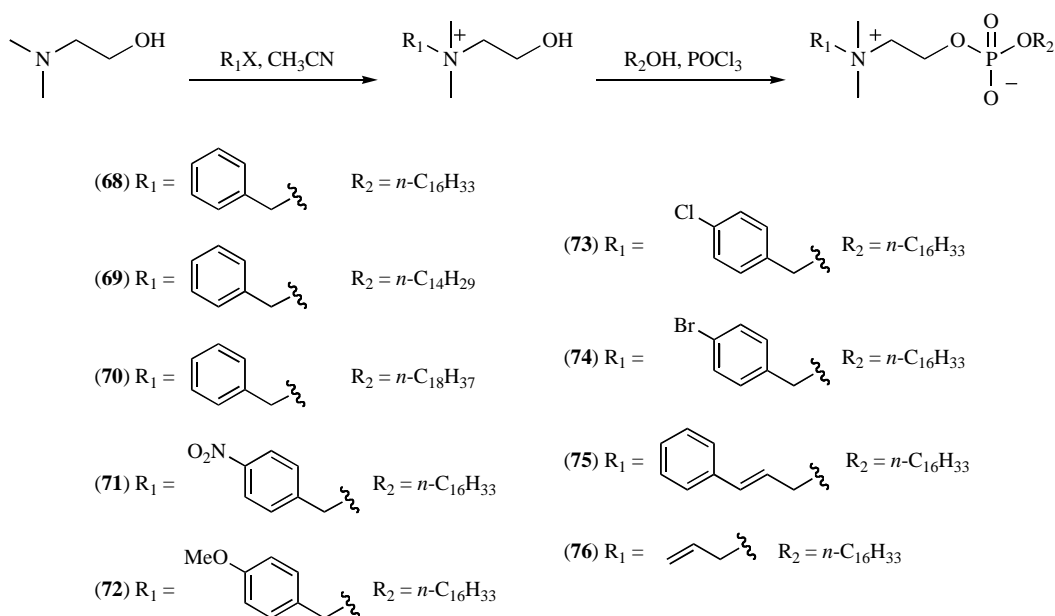
the antifungal and hemolytic activities of a number of alkylphosphocholines and alkylglycerophosphocholine analogues of miltefosine in order to determine whether structural features could be altered to achieve better antifungal activity with fewer adverse effects. Based on previous studies that indicate that changes in the alkyl chain are effective in reducing the cytotoxicity, Obando's group focused on modifying this portion of the molecule while keeping the phosphocholine group intact. The antifungal activity obtained for the series of derivatives showed that a hydrophobic chain of at least 16 carbon atoms is crucial to maintain antifungal activity. Increasing the alkyl chain slightly improved the antifungal activity but also enhanced the hemolytic activity. Insertion of ester and amide bonds in the middle of this chain significantly decreased the hemolytic activity of these compounds but abolished antifungal activity. Derivatives **65**, **66**, and **67** (Fig. 14) proved to be as active as miltefosine against *C. neoformans*, exhibiting MIC values of 1.40, 2.75 and 2.75 $\mu\text{mol}\cdot\text{L}^{-1}$, respectively. However, these compounds also exhibited hemolytic activity similar to or greater than that of miltefosine.

There are many protocols in the literature for the synthesis of alkylphospholipid analogues [136-138]. The phosphorylation of the appropriate alcohols using phosphorus oxychloride as starting material is usual [136]. The phosphocholine group can also be introduced in different alcohols by reaction with 2-chloro-1,3,2-dioxaphospholane-2-oxide, followed by treatment with trimethylamine [137]. The best procedure our group had access to prepare miltefosine analogues was using the phosphocholine chloride calcium salt as starting material (Scheme 6) [138, 139].

Ravu *et al.* [135] synthesized nine miltefosine analogues by modifying the choline structural moiety and the alkyl chain length (Scheme 7). Based on previous structure-activity relationship studies the authors initially decided to synthesize novel compounds by slightly modifying the structure of miltefosine, replacing one methyl group of the choline structural moiety with benzyl groups with different substituents. This modification did not improve antifungal activity of the analogues against *C. neoformans* since the derivatives **68**, **71**, and **72** showed similar MIC values (2.5-4.2 $\text{mg}\cdot\text{mL}^{-1}$) to miltefosine (MIC = 2.1 $\text{mg}\cdot\text{mL}^{-1}$). However, the pres-



Scheme 6. Synthetic strategies used in the preparation of phospholipidic derivatives.



Scheme 7. Novel miltefosine derivatives with structural modifications on choline moiety and alkyl chain.

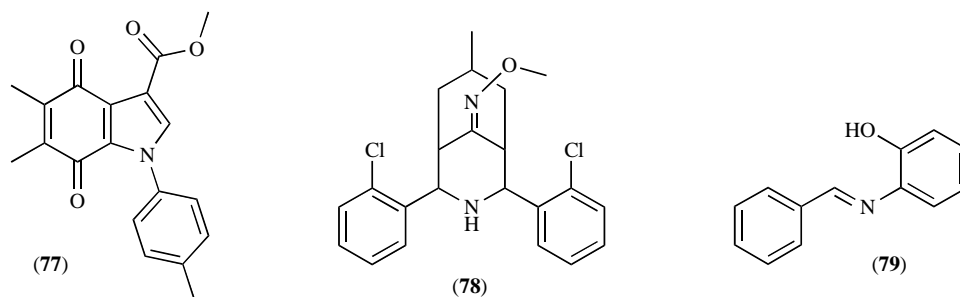


Fig. (15). Some examples of lead compounds for the development of new anticryptococcal agents.

ence of halogens in the *para* position of the aromatic ring or the substitution of methyl group for cinnamyl or allyl groups led to less active compounds, since derivatives **73**, **74**, **75**, and **76** were inactive at a concentration of $20 \mu\text{g}\cdot\text{mL}^{-1}$. To investigate the influence of the chain length on the antifungal activity, analogues **69** and **70**, with the same head group but an alkyl chain length of C14 and C18, respectively, were synthesized. Both compounds were less active than miltefosine, indicating that C16 is an optimal alkyl chain length.

MISCELLANEOUS

In the search for novel antifungal agents, studies have revealed that quinone derivatives possess *in vitro* antifungal activity against various pathogenic fungi [140-142]. Compound **77** (Fig 15), with MIC of $0.8 \mu\text{g}\cdot\text{mL}^{-1}$ against *C. neoformans*, is a promising lead compound for the development a new class of anticryptococcal agents [142]. Oxime derivative **78** (Fig 15) proved to be as potent as fluconazole against the same microorganism [143]. In 2011, da Silva *et al.* [144] verified that aryl aldimines also exhibit promising

anticytotoxic activity. Compound **79** (Fig. 15), with MIC of 8.0 $\mu\text{g}\cdot\text{mL}^{-1}$, was shown to be twice as active as fluconazole against *C. neoformans*. Additionally, **79** was able to reduce the metabolic activity of *C. neoformans* mature biofilm. Subsequently, in a systematic study of the anticytotoxic activity of a series of hydroxyaldimines, this same group has identified a number of derivatives active against *C. gattii* and *C. neoformans* [145].

CONCLUDING REMARKS

Cryptococcal disease affects humans worldwide and limited treatment options are currently available. In recent years, numerous research groups have concentrated their efforts on the search for more effective and safer antifungal agents. A large number of synthetic and natural product derivatives, such as those belonging to the classes herein discussed were demonstrated to be potential anti-*Cryptococcus* agents. Among them, the triazole CS-758 **20** had MIC values lower than those of the reference drugs fluconazole, itraconazole, and amphotericin B, while being more potent than fluconazole in an *in vivo* model of *C. neoformans* infection. In addition, anhydrodihydro-artemisinin **59**, a natural plant derivative, was determined to be more potent than amphotericin B and selective against *C. neoformans*. Indeed, further *in vivo* studies will be valuable in confirming the potential of these compounds as antifungals and expanding the knowledge of their mechanisms of action and pharmacokinetic properties.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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