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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF N-ARYL-3,4-DICHLOROMALEIMIDES AND N-SUBSTITUTED 3-CHLORO-4-ARYLOXYMALEIMIDES

Aim. In the course of search for novel antimicrobials against the critical fungal pathogens a series of 3,4-dichloromaleimide and 3-chloro-4-aryloxymaleimide derivatives was synthesized. **Methods.** The structure of compounds was confirmed using ¹H NMR spectroscopic analysis and LC-MS analysis. The antifungal assay was performed against *Candida albicans* and *Cryptococcus neoformans* as well as the cytotoxicity and hemolysis assays. **Results.** The compounds comparable with fluconazole in activity against *C. neoformans* were found in both classes: 3,4-dichloro-1-(2,4-dichlorophenyl)-2,5-dihydro-1H-pyrrole-2,5-dione showing minimum inhibitory concentration (MIC) 16 µg/mL (52 µmol/L) and 1-benzyl-3-chloro-4-(4-nitrophenoxy)-2,5-dihydro-1H-pyrrole-2,5-dione with MIC = 6 µg/mL (17 µmol/L). **Conclusion.** 3,4-dichloromaleimide and 3-chloro-4-aryloxymaleimide moieties were identified as a promising basis for the search for new antimicrobial agents active against *C. albicans* and *C. neoformans*.

Keywords: 3,4-dichloromaleimides, 3-chloro-4-aryloxymaleimides, antifungal activity, *Candida albicans*, *Cryptococcus neoformans*

Introduction

Fungal infections are becoming an increasingly serious public health problem as common patho-

gens — such as *Candida* yeasts — develop resistance to existing treatments.

Although invasive fungal infections primarily affect immunocompromised individuals, such as

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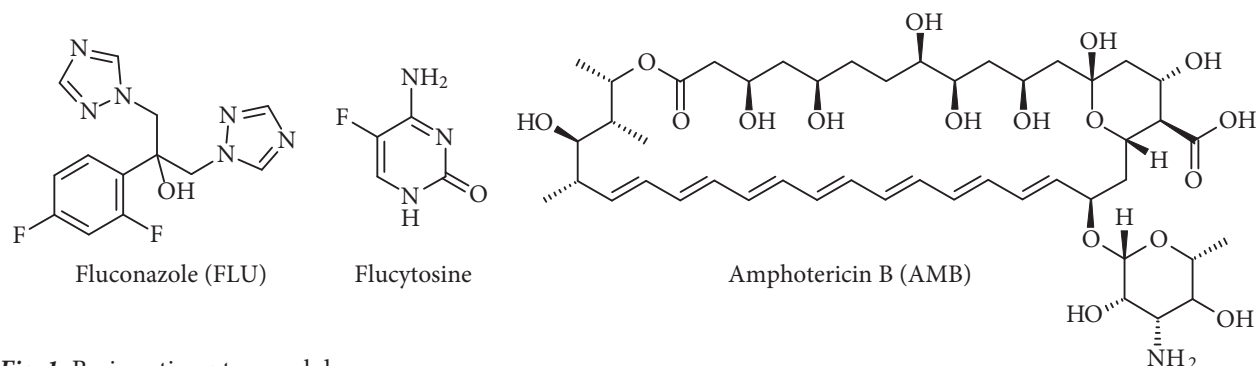


Fig. 1. Basic anticyptococcal drugs

those undergoing chemotherapy for cancer, living with HIV or having received an organ transplant, a recent report estimates worldwide number of severe fungal infections at 6.5 million yearly resulting in 3.8 million deaths, approximately 68% of which are directly caused by the infection itself [1, 2]. A further increase is projected in the number of people at risk due to conflicts, natural disasters, forced displacement and poverty[3].

C. neoformans, *Candida auris*, *Aspergillus fumigatus* and *C. albicans* have been classified as critical fungal pathogens due to their resistance to antifungal drugs, lack of scientifically proven diagnostic methods, notable mortality rates, complications and consequences [4]. Invasive disease mainly occurs in immunocompromised individuals and typically manifests as meningoencephalitis or less commonly — pulmonary cryptococcosis. Cryptococcal meningitis is estimated to affect 194,000 people annually, resulting in 147,000 deaths (75.8% mortality), and poses a significant health challenge in the countries with high HIV prevalence and limited healthcare resources [2].

To date, three classes of antifungal drug have been used to treat invasive fungal infections caused by *C. neoformans* and *C. albicans*: polyenes, flucytosine and azoles (Fig. 1) [5, 6]. Azoles, such as fluconazole, target biosynthesis of ergosterol in fungal cells inhibiting a cytochrome P 450-dependent fungal enzyme called lanosterol 14 α -demethylase. 5-Fluorocytosine (flucytosine) enters fungal cells via the permease of the cytosine transporter where it disrupts metabo-

lism of DNA and RNA undergoing partial conversion into 5-fluorouracil. Amphotericin B, a polyenes antibiotic, was the first antifungal agent isolated in the late 1950s. It binds to the ergosterol component of the cell wall, forming pores through which monovalent ions: K^+ , Na^+ , H^+ and Cl^- leak from the cell, causing cell death.

Despite the availability of other polyenes and azoles the only three drugs — amphotericin B, flucytosine and fluconazole are generally recommended in current clinical practice for treating infections caused by *C. neoformans* and *C. albicans*. Widespread use of a limited number of antifungal agents in medicine and agriculture led to the emergence of resistance to antifungal drugs [5, 6] and the need to search for novel classes of drugs with different mechanisms of action.

This study is planned as a continuation of our search for new antifungals [7, 8]. 3,4-Dichloromaleimides show a broad spectrum of both antibacterial and antifungal activities [9–11]. In particular, 2,3-dichloro-N-(4-nitrophenyl)maleimide shows noticeable antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* [12]. Furthermore, 2,3-dichloro-N-(3-trifluoromethyl)phenylmaleimide demonstrates pronounced antifungal efficacy against several phytopathogenic fungi including *Puccinia triticina*, *Erysiphe cichoracearum* on *Cucumis sativus*, *Podosphaera leucotricha* on apple (*Malus domestica*) trees, *Septoria agricola* on celery (*Apium graveolens*), *Erysiphe graminis* on wheat (*Triticum aestivum*) and *Plasmopara viticola* on grapevines (*Vitis vinifera*) [13]. Moreover, 2,3-di-

chloro-*N*-(4-butylphenyl)maleimide, when applied to rice plants at a concentration of 500 ppm, completely suppressed fungal infection caused by *Pyricularia oryzae* [14]. Based on these results, we have synthesized a series of novel 3,4-dichloromaleimides and 3-chloro-4-aryloxymaleimides and revealed notable antifungal activity.

Materials and Methods

Chemistry

All reagents were purchased from Merck KGaA company (Germany). The solvents were purchased from Macrochim (Ukraine). Melting points were measured on a Kofler melting point-device and are uncorrected. Thin layer chromatography was performed on DC-Alufolien Kieselgel 60 F₂₅₄ plates (Merck, Germany) in CHCl₃–MeOH 19:1. ¹H NMR spectra were recorded in DMSO-*d*₆ on Varian Gemini-2000 instrument (400 MHz, Varian, USA) using tetramethylsilane as an internal standard; chemical shifts are given in ppm. LC-MS analysis was performed on Agilent 1100LC/MSD SL instrument (Agilent Technologies, USA) equipped with Zorbax SB-C18 Rapid Resolution HT Cartridge (2.1 × 30 mm, 1.8 μm) using a 0–100% gradient (2 min) of CH₃CN in 0.1% formic acid.

General procedure for the synthesis of N-substituted 3,4-dichloromaleimides 2a–e.

The target 3,4-dichloromaleimides (**2a–h**) were synthesized according to a modified procedure reported previously [15]. A solution of the corresponding *N*-substituted maleimide (20 mmol) in thionyl chloride (60 mL) was prepared in a round-bottom flask equipped with a magnetic stirrer and a reflux condenser. Pyridine (44 mmol) was added dropwise to the stirred solution at 0–5 °C for over 1 h. Then the reaction mixture was heated under reflux for 4 h, cooled to room temperature, and the excess thionyl chloride was removed under reduced pressure with the co-addition of benzene to assist solvent elimination. The resulting residue was treated with water (100 mL) and the crude 3,4-dichloromaleimide derivatives (**2a–h**) were collected by filtration and washed twice with ethanol

(2 × 10 mL). Recrystallization from ethanol (20 mL) afforded the pure compounds **2a–h** as crystalline solids.

General procedure for the synthesis of N-substituted 3-chloro-4-aryloxymaleimides 3f–h.

The target *N*-substituted 3-chloro-4-phenoxy-maleimides (**3f–h**) were synthesized according to a general method described previously [16]. A solution of the corresponding 3,4-dichloromaleimide **2f–h** (10 mmol) in isopropanol (40 mL) was prepared in a round-bottom flask equipped with a magnetic stirrer. The corresponding phenol (11 mmol) and triethylamine (11 mmol) were added dropwise to the stirred solution at a room temperature. The reaction mixture was then heated under reflux for 2 h, after which it was allowed to stand and cool to room temperature overnight. The resulting crude crystals of *N*-substituted 3-chloro-4-phenoxy-maleimides (**3f–h**) were collected by filtration and washed twice with isopropanol (2 × 5 mL). Recrystallization from ethanol (20 mL) afforded the pure compounds **3f–h** as crystalline solids.

3,4-Dichloro-1-(4-nitrophenyl)-2,5-dihydro-1H-pyrrole-2,5-dione (2a) was synthesized and characterized earlier according to [12, 17].

3,4-Dichloro-1-(2,4-dichlorophenyl)-2,5-dihydro-1H-pyrrole-2,5-dione (2b). Yield 64%. M.p. 196–198 °C. R_f 0.75. ¹H NMR (DMSO-*D*₆): δ 7.58 (1H, s, -3' Ar), 7.37 (1H, dd, J₁ = 4.7 Hz, -5' Ar), 7.24 (1H, dd, J₁ = 4.7 Hz, -6' Ar). LC-MS: r.t. 1.18 min *m/z* 311.2 [M+1]⁺.

3,4-Dichloro-1-(2,5-dichlorophenyl)-2,5-dihydro-1H-pyrrole-2,5-dione (2c). Yield 63%. M.p. 174–176 °C. R_f 0.75. ¹H NMR (DMSO-*D*₆): δ 7.95 (1H, s, -6' Ar), 7.60 (1H, d, J = 4.7 Hz, -3' Ar), (1H, d, J = 4.7 Hz, -4' Ar). LC-MS: r.t. 1.17 min *m/z* 311.2 [M+1]⁺.

3,4-Dichloro-1-[3-(trifluoromethyl)-phenyl]-2,5-dihydro-1H-pyrrole-2,5-dione (2d) was synthesized and characterized earlier according to [13]. Yield 66%. M.p. 85–86 °C.

1-(4-Butylphenyl)-3,4-dichloro-2,5-dihydro-1H-pyrrole-2,5-dione (2e) was synthesized and characterized earlier according to [14]. Yield 67%. M.p. 185–186 °C.

1-Benzyl-3-chloro-4-(4-nitrophenoxy)-2,5-dihydro-1H-pyrrole-2,5-dione (3f). Yield 66%. M.p. 105–106 °C. R_f 0.65. ^1H NMR ($\text{DMSO}-d_6$): δ 8.28 (2H, d, $J = 8.2$ Hz, -3',5' ArO), 7.55 (2H, d, $J = 8.2$ Hz, -2',6' ArO), 7.40–7.24 (5H, m, Ar), 4.67 (2H, s, -CH₂). LC-MS: r.t. 1.33 min m/z 359.2 $[\text{M}+1]^+$.

3-Chloro-1-(2-methylphenyl)-4-(4-nitrophenoxy)-2,5-dihydro-1H-pyrrole-2,5-dione (3g). Yield 66%. M.p. 175–176 °C. R_f 0.66. ^1H NMR ($\text{DMSO}-d_6$): δ 8.38 (2H, d, $J = 8.2$ Hz, -3',5' ArO), 7.70 (2H, d, $J = 8.2$ Hz, -2',6' ArO), 7.40–7.36 (4H, m, Ar), 2.20 (3H, s, -CH₃). LC-MS: r.t. 1.32 min m/z 359.2 $[\text{M}+1]^+$.

3-Chloro-1-cyclohexyl-4-(4-propylphenoxy)-2,5-dihydro-1H-pyrrole-2,5-dione (3h). Yield 77%. M.p. 100–101 °C. R_f 0.75. ^1H NMR ($\text{DMSO}-d_6$): δ 7.26–7.29 (4H, m, -Ar), 5.85 (1H, q, $J = 4.8$ Hz, -CH), 2.55 (2H, t, $J = 4.8$ Hz, -CH₂ (Pr)), 1.52–1.92 (10H, m, -CH₂), 1.10–1.42 (2H, m, -CH₂ (Pr)). LC-MS: r.t. 1.34 min m/z 348.1 $[\text{M}+1]^+$.

Antifungal assays

Determination of antifungal activity of 3,4-dichloromaleimides and 3-chloro-4-aryloxymaleimides as well as a reference fluconazole was carried out according to the standard protocols of the Community for Open Antimicrobial Drug Discovery laboratory at The University of Queensland (Australia) with the determination of the minimum inhibitory concentration (MIC) at which complete/partial inhibition of growth and reproduction of fungi was observed. Strains ATCC 208821 of yeast-like fungi *C. neoformans* and ATCC 90028 of *C. albicans* were used for antifungal screening. The work was performed using 384-well non-binding polystyrene plates (Fisher Scientific). Fluconazole antifungal agent served as a reference.

Fungi strains were cultured for 72 hours on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of $1\text{--}5 \times 10^6$ colony-forming units — CFU/mL (determined measuring absorbance at 530 nm — OD_{530}) was prepared from five colonies. The suspension was subse-

quently diluted and added to each well of the compound-containing plates giving a final cell density of fungi suspension of 2.5×10^3 CFU/mL and a total volume of 50 μL . All plates were covered and incubated at 35 °C for 24 h without shaking.

Growth inhibition of *C. albicans* was determined measuring absorbance at 530 nm (OD_{530}), while the growth inhibition of *C. neoformans* was determined measuring the difference in absorbance between 600 and 570 nm ($\text{OD}_{600-570}$), after the addition of resazurin (0.001% final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader. The percentage of growth inhibition was calculated for each well, using the negative control (media only) and positive control (fungi without inhibitors) on the same plate.

The minimal inhibitory concentration of the tested compounds was determined by serial two-fold dilutions. The concentrations of the substances were in the range of 32–0.25 $\mu\text{g/mL}$. Inoculates of fungi in Mueller-Hinton liquid medium with a final suspension density of 2.5×10^3 CFU/mL were added to plates containing appropriate concentrations of compounds. The cultures were incubated without aeration (mixing) for 24 hours at 37 °C.

The assessment of antimicrobial activity was carried out according to CLSI recommendations, by determining the minimum inhibitory concentration (MIC), at which a complete/partial inhibition of the fungal growth and reproduction was observed.

The antifungal agent fluconazole served as a reference. The antifungals under study were dissolved in water for injection in the appropriate concentrations.

Cytotoxicity assay

HEK293 (human embryonic kidney) cells ATCC CRL-1573 were counted manually in a Neubauer hemocytometer and then plated in 384-well tissue culture plates (Corning 3712) containing compounds to obtain a density of 500 cells/well in a final volume of 50 μL . DMEM supplemented with 10%

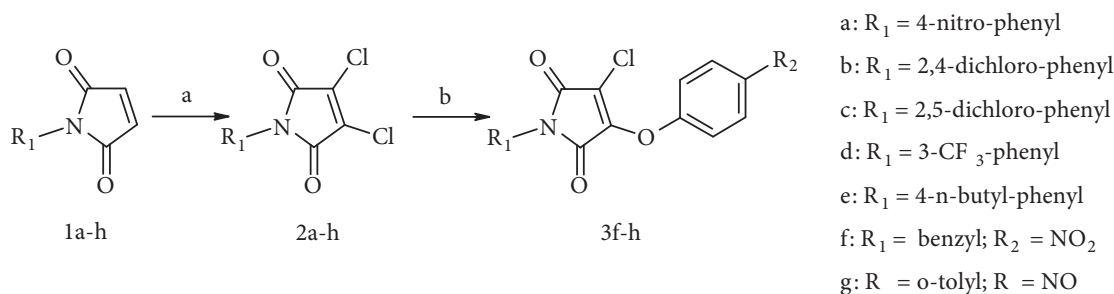


Fig. 2. General method of syntheses of 3,4-dichloromaleimides **2a-e** and 3-chloro-4-phenoxy-maleimides **3f-h**. Conditions: a) SOCl_2 , pyridine; b) 4-R₂-C₆H₄-OH, Et₃N, iPrOH

FBS was used as the culture medium and the cells were incubated with the compounds for 20 hours at 37 °C in 5% CO₂. Cytotoxicity (or cell viability) was measured by fluorescence, ex: 560/10 nm, em: 590/10 nm ($F_{560/590}$), after addition of 5 μL of resazurin at a concentration of 25 $\mu\text{g/mL}$ (final concentration 2.3 $\mu\text{g/mL}$) and incubation for an additional 3 hours at 37 °C in 5% CO₂. Fluorescence intensity was measured with a Tecan M1000 Pro plate reader monochromator using automatic gain calculation. CC₅₀ (concentration at 50% cytotoxicity) was calculated by fitting the inhibition values against logarithm (concentration) using a sigmoidal dose-response function with variable fit values for the bottom, top and slope.

Hemolysis assay

A sample of human whole blood was washed three times with 3 equal volumes of 0.9% NaCl and then resuspended in it to a concentration of 0.5×10^8 cells/mL, as determined by manual cell counting in a Neubauer hemocytometer. The washed cells were added to 384-well polystyrene plates (Corning 3657) to a final volume of 50 μL . After 10 min of shaking on a shaker, the plates were incubated for 1 h at 37 °C. After incubation, the plates were centrifuged at 1000 g for 10 min to pellet cells and other undissolved particles, then 25 μL of the supernatant were transferred to a 384-well polystyrene assay plate (Corning 3680). Hemolysis was determined by measuring the absorbance of the supernatant at 405 nm (OD_{405}) using a Tecan M1000

monochromator for plate reading. HC₁₀ (concentration causing 10% haemolysis) was calculated by fitting the inhibition values against logarithm (concentration) using a sigmoidal dose-response function with variable fit values for the top, bottom and slope. The use of human blood (obtained from the Australian Red Cross Blood Service) for haemolysis assays was approved by The University of Queensland Institutional Human Research Ethics Committee, Approval Number 2014000031.

Results and Discussion

Chemistry

Five 3,4-dichloro-*N*-substituted maleimides (**2a-e**) were synthesized following the previously described general procedure [15] by reaction of the corresponding *N*-substituted maleimides with double molar amount of pyridine in thionyl chloride. The reaction gave the desired products in 63–67% yields. Subsequent reaction of *N*-substituted 3,4-dichloromaleimides with phenols [16] in presence of triethylamine gave the corresponding *N*-substituted 3-chloro-4-phenoxy-maleimides (**3f-h**) in 66–77% yields, as indicated in Fig. 2. All the final products were purified by recrystallization from ethanol to about 95% purity.

Antifungal activity

The antifungal activity of synthesized 3,4-dichloromaleimides **2a-e** and 3-chloro-4-phenoxy-maleimides **3f-h** against *C. albicans* (Ca) and

Antifungal activity (MIC — minimum inhibitory concentration), cytotoxicity (CC₅₀ — concentration at 50% cytotoxicity) and hemolytic activity (HC₁₀ — concentration causing 10% haemolysis) of N-aryl-3,4-dichloromaleimides 2a-e and N-substituted 3-chloro-4-aryloxymaleimides 3f-h

Number	Compound structure	MIC, µg/mL <i>Ca</i>	MIC, µg/mL <i>Cn</i>	CC ₅₀ , µg/mL, Hek	HC ₁₀ , µg/mL, RBC
2a		16	>32	15.0	>32
2b		16	16	>32	>32
2c		>64	>64	n.d.	n.d.
2d		>64	>64	n.d.	n.d.
2e		>64	>64	n.d.	n.d.
3f		8	6	4.62	>32
3g		>64	>64	n.d.	n.d.
3h		>64	>64	n.d.	n.d.
	FLU	0.125	8		

Notes: **Cn** — *C. neoformans* ATCC 208821; **Ca** — *C. albicans* ATCC 90028; **Hek** — HEK293, human embryonic kidney cells ATCC CRL-1573; **RBC** — human red blood cells; **n.d.** — not determined; **FLU** — fluconazole.

C. neoformans (Cn) tested in the assay is represented in the Table along with results of cytotoxicity and hemolysis assays.

Both classes of compounds show activity against *C. albicans* and *C. neoformans*. Among the N-aryl-3,4-dichloromaleimides **2a-e** — compound **2a** inhibits growth and reproduction of the only *C. albicans* with a MIC = 16 µg/mL but, unfortunately, it also shows cytotoxic activity at this concentration having CC₅₀ = 15 µg/mL. The most active compound — **2b** inhibits growth and reproduction of both *C. albicans* and *C. neoformans* with the same MIC = 16 µg/mL showing at the same time the minimal cytotoxic and hemolytic activities. Compound **2c-e** didn't reveal antifungal activity, thus didn't proceed cytotoxic and hemolytic assays. Summarizing structural features — substituent at the 4-position of phenyl ring depending of its structure can increase antifungal activity, at the 3-position of phenyl ring — no. Probably substituent at the 2-position of phenyl ring can enhance antifungal activity of 4-substituted N-aryl-3,4-dichloromaleimides if not increasing affinity then increasing poor water solubility.

3-chloro-4-phenoxy maleimide **3f** shows the highest activity among the all studied compounds against both fungi with MIC = 8 µg/mL for *C. albicans* and MIC = 6 µg/mL reaching the efficiency of reference drug fluconazole against *C. neoformans*. However with CC₅₀ = 4.62 µg/mL **3f** shows also

visible cytotoxicity, the highest among tested compounds, thus need further structural improvement. Other N-substituted 3-chloro-4-aryloxymaleimides **3g** and **3h** shows no antifungal activity at a studied range of concentrations.

Conclusions

Brief screening of 3,4-dichloromaleimide and 3-chloro-4-aryloxymaleimide derivatives on antifungal activity revealed 3 active compounds among the 8 examined ones that allows us to consider these templates as promising backbones for further optimization. These classes of compounds without pronounced cytotoxic or hemolytic effect might be a fruitful ground for novel antifungals against *C. neoformans* or *C. albicans* with a probably different mechanism of action compared to the current drugs.

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СИНТЕЗ ТА ПРОТИГРИБКОВА АКТИВНІСТЬ N-АРИЛ-3,4-ДИХЛОРОМАЛЕІМІДІВ ТА N-ЗАМІЩЕНИХ 3-ХЛОРО-4-ФЕНОКСИМАЛЕІМІДІВ.

Мета. В рамках пошуку антимікробних агентів проти грибкових патогенів з критичного переліку було виконано синтез нових похідних 3,4-дихлоромалеїміда та 3-хлоро-4-феноксималеїміда. **Методи.** Було підтверджено структуру отриманих речовин методами спектроскопії ¹H ЯМР та РХ-МС та виконано тестування на протигрибкову активність проти *Candida albicans* та *Cryptococcus neoformans*, цитотоксичність і гемоліз. **Результати.** Серед обох класів сполук отримано речовини, які виявили порівнювану з флуконазолом активність проти *C. neoformans*: 3,4-дихлор-1-(2,4-дихлорофеніл)-2,5-дигідро-1H-пірол-2,5-діон показав мінімальну інгібувальну концентрацію (МІК) = 16 мкг/мл (52 мкмоль/л), а 1-бензил-3-хлор-4-(4-нітрофенокси)-2,5-дигідро-1H-пірол-2,5-діон — МІК = 6 мкг/мл (17 мкмоль/л). **Висновки.** 3,4-дихлоромалеїмідний та 3-хлоро-4-феноксималеїмідний фрагменти було ідентифіковано як перспективні основи для пошуку нових антимікробних засобів проти *C. albicans* та *C. neoformans*.

Ключові слова: 3,4-дихлоромалеїміди, 3-хлоро-4-феноксималеїміди, протигрибкова активність, *Cryptococcus neoformans*, *Candida albicans*.