Nowe pochodne sulfonowe i sulfanylowe o działaniu przeciwgrzybicznym

New sulfone and sulfanyl derivatives with antifungal activity

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Wzrastająca częstotliwość występowania kandydoz i trudność ich leczenia stwarzają potrzebę poszukiwania nowych antymikotyków ukierunkowanych na czynniki wirulencji *Candida albicans*. W prezentowanej pracy, przy użyciu metody mikrorozcieńczeń M27-A3, zidentyfikowano nowe pochodne sulfonowe i sulfanylowe aktywne wobec *C. albicans*. Wykazano, że delekcje w genach *SAP* kodujących izoenzymy proteazy aspartylowej warunkują mutantom *sapΔ* zwiększoną wrażliwość na badane związki. Nowe pochodne siarkoorganiczne (1, 5 oraz 6) efektywnie hamowały morfogenezę *C. albicans* w warunkach indukujących formowanie strzępek. Efektem końcowym prowadzonych analiz było wytypowanie wiodącej struktury 6 do dalszej optymalizacji.

Słowa kluczowe: *Candida albicans*, pochodne sulfonowe, zjadliwość

ABSTRACT

Introduction: Increasing occurrence of fungal infections raises the need to develop novel antifungal agents. In this context, an inhibition of morphological switch may provide an alternative approach to find compounds with a potential to control the *Candida albicans* infections.

Methods: A series of 17 sulfone and sulfanyl derivatives was synthesized and evaluated for activity against the *C. albicans* wild type (SC5314, ATCC) and *SAP*-deficient mutant strains using the broth microdilution method M27-A3. Afterwards, phase-contrast microscopy was applied to evaluate the inhibition of fungal morphogenesis under the influence of randomly selected active compounds: 1, 5 and 6.

Results: By *in vitro* susceptibility testing of *C. albicans*, we identified the effective antifungal agents displaying moderate-to-good activity. Newly synthesized sulfanyl and sulfone derivatives strongly inhibited the *C. albicans* morphogenetic transition under the hyphae inducing conditions.

Conclusions: The leading compound 6 has the potential to be used as a base structure in antifungal drug development, however further structural optimization and toxicity studies are required.

Key words: *Candida albicans*, sulfone derivatives, virulence

INTRODUCTION

Candida albicans commonly colonizes the skin and mucosal surfaces of healthy individuals; however in immunocompromised hosts this opportunistic pathogen may cause life-threatening invasive infections (9). Invasive candidiasis (IC) is associated with high mortality rates (46–75%), even with treatment using available antifungals (16). Currently, there are only four classes of antifungals used for the IC treatment, such as the following: polyenes, azoles, echinocandins, and flucytosine (11). Classical antifungals were designed to exert either fungicidal or fungistatic effects by interfering with essential processes of pathogenic fungi (8, 12). Therefore their intensive therapeutic use and prolonged treatment contribute to a selection for drug-resistant isolates (11). Recently, interfering with fungal virulence factors became a new paradigm in the development of new antifungal compounds (8, 12). This alternative approach does not pose a direct selective pressure for drug resistance, since virulence determinants that contribute to *C. albicans* pathogenicity are generally considered as not essential for the survival of this pathogen (8). Among *C. albicans* features that contribute to pathogenesis, filamentation and secreted hydrolytic enzymes represent promising antifungal targets (16). Morphogenesis represents an important virulence trait of *C. albicans*, since the locked in either yeast or hyphal forms mutants are attenuated virulence in IC (2, 12). The ability to reversibly switch between different morphologies (yeast, germ-tube, pseudohyphae, or true hyphae) is crucial for adaptation and persistence in different environmental niches inside the host (16). Both yeast and hyphal cells are found in the *C. albicans* infected organs, indicating that different morphologies are important for the virulence and have distinct functions during infection (2). In addition, the yeast-to-hyphae transition is necessary for the biofilm formation and maintenance (9, 12). The yeast forms are important for the establishment and dispersion of biofilms, while the hyphal morphologies stabilize the biofilm structure (9). Additionally, the hyphae formation is linked to the expression of subset of genes encoding the virulence determinants, such as the following: adhesins (Hwp1, Als3), secreted aspartyl proteases (Sap4-6) and other hyphae-associated proteins (Ecel, Hyr1) (8).

In this context, a series of 17 sulfone derivatives were synthesised and evaluated against *C. albicans*. The study aimed to determine: (a) which compound possesses a good anti-*Candida* activity and could be used as a base scaffold in the development of antifungal agents; (b) effect of *C. albicans* mutations in the *SAP1-3*, *SAP4-6* and *SAP9-10* genes on the antimicrobial activity of sulfone derivatives *in vitro*; (c) morphogenesis-inhibition effect of tested derivatives under hyphae inducing conditions.

MATERIAL AND METHODS

Fungal strains, media and growth conditions. All *C. albicans* strains used in the study are listed in Table I. Fungal strains were stored on ceramic beads in a Microbank tube (Prolab Diagnostics, Canada) at -70°C. Prior to the respective examinations, routine cultures were conducted at 30 °C for 18 h in the yeast extract–peptone–dextrose (YEPD) medium (Bacto peptone 2%, Yeast Extract 1%, Dextrose 2%).

Synthesis of sulfone and sulfanyl derivatives used in the study. The sulfur-organic compounds evaluated in the present study were listed in Table II. All compounds were synthesized at the Faculty of Chemistry of the Warsaw University of Technology (Poland). The synthetic pathway for the synthesis of the target compounds had been previously described (10).

Table I. Strains used in the study

Strain	Genotype	Reference
SC5314	Wild type	(5)
sap1-3Δ	<i>sap1Δ :: FRT/sap1Δ :: FRT; sap2-1Δ :: FRT/sap2-2Δ :: FRT; sap3Δ :: FRT/sap3Δ :: FRT</i>	(7)
sap6Δ	<i>sap6-1Δ::FRT/sap6-2Δ::FRT</i>	(7)
sap4-6Δ	<i>sap4-1Δ :: FRT/sap4-2Δ :: FRT; sap5-1Δ :: FRT/sap5-2Δ :: FRT; sap6-1Δ :: FRT/sap6-2Δ :: FRT</i>	(7)
sap9/10Δ	<i>ura3Δ::imm434/ura3Δ::imm434 sap10Δ::hisG/sap10Δ::hisG sap9Δ::hisG/sap9Δ::hisG-URA3-hisG</i>	(1)

Antifungal activity assay against *C. albicans*. Susceptibility of the planktonic cells of *C. albicans* SC5314 to the new sulfone derivatives was determined using the broth microdilution method M27-A3 (3). The final inoculum of 1.8×10^3 cfu/mL of PBS was prepared in the synthetic RPMI 1640 medium at pH 7.0 buffered with morpholinepropanesulfonic acid (MOPS). Compounds' concentrations (ranging from 0.0313 to 160 µg/mL) were prepared with the stock solution of compounds (1600 µg/mL) dissolved in ethanol at final concentration of 0.09%. Amphotericin B (Sigma–Aldrich, USA) at 0.5 µg/mL was used as a reference antifungal. Microtiter plates were incubated at 35°C without agitation for 18 h. Ethanol at 0.09 % (v/v) was used as a control, unable to inhibit the growth of *C. albicans*. According the criteria described in the method M27-A3, minimal inhibitory concentration (MIC), defined as the lowest compound concentration that yielded no visible growth, it was determined visually after 18 h of incubation (3). Tests were performed in triplicate and results were confirmed in two separate experiments on different days. Activity of benzothiazole, benzimidazole, and nitrophenyl derivatives displaying different MIC against the wild type (*wt*) strain was further evaluated against *C. albicans sapΔ* mutants.

Phase-contrast microscopy (Docuval, Carl Zeiss, Germany). Phase-contrast microscopy was applied to evaluate the inhibition of *C. albicans* morphogenesis under influence of randomly selected active compounds: 1, 5, 6, and 7. Samples were prepared as described previously (14). Briefly, the cells of SC5314 were pre-treated with the selected compounds at concentrations ranging from 4 to 16 µg/mL for 18 h, according to the reference M27-A3 method (3). Afterwards, samples were washed once and suspended in 250 µL of water. Next, 50 µL of the suspension were pipetted onto the microscope glass slides and examined under phase-contrast microscope (Docuval, Carl Zeiss, Germany). The control morphologies were prepared by the pre-treatment of SC5314 with 0.09% ethanol.

Scanning electron microscope (SEM, Hitachi S-5500, Japan).

The lead compound **6** was further examined against the mature biofilm of the *C. albicans wt* and *SAP4-6* mutants generated on the Caco-2 monolayer. Briefly, the Caco-2 cell line was seeded at the density of 1.2×10^5 cells/mL of EMEM on cover sleeps located in the bottom of 24-well-plates (Corning, USA) (13). Cells were cultured in the EMEM medium (10 vol. % FCS, 1 mM pyruvic acid; ATCC, USA) without antibiotics or antifungal agents for 18 h. To assess the influence of **6** on the *C. albicans* biofilm formation, the Caco-2 cell line after 21-day post seeding was inoculated with 1.0 – 1.2×10^5 /mL of the log-phase yeast cells of SC5314 ATCC. Afterwards, the biofilms were treated with **6** at 16 or 8 µg/mL separately for 18 h (37°C in 5 vol % CO₂). After double washing with PBS, samples were

prepared as described previously Staniszevska et al. (15). Subsequently, cells were fixated with 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.2) for 18 h at a low temperature (5–6°C); carried out with 2% osmium tetroxide (2 h at room temperature); dehydrated with series of ethanol gradients and acetone until they were dried by the critical point method in liquid CO₂. Then, the specimens were coated with gold in a vacuum evaporator and examined with SEM. Images were assembled with Photoshop (Adobe Photoshop CS3 Extended).

RESULTS

In the study, the series of new sulfanyl and sulfone derivatives were synthesized and screened for activity against *C. albicans*. The structures and yields of the examined compounds are presented in Table II. Among benzothiazole derivatives only compound 1 was active against *C. albicans*, whereas replacement of propanone group with phenylethanone- (as in 2) or ethanethioate- moieties (as in 3) resulted in the activity loss of these compounds. Interestingly, benzoxazole (named 5) displayed 2-fold higher antifungal activity than an equivalent agent with the benzothiazol ring (named 1).

Table II. The sulfone derivatives evaluated in this study

No.	Compound	Structure	Yield (%)	Chemical Formula	MIC* μg/mL
1	1-(1,3-benzothiazol-2-ylsulfanyl) propan-2-one		87	C ₁₀ H ₉ NOS ₂	80
2	2-(1,3-benzothiazol-2-ylsulfanyl) -1-phenylethanone		84	C ₁₅ H ₁₁ NOS ₂	>160
3	S-1,3-benzothiazol-2-yl ethanethioate		87	C ₉ H ₇ NOS ₂	>160
4	1-(1H-benzimidazol-2-ylsulfanyl) propan-2-one		93	C ₁₀ H ₁₀ N ₂ OS	>160
5	1-(1,3-benzoxazol-2-ylsulfanyl) propan-2-one		82	C ₁₀ H ₉ NO ₂ S	40
6	5-(chloromethylsulfonyl)-1-methyl-2-trifluoromethyl -1H-benzimidazole		79	C ₁₀ H ₈ ClF ₃ N ₂ O ₂ S	20

7	2-amine-5-(trifluoromethylsulfonyl)-1 <i>H</i> -benzimidazole		79	$C_8H_6F_3N_3O_2S$	40
8	5-(chloromethylsulfonyl)-1,2-dimethyl-1 <i>H</i> -benzimidazole		91	$C_{10}H_{11}ClN_2O_2S$	>160
9	4-chloro-3-nitrophenylmethyl sulfone		92	$C_7H_6ClNO_4S$	20
10	bromodichloromethyl 4-(2,4-dichlorophenoxy)-3-nitrophenyl sulfone		88	$C_{13}H_6BrCl_4NO_5S$	40
11	4-chloro-3-nitrophenylchloromethyl sulfone		89	$C_7H_5Cl_2NO_4S$	>160
12	chloromethyl 4-(2,6-dichlorophenoxy)-3-nitrophenyl sulfone		78	$C_{13}H_8Cl_3NO_5S$	>160
13	1-(4-bromodichloromethylsulfonyl)-2-nitrophenyl-4-methylpiperazine		85	$C_{12}H_{14}BrCl_2N_3O_4S$	40
14	4-(difluoromethylsulfonyl)- <i>N</i> -(2-methylpropyl)-2-nitroaniline		88	$C_{11}H_{14}F_2N_2O_4S$	40
15	4-(bromodichloromethylsulfonyl)- <i>N</i> -methyl-2-nitro- <i>N</i> -phenylaniline		91	$C_{14}H_{11}BrCl_2N_2O_4S$	>160
16	2-(4-chloro-3-nitrophenylsulfonyl)acetamide		84	$C_8H_7ClN_2O_5S$	>160
17	1-(4-(chloromethyl)sulfonyl-2-nitrophenyl)pyrrolidine		83	$C_{11}H_{13}ClN_2O_4S$	>160

Legend: MIC was evaluated after 18 h of incubation

In case of benzimidazoles, derivatives bearing fluorine atoms in the main ring (as in 6) or in halogenomethylsulfonyl moiety (as in 7) displayed good antifungal activity. However, this activity was fully diminished by the substitution of trifluoromethyl with the methyl moiety in the main ring (8). Antifungal properties of nitrophenyl sulfones were attributed to the presence of methylsulfonyl group (9). Interestingly, a single substitution of hydrogen with the chlorine moiety fully diminished the antifungal potential of resultant chloromethyl sulfone (11). Contrariwise, a further addition of halogens to the halogenomethyl sulfonyl group, such as bromine (as in 10 and 13) or fluorine (as in 14) atoms enhanced the antifungal potential of tested derivatives. In order to test the influence of the *C. albicans* *SAP* gene deletion on the susceptibility to new derivatives, randomly selected (active and unactive) benzothiazole, benzimidazole, and nitrophenyl sulfones were further screened against the *C. albicans* *sap* Δ strains. Changes in the mutant's susceptibility to sulfone derivatives were presented in Table III. Interestingly, the *SAP* gene deletion did not impact the activity of the tested benzimidazole sulfones. While, deletion of *SAP9/10* increased susceptibility from 2- (1) to 4-fold (3) to benzothiazole derivatives, lack of the hyphae-associated *SAP4-6* genes increased susceptibility to nitrophenyl sulfones.

Table III. Susceptibility of *C. albicans* *SAP*-deficient strains to sulfone derivatives after 18-h incubation

Strains	MIC (μ g/mL) of Compounds						
	1	3	6	8	11	14	17
SC5314	80	>160	20	>160	>160	40	>160
<i>sap1-3</i> Δ	80	160	20	>160	160	40	>160
<i>sap4-6</i> Δ	80	80	20	>160	40	20	160
<i>sap9/10</i> Δ	40	40	20	>160	>160	20	>160

Legend: 1 means 1-(1,3-benzothiazol-2-ylsulfonyl)propan-2-one; 3 means 2-(1,3-benzothiazol-2-ylsulfonyl)-1-phenylethanone; 6 means 5-(chloromethylsulfonyl)-1-methyl-2-trifluoromethyl-1*H*-benzimidazole; 8 means 5-(chloromethylsulfonyl)-1,2-dimethyl-1*H*-benzimidazole; 11 means 4-chloro-3-nitrophenylchloromethyl sulfone; 14 means 4-(difluoromethylsulfonyl)-*N*-(2-methylpropyl)-2-nitroaniline; 17 means 1-(4-(chloromethyl)sulfonyl-2-nitrophenyl)pyrrolidine.

Since yeast-to-hyphae transition represents a major virulence factor of *C. albicans*, we examined the ability of chosen benzothiazole, benzoimidazole, and benzoxazole sulfone derivatives to inhibit the yeast-to-hyphae transition. Phase-contrast microscopy was applied to visualize an effect of sub-MIC concentrations of selected derivatives: 1, 5, 6, and, 7 on the *C. albicans*' morphogenesis under hyphae inducing conditions (Fig. 1). Obtained images revealed that compounds (1, 5, and 6) inhibited morphogenesis in the concentrations ranging from 0.2 $\times$ to 0.4 $\times$ MIC. Compound 7 failed to inhibit the *C. albicans* morphogenesis. Lead compound 6 was further examined for inhibition of the *C. albicans* mature biofilm using the SEM analysis. Compound 6 efficiently inhibited the hyphae formation in biofilm formed by *sap6* Δ and *sap456* Δ strains, however, it failed to inhibit morphogenesis in *wt* biofilm (Fig. 2).

Fig. 1 Inhibition of morphogenesis of *C. albicans* by new sulfanyl and sulfone derivatives. (A) Inhibitory effect of compounds: 1, 5, and 6 on the *C. albicans* hyphae formation, blastoconidial forms were noted (arrow). Under compound 7, long filaments were observed (arrowhead); (B): non-treated control cells grown in RPMI medium (with EtOH at final concentration of 0.09%), abundant hyphae formation was observed (arrowhead).

Fig. 2 SEM analysis of sulfone 6 against *C. albicans* mature biofilms. (A) *C. albicans sap6Δ* biofilm treated with 6 at 16 $\mu\text{g/mL}$, blastoconidial cell aggregates (arrow) and residue of Caco-2 (arrowhead) were noted; (B) *C. albicans sap6Δ* biofilm treated with 6 at 8 $\mu\text{g/mL}$, compound failed to inhibit fungal morphogenesis - hyphae (open arrow) were observed; (C) *C. albicans sap6Δ* untreated biofilm (control), abundant hyphal growth (open arrow) was observed; (D) *C. albicans sap456Δ* biofilm treated with 6 at 16 $\mu\text{g/mL}$, highly aggregated blastoconidia (arrow) were seen; (E) *C. albicans sap456Δ* biofilm treated with 6 at 8 $\mu\text{g/mL}$, hyphal growth (open arrow) was observed; (F) *C. albicans sap456Δ* untreated biofilm (control), hyphae (open arrow) were noted; (G) *C. albicans* wild type (wt) SC5314 biofilm treated with 6 at 16 $\mu\text{g/mL}$, 6 failed to inhibit fungal morphogenesis, hyphae (open arrow) were observed; (H) SC5314 wt biofilm treated with 6 at 8 $\mu\text{g/mL}$ displayed long true-hyphae (open arrow) (I) *C. albicans* wt untreated biofilm (control), abundant hyphal growth (open arrow) was observed.

DISCUSSION

The excessive use of antifungals together with limited therapeutic choices led to the development of antifungal resistance. Therefore, new compounds with different action modes are urgently needed (11). In this context, sulfone moiety constitutes an important core of many therapeutic agents as well as in drug candidates currently being under development (4). The present study was focused on the investigation of a series of new 17 synthesized sulfanyl and sulfone derivatives for their anti-*Candida* activity. Benzothiazole, benzoxazole, nitrobenzene or benzimidazole rings were chosen as scaffolds for the synthesis of sulfur-organic derivatives based on their antifungal potential (6, 17). Many of these derivatives, particularly compounds: 6 and 9 showed good antifungal activity against *C. albicans*. In line with previous studies (6, 17), performed structure-activity analysis revealed that the presence of the electron-withdrawing groups such as $-\text{CF}_3$ and/or halogens: $-\text{F}$, $-\text{Br}$, $-\text{Cl}$, and $-\text{I}$, generally enhanced the antifungal potential of the tested derivatives. On the contrary to results obtained by Zhao et al. (17), we found that electron-donating groups, such as $-\text{CH}_3$ also contribute to increased antifungal potential.

Inhibition of the *C. albicans* virulence factors instead of cell viability represents new promising antifungal strategy (8, 12). Especially the relationship between *SAP* expression and the susceptibility profile of *C. albicans* isolates are of great interest (8). In this study, we used strains with genetic alternations in the genes encoding Sap1-10 isoenzymes to estimate whether these genes are important for the *C. albicans* susceptibility to new sulfone derivatives based on scaffolds such as the following: nitrophenyl, benzothiazole, and benzimidazole. Previously we demonstrated that the halogenomethyl nitrophenyl sulfone's action mode was associated with a reduced virulence arsenal in terms of pathogenic potential related to the expression of the *SAP4-6* genes, adhesion, and the morphogenesis factors. Sulfones were active against the virulence attributes of *C. albicans*, which is unique to antimycotics (14). Current study confirmed that new nitrophenyl sulfone derivatives share this action mechanism. Moreover, derivatives inactive against *C. albicans* *wt* were effective against the strains attenuated in the hyphae-associated *SAP4-6*, further supporting the role of *SAPs* in the antifungal resistance. Interestingly, we found a clear link between the disruption of *SAP9-10* and the susceptibility profile of *C. albicans* towards benzothiazole sulfones. Sap9 and Sap10 are *C. albicans*' glycosylphosphatidylinositol (GPI)-anchored surface-associated proteinases that play a role in maintenance of the cell wall integrity by proteolytic cleavage of covalently linked cell wall proteins (1). Hypersensitivity of mutant lacking *SAP9/10* to benzothiazole-based sulfones indicates that these compounds target the fungal cell wall and/or cell membrane components.

The ability of *C. albicans* to form biofilms is a major virulence attribute and a challenge to be managed. The effect of biofilm formation on pathogenicity and their inherent resistance to the majority of known antifungals emphasize the need for the development of new antifungals with efficiency against the biofilm mode of growth (9). Hyphae are required for the stable biofilm formation, which suggests that this cell type has unique role in this process (16). Previously we demonstrated that the use of sulfone derivatives can successfully inhibit degradative enzyme production and the induction of hyphal forms constitutively expressed in the *C. albicans* biofilms difficult to prevent by the current antifungal drugs (14). Following current trends (16) that inhibition of morphological

switch may provide an alternative approach to find compounds with a potential to control the *C. albicans* infections, we found compounds: 1, 5 and 6, inhibiting the morphogenesis process at concentrations below their MICs.

Our findings with the lead compound 6 suggest a general strategy for the antifungal agent development that might be useful in limiting the emergence of resistance in the *Candida* strains. Compound 6 combines the classical antifungal activity (MIC=20 µg/mL) with potent inhibition of the fungal morphogenesis, and it can be considered as the lead structure for further optimization.

Acknowledgements

MS and MG were supported by the project 11/EM 1/2018 founded by the National Institute of Public Health-National Institute of Hygiene. ZO was supported by Warsaw University of Technology, Faculty of Chemistry.

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Received: 10 VII 2018

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