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Evaluation of antifungal potential of novel quaternary aryloxyethoxy dialkyl ammonium salts against *Candida* strains

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The spread of resistance to antimycotic drugs among *Candida*, microorganisms that play an important role as pathogens of fungal origin, is a serious problem for the modern medical system. The study aimed to investigate the antifungal properties of aryl acyclic amino alcohols. Previous studies selected ten preparations with the conventional names Kc2, Kc3, Kc14, Kc15, Kc16, Kc22, Kp4, Kp8, Kp18 and Kp19. The antifungal activity of fluconazole, amphotericin B, nystatin, and the surface antiseptics miramistin and decamethoxin was studied. Among these drugs, amphotericin B demonstrated declared efficacy against all strains. Nystatin showed variable effects, and fluconazole showed low efficacy (MIC > 10 µg/mL), especially against *Pichia kudriavzevii* (*Candida krusei*) and *Nakaseomyces glabratus* (*C. glabrata*). Miramistin and decamethoxin had a moderate effect only against some species (MIC 3–5 µg/mL). Compounds Kc14, Kc15, Kc16, Kp8 and Kp18 showed exceptional activity *in vitro*, approaching the efficacy of amphotericin B against *C. parapsilosis*, *C. kefir*, *C. tropicalis* and *C. utilis*. Kc22 demonstrated a broad spectrum of activity. Compounds Kc2, Kc3, Kp4 and Kp19 were more effective than fluconazole, miramistin and decamethoxine, showing similar effects to nystatin. The time-kill assay confirmed the concentration dependence, showing a fungistatic effect at ¼*MIC and a rapid bactericidal effect at 2*MIC. Although the mechanisms of action have not been studied, they are likely related to the disruption of membrane integrity and metabolic processes of fungal cells.

Keywords: *Candida krusei*; *Candida glabrata*; *Candida utilis*; *Candida parapsilosis*; *Candida tropicalis*; *Candida kefir*; *Candida lusitaniae*; MIC; dialkyl ammonium salts.

Introduction

Fungal infections, especially those caused by species of the genus *Candida*, are one of the leading causes of morbidity and mortality among immunocompromised patients, patients in intensive care units or after organ transplantation, etc. *Candida albicans* is the most common causative agent of candidiasis, but recently there has been an alarming trend towards an increase in infections caused by *Candida* non-*albicans* (e.g., *C. tropicalis*, *C. parapsilosis*, etc.), which often exhibit natural or acquired resistance to traditional antimicrobial agents such as fluconazole or other azoles (Keyvanfar et al., 2024).

Since the adoption of the new taxonomic classification in 2022, *C. glabrata* was renamed *Nakaseomyces glabratus* and *C. krusei* was renamed *Pichia kudriavzevii* (Nguyen et al., 2024; Rodríguez-Cerdeira et al., 2024). However, despite the taxonomic changes, most literature still uses the old species names. To avoid possible confusion and provide a better understanding of the material presented, the previous names of yeast-like fungi will be used in this paper.

The problem of antifungal drug resistance is one of the key issues in modern clinical mycology and it is constantly becoming more complex due to the long-term use of existing drugs (Cowen et al., 2015). Resistance can occur due to various mechanisms, including mutations in drug target genes, active drug efflux from cells, and changes in fungal metabolism (Whaley et al., 2017). In particular, the prevalence of infections caused by *Candida* non-*albicans* (*C. glabrata* and *C. krusei*) resistant to fluconazole and other azoles is increasing, making their treatment particularly challenging. According to Arendrup et al. (2023), in the European region, fluconazole resistance of *C. glabrata* strains reaches 30%. Particular attention is drawn to the spread of *C. auris*, which is multidrug-resistant to azoles, echinocandins and, in some cases, even polyenes such as amphotericin B (AmB). Cases of this species have been reported in more than 50 countries on all continents (Pal et al., 2024). Such resistance to multiple classes of antimycotics makes treatment extremely challenging, with limited therapeutic options and high mortality. Analysis of global data reveals significant variations in resistance levels depending on the *Candida* species, geographic region and antimicrobial agents used, highlighting the need for local monitoring and the development of individualised treatment strategies (Arastehfar et al., 2020).

WHO report for 2022 identifies *Candida* spp. as priority pathogens requiring urgent research and development of new treatments. The report highlights the high level of resistance of *Candida* to available antimicrobials, which poses a threat to global health (Alffenaar et al., 2022).

In Ukraine, no systematic nationwide studies of the spread of antimicrobial resistance have been conducted, and local studies and clinical observations indicate an increase in the number of infections caused by resistant species, in particular *C. glabrata* and *C. krusei*, which show reduced sensitivity to fluconazole and other azoles, and even polyenes, which complicates their treatment (Ananyeva, 2019). Growing resistance to antimicrobial agents requires the development of new treatment strategies, including the search and development of new drugs with alternative mechanisms of action that can overcome resistance and have a sufficient level of efficacy (Soriano et al., 2023).

In addition to their clinical impact, candidiasis poses a significant economic burden to healthcare systems. Research conducted by Kullberg & Arendrup (2015) showed that invasive fungal infections lead to increased treatment costs, hospitalisation and mortality, making them an important public health issue.

Against the backdrop of growing resistance to existing antimycotics, the search for new targets for drug development is critical. Researchers are actively exploring alternative treatment strategies, such as inhibiting biofilm formation, modulating the host immune response, and developing antimycotics that act on novel, unconventional targets in fungal cells (Ghannoum & Rice, 2019). Understanding the fundamental mechanisms of resistance and identifying new drug targets is

key to overcoming the problem of *Candida* resistance and improving treatment outcomes for patients with invasive fungal infections (Perlin et al., 2015).

In the context of the search for new antimicrobial agents, compounds belonging to the class of quaternary ammonium salts – aryloxyethoxy dialkyl ammonium derivatives – have attracted particular attention due to their antimicrobial properties (Korotkii et al., 2019). Quaternary ammonium salts are cationic compounds with a broad spectrum of action, including antibacterial, antiviral and antifungal activity (Gilbert & McBain, 2003; Sugii, 2019). The presence of an aryl fragment and an ethoxy group improves pharmacokinetic and pharmacodynamic properties, making them promising candidates for further research (Tang et al., 2013). Research results indicate a wide range of activity of the studied compounds, including antimycotic action (Dronova., 2016; Nastenko et al., 2018).

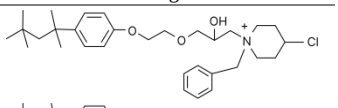
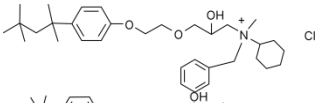
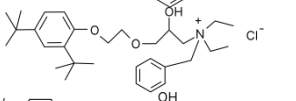
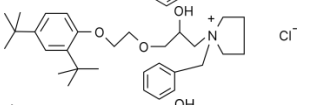
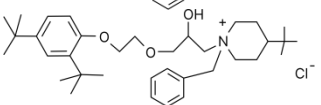
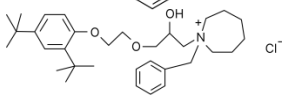
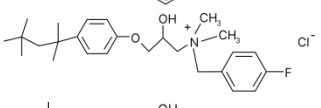
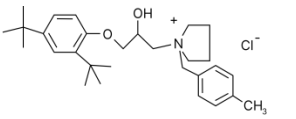
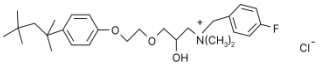
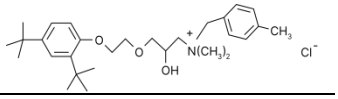
The growing incidence of resistance of *Candida* to traditional antimicrobial drugs necessitates the search for new compounds with improved pharmacological characteristics. In this context, quaternary ammonium salt derivatives represent a promising class of compounds. The study of their antimycotic activity may contribute to the development of new effective therapeutic approaches. The aim of this study was to evaluate the *in vitro* antimycotic activity of newly synthesised compounds, namely quaternary aryloxyethoxy-dialkylammonium salts, against museum strains of *Candida* non-*albicans*.

Materials and methods

The experimental part of the study was carried out at the Department of Microbiology and Parasitology with the Basics of Immunology of the Bogomolets National Medical University. The investigated substances were synthesised at the Institute of Chemistry of the National Academy of Sciences of Ukraine. 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-2,3-epoxypropane was obtained by the reaction of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy]-1-ethanol with epichlorohydrin in the presence of sodium hydroxide (NaOH) and tetrabutylammonium chloride under interfacial catalysis. The resulting glycidyl ester reacted with secondary amines (dimethylamine, diethylamine, 4-methylpiperidine, pyrrolidine, N-methylcyclohexylamine) in ethanol at 50–60 °C to give phenoxy-1-ethoxy-3-(dialkylamino)-2-propanol derivatives. Further interaction of the amino derivative with alkyl halides (benzyl chloride, 4-methylbenzyl chloride, 4-fluorobenzyl chloride) in acetone at 40–50 °C formed the final quaternary salts. The investigated substances were synthesised at the Institute of Chemistry of the National Academy of Sciences of Ukraine. 1-[4-(1,1,3,3-tetramethyl butyl)phenoxy-1-ethoxy]-2,3-epoxypropane was obtained by the reaction of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy]-1-ethanol with epichlorohydrin in the presence of sodium hydroxide (NaOH) and tetrabutylammonium chloride under interfacial catalysis. The quaternary salts presented in this study have been previously patented under Patent Nos. 86109 and 93482 by Korotkyi and Smertenko in 2013 and 2014.

The selection of substances for the study was based on previous studies of the spectrum and degree of activity of aryloxyethoxy dialkyl ammonium quaternary salts against *Candida* (Nastenko et al., 2018). To evaluate the efficacy, comparison drugs, standard antimycotics of polyene and triazole groups (AmB, nystatin and fluconazole) and surface antiseptics of the group of quaternary ammonium salt derivatives (miramistin and decamethoxine) were selected. The full list of compounds is given in Table 1.

Table 1
Structure of the investigated quaternary aryloxyethoxy dialkyl ammonium salts

Connection	R_1	R_2	R_3	R_4	n	Structural name	Image
Kc2	4-(1,1,3,3-tetramethylbutyl) phenoxy	-	-4-$CH_3CH(CH_2)_4$	benzyl	2	1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-benzyl 4-methylpiperidinium)-2-propanol chloride	
Kc3	4-(1,1,3,3-tetramethylbutyl) phenoxy	methyl	cyclohexyl	benzyl	2	1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-benzyl N-methyl cyclohexalamino)-2-propanol chloride	
Kc14	4-(1,1,3,3-tetramethylbutyl) phenoxy	-	-$(CH_2)_6$	benzyl	2	1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl dimethylamino)-2-propanol chloride	
Kc15	2,4-ditrobutylphenox	-	-$(CH_2)_4$	benzyl	2	1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl pyrrolidinium)-2-propanol chloride	
Kc16	2,4-ditrobutylphenox	-	4-$CH_3CH(CH_2)_4$	benzyl	2	1-[2,4-ditrobutylphenoxy-1-ethoxy]-3-(N-(4-methyl benzyl)dimethylamino)-2-propanol chloride	
Kc22	2,4-ditrobutylphenox	-	-$(CH_2)_6$	benzyl	2	1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl hexamethylenimine)-2-propanol chloride	
Kp4	4-(1,1,3,3-tetramethylbutyl) phenoxy	methyl	methyl	4-F-benzyl	0	1-[4-(1,1,3,3)-tetramethyl butyl)-phenoxy]-3-(N-(4-F-benzyl)-dimethylammonium)-2-propanol chloride	
Kp8	2,4-ditrobutylphenox	-	-$(CH_2)_4$	-$(CH_2)_4$	0	1-(2,4-ditrobutyl phenoxy)-3-N-(4-CH3-benzyl)-pyrrolidinium)-2-propanol chloride	
Kp18	4-(1,1,3,3-tetramethylbutyl) phenoxy	methyl	methyl	4-F-benzyl	2	(1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-(N-(4-F benzyl)dimethylamino)-2-propanol chloride	
Kp19	4-(1,1,3,3-tetramethylbutyl) phenoxy	methyl	methyl	4-methyl benzyl	2	1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-(4-methyl benzyl)dimethylamino)-2-propanol chloride	

To test the antifungal properties of the compounds, we used test microorganisms obtained from the L. V. Gromashevsky Institute of Epidemiology and Infectious Diseases of the National Academy of Medical Sciences of Ukraine: *Candida krusei* RN 71062, *Candida utilis* UCM Y-1597, *Candida parapsilosis* UCM Y-73, *Candida tropicalis* UCM Y-2502, *Candida kefir* UCM Y-60, *Candida glabrata* No. 199, *Candida lusitaniae* No. 168.

The experimental part was divided into 3 parts: determination of the activity of comparison drugs against non-*albicans* museum representatives, study of the activity of compounds and study of the kinetics of death of test microorganisms of isolates.

For all experiments, daily cultures of *Candida* were used to prepare inoculum (1.5×10^6 CFU/mL) in RPMI-1640 medium (Hi-Media). Cultivation was performed at 37 °C for 48 hours, after which the results were recorded.

The study of the antifungal effect of compounds on museum strains of *Candida* was carried out by the method of serial dilutions. An inoculum of a daily culture of microorganisms was added to the culture medium to determine the minimum inhibitory concentration (MIC). The concentration at which there were no signs of microbial growth was taken as the MIC. The antifungal activity was monitored by direct inoculation of the suspension into a sterile culture medium (Berkow et al., 2020).

To assess the kinetics of microbial death, time-kill curves were constructed. This method allows us to study the effect of the antimicrobial compounds on the viability of the *Candida* and to build a kinetic curve. The inoculum of the daily culture was inoculated into RPMI-1640 nutrient medium containing the compounds at concentrations of 0.25*MIC, 1*MIC and 2*MIC, as well as into control vials without antimicrobial agents.

During the experiment, 500 µL samples were taken at 0, 2, 4, 8 and 24 hours. To determine the number of viable cells, serial tenfold dilutions were performed using sterile saline. An aliquot of the diluted suspension was mixed with Sabouraud's agar, and the resulting mixture was plated onto Petri dishes and incubated. At specified intervals from the start of cultivation (0, 2, 4, 8 and 24 hours), 500 µL of culture was taken from each vial and diluted 10 and 100 times with sterile saline. The resulting aliquot was added to a molten medium cooled to 45 °C at a suspension to medium ratio of 1:9. The content of the tube was poured into Petri dishes, which were then incubated in a thermostat. The results were analysed by plotting the percentage decrease in log 10 CFU/mL against time. The fungicidal activity of the compounds was considered to be achieved if a 99.9% reduction in the number of viable cells was observed compared to the initial inoculum density (Klepser et al., 1998).

The results were analysed statistically and presented as x ± SD (mean ± standard deviation). For comparisons between groups, the ANOVA method was used, followed by the Tukey's post-hoc test to identify statistically significant differences. The Mann-Whitney test was used to compare two independent groups in the case of non-normal distribution. The results were considered reliable at P values < 0.05.

Results

Among the comparison drugs, polyene antibiotics demonstrated the highest efficacy. AmB was effective against all tested *Candida* species. The mean values of the minimum inhibitory concentration (MIC) ranged from 0.22 ± 0.09 µg/mL for *C. utilis* to 0.87 ± 0.13 for *C. krusei*. The MIC for *C. kefir* was 0.24 ± 0.08 µg/mL, *C. tropicalis* – 0.48 ± 0.17, *C. lusitaniae* – 0.58 ± 0.13, *C. parapsilosis* – 0.68 ± 0.15 and *C. glabrata* – 0.68 ± 0.16.

Nystatin showed variable efficacy. Thus, a relatively high inhibitory effect was observed against *C. utilis* (MIC – 0.58 ± 0.13 µg/mL), *C. kefir* (0.68 ± 0.15) and *C. lusitaniae* (0.77 ± 0.15). As for *C. tropicalis* and *C. parapsilosis*, the MICs were 1.56 ± 0.31 and 2.14 ± 0.62 µg/mL, respectively. In contrast, *C. krusei* (5.46 ± 1.24) and *C. glabrata* (6.25 ± 1.24) showed significantly reduced susceptibility to nystatin.

Triazole derivatives showed little activity against *Candida*. The MIC value of fluconazole against *C. kefir* was 3.51 ± 0.50 µg/mL, for *C. lusitania* – 5.07 ± 1.51, and for *C. parapsilosis* – 5.46 ± 1.24. The concentration that inhibited *C. utilis* was 10.16 ± 3.03, and *C. tropicalis* increased to 11.72 ± 3.19 µg/mL. The MIC values for other *Candida* significantly exceeded the susceptibility values of other strains. The MIC of *C. krusei* was 87.50 ± 19.76, and *C. glabrata* – 225.00 ± 32.27 µg/mL.

Miramistin demonstrated variable efficacy against different *Candida* species. The drug was effective against *C. kefir* and *C. lusitaniae* (MIC – 3.12 ± 0.62 µg/mL), with a decrease to 4.29 ± 1.24 and 4.68 ± 1.01 against *C. utilis* and *C. parapsilosis*. As for the other candidates, the representative of ammonium derivatives demonstrated low efficacy, with MICs exceeding 10 µg/mL.

Candida utilis was the most sensitive to decametoxin (MIC – 4.29 ± 1.24 µg/mL). For *C. parapsilosis*, *C. kefir* and *C. lusitaniae*, the MIC was 4.68 ± 1.01, and for *C. glabrata* – 5.46 ± 1.24. The least sensitive representative was *C. krusei*, the MIC of decametoxin for this non-albicans representative exceeded 10 µg/mL – 10.94 ± 2.47.

The study of the activity of the compounds against museum representatives of non-*albicans* allowed us to expand the knowledge of the spectrum of activity of quaternary aryloxyethoxy dialkyl ammonium salts against fungi of the genus *Candida*. According to the data presented in Figure 1, the peculiarities of the antimycotic action of the compounds varied in different species of *Candida*.

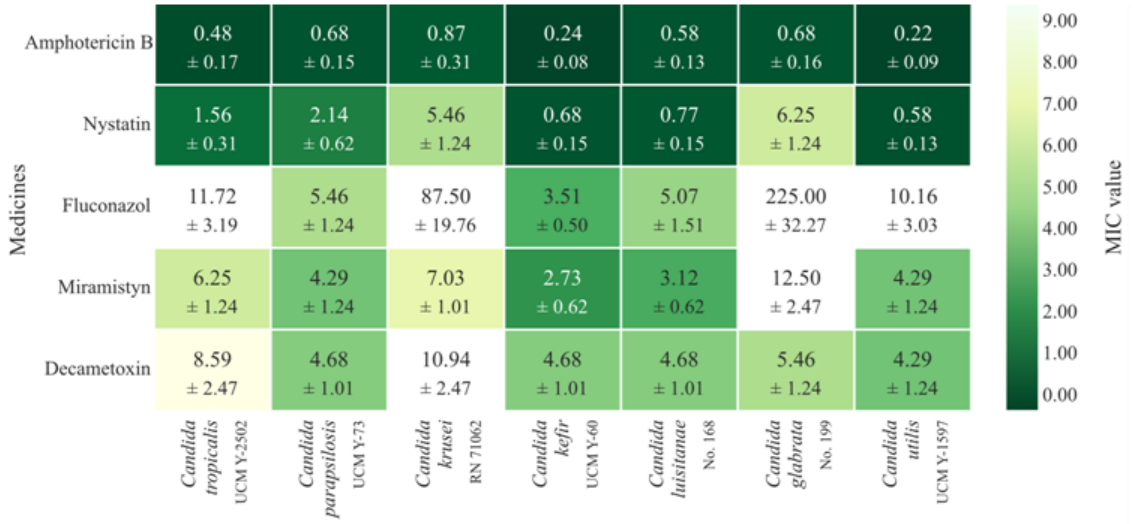


Fig. 1. Heatmap of MIC values (mean ± SD, n = 3) for commercial antimicrobials against museum strains of *Candida* spp.: the MIC values (µg/mL) were determined for amphotericin B, nystatin, fluconazole, miramistin, and decamethoxin against different *Candida* species; darker green shades indicate lower MIC values, whereas lighter shades represent higher MIC values

Compound Kc2 demonstrated moderate antifungal activity against *Candida* strains. The highest MIC values were obtained against *C. parapsilosis* (0.73 ± 0.20) and *C. kefir* (1.17 ± 0.25). The MICs for *C. luisitanae*, *C. glabrata*, and *C. utilis* were 1.85 ± 0.76, 1.95 ± 0.69, and 2.14 ± 0.62 μg/mL. As for *C. tropicalis* and *C. krusei*, the test substance showed relatively weak activity compared to the entire sample. The MICs of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-benzyl 4-methylpiperidinium)-2-propanol chloride for these species were 3.71 ± 1.51 and 2.93 ± 0.80 μg/mL, respectively.

Kc3 has a broad antifungal spectrum with marked efficacy against most *Candida* strains. The compound showed the highest activity against *C. tropicalis*, *C. utilis* (MIC – 0.53 ± 0.15) and *C. parapsilosis* (MIC – 0.73 ± 0.40). The determined MICs of the test substance for the museum strains of *C. kefir*, *C. luisitanae* and *C. glabrata* are as follows: 1.07 ± 0.31, 1.26 ± 0.38, 1.56 ± 0.76 μg/mL. Moderate efficacy was observed against *C. krusei*, with the MIC of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-benzyl N-methyl cyclohexalamino)-2-propanol chloride being 3.51 ± 0.50 μg/mL.

The compound Kc14 demonstrated the highest efficacy against *C. parapsilosis* (MIC – 0.31 ± 0.09) and C. kefir (0.53 ± 0.15). Most microorganisms showed moderate sensitivity to the test substance. The MIC for *C. glabrata* was 1.17 ± 0.43 μg/mL, for *C. utilis* – 1.65 ± 0.79 and 2.14 ± 0.62 for *C. luisitanae*. The lowest antifungal effect was determined for *C. tropicalis* (2.92 ± 0.80) and *C. krusei* (3.12 ± 0.62).

The compound Kc15 showed significant efficacy against *C. kefir* – 0.34 ± 0.08 and *C. parapsilosis* – 0.48 ± 0.17 μg/mL with a moderate decrease against other strains. Activity against most test microorganisms was determined in the range of 2–3 μg/mL. *C. krusei* showed the lowest sensitivity to the compound. The MIC of 1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl pyrrolidinium)-2-propanol chloride for this *Candida* species was 3.51 ± 0.50 μg/mL.

The compound Kc16 has high specific activity against *C. kefir*, *C. parapsilosis* and *C. utilis*. The MIC of the compound against these species was 0.68 ± 0.15 μg/mL. The MIC value for *C. tropicalis* increased to a concentration of 1.07 ± 0.31, and for *C. luisitanae* – to 1.95 ± 0.69 μg/mL. The lowest activity was recorded against *C. glabrata* and *C. krusei*, with the MIC of 1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-(4-methyl benzyl)dimethylamino)-2-propanol chloride being 3.12 ± 0.62 and 4.68 ± 1.01 μg/mL, respectively.

Compound Kc22 demonstrated high efficacy against most *Candida*. A concentration of 1 μg/mL had an inhibitory effect against *C. utilis* (0.48 ± 0.17), *C. tropicalis* (0.53 ± 0.15), *C. parapsilosis* (0.63 ± 0.19). Moderate efficacy of 1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl hexamethylenimine)-2-propanol chloride was recorded against *C. luisitanae* (1.26 ± 0.38), *C. kefir* (1.36 ± 0.31) and *C. glabrata* (2.73 ± 0.62), with a decrease in effectiveness against *C. krusei* (4.29 ± 1.24), which is consistent with the general pattern of activity of the substances.

The next compound, Kp4, demonstrated significant antifungal activity against *C. tropicalis*, MIC – 0.87 ± 0.13 μg/mL. The compound showed MICs in the range of 1–2 μg/mL against *C. kefir* (1.17 ± 0.25), *C. utilis* (1.46 ± 0.40), *C. parapsilosis* (1.56 ± 0.31), *C. glabrata* (1.95 ± 0.69), *C. luisitanae* (2.14 ± 0.62). *C. krusei* showed the lowest sensitivity to 1-[4-(1,1,3,3)-tetramethyl butyl)-phenoxy]-3-(N-(4-F-benzyl)-dimethylammonium)-2-propanol chloride compared to other MIC species – 3.12 ± 0.62 μg/mL.

The study of Kp8 revealed a strong inhibitory effect on *C. parapsilosis* (0.38 ± 0.08), *C. kefir* (0.53 ± 0.15) and *C. tropicalis* (0.73 ± 0.20). The MIC for other representatives of yeast-like fungi exceeded 1 μg/mL, in *C. luisitanae* 1.56 ± 0.31, *C. glabrata* 1.46 ± 0.33, *C. utilis* 1.07 ± 0.31 μg/mL. At the same time, for *C. krusei*, the MIC of 1-(2,4-ditrobutyl phenoxy)-3-N-(4-CH3-benzyl)-pyrrolidinium)-2-propanol chloride was 2.53 ± 0.76 μg/mL, which means lower efficiency of the compound compared to other strains.

The highest susceptibility to Kp18 was observed in *C. tropicalis* (0.43 ± 0.06), *C. kefir* (0.63 ± 0.19), *C. luisitanae* (0.68 ± 0.15) and *C. utilis* (0.53 ± 0.15). Moderate activity of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-(N-(4-F benzyl)dimethylamino)-2-propanol chloride was observed against *C. parapsilosis*, *C. krusei* (1.26 ± 0.38) and *C. glabrata* (2.14 ± 0.62). The compound Kp19 demonstrates promising antifungal properties, in particular, high activity against *C. tropicalis* (0.77 ± 0.15), *C. kefir* (0.82 ± 0.19) and *C. utilis* (0.93 ± 0.37). At the same time, its effectiveness is significantly reduced against other yeast-like fungi, the MIC against *C. parapsilosis* was 1.26 ± 0.38, *C. luisitanae* 1.17 ± 0.43 μg/mL. The lowest activity of 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-3-(N-(4-methyl benzyl)dimethylamino)-2-propanol chloride was observed against *C. glabrata* (2.53 ± 0.76) and *C. krusei* (2.92 ± 0.80), which demonstrates the general trend of the study. The results of the activity of all studied quaternary salts of aryloxyethoxy dialkyl ammonium are shown in Figure 2.

The time-kill study allowed us to study the dynamics of growth inhibition of non-albicans depending on the time and concentration of the drugs under study. Control groups that were not exposed to the drugs showed the expected stable increase in cell concentration throughout the study period, which confirms their normal growth in the absence of inhibitors.

The effect of Kc2 compound at a concentration of ¼*MIC was manifested in the slowing of growth and reduction of the number of *Candida* spp. cells during the first eight hours of the study. The initial concentration corresponding to the MIC during the first thirty minutes did not lead to a significant decrease in the number of cells. However, two hours after the start of the study, the proportion of live cells was 36.3 ± 2.3%. Complete inhibition of population growth was observed after four hours. The use of 2*MICs had a rapid and pronounced effect, achieving complete cell destruction in 120 minutes.

The study of the effect of the compound Kc3 showed that at a concentration of ¼*MIC, no inhibitory effect was observed during the first 30 minutes of exposure. However, a gradual decrease in the number of cells to 68.2 ± 2.3% was observed within eight hours. After this time interval, the growth of the culture was restored. The application of a concentration equal to the MIC (1*MIC) led to uniform cell death, reaching a level of 3.5% after four hours, followed by a decrease to 0%. The concentration of 2*MIC showed a sharp decrease in cell viability, reaching zero after 120 minutes.

In the time-kill experiment of Kc14 compound at a concentration of ¼*MIC, a slight decrease in the number of cells to 96.1% was recorded after 30 minutes. Subsequently, there was a gradual decrease to 63.5 ± 3.3% by the eighth hour. At the end of the study, the number of microorganisms partially recovered to 88.7% ± 3.9%. The concentration of 1*MIC caused a gradual death of yeast-like fungi of the genus *Candida*, and complete elimination was recorded four hours after the start of the experiment. As in the case of the previous two compounds, Kc14 at 2*MIC caused complete death of the test cultures within 120 minutes.

The study of the compound Kc15 (¼*MIC) showed a slight inhibitory effect during the first eight hours of the study. At the end of this period, the number of fungal cells was restored to 90%. At a concentration of 1*MIC, the number of cells gradually decreased to 60.9% (standard deviation – 2.3%) after 60 minutes, and at the second hour to 43.8 ± 2.2%. Complete inhibition of growth of all species, except *C. utilis*, occurred at the fourth hour. The use of double MIC (2*MIC) caused the death of more than 40% of cells after 60 minutes, and after 2 hours, complete cell destruction was achieved.

The results of the study of the dynamics of *Candida* growth inhibition by compounds Kc2, Kc3, Kc14, Kc15, Kc16, Kc22 are shown in Figure 3. The visible inhibitory effect of Kc16 at a concentration of ¼*MIC was a gradual decrease in the number of cells to the level of 60.8 ± 3.8% within eight hours. However, the antifungal effect of this concentration was not long-lasting, and 48 hours after the start of the study, the cell concentration was 92.2 ± 4.0%. The 1*MIC concentration caused a gradual decrease in cell viability to 13.9% after 240 minutes and then to 0% after 480 minutes.

The visible inhibitory effect of Kc16 at a concentration of ¼*MIC was a gradual decrease in the number of cells to the level of 60.8 ± 3.8% within eight hours. However, the antifungal effect of this concentration was not long-lasting, and 48 hours after the start of the experiment, the cell concentration was 92.2 ± 4.0%. The concentration of 1*MIC caused a gradual decrease in cell viability to 13.9%

after 240 minutes and then to 0% after 480 minutes. These results can be explained by the fact that this concentration completely inhibited the viability of *C. krusei*, *C. tropicalis*, *C. parapsilosis* and *C. kefir* species within four hours. Inhibition of other *Candida* species occurred in eight hours. As in all previous cases, the concentration of 2*MIC 1-(2,4-ditrobutylphenoxy-1-ethoxy)-3-(N-benzyl 4-methylpiperidyl)-2-propanol chloride completely inhibited all *Candida* within two hours.

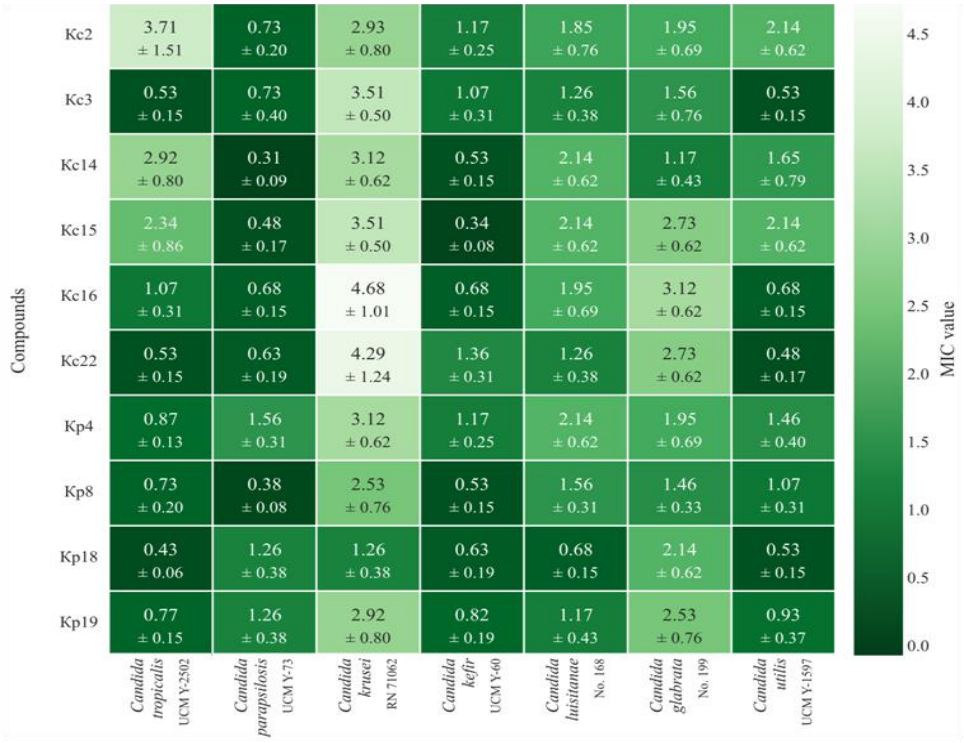


Fig. 2. Heatmap of MIC values (mean ± SD, n = 3) for quaternary salts of aryloxyethoxy dialkyl ammonium against museum strains of *Candida* spp.: the minimum inhibitory concentration (MIC) values (μg/mL) were determined for amphotericin B, nystatin, fluconazole, miramistin, and decamethoxin against different *Candida* species; darker green shades indicate lower MIC values, whereas lighter shades represent higher MIC values

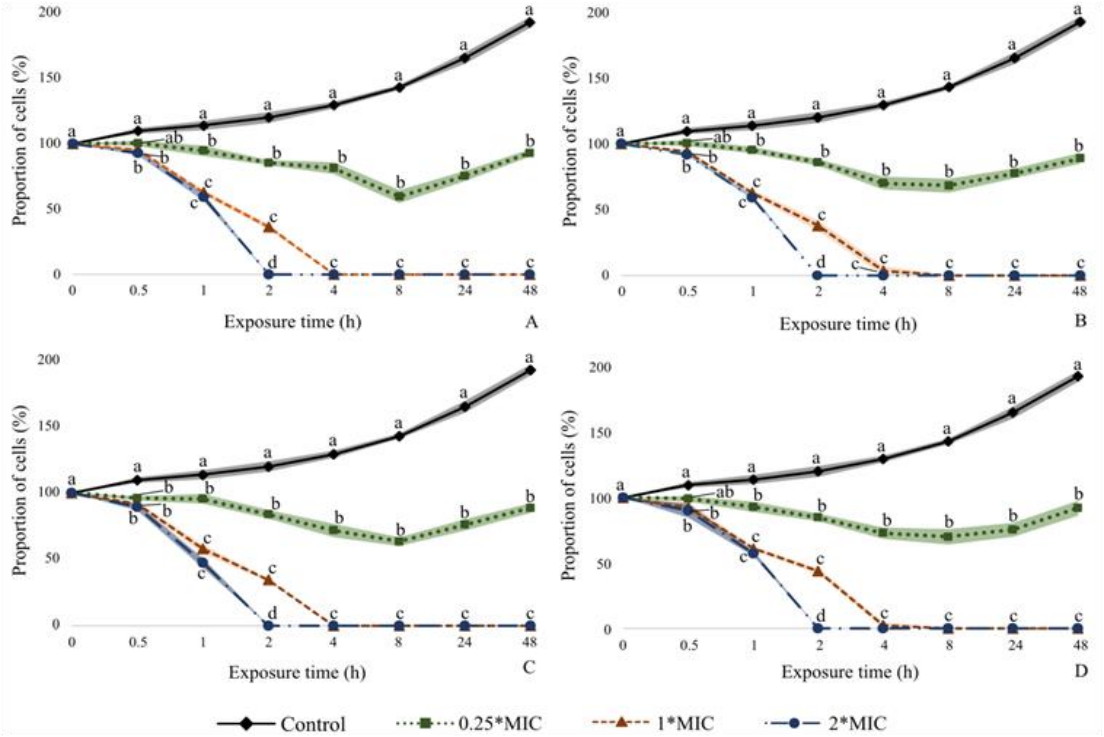


Fig. 3. Time-kill curves of *Candida* yeast strains exposed to newly synthesized quaternary aryloxyethoxy dialkyl ammonium derivatives (A – Kc2, B – Kc3, C – Kc14, D – Kc15) at concentrations of 0.25*MIC, 1*MIC, and 2*MIC (n = 21): cell concentration (mean ± SD) is expressed as a percentage, with 100% corresponding to Log 10^6 CFU/mL, and was measured at different exposure times (0.5, 1, 2, 4, 8, 24, and 48 h); the control group (black solid line) represents yeast growth without compound exposure; the dotted green line represents 0.25*MIC, the dashed brown line represents 1*MIC, and the solid blue line represents 2*MIC; different letters (a, b, c, d) indicate significant differences in yeast cell concentration at each time point according to ANOVA followed by Tukey's post-hoc test ($P < 0.05$)

Eight hours after the start of the study, the Kc22 compound at a concentration of ¼*MIC inhibited almost 40% of cells among all tested *Candida* species. However, after 48 hours, the inhibitory effect of the compound decreased, and the proportion of viable cells was restored to 95%. The 1*MIC concentration demonstrated high efficacy against candida. After four hours, the average value of the proportion of live cells decreased to 3.5%. The 4-hour exposure time was sufficient to inhibit the growth of all *Candida* species, except *C. utilis*. The 2*MIC concentration again showed the highest efficiency, causing the complete killing of the sample after 2 hours. The results of the study of the dynamics of *Candida* growth inhibition are shown in Figure 3.

The compound Kp4 showed a typical effect for all aryl acyclic amino alcohols studied. The concentration of ¼*MIC caused cell death up to 57.2 ± 3.9% during the first eight hours, after which the culture growth was restored. The 1*MIC concentration completely inhibited the growth of all strains after eight hours. Within four hours, the average cell survival rate decreased to 11.3 ± 5.0%, with complete inhibition of growth of *C. krusei*, *C. tropicalis*, *C. parapsilosis* achieved within this time period. The use of 2*MIC concentration increased the effectiveness of the drug, achieving complete cell death in two hours.

The results of the time-kill assay for Kp8 demonstrate the general trend of all previously analysed compounds. The concentration of ¼*MIC caused a smooth death of the culture followed by the recovery of the culture (from 61.5% to 98.4%). The dilution corresponding to the MIC after four hours caused the death of all *Candida* species except *C. utilis*, which was completely inhibited after eight hours. The concentration of 2*MIC caused a complete decrease in cell viability to 0% after 120 minutes.

The concentration of ¼*MIC Kp18, similar to the previous compounds studied, initially caused a gradual decrease in the number of cells. However, after eight hours, growth resumed. A concentration equal to the MIC caused complete death of all species within four hours, except for *C. krusei*, which was completely inhibited after eight hours. A concentration of 2*MIC of the compound 1-[4-(1,1,3,3-tetramethylbutyl)phenoxy-1-ethoxy]-(N-(4-F benzyl)dimethylamino)-2-propanol chloride, similar to other compounds in this concentration, caused the destruction of the cell population in two hours.

In the time-kill study, the compound Kp19 at a concentration of 0.25*MIC caused a gradual decrease in the number of cells, after which the culture growth was restored. At a concentration of 1*MIC, the number of cells decreased to 27.3 ± 3.5 % after 4 hours. Complete inhibition of growth with the achievement of zero cell count occurred after 8 hours. The concentration of 2*MIC, as in other cases, led to a rapid decrease to 0% already at 120 minutes of exposure. The results of the study of the dynamics of *Candida* growth inhibition by compounds Kp4, Kp8, Kp18, Kp19 are shown in Figure 4.

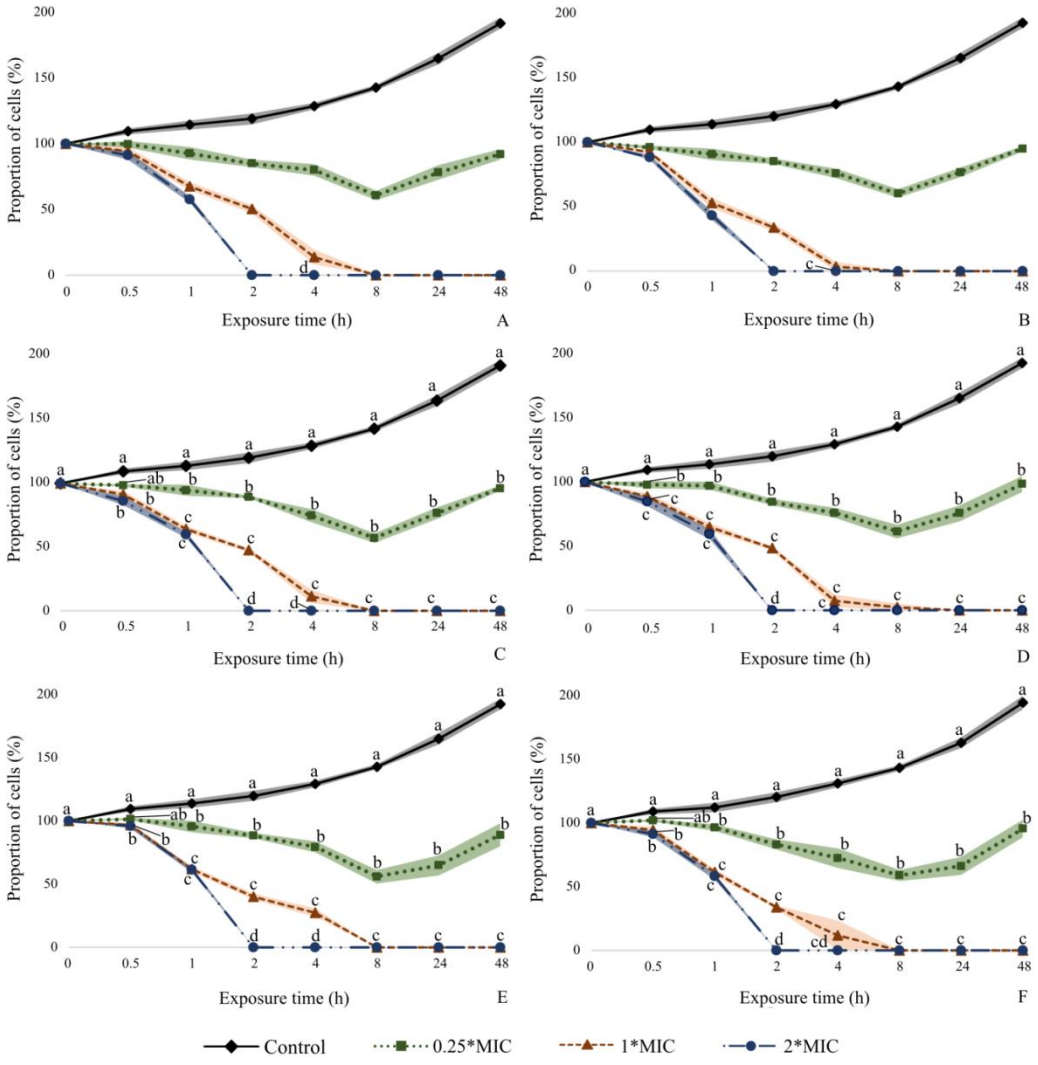


Fig. 4. Time-kill curves of *Candida* yeast strains exposed to newly synthesized quaternary aryloxyethoxy dialkyl ammonium derivatives (A – Kc16, B – Kc22, C – Kp4, D – Kp8, E – Kp18, F – Kp19) at concentrations of 0.25*MIC, 1*MIC, and 2*MIC (n = 21): cell concentration (mean ± SD) is expressed as a percentage, with 100% corresponding to Log 10^6 CFU/mL, and was measured at different exposure times (0.5, 1, 2, 4, 8, 24, and 48 h); the control group (black solid line) represents yeast growth without compound exposure; the dotted green line represents 0.25*MIC, the dashed brown line represents 1*MIC, and the solid blue line represents 2*MIC; different letters (a, b, c, d) indicate significant differences in yeast cell concentration at each time point according to ANOVA followed by Tukey's post-hoc test ($P < 0.05$)

Discussion

The results of our study aimed at evaluating the *in vitro* antimycotic activity of comparison drugs and aryl acyclic amino alcohols against museum strains of *C. albicans* allowed us to expand our knowledge of the antimycotic properties of aryl acyclic amino alcohols.

AmB demonstrated the highest activity against all *Candida* species studied, with the MIC of the antibiotic not exceeding 1 μg/mL. This result is in line with its widely recognised efficacy as the "gold standard" in the treatment of mycoses (Ghannoum & Rice, 1999). Despite its toxicity, AmB remains an important treatment option, especially for infections caused by resistant strains (Akinosoglou et al., 2024).

Nystatin showed variable efficacy with better results against *C. utilis*, *C. kefir*, and *C. lusitaniae* and significantly reduced activity against *C. krusei* and *C. glabrata*. These results confirm the known resistance of *C. glabrata* to nystatin and some other antifungal drugs (Frías-Deleón et al., 2021).

Fluconazole was the least effective of the drugs studied. The MIC values exceeded the recommended values, indicating low efficacy of the drug against these representatives (Berkow & Lockhart, 2017). A similar decrease in the effectiveness of fluconazole is also observed in clinical practice, which emphasises the need to use alternative treatment for infections caused by these species (Lee et al., 2021).

The antiseptic drugs miramistin and decamethoxin demonstrated moderate efficacy against *C. utilis*, *C. parapsilosis*, *C. kefir* and *C. lusitaniae*, but their effect was significantly reduced against other strains. In particular, *C. krusei* showed low sensitivity to both drugs. The MIC of the compounds exceeded 10 μg/mL. It is worth noting that the corresponding result is typical for these compounds and is confirmed by the sources reviewed (Sydorchuk et al., 2022).

Particular attention is drawn to the results of the study of new compounds that are derivatives of quaternary salts of aryloxyethoxy dialkyl ammonium. The antifungal properties of these substances have been repeatedly described in the literature (Korotkii et al., 2019). Out of the studied sample of aryl acyclic amino alcohols, Kc14, Kc15, Kc16, Kc22, Kp8 and Kp18 demonstrated high activity against many *Candida* species, including those known to be resistant to traditional antifungal drugs.

Compounds Kc14, Kc15, Kc16, Kc22, Kp8 and Kp18 showed more pronounced efficacy. In particular, Kc14 and Kc15 showed exceptional efficacy against *C. parapsilosis* and *C. kefir*, which was comparable to that of AmB. Compounds Kc16 and Kc22 were highly active against *C. kefir*, *C. parapsilosis* and *C. utilis*. Compound Kp8 showed a pronounced antimycotic effect against *C. parapsilosis*, *C. kefir* and *C. tropicalis*. Kp18 showed high activity against all strains, especially against *C. tropicalis*, *C. kefir*, *C. luisitanae* and *C. utilis*, demonstrating performance on par with AmB.

The compounds Kc2, Kc3, Kp4 and Kp19 showed moderate or variable efficacy. These substances showed moderate activity against all representatives of yeast-like fungi. The antifungal effect of the studied aryl acyclic amino alcohols exceeded that of fluconazole, miramistin and decamethoxine, demonstrating an effect similar to that of nystatin, which confirms their potential.

The study of the time-kill dynamics of *Candida* growth inhibition allowed us to evaluate the antimycotic dynamics of the newly synthesised compounds, derivatives of quaternary aryloxyethoxy dialkyl ammonium salts. All compounds at a concentration of ¼*MIC initially showed a slowdown in growth, but later the population recovery was observed, indicating their fungistatic effect at low concentrations. When using 1*MIC, gradual cell death was observed, with complete growth inhibition achieved after 4–8 hours. Increasing the concentration to 2*MIC resulted in rapid and complete cell killing in all cases within two hours.

It is known from the literature that the antimicrobial properties of quaternary aryl acyclic amino alcohol derivatives are due to an increase in cytoplasmic membrane permeability, changes in the ratio of fatty acids and monosaccharides in the cell wall, and disruption of metabolic and respiratory processes (Dronova, 2015). This explains the fungostatic effect at concentrations of ¼*MIC, when the concentration of the compound is insufficient to destroy the entire volume of cells, but the changes caused by aryl acyclic alcohols are noticeable for instant recovery, so the mechanisms of antifungal action of compounds require detailed study.

Conclusion

The *in vitro* antimycotic activity of the newly synthesised compounds, derivatives of quaternary salts of aryloxyethoxy dialkyl ammonium, revealed their significant potential against *Candida* non-*albicans*. AmB demonstrated the highest efficacy among the comparison drugs against all species. Nystatin showed variable activity, decreasing effectiveness against *C. krusei* and *C. glabrata*. Fluconazole was the least effective, indicating an existing resistance problem. The antiseptics miramistin and decamethoxin also showed limited effect against most of the strains tested, which is in line with the results of previous studies.

The newly synthesised compounds Kc14, Kc15, Kc16, Kp8 and Kp18 demonstrated exceptional efficacy, often approaching AmB in terms of their performance, especially against *C. parapsilosis*, *C. kefir*, *C. tropicalis* and *C. utilis*. The compound Kc22 showed a broad spectrum of action, effectively inhibiting the growth of many *Candida* species. The compounds Kc2, Kc3, Kp4 and Kp19 outperformed the efficacy of fluconazole, miramistin and decamethoxine.

The results of the time-kill assay characterised the dependence of the compounds' effectiveness on concentration and exposure time. Low concentrations had a predominantly fungistatic effect, while higher concentrations resulted in a rapid fungicidal effect. Thus, the results obtained made it possible to identify the most promising compounds for the development of new antifungal drugs, as they have a high antimycotic effect, especially against *Candida* non-*albicans* species that are resistant to traditional antifungal agents.

Further research will be aimed at studying the mechanisms of action, toxicity and pharmacokinetic properties of these compounds, which is necessary for their possible clinical use.

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