

Synergic Effect of Phthalide Lactones and Fluconazole and Its New Analogues as a Factor Limiting the Use of Azole Drugs against Candidiasis

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Streszczenie

The resistance of *Candida albicans* and other pathogenic yeasts to azole antifungal drugs has increased rapidly in recent years and is a significant problem in clinical therapy. The current state of pharmacological knowledge precludes the withdrawal of azole drugs, as no other active substances have yet been developed that could effectively replace them. Therefore, one of the anti-yeast strategies may be therapies that can rely on the synergistic action of natural compounds and azoles, limiting the use of azole drugs against candidiasis. Synergy assays performed in vitro were used to assess drug interactions Fractional Inhibitory Concentration Index. The synergistic effect of fluconazole (**1**) and three synthetic lactones identical to those naturally occurring in celery plants—3-n-butylphthalide (**2**), 3-n-butylidenephthalide (**3**), 3-n-butyl-4,5,6,7-tetrahydrophthalide (**4**)—against *Candida albicans* ATCC 10231, *C. albicans* ATCC 2091, and *C. guilliermondii* KKP 3390 was compared with the performance of the individual compounds separately. MIC₉₀ (the amount of fungistatic substance (in µg/mL) inhibiting yeast growth by 90%) was determined as 5.96–6.25 µg/mL for fluconazole (**1**) and 92–150 µg/mL for lactones **2–4**. With the simultaneous administration of fluconazole (**1**) and one of the lactones **2–4**, it was found that they act synergistically, and to achieve the same effect it is sufficient to use 0.58–6.73 µg/mL fluconazole (**1**) and 1.26–20.18 µg/mL of lactones **2–4**. As fluconazole and phthalide lactones show synergy, 11 new fluconazole analogues with lower toxicity and lower inhibitory activity for CYP2C19, CYP1A2, and CYP2C9, were designed after in silico testing. The lipophilicity was also analyzed. A three-carbon alcohol with two rings was preserved. In all compounds 5–15, the 1,2,4-triazole rings were replaced with 1,2,3-triazole or tetrazole rings. The hydroxyl group was free or esterified with phenylacetic acid or thiophene-2-carboxylic acid chlorides or

with adipic acid. In structures **11** and **12** the hydroxyl group was replaced with the fragment $-\text{CH}_2\text{Cl}$ or $=\text{CH}_2$. Additionally, the difluorophenyl ring was replaced with unsubstituted phenyl. The structures of the obtained compounds were determined by ^1H NMR, and ^{13}C NMR spectroscopy. Molecular masses were established by GC-MS or elemental analysis. The MIC_{50} and MIC_{90} of all compounds **1–15** were determined against *Candida albicans* ATCC 10231, *C. albicans* ATCC 2091, AM 38/20, *C. guilliermondii* KKP 3390, and *C. zeylanoides* KKP 3528. The MIC_{50} values for the newly prepared compounds ranged from 38.45 to 260.81 $\mu\text{g/mL}$. The 90% inhibitory dose was at least twice as high. Large differences in the effect of fluconazole analogues **5–15** on individual strains were observed. A synergistic effect on three strains—*Candida albicans* ATCC 10231, *C. albicans* ATCC 2091, *C. guilliermondii* KKP 339—was observed. Fractional inhibitory concentrations FIC_{50} and FIC_{90} were tested for the most active lactone, 3-n-butylphthalide, and seven fluconazole analogues. The strongest synergistic effect was observed for the strain *C. albicans* ATCC 10231, FIC 0.04–0.48. The growth inhibitory amount of azole is from 25 to 55 $\mu\text{g/mL}$ and from 3.13 to 25.3 $\mu\text{g/mL}$ for 3-n-butylphthalide. Based on biological research, the influence of the structure on the fungistatic activity and the synergistic effect were determined.

Słowa kluczowe

synergic effect, FIC , MIC , in silico studies, *Candida albicans*, 3-n-butylphthalide, fluconazole, azoles, atom, molecule, 1,2,3-triazole

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