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Design, synthesis and evaluation of antimycotic and fungicidal activities of novel substituted 1-[(2-benzyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles

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Abstract

In vitro tests of substituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles showed high antimycotic activity against pathogens of *C. albicans* and *S. salmonicolor*, as well as opportunistic pathogens of *F. oxysporum* and *F. moniliforme*. The target compounds were derived by cyclization of substituted ketones with 3-chloro-1,2-propanediol followed by alkylation of the derived 4-chloromethyl-1,3-dioxolanes of sodium salts of imidazole.

Keywords: alkylation, antimycotic activity, 1,3-dioxolane, imidazole, fungicidal activity, ketalization, ketals.

INTRODUCTION

Fungal diseases (mycoses) constitute a significant part of human infectious pathology. There are more than 400 pathogenic fungi which cause mycoses. Mycosis pathogens are anthropophilic fungi, parasitizing on humans, zoophilic fungi, carried by animals, as well as pathogenic organisms, mainly yeast-like fungi of the genus *Candida*. The increase in the candidiasis incidence rate is associated with the widespread use of modern chemotherapy, environmental pollution, increased radiation background and other factors that weaken the body defenses. Fungal diseases often occur without visible symptoms and pain, so they are not properly treated. Mycoses are especially dangerous for people with HIV: more than 30% of the deaths of such patients are due to systemic mycoses, including those caused by *Sporidiobolus salmonicolor* [1]. Phytopathogenic fungi, such as *Fusarium oxysporum* and *Fusarium moniliforme*, are dangerous for people with reduced immunity. Therefore, in the modern medical practice of HIV treatment, antimycotics are becoming increasingly important as they are indispensable for the survival of immunocompromised patients [2]. Many existing antimycotic drugs can only slow down the development of pathogenic fungi. In this regard, an important task is to find new effective synthetic antimycotic drugs that have low toxicity for humans.

Among the known antimycotic drugs, imidazole derivatives have been most widely used [3,4], and the priority amongst the highly active fungicides is given to derivatives of 1,2,4-triazole [5]. In terms of the mechanism of action, they are inhibitors of steroid biosynthesis during the demethylation stage of lanosterol. Sterin-14α-demethylase (CYP51), a member of the P450-cytochrome superfamily, catalyzes the oxidative removal of the 14α-methyl group of lanosterol, forming an $\Delta^{14,15}$–unsaturated intermediate of ergosterol biosynthesis, an essential component of the fungal pathogen cell membrane. Azole fungicides and antimycotics inhibit CYP51 by the binding of the nitrogen atom of 1,2,4-triazole or imidazole with the heme iron atom in the active site of the enzyme [6,7]. An important distinctive feature of azole antimycotic drugs and fungicides is their systemic action and rather low toxicity [5]. Well-known azole antimycotics are clotrimazole (**I**), miconazole (**II**), fluconazole (**III**), ketoconazole (**IV**) (Fig. 1).

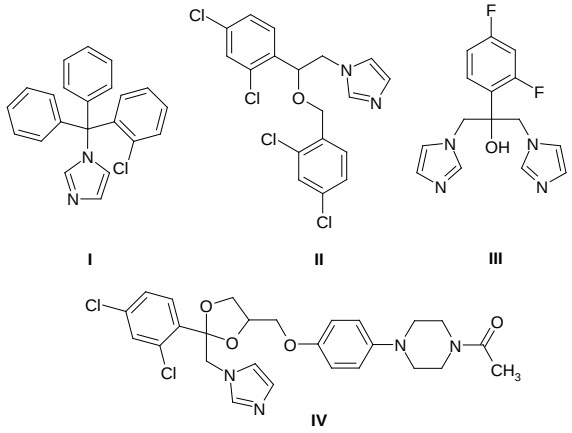


Fig 1.

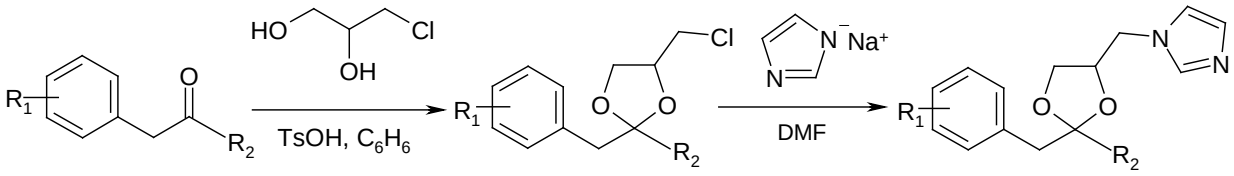
The earlier synthesized 2,2-disubstituted 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles and 1-[(1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazoles demonstrated a wide range of biological activity: antimycobacterial [8], growth-regulating [9,10], antiradical [11], antibacterial [12], cytotoxic [13], as well as pronounced fungicidal [14-21] and antimycotic activity [22]. To continue the study of biological activity, we extended this series of compounds and studied their antimycotic activity against the causative agent of human candida *C. albicans* and pathogen *S. salmonicolor*, and fungicidal activity against Fusarium pathogens – phytopathogenic and human opportunistic pathogens *F. oxysporum* and *F. moniliforme.*

MATERIALS AND METHODS

^{1}H NMR spectra were recorded on Bruker AM-300 instrument (300.13 MHz). IR spectra were recorded on a Specord M-80 instrument (Nujol). The course of reaction was monitored and the purity of the compounds was checked by TLC (Silufol UV-254).

We synthesized the target compounds according to **Scheme 1**:

Compounds **1a, 9a**, **1b, 9b**, **1c, 9c** were synthesized earlier and described in [8].



Scheme 1.

Benzylphenylketones **1a-6a** were prepared in high yields according to Friedel-Crafts. Dibenzylketones **7a-10a** were derived in 27-45% yields by acylation of 4-chlorobenzyl cyanide with 4-fluorophenylacetic acid ethyl ester, followed by hydrolysis and decarboxylation. Intermediate substituted 4-chloromethyl-1,3-dioxolanes **1b–10b** were obtained with 65–99% yields by condensation of ketones **1a–10a** with 3-chloro-1,2-propanediol in benzene catalyzed by *p*-toluenesulfonic acid with azeotropic removal of water. The target compounds **1c-10c** were derived with 15–89% yields by alkylation of sodium salts of imidazole with substituted 4-chloromethyl-1,3-dioxolanes **1b–10b** with boiling in DMF for 8 h. The target compounds were purified from the by-products of azole's alkylation using gradient flash chromatography. Sodium salts of imidazole were prepared in quantitative yield by the reaction of sodium isopropylate with azoles in isopropanol [23].

The following compounds were synthesized according to the methods described by us earlier [8, 11, 14]:

2-Benzyl-4-chloromethyl-2-phenyl-1,3-dioxolane (2b), yield 80%, n_D^{20}=1.5644. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.15 (s, 2H, $PhCH_2\underline{CH_2}$); 2.64 (s, 2H, $Ph\underline{CH_2}CH_2$); 3.11−3.47 (m, 2H, CH_2Cl); 3.89−4.05 (m, 1H, CH_2O); 4.44 (q, 1H, CHO); 7.47 (m, 4H, Ar); 7.59 (t, 2H, Ar, ^3J= 8.9); 8.05 (d, 2H, ^3J = 8.9); 8.11 (d, 2H, ^3J = 8.9). IR (Nujol, ν/sm^{-1}): 1245, 1210, 1194, 1174, 1078 (COCOC); 788(C-Cl).

2-(4-Chlorobenzyl)-4-chloromethyl-2-(4-methylphenyl)-1,3-dioxolane (3b), yield 65%, m.p. 92-93°C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.36 (s, 3H, CH_3); 3.11 (d, 2H, *n*-$ClPh\underline{CH_2}$); 3.33 (d.d, 1H, CH_2Cl, ^3J = 7.3, ^2J = 8.6); 3.49 (d.d, 1H, CH_2Cl , ^3J = 7.3, ^2J = 8.6); 3.62 (d.d, 1H, CH_2O, ^3J = 8.2, ^2J = 9.5); 4.03 (d.d, 1H, CH_2O, ^3J = 7.2, ^2J = 9.5); 4.15 (q, 1H, CHO, ^3J =5.3); 6.98-7.48 (m, 8HAr). IR (Nujol, ν/sm^{-1}): 1245, 1220, 1164, 1075 (COCOC); 784 (C-Cl).

2-(4-Chlorobenzyl)-4-chloromethyl-2-(4-fluorophenyl)-1,3-dioxolane (4b), yield 90%, m.p. 57-58°C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.09 (s, 1H, CH_2Ph); 3.11 (s, 1H, CH_2Ph); 3.32 (d.d, 1H, CH_2Cl, ^3J =5.16, ^2J =11.0); 3.47 (d.d, 0,5 H, CH_2Cl, ^3J=5.16, ^2J =11.0); 3.60 (d.d, 0.5H, CH_2O, ^3J=6.6, ^2J =8.8); 3.71-3.82 (m, 1.5H, CH_2O+CH_2Cl+CHO); 4.06 (d.d, 0.5H, CH_2O, ^3J=7.1, ^3J=8.8); 4.16 (q, 1H, CHO, ^3J=6.6); 6.93-7.12 (m, 4H, Ar); 7.19 (d, 1H, Ar, ^3J=8.8); 7.21 (d, 1H, Ar,, ^3J=8.8); 7.31 (d, 1H, Ar, ^3J=8.2); 7.34 (d, 1H, Ar, ^3J=8.2). IR (Nujol, ν/sm^{-1}): 1245, 1224, 1180, 1090, (COCOC); 794 (C-Cl).

2-(4-Bromophenyl)-2-(4-chlorobenzyl)-4-chloromethyl-1,3-dioxolane (5b), yield 90%, m.p. 83-84°C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.98-3.16 (m, 3H, CH_2Ph, CH_2Cl); 3.31 (d.d, 0.61 H, CH_2Cl, ^3J=4.4, ^2J=11.0); 3.46 (d.d, 0.39 H, CH_2Cl, ^3J=5.2, ^2J=11.0); 3.59 (d.d, 0.61 H, CH_2O, ^3J=6.6, ^2J=8.1); 3.70-3.82 (m, 1.22H, CH_2O); 4.04 (d.d, 0.39H, CH_2O, ^3J=5.9); 4.16 (q, 1H, CHO, ^3J=7.4); 7.06 (d, 2H, $C^{2,6}$H Bz, ^3J=6.6); 7.17-7.29 (m, 4H, BrPh); 7.46 (d, 2H, $C^{3,5}$H, C_6H_4Br, ^3J=8.1). IR (Nujol, ν/sm^{-1}): 1243, 1192, 1170, 1088 (COCOC);792 (C-Cl); 676 (CBr).

2-(4-Chlorobenzyl)-4-chloromethyl-2-(1-naphtyl)-1,3-dioxolane (6b), yield 98%, m.p. 56-58°C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.04 (d, 1H, CH_2Ph, ^2J=11.7); 3.09 (d, 1H, CH_2Ph, ^2J=11.7); 3.28−3.54 (m, 2H, CH_2Cl); 3.57−3.91 (m, 1.89H, CH_2O); 4.00−4.13 (m, 0.22H, CH_2O+CHO); 4.15−4.30 (m, 0.89H, CHO); 6.99−7.47 (m, 7H, 4-ClPh+C^{5-7}H napht.); 7.54 (d, 1H, C^3Hnapht.,^3J=6.9); 7.61 (d, 1H, C^2Hnapht., ^3J=6.9); 7.83 (d, 1H, C^4Hnapht., ^3J=7.8); 7.90 (d, 1H, C^8Hnapht., ^3J=7.8). IR (Nujol, ν/sm^{-1}): 1240, 1192, 1170, 1088 (COCOC); 788(C-Cl)

2,2-Dibenzyl-4-chloromethyl-1,3-dioxolane (7b), yield 87%, n_D^{20}=1.5578. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.71 (d.d, 1H, CH_2Cl, ^3J=10.8); 2.89-3.05 (m, 4H, $(Ph\underline{CH_2})_2$); 3.11 (d.d, 2H, CH_2Cl , ^3J=10.3); 3.31 (d.d, 1H, CH_2O, ^3J=8.1); 3.69 (d.d, 1H, CH_2O, ^3J=8.1); 3.81 (q, 1H, CHO, ^3J=5.9); 7.28 (d, 10H, Ar). IR (Nujol, ν/sm^{-1}): 1240, 1215, 1162,1074 (COCOC); 784 (C-Cl).

2-Benzyl-2-(4-chlorobenzyl)-4-chloromethyl-1,3-dioxolane (8b), yield 99%, n_D^{20}=1.5560. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz):2.90 (s, 2H, CH_2Ph); 2.93 (s, 2H, $CH_2$4-ClPh); 3.49−3.85 (m, 4.82H, CH_2Cl+CH_2O+CHO); 4.04 (q, 0.18H, CHO, ^3J=5.9); 7.13−7.37 (m, 9H, Ar). IR (Nujol, ν/sm^{-1}): 1222, 1132, 1088 (COCOC); 776 (C-Cl).

2,2-Bis(4-chlorobenzyl)-4-chloromethyl-1,3-dioxolane (10b), yield 85%, n_D^{20}=1.5468. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.88 (s, 4H, CH_2Ph); 3.49−3.84 (m, 4.68H, CH_2Cl + CH_2O + CHO); 4.05 (q, 0.32H, CHO, ^3J=5.9); 7.22 (d, 4H, $C^{2,6}$, $C^{2',6'}$H, CH_2Ar); 7.30 (d, 4H, $C^{3,5}$, $C^{3',5'}$H, CH_2Ar). IR (Nujol, ν/sm^{-1}): 1245, 1200, 1146, 1088 (COCOC); 778(C-Cl)

1-[(2-Benzyl-2-phenyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazole (2c), yield 65%, semisolid. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.08 (s, 2H, $PhCH_2\underline{CH_2}$); 2.50 (s, 2H, $Ph\underline{CH_2}$); 3.63 (д.д., 0,21H, CH_2O, ^3J=6.6, ^2J=8.8); 3.77 (д.д., 0.79H, CH_2O, ^3J=6.2, ^2J=8.8); 3.98−4.79 (m, 4H, CH_2O+CH_2N+CHO); 7.34−7.73 (m, 7H, aryl.+ C^4H imidaz.); 7.81 (m, 4H, aryl.); 8.18 (s, 0,21H, C^5H imidaz.); 8.28 (s, 0.79H, C^5H imidaz.); 8.72 (c (0.21H; C^2H imidaz.); 8.84 (s, 0.79H, C^2H imidaz.). IR (Nujol, ν/sm^{-1}): 1272 (β CHimidaz.), 1240, 1225, 1194, 1174, 1078 (COCOC).

1-{[2-(4-Chlorobenzyl)-2-(4-methylphenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (3c), yield 89%, m.p. 159–160°C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.27 (d, 3H CH_3); 3.12 (s, 2H, *n*-$ClPh\underline{CH_2}$); 3.55 (d.d, 1H, CH_2O, ^3J=8.1); 3.70 (d, 1H, CH_2N, ^3J=5.9); 3.84-4.55 (m, 4H, CH_2O+CH_2N+CHO); 7.01 (s, 1H, C^4H imidaz.); 7,05 (d, 2H, $C^{2,6}$H, *n*-$ClPhCH_2$, ^3J=8.4); 7.05 (d, 2H, $C^{3,5}$H, C_6H_4Cl, ^3J=8.6); 7.16-7.50 (m, 5H, $C^{3,5}$H,*n*-$ClPhCH_2$,$C^{2,6}$H, C_6H_4Cl, C^5H imidaz.); 8.20 (s, 1H, C^2H imidaz.); 8.35 (s, 1H, C^2H imidaz.). IR (Nujol, ν/sm^{-1}): 1282(β CH imidaz.); 1245, 1215, 1190, 1146, 1088 (COCOC);784 (C-Cl).

1-{[2-(4-Chlorobenzyl)-2-(4-fluorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (4c), yield 71%, m.p. 172–173°C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.13 (s, 2H, $\underline{CH_2}$Ph); 3.57 (d.d, 0,33 H, CH_2O, ^3J=7.33, ^2J=8.1); 3.66-3.84 (m, 1.67H, CH_2O); 3.89-4.10 (m, 1H, CH_2N+CHO); 4.10-4.52 (m, 2.60H, CH_2N+CHO); 6.96-7.19 (m, 5H, 4F-Ar, C^4Himidaz.); 7.20-7.44 (m, 4H, aryl.); 7.37 (s, 0.33H, C^5Himidaz.); 7.47 (s, 0.67H, C^5Himidaz.); 8.29 (s, 0.33H, C^2Himidaz.); 8.43 (s, 0.67H, C^2Himidaz.). IR (Nujol, ν/sm^{-1}): 1284 (β CH imidaz.); 1224, 1221, 1190, 1164, 1090 (COCOC), 792 (C-Cl).

1-{[2-(4-Bromophenyl)-2-(4-chlorobenzyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (5c), yield 72%, m.p. 163–164°C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.13 (s, 2H, $\underline{CH_2}$Ar); 3.56 (d.d, 0.37H; CH_2O; ^3J=7.3; ^2J=8.2); 3.65-3.86 (m, 1.37H, CH_2O); 3.91-4.12 (m, 1H, CH_2O+CH_2N); 4.13-4.51 (m, 2.26H, CH_2N+CHO+CH_2O); 7.04 (d.d, 2H, $C^{2,6}$H; 4-ClBz,

^3J=6.1); 7.14 (s, 0.37H^B, C^{4}Himidaz.); 7.18 (s, 0.63H^A, C^{4}Himidaz.); 4.19-7.34 (m, 4H, aryl.); 7.36 (s, 0.63H^A, C^{5}Himidaz.); 7.39 (s, 0.37H^B, C^{5}Himidaz.); 7.50 (d, 2H, C^{3,5}H, 4-BrPh, ^3J=7.8); 8.35 (s, 0,37H^B, C^{2}Himidaz.); 8.49 (s, 0.63H^A, C^{2}Himidaz.). IR (Nujol, ν/sm^{-1}): 1282 (β CH imidaz.); 1192, 1170, 1088, 1058, 1008 (COCOC);792 (C-Cl).

1-{[2-(4-Chlorobenzyl)-2-(1-naphtyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole (6c), yield 15%, semisolid. NMR^{1}H (CDCl$_3$, δ, ppm, *J*/Hz): 3.34-3.47 (m, 2H; $\underline{CH_2}$Ar); 3.62 (d.d, 0.15H^B, CH_2O, ^3J=6.8, ^2J=8.2); 3.75 (d.d, 0.85H^A, CH_2O, ^3J=6.8, ^2J=8.2); 3.91-4.10 (m, 1.15H, CH_2O+CH_2N); 4.12-4.43 (м (2.85H, CH_2N+CHO); 6.98 (d, 2H, C^{2,6}H, 4-ClBz, ^3J=8.2); 7.22 (d, 2H, C^{3,5}H, 4-ClBz, ^2J=8.2); 7.26 (s, 1H, C^{4}H imidaz.); 7.32-7.33 (m, 6H, aryl.+C^{5}H imidaz.); 7.88 (d, 1H, C^{4}H napht., ^3J=7.8); 7.95 (d, 1H, C^{3}H napht, ^3J =7.8); 8.46 (s, 0.15 H^B, C^{2}H imidaz.); 8.57 (d, 0.85H^A, C^{2}H imidaz.). IR (Nujol, ν/sm^{-1}): 1280 (β CHimidaz.); 1245, 1220, 1192, 1170, 1088 (COCOC).

1-[(2,2-Dibenzyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazole oxalate(7c), yield 64%, m.p. 163–164^{o}C. NMR^{1}H (DMSO-d$_6$, δ, ppm, *J*/Hz): 2.75-2.95 (m, 4H, ($\underline{CH_2}$Ph)$_2$); 3.57 (d.d, 1H, CH_2O, ^3J=7.6, ^2J=8.7); 3.62 (d.d, 1H, CH_2O, ^3J=6.9, ^2J=8.7); 3.91 (d.d, 1H, CH_2N, ^3J=6.6 Гц); 4.02-4.47 (m, 2H, CH_2N, CHO); 7.16 (s, 1H, C^{4}Himidaz.); 7.19 (s, 1H, C^{5}Himidaz.); 7.20-7.35 (m, 10H, aryl.); 8.16 (s, 1H, C^{2}Himidaz.). IR (Nujol, ν/sm^{-1}): 1282 (β CHimidaz.); 1245, 1210, 1192, 1164, 1076 (COCOC)

1-{[2-Benzyl-2-(4-chlorobenzyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (8c), yield 59%, m.p. 102–103^{o}C. NMR^{1}H (DMSO-d$_6$, δ, ppm, *J*/Hz): 2.48 (s, 2H, $\underline{CH_2}$Ar); 2.80 (s, 2H, CH_2PhCl); 3.28-3.41 (m, 2H, CH_2O); 3.70-4.05 (m, 3H, CH_2N+CHO); 7.11-7.42 (m, 9H, aryl.); 7.14 (s, 1H, C^{4}H imidaz.); 7.28 (s, 1H, C^{5}H imidaz.); 8.10 (s, 1H, C^{2}H imidaz.). IR (Nujol, ν/sm^{-1}): 1280 (β CH imidaz.); 1240, 1230, 1190, 1136, 1076 (COCOC).

1-[(2,2-Bis(4-chlorobenzyl)-1,3-dioxolan-4-yl)methyl]-1*H*-imidazole (10c), yield 68%, semisolid. NMR^{1}H (CDCl$_3$, δ, ppm, *J*/Hz):2.88 (s, 4H, CH_2Ar); 3.59-3.75 (m, 1H, CH_2O); 3.77-3.92 (m, 1.71H, CH_2O+CH_2N); 3.98-4.20 (m, 2H, CH_2N+CHO); 4.29 (q, 0.29H, CHO, ^3J=5.9); 7.19 (s, 1H, C^{4}Himidaz.); 7.24 (d, 4H, C^{2,6}H, C$^{2',6'}$HBz, ^3J=8.1); 7.32 (d, 4H, C^{3,5}H, C$^{3',5'}$HBz, ^3J=8.1); 7.37 (s, 1H, C^{5}Himidaz.); 7.59 (s, 0.29H, C^{2}Himidaz.); 7.63 (s, 0.71H, C^{2}Himidaz.). IR (Nujol, ν/sm^{-1}): 1280 (β CH imidaz.); 1245, 1200, 1190, 1146, 1088 (COCOC); 778см$^{-1}$ (C-Cl).

To analyze the relationship of the structure of synthesized compounds with their antimycotic and fungicidal activity, logPow of synthesized compounds was calculated [24].

The structure of synthesized compounds is given in **Table 1**.

Table 1. Structure of substituted 1-[(2-benzyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles

№	R1	R2	№	R1	R2
1c	4-Cl	4-ClC_6H_4	**6c**	4-Cl	1-naphtyl
2c	H	C_6H_5	**7c**	H	$C_6H_4CH_2$-
3c	4-Cl	4-$CH_3C_6H_4$	**8c**	4-Cl	$C_6H_4CH_2$-
4c	4-Cl	4-FC_6H_4	**9c**	4-Cl	4-F$C_6H_4CH_2$-
5c	4-Cl	4-BrC_6H_4	**10c**	4-Cl	4-Cl$C_6H_4CH_2$-

Table 2. Zones of inhibition of pathogenic fungi under the action of the test compounds.

Compound	*Candida albicans**	*Sporidiobolus salmonicolor**	logPow
1c	27	12	5,09
2c	28	16	3,90
Amphotericin B	17	18	

*** Inhibiting area (diameter) after 24 h, mm**

Table 3. Inhibition of mycelial growth of phytopathogenic fungi under the action of test compounds.

Compound	*Fusarium oxysporum**	*Fusarium moniliforme**	logPow
1c	85	88	5,09
2c	29	45	3,90
3c	72	89	4,96
4c	79	83	4,55
5c	79	81	5,27
6c	61	72	5,73
7c	46	70	3,66
8c	69	83	4,26
9c	60	78	4,31
10c	31	44	4,85
Triadimefon	82	89	

*** Inhibition of mycelial growth after 72 h, %**

RESULTS AND DISCUSSION

The antimycotic activity of the synthesized compounds was studied at Leibniz Institute for Natural Product Research and Infection Biology Hans Knöll Institute (HKI) (Jena, Germany). The Substances were tested against *C. albicans* and *S. salmonicolor*. Tests of compounds at a concentration of 0.1 μg/ml were carried out *in vitro* on a dense medium by diffusion method, using wells in Sabouraud dextrose agar, measuring the diameter of the inhibition zones after 24 hours. The concentration of Amphotericin B was 0.1 μg /ml.

The synthesized compounds showed activity exceeding the activity of the reference substance (Amphotericin B). The results of antimycotic activity tests of the synthesized compounds are shown in **Table 2**.

Fungicidal activity against the phytopathogens *F. oxysporum* and *F. moniliforme* was investigated at the D. Mendeleev University of Chemical Technology of Russia. The effect of the compounds on the radial growth of the mycelium was studied on potato-sucrose agar in a concentration of 30 mg/l, the reference substance was triadimefon. The tested compounds showed activity comparable to reference substance triadimefon. The greatest activity was shown by compound **1c.** The results of fungicidal activity tests of the synthesized compounds are shown in **Table 3**.

In previous paper we have shown high fungicidal activity of substituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-azoles with logP in the range 3.0–4.0, having bulky lipophilic substituent at the *para*-position of the aryl radical [14,19]. Therefore, the design of the target compounds is based on the modification of the structure by various bulky and lipophilic substituents in the *para*-position of aryl group and preliminary calculation of logP by experimental and calculation methods. In addition, the structures were modified by replacing aryl substituents with benzyl ones to study the effect of conformational mobility on biological activity. The calculated values of logP_{OW} [24] of target compounds equal are 3.66-5.73 and they are analogically comparable with experimental data as we showed earlier [25].

Analysis of the structure-fungicidal activity relationship showed the greatest fungicidal activity observed in compounds with logP in the range of 4.5-5.1 in a series of 1-[(2-benzyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles. The introduction of halogens such as chlorine and bromine in the aryl substituent increased fungicidal activity. Benzylphenylketones derivatives **1c-6c** in general showed higher activity than dibenzylketones derivatives **7c-10c**.

CONCLUSIONS

Antimycotic and fungicidal activity tests of 1-[(2-benzyl-1,3-dioxolan-4-yl)methyl]-1*H*-imidazoles have shown prospects of searching for new active antimycotics and fungicides in this series.

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