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Design, synthesis and antibacterial activity of substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1*H*-azoles

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Abstract
Substituted 2-aryl- and 2-alkyl- 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-azoles showed antibacterial activity similar to that of ciprofloxacin against Gram-positive bacteria: *Bacillus subtilis, Staphylococcus aureus, Enterococcus faecalis*. The target compounds were derived by cyclization of substituted aryl ketones with 3-chloro-1,2-propanediol followed by alkylation of the derived 4-chloromethyl-1,3-dioxolanes of sodium salts of 1,2,4-triazole or imidazole.
Keywords: alkylation, antibacterial activity, 1,3-dioxolane, imidazole, ketalization, ketals, 1,2,4-triazole.

INTRODUCTION

Despite a large number of antimicrobial drugs are used in medical practice, the nomenclature of it includes several hundred names, their number is constantly increasing. The reasons for design of new drugs are diverse: expansion of the antimicrobial spectrum, increased activity against certain microorganisms, improved pharmacokinetic properties and reduced toxicity. The main reason for the search of new compounds is the increasing resistance of microbes to antimicrobials, and its severity is so great that many widely used drugs completely lose their value against a number of infections.

Well known, the the substituted 1,3-dioxolanes, compounds have been found possessing activity against HIV infection [1–8], antiplasmodial activity [9], activity against hepadnaviruses [10], antimycotic [11–13], fungicidal [14–20], anti-cancer [21], as well as antimicrobial activity against both Gram-positive and Gram-negative bacteria [22-26].

Derivatives of 1,2,4-triazole [27–51] and imidazole [52–60] also show noticeable antimicrobial and antibacterial activity.

The presence of biological activity, including antimicrobial activity, both of 1,3-dioxolane derivatives and in 1,2,4-triazole or imidazole derivatives, justifies the search for new antimicrobial agents in a series of compounds that contain both azole and dioxolane cycles.

MATERIALS AND METHODS

1H 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).

2,2-Disubstituted 4-(chloromethyl)-1,3-dioxolanes (general procedure).

A mixture 0,05 mol of substituted ketone, 0,1 mol 3-chloropropane-1,2-diol and 0,0025 mol monohydrate p-toluenesulfonic acid was refluxed in benzene for 8 h with azeotropic removal of water. The reaction mixture was neutralized with 100 ml 2% NaOH and washed with 200 ml water. The solvent was removed and residue was fractionated in *vacuo*.

4-(chloromethyl)-2-(4-chlorophenyl)-2-propyl-1,3-dioxolane (1a), yield 89%, b.p. 130–136 °C/0.5 Topp, n_D^{20}=1.5262, n_D^{20}=1.5262. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.81 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.4); 1.17 (sext., 2H, $\underline{CH_2}CH_3$, ^3J = 7.6); 1.74-1.89 (m, 2H, $\underline{CH_2}CH_2CH_3$); 2.91 (d.d, 0.39H, CH_2Cl, ^3J = 7.6, ^2J = 8.6); 3.19 (d.d, 0.61H, CH_2Cl, ^3J = 5.8, ^2J = 8.6); 3.44 (d.d, 0.61H, CH_2Cl, ^3J = 5.8, ^2J = 8.6); 3.76 (d.d, 0.39H, CH_2Cl, ^3J = 7.8, ^2J = 8.6); 4.87-4.14 (m, 2H, CH_2O); 4.36 (q, 1H, CHO, ^3J = 5.1); 7.32-7.45 (m, 4H, Ar.). IR (Nujol, ν/sm^{-1}): 1243, 1220, 1180, 1130, 1075 (COCOC), 778 (CCl).

4-(chloromethyl)-2,2-bis(4-chlorophenyl)-1,3-dioxolane (2a), yield 80%, b.p. 168–170 °C/0.4 Topp, n_D^{20}=1.5954. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.49 (d.d, 1 H, CH_2Cl, ^3J = 8.2, ^2J = 11.0); 3.64 (d.d, 1H, CH_2Cl, ^3J = 5.6, ^2J = 11.0); 4.03 (d.d, 1H, CH_2O, ^3J = 5.8, ^2J = 7.6); 4.12 (d.d, 1H, CH_2O, ^3J = 7.0, ^2J = 7.6); 4.45 (q, 1H, CHO, ^3J = 5.8); 7.35, 7.46 (both d, of 4H, Ar, ^3J = 8.8). IR (Nujol, ν/sm^{-1}): 1245, 1225, 1170, 1115, 1087 (COCOC); 732 (CCl).

2-(4-*tert*butylphenyl)-4-(chloromethyl)-2-(4-chlorophenyl)-1,3-dioxolane (3a), yield 95%, b.p. 189–191 °C/0.5 Topp, n_D^{20}=1.5670. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.33 (s, 9H, $(CH_3)_3$); 3.49 (d.d, 1 H, CH_2Cl, ^3J = 8.8, ^2J = 11.0); 3.67 (d.d, 1H, CH_2Cl, ^3J = 5.2, ^2J = 11.0); 4.02 (d.d, 1H, CH_2O, ^3J = 5.2, ^2J = 8.0); 4.11 (d.d, 1H, CH_2O, ^3J = 6.7, ^2J = 8.0); 4.44 (q, 1H, CHO, ^3J = 5.9); 7.18–7.54 (m, 8H, Ar). IR (Nujol, ν/sm^{-1}): 1248, 1222, 1170, 1115, 1085 (COCOC); 735 (CCl).

4-(chloromethyl)-2-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-1,3-dioxolane (4a), yield 96%, b.p. 205–207 °C/0.5 Topp, n_D^{20}=1.5960. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.48 (d.d, 0.43 H, CH_2Cl, ^3J = 8.0, ^2J = 8.8); 3.64 (d.d, 0.57H, CH_2Cl, ^3J = 5.8, ^2J = 8.8); 3.75–3.80 (m, 1.43H, CH_2Cl; CH_2O); 4.02 (d, 1H, CH_2O, ^3J = 8.8); 4.25 (d.d, 0.57H, CH_2O, ^3J = 6.2, ^2J = 8.8); 4.45 (q, 0.57H, CHO, ^3J = 5.6); 4.55 (q, 0.47H, CHO, ^3J = 5.6); 7.32–7.46 (m, 4H, Ar); 7.51–7.69 (m, 2H, Ar); 7.75 (d, 0.57H, Ar, ^4J = 7.2); 7.81 (d, 0.43H, Ar, ^4J = 7.2). IR (Nujol, ν/sm^{-1}): 1248, 1225, 1175, 1117, 1085 (COCOC); 736 (CCl)

4-(chloromethyl)-2-(3,4-dichlorophenyl)-2-nonyl-1,3-dioxolane (5a), yield 84%, b.p. 194–200 °C/0.3 Topp, n_D^{20}=1.5146. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.89 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.3); 1.21-1.39 (m, 10H, $(\underline{CH_2})_5CH_3$); 1.84 (t, 2H, $\underline{CH_2}(CH_2)_5CH_3$, ^3J = 5.1); 3.17 (d.d, 0.27H, CH_2Cl, ^3J = 5.4, ^2J = 7.3); 3.53 (d.d, 0.73H, CH_2Cl, ^3J = 5.4, ^2J = 7.3); 3.64 (d.d, 1H, CH_2Cl, ^3J = 4.8, ^2J = 7.3); 3.80 (d.d, 0.73H, CH_2O, ^3J = 4.4, ^2J = 5.2); 3.94 (d.d, 0.73H, CH_2O, ^3J = 4.2, ^2J = 5.2); 4.13-4.23 (m, 0.54H, CH_2O +CHO); 4.27 (d.d, 0.37H, CH_2O, ^3J = 4.8, ^2J = 5.2); 4.42 (q, 0.37H, CHO, ^3J = 6.6); 7.55 (d, 2H, Ar, ^3J = 8.6); 7.79 (d, 2H, Ar, ^3J = 8.6); 8.03 (d, 1H, Ar, ^4J = 1.9). IR (Nujol, ν/sm^{-1}): 1241, 1235, 1185, 1125, 1078 (COCOC), 762 (CCl).

4-(chloromethyl)-2-(4-chlorophenyl)-2-*cyclo*hexyl-1,3-dioxolane (6a), yield 90%, b.p. 167–171 °C/0.6 Topp,

n_D^{20}=1.5395. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.81-0.99 (m, 2H, CH_2 cycl.); 1.01-1.19 (m, 3H, CH_2 cycl.); 1.51-1.74 (m, 6H, CH_2 cycl.); 2.99 (d.d, 0.32H, CH_2Cl, ^3J = 7.4, ^2J = 8.4); 3.12 (d.d, 0.68H, CH_2Cl, ^3J = 7.6, ^2J = 8.4); 3.24-3.47 (m, 1H, CH_2Cl); 3.79 (d.d, 0.68H, CH_2O, ^3J = 7.0, ^2J = 8.2); 4.88-4.13 (m, 2H, CH_2O+CHO); 4.32 (q, 0.32H, CHO, ^3J = 5.4); 7.29 (d, 2H Ar, ^3J = 8.6); 7.41 (d, 2H Ar, ^3J = 8.6). IR (Nujol, ν/sm^{-1}): 1245, 1230, 1185, 1125, 1090 (COCOC), 762 (CCl).

4-(chloromethyl)-2-(4-*cyclo*hexylphenyl)-2-propyl-1,3-dioxolane (7a), yield 89%, b.p. 153–159 °C/0.5 Topp, n_D^{20}=1.5112. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.82 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.1); 1.05-1.39 (m, 8H, $(\underline{CH_2})_4CH_3$); 1.77 (t, 2H, $\underline{CH_2}(CH_2)_4CH_3$, ^3J = 5.1); 3.05 (d.d, 0.33H, CH_2Cl, ^3J = 7.6, ^2J = 8.6); 3.17-3.51 (m, 1.67H, CH_2Cl); 3.80 (d.d, 0.67H, CH_2O, ^3J = 6.5, ^2J = 8.4); 4.89-4.13 (m, 2H, CH_2O+ CHO); 4.32 (q, 0.33H, CHO, ^3J = 5.4); 7.35-7.62 (m, 4H Ar). IR (Nujol, ν/sm^{-1}): 1245, 1225, 1185, 1125, 1090 (COCOC), 756 (CCl).

4-(chloromethyl)-2-(4-chlorophenyl)-2-hexyl-1,3-dioxolane (8a), yield 93%, b.p. 182–187 °C/0.4 Topp, n_D^{20}=1.5299. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.88 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.6); 1.41 (sixt., 8H, $\underline{CH_2}CH_3$, $(CH_2)_3$, ^3J = 5.8); 1.68-2.00 (m, 6H, $\underline{CH_2}CH_2CH_3$, ($\underline{CH_2}CH\underline{CH_2}$); 2.51 (q, 1H, $CH_2C\underline{H}CH_2$, ^3J = 11.5); 2.93 (d.d, 0.29H, CH_2Cl, ^3J = 8.2, ^2J = 8.6); 3.13 (d.d, 0.29H, CH_2Cl, ^3J = 6.2, ^2J = 8.6); 3.46-3.71 (m, 3.42H, CH_2Cl+CH_2O + CHO); 4.11-4.32 (m, 1H, CH_2O + CHO); 4.32 (q, 0.29H, CHO, ^3J = 5.4); 7.17 (d, 2H, Ar, ^3J = 8.6); 7.34 (d, 2H, Ar, ^3J = 8.6). IR (Nujol, ν/sm^{-1}): 1245, 1220, 1180, 1130, 1075 (COCOC).

2-(4-*tert*butylphenyl)-4-(chloromethyl)-2-{3-[(4-chlorophenyl)thio]propyl}-1,3-dioxolane (9a), yield 80%, b.p. 155–160 °C/0.5 Topp, n_D^{20}=1.5423. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 1.06 (s, 9H, $(CH_3)_3$); 1.94 (d, 2H, $C\underline{H_2}C(CH_3)_3$, ^2J = 12.4); 3.02 (d.d, 0.3H CH_2Cl, ^3J = 7.6, ^2J = 8.6) 3.13 (d.d, 0.7H, CH_2Cl, ^3J = 7.2, ^2J = 8.6); 3.26 (d.d, 0.7H, CH_2Cl, ^3J = 7.2, ^2J = 8.6); 3.48 (d.d, 0.3H, CH_2Cl, ^3J = 7.2, ^2J = 8.6); 3.79-4.07 (m, 2.7H, CH_2O+CHO); 7.57 (d, 2H, Ar, ^3J = 8.2); 7.80 (s, 1H, Ar); IR (Nujol, ν/sm^{-1}): 1245, 1220, 1180, 1125, 1085 (COCOC), 745 (CCl).

Substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1*H*-azoles (general procedure).

A mixture of 0,03 mol a 4-chloromethyl-1,3-dioxolane (**1a-9a**) and 0,03 mol a sodium salt of 1,2,4-triazole or imidazole was refluxed in 50 ml DMF for 16 h, filtered and evaporated. The residue was chromatographed on silica gel by gradient eluation in acetone-hexane with a concentration gradient of acetone from 10% to 40%. Non crystallized products were dissolved in 10 ml acetone and treated with an equimolar amount of oxalic acid, dissolved in 10 ml acetone. The resulting crystals of product's oxalates were filtered off, washed with 10 ml acetone and 40 ml hexane and dried in air.

1-{[2-(4-chlorophenyl)-2-propyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole (1b), yield 68%, m.p. 62–63 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.68 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.3); 1.06 (sext, 2H, $\underline{CH_2}CH_3$, ^3J = 7.8, ^2J = 16.1); 1.56-1.71 (m, 2H, $\underline{CH_2}CH_2CH_3$); 3.44 (d.d, 0.45H, CH_2O, ^3J = 7.9, ^2J = 8.6); 3.60 (d.d, 0.55H, CH_2O, ^3J = 7.9, ^2J = 8.6); 3.80 (d.d, 0.55H, CH_2O, ^3J = 5.8, ^2J = 8.6); 3.94-4.49 (m, 3.45H, CH_2O +CH_2N + CHO); 7.18-7.36 (m, 4H, Ar); 7.83 (s, 0.45H, C^{3}H triaz.); 7.90 (s, 0.55H, C^{3}H triaz.); 8.31 (s, 0.45H, C^{5}H triaz.). 8.45 (s, 0.55H, C^{5}H triaz.); IR (Nujol, ν/sm^{-1}): 1265 (β CH triaz.); 1180, 1125, 1078 (COCOC).

1-{[2,2-bis(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (2b), yield 74%, m.p. 173–174 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.97 (d.d, 1 H, CH_2O, ^3J = 5.5, ^2J = 8.8); 4.05 (d.d, 1H, CH_2O, ^3J = 6.8, ^2J = 8.8); 4.38 (d.d, 1H, CH_2N, ^3J = 6.6, ^2J = 13.9); 4.44 (d.d, 1H, CH_2N, ^3J = 5.2, ^2J = 13.9); 4.54 (q, 1H, CHO, ^3J = 5.9); 7.35, 7.42 (both d, for 4H, Ar, ^3J = 8.8); 7.98 (s, 1H, C^{3}H triaz.); 8.45 (s, 1H, C^{5}H triaz.); IR (Nujol, ν/sm^{-1}): 1275 (β CH triaz.); 1245, 1215, 1175, 1115, 1085 (COCOC); 725 (CCl).

1-{[2,2-bis(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (2c), yield 42%, m.p. 192–193 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.87 (d.d, 2 H, CH_2O, ^3J = 5.4, ^2J = 8.8); 4.05 (d.d, 1H, CH_2N, ^3J = 6.8, ^2J = 13.2); 4.14 (d.d, 1H, CH_2N, ^3J = 4.8, ^2J = 13.2); 4.47 (q, 1H, CHO, ^3J = 5.4); 6.97 (s, 1H, C^{4}H imid.); 7.29 (s, 1H, C^{5}H imid.); 7.34, 7.41 (both d, for 4H, Ar, ^3J = 8.8); 7.67 (s, 1H, C^{2}H imid.). IR (Nujol, ν/sm^{-1}): 1280 (β CH imid.); 1247, 1220, 1170, 1115, 1085 (COCOC); 720 (CCl).

1-{[2-(4-*tert*butylphenyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (3b), yield 59%, m.p. 162–163 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.29 (s, 9H, $(CH_3)_3$); 3.94–4.18 (m, 2 H, CH_2O); 4.35 (d, 2H, CH_2N, ^3J = 5.9); 4.59 (q, 1H, CHO, ^3J = 5.8); 7.25–7.47 (m, 8H, Ar); 7.97 (c, 1H, C^{3}H triaz.); 8.09 (s, 1H, C^{5}H triaz.), IR (Nujol, ν/sm^{-1}): 1274 (β CH triaz.), 1247, 1220, 1172, 1115, 1087 (COCOC), 720 (CCl).

1-{[2-(4-*tert*butylphenyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (3c), yield 63%, m.p. 177–178 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.28 (s, 9H, $(CH_3)_3$); 3.87 (d.d, 1 H, CH_2O, ^3J = 5.6, ^2J = 8.6); 4.02 (d.d, 1H, CH_2O, ^3J = 7.2, ^2J = 8.6); 4.18 (d.d, 1H, CH_2N, ^3J = 7.0, ^2J = 14.0); 4.35 (d.d, 1H, CH_2N, ^3J = 3.5, ^2J = 14.0); 4.48 (q, 1H, CHO, ^3J = 5.8); 7.12 (s, 1H, C^{4}H imid.); 7.28–7.45 (m, 9H, Ar; + C^{4}H imid.); 8.17 (s, 1H, C^{2}H imid.). IR (Nujol, ν/sm^{-1}): 1280 (β CH imid.); 1247, 1220, 1172, 1115, 1087 (COCOC); 720(CCl).

1-{[2-(2,4-dichlorophenyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (4b), yield 65%, m.p. 193–195 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.87 (d.d, 0.18 H^B, CH_2O, ^3J = 5.6, ^2J = 8.8); 4.02 (d.d, 0.82H^A, CH_2O, ^3J = 5.6, ^2J = 8.8); 4.08 (d.d, 0.82H^A, CH_2O, ^3J = 6.8, ^2J = 8.8); 4.24 (d.d, 0.18H^B, CH_2O, ^3J = 6.8, ^2J = 8.8); 4.33 (d.d, 0.18H^B, CH_2N, ^3J = 6.6, ^2J = 14.0); 4.42–4.58 (m, 3.82H, CH_2N + CHO); 4.54 (q, 0.18H^B, CHO, ^3J = 5.6); 7.24 , 7.47 (both d, for 2H, Ar, ^3J = 8.0); 7.53 (d, 2H, Ar, ^3J = 8.2); 7.79 (s, 1H, Ar); 7.98 (s, 1H, H(3) triaz.); 8.45 (s, 1H, H(5) triaz.). IR (Nujol, ν/sm^{-1}): 1247, 1220, 1172, 1115, 1087 (COCOC); 727 (C-Cl).

1-{[2-(3,4-dichlorophenyl)-2-nonyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (5b), yield 65%, m.p. 137–138 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.84 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.2); 1.08-1.29 (m, 14H, $(\underline{CH_2})_7CH_3$); 1.78 (t, 2H, $\underline{CH_2}(CH_2)_7CH_3$, ^3J = 5.3); 3.59 (d.d, 0.43H, CH_2O, ^3J = 7.8, ^2J = 8.8); 3.75 (d.d, 0.57H, CH_2O, ^3J = 7.0, ^2J = 8.8); 3.85 (d.d, 0.43H, CH_2O, ^3J = 6.5, ^2J = 8.8); 4.15 (d.d, 0.57H, CH_2O, ^3J = 7.0, ^2J = 8.8); 4.20-4.42 (m, 2.57H, CH_2N + CHO); 4.48 (q, 0.43H, CHO, ^3J = 5.4); 7.31 (d.d, C^{6}H Ar, ^3J = 8.3, ^4J = 2.1); 7.48 (s, 1H, C^{2}HAr); 7.58 (m, C^{5}H Ar); 7.88 (s, 0.43H, C^{3}H triaz.); 7.97 (s, 0.57H, C^{3}H triaz.); 8.33 (s, 0.43H, C^{5}H triaz.). 8.50 (s, 0.57H, C^{5}H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1190, 1145, 1085 (COCOC).

1-{[2-(4-chlorophenyl)-2-*cyclo*hexyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (6b), yield 74%, m.p. 168–169 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.81-0.99 (m, 2H, CH_2cycl.); 0.99-1.17 (m, 3H, CH_2cycl.); 1.49-1.73 (m, 6H, CH_2cycl.); 3.53 (d.d, 0.66H, CH_2O, ^3J = 7.9, ^2J = 8.6); 3.66 (d.d, 0.34H, CH_2O, ^3J = 7.6, ^2J = 8.6); 3.91 (d.d, 0.66H, CH_2O, ^3J = 6.2, ^2J = 8.6); 4.04-4.24 (m, 2.34H, CH_2O, CH_2N); 4.39 (d.d, 0.66H, CH_2N, ^3J = 8.0, ^2J = 8.8); 4.44 (q, 0.34H, CHO, ^3J = 5.8); 7.27 (d, 2H Ar, ^3J = 8.6); 7.39 (d, 2H Ar, ^3J = 8.6); 7.88 (s, 0.34H, C^{3}H triaz.); 7.96 (s, 0.66H, C^{3}H triaz.); 8.38 (s, 0.34H, C^{5}H triaz.). 8.52 (c, 0.66H, C^{5}H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1180, 1150, 1085 (COCOC).

1-{[2-(4-*cyclo*hexylphenyl)-2-propyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole (7b), yield 62%, m.p. 61–62 °C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.87 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.5); 1.12-1.57 (m, 8H, $\underline{CH_2}CH_3$, $(CH_2)_3$); 1.65-1.99 (m, 6H, $\underline{CH_2}CH_2CH_3$, ($\underline{CH_2}CH\underline{CH_2}$); 2.50 (q, 1H, $CH_2C\underline{H}CH_2$, ^3J = 11.5); 3.71 (d.d, 0.13H, CH_2O, ^3J = 6.9, ^2J = 8.3); 3.84 (d, 0.87H, CH_2O, ^3J = 5.2); 3.84 (d, 0.87H, CH_2O, ^3J = 5.2); 4.05 (d, 0.13H, CH_2N, ^3J = 6.3); 4.19-4.41 (m, 2.74H, CH_2N + CHO); 4.60 (q, 0.13H, CHO, ^3J = 6.2); 7.15 (d, 0.13H, Ar, ^3J = 8.6); 7.20 (d, 0.87H, Ar, ^3J = 8.6); 7.27 (d, 0.87H, Ar, ^3J = 8.6); 7.31 (d, 0.13H, Ar, ^3J = 8.6); 7.48 (d, 0.87H, C^3H Ar, ^3J = 8.3); 7.50 (d, 0.13H, C^3H Ar, ^3J = 8.3); 7.89 (s, 0.13H, C^3H triaz.); 7.95 (s, 0.87H, C^3H triaz.); 7.97 (s, 0.13H, C^5H triaz.). 8.24 (s, 0.87H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1195, 1125, 1085 (COCOC).

1-{[2-(4-chlorophenyl)-2-hexyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (8b), yield 76%, m.p. 147-148 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.71 (t, 3H, CH_3, ^3J = 7.3); 1.07-1.19 (m, 8H, $(CH_2)_4$); 1.73 (t, 2H, $\underline{CH_2}(CH_2)_4$, ^3J = 7.3); 3.55 (d.d, 0.41H, CH_2O, ^3J = 7.6, ^2J = 8.8); 3.72 (d.d, 0.59H, CH_2O, ^3J = 7.0, ^2J = 8.8); 3.89 (d.d, 0.59H, CH_2O, ^3J = 5.8, ^2J = 8.8); 4.09–4.44 (m, 3H, CH_2O, CH_2N, CHO); 4.56 (q, 0.41H, CHO, ^3J = 5.4); 7.30–7.41 (m, 4H, C_6H_4Cl); 7.89 (s, 0.41H, C^3H triaz.), 7.95 (s, 0.59H, C^3H^A triaz.), 8.37 (s, 0.41H, C^5H triaz.), 8.49 (s, 0.59H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (β CH triaz.); 1190, 1150, 1085 (COCOC).

1-[(2-(4-*tert*butylphenyl)-2-{3-[(4-chlorophenyl)thio]propyl}-1,3-dioxolan-4-yl)methyl]-1*H*-1,2,4-triazole oxalate (9b), yield 76%, m.p. 127–128 °C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 1.04 (s, 9H, $(CH_3)_3$); 1.92 (d, 2H, $C\underline{H_2}C(CH_3)_3$, ^2J = 12.6); 3.67 (d.d, 1H CH_2O, ^3J = 7.6, ^2J = 8.8) 3.83 (d.d, 1H, CH_2O, ^3J = 7.2, ^2J = 8.8); 4.13-4.46 (m, 3H, CH_2N, CHO); 7.55 (d, 2H, Ar, ^3J = 8.2); 7.78(s, 1H, Ar); 7.98 (s, 1H, C^3Htriaz.); 8.52 (s,1H C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1265 (β CH triaz.); 1190, 1150, 1085 (COCOC).

RESULTS AND DISCUSSION

In previous paper we have shown high fungicidal activity of 1-[(2-aryl-1,3-dioxolan-4-yl) methyl]-1H-azoles with logP in the range 3.0–4.0, having bulky lipophilic substituent at the *para*-position of the aryl cycle [15]. Therefore, the design of the target compounds consisted of the modification of the structure by various bulky and lipophilic substituents in the *para*-position (chloro-, *cyclo*hexyl-, *tert*butyl-), and preliminary calculation of logP by experimental and calculation methods [61]. The calculated values of $logP_{OW}$ [61] of target compounds equal to 3.17-6.95 and we assume it will be similar with experimental values, analogically [62].

The target compounds were derived in three stages (**Tab. 1, Fig.**). In the first stage, arylketones (**1–5,7,8**) were prepared according to Friedel-Crafts, (**6**) Grignard and (**9**) Williamson reactions by well-known procedures [63].

Intermediate substituted 4-chloromethyl-1,3-dioxolanes (**1a–9a**) were derived with 80–96% yields by condensation of ketones (**1–9**) with 3-chloro-1,2-propanediol in benzene catalyzed by *p*-toluenesulfonic acid with azeotropic removal of water. Due to high yields and ease of implementation, this method had an advantage over the previously investigated way of cyclization of epichlorohydrin with ketones catalyzed by Lewis acids [14].

The target substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-1,2,4-triazoles (**1b-9b**) and 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-imidazoles (**2c, 3c**) were derived with 42–76% yields by alkylation of sodium salts of 1,2,4-triazole or imidazole substituted with 4-chloromethyl-1,3-dioxolanes with boiling in DFM for 8 hours. The target compounds were purified from the by-products of azole's alkylation using gradient flash chromatography. Sodium salts of 1,2,4-triazole or imidazole were prepared in quantitative yield by the reaction of sodium isopropylate with azoles in isopropanol [64].

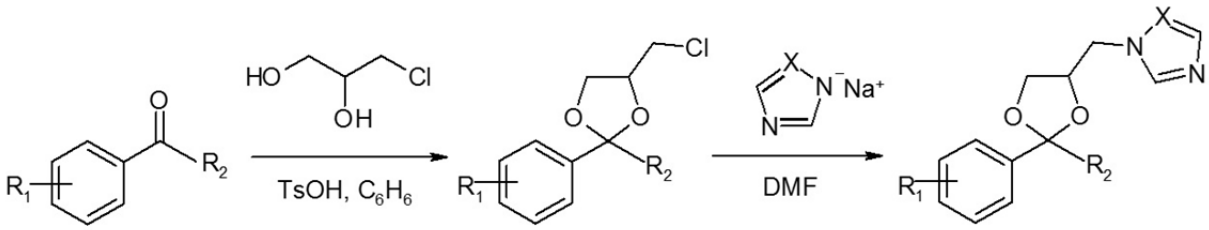

Fig.

Table 1. Structure of substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-azoles

№	R_1	R_2	X	$logP_{ow}$*
1b	4-Cl	*n*-C_3H_7	N	3,17
2b	4-Cl	4-ClC_6H_4	N	4,48
2c	4-Cl	4-ClC_6H_4	CH	5,13
3b	4-$C(CH_3)_3$	4-ClC_6H_4	N	5,57
3c	4-$C(CH_3)_3$	4-ClC_6H_4	CH	6,23
4b	2,4-Cl_2	4-ClC_6H_4	N	5,09
5b	3,4-Cl_2	C_9H_{19}	N	6,82
6b	4-Cl	*cyclo*C_6H_{11}	N	4,81
7b	4-*cyclo*C_6H_{11}	*n*-C_3H_7	N	5,09
8b	4-Cl	C_6H_{13}	N	4,76
9b	4-$C(CH_3)_3$	$C_3H_6S(4\text{-}ClC_6H_4)$	N	6,95

Table 2. Growth inhibition of bacteria by substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-azoles

Compound	*IA * diameter, mm*		
	***Bacillus subtilis* ATCC 6633**	***Staphylococcus aurelius* SG511**	***Enterococcus faecalis* 1528**
1b	12	11	0
2b	12	12	0
2c	24	22	12
3b	12	12	11
3c	20	15	13
4b	12	13	11
5b	12	11	0
6b	12	12	11
7b	13	13	11
8b	13	13	12
9b	11	11	0
Ciprofloxacin	29	18	18

**** IA* – inhibiting area after 24 h**

The antimicrobial activity of the synthesized compounds was studied at Hans-Knoell-Institute for Natural Products Research (Germany) against Gram-positive bacteria: *Bacillus subtilis*, *Staphylococcus aureus*, *Enterococcus faecalis*. Tests of compounds at a concentration of 1μg/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 ciprofloxacin was 1 μg/ml.

The synthesized compounds showed activity comparable to the reference compound (ciprofloxacin). The activity of compound **2c** exceeded the activity of ciprofloxacin against *Staphylococcus aureus.* The results of antimicrobial activity tests of the synthesized compounds are shown in Table 2.

CONCLUSIONS

Alkylation of sodium salts of 1,2,4-triazole or imidazole with 4-chloromethyl-1,3-dioxolanes leads to derivation of 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-1,2,4-triazoles and 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-imidazoles with high yields. Based on the results of biological tests, it was shown that all synthesized compounds possess antimicrobial activity, and 1-{[2,2-bis(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole exceeds ciprofloxacin in activity against *Staphylococcus aurelius* that confirms the prospect of searching for new antibacterial substances in the series of substituted 1-[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-azoles.

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