Design, synthesis and antibacterial activity of substituted 1-
[(2-aryl-1,3-dioxolan-4-yl)methyl]-1H-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], antiplasmoidal activity [9], activity against hepadnaviruses [10], antymycotic [11–13], fungidical [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 acetotropic 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 0C.0.5 Topp, nD19=1.5262, nD30=1.5262. NMR’H (CDCl3, δ, ppm, J/Hz): 0.81 (t, 3H, CH3CH2, J = 7.4); 1.17 (sext, 2H, CH2CH2, J = 7.6); 1.74–1.89 (m, 2H, CH2CH2CH3); 2.91 (dd, 0.39H, CH2Cl, J = 7.6, J = 8.6); 3.19 (dd, 0.61H, CH2Cl, J = 5.8, J = 8.6); 3.44 (d.d, 0.61H, CH2Cl, J = 5.8, J = 8.6); 3.76 (d.d, 0.39H, CH2Cl, J = 7.8, J = 8.6); 4.87–4.14 (m, 2H, CH2O); 4.36 (q, 1H, CHO, J = 5.1); 7.32–7.45 (m, 4H, Ar). IR (Nujol, v/mm-1): 1243, 1220, 1180, 1130, 1075 (COOC), 778 (CCI).

4-(4-chlorobutyl)-2-(4-bis-(chloromethyl)-1,3-dioxolane (2a), yield 80%, b.p. 168–170 0C.0.4 Topp, nD19=1.5954. NMR’H (CDCl3, δ, ppm, J/Hz): 3.49 (d, 1H, CH2Cl, J = 8.2, J = 11.0); 3.64 (d.d, 1H, CH2Cl, J = 5.6, J = 11.0); 4.03 (d.d, 1H, CH2O, J = 5.8, J = 7.6); 4.12 (d.d, 1H, CH2O, J = 5.2, J = 7.6); 4.45 (q, 1H, CHO, J = 5.8); 7.35, 7.46 (both d, of 4H, Ar, J = 8.8). IR (Nujol, v/mm-1): 1245, 1225, 1170, 1115, 1087 (COOC), 732 (CCI).

4-(4-chloromethyl)-2-(4-(chloromethyl)-1,3-dioxolane (3a), yield 95%, b.p. 189–191 0C.0.5 Topp, nD19=1.5670. NMR’H (CDCl3, δ, ppm, J/Hz): 1.33 (s, 9H, (CH3)); 3.49 (d.d, 1H, CH2Cl, J = 8.8, J = 11.0); 3.67 (d.d, 1H, CH2Cl, J = 5.2, J = 11.0); 4.02 (d.d, 1H, CH2O, J = 5.2, J = 8.0); 4.11 (d.d, 1H, CH2O, J = 6.7, J = 8.0); 4.44 (q, 1H, CHO, J = 5.9); 7.18–7.54 (m, 8H, Ar). IR (Nujol, v/mm-1): 1248, 1222, 1170, 1115, 1085 (COOC), 735 (CCI).

4-(chloromethyl)-2-(2,4-dichlorophenyl)-2-(4-(chloromethyl)-1,3-dioxolane (4a), yield 96%, b.p. 205–207 0C.0.5 Topp, nD19=1.5960. NMR’H (CDCl3, δ, ppm, J/Hz): 3.48 (d, 0.43 H, CH2Cl, J = 8.0, J = 8.8); 3.64 (d.d, 0.57H, CH2Cl, J = 5.8, J = 8.8); 3.75–3.80 (m, 1.43H, CH2Cl; CH2O); 4.02 (d, 1H, CH2O, J = 8.8); 4.25 (d.d, 0.57H, CH2O, J = 6.2, J = 8.8); 4.45 (q, 0.57H, CHO, J = 5.6); 4.55 (q, 0.47H, CHO, J = 5.6); 7.32–7.46 (m, 4H, Ar); 7.51–7.69 (m, 2H, Ar); 7.75 (d, 0.57H, Ar, J = 7.2); 7.81 (d, 0.43H, Ar, J = 7.2) IR (Nujol, v/mm-1): 1248, 1225, 1175, 1117, 1085 (COOC); 736 (CCI).

4-(chloromethyl)-2-(3,4-dichloromethyl)-2-nonyl-1,3-dioxolane (5a), yield 84%, b.p. 194–200 0C.0.3 Topp, nD19=1.5146. NMR’H (CDCl3, δ, ppm, J/Hz): 0.89 (t, 3H, CH3CH2, J = 7.3); 1.21–1.39 (m, 10H, (CH3)2CH); 1.84 (t, 2H, CH2(CH3)2CH2, J = 5.1); 3.17 (d.d, 0.27H, CH2Cl, J = 5.4, J = 7.3); 3.53 (d.d, 0.73H, CH2Cl, J = 5.4, J = 7.3); 3.64 (d.d, 1H, CH2Cl, J = 4.8, J = 7.3); 3.80 (d.d, 0.73H, CH2O, J = 4.4, J = 5.2); 3.94 (d.d, 0.73H, CH2O, J = 4.2, J = 5.2); 4.13–4.23 (m, 0.54H, CH2O + CHO); 4.27 (d.d, 0.37H, CH2O, J = 4.8, J = 5.2); 4.42 (q, 0.37H, CHO, J = 6.6); 7.55 (d, 2H, Ar, J = 8.6); 7.79 (d, 2H, Ar, J = 8.6); 8.03 (d, 1H, Ar, J = 1.9). IR (Nujol, v/mm-1): 1241, 1235, 1185, 1125, 1078 (COOC), 762 (CCI).

4-(chloromethyl)-2-(4-chlorophenyl)-2-cyclohexyl-1,3-dioxolane (6a), yield 90%, b.p. 167–171 0C.0.6 Topp,
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 elution 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)-1,3-dioxolan-4-ylmethyl]-1H-imidazole oxalate (2c), yield 42%, mp. 192–193 °C. NMR ’H (DMSO-d6, δ, ppm, JHz): 3.87 (d, 2 H, CH2O, J = 5.4, J = 8.8); 4.05 (d, 1 H, CH, J = 6.8, J = 13.2); 4.14 (d, 1 H, CHN, J = 4.8, J = 13.2); 4.47 (q, 1H, CHO, J = 5.4); 6.97 (s, 1 H, CH1 imid); 7.29 (s, 1H, CH2 imid); 7.34, 7.41 (both d, 1 H, CH, J = 8.8); 7.67 (s, 1H, CH imid). IR (Nujol, vsm): 1280 (β CH imid). 1247, 1220, 1170, 1105, 1085 (COCCO); 720 (CCI).

1-[[2-(4-bis-(4-chlorophenyl)-1,3-dioxolan-4-ylmethyl)-1H-imidazole oxalate (3b), yield 59%, mp. 162–163 °C. NMR ’H (DMSO-d6, δ, ppm, JHz): 1.29 (s, 9H, (CH3)); 3.94–4.18 (m, 2 H, CH2O); 4.35 (2H, CH2N, J = 5.9); 5.49 (q, 1H, CH, J = 5.8); 7.25–7.47 (m, 8H, Ar); 7.97 (1H, CH triaz); 8.09 (1H, CH2 triaz), IR (Nujol, vsm): 1274 (β CH triaz), 1247, 1220, 1172, 1105, 1087 (COCCO), 720 (CCI).

1-[[2-(4-tert-butylphenyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-ylmethyl)-1H-1,2,4-triazole oxalate (3b), yield 59%, mp. 162–163 °C. NMR ’H (DMSO-d6, δ, ppm, JHz): 1.29 (s, 9H, (CH3)); 3.94–4.18 (m, 2 H, CH2O); 4.35 (2H, CH2N, J = 5.9); 5.49 (q, 1H, CH, J = 5.8); 7.25–7.47 (m, 8H, Ar); 7.97 (1H, CH triaz); 8.09 (1H, CH2 triaz), IR (Nujol, vsm): 1274 (β CH triaz), 1247, 1220, 1172, 1105, 1087 (COCCO), 720 (CCI).

1-[[2-(4-bis-(4-chlorophenyl)-1,3-dioxolan-4-ylmethyl)-1H-imidazole oxalate (3c), yield 63%, mp. 177–178 °C. NMR ’H (DMSO-d6, δ, ppm, JHz): 1.28 (s, 9H, (CH3)); 3.87 (d, 1 H, CH, J = 6.8, J = 8.6); 4.02 (d, 1H, CH, J = 7.2, J = 8.6); 4.18 (d, 1H, CHN, J = 7.0, J = 14.0); 4.35 (d, 1H, CHN, J = 3.5, J = 14.0); 4.48 (q, 1H, CHO, J = 5.8); 7.12 (s, 1H, CH imid); 7.28–7.45 (m, 9H, Ar, + CH imid); 8.17 (s, 1H, CH imid). IR (Nujol, vsm): 1280 (β CH imid); 1247, 1220, 1172, 1105, 1087 (COCCO), 720 (CCI).
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-, cyclohexyl-, tertbutyl-), 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 (Table 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-toluene sulfonic acid with azetric 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 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.](image_url)
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 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 zone 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-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]-1H-imidazole exceeds ciprofloxacin in activity against *Staphylococcus aureus* 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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## REFERENCES


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

<table>
<thead>
<tr>
<th>Compound</th>
<th><em>Bacillus subtilis</em> ATCC 6633</th>
<th><em>Staphylococcus aureus</em> SG11</th>
<th><em>Enterococcus faecalis</em> 1528</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>12</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>2b</td>
<td>12</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>2c</td>
<td>24</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>3b</td>
<td>12</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>4b</td>
<td>20</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>5b</td>
<td>12</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>6b</td>
<td>12</td>
<td>11</td>
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<td>13</td>
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</tr>
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<td>11</td>
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</tr>
<tr>
<td>9b</td>
<td>11</td>
<td>11</td>
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</table>

Ciprofloxacin: 29 μg/ml

IA * diameter, mm

*IA* = inhibiting area after 24 h