V.S. Talismanov et al /J. Pharm. Sci. & Res. Vol. 10(4), 2018, 950-955

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis and evaluation of antimycobacterial activities of novel 2,2-disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles

V.S. Talismanov[1], S.V. Popkov[2], S.S. Zykova[3], O.G. Karmanova[1]

[1]Moscow Institute of Physics and Technology
9, Institutskiy per., Dolgoprudny, Moscow Region, 141701, Russian Federation

[2]D. Mendeleev University of Chemical Technology of Russia
9, Miusskaya sq., Moscow, 125047, Russian Federation

[3]Perm Penal Service Institute
125 Karpinskii street, Perm, 614012, Russian Federation

Abstract

2,2-Disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles possesses an antimycobacterial activity equal to or comparable the reference standard against mycobacterium: *Mycobacterium smegmatis, Mycobacterium aurum, Mycobacterium vaccae, Mycobacterium fortuitum.* 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 1,2,4-triazole or imidazole.

Keywords: alkylation, antimycobacterial activity, antitubercular activity, 1,3-dioxolane, imidazole, ketalization, ketals, 1,2,4-triazole.

INTRODUCTION

Tuberculosis (TB), a bacterial infection caused predominantly by *Mycobacterium tuberculosis*, while other strains of mycobacteria that can cause this disease includes *Mycobacterium avium* and *Mycobacterium africanum*. TB remains one of the world's deadliest communicable diseases. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease, 360 000 of whom were HIV-positive. Globally, 3.5% of new and 20.5% of previously treated TB cases were estimated to have had multidrug-resistant TB (MDR-TB) in 2013 [1].

The anti-TB drugs currently used in first-line treatments are more than 40 years old. The regimen that is currently recommended by WHO for new cases of drug-susceptible TB is highly efficient, with cure rates of around 90% in HIV-negative patients. Nonetheless, it requires six months of treatment with first-line drugs. The regimens for treatment of MDR-TB currently recommended by WHO are lengthy (at least 20 months of treatment with second-line drugs for most patients), and are associated with multiple and sometimes serious side-effects and compounded by low cure rates. New drugs are required to shorten treatment, to improve the efficacy and tolerability of treatment for MDR-TB and to improve the treatment of TB among people living with HIV [1].

Characteristics of *Mycobacterium tuberculosis (Mbt):* slow growth, large thickness and high hydrophobicity of the cell wall, intracellular pathogenesis, genetic homogeneity, ability to long-term existence in the dormant state. *Mbt* within an intact phagosome is able to avoid the antimicrobial action of the macrophage lysosome and, in conditions of lack or absence of oxygen, is able to form dormant forms resistant to drugs [2].

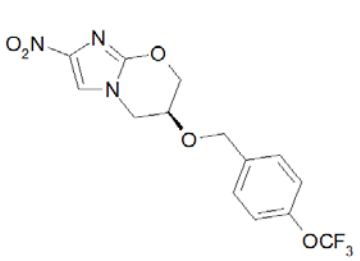
In the last decade, several review articles have been published on the subject matter ranging from target identification, validation, individual class of compounds, and clinical status of various anti-TB agents [3,4].

There are 10 new or repurposed anti-TB drugs currently in the late phases of clinical development include members of the fluoroquinolone, oxazolidinone, riminophenazine and rifamycin families. Among the most advanced NCE in phase II and phase III clinical trials are the diarylquinoline bedaquiline (TMC-207) [5, 6], the bicyclic nitroimidazoles delamanid (OPC67683) [7, 8], PA-824 [9]; oxazolidinones linezolid, sutezolid (PNU-100480), AZD-5847; fluoroquinolones gatifloxacin, moxifloxacin; rifapentine; a novel 1,2-ethylenediamine-based analogue SQ109 [10].

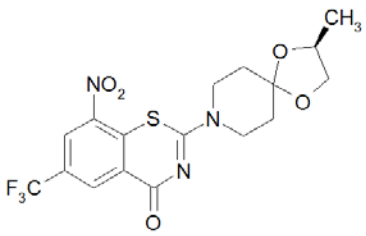
The current TB drug development pipeline also has extensive activity in the early stages, but there is a gap, corresponding to late preclinical development and phase I clinical trials, that needs filling to ensure continuity of clinical activity and to compensate for the probable attrition among the more advanced candidates. One New Chemical Essences (NCE) is nearing phase I clinical trials is the benzothiazinones BTZ043, PBTZ169 [11, 12], bicyclic nitroimidazole TBA-354 .

Most first-line drugs refer to derivatives of nitrogen-containing heterocyclic compounds. It is not surprising that an extensive search for tituberculostatic agents is carried out among triazole [13-40] and imidazole derivatives [24, 32, 36, 41-52]. Nitroimidazopyran PA-824, containing the imidazole and oxazinane rings, shows a high activity against both latent mycobacteria and in the clinical treatment of tuberculosis. Benzothiazinones BTZ043 with nanogram activity could be an excellent candidate for further exploration. We expect a good lead from this for clinical trials. The target of BTZs is decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1, Rv3790). BTZ043 contained 1,3-dioxolane fragment [11]. The new antituberculosis target in MT is the P450 cytochrome mono-oxygenases. Azole antifungal drugs were shown to be potent inhibitors of the growth of *Mycobacterium smegmatis* and of *Streptomyces* strains, indicating that one or more of the P450s in these bacteria were viable drug targets. The drugs econazole and clotrimazole were most effective against *Mycobacterium smegmatis* (MIC values of <0.2μM and 0.3 μM, respectively) and were superior inhibitors of mycobacterial growth compared to rifampicin and isoniazid (which had MIC values of 1.2 and 36.5 μM, respectively). It is suggested CYP121 is more realistic target enzyme for the azole drugs than CYP51 [53]. Consequently, it is reasonable to search for antituberculosis drugs among azol-1-ylmethyl-1,3-dioxolanes.

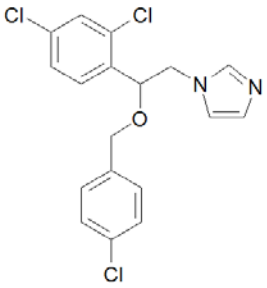
The most convenient test objects for the search of anti-tuberculosis agents are such relatively fast-growing forms of mycobacteria as *Mycobacterium smegmatis, Mycobacterium aurum, Mycobacterium vaccae, Mycobacterium fortuitum* [2].



PA-824



BTZ-043



Econazole

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).

Compounds **7b-15b, 8c, 9c, 7d-15d** have been synthesized and described by us earlier [54].

4-Bromo-4`-chlorobenzophenone (1a). 46.0 g (0.20 mol) of *p*-bromobenzoyl chloride were added portionwise with stirring to 36.3 g (0.26 mol) of anhydrous aluminum chloride suspension in 150 ml of chlorobenzene at 30–40 °C, the reaction mixture was stirred for 5 hours, raising the temperature by 10°C every hour. After completion of the hydrogen chloride, the reaction mass was stirred for 1 h at room temperature and then poured onto a mixture of 500 g of crushed ice and 300 ml of hydrochloric acid, then stirred for 30 min, the precipitated semicrystalline mass was extracted with chloroform (3 × 100 ml). The chloroform extracts were combined, washed with 5% sodium hydrogen carbonate solution (2x100 ml), water (2x150 ml), dried over anhydrous magnesium sulfate, and chloroform was evaporated. The solid residue was recrystallized from a mixture of 260 ml of ethanol and 40 ml of tetrahydrofuran gave 4-bromo-4'-chlorobenzophenone 51.1 g (87%) in the form of pinkish crystals with melting point of 149–150 °C.IR (Nujol, ν/sm^{-1}): 1672 (CO); 734 (CCl).

The following ketones were derived by a similar method:

4-Bromo-2`-chlorobenzophenone (2a). Yield 65%, m.p. 44-45°C, IR (Nujol, ν/sm^{-1}): 1679 (CO), 744 (CCl);

1-(4-Chlorophenyl)hexan-1-one (3a). Yield 72%, b.p. 173–178°C/30 Topp, IR (Nujol, ν/sm^{-1}): 1680 (C=O); 738 (CCl);

1-(4-Chlorophenyl)heptan-1-one (4a). Yield 68%, m.p 60-61°C, IR (Nujol, ν/sm^{-1}): 1676 (C=O); 736 (CCl);

1,2-Bis(4-chlorophenyl)ethanone (5a). Yield 60%, m.p 60-61°C, IR (Nujol, ν/sm^{-1}): 1680(CO), 744 (CCl).

1-(4-Chlorophenyl)-3-(4-fluorophenyl)propan-2-one (6a). A mixture of 8.94 g (0.06 mol) of 4-chlorobenzyl cyanide and 12.75 g (0.07 mol) of ethyl 4-fluorophenylacetic acid was added during 1 hour to a solution of sodium ethylate obtained by dissolving 2.70 g (0.12 mol) of sodium metal in 35 ml of absolute ethyl alcohol, with stirring and boiling, boiled for 3 hours, cooled and added 150 ml of cold water, extracted with ether (3×50 ml) and the ether extracts were discarded. The aqueous solution was acidified to neutral reaction with chilled 10% hydrochloric acid and extracted with ether (3×50 ml). The organic layer was washed with 20 ml of water, 10% solution of sodium bicarbonate (2×20 ml) and 20 ml of water, dried over anhydrous sodium sulfate, filtered and the solvent was distilled off in vacuum to gave 4-(4-chlorophenyl)-2-(4-fluorophenyl)-3-oxobutanenitrile 5.44 g (27%) in the form of yellow crystals with melting point of 74–76°C. IR (Nujol, ν/sm^{-1}):2218(CN); 1694 (CO).

A mixture of 25 ml of 60% sulfuric acid and 5.44 g (0.019 mol) of 4-(4-chlorophenyl)-2-(4-fluorophenyl)-3-oxobutanenitrile was boiled for about 24 hours until the carbon dioxide isolation ceased, cooled, with 50 ml of water cooled to 1 °C and extracted with methylene chloride (3×40 ml). The organic phase was washed with 10 ml of water, 10% sodium hydroxide solution (2×25 ml) and 10 ml of water, dried over anhydrous sodium sulfate, and the methylene chloride was distilled off vacuum gave **1-(4-chlorophenyl)-3-(4-fluorophenyl) propan-2-one** 3.32 g (67%) in the form of yellow crystals with melting point of 65–66 °C. IR (Nujol, ν/sm^{-1}): 1716 (CO), 745 (CCl), 720 (C-F).

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*.

2-(4-bromophenyl)-4-(chloromethyl)-2-(4-chlorophenyl)-1,3-dioxolane (1b), yield 93%, b.p. 183–185°C/0.5 Topp, n_D^{20}=1.5953. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.48 (d.d, 1 H, CH_2Cl, ^3J = 8.1, ^2J = 11.0); 3.66 (d.d, 1H, CH_2Cl, ^3J = 4.4, ^2J = 11.0); 4.02 (d.d, 1H, CH_2O, ^3J = 5.2, ^2J = 7.4); 4.11 (d.d, 1H, CH_2O, ^3J = 7.0, ^2J = 7.4); 4.43 (q, 1H, CHO, ^3J = 5.9); 7.25–7.53 (m, 8H, Ar). IR (Nujol, ν/sm^{-1}): 1245, 1225, 1175, 1115, 1085 (COCOC); 736 (CCl).

2-(4-bromophenyl)-4-(chloromethyl)-2-(2-chlorophenyl)-1,3-dioxolane (2b), yield 86%, b.p. 208-212°C/1 Topp, n_D^{20}=1.6042. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.49 (d.d, 1H, CH_2Cl, ^3J = 7.4, ^2J = 8.6); 3.56 (d.d, 1H, CH_2Cl, ^3J = 6.9, ^2J = 8.6); 3.96-4.18 (m, 2H, CH_2O); 4.44 (q, 1H, CHO, ^3J = 5.4); 7.21 (d, 2H, Ar, ^3J = 8.6); 7.37-7.45 (m, 4H, Ar); 7.78 (d, 2H, Ar, ^3J = 8.6).IR (Nujol, ν/sm^{-1}): 1245, 1225, 1185, 1120, 1080 (COCOC); 750 (CCl).

4-(chloromethyl)-2-(4-chlorophenyl)-2-pentyl-1,3-dioxolane (3b), yield 84%, b.p. 123–126°C/0.2 Topp, n_D^{20}=1.5184. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.82 (s, 3H, CH_3), 1.13–1.44 (m, 6H, $(CH_2)_3$), 1.77–1.94 (m, 2H, CH_2CPh), 3.13 (d.d, 0.33H, CH_2Cl, ^3J= 7.9, ^2J = 8.6), 3.48–3.70 (m, 2H, CH_2Cl, CH_2O), 3.78 (d.d, 0.67H, CH_2Cl, ^3J = 7.9, ^2J = 8.6), 3.93 (d.d, 0.67H, CH_2O, ^3J = 8.3, ^2J = 8.8), 4.16 (q, 0.67H, CHO, ^3J = 6.6), 4.28 (d.d, 0.33H, CH_2O, ^3J = 8.3, ^2J = 8.8), 4.42 (q, 0.33H, CHO, ^3J = 6.6), 7.23-7.43 (m, 4H, C_6H_4Cl). IR (Nujol, ν/sm^{-1}): 1245, 1210, 1170, 1110, 1090 (COCOC), 720 (CCl).

4-(chloromethyl)-2-(4-chlorophenyl)-2-heptyl-1,3-dioxolane (4b), yield 93%, b.p. 169–173°C/0.5 Topp, n_D^{20}=1.5150. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 0.84 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.1); 1.07-1.44 (m, 10H, $(\underline{CH_2})_5CH_3$); 1.79 (t, 2H, $\underline{CH_2}(CH_2)_5CH_3$, ^3J = 5.1); 3.07 (d.d, 0.33H, CH_2Cl, ^3J = 7.6, ^2J = 8.6); 3.19-3.55 (m, 1.67H, CH_2Cl); 3.81 (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, 4HAr). IR (Nujol, ν/sm^{-1}): 1245, 1232, 1180, 1120, 1075 (COCOC), 772 (CCl).

2-(4-chlorobenzyl)-4-(chloromethyl)-2-(4-chlorophenyl)-1,3-dioxolane (5b), yield 99%, m.p. 89-90^{o}C. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 3.05-3.09 (m, 2H, *p*-ClPh$\underline{CH_2}$); 3.33 (d.d, 1H, CH_2Cl, ^3J=5.1); 3.46 (d.d, 1H, CH_2Cl , ^3J=5.1); 3.59 (d.d, 1H, CH_2O, ^3J=6.6); 3.71-3.81 (m, 1H, CH_2O, CHO); 4.04 (d.d, 1H, CH_2O, ^3J=6.6); 4.16 (q, 1H, CHO, ^3J=5.9); 7.05 (d.d, 2H, $C^{2,6}H$, $C_6H_4ClCH_2$, ^3J=8.1); 7.21 (d.d, 2H, $C^{2,6}H$, C_6H_4Cl, ^3J=8.1); 7.25-7.33 (m, 4H, $C^{3,5}H$,$C_6H_4ClCH_2$, $C^{3,5}HC_6H_4Cl$). IR (Nujol, ν/sm^{-1}): 1240, 1219, 1164, 1075(COCOC); 788 (C-Cl).

2-(4-chlorobenzyl)-4-(chloromethyl)-2-(4-fluorophenyl)-1,3-dioxolane (6b), yield 68%, n_D^{20}=1.5529. NMR^{1}H ($CDCl_3$, δ, ppm, *J*/Hz): 2.88 (s, 2H, CH_2Ar); 2.91 (s, 2H, CH_2Ar); 3.47−3.87 (m, 4.7H, CH_2Cl+CH_2O+CHO); 4.05 (q, 0.3H, CHO, ^3J=5.6); 6.97 (t, 2H, $C^{3,5}HC_6H_4F$, ^3J=8.6); 7.13−7.36 (m, 6H, $C^{2,6}HC_6H_4F$+C_6H_4Cl). IR (Nujol, ν/sm^{-1}): 1245, 1218, 1180, 1090 (COCOC); 780 (C-Cl).

2,2-Disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles (general procedure).

A mixture of 0,03 mol a 4-chloromethyl-1,3-dioxolane (**1b-6b**) 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-bromophenyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole (1d), yield 72%, m.p. 128–129^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 4.04 (d.d, 1 H, CH_2O, ^3J = 5.2, ^2J = 8.8); 4.09 (d.d, 1H, CH_2O, ^3J = 6.6, ^2J = 8.8); 4.33 (d, 2H, CH_2N, ^3J = 5.2); 4.58 (q, 1H, CHO, ^3J = 5.2); 7.23–7.42 (m, 6 H, Ar); 7.47 (d, 2H, Ar, *J* = 8.8); 7.94 (s, 1H, C^3H triaz.); 8.01 (c, 1H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (βCH triaz.); 1245, 1215, 1177, 1115, 1080 (COCOC); 715 (CCl).

1-{[2-(4-bromophenyl)-2-(2-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (2d), yield 75%, m.p. 174–175^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.88 (d.d, 0.20H, CH_2O, ^3J = 7.2, ^2J = 8.8); 3.98-4.07 (m, 1.80H, CH_2O); 4.21 (d.d, 0.20H, CH_2N, ^3J = 7.0, ^2J = 8.9); 4.41-4.48 (m, 1.80H, CH_2N); 4.52 (q, 0.90H, CHO, ^3J = 5.4); 4.62 (q, 0.10H, CHO, ^3J = 5.4); 7.19 (d, 1.80H, Ar, ^3J = 8.6); 7.29 (d, 0.20H, Ar, ^3J = 8.6); 7.35-7.44 (m, 4H, Ar); 7.76 (d, 1.80H, Ar, ^3J = 8.6); 8.04 (d, 0.20H, Ar,^3J = 8.6); 7.89 (s, 0.10H, C^3H triaz.); 7.96 (s, 0.90H, C^3H triaz.); 8.34 (s, 0.10H, C^5H triaz.); 8.45 (s, 0.90H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (βCH triaz.); 1245, 1225, 1185, 1145, 1075 (COCOC); 730 (CCl).

1-{[2-(4-chlorophenyl)-2-pentyl-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (3c), yield 62%, m.p. 148–149^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.73 (s, 3H, CH_3), 0.96–1.29 (m, 6H, $(CH_2)_3$), 1.53–1.65 (m, 2H, CH_2CAr), 3.49 (d.d, 0.3H, CH_2O, ^3J = 7.8, ^2J = 8.4); 3.63 (d.d, 0.7H, CH_2O, ^3J = 7.8, ^2J = 8.4); 3.85 (d.d, 0.7H, CH_2O, ^3J = 5.6, ^2J = 8.4); 3.97–4.46 (m, 3.3H, CH_2O, CH_2N, CHO); 7.19–7.47 (m, 5H, C_6H_4Cl+C^4H imid.); 7.66 (s, 0.3H, C^5H imid.); 7.68 (s, 0.7H, C^5H imid.); 8.05 (s, 0.3H, C^2H imid.); 8.32 (s, 0.7H, C^2H imid.). IR (Nujol, ν/sm^{-1}): 1280 (βCH imid.); 1195, 1145, 1080 (COCOC).

1-{[2-(4-chlorophenyl)-2-heptyl-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole oxalate (4d), yield 84%, m.p. 149–150^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 0.83 (t, 3H, $CH_2\underline{CH_3}$, ^3J = 7.1); 1.06-1.41 (m, 10H, $(\underline{CH_2})_5CH_3$); 1.77 (t, 2H, $\underline{CH_2}(CH_2)_5CH_3$, ^3J = 5.1); 3.55 (d.d, 0.68H, CH_2O, ^3J = 7.6, ^2J = 8.6); 3.72 (d.d, 0.32H, CH_2O, ^3J = 7.0, ^2J = 8.6); 3.91 (d.d, 0.68H, CH_2O, ^3J = 6.5, ^2J = 8.6); 4.06-4.60 (m, 3.32H, CH_2N + CHO); 7.35-7.62 (m, 4HAr); 7.94 (s, 0.32H, C^3H triaz.); 7.99 (s, 0.68H, C^3H triaz.); 8.41 (s, 0.32H, C^5H triaz.); 8.54 (s, 0.68H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1270 (βCH triaz.); 1180, 1148, 1078 (COCOC).

1-{[2-(4-chlorobenzyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-1,2,4-triazole (5d), yield 48%, m.p. 102–103^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.08 (s, 2H, *p*-ClPh$\underline{CH_2}$); 3.59-3.82 (m, 2H, CH_2O); 3.88-4.08 (m, 2H, CH_2N); 4.31 (q, 1H, CHO, ^3J=5.1); 7.03 (d.d, 2H, $C^{2,6}H$, $C_6H_4ClCH_2$, ^3J=8.1); 7.15-7.35 (m, 6H, $C^{2,6}H$, C_6H_4Cl, $C^{3,5}H$, $C_6H_4ClCH_2$, $C^{3,5}H$, C_6H_4Cl); 7.88 (s, 1H, C^3H triaz.); 7.92 (s, 1H, $C^{3,5}H$ triaz.); 7.99 (s, 1H, C^5H triaz.). IR (Nujol, ν/sm^{-1}): 1266 (β CH triaz.); 1240, 1172, 1084 (COCOC).

1-{[2-(4-chlorobenzyl)-2-(4-chlorophenyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (5c), yield 68%, m.p. 173–174 ^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 3.14 (d, 2H, *p*-ClPh$\underline{CH_2}$, ^2J=4.4); 3.56 (d.d, 1H, CH_2O, ^3J=8.1); 3.73 (d, 1H, CH_2N, ^3J=5.9); 4.01 (d.d, 1H, CH_2O, J^3=8.1); 4.11-4.44 (m, 3H, CH_2N+CHO); 7.00 (s, 1H, C^4H imid.); 7.05 (d, 2H, $C^{2,6}H$, *p*-ClPhCH_2); 7.15-7.49 (m, 7H, $C^{3,5}H$, *p*-ClPhCH_2 , C_6H_4Cl, C^5H imid.); 8.16 (s, 1H, C^2H imid.); 8.29 (s, 1H, C^2H imid.). IR (Nujol, ν/sm^{-1}):1282 (βCH imid.); 1245, 1220, 1190, 1146, 1076 (COCOC); 784 (C-Cl).

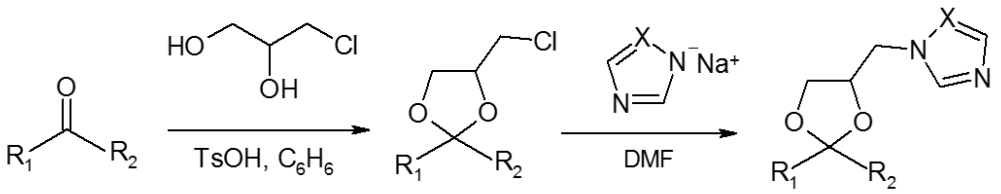
1-{[2-(4-chlorobenzyl)-2-(4-fluorobenzyl)-1,3-dioxolan-4-yl]methyl}-1*H*-imidazole oxalate (6c), yield 53%, m.p. 161–162 ^{o}C. NMR^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 2.86 (s, 2H, $CH_2C_6H_4F$); 3.25 (q, 2H, $\underline{CH_2}C_6H_4Cl$, ^2J=5.1); 3.59-3.75 (m, 2H, CH_2O); 3.79-3.90 (m, 2H, CH_2N); 3.92-4.10 (m, 1H, CHO); 7.00-7.40 (m, 10H, C_6H_4F, C_6H_4Cl, $C^{4,5}H$ imid.); 8.10 (s, 1H, C^2H imid.). IR (Nujol, ν/sm^{-1}): 1282 (βCH imid.); 1240, 1220, 1190, 1154, 1080 (COCOC); 780 (C-Cl).

RESULTS AND DISCUSSION

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 [55]. Substituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-azoles also demonstrated anti-cancer [56], antimicrobial [54], growth-regulating [57, 58] and fungicidal activity [59-64]. 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 (chloro-, *cyclo*hexyl-, *tert*butyl-), and preliminary calculation of logP by experimental and calculation methods. The calculated values of $logP_{OW}$ [65] of target compounds equal are 3.17-6.95 and they are analogically comparable with experimental data as we showed earlier [66].

The target compounds were derived in three stages (**Tab. 1, Fig.**). In the first stage, arylketones **1a–5a** were prepared in high yields according to Friedel-Crafts. The dibenzylketone **6a** were derived 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–6b**) were derived with 68–99% yields by condensation of ketones (**1a–6a**) with 3-chloro-1,2-propanediol in benzene catalyzed by *p*-toluenesulfonic acid with azeotropic removal of water.



1a-6a **1b-6b** **3c, 5c, 6c; 1d, 2d, 4d, 5d**

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

№	R_1	R_2	X	$logP_{ow}$*
1d	4-BrC_6H_4	4-ClC_6H_4	N	4,66
2d	4-BrC_6H_4	2-ClC_6H_4	N	4,66
3c	4-ClC_6H_4	*n*-C_5H_{11}	CH	4,88
4d	4-ClC_6H_4	*n*-C_7H_{15}	N	5,29
5c	4-ClC_6H_4	4-$ClC_6H_4CH_2$-	CH	5,09
5d	4-ClC_6H_4	4-$ClC_6H_4CH_2$-	N	4,44
6c	4-$ClC_6H_4CH_2$-	4-$FC_6H_4CH_2$-	CH	4,31
7d	4-ClC_6H_4	*n*-C_3H_7	N	3,17
8c	4-ClC_6H_4	4-ClC_6H_4	CH	5,13
8d	4-ClC_6H_4	4-ClC_6H_4	N	4,48
9c	4-$C(CH_3)_3C_6H_4$	4-ClC_6H_4	CH	6,23
9d	4-$C(CH_3)_3C_6H_4$	4-ClC_6H_4	N	5,57
10d	2,4-$Cl_2C_6H_3$	4-ClC_6H_4	N	5,09
11d	3,4-$Cl_2C_6H_3$	C_9H_{19}	N	6,82
12d	4-ClC_6H_4	*cyclo*C_6H_{11}	N	4,81
13d	4-*cyclo*$C_6H_{11}C_6H_4$	*n*-C_3H_7	N	5,09
14d	4-ClC_6H_4	C_6H_{13}	N	4,76
15d	4-$C(CH_3)_3C_6H_4$	C_3H_6S(4-ClC_6H_4)	N	6,95

* calculated values of $logP_{OW}$ [65]

Table 2. Growth inhibition of mycobacterium by 2,2-disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles

Compound	IA * diameter, mm			
	Mycobacterium smegmatis SG987	*Mycobacterium aurum* SB66	*Mycobacterium vaccae* 10670	*Mycobacterium fortuitum*
1d	14	12	19	11
2d	20	0	29	23
3c	24	21	26	28
4d	15	15	19	12
5c	20	20	21	14
5d	21	21	15	26
6c	20	19	19	19
7d	0	0	12	0
8c	26	26	27	19
8d	12	13	14	0
9c	22	21	20	16
9d	14	12	14	0
10d	17	25	23	14
11d	11	13	13	0
12d	13	13	17	13
13d	16	13	17	12
14d	15	17	20	13
15d	12	15	15	0
Ciprofloxacin	16	26	20	24

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

Table 3. The minimum concentration of 2,2-disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles, that inhibits the growth of mycobacterium

Compound	MIC, μg/ml			
	Mycobacterium smegmatis SG987	*Mycobacterium aurum* SB66	*Mycobacterium vaccae* 10670	*Mycobacterium fortuitum*
8c	12,5	12,5	6,25	12,5
9c	6,25	6,25	3,12	12,5
9d	12,5	12,5	12,5	50
10d	12,5	6,25	6,25	12,5
12d	25	12,5	12,5	25
13d	25	12,5	12,5	12,5
14d	25	12,5	12,5	25
15d	50	12,5	12,5	25

The target 2,2-disubstituted 1-(1,3-dioxolan-4-ylmethyl)-1*H*-imidazoles (**3c, 5c, 6c**) and 1-(1,3-dioxolan-4-ylmethyl)-1*H*-1,2,4-triazoles (**1d, 2d, 4d, 5d**) were derived with 48–84% yields by alkylation of sodium salts of 1,2,4-triazole or imidazole with substituted 4-chloromethyl-1,3-dioxolanes 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 1,2,4-triazole or imidazole were prepared in quantitative yield by the reaction of sodium isopropylate with azoles in isopropanol [67].

The antitubercular 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 opportunistic (fast-growing) mycobacterium: *Mycobacterium smegmatis, Mycobacterium aurum, Mycobacterium vaccae, Mycobacterium fortuitum.* 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 1μg/ml.

The synthesized compounds showed activity comparable to the reference compound (ciprofloxacin). The activity of compounds **3c, 8c** exceeded the activity of ciprofloxacin against *Mycobacterium smegmatis* and *Mycobacterium vaccae*. The results of antimicrobial activity tests of the synthesized compounds are shown in **Table 2**.

Also, for some of the most active compounds, the minimum inhibitory concentration (MIC) was determined by serial dilution [68]. Compounds **9c** and **10d** inhibited the growth of mycobacteria at a lower concentration than the other compounds (**Table 3**). It should be noted that for the pair of the most active analogues, the MIC of the imidazole derivative **9c** is two times less than the MIC of the 1,2,4-triazole derivative **9d**.

ACKNOWLEDGEMENTS

We express our gratitude to Makarov V.A., A.N. Bach Institute of Biochemistry, Russian Academy of Sciences and Leibniz Institute for Natural Product Research and Infection Biology Hans Knöll Institute (HKI), (Jena, Germany) for biological testing of compounds.

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