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SYNTHESIS AND ANTILEPROTIC ACTIVITY OF COMPOUNDS WITH BENZOFURAN, INDENE, TRIAZENE, AND HYDRAZONE FRAGMENTS

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A synthesis of 11 new functionalized polycyclic compounds with benzofuran, benzodiazocine, triazene, and hydrazone fragments was developed. Their antileprotic activity against *Mycobacterium lufu* was studied. It was established that methyl *N*-{4*b*,9*b*-dihydroxy-6-[(methoxycarbonyl)amino]-10-oxo-9*b*,10-dihydro-4*bH*-indeno[1,2-*b*]benzofuran-8-yl}carbamate (MIC 1.0 ± 0 μg/ml, MBC 14 ± 2 μg/ml), 4-methyl-*N*′-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)benzenesulfonohydrazide (MIC 1.25 ± 0.25 μg/ml, MBC 9 ± 2.52 μg/ml), and 2,4-dihydroxybenzenecarbaldehyde *N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (MIC 1.5 ± 0.29 μg/ml, MBC 12 ± 2.31 μg/ml) were most promising for further research.

Keywords: polycyclic compounds, hydrazones, benzofuran derivatives, *Mycobacterium lufu*, antileprotic activity, minimum inhibitory concentration, minimum bactericidal concentration.

Hansen's disease or leprosy continues to be endemic in many parts of the world. This disease is caused by mycobacterial agents uncultivated *in vitro*, namely *Mycobacterium leprae* and *M. lepromatosis*. Greater than 200,000 new cases of leprosy in greater than 14 countries are recorded yearly worldwide. Of these, almost two thirds are recorded in India and Brazil [1].

Modern multidrug chemotherapy of leprosy includes the three main antileprotic drugs according to the World Health Organization (WHO) plan (dapsone, rifampicin, clofazimine) and can cure patients and reduce the probability of reemergence. However, the treatment is still prolonged and causes complications associated with drug side effects and sometimes with intolerance to some antileprotic drugs or others and the development of drug resistance. Also, it should be emphasized that only dapsone and rifampicin are registered in the Russian Federation. The lack of clofazimine in the therapy plan reduces the efficacy of the antileprotic treatment and increases the chances of developing complications and resistance of *M. leprae* to the employed drugs. This attests to the promise of seeking antimycobacterial compounds, including antileprotic drugs [2, 3]. Effective treatment plans for this pathology using pharmacologically active compounds with known biological activity that can serve as prototypes for designing analogs with improved properties must be created for a comprehensive etiotropic treatment of leprosy patients and assurance of the epidemiological safety of the country. Compounds with potential antileprotic activity among newly synthesized pyrimidine derivatives underwent microbiological screening [4]. Thus, new antileprotic compounds of natural or semisynthetic origin must still be developed [5].

Hydrazones still attract constant attention in medicinal chemistry because of the variety and broad spectrum of biological properties [6-9]. Also, they are universal compounds for synthesizing heterocyclic systems [6, 8, 10, 11] and producing metal complexes and are used as ligands in coordination chemistry [12]. Antimicrobial properties are most common among the bioactivity profiles of hydrazones in the scientific literature [13-16]. This is especially important because bacterial and fungal infections are becoming more difficult to treat because of the increased number of strains

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resistant to antibiotics and chemotherapy [17]. It is worth noting that the hydrazone moiety is also present in the chemical structure of drugs with antimicrobial activity such as nitrofurazone, furazolidone, or nitrofurantoin [8].

Benzofuran derivatives also possess broad spectra of pharmacological activity [18-23], including antimycobacterial activity [24, 25]. Some 2,2-diaryl-substituted indenes are also known to exhibit antimicrobial activity [26].

New drugs are now being sought not only by the traditional route but also by using molecular docking and bioinformatics. The identification of new targets for potential drugs against *M. leprae* is highly significant. The full genome of *M. leprae* was published three years later than that of *M. tuberculosis*, which is phylogenetically the closest species, although the number of 3D structures deposited in the protein database (PDB) is 12, which is 1000 times less than for *M. tuberculosis*. This is probably related to the large number of pseudogenes in the *M. leprae* genome [27]. *M. leprae* is an intracellular parasite. Detection of targets for action on it requires combined *in silico* and *in vitro* approaches. Considering the lack of experimental data on the structures of *M. leprae* proteomics, data analysis for other mycobacteria species must be used. A total of 45 mycobacterial targets were found [28], several of which are dnaZX, nrdE, fabG1, and RFBA.

Dihydropteroate synthase (DHPS) of *M. leprae* was previously chosen as a biotarget [29]. Because DHPS is unavailable in the PDB, it was modeled by the homology model method and validated with the Ramachandran plot along with other bioinformatics approaches. Two mutations were introduced at codons 53 (from Thr to Ile) and 55 (from Pro to Leu) for docking with studied compounds for which effective antileprotic activity was recorded. The chemical structure of the compounds and the standard dapsone structure were retrieved from the PubChem database and prepared accordingly for a docking study with the virtual-screening platform of PyRx-AutoDock 4.1. Molecular docking found a higher degree of docking of the studied compounds with the target than that of dapsone.

The newly found targets will be effective only if they are related to structural features of leprosy agents, in particular, aimed at inhibition of enzymes in the biosynthesis of phenolic glycolipid-1 (PGL-1) that is specific for *M. leprae* [30].

EXPERIMENTAL CHEMICAL PART

PMR and ^{13}C NMR spectra were obtained in $CDCl_3$ and DMSO-d_6 on a DRX 500 spectrometer (500 and 126 MHz; Bruker, USA). IR spectra were measured in KBr in the range 4000-400 cm^{-1} on an InfraLUM FT-02 FTIR spectrometer (Russia). The purity of products was monitored by TLC on Silufol UV-254 plates (Chemapol, Czechia) with detection in I_2 vapor. Elemental analysis used a Series II 2400 instrument (PerkinElmer, USA). Commercial reagents (Aldrich, Alfa Aesar, USA) were used in the work.

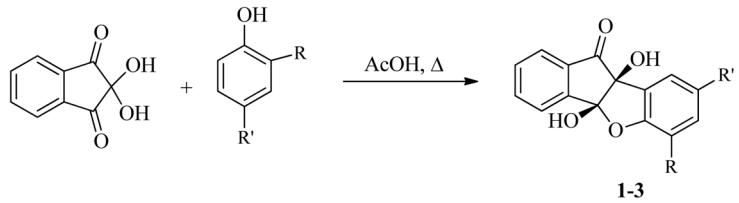
Methyl *N*-{4*b*,9*b*-dihydroxy-6-[(methoxycarbonyl)amino]-10-oxo-9*b*,10-dihydro-4*bH*-indeno[1,2-*b*]benzofuran-8-yl}carbamate (1). A mixture of 2,2-dihydroxyindane-1,3-dione (0.356 g, 2 mmol) and dimethyl (4-hydroxybenzene-1,3-diyl)biscarbamate (0.48 g, 2 mmol) in glacial HOAc (10 mL) was refluxed for 3 h, cooled, and transferred onto ice. The resulting precipitate was filtered off, rinsed on the filter with H_2O, and dried in air. Yield 0.76 g (95%), colorless crystals, mp 187 – 189°C ($CHCl_3$). IR spectrum (KBr), ν, cm^{-1}: 3365 (OH), 1680 (C=O), 1610, 1575, 1478 (C-C_{arom}). PMR spectrum ($CDCl_3$), δ, ppm: 3.71 (s, 6H, $NHCO_2C\underline{H}_3$), 3.94 (s, 1H, OH), 4.73 (s, 1H, OH), 7.20 (s, 1H_{arom}), 7.37 – 7.43 (m, 1H_{arom}), 7.65 (s, 1H_{arom}), 7.71 – 7.73 (m, 2H_{arom}), 7.79 – 7.81 (m, 1H_{arom}), 8.77 (br.s, 1H, $NHCO_2Me$), 8.94 (br.s, 1H, $NHCO_2Me$). Found, %: C 56.66; H 4.08; N 6.59. $C_{19}H_{16}N_2O_8$. Calc., %: C 57.00; H 4.00; N 7.00.

Methyl *N*-(4*b*,9*b*-dihydroxy-8-nitro-10-oxo-9*b*,10-dihydro-4*bH*-indeno[1,2-*b*]benzofuran-6-yl}carbamate (2) was prepared analogously to **1** by reacting 2,2-dihydroxyindeane-1,3-dione (0.356 g, 2 mmol) and methyl (4-hydroxy-3-nitrophenyl)carbamate (0.424 g, 2 mmol). Yield 0.7 g (94%), light-yellow crystals, mp 104 – 105°C (EtOH(petroleum ether, 1:2). IR spectrum (KBr), ν, cm^{-1}: 3360 (OH), 1680 (C=O), 1610, 1575, 1478 (C-C_{arom}), 1520, 1365 (NO_2). PMR spectrum ($CDCl_3$), δ, ppm: 3.71 (s, 3H, $NHCO_2Me$), 3.96 (s, 1H, OH), 4.72 (s, 1H, OH), 7.40 (t, 1H_{arom}, J 7.2 Hz), 7.69 (s, 1H_{arom}), 7.73 (t, 1H_{arom}, J 7.2 Hz), 7.79 (d, 2H_{arom}, J 7.2 Hz), 8.65 (s, 1H_{arom}), 9.65 (br.s, 1H, NH). Found, %: C 54.47; H 3.11; N 7.38. $C_{17}H_{12}N_2O_8$. Calc., %: C 54.85; H 3.25; N 7.52.

4-Methyl-*N*′-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-benzenesulfonohydrazide (4). A mixture of isatin (1.47 g, 10 mmol) and tosyl hydrazine (1.86 g, 10 mmol) in EtOH (40 mL) in the presence of glacial HOAc (3 drops) was refluxed for 8 h and cooled. The resulting precipitate was filtered off, dried in air, and recrystallized from dioxane. Yield 3.02 g (96%), golden-yellow crystals, mp 227 – 229°C. IR spectrum, ν, cm^{-1}: 3330 – 3410 (NH), 1680 (C=O), 1642 (C=N), 1615, 1585 (C-C_{arom}), 1430, 1160 (SO_2), 900 (S-N). PMR spectrum, δ, ppm: 2.37 (s, 3H, CH_3), 7.09 (d, 1H_{arom}, J 7.8 Hz), 7.20 – 7.27 (m, 2H_{arom}), 7.39 (d, 2H_{arom}, J 8.5 Hz), 7.76 (d, 2H_{arom}, J 8.5 Hz), 8.18 (d, 1H_{arom}, J 7.8 Hz), 10.98 (s, 1H, NH), 13.13 (br.s, 1H, NH). Found, %: C 56.88; H 3.95; N 13.06. $C_{15}H_{13}N_3O_3S$. Calc., %: C 57.14; H 4.13; N 13.33.

4-Methyl-*N*′-[2-thienylmethylidene]benzenesulfonohydrazide (5). A mixture of tosyl hydrazine (0.93 g, 5 mmol) and thiophene-2-carbaldehyde (0.47 mL, 5 mmol) in EtOH (10 mL) was refluxed for 3 h and cooled. The resulting precipitate was filtered off and recrystallized from EtOH(dioxane (2:1, v/v). Yield 1.25 g (89%), yellow crystals, mp 142 – 144°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 1670 (C=O), 1640 (C=N), 1615, 1570 (C-C_{arom}). PMR spec-

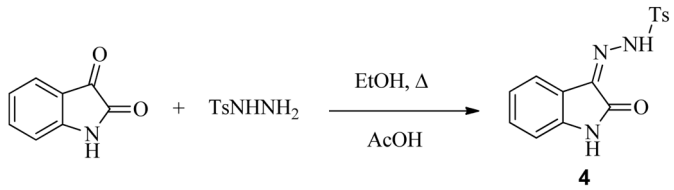
Scheme 1



1-3

R = R′ = $NHCO_2Me$ (**1**), R = NO_2, R′ = $NHCO_2Me$ (**2**), R = 1-Ad, R′ =Me (**3**).

Scheme 2



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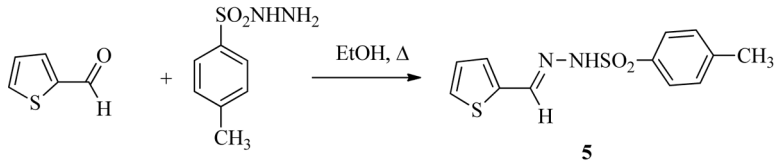
Scheme 3



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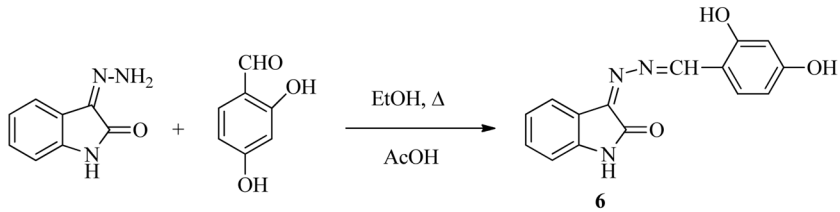
Scheme 4



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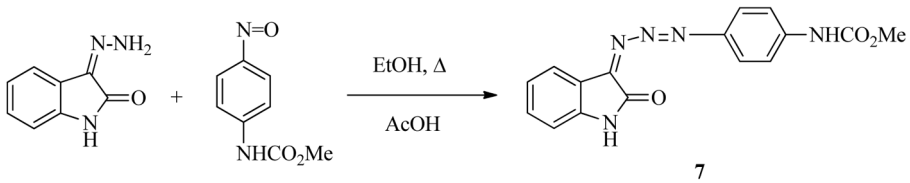
trum, δ, ppm: 3.76 (c, 3H, $NHCO_2Me$), 7.40 (d, $1H_{arom}$, J 7.5 Hz), 7.57 (t, $2H_{arom}$, J 7.5 Hz), 7.76 (d, $1H_{arom}$, J 8.6 Hz), 7.84 (d, $2H_{arom}$, J 8.6 Hz), 8.60 (d, $1H_{arom}$, J 7.5 Hz), 9.67 (s, 1H, NH), 11.03 (s, 1H, NH). Found, %: C 51.24; H 4.05; N 9.76. $C_{12}H_{12}N_2O_2S_2$. Calc., %: C 51.41; H 4.31; N 9.99.

2,4-Dihydroxybenzenecarbaldehyde *N*-(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)hydrazone (6). A mixture of 1*H*-indole-2,3-dione-3-hydrazone (0.805 g, 5 mmol) [31] and 2,4-dihydroxybenzaldehyde (0.69 g, 5 mmol) in EtOH (10 mL) was refluxed for 5 h and cooled. The resulting precipitate was filtered off and recrystallized from dioxane. Yield 1.22 g (87%), wine-colored crystals, mp 318 – 321°C (dec.). IR spectrum, ν, cm^{-1}: 3450 (OH), 3370 (NH), 1680 (C=O), 1260 (C-O), 1610, 1575 (C-C_{arom}). PMR spectrum, δ, ppm: 6.54 (d, $1H_{arom}$, J 8.6 Hz), 6.70 (s, $1H_{arom}$), 6.90 (d, $1H_{arom}$, J 8.6 Hz), 7.03 (d, $1H_{arom}$, J 7.8 Hz), 7.20 (t, $1H_{arom}$, J 7.8 Hz), 7.39 (t, $1H_{arom}$, J 7.8 Hz), 8.25 (s, 1H, CH=N), 8.45 (d, $1H_{arom}$, J 7.8 Hz), 10.20 (s, 2H, 2OH), 10.65 (1H, NH). Found, %: C 63.89; H 3.85; N 14.90. $C_{15}H_{11}N_3O_3$. Calc., %: C 64.05; H 3.94; N 14.94.

Methyl *N*-{4-[(*E*)-3-(2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene)-1-triazenyl]phenyl}carbamate (7). A mixture of 1*H*-indole-2,3-dione-3-hydrazone (0.805 g, 5 mmol) [31] and methyl *N*-(4-nitrosophenyl)carbamate (0.90 g, 5 mmol) in EtOH (15 mL) was refluxed for 4 h and cooled. The resulting crystalline product was filtered off and recrystallized from dioxane. Yield 1.53 g (95%), yellow crystals, mp 245 – 247°C (dec.). IR spectrum, ν, cm^{-1}: 3400, 3310 (NH), 1680, 1710 (CO), 1610, 1573 (C-C_{arom}), 1400, 1210 (triazene group). PMR spectrum, δ, ppm: 2.13 (c, 3H, CH_3), 7.08 (s,

Scheme 5



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1H, CH=N), 7.25 (d, $2H_{Fu}$, J 5.2 Hz), 7.76 (d, $1H_{Fu}$, J 4.2 Hz), 7.80 (d, $2H_{arom}$, J 8.5 Hz), 7.85 (d, $2H_{arom}$, J 8.5 Hz), 11.87 (s, 1H, NH). Found, %: C 59.27; H 3.80; N 21.47. $C_{16}H_{13}N_5O_3$. Calc., %: C 59.44; H 4.05; N 21.66.

The preparation of 6-(1-adamantyl)-4*b*,9*b*-dihydroxy-8-methyl-4*b*,9*b*-dihydro-10*H*-indeno[1,2-*b*]benzofuran-10-one (**3**), 5-{(1*E*)-1-[2-(1-benzothiophen-2-yl)hydrazinylidene]ethyl}-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione (**8**), 2,2-diaryl-substituted indenes (**9** and **10**), and benzodiazocine (**11**) and their physicochemical and spectral characteristics have been reported before [30, 32, 33].

EXPERIMENTAL BIOLOGICAL PART

The antileprotic activity of **1 – 11** dissolved in DMSO was studied *in vitro* in *M. lufu* mycobacteria culture (proposed for preliminary selection of agents with antileprotic activity [34]), which was inoculated in a series of serial dilutions of the drug in Shkolnikova liquid growth medium [35]. The reference drug was the main antileprotic drug dapsone (4,4?-diaminodiphenyl sulfone; NPTs Farmzashchita, FGUP FMBA of Russia, tablet dosage form).

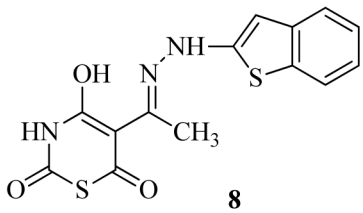
The study included four series of experiments. Series of tubes containing dilutions in DMSO of each compound from 128 to 0.25 μg/mL were inoculated with *M. lufu* (1×10^6). The inoculations were incubated in a thermostat at 37°C for 12 d and then removed from it. An aliquot from each tube (0.1 mL of the formed mycobacterium suspension) was inoculated on Lowenstein(Jensen dense medium [35]. The inoculations were again incubated in a thermostat at 37°C for 12 d. The number of colonies grown on the Lowenstein(Jensen medium plate was counted.

Then, the minimum inhibitory concentration (MIC) at which growth of the mycobacteria was inhibited by 50% as compared to a control and the minimum bactericidal concentration (MBC) at which growth of colonies was not observed after incubation [36] were determined.

RESULTS AND DISCUSSION

An analysis of the literature showed that functionalized hydrazones and benzofurans have been used as antibacterial and antifungal agents [5 – 24]. Therefore, the synthesis of new representatives of these compound classes (**1-7**) and the study of their antimycobacterial activity is a timely problem for medicinal chemistry and pharmacology.

Benzofuran derivatives **1-3** were prepared via condensation of ninhydrin with dimethyl (4-hydroxybenzene-1,3-diyl)biscarbamate, methyl (4-hydroxy-3-nitrophenyl)carbamate, and 2-(1-adamantyl)-4-methylphenol, respectively, in glacial HOAc [37] (Scheme 1).



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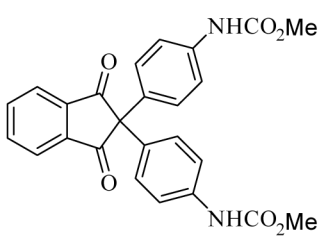

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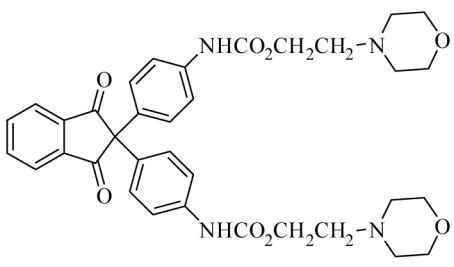

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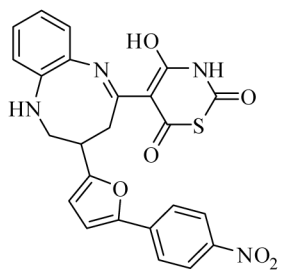

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Fig. 1. Derivatives of 5,5-disubstituted indenes (**9** and **10**) and benzodiazocine (**11**).

TABLE 1. Parameters for Visual Assessment of the Activity of Tested Compounds Against Growth of *M. lufu* (MBT broth)

Compound	Compound concentration, μg/mL									
	128	64	32	16	8	4	2	1	0.5	0.25
1	+	+	++	++	++	+++	+++	+++	+++	+++
2	–	–	–	–	+	+	++	++	+++	+++
3	–	–	–	–	–	+	+	++	+++	+++
4	–	–	–	–	–	+	++	++	+++	+++
5	–	–	–	+	+	+	+	++	+++	+++
6	–	–	–	–	–	+	++	++	+++	+++
7	–	–	+	+	++	++	++	+++	+++	+++
8	++	++	++	++	++	+++	+++	+++	+++	+++
9	+	+	+	+	+	+	+	++	+++	+++
10	–	–	+	+	+	+	++	++	+++	+++
11	–	–	–	–	+	+	++	+++	+++	+++
Dapsone	–	–	–	–	–	–	–	–	–	
Control	+++									

Note: "(", completely transparent medium; "+", weak growth; "++", moderate growth; "+++", strong growth.

Hydrazones **4** and **5** were prepared by condensing isatin and thiophene-2-carbaldehyde, respectively, with tosyl hydrazide (Schemes 2 and 3); hydrazone **6**, by condensing 3-hydrazinylidene-1,3-dihydro-2*H*-indol-2-one [31] with 2,4-dihydroxybenzaldehyde (Scheme 4).

Also, it seemed interesting to synthesize and study the antimycobacterial activity of several other polycyclic compounds, particularly a triazene derivative (**7**), hydrazone (**8**), 2,2-diaryl-substituted indenes (**9** and **10**) [37], and a benzodiazocine derivative (**11**) (Fig. 1) [30].

The triazene derivative (**7**) was prepared via condensation of 3-hydrazinylidene-1,3-dihydro-2*H*-indol-2-one with methyl (4-nitrosophenyl)carbamate (Scheme 5).

It is noteworthy that triazene derivatives of *N*-arylcarbamates were prepared earlier by us. Their antimycobacterial activity was studied *in vitro* in *M. tuberculosis* (laboratory strain $H_{37}R_V$) and *M. lufu* cultures [38].

TABLE 1 presents parameters of a visual assessment of the antimycobacterial activity of the synthesized compounds against growth of *M. lufu*.

TABLE 1 shows that the medium in tubes with compounds **3**, **4**, and **6** began to become cloudy at a concentration of 4 μg/mL; with **2** and **11**, at 8 μg/mL. The growth of mycobacteria increased if the concentrations of the compounds were decreased further. Compound **8**, even at the highest used concentrations, could not completely suppress growth of the test culture. Moderate growth of mycobacteria was noted at concentrations of 128 – 8 μg/mL. Then, the medium became completely opaque.

TABLE 2 presents results from statistical processing of the determined MIC and MBC values using the Student *t*-criterion.

The MIC value of dapsone and the MBC values of **1**, **8**, and **9** could not be determined at the used dilutions. The results were indicative of low antimycobacterial activity against *M. lufu* culture. Compound **9** as compared to **1** and **8** had considerably more pronounced antimycobacterial activity. However, its inhibitory activity on *M. lufu* culture was significantly inferior to that of the reference drug dapsone.

TABLE 2. Antimycobacterial Activity of Compounds Against *M. lufu*

Compound	Antimycobacterial activity	
	MIC, μg/mL	MBC, μg/mL
1	8.0 ± 0	–
2	1.25 ± 0.25	40 ± 8***
3	1.0 ± 0	14 ± 2*
4	1.25 ± 0.25	9 ± 2.52***
5	0.88 ± 0.13	28 ± 4*
6	1.5 ± 0.29	12 ± 2.31***
7	1.5 ± 0.29	48 ± 9.24***
8	10.0 ± 2.0	-
9	1.13 ± 0.31	-
10	1.25 ± 0.25	80 ± 16***
11	2.5 ± 0.5	20 ± 4***
Dapsone	–	0.56 ± 0.16

Note: *p*, criterion of statistical significance of differences relative to dapsone; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

Synthesized compounds of the benzofuran (**3**) and hydrazone classes (**4** and **6**) had the highest antimycobacterial activity against *M. lufu* that was comparable with that of dapsone.

Thus, an analysis of the results showed that these compounds could be considered promising for further studies of the antimycobacterial and antileprotic activity.

Conflict of interest

We declare no conflict of interest.

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Contributions of authors

All authors contributed equally to the article. AVV, LVS, and ASZ formulated the general concept. AVV, LVS, ASZ, ENK, EASh, and AVN analyzed and interpreted the results. EASh and ASZ wrote the article.

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