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SYNTHESIS OF 5-(4-AMINOPHENYL)-2-(ARYLAMINO)-1,3,4-THIADIAZOLES AND THEIR SCHIFF BASE DERIVATIVES AS ANTIMYCOBACTERIAL AGENTS

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The condensation reaction of 5-(4-aminophenyl)-N-aryl-1,3,4-thiadiazol-2-ylamines with salicylaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde, 5-bromosalicylaldehyde, 5-chlorosalicylaldehyde, 4-methoxybenzaldehyde, 3-nitrobenzaldehyde, and 4-nitrobenzaldehyde results in series of new Schiff bases. The synthesized compounds were tested for their antimicrobial efficiency against Mycobacterium smegmatis PTCC 1307 in vitro. All compounds showed significant antiproliferative activity against M. smegmatis.

Keywords: salicylaldehyde, 1,3,4-thiadiazole, *in vitro*, *Mycobacterium smegmatis*, Schiff base.

Tuberculosis is responsible for nearly three million deaths and eight million new patients annually [1]. This situation has worsened because of emergence of drug-resistant isolates of *Mycobacterium tuberculosis*. Therefore there is a need for identification of new drugs possessing positive therapeutic effects towards this pathogen. A common drawback of the most available methods is that they require the use of virulent *M. tuberculosi*s. *Mycobacterium smegmatis* is a nonpathogenic, fast-growing *Mycobacterium* species that could serve as a model for evaluation of antimycobacterial effects of different drug candidates, and it shows higher resistance to antituberculosis drugs among the other fast growing genera [2].

A wide variety of heterocyclic systems has been utilized for designing pharmaceutically active molecules. Among them the derivatives of thiadiazoles and oxadiazoles have played an important role in medicinal chemistry. The 1,3,4-thiadiazole derivatives have attracted continuing interest over the years due to their varied biological activities [3–5], such as anticancer [6–10], antimicrobial [11], antibacterial [12], antitubercular [13], anti-inflammatory [14, 15], antifungal [16], antihypertensive [17], antidepressant [18], antileishmanial [19], and antimycobacterial [20–24] properties.

On the other hand, Schiff bases containing the azomethine group have attracted much interest due to their synthetic availability along with antibacterial [25–27], anti-inflammatory [28], antitumor [29], and antimycobacterial [30] properties.

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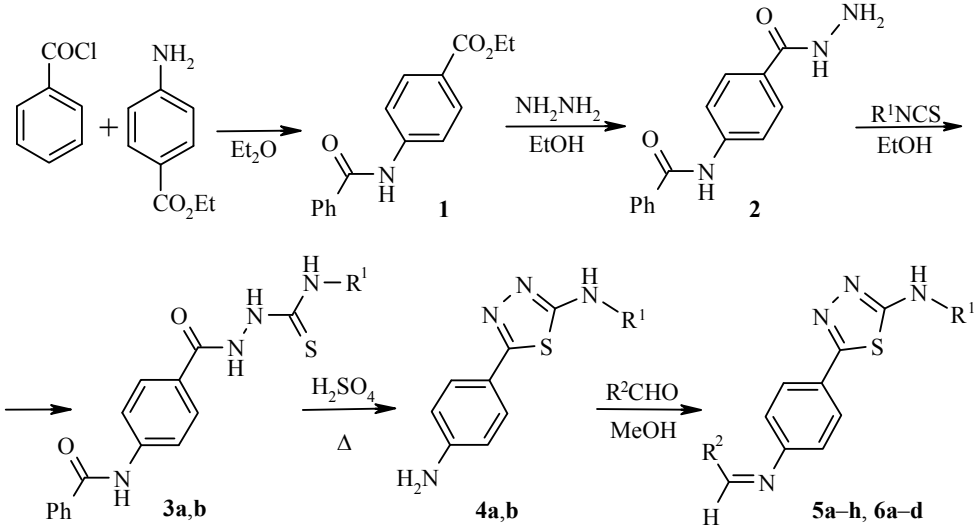
In this paper we report the synthesis of 2,5-disubstituted 1,3,4-thiadiazole Schiff base derivatives and their antimycobacterial and antimicrobial activity. 5-(4-Aminophenyl)-2-(arylamino)-1,3,4-thiadiazoles and their Schiff base derivatives were obtained by a versatile and efficient synthetic route outlined in scheme below.

The reaction of benzoyl chloride and benzocaine in diethyl ether gave ethyl 4-(benzoylamino)benzoate (**1**). The hydrazide **2** was prepared by refluxing compound **1** with hydrazine hydrate [31]. The resulting compound was treated with aryl isothiocyanate providing 4-aryl-1-[4-(benzoylamino)benzoyl]thiosemicarbazides **3a**,**b**, which were cyclized in sulfuric acid into 5-(4-aminophenyl)-2-(arylamino)-1,3,4-thiadiazoles **4a**,**b** [32]. Schiff bases **5a**–**h**, **6a**–**d** were synthesized by the reaction of the corresponding 1,3,4-thiadiazoles **4a**,**b** and benzaldehyde derivatives in MeOH.



3a, **4a**, **5a**–**h** R^1 = 4-BrC_6H_4; **3b**, **4b**, **6a**–**d** R^1 = 4-$O_2NC_6H_4$; **5a** R^2 = 2-HO-5-ClC_6H_3, **5d** R^2 = 3-HOC_6H_4, **5e** R^2 = 4-HOC_6H_4, **5f** R^2 = 4-$MeOC_6H_4$; **5c, 6a** R^2 = 2-HOC_6H_4; **5b**, **6b** R^2 = 2-HO-5-B-C_6H_3; **5g**, **6c** R^2 = 3-$O_2NC_6H_4$; **5h**, **6d** R^2 = 4-$O_2NC_6H_4$

The structure of the Schiff bases was confirmed by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy. The chemical shifts of imine (CH=N) and N–H protons were observed as singlets at 8.50–10.50 and 9.70-11.35 ppm, respectively, in the ^{1}H NMR spectra. Hydroxyl protons of the derivatives **5a**–**e** and **6a**,**b** showed resonance within the range of 10.65–12.85 ppm as a result of the intramolecular hydrogen bond between the hydroxyl proton and the imine group nitrogen [34]. The imine group stretching vibration in the Schiff bases **5** and **6** was indicated by the 1616–1644 cm^{-1} band in the IR spectra. Compounds **5h** and **6d** had poor solubility in DMSO; therefore their ^{13}C NMR spectra could not be recorded.

The antimycobacterial activity of the synthesized compounds was tested against *Mycobacterium smegmatis* PTCC 1307 (CIP 73.26) from the Persian Type Culture Collection (Shahriar, Iran). *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 25923 were also used for determinating of antimicrobial activity of the compounds. The antimycobacterial activity of the tested compounds was compared with that of the known chemotherapeutic ciprofloxacin (Table 1).

Thus, compounds **4**–**6** were not active against *E. coli* and *S. aureus* at concentrations up to 50 μg/ml. However, they were active against *M. smegmatis* with minimum inhibitory concentration (MIC) values in the range of 1.6–12.5 μg/ml (Table).

In general, the antimycobacterial activity of all the tested compounds was slightly lower compared to ciprofloxacin (0.5 μg/ml), whereas compounds **5**, having the 4-bromoanilino substituent at the thiadiazole ring, tend to have slightly higher activity than compounds **6** that have the 4-nitroanilino substituent in the same position. Compounds **5g** and **5c** showed the highest effect against the test species. In addition, the MIC values

for compounds **6** showed no difference or even an increase with respect to the "parent" amine **4b**, whereas Schiff bases **5** showed a tendency to lower MIC values compared to free amine **4a**.

TABLE 1. Antibacterial activity of synthesized compounds against *Mycobacterium smegmatis* PTCC 1307

Compound	MIC, μg/ml	Compound	MIC, μg/ml
4a	6.2	**5g**	1.6
5a	3.1	**5h**	2.9
5b	6.2	**4b**	3.1
5c	1.9	**6a**	12.5
5d	3.1	**6b**	3.1
5e	3.1	**6c**	6.2
5f	3.1	**6d**	3.1
		Ciprofloxacin	0.5

EXPERIMENTAL

IR spectra were recorded on a Thermo Nicolet 610 Nexus FT-IR spectrometer in KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 spectrometer at 300 and 75 MHz, respectively, in DMSO-d_6 using TMS as internal standard. High resolution mass spectra were obtained with an HPLC-Q-TOF system equipped with a Q-TOF micromass spectrometer (dual ESI). Melting points were measured on a Philip Harris C4954718 apparatus without calibration. Thin layer chromatography (TLC) analyses were carried out on silica gel plates. All chemicals were purchased from Merck and used as received.

Ethyl 4-(benzoylamino)benzoate (**1**), 4-(benzoylamino)benzoylhydrazine (**2**), and 1-(4-benzoylamino)-benzoyl-4-arylthiosemicarbazides **3a**,**b** were prepared by the previously reported methods [31].

Synthesis of Thiadiazoles 4a,b. A mixture of corresponding compound **3a**,**b** (6 mmol) in 50% aq. H_2SO_4 (15.0 ml) was refluxed for 6 h. The mixture was cooled to room temperature and then neutralized with 2 N NaOH (pH 1). The precipitate that formed was filtered, washed with water, and recrystallized from ethanol [32-34].

Synthesis of Schiff Bases 5a–h and 6a–d. The respective compound **4a**,**b** (1 mmol) and aldehyde (1 mmol) were dissolved in methanol (10 ml), and the reaction mixture was refluxed for 8 h. After cooling, the resulting precipitate was recrystallized from methanol.

2-{[(4-{5-[(4-Bromophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}-4-chlorophenol (5a). Yield 49%. Orange powder, mp 230-232°C. IR spectrum, ν, cm^{-1}: 3338 (OH, NH), 1619 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.00 (1H, d, *J* = 9.0, H Ar); 7.45 (1H, d, *J* = 9.0, H Ar); 7.52 (4H, d, *J* = 8.4, H Ar); 7.63 (2H, d, *J* = 8.4, H Ar); 7.70 (1H, s, H Ar); 7.93 (2H, d, *J* = 8.4, H Ar); 8.98 (1H, s, CH=N); 10.68 (1H, s, NH); 12.72 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 113.8; 119.2; 119.9; 121.2; 122.8; 123.2; 128.4; 129.3; 131.3; 132.3; 133.5; 140.2; 150.0; 157.9; 159.3; 162.8; 164.2. Found, *m/z*: 484.9920 $[M+H]^+$. $C_{21}H_{14}BrClN_4OS$. Calculated, *m/z*: 484.9838.

4-Bromo-2-{[(4-{5-[(4-bromophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (5b). Yield 42%. Orange powder, mp 211-214°C. IR spectrum, ν, cm^{-1}: 3242 (NH), 1616 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.96 (1H, d, *J* = 8.7, H Ar); 7.53 (4H, d, *J* = 9.0, H Ar); 7.57 (1H, dd, *J* = 8.7, *J* = 2.7, H Ar); 7.64 (2H, d, *J* = 8.7, H Ar); 7.90 (1H, d, *J* = 2.7, H Ar); 7.94 (2H, d, *J* = 8.7, H Ar); 8.98 (1H, s, CH=N); 10.70 (1H, s, NH); 12.76 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 110.5; 113.8; 119.6; 119.9; 121.8; 122.8; 128.5; 129.3; 132.3; 134.3; 136.3; 140.2; 150.0; 159.5; 159.8; 162.7; 164.2. Found, *m/z*: 528.9419 $[M+H]^+$. $C_{21}H_{14}Br_2N_4OS$. Calculated, *m/z*: 528.9333.

2-{[(4-{5-[(4-Bromophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (5c). Yield 44%. Orange powder, mp 218-220°C. IR spectrum, ν, cm^{-1}: 3311 (NH), 1621 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.97 (2H, d, *J* = 8.1, H Ar); 7.43 (1H, t, *J* = 7.5, H Ar); 7.53 (4H, d, *J* = 6.3, H Ar); 7.60-7.74 (3H, m, H Ar); 7.93 (2H, d, *J* = 8.1, H Ar); 9.01 (1H, s, CH=N); 10.70 (1H, s, NH); 12.85 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 113.8; 117.1; 119.7; 119.8; 119.9; 122.8; 128.4; 129.0; 132.3; 133.1; 134.1; 140.2; 150.1; 158.0; 160.8; 164.1; 164.5. Found, *m/z*: 451.0310 $[M+H]^+$. $C_{21}H_{15}BrN_4OS$. Calculated, *m/z*: 451.0228.

3-{[(4-{5-[(4-Bromophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (5d). Yield 47%. Orange powder, mp 208-209°C. IR spectrum, ν, cm^{-1}: 3421 (NH), 1623 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.95 (1H, d, *J* = 7.5, H Ar); 7.27-7.40 (4H, m, H Ar); 7.45-7.57 (3H, m, H Ar); 7.65 (2H, d, *J* = 9.0, H Ar), 7.90 (2H, d, *J* = 8.4, H Ar); 8.57 (1H, s, CH=N); 9.72 (1H, s, NH); 10.67 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 114.9; 119.6; 119.9; 121.0; 122.4; 128.2; 128.3; 128.6; 130.4; 132.2; 132.3; 137.6; 140.3; 153.5; 158.2; 162.2; 164.0. Found, *m/z*: 451.0314 $[M+H]^+$. $C_{21}H_{15}BrN_4OS$. Calculated, *m/z*: 451.0228.

4-{[(4-{5-[(4-Bromophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (5e). Yield 50%. Orange powder, mp 210-212°C. IR spectrum, ν, cm^{-1}: 3432 (NH), 1623 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.88 (2H, d, *J* = 7.8, H Ar); 7.32 (2H, d, *J* = 7.8, H Ar); 7.52 (2H, d, *J* = 8.7, H Ar); 7.64 (2H, d, *J* = 8.7, H Ar); 7.79 (2H, d, *J* = 7.8, H Ar), 7.86 (2H, d, *J* = 7.8, H Ar); 8.51 (1H, s, CH=N); 10.18 (1H, s, NH); 10.65 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 113.7; 116.2; 119.9; 122.3; 127.8; 128.3; 128.6; 131.4; 132.3; 140.3; 154.0; 158.3; 161.3; 161.4; 163.9. Found, *m/z*: 451.0311 $[M+H]^+$. $C_{21}H_{15}BrN_4OS$. Calculated, *m/z*: 451.0228.

N-(4-Bromophenyl)-5-(4-{[(4-methoxyphenyl)methylidene]amino}phenyl)-1,3,4-thiadiazol-2-amine (5f). Yield 61%. Yellowish-white powder, mp 258°C. IR spectrum, ν, cm^{-1}: 3335 (NH), 1621 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.83 (3H, s, CH_3O); 7.06 (2H, d, *J* = 8.7, H Ar); 7.33 (2H, d, *J* = 8.7, H Ar); 7.51 (2H, d, *J* = 8.7, H Ar); 7.64 (2H, d, *J* = 8.7, H Ar); 7.87 (2H, d, *J* = 9.0, H Ar); 7.90 (2H, d, *J* = 9.0, H Ar); 8.56 (1H, s, CH=N); 10.64 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 55.9; 113.7; 114.8; 119.9; 122.3; 127.8; 128.3; 129.2; 131.2; 132.3; 140.3; 153.8; 158.3; 161.2; 162.6; 163.9. Found *m/z*: 465.0469 $[M+H]^+$. $C_{22}H_{17}BrN_4OS$. Calculated, *m/z*: 465.0385.

***N*-(4-Bromophenyl)-5-(4-{[(3-nitrophenyl)methylidene]amino}phenyl)-1,3,4-thiadiazol-2-amine (5g)**. Yield 57%. Yellow powder, mp 246-248°C. IR spectrum, ν, cm^{-1}: 3244 (NH), 1623 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.43 (2H, d, *J* = 8.1, H Ar); 7.50 (2H, d, *J* = 8.1, H Ar); 7.63 (2H, d, *J* = 8.1, H Ar); 7.81 (1H, t, *J* = 8.1, H Ar); 7.90 (2H, d, *J* = 8.1, H Ar); 8.36 (2H, d, *J* = 8.1, H Ar); 8.73 (1H, s, H Ar); 8.85 (1H, s, CH=N); 10.66 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 113.8; 119.9; 122.6; 123.4; 126.4; 128.3; 128.9; 131.0; 132.3; 135.2; 137.8; 140.2; 148.7; 152.4; 158.0; 160.2; 164.1. Found, *m/z*: 480.0217 $[M+H]^+$. $C_{21}H_{14}BrN_5O_2S$. Calculated, *m/z*: 480.0130.

***N*-(4-Bromophenyl)-5-(4-{[(4-nitrophenyl)methylidene]amino}phenyl)-1,3,4-thiadiazol-2-amine (5h)**. Yield 45%. Yellow powder, mp 242-244°C. IR spectrum, ν, cm^{-1}: 3238 (NH), 1625 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.45 (2H, d, *J* = 8.4, H Ar); 7.78 (2H, d, *J* = 8.1, H Ar); 7.89 (2H, d, *J* = 8.1, H Ar); 8.16-8.28 (4H, m, H Ar); 8.36 (2H, d, *J* = 9.0, H Ar); 8.85 (1H, s, CH=N); 11.09 (1H, s, NH). Found, *m/z*: 480.0213 $[M+H]^+$. $C_{21}H_{14}BrN_5O_2S$. Calculated, *m/z*: 480.0130.

2-{[(4-{5-[(4-Nitrophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (6a). Yield 54%. Orange powder, mp 263-265°C. IR spectrum, ν, cm^{-1}: 3448 (OH, NH), 1623 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.96 (2H, d, *J* = 8.6, H Ar); 7.42 (1H, t, *J* = 7.5, H Ar); 7.52 (2H, d, *J* = 8.4, H Ar); 7.66 (1H, d, *J* = 7.5, H Ar); 7.78-7.89 (2H, m, H Ar); 7.94 (2H, d, *J* = 8.4, H Ar); 8.23 (2H, d, *J* = 8.6, H Ar); 8.99 (1H, s, CH=N); 11.24 (1H, s, NH); 12.81 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 114.1; 117.1; 117.5; 119.7; 122.8; 126.0; 128.6; 128.8; 133.0; 134.1; 141.4; 146.6; 150.4; 151.8; 160.8; 163.4; 164.5. Found, *m/z*: 418.1057 $[M+H]^+$. $C_{21}H_{15}N_5O_4S$. Calculated, *m/z*: 418.0974.

4-Bromo-2-{[(4-{5-[(4-nitrophenyl)amino]-1,3,4-thiadiazol-2-yl}phenyl)imino]methyl}phenol (6b). Yield 47%. Yellow powder, mp 278-279°C. IR spectrum, ν, cm^{-1}: 2920 (NH), 1619 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.95 (1H, d, *J* = 8.7, H Ar); 7.52 (2H, d, *J* = 8.4, H Ar); 7.56 (1H, dd, *J* = 8.7, *J* = 2.1, H Ar);

7.84–7.91 (3H, m, H Ar); 7.87 (2H, d, *J* = 9.3, H Ar); 7.97 (2H, d, *J* = 8.4, H Ar); 8.26 (2H, d, *J* = 9.3, H Ar); 8.98 (1H, s, CH=N); 11.30 (1H, s, NH); 12.72 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 110.5; 114.1; 117.2; 117.5; 119.6; 121.8; 122.9; 126.0; 128.7; 134.3; 136.3; 141.4; 146.6; 150.3; 159.7; 162.8; 163.5. Found, *m/z*: 496.0167 $[M+H]^+$. $C_{21}H_{14}BrN_5O_3S$. Calculated, *m/z*: 496.0079.

***N*-(4-Nitrophenyl)-5-(4-{[(3-nitrophenyl)methylidene]amino}phenyl)-1,3,4-thiadiazol-2-amine (6c)**. Yield 42%. Orange powder, mp 231-234°C. IR spectrum, ν, cm^{-1}: 3265 (NH), 1644 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.56 (4H, m, H Ar); 7.91 (6H, m, H Ar); 8.20–8.29 (2H, m, H Ar); 10.49 (1H, s, CH=N); 11.23 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 117.4; 120.9; 122.6; 125.4; 126.0; 128.0; 128.2; 128.5; 128.9; 132.2; 135.1; 141.3; 141.8; 146.7; 159.9; 163.0; 166.3. Found, *m/z*: 447.0964 $[M+H]^+$. $C_{21}H_{14}N_6O_4S$. Calculated, *m/z*: 447.00875.

***N*-(4-Nitrophenyl)-5-(4-{[(4-nitrophenyl)methylidene]amino}phenyl)-1,3,4-thiadiazol-2-amine (6d)**. Yield 43%. Orange powder, mp 240-242°C. IR spectrum, ν, cm^{-1}: 3421 (NH), 1624 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.50 (2H, d, *J* = 8.4, H Ar); 7.89 (2H, d, *J* = 9.0, H Ar); 7.99 (2H, d, *J* = 9.0, H Ar); 8.20–8.31 (4H, m, H Ar); 8.38 (2H, d, *J* = 9.0, H Ar); 8.89 (1H, s, CH=N); 11.34 (1H, s, NH). Found, *m/z*: 447.0961 $[M+H]^+$. $C_{21}H_{14}N_6O_4S$. Calculated, *m*/*z*: 447.00875.

Preparation of Test Compounds and Antibacterial and Antimycobacterial Activity Assays. Stock solutions of compounds were prepared in DMSO at an initial concentration of 1 mg/ml. The susceptibility of *Mycobacterium smegmatis* to the test compounds was determined using the microdilution method, and the MIC values for the compounds were determined using MB 7H10 agar medium for *Mycobacterium smegmatis* [2]. 500 μl of serial twofold dilutions of the stock solution (1 mg/ml) of each compound were incorporated in 9.5 ml of medium (initial concentration 50 μg/ml and final concentration 0.39 μg/ml of culture media). The tubes were kept in slanting position until the medium solidified. 10 μl of *M. smegmatis* (2×10^7 CFU/ml) were spread on the medium in each tube, and the tubes were incubated at 37°C. Results were available within 3 days. The lowest concentration of a compound that inhibited the growth of the bacterium was taken as its (MIC). Experiments were performed at least three times [2]. The susceptibility of *E. coli* and *S. aureus* to the compounds was determined using the microdilution method in Mueller–Hinton broth [35].

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