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Synthesis and antimicrobial activity of some novel 2-(*p*-substituted-phenyl)-5-substituted-carbonylaminobenzoxazoles

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Abstract

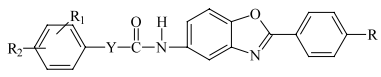
A series of 2-(*p*-substituted-phenyl)-5-substitued-carbonylamino benzoxazole derivatives (**5**–**22**) was synthesized and their antimicrobial activities determined in comparison to several control drugs. The synthesized compounds were tested in vitro against *Staphylococcus aureus*, *Streptococcus faecalis* and *Bacillus subtilis* as Gram-positive, *Pseudomonas aeruginosa* and *Escherichia coli* as Gram-negative bacteria and the yeast *Candida albicans*. Microbiological results showed that the compounds possessed a diffuse spectrum of antibacterial activity against these microorganisms. Compound **9** which bears a phenylacetamido moiety at position 5 and a 4-fluorophenyl group at the 2-position of benzoxazole ring was the most active derivative against *S. aureus*, *S. faecalis* and *P. aeruginosa* with a MIC value of 12.5 μg/ml. Compound **11** provided higher potency than the other tested compounds against *B. subtilis* at a MIC value of 12.5 μg/ml. Compounds **5**–**22** showed antifungal activity against *C. albicans* with MIC values between 50 and 12.5 μg/ml. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Benzoxazole; Carbonylamino; Synthesis; Antimicrobial activity

1. Introduction

Benzoxazoles and related fused heterocycles such as benzimidazoles and benzothiazoles were studied for their antitumor, antiviral and antimicrobial activities [1–6]. In the last few years, we reported the synthesis and the antimicrobial activity of various 2,5-disubstituted and 2,5,6-trisubstituted benzoxazoles, benzimidazoles, benzothiazoles and oxazolo[4,5-*b*]pyridines against some Gram-positive, Gram-negative bacteria and the yeast *Candida albicans* [5–12] and these compounds provided a wide variety of in vitro antimicrobial effects especially against the enterobacter *Pseudomonas aeruginosa* and the yeast *C. albicans* [6,8].

Recently, we reported the synthesis and microbiological study of a series of 5-benzamido- and 5-phenylacetamidosubstituted-2-phenylbenzoxazole derivatives (Formula 1). Among the synthesized compounds the 5-benzamido-, 5-(4-propyloxyphenyl)acetamido- and 5-(2-chlorophenyl)acetamido-2-phenylbenzoxazoles were found active against *P. aeruginosa* showing MIC values as 25 μg/ml [13].



Y ; —, -CH_2-

R ; -H, -C_2H_5

R_1 ; -H, -F, -Cl, -Br, -OCH_3, -CH_3, -C_2H_5, -NO_2, -$C(CH_3)_3$, -OC_3H_7

R_2 ; -H, -Cl, -OCH_3, -CH_3

Formula 1

In the present study, some novel 5-benzamido-, 5-(*p*-substitutedphenyl)acetamido-, 5-phenylpropionamido-, 5-(*p*-substitutedphenyl)oxyacetamido- and 5-phenylthioacetamido-2-(*p*-substitutedphenyl)benzoxazole have been synthesized in order to examine their in vitro antimicrobial activities against different Gram-positive, Gram-negative bacteria and *C. albicans* as a fungus in comparison with several control drugs.

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2. Chemistry

The synthesis of the compounds **5**–**22** was performed in two steps as shown in Scheme 1. In the first step, 5-amino-2-phenyl- or 5-amino-2-(*p*-ethylphenyl)- or 5-amino-2-(*p*-flourophenyl)- or 5-amino-2-(*p*-dimethylaminophenyl)benzoxazoles (**1**–**4**) were obtained by heating benzoic acid or *p*-ethylbenzoic acid or *p*-fluorobenzoic acid or *p*-dimethylaminobenzoic acid with 2,4-diaminophenol in PPA (polyphosphoric acid) as cyclodehydration reagent [14].

In the second step, the compounds (**5**–**22**) were prepared by reacting 5-amino-2-phenyl- or 5-amino-2-*p*-ethylphenyl)- or 5-amino-2-(*p*-flourophenyl)- or 5-amino-2-(*p*-dimethylaminophenyl)benzoxazoles with appropriate carboxylic acid chlorides [13,15].

All compounds are novel except **1**–**4**. The structure of the synthesized compounds **5**–**22** were supported by spectral data and the IR, ^{1}H NMR spectra are in agreement with the proposed structures. Physical and spectral data of the compounds are reported in Table 1.

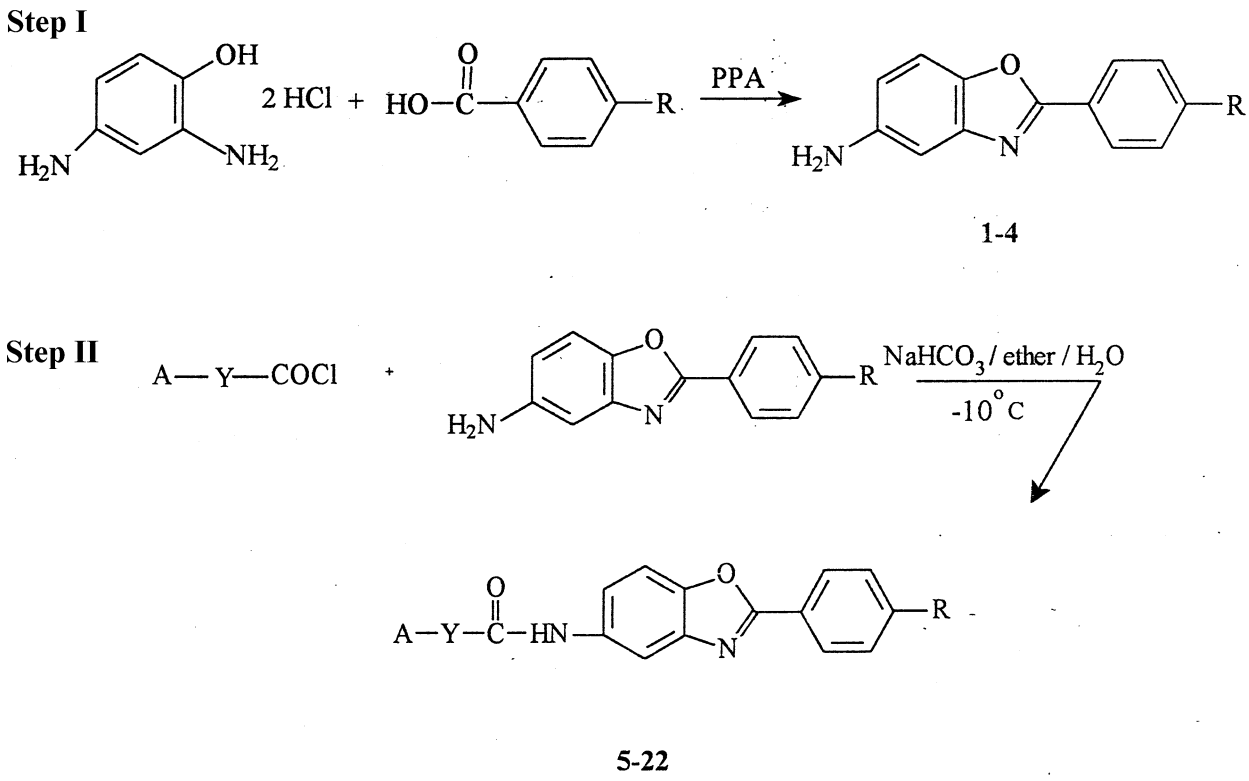
3. Experimental procedures

3.1. Chemistry

Silica gel HF_{254} chromatoplates (0.3 mm) were used for TLC and the solvent systems were chloroform:methanol (15:0.5) for compounds **5**–**22.** All the melting points were taken on a Buchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded by FT/IR-420 with KBr discs. ^{1}H NMR spectra were obtained with a Bruker 400 MHz spectrometer in d_6-chloroform and tetramethylsilan (TMS) was used as an internal standard. Elemental analyses were carried out with a Perkin Elmer model 240-C apparatus. The results of the elemental analyses (C, H, N) were within $\pm$0.4% of the calculated amounts.

3.2. General procedure for the synthesis of 5-amino-2-(*p*-substitutedphenyl)benzoxazole derivatives (*1*–*4*)

5-Amino-2-(*p*-substitutedphenyl)benzoxazole derivatives were synthesized by heating 0.01 mol 2,4-



5-22

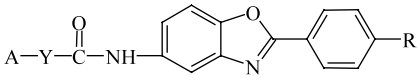
A= substitutedphenyl

Y= -CH_2-, -SCH_2-, OCH_2-, - CH_2CH_2-, —

R= -H, -C_2H_5 –F, -$N(CH_3)_2$

Scheme 1.

Table 1
Physical properties and spectral data of the compounds **5–22**



Comp. number	A	Y	R	m.p. (°C)	Yield (%)	Empirical formula	IR (cm^{-1})	^1H NMR δ ppm (J = Hz)
5	phenyl	OCH_2	H	182	95.65	$C_{21}H_{16}O_3N_2$	3399, 3063, 2960, 1681, 1550, 1483, 1234, 1056, 962–503	4.68 (2H, s), 7.11–7.03 (3H, m), 7.56–7.28 (7H, m), 8.07 (1H, s), 8.27–8.25 (2H, dd, J = 1.49, J = 6.84), 8.43 (1H, s)
6	4-chlorophenyl	OCH_2	H	206	87.72	$C_{21}H_{15}O_3N_2Cl$	3391, 2950, 1684, 1551, 1486, 1286, 1241, 1060, 960–500	4.68 (2H, s), 7.00–7.03 (2H, d, J = 8.90), 7.27–7.29 (2H, d, J = 8.91), 7.53–7.59 (5H, m), 8.11–8.19 (3H, m)
7	phenyl	SCH_2	H	166	74.75	$C_{21}H_{16}O_2N_2S$	3277, 3030, 2985, 1655, 1550, 1480, 1325, 1274, 1056, 976–418	3.83 (2H, s), 7.55–7.24 (10H, m), 7.91–7.92 (1H, d, J = 1.50), 8.26–8.23 (2H, dd, J = 6.90, J = 1.43), 8.70 (1H, s)
8	phenyl		F	211	50.50	$C_{20}H_{13}O_2N_2F$	3350, 3020, 1647, 1533, 1498, 1412, 1346, 1233, 1054, 927–514	7.21–7.17 (2H, dd, J = 8.67, J = 1.91), 7.50–7.41 (4H, m), 7.67–7.72 (2H, dd, J = 6.99, 1.49), 8.23–8.17 (3H, m), 10.07 (1H, s)
9	phenyl	CH_2	F	205	74.07	$C_{21}H_{15}O_2N_2F$	3262, 3010, 1650, 1528, 1502, 1414, 1274, 1240, 1054, 868–693	3.80 (2H, s), 7.23–7.19 (3H, m), 7.48–7.36 (6H, m), 7.89–7.88 (1H, d, J = 1.73), 8.26–8.21 (2H, m)
10	4-nitrophenyl	CH_2	F	215	37.78	$C_{21}H_{14}O_4N_3F$	3260, 2955, 1659, 1540, 1479, 1350, 1226, 1053, 973–515	3.96 (2H, s), 7.55–7.51 (2H, m), 7.73–7.71 (2H, d, J = 8.68), 7.82–7.79 (2H, d, J = 8.80), 8.20–8.21 (1H, d, J = 1.88), 8.34–8.29 (4H, m), 10.55 (1H, s)
11	phenyl	CH_2CH_2	F	188	45.61	$C_{22}H_{17}O_2N_2F$	3290, 2980, 1650, 1531, 1502, 1482, 1413, 1240, 1157, 1056, 977–517	2.61–2.65 (2H, t, J = 7.90), 2.94–2.98 (2H, t, J = 7.45), 7.74–7.11 (9H, m), 8.19–8.05 (3H, m), 9.72 (1H, s)
12	phenyl	OCH_2	F	186	35.20	$C_{21}H_{15}O_3N_2F$	3402, 3063, 1681, 1600, 1488, 1238, 1057, 961–509	4.59 (2H, s), 6.94–7.02 (3H, dd, J = 7.38, J = 8.71), 7.18–7.11 (2H, dd, J = 9.03, J = 8.67), 7.31–7.27 (2H, d, J = 7.48), 7.46–7.45 (2H, d, J = 1.26), 7.96–8.19 (3H, m), 8.32 (1H, s)
13	4-chlorophenyl	OCH_2	F	200	68.71	$C_{21}H_{14}O_3N_2ClF$	3399, 2918, 1691, 1609, 1549, 1488, 1239, 1059, 959–498	4.83 (2H, s), 7.15–7.13 (2H, d, J = 8.78), 7.44–7.46 (2H, d, J = 8.79), 7.55–7.51 (2H, d, J = 8.74), 7.70–7.67 (1H, d, J = 8.66), 7.83–7.81 (1H, d, J = 8.78), 8.23–8.34 (3H, m), 10.30 (1H, s)
14	phenyl	SCH_2	F	169.5	52.67	$C_{21}H_{15}O_2N_2FS$	3277, 1655, 1607, 1503, 1480, 1240, 1056, 951–500	3.83 (2H, s), 7.52–7.20 (9H, m), 7.91–7.92 (1H, d, J = 1.98), 8.27–8.23 (2H,m), 8.86 (1H, s)
15	phenyl	CH_2CH_2	ethyl	187	70.08	$C_{24}H_{22}O_2N_2$	3244, 3060, 2962, 1531, 1479, 1418, 1180, 1062, 970–411	1.29–1.67 (4H, m), 2.69–2.78 (3H, q, J = 7.50), 3.08–3.12 (2H, t, J = 8.66), 7.37–7.27 (6H, m), 7.78 (1H, s), 8.16–8.14 (2H, d, J = 8.12)
16	phenyl	OCH_2	ethyl	173.5	45.47	$C_{23}H_{20}O_3N_2$	3410, 2972, 1686, 1599, 1540, 1490, 1232, 1059, 960–578	1.29–1.33 (3H, t, J = 7.59), 2.73–2.79 (2H, q, J = 7.59), 4.68 (2H, s), 7.03–7.11 (2H, dd, J = 8.30, J = 7.36), 7.28–7.55 (7H, m), 8.04 (1H, s), 8.17–8.19 (2H, d, J = 8.15), 8.31 (1H, s)
17	4-chlorophenyl	OCH_2	ethyl	194	60.11	$C_{23}H_{19}O_3N_2Cl$	3393, 2965, 1684, 1545, 1489, 1241, 1062, 960–580	1.29–1.33 (3H, t, J = 7.59), 2.77–2.75 (2H, q, J = 7.60), 4.46 (2H, s), 6.99–6.96 (2H, dd, J = 6.86, J = 2.10), 7.39–7.28 (3H, J = 8.23, J = 2.10), 8.03–7.54 (3H, m)

Table 1 (*Continued*)

Comp. number	A	Y	R	m.p. (°C)	Yield (%)	Empirical formula	IR (cm^{-1})	^1H NMR δ ppm (J = Hz)
18	phenyl	SCH_2	ethyl	165	56.53	$C_{23}H_{20}O_2N_2S$	3281, 2963, 1655, 1558, 1536, 1480, 1272, 1060, 975–688	1.29–1.33 (3H, t, $J = 7.63$), 2.72–2.78 (2H, q, $J = 7.59$), 3.83 (2H, s), 7.24–7.44 (8H, m), 7.49–7.51 (1H, d, $J = 8.70$), 7.88–7.90 (1H, d, $J = 1.98$), 8.15–8.17 (2H, d, $J = 8.20$), 8.68 (1H, s)
19	phenyl	ethyl	$N(CH_3)_2$	219.5	45.45	$C_{24}H_{23}O_2N_3$	3285, 2924, 1650, 1573, 1509, 1276, 1058, 974–515	1.55 (6H, s), 3.11–2.71 (4H, m), 6.79–6.77 (2H, dd, $J = 7.20$, 2.00), 7.28–7.67 (8H, m), 8.11–8.09 (2H, dd, $J = 6.99$, $J = 2.04$)
20	phenyl	OCH_2	$N(CH_3)_2$	204.5	35.58	$C_{23}H_{21}O_3N_3$	3383, 1683, 1609, 1572, 1482, 1439, 1285, 1061, 960–514	3.09 (6H, s), 4.67 (2H, s), 6.79–6.77 (2H, d, $J = 8.93$), 7.03–7.28 (3H, m), 7.36–7.48 (4H, m), 7.94–8.12 (3H, m), 8.38 (1H, s)
21	4-chlorophenyl	Och_2	$N(CH_3)_2$	231.5	70.50	$C_{23}H_{20}O_3N_3Cl$	3396, 1683, 1572, 1489, 1432, 1062, 945–503	3.49 (6H, s), 4.68 (2H, s), 6.80–6.78 (2H, d, $J = 9.02$), 7.03–7.01 (2H, d, $J = 8.929$, 7.28–7.30 (1H, d, $J = 8.94$), 7.49–7.50 (2H, d, $J = 2.12$), 8.14–7.96 (4H, m), 10.06 (1H, s)
22	phenyl	Sch_2	$N(CH_3)_2$	221.5	19.20	$C_{23}H_{21}O_2N_3S$	3326, 1667, 1609, 1573, 1509, 1481, 1431, 1279, 1057, 921–700	3.27 (6H, s), 3.84 (2H,s), 6.80–6.82 (2H, d, $J = 8.60$), 7.54–7.19 (6H, m), 7.94–7.98 (3H, m), 8.22 (1H, s), 10.22 (1H, s)

diaminophenol·2HCl with 0.01 mol *p*-substituted benzoic acid in 24 g polyphosphoric acid and stirring for 2.5 h. At the end of the reaction period, the residue was poured into ice-water mixture and neutralized with excess of % 10 NaOH solution extracted with benzene; the benzene solution was dried over anhydrous sodium sulfate and evaporated under diminished pressure. The residue was boiled with 200 mg charcoal in ethanol and filtered. After the evaporation of the solvent in vacuo, the crude product was obtained and recrystallized.

3.3. General procedure for amide derivatives (5–22)

Appropriate carboxylic acid (0.5 mmol) and thionyl chloride (1.5 ml) were refluxed in benzene (5 ml) at 80 °C for 3 h. Excess thionyl chloride was then removed in vacuo. The residue was dissolved in ether (10 ml) and solution added during 1 h to a stirred, ice-cold mixture of 5-amino-2-(*p*-substituted-phenyl)benzoxazoles (0.5 mmol), sodium bicarbonate (0.5 mmol), diethyl ether (10 ml) and water (10 ml). The mixture was kept stirred overnight at room temperature and filtered. The precipitate was washed with water, 2 N HCl and water, respectively and finally with ether to give **5**–**22**. The products were recrystallized from ethanol–water mixture and needles are dried in vacuo. The chemical, physical and spectral data of the compounds **5**–**22** are reported in Table 1.

3.4. Microbiology

For both the antibacterial and antimycotic assays, the compounds were dissolved in absolute ethanol (0.8 mg/ml). Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 μg/ml concentrations with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC), were determined using the method of two-fold serial dilution technique [11,16,17]. In order to ensure that the solvent per se had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only ethanol at the same dilutions used in our experiments and found inactive in culture medium. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and the yeast *C. albicans* RSKK 628. Origin of bacterial strains are *Staphylococcus aureus* ATCC 6538, *Streptococcus faecalis* ATCC 10541 and *Bacillus subtilis* ATCC 6033 as Gram-positive and *Escherichia coli* ATCC 10536, and *P. aeruginosa* RSKK 355 as Gram-negative bacteria. RSKK strains of the microorganisms used in this study were obtained from the culture collection of Refik Saydam Health Institution of Health Ministry, Ankara and maintained at the Microbiology Department of Faculty of Pharmacy of Ankara University.

Ampicillin, amoxycillin, tetracycline, streptomycin, ketoconazole and fluconazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and the control drugs are given in Table 2.

3.5. Antibacterial and antifungal assay

The cultures were obtained from Mueller–Hinton broth (Difco) for all the bacterial strains after 24 h of incubation at 37 ± 1 °C. The yeast *C. albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at 25 ± 1 °C. Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth (Difco) at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculum size was 10^5 CFU/ml for the antibacterial assay and 10^4 CFU/ml for the antifungal assay. A set of tubes containing only inoculated broth was kept as controls. For the antibacterial assay after incubation for 24 h at 37 ± 1 °C and after incubation for 48 h at 25 ± 1 °C for the antifungal assay, the last tube with no growth of microorganism and/or yeast was recorded to represent the MIC expressed in μg/ml. Every experiment in the antibacterial and antifungal assays was replicated twice in order to define the MIC values.

4. Results and discussion

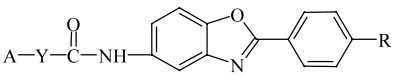
The synthesized compounds **5**–**22** exhibited in vitro antimicrobial activity showing MIC values between 100 and 12.5 μg/ml and their potencies were compared to some control drugs as given in Table 2.

Table 2 shows that the synthesized compounds **5**–**22** exhibited antibacterial activity against *S. aureus* and *S. faecalis* with MIC values generally between 100 and 12.5 μg/ml, **9** and **11** being the most active compounds of the series. However, all the synthesized compounds exhibited lower activity than the control drugs against Gram-positive bacterial strains and *E. coli*. Compounds **6** and **9** were found more active the other tested compounds against *P. aeruginosa* providing a MIC value of 12.5 μg/ml.

All the compounds showed antifungal potencies at a MIC values of 50–12.5 μg/ml. The compounds **9**, **10**, **11**, **15** and **21** were more found active than the other compounds at a MIC value 12.5 μg/ml. However the control drugs ketoconazole and fluconazole exhibited better antifungal activity than any of the synthesized compounds.

Qualitatively, the importance of the substitution pattern of the 2-phenyl and of the 5-arylalkyl or 5-aryloxyalkyl groups both for the antifungal and antibacterial activity is evident. The explored set, however, is too small to allow any significant structure–activity relationship.

Table 2
The in vitro antimicrobial activity of the compounds **5**–**22** and the control drugs (MIC in μg/ml)



Comp. number	A	Y	R	Sa	Sf	Bs	Ec	Pa	Ca
5	phenyl	OCH_2	H	50	100	50	50	25	50
6	4-clorophenyl	OCH_2	H	50	50	50	50	12.5	25
7	phenyl	SCH_2	H	50	50	100	100	50	50
8	phenyl		F	50	25	25	50	25	25
9	phenyl	CH_2	F	12.5	12.5	50	25	12.5	12.5
10	4-nitrophenyl	CH_2	F	25	25	25	25	50	12.5
11	phenyl	CH_2CH_2	F	25	50	12.5	25	25	12.5
12	phenyl	OCH_2	F	50	50	50	50	50	25
13	4-chlorophenyl	OCH_2	F	100	100	50	50	25	50
14	phenyl	SCH_2	F	50	100	25	50	25	25
15	phenyl	CH_2CH_2	C_2H_5	25	25	50	50	50	12.5
16	phenyl	OCH_2	C_2H_5	50	50	50	50	50	50
17	4-chlorophenyl	OCH_2	C_2H_5	50	25	50	25	25	25
18	phenyl	SCH_2	C_2H_5	100	100	50	50	25	25
19	phenyl	CH_2CH_2	$N(CH_3)_2$	25	50	50	50	50	25
20	phenyl	OCH_2	$N(CH_3)_2$	25	25	50	50	100	25
21	4-chlorophenyl	OCH_2	$N(CH_3)_2$	25	25	25	25	50	12.5
22	phenyl	SCH_2	$N(CH_3)_2$	25	25	25	25	50	25
Ampicillin				1.56	1.56	1.56	12.5	>200	
Amoxycillin				1.56	1.56	1.56	3.12	>200	
Tetracycline				1.56	1.56	1.56	3.12	50	
Streptomycin				3.12	100	50	1.56	100	
Clotrimazole									6.2
Haloprogin									3.1

Sa.: *S. aureus*; E.c.: *E. coli*; S.f.: *S. faecalis*; P.a.: *P. aeruginosa*; B.s.: *B. subtilis*; C.a.: *C. albicans*.

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