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Synthesis and microbiological activity of some novel 5-benzamido- and 5-phenylacetamido- substituted 2-phenylbenzoxazole derivatives

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Abstract

The synthesis and microbiological activity of a new series of 5-benzamido- and 5-phenylacetamidosubstituted-2-phenylbenzoxazole derivatives (**1**–**26**) were described. The in vitro microbiological activity of the compounds was determined against Gram-positive, Gram-negative bacteria and the yeast *Candida albicans* in comparison with standard drugs. Microbiological results indicated that the synthesized compounds possessed a broad spectrum of activity against the tested microorganisms. The compounds **1**, **21**, **25** showed higher activity than tetracycline and streptomycin against *Pseudomonas aeruginosa*.

Keywords: Benzoxazole; Synthesis; Antimicrobial activity

1. Introduction

Benzoxazoles and related heterocycles such as benzimidazoles have been extensively studied for their potential chemotherapeutic activity with lower toxicities in man [1–9].

A series of 5-formyl-, 5-(aminocarbonyl)-, or 5- and 6-nitro derivatives of 2-(4-metoxyphenyl)benzoxazoles were synthesized as topoisomerase 1 inhibitors [10]. Furthermore, the compound, 3-[(benzoxazol-2-yl)ethyl]-5-ethyl-6-methylpyridin-2-(1H)-on (L-696,299), which was found to be a highly selective antagonist of the reverse transcriptase enzyme and inhibited the spread of HIV-1 III-b infection by $>95\%$ in MT4 human T-lymphoid cell culture has been selected for clinical evaluation as an antiviral agent [11–13]. A benzoxazole derivative, 3-(4,7-dichlorobenzoxazol-2-ylmethylamino)-5-ethyl-6-methyl pyridin-2(1H)-one (L-697,661), was also observed as a specific non-nucleoside reverse transcriptase inhibitor for the human immunodeficiency virus HIV-1 type and combined therapy with zidovudine and L-697, 661 achieved a marked decrease of viremia in some primary HIV infected patients [7,14,15].

Moreover, a new series of 2-(4-aminophenyl)-benzothiazoles and their benzoxazole analogues were found as potent inhibitors against human breast cancer cell lines in vitro and in vivo [16].

In the last few years, we reported the synthesis and the antimicrobial activity of 2,5- or 2,6-disubstituted benzoxazole derivatives as given in general Formulae I–III [8,9,17] which showed significant in vitro antimicrobial activity against some Gram-positive, Gram-negative bacteria and the fungus, *Candida albicans*.

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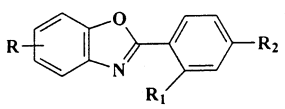
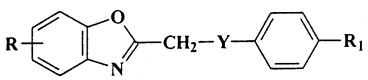


Ia: R = 5-CH_3 R_1 = Cl, F, OCH_3, NO_2 R_2 = H, Cl, OCH_3, CH_3

Ib: R = 6-CH_3 R_1 = Cl, F, OCH_3, NO_2 R_2 = H, Cl, OCH_3, CH_3

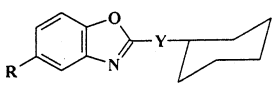
Formula I



IIa: R = 5-CH_3 Y = —, O, S R_1 = H, Cl, F, NO_2, NH_2

IIb: R = 6-CH_3 Y = —, O, S R_1 = H, Cl, Br

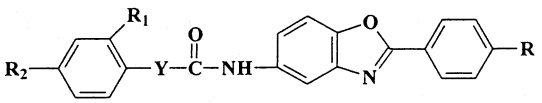
Formula II



Y = —, CH_2 R = H, Cl, NO_2

Formula III

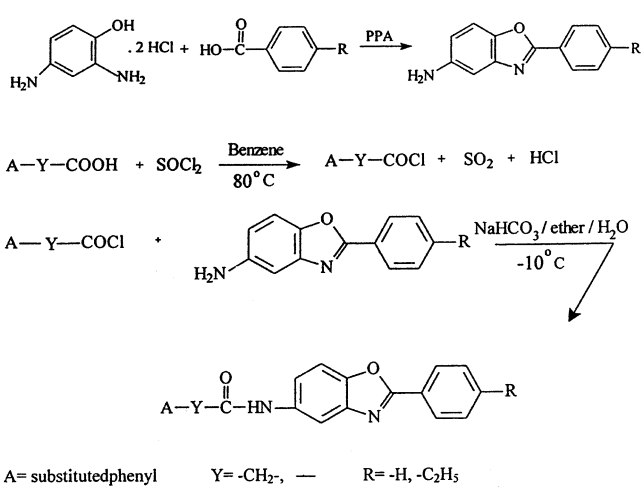
In this study, a series of novel 5-benzamido-, 5-phenylacetamido-2-phenyl-benzoxazoles (**1**–**26**) have been synthesized in order to examine the microbiological activitiy against different Gram-positive, Gram-negative bacteria and the yeast *C. albicans* in comparison with several control drugs (Formula IV).



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

Y= CH_2, — R_2 = H, Cl, OCH_3, CH_3

Formula IV



Scheme 1.

2. Chemistry

The synthesis of the compounds (**1**–**26**) was performed by reacting 5-amino-2-phenyl- or 5-amino-2-(*p*-ethylphenyl)benzoxazoles with appropriate carboxylic acid chlorides obtained by treating carboxylic acids with thionyl chloride [18,19].

5-Amino-2-phenyl- or 5-amino-2-(*p*-ethylphenyl)-benzoxazoles were obtained by heating benzoic acids or *p*-ethylbenzoic acids with 2,4-diaminophenol in PPA (polyphosphoric acid) as the cyclodehydration reagent in a one step procedure. All of these syntheses are shown at Scheme 1

The compounds **1**–**26** were prepared as new products. The structures of **1**–**26** were supported by spectral data. The IR, ^{1}H-NMR and Mass spectra are in agreement with the proposed structures. Physical and spectral data of the compounds are reported in Table 1.

3. Experimental

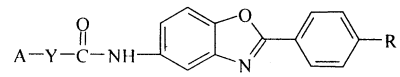
3.1. Chemistry

Kieselgel HF_{254} chromatoplates (0.3 mm) were used for TLC and the solvent systems were chloroform–methanol–ether (20:0.5:4) for **1**–**6**, **8**, **11**–**22**, chloroform–methanol (20:0.5) for **7**, **9**–**10**, **23**–**24**. All the melting points were taken on a Buchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded by Pye Unicam SP-1025 with KBr discs. ^{1}H-NMR spectra were obtained with a Bruker GMBH-DPX 400 MHz spectrometer in *d*-chloroform or *d*-chloroform–d_6-dimethylsulfoxide and tetramethylsilane (TMS) was used as an internal standard. Mass analysis were carried out with a Fisions Instruments VG Platform II mass spectrometer using electron ionization.

3.2. General procedure for the synthesis of 5-amino-2-phenylbenzoxazole and 5-amino-2-(p-ethylphenyl)benzoxazole

5-Amino-2-phenylbenzoxazole and 5-amino-2-(*p*-ethylphenyl)benzoxazole were synthesized by heating 0.01 mol 2,4-diaminophenol.2 HCl with 0.01 mol benzoic acid and *p*-ethylbenzoic acid in 24 g polyphosphoric acid and stirring for 2.5 h. At the end of the reaction

Table 1
Physical properties and spectral data of the compounds **1**–**26**



Comp. no.	A	Y	R	M.P. (°C)	Yield (%)	Emperical formula	IR (cm^{-1})	^{1}H-NMR δ ppm (J = Hz)	Mass m/e (%X)
1	Phenyl	–	H	188–189	63.69	$C_{20}H_{14}O_2N_2$	3340, 3060–3100, 1660, 1530–1565, 1480, 1020–1290, 690–960	7.50–8.04 (m, 10H), 8.05 (s, 1H), 8.20–8.30 (m, 2H)	314 (21.43), 105 (100)
2	4-Fluorophenyl	–	H	205–206	75.30	$C_{20}H_{13}O_2N_2F$	3320, 3050–3090, 1650, 1510–1560, 1480, 1050–1230, 690–960	7.13–7.21 (t, 2H, J = 8.59), 7.50–7.80 (m, 5H), 8.06–8.12 (dd, 2H, J = 8.59), 8.20–8.30 (m, 3H), 10.10 (s, 1H)	332 (33.11)6.29), 210 (40.39), 123 (74.17), 69 (100)
3	4-Bromophenyl	–	H	210–211	66.30	$C_{20}H_{13}O_2N_2Br$	3300, 3060–3080, 1650, 1530–1560, 1480, 1040–1220, 690–970	7.52–7.80 (m, 5H), 7.65–7.70 (dd, 1H, J = 8.46), 7.95–8.00 (dd, 1H, J = 8.47), 8.22–8.27 (m, 2H), 8.29–8.32 (d, 1H, J = 1.75), 10.30 (s,1H)	394 (22.86)– 392 (22.04), 76 (100)
4	4-Chlorophenyl	–	H	213–214	57.38	$C_{20}H_{13}O_2N_2Cl$	3380, 3000–3030, 1660, 1530–1560, 1485, 1050–1220, 700–940	7.48–7.54 (dd, 2H, J = 7.57), 7.55–7.80 (m, 5H), 8.00–8.07 (dd, 2H, J = 7.54), 8.20–8.30 (m, 3H), 10.25 (s, 1H)	350 (12.80)–348 (34.65), 139 (100)
5	4-Methoxyphenyl	–	H	201	72.67	$C_{21}H_{16}O_3N_2$	3320, 3060–3100, 2860–2920, 1650, 1500–1530, 1430, 1030–1260, 700–920	3.90 (s, 3H), 6.78–7.24 (dd, 2H, J = 7.07), 7.50–7.80 (m, 5H), 7.98–8.04 (dd, 2H, J = 6.99), 8.20–8.24 (m, 2H), 8.27–8.30 (d, 1H, J = 1.93), 10.00 (s,1H)	345 (32.77), 135 (100)
6	4-Methylphenyl	–	H	185–186	76.22	$C_{21}H_{16}O_2N_2$	3400, 3050–3100, 2850–2920, 1660, 1530–1565, 1480, 1020–1290, 700–930	3.15 (s, 3H), 7.25–7.32 (dd, 2H, J = 7.84), 7.55–7.82 (m, 5H), 7.88–7.95 (dd, 2H, J = 7.85), 8.20–8.26 (m, 2H), 8.30 (s, 1H), 10.05 (s, 1H)	329 (2.70), 119 (97.35), 104 (97.35), 91 (97.35), 77 (97.35)
7	4-Ethylphenyl	–	H	174–175	87.72	$C_{22}H_{18}O_2N_2$	3340, 3100–3060, 2860–2940, 1650, 1530–1560, 1480, 1025–1250, 690–920	1.22–1.30 (t, 3H, J = 7.40), 2.67–2.76 (q, 2H, J = 7.45), 7.28–7.34 (dd, 2H, J = 7.71), 7.50–7.79 (m, 5H), 7.91–7.96 (dd, 2H, J = 7.85), 8.20–8.30 (m, 2H), 8.30 (s, 1H), 10.00 (s, 1H)	343 (11.58), 133 (100)
8	4-Nitrophenyl	–	H	254–256	73.82	$C_{20}H_{13}O_4N_3$	3300, 3060, 1660, 1520–1550, 1480, 1020–1260, 700–960	7.50–7.70 (m, 5H), 7.95 (s, 1H), 8.10–8.20 (dd, 2H, J = 8.47), 8.28–8.34 (m, 2H), 8.37–8.48 (dd, 2H, J = 8.45),	359 (7.15), 76 (100)

Table 1 (*Continued*)

Comp. no.	A	Y	R	M.P. (°C)	Yield (%)	Emperical formula	IR (cm^{-1})	^{1}H-NMR δ ppm (J = Hz)	Mass m/e (%X)
9	4-*tert*-Butyl phenyl	–	H	208	81.08	$C_{24}H_{22}O_2N_2$	3340, 3010–3040, 2860–2960, 1670, 1540–1570, 1485, 1030–1280, 710–970	0.90 (s, 9H), 7.05–7.14 (dd, 2H, J = 8.05), 7.15–7.40 (m, 5H), 7.55–7.60 (dd, 2H, J = 8.12), 7.80–7.90 (m, 2H), 7.90 (s, 1H), 9.70 (s, 1H)	370 (27.15), 161 (100)
10	Phenyl	–	Ethyl	209–210	58.48	$C_{22}H_{18}O_2N_2$	3300, 3060–3100, 2860–2940, 1640, 1550–1580, 1480, 1060–1290, 700–970	1.24–1.32 (t, 3H, J = 7.60), 2.70–2.78 (q, 2H, J = 7.60), 7.35–7.40 (dd, 2H, J = 7.93), 7.47–7.50 (dd, 2H, J = 7.38), 7.50–8.02 (m, 5H), 8.12–8.16 (d, 2H, J = 7.88), 8.26 (s, 1H), 10.10 (s, 1H)	342 (19.09), 105 (100)
11	4-Methylphenyl	–	Ethyl	190–191	56.18	$C_{23}H_{20}O_2N_2$	3300, 3080–3100, 2860–2960, 1650, 1550–1580, 1480, 1030–1280, 700–970	1.25–1.35 (t, 3H, J = 6.37), 2.40 (s, 3H), 2.70–2.78 (q, 2H, J = 7.45), 7.24–7.30 (dd, 2H, J = 7.88), 7.30–7.40 (dd, 2H, J = 8.06), 7.48–7.78 (m,2H), 7.87–7.95 (dd, 2H, J = 7.96), 8.11–8.17 (dd, 2H, J = 8.07), 8.24 (s,1H), 9.85 (s,1H)	356 (24.33), 119 (100)
12	4-Ethylphenyl	–	Ethyl	188	54.05	$C_{24}H_{22}O_2N_2$	3320, 3020–3080, 2860–2960, 1650, 1540–1580, 1480, 1020–1280, 690–960	1.25–1.34 (m, 6H), 2.68–2.76 (m, 4H), 7.27–7.31 (dd, 2H, J = 8.20), 7.31–7.36 (dd, 2H, J = 8.27), 7.50–7.78 (m, 2H), 7.83–7.89 (dd, 2H, J = 8.19), 8.11–8.17 (dd, 2H, J = 8.49), 8.24–8.26 (d, 1H, J = 1.88), 9.90 (s,1H)	371 (11.98), 133 (100)
13	2-Methoxyphenyl	–	H	165–166	87.21	$C_{21}H_{16}O_3N_2$	3380, 3020–3080, 2880–2980, 1670, 1550–1580, 1485, 1030–1250, 680–970	4.00 (s, 3H), 7.08–7.04 (d,1H, J = 8.33), 7.13–7.18 (t, 1H, J = 7.66), 7.50–7.60 (m, 5H), 7.70–8.40 (m, 5H), 10.00 (s, 1H)	345 (11.30), 135 (100)
14	2-Chlorophenyl	–	H	191–192	57.47	$C_{20}H_{13}O_2N_2Cl$	3300, 3060–3100, 1670, 1540–1580, 1485, 1020–1270, 690–980	7.30–7.70 (m, 7H), 7.80–8.20 (m, 3H), 8.25–8.30 (dd, 2H, J = 6.51, J = 1.47)	350 (12.59), 348 (32.59), 139 (100)
15	2,4-Dimethoxy phenyl	–	H	129–130	53.48	$C_{22}H_{18}O_4N_2$	3380, 3080–3100, 2850–2960, 1660, 1540–1570, 1480, 1020–1240, 640–950	3.90, 4.10 (s, 3H), 6.55 (s, 1H), 6.60–6.70 (d, 1H, J = 8.06), 7.50–7.70 (m, 5H), 8.10 (s, 1H), 8.20–8.40 (m, 3H), 9.80 (s, 1H)	374 (17.17), 165 (100)

Table 1 (*Continued*)

Comp. no.	A	Y	R	M.P. (°C)	Yield (%)	Emperical formula	IR (cm^{-1})	^{1}H-NMR δ ppm (J = Hz)	Mass m/e (%X)
16	2,4-Dimethyl phenyl	–	H	168–169	73.09	$C_{22}H_{18}O_2N_2$	3300, 3080–3120, 2860–2920, 1660, 1500–1565, 1440, 1030–1260, 690–970	2.36, 2.50 (2s, 3H), 7.00–7.10 (m, 2H), 7.40–7.45 (d, 1H, J = 7.63), 7.50–7.80 (m, 5H), 8.00 (s, 1H), 8.20–8.30 (m, 2H)	342 (8.84), 133 (100)
17	Phenyl	CH_2	H	170–171	60.98	$C_{21}H_{16}O_2N_2$	3320, 3020–3080, 2940–2960, 1660, 1540–1560, 1480, 1030–1280, 690–980	3.65 (s, 2H), 7.20–7.60 (m, 10H), 8.10 (s, 1H), 8.18–8.25 (m, 2H), 9.95 (s, 1H)	329 (14.70), 91 (100)
18	4-Bromophenyl	CH_2	H	209–210	49.14	$C_{21}H_{15}O_2N_2Br$	3300, 3090, 2860–2930, 1670, 1530–1560, 1480, 1000–1270, 700–970	3.70 (s, 2H), 7.30–7.35 (dd, 2H, J = 8.29), 7.42–7.47 (dd, 2H, J = 8.30), 7.48–7.58 (m, 5H), 8.12–8.14 (d, 1H, J = 1.56), 8.19–8.23 (m, 2H), 10.00 (s, 1H)	408 (13.10), 406 (12.46), 89 (100)
19	4-Chlorophenyl	CH_2	H	211–212	55.17	$C_{21}H_{15}O_2N_2Cl$	3300, 3060–3100, 2860–2920, 1660, 1560, 1480, 1050–1230, 700–970	3.70 (s, 2H), 7.28–7.34 (dd, 2H, J = 8.36), 7.34–7.40 (dd, 2H, J = 8.33), 7.50–7.60 (m, 5H), 8.11–8.14 (d, 1H, J = 1.39), 8.18–8.22 (m, 2H), 10.05 (s, 1H)	362 (21.85), 105 (100)
20	4-Nitrophenyl	CH_2	H	210	63.00	$C_{21}H_{15}O_4N_3$	3300, 3080–3100, 2860–2920, 1650, 1520–1550, 1470, 1020–1270, 690–970	3.40 (s, 2H), 7.00–7.30 (m, 7H), 7.60–7.80 (m, 5H), 9.70 (s, 1H)	373 (2.13), 89 (100)
21	4-Propyloxyphenyl	CH_2	H	169	54.40	$C_{24}H_{22}O_3N_2$	3300, 3040–3100, 2860–2980, 1660, 1510–1560, 1470, 1020–1240, 690–970	0.98 (t, 3H, J = 7.00), 1.70–1.80 (m, 2H), 3.65 (s, 2H), 3.85–3.95 (t, 2H, J = 5.79, J = 7.07), 6.86–6.82 (dd, 2H, J = 8.56), 7.24–7.30 (dd, 2H, J = 9.08), 7.45–7.60 (m, 5H), 8.10–8.12 (d, 1H, J = 1.49), 8.17–8.27 (m, 2H), 9.80 (s, 1H)	387 (10.56), 107 (100)
22	Phenyl	CH_2	Ethyl	164–165	70.22	$C_{23}H_{20}O_2N_2$	3300, 3040–3100, 2860–2960, 1655, 1520–1560, 1480, 1060–1280, 700–970	1.22–1.32 (t, 3H, J = 8.14), 2.70–2.80 (q, 2H, J = 7.40), 3.70 (s, 2H), 7.20–7.40 (m, 7H), 7.47–7.60 (m, 2H), 8.08–8.15 (m, 3H), 10.00 (s, 1H)	357 (42.35), 356 (100), 91 (100), 51 (100)
23	4-Bromophenyl	CH_2	Ethyl	202	57.47	$C_{23}H_{19}O_2N_2Br$	3300, 3020–3100, 2840–2960, 1650, 1520–1560, 1480, 1010–1270, 710–980	1.25–1.32 (t, 3H, J = 7.60), 2.70–2.80 (q, 2H, J = 7.55), 3.70 (s, 2H), 7.28–7.56 (m, 8H), 8.08–8.15 (m, 3H), 10.05 (s, 1H)	436 (16.59), 434 (15.63), 89 (100)

Table 1 (*Continued*)

Comp. no.	A	Y	R	M.P. (°C)	Yield (%)	Emperical formula	IR (cm^{-1})	^{1}H-NMR δ ppm (J = Hz)	Mass m/e (%X)
24	4-Chlorophenyl	CH_2	Ethyl	194–195	76.82	$C_{23}H_{19}O_2N_2Cl$	3300, 3040–3100, 2840–2960, 1650, 1530–1580, 1490, 1020–1270, 710–970	1.22–1.32 (t, 3H, J = 7.60), 2.70–2.78 (q, 2H, J = 07.559, 3.65 (s, 2H), 7.28–7.57 (m, 8H), 8.08–8.14 (m, 3H), 10.00 (s, 1H)	392 (23.45), 390 (60.31), 238 (100)
25	2-Chlorophenyl	CH_2	H	206	55.17	$C_{21}H_{15}O_2N_2Cl$	3340, 3100, 2920–2990, 1680, 1550–1580, 1490, 1045–1290, 710–950	3.85 (s, 2H), 7.20–7.62 (m, 9H), 8.10–8.12 (d, 1H, J = 1.58), 8.20–8.24 (m, 2H), 9.80 (s, 1H)	364 (19.12), 362 (48.28), 125 (100)
26	3,5-Dimethoxyphenyl	–	H	149–150	37.43	$C_{22}H_{18}O_4N_2$	3480, 3060–3100, 2840–2940, 1650, 1550–1570, 1480, 1040–1240, 690–970	3.85 (s, 6H), 6.60–6.63 (t, 1H, J = 2.21), 7.16–7.20 (dd, 2H, J = 2.25, 2.04), 7.52–7.80 (m, 5H), 8.20–8.25 (m, 2H), 8.28–8.30 (d, 1H, J = 1.80), 10.05 (s, 1H)	375 (14.19), 165 (100)

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 sulphate and evaporated under diminished pressure. The residue was boiled with 200 mg charcoal in ethanol and filtered. After the evaporation of solvent in vacuo, the crude product was obtained and recrystallized.

3.3. General procedure for amide derivatives (**1**–**26**)

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-cooled mixture of 5-amino-2-phenylbenzoxazole or 5-amino-2-(*p*-ethylphenyl)benzoxazole (0.5 mmol), sodiumbicarbonate (0.5 mmol), diethylether (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 **1**–**26**. The product was recrystallized from ethanol–water mixture and needles are dried in vacuo.

3.4. Microbiology

For the antibacterial and antimycotic assays, the compounds **1**–**26** 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, 0.78 μg/ml concentrations. The minimum inhibitory concentrations (MIC) were determined using the method of two fold serial dilution technique [20–22]. 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 of the compounds were tested for their in vitro growth inhibitory activity against different bacteria and a fungus *C. albicans* RSKK 628. Origin of the bacterial strains are *Staphylococcus aureus* RSSK 250, *Streptococcus faecalis* RSKK 500, *Bacillus subtilis* ATCC 6033 as Gram-positive and *Escherichia coli* RSKK 256, *Pseudomonas aeruginosa* RSKK 356 as Gram-negative bacteria which were maintained at the microbiology department, faculty of pharmacy, Ankara University.

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

3.4.1. Antibacterial assay

The culture were obtained in Mueller–Hinton broth (Difco) for all the bacteria after 24 h of incubation at 37 ± 1°C. Testing was carried out in Mueller–Hinton Broth at pH 7.4 and the two fold serial dilution tecnique was applied. The final inocolum size was 10^5 CFU/ml. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 h at 37 ± 1°C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μg/ml.

3.4.2. Antimycotic assay

The yeast *C. albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h of incubation at 25 ± 1°C. Testing was performed in Sabouraud dextrose broth at pH 7.4 and the two fold serial dilution tecnique was applied. The final inocolum size was 10^4 CFU/ml. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at 25 ± 1°C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μg/ml

4. Results and discussion

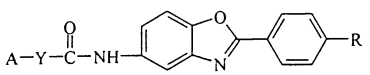
The chemical, physical and spectral data of the synthesized compounds **1**–**26** are reported in Table 1. The antimicrobial activity of the compounds was investigated against two Gram-positive, three Gram-negative bacteria strains and the yeast *C. albicans* using two fold serial dilution technique in comparison to control drugs such as ampicillin, amoxycillin, tetracycline, streptomycin, clotrimazole, haloprogine and the results reported at Table 2.

The synthesized compounds showed some antibacterial activity against the Gram-positive bacteria such as *S. aureus* and *S. faecalis* possesing MIC values between 50 and 100 μg/ml, except the compound **13** having a MIC value of 25 μg/ml.

Furthermore, the antibacterial activity of the compounds **1**–**26** against *E. coli* as Gram-negative bacteria revealed lower potencies than the compared control drugs. However, the activity against the Gram-negative enterobacter *P. aeruginosa*, which is effective in nosocomial infections and often resistant to antibiotic therapy, the compounds **1**, **21**, and **25** indicated significant activity, with a MIC value of 25 μg/ml, being more potent than the compared control drugs tetracycline and streptomycin.

The compounds **1**–**26** were also tested against *C. albicans* for their antimycotic activity and most of the compounds indicated significant antimycotic activity performing MIC values between 25 and 50 μg/ml except the compounds **7** and **9**. However, antimycotic potencies of the compared control drugs clotrimazole

Table 2
The in vitro antimicrobial activity of the compounds **1**–**26** and the control drugs (MIC in μg/ml)



Comp. no.	A	Y	R	Sa [a]	Sf [b]	Bs [c]	Ec [d]	Pa [e]	Ca [f]
1	Phenyl		H	50	50	50	50	25	25
2	4-Fluorophenyl		H	100	100	100	200	200	50
3	4-Bromophenyl		H	50	50	50	50	50	50
4	4-Chlorophenyl		H	50	50	50	50	50	50
5	4-Methoxyphenyl		H	50	50	50	50	50	50
6	4-Methylphenyl		H	50	50	50	50	50	25
7	4-Ethylphenyl		H	100	100	50	100	50	100
8	4-Nitrophenyl		H	100	100	200	100	50	25
9	4-*tert*-Butylphenyl		H	100	100	100	100	100	100
10	Phenyl		C_2H_5	50	50	50	50	50	50
11	4-Methylphenyl		C_2H_5	100	100	100	50	50	50
12	4-Ethylphenyl		C_2H_5	50	50	50	50	50	50
13	2-Methoxyphenyl		H	25	25	25	50	50	25
14	2-Chlorophenyl		H	50	50	50	50	50	25
15	2,4-Dimethoxyphenyl		H	100	50	200	50	100	25
16	2,4-Dimethylphenyl		H	50	50	25	50	100	25
17	Phenyl	CH_2	H	100	100	50	100	100	50
18	4-Bromophenyl	CH_2	H	50	50	50	50	50	25
19	4-Chlorophenyl	CH_2	H	100	100	50	100	50	50
20	4-Nitrophenyl	CH_2	H	50	50	200	50	50	25
21	4-Propyloxyphenyl	CH_2	H	50	50	200	25	25	25
22	Phenyl	CH_2	C_2H_5	50	50	50	50	50	50
23	4-Bromophenyl	CH_2	C_2H_5	50	50	50	50	50	50
24	4-Chlorophenyl	CH_2	C_2H_5	50	50	50	50	50	50
25	2-Chlorophenyl	CH_2	H	50	50	100	25	25	25
26	3,5-Dimethoxyphenyl		H	100	100	200	50	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

[a] Sa, *Staphylococcus aureus*
[b] Sf, *Streptococcus faecalis*
[c] Bs, *Bacillus subtilis*
[d] Ec, *Escherichiae coli*
[e] Pa, *Pseudomanas aeruginosa*
[f] Ca, *Candida albicans*

and haloprogin were found more active than the corresponding compounds, showing MIC values of 6.2 μg/ml and 3.1 μg/ml, respectively.

As a result of structure and antimicrobial activity relationships against Gram-positive bacteria substition at position five of the benzoxazole ring with a 2-methoxybenzamido moiety for the compounds **1-26** causes an increase in the activity compared to other substitutions.

If the benzoxazole ring holds a 4-propyloxyphenyacetamido or a 2-chlorophenylacetamido group at position five, the activity increases against *E. coli* and *P. aeruginosae* as Gram-negative bacteria whereas substitution with 4-florobenzamido at the same position causes a decrease in the activity.

On the other side, 4-*tert*-butylbenzamido group at the fifth position of the benzoxazole nucleus decreases the potency against *C. albicans*.

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