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Synthesis and Antimicrobial Activity of Some 2-[*p*-Substituted-phenyl]benzoxazol-5-yl-arylcarboxyamides

New 2-[*p*-substituted-phenyl]benzoxazol-5-yl-arylcarboxyamides derivatives have been synthesized by reacting 5-amino-2-[*p*-substituted-phenyl]benzoxazoles with substituted-arylcarboxylic acid chlorides. The structures of the synthesized compounds were confirmed by IR and ^{1}H NMR spectral data. Antimicrobial activities of the compounds were investigated using the two-fold serial dilution technique against different Gram-positive and Gram-negative bacteria and the yeast *C. albicans* in comparison with standard drugs. Microbiological results indicated that the synthesized compounds possess a broad spectrum of activity, having an MIC value of 25–200 µg/mL at molar concentration values of 3.45×10^{-5} and 5.74×10^{-4} against the tested microorganisms.

Keywords: Benzoxazole-5-yl-arylcarboxyamides; Antibacterial and antifungal activity

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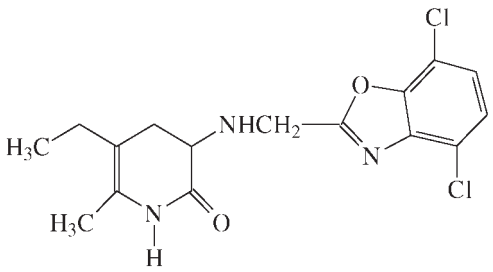
Introduction

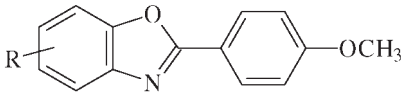
Benzoxazole derivatives have been at the focus of many researchers' interest for many years because they constitute an important class of heterocyclic compounds [1–22] with antibacterial and antifungal [1–4], HIV-1 reverse transcriptase inhibitor [5–10], topoisomerase I inhibitors [11] and antitumor activities [12–17].



L-697, 661

Formula I

A benzoxazole derivative, 3-(4,7-dichlorobenzoxazol-2-ylmethylamino)-5-ethyl-6-methylpyridin-2(1H)-one (L-697, 661) (Formula I), prevents the spread of human immunodeficiency virus type-1 (HIV-1) infection in cell culture by inhibiting HIV-1 reverse transcriptase [9, 10]. A series of 5-formyl-, 5-(aminocarbonyl)-, and 5- or 6-nitro derivatives of 2-(4-methoxyphenyl)benzoxazoles (Formula II) was synthesized and tested as topoisomerase I inhibitors [11].



R = 5-formyl, 5-(aminocarbonyl), 5-nitro, 6-nitro

Formula II

An antibiotic, calcymycin (A 23187) which is isolated from a strain of *Streptomyces chartreusis* and includes a benzoxazole ring in its molecular structure, was found to be very active, especially against some Gram-positive bacteria by acting as a good ionophore [2].

Moreover, structure-activity relationships of benzoxazole derivatives have revealed that the substitution of the 2nd position is decisive for the biological activity and position 5 is important for the intensity of the activity [23–25].

Therefore, in this study, a series of novel 2-[*p*-substituted-phenyl]benzoxazole-5-yl-arylcarboxyamides (**5**–**17**) (Formula III) has been synthesized as the target compounds in order to examine their microbiological activitiy against various Gram-positive and Gram-negative bacteria and against the yeast *C. albicans* in comparison

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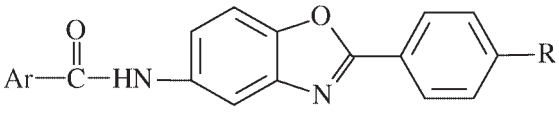
with several control drugs because of the need for new and different antibacterial agents that are resistant to inactivation by bacterial enzymes. Their structure-activity relationships (SAR) were studied as well.



R = H, C_2H_5, F, $N(CH_3)_2$

Ar = 2-furyl, 2-thienyl, substitutedphenyl

Formula III

Chemistry

5-Amino-2-phenyl- or 5-amino-2-(p-substituted-phenyl)benzoxazoles (**1**–**4**) were obtained by heating substituted benzoic acids with 2,4-diaminophenol in PPA (polyphosphoric acid) [26].

Compounds (**5**–**17**) were prepared from 5-amino-2-phenyl- or 5-amino-2-(substituted-phenyl)benzoxazoles with substituted benzoic acids or furan-2-carboxylic acid or thiophene-2-carboxylic acid chlorides obtained by treating carboxylic acids with thionyl chloride [27, 28].

Compounds **5**–**17** are new and their structures were supported by spectral data. The IR and ^{1}H NMR spectra are in agreement with the proposed structures (Table 1).

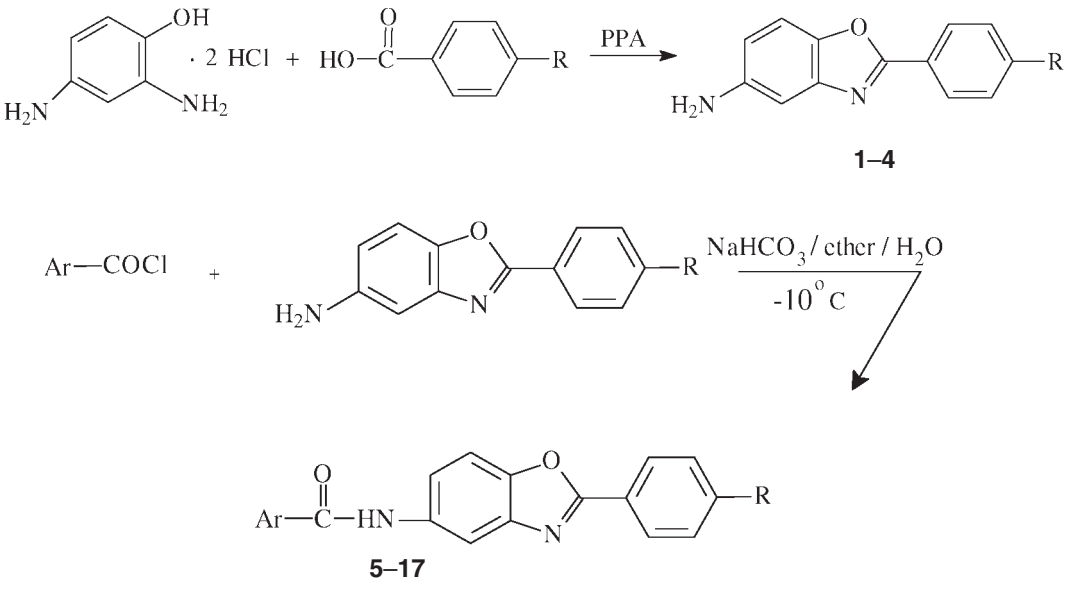
Results and discussion

The synthesized compounds showed some antibacterial activity against the Gram-positive bacteria *S. aureus* and *S. faecalis*, possessing MIC values between 25 and 100 µg/mL (6.64×10^{-5} and 1.64×10^{-4} molar) as given in Table 2.

Furthermore, the antibacterial activity of compounds **5**–**17** against *E. coli* as a Gram-negative bacteria revealed lower potencies than the comparison control drugs. However, compound **15** indicated significant activity with a molar concentration (C) 6.9×10^{-5} possessing MIC value of 25 µg/mL against the Gram-negative enterobacter *P. aeruginosa*, which is effective in nosocomial infections and often resistant to antibiotic therapy.

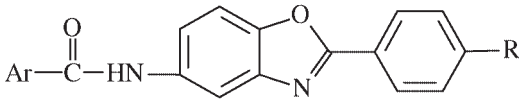
Compounds **5**–**17** were also tested against *C. albicans* for their antimycotic activity and most of the compounds indicated significant antimycotic activity, giving MIC values between 12.5 and 50 µg/mL at molar concentration values of 1.56×10^{-4} and 3.45×10^{-5}. Compounds **11** and **15** were more active than the other tested compounds, having a MIC value of 12.5 µg/mL at a molar concentration value of 3.45×10^{-5}. However, antimycotic potencies of the comparison control drugs clotrimazole and haloprogin were higher than those of our corresponding compounds, showing MIC values of 6.2 µg/mL and 3.1 µg/mL at molar concentrations values of 1.79×10^{-5} and 8.57×10^{-6}.

In conclusion, compound **15** is the most active one in this series against *C. albicans* and *P. aeruginosa.* Structure-



Scheme 1. Ar = substituted phenyl, 2-furyl, 2-thienyl; R = -H, $-C_2H_5$, F, $N(CH_3)_2$

Table 1. Data of the compounds **5**–**17**.



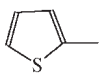
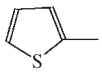
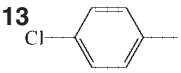
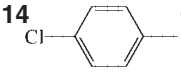
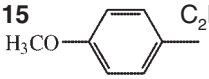
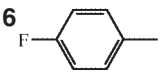
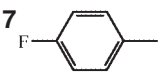
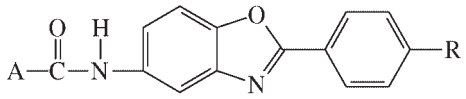
Com. No.	Ar	R	Mp (°C)	Yield (%)	Empirical formula	IR (cm^{-1})	^1H NMR δ ppm (*J* = Hz)
5		F	212	47	$C_{18}H_{11}FN_2O_2S$	3320, 3100, 1660, 1620, 1566, 1478, 1290, 1250, 960–404	7.00–7.40 (4H, m), 7.50–8.00 (4 H, m), 8.1–8.3 (2 H, m)
6		H	179	43	$C_{18}H_{12}N_2O_2S$	3340, 3120, 1600, 1580, 1480, 1230, 1020, 970–690	7.10–7.20 (1 H, t, *J* = 7.30), 7.50–7.90 (7 H, m), 8.02 (1 H, s), 8.24–8.30 (2 H, m)
7		F	202	39	$C_{18}H_{11}FN_2O_3$	3342, 3095, 1670, 1623, 1565, 1484, 1290, 1059, 927–418	6.45–6.60 (1 H, s), 6.85–7.70 (5 H, m), 7.9–8.30 (4 H, m)
8		H	172	46	$C_{18}H_{12}N_2O_3$	3410, 3100, 1670, 1545, 1480, 1040, 1230, 970–730	6.55–6.60 (1 H, d, *J* = 2.37), 7.50–7.90 (7 H, m), 8.10 (1 H, s), 8.22–8.32 (2 H, m)
9		C_2H_5	186	64	$C_{20}H_{16}N_2O_2S$	3270, 3080, 2960, 1621, 1557, 1480, 1294, 1060, 926–618	1.00–1.400 (3 H, t, *J* = 7.20), 2.10–2.30 (2 H, q, *J* = 7.30), 7.00–7.70 (6 H, m), 7.80–8.30 (4 H, m)
10		C_2H_5	162	43	$C_{20}H_{16}N_2O_3S$	3274, 3120, 2965, 1656, 1623, 1541, 1481, 1289, 1060, 939–518	1.00–1.30 (3 H, t, *J* = 7.20), 2.50–2.90 (2 H, q, *J* = 7.30), 6.50–6.60 (1 H, s), 7.20–7.70 (5 H, m), 8.00–8.30 (4 H, m)
11		$N(CH_3)_2$	241	32	$C_{20}H_{17}N_3O_2S$	3422, 3083, 1650, 1612, 1562, 1473, 1296, 1064, 943–410	3.20 (6 H, s), 7.70–8.00 (5 H, m), 8.00–8.20 (5 H, m), 10.5 (1 H, s)
12		$N(CH_3)_2$	235	21	$C_{20}H_{17}N_2O_3$	3322, 3095, 1654, 1608, 1552, 1424, 1296, 1059, 943–435	3.00 (6 H, s), 6.50–6.90 (4 H, m), 7.20–7.70 (2 H, m), 7.90–8.30 (4 H, m)
13		F	224	55	$C_{20}H_{12}ClFN_2O_2$	3359, 3100, 1652, 1610, 1566, 1488, 1244, 1056, 926–411	7.10–7.70 (5 H, m), 7.80–8.00 (4 H, m), 8.10–8.30 (2 H, m)
14		C_2H_5	233	36	$C_{22}H_{17}ClN_2O_2$	3337, 3095, 2967, 1645, 1486, 1288, 1088, 924–473	1.00–1.40 (3 H, t, *J* = 7.10), 2.60–3.00 (2 H, q, *J* = 7.30), 7.20–7.60 (5 H, m), 7.70–8.20 (6 H, m)
15		C_2H_5	182	45	$C_{23}H_{20}NO_3$	3276, 3100, 2990, 1632, 1557, 1480, 1253, 1031, 867–455	1.00–1.40 (3 H, t, *J* = 7.20), 2.60–2.90 (2 H, q, *J* = 7.30), 3.9 (3 H, s), 6.80–7.00 (2 H,d), 7.2–7.7 (4 H, m), 7.8–8.3 (4 H, m)
16		F	227	20	$C_{20}H_{12}F_2N_2O_2$	3291, 3100, 1644, 1607, 1549, 1503, 1287, 1056, 926–414	6.65–7.00 (4 H, m), 7.40–7.70 (2 H, m), 7.80–8.20 (5 H, m), 10.60 (1 H,s)
17		C_2H_5	220	48	$C_{22}H_{17}FN_2O_2$	3274, 3074, 2968, 1635, 1557, 1479, 1270, 1058, 967–547	1.00–1.30 (3 H, t, *J* = 7.20), 2.60–2.90 (2 H, q, *J* = 7.20), 7.00–7.60 (6 H, m), 7.80–8.30 (5 H,m)

Table 2. The *in vitro* antimicrobial activity of the compounds **5–17** and the control drugs (MIC in μg/mL and molar concentration).



Com. No.	*A*	*R*	*S.a.*		*S.f.*		*B.s.*		*E.c*		*P.a.*		*C.a.*	
			μg/mL	C	μg/mL	C	μg/mL	C	μg/mL	C	μg/mL	C	μg/mL	C
5	2-thienyl	F	50	1.48×10^{-4}	50	1.48×10^{-4}	100	2.95×10^{-4}	50	1.48×10^{-4}	100	2.95×10^{-4}	50	1.48×10^{-4}
6	2-thienyl	H	50	1.56×10^{-4}	50	1.56×10^{-4}	50	1.56×10^{-4}	50	1.56×10^{-4}	50	1.56×10^{-4}	50	1.56×10^{-4}
7	2-furyl	F	50	1.55×10^{-4}	50	1.55×10^{-4}	25	7.76×10^{-5}	25	7.76×10^{-5}	50	1.55×10^{-4}	25	7.76×10^{-5}
8	2-furyl	H	50	1.64×10^{-4}	50	1.64×10^{-4}	25	8.22×10^{-5}	50	1.64×10^{-4}	50	1.64×10^{-4}	25	8.22×10^{-5}
9	2-thienyl	C_2H_5	50	1.44×10^{-4}	100	2.87×10^{-4}	100	2.87×10^{-4}	200	5.74×10^{-4}	200	5.74×10^{-4}	50	1.44×10^{-4}
10	2-furyl	C_2H_5	25	7.53×10^{-5}	50	1.50×10^{-4}	25	7.53×10^{-5}	100	3×10^{-4}	100	3×10^{-4}	50	1.50×10^{-4}
11	2-thienyl	$N(CH_3)_2$	25	6.9×10^{-5}	25	6.9×10^{-5}	25	6.9×10^{-5}	25	6.9×10^{-5}	50	1.38×10^{-4}	12.5	3.45×10^{-5}
12	2-furyl	$N(CH_3)_2$	25	7.2×10^{-5}	25	7.2×10^{-5}	50	1.44×10^{-4}	50	1.44×10^{-4}	50	1.44×10^{-4}	25	7.2×10^{-5}
13	4-Chlorophenyl	F	25	6.82×10^{-5}	25	6.82×10^{-5}	25	6.82×10^{-5}	25	6.82×10^{-5}	50	1.36×10^{-4}	25	6.82×10^{-5}
14	4-Chlorophenyl	C_2H_5	25	6.64×10^{-5}	25	6.64×10^{-5}	25	6.64×10^{-5}	25	6.64×10^{-5}	50	1.32×10^{-4}	25	6.64×10^{-5}
15	4-methoxyphenyl	C_2H_5	25	6.9×10^{-5}	25	6.9×10^{-5}	25	6.9×10^{-5}	25	6.9×10^{-5}	25	6.9×10^{-5}	12.5	3.45×10^{-5}
16	4-fluorophenyl	F	25	6.72×10^{-5}	25	6.72×10^{-5}	25	6.72×10^{-5}	25	6.72×10^{-5}	50	1.34×10^{-4}	25	6.72×10^{-5}
17	4-fluorophenyl	C_2H_5	25	7.14×10^{-5}	25	7.14×10^{-5}	25	7.14×10^{-5}	25	7.14×10^{-5}	50	1.43×10^{-4}	25	7.14×10^{-5}
Ampicillin			1.56	4.47×10^{-6}	1.56	4.47×10^{-6}	1.56	4.47×10^{-6}	12.5	3.58×10^{-5}	>200	$>5.73\times10^{-4}$	–	–
Amoxycillin			1.56	4.27×10^{-6}	1.56	4.27×10^{-6}	1.56	4.27×10^{-6}	3.12	8.53×10^{-6}	>200	$>5.47\times10^{-4}$	–	–
Tetracycline			1.56	3.51×10^{-6}	1.56	3.51×10^{-6}	1.56	3.51×10^{-6}	3.12	7.02×10^{-6}	50	1.12×10^{-4}	–	–
Streptomycin			3.12	5.36×10^{-6}	100	1.71×10^{-4}	50	8.59×10^{-5}	1.56	2.68×10^{-6}	100	1.71×10^{-4}	–	–
Clotrimazole			–	–	–	–	–	–	–	–	–	–	6.2	1.79×10^{-5}
Haloprogin			–	–	–	–	–	–	–	–	–	–	3.1	8.57×10^{-6}

S.a.: Staphylococcus aureus E.c.: Escherichia coli; S.f.: Streptococcus faecalis; P.a.: Pseudomonas aeruginosa; B.s.: Bacillus subtilis; C.a.: Candida albicans.

activity relationships of the synthesized compounds, which reveal that the presence of a 2-(thienyl)carbonylamino group at position 5 of the fused heterocyclic system with a dimethylamino group at the para position of the 2-phenyl moiety increases the antimicrobial activity against *S. aureus, S. feacalis, B. subtilis,* and *E. coli,* and the antimycotic activity against *C. albicans.* These observations offer some predictions of value in the design of further antimicrobial active compounds prior to their synthesis.

Acknowledgment

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Experimental procedures

Chemistry

Silicagel HF_{254} chromatoplates (0.3 mm) were used for TLC. The solvent systems was chloroform:methanol (15:0.5) for compounds **5**–**17**. Melting points were measured on a Büchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded by FT/IR 420 on a Shimadzu IR-470 spectrometer (Shimadzu, Japan) on KBr discs. ^{1}H NMR spectra were obtained with a Bruker 80 MHz spectrometer in chloroform; tetramethylsilane (TMS) was used as an internal standard. Elemental analyses were carried out with a Perkin Elmer model 240-C analyzer. The results (C, H, N) were within ± 0.4 % of the calculated values.

General procedure for amide derivatives **5**–**17**

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 removed *in vacuo.* The residue was dissolved in ether (10 mL) and this solution added over 1 h to a stirred, ice-cold mixture of 5-amino-2-(*p*-substituted-phenyl)-benzoxazoles 4 (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**–**17**. The products were recrystallized from ethanol-water as needles which are dried *in vacuo.* The chemical, physical and spectral data of the compounds **5**–**17** are reported in Table 1.

Microbiology

For the antibacterial and antimycotic assays, the compounds were dissolved in absol. 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 with Mueller-Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the two-fold serial dilution technique [29, 30]. A control test was also performed containing inoculated broth supplemented with only ethanol at the same dilutions used in our experiments and found to be inactive in the culture medium. All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and the yeast *Candida albicans* RSKK 628. The 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 Pseudomonas 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 data on the antimicrobial activity of the compounds and the control drugs as MIC, mg/mL, and molar concentration values are given in Table 2.

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. *Candida 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 used 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.

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